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Ferri's CLINICAL ADVISOR

Diseases and Disorders I

Differential Diagnosis II

Clinical Algorithms III

Laboratory Tests and Interpretation of Results IV

Clinical Practice Guidelines V

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5 BOOKS IN 1

PTG Patient Teaching Guides

FRED F. FERRI

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CLINICAL DISORDERS

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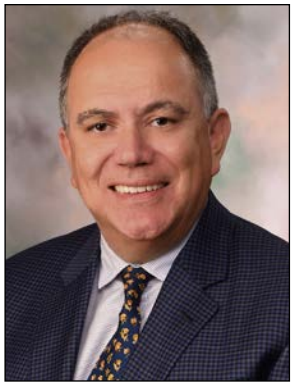

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To my sons, Dr. Vito F. Ferri and Dr. Christopher A. Ferri, and my daughter-in-law, Dr. Heather A. Ferri, for their help and constant support, and to my wife, Christina, for her patience during manuscript preparation. A special thanks to all the readers who have personally commented on the merits of this book and through their suggestions have helped make this product a bestseller in the medical field.

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Preface

This book is intended to be a clear and concise reference for physicians and allied health professionals. Its user-friendly format is designed to provide a fast and efficient way to identify important clinical information and to offer practical guidance in patient management. The book is divided into five sections and an appendix, each with emphasis on clinical information.

The tremendous success of the previous editions and the enthusiastic comments from numerous colleagues have brought about several positive changes over time. Each section has been significantly expanded from prior editions, bringing the total number of medical topics covered in this book to more than 1200. Hundreds of new illustrations, tables, and boxes have been added to this edition to enhance recollection of clinically important facts. The expedited claims submission and reimbursement ICD-10CM codes are included in all topics.

Section I describes in detail 988 medical disorders and diseases—including 25 new topics this edition—arranged alphabetically and presented in outline format for ease of retrieval. Topics with an accompanying algorithm are identified with an ALG icon. Similarly, those topics with an accompanying online Patient Teaching Guide (PTG) are identified with a PTG symbol. Throughout the text, key quick-access information is consistently highlighted, with clinical photographs to further illustrate selected medical conditions, and relevant ICD-10CM codes listed. Most references focus on current peer-reviewed journal articles rather than outdated textbooks and old review articles.

Topics in **Section I** use the following structured approach:

1. Basic Information (Definition, Synonyms, ICD-10CM Codes, Epidemiology & Demographics, Physical Findings & Clinical Presentation, Etiology)
2. Diagnosis (Differential Diagnosis, Workup, Laboratory Tests, Imaging Studies)
3. Treatment (Nonpharmacologic Therapy, Acute General Rx, Chronic Rx, Disposition, Referral)
4. Pearls & Considerations (Comments, Suggested Readings)

Section II includes the differential diagnosis, etiology, and classification of signs and symptoms. This practical section allows the user investigating a physical complaint or abnormal laboratory value to follow a "workup" leading to a diagnosis. The physician can then easily look up the presumptive diagnosis in Section I for information specific to that illness.

Section III includes more than 150 clinical algorithms to guide and expedite the patient's workup and therapy. For the 2021 edition, we have continued to update algorithms and colorize online versions for improved readability. Physicians describe this section as particularly valuable in today's managed-care environment.

Section IV includes normal laboratory values and interpretation of results of commonly ordered laboratory tests. By providing interpretation of abnormal results, this section facilitates the diagnosis of medical disorders and further adds to the comprehensive "one-stop" nature of our text. New illustrations and tables have been added for this edition.

Section V focuses on preventive medicine. Information here includes screening recommendations for major diseases and disorders, patient counseling, and immunization and chemoprophylaxis recommendations.

The **Appendix** is divided into nine major sections. Appendix I contains extensive information on complementary and alternative medicine (CAM), now expanded to include Common Herbs in Integrated Medicine, as well as Herbal Activities Against Pain and Chronic Diseases. With this material, we aim to lessen the current scarcity of exposure of allopathic and osteopathic physicians to the diversity of CAM therapies. Appendix II focuses on nutrition, with an emphasis on dietary supplements, vitamins, and minerals. Appendix III deals with diagnosis and treatment of acute poisoning. Appendix IV is a guide on impairment and disability evaluation. Appendix V focuses on the protection of travelers. Appendix VI addresses Physician Quality Reporting System (PQRS) measures. Appendix VII—available in the online version of *Ferri's Clinical Advisor*—is a repository of practical patient instruction sheets, organized alphabetically and covers the majority of topics in this book. These guides can be easily customized and printed and serve as valuable tools for improving physician-patient communication, patient satisfaction, and ultimately quality of care. Appendix VIII and IX are both new to this edition and offer guidance related to palliative care and preoperative evaluation, respectively.

I believe that we have produced a state-of-the-art information system with significant differences from existing texts. The information offered in all five sections and patient education guides could be sold separately based on their content, yet are available under a single cover, offering the reader tremendous value. I hope that the *Clinical Advisor*'s user-friendly approach, numerous unique features, and yearly updates will make this book a valuable medical reference, not only to primary care physicians but also to physicians in other specialties, medical students, and allied health professionals.

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Ferri's Clinical Advisor 2021—How to Use This Book

Mouse icon: Indicates content with additional references, figures, or tables available at ExpertConsult.com.

PTG

PTG icon: Indicates an accompanying Patient Teaching Guide available at ExpertConsult.com. Many additional PTGs are available online that are not connected to topics in Section I.

ALG

ALG icon: Indicates a topic with an accompanying algorithm.

BASIC INFORMATION

DEFINITION

An abdominal aortic aneurysm (AAA) is a focal full-thickness dilation of the abdominal aortic artery to at least 1.5 times the diameter measured at the level of the renal arteries, or exceeding the normal diameter of the abdominal aorta by 50%. The normal diameter at the renal arteries is 2 cm (range 1.4 to 3.0 cm), and a diameter 3 cm or larger is generally considered aneurysmal.

ICD-10CM CODES

I71.4 Abdominal aortic aneurysm, without rupture
I71.3 Abdominal aortic aneurysm, ruptured

EPIDEMIOLOGY & DEMOGRAPHICS

- Approximately 15,000 deaths/yr in the United States are attributed to AAA.
- AAA is predominantly a disease of older adults, affecting men more than women (4:1).
- The prevalence rate ranges from 4% to 9% in men in developed countries.
- Clinically important AAAs ≥4 cm are present in 1% of men between age 55 and 64; and the prevalence rate increases by 2% to 4% per decade thereafter.
- The peak incidence is among men approximately 70 yr old.
- The frequency is much higher in smokers than in nonsmokers (8:1); and the risk decreases with smoking cessation.
- Risk factors for AAA are similar to those for other atherosclerotic cardiovascular diseases. They include age, Caucasian race, smoking, male gender, family history, hypertension, hyperlipidemia, peripheral vascular disease, and aneurysm of other large vessels.
- AAA is two to four times more common in first-degree male relatives of known AAA patients.
- A decreased risk of AAA is associated with female gender, non-Caucasian race, and diabetes.
- Rupture of the AAA occurs in 1% to 3% of men age 65 or older.
  1. Rupture is the 10th leading cause of death in men older than age 55.
  2. Mortality from rupture is 70% to 95%.
  3. Risk factors for rupture include cardiac or renal transplants, severe obstructive lung disease, uncontrolled blood pressure, female sex, and ongoing tobacco use.
- A recent decline in incidence and prevalence of AAA and related mortality has been attributed to reductions in tobacco use. However, AAA are at least 9× more common than thoracic aortic aneurysms.

ETIOLOGY

- Exact etiology is unknown and is likely multifactorial.
  1. Degenerative:
     a. Alterations in vascular wall biology leading to a loss of vascular structural proteins and wall strength.
     b. The most common association is atherosclerosis. It is uncertain whether atherosclerosis causes or results from AAAs.
     c. Tobacco use: >90% of people who develop an AAA have smoked at some point in their lives.
  2. Inherited: Familial clusters are common. High familial prevalence rate is notable in male individuals. The nature of the genetic disorder is unclear but may be linked to alpha-1-antitrypsin deficiency or X-linked mutation. Connective tissue disorders, such as Marfan syndrome and Ehlers-Danlos syndrome, have also been strongly associated with AAA.
  3. Inflammatory: AAA is a progressive inflammatory disease of the artery walls. Activated B lymphocytes promote AAA by producing immunoglobulins, cytokines, and matrix metalloproteinases (MMPs), resulting in the activation of macrophages, mast cells (MCs), and complement pathways that lead to the degradation of collagen and matrix proteins and to aortic wall remodeling.
  4. Infection, mycotic: Syphilis, *Salmonella.*

NATURAL HISTORY

- AAAs tend to develop in the infrarenal aorta and to expand, on average, at a rate of 0.2 to 0.5 cm per yr.
- The risk of aneurysmal rupture is largely influenced by aneurysm size, rate of expansion, and sex. Other factors associated with increased risk for rupture include continued smoking, uncontrolled hypertension, and increased wall stress.
- Higher tension in the abdominal aorta (together with histopathologic changes such as accumulation of foam cells, cholesterol crystals, and matrix metalloproteinases) renders the abdominal aortic wall more susceptible to dilation and subsequent rupture.
- The 5-yr rupture rate of asymptomatic AAAs is 25% to 40% for aneurysms >5.0 cm in diameter, 1% to 7% for AAAs 4.0 to 5.0 cm, and nearly 0% for AAAs <4.0 cm. The likelihood that an aneurysm will rupture is increased in aneurysms with a diameter >5.5 cm; this size also demonstrates a faster rate of expansion (>0.5 cm over 6 months) and is more likely to be found in those who continue to smoke and in females.
- Mortality rate after rupture can be as high as 90% because most patients do not reach the hospital in time for surgical repair. Of those who reach the hospital, the mortality rate is still 50%, compared with the 1% to 4% mortality rate for elective repair of a nonruptured AAA.

SCREENING AND MONITORING

- The USPSTF recommends one-time screening for AAA by ultrasonography in men ages 65 to 75 who have a history of smoking, and in those 60 yr of age or older with a history of AAA in a parent or sibling. These populations have been shown to have a higher prevalence of AAA, and selectively screening this group has been shown to decrease AAA-specific mortality.
- The USPSTF has found little benefit in repeat screening in men with a negative ultrasound and has determined that men over the age of 75 are unlikely to benefit from screening. It was also concluded that the current evidence is insufficient to assess the balance of the harms and benefits of screening for AAA in women ages 65 to 75 who have ever smoked.
- The Society for Vascular Surgery Guidelines recommend monitoring by ultrasound or CT scan should be performed every 6 months for patients with AAAs measuring 5.0 to 5.4 cm in diameter, every 12 months for AAAs measuring 4.0 to 4.9 cm in diameter, and every 3 yr for AAAs 3.0 to 3.9 cm in diameter.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most aneurysms are asymptomatic and incidentally discovered on imaging studies; however, symptomatic aneurysms are at an increased risk for rupture.
- Physical examination has a sensitivity of 76% for detecting AAAs >5 cm and only 29% for AAAs 3.0 to 3.9 cm. The accuracy of the physical examination is markedly diminished by obese body habitus.
- Symptomatic patients may present with abdominal, back, flank, or groin pain.
- A pulsatile epigastric mass that may or may not be tender may be present
- Abdominal bruits can be present in case of renal or visceral arterial stenosis.
- Common iliac arteries can be aneurysmal and palpable in the lower abdominal quadrants. In addition, prominent femoral and popliteal pulses warrant an abdominal ultrasound and lower extremity ultrasound.
- Early satiety, nausea, and vomiting may be caused by compression of adjacent bowel.
- Venous thrombosis or insufficiency may occur from iliocaval venous compression.
- Thromboembolization can cause lower extremity pain and discoloration.
- Ureteral obstruction and hydronephrosis can cause flank and groin pain and lead to obstructive renal failure.
- Rupture classically presents as a triad of abdominal or back pain, hypotension, and a pulsatile abdominal mass in 50% of patients.
- Acute blood loss may lead to myocardial infarction; arteriovenous fistulas may present as heart failure; aortoenteric fistulas may present as hematemesis or melena associated with abdominal and back pain.

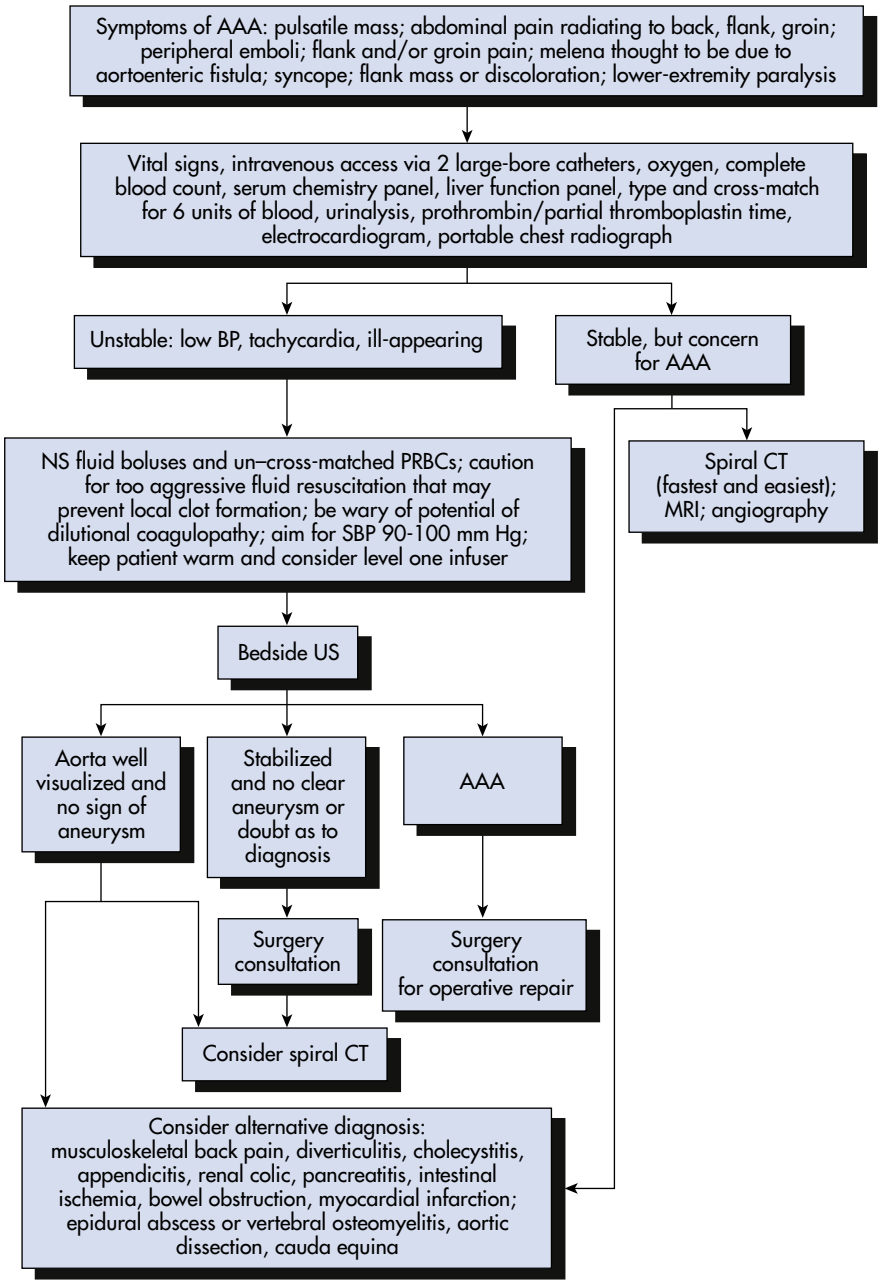

FIG. 1 Algorithm for the diagnosis and treatment of abdominal aortic aneurysms *(AAAs).* *BP,* Blood pressure; *CT,* computed tomography; *MRI,* magnetic resonance imaging; *NS,* normal saline; *PRBCs,* packed red blood cells; *SBP,* systolic blood pressure; *US,* ultrasonography. (From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

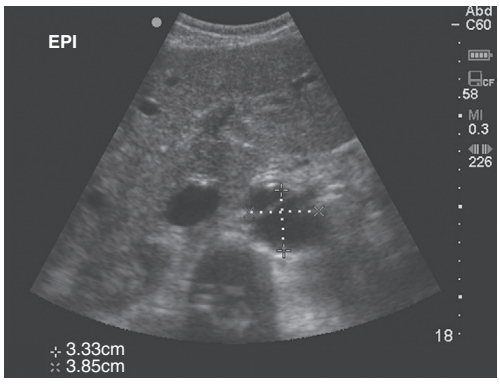

FIG. 2 Transverse image of an abdominal aortic aneurysm. Note the measurements of 3.33 × 3.85 cm. The inferior vena cava is seen to the patient's right of the aorta, and the vertebral body is seen below the two vessels. Note also that there appears to be an echogenic flap within the aorta, possibly representing an aortic dissection. (From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

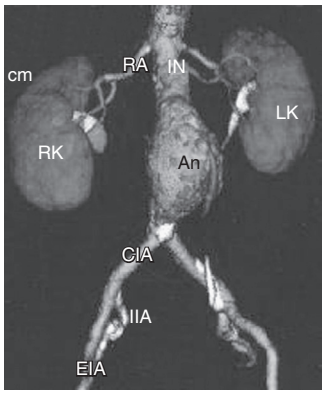

FIG. 3 Three-dimensional computed tomography image illustrates the presence of an infrarenal abdominal aortic aneurysm. *An,* Aneurysm; *CIA,* common iliac artery; *EIA,* external iliac artery; *IIA,* internal iliac artery; *IN,* infrarenal neck; *LK,* left kidney; *RA,* renal artery; *RK,* right kidney. (From Townsend CM et al [eds]: *Sabiston textbook of surgery*, ed 17, Philadelphia, 2004, Saunders.)

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Almost 75% of patients with AAA are asymptomatic, and the condition is discovered on routine examination or serendipitously when ordering studies for other symptoms. Diagnosis of AAA should be considered in the differential of the following symptoms: abdominal pain, back pain, and/or pulsatile abdominal mass. The differential diagnosis includes peptic ulcer disease, mesenteric ischemia, renal calculi, pyelonephritis, and diverticulitis.

LABORATORY TESTS

Not routinely indicated. For suspected infected or inflammatory aneurysms, WBC, ESR/CRP, and blood cultures can be considered. An elevated D-dimer may indicate a thrombus within the aneurysm. Fig. 1 describes an algorithm for the diagnosis and treatment of abdominal aortic aneurysms.

IMAGING STUDIES

- Abdominal ultrasound (Fig. 2) has nearly 100% sensitivity and specificity in identifying an aneurysm and estimating the size to within 0.3 to 0.4 cm. It is not accurate in estimating the extension to the renal arteries or the iliac arteries.
- Computed tomography (CT) (Fig. 3) scan is recommended for preoperative aneurysm imaging and estimates the size of the AAA to within 0.3 mm. There are no false-negative results, and the scan can identify extension to renal vessels with more precision than ultrasound. It is the imaging modality of choice for symptomatic AAA. Intravenous contrast is not required to establish a diagnosis of ruptured AAA. CT can also detect the integrity of the wall (Fig. 4) and exclude rupture.

- Magnetic resonance angiography (MRA) may also be used and is at least as accurate as CT.
- Plain radiographs may show the outline of an aneurysm in calcified aortas. This is an insensitive test for diagnosing AAA.
- Diagnostic aortography has essentially been replaced by other noninvasive imaging modalities such as CT or MR angiography. Intraoperative angiography is still used for determining treatment options and post-procedure efficacy (Fig. 5).
- Endovascular aneurysm repair (EVAR) needs close and lifelong imaging surveillance of the aneurysm site for the timely detection of possible complications, including endoleaks, graft migration, fractures, graft infection, and enlargement of aneurysm sac size with eventual rupture. The rate of complications after EVAR is approximately 30% with 2% to 3% of these requiring reintervention. Contrast-enhanced computed tomography (CTA) is considered the gold standard in EVAR follow-up (Fig. 6), but it is accompanied with radiation burden and renal injury because of the use of contrast media. In the past 2 decades, several studies have shown the role of contrast-enhanced ultrasonography (CEUS) in post-EVAR surveillance, with very good diagnostic performance, absence of renal impairment, and no radiation, accompanied by low costs, in comparison with CTA. In numerous prospective studies and meta-analyses, the detection and characterization of endoleaks with CEUS is comparable to that of CTA imaging.

FIG. 4 Aneurysm of the abdominal aorta. A large aortic aneurysm is evident. The aorta exceeds 5 cm in diameter. A large amount of thrombus *(T)* partially surrounds the contrast-enhanced patent lumen *(L)*. Note the atherosclerotic calcification (*arrowhead*) in the wall of the aneurysm.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Despite lack of data substantiating reduction in expansion rate through treatment of cardiac risk factors, nonpharmacologic treatment continues to focus on risk factor modification (most importantly smoking cessation, diet, and exercise). Of note, moderate exercise does not increase the rate of aneurysm expansion or the risk of rupture.
- Serial studies have shown that expansion rates are faster in current smokers than in former smokers. Patients with known AAA or a family history of aneurysms should be advised to stop smoking and be offered smoking cessation interventions.
- Definitive treatment depends on the size of the aneurysm (see "Chronic Rx").

ACUTE GENERAL Rx

- Acute symptomatic or ruptured AAA can be treated with open surgical repair (OSR) or EVAR. The choice is determined by anatomic considerations, operative risks, and availability of regular patient follow-up for EVAR.

FIG. 6 Completion digital subtraction angiogram following endovascular aneurysm repair. (From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology*, ed 8, Philadelphia, 2017, Elsevier.)

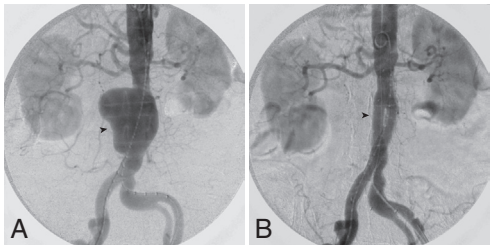

FIG. 5 A, Conventional catheter angiography with bilateral marked catheters in place demonstrates a large, lobulated, infrarenal aortic aneurysm (*arrowhead*) with a 4-cm proximal neck suitable for endovascular repair. **B,** An image after endovascular repair demonstrates complete exclusion of the aneurysm (*arrowhead*) with no endoleak and preservation of the renal and hypogastric arteries. (From Soto JA, Lucey BC: *Emergency radiology: the requisites*, ed 2, Philadelphia, 2017, Elsevier.)

- Emergent open repair has been the traditional method of treatment. However, multiple trials have shown lower mortality and shorter hospital stay with EVAR. More centers are increasingly using endovascular repair for patients who fit certain anatomic and physiologic criteria.
- A recent Cochrane meta-analysis involving pooled data for four trials comparing EVAR versus open repair for ruptured abdominal aortic aneurysm failed to show a difference in 30-day mortality between EVAR versus open repair. There was a higher incidence of reintervention for patients undergoing EVAR, although interventions to deal with procedural complications were generally less invasive and involved catheter-based approaches.
- The major limitations for EVAR include anatomical issues such as tortuosity or small caliber iliac arteries and inability to follow up patients to exclude late failure of stent-grafts and development of endoleaks.

CHRONIC Rx

- Blood pressure and fasting lipids should be monitored and controlled as recommended for patients with atherosclerotic disease. Statins are associated with decreased mortality after successful AAA repair, and are recommended for those with known AAA to reduce the progression of atherosclerosis and overall cardiovascular risk.
- The most commonly used predictor of rupture is the maximum diameter of the AAA.
- Long-term beta-blocker therapy has slowed the rate of aortic dilation and decreased the incidence of aortic complications in patients with Marfan syndrome. Several studies have also suggested that beta-blocker therapy may reduce the rate of expansion and risk of rupture; however, conclusive evidence is lacking.
- A recent multicenter study of 5362 patients with AAA found no significant association between AAA progression and the use of statins, beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers.
- Antibiotics such as doxycycline and roxithromycin have been shown to limit the expansion of small AAAs.
- AAA repair to eliminate the risk for rupture should be performed for patients with infrarenal or juxtarenal AAA of approximately 5.5 cm or larger in diameter. Repair in females can be considered at diameters larger than 5 cm. Additionally, AAAs with a rate of enlargement greater than 0.5 cm over 6 months should be considered for repair. All patients who are symptomatic should undergo repair, regardless of size. Timing of repair in symptomatic unruptured AAA is still under debate.
- There is no clear advantage to early repair (open or endovascular) for small asymptomatic AAAs (less than 5.5 cm).
- Percutaneous, endovascular, stent-anchored grafts placed with the patient under local anesthesia have provided an alternative approach for patients with favorable anatomy.

In patients who have undergone EVAR, long-term surveillance is required to assess for an endoleak, stent migration, change in aneurysm size, and need for re-intervention.

- EVAR with proximally fenestrated grafts is an alternative to open repair in the management of juxtarenal aortic aneurysms and short-neck abdominal aortic aneurysms (the "neck" is the distance from the lowest main renal artery to the beginning of the aneurysm). Contemporary literature shows it is a safe and efficacious treatment, particularly for those deemed surgically high risk.
- Randomized trials and meta-analyses comparing EVAR with OSR have shown that EVAR is associated with lower 30-day mortality and MI rates, shorter hospital stays, and better health-related quality of life up to 12 months postoperatively. However, EVAR also has increased rates of graft-related complications and is more costly. Additionally, a recent meta-analysis showed that 5 to 9 yr postoperatively, EVAR is associated with higher all-cause mortality, reintervention, and secondary rupture rates compared with OSR. Over >10 yr, EVAR is associated with higher reintervention and secondary rupture rates.
- Based on current data, less than 2% of endovascular repairs require open conversion, and approximately half of all early endoleaks resolve spontaneously within a period of 30 days.
- Open surgical repair of AAAs is the preferred approach for patients with a long life expectancy.
- Endovascular AAA repair is the preferred approach for most patients with a reasonable life expectancy and suitable anatomy.
- For patients with limited life expectancy, elective AAA repair is not recommended.
- Surveillance for endovascular AAA repair has typically involved use of periodic CT scans, but abdominal ultrasound is gaining widespread adoption for postprocedure monitoring. Surveillance is recommended to occur 1 and 12 months postoperatively and then annually thereafter.
- In high-risk patients undergoing AAA repair, specifically those with coronary artery disease or those with more than one clinical risk factor based on the American Heart Association (AHA) guidelines, preoperative administration of beta-blockers titrated to a goal heart rate of 60 have been shown to decrease incidence of death from cardiac causes or nonfatal myocardial infarctions. Beta-blockers initiated within 24 hours of the procedure have not shown an advantage; however beta-blockers the patient is already taking should be continued.
- Patients with chronic obstructive pulmonary disease (COPD) are at higher risk for major clinical complications, particularly if the COPD is suboptimally managed or if it is present in conjunction with cardiac or renal disease. Smoking cessation for 2 months before surgery has also been shown to decrease pulmonary morbidity.
- Renal dysfunction is a strong predictor of mortality, showing up to as high as 41% mortality in those with impaired renal function compared with 6% in those without renal dysfunction.

REFERRAL

- Vascular surgical referral should be made in asymptomatic patients with AAAs that are approximately 4.5 cm.
- In patients with an expansion rate of 0.5 cm over 6 months, it is reasonable to offer repair, although small studies have shown that using expansion as a criterion for surgical referral is of unclear benefit.
- It is important to optimize any comorbid conditions before surgical referral.

PEARLS & CONSIDERATIONS

- Repairing asymptomatic AAAs smaller than 5.5 cm has not been shown to improve survival because the risk of rupture is lower than the risk of surgery.
- The results from multiple trials to date demonstrate no advantage to immediate repair for small AAA (4.0 to 5.5 cm), regardless of whether open or endovascular repair is used and, at least for open repair, regardless of patient age and AAA diameter. Thus, neither immediate open nor immediate endovascular repair of small AAAs is supported by the currently available evidence.
- Five-yr survival remains poor after elective AAA repair despite advances in short-term outcomes and is associated with AAA diameter and patient age at the time of surgery. Research in this field should attempt to improve the life expectancy of patients with repaired AAA and to optimize patient selection.

COMMENTS

- Most AAAs are infrarenal. This is thought to be due in part to decreased lamellar structural proteins in the vascular wall below the renal arteries leading to decreased vascular wall strength.
- Surgical risk is increased in patients with coexisting coronary artery disease, pulmonary disease, or chronic renal failure. Evaluation for ischemia and aggressive perioperative hemodynamic monitoring help identify high-risk patients and decrease postoperative complications.
- It is estimated that AAAs at <5 cm expand at a rate of 0.2 to 0.3 cm/yr, and AAAs at >5 cm expand at a rate of 0.3 to 0.5 cm/yr.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Abdominal Aortic Aneurysm (Patient Information)

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Abdominal Compartment Syndrome

BASIC INFORMATION

DEFINITION

Abdominal compartment syndrome (ACS) is defined by the presence of organ dysfunction as a result of increased abdominal pressure or intraabdominal hypertension. The increased abdominal pressure reduces blood flow to internal organs, which can lead to multiple system failure and death if not promptly recognized and treated.

ICD-10CM CODE
M79.A3 Nontraumatic compartment syndrome of abdomen

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Very few studies have examined the incidence of ACS outside of trauma patients, among whom it ranges from 1% to 14%, depending on the population and type of trauma studied. The incidence is the highest among critically ill patients.

RISK FACTORS: The biggest risk factor for developing ACS is critical illness stemming from a wide array of medical and surgical conditions (Table E1). In particular, any illness that requires a patient to undergo large volume intravenous fluid resuscitation can be associated with ACS; the third-spacing of fluid can lead to increased intraabdominal pressures secondary to tissue edema. Due to large volume fluid resuscitation, ACS is commonly seen in severe burns, trauma, post-surgical patients, and sepsis. Other conditions associated with ACS include intraabdominal and retroperitoneal pathologies such as significant bowel distention, liver transplantation, massive ascites, ruptured abdominal aortic aneurysm with resulting hemoperitoneum, pancreatitis, and abdominal surgery (Table E2).

TABLE E1 Causes of Intraabdominal Hypertension and Abdominal Compartment Syndrome

Increased Abdominal Contents	Decreased Abdominal Volume
Ascites	Reduction of large long-standing hernia
Hemoperitoneum	Direct closure of large, long-standing abdominal wall defect
Abdominal packs	
Peritonitis	
Retroperitoneal edema (pancreatitis)	Retroperitoneal edema (pancreatitis)
Large pelvic, retroperitoneal hematoma	Large pelvic, retroperitoneal hematoma
Intestinal obstruction	
Ileus	
Gastric distention (esophageal ventilation)	
Abdominal aortic aneurysm	
Severe constipation	
Large abdominal tumor (chronic)	
Morbid obesity (chronic)	
Pregnancy (chronic)	

From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.

TABLE E2 Independent Predictors of Postinjury Primary and Secondary Abdominal Compartment Syndrome

	ED Model Independent Predictors	ICU Model Independent Predictors
Primary ACS	To OR <75 min Crystalloids ≥3 L	Temp ≤34° C $GAPco_2$ ≥16 Hb ≤8/dl BD ≥12 mEq/L
Secondary ACS	Crystalloids ≥3 L No urgent surgery PRBC ≥3 units	$GAPco_2$ ≥16 Crystalloids ≥7.5 L UO ≤150 ml

ACS, Abdominal compartment syndrome; *BD*, arterial base deficit; *CI*, confidence interval; *ED*, emergency department; *$GAPco_2$*, carbon dioxide gap; *Hb*, hemoglobin concentration; *ICU*, intensive care unit; *OR*, operating room; *PRBC*, packed red blood cells; *Temp*, temperature; *UO*, urine output.
From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The most striking physical examination finding is often massive abdominal distention.
- Difficulty maintaining respiratory support and decreased urine output are also typical hallmarks.
- Other common findings include those associated with poor perfusion states and hypotension such as skin mottling, cool extremities, and obtundation. Patients will often have abdominal tenderness, signs of volume overload such as edema and elevated jugular venous pressures, and may present with acute respiratory decompensation.

ETIOLOGY

ACS can affect nearly every organ system. High intraabdominal pressures are associated with increased intracranial pressures, which can precipitate cerebral ischemia. Elevated abdominal pressures can cause cardiac compression by decreasing ventricular compliance and contractility as well as impairing inferior vena cava venous return, leading to increased central venous and pulmonary pressures. Due to elevation of the diaphragm, patients will often have reduced tidal volumes and lower chest wall compliance, which can lead to atelectasis, pneumonia, hypoxemia, and hypercarbia. Mechanically ventilated patients will also require increased airway pressures that can lead to barotrauma. In addition, renal vein compression and renal artery vasoconstriction lead to decreased urine output. Reduced mesenteric blood flow can lead to intestinal ischemia and lactic acidosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Mesenteric ischemia
- Sepsis
- Shock
- Acute kidney injury
- Adult respiratory distress syndrome

WORKUP

Measurement of intraabdominal pressure is required to make a definitive diagnosis. Bladder pressure is the most common surrogate used to estimate intraabdominal pressures and is measured using a bladder catheter. The most accurate measurements can be obtained with the patient in supine position at end expiration in the absence of abdominal contractions. The threshold abdominal pressure often set for research purposes to define ACS is >20 mm Hg, but patients may have ACS with pressures of >10 mm Hg and above. Oliguria tends to develop at a pressure of 15 mm Hg, and anuria occurs around 30 mm Hg. Intraabdominal pressures can also be estimated using intragastric, intracolonic, and inferior vena cava approaches (Table E3).

TABLE E3 Classification of Abdominal Compartment Syndrome

Basis of Classification	Subcategories
Time frame	Acute
	Chronic
Relation to peritoneal cavity	Primary
	Secondary
Etiology	Trauma
	Burn
	Postoperative
	Pancreatitis
	Bowel obstruction
	Ileus
	Abdominal aortic aneurysm
	Oncologic
	Gynecologic

From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.

LABORATORY TESTS

Laboratory testing is generally not helpful for the diagnosis of ACS. The presence of lactic acidosis suggests bowel ischemia, which portends a poorer prognosis.

IMAGING STUDIES

Imaging alone has no diagnostic value in ACS, but chest imaging can be helpful to evaluate for diaphragmatic elevation and evidence of pulmonary complications (atelectasis, volume overload, pneumonia, etc.). Abdominal computed tomography imaging will sometimes show renal displacement, inferior vena cava compression, abdominal wall thickening, or bowel injury related to ischemia but should not be relied on to make the diagnosis of ACS.

Rx TREATMENT

Supportive care and, when appropriate, surgical abdominal decompression are the mainstays of ACS treatment.

NONPHARMACOLOGIC THERAPY

- Supportive care, often with hemodynamic and ventilatory support, as well as techniques to improve abdominal wall compliance, are the foundations of ACS management.
- Severe burns to the abdomen leading to ACS will require surgical escharotomy to improve abdominal wall compliance.
- Patients with tense ascites leading to ACS will require large volume paracentesis to decrease intraabdominal pressures.
- Patients should be positioned supine if possible as any elevation of the head will increase abdominal pressures.
- Rectal and nasogastric decompression is required if ACS is due to massive bowel distention.

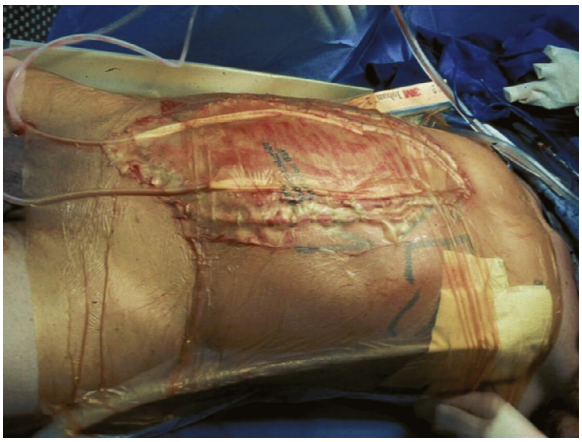

FIG. E1 Open abdomen management of abdominal compartment syndrome. The sterile saline bag was sewn to the skin edges. Closed suction drains were placed to limit fluid accumulation, and occlusive dressing was applied to cover the abdominal wall. (Courtesy Brian J. Kimbrell, MD, In Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.)

FIG. E2 Open abdomen management of abdominal compartment syndrome using a vacuum-assisted closure (VAC) system. The bowel is covered with omentum if possible. Nonadherent dressing is layered under a VAC sponge, or a smaller pore sponge is used against the viscera. Negative pressure is applied to the wound closure to drain fluid, facilitate closure, and prevent evisceration. (Courtesy Brian J. Kimbrell, MD, In Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.)

- Proper sedation and pain control can decrease intraabdominal pressures, and some patients may require ventilatory support and chemical paralysis to maximize abdominal wall relaxation.
- Mechanical ventilation is often difficult due to the high pressures that need to be generated to overcome the increased intraabdominal pressures. Often a combination of low tidal volumes, permissive hypercapnia, chemical paralysis, and high positive end-expiratory pressure are required to ensure adequate ventilatory support.
- Although there is little data to support its use, the administration of colloid may be superior to crystalloid if the patient requires further volume resuscitation. The administration of intravenous fluids will transiently increase renal blood flow, leading to increased urine output and improved organ perfusion and cardiac output. Pressors may also have a role to maintain perfusion pressures, but all of these measures are temporizing and supportive until definitive action through surgical decompression is performed.
- The threshold to perform surgical decompression for ACS has yet to be established; however, data suggest that early decompression prior to the development of ACS may lead to better outcomes. If appropriate, consensus dictates that surgical decompression should be performed on all patients with intraabdominal pressure >25 mm Hg; however, some surgeons are more aggressive and will consider decompression with pressures of 15 to 25 mm Hg in the right clinical setting. Surgical decompression (Fig. E1, Fig. E2) by incising vertically through the linea alba can be performed at the bedside in emergent situations and most surgeons will then keep the abdomen open through the use of a temporary abdominal closure device that retains heat/fluid and prevents evisceration until the time is appropriate to attempt to close the abdomen again.

ACUTE GENERAL Rx

There are no direct pharmacologic agents that treat ACS other than pressors, sedatives, pain medications, and paralytics required for

supportive care as described above. Despite underlying volume overload, diuretics have no role in therapy. Definitive management is surgical decompression.

DISPOSITION

Close inpatient monitoring, preferably in an intensive care setting, is indicated as mortality can be extremely high (>40%) with ACS.

REFERRAL

Patients with ACS often require admission to an intensive care setting with surgical consultation in case decompression is required.

PEARLS & CONSIDERATIONS

COMMENTS

- ACS is seen in critically ill medical and surgical patients, and its diagnosis requires both the presence of intraabdominal hypertension and end organ dysfunction.
- ACS is truly a systemic illness that can lead to multisystem organ failure and is therefore associated with a high mortality.
- Definitive diagnosis of ACS requires measurement of intraabdominal pressure, which is most frequently estimated using bladder pressure as a surrogate.
- Supportive care, including hemodynamic support with colloids, pressors, and ventilatory support, is often required, but surgical decompression is the only definitive treatment.
- Surgical decompression is indicated for intraabdominal pressures >25 mm Hg; however, precise thresholds have not been established, and earlier decompression may lead to better outcomes.

AUTHOR: **Jason D. Ferreira, MD**

SUGGESTED READINGS

Maluso P et al: Abdominal compartment hypertension and abdominal compartment syndrome, *Crit Care Clin* 32:213-222, 2016.

Roberts DJ et al: Increased pressure within the abdominal compartment: intraabdominal hypertension and the abdominal compartment syndrome, *Curr Opin Crit Care* 22:174-185, 2016.

Rogers WK et al: Intraabdominal hypertension, abdominal compartment syndrome and the open abdomen, *Chest* 153(1):238-259, 2018.

Van Damme L et al: Effect of decompressive laparotomy on organ function in patient with abdominal compartment syndrome: a systematic review and meta-analysis, *Crit Care* 22(1):179, 2018.

BASIC INFORMATION

DEFINITION

Abnormal uterine bleeding (AUB) describes uterine bleeding that is abnormal in regularity, quantity, frequency, or duration, in the nonpregnant person. Historically, AUB was described as in Table 1. The term "dysfunctional uterine bleeding" was applied when no clear etiology could be identified. These terms have fallen out of favor. In 2011, the FIGO Working Group on Menstrual Disorders released a classification system intended to simplify these definitions. It is known by the acronym PALM-COEIN, described later. Today, AUB is described according to these criteria.

A normal menstrual cycle is typically described as lasting 21 to 35 days with 5 days of bleeding per cycle. Total blood loss for normal menses is thought to be less than 80 ml.

SYNONYMS

Abnormal uterine bleeding (AUB)
Dysfunctional uterine bleeding

ICD-10CM CODES

N92.5 Other specified irregular menstruation
N92.0 Excessive and frequent menstruation with regular cycle
N91.5 Oligomenorrhea, unspecified
N92.1 Excessive and frequent menstruation with irregular cycle
N94.6 Dysmenorrhea, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Most cases of AUB result from uterine pathology (the PALM portion of the acronym).
- Up to 20% of women presenting with heavy menstrual bleeding will be found to have a coagulopathy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical findings depend on the etiology. For example, an enlarged/irregular uterine contour may suggest fibroids, or a polyp may be seen on the cervix during a speculum examination.
- The clinical presentation is also variable. Although many patients complain of the abnormality of their cycles, some will present with symptoms of anemia, with AUB being elicited only with a careful history. Patients may note recent weight gain or on examination, may have other findings (as noted later) suggestive of the etiology for their bleeding.
- Thorough physical and pelvic examination to exclude the other causes of abnormal bleeding:
  1. Includes thyroid, breast, liver (e.g., presence or absence of ecchymotic lesions)
  2. Patient habitus: Obese and hirsute (polycystic ovarian disease) or thin (think eating disorders or excessive exercise)
  3. Presence or absence of vulvar, vaginal, or cervical lesions, uterine (fibroid) or ovarian tumors, urethral caruncles or diverticula, hemorrhoids, anal fissures, colorectal lesions
  4. Bimanual pelvic examination: Normal-sized or enlarged uterus, regular or irregular contour

ETIOLOGY

- Table 2 describes many of the various causes of AUB. The causes of AUB in the fourth and fifth decade are summarized in Table 3.
- Endocrinopathies, including hyperprolactinemia and thyroid disorders, may also contribute to heavy or irregular menstrual bleeding.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- PALM–COEIN:
  1. Polyps (AUB-P)
  2. Adenomyosis (AUB-A)
  3. Leiomyoma (AUB-L)
  4. Malignancy/hyperplasia (AUB-M)
  5. Coagulopathy (AUB-C; most commonly von Willebrand disease)
  6. Ovulatory dysfunction (AUB-O; most commonly polycystic ovarian syndrome)
  7. Endometrial (AUB-E)
  8. Iatrogenic (AUB-I; e.g., anticoagulants, hormonal contraception, and some herbal remedies)
  9. Not yet classified (AUB-N)
- Anatomic nonuterine causes:
  1. Cervical neoplasia, cervicitis
  2. Vaginal neoplasia, adhesions, trauma, foreign body, atrophic vaginitis, infections, condyloma
  3. Vulvar trauma, infections, neoplasia, condyloma, dystrophy, varices
  4. Urinary tract: Urethral caruncle, diverticulum, hematuria
  5. Gastrointestinal tract: Hemorrhoids, anal fissure, colorectal lesions
- Systemic diseases/effects:
  1. Exogenous hormone intake: Hormone replacement therapy

TABLE 1 Definitions of Abnormal Uterine Bleeding

Term	Description
Oligomenorrhea	Bleeding at intervals greater than 35 days
Polymenorrhea	Bleeding at intervals less than 21 days
Hypermenorrhea (menorrhagia)	Excessive flow or bleeding with normal intervals
Metrorrhagia	Bleeding between menses
Menometrorrhagia	Excessive flow or duration with periods and between periods
Withdrawal bleeding	Bleeding after the withdrawal of hormones

Crum CP et al: *Diagnostic gynecologic and obstetric pathology,* ed 3, Philadelphia, 2018, Elsevier.

TABLE 2 Causes of Abnormal Uterine Bleeding

Age (Years)	Causes (In Order of Decreasing Frequency)
Prepubertal	Precocious puberty (hypothalamic, pituitary, ovarian)
Adolescence	• Disorders in the hypothalamic-pituitary axis (transient) • Disorders in folliculogenesis (transient) • Sexually transmitted infections, undiscovered pregnancy • Hematologic disorders (von Willebrand factors VII, XI)
Third and fourth decades	• Oral contraceptive pill-related • Postpregnancy • Benign organic lesions (polyps, leiomyomata, endometritis) • Anovulatory cycle
Fifth decade	• Anovulatory or altered cycle • Benign organic lesions (polyps, adenomyosis, leiomyomata, or endometritis) • Neoplasia
Sixth decade	• Hormone replacement therapy • Benign organic lesions (polyps, adenomyosis, leiomyomata, endometritis) • Atrophy • Neoplasia

Crum CP et al: *Diagnostic gynecologic and obstetric pathology,* ed 3, Philadelphia, 2018, Elsevier.

TABLE 3 Causes of Abnormal Uterine Bleeding in the Fourth and Fifth Decades

Cause	Differential Diagnosis
Anovulation	• Endometrial polyp • Basalis
Endometrial polyp	• Basalis/lower uterine segment • Tangentially sectioned functionalis • Atypical polypoid adenomyoma • Adenomyomatous polyp • Intraendometrial leiomyoma • Adenosarcoma
Chronic endometritis	• Late menstrual endometrium • Postpartum/postabortal endometrium • Cervical tissue (plasma cells) • Menstrual endometrium • Lymphoproliferative disorder
Submucosal leiomyoma	• Progestin/tamoxifen therapy • Endometrial polyp • Stromal neoplasm

Crum CP et al: *Diagnostic gynecologic and obstetric pathology,* ed 3, Philadelphia, 2018, Elsevier.

2. Medications
3. Coagulopathies: Von Willebrand disease, thrombocytopenia, hepatic failure
4. Endocrinopathies: Thyroid disorder, hyperprolactinemia, diabetes mellitus
5. Renal diseases: Generally causing acquired coagulopathy
6. Impaired nutritional status: Anorexia/bulimia

- Section II describes a differential diagnosis of vaginal bleeding abnormalities.

WORKUP

- Detailed history:
  1. Age of menarche
  2. Prior menstrual characteristics (newly abnormal or always so)
  3. Severity of bleeding
  4. Surgical and medical history suggestive of other causes/contributors
- Thorough physical examination, including a pelvic examination (bimanual and speculum) to exclude causes mentioned above
- Includes thyroid, breast, liver (e.g., presence or absence of goiter, galactorrhea, or ecchymotic lesions)
  1. Patient habitus: Obese and hirsute (polycystic ovarian disease) or thin (think eating disorders or excessive exercise)
  2. Presence or absence of vulvar, vaginal, or cervical lesions, uterine (fibroid) or ovarian tumors, urethral caruncles or diverticula, hemorrhoids, anal fissures, or colorectal lesions

LABORATORY TESTS (AS INDICATED BY HISTORY AND PHYSICAL)

- Complete blood count with platelets to evaluate for possible iron-deficiency anemia or thrombocytopenia
- Prothrombin/INR and partial thromboplastin (or PFA-100 assay) if coagulopathy is suspected
- von Willebrand panel, particularly in women with heavy bleeding since menarche if initial testing suggests coagulopathy
- Serum or urine human chorionic gonadotropin
- Chemistry profile, including liver function tests
- Thyroid profile
- Pap smear if not up to date
- Cultures for gonorrhea and chlamydia
- Serum gonadotropins and prolactin
- Serum androgens
- Endometrial biopsy or dilation and curettage, especially in patients over 45, or in younger patients with a long-standing history of anovulatory bleeding with fewer than three menstrual cycles per yr or with a high risk of endometrial neoplasia with prolonged unopposed estrogen exposure
- Stool testing for occult blood
- Urinalysis for hematuria

IMAGING STUDIES

- Pelvic ultrasound, including measurement of endometrial thickness in the postmenopausal woman and assessment of myometrial or endometrial defects. This is considered first line.
- Fluid contrast ultrasound (also called saline sonogram, sonohysterogram, saline infusion sonogram, etc.) may be indicated if the endometrium appears thickened or irregular. It distends the uterine cavity so that "filling defects" of the endometrium can be assessed for possible endometrial polyp, uterine fibroid, or neoplasm.
- Hysteroscopy may be performed to assess intracavitary fibroids or polyps.
- Magnetic resonance imaging may help better characterize large fibroids or uterine pathology but is rarely needed.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Increase iron intake in the form of pills and a diet rich in iron to combat anemia.
- Initiate lifestyle changes, including weight loss, exercise, and low-carb diet, if indicated.

ACUTE GENERAL Rx

- Progestins:
  1. Medroxyprogesterone acetate (oral), 10 to 20 mg daily for 15 days
  2. Megestrol acetate, 40 to 120 mg daily in divided doses for 15 days
  3. Oral contraceptives: One tablet tid for 5 to 7 days; patient should then continue on oral contraceptives daily
- Estrogens:
  1. Conjugated estrogen 25 mg IV q4h until bleeding is under control (in cases of severe or life-threatening bleeding); maximum 24 hr
  2. For prolonged bleeding that is not life threatening: Premarin 1.25 mg (Estrace 2 mg) q4h for 24 hr, followed by Provera to bring on withdrawal bleeding; then sequential regimen of estrogen and progestin (Premarin 1.25 mg qd for 24 days, Provera 10 mg for last 10 days) or oral contraceptives

CHRONIC Rx

- Progestins:
  1. Medroxyprogesterone acetate 10 mg daily for 12 days, then cyclically to induce monthly withdrawal bleeding
  2. Norethindrone 2.5 to 10 mg qd for 12 days each mo or 0.35 mg daily (marketed as the "mini-pill")
  3. Depo-Provera 150 mg IM every 3 mo
  4. Oral contraceptives, one tablet qd either cyclically or continuously using only active pills
  5. Levonorgestrel-releasing intrauterine device (Mirena has an FDA indication for heavy menstrual bleeding)
- Letrozole or clomiphene citrate: Not typically a treatment for abnormal bleeding but may help patients with anovulatory bleeding who want to become pregnant. Progesterone withdrawal may be counterproductive in patients wishing to start an ovulation induction regimen. Pregnancy rates are lower when patients undergo withdrawal compared to when random ovulation induction start is used. Letrozole is superior to clomiphene citrate in ovulation induction in women with PCOS. Human menopausal gonadotropin (HMG) can be used for women who do not ovulate with oral agents or who have hypothalamic dysfunction.
- Others:
  1. Anti-prostaglandins (ibuprofen or naproxen sodium can reduce bleeding by 40%).
  2. Danazol (rarely used due to side-effect profile).
  3. Gonadotropin-releasing hormone (GnRH) analogues; often used to reduce bleeding and ameliorate anemia and in preparation for a surgical procedure.
  4. Tranexamic acid (Lysteda) is an antifibrinolytic agent FDA approved for cyclic heavy menstrual bleeding. Dosage in normal renal function is 3900 mg daily (650 mg tablets, 2 tablets tid) for up to five days during menses.
  5. Endometrial tamponade with Foley catheter.
- Surgical treatment:
  1. Dilation and curettage and operative hysteroscopy
  2. Endometrial ablation
  3. Uterine artery embolization
  4. Hysterectomy

DISPOSITION

Cyclical treatment on birth control pills or Provera for several cycles, then discontinue pill and watch patient for onset of regular menses. If the patient does not want to conceive, continued cycle management with a hormonal contraceptive is commonly used.

REFERRAL

To gynecologist in case of failure of treatment

PEARLS & CONSIDERATIONS

- Always get a pregnancy test.
- If a young patient presents at menarche with bleeding severe enough to warrant emergency evaluation, there is a higher risk of a bleeding disorder, such as von Willebrand disease.
- Endometrial sampling is indicated in patients over 45 yr of age with new AUB.

COMMENTS

Patient education material may be obtained from the American College of Obstetricians and Gynecologists, 409 12th Street SW, Washington, DC 20024-2188; phone 202-638-5577.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Abnormal Uterine Bleeding (Patient Information)
Endometrial Cancer (Related Key Topic)
Heavy Menstrual Bleeding (Menorrhagia) (Related Key Topic)
Uterine Fibroids (Related Key Topic)

AUTHOR: **Nicole A. Roberts, MD**

SUGGESTED READING

Munro MG et al: FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age, *Int J Gynaecol Obstet* 113:3-13, 2011.

BASIC INFORMATION

DEFINITION

Abruptio placentae is the separation of placenta from the uterine wall before delivery of the fetus. The condition occurs in approximately 1% of pregnancies. There are three classes of abruption (Fig. 1) based on maternal and fetal status, including an assessment of uterine contractions, quantity of bleeding, fetal heart rate monitoring, and abnormal coagulation studies (fibrinogen, prothrombin time, partial thromboplastin time).

- Grade I: Mild vaginal bleeding, uterine irritability, stable vital signs, reassuring fetal heart rate, normal coagulation profile (fibrinogen 450 mg/dl). Approximately half of abruptions are grade I.
- Grade II: Moderate vaginal bleeding, hypertonic uterine contractions, orthostatic blood pressure measurements, unfavorable fetal status, fibrinogen 150 to 250 mg. Approximately a quarter of abruptions are grade II.
- Grade III: Severe bleeding (may be concealed), hypertonic uterine contractions, overt signs of hypovolemic shock, fetal death, thrombocytopenia, fibrinogen <150 mg/dl. Approximately a quarter of abruptions are grade III.

SYNONYM

Premature separation of placenta

ICD-10CM CODES

O45.8X9	Other premature separation of placenta, unspecified trimester
O45.8X1	Other premature separation of placenta, first trimester
O45.8X2	Other premature separation of placenta, second trimester
O45.8X3	Other premature separation of placenta, third trimester
O45.91	Premature separation of placenta, unspecified, first trimester
O45.92	Premature separation of placenta, unspecified, second trimester
O45.93	Premature separation of placenta, unspecified, third trimester

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 9.6 per 1000 births; 80% occur before the onset of labor.

RISK FACTORS: Hypertension (greatest association), trauma, polyhydramnios, multifetal gestation, smoking, use of cocaine, chorioamnionitis, preterm premature rupture of membranes. Table 1 summarizes placental abruption risk factors.

RECURRENCE RATE: 5% to 17%, some studies showing a 5- to 10-fold increase in risk; with two prior episodes, 25%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Triad of uterine bleeding (concealed or per vagina), hypertonic uterine contractions or signs of preterm labor, and evidence of fetal compromise exists.
- More than 80% of cases have external bleeding; 20% of cases have no bleeding but have indirect evidence of abruption, such as failed tocolysis for preterm labor.
- Tetanic uterine contractions are found in only 17%.

ETIOLOGY

- Primary etiology: Unknown
- Hypertension: Found in 40% to 50% of grade III abruptions
- Rapid decompression of uterine cavity, as can occur in polyhydramnios or multifetal gestation
- Blunt external trauma (motor vehicle accident, spousal abuse)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Placenta previa
- Cervical or vaginal trauma
- Labor
- Cervical cancer
- Rupture of membranes
- The differential diagnosis of vaginal bleeding in pregnancy is described in Section III

WORKUP

- Placental abruption is primarily a clinical diagnosis that is supported by laboratory, radiographic (Fig. 2), and pathologic studies.
- Initial assessment should evaluate for the source of bleeding, ruling out placenta previa that may contraindicate any type of vaginal examination (e.g., pelvic speculum examination).
- Continuous fetal heart monitoring is indicated for all viable gestations (60% incidence of fetal distress in labor); may show early signs of maternal hypovolemia (late decelerations or fetal tachycardia) before overt maternal vital sign changes.
- Actual amount of blood loss is often greater than initially perceived because of the possibility of concealed retroplacental bleeding and apparent "normal" vital signs. The relative hypervolemia of pregnancy initially protects the patient until late in the course of bleeding, when abrupt and sudden cardiovascular collapse can occur.

LABORATORY TESTS

- Baseline serum hemoglobin helps quantify blood loss and establish baseline values for serial comparisons during expectant management.
- Coagulation profile: Platelets, fibrinogen, prothrombin, and partial thromboplastin time. Diffuse intravascular coagulation can develop with severe abruption. If fibrinogen is <150 mg/dl, estimated blood loss is approximately 2000 ml; if fibrinogen is <100 mg/dl, consider fresh frozen plasma to prevent further bleeding.
- Type and antibody screen is important to identify Rh-negative patients who need Rh immune globulin.

IMAGING STUDIES

Ultrasound should include fetal presentation and status, amniotic fluid volume, placental location, as well as any evidence of hematoma (retroplacental, subchorionic, or preplacental) (Fig. E3).

TREATMENT

ACUTE GENERAL Rx

- Stabilization of the mother is the first priority.
- Treatment depends on gestational age of the fetus, severity of the abruption, and maternal status.
- Initial assessment for signs of maternal hemodynamic compromise or hemorrhagic shock; large-bore intravenous access, with crystalloid fluid resuscitation using a replacement of 3 ml lactated Ringer solution for every 1 ml estimated blood loss.

TABLE 1 Placental Abruption Risk Factors

Increasing parity or maternal age
Cigarette smoking
Cocaine abuse
Trauma
Maternal hypertension
Preterm premature rupture of membranes
Rapid uterine decompression associated with multiple gestation and polyhydramnios
Inherited or acquired thrombophilia
Uterine malformations or fibroids
Placental abnormalities or ischemia
Prior abruption

From Gabbe SG: *Obstetrics*, ed 6, Philadelphia, 2012, Saunders.

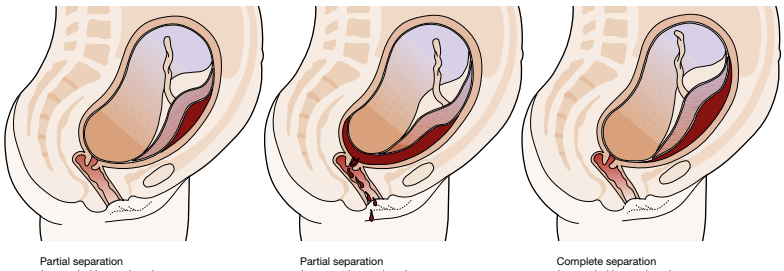

FIG. 1 Classification of placental abruption. (From Magowan BA: *Clinical obstetrics & gynecology,* ed 4, 2019, Elsevier.)

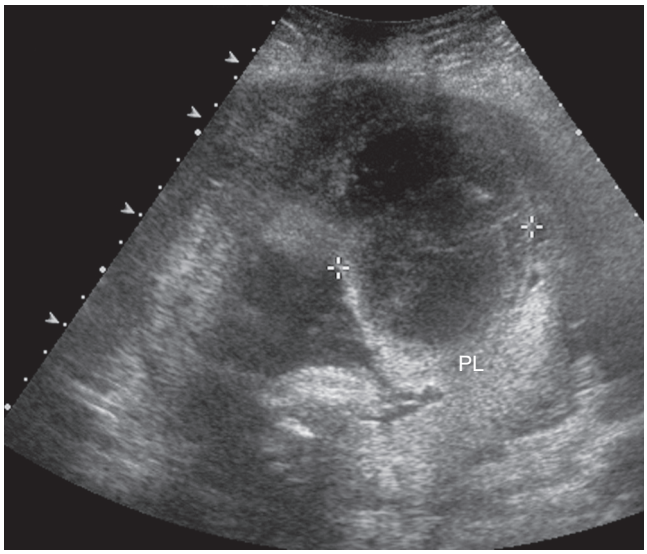

FIG. 2 Placental abruption. Transabdominal sonogram of the placenta *(PL)* with a hematoma *(calipers)* lifting the placenta away from the uterine wall. (From Rumack CM et al [eds]: *Diagnostic ultrasound*, ed 4, Philadelphia, 2011, Mosby.)

- Indwelling Foley catheter to monitor urine output and maternal volume status, with a goal of 30 ml/hr urine output.
- Assess fetal status and gestational age by sonogram and continuous fetal heart rate monitoring.
- Because of the unpredictable nature of abruptions, cross-matched blood should be made available during the initial resuscitation period.

CHRONIC Rx

- In the term fetus, delivery is indicated.
- In the preterm fetus, consider betamethasone 12.5 mg IM q24h for two doses and then delivery, depending on the severity of the abruption and the likelihood of fetal complications from preterm birth.
- Cesarean section should be reserved for cases of fetal distress or for standard obstetric indications. While cesarean delivery may be needed to stabilize the fetal and/or maternal status, the mother's coagulation status may complicate the procedure and availability of blood products may be critical.
- In cases of maternal stability and fetal prematurity, expectant management can occur in the setting of close follow-up, including regular evaluation of fetal growth and reassuring antenatal testing.

DISPOSITION

Because of the unpredictable nature of abruptions, expectant management should occur only under controlled circumstances.

REFERRAL

Abruptio placentae places mother and fetus in a high-risk situation and should be managed by a qualified obstetrician in a facility with capability for neonatal and maternal resuscitation, for supporting a preterm infant if delivery is indicated at an early gestational age, and for performing emergency cesarean sections.

RELATED CONTENT

Abruptio Placentae (Patient Information)
Premature Labor (Related Key Topic)
Vaginal Bleeding during Pregnancy (Related Key Topic)

AUTHOR: **Kelly Ruhstaller, MD**

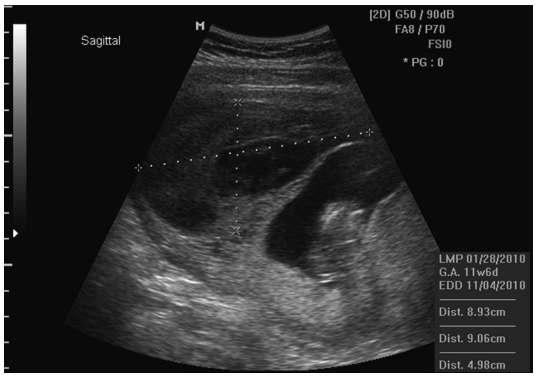

FIG. E3 Ultrasonic image of a subchorionic abruption. (Courtesy K. Francois; from Gabbe SG: *Obstetrics,* ed 6, Philadelphia, 2012, Saunders.)

BASIC INFORMATION

DEFINITION

Absence seizures are a type of generalized seizure characterized by brief episodes of staring with impairment of consciousness (absence). They usually last no more than 20 to 30 sec. The onset and the end of the seizures are sudden. Usually the patients are not aware of them and resume the activity they were performing before the seizure. The electroencephalogram signature of absence seizures consists of a generalized 3-Hz spike and slow wave discharges.

SYNONYMS

Childhood absence epilepsy
Seizures, absence

ICD-10CM CODE

G40.309 Generalized idiopathic epilepsy and epileptic syndromes, not intractable, without status epilepticus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1 to 10 cases per 100,000 population
PEAK INCIDENCE: 6 to 7 yr
PREVALENCE: Represents up to 18% of all pediatric epilepsy syndromes
PREDOMINANT SEX AND AGE: More common in girls than in boys, absences typically begin between 4 and 8 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with absence seizures usually have normal physical and neurologic examinations.
- During the seizures, the patients are unresponsive and can have motor phenomena (automatisms, eye blinks, mouth and hand movements).
- Absence seizures are not associated with postictal confusion.
- They may be triggered by hyperventilation associated with activity.
- Tonic clonic seizures are not usually a feature of this syndrome. If the patient also experiences tonic clonic seizures, other etiologies should be investigated, such as juvenile absence epilepsy, juvenile myoclonic epilepsy, complex partial seizures, etc.

ETIOLOGY

Genetic

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy
- Complex partial seizures
- Focal seizures with altered consciousness (Table E1)
- Nonepileptic spells comprised of staring

WORKUP

- EEG with hyperventilation and photic stimulation is crucial in the diagnosis.
- Ambulatory EEG and video EEG are recommended for patients with diagnostic uncertainty.

LABORATORY TESTS

No specific studies needed

IMAGING STUDIES

- MRI of the brain should be performed in all epilepsy patients, especially if the EEG does not show the typical characteristic of absence seizures (3-Hz spike and slow wave discharges).
- CT scans of the head should be avoided in children due to unnecessary exposure to radiation and low yield of the test except when MRI cannot be obtained.

TREATMENT

The medication of choice based on the best current evidence available is ethosuximide, followed by valproic acid and lamotrigine.

NONPHARMACOLOGIC THERAPY

Not applicable

GENERAL Rx

- Ethosuximide: Initial dose: 10 mg/kg/day; then after 7 days, 20 mg/kg
- Divalproex sodium (Depakote): Initial dose: 5 to 10 mg/kg/day (divided bid), maximum dose: 60 mg/kg/day
- Lamotrigine (Lamictal): Dose for patients on no other antiepileptic drugs. Wk 1 and 2: 0.3 mg/kg/day. Wk 3 and 4: 0.6 mg/kg/day. Wk 5 onward: Increase every 1 to 2 wk by 0.6 mg/kg/day. Maintenance: 4.5 to 7.5 mg/kg/day. Warning: Should be used with caution due to the potential for toxicity and Stevens-Johnson syndrome. Patients on other antiepileptic drugs can also have severe adverse reactions (e.g., valproate can cause increased levels of lamotrigine, and lamotrigine must be titrated much more slowly in patients on valproate therapy).

CHRONIC Rx

- Children with recurrent seizures require chronic treatment.
- If children are seizure-free for a period of 1 to 2 yr, a trial on no medications should be considered; children typically outgrow childhood absence seizures.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Not applicable

DISPOSITION

- Response to treatment is excellent.
- Absence seizures tend to remit in teenage yr.
- Epilepsy can be considered as resolved once 10 yr have elapsed since the last event, including 5 yr free from medications.

REFERRAL

Patients with epilepsy and seizures should be referred for a consultation by a neurologist, preferably one specializing in epilepsy.

PEARLS & CONSIDERATIONS

COMMENTS

- Absence seizures can be present in other epilepsy syndromes.
- Valproate should be avoided in girls and women with childbearing potential due to the risk of teratogenicity.
- Carbamazepine and phenytoin should be avoided in the treatment of absence seizures, since these medications may worsen seizures and could provoke absence status epilepticus.
- All women of childbearing age taking antiepileptic drugs should take folic acid supplementation (1 to 4 mg/day) for the prevention of neural tube defects.

PREVENTION

Sleep deprivation and alcohol consumption should be avoided.

PATIENT & FAMILY EDUCATION

- Patients with ongoing seizures are forbidden to drive; check state regulations and laws regarding driving and epilepsy.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Absence Seizures (Patient Information)

AUTHOR: **Joseph S. Kass, MD, JD, FAAN**

Absence Seizures

TABLE E1 Comparison of Focal Seizures with Altered Consciousness and Absence Seizures

Feature	Focal Seizure with Altered Consciousness	Absence
Aura	Often	Never
Consciousness	Impaired	Lost at onset
Movements	Usually simple, repetitive but may include complex	Blinking and facial and finger automatism activity
Postictal behavior	Amnesia, confusion, and tendency to sleep	No abnormality, except amnesia for ictus
Frequency	1-2 per week	Several daily
Duration	2-3 minutes	1-10 seconds
Precipitants		Hyperventilation, photic stimulation
EEG	Spikes and poly spike and waves, usually over one or both temporal regions	Generalized 3-Hz spike-and-wave complexes
Treatment	Carbamazepine, phenytoin	Ethosuximide, valproate

From Kaufman DM, Geyer HL, Milstein MJ: *Kaufman's clinical neurology for psychiatrists*, ed 8, Philadelphia, 2017, Elsevier.

SUGGESTED READING

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Acetaminophen Poisoning ALG PTG

BASIC INFORMATION

DEFINITION

Acetaminophen (APAP) poisoning is a disorder caused by excessive intake of APAP and is manifested by jaundice, nausea, vomiting, abdominal discomfort, and potential death from hepatic necrosis if not treated appropriately.

SYNONYM

Paracetamol poisoning

ICD-10CM CODES

T39.1	Poisoning by 4-aminophenol derivatives, accidental
X60	Intentional self-poisoning by 4-aminophenol derivatives

EPIDEMIOLOGY & DEMOGRAPHICS

- APAP is one of the most widely prescribed antipyretics and analgesics in the U.S. Potentially toxic ingestions, both intentional and unintentional, exceed 100,000 cases annually in the U.S.
- APAP toxicity is the number one cause of acute liver failure in the U.S.
- Death rate is approximately one in 1000 persons. Nearly 50% of exposures occur in children ≤6 yr.
- Hepatic necrosis is most likely to occur in people who (1) are chronically malnourished, (2) regularly abuse alcohol, (3) have chronic liver disease, and (4) use other potentially hepatotoxic medications.
- Combination opioid and acetaminophen medications are an important source of APAP toxicity.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The physical examination may vary depending on the amount of time since ingestion.
- Phase I (0 to 24 hr): Initial symptoms may be mild or absent and may consist of anorexia, diaphoresis, malaise, nausea, vomiting, lethargy, and a subclinical rise in transaminase levels.
- Phase II (24 to 72 hr): Right upper quadrant pain, vomiting, somnolence, tachycardia, jaundice, hypotension, and continued increase in transaminases.
- Phase III (72 to 96 hr): Hepatic necrosis with abdominal pain, jaundice, hepatic encephalopathy, coagulopathy, hypoglycemia, renal failure, fatality from multi-organ failure.
- Phase IV (4 days to 2 wk): Complete resolution of symptoms and resolution of organ failure.
- Table E1 summarizes the four phases/stages of acetaminophen poisoning.

ETIOLOGY

- The amount of APAP necessary for hepatic toxicity varies with the patient's body size and hepatic function. It is recommended that APAP intake should not exceed 3 to 4 g for adults and 90 mg/kg in children within a 24-hr period.
- A standardized nomogram is used to determine potential hepatic toxicity by knowing the APAP plasma level and the number of hours after ingestion. See the APAP ingestion algorithm (Fig. E1).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Liver disease from alcohol abuse or viral hepatitis
- Ingestion of other hepatotoxic substances
- Bacterial/viral gastroenteritis

WORKUP

Initial workup is aimed at confirming APAP overdose with plasma APAP level and assessment of hepatic damage. A careful history should elicit the time of APAP ingestion, amount, preparation (e.g., extended release), and possible coingestants (see "Laboratory Tests").

LABORATORY TESTS

- Initial laboratory evaluation should include an initial plasma APAP level with a second level drawn approximately 4 hr after the initial ingestion. Subsequent levels can be obtained every 2 to 4 hr until the levels stabilize or decline. Levels starting from 4 hr postingestion should be plotted on the Rumack-Matthew nomogram (see acetaminophen ingestion algorithm [Fig. E1] to calculate potential hepatic toxicity). The nomogram cannot be used with patients who present >24 hr after ingestion, took extended-release preparations, had chronic ingestions, or when the time of ingestion is unknown.
- Transaminases (aminotransferase [AST], alanine aminotransferase [ALT]), serum glucose, bilirubin level, lipase level, prothrombin time (INR), blood urea nitrogen, creatinine, EKG, and urinalysis should be initially obtained on all patients.
- Serum and urine toxicology screens for other potential toxic substances (e.g., salicylate level, ethanol level, urine drugs of abuse screening) is also recommended on admission. Screening for infectious hepatitis should also be considered.
- Urine for β-hCG should be obtained from all women of childbearing age.

TREATMENT

NONPHARMACOLOGIC THERAPY

Consultation with a Poison Control Center is recommended for patients who have ingested a large amount of APAP and/or other toxic substances. A single toxic dose of APAP usually exceeds 7 g or 150 mg/kg in adults.

ACUTE GENERAL Rx

- Hepatotoxicity is defined as any increase in ALT or aspartate AST >1000 IU/L, and hepatic failure manifests as hepatotoxicity with hepatic encephalopathy. For those who cannot be risk stratified using the nomogram, the American College of Emergency Physicians recommends that *N*-acetylcysteine be administered without delay to those >12 yr and >8 hr after ingestion at presentation. This would include anyone with an ingestion of APAP over many days with an APAP level <20 μg/ml (with or without ALT elevation) or anyone with undetectable APAP levels with an elevated ALT and a history of excessive APAP intake.
- Administer activated charcoal 1g/kg PO if the patient is seen within 1 hr of ingestion or the clinician suspects polysubstance ingestion that delays gastric emptying.
- Determine serum acetaminophen levels 4 hr after ingestion; if in the toxic range based on the Rumack-Matthew nomogram, start *N*-acetylcysteine (NAC) either IV (Acetadote) or PO (Mucomyst). Acetylcysteine IV loading dose is 150 mg/kg ×1 diluted in 200 ml D5W over 15 to 60 min. Maintenance dose is 50 mg/kg diluted in 500 ml D5W over 4 hr, followed by 100 mg/kg diluted in 1000 ml D5W over 16 hr. The dose does not require adjustment for renal or hepatic impairment or for dialysis. Total administration time is 21 hours.
- Oral administration is 140 mg/kg PO as a loading dose, followed after 4 hr by 70 mg/kg PO q4h for a total of 18 doses. *N*-acetylcysteine therapy should be started within 24 hr of APAP overdose. Total administration time is 72 hours.
- Advantages of IV administration include more reliable absorption, fewer doses, and shorter duration of treatment. Disadvantages include cost and lower hepatic concentrations from first-pass flow as compared to oral acetylcysteine.
- Monitor APAP level; use Rumack-Matthew nomogram to trend hepatic toxicity. Repeat AST/ALT and APAP levels after 12 to 14 hr of IV acetylcysteine infusion and continue infusion longer than 16 hr if transaminases are elevated, if APAP concentration is still measurable, or if coagulopathy exists (INR >1.5 to 2.0). Patients with severe, irreversible liver failure may need to continue NAC until liver transplantation is available.
- Provide adequate IV hydration (e.g., D_5½NS at 150 ml/hr).
- Patients on IV *N*-acetylcysteine with liver failure require frequent monitoring of vital signs, oxygen saturation by pulse oximetry, and frequent blood draws. Frequent reassessment for hypoglycemia and infection is also essential.
- If APAP level is nontoxic, *N*-acetylcysteine therapy may be discontinued.

DISPOSITION

All patients with confirmed APAP poisoning will require admission, usually to an intensive care unit. Most patients (90%) will recover fully without persistent hepatic abnormalities. Hepatic failure is particularly unusual in children <6 yr.

REFERRAL

Psychiatric referral is recommended after intentional ingestions.

RELATED CONTENT

Acetaminophen Overdose (Patient Information)

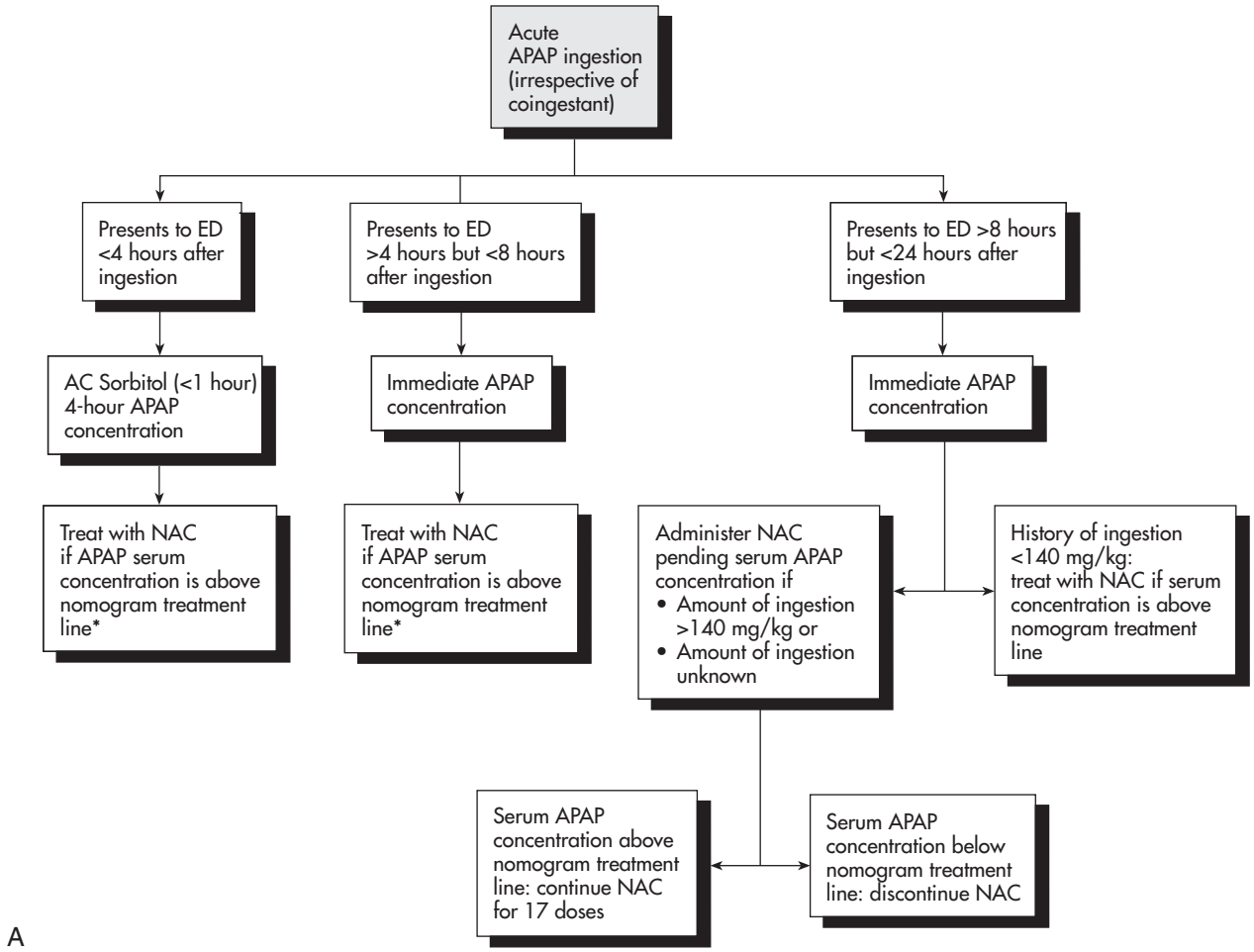
AUTHOR: **Rory Merritt, MD, MEHP**

Acetaminophen Poisoning

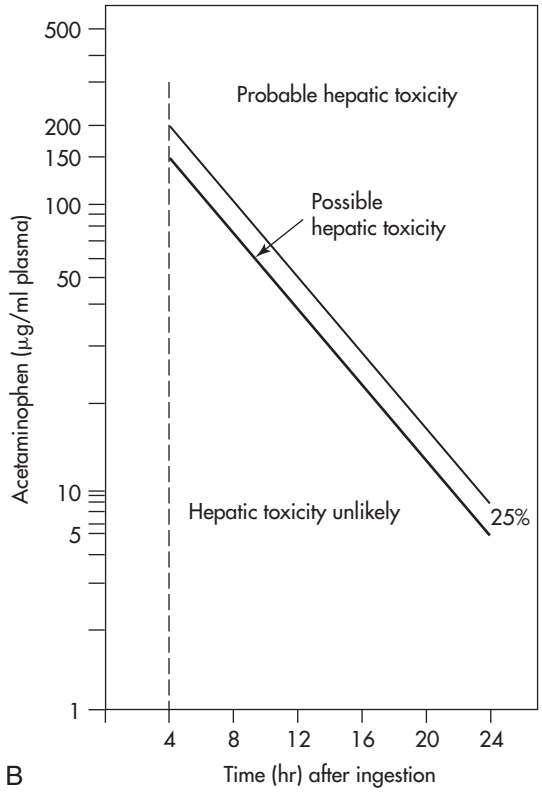
TABLE E1 Four Stages of Acetaminophen Poisoning

Stage 1 (0-24 hr)	Asymptomatic	Patients are initially asymptomatic, with normal vital signs and no physical findings. Laboratory results are normal. Nonspecific complaints of nausea, vomiting, and malaise may start to develop near the end of this stage.
Stage 2 (24-72 hr)	Onset of hepatotoxicity	Right upper quadrant abdominal pain may develop. Levels of AST, the most sensitive indicator of hepatotoxicity, and ALT begin to rise. Later, INR values may begin to rise and renal function to deteriorate.
Stage 3 (72-96 hr)	Maximal hepatotoxicity	The patient exhibits clinical and laboratory manifestations of hepatic necrosis: Varying degrees of hepatic encephalopathy, jaundice, renal failure, coagulation defects, and myocardial abnormalities. AST and ALT levels peak, the INR value rises, blood urea nitrogen and creatinine levels rise, and pH drops. Death may occur, typically 3-5 days after overdose. Death from fulminant hepatic failure may be characterized by cerebral edema, sepsis, multisystem organ failure, hemorrhage, and acute respiratory distress syndrome.
Stage 4 (4 days to 2 wk)	Recovery phase	Patients who survive stage 3 undergo complete regeneration of the liver. Laboratory abnormalities typically return to normal 5-7 days after overdose.

ALT, Alanine transaminase; *AST,* aspartate transaminase; *INR,* international normalized ratio.
From Adams J (ed), Barton E et al (associate eds): *Emergency medicine: clinical essentials,* ed 2, Philadelphia, 2013, Saunders.



A



B

FIG. E1 A, Treatment of acetaminophen ingestion. **B,** Rumack-Matthew nomogram for acetaminophen poisoning. *APAP,* Acetaminophen; *ED,* emergency department; *NAC, N*-acetylcysteine. (*See Fig. E1, *B.*) (**A,** from Marx J [ed]: *Rosen's emergency medicine,* ed 5, St Louis, 2002, Mosby. **B,** modified and updated from Rumack BH, Matthew H: *Pediatrics* 55:871, 1975. In Marx J [ed]: *Rosen's emergency medicine,* ed 6, St Louis, 2006, Mosby.)

BASIC INFORMATION

DEFINITION

Achalasia is a motility disorder of the esophagus classically characterized by incomplete relaxation of the lower esophageal sphincter (LES) and aperistalsis of the esophageal smooth muscle. The result is functional obstruction of the esophagus.

SYNONYMS

Achalasia and cardiospasm
Achalasia (of cardia)
Aperistalsis of esophagus
Megaesophagus
Esophageal achalasia
Esophageal cardiospasm

ICD-10CM CODE
K22.0 Achalasia of cardia

EPIDEMIOLOGY & DEMOGRAPHICS

- Annual incidence is approximately 0.5 to 1.0 in 100,000 persons.
- Prevalence is <10 per 100,000 persons.
- Although the onset of symptoms may occur at any age, incidence is typically bimodal, 20 to 40 yr, then after 60 yr, with greater incidence in the older group.
- Men and women are affected equally.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms:
- Dysphagia (most commonly with both solids and liquids)
- Difficulty belching
- Regurgitation
- Chest pain and/or heartburn
- Globus
- Frequent hiccups
- Vomiting of undigested food
- Symptoms of aspiration such as nocturnal cough; possible dyspnea and pneumonia
- Weight loss
- The Eckardt symptom score (assessing dysphagia, regurgitation, retrosternal pain, and weight loss), a fairly reliable and valid measure of achalasia severity, may be used to assess response to therapy

Physical findings:
- Focal lung examination abnormalities and wheezing are also possible.

ETIOLOGY

- Etiology is poorly understood.
- Loss of intrinsic inhibitory neurons in the myenteric plexus in the LES and smooth muscle portion of the esophagus as well as depletion of networks of interstitial cells of Cajal of the LES result in the loss of inhibitory neurotransmitters nitric oxide and vasoactive intestinal polypeptide and unopposed excitatory cholinergic activity, leading to incomplete relaxation of the LES and loss of esophageal peristalsis.
- Loss of myenteric nerve fibers is associated with lymphocytic and eosinophilic infiltrates, capillaritis, plexitis, venulitis, nerve hypertrophy, and fibrosis.
- This disorder may be caused by autoimmune degeneration of the esophageal myenteric plexus in association with several HLA class II DQ antigens. An eight amino-acid insertion in the cytoplasmic tail of HLA-DQβ1 has been identified as a strong achalasia risk factor. Antimyenteric plexus and other antineural autoantibodies have also been described. Patients with achalasia are more likely to have other autoimmune diseases.
- Abnormal immune reactions to neurotropic viruses, such as varicella zoster, measles, and particularly herpes simplex type 1, have been implicated. A host T-cell–mediated response may lead to neuronal injury; this has been suggested as the cause of types I and II achalasia (see "Imaging Studies" section).
- Achalasia is also seen in the rare autosomal recessive disorder, Allgrove syndrome (achalasia, alacrima, autonomic disturbance, and acetylcholine insensitivity), which has been linked to a gene mutation on chromosome 12q13. Neurons in this syndrome may be susceptible to oxidative injury.
- Recent studies suggest that type III achalasia (see "Imaging Studies" section) is associated with myenteric inflammation but not neuronal loss and that downregulation of nitric oxide synthase expression and increased cholinergic sensitivity are cytokine-mediated.
- A type III achalasia pattern has been described in chronic daily opiate users.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary achalasia:
  1. Idiopathic
- Secondary achalasia:
  1. Chagas disease
  2. Vagal injury or surgery, including fundoplication
  3. Achalasia-like esophageal dilation has been described after laparoscopic gastric banding
- Pseudoachalasia (diseases that may mimic achalasia):
  1. Esophageal cancer
  2. Infiltrating gastric cancer
  3. Oat cell and bronchogenic lung cancer
  4. Lymphoma
  5. Amyloidosis
  6. Paraneoplastic syndrome
- Angina
- Bulimia
- Anorexia nervosa
- Gastric bezoar
- Gastritis
- Peptic ulcer disease
- Postvagotomy dysmotility
- Esophageal disease (Table 1):
  1. Gastroesophageal reflux disease
  2. Sarcoidosis
  3. Amyloidosis
  4. Esophageal stricture
  5. Esophageal webs and rings
  6. Scleroderma
  7. Barrett esophagus
  8. Esophagitis
  9. Diffuse esophageal spasm

WORKUP

- Physical examination and laboratory analyses to rule out other causes (Fig. 1, Table 2) and assess complications
- Imaging studies, manometry, and endoscopy (may be supportive or complementary)

LABORATORY TESTS

- Assessment of nutritional status
- Complete blood count, ECG, stress test if diagnosis is in doubt
- Serologic assays for *Trypanosoma cruzi* (Chagas disease) in appropriate individuals

IMAGING STUDIES

Barium swallow with fluoroscopy (particularly a timed barium esophagogram) may demonstrate:
- Uncoordinated or absent esophageal contractions (loss of peristalsis)

TABLE 1 Esophageal Motor Disorders

	Achalasia	Scleroderma	Diffuse Esophageal Spasm
Symptoms	Dysphagia Regurgitation of nonacidic material	Gastroesophageal reflux disease Dysphagia	Substernal chest pain (angina-like) Dysphagia with pain
Radiographic appearance	Dilated, fluid-filled esophagus Distal *bird-beak* stricture	Aperistaltic esophagus Free reflux Peptic stricture	Simultaneous noncoordinated contractions
Manometric findings	High resting pressure	Low resting pressure	Normal pressure
Lower esophageal sphincter	Incomplete or abnormal relaxation with swallow		
Body	Low-amplitude, simultaneous contractions after swallowing	Low-amplitude peristaltic contractions or no peristalsis	Some peristalsis Diffuse and simultaneous nonperistaltic contractions, occasionally high amplitude

From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine*, ed 8, Philadelphia, 2010, Saunders.

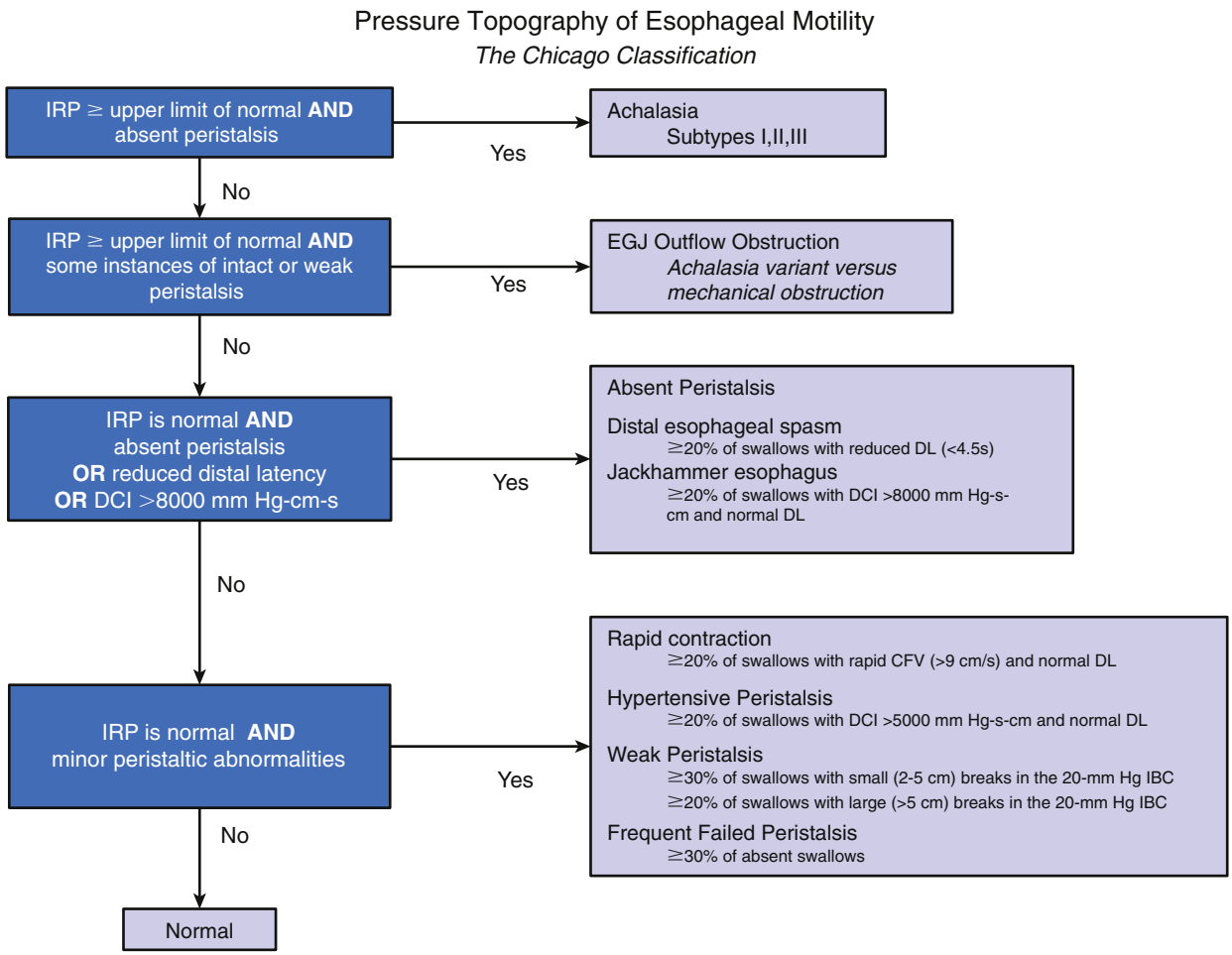


FIG. 1 Algorithm for applying the Chicago Classification of esophageal motor disorders. *CFV,* Contractile front velocity; *DCI,* distal contractile interval; *DL,* distal latency; *EGJ,* esophagogastric junction; *IBC,* isobar contour; *IRP,* integrated relaxation pressure (see Table 2 for more details). (From Feldman M et al: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

TABLE 2 Chicago Classification of Esophageal Motility Disorders

Diagnosis	Diagnostic Criteria
Achalasia	
Type I	100% failed peristalsis, mean IRP >10 mm Hg
Type II	No esophageal contraction and panesophageal pressurization with ≥20% of swallows; mean IRP >10 mm Hg
Type III	Premature contractions with ≥20% of swallows, mean IRP ≥17 mm Hg
EGJ outflow obstruction	Mean IRP ≥15 mm Hg; mix of normal, weak, rapid, hypertensive, failed peristalsis or panesophageal pressurization
Motility Disorders	(Patterns not observed in normal individuals)
Distal esophageal spasm	Mean IRP <17 mm Hg, ≥20% premature contractions
Hypercontractile esophagus (jackhammer esophagus)	At least one swallow DCI >8000 mm Hg·s·cm
Absent peristalsis	Mean IRP ≤10 mm Hg, 100% failed peristalsis
Peristaltic Abnormality	(Defined by exceeding statistical limits of normal)
Weak peristalsis	Mean IRP <15 mm Hg and ≥20% swallows with large breaks (≥5 cm) or ≥30% with small breaks (2-5 cm) in the 20-mm Hg isobaric contour Or DCI of 150-450 mm Hg·s·cm in ≥30% test swallows
Frequent failed peristalsis	>30%, but <100% of swallows with failed peristalsis
Rapid peristalsis	Rapid contraction with ≥20% of swallows, DL >4.5 s
Hypertensive peristalsis (nutcracker esophagus)	Mean DCI >5000 mm Hg·s·cm, but not meeting criteria for hypercontractile esophagus
Normal	Not achieving any of the above diagnostic criteria

DCI, Distal contractile interval; *DL,* distal latency; *EGJ,* esophagogastric junction; *IRP,* integrated relaxation pressure.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.

- An acutely tapered contrast column ("bird's beak"; Fig. E2)
- Dilation of the distal esophagus (smooth muscle portion)
- Esophageal air-fluid level with evidence of poor esophageal emptying
- Late-stage changes include tortuosity, angulation, dilated megaesophagus, retained food, and secretions

Manometry is considered the "gold standard" test to confirm the diagnosis.

- In classic achalasia (type I achalasia), conventional manometric abnormalities include low-amplitude disorganized contractions/aperistalsis, incomplete or absent LES relaxation (with residual pressure >10 mm Hg) after swallow, and high resting LES pressure.
- A subset of patients with "vigorous achalasia" may have high-amplitude, long-duration, simultaneous esophageal contractions. This term is now thought to be imprecise because of a newer classification of the disease.
- High-resolution manometry (HRM), or high-resolution esophageal pressure topography (HREPT), has defined subsets of patients with achalasia who may have different responses to medical or surgical therapies and prognoses. Unlike type I achalasia, type II achalasia shows panesophageal pressurization to greater than 30 mm Hg with ≥20% of test swallows, and type III achalasia shows spastic, lumen-obliterating contractions of the distal esophagus with ≥20% of swallows. This technique uses the integrated relaxation pressure (IRP) >15 mm Hg to define better the failure of esophagogastric junction relaxation. HRM also utilizes the distal contraction integral (DCI) to define hypercontractile vs. weak swallows vs. failed peristalsis. The distal latency (DL) defines premature contractions, seen with diffuse esophageal spasm and type III achalasia.
- HREPT has also defined an achalasia variant described as esophagogastric junction outflow obstruction, where the IRP is >15 mm Hg, but peristalsis is present. Some are associated with secondary causes; a small percentage may progress to achalasia; and, in many, the natural history is unclear and response to therapy is variable.
- Direct visualization by endoscopy, including careful visualization of the esophagogastric junction and cardia, should be performed to exclude other causes of dysphagia, including "functional esophagogastric junction obstruction," strictures, secondary causes of achalasia (including infiltrating cancers), and pseudoachalasia.
- Functional luminal imaging probe (FLIP) technology is a new technique that can measure compliance and distensibility across the esophagogastric junction and may demonstrate both impaired LES relaxation and response to achalasia therapy.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- The goals of therapy are to decrease LES pressure to relieve the functional obstruction, relieve symptoms, and prevent progression to a dilated esophagus, sometimes referred to as a megaesophagus. Treatment does not improve esophageal peristalsis. Achalasia is treatable but incurable.
- Pneumatic dilation (PD) to disrupt the LES muscle fibers may benefit 65% to 90% of patients. Multiple sessions may be required, and most protocols use a graded dilation approach, starting with a 30-mm balloon, and repeating if required with a 35-mm or 40-mm balloon. Some studies suggest this may be more effective in females, older patients, and particularly HRM type II patients. Esophageal rupture or perforation is a rare complication (2% to 4%) that may be managed conservatively in some stable patients with a small perforation.
- Surgical: Laparoscopic, or less commonly, open Heller esophagomyotomy (HM) is effective (90%). Approximately 35% of patients undergoing surgery will develop reflux disease. As a result, some surgeons will perform a "loose" or partial antireflux repair (fundoplication) as part of the surgical procedure. Some studies suggest this may be more effective in men and younger patients. An observational study has suggested that those who have had prior endoscopic treatment before myotomy may not do as well as those who have a primary myotomy.
- A large European study suggested that in experienced hands, patients may expect similar medium-term outcomes from myotomy and balloon dilation. A meta-analysis suggests better long-term durability of myotomy. Balloon dilation may be the more cost-effective treatment. A small percentage (20% to 30%) of patients undergoing either therapy may require re-treatment within 5 to 7 yr.
- Endoscopic submucosal myotomy (per-oral endoscopic myotomy [POEM]) has a high success rate comparable to laparoscopic HM (particularly in HRM type III patients in whom a longer myotomy, tailored to the length of the diseased segment, improves outcome), few adverse events (which can include pneumomediastinum, pneumothorax, pneumoperitoneum, pleural effusion, pneumonia, and bleeding), and exceedingly rare mortality. Because no antireflux procedure is performed, there is a modest risk (up to 53%) of developing pathologic reflux. It should only be performed at high-volume centers. A randomized multicenter study showed a higher treatment success rate for POEM at 2 years when compared with pneumatic dilation.
- FLIP and timed barium esophagogram may help determine response to therapy.
- Esophagectomy has been performed in patients with end-stage achalasia with a dilated, often sigmoid-shaped or megaesophagus, who have failed myotomy or pneumatic dilation.

ACUTE GENERAL Rx

- Medications may be useful for short-term symptom relief and in patients with refractory chest pain. They should only be considered in patients unable to receive, or who are scheduled for, more definitive procedures. LES pressure may be lowered by up to 50% through sublingual use of long-acting nitrates (e.g., isosorbide dinitrate 5 to 20 mg) or calcium channel blockers (e.g., nifedipine 10 to 30 mg). Side effects are common and duration of relief tends to be short. Sildenafil was shown to be effective in a few small, short-term studies, but it is generally not recommended.
- Botulinum toxin injection will benefit up to 85% of patients by inhibiting acetylcholine release from cholinergic nerve endings, blocking the unopposed cholinergic stimulation of the LES, but having no impact on the myogenic tone. Up to half of these patients will require repeat injections by 6 months. A few studies have suggested that repeated injections may have diminished efficacy and can lead to fibrosis, which may complicate subsequent attempts at surgical therapy.
- Many patients will require proton pump inhibitor therapy for gastroesophageal reflux after effective disruption of the LES.

PEARLS & CONSIDERATIONS

COMMENTS

- Medication has a limited role in treatment.
- Botulinum toxin is transiently effective in improving symptoms.
- Pneumatic dilation, surgical myotomy, and POEM provide more durable long-term responses and are the treatment of choice for most patients. Botulinum toxin should be considered primarily in patients too elderly or ill to be considered for these other therapies.
- Patients with achalasia may be at long-term risk of squamous cell carcinoma of the esophagus and non–reflux-associated esophagitis. Treated patients may be at long-term risk for reflux esophagitis, Barrett esophagus, and adenocarcinoma. Endoscopic surveillance is not routinely recommended in these patients.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Achalasia (Patient Information)
Dysphagia (Related Key Topic)

AUTHOR: **Harlan G. Rich, MD, FACP, AGAF**

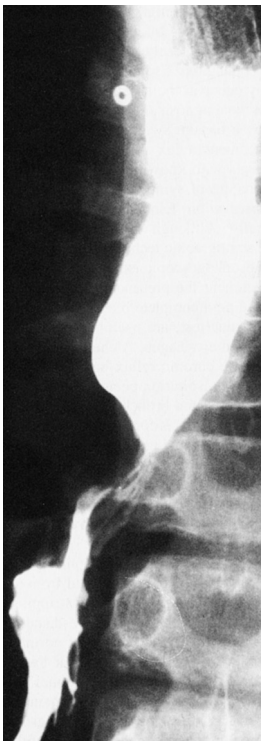


FIG. E2 Classic appearance of achalasia of the esophagus. The dilated esophagus ends in a narrow segment. (From Hoekelman R [ed]: *Primary pediatric care*, ed 3, St Louis, 1997, Mosby.)

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Achilles Tendon Rupture (PTG)

BASIC INFORMATION

DEFINITION

Achilles tendon rupture is a disruption of the continuity of the Achilles tendon that either occurs as a result of forced dorsiflexion of the foot in plantar flexion or forced plantar flexion against resistance.

ICD-10CM CODES

S86.0	Unspecified injury of Achilles tendon
S86.012	Achilles tendon rupture left
S86.011	Achilles tendon rupture right
M66.871	Non traumatic Achilles tendon rupture right
M66.872	Non traumatic Achilles tendon rupture left

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: In the general population, Achilles tendon ruptures occur in 18 per 100,000 individuals per year and are the most common large tendon ruptures, accounting for 20% to 35% of all large tendon injuries in the human body. They can often be missed and initially diagnosed as an ankle sprain.
PEAK INCIDENCE: 30- to 40-year-old males
PREDOMINANT AGE: 30- to 55-years-old
RISK FACTORS: General risk factors include recreational athletes, stop-and-go sports (e.g., basketball, tennis, and soccer), preexisting Achilles tendinopathy, increase in duration or intensity of running, advanced age, male gender, and poor running mechanics. Fluoroquinolone antibiotics have been associated with Achilles tendon ruptures, with an incidence of 12 per 100,000. This is more likely to occur in first-time users of fluoroquinolones and usually occurs within the first 90 days of therapy. Additionally, corticosteroid use has been implicated in Achilles tendon rupture.

CLINICAL PRESENTATION

A classic presentation for acute Achilles tendon rupture is a middle-aged male who participates in strenuous activities involving sudden pivoting on a foot or rapid deceleration as in recreational sports. A popping sensation of the tendon may be described by some patients, followed by an acute onset of severe pain in the calf and lower leg. Patients who also attempt new strenuous activities without proper training and stretching or who typically lead a sedentary lifestyle are more likely to experience Achilles tendinopathy, including ruptures. It is important to note that pain is not always an initial presenting symptom.

PHYSICAL FINDINGS

A palpable defect in the posterior distal third of the Achilles tendon may be appreciated with palpation. Depending on the severity of the rupture, pain, ecchymosis and diffuse edema may be noted. The patient may present with an antalgic gait and the inability to perform a single heel raise on the injured limb secondary to weakened plantar flexion power. Additionally, the patient may not be able to plantarflex against resistance. Having them lie prone with their legs off the examination table may show their injured side to be more dorsiflexed compared to the contralateral side and squeezing the affected calf will not produce plantarflexion of the foot.

ETIOLOGY/MECHANISM OF INJURY

Indirect trauma is most often associated with Achilles tendon ruptures, which typically fall under three categories: mechanical, vascular, and poor tissue quality.

- Mechanical: Involves variations of a rapid loading process on an already tensed tendon such as a sudden dorsiflexion of the ankle with the knee extended while an eccentric load is applied.
- Vascular: Located 2 to 6 cm proximal to the Achilles tendon insertion is a known area of hypo vascularity.
- Poor tissue quality: Tendonitis, which is inflammation that occurs within the tendon after an acute injury, and tendinosis, which is a degeneration process from repetitive tears related to chronic injuries, are known to weaken the tendon before it is ruptured. This often occurs in the form of repetitive microtrauma from improper training techniques.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Achilles tendinopathy (tendinosis vs. tendonitis)
- Retrocalcaneal bursitis
- Ankle sprain
- Calcaneal avulsion fracture
- Partial rupture of gastrocnemius
- Plantaris rupture
- Os trigonum syndrome
- Calcaneal apophysitis

WORKUP

A thorough history and physical examination, along with a high clinical suspicion, is key to distinguishing Achilles tendon ruptures from other Achilles tendinopathies. The clinical history in most presentations is very specific, and the physical examination is usually diagnostic. The following is a list of specific clinical tests and imaging modalities.

- **Thompson test (Fig. E1):** Also known as the "calf squeeze test," it is an accurate means of detecting Achilles tendon ruptures. The patient is placed in a prone position with the knee flexed. While squeezing the gastrocnemius, the clinician evaluates for the presence or absence of ankle plantar flexion. If ankle plantar flexion is absent, the test is said to be positive and indicative of Achilles tendon rupture.
- **Matles test (knee flexion test):** The test is an additional physical examination finding utilized to assess Achilles tendon ruptures. The patient is placed in the prone position with the knees flexed at 90 degrees. If the injured foot falls in an increased dorsiflexed position instead of a resting plantar flexed position when compared to the contralateral limb, the test of the injured limb is positive for Achilles tendon rupture.

IMAGING STUDIES

- Ultrasound imaging may be used to assess Achilles tendinopathy and is considered by some the first-line imaging modality. Ultrasound provides clinicians with a practical means of evaluating Achilles tendinopathy and ruptures at the bedside.
- MRI (Fig. E2) is often utilized to further evaluate Achilles tendinopathy, especially ruptures. Discontinuity of the Achilles tendon can be seen on T2-weighted images, where the signal in the tendon is increased at the area of rupture and the tendon diameter is increased. MRI provides greater anatomic detail as well as greater accuracy in detecting partial Achilles tendon tears. MRI has proved to be superior to ultrasound in defining ruptures histologically.

TREATMENT

Initial treatment should consist of the RICE protocol (**r**est, **i**ce, **c**ompression to reduce swelling, and **e**levation). Adequate analgesics for at-home use can include acetaminophen and/or nonsteroidal antiinflammatory drugs. The patient should also be placed into a posterior slab splint with the foot in resting equinus (held at its natural plantarflexed position).

The typical course of immobilization of the injured limb ranges from a minimum of 8 to 12 weeks. Over the past few years there has been a trend in nonoperative management of Achilles tendon ruptures that include accelerated protocol to rehabilitation. These accelerated protocols have been shown to improve outcomes of nonoperative Achilles tendon management. These protocols have the patient non–weight bearing in a posterior splint or short leg cast in equinus with crutches for 2 weeks. A controlled ankle motion walker with special sequential heel wedges then follows this for the next 4 weeks of non–weight bearing with crutches. After 4 to 6 weeks the patient may return to regular shoe gear, with a heel wedge modification for an additional 2 months. During this period, it is recommended that patients start resistance exercises, proprioception and gait retraining, and sport retraining.

SURGICAL TREATMENT

If surgical intervention is warranted, it should be done within 4 weeks of the initial injury, although within 7 to 14 days of injury is ideal. Proper timing of surgical repair is imperative to postsurgical recovery. The inflammatory phase of wound healing occurs within the first 7 to 14 days following an acute Achilles tendon rupture. During this phase, vascularity to the injured tendon increases, aiding in postoperative healing.

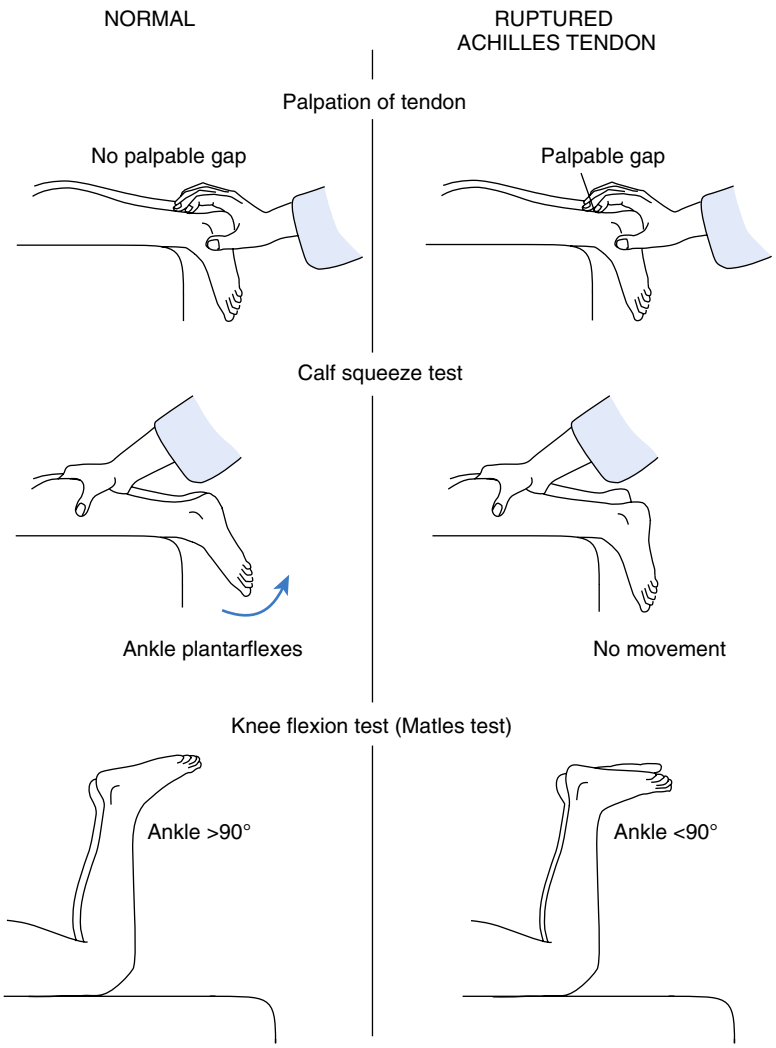

FIG. E1 Tests for rupture of the Achilles tendon. All tests are performed with the patient lying prone with his or her feet extending over the end of the examination table. [1] The patient's asymptomatic side serves as a control (for each test, a patient with an intact Achilles tendon is depicted on the *left*, compared with a patient with a ruptured Achilles tendon on the *right*). (1) Palpable gap in tendon (*top*): The clinician gently palpates the course of the tendon, searching for gaps, which if present usually lie between 2 and 6 cm from the calcaneus.[2] (2) Calf squeeze test (Thompson test, *middle*): The clinician gently squeezes the patient's calf in its middle third and just below the place of widest girth, observing the ankle for movement. If the tendon is intact, the ankle should plantarflex. Absence of movement or minimal movement is a positive response. The normal plantar flexion of the ankle results from compression of the soleus muscle, which bows the Achilles tendon posteriorly.[3] (3) Knee flexion test (Matles test, *bottom*): The clinician observes the position of the patient's ankles as the patient flexes both knees to 90 degrees (the knees may be flexed individually or simultaneously). The ankle remains slightly plantar flexed if the tendon is intact; slight dorsiflexion or a neutral position of the ankle is the positive response. Thompson described the calf squeeze test in 1962,[2] pointing out that the test could be performed with the patient prone or kneeling on a chair. Simmonds described the identical test in 1957.[4] Matles described the knee flexion test in 1975.[5] (From McGee S. *Evidence-based physical diagnosis*, ed 4, Philadelphia, 2017, Elsevier. [1] Maffulli N: The clinical diagnosis of subcutaneous tear of the Achilles tendon: a prospective study in 174 patients, *Am J Sports Med* 26[2]:266-270, 1998; [2] Thompson TC, Doherty JH: Spontaneous rupture of tendon of Achilles: a new clinical diagnostic test, *J Trauma* 2:126-129, 1962; [3] Scott BW, Chalabi AA: How the Simmonds–Thompson test works, *J Bone Joint Surg Br* 74B[2]:314-315, 1992; [4] Simmonds FA: The diagnosis of the ruptured Achilles tendon, *Practitioner* 179[1069]: 56-58, 1957; [5] Matles AL: Rupture of the tendon Achilles, *Bull Hosp Jt Dis* 36[1]:48-51, 1975.)

The primary goal of surgical treatment of Achilles tendon rupture is to reestablish appropriate tendon length and ankle plantar flexion. This is usually achieved when there is an end-to-end apposition of the damaged Achilles tendon. Several surgical techniques exist to repair the ruptured Achilles tendon, which include percutaneous repair and open operative techniques. Percutaneous repair has some advantages, including decreased operative times and decreased postoperative deep infections. However, it comes with the risk of increased sural nerve damage. After surgery, 10 to 12 weeks of immobilization followed by rehabilitation is recommended.

REFERRAL

Acute and/or complete Achilles tendon ruptures warrant surgical evaluation. Acute complete Achilles tendon ruptures are more likely to have better postoperative outcomes if addressed within 14 days of initial injury. Orthopedic surgery consultation should be obtained for symptomatic acute or chronic Achilles tendinopathy or ruptures.

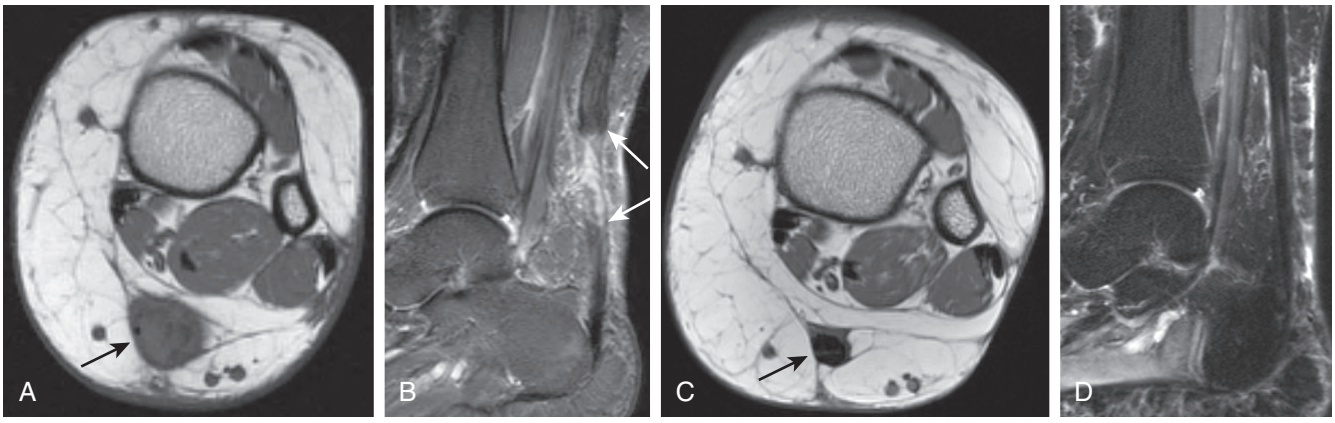

FIG. E2 Complete Achilles tendon rupture managed nonoperatively with 6 weeks of ankle casting in plantar flexion. A, Transverse T1-weighted magnetic resonance image *(MRI).* Shown is severe Achilles tendinopathy (*arrow*). **B,** Sagittal short tau inversion recovery *(STIR)* MRI reveals tendon fiber discontinuity with fluid-filled gap (*arrows*). Transverse T1-weighted **(C)** and sagittal STIR **(D)** MRIs obtained in follow-up 18 months after casting show thinning and attenuation of the tendon but reestablished tendon fiber continuity (*arrow* in **C**).

PEARLS & CONSIDERATIONS

- Patients who experience Achilles tendon ruptures may present with or without pain and may still maintain their ability to ambulate or flex their ankles. If pain is present, it usually occurs 2 to 6 cm proximal to the Achilles tendon insertion on the calcaneus.
- When evaluating Achilles tendinopathy, palpate the course of the Achilles tendon with particular attention to any edema, ecchymosis, or palpable defect or discontinuity of the tendon.
- A positive Thompson test is an accurate means for assessing Achilles tendon ruptures.
- Acute Achilles tendon ruptures should be treated within 14 days. Surgical intervention has been shown to decrease re-rupture rates when compared to nonsurgical treatment options but have higher associated complication rates.
- Although autologous platelet-rich plasma (PRP) is commonly used, trials[1] have shown that it is no better than placebo for acute Achilles tendon rupture.

[1]Keene DJ et al: Platelet rich plasma injection for acute Achilles tendon rupture: PATH-2 randomised, placebo controlled, superiority trial, *BMJ* l6132, Nov 20, 2019.

PREVENTION

- Previous tendinopathy or previous Achilles tendon ruptures are known risk factors and are associated with up to 10% of re-rupture rates.
- Physical therapy as well as physical rehabilitation protocol should be maintained following both operative and nonoperative therapies. Eccentric and concentric exercise should be continued on a regular basis following Achilles tendon ruptures and particularly before engaging in any vigorous exercise.
- The patient should reduce his or her training intensity during fluoroquinolone use and anabolic steroid use.

RELATED CONTENT

Achilles Tendon Rupture (Patient Information)

AUTHORS: **Christopher McDonald, MD,** and **Brad Blankenhorn, MD**

SUGGESTED READINGS

Dakin SG et al: Chronic inflammation is a feature of Achilles tendinopathy and rupture, *Br J Sports Med* 52(6):359-367, 2017.

Deng S et al: Surgical treatment versus conservative management for acute Achilles tendon rupture: a systematic review and meta-analysis of randomized controlled trials, *J Foot Ankle Surg* 56:1236-1243, 2017.

Kadakia A et al: Acute Achilles tendon ruptures: an update on treatment, *J Am Acad Orthop Surg* 25(1):23-31, 2017.

Lantto I: A prospective randomized trial comparing surgical and nonsurgical treatments of acute Achilles tendon ruptures, *Am J Sports Med* 44:2406-2414, 2016.

Lim CS et al: Functional outcome of acute Achilles tendon rupture with and without operative treatment using identical functional bracing protocol, *Foot and Ankle Int* 1:1-6, 2017.

Magnan B et al: The pathogenesis of Achilles tendinopathy: a systematic review, *Foot Ankle Surg* 20:154-159, 2014.

Willits K et al: Operative versus nonoperative treatment of acute Achilles tendon ruptures: a multicenter randomized trial using accelerated functional rehabilitation, *J Bone Surg Am* 92:2767-2775, 2010.

BASIC INFORMATION

DEFINITION

Acne vulgaris is a chronic disorder of the pilosebaceous apparatus caused by abnormal desquamation of follicular epithelium leading to obstruction of the pilosebaceous canal, resulting in inflammation and subsequent formation of papules, pustules, nodules, comedones, and scarring. Based on their appearance, the acne lesions can be divided into inflammatory (presence of papules, pustules, and nodules) or noninflammatory (open and closed comedones) For inflammatory acne, lesions can be classified as papulopustular, nodular, or both. The American Academy of Dermatology classification scheme for acne denotes the following three levels:

1. Mild acne: Characterized by the presence of comedones (Figs. E1 and E2) (noninflammatory lesions), few papules and pustules (generally <10), but no nodules.
2. Moderate acne: Presence of several to many papules and pustules (10 to 40) along with comedones (10 to 40). The presence of >40 papules and pustules along with larger, deeper nodular inflamed lesions (Figs. E3 and E4) (up to five) denotes moderately severe acne.
3. Severe acne: Presence of numerous or extensive papules and pustules as well as many nodular lesions (Fig. E5).

SYNONYM

Acne

ICD-10CM CODES

L70.0	Acne vulgaris
L70.1	Acne conglobata
L70.2	Acne varioliformis
L70.3	Acne tropica
L70.4	Infantile acne
L70.5	Acne excoriee des jeunes filles
L70.8	Other acne
L70.9	Acne, unspecified
L73.0	Acne keloid

EPIDEMIOLOGY & DEMOGRAPHICS

- Acne is the most common skin disease in the U.S.
- It is most common in teenagers, with 85% of all teenagers being affected to some degree.
- Highest incidence between ages of 15 and 18 yr in both genders.
- Involution of the disease usually occurs before age 25 yr, but 26% of women and 12% of men will continue to have clinical acne until the mid-40s.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Open comedones (blackheads), closed comedones (whiteheads)
- Greasiness (oily skin)
- Presence of scars from prior acne cysts
- Various stages of development and severity may be present concomitantly
- Common distribution of acne: face, back, and upper chest
- Inflammatory papules, pustules, and ectatic pores

ETIOLOGY

- Acne vulgaris is exclusively a follicular disease, with the principal abnormality being comedone formation.
- Overactivity of the sebaceous glands and blockage in the ducts. The obstruction leads to the formation of comedones, which can become inflamed because of overgrowth of *Propionibacterium acnes.*
- Exacerbated by environmental factors (hot, humid, tropical climate), medications (e.g., iodine in cough mixtures, hair greases), industrial exposure to halogenated hydrocarbons.
- Mechanical or frictional forces can aggravate existing acne (e.g., excessive washing by some patients to help rid them of their blackheads or oiliness).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gram-negative folliculitis
- Staphylococcal pyoderma
- Acne rosacea
- Drug eruption
- Sebaceous hyperplasia
- Angiofibromas, basal cell carcinomas, osteoma cutis
- Occupational exposures to oils or grease
- Steroid acne
- Hidradenitis suppurativa
- Perioral dermatitis
- Pseudofolliculitis barbae
- Miliaria
- Seborrheic dermatitis

WORKUP

History and physical examination:

- Inquire about previous treatment
- Careful drug history (including all OTC products)
- Family history, history of cyclic menstrual flares
- History of use of cosmetics and cleansers
- Oral contraceptive use
- Use of medications that may worsen acne such as corticosteroids, anabolic steroids, lithium, neuroleptics, cyclosporine
- Consider the possibility of hyperandrogenic state in all women (hirsutism, irregular menses, androgenic alopecia) or children (seborrhea, acanthosis nigricans, onset of acne between ages 1 and 7 yr and no obvious external factors)

LABORATORY TESTS

- Laboratory evaluation is generally not helpful. Patients who are candidates for therapy with isotretinoin should have baseline liver enzymes, cholesterol, and triglycerides checked because this medication may result in elevation of lipids and liver enzymes.
- A negative serum pregnancy test or two negative urine pregnancy tests should also be obtained in females 1 wk before initiation of isotretinoin; it is also imperative to maintain effective contraception during and 1 mo after therapy with isotretinoin ends because of its teratogenic effects. Pregnancy status should be rechecked at monthly visits.
- If hyperandrogenism is suspected in female patients, levels of dehydroepiandrosterone sulfate (DHEAS), testosterone (total and free), and androstenedione should be measured. For women with regular menstrual cycles, serum androgen measurements generally are not necessary.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Blue light (ClearLight therapy system) can be used for treatment of moderate inflammatory acne vulgaris. Light in the violet/blue range can cause bacterial death by a photoreaction in which porphyrins react with oxygen to generate reactive oxygen species, which damage the cell membranes of *P. acnes.* Treatment usually consists of 15-min exposures twice weekly for 4 wk. Phototherapy may be effective for short-term treatment of acne, but long-term efficacy and how it compares with conventional acne therapy is unclear.
- Diet: In obese patients, dietary counseling is recommended. A high-glycemic diet may worsen acne, although the strength of its influence is controversial.

ACUTE GENERAL Rx

Treatment generally varies with the type of lesions (comedones, papules, pustules, cystic lesions) and the severity of acne. Table 1 summarizes an acne treatment algorithm. First-line treatment for mild acne vulgaris includes benzoyl peroxide, a topical retinoid, or a combination of topical medications, including topical antibiotics. Use of topical treatments for 6 to 8 weeks is required to judge their efficacy. Table E2 describes prescription topical therapies for acne.

- Comedones (noninflammatory acne) can be treated with retinoids or retinoid analogs. Topical retinoids are comedolytic and work by normalizing follicular keratinization. Commonly available agents are Adapalene (Differin, 0.1% gel or cream, applied once or twice daily), tazarotene (Tazorac 0.1% cream or gel applied daily), tretinoin (Retin-A 0.1% cream or 0.025 gel applied once daily), tretinoin microsphere (Retin-A Micro, 0.1% gel, applied at bedtime). Tretinoin is inactivated by ultraviolet light and oxidized by benzoyl peroxide; therefore it should only be applied at night and not used concomitantly with benzoyl peroxide.
- Tretinoin is pregnancy category C and tazarotene is pregnancy category X. Salicylic acid preparations (e.g., Neutrogena 2% wash) have keratolytic and antiinflammatory properties and are also useful in the treatment of comedones. Large, open comedones (blackheads) should be expressed.
- Patients should be reevaluated after 4 to 6 wk. Benzoyl peroxide gel (2.5% or 5%) may be added if the comedones become inflamed or form pustules. The most common adverse effects are dryness, erythema, and peeling. Topical antibiotics (erythromycin, clindamycin lotions or pads) can also be used in patients with significant inflammation. They reduce *P. acnes* in the pilosebaceous follicle and have

TABLE 1 Acne Treatment Algorithm

Therapy	Severity (Lesion Type)				
	Mild (Comedonal)	**Mild (Inflammatory/ Mixed)**	**Moderate (Inflammatory/Mixed)**	**Severe (Inflammatory/ Mixed)**	**Severe (Nodular/ Scarring)**
Initial therapy options[*,†]	Topical retinoid BP Salicylic acid cleanser	BP/retinoid combo BP/antibiotic combo Antibiotic/retinoid combo + BP	BP/retinoid combo BP/antibiotic combo ± topical retinoid Antibiotic/retinoid combo + BP ± oral antibiotic	BP/retinoid combo + oral antibiotic BP/antibiotic combo + topical retinoid + oral antibiotic Antibiotic/retinoid combo + BP + oral antibiotic	Isotretinoin
Alternative therapy options[*,†,‡]	Add BP or retinoid if not already prescribed BP/antibiotic combo BP/retinoid combo Antibiotic/retinoid combo	Substitute another combo product Add missing component (i.e., topical retinoid, BP, topical antibiotic) Change type, strength, or formulation of topical retinoid	Substitute another combo product Add missing component (i.e., topical retinoid, BP, topical antibiotic, oral antibiotic) Change type, strength, or formulation of topical retinoid Consider hormonal therapy for females Consider oral isotretinoin	Consider changing oral antibiotic Consider isotretinoin Consider hormonal therapy for females	Consider hormonal therapy for females
Maintenance therapy	Topical retinoid or BP/retinoid combo	Topical retinoid or BP/ retinoid combo	Topical retinoid or BP/retinoid combo	Topical retinoid or BP/retinoid combo	Topical retinoid or BP/ retinoid combo

BP, Benzoyl peroxide.
*If combination products not available to patient, consider substitution of individual components as separate prescriptions.
†Topical dapsone may be considered in place of topical antibiotic.
‡If needed as determined by physician assessment and patient satisfaction.
Modified from Zaenglein AL, Thiboutot DM: Expert committee recommendations for acne management, *Pediatrics* 118(3):1188-99, 2006; Thiboutot D et al: New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne Group, *J Am Acad Dermatol* 60:S1-50, 2009; Eichenfield LF et al: Evidence-based recommendations for the diagnosis and treatment of pediatric acne, *Pediatrics* 131(3):S163-86, 2013; Thiboutot DM, Gollnick HP: Treatment considerations for inflammatory acne: clinical evidence for adapalene 0.1% in combination therapies, *J Drugs Dermatol* 5(8):785-94, 2006; Gollnick H et al: Management of acne: a report from a Global Alliance to Improve Outcomes in Acne, *J Am Acad Dermatol* 49(Suppl. 1):S1-37, 2003.

some antiinflammatory effects. The combination of 5% benzoyl peroxide and 3% erythromycin (Benzamycin) or 1% clindamycin with 5% benzoyl peroxide (BenzaClin) is highly effective in patients who have a mixture of comedonal and inflammatory acne lesions.

- Fixed-dose combinations of clindamycin phosphate 1.2% and tretinoin 0.025% are available (Veltin gel, Ziana) and are more effective than either product used alone; however, they are much more expensive than the individual generic components.
- Pustular acne can be treated with tretinoin and benzoyl peroxide gel applied on alternate evenings; drying agents (sulfacetamide-sulfa lotions [Novacet, Sulfacet]) are also effective when used in combination with benzoyl peroxide; oral antibiotics (doxycycline 100 mg qd or erythromycin 1 g qd given in 2 to 3 divided doses) are effective in patients with moderate to severe pustular acne. Patients not responding well to these antibiotics can be switched to minocycline 50 to 100 mg bid. Table E3 summarizes oral antibiotics for acne vulgaris.
- Patients with nodular cystic acne and those with moderate to severe inflammatory acne unresponsive to topical drugs can be treated with systemic agents: antibiotics (erythromycin, tetracycline, doxycycline, minocycline), isotretinoin (available on a restricted basis), or oral contraceptives. Periodic intralesional triamcinolone (Kenalog) injections by a dermatologist are also effective. The possibility of endocrinopathy should be considered in patients responding poorly to therapy.
- Isotretinoin is the most effective drug available for treatment of severe nodulocystic acne. It is indicated for acne resistant to antibiotic therapy and severe acne. It inhibits *P. acne's* colonization by reducing sebum production and has antiinflammatory and keratolytic effects. It is available only on a restricted basis. Dosage is 0.5 to 1 mg/kg/day in 2 divided doses (maximum of 2 mg/kg/day); duration of therapy is generally 20 wk for a cumulative dose ≥120 mg/kg for severe cystic acne. Before using this medication patients should undergo baseline laboratory evaluation (see "Laboratory Tests"). This drug is absolutely contraindicated during pregnancy because of its teratogenicity. It should be used with caution in patients with history of depression. Physicians, distributors, pharmacies, and patients must register in the iPLEDGE program (www.ipledgeprogram.com) before using isotretinoin.
- Azelaic acid is a bacteriostatic dicarboxylic acid used to normalize keratinization and reduce inflammation. It can be used in pregnant women.
- Oral contraceptives reduce androgen levels and therefore sebum production. They represent a useful adjunctive therapy for all types of acne in women and adolescent girls. Commonly used agents are norgestimate/ethinyl estradiol (Ortho Tri-Cyclen) and drospirenone/ethinyl estradiol (Yasmin).

REFERRAL

Referral for intralesional injection and dermabrasion should be considered in patients with severe acne unresponsive to conventional therapy. Table E4 summarizes alternative treatments for acne vulgaris.

PEARLS & CONSIDERATIONS

- Gram-negative folliculitis should be suspected if inflammatory acne worsens after several months of oral antibiotic therapy.
- Acne may worsen during the first 3 to 4 wk of retinoid therapy before improving.

COMMENTS

Indications for systemic therapy of acne are:

- Painful deep papules or nodules
- Extensive lesions
- Active acne with severe scarring or hyperpigmentation
- Patient's morale

Patients should be educated that in most cases acne can be controlled but not cured and that at least 4 to 6 wk of initial therapy should be required before significant improvement is noted.

- The negative psychological effect of acne may be severe and long-lasting.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Acne (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

TABLE E2 Prescription Topical Therapies for Acne Vulgaris

Drug	Brand*	Formulation
Antibiotics		
Clindamycin	Cleocin T	1% solution, gel, pledgets, lotion
	ClindaMax	1% lotion
	Clindets	1% pledgets
	Clindagel	1% gel
	Evoclin	1% foam
Clindamycin/BP†	BenzaClin	1% (5% BP) gel
	Duac	1% (5% BP) gel
	Acanya	1.2% (2.5% BP) gel
	Onexton	1.2% (3.75% BP) gel
Dapsone	Aczone	5% gel
Erythromycin	Emgel, Erygel	2% gel
	Eryderm, Erymax, T-Stat	2% solution
	Staticin	1.5% solution
	Akne-Mycin	2% ointment
	Theramycin Z	2% solution + ZA
Erythromycin/BP†	Benzamycin	3% (5% BP) gel, pak
Sulfacetamide	Klaron	10% lotion
	Plexion	10% (5% sulfur) cloths, wash
	Clenia	10% (5% sulfur) cream, wash
	Rosula	10% (4% sulfur) wash
Azelaic acid	Azelex	20% cream
Retinoids		
Adapalene	Differin	0.1% cream, gel, lotion
		0.3% gel
Adapalene/BP†	Epiduo	0.1% (2.5% BP) gel
Tazarotene	Tazorac	0.05, 0.1% cream
		0.05, 0.1% gel
	Fabior	0.1% foam
Tretinoin	Retin-A	0.025, 0.05, 0.1% cream
		0.01, 0.025% gel
	Retin-A Micro	0.04, 0.1% gel
	Avita	0.025% cream, gel
	Atralin	0.05% gel
Tretinoin/Clindamycin†	Ziana	0.025% (1.2% clindamycin) gel
	Veltin	0.025% (1.2% clindamycin) gel

BP, Benzoyl peroxide; *ZA*, zinc acetate.
*Listed are examples; this list is not exhaustive. Many of these preparations have generic alternatives.
†Combination therapy product.
From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.

TABLE E3 Oral Antibiotics for Acne Vulgaris

Drug	Usual Dosage*	Comments/Side-Effects
Commonly used		
Tetracycline	250-500 mg	Dental staining <9 yr
		Dairy products decrease absorption
		GI upset, photosensitivity, teratogenic, PTC, VVC, IBD
Minocycline	50-100 mg	Dental staining <9 yr
	55, 65, 80, 105, 115 mg ER (1 mg/kg once daily)	Dairy products decrease absorption
		Vertigo (lower incidence with ER preparation), GI upset, blue-gray skin pigmentation, severe drug reactions with hepatitis/pneumonitis, lupus-like reactions, SJS, teratogenic, hepatitis, PTC, VVC, IBD
Doxycycline	50-100 mg	Dental staining <9 yr
	75, 100, 150 mg ER, once daily	Dairy products decrease absorption
	20 mg ("subantimicrobial dose")	Photosensitivity, photoonycholysis, GI upset (rare), teratogenic, PTC, VVC, IBD
Erythromycin	250-500 mg	GI upset (common), VVC, drug–drug interactions, prolongation of the QT interval; no longer recommended by most experts given increased resistance
Less commonly used		
Trimethoprim-sulfamethoxazole	80/400 mg, 160/800 mg	Severe drug reactions, SJS, bone marrow suppression, hepatitis, GI upset, VVC, fixed drug eruption; routine use for acne strongly discouraged
Clindamycin	75-150 mg	Pseudomembranous colitis, GI upset, drug reactions, VVC
Cephalexin	250-500 mg	GI upset, drug reactions, VVC

ER, Extended release formulation; *GI,* gastrointestinal; *IBD,* inflammatory bowel disease; *PTC,* pseudotumor cerebri; *SJS,* Stevens–Johnson syndrome; *VVC,* vulvovaginal candidiasis.
*Usually given twice daily for acne unless otherwise noted in table.
From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.

TABLE E4 Alternative Treatments for Acne Vulgaris

Treatment	Comment
Comedone extraction	Performed with comedone extractor
Injections	Intralesional triamcinolone injected into large cysts or nodules
Light therapy	Blue light (may photoinactivate *P. acnes*)
	Red light (may have antiinflammatory effect)
	Combination blue-red light
	Intense pulsed light (IPL)
	Photodynamic therapy (PDT)
Laser therapy	KTP, pulsed dye laser (rarely used)
	Resurfacing laser (including both nonablative and ablative resurfacing lasers); useful for acne scarring
Dermabrasion/dermasanding	Useful for acne scarring
Collagen injection	Useful for acne scarring
Chemical peels	Useful for acne scarring and hyperpigmentation
Punch grafts/tissue augmentation	Useful for acne scarring
Trichloroacetic acid	Useful for atrophic acne scars
Radiation therapy	Outdated modality

KTP, Potassium titanyl phosphate.
From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.

FIG. E1 Acne vulgaris: comedonal. Open comedones present as blackheads. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

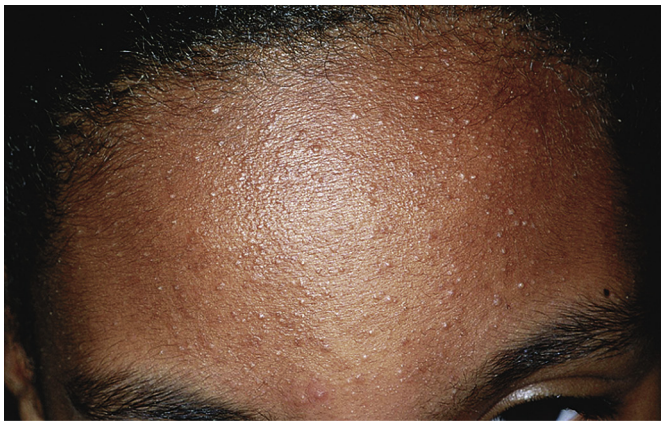

FIG. E2 Acne vulgaris: comedonal. Closed comedones present as whiteheads. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

FIG. E3 Acne vulgaris: inflammatory. Note the erythematous papules and pustules, as well as open and closed comedones. (From Paller AS, Mancini, AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

FIG. E4 Acne vulgaris: inflammatory. This adolescent female has inflammatory papules and papulopustules, as well as hirsutism. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

FIG. E5 Acne vulgaris: nodulocystic. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

SUGGESTED READINGS

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Titus S, Hodge J: Diagnosis and treatment of acne, *Am Fam Physician* 86: 736-740, 2012.

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Acoustic Neuroma PTG

BASIC INFORMATION

DEFINITION

Acoustic neuroma is a benign proliferation of the Schwann cells that cover the vestibular branch of the eighth cranial nerve (CN VIII). Symptoms are commonly a result of compression of the acoustic branch of CN VIII, the facial nerve (CN VII), and the trigeminal nerve (CN V). The glossopharyngeal nerve (CN IX) and vagus nerve (CN X) are less commonly involved. In extreme cases, compression of the brain stem may lead to obstruction of cerebrospinal fluid (CSF) outflow and elevated intracranial pressure (ICP).

SYNONYMS

Vestibular schwannoma
Acoustic schwannoma

ICD-10CM CODE
D33.3 Benign neoplasm of cranial nerves

EPIDEMIOLOGY & DEMOGRAPHICS

Overall incidence is approximately 1 in 100,000 person-yr with a higher incidence in patients with neurofibromatosis type 2 (NF2). In the U.S., there are about 3000 new cases of acoustic neuroma diagnosed each year. The tumor most commonly presents in the fifth and sixth decades.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most frequently unilateral hearing loss and/or tinnitus. Also balance problems, vertigo, facial pain (trigeminal neuralgia) and weakness, difficulty swallowing, fullness or pain of the involved ear. Headache may occur.
- With elevated ICP, patients may also have vomiting, fever, and visual changes.
- Hearing loss is the most common presenting complaint and is usually high frequency.

ETIOLOGY

The etiology is incompletely understood, but long-term exposure to acoustic trauma has been implicated. Bilateral acoustic neuromas may be inherited in an autosomal-dominant manner as part of NF2. This disease is associated with a defect on chromosome 22q1. Childhood exposure to low-dose radiation for benign head and neck conditions may increase risk for acoustic neuromas. There is inconclusive evidence to link chronic exposure to radiofrequency radiation from cellular telephone use and the risk for developing brain tumors.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Benign positional vertigo
- Menière disease
- Trigeminal neuralgia
- Cerebellar disease
- Normal-pressure hydrocephalus
- Presbycusis
- Glomus tumors
- Vertebrobasilar insufficiency
- Ototoxicity from medications
- Other tumors:
  1. Meningioma, glioma
  2. Facial nerve schwannoma
  3. Cavernous hemangioma
  4. Metastatic tumors

WORKUP

- A detailed neurologic examination with special attention to the cranial nerves is crucial.
- Rinne and Weber tests help determine conductive or sensorineural hearing loss.
- Common office balance tests (i.e., Romberg, Dix-Hallpike) are typically normal.
- Otoscopic evaluation may help rule out other causes of hearing loss.

LABORATORY TESTS

- Audiometry is useful, often showing asymmetric, sensorineural, high-frequency hearing loss.
- CSF protein may be elevated.

IMAGING STUDIES

- MRI with gadolinium (Fig. 1) is the preferred test. It can detect tumors as small as 2 mm in diameter.
- High-resolution CT scan with and without contrast can detect tumors 1 cm in diameter or larger.
- Treatment decisions should be based on the size of the tumor, rate of growth (older patients tend to have slower-growing tumors), degree of neurologic deficit, desire to preserve hearing, life expectancy, age of the patient, and surgical risk. A combination of treatments can also be used.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Surgery is the definitive treatment. Choice of approach (middle cranial fossa, translabyrinthine, or retromastoid suboccipital) may vary depending on the size of the tumor, amount of residual hearing desired, and degree of surgical risk that can be tolerated. Partial resection is sometimes undertaken to minimize the risk of injury to nearby structures. Intraoperative facial nerve monitoring is recommended.
- Radiation therapy (stereotactic radiotherapy, stereotactic radiosurgery, or proton beam radiotherapy) is useful for tumors <3 cm in diameter or for those in whom surgery is not an option. Radiotherapy after partial resection has also been used to minimize complications.
- Age alone is not a contraindication to surgery.

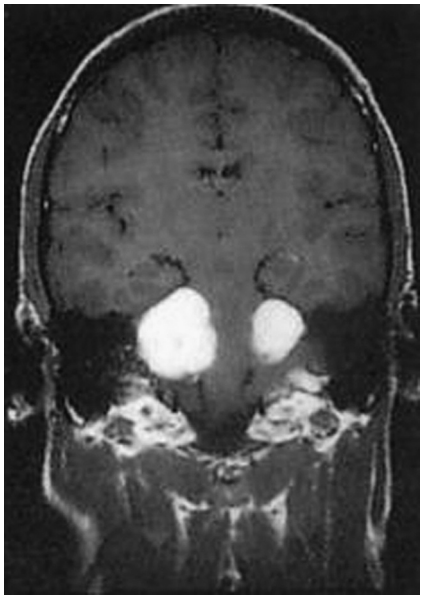

FIG. 1 Magnetic resonance imaging with enhancement shows bilateral acoustic neuromas. Coronal view. (From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach*, ed 7, Philadelphia, 2011, Saunders.)

GENERAL Rx

- Bevacizumab, an antivascular endothelial growth factor (VEGF) monoclonal antibody, has been shown to improve hearing and reduce the volume of growing acoustic neuromas in some neurofibromatosis type 2 patients.
- Observation with MRI every 6 to 12 mo may be appropriate for frail patients with small tumors, but risk of unrecoverable hearing loss may increase if surgery is delayed. Also, progressive hearing loss may occur despite absence of growth on subsequent imaging.

DISPOSITION

Hearing can be preserved at near-preoperative levels in more than two thirds of patients with small- to medium-sized tumors. Occurrence of secondary radiation-related tumors following radiosurgery is rare. There are no standard posttreatment follow-up recommendations. Therefore, an individualized approach to follow-up imaging and audiometry is recommended.

REFERRAL

Prompt referral to an otolaryngologist or neurosurgeon who is facile with all three surgical approaches is recommended.

PEARLS & CONSIDERATIONS

COMMENTS

- Presents most commonly as unilateral, sensorineural hearing loss.
- Treatment outcomes are excellent, with surgical cure rates greater than 95%.
- Of those who are managed with observation only, approximately half have continued enlargement, and approximately one-fifth eventually have a surgical intervention.

PATIENT & FAMILY EDUCATION

Acoustic Neuroma Association: https://www.anausa.org/

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Acoustic Neuroma (Patient Information)
Tinnitus (Related Key Topic)

AUTHOR: **Courtney Clark Bilodeau, MD, FACP**

SUGGESTED READINGS

Boari N et al: Gamma knife radiosurgery for vestibular schwannoma: clinical results at long-term follow-up in a series of 379 patients, *J Neurosurg* 121(Suppl):123-142, 2014.

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BASIC INFORMATION

DEFINITION

Acquired immunodeficiency syndrome (AIDS) is a disorder caused by infection with the human immunodeficiency virus (HIV) and marked by progressive deterioration of the cellular immune system, leading to secondary (opportunistic) infections and/or malignancies.

SYNONYM

AIDS

ICD-10CM CODE

B20 Human immunodeficiency virus [HIV] disease

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- The estimated number of persons diagnosed with AIDS in the U.S. is approximately 18,000/yr.
- There is a disproportionate number of new AIDS cases among black/African Americans and Latino/Hispanic Americans compared with white Americans.
- The majority of all new AIDS diagnoses are among gay, bisexual, or other men who have sex with men (MSM).

PREVALENCE (IN U.S.): The cumulative number of AIDS diagnoses in the U.S. exceeds 1.2 million.

PREDOMINANT SEX: Men constitute approximately 75% of incident AIDS diagnoses in the U.S.; more than half of AIDS diagnoses occur in MSM.

PREDOMINANT AGE: The predominant age group diagnosed with AIDS is 25 to 59 yr of age.

PEAK INCIDENCE: Ages 25 to 59 yr

GENETICS:

- Familial disposition: Although there is no proven genetic predisposition, individuals with deletions in the *CCR5* gene are less susceptible to HIV infection with macrophage tropic virus (the predominant virus in sexual transmission) and may progress to AIDS more slowly.
- Congenital infection:
  1. HIV is transmittable from an infected mother to the fetus in utero in as many as 30% of pregnancies if untreated.
  2. No specific congenital malformations associated with infection; low birth weight and spontaneous abortion are possible.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Nonspecific findings: Fever, weight loss, anorexia
- Specific syndromes:
  1. Seen in association with specific opportunistic infections and malignancies. These include:
     a. Opportunistic infections:
        (1) Disseminated strongyloidiasis
        (2) Disseminated toxoplasmosis, cryptococcosis, histoplasmosis, cytomegalovirus (CMV), herpes simplex virus (HSV), or mycobacterial disease (most common is mycobacterium avium complex)
        (3) *Candida* esophagitis or bronchopulmonary disease
        (4) Chronic cryptosporidiosis diarrhea
        (5) *Pneumocystis jiroveci* pneumonia (PJP)
        (6) Extensive pulmonary and extrapulmonary tuberculosis (TB)
        (7) Recurrent pneumonia or other bacterial infections
        (8) Progressive multifocal leukoencephalopathy (PML)
     b. AIDS-related neoplasms:
        (1) Kaposi sarcoma
        (2) Primary brain lymphoma
        (3) Invasive cervical carcinoma
        (4) High-grade B-cell non-Hodgkin lymphoma, Burkitt lymphoma, undifferentiated non-Hodgkin lymphoma, or immunoblastic lymphoma
  2. Most common:
     a. Respiratory infections (*Pneumocystis jiroveci* [formerly known as *Pneumocystis carinii*] pneumonia, TB, bacterial pneumonia, fungal infection)
     b. CNS infections (toxoplasmosis, TB)
     c. GI (cryptosporidiosis, isosporiasis, CMV); Sections II and III describe organisms associated with diarrhea in patients with AIDS
     d. Eye infections (CMV, toxoplasmosis)
     e. Kaposi sarcoma (cutaneous or visceral) or lymphoma (nodal or extranodal)
- Possibly asymptomatic
- Diagnosis of AIDS if the CD4 cell count is <200 or <14% of total lymphocyte in the presence of proven HIV infection, even in the absence of other infections
- The various manifestations of HIV infection are described in Section II

ETIOLOGY

- Caused by infection with HIV-1 or HIV-2 (less common).
- HIV is transmitted by sexual contact, needle-sharing (during IV drug use), transfusion of contaminated blood or blood products, and from infected mother to fetus or neonate.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other wasting illnesses mimicking the nonspecific features of AIDS:
  1. TB
  2. Neoplasms
  3. Disseminated fungal infection
  4. Malabsorption syndromes
  5. Depression
- Other disorders associated with dementia or demyelination producing encephalopathy, myelopathy, or neuropathy

WORKUP

Prompt evaluation of respiratory, CNS, and GI complaints

LABORATORY TESTS

- HIV antibody testing. See "Human Immunodeficiency Virus" topic for the updated surveillance case definition for HIV infection.
- CD4 cell count: Performed to determine the degree of immunodeficiency.
- Viral load assay: To plan long-term antiviral therapy and to follow progression and success of treatment (i.e., HIV RNA PCR).
- CSF examination: For meningitis or neurologic disease (if indicated).
- Serologic tests for syphilis, hepatitis A, hepatitis B, hepatitis C, and toxoplasmosis.
- Testing for other sexually transmitted infections (STIs) such as syphilis, gonorrhea, and chlamydia.
- Genotypic resistance testing: Used to assess for primary resistance in naïve patients and secondary resistance in patients failing a regimen.
- Eye exam: To evaluate for CMV retinitis in patients with CD4 counts <50 cells/mm^3.
- Cryptococcal antigen: Part of the evaluation in AIDS patients with CD4 counts <100 cells/mm^3 who have fever, diffuse pneumonia, or evidence of meningitis.
- Evaluation for infection with mycobacterium (TB or MAI) including a tuberculin skin test (TST) or interferon-gamma release assay (IGRA), sputum cultures, chest radiograph, and blood cultures for acid-fast bacteria, depending on clinical presentation.

IMAGING STUDIES

- MRI or CT of head for encephalopathy or focal CNS complications (e.g., toxoplasmosis [Fig. E1], lymphoma)
- Chest radiography or CT to aid in the diagnosis of *Pneumocystis jiroveci* pneumonia (PJP), TB, or bacterial pneumonia

TREATMENT

The most important aspect in management of AIDS due to HIV infection is the timely initiation of antiretroviral therapy.

NONPHARMACOLOGIC THERAPY

- Maintain adequate caloric intake.
- Encourage good oral hygiene and regular dental care.
- Avoid high-risk behaviors that increase the risk of other potential pathogens—use condoms, avoid sharing needles, etc.
- Update vaccines—particularly Tdap (tetanus, diphtheria, and pertussis), pneumococcal, meningococcal, and hepatitis A/B vaccines along with annual influenza vaccines.

- Avoid administration of any live attenuated vaccines that may be a risk to these immunocompromised patients (e.g., MMR, varicella). (See Section V for immunization schedules for HIV-infected children.)
- When feasible, avoid activities that might increase risk of exposure to opportunistic infections (e.g., cleaning out a cat litter box [toxoplasmosis], getting scratched by a cat [*Bartonella* infections], exposure to pet reptiles [salmonellosis], traveling to developing countries [cryptosporidiosis, tuberculosis], eating undercooked foods and drinking from unsafe water supplies, etc.). A description of enteropathogens causing infections in HIV-infected patients is provided in Table 1.

ACUTE GENERAL Rx

Acute management of opportunistic infections is summarized in Table 2 and reviewed elsewhere in this text under specific AIDS-related disorders. For management of AIDS-related malignancies, please refer to the specific malignancy elsewhere in this text.

CHRONIC Rx

For all HIV-infected patients, particularly those meeting the case definition of AIDS:

- Preventive therapy for *Pneumocystis jiroveci* pneumonia and *Mycobacterium avium* (see specific chapters elsewhere in this text). With appropriate antiretroviral therapy, many patients experience substantial restoration of cellular immune function. Preventive therapy for *Pneumocystis jiroveci* can be safely stopped if the CD4 cell count rises above 200 for at least 3 mo
- Based on the Department of Health and Human Services (DHHS) Guidelines, active antiretroviral therapy (ART) should be started regardless of CD4 cell count. Individuals with CD4 cell counts <350 and especially CD4 cell counts <200 should be strongly encouraged to start ART in a timely fashion
- ART usually includes three-drug combinations of:
  1. Nucleoside reverse transcriptase inhibitors (NRTI): Tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF), lamivudine (3TC), emtricitabine (FTC), and abacavir (ABC). Older drugs such as zidovudine (AZT), didanosine (ddI), and stavudine (d4T) are generally not recommended.
  2. Protease inhibitors (PI): Atazanavir or darunavir
  3. Nonnucleoside reverse transcriptase inhibitors (NNRTI): Nevirapine, efavirenz (EFV), etravirine, and rilpivirine
  4. Integrase inhibitors: Raltegravir, elvitegravir, bictegravir, and dolutegravir
  5. Others: Maraviroc, enfuvirtide, and ibalizumab

TABLE 1 Organisms That Cause Gastrointestinal Tract Infections in Patients with HIV/AIDS

	Organisms
Esophagus	*Candida albicans*[a]
	Cytomegalovirus[a]
	Herpes simplex virus[a]
Hepatobiliary	Cytomegalovirus
	Cryptosporidium[a]
	Hepatotropic viruses
	Mycobacterium avium complex[a]
Small intestine	*Campylobacter* species
	Cytomegalovirus[a]
	Cryptosporidium[a]
	Giardia lamblia[a]
	Isospora belli[a]
	Mycobacterium avium complex[a]
	Microsporidia[a] (*Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*)
	Salmonella species[a]
	Enteroaggregative *E. coli*
	Strongyloides stercoralis
Large intestine	*Campylobacter* species
	Clostridium difficile
	Cytomegalovirus[a]
	Entamoeba histolytica
	Herpes simplex virus[a]
	Salmonella species[a]
	Enteroaggregative *E. coli*
	Shigella species

[a]Diseases of the gastrointestinal tract that fulfill the Centers for Disease Control and Prevention surveillance case definition of AIDS.

From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

The medications ritonavir or cobicistat are usually used in combination with other protease inhibitors or integrase inhibitors to obtain more sustained drug levels. Usual initial dosing regimens include two NRTIs and an NNRTI or PI or integrase inhibitor. Currently, integrase inhibitors are recommended as first-line drugs because of tolerability. Examples of initial regimens recommended by the guidelines:

1. Bictegravir/tenofovir/emtricitabine
2. Dolutegravir/abacavir/lamivudine (in patients who are HLA-B*5701 NEGATIVE)
3. Dolutegravir plus tenofovir/emtricitabine*
4. Raltegravir plus tenofovir/emtricitabine*
5. Elvitegravir/cobicistat/tenofovir/emtricitabine
6. Darunavir/ritonavir or darunavir/cobicistat plus tenofovir/emtricitabine

*Tenofovir-based formulations can include tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF).

Previous first-line drugs, including efavirenz/tenofovir/emtricitabine and rilpivirine/tenofovir/emtricitabine, are now considered alternative regimens.

All these drugs have unique and class-specific side effects and require careful and expert follow-up to achieve optimal antiviral effects, ensure compliance, and maintain efficacy. Antiviral response should be monitored by baseline HIV viral load and CD4 count and repeat measurement at 2 wk and 4 wk into treatment and then periodically (3 to 6 mo) to ensure viral suppression.

- The approach to a patient with CNS signs and symptoms is described in Fig. E2, and Fig. E3 describes the management of CNS mass lesions.
- Genotypic resistance testing is strongly encouraged for all patients initiating treatment and for any patient failing antiretroviral therapy. Poor adherence to therapy, however, often underlies virologic failure.

DISPOSITION

The outlook for HIV has changed radically since the advent of ART from an essentially fatal disease to a chronic medical illness compatible with long-term survival and remarkably good quality of life. Patients should be aggressively treated for severe illnesses as outcomes following ICU admissions remain good. This is accomplished through expert and continuous follow-up, use of ART, and careful detail to compliance to medications and lifestyle modification.

REFERRAL

All patients with HIV should be referred to a physician knowledgeable and experienced in the management of the disease and its complications.

RELATED CONTENT

Acquired Immunodeficiency Syndrome (AIDS) (Patient Information)
Candidiasis, Cutaneous (Related Key Topic)
Candidiasis, Invasive (Related Key Topic)
Cryptosporidium Infection (Related Key Topic)
Cytomegalovirus Infection (Related Key Topic)
Herpes Simplex (Related Key Topic)
Histoplasmosis (Related Key Topic)
HIV-Associated Cognitive Dysfunction (Related Key Topic)
Human Immunodeficiency Virus (Related Key Topic)
Kaposi Sarcoma (Related Key Topic)
Pneumonia, *pneumocystis jiroveci (carinii)* (Related Key Topic)
Progressive Multifocal Leukoencephalopathy (Related Key Topic)
Toxoplasmosis (Related Key Topic)
Tuberculosis, Pulmonary (Related Key Topic)

AUTHOR: **Philip A. Chan, MD, MS**

TABLE 2 Treatment of AIDS-Associated Opportunistic Infections

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
PJP	• Patients who develop PJP despite TMP-SMX prophylaxis can usually be treated with standard doses of TMP-SMX. • Duration of PJP treatment: 21 days. • *For Moderate to Severe PJP:* • TMP-SMX: (TMP 15-20 mg and SMX 75-100 mg/kg/day) IV given q6h or q8h, may switch to PO after clinical improvement. • *For Mild to Moderate PJP:* • TMP-SMX: (TMP 15-20 mg and SMX 75-100 mg/kg/day), given PO in 3 divided doses, *or* • TMP-SMX: (160 mg/800 mg or DS) 2 tablets PO tid. • *Secondary Prophylaxis, after completion of PJP treatment:* • TMP-SMX DS: 1 tablet PO daily *or* • TMP-SMX (80 mg/400 mg or SS): 1 tablet PO daily.	*For Moderate to Severe PJP:* • Pentamidine 4 mg/kg IV daily infused over ≥60 minutes; can reduce dose to 3 mg/kg IV daily because of toxicities, *or* • Primaquine 30 mg (base) PO daily + (clindamycin 600 mg q6h IV or 900 mg IV q8h) or (clindamycin 300 mg PO q6h or 450 mg PO q8h). • *For Mild to Moderate PJP:* • Dapsone 100 mg PO daily + TMP 5 mg/kg PO tid, *or* • Primaquine 30 mg (base) PO daily + (clindamycin 300 mg PO q6h or 450 mg PO q8h), *or* • Atovaquone 750 mg PO bid with food. • *Secondary Prophylaxis, after completion of PJP treatment:* • TMP-SMX DS: 1 tablet PO tiw, *or* • Dapsone 100 mg PO daily, *or* • Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly, *or* • (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly, *or* • Aerosolized pentamidine 300 mg monthly via Respirgard II nebulizer, *or* • Atovaquone 1500 mg PO daily, *or* • (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily.	*Indications for Adjunctive Corticosteroids:* • Pao_2 <70 mm Hg at room air, *or* • Alveolar-arterial O_2 gradient >35 mm Hg. • *Prednisone Doses (beginning as early as possible and within 72 hours of PJP therapy):* • Days 1-5: 40 mg PO bid. • Days 6-10: 40 mg PO daily. • Days 11-21: 20 mg PO daily. • IV methylprednisolone can be administered as 75% of prednisone dose. • Benefit of corticosteroid if started after 72 hours of treatment is unknown, but some clinicians will use it for moderate-to-severe PJP. • Whenever possible, patients should be tested for G6PD before use of dapsone or primaquine. Alternative therapy should be used in patients found to have G6PD deficiency. • Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PJP prophylaxis. • If TMP-SMX is discontinued because of a mild adverse reaction, reinstitution should be considered after the reaction resolves. The dose can be increased gradually (desensitization) or be reduced, or the frequency can be modified. • TMP-SMX should be permanently discontinued in patients with possible or definite Stevens–Johnson syndrome or toxic epidermal necrosis.
Toxoplasma gondii encephalitis	*Treatment of Acute Infection:* • Pyrimethamine 200 mg PO 1 time, followed by weight-based therapy: • If <60 kg, pyrimethamine 50 mg PO once daily + sulfadiazine 1000 mg PO q6h + leucovorin 10-25 mg PO once daily. • If ≥60 kg, pyrimethamine 75 mg PO once daily + sulfadiazine 1500 mg PO q6h + leucovorin 10-25 mg PO once daily. • Leucovorin dose can be increased to 50 mg daily or bid. • *Duration for Acute Therapy:* • At least 6 wk; longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 wk. • *Chronic Maintenance Therapy:* • Pyrimethamine 25-50 mg PO daily + sulfadiazine 2000-4000 mg PO daily (in 2-4 divided doses) + leucovorin 10-25 mg PO daily (AI). • After collecting specimen for culture and molecular diagnostic tests, empiric TB treatment should be started in individuals with clinical and radiographic presentation suggestive of TB. • *Initial Phase (2 mo, given daily):* • INH + [RIF or RFB] + PZA + EMB.	*Treatment of Acute Infection:* • Pyrimethamine (leucovorin)* + clindamycin 600 mg IV or PO q6h *or* • TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) IV or PO bid, *or* • Atovaquone 1500 mg PO bid with food + pyrimethamine (leucovorin), *or* • Atovaquone 1500 mg PO bid with food + sulfadiazine 1000-1500 mg PO q6h (weight-based dosing, as in preferred therapy) *or* • Atovaquone 1500 mg PO bid with food, *or* • Pyrimethamine (leucovorin)* + azithromycin 900-1200 mg PO daily. • *Chronic Maintenance Therapy:* • Clindamycin 600 mg PO q8h + (pyrimethamine 25-50 mg + leucovorin 10-25 mg) PO daily *or* • TMP-SMX DS 1 tablet bid, *or* • Atovaquone 750-1500 mg PO bid + (pyrimethamine 25 mg + leucovorin 10 mg) PO daily, *or* • Atovaquone 750-1500 mg PO bid + sulfadiazine 2000-4000 mg PO daily (in 2-4 divided doses), *or* • Atovaquone 750-1500 mg PO bid with food.	• Adjunctive corticosteroids (e.g., dexamethasone) should only be administered when clinically indicated to treat mass effect associated with focal lesions or associated edema; discontinue as soon as clinically feasible. • Anticonvulsants should be administered to patients with a history of seizures and continued through acute treatment but should not be used as seizure prophylaxis. • If clindamycin is used in place of sulfadiazine, additional therapy must be added to prevent PCP.
Mycobacterium tuberculosis disease (TB)	• *Continuation Phase:* • INH + (RIF or RFB) daily. • *Total Duration of Therapy (for drug-susceptible TB):* • Pulmonary TB: 6 mo.	*Treatment for Drug-Resistant TB* • *Resistant to INH:* • (RIF or RFB) + EMB + PZA + (moxifloxacin or levofloxacin) for 2 mo; followed by (RIF or RFB) + EMB + (moxifloxacin or levofloxacin) for 7 mo.	• Adjunctive corticosteroid improves survival for TB meningitis and pericarditis. See text for drug, dose, and duration recommendations. • RIF *is not recommended* for patients receiving HIV PI because of its induction of PI metabolism. • RFB is a less potent CYP3A4 inducer than RIF and is preferred in patients receiving PIs.

Continued

TABLE 2 Treatment of AIDS-Associated Opportunistic Infections—cont'd

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	• Pulmonary TB and culture-positive after 2 mo of TB treatment: 9 mo. • Extrapulmonary TB with CNS infection: 9-12 mo. • Extrapulmonary TB with bone or joint involvement: 6 to 9 mo. • Extrapulmonary TB in other sites: 6 mo. • Total duration of therapy should be based on number of doses received, not on calendar time.	• *Resistant to Rifamycins ± Other Drugs:* • Regimen and duration of treatment should be individualized based on resistance pattern, clinical and microbiologic responses, and in close consultation with experienced specialists.	• Once-weekly rifapentine can result in development of rifamycin resistance in HIV-infected patients and *is not recommended.* • Therapeutic drug monitoring should be considered in patients receiving rifamycin and interacting ART. • Paradoxical IRIS that is not severe can be treated with NSAIDs without a change in TB or HIV therapy. • For severe IRIS reaction, consider prednisone and taper over 4 wk based on clinical symptoms. For example: • *If receiving RIF:* Prednisone 1.5 mg/kg/day for 2 wk, then 0.75 mg/kg/day for 2 weeks. • *If receiving RFB:* Prednisone 1.0 mg/kg/day for 2 wk, then 0.5 mg/kg/day for 2 wk. • A more gradual tapering schedule over a few mo may be necessary for some patients.
Disseminated MAC disease	*At Least 2 Drugs as Initial Therapy with:* • Clarithromycin 500 mg PO bid + ethambutol 15 mg/kg PO daily, *or* • Azithromycin 500-600 mg + ethambutol 15 mg/kg PO daily if drug interaction or intolerance precludes the use of clarithromycin. • *Duration:* • At least 12 mo of therapy, can discontinue if no signs and symptoms of MAC disease and sustained (>6 mo) CD4 count >100 cells/μl in response to ART.	• Addition of a third or fourth drug should be considered for patients with advanced immunosuppression (CD4 counts <50 cells/μl), high mycobacterial loads (>2 log CFU/ml of blood), or in the absence of effective ART. *Third or Fourth Drug Options May Include:* • RFB 300 mg PO daily (dosage adjustment may be necessary based on drug interactions), *or* • Amikacin 10-15 mg/kg IV daily, *or* • Streptomycin 1 g IV or IM daily, *or* • Moxifloxacin 400 mg PO daily or levofloxacin 500 mg PO daily.	• Testing of susceptibility to clarithromycin and azithromycin is recommended. • NSAIDs can be used for patients who experience moderate to severe symptoms attributed to IRIS. • If IRIS symptoms persist, short-term (4-8 wk) systemic corticosteroids (equivalent to 20-40 mg prednisone) can be used.
Bacterial respiratory diseases *(with focus on pneumonia)*	Empiric antibiotic therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia. The recommendations listed are suggested empiric therapy. The regimen should be modified as needed once microbiologic results are available. *Empiric Outpatient Therapy:* • A PO β-lactam + a PO macrolide (azithromycin or clarithromycin). • *Preferred β-lactams*: High-dose amoxicillin or amoxicillin/clavulanate. • *Alternative β-lactams*: Cefpodoxime or cefuroxime, *or* • *For penicillin-allergic patients:* Levofloxacin 750 mg PO once daily, or moxifloxacin 400 mg PO once daily. • *Duration:* 7-10 days (a minimum of 5 days). Patients should be afebrile for 48-72 hours and clinically stable before stopping antibiotics. • *Empiric Therapy for Non-ICU Hospitalized Patients:* • An IV β-lactam + a macrolide (azithromycin or clarithromycin). • *Preferred β-lactams:* Ceftriaxone, cefotaxime, *or* ampicillin-sulbactam. • *For penicillin-allergic patients:* • Levofloxacin, 750 mg IV once daily, *or* moxifloxacin, 400 mg IV once daily. • *Empiric Therapy for ICU Patients:* • An IV β-lactam + IV azithromycin, *or*	*Empiric Outpatient Therapy:* • A PO β-lactam + PO doxycycline. • *Preferred β-lactams*: High-dose amoxicillin or amoxicillin/clavulanate. • *Alternative β-lactams*: Cefpodoxime or cefuroxime. • *Empiric Therapy for Non-ICU Hospitalized Patients:* • An IV β-lactam + doxycycline. • *Empiric Therapy for ICU Patients:* • *For penicillin-allergic patients:* Aztreonam IV + (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily). *Empiric Therapy for Patients at Risk of Pseudomonas Pneumonia:* • An IV antipneumococcal, antipseudomonal β-lactam + an aminoglycoside + azithromycin, *or*	• Fluoroquinolones should be used with caution in patients in whom TB is suspected but is not being treated. • Empiric therapy with a macrolide alone is not routinely recommended because of increasing pneumococcal resistance. • Patients receiving a macrolide for MAC prophylaxis should not receive macrolide monotherapy for empiric treatment of bacterial pneumonia. • For patients begun on IV antibiotic therapy, switching to PO should be considered when they are clinically improved and able to tolerate oral medications. • Chemoprophylaxis can be considered for patients with frequent recurrences of serious bacterial pneumonia.

TABLE 2 Treatment of AIDS-Associated Opportunistic Infections—cont'd

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	• An IV β-lactam + (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily). • *Preferred β-lactams*: Ceftriaxone, cefotaxime, or ampicillin-sulbactam. • *Empiric Therapy for Patients at Risk of* Pseudomonas *Pneumonia:* • An IV antipneumococcal, antipseudomonal β-lactam + ciprofloxacin 400 mg IV q8-12h or levofloxacin 750 mg IV once daily. • *Preferred β-lactams*: Piperacillin-tazobactam, cefepime, imipenem, or meropenem. • *Empiric Therapy for Patients at Risk for Methicillin-Resistant* Staphylococcus aureus *Pneumonia:* • Add vancomycin IV or linezolid (IV or PO) to the baseline regimen. • Addition of clindamycin to vancomycin (but not to linezolid) can be considered for severe necrotizing pneumonia to minimize bacterial toxin production.	• Above β-lactam + an aminoglycoside + (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily), *or* • *For penicillin-allergic patients*: Replace the β-lactam with aztreonam.	• Clinicians should be cautious about using antibiotics to prevent recurrences because of the potential for developing drug resistance and drug toxicities.
Bacterial enteric infections *Empiric therapy pending definitive diagnosis*	• Diagnostic fecal specimens should be obtained before initiation of empiric antibiotic therapy. • Empiric antibiotic therapy is indicated for patients with advanced HIV (CD4 count <200 cells/μl or concomitant AIDS-defining illnesses), with clinically severe diarrhea (>6 stools/day), and/or accompanying fever or chills. • *Empiric Therapy:* • Ciprofloxacin 500-750 mg PO (or 400 mg IV) q12h. • Therapy should be adjusted based on the results of diagnostic workup. • For patients with chronic diarrhea (>14 days) without severe clinical signs, empiric antibiotics therapy is not necessary; can withhold treatment until a diagnosis is made.	*Empiric Therapy:* • Ceftriaxone 1 g IV q24h, *or* • Cefotaxime 1 g IV q8h.	• Hospitalization with IV antibiotics should be considered in patients with marked nausea, vomiting, diarrhea, electrolyte abnormalities, acidosis, and blood pressure instability. • Oral or IV rehydration if indicated. • Antimotility agents should be avoided if there is concern about inflammatory diarrhea, including *Clostridium difficile*–associated diarrhea. • If no clinical response after 5-7 days, consider follow-up stool culture with antibiotic susceptibility testing or alternative diagnostic tests (e.g., toxin assays, molecular testing), alternative diagnosis, or antibiotic resistance.
Salmonellosis	All HIV-infected patients with salmonellosis should be treated because of high risk of bacteremia. • Ciprofloxacin 500-750 mg PO (or 400 mg IV) q12h, if susceptible. • *Duration of Therapy:* • *For gastroenteritis without bacteremia:* • If CD4 count ≥200 cells/μl: 7-14 days. • If CD4 count <200 cells/μl: 2-6 wk. *For gastroenteritis with bacteremia:* • If CD4 count ≥200/μl: 14 days; longer duration if bacteremia persists or if the infection is complicated (e.g., if metastatic foci of infection are present). • If CD4 count <200 cells/μl: 2-6 wk. *Secondary Prophylaxis Should Be Considered for:* • Patients with recurrent *Salmonella* gastroenteritis ± bacteremia, *or* • Patients with CD4 <200 cells/μl with severe diarrhea.	• Levofloxacin 750 mg (PO or IV) q24h, *or* • Moxifloxacin 400 mg (PO or IV) q24h, *or* • TMP, 160 mg-SMX 800 mg (PO or IV) q12h, *or* • Ceftriaxone 1 g IV q24h, *or* • Cefotaxime 1 g IV q8h.	• Oral or IV rehydration if indicated. • Antimotility agents should be avoided. • The role of long-term secondary prophylaxis in patients with recurrent *Salmonella* bacteremia is not well established. Must weigh benefit against risks of long-term antibiotic exposure. • Effective ART may reduce the frequency, severity, and recurrence of *Salmonella* infections.

Continued

TABLE 2 Treatment of AIDS-Associated Opportunistic Infections—cont'd

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Mucocutaneous candidiasis	*For Oropharyngeal Candidiasis; Initial Episodes (for 7-14 days):* • *Oral therapy* • Fluconazole 100 mg PO daily, *or* • *Topical therapy* • Clotrimazole troches, 10 mg PO 5 times daily, *or* • Miconazole mucoadhesive buccal 50-mg tablet—apply to mucosal surface over the canine fossa once daily (do not swallow, chew, or crush). *For Esophageal Candidiasis (for 14-21 days):* • Fluconazole 100 mg (up to 400 mg) PO or IV daily, *or* • Itraconazole oral solution 200 mg PO daily. *For Uncomplicated Vulvovaginal Candidiasis:* • Oral fluconazole 150 mg for 1 dose, *or* • Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3-7 days. *For Severe or Recurrent Vulvovaginal Candidiasis:* • Fluconazole 100-200 mg PO daily for ≥7 days, *or* • Topical antifungal ≥7 days.	*For Oropharyngeal Candidiasis; Initial Episodes (for 7-14 days):* • *Oral therapy* • Itraconazole oral solution 200 mg PO daily, *or* • Posaconazole oral solution 400 mg PO bid for 1 day, then 400 mg daily. • *Topical therapy* • Nystatin suspension 4-6 ml qid or 1-2 flavored pastilles 4-5 times daily. *For Esophageal Candidiasis (for 14-21 days):* • Voriconazole 200 mg PO or IV bid, *or* • Posaconazole 400 mg PO bid, *or* • Anidulafungin 100 mg IV 1 time, then 50 mg IV daily, *or* • Caspofungin 50 mg IV daily, *or* • Micafungin 150 mg IV daily, *or* • Amphotericin B deoxycholate 0.6 mg/kg IV daily, *or* • Lipid formulation of amphotericin B 3-4 mg/kg IV daily. *For Uncomplicated Vulvovaginal Candidiasis:* • Itraconazole oral solution 200 mg PO daily for 3-7 days.	• Chronic or prolonged use of azoles may promote development of resistance. • Higher relapse rate for esophageal candidiasis is seen with echinocandins than with fluconazole use. • Suppressive therapy is usually not recommended unless patients have frequent or severe recurrences. If Decision Is to Use Suppressive Therapy: *Oropharyngeal Candidiasis:* • Fluconazole 100 mg PO daily or tiw. • Itraconazole oral solution 200 mg PO daily. • Esophageal Candidiasis: • Fluconazole 100-200 mg PO daily. • Posaconazole 400 mg PO bid. *Vulvovaginal Candidiasis:* • Fluconazole 150 mg PO once weekly.
Cryptococcosis	*Cryptococcal Meningitis* • *Induction Therapy (for at least 2 wk, followed by consolidation therapy):* • Liposomal amphotericin B 3-4 mg/kg IV daily + flucytosine 25 mg/kg PO qid. (NOTE: Flucytosine dose should be adjusted in patients with renal dysfunction.) • *Consolidation Therapy (for at least 8 wk followed by maintenance therapy):* • Fluconazole 400 mg PO (or IV) daily. • *Maintenance therapy:* • Fluconazole 200 mg PO daily for at least 12 mo. *For Non-CNS, Extrapulmonary Cryptococcosis and Diffuse Pulmonary Disease:* • Treatment same as for cryptococcal meningitis. *Non-CNS Cryptococcosis with Mild to Moderate Symptoms and Focal Pulmonary Infiltrates:* • Fluconazole, 400 mg PO daily for 12 mo.	*Cryptococcal Meningitis* • *Induction Therapy (for at least 2 wk, followed by consolidation therapy):* • Amphotericin B deoxycholate 0.7 mg/kg IV daily + flucytosine 25 mg/kg PO qid, *or* • Amphotericin B lipid complex 5 mg/kg IV daily + flucytosine 25 mg/kg PO qid, *or* • Liposomal amphotericin B 3-4 mg/kg IV daily + fluconazole 800 mg PO or IV daily, *or* • Amphotericin B deoxycholate 0.7 mg/kg IV daily + fluconazole 800 mg PO or IV daily, *or* • Fluconazole 400-800 mg PO or IV daily + flucytosine 25 mg/kg PO qid, *or* • Fluconazole 1200 mg PO or IV daily. • *Consolidation Therapy (for at least 8 wk followed by maintenance therapy):* • Itraconazole 200 mg PO bid for 8 wk—less effective than fluconazole. • *Maintenance therapy:* • No alternative therapy recommendation.	• Addition of flucytosine to amphotericin B has been associated with more rapid sterilization of CSF and decreased risk for subsequent relapse. • Patients receiving flucytosine should have either blood levels monitored (peak level 2 hours after dose should be 30-80 μg/ml) or close monitoring of blood counts for development of cytopenia. Dosage should be adjusted in patients with renal insufficiency. • Opening pressure should always be measured when an LP is performed. Repeated LPs or CSF shunting are essential to effectively manage increased intracranial pressure. • Corticosteroids and mannitol are ineffective in reducing intracranial pressure and are *not* recommended. • Some specialists recommend a brief course of corticosteroid for management of severe IRIS symptoms.

TABLE 2 Treatment of AIDS-Associated Opportunistic Infections—cont'd

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Histoplasmosis	*Moderately Severe to Severe Disseminated Disease Induction Therapy (for at least 2 wk or until clinically improved):* • Liposomal amphotericin B 3 mg/kg IV daily. • *Maintenance Therapy:* • Itraconazole 200 mg PO tid for 3 days, then 200 mg PO bid. *Less Severe Disseminated Disease* • Induction and Maintenance Therapy: • Itraconazole 200 mg PO tid for 3 days, then 200 mg PO bid. • *Duration of Therapy:* • At least 12 mo. *Meningitis* • *Induction Therapy (4-6 wk):* • Liposomal amphotericin B 5 mg/kg/day. • *Maintenance Therapy:* • Itraconazole 200 mg PO bid to tid for ≥1 yr and until resolution of abnormal CSF findings. • *Long-Term Suppression Therapy:* • *For patients with severe disseminated or CNS infection after completion of at least 12 mo of therapy; and those who relapse despite appropriate therapy* • Itraconazole 200 mg PO daily.	*Moderately Severe to Severe Disseminated Disease Induction Therapy (for at least 2 wk or until clinically improved):* • Amphotericin B lipid complex 3 mg/kg IV daily, *or* • Amphotericin B cholesteryl sulfate complete 3 mg/kg IV daily. • *Alternatives to Itraconazole for Maintenance Therapy or Treatment of Less Severe Disease:* • Voriconazole 400 mg PO bid for 1 day, then 200 mg bid, *or* • Posaconazole 400 mg PO bid. • Fluconazole 800 mg PO daily. *Meningitis* • No alternative therapy recommendation. • *Long-Term Suppression Therapy:* • Fluconazole 400 mg PO daily.	• Itraconazole, posaconazole, and voriconazole may have significant interactions with certain ARV agents. These interactions are complex and can be bidirectional. • Therapeutic drug monitoring and dosage adjustment may be necessary to ensure triazole antifungal and ARV efficacy and to reduce concentration-related toxicities. • Random serum concentration of itraconazole + hydroxyitraconazole should be >1 μg/ml. • Clinical experience with voriconazole or posaconazole in the treatment of histoplasmosis is limited. • Acute pulmonary histoplasmosis in HIV-infected patients with CD4 counts >300 cells/μl should be managed as nonimmunocompromised host.
Coccidioidomycosis	*Clinically Mild Infections (e.g., focal pneumonia):* • Fluconazole 400 mg PO daily *or* • Itraconazole 200 mg PO bid. *Severe, Nonmeningeal Infection (diffuse pulmonary infection or severely ill patients with extrathoracic, disseminated disease):* • Amphotericin B deoxycholate 0.7-1.0 mg/kg IV daily. • Lipid formulation amphotericin B 4-6 mg/kg IV daily. • Duration of therapy: Continue until clinical improvement, then switch to an azole. *Meningeal Infections:* • Fluconazole 400-800 mg IV or PO daily. • *Chronic Suppressive Therapy:* • Fluconazole 400 mg PO daily, *or* • Itraconazole 200 mg PO bid.	*Mild Infections (focal pneumonia) for patients who failed to respond to fluconazole or itraconazole:* • Posaconazole 200 mg PO bid, *or* • Voriconazole 200 mg PO bid. *Severe, Nonmeningeal Infection (diffuse pulmonary infection or severely ill patients with extrathoracic, disseminated disease):* • Some specialists will add a triazole (fluconazole or itraconazole, with itraconazole preferred for bone disease) 400 mg per day to amphotericin B therapy and continue triazole once amphotericin B is stopped. *Meningeal Infections:* • Itraconazole 200 mg PO tid for 3 days, then 200 mg PO bid, *or* • Posaconazole 200 mg PO bid, *or* • Voriconazole 200-400 mg PO bid, *or* • Intrathecal amphotericin B deoxycholate, when triazole antifungals are ineffective. • *Chronic suppressive therapy:* • Posaconazole 200 mg PO bid, *or* • Voriconazole 200 mg PO bid.	• Some patients with meningitis may develop hydrocephalus and require CSF shunting. • Therapy should be continued indefinitely in patients with diffuse pulmonary or disseminated diseases because relapse can occur in 25%-33% of HIV-negative patients. It can also occur in HIV-infected patients with CD4 counts >250 cells/μL. • Therapy should be lifelong in patients with meningeal infections because relapse occurs in 80% of HIV-infected patients after discontinuation of triazole therapy. • Itraconazole, posaconazole, and voriconazole may have significant interactions with certain ARV agents. These interactions are complex and can be bidirectional. Therapeutic drug monitoring and dosage adjustment may be necessary to ensure triazole antifungal and antiretroviral efficacy and to reduce concentration-related toxicities. • Intrathecal amphotericin B should be given only in consultation with a specialist and should be administered by an individual with experience with the technique.
Aspergillosis, invasive	*Preferred Therapy:* • Voriconazole 6 mg/kg IV q12h for 1 day, then 4 mg/kg IV q12h, followed by voriconazole 200 mg PO q12h after clinical improvement. • *Duration of Therapy:* • Until CD4 cell count >200 cells/μl and the infection appears to be resolved.	*Alternative Therapy:* • Lipid formulation of amphotericin B 5 mg/kg IV daily, *or* • Amphotericin B deoxycholate 1 mg/kg IV daily, *or* • Caspofungin 70 mg IV 1 time, then 50 mg IV daily, *or* • Micafungin 100-150 mg IV daily, *or* • Anidulafungin 200 mg IV 1 time, then 100 mg IV daily, *or* • Posaconazole 200 mg PO qid, then, after condition improved, 400 mg PO bid.	• Potential for significant pharmacokinetic interactions between certain ARV agents and voriconazole; they should be used cautiously in these situations. Consider therapeutic drug monitoring and dosage adjustment if necessary.

Continued

TABLE 2 Treatment of AIDS-Associated Opportunistic Infections—cont'd

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
CMV disease	*CMV Retinitis Induction Therapy for Immediate Sight-Threatening Lesions (adjacent to the optic nerve or fovea)* • Consult ophthalmologist; ganciclovir implant no longer available: • Ganciclovir 5 mg/kg IV q12h for 14-21 days followed by Valganciclovir 900 mg PO bid. *For Small Peripheral Lesions:* • Valganciclovir 900 mg PO bid for 14-21 days. • One dose of intravitreal ganciclovir can be administered immediately after diagnosis until steady-state plasma ganciclovir concentration is achieved with oral valganciclovir. • *Chronic Maintenance (secondary prophylaxis):* • Valganciclovir 900 mg PO daily (for small peripheral lesion). *CMV Esophagitis or Colitis:* • Ganciclovir 5 mg/kg IV q12h; may switch to valganciclovir 900 mg PO q12h once patient can tolerate oral therapy.	*CMV Retinitis Induction Therapy:* • Ganciclovir 5 mg/kg IV q12h for 14-21 days, *or* • Foscarnet 90 mg/kg IV q12h or 60 mg q8h for 14-21 days, *or* • Cidofovir 5 mg/kg/wk IV for 2 wk; saline hydration before and after therapy and probenecid, 2 g PO 3 hours before dose, followed by 1 g PO 2 hours and 8 hours after the dose (total of 4 g). (Note: This regimen should be avoided in patients with sulfa allergy because of cross-hypersensitivity with probenecid.) • *Chronic Maintenance (secondary prophylaxis):* • Ganciclovir 5 mg/kg IV 5-7 times weekly, *or*	• The choice of therapy for CMV retinitis should be individualized, based on location and severity of the lesions, level of immunosuppression, and other factors (e.g., concomitant medications and ability to adhere to treatment). • The choice of chronic maintenance therapy (route of administration and drug choices) should be made in consultation with an ophthalmologist. Considerations should include the anatomic location of the retinal lesion, vision in the contralateral eye, the patients' immunologic and virologic status, and response to ART.
	• Duration: 21-42 days or until symptoms have resolved. • Maintenance therapy is usually not necessary but should be considered after relapses. *Well-Documented, Histologically Confirmed CMV Pneumonia:* • Experience for treating CMV pneumonitis in HIV patients is limited. Use of IV ganciclovir or IV foscarnet is reasonable (doses same as for CMV retinitis). • The optimal duration of therapy and the role of oral valganciclovir have not been established. • *CMV Neurologic Disease* • Note: Treatment should be initiated promptly. • Ganciclovir 5 mg/kg IV q12h + (foscarnet 90 mg/kg IV q12h or 60 mg/kg IV q8h) to stabilize disease and maximize response; continue until symptomatic improvement and resolution of neurologic symptoms. • The optimal duration of therapy and the role of oral valganciclovir have not been established.	• Foscarnet 90-120 mg/kg IV once daily, *or* • Cidofovir 5 mg/kg IV every other wk with saline hydration and probenecid as above. *CMV Esophagitis or Colitis:* • Foscarnet 90 mg/kg IV q12h or 60 mg/kg q8h for patients with treatment-limiting toxicities to ganciclovir or with ganciclovir resistance, *or* • Valganciclovir 900 mg PO q12h in milder disease and if able to tolerate PO therapy, *or* • For mild cases, if ART can be initiated without delay, consider withholding CMV therapy. • Duration: 21-42 days or until symptoms have resolved.	• Patients with CMV retinitis who discontinue maintenance therapy should undergo regular eye examinations for early detection of relapse IRU—optimally every 3 mo and then annually after immune reconstitution. • IRU may develop in the setting of immune reconstitution. • *Treatment of IRU:* • Periocular corticosteroid or short courses of systemic steroid. • Initial therapy in patients with CMV retinitis, esophagitis, colitis, and pneumonitis should include initiation or optimization of ART.
HSV disease	*Orolabial Lesions (for 5-10 days):* • Valacyclovir 1 g PO bid *or* • Famciclovir 500 mg PO bid *or* • Acyclovir 400 mg PO tid. *Initial or Recurrent Genital HSV (for 5-14 days):* • Valacyclovir 1 g PO bid, *or* • Famciclovir 500 mg PO bid, *or* • Acyclovir 400 mg PO tid. Severe Mucocutaneous HSV: • Initial therapy acyclovir 5 mg/kg IV q8h • After lesions begin to regress, change to PO therapy as previously. Continue until lesions are completely healed. • *Chronic Suppressive Therapy for Patients with Severe Recurrences of Genital Herpes or for Patients Who Want to Minimize Frequency of Recurrences:* • Valacyclovir 500 mg PO bid. • Famciclovir 500 mg PO bid. • Acyclovir 400 mg PO bid. • Continue indefinitely regardless of CD4 cell count.	*For Acyclovir-Resistant HSV* • *Preferred Therapy:* • Foscarnet 80-120 mg/kg/day IV in 2-3 divided doses until clinical response. • *Alternative Therapy* • IV cidofovir (dosage as in CMV retinitis), *or* • Topical trifluridine, *or* • Topical cidofovir, *or* • Topical imiquimod. • *Duration of Therapy:* • 21-28 days or longer.	• Patients with HSV infections can be treated with episodic therapy when symptomatic lesions occur, or with daily suppressive therapy to prevent recurrences. • Topical formulations of trifluridine and cidofovir are not commercially available. • Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir.

TABLE 2 Treatment of AIDS-Associated Opportunistic Infections—cont'd

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
VZV disease	*Primary Varicella Infection (Chickenpox):* • *Uncomplicated Cases (for 5-7 days):* • Valacyclovir 1 g PO tid *or* • Famciclovir 500 mg PO tid. • *Severe or Complicated Cases:* • Acyclovir 10-15 mg/kg IV q8h for 7-10 days. • May switch to oral valacyclovir, famciclovir, or acyclovir after defervescence if no evidence of visceral involvement. *Herpes Zoster (Shingles) Acute Localized Dermatomal:* • For 7-10 days; consider longer duration if lesions are slow to resolve. • Valacyclovir 1 g PO tid *or* • Famciclovir 500 mg tid. *Extensive Cutaneous Lesion or Visceral Involvement:* • Acyclovir 10-15 mg/kg IV q8h until clinical improvement is evident. • May switch to PO therapy (valacyclovir, famciclovir, or acyclovir) after clinical improvement (i.e., when no new vesicle formation or improvement of signs and symptoms of visceral VZV), to complete a 10- to 14-day course. *Progressive Outer Retinal Necrosis:* • Ganciclovir 5 mg/kg + foscarnet 90 mg/kg IV q12h + ganciclovir 2 mg/0.05 ml ± foscarnet 1.2 mg/0.05 ml intravitreal injection twice weekly *or* • Initiate or optimize ART. *Acute Retinal Necrosis:* • Acyclovir 10 mg/kg IV q8h for 10-14 days, followed by valacyclovir 1 g PO tid for 6 wk.	*Primary Varicella Infection (Chickenpox):* • *Uncomplicated Cases (for 5-7 days):* • Acyclovir 800 mg PO 5 times/day. *Herpes Zoster (Shingles)* • Acute Localized Dermatomal: • For 7-10 days; consider longer duration if lesions are slow to resolve. • Acyclovir 800 mg PO 5 times/day.	• In managing VZV retinitis: Consultation with an ophthalmologist experienced in management of VZV retinitis is strongly recommended. • Duration of therapy for VZV retinitis is not well defined and should be determined based on clinical, virologic, immunologic, and ophthalmologic responses. • Optimization of ART is recommended for serious and difficult-to-treat VZV infections (e.g., retinitis, encephalitis).
Progressive multifocal leukoencephalopathy (JC virus infections)	• There is no specific antiviral therapy for JC virus infection. The main treatment approach is to reverse the immunosuppression caused by HIV. • Initiate ART immediately in ART-naïve patients. • Optimize ART in patients who develop PML in phase of HIV viremia on ART.	None.	• Corticosteroids may be used for PML-IRIS characterized by contrast enhancement, edema, or mass effect and with clinical deterioration.

AIDS, Acquired immunodeficiency syndrome; *ART,* antiretroviral therapy; *ARV,* antiretroviral; bid, twice a day; *CD4,* CD4 T lymphocyte cell; *CFU,* colony-forming unit; *CMV,* cytomegalovirus; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *CYP3A4*, cytochrome P-450 3A4; *DS,* double strength; *EMB*, ethambutol; *G6PD*, glucose-6-phosphate dehydrogenase; *HIV,* human immunodeficiency virus; *HSV*, herpes simplex virus; *ICU*, intensive care unit; *IM*, intramuscular; *INH*, isoniazid; *IRIS*, immune reconstitution inflammatory syndrome; *IRU,* immune recovery uveitis; *IV*, intravenous; *LP*, lumbar puncture; *MAC, Mycobacterium avium* complex; *NSAID*, nonsteroidal anti-inflammatory drugs; *PCP*, *Pneumocystis* pneumonia; *PI*, protease inhibitor; *PJP,* Pneumocystis jiroveci pneumonia; *PML*, progressive multifocal leukoencephalopathy; *PO*, oral; *PZA*, pyrazinamide; *qid*, four times a day; *RFB*, rifabutin; *RIF*, rifampin; *SS*, single strength; *TB,* tuberculosis; *tid*, three times daily; *tiw*, three times weekly; *TMP-SMX*, trimethoprim-sulfamethoxazole; *VZV*, varicella zoster virus. *Quality of Evidence for the Recommendation:*

I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints

II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes

III: Expert opinion

*Pyrimethamine and leucovorin doses are the same as for preferred therapy.

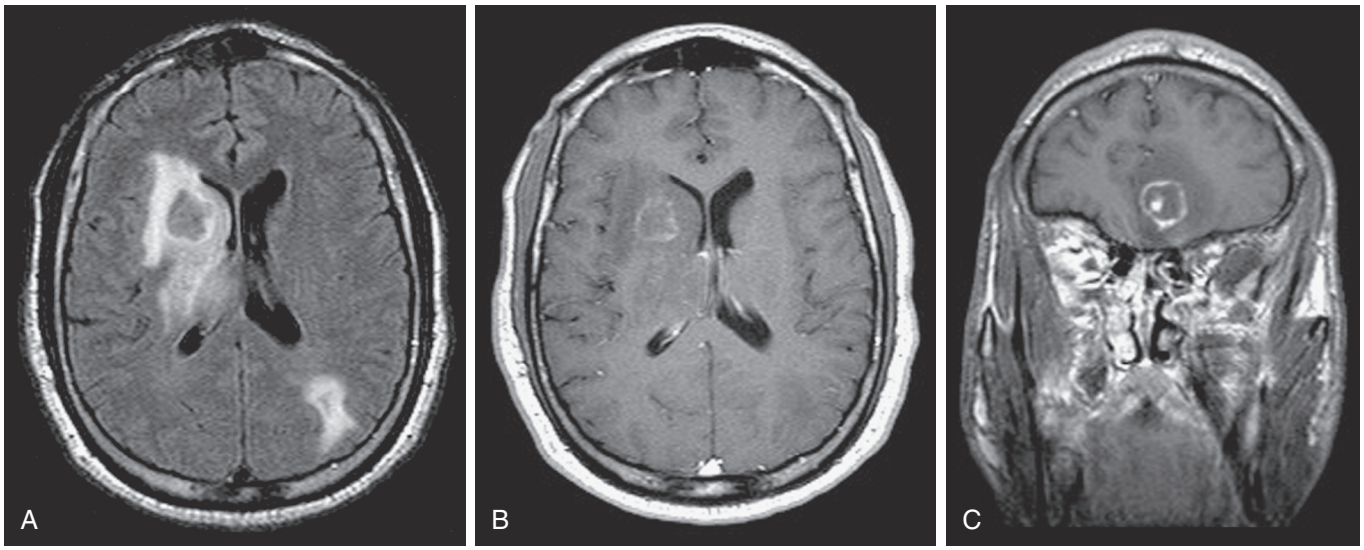

FIG. E1 Toxoplasmosis. A, A fluid-attenuated inversion recovery image shows isointense lesions in the right basal ganglia and left parietal lobe with surrounding edema. **B,** A postgadolinium T1-weighted image shows faint rim enhancement of right basal ganglia lesion. **C,** A postgadolinium T1-weighted image shows a typical "target" sign in a left frontal lobe lesion. (From Soto JA, Lucey BC: *Emergency radiology: the requisites,* ed 2, Philadelphia, 2017, Elsevier.)

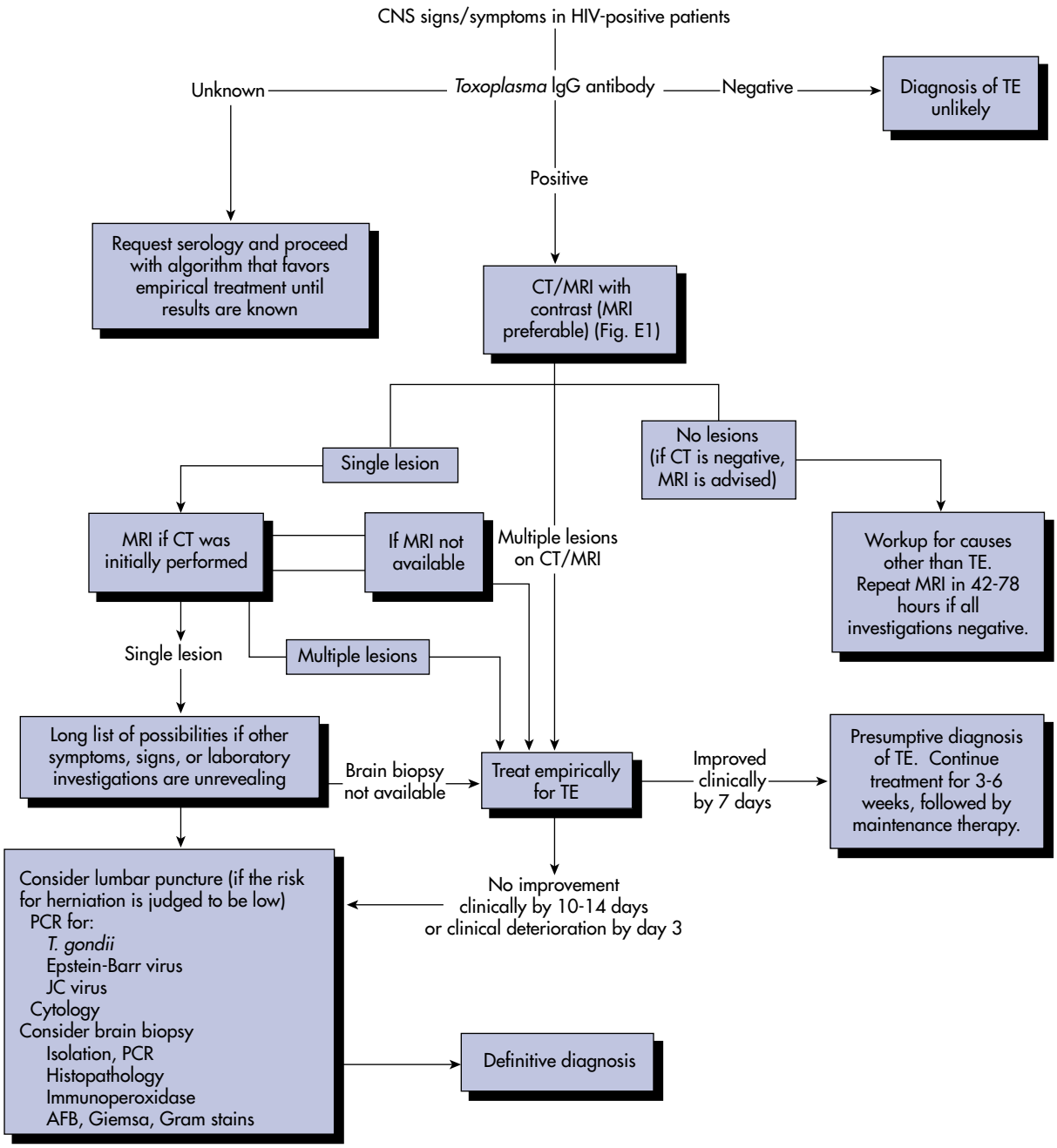

FIG. E2 Diagnostic approach and management algorithm for human immunodeficiency virus *(HIV)*–infected patients with central nervous system *(CNS)* symptoms or signs that might potentially be toxoplasmic encephalitis *(TE)*. *AFB*, Acid-fast bacilli; *CT*, computed tomography; *IgG*, immunoglobulin G; *MRI*, magnetic resonance imaging; *PCR*, polymerase chain reaction. (From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.)

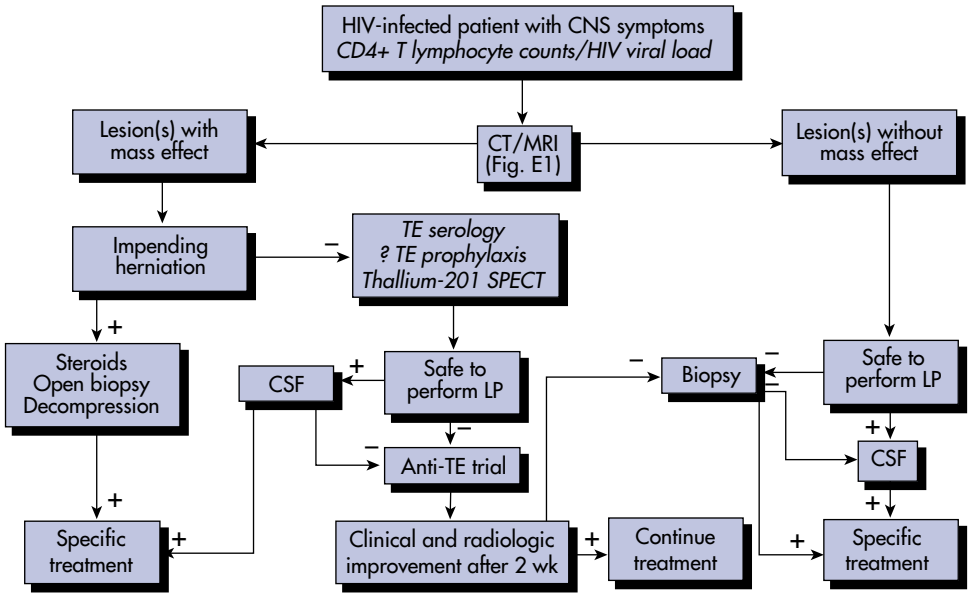

FIG. E3 Management of the human immunodeficiency virus *(HIV)* type 1–infected patient with central nervous system *(CNS)* mass lesions. The elements in italics represent data that contribute to the decision-making process (see text for details). *CSF*, Cerebrospinal fluid; *CT*, computed tomography; *LP*, lumbar puncture; *MRI*, magnetic resonance imaging; *SPECT*, single-photon emission computed tomography; *TE*, *Toxoplasma* encephalitis. (From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.)

BASIC INFORMATION

DEFINITION

Acromegaly occurs due to hypersecretion of growth hormone (GH) or increased amounts of insulin-like growth factor I (IGF-I). It is a chronic debilitating disease with an insidious onset.

SYNONYM

Marie disease

ICD-10CM CODE
E22.0 Acromegaly and pituitary gigantism

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 3 to 4 new cases per 1 million persons annually
PREVALENCE: 50 to 60 cases per 1 million persons, with some estimates as high as 90 cases per 1 million persons
PREDOMINANT SEX: No sexual predominance
MEAN AGE AT DIAGNOSIS: Men: 40 yr; women: 45 yr
RISK FACTORS:

- Increased mortality rate, primarily from cardiovascular and respiratory causes
- Death in 50% of untreated patients by age 50 yr
- Increased prevalence of colon carcinoma and other malignancies (esophagus, stomach, melanoma, thyroid)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Coarse features resulting from growth of soft tissue
- Coarse, oily skin
- Macrocephaly
- Hands and feet that are spadelike (Fig. E1), fleshy, and moist
- Prognathism, which can give an underbite
- Carpal tunnel syndrome
- Excessive sweating
- Arthralgias and severe osteoarthritis
- History of increased hat, glove, and/or shoe size. Epiphyseal growth plates require sex hormones to close; therefore, prior to puberty, these patients will develop excessive longitudinal growth and gigantism
- Enlargement of nose, brow, and jaw (Fig. E2)
- Hypertension
- Muscle weakness and decreased exercise capacity
- Headache, often severe
- Diabetes mellitus
- Visual field defects
- Severe obstructive sleep apnea due to soft tissue swelling and macroglossia
- Cardiac abnormalities (cardiomyopathy, left ventricular hypertrophy, valvular heart disease, diastolic failure, arrhythmias)
- Tall stature
- Mild to moderate obesity
- Benign tumors (uterine myoma, skin tags, prostatic hypertrophy, colon polyps)

ETIOLOGY

Cause is usually a pituitary adenoma affecting the anterior lobe. In rare cases, extrapituitary production of either GH or GH-releasing hormone (GHRH) can also lead to clinical manifestations.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Ectopic production of GHRH from a carcinoid or other neuroendocrine tumor

- McCune-Albright syndrome
- Pachydermoperiostosis

WORKUP

- First screening test: Measure serum IGF-I level.
  1. Direct measurement of the GH level is not as useful because it is secreted in a pulsatile fashion and a random level may be falsely normal.
  2. Upper limits of a normal IGF-I level, depending on the assay: >380 ng/ml or 2.5 U/ml.
- Failure to suppress serum GH to less than 2 ng/ml after 100 g oral glucose is considered conclusive.
  1. Patients may show suppression of GH (paradoxic response).
  2. Patients will not suppress GH to ≤2 ng/ml (typical response in patients with acromegaly).
  3. GHRH level >300 ng/ml is indicative of an ectopic source of GHRH such as from carcinoid tumors of the pancreas or lung.

LABORATORY TESTS

- Elevated IGF-I level
- Elevated serum phosphate
- Elevated urine calcium

IMAGING STUDIES

- Imaging studies of choice: MRI of the pituitary and hypothalamus

FIG. E1 Acromegaly. Patient with acromegaly of hand on the left compared with normal-sized hand on the right. (James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

FIG. E2 Facial features of acromegaly with enlargement of brow, nose, and jaw. (Floege J, Johnson RJ, Feehally J [eds]: *Comprehensive clinical nephrology,* ed 4, 2010, Saunders.)

- CT of the pituitary and hypothalamus sometimes used initially

Rx TREATMENT

SURGERY

- Treatment of choice: Transsphenoidal microsurgical adenomectomy
- Surgical failure rate: Approximately 13.3% for microadenomas (tumors <10 mm) and 11.1% for macroadenomas (tumors ≥10 mm confined to the sella)
- Preoperative IGF-I level: Indicator of surgical outcome with higher levels associated with surgical failure

RADIOTHERAPY

- Stereotactic radiosurgery (gamma knife) can be used to increase the chance of remission or cure.
- Radiotherapy is usually reserved for tumor recurrence or persistence after surgery in patients with resistance to or intolerance of medical treatment.
- Major complication: Hypopituitarism, which may occur in up to 50% of patients; this complication is more likely in patients who had postoperative radiotherapy.

MEDICAL THERAPY

- Indicated when patients have not responded to surgical therapy (persistent elevation of IGF-1, abnormal glucose tolerance test), when surgery is contraindicated, and in patients waiting for the effects of radiotherapy to begin
- Somatostatin receptor ligands: Octreotide, lanreotide
  1. Important in the preoperative shrinkage of pituitary tumors and softening of adenomatous tissue.
  2. Pegvisomant is a GH receptor antagonist that has shown promising results in the treatment of acromegaly. It is generally used in patients with resistance to or intolerance of somatostatin analogs. It should be used in patients who do not have central compressive symptoms and those with resistant diabetes.
  3. Somatostatin agonist therapy has been shown to be effective as first-line medical therapy in reducing tumor volume. Dopamine receptor agonists (bromocriptine, cabergoline): Can be used in addition to somatostatin receptor ligands.

CHRONIC Rx

Combination of bromocriptine and octreotide may be synergistic, allowing a lower combination dosage than either alone.

DISPOSITION

- Patients receiving radiotherapy need long-term follow-up to monitor the potential development of hypopituitarism.
- Continuation of medical therapy should be based on the normalization of IGF-I levels.

RELATED CONTENT

Pituitary Adenoma (Related Key Topic)
Acromegaly (Patient Information)

AUTHORS: **Yaneve Fonge, MD,** and **Rachel Wright Heinle, MD, FACOG**

Actinic Keratosis

BASIC INFORMATION

DEFINITION

Actinic keratoses (AKs) are common skin lesions usually presenting as multiple erythematous or yellow-brown, dry, scaly lesions in the middle aged or elderly.

SYNONYMS

Solar keratosis
Senile keratosis
AK

ICD-10CM CODE
L57.0 Actinic keratosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: In regions of the northern hemisphere, 11% to 25% of adults have a minimum of one AK. In regions closer to the equator, 40% to 60% of adults have a minimum of one AK.
PEAK INCIDENCE: The risk of squamous cell carcinoma in patients with AK is 6% to 10%. Risk factors associated with increased risk of invasive squamous cell carcinoma arising from actinic keratosis include lesion location (lip, ear, extremities), lesion characteristics (ulceration, induration, hyperkeratotic, proliferative, inflamed, bleeding, large surface area and depth), pigmentation (any rapid changes in presentation, presence of multiple lesions, evidence of greater ultraviolet [UV]-induced skin damage), presence of concomitant illness (lymphoma, leukemia), and use of concomitant medications (immunosuppressive agents, medications that increase sun sensitivity).[1]
PREVALENCE:
- In the United States, 58.08 million/yr.
- Highest prevalence in those with fair complexions with high sun exposure.
- Approximately 60% of predisposed individuals older than 40 yr will have one AK.
- Caucasians' risk increases with age: At age 20 to 29 prevalence is <10%, at age 80 to 89 prevalence is approximately 75%.

PREDOMINANT SEX AND AGE: Males > females, age 65 to 74. Occurs most in those with fair complexions who burn rather than tan following sun exposure.
GENETICS: There is increased frequency of nonmelanoma skin cancers connected to squamous cell cancers with the genetic conditions xeroderma pigmentosum, oculocutaneous albinism, epidermodysplasia verruciformis, dystrophic epidermolysis bullosa, Ferguson-Smith syndrome, and Muir-Torre syndrome.
RISK FACTORS:
- Immunosuppression, exposure to UV light, ionizing radiation, arsenic, human papillomavirus, cigarette smoke, chronic ulcers, thermal burns, chronic discoid lupus erythematosus, and nonhealing wounds
- Lichen planus, lichen sclerosis, linear and classic porokeratosis, and disseminated superficial actinic porokeratosis
- Age, gender, skin color, and mutations in p53 tumor suppressor gene

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typical lesions occur on sun-damaged skin, usually on the face and neck and the dorsal aspects of hands and forearms (Fig. E1).
- Advanced lesions are characterized by a hard, spiky scale and usually measure 1 cm in diameter or less. Early lesions manifest with redness and minimal scale. With progression, scales become thicker and yellow and may resemble a small squamous cell carcinoma. On examinations, lesions are rough and gritty.
- The surrounding skin frequently shows additional features of sun damage, including atrophy, pigment changes, and telangiectasia.
- Classifications:
  1. Hypertrophic AK with a cutaneous horn: Biopsy is necessary to distinguish the cutaneous horn from squamous cell carcinoma, seborrheic keratosis, verruca, and trichilemmoma and basal cell carcinoma. Hypertrophic AK has appearance of thick, scaling skin elevations.
  2. Lichenoid AK: Most commonly found on the torso and upper extremities. Must be distinguished from BCC due to pink and pearly characteristics.
  3. Proliferative AK: Often reappear after treatment and are characterized by a diameter >1 cm. Often occurs in same differential as Bowen's disease or SCC.
  4. Spreading pigmented AK: Must be biopsied to distinguish from lentigo maligna–type melanoma in situ as well as solar lentigo.
  5. Actinic cheilitis: Characterized by red and sometimes abrasive lesions around the border of the lips and skin.

ETIOLOGY

- Sun exposure, ionizing radiation
- Arsenic, polycyclic hydrocarbon exposure

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Heavily pigmented variants may be clinically mistaken for lentigo maligna
- Basal cell or squamous cell carcinoma
- Seborrheic keratosis
- Eczema
- Bowen disease (intraepithelial carcinoma)
- Wart
- Lichenoid keratosis
- Cutaneous lupus

WORKUP

History, physical, and lesion biopsy. Include risk assessment and family or personal history of skin cancers or previous skin lesions.

LABORATORY TESTS

- Skin biopsy in recurrent lesions or when diagnosis is unclear to rule out squamous cell or basal cell carcinoma.
- Microscopy reveals atypical keratinocytes in the lower epidermis basal layers. They are enlarged and often lack normal polarity. The thickness of the epidermis can be compromised with a distribution of atrophic to hyperplastic. Abnormal keratinocytes can cause parakeratosis of the overlying stratum corneum. Visible signs of an alternating orthohyperkeratosis can overlie the spared epithelium, causing the signature "flag sign." Additionally, there is a distinct margin between normal epidermis and the region of AK at lateral edges. Histologic subtypes are hypertrophic, acantholytic, lichenoid, and bowenoid, which are characterized by a thick stratum corneum, lack of intracellular cohesion, presence of lymphocytic infiltrate in papillary dermis, and either lack of association of adnexal epithelium or full epithelial thickness with pleomorphic keratinocytes, respectively.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cryotherapy with liquid nitrogen: Treatment of choice for most isolated, superficial AKs
- Carbon dioxide laser
- Dermabrasion
- Chemical peel
- Curettage
- Excision
- Photodynamic therapy with 5-aminolevulinic acid and blue light (16 minutes) or methyl aminolevulinate and red light (7 to 10 minutes)

ACUTE GENERAL Rx

- Topical 5-fluorouracil (5-FU) bid for 4 to 6 weeks. Table E1 summarizes guidelines for duration of 5-FU therapy according to site.
- Topical diclofenac sodium 3% gel bid for 60 to 90 days.
- Topical imiquimod 5% cream bid for 3 to 4 months.
- Oral retinoids.
- Topical ingenol mebutate 0.05% gel applied for 2 days with exception of face—or 0.015% for 3 days. Combination medication therapy or nonpharmacologic therapy with pharmacologic therapy is common (especially in refractory AK).
- A 10% nanoemulsion gel formulation of the porphyrin-based photosensitizers aminolevulinic acid (Ameluz) is available for use in combination with a narrow-band red light photodynamic therapy (PDT) lamp (BF-RhodoLED) for mild to moderate severity AK on face and scalp.
- Table E2 describes preparations for treatment of actinic keratosis.

[1]Rigel DS, Stein Goold LF: The importance of early diagnosis and treatment of actinic keratosis. *J Am Acad Dermatol* 68:S20-27, 2013.

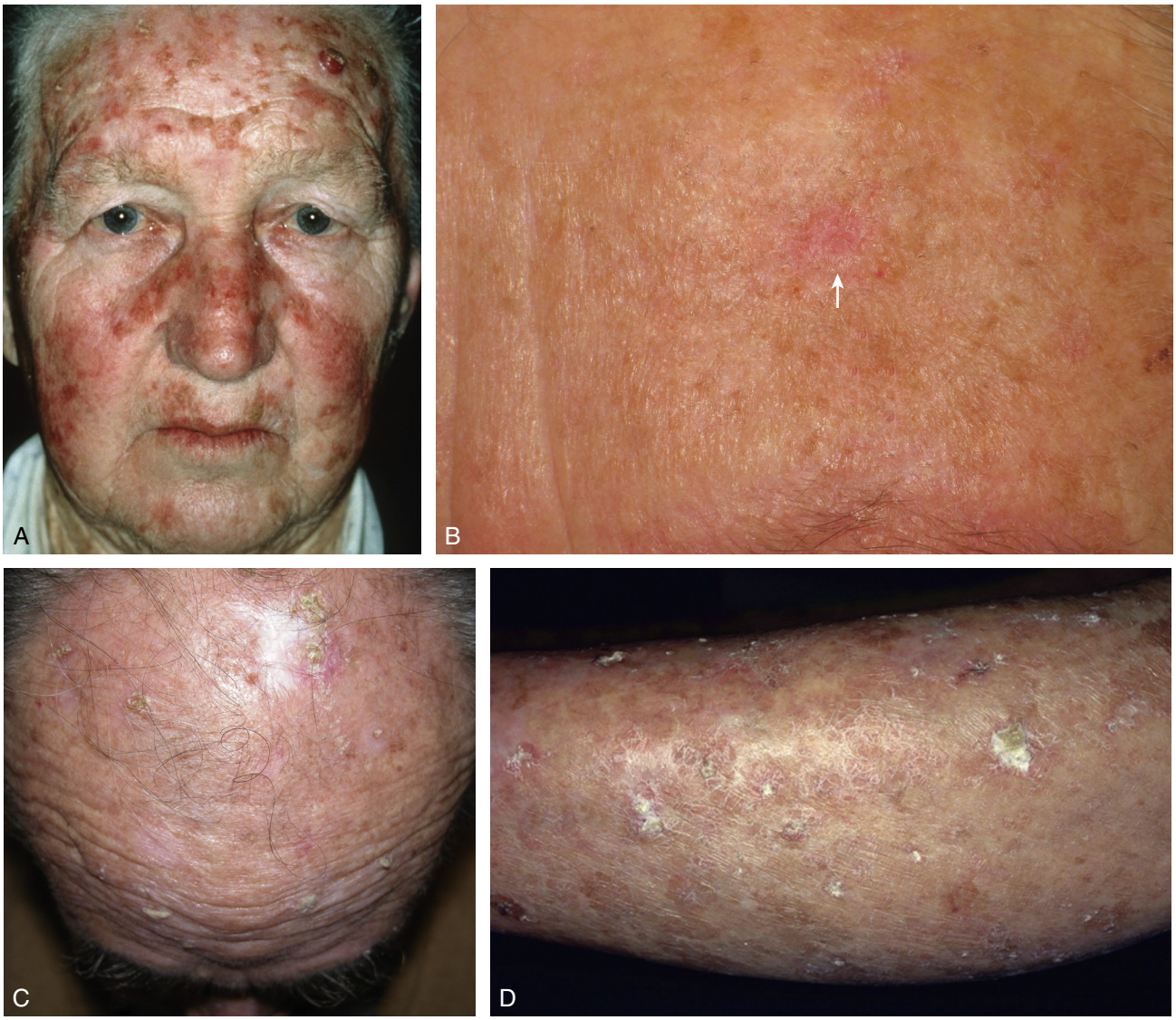

FIG. E1 Actinic keratosis (AKs). A, Multiple AKs on the face of an elderly woman with fair complexion, blue eyes, and moderate to severe photodamage; the AKs vary in size from a few millimeters to more than a centimeter. On the left forehead, the red nodule with slight scale-crust represents a well-differentiated SCC. **B,** Pink-colored atrophic AK with minimal scale on the forehead. **C,** Multiple AKs on the bald scalp, some of which are hyperkeratotic; the area of hypopigmentation represents a site of previous treatment and due to the field defect, recurrence at the edge is commonly observed. **D,** Multiple, large hypertrophic AKs on the skin of an elderly woman; note the thick scale. (From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier. **B,** Courtesy, Iris Zalaudek, MD; **D,** Courtesy, Jean L Bolognia, MD.)

TABLE E1 Guidelines for Duration of 5-Fluorouracil Therapy According to Site

Site	Early Signs of Inflammation (days)	Duration of Treatment (weeks)
Face, lips	3-5	2-4
Scalp	4-7	3-5
Neck	4-7	2-4
Arms, hands, legs	10-14	4-8
Back	10-14	4-6
Chest	10-14	4-6

From Habif TP: *Clinical dermatology,* ed 6, Philadelphia, 2016, Elsevier.

TABLE E2 Preparations for Treatment of Actinic Keratosis

Product	Active Ingredient	Packaging
Carac	0.5% fluorouracil	30-g cream
Efudex	2% fluorouracil 5% fluorouracil 5% fluorouracil	10-ml liquid 10-ml liquid 25-g cream
Fluoroplex	1% fluorouracil 1% fluorouracil	30-ml solution, 30-g cream
Aldara	5% imiquimod	Cream—box of 12 or 24 packets
Zyclara	2.5%, 3.75% imiquimod	Cream—box of 28 packets, 7.5- and 15-g pump bottle

From Habif TP: *Clinical dermatology,* ed 6, Philadelphia, 2016, Elsevier.

REFERRAL

To a dermatologist for biopsy of suspicious lesions, then follow up minimum annually or semiannually

PEARLS & CONSIDERATIONS

COMMENTS

- AKs are of particular importance because they are a sensitive indicator of exposure to UV light and strongly predict the likelihood of developing cutaneous squamous cell carcinoma.
- The cumulative probability of development of invasive squamous cell carcinoma in patients with 10 or more AKs has been estimated at 14% in a 5-yr period.
- It is estimated that up to 10% of AKs tend to progress to invasive carcinoma. Factors associated with increased risk of invasive squamous cell carcinoma include presence of multiple lesions, large surface area and depth, hyperkeratotic proliferative lesions, location on lip, ear, and extremities and concomitant illness (leukemia, lymphoma), and use of immunosuppressive agents and agents that increase sun sensitivity.

PREVENTION

- Avoidance of sun exposure or tanning booths
- Use of sunscreens
- Routine self-skin examinations
- Pharmaceutical prevention:
  1. Mild to moderate reduction of AK formation has been documented with the use of topical tretinoin, isotretinoin, and arotinoid methylsulfonyl.
  2. Nicotinamide as preventive rx has been documented to have a possible 30% relative reduction in AK.
  3. Decreased AK development has been documented with the use of high-SPF sunscreens.
  4. Decreased AK development has been seen in patients with xeroderma pigmentosum who used DNA repair enzymes.
  5. Decreased AK formation has been documented in high-risk patients (specifically those with xeroderma pigmentosum, nevoid basal cell carcinoma syndrome, and organ transplantation recipients) with the use of oral retinoids.

SUGGESTED READING

Jansen MHE et al: Randomized trial of four treatment approaches for actinic keratosis, *N Engl J Med* 380:935-946, 2019.

Uhlenhake E: Optimal treatment of actinic keratosis, *Clin Interv Aging* 8:29-35, 2013.

AUTHORS: **Fred F. Ferri, MD,** and **Heather Ferri, DO**

BASIC INFORMATION

DEFINITION

Actinomycosis is an indolent, slowly progressive infection caused by anaerobic or microaerophilic bacteria, mostly from the genus *Actinomyces,* that normally colonize the mouth, vagina, and colon. Actinomycosis is characterized by the formation of painful abscesses, soft tissue infiltration, and draining sinuses.

SYNONYMS

Actinomyces infection
Lumpy jaw

ICD-10CM CODES

A42.9	Actinomycosis, unspecified
A42.0	Pulmonary actinomycosis
A42.1	Abdominal actinomycosis
A42.2	Cervicofacial actinomycosis
A42.89	Other forms of actinomycosis

EPIDEMIOLOGY & DEMOGRAPHICS

GEOGRAPHIC DISTRIBUTION:

- Actinomycosis infections are seen worldwide.
- Commonly found as normal flora of the oral cavity (within gingival crevices, tonsillar crypts, periodontal pockets, dental plaques, and carious teeth), pharynx, tracheobronchial tree, gastrointestinal tract, and female urogenital tract. However, actinomyces are not found in the environment.

INCIDENCE:

- 1:300,000 in 1970s but now less with better oral hygiene and antibiotic use
- Males infected more often than females (3:1)
- Can occur at any age but commonly seen in midlife

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Actinomycosis can affect any organ. Although not typically considered as opportunistic pathogens, *Actinomyces* species capitalize on tissue injury or mucosal breach to invade adjacent structures in the head and neck regions. As a result, dental infections and oromaxillofacial trauma are common antecedent events. Characteristic manifestations include:

- Cervicofacial disease (most common site with 60% of cases):
  1. Occurs in the setting of poor dental hygiene, recent dental surgery, or minor oral trauma.
  2. Painful soft tissue swelling (Fig. E1) commonly seen at the angle of the mandible.
  3. Fever, chills, and weight loss.
  4. Trismus.
  5. Soft tissue facial infection with sinus tract or fistula formation.
- Thoracic disease:
  1. Can involve the lungs, pleura, mediastinum, or chest wall.
  2. Presumed secondary to aspiration of *Actinomyces* organisms in patients with poor oral hygiene.
  3. Fever, cough, weight loss, and pleuritic chest pains are common symptoms.
  4. Signs of pneumonia or pleural effusion may be present.
  5. With extension beyond the lungs to mediastinal structures and the chest wall, signs and symptoms of pericarditis, empyema, chest wall sinus drainage, and tracheoesophageal fistula can all occur (Fig. E2).
- Abdominal disease:
  1. Occurs most commonly after appendectomy, perforated bowel, diverticulitis, or surgery to the gastrointestinal tract.
  2. Lesions develop most commonly in the ileocecal valve, causing abdominal pain, fever, weight loss, and a palpable mass.
  3. Extension may occur to the liver, causing jaundice and abscess formation.
  4. Sinus tracts to the abdominal wall can occur.
- Pelvic disease:
  1. Commonly occurs by extension from abdominal disease of the ileocecal valve to the right adnexa (80% of cases).
  2. Endometritis.

ETIOLOGY

- Actinomycosis is most commonly caused by *Actinomyces israelii.* Other causes are *A. naeslundii, A. odontolyticus, A. viscosus,* and *A. meyeri.*
- *Actinomyces* are gram-positive, non–spore-forming, filamentous, anaerobic or microaerophilic rods.
- Actinomycosis infections are polymicrobial, usually associated with *Eikenella corrodens,* and *Streptococcus, Bacteroides, Enterococcus,* and *Fusobacterium* spp.

FIG. E1 Actinomycosis of the jaw, observed at Letterman General Hospital, San Francisco, in a sergeant who had punctured the floor of his mouth while picking his teeth. (Office of Medical History, Office of the Surgeon General, U.S. Army; from Goldman L, Schaefer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

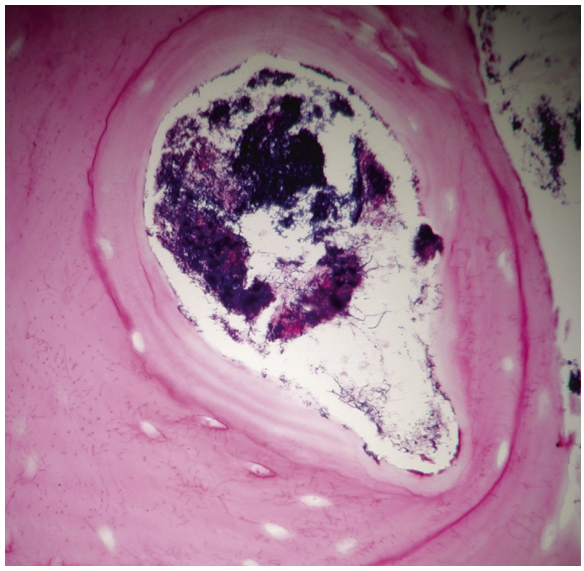

FIG. E2 Maxillary osteomyelitis due to *Actinomyces viscosus* in a patient with multiple myeloma who was treated with bisphosphonates and underwent several dental procedures. Pictured is a sulfur granule within necrotic maxilla. (From Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 8, Philadelphia, 2015, Saunders.)

- Infects individuals only after entry into disrupted mucosa or tissue injury.
- Predisposing conditions include diabetes mellitus, malnutrition, and immunosuppression.

Dx DIAGNOSIS

Isolating the bacteria in the proper clinical setting makes the diagnosis of actinomycosis.

DIFFERENTIAL DIAGNOSIS

- Cervicofacial disease: Odontogenic abscesses, brachial cleft cyst
- Pulmonary disease: Nocardiosis, botryomycosis, chromomycosis, fungal disease of the lung, tuberculosis
- Intestinal disease: Intestinal tuberculosis, ameboma, Crohn disease, colon cancer
- Pelvic disease: Chronic pelvic inflammatory disease, Crohn disease
- CNS disease: Other forms of brain abscess, brain tumors, toxoplasmosis, intracranial hematoma

WORKUP

The workup includes obtaining specimens either by aspirating abscesses, excising sinus tracts, or tissue biopsies. All specimens should be set up to culture anaerobic bacteria and held at least 5 to 7 days.

LABORATORY TESTS

- Isolating "sulfur granules" from tissue specimens or draining sinuses confirms the diagnosis of actinomycosis. *Actinomyces* are noted for forming characteristic sulfur granules in infected tissue but not in vitro. The term *sulfur granule* is a misnomer, reflecting only the yellow color of the granule in pus, because the granules are not composed of any sulfur at all.
  1. Sulfur granules are nests of *Actinomyces* species. Sulfur granules may be macroscopic or microscopic.
  2. Sulfur granules are crushed and stained for identification of *Actinomyces* organisms and may take up to 3 wk to grow in culture media.

IMAGING STUDIES

Imaging studies are useful adjunctive tests in localizing the site and spread of infection.

- Chest x-ray examination.
- CT scan of the head, chest, abdomen, and pelvic areas is useful.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Incision and drainage of abscesses
- Excision of sinus tract

ACUTE GENERAL Rx

- Ampicillin 50 mg/kg/day in 3 to 4 divided doses x 4 to 6 wk; then Pen VK 2 to 4 g/day PO x 4 to 6 wk. In place of ampicillin, can also use penicillin 3 to 4 million units IV q4h for 4 to 6 wk.
- In penicillin-allergic patients, erythromycin (500 to 1000 mg IV q6h), tetracycline or doxycycline (100 mg IV q12h), and clindamycin (900 mg IV q8h) are reasonable alternatives. Other alternatives include ceftriaxone, imipenem, and piperacillin/tazobactam.
- Avoid use of metronidazole, aminoglycosides, oxacillin, and cephalexin.

CHRONIC Rx

- After 4 to 6 wk IV ampicillin (2 g IV q 4 to 6 hr) or penicillin (10 to 20 million units per day divided q 4 to 6 hr), can switch to oral penicillin V 500 mg PO qid for 4 to 6 wk. Longer treatment with 6 to 12 months of antibiotic therapy is often necessary in some cases.
- Other available oral agents are erythromycin, doxycycline, and clindamycin.
- Treatment of associated microorganisms is not needed.
- Surgical debridement for complicated abscesses, fibrous tracts, necrotic tissues, fistulas, and bone involvement may also be required.

DISPOSITION

- Clinical actinomycosis, if not treated, spreads to contiguous tissues and structures ignoring tissue planes. Hematogenous spread, although possible, is rare.
- Actinomycosis is very sensitive to antibiotics but requires chronic long-term treatment to prevent relapse.

REFERRAL

If the diagnosis of actinomycosis is suspected, consultation with an infectious disease specialist is suggested. General surgical consultation for excision of sinus tracts and abscess incision and drainage is recommended.

! PEARLS & CONSIDERATIONS

COMMENTS

- There is no person-to-person transmission of *Actinomyces.*
- Isolation of the organism in an asymptomatic individual does not mean the person has actinomycosis. Active symptoms must be present to make the diagnosis.
- Pelvic actinomycosis has been associated with use of an intrauterine device (IUD).
- Actinomycosis can also involve the CNS, causing multiple brain abscesses.
- HIV, solid organ transplantation of lungs or kidneys, biologic agents like infliximab, and acute lymphoblastic leukemia treated with chemotherapy are other risk factors.

SUGGESTED READING

Bonnefond S et al: Clinical features of actinomycosis: a retrospective, multicenter study of 28 cases of miscellaneous presentations, *Medicine (Baltimore)* 95(24):e3923, 2016.

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Kononen E, Wade WG: Actinomycosis and related organisms in human infections, *Clin Microbiol Rev* 28:419-442, 2015.

Valour F et al: Actinomycosis: etiology, clinical features, diagnosis, treatment and management, *Infect Drug Resist* 7:183-197, 2014.

AUTHOR: **Glenn G. Fort, MD, MPH**

Acute Bronchitis PTG

BASIC INFORMATION

DEFINITION

Acute bronchitis is a self-limited inflammation of trachea and bronchi.

SYNONYM

Chest cold

ICD-10CM CODE
J20.9 Acute bronchitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Highest incidence in smokers, older adults, and young children and during winter months.
- In the U.S. there are nearly 30 million ambulatory visits annually for cough, leading to more than 12 million diagnoses of "bronchitis."
- Acute lower respiratory tract infection is the most common condition treated in primary care.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- In most cases, acute bronchitis begins with signs and symptoms typical of the common cold syndrome (nasal congestion, sore throat), followed shortly by the onset of cough
- Cough, usually worse in the morning, often productive; mainly caused by transient bronchial hyperresponsiveness
- Low-grade fever
- Substernal discomfort worsened by coughing
- Postnasal drip, pharyngeal injection
- Rhonchi that may clear after cough, occasional wheezing
- Various host factors (age, immune status, smoking, underlying medical conditions) can influence illness severity and clinical presentation
- In mild cases, the illness lasts only 7 to 10 days, whereas in others, cough may persist for up to 3 weeks or longer

ETIOLOGY

- Viral infections are the leading cause of bronchitis (rhinovirus, influenza virus, adenovirus, respiratory syncytial virus)
- Atypical organisms *(Mycoplasma, Chlamydia pneumoniae)*
- Bacterial infections *(Bordetella pertussis, Haemophilus influenzae, Moraxella, Streptococcus pneumoniae)*
- Table 1 summarizes viral and bacterial causes of acute bronchitis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pneumonia
- Asthma
- Sinusitis
- Bronchiolitis
- Aspiration
- Cystic fibrosis
- Pharyngitis
- Cough secondary to medications
- Neoplasm (elderly patients)
- Influenza
- Allergic aspergillosis
- Gastroesophageal reflux disease
- Congestive heart failure (in elderly patients)
- Bronchogenic neoplasm

WORKUP

Seldom necessary (e.g., to rule out pneumonia, neoplasm)

LABORATORY TESTS

Laboratory tests are generally not necessary.

IMAGING STUDIES

Chest x-ray is usually reserved for patients with suspected pneumonia, influenza, or underlying chronic obstructive pulmonary disease (COPD) and no improvement with therapy.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of tobacco and other pulmonary irritants
- Increased fluid intake
- Use of vaporizer to increase room humidity

TABLE 1 Viral and Bacterial Causes of Acute Bronchitis

Pathogen	Seasonality	Comments
Influenza viruses	Winter	Local epidemics last 6-8 wk during which clinical illness of cough and fever has high predictive value; laboratory diagnosis readily available; early neuraminidase inhibitor therapy effective
Rhinoviruses	Fall and spring	Most frequent cause of common cold syndrome; immunity is serotype specific
Coronaviruses	Winter to spring	Cause common cold syndrome; newer strains are difficult to culture and require RT-PCR for diagnosis
Adenoviruses	Yr round, winter epidemics	High attack rates in closed populations such as persons living in military barracks or college dormitories; serotype-specific immunity
Respiratory syncytial virus (RSV)	Late fall to early spring	Attack rates approach 75% in neonates, 3%-5% in adults; associated with wheezing in all age groups; rapid antigen test accurate in children but requires culture or RT-PCR to diagnose in adults
Human metapneumovirus (hMPV)	Winter to early spring	Associated with wheezing in adults and in infants; difficult to isolate in tissue culture and often requires RT-PCR
Parainfluenza viruses	Fall to winter	Similar to RSV and hMPV, parainfluenza viruses primarily pediatric pathogens but can cause severe acute disease in some adults
Measles virus	Yr round	Can cause respiratory disease in malnourished children; illness causes transient immune suppression
Mycoplasma pneumoniae	Yr round, fall outbreaks	Long incubation period (10-21 days) results in staggered epidemic pattern in families; nonproductive persistent cough typical; diagnosed by IgM serology; treated with macrolide, quinolone, or tetracycline antibiotics
Chlamydia pneumoniae	Yr round	Associated with sinusitis; diagnosis by RT-PCR not readily available
Bordetella pertussis	Yr round	Severe illness in nonimmunized children; illness milder in partially immune adults; can be associated with prolonged cough; adults often reservoir for epidemics; early therapy with antibiotics can reduce spread

RT-PCR, Reverse-transcriptase polymerase chain reaction.
From Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.

ACUTE GENERAL Rx

- Therapy is generally symptomatic and directed at relief of cough and wheezing.
- Inhaled bronchodilators (e.g., albuterol, metaproterenol) PRN for 1 to 2 wk in patients with wheezing or troublesome cough. Inhaled albuterol has been proven effective in reducing the duration of cough in adults with uncomplicated acute bronchitis.
- Cough suppression with dextromethorphan and guaifenesin is commonly recommended; addition of codeine for cough suppression if cough is severe and is significantly interrupting patient's sleep pattern.
- Use of antibiotics (TMP-SMX, amoxicillin, doxycycline, cefuroxime) for acute bronchitis is generally not indicated; should be considered only in patients with concomitant COPD and purulent sputum or in patients with suspected pertussis. In the few cases of acute bronchitis caused by *B. pertussis* or atypical bacteria such as *C. pneumoniae* or *Mycoplasma pneumoniae,* early use of macrolide antibiotics is reasonable.
- Antibiotics are overused in patients with acute bronchitis (70% to 90% of office visits for acute bronchitis result in treatment with antibiotics); this practice pattern is contributing to increases in resistant organisms.
- Trials have shown that there are no significant differences in patients receiving antibiotics compared with those receiving placebo in overall clinical improvements or limitations in work or other activities. There was a significant increase in adverse effects in the antibiotic group, particularly gastrointestinal symptoms.[1]

CHRONIC Rx

Avoidance of tobacco and other pulmonary irritants

DISPOSITION

- Complete recovery within 7 to 10 days in most patients.
- Patients should be informed to expect to have a cough for 10 to 14 days after the visit.

REFERRAL

For pulmonary function testing only in patients with recurrent bronchitis and suspected underlying pulmonary disease

PEARLS & CONSIDERATIONS

COMMENTS

- Patients are more likely to receive prescriptions for antibiotics from mid- or late-career physicians with high patient volumes and from physicians who were trained outside of Canada or the U.S.[2] Intervention studies reveal that patient and physician education are effective in reducing the use of antibiotic therapy. No offer or delayed offer of antibiotics for acute uncomplicated lower respiratory tract infection is acceptable, is associated with little difference in symptom resolution, and is likely to reduce antibiotic use and beliefs in the effectiveness of antibiotics.
- It is helpful to refer to acute bronchitis as a "chest cold." Patients should be informed that antibiotics are probably not going to be beneficial and may result in significant side effects.

RELATED CONTENT

Acute Bronchitis (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

[1] Smith SM, Smucny J, Fahey T: Antibiotics for acute bronchitis, *JAMA* 312:2678, 2014.

[2] Silverman M et al: Antibiotic prescribing for nonbacterial acute upper respiratory infections in elderly persons. *Ann Intern Med* 166:765-774, 2017.

BASIC INFORMATION

DEFINITION

Ogilvie syndrome is characterized by acute massive dilation of the cecum and right colon, with occasional extension to the rectum, in the absence of any mechanical obstruction. Oftentimes, acute colonic pseudo-obstruction occurs after surgery, and it can also be seen in patients with significant underlying medical illnesses. Cecal diameter on abdominal radiographs greater than 12 cm is considered to be the threshold where spontaneous perforation becomes more likely. Medications such as opioids and anticholinergics also contribute to the development of this condition.

SYNONYMS

Ogilvie syndrome
ACPO
Acute megacolon

ICD-10CM CODE
K56.6 Other and unspecified intestinal obstruction

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown
PREVALENCE: Unknown
PREDOMINANT SEX AND AGE: Although recent data is lacking, data from a retrospective study in 1986 suggested a male predominance with average age of onset in the sixth decade. In general, prevalence is thought to increase with age, although affected females tend to be younger because of the association of acute colonic pseudo-obstruction with obstetric complications.
PEAK INCIDENCE: Unknown
RISK FACTORS: Elderly patients seem to be at greatest risk. Other risk factors include significant underlying medical illness, sepsis, electrolyte abnormalities, recent cardiac events, certain medications (opioids, anticholinergics, phenothiazines, benzodiazepines, calcium channel blockers, chemotherapeutic agents, and antiparkinsonian agents), and postoperative patients (Box E1).
GENETICS: None

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute abdominal distention and crampy abdominal pain are the most common symptoms associated with Ogilvie syndrome. The distention can be so severe that it may lead to labored breathing. Nausea, vomiting, obstipation, constipation, and, paradoxically, diarrhea, can also be seen but are not consistently present. It has been estimated that 40% to 50% of patients continue to pass flatus.
- Physical exam is significant for massive abdominal distention that is tympanic to percussion and varying degrees of abdominal pain or discomfort are also present. Hypoactive or hyperactive bowel sounds are often described. Peritoneal signs are often absent early on but their presence is concerning for imminent perforation.

ETIOLOGY

Colonic motor and secretory functions are mediated by the autonomic nervous system with the ascending colon receiving parasympathetic innervation from the medulla oblongata via the vagus nerve, which increases gut motility, and sympathetic innervation from the spinal cord, which decreases motility. It is thought that parasympathetic dysfunction is the main driving force that leads to Ogilvie syndrome but the exact mechanism is unknown.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Mechanical obstruction
- Volvulus
- Intussusception
- Ileus
- Toxic megacolon

BOX E1 Clinical Factors Predisposing to Ogilvie Syndrome or Acute Colonic Pseudo-Obstruction

Cardiovascular
- Heart failure, stroke
- Gut ischemia

Critical illness
- Severe sepsis
- Acute pancreatitis
- Shock or hypoxemia

Postoperative state or trauma
- Intestinal manipulation
- Peritonitis
- Immobility and dehydration
- Vertebral, pelvic or hip fracture/surgery
- Retroperitoneal hematoma

Metabolic factors
- Hypokalemia and hyperglycemia
- Hypothyroidism, diabetes mellitus
- Liver or renal failure
- Amyloidosis

Drugs
- α-Adrenergic agonists, dopamine
- Clonidine and dexmedetomidine
- Opioids
- Anticholinergics, calcium channel antagonists
- Antipsychotics
- Antidepressants
- High-dose phosphodiesterase inhibitors

Gastrointestinal infections
- Cytomegalovirus, herpes zoster
- Tuberculosis

Neurologic
- Transection of the spinal cord
- Low spinal cord disease
- Parkinson disease

Obstetric
- Caesarean section
- Normal delivery

From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.

WORKUP

- History should be focused on the perceived progression of distention and timing of most recent flatus or bowel movement as well as determining any predisposing factors such as recent surgery, severe illness, and recent medication changes.
- Physical examination should focus on assessing the degree of abdominal distention and percussion to evaluate for tympanic sounds, which is a hallmark of Ogilvie syndrome. Serial abdominal exams should be performed to ensure no peritoneal signs such a rebound, guarding, or rigidity that would suggest impending or frank perforation.
- Laboratory evaluation should center on metabolic abnormalities as well as lactic acidosis and leukocytosis, which can both be used as a barometer of the severity of the patient's underlying illness as well as a marker for impending perforation.
- Imaging of the abdomen with plain radiograph is important for tracking degree of distention.

LABORATORY TESTS

- Metabolic abnormalities such as hypocalcemia, hypomagnesemia, and hypokalemia are commonly present and should be corrected accordingly.
- Leukocytosis as well as lactic acidosis are markers of underlying disease and impending perforation.

IMAGING STUDIES

- Plain and upright abdominal radiographs (Fig. E1) are important to establish degree of colonic distention, which often involves

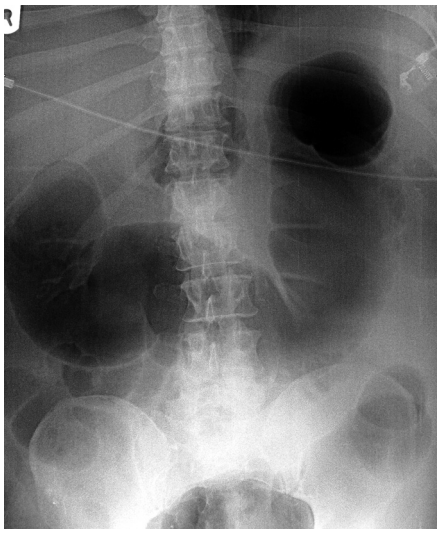

FIG. E1 Plain abdominal radiograph of patient with Ogilvie syndrome 11 days after surgery for ruptured aneurysm of abdominal aorta. Dilation (probably due to ischemia) is present in both right and left colon. Syndrome resolved with vasodilators and intravenous neostigmine. (From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.)

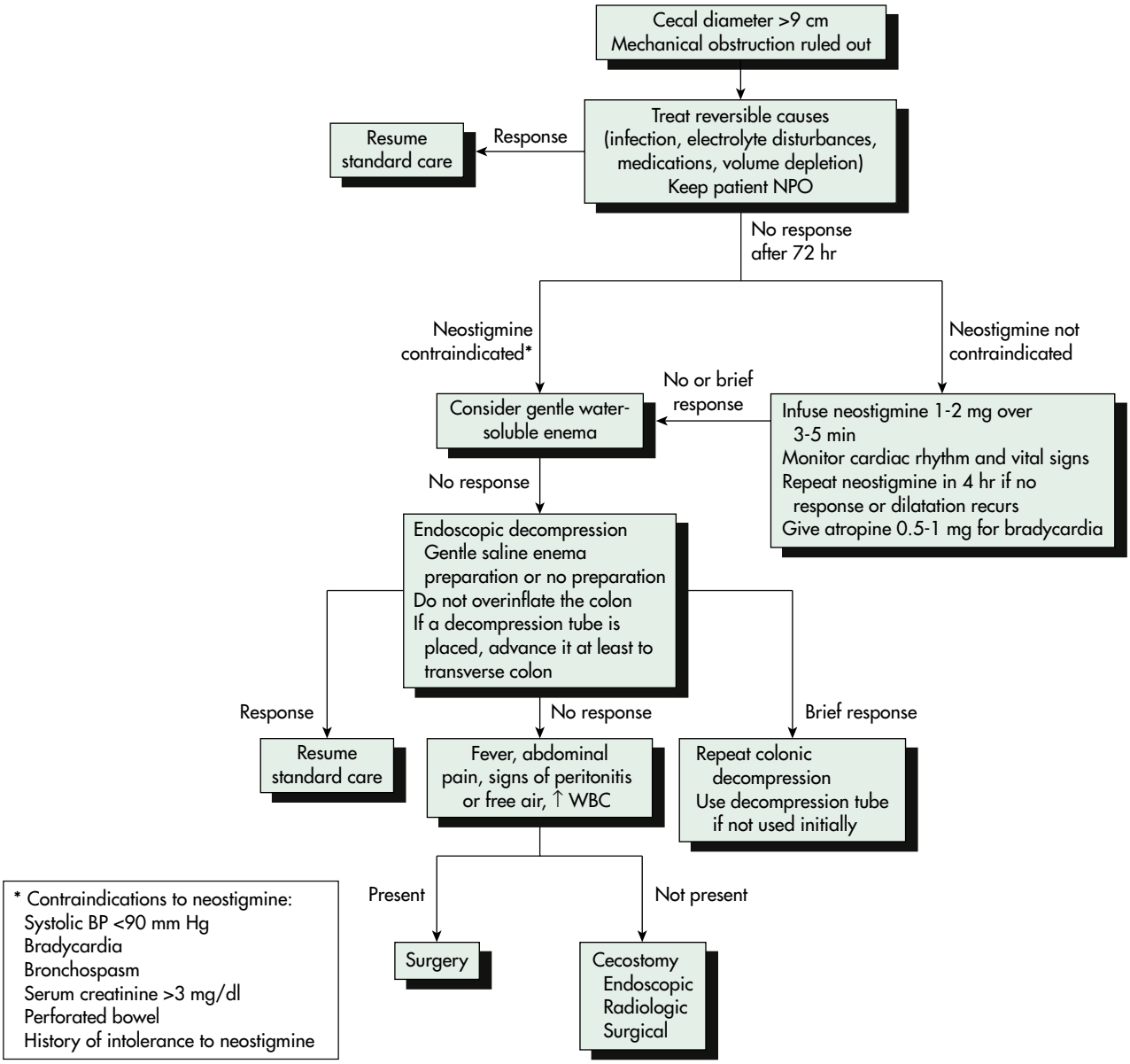

FIG. E2 Algorithm for the treatment of acute colonic pseudo-obstruction. *BP,* Blood pressure; *NPO*, nothing by mouth; *WBC*, white blood cell. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

the cecum but can also extend to the splenic flexure or rectum. Haustral markings are usually normal.

- CT scan or enema-enhanced radiograph is imperative to confirm the diagnosis and rule out underlying mechanical obstruction.

Rx TREATMENT

The goals of treatment are to decompress the colon in order to relieve the patient's abdominal discomfort and also mitigate the risk of developing intestinal ischemia or frank perforation. Fig. E2 illustrates an algorithm for the treatment of acute colonic pseudo-obstruction.

NONPHARMACOLOGIC THERAPY

- Supportive care with plain radiographs every 12 to 24 hr, serial abdominal exams, elimination of potential precipitants (medications, treatment of underlying medical illness), correction of electrolyte abnormalities, restricting PO intake, gastric decompression with nasogastric tube tube to intermittent suction, rectal decompression with rectal tube attached to gravity, IV fluids, encouraging ambulation if possible, and alternating the patient in bed between right and left lateral decubitus as well as prone positioning with hips elevated are all appropriate nonpharmacologic approaches that can be made initially in the absence of colonic distention >12 cm or significant abdominal pain.
- Colonoscopic decompression with or without placement of a decompression tube is often the next step in management, although use of this technique remains controversial as some studies indicate that the majority of patients spontaneously resolve within 48 hr. The risk of complication with colonoscopy in this setting is 3%, with a quoted death rate of 1%. Other studies suggest a success rate of 69% to 90% with colonoscopic decompression.
- Colonoscopic decompression is indicated when supportive measures fail, there is clinical deterioration, or colonic diameter is between 11 and 13 cm. Placement of a decompression tube at the time of colonoscopy is thought to reduce the need for repeat colonoscopic decompression, which is required in about 40% of cases, but no trials have been done to compare rates of repeat decompression with and without decompression tube placement.
- Alternative minimally invasive options which are usually reserved for failed colonoscopic decompression include percutaneous tube cecostomy performed under radiologic

guidance and percutaneous endoscopic colostomy, which are both techniques that grant percutaneous access to the colon for both decompression and irrigation to promote transit.
- Surgical management is reserved for those who have failed minimally invasive approaches or for patients with peritonitis or perforation. Surgical cecostomy tube or right hemicolectomy can be performed in the absence of perforation whereas ileostomy, colectomy, and Hartmann procedure can be performed in patients who have perforated or who have significant ischemia.

ACUTE GENERAL Rx

- Neostigmine is an IV anticholinesterase inhibitor that induces rapid colonic decompression in 80% to 100% of appropriate candidates with a median response rate of 4 min at a starting dose of 2 mg, but requires close cardiovascular monitoring at the time of its administration and has several contraindications. Dose adjustments are required in chronic kidney disease and caution should be used in patients who have bradyarrhythmias, recent myocardial infarction, beta-blocker use, and asthma. Atropine should be made available at bedside and administration of glycopyrrolate, an anticholinergic agent, should be considered to decrease the risk of bradycardia and bronchoconstriction.
- Methylnaltrexone, a peripherally acting opiate receptor antagonist, can also be considered in cases thought to be precipitated by opioids but little data supports its use at this time.

CHRONIC Rx

None

COMPLEMENTARY AND ALTERNATIVE MEDICINE

None

DISPOSITION

- Close inpatient monitoring is indicated until there is return of spontaneous bowel function and resolution of abdominal distention.

BOX E2 Strategies to Prevent Ogilvie Syndrome in the Critically Ill

- Early resuscitation of the circulation
- Minimizing prolonged infusion of high doses of α-adrenergic drugs
- Minimizing the use of dopamine
- Minimizing the prolonged use of opioids
- Use of thoracic epidural anesthesia
- Minimally invasive or laparoscopic surgery
- Selective decontamination of the digestive tract
- Avoiding antibiotics that disrupt growth of anaerobic fecal bacteria
- Early oral or enteral feeding
- Avoidance of proton pump inhibitors
- Early mobilization and ambulation
- Promoting timely defecation with:
  1. Oral polyethylene glycol from day 3
  2. Intravenous neostigmine from day 5

From Vincent JLet al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.

REFERRAL

Ogilvie syndrome is best managed in a team approach involving both surgeons and gastroenterologists. Administration of neostigmine in proper candidates or decompressive colonoscopy should be pursued in patients with absence of peritoneal signs. If there is evidence of perforation, surgical management is indicated.

PEARLS & CONSIDERATIONS

COMMENTS

- Maximal supportive care should be initiated for up to 48 hr barring any significant abdominal pain or massive distention >12 cm on imaging.
- Administration of neostigmine is suggested in appropriate candidates.
- Colonic decompression should be attempted with or without decompression tube placement in patients who fail neostigmine or those who have contraindications to its use.
- Minimally invasive fluoroscopic, endoscopic, or surgical approaches are rarely needed.
- Surgery is reserved for patients who show signs of perforation.
- Oral laxatives should be discontinued with diagnosis but should be restarted once decompression is achieved.

PREVENTION

Box E2 describes some prevention strategies for Ogilvie syndrome in the critically ill.

SUGGESTED READINGS

Chudzinski AP, Thompson EV, Ayscue JM: Acute colonic pseudoobstruction, *Clin Colon Rectal Surg* 28:112-117, 2015.

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Vogel JD et al: Clinical practice guidelines for colon volvulus and acute colonic pseudo-obstruction, *Dis Colon Rectum* 59:589-600, 2016.

Wells CI et al: Acute colonic pseudo-obstruction: a systematic review of aetiology and mechanisms, *World J Gastroenterol* 23(30):5634-5644, 2017.

AUTHOR: **Jason D. Ferreira, MD**

BASIC INFORMATION

Acute coronary syndrome (ACS) represents a spectrum of clinical disorders that includes unstable angina (UA), non–ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). Although the severity of disease will vary between the three subsets of ACS, they share a common clinical presentation and pathophysiology. This syndrome is typically caused by atherosclerotic coronary artery disease (CAD) and abrupt reduction in coronary blood flow. In this spectrum, UA and NSTEMI are represented electrocardiographically by the absence of ST-segment elevation in the appropriate clinical setting (i.e., chest discomfort). NSTEMI is additionally characterized by positive cardiac biomarkers because ischemia is severe enough to cause myocardial damage. STEMI is characterized by ST-segment elevation or presumed new left bundle branch block on electrocardiogram (ECG) in the appropriate clinical setting. ACS should be thought of as a continuous spectrum as UA will often progress to a myocardial infarction if left untreated (Table 1). Because of this continuum, the 2014 American College of Cardiology/American Heart Association (ACC/AHA) guidelines have grouped UA and NSTEMI into a single category called non–ST-elevation ACS (NSTE-ACS).

SYNONYMS

ACS
Unstable angina
NSTEMI
STEMI
Acute myocardial infarction

ICD-10CM CODES	
I20.0	Unstable angina
I21.0-I21.3	ST elevation (STEMI)
I21.4	Non-ST elevation (NSTEMI) myocardial infarction
I24.9	Acute ischemic heart disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: In the U.S., cardiovascular disease accounts for approximately 841,000 deaths each yr. The estimated annual incidence of heart attack in the U.S. is 720,000 new attacks and 335,000 recurrent attacks. Approximately 70% of myocardial infarctions are listed as NSTEMI, with the remainder being listed as STEMI. Patients with NSTE-ACS have more cardiac and noncardiac comorbidities than patients with STEMI. The underlying etiology, atherosclerotic CAD, is the number one cause of mortality.

PREDOMINANT SEX AND AGE: In evaluating chest pain, male gender and older age are important clinical factors that can identify ACS as a potential cause. The average age of first myocardial infarction is 65.6 yr old for men and 72.0 yr old for women. In a 2005-2011 study sponsored by National Heart, Lung, and Blood Institute, the average age-adjusted first MI or fatal coronary heart disease rates per 1000 population in patients age 35 to 84 yr of age were 3.7 for white men, 5.9 for black men, 2.1 for white women, and 4.0 for black women. As noted in this study, heart disease affects African Americans disproportionately. Heart disease is also the leading cause of death in women, surpassing all forms of cancer.

RISK FACTORS: Hypertension, diabetes mellitus, dyslipidemia, tobacco use, and family history of premature CAD (CAD in a male first-degree relative younger than 55 yr or a female younger than 65 yr) are all associated risk factors for CAD. There are also female-specific risk factors for CAD, including disorders of pregnancy and early onset of menopause. Refer to the topic "Angina Pectoris" for an extensive list of risk factors. Presence of these risk factors causes damage to the vascular endothelium and progression of atherosclerotic coronary artery plaques.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms often, but not always, include chest discomfort described as a pressure that may radiate to the shoulders, neck, jaw, or back. Typical angina is substernal in location, brought on by emotional or physical stress, and relieved with rest and/or nitroglycerin. The pain and discomfort associated with an ACS event is often diffuse rather than localized. It is often associated with diaphoresis.
- Women, diabetics, the elderly (>75 yr old), and postoperative patients often have an atypical presentation for ACS.
- Unstable angina has three typical presentations:
  1. Rest angina: Angina occurring at rest and prolonged usually for longer than 20 minutes.
  2. New-onset angina: New-onset angina of at least Canadian Cardiovascular Society (CCS) class III symptoms (Table 2).
  3. Increasing angina: Previously diagnosed angina that has become distinctly more frequent, longer in duration, or lower in threshold (i.e., increased by ≥1 CCS class to at least CCS class III severity).
- "Anginal equivalents" may include dyspnea, nausea, vomiting, and fatigue.
- ECG for NSTE-ACS may reveal transient ST-segment elevation, ST-segment depression, and/or new T-wave inversion. ECG for definition of STEMI will reveal at least 1-mm ST-segment elevation in two contiguous leads or new left bundle branch block in the appropriate clinical presentation.
- Physical examination findings alone are insufficient for the diagnosis of ACS. The physical examination may provide clues as to alternative diagnoses, such as aortic dissection (differences in pulse and blood pressure between the arms, murmur of aortic regurgitation), pericarditis (friction rub), cardiac tamponade (pulsus paradoxus), and pneumothorax (differential breath sounds.) In ACS it is important to assess the patient's hemodynamic stability, as signs of heart failure may be present. These signs include elevated jugular venous pressure (JVP), presence of an S3 gallop, and peripheral edema. The degree of heart failure with MI can be represented by the Killip classification, with the greater the Killip classification, the greater the mortality noted:
  1. Killip Class 1 is no heart failure.
  2. Killip Class 2 includes individuals with rales, elevated JVP, and S3 on examination.
  3. Killip Class 3 includes individuals with frank pulmonary edema.
  4. Killip Class 4 describes individuals in cardiogenic shock or hypotension with evidence of vasoconstriction noted.

ETIOLOGY

Atherosclerotic CAD is the underlying etiology. The hallmark of ACS is the vulnerable atherosclerotic plaque, which typically has a thin fibrous cap and a large lipid core. This vulnerable plaque ultimately ruptures, which leads to platelet activation and aggregation, leading to thrombus formation. STEMI typically results from complete thrombotic occlusion of a coronary artery, whereas NSTE-ACS often has partial occlusion. Angiographically, it is often the intermediate coronary artery lesions (30% to 50% diameter vessel stenosis) that lead to subtotal or total vessel occlusion in two thirds of STEMI cases.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Chest pain mimicking ACS may be the result of various underlying disorders, some of which are also accompanied by ECG changes and/or cardiac biomarker release. Examples include acute pulmonary embolism, acute aortic dissection, pericarditis, myocarditis, costochondritis, pneumonia, tension pneumothorax, perforating ulcer, or Boerhaave syndrome. Refer to topics "Angina Pectoris," "Coronary Artery Syndrome," and "Myocardial Infarction" for extensive differential diagnoses of chest pain.

TABLE 1 Acute Coronary Syndromes

	Spectrum of Acute Coronary Syndrome		
	Unstable Angina	**NSTEMI**	**STEMI**
Chest discomfort	1	1	1
Cardiac biomarkers	2	1	1
ECG changes	TWI and/or ST depression	TWI and/or ST depression	ST elevation or presumed new left bundle branch block
Pathophysiology	Partial/transient thrombotic occlusion	Partial/transient thrombotic occlusion	Complete thrombotic occlusion

ECG, Electrocardiogram; *NSTEMI,* non–ST-segment elevation myocardial infarction; *STEMI,* ST-segment myocardial infarction; *TWI,* T-wave inversion.

TABLE 2 Grading of Angina Pectoris According to CCS Classification

Class	Description of Stage
I	"Ordinary physical activity does not cause ... angina," such as walking or climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
II	"Slight limitation of ordinary activity." Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking 0.2 blocks on the level and climbing 0.1 flight of ordinary stairs at a normal pace and under normal conditions.
III	"Marked limitations of ordinary physical activity." Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace.
IV	"Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest."

Adapted with permission from Campeau L. Grading of angina pectoris (letter), *Circulation* 54:522-523, 1976. © 1976, American Heart Association, Inc.

From Braunwald E et al: ACC/AHA guidelines for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina), *J Am Coll Cardiol* 36:970-1062, 2000.

WORKUP

Focused history and physical exam, 12-lead ECG, cardiac biomarkers, and chest radiograph (CXR). Initial biomarkers may not be positive early in the disease process. Often serial biomarkers are drawn every 6 to 8 hours for a total of three sets for the purposes of ruling out myocardial infarction (MI), or until peak to determine the severity of an established MI. Echocardiogram may reveal new regional wall motion abnormalities or newly depressed LV function or aneurysm formation. Fig. 1 summarizes the evaluation of patients for acute coronary syndrome.

LABORATORY TESTS:

- Biomarkers and, in particular, the rising and/or falling pattern play an important role in the early detection and diagnosis of acute coronary syndrome (ACS). While troponin is essential to the diagnosis of acute myocardial infarction, other markers have demonstrated utility in the setting of acute chest pain and ACS. CK-MB and myoglobin are two traditional markers that are frequently used in combination with troponin and will be elevated in the setting of NSTEMI or STEMI. See Fig. E2, *A* for timing of release of each biomarker. Troponin I is the most sensitive biomarker for cardiac myocyte damage and also predicts 42-day mortality in ACS. Troponin I is considered the gold standard biomarker for diagnosis of myocardial infarction (Fig. E2, *B*).
- Creatinine kinase-myocardial band (CK-MB) is the cardiac specific isoform of creatinine kinase (CK) and is found in high concentrations in the myocardium. After an acute myocardial injury, CK-MB levels peak within 4-6 hours. Its shorter half-life leads to normal values within 24 to 48 hours after an event. As such, CK-MB is especially useful when assessing a patient for possible reinfarction because troponin levels can often be elevated up to 2 wk after an acute myocardial infarction.
- Myocardial infarction cannot always be assumed to be the etiology of elevations in troponin levels. Cardiac conditions, including arrhythmias, hypotension/hypertension, heart failure, and myocarditis, are a few of the common conditions that can lead to elevated levels. Noncardiac conditions, including renal failure, sepsis, respiratory failure, and neurological diseases, may also lead to elevations in troponin.
- Meanwhile, other biomarkers also have significant prognostic value. Testing for B-type natriuretic peptide (BNP) has a class IIb recommendation in the 2014 NSTE-ACS guidelines for use as a prognostic tool in patients presenting with an MI. BNP >80 portends a high risk of death at initial presentation of a STEMI.

RISK MODELS & RISK SCORES

Risk models and scores such as TIMI (see "Risk Assessment" in "Myocardial Infarction" topic), PURSUIT, and GRACE based on clinical, ECG, and laboratory data at presentation help to discriminate patients at high risk versus low risk for short- and intermediate-term adverse outcomes (Fig. E2, *C*).

IMAGING STUDIES

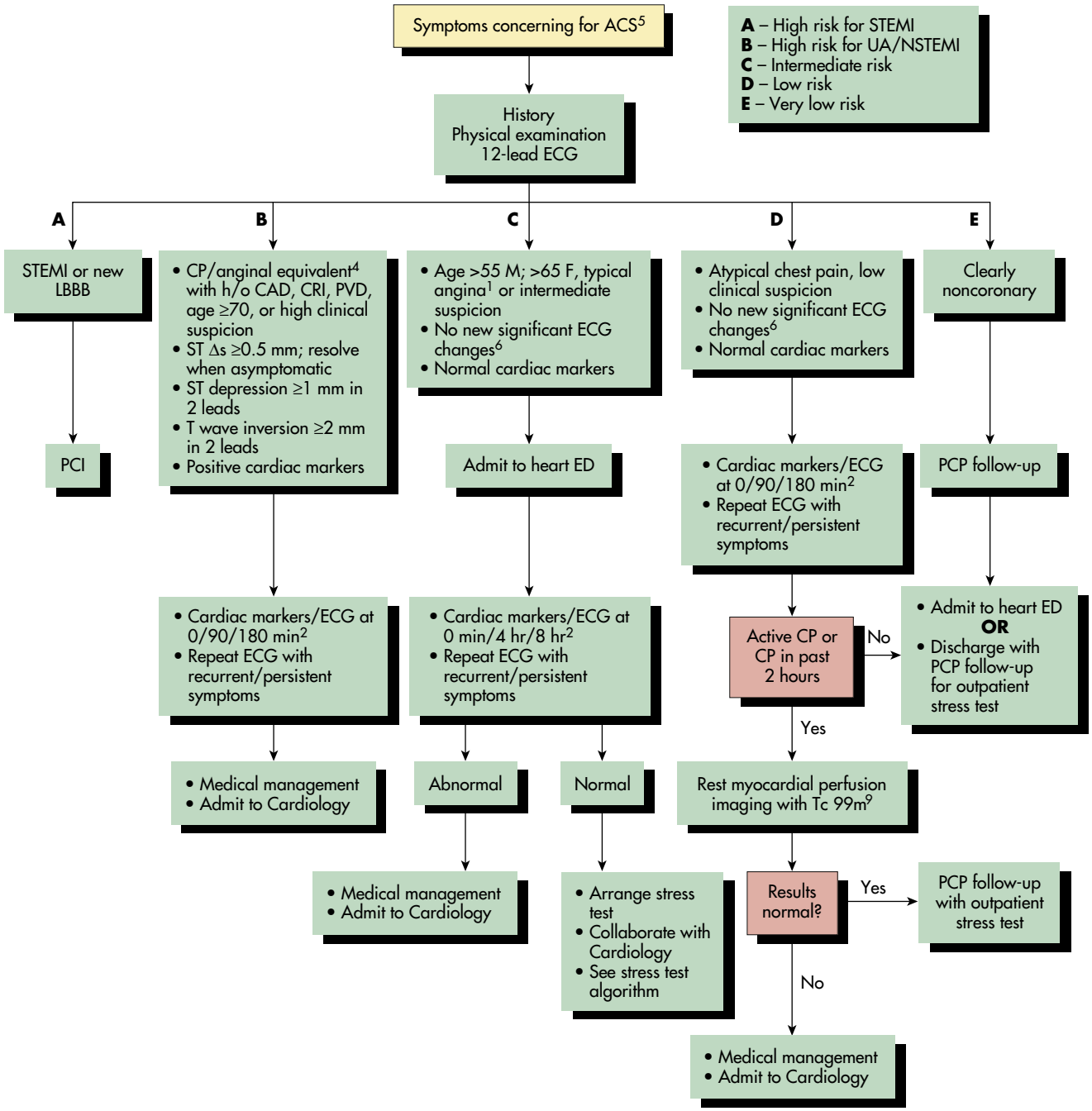
- A CXR to assist in evaluating for volume overload and possible widened mediastinum, which could be indicative of an aortic dissection. CXR can be useful in assessing for pneumonia, pneumothorax, and other pulmonary causes of chest pain.
- In patients for whom ECG and cardiac biomarkers are nondiagnostic but the suspicion for ACS is high given the history, an echocardiogram may be helpful to assess left ventricular (LV) function and regional wall motion abnormalities.
- Coronary CT angiography can be performed in patients with possible ACS, a normal 12-lead EKG result, negative troponin results, and no history of coronary artery disease (Class IIa).
- Cardiac stress testing (treadmill ECG, imaging stress studies using echocardiography or nuclear modalities) may further help to diagnose and risk stratify these patients. (See "Coronary Artery Syndrome" in Section I.)
- Coronary angiogram/cardiac catheterization will reveal coronary artery luminal irregularities/stenotic lesions. In patients with ACS who undergo coronary angiography, approximately 25% will have one vessel disease, 25% will have two vessel disease, 25% will have three vessel disease, 10% will have left main disease, and 15% will have coronary stenosis of <50% or normal coronaries.

Rx TREATMENT

The overall goal for patients with NSTE-ACS is to relieve myocardial ischemia and to prevent recurrent cardiovascular events. Antithrombotic therapy is needed to reduce thrombus burden, prevent further thrombosis, and improve coronary artery flow. Revascularization is needed to prevent further events and improve flow within the coronary artery lumen. For patients with STEMI, the goal is immediate reperfusion therapy, whether it is chemical (i.e., thrombolysis) or mechanical (i.e., percutaneous coronary intervention [PCI]), and time from onset of ischemia to revascularization is an important prognostic factor. STEMI patients presenting to a hospital with PCI capability should be treated with primary PCI within 90 minutes of first medical contact (Figs. 3 and 4). At non–PCI-capable hospitals where the first medical contact to balloon time is more than 120 minutes, thrombolytic therapy should be given if no contraindications are present; thrombolytics should not be administered 24 hours after initial diagnosis of STEMI. Absolute contraindications to thrombolytic therapy include the following: History of intracranial hemorrhage, known structural cerebral vascular lesion, known intracranial neoplasm, ischemic stroke within 3 mo, suspected aortic dissection, active bleeding, head trauma within 3 mo, or intracranial surgery within 2 mo. Relative contraindications include ischemic stroke more than 3 mo prior, dementia, major surgery within 3 wk, current oral anticoagulant therapy, and traumatic or prolonged CPR.

NONPHARMACOLOGIC THERAPY

- STEMI is a medical emergency and requires immediate reperfusion therapy; the best outcomes are seen with cardiac catheterization with primary PCI. Guidelines call for a goal door-to-balloon time of ≤90 minutes
- Patients with NSTE-ACS should be risk stratified in conjunction with the cardiology consult service. Risk scores such as the TIMI and GRACE scores can be used to decide between an early invasive strategy and an ischemia-guided strategy. Overall, an early invasive strategy is associated with better outcomes in patients with higher risk (i.e., TIMI score >3 or GRACE >140) and involves cardiac catheterization followed by revascularization with PCI or coronary artery bypass grafting (CABG) within 4 to 24 hours of presentation. An ischemia-guided strategy involves aggressive medical management and revascularization only if ischemia recurs or is documented on noninvasive testing. This should only be reserved for selected patients with low-risk scores (TIMI score 0 to 2). The early invasive strategy can be further stratified by timing:
  1. Immediate (within 2 hours): Patients with refractory or recurrent angina despite opti-



DEFINITIONS:

[1]Typical angina:
(1) Substernal chest pain or discomfort that is (2) provoked by exertion or emotional stress and (3) relieved by rest and/or nitroglycerin

[2]Cardiac marker timing: Based on symptom onset; in cases of uncertainty assume symptom onset at ED arrival

[3]ECG normal: No significant ST depression/T wave inversions, BBB, LVH with repolarization, conduction defect, digoxin effect

[4]Anginal equivalent:
- Any symptoms that the physician feels may represent ACS
- Exertional dyspnea—most common anginal equivalent symptom

[5]ACS:
- STE-ACS—1 mm ST elevation in 2 leads
- NSTE-ACS
  - NSTEMI—positive cardiac biomarkers
  - Unstable angina—ischemia with negative biomarkers

[6]New significant ECG changes:
- ST Δs ≥0.5 mm; resolve when asymptomatic
- ST depression ≥1 mm in 2 leads
- T wave inversion ≥2 mm in 2 leads

[7]Regadenoson is preferred agent for chemical nuclear stress test. Technetium Tc-99m tetrofosmin is the preferred tracer.

FIG. 1 Evaluation of patients for acute coronary syndrome *(ACS).* *CAD,* Coronary artery disease; *CP,* chest pain; *CRI,* chronic renal insufficiency; *ECG,* electrocardiogram; *ED,* emergency department; *h/o,* history of; *LBBB,* left bundle branch block; *NSTE,* non–ST-segment elevation; *NSTEMI,* non–ST-segment elevation myocardial infarction; *PCP,* primary care physician; *PVD,* peripheral vascular disease; *STE,* ST-segment elevation; *STEMI,* ST-segment elevation myocardial infarction; *UA,* unstable angina. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

mal initial treatment, signs or symptoms of heart failure, new or worsening mitral regurgitation, hemodynamic instability, sustained ventricular tachycardia or ventricular fibrillation

2. Early (within 24 hours): No characteristics from the immediate category but new ST-segment depression, a GRACE risk score >140 or temporal change in troponin

3. Delayed invasive (25 to 72 hours): None of the immediate or early characteristics but renal insufficiency, left ventricular ejection fraction of <40%, early post-infarct angina, history of PCI within the past 6 mo, prior coronary artery bypass graft, GRACE risk score of 109 to 140, or TIMI score of 2 or more

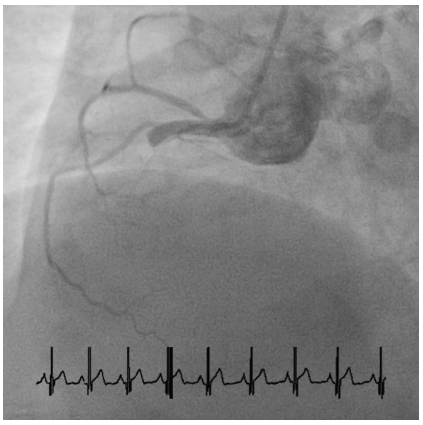


FIG. 3 Right coronary artery totally occluded proximally during ST-elevation myocardial infarction.

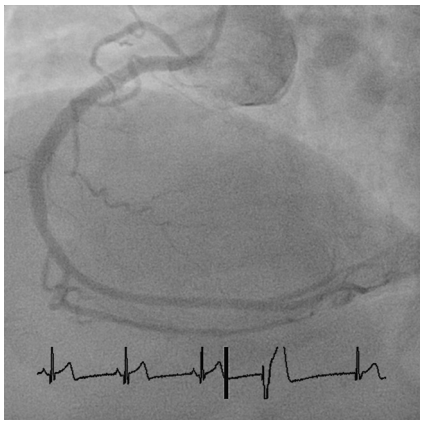


FIG. 4 Right coronary artery after successful percutaneous coronary artery stenting during ST-elevation myocardial infarction.

- Continuous ECG monitoring is recommended for all ACS patients. Supplemental oxygen should be administered to patients with arterial oxygen saturation of less than 90%, respiratory distress, or other high-risk features of hypoxemia. Finger pulse oximetry should be utilized to assess arterial oxygen saturation.

ACUTE GENERAL Rx

- Table 3 is a summary of recommendations for standard medical therapy in the early hospital care phase of management of patients with NSTE-ACS.
- Antithrombotic therapy (Table 4) is critical in treating the underlying pathophysiology

TABLE 3 Summary of Recommendations for Standard Medical Therapy in the Early Hospital Care Phase of Management of Patients with Non–ST-Elevation Acute Coronary Syndromes (NSTE-ACS)

Recommendations	COR	LOE
Oxygen		
Administer supplemental oxygen only with oxygen saturation <90%, respiratory distress, or other high-risk features for hypoxemia.	I	C
Nitrates		
Administer sublingual NTG every 5 min ×3 for continuing ischemic pain and then assess need for IV NTG.	I	C
Administer IV NTG for persistent ischemia, HF, or hypertension.	I	B
Nitrates are contraindicated with recent use of a phosphodiesterase inhibitor.	III: Harm	B
Analgesic Therapy		
IV morphine sulfate may be reasonable for continued ischemic chest pain despite maximally tolerated anti-ischemic medications.	IIb	B
NSAIDs (except aspirin) should not be initiated and should be discontinued during hospitalization for NSTE-ACS because of the increased risk of MACE associated with their use.	III: Harm	B
Beta-Adrenergic Blockers		
Initiate oral beta blockers within the first 24 hr in the absence of HF, low-output state, risk for cardiogenic shock, or other contraindications to beta blockade.	I	A
Use of sustained-release metoprolol succinate, carvedilol, or bisoprolol is recommended for beta-blocker therapy with concomitant NSTE-ACS, *stabilized* HF, and reduced systolic function.	I	C
Reevaluate to determine subsequent eligibility in patients with initial contraindications to beta blockers.	I	C
It is reasonable to continue beta-blocker therapy in patients with normal LV function with NSTE-ACS.	IIa	C
IV beta blockers are potentially harmful when risk factors for shock are present.	III: Harm	B
Calcium Channel Blockers (CCBs)		
Administer initial therapy with nondihydropyridine CCBs with recurrent ischemia and contraindications to beta blockers in the absence of LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 sec, or second- or third-degree atrioventricular block without a cardiac pacemaker.	I	B
Administer oral nondihydropyridine calcium antagonists with recurrent ischemia after use of beta blocker and nitrates in the absence of contraindications.	I	C
CCBs are recommended for ischemic symptoms when beta blockers are not successful, are contraindicated, or cause unacceptable side effects.*	I	C
Long-acting CCBs and nitrates are recommended for patients with coronary artery spasm.	I	C
Immediate-release nifedipine is contraindicated in the absence of a beta-blocker.	III: Harm	B
Cholesterol Management		
Initiate or continue high-intensity statin therapy in patients with no contraindications.	I	A
Obtain a fasting lipid profile, preferably within 24 hr.	IIa	C

*Short-acting dihydropyridine calcium channel antagonists should be avoided.

COR, Class of recommendation; *HF,* heart failure; *IV,* intravenous; *LOE,* level of evidence; *LV,* left ventricular; *MACE,* major adverse cardiovascular events; *N/A,* not available; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *NTG,* nitroglycerin.

From Amsterdam EA et al: 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 64:e139-228, 2014 in Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

of ACS. This consists of administering antiplatelet and anticoagulant agents (Table 5).

- Antiplatelet agents (Table 6) inhibit platelet activation and aggregation. Aspirin is a cyclooxygenase inhibitor that blocks platelet aggregation and should be administered to all ACS patients without contraindications.
- All patients with ACS should receive full-dose non–enteric-coated chewable aspirin of 162 to 325 mg to establish a high blood level for its antiplatelet effects. Thereafter, daily dose of 81mg should be continued indefinitely.
- Clopidogrel is a thienopyridine agent that inhibits platelet activation and aggregation. It should be administered in all ACS patients, with the timing dependent on the clinical scenario and management strategy. It requires a loading dose of 300 to 600 mg followed by 75 mg daily. It should be discontinued at least 5 days before CABG. If a patient is unable to take aspirin in the setting of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by daily maintenance should be started.
- Other antiplatelet agents that can be substituted instead of clopidogrel include prasugrel and ticagrelor. Ticagrelor has a half-life of 12 hours with a more rapid onset and more consistent onset of action. There was a reduction in death from vascular causes, MI, and stroke in patients with NSTE-ACS over clopidogrel. This benefit is limited to patients taking aspirin 75 to 100 mg per day. Prasugrel is not recommended in patients with NSTE-ACS. Multiple studies have demonstrated an increase in bleeding in patients taking Prasugrel, in particular those with a history of cerebrovascular events. Cangrelor is an IV ADP-P2Y12 receptor antagonist that may be used initially as a load in the emergency department before an invasive strategy, given its initial action and quick platelet recovery time. As a rule, all ACS patients should have two antiplatelet agents initiated and should be continued up to 12 mo regardless of ischemia-guided vs. invasive strategy.
- GP IIB/III a inhibitors (Table 7) may be considered as an intravenous antiplatelet therapy in addition to aspirin for medium- or high-risk patients with NSTE-ACS in whom an invasive strategy is planned (Class IIb). Eptifibatide and tirofiban are preferred agents over abciximab for NSTE-ACS patients; however, for STEMI patients undergoing primary PCI, IV abciximab has the same Class IIa indication as tirofiban and eptifibatide.
- Anticoagulant agents should be administered to all ACS patients, irrespective of initial treatment strategy. Options include either unfractionated heparin (UFH), or low-molecular-weight heparin (enoxaparin), or factor Xa inhibitors such as fondaparinux, or direct thrombin inhibitors such as bivalirudin (Table 8).
- For STEMI, fondaparinux can be used for anticoagulation. It has been shown to decrease bleeding complications as compared with either UFH or LMWH. However, it should not

TABLE 4 Summary of Recommendations for Antithrombotic Therapy

Recommendations	Dosing, special considerations	COR	LOE
Aspirin			
Non–enteric-coated aspirin to all patients promptly after presentation	162-325 mg	I	A
Aspirin maintenance dose continued indefinitely	81-325 mg/day*	I	A
$P2Y_{12}$ Inhibitors			
Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin	75 mg	I	B
$P2Y_{12}$ inhibitor, in addition to aspirin, for up to 12 mo for patients treated initially with either an early invasive or initial ischemia-guided strategy:		I	B
• Clopidogrel	300- or 600-mg loading dose, then 75 mg/day		
• Ticagrelor	180-mg loading dose, then 90 mg twice daily		
$P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) continued for at least 12 mo in post-PCI patients treated with coronary stents	N/A	I	B
Ticagrelor in preference to clopidogrel for patients treated with an early invasive or ischemia-guided strategy	N/A	IIa	B
Glycoprotein (GP) IIb/IIIa Inhibitors			
GP IIb/IIIa inhibitor in patients treated with an early invasive strategy and DAPT with intermediate/high-risk features (e.g., positive troponin)	Preferred options are eptifibatide or tirofiban	IIb	B
Parenteral Anticoagulant and Fibrinolytic Therapy			
SC enoxaparin for duration of hospitalization or until PCI is performed	1 mg/kg SC every 12 hr (reduce dose to 1 mg/kg/day SC in patients with CrCl <30 ml/min) Initial 30-mg IV loading dose in select patients	I	A
Bivalirudin until diagnostic angiography or PCI is performed in patients with early invasive strategy only	Loading dose 0.10 mg/kg, followed by 0.25 mg/kg/hr Only provisional use of GP IIb/IIIa inhibitor in patients also treated with DAPT	I	B
SC fondaparinux for the duration of hospitalization or until PCI is performed	2.5 mg SC daily	I	B
Administer additional anticoagulant with anti-IIa activity if PCI is performed while patient is on fondaparinux	N/A	I	B
IV UFH for 48 hr or until PCI is performed	Initial loading dose 60 IU/kg (max 4000 IU) with initial infusion 12 IU/kg/hr (max 1000 IU/hr) Adjusted to therapeutic APTT range	I	B
IV fibrinolytic treatment not recommended in patients with NSTE-ACS	N/A	III: Harm	A

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.[10]

APTT, Activated partial thromboplastin time; *COR,* class of recommendation; *CrCl,* creatinine clearance; *DAPT,* dual antiplatelet therapy; *IV,* intravenous; *LOE,* level of evidence; *max,* maximum; *N/A,* not available; *NSTE-ACS,* non–ST-elevation acute coronary syndromes; *PCI,* percutaneous coronary intervention; *SC,* subcutaneous; *UFH,* unfractionated heparin.

Modified from Amsterdam EA et al: 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *J Am Coll Cardiol* 64:e139-228 , 2014, in Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 5 2014 Guideline Recommendations for Antithrombotic Agents in Patients with Non–ST-Elevation Acute Coronary Syndromes

Antiplatelet Therapy

Non–enteric-coated, chewable aspirin (162 to 325 mg) should be given to all patients without contraindications on presentation, and a maintenance dose of aspirin (81 to 325 mg/day) continued indefinitely.

In patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel (300 or 600 mg) followed by a daily maintenance dose of 75 mg should be substituted.

Either clopidogrel or ticagrelor can be used initially with either an early invasive or ischemic guided strategy (COR I, LOE: B).

Ticagrelor may be preferred over clopidogrel as the initial treatment (COR IIa, LOE: B).

In patients treated with ticagrelor, the preferred aspirin maintenance dose is 81 mg/day.

Use prasugrel only in patients receiving coronary stents (COR I, LOE: B).

The use of glycoprotein IIb/IIIa receptor inhibitors is reserved mainly to the time of PCI in high-risk patients who were not adequately pretreated with $P2Y_{12}$ inhibitors (COR I, LOE: A) or in those patients who were adequately pretreated with $P2Y_{12}$ inhibitors but have a high-risk profile (COR IIa, LOE: B).

Clopidogrel and ticagrelor should be discontinued at least 5 days (COR I, LOE: B) and prasugrel at least 7 days (COR I, LOE: C) before major surgery.

Anticoagulant Therapy

Enoxaparin is recommended at presentation (COR I, LOE: A); other options include unfractionated heparin (UFH) (COR I, B) and fondaparinux (COR I, LOE: B). If an early invasive strategy is planned, bivalirudin (COR I, LOE: B) is also an option.

If fondaparinux is used initially, add UFH or bivalirudin just before or during PCI to prevent catheter-related thrombosis (COR I, LOE: B).

Bivalirudin is preferred over UFH plus GP IIb/IIIa inhibitor in patients undergoing PCI who are at high risk of bleeding (COR IIa, LOE: B).

It is reasonable to use enoxaparin during PCI if it was used as the initial anticoagulant (COR IIb, LOE: B).

COR, Class of recommendation; *LOE,* level of evidence; *PCI,* percutaneous coronary intervention.

Modified from Eisen A, Giugliano RP. Antiplatelet and anticoagulation treatment in patients with non–ST-segment elevation acute coronary syndrome: comparison of the updated North American and European guidelines. *Cardiol Rev* 24:170-6, 2016; and Amsterdam EA et al: 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 64: e139-228, 2014, in Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 6 Pharmacologic Characteristics of Oral Antiplatelet Drugs Commonly Used in the Management of Acute Coronary Syndromes

		ADP Receptor Antagonists		
Characteristic	**Aspirin**	**Clopidogrel**	**Prasugrel**	**Ticagrelor**
Class	COX inhibitor	Thienopyridine (second generation)	Thienopyridine (third generation)	Cyclopentyl triazolopyrimidine
Target	COX-1	P2Y12	P2Y12	P2Y12
Dose	162–325-mg loading dose; 75-325mg/day maintenance dose	300–600-mg loading dose; 75mg/day maintenance dose	60-mg loading dose; 10mg/day maintenance dose	180-mg loading dose; 90 mg bid maintenance dose
Prodrug	No	Yes	Yes	No
Time to effect[a]	<1 hour	4-6 hours[b]	<1 hour	<1 hour
Drug half-life	20 min	Minutes	Minutes	12 hours
Reversible	No	No	No	Yes

ADP, Adenosine diphosphate; bid, twice daily; *COX,* cyclooxygenase.

[a]After loading dose

[b]Increased antithrombotic benefit was seen after the first hour in patients enrolled in the COMMIT trial who did not receive a loading dose, but maximum effect is not seen until after 4-6 hours.

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

be used as the sole anticoagulant in PCI because of the risk of catheter thrombosis.

- Bivalirudin is a reversible direct thrombin inhibitor and may be considered as an alternative to UFH and GP IIb/IIIa inhibitors in patients with STEMI (HORIZONS AMI trial) who are undergoing primary PCI. When bivalirudin was compared to UFH plus a glycoprotein IIb/IIIa inhibitor in patients with STEMI and PCI, less bleeding and a short- and long-term reduction in cardiac events and overall mortality was observed. With bivalirudin, there is no risk of heparin-induced thrombocytopenia, less bleeding is observed, and the anticoagulant effect can be monitored during intervention by the activated clotting time. Similar results were reported in the use of bivalirudin alone in patients with UA/NSTEMI in the ACUITY trial when compared to enoxaparin/UFH with GP IIb/IIIa arms.
- Beta-blocker therapy reduces ischemia by decreasing myocardial oxygen demand and has a proven long-term mortality benefit. Oral therapy should be initiated within 24 hours of onset of ACS unless signs or symptoms of heart failure and shock are present or arrhythmias preclude its use. Oral administration, titrated to a heart rate of 50-60 beats/min, is preferred. Intravenous beta-blockers can be administered to STEMI patients who are hypertensive or have ongoing ischemia; they should be avoided if the patients have any of the following:
  1. Signs of heart failure.
  2. Evidence of a low output state.
  3. Increased risk for cardiogenic shock.
  4. Other relative contraindications to beta-blockade (PR interval >0.24 second, second- or third-degree heart block, active asthma, or reactive airway disease).
- Nitroglycerin is a vasodilator that should be administered to relieve chest discomfort in all ACS patients. It can be administered sublingually at first, up to 3 doses, followed by intravenous administration if symptoms persist. In the setting of an inferior STEMI, it is necessary to rule out a right ventricular (RV) infarct with a right-sided ECG before the administration of nitroglycerin. This is because RV infarcts are preload dependent and nitroglycerin decreases preload through venodilation, which leads to hypotension in this setting. This can be corrected by discontinuing nitroglycerin and starting bolus intravenous fluids. Nitrates should not be administered in patients who recently received a phosphodiesterase inhibitor. Nitroglycerin provides no mortality benefit in ACS patients.
- Oxygen should be administered to patients with shortness of breath, signs of acute heart failure, cardiogenic shock, or an arterial oxyhemoglobin saturation of less than 90%. The 2014 ACC/AHA guidelines report no demonstrated benefit for routine use of supplemental oxygen in normoxic patients

TABLE 7 Pharmacologic Characteristics of Intravenous Antiplatelet Drugs Used in the Management of Acute Coronary Syndrome

	GP IIb/IIIa inhibitors			ADP Receptor Antagonists
Characteristic	**Abciximab**	**Eptifibatide**	**Tirofiban**	**Cangrelor**
Class	Fab fragment	Nonpeptide	Cyclic heptapeptide	Nonthienopyridine
Onset	Rapid	Rapid	Rapid	Rapid
Drug half-life	10-30 min	2 hours	2.5 hours	3-6 min
Reversibility of platelet inhibition	Slow	Rapid	Rapid	Rapid
Excretion	Unknown	40%-70% renal	50% renal	Dephosphorylation

ADP, Adenosine diphosphate; *GP,* glycoprotein.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 8 Pharmacologic Characteristics of Parenteral Anticoagulants Commonly Used in the Management of Patients with Acute Coronary Syndromes

	Unfractionated Heparin	**Enoxaparin**	**Bivalirudin**	**Fondaparinux**
Route of administration	IV	SC (first dose IV[a])	IV	SC (first dose IV[a])
Frequency of dosing	Continuous IV infusion	Twice daily; once daily if CrCl <30 ml/min	Continuous IV infusion	Once-daily injection
Clearance	Primarily nonrenal	Renal	Renal, proteolytic cleavage	Renal
Use in ACS patients with moderate renal impairment	Yes	Yes (dose reduction)	Yes (dose reduction)	Yes[b]
Use in ACS patients undergoing dialysis	Yes	No experience	Yes (dose reduction)	No experience[c]
Routine laboratory monitoring	Yes	No	No[d]	No
Dose	Adjust dose according to the results of the aPTT	Fixed weight adjusted	Fixed weight adjusted	Fixed
Accumulation in renal failure	No	Yes	Yes	Yes
Nonanticoagulant side effects	Allergy, HIT	HIT (rare)	—	—
Nonbleeding contraindications	Allergy, immune HIT	Allergy, immune HIT	Allergy	Allergy
Antidote	Protamine sulfate	Protamine sulfate partially reverses	No	No

ACS, Acute coronary syndromes; *aPTT,* activated partial thromboplastin time; *CrCl,* creatinine clearance; *HIT,* heparin-induced thrombocytopenia; *IV,* intravenous; *SC,* subcutaneous.
[a]The first dose of enoxaparin was given by the intravenous route in the TIMI-11B (Thrombolysis In Myocardial Infarction 11B) and EXTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment, Thrombolysis in Myocardial Infarction 25) studies. The first dose of fondaparinux was given by the intravenous route in the OASIS-6 (Optimal Antiplatelet Strategy for Interventions 6) trial.
[b]Acute coronary syndrome patients with creatinine up to 265 μmol/L were eligible for inclusion in the OASIS-5 and -6 trials (equivalent to an estimated creatinine clearance of 15-20 ml/min in a 70-kg patient who is 70 yr of age).
[c]Fondaparinux is contraindicated in patients with venous thromboembolism who have severe renal impairment.
[d]Monitoring and dose adjustment required in patients with creatinine clearance below 30 ml/min.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

with NSTE-ACS; rather, emerging data suggest that routine use of oxygen can lead to adverse effects such as increased coronary vascular resistance, reduced coronary blood flow, and increased mortality rate.

- Morphine can be used intravenously in patients with NSTE-ACS if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications (Class IIb).
- Calcium channel blockers (nondihydropyridine) may be used in patients with persisting or recurrent symptoms, despite treatment with beta-blockers and nitroglycerin. They work by having negative inotropic and chronotropic effects and causing coronary vasodilation. They are especially useful when beta-blockers are contraindicated and in patients with coronary artery spasm. Calcium channel blockers should not be used in cases of severe LV dysfunction, pulmonary edema, increased risk for cardiogenic shock or advanced heart blocks.
- Patients routinely taking nonsteroidal antiinflammatory drugs (NSAIDs) (except for aspirin), both nonselective as well as COX-2 selective agents, before ACS should discontinue those agents at the time of presentation because of the increased risks of mortality, reinfarction, hypertension, heart failure, and myocardial rupture associated with their use.
- Angiotensin-converting enzyme (ACE) inhibitors may be added and should be used within 24 hours of onset of ACS in all patients with depressed LV function (ejection fraction [EF] <40%) and those with a history of hypertension, diabetes mellitus, or stable chronic kidney disease. Angiotensin receptor blockers (ARBs) should be used in patients who are ACE inhibitor intolerant.
- Table 9 summarizes indications and cautions for adjunctive medical therapies for patients with ST-elevation myocardial infarction.
- Refer to topic "Cocaine Overdose" for treatment of cocaine-related ACS.

CHRONIC Rx

- Post-ACS medical therapy involves aspirin, statin, beta-blocker, and a second anti-platelet agent such as clopidogrel, ticagrelor, or prasugrel.
- In patients already on an oral anticoagulant for another diagnosis such as atrial fibrillation, the duration of triple therapy should be minimized. Strategies aimed at minimizing the risk of bleeding in patients treated with triple therapy (dual antiplatelet therapy and an oral anticoagulant) are summarized in Table 10. The WOEST trial showed that using clopidogrel along with an oral anticoagulant but without aspirin resulted in a significant reduction in bleeding complications with those patients on a triple therapy of oral anticoagulant, aspirin, and clopidogrel. It is a class IIB recommendation in those patients with atrial fibrillation and a CHADS-VASC score of 2 or greater after coronary revascularization to consider using clopidogrel concurrently

with oral anticoagulant (Table 11) but without aspirin. Similarly, the AUGUSTUS trial in 2019 demonstrated that triple therapy (ASA, P2Y12 inhibitor, DOAC or warfarin) was associated with substantial increases in bleeding without improved thrombotic protection compared with P2Y12 inhibitor and oral anticoagulation alone.

- Lipid lowering with statins has been evaluated in trials such as the MIRACL study, in which high-dose atorvastatin 80 mg reduced death, MI, and cardiac events at 16 wk when administered early, within 24 to 96 hours after an ACS. The A-Z trial and PROVE IT-TIMI 22 trials demonstrated benefit of early high-intensity statin therapy with LDL targets <70 mg/dl in ACS.
- ACE inhibitors may be added to treat hypertension and should be used in all patients with depressed LV function (EF <40%) or pulmonary vascular congestion. ARBs should be used in patients who are ACE inhibitor intolerant.
- An aldosterone blocker should be used in post-MI patients without significant renal dysfunction (creatinine >2.5 mg/dl in men or creatinine >2.0 mg/dl in women) or hyperkalemia (K >5.0 mEq/L) who have an ejection fraction of less than 40% and are already on therapeutic doses of an ACE inhibitor and a beta-blocker.
- Cardiac rehabilitation and a monitored exercise program should be recommended at the time of discharge.
- Aggressive risk factor management, including smoking cessation, weight loss, diet and exercise, diabetes control, and so on, for secondary prevention of future events is crucial.

REFERRAL

- All ACS patients should be cared for in conjunction with the cardiology consult service.
- When appropriate, referral to a cardiac surgeon may be necessary for CABG and heart team approach.
- At the time of discharge, patients should be referred for cardiac rehabilitation.

PEARLS & CONSIDERATIONS

COMMENTS

- ACS is common and a leading cause of mortality in the U.S.
- The diagnosis hinges on the basics—history and physical, ECG, biomarkers, and CXR.
- Remember the potentially fatal non-ACS causes of chest discomfort, which include acute pulmonary embolism and acute ascending aortic dissection.
- STEMI patients presenting to a hospital with PCI capability should be treated with primary PCI within 90 minutes of first medical contact.
- STEMI patients presenting to a hospital without PCI capability and who cannot be transferred to a PCI center and undergo PCI within 120 minutes of first medical contact should be treated with fibrinolytic therapy within 30 minutes of hospital presentation unless fibrinolytic therapy is contraindicated.
- Refer to topics "Angina Pectoris" and "Myocardial Infarction" for additional discussion of this subject matter.

PREVENTION

Primary prevention of ACS is based on recognizing the major risk factors for CAD:

- Patients should be counseled to end all tobacco use by developing a plan for quitting that may include pharmacotherapy or a referral to a smoking cessation program.
- Patients with blood pressure ≥130/80 mm Hg should be treated, as tolerated, with blood pressure medication, treating initially with β-blockers and/or ACE inhibitors, with addition of other drugs as needed to achieve goal blood pressure.
- All patients should be counseled regarding the need for lifestyle modification: Weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products.
- It may also be reasonable to add omega 3 fatty acids from fish or fish oil capsules for cardiovascular disease reduction.
- Patients should be encouraged to perform 30 to 60 minutes of moderate intensity aerobic activity for a minimum of 5 days a week.
- Body mass index and waist circumference should be assessed at every visit and patients should be encouraged to maintain/achieve a body mass index between 18.5 and 24.9 kg/m^2.
- Patients with diabetes mellitus should maintain strict control of their glucose and A1C, under the care of their primary care physician or endocrinologist. Metformin is first-line pharmacotherapy. Target HbA1c of ≤7% may be considered.
- For patients with recent myocardial infarction or coronary artery bypass surgery, it is beneficial to screen for depression.

TABLE 9 Indications and Cautions for Adjunctive Medical Therapies for Patients with ST-Elevation Myocardial Infarction

Therapy	Indications	Cautions
Beta-adrenergic receptor–blocking agents	Oral: All patients without contraindication IV: Patients with refractory hypertension or ongoing ischemia without contraindication	Signs of congestive heart failure Low-output state Increased risk for cardiogenic shock Prolonged first-degree or high-grade atrioventricular block Reactive airways disease
Angiotensin-converting enzyme (ACE) inhibitors	Anterior myocardial infarction and LVEF ≤0.40 or congestive heart failure All patients without contraindication	Hypotension Renal failure Hyperkalemia
Angiotensin receptor–blocking agents (ARBs)	Intolerant of ACE inhibitors	Hypotension Renal failure Hyperkalemia
Statins	All patients without contraindications	With drugs metabolized via CYP3A4, fibrates Monitor for myopathy, hepatotoxicity Adjust dose for lipid targets
Nitroglycerin	Ongoing chest pain Hypertension and congestive heart failure	Suspected right ventricular infarction SBP <90 (or 30 mm Hg below baseline) Recent use of a type 5 PDE inhibitor
Oxygen	Clinically significant hypoxemia (Spo_2 <90) Congestive heart failure Dyspnea	Chronic obstructive pulmonary disease and CO_2 retention
Morphine	Pain Anxiety Pulmonary edema	Lethargic or moribund patient Hypotension Bradycardia Known hypersensitivity

IV, Intravenous; *LVEF,* left ventricular ejection fraction; *PDE,* phosphodiesterase; *SBP,* systolic blood pressure.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

- All eligible patients should be referred to a comprehensive cardiac rehabilitation program.
- Patients with depressed LV function (ejection fraction <35%) at least 40 days after an acute MI benefit from an implantable cardioverter defibrillator (ICD) for the prevention of sudden cardiac death.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Acute Coronary Syndrome (Patient Information)
Angina Pectoris (Related Key Topic)
Coronary Artery Disease (Related Key Topic)
Myocardial Infarction (Related Key Topic)
Hypertension (Related Key Topic)

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TABLE 10 Strategies Aimed at Minimizing the Risk of Bleeding in Patients Treated with Triple Therapy (Dual Antiplatelet Therapy and an Oral Anticoagulant)

Proposed Approach	Rationale
Aspirin maintenance dose ≤100 mg/day	Higher aspirin maintenance doses increase bleeding, and there is no evidence that they improve efficacy.
PPI with a preference for agents that interfere less with CYP 2C19 (e.g., pantoprazole)	Much of the excess bleeding is from the GI tract. The use of acid-suppressive agents that interfere less with CYP 2C19 minimizes the potential for a negative interaction with clopidogrel.
Preference for a non–vitamin K antagonist oral anticoagulant	Dabigatran 110 mg twice daily and apixaban 2.5 or 5.0 mg twice daily are associated with lower rates of bleeding than warfarin.
For warfarin, use a target INR of 2–2.5	Some evidence that a restricted target INR range reduces the risk of bleeding.
Manage warfarin in a specialized anticoagulation clinic	Compared with usual care, specialist clinics achieve a higher TTR of the INR.
Minimize duration of triple therapy	The risk of bleeding is highest during the first 30 days but remains elevated with long-term treatment.
Avoid NSAIDs	NSAIDs are a common cause of upper GI bleeding.
Avoid prasugrel and ticagrelor	Prasugrel and ticagrelor cannot be recommended because they are more potent than clopidogrel and cause more bleeding.

CYP, Cytochrome P450; *GI,* gastrointestinal; *INR,* international normalized ratio; *NSAID,* nonsteroidal antiinflammatory drug; *PPI,* proton pump inhibitor; *TTR,* time in therapeutic range.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 11 Pharmacological Characteristics of Warfarin and New Oral Anticoagulants Evaluated in Phase III Trials for the Long-Term Management of Acute Coronary Syndromes

Characteristic	Warfarin	Rivaroxaban	Apixaban
Target	VKORC1	Factor Xa	Factor Xa
Prodrug	No	No	No
Bioavailability (%)	100	80	60
Dosing	Variable, once daily	Fixed, 2.5 or 5 mg twice daily[a]	Fixed, 5 mg twice daily (2.5 mg twice daily in selected patients)
Half-life	Mean: 40 hours (range: 20–60 hours)	7-11 hours	12 hours
Renal clearance (%)	Nil	66[b]	25
Routine coagulation monitoring	Yes (INR)	No	No
Drug interactions	Multiple	Potent inhibitors of CYP3A4 and P-gp[c]	Potent inhibitors of CYP3A4 and P-gp[c]
Antidote	Yes (vitamin K, PCC, FFP)	Yes (Andexanet alfa)	Yes (Andexanet alfa)
Approved for ACS management	Yes	Yes, in Europe	No

ACS, Acute coronary syndromes; *CYP-3A4,* cytochrome P450 3A4; *FFP,* fresh frozen plasma; *fXa,* activated factor X; *INR,* international normalized ratio; *PCC,* prothrombin complex concentrates; *P-gp,* P-glycoprotein; *VKORC1,* C1 subunit of vitamin K epoxide reductase. Strategies Aimed at Minimizing the Risk of Bleeding in Patients Treated with Triple Therapy (Dual Antiplatelet Therapy and an Oral Anticoagulant).
[a]A once-daily regimen was tested in atrial fibrillation.
[b]Half of renally cleared rivaroxaban is cleared as unchanged drug and half as inactive metabolites.
[c]Potent inhibitors of both CYP3A4 and P-glycoprotein include azole antifungals (e.g., ketoconazole, itraconazole, voriconazole, posaconazole) and protease inhibitors, such as ritonavir. Potent inhibitors of CYP3A4 include azole antifungals, macrolide antibiotics (e.g., clarithromycin), and protease inhibitors (e.g., atazanavir).
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

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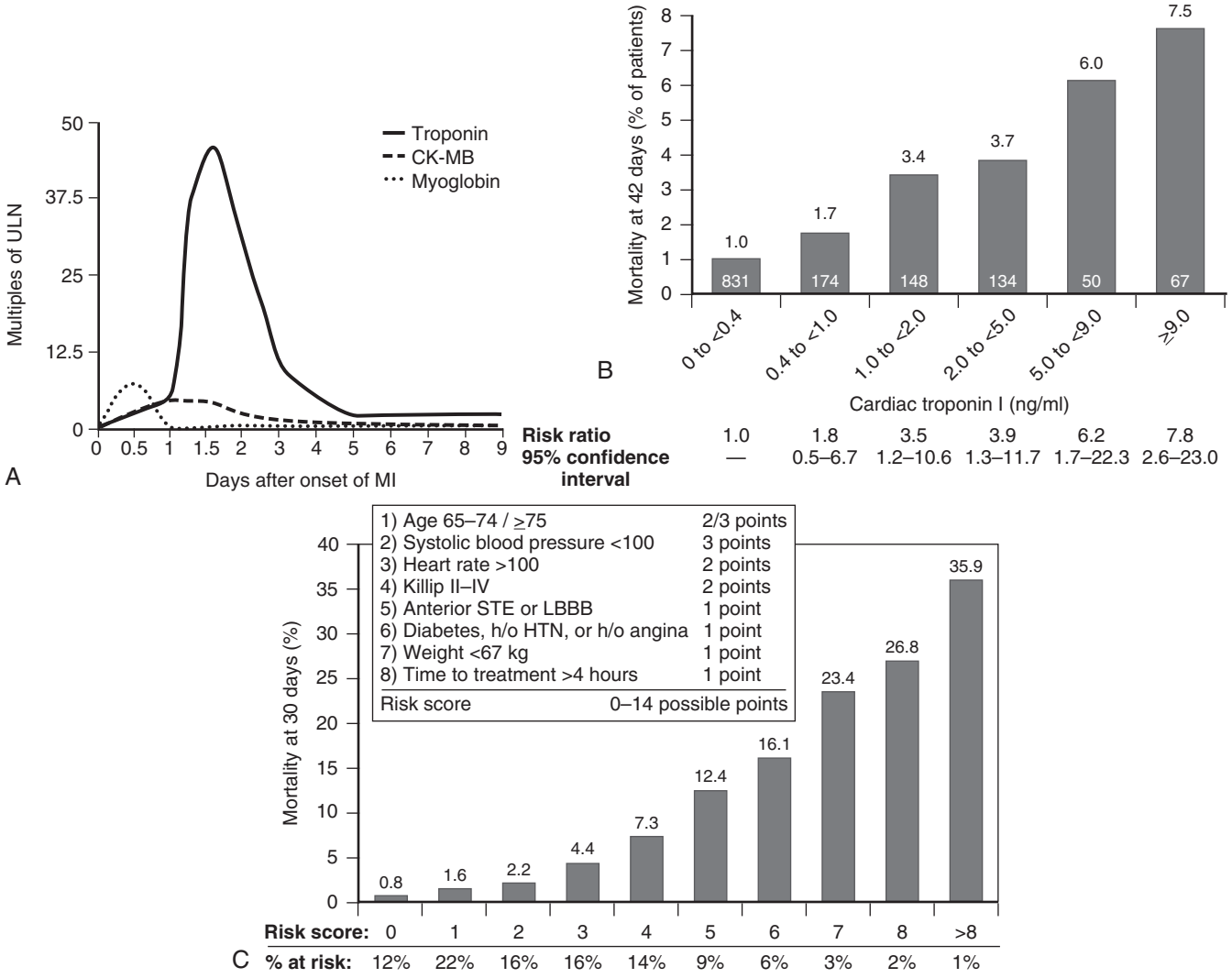

FIG. E2 Timing of release of cardiac biomarkers in acute coronary syndrome. *HTN,* Hypertension; *LBBB,* left bundle branch block; *MI,* myocardial infarction; *STE,* ST elevation; *ULN,* upper limit of normal. (Modified from Shapiro BP, Jaffe AS: Cardiac biomarkers. In Murphy JG, Lloyd MA [eds]: *Mayo Clinic cardiology: concise textbook,* ed 3, Rochester, MN: Mayo Clinic Scientific Press and New York, 2007, Informa Healthcare USA, pp 773-780; and Anderson JL et al: *J Am Coll Cardiol* 50:e1-e157, 2007, Fig. 5.)

BASIC INFORMATION

DEFINITION

Acute glomerulonephritis (GN) is inflammation of the glomeruli, usually caused by deposition of immunoreactants. Clinically, patients present with blood and protein in the urine and high blood pressure. If untreated, chronic glomerular inflammation leads to progressive chronic kidney disease.

SYNONYMS

Acute nephritic syndrome
Glomerulonephritis, acute GN

ICD-10CM CODES

N00.0	Acute nephritic syndrome with minor glomerular abnormality
N00.1	Acute nephritic syndrome with focal and segmental glomerular lesions
N00.2	Acute nephritic syndrome with diffuse membranous glomerulonephritis
N00.3	Acute nephritic syndrome with diffuse mesangial proliferative glomerulonephritis
N00.4	Acute nephritic syndrome with diffuse endocapillary proliferative glomerulonephritis
N00.5	Acute nephritic syndrome with diffuse mesangiocapillary glomerulonephritis
N00.6	Acute nephritic syndrome with dense deposit disease
N00.7	Acute nephritic syndrome with diffuse crescentic glomerulonephritis
N00.8	Acute nephritic syndrome with other morphologic changes
N00.9	Acute nephritic syndrome with unspecified morphologic changes

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence of primary glomerulonephritis varies between 0.2/100,000 per yr and 2.5/100,000 per yr.
- Immunoglobulin A (IgA) nephropathy is the most common form of glomerulonephritis worldwide.
- Glomerulonephritis accounts for 23% of end-stage kidney disease cases worldwide.
- Glomerulonephritis affects adults and children.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute onset of hypertension.
- Dark, "tea-colored" urine.
- Edema (peripheral, periorbital, or pulmonary).
- Fatigue.
- Concurrent pulmonary hemorrhage and rapidly progressive decline in kidney function may indicate antineutrophil cytoplasmic antibody (ANCA) vasculitis or anti-glomerular basement membrane (anti-GBM) disease.
- Joint pains, oral ulcers, and malar rash are frequently seen with systemic lupus erythematosus (SLE).
- Palpable purpura may be seen in patients with systemic vasculitides such as Henoch-Schönlein purpura, ANCA-associated vasculitis, SLE, or cryoglobulinemia.
- A recent history of endocarditis, cellulitis, or pharyngitis preceding urinary abnormalities may indicate infection-related glomerulonephritis.
- Hepatitis C virus infection may cause membranoproliferative glomerulonephritis (MPGN) with or without cryoglobulinemia.
- Concurrent upper respiratory tract infection (synpharyngitic infection) and gross hematuria may indicate IgA nephropathy.
- Table 1 summarizes the clinical and laboratory features of the different causes of rapidly progressive glomerulonephritis.

ETIOLOGY

Acute glomerulonephritis (GN) may occur as a renal-limited disease or part of a systemic disorder. A description of target antigens is included in Table 2.

In the past decade, the knowledge of the pathogeneses of several acute GNs has greatly expanded. IgA nephropathy is thought to be caused by a multi-hit process that involves under-galactosylated IgA1, development of anti-glycan antibodies, and deposition of immune complexes in the kidney. Post-streptococcal GN is now part of infection-related glomerulonephritis, a broader category that includes IgA-dominant staphylococcus-associated GN. ANCA-associated vasculitis is associated with antibodies to myeloperoxidase and proteinase 3, although not all studies have supported direct disease causation. C3 glomerulopathy, composed of C3 glomerulonephritis and dense deposit disease, is caused by dysregulation of the alternative complement pathway. The alternative complement pathway is now implicated in several different GNs, including IgA nephropathy and ANCA-associated vasculitis, which may have treatment implications in the future.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS FOR HEMATURIA AND/OR PROTEINURIA, IN ADDITION TO ACUTE GLOMERULONEPHRITIS

- Urinary tract infection
- Nephrolithiasis
- Urothelial malignancy
- Polycystic kidney disease
- Acute interstitial nephritis
- Acute tubular necrosis
- Nephrotic syndrome
- Hereditary nephritis (Alport syndrome and thin basement membrane nephropathy)
- Diabetic nephropathy

WORKUP

Initial evaluation of suspected glomerulonephritis consists of laboratory testing.

LABORATORY TESTS

- Urinalysis, with albuminuria (majority of proteinuria in glomerulonephritis is albuminuria) and hematuria (dysmorphic erythrocytes and red cell casts).
- Blood urea nitrogen and serum creatinine to estimate glomerular filtration rate (GFR).
- 24-hour urine collection for total protein excretion (includes albumin plus tubular proteins) and creatinine clearance to document degree of renal dysfunction. Random urine (spot) specimen for evaluation of the protein-to-creatinine ratio instead of a 24-hour collection is also acceptable. Proteinuria in acute glomerulonephritis typically ranges from 500 mg/day to 3 gram/day, but nephrotic-range proteinuria (>3.5 g/day) may be present.
- Streptococcal tests (Streptozyme) and anti-streptolysin O (ASO) quantitative titer (highest in 3 to 5 weeks). The ASO titer is not related to severity of kidney disease, duration, or prognosis.
- Additional serologic testing, including anti-nuclear antibody (ANA), antibody directed against double-stranded DNA (anti-dsDNA), C3, C4, hepatitis B and C viral serologies, HIV, ANCA (myeloperoxidase and proteinase-3 antigens), anti-glomerular basement membrane (GBM) antibodies, cryoglobulins, rheumatoid factor, serum and urine protein electrophoresis with immunofixation, and serum free light chain analysis.
- Hematocrit and platelet count are decreased in thrombotic microangiopathies.
- Blood cultures are indicated in all febrile patients.

IMAGING STUDIES

- Chest x-ray: If opacities present, consider diffuse alveolar hemorrhage as seen in ANCA-associated vasculitis and anti-GBM disease (Goodpasture syndrome).
- Renal ultrasound to exclude structural causes of hematuria and proteinuria. A kidney size of <9 cm in sagittal length may indicate extensive scarring and a low likelihood of reversibility.
- Echocardiogram in patients with new cardiac murmurs or positive blood cultures to rule-out endocarditis and pericardial effusion.
- Kidney biopsy with light, electron, and immunofluorescence microscopy to establish diagnosis.
- Biopsy of other affected organs if systemic vasculitis is suspected.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Low-salt diet if edema or hypertension is present.
- Avoidance of high-potassium foods if patient is hyperkalemic.

ACUTE GENERAL Rx

- Diuretics in patients with significant edema or hypertension.
- Correction of electrolyte abnormalities (hypocalcemia, hyperkalemia) and acidosis.
- High-dose steroids (1 mg/kg/day) for rapidly progressive glomerulonephritis.
- Additional immunosuppressive treatment with alkylating agents, calcineurin inhibitors, antimetabolites, or biologic agents may be required depending on the underlying disease.

TABLE 1 Clinical and Laboratory Features in the Different Causes of Rapidly Progressive Glomerulonephritis

Disease	Typical Clinical Features	Serologic Findings	Complement Levels	Immune Deposits in Glomerulus on Renal Biopsy
Vasculitis				Few/pauci-immune
Granulomatosis with polyangiitis (Wegener granulomatosis)	Prodrome of nasal stuffiness, blocked ears, arthralgia; then onset of hemoptysis, purpura, peripheral neuropathy	C-ANCA	Normal or increased	
Microscopic polyangiitis	Similar to granulomatosis with polyangiitis (Wegener granulomatosis) or affecting the kidneys only (renal-limited) or overlap with polyarteritis nodosa	P-ANCA	Normal or increased	
Anti-GBM disease	Macroscopic hematuria and hemoptysis	Anti-GBM antibodies	Normal or increased	Linear staining for IgG and C3
SLE (diffuse proliferative, WHO class IV)	Previous history of SLE, marked hematuria and proteinuria, hypertension "telescoping" urinary sediment	ANA, anti–dsDNA antibodies	Low C3, low C4	Granular immune deposits
IgA disease	Persistent microscopic hematuria with episodes of synpharyngitic macroscopic hematuria, with proteinuria, hypertension	IgA (increased in about half of cases)	Normal or increased	
Poststreptococcal glomerulonephritis	At 1 to 3 weeks after streptococcal pharyngitis or impetigo, macroscopic hematuria, edema, hypertension, oliguria	ASO, anti-DNase B antibodies	Low C3, normal C4	

ANA, antinuclear antibody; *anti-DNase B,* anti-deoxyribonuclease B antibody; *anti–dsDNA*, anti–double-stranded DNA antibody; anti-GBM, glomerular basement membrane antibody; *ASO*, antistreptolysin O antibody; *C-ANCA,* cytoplasmic antineutrophil cytoplasmic antibody; *IgA,* immunoglobulin A; *IgG,* immunoglobin G; *P-ANCA,* perinuclear antineutrophil cytoplasmic antibody; *SLE,* systemic lupus erythematosus; *WHO,* World Health Organization.
Ronco C et al: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.

TABLE 2 Antigens Identified in Glomerulonephritis

Poststreptococcal GN	Streptococcal Pyrogenic Exotoxin B, Plasmin Receptor
Anti-GBM disease	α3 type IV collagen (likely induced by molecular mimicry)
IgA nephropathy	Immune complex of anti-glycan antibodies and complement components
Membranous nephropathy	Phospholipase A_2 receptor (idiopathic), neutral endopeptidase in podocyte (congenital), HBeAg (hepatitis associated)
Staphylococcus aureus–associated GN	*Staphylococcus* superantigens induce polyclonal response; not necessarily antigen in glomeruli
Membranoproliferative GN	HCV and HBsAg in hepatitis-associated MPGN
ANCA-associated vasculitis	Proteinase 3 (C-ANCA) and myeloperoxidase (P-ANCA) in neutrophils; antibodies to lysosome-associated membrane protein 2 (LAMP2) on endothelial cells (likely induced by molecular mimicry to fimbriated bacterial antigens)

ANCA, Antineutrophil cytoplasmic antibody; *GBM,* glomerular basement membrane; *GN,* glomerulonephritis; *HBeAg,* hepatitis B virus early antigen; *HBsAg,* hepatitis B surface antigen; *HCV,* hepatitis C virus; *IgA,* immunoglobulin A; *MPGN,* membranoproliferative glomerulonephritis.
Adapted from Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

- Treatment of streptococcal infection with penicillin (or erythromycin in penicillin-allergic patients). Hemodialysis in patients with diuretic-resistant volume overload, refractory hyperkalemia, uremic symptoms, and severe metabolic acidosis. Plasma exchange therapy for antibody removal for diffuse alveolar hemorrhage or rapidly progressive glomerulonephritis should be considered.

CHRONIC Rx

- Periodic monitoring of blood pressure, urinalysis, serum creatinine and blood urea nitrogen, serum albumin, and random urine protein-to-creatinine ratio.
- Angiotensin–converting-enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) to reduce proteinuria.
- Lipid management with statins and fibrates as indicated.
- Monitor for side effects related to immunosuppression such as infection, leukopenia and anemia, osteoporosis or osteopenia, gastrointestinal ulcers, high blood pressure, and tumors.
- Routine health maintenance with vaccinations for influenza and pneumococcus, age-appropriate vaccinations, and age-appropriate malignancy screening. Live vaccines are contraindicated in patients treated with immunosuppressants.

DISPOSITION

- Prognosis is generally correlated to initial serum creatinine and degree of renal fibrosis on biopsy.
- In general, prognosis is worse in patients with heavy albuminuria/proteinuria, low GFR at presentation, severe hypertension, and kidney biopsy-proven crescentic glomerulonephritis.
- Recovery of kidney function occurs within 8 to 12 weeks in 95% of patients with poststreptococcal glomerulonephritis.

REFERRAL

- Nephrology consultation for all patients with suspected glomerulonephritis. Urgent consultation is recommended if hyperkalemia, acidosis, or azotemia is present.

PEARLS & CONSIDERATIONS

COMMENTS

- Diagnosis of acute GN is established by kidney biopsy. Biopsy is indicated when the histologic diagnosis will alter the treatment plan, especially with systemic illnesses; significant proteinuria (>500 mg to 1 g per day); or increasing serum creatinine. A search for systemic illness, including infections, autoimmune disease, and malignancy is required with careful history, physical examination, and serologic tests. Some patients with suspected glomerulonephritis may not require a kidney biopsy because of the success of supportive therapies (e.g., infection-related GN).
- Nephrology consultation should be obtained before initiating immunosuppressive therapy. ACE inhibitor or ARB therapy is essential for proteinuria reduction, unless contraindicated. Spironolactone has been added to ACE inhibitor treatment for greater proteinuria reduction.
- Periodic monitoring for side effects of immunosuppressive drugs and complications of corticosteroids is necessary.
- Monitor lipids and treat persistent hyperlipidemia.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Glomerulonephritis (Patient Information)
Acute Kidney Injury (Related Key Topic)

AUTHOR: **Rupali Avasare, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Acute kidney injury (AKI) is defined as a rapid impairment in kidney function that results in retention of products in the blood normally excreted by the kidneys. The decline in kidney function can result in volume overload and dysregulation of acid-base status and electrolytes. Current consensus criteria for diagnosis of AKI requires an increase in serum creatinine of 0.3 mg/dl within 48 hours or 1.5 times baseline serum creatinine over 7 days, and/or a decline in urine in output to <0.5 ml/kg/hour for 6 to 12 hours. AKI is further graded by severity as described in Table 1.

SYNONYMS

AKI
Acute renal failure (ARF)
Acute renal insufficiency syndrome
Acute kidney failure

ICD-10CM CODES

N17.9	Acute kidney failure, unspecified
N17.0	Acute kidney failure with tubular necrosis
N17.1	Acute kidney failure with acute cortical necrosis
N17.2	Acute kidney failure with medullary necrosis
N17.8	Other acute kidney failure
N99.0	Postprocedural (acute) (chronic) kidney failure
O90.4	Postpartum acute kidney failure

EPIDEMIOLOGY & DEMOGRAPHICS

- Using consensus criteria, an estimated 20% of hospitalized patients and nearly 60% of intensive care unit patients develop AKI.
- AKI occurs in 20% of patients with moderate sepsis and in >50% of patients with septic shock and positive blood cultures.
- Greater than 40% of hospital-associated AKI is iatrogenic.
- AKI in hospitalized patients is associated with increased hospital length-of-stay and cost.
- Most common cause of AKI in hospitalized patients is intrinsic kidney failure caused by acute tubular necrosis (ATN) and prerenal azotemia.
- Key risk factors for AKI include older age, preexisting chronic kidney disease, diabetes mellitus, and preexisting proteinuria.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Early or mild AKI may be asymptomatic
- Frequent presenting symptoms include weakness, anorexia, generalized malaise, and nausea
- Patients may develop oliguric or nonoliguric kidney injury
- Oliguria is defined as <400 to 500 ml of urine per 24 hours
- Physical examination should focus on evaluation of volume status
- Findings vary with duration and rapidity of onset of renal failure and underlying cause of AKI
- Peripheral edema from volume overload, heart failure, liver failure, or nephrotic syndrome
- Pulmonary edema
- Arrhythmias from electrolyte imbalances and metabolic acidosis
- Neurologic findings include altered mental status, delirium, lethargy, myoclonus, seizures, and flapping tremor (asterixis)
- Pruritus, uremic odor
- Flank pain
- Painless hematuria may be seen with glomerulonephritis, whereas painful hematuria is more consistent with obstructive uropathy
- Fasciculations, myoclonus, muscle cramps
- Pericardial effusion and/or pericardial rub
- Fever, skin rash, and arthralgia can be seen with systemic vasculitis
- Classic triad of fever, rash, and eosinophilia in the setting of AKI suggests allergic interstitial nephritis (AIN) and occurs in only 30% of cases. When considering AIN as the cause of AKI, a careful review of medications is required

ETIOLOGY

- **Prerenal:** Inadequate renal perfusion caused by hypovolemia, congestive heart failure (impaired cardiac output), cirrhosis (fluid third-spacing), sepsis (vasodilation), abdominal compartment syndrome, or other. Sixty percent of community-acquired cases of AKI are from prerenal conditions.
- **Postrenal:** Bladder outlet obstruction (prostatic enlargement, urethral fibrosis), ureteral obstruction (stones, bladder masses, retroperitoneal fibrosis, ureteral fibrosis), or renal vein occlusion. With two functioning kidneys, bilateral obstruction is usually required to cause significant AKI. Postrenal causes of AKI account for 5% to 15% of community-acquired AKI.
- **Intrinsic renal:** ATN, glomerulonephritis, AIN. Common causes of ATN include ischemia (e.g., hypotension or shock, postcardiac bypass, or aorta surgery), rhabdomyolysis, sepsis, drug toxicity (e.g., aminoglycosides, amphotericin, cisplatin), and iodinated radiocontrast nephropathy. Contrast-induced nephropathy is the third-most common cause of new-onset AKI in hospitalized patients. AIN can develop after exposure to a variety of medications, most commonly nonsteroidal antiinflammatory drugs, antibiotics, and proton pump inhibitors. Microvascular diseases that cause AKI include thrombotic microangiopathies (e.g., thrombotic thrombocytopenic purpura, classical and atypical hemolytic uremic syndrome, or preeclampsia) and cholesterol emboli.
- Causes of AKI are listed in Table 2.
- Nearly one third of cases of AKI may be prevented or mitigated by appropriate intervention.

DIAGNOSIS

Table 3 summarizes useful clinical features, urinary findings, and confirmatory tests in the differential diagnosis of AKI.

DIFFERENTIAL DIAGNOSIS

Refer to "Etiology." Diagnostic tests to distinguish prerenal and renal AKI are described in Table 4. A diagnostic approach to patients with suspected AKI is shown in Fig. 1.

LABORATORY TESTS

- Elevated serum creatinine: Rate of rise is approximately 0.5 to 2 mg/dl per day in complete kidney failure.
- Standard estimating equations for glomerular filtration rate (GFR) require steady-state creatinine levels and are not recommended to estimate GFR during AKI.
- Elevated blood urea nitrogen (BUN): BUN-to-creatinine ratio is commonly >20:1 in prerenal azotemia, postrenal azotemia, and acute glomerulonephritis.
- BUN-to-creatinine ratio is <20:1 in acute interstitial nephritis and ATN.
- Hyperkalemia, hyperphosphatemia, and metabolic acidosis are common.
- Hypocalcemia and hyponatremia or hypernatremia may occur, depending on underlying etiology.
- Urinalysis is the initial step of diagnostic evaluation. Prerenal and postrenal AKI are typically characterized by a normal urinalysis. Conversely, abnormal findings should prompt further work-up for specific intrinsic causes of AKI that may require urgent intervention. Hematuria and proteinuria imply glomerulonephritis, heavy

TABLE 1 Kidney Disease: Improving Global Outcomes (KDIGO) Criteria for Diagnosis of Acute Kidney Injury

AKI Definition and Staging		
Stage	**Serum Creatinine Criteria**	**Urine Output Criteria**
1	ΔS_{Cr} ≥0.3 mg/dl (30 μmol/L) or S_{Cr}≥1.5, <2.0 × baseline*	UO <0.5 ml/kg per hour × 6-12 h
2	S_{Cr} >2.0, <3.0 × baseline	UO <0.5 ml/kg per hour >12 h
3	S_{Cr} >3.0 × baseline or	
	S_{Cr} ≥4.0 mg/dl with an acute rise ≥0.5 mg/dl (50 μmol/L) or on renal replacement therapy	UO <0.3 ml/kg per hour × 24 h or anuria × 12 h

AKI, Acute kidney injury; *S_{Cr},* serum creatinine; *UO,* urinary output.
*To fulfill AKI criteria, an S_{Cr} rise of ≥0.3 mg/dl must occur within 48 hours; or increase to ≥1.5 times baseline SCr is known or presumed to have occurred within previous 7 days.
Adapted from KDIGO Clinical Practice Guideline for Acute Kidney Injury, 2012.

TABLE 2 Etiologies of Acute Kidney Injury

Prerenal Causes (Decreased Renal Blood Flow)	Intrinsic Renal Causes	Postrenal Causes
Hypovolemia	**Vascular: Large and Small Vessels**	**Ureteral Obstruction**
Renal losses (diuretics, osmotic agents, polyuria)	Trauma	Calculus
Gastrointestinal losses (vomiting, diarrhea)	Renal vein obstruction (thrombosis, ventilation with high-level PEEP, abdominal compartment syndrome)	Tumor (intrinsic or extrinsic)
Cutaneous losses (burns, exfoliative syndromes)	Microangiopathy (thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, preeclampsia)	Fibrosis
Hemorrhage	Malignant hypertension	Ligation during pelvic surgery
Pancreatitis	Scleroderma renal crisis	**Bladder Neck Obstruction**
Decreased Cardiac Output	Transplant rejection	Benign prostatic hypertrophy
Congestive heart failure	Atheroembolic disease	Prostate cancer
Pulmonary embolism	**Glomerular**	Neurogenic bladder
Acute myocardial infarction	Antiglomerular basement membrane disease (Goodpasture syndrome)	Tricyclic antidepressants
Severe valvular heart disease	Antineutrophil cytoplasmic antibody-associated glomerulonephritis (Wegener granulomatosis)	Ganglionic blockers
Abdominal compartment syndrome	Immune complex glomerulonephritis, systemic lupus erythematosus, postinfectious cryoglobulinemia, primary membranoproliferative glomerulonephritis	Bladder tumor
Renal artery obstruction (stenosis, embolism, thrombosis, dissection)	**Tubular**	Calculus
Systemic Vasodilation	Ischemic	Hemorrhage/clot
Sepsis	Cytotoxic	**Urethral Obstruction**
Anaphylaxis	Heme pigment (rhabdomyolysis, intravascular hemolysis)	Strictures
Anesthetics	Crystals (tumor lysis syndrome, seizures, ethylene glycol poisoning, vitamin C megadose, acyclovir, indinavir, methotrexate)	Tumor
Drug overdose	Drugs (aminoglycosides, lithium, amphotericin B, pentamidine, cisplatin, ifosfamide, radiocontrast agents), synthetic cannabinoid use	Phimosis
Afferent Arteriolar Vasoconstriction	**Interstitial**	Renal calcinosis
Hypercalcemia	Drugs (penicillins, cephalosporins, NSAIDs, proton pump inhibitors, allopurinol, rifampin, indinavir, mesalamine, sulfonamides, trimethoprim)	Obstructed urinary catheter, ureteral stent, or ileal conduit
Drugs (NSAIDs, amphotericin B, calcineurin inhibitors, norepinephrine, radiocontrast agents, aminoglycosides)	Infection (pyelonephritis, viral infection)	Pelvic trauma, retroperitoneal hematoma
Hepatorenal syndrome	**Systemic Disease**	
Efferent arteriolar vasodilation (angiotensin converting enzyme inhibitors, aldosterone receptor blockers)	Sjögren syndrome, sarcoidosis, systemic lupus erythematosus, lymphoma, leukemia, tubulonephritis, uveitis	

NSAIDs, Nonsteroidal antiinflammatory drugs; *PEEP,* positive end-expiratory pressure.
Modified from Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

(>3+) proteinuria is associated with nephrotic syndrome, and leukocyturia may signify AIN. Microscopic examination of urine sediment may facilitate diagnosis: Granular casts in ATN, dysmorphic red blood cells or red blood cell casts in acute glomerulonephritis, and white blood cell casts in AIN.

- In oliguric patients, obtain urine sodium and creatinine concentrations for determination of fractional excretion of sodium [$FE_{Na} = 100\% \times (U_{Na} \times P_{Cr})/(P_{Na} \times U_{Cr})$]. FE_{Na} <1% is seen in prerenal AKI and >1% in intrinsic AKI. FE_{Na} may be falsely elevated in patients taking diuretics or falsely low in several intrinsic renal conditions, including acute glomerulonephritis, contrast-induced nephropathy, and rhabdomyolysis.
- Fractional excretion of urea (FE_{Urea}) may be used to assess renal dysfunction in AKI. FE_{Urea} is calculated as [$FE_{Urea} = 100\% \times (U_{Urea} \times P_{Cr}) / (P_{Urea} \times U_{Cr})$]. FE_{Urea} <35% suggests prerenal acute kidney injury, and FE_{Urea} >50% indicates intrinsic AKI. FE_{Urea} is more useful than FE_{Na} during diuretic therapy.
- Urinary osmolarity is 250 to 300 mOsm/kg in ATN (isosthenuria), <400 mOsm/kg in postrenal azotemia, and >500 mOsm/kg in prerenal azotemia and acute glomerulonephritis.
- Blood cultures for suspected sepsis.
- In suspected glomerulonephritis (GN) (e.g., hematuria plus proteinuria, suggestive systemic clinical picture), additional serologic testing may be warranted. Abnormal liver function tests and elevated inflammatory markers are nonspecific. Immune complex deposition disorders (e.g., infectious GN, lupus nephritis, cryoglobulinemic vasculitis) are characterized by decreased complement (C3, C4) levels. Specific testing may include antinuclear antibodies (lupus), antineutrophil cytoplasmic antibodies (ANCA-associated vasculitis), anti-glomerular basement membrane antibodies (Goodpasture syndrome), and cryoglobulins. Kidney biopsy is frequently required for diagnostic confirmation.
- Creatinine kinase level is indicated if rhabdomyolysis is suspected; positive blood reaction on a urine dipstick with few or no red blood cells by microscopy may indicate myoglobinuria from rhabdomyolysis, but this finding is not invariable.
- Serum free light chain analysis, serum and urine protein electrophoresis, and serum and urine immunofixation electrophoresis for suspected multiple myeloma or other plasma cell dyscrasias. Myeloma can cause AKI via a variety of mechanisms, including tubular precipitation of light chains (cast nephropathy), hypercalcemia, and amyloidosis, among others.
- Kidney biopsy may be indicated in patients with intrinsic kidney failure when considering specific therapy. The major reasons for renal biopsy are for the differential diagnosis of nephrotic syndrome, distinguishing lupus vasculitis from other vasculitides, and lupus membranous nephropathy from idiopathic membranous nephropathy, confirmation of hereditary nephropathies based on ultrastructure, diagnosis of rapidly progressive glomerulonephritis, distinguishing AIN from ATN, and separation of primary glomerulonephritides. In addition to establishing a diagnosis, biopsy may determine renal prognosis and guide direction of management. Severe interstitial fibrosis is associated with poor renal outcomes.
- Biomarkers of kidney injury have been explored for earlier diagnosis of AKI or to separate intrinsic from prerenal causes. Candidate markers include cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), kidney-injury molecule 1 (KIM-1), and liver fatty acid binding protein (LFABP).
- In 2014, tissue inhibitor of metalloproteinases and insulin-like growth-factor binding protein 7 (TIMP2*IGFBP7) became the first biomarker for AKI risk prediction approved in the U.S. However, there remains little published experience with this test, and the clinical role remains undefined.

IMAGING STUDIES

- ECG for arrhythmia detection, especially in hyperkalemia: Peaked T waves in precordial leads, widening QRS interval, and/or bradycardia with AV nodal blockade

TABLE 3 Useful Clinical Features, Urinary Findings, and Confirmatory Tests in the Differential Diagnosis of Acute Kidney Injury

Cause of Acute Kidney Injury	Some Suggestive Clinical Features	Typical Urinalysis Results	Some Confirmatory Tests
Prerenal azotemia	Evidence of true volume depletion (thirst, postural or absolute hypotension and tachycardia, low jugular venous pressure, dry mucous membranes and axillae, weight loss, fluid output greater than input) or decreased effective circulatory volume (e.g., heart failure, liver failure), treatment with NSAID, diuretic, or ACE inhibitor/ARB	Hyaline casts FE_{Na} <1% U_{Na} <10 mmol/L SG >1.018	Occasionally requires invasive hemodynamic monitoring; rapid resolution of AKI with restoration of renal perfusion
Diseases Involving Large Renal Vessels			
Renal artery thrombosis	History of atrial fibrillation or recent myocardial infarction, nausea, vomiting, flank or abdominal pain	Mild proteinuria Occasionally RBCs	Elevated LDH level with normal transaminase levels, renal arteriogram, MAG3 renal scan, MRA*
Atheroembolism	Usually age >50 yr, recent manipulation of aorta, retinal plaques, subcutaneous nodules, palpable purpura, livedo reticularis	Often normal Eosinophiluria Rarely casts	Eosinophilia, hypocomplementemia, skin biopsy, renal biopsy
Renal vein thrombosis	Evidence of nephrotic syndrome or pulmonary embolism, flank pain	Proteinuria, hematuria	Inferior venacavogram, Doppler flow studies, MRV*
Diseases of Small Renal Vessels and Glomeruli			
Glomerulonephritis or vasculitis	Compatible clinical history (e.g., recent infection), sinusitis, lung hemorrhage, rash or skin ulcers, arthralgias, hypertension, edema	RBC or granular casts, RBCs, white blood cells, proteinuria	Low complement levels; positive antineutrophil cytoplasmic antibodies, antiglomerular basement membrane antibodies, anti-streptolysin O antibodies, anti-DNase, cryoglobulins; renal biopsy
HUS/TTP	Compatible clinical history (e.g., recent gastrointestinal infection, cyclosporine, anovulants), pallor, ecchymoses, neurologic findings	May be normal, RBCs, mild proteinuria, rarely RBC or granular casts	Anemia, thrombocytopenia, schistocytes on peripheral blood smear, low haptoglobin level, increased LDH, renal biopsy
Malignant hypertension	Severe hypertension with headaches, cardiac failure, retinopathy, neurologic dysfunction, papilledema	May be normal, RBCs, mild proteinuria, rarely RBC casts	LVH by echocardiography or ECG, resolution of AKI with BP control
Ischemic or Nephrotoxic Acute Tubular Necrosis			
Ischemia	Recent hemorrhage, hypotension, surgery often in combination with vasoactive medication (e.g., ACE inhibitor, NSAID)	Muddy-brown granular or tubular epithelial cell casts FE_{Na} >1%, U_{Na} >20 mmol/L SG ≈ 1.010	Clinical assessment and urinalysis usually inform diagnosis
Exogenous toxin	Recent contrast medium-enhanced procedure; nephrotoxic medications; certain chemotherapeutic agents often with coexistent volume depletion, sepsis, or chronic kidney disease	Muddy-brown granular or tubular epithelial cell casts FE_{Na} >1%, U_{Na} >20 mmol/L SG ≈ 1.010	Clinical assessment and urinalysis usually inform diagnosis
Endogenous toxin	History suggestive of rhabdomyolysis (coma, seizures, drug abuse, trauma)	Urine supernatant tests positive for heme in absence of RBCs	Hyperkalemia, hyperphosphatemia, hypocalcemia, increased CK, myoglobin
	History suggestive of hemolysis (recent blood transfusion)	Urine supernatant pink and tests positive for heme in absence of RBCs	Hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, and free circulating hemoglobin
	History suggestive of tumor lysis (recent chemotherapy), myeloma (bone pain), or ethylene glycol ingestion	Urate crystals, dipstick-negative proteinuria, oxalate crystals, respectively	Hyperuricemia, hyperkalemia, hyperphosphatemia (for tumor lysis); circulating or urinary monoclonal protein (for myeloma); toxicology screen, acidosis, osmolal gap (for ethylene glycol)
Diseases of the Tubulointerstitium			
Allergic interstitial nephritis	Recent ingestion of drug and fever, rash, loin pain, or arthralgias	White blood cell casts, white blood cells (frequently eosinophiluria), RBCs, rarely RBC casts, proteinuria (occasionally nephritic)	Systemic eosinophilia, renal biopsy
Acute bilateral pyelonephritis	Fever, flank pain and tenderness, toxic state	Leukocytes, occasionally white blood cell casts, RBCs, bacteria	Urine and blood cultures
Postrenal AKI	Abdominal and flank pain, palpable bladder	Frequently normal, hematuria if stones, prostatic hypertrophy	Plain abdominal radiography, renal ultrasonography, postvoid residual bladder volume, computed tomography, retrograde or antegrade pyelography

ACE, Angiotensin-converting enzyme; *AKI,* acute kidney injury; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CK,* creatine kinase; *DNase,* deoxyribonuclease; *ECG,* electrocardiography; FE_{Na}, fractional excretion of sodium; *HUS,* hemolytic uremic syndrome; *LDH,* lactate dehydrogenase; *LVH,* left ventricular hypertrophy; *MAG3,* mercaptoacetyltriglycine; *MRA,* magnetic resonance angiography; *MRV,* magnetic resonance venography; *NSAID,* nonsteroidal antiinflammatory drug; *RBC,* red blood cell; *SG,* specific gravity; *TTP,* thrombotic thrombocytopenic purpura; U_{Na}, urinary sodium concentration.

*Contrast-enhanced MRA and MRV should be used with extreme caution in patients with AKI.

From Skorecki K et al: *Brenner & Rector's the kidney*, ed 10, Philadelphia, 2016, Elsevier.

TABLE 4 Diagnostic Tests to Distinguish between Prerenal and Renal Acute Kidney Injury

Index	Prerenal Causes	Renal Causes
FE_{Na}	<1%	>2%
Urine sodium	<10 mmol/L	>40 mmol/L
Urine/plasma osmolality	>1.5	1 to 1.5
Renal failure index	<1	>2
BUN/creatinine ratio	>20	<10

BUN, Blood urea nitrogen; *FE_{Na},* fractional excretion of sodium. Calculation of FE_{Na}: (Urine sodium × Plasma creatinine)/(Plasma sodium × Serum creatinine) × 100. Renal failure index: (Urine sodium × Urine creatinine)/Plasma creatinine.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

- Chest radiograph to detect signs of congestive heart failure and pulmonary renal syndromes, which frequently present with alveolar hemorrhage (Goodpasture syndrome, ANCA-associated vasculitis)
- Kidney ultrasonography to determine kidney sizes (distinguishes acute from chronic kidney disease), presence of obstruction, and renal vascular status (Doppler study)
- Bladder scan to assess post-void residual urine when urinary obstruction is suspected
- Computed tomography (CT) with radiocontrast administration is typically avoided in AKI. However, unenhanced CT scans may identify obstructing ureteral stones

Rx TREATMENT

Management of AKI depends on the underlying etiology. Some conditions (e.g., glomerulonephritis) require specific therapy, but the general focus of treatment for established AKI is supportive care and limiting additional injury. Fig. 2 illustrates an algorithm for management of AKI.

NONPHARMACOLOGIC THERAPY

- Withdraw nephrotoxic medications.
- Evaluate volume status and correct hypovolemia. Goal of therapy is to increase cardiac output and improve tissue perfusion.
- Among patients in intensive care units, utilize hemodynamic tools to avoid excessive fluid administration in patients who are non-volume responsive.
- Dietary modification: (1) Energy prescription of 29 to 36 Kcal/kg per day, (2) potassium restriction (60 mEq per day), (3) sodium restriction (90 mEq per day), (4) phosphorus restriction (800 mg per day), and (5) protein supplementation of 0.6 to 1.4 g/kg per day depending on requirement for dialysis.
- Daily weight to monitor for fluid retention (in addition to intake and output measurement).
- Modification of drug dosages or schedules of renally excreted medications. Dosing should consider the trajectory of renal function (during evolving and recovering AKI) and may require additional adjustments in patients who require dialysis.

ACUTE GENERAL Rx

- Correct electrolyte abnormalities and metabolic acidosis.
- Administer loop diuretics for volume overload.
- Administer vasopressors or vasodilators, when appropriate, to optimize cardiac output in congestive heart failure.

Specific treatment is variable and dependent on etiology of AKI:

- Prerenal: IV volume expansion with isotonic solutions in hypovolemic patients or those with shock.
- Intrinsic kidney failure: Discontinue all potential nephrotoxins and treat condition(s) causing kidney failure. In severe AIN cases, consider a trial of corticosteroids. For acute noninfectious glomerulonephritis, high-dose pulse corticosteroids are first-line therapy, typically in conjunction with other immunomodulatory therapy and plasma exchange, depending on the clinical scenario.
- Postrenal: Eliminate cause of obstruction. Immediate bladder catheter insertion for suspected bladder outlet obstruction. Percutaneous nephrostomy tubes or ureteral stents may be required for upper tract obstruction.
- Hyperkalemia-related ECG changes: IV (intravenous) calcium if electrocardiographic changes present; IV insulin and/or glucose to shift potassium into cells; and IV bicarbonate therapy when metabolic acidosis is present to shift potassium into cells. These three treatments are temporary, and definitive therapy requires potassium removal via the gastrointestinal tract (potassium-binding agents or cathartics) or urinary tract by diuretics or dialytic therapy.

Dialysis in AKI:

- General indications for initiation of dialysis during AKI
  1. Uremic symptoms (encephalopathy, pericarditis)
  2. Extracellular fluid volume overload refractory to medical management
  3. Severe acid-base imbalance refractory to medical management
  4. Significant electrolyte derangement (e.g., hyperkalemia, hyponatremia) refractory to medical management
- Among critically ill patients, dialysis may be warranted even in the absence of the previous indications. Optimal timing of initiation of dialysis remains controversial and is not solely dependent on previous metabolic parameters. Recent clinical trials have not shown early dialysis in AKI to carry a mortality benefit.
- Intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT) have similar outcomes for patients with AKI. However, CRRT is associated with greater hemodynamic stability and fluid removal compared to conventional IHD. CRRT is the preferred modality in critically ill patients with hemodynamic instability.

ADJUNCTIVE Rx

- Monitoring of renal function parameters and electrolytes.
- Renally excreted drugs are adjusted according to creatinine clearance or glomerular filtration rate to prevent further kidney damage or other medication-related toxicities.
- Prevent further renal insult with appropriate volume expansion, particularly before contrast administration, and avoid nephrotoxic agents. Volume expansion with isotonic solutions is more effective than hydration with hypotonic solutions. Isotonic saline or bicarbonate-containing solutions are effective, with or without concomitant N-acetylcysteine prophylaxis, which has shown conflicting results regarding its ability to reduce the risk of iodinated radiocontrast-induced nephropathy.
- Renal function recovery (ability to discontinue dialysis) varies from 50% to 75% in AKI survivors. Preexisting CKD, longer duration of dialysis dependence, congestive heart failure, and older age are negative prognostic factors for renal function recovery.
- Overall mortality rate in AKI is nearly 25% and approaches 50% to 60% in patients who require acute dialysis.
- The combination of AKI and sepsis is associated with a mortality rate as high as 70%.

PEARLS & CONSIDERATIONS

- Patients with AKI are susceptible to infections and sepsis.
- In patients with community-acquired AKI, it is important to obtain a thorough medication history, including nonprescription medications or supplements.
- AKI survivors are at risk for development of CKD, and follow-up with monitoring of kidney function is essential even after apparent renal recovery.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Acute Renal Failure (Patient Information)
Chronic Kidney Disease (Related Key Topic)

AUTHOR: **Junior Uduman, MD**

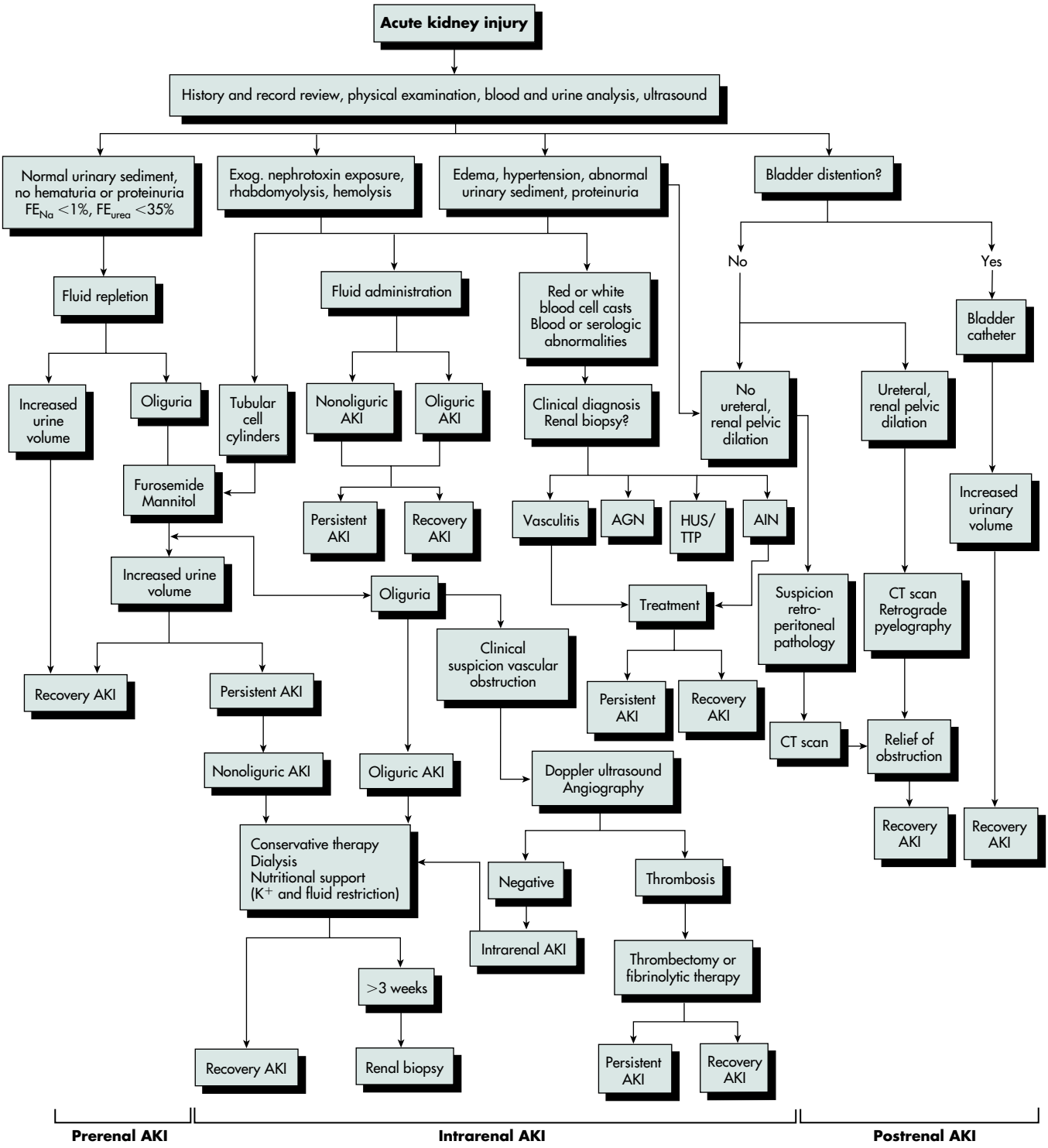

FIG. 1 Diagnostic approach to patients with suspected acute kidney injury *(AKI).* *AGN,* Acute glomerulonephritis; *AIN,* acute interstitial nephritis; *CT,* computed tomography; *Exog.,* exogenous; *HUS/TTP,* hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

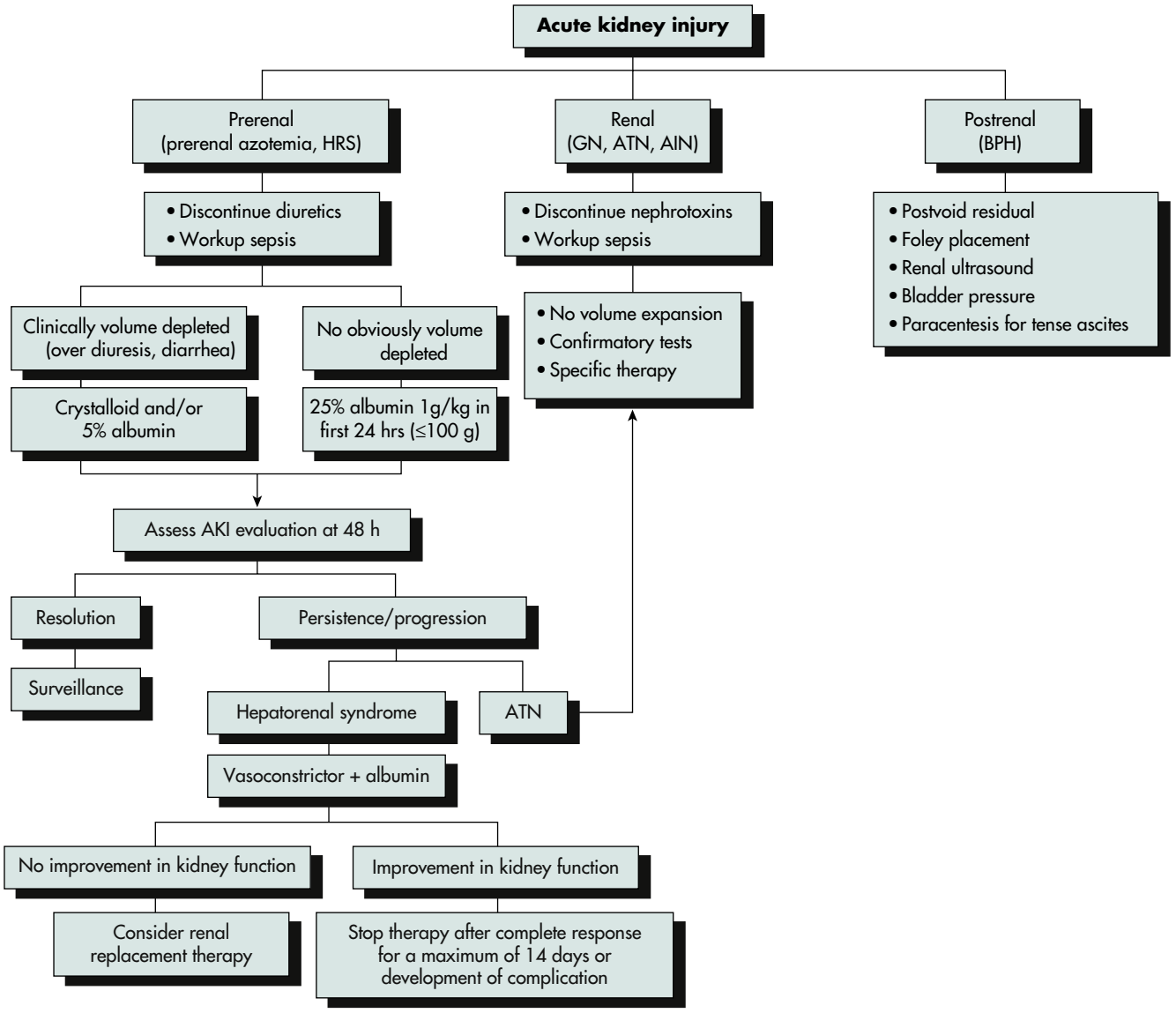

FIG. 2 Algorithm for management of acute kidney injury *(AKI).* *AIN,* Acute interstitial nephritis; *ATN,* acute tubular necrosis; *BPH,* benign prostatic hypertrophy; *GN,* glomerulonephritis; *HRS,* hepatorenal syndrome. (From Ronco C et al: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.)

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BASIC INFORMATION

DEFINITION

Acute liver failure (ALF) is defined as the constellation of acute (<26 wk) severe hepatic injury; synthetic liver dysfunction, specifically coagulopathy (international normalized ratio [INR] >1.5); and any degree of mental alteration (encephalopathy) in a patient without preexisting liver disease, in the absence of acute alcoholic hepatitis. ALF can also be diagnosed in patients with preexisting liver disease, such as Wilson disease, vertically acquired hepatitis B, and autoimmune hepatitis, provided that diagnosis of these conditions was made within the preceding 26 weeks. Box 1 summarizes classifications of acute liver failure.

SYNONYMS

Fulminant hepatic failure
Fulminant hepatitis
Fulminant hepatic necrosis
Acute hepatic necrosis
Acute and subacute necrosis of liver
ALF

ICD-10CM CODES

K72	Hepatic failure, not elsewhere classified
K72.0	Acute and subacute hepatic failure
K72.00	Acute and subacute hepatic failure without coma
K72.01	Acute and subacute hepatic failure with coma

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Affects approximately 2000 people/yr in U.S. and 1-8 people per million population in the U.K.

PREDOMINANT SEX AND AGE: Seen more often in women (90% of cases), average age 38 yr

RISK FACTORS:

- Intentional or inadvertent drug overdose
- Risk factors for viral hepatitis:
  1. Intravenous drug use
  2. Occupational exposure to blood or body fluids
  3. Blood transfusions
  4. Hemodialysis
  5. Intranasal cocaine use
  6. Imprisonment
  7. Travel to endemic hepatitis areas
- Previous alcohol use
- Hepatotoxic medications
- Critical illness

ETIOLOGY

- Common causes in the Western world:
  1. Acetaminophen toxicity (46%)
  2. Indeterminate (14%)
  3. Idiosyncratic drug reaction (12%)
  4. Viral hepatitis (A, B) (10%)

Other, more rare causes include alcoholic hepatitis, autoimmune hepatitis, Wilson disease, ischemic hepatopathy, Budd-Chiari syndrome, acute fatty liver of pregnancy, venoocclusive disease, toxin ingestion (e.g., mushroom poisoning *[Amanita phalloides]*), sepsis, infiltrative malignancy (breast cancer, lymphoma, myeloma, melanoma, small cell lung cancer), and other viruses (adenovirus, hepatitis E, HSV). Box 2 summarizes possible etiologies of liver failure.

CLINICIAN PRESENTATION & PHYSICAL FINDINGS

- **CLINICAL PRESENTATION** Initial symptoms of ALF are mostly nonspecific, such as fatigue, lethargy, anorexia, and nausea/vomiting. Pruritus, jaundice, and right upper quadrant abdominal pain and distention may be present.
- **PHYSICAL EXAMINATION** Findings include, by definition, abnormal neurologic findings of encephalopathy (see Table 1). Other findings may include jaundice, asterixis, hepatomegaly, decreased hepatic mass on percussion, and ascites. Multisystem organ failure can ensue. In rare cases, as the hepatic encephalopathy progresses, cerebral edema and increased intracranial pressure can occur, with abnormal pupillary exam findings, hypertension, bradycardia, respiratory depression (Cushing's triad), seizures, and loss of brain stem reflexes. Vesicular skin lesions are suggestive of herpes simplex virus (HSV).
- Family history of unexplained liver disease/cirrhosis should prompt slit lamp ocular examination for the identification of Kayser-Fleischer rings (copper rings around the iris seen in Wilson disease).

LABORATORY FINDINGS

- Patients with ALF typically have a prolonged prothrombin time (INR >1.5), elevated transaminases, and elevated bilirubin, and may have a low platelet count (<150,000).
- Other possible laboratory findings can include an elevated BUN/creatinine (studies show 30% to 50% also have acute kidney injury), hypoglycemia (impairment of gluconeogenesis), hypophosphatemia, hypomagnesemia, hypokalemia, metabolic acidosis or respiratory alkalosis, elevated LDH, and elevated ammonia.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Severe acute hepatitis, also known as acute liver injury (including alcoholic hepatitis): Jaundice and coagulopathy without encephalopathy
- Acute on chronic liver failure (in patients with liver disease duration >26 weeks)
- Cirrhosis (includes decompensated cirrhosis)
- Hepatocellular carcinoma

WORKUP (BOX 3)

- Fig. 1 describes an algorithm for evaluation of acute liver failure.
- Clinical history is critical, but in the case of patients with severe encephalopathy, the history may be limited, and efforts should be made to obtain information from the patient's family. Important history components include medication use (6-month history of prescriptions, over-the-counter medications, herbal supplements), alcohol use, recreational drug use, prior symptoms of jaundice, onset of symptoms, history of depression and suicide attempts, recent travel to endemic areas of viral hepatitis, sexual exposures, previous blood transfusions, family history of liver failure/disease, history of malignancy, or hypercoagulable state.

BOX 1 Classifications of Acute Liver Failure

Trey and Davidson
Fulminant hepatic failure: Development of HE within 8 weeks of onset of symptoms

British Classification
Acute liver failure (includes only patients with encephalopathy)

Subclassification Depending on the Interval between the Onset of Jaundice and HE
- Hyperacute liver failure: 0 to 7 days
- Acute liver failure: 8 to 28 days
- Subacute liver failure: 29 to 72 days
- Late-onset acute liver failure: 56 to 182 days

French Classification
Acute hepatic failure: A rapidly developing impairment of liver function
Severe acute hepatic failure: Prothrombin time or factor V concentration below 50% of normal with or without HE

Subclassification
- Fulminant hepatic failure: HE within 2 weeks of onset of jaundice
- Subfulminant hepatic failure: HE between 3 and 12 weeks of onset of jaundice

International Association for the Study of Acute Liver Failure
Acute liver failure (occurrence of HE within 4 weeks after onset of symptoms)

Subclassification
- Acute liver failure—hyperacute: Within 10 days
- Acute liver failure—fulminant: 10 to 30 days
- Acute liver failure—not otherwise specified
- Subacute liver failure (development of ascites and/or HE from 5 to 24 weeks after onset of symptoms)

HE, Hepatic encephalopathy.

From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.

BOX 2 Etiologic Classification of Acute Liver Failure

Acetaminophen Toxicity
Idiosyncratic Drug Injury

Infrequent Agents
Isoniazid
Valproate
Halothane
Phenytoin
Sulfonamide
Propylthiouracil
Amiodarone
Disulfiram
Dapsone
Bromfenac
Troglitazone
Zidovudine
Lamivudine
Lamotrigine
Gatifloxacin
Methotrexate

Miscellaneous Agents
Ecstasy
Cocaine
Phencyclidine

Rare Agents
Carbamazepine
Ofloxacin
Ketoconazole
Lisinopril
Nicotinic acid
Labetalol
Etoposide
Imipramine
Interferon alfa
Flutamide
Tolcapone
Nefazodone
Oral contraceptives

Combination Agents with Enhanced Hepatotoxicity
Alcohol-acetaminophen
Trimethoprim-sulfamethoxazole
Rifampicin-isoniazid
Amoxicillin-clavulanic acid

Viral Hepatitides
Hepatitis A, B, C, D, E, G
Human herpesvirus
Cytomegalovirus
Epstein-Barr virus
Herpes simplex virus
Varicella zoster virus
Paramyxovirus
Parvovirus B19
Adenovirus
Togavirus
Parvovirus
SEN virus
TT virus
Yellow fever virus

Toxins
CCl_4
Amanita phalloides
Yellow phosphorus
Herbal products

Vascular
Ischemic
Veno-occlusive disease
Budd-Chiari syndrome
Malignant infiltration
Non-Hodgkin's lymphoma

Miscellaneous
Wilson disease
Autoimmune hepatitis
Acute fatty liver of pregnancy
Reye syndrome

CCl4, Carbon tetrachloride.
From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

TABLE 1 Grades of Encephalopathy

Grade	Description
I	Changes in behavior with minimal change in level of consciousness (mild confusion, slurred speech, disordered sleep)
II	Gross disorientation, drowsiness, possibly asterixis, inappropriate behavior
III	Marked confusion (stupor), incoherent speech, sleeping most of the time but rousable to vocal stimuli
IV	Comatose, unresponsiveness to pain, decorticate or decerebrate posturing

- Physical examination should include mental status examination. Grading of hepatic encephalopathy should be performed (Table 1). Perform an asterixis maneuver, consider psychometric tests (i.e., number connection test) to detect subtle degree of encephalopathy. Looking for stigmata of chronic liver disease is also important as their presence has different diagnostic and management implications.
- Laboratory evaluation should be targeted to assess the severity of ALF, as well as its etiology. Early testing includes complete blood count, liver function tests (LFTs) including prothrombin time and INR, chemistry panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, magnesium, phosphate, calcium), arterial blood gas, arterial lactate, blood type and screen, acetaminophen level, ethanol level, toxicology screen, viral hepatitis serologies (hepatitis A IgM, hepatitis B surface antigen, anti-hepatitis B core IgM, anti-hepatitis C antibody [IgM and IgG]), hepatitis C viral load (HCV RNA), anti-hepatitis E IgM and IgG, HSV-1 IgM and HSV PCR, EBV DNA PCR, CMV DNA PCR, anti-hepatitis D IgM and IgG, hepatitis D viral load (HDV RNA), ceruloplasmin level (as well as serum copper and 24-hour urine copper if high suspicion), pregnancy test, arterial ammonia level, autoimmune markers (ANA, ASMA, anti-LKM-1, total IgG levels), HIV-1, HIV-2, amylase, lipase. Imaging studies include abdominal ultrasound with Doppler to evaluate for Budd-Chiari syndrome, portal hypertension, hepatic congestion, and hepatic steatosis. Cirrhosis cannot be diagnosed in the setting of ALF, as the liver may appear nodular in ALF due to massive necrosis; consider cross-sectional imaging of the liver (triphasic CT, MRCP, or MRI with gadolinium). CT or MRI of the head should be considered to ensure no other causes for altered mental status.
- Prompt liver biopsy (via transjugular approach to decrease risk of bleeding) should be performed in cases in which:
  1. The etiology is unknown after the initial workup; *or*
  2. Etiology is thought to be secondary to autoimmune hepatitis, malignancy, or HSV.

BOX 3 Investigations in Fulminant Hepatic Failure

Baseline essential investigations
Biochemistry
- Bilirubin, transaminases
- Alkaline phosphatase
- Albumin
- Urea and electrolytes
- Creatinine
- Calcium, phosphate
- Ammonia
- Acid-base, lactate
- Glucose

Hematology
- Full blood count, platelets
- PT, PTT
- Factors V or VII
- Blood group cross-match
  Septic screen

Omitting lumbar puncture
- Radiology
- Chest radiograph
- Abdominal ultrasound
- Head CT scan or MRI

Neurophysiology
- Electroencephalogram

Diagnostic investigations
  Serum
- Acetaminophen levels
- Cu, ceruloplasmin (>3 yr)
- Autoantibodies
- Immunoglobulins
- Amino acids
- Lactate
- Pyruvate
- Hepatitis A, B, C, E
- EBV, CMV, HSV viral loads
- Other viruses

Urine
- Toxic metabolites
- Amino acids, succinylacetone
- Organic acids
- Reducing sugars

CMV, Cytomegalovirus; *CT,* computed tomography; *EBV,* Epstein-Barr virus; *HSV,* herpes simplex virus; *PT,* prothrombin time; *PTT,* partial thromboplastin time.
From Fuhrman BP, Zimmerman JJ: *Fuhrman and Zimmerman's pediatric critical care,* ed 4, Philadelphia, 2011, Mosby.

COMPLICATIONS

Complications or progression of liver failure may result in cerebral edema due to increased intracranial pressure (in up to 40% of patients), high-output cardiac failure, hypoglycemia, lactic acidosis, acute respiratory distress syndrome,

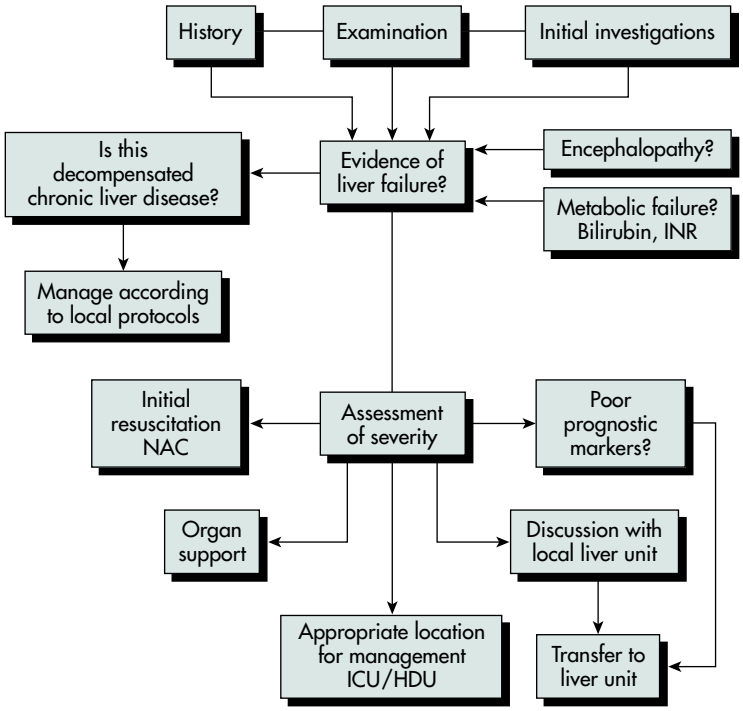

FIG. 1 Initial management of a patient presenting with liver failure. *HDU,* High-dependency unit; *ICU,* intensive care unit; *INR,* international normalized ratio; *NAC,* N-acetylcysteine. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

upper gastrointestinal hemorrhage (in 1.5% of patients), infectious disease from impaired leukocyte function (in nearly 80% patients), acute kidney injury, and pancreatitis (particularly in acetaminophen-induced ALF). Hypotension can occur due to decreased oral intake as well as extravasation of fluid into extravascular space.

Rx TREATMENT (BOXES 4 AND 5)

NONPHARMACOLOGIC THERAPY

- Initial treatment should focus on the patient's mental status.
  1. Grade I encephalopathy may be managed on a medical ward (neuro vital signs q4h).
  2. Grade II, III, and IV encephalopathy should be managed in ICU (elevate head of the bed to 30 degrees).
  3. Decrease stimulation (dimly lit, quiet room, no audible monitor alarms).
- A liver specialist should be notified urgently, and arrangements should be made for imminent transfer to a transplant center.
- Nutritional support should be initiated early. A daily intake goal of 60 g of protein is recommended to prevent catabolism of protein stores. Enteral feeding should be initiated in patients with grade III or IV encephalopathy.
- Fluid support should be initiated if patient is not tolerating oral intake, or signs of hypoperfusion are present. Crystalloid solutions (normal saline in hypotensive patients, ½ normal saline + 75 mEq/L $NaCO_3$ in acidotic patients, normal saline + dextrose in hypoglycemic patients) can be used.

MONITORING

- In patients with high-grade HE awaiting transplant, intracranial pressure (ICP) monitoring is recommended in centers with expertise in ICP monitoring.
- Neurologic examination every 1 to 4 hours is recommended in the absence of ICP monitoring.
- Patients with suspected acetaminophen toxicity should have LFTs monitored every 12 hr. Otherwise, LFTs can be monitored daily.
- Chemistry panels and PT/INR should be monitored every 8 to 12 hr. Correction of coagulopathy should be avoided because it can interfere with assessment of liver function. In the setting of life-threatening bleeding, fresh frozen plasma (FFP) and recombinant factor VIIa can be considered.
- Glucose finger sticks should be checked every 4 hr initially to evaluate for hypoglycemia. If hypoglycemia is detected, dextrose should be added to crystalloid solution.
- Because of the increased risk of infection, daily urine, sputum, and blood cultures, as well as chest radiographs, should be checked in the absence of signs or symptoms of infection.

PHARMACOLOGIC TREATMENT

- If acetaminophen is the known or suspected cause, an IV acetylcysteine protocol must be initiated. *N*-acetylcysteine is not harmful and dramatically alters the course in acetaminophen toxicity, so there should be a low threshold to start, particularly in young patients or those with no known cause of ALF.

BOX 4 Management of Fulminant Hepatic Failure

No sedation except for procedures
Minimal handling
Enteric precautions until infection ruled out
Monitor:
- Heart and respiratory rate
- Arterial BP, CVP
- Core/toe temperature
- Neurologic observations
- Gastric pH (>5.0)
- Blood glucose (>4 mmol/L)
- Acid-base
- Electrolytes
- PT, PTT

Fluid balance
- 75% maintenance
- Dextrose 10% to 50% (provide 6 to 10 mg/kg/min)
- Sodium (0.5 to 1 mmol/L)
- Potassium (2 to 4 mmol/L)

Maintain circulating volume with colloid/FFP
Coagulation support only if required
Drugs
- Vitamin K
- H_2 antagonist
- Antacids
- Lactulose
- *N*-acetylcysteine for acetaminophen toxicity
- Broad-spectrum antibiotics
- Antifungals

Nutrition
- Enteral feeding (1 to 2 g protein/kg/day)
- PN if ventilated

BP, Blood pressure; *CVP,* central venous pressure; *FFP,* fresh frozen plasma; *PN,* parenteral nutrition; *PT,* prothrombin time; *PTT,* partial thromboplastin time.

From Fuhrman BP, Zimmerman JJ: *Fuhrman and Zimmerman's pediatric critical care,* ed 4, Philadelphia, 2011, Mosby.

- The 20-hr protocol is:
  1. Initial loading dose of 150 mg/kg IV given over 60 min followed by;
  2. 12.5 mg/kg IV/hr over 4 hr followed by;
  3. 6.25 mg/kg IV/hr for 16 hr.
- A repeat acetaminophen level and ALT should be checked at hour 18 of NAC treatment. If either the acetaminophen level or the ALT is elevated, the 16-hour portion of treatment (6.25 mg/kg) should be extended and another ALT, INR, or acetaminophen level should be checked every 12 hr. The acetylcysteine can be stopped once the acetaminophen level is undetectable, INR <2, or ALT is shown to be either normal or decreasing. Additional information on acetaminophen overdose is available in the topic "Acetaminophen Poisoning."
- *N*-acetylcysteine therapy outside of acetaminophen poisoning has been investigated and may be beneficial; however, its routine use is not currently recommended by practice guidelines and is center specific.
- Patients should be placed on stress ulcer prophylaxis given the risk of gastrointestinal bleeding.

BOX 5 Hepatic Replacement Therapeutic Options Available to Patients with Fulminant Hepatic Failure

Liver Transplantation
- Cadaveric transplantation
- Whole liver
- Reduced-size liver
- Split liver
- Auxiliary partial liver
- Orthotopic position
- Heterotopic position
- Auxiliary whole liver
- Living-related transplantation
- Left lateral segment
- Left lobe
- Extended left lobe
- Right lobe

Artificial Liver Assist Devices
- Non–cell-based systems
- Charcoal hemoperfusion
- High-volume plasmapheresis
- Continuous high-frequency hemodiafiltration
- Molecular adsorbent recirculating system (MARS)
- Cell-based systems (bioartificial liver assist devices)
- Primary porcine hepatocytes
- Human hepatoblastoma cells
- Extracorporeal liver assist device (ELAD)

Hepatocyte Transplantation

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

- Broad-spectrum antibiotics should be started immediately if infection is suspected. Sources usually include respiratory, urinary, and blood; there is no evidence for empiric antibiotic treatment. Antifungals should be initiated if no initial improvement with antibiotics occurs.
- Norepinephrine is the initial vasopressor of choice; vasopressin can be added as a second pressor to maintain MAP >75 mm Hg. Persistent hypotension despite fluid resuscitation and pressor support should prompt concern for adrenal insufficiency.
- Lactulose is not routinely recommended for encephalopathy treatment; neomycin should be avoided due to concerns of nephrotoxicity.
- Sedative medications should also be avoided as they are not cleared well and may mask signs of worsening encephalopathy or cerebral edema.
- If cerebral edema develops leading to increased ICP, intravenous mannitol is recommended to reduce cerebral edema transiently. Prophylactic hyperventilation is not recommended in patients with ALF.

TABLE 2 King's College Hospital Criteria for Liver Transplantation in Acute Liver Failure

Acetaminophen-Induced Acute Liver Failure	Non–Acetaminophen-Induced Acute Liver Failure
Arterial pH <7.3 (irrespective of grade of encephalopathy) *OR* Grade III or IV encephalopathy *and* Prothrombin time >100 sec *and* Serum creatinine >3.4 mg/dl	Prothrombin time >100 sec (irrespective of grade of encephalopathy *OR* Any of three of the following variables (irrespective of grade of encephalopathy): 1. Age <10 yr or >40 yr 2. Etiology: Non-A hepatitis, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions 3. Duration of jaundice before onset of encephalopathy >7 days 4. Prothrombin time >50 sec 5. Serum bilirubin >18 mg/dl

Sec, Seconds.

Liver support systems:
- Liver support systems have been trialed either to support the patient until the liver recovers or as a bridge to liver transplantation.
- Plasmapheresis can improve hepatic encephalopathy, but no survival benefit has been shown.
- The molecular absorbents recirculation system (MARS) allows albumin-bound toxins to be removed. But this too has failed to show a survival benefit in patients with ALF.

PROGNOSIS

- Overall mortality from ALF is 30% to 40% and improved significantly over the last 20 yr.
- Transplant-free survival in ALF in the setting of acetaminophen, hepatitis A, shock liver, and pregnancy-related disease is >50%; for all other causes of ALF, transplant-free survival is <25%.
- Multiple models have been developed to predict spontaneous recovery in ALF patients (King's College criteria, Clichy criteria, MELD score, APACHE II score).
- The King's College criteria form the basis of the model most commonly used for prognostication (Table 2).
- Transplantation:
  1. Patients with ALF are given the highest priority for liver transplantation.
  2. Contraindications to listing include medical history of psychiatric illness severe enough to affect patients' survival or likelihood of compliance with medications, active sepsis, severe medical comorbidities including malignancy, increasing dependence on ventilator/inotropic support, acute substance abuse, previous episodes of self-harm (>5 episodes), refractory mental illness.
  3. For patients with alcoholic liver disease, many centers require a 6-month abstinence period, but several transplant centers in North America and Europe have transplanted selected patients with alcoholic hepatitis who were unlikely to survive 6 months.
  4. Mortality on the waiting list is 25%; 1-yr and 5-yr survival after transplantation is 73% and 67%, respectively.
  5. Various prognostic criteria used for liver transplantation in patients with fulminant hepatic failure are summarized in Box E6.

PEARLS & CONSIDERATIONS

- ALF is defined as severe hepatic injury (as evidenced by elevated liver enzymes) with INR >1.5 and hepatic encephalopathy occurring <26 wk before presentation in a patient with no prior history of liver disease.
- Close to half of ALF is caused by drug ingestion, usually acetaminophen.
- Given the potential rapidity of deterioration, referral must be made as soon as possible to a liver transplant center.
- There should be a low threshold to start *N*-acetylcysteine.
- Coagulopathy should not be corrected unless life-threatening bleeding occurs or it is recommended by the liver transplant hepatologist.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Acetaminophen Poisoning (Related Key Topic)
Ascites (Related Key Topic)
Encephalopathy (Related Key Topic)
Hepatopulmonary Syndrome (Related Key Topic)
Hepatorenal Syndrome (Related Key Topic)

AUTHORS: **Roxana Chis, MD, Marc Monachese, MD,** and **Talia Zenlea, MD**

BOX E6 Various Prognostic Criteria Used for Liver Transplantation in Patients with Fulminant Hepatic Failure

King's College Criteria

Acetaminophen Overdose

- Arterial pH <7.3 (irrespective of grade of encephalopathy)
  or
- PT >100 sec (INR >6.5) *and*
- Serum creatinine >3.4 mg/dl (>300 μmol/L) *and*
- Patients with grade III and IV hepatic encephalopathy

Non–Acetaminophen-Induced Liver Injury

Acute form (delayed jaundice-encephalopathy <7 days):

- PT >100 sec (INR >6.5) (irrespective of grade of encephalopathy) or any three of the following variables:
- Aged <10 or >40 yr
- Non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions
- Subacute form: Delayed encephalopathy >7 days
- Serum bilirubin 17.4 mg/dl (300 μmol/L)
- PT >50 sec

Clichy Criteria

- Grade III or IV encephalopathy
  and
- Factor V <20% in patients <30 yr
  or
- Factor V <30% in patients >30 yr

Serum Gc Globulin Levels

Decreasing Gc levels due to dying hepatocytes

Serum α-Fetoprotein Levels

Serial increase from day 1 to day 3 has been correlated with survival

Liver Biopsy

70% necrosis is discriminant of 90% mortality

Gc, Plasma group-specific component protein; *INR,* international normalized ratio; *PT,* prothrombin time.

From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Acute lower gastrointestinal bleeding is defined as sudden colonic blood loss.

SYNONYMS

Acute colonic bleeding
Gastrointestinal hemorrhage
Melena
Hematochezia

ICD-10CM CODES

K92.2 Gastrointestinal hemorrhage, unspecified
K92.1 Melena
K62.5 Hemorrhage of rectum and anus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Annual incidence in U.S. of lower gastrointestinal (GI) bleeding is 72/100,000.
- Annual incidence in U.S. of hospitalization is 36/100,000 (about half of that for upper GI bleeding).

PEAK INCIDENCE: The rate of lower GI bleeding, including that necessitating hospitalization, is higher in the elderly.

PREDOMINANT SEX AND AGE: 24.2/100,000 in males versus 17.2/100,000 in females. This increases 200-fold by the ninth decade of life

RISK FACTORS: Risk factors include NSAID use, aspirin use, alcohol abuse, GI malignancy, atrial fibrillation, coagulopathies, prior GI bleed, cirrhosis, constipation, congenital malformations, radiation exposure, recent infectious illness, recent travel, abdominal aortic aneurysm (AAA) repair, and inflammatory bowel disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Attention should be paid in the history to details suggesting the location and etiology of the bleed. For instance, weight loss and abdominal pain suggest inflammatory bowel disease; recent AAA repair, especially with history of a sentinel bleed, raises suspicion for aortoenteric fistula; a history of cirrhosis suggests bleeding from portal hypertension, e.g., varices. Bright red blood is typically from a brisk upper GI bleed, distal colon, or anorectal disease. Melena arises from the upper GI tract, small bowel, or proximal colon. Take a detailed medication history, noting NSAIDs or other drugs that may cause or mimic GI bleeding as well as beta blockers that may mask tachycardia in the setting of significant blood loss.
- The clinician should first and foremost check vital signs, including orthostatics, if stable. Perform ABCs as indicated. Check for pallor and signs of volume depletion, such as delayed capillary refill and skin tenting. Observe for stigmata of liver disease, such as telangiectasias and jaundice. Auscultate for bowel sounds. Absence of bowel sounds may indicate perforation. Palpate the abdomen for pain, masses, and hepatosplenomegaly. Rectal exam should be performed, noting the presence of blood, rate of bleeding, masses, fissures, hemorrhoids, tenderness, and skin changes. If no gross bleed is seen, perform hemoccult testing. Ensure that the bleeding is, in fact, gastrointestinal, excluding hematuria, vaginal bleeding, and wounds.

ETIOLOGY

Diverticulosis is the most common cause of lower GI bleeding at 30%. Internal hemorrhoids are the second most common cause. 15% of lower GI bleeds are due to upper GI bleeding.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Upper GI bleed
- Diverticulosis
- Diverticulitis
- Ischemic colitis
- Postpolypectomy bleeding
- Vascular ectasias (angiodysplasia, arteriovenous malformation)
- Anal fissure
- Rectal ulcer
- Colonic polyps
- Advanced neoplasms
- Hemorrhoids
- Intussusception
- Coagulopathies
- Infectious colitis (*E. coli, Shigella, Salmonella, Giardia*)
- Autoimmune (hemolytic uremic syndrome)
- Radiation colitis or proctitis
- Aortoenteric fistula
- Vasculitis
- Inflammatory (ulcerative colitis, Crohn disease)
- Colonic varices
- Drugs (iron, NSAIDs)
- Foreign body

WORKUP

Establish large-bore intravenous access. If the patient has significant hematochezia without hematemesis, consider performing nasogastric lavage to evaluate for upper GI bleeding. An algorithm for the management of severe hematochezia is illustrated in Fig. 1.

LABORATORY TESTS

- Complete blood count may reveal anemia and/or thrombocytopenia. The hematocrit and hemoglobin should generally be trended every 4 to 6 hours to document the status of the bleed
- Order a comprehensive metabolic panel to evaluate the following: elevated blood urea nitrogen, which indicates reabsorption of red blood cells; elevated creatinine, which indicates poor renal perfusion; liver function tests, which could reveal liver disease that is exacerbating bleeding
- International normalized ratio, especially if patient is taking warfarin
- Partial thromboplastin time, especially if the patient is on heparin
- Type and screen/cross in anticipation of the need for blood products
- Stool studies, including white blood cell count, gram stain, culture, and pathogen-specific testing to identify infectious etiologies

IMAGING STUDIES

- Computed tomography (CT) angiography can potentially identify the location of the bleed as well as abnormal vasculature.
- Perform a tagged red blood cell scan if source is not identified on CT angiography.
- CT scan of the abdomen and pelvis may identify malignancy as the source of bleeding.
- If free air is suspected from perforation, an abdominal or chest plain film should be ordered immediately. An abdominal plain film can also identify radiopaque foreign bodies.
- Abdominal ultrasound if intussusception is suspected.
- Meckel (technetium-99) scan if Meckel diverticulum is suspected.

TREATMENT

Begin crystalloid bolus to maintain a systolic blood pressure of at least 100 mm Hg. Transfuse for hemoglobin and hematocrit of 7 and 21, respectively, or less. If the patient has coronary artery disease or multiple medical comorbidities and is older than 65 yr, the goal hemoglobin and hematocrit are 8 and 24, respectively. Platelets should be maintained above 50,000 mm and international normalized ratio 1.5 or less.

NONPHARMACOLOGIC THERAPY

- Colonoscopy defines the colonic anatomy, can identify the source of bleeding, and allows for potential therapy.
- Endoscopy can be performed if the source of the bleed is suspected to be proximal to the ligament of Treitz.
- Anoscopy can be performed for bleeding internal hemorrhoids or other anorectal disorders.
- Balloon tamponade of esophageal or anorectal bleeds.
- Perform surgery if the source of the bleed cannot be otherwise identified, for aortoenteric fistula, or if air enema for intussusception is unsuccessful.
- Interventional radiology for embolization.
- Ablation.

ACUTE GENERAL Rx

Proton pump inhibitor, histamine 2 blocker if suspecting UGI blood with rapid transit

CHRONIC Rx

Avoid NSAIDs and alcohol. Treat the underlying cause of the bleed, e.g., coagulopathy, portal hypertension, etc. Most patients are prescribed

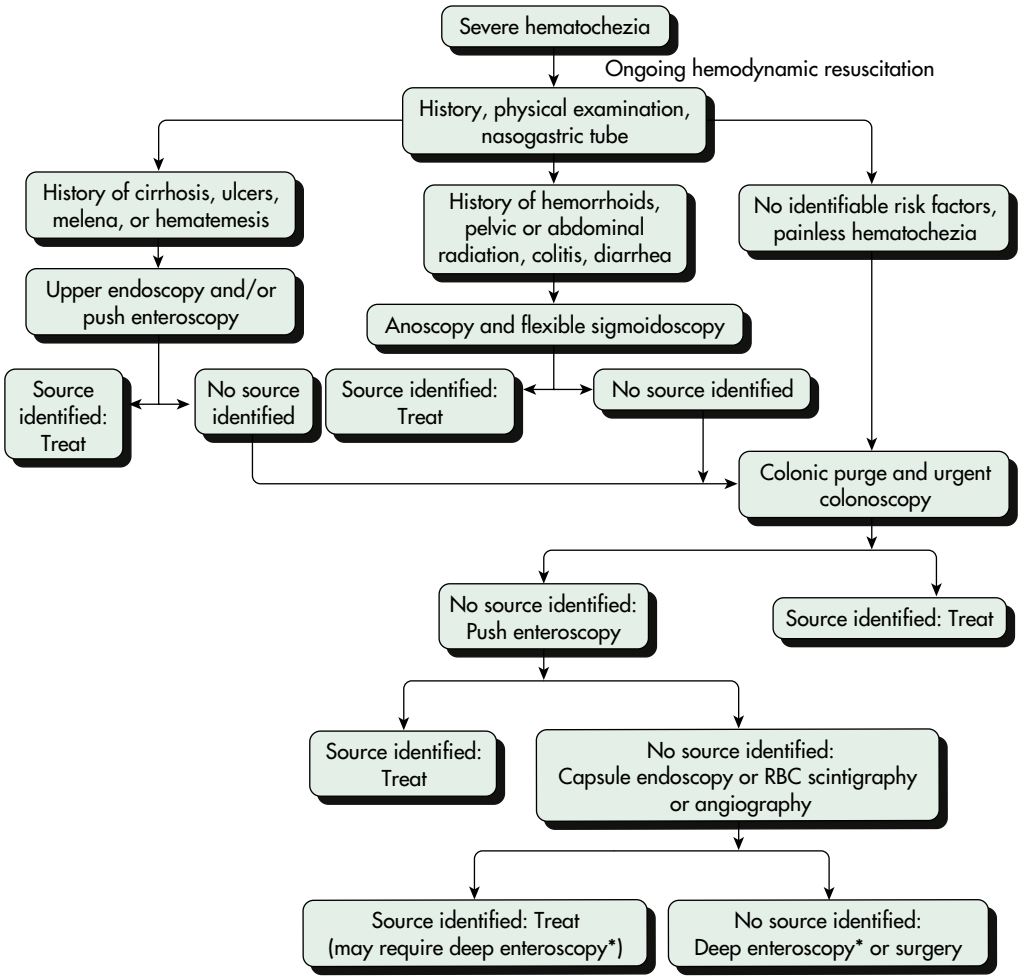

FIG. 1 Algorithm for the management of severe hematochezia modified according to patient's history. *Deep enteroscopy includes double-balloon enteroscopy, single-balloon enteroscopy, and spiral enteroscopy. *RBC,* Red blood cell. (From Feldman M et al: *Sleisenger and Fortran's gastrointestinal liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

daily proton pump inhibitors. Fiber, stool softeners, and analgesic creams may alleviate development and/or symptoms of hemorrhoids.

DISPOSITION

Lower GI bleeding will resolve spontaneously in 80% to 85% of patients. Therefore, if the patient is hemodynamically stable without symptomatic anemia or brisk bleeding, he or she may follow up with his or her primary care physician or a gastroenterologist. However, patients with shock or other hemodynamic compromise, severe bleeding, or significant comorbidities should be admitted to the intensive care unit. These patients are at high risk for acute decompensation and as such require close monitoring and aggressive resuscitation; furthermore, they will require urgent diagnosis and intervention to stop the bleeding. Clinical factors predictive of severe colonic bleeding include aspirin use, at least two comorbid illnesses, pulse greater than 100 beats/minute, and systolic blood pressure <115 mm Hg. The overall mortality rate from colonic bleeding is 2.4% to 3.9%. Independent predictors of in-hospital mortality are age over 70 yr, intestinal ischemia, and two or more comorbidities.

REFERRAL

Patients should be referred to gastroenterology for follow-up.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Bleeding, Gastrointestinal (Algorithm)
Colorectal Cancer (Related Key Topic)
Diverticular Disease (Related Key Topic)
Meckel Diverticulum (Related Key Topic)

AUTHORS: **Ana Castaneda-Guarderas, MD,** and **Michael S. Reich, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Acute lymphoblastic leukemia (ALL) is a malignancy of precursor B or T lymphocytes (lymphoblasts) characterized by uncontrolled proliferation of malignant lymphocytic cells with replacement of normal bone marrow elements and bone marrow failure. Lymphoblastic lymphoma is diagnosed when the disease presents in extramedullary sites (most commonly as mediastinal mass in T-cell disease) *and* less than 25% of the bone marrow is involved.

SYNONYMS

Acute lymphocytic leukemia
Acute lymphoblastic leukemia
ALL

ICD-10CM CODES

C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse

EPIDEMIOLOGY & DEMOGRAPHICS

- ALL is primarily a disease of children (peak incidence occurring at 3 to 5 yr of age).
- Overall incidence is 4.5 cases per 100,000 persons per yr; 60% are under age 20. It is the most common malignancy of childhood. (SEER database accessed 11/26/15.)
- Incidence varies according to race and ethnic group: 14.8 cases per million for blacks, 35.6 cases per million for whites, and 40.9 cases per million for Hispanics.
- Male:female ratio is 55% to 45%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Findings consistent with bone marrow failure and peripheral cytopenias—pallor, bruising, petechiae
- Lymphadenopathy or hepatosplenomegaly
- Fever (disease related or infectious), bone pain, weakness, weight loss, mental status changes, and neurologic findings associated with central nervous system (CNS) involvement (if present)
- T-cell lymphoblastic lymphoma is usually associated with a mediastinal mass
- Table 1 summarizes the clinical presentation of acute lymphoblastic leukemia

ETIOLOGY

- Most cases are sporadic without established risk factors.
- Ionizing radiation exposure appears to be a risk factor.
- Down syndrome (trisomy 21) is associated with an approximately 3% risk of developing leukemia by age 30, predominantly ALL. ALL may be seen with other hereditary premalignancy syndromes (e.g., ataxia-telangiectasia)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Disorders associated with lymphocytosis (lymphocytes >5000/mcl):

- Adults: Chronic lymphocytic leukemia, mantle cell lymphoma, marginal zone lymphoma, hairy cell leukemia
- Adolescents/young adults: Infectious mononucleosis syndromes due to Epstein-Barr virus or cytomegalovirus, among others, may present with lymphocyte abnormalities with appearance suggestive of leukemic blasts
- Disorders associated with circulating blasts or blastlike cells such as acute myeloid leukemia, prolymphocytic leukemia, blastoid mantle cell lymphoma, and Burkitt lymphoma (mature B-cell leukemia/lymphoma)
- Lymphoblastic lymphoma
- Aplastic anemia; ALL may present without circulating leukemia cells and with only manifestations of bone marrow failure

WORKUP

- Identification of circulating abnormal cell population by flow cytometry. CD19 identifies most precursor B cells. Immature leukemic blasts should have *absence* of surface immunoglobulin and will usually express CD34 and stain positive for terminal deoxynucleotidyltransferase (TdT). Cytoplasmic CD3 and CD7 establish immature T-cell lineage in most cases. Aberrant myeloid markers (CD13, CD33) can be seen.
- Cytochemical stains are sometimes easier to perform and may be available sooner but are less specific. ALL blasts should be negative for myeloperoxidase and esterase stains.
- Bone marrow examination (Fig. E1).
- Genetic studies define important treatment categories, of which the most important is Philadelphia chromosome positive (Ph+) vs. Philadelphia chromosome negative (Ph–) disease, as these are treated differently. Ph status can be determined rapidly by polymerase chain reaction (PCR) or fluorescence *in situ* hybridization (FISH) and should be available within 24 to 48 hours of diagnosis. The WHO classification recognizes genetic variants of ALL as distinct syndromes (Table 2), and the clinical significance of common abnormalities is outlined in Table 3.
- Genetic profiling for "Ph-like" ALL (genetic profile similar to Ph+ disease, but no BCR/ABL abnormality) or IKZF1 (IKAROS) mutations may provide additional prognostic information, but may not be uniformly available. Ph-like ALL may respond to tyrosine kinase inhibitor therapy and may behave more like Ph+ ALL.
- Lumbar puncture is usually done at diagnosis, if practical, to assess for CNS involvement and to initiate CNS prophylactic therapy.

LABORATORY TESTS

- Complete blood count reveals normochromic, normocytic anemia, thrombocytopenia.
- Peripheral smear will usually reveal lymphoblasts, but in some cases only the marrow is involved.
- Initial blood work should also include assessment for basic organ function (creatinine, bilirubin), blood glucose (glucocorticoids are part of therapy), and spontaneous tumor lysis syndrome (K^+, Ca^{++}, $PO4^{++}$, uric acid).
- Coagulation studies (full disseminated intravascular coagulation [DIC] screen) prior to lumbar puncture.
- Studies appropriate to identifying and risk-stratifying leukemia as outlined previously.

IMAGING STUDIES

- Chest x-ray to evaluate fever and for the presence of mediastinal mass.
- CT for symptomatic complaints. Be cautious about contrast dye exposure in patients with evidence of spontaneous tumor lysis syndrome to avoid further renal injury.

TREATMENT

ACUTE GENERAL Rx

- Survival of children with ALL has improved from 10% to 90% in the last 40 yr and is a major success story of modern medical science and research. Adults have fared less

TABLE 1 Clinical Presentation of Acute Lymphoblastic Leukemia

Symptoms/ Signs	Etiology	Management
Fever	Disease or infection	Always conduct fever work up and provide broad antimicrobial coverage until infectious etiology is ruled out
Fatigue, pallor	Anemia (ALL infiltrating bone marrow)	Packed red blood cell transfusion (slow if anemia is severe, avoid in hyperleukocytosis)
Petechiae, bruising, bleeding	Thrombocytopenia (ALL infiltrating bone marrow)	Transfuse with platelets
Pain	Leukemia infiltrating bones/ joints, or expanding marrow cavity	Establish diagnosis and start chemotherapy
Respiratory distress/ superior vena cava syndrome	Mediastinal mass	Avoid sedation in presence of tracheal compression. Establish diagnosis as soon as possible and start chemotherapy

ALL, Acute lymphoblastic leukemia.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 2 WHO Classification of Precursor Lymphoid Neoplasms

B-lymphoblastic leukemia/lymphoma, not otherwise specified
B-lymphoblastic leukemia/lymphoma with recurrent cytogenetic abnormalities:
- B-lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*
- B-lymphoblastic leukemia/lymphoma with t(v*;11q23) *MLL* rearranged.
- B-lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22); *TEL-AML1 (ETV6-RUNX1)*
- B-lymphoblastic leukemia/lymphoma with hyperdiploidy
- B-lymphoblastic leukemia/lymphoma with hypodiploidy
- B-lymphoblastic leukemia/lymphoma with t(5;14)(q32;q32); IL3-IGH
- B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); EZA-PBX1 (TCF3-PBX-1)

T-lymphoblastic leukemia/lymphoma
Provisional entities:
- B-lymphoblastic leukemia/lymphoma BCR/ABL1 like
- B lymphoblastic leukemia/lymphoma with iAMP21

Early T-cell precursor lymphoblastic leukemia/lymphoma

*v**, Variable gene partners; *WHO,* World Health Organization.

TABLE 3 More Common Recurrent Cytogenetic Abnormalities in B-Lymphoblastic Leukemia/Lymphoma

Abnormality	Clinical Relevance
t(9;22)(q34;q11.2); *BCR-ABL1*	Incidence approximately 3% in children, 25% in adults, rising with age; requires therapy with tyrosine kinase inhibitors.
t(v*;11q23) *MLL* rearranged	Most common variant is t(4;11); often presents with very high WBC; confers worse prognosis; rare in adults; common in infant leukemia.
t(12;21)(p13;q22); *TEL-AML1*	Common in children (20%-30%); rare in adults; confers improved prognosis.
Hyperdiploidy	Seen in about 25% of children, less in adults; confers favorable prognosis.
Hypodiploidy	Uncommon; confers worse prognosis.
t(5;14)(q32;q32); *IL3-IGH*	Rare; commonly associated with eosinophilia; T-cell disease, ? neutral prognostically
t(1;19)(q23;p13.3); *TCF3-PBX1*	Incidence approximately 5%; intermediate/favorable in children, intermediate/poor in adults.

*v**, Variable gene partners.
Many of these disorders also have distinct immunophenotypes by flow cytometry. Additional molecular abnormalities of recently defined relevance include mutations of *IKZF1,* which encodes a lymphoid transcription factor IKAROS, is associated with high relapse rates and gene expression profile similar to *BCR-ABL1* translocated disease. Gene expression profiling has identified a subgroup of "Philadelphia chromosome-like" acute lymphoblastic leukemia (ALL) with a gene expression similar to *BCR-ABL1* translocation associated disease, which confers worse prognosis, but which may identify new opportunities for targeted therapies.

well, but cure rates have also improved to about 60% to 70% in standard-risk patients in recent trials. Adults in particular have benefited from tyrosine kinase inhibitor therapy for Ph+ ALL, since this disease is more common in adults and may represent 50% or more of disease in patients over 50.

- **Hyperleukocytic leukemia** (WBC >100,000/mcl) is uncommon in ALL and lymphocyte counts of 100,000 may be well tolerated. Prednisone and vincristine usually offer rapid cytoreduction and leukapheresis is rarely (but sometimes) required.
- **Tumor lysis syndrome** is common in ALL and was seen in 23% of patients in one large series. It is sometimes spontaneous—i.e., present before therapy is given—and is a potential cause of early death. Tumor lysis syndrome is caused by release of intracellular potassium, phosphate, and nucleic acids. The nucleic acids adenosine and guanosine are eventually metabolized to uric acid. Elevated potassium may cause cardiac dysrhythmia and death. Elevated uric acid may cause renal failure through renal urate crystal deposition and possibly other mechanisms. Elevated phosphates cause renal calcium phosphate deposition and kidney injury while also lowering serum calcium, which can cause cardiac dysrhythmia and spasms. Therapy is directed mainly at maintaining renal function through vigorous hydration (3 liters normal saline per day if practical, alkalinization not recommended); "forced diuresis" if necessary to maintain urine output at 2 ml/kg/h; and dialysis if necessary to control K^+, phosphates, or fluid balance. Allopurinol, up to 800 mg/day for adults, 300 to 450 mg/m2/day for children, is given routinely. Rasburicase is a recombinant urate oxidase that rapidly lowers uric acid levels. The dose is 0.2 mg/kg, and one dose is usually enough. Rasburicase should be avoided in patients with G6PD deficiency. Phosphate binders are of uncertain value but are usually given. Asymptomatic hypocalcemia is not treated to avoid increasing calcium phosphate deposition. Definitions of laboratory and clinical tumor lysis and defined risk categories are outlined in Table 4.
- Numerous protocols have been used for Ph-ALL, and the specific protocol is likely to be determined by institution/physician familiarity and access to clinical trials, among other factors.
- In the 1990s and early 2000s, it was noted that adolescents and young adult (AYA) patients had better outcomes on pediatric trials than on adult trials. Consequently, this group (currently defined as ages 15 to 39) is now often (especially younger AYAs) treated on pediatric protocols by pediatric services or on adult "pediatric inspired" protocols.
- Therapy for Ph-negative ALL generally has four components:
  1. Induction therapy, typically with corticosteroids, cyclophosphamide (some regimens), vincristine, an anthracycline (doxorubicin or daunorubicin usually), and asparaginase. The CD20 directed antibody rituximab has shown benefit in patients with greater than 20% CD20 expression on their blast cells.
  2. Consolidation therapy is high-dose chemotherapy aimed at preventing relapse after remission and commonly consists of cytarabine and methotrexate in combination with other agents.
  3. Maintenance therapy is low-intensity outpatient therapy that is continued for 2 to 3 yr after completion of consolidation. Prednisone, monthly vincristine, methotrexate, and oral 6-mercaptopurine (POMP regimen) are commonly used.
  4. CNS prophylaxis is universal and is usually done with intrathecal therapy (methotrexate alone or in combination with cytarabine and hydrocortisone) administered by lumbar puncture or an Ommaya reservoir. Due to increased toxicity, cranial radiotherapy is reserved for patients with high-risk features, such as active CNS disease at diagnosis.
- Allogeneic bone marrow transplant in first remission of ALL is controversial because of improving results with current nontransplant therapies. It is usually recommended for patients in whom the likelihood of cure is considered less than 50% to 60% with chemotherapy alone, depending on age and donor availability. Autologous bone marrow transplant is rarely used in Ph-ALL. In 2008, the final results of the MRC/UKALL XII/ECOG E2993 study were published. This study evaluated the relative safety and efficacy of chemotherapy, and autologous and allogeneic transplant after first CR in Ph− patients. This was a randomized trial of 1826 patients with newly diagnosed ALL. Patients who had a matched related donor were offered an allogeneic transplant. Patients without a donor were further randomized to an autologous transplant or chemotherapy and maintenance. The key conclusions of this study were:
  1. Allogeneic transplant in first complete remission is associated with lower relapse rates versus autologous transplant or chemotherapy/maintenance therapy alone in Ph− patients.
  2. Allogeneic transplant in first complete remission improved overall survival in standard risk patients. There was a lower risk of relapse in both standard and high-risk patients. There was high treatment-related mortality in high-risk older

TABLE 4 Tumor Lysis Syndrome

Laboratory Tumor Lysis Syndrome[a]
Uric acid: ≥8 mg/dl or 476 μmol/L
Potassium: ≥6.0 mmol/L
Phosphorus: ≥4.5 mg/dl or 1.5 mmol/L (adults), ≥6.5 mg/dl or 2.1 mmol (children)
- Calcium: Corrected[b] Ca^{++} <7.0 mg/dl or 1.75 mmol/L or ionized Ca^{++} <1.12 mg/dl or 0.3 mmol/L, or 25% increase from baseline uric acid, potassium, phosphorus; 25% decrease for calcium.

Clinical Tumor Lysis Syndrome
Acute kidney injury
- Rise in serum creatinine ≥0.3 mg/dl (26.5 μmol/L).
- Any creatinine >1.5 age-appropriate upper limit normal if no baseline available.
- Oliguria defined as urine output <0.5 ml/kg/hr for 6 hours.

Cardiac arrhythmia
Seizure
Symptomatic hypocalcemia (e.g., neuromuscular irritability such as tetany)

[a]Laboratory tumor lysis syndrome present if two or more abnormalities are present within 3 days before or 7 days after therapy.
[b]Corrected calcium is measured calcium (mg/dl) + 0.8 × (4 – measured albumin g/dl).
From Arber DA et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, *Blood* 127:2391-2405, 2016.

TABLE 5 Risk Factors for Treatment Failure in Recent ALL Trials

t(v*;11q23) *MLL* rearranged.
Hypodiploidy
Minimal residual disease after remission or consolidation*
Philadelphia chromosome-like genomic signature (in Ph-ALL)†
Early precursor T (ETP) ALL (absent CD1a, CD8, weak CD5, myeloid or stem cell antigen expression).

ALL, Acute lymphoblastic leukemia.
*Measured variously after induction or consolidation therapy.
†Standardized testing for this is still in development, but it may have important treatment implications. Note also that many historic risk factors (e.g., T-cell vs B-cell disease) have not been independent risk factors in current trials.
From Roberts KG et al: Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia, *N Engl J Med* 371(11):1005-1015, 2014.

patients. The increased mortality offsets the benefit of lower relapse risk for the patient group.
- The findings did not support autologous transplant as replacement therapy in any ALL group.
- Risk factors for treatment failure in recent protocols are outlined in Table 5. Prognostic factors in ALL are summarized in Tables 6 and 7.
- Therapy of Ph+ ALL consists of a tyrosine kinase inhibitor—imatinib, dasatinib, nilotinib, ponatinib have been used—with chemotherapy.
  1. 2-yr survival rates are reported at 50% to 65%, with various regimens.
  2. Low-intensity induction chemotherapy with dasatinib and prednisone or imatinib, vincristine, and prednisone have resulted in remission rates of 100% and 98% and may allow for less toxicity and hospitalization at diagnosis.
  3. Allogeneic bone marrow transplant is commonly used as consolidative therapy if available but has become more controversial. Maintenance therapy with tyrosine kinase inhibitor is usually given after BMT or non-BMT therapy.
- Therapy of relapsed disease:
  1. Allogeneic bone marrow transplant is offered for relapsed disease, but relapse after BMT is common, and long-term cure rates have been low at about 20%.
  2. In 2017, the FDA approved three new therapies for relapsed ALL: Chimeric antigen receptor T-cell (CAR-T) therapy, a form of targeted immunotherapy, yielded a remission rate of 90% in pediatric and young adult (under age 26 yr) patients with relapsed B-cell ALL. Chimeric antigen T-cells are created by harvesting the patient's T cells, then transfecting them with lentivirus vector that inserts DNA expressing an anti-CD19 domain (the target antigen on B cells) coupled to a T-cell receptor. The T cells expressing the chimeric anti-CD19/T-cell receptor specifically target CD19-expressing B cells. The CAR-T cell population is then expanded ex vivo and reinfused to the patient. About 70% of remissions were durable at 6 months. The main side effect is cytokine release syndrome (CRS) associated with "vascular leak," hypotension, respiratory and renal insufficiency, and coagulopathy. CRS is treated with tocilizumab and anti-IL6 receptor blocking antibody. CAR-T cells for ALL have been given the generic designation tisagenlecleucel (trade name Kymriah). It currently costs $475,000 and is available at centers certified for its use.
  3. Blinatumomab is a bispecific antibody that binds CD19 and CD3, redirecting T cells to leukemia cells. It was FDA-approved for relapsed ALL, including Ph+ ALL, in adults and children. Blinatumomab is administered as a continuous infusion for 4 wk (9 μg/day wk 1, 28 μg/day thereafter), with maintenance therapy for 4 wk every 12 wk. In a large phase III trial, the remission rate was 44% (vs. 25% with chemotherapy), a small number durable. In a smaller phase II trial for Ph+ ALL, the remission rate was 36%. A small number of blinatumomab responses have been durable. Blinatumomab can also be associated with cytokine release syndrome.
- Inotuzumab ozogamicin (IO) is an antibody drug conjugate, in which chemotherapeutic agent calicheamicin is bound to an anti-CD22 antibody. In a large phase III trial, the remission rate was 81% vs. 33% for standard chemotherapy, with a median duration of 4.6 mo. Approximately 40% of IO patients were successfully bridged to transplant vs. 10% with chemotherapy. A small number of responses were durable.
- Survivorship:
  1. Survivors of childhood and adult ALL are increasingly being seen in primary care practices; as of 2006 there were estimated >50,000 survivors, likely increasing by about 2000+ per yr.
  2. Long-term complications of ALL therapy include secondary malignancy from chemotherapy (usually in first 5 to 10 yr) or from radiation (if given, no plateau in risk, congestive heart failure from anthracycline therapy (often manifesting 20 to 30 yr after treatment), osteopenia and avascular necrosis from glucocorticoid therapy, obesity, and neurocognitive defects. Key recommendations include the following:
     a. Echocardiography every 3 to 5 yr for asymptomatic congestive heart failure, more often if anthracycline exposure was >250 to 300 mg/m^2, since asymptomatic congestive heart failure may warrant therapy. This may show up decades after therapy.
     b. Screening for malignancy and endocrinopathies in pertinent radiation fields.
     c. Attention to the increased risk of obesity and metabolic derangement in survivors.
     d. Recent reviews (see references) summarizing current recommendations and guidelines are accessible online (www.survivorshipguidelines.org/pdf/LTFUGuidelines_40.pdf, http://www.sign.ac.uk/pdf/sign132.pdf).

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Acute Lymphocytic Leukemia (ALL) (Patient Information)
Tumor Lysis Syndrome (Related Key Topic)

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TABLE 6 Prognostic Factors in Acute Lymphoblastic Leukemia

Factor	Prognosis	Clinical Application
Age		
<1 yr	MLL+ (70%-80% infants) poor outcome; MLL– same outcome as older children	MLL–do well on standard ALL therapy Potential role for FLT3 inhibitors, proteasome inhibitors, histone deacetylase inhibitors, and hypomethylating agents for MLL+
1-9 yr	Lower (standard) risk	ALL biology may change risk
>9 yr	Higher risk	ALL biology may change risk
WBC		
$<50 \times 10^9$/L	Lower (standard) risk	ALL biology may change risk
$\geq 50 \times 10^9$/L	Higher risk	ALL biology may change risk
CNS		
CNS3	Higher risk of CNS and bone marrow relapse	Therapy intensification
CNS2 Traumatic lumbar puncture with blasts	Higher risk of CNS relapse	CNS directed therapy intensification
Testicular	Higher risk	Therapy intensification
Immunophenotype		
T cell	Higher risk	Poor outcome abolished with current therapy
pre-B (cIgM+)	Standard risk	Poor outcome abolished with current therapy
Early pre-B	Standard risk	Genetics may change risk
Early T-cell precursor	Adverse prognosis	Ongoing studies exploring targeted therapies
Ploidy		
>50 (DI >1.16)	Low risk	Good response to antimetabolites
<44	Higher risk	Therapy intensification
Genetic Alterations		
t(9;22)/*BCR-ABL1*	Higher risk	ABL TKI
t(4;11)/*MLL-AF4*	Higher risk	Potential role for FLT3 inhibitors, proteasome inhibitors, histone deacetylase inhibitors, and hypomethylating agents
t(1;19)/*E2A-PBX1*	Higher risk of CNS relapse	Improved outcome with current therapy
t(12;21)/*ETV6-RUNX1*	Low risk	
IKZF1	Poor prognosis. Present in 80% Ph+ and also in Ph-like ALL	Potential role for tyrosine kinase, JAK inhibitors
NUP214-ABL1	High risk	Potential benefits from TKI
CRLF2	In half of Ph-like cases, associated with Hispanic/Latino, poor outcome	Potential role for JAK inhibitors
CREBBP	Associated with drug resistance and relapse	Potential benefit from histone deacetylase inhibitors
MRD		
Day 15 <0.01%	Excellent outcome	No benefit from 2nd delayed intensification
Slow early responders	Higher MRD = higher risk of relapse	Benefit from augmented delayed intensification
End of induction >1%	Dismal prognosis	Transplantation in first CR
4 months after diagnosis >0.01%	Dismal outcome	Transplantation in first CR

ALL, Acute lymphoblastic leukemia; *CNS,* central nervous system; *CR,* complete remission; *DI,* deoxyribonucleic acid index; *JAK,* Janus kinase; *MLL,* mixed-lineage leukemia; *MRD,* minimal residual disease; *TKI,* tyrosine kinase inhibitor; *WBC,* white blood cell.

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 7 Markers for Poor Prognosis in Adult Acute Lymphoblastic Leukemia

Established Risk Factors	
Age	>60 yr
Presenting WBC count	>30,000/μL (B-cell ALL); >100,000/μL (T-cell ALL)
Immunophenotype	Pro-B cell; early T cell[a]
Cytogenetics	t(4;11)(q21;q23) and other *MLL* rearrangements
	t(9;22)(q34;q11.2) – Philadelphia chromosome
	Hypodiploidy (<44 chromosomes)
	Complex (>5 abnormalities)
Therapy response	Time to complete remission >4 wk
MRD	≥0.01% at 3-6 mo after initiation of therapy[b]
Emerging Risk Factors	
Immunophenotype	CD20
Molecular	BAALC
	FUS
	ERG
	IKZF1[c]
	Ph-like ALL

ALL, Acute lymphoblastic leukemia; *ETP,* early T-cell precursor; *MRD,* minimal residual disease; *Ph,* Philadelphia chromosome; *WBC,* white blood cell.

[a]Initial report characterizing ETP ALL showed a poor outcome. However, subsequent studies have shown variable association with response to therapy.

[b]Different studies have used different time points for MRD assessment.

[c]Focal deletions in IKZF1 are present in up to 70% of Ph-like ALL. However, IKZF1 deletions are associated with adverse outcome irrespective of association with Ph-like phenotype.

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

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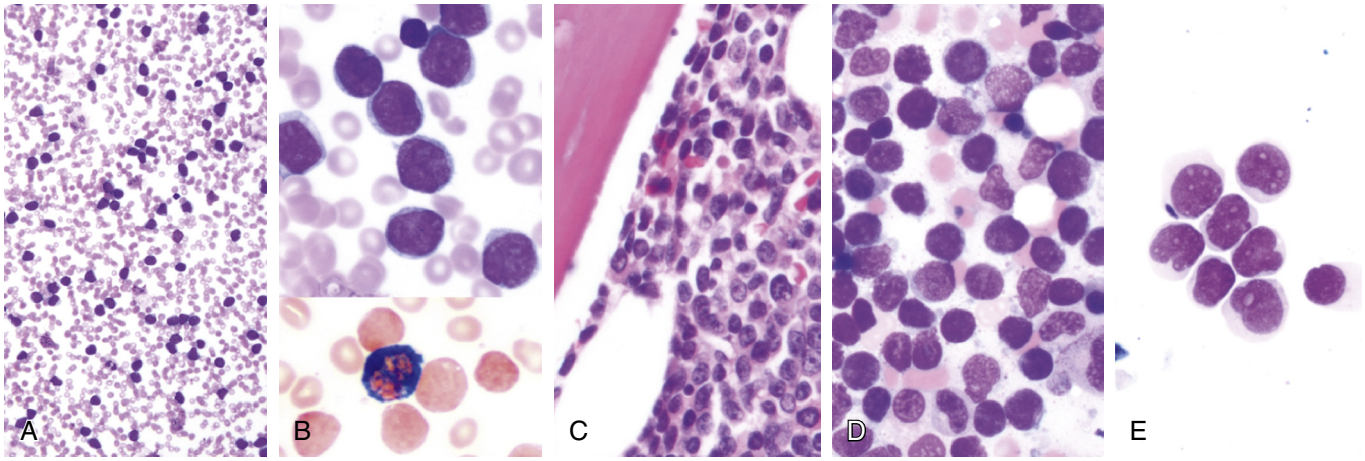

FIG. E1 Acute lymphoblastic leukemia: Peripheral blood, bone marrow biopsy and aspirate, and cerebral spinal fluid. The illustration is from a 37-yr-old male who presented with a white blood count of 170,000/L and more than 90% blasts with lymphoid morphology (**A** and **B,** *top*). An initial myeloperoxidase reaction (**B,** *bottom*) showed the blasts to be negative (positive cell is a segmented neutrophil that serves as an internal control). The bone marrow was packed with blasts as seen on the biopsy and aspirated material **(C** and **D)**. The blasts were immunophenotyped by flow cytometry and were shown to be precursor-B lymphoblasts with the following phenotype: CD34+, HLA–DR+, TdT+, CD19+, CDI0+, cyCD79A+, cylgM–, and slg–. Cytogenetic studies illustrated the t(9;22), and molecular analysis revealed the p190 *BCR/ABL*. A spinal tap showed a WBC count of 120/L with an RBC count of 37/L. The differential showed 80% blasts. The morphology of the blasts on the cytospin of the cerebrospinal fluid **(E)** is somewhat altered by the preparation. Note the absence of significant red blood cells in the specimen. Given the high number of blasts in the peripheral blood, a more traumatic tap would have made it difficult to distinguish between central nervous system disease and contamination of the cerebrospinal fluid specimen by blood. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Acute mesenteric ischemia (AMI) is the sudden onset of intestinal hypoperfusion to all or part of the small bowel caused by emboli, arterial or venous thrombosis, or vasoconstriction from low-flow states, which ultimately leads to ischemia and secondary inflammatory changes.

SYNONYMS

AMI
Mesenteric ischemia, acute

ICD-10CM CODE
K55.0 Acute vascular disorders of intestine

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Accounts for 0.09% to 0.2% of all acute admissions to emergency departments.
- Mortality ranges between 50% and 80%.
- The incidence appears to be increasing. Factors for this include increased awareness among clinicians, improved diagnostic modalities, the aging of the population, and improved intensive care leading to longer survival of sicker patients.

PREDOMINANT SEX AND AGE:

- AMI caused by arterial embolism or thrombosis occurs more frequently in the elderly.
- AMI due to mesenteric venous thrombosis often presents in younger age groups.

GENETICS: No specific genetic predisposition but may be related to underlying factors such as cardiac disease, atherosclerosis, and hypercoagulable states.

RISK FACTORS:

- Advanced age, atherosclerosis, low cardiac output (especially atrial fibrillation), severe cardiac valvular disease, intraabdominal malignancy.
- In the subgroup of cases caused by venous thrombosis, risk factors include hypercoagulable states, portal hypertension, abdominal infection, blunt trauma, pancreatitis, and portal malignancy.
- Additional risk factors for AMI caused by non-occlusive mesenteric ischemia include recent cardiac or aortic surgery, dialysis, hypovolemia, and vasoconstrictive medications (including illicit drugs such as cocaine).
- Table 1 summarizes risk factors for ischemic bowel disease.
- AMI may also occur rarely in patients with no identifiable risk factors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The classic presentation is rapid onset of severe periumbilical pain "out of proportion to physical examination findings."
- Approximately one third of patients present with the triad of abdominal pain, fever, and hemoccult-positive stools. Nausea and vomiting are commonly associated.
- Generally patients with mesenteric venous thrombosis tend to present with less abrupt onset of abdominal pain than those with acute arterial occlusion.
- Initial abdominal examination may be normal, with no rebound or guarding, or may include minimal distention or stool positive for occult blood. An epigastric bruit may be present in some patients.
- Later in the disease course the patient may present with septic shock, gross abdominal distention, absence of bowel sounds, and peritoneal signs. In the elderly, mental status changes may occur.
- If the physical examination demonstrates signs of peritonitis, there is likely irreversible intestinal ischemia with bowel necrosis.

ETIOLOGY

Conventionally, AMI is stratified into four groups by etiology: arterial embolism, arterial thrombosis, venous thrombosis, and nonocclusive mesenteric ischemia (NOMI). The pathophysiology behind these different etiologies is summarized in Table 2. Causes and approximate frequencies of acute mesenteric ischemia are summarized in Table 3. The pathophysiologic mechanisms that cause AMI include:

TABLE 1 Risk Factors for Ischemic Bowel Diseases*

Risk Factor	Arterial Thrombosis	Embolus	Mesenteric Vein Thrombosis	Nonobstructive Mesenteric Ischemia
Advanced age	+	+	+	+
Atherosclerosis	+			
Aortic dissection	+			
Low cardiac output	+	+		+
Congestive heart failure				+
Shock				+
Severe dehydration	+		+	
Cardiac arrhythmias, especially atrial fibrillation		+		+
Severe cardiac valvular disease		+		
Recent myocardial infarction	+			+
Intraabdominal malignancy			+	
Abdominal trauma			+	
Intraabdominal infection			+	
Intraabdominal inflammatory conditions			+	
Parasitic infection (ascariasis)			+	
Hypercoagulable states (venous thrombosis)			+	
Sickle cell anemia			+	
Recent cardiac surgery	+	+		+
Recent abdominal surgery			+	
Vascular aortic prosthetic grafts proximal to the superior mesenteric artery		+		
Hemodialysis				+
Vasculitis	+		+	
Pregnancy			+	
Decompression sickness			+	
Blast lung caused by systemic air embolism		+		
Drugs that cause constriction:				
• Digitalis				+
• Cocaine				+
• Amphetamines				+
• Pseudoephedrine				+
• Vasopressin			+†	+
Estrogen therapy			+	

*A plus sign (+) indicates that the factor is a risk for the disease subtype.
†Especially table after sclerotherapy.
From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

TABLE 2 Pathophysiology of the Four Different Causes of Acute Mesenteric Ischemia (AMI)

Cause	Pathophysiology
Embolism	• Often in patients with atrial fibrillation • Emboli lodge 3-10 cm distal to origin of SMA, often past branching of middle colic artery • Proximal midjejunum is spared
Thrombosis	• Typically these patients have a history of symptomatic stenosis of mesenteric arteries • Any clinical scenario that leads to low flow or hypotension can result in acute-on-chronic arterial thrombosis • Affects the orifice of the SMA • Flush occlusion of the SMA and the entire middle gut is involved during the initial presentation
Nonocclusive	• Low flow state resulting from any type of shock or the use of vasoconstrictors • The entire bowel may be involved
Mesenteric venous thrombosis	• Thrombosis of the veins draining the intestines; SMV, IMV, splenic and portal veins among hypercoagulable patients with cancer or hypercoagulable state • Decreased venous outflow, bowel edema, distension, and decreased mesenteric perfusion

IMV, Inferior mesenteric vein; *SMA,* superior mesenteric artery.
Modified from Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

TABLE 3 Causes and Approximate Frequencies of Acute Mesenteric Ischemia

Cause	Frequency (%)
SMA thrombosis	54-68
SMA embolus	26-32
Nonocclusive mesenteric ischemia	10
Mesenteric venous thrombosis	5
Focal segmental ischemia of the small intestine	5

SMA, Superior mesenteric artery.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

- Mesenteric arterial embolism (40% to 50% of cases of AMI) typically arises from a cardiac source: left atrium associated with cardiac dysrhythmias such as atrial fibrillation, left ventricle with global myocardial dysfunction associated with poor ejection fraction, or cardiac valves due to endocarditis. The superior mesenteric artery (SMA) is most commonly affected because of its relatively large diameter and low takeoff angle from the aorta.
- Mesenteric arterial thrombosis (20% to 35% of cases of AMI) is often seen in patients with prior progressive atherosclerotic stenosis, with superimposed abdominal trauma or infection. Many of these patients have a history consistent with chronic mesenteric ischemia (CMI), including postprandial pain, weight loss, or "food fear."
- Nonocclusive mesenteric ischemia (20% of cases of AMI) is usually a consequence of SMA vasoconstriction associated with low splanchnic blood flow as seen with hypotension, hypovolemia, vasoconstricting drugs, and hemodialysis.
- Mesenteric venous thrombosis (less than 10% of cases of AMI) may occur in the setting of hypercoagulable states (acquired or inherited), blunt trauma, abdominal infection, portal hypertension, pancreatitis, and portal malignancy. In these situations, the consequences of bowel edema and increased vascular resistance secondary to venous thrombosis result in reduced arterial blood flow, leading to bowel ischemia.
- Dissection or inflammation of the mesenteric artery accounts for less than 5% of cases of AMI.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Initially include other causes of acute-onset abdominal pain, including perforated peptic ulcer, acute pancreatitis, and early appendicitis, as well as the varied causes of peritonitis.

WORKUP

- Early diagnosis is key, and the key to early diagnosis is a high level of clinical suspicion.
- Treatment success is related to the duration of symptoms before diagnosis. Consider early laparotomy for diagnosis in cases with a high index of suspicion when imaging is not readily available.

LABORATORY TESTS

- Classically, patients with AMI have leukocytosis, metabolic acidosis, elevated D-dimer, and elevated serum lactate; however, these laboratory test results are nonspecific, especially early in the course. Elevated lactic acid, leukocytosis, and elevated hematocrit from hemoconcentration can occur later in the course, often after progression to bowel necrosis has occurred, hence are not useful for early diagnosis.
- D-Dimer has been reported to be an independent risk factor of intestinal ischemia, reflecting ongoing clot formation and endogenous degradation via fibrinolysis. Normal D-dimer testing may help rule out AMI while elevated levels are nonspecific.
- When a hypercoagulable state is suspected, workup may include proteins C and S, antithrombin III, and factor V Leiden. This will likely not affect the diagnosis of AMI but may help guide long-term therapy.
- Amylase levels may be elevated in up to 50% of individuals with intestinal ischemia; phosphate levels may be elevated in up to 80% of affected individuals.

IMAGING STUDIES

- Contrast-enhanced computed tomography (CT) has replaced conventional angiography as the gold standard imaging modality in AMI. It is more readily available and has similar sensitivity to angiography, the prior gold standard test. Computed tomographic angiography (CTA) has 95% to 100% accuracy for the diagnosis of visceral ischemic syndromes and is also useful in detecting potential sources of emboli and other pathologic processes.
- Plain CT findings are nonspecific and more often found late in the course. Portal venous gas or intramural gas may be seen after the development of gangrene (Fig. E1). In many cases, CT findings remain nonspecific even at advanced stages.
- Gadolinium-enhanced magnetic resonance imaging (MRI) can be used to detect proximal obstruction of the SMA and celiac axis, but it has less value in the evaluation of distal arterial occlusions and other intestinal findings in AMI. Magnetic resonance angiography (MRA) may be more useful in cases of mesenteric vein thrombosis causing AMI. It has also been found useful in monitoring the progress of patients with superior mesenteric venous thrombosis who are treated non-surgically. MRA, however, takes longer than CTA to perform and can overestimate the degree of stenosis.
- Plain radiographs are not useful in AMI; plain films are normal 25% of the time in early stages. Suggestive findings may include ileus (Fig. E2), bowel wall thickening, or intramural gas. Gas in the portal veins is a sign of extensive intestinal pneumatosis and implies that bowel necrosis has developed. Free air under the diaphragm may support early surgical intervention before further radiologic evaluation.
- Ultrasound is not recommended in AMI if CT is available. Doppler ultrasound evaluation of intestinal blood flow is time consuming and is often limited by the presence of air-filled loops of bowel.

Angiography may be considered if the diagnosis remains unclear after CT or MRI.

Rx TREATMENT

- The goal of treatment is to restore blood flow to ischemic bowel as rapidly as possible (Fig. E3) before the occurrence of infarction.
- Treatment varies depending on specific etiology.

ACUTE GENERAL Rx

- Initial management should include hemodynamic monitoring and support, including fluid resuscitation with crystalloid and blood products, correction of acidosis, pain control (using parenteral opioids), administration of broad-spectrum antibiotics, and gastric decompression by nasogastric tube.
- Vasopressors should be used with caution and only to avoid fluid overload and abdominal compartment syndrome. Dobutamine, low-dose dopamine, and milrinone to improve cardiac function have been shown to have less impact on mesenteric blood flow.
- In the absence of active bleeding, the use of systemic anticoagulation is usually indicated. The optimal timing of initiation is unclear.

NONPHARMACOLOGIC THERAPY

- Specific management will depend on patient status and most likely etiology of the ischemia. Signs of peritonitis mandate early laparotomy and resection of infarcted bowel.
- When workup is positive for major SMA embolus, embolectomy is considered standard treatment in the absence of peritoneal signs. Depending on the location and degree of occlusion of the embolus, surgical revascularization, intraarterial infusion of thrombolytics or vasodilators, or systemic anticoagulation may be considered.
- In cases of SMA thrombosis, emergency surgical revascularization is the treatment of choice. Stent placement may be a viable alternative.
- Management of NOMI is based on treatment of the underlying precipitating cause. Fluid resuscitation, optimization of cardiac output, and elimination of vasopressors remain important primary measures. Additional treatment may include systemic anticoagulation and the use of catheter-directed infusion of vasodilatory and antispasmodic agents, most commonly papaverine hydrochloride.
- In patients with mesenteric vein thrombosis, treatment depends on the presence or absence of peritoneal signs. Laparotomy and resection of infarcted bowel is indicated in more advanced cases. If there are no peritoneal signs, immediate anticoagulant therapy with heparin, and ultimately warfarin, may be adequate treatment.
- In general, percutaneous treatment with lytic therapy, balloon angioplasty, or stenting may be limited by the frequent presence of nonviable bowel, which would require laparotomy despite success with percutaneous treatment.
- A "second look" procedure is indicated in most patients, 24 to 48 hours after initial revascularization.

CHRONIC Rx

Patients should be followed up in an outpatient clinical setting at regular intervals.

- Patients who receive endovascular treatment should be managed with 3 to 6 months of clopidogrel; additionally, periodic surveillance for restenosis with duplex ultrasound or CTA is indicated.
- In the subgroup of patients with mesenteric venous thrombosis, prevention of further thrombosis is indicated. The optimal duration of anticoagulation is unclear.

DISPOSITION

- Prognosis is best in AMI due to mesenteric venous thrombosis and after surgical treatment for acute arterial embolism. It remains poor in cases of arterial thrombosis and nonocclusive ischemia.
- With delayed diagnosis, intestinal infarction—resulting in perforation or gangrenous bowel, sepsis, shock, and death—is typical.

REFERRAL

- Early surgical consultation should be considered. There should be no delay in patients with peritoneal signs.
- Surgery may also be warranted for diagnostic purposes.

PEARLS & CONSIDERATIONS

COMMENTS

- The diagnosis of AMI should be considered in any patient with acute onset of abdominal pain out of proportion to physical findings, particularly in at-risk patients.
- Early diagnosis, before intestinal infarction occurs, is critical and correlates with improved survival rates.
- The use of endovascular procedures for AMI is becoming more common and may be most appropriate for patients with ischemia that is not severe and for those who have severe coexisting conditions that place them at high risk for complications and death associated with open surgery.

PREVENTION

Prevention of underlying factors, most notably atherosclerotic disease (smoking cessation, management of hypertension, and use of statins) is indicated for primary prevention as well as prevention of recurrence.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Mesenteric Venous Thrombosis (Related Key Topic)

AUTHORS: **Sehrish Jamot, MD,** and **Sarah Hyder, MD**

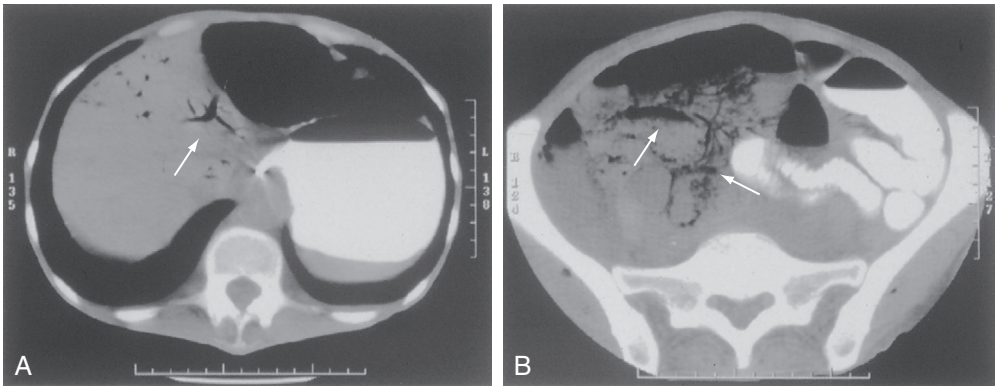

FIG. E1 Computed tomography of a patient with acute mesenteric ischemia showing gas *(arrow)* in the portal veins **(A)** and gas *(arrows)* in the wall of the intestine as well as the mesentery and its vessels **(B)**. Pneumatosis intestinalis (linearis) is a late sign of ischemic injury, connotes bowel necrosis, and mandates explorative laparotomy. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

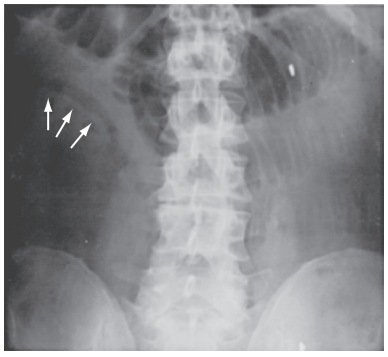

FIG. E2 Plain film of the abdomen showing an ileus and a formless fixed loop of small intestine *(arrows)* in a patient with acute mesenteric ischemia from a superior mesenteric artery embolus. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disea*se, ed 10, Philadelphia, 2016, Elsevier.)

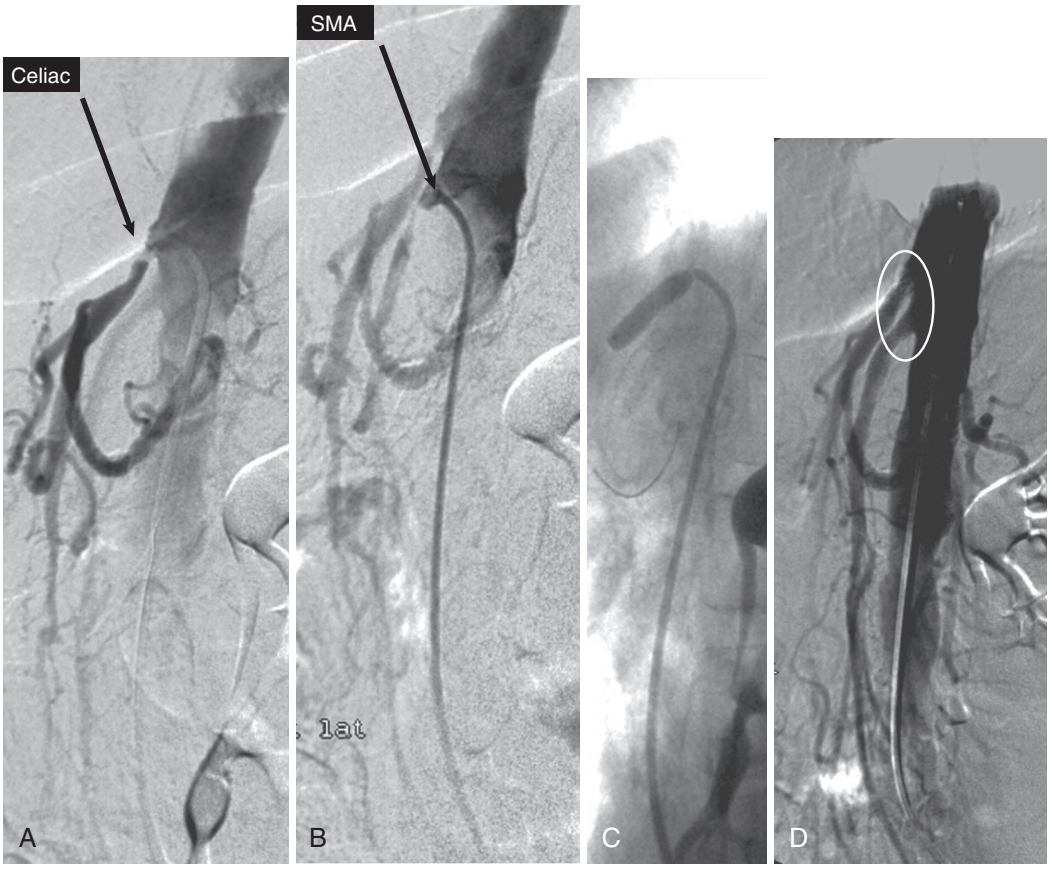

FIG. E3 Mesenteric stenosis. A and B, Both these vessels proved to be critically stenosed. **C,** The celiac artery and SMA were treated interventionally to restore wide patency in both, as outlined in **D.** The patient's symptoms abated, and she began to gain weight. *SMA,* Superior mesenteric artery. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.)

SUGGESTED READINGS

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Acute Myeloid Leukemia ALG PTG

BASIC INFORMATION

DEFINITION

Acute myeloid leukemia (AML) is a malignancy of hematopoietic progenitor cells that would normally give rise to mature granulocytes. Strictly speaking, AML is a subset of acute nonlymphocytic leukemia (ANLL), a designation that broadly distinguishes these diseases from the biologically distinct leukemias of lymphocytic origin. ANLL includes leukemias involving the spectrum of myeloid stem cells, including precursors of granulocytes, monocytes, erythrocytes, and megakaryocytes. Acute promyelocytic leukemia is a distinct leukemia syndrome that is part of the ANLL spectrum, but that has very different treatment implications. ANLL is characterized by maturation failure of myeloid progenitors, excessive numbers of immature progenitors ("blasts"), and various degrees of bone marrow failure (neutropenia, thrombocytopenia, anemia).

SYNONYMS

Acute nonlymphocytic leukemia (ANLL)
Acute myelogenous leukemia (AML)

ICD-10CM CODES

C92.60	Acute myeloid leukemia with 11q23-abnormality not having achieved remission
C92.61	Acute myeloid leukemia with 11q23-abnormality in remission
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.90	Myeloid leukemia, unspecified, not having achieved remission
C92.91	Myeloid leukemia, unspecified in remission
C92.92	Myeloid leukemia, unspecified in relapse
C92.A0	Acute myeloid leukemia with multilineage dysplasia, not having achieved remission
C92.A1	Acute myeloid leukemia with multilineage dysplasia, in remission
C92.A2	Acute myeloid leukemia with multilineage dysplasia, in relapse
C92.Z0	Other myeloid leukemia not having achieved remission
C92.Z1	Other myeloid leukemia, in remission
C92.Z2	Other myeloid leukemia, in relapse
C92.00	Acute myeloblastic leukemia, not having achieved remission
C92.01	Acute myeloblastic leukemia, in remission
C92.02	Acute myeloblastic leukemia, in relapse

EPIDEMIOLOGY & DEMOGRAPHICS

- AML incidence rises with age:
  1. Incidence 20 to 55 yr old: 1 to 3/100,000 persons/yr
  2. Incidence 65 to 80 yr old: 11 to 20/100,000 persons/yr
- Annual incidence is 4 cases/100,000 persons/yr
- Males slightly > females; European ancestry slightly > African ancestry

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms/exam findings:

- Complications of bone marrow failure:
  1. Thrombocytopenia-associated bleeding
  2. Fatigue and shortness of breath associated with anemia
  3. Infection associated with neutropenia
- Complications of leukocytosis (hyperleukocytic leukemia, WBC >100,000/mcl):
  1. Retinal hemorrhage with visual symptoms
  2. Headache and intracranial bleeding
  3. Respiratory symptoms from pulmonary involvement
- Systemic symptoms:
  1. Fatigue, fever (usually infectious, rarely tumor), bone pain (more common in ALL)
- Hemorrhagic complications of disseminated intravascular coagulation (DIC), especially with acute promyelocytic leukemia (APML)
- Physical exam will reflect consequences of cytopenias (bruising from thrombocytopenia, pallor from anemia). Enlarged lymph nodes and enlarged liver and spleen are rare. Exam is often normal
- Rarely disease will present as skin lesions (leukemia cutis) or mass lesions (granulocytic sarcoma)
- Gum hypertrophy and organ/skin involvement is more common in monocytic leukemia

ETIOLOGY

- Environmental/exposure related: Benzene (best documented), organic solvents (including gasoline), cigarette smoking (≥20 pack-yr 1.34 relative risk), obesity, best documented in women
- Hereditary disorders: Numerous, including Fanconi anemia, Bloom syndrome, Schwachman Diamond syndrome, Diamond Blackfan anemia, among others
- Therapy related:
  1. Alkylator (e.g., melphalan, busulfan, cisplatin) related: Typical latency 5 to 7 yr, associated with chromosome 5 and 7 abnormalities
  2. Topoisomerase II inhibitor (e.g. etoposide, doxorubicin): Typical latency 1 to 3 yr, associated with 11q23 (mixed lineage leukemia [MLL] gene) rearrangements
- Radiation exposures (therapeutic—generally low risk), occupational
- Antecedent hematologic disorders: Myelodysplasia, myeloproliferative disorders, aplastic anemia

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Disorders that can present with circulating blasts or cells with blastlike appearance:
  1. Acute myeloid leukemia/acute lymphocytic leukemia
  2. Myelodysplasia (up to 20% circulating blasts, if ≥20% = AML)
  3. Primary myelofibrosis
  4. Chronic myeloid leukemia
  5. Blastoid variant of mantle cell lymphoma
  6. Prolymphocytic leukemia
  7. Blastic plasmacytoid dendritic cell neoplasm
  8. Atypical lymphocytes of Epstein-Barr and cytomegalovirus infection may have blastlike appearance

WORKUP

The diagnostic workup consists of a morphologic assessment, immunophenotyping by flow cytometry, assessment of karyotype, and a panel of gene mutations (Fig. 1).

LABORATORY TESTS

- Complete blood counts and blood smear evaluation. Note that morphologic evaluation of blasts may suggest myeloid or lymphoid origin, but flow cytometry or cytochemistries (often faster) are needed to confirm. Auer rods are seen in blasts of myeloid origin.
- LDH is commonly elevated. Other biochemistries to assess organ function (creatinine, liver enzymes) and spontaneous tumor lysis syndrome (uric acid, potassium, phosphate, calcium).
- Coagulation studies to assess DIC. DIC is always present in APML, but can be present in ***all*** forms of acute leukemia, especially acute monocytic leukemia.
- HLA typing for possible bone marrow transplant and platelet support.
- Cytochemical stains:
  1. Myeloperoxidase can be performed in minutes, + in myeloid origin leukemia.
  2. Alpha naphthyl acetate esterase ("nonspecific esterase") stains mainly monocytic cells.
- Flow cytometry on blood and/or bone marrow (see Table E1).
- Cytogenetic studies, ideally on bone marrow, but can be done on peripheral blood. Fluorescence in situ hybridization (FISH) is often used as an adjunct to conventional chromosome analysis.
- Next Generation Sequencing (NGS) by PCR to detect specific prognostic gene mutations
- Molecular studies to further stratify risk and prognosis, which may affect treatment choices (see Tables E2, 3, and 4). Directing this workup should be done with combined hematology and laboratory expertise and typically will consist of studies for fms-related tyrosine kinase gene (FLT3) mutations, nucleophosmin gene (NPM) mutations, and CCAAT/enhancer binding protein α gene (CEBPA) mutations. Wider molecular panels are increasingly common because of the increasing numbers of potential markers and the potential availability of targeted therapies for FLT3 mutated disease and those with isocitrate dehydrogenase mutations, among others. TP53 mutation, mutated RUNX1, and mutated ASXL1 have recently been added to the NCCN poor-risk category for AML in 2018. Table E5 summarizes common recurrent mutations in adult acute myeloid leukemia.

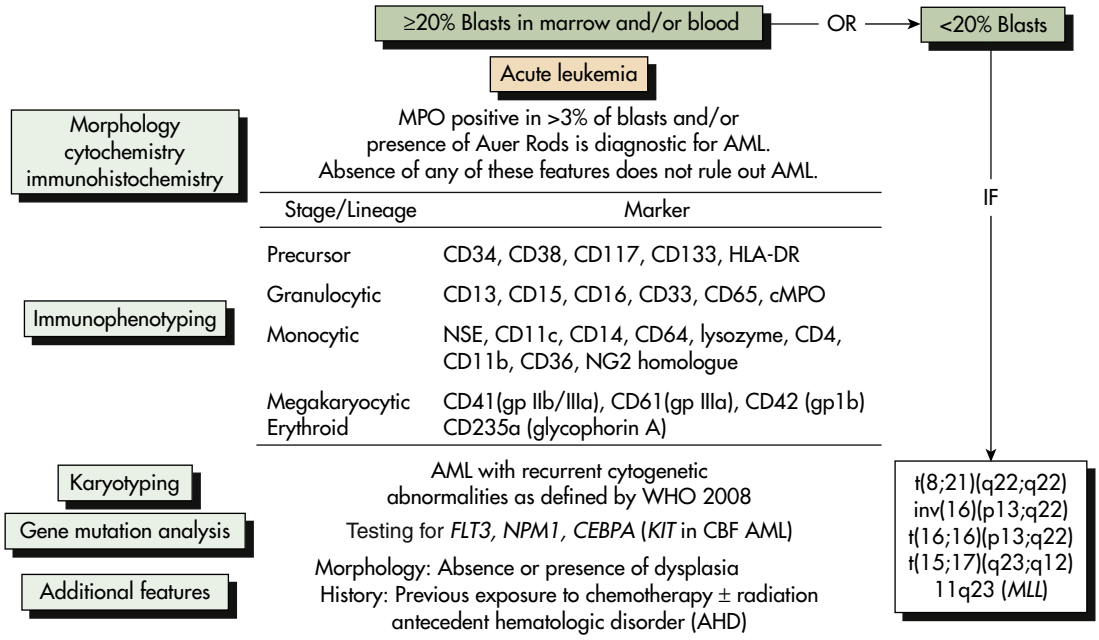

FIG. 1 Workup of acute myeloid leukemia. The diagnostic workup consists of a morphologic assessment, immunophenotyping by flow cytometry, assessment of the karyotype, and a panel of gene mutations. Whereas morphologic assessment by itself is often not sufficient to render a diagnosis, flow cytometry will confirm the lineage assignment (myeloid vs. lymphoid) and stage of differentiation in more than 95% of cases. In the remainder, either no lineage-specific antigens are expressed (acute undifferentiated leukemia) or antigens of more than one lineage are present (mixed-phenotype acute leukemia). In the latter scenario, antigens of several lineages can be found on one (biphenotypic) or separate populations of blasts (bilineal). Karyotyping and gene mutation analysis may add diagnostic information in morphologically ambiguous situations but is otherwise of more interest in determining prognosis. Additional information (exposure to previous chemotherapy and/or radiation therapy, history of an antecedent hematologic disorder, dysplasia) forms the basis for the 2008 revision of the WHO classification of AML. *AHD,* Antecedent hematologic disorder; *AML,* acute myeloid leukemia; *ANLL,* acute nonlymphocytic leukemia; *CBF,* core-binding factor; *MPO,* myeloperoxidase; *WHO,* World Health Organization. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

TABLE 3 European LeukemiaNet AML Risk Classification

Genetic Group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD (normal karyotype)
	Mutated *CEBPA* (normal karyotype)
Intermediate-I[a]	Mutated *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)
	Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL*
	Cytogenetic abnormalities not classified as favorable or adverse[b]
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
	t(6;9)(p23;q34); *DEK-NUP214*
	t(v;11)(v;q23); *MLL* rearranged
	–5 or del(5q); –7; abnl(17p); complex karyotype[c]

[a]Includes all AMLs with normal karyotype except for those included in the favorable subgroup; most of these cases are associated with poor prognosis.
[b]For most abnormalities, adequate numbers have not been studied to draw firm conclusions regarding their prognostic significance.
[c]Three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions, that is, t(15;17), t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), inv(3), or t(3;3).
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

- Formal diagnosis of acute nonlymphocytic leukemia is established if the marrow or peripheral blood blast percentage is ≥20%, unless t(8;21), inv(16), t(16;16) or t(15;17) are present, in which case the percentage of blasts may be lower.

1. Myeloperoxidase (MPO) staining of 3% of blasts establishes myeloid lineage, but MPO may be negative in some AML cases diagnosed by flow cytometry.
2. Specific criteria exist for diagnosing other forms of ANLL, mainly to distinguish it from myelodysplasia. The WHO AML classification is outlined in Table 6.
3. Bone marrow findings are described in Fig. E2.

IMAGING STUDIES

- Imaging studies are typically directed to evaluating specific complaints.
- Echocardiogram or multigated acquisition scan is usually performed to verify that cardiac function is adequate to tolerate anthracycline (usually daunorubicin) therapy, with left ventricular ejection fraction (LVEF) of >50% typically considered acceptable.

Rx TREATMENT

ACUTE GENERAL Rx

- The general approach to AML is summarized in Fig. 3. Therapy of AML typically has three components:

1. Immediate therapy to correct metabolic, infectious, or hyperleukocytic emergencies (if needed). Therapy for AML is always urgent but not always an emergency. However, treatment for APML should be considered a medical emergency to prevent catastrophic bleeding.
2. Induction therapy, which is therapy of active disease intended to obtain remis-

TABLE 4 Allogeneic Transplantation Guidelines for Adult Acute Myeloid Leukemia Based on Commonly Assessed Cytogenetic and Molecular Markers

AML Category	Prognostic Impact	Allogeneic Transplantation	Notes
AML-CR1: Younger Adults			
Good-risk disease			
APL	Favorable	No	APL is treatable by chemotherapy.
CBF-AML *without mKIT*	Favorable	No	t(8;21) AML with high WBC count at diagnosis may have worse prognosis.
CBF-AML *with mKIT*	Intermediate	Possible: MRD, MUD Uncertain: MMUD, UCB, haplo	
Intermediate-Risk Disease			
CN-AML *with CEBPA*	Favorable	No	Benefit likely restricted to *DM-CEBPA*
CN-AML *with mutant NPM1 but not FLT-3-ITD*	Favorable	Possible: MRD	Emerging data suggests allogeneic HSCT benefit for this category, with reduced relapse and improved DFS in patients >40 yr.
CN-AML *with FLT-3-ITD*	Unfavorable[a]	Yes: MRD, MUD Possible[b]: MMUD, UCB, haplo	Unfavorable risk may be restricted to AML *with FLT-3-ITD allelic ratio >0.51*
Other intermediate-risk disease	Intermediate or Unfavorable	Yes: MRD Likely acceptable[a]: MUD Possible[b]: MMUD, UCB, haplo	Likely considerable underlying clinical heterogeneity. Molecular risk profiling may further delineate risk in this category.
Poor-Risk Disease			
Monosomal karyotype *absent*	Unfavorable	Yes: MRD, MUD Likely acceptable[b]: MMUD, UCB, haplo	
Monosomal karyotype *present*	Very unfavorable	Yes: MRD, MUD Acceptable[b]: MMUD, UCB, haplo	
Abnormal 17(p)	Very unfavorable	Yes: MRD, MUD Acceptable[b]: MMUD, UCB, haplo	
AML-CR1: Older adults	Unfavorable	Yes: MRD, MUD Likely acceptable[b]: MMUD, UCB, haplo	
AML-CR1: t-AML, AML/MDS	Unfavorable	Yes: MRD, MUD Acceptable[b]: MMUD, UCB, haplo	Molecular risk profiling may supersede clinical classification of secondary AML, especially in older patients.
AML-CR2	Very unfavorable	Yes: MRD, MUD Acceptable[b]: MMUD, UCB, haplo	
AML not in remission	Very unfavorable	Yes: MRD, MUD Uncertain: MMUD, UCB, haplo	For selected patients: Good performance status, little comorbidity, lower leukemic burden; CIBMTR risk score may be useful.

AML, Acute myeloid leukemia; *APL,* acute promyelocytic leukemia; *CBF,* core binding factor; *CIBMTR,* Center for International Blood and Marrow Transplant Research; *CN,* cytogenetically normal; *CR1,* first complete remission; *CR2,* second complete remission; *haplo,* haploidentical; *MDS,* myelodysplastic syndrome; *MMUD,* mismatched unrelated donor; *MRD,* matched related donor; *MUD,* matched unrelated donor; *t-AML,* therapy-related AML; *UCB,* umbilical cord blood; *WBC,* white blood cell.

[a]If no sibling donor available.

[b]If no timely matched donor available.

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

sion and restore normal bone marrow function. Remission is defined as blasts <5% in the bone marrow, absolute neutrophils (ANC) of >1000/mcl, platelets >100,000/mcl, and transfusion independence. Complete remission with incomplete marrow recovery (CRi) indicates absence of leukemic blasts in the marrow but persistent cytopenias.

3. Consolidation therapy, typically some form of intensive chemotherapy or stem cell transplant therapy intended to prevent relapse.
4. Hyperleukocytic symptoms are typically seen with WBC >100,000/ml. Leukapheresis requires catheter placement and pheresis but spares tumor lysis. Rapid cytoreduction with chemotherapy (hydroxyurea 3 to 6 g orally or cytarabine) is often adequate and easier but risks tumor lysis. Optimal management is therefore individualized.
5. Tumor lysis syndrome (TLS) is associated with a rise in uric acid, potassium, and serum phosphate, the last causing a reciprocal fall in calcium. The metabolic changes may result in renal failure, cardiac dysrhythmias, muscle spasms (due to low calcium), seizures, and death (a more detailed discussion is in the section on acute lymphocytic leukemia).
6. The mainstays of therapy for AML are medications dating from the 1970s—daunorubicin and cytarabine—with few medications having meaningful impact on therapy in the last four decades. In 2017, the U.S. FDA approved four new agents, including three targeted agents, for treatment of AML. The role of these agents and their relation to standard therapy is outlined below.
7. Induction chemotherapy typically consists of daunorubicin 60 or 90 mg/m^2 IV for 3 days and cytarabine (Ara-C) 100 or 200 mg/m^2/day as continuous infusion for 7 days ("7+3"). Success rates are 60% to 80% and have been better in recent trials. Other agents that are used include etoposide, idarubicin, fludarabine, and cladribine. Bone marrow examination is usually performed at day 14 of therapy to assess the response.
8. Gemtuzumab ozogamicin (GO, Mylotarg) is an antibody-drug conjugate binding an anti-CD33 antibody to the chemotherapeutic agent calicheamicin that was approved in 2017 for therapy of newly diagnosed CD33+ AML. In newly diagnosed AML, the use of low-dose GO when added to standard 7+3 induction had a success rate of 81%, with 2-yr relapse-free survival improving from 22.7% to 50.3% compared with standard therapy alone. The benefit was seen in favorable and intermediate-risk patients.
9. Midostaurin was also approved in 2017 for treatment of newly diagnosed AML with mutations in the fms-related tyrosine kinase 3 *(FLT3)* gene in combination with standard induction therapy. Four-yr

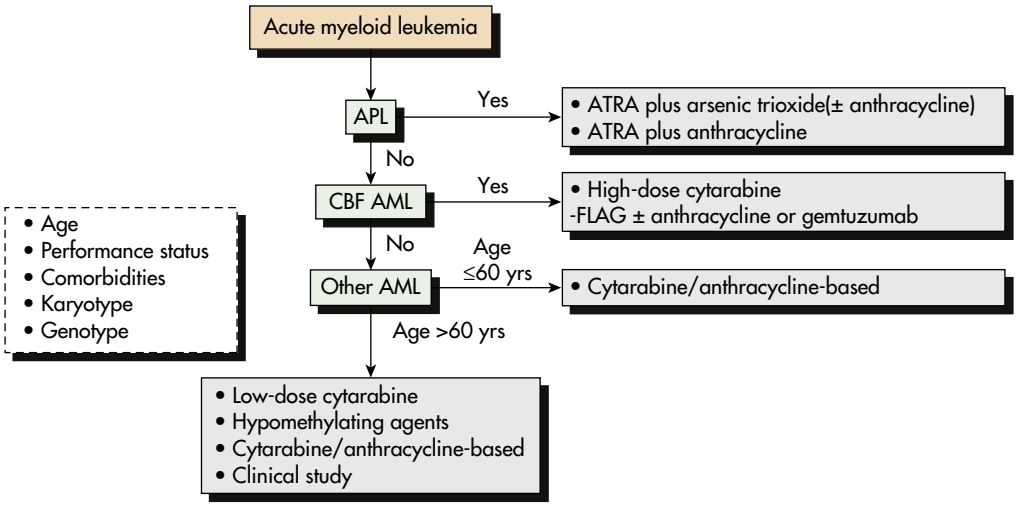

FIG. 3 General approach to acute myeloid leukemia therapy. *AML,* Acute myeloid leukemia; *APL,* acute promyelocytic leukemia; *ATRA,* all-trans retinoic acid; *CBF,* core binding factor; *FLAG*, fludarabine, cytarabine (ara-C), and granulocyte colony-stimulating factor. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

overall survival was 51.4% in FLT3-positive patients receiving midostaurin vs. 44.3% in the placebo arm, with improved durability of remissions in patients achieving remission. The optimal use of these therapies requires rapid access to genetic data at the time of diagnosis. Also approved in 2017 was CPX-351, a liposomal formulation of cytarabine and daunorubicin encapsulated in a 5:1 ratio, for patients with AML related to previous therapy (t-AML) or with AML with myelodysplasia-related change (AML-MRC). In a trial of t-AML and AML evolving from myelodysplasia or with WHO-defined myelodysplasia-related cytogenetic changes in patients ages 60 to 75 yr, CPX-351 improved survival to 9.56 mo vs. 5.95 mo with standard 7+3 induction.

10. Gilteritinib was FDA approved in 2018 for treatment of adult patients who have relapsed or refractory acute myeloid leukemia with a FLT3 mutation. Approval was based on an interim analysis of a trial, which included 138 adult patients with relapsed or refractory AML having a FLT3 ITD, D835, or I836 mutation. Gilteritinib was given orally at a dose of 120 mg daily until unacceptable toxicity or lack of clinical benefit. After a median follow-up of 4.6 mo, 21% of patients achieved complete remission (CR) or CR with partial hematologic recovery (CRh).
11. In 2018, the FDA granted accelerated approval to Venetoclax, a BCL-2 inhibitor, in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia in adults who are age 75 yr or older, or who have comorbidities that preclude the use of intensive induction chemotherapy. The recommended Venetoclax dose depends upon the combination regimen.

- Consolidation therapy is controversial. For patients managed with chemotherapy, cytarabine 3 g/m^2 for six doses is commonly used (day 1, 3, 5), but intermediate doses (1000 to 1500 mg/m^2) for six doses appear equally effective and less toxic. Doses above 1000 mg/m^2 are poorly tolerated in patients over 60 yr because of cerebellar toxicity. Renal insufficiency also increases the risk of cerebellar toxicity from Ara-C, which can be severe.
  1. For favorable risk disease, consolidation with chemotherapy alone with two to four cycles of intermediate/high-dose cytarabine is typically given, with long-term survival of 60% to 70%.
  2. For intermediate-risk and unfavorable-risk disease, first-remission allogeneic stem cell marrow transplant is often recommended if a donor is available. If not, chemotherapy consolidation chemotherapy is offered, although the optimal therapy and schedule, especially for unfavorable disease, is uncertain.
  3. In the trial of GO as initial therapy, GO was also used in consolidation with high-dose cytarabine and daunorubicin.
  4. The role of autologous bone marrow transplant is controversial, with some evidence of decreased relapse rates after chemotherapy but no clear benefit in overall survival.
  5. Allogeneic bone marrow transplant is offered to patients with relapsed disease if a second remission can be obtained in good risk patients. It is offered to high-risk and intermediate-risk patients in first remission if a donor is available. In 2018, most patients will be able to find a donor from either a matched related donor, matched unrelated donor, mismatched unrelated donor, haploidentical donor, or cord blood donor. The Center for International Blood and Marrow Transplant Research (CIBMTR) has published data for 12,309 patients receiving an HLA-matched sibling transplant and 15,632 patients receiving a matched unrelated donor for AML between 2002 and 2012. Their disease status at the time of transplant and the donor type were found to be the best predictors of post-transplant survival. The 3-yr probabilities of survival after HLA-matched sibling transplant in this cohort was 58% ±1%, 50% ± 1%, and 24% ± 1% for patients with early, intermediate, and advanced disease, respectively. The probabilities of survival after an unrelated donor transplant were 49% ± 1%, 47% ± 1%, and 22% ± 1% for patient with early, intermediate, and advanced disease, respectively.
  6. Enasidenib, a selective inhibitor of mutated isocitrate dehydrogenase 2 (IDH-2), was approved by the FDA in 2017 for relapsed or refractory AML with IDH-2 mutations. IDH-2 mutations are found in about 12% of AML patients. At a dose of 100 mg orally, the response rate was 40.3%, with 19.3% achieving remission, some durable. Differentiation syndrome can be seen with enasidenib, similar to therapy for APML.
  7. Ivosidenib, a selective inhibitor of isocitrate dehydrogenase-1 (IDH-1) mutation, was approved by the FDA in 2018 as the first treatment of adult patients with relapsed/refractory acute myeloid leukemia with an IDH-1 mutation. Approval was based on results from a phase 1, open-label, single-arm, multicenter, dose-escalation, expansion trial of adult patients in this population. The primary end point was combined complete remis-

TABLE 6 Classification of Acute Myeloid Leukemia According to the Revised World Health Organization Classification (2016)

Category	Subtype/Definition*
AML with recurrent cytogenetic abnormalities	t(8;21)(q22;q22); RUNX1-RUNX1T1†
	inv(16)(p13.1q22); CBFB-MYH11†
	t(16;16)(p13.1q22); CBFB-MYH11†
	t(15;17)(q22;q12); PML-RARA† (= acute promyelocytic leukemia)
	t(9;11)(p22;q23); MLLT3-KMT2A
	t(6;9)(p23;q34); DEK-NUP214
	inv(3)(q21q26.2); GATA2, MECOM
	t(3;3)(q21;q26.2); RPN1-EVI1
	t(1;22)(p13q13); RBM15-MKL1 (megakaryoblastic)
	with mutated NPM1
	with biallelic mutations of CEBPA
AML with MDS-related changes	Morphologic features of MDS, or prior history of MDS or MDS/MPN, or MDS-related karyotype, and none of the recurrent genetic abnormalities above
Therapy-related myeloid neoplasms	Late complications of cytotoxic chemotherapy (alkylating agents, topoisomerase II inhibitors) and/or ionizing radiation therapy†
AML, not otherwise specified	AML with minimal differentiation
	AML without maturation
	AML with maturation
	Acute myelomonocytic leukemia
	Acute monoblastic/monocytic leukemia
	Pure erythroid leukemia
	Acute megakaryoblastic leukemia
	Acute basophilic leukemia
	Acute panmyelosis with myelofibrosis
Myeloid Sarcoma	
Myeloid proliferations related to Down syndrome	Transient abnormal myelopoiesis
	Myeloid leukemia associated with Down syndrome
Blastic Plasmacytoid Dendritic Cell Neoplasm	
Acute leukemia of ambiguous lineage	Acute undifferentiated leukemia
	Mixed-phenotype acute leukemia with: t(9;22)(q34;q11.2); BCR-ABL1 t(v;11q23); KMT2A rearranged
	Mixed-phenotype acute leukemia, B/myeloid, NOS
	Mixed-phenotype acute leukemia, T/myeloid, NOS
Provisional entities	AML with mutated NPM1
	AML with mutated CEBPA
	NK-cell lymphoblastic leukemia/lymphoma

AML, Acute myeloid leukemia; *MDS,* myelodysplastic syndrome; *MPN,* myeloproliferative neoplasm; *NK,* natural killer; *NOS,* not otherwise specified. For AML with recurrent genetic abnormalities, specific genes rearranged follow the chromosome rearrangement. In 2016, the *MLL* gene has been renamed *KMT2A.*

*Diagnosis of AML regardless of percentage of blasts.

†Excluded are patients with AML who have transformed from MPN.

sion and complete remission with partial hematologic improvement; the combined rate was 32.8%, and the median duration of remission was 8.2 mo.

8. Relapses after bone marrow transplant can sometimes be managed with donor lymphocyte infusions, adjustment of immune suppression, and chemotherapy (often low intensity). In general, outcomes are poor with posttransplant relapses.

- Treatment of older patients (>60 yr) is problematic, with cure rates of 10% to 15%. Older patients do worse because they are more likely to have high-risk features and less likely to tolerate therapy. Several models have been devised to identify variables that predict which patients may do well with conventional therapy versus those who will not (Table 7). Options for these patients include:
  1. Standard induction therapy is reasonable for patients likely to tolerate it. Even in the absence of cure, quality of life is often excellent in remission. More recent studies suggest that the early death rate (within 30 days of diagnosis) was lower for patients in their 70s and 80s receiving standard induction. There is no standardized approach to evaluating fitness for therapy; one algorithm is at www.aml-score.org/.
  2. Hypomethylating agents—decitabine and azacytidine—may be considered in patients unlikely to tolerate induction therapy. Azacytidine (75 mg/m^2 daily for 7 days every 28 days) and decitabine (20 mg/m^2 for 5 days every 28 days) are considered in older patients who are not considered appropriate for induction chemotherapy. Both are outpatient regimens, and decitabine especially is very well tolerated. Recent data with azacytidine suggest benefit in about 20% to 30% lasting 14 to 16 mo in responders, with equivalent results in low blast count (20% to 30% in the bone marrow) vs. higher blast count disease.
  3. Single-agent gemtuzumab ozogamicin is an option for treatment of CD33+ AML in patients considered unfit for induction. The benefit compared to best supportive care (BSC) was mainly seen in patients with CD33 expression of greater than 80% and favorable/intermediate cytogenetics (1 yr survival 22% and 37% respectively, BSC <10%), with no benefit in patients with high-risk cytogenetics.
  4. Low-dose cytarabine 20 mg/m^2 twice daily or 40 mg/m^2 daily for 10 days subcutaneously) has shown survival benefit over hydroxyurea in low-/intermediate-risk patients.
  5. In November 2018, the FDA granted the accelerated approval to venetoclax (a bcl-2 protein inhibitor) in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia in adults who are age 75 yr or older, or who have comorbidities that preclude use of intensive induction chemotherapy. The recommended venetoclax dose depends upon the combination regimen and is described in prescribing information of venetoclax.
  6. In November 2018 the FDA approved glasdegib (a small molecule inhibitor of Sonic hedgehog pathway) in combination with low-dose cytarabine (LDAC), for newly diagnosed acute myeloid leukemia in patients who are 75 yr old or older or who have comorbidities that preclude intensive induction chemotherapy. Approval was based upon a multicenter, open-label, randomized study that randomized eligible patients 2:1 to receive glasdegib, 100 mg daily, with LDAC 20 mg subcutaneously twice daily on days 1 to 10 of a 28-day cycle or LDAC alone in 28-day cycles until disease progression or unacceptable toxicity. Efficacy was established based on an improvement in overall survival, 8.3 mo for LDAC + glasdegib versus 4.3 mo for LDAC alone. HR of 0.46 (95% CI: 0.30, 0.71; p=0.0002).
  7. Oral hydroxyurea dosed to counts and cytopenias.
  8. Best supportive care.
  9. Reduced-intensity allogeneic stem cell transplant is an option for patients in remission after standard therapy. A recent meta-analysis of studies including 749 patients over 60 receiving RIT identified a 3-yr relapse-free survival of 35%.

- **Acute Promyelocytic Leukemia (APML):** APML is a distinct leukemia syndrome with very different treatment implications. Cure rates greater than 95% have been seen in current protocols in the absence of high-risk features. It is associated with t(15;17), which translocates the *PML* gene to retinoic acid receptor α (PML-RARa). Uncommon variants are t(11;17) and t(5;17). Risk groups for relapse were defined in studies using retinoic acid and chemotherapy. Patients with presenting WBC >10,000/mcl were considered high risk, patients with WBC <10,000 and platelets >40,000 were considered low risk, and all others were considered intermediate

TABLE 7 Prognostic Models in Older Patients with Acute Myeloid Leukemia

Study	Outcome	Unfavorable Characteristics
Study Alliance Leukemia	Survival Disease-free survival	CD34 expression >10% WBC >20 × 10^9/L Age >65 yr LDH >700 U/L NPM1 status wild-type[a]
UK Medical Research Council	Survival	Adverse cytogenetic group Elevated WBC[b] Poor performance status[b] Older age[b] Secondary AML
Acute Leukemia French Association	Survival	High-risk cytogenetics ± Age ≥75 yr Performance status ≥2 WBC ≥50 × 10^9/L
MD Anderson Cancer Center	Remission rate Induction mortality Survival	Age ≥75 yr Secondary AML[c] AHD duration ≥6[c] (12) mo Treatment outside LAFR Unfavorable cytogenetics WBC ≥25 × 10^9/L[c] Hemoglobin ≤8 g/dl[c] Creatinine >1.3 mg/dl Performance status >2 LDH >600 U/L[d]
Hematopoietic Cell Transplantation Comorbidity Index	Early mortality Survival	Dyspnea Coronary artery disease, CHF, MI, or EF <50% Chronic hepatitis, elevation of bilirubin and/or transaminases Cirrhosis Elevations of creatinine, dialysis, renal transplant Secondary AML Depression/anxiety requiring therapy Continued use of antimicrobial therapy after day 0 BMI >35 kg/m^2

AHD, Antecedent hematologic disorder; *AML,* acute myeloid leukemia; *BMI,* body mass index; *CHF,* congestive heart failure; *EF,* ejection fraction; *LAFR,* laminar air flow room (isolation floor); *LDH,* lactate dehydrogenase; *MI,* myocardial infarction; *WBC,* white blood cell count.
[a]Favorable and high-risk groups were defined solely by cytogenetic aberrations. Above factors served to further divide the intermediate risk group into good intermediate versus adverse intermediate.
[b]As continuous variables.
[c]Only significant for prediction of remission.
[d]Only significant for prediction of survival.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

risk. In current protocols, high-risk patients receive some form of intensified therapy.

- APML is a medical emergency because of the high risk of bleeding complications.
  1. All patients with APML have DIC, caused by overexpression of annexin II, (which increases generation of plasmin, degrading fibrin), elastases (which degrade fibrinogen and fibrinolytic inhibitors), and increased endothelial tissue plasminogen activator release.
  2. Early death due to hemorrhage is seen in 5% to 17% of newly diagnosed APML patients, usually intracranial or pulmonary. Risk factors include elevated WBC, increased age, and elevated creatinine.
  3. Retinoic acid rapidly stabilizes the coagulopathy of APML; consideration should be given to starting this immediately for suspected cases.
  4. Cryoprecipitate (usual dose 10 bags) to raise the fibrinogen level to 150 mg/dl and platelet transfusion to raise the count to >50,000mcl should be given as needed.
  5. Unfractionated heparin may paradoxically stop bleeding in APML by inhibiting DIC, but is rarely used in the retinoic acid treatment era.
- Diagnosis of APML.
  1. Rapid diagnosis is essential due to treatment implications.
  2. Diagnosis by classic APML blast morphology and clinical syndrome (especially DIC with low fibrinogen) is sufficient to justify starting treatment with retinoic acid pending confirmation with molecular studies. Immediate therapy with retinoic acid will rapidly stabilize the coagulopathy and help prevent catastrophic bleeding.
  3. Polymerase chain reaction for PML/RARa.
  4. FISH for t(15;17) or variants.
  5. Flow cytometry is typically distinct with lack of HLA-DR and CD34; CD13, CD33 and CD64 are usually positive.
- Therapy of APML.
  1. Emergency measures to stabilize coagulopathy as outlined previously.
  2. Patients with WBC ≤10,000 (low/intermediate risk) are treated with retinoic acid and arsenic trioxide ("differentiation therapy").
  3. Therapy of high-risk patients is less well standardized but has included intensification with cytarabine, anthracyclines, and gemtuzumab ozogamicin. A recent trial using arsenic and retinoic acid with GO demonstrated 100% 4-yr survival in high-risk patients after 30 days, emphasizing the importance of preventing early deaths in APML.
  4. Maintenance therapy for 2 yr is given in some APML protocols.
  5. Patients with high-risk disease receive central nervous system prophylaxis with intrathecal chemotherapy.
  6. Treatment of relapsed disease typically consists of autologous bone marrow transplant after obtaining second remission.
- Differentiation syndrome (DS) is a potentially fatal complication of therapy with retinoic acid and arsenic trioxide. It is associated with fever, interstitial pulmonary infiltrates, peripheral edema, pleural and pericardial effusions and renal failure; it is commonly associated with rising WBC seen in patients on differentiation therapy.
  1. Therapy for suspected differentiation syndrome is dexamethasone 10 mg/m^2 every 12 hr. Cytoreductive therapy (hydroxyurea, idarubicin) and stopping retinoic acid and arsenic are appropriate for inadequate response to dexamethasone.
  2. Prophylaxis for differentiation syndrome with dexamethasone 2.5 mg/m^2 every 12 hr has been suggested for WBC >5000 or creatinine >1.4 mg/dl. Hydroxyurea is used to keep the WBC below 10,000/mcl in some protocols.

PEARLS & CONSIDERATIONS

- The diagnosis of acute myeloid leukemia or variants is often, but not always, a medical emergency requiring rapid clinical and laboratory assessment by appropriate expertise.
- APML is a distinct clinical entity that has a high cure rate with current protocols, but which requires intensive supportive care at the time of diagnosis.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Acute Myelogenous Leukemia (Patient Information)

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TABLE E1 Flow Cytometry Markers Used For Diagnosis of ANLL

Precursor stage	CD34, CD38, CD117, CD133, HLA-DR
Granulocytic (myeloid) markers	CD13, CD15 CD16, CD33, CD65, cytoplasmic myeloperoxidase
Monocytic markers	CD11c, CD14, CD64, CD4, CD11b, CD36, NG2 homologue
Megakaryocytic markers	CD41 (glycoprotein IIb/IIIa), CD61 (glycoprotein IIIa), CD42 glycoprotein 1b
Erythroid markers	CD235 (glycophorin A)

ANLL, Acute nonlymphocytic leukemia.

Adapted from Doehner H et al: Diagnosis and management of acute myeloid leukemia in adults, recommendations from an international expert panel, on behalf of the European Leukemia Net, *Blood* 115: 453-474, 2010.

TABLE E2 Significance of Molecular Abnormalities in Cytogenetically Normal Patients With AML

Molecular Profile	Patients	4-yr Overall Survival
Mutant CEBPA	67	62%
Mutant NPM, without FLT-3 ITD	150	60%
FLT-3 ITD present	164	24%
FLT-3 ITD absent, wild type NPM, wild type CEBPA (triple negative leukemia)	69	33%

AML, Acute myeloid leukemia; *CEBPA,* CCAAT/enhancer binding protein α gene; *FLT-3 ITD,* FMS-related tyrosine kinase gene internal tandem duplication; *NPM,* nucleophosmin gene.

Improved prognosis in patients with CEBPA mutations is limited to patients who lack FLT-3 ITD and have biallelic mutations. CEBPA mutations are seen in approximately 6% to 10% of AML cases, NPM mutations in 25% to 35% (more common in cytogenetically normal cases) and FLT-3 ITD in approximately 20% to 30% of cases.

The updated 2018 NCCN guidelines for AML risk stratification contain favorable, intermediate, and poor risk categories. Molecular abnormalities now included in this updated version in addition to NPM1, FLT3-ITD, and biallelic CEBPA mutation include TP53 mutation, mutated RUNX1, and mutated ASXL1. Molecular abnormalities validation and prognostication is a rapidly evolving field, and risk stratification should be modified on the continuous evaluation of research data. See the NCCN Guidelines Version 3.2018 AML Risk stratification for specific details.

Data from Schlenk RF et al: *N Engl J Med* 358: 1909-18, 2008, and Green CL et al: *J Clin Oncol* 28: 2739-47, 2010.

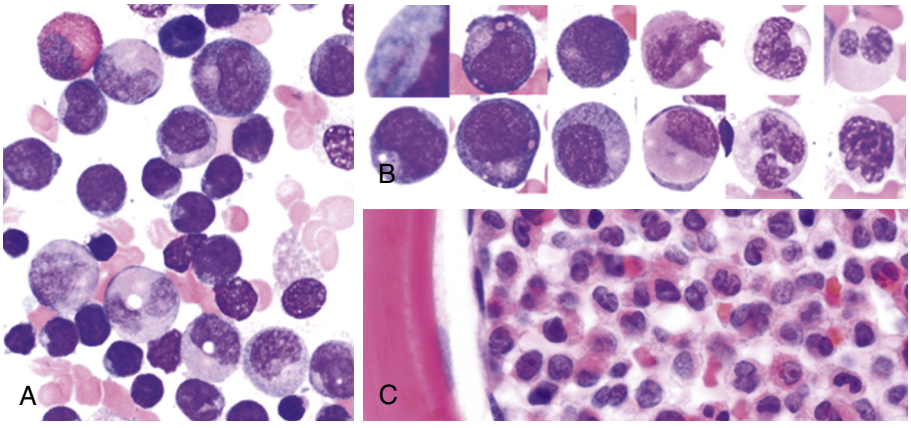

FIG. E2 Acute myeloid leukemia with t(8;21)(q22;q22), *(AML/ETO).* A, Low-power, Wright-stained bone marrow aspirate smear showing increased blasts associated with differentiating myeloid cells. **B,** Details illustrating some of the features associated with the leukemia. They include blasts with long thin Auer rods *(top left),* immature cells with abnormal eosinophilic globules *(top and bottom, second from left),* abnormal salmon-colored granulation in the maturing cells, sometimes associated with a basophilic periphery *(top and bottom, fourth from left),* and slightly abnormal features in the mature neutrophils *(far right).* Pseudo–Chédiak-Higashi granules were not seen in this case. **C,** Biopsy shows the significant degree of maturation that is sometimes seen. In some cases the blast count is less than 20%, but the diagnosis of acute myeloid leukemia still can be made with the cytogenetic finding of t(8;21). (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

TABLE E5 Common Recurrent Mutations in Adult Acute Myeloid Leukemia

Gene Class	Gene	Frequency % of Patients	Clinical Significance
NPM1	*NPM1*	25-30	Improved outcome, especially without *FLT-ITD*; genetic marker for assessment of MRD
Tumor suppressor	*TP53*	8	Very poor outcome; incidence increases with older age; often associated with complex cytogenetics
DNA methylation	*DNMT3A*	18-22	Early event in leukemogenesis; incidence increases with age
	TET2	7-25	Early event in leukemogenesis; incidence increases with age; mutually exclusive of *IDH* mutations
	IDH1	7-14	*IDH1* and *2* inhibitors are in clinical development
	IDH2	8-19	Incidence increases with age
Activated signaling	*FLT3-ITD*	20	Associated with high WBC count and unfavorable outcomes, particularly if high allelic ratio; may benefit from *FLT3* inhibitor and HCT in first remission
	KIT	<5	Mostly detected in core binding factor AML; associated with worse prognosis in t(8;21) AML
	NRAS	15	Efforts to target have so far failed
Myeloid transcription factor	*RUNX1*	5-15	Poor outcome; associated with autosomal dominant predisposition syndrome; incidence increases with age
	CEBPA	6-10	Biallelic *CEBPA* mutations associated with favorable outcome; associated with familial AML
Chromatin modifier	*ASXL1*	5-17	Early event in leukemogenesis; increases with age; predictive of inferior outcome

AML, Acute myeloid leukemia; *HCT,* hematopoietic cell transplantation; *MRD,* minimal residual disease; *WBC,* white blood cell.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

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Acute Pelvic Pain in Women

BASIC INFORMATION

DEFINITION

Acute pelvic pain in women is defined as pain in either the pelvis or the bilateral lower quadrants of the abdomen that has been present less than 3 months and is usually sudden in onset.

SYNONYMS

Acute lower abdominal pain
Acute suprapubic pain

ICD-10CM CODE

R10.2 Pelvic and perineal pain/acute female pelvic pain/pelvic pain, acute

EPIDEMIOLOGY & DEMOGRAPHICS

- Acute pelvic pain occurs in women of all ages.

PEAK INCIDENCE: Women of reproductive age report the greatest amount of acute pelvic pain.
PREVALENCE: Acute pelvic pain is a very broad term with multiple etiologies, thus not lending itself to a single calculable prevalence. However, the prevalence of some of the most documented common causes in the U.S. include PID (2,500,000 women with a personal history in the U.S. as of 2015), ovarian torsion (2.7% of emergent gynecologic surgeries each yr), ectopic pregnancy (0.6% to 2.1% of all pregnancies), and appendicitis (6.7% lifetime risk in women).
PREDOMINANT SEX AND AGE: Women of reproductive age report the greatest amount of acute pelvic pain.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The history and physical examination are key to narrowing the diagnosis when a patient presents with acute pelvic pain.
- Standard thorough history-taking techniques should be employed, and the patient should be asked about location, onset, severity, radiation, exacerbating and alleviating factors, as well as the quality of the pain.
- Associated symptoms such as nausea, vomiting, anorexia, vaginal discharge, dyspareunia, dysuria, hematuria, urinary frequency, fever, recent upper respiratory infection (URI) symptoms, cyclic midcycle pelvic pain, or any missed or irregular menses should also be inquired about.
- A thorough sexual history should also be taken, including form of birth control used. Patients should also be asked about any history of ovarian cysts, uterine fibroids, recent pregnancies (including ectopic pregnancies), or other pelvic infections.
- Physical examination is focused on the abdominal and pelvic examination, as described under Workup later in this chapter.

ETIOLOGY

Etiologies of acute pelvic pain are varied and depend on the age and pregnancy status of the patient. Please see differential diagnosis for further information.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

GYNECOLOGIC CAUSES:

- Pelvic inflammatory disease
- Ruptured ovarian cyst
- Adnexal mass (most pain from ovarian cysts >4 to 5 cm in size and hemorrhagic in nature)
- Ovarian torsion
- Degenerating or torsed uterine fibroid
- Mittelschmerz pain
- Tubo-ovarian abscess
- Endometriosis
- Dysmenorrhea
- Hematometra/Hematocolpos

EARLY PREGNANCY/POSTPARTUM-RELATED CAUSES:

- Miscarriage
- Ectopic pregnancy (especially with ruptured ectopic)
- Postpartum endometritis

NONOBSTETRIC OR GYNECOLOGIC CAUSES:

- Appendicitis
- Urinary tract infection
- Nephrolithiasis
- Diverticulitis
- Colitis
- Bowel obstruction
- Mesenteric lymphadenitis
- Inflammatory bowel disease
- Meckel diverticulum
- Constipation
- Hernia
- Gastroenteritis
- Musculoskeletal dysfunction
- Trauma

WORKUP

The workup of acute pelvic pain begins with a thorough history and physical examination, then targeted imaging and laboratory studies are ordered to further the diagnosis.

The pelvic examination includes vaginal speculum examination, as well as bimanual and rectovaginal pelvic examinations. During the speculum examination the patient is evaluated for any active vaginal bleeding, any vaginal or cervical discharge, and any vulvar or vaginal lesions and masses.

- Testing for gonorrhea and chlamydia should be collected via nucleic acid probe.
- The bimanual and rectovaginal examinations help elucidate the size and contour of the uterus, the presence of any adnexal masses or tenderness, and whether the patient has cervical motion tenderness.

LABORATORY TESTS

- Erythrocyte sedimentation rate (ESR)
- First and foremost, one must determine the pregnancy status of the patient. The most common pregnancy-related causes of acute pelvic pain are ectopic pregnancy (approximately 1 in 7000 spontaneously conceived pregnancies and 1 in 100 pregnancies conceived via artificial reproduction) and spontaneous or threatened miscarriage. In both of these cases, the Rh status of the patient must be determined and RhoGAM administered if she is Rh negative
  - Pregnancy testing via urine or serum
- Urinalysis will assist with the diagnosis of both acute cystitis and nephrolithiasis and urine culture should be ordered as well when appropriate. Nucleic acid probes for gonorrhea and chlamydia are very sensitive and specific tests and should be collected on any patient with pelvic pain. CBC and ESR can be utilized in the patient with suspected gastrointestinal disease, appendicitis, and pelvic infection of any kind to help determine the severity of disease

IMAGING STUDIES

- Pelvic ultrasound is the primary imaging modality for acute pelvic pain in women that is suspected to be of gynecologic origin. Ultrasound can be used to diagnose intrauterine and ectopic pregnancy (Fig. 1), uterine fibroids, adnexal masses, nephrolithiasis, and even appendicitis, thus assisting with the diagnosis of the vast majority of the differential diagnosis of acute pelvic pain in women. However, there are limitations to the test, such as the level of expertise of the individual sonographer and patient body habitus interfering with the quality of the images.
- In the case of the patient with nonfocal symptoms or an inconclusive ultrasound, computed tomography (CT) of the abdomen and pelvis can be performed. CT is highly useful in the patient with early pelvic inflammatory disease (PID) or tubo-ovarian abscess, as well as in the nonpregnant patient with appendicitis or other gastrointestinal pathology not seen on ultrasound.
- Magnetic resonance imaging (MRI) also plays a role when CT is unable to discern whether a mass in the pelvis is of uterine or adnexal origin such as with a degenerating fibroid or when one must further characterize an ovarian mass. MRI is also extremely helpful in the pregnant patient who presents with many signs and symptoms of appendicitis but has an inconclusive ultrasound result. Pediatric patients are also excellent candidates for MRI when ultrasound is inconclusive. Lower levels of ionizing radiation and its excellent diagnostic capabilities make it a very useful test in this population.

TREATMENT

NONPHARMACOLOGIC THERAPY

- The underlying cause of acute pelvic pain cannot always be diagnosed with history, exam, laboratory, and imaging studies alone. In many cases, diagnostic laparoscopy is necessary to complete the diagnosis. In fact, even when the diagnosis seems sure, laparoscopy can reveal an entirely different finding as was illustrated in one study where

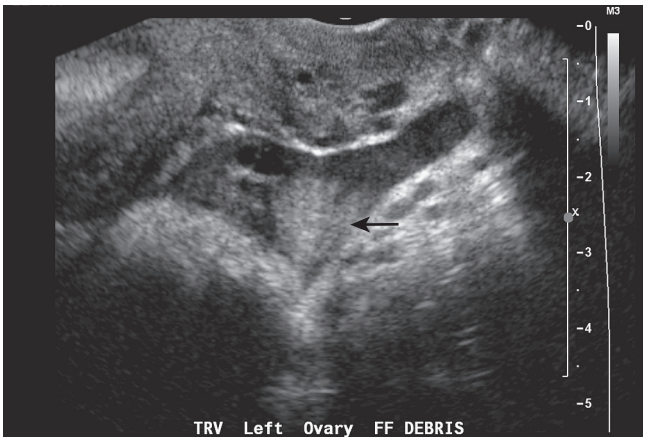

FIG. 1 A sonographic image of a 23-year-old patient with a ruptured ectopic pregnancy. The free fluid containing echogenic debris representing blood is seen in the cul-de-sac *(arrow).* (From Soto JA, Lucey BC: *Emergency radiology, the requisites,* ed 2, Philadelphia, 2017, Elsevier.)

just over half of women clinically diagnosed with appendicitis actually had the disease.

- The practitioner should not hesitate to take the patient with unstable vital signs and suspected intraabdominal bleeding or findings suggestive of ruptured appendix to the operating room. When one's clinical suspicion is quite high for such diagnoses, laboratory data and imaging studies should be forgone to expedite getting the patient the surgical interventions she needs.

ACUTE GENERAL Rx

The initial treatment of the woman with acute pelvic pain must be tailored to the underlying cause. However, as the workup is in progress, her pain must be managed. Although narcotic pain medications are sometimes initially necessary to control pain, NSAIDs are the traditional first-line pharmacotherapy for the patient with pelvic pain of an inflammatory nature. Such medications are highly useful in cases of endometriosis, dysmenorrhea, nonsurgical cases of ovarian masses and ruptured ovarian cysts, spontaneous miscarriage, nephrolithiasis, musculoskeletal dysfunction, and PID/tubo-ovarian abscess. Heat and ice can also be employed as needed for additional symptomatic relief in the appropriate patient.

CHRONIC Rx

Once a diagnosis is made, treatment is based on the underlying cause of the pain. Most patients are managed on a combination of NSAID and narcotic pain medications for a short course until the pathology has resolved or after any surgical interventions. Antibiotic therapy is routinely included in the case of an infectious cause.

REFERRAL

Patients with pain lasting greater than 3 to 6 months should be seen by a specialist in the appropriate field—gynecology, gastroenterology, general surgery, or musculoskeletal medicine—for further workup and management of their now chronic pelvic pain. Referral should also be considered when the underlying cause of pain cannot be found.

PEARLS & CONSIDERATIONS

A solid knowledge of the differential diagnosis of acute pelvic pain in women and a thorough history and physical examination will lead the practitioner to the underlying cause in the vast majority of cases. But all women who present with acute pelvic pain MUST have a pregnancy test as a part of their initial workup. If imaging is needed, pelvic ultrasound is an excellent tool and should be utilized first before CT and MRI in most cases.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Appendicitis (Related Key Topic)
Crohn Disease (Related Key Topic)
Diverticular Disease (Diverticulosis, Diverticulitis, Diverticular Hemorrhage) (Related Key Topic)
Ectopic Pregnancy (Related Key Topic)
Endometriosis (Related Key Topic)
Endometritis (Related Key Topic)
Pelvic Inflammatory Disease (Related Key Topic)
Spontaneous Abortion (Related Key Topic)
Ulcerative Colitis (Related Key Topic)
Urinary Tract Infection (Related Key Topic)
Urolithiasis (Nephrolithiasis) (Related Key Topic)
Uterine Fibroids (Related Key Topic)

AUTHORS: **Anthony Sciscione, DO,** and **Ghamar Bitar, MD**

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Acute Respiratory Distress Syndrome PTG

BASIC INFORMATION

DEFINITION

Acute respiratory distress syndrome (ARDS) is a form of noncardiogenic pulmonary edema that results from acute damage to the alveoli. It is characterized by acute diffuse infiltrative lung lesions with resulting interstitial and alveolar edema, severe hypoxemia, and respiratory failure. The cardinal feature of ARDS, refractory hypoxemia, is caused by formation of protein-rich alveolar edema after damage to the integrity of the lung's alveolar-capillary barrier.

The definition of ARDS based on the American–European Consensus Conference (AECC) from 1994 included the following components:

1. The syndrome must present acutely
2. A ratio of Pa_{O_2} to Fi_{O_2} ≤200 regardless of the level of positive end expiratory pressure (PEEP)
3. The detection of bilateral pulmonary infiltrates on frontal chest radiograph
4. Absence of congestive heart failure (pulmonary artery wedge pressure [PAWP] ≤18 mm Hg or no clinical evidence of elevated left atrial pressure on the basis of chest radiograph or other clinical data)

The Berlin definition of ARDS (Table 1) adopted in 2011 addresses some of the limitations of the AECC definition and establishes the following criteria for ARDS:

- Timing: Within 1 week of a known clinical insult or new or worsening respiratory symptoms
- Chest imaging (chest x-ray or computed tomography [CT] scan): Bilateral opacities, not fully explained by effusions, lobar/lung collapse, or nodules
- Origin of edema: Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
- Oxygenation (if altitude is higher than 1000 m, the correction factor should be calculated as follows: [Pa_{O_2}/Fi_{O_2} × {barometric pressure/760}]
- Mild: 200 mm Hg < Pa_{O_2}/Fi_{O_2} ≤300 mm Hg with PEEP or CPAP ≥5 cm H_2O (this may be delivered noninvasively in the mild ARDS group)
- Moderate: 100 mm Hg < Pa_{O_2}/Fi_{O_2} ≤200 mm Hg with PEEP or CPAP ≥5 cm H_2O
- Severe: Pa_{O_2}/Fi_{O_2} ≤100 mm Hg with PEEP or CPAP ≥5 cm H_2O

SYNONYMS

ARDS
Adult respiratory distress syndrome

ICD-10CM CODE
J80 Acute respiratory distress syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- More than 150,000 ARDS cases/yr in the U.S. 7.1% of all patients admitted to an intensive care unit (ICU) and 16.1% of all patients on mechanical ventilation develop ARDS.
- An international study of 50 countries revealed that 10% of those admitted to an ICU fulfilled criteria for ARDS, and of these, 93% developed it within 48 hours of admission. The study reinforced the notion that ARDS is underrecognized.
- Black, Hispanic, and other patients belonging to racial minorities in the United States were observed to exhibit significantly higher in-hospital sepsis-related respiratory failure and associated mortality.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Signs and symptoms:
  1. Dyspnea
  2. Chest discomfort
  3. Cough
  4. Anxiety
- Physical examination:
  1. Tachypnea
  2. Tachycardia
  3. Hypertension
  4. Paradoxical breathing and use of accessory muscles
  5. Coarse crepitations or crackles of both lungs
  6. Fever may be present if infection is the underlying etiology

ETIOLOGY

- Sepsis (>40% of cases)
- Aspiration: Near-drowning, aspiration of gastric contents (>30% of cases)
- Trauma (>20% of cases)
- Pneumonia (aspiration of gastric contents and sepsis together account for more than 85% of cases of ARDS in recent clinical trials)
- Multiple transfusions, blood products
- Drugs (e.g., overdose of morphine, methadone, heroin; reaction to nitrofurantoin)
- Noxious inhalation (e.g., chlorine gas, high O_2 concentration)
- Post-resuscitation
- Cardiopulmonary bypass
- Burns
- Pancreatitis
- A history of chronic alcohol abuse significantly increases the risk of developing ARDS in critically ill patients
- Table 2 describes risk factors associated with development of ARDS

TABLE 1 2012 Berlin Definition of Acute Respiratory Distress Syndrome (All Components Must Be Present)

Timing	Within 1 week of a known clinical insult or new/worsening respiratory symptoms		
Chest imaging	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules		
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload; need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor for ARDS is present		
Oxygenation	*Mild ARDS*	*Moderate ARDS*	*Severe ARDS*
	200 < Pa_{O_2}/Fi_{O_2} ≤300 with PEEP or CPAP ≥5 cm H_2O	100 < Pa_{O_2}/Fi_{O_2} ≤200 PEEP ≥5 cm H_2O	Pa_{O_2}/Fi_{O_2} ≤100 with PEEP ≥5 cm H_2O

ARDS, Acute respiratory distress syndrome.
From Weinberger SE: *Principles of pulmonary medicine,* ed 7, Philadelphia, 2019, Elsevier.

TABLE 2 Risk Factors Associated with Development of Acute Lung Injury and Acute Respiratory Distress Syndrome

Direct Lung Injury	Indirect Lung Injury
Pneumonia	Sepsis
Aspiration of gastric contents	Multiple trauma
Pulmonary contusion	Cardiopulmonary bypass
Fat, amniotic fluid, or air emboli	Drug overdose
Near-drowning	Acute pancreatitis
Inhalational injury	Transfusion of blood products
Reperfusion pulmonary edema	

From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Congestive heart failure
- Interstitial lung disease (acute interstitial pneumonia, nonspecific interstitial pneumonia [NSIP], cryptogenic organizing pneumonia [COP], acute eosinophilic pneumonia, hypersensitivity pneumonia, pulmonary alveolar proteinosis)
- Connective tissue diseases, such as polymyositis
- Diffuse alveolar hemorrhage
- Lymphangitic carcinomatosis from T-cell or B-cell lymphomas
- Drug-induced lung diseases (amiodarone, bleomycin)

WORKUP

The search for an underlying cause should focus on treatable causes (e.g., infections such as sepsis or pneumonia)

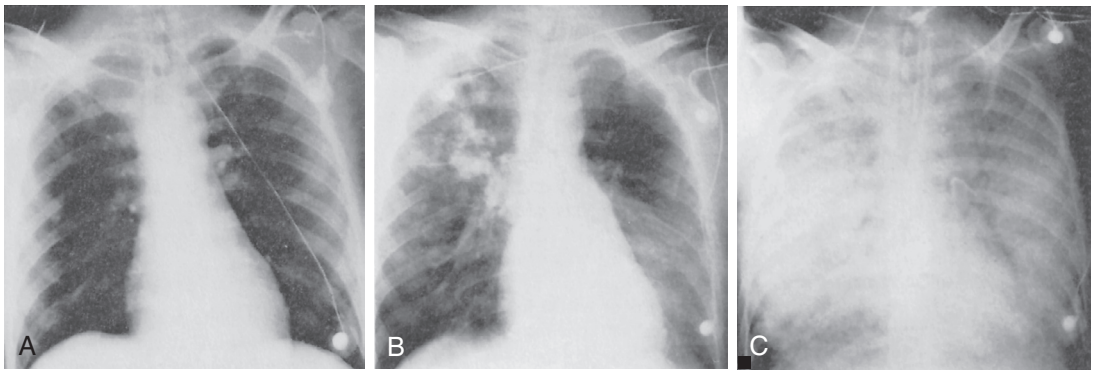

FIG. 1 Acute respiratory distress syndrome. X-ray of a young man who had sustained severe trauma and blood loss in a road traffic accident; the lungs cover a period of 5 days from a relatively normal x-ray **(A),** to bilateral infiltrates **(B),** to bilateral "whiteout" **(C),** accompanied by severe hypoxemia. A Swan-Ganz catheter for measurement of pulmonary artery "wedge" pressure (as a reflection of left atrial pressure) can be seen *in situ* on the x-ray in **C.** The patient died shortly after the last film. (From Souhami RL, Moxham J: *Textbook of medicine,* ed 4, London, 2002, Churchill Livingstone.)

- Arterial blood gases (ABGs)
- Hemodynamic monitoring
- Bronchoalveolar lavage (selected patients)

LABORATORY TESTS

- ABGs:
  1. Initially: Varying degrees of hypoxemia, generally resistant to supplemental oxygen
  2. Respiratory alkalosis, decreased P_{CO_2}
  3. Widened alveolar-arterial gradient
  4. Hypercapnia as the disease progresses
- Bronchoalveolar lavage:
  1. The most prominent finding is an increased number of polymorphonucleocytes.
  2. The presence of eosinophilia has therapeutic implications because these patients respond to corticosteroids.
- Blood and urine cultures
- Blood work:
  1. Increased or reduced white blood cell count with left shift if concomitant infectious process
  2. Normal or mildly elevated B-type natriuretic peptide level
  3. Increased lactate level if concomitant sepsis or septic shock

IMAGING STUDIES

Chest radiograph (Fig. 1).

- The initial chest radiograph might be normal in the initial hours after the precipitating event.
- Bilateral interstitial infiltrates are usually seen within 24 hr; they often are more prominent in the bases and periphery.
- CT scan of chest: Bilateral diffuse, dense consolidations with air bronchograms.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Treatment of ARDS is supportive.

Hemodynamic monitoring:

- Can be used for the initial evaluation of ARDS (in ruling out cardiogenic pulmonary edema) and its subsequent management. However, a pulmonary catheter is not indicated in the routine management of ARDS and trials have shown that clinical management involving the early use of pulmonary artery catheters in patients with ARDS did not significantly affect mortality and morbidity rates and may result in more complications as compared with a central venous catheter.
- Although no dynamic profile is diagnostic of ARDS, the presence of pulmonary edema, a high cardiac output, and a low pulmonary capillary wedge pressure (PCWP) is characteristic of ARDS.
- It is important to remember that partially treated intravascular volume overload and flash pulmonary edema can have the hemodynamic features of ARDS; filling pressures can also be elevated by increased intrathoracic pressures or with fluid administration; cardiac function can be depressed by acidosis, hypoxemia, or other factors associated with sepsis.

Ventilatory support:

- Noninvasive positive-pressure ventilation (NIPPV) (i.e., BiPAP) should only be used in selected cases in patients with hypoxic respiratory failure. A recent randomized control study showed that high-flow oxygen by nasal cannula reduced ventilator-free days and mortality compared with NIPPV in patients with hypoxemic respiratory failure without hypercapnia. Either modality should not delay intubation and mechanical ventilation initiation in patients with rapidly progressing clinical deterioration.
- Mechanical ventilation is generally necessary to maintain adequate gas exchange (Table 3). General recommendations for ventilator settings in ARDS are described in Table 4. A low tidal volume and low plateau pressure ventilator strategy are recommended to avoid ventilator-induced injury. Assist-control is generally preferred initially with the following ventilator settings:
  1. F_{IO_2} 1.0 (until a lower value can be used to achieve adequate oxygenation). When possible, minimize oxygen toxicity by maintaining F_{IO_2} at <60%.
- Tidal volume: Set initial tidal volume at 6 ml/kg of predicted body weight (PBW). Tidal volumes are reduced from 6 ml/kg of PBW to a minimum of 4 ml/kg if plateau airway pressures exceed 30 cm of water. The concept of using PBW is based on the fact that lung size depends most strongly on height and sex; PBW normalizes the tidal volume to lung size. Aim to maintain plateau pressure (Pplat) at <30 mm Hg.
- PEEP 5 cm H_2O or greater (to increase lung volume and keep alveoli open). PEEP should be applied in small increments of 3 to 5 cm H_2O (see Table 3) to achieve acceptable arterial saturation (>0.9) with nontoxic F_{IO_2} values (<0.6) and acceptable airway plateau pressures (<30 to 35 cm H_2O). It is important to remember that an increase in PEEP may lower cardiac output and, despite improvement in P_{AO_2}, may actually have a negative effect on tissue oxygenation (the major determinants of tissue oxygenation are hemoglobin, percent saturation, and cardiac output). The optimal level of PEEP remains unestablished. Although higher levels of PEEP may help prevent life-threatening hypoxemia and be associated with lower hospital mortality in patients meeting criteria for ARDS, such benefit is unlikely in patients with less severe lung injury (P_{AO_2}/F_{IO_2} >200) and a strategy of treating such patients with high PEEP levels may be harmful. In fact, a new study published in 2017 demonstrated that the open lung approach increases mortality in patients with moderate to severe ARDS.
- Inspiratory flow: 60 L/min.
- Ventilatory rate: High ventilatory rates of up to 35 breaths/min are often necessary in patients with ARDS to achieve the desired minute ventilation because of their increased physiologic dead space and smaller lung volumes. Patients must be monitored for excessive intrathoracic gas trapping (auto-PEEP or intrinsic PEEP) that can depress cardiac output.
- Permissive hypercapnia: To maintain a low plateau pressure, a low tidal volume is

TABLE 3 Ventilator Management of Patients with Acute Respiratory Distress Syndrome

Calculate predicted body weight (PBW)	• Males: PBW (kg) = 50 + 2.3 [(height in inches) – 60] *or* 50 + 0.91 [(height in cm) – 152.4] • Females: IBW (kg) = 45.5 + 2.3 [(height in inches) – 60] *or* 45.5 + 0.91 [(height in cm) – 152.4]
Ventilator mode	• Volume assist/control until weaning
Tidal volume (Vt)	• Initial Vt: 6 ml/kg predicted body weight • Measure inspiratory plateau pressure (Pplat, 0.5 sec inspiratory pause) every 4 hours *and* after each change in positive end-expiratory pressure (PEEP) or Vt. • If Pplat is >30 cm H_2O, decrease Vt to 5 or 4 ml/kg. • If Pplat is <25 cm H_2O and Vt <6 ml/kg PBW, increase Vt by 1 ml/kg PBW.
Respiratory rate (RR)	• With initial change in Vt, adjust RR to maintain minute ventilation. • Make subsequent adjustments to RR to maintain pH 7.30-7.45, but do not exceed RR = 35/min and do not increase set rate if $Paco_2$ is <25 mm Hg.
I:E ratio	• Acceptable range, 1:1-1:3 (no inverse ratio)
Fio_2, PEEP, and arterial oxygenation	• Maintain Pao_2 = 55-80 mm Hg or Spo_2 = 88%-95% using the following PEEP/Fio_2 combinations:

Fio_2	0.3-0.4	0.4	0.5	0.6	0.7	0.8	0.9	1
PEEP	5-8	8-14	8-16	10-20	10-20	14-22	16-22	18-25

Acidosis management	• If pH is <7.30, increase RR until pH is ≥7.30 or RR = 35/min. • If pH remains <7.30 with RR = 35, consider bicarbonate infusion. • If pH is <7.15, Vt may be increased (Pplat may exceed 30 cm H_2O).
Alkalosis management	• If pH is >7.45 and patient is not triggering ventilator, decrease set RR but not below 6/min.
Fluid management	• Once patients are out of shock, adopt a conservative fluid management strategy. • Use diuretics or fluids to target a central venous pressure (CVP) of <4 or a pulmonary artery occlusion pressure (PAOP) of <8.
Liberation from mechanical ventilation	• Daily interruption of sedation • Daily screen for spontaneous breathing trial (SBT) • SBT when all of the following criteria are present: 1. Fio_2 <0.40 and PEEP <8 cm H_2O 2. Not receiving neuromuscular blocking agents 3. Patient is awake and following commands 4. Systolic arterial pressure >90 mm Hg without vasopressor support 5. Tracheal secretions are minimal, and the patient has a good cough and gag reflex
Spontaneous breathing trial	• Place patient on 5 mm Hg pressure support with 5 mm Hg PEEP *or* T-piece. • Monitor heart rate, RR, oxygen saturation for 30-90 minutes. • Extubate if there are no signs of distress (tachycardia, tachypnea, agitation, hypoxia, diaphoresis).

FiO_2, Fraction of inspired oxygen; *IBW,* ideal body weight; *$PaCO_2$,* partial pressure of carbon dioxide in the arterial blood; *PaO_2,* partial pressure of oxygen in arterial blood; *SpO_2,* saturation of arterial blood with oxygen as measured by pulse oximetry.
From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

TABLE 4 Recommendations for Ventilator Settings in Acute Respiratory Distress Syndrome

Conventional Mechanical Ventilation		
Mode		Volume- or pressure-controlled "Airway pressure release ventilation" preferred when preservation of spontaneous ventilation is desired
Tidal volume	6-10 ml/kg	Permissive hypercapnia (increase <5 mm Hg/h) $PaCO_2$ 65-85 mm Hg well tolerated unless increased ICP Arterial pH >7.15
End-inspiratory plateau pressure	<30 cm H_2O	Above this limit, increased risks of barotrauma and air leaks
Positive end-expiratory pressure	10-15 cm H_2O	Lower PEEP levels, if heterogeneous lung injury Higher PEEP levels, if diffuse lung injury Consider early prone positioning (6-12 h)
Respiratory rate	20-60 beats/min	Adjusted to age; higher than normal may limit hypercapnia
Inspiratory/expiratory ratio	1:2 to 1:1	Check for inadvertent PEEP
FiO_2	<60%-80%	Depends on how the diseased lung may be recruited PaO_2 40-60 mm Hg, SpO_2 85%-95%
High-Frequency Oscillatory Ventilation		
Amplitude pressure	30-50 cm H_2O	To achieve visible chest vibrations
Mean airway pressure	15-30 cm H_2O	To achieve adequate chest recruitment (7 to 9 ribs)
Respiratory rate	3-10 Hz	Decrease to increase tidal volume (usually not measured)
Inspiratory/expiratory ratio	1:3 to 1:1	1:1 more appropriate in diffuse lung injury
FiO_2	<60%-80%	Depends on whether the lung may be recruited

FiO_2, Fraction of inspired oxygen; *ICP,* intracranial pressure; *$PaCO_2$,* partial pressure of carbon dioxide in the arterial blood; *PaO_2,* partial pressure of oxygen in arterial blood; *PEEP,* positive end-expiratory pressure; *SpO_2,* saturation of arterial blood with oxygen as measured by pulse oximetry.
From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

frequently required, leading to a reduced minute ventilation and hypoventilation with consequently a respiratory acidosis (elevated PCO_2 and reduced pH). Most patients (excluding patients with cerebral edema, acute coronary syndrome, seizures, cardiac arrhythmias, and so on) can tolerate a low pH without major consequences. Bicarbonate replacement is suggested when the pH falls to below 7.20.

- Sedation: Gamma-aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepines) have traditionally been the most commonly administered sedative drugs for ICU patients. Recent trials indicate that the alpha-2 agonist dexmedetomidine (Precedex) may have distinct advantages. At comparable sedation levels, dexmedetomidine-treated patients spent less time on ventilator, experienced less delirium, and developed less tachycardia and hypertension. The most notable adverse effect of dexmedetomidine was bradycardia. The benefits of early continuous neuromuscular blockade in patients with ARDS who are receiving mechanical ventilation remains unclear. In a recent trial among patients with moderate-to-severe ARDS who were treated with a strategy involving a high PEEP, there was no significant difference in mortality at 90 days between patients who received an early and continuous infusion of the neuromuscular blocking agent cisatracurium and those who were treated with a usual-care approach with lighter sedation targets.

ACUTE GENERAL Rx

Identify and treat precipitating conditions:

- Blood and urine cultures and trial of antibiotics in presumed sepsis (routine administration of antibiotics in all cases of ARDS is not recommended).
- Prompt repair of bone fractures in patients with major trauma.
- Crystalloid resuscitation in pancreatitis.
- Fluid management: In most patients with ARDS, fluid restriction is associated with better outcomes than a liberal fluid policy. Optimal fluid and hemodynamic management of patients with ARDS should be patient specific; in general, administration of crystalloids is recommended if a downward trend in PCWP is associated with diminished cardiac index, resulting in prerenal azotemia, oliguria, and relative tachycardia.
- Positioning the patient: Changes in position can improve oxygenation by improving the distribution of perfusion to ventilated lung regions; repositioning (lateral decubitus positioning) should be attempted in patients with hypoxemia that is not responsive to other medical interventions. Placing patients with moderate and severe hypoxemia in a prone position may improve their oxygenation. A meta-analysis that included the recent trials by Guerin et al have shown that in patients with severe ARDS, early application of prolonged (over 16 hours/day) prone-positioning sessions significantly decreases 28-day and 90-day mortality.
- Corticosteroids: Routine use of corticosteroids in ARDS is not recommended; corticosteroids may be beneficial in patients with many eosinophils in the bronchoalveolar lavage fluid or in patients with severe pneumonia. Systemic infections should be ruled out or adequately treated before administration of corticosteroids. Use of methylprednisolone has not been shown to increase the rate of infectious complications but is associated with a higher rate of neuromuscular weakness. In addition, starting methylprednisolone therapy more than 2 wk after the onset of ARDS may increase the risk of death.
- Nutritional support: Nutritional support, preferably administered by the enteral route, is necessary to maintain adequate colloid oncotic pressure and intravascular volume. The use of antioxidants and dietary oil supplements is still equivocal and cannot be recommended at this time.
- Tracheostomy: Tracheostomy is warranted in patients requiring >2 wk of mechanical ventilation; discussion regarding tracheostomy should begin with patient (if alert and oriented) and/or family members/legal guardian after 5 to 7 days of ventilatory support. Early tracheostomy (within 4 days of admission to critical care) does not limit mortality and results in many unneeded procedures (Young et al, 2013).
- Some form of deep vein thrombosis prophylaxis is indicated in all patients with ARDS.
- Stress ulcer prophylaxis with sucralfate suspension (by nasogastric tube), or proton pump inhibitors (PO or IV) or H_2 blockers (PO or IV). Should be reserved for seriously ill patients who are at high risk for this complication.
- The use of surfactant remains controversial. Patients who receive surfactant have a greater improvement in gas exchange in the initial 24-hour period than patients who receive standard therapy alone; however, the use of exogenous surfactant does not improve survival.

DISPOSITION

- Patients who survive ARDS are at risk of diminished functional capacity, mental illness, and decreased quality of life. Prognosis for ARDS varies with the underlying cause. Prognosis is worse in patients with chronic liver disease, non-pulmonary organ dysfunction, sepsis, and advanced age. ARDS survivors are at high risk for incident joblessness and substantial loss of wages, and 58% of those returning to work received disability.
- Elevated values of dead space fraction ($[Paco_2 > 2\ Peco_2]/Paco_2$; normal is <0.3) is associated with an increased risk of death.
- In ARDS, the percentage of potentially recruitable lung is variable and associated with the response to PEEP.
- Overall mortality rate varies between 32% and 45%. Most deaths are attributable to sepsis or multiorgan dysfunction rather than primary respiratory causes.
- Recent trials have shown that as compared with the current standard of care, a ventilator strategy using esophageal measures to estimate the transpulmonary pressure significantly improves oxygenation and compliance. Further trials will determine if this approach should be widely adapted.
- Strategies for treatment of life-threatening refractory hypoxemia (prone positioning, inhaled nitric acid, extracorporeal membrane oxygenation [ECMO], high-frequency oscillatory ventilation, recruitment maneuvers) may improve oxygenation, but their impact on mortality remains unproven. Use of ECMO in combination with lung-protective ventilation was found to be beneficial as a treatment strategy early in the course of ARDS related to H1N1 infection. Extracorporeal gas exchange may allow the use of low tidal volumes and lower levels of inspired oxygen and use of higher PEEP if desired. ECMO is costly and labor-intensive. The role and proper use of ECMO for patients with ARDS have not been clearly defined.
- General indications for venovenous ECMO in severe cases of ARDS are:
  1. Severe hypoxemia (e.g., ratio of Pa_{O_2} to Fi_{O_2} <80 despite the application of high levels of PEEP [typically 15 to 20 cm H_2O]) for at least 6 hr in patients with potentially reversible respiratory failure
  2. Uncompensated hypercapnia with acidemia (pH <7.15) despite the best accepted standard of care for management with a ventilator
  3. Excessively high end inspiratory plateau pressure (>35 to 45 cm H_20, according to the patient's body size) despite the best accepted standard of care for management with a ventilator

REFERRAL

Surgical referral for tracheostomy (see "Acute General Rx").

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Acute Respiratory Distress Syndrome (ARDS) (Patient Information)

AUTHOR: **Jorge Mercado, MD**

SUGGESTED READINGS

ARDS Definition Task Force: Acute respiratory distress syndrome, the Berlin definition, *JAMA* 307(23):2526-2533, 2012.

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Acute Respiratory Failure (ARF)

BASIC INFORMATION

DEFINITION

Respiratory failure is a condition in which the respiratory system fails in one or both of its gas exchanging functions (oxygenation and carbon dioxide elimination). Traditionally, there are two types of acute respiratory failure: type I (hypoxic) and type II (hypercapnic). Other sources have defined a type III and a type IV; type III is respiratory failure related to atelectasis, and type IV is related to hypoperfusion of respiratory muscles in patients with shock. Type I is described in detail in another chapter (see ARDS). This chapter focuses on type II respiratory failure. Table 1 summarizes the classification of Acute Respiratory Failure.

Type II Respiratory failure is defined as an elevation in arterial carbon dioxide tension, greater than 45 mm Hg. This is directly proportional to the rate of CO_2 production and inversely proportional to the rate of CO_2 elimination by the lungs. Both hypoxemia and hypercapnia can occur at the same time, depending on the location of the underlying disorder and mechanism.

Respiratory failure can be acute (ARF) or chronic. The acute presentation occurs within minutes to hours, whereas the chronic form develops over days or longer.

SYNONYMS

Respiratory insufficiency
Hypercarbic respiratory failure
Hypoxemic respiratory failure
ARF

ICD-10CM CODES

J96.00 Acute respiratory failure
J96.01 Acute respiratory failure with hypoxia
J96.02 Acute respiratory failure with hypercapnia
J96.90 Respiratory failure, unspecified
J96.91 Respiratory failure, unspecified with hypoxia
J96.92 Respiratory failure, unspecified with hypercapnia

EPIDEMIOLOGY & DEMOGRAPHICS

- An estimated 1.9 million patients discharged from acute care hospitals nationwide meet study criteria for ARF.
- The winter months seem to be where upper and lower respiratory infections are more prevalent, and therefore when there will be a peak incidence of acute respiratory failure cases.
- Comorbid conditions, including chronic disorders of the cardiac, pulmonary, neurologic, renal, hepatic systems, and the patient's advanced age elevate the risk of mortality.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Decreased level of consciousness
- Increased cerebral blood flow, with increased intracranial pressure
- Decreased myocardial contractility
- Decreased diaphragmatic function
- Shift of the oxyhemoglobin dissociation curve to the right
- Physical signs:
  1. Dyspnea
  2. Somnolence
  3. Headaches
  4. Confusion
  5. Asterixis
  6. Coma

ETIOLOGY

See Tables 2 and 3.

DIAGNOSIS

Diagnosis is made clinically according to physical findings, and it is confirmed by arterial blood gases.

Table 4 summarizes common clues obtained from the history and physical examination.

DIFFERENTIAL DIAGNOSIS

See Table 2.

WORKUP

After supportive therapy is initiated, a careful search for the underlying cause of the respiratory failure is critical, as this may have important implications on its ultimate therapy.

LABORATORY TESTS

- Arterial blood gas (Fig. 1), showing elevated CO_2 level
- Basal metabolic panel, showing elevated bicarbonate level

IMAGING STUDIES

- Chest imaging studies include:
  1. Chest x-ray
  2. CT scan of the chest (with angiography when suspecting pulmonary embolism)
  3. Chest ultrasound

TREATMENT

The treatment of respiratory failure is initially supportive, aiming to determine first the acuity and/or severity of the presentation. Correction of the hypoxemia, hypercapnia, and management of the underlying etiology of the condition are essential to its treatment. Potential indications for mechanical ventilation are summarized in Table 5.

NONPHARMACOLOGIC THERAPY

- Treat the hypoxemia with oxygen support, which may require pressure support in the way of noninvasive ventilation (Bi-PAP) or mechanical ventilation, for the more severe cases.
- Treat hypercapnia with ventilatory support, noninvasive or invasively. The decision for either can be difficult and it is mainly based on clinical presentation, severity of

TABLE 1 Classification of Acute Respiratory Failure

	Type I	Type II	Type III	Type IV
MECHANISM OF HYPOXEMIA	Low Fio_2 ventilation/perfusion (V/Q) mismatch Shunting Reduced diffusing capacity	Hypoventilation	Shunting Hypoventilation V/Q mismatch	Hypoperfusion or inadequate oxygenation of peripheral tissues
LOCATION OF PATHOLOGICAL PROCESS	Inhaled air composition Alveolar-capillary unit Oxygen-carrying capacity of blood	Airway Central nervous system (CNS) Neuromuscular system Chest wall	Alveolar-capillary unit collapse with regional hypoventilation	Cardiovascular system Peripheral tissues
CLINICAL SYNDROMES	Cardiogenic pulmonary edema Acute respiratory distress syndrome Pneumonia Interstitial lung disease Pulmonary embolism Pulmonary hypertension Atelectasis Alveolar hemorrhage Carbon monoxide poisoning Anatomic shunts	Chronic obstructive pulmonary disease Asthma CNS depression (intoxication) CNS trauma or injury Neuromuscular disorders Skeletal disorders Obesity-hypoventilation syndrome	Thoracic or upper abdominal surgery or trauma Inadequate postoperative analgesia Pleural tumor or inflammation Trapped lung Subdiaphragmatic tumor or inflammation Obesity	Septic (distributive) shock Hypovolemic shock Cardiogenic shock Compromised cellular oxidation Hypermetabolic states

FiO_2, Fraction of inspired oxygen.
Modified from Jean-Louis V: *Intensive care medicine: annual update 2008,* Berlin Heidelberg, 2008, Springer-Verlag.

TABLE 2 Differential Diagnosis of Potential Causes of Acute Respiratory Failure

Central Nervous System	Spinal Cord, Nerves, Muscle	Chest Wall, Thoracic Cage	Increased Dead Space
Medications (anesthetics and/or opioids)	Medications	Trauma	Obstructive airways disorders
Alveolar hypoventilation	Trauma	Kyphoscoliosis	Upper: Acute epiglottitis, foreign body aspiration, tracheal tumor
Trauma	Myasthenia gravis	Flail chest	Lower: COPD, asthma, cystic fibrosis
Meningoencephalitis	Guillain-Barre syndrome	Pleural disease	
Localized tumors or vascular abnormalities of the medulla	Electrolyte abnormalities	Scleroderma	
		Morbid obesity	
Strokes affecting medullary control centers		Ascites	
Severe alkalosis		Severe ileus	

COPD, Chronic obstructive pulmonary disease.

symptoms, comorbidities, and level of acid base derangement, as well as mental status.
- Contraindications to noninvasive ventilation include respiratory arrest, hemodynamic or cardiac instability, or inability to protect the airway.
- Monitoring carbon dioxide levels has not been standardized, but a change in symptoms and or worsening in mental status can prompt a repeat in blood gas analysis.
- Worsening blood gas levels can be remediated with changes in the pressures on the noninvasive ventilator or by switching to a mechanical ventilator.

ACUTE GENERAL Rx

Ventilatory support, either invasive (mechanical ventilation) or noninvasive. Table 6 provides

TABLE 3 Pathophysiological Mechanisms That Lead to Hypoxia and Respiratory Insufficiency

Extrapulmonary processes including chest wall and skeletal abnormalities (hypoxic hypoxia)	Deficiency of oxygen in inspired air (high altitude, suffocation) Hypoactive hypoventilation (central nervous system trauma, drug toxicities, and neuromuscular and skeletal disorders) Upper airway obstruction leading to hypoventilation (trauma and angioedema)
Pulmonary etiologies (hypoxic hypoxia)	Hypoventilation caused by increased airway resistance (chronic obstructive pulmonary disease and asthma) Abnormal alveolar ventilation-perfusion ratio (pulmonary embolism, pneumonia, aspiration, and emphysema) Diminished diffusing capacity via the alveolar-capillary membrane (interstitial lung disease and pulmonary vascular disease) Pulmonary shunting (atelectasis, pneumonia, hepatopulmonary syndrome, and arteriovenous malformations)
Cardiac right-to-left shunts; e.g., atrial septal defect (hypoxic hypoxia)	—
Inadequate capacity of blood to transport oxygen (anemic hypoxia)	Anemia Hemoglobinopathies (methemoglobinemia and carbon monoxide poisoning)
Inadequate oxygen transport due to a circulatory defect (static hypoxia)	General circulatory deficiency or collapse (shock or cardiac failure) Localized circulatory deficiency (peripheral, cerebral, and coronary vessels)
Abnormal tissue capability for using oxygen (histotoxic hypoxia)	Late-stage irreversible shock Poisoning of cellular oxidation enzymes (cyanide or arsenic toxicity and heavy ethanol intoxication) Diminished cellular metabolic capacity for using oxygen (severe vitamin deficiencies; e.g., beri-beri)

Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.

TABLE 4 Common Clues Obtained from the History, Symptoms, and Clinical Examination Findings That Can Help in the Initial Diagnostic Workup and Management of Acute Respiratory Failure

History and Symptoms	Signs on Physical Examination	Diagnosis
Cough, sputum, secretions	Rales or wheezing	Pneumonia, chronic obstructive pulmonary disease (COPD) exacerbation, bronchiectasis
Sudden onset of shortness of breath	Normal auscultation and percussion, possible signs of leg swelling to suggest deep vein thrombosis	Pulmonary embolism
History of heavy smoking	Wheezing, rhonchi	Emphysema, chronic bronchitis
Orthopnea, chest pain, paroxysmal nocturnal dyspnea	Arrhythmia, peripheral edema, jugular venous distention, peripheral hypoperfusion	Congestive heart failure or acute coronary syndrome
Trauma, aspiration, blood transfusions	Diffuse crackles	Acute respiratory distress syndrome
History of allergies, wheezing or airway disease	Wheezing	Asthma, COPD
Exposure to heavy metals, handling of animals, dust or other significant environmental exposures	"Velcro" rales, clubbing	Chronic interstitial lung disease
Choking, aspiration, vomiting, dental procedures	Inspiratory stridor, poor air entry	Foreign body
Drug abuse	Constricted or dilated pupils, altered mental status, skin marks, perforated nasal septum, hypersalivation, decreased respiratory frequency	Central nervous system depression, intoxication
Exposure to a new drug/chemical or foods known to be allergenic	Swollen oral mucosa and tongue; stridor or wheezing	Angioedema, anaphylaxis
Progressive muscle weakness or immobility	Sensory abnormalities	Neuromuscular disorders
Trauma, procedures, inhalational injury	Absent breath sounds unilaterally, hypertympanic, tracheal deviation	Pneumothorax
Trauma, procedures	Absent breath sounds, dull on percussion, tracheal deviation	Hemothorax

Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.

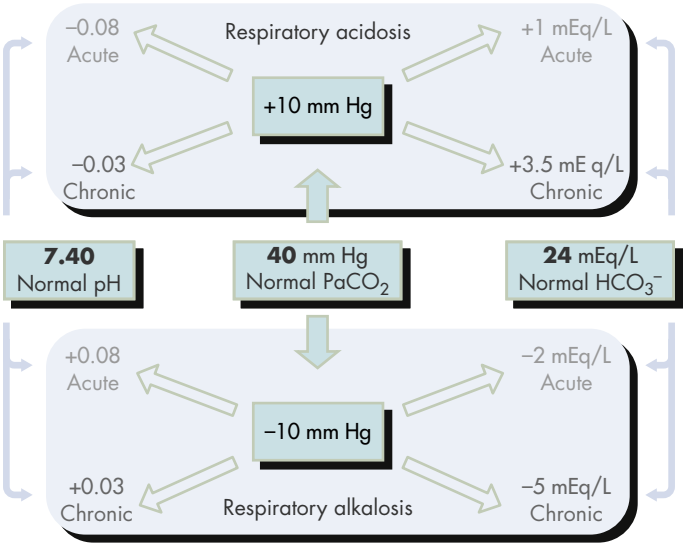

FIG. 1 Interpretation of an arterial blood gas in the setting of respiratory failure. (From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.)

an overview of features of selected modes of mechanical ventilation. Potential advantages and disadvantages of each mode are summarized in Table 7.

CHRONIC Rx

- Some patients require chronic ventilatory support, such as obesity hypoventilation syndrome patients (alveolar hypoventilation), neuromuscular disease patients (ALS), or those with chronic obstructive pulmonary disease.
- In these cases, the noninvasive form of ventilation is used during sleep.

REFERRAL

Pulmonologist

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Acute Respiratory Distress Syndrome (Related key topic)
Pulmonary Edema (Related key topic)
Chronic Obstructive Pulmonary Disease (Related key topic)
Asthma (Related key topic)
Interstitial Lung Disease (Related key topic)
Pneumonia, Bacterial (Related key topic)
Pneumonia, Mycoplasma (Related key topic)
Pneumonia, Pneumocystis Jiroveci (Related key topic)
Pneumonia, Viral (Related key topic)
Pulmonary Embolism (Related key topic)
Carbon Monoxide Poisoning (Related key topic)

AUTHOR: **Jorge Mercado, MD**

TABLE 5 Potential Indications for Mechanical Ventilation

Physiologic Mechanism	Clinical Assessment	Normal Range	Value(s)/Finding(s) Supporting Need for Mechanical Ventilation
Hypoxemia	$P_{(A\text{-}a)}O_2$ gradient (mm Hg)	25-65	>350
	Pa_{O_2}/fi_{O_2} ratio	425-475	<300
	Sa_{O_2}	98%	<90% despite supplemental oxygen
Hypercarbia/inadequate alveolar ventilation	Pa_{CO_2}	35-45 mm Hg	Acute increase from patient's baseline pH <7.20 Mental status decline
Oxygen delivery/oxygen consumption imbalance	Elevated lactate	≤2.2 mg/dl	≥4 mg/dl despite adequate resuscitation
	Decreased mixed venous oxygen saturation	70%	<70% despite adequate acute resuscitation
Increased work of breathing	Minute ventilation	5-10 L/min	>15-20 L/min
	Dead space	0.15-0.30	≥0.5 (acute)
Inspiratory muscle weakness	NIP	80-100 cm H_2O	<20-30
	VC	60-75 ml/kg	<15-20
Acute decompensated heart failure	Jugular venous distention Pulmonary edema Decreased EF		Clinical judgment combined with the listed factors
Inadequate lung expansion	V_T (ml/kg)	5-8	<4-5
	VC (ml/kg)	60-75	<10-15
	Respiratory rate (breaths/min)	12-20	≥35

EF, Ejection fraction; *Fi_{O_2},* fraction of inspired oxygen; *NIP,* negative inspiratory pressure; *$P_{(A\text{-}a)}O_2$,* alveolar-arterial oxygen pressure difference; *Pa_{O_2},* partial pressure of oxygen; *Pa_{CO_2},* partial pressure of carbon dioxide; *Sa_{O_2},* arterial oxygen saturation; *VC,* vital capacity; *V_T,* tidal volume.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

TABLE 6 Overview of Features of Selected Modes of Mechanical Ventilation

Ventilator Mode	Trigger	Control	Cycling	Inspiratory Flow
Continuous mandatory ventilation	Time	Flow or pressure	Volume or time	Selected or decelerating
Volume control/assist control (VC/AC)	Patient or time	Flow	Volume	Square, decelerating, or sinusoidal
Pressure control/assist control (PC/AC)	Patient or time	Pressure	Time	Decelerating
Synchronized intermittent mandatory ventilation	Patient or time	Pressure for patient breaths	Flow for spontaneous breaths	Decelerating for spontaneous breath
		Flow (VC) or pressure (PC) for ventilator breaths	Volume or time for ventilator breaths	Square (VC), decelerating (VC or PC), sinusoidal for spontaneous breaths
Stand-alone pressure-support ventilation	Patient	None	Flow	Decelerating

From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

TABLE 7 Potential Advantages and Disadvantages of Selected Modes of Mechanical Ventilation

Mode	Advantage(s)	Disadvantage(s)
Controlled mechanical ventilation	Rests muscles of respiration	Requires use of heavy sedation/neuromuscular blockade
Assist volume control	Reduced work of breathing Guarantees delivery of set tidal volume (unless peak pressure limit alarm is exceeded)	Potential adverse hemodynamic effects May lead to inappropriate hyperventilation and excessive inspiration pressures
Assist pressure control	Allows limitation of peak inspiratory pressures	Same as for assist volume control Potential hyperventilation or hypoventilation with lung resistance/compliance changes
Synchronized intermittent mandatory ventilation	Less interference with normal cardiovascular function	Increased work of breathing compared with assist control Patient may find it difficult to adjust to two different types of ventilator breaths
Stand-alone pressure-support ventilation	Patient comfort Improved patient-ventilator interaction Decreased work of breathing	Apnea alarm is only backup Variable patient tolerance

From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

SUGGESTED READINGS

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Acute Stress Disorder

BASIC INFORMATION

DEFINITION

Acute stress disorder (ASD) features severe acute stress reactions (ASRs) that occur between 3 days to 1 month after exposure to a traumatic event (direct exposure or indirectly experienced).

SYNONYMS

ASD
ASR

ICD-10CM CODES
F43.0 Acute stress reaction
F43.11 Post-traumatic stress disorder, acute
DSM-5 CODE
308.3 Other acute reactions to stress

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: The prevalence of ASD varies according to the nature of the traumatic event. Prevalence is estimated at less than 20% in cases that do not involve a personal assault (e.g., motor vehicles accidents, traumatic brain injury, severe burns, etc.) and at 20% to 50% in cases of interpersonal trauma (e.g., sexual assault, witnessing a mass shooting).
PREDOMINANT AGE: ASD can be diagnosed at all ages. Children tend to manifest symptoms differently (e.g., frightening dreams that do not directly reflect the trauma). Young children may not report fear at the time of the trauma or when reexperiencing the trauma.
PREDOMINANT SEX: ASD occurs more frequently in females compared with males. Rate of incidence in individuals who do not identify on the gender binary is unclear.
GENETICS: Differential function of the serotonin transporter may mediate differential responses to trauma. The 5-HTTLPR may constitute a genetic candidate region. Higher rates of ASD among women may be attributable to higher rates of violence against women and sex-linked neurobiological differences in the stress response.
RISK FACTORS: Greater perceived severity of the trauma (i.e., catastrophic interpretations of the event, exaggerated appraisals of future harm, hopelessness), high levels of negative affect, avoidant coping style, history of prior trauma, lack of social support, premorbid mental disorder (e.g., preexisting anxiety or depressive disorders)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

DSM-5 criteria are met when the following criteria are satisfied:

A. Exposure to actual or threatened serious injury, death, or sexual violation in one or more of the following ways:
   1. Personally experiencing a traumatic event
   2. Witnessing a traumatic event as it occurred
   3. Learning that a traumatic event occurred to a family member or close friend
   4. Repeated or extreme exposure to the details of a traumatic event
B. Presence of nine or more of the following symptoms from any of the following five categories: (1) intrusion, (2) negative mood, (3) dissociation, (4) avoidance, and (5) arousal:
   1. Recurrent, distressing, involuntary memories of the trauma (intrusion)
   2. Recurrent distressing dreams relating to the trauma (intrusion)
   3. Flashbacks to the event, in which the individual feels/acts as if the event is recurring (intrusion)
   4. Intense or prolonged psychological distress or physiological reaction in response to cues that are reminiscent of the trauma (intrusion)
   5. Continual inability to experience positive emotions (negative mood)
   6. Altered sense of reality (dissociation)
   7. Inability to recall components of the trauma (dissociation)
   8. Avoidance of memories, thoughts, or feelings associated with the event (avoidance)
   9. Avoidance of external reminders of the event (avoidance)
   10. Sleep disturbance (arousal)
   11. Irritability and anger outbursts (arousal)
   12. Hypervigilance (arousal)
   13. Difficulties concentrating (arousal)
   14. Exaggerated startle response (arousal)
C. Symptoms typically begin immediately after the trauma and must persist for at least 3 days, and up to 1 month, following exposure to trauma. If symptoms persist for longer than 1 month, a diagnosis of posttraumatic stress disorder (PTSD) may be considered.
D. Exposure to trauma must result in clinically significant impairment in functioning.
E. Symptoms must not be attributable to a medical condition or substance use, and cannot be better explained by brief psychotic disorder.

ETIOLOGY

Factors predicting the development of ASD have not been established; however, multiple theoretical models have been proposed. Dissociative models propose that individuals minimize the emotional consequences of trauma by restricting awareness of the event to reduce fear. Cognitive perspectives propose that intentional cognitive processes (e.g., avoidance, distraction, dysfunctional appraisals, attribution of responsibility) result in pathological reactions to trauma. Biological theories focus on the immediate effects of trauma on neuronal function, including cortisol, catecholamines, glucocorticoids, serotonin, and endogenous opioids as mediating factors of the trauma response.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Adjustment disorder
- Panic disorder
- PTSD
- Obsessive-compulsive disorder
- Dissociative identity disorder
- Dissociative amnesia
- Depersonalization-derealization disorder
- Psychotic disorders
- Traumatic brain injury

WORKUP

Diagnosis is made based on individual interviews, including a history of past trauma, age at the time of the trauma, and duration of the trauma. Structured clinical interviews may be used and supplemented with standardized self-report measures. It should be noted that dissociative symptoms may prevent individuals from remembering components of the trauma, as well as remembering feelings of fear, helplessness, or horror. Clinicians often seek collateral data from other sources (e.g., family, close friends, medical providers, therapists) in diagnosing this disorder. Structured measurements such as the Stanford Acute Stress Reaction Questionnaire, Acute Stress Disorder Interview, or Acute Stress Disorder Scale, which is most useful for severity assessment, are also used by clinicians to assist with diagnosis and treatment evaluation.

LABORATORY TESTS

None indicated

IMAGING STUDIES

None indicated

TREATMENT

- Early treatment should focus on establishing a therapeutic alliance and acknowledging negative emotions (i.e., fear) of future exposure to traumatic agents.
- Resilience-focused psychosocial interventions may focus on better tolerating the distress of trauma-related memories, identifying triggers associated with traumatic events to reduce emotional reactivity or reexperiencing trauma, reducing trauma-related avoidance and sleep disturbances and nightmares, increasing social support, decreasing behaviors that interfere with daily life, limiting generalization of the danger experienced, and altering maladaptive attributions and appraisals.
- Early behavioral and educational interventions demonstrate small to moderate effects for reducing symptoms of psychological trauma.
- In cases of trauma related to experiences of interpersonal violence, safety planning is necessary for individuals who remain in unsafe situations or relationships.
- Pharmacological treatment is typically reserved for individuals who have already received psychotherapy. There are few controlled pharmacological treatment trials for ASD.
- There are currently no medications approved by the FDA for treatment of ASD. Clinicians may consider FDA-approved medications for PTSD, such as paroxetine and sertraline.

NONPHARMACOLOGIC THERAPY

- Cognitive behavioral therapy (CBT)
- Cognitive processing therapy (CPT)
- Relaxation and mindfulness

ACUTE GENERAL Rx

- Acute medication may be necessary when the individual is dangerous, agitated, or psychotic. In emergencies, short-acting benzodiazepines or neuroleptics with minimal side effects may be effective.
- Antiadrenergic agents, such as beta-blockers, may be useful for treatment of arousal.
- Brief, short-term treatment using benzodiazepines (i.e., alprazolam, clonazepam, Temazepam) may be useful for treating arousal, insomnia, and anxiety. It should be noted that prolonged use of benzodiazepines has been associated with increased risk of long-term PTSD symptoms.
- Prazosin is recommended for treatment of nightmares.
- SSRIs and other antidepressants may be useful for reexperiencing symptoms, avoidance, and hyperarousal.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Patients may find activities that increase relaxation (e.g., yoga, meditative approaches including relaxation response breathing techniques, mindfulness, and progressive muscle relaxation) useful.
- Eye movement desensitization and reprocessing (EMDR) has shown promise in alleviating symptoms in patients diagnosed with ASD; however, future research is needed to further understand the relationship between the effects of EMDR treatment and the natural recovery from traumatic stress.

DISPOSITION

Treatment should be delivered in the least restrictive environment that can ensure patient safety. Most patients with ASD can be managed in an outpatient setting. Partial or inpatient hospitalization may be necessary for crisis management and may be considered for patients who have comorbid psychiatric/medical diagnoses; who are experiencing suicidal or homicidal ideation, plans, or intention; or who are severely ill.

REFERRAL

Patients are to be treated by a mental health clinician.

PEARLS & CONSIDERATIONS

COMMENTS

- Although many individuals with ASD go on to develop PTSD, many with ASD do not. Available data at this time suggest that ASD criteria are not adequate for identifying individuals at risk for developing PTSD.
- There is evidence to suggest that the identification of subtypes of ASD, as well as a focus on high levels of arousal symptoms, could lead to better predictability of subsequent diagnoses of PTSD.

PREVENTION

Critical incident stress debriefing (CISD) after a trauma is typically administered in one 2- to 3-hour group session within 72 hours of the trauma, with the goals of allowing survivors to "vent." There is some evidence that CISD does not prevent PTSD and may contribute to poor recovery. Psychological first aid (PFA) is designed to improve outcomes after trauma by fostering safety, calmness, social connectedness, and optimism. Although PFA has received some empirical support, questions remain regarding the optimal format of administration.

PATIENT & FAMILY EDUCATION

National Center for PTSD, Public Section, Information on Trauma and PTSD for Veterans, the General Public and Families: Acute Stress Disorder (www.ptsd.va.gov/professional/treatment/early/acute-stress-disorder.asp)

RELATED CONTENT

Posttraumatic Stress Disorder (Related Key Topic)

AUTHORS: **Lindsay M. Orchowski, PhD,** and **Nykia Leach, BA**

SUGGESTED READINGS

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Gradus JL: Prevalence and prognosis of stress disorders: a review of the epidemiologic literature, *Clin Epidemiol* 9:251-260, 2017.

Tol WA et al: Management of acute stress, PTSD, and bereavement: WHO recommendations, *J Am Med Assoc* 310:477-478, 2013.

BASIC INFORMATION

DEFINITION

Acute tubular necrosis (ATN) is a form of acute kidney injury (AKI) characterized by acute tubular cell injury and dysfunction. It is the most common form of AKI in the hospital. ATN may be secondary to ischemic injury, nephrotoxic injury, septic injury, or multifactorial.

SYNONYMS

ATN
Acute tubular injury
Ischemic or nephrotoxic acute renal failure (ARF)
Tubular necrosis, acute

ICD-10CM CODES

N17.0	Acute kidney failure with tubular necrosis
N17.2	Acute kidney failure with medullary necrosis
N19	Unspecified kidney failure

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common cause of AKI among hospitalized patients.
- In the intensive care setting, sepsis or hypotension accounts for 50% of all ATN.
- More than 50% of cases will require renal replacement therapy.
- In-hospital mortality is about 40% to 60% among patients with AKI who require dialysis, and mortality is lower when AKI is less severe.
- Risk factors: Advanced age, diabetes mellitus, chronic kidney disease, hypertension, NSAID use, and/or other nephrotoxins, preexisting hypovolemia, or poor renal perfusion.
- Early recognition of ATN is important to prevent further tubular injury by repeated exposure to nephrotoxins.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination is nonspecific.
- Suspect ischemic ATN in the setting of hemorrhage, hypotension, recent surgery, and/or sepsis.
- Suspect nephrotoxic ATN in the setting of iodinated radiocontrast imaging, nephrotoxic medications, rhabdomyolysis, hemolysis, or multiple myeloma.
- Classic progression of ischemic ATN includes three phases, but can be highly variable:
  1. Initiation phase (hours to days): Renal hypoperfusion with evolving ischemia. Acute decrease in glomerular filtration rate (GFR), abrupt elevation of BUN and serum creatinine, and/or decrease in urine output
  2. Maintenance phase (1 to 2 weeks): Renal cell injury established and GFR stabilizes. At the nadir of GFR, urine output is at its lowest rate (usually 40 to 400 ml/day). ATN is complicated by hyperkalemia, metabolic acidosis, uremia, and sodium and/or fluid overload. Patients are at an increased risk of infection, and approximately 25% of deaths from ATN occur during the maintenance phase
  3. Recovery phase (>2 weeks): Tubular cell repair and regeneration, with gradual, partial or complete return of kidney function to baseline levels, frequently in association with marked osmotic diuresis and polyuria

PATHOLOGIC FINDINGS

Vacuolization and loss of brush border in proximal tubular cells, basement membrane disruption, sloughing of tubular cells, and occlusion of the tubular lumens by casts. Interstitial edema and mild leukocyte accumulation are variably present.

ETIOLOGY

- Diagnosis of exclusion. Prerenal, postrenal, and other intrinsic parenchymal causes of AKI must be ruled out first
- Injury is instigated 24 to 48 hours prior to development of AKI. Careful review of hemodynamic parameters and medications 2 to 3 days prior to decline in renal function will reveal an etiology in most cases
- Ischemic processes that contribute to ATN include hypotension, shock, prolonged prerenal azotemia, and surgery
- Renal hypoperfusion may occur without systemic hypotension (normotensive AKI)
- Medications: NSAIDs, COX-2 inhibitors, antimicrobial agents (acyclovir, foscarnet, tenofovir, cidofovir, adefovir, aminoglycosides, polymyxins, vancomycin, amphotericin B, pentamidine), calcineurin inhibitors, cisplatin, ifosfamide, angiotensin–converting-enzyme inhibitors, angiotensin II receptor blockers, and intravenous immunoglobulin
- Iodinated radiocontrast medium (contrast nephropathy)
- Hemoglobin and myoglobin (rhabdomyolysis, intravascular hemolysis)
- Heavy metals
- Synthetic cannabinoids
- Cast nephropathy secondary to multiple myeloma

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Prerenal disease (e.g., hypovolemia, cirrhosis, nephrosis, heart failure), postrenal disease (e.g., obstructive nephropathy), intrinsic renal vascular diseases (e.g., vasculitis, thrombotic thrombocytopenic purpura [TTP], hemolytic uremic syndrome [HUS], scleroderma, malignant hypertension, and renal infarction from aortic dissection), acute glomerulonephritis, acute interstitial nephritis, and atheroembolic renal disease.

LABORATORY TESTS & FINDINGS

- Urinalysis with specific gravity <1.015 and low-grade albuminuria with more severe ATN.
- Urine osmolality <450 mOsm/kg (usually <350 mOsm/kg). Urine sediment examination reveals muddy brown casts (Fig. E1) and renal tubular epithelial cells.
- Fractional excretion of sodium [FE_{Na} (%) = 100% × (U_{Na} × P_{Cr})/(P_{Na} × U_{Cr})] typically exceeds 1%.
- Multiple biomarkers for early diagnosis of ATN are currently under investigation. The FDA approved the use of urinary insulin-like growth factor-binding protein 7 and tissue inhibitor of metalloproteinases-2 for early identification of patients at risk for AKI. More clinical studies are needed to identify its use in routine clinical practice.

IMAGING STUDIES

No specific studies are indicated, but appropriate studies may be ordered to diagnose the etiology of ATN or rule out other causes of AKI (e.g., kidney ultrasound to rule out obstruction).

TREATMENT

ACUTE GENERAL Rx

The general management of ATN is the same as that for acute kidney injury. Hemodynamic

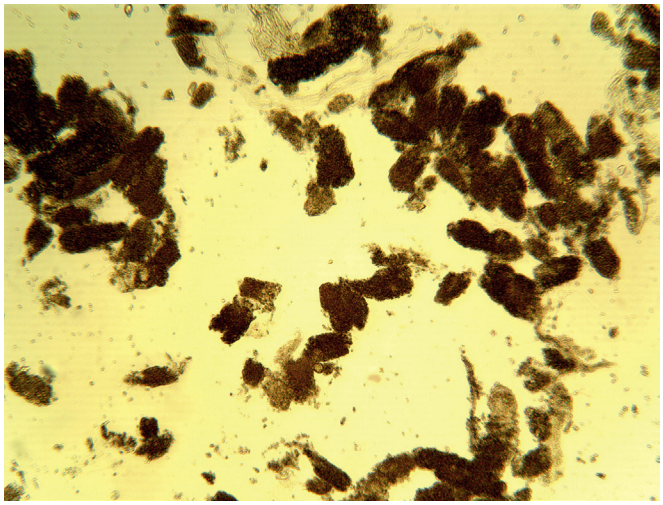

FIG. E1 Urine sediment demonstrating muddy brown, granular casts. The presence of this finding is consistent with a diagnosis of acute tubular necrosis in a patient with acute kidney injury.

abnormalities should be corrected and potentially nephrotoxic agents discontinued. Renal replacement therapy may be required until renal function is restored. There is no significant evidence that diuretic administration reduces the requirement for dialysis or improves renal recovery. However, diuretic use may facilitate fluid balance management.

DISPOSITION

Kidney function typically recovers within 2 to 3 weeks after onset. Outcomes are variable and depend on premorbid kidney function, mechanism of injury, and superimposed renal insults. Patients who are younger or nonoliguric have a better prognosis than patients who are older or oliguric. Patients may remain dialysis-dependent for up to 3 months before sufficient tubular regeneration occurs. Of patients surviving an ATN episode (~50%), approximately 5% to 10% never recover kidney function and remain dialysis-dependent.

REFERRAL

Nephrology consultation

PEARLS & CONSIDERATIONS

COMMENTS

Some patients with ATN may have FE_{Na} <1%: patients taking ACEIs, ARBs, or NSAIDs; cirrhosis; heart failure; radiocontrast injury; heme pigment-induced injury (e.g., myoglobinuria or hemoglobinuria); and early sepsis.

PREVENTION

- Aggressive intravascular volume resuscitation in hypovolemic surgical/trauma patients
- Discontinuation of potentially nephrotoxic agents
- Lowest volume of nonionic radiocontrast agents with preprocedural and postprocedural isotonic intravenous fluid administration (e.g., sodium chloride or sodium bicarbonate)

RELATED CONTENT

Acute Kidney Injury (Related Key Topic)

AUTHOR: **Junior Uduman, MD**

SUGGESTED READINGS

Jefferson JA et al: Pathophysiology and etiology of acute kidney injury. In Johnson RJ et al: *Comprehensive clinical nephrology*, ed 5, Philadelphia, 2017, Elsevier Saunders, pp 802-817.

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Acute Urinary Retention (AUR)

BASIC INFORMATION

DEFINITION

The acute inability to urinate when the bladder is full. This is often but not always painful, and the distended bladder may be palpable and percussible. Acute urinary retention is distinct from chronic urinary retention, a condition in which patients can still void but chronically retain a significant volume of urine in the bladder after voiding. Chronic urinary retention is not painful.

SYNONYMS

Acute urinary retention (AUR)
Urinary retention
Retaining urine

ICD-10CM CODES

R33 Retention of urine
R33.8 Other retention of urine
R33.9 Retention of urine, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- One of the most common urologic emergencies.
- Typically occurs in aging men, especially those older than 60 yrs. However, it may occur in any age group, and in either sex.
- Over a 5-yr period, AUR will occur in 10% of men older than 70 yrs and in one-third of men older than 80 yrs. There is a near-linear increase in age-specific incidence for men ages 40 to 80 yrs.

PREVALENCE: Estimates are 40/100,000 in males and 3/100,000 in females. Prevalence has increased as average lifespan has increased.
GENETICS: None known.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute inability to pass urine or only small amounts of urine.
- Pain and/or pressure in the lower abdomen and suprapubic region is typical. Low back pain may also occur. Pain may be absent, especially in older patients, patients with underlying neurologic disorders, and during chronic urinary retention.
- Palpable and/or percussible bladder may be detected.
- Suprapubic or bladder tenderness with deep palpation may be elicited.
- Increased urge to urinate with bladder palpation.
- Rarely, flank pain and costovertebral angle tenderness are present when high bladder pressures are transmitted to the ureters and kidney.
- Increased severity of lower urinary tract symptoms (LUTS) is associated with increased risk of AUR. Patients may complain of worsening LUTS prior to episode, including increased urinary urgency, incontinence, nocturia, stranguria, hesitancy, and intermittency. These symptoms usually develop between 1 day and a few weeks prior to AUR.
- Patients with cognitive deficits or inability to communicate may present with restlessness, discomfort, confusion, or delirium.
- Acute kidney injury, electrolyte abnormalities, nausea, lower extremity edema, and kidney failure may be present with delayed presentation.

ETIOLOGY

- Acute urinary retention may be spontaneous or precipitated by a triggering event. Spontaneous AUR may arise from the natural progression of bladder outlet obstruction, more commonly from benign prostatic hyperplasia (BPH), and less commonly from pelvic masses and urethral stricture disease. Conversely, precipitated AUR episodes have an identifiable triggering event, such as acute trauma, surgical procedures (e.g., spinal, orthopedic, and urologic), medications (e.g., over-the-counter [OTC] antihistamines and sympathomimetic agents commonly found in cough medications, anticholinergic drugs), excessive fluid intake (e.g., alcohol), urinary tract infection, central nervous system insults (e.g., strokes, hemorrhage, spinal cord injuries), and severe constipation. There is overlap between spontaneous and precipitated AUR, particularly when triggering events are superimposed on underlying obstructive risk factors.
- Urinary retention generally result from one of three categories: (1) Increased bladder outflow obstruction, as seen in BPH, urethral stricture disease, extrinsic compression from malignancy, constipation, and in gross hematuria where large clots can obstruct the urethra or bladder neck; (2) disruption of detrusor muscle innervation in association with diabetic neuropathy, spinal cord injury, progressive neurologic pathologies, and bladder contractile dysfunction and decompensation, secondary to prolonged outlet obstruction; and (3) bladder overdistension can lead to impaired contractility, and may result from general anesthesia, epidural anesthesia, or anticholinergic use.
- Acute retention is often multifactorial in older patients, with an underlying obstructive risk factor and acute precipitant.
- In women, obstructive factors can include benign tumors (especially, fibroid tumors); malignant tumors of pelvic, urethral, or vaginal origin; urethral strictures and urethral meatal stenosis; postpartum vulvar edema; and labial fusion. Pelvic organ prolapse, including cystocele, rectocele, and uterine prolapse, can also lead to urinary retention.
- Infection including prostatitis, urethritis, cystitis, genital herpes, and herpes zoster may also produce AUR.
- AUR is common in the postoperative period when patients are less mobile, are constipated, or have received opioid medications.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- AUR is typically self-evident to the cognitively intact patient and the treating physician.
- Chronic urinary retention.
- Pelvic masses, fluid collections, uterine fibroids, pregnancies, or ascites may be confused for a full bladder, particularly when using bedside ultrasonic bladder capacity-measuring instruments.

WORKUP

- History should focus on urologic symptoms: dysuria, hematuria, baseline voiding symptoms (caliber of stream, nocturia, sensation of incomplete emptying, double-voiding, incontinence, hesitancy), past episodes of retention, surgical history (urologic and other surgical procedures, particularly recent ones), and urologic cancer.
- History should include a complete list of prescribed and over-the-counter medications, and recent medication changes.
- Review of symptoms should include presence of fever, back pain, neurologic symptoms, and rash.
- Rectal examination for masses, fecal impaction, perineal and perianal sensation, prostate size, and sphincter tone.
- Genitourinary examination in men, with special attention for meatal stenosis and phimosis or paraphimosis.
- Pelvic examination in women with vigilance for any pelvic organ prolapse(s).
- Neurologic examination, with particular evaluation for "saddle" anesthesia (i.e., cauda equina syndrome) and pelvic sensory or motor deficits, to rule out an underlying neurologic cause.

LABORATORY TESTS

- Electrolytes, BUN, and serum creatinine.
- Urinalysis and culture, obtained via bladder or suprapubic catheterization.
- Prostate-specific antigen (PSA) testing is not helpful in AUR and may be falsely elevated after catheter placement. This test should not be routinely checked in the acute setting.

IMAGING STUDIES

- Bladder ultrasound or a bedside post-void residual urine scan ("bladder scan") can be diagnostic. However, ascites, pelvic fluid collections, body habitus, and presence of surgical implants (e.g., reservoirs for inflatable penile prostheses or artificial urinary sphincters) may confound accurate volume measurement with these devices.
- Abdominal ultrasound or computed tomography (CT) may be helpful if there is suspicion of a pelvic mass.
- CT (Fig. 1) can be helpful when high volumes are measured by a bedside bladder scan, but low volumes are returned upon bladder catheterization.
- MRI should be obtained when a spinal cord problem is suspected.

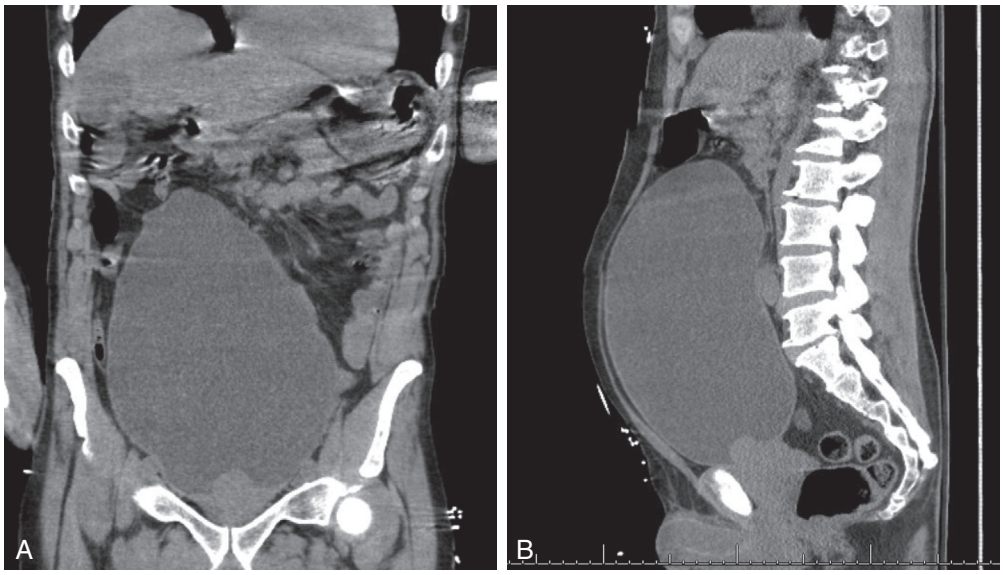

FIG. 1 Large volume urinary retention. Computed tomography images of coronal view **(A)** and sagittal view **(B)** of greatly distended bladder. The bladder extends into the mid-abdomen and above the pubic symphysis. More than 2 liters of urine was drained on bladder catheterization.

- Renal ultrasound or abdominopelvic CT may be obtained when there is kidney functional impairment and/or hydronephrosis is suspected.
- Evaluation of bladder function via urodynamic testing may be considered after initial management, particularly in females with no evidence of anatomic obstruction, or patients with longstanding obstruction and/or other neurologic conditions that affect bladder contractility.
- X-rays are of limited utility in evaluating AUR, but may show underlying constipation.

Rx TREATMENT

ACUTE GENERAL Rx

- Prompt bladder decompression and drainage is the initial management of AUR, generally by indwelling urethral catheterization. Coude-tip (angled-tip) catheters can facilitate catheter placement in men with large prostates. Clean intermittent catheterization is an option for patients with sufficient dexterity, vision, and motivation.
- Urological consultation is advised after recent genitourinary surgery, history of urethral stricture disease, or history of difficult catheterizations.
- When urethral catheterization is not possible or contraindicated, suprapubic catheter placement is required.
- Post-decompression hematuria may develop shortly after bladder drainage due to small vessel injury of the overstretched bladder wall.
- Monitor for post-obstructive diuresis, which results from a mixed osmotic and saline diuresis due to urea and salt retention during the period of obstruction.
- Avoid and/or discontinue medications that precipitate AUR (e.g., narcotics, anticholinergics, antihistamines).

CHRONIC Rx

- A voiding trial is reasonable 5 to 7 days after relief of obstruction in most patients.
- α-blockers are effective for treatment of BPH symptoms in males. These agents increase the success rate of early catheter removal and should be initiated, unless contraindicated. There is limited evidence to suggest benefit in females.
- If feasible, discontinue medications that increase the risk of AUR.
- Correct constipation and increase patient mobility.
- Inability to void after 5 to 7 days of catheterization mandates urologic consultation, with more intensive evaluation of AUR, including possible cystoscopic evaluation and/or urodynamic studies.
- Patients who unable to void after a voiding trial can either initiate clean intermittent catheterization, often 2 to 3 times a day, or have the urinary bladder catheter replaced.

DISPOSITION

- Patients can be discharged home when close follow-up is feasible, and progressive kidney injury and post-obstructive diuresis are absent
- Hospital admission if sepsis; complicated urinary tract infection; acute kidney injury; severe post-obstructive diuresis; hyperkalemia; acidemia or azotemia; or if AUR is from malignancy, hematuria, or spinal cord compression

REFERRAL

- Urologist if initial bladder catheterization is unsuccessful, or in surgical scenarios of radical prostatectomy, transurethral resection of prostate, urethral stricture surgery, and other bladder/prostate surgeries
- Urologic referral for recurrent AUR in men
- Gynecologic referral is mandatory if a pelvic mass is determined as etiology of AUR in females

PEARLS & CONSIDERATIONS

- AUR is often painful.
- Rapid bladder drainage is of paramount importance.
- Monitor for postobstructive diuresis and correct electrolyte abnormalities.
- Request urologic advice or referral for AUR after urologic surgery.

PREVENTION

Patients with BPH should be cautious regarding medications that may precipitate AUR, including antihistamines, sympathomimetics, sedatives, and anticholinergics. On a chronic basis, 5-α reductase inhibitors (e.g., finasteride, dutasteride) may reduce the risk of AUR in men with BPH and large prostates.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Benign Prostatic Hyperplasia (Related Key Topic)

AUTHORS: **Alex F. Borchert, MD,** and **David A. Leavitt, MD**

SUGGESTED READINGS

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Adhesive Capsulitis (Frozen Shoulder) (PTG)

BASIC INFORMATION

DEFINITION

Adhesive capsulitis of the shoulder, commonly known as "frozen shoulder," is a clinical diagnosis that describes a stiff glenohumeral (GH) joint characterized by pain and restricted passive and active range of motion (ROM). The condition is often idiopathic, although secondary causes include diabetes mellitus (most common nonidiopathic cause), trauma, shoulder surgery, other endocrine disorders such as thyroid disease, autoimmune diseases, neurologic disease such as stroke and Parkinson's disease, and antiretroviral therapy used to treat HIV.

SYNONYM

Frozen shoulder

ICD-10CM CODES

M75.00	Adhesive capsulitis of unspecified shoulder
M75.01	Adhesive capsulitis of right shoulder
M75.02	Adhesive capsulitis of left shoulder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Peaks in the mid-50s.
- Left shoulder is affected more commonly than right.

PREVALENCE: 2% to 5% in the general population and a higher incidence of up to 10% to 20% in patients with diabetes.

PREDOMINANT SEX: Females are more commonly affected than males.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The natural history of frozen shoulder occurs in three phases:

- Painful "freezing" phase: Gradual onset of severe shoulder pain that is usually worse at night and difficulty lying on the affected side. This phase may last from weeks up to 10 months. There is minimal loss of motion.
- "Frozen" or intermediate phase: Characterized by shoulder stiffness and limitation in ROM that may last for 1 yr. Pain often is present at terminal ROM during this phase. In addition to tenderness on palpation of the GH joint, there is variable loss in the degrees of active and passive shoulder abduction and external rotation.
- "Thawing" or recovery phase: Gradual improvement in pain and increase in ROM lasting for 1 to 3 yr.
- Easily confused for rotator cuff tear, especially during painful phase—distinguishing feature is diminished passive ROM, which is not found with rotator cuff tear.

ETIOLOGY

The pathology of frozen shoulder is not completely understood. The most agreed-upon theory involves a chronic inflammatory response with fibroblastic proliferation that results in thickening and contraction of the GH joint capsule, coracohumeral ligament, and rotator interval, and, ultimately, significant loss of ROM of the joint.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rotator cuff tear: May present with pain and limited ROM, but strength is more likely diminished with rotator cuff disease and passive motion is preserved.
- Calcific tendonitis: May present with painful active and passive ROM; however, testing is often limited to a single rotator cuff tendon. Calcified intratendinous bodies are visible on x-ray. An acute ruptured calcific tendonitis presents with severe, acute onset atraumatic pain. Adhesive capsulitis has a gradual onset.
- Glenohumeral osteoarthritis: May be diagnosed by degenerative changes on x-ray and marked glenohumeral crepitus on exam
- Septic arthritis: Often acute and associated with effusion.
- Trauma: Shoulder sprain, dislocation, glenoid labrum tear, rotator cuff tear.
- Cervical/neurological pathology: Evaluate all patients with shoulder complaints for cervical radiculopathy/myelopathy.

WORKUP

- Diagnosis of frozen shoulder typically is based on history and physical exam, although additional testing may help to rule out alternative diagnoses.
- Laboratory studies are not needed but can contribute to the diagnosis.
- An intra-articular injection of local anesthetic may help aid in diagnosis is there is continued loss of passive motion without pain.
- Imaging of the shoulder with plain radiography, ultrasound, MRI, or MR arthrography should be considered to rule out other pathologic conditions if there is clinical concern.
- Characteristic MRI findings include thickening of the coracohumeral ligament and the inferior joint capsule >5 mm.

TREATMENT

NONPHARMACOLOGIC THERAPY

Patient education is important for improving compliance and outcome expectations. The disease is self-limited, but many patients will experience frustration because it requires 18 to 24 months to fully resolve without treatment.

ACUTE GENERAL Rx

- Initial conservative therapy with heat and analgesics (generally NSAIDs).
- Physical therapy with passive mobilization and capsular stretching to increase ROM in the affected shoulder is an important component of therapy. Physical therapy should be supervised and last for 3 to 6 months minimum. It should be gentle and gradual and be performed multiple times/day. Strengthening of the shoulder should be avoided.
- Intraarticular corticosteroid and lidocaine injection into the glenohumeral joint—particularly effective in alleviating symptoms in short to middle-term compared to placebo. Most affective in the earlier stages.
- When conservative treatment fails (generally >4 to 6 months of stretching), the following surgical methods may be considered:
  1. Shoulder manipulation under anesthesia (rarely needed)
  2. Arthroscopic and, rarely, open capsular release

DISPOSITION

- The condition is mostly self-limited. Most patients regain 90% of shoulder motion over time and have improved pain, but symptoms can last from several months to more than 3 yr.
- Recurrence in the same shoulder is rare, although it can affect the opposite limb in up to 6% to 17% of patients. There is a higher rate of occurrence in the opposite limb in type 1 diabetics.

REFERRAL

Rheumatology or orthopedic consultation in patients who fail to respond to conservative treatment

PEARLS & CONSIDERATIONS

COMMENTS

Surgical treatment is very rarely needed for this condition. Accurate diagnosis involves a thorough assessment of active AND passive range of motion of the glenohumeral joint. Appropriate treatment is critical with corticosteroids improving symptoms more rapidly, especially during the early phases and appropriate therapeutic exercises focused on gentle, passive stretching multiple times/day.

RELATED CONTENT

Adhesive Capsulitis (Frozen Shoulder) (Patient Information)
Rotator Cuff Disease (Related Key Topic)

AUTHORS: **Shashank Dwivedi, MD,** and **E. Scott Paxton, MD**

SUGGESTED READINGS

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Adnexal Masses ALG

BASIC INFORMATION

DEFINITION

The adnexa refer to the region adjacent to the uterus that includes the ovary, fallopian tube, and associated structures. Masses that arise in these regions are collectively referred to as *adnexal masses.*

SYNONYM

Pelvic mass

ICD-10CM CODES

R19.09	Other intra-abdominal and pelvic swelling, mass, and lump
C57.4	Malignant neoplasm of uterine adnexa, unspecified
N83.209	Unspecified ovarian cyst, unspecified side
N83.2	Other and unspecified ovarian cysts

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Because the etiology of adnexal masses is so broad and ranges from benign to malignant and can be gynecologic or nongynecologic in origin, a single prevalence is difficult to establish and not particularly useful in this case.

PREDOMINANT SEX AND AGE: Adnexal masses can be found in females of all ages ranging from childhood to the reproductive years to postmenopause.

RISK FACTORS: It is important to consider risk factors for malignancy. While age is the most important independent risk factor for ovarian cancer, it is also important to consider family history. The most important personal risk factor for ovarian cancer is a significant family history of breast or ovarian cancer.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The majority of adnexal masses are found incidentally when pelvic imaging is performed or on physical examination.
- Though less common, they are sometimes detected when a woman presents with acute or intermittent pelvic or abdominal pain.
- Urgent conditions such as adnexal torsion or ectopic pregnancy typically present with fairly specific symptoms such as severe pain or first trimester bleeding and should be evaluated immediately.

ETIOLOGY

The etiology of an adnexal mass depends on the organ from which the mass arises. Masses can be benign or malignant. They can be ovarian, tubal, or uterine in origin. Additionally, nongynecologic etiologies include masses arising from other organs in the pelvis such as the bladder, kidney, bowel, or peritoneum. Masses could also be due to cancer metastases.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis of adnexal masses is best divided into gynecologic and nongynecologic and then further into benign and malignant.
- Gynecologic:
  1. Benign:
     a. Physiologic cyst
     b. Corpus luteal cyst
     c. Theca lutein cyst
     d. Endometrioma
     e. Cystadenoma
     f. Benign ovarian germ cell tumor (mature teratoma)
     g. Benign sex cord-stromal tumor
     h. Ectopic pregnancy
     i. Hydrosalpinx
     j. Paratubal cyst
     k. Uterine leiomyoma (pedunculated or cervical)
     l. Tubo-ovarian abscess
     m. Adnexal torsion
     n. Müllerian anomalies
  2. Malignant:
     a. Epithelial carcinoma
     b. Epithelial borderline carcinoma
     c. Germ cell tumor
     d. Sex-cord or stromal tumor
     e. Metastatic cancer
- Nongynecologic:
  1. Benign:
     a. Abscess: pelvic, appendiceal, diverticular
     b. Bladder diverticulum
     c. Ureteral diverticulum
     d. Pelvic kidney
     e. Nerve sheath tumors
  2. Malignant:
     a. Bowel neoplasm
     b. Appendiceal neoplasm
     c. Retroperitoneal sarcoma
     d. Metastasis (breast, colon, lymphoma, etc.)

WORKUP

- Evaluation of an adnexal mass (Fig. 1) begins with a thorough history that considers individual patient characteristics and the physical examination.
- A detailed gynecologic history should be obtained as well as a thorough family history and review of other risk factors.
- A full set of vital signs, the general physical appearance of the patient, and the patient's symptoms should be evaluated.
- A comprehensive physical examination including palpation of cervical, supraclavicular, axillary, and groin lymph nodes, abdominal examination, and thorough pelvic examination should be performed.
- Laboratory studies and imaging should be considered as outlined below.

LABORATORY TESTS

- A pregnancy test should be obtained on all women of reproductive age.
- If infection is suspected, CBC and cultures for gonorrhea and chlamydia should be obtained.
- Other laboratory tests that may be helpful include urinalysis and/or urine culture, fecal occult testing, and serum marker testing such as CA-125, B-hCG, AFP, and LDH if malignancy is suspected.

IMAGING STUDIES

- Transvaginal ultrasonography is the initial imaging modality of choice for evaluation of adnexal masses, including size, composition (cystic, solid, mixed), laterality, presence or absence of septations, and papillary excrescences. Abdominal ultrasonography should also be performed and can be useful if pelvic structures are distorted by prior surgery or if the mass extends above the pelvis.
- CT and MRI are not recommended for initial evaluation.
- MRI can be helpful to differentiate masses that are not ovarian in origin, especially leiomyomas.
- CT scans are most useful for evaluating metastasis if cancer is suspected as well as ascites, pelvic or periaortic lymph node enlargement, obstructive uropathy, or an alternate primary cancer site.

TREATMENT

Treatment of adnexal masses (Fig. 2) depends on the etiology of the mass, stability of the patient, and level of suspicion for malignancy.

ACUTE GENERAL Rx

- A ruptured ectopic pregnancy or ovarian torsion is a surgical emergency and warrants immediate surgical intervention. Surgical intervention may also be necessary for nongynecologic causes of adnexal masses such as appendicitis. Table 1 summarizes indications for surgery in a patient with adnexal mass.
- Ultrasound imaging with features concerning for malignancy (cyst >10 cm, papillary or solid components, irregularity, ascites, and high color doppler flow) warrants surgical intervention. Fig. 3 illustrates the management of a premenopausal woman with adnexal mass.
- Masses that appear benign but are greater than 5 cm in size are at increased risk of ovarian torsion, therefore surgical intervention needs to be considered.

CHRONIC Rx

Adnexal masses can be observed if imaging suggests benign disease or if there is a compelling reason to avoid surgical intervention. There is no established interval for ultrasound follow-up. Timing of a follow-up ultrasound should be determined on an individual basis considering patient risk factors, symptoms, premenopausal vs. postmenopausal status, and suspicion for malignancy. 6-mo follow-up is reasonable for masses larger than 5 cm, for patients

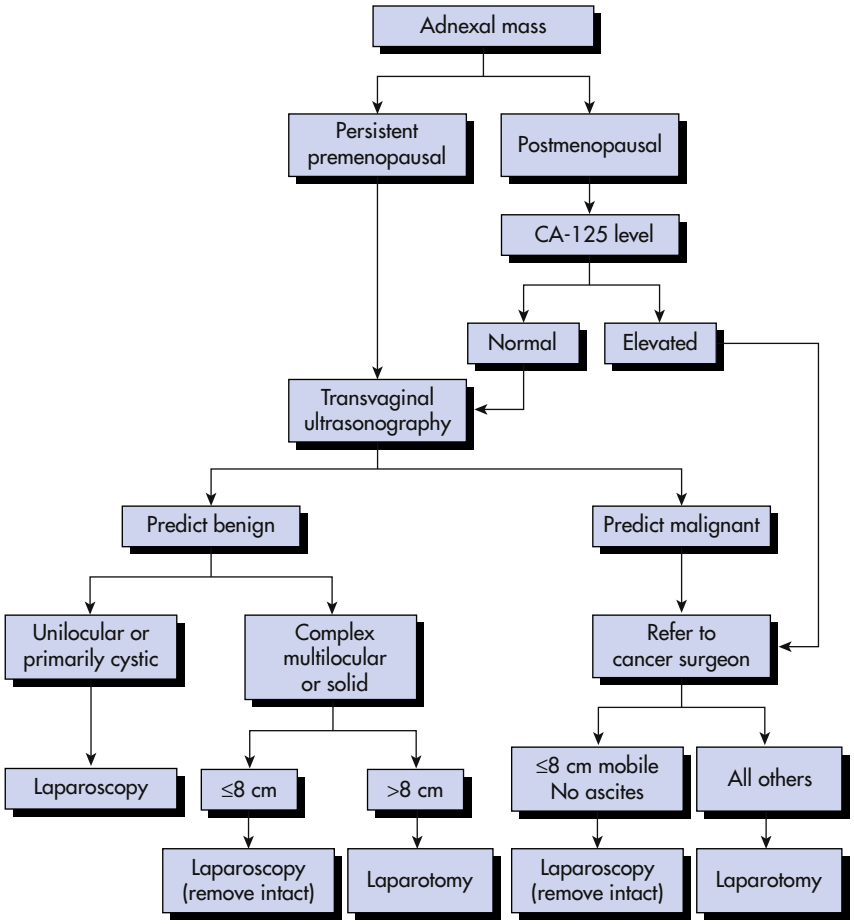

FIG. 1 Suggested management of an adnexal mass. *CA-125,* Cancer antigen 125. (From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2018, Elsevier.)

who are symptomatic, or when concern for malignancy is higher. For patients who are otherwise asymptomatic, who have a small mass, who are premenopausal, and in whom suspicion for malignancy is low, repeat ultrasound in 1 yr is reasonable.

REFERRAL

- A referral to a gynecologic oncologist is recommended when ultrasound findings are suggestive of malignancy. Referral guidelines for women with a newly diagnosed pelvic mass are summarized in Table 2.
- A referral to general surgery or surgical oncologist should be considered if the mass is nongynecologic in origin.

AUTHORS: **Helen Toma, MD, MSPH,** and **Anthony Sciscione, DO**

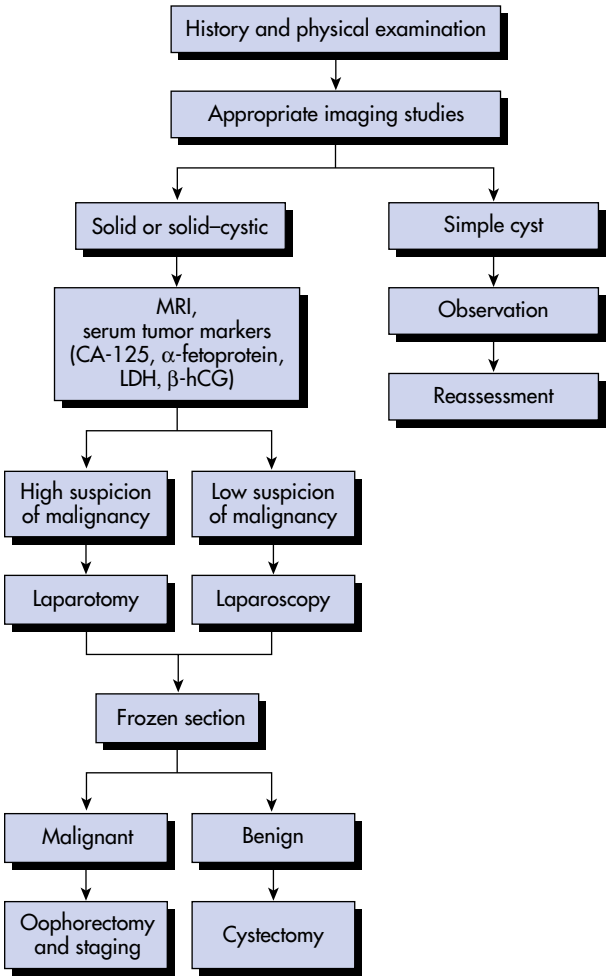

FIG. 2 Management of an ovarian mass during childhood. *β-hCG, β* human chorionic gonadotropin; *CA-125,* cancer antigen 125; *LDH,* lactate dehydrogenase; *MRI,* magnetic resonance imaging. (From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2018, Elsevier.)

TABLE 1 Adnexal Mass: Indications for Surgery

- Ovarian cystic structure >5 cm that has been observed 6-8 wk without regression
- Any solid ovarian lesion
- Any ovarian lesion with papillary vegetation on the cyst wall
- Any adnexal mass >10 cm in diameter
- Ascites
- Palpable adnexal mass in a premenarchal or postmenopausal patient
- Torsion or rupture suspected

From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2018, Elsevier.

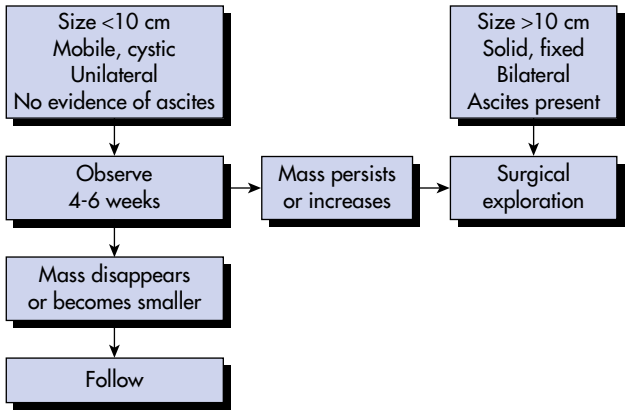

FIG. 3 Management of a premenopausal woman with an adnexal mass. (From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2018, Elsevier.)

TABLE 2 Society of Gynecologic Oncologists and American College of Obstetricians and Gynecologists Referral Guidelines for Women with a Newly Diagnosed Pelvic Mass

Premenopausal Patients (<50 Yr Old)
CA-125 >200 units/ml
Presence of ascites
Evidence of intraperitoneal or distant metastasis (based on examination or imaging studies)
Family history (first-degree relative) of breast or ovarian cancer
Postmenopausal Patients (>50 Yr)
Elevated CA-125 level
Ascites
Evidence of intraperitoneal or distant metastasis (based on examination or imaging studies)
Family history (first-degree relative) of breast or ovarian cancer

CA-125, Cancer antigen 125.

Adapted from ACOG Practice Bulletin. Management of adnexal mass. *Obstet Gynecol* 2007;110:207. In Disaia PJ et al: *Clinical gynecologic oncology*, ed 9, Philadelphia, 2018, Elsevier.

SUGGESTED READINGS

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Evaluation and management of adnexal masses. Practice Bulletin No. 174. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2016;128:e210-26.

Adrenal Incidentaloma ALG

BASIC INFORMATION

DEFINITION

Adrenal mass discovered inadvertently on thoracic or abdominal imaging, including CT, MRI, and ultrasound.

SYNONYM

Unsuspected adrenal mass

ICD-10CM CODE

D44.1 Neoplasm of uncertain behavior of adrenal gland

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Adrenal incidentalomas are found in about 5% of the population (4% to 7% on advanced imaging, up to 10% on autopsy).
PREDOMINANT SEX AND AGE: Prevalence increases with age.
GENETICS: Vary based on etiology of the incidentaloma.
RISK FACTORS: More common in Caucasian, obese, diabetic, and hypertensive patients.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Following the discovery of an incidentaloma on advanced imaging, history and physical examination should focus on identifying signs and symptoms associated with several functional tumors (Table 1).

ETIOLOGY

Up to 80% of adrenal incidentalomas are benign, nonfunctional adenomas.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Benign adenoma
- Functional adenoma (aldosteronoma, cortisol producing)
- Pheochromocytoma
- Adrenocortical carcinoma (ACC)
- Metastasis
- Lymphoma

WORKUP

- Primary focus is on establishing malignant potential and functionality of an incidentaloma (Box 1, Fig. 1).
- Functionality should be assessed in all adrenal incidentalomas >1 cm.

LABORATORY TESTS

- Low-dose dexamethasone suppression test, 24-hr urinary free cortisol, serum ACTH, and serum dehydroepiandrosterone sulfate (DHEAS)
- 24-hour urine metanephrines, fractionated catecholamines
- Basic metabolic profile
- Plasma aldosterone, renin activity levels in hypertensive patients

TABLE 1 Signs and Symptoms of Adrenal Tumor by Type

Tumor Type	Symptoms	Signs
Cortisol producing	Muscle weakness, easy bruising/bleeding, poor wound healing, decreased libido, psychiatric disturbances, insomnia, flushing, palpitations	Moon facies, buffalo hump, hirsutism, abdominal striae, central obesity with peripheral wasting, thinning of skin, hypertension, hyperglycemia
Aldosteronoma	Muscle cramping, muscle weakness, fatigue, headache, polydipsia, polyuria	Refractory hypertension, hypokalemia
Pheochromocytoma	Episodic headache, sweating, palpitations, pallor, anxiety, sense of impending doom, flushing/hot flashes	Hypertension, tachycardia, cardiac arrhythmias, acute myocardial infarction, congestive heart failure, tremor
Adrenocortical carcinoma (ACC)	Large: Mass effect Productive: Cushing syndrome, virilization	Large: None, may be able to palpate Productive: Related to the hormone produced
Secondary metastasis to the adrenal gland	Generally none related to the adrenal tumor	Findings consistent with primary tumor source, adrenal insufficiency if adrenal tissue compromised
Nonfunctional mass	Small: None Large: Vague abdominal complaints/mass effect/pain	Small: None Large: None, may be able to palpate

From Jason DS, Oltmann SC: Evaluation of an adrenal incidentaloma, *Surg Clin North Am, 99*(4), 721-729.

BOX 1 Differential Diagnosis for Adrenal Incidentaloma

Functional Tumors
Pheochromocytoma
Cortisol-producing adenoma/subclinical Cushing syndrome
Aldosteronoma
Primary adrenal hyperplasia

Nonfunctional Lesions
Nonfunctioning cortical adenoma
Myelolipoma
Adrenal hemorrhage
Adrenal cyst
Ganglioneuroma

Malignant
Adrenocortical carcinoma
Metastases to the adrenal gland

From Cameron JL, Cameron AM: *Surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

IMAGING STUDIES

- CT scan (Figs. 2 and E3) is the imaging modality of choice if not already performed.
- Patients with a history of malignancy or other history and/or physical findings concerning for metastatic disease may benefit from PET scan.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Hormonally functional incidentalomas and masses suspicious for ACC require surgical intervention.
- Nonfunctional incidentalomas can be monitored for growth but may require surgical excision depending on size of the lesion, rate of monitored growth, age of the patient, and presence of clinically significant mass effect.
- Fine-needle aspiration (FNA) should not routinely be performed on all incidentalomas; however, if the patient has a known primary lesion, the mass is nonfunctional, and there is concern for metastatic disease, FNA may be indicated.

GENERAL Rx

- Functional masses, masses suspicious for ACC, nonfunctional masses >4 cm should be referred to general or endocrine surgery
- Nonfunctional adrenal adenomas <4 cm:
  - Follow-up imaging at 6 to 12 mo
  - Surgical consultation for enlargement >1 cm

REFERRAL

- General/endocrine surgery
- Endocrinology

PEARLS & CONSIDERATIONS

COMMENTS

Most masses are nonfunctional and do not require surgery.

RELATED TOPICS

Aldosteronism (Hyperaldosteronism, Primary) (Related Key Topic)
Cushing Disease and Syndrome (Related Key Topic)
Hypertension (Related Key Topic)
Pheochromocytoma (Related Key Topic)

AUTHORS: **Brett L. Tooley, MD,** and **Ray Walther, MD**

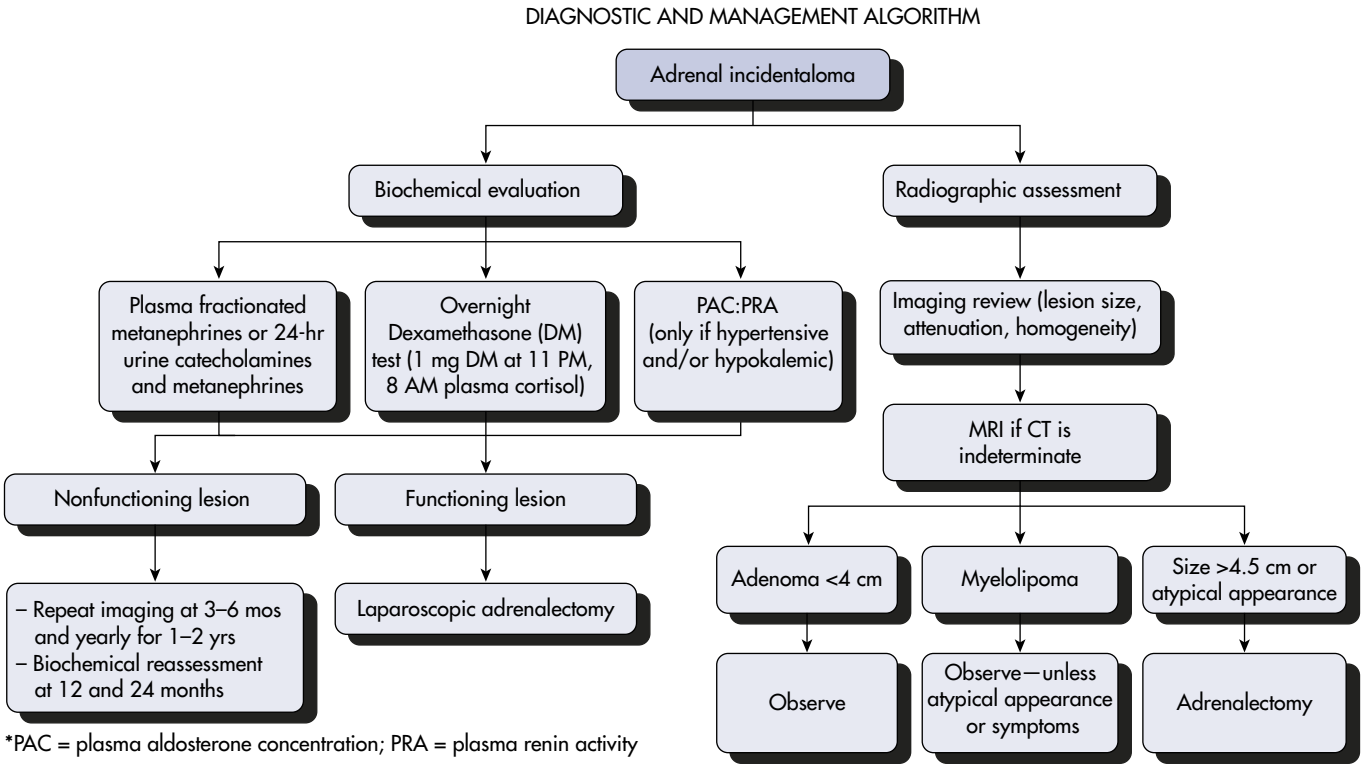

FIG. 1 Diagnostic and management algorithm for adrenal incidentaloma. *CT,* Computed tomography. (From Cameron JL, Cameron AM: *Surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

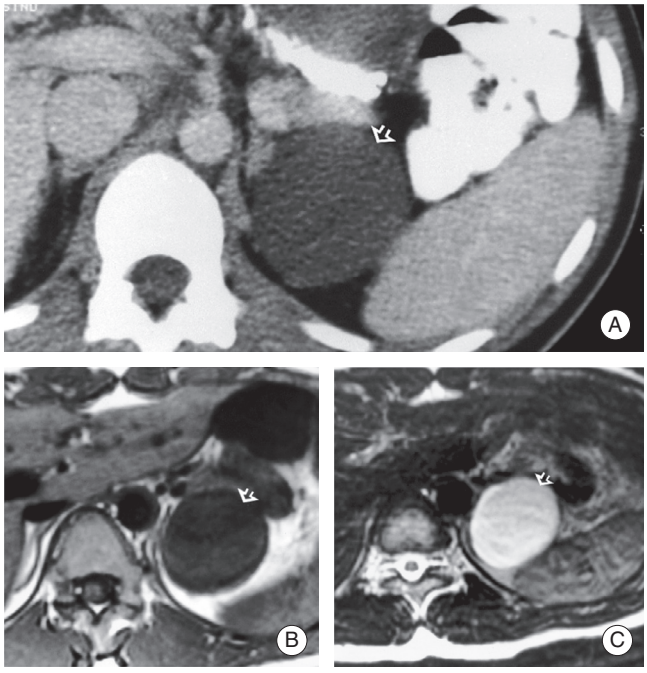

FIG. 2 Adrenal cyst. A, Contrast enhanced computed tomography showing the typical appearance of a cyst *(arrow)* within the left adrenal gland. **B,** T1-weighted image (WI) shows the low signal intensity of a simple cyst *(arrow).* **C,** T2WI shows the uniformly high signal intensity of fluid-filled lesion *(arrow).* (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

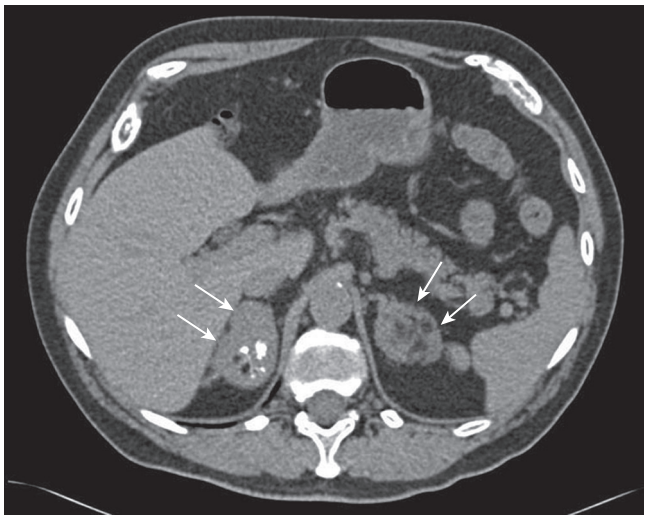

FIG. E3 Computed tomography scan of bilateral adrenal myelolipomas *(arrows).* Note the areas of macroscopic fat (hypodense areas) that are typical for this lesion. (From Cameron JL, Cameron AM: *Surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

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Adrenal Insufficiency PTG

BASIC INFORMATION

DEFINITION

Adrenal insufficiency is characterized by inadequate secretion of corticosteroids resulting from partial or complete destruction of the adrenal glands (primary adrenal failure). Inadequate secretion of cortisol from the adrenals due to critical illness and pituitary insufficiency is known as secondary cortisol deficiency.

SYNONYMS

Primary adrenocortical insufficiency
Addison disease

ICD-10CM CODES

E27.1	Primary adrenocortical insufficiency
E27.2	Addisonian crisis
E27.40	Unspecified adrenocortical insufficiency
E27.49	Other adrenocortical insufficiency
E27.3	Drug-induced adrenocortical insufficiency
E23.3	Hypopituitarism

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 10 to 15 per 100,000 persons
PREDOMINANT SEX: Female:male ratio of 2:1

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Adrenal insufficiency may present insidiously with nonspecific symptoms. A high index of suspicion is required for diagnosis. About half of patients may present acutely with adrenal crises. Table 1 summarizes the clinical features of primary adrenal insufficiency.
- Hyperpigmentation of skin (Figs. E1 and E2) and mucous membranes is a cardinal sign of adrenal insufficiency: more prominent in palmar creases, buccal mucosa, pressure points (elbows, knees, knuckles), perianal mucosa, and around areolas of nipples
- Hypotension, postural dizziness
- Generalized weakness, chronic fatigue, malaise, anorexia
- Amenorrhea and loss of axillary hair in females

ETIOLOGY

- Autoimmune destruction of the adrenal glands (80% of cases)
- Tuberculosis (TB) (7% to 20% of cases)
- Carcinomatous destruction of the adrenal glands, lymphoma
- Adrenal hemorrhage (anticoagulants, trauma, coagulopathies, pregnancy, sepsis)
- Adrenal infarction (antiphospholipid syndrome, arteritis, thrombosis)
- AIDS (adrenal insufficiency develops in 30% of patients with AIDS, often cytomegalovirus [CMV] adrenalitis)

TABLE 1 Clinical Features of Primary Adrenal Insufficiency

Feature	Frequency (%)
Symptoms	
Weakness, tiredness, fatigue	100
Anorexia	100
Gastrointestinal symptoms	92
Nausea	86
Vomiting	75
Constipation	33
Abdominal pain	31
Diarrhea	16
Salt craving	16
Postural dizziness	12
Muscle or joint pains	13
Signs	
Weight loss	100
Hyperpigmentation	94
Hypotension (<110 mm Hg systolic)	88-94
Vitiligo	10-20
Auricular calcification	5
Laboratory Findings	
Electrolyte disturbances	92
Hyponatremia	88
Hyperkalemia	64
Hypercalcemia	6
Azotemia	55
Anemia	40
Eosinophilia	17

From Melmed SZ et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

- Genetic causes: Autoimmune polyglandular syndromes (APS) types 1 and 2, X-linked adrenoleukodystrophy, congenital adrenal hyperplasia
- Other: Sarcoidosis, amyloidosis, hemochromatosis, Wegener granulomatosis, postoperative, fungal infections (candidiasis, histoplasmosis)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Sepsis, hypovolemic shock, acute abdomen, apathetic hyperthyroidism in the elderly, myopathies, gastrointestinal malignancy, major depression, anorexia nervosa, hemochromatosis, salt-losing nephritis, chronic infection

WORKUP

- An early morning (8 A.M.) serum cortisol <3 mcg/dl (82.8 mmol/L) is consistent with cortisol deficiency.
- If the cortisol level is 3 to 15 mcg/dl, the diagnosis can be confirmed with the rapid adrenocorticotropic hormone (ACTH) test:
  1. Give 250 mcg ACTH (Sinachten, tetracosatrin) by IV push and measure cortisol levels at 0, 30, and 60 min.
  2. An increase in serum cortisol level to peak concentration >500 nmol/L (18 mcg/dl) indicates a normal response. Cortisol level ≤18 mcg/dl at 30 or 60 min is suggestive of adrenal insufficiency.
  3. Measure plasma ACTH. A high ACTH level (>200 pg/ml [44 pmol/L]) confirms primary adrenal insufficiency.
- Critical illness-related corticosteroid insufficiency (e.g., in sepsis) is best established with the 1-mcg ACTH stimulation test in which cortisol levels are measured at baseline and 30 min after administration of ACTH. A level <25 mcg/dl (690 nmol/L) or an increment over baseline of <9 mcg (250 nmol/L) represents an inadequate adrenal response.
- Secondary adrenocortical insufficiency (caused by pituitary dysfunction) can be distinguished from primary adrenal insufficiency by the following:
  1. Normal or low plasma ACTH level after rapid ACTH
  2. Absence of hyperpigmentation
  3. No significant impairment of aldosterone secretion (because aldosterone secretion is under control of the renin-angiotensin system)
  4. Additional evidence of hypopituitarism (e.g., hypogonadism, hypothyroidism)

LABORATORY TESTS

- Hyponatremia, hyperkalemia
- Decreased glucose
- Increased BUN/creatinine ratio (prerenal azotemia)
- Mild normocytic, normochromic anemia, neutropenia, lymphocytosis, eosinophilia (significant dehydration may mask hyponatremia and anemia), hypercalcemia, metabolic acidosis

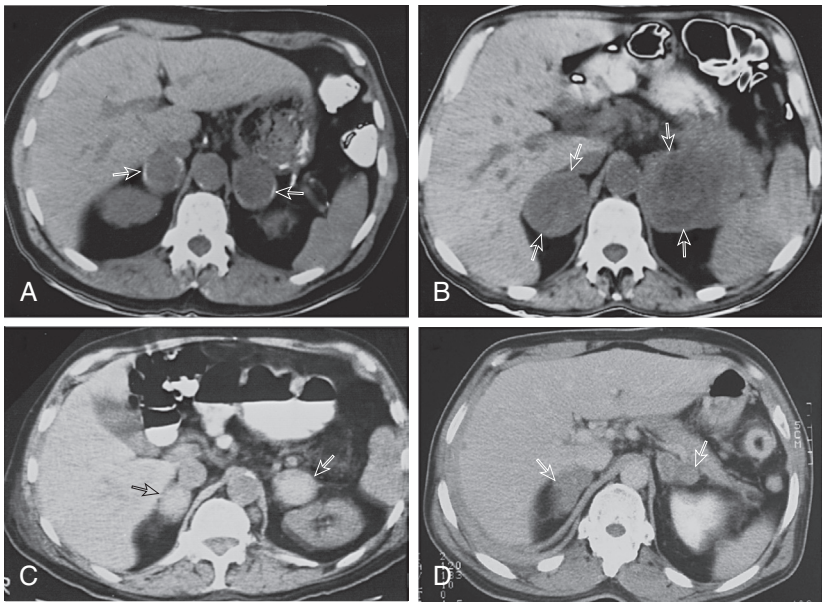

FIG. 3 Computed tomographic (CT) scans of patients with primary adrenal insufficiency. The affected adrenal glands are indicated by arrows. **A,** CT scan of a 59-year-old man with histoplasmosis. Notice the subcapsular calcium in both glands. **B,** CT scan of a 59-year-old man with metastatic melanoma. **C,** CT scan of an 80-year-old man with bilateral adrenal hemorrhage resulting from anticoagulation for pulmonary emboli. **D,** Bilateral adrenal tuberculomas in a 79-year-old man with tuberculosis affecting the urogenital tract. (**A** and **B** courtesy Dr. William D. Salmon, Jr.; **C,** courtesy Dr. Craig R. Sussman.) (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

- A morning cortisol level >500 mmol/L (18 mcg/dl) generally excludes the diagnosis whereas a level <165 mmol/L (6 mcg/dl) is suggestive of Addison disease and a level <3 mcg/dl requires further evaluation (see "Workup")
- Additional evaluation may include 21-hydroxylase antibodies present in 90% of autoimmune adrenalitis cases. If negative, obtain CT scan of adrenal glands
- PPD or QuantiFERON Gold test to rule out TB

IMAGING STUDIES

- Imaging is not necessary for diagnosis but may help identify potential causes.
- Abdominal CT scan (Fig. 3): Small adrenal glands generally indicate either idiopathic atrophy or longstanding TB, whereas enlarged glands are suggestive of early TB or potentially treatable diseases.
- Chest radiograph may reveal a small heart (Fig. E4).
- Abdominal radiograph: Adrenal calcifications may be noted if the adrenocortical insufficiency is secondary to TB or fungal infection.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Perform periodic monitoring of serum electrolytes, vital signs, and body weight; liberal sodium intake is suggested.
- Periodic measurement of bone density may be helpful in identifying patients at risk for the development of osteoporosis.
- Patients should carry a MedicAlert bracelet and an emergency pack containing hydrocortisone 100-mg ampule, syringe, and needle.
- Patients and partners should be educated on how to give IM injection in case of vomiting or coma.

ACUTE GENERAL Rx

- Adrenal crisis is an acute complication of adrenal insufficiency characterized by circulatory collapse, dehydration, nausea, vomiting, hypoglycemia, and hyperkalemia.
  1. Draw plasma cortisol level; do not delay therapy while waiting for confirming laboratory results.
  2. Administer hydrocortisone 100 mg IV immediately, followed by 100 to 200 mg of hydrocortisone every 24 hours administered as a continuous infusion or divided into 3 or 4 doses; if patient shows good clinical response, gradually taper dosage and change to oral maintenance dose (usually prednisone 7.5 mg/day).
  3. Provide adequate volume replacement with D_5NS solution until hypotension, dehydration, and hypoglycemia are completely corrected. Large volumes (2 to 3 L) under continuous cardiac monitoring may be necessary in the first 2 to 3 hr to correct the volume deficit and hypoglycemia and to avoid further hyponatremia.
- Identify and correct any precipitating factor (e.g., sepsis, hemorrhage).

CHRONIC Rx

- Give hydrocortisone 15 to 20 mg PO every morning and 5 to 10 mg in late afternoon or prednisone 5 mg in morning and 2.5 mg hs.
- Give oral fludrocortisone 0.05 mg/day to 0.20 mg/day. This mineralocorticoid is necessary if the patient has primary adrenocortical insufficiency. The dose is adjusted based on the serum sodium level and the presence of postural hypotension or marked orthostasis.
- Instruct patients to increase glucocorticoid replacement in times of stress and to receive parenteral glucocorticoids if diarrhea or vomiting occurs. Typical supplementation varies from 25 mg PO qd of hydrocortisone for minor medical and surgical stress to 50 to 100 mg IV hydrocortisone q8h for sepsis-induced hypotension or shock.
- The administration of dehydroepiandrosterone (DHEA) is controversial due to lack of robust data. It is not indicated in men but may be considered in women with primary adrenal failure. A dose of 50 mg PO qd may improve well-being and sexuality in women with adrenal insufficiency.
- Patients with concomitant hypothyroidism should be treated with glucocorticoids first before correcting hypothyroidism because correction of thyroid hormone deficiency will accelerate cortisol clearance and can precipitate adrenal crisis.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Addison Disease (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

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Michels A, Michels N: Addison disease: early detection and treatment principles, *Am Fam Physician* 89(7):563-568, 2014.
Rushworth RL et al: Adrenal crisis, *N Engl J Med* 381:852-861, 2019.
Werumeus B et al: Effects of hydrocortisone on the regulation of blood pressure: results from a randomized controlled trial, *J Clin Endocrinol Metab* 101:3681, 2016.

FIG. E1 Pigmentation in Addison disease. A, Hands of an 18-year-old woman with autoimmune polyendocrine syndrome and Addison disease. Pigmentation in a patient with Addison disease before **(B)** and after **(C)** treatment with hydrocortisone and fludrocortisone. Notice the additional presence of vitiligo. **D,** Similar changes in a 60-year-old man with tuberculous Addison disease before *(left)* and after *(right)* corticosteroid therapy. **E,** Buccal pigmentation in the same patient as in **D.** (**B** and **C** courtesy Professor CRW Edwards; From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

FIG. E2 Pigmentation of scars is a particular feature of Addison disease resulting from adrenal failure or surgery. (From White GM, Cox NH [eds]: *Diseases of the skin,* ed 2, St Louis, 2006, Mosby.)

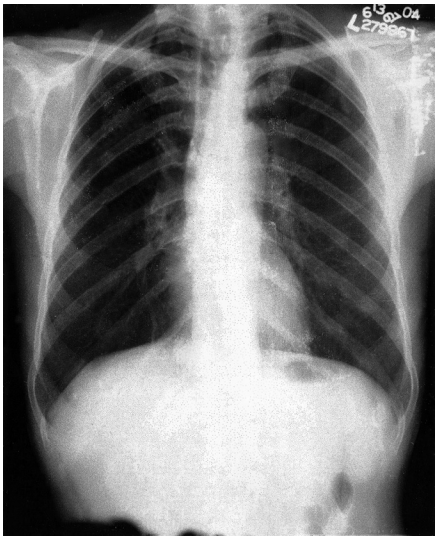

FIG. E4 Routine chest radiograph of a patient with Addison disease related to tuberculosis. In addition to the small cardiac silhouette, there are calcified lymph nodes in the hilum of the right lung. (Courtesy Dr. J. B. Naldich.)

BASIC INFORMATION

DEFINITION

Adult-onset Still disease (AOSD) is a rare systemic inflammatory disorder of uncertain etiology, first described by George Frederic Still in 1897 as an insidious polyarthritis marked by episodes of fever, lymphadenopathy, and splenomegaly. AOSD is primarily characterized by transient fever, evanescent skin rash, arthralgias/arthritis, hepatosplenomegaly, and elevated serum ferritin. A prodromal sore throat is seen in up to 70% of cases. Daily high-spiking fever is among the most striking manifestations and may be accompanied by transitory salmon-colored maculopapular rash. Myalgias and arthralgias are nearly universal, and inflammatory arthritis may ultimately result in joint destruction.

SYNONYMS

Still disease
Systemic juvenile idiopathic arthritis (systemic JIA)
Wissler syndrome/Wissler-Fanconi syndrome
AOSD

ICD-10CM CODE
M06.1 Adult-onset Still disease

EPIDEMIOLOGY & DEMOGRAPHICS

The rarity of AOSD precludes definite epidemiologic data. Prevalence ranges from 1 to 34 per 1,000,000. Incidence is 0.1 to 0.4 cases per 100,000. Bimodal age distribution with peak between ages 15 to 25 and 36 to 46. There is no clear gender predisposition.

GENETICS: Studies suggest a genetic component. Various HLA antigens have been linked to both susceptibility (class II types DRB1*15 and DRB1*12) and prognosis (class I types B35 with self-limited disease, DR2 and DR5 with chronic disease), but results remain unverified.

RISK FACTORS: Infectious triggers are suspected to underlie the onset of AOSD in genetically susceptible hosts. Many patients have preceding exposures, and disease onset or relapse often follows a viral-like prodrome of pharyngitis, malaise, fever, and rash. Investigation of specific viral and bacterial organisms, however, is still unrevealing.

ETIOLOGY

Exact pathogenesis is unclear. Abnormal macrophage activation plays a role, given elevated levels of IL-1, IL-6, IL-18, tumor necrosis factor alpha (TNF-α), interferon gamma, migration inhibiting factor, and heme oxygenase-1 in serum of patients with AOSD. Recent studies have shown a higher amount of neutrophil extracellular trap (NET) molecules in the serum of patients with active AOSD compared with controls, and levels of these molecules decreased after treatment. Research is ongoing to evaluate the clinical implications of these results.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The "cardinal symptoms" of AOSD are fever, arthralgias/arthritis, and skin rash. This triad is seen in 75% to 95% of patients. Quotidian pattern fever usually occurs in late afternoon or early evening, with body temperature >102 °F (38.9 °C) lasting 2 to 4 hours before returning to normal. Up to 20% of patients have a "double quotidian" fever with a second spike in the early morning. Classic evanescent maculopapular rash is salmon-pink and nonpruritic, mainly affecting the trunk and proximal extremities. Koebner phenomenon is noted in up to 40% of patients. Visible rash may accompany fever and resolve when the patient is afebrile, making evaluation difficult. Arthralgias are nearly ubiquitous. Inflammatory joint involvement typically manifests as symmetric polyarthritis of larger joints. Progressive destructive arthritis affects up to half of patients. Other nonspecific symptoms include prodromal pharyngitis, lymphadenopathy, myalgias, hepatosplenomegaly, and serositis.

DIAGNOSIS

There is no pathognomonic finding in AOSD. Diagnosis depends on the recognition of a constellation of clinical and laboratory factors. It is a diagnosis of exclusion and requires rule-out of an extensive list of alternative infectious, neoplastic, and inflammatory etiologies.

DIFFERENTIAL DIAGNOSIS

See Fig. E1.

LABORATORY TESTS

Lab abnormalities include neutrophilic leukocytosis (WBC >12, >80% PMNs), markedly elevated inflammatory markers (ESR >50, CRP often >10× ULN). Normocytic anemia (Hg <10), thrombocytosis, hypoalbuminemia, and mild transaminitis can also be seen. Aldolase may be elevated with liver injury, but CPK levels are typically normal. Hyperferritinemia is a highly suggestive finding and levels >5 times upper limit of normal can be seen. Antinuclear antibodies and rheumatoid factor are negative.

IMAGING STUDIES

- Radiographs (Figs. E2 and E3): Early changes include soft tissue swelling, joint effusion, periarticular osteopenia; with later destructive arthropathy may see narrowed carpometacarpal and intercarpal joint spaces of wrist, eventually leading to ankylosis

CATEGORY	DISEASE	EVALUATION RECS
INFECTIOUS		
Bacterial	Septicemia, endocarditis, tuberculosis, brucellosis, yersinia, Lyme disease	Cultures, TTE, IGRA, PCR
Viral	Hepatitis, parvo B19, HIV, CMV, EBV, rubella, mumps, coxsackie, adenovirus	Serologies, PCR
Parasitic	Toxoplasmosis, parasitic abscess	
MALIGNANT		
Hematologic	Lymphoma, leukemia, angioblastic T-cell lymphoma, myeloproliferative disease, Castleman disease	Lymph node biopsy, bone marrow biopsy, PET/CT
Solid tumors	Colon, lung, kidney, paraneoplastic syndromes	
SYSTEMIC		
Rheumatologic	Systemic lupus erythematosus, rheumatoid arthritis, reactive arthritis, necrotizing or other vasculitides, poly-/dermato-myositis	Antibody testing, imaging, muscle biopsy
Autoinflammatory	Schnitzler's syndrome, Sweet syndrome, hemophagocytic lymphohistiocytosis, Kikuchi-Fujimoto disease, periodic fever syndromes (i.e., familial Mediterranean fever FMF, TNF receptor associated period syndrome [TRAPS], Cryopyrin associated periodic syndromes [CAPS], etc.)	Skin biopsy, bone marrow biopsy, family history, gene sequence analysis
Other	Drug hypersensitivity (i.e., drug rash with eosinophilia and systemic symptoms [DRESS]), sarcoidosis	CBC, ACE, biopsy

FIG. E1 Differential diagnosis of adult-onset Still disease. *ACE,* Angiotensin-converting enzyme; *CBC,* complete blood count; *CMV,* cytomegalovirus; *CT,* computed tomography; *EBV,* Epstein-Barr virus; *FMF,* familial Mediterranean fever; *HIV,* human immunodeficiency virus; *IGRA,* interferon gamma release assay; *PCR,* polymerase chain reaction; *PET,* positron-emission tomography; *TNF,* tumor necrosis factor; *TTE,* transthoracic echocardiogram.

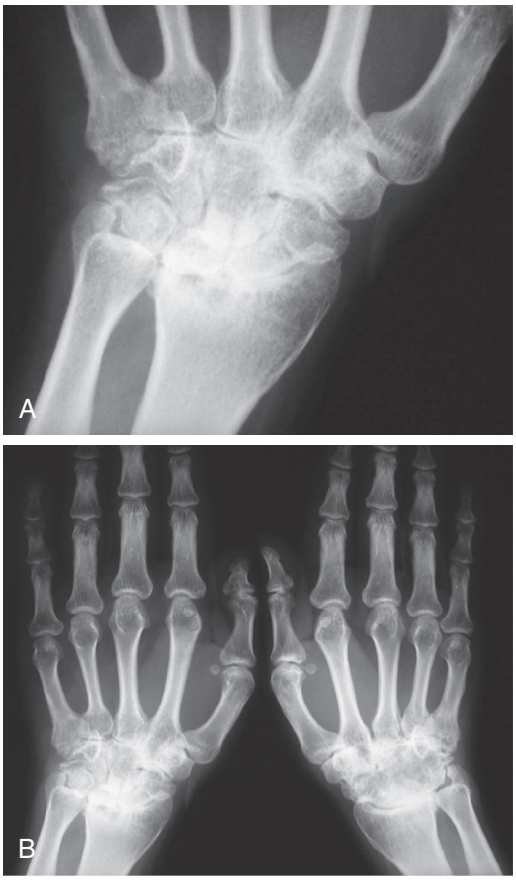

FIG. E2 (A and B) Radiographs of wrists in a patient with adult-onset Still disease showing a narrowing of the carpometacarpal and intercarpal spaces and focal erosive alterations that have led to bone ankylosis in the left wrist. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

- CT and MRI studies: May show lymphadenopathy, organomegaly, early bone changes
- FDG PET/CT scans: Increased FDG uptake in spleen, bone marrow, and hyperplastic lymph nodes with concurrent decreased uptake in blood pool and liver

DIAGNOSTIC CRITERIA

Multiple diagnostic criteria have been proposed for evaluation of patients with suspected AOSD. Fautrel criteria are the most specific but require measurement of glycosylated ferritin, which is not readily available. The Yamaguchi criteria are more sensitive and widely used (Fig. E4).

DISPOSITION

Overall survival is good with 5-yr survival rates of 90% to 95%, but long-term therapy may be required to control symptoms or prevent recurrence. Patients follow one of three distinct clinical courses:

1. Self-limited/monophasic: Symptoms last <1 yr, then entirely remit.
2. Intermittent/relapsing: Recurrent flares over years of gradually more mild disease, alternating with periods of complete remission.
3. Chronic/progressive: Persistent primarily articular disease, with eventual erosive destruction leading to disability and need for arthroplasty.

Polyarthritis and large joint involvement with high ferritin level at onset of disease are poor prognosticators associated with progression to chronic disease.

Rx TREATMENT

ACUTE GENERAL Rx

Mild disease may be treated with full-dose NSAIDs alone, though less than a quarter of patients effectively respond to this. In most cases, glucocorticoids and/or other immunosuppressives are required. A treatment strategy for AOSD is illustrated in Fig. E5.

CHRONIC Rx

Immunomodulatory therapies are required for severe disease and persistent or recurrent symptoms during steroid taper. Oral and injectable methotrexate has been used for steroid-sparing effect, particularly for arthritis-predominant symptoms. IL-1 blockade (anakinra, canakinumab) is particularly beneficial for symptom resolution. More recently, anti-IL-6 agents (tocilizumab, sarilumab) and TNF inhibitors (etanercept, infliximab) have been used both alone and in combination with methotrexate, with efficacious results. Clinical response should be evaluated after 2 to 3 mo on therapy, and if poor response, should be switched to a biologic with different mechanism of action. Once prolonged remission is achieved, biologics may cautiously be tapered. Limited evidence exists for use of rituximab, abatacept, or IVIG in particularly severe or refractory disease.

TREATMENT SUMMARY

See Fig. E6.

PEARLS & CONSIDERATIONS

MACROPHAGE ACTIVATION SYNDROME

Reactive hemophagocytic lymphohistiocytosis (RHL), also known as macrophage activation syndrome (MAS), is reported in 12% to 17% of AOSD patients. The syndrome comprises uncontrolled inflammatory activation leading to phagocytosis of hematopoietic cells by macrophages, and mortality ranges from 10% to 22%. The clinical picture can be difficult to differentiate from flare of AOSD, but a few features are more closely correlated with MAS (i.e., hypofibrogenemia, leukopenia, thrombocytopenia, hypertriglyceridemia, and normalization of ESR all raise suspicion for MAS). Bone marrow aspiration is the gold standard for diagnosis, and initial treatment consists of pulse steroids, IVIG, and biologics (IL-1 or IL-6 blockade).

COMMENTS

- AOSD is a systemic illness comprising quotidian fever, evanescent rash, inflammatory polyarthritis, neutrophilic leukocytosis, and hyperferritinemia.
- Current treatment options include steroids, DMARDs, anti-IL-1 agents, anti-IL-6 agents, and TNF inhibitors.
- Macrophage activation syndrome is a rare but life-threatening complication of AOSD.

PATIENT & FAMILY EDUCATION

NIH: https://rarediseases.info.nih.gov/diseases/436/adult-onset-stills-disease

ACKNOWLEDGMENT

The author wishes to acknowledge the contributions of Bernard Zimmermann, MD, author of this chapter in a previous edition.

RELATED TOPICS

Juvenile Idiopathic Arthritis (Related Key Topic)
Fever of Undetermined Origin (Related Key Topic)

AUTHOR: **Shivani K. Patel, MD**

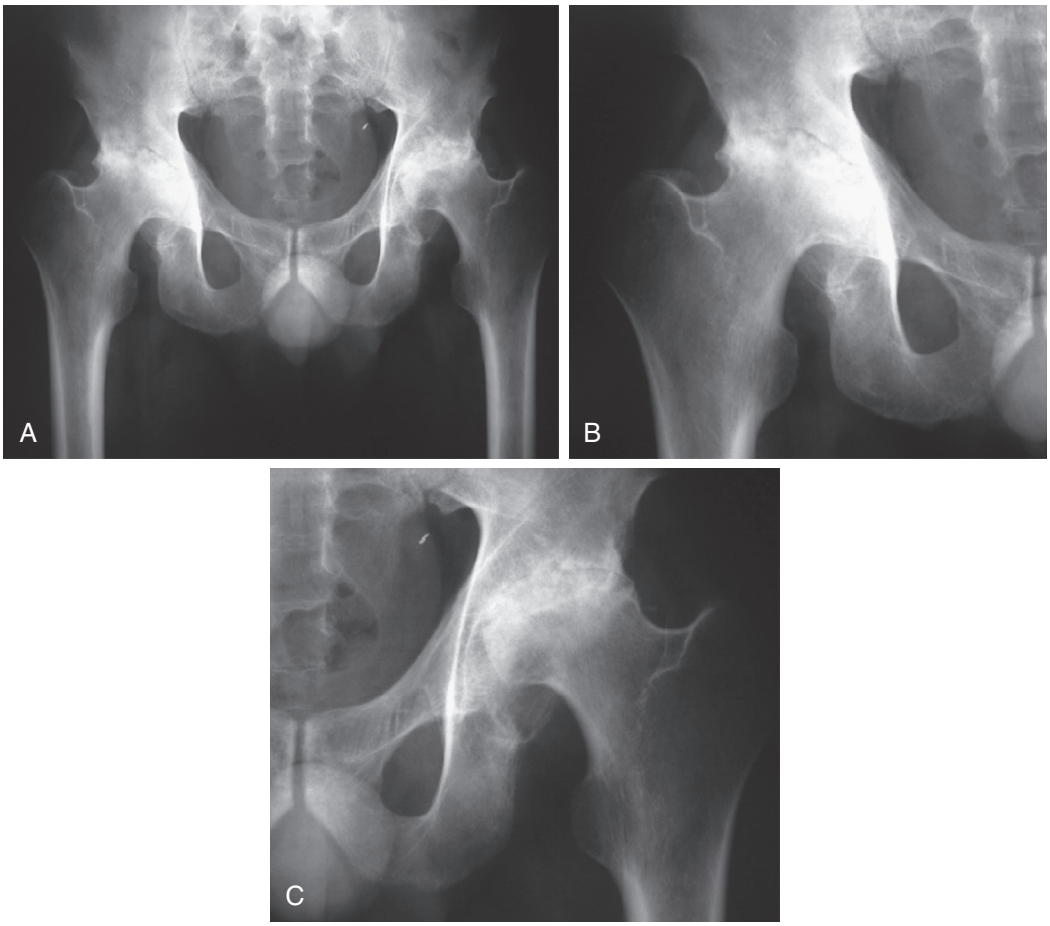

FIG. E3 (A to C) Radiograph of the pelvis showing the typical hip involvement leading to joint destruction. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

	YAMAGUCHI et al (1992)	FAUTREL et al (2008)
MAJOR CRITERIA	• Fever ≥102.2 °F (39 °C) for ≥7 days • Arthralgias for ≥2 weeks • Maculopapular nonpruritic salmon-pink rash • Leukocytosis (WBC ≥10 with ≥80% PMNs)	• Spiking fever ≥102.2 °F (39 °C) • Arthralgias • Transient erythematous rash • Pharyngitis • Neutrophils ≥80% • Glycosylated ferritin fraction ≤20%
MINOR CRITERIA	• Pharyngitis • Lymphadenopathy • Hepatomegaly and/or splenomegaly • Transaminitis • Negative ANA and RF	• Typical maculopapular Still rash • Leukocytosis (WBC ≥10)
EXCLUSION CRITERIA	• Malignancy (i.e., lymphoma) • Infection (i.e., EBV) • Connective tissue disease (i.e., vasculitis) • Drug reactions	
POSITIVE RESULTS	Presence of 5+ criteria, with 2+ being major	4+ major criteria OR 3 major and 2 minor
TEST MEASURES	96% sensitive/92% specific	81% sensitive/98% specific

FIG. E4 Yamaguchi criteria. *ANA,* Antinuclear antibodies; *EBV,* Epstein-Barr virus; *PMN,* polymorphonuclear neutrophil; *RF,* rheumatoid factor; *WBC,* white blood count.

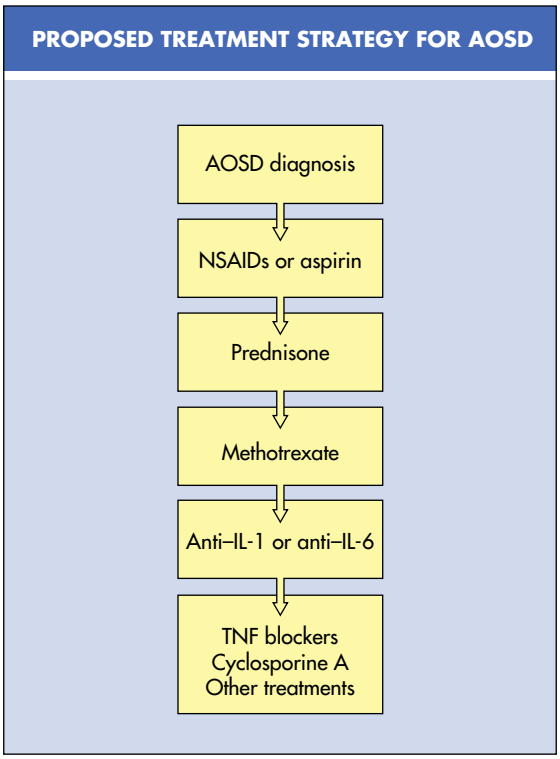

FIG. E5 Principal treatment regimens for adult-onset Still disease *(AOSD)* include nonsteroidal anti-inflammatory drugs *(NSAIDs)*, glucocorticoids, methotrexate, and biologic agents. *IL-1,* Interleukin-1; *TNF,* tumor necrosis factor. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

MEDICATION	TENTATIVE DOSAGE RECOMMENDATIONS
NSAIDs	Indomethacin 150-200mg PO daily; naproxen 500mg PO BID
Glucocorticoids	Prednisone 0.5-1 mg/kg daily; taper after ~6 weeks if response Methylprednisolone 1g IV x3 days for severe or life-threatening disease
DMARDs	
Methotrexate	10-20 (max 25) mg PO/SQ weekly
IL-1 inhibitors	
Anakinra (Kineret)	100 mg SQ daily
Canakinumab (Ilaris)	4 mg/kg SQ monthly
Rilonacept (Arcalyst)	200mg SQ loading, then 160mg SQ weekly maintenance
IL-6 inhibitors	
Tocilizumab (Actemra)	8 mg/kg IV q4 weeks until adequate clinical response Reduce to 4 mg/kg q4 weeks once stable for 6+ months
Sarilumab (Kevzara)	200mg q2 weeks until biological remission
TNF inhibitors	
Infliximab (Remicade)	3-5 (max 10) mg/kg at weeks 0, 2, 6 then q8 weeks

FIG. E6 Treatment strategy for adult-onset Still disease. *BID,* twice daily; *DMARDs,* disease-modifying antirheumatic drugs; *IL,* interleukin; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PO,* by mouth; *TNF,* tumor necrosis factor; *IV,* intravenous.

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Akathisia

BASIC INFORMATION

DEFINITION

Akathisia is a movement disorder associated with an intense inner sense of subjective motor restlessness usually involving the lower extremities and leading to difficulty remaining still. In most cases the movement is repetitive and may involve crossing, uncrossing, and swinging of legs, or shifting weight from one foot to the other. Antipsychotic-related akathisia is most common and can be classified according to the time of onset in the course of antipsychotic treatment (acute, tardive, withdrawal, and chronic akathisia).

SYNONYMS

Acathisia
Restless Legs Syndrome

ICD-10CM CODES

G25.71 Drug-induced akathisia
- Neuroleptic induced acute akathisia
- Tardive akathisia
- Acathisia (drug induced)
- Akathisia (drug-induced) (treatment-induced)

DSM-5 CODE

333.99 Medication induced acute akathisia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Varies widely from 21% to 75%. Occurrence higher with first generation, or typical, antipsychotics, particularly high-potency agents such as haloperidol, than with atypical antipsychotics.

PREVALENCE: Varies from 20% to 35%. Reported prevalence rates vary between 5% and 36.8%.

PREDOMINANT SEX AND AGE: Akathisia occurs predominantly in younger patients. Incidence appears to decrease with age.

RISK FACTORS: Younger age when treated with antipsychotic medications, Parkinson disease, traumatic brain injury (TBI), encephalitides, and deficiencies of vitamin D or iron.

Akathisia usually occurs within first few days of treatment but also with dosage advancements or switch to a higher potency neuroleptic or withdrawal of an antiparkinsonian drug. Akathisia is more commonly associated with first generation antipsychotics. It occurs in patients taking second generation antipsychotics, although usually at lower rates.

GENETICS: Generally, akathisia is not considered a highly heritable condition, but a genetic predisposition to or family history of akathisia can confer some added risk. There is recent evidence of *PI4K2A* deficiency leading to intellectual disability, epilepsy, myoclonus, and an akathisia syndrome beginning in childhood as products of a consanguineous relationship.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients typically describe a subjective feeling of restlessness with the impulse to move and will objectively be seen pacing, rocking, and shifting position. Motor activity consists of complex, quasi-purposeful and repetitive movements. Milder cases present with subjective inner restlessness deep in the legs predominantly. Moderate cases are characterized by a tendency to rock back and forth from foot to foot accompanied by a coarse tremor or foot myoclonus. Severe akathisia patients have difficulty maintaining a position, often shuffling their feet when sitting and then getting up repeatedly and pacing. Akathisia is most severe when the patient cannot tolerate any position for more than a few moments. Acute cases usually last less than 6 mo. Chronic cases last for more than 6 mo after last dose increase. Dysphoria and subjective restlessness may be less marked in chronic cases, but dyskinesias are not uncommon. Pseudoakathisia, occurring mostly in men, is associated with motor signs such as fidgetiness without subjective restlessness complaints and with less dysphoria. Tardive akathisia can occur in situations with delayed onset in the setting of a tardive dyskinesia/tardive syndrome. Rebound withdrawal akathisia refers to onsets within 6 wk of discontinuation or dose decrease of an antipsychotic.
- To assess the severity of akathisia, tools such as the Barnes Akathisia Rating Scale (BARS), the Hillside Akathisia Scale, or the Drug-Induced Extrapyramidal Symptoms Scale are used.
- The inner restlessness of patients with akathisia can lead to extreme anxiety and depressed mood. In chronic cases, akathisia has also been associated with a high risk of self-harm or suicidal behavior. A careful evaluation for depression, anxiety, and suicidal ideation is necessary.
- Prognosis is good if the condition is recognized and the offending drug is discontinued. If the condition is left untreated, it can become disabling with high morbidity and can also lead to suicidal ideation. Suicidal, aggressive, and violent behaviors have been reported.
- Use of the term *akathisia* is often reserved for medication-related and antipsychotic-induced akathisia, although the broad definition of akathisia includes the inner and motor restlessness observed in patients with idiopathic Parkinson disease, postencephalitic parkinsonism, and restless legs syndrome.

ETIOLOGY

- Pathophysiology is poorly understood, though a complex mixture of neurotransmitter effects is suspected. Given its association with extrapyramidal side effects such as dystonia and parkinsonism, akathisia is suspected to be secondary to antipsychotic-related dopamine type 2 receptor downregulation and acetylcholine upregulation in basal ganglia regions. Central adrenergic and GABAergic mechanisms likely play a role, and neurosteroids have been implicated. Serotoninergic drugs can exacerbate akathisia. The pathophysiologies of acute akathisia and tardive akathisia may differ in that neuroleptics worsen the former and tend to be less distressing in the latter.
- In addition to antipsychotics, akathisia has been associated with calcium channel blockers, antiemetics, antimigraine agents, antivertigo drugs, antidepressants (selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors), and sedatives used in anesthesia. Akathisia has also been noted to occur following abuse of cocaine and during withdrawal from alcohol, benzodiazepines, barbiturates, or opiates.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Akathisia is often underdiagnosed because symptoms often mimic osr overlap other psychiatric disorders such as psychosis, mania, attention deficit hyperactivity disorder (ADHD), or agitated depression. Agitation is transdiagnostic, occurring in psychoses, affective disorders, anxiety disorders, restless legs syndrome, insomnia, and drug withdrawal. Thus it is important to obtain a complete medical history and rule out other psychiatric disorders (Table 1).

WORKUP

The Barnes Akathisia Rating Scale or another akathisia scale may be used to assess patients with akathisia. However, most clinicians will rely on clinical observation.

LABORATORY TESTS

There are no discriminatory laboratory tests involved in the diagnosis of akathisia.

TABLE 1 Akathisia Differential Diagnoses

- Agitation secondary to multiple psychiatric conditions
- Attention deficit hyperactivity disorder
- Antipsychotic-induced dysphoria
- Restless legs syndrome
- Tardive dyskinesia
- Drug and alcohol withdrawal
- Insomnia
- Neuropsychiatric disorders including catatonic excitement, TBI, delirium, encephalitides, hypoglycemia, CNS autoimmune diseases
- Neurodegenerative disorders including dementia, Parkinson disease, Huntington disease

CNS, Central nervous system; *TBI,* traumatic brain injury.

IMAGING STUDIES

There are no discriminatory radiographic tests involved in the diagnosis of akathisia.

Rx TREATMENT

The most reliable treatment for acute akathisia is the reduction or the withdrawal of antipsychotic medication. However, this is often not possible because of the patient's mental condition. Use of adjunctive medications that dampen akathisia can be helpful (Table 2). Other agents that have been investigated include ritanserin, piracetam, valproic acid, trazodone, and tricyclic antidepressants. The treatment of tardive akathisia has been unsatisfactory, and more research is needed.

COMPLEMENTARY & ALTERNATIVE MEDICINE

If anxiety and stress are major contributors to subjective complaints, mind-body approaches such as relaxation breathing, meditation, or progressive muscle relaxation can be tried.

DISPOSITION

Psychiatric and neurologic outpatient care

REFERRAL

Once the diagnosis of akathisia is made, the patient should be referred to a neurologist and a psychiatrist. Making decisions on the medications can be challenging because most patients rely on antipsychotics for their mental health condition.

PEARLS & CONSIDERATIONS

- It may be difficult to determine whether a patient is experiencing akathisia or anxiety or agitation.
- Early identification and management are important as akathisia may be associated with treatment nonadherence.
- Antipsychotic-induced akathisia may be managed by reducing the dose of the offending agent or switching to an alternative antipsychotic agent.
- Beta-blockers such as propranolol and benzodiazepines have historically been used, although research is limited.
- Anticholinergic agents such as benztropine may be used if concomitant parkinsonism is present.

PREVENTION

As a medication side effect, prevention is the best approach to minimizing akathisia. Knowledge of past medication effects is essential. Strict adherence to standard titration and dose schedules, recognition of drug-drug interaction challenges, and preference for second generation antipsychotic medications all aid in akathisia prevention.

PATIENT & FAMILY EDUCATION

Patient education is essential. It should include open discussion of benefits vs. risks. Time of onset, duration of symptoms, other treatment options, and need to call parameters are important topic areas. Clear discussion of the therapeutic strategies that can be helpful if akathisia emerges should be discussed. Establishment of a trusting relationship can modify the anxiety and stress that can exacerbate akathisia.

RELATED TOPICS

Restless Legs Syndrome (Related Key Topic)

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TABLE 2 Adjunctive Pharmacotherapies for Akathisia

- Beta-adrenergic antagonists (e.g., propranolol: Initiate at low doses 10 mg TID with titration up every few days to a maximum of 90-120 mg/day)
- Benzodiazepines (e.g., lorazepam 1.5-3 mg/day in divided doses or clonazepam 0.5 mg/day)
- Anticholinergics (e.g., benztropine 2 mg/day if other EPS in addition to akathisia)
- 5-HT2A antagonist (e.g., cyproheptadine 16 mg/day)
- Alpha-2-adrenergic agonists (e.g., clonidine 0.2-0.8 mg/day)
- Noradrenergic and specific serotonergic antidepressant (e.g., mirtazapine 7.5-15 mg/day; do not use higher dose that increases noradrenergic action)
- NMDA antagonist/indirect dopamine agonist (e.g., amantadine, 100 mg BID-TID)

BID, Twice a day; *NMDA,* N-methyl-d-aspartate; *TID,* three times a day.

SUGGESTED READINGS

Flaherty AW, Ivkovic A: Chapter 81. Movement disorders. In Stern TA et al (eds): *Massachusetts general hospital comprehensive clinical psychiatry*, ed 2, NY, 2016, Elsevier, pp 871-882.

Henderson M, Mellers JDC: Chapter 12. Movement disorders. In David AS et al (eds): *Lishman's organic psychiatry. A textbook of neuropsychiatry*, ed 4, Oxford, 2009, Wiley-Blackwell, pp 745-816.

Hirjak D et al: Nervenarzt 90:1, 2019. https://doi.org/10.1007/s00115-018-0582-5.

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Alcohol Use Disorder ALG PTG

BASIC INFORMATION

DEFINITION

Moderate drinking has been defined as two standard drinks (e.g., 12 oz of beer) per day and one drink per day for women and persons older than 65 yr. Although not generally included under the alcoholism topic, hazardous or at-risk drinking should also be considered. For men, *at-risk drinking* is defined as more than 14 drinks/wk or more than 4 drinks/occasion. For women, at-risk drinking is defined as approximately half that given for men.

The American Psychiatric Association defines diagnostic criteria for *alcohol withdrawal* as follows:

A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
B. Two (or more) of the following, developing within several hours to a few days after criterion A:
   1. Autonomic hyperactivity (e.g., sweating or pulse rate >100 beats/min)
   2. Increased hand tremor
   3. Insomnia
   4. Nausea and vomiting
   5. Transient visual, tactile, or auditory hallucinations or illusions
   6. Psychomotor agitation
   7. Anxiety
   8. Grand mal seizures
C. The symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The symptoms are not attributable to a general medical condition and are not better accounted for by another mental disorder.

SYNONYMS

Alcohol dependence syndrome
Substance abuse
Alcohol withdrawal syndrome
Alcoholism

ICD-10CM CODES

F10	Mental and behavioral disorders due to use of alcohol
F10.1	Mental and behavioral disorders due to use of alcohol: harmful use
F10.2	Mental and behavioral disorders due to use of alcohol: dependence syndrome
F10.3	Mental and behavioral disorders due to use of alcohol: withdrawal state
F10.4	Mental and behavioral disorders due to use of alcohol: withdrawal state with delirium
F10.5	Mental and behavioral disorders due to use of alcohol: psychotic disorder
F10.6	Mental and behavioral disorders due to use of alcohol: amnesic syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- The clinical history suggests alcohol problems in 15% to 20% of patients in primary care and hospitalized patients. In the U.S., alcohol use disorder generates nearly $223 billion in annual economic costs. An estimated 14% of adults in the U.S. have alcohol dependence. Alcohol accounts for 6.8% of age-standardized deaths in men and 2.2% in women.
- 20% achieve abstinence without help; 70% achieve sobriety for 1 yr.

PREVALENCE (IN U.S.): 7% of population ≥18 yr

PREDOMINANT SEX:

- Lifetime risk for males 8% to 10%
- Lifetime risk for females 3% to 5%

PEAK INCIDENCE: 20 to 40 yr. The most common age range for initial treatment of alcohol dependence is 35 to 45 yr. However, the peak period for meeting alcohol dependence criteria is ≥10 yr earlier.

GENETICS: More common with a family history of alcoholism and in patients of Irish, Scandinavian, and Native American descent

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Recurring minor trauma
- Gastrointestinal bleeding from gastritis and/or varices
- Pancreatitis (acute and chronic)
- Liver disease
- Odor of alcohol on breath
- Tremulousness
- Tachycardia
- Peripheral neuropathy
- Recent memory loss

ETIOLOGY

- Social and genetic factors important
- Risk factors:
  1. Broken homes
  2. Unemployment
  3. Divorce
  4. Recurrent depression
  5. Addiction to another substance, including tobacco
  6. Working long hours (≥55 hours/week)

DIAGNOSIS

WORKUP

- The USPSTF recommends that clinicians screen adults 18 yr and older for alcohol misuse and provide persons engaged in risky or hazardous drinking with brief behavioral counseling interventions to reduce alcohol misuse. Several screening tests (CAGE [Table 1], TWEAK, CRAFFT, AUDIT-C [Table 2]) are available. The four-item CAGE (feeling need to **C**ut down, **A**nnoyed by criticism, **G**uilty about drinking, and need for an **E**ye-opener in the morning) is the most popular screening test in primary care. A positive response should lead to further questioning. The sensitivity of the CAGE ranges from 43% to 94% and its specificity ranges from 70% to 97%. The five-item TWEAK scale (**T**olerance, **W**orry, **E**ye-openers, **A**mnesia, [**K**] cut down) and the TACE questionnaire (**T**olerance, **A**nnoyance, **C**ut down, **E**ye-opener) are designed to screen pregnant women for alcohol misuse. They detect lower levels of alcohol consumption that may pose risks during pregnancy. The CRAFFT questionnaire (riding in **C**ar with someone who was drinking, using alcohol to **R**elax, using alcohol while **A**lone, **F**orgetfulness, criticism from **F**riends and **F**amily, **T**rouble) is useful as a screening tool for adolescents. Its sensitivity is 92% and specificity 64% for alcohol use disorder. Single-question screening about alcohol consumption in a day ("When was the last time you had more than X drinks in a day?" [where X is 5 for men and 4 for women]) with the threshold set at "in the past 3 months" is 85% sensitive and 70% specific in men and 82% and 70% in women for unhealthy alcohol use. The 3-question AUDIT-C is a shorter form of the 10-item AUDIT, and the questions center on the quantity and frequency of alcohol use. It asks how often someone has had a drink containing alcohol, how many standard drinks containing alcohol one consumes on a typical day when one is drinking, and how often one has six or more drinks on one occasion. Scoring ranges from 0 to 4 on each question with a total score range of 0 to 12. A total score of 3 or higher for women and 4 or higher for men indicates alcohol use disorder and need for further assessment. Its sensitivity ranges from 85% in Hispanic women to 95% in white men.
- Laboratory evaluation (see below).

LABORATORY TESTS

Lab tests alone do not accurately detect alcohol problems but can help identify medical complications related to alcohol use, such as pancreatitis or cirrhosis.

TABLE 1 CAGE Questionnaire for Alcohol Problems Screening[a]

C	Have you felt the need to **C**ut down on your drinking?
A	Have people **A**nnoyed you by criticizing your drinking?
G	Have you ever felt bad or **G**uilty about your drinking?
E	Have you had a drink first thing in the morning to steady your nerves or to get rid of a hangover (i.e., an "**E**ye opener")?

From Stern TA et al: *Massachusetts General Hospital handbook of general hospital psychiatry,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 2 AUDIT-C Questionnaire for Alcohol Problems Screening[a]

Question	Score
How often did you have a drink containing alcohol in the past year?	Never (0 points) Monthly or less (1 point) 2-4 times per month (2 points) 2-3 times per week (3 points) >4 times per week (4 points)

[a]AUDIT-C is scored 0-12, with score >4 (men) and >3 (women) considered positive for problematic drinking.

From Stern TA et al: *Massachusetts General Hospital handbook of general hospital psychiatry,* ed 7, Philadelphia, 2018, Elsevier.

- Gamma-glutamyltransferase (GGTP), generally elevated
- Liver transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), often elevated, may be normal or low in advanced liver disease.
- Low albumin level, hypophosphatemia, hypomagnesemia from malnutrition
- Complete blood count (CBC) reveals elevated mean corpuscular volume from toxic effect of alcohol on erythrocyte development in nutritional deficiencies.
- Stool for occult blood may be positive as a result of gastritis or variceal bleeding.
- RBC folate, vitamin B_{12} level, vitamin B_6, vitamin B_1 level

IMAGING STUDIES

Indicated only with a history of trauma. CT or ultrasound of abdomen may reveal fatty liver or cirrhosis in advanced stages.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Twelve-step facilitation, cognitive behavioral therapy, and motivational enhancement therapy improve the chances of recovery in patients with alcohol use disorder and dependence.
- Depression, if present, should be treated at same time alcohol is withdrawn.

ACUTE GENERAL Rx

Alcohol withdrawal syndrome (AWS) occurs when a person stops ingesting alcohol after prolonged consumption. It can result in four possible clinical patterns depending on the severity of the patient's alcohol use and the time from the patient's previous alcohol ingestion. Blood ethanol level decreases by ~20 mg/dl/hr in a normal person. Although discussed separately, these withdrawal states blend together in real life. Table 3 summarizes medications for the treatment of alcohol dependence. The cornerstone of treatment for alcohol withdrawal syndrome is the use of benzodiazepines.

- **Tremulous state** (early alcohol withdrawal, "impending DTs," "shakes," "jitters").
  1. Time interval: usually occurs 6 to 8 hr after the last drink or 12 to 48 hr after reduction of alcohol intake; becomes most pronounced at 24 to 36 hr.
  2. Manifestation: tremors, mild agitation, insomnia, tachycardia; symptoms are relieved by alcohol.
  3. Detoxification can be in the outpatient (ambulatory) or inpatient setting. Candidates for outpatient detoxification should have a reasonable support system (e.g., reliable contact person) who can monitor progress and lack of any significant comorbid conditions (e.g., suicide risk, seizure disorder, coexisting benzodiazepine dependence, prior unsuccessful outpatient detoxification, pregnancy, cirrhosis) or risk factors for severe withdrawal (age >40 yr, drinking >100 g of ethanol daily [e.g., 1 pint of liquor or eight 12-oz cans of beer, random blood alcohol concentration >200 mg/dl]).
  4. Inpatient treatment:
     a. Admit to medical floor (private room); monitor vital signs q4h; institute seizure precautions; maintain adequate sedation.
     b. Administer lorazepam as follows:
        (1) Day 1: 2 mg PO q4h while awake and not lethargic.
        (2) Day 2: 1 mg PO q4h while awake and not lethargic.
        (3) Day 3: 0.5 mg PO q4h while awake and not lethargic.
        (4) NOTE: Hold sedation for lethargy or abnormal vital or neurologic signs. The preceding doses are only guidelines; it is best to titrate the dose case by case.
     c. In patients with mild to moderate withdrawal and without history of seizures, individualized benzodiazepine administration (rather than a fixed-dose regimen) results in lower benzodiazepine administration and avoids unnecessary sedation. The Clinical Institute Withdrawal Assessment Scale for Alcohol, Revised (CIWA-Ar) scale (Box 1) can be used to measure the severity of alcohol withdrawal. It consists of 10 items: nausea; tremor; autonomic hyperactivity; anxiety; agitation; tactile, visual, and auditory disturbances; headache; and disorientation. Each item is assigned a score from 0 to 7. For example, in the "agitation" category 0 indicates normal activity, and 7 indicates that the patient constantly thrashes about. For the category of "tremor," 0 indicates that tremor is not present and 7 that tremor is severe, even with arms not extended. The maximum total score is 67. Patients with mild AWS symptoms (CIWA-Ar score <8)

TABLE 3 Medications for the Treatment of Alcohol Dependence*

Medication	Dose and Route	Frequency	Effects	Major Common Adverse Effects
Alcohol Withdrawal				
		Benzodiazepines†		
Chlordiazepoxide*	25-100 mg, PO/IV/IM†	Every 4-6 hr	Decreased severity of withdrawal; stabilization of vital signs; prevention of seizures and delirium tremens	Confusion, oversedation, respiratory depression
Diazepam‡	5-10 mg, PO/IV/IM†	Every 6-8 hr		
Oxazepam‡	15-30 mg, PO†	Every 6-8 hr		
Lorazepam‡	1-4 mg, PO/IV/IM†	Every 4-8 hr		
		β-Blockers		
Atenolol	25-50 mg, PO	Once a day	Improvement in vital signs	Bradycardia, hypotension
Propranolol	10-40 mg, PO	Every 6-8 hr	Reduction in craving	
		α-Agonists		
Clonidine	0.1-0.2 mg, PO	Every 6 hr	Decreased withdrawal symptoms	Hypotension, fatigue
		Antiepileptics		
Carbamazepine	200 mg, PO	Every 6-8 hr	Decreased severity of withdrawal; prevention of seizures	Dizziness, fatigue, red blood cell abnormalities
		Prevention of Relapse		
Disulfiram‡	125-500 mg, PO	Daily	Decreased alcohol use among those who relapse	Disulfiram-alcohol reaction, rash, drowsiness, peripheral neuropathy
Naltrexone‡	50 mg, PO	Daily	Increased abstinence, decreased drinking days	Nausea, abdominal pain, myalgias-arthralgias
	380 mg, IM	Every 4 wk		
Acamprosate‡	666 mg, PO	Three times a day	Increased abstinence	Diarrhea

*Most commonly used medications listed.
†Currently approved by U.S. Food and Drug Administration for the indication noted.
‡Dose and routes given for standard fixed-dose regimens, which include dose tapers over time.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

can be monitored on an outpatient basis. Benzodiazepines are beneficial for most patients with a CIWA-AR score ≥8 and are strongly recommended in patients with substantial withdrawal symptoms (CIWA-Ar score >12). Patients with CIWA-Ar score of ≥15 should be admitted to detox unit. In-patient treatment is also recommended for patients with history of withdrawal seizures and for those with suicidal ideation and significant comorbidities.

d. Beta-adrenergic blockers: Beta-blockers are useful for controlling blood pressure and tachyarrhythmias. However, they do not prevent progression to more serious symptoms of withdrawal and, if used, should not be administered alone but in conjunction with benzodiazepines. Beta-blockers should be avoided in patients with contraindications to their use (e.g., bronchospasm, bradycardia, or severe congestive heart failure). Centrally acting alpha-adrenergic agonists such as clonidine ameliorate symptoms in patients with mild to moderate withdrawal but do not reduce delirium or seizures.

e. Vitamin replacement: Thiamine 100 mg IV or IM for at least 5 days plus oral multivitamins. The IV administration of glucose can precipitate Wernicke encephalopathy in alcoholics with thiamine deficiency; therefore thiamine administration should precede IV dextrose.

f. Hydration PO or IV (high-caloric solution): If IV, glucose with Na+, K+, Mg2+, and phosphate replacement prn.

g. Laboratory studies:
   (1) CBC, platelet count, INR.
   (2) Electrolytes, glucose, blood urea nitrogen, creatinine.
   (3) GGTP, ALT, AST.
   (4) Phosphorus and magnesium.
   (5) Serum vitamin B_{12} and folic acid (if megaloblastic features in blood smear).

h. Diagnostic imaging: Generally not necessary; if subdural hematoma is suspected (evidence of trauma, persistent lethargy), a CT scan should be ordered.

i. Social rehabilitation: Group therapy such as Alcoholics Anonymous; identification and treatment of social and family problems should be initiated during the patient's hospital stay.

- **Alcoholic hallucinosis:**
  1. Manifestations: Hallucinations usually are auditory, but hallucinations occasionally are visual, tactile, or olfactory; usually there is no clouding of sensorium as in delirium (clinical presentation may be mistaken for an acute schizophrenic episode). Disordered perceptions become most pronounced after 24 to 36 hr of abstinence.
  2. Treatment: Same as for DTs (see "Withdrawal seizures").

- **Withdrawal seizures ("rum fits"):**
  1. Time interval: Usually occurs 7 to 30 hr after cessation of drinking, with a peak incidence between 13 and 24 hr.
  2. Manifestations: Generalized convulsions with loss of consciousness; focal signs are usually absent; consider further investigation with CT scan of head and electroencephalography if clearly indicated (e.g., presence of focal neurologic deficits, prolonged postictal confusion state). In addition, in a febrile patient who is having a seizure or altered mental state, a lumbar puncture is necessary.
  3. Treatment:
     a. Diazepam 2.5 mg/min IV until seizure is controlled (check for respiratory depression or hypotension) may be beneficial for prolonged seizure activity; IV lorazepam 1 to 2 mg q2h can be used in place of diazepam. Withdrawal seizures generally are self-limited and treatment is not required; the use of phenytoin or other anticonvulsants for short-term treatment of alcohol withdrawal seizures is not recommended.
     b. Thiamine 100 mg IV, followed by IV dextrose, should also be administered.
     c. Electrolyte imbalances (increased Mg^{2+}, decreased K^+, increased or decreased Na^+, decreased PO_4^{3-}) that may exacerbate seizures should be corrected.

BOX 1 Alcohol Withdrawal Assessment Scoring Guidelines (Revised Clinical Institute Withdrawal Assessment for Alcohol Scale)

Nausea and Vomiting (0-7)
0, none; 1, mild nausea with no vomiting; 4, intermittent nausea; 7, constant nausea, frequent dry heaves and vomiting

Tremor (0-7)
0, no tremor; 1, not visible, but can be felt fingertip to fingertip; 4, moderate, with patient's arms extended; 7, severe, even with arms not extended

Paroxysmal Sweats (0-7)
0, no sweats; 1, barely perceptible sweating, palms moist; 4, beads of sweat obvious on forehead; 7, drenching sweats

Anxiety (0-7)
0, no anxiety, patient at ease; 1, mildly anxious; 4, moderately anxious or guarded, so anxiety is inferred; 7, equivalent to acute panic states seen in severe delirium or acute schizophrenic reactions

Agitation (0-7)
0, normal activity; 1, somewhat more than normal activity; 4, moderately fidgety and restless; 7, pacing back and forth during, or constantly thrashing about

Tactile Disturbances (0-7)
Ask, "Have you experienced any itching, pins and needles sensation, burning or numbness, or a feeling of bugs crawling on or under your skin?"
0, none; 1, very mild itching, pins and needles, burning, or numbness; 2, mild itching, pins and needles, burning, or numbness; 3, moderate itching, pins and needles, burning, or numbness; 4, moderately severe tactile hallucinations; 5, severe hallucinations; 6, extremely severe hallucinations; 7, continuous hallucinations

Auditory Disturbances (0-7)
Ask, "Are you more aware of sounds around you? Are they harsh? Do they startle you? Do you hear anything that disturbs you or that you know isn't there?"
0, not present; 1, very mild harshness or ability to startle; 2, mild harshness or ability to startle; 3, moderate harshness or ability to startle; 4, moderate hallucinations; 5, severe hallucinations; 6, extremely severe hallucinations; 7, continuous hallucinations

Visual Disturbances (0-7)
Ask, "Does the light appear to be too bright? Is its color different than normal? Does it hurt your eyes? Are you seeing anything that disturbs you?"
0, not present; 1, very mild sensitivity to light; 2, mild sensitivity; 3, moderate sensitivity; 4, moderate hallucinations; 5, severe hallucinations; 6, extremely severe hallucinations; 7, continuous hallucinations

Headache (0-7)
0, not present; 1, very mild; 2, mild; 3, moderate; 4, moderately severe; 5, severe; 6, very severe; 7, extremely severe

Orientation and Clouding of Sensorium (0-4)
Ask, "What day is this? Where are you? Who am I?"
0, oriented; 1, cannot do serial additions or is uncertain about date; 2, disoriented to date by no more than 2 calendar days; 3, disoriented to date by more than 2 calendar days; 4, disoriented to place and/or person

Total Score
0 to 9: absent or minimal withdrawal
10 to 19: mild to moderate withdrawal
More than 20: severe withdrawal

From Sullivan JT et al: Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict* 84:1353-1357, 1989.

- **DTs:**
  1. Time interval: Variable; usually occurs within 1 wk after reduction or cessation of heavy alcohol intake and persists for 1 to 3 days. Peak incidence is 72 hr and 96 hr after the cessation of alcohol consumption.
  2. Manifestations: Profound confusion, tremors, vivid visual and tactile hallucinations, autonomic hyperactivity; this is the most serious clinical presentation of alcohol withdrawal (mortality rate is approximately 15% in untreated patients).
  3. Treatment:
     a. Admission to a detoxification unit where patient can be observed closely.
     b. Vital signs q30min (neurologic signs, if necessary).
     c. Use of lateral decubitus or prone position if restraints are necessary.
     d. NPO: Nasogastric tube for abdominal distention may be necessary but should not be routinely used.
     e. Laboratory studies: Same as for early alcohol withdrawal.
     f. Vigorous hydration (4 to 6 L/day): IV with glucose (Na^+, K^+, PO_4^{3-} and Mg^{2+} replacement [if patient has hypophosphatemia or hypomagnesemia]).
     g. Vitamins: Thiamine 100 mg IV qd. The initial dose of thiamine should precede the administration of IV dextrose; multivitamins (may be added to the hydrating solution).
     h. Sedation: Control of agitation should be achieved with rapid-acting sedative-hypnotic agents in adequate doses to maintain light somnolence for the duration of delirium.
        (1) Initially: Lorazepam 2 to 5 mg IM/IV repeated prn.
        (2) Maintenance (individualized dosage): Chlordiazepoxide, 50 to 100 mg PO q4-6h, lorazepam 2 mg PO q4h, or diazepam 5 to 10 mg PO tid; withhold doses or decrease subsequent doses if signs of oversedation are apparent.
        (3) Midazolam is also effective for managing DTs. Its rapid onset (sedation within 2 to 4 min of IV injection) and short duration of action (approximately 30 min) make it an ideal agent for titration in continuous infusion.
     i. Treatment of seizures (as previously described).
     j. Diagnosis and treatment of concomitant medical, surgical, or psychiatric conditions.

CHRONIC Rx

- See "Referral."
- Pharmacotherapies for alcoholism include:
  1. Acamprosate is a synthetic compound with a chemical structure similar to the neurotransmitter gamma-aminobutyric acid and the amino acid neuromodulator taurine. Its mechanism of action is not completely understood. It is indicated for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation. It should be used only as part of a comprehensive psychosocial treatment program. It does not cause a disulfiram-like reaction as a result of ethanol ingestion. Dose is two 333-mg tablets tid. Treatment should be initiated as soon as possible after the period of alcohol withdrawal, when the patient has achieved abstinence, and should be maintained if the patient relapses. Avoid acamprosate if severe renal impairment is present.
  2. The long-acting opiate antagonist naltrexone inhibits the rewarding effects of alcohol. The starting dose is 25 mg/day, increased to 50 mg PO qd after 1 wk. An extended-release, once-monthly injection of naltrexone is also available and can be used along with psychosocial support to maintain alcohol abstinence. In patients with opioid dependence, naltrexone can precipitate acute withdrawal syndrome and should not be used at least 7 days from last opioid use. There are no established guidelines on the appropriate length of naltrexone treatment for alcohol dependence. One study recommends at least 3 mo of treatment. Avoid naltrexone if acute hepatitis, hepatic failure, or ongoing opioid use is present.
  3. Topiramate or gabapentin can be offered as second line drugs; to patients with moderate to severe alcohol use disorder topiramate might be preferable.
  4. Disulfiram (Antabuse): Dosage is 500 mg max qd for 1 to 2 wk, then 125 to 500 mg qd. It interferes with the metabolism of alcohol by inhibiting aldehyde dehydrogenase, causing an accumulation of acetaldehyde. It produces unpleasant symptoms (nausea, flushing, elevated blood pressure, headache, weakness) when alcohol is ingested. It is an older drug that is now rarely used.
  5. Avoid pharmacological treatments in pregnant or breastfeeding women.

DISPOSITION

See "Referral."

REFERRAL

- To Alcoholics Anonymous or Adult Children of Alcoholics
- Family members to Al-Anon or Al-A-Teen
- Many cities have Salvation Army Adult Rehabilitation centers; all patients accepted, regardless of ability to pay

PEARLS & CONSIDERATIONS

COMMENTS

- Relative indications for inpatient alcohol detoxification are as follows: history of DTs or withdrawal seizures, severe withdrawal symptoms, concomitant psychiatric or medical illness, pregnancy, multiple previous detoxifications, recent high levels of alcohol consumption, and lack of reliable support network.
- Detoxification is not a stand-alone treatment but should serve as a bridge to a formal treatment program for alcohol dependence.
- The cure rate for alcoholism is highly disappointing, regardless of the modality. Only those who want to be helped will be helped. An effective strategy for the primary care physician is a prominently displayed sign in the office that states, "If you think you consume too many alcoholic beverages, please discuss it with me." Those who do open up the discussion can be given the facts in a nonjudgmental way and often can be helped. All too often problem drinkers lie on the questionnaire until they face a life-threatening health issue—and even then denial often reigns supreme.
- In a recent clinical trial, patients receiving medical management with naltrexone (100 mg/day), combined behavioral intervention (CBI), or both fared better on drinking outcomes, whereas acamprosate showed no evidence of efficacy, with or without CBI. No combination produced better efficacy than naltrexone or CBI alone in the presence of medical management.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Alcohol Use Disorder (Patient Information)
Drug Use Disorder (Related Key Topic)
Alcoholic Hepatitis (Related Key Topic)
Substance Use Disorder (Related Key Topic)
Wernicke Syndrome (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

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Alcoholic Hepatitis PTG ALG

BASIC INFORMATION

DEFINITION

Alcoholic hepatitis (AH) is a severe, progressive, inflammatory, and cholestatic liver disease occurring in patients with long-term heavy alcohol use (60 to 80 g/day in men and 20 to 40 g/day in women)

SYNONYM

AH

ICD-10CM CODES
K70.10 Alcoholic hepatitis without ascites
K70.9 Alcoholic liver disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Approximately 2 million people in the U.S. (about 1% of the population) are affected by alcoholic liver disease.
- Alcoholic hepatitis accounts for 0.8% of all admissions in the U.S.
- Typical presentation age: 40 to 50 yr. Majority occurs before age 60.
- Patients with alcoholic hepatitis typically drink more than 100 g of alcohol daily for two or more decades.

PREVALENCE: Approximately 25% to 30%
PREDOMINANT SEX AND AGE: The majority of patients are males. Males are two times as likely as women to abuse alcohol. However, women develop alcoholic hepatitis after a shorter time and smaller amount of alcoholic exposure than men.
GENETICS: No genetic predilection for any one race. In the U.S., however, there is increased incidence in minority groups.
RISK FACTORS: Drinking multiple alcohol types, drinking alcohol between meal times, poor nutrition, female gender, obesity, Hispanic ethnicity, long-term ingestion of >10 to 20 g/day of alcohol in women and >20 to 40 g/day in men

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Common presenting symptoms include:
- Rapid onset of jaundice
- Jaundice with duration <3 months
- Right upper quadrant pain
- Nausea/vomiting
- Malaise
- Low-grade fever
- Anorexia
- Abdominal distention/pain (due to ascites)
- Weight loss or malnourishment
- Proximal muscle wasting and weakness
- Complications of liver impairment (GI bleed; confusion, lethargy, ascites)

Findings on physical examination include:
- Jaundice and ascites
- Hepatomegaly, with tender liver on palpation
- Fever (first exclude other causes of fever, such as spontaneous bacterial peritonitis, urinary tract infection [UTI], pneumonia)
- Asterixis (a flapping tremor)
- Splenomegaly
- Tachycardia
- Hypotension
- Peripheral edema
- Abdominal distention with shifting dullness (ascites)
- Hepatic bruit
- With coexistent cirrhosis, look for:
  1. Gynecomastia
  2. Proximal muscles wasting
  3. Spider angiomata
  4. Altered hair distribution

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hepatitis B
- Hepatitis C
- Nonalcoholic steatohepatitis (NASH)
- Chronic pancreatitis
- Drug-induced liver injury
- Hemochromatosis
- Cholangitis

WORKUP

- The standard screening test for alcohol abuse is the Alcohol Use Disorders Identification Test (AUDIT).
- A thorough and detailed history is needed.
- Relevant questions may include:
  1. When patient started drinking
  2. Number of times patient drinks per day
  3. How many yr of regular/daily drinking
  4. Types of alcohol
  5. Home or bar drinking
  6. Rehabilitation for drinking
  7. Social problems (e.g., arrest for public intoxication or driving under the influence, marital discord due to alcoholism)

LABORATORY TESTS

The best biomarkers of harmful ethanol use are gamma glutamyltransferase (GGT), aspartate aminotransferase (AST), ethyl glucuronide (ETG), and phosphatidyl ethanol.
- Elevated transaminase (aspartate aminotransferase [AST] >45 U/L but <500 U/L; however, some patients may not have elevations in ALT, AST in early phases)
- AST:Alanine aminotransferase [ALT] ratio ≥2:1
- S-bilirubin >5 mg/dl
- Increased prothrombin time [PT]/international normalized ratio [INR]
- Elevated gamma glutamyltransferase (GGT)
- Carbohydrate-deficient transferrin (CDT) is a reliable marker for chronic alcoholism
- Elevated C-reactive protein
- Electrolyte disorder (hypokalemia, hypomagnesemia, low zinc, hypophosphatemia)
- Hypoalbuminemia
- Hyperferritinemia
- CBC (may reveal leukocytosis with bandemia or anemia or thrombocytopenia); mean corpuscular volume (MCV) may be elevated
- Screening tests to rule out other conditions include checking:
  1. Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HB_cAb) (IgM), hepatitis A antibody (IgM)
  2. Anti-hepatitis C antibody, hepatitis C ribonucleic acid (RNA)
  3. Ferritin-transferrin saturation
  4. Alpha-fetoprotein
  5. Alkaline phosphatase
- Laboratory criteria of severe alcoholic hepatitis are defined as
  1. Maddrey Discriminant Function (MDF) score >32, which is calculated as follows:
     MDF = 4.6 × prothrombin time – control prothrombin time + total bilirubin (mg/dl)
     OR
  2. Model for End-Stage Liver Disease (MELD) >21
     AND/OR
  3. Hepatic encephalopathy

There are other models for determining severity such as the Alcohol Hepatitis Histologic Score (AHHS) or for prognostication such as the MELD + Lille combination models.

IMAGING STUDIES

Ultrasonography is the preferred imaging study. The earliest histologic change in alcoholic liver disease is macrovesicular steatosis.

LIVER BIOPSY

- Liver biopsy is rarely needed.
- Useful to:
  1. Confirm the diagnosis.
  2. Evaluate the effect of coexisting disease.
  3. Rule out cirrhosis.
  4. Exclude other diagnoses (especially other causes of liver diseases, biliary obstruction, Budd-Chiari syndrome).
- Typical histologic findings include:
  1. Micro- or macrovesicular steatosis
  2. Hepatocyte injury (ballooning degeneration and focal hepatocyte necrosis)
  3. Mallory-Denk bodies (characteristic of alcoholic hepatitis)
  4. Perivenular fibrosis
  5. Portal and lobular inflammation with neutrophils or lymphocyte infiltration

TREATMENT

An algorithm for the management of patients with alcoholic hepatitis is described in Fig. 1. Treatment can be divided into three main components:
1. Lifestyle modifications
2. Nutritional support
3. Pharmacologic therapy

LIFESTYLE MODIFICATIONS

- Abstinence from alcohol (this improves both short- and long-term survival). Fig. E2 describes the effect of subsequent alcohol intake on 5-yr survival in patients with alcoholic hepatitis.
- Nonpharmacologic methods to promote abstinence include cognitive-behavioral therapy (CBT), Alcoholic Anonymous (AA) attendance, and motivational interviewing.
- Pharmacologic aids include using naltrexone, acamprosate, or baclofen.
- Monitor abstinence with breath test or urine drug screen (for use in past 3 days) or hair sample analysis for ethyl glucuronide (test alcohol intake within the last few months).
- Smoking cessation (to decrease oxidative stress).
- Treatment of substance abuse.

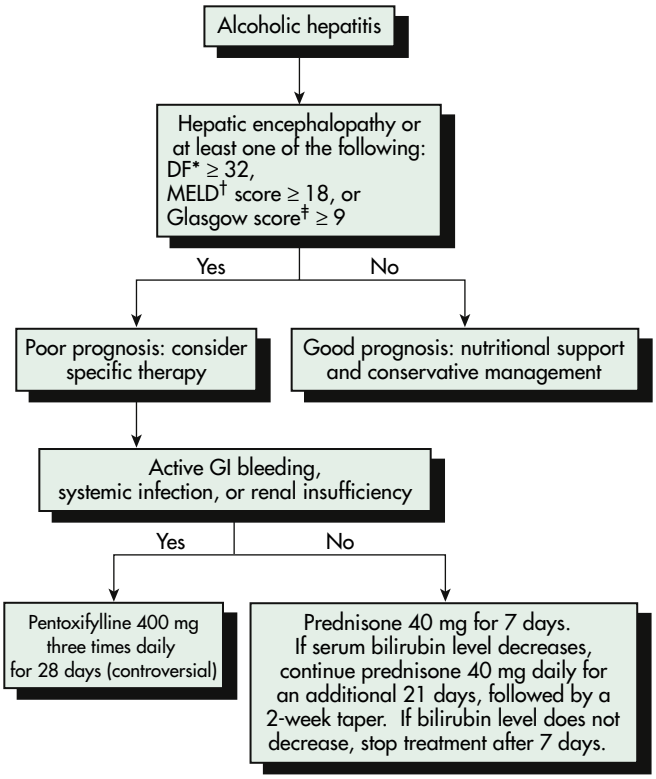

FIG. 1 Algorithm for the management of patients with alcoholic hepatitis. *The DF is calculated as follows: 4.6 (prothrombin time of patient – prothrombin time of control) + serum bilirubin level (in mg/dl). †The Model for End-Stage Liver Disease *(MELD)* score is based on the serum bilirubin level, INR, and serum creatinine level. ‡The Glasgow alcoholic hepatitis score is based on the patient's age, white blood cell count, blood urea nitrogen level, ratio of prothrombin time to a control value, and serum bilirubin level. *DF,* Discriminant function; *GI,* gastrointestinal. Online calculators for these various models are available at www.lillemodel.com. (Modified from Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

NUTRITIONAL SUPPORT

- Good nutrition is an essential part of treatment because many patients with alcoholic hepatitis have severe protein-calorie malnutrition as well as deficiencies of trace minerals and several vitamins.
- Nutritional support includes:
  1. Liberal vitamin supplementation (especially thiamine, folic acid, vitamin K)
  2. Mineral supplementation **(but not iron)**
  3. Calorie counting is essential. A high calorie intake (1.2 to 1.4 times the normal resting intake) may be required.
  4. Protein intake of 1.2 to 1.5 g/kg of ideal body weight per day will provide adequate support. **Exception: In patients with severe encephalopathy, protein restriction may be required.**
  5. Fluid management

PHARMACOLOGIC THERAPY

Severe alcoholic hepatitis may require treatment. Severity can be assessed by calculating the MELD score or MDF score or the Glasgow score.

- An MDF score ≥32 indicates significant or severe alcoholic hepatitis (30-day mortality of 50%).
- MELD score can easily be calculated (visit https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/). This score predicts short-term survival in patients with cirrhosis. A score >20 predicts increased short-term mortality.
- Glasgow score: Contains four variables (BUN, PT, WBC count, and bilirubin). A score ≥9 indicates increased mortality.

Indications for hospitalization include:

- MDF ≥32
- MELD >20
- Glasgow score >8
- Hepatic encephalopathy

Patients with severe alcoholic hepatitis may be treated with glucocorticosteroids (prednisolone 40 mg/day for 28 days with a 2-wk taper). Glucocorticosteroids reduce hepatic injury, suppress inflammation, and promote liver regeneration. However, not all studies have demonstrated consistent therapeutic benefits for steroids, even in high-risk patients. Prednisolone should be discontinued if bilirubin does not decrease by day 17. An alternative agent for patients with contraindications to corticosteroids is pentoxifylline. Pentoxifylline is not effective in patients who do not respond to prednisone, and data supporting its use is weak.

LIVER TRANSPLANTATION

- Usually reserved for patients with end-stage liver disease. Patients whose hepatitis is not responding to medical therapy have a 6-month survival rate of approximately 30%. Since most hepatitis deaths occur within 2 months, early liver transplantation is attractive and associated with higher than 80% survival at 3 yr.
- Patients with alcoholic hepatitis must be sober for at least 6 mo before they can be eligible for consideration for liver transplantation. However, transplantation candidates should not be based solely on 6 mo abstinence, and other factors, such as social support and need for rehabilitation, should be considered.

REFERRAL

Severe acute alcoholic hepatitis may require intensive care unit (ICU) care and referral to different subspecialists:

- GI/hepatology (for patients with evidence of GI hemorrhage)
- Nutritional services
- Nephrology (for acute renal failure, hepatorenal syndrome)
- Neurology (for change in mental status, seizures)
- Infectious disease (for fever/leukocytosis)

PEARLS & CONSIDERATIONS

COMMENTS

- Referral to substance abuse treatment programs may be helpful.
  1. Stress to patients that there are limited long-term drug treatments for alcoholic hepatitis.
  2. Maintaining good general nutrition is important.
  3. Advise patient about the risk of taking certain medications, especially acetaminophen.
- Periodic follow-up to monitor patient's response to check basic metabolic panel (BMP) and liver function tests (LFTs).
- Encourage alcohol abstinence. Abstinence improves long-term survival.
- If patient develops liver cirrhosis, check serum alpha-fetoprotein every 6 mo and liver ultrasound annually to rule out hepatocellular carcinoma.
- Vaccinate patient against hepatitis A and B viruses, pneumococci, influenza A virus, and routine adult vaccinations, if appropriate.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Alcoholic Hepatitis (Patient Information)

AUTHOR: **Daniel K. Asiedu, MD, PhD, FACP**

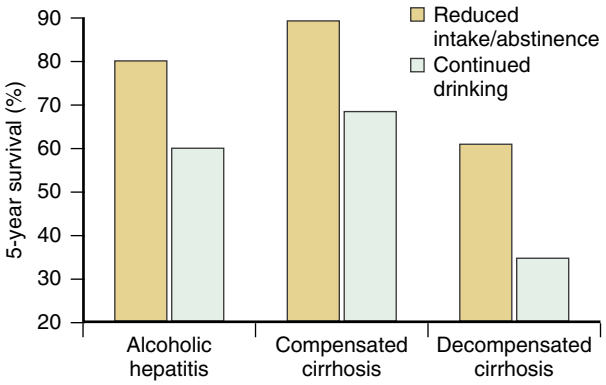

FIG. E2 Effect of subsequent alcohol intake on 5-year survival in patients with alcoholic hepatitis and cirrhosis. (From Day CP: Liver disorder part 1 of 2, *Medicine* 35(1):22-25, 2007.)

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Aldosteronism (Hyperaldosteronism, Primary) PTG

BASIC INFORMATION

DEFINITION

Primary aldosteronism is a group of disorders distinguished by inappropriate, autonomous production of aldosterone resulting in renal sodium retention, plasma renin suppression, and secondary hypertension classically characterized by hypokalemia and metabolic alkalosis.

SYNONYMS

Hyperaldosteronism
Conn syndrome

ICD-10CM CODES

E26.01	Conn syndrome
E26.02	Glucocorticoid-remediable aldosteronism
E26.1	Secondary hyperaldosteronism
E26.9	Hyperaldosteronism, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 5% to 13% of patients with hypertension; 11% to 23% of patients with resistant hypertension

GENETICS: Familial hyperaldosteronism is a subset of inheritable forms of hyperaldosteronism. It should be suspected in patients with any of the following:

- Onset of hypertension before age 21 years and a family history of hypertension
- A family history of primary aldosteronism
  A family history of stroke before age 40 yr

ETIOLOGY

- Bilateral idiopathic adrenal hyperplasia (60% to 70%)
- Unilateral aldosterone-producing adenoma (Conn syndrome) (30% to 40%)
- Unilateral adrenal hyperplasia (~2%)
- Familial hyperaldosteronism (<1%)
- Aldosterone-producing carcinoma (<0.1%)
- Ectopic production of aldosterone (<0.1%)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Generally asymptomatic
- Hypertension: Often resistant hypertension
- Spontaneous hypokalemia
- Family history of early-onset hypertension or cerebrovascular accident <40 yr

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diuretic use
- Hypokalemia from vomiting and/or diarrhea
- Renovascular hypertension
- Other endocrine neoplasm (pheochromocytoma, deoxycorticosterone-producing tumor, renin-secreting tumor)

WORKUP

Primary aldosteronism is characterized by suppressed plasma renin activity (PRA) and an elevated serum aldosterone level, usually exceeding 15 ng/dl. Fig. 1 provides guidance on when to consider testing for primary aldosteronism. Fig. 2 describes a diagnostic approach to patients with suspected primary aldosteronism. CT, MRI, and adrenal vein sampling (AVS) are used to distinguish unilateral from bilateral increased aldosterone secretion. This distinction will dictate treatment options since unilateral primary aldosteronism is treated by surgical resection rather than medically.

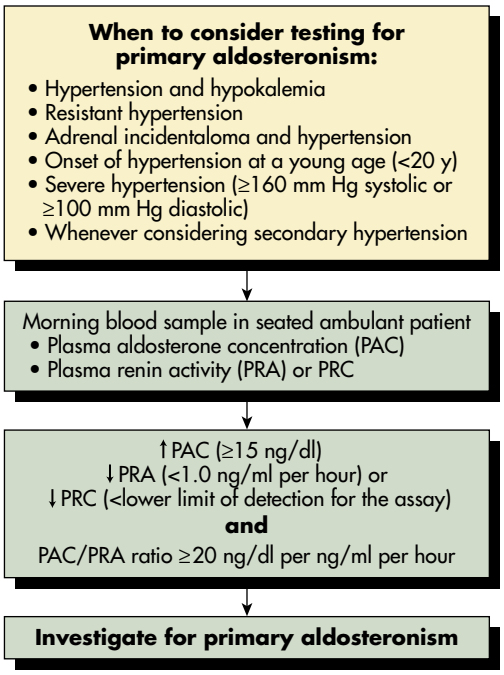

FIG. 1 Algorithm provides guidance on when to consider testing for primary aldosteronism and use of the ratio of plasma aldosterone concentration *(PAC)* to plasma renin activity *(PRA)* as a case-detection tool. *PRC,* Plasma renin concentration. (Melmed S et al (eds): *Williams textbook of endocrinology,* ed 13, Philadelphia, 2016, Elsevier.)

LABORATORY TESTS

Routine laboratory tests can be suggestive but are not diagnostic of primary aldosteronism. Common abnormalities are:

- Spontaneous hypokalemia (9% to 37% of cases) or severe hypokalemia while receiving conventional doses of diuretics
- Possible alkalosis and hypernatremia

IMAGING STUDIES

- Adrenal CT scan (Fig. E3) is preferred as adrenal adenomas have a high lipid content and are better visualized on CT scan.
- MRI may be used as an alternative.

TREATMENT

NONPHARMACOLOGIC THERAPY

Regular blood pressure monitoring, low-sodium diet, tobacco avoidance, maintenance of ideal body weight, and regular exercise

ACUTE GENERAL Rx

- Control of blood pressure and hypokalemia with spironolactone, eplerenone, or amiloride
- Surgery (unilateral adrenalectomy) for aldosterone-producing adenoma (APA) or unilateral adrenal hyperplasia (UAH)

CHRONIC Rx

A mineralocorticoid receptor antagonist, spironolactone (starting dose, 25 mg daily) or eplerenone (starting dose, 25 mg twice daily), is titrated upward until a serum potassium concentration target that is mid- to high-normal is achieved without the aid of potassium supplements. The dose is increased at 2-week intervals. Eplerenone causes less gynecomastia in men and less menstrual irregularities in women because of greater mineralocorticoid receptor selectivity. Amiloride (starting dose, 5 mg twice daily) may be used for patients intolerant of both spironolactone and eplerenone.

DISPOSITION

Treatment of primary aldosteronism with either mineralocorticoid receptor antagonism or unilateral adrenalectomy resolves hypokalemia, reduces blood pressure, and improves parameters of impaired cardiac and renal function.

Hypertension persists in 40% to 65% of patients after unilateral adrenalectomy. Patients more likely to experience complete resolution of hypertension are younger, take 2 or less antihypertensive agents preoperatively, have a short duration of hypertension, lack family history of hypertension, and/or have a higher PAC/PRA ratio.

REFERRAL

Referral to an experienced interventional radiologist for arteriovenous sampling. If lateralization occurs, surgical referral for unilateral adrenalectomy should proceed after confirmation of unilateral APA, UAH, or carcinoma.

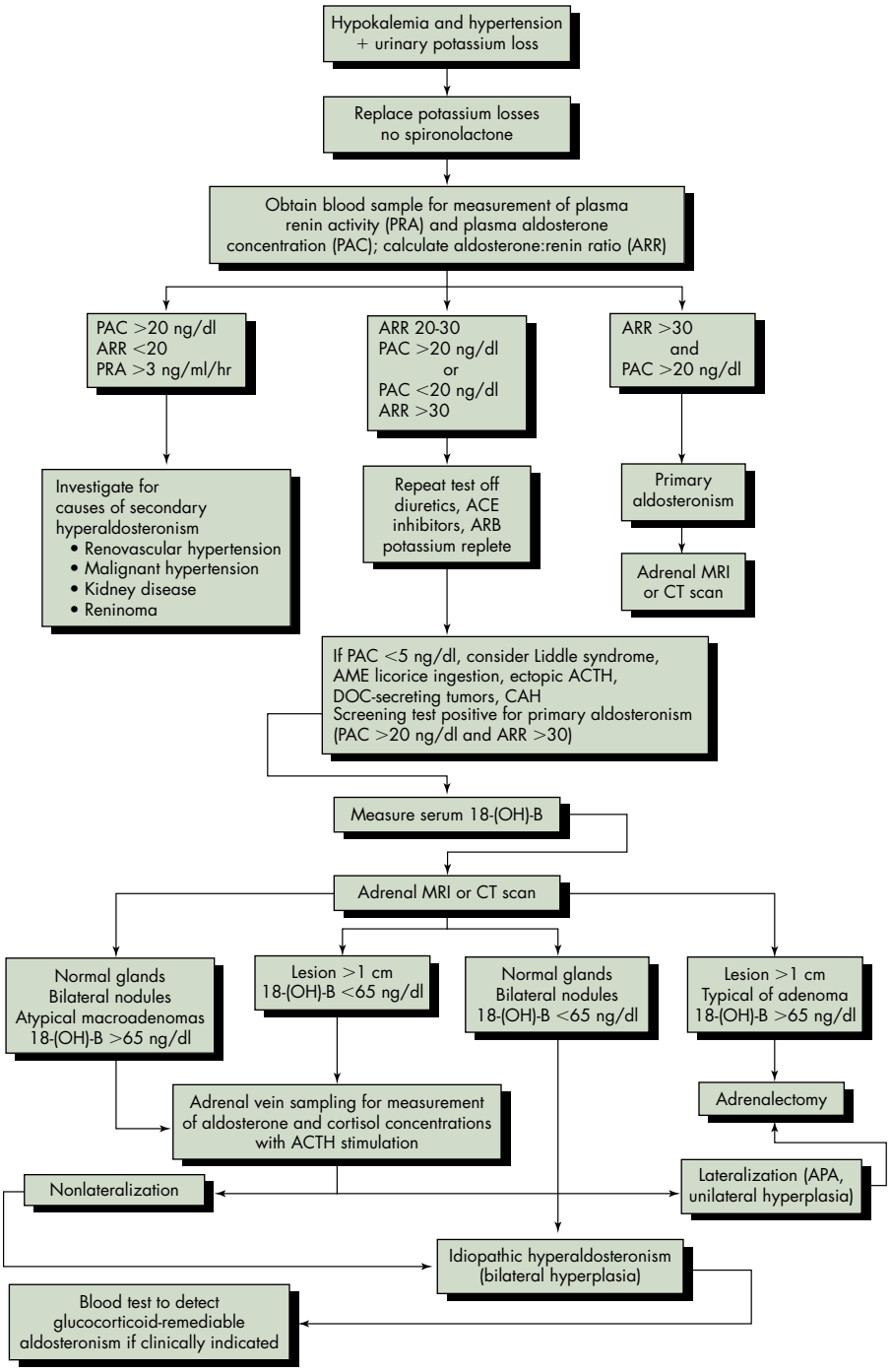

FIG. 2 Diagnostic approach to patients with suspected primary aldosteronism. Cortisol concentration ratio in an adrenal vein four times greater than that in the other adrenal vein and/or an aldosterone/cortisol concentration ratio from the vein of the unaffected adrenal that is less than the ratio in the vena cava. Urinary loss of potassium can be documented by measuring potassium excretion in a 24-hour urine collection; excretion of more than 30 mEq per day in the presence of hypokalemia indicates potassium wasting. An alternative and simpler approach is to obtain a random sample of urine to calculate the fractional excretion of potassium. A fractional excretion exceeding 10% when hypokalemia is present indicates potassium wasting. *AME,* Syndrome of apparent mineralocorticoid excess; *APA,* aldosterone-producing adenoma; *CAH,* congenital adrenal hyperplasia; *CT,* computed tomography; *DOC,* deoxycorticosterone; *ectopic ACTH,* production of corticotrophin by a tumor outside the pituitary gland; *serum 18-(OH)-B,* serum concentration of 18-hydroxycorticosterone. (From Runge MS, Greganti MA: *Netter's internal medicine,* Philadelphia, 2008, Saunders.)

PEARLS & CONSIDERATIONS

- Primary aldosteronism is more common than previously thought and should be considered in all patients with apparent resistant hypertension.
- There is more rapid decline in eGFR, increased LV mass, and increased relative risk of stroke, myocardial infarction, and atrial fibrillation in patients with primary aldosteronism than in patients with essential hypertension matched for age, gender, and blood pressure. Increased risk is attenuated but persists even when treated with a mineralocorticoid antagonist. Adrenalectomy decreases these risks to below that of the matched essential hypertension cohort.
- Frequent monitoring of blood pressure and electrolytes after adrenalectomy is necessary because normalization of blood pressure after unilateral adrenalectomy may take up to 4 months.
- Caution must be taken during interpretation of direct renin concentration (DRC) and PRA testing results because of different units used for each assay. The aldosterone-to-DRC ratio is yet to be as widely validated as the aldosterone-to-PRA ratio.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Aldosteronism (Hyperaldosteronism, Primary) (Patient Information)
Hypertension (Related Key Topic)

AUTHORS: **Kevin Fay, MD,** and **Debbie L. Cohen, MD**

SUGGESTED READINGS

Brown JM et al: The spectrum of subclinical primary aldosteronism and incident hypertension, *Ann Int Med* 167:630-641, 2017.

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Vilela LAP, Almeida MQ: Diagnosis and management of primary aldosteronism, *Arch Endocrinol Metab* 61(3):305-312, 2017.

FIG. E3 Aldosterone-secreting adenoma. A tiny left adrenal nodule *(arrow)* was identified as a benign aldosterone-secreting adenoma by adrenal vein sampling and surgical resection. (From Webb WR, Brant WE, Major NM: *Fundamentals of body CT,* ed 4, Philadelphia, 2015, Saunders.)

Allergic Rhinitis PTG

BASIC INFORMATION

DEFINITION

Allergic rhinitis is an immunoglobulin E (IgE)-mediated hypersensitivity response to nasally inhaled allergens that involves mucosal inflammation driven by type 2 helper T (Th2) cells that causes sneezing, rhinorrhea, nasal pruritus, and congestion. It may be seasonal or perennial.

SYNONYMS

Hay fever
IgE-mediated rhinitis
Seasonal allergic rhinitis
SAR

ICD-10CM CODES
J30.1 Allergic rhinitis due to pollen
J30.2 Other seasonal allergic rhinitis
J30.3 Other allergic rhinitis
J30.4 Allergic rhinitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Allergic rhinitis affects approximately 10% to 20% of the U.S. population and 40% of children.
- Mean age of onset is 8 to 12 yrs.
- The prevalence of allergic rhinitis in patients presenting to their primary care provider with nasal symptoms is estimated to be 30% to 60%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pale or violaceous mucosa of the turbinates caused by venous engorgement (this can distinguish it from erythema present in viral rhinitis)
- Nasal polyps
- Lymphoid hyperplasia in the posterior oropharynx with cobblestone appearance
- Erythema of the throat, conjunctival and scleral injection
- Clear nasal discharge
- Clinical presentation: Usually consists of sneezing, nasal congestion, cough, postnasal drip, loss of or alteration of smell, and sensation of plugged ears

ETIOLOGY

- Pollens in the springtime, ragweed in fall, grasses in the summer
- Dust, mites, animal allergens
- Smoke or any irritants
- Perfumes, detergents, soaps
- Emotion, changes in atmospheric pressure or temperature

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infections (sinusitis; viral, bacterial, or fungal rhinitis)
- Rhinitis medicamentosa (cocaine, sympathomimetic nasal drops)
- Vasomotor rhinitis (e.g., secondary to air pollutants)
- Septal obstruction (e.g., deviated septum), nasal polyps, nasal neoplasms
- Systemic diseases (e.g., Wegener granulomatosis, hypothyroidism [rare])

WORKUP

- The initial strategy should be to determine whether patients should undergo diagnostic testing or receive empirical treatment.
- Workup is often unnecessary if the diagnosis is apparent. A detailed medical history is useful in identifying the culprit allergen.
- Selected patients with allergic rhinitis that is not controlled with standard therapy may benefit from allergy testing to target allergen avoidance measures or guide immunotherapy. Allergy testing can be performed using skin testing or radioallergosorbent (RAST) testing. Immunoglobulin E (IgE) testing using newest-generation assays is also an excellent tool for diagnosing the cause of symptoms related to rhinitis. Allergy testing with skin or blood testing is most useful as confirmatory tests when the patient's history is compatible with an IgE-mediated reaction and should generally be reserved for ambiguous or complicated cases.
- Examination of nasal smears for the presence of neutrophils to rule out infectious causes and the presence of eosinophils (suggestive of allergy) may be useful in selected patients.
- Peripheral blood eosinophil counts are not useful in allergy diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Maintain allergen-free environment by covering mattresses and pillows with allergen-proof casings, eliminating carpeting, eliminating animal products, and removing dust-collecting fixtures.
- Use of air purifiers and dust filters is helpful.
- Maintain humidity in the environment below 50% to prevent dust mites and mold.
- Use air conditioners, especially in the bedroom.
- Remove pets from homes of patients with suspected sensitivity to animal allergens.
- Use of acupuncture to treat seasonal allergic rhinitis is controversial. A recent trial showed that acupuncture led to statistically significant improvement in disease-specific quality of life and antihistamine use measures after 8 weeks of treatment compared with sham acupuncture and with rescue medication alone.
- Nasal saline sprays are effective in relieving nasal dryness and congestion. Nasal irrigations can be administered via neti pot or bulb syringes or with premade saline solutions available OTC.

ACUTE GENERAL Rx

- Determine if the patient is troubled by swollen turbinates (best treated with decongestants) or blockages secondary to mucus (effectively treated by antihistamines).
- Topical nasal steroids are very effective and are preferred by many as first-line treatment for allergic rhinitis in persons 12 and older. Patients should be instructed on proper use and informed that improvement might not occur for at least 1 wk after initiation of therapy. Commonly available inhalers follow.
  1. Beclomethasone dipropionate: One to two sprays in each nostril bid
  2. Fluticasone: Initially two sprays in each nostril qd or one spray in each nostril bid, decreasing to one spray in each nostril qd based on response
  3. Flunisolide: Initially two sprays in each nostril bid
  4. Budesonide: Two sprays in each nostril bid or four sprays in each nostril qam
  5. For treatment of moderate to severe seasonal allergic rhinitis in persons age 12 or older, the best initial treatment is a combination of intranasal corticosteroid and an intranasal antihistamine. Intranasal decongestants can cause dryness, burning, and stinging of the nose and throat. They can also cause rebound nasal congestion if used as monotherapy >5 consecutive days.
  6. Azelastine is an antihistamine nasal spray effective for seasonal allergic rhinitis. Olopatadine is an intranasal H1-antihistamine alternative to azelastine in mild to moderate seasonal allergic rhinitis.
- Most oral first-generation antihistamines can cause considerable sedation and anticholinergic symptoms. The second-generation antihistamines (loratadine, fexofenadine, cetirizine, levocetirizine, desloratadine) are preferred because they do not have any significant anticholinergic or sedative effects.
- Montelukast, a leukotriene receptor antagonist commonly used for asthma, is also effective for allergic rhinitis. Usual adult dose is 10 mg qd.
- Oral decongestants such as pseudoephedrine are often used in combination with an oral H1-antihistamine for treatment of allergic rhinitis.

CHRONIC Rx

- Cromolyn sodium: One spray to each nostril three to four times daily can be used for prophylaxis (mast cell stabilizer). It should be started 2 weeks before exposure to an allergen and is typically used 3 to 4 times/day.
- Immunotherapy is generally reserved for patients responding poorly to the above treatments. Traditionally, immunotherapy consisted of subcutaneous injections of gradually increased doses of allergens. The FDA has approved several allergen extracts (Oralair, Grastek, Ragwitek, Odactra) for sublingual administration as immunotherapy.

DISPOSITION

Most patients experience significant relief with avoidance of allergens and proper use of medications.

REFERRAL

Allergy testing in patients with severe symptoms who are unresponsive to therapy or when the diagnosis is uncertain

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Allergic Rhinitis (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Brinkhaus B et al: Acupuncture in patients with seasonal allergic rhinitis, *Ann Intern Med* 158(225):234, 2013.

Wallace DV: Pharmacological treatment of seasonal allergic rhinitis: synopsis of guidance from the 2017 joint force on practice parameters, *Ann Intern Med* 167:876-881, 2017.

Wheatley LM, Togias A: Allergic rhinitis, *N Engl J Med* 372:456-463, 2015.

BASIC INFORMATION

DEFINITION

Alopecia is the term used to describe involuntary hair loss, typically on the scalp but can occur anywhere over the body. *Nonscarring alopecia* is hair loss without clinically apparent scarring, inflammation, or skin atrophy. *Scarring alopecia* is characterized by permanent hair loss accompanied by tissue destruction in the form of scarring, inflammation, and/or skin atrophy.

SYNONYMS

Hair loss
Balding

ICD-10CM CODES

L63	Alopecia aerata
L63.0	Alopecia (capitis) totalis
L64	Androgenic alopecia
L64.0	Drug-induced androgenic alopecia
L64.8	Other androgenic alopecia
L64.9	Androgenic alopecia, unspecified
L65	Other nonscarring hair loss
L66	Cicatricial alopecia
L65.9	Nonscarring hair loss, unspecified
L63.8	Other alopecia areata
L65.0	Telogen effluvium

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Depends on etiology, for example:

- Alopecia areata affects 1% of the U.S. population by age 50 yr. There is a higher incidence at a younger age and both sexes are affected equally.
- Androgenetic alopecia affects males > females with 50% of Caucasian men affected by age 50 yr. Less common in Asians and African-American men, and often has later onset. By age 70, 40% of females are affected, with incidence increasing after menopause.

GENETICS: Depends on etiology, for example:

- Androgenetic alopecia is polygenic with variable penetrance and can be inherited from one or both parents.
- Certain scarring alopecias are more predominant in people with coarser hair.

ETIOLOGY

NONSCARRING:

- Failure of follicle production
- Hair shaft abnormality
- Pattern hair loss, i.e., androgenetic alopecia
- Hair breakage, i.e., trichotillomania, traction alopecia, cosmetic overprocessing
- Problem with cycling (excess shedding), i.e., telogen effluvium, anagen effluvium, loose chemotherapy anagen syndrome, alopecia areata, syphilis

SCARRING:

- Infectious: Tinea capitis with inflammation (kerion), bacterial folliculitis as in dissecting folliculitis and folliculitis decalvans
- Neoplasm: Alopecia mucinosa in cutaneous T-cell lymphoma or alopecia neoplastica due to metastatic carcinoma (breast cancer)
- Autoimmune: Chronic cutaneous lupus erythematosus
- Congenital

CLINICAL FEATURES

HISTORY: A careful history must be taken and should include time course for hair loss, the pattern of hair loss, any recent change in life situation/stresses, any associated medical conditions, new medications, any family history of hair loss, diet, hair care practices, and other skin/nail symptoms.

PHYSICAL EXAMINATION:

- General: Patient's emotional response to hair loss
- Hair/skin:
  1. Hair thinning/loss
  2. May have fine downy hairs also referred to as vellus hairs
  3. Skin may show changes consistent with inflammation, infection, and/or atrophy
  4. Women may show virilization (e.g., hirsutism)
  5. Exclamation-point hairs can be seen in alopecia areata
  6. Broken hairs of different length may be seen in traumatic alopecia
  7. Hairs that crack or crumble with palpation most often signify shaft damage due to overprocessing

DIAGNOSIS

WORKUP

- Pull test: No shower for 24 hr, 60 hairs are gently pulled from the scalp, removal of 6 or more hairs is considered positive result and indicates telogen effluvium (active shedding). Look for telogen bulbs on recovered hairs to differentiate from breaking (blunt ends).
- Punch biopsy: Mandatory when suspecting scarring alopecia. Send two punches: one for vertical and one for horizontal sectioning for histopathologic analysis, preferably by a dermatopathologist.
- Trichogram: Quantifies hair loss. Pull 25 to 50 hairs and measure proportion of anagen to catagen and telogen hairs under light microscopy: 10% to 20% telogen hairs is normal, whereas >35% is highly suspicious for telogen effluvium.
- Fig. E1 describes the evaluation and treatment of alopecia in females.

LABORATORY TESTS

Initiate laboratory studies if not clear based on clinical presentation:

- CBC: Rule out Fe deficiency
- Total Fe/ferritin: Rule out subclinical Fe deficiency
- TSH: Rule out underlying thyroid disease
- ANA: Screen for autoimmune disease
- RPR: Rule out cutaneous syphilis if history suggestive of increased risk

DIFFERENTIAL DIAGNOSIS

NONSCARRING:

- *Telogen effluvium:* This type of alopecia is usually diffuse thinning that follows significant life stress (death of loved one, high fever, severe infection, crash dieting) or change in hormones (postpartum, change in or cessation of oral contraceptives). Patient often presents with a bag of hair that has fallen out. This is caused by a large number of anagen (growing) hairs entering telogen (dying phase) simultaneously. Telogen effluvium is more common in women.
- *Androgenetic alopecia:* Gradual thinning of hair and a trend toward finer hair, which in men has a typical pattern of receding anterior bitemporal hairline resulting in an M-shaped pattern and hair loss at the vertex (Fig. E2) and in women has a typical pattern of thinning along vertex with or without frontotemporal thinning. This type of thinning is due to a combination of genetic predisposition and androgenic conversion of hair follicles into vellus-like follicles. Widening of the central hair part is often seen, leading to scalp visibility (Fig. E3). This female pattern of more diffuse hair loss is seen in 20% to 30% of adolescent males.
- *Alopecia areata:* Patches of acute hair loss (Fig. E4), typically 2 to 5 cm in diameter, with normal-appearing skin, black dots (cadaver hairs, point noir) from hair that breaks before reaching the skin's surface, and occasional "exclamation point hairs," which are evidence of hairs breaking off as they are pushed from the follicle. Fingernails may show fine pitting. On biopsy, lymphocytes surround the hair bulb and resemble a "swarm of bees," evidence of the autoimmune etiology. Patients often have positive family history. AA Universalis (AAU)—generalized loss of body hair AA Totalis (AAT)—complete loss of scalp hair.
- *Tinea:* This type of hair loss is evident in round patches, possibly with scarring, erythema, and lymphadenopathy. This is the most common type of hair loss in children. Diagnosis can be made by scraping the erythematous edge and placing the scraping with KOH under a microscope to check for hyphae. Wood's lamp only fluoresces if tinea is caused by *Microsporum* spp.; however, the most common (in the U.S.) *Trichophyton* spp. does not fluoresce. If a kerion (severe alopecia associated with bogginess) is present, it may cause scarring.
- *Traumatic alopecia (traction alopecia):* This type of hair loss is in a pattern consistent with breaking off of hairs due to traction (hair pulling) (Fig. E5) or chemical or heating agents (hair straightening or permanent). Etiology usually becomes apparent with careful history taking and visualizing the pattern of hair loss. In trichotillomania (Fig. E6), the alopecia area has an irregular shape, scalp excoriations may present, and hairs are broken at different lengths.

SCARRING:

- *Lichen planus:* The hair loss associated with LP is typically associated with scaling and atrophy of pruritic, painful skin underlying the hair loss. This hair loss is more common in middle-aged women. While there are

numerous variations in clinical presentation, the general clinical picture is one of a chronic inflammatory condition of the skin, nails, mucous membranes, and/or hair. The typical skin lesions are flat topped, violaceous lesions with white lines (Wickham striae), while the typical oral lesions are milky white.

- *Chronic cutaneous (discoid) lupus erythematosus:* This type of hair loss frequently is evident in well-demarcated, erythematous plaques in chronically sun-exposed areas of skin. Lesions exhibit hypopigmentations or hyperpigmentations, atrophy, erythema, and scaling. It may be present concurrently with SLE or be the first presenting symptom of SLE, but in most cases it is a purely cutaneous condition.
- *Tinea with kerion:* A kerion represents an exuberant delayed-type hypersensitivity reaction to the tinea capitis, resulting in one (or many) inflamed boggy plaque(s) on the scalp depending on the severity of the infection.

Rx TREATMENT

- *Telogen effluvium:* Stop offending stress/medication and in 3 to 4 months anagen recurs. Hair density should be normalized by 12 months. Multiple medications have been shown to be an inciting factor and one should consider stopping them (these include, but are not limited to, enalapril, colchicine, levodopa, metoprolol, propranolol, oral contraceptives, and lithium). Full regrowth is expected in most cases.
- *Androgenetic alopecia:* For men, the most likely first-line treatment is oral finasteride (type II 5α-reductase inhibitor) which leads to lower levels of dihydrotestosterone. This leads to hair regrowth in about 6 months, but with cessation, hair returns to pattern of loss within 6 to 9 months. Topical minoxidil has shown similar results to finasteride and can be useful in partially restoring lost hair in both men and women. Dutasteride (off-label) has been shown to be superior to finasteride in a randomized trial but requires higher doses than that used for BPH. Discontinuation of minoxidil will result in loss of regrown hair often over several months. Other options include surgical intervention with hair transplantation or hair flaps, camouflaging agents, the use of a hairpiece, or low-level light therapy. In women with elevated androgens, antiandrogens such as spironolactone, flutamide, and cimetidine may be considered.
- *Alopecia areata (AA):* Spontaneous remission occurs in patchy AA, but less commonly in AAT or AAU. Glucocorticoids (GCs) are the mainstay of treatment but have little effect on the long-term outcome of hair loss—topical GC for small patches, intralesional injection of high-potency GC, and even systemic steroids can all be temporarily effective but at the cost of glucocorticoid exposure. Induction of allergic contact dermatitis using short-contact anthralin therapy or squaric acid sensitization can be effective but tends to have significant local discomfort, thereby limiting its use. Photochemotherapy has shown some beneficial outcomes, although there is a high relapse rate after discontinuation.
- *Tinea capitis:* To effectively treat tinea capitis, oral antifungal agents must be used. Griseofulvin is considered the drug of choice in the U.S., and the recommended time course is 6 weeks to several months. Other oral agents to consider include terbinafine, itraconazole, fluconazole, and ketoconazole. If there is a kerion (area of boggy, purulent inflammation underlying the area of hair loss), the patient is at increased risk for scarring alopecia due to bacterial superinfection, and a short course of oral steroids and oral antibiotic must be considered.
- *Traumatic alopecia (traction alopecia):* First priority is stopping inciting activity/agent, ideally leading to gradual resolution of hair loss and hair regrowth.
- *Lichen planus:* Associated hair loss is often permanent; however, for symptomatic control of itching and pain, topical or oral glucocorticoids may be considered.
- *Chronic cutaneous discoid erythematosus:* The best prevention is sun protection, with SPF lotion. Treatment options center around the cautious use of topical or intralesional glucocorticoids. Hydroxychloroquine and retinoids are also used with caution.
- *Chemotherapy-induced alopecia:* Scalp cooling devices may be effective in reducing chemotherapy-induced alopecia. In a recent trial among women with stage I to II breast cancer receiving chemotherapy with taxane, anthracycline, or both, those who underwent scalp cooling were significantly more likely to have less than 50% hair loss after the fourth chemotherapy cycle compared with those who received no scalp cooling.[1]

REFERRAL

Dermatology

PATIENT & FAMILY EDUCATION

Alopecia areata: www.naaf.org

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Alopecia (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

[1] Nangia J et al: Effect of a scalp cooling device on alopecia in women undergoing chemotherapy for breast cancer. The SCALP randomized clinical trial, *JAMA* 317(6):596-605, 2017.

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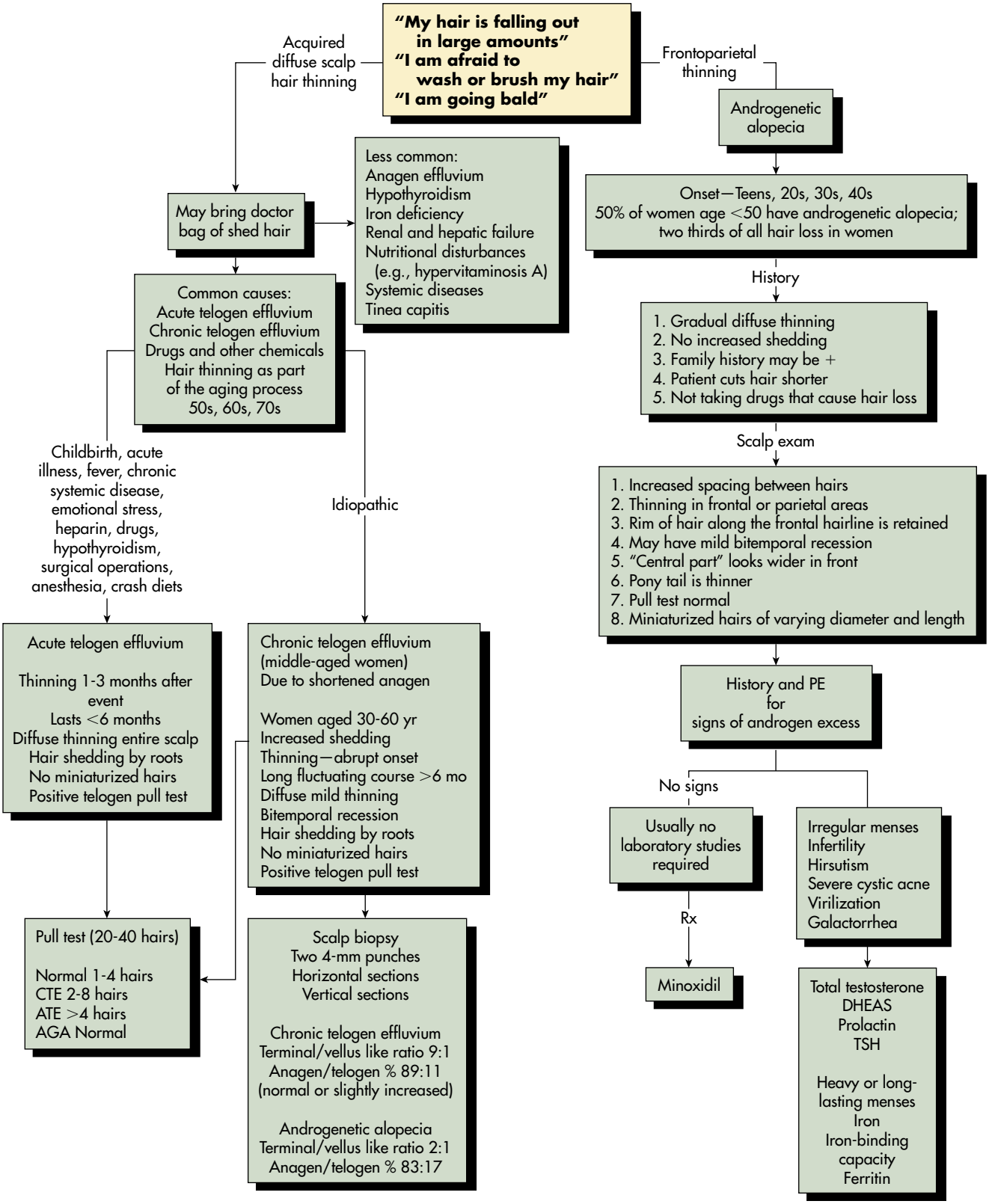

FIG. E1 Evaluation and treatment of alopecia in females. *AGA,* Androgenetic alopecia; *ATE,* acute telogen effluvium; *CTE,* chronic telogen effluvium; *DHEAS,* dehydroepiandrosterone-sulfate; *PE,* physical examination; *TSH,* thyroid-stimulating hormone. (Modified from Habif TA: *Clinical dermatology,* ed 4, St Louis, 2004, Mosby.)

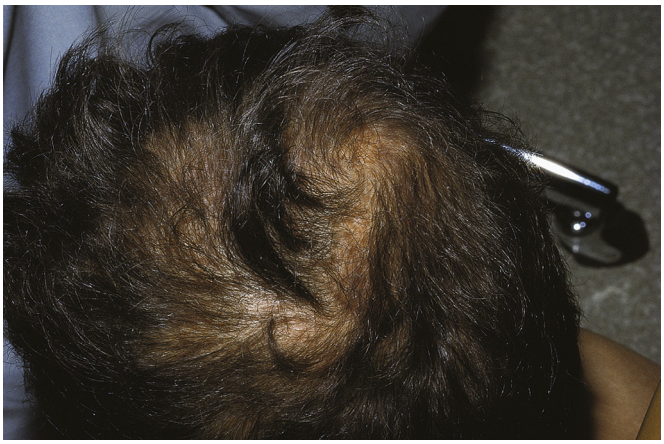

FIG. E2 Androgenetic alopecia. The scalp hair is thinned progressively but most notably between the frontal region of the scalp and the vertex. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E3 Androgenetic alopecia. Widening of the central hair part is often seen, leading to scalp visibility. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E4 Alopecia areata: patchy hair loss. The alopecic area is devoid of hairs, and the scalp does not present inflammatory changes. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

FIG. E5 Traction alopecia. Hair loss can be seen at the margins where hair is pulled most tightly through use of barrettes. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E6 Trichotillomania: patchy hair loss. The alopecic area has an irregular shape and present hairs are broken at different lengths. Also note scalp excoriations. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

Alpha-1-Antitrypsin Deficiency (PTG)

BASIC INFORMATION

DEFINITION

Alpha-1-antitrypsin deficiency (AATD) is a genetic deficiency of the protease inhibitor alpha-1-antitrypsin that results in a predisposition to pulmonary emphysema and hepatic cirrhosis.

SYNONYM

AATD

ICD-10CM CODE
E88.01 Alpha-1-antitrypsin deficiency

EPIDEMIOLOGY & DEMOGRAPHICS

- Underrecognized by clinicians, but accounts for approximately 0.2% to 0.5% of chronic obstructive pulmonary disease (COPD) cases in the U.S.
- Prevalence is about 1 per 2000 to 5000 people in the United States
- Inherited as an autosomal, codominant disorder
- Most frequent mutation is in the *SERPINA 1* gene (previously known as *PI* gene)
- Most common alleles are:
  1. Normal "M" allele (MM phenotype 95% frequency in the U.S.)
  2. Deficient variant "Z" allele (1% to 2%)
  3. Deficient variant "S" allele (2% to 3%)
- Severe deficiency is most commonly due to homozygotes ZZ
- Risk of lung disease is uncertain with MZ genotype, but increased with SZ genotype (especially in smokers)
- One in 10 individuals of European descent carries one of two mutations that may result in partial alpha-1-antitrypsin deficiency

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical findings and clinical presentation are varied and depend on phenotype (see "Etiology").
- Most often affects the lungs but can also involve liver and skin.
- Classically associated with early-onset, severe, lower-lobe predominant panacinar emphysema; bronchiectasis may also be seen.
- Symptoms are similar to "typical" COPD presentation (dyspnea, cough, sputum production).
- Liver involvement includes neonatal cholestasis, cirrhosis in children and adults, and primary carcinoma of the liver.
- Panniculitis is the major dermatologic manifestation (Rare: 1 in 1000 AATD individuals).

ETIOLOGY

- Autosomal recessive genetic disorder.
- Degree of alpha-1-antitrypsin deficiency depends on phenotype.
- "MM" represents the normal genotype and is associated with alpha-1-antitrypsin levels in the normal range.
- Mutation most commonly associated with emphysema is Z, with homozygote (ZZ) resulting in approximately 85% deficit in plasma alpha-1-antitrypsin concentrations.
- Development of emphysema is believed to result from an imbalance between the proteolytic enzyme elastase, produced by neutrophils, and alpha-1-antitrypsin, which normally protects lung elastin by inhibiting elastase.
- Deficiency of alpha-1-antitrypsin increases risk of early-onset emphysema, but not all alpha-1-antitrypsin deficient individuals will develop lung disease.
- Smoking increases risk and accelerates onset of COPD.
- Liver disease is caused by pathologic accumulation of alpha-1-antitrypsin in hepatocytes.
- Similar to lung disease, skin involvement is thought to be attributable to unopposed proteolysis in skin.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

See "Chronic Obstructive Pulmonary Disease."
See "Cirrhosis."

WORKUP

Suspicion for alpha-1-antitrypsin deficiency usually results from emphysema developing at an early age (45 yr old or younger) or emphysema without risk factors (e.g., smoking, dust exposure) and with basilar predominance of disease.

LABORATORY TESTS

- Serum level of alpha-1-antitrypsin can confirm or reject suspicion of deficiency.
- Investigate possibility of abnormal alleles with genotyping.
- Pulmonary function testing is generally consistent with "typical" COPD.

IMAGING STUDIES

- Chest radiograph shows characteristic emphysematous changes at lung bases.
- High-resolution chest computed tomography (CT) usually confirms the basal-predominant emphysema (64%) and may also show significant bronchiectasis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of smoking is of paramount importance.
- Avoidance of other environmental and occupational exposures that may increase risk of COPD. Routine vaccinations are also recommended.

ACUTE GENERAL Rx

Acute exacerbations of COPD from alpha-1-antitrypsin deficiency are treated in a similar fashion to "typical" COPD exacerbations.

CHRONIC Rx

- The goal of treatment in alpha-1-antitrypsin deficiency is to increase serum alpha-1-antitrypsin levels above a minimum, "protective" threshold of 50 mg/dl.
- Although several therapeutic options are under investigation, IV administration of pooled human alpha-1-antitrypsin is currently the only approved method to raise serum alpha-1-antitrypsin levels. Alpha-1-antitrypsin (AAT) augmentation therapy has been approved by the FDA for patients with AAT deficiency who have COPD. Augmentation therapy is expensive and requires lifelong treatment. Supplemental alpha-1-antitrypsin prevents progressive lung injury but does not affect the progression of cirrhosis.
- Organ transplantation for patients with end-stage lung or liver disease is also an option.

DISPOSITION

- Prognosis of patients with alpha-1-antitrypsin deficiency will depend on phenotype and level of deficiency.
- Among patients with severe alpha-1-antitrypsin deficiency, the most common underlying causes of death are respiratory failure (45% to 72%) and cirrhosis (10% to 13%).

REFERRAL

- Referral to specialists with experience in AAT deficiency is preferred
- Pulmonary and hepatology referrals for advanced lung and liver disease, or if replacement therapy is contemplated (e.g., moderate-severe lung disease)
- Lung and liver transplantation in suitable cases

PEARLS & CONSIDERATIONS

- The liver damage arising from the mutation is not from a deficiency in alpha-1-antitrypsin but from a pathologic accumulation of alpha-1-antitrypsin in hepatocytes.
- Strong association between PI*ZZ phenotypes and liver disease has prompted recommendations for AATD testing in individuals with unexplained liver disease.
- Consider alpha-1-antitrypsin deficiency in patients presenting with lower-lobe predominant emphysema; in most smokers without alpha-1-antitrypsin deficiency, emphysema predominates in the upper lobes.
- Alpha-1-antitrypsin deficiency is believed to be under-recognized.
- The American Thoracic Society and the European Respiratory Society recommend testing for AAT deficiency in all symptomatic patients with COPD, emphysema, or asthma with irreversible obstruction, and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) currently suggests, citing from WHO recommendation, that all patients with a diagnosis of COPD to be screened as well because the classic pattern with early-onset COPD (age <45 yrs) with panlobular basal emphysema may not be always observed.

SUGGESTED READINGS

Brode SK et al: Alpha-1-antitrypsin deficiency: a commonly overlooked cause of lung disease, *CMAJ* 184(12), 2012.

Kelly E et al: Alpha-1-antitrypsin deficiency, *Respir Med* 104(6):763-772, 2010.

Marciniuk DD et al: Alpha-1-antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline, *Can Respir J* 19(2):109-116, 2012.

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RELATED CONTENT

Alpha-1-Antitrypsin Deficiency (Patient Information)
Chronic Obstructive Pulmonary Disease (Related Key Topic)
Cirrhosis (Related Key Topic)

AUTHORS: **Taro Minami, MD,** and **Joseph A. Diaz, MD, MPH**

BASIC INFORMATION

DEFINITION

Dementia is a syndrome characterized by progressive loss of previously acquired cognitive skills including memory, language, insight, and judgment. Alzheimer disease (AD) is thought to account for the majority (50% to 75%) of all cases of dementia.

ICD-10CM CODES

G30.0 Alzheimer disease with early onset
G30.1 Alzheimer disease with late onset
G30.8 Other Alzheimer disease
G30.9 Alzheimer disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Risk doubles every 5 yrs after the age of 65; above the age of 85, the annual incidence is about 10%.
PREVALENCE: Currently an estimated 5.4 million Americans have AD; 3% of the population between the ages of 65 and 74, 17% between 75 and 84, and 32% at 85 yr and older.
PREDOMINANT SEX: Female greater than male.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Spouse or other family member, usually not the patient, notes insidious memory impairment.
- Patients have difficulties learning and retaining new information and handling complex tasks (e.g., balancing the checkbook) and have impairments in reasoning, judgment, spatial ability, and orientation (e.g., difficulty driving, getting lost away from home).
- Behavioral changes, such as mood changes and apathy, may accompany memory impairment. In later stages, patients may develop agitation and psychosis.
- Atypical presentations include early and severe behavioral changes, focal findings on examination, parkinsonism, hallucinations, falls, or onset of symptoms younger than the age of 65.

DIAGNOSIS

Diagnosis of AD has evolved with the development of biomarkers that indicate AD pathology *in vivo* such as brain amyloidosis and pathological tau accumulation. Although not yet commonly used in the clinic, the integration of biomarkers into the diagnosis of AD does transform the diagnosis into one that can be established definitively while the patient is still alive. In clinical practice, the diagnosis is commonly made based on clinical history, a thorough physical and neurologic examination, and use of reliable and valid diagnostic criteria (i.e., DSM or NINDCS-ADRDA) such as the following:

- Loss of memory and one or more additional cognitive abilities (aphasia, apraxia, agnosia, or other disturbance in executive functioning)
- Impairment in social or occupational functioning that represents a decline from a previous level of functioning and results in significant disability
- Deficits that do not occur exclusively during the course of delirium
- Insidious onset and gradual progression of symptoms
- Cognitive loss documented by neuropsychologic tests
- No physical signs, neuroimaging, or laboratory evidence of other diseases that can cause dementia (i.e., metabolic abnormalities, medication or toxin effects, infection, stroke, Parkinson disease, subdural hematoma, or tumors)

Red flags for an AD diagnosis are summarized in Box 1.

The National Institute on Aging (NIA) and the Alzheimer Association (AA) recommended new diagnostic criteria and guidelines for AD in 2011, and these criteria were further revised in 2018 (Tables 1 and 2). The 100 NIA-AA criteria differed from prior DSM or NINDCS-ADRDA criteria in the following ways: (1) they recommend AD be considered a disease well before the onset of symptoms by incorporating the biomarkers in diagnosis; and (2) they define three distinct stages of AD: (1) *preclinical* AD, in which there is measurable biologic evidence of AD pathology but no symptoms; (2) *mild cognitive impairment* (MCI) due to AD, in which the patient experiences mild memory loss but no functional impairment at home or work plus biomarker evidence of AD; and (3) *dementia* due to AD, in which the patient experiences cognitive decline causing functional impairment plus biomarker evidence of AD. The 2018 NIA-AA criteria define Alzheimer disease not as three clinical syndromes but as a biologic process defined by biomarkers indicating the presence of beta amyloid (A+), pathologic tau (T+), and neurodegeneration or neuronal injury (N+). Using the ATN system and clinical status together allows an entire study population to be characterized (Fig. 1).

DIFFERENTIAL DIAGNOSIS

- Other neurodegenerative dementia (see Table 3): Frontotemporal lobar degeneration dementia with Lewy bodies, corticobasal syndrome, progressive supranuclear palsy
- Cancer (brain tumor, leptomeningeal disease)
- Infection (HIV-associated dementia, neurosyphilis, progressive multifocal leukoencephalopathy [PML])
- Toxic/metabolic (EtOH, hypothyroidism, vitamin B_{12} deficiency, mercury exposure, drug effects)
- Organ failure (dialysis dementia, Wilson disease)
- Vascular disorder (vascular dementia due to multiple strokes, severe small vessel changes, chronic vasculitis, or chronic subdural hematoma)
- Subject memory loss
- Depression (pseudodementia)

WORKUP

HISTORY & GENERAL PHYSICAL EXAMINATION:

- Medication lists should always be reviewed for drugs or home remedies that may cause mental status changes, especially anticholinergic medications, benzodiazepines, opiates, barbiturates, and neuroleptics.
- Patients should be screened for depression, because it can sometimes mimic dementia but also often occurs as a coexisting condition and should be treated.
- On examination, look for signs of metabolic disturbance, presence of psychiatric features, or focal neurologic deficits.

MENTAL STATUS TESTING: Brief mental status testing can be done easily and quickly in the office. Commonly used cognitive tests to detect dementia include the Folstein Mini-Mental State Examination (MMSE), the Mini-Cog test, and the Montreal Cognitive Assessment. The Montreal Cognitive Assessment (MoCA, www.mocatest.org/) is a highly sensitive 30-point test that takes approximately 10 minutes to administer. Cognitive domains tested include visual-spatial, attention, verbal recall, language, abstraction, and orientation. A score of 25 points or less (26 points if the patient has less than 12 yrs of education) indicates cognitive impairment. The test is available in over 35 languages, and multiple forms in English allow for repeated assessments over time. A summary of commonly used tests may be found in Table 4.

Mental status testing should include tests that assess the following cognitive functions:

BOX 1 Red Flags for an Alzheimer Disease Diagnosis

- Age younger than 65 yr
- Fluctuating level of consciousness (consider toxic-metabolic encephalopathy, Lewy body dementia)
- Behavioral, emotional, or personality disturbances overshadowing cognitive impairment (consider frontotemporal dementia, HIV dementia)
- Rapidly (6-12 mo) progressive development (consider Creutzfeldt–Jakob disease, paraneoplastic limbic encephalitis, HIV dementia, frontotemporal dementia)
- Presence of physical abnormalities:
  1. Gait impairment (consider vascular dementia, HIV dementia, NPH)
  2. Lateralized signs, e.g., hemiparesis, spasticity, other corticospinal tract signs (consider vascular dementia)
  3. Movement disorders
  4. Myoclonus (consider Creutzfeldt–Jakob disease, paraneoplastic encephalitis)
  5. Rigidity, bradykinesia (parkinsonism) (consider dementia with Lewy bodies and Parkinson disease)

Modified from Kaufman DM, Geyer HL, Milstein MJ: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.

TABLE 1 New Diagnostic Criteria

Criteria for Probable Alzheimer Disease	DSM-5 2013	Research Criteria NINCDS–ADRDA 2007	 NIA-AA 2011
Insidious onset	X	X	X
Onset over months to yrs		X	X
Progressive decline	X	X	X
Deficits are not explained by delirium or other medical or psychiatric conditions	X	X	X
Social/occupational impairment	X		X
Presence of episodic memory deficit	X	X	
Cognitive deficits in at least two domains	X		X
Neuropsychological testing required for diagnosis?	Preferably	X	Only if routine history and mental status testing are inconclusive
Abnormal PET or MRI scan		Supportive feature*	For research purposes
Genetic markers?	X	Supportive feature*	For research purposes
	Required only if there is evidence of multiple causes and no clear evidence of progression and decline in memory and another cognitive domain		
Abnormal cerebrospinal fluid marker required?		Supportive feature*	For research purposes

DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; *MRI,* magnetic resonance imaging; *NIA-AA,* National Institute on Aging–Alzheimer's Association; *NINCDS-ADRDA,* National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; *PET,* positron emission tomography.
*At least one supportive feature is required for diagnosis of probable AD.
From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

TABLE 2 National Institute on Aging–Alzheimer's Association Criteria for Alzheimer Disease (AD)

I. Core Clinical Criteria

- Interferes with work or usual activities *and*
- Represents a decline from previous level of functioning *and*
- Not explained by delirium of psychiatric disorder.
- Documented cognitive impairment by history taking and objective cognitive assessment (bedside mental status examination or neuropsychological testing).
- A minimum of two of the following domains should be impaired:
  1. Impairment in acquisition and recall of new information (symptoms—repetitive questions and/or conversations, misplaced belongings, forgetting appointments, getting lost)
  2. Impairment in reasoning of complex tasks, poor judgment (symptoms—poor safety assessment, poor financial management, poor decision making, inability to plan complex activities)
  3. Impairment in visuospatial abilities (symptoms—inability to recognizes faces or objects or finding objects in plain view, despite good visual acuity; inability to operate simple tools; inability to orient clothing to the body)
  4. Impaired language functions (speaking, reading, writing; symptoms—difficulty thinking of common words while speaking, hesitation; speech, spelling, writing errors)
  5. Changes in personality, behavior, or comportment (symptoms—uncharacteristic mood fluctuations, e.g., agitation, poor motivation, apathy, social withdrawal, decreased interest in previous activities, loss of empathy, compulsions and/or obsessions, social impairment)

II. Probable AD Dementia (meets core criteria plus the following)

- Insidious onset (gradual over months to yrs)
- Clear history of worsening cognition *and*
- Initial and most prominent cognitive deficits fall into two categories (all must include cognitive dysfunction in at least one other domain).
  1. Amnestic—most common presentation; impairment in learning and recall of recent information
  2. Nonamnestic
     a. Language presentation—most prominent in word finding
     b. Visuospatial presentation—most prominent in spatial cognition (object agnosia, face recognition, simultanagnosia, alexia)
     c. Executive dysfunction—impaired reasoning, judgment, problem solving.
- Should not be applied if substantial cerebrovascular disease or core features of dementia with Lewy bodies (other than dementia) are present; features consistent with behavioral variant of frontotemporal dementia, primary progressive aphasia (semantic, nonfluent, or agrammatic variants), or evidence of other neurologic disease or medical comorbidity that could affect cognition
- Increased certainty if there is documented decline based on subsequent evaluations and in persons who have evidence of causative genetic mutations

III. Probable AD With Evidence of AD Pathophysiologic Process

- High probability of AD pathology if both of the following are present:
  1. β-Amyloid level is low in the cerebrospinal fluid (CSF) or there is a positive positron emission tomography (PET) scan
  2. Neuronal injury is proven with high CSF tau levels, decreased fluorodeoxyglucose-PET uptake in the temporoparietal cortex, or disproportionate atrophy in the mediobasolateral temporal lobe and medial parietal cortex on a structural MRI scan.
- Intermediate probability of AD pathology if only one of the two criteria above are met (and the other is absent or negative)

IV. Possible AD Dementia (meets core clinical criteria but has the following features)

- Atypical course—sudden onset of cognitive impairment, insufficient historical details of objective cognitive decline or progressive decline
- Causally mixed presentation—evidence of cerebrovascular disease; features of dementia with Lewy bodies (other than dementia); evidence of other neurologic disease, medical comorbidity, or pharmaceutical use that could have a substantial effect on cognition

TABLE 2 National Institute on Aging–Alzheimer's Association Criteria for Alzheimer Disease (AD)—cont'd

V. Possible AD with Evidence of AD Pathophysiologic Process

- High probability of AD pathology if both of the following are present:
  1. β-Amyloid level is low in the CSF or there is a positive PET scan
  2. Neuronal injury is proven with high CSF tau levels, decreased fluorodeoxyglucose-PET uptake in the temporoparietal cortex, or disproportionate atrophy in the mediobasolateral temporal lobe and medial parietal cortex on a structural MRI scan
- Uninformative unless the above criteria are met
- May also be a second pathophysiologic condition present to explain why the patient does not meet AD criteria (e.g., concomitant dementia with Lewy bodies)

VI. Pathophysiologically Proven AD Dementia

- Clinical and cognitive criteria for AD are satisfied *and* neuropathologic criteria demonstrate presence of AD pathology

VI. Dementia Unlikely to Be Due to AD

- Does not meet clinical criteria for AD dementia *or*
- Regardless of meeting clinical criteria for probable or possible AD dementia, there is sufficient evidence for an alternative diagnosis (e.g., HIV dementia, Huntington disease).
- Regardless of meeting clinical criteria for possible AD dementia, both β-amyloid and neuronal injury biomarkers are negative.

Adapted from McKhann GM, Knopman DS, Chertkow H: The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, *Alzheimers Dement* 7:263-269, 2011; Albert MS, DeKosky ST, Dickson D: The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, *Alzheimers Dement* 7:270-279, 2011; and Sperling RA, Aisen PS, Beckett LA: Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, *Alzheimers Dement* 7:280-292, 2011.

		Cognitive Stage		
		Cognitively Unimpaired	**Mild Cognitive Impairment**	**Dementia**
Biomarker Profile	$A^-T^-(N)^-$	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
	$A^+T^-(N)^-$	Preclinical Alzheimer pathologic change	Alzheimer pathologic change with MCI	Alzheimer pathologic change with dementia
	$A^+T^+(N)^-$	Preclinical Alzheimer disease	Alzheimer disease with MCI (Prodromal AD)	Alzheimer disease with dementia
	$A^+T^+(N)^+$			
	$A^+T^-(N)^+$	Alzheimer and concomitant suspected non Alzheimer pathologic change, cognitively unimpaired	Alzheimer and concomitant suspected non Alzheimer pathologic change with MCI	Alzheimer and concomitant suspected non Alzheimer pathologic change with dementia
	$A^-T^+(N)^-$	non-Alzheimer pathologic change, cognitively unimpaired	non-Alzheimer pathologic change with MCI	non-Alzheimer pathologic change with dementia
	$A^-T^-(N)^+$			
	$A^-T^+(N)^+$			

FIG. 1 Descriptive nomenclature: Syndromal cognitive staging combined with biomarkers. *AD,* Alzheimer disease; *MCI,* mild cognitive impairment. NOTE: Formatting denotes three general biomarker "categories" based on biomarker profiles: those with normal AD biomarkers (no color), those with non-AD pathologic change (dark gray), and those who are in the Alzheimer continuum (light gray). (From Clifford RJ Jr et al: NIA-AA research framework: toward a biological definition of Alzheimer's disease, *Alzheimer's & Dementia* 14:535-562, 2018.)

TABLE 3 Features Distinguishing Alzheimer Disease and Frontotemporal Dementia

Feature	Alzheimer Disease	Frontotemporal Dementia
Age at onset (yr)	>65	53 (mean)
Memory impairments	Early, pronounced	Subtle, at least initially, with preserved visual-spatial ability
Behavior abnormalities	None until middle or late stage	Early and prominent perseverative and compulsive behavior; hyperorality; impaired executive ability
Language impairment	Except for anomia, none until late stage	Paraphasias, anomia, decreased fluency
CT/MRI appearance	General atrophy, but especially parietal and temporal lobes	Frontal and temporal lobe atrophy
Histologic marker	Aβ accumulation	Tau accumulation

CT, Computed tomography; *MRI,* magnetic resonance imaging.
From Kaufman DM, Geyer HL, Milstein MJ: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.

TABLE 4 Commonly Used Neuropsychological Tests

Domains to Be Assessed	Tests Used with Age-Corrected and/or Education Norms for Adults Older Than 65 Yr
Premorbid ability	• North American Reading Test (NART) • Vocabulary (WAIS-IV)
Verbal memory	• Rey Auditory Verbal Learning Test (RAVLT) • California Verbal Learning Test (CVLT) • Logical Memory Test (from WMS-IV) • CERAD Word List Test
Visual memory	• Visual Reproduction (from WMS-IV) • Rey Complex Figure Drawing Test (RCFT)
Simple attention	• Digit Span (from WAIS-IV) • Trail-Making Part A
Language	• Animal Naming Test (ANT) • Controlled Oral Word Association Test (COWAT) • Boston Naming Test (BNT)
Executive function	• Trail-Making Part B • Wisconsin Card Sort Test (WCST) • Stroop • Similarities (from WAIS-IV)
Visuospatial	• Coding (from WAIS-IV) • Rey Complex Figure Test (RCFT) • Clock Drawing Test
Motor	• Grooved Pegboard Test • Finger Tapping Test
Mood	• Geriatric Depression Scale (GDS) • Hamilton Depression Rating Scale (HDRS) • Beck Anxiety Inventory (BAI)

WAIS-IV, Wechsler Adult Intelligence Scale, fourth edition; *WMS-IV,* Wechsler Memory Scale, fourth edition.
From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

- Orientation: Ask the patient to give the day, date, month, yr, and place and to name the current president.
- Attention: Ask the patient to recite the months of the yr forward and in reverse.
- Verbal recall: Ask the patient to remember three items; test for recall after a 1- and 5-min delay.
- Language: Ask the patient to write and then read a sentence; have the patient name both common and less common objects.
- Visual-spatial: Ask the patient to draw a clock and to set the hands of the clock at 11:10.

Patients with AD typically have trouble with verbal recall plus visuospatial or language deficits. Attention is usually preserved until the later stages of AD, so consider alternate diagnoses in patients who perform poorly on tests of attention. A summary of the pattern of cognitive deficits associated with different dementias and depression may be found in Table 5.

LABORATORY TESTS (TABLE 6)

- CBC
- Serum electrolytes
- Glucose
- BUN/creatinine
- Liver and thyroid function tests
- Serum vitamin B_{12}
- Syphilis serology (RPR), if supported by clinical history
- HIV screening as appropriate
- Lumbar puncture if history or signs of cancer, infectious process, or unusual clinical presentation (e.g., rapid progression of symptoms)
- EEG if there is history of seizures, episodic confusion, rapid clinical decline, or suspicion of Creutzfeldt-Jakob disease
- Apolipoprotein E genotyping, measurement of CSF tau, and amyloid, and functional imaging including positron emission tomography (PET), single-photon emission computed tomography (SPECT), or amyloid PET imaging using florbetapir (Amyvid) are not yet routinely indicated but are used in clinical trials
- Brain biopsy is usually reserved for diagnoses such as prion disease and cerebral vasculitis. Generally performed postmortem

IMAGING STUDIES

- MRI to rule out hydrocephalus, cerebrovascular disease, and mass lesions, including subdural hematoma and to look for typical patterns of atrophy such as hippocampal atrophy. CT can be used if MRI is unobtainable.
- Florbetapir-PET imaging of the brain correlates with the presence and density of beta-amyloid with high sensitivity and specificity of plaque detection, but it is not covered by most payers. Amyloid scans are not part of routine clinical practice but can be considered on a case-by-case basis. PET scans with tracers detecting tau are available as part of research protocols, correlate with the presence of neurofibrillary tangles, but are not yet FDA approved for clinical use.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient safety, including risks associated with impaired driving, wandering behavior, leaving stoves unattended, and accidents, must be addressed with the patient and family early and appropriate measures implemented.
- Wandering, hoarding or hiding objects, repetitive questioning, withdrawal, and social inappropriateness often respond to behavioral therapies.
- Cognitive stimulation programs are beneficial for maintenance of cognitive function and improved self-reported quality of life in patients with mild to moderate Alzheimer disease.

ACUTE GENERAL Rx

None

CHRONIC Rx

- Symptomatic treatment of memory disturbance (Table 7):
  1. Cholinesterase inhibitors (ChEIs): Donepezil (Aricept), galantamine (Razadyne), and rivastigmine (Exelon)
     a. FDA approved for the treatment of mild to moderate AD with the exception of donepezil, which is approved for mild, moderate, and severe dementia. Common side effects include vivid dreams, bradycardia, and gastrointestinal side effects (nausea, diarrhea, and anorexia). Gastrointestinal side effects may be bothersome enough to require either a slower escalation of dosage or switching to another agent. The rivastigmine patch has lower rates of gastrointestinal side effects than the oral agents. Table 8 summarizes some instruments used to monitor clinical response of AD to pharmacologic therapy.

TABLE 5 Patterns of Cognitive Impairment by Domain and Dementia

Episodic Memory	Attention	Language	Executive	Visuospatial		Behavioral Symptoms
Alzheimer disease	(I)	Simple (P) Divided (I)	Phonemic (P) Semantic (I) Naming (I)	(I)	Simple (P) Complex (I)	Early apathy, late psychotic symptoms
Mild cognitive impairment—amnestic	Immediate and Delayed recall (I); Recognition (I)	Simple (P) Divided (P)	(P)	(P)	(P)	(P)
Vascular dementia	Immediate and Delayed recall (V) Recognition (P)	Simple (P) Divided (I)	(I)	(I)	(P)	Depression
Behavioral variant FTLD	(V)	Simple (P) Divided (I)	(I)	(I)	(P)	Disinhibition, apathy, hyperorality, inappropriate social interaction
Semantic variant PPA	(P)	(P)	(I) Comprehension (I) Fluency	(P)	(P) (I) Visual agnosia	(P)
Nonfluent variant PPA	(P)	(P)	(I) Fluency (P) Comprehension, (I) Expressive speech	(P)	(P)	(P)
Parkinson disease dementia	(V) Immediate and Delayed recall (P) recognition	(I)	(P)	(I)	(I)	Depression, possible hallucinations, psychomotor slowing
Dementia with Lewy bodies	(V) Immediate and Delayed recall (P) Recognition	(V)	(V)	(I)	(I)	Hallucinations, delusions
Depression	(V) Immediate and Delayed recall (P) Recognition +	(V)	(V) Fluency (P) Naming	I/V	(P)	Psychomotor slowing, apathy

FTLD, Frontotemporal lobar degeneration; *I,* impaired; *P,* preserved; *PPA,* primary progressive aphasia; *V,* variable.
From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

TABLE 6 Laboratory Evaluation of Patients with Dementia

Type of Study	Examples
Basic studies, excluding reversible with specific indication from history for causes of dementia or examination	• Complete blood count (CBC) • Chemistry or metabolic panel (SM-17) • Thyroid function tests (thyroid-stimulating hormone [TSH]) • Vitamin B_{12}, folate levels • Computed tomography (CT) or magnetic resonance imaging (MRI) • HIV testing • Sedimentation rate • Hemoglobin A1C (Hb A1C) • Urinalysis • Chest x-ray • Urine or plasma for drugs or heavy metals
Adjuvant studies to aid diagnosis	
Other tests as indicated by history or physical or neurologic examination	• Single-photon emission computed tomography (SPECT) • Positron emission tomography (PET) • Lumbar puncture with cerebrospinal fluid for β-amyloid

From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

2. NMDA receptor antagonist: Memantine (Namenda)
   a. FDA approved for the treatment of moderate to severe AD. Common side effects include constipation, dizziness, or headache. Memantine is contraindicated in patients with renal insufficiency or history of seizures.
- Symptomatic treatment of neuropsychiatric and behavioral disturbances (Table 9).
- Depression, agitation, delusions, or hallucinations may respond to medications.

DISPOSITION & REFERRAL

- Patients with complex or atypical presentations or challenging management issues should be referred to a neurologist or another specialist with expertise in dementia.
- Approximately 1 in 8 hospitalized patients with AD who develop delirium will have at least one adverse outcome (e.g., institutionalization, cognitive decline, death) associated with delirium.
- Family education and support may help reduce need for skilled nursing facility and reduce caregiver stress, depression, and burnout.

PEARLS & CONSIDERATIONS

The physician should make a thorough search for the treatable causes of dementia. Current American Academy of Neurology practice parameters recommend:
- Treat cognitive symptoms of AD with ChEIs.
- Treat agitation, psychosis, and depression.
- Encourage caregivers to participate in educational programs and support groups.

TABLE 7 Symptomatic Treatment of Memory Disturbance

	Initial Dose	Target Dose
Donepezil	5 mg qd for 4-6 wk	10 mg qd
Rivastigmine	1.5 mg bid with food, increase by 1.5 mg bid weekly	3-6 mg bid
Galantamine	4 mg bid with food, increase by 4 mg bid every 4 wk	8-12 mg bid
Memantine	5 mg qd, increase by 5 mg weekly	10 mg bid

TABLE 8 Instruments Used to Monitor Clinical Response of Alzheimer Disease (AD) to Pharmacologic Therapy

Mini-Mental State Examination

- Global measure of cognition widely used by physicians and third-party caregivers
- Assesses orientation, registration, recall, language, and attention
- Uses a 30-point scale
- Requires ≈5-10 min to complete
- Sensitivity, 80% to 90%; specificity, 80%
- Administered by psychometricians, nurses, and physicians
- AD typically advances by 3 points/yr

Clock Drawing

- Global measure of cognition widely used by physicians
- Multiple scoring systems with proven validity; sensitivity, 59%; specificity, 90%
- Assesses multiple cognitive domains in a single test
- 1-2 min to complete
- Minimal training to administer

Geriatric Depression Scale

- Evaluates depressive symptoms in patients
- Requires 5 min to complete
- Very useful in assessing depression in new patients and in follow-up
- Minimal training to administer
- Ease of administration has led to rapid spread in its use.

From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

TABLE 9 Treatment of Behavioral and Neuropsychiatric Symptoms

	Initial Dose	Maximum Dose
Atypical Antipsychotics		
Olanzapine	2.5 mg qd to bid, may increase by 2.5 mg as needed	7.5 mg bid
Quetiapine	25 mg bid, may increase by 25 mg every 2 days	250 mg tid
Antidepressants		
Sertraline	25-50 mg qd, may increase by 25 mg every wk	200 mg qd
Escitalopram	10 mg qd, may increase after 1 wk to 20 mg qd	10 mg qd

COMMENTS

- Ginkgo biloba is marketed widely as effective in delaying cognitive impairment; however, trials have shown that it is not effective in reducing the incidence of Alzheimer dementia or dementia overall.
- Higher midlife fitness levels seem to be associated with lower hazards of developing all-cause dementia later in life independent of cerebrovascular disease. Exercise also may slow the rate of functional deterioration in mild AD.
- Even moderate adherence to the MIND (the Mediterranean-DASH Intervention for Neurodegenerative Delay) diet, a hybrid of the Mediterranean and DASH diets specifically designed to optimize brain health, has been shown to reduce the incidence of AD.
- Antipsychotics should be used with extreme caution in treating dementia-related psychosis. All antipsychotics carry a warning from the FDA stating that the medication is not approved for dementia-related psychosis because elderly patients on either conventional or atypical antipsychotics experience an increased risk of death due to cardiovascular or infectious causes.
- Lower plasma beta-amyloid 42/40 is associated with greater cognitive decline among elderly persons without dementia over 9 yr, and this association is stronger among those with low measures of cognitive reserve.
- Apolipoprotein E (APOE) is the main cholesterol-carrying molecule in the brain, and it exists in three allelic variants: E2, E3, and E4. The E3 allele is most common and has a neutral influence on developing AD, whereas the E2 allele, the rarest allele, may be protective against AD. The E4 alleles are well-established heterozygotes at approximately 3 times AD risk factor. However, neither E4 heterozygosity or homozygosity is required or sufficient to cause AD. Among Caucasians, E4 heterozygosity increases the risk of developing AD approximately threefold, whereas E4 homozygosity increases AD risk by approximately 15 times compared to the E3/E3 baseline. The APOE E4 allele is also associated with an earlier age of onset of AD. Because the benefits of genetic testing are often modest, and the tests themselves are often imprecise in identifying risk, the test is generally discouraged. Recent trials, however, reveal that the disclosure of *APOE* genotyping results to adult children of patients with AD did not result in significant short-term psychological risks. Test-related distress was reduced among those who learned that they were *APOE4* negative. Persons with high levels of emotional distress before undergoing genetic testing are more likely to have emotional difficulties after disclosure.

For additional information for patients, families, and clinicians, contact the following organizations:

- Alzheimer's Association (www.alz.org; 800-272-3900)
- Alzheimer's Disease Education and Referral Center (www.nia.nih.gov/Alzheimers; 800-438-4380)

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Alzheimer Disease (Patient Information)
Dementia with Lewy Bodies (Related Key Topic)
Frontotemporal Dementia (Related Key Topic)
Mild Cognitive Impairment (Related Key Topic)

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BASIC INFORMATION

DEFINITION

Amaurosis fugax is a temporary loss of monocular vision caused by transient retinal ischemia.

ICD-10CM CODE
G45.3 Amaurosis fugax

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): An uncommon but important presentation of carotid artery disease
PEAK INCIDENCE: Approximately 55 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Onset is sudden, typically lasting seconds to minutes, and often accompanied by scotomas such as a shade or curtain being pulled over the front of the eye (usually downward).
- Vision loss can be complete, hemianopic, or quadrantic.
- Acute stage: Cholesterol emboli may be seen in retinal artery (*Hollenhorst plaque*).

ETIOLOGY

- Usually embolic from either the internal carotid artery or the heart
- Cardiac embolus most commonly due to atrial fibrillation
- Internal carotid artery embolus will be apparent as carotid stenosis on carotid imaging such as CT angiography, MR angiography, or carotid ultrasound
- Giant cell arteritis causing inflammation of retinal arteries
- Hyperviscosity syndromes, such as sickle cell disease, which causes ischemia in the vascular territory of the ophthalmic artery
- Hypercoagulable states
- Reversible cerebral vasoconstriction syndrome

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Retinal migraine: In contrast to amaurosis, the onset of visual loss develops more slowly, usually over 15 to 20 min.
- Transient visual obscurations occur in the setting of papilledema; intermittent rises in intracranial pressure briefly compromise optic disc perfusion and cause transient visual loss lasting 1 to 2 seconds. The episodes may be binocular. If the visual loss persists at the time of evaluation (i.e., vision has not yet recovered), then the differential diagnosis should be broadened to include:
  1. Anterior ischemic optic neuropathy: Arteritic (classically giant cell arteritis [GCA]) or nonarteritic
  2. Central retinal vein occlusion

WORKUP

- Workup should focus on embolic sources, but GCA should always be considered.
- Careful examination of retina; embolus may be visible and confirm the diagnosis (Fig. 1).
- Auscultation of arteries for carotid bruits.
- Examination of all pulses and for temporal artery tenderness.
- Inquire about symptoms of GCA (scalp tenderness, headache, fever, jaw claudication).
- Examine for signs of hemispheric stroke resulting from intracranial atherosclerosis (contralateral limb and facial weakness or sensory loss, aphasia, etc.).

LABORATORY TESTS

- Complete blood count with erythrocyte sedimentation rate and C-reactive protein.
- Serum chemistries, including lipid profile.
- Cardiac enzymes and ECG.
- Hypercoagulable workup is discretionary based on younger age and history.

IMAGING STUDIES

- CT or MR angiography of head and neck preferred to examine carotid and intracranial vasculature. Carotid ultrasound if contraindication to MR or CT angiography
- MRI of the brain with diffusion-weighted imaging to look for infarcts, especially those presenting with focal neurologic disturbances
- Transthoracic echocardiography is indicated to screen for sources of emboli in patients with evidence of heart disease and in patients without an evident source for transient neurologic deficit. Transesophageal echocardiography is more sensitive for detecting cardiac sources of emboli (ventricular mural thrombus, atrial appendage, patent foramen ovale, aortic arch)
- Extended monitoring for atrial fibrillation if neither carotid stenosis nor giant cell arteritis is found to be the etiology

TREATMENT

NONPHARMACOLOGIC THERAPY

- Diet (decrease saturated fatty acids and high-cholesterol foods)
- Exercise
- Cessation of tobacco use

FIG. 1 A cholesterol crystal embolus lodged at an arterial bifurcation. (From Stein JH [ed]: *Internal medicine,* ed 5, St Louis, 1998, Mosby.)

ACUTE GENERAL Rx

- Investigate as an emergency
- Aspirin
- If GCA is suspected, start prednisone and refer for temporal artery biopsy within 48 hr (see "Giant Cell Arteritis" in Section I)

CHRONIC Rx

- Reduce risks by carotid endarterectomy if stenosis >50%. Carotid stenting may be performed in high-risk surgical candidates.
- Manage vascular risk factors such as hypertension, hyperlipidemia (statin therapy), diabetes, smoking cessation, etc.
- Antiplatelet therapy due to arterial atherosclerosis and postcarotid intervention; anticoagulation if etiology is atrial fibrillation.

DISPOSITION

Among patients with >50% carotid stenosis who do not undergo carotid endarterectomy, those who present with transient monocular blindness have an approximate 10% risk of stroke within 3 yr compared with an approximate 20% risk in patients who present with a hemispheric transient ischemic attack (TIA).

REFERRAL

- As with any TIA, emergent inpatient workup in a hospital that is a certified stroke center, if possible.
- If significant carotid stenosis, consider either carotid endarterectomy or carotid stenting for the following:
  1. Ipsilateral high-grade (≥70%) stenosis, but consider for ipsilateral stenosis of 50% to 69%
  2. Multiple TIAs despite medical therapy in the setting of high-grade or ulcerative disease

PEARLS & CONSIDERATIONS

- Cholesterol emboli in retinal arteries on fundoscopy confirm the diagnosis.
- Recognize that transient visual loss has multiple other causes.
- Refer to emergent evaluation like any other transient ischemic attack.

RELATED CONTENT

Amaurosis Fugax (Patient Information)
Carotid Artery Stenosis (Related Key Topic)
Giant Cell Arteritis (Related Key Topic)
Transient Ischemic Attack (Related Key Topic)

AUTHORS: **Joseph S. Kass, MD, JD, FAAN** and **Tzu-Ching (Teddy) Wu, MD, MPH**

BASIC INFORMATION

DEFINITION

Amblyopia refers to decreased vision in one or both eyes as a result of insufficient stimulation of the developing visual system. The most common etiologies of amblyopia are ocular misalignment (strabismus) and unequal refractive error (anisometropia). Less commonly, amblyopia results from bilateral high refractive error (ametropic) or blockage of the ocular media (deprivation).

SYNONYMS

Deprivation amblyopia (formerly amblyopia ex anopsia)
Occlusion amblyopia
Strabismic amblyopia
Refractive amblyopia
Lazy eye

ICD-10CM CODES

H53.009	Unspecified amblyopia, unspecified eye
H53.001	Unspecified amblyopia, right eye
H53.002	Unspecified amblyopia, left eye
H53.009	Unspecified amblyopia, unspecified eye
H53.019	Deprivation amblyopia, unspecified eye
H53.011	Deprivation amblyopia, right eye
H53.012	Deprivation amblyopia, left eye
H53.013	Deprivation amblyopia, bilateral
H53.029	Refractive amblyopia, unspecified eye
H53.021	Refractive amblyopia, right eye
H53.022	Refractive amblyopia, left eye
H53.023	Refractive amblyopia, bilateral
H53.039	Strabismic amblyopia, unspecified eye
H53.031	Strabismic amblyopia, right eye
H53.032	Strabismic amblyopia, left eye
H53.033	Strabismic amblyopia, bilateral

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 1% to 5% of the general population. Amblyopia is the leading cause of vision loss in children. It is also the cause of permanent vision loss in approximately 2.9% of adults.
PREVALENCE (IN U.S.): High incidence in premature infants with drug-dependent mothers and in neurologically impaired children. Children with a family history of strabismus, amblyopia, or high refractive errors are at increased risk.
PREDOMINANT SEX: None
PREDOMINANT AGE: Childhood
PEAK INCIDENCE: Childhood

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Decreased vision using best refraction in the presence of normal retinal and optic nerve appearance (Fig. E1).

ETIOLOGY

- Refractive errors
- Strabismus
- Visual deprivation from congenital cataract, corneal opacities, ptosis or nystagmus
- Occlusion from patching (rare)
- Malnutrition or vitamin deficiency

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Central nervous system (CNS) disease (i.e., cortical visual impairment)
- Optic nerve disorders
- Corneal or other eye diseases
- Retinal disorders
- Malingering or secondary gain (i.e., desire for glasses in children—more commonly girls)

WORKUP

- Complete eye examination to find the cause of decreased vision. Referral to an ophthalmologist is recommended for any child with a visual acuity in either eye of ≤20/40 or a two-line difference in acuity between the eyes, or for a preverbal or nonverbal child who fails a photoscreening test.
- Ocular motility evaluation.

LABORATORY TESTS

Usually none

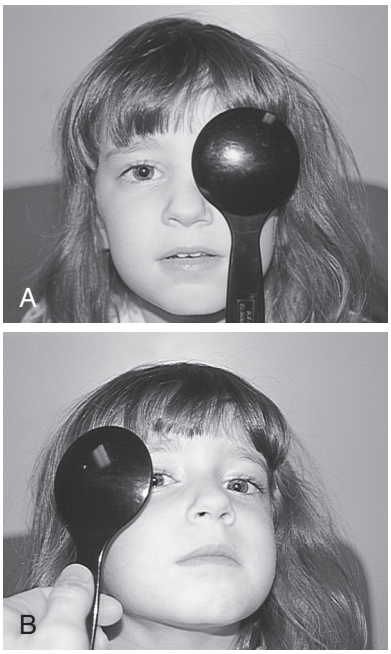

FIG. E1 A, This child happily fixes with her right eye and does not object if the left eye is covered. **B,** When the right eye is covered, she moves her head away and tries to remove the cover, demonstrating a fixation preference for the right eye and amblyopia of the left eye. (From Hoekelman R [ed]: *Primary pediatric care,* ed 3, St Louis, 1997, Mosby.)

IMAGING STUDIES

Usually not necessary unless a CNS abnormality is suspected.

TREATMENT

- Treatment depends on the age of the patient and etiology of the amblyopia.
- Glasses to align eyes in certain types of strabismus and/or to correct significant refractive errors.
- Patching or atropine eye drops are both effective depending on the type of amblyopia. Penalization of the better-seeing eye with atropine 1% drops or patching are used for varying lengths of time, usually months, depending on patient age, response, and compliance. In general, younger patients (<age 5 yr) respond faster and more fully than older children. Older children (>10 yr) who have never been treated can sometimes still respond to amblyopia therapy.
- Digital "virtual reality" viewing devices that selectively stimulate the amblyopic eye are currently under development and beginning to be marketed as treatment for amblyopia.
- Surgery for deprivation amblyopia (i.e., congenital cataract, severe congenital ptosis).

CHRONIC RX

- Maintenance treatment with glasses, patching, or atropine may be necessary until age 9 or 10 yr.
- Monitoring until visual maturity, which occurs around age 9 or 10 yr, is important to avoid relapses.

REFERRAL

To ophthalmologist if vision is compromised

PEARLS & CONSIDERATIONS

COMMENTS

- The earlier the diagnosis, the better the outcome. Amblyopia is more responsive to treatment in children younger than 5 yr of age. Although the average treatment response is weaker in children over age 5 yr, some older children show response to treatment.
- The success of therapy is highly dependent on treatment compliance.
- Amblyopia recurs in 25% of children after patching is discontinued.

SUGGESTED READING

Bradfield YS: Identification and treatment of amblyopia, *Am Fam Physician* 87:348-352, 2013.

AUTHORS: **David Robbins Tien, MD,** and **Alexandra Meyer Tien, MD**

Amebiasis

BASIC INFORMATION

DEFINITION

Amebiasis is an infection caused by the protozoal parasite *Entamoeba histolytica.* Although primarily an infection of the colon, amebiasis may cause extraintestinal disease, particularly liver abscess.

SYNONYM

Amebic dysentery (when severe intestinal infection)

ICD-10CM CODES

A06.9 Amebiasis, unspecified
A06.1 Chronic intestinal amebiasis
A06.7 Cutaneous amebiasis

EPIDEMIOLOGY & DEMOGRAPHIC

INCIDENCE (IN U.S.): 1.2 cases per 100,000 U.S. population. Highest in institutionalized patients, travelers to/immigrants from developing nations, and those who practice oral-anal sex

PREVALENCE: In U.S.: 4% (80% of infections asymptomatic). In the developing world: Still accounts for 9% of all deaths in children <5 yr of age

PREDOMINANT SEX:

- Equal sex distribution in general
- Striking male predominance of liver abscess

PREDOMINANT AGE: Second through sixth decades

PEAK INCIDENCE: Peaks at age 2 to 3 yr and >40 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Often nonspecific
- Approximately 20% of cases symptomatic:
  1. Diarrhea, which may be bloody
  2. Abdominal and back pain
- Abdominal tenderness in 83% of severe cases
- Fever in 38% of severe cases
- Hepatomegaly, right upper quadrant tenderness, and fever in almost all patients with liver abscess (may be absent in fulminant cases)

ETIOLOGY

- Caused by the protozoal parasite *E. histolytica, E. dispar, and E. moshkovskii.* The latter two are 10 times more common but nonpathogenic and difficult to distinguish from *E. histolytica* morphologically.
- Transmission by the fecal-oral route. Risk factors are summarized in Box E1. It is highly infectious requiring ingestion of only a small number of cysts in contaminated water or food for infection.
- Infection usually localized to the large bowel, particularly the cecum where a localized mass lesion (ameboma) may form.
- Extraintestinal infection in which the organism invades the bowel mucosa and gains access to the portal circulation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Severe intestinal infection possibly confused with ulcerative colitis or other infectious enterocolitis syndromes, such as those caused by *Shigella, Salmonella, Campylobacter,* or invasive *Escherichia coli*
- In elderly patients: Ischemic bowel possibly producing a similar picture

WORKUP

- Stool antigen testing is more sensitive than ova and parasite examination for the diagnosis of amebiasis
- Three stool specimens over a period of 7 to 10 days to search for cysts or trophozoites has a sensitivity of 85% to 95%, but microscopy cannot differentiate between the species
- Concentration and staining the specimen with Lugol iodine or methylene blue to increase the diagnostic yield
- Fecal leukocytes not always present

LABORATORY TESTS

- Fecal enzyme-linked immunosorbent assay (ELISA) antigen detection is specific for *E. histolytica* (87% percent sensitivity and >90% specificity as compared with culture) and also useful for diagnosis of liver abscess.
- PCR-based assays on stool: 90% to 95% sensitive; 95% to 100% specific.
- Mucosal biopsy is occasionally necessary to look for cysts or trophozoites.
- Serum antibody assays specific for *E. histolytica* are available and are particularly sensitive and specific for extraintestinal infection or severe intestinal disease but may not distinguish recent from remote infection.
- Aspiration of abscess fluid is used to distinguish amebic from bacterial abscesses.

Box E1 Risk Factors for Amebiasis in the United States

- Hispanic/Asian/Pacific Islanders: 50% of U.S. cases reported to the Centers for Disease Control and Prevention
- Travelers to endemic regions of the world: 0.3% incidence in one study
- Institutions for intellectually disabled
- Men who have sex with men
- Men: 90% amebic liver abscesses found in men; rare in children
- Immunodeficiency

Modified from Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

IMAGING STUDIES

Abdominal imaging studies (sonography or CT scan) to diagnose liver abscess

TREATMENT

ACUTE GENERAL Rx

- *Entamoeba histolytica* causes amoebic dysentery and requires treatment. Treatment is recommended for all infected patients. Other species of *Entamoeba* may colonize the gastrointestinal tract but are not pathogenic and do not mandate treatment.
- Table E1 summarizes drug treatment options for amebiasis in adults and children. Metronidazole or tinidazole is recommended initially for parasitic clearance. It is then followed by an intraluminal amebicide (paromomycin or diloxanide) for cyst clearance.
- Liver abscess is generally responsive to medical management but surgical intervention indicated for extension of liver abscess into pericardium or for toxic megacolon.

DISPOSITION

Host immunity incomplete and reinfection rate high for patients remaining at risk

REFERRAL

- For consultation with infectious diseases specialist for extraintestinal infection or persistent or relapsing intestinal infection
- For surgical consultation:
  1. For toxic megacolon
  2. For impending rupture of or extension of liver abscess into adjacent structures

PEARLS & CONSIDERATIONS

COMMENTS

- Infection with other intestinal parasites, particularly *Giardia lamblia,* may coexist with amebiasis.
- There is a high prevalence of *E. dispar* in homosexual males, which is nonpathogenic but may be difficult to distinguish from the pathogen *E. histolytica.*
- In the U.S., *E. histolytica* is still the third most frequently isolated pathogen in returning travelers with infectious gastroenteritis.

RELATED CONTENT

Amebiasis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Cooper CJ et al: Varied clinical manifestations of amebic colitis, *South Med J* 108:676-681, 2015.

Kantor M et al: Entamoeba histolytica: updates in clinical manifestation, pathogenesis, and vaccine development, *Can J Gastroenterol Hepatol* 4601420, 2018.

Shirley DT et al: A review of the global burden, new diagnostics, and current therapeutics for amebiasis, *Open Forum Infect Dis* 5(7): ofy 161, 2018.

Skappak C et al: Invasive amoebiasis: a review of Entamoeba infections highlighted with case reports, *Can J Gastroenterol Hepatol* 28:355-359, 2014.

TABLE E1 Drug Treatment for Amebiasis

Medication	Adult Dosage (Oral)	Pediatric Dosage (Oral)*
Invasive Disease		
Metronidazole	Colitis or liver abscess: 750 mg tid for 7-10 days	Colitis or liver abscess: 35-50 mg/kg/day in three divided doses for 7-10 days
or		
Tinidazole	Colitis: 2 g once daily for 3 days Liver abscess: 2 g once daily for 3-5 days	Colitis: 50 mg/kg/day once daily for 3 days Liver abscess: 50 mg/kg/day once daily for 3-5 days
Followed by:		
Paromomycin (preferred)	500 mg tid for 7 days	25-35 mg/kg/day in three divided doses for 7 days
or		
Diloxanide furoate† or	500 mg tid for 10 days	20 mg/kg/day in three divided doses for 7 days
Iodoquinol	650 mg tid for 20 days	30-40 mg/kg/day in three divided doses for 20 days
Asymptomatic Intestinal Colonization		
Paromomycin (preferred) *or* Diloxanide furoate† *or* Iodoquinol	As for invasive disease	As for invasive disease

tid, Three times a day.
*All pediatric dosages are up to a maximum of the adult dose.
†Not available in the United States.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

Amenorrhea ALG PTG

BASIC INFORMATION

DESCRIPTION

- *Amenorrhea* means absence of menstruation. It is classified as either primary or secondary depending on whether the patient has had previous menstrual cycles.
- Primary amenorrhea is defined as the absence of menses by age 15 in the presence of secondary sexual characteristics. However, in the absence of these secondary sexual features by the age of 13 yr old, one should begin the workup for primary amenorrhea.
- Secondary amenorrhea is the absence of menses for more than 6 mo in a patient who has had previous normal menstrual progesterone withdrawal cycles.

ICD-10CM CODES

N91.0 Primary amenorrhea
N91.1 Secondary amenorrhea
N91.2 Amenorrhea, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence of primary amenorrhea and secondary amenorrhea in the U.S. is <1% and 5% to 7%, respectively.
- There is no racial or ethnic predilection.

ETIOLOGY

- Physiologic amenorrhea
  1. Pregnancy
  2. Lactation
  3. Constitutional Delay of Puberty
  4. Menopause
- Pathologic amenorrhea
  1. Primary amenorrhea (% frequency)
     a. Hypergonadotropic hypogonadism (43%)
        (1) 45 X (27%)
        (2) 46 XX (14%)
        (3) 46 XY (2%)
     b. Eugonadism (30%)
        (1) Müllerian agenesis (15%)
        (2) Vaginal septum (3%)
        (3) Imperforate hymen (1%)
        (4) Polycystic ovarian syndrome (7%)
        (5) Congenital adrenal hyperplasia (1%)
        (6) Cushing and thyroid disease (2%)
        (7) Androgen insensitivity (1%, Table E1)
     c. Hypogonadotropic hypogonadism (27%)
        (1) Constitutional delay (14%)
        (2) GnRH deficiency (5%)
        (3) Other CNS disease (1%)
        (4) Pituitary diseases (5%)
        (5) Eating disorders, stress (2%)
  2. Secondary amenorrhea
     a. Hypergonadotropic hypogonadism (10.5%)
        (1) 46, XX with gonadal failure (10%)
        (2) Abnormal karyotype (0.5%)
     b. Hypogonadotropic hypogonadism (67.5%)
        (1) Polycystic ovary syndrome (PCOS) (28%)
        (2) Eating disorders, stress (15.5%)
        (3) Hypothyroidism (1.5%)
        (4) Sheehan syndrome (1.5%)
        (5) Cushing syndrome (1%)
        (6) Pituitary tumor/empty sella (2%)
     c. Hyperandrogenism (2%)
        (1) Nonclassic congenital adrenal hyperplasia (0.5%)
        (2) Ovarian tumor (1%)
     d. High prolactin (13%)
     e. Anatomic (7%, Asherman syndrome)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Turner syndrome
  1. Usually presents with primary amenorrhea unless mosaic
  2. Short stature
  3. Epicanthic folds
  4. Low-set ears
  5. High-arched palate
  6. Micrognathia
  7. Sensorineural hearing loss
  8. Otitis media
  9. Webbing of the neck
  10. Pigmented nevi
  11. Square/shield chest
  12. Widely spaced nipples
  13. Absent breast development
  14. Bicuspid aortic valve
  15. Coarctation of aorta
  16. Cubit valgus
  17. Short fourth metacarpal
  18. Hyperconvex nails
  19. Leg edema
  20. Renal abnormalities
  21. Autoimmune disorders including thyroiditis
  22. Diabetes mellitus
- Pure gonadal dysgenesis
  1. Unlike Turner syndrome, has no dysmorphic features
- Müllerian agenesis
  1. Sporadic inheritance
  2. Primary amenorrhea
  3. Normal breast development
  4. Normal pubic and axillary hair
  5. Normal female external genitalia
  6. Absent uterus and upper part of vagina
  7. Ovaries present
  8. Renal and vertebral anomalies in some patients; renal agenesis should be evaluated
- Transverse vaginal septum and imperforate hymen
  1. Primary amenorrhea
  2. Progressive cyclic lower abdominal pain
  3. Imperforate hymen or transverse vaginal septum on pelvic examination
  4. Perirectal fullness from hematocolpos
- Androgen insensitivity syndrome
  1. Primary amenorrhea
  2. X-linked recessive inheritance in some patients
  3. Normal breast development
  4. Absent pubic and axillary hair
  5. Testis may be present in the groin or inguinal canal
  6. Uterus and vagina absent
  7. No associated renal or vertebral anomalies
- Adult-onset congenital adrenal hyperplasia
  1. More frequently seen in Ashkenazi Jewish, Inuit Native American, French Canadian, and Mexican populations than other populations
  2. Mimics the presentation of PCOS
  3. Features of hyperandrogenism (virilization, hirsutism, acne)
  4. Hypertension
- 5-alpha reductase deficiency
  1. Primary amenorrhea
  2. Undergo virilization at puberty
- PCOS
  1. Usually presents with secondary amenorrhea and oligomenorrhea
  2. Diagnosed with ≥2/3 of the Rotterdam Criteria:
     a. Oligo/anovulation
     b. Hyperandrogenism
     c. Polycystic ovaries on ultrasound
  3. Associated with the metabolic syndrome and obesity (60% to 80% of PCOS patients)
  4. Insulin resistance, predisposition to type 2 diabetes mellitus
- Cushing syndrome (rare disorder, prevalence 1/1,000,000)
  1. Secondary amenorrhea
  2. Features of hyperandrogenism
  3. Abnormal fat distribution (dorsocervical fat pad [buffalo hump], spider legs, significant central obesity)
  4. Abdominal striae due to weakening of skin integument
  5. Easy bruising
  6. Hypertension
  7. Proximal muscle weakness
- Hypothyroidism
  1. Secondary amenorrhea
  2. Lethargy
  3. Constipation
  4. Decreased appetite
  5. Weight gain
  6. Cold intolerance
  7. Hair loss
  8. Dry skin
  9. Bradycardia
- Primary ovarian insufficiency (previously premature ovarian failure)
  1. Secondary amenorrhea prior to the age of 40 and elevated gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH])
  2. History of oophorectomy or pelvic radiation or chemotherapy
  3. Vasomotor symptoms
  4. Dry, thin vaginal mucosa without rugosity
  5. Associated autoimmune or karyotypic abnormalities possible
- Hyperprolactinemia
  1. Usually presents with secondary amenorrhea
  2. History of use of drugs such as antipsychotics, oral contraceptive (OC) pills, antidepressants, antihypertensives, H2 blockers, opioids, etc.

TABLE E1 Congenital Anatomic Causes of Primary Amenorrhea with Normal Breast Development*

Diagnosis	Müllerian Agenesis	Androgen Insensitivity (AI)	Transverse Vaginal Septum	Imperforate Hymen
Patients with primary amenorrhea†	15%	1%	3%	1%
Patients with primary amenorrhea and apparent obstruction or absence of vagina†	75%	5%	15%	5%
Chromosomes‡	46,XX	46,XY	46,XX	46,XX
Gonads	Ovaries	Testes	Ovaries	Ovaries
Serum testosterone‡	Normal female level	Normal male level (high)	Normal female level	Normal female level
Vagina	Absent or shallow	Absent or shallow	Obstructed by septum which may be thick or thin, high or low	Obstructed by thin membrane, which may look blue from hematocolpos
Axillary/pubic hair	+	Absent unless AI is incomplete	+	+
Cyclic pain	±	–	+	+
Uterus	Absent or rudimentary	–	+	+
Mass	–	–	+ Can present with acute urinary retention as hematocolpos mass obstructs urethra	+ Can present with acute urinary retention
Introitus bulges with Valsalva maneuver	–	–	–	+
Associated anomalies	Urinary tract and skeletal	Inguinal hernias; gonadal malignancy in adulthood	Major urinary tract abnormalities in 15%	Possibly some increase in urinary tract abnormalities
Treatment	Vaginal dilation or surgical neovagina	Gonadectomy after age 16-18 yr Vaginal dilation or surgical neovagina	Surgical approach depends on extent and location of septum; may be extensive; should be done as soon as possible	Excision of hymen as soon as possible; diagnostic needle aspiration contraindicated because of risk of infection
Fertility	Advanced reproductive technology required; in vitro fertilization surrogate with uterus to gestate pregnancy	Not fertile	Variable, low septa have a better prognosis than do high septa	Usually fertile

+, Present; –, absent; ±, may be present or absent.
*Cervix not visible on pelvic examination. Short vagina; may be absent or obstructed.
†Data from Reindollar RH, Byrd JR, McDonough PG: Delayed sexual development: a study of 252 patients, *Am J Obstet Gynecol* 140:371, 1981.
‡Sometimes useful in differentiating Müllerian agenesis from androgen insensitivity.
From Kliegman RM et al: *Practical strategies in pediatric diagnosis and therapy,* ed 2, Philadelphia, 2004, Elsevier.

3. Pituitary adenomas may be associated with headache, vomiting, vision changes
4. Galactorrhea

- Sheehan syndrome
  1. History of secondary amenorrhea following postpartum hemorrhage
  2. Failure of lactation
  3. Other features of hypopituitarism
- Asherman syndrome
  1. History of D&C
  2. Secondary amenorrhea
  3. Recurrent miscarriage/infertility
- Functional hypothalamic disorders
  1. Usually presents with secondary amenorrhea
  2. History of eating disorders, severe exercise or stress
  3. Use of street drugs
- Kallmann syndrome
  1. Usually presents with anosmia, congenital defect of development of both the GnRH neurons and olfactory placode

DX DIAGNOSIS

- First step in the workup of amenorrhea is to rule out pregnancy by serum/urine pregnancy test.
- Diagnostic workup depends on history and physical (Fig. E1).
- Physical examination, determining the presence or absence of advanced breast Tanner stage and presence or absence of uterus can help guide evaluation (e.g., presence of breasts but absence of uterus can only be Müllerian agenesis or androgen insensitivity syndrome).
- Primary amenorrhea:
  1. Pelvic ultrasonography or MRI to detect any anatomic abnormalities of uterus, cervix, ovaries, or vagina.
  2. Karyotyping (46,XX in Müllerian agenesis; 46,XY in AIS; 45,XO in Turner syndrome) is done when uterus is absent or Turner syndrome is suspected.
  3. Serum FSH, thyroid-stimulating hormone [TSH]/FT4, prolactin, estradiol:
     a. FSH 40 mIU/ml along with estradiol <20 pg/ml is indicative of primary ovarian insufficiency.
     b. Prolactin >200 ng/ml is suggestive of prolactinoma. Threshold levels may vary by laboratory, and providers are advised to become familiar with their institution's normal range.

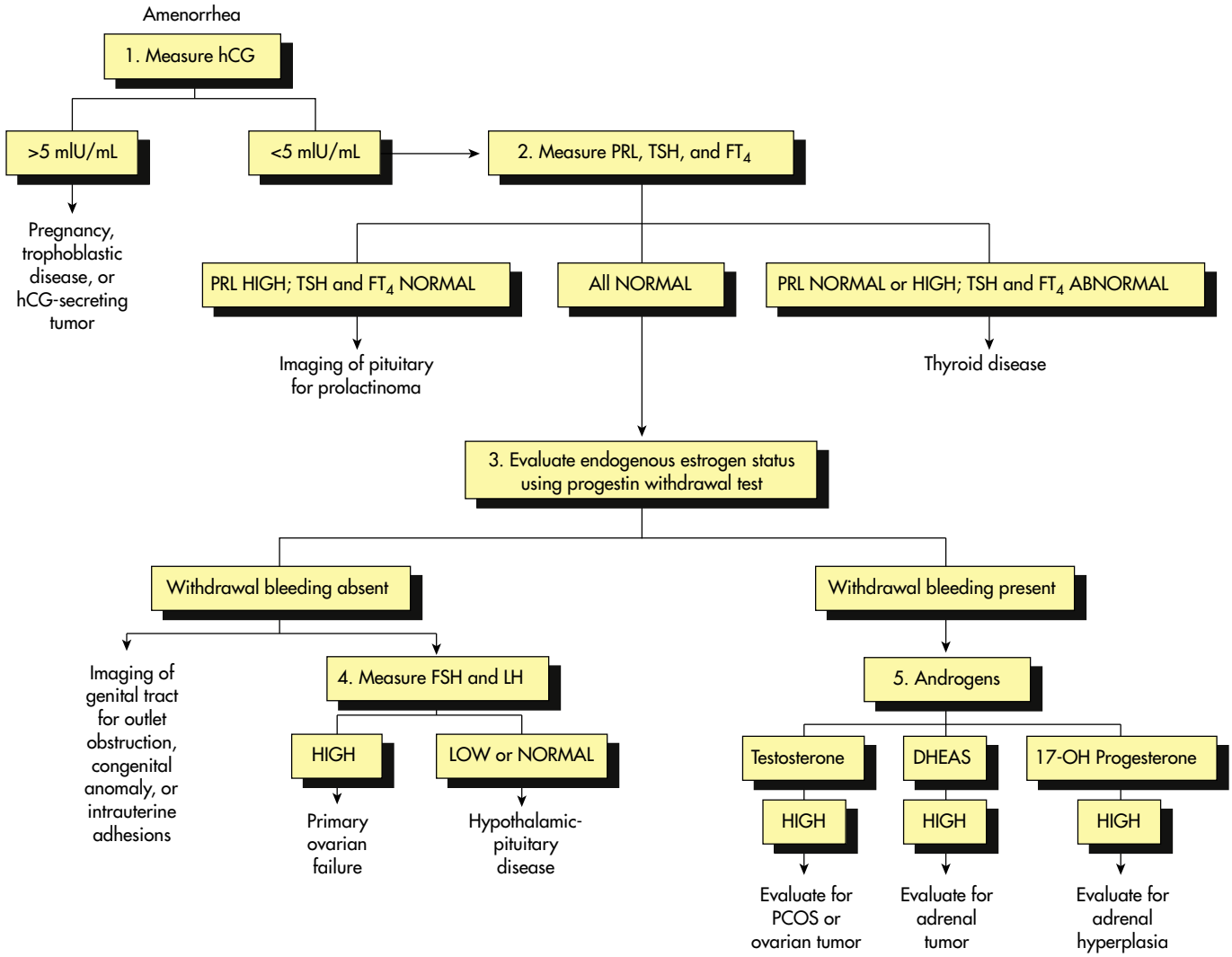

FIG. E1 A diagnostic algorithm for amenorrhea. *DHEAS,* Dehydroepiandrosterone sulfate; *FSH,* follicle stimulating hormone; *FT_4,* free thyroxine; *hCG,* human chorionic gonadotropin; *LH,* luteinizing hormone; *PCOS,* polycystic ovary syndrome; *PRL,* prolactin; *TSH,* thyroid stimulating hormone. (From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, Philadelphia, 2017, Elsevier.)

4. Check serum testosterone (male range in AIS; female range in Müllerian agenesis) when uterus is absent or in presence of features of hyperandrogenism.
5. 17-alpha hydroxyprogesterone level in presence of features of hyperandrogenism to rule out CAH. In addition to high level of 17 alpha hydroxyprogesterone due to compromised 21-hydroxylase activity, these patients may have elevated level of serum progesterone and deoxycorticosterone, hypernatremia, and hypokalemia.
6. MRI of head in presence of:
   a. Hyperprolactinemia.
   b. Visual field defects.
   c. Signs of hypothalamic pituitary dysfunction.

- Secondary amenorrhea:
  1. Serum FSH, TSH/FT4, prolactin, estradiol:
     a. Low serum FSH with low estradiol indicates hypogonadotropic hypogonadism.
     b. High serum FSH with low estradiol suggests hypergonadotropic hypogonadism.
  2. Progesterone withdrawal bleeding.
     a. 10 mg medroxyprogesterone is given for 10 days.
     b. Withdrawal bleeding suggests eustrogenic anovulation in presence of normal end organ (outflow tract) and ovarian function.
  3. Estrogen-progesterone withdrawal bleeding:
     a. In the absence of progesterone withdrawal bleeding, the patients are exposed to 25 to 35 days of estrogen (0.625 to 2.5 mg Premarin daily) followed by 10 days of medroxyprogesterone.
     b. Withdrawal bleeding indicates hypogonadism.
     c. Absence of bleeding suggests defects with end organ (e.g., Asherman syndrome).
  4. Serum LH, testosterone and DHEA-S:
     a. When features of hyperandrogenism are seen these tests are ordered.
     b. Serum testosterone >200 ng/ml suggests androgen-producing adrenal or ovarian tumors (high index of suspicion with moderate elevation; threshold value not required in cases of ovarian or adrenal tumors). This level may be mildly elevated in patients with PCOS.
     c. DHEA-S >700 mcg/dl suggests adrenal origin over ovarian (high index of suspicion with moderate elevation; threshold value not required in cases of ovarian or adrenal tumors).
     d. LH/FSH ratio >2 may be present in patients with PCOS, although this is not part of diagnostic criteria according to the Rotterdam consensus conference.
  5. Imaging:
     a. Pelvic ultrasound when PCOS or ovarian tumor suspected.
     b. Abdominal CT when adrenal tumor suspected.
     c. MRI of head when indicated.
     d. HSG, sonohysterography, or diagnostic hysteroscopy in patients with suspected Asherman syndrome.
  6. Other tests which are rarely needed:
     a. Serum transferrin when hemochromatosis is suspected.

b. Serum ACE when sarcoidosis is suspected.
c. Karyotyping is indicated when primary ovarian insufficiency occurs before the age of 40.

Rx TREATMENT

- The treatment of amenorrhea depends on the etiology, as well as the aims of the patient, such as a desire to treat hirsutism or to become pregnant.
- Estrogen replacement along with calcium and vitamin D should be instituted in patients with hypogonadism to avoid osteoporosis. Women with a uterus require continuous or intermittent progesterone administration to protect against endometrial hyperplasia or cancer. Often, combination oral contraceptive pills are used.
- Many patients with anatomic abnormalities may require surgical correction. Creation of a new vagina for patients with Müllerian agenesis is usually delayed until the woman is emotionally mature and ready to participate in the serial dilation or postoperative care required to maintain vaginal patency. However, if adequate correction is impossible, pregnancy will often require a surrogate to carry a gestation. Always assess for the associated urogenital anomalies, such as renal agenesis, in these patients and, when present, treat them appropriately.
- In patients with androgen insensitivity syndrome, the incidence of gonadal malignancy is 22%. However, it rarely occurs before the age of 20. Gonadectomy is performed by laparoscopy following breast development and the attainment of adult stature. In the absence of a uterus these individuals only need estrogen replacement without progesterone.
- Women with adult-onset CAH may be treated with low-dose corticosteroids in addition to sex steroids to partially block ACTH stimulation of adrenal function and thereby decrease overproduction of adrenal androgens.
- Patients with primary ovarian insufficiency (POI) will need estrogen and progesterone replacement. These patients will require in vitro fertilization using donor oocytes to conceive. These patients have an increased risk of osteoporosis and heart disease. It can also be associated with autoimmune disorders such as hypothyroidism, Addison disease, and diabetes mellitus. Therefore, fasting blood glucose, TSH, and, if clinically appropriate, morning cortisol should be measured. In the presence of a Y chromosome, removal of gonadal tissue is recommended at the time of diagnosis to avoid gonadal tumors.
- Hypothyroidism should be treated with thyroid replacement.
- Hyperprolactinemia is treated by avoiding the culprit drugs or by giving dopamine agonists, such as bromocriptine or cabergoline. Pituitary adenomas rarely require surgery but surgery may be performed if secondary deficits such as visual changes are observed, when they are resistant to medical therapy, or the lesion is rapidly growing.
- Treatment of hypothalamic amenorrhea depends on the etiology. Patients with eating disorders or who exercise excessively will require behavioral modification and nutritional counseling. Elite athletes may choose not to alter their exercise regimens and will therefore require estrogen treatment and prevention of osteoporosis. When associated with infertility, ovulation induction with clomiphene citrate, exogenous gonadotropins, or pulsatile GnRH therapy should be offered.
- The primary treatment of PCOS is weight loss through diet and exercise. Other treatment options include:
  1. Use of oral contraceptive pills or cyclic progestational agents to help maintain a normal endometrium.
  2. Insulin-sensitizing agents such as metformin to reduce insulin resistance and improve ovulatory function. Recent studies suggest that insulin-sensitizing agents may not be as effective in improving ovulatory effort.
  3. Oral contraceptives and/or spironolactone to treat hyperandrogenism.
  4. Clomiphene citrate or an aromatase inhibitor such as letrozole to induce ovulation.
- In patients with Asherman syndrome, hysteroscopic lysis of intrauterine adhesions is followed by administration of long-term exogenous estrogen to stimulate regrowth of endometrial tissue.
- Geneticist consult is given in patients with hereditary causes of amenorrhea.
- Psychiatrist consult is needed in patients with major depression, anorexia nervosa, bulimia nervosa, or other major psychiatric disorders.

COMPLICATIONS

- Osteoporosis
- Endometrial hyperplasia and uterine cancer
- Infertility

PROGNOSIS

Depends on the etiology of amenorrhea.

PATIENT & FAMILY EDUCATION

- Patients with amenorrhea should be reassured that this is, in and of itself, not a concern.
- All women with an intact endometrium should understand the risks of unopposed estrogen action, whether the estrogen is exogenous such as through hormone therapy, or endogenous such as PCOS.
- Hypoestrogenic women should be counseled about the importance of estrogen replacement to protect against bone loss.
- Potential for future childbearing should be discussed.

SUGGESTED READINGS

Gordon Catherine M et al: Functional hypothalamic amenorrhea: an endocrine society clinical practice guideline, *J Clin Endocrinol Metab* 102(5):1413-1439, 2017.

Klein DA, Path MA: Amenorrhea: an approach to diagnosis and management, *Am Fam Physician* 87(11):781-788, 2013.

RELATED CONTENT

Hypothalamic Amenorrhea (Patient Information)
Infertility (Related Key Topic)
Pituitary Adenoma (Related Key Topic)
Polycystic Ovary Syndrome (Related Key Topic)
Prolactinoma (Related Key Topic)
Sheehan Syndrome (Related Key Topic)
Turner Syndrome (Related Key Topic)

AUTHORS: **Rachel Wright Heinle, MD,** and **T. Caroline Bank, MD**

BASIC INFORMATION

DEFINITION

The term *amyloidosis* refers to a heterogeneous group of disorders (Table E1) that are all characterized by the deposition of an amorphous, extracellular fibrillar protein in various organs and tissues of the body (Table E2). It has the following subtypes:

- Primary amyloidosis (AL)
- Secondary amyloidosis (AA)
- Hereditary amyloidosis
- Localized amyloidosis

ICD-10CM CODES

E85.9 Amyloidosis, unspecified
E85.0 Non-neuropathic heredofamilial amyloidosis
E85.1 Neuropathic heredofamilial amyloidosis
E85.2 Heredofamilial amyloidosis, unspecified
E85.3 Secondary systemic amyloidosis
E85.4 Organ-limited amyloidosis
E85.8 Other amyloidosis

TABLE E1 Nomenclature of Amyloidosis

Protein	Precursor	Clinical Characteristics
AL or AH	Immunoglobulin light or heavy chain	Primary or localized; myeloma or macroglobulinemia associated
AA	SAA	Secondary or familial Mediterranean fever, familial periodic fever syndromes
ATTR	Transthyretin	Familial and senile
A fibrinogen	Fibrinogen	Familial renal amyloidosis (Ostertag type)
$A\beta_2M$	β_2-Microglobulin	Dialysis associated; carpal tunnel syndrome
$A\beta$	ABPP	Alzheimer disease
A Apo A-I/A-II	Apolipoprotein A-I	Proteinuria
	Apolipoprotein A-II	Cardiac
		Neuropathy
A lysozyme	Lysozyme	GI tract
		Liver
		Renal
ALECT2	Renal	

AA, Amyloid A; *Aβ,* amyloid-β; *ABPP,* amyloid-β precursor protein; *$A\beta_2M$,* β_2-microglobulin-related amyloid; *AH,* amyloid heavy chain; *AL,* amyloid light chain; *ALECT2,* leukocyte chemotactic factor 2 amyloidosis; *Apo,* apolipoprotein; *ATTR,* transthyretin-related hereditary amyloidosis; *GI,* gastrointestinal; *SAA,* serum amyloid A.
Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Between 1500 and 3500 new cases are diagnosed annually. The most common type is AL.

PREVALENCE: Amyloidosis primarily affects men between the ages of 60 and 70 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The most common presenting symptoms of amyloidosis are fatigue, dyspnea, edema, paresthesias, and weight loss. Other findings depend on organ system involvement. Syndromes in primary amyloidosis are summarized in Table E3.
- Signs and symptoms of nephrotic syndrome may be present with renal involvement.
- Fatigue and dyspnea may occur with pulmonary involvement.
- GI involvement is uncommon but presents with diarrhea, nausea, abdominal pain, and macroglossia (Fig. E1).
- Patients with cardiac involvement have an infiltrative cardiomyopathy and present with a preserved ejection fraction (EF) and diastolic dysfunction.
- Patients may present with bleeding problems caused by either factor X deficiency or fragile blood vessels caused by infiltration by amyloid. Bleeding around the eyes (raccoon eyes) is a characteristic finding (Fig. E2).
- Involvement of the nervous system presents with peripheral neuropathy, tendinopathy (Fig. E3), muscle weakness, numbness, syncope, or dizziness. Associated autonomic neuropathy can also cause severe disabling symptoms.

ETIOLOGY

The deposition of an amorphous, extracellular fibrillar protein in various tissues that stains with Congo red is the common underlying mechanism, but there are important differences among various subtypes:

- AL is associated with an underlying clonal plasma cell disorder making an abnormal light chain protein with possible deposition in multiple organ systems.
- AA has no underlying plasma cell disorder and is a consequence of longstanding systemic inflammation (e.g., tuberculosis, leprosy, malaria, untreated syphilis).
- Localized amyloidosis results from localized synthesis of fibrillar material with no underlying plasma cell disorder.
- Familial amyloidosis is another subtype, with the most common form resulting from mutation of transthyretin gene (TTR). Transthyretin amyloidosis is caused by the deposition of hepatocyte-derived transthyretin amyloid in peripheral nerves and the heart.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Differential diagnosis varies depending on the organ involvement:

- Renal involvement (toxin- or drug-induced necrosis, glomerulonephritis, renal vein thrombosis)
- Interstitial lung disease (sarcoidosis, connective tissue disease, infectious causative factors)
- Restrictive cardiomyopathy (endomyocardial fibrosis, viral myocarditis)
- Carpal tunnel (rheumatoid arthritis, hypothyroidism, overuse)
- Peripheral neuropathy (alcohol abuse, vitamin deficiencies, diabetes mellitus)

WORKUP

Workup consists of performing blood and urine tests to look for abnormal light chain in urine or blood, performing various tests to look for target organ damage, and getting histologic confirmation by doing a fat pad and bone marrow biopsy and then performing Congo red staining (Fig. E4) on that. Box E1 summarizes recommended diagnostic evaluation for amyloidosis. Fig. E5 describes an algorithm for diagnosis of amyloidosis. Amyloid staging is described in Box E2.

LABORATORY TESTS

- Immunofixation of serum and urine (serum protein electrophoresis [SPEP], urine protein electrophoresis [UPEP]) to look for immunoglobulin light chain is a sensitive screening test.
- CBC, blood urea nitrogen (BUN)/creatinine, liver function tests, thyroid functions, and urine for albumin.
- Histologic confirmation is necessary with a fat pad and bone marrow biopsy with Congo red staining to establish a diagnosis.
- If a noninvasive fat pad biopsy does not establish a diagnosis, then a biopsy of the affected organ may be needed.

IMAGING STUDIES

- Cardiac MRI has a distinctive pattern.
- Two-dimensional Doppler echocardiography to study diagnostic filling is useful to evaluate for cardiac involvement but is not as sensitive as cardiac MRI.
- Nuclear imaging with technetium-labeled aprotinin may detect cardiac amyloidosis. Labeled diphosphonates play an important role in the typing of amyloidosis and in diagnosing heart involvement in patients with transthyretin cardiac amyloidosis.

TABLE E2 Classification of Amyloidosis*

Type	Fibril Precursor Protein	Clinical Syndrome
AA	Serum amyloid A protein	Systemic amyloidosis usually with predominantly renal involvement associated with acquired or hereditary chronic inflammatory diseases. Formerly known as *secondary* or *reactive amyloidosis.*
AL	Monoclonal immunoglobulin light chains	Systemic amyloidosis potentially involving many organ systems associated with myeloma, monoclonal gammopathy, and occult B-cell dyscrasias. Formerly known as *primary amyloidosis.*
ATTR	Normal plasma transthyretin	Wild-type (nonhereditary) systemic amyloidosis with predominantly cardiac involvement (formerly known as *senile cardiac amyloidosis*).
ATTR	Genetic variants of transthyretin (e.g., ATTR Met30, Ala60, Ile122)	FAP, often with prominent amyloid cardiomyopathy. Predominantly cardiac involvement without neuropathy with certain mutations (e.g., TTR Ile122).
$A\beta_2M$	β_2-Microglobulin	Dialysis-related amyloidosis associated with renal failure and long-term dialysis. Predominantly articular and periarticular involvement.
$A\beta$	β-Protein precursor (and rare genetic variants)	Cerebrovascular and intracerebral plaque amyloid in Alzheimer disease. Occasionally familial.
AApoAI	Genetic variants of apolipoprotein AI (e.g., AApoAI Arg26, Arg60)	Autosomal dominant systemic amyloidosis. Predominantly nonneuropathic with prominent visceral involvement, especially nephropathy. Minor wild-type apolipoprotein AI amyloid deposits may occur in the aorta in aging individuals.
AApoAII	Genetic variants of apolipoprotein AII	Autosomal dominant systemic amyloidosis with predominantly renal involvement.
AFib	Genetic variants of fibrinogen A α chain (e.g., AFib Val526)	Autosomal dominant systemic amyloidosis. Nonneuropathic with predominant nephropathy.
ALys	Genetic variants of lysozyme (e.g., ALys His67)	Autosomal dominant systemic amyloidosis. Nonneuropathic with predominantly renal and GI involvement. Rarely presents with hepatic rupture.
ACys	Genetic variant of cystatin C (ACys Gln68)	Hereditary cerebral hemorrhage with cerebral and systemic amyloidosis in Icelandic individuals.
AGel	Genetic variants of gelsolin (e.g., AGel Asn187)	Autosomal dominant systemic amyloidosis. Predominantly cranial nerve involvement plus lattice corneal dystrophy. Described and most common in Finland.

FAP, Familial amyloid polyneuropathy; *GI,* gastrointestinal.
*Not exhaustive and amyloid composed of peptide hormones, prion protein, and unknown proteins not included.
Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE E3 Syndromes in Primary Amyloidosis

Syndrome	Patients (%)
Nephrotic or nephrotic and renal failure	30
Hepatomegaly	24
Congestive heart failure	22
Carpal tunnel	21
Neuropathy	17
Orthostatic hypotension	12

From Hoffman R: *Hematology: Basic principles and practice,* ed 7, 2018, Elsevier.

Cardiac involvement in transthyretin patients may be diagnosed earlier with bone scintigraphy in transthyretin patients compared with echocardiography. Serum amyloid P component (SAP) scintigraphy has high sensitivity for the detection of amyloid deposits in liver, spleen, kidneys, adrenal glands, and bones.

FIG. E1 Macroglossia in a patient with primary amyloidosis, demonstrating peripheral ridging caused by teeth indentation. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

Rx TREATMENT

ACUTE GENERAL RX

- Patients with AL amyloidosis should be evaluated for autologous hematopoietic stem cell transplantation (HSCT). Patients with good performance status, age under 70 and limited organ involvement are good candidates.
- The goal of chemotherapy is to decrease the production of the amyloidogenic light chain with therapy directed at the clonal plasma cells.
- All agents used to treat multiple myeloma are effective against AL, including melphalan, and prednisone. Immunomodulatory compounds (IMiDs) such as thalidomide or lenalidomide, or proteasome inhibitors are also effected. Patients ineligible for autologous HSCT should receive chemotherapy with melphalan- or bortezomib-based

FIG. E2 Classic amyloid purpura. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

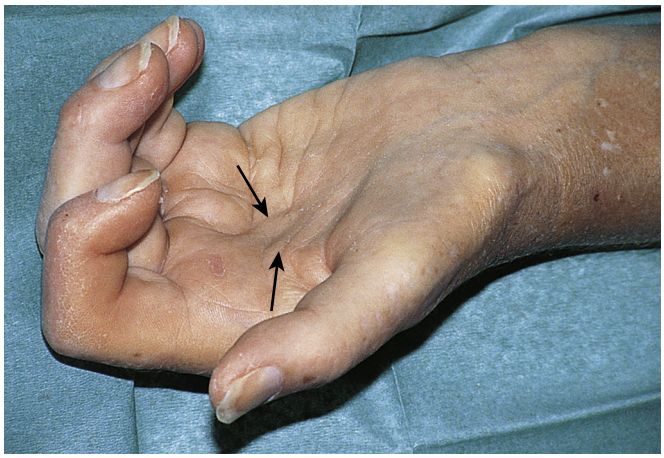

FIG. E3 Hand involvement in $A\beta_2M$ amyloidosis. Hand of a long-term hemodialysis patient showing maximal extension. Note the prominence of shrunken flexor tendons *(arrows).* This is also known as the "guitar string" sign. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

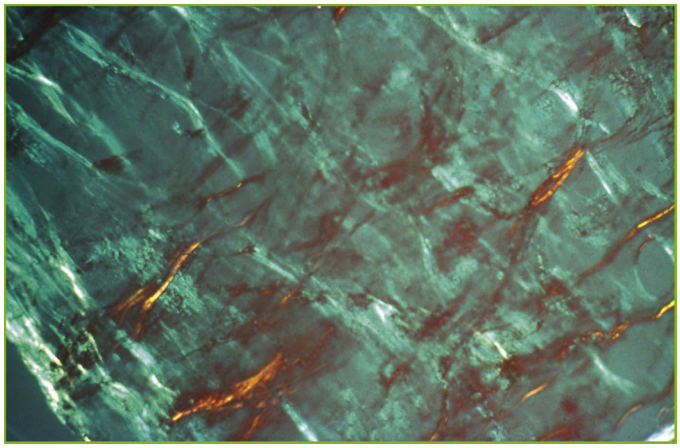

FIG. E4 Fat aspiration. (Congo red stain; original magnification, ×1000.) Note preserved fat cell interstices. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

BOX E1 Recommended Diagnostic Evaluation for Amyloidosis

- CBC
- Sodium, potassium, alkaline phosphatase, calcium, phosphorus, AST, bilirubin, creatinine, β_2-microglobulin, glucose, cholesterol, uric acid, thyroid profile
- Immunofixation; serum; immunofixation urine; nephelometric assay if immunoglobulin free light chains; immunoglobulins G, A, and M
- Troponin, NT-proBNP
- Factor X and prothrombin time
- Chest x-ray, ECG, echocardiogram with Doppler and strain imaging

AST, Aspartate aminotransferase; *ECG,* electrocardiogram; *NT-proBNP,* N-terminal pro b-type natriuretic peptide.
Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

regimens. Table E4 summarizes major treatment options for amyloidosis.
- Trials with oligonucleotide drugs (inotersen, patisiran) have shown improved multiple clinical manifestations of hereditary transthyretin amyloidosis.
- Patients who develop renal failure can be supported with hemodialysis or renal transplant.
- Liver transplantation has been used successfully in patients with familial amyloidosis.
- Recognition and treatment of the underlying disorder is needed for secondary amyloidosis.
- Table E5 summarizes supportive treatment options for all types of amyloidosis.

DISPOSITION

Prognosis is determined primarily by the presence or absence of cardiac involvement and the form of amyloidosis:
- In patients with endomyocardial biopsy–documented cardiac amyloidosis, longer-term survival is more strongly associated with New York Heart Association functional class compared with ECG or echocardiography variables.
- In AA, eradication of the predisposing disease slows and can occasionally reverse the progression of amyloid disease. Median survival after diagnosis is 133 mo.
- Patients with familial amyloidotic polyneuropathy generally have a prolonged course lasting 10 to 15 yr.
- The progression of amyloidosis associated with renal hemodialysis can be improved with newer dialysis membranes that can pass beta 2-microglobulin.
- Median survival in patients with overt congestive heart failure (CHF) is ~6 mo; it is 30 mo without CHF.

AUTHOR: **Fred F. Ferri, MD**

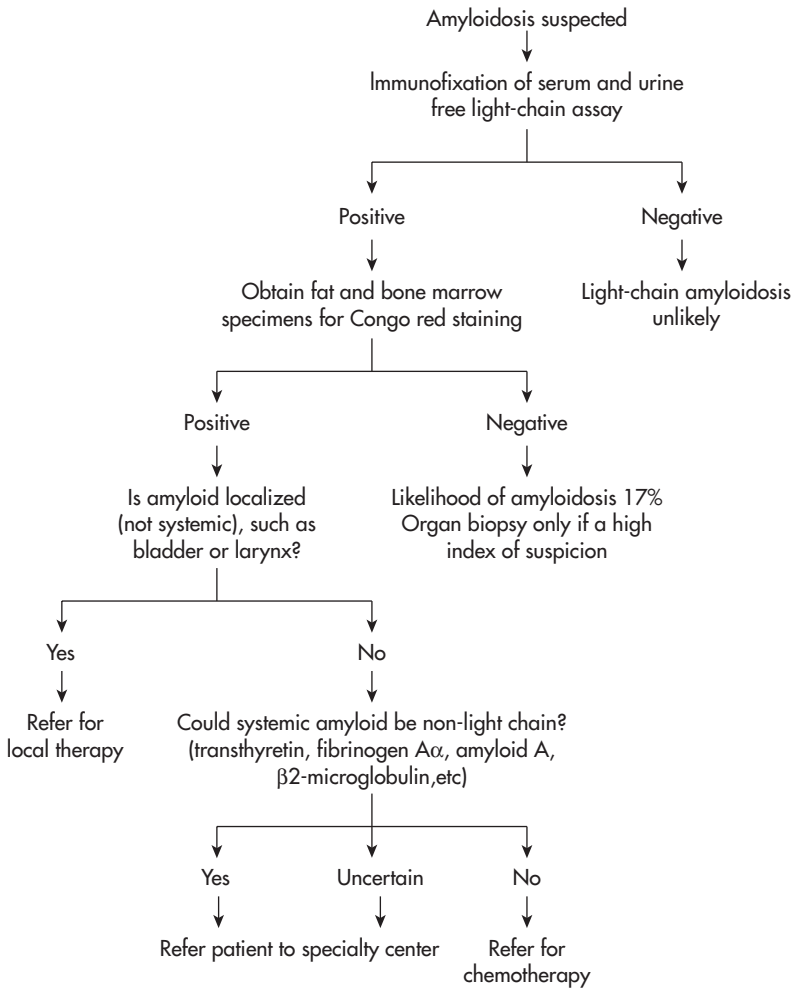

FIG. E5 Diagnostic algorithm for use when amyloidosis is suspected. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

BOX E2 Amyloid Staging

Patients are assigned a score of 1 point for each of the following:
- FLC-diff ≥18 mg/dl
- cTnT ≥0.025 ng/ml
- NT-proBNP ≥1800 pg/ml

This creates stages I–IV with scores of 0–3 points, respectively
Median survival (months):
- 94.1
- 40.3
- 14
- 5.8

1. Difference between the involved and uninvolved serum light chain levels
2. Cardiac troponin T
3. N-terminal pro-brain natriuretic peptide

cTnT, Cardiac troponin T; *FLC-diff,* difference between involved and uninvolved free light chains; *NT-proBNP,* N-terminal pro-B-type natriuretic peptide
Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE E4 Major Treatment Options for Amyloidosis

AL Amyloidosis

Intravenous melphalan with autologous stem cell rescue
- Granulocyte colony-stimulating factor–mobilized peripheral blood stem cell collection
- Intravenous melphalan 140-200 mg/m^2
- Autologous stem cell reinfusion

Cyclic oral melphalan and dexamethasone
- Melphalan 0.22 mg/kg/day × 4 days
- Dexamethasone 20-40 mg/day × 4 days, or weekly
- Repeat administration every 4 weeks

Immunomodulators
- Lenalidomide 5-15 mg/day × 21 days
- Dexamethasone 20-40 mg/day weekly
- Repeat administration every 4 weeks

Proteasome inhibitors
- Intravenous bortezomib, 0.7-1.6 mg/m^2 1-2 times per week
- Repeat every 3-5 weeks

AA Amyloidosis
- Aggressive treatment of underlying inflammatory disease
- Medical or surgical treatment of underlying infection
- Colchicine 1.2-1.8 mg/day for AA amyloidosis secondary to familial Mediterranean fever
- Antifibril drug, eprosidate (investigational)

ATTR Amyloidosis
- Orthotopic liver transplantation
- Transthyretin stabilizers: Tafamidis, diflunisal (investigational)
- Oligonucleotide drugs: Inotersen, patisiran (investigational)

AA, Primary amyloidosis; *AL,* secondary amyloidosis; *ATTR,* transthyretin-related hereditary amyloidosis.
Modified from Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.

TABLE E5 Supportive Treatment for All Types of Amyloidosis

Organ System	Symptom	Treatment Options
Cardiac	Congestive failure	Salt restriction of 1-2 g/day
		Diuretics: Furosemide, spironolactone, metolazone
	Arrhythmia	Pacemaker
		Automatic implantable cardiac defibrillator
		Antiarrhythmics
Renal	Nephrotic syndrome	Salt restriction of 1-2 g/day
		Elastic stockings, leg elevation
		Maintaining dietary protein
		Angiotensin-converting enzyme inhibitor, if blood pressure tolerates
	Renal failure	Dialysis (long-term ambulatory peritoneal dialysis or hemodialysis)
Autonomic nervous	Orthostatic hypotension	Midodrine
		Increased dietary salt or added fludrocortisone, depending on edema
		Elastic stockings
	Gastric atony or ileus	Small frequent feedings (6/day) low in fat
		Oral nutritional supplements
		Jejunostomy tube feeding
		Parenteral nutrition
Gastrointestinal	Diarrhea	Low-fat diet (≤40 g)
		Psyllium hydrophilic mucilloid (Metamucil)
		Loperamide hydrochloride (Imodium)
		Tincture of opium
		Parenteral nutrition
	Macroglossia	Soft solid diet
		Partial glossectomy (rarely effective)
Peripheral nervous	Sensory neuropathy	Avoiding trauma
		Gabapentin (Neurontin) 100-300 mg 3 times daily
		Amitriptyline 25-50 mg at bedtime
		Pregabalin (Lyrica) 50-100 mg 3 times daily
	Motor neuropathy	Ankle-foot orthotics for footdrop
		Physical therapy
Hematologic	Intracutaneous bleeding	Avoiding trauma, antiplatelet agents
	Factor X deficiency	Factor replacement (recombinant factor VIIa, prothrombin complex concentrates)
		Splenectomy for splenomegaly

SUGGESTED READINGS

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Benson MD et al: Inotersen treatment for patients with hereditary transthyretin amyloidosis, *N Engl J Med* 379:22-31, 2018.

Coelho T et al: Safety and efficacy of RNA: therapy for transthyretin amyloidosis, *N Engl J Med* 369:819-829, 2013.

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Kumar SK et al: Recent improvements in survival in primary systemic amyloidosis and the importance of an early mortality risk score, *Mayo Clin Proc* 86(1):12-18, 2011.

Maurer MS et al: Non-invasive identification of ATTRwt cardiac amyloid: the re-emergence of nuclear cardiology, *Am J Med* 128:1275-1280, 2015.

Maurer MS et al: Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy, *N Engl J Med* 379:1007-1016, 2018.

BASIC INFORMATION

DEFINITION

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal degenerative neuromuscular condition of undetermined etiology affecting corticospinal tracts and anterior horn cells, thereby resulting in dysfunction of both upper motor neurons (UMNs) and lower motor neurons (LMNs).

SYNONYMS

Lou Gehrig disease
ALS

ICD-10CM CODE
G12.21 Amyotrophic lateral sclerosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Two new cases per 100,000 persons per yr.
- Onset is usually between the ages of 50 and 70 yr.
- Male:female ratio is 1.8:1.

PREVALENCE: The estimated prevalence of ALS is 5.2 per 100,000 population. Whites, males, and Hispanics, persons aged ≥60 yr, and those with a family history of ALS are more likely to develop the disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- LMN signs (weakness, hypotonia, muscle wasting, fasciculations, hyporeflexia or areflexia).
- UMN signs (loss of fine motor dexterity, spasticity, extensor plantar responses, hyperreflexia, clonus).
- Preservation of extraocular movements, sensation, bowel and bladder function.
- Dysarthria, dysphagia, pseudobulbar affect, frontal lobe dysfunction.
- Respiratory insufficiency progressing to respiratory failure and death typically occurs late in the disease.
- Concomitant frontotemporal dementia in 15% and executive dysfunction in another 50%.
- Pseudobulbar affect, characterized by inappropriate crying or laughing not provoked by typical emotional triggers, is common and treatable.
- ALS comprises approximately 90% of adult-onset motor neuron diseases. Other presentations of motor neuron disease include progressive muscular atrophy, primary lateral sclerosis, progressive bulbar palsy, progressive pseudobulbar palsy, and ALS-parkinsonism-dementia complex.

ETIOLOGY

- 90% to 95% of all cases are sporadic. 5% to 10% of cases are familial; known genetic mutations include C9orf72 hexanucleotide repeat expansion (chromosome 9 open reading frame 72), responsible for 40% of familial ALS and 7% of sporadic ALS (and virtually all cases of ALS associated with frontotemporal dementia); copper-zinc superoxide dismutase enzyme (SOD1) mutations (12% of familial cases), TAR DNA-binding protein mutations (4% of familial cases), FUS (4% of familial cases and rarely associated with frontotemporal dementia), among many others.
- Increased risk factors in whites, non-Hispanics, age >60 yr, family history of ALS, previous exposure to heavy metals, pesticides, BMAA.[1]

[1]Mehta P et al: Prevalence of ALS in USA, 2012–2013, *MMWR* 65(8), 2016.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Multifocal motor neuropathy with conduction block
- Cervical spondylotic myelopathy with polyradiculopathy
- Spinal stenosis with compression of lumbosacral nerve roots
- Chronic inflammatory demyelinating polyneuropathy with central nervous system lesions
- Syringomyelia
- Syringobulbia
- Foramen magnum tumor
- Meningeal carcinomatosis
- Spinal muscular atrophy
- Polyglucosan body disease
- Bulbospinal muscular atrophy (Kennedy disease)
- Monomelic amyotrophy
- Lyme disease
- ALS-like syndromes have been reported in the setting of lead intoxication, HIV, hyperparathyroidism, hyperthyroidism, lymphoma, and vitamin B_{12} deficiency.

WORKUP

- Diagnosis is based on clinical findings, EMG results, and exclusion of alternative causes.
- MRI of brain and spine to exclude alternative causes
- Electromyography and nerve conduction studies (El Escorial criteria; see Table E1)
- Assessment of respiratory function (forced vital capacity [FVC], negative inspiratory force)
- Assessment of swallowing ability and nutritional status

TABLE E1 Revised El Escorial Diagnostic Criteria for Amyotrophic Lateral Sclerosis (ALS)

The Diagnosis of ALS Requires:

- [A:1] Evidence of LMN degeneration by clinical, electrophysiologic, or neuropathologic examination
- [A:2] Evidence of UMN degeneration by clinical examination and
- [A:3] Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination

Together with the Absence of:

- [B:1] Electrophysiologic and pathologic evidence of another disease that might explain the signs of LMN and/or UMN degeneration and
- [B:2] Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiologic signs

Levels of Diagnostic Certainty:

Definite ALS
- UMN signs and LMN signs in 3 regions

Probable ALS
- UMN signs and LMN signs in 2 regions with UMN signs rostral to LMN signs

Probable ALS—Laboratory Supported
- UMN signs in 1 or more regions *and* LMN signs defined by EMG in at least 2 regions

Possible ALS
- UMN signs and LMN signs in 1 region (together) or
- UMN signs in 2 or more regions
- UMN and LMN signs in 2 regions with *no* UMN signs rostral to LMN signs

EMG, Electromyography; *LMN,* lower motor neuron; *UMN,* upper motor neuron.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

LABORATORY TESTS

- Vitamin B_{12}, thyroid function, parathyroid hormone, HIV may be considered
- Serum protein electrophoresis with immunofixation
- Consider DNA studies for spinal muscular atrophy, bulbospinal atrophy (Kennedy disease), hexosaminidase levels (late onset Tay Sachs) in a pure LMN syndromes
- 24-hour urine for heavy metals if indicated
- Genetic studies in familial ALS with appropriate genetic counseling

IMAGING STUDIES

- Craniospinal neuroimaging contingent on clinical scenario. MRI of the brain and spinal cord are useful to help exclude structural mimics.
- Modified barium swallow to evaluate aspiration risk.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Bilevel positive airway pressure (BiPAP) ventilation may improve quality of life and may increase tracheostomy-free survival in patients with respiratory difficulty (defined by orthopnea or FVC 50% of predicted).
- Percutaneous endoscopic gastrostomy (PEG) tube placement improves nutritional intake, promotes weight stabilization, and eases medication administration. Some studies suggest PEG placement may prolong life 1 to 4 mo, particularly when placed before FVC falls to ≤50% of predicted value.
- Nutrition, speech therapy, physical and occupational therapy services.
- Suction device for sialorrhea.
- Cough assist device for ineffective coughing and maintaining a clear airway.
- Communication may be eased with computerized assistive devices.
- Early discussion of living will, resuscitation orders, desire for PEG and tracheostomy, potential long-term care options.
- Encourage contact with local support groups.

ACUTE GENERAL Rx

- Treatments currently available, riluzole and edaravone, do not cure ALS but slow disease progression in certain patients.
- Riluzole, a glutamate antagonist, was the first FDA-approved medication known to extend tracheostomy-free survival in patients with ALS. Dosage is 50 mg q12h, at least 1 hr before or 2 hr after meals. It is shown to prolong survival by 2 to 3 months. Manufacturer recommends checking alanine aminotransferase (ALT) once a month for 3 months initially, followed by once every 3 months until the first yr of therapy is completed. ALT should be checked periodically thereafter.
- Edaravone was FDA approved in 2017 and was found to slow down physical decline by 33% compared with placebo in a phase III trial lasting 6 months. It is administered intravenously, requiring an initial cycle of daily infusions for 14 consecutive days, followed by 14 days without infusion. Subsequent treatment cycles require ten infusions over 14 days, followed by 14 days without infusions. Cost is a factor, and insurance coverage is variable.

CHRONIC Rx

- Sialorrhea may respond to either glycopyrrolate or amitriptyline (consider either propranolol or metoprolol if secretions are thick). Botulinum toxin may be effective in medically refractory cases.
- Spasticity may be treated pharmacologically with baclofen, tizanidine, clonazepam.
- Pseudobulbar affect may improve with amitriptyline, sertraline, or dextromethorphan/quinine.

DISPOSITION

- Currently there is no cure for ALS.
- Mean duration of symptoms is 3 to 5 yr.
- Approximately 20% of patients survive >5 yr.

REFERRAL

- A neurologist experienced in neuromuscular disease is recommended to confirm the diagnosis. One prospective, population-based study suggested improved survival in subjects treated in a multidisciplinary ALS clinic.
- Gastroenterology referral for PEG placement is recommended while FVC remains >50% to minimize morbidity attributable to risks inherent to the procedure.
- Pulmonology referral for bilevel positive pressure airway ventilation (BiPAP).

PEARLS & CONSIDERATIONS

- Patient-physician communication is an integral and essential part in both the initial diagnosis and subsequent treatment of ALS.
- A multidisciplinary approach to supportive care may lead to an improved level of daily functioning and foster an increased sense of independence.

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RELATED CONTENT

Amyotrophic Lateral Sclerosis (Patient Information)

AUTHORS: **Taylor Harrison, MD,** and **Joseph S. Kass, MD, JD, FAAN**

BASIC INFORMATION

DEFINITION

An anaerobic infection is caused by one of a group of bacteria that requires a reduced oxygen tension for growth.

ICD-10CM CODES

A41.4	Sepsis, anaerobic
A48	Cellulitis, anaerobic

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- May occur at any site, but most are anatomically related to mucosal surfaces
- Should be suspected when there is foul-smelling tissue, soft tissue gas, necrotic tissue, or abscesses
- Head and neck:
  1. Odontogenic infections from dental or soft tissue possibly progressing to periapical abscesses, at times extending to bone
  2. Both anaerobic and aerobic pathogens in chronic sinusitis, chronic mastoiditis, peritonsillar abscess, and chronic otitis media
  3. Complications: Deep neck space infections, brain abscesses, mediastinitis
  4. Specific examples of anaerobic infections in head and neck:
     a. Ludwig angina: Bilateral infection of sublingual and submandibular spaces that causes swelling of the base of the tongue with potential airway compromise. Usually mixed aerobic and anaerobic flora
     b. Lemierre syndrome: Jugular vein suppurative thrombophlebitis caused by anaerobic bacteria: *Fusobacterium necrophorum*
- Pleuropulmonary:
  1. May involve anaerobes present in the oropharynx
  2. Aspiration more common in persons with altered mental status or seizures
  3. Anaerobic bacteria more likely in those with gingivitis or periodontitis
  4. Manifestations: Necrotizing pneumonia, empyema, lung abscess
- Intraabdominal:
  1. Disruption of intestinal integrity leading to infection involving anaerobic bacteria
  2. Bacteria from colonic neoplasm, perforated appendicitis, diverticulitis, or bowel surgery, causing bacteremia, peritonitis, at times intraabdominal abscesses
  3. Resulting infections usually mixed, containing both anaerobes and aerobes
- Female genital tract:
  1. Anaerobes in bacterial vaginosis, salpingitis, endometritis, pelvic abscesses, septic abortion; infections tend to be mixed
  2. Possible pelvic thrombophlebitis when resolving pelvic infection is accompanied by new or persistent fever
- Other anaerobic infections:
  1. Skin and soft tissue infection at any site
  2. More commonly associated infections: Synergistic gangrene, bite wound infections, infected decubitus ulcers
  3. Clinical significance of anaerobes in diabetic foot infections unclear
  4. Anaerobic bacteremia is not common with source usually intraabdominal, followed by female genital tract, pleuropulmonary, and head and neck infections
  5. Osteomyelitis especially when associated with decubitus ulcers or vascular insufficiency
  6. Facial bone osteomyelitis from adjacent infections of the teeth or sinuses

ETIOLOGY

- Most commonly endogenous, arising from bacteria that normally line mucosal surfaces
- Disruption of mucosal barriers resulting from various conditions (trauma, ischemia, surgery, perforation), with infection occurring when organisms gain access to normally sterile sites, causing tissue destruction and abscess formation
- Synergy between different anaerobes or between anaerobes and aerobes important
- Examples of anaerobic bacteria include gram-negative bacteria such as *Bacteroides* species, *Fusobacterium* and *Prevotella* species; and gram-positive bacteria such as *Peptostreptococcus, Clostridium* species, and *Actinomyces* species

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary differential possibility is an aerobic bacterial infection without the presence of anaerobic bacteria.
- Ischemic necrosis without accompanying anaerobic infection (or "dry" gangrene [non-infected necrosis] vs. "wet" gangrene [infected tissue with anaerobic infection]).

WORKUP

- Specimens submitted for anaerobic culture should be processed within 30 min and may take up to 5 to 7 days to grow
- Large volume of material more likely to have significant growth; swabs less efficient for transporting infected material
- Blood cultures—preferably before antibiotic administration

LABORATORY TESTS

- Elevated white blood cell (WBC) count, with extremely high WBC counts sometimes seen with pseudomembranous colitis
- Positive stool *C. difficile* by polymerase chain reaction (PCR) or nucleic acid amplification test (NAAT)
- Increased lactate levels in ischemia or perforation
- Possible positive blood or wound cultures, but failure to grow anaerobes in culture may be common, attributed to inadequate culturing techniques or fastidious organisms

IMAGING STUDIES

- Plain film of an affected area to show gas in tissues, free air resulting from a perforated viscus, or an air/fluid level inside an abscess
- Ultrasound, computed tomography (CT) scan, or MRI to reveal abscesses or tissue destruction

TREATMENT

NONPHARMACOLOGIC THERAPY

- Removal of necrotic tissue
- Drainage of abscesses (accomplished by CT scan–guided percutaneous drainage)

ACUTE GENERAL Rx

Oral antibiotics with anaerobic activity: Clindamycin, metronidazole, and chloramphenicol

- Broader spectrum of activity with amoxicillin/clavulanate
- Penicillin VK in odontogenic infections
- Oral vancomycin is now the preferred agent for *C. difficile*–associated diarrhea, and metronidazole is now considered a second line agent. Use oral vancomycin for subsequent episodes and for pulse or taper regimens of *C difficile*–associated diarrhea treatment

Parenteral antibiotics for more serious illness

- IV clindamycin, metronidazole, and chloramphenicol
- Cephalosporins (with anaerobic or mixed infections coverage): Cefoxitin and cefotetan
- Extended-spectrum penicillins (e.g., piperacillin) and combination beta-lactamase plus beta-lactamase inhibitor drugs (e.g., clavulanic acid, sulbactam, tazobactam)
  1. Significant anaerobic activity, plus various degrees of broad-spectrum coverage
  2. Include ampicillin/sulbactam, ticarcillin/clavulanate, and piperacillin/tazobactam
- Imipenem or other carbapenems, such as meropenem, doripenem, or ertapenem, which are broad-spectrum agents with extensive anaerobic activity
- Actinomycosis treated with penicillin for 6 to 12 mo
- SMX/TMP and fluoroquinolones are generally ineffective, but some newer quinolones (e.g., moxifloxacin) have inhibitory activity against anaerobes

DISPOSITION

It is essential that all necrotic debris be removed when treating an anaerobic infection or it will recur; follow-up is critically important to ensure resolution of the process.

REFERRAL

Refer to a surgeon if drainage is required; infectious disease consultation may be useful in complicated patients or if treatment regimen is failing or slow to respond.

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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Brook I: Spectrum and treatment of anaerobic infections, *J Infect Chemother* 22:1-13, 2016.

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Nagy E: Anaerobic infections: update on treatment considerations, *Drugs* 70(7):841-858, 2010.

BASIC INFORMATION

DEFINITION

A fissure is a tear in the epithelial lining of the anal canal (i.e., from the dentate line to the anal verge). Acute anal fissures typically heal with conservative management within 6 weeks. Chronic fissures require a more aggressive, surgical approach.

SYNONYMS

Anorectal fissure
Anal ulcer

ICD-10CM CODES

K60.0	Acute anal fissure
K60.1	Chronic anal fissure
K60.2	Anal fissure, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

An estimated 235,000 new cases of anal fissure occur annually in the U.S. Although they can occur at any age, they are more common in infants and middle-aged adults. They occur more in men than women. Women are more likely to have anterior fissure than men (10% vs. 1%, respectively).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

With separation of the buttocks will see a tear in the posterior midline or, less frequently, in the anterior midline

- Acute anal fissure:
  1. Sharp burning or tearing pain accompanying the passage of stool
  2. Bright-red blood on toilet paper, a streak of blood on the stool or in the water
  3. Appear as a fresh laceration (Fig. E1)
- Chronic anal fissure:
  1. Perianal pruritus or skin irritation
  2. Pain less intense or not present
  3. Intermittent bleeding
  4. Sentinel tag at the caudal aspect of the fissure, hypertrophied anal papilla at the proximal end (Fig. E2)
  5. Have raised edges exposing the horizontally oriented fibers of the internal anal sphincter; appearance due to chronic infection and fibrosis
- Atypical fissure can be acute or chronic:
  1. More likely to occur at locations other than the midline
  2. Extends proximal to the dentate line
  3. Unusually wide or deep; multiple, recurring, or nonhealing
  4. Associated with perianal tag that is edematous and tender
  5. More commonly associated with an underlying disease process

ETIOLOGY

- Most initiated after passage of a large, hard stool
- May result from frequent defecation and diarrhea
- Bacterial infections: Tuberculosis (TB), syphilis, gonorrhea, chancroid, lymphogranuloma venereum
- Viral infections: Herpes simplex virus, cytomegalovirus, human immunodeficiency virus
- Inflammatory bowel disease (IBD): Crohn disease, ulcerative colitis
- Trauma: Surgery (hemorrhoidectomy), foreign bodies, anal intercourse
- Malignancy: Carcinoma, lymphoma, Kaposi sarcoma

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Proctalgia fugax
- Thrombosed hemorrhoid
- Carcinoma
- Anal fistula

WORKUP

- Digital rectal examination after lubricating the entire anus with anesthetic jelly (i.e., 2% lidocaine) and waiting 5 to 10 min
- Anoscopy
- Proctosigmoidoscopy to exclude inflammatory or neoplastic disease
- Biopsy if doubt exists about the etiology of the condition
- All studies done under adequate anesthesia

IMAGING STUDIES

- Colonoscopy if diagnosis of IBD or malignancy is suspected
- Small-bowel series occasionally obtained for similar reasons

TREATMENT

NONPHARMACOLOGIC THERAPY

- Sitz baths
- High-fiber diet and increased oral fluid intake

ACUTE GENERAL Rx

- Bulk-producing agent (e.g., Metamucil) and/or stool softener

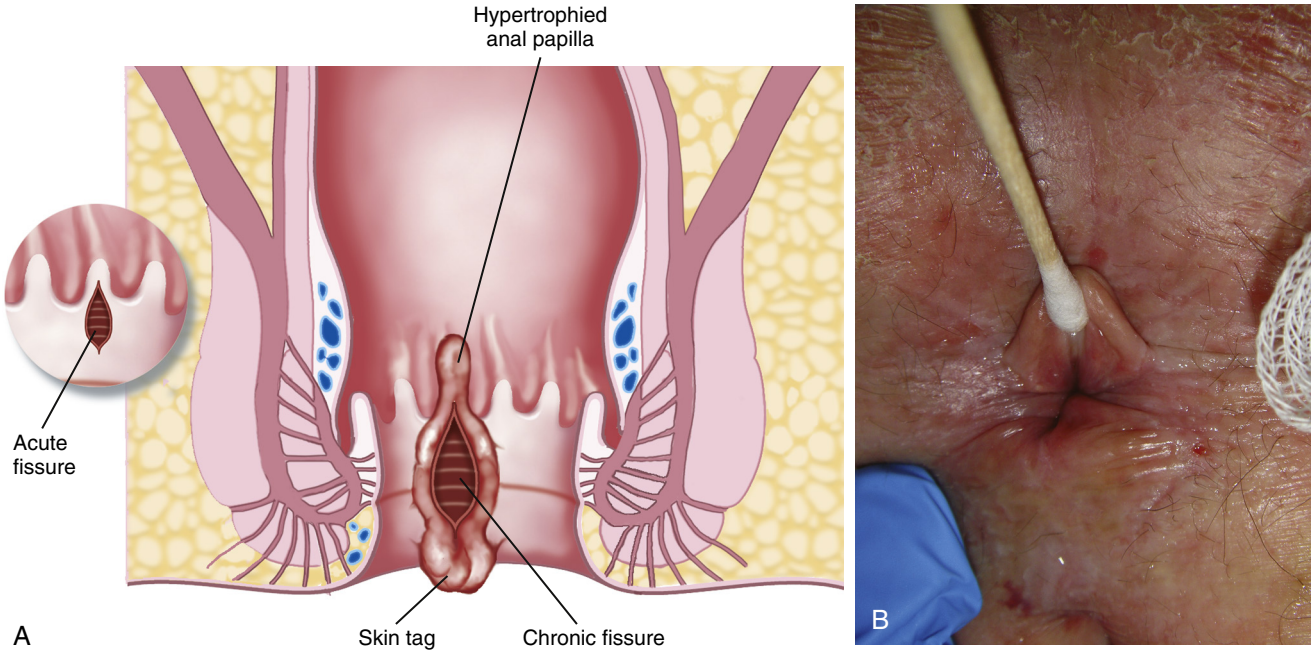

FIG. E1 A, Schematic depiction of acute and chronic anal fissures. An acute fissure is simply a split in the anoderm *(inset).* A chronic fissure can show signs of chronicity with rolled edges, fibrosis, a hypertrophied anal papilla proximally, a tender distal skin tag, and exposed internal anal musculature. **B,** Inspection of an acute anal fissure with a cotton-tipped swab. Once an acute fissure is identified, no internal examination is needed until the fissure is healed. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

FIG. E2 Chronic fissures are characterized by fibrosis, a skin tag at the distal extent of the fissure, and/or a hypertrophied papilla at the proximal end. The internal sphincter muscle may be visible at the base of the fissure. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

- Local anesthetic jelly (may exacerbate pruritus ani)
- Nitroglycerin ointment (0.4%): Apply 1 inch of ointment (equivalent to 1.5 mg of nitroglycerin) intraanally every 12 hours for up to 3 weeks. This medication (Rectiv) is expensive. Topical diltiazem (compounded by pharmacist) is also effective and much less expensive
- Suppositories *not* recommended
- Surgery, if failed medical management after 2 months
- An algorithm for the management of acute, chronic, and recurrent fissures is illustrated in Fig. E3

CHRONIC Rx

- Although less effective, medical treatment should be offered, as it is better tolerated and does not incur the risk of fecal incontinence.
- Surgery: Lateral internal anal sphincterotomy (Fig. E4, Fig. E5). It is a more durable treatment for chronic anal fissure compared with topical nitroglycerin therapy and does not compromise long-term fecal continence.
- Topical glyceryl trinitrate ointment.
- Injection of botulinum toxin (Fig. E6) (an injection into each side of the internal anal sphincter) is effective in healing chronic anal fissures in more than 90% of patients.
- Table E1 summarizes treatment of anal fissures.

DISPOSITION

Outpatient surgery

REFERRAL

- If fissure does not resolve with conservative therapy in 4 to 6 wk
- If patient prefers surgery for acute fissure
- If patient has chronic fissure

PEARLS & CONSIDERATIONS

COMMENTS

HIV-positive patients should be referred to clinicians who are well versed in the myriad infectious and neoplastic conditions that masquerade as anal ulcers in these patients.

RELATED CONTENT

Anal Fissure (Patient Information)
Anorectal Fistula (Related Key Topic)
Hemorrhoids (Related Key Topic)

AUTHOR: **Maria E. Soler, MD, MPH, MBA**

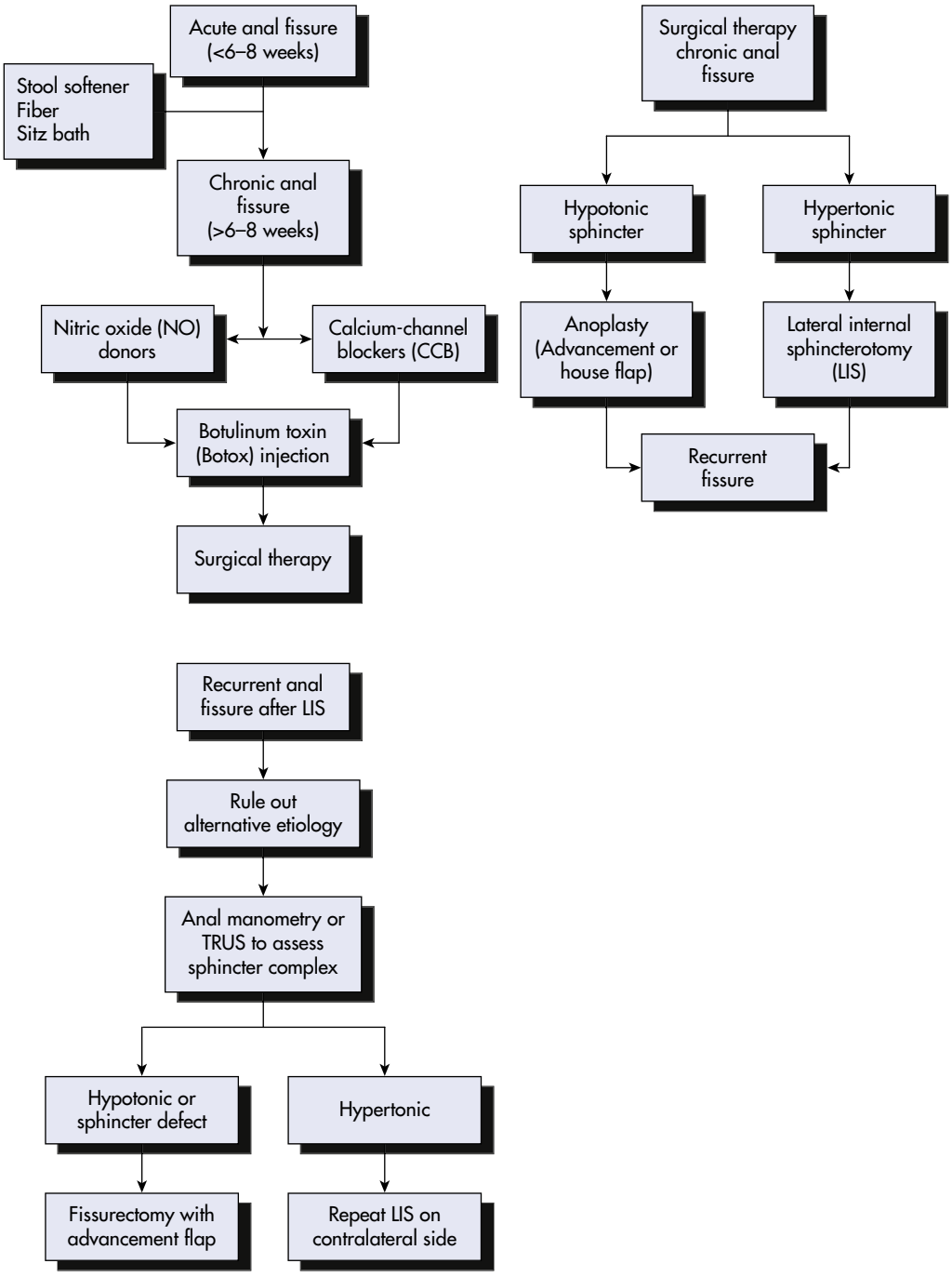

FIG. E3 Algorithm: Management of acute, chronic, and recurrent fissures. *TRUS,* Transrectal ultrasound. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

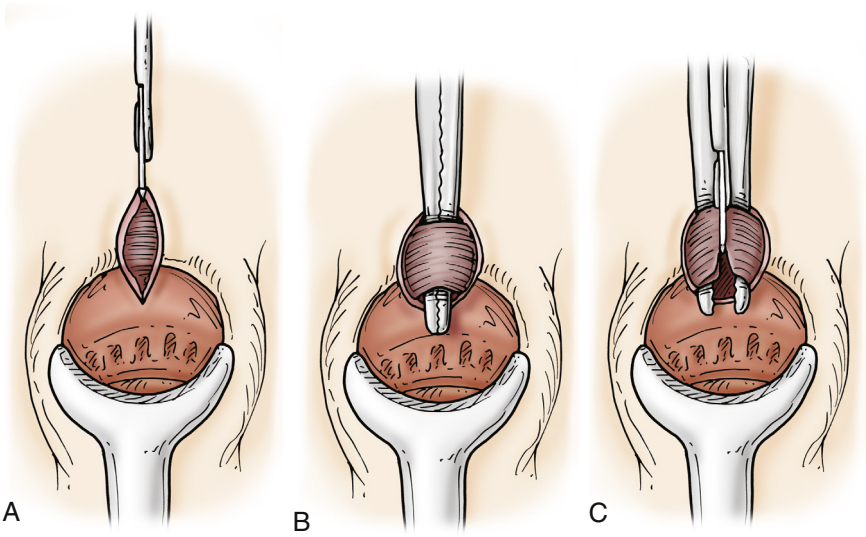

FIG. E4 Open lateral internal sphincterotomy. A, First the overlying anoderm is incised. The internal sphincter muscle is then dissected free **(B)** and divided **(C).** (Reprinted with permission from Wexner SW, Beck DE [eds]: *Fundamentals of anorectal surgery*, ed 2, London, 1998, Saunders; pp. 214-215. In Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

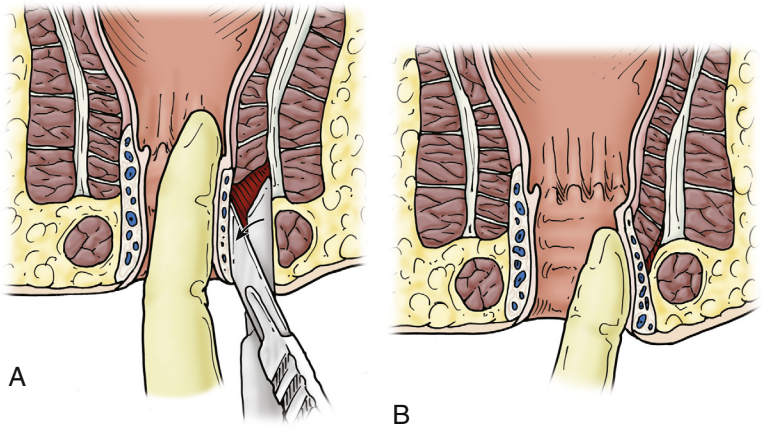

FIG. E5 Closed lateral internal sphincterotomy. A, After anesthetizing the perianal area, the finger is inserted into the anal canal, a #11 blade scalpel is inserted in the intersphincteric groove, and the muscle is cut toward the finger. **B,** After cutting the muscle, a wedge defect should be felt in the internal sphincter muscle. (Reprinted with permission from Wexner SW, Beck DE [eds]: *Fundamentals of anorectal surgery*, ed 2, London, 1998, Saunders; pp. 214-215. In Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

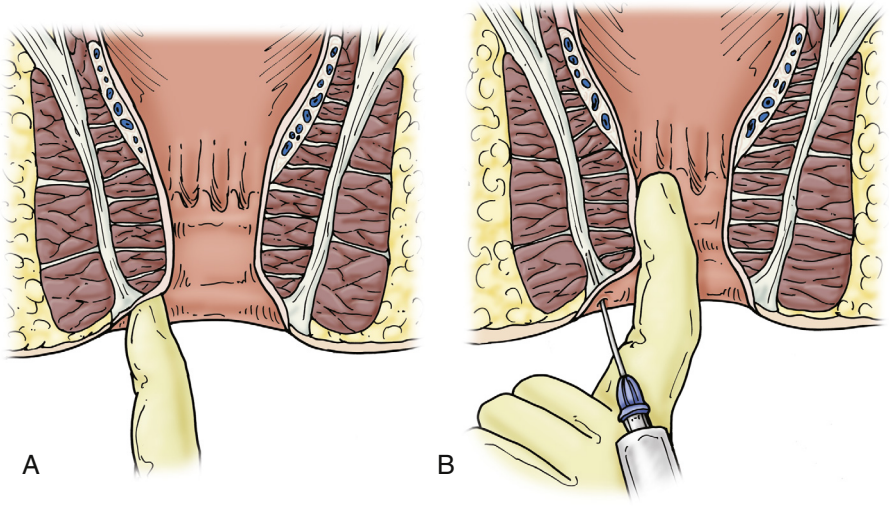

FIG. E6 Botox injection is performed by injection of Botox at 10 and 2 o'clock anteriorly in the intersphincteric groove. First, the index finger palpates the intersphincteric groove **(A),** and the needle is then placed within the groove **(B)** to inject the Botox. (Reprinted with permission from Braasch C, Sedgwick K, Veidenheimer M, Ellis H [eds]: *Atlas of abdominal surgery*, Philadelphia, 1991, Saunders; p. 199. In Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

TABLE E1 Treatment of Acute and Chronic Anal Fissures

Treatment	Comments
Acute	
Increase oral fluids, high-fiber diet, fiber supplements, Sitz baths, and stool softeners if needed	Avoid digital rectal examination until the fissure is healed unless the diagnosis is in doubt (then perform the examination in the operating room)
	Usually responds to these measures
Chronic	
As for acute, usually with the addition of one of the following:	Avoid digital examination unless the diagnosis is in doubt
0.2%-0.4% nitroglycerin ointment applied to the anal area	Headache is a common side effect
	Long-term success has been questioned
Calcium channel blockers (topical nifedipine or topical 2% diltiazem cream) applied to the anal area	Seem promising, but long-term success has been questioned
	Side effects (especially headache) may be less common than with nitroglycerin ointment
Botulinum toxin A injected into the anal muscle	Dose and optimal injection site are not clear
	Expensive
	Long-term success is unknown
Lateral internal sphincterotomy	Standard treatment
	Best results, with >90% long-term healing rate
	Durable
	Can lead to fecal incontinence

From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

Anaphylaxis

BASIC INFORMATION

DEFINITION

Anaphylaxis is a severe allergic reaction that is rapid in onset and life-threatening. It is characterized by respiratory, cardiovascular, gastrointestinal, and cutaneous manifestations, as well as vasodilatory hemodynamic changes in response to a particular allergen. Anaphylactoid reaction is an entity closely related to anaphylaxis and is caused by release of mast cells and basophil mediators triggered by non–immunoglobulin E (IgE)-mediated events.

SYNONYM

Anaphylactoid reaction

ICD-10CM CODES	
T78.2	Anaphylactic shock, unspecified, initial encounter
T78.00XA	Anaphylactic reaction due to unspecified food, initial encounter
T80.52XA	Anaphylactic reaction due to vaccination, initial encounter
T63.94XA	Toxic effect of contact with unspecified venomous animal, undetermined, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The incidence of anaphylaxis in the U.S. is 50 to 2000 episodes per 100,000 persons. Lifetime prevalence is 0.05% to 2%, with a mortality rate of 1%. Anaphylaxis rates are 0.0004% for food, 0.7% to 10% for penicillin, 0.22% to 1% for contrast media, and 0.5% to 5% after insect stings. Annual mortality is nearly 2000 persons/yr in the U.S.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Urticaria, pruritus, skin flushing, angioedema (Table E1)
- Dyspnea, cough, wheezing, shortness of breath
- Nausea, vomiting, diarrhea, difficulty swallowing
- Hypotension, tachycardia, weakness, dizziness, malaise, vascular collapse (Table E2)

ETIOLOGY

Anaphylaxis results from a sudden systematic release of histamine and other inflammatory mediators from basophils and mast cells. This causes swelling of the mucous membranes and the urticarial rash on the skin. Virtually any substance may induce anaphylaxis. In an acute setting, the cause of anaphylaxis is often unidentifiable.

- Foods and food additives: Peanuts, tree nuts, eggs, shellfish, fish, cow's milk, fruits, soy
- Medications: Antibiotics (especially penicillins and sulfa-based agents), insulin, allergen extracts, opiates, vaccines, NSAIDs, contrast media, streptokinase
- Environmental exposures: Bee or wasp sting, snake venom, fire ant venom
- Blood products: Plasma, immunoglobulin, cryoprecipitate, whole blood
- Latex
- Box 1 summarizes agents frequently associated with immune and nonimmune types of anaphylaxis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Endocrine disorders (carcinoid, pheochromocytoma)
- Globus hystericus, anxiety disorder
- Systemic mastocytosis
- Pulmonary embolism, serum sickness, vasovagal reactions
- Severe asthma (the key clinical difference is the abrupt onset of symptoms in anaphylaxis versus a history of progressive worsening of symptoms)
- Scombroid poisoning
- Localized angioedema
- Septic shock or other form of vasodilatory shock
- Airway foreign body

WORKUP

Workup is aimed at ruling out other conditions that may mimic anaphylaxis. Given the potentially life-threatening nature of anaphylaxis, treatment should not be delayed. Clinical criteria for diagnosing anaphylaxis are summarized in Box 2.

LABORATORY TESTS

- Laboratory evaluation is generally not helpful because anaphylaxis is typically a clinical diagnosis.
- Elevated serum and urine histamine levels and serum tryptase levels can be useful for diagnosis of anaphylaxis, but these tests are not commonly available in the emergency setting.

IMAGING STUDIES

- Generally not helpful.
- Chest radiography for evaluation of foreign body aspiration or pulmonary pathology is indicated in patients with acute respiratory compromise.
- Consider ECG in all patients with sudden loss of consciousness or reports of chest pain or dyspnea and in any elderly patient. ECG in anaphylaxis usually reveals sinus tachycardia.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Establish and protect airway. Provide supplemental O_2 if indicated.
- Intravenous (IV) access should be rapidly established, and IV fluids (i.e., normal saline) should be administered.
- Cardiac monitoring is recommended.

ACUTE GENERAL Rx

- 0.3 to 0.5 mg intramuscular epinephrine (1:1000 concentration) should be rapidly administered for adults and children >30 kg in the lateral thigh. 0.01 mg/kg intramuscular epinephrine (1:1000 concentration) should be administered for children <30 kg. Intramuscular administration is preferred because it provides more reliable and quicker rise to effective plasma levels. The dose may be repeated after approximately 5 to 15 min if symptoms persist.
- Adjunct therapies include H_1 and H_2 receptor antagonists such as diphenhydramine 25 to 50 mg IV or IM (or PO in mild cases) and famotidine 20 to 40 mg IV (or PO in mild cases). Although useful to improve cutaneous erythema and pruritus, H_1 antagonists are not as effective as epinephrine, since onset of action is 1 to 2 hours and they are not effective in reversing upper airway obstruction or improving hypotension.
- Corticosteroids are not useful in the acute episode because of their slow onset of action; however, they should be administered in most cases to prevent prolonged or recurrent anaphylaxis. Commonly used agents are prednisone, methylprednisolone 40 to 250 mg IV in adults (1 to 2 mg/kg in children), or dexamethasone.
- Aerosolized β-agonists (e.g., albuterol, 2.5 to 5.0 mg, repeat prn 20 min) are useful to control bronchospasm.
- Vasopressor therapy with IV epinephrine (1:10,000 concentration) indicated in patients with refractory hypotension/cardiovascular collapse after crystalloid resuscitation.
- Patients taking beta-blocking medications may be refractory to initial treatment; consider administration of IV glucagon.
- Table 3 summarizes drugs and other agents used in anaphylaxis therapy.
- Fig. E1 illustrates an algorithm for the management of a patient with severe anaphylaxis.

PEARLS & CONSIDERATIONS

COMMENTS

- Patient education regarding the nature of the illness and preventive measures is recommended. A documented history of previous anaphylactic episodes or known triggers is the most reliable method of identifying individuals at risk.
- Prescription for a prefilled epinephrine syringe (EpiPen or EpiPen Jr.) should be given, and the patient should be instructed on the use of this emergency kit, and to carry it with them at all times. School-aged children should keep an additional EpiPen at school with the appropriate staff.

BOX 1 Agents Frequently Associated with Immune and Nonimmune Types of Anaphylaxis

Immunologic Mechanisms
IgE-mediated:
- Food (nuts, shellfish, fruits, etc.)
- Venoms (stinging insects)
- Medications (β-lactam antibiotics, NSAIDs, neuromuscular blocking agents, etc.)
- Natural rubber latex
- Seminal fluid
- Radiocontrast media (in some cases)

IgE-Independent
- Radiocontrast media (in most cases)
- Dextrans
- Monoclonal antibodies (Rituximab)
- Medications (β-lactam antibiotics, NSAIDs, etc.)
- Natural rubber latex
- Seminal fluid

Nonimmunologic Mechanisms
- Medications (opioids, protamine, etc.)

NSAIDs, Nonsteroidal antiinflammatory drugs.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

BOX 2 Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized urticaria, itching or flushing, swollen lips/tongue/uvula) and at least one of the following:
   a. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia collapse, syncope, incontinence)
   OR
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized urticaria, itch/flush, swollen lips/tongue/uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced blood pressure or associated symptoms (e.g., hypotonia collapse, syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
   OR
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours)
   a. Infants and children: low systolic blood pressure (age-specific) or >30% decrease in systolic blood pressure
   b. Adults: systolic blood pressure of <90 mm Hg or >30% decrease from that person's baseline

PEF, Peak expiratory flow.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

TABLE 3 Management of a Patient with Anaphylaxis

Treatment	Mechanism(s) of Effect	Dosage(s)	Comments; Adverse Reactions
PATIENT EMERGENCY MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)			
Epinephrine (adrenaline)	α_1-, β_1-, β_2-Adrenergic effects	0.01 mg/kg, up to 0.5 mg IM in lateral thigh Adrenaclick, Auvi-Q, EpiPen Jr./EpiPen: 0.15 mg IM for 8-25 kg 0.3 mg IM for 25 kg or more Epinephrine autoinjector: 0.1 mg for 7.5-15 kg 0.15 mg for 15 to 25 kg 0.3 mg for 25 kg or more	Tachycardia, hypertension, nervousness, headache, nausea, irritability, tremor
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid: 5 mg/5 ml 0.25 mg/kg, up to 10 mg PO	Hypotension, tachycardia, somnolence
Alternative: Diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg up to 50 mg PO or IM	Hypotension, tachycardia, somnolence, paradoxic excitement
Transport to an emergency facility			
EMERGENCY PERSONNEL MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)			
Epinephrine (adrenaline)	α_1-, β_1-, β_2-Adrenergic effects	0.01 mg/kg, up to 0.5 mg IM in lateral thigh Epinephrine autoinjector: 0.1 mg for 7.5-15 kg 0.15 mg for 15 to 25 kg 0.3 mg for 25 kg or more 0.01 ml/kg/dose of 1:1,000 (vial) solution, up to 0.5 ml IM May repeat every 10-15 min For severe hypotension: 0.01 ml/kg/dose of 1:10,000 slow IV push	Tachycardia, hypertension, nervousness, headache, nausea, irritability, tremor

TABLE 3 Management of a Patient with Anaphylaxis—cont'd

Treatment	Mechanism(s) of Effect	Dosage(s)	Comments; Adverse Reactions
SUPPLEMENTAL OXYGEN AND AIRWAY MANAGEMENT			
Volume Expanders			
Crystalloids (normal saline or Ringer lactate)		30 ml/kg in 1st hr	Rate titrated against BP response If tolerated, place patient supine with legs raised.
Colloids (hydroxyethyl starch)		10 ml/kg rapidly followed by slow infusion	Rate titrated against BP response If tolerated, place patient supine with legs raised.
Antihistamines			
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid: 5 mg/5 ml 0.25 mg/kg, up to 10 mg PO	Hypotension, tachycardia, somnolence
Alternative: Diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg, up to 50 mg PO, IM, or IV	Hypotension, tachycardia, somnolence, paradoxic excitement
Ranitidine	Antihistamine (competitive of H_2 receptor)	1 mg/kg, up to 50 mg IV Should be administered slowly	Headache, mental confusion
Alternative: Cimetidine	Antihistamine (competitive of H_2 receptor)	4 mg/kg, up to 200 mg IV Should be administered slowly	Headache, mental confusion
Corticosteroids			
Methylprednisolone	Antiinflammatory	Solu-Medrol (IV): 1-2 mg/kg, up to 125 mg IV Depo-Medrol (IM): 1 mg/kg, up to 80 mg IM	Hypertension, edema, nervousness, agitation
Prednisone	Antiinflammatory	1 mg/kg up, to 75 mg PO	Hypertension, edema, nervousness, agitation
Nebulized albuterol	β-Agonist	0.83 mg/ml (3 ml) via mask with O_2	Palpitations, nervousness, CNS stimulation, tachycardia; use to supplement epinephrine when bronchospasm appears unresponsive; may repeat
POSTEMERGENCY MANAGEMENT			
Antihistamine	Cetirizine (5-10 mg qd) or loratadine (5-10 mg qd) for 3 days		
Corticosteroids	*Optional:* Oral prednisone (1 mg/kg up to 75 mg) daily for 3 days		
Preventive Treatment			
Prescription for epinephrine autoinjector and antihistamine Provide written plan outlining patient emergency management (may download form from http://www.aap.org or http://www.foodallergy.org) Follow-up evaluation to determine/confirm etiology Immunotherapy for insect sting allergy			
Patient Education			
Instruction on avoidance of causative agent Information on recognizing early signs of anaphylaxis Stress early treatment of allergic symptoms to avoid systemic anaphylaxis Encourage wearing medical identification jewelry			

BP, Blood pressure; *CNS,* central nervous system; *IM,* intramuscularly; *IV,* intravenously; *PO,* orally; *qd,* every day.
From Kliegman, RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

- Patients should also be advised to carry or wear a MedicAlert ID describing substances that have caused anaphylaxis.
- Avoidance of radiologic contrast is also recommended in those who have had a prior reaction. However, pretreatment regimens with methylprednisolone or diphenhydramine, exist for those who have had contrast reactions in the past.
- Venom immunotherapy immediately after a sting is effective and recommended for up to 5 yr after the anaphylactic incident.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Rory Merritt, MD, MEHP**

SUGGESTED READINGS

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Williams PM, Arnold JJ: Anaphylaxis: recognition and management, *Am Fam Physician* 84(10):1111-1118, 2011.

TABLE E1 Dynamics of Cardiovascular Abnormalities in Anaphylactic Shock

	At Onset of Reaction	Early Stage (Minutes) with No Treatment	Prolonged Shock
Blood pressure	↓	↓↓	↓↓↓
Pulse	↑	↑	↑↑
Cardiac output	↑	↓	↓↓
PVR	↓	→↓(*)	→↑↓(*)
Intravascular volume	→↓	↓	↓↓↓

*Peripheral vascular resistance (PVR) can vary, likely depending on internal compensation response.

TABLE E2 Signs and Symptoms of Anaphylaxis: Frequency of Occurrence

Sign or Symptom	Percentage of Cases (%)
Cutaneous	>90
Urticaria and angioedema	85-90
Flush	45-55
Pruritus without rash	2-5
Respiratory	40-60
Dyspnea, wheeze	45-50
Upper airway angioedema	50-60
Rhinitis	15-20
Dizziness, syncope, hypotension	30-35
Abdominal	
Nausea, vomiting, diarrhea, cramping pain	25-30
Miscellaneous	
Headache	5-8
Substernal pain	4-6
Seizure	1-2

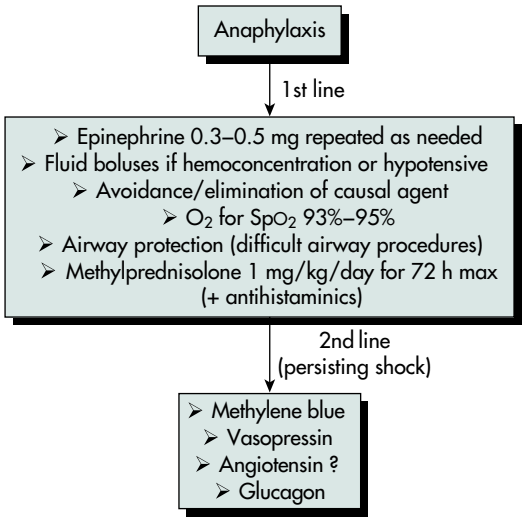

FIG. E1 Management of a patient with severe anaphylaxis. *O_2,* Oxygen; *SpO_2,* oxygen saturation measured by pulse oximetry. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Aplastic anemia (AA) refers to a bone marrow failure syndrome characterized by immune-mediated bone marrow destruction and peripheral blood pancytopenia. Severe aplastic anemia (SAA) is defined by the presence of two of the following criteria: Neutrophil counts $<50 \times 10^9$/L, platelet counts $<20 \times 10^9$/L, or corrected reticulocyte count <1%.

SYNONYMS

Aplastic anemia
AA
Refractory anemia
Hypoplastic anemia

ICD-10CM CODES

D61.9	Aplastic anemia, unspecified
D60.9	Acquired pure red cell aplasia, unspecified
D60.8	Other acquired pure red cell aplasias
D61.09	Other constitutional aplastic anemia
D61.1	Drug-induced aplastic anemia
D61.2	Aplastic anemia due to other external agents
D61.3	Idiopathic aplastic anemia
D61.89	Other specified aplastic anemias and other bone marrow failure syndromes

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The annual incidence of aplastic anemia is 2 cases per million in the Western population and 2 to 3 times higher in Asia.
PREDOMINANT SEX AND AGE: The incidence has two peaks, with most patients presenting between ages 15 and 30 yr or after 60 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fatigue, pallor, exertional shortness of breath, or palpitations are seen secondary to anemia.
- Mucosal bleeding, easy bruising (Fig. E1), petechiae or heavy menstrual bleeding is seen secondary to thrombocytopenia.
- Infection is uncommon at clinical presentation, but severe neutropenia may lead to fever and sore throat.
- Various physical manifestations like short stature, skeletal or nail changes may be seen in congenital forms of aplastic anemia.

ETIOLOGY

- In most patients with idiopathic aplastic anemia, bone marrow failure results from immunologically mediated, active destruction of hematopoietic cells by lymphocytes.
- Mutations in *TERT,* the gene for the RNA component of telomerase, cause short telomerases in congenital aplastic anemia and in some cases of apparently acquired hematopoietic failure. In patients with severe aplastic anemia receiving immunosuppressive therapy (IST), telomere length is unrelated to response but is associated with risk of relapse, clonal evolution, and overall survival.
- Table E1 summarizes a classification of aplastic anemia.
- Common etiologic factors in acquired aplastic anemia include:
  1. Toxins (e.g., benzene, insecticides)
  2. Drugs (e.g., felbamate, cimetidine, NSAIDs, antiepileptics, gold salts, chloramphenicol, sulfonamides, trimethadione, quinacrine, phenylbutazone). Table E2 describes a classification of drugs and chemicals associated with aplastic anemia
  3. Ionizing radiation
  4. Infections (e.g., hepatitis C, HIV, Epstein-Barr virus, parvovirus B19)
- Inherited aplastic anemia:
  1. Fanconi anemia
  2. Reticular dysgenesis
  3. Dyskeratosis congenita
  4. Nonhematologic syndromes (Down syndrome, etc.)
  5. Shwachman-Diamond syndrome
- Pregnancy.
- Idiopathic.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bone marrow infiltration from lymphoma, carcinoma, myelofibrosis
- Severe infection
- Hypoplastic myelodysplastic syndrome
- Hypersplenism
- Hairy cell leukemia

WORKUP

- Diagnostic workup (Fig. E2) consists primarily of bone marrow aspiration and biopsy, and laboratory evaluation (CBC and examination of peripheral blood smear).
- Bone marrow examination generally shows paucity or absence of hematopoietic precursor cells (Fig. E3, *B* and *C,* and Fig. E4); patients with pure red cell aplasia demonstrate only absence of red blood cell (RBC) precursors in the marrow.

LABORATORY TESTS

- CBC reveals pancytopenia (Fig. E3, *A*). Macrocytosis and toxic granulation of neutrophils may also be present. Isolated cytopenias may occur in the early stages.
- Reticulocytopenia can be seen.
- Additional laboratory evaluation should include Ham test and/or peripheral blood flow cytometry to exclude paroxysmal nocturnal hemoglobinuria (PNH) and testing for hepatitis C.

IMAGING STUDIES

MRI with spin-echo sequence is helpful in the study of bone marrow disease, and the high fat content of an aplastic marrow can be easily seen on MRI.

TREATMENT

NONPHARMACOLOGIC THERAPY

Discontinue any potential offending drugs or agents.

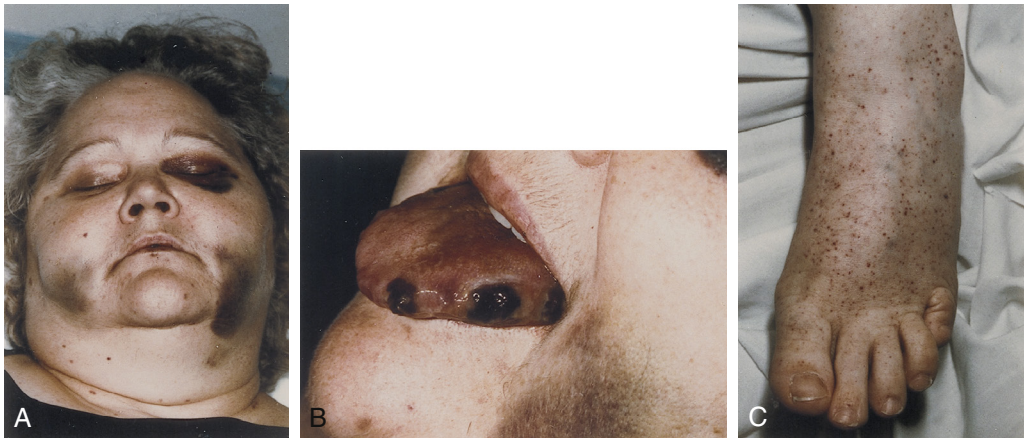

FIG. E1 Clinical presentation of aplastic anemia. A, Ecchymosis in women with pancytopenia. **B,** Submucosal hematomas. **C,** Petechial eruptions in a patient with thrombocytopenia. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

TABLE E1 A Classification of Aplastic Anemia

Acquired Aplastic Anemia

- Secondary aplastic anemia
- Irradiation
- Drugs and chemicals
- Regular effects
- Cytotoxic agents
- Benzene
- Idiosyncratic reactions
- Chloramphenicol
- Nonsteroidal antiinflammatory drugs
- Antiepileptics
- Gold
- Other drugs and chemicals
- Viruses
- Epstein-Barr virus (infectious mononucleosis)
- Hepatitis virus (non-A, non-B, non-C, non-G hepatitis)
- Parvovirus (transient aplastic crisis, some pure red cell aplasia)
- HIV (acquired immunodeficiency syndrome [AIDS])
- Immune diseases
- Eosinophilic fasciitis
- Hyperimmunoglobulinemia
- Thymoma and thymic carcinoma
- Graft-versus-host disease in immunodeficiency
- Paroxysmal nocturnal hemoglobinuria
- Pregnancy
- Idiopathic aplastic anemia

Inherited Aplastic Anemia

- Fanconi anemia
- Dyskeratosis congenita
- Shwachman-Diamond syndrome
- Reticular dysgenesis
- Amegakaryocytic thrombocytopenia
- Familial aplastic anemias
- Preleukemia (e.g., monosomy 7)
- Nonhematologic syndromes (e.g., Down, Dubowitz, Seckel)

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE E2 Classification of Drugs and Chemicals Associated with Aplastic Anemia

Agents That Regularly Produce Bone Marrow Depression as a Major Toxic Effect When Used in Commonly Used Doses or Normal Exposures

- Cytotoxic drugs used in cancer chemotherapy
- Alkylating agents (busulfan, melphalan, cyclophosphamide)
- Antimetabolites (antifolic compounds, nucleotide analogues), antimitotics (vincristine, vinblastine, colchicine)
- Some antibiotics (daunorubicin, doxorubicin [Adriamycin])
- Benzene (and less often benzene-containing chemicals: Kerosene, carbon tetrachloride, Stoddard solvent, chlorophenols)

Agents Probably Associated with Aplastic Anemia but with a Relatively Low Probability Relative to Their Use

- Chloramphenicol
- Insecticides
- Antiprotozoals (quinacrine and chloroquine)
- Nonsteroidal antiinflammatory drugs (including phenylbutazone, indomethacin, ibuprofen, sulindac, diclofenac, naproxen, piroxicam, fenoprofen, fenbufen, aspirin)
- Anticonvulsants (hydantoins, carbamazepine, phenacemide, ethosuximide)
- Gold, arsenic, and other heavy metals, such as bismuth and mercury
- Sulfonamides as a class
- Antithyroid medications (methimazole, methylthiouracil, propylthiouracil)
- Antidiabetes drugs (tolbutamide, carbutamide, chlorpropamide)
- Carbonic anhydrase inhibitors (acetazolamide, methazolamide, mesalazine)
- D-Penicillamine
- 2-Chlorodeoxyadenosine

Agents More Rarely Associated with Aplastic Anemia

- Antibiotics (streptomycin, tetracycline, methicillin, ampicillin, mebendazole and albendazole, sulfonamides, flucytosine, mefloquine, dapsone)
- Antihistamines (cimetidine, ranitidine, chlorpheniramine)
- Sedatives and tranquilizers (chlorpromazine, prochlorperazine, piperacetazine, chlordiazepoxide, meprobamate, methyprylon, remoxipride)
- Antiarrhythmics (tocainide, amiodarone)
- Allopurinol (can potentiate marrow suppression by cytotoxic drugs)
- Ticlopidine
- Methyldopa
- Quinidine
- Lithium
- Guanidine
- Canthaxanthin
- Thiocyanate
- Carbimazole
- Cyanamide
- Deferoxamine
- Amphetamines

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, WB Saunders.

ACUTE GENERAL Rx

- Aggressive treatment of neutropenic fevers with empiric broad-spectrum antibiotics.
- Administer platelet and packed RBC transfusions as needed; however, it is important to avoid frequent transfusions in patients who are candidates for stem cell transplantation (SCT) so as to reduce the incidence of alloimmunization.
- Fig. E5 describes a treatment algorithm for aplastic anemia.

CHRONIC Rx

- Initial treatment can include observation and supportive care alone. Progression to transfusion dependence or to criteria meeting definition of SAA necessitates definitive treatment. Upfront HLA-typing of the patient is also required upon confirmation of a diagnosis of SAA.
- The major treatment options for SAA are IST and allogeneic SCT. Treatment decisions are based on age, availability of histocompatible stem cell donor, and presence of comorbidities. Patients <40 yr are treated with upfront allogeneic SCT

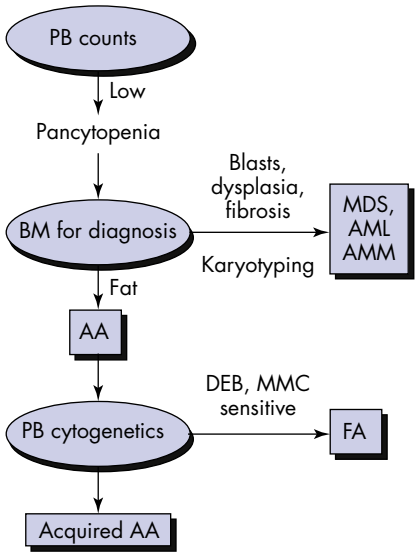

FIG. E2 Diagnostic algorithm in aplastic anemia *(AA).* *AML,* Acute myeloid leukemia; *AMM,* agnogenic myeloid metaplasia; *BM,* bone marrow; *DEB,* diepoxybutane; *FA,* Fanconi anemia; *MDS,* myelodysplastic syndrome; *MMC,* mitomycin C; *PB,* peripheral blood. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

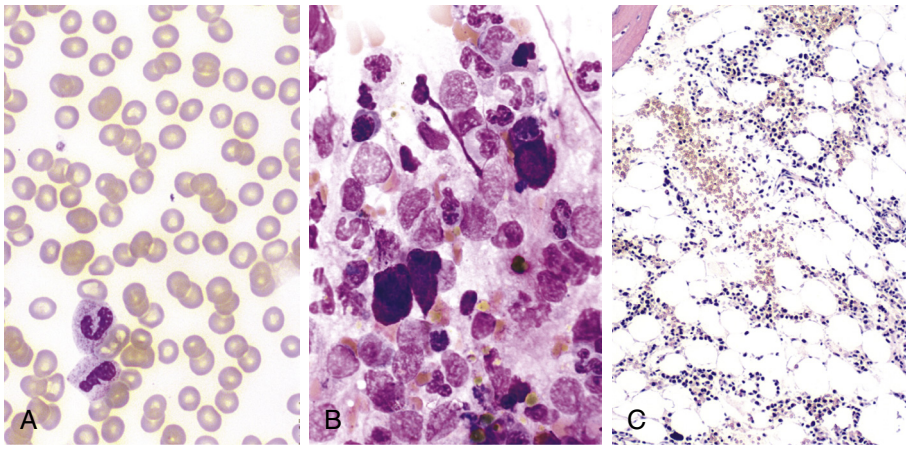

FIG. E3 Pancytopenia in measles-associated aplastic anemia. A, Note the toxic granulation in the neutrophils. The hypocellular bone marrow smear contains numerous mast cells **(B),** and the trephine biopsy reflects subtotal aplasia **(C).** (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.)

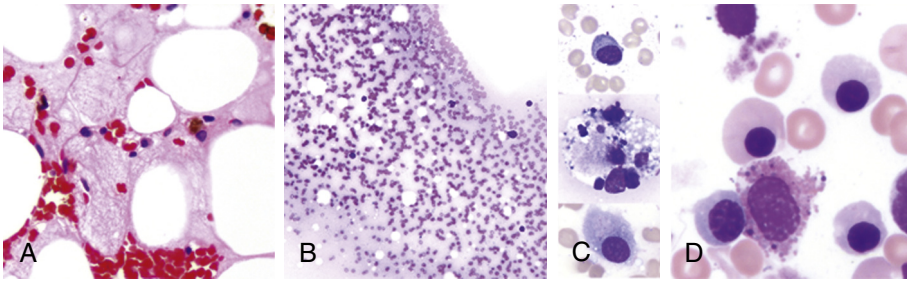

FIG. E4 Some morphologic features occasionally observed in patients with aplastic anemia. Empty marrow with eosinophilic ground substance consistent with serous atrophy or stromal injury **(A),** possibly indicative of marrow damage. Scanty marrow aspirate in severe disease **(B)** showing only rare nucleated elements, many of which are from blood. Presence of plasma cells, histiocytes, and osteoblasts **(C)** confirms marrow nature of aspirate. note: Sometimes the histiocytes can show hemophagocytosis. Megaloblastoid erythropoiesis **(D)** is sometimes seen in aplastic anemia and in recovery. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 6, Philadelphia, 2013, Elsevier.)

whereas patients >40 yrs old have traditionally been treated with IST initially. Patients who are >40 yrs old can be recommended for SCT if there is suboptimal response to IST after 4 mo of therapy.

- Allogeneic SCT from a human leukocyte antigen (HLA)-matched sibling donor is potentially curative. Patients who do not have a matched sibling can be treated with a matched unrelated donor (MUD) SCT. Finally, there is increasing efficacy data with the use of haploidentical donor SCT when related donors are unavailable.
- IST typically consists of the regimen of cyclosporine with or without antithymocyte globulin (ATG) in patients <60 yr; in older patients, ATG is administered only in fit patients with low comorbidities.
- The use of hematopoietic growth factors such as granulocytic colony-stimulating factor (G-CSF) is not associated with improvement in survival outcomes in this setting.
- Studies have shown an association between leukocyte telomere length and outcomes in MUD-SCT. Longer donor leukocyte telomere length was associated with increased 5-yr survival.
- Patients who fail to respond to initial IST are candidates for alternative donor SCT or other immunosuppressive therapy such as Alemtuzumab (anti-CD52 monoclonal antibody).
- Other immunosuppressive agents such as cyclophosphamide or corticosteroids also have a supportive role in the treatment of SAA.
- Androgens such as danazol are effective second-line agents.
- The oral thrombopoietin mimetic eltrombopag is used for platelet recovery in refractory SAA. Recent data have demonstrated encouraging outcomes when used in combination with IST in the treatment of newly diagnosed patients.

DISPOSITION

- A recent retrospective analysis revealed 10-yr survival rates of 86%, 76%, and 55% with allogeneic SCT performed between 2000 and 2010 in patients <20 yr, 21 to 40 yrs old, and >40 yrs old, respectively.
- Recent data with the use of allogeneic SCT in patients >50 yr have demonstrated improved survival outcomes especially in patients with higher performance scores and matched sibling donors, but patients >65 yr are likely to have higher rates of severe graft versus host disease.
- Approximately 50% of patients treated with IST alone achieve long-term remissions and do not have disease relapse.
- Graft rejection and graft-versus-host disease are the major complications of allogeneic SCT.
- Approximately 10% to 15% of patients develop clonal evolution, which manifests as myelodysplastic syndrome or acute myeloid leukemia.
- The improved outcomes with allogeneic SCT have prompted recommendations for its earlier use in the majority of patients.

REFERRAL

Hematology referral is indicated in all patients with aplastic anemia.

RELATED CONTENT

Aplastic Anemia (Patient Information)

AUTHOR: **Ritesh Rathore, MD**

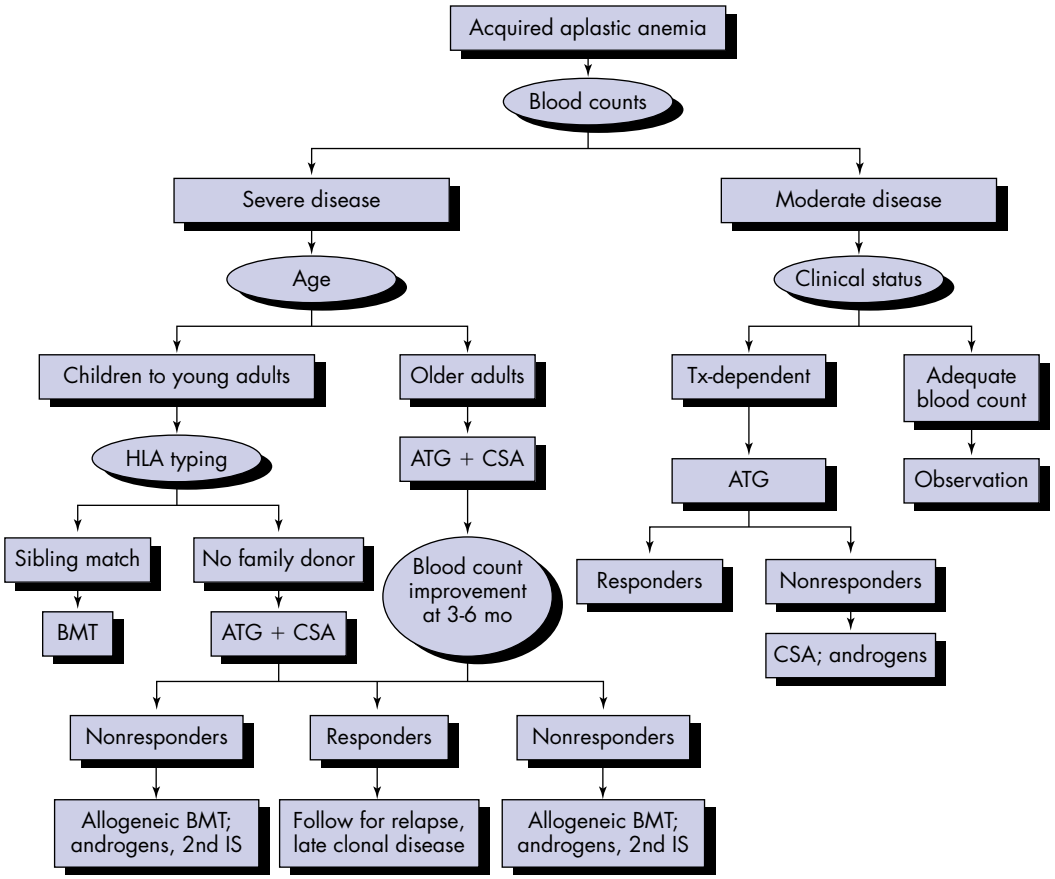

FIG. E5 Treatment algorithm in aplastic anemia. Algorithm-based selection of treatment for patients with aplastic anemia. *ATG,* Antithymocyte globulin; *BMT,* bone marrow transplantation; *CSA,* cyclosporine A; *HLA,* human leukocyte antigen; *IS,* immunosuppression; *Tx,* treatment. (From Hoffmann R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

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BASIC INFORMATION

DEFINITION

Autoimmune hemolytic anemia (AIHA) is anemia secondary to premature clearance of red blood cells (RBCs) caused by binding of autoantibodies and/or complement to RBCs. Primary AIHA comprises approximately 50% of cases, whereas secondary AIHA is usually associated with diseases or drugs. The classification of the hemolytic anemias is described in Table 1.

SYNONYMS

Autoimmune hemolytic anemia
Cold agglutinin disease
Drug-induced hemolytic anemia
Warm autoimmune hemolytic anemia

ICD-10CM CODES

D59.0	Drug-induced autoimmune hemolytic anemia
D59.1	Other autoimmune hemolytic anemias

EPIDEMIOLOGY & DEMOGRAPHICS

The annual incidence is 1 to 3 cases per 100,000 persons, with 10% mortality; most common in women <50 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most common presentation is dyspnea and fatigue.
- Pallor, jaundice may be present.
- Tachycardia with a flow murmur may be present if anemia is pronounced.
- Patients with intravascular hemolysis may present with dark urine and back pain.
- The presence of hepatomegaly and/or lymphadenopathy suggests an underlying lymphoproliferative disorder or malignancy; splenomegaly may indicate hypersplenism as a cause of hemolysis.
- Chronic process with multiple relapses typically seen during the course of the disease.

TABLE 1 Classification of the Hemolytic Anemias

Acquired

Environmental factors
- Antibody: Immunohemolytic anemias
- Mechanical trauma: TTP, HUS, heart valve
- Toxins, infectious agents: Malaria, etc.

Membrane defects
- Paroxysmal nocturnal hemoglobinuria
- Spur cell anemia
- Hereditary spherocytosis, etc.

Congenital

Defects of cell interior
- Hemoglobinopathies: Sickle cell, thalassemia
- Enzymopathies: G6PD deficiency, etc.

G6PD, Glucose-6-phosphate dehydrogenase; *HUS,* hemolytic-uremic syndrome; *TTP,* thrombotic thrombocytopenic purpura.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.

ETIOLOGY

- Warm antibody mediated: IgG only (often idiopathic or associated with leukemia, lymphoma [Table 2], thymoma, myeloma, viral infections [Table 3], babesiosis, and collagen-vascular disease)
- Cold antibody mediated: IgM and complement in majority of cases (often idiopathic; at times associated with infections, lymphoma, or cold agglutinin disease)
- Il-33 may have a role in promoting increasing RBC autoantibodies in AIHA
- Drug induced (Table 4): Three major mechanisms:
  1. Antibody directed against Rh complex (e.g., methyldopa)
  2. Antibody directed against RBC-drug complex (hapten induced; e.g., penicillin)
  3. Antibody directed against complex formed by drug and plasma proteins; the drug-plasma protein-antibody complex causes destruction of RBCs (innocent bystander; e.g., quinidine)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hemolytic anemia caused by membrane defects (acquired: paroxysmal nocturnal hemoglobinuria, spur cell anemia, Wilson disease; inherited: spherocytosis, elliptosis), hemoglobinopathies, and enzyme deficiencies (G6PD, pyruvate kinase)
- Non–immune mediated (microangiopathic hemolytic anemias, hypersplenism, cardiac valve prosthesis, giant cavernous hemangiomas, march hemoglobinuria, physical agents, infections, heavy metals, certain drugs [nitrofurantoin, sulfonamides, ribavirin])
- Chronic lymphocytic leukemia (CLL) can be a cause of direct antiglobulin test (DAT) positivity (15% of CLL cases) without AIHA. In a series of patients treated with fludarabine and cyclophosphamide, only 30% of patients with DAT+ disease developed AIHA after therapy; conversely, 85% of patients with AIHA were previously positive for DAT

TABLE 2 Secondary Autoimmune Hemolytic Anemia in Malignancies

Malignancy	Prevalence	WAIHAs	CAIHAs
MGUS	Very low	None	All
All NHL	0.23%-2.6%		
CLL	4.3%-9%	90%	10%
SMZL	10%	2/3	1/3
LPL	3%-5%	None	Most
Angioimmunoblastic T-cell lymphoma	13%	One third	Two thirds
Hodgkin lymphoma	0.19%-1.7%	All	None
Ovarian teratoma	Very low	All	None
Solid tumors	Very low	Two thirds	One third

CAIHAs, Cold antibody autoimmune hemolytic anemias; *CLL,* chronic lymphocytic leukemia; *LPL,* lymphoplasmacytic lymphoma; *MGUS,* monoclonal gammopathy with unknown significance; *NHL,* non-Hodgkin lymphoma; *SMZL,* splenic marginal zone lymphoma; *WAIHAs,* warm antibody autoimmune hemolytic anemias.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 3 Autoimmune Hemolytic Anemia after Infections

	Infection	WAIHA	CAIHA (Specificities)
Respiratory tract infections (unspecified)	—	—	+ (DL)/PCH
Viral infections (specific)	EBV	+/–	+ (anti-i)
	CMV	+	+/– (anti-i)
	Parvovirus (B19)	+ (often with PRCA)	+/– (DL)
	Varicella	+/–	+ (anti-Pr, anti-I, anti-DL)
	Rubella	—	+ (anti-Pr1) Monotypic IgM
	HIV	+	+ (anti-I, anti-i, anti-Pr)
Bacterial infections (specific)	Mycoplasma	+/–	+ (anti-I, anti-Pr)
	Brucellosis	+/–	+ (anti-I)
	Haemophilus influenzae		+ (DL)
Parasitic infections (specific)	Visceral leishmaniosis	+	—

—, Not reported; +, predominant type of autoimmune hemolytic anemia; +/–, single or few cases reported; *CAIHA,* cold antibody autoimmune hemolytic anemia; *CMV,* cytomegalovirus; *EBV,* Epstein-Barr virus; *HIV,* human immunodeficiency virus; *IgM,* immunoglobulin M; *PCH,* paroxysmal cold hemoglobinuria; *PRCA,* pure red blood cell aplasia; *WAIHA,* warm antibody autoimmune hemolytic anemia.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 4 Drug-Induced Autoimmune Hemolytic Anemia

Drug	Risk Factors	AIHA Onset	Type of AIHA	Response to Treatment	Diseases Treated
Methyldopa	Not known	Delayed	WAIHA	Resolution after withdrawal	Hypertension
IFN-α	Pretherapeutic positive DAT	Delayed (8-11 mo)	WAIHA	Resolution spontaneous or after steroids	Hepatitis C; hematologic malignancies
Efazulimab	Not known	Many mo	WAIHA	Resolution after withdrawal	Arthritis (rare)
Etanercept	Not known	Delayed	CAIHA	Resolution after rituximab	Rheumatoid arthritis (rare)
Fludarabine Cladribine Pentostatin	CLL Pretherapeutic positive DAT result	Early (median, 3-4 cycle) or delayed	WAIHA Mixed AIHA	Half of AIHA resolve after steroids	CLL Lymphomas[a] AML[a]
Bendamustin	CLL	No or only very low risk of AIHA			CLL Lymphomas
Chlorambucil	CLL	Delayed onset	WAIHA		CLL
Eculizumab	Patients with incomplete response	After treatment	CAIHA		PNH
Lenalidomide		During treatment	WAIHA	Resolution after withdrawal	One case treated for lymphoma
Checkpoint inhibitors (anti-CTLA4, anti-PD1/PD1L)		During treatment	WAIHA		Solid tumors, Hodgkin lymphoma

AIHA, Autoimmune hemolytic anemia; *AML,* acute myeloid leukemia; *CAIHA,* cold autoimmune hemolytic anemia; *CLL,* chronic lymphocytic leukemia; *DAT,* direct antiglobulin test; *IFN,* interferon; *PNH,* paroxysmal nocturnal hemoglobinuria; *WAIHA,* warm autoimmune hemolytic anemia.
[a]No or very low risk.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 5 Positive Direct Antiglobulin Test Findings, Characteristic Features of Autoantibody in Autoimmune Hemolytic Anemia

	Warm AIHA	CHAD	Mixed-AIHA	PCH	IgA AIHA
DAT	IgG or IgG + C3 or IgG + C3 + IgM	C3 or C3 + IgM	IgG + C3 + IgM	C3	Neg with polyspecific reagent Pos with anti-IgA
Antibody characteristic					
1) Antibody subclass	IgG	IgM	IgG + IgM	IgG	IgA
1) Specificity	Apparent Rh specificity (common)	I, i, Pr		P	
1) Thermal reactivity (in vitro)	Optimal at 37°C (98.6° F) by IAT	0-30° C (32-86° F) by saline agglutination	Combined	0-24° C (32-75.2° F), biphasic in nature	
1) Antibody titer at 4° C (39.2° F)	Not applicable	≥256	Usually <64 but can be >256	Usually <32	
Autoagglutination	No	Common	Common	Less common	No

AIHA, Autoimmune hemolytic anemia; *C,* complement; *CHAD,* cold hemagglutinin disease; *DAT,* direct antiglobulin test; *IAT,* indirect antiglobulin test; *Ig,* immunoglobulin; *Neg,* negative; *PCH,* Paroxysmal cold hemoglobinuria; *Pos,* positive.
The determination of autospecificity is not required for diagnosis of CHAD, but confirmation of high thermal amplitude (i.e., cold autoagglutinin reacting at or above 30° C [86° F]) is essential.
From Bain BJ et al: *Dacie and Lewis practical haematology,* ed 12, Philadelphia, 2017, Elsevier.

WORKUP

Evaluation consists primarily of laboratory evaluation to confirm hemolysis and exclude other causes of the anemia. Although most cases of AIHA are idiopathic, potential causes should always be sought.

LABORATORY TESTS

- The basic features of hemolytic anemia are reticulocytosis (if no concurrent bone marrow suppression), low haptoglobin levels, elevated indirect bilirubin, and elevated LDH.
- Initial laboratory tests: Complete blood count (anemia), reticulocyte count (elevated), liver function studies (elevated indirect bilirubin, LDH), evaluation of peripheral smear (Fig. E1).
- A direct antiglobulin test (DAT, Coombs test) is initially performed with a polyspecific antibody to detect IgG or complement C3d bound to RBCs. If the DAT is positive, the diagnosis of autoimmune hemolytic anemia (AIHA) is confirmed. A positive direct Coombs test indicates presence of antibodies or complement on the surface of RBCs; positive indirect Coombs test implies presence of anti-RBC antibodies freely circulating in the patient's serum. Positive DAT findings and characteristic features of autoantibody in AIHA are summarized in Table 5. Typical serologic features of the different types of drug-induced hemolytic anemia of immunologic origin are summarized in Table 6.
- If the DAT is positive with IgG alone or with IgG + C3d, the AIHA is most likely due to warm antibody (WAIHA), whereas if the DAT is positive with C3d only, it is most likely caused by a cold antibody (CAIHA).
- Hepatitis serology, antinuclear antibody.
- Urinary tests may reveal hemosiderinuria or hemoglobinuria (documenting intravascular hemolysis).

IMAGING STUDIES

- Chest x-ray.
- CT scans of chest, abdomen, and pelvis should be considered if underlying lymphoproliferative disorder is suspected.

TABLE 6 Serologic Features of the Different Types of Drug-Induced Hemolytic Anemia of Immunologic Origin

Mechanism	Prototype drug	DAT	IAT		
Drug-dependent antibody			No drug	Serum + drug	Eluate + drug
C′ activation	Quin(id)ine	C′*	Neg	C′*	Neg
No C′ activation	Penicillin	IgG	Neg	IgG	IgG
Autoantibody	α-Methyldopa	IgG	IgG	NA	NA

C′, Complement; *IgG,* immunoglobulin G; *NA,* not applicable; *Neg,* negative.
*Occasionally also IgG.
From Bain BJ et al: *Dacie and Lewis practical haematology,* ed 12, Philadelphia, 2017, Elsevier.

TABLE 7 Treatment Options for Primary and Secondary Warm Autoimmune Hemolytic Anemia and Cold Autoimmune Hemolytic Anemia

Disease or Condition	First Line	Second Line	Beyond Second Line	Last Resort
Primary AIHA	Steroids (trituximab)	Splenectomy Rituximab	Azathioprine, MMF, cyclosporine, cyclophosphamide	High-dose cyclophosphamide, alemtuzumab
B- and T-cell NHL	Steroids	Chemotherapy +/– rituximab (splenectomy in SMZL)	Other anti-CD23 antibodies/ ibrutinib	
Hodgkin lymphoma	Steroids	Chemotherapy		
Solid tumors	Steroids Surgery			
Ovarian dermoid cyst	Ovariectomy			
SLE	Steroids	Azathioprine	MMF	Rituximab Autologous SCT
Ulcerative colitis	Steroids	Azathioprine		Total colectomy
CVID	Steroids + IgG replacement			
ALPD	Steroids	MMF	Sirolimus	
Wiskott-Aldrich syndrome	Steroids	Allogeneic SCT		
Allogeneic SCT	Steroids	Rituximab*	Splenectomy T-cells infusion	
Organ transplantation	Reduction of immune suppression, steroids			
Drug induced	Withdrawal	Steroids		
Primary CAD	Protection from cold exposure	Rituximab Chlorambucil	Fludarabine + rituximab	Eculizumab,† bortezomib†
PCH	Supportive treatment (postinfectious)	Rituximab* (chronic)		

AIHA, Autoimmune hemolytic anemia; *ALPD,* autoimmune lymphoproliferative disorders; *CAD,* cold agglutinin disease; *CVID,* common variable immune deficiency; *IgG,* immunoglobulin G; *MMF,* mycophenolate mofetil; *NHL,* non-Hodgkin lymphoma; *PCH,* paroxysmal cold hemoglobinuria; *SCT,* stem cell transplantation; *SLE,* systemic lupus erythematosus; *SMZL,* splenic marginal zone lymphoma.
*Early second-line treatment because of known poor response to steroids.
†Off-label use in single cases.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, WB Saunders.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Discontinuation of any potentially offending drugs
- Plasmapheresis and exchange transfusion for severe life-threatening cases only
- Avoid cold exposure in patients with cold antibody

ACUTE GENERAL Rx

- Prednisone 1 to 2 mg/kg/day in divided doses is initially used in warm antibody AIHA. Corticosteroids are generally ineffective in cold antibody AIHA. In cold agglutinin disease treatment, modalities consist of cold avoidance, therapy of underlying lymphoproliferative disorder, and use of rituximab and plasmapheresis in severe cases.
- Two randomized controlled trials have demonstrated improved outcomes and duration of response with the combined upfront use of steroids and rituximab, and this is also a standard option in clinical use.
- For patients relapsing or refractory to initial steroid therapy, the use of rituximab has in most cases replaced the use of splenectomy. Splenectomy now is more often used in patients refractory to both corticosteroids and rituximab use previously.
- Immunosuppressive drugs and/or immunoglobulins are recommended after failure of the above approaches to produce an adequate remission.
- Danazol, typically used in conjunction with corticosteroids (may be useful in warm antibody AIHA).
- Immunosuppressive drugs (azathioprine, cyclophosphamide) may be useful in warm antibody AIHA but are indicated only after both corticosteroids and splenectomy (unless surgery is contraindicated) have failed to produce an adequate remission.
- Table 7 summarizes treatment options for primary and secondary warm autoimmune hemolytic anemia and cold autoimmune

TABLE 8 Second-Line Treatment Options after Steroids

Treatment	Dosing and Application	Side Effects	Precautions
Splenectomy (acute)	Preferentially laparoscopic	Infections, thrombosis	Postoperative thromboprophylaxis
Splenectomy (long term)	—	Infections Venous thrombosis	Vaccination, patient information
Rituximab	375 mg/m^2 on days 1, 8, 15, and 22 IV	Infusional reactions Infections	Premedication with antihistamines (and steroids)
Danazol	200-400/day PO	Hepatotoxicity	None
Cyclophosphamide	PO or IV Dose adjusted to neutrophil count	Neutropenia Mutagenesis	Neutrophil count monitoring, bladder protection after high doses
Azathioprine	2.0-3.mg/kg/day PO Dose adjusted to neutrophil count	Neutropenia	Neutrophil count monitoring; avoid interaction with other drugs (e.g., allopurinol)
MFF	1-2 × 1 g/day PO	Gastrointestinal	
Cyclosporine	PO Dose adjusted to blood levels of CyA Target level, 200-400 ng/ml	Nephrotoxicity Gum hyperplasia	Monitoring of CyA levels and creatinine
Alemtuzumab	SC (variable doses)	Neutropenia	Antiinfectious prophylaxis
Complement inhibition with eculizumab, TNT009		Infections	Vaccination

CyA, Cyclosporine A; *IV,* intravenous; *MMF,* mycophenolate mofetil; *PO,* oral; *SC,* subcutaneous.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

hemolytic anemia. Second-line treatment options after steroids are described in Table 8.

DISPOSITION

Prognosis is generally good unless anemia is associated with underlying disorder with a poor prognosis (e.g., leukemia, myeloma).

REFERRAL

- Hematology referral in all cases of AIHA
- Surgical referral for splenectomy in refractory cases

PEARLS & CONSIDERATIONS

COMMENTS

- The direct antiglobulin test demonstrates the presence of antibodies or complement on the surface of RBCs and is the hallmark of autoimmune hemolysis.
- Warm AIHA is often associated with autoimmune diseases, whereas cold AIHA often follows viral infections (e.g., mononucleosis) and *Mycoplasma pneumoniae* infections.
- HIV can induce both warm and cold AIHA.
- Hemolytic anemia is a common autoimmune complication of hematopoietic stem cell transplantation occurring in up to 6% of patients as a late complication (median 202 days); it presents as either warm or cold AIHA.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Bharti Rathore, MD**

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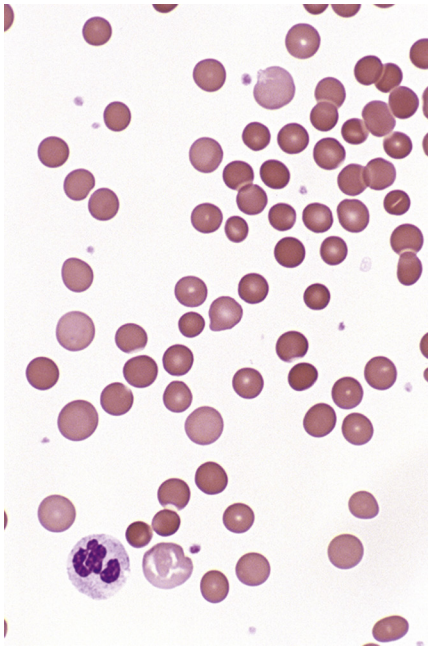

FIG. E1 In warm antibody hemolytic anemia, numerous spherocytes are seen. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.)

BASIC INFORMATION

DEFINITION

Inflammatory anemia, also known as *anemia of chronic disease (ACD),* is a disorder of iron homeostasis (Table 1) promoted by hepcidin-25 in response to an inflammatory condition.

SYNONYMS

Inflammatory anemia
Anemia of chronic disease
ACD

ICD-10CM CODES

D63.8	Anemia in chronic diseases classified elsewhere
D63.0	Anemia in neoplastic disease
D64.8	Anemia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- Second-most prevalent anemia after iron deficiency anemia:
  1. Around 11% of men and 10% of women ages 65 to 85 yr
  2. >20% of adults older than 85 yr

Pathophysiology (Fig. 1)

Iron is carried in the bloodstream shelled by a hollow protein called transferrin (<0.2% of total iron body content) or at the core of hemoglobin in RBCs (60% of total iron body content). It is mainly stored (15% to 30% of total iron body content) inside the liver, spleen, and skeletal muscle as ferritin and in lysosomes as hemosiderin. The rest of the iron body content is trapped in myoglobin in skeletal muscle and cytochromes in mitochondria. In clinical practice, ferritin is a surrogate for iron stores, and total iron binding capacity (TIBC) is a surrogate for transferrin and the carrying capacity of iron.

Cells involved in the response to inflammatory insults cause the release of cytokines, such as IL-6, which stimulates hepatic release of hepcidin. Hepcidin is a circulating protein that blocks ferroportin, an iron channel responsible for the exit of iron from enterocytes (and thus gastrointestinal absorption) and macrophages (which accumulate iron from engulfed senescent blood cells). IL-1 and TNF-alpha stimulate IFN-gamma release by marrow stromal cells, which in turn suppress the erythroid response to erythropoietin (EPO). In chronic kidney disease, ACD is a consequence of decreased production of EPO and decreased renal clearance of hepcidin. The low availability of serum iron causes iron deficiency in the bone marrow compartment and decreased reticulocyte levels.

TABLE 1 Suspected Causes of Anemia of Chronic Disease

Shortened erythrocyte survival
Block in reuse of iron by erythrocyte
Direct inhibition of erythropoiesis
Relative deficiency of erythropoietin

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

CLINICAL PRESENTATION

- Besides fatigue, shortness of breath, and generalized weakness from the anemia itself, it is important to consider other complaints if the underlying diagnosis is unknown, such as weight loss (malignancy, chronic infections, connective tissue diseases), anorexia, nausea, paresthesias, pleuritic chest pain, weight gain (CKD), diarrhea, bloody stools, abdominal pain, oral ulcers (IBD), and fevers (HIV, chronic infections).
- Physical findings may include pallor, lymphadenopathy, stigmatas of connective tissue diseases (malar rash, sclerodactyly), palpable or visible masses, and localized findings for infection or malignancy.

DIAGNOSIS

Isolated ACD:

- CBC with differential: Normocytic, normochromic, moderate (Hb rarely <8 g/dl) anemia
- Hypoproliferative anemia (low reticulocyte index; corrected reticulocyte count <2%)

Iron studies:

- Low iron concentration as in IDA (iron deficiency anemia)
- Normal/high ferritin (>35 mg/dl) in ACD as it is an acute phase reactant (Fig. 2)
- Low/normal TIBC (as opposed to IDA) and low transferrin saturation (as in IDA)
- Normal soluble transferrin receptor (sTfR, high in IDA)

Combined ACD/IDA:

- If normal to high ferritin, sTfR/log ferritin ratio <1 defines isolated ACD, and ratio >2 defines combined IDA/ACD

ETIOLOGY

- Malignancy
- CKD (patients with CKD stage IV [GFR<30 ml/min] should be screened for ACD)
- CHF (ACD is the main cause of anemia in CHF patients)
- Chronic infections
- Anemia of critical illness (develops within days)
- Connective tissue diseases

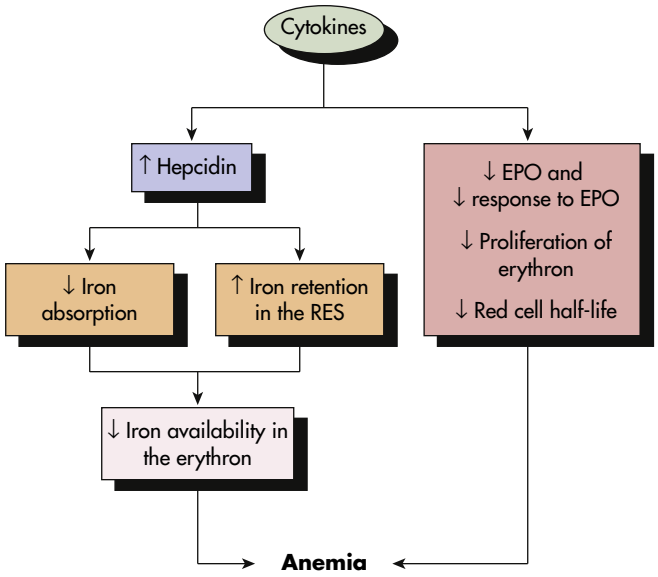

FIG. 1 Pathophysiologic factors associated with the development of anemia of chronic disease. *EPO,* Erythropoietin; *RES,* reticuloendothelial system. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

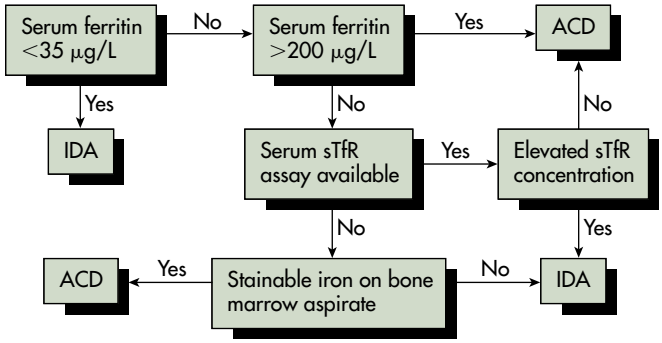

FIG. 2 Differential diagnosis of anemia with low serum iron. *ACD,* Anemia of chronic disease; *IDA,* iron deficiency anemia; *sTfR,* soluble transferrin receptor.

TABLE 2 Laboratory Features in Microcytic Hypochromic Anemias

				MARROW					
	Serum Iron	Serum TIBC	% Saturation	% Sideroblasts	Iron Stores	Serum Ferritin	ZPP	Hb A_2	Hb F
Iron deficiency	↓	↑	↓	↓	↓	↓	↑	N-↓	N
β-Thalassemia trait	N (↑)	N	N	N	N-↑	N-↑	N	↑	N-↑
ACD	↓	N-↓	↓	↓	N-↑	N-↑	↑	N	N
Sideroblastic anemia	↑	↓	↑	↑	↑	↑	↑ (↓)	N	N-↑

ACD, Anemia of chronic disease; *Hb,* hemoglobin; *N,* normal; *TIBC,* total iron-binding capacity; *ZPP,* zinc protoporphyrins; ↓, decreased; ↑, increased.
McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, Philadelphia, 2017, Elsevier.

TABLE 3 Laboratory Characteristics of ACD, IDA, and IDA with Inflammation

	Anemia of Chronic Disease (ACD)	Iron Deficiency Anemia (IDA)	IDA with Inflammation
Mean corpuscular volume (MCV)	72-100 fL	<85 fL	<100 fL
Mean corpuscular hemoglobin concentration (MCHC)	<36 g/dl	<32 g/dl	<32 g/dl
Serum iron	Decreased	Decreased	Decreased
Serum total iron-binding capacity (TIBC)	Typical below mid-normal range	Elevated	Less than upper limit of normal range
Transferrin saturation*	2%-20%	<15% (usually <10%)	<15%
Serum ferritin	>35 μg/L	<35 μg/L	>35 μg/L, <200μg/L
Serum soluble transferrin receptor concentration (sTfR)	Normal (may be increased if serum ferritin >200 μg/L)	Increased	Increased
TfR index (sTfR/log ferritin)	<1	>2	>2
Hepcidin	High	Low	Normal
Stainable iron in bone marrow	Present	Absent	Absent

*Serum iron/TIBC * 100.

DIFFERENTIAL DIAGNOSIS

- Liver injury (increases ferritin):
  1. Iron deficiency anemia:
     a. Other causes of normocytic anemia or microcytic anemia (Table 2)
     b. Red blood cell loss or destruction:
        (1) Acute blood loss
        (2) Hypersplenism
        (3) Hemolysis
     c. Decreased red blood cell production:
        (1) Primary causes:
            (a) Bone marrow hypoplasia or aplasia
            (b) Myeloproliferative disease
            (c) Pure red blood cell aplasia
     d. Secondary causes:
        (1) Chronic renal failure
        (2) Liver disease
        (3) Endocrine deficiency states
        (4) Sideroblastic anemia

WORKUP

CBC, reticulocyte count, peripheral smear (Fig. E3), iron level, ferritin, TIBC. Table 3 summarizes characteristic findings in inflammatory anemia. Characteristic bone marrow findings of increased iron stores in stromal histiocytes and impaired erythroid iron incorporation are shown in Fig. E4.

Rx TREATMENT

Treat the underlying disorder/disease.

ACUTE GENERAL Rx

- The treatment of inflammatory anemia is directed primarily at treatment of underlying conditions, which can improve symptoms and facilitate hemoglobin recovery.
- Blood transfusion is usually reserved for severe anemia (with Hb level <7 g/dl or <8 g/dl in patients with cardiac disease), especially if complicated with ongoing bleeding.

CHRONIC Rx

- Erythropoiesis-stimulating agents (ESA) (epoetin alfa and darbepoetin alfa) are FDA approved for use in patients with anemia resulting from:
  1. Chronic kidney disease
  2. Chemotherapy
  3. Zidovudine therapy
- A 1998 study, the Normal Hematocrit Cardiac Trial (NHCT), showed a nonsignificant increase in the combined endpoint death and nonfatal MI in patients with goal hematocrit of 33% versus 27%. Subsequent studies (CHOIR, CREATE, and TREAT) showed that higher doses and higher hematocrit targets were associated with increased cardiovascular events.
- ESA dose should be individualized for each patient, and the lowest sufficient dose to reduce blood transfusions should be used. A hemoglobin target of approximately 10 g% is widely acceptable. Iron deficiency should be ruled out before ESA is started. After starting ESA therapy, ASH/ASCO guidelines recommend periodic monitoring of iron status. When there is no or suboptimal response to oral therapy, parenteral iron therapy should be considered before concluding that a patient is nonresponsive to iron therapy.
  - The hepcidin–ferroportin axis is the target of development of novel agents of which the most promising are hypoxia-induced factor modulators. HIF is a transcription factor that promotes expression of erythropoietin. HIF is upregulated by inhibition of PHD. Clinical trials of vadadustat, an oral hypoxia-inducible factor, in patients with anemia of kidney disease have demonstrated efficacy in achieving a hemoglobin of 11 g/dl or an increase of 1.2 g/dl. Also, mean hemoglobin levels were maintained in patients with CKD who were previously receiving ESA. Additional drugs in trials include oral inhibitors and antibodies and bone morphogenetic protein (BMP) receptor.

SUGGESTED READINGS

Available at ExpertConsult.com

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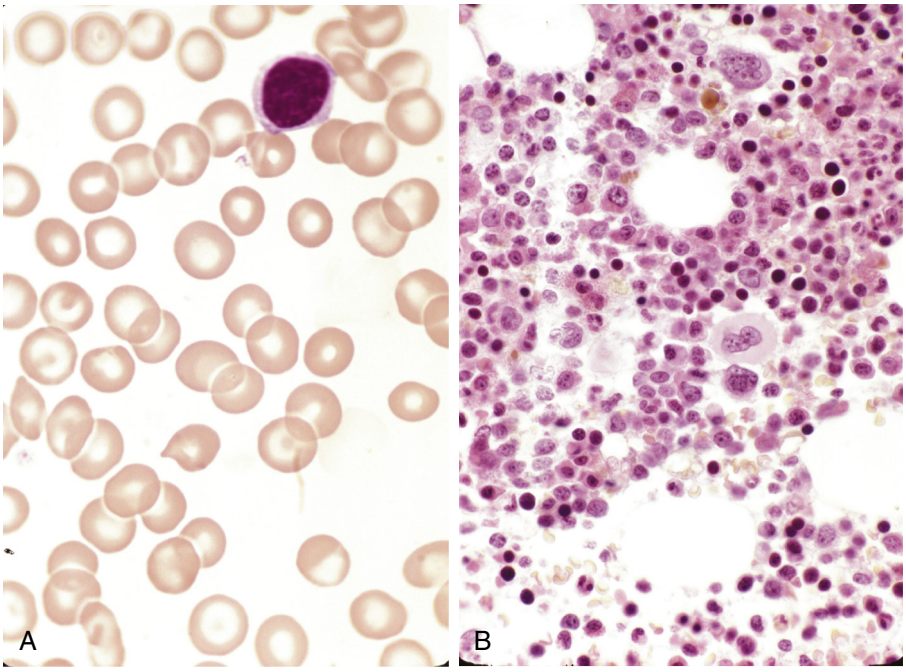


FIG. E3 Slightly hypochromic normocytic red cells in anemia of chronic disease associated with rheumatoid arthritis **(A).** Bone marrow erythroid precursors are present in normal numbers **(B).** (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.)

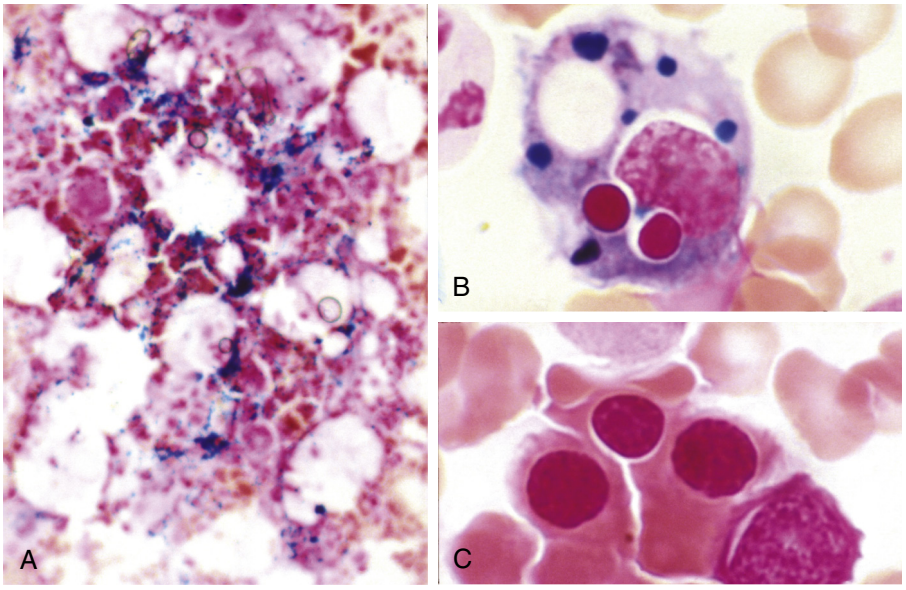


FIG. E4 In anemia of chronic disease, iron stores are increased in stromal histiocytes **(A** and **B).** Erythroid iron incorporation is decreased or undetectable **(C).** (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.)

BASIC INFORMATION

DEFINITION

Anemia is defined as a hemoglobin level 2 standard deviations below normal for age and sex. Iron deficiency anemia is anemia resulting from inadequate iron supplementation or excessive blood loss.

ICD-10CM CODES	
D50.9	Iron deficiency anemia, unspecified
O99.019	Anemia complicating pregnancy, unspecified trimester
D50.0	Iron deficiency anemia secondary to blood loss (chronic)
D50.8	Other iron deficiency anemias

EPIDEMIOLOGY & DEMOGRAPHICS

- Dietary iron deficiency occurs often in infants as a result of unsupplemented milk diets. It is also commonly seen in women during their reproductive years, as a result of heavy menstrual periods, and during pregnancy (increased demand).
- Iron deficiency is the most common nutritional deficiency worldwide.
- The prevalence of iron deficiency is greatest among toddlers ages 1 to 2 yr (7%) from inadequate intake and female individuals ages 12 to 49 yr (9% to 16%) from menstrual losses.
- The prevalence of iron deficiency is 2% in adult men, 9% to 12% in non-Hispanic white women, and 20% in black and Mexican American women.
- GI cancer is diagnosed in 10% of elderly patients with iron deficiency anemia.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most patients have normal examination results.
- Skin pallor and conjunctival pallor may be present.
- Signs and symptoms specific for iron deficiency are koilonychias, pica, pagophagia, blue sclera, glossitis, and angular stomatitis (Fig. E1).
- Patients with severe anemia can have palpitations, headache, weakness, dizziness, and easy fatigability.

ETIOLOGY

- Blood loss from GI or menstrual bleeding (genitourinary blood loss less often the cause)
- Dietary iron deficiency (rare in adults)
- Poor iron absorption in patients with gastric or small-bowel surgery
- Repeated phlebotomy
- Increased requirements (e.g., during pregnancy)
- Other: Traumatic hemolysis (abnormally functioning cardiac valves), idiopathic pulmonary hemosiderosis (iron sequestration in pulmonary macrophages), paroxysmal nocturnal hemoglobinuria (intravascular hemolysis)
- The most common cause worldwide is hookworm infection

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Anemia of chronic disease
- Sideroblastic anemia
- Thalassemia trait
- Lead poisoning

WORKUP

Diagnostic workup consists primarily of laboratory evaluation. Table 1 describes laboratory studies differentiating the most common microcytic anemias. Most patients with iron deficiency anemia are asymptomatic in the early stages. With progressive anemia, the major symptoms are fatigue, dizziness, exertional dyspnea, pagophagia (ice eating), and pica. Patient history may also suggest GI blood loss (melena, hematochezia, hemoptysis).

LABORATORY TESTS

- Laboratory results vary with the stage of deficiency.
- Absent iron marrow stores and decreased serum ferritin are the initial abnormalities.
- Decreased serum iron and increased total iron-binding capacity (TIBC) are the next abnormalities.
- Hypochromic microcytic anemia is present with significant iron deficiency.
- Peripheral smear in patients with iron deficiency generally reveals microcytic hypochromic red blood cells (Fig. E2) with a wide area of central pallor, anisocytosis, and poikilocytosis when severe.
- Laboratory abnormalities consistent with iron deficiency are low serum ferritin level, increased RBC distribution width with values generally >15, low mean corpuscular volume, low mean corpuscular hemoglobin, increased TIBC, and low serum iron.
- In patients diagnosed with iron deficiency anemia, a GI workup including an upper endoscopy and colonoscopy is recommended to look for source of iron loss.

TREATMENT

The goal of therapy is to supply sufficient iron to correct the low hemoglobin and replenish iron stores.

NONPHARMACOLOGIC THERAPY

Patients should be instructed to consume foods that contain large amounts of iron, such as liver, red meat, and legumes.

ACUTE GENERAL Rx

- Iron supplementation will result in reticulocytosis and will generally increase hemoglobin levels by 0.5 to 1 g per wk.
- Treatment consists of ferrous sulfate 325 mg PO daily for 3 to 6 mo. Doses higher than 325 mg/day are poorly tolerated. Calcium supplements can decrease iron absorption; therefore, these medications should be staggered. Supplemental vitamin C can increase oral absorption.
- Parenteral iron therapy is reserved for patients with poor tolerance, noncompliance with oral preparations, or malabsorption.
- Transfusion of packed RBCs is indicated in patients with severe symptomatic anemia.

CHRONIC Rx

Patients should be instructed to continue their iron supplements for at least 6 mo or longer to correct depleted body iron stores.

DISPOSITION

- Most patients respond rapidly to iron supplementation with improvement in CBC and general well-being (Table 2). GI side effects from oral iron therapy are common and may require decreased dosage to once every other day or to change to parenteral iron.
- A differential diagnosis of microcytic anemia that fails to respond to oral iron is described in Table 3.

REFERRAL

GI referral for evaluation of GI malignancy is recommended in all patients with iron deficiency and suspected GI blood loss.

TABLE 1 Laboratory Studies Differentiating the Most Common Microcytic Anemias

Study	Iron Deficiency Anemia	α or β Thalassemia	Anemia of Chronic Disease
Hemoglobin	Decreased	Decreased	Decreased
MCV	Decreased	Decreased	Normal-decreased
RDW	Increased	Normal	Normal-increased
RBC	Decreased	Normal-increased	Normal-decreased
Serum ferritin	Decreased	Normal	Increased
Total Fe binding capacity	Increased	Normal	Decreased
Transferrin saturation	Decreased	Normal	Decreased
FEP	Increased	Normal	Increased
Transferrin receptor	Increased	Normal	Increased
Reticulocyte hemoglobin concentration	Decreased	Normal	Normal-decreased

Fe, Ferritin; *FEP,* free erythrocyte protoporphyrin; *MCV,* mean corpuscular volume; *RBC,* red blood cell; *RDW,* red cell distribution width.

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

TABLE 2 Responses to Iron Therapy in Iron Deficiency Anemia

Time after Iron Administration	Response
12-24 hr	Replacement of intracellular iron enzymes; subjective improvement; decreased irritability; increased appetite
36-48 hr	Initial bone marrow response; erythroid hyperplasia
48-72 hr	Reticulocytosis, peaking at 5-7 days
4-30 days	Increase in hemoglobin level
1-3 mo	Repletion of stores

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

TABLE 3 Differential Diagnosis of Microcytic Anemia That Fails to Respond to Oral Iron

Poor compliance (true intolerance of iron is uncommon)

Incorrect dose or medication

Malabsorption of administered iron

Ongoing blood loss including gastrointestinal, menstrual, and pulmonary

Concurrent infection or inflammatory disorder inhibiting the response to iron

Concurrent vitamin B_{12} or folate deficiency

Diagnosis other than iron deficiency

- Thalassemias
- Hemoglobin C and E disorders
- Anemia of chronic disease
- Lead poisoning
- Sickle thalassemias, hemoglobin SC disease
- Rare microcytic anemias

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

PEARLS & CONSIDERATIONS

COMMENTS

- Iron deficiency may impair aerobic performance and worsen symptoms in patients with heart failure. Treatment with IV iron in patients with chronic heart failure and iron deficiency has been shown to improve symptoms, quality of life, and functional capacity.
- If the diagnosis of iron deficiency anemia is made, locating the suspected site of iron loss is mandatory.

RELATED CONTENT

Algorithm for Diagnosis of Anemias (Algorithm in Section III)

Algorithm for Diagnosis of Anemias (Patient Information)

Anemia (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

FIG. E1 Iron deficiency. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

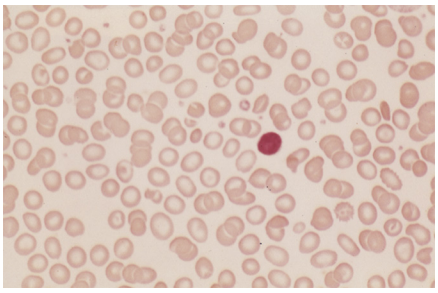


FIG. E2 Iron deficiency anemia. Many of these red blood cells are microcytic (smaller than the nucleus of the normal lymphocyte near the center of the field) and hypochromic (with central areas of pallor that exceed half the diameter of the cells). (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

BASIC INFORMATION

DEFINITION

Pernicious anemia (PA) is an autoimmune disease resulting from antibodies against gastric intrinsic factor and gastric parietal cells.

SYNONYMS

Megaloblastic anemia resulting from vitamin B_{12} deficiency
Addison-Biermer anemia

ICD-10CM CODES

D51.0 Vitamin B_{12} deficiency anemia due to intrinsic factor deficiency
D51.8 Other vitamin B_{12} deficiency anemias
D51.9 Vitamin B_{12} deficiency anemia, unspecified
D51.1 Vitamin B_{12} deficiency anemia due to selective vitamin B_{12} malabsorption with proteinuria

EPIDEMIOLOGY & DEMOGRAPHICS

- Increased incidence in females and older adults (40 to 70 yr)
- More frequent in patients of northern European ancestry
- Overall prevalence of undiagnosed PA after age 60 yr is 1.9%
- Prevalence is higher in women (2.7%), particularly in black women (4.3%)
- Associated with other autoimmune diseases (e.g., type 1 diabetes mellitus, Graves disease, Addison disease), along with possible *Helicobacter pylori* association

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Mucosal pallor and/or glossitis
- Angular cheilosis
- Mild jaundice (representative of intramedullary hemolysis of megaloblastic cells); "lemon yellow" skin due to pallor and jaundice
- Peripheral sensory neuropathy with paresthesias initially and absent reflexes in advanced disease
- Delirium or dementia
- Worsening weakness and possible subacute combined degeneration of spinal cord (Fig. E1)
- Loss of proprioception and an unsteady gait
- Gastrointestinal symptoms including anorexia, pyrosis, nausea, and vomiting
- Possible splenomegaly and mild hepatomegaly

ETIOLOGY

- Parietal cell antibodies are present in >70% of patients, while intrinsic factor antibodies are noted in >50% of patients.
- Atrophic gastric mucosa (Fig. E2) with achlorhydria.
- Inborn errors of cobalamin-cofactor synthesis are rare. Fig. E3 illustrates the components and mechanism of cobalamin absorption. An etiopathophysiologic classification of cobalamin deficiency is described in Section II.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Nutritional vitamin B_{12} deficiency
- Malabsorption (e.g., celiac disease)
- Chronic alcoholism (multifactorial)
- Chronic gastritis related to *H. pylori* infection
- Folic acid deficiency
- Myelodysplasia
- Thyroid abnormalities
- Atrophic gastritis
- Paraproteinemias

WORKUP

- The clinical presentation of PA varies with the stage. Initially, patients may be asymptomatic. In advanced stages patients may have impaired memory, depression, gait disturbances, paresthesias, and generalized weakness.
- Investigation consists primarily of laboratory evaluation. Table 1 describes a step-wise approach to the diagnosis of cobalamin and folate deficiency.
- Endoscopy and biopsy for atrophic gastritis may be performed in selected cases.
- Diagnosis is crucial because failure to treat may result in irreversible neurologic deficits.

LABORATORY TESTS

- Complete blood count generally reveals macrocytic anemia, thrombocytopenia, and mild leukopenia with hypersegmented neutrophils (Fig. E4).
- Mean corpuscular volume (MCV) is significantly elevated in advanced stages.
- Reticulocyte count is low to normal.
- False low serum cobalamin levels can occur in patients who are pregnant or taking oral contraceptives, have multiple myeloma, have transcobalamin I (TCI) deficiency, have severe folic acid deficiency, or are taking large doses of ascorbic acid. False high normal levels in patients with cobalamin deficiency can occur in several conditions including hepatomas, severe liver disease, or monoblastic leukemias (Table 2).
- The absence of anemia or macrocytosis does not exclude the diagnosis of cobalamin deficiency. Anemia is absent in 20% of patients with cobalamin deficiency, and macrocytosis is absent in >30% of patients at the time of diagnosis. Macrocytosis can be masked by concurrent iron deficiency, anemia of chronic disease, or thalassemia trait.
- Laboratory tests used for detecting cobalamin deficiency in patients with normal vitamin B_{12} levels include serum and urinary methylmalonic acid (MMA) level (elevated), total homocysteine level (elevated), and intrinsic factor antibody (positive). Cobalamin is a cofactor for the enzymes L-methylmalonyl coenzyme A mutase and methionine synthase. Inadequate levels of cobalamin will thus result in increased MMA and homocysteine levels. Plasma MMA levels can also be used to differentiate cobalamin deficiency from folate deficiency because patients with folate deficiency have normal or mild elevations of MMA levels.
- An increased concentration of plasma MMA does not predict clinical manifestations of vitamin B_{12} deficiency and should not be used as the only marker for diagnosis of B_{12} deficiency.

TABLE 1 Stepwise Approach to the Diagnosis of Cobalamin and Folate Deficiency

Megaloblastic Anemia or Neurologic-Psychiatric Manifestations Consistent with Cobalamin Deficiency *Plus* Test Results on Serum Cobalamin and Serum Folate

Cobalamin[a] (pg/ml)	Folate[b] (ng/ml)	Provisional Diagnosis	Proceed with Metabolites?[c]
>300	>4	Cobalamin or folate deficiency is unlikely	No
<200	>4	Consistent with cobalamin deficiency	No
200-300	>4	Rule out cobalamin deficiency	Yes
>300	<2	Consistent with folate deficiency	No
<200	<2	Consistent with (1) combined cobalamin plus folate deficiency or (2) isolated folate deficiency	Yes
>300	2-4	Consistent with (1) folate deficiency or (2) an anemia unrelated to vitamin deficiency	Yes

Test Results on Metabolites: Serum Methylmalonic Acid and Total Homocysteine

Methylmalonic Acid (Normal, 70-270 nM)	Total Homocysteine (Normal, 5-14 μM)	Diagnosis
Increased	Increased	Cobalamin deficiency confirmed; folate deficiency still possible (i.e., combined cobalamin plus folate deficiency possible)
Normal	Increased	Folate deficiency is likely
Normal	Normal	Cobalamin and folate deficiency is excluded

[a]Serum cobalamin levels: Abnormally low, <200 pg/ml; clinically relevant low-normal range, 200-300 pg/ml.
[b]Serum folate levels: Abnormally low, <2 ng/ml; clinically relevant low-normal range, 2-4 ng/ml.
[c]Any frozen-over sample from serum folate/cobalamin determination can be subjected to metabolite tests.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, WB Saunders.

TABLE 2 Serum Cobalamin: False-Positive and False-Negative Test Results

Falsely Low Serum Cobalamin in the Absence of True Cobalamin Deficiency

- Folate deficiency (one third of patients)
- Multiple myeloma
- TCI deficiency
- Megadose vitamin C therapy
- Pregnancy
- Oral contraceptives

Falsely Raised Cobalamin Levels in the Presence of a True Deficiency[a]

- Cobalamin binders (TCI and II) increased (e.g., myeloproliferative states, hepatomas, and fibrolamellar hepatic tumors)
- TCII-producing macrophages are activated (e.g., autoimmune diseases, monoblastic leukemias and lymphomas)
- Release of cobalamin from hepatocytes (e.g., active liver disease)
- High serum anti-IF antibody titer

IF, Intrinsic factor; *TC,* transcobalamin.

[a]Although a low serum cobalamin level is not synonymous with cobalamin deficiency, 5% of patients with true cobalamin deficiency have low-normal cobalamin levels, a potentially serious problem because the patient's underlying cobalamin deficiency will progress if uncorrected.

From Hoffman R et al: *Hematology, basic principles and practice,* ed 6, Philadelphia, 2013, WB Saunders.

- Additional laboratory abnormalities can include elevated lactate dehydrogenase, direct hyperbilirubinemia, and decreased haptoglobin.
- Bone marrow aspirate is not necessary to diagnose cobalamin deficiency. It may show giant C-shaped neutrophil bands and megaloblastic normoblasts (Fig. E5).
- Schilling test: No longer used. It was historically used to identify the locus of cobalamin malabsorption and the cause of cobalamin deficiency.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Avoid folic acid supplementation without proper vitamin B_{12} supplementation. Folic acid supplementation alone may result in hematologic remission in patients with vitamin B_{12} deficiency but will not treat or prevent neurologic manifestations.

ACUTE GENERAL Rx

Traditional therapy of cobalamin deficiency consists of intramuscular (IM) or deep subcutaneous (SC) injections of vitamin B_{12} 1000 mcg/day for 1 wk, followed by 1000 mcg/mo, indefinitely. Monitor response and increase dosing if serum B_{12} levels decline.

CHRONIC Rx

- Parenteral vitamin B_{12} 1000 mcg/mo or intranasal cyanocobalamin 500 mcg/wk for the remainder of life.
- In patients who have no nervous system involvement, intranasal cyanocobalamin may be used in place of parenteral cyanocobalamin after hematologic parameters have returned to normal range. The initial dose of intranasal cyanocobalamin is 1 spray (500 mcg) in one nostril once per week. Nasal cyanocobalamin is expensive.
- Oral cobalamin (1000 to 2000 mcg/day) is also being effective in mild cases of pernicious anemia because approximately 1% of an oral dose is absorbed by passive diffusion, a pathway that does not require intrinsic factor. Cost for 1 mo of therapy is approximately $5. Consider returning to IM vitamin B_{12} supplementation if decline recurs.

DISPOSITION

Anemia generally resolves with appropriate cobalamin replacement therapy. Neurologic deficits, on the other hand, may be corrected only if treated early on.

REFERRAL

Gastroenterology referral for endoscopy on diagnosis of PA followed by periodic surveillance endoscopies to rule out gastric adenocarcinoma or carcinoid tumors.

PEARLS & CONSIDERATIONS

COMMENTS

- Early manifestations of negative cobalamin balance are increased serum methylmalonic acid and total homocysteine levels. This occurs when the total cobalamin in serum is still in the low-normal range.
- Vitamin B_{12} deficiency that is allowed to progress for longer than 3 mo may produce permanent degenerative lesions of the spinal cord (e.g., subacute combined degeneration of spinal cord).
- Vitamin B_{12} deficiency may suppress signs of polycythemia vera; treatment of B_{12} deficiency may unmask this disorder.
- Blunted or impeded therapeutic response to vitamin B_{12} may be due to concurrent iron or folic acid deficiency, uremia, infections, or use of drugs with bone marrow suppressant properties. Causes of megaloblastosis not responding to therapy with cobalamin or folate are summarized in Table 3.
- Drugs that interfere with B_{12} absorption include metformin, colchicine, neomycin, and aminosalicylic acid.
- Patients must understand that cobalamin replacement therapy is lifelong.
- Self-injection of vitamin B_{12} may be taught in selected patients. Cost of monthly injections is less than $10.
- Patients who have had bariatric surgery should receive 1 mg of oral vitamin B_{12} per day indefinitely.

TABLE 3 Causes of Megaloblastosis Not Responding to Therapy with Cobalamin or Folate

Wrong Diagnosis

Combined folate and cobalamin deficiencies being treated with only one vitamin

Associated iron deficiency

Associated hemoglobinopathy (e.g., sickle cell disease, thalassemia)

Associated anemia of chronic disease

Associated hypothyroidism

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pernicious Anemia (Patient Information)

AUTHOR: **Shiva Kumar R. Mukkamalla, MD, MPH**

SUGGESTED READINGS

Annibale B et al: Diagnosis and management of pernicious anemia, *Curr Gastroenterol Rep* 13:518-524, 2011.

Bizzaro N, Antico A: Diagnosis and classification of pernicious anemia, *Autoimmun Rev* 13:565-568, 2014.

Green R, Datta Mitra A: Megaloblastic anemias: nutritional and other causes, *Med Clin North Am* 101(2):297-317, 2017.

Hesdorffer CS, Longo DL: Drug-induced megaloblastic anemia, *N Engl J Med* 373:1649-1658, 2015.

Langan RC, Goobred AJ: Vitamin B_{12} deficiency: recognition and management, *Am Fam Physician* 96(6):384-389, 2017.

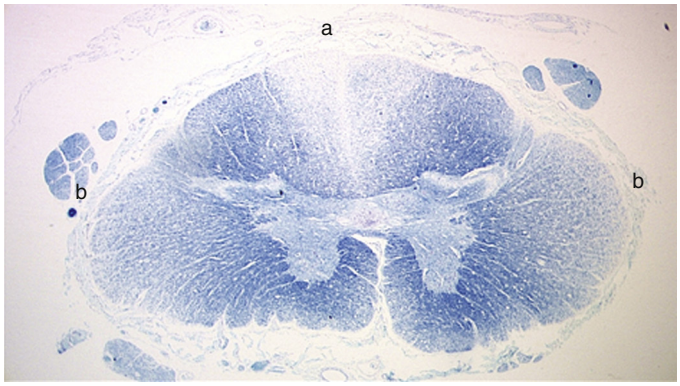


FIG. E1 Spinal cord in cobalamin deficiency. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

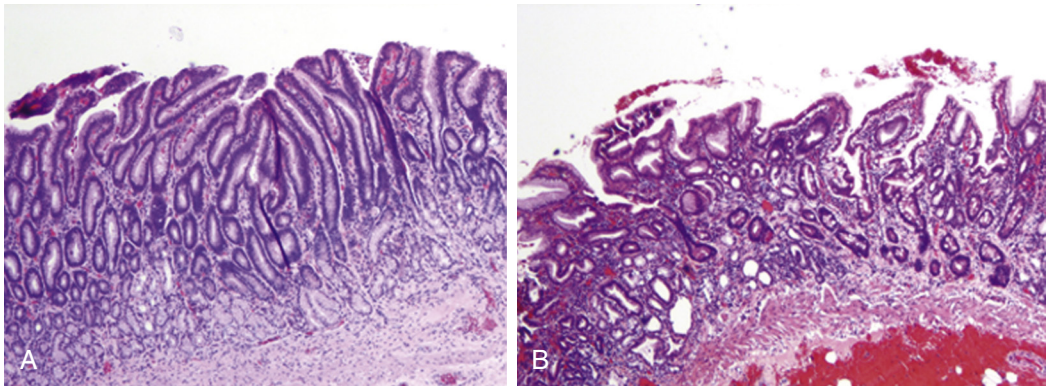


FIG. E2 Histologic features of stomach in pernicious anemia compared with normal. The normal gastric mucosa **(A)** is contrasted with that seen in pernicious anemia **(B),** in which there is atrophy of gastric glands, intestinal metaplasia with goblet cells, and loss of parietal cells (not visible at this magnification). (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

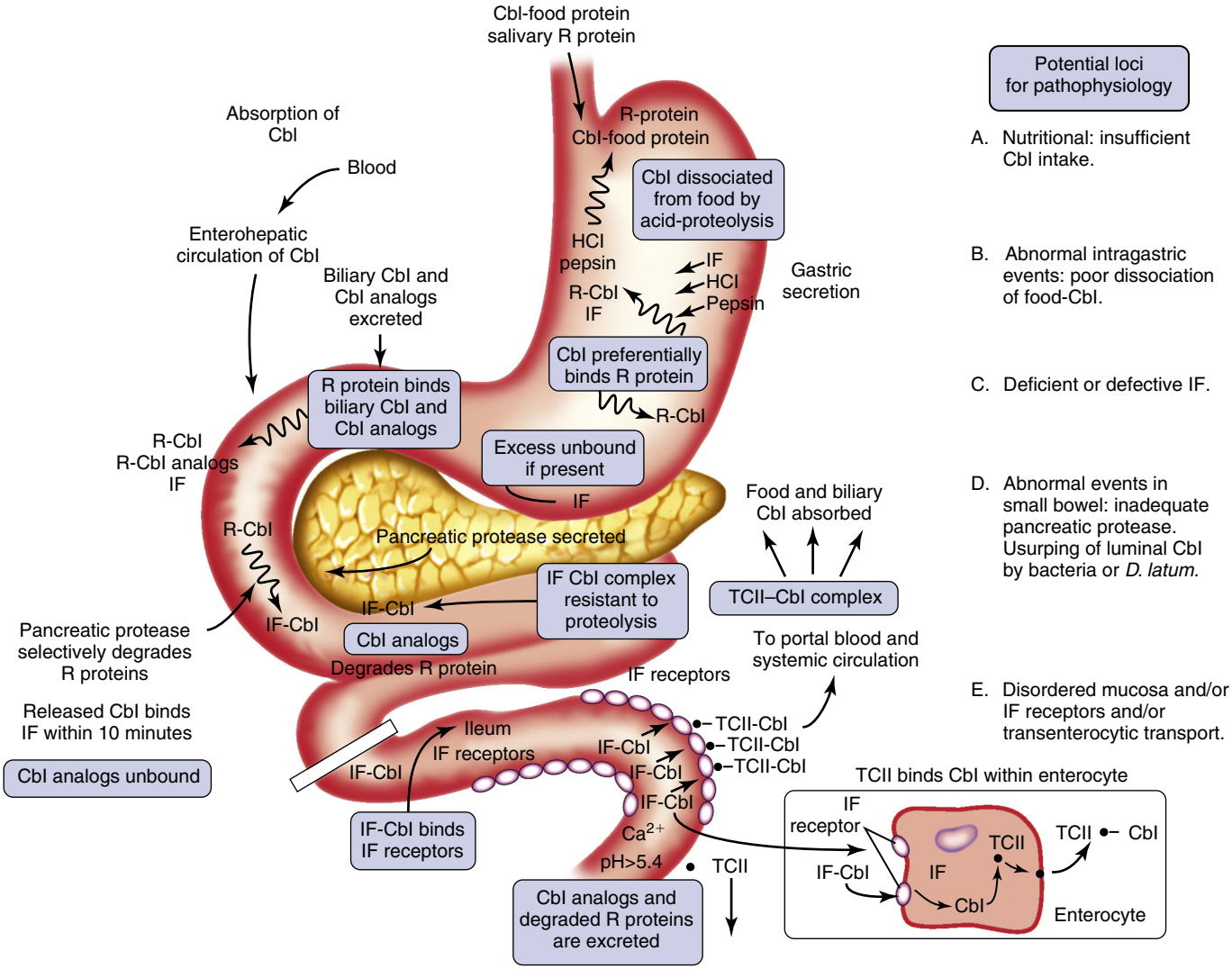


FIG. E3 Components and mechanism of cobalamin absorption. *Cbl,* Cobalamin; *HCl,* hydrochloric acid; *IF,* intrinsic factor; *R,* protein ligand; *TCII,* transcobalamin II. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 6, Philadelphia, 2013, Elsevier.)

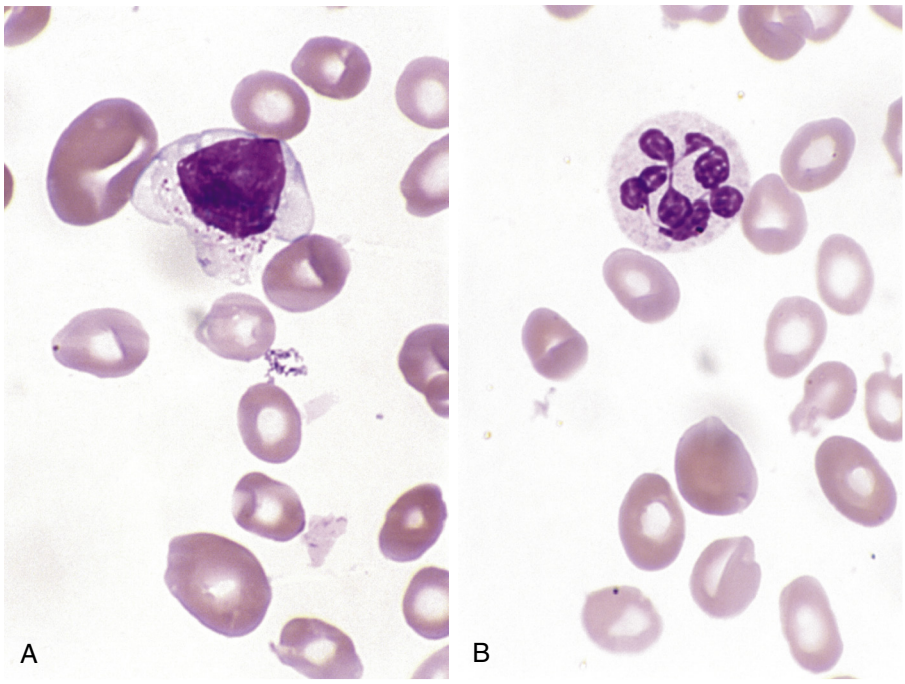


FIG. E4 Macroovalocytes **(A)** and hypersegmented neutrophils **(B)** are typical features of megaloblastic anemia. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.)

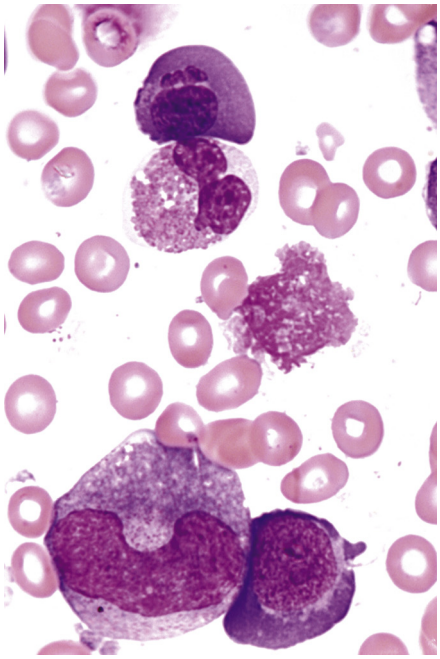


FIG. E5 Bone marrow aspirate from a patient with cobalamin deficiency illustrates a giant C-shaped neutrophil band and megaloblastic normoblasts. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.)

Anemia, Sideroblastic

BASIC INFORMATION

DEFINITION

Sideroblastic anemias (SAs) are a heterogeneous group of blood disorders characterized by ring sideroblasts in the bone marrow (abnormal erythroblasts with pathologic iron deposits in the mitochondria distributed in a "ringlike" fashion around the nucleus) and impaired heme biosynthesis.

CLASSIFICATION (TABLE E1)

- Congenital sideroblastic anemia (CSA)
- Acquired clonal sideroblastic anemia (ACSA)
- Acquired reversible sideroblastic anemia (ARSA)
- Sideroblastic anemia

ICD-10CM CODES

D64.0	Hereditary sideroblastic anemia
D64.1	Secondary sideroblastic anemia due to disease
D64.2	Secondary sideroblastic anemia due to drugs and toxins
D64.3	Other sideroblastic anemias

EPIDEMIOLOGY & DEMOGRAPHICS

- X-linked (40% of CSAs); primarily affects males
- Autosomal recessive (15% of CSAs)
- ACSAs affect middle-aged and older adults

TABLE E1 Classification of Sideroblastic Anemias

Hereditary (Nonsyndromic)

- X-linked
- Autosomal dominant or recessive
- Acquired
- Idiopathic acquired[a] (refractory anemia with ring sideroblasts)
- Associated with previous chemotherapy, irradiation, or in transition myelodysplasia or myeloproliferative diseases

Drugs

- Alcohol
- Isoniazid
- Chloramphenicol
- Other drugs

Rare Causes

- Erythropoietic protoporphyria
- Copper deficiency or zinc overload
- Hypothermia

Hereditary (Syndromic)

- X-linked sideroblastic anemia with ring sideroblasts and cerebellar ataxia
- Myopathy, lactic acidosis, and sideroblastic anemia
- Pearson syndrome
- Thiamine-responsive megaloblastic anemia
- Sideroblastic anemia with immunodeficiency, fevers, and developmental delay

[a]Trial of pyridoxine indicated.

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms of SA are similar to those of anemia and iron overload with additional features and variations noted based on the type.

- Mild to moderate anemia with other cytopenias
- Photosensitivity
- Hepatosplenomegaly
- Neurologic deficits
- Cardiomyopathy
- Pancreatic insufficiency
- Hepatic/renal failure

ETIOLOGY

- Congenital forms can be X-linked or autosomal recessive.
- Acquired clonal forms may be associated with chemotherapy or irradiation.
- RARS develops as a subtype of myelodysplasia.
- Reversible SA can be caused by alcohol, medications (isoniazid, pyrazinamide, cycloserine, chloramphenicol), thiamine deficiency, and copper deficiency.

DIAGNOSIS

The principal feature of SA is mild to moderate anemia in middle-aged or elderly patients, although severe anemias have been reported. SAs are usually microcytic, but normocytic and dimorphic smears are not uncommon. Symptoms of iron overload may be the presenting feature in some. History and clinical findings, together with typical laboratory evidence, usually permit accurate diagnosis of different types of SAs. Molecular defects can be identified in several hereditary forms and in some patients with acquired clonal SAs.

DIFFERENTIAL DIAGNOSIS

- SA must be differentiated from other causes of microcytic hypochromic anemia, including iron deficiency anemia, thalassemia, anemia of chronic disease, and lead poisoning.
- Tissue iron overload from SA may present similar to hereditary hemochromatosis with liver cirrhosis, diabetes, congestive heart failure, or cardiac arrhythmias.

WORKUP

- CBC, peripheral smear, iron studies, free erythrocyte protoporphyrin level, serum copper level, serum lead level, MRI, bone marrow aspiration and biopsy (Fig. E1).
- CBC counts reveal anemia, mostly moderate, although severe anemias have been reported.
- Microcytic, normocytic, or macrocytic and classic dimorphic anemias may be seen along with siderocytes with Pappenheimer bodies (mature hypochromic erythrocytes with basophilic iron deposits).
- High serum iron levels, low transferrin along with increased transferrin saturation and high serum ferritin.
- Bone marrow shows increased iron stores and the classic ring sideroblasts, not seen in normal bone marrow tissue. The ring sideroblasts represent pathologic iron deposits in the perinuclear mitochondria of erythroblasts.
- In transfusion-dependent anemias, monitoring of ferritin and transferrin saturation levels is essential to avoid iron overload.
- Features of ineffective erythropoiesis like increase in indirect bilirubin concentration, decrease in haptoglobin, increase in LDH, and normal or increase in reticulocyte number may be seen.
- MRI of posterior cranial fossa is indicated in anemia-ataxia syndromes.

TREATMENT

Treatment is directed at controlling symptoms of anemia and preventing organ damage from iron overload.

NONPHARMACOLOGIC THERAPY

Removal of toxic agents that are potentially predisposing to SA is necessary.

ACUTE GENERAL Rx

- A trial of pyridoxine (50 to 200 mg/day) is indicated for all patients with congenital SAs.
- 25% to 50% may show full or partial response to pyridoxine.
- Folic acid given along with pyridoxine ensures adequate substrate availability during increased hemoglobin synthesis.
- Patients who do not respond require support with PRBC transfusions.
- Chelation therapy is needed for patients with transfusion-dependent anemia to prevent complications of iron overload.
- Erythropoietin and granulocyte colony-stimulating factor use may show some success in treating myelodysplasia-associated refractory anemia with ring sideroblasts.
- Secondary SA caused by medications can be reversed by withdrawing the medication and administering vitamin B_6.

CHRONIC Rx

Organ dysfunction resulting from iron overload will require periodic phlebotomy to keep serum ferritin level <300 ng/ml, as long as the patient is not anemic.

- Iron chelating therapy for patients with moderate to severe anemia who require regular red cell transfusion: Deferoxamine is given as subcutaneous or intravenous infusion; deferiprone and deferasirox are given orally.
- Splenectomy should be avoided at all costs.
- Bone marrow transplant is a last resort in young patients who are pyridoxine resistant and transfusion dependent with iron overload.

PROGNOSIS

In patients with anemia alone, life expectancy is normal. In patients dependent on blood transfusions, morbidity from iron overload can be expected.

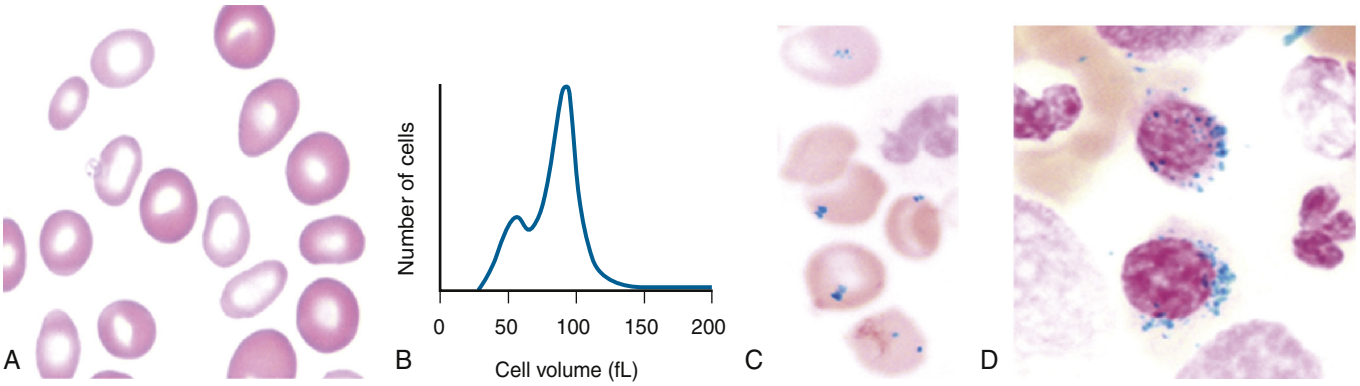


FIG. E1 **A,** Peripheral blood smear from a patient with hereditary sideroblastic anemia shows a population of hypochromic and microcytic erythrocytes. **B,** Erythrocyte volume distribution curve of a patient with hereditary sideroblastic anemia. A dimorphic size distribution is evident. **C,** Peripheral blood showing Pappenheimer bodies (Prussian blue stain). **D,** The bone marrow smear stained with Prussian blue shows ring sideroblasts. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

- RARS: With dysplasia confined to the erythroid cell lineage; survival similar to age-matched controls; no incidence of leukemic transformation.
- RCMD-RS: Approximately 5% will develop acute leukemia. Erythropoietin and granulocyte colony-stimulating factor therapy do not change survival.

REFERRAL

- Hematologist
- Neurologist (in anemia-ataxia and myopathy-anemia syndromes)
- Families with severe forms of hereditary sideroblastic anemia should receive genetic counseling

PEARLS & CONSIDERATIONS

- SA can be thought of as an iron-loading anemia secondary to defective heme synthesis.
- A predisposition to leukemia evolution has not been observed in patients with congenital forms.
- Symptoms rather than an absolute hemoglobin level or hematocrit should guide transfusion therapy.

COMMENTS

Vitamin B_6, or pyridoxal phosphate, is a required cofactor in heme synthesis, and drugs such as isoniazid, cycloserine, and pyrazinamide can inhibit its function.

SUGGESTED READING

Bottomley SS et al: Sideroblastic anemia: diagnosis and management, *Hematol Oncol Clin North Am* 28(4):653-670, 2014.

AUTHOR: **Shiva Kumar R. Mukkamalla, MD, MPH**

BASIC INFORMATION

DEFINITION

Angina pectoris is a term used to describe a clinical syndrome, typically characterized by chest, jaw, shoulder, back or arm discomfort that is caused by myocardial ischemia. This is most commonly related to atheromatous plaque in one or more than one large epicardial coronary artery; however, myocardial ischemia may occur in the absence of obstructive coronary artery disease (CAD), such as uncontrolled hypertension, microvascular disease, valvular heart disease, hypertrophic cardiomyopathy, coronary spasm, or endothelial dysfunction. Any situation that causes an imbalance in myocardial oxygen supply and demand can cause an angina syndrome. Angina can be classified as follows:

- Chronic stable angina, stable ischemic heart disease (SIHD), or chronic coronary artery disease:
  1. Predictable. Usually follows a precipitating event (e.g., climbing stairs, sexual intercourse, a heavy meal, emotional stress, cold weather).
  2. Generally has the same severity as previous attacks; relieved by rest or by the customary dose of sublingual nitroglycerin.
  3. Caused by a fixed coronary artery obstruction secondary to atherosclerosis. The presence of one or more obstructions in major coronary arteries is likely; the severity of stenosis is usually >70%.
- Unstable (rest, recent onset, crescendo angina; will be reviewed under Acute Coronary Syndrome):
  1. Rest angina: Angina occurring at rest and usually prolonged >20 min, occurring within 1 week of presentation.
  2. Recent onset: Angina of at least CCS Class III severity occurring less than 2 months after the onset of the symptoms.
  3. Crescendo angina: Previously diagnosed angina that is distinctly more frequent, longer in duration, or lower in threshold (i.e., increased by >1 CCS class within 2 months of initial presentation to at least CCS Class III severity).
- Prinzmetal variant:
  1. Occurs at rest, common after cold exposure.
  2. Cyclical in nature.
  3. EKG finding of episodic ST-segment elevations.
  4. Caused by coronary artery spasm with or without superimposed CAD.
  5. Patients are more likely to develop ventricular arrhythmias.
- Microvascular angina (syndrome X):
  1. Refers to patients with angina symptoms, positive exercise test, normal coronary angiograms and no coronary spasm. Defective endothelium-dependent dilation in the coronary microcirculation contributes to the altered regulation of myocardial perfusion and the ischemic manifestations in these patients.
  2. Patients with chest pain and normal or nonobstructive coronary angiograms are predominantly women, and many have a prognosis that is not as benign as commonly thought (2% risk of death or myocardial infarction [MI] at 30 days of follow-up).
- Refractory angina:
  1. Refers to patients whom, despite optimal medical therapy with at least maximal doses, or as tolerated of two antianginal medications, in addition to aspirin, aggressive risk factor modification, such as smoking cessation, adequate control of hypertension, diabetes, and hyperlipidemia, still have both angina and objective evidence of ischemia.
- Other:
  1. Angina due to aortic stenosis and idiopathic hypertrophic subaortic stenosis, cocaine-induced coronary vasoconstriction.

FUNCTIONAL CLASSIFICATION

Stable angina should be classified using a grading system. The most commonly adopted is that of the Canadian Cardiovascular Society (CCS):

- Class I: Ordinary physical activity, such as walking or climbing stairs, does not cause angina. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
- Class II: Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals, in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking more than two level blocks and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
- Class III: Marked limitations of ordinary physical activity. Angina occurs on walking one to two level blocks and climbing one flight of stairs in normal conditions and at a normal pace.
- Class IV: Inability to carry on any physical activity without discomfort; anginal symptoms may be present at rest.

ICD-10CM CODES

I20.8	Other forms of angina pectoris
I20.9	Angina pectoris, unspecified
I20.1	Angina pectoris with documented spasm
I25.110	Atherosclerotic heart disease of native coronary artery with unstable angina pectoris
I25.111	Atherosclerotic heart disease of native coronary artery with angina pectoris with documented spasm
I25.118	Atherosclerotic heart disease of native coronary artery with other forms of angina pectoris
I25.119	Atherosclerotic heart disease of native coronary artery with unspecified angina pectoris
I25.700	Atherosclerosis of coronary artery bypass graft(s), unspecified, with unstable angina pectoris
I25.790	Atherosclerosis of other coronary artery bypass graft(s) with unstable angina pectoris
I25.791	Atherosclerosis of other coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.798	Atherosclerosis of other coronary artery bypass graft(s) with other forms of angina pectoris
I25.799	Atherosclerosis of other coronary artery bypass graft(s) with unspecified angina pectoris

EPIDEMIOLOGY & DEMOGRAPHICS

- It is estimated that one in three adults in the U.S. (about 81 million) has some form of cardiovascular disease. Based on the NHANES survey 2007-2010, an estimated 15.4 million have coronary heart disease of which 7.8 million have angina.
- Angina is most common in middle-aged and elderly men. Among persons 60 to 79 yr of age, approximately 25% of men and 16% of women have coronary heart disease, and these figures rise to 37% and 23% among men and women >80 yr of age, respectively.
- The incidence of coronary heart disease and angina in women after menopause is similar to that of men.
- Although the survival rate has steadily improved over time, SIHD remains the number one cause of death in men and women (27% of deaths).
- The initial manifestation of ischemic heart disease is angina pectoris in 50%, and about 50% of patients presenting to the hospital with acute coronary syndrome have preceding angina.
- Two older population-based studies from Olmstead County, MN, and Framingham, MA, showed annual rate of myocardial infarction in patients with symptomatic angina of 3 to 3.5%/yr.
- Within 12 months of initial diagnosis, 10% to 20% of patients with diagnosis of stable angina progress to MI or unstable angina.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The assessment of chest pain should include quality, location, severity, and duration of pain; radiation; associated symptoms; provocative factors; and alleviating factors. Anginal pain can be described as "squeezing," "griplike," "suffocating," and "heavy," but it is rarely sharp or stabbing and typically does not vary with position or respiration. The classic Levine sign is placing a clenched fist over the precordium to describe the pain. Many patients do not, however, describe angina as frank pain but as tightness, pressure, or discomfort. Other patients, in particular women and older adults, can present with atypical symptoms such as nausea, vomiting, midepigastric discomfort, sharp (atypical) chest pain, dizziness, or syncope.

- Ischemic pain of more than 20 minutes' duration should raise concern for possible acute coronary syndrome.
- Women are more likely than men to report atypical chest pain or discomfort (65% reported on Women's Ischemic Syndrome Evaluation [WISE] study).
- Elderly and diabetics may report symptoms other than chest pain, such as dyspnea, fatigue, or diaphoresis.

ETIOLOGY

RISK FACTORS:

- Advanced age
- Male sex
- Genetic predisposition, family history of premature coronary artery disease (CAD) in first-degree relatives (men younger than 55 yr of age, and women younger than 65 yr of age)
- Smoking (risk of first MI is increased by near threefold)
- Hypertension
- Hyperlipidemia
- Impaired glucose tolerance or diabetes mellitus
- History of stroke or peripheral arterial disease
- Chronic kidney disease (CKD)
- Metabolic syndrome
- Physical inactivity
- Obesity (body mass index >30% over ideal). A higher body mass index during childhood is also associated with an increased risk of coronary heart disease (CHD) in adulthood
- Entities that cause increased oxygen demand include hyperthermia (particularly if accompanied by volume contraction), hyperthyroidism, and cocaine or methamphetamine abuse
- Cocaine is used by >5 million Americans regularly and is responsible for >64,000 emergency department (ED) evaluations yearly to rule out myocardial ischemia. Cocaine causes sympathomimetic toxicity and not only increases myocardial oxygen demand but also induces coronary vasospasm and can cause infarction in young patients. Long-term cocaine use can cause premature development of SIHD
- Severe uncontrolled hypertension causes increased myocardial oxygen demand and decreased subendocardial perfusion that increases LV wall tension. Hypertrophic cardiomyopathy and aortic stenosis can induce even more severe LV hypertrophy and resultant wall tension
- Other causes of increased myocardial oxygen demand are ventricular or supraventricular tachycardias. Ambulatory monitoring may be required to diagnose these
- Entities that limit myocardial oxygen supply such as anemia may cause angina when the hemoglobin drops to <9 g/dl, and ST-T-wave changes (depression or inversion) can occur at levels <7 g/dl
- Hypoxemia resulting from pulmonary disease (e.g., pneumonia, asthma, chronic obstructive pulmonary disease, pulmonary hypertension, interstitial fibrosis, or obstructive sleep apnea) can also precipitate angina
- Polycythemia, leukemia, thrombocytosis, and hypergammaglobulinemia
- Oral contraceptive and HRT use
- Coronary artery calcium is associated with an increased risk of MI
- Long-term use of nonsteroidal antiinflammatory drugs (NSAIDs)
- Exposure to air pollution from traffic (dilute diesel exhaust) promotes myocardial ischemia and is associated with adverse cardiovascular events
- Low serum folate levels required for conversion of homocysteine to methionine are associated with an increased risk of fatal CHD. Hyperhomocysteinemia has a toxic effect on vascular endothelium and interferes with proliferation of arterial wall smooth muscle cells. Elevated plasma homocysteine level is a strong and independent risk factor for CHD events, especially in patients with type 2 diabetes mellitus
- Elevated levels of highly sensitive C-reactive protein (hs-CRP, cardio CRP). Diseases associated with systemic inflammation can lead to accelerated atherosclerosis
- Depression
- Vasculitis
- Elevated levels of lipoprotein-associated phospholipase A_2
- Elevated fibrinogen levels
- Low level of red blood cell glutathione peroxidase-1 activity
- Radiation therapy

DX DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- **Nonischemic cardiovascular:** Aortic dissection, pericarditis
- **Pulmonary:** Pulmonary embolism, pneumothorax, pneumonia, pleuritis
- **Gastrointestinal:** Esophageal, esophagitis, spasm, reflux, biliary colic, cholecystitis, choledocholithiasis, cholangitis, peptic ulcer, pancreatitis
- **Chest wall:** Costochondritis, fibrositis, rib fracture, sternoclavicular arthritis, herpes zoster (before the rash)
- **Psychiatric:** Anxiety disorders, hyperventilation, panic disorder, primary anxiety, affective disorders (i.e., depression), somatoform disorders, thought disorders (i.e., fixed delusions)

WORKUP

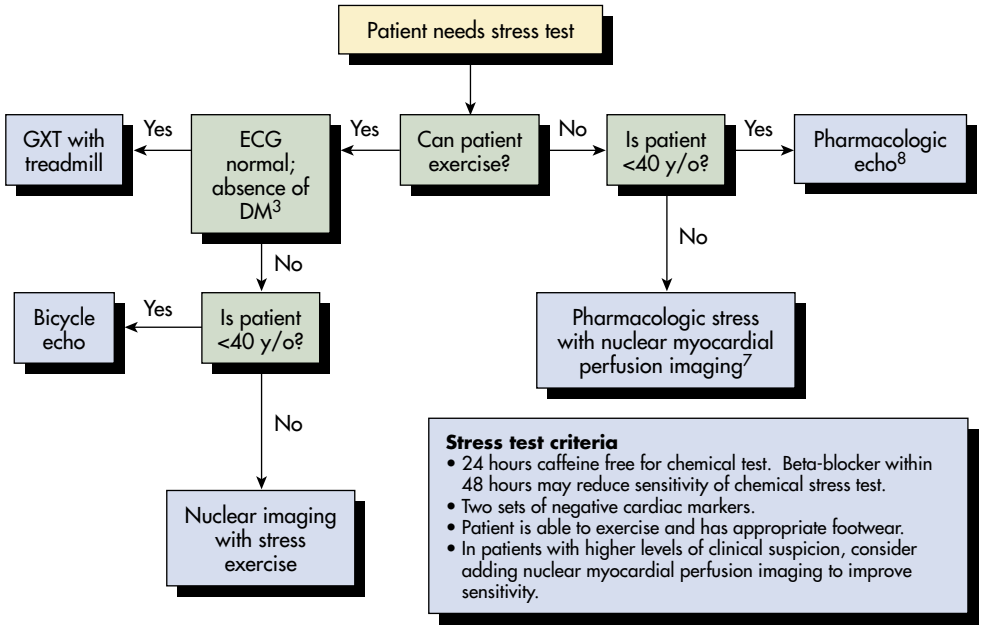
- In patients with chest pain, the probability of CAD should be estimated on the basis of patient age, sex, cardiovascular risk factors, and pain characteristics.
- The most important diagnostic element is the history. Chest pain or left arm pain or discomfort occurring with exertion and relieved by rest in a patient with cardiovascular risk factors is consistent with a high likelihood of CAD.
- In assessing the likelihood of underlying SIHD it is helpful to classify the chest pain as typical angina, atypical angina, and/or noncardiac chest pain.
- Typical angina, (definite) will have the following three features: (1) Substernal chest discomfort with a characteristic quality and duration, (2) provoked by exertion or emotional stress, and (3) relieved by rest and/or sublingual nitroglycerin (NTG).
- Atypical angina, (probable) will have two of the above listed three features.
- Noncardiac chest pain will have one or none of the previously listed features.
- Physical examination may be completely normal in many patients; however, certain findings may be helpful in the assessment of the patient with suspected SIHD. Some findings may identify consequences of ischemia or possible causes of the anginal syndrome other than CAD. The presence of hypertension, arcus senilis, xanthelasma, carotid or peripheral bruits, and a prominent S4 are all physical signs that could raise concern for the presence of CAD. A murmur of mitral regurgitation may be a marker of an ischemic cardiomyopathy or transient ischemia. A murmur suggestive of hypertrophic cardiomyopathy or aortic stenosis may suggest a cause of angina other than CAD.
- The ultimate goal for an SIHD patient's evaluation is to identify high-risk coronary artery disease patients with minimal use of resources. In general, four common steps would help a clinician to assess high feature of SIHD. Those are (1) CAD risk assessment based on various classical risk factors, (2) functional capacity and stress test result, (3) LV and RV function, and (4) coronary anatomy. Every patient does not need each of the modalities. One should classify stable angina without history of CAD patients to low, intermediate, and high pretest probability or likelihood for CAD after assessment of comorbidities. Consider functional capacity and stress test (ETT, ETT-MIBI, or Stress echo) for low and intermediate pretest probability patients. Exercise testing (Fig. 1) is preferred to pharmacologic stress tests when possible. Functional capacity and stress test results categorize SIHD patients based on their risk of annual mortality. Patients with an estimated annual mortality of <1% classify as low risk, 1% to 3% are considered as intermediate risk, and >3% annual mortality belongs to high-risk patient population (please see "Coronary Artery Disease" chapter).

LABORATORY TESTS

- Screen for hypertension, diabetes, and hyperlipidemia per routine guidelines.
- Electrocardiogram should be obtained during pain and when the patient is free of any discomfort. A normal resting electrocardiogram is not unusual in patients with SIHD; in patients who present with chest pain, 1% to 6% who have an acute MI will have a normal or nondiagnostic electrocardiogram.
- Chest x-ray PA and lateral, if symptoms suggestive of heart failure, pericardial disease, aortic aneurysm/dissection.
- Cardio-CRP (hs-CRP): Its elevation is a relatively moderate predictor of CHD, and it adds prognostic information to that conveyed by the Framingham risk score.

EXERCISE TESTING AND IMAGING STUDIES (PLEASE SEE "CORONARY ARTERY DISEASE" CHAPTER, FIG. 1)

- Exercise testing is used for diagnosis as well as prognosis of SIHD. If the patient is physically capable to perform at least moderate physical exercise, exercise stress testing (Fig. 1) is useful because of the important prognostic information obtained from exercise performance and the hemodynamic response. Risk stratification based on non-invasive testing is summarized in Table 1. Patients who have an intermediate likelihood of CAD, as patients in a low-risk or high-likelihood category are more likely to have a false-positive or false-negative result, respectively. Risk assessment is also indicated in patients with SIHD who are being considered for revascularization of known coronary stenosis of unclear physiological significance. The exercise treadmill test is contraindicated in patients with presence of ST depression >0.5 mm or WPW syndrome or LBBB or pacemaker rhythm in baseline ECG.
- Stress echocardiography or stress testing with myocardial perfusion imaging may be employed when baseline electrocardiographic abnormalities are present that render the electrocardiographic response to exercise uninterpretable. Stress echocardiography has the advantage of higher specificity and a lower cost. Stress radionuclide perfusion imaging has a higher sensitivity, particularly for single-vessel coronary disease, and has a higher technical success rate. When the patient is unable to exercise adequately, pharmacologic stress testing



DEFINITIONS:

[1]Typical angina:
(1) Substernal chest pain or discomfort that is (2) provoked by exertion or emotional stress and (3) relieved by rest and/or nitroglycerin

[2]Cardiac marker timing: based on symptom onset; in cases of uncertainty assume symptom onset at ED arrival

[3]ECG normal: no significant ST depression/T wave inversions, BBB, LVH with repolarization, conduction defect, digoxin effect

[4]Anginal equivalent:
- Any symptoms that the physician feels may represent ACS
- Exertional dyspnea—most common anginal equivalent symptom

[5]ACS:
- STE-ACS—1 mm ST elevation in 2 leads
- NSTE-ACS
  - NSTEMI—positive cardiac biomarkers
  - Unstable angina—ischemia with negative biomarkers

[6]New significant ECG changes:
- ST Δs ≥ 0.5 mm; resolve when asymptomatic
- ST depression ≥1 mm in 2 leads
- T wave inversion ≥2 mm in 2 leads

[7]Regadenoson is preferred agent for chemical nuclear stress test. Technitium Tc 99m tetrofosmin is the preferred tracer.

FIG. 1 Stress test algorithm. *ACS,* Acute coronary syndrome; *BBB,* bundle branch block; *DM,* diabetes mellitus; *ECG,* electrocardiogram; *echo,* echocardiography; *ED,* emergency department; *GTX,* graded exercise test; *LVH,* left ventricular hypertrophy; *NSTE,* non–ST-segment elevation; *NSTEMI,* NSTE myocardial infarction; *STE,* ST-segment elevation; *y/o,* years old. (From Adams JG et al: *Emergency medicine: clinical essentials,* ed 2, Philadelphia, 2013, Saunders.)

TABLE 1 Risk Stratification Based on Noninvasive Testing

High Risk (>3% Annual Risk for Death or Myocardial Infarction)

1. Severe resting left ventricular dysfunction (LVEF <35%) not readily explained by noncoronary causes
2. Resting perfusion abnormalities involving ≥10% of the myocardium without previous known MI
3. High-risk stress findings on the ECG, including
   - ≥2-mm ST-segment depression at low workload or persisting into recovery
   - Exercise-induced ST-segment elevation
   - Exercise-induced VT/VF
4. Severe stress-induced LV dysfunction (peak exercise LVEF <45% or drop in LVEF with stress ≥10%)
5. Stress-induced perfusion abnormalities encumbering ≥10% of the myocardium or stress segmental scores indicating multiple vascular territories with abnormalities
6. Stress-induced LV dilation
7. Inducible wall motion abnormality (involving >2 segments or 2 coronary beds)
8. Wall motion abnormality developing at a low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 beats/min)
9. Multivessel obstructive CAD (≥70% stenosis) or left main stenosis (≥50% stenosis) on CCTA

Intermediate Risk (1%-3% Annual Risk for Death or Myocardial Infarction)

1. Mild to moderate resting LV dysfunction (LVEF of 35% to 49%) not readily explained by noncoronary causes
2. Resting perfusion abnormalities involving 5%-9.9% of the myocardium in patients without a history or previous evidence of MI
3. ≥1-mm ST-segment depression occurring with exertional symptoms
4. Stress-induced perfusion abnormalities encumbering 5%-9.9% of the myocardium or stress segmental scores indicating 1 vascular territory with abnormalities but without LV dilation
5. Small wall motion abnormality involving 1-2 segments and only 1 coronary bed
6. 1-vessel CAD with ≥70% stenosis or moderate CAD stenosis (50%-69% stenosis) in ≥2 arteries on CCTA

Low Risk (<1% Annual Risk for Death or Myocardial Infarction)

1. Low-risk treadmill score (score ≥5) or no new ST-segment changes or exercise-induced chest pain symptoms when achieving maximal levels of exercise
2. Normal or small myocardial perfusion defect at rest or with stress encumbering <5% of the myocardium*
3. Normal stress or no change in limited resting wall motion abnormalities during stress
4. No coronary stenosis >50% on CCTA

CCTA, Cardiac computed tomography angiography; *LVEF,* left ventricular ejection fraction; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia.
*Although the published data are limited, patients with these findings will probably not be at low risk in the presence of either a high-risk treadmill score or severe resting LV dysfunction (LVEF <35%). Assessment of coronary artery calcium (CAC) can also be used to contribute to risk assessment.
Modified from Fihn SD et al: ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, *Circulation* 126:e354, 2012; in Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

(i.e., dobutamine, adenosine, regadenoson) may be used with these imaging modalities.

- A good predictor of risk for a patient with stable angina is the Duke treadmill score, which incorporates the patient's functional status (METS or time in minutes during the Bruce protocol), ST-segment depression in millimeters, and an angina index (yes or no). Patients with favorable Duke scores (>5) have a 5-yr survival rate of >97%; this is independent of other factors such as coronary anatomy and LV function.
- Echocardiography is indicated in patients with murmurs suggestive of aortic stenosis, hypertrophic cardiomyopathy, mitral regurgitation, mitral valve prolapse, previous MI, pathological Q waves, complex ventricular arrhythmias, heart failure, hypertension, diabetes, and abnormal EKG.
- Cardiac computed tomography (CCTA; Fig. 2) is useful for the detection of subclinical CAD in asymptomatic patients with an intermediate Framingham 10-yr risk estimate of 10% to 20%. Detects and quantifies coronary calcium and evaluates the lumen and wall of the coronary artery. CCTA can be useful as a first-line test for risk assessment in patients with SIHD who are unable to exercise to an adequate workload regardless of interpretability of ECG. Also can be used when a functional test has an indeterminate result and to assess bypass graft patency or patency of previous stents >3 mm diameter. CCTA CT cost and radiation exposure are limiting factors to recommending widespread routine use of this marker. CCTA has an excellent negative predictive value to rule out severe CAD in the setting of active chest pain evaluation in the emergency room (ROMICAT-II trial). In 2018 the SCOT-HEART trial showed coronary CTA resulted in a lower risk of nonfatal myocardial infarction than standard care alone (ETT) in stable angina patients.
- Coronary artery calcium (CAC) score is a strong predictor of incidence of CAD and provides predictive information in patients with low to intermediate pretest probability of CAD beyond that provided by standard risk factors. A score below 100 indicates low risk, and a score above 400 high risk.
- Cardiac magnetic resonance imaging (CMRA), in addition to its use for diagnosis of arrhythmogenic right ventricular dysplasia, can also be used to assess myocardial perfusion and viability as well as function in patients unable to exercise. Additional studies are needed to determine the cost effectiveness of these studies in patients with ischemic cardiomyopathy.
- Invasive coronary angiography remains the gold standard for the identification of clinically significant CAD. Angiography is performed to define the location and extent of coronary disease; indicated in selected patients who are candidates for coronary revascularization (either coronary artery bypass graft [CABG] surgery or angioplasty).

Rx TREATMENT

FIVE FUNDAMENTAL OVERLAPPING STRATEGIES ARE RECOMMENDED

- Patient education: Support active participation of patients in the decision-making process of their treatment.
- Management of comorbid conditions that contribute or worsen SIHD.
- Aggressive modification of preventable risk factors such as smoking cessation, weight reduction in obese patients, regular aerobic exercise program (at least 30 to 60 min/day for 5 days a week), correction of folate deficiency, reduced intake of saturated fats (to <7% of total calories) and trans fatty acids (to <1% of total calories), low-sodium diet (<2 g/day), and teaching importance of medication adherence. Whole grains as the main form of carbohydrates, an abundance of fruits and vegetables, and adequate omega-3 fatty acids are optimal for prevention of SIHD.

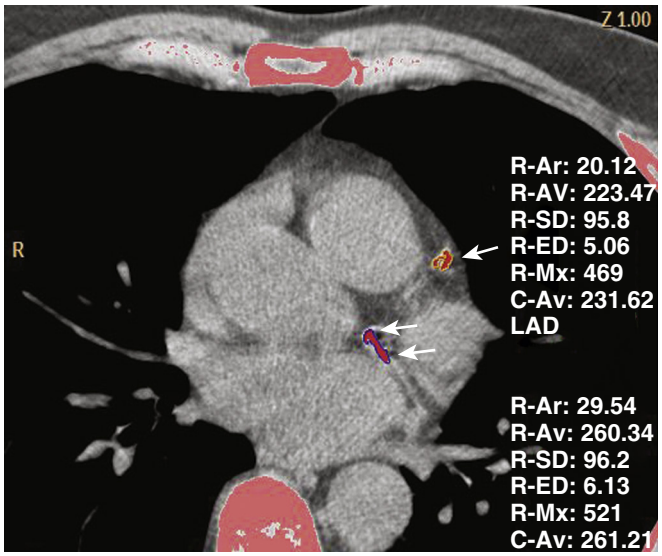


FIG. 2 Example of coronary artery calcium scoring in which calcified foci are identified within the left anterior descending *(orange; single arrow)* and left circumflex *(pink outlined in blue; double arrow)* coronary arteries. The region's area *(R-Ar)* and its average density in Hounsfield units *(R-Av)* are displayed and used in the area-density calcium scoring calculation. (From Bonow RO et al: *Heart disease,* ed 9, Philadelphia, 2012, Saunders.)

- Evidence-based pharmacologic management to improve quality of life and survival.
- Use appropriate revascularization procedures to improve survival and long-term outcomes in selected patients.

PHARMACOLOGIC THERAPY (PLEASE SEE "CORONARY ARTERY DISEASE" CHAPTER)

Treatment can be classified based on medications that prevent MI and death.

- Aspirin reduces cardiovascular mortality and morbidity rates by 20% to 25% among patients with CAD. Appropriate dose is 75 to 162 mg/day in the absence of contraindications. It inhibits the enzyme cyclooxygenase and synthesis of thromboxane A2 and reduces the risk of adverse cardiovascular events by 33% in patients with unstable angina. Patients intolerant to aspirin can be treated with clopidogrel or can undergo aspirin desensitization. Clopidogrel irreversibly blocks the P2Y12 adenosine diphosphate receptor on the platelet surface, thereby interrupting platelet activation and aggregation. Clopidogrel can be combined with ASA in high-risk patients with SIHD with low risk for bleeding complications or can be given alone in patients that are aspirin intolerant. Dose is 75 mg/day.
- Ticagrelor, the newest CTPT inhibitor (P2Y12 antagonist), in the PEGASUS-TIMI-54 reduced the risk of death, cardiovascular MI, or stroke in patients after 1 yr of MI. However, it is associated with an increased risk of bleeding when compared to placebo.
- Dipyridamole is not recommended as an antiplatelet therapy for the treatment of patients with SIHD.
- Beta-adrenergic blockers, which prevent MI and death, are first-line therapy in the management of angina pectoris. They achieve their major antianginal effect by decreasing myocardial oxygen demand in reducing heart rate and systolic blood pressure product, AV nodal conduction, and myocardial contractility, in this manner contributing to a reduction in angina onset, with improvement in the ischemic threshold during exercise and during the usual daily activities. Absent contraindications, they should be regarded as initial therapy for stable angina for all patients. Their dose should generally be adjusted to reduce the resting heart rate to 55 to 60 beats/min. Despite the difference among the available beta-blockers, they all seem to be equally efficacious in SIHD. Beta-blockers recommended for at least 2 to 3 yr after MI, and lifelong for patients with LV ejection fraction of <40% with heart failure or prior MI.
- Nitrates cause venodilation and relaxation of vascular smooth muscle; the decreased venous return from venodilation decreases diastolic ventricular wall tension (preload) and thereby reduces mechanical activity (and myocardial oxygen consumption) during systole. Relaxation of vascular smooth muscle increases coronary blood flow and reduces systemic pressure. Dilatation of the arterial wall will not be affected by plaque, but independent of an intact endothelium, leads to reduced resistance across the obstructed lumen. Nitroglycerin contributes to coronary blood flow redistribution by augmenting collateral flow and lowering ventricular diastolic pressure from areas of normal perfusion to ischemic zones. Nitroglycerin also has demonstrated antithrombotic and antiplatelet effects. Sublingual nitroglycerin or nitroglycerin spray should be prescribed to all patients with SIHD for immediate angina relief. Tolerance to nitrates can be minimized by avoiding sustained blood levels with a daily nitrate-free period (e.g., omission of bedtime dose of oral isosorbide dinitrate or 12 hr on/12 hr off transdermal nitroglycerin therapy). Nitrates are relatively contraindicated in patients with hypertrophic obstructive cardiomyopathy, and should also be avoided in patients with severe aortic stenosis. Nitrates should not be used within 24 hr of sildenafil (Viagra) or vardenafil (Levitra) or within 48 hr of tadalafil (Cialis) because of the potential for hypotension.
- Calcium channel blockers are antiischemic medications that have no proven mortality benefit in SIHD. They improve myocardial oxygen supply by decreasing coronary vascular resistance and augmenting epicardial conduit vessel and systemic arterial blood flow. Myocardial demand is decreased by a reduction in myocardial contractility, systemic vascular resistance, and arterial pressure. They are first-line treatment when beta-blockers are contraindicated. They play a major role in preventing and terminating myocardial ischemia induced by coronary artery spasm. They are particularly effective in treating microvascular angina. All classes of calcium channel blockers reduce anginal episodes, increase exercise duration, and reduce use of sublingual nitroglycerin in patients with effort-induced angina. Short-acting calcium channel blockers should be avoided. Calcium channel blockers (particularly non-dihydropyridine) should generally also be avoided in patients with CHF secondary to systolic dysfunction due to its negative inotropic effect.
- Ranolazine, which has been tested in four different studies with a total of 1737 patients (MARISA, CARISA, RAN080, and ERICA), inhibits the late inward sodium current, indirectly reducing the sodium-dependent calcium current during ischemic conditions and leading to improvement in ventricular diastolic

tension and oxygen consumption. It seems to increase the efficiency of energy production in the heart, maintaining cardiac function. Its antianginal and antiischemic effects do not depend on reductions in heart rate or blood pressure. It is indicated for treatment of chronic angina that is inadequately controlled with other antianginals. It represents a new class of drugs known as metabolic modulators and can be useful when prescribed as substitute for beta-blockers or in combination with them for relief of symptoms when initial treatment with beta-blockers is not successful or is contraindicated. Side effects include prolongation of QT interval. Low doses of diltiazem and verapamil should be used with ranolazine. The extended-release preparation reduces the frequency of angina, improves exercise performance, and delays the development of exercise-induced angina and ST-segment depression.

- Angiotensin-converting enzyme (ACE) inhibition through changes in the physiologic balance between angiotensin II and bradykinin could contribute to the reductions in LV and vascular hypertrophy, atherosclerosis progression, plaque rupture, and thrombosis; the favorable changes in cardiac hemodynamics; and the improved myocardial oxygen supply/demand. It has been shown to be effective in reducing cardiovascular death, MI, and stroke in patients who are at risk for or who had vascular disease. They are indicated in patients with hypertension, diabetes, LVEF <40%, and CKD. Angiotensin receptor blockers (ARBs) can be given to patients with SIHD who are intolerant to ACEI and qualify for them.
- Use of high-intensity statin drugs is recommended in all patients with CAD. In late 2018 the American College of Cardiology (ACC) recommended an LDL goal of <70 mg/dl for secondary prevention of atherosclerotic cardiovascular disease. There is no LDL goal for primary prevention. The FDA approved PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (Alirocumab and Evolocumab) for heterozygous familial hypercholesterolemia in those who maximally tolerated statins. Newer 2018 lipid guidelines suggested starting PCSK9 inhibitor in very-high-risk atherosclerotic cardiovascular disease patients who did not meet the LDL goal on high-intensity statin and ezetimibe. One should always consider adding ezetimibe to high-intensity statin prior to initiation of PCSK9 inhibitor due to cost issues.
- Influenza vaccine is recommended for patients with SIHD on annual basis to prevent all-cause mortality, morbidity, and hospitalization caused by the exacerbation of underlying medical conditions produced by influenza.

NEW MODALITIES FOR THE TREATMENT OF CHRONIC STABLE ANGINA PECTORIS

- Although a significant amount of progress has been made in the management of CAD with percutaneous coronary intervention (PCI) and CABG, many patients with the condition require additional therapeutic modalities for relief of symptoms and improvement in quality of life. This group of patients includes those with diffuse CAD who are not suitable for revascularization, patients with previous multiple PCIs or CABG limiting the chances for further revascularization, the lack of vascular conduits for CABG, severe left ventricular systolic dysfunction in patients with previous CABG or PCI, and comorbidities that would render the patients at high risk for revascularization.
- The following pharmacologic agents have been used for the management of stable angina in combination with the standard protocol of nitrates, beta-blockers, calcium channel blockers, and ranolazine: High-dose statin therapy, trimetazidine, perhexiline, nicorandil, allopurinol, ivabradine, fasudil, and testosterone.
- Other, nonpharmacologic modalities that are highly experimental include stem cell therapy, therapeutic angiogenesis, and mechanical therapies like external counterpulsation, spinal cord stimulation, transmyocardial laser revascularization, and coronary sinus reducing device.
- In TACT (Trial to Assess Chelation Therapy), Ethylenediaminetetraacetic acid (EDTA) intravenous infusion resulted significant decrease in total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina. Thus chelation therapy was upgraded from Class III (not recommended) to Class IIb in the 2014 SIHD guidelines. Allopurinol, a xanthine oxidase inhibitor, was shown to reduce myocardial oxygen demand per unit of cardiac output in patients with heart failure in a small crossover study of 65 patients given 600 mg of allopurinol daily for 6 weeks. Allopurinol increased the median time to ST depression from 232 seconds at baseline to 393 seconds. Further and larger studies are necessary to recommend allopurinol as an adjunctive therapy for stable angina.
- Testosterone improves endothelial dysfunction and may be an effective antiangina agent. However, given the potential side effects, additional trials are necessary to recommend testosterone as an adjunctive drug for chronic angina.

The value of enhanced external counterpulsation, or EECP, was assessed with the MUST-EECP trial, which randomly assigned 139 outpatients with angina, documented CAD, and a positive stress test to 35 hours of active EECP. The results indicated the following regarding EECP: (1) Was well tolerated; (2) exercise duration increased in both groups; (3) active EECP patients had a significant increase in time to 1-mm ST-segment depression, while there was no change in the inactive group; (4) more patients undergoing active EECP had a decrease in angina episodes, and fewer had an increase in angina symptoms compared with the active group. These data corroborate similar data from multicenter registries. The American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American Thoracic Society, and Society of Thoracic Surgeons focused update states that EECP may be considered for relief of refractory angina.

The following treatments have NOT been shown to be beneficial in reducing cardiovascular risk or improving clinical outcomes: Estrogen therapy, vitamin C, vitamin E, and beta-carotene supplementation; treatment of elevated homocysteine with folate or vitamins B_6 and B_{12}; chelation therapy; garlic; coenzyme Q10; selenium; and chromium.

REFERRAL

Revascularization:

- Revascularization methods should be formulated taking into consideration improved survival or improved symptoms. Revascularization includes either percutaneous coronary intervention (balloon angioplasty and stenting) or CABG. However, note that although the role of PCI is unquestionable in the presence of an acute myocardial infarction, its role is not so clear in stable CAD. The utilization of PCI for stable CAD was reduced by 51.7% from 2007 to 2011, and hospitals with higher volumes of PCI had the largest reduction of these procedures.
- **To improve survival:**
  1. Perform CABG for patients with significant (>50% diameter stenosis) left main coronary artery stenosis, more than 70% diameter stenosis in proximal left anterior descending artery (LAD), or more than 70% diameter stenosis in three major epicardial vessels, >70% diameter stenosis in two major coronary arteries with severe or extensive myocardial ischemia, and in patients with mild to moderate LV systolic dysfunction (EF 35% to 50%) and significant multivessel CAD. Left internal mammary artery (LIMA) graft improves survival when used to bypass a proximal LAD artery stenosis. CABG is recommended in preference to PCI to improve survival in patients with multivessel CAD and diabetes, particularly if a LIMA graft to LAD is used.
  2. PCI is reasonable as an alternative to CABG in selected stable patients (low or intermediate SYNTAX score and[or] high STS score) with unprotected left main CAD, low risk of PCI procedural complications, and a high likelihood of good long-term outcome *and* clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (e.g., STS-predicted risk of operative mortality >5).
- **To improve symptoms:**
  1. CABG or PCI to improve symptoms is beneficial in patients with one or more significant (>70% diameter) coronary artery stenosis amenable to revascularization and unacceptable angina despite maximal medical treatment, or in whom increasing medical therapy cannot be implemented because of medication contraindications,

adverse effects, or patient preferences. In 2017, ORBITA trial showed no significant improvement in angina score after PCI for optimally treated stable angina patients. However, 85% of study patients in placebo group underwent PCI within 6 weeks after ORBITA trial completed.

2. Hybrid coronary revascularization: LIMA-to-LAD artery grafting and of >1 non-LAD coronary artery can be used in patients who have an unfavorable aorta, have poor target vessels for CABG, have unsuitable graft conduits, or have unfavorable LAD for PCI.

- Compared with percutaneous coronary intervention (PCI), CABG is more effective in relieving angina and leads to fewer repeated revascularizations but has a higher risk for procedural stroke. Survival to 10 yr is similar for both procedures.
- Angioplasty and coronary stents (Fig. E3).
- PCI has an established place in treating angina but is not superior to intensive medical therapy to prevent MI and death in symptomatic or asymptomatic patients. Patients selected for PCI should also be candidates for CABG. Approximately 80% of patients show immediate benefit after PCI. The development of coronary stents has increased the number of patients who can be treated in the cardiac laboratory. Cardiac stents (Fig. E4) are currently used in nearly 95% of all patients with PCI lesions. The rate of restenosis is reduced by placing a stent electively in primary atheromatous lesions. The major limitations of stenting are subacute thrombosis, restenosis within the stent, bleeding complications when antiplatelets are used after stenting, and higher cost. The combination of aspirin and P2Y12 antagonists is effective in preventing coronary stent thrombosis and the duration of therapy depends on whether bare metal stents (BMS) or drug-eluting stents (DES) are used. Duration of dual antiplatelet therapy can be as short as 4 weeks for BMS, but 6 to 12 months of therapy is generally required for DES. This difference in duration is due to the lack of endothelium proliferation in DES initially. New drug-eluting stents with thin struts releasing Limus-family analogs from durable polymers have lowered the risk of stent thrombosis compared with early-generation stents releasing sirolimus or paclitaxel. Current evidence supports the use of drug-eluting stents in most clinical settings without safety concerns (unless there are contraindications to use of dual antiplatelet therapy).

PEARLS & CONSIDERATIONS

COMMENTS

- Although nitrate responsiveness is usually an integral part of a diagnostic strategy for SIHD, recent reports question its value and conclude that in a general population admitted for chest pain, relief of pain after nitroglycerin treatment does not predict active CAD and should not be used to guide diagnosis in the acute care setting.
- CABG is associated with higher long-term survival rates and lower rates of repeat revascularization than PCI and stenting; however, patients often prefer stenting because it is less invasive, involves a shorter hospital stay, and has a lower in-hospital mortality rate.

SUGGESTED READINGS

Available at: ExpertConsult.com

RELATED CONTENT

Angina (Patient Information)
Unstable Angina (Patient Information)
Acute Coronary Syndrome (Related Key Topic)
Coronary Artery Disease (Related Key Topic)
Myocardial Infarction (Related Key Topic)

AUTHOR: **Maheswara Satya Gangadhara Rao Golla, MD**

SUGGESTED READINGS

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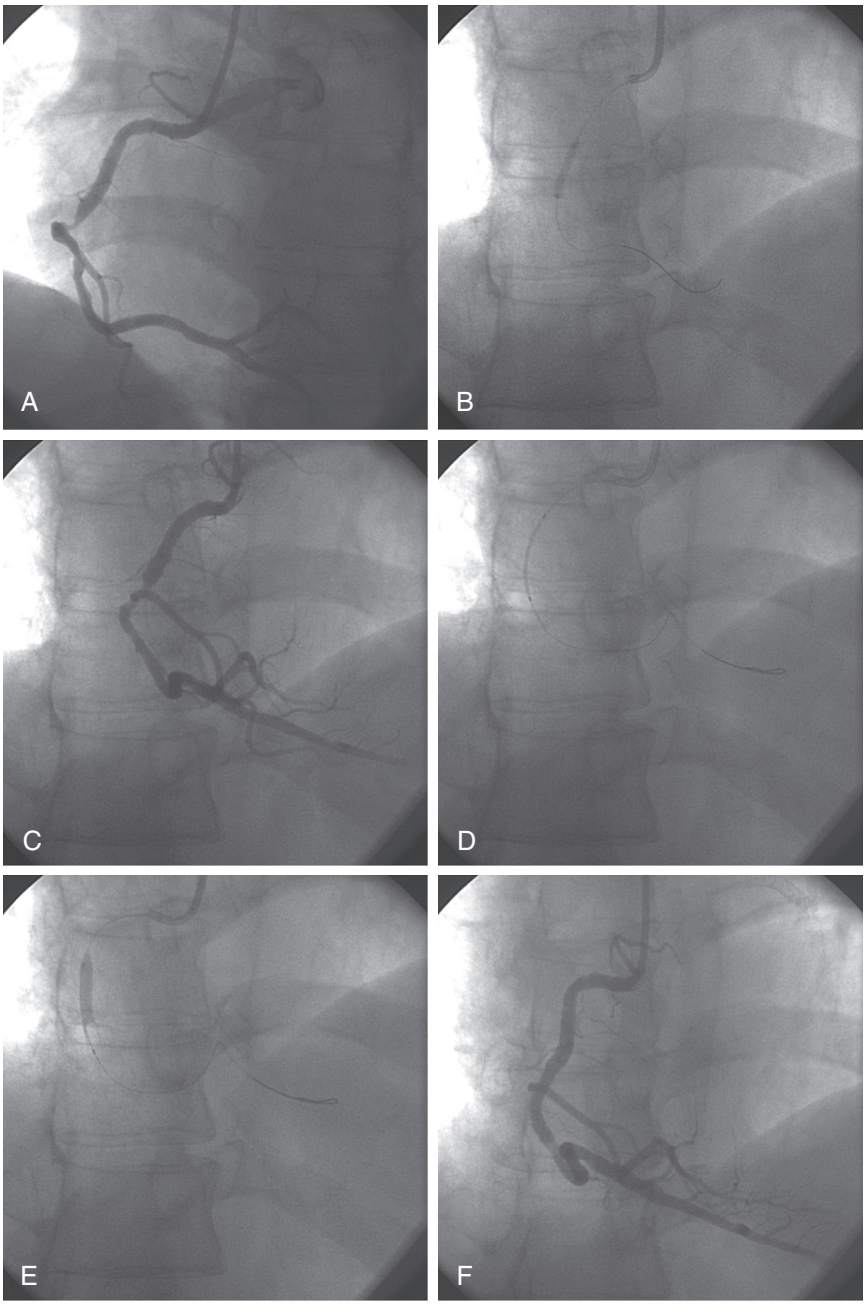

FIG. E3 Coronary angioplasty procedure. A, Critical stenosis in midsegment of a right coronary artery. **B,** Inflation of a 3.5-mm-diameter angioplasty balloon. **C,** Angiographic control after balloon inflation. **D,** Placement of a 3.5-mm-diameter, 18-mm-long metal stent. **E,** Inflation of the balloon. **F,** Final result. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

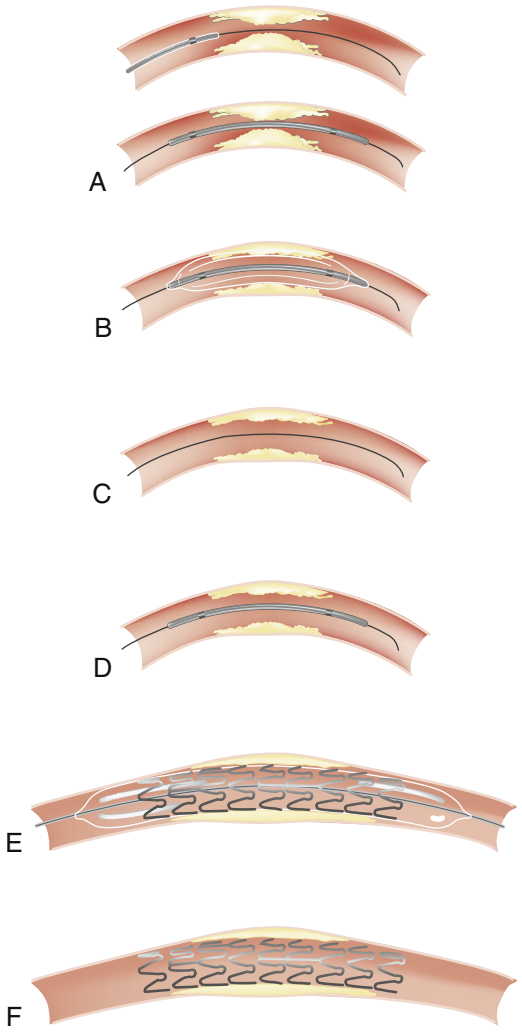

FIG. E4 Implantation of a coronary stent. A, Placement of balloon catheter. **B,** Predilation with balloon catheter. **C,** Balloon is withdrawn. **D,** Placement of coronary stent, which has been crimped on a balloon catheter. **E,** Inflation of balloon and expansion of stent. **F,** Withdrawal of balloon catheter and final result. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

Angioedema PTG ALG

BASIC INFORMATION

DEFINITION

- The mucocutaneous swelling caused by the release of vasoactive mediators is called urticaria and angioedema.
- Urticaria causes edema of the superficial dermis.
- Angioedema involves the deep layers of the dermis and the subcutaneous tissue.

SYNONYMS

Angioneurotic edema
HAE (hereditary angioedema)

ICD-10CM CODES
T78.3 Angioedema
D84.1 Angioedema, hereditary

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 100 to 3000/100,000 persons (for urticaria and angioedema)
LIFETIME PREVALENCE: Approximately 20% of the population experiences urticaria and/or angioedema at some time during life. The prevalence of hereditary angioedema is 1 case per 50,000 persons.
DEMOGRAPHICS:

- Race: Slightly more common among African Americans.
- Sex: More occurrences in women than men.
- Angioedema commonly occurs after adolescence in the third decade of life.
- Angioedema can occur together with urticaria (40%) or alone (20%); the remaining 40% have urticaria alone.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Angioedema may be acute or chronic
  1. Acute angioedema is defined as symptoms lasting 6 wk
  2. Chronic angioedema is defined as symptoms lasting >6 wk
- Urticaria is commonly known as "hives" and is:
  1. Pruritic
  2. Palpable and well demarcated
  3. Erythematous
  4. Millimeters to centimeters in size
  5. Multiple in number
  6. Fades within 12 to 24 hr
  7. Reappears at other sites
- Angioedema is characterized by the following:
  1. Nonpruritic
  2. Burning
  3. Not well demarcated
  4. Involves eyelids, lips (Fig. 1), tongue, and extremities
  5. Can involve the upper airway, causing respiratory distress
  6. Can involve the gastrointestinal tract, leading to cyclic abdominal pain, nausea, vomiting, and diarrhea
  7. Resolves slowly

ETIOLOGY

- Angioedema, with or without urticaria, is classified as acquired (allergic or idiopathic) or hereditary.
- Angioedema is primarily caused by mast cell activation and degranulation with release of vasoactive mediators (e.g., histamine, serotonin, bradykinins), resulting in postcapillary venule inflammation, vascular leakage, and edema in the deep layers of the dermis and subcutaneous tissue.
- Pathologically, angioedema has both immunologic- and nonimmunologic-mediated mechanisms (Fig. 2).
  1. Immunoglobulin E–mediated angioedema may result from antigen exposure (e.g., foods [milk, eggs, peanuts, shellfish, tomatoes, chocolate, sulfites] or drugs [penicillin, aspirin, nonsteroidal antiinflammatory drugs, phenytoin, sulfonamides, recombinant tissue plasminogen activator]).
  2. Complement-mediated angioedema involving immune complex mechanisms can also lead to mast cell activation that manifests as serum sickness.
  3. Hereditary angioedema is an autosomal-dominant disease caused by a deficiency of or mutation in C1 esterase inhibitor (C1-INH). C1-INH is a protease inhibitor normally present in high concentrations in the plasma. C1-INH serves many functions, one of which is to inhibit plasma kallikrein, a protease that cleaves kininogen and releases bradykinin. Deficient C1-INH activity results in excess concentration of kininogen and the subsequent release of kinin mediators.
  4. Acquired angioedema is usually associated with other diseases, most commonly B-cell lymphoproliferative disorders, but may also result from the formation of autoantibodies directed against C1 inhibitor protein.
  5. Other causes of angioedema include infection (e.g., herpes simplex, hepatitis B, Coxsackie A and B, *Streptococcus, Candida, Ascaris,* and *Strongyloides*), insect bites and stings, stress, physical factors (e.g., cold, exercise, pressure, and vibration), connective tissue diseases (e.g., systemic lupus erythematosus, Henoch-Schönlein purpura), and idiopathic causes. Angiotensin-converting enzyme (ACE) inhibitors can increase kinin activity and lead to angioedema.

FIG. 1 Angioedema. The swelling is deeper than wheals and may affect mucosal surfaces. Note the swelling of the lips and periorbital region and the lack of erythema. (From Bolognia J et al: *Dermatology,* ed 4, London, 2018, Elsevier Limited.)

DIAGNOSIS

A detailed history and physical examination usually establish the diagnosis of angioedema. Extensive laboratory testing is of limited value.

DIFFERENTIAL DIAGNOSIS

- Cellulitis
- Arthropod bite
- Hypothyroidism
- Contact dermatitis
- Atopic dermatitis
- Mastocytosis
- Granulomatous cheilitis
- Bullous pemphigoid
- Urticaria pigmentosa
- Anaphylaxis
- Erythema multiforme
- Epiglottitis
- Peritonsillar abscess

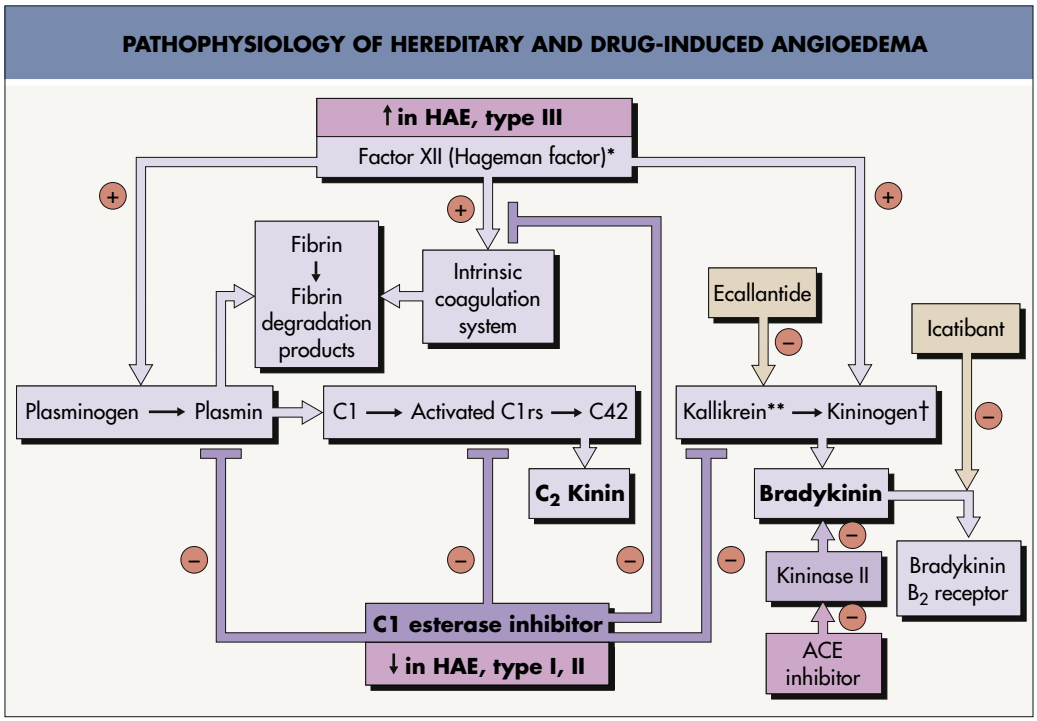

FIG. 2 Pathophysiology of hereditary and drug-induced angioedema. Angiotensin-converting enzyme *(ACE)* inhibitor-induced urticaria is believed to result from the inhibition of endogenous kininase and a subsequent increase in bradykinin. Icatibant and ecallantide have been approved for the emergency treatment of hereditary angioedema *(HAE)* as alternatives to C1 esterase inhibitor (C1-INH) concentrate (derived from human plasma) or recombinant C1-INH (derived from milk of transgenic rabbits). Icatibant, a decapeptide, is a specific bradykinin B2 receptor antagonist. Ecallantide, a 60-amino acid recombinant protein, selectively inhibits kallikrein. Off label, icatibant has been used to treat ACE inhibitor-induced angioedema. Two forms of C1-INH, one of which is administered intravenously and the other subcutaneously, are approved for prevention of attacks. At the time of writing, twice-monthly administration of lanadelumab, a human monoclonal antibody that inhibits plasma kallikrein, is under investigation for prevention of attacks. *The active form of factor XII (Hageman factor) is XIIa. **Kallikrein is formed from prekallikrein. †High-molecular-weight. (From Bolognia J et al: *Dermatology,* ed 4, London, 2018, Elsevier Limited.)

WORKUP

- An extensive workup searching for the cause of angioedema is often unrevealing (90%).
- Workup, including diagnostic blood tests and allergy testing, is performed according to results of the history and physical examination. Fig. 3 illustrates an algorithm for the diagnosis of angioedema.

LABORATORY TESTS

- Complete blood count, erythrocyte sedimentation rate, and urinalysis are sometimes helpful as part of the initial evaluation.
- Stools for ova and parasites.
- Serology testing.
- C4 levels are usually reduced in acquired and hereditary angioedema (occurring without urticaria). If C4 levels are low, C1-INH levels and activity should be obtained. There are isolated reports of hereditary angioedema with normal C4 levels but reduced C1-INH levels.
- Skin and radioallergosorbent testing may be done if food allergies are suspected.
- Skin biopsy is usually done in patients with chronic angioedema refractory to corticosteroid treatment.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Eliminate the offending agent
- Avoid triggering factors (e.g., cold, stress)
- Cold compresses to affected areas

ACUTE GENERAL Rx

- Acute life-threatening angioedema involving the larynx is treated with:
  1. Epinephrine 0.3 mg in a solution of 1:1000 given SC
  2. Diphenhydramine 25 to 50 mg IV or IM
  3. Cimetidine 300 mg IV or ranitidine 50 mg IV
  4. Methylprednisolone 125 mg IV
- Mainstay therapy in nonhereditary angioedema is H_1 antihistamines:
  1. Diphenhydramine 25 to 50 mg q6h
  2. Chlorpheniramine 4 mg q6h
  3. Hydroxyzine 10 to 25 mg q6h
  4. Cetirizine 5 to 10 mg qd
  5. Loratadine 10 mg qd
  6. Fexofenadine 60 mg qd
- H_2 antihistamines can be added to H_1 antihistamines:
  1. Ranitidine 150 mg bid
  2. Cimetidine 400 mg bid
  3. Famotidine 20 mg bid
- Tricyclic antidepressants:
  1. Doxepin 25 to 50 mg qd
- Corticosteroids are rarely required for symptomatic relief of acute angioedema
- Antihistamines are probably ineffective in acute hereditary angioedema.
- Purified plasma-derived C1-INH replacement therapy is effective and safe in treating acute attacks of hereditary angioedema caused by C1 inhibitor deficiency. Cost is a limiting factor. Acute attacks can be managed with plasma-derived or recombinant preparations of C1 inhibitor, with ecallantide, a specific plasma kallikrein inhibitor, or with the use of the B2 bradykinin-receptor antagonist icatibant

CHRONIC Rx

- Chronic angioedema is treated as described under "Acute General Rx." Corticosteroids are used more often in chronic nonhereditary angioedema.
- Prednisone 1 mg/kg/day for 5 days and then tapered over a period of weeks.

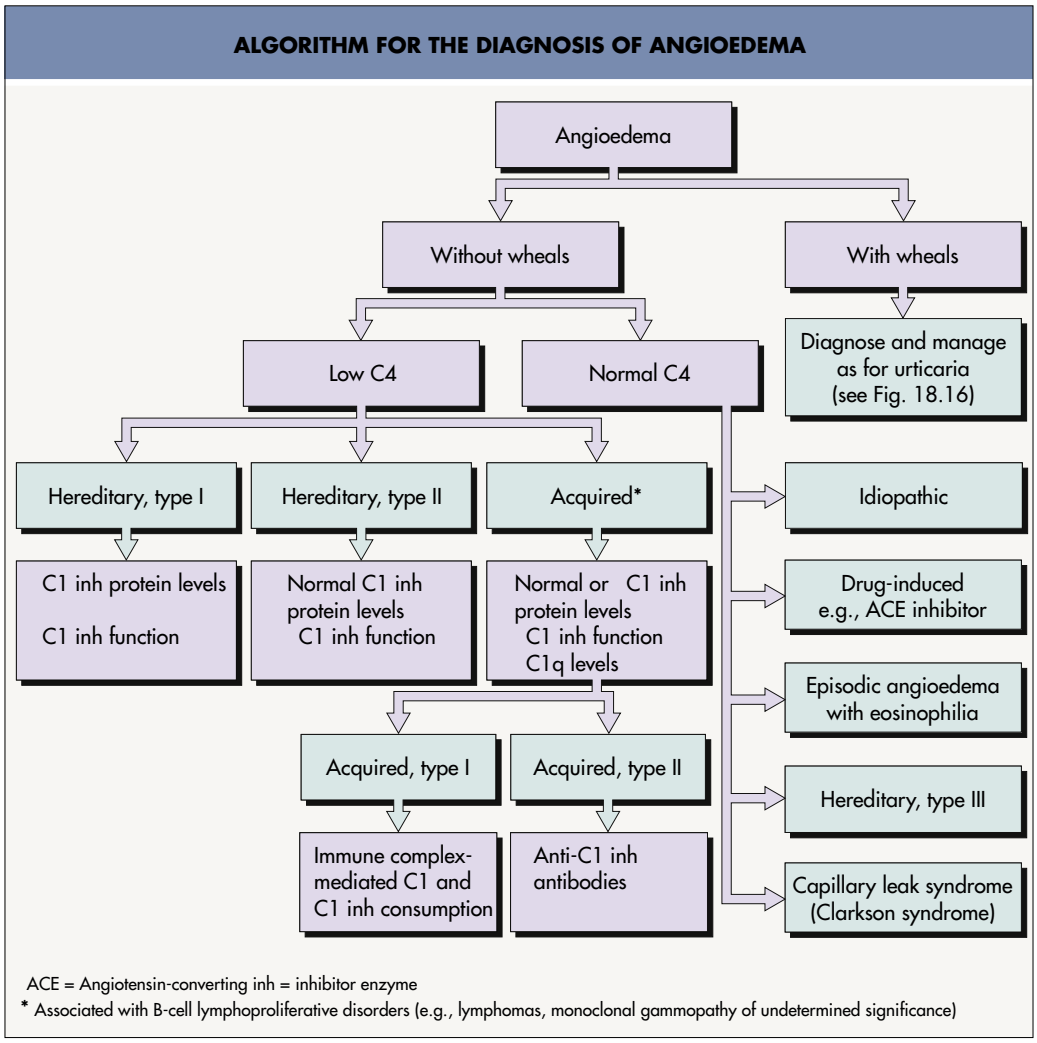

FIG. 3 Algorithm for the diagnosis of angioedema. Episodic angioedema with hypereosinophilia, along with weight gain and fever, is known as Gleich syndrome. (From Bolognia J et al: *Dermatology,* ed 4, London, 2018, Elsevier Limited.)

- Androgens (danazol, stanozolol, oxandrolone, methyltestosterone) and antifibrinolytic agents can be used for the treatment of chronic hereditary angioedema, which does not respond to antihistamines or corticosteroids but these agents are associated with many adverse effects.
- Long-term prophylaxis with intravenous plasma-derived C1 inhibitors (Cinryze, Berinert) are safe and effective and may be used in patients who have frequent or severe attacks. Cost can be a limiting factor. A twice-weekly subcutaneous formulation (Haegarda/CSL830, CSL Behring) is approved by the FDA to treat type I and type II hereditary angioedema. Icatibant is a bradykinin-receptor antagonist effective in hereditary angioedema. Lanadelumab is a kallikrein inhibitor shown in preliminary studies to reduce attack frequency, although it is not yet FDA approved.

DISPOSITION

- Antihistamines achieve symptomatic relief in more than 80% of patients with nonhereditary acute angioedema.
- In chronic nonhereditary angioedema, corticosteroids are given in addition to antihistamines.
- A small percentage of people will have recurrence of symptoms after steroid treatment.
- Chronic angioedema can last for months and even yrs.

REFERRAL

Consultation with dermatologist and allergist is recommended in patients with chronic angioedema, hereditary angioedema, and recurring angioedema.

PEARLS & CONSIDERATIONS

ACE inhibitors can cause angioedema up to many months after initiation. There are multiple case reports and case series of angiotensin receptor blocker (ARB)–induced angioedema, although the risk is substantially less than that of ACE inhibitors. (Incidence rates per 1000 person-yr are 4.38 cases for ACE inhibitors, 1.66 cases for ARBs.) The incidence rate is also very high for the direct renin inhibitor aliskiren (4.67).

COMMENTS

- Identifying a cause for angioedema in patients is often difficult and met with frustration.
- Chronic angioedema, unlike acute angioedema, is rarely caused by an allergic reaction.

SUGGESTED READINGS

Available at: ExpertConsult.com

RELATED CONTENT

Angioedema (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Banerji A et al: Inhibiting plasma kallikrein for hereditary angioedema prophylaxis, *N Engl J Med* 376:717-728, 2017.

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Angular Cheilitis

BASIC INFORMATION

DEFINITION

Angular cheilitis refers to inflammation of one, or both, of the corners of the mouth resulting in erythema, fissuring, and exudate of the mouth angle (Fig. E1). Most commonly, it represents an infectious etiology, as an opportunistic fungal or bacterial pathogen, and leads to a spectrum of varying severities.

SYNONYMS

Angular cheilosis
Rhagades
Commissural cheilitis
Perleche
Angular stomatitis

ICD-10CM CODES	
K13.0	Diseases of lips
B37.83	Candidal cheilitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown
PEAK INCIDENCE: Advanced age
PREVALENCE: Suspected of causing 0.5% to 5% of lip infections in adults
PREDOMINANT SEX AND AGE: This form of lip inflammation has a predilection for the elderly, seen with denture use as an example.
GENETICS: No identified correlation
RISK FACTORS: These include dry mouth, nutritional deficiencies (B vitamins, iron), immunosuppression, or chronic irritation as with lip licking, drooling, oral hardware, or dentures.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The majority of cases of this lip condition involve both sides of the mouth, which initially involves erythema and swelling (Fig. E2). Over time, the erythema and subsequent linear fissures, or rhagades, may become cracked or ulcerated. Skin thickening is common during the progression of inflammation. It is important to note that this progression may involve strictly the mucosa of the lips or may propagate to the facial dermis, crossing the vermillion border.

ETIOLOGY

Microorganisms commonly represent underlying infectious causes. These include *Candida* species*, Staphylococcal aureus,* beta-hemolytic *Streptococcus* species, or polymicrobial findings. Another common cause of this condition includes direct irritation of saliva on the corners of the mouth with overclosure of the lower jaw, as evident in edentulous individuals and those who wear dentures. Nearly any condition that leads to chronic irritation or moisture settling in the corners of the mouth, including lip licking, drooling, or habits of oral fixation, may lead to this state. Nutritional deficiencies, specifically of iron, B vitamins, and zinc, are also associated with angular cheilitis. Varying levels of immunosuppression, as seen in diabetes mellitus, HIV, and so on, predispose to subacute infection as well. Patients on medications leading to xerostomia or hypersalivation can develop bilateral involvement.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Oral candidiasis or oral-associated angular cheilitis; *S. aureus* infection or impetigo; contact dermatitis; angular herpes simplex

WORKUP

Primarily clinical in nature, taking into consideration full details of the patient's medical history and medications

LABORATORY TESTS

If applicable, bacterial and fungal cultures may be beneficial to detect probable infectious component with routine lab testing, including CBC, HIV, BMP, iron, folate, and vitamin B_{12}, to be performed as well.

IMAGING STUDIES

None needed

TREATMENT

The hallmark of treatment used in this condition revolves around proper identification and understanding of the etiology of the inflammation. With the highest prevalence of this condition seen in those with dentures, proper oral fit and dental hygiene are of the utmost importance.

Certainly, good oral hygiene also includes smoking and tobacco use cessation. Topical antifungal use is at the cornerstone of treatment (details follow). Proper identification may include the presence of *S. aureus, Streptococcus* species, and other pathogens, which will need focused treatment. Treatment-refractory cheilitis may require additional workup to identify possible systemic etiology.

NONPHARMACOLOGIC THERAPY

Dental hygiene, specifically, with a focus on proper cleaning of dentures, plays a pivotal role in prevention. Alcohol or bleach-based solutions are commonly available OTC. If significant lag is noted in the corners of the mouth, surgery and collagen injections have been successful. Petrolatum jelly has been used for preventive measures as well.

ACUTE GENERAL Rx

With the underlying pathology involving inflammation, topical corticosteroid creams are commonly used. If *S. aureus* has been implicated, topical mupirocin or fusidic acid has a role. Clotrimazole or ketoconazole can be used for combating *Candida albicans*, implicated in >50% of cases.

FIG. E1 Perlèche (angular cheilitis). Erythema, fissuring, and exudate of the mouth angle. (From Paller AS, Mancini, AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E2 Angular cheilitis. (From Swartz MH: *Textbook of physical diagnosis, history and examination,* ed 7, Philadelphia, 2014, Saunders.)

CHRONIC Rx

Pending laboratory workup and identification of a nutritional deficiency, iron, B vitamins, or folate supplementation will likely lead to reduction. Proper alignment of dentures, involving possible surgical repair and fitment, may be needed.

DISPOSITION

Outpatient workup and assessment

REFERRAL

Dermatology assessment may be needed in refractory cases of angular cheilitis.

PEARLS & CONSIDERATIONS

COMMENTS

Identification of etiology is of utmost importance for further workup.

PREVENTION

See previously.

AUTHOR: **Fred F. Ferri, M.D.**

BASIC INFORMATION

DEFINITION

Ankle fractures typically involve the lateral, medial, and/or posterior malleolus of the ankle. These structures can be affected in isolation or as part of a combined injury pattern. Ligamentous and syndesmotic injuries are commonly seen in addition to bony injuries. Ankle fractures can occur as a result of high-energy trauma or simple ground-level falls.

CLASSIFICATION

The Danis-Weber (Figs. E1, E2, E3) and Lauge-Hansen classifications of ankle fractures are described in Table E1.

ICD-10CM CODES

S82.63XA	Displaced fracture of lateral malleolus of unspecified fibula, initial encounter for closed fracture
S82.53XA	Displaced fracture of medial malleolus of unspecified tibia, initial encounter for closed fracture
S82.841(A-S)	Displaced bimalleolar fracture of right lower leg
S82.842(A-S)	Displaced bimalleolar fracture of left lower leg
S82.851(A-S)	Displaced trimalleolar fracture of right lower leg
S82.852(A-S)	Displaced trimalleolar fracture of left lower leg
S82.899	Other fracture of unspecified lower leg, initial encounter for closed fracture

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Deformity usually depends on extent of displacement (i.e., dislocation)

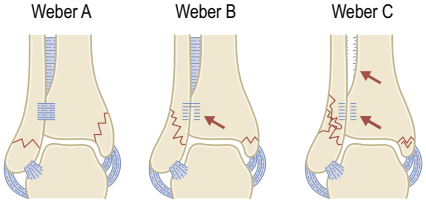

FIG. E1 Diagram showing the Weber classification for ankle fractures. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.)

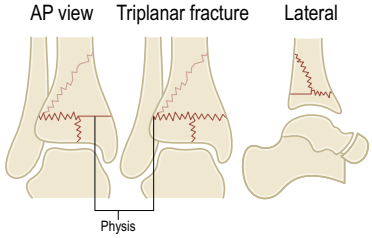

FIG. E2 Diagram showing the fracture configuration in a triplanar fracture. *AP,* Anteroposterior. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

- Pain, tenderness, and ecchymosis at the site of injury
- Evaluation of neurovascular status before and after reduction/splinting

ETIOLOGY

- The ankle depends on its ligamentous and bony support for stability. The joint, or *mortise*, is an inverted U with the dome of the talus fitting into the medial and lateral malleoli. The posterior margin of the tibia is often called the *posterior malleolus.*
- The most common ankle fractures are the result of eversion or lateral rotation forces on the talus (in contrast with common sprains, which are usually caused by inversion).

DIAGNOSIS

The diagnosis is usually established on the basis of the nature of the injury, the presence of typical findings of bony tenderness with swelling, and abnormal imaging studies.

DIFFERENTIAL DIAGNOSIS

- Ankle sprain
- Fracture of hindfoot or metatarsal
- Osteochondral lesion
- Tendon tear or rupture
- Syndesmotic injury

IMAGING STUDIES

Standard AP and lateral views (Fig. E4) accompanied by a mortise view taken with 10 degrees of internal rotation. The last view is taken to properly visualize the mortise. Fig. E5 illustrates the Ottawa ankle rules for ankle or midfoot fracture.

TREATMENT

All fractures: Elevation, compression, and ice to control swelling for 48 to 72 hr; immobilization in splint or fracture boot with ambulatory aid as needed.

ACUTE GENERAL Rx

- Clinical and radiographic assessment of the status of the ankle mortise and stability of the injury is indicated to determine treatment.
- There is potential for instability if both sides of the ankle joint are significantly injured (e.g., fracture of the lateral malleolus with medial deltoid ligament injury).

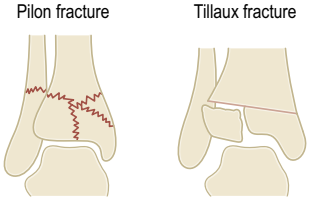

FIG. E3 Diagram showing the fracture configuration in a Pilon fracture and Tillaux fracture. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

- Deviation of the position of the talus in the mortise can lead to traumatic arthritis.
- If there is no widening of the ankle mortise on stress or weight-bearing radiographs, many isolated lateral malleolus injuries can be safely treated with simple splinting or bracing without reduction:
  1. Isolated fractures of the lateral malleolus without evidence of medial clear space widening on stress or weight-bearing radiographs:
     a. May be treated with a controlled ankle movement (CAM) boot if no medial injury is present.
     b. Weight bearing as tolerated.
     c. From 4 to 6 wk of immobilization is usually sufficient.
     d. If signs of instability are already present at initial examination (widening of the medial clear space), referral for possible operative intervention is indicated.
- Lateral malleolus fractures with medial clear space widening, bimalleolar ankle fractures, and trimalleolar fractures:
  1. These injuries typically necessitate reduction and splinting if displaced or dislocated followed by orthopedic surgery follow-up and possible operative intervention.
  2. Operative intervention typically includes reduction and fixation of the fibula with a plate and screws as well as screw fixation of the medial malleolus plus or minus syndesmotic fixation.
  3. These patients are typically kept non–weight-bearing for 6 to 8 wk.

CHRONIC Rx

- Early range of motion is encouraged through a home exercise program.
- Protection from reinjury is appropriate for 4 to 6 wk after cast or brace removal.
- A temporary increase in lower extremity swelling that frequently occurs after short leg cast removal may benefit from the use of support hose and continued elevation.

DISPOSITION

Significant factors involved in the development of traumatic arthritis:

- Extent of joint trauma at the time of injury
- Eventual position of the talus in the mortise

REFERRAL

Orthopedic consultation for:

- Unstable or dislocated ankle joint
- Widened ankle mortise
- Bimalleolar or trimalleolar fracture pattern
- Posterior malleolus fracture over 20% of joint with incongruity
- Marked displacement of fracture fragment
- Open fracture

Box E1 summarizes ankle fractures for which orthopedic consultation in the emergency department is recommended.

RELATED CONTENT

Ankle Fracture (Patient Information)
Ankle Sprain (Related Key Topic)

AUTHOR: **Andrew P. Thome Jr., MD**

TABLE E1 Classifications and Treatment of Ankle Fractures

	Normal	Abnormal
Medial clear space—distance between lateral border of medial malleolus and medial border of talus	<4 mm	>4 mm = lateral talar shift and concern for **instability**
Tibiofibular clear space—distance between medial wall of fibula and tibial incisura 1 cm above the ankle joint	<6 mm on AP and mortise views	>6 mm = concern for **syndesmotic disruption (instability)**
Tibiofibular overlap—maximum amount of fibular overlap of tibia	>6 mm on AP view >1 mm on mortise view	<6 mm = concern for **instability** <1 mm on mortise = concern for **instability**
Classification:		
1. **Danis-Weber**—based on location of fibula fracture A. Below the level of the syndesmosis B. At the level of the syndesmosis C. Above the level of the syndesmosis	1. **Lauge-Hansen**—based on position of foot and deforming force A. Supination external rotation—most common B. Supination adduction C. Pronation external rotation D. Pronation abduction	
Treatment: Decision for operative versus nonoperative treatment relies mostly on stability of fracture pattern		
Stable	**Unstable**	
Isolated lateral malleolar fractions if:	**Lateral malleolus fractures** if:	
No indication of medial ligamentous injury or medial clear space widening on stress examination	Evidence of instability (medial clear space widening) on stress or weight-bearing radiographs	
No fibular shortening	Fibular shortening	
	Bimalleolar or trimalleolar ankle fractures (consider fixation of posterior malleolus if >20% of articular surface involved)	
	Maisonneuve fractures (rotational injury)	

Updated from Parvizi J: *High-yield orthopedics,* Philadelphia, 2010, Saunders.

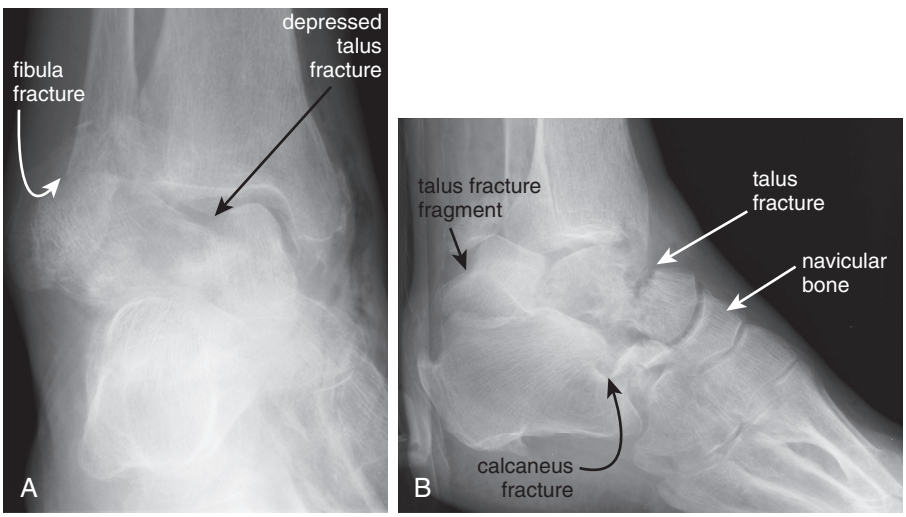

FIG. E4 A, Anteroposterior view. **B,** Lateral view. A depressed talus fracture is visible. In **B,** this fracture is seen to run through the midbody of the talus. **A** also demonstrates a distal fibula fracture, but in **B,** a calcaneal fracture is seen. The patient underwent computed tomography to characterize these fractures further. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

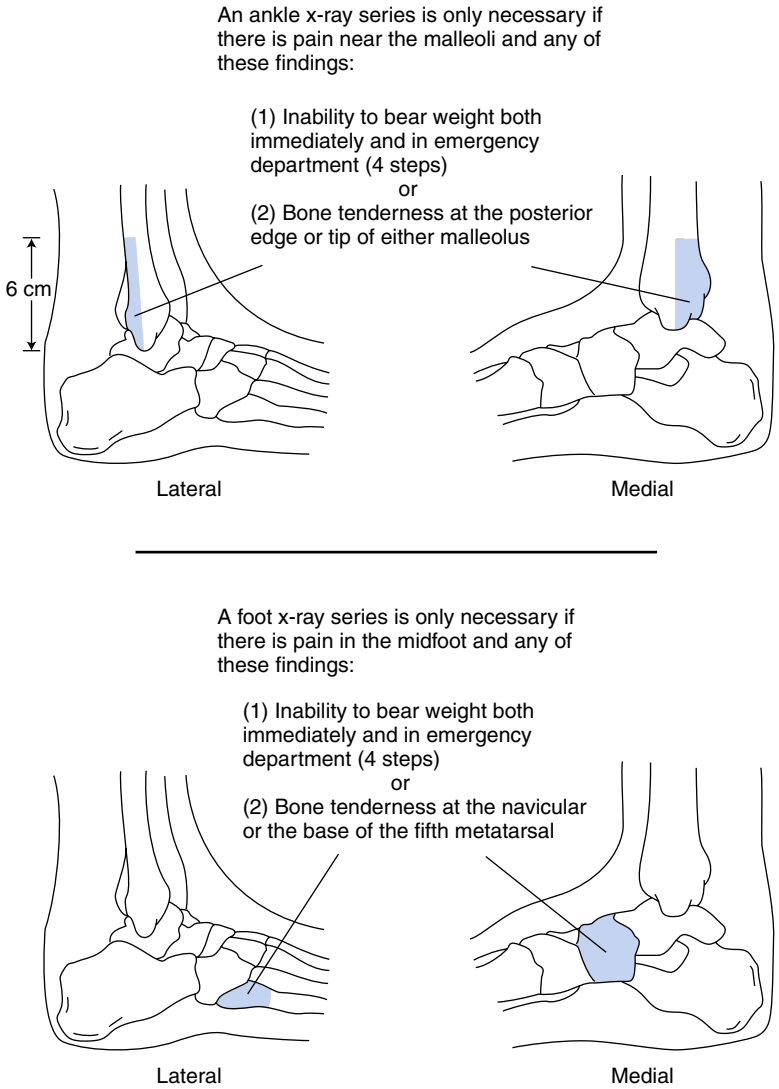

FIG. E5 Ottawa rules for ankle or midfoot fracture. The rule for ankle pain is the top figure; the rule for midfoot pain is the bottom figure. The rule is positive if any indication for radiography is met. "Inability to take four steps" means the patient is unable to transfer weight twice onto each lower limb regardless of limping. Importantly, these rules apply *only* to patients with injury of the ankle or midfoot, and they exclude patients with injury to the body or tuberosities of the calcaneus. (Adapted from Stiell IG et al: A study to develop clinical decision rules for the use of radiography in acute ankle injuries. In McGee S: *Evidence-based physical diagnosis,* ed 4, Philadelphia, 2018, Elsevier.)

BOX E1 Ankle Fractures for Which Orthopedic Consultation in the Emergency Department Is Recommended

- Unimalleolar fractures
- Displaced medial malleolar fracture
- Displaced lateral malleolar fracture
- Lateral malleolar fracture with deltoid ligament rupture
- Lateral malleolar fracture with widened medial clear space or syndesmotic diastasis
- Fibula fracture at or proximal to the tibiotalar joint line
- Displaced posterior malleolar fracture
- Posterior malleolar fracture involving more than 20% of articular surface
- All bimalleolar fractures
- All trimalleolar fractures
- All intraarticular fractures with displacement
- All open fractures

From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Saunders.

SUGGESTED READINGS

Julian TH et al: Surgical vs non-surgical management of Weber B fractures: a systematic review, *Foot Ankle Surg*, 2019, https://doi.org/10.1016/j.fas.2019.06.006.

Toth MJ et al: What's New in ankle fractures, *Injury* 48(10):2035-2041, 2017, https://doi.org/10.1016/j.injury.2017.08.016.

Utvåg SE et al: Functional outcome 3-6 years after operative treatment of closed Weber B ankle fractures with or without syndesmotic fixation, *Foot Ankle Surg*, 2019, https://doi.org/10.1016/j.fas.2019.04.013.

van Zuuren WJ et al: Acute syndesmotic instability in ankle fractures: a review, *Foot Ankle Surg* 23(3):135-141, 2017, https://doi.org/10.1016/j.fas.2016.04.001.

BASIC INFORMATION

DEFINITION

An ankle sprain is an injury to the ligamentous structures that support the ankle joint. Most (85%) involve the lateral ligament complex (Fig. E1). The anterior inferior tibiofibular ligament (AITFL), deltoid ligament, and interosseous membrane may also be injured. A severe form of ankle sprain involves disruption of the ankle syndesmosis, known as a high ankle sprain. Lateral ankle sprains are classically graded I, II, or III in respect to specific ligament involvement and their integrity. Table E1 describes a classification of ankle sprains. The anterior talofibular ligament (ATFL) is the most commonly affected lateral ligament.

ICD-10CM CODES

S93.409A	Sprain of unspecified ligament of unspecified ankle, initial encounter
S93.411A	Sprain of calcaneofibular ligament of right ankle, initial encounter
S93.411D	Sprain of calcaneofibular ligament of right ankle, subsequent encounter
S93.411S	Sprain of calcaneofibular ligament of right ankle, sequela
S93.412A	Sprain of calcaneofibular ligament of left ankle, initial encounter
S93.412D	Sprain of calcaneofibular ligament of left ankle, subsequent encounter
S93.412S	Sprain of calcaneofibular ligament of left ankle, sequela
S93.419A	Sprain of calcaneofibular ligament of unspecified ankle, initial encounter
S93.419D	Sprain of calcaneofibular ligament of unspecified ankle, subsequent encounter
S93.419S	Sprain of calcaneofibular ligament of unspecified ankle, sequela
S93.421A	Sprain of deltoid ligament of right ankle, initial encounter
S93.421D	Sprain of deltoid ligament of right ankle, subsequent encounter
S93.421S	Sprain of deltoid ligament of right ankle, sequela
S93.422A	Sprain of deltoid ligament of left ankle, initial encounter
S93.422D	Sprain of deltoid ligament of left ankle, subsequent encounter
S93.422S	Sprain of deltoid ligament of left ankle, sequela
S93.429A	Sprain of deltoid ligament of unspecified ankle, initial encounter
S93.429D	Sprain of deltoid ligament of unspecified ankle, subsequent encounter
S93.429S	Sprain of deltoid ligament of unspecified ankle, sequela
S93.431A	Sprain of tibiofibular ligament of right ankle, initial encounter
S93.431D	Sprain of tibiofibular ligament of right ankle, subsequent encounter
S93.431S	Sprain of tibiofibular ligament of right ankle, sequela
S93.432A	Sprain of tibiofibular ligament of left ankle, initial encounter
S93.432D	Sprain of tibiofibular ligament of left ankle, subsequent encounter
S93.432S	Sprain of tibiofibular ligament of left ankle, sequela
S93.439A	Sprain of tibiofibular ligament of unspecified ankle, initial encounter
S93.439D	Sprain of tibiofibular ligament of unspecified ankle, subsequent encounter
S93.439S	Sprain of tibiofibular ligament of unspecified ankle, sequela

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: One case/10,000 people each day. Especially prevalent in rigorous sports and training such as for basketball, football, and soccer
PREDOMINANT SEX: Varies according to age and level of physical activity

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Often a history of a "pop."
- Variable amounts of tenderness and hemorrhage (inversion sprains: Tender laterally; syndesmotic injury: Tender anterior leg about middle third of the leg).
- Anterior talofibular ligament (ATFL) evaluation: Anterior drawer test. With the patient in the sitting position and knee flexed allow the ankle to plantar-flex slightly and apply an anterolateral rotatory force to the heel. Positive if abnormal increase in forward movement of the talus on the tibia (Fig. E2).
- Syndesmotic evaluation: Manual squeeze test. (Compress the tibia and fibula toward each other at the middle third of the anterior leg. Splaying and pain are indicative of injury.)
- Talar tilt test or inversion stress test (Fig. E3).
- Severe tenderness to direct palpation of ligamentous structure.

ETIOLOGY

- Lateral injuries usually result from inversion and plantar flexion injuries.
- Eversion and rotational forces may injure the deltoid ligament, AITFL, or the interosseous membrane.
- Balance deficits/diminished proprioception.
- Evertor muscle weakness.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Fracture of the ankle or foot, particularly involving the distal fibular physis in the immature patient (e.g., calcaneal fracture, lateral and/or medial malleoli fracture, talar dome fracture, Lisfranc injury)
- Avulsion fracture of the fifth metatarsal base
- Achilles tendon rupture
- Peroneal tendon rupture

WORKUP

- History and clinical examination are usually sufficient to establish the diagnosis.
- Plain radiographs are not always needed.

IMAGING STUDIES

Radiographic evaluation (Fig. E4 and Fig. E5): According to the Ottawa ankle rules (Table E2), radiography is indicated if there is pain in the malleolar or midfoot zone and either bone

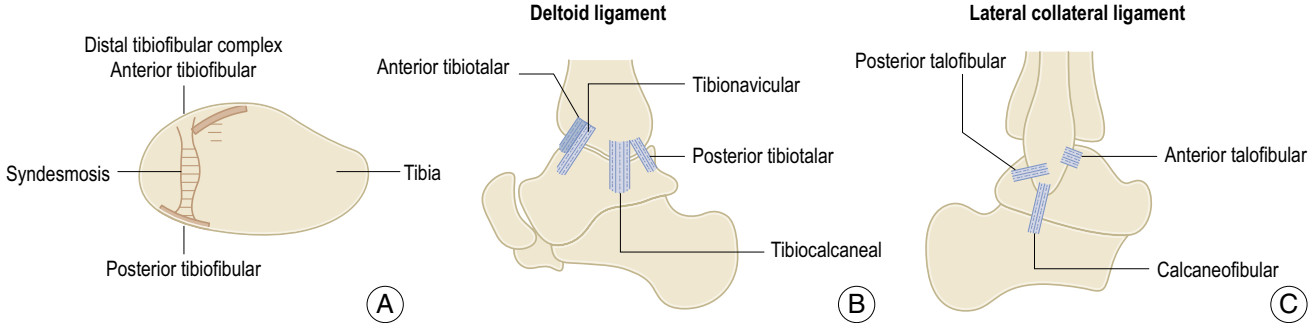

FIG. E1 A, Diagram showing the anatomy of the ligaments around the ankle when viewed from above. **B** and **C,** Diagrams showing the components of the deltoid and lateral collateral ligaments of the ankle. The distal tibiofibular complex (including the anterior and posterior tibiofibular ligaments and syndesmosis) is an important ankle stabilizer. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

TABLE E1 Classifications of Ankle Sprains

Grade	Extent of Injury	Physical Findings	Treatments
I	Sprain of ATFL (mid-stretching of lateral ligament complex)	Mild swelling and tenderness; no joint instability	Weight bear as tolerated; free ROM exercises
II	ATFL tear CFL sprain	Moderate swelling and tenderness; laxity with positive anterior drawer test	Immobilization (air splint, CAM boot), physical therapy
III	ATFL tear CFL tear	Severe swelling and tenderness; instability with anterior drawer test and talar tilt; inability to bear weight	Immobilization, physical therapy (longer duration than grade II); surgery if symptoms unresolved

ATFL, Anterior talofibular ligament; *CAM,* controlled ankle movement; *CFL,* calcaneofibular ligament; *ROM,* range of motion.

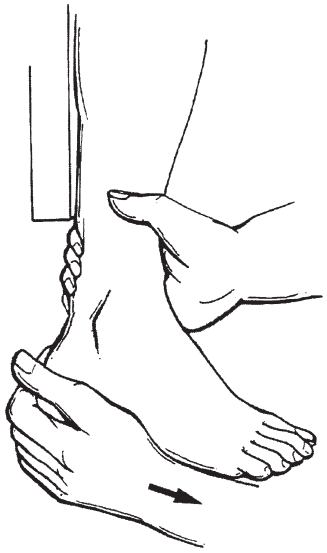

FIG. E2 Anterior drawer test of the ankle (tests the integrity of the anterior talofibular ligament). (From Brinker MR, Miller MD: *Fundamentals of orthopaedics,* Philadelphia, 1999, WB Saunders.)

FIG. E3 Talar tilt test (inversion stress) of the ankle (tests the integrity of the anterior talofibular ligament and the calcaneofibular ligament). (From Brinker MR, Miller MD: *Fundamentals of orthopaedics,* Philadelphia, 1999, WB Saunders.)

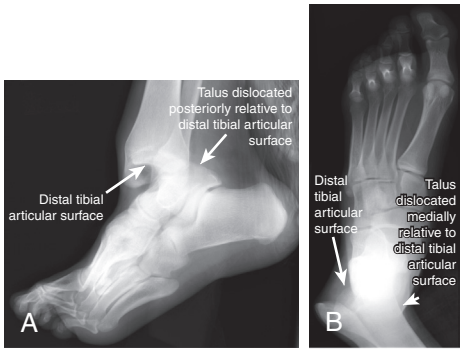

FIG. E4 Tibiotalar dislocation. This 17-yr-old male landed on his left ankle after dunking a basketball, sustaining a deformity. His tibiotalar joint is dislocated, with the talus dislocated posteriorly (visible on the lateral view, **A)** and medially (visible on the anterior-posterior view, **B)**. No fractures are present in this case, although fractures are commonly associated with this injury because of the amount of force required to dislocate the ankle. This was an open injury, and the patient underwent exploration, irrigation, and debridement with primary closure. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, WB Saunders.)

tenderness over an area of potential fracture or an inability to bear weight immediately after the injury and in the physician's office. These rules can reduce radiographic evaluation by 30% to 40%. Pearls: Palpate entire distal 6 cm of the fibula and tibia; do not use rule if the patient is younger than 18 yr of age.

Initial imaging should include weight-bearing ankle series (AP, lateral, mortise). Consider manual or gravity external rotation stress view or varus stress view to assess stability.

Rx TREATMENT

ACUTE GENERAL Rx

- The first line of treatment is described by the mnemonic *PRICE:*
  1. ***P***rotection (CAM boot, etc.)
  2. ***R***est
  3. ***I***ce (3 to 7 days)
  4. ***C***ompression
  5. ***E***levation
- Pain control with NSAIDs, acetaminophen, mild opioids.
- In 48 hours, early controlled motion in a functional ankle brace.
- Compression, support, and bracing is best achieved with an Air-Stirrup brace combined with an elastic compression wrap, or lace-up support alone (functional bracing for active patients).
- In 4 to 5 days, exercise against resistance added.
- Short period of immobilization (up to 10 days) in a below-knee cast or Aircast may shorten the recovery period.
- Physical therapy may be indicated to improve proprioception, strengthen the soft tissue structures about the ankle (ligaments, peroneal tendons), and restore ROM.
- Kinesiotaping.
- Surgery is typically recommended for grade III sprains, which consist of a complete torn ligament and significant ligament laxity/instability in young, healthy, athletic patients.
- If there is syndesmotic or deltoid ligament involvement, surgery is also the primary treatment of choice in athletes.

CHRONIC Rx

- Lateral heel and sole wedge to prevent inversion
- Protective taping or bracing during vigorous activities (Fig. E6)
- Strengthening exercises
- Protective bracing or taping indicated for 6 mo in patients with symptomatic grade II and III injuries

DISPOSITION

- Lateral sprains of any severity may cause lingering symptoms for weeks and months.
  1. Some syndesmotic sprains take even longer to heal.
  2. Heterotopic ossification may even develop in the interosseous membrane, but

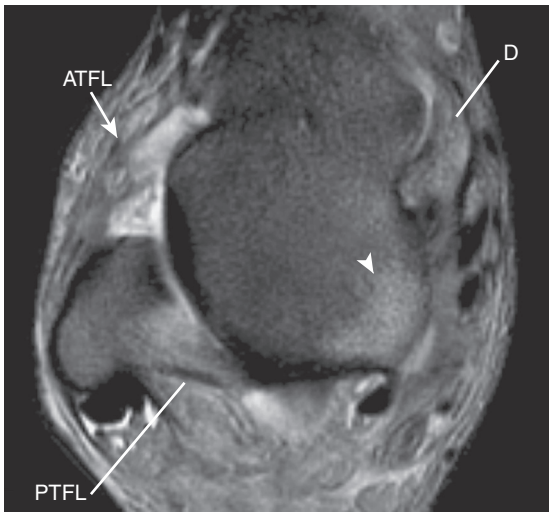

FIG. E5 Acute lateral ankle sprain with multiple ligamentous injuries. Axial fat-suppressed, T2-weighted MR image shows a tear of the anterior talofibular *(ATFL)* ligament *(arrow)*. Other ligamentous injuries include sprain to both the posterior talofibular *(PTFL)* and the deltoid *(D)* ligaments, characterized by loss of normal striation and increased signal on T2-weighted images in these ligaments. Bone bruise of the medial talar dome *(arrowhead)* is present. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2014, WB Saunders.)

TABLE E2 Ottawa Ankle Rules

Accepted Indications: Ankle Radiographs	Accepted Indications: Midfoot Radiographs
Point tenderness about the inferior or posterior aspect of either malleolus (to include the distal 6 cm of the lateral malleolus)	Point tenderness about the navicular or the base of the fifth metatarsal
Inability to bear weight at the time of injury or clinical evaluation (four independent steps)	Inability to bear weight at the time of injury or clinical evaluation (four independent steps)

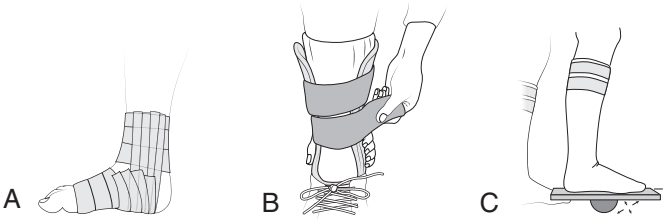

FIG. E6 A, The most effective method of supporting most acute ankle sprains is by using an ACE wrap (BD, Franklin Lakes, NJ) reinforced with 1-inch medial and lateral tape strips. The anterior and posterior aspects of the ankle are left free to allow the patient to flex and extend the ankle. The patient is encouraged to bear weight with crutches. **B,** Diagram of an air splint. Straps are adjusted to heel size, the lower straps are wrapped about the ankle, and the side extensions are centered. The splint is then pressurized, and straps adjusted until comfortable support and pressure are attained. **C,** As the ankle pain subsides, about the third to fifth day, balancing exercises can begin to allow the patient to regain ankle proprioception and avoid recurrent instability problems. (From Jardon OM, Mathews MS: Orthopedics. In Rakel RE [ed]: *Textbook of family practice,* ed 5, Philadelphia, 1995, WB Saunders.)

long-term results do not seem to be affected by such ossification.
- Continuing lateral symptoms may require surgical reconstruction, although late traumatic arthritis or long-term instability is rare regardless of treatment.
- Approximately 15% to 20% of patients require surgical intervention after continued lateral ankle instability after 6 to 8 mo of rigorous physical rehabilitation.

REFERRAL

Orthopedic consultation for patients who do not respond to conservative treatment. Most ankle sprains resolve in 2 to 6 wk.

PEARLS & CONSIDERATIONS

COMMENTS

If healing seems delayed (more than 6 wk), the following conditions should be considered:
- Talar dome fracture
- Reflex sympathetic dystrophy
- Chronic tendinitis
- Peroneal tendon subluxation
- Other occult fracture
- Peroneal weakness (poor rehabilitation)
- A "high" (syndesmotic) sprain

Repeat plain radiographs, bone scan, or MRI may be indicated.

RELATED CONTENT

Ankle Sprain (Patient Information)
Ankle Fracture (Related Key Topic)

AUTHOR: **Michael Bergen, MD**

SUGGESTED READINGS

Corey SV: Surgical versus conservative treatment of acute lateral ankle sprains in athletes, *Podiatry Institute* 14:67-70, 2011.

Tiemstra JD: Update on acute ankle sprains, *Am Fam Physician* 85:1170-1176, 2012.

BASIC INFORMATION

DEFINITION

Ankylosing spondylitis (AS) is a type of inflammatory arthritis involving the sacroiliac joints and axial skeleton characterized by ankylosis and enthesitis (inflammation at tendon insertions). It is one of a family of overlapping syndromes called seronegative spondyloarthropathies (SpA) that includes reactive arthritis (formerly Reiter syndrome), psoriatic spondylitis, and enteropathic arthritis.

SYNONYM

Marie-Strümpell disease

ICD-10CM CODES

M45.9	Ankylosing spondylitis of unspecified sites in spine
M08.1	Juvenile ankylosing spondylitis
M45.0	Ankylosing spondylitis of multiple sites in spine
M45.1	Ankylosing spondylitis of occipito-atlanto-axial region
M45.2	Ankylosing spondylitis of cervical region
M45.3	Ankylosing spondylitis of cervicothoracic region
M45.4	Ankylosing spondylitis of thoracic region
M45.5	Ankylosing spondylitis of thoracolumbar region
M45.6	Ankylosing spondylitis lumbar region
M45.7	Ankylosing spondylitis of lumbosacral region
M45.8	Ankylosing spondylitis sacral and sacrococcygeal region

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Between 0.1% and 1% of the population. Varies with prevalence of HLA-B27 and ethnicity. Much higher in those with positive family history of spondyloarthropathy.
PREDOMINANT AGE AT ONSET: 15 to 35 yr, usually symptoms present before age 45
PREDOMINANT SEX: Male:female ratio 2 to 3:1

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Prolonged morning back stiffness of insidious onset lasting more than 3 mo
- Bilateral sacroiliac tenderness (sacroiliitis)
- Inflammatory back pain; often improves with exercise and is worse with rest
- Limited lumbar spine motion
- Tenderness at tendon insertion sites, especially the Achilles tendons and plantar fascia
- Loss of chest expansion reflecting rib cage involvement
- Possible to have peripheral joint arthritis, usually involving lower extremity
- In advanced cases the typical posture consists of compensatory hyperextension of neck, fixed flexion of hips, and compensatory flexion of knees (Fig. 1)
- There is an increased incidence of iritis and uveitis (30% to 40% lifetime prevalence)
- Other extraskeletal manifestations include effects on the cardiovascular system (aortic insufficiency, cardiovascular disease) and lungs (pulmonary fibrosis). There is also an increased risk for osteoporosis

ETIOLOGY

Genetic factors, particularly HLA-B27, play an important role in susceptibility to the spondyloarthropathies. Infectious triggers have been implicated in some cases. Tumor necrosis factor is important in the inflammatory response.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diffuse idiopathic skeletal hyperostosis (Forestier disease)

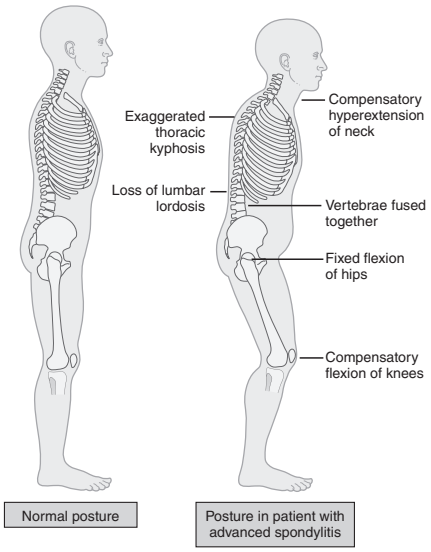

FIG. 1 Ankylosing spondylitis. Typical posture in advanced cases compared with normal posture. (From Ballinger A: *Kumar & Clark's essentials of clinical medicine,* ed 6, Edinburgh, 2012, WB Saunders.)

- Noninflammatory back pain (a clinical algorithm for the evaluation of back pain is described in Section III)
- Table 1 compares ankylosing spondylitis and related disorders

LABORATORY TESTS

- Elevated sedimentation rate, C-reactive protein
- Mild hyperchromic anemia
- Demonstration of inflammatory sacroiliitis by radiography or MRI is diagnostic for most patients, although some patients may meet criteria for "pre-radiographic spondyloarthropathy" based on compelling clinical evaluation
- HLA-B27 antigen is not useful in the evaluation of noninflammatory back pain because it is present in up to 10% of the normal population (varies based on ethnicity)

IMAGING STUDIES

- Classic feature is bilateral sacroiliitis on pelvic radiographs (modified NY criteria).
- Vertebral bodies lose anterior concave shape and become square.
- With progression, calcification of the annulus fibrosus and paravertebral ligaments develops, giving rise to the so-called *bamboo spine.* (Figs. E2 through E6).
- Severe diskovertebral erosions and destruction may occur (Andersson lesion, Fig. 7).
- MRI (Fig. E8) may be useful in detecting early inflammatory lesions and is especially helpful when the history is suggestive but radiographs are equivocal; can see bone marrow edema, fatty metaplasia, sacroiliitis, erosions, shiny corners.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Exercises primarily to maintain flexibility and aerobic activity are important (Fig. E9).
- Postural training:
  1. Patients must be instructed on spinal extension exercises to avoid fusion in a flexed position.

TABLE 1 Comparison of ankylosing spondylitis and related disorders

Feature	Ankylosing spondylitis	Psoriatic arthritis	Reactive arthritis	Enteropathic arthropathy
Gender (male : female)	2-3 : 1	1 : 1	1 : 1	1 : 1
Age of onset	<40 yr	35-55 yr	20-40 yr	Any age
Sacroiliitis or spondylitis (%)	100	~20	~40	<20
Symmetry of sacroiliitis	Symmetrical	Asymmetrical	Asymmetrical	Symmetrical
Peripheral arthritis (%)	~25	95	90	5-20
Distribution	Axial and lower limbs	Variable	Lower limbs	Variable
HLA-B27 positivity (%)	85-95	25-60*	30-70	7-70†
Uveitis	0-40	~20	~50	<15

*60% when spondylitis is present.
†70% when spondylitis is present.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

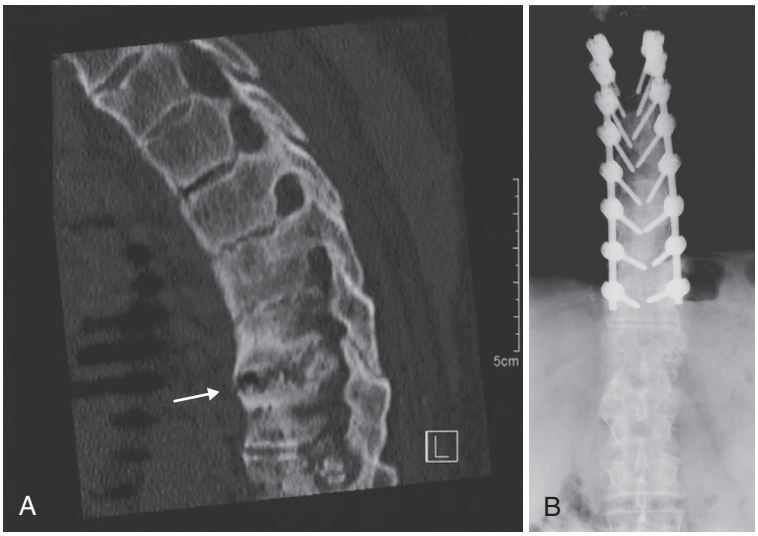

FIG. 7 Severe Andersson lesion (diskovertebral erosions and destruction) (**A,** *arrow*) of the thoracic spine in a patient with ankylosing spondylitis resulting in instability and severe pain, which was treated with a fusion operation **(B).** (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

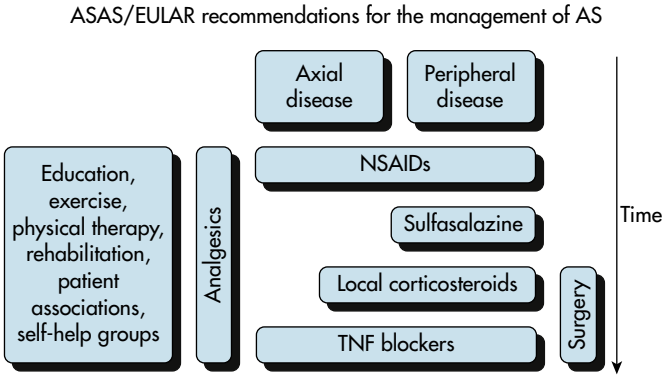

FIG. 10 ASAS/EULAR recommendations for the management of AS. *AS,* Ankylosing spondylitis; *ASAS,* Assessment of SpondyloArthritis international Society; *EULAR,* The European League Against Rheumatism; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *TNF,* tumor necrosis factor. (From van der Linden et al: Ankylosing Spondylitis. In Firestein G et al [eds]: *Kelley & Firestein's textbook of rheumatology,* ed 10, Philadelphia, 2017, Elsevier, Table 75-3, pp. 1271.)

2. Sleeping should be in the supine position on a firm mattress; pillows should not be placed under the head or knees.

PHARMACOLOGIC THERAPY

- NSAIDs: Patients with ankylosing spondylitis should be trialed on full-dose continuous NSAID therapy. There is anecdotal evidence suggesting that indomethacin may be more effective than other NSAIDs, but other NSAIDs are also efficacious and may be better tolerated. One study suggested that continuous NSAID therapy may retard the radiographic progression of ankylosing spondylitis, but data are conflicting.
- Sulfasalazine may be efficacious in patients with peripheral arthritis.
- Numerous controlled trials have shown that tumor necrosis factor (TNF) antagonists such as etanercept, infliximab, and adalimumab are very effective for relieving symptoms of spinal inflammatory arthritis. Anti-TNF therapy should be recommended for patients whose symptoms are not completely controlled with NSAIDs, and it can result in dramatic improvement in symptoms, range of motion of the spine, and quality of life for these patients. There is evidence suggesting that anti-TNF therapy slows the radiographic progression of the disease. Etanercept should generally be avoided if history of uveitis.
- Secukinumab, an anti-interleukin-17A monoclonal antibody, has been approved for treating AS. Ixekizumab, another IL-17A antibody, was also just approved in 2019.
- Fig. 10 shows American College of Rheumatology (ACR)/The European League Against Rheumatism (EULAR) recommendations for management.

DISPOSITION

Most patients have a normal life span but many can suffer significant disability from loss of spinal mobility.

REFERRAL

All patients with seronegative spondyloarthropathy should be referred to a rheumatologist for further evaluation and treatment.

PEARLS & CONSIDERATIONS

A family history of seronegative spondyloarthropathy increases the specificity of testing for HLA-B27. Surgical osteotomy may benefit selected patients with severe spinal deformity. Recent data suggest that men with AS have increased risk of vascular mortality.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Ankylosing Spondylitis (Patient Information)

AUTHOR: **Daphne Scaramangas-Plumley, MD**

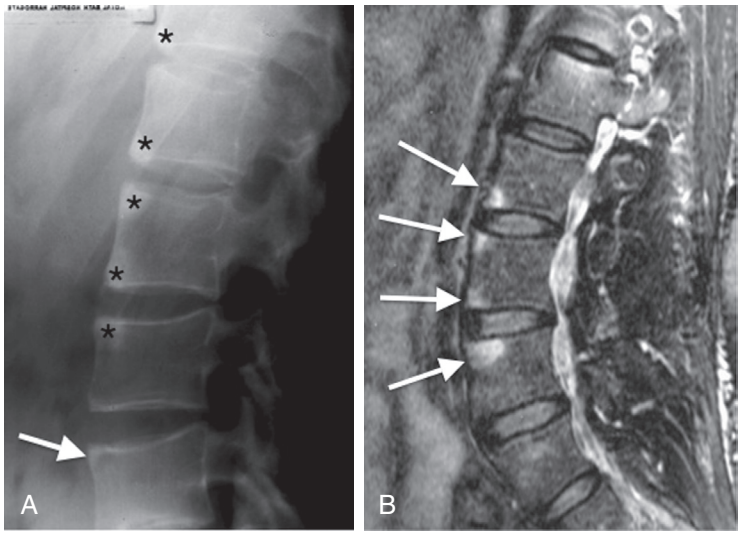

FIG. E2 (A) Ankylosing spondylitis (AS) with sclerosis of the vertebral corners (Romanus lesions). The radiograph shows advanced lesions (*) and an early lesion *(arrow).* **(B)** STIR sagittal MR image of a different AS patient with edema of the vertebral corners *(arrows)* termed *MR Romanus lesions.* (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

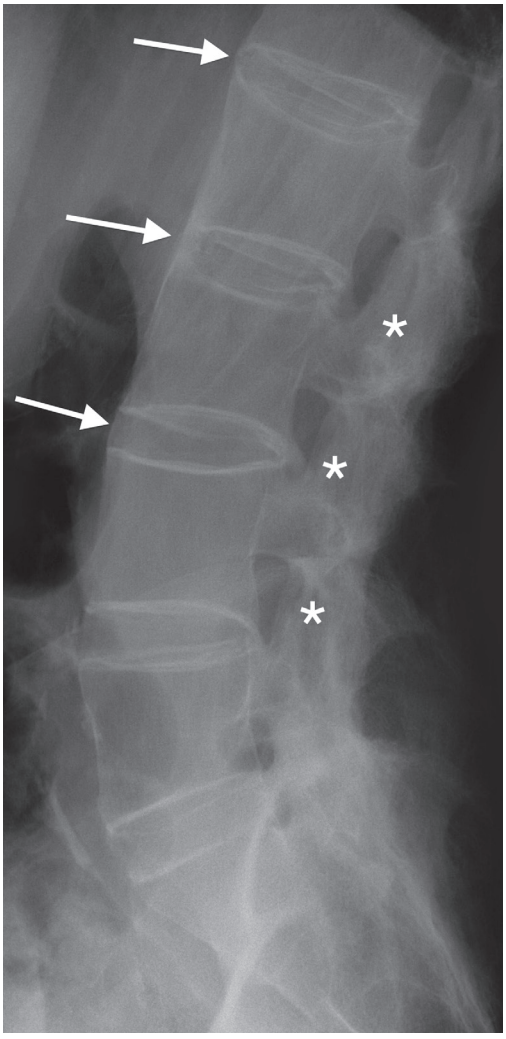

FIG. E3 T1-weighted **(A)** and T2 fat-suppressed **(B)** coronal magnetic resonance images of the sacroiliac joints (SIJ) in ankylosing spondylitis. The T1-weighted image readily demonstrates erosion *(arrows)* in the right SIJ with joint space loss on the left (*), all indicative of damage. Note how poor the T2-weighted image is at demonstrating erosion; however, it shows subchondral edema *(arrows)* more reflective of disease activity. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

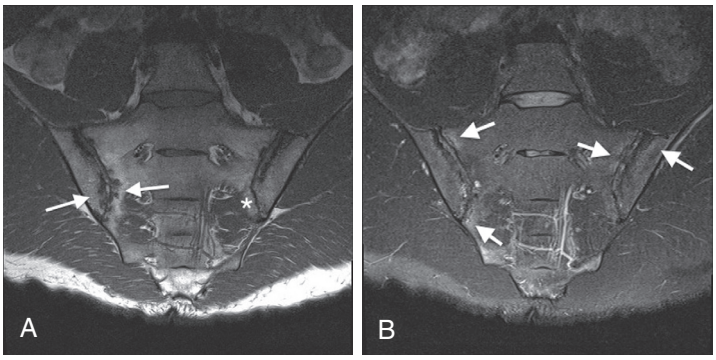

FIG. E4 Ankylosing spondylitis with bamboo spine. Bridging vertical syndesmophytes are seen around the intervertebral discs *(arrows).* Note no facet joint spaces are visualized, indicating fusion of the posterior joints between L3 and S1. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

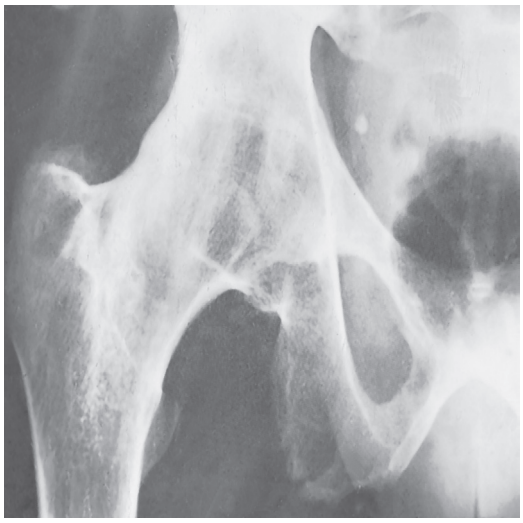

FIG. E5 Ankylosing spondylitis. Bone ankylosis across the joint cartilage. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

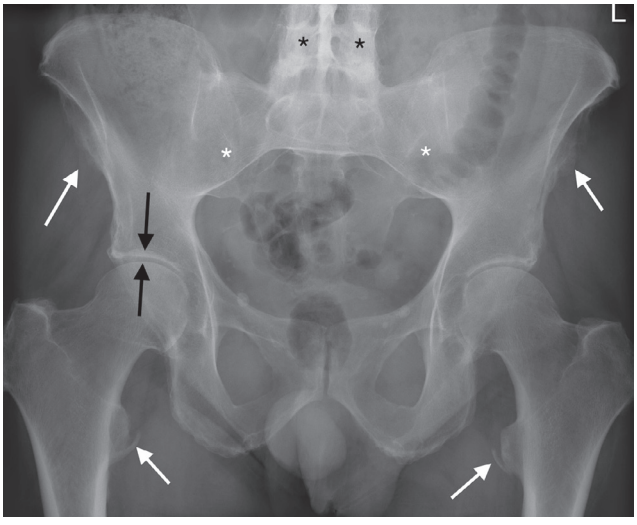

FIG. E6 Patient with ankylosing spondylitis with spinal fusion *(black*)* and SIJ fusion *(white*).* There is hip arthropathy with diffuse loss of joint space *(black arrows)* and flattened configuration of the femoral heads. Widespread entheseal new bone formation is noted around the pelvis *(white arrows).* (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

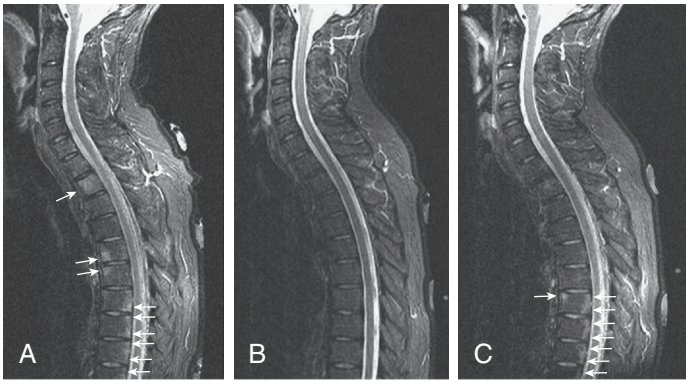

FIG. E8 Spine inflammation in ankylosing spondylitis (magnetic resonance imaging [MRI]). A 43-yr-old man with HLA-B27–positive ankylosing spondylitis with deteriorating symptoms, including inflammatory back pain, had an MRI scan before starting biologic therapy. Baseline sagittal short tau inversion recovery (STIR) MRI **(A)** shows diffuse increased signal (edema) in the T2 vertebral body and multiple foci of corner inflammation anteriorly at T5 and T6, and posteriorly at T7, T8, T9, and T10 *(arrows).* Other images confirmed extensive active inflammation in the spine. The patient responded very well, and after 6 mo of therapy, a repeat STIR MRI **(B)** showed complete resolution of bone marrow inflammation. Subsequently, the patient experienced recurrence of symptoms, and a third MRI **(C)** was performed (2 mo after anti-TNF therapy was stopped). This MRI shows no edema at T5 to T6, a conspicuous new lesion anteriorly at T7, and recurrent inflammation posteriorly in the lower thoracic spine *(arrows).* (From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, WB Saunders.)

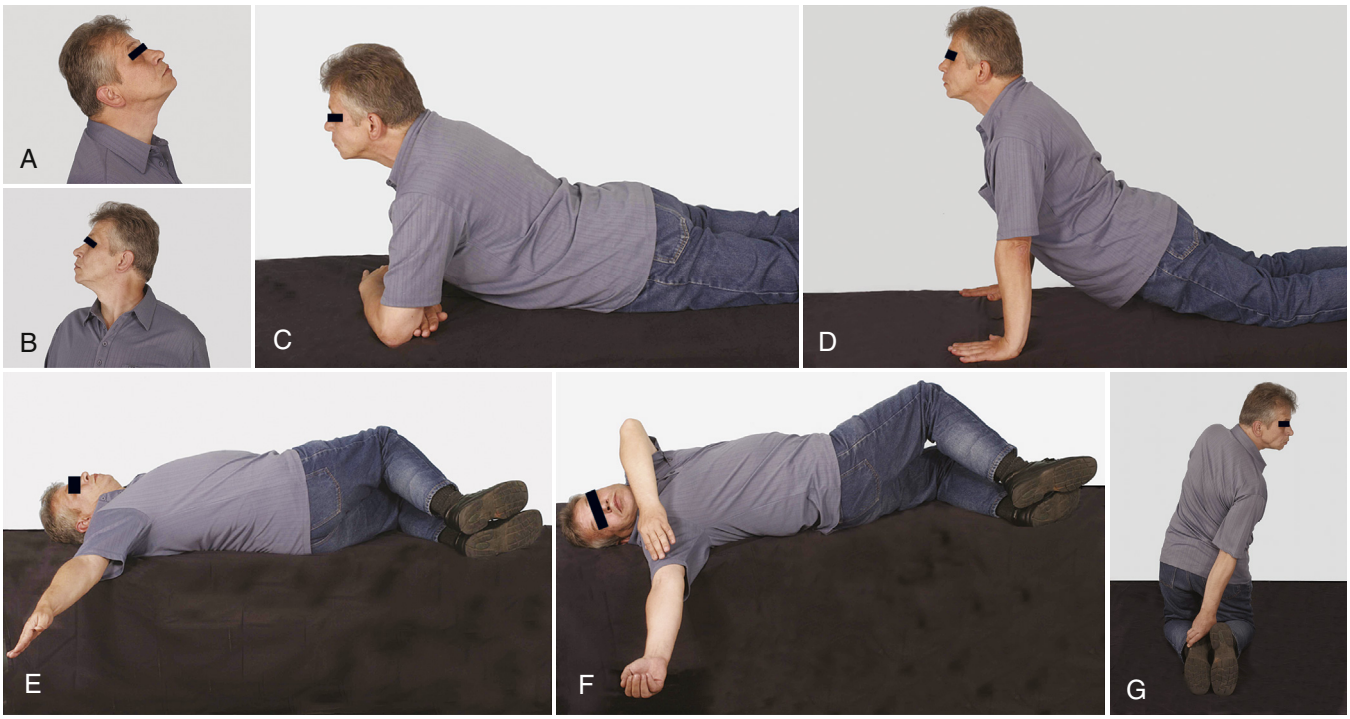

FIG. E9 An exercise sequence used in patients with ankylosing spondylitis. Cervical spine exercises include full extension **(A)** and rotation **(B).** A sequence of back extension **(C** and **D)** is followed by rotation in the lying **(E** and **F)** and upright kneeling **(G)** positions. Finally, breathing with the thoracic muscles is practiced (not shown). (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

SUGGESTED READINGS

Bengtsson K et al: Are ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis associated with an increased risk of cardiovascular events? A prospective nationwide population-based cohort study, *Arthritis Res Ther* 19(1):102, 2017, https://doi.org/10.1186/s13075-017-1315-z. 28521824.

Griffith JF et al: Computer-aided assessment of spinal inflammation on magnetic resonance images in patients with spondyloarthritis, *Arthritis Rheum* 67:1789-1797, 2015.

Haroon N et al: The impact of tumor necrosis factor inhibitors on radiographic progression in ankylosing spondylitis, *Arthritis Rheum* 65:2645, 2013.

Haroon N et al: Patients with ankylosing spondylitis have increased cardiovascular and cerebrovascular mortality, *Ann Intern Med* 163:409-416, 2015.

Kim KT et al: Results of corrective osteotomy and treatment strategy for ankylosing spondylitis with kyphotic deformity, *Clin Orthop Surg* 7:330-336, 2015.

Marzo-Ortega H et al: Secukinumab and sustained improvement in signs and symptoms of patients with active ankylosing spondylitis through two years: results from a Phase III study, *Arthritis Care Res* 69(7):1020-1029, 2017.

Taurog JD et al: Ankylosing spondylitis and axial spondyloarthritis, *N Engl J Med* 374:2563-2574, 2016.

Anorectal Fistula

BASIC INFORMATION

DEFINITION

An anorectal fistula is an inflammatory tract with a secondary (external) opening in the perianal skin and a primary (internal) opening in the anal canal at the dentate line. Anorectal fistulae usually originate as a complication of a perianal abscess, which develops from an infected anal crypt gland. If that abscess ruptures and the tract epithelializes, then a fistula develops. Anorectal fistulae can be classified as follows (based on their relationship to the anal sphincter complex):

- Intersphincteric: Fistula track passes within the intersphincteric plane to the perianal skin (most common)
- Transsphincteric (Fig. E1): Fistula track passes from the internal opening, through the internal and external sphincter, and into the ischiorectal fossa to the perianal skin (frequent)
- Suprasphincteric: After passing through the internal sphincter, fistula tract passes above the puborectalis and then tracts downward, lateral to the external sphincter, into the ischiorectal space to the perianal skin (uncommon); if abscess cavity extends cephalad, a supralevator abscess possibly palpable on rectal examination
- Extrasphincteric: Fistula tract passes from the rectum, above the levators, through the levator muscles to the ischiorectal space and perianal skin (rare)
- Submucosal: Originate at the level of the dentate line in an infected crypt not involving the sphincter muscles

With a horseshoe fistula, the tract passes from one ischiorectal fossa to the other behind the rectum.

SYNONYM

Fistula-in-ano

ICD-10CM CODES
K60.3 Anal fistula
K60.5 Anorectal fistula

EPIDEMIOLOGY & DEMOGRAPHICS

- Common in all ages (average age is 39 yr)
- Occurs twice as often in men as compared to women (12.1/100,000 vs. 5.5/100,000)
- Associated with inflammatory bowel disease and constipation
- Pediatric age group: More common in infants; boys more than girls

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute stage: Perianal swelling, pain with defecation and sitting, and fever
- Chronic stage: Pain, malodorous perianal drainage or bleeding, anal pruritus
- Tender, inflamed external fistulous opening, within 2 to 3 cm of the anal verge, with purulent or serosanguineous drainage on compression; the greater the distance from the anal margin, the greater the probability of a complicated upward extension
- Goodsall rule:
  1. Location of the internal opening related to the location of the external opening.
  2. With external opening anterior to an imaginary line drawn horizontally across the midpoint of the anus: Fistulous tract runs radially into the anal canal.
  3. With opening posterior to the transanal line: Tract is usually curvilinear, entering the anal canal in the posterior midline.
  4. Exception to this rule: An external anterior opening that is >3 cm from the anus. In this case the tract may curve posteriorly and end in the posterior midline.
- If perianal abscess recurs, presence of a fistula is suggested.

ETIOLOGY

- Most common: Nonspecific infection of anal crypt gland (skin or intestinal flora)
- Fistulas more common when intestinal microorganisms are cultured from the anorectal abscess
- Tuberculosis
- Lymphogranuloma venereum
- Actinomycosis
- Inflammatory bowel disease (IBD): Crohn disease, ulcerative colitis
- Trauma: Surgery (episiotomy, prostatectomy), foreign bodies, anal intercourse
- Malignancy: Carcinoma, leukemia, lymphoma
- Treatment of malignancy: Surgery, radiation

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Anal abscess
- Anal ulcer or fissure
- Hidradenitis suppurativa
- Pilonidal sinus
- Bartholin gland abscess or sinus
- Infected perianal sebaceous cysts

WORKUP

- Digital rectal examination:
  1. Assess sphincter tone and voluntary squeeze pressure.
  2. Determine the presence of an extraluminal mass.
  3. Identify an indurated fistula tract.
  4. Palpate an internal opening or pit.
- Gentle probing of external orifice to avoid creating a false tract; 50% do not have clinically detectable opening
- Exam alone can be adequate for most simple anorectal fistulas
- Anoscopy
- Proctosigmoidoscopy to exclude inflammatory or neoplastic disease
- All studies done under adequate anesthesia

LABORATORY TESTS

- Complete blood count
- Rectal biopsy if diagnosis of IBD or malignancy suspected; biopsy of external orifice is useless

IMAGING STUDIES

- Transanal endosonography (EUS) can be useful to predict the amount of sphincter that would be divided if primary fistulotomy is performed and to identify undrained sepsis, complex anatomy, and high blind tracts (Fig. E2). MRI can be used to identify suprasphincteric or extrasphincteric tracts. MRI and EUS are more accurate in describing fistulas than clinical exam. CT lacks adequate resolution to identify tracts and their relationship to the sphincters and levators.
- Fistulography, in which contrast is injected into the external opening and the fistula course is traced with fluoroscopy, is rarely necessary in view of recent technological advancements.
- Colonoscopy or barium enema if:
  1. Diagnosis of IBD or malignancy is suspected
  2. History of recurrent or multiple fistulas
  3. Patient <25 yr
- Small bowel series: Occasionally obtained for reasons similar to previous advancements.

TREATMENT

NONPHARMACOLOGIC THERAPY

Sitz baths

PHARMACOLOGIC THERAPY (RARELY RECOMMENDED)

Immunomodulators (Infliximab)

ACUTE GENERAL Rx

- Treatment of choice: Surgery
- Broad-spectrum antibiotic given if:
  1. Cellulitis present
  2. Patient is immunocompromised
  3. Valvular heart disease present
  4. Prosthetic devices present
- Stool softener/laxative

CHRONIC Rx

- Surgery: Table E1 summarizes management strategy by fistula classification
- Surgical goals are as follows:
  1. Remove the fistula
  2. Prevent recurrence
  3. Preserve sphincter function
  4. Minimize healing time
- Methods for the management of anal fistulas: Fistulotomy, fistulectomy, setons (Fig. E3) (maintains fistula patent for drainage while spontaneous healing occurs), fibrin glue (clot formation within the fistulous tract), fistula plugs (Fig. E4) (promote closure of fistula), LIFT procedure, rectal advancement flaps, and colostomy

DISPOSITION

Outpatient surgery

REFERRAL

Refer to a surgeon with expertise in this area.

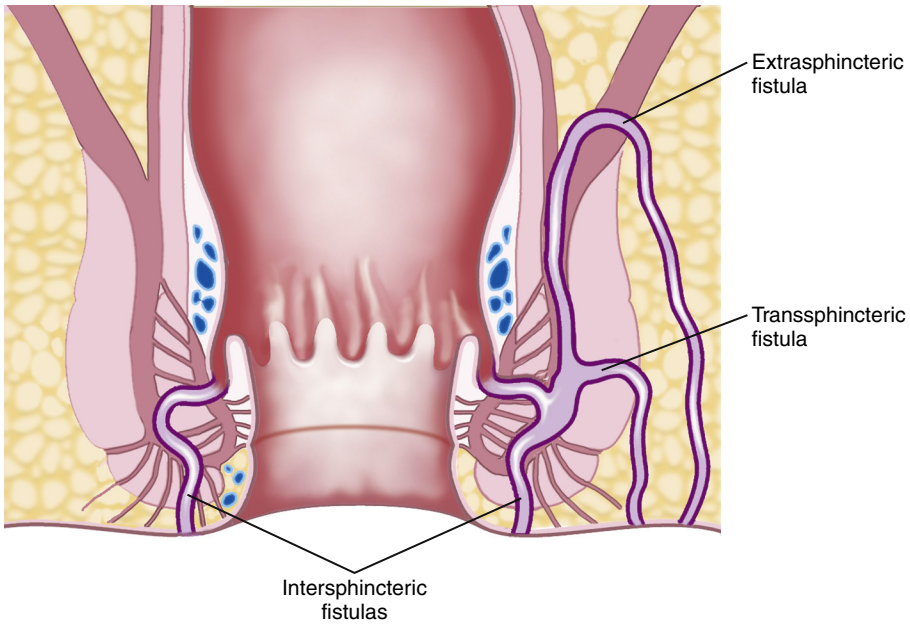

FIG. E1 Schematic depiction of the classification of fistula-in-ano. Fistulotomy is not appropriate for extrasphincteric fistulas, because it would leave the patient incontinent. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

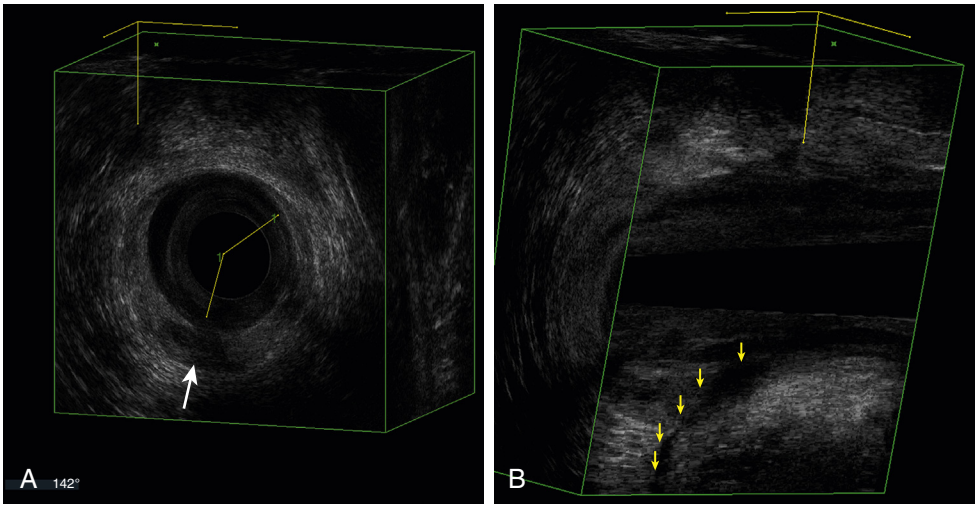

FIG. E2 Ultrasound of right posterior transsphincteric fistula. A, Coronal view revealing a 142-degree internal sphincter defect on the left side from a previous hemorrhoidectomy. The hypoechoic internal opening of a right transsphincteric fistula is noted with an arrow. Given the edge of the internal sphincter defect abuts the fistula tract, a LIFT procedure may not be feasible. **B,** Angled sagittal view showing the hypoechoic transsphincteric fistula. Note the internal opening nears the half length of the hyperechoic external sphincter; therefore a fistulotomy would not be appropriate. (Photo credit Amy Thorsen, MD, in Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

TABLE E1 Management Strategy by Fistula Classification

Type of Fistula	Fistulotomy	Seton *	LIFT	Advancement Flap	Fibrin Glue	Collagen Plug	Address Intraabdominal or Pelvic Source
Superficial/intersphincteric	•						
Low transsphincteric	•	•	•	•	•	•	
High transsphincteric		•	•	•	•	•	
Suprasphincteric		•		•		•	•
Extrasphincteric						•	•

LIFT, Ligation of intersphincteric fistula tract.
*Seton placement can be a first stage or definitive treatment option.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

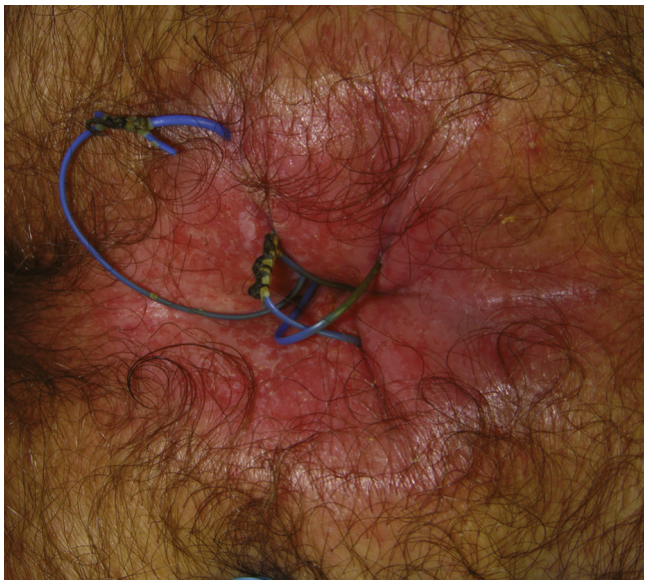

FIG. E3 Blue setons placed through fistulous tracts in a patient with anal Crohn disease. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

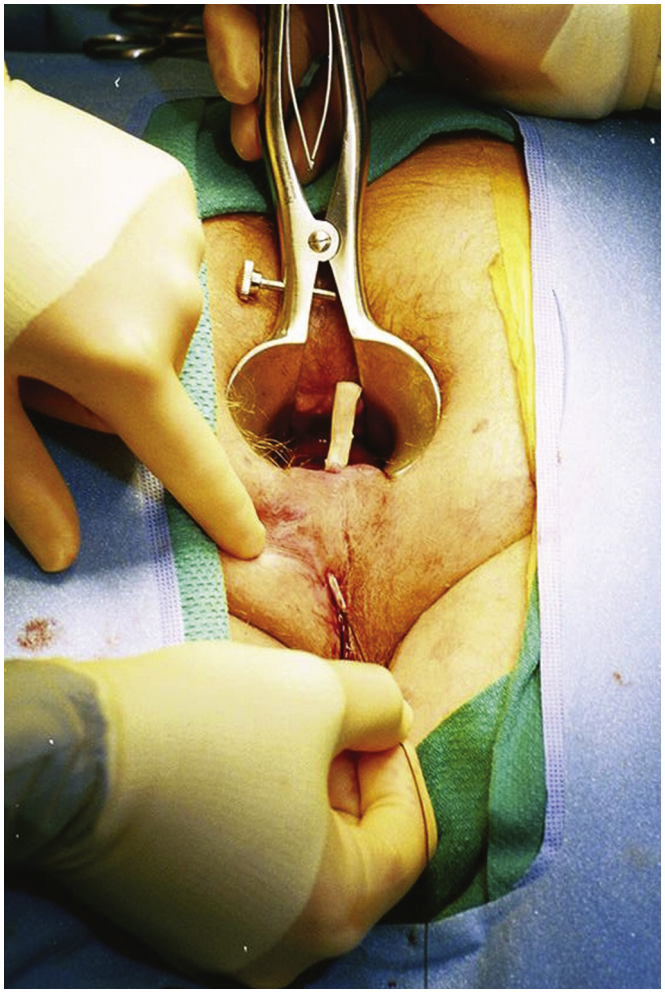

FIG. E4 Anal fistula plug being placed through an anterior anal fistula tract. Once it is pulled snugly through the tract, the plug is secured internally and the internal opening closed. Excess plug projecting externally is also trimmed. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

PEARLS & CONSIDERATIONS

COMMENTS

- HIV-positive and diabetic patients with perirectal abscesses/fistulas are true surgical emergencies.
- Risk of septicemia, Fournier's gangrene, and other septic complications make immediate drainage imperative.

RELATED CONTENT

Anal Fissure (Related Key Topic)
Hemorrhoids (Related Key Topic)

AUTHORS: **Babak Vakili, MD,** and **Adrienne Werth, MD**

SUGGESTED READING

Sneider EB, Maykel JA: Anal abscess and fistula, *Gastroenterol Clin N Am* 42:773-784, 2013.

BASIC INFORMATION

DEFINITION

Abnormal narrowing of the anal canal. Anorectal strictures can be classified based on severity and location (Table E1).

SYNONYMS

Anal stenosis
Küss disease

ICD-10CM CODE
K62.4 Stenosis of anus and rectum

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 5% to 10% of post-radical hemorrhoidectomy surgeries
RISK FACTORS: Previous anorectal surgery, inflammatory bowel disease, prior radiation, hemorrhoids

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History:
  1. Most common symptom is pain with defecation
  2. Patients also may report bleeding, narrowing of stools, constipation, fecal incontinence, tenesmus, and urgency
  3. Important to ask about past anorectal surgeries, Crohn disease, or perianal trauma
- Physical examination:
  1. Visual inspection of the anus may demonstrate skin tags or chronic fissures
  2. Digital rectal examination will demonstrate a narrowed anal canal through which it is difficult to pass a lubricated finger
  3. In severe cases, examination under anesthesia may be required

TABLE E1 Classification of Anorectal Stricture

Severity	Location
Mild: Stricture present, but allows passage of well-lubricated finger or medium Hill-Ferguson retractor	**Low:** At least 0.5 cm distal to the dentate line
Moderate: Passage of well-lubricated finger or medium Hill-Ferguson retractor only with forceful dilation	**Middle:** 0.5 cm on either side of the dentate line
Severe: No passage of well-lubricated finger or medium Hill-Ferguson retractor	**High:** At least 0.5 cm proximal to the dentate line

Adapted from Liberman H, Thorson AG: How I do it. Anal stenosis. *Am J Surg* 179:325-329, 2000. In Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

ETIOLOGY

- Congenital malformation
- Fibrosis of anoderm or distal rectal mucosa due to a surgical procedure:
  1. Hemorrhoidectomy
  2. Low anterior resection
  3. Ileal pouch-anal anastomosis
  4. Anopexy
  5. Excision of perianal skin lesion
- Anal canal muscle hypertrophy
- Anal canal muscle spasm (anismus) secondary to anal fissure
- Neoplasia:
  1. Bowen disease
  2. Paget disease
  3. Anal squamous cell carcinoma
  4. Rectal adenocarcinoma
  5. Condyloma acuminata
- Inflammation:
  1. Anal fissure
  2. Crohn disease
  3. Tuberculosis
  4. Actinomycosis
  5. Lymphogranuloma venereum
  6. Chronic suppuration
- Trauma:
  1. Radiation therapy
  2. Perineal burns
  3. Hot water enemas
  4. Ibuprofen suppositories
  5. Chronic laxative abuse
- Sexually transmitted disease
- Box E1 summarizes common causes of anorectal strictures

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Anorectal stricture/stenosis
- Neoplasm

BOX E1 Cause of Anorectal Stricture

Surgical Procedures
Hemorrhoidectomy
Low anterior resection
Ileal pouch-anal anastomosis
Anopexy
Excision of perianal skin lesions

Neoplastic
Bowen disease
Paget disease
Anal squamous cell carcinoma
Rectal adenocarcinoma
Condyloma acuminata

Inflammatory
Anal fistula
Crohn disease
Tuberculosis
Actinomycosis
Lymphogranuloma venereum

Trauma
Radiation therapy
Perineal burns
Hot water enemas
Ibuprofen suppositories
Chronic laxative abuse

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

- Inflammatory bowel disease
- Trauma

WORKUP

- Hydration, fiber supplementation, and stool softeners should be started in all patients regardless of ultimate etiology.
- Suspicious lesions should be biopsied.

LABORATORY TESTS

None

IMAGING STUDIES

None

TREATMENT

NONPHARMACOLOGIC THERAPY

- Manual dilation using digital method or commercial dilators may be started in the clinic or operating room and continued on an outpatient basis
- Resection of neoplasm
- Stricturoplasty
- Anoplasty

CHRONIC Rx

For mild disease, stool softeners, fiber supplementation, and dietary modification are all that is necessary.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

None

DISPOSITION

Mild strictures can be treated on an outpatient basis in clinic; moderate to severe strictures require colorectal surgical evaluation.

REFERRAL

Referral is indicated when there is concern for neoplasm, patients who fail conservative medical management, or if the provider is unable to pass a lubricated finger into the rectum.

SUGGESTED READINGS

Abdelnaby A, Downs JM: Diseases of the Anorectum. In Felman M, Friedman LS, Brand LJ, editors: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier, p 2332.

Cohan JN, Varma MG: The Management of Anorectal Stricture. In Cameron JL, Cameron AM, editors: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier, pp 291-295.

Eisenstat TE, Penzer J: Cause and Management of Anal Stenosis. In Fazio VW, editor: *Current therapy in colon and rectal surgery*, ed 3, Philadelphia, 2017, Elsevier, pp 48-52.

AUTHORS: **W. Peyton Adkins, MD,** and **Craig Blakeney, MD**

Anorexia Nervosa ALG PTG

BASIC INFORMATION

DEFINITION

Anorexia nervosa is a psychiatric disorder characterized by abnormal eating behavior, severe self-induced weight loss, and a specific psychopathology (see "Workup").

ICD-10CM CODES

F50.00	Anorexia nervosa, unspecified
F50.01	Restricting type
F50.02	Binge-eating/purging type

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE (IN U.S.):

- Anorexia nervosa occurs in 0.2% to 1.3% of the general population, with an annual incidence of 5 to 10 cases per 100,000 persons.
- Participation in activities that promote thinness (athletics, modeling) is associated with a higher incidence of anorexia nervosa.

PREDOMINANT SEX: Female:male ratio is 9:1. Approximately 0.5% to 1% of women between the ages of 15 and 30 yr have anorexia nervosa.

PREDOMINANT AGE: Adolescence to young adulthood is the predominant age. Mean age of onset is 17 yr. Approximately 0.5% to 1% of college-aged women have anorexia nervosa.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Eating disorders can affect every organ system. Primary care physicians must be skilled at recognizing this disorder because patients with mild cases usually present with nonspecific symptoms such as asthenia, cold intolerance, lack of energy, or dizziness. Children and adolescents are at particular risk due to their active phase of growth and development. The physical examination may be normal in the early stages or in mild cases. Patients with moderate to severe anorexia have the following physical characteristics:

- Patient is emaciated and bundled in clothing.
- Skin is dry and has excessive growth of lanugo. Skin may also be yellow-tinged from carotenodermia.
- Brittle nails, thinning scalp hair are present.
- Bradycardia, hypotension, hypothermia, and bradypnea are common.
- Female fat distribution pattern is no longer evident.
- Axillary and pubic hair is preserved.
- Peripheral edema may be present.

ETIOLOGY

- Etiology is unknown, but probably multifactorial (sociocultural, psychological, familial, and genetic factors).
- A history of sexual abuse has been reported in as many as 50% of patients with anorexia nervosa.
- Psychological factors: Anorexics often have an incompletely developed personal identity. They struggle to maintain a sense of control over their environment, they usually have a low self-esteem, and they lack the sense that they are valued and loved for themselves.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other eating disorders (bulimia nervosa, binge eating disorder [Table E1])
- Substance abuse
- Depression with loss of appetite
- Obsessive compulsive disorder
- Schizophrenia
- Conversion disorder
- Occult carcinoma, lymphoma
- Endocrine disorders: Addison disease, diabetes mellitus, hypothyroidism or hyperthyroidism, panhypopituitarism
- Gastrointestinal disorders: Celiac disease, Crohn disease, intestinal parasitosis
- Infectious disorders: AIDS, tuberculosis
- A clinical algorithm for the evaluation of anorexia is described in Section III

WORKUP

- A diagnosis can be made by using the following *DSM-5* diagnostic criteria for anorexia nervosa.
  1. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children or adolescents, less than that minimally expected.
  2. Intense fear of gaining weight or becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
  3. Disturbance in the way in which one's body or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.
- Specify type:
  1. Restricting type: During the last 3 mo, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.
  2. *Binge-eating/purging type:* During the last 3 mo, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).
- Severity level: See "Acute General Rx" section

The SCOFF questionnaire is a screening tool for eating disorders used in England. It consists of the following five questions:

1. Do you make yourself ***s***ick because you feel full?
2. Have you lost ***c***ontrol over how much you eat?
3. Have you lost more than ***o***ne stone (approximately 6 kg) recently?
4. Do you believe yourself to be ***f***at when others say you are thin?
5. Does ***f***ood dominate your life?

A positive response to two or more questions has a reported sensitivity of 100% for anorexia and bulimia and an overall specificity of 87.5%.

In college-aged women a positive response to any of the following screening questions also warrants further evaluation:

1. How many diets have you been on in the past year?
2. Do you think you should be dieting?
3. Are you dissatisfied with your body size?
4. Does your weight affect the way you think about yourself?

Baseline ECG should be performed on all patients with anorexia nervosa. Routine monitoring of patients with prolonged QT interval is necessary; sudden death in these patients is often caused by ventricular arrhythmias related to QT interval prolongation.

A dual-energy x-ray absorptiometry (DEXA) scan to screen for osteopenia should be considered after 6 mo of amenorrhea in patients suspected of anorexia nervosa.

LABORATORY TESTS

- In mild cases, laboratory findings may be completely normal.
- Endocrine abnormalities:
  1. Decreased follicle-stimulating hormone, luteinizing hormone, T_4, T_3, estrogens, urinary 17-OH steroids, estrone, and estradiol
  2. Normal free T_4, thyroid-stimulating hormone
  3. Increased cortisol, growth hormone, rT_3, T_3RU
  4. Absence of cyclic surge of luteinizing hormone

TABLE E1 Diagnostic Features of Eating Disorders

Anorexia nervosa	Body weight willfully maintained below normal level Abnormal perception of body morphology Intense fear of weight gain Amenorrhea
Bulimia nervosa	Large uncontrolled eating binges at least twice weekly Inappropriate compensatory behavior (e.g., vomiting, purging)
Binge eating disorder	Large uncontrolled eating binges at least twice weekly No regular inappropriate compensatory disorders Marked distress about binges

Modified and updated from Besser CM, Thorner MO: *Comprehensive clinical endocrinology,* ed 3, St Louis, 2002, Mosby.

- Leukopenia, thrombocytopenia, anemia, reduced erythrocyte sedimentation rate, reduced complement levels, and reduced CD4 and CD8 cells may be present.
- Metabolic alkalosis, hypocalcemia, hypokalemia, hypomagnesemia, hypercholesterolemia, and hypophosphatemia may be present.
- Increased plasma β-carotene levels are useful to distinguish these patients from others on starvation diets.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- A multidisciplinary approach with psychological, medical, and nutritional support is necessary.
- A goal weight should be set and the patient should be initially monitored at least once a week in the office setting. The target weight is 100% of ideal body weight (BW) for teenagers and 90% to 100% for older patients.
- Weight gain should be gradual (1 to 3 lb/wk) to prevent gastric dilation. Begin with 800 to 1200 kcal in frequent small meals (to avoid bloating sensation), then increase calories to 1500 to 3000 depending on height and age.
- Add, as necessary, vitamin and mineral supplements.
- In severe cases, total parenteral nutrition must be used (starting at 800 to 1200 kcal/day).
- Electrolyte levels should be strictly monitored.
- Mealtime should be a time for social interaction, not confrontation.
- Postprandially, sedentary activities are recommended. The patient's access to a bathroom should be monitored to prevent purging.

ACUTE GENERAL Rx

- Criteria to decide on the appropriate initial course of treatment for patients with anorexia nervosa are usually based on the presence of complications, percentage of ideal BW, and severity of body image distortion. According to *DSM-5*,[1] the minimum level of severity is based, for adults, on current body mass index (BMI; see below) or, for children and adolescents, on BMI percentile. The level of severity may be increased to reflect clinical symptoms, the degree of functional disability, and need for supervision.
  Mild: BMI ≥17 kg/m^2
  Moderate: BMI 16 to 16.99 kg/m^2
  Severe: BMI 15 to 15.99 kg/m^2
  Extreme: BMI <15 kg/m^2
- Outpatient treatment is adequate for most patients.
- Indications for inpatient-level care are described under "Referral" section and summarized in Table E2.
- Medically stable patients who are within 85% of ideal BW can be followed up by the primary care physician at 3- or 4-wk intervals, which can be lengthened as the patient improves.

[1] American Psychiatric Association: Desk Reference to the Diagnostic Criteria from DSM-5, Arlington, VA, 2013, American Psychiatric Association.

- Pharmacologic treatment generally has no role in anorexia nervosa unless major depression or another psychiatric disorder is present. Selective serotonin reuptake inhibitors can be used to alleviate the depressed mood and moderate obsessive-compulsive behavior in some individuals.

CHRONIC Rx

- Psychotherapy continued for years and focused specifically on self-image, family and peer interactions, and relapse prevention is an integral part of a successful recovery.
- Family therapy is also recommended, especially in younger patients.

DISPOSITION

- The long-term prognosis is generally poor and marked by recurrent exacerbations. The percentage of patients with anorexia nervosa who fully recover is modest. Most patients continue to have a distorted body image, disordered eating habits, and psychic difficulties.
- Most patients with anorexia nervosa will recover menses within 6 mo of reaching 90% of their ideal BW. It is important to note that patients with anorexia nervosa can become pregnant despite amenorrhea.
- Mortality rates vary from 5% to 20% and are six times that of peers without anorexia. Frequent causes of death are electrolyte abnormalities, starvation, or suicide.
- Factors that predict improved outcome in patients with eating disorders include early age at diagnosis, brief interval before initiation of treatment, good parent-child

TABLE E2 Clinical Signs and Criteria Warranting Inpatient-Level Care to Stabilize or Treat an Eating Disorder

Domain	General Symptom[a]	Example[b]
Weight	Substantially low weight for height and age Rapidly falling weight	<75% to 85% expected body weight for height and age
Behavioral	Acute food or water refusal Episodes of bingeing and purging of very high and/or escalating frequency Compensatory behaviors likely to result in acute and severe medical complications	Bingeing and/or vomiting multiple times per day resulting in social or occupational impairment and/or serious medical complications; inappropriate withholding of insulin
Other medical compromise	Abnormal vital signs reflecting nutritional compromise Severe medical complications	Severe hematemesis Severe neutropenia and/or thrombocytopenia Severe hypokalemia Uncontrolled type I diabetes Syncope
Psychiatric comorbidity and risk of self-harm	Substantial risk of self-harm or suicide Comorbid psychiatric illness resulting in safety risk or seriously undermining treatment Inability to adhere to treatment plan that will sustain minimal level of safety	Comorbid substance use escalating in the setting of treatment for the eating disorder
Treatment-related	Lack of clinically meaningful progress in an outpatient setting resulting in social or occupational impairment or medical risk Necessity of close supervision to maintain symptom control Previously agreed-on criterion for hospitalization based on patient history	An adolescent's low weight poses risk for decreased peak bone mass or short stature Sustained or persistent inability to eat without supervision or to abstain from intractable purging after food intake Reaching a threshold weight at which the patient repeatedly has rapidly deteriorated

[a] These criteria may be sufficient but do not necessarily need to be present to indicate inpatient care.
[b] Weight, vital signs, metabolic, and other parameters for hospitalization are best interpreted in the context of the patient's overall health, medical and psychiatric history, support systems, and engagement in treatment.
Stern TA et al: *Massachusetts General Hospital handbook of general hospital psychiatry,* ed 7, Philadelphia, 2018, Elsevier.

relationships, and having other healthy relationships with friends or therapists.
- A prolonged QT interval is a marker for risk of sudden death.

REFERRAL

Hospitalization should be considered in the following situations:
- Severe dehydration or electrolyte imbalance
- ECG abnormalities (prolonged QT interval, arrhythmias)
- Significant physiologic instability (hypotension, orthostatic changes)
- Intractable vomiting, purging, or bingeing
- Suicidal thoughts
- Weight loss exceeding 30% of ideal BW and unresponsiveness to outpatient treatment
- Rapidly progressing weight loss (>2 lb in a week)
- Failure to progress in nutritional rehabilitation in outpatient treatment

SUGGESTED READING

DerMarderosian D, Hall A: Early identification of eating disorders in primary care pediatrics, *Med Health R I* 94(7):197, 2011.

RELATED CONTENT

Anorexia Nervosa (Patient Information)
Binge Eating Disorder (Related Key Topic)
Bulimia Nervosa (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

BASIC INFORMATION

DEFINITION

Anorexia-cachexia is a complex metabolic syndrome associated with underlying malignancy and is characterized by loss of appetite and ongoing loss of skeletal muscle mass, with or without loss of fat mass that can be partially, but not entirely, reversed by conventional nutritional support.

SYNONYM

Cancer cachexia

ICD-10CM CODE
R64 Cachexia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Estimates of the prevalence of cancer cachexia vary widely due to variable diagnostic criteria used in prior studies. In one study of 405 patients, the incidence of cachexia ranged from 12% to 85% using different available definitions. In another study, more than half of 644 cancer patients were reported as having cachexia using anorexia and weight loss exceeding 5% of premorbid weight. The highest incidence is reported in patients with lung and gastrointestinal cancers.

ETIOLOGY

In cancer patients, anorexia is common and results in decreased oral intake and malnourishment. Cancer cachexia is characterized by an upregulation of muscle proteolysis and lipolysis due to an increased inflammatory response from cytokines (interleukins [IL-6 and IL-1] and tumor necrosis factor α [TNF- α)]. These cytokines activate the ubiquitin-proteasome pathway via nuclear factor kappa B, resulting in a protein degradation pathway in the myocytes. At the same time, protein synthesis is downregulated by the human myogenic differentiation protein, MyoD. Furthermore, the increased cytokine levels induce an overall hypermetabolic state and shift the balance toward catabolism.

GENETICS: In patients with elevated inflammatory markers, cachexia is associated with specific vitamin D receptor polymorphisms, thus representing a possible early clinical predictor phenomenon for the development of a more aggressive form. Polymorphisms resulting in an increase in levels of inflammatory cytokines, a decrease in lean or fat mass, and decreased survival in cancer are likely to be cachexia-prone variants. However, to date, no specific single nucleotide polymorphisms (SNPs) have been found in association with cancer cachectic patients.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Starvation
- Malabsorption
- Hyperthyroidism
- Anorexia nervosa
- Depression

WORKUP

Patients can be categorized into three consecutive stages of cancer cachexia (Fig. 1): Precachexia, cachexia, and refractory cachexia using available cachexia staging systems. Furthermore, there are five domains to assess including: Food intake, catabolic derangements, functional and psychosocial impact, and assessments of body composition including stores of adipose tissue and muscle mass. A diagnosis can be made in a patient with weight loss >5% in the absence of starvation, BMI <20 and 2% weight loss, or appendicular skeletal muscle index consistent with sarcopenia and >2% weight loss.

LABORATORY TESTS

- Complete blood count, complete chemistry panel including albumin and prealbumin
- Inflammatory markers including ESR and C-reactive protein
- Endocrine assessment with TSH, cortisol, ACTH, testosterone

IMAGING STUDIES

CT or MR imaging of the abdomen can be used to assess for sarcopenia by analyzing the body and muscle composition

TREATMENT

The mainstay of treatment is directed at aggressive nutritional and supportive therapy (Fig. 2). Functional causes of malabsorption or gastrointestinal obstruction should be evaluated at the start. It has been proposed that the *T.A.R.G.E.T.* approach, encompassing different domains, namely *Teaching, Awareness, Recognition, Genetics, Exercise/Early intervention* and *Treatment* of cancer cachexia, should be utilized in all patients.

NONPHARMACOLOGIC THERAPY

- The general approach is to increase caloric intake by encouraging frequent (up to 5 to 6 times), small, and calorie-dense meals during the day along with supplemental liquid nutrition typically utilized alongside consultation with nutritionists.
- Physical activity may attenuate the effects of cachexia by modulating muscle metabolism, insulin sensitivity, and inflammation. In particular, exercise has been shown to have antiinflammatory properties, preserve muscle mass and function, enhance protein synthesis, decrease protein catabolism, and contribute to a better muscle performance.

ACUTE GENERAL Rx

- Multimodal interventions should be scheduled in parallel with anticancer therapies and may consist of nutritional intervention and multitargeted pharmacologic therapies.
- Enteral nutrition should be started if undernutrition already exists or if food intake is markedly reduced for more than 1 to 2 wk. When enteral nutrition cannot be effectively used, parenteral nutrition may be considered instead as a supporting measure or as total nutritional requirement.
- Appetite stimulants are the mainstay of pharmacologic intervention in cancer cachexia. Glucocorticoids have been extensively studied in patients with advanced cancer and are known to stimulate the appetite. Prednisone (at 20 to 40 mg/day) or dexamethasone (at 2 to 4 mg/day) are used commonly, but major side effects include insulin resistance, immune suppression, muscle myopathy, and adrenal insufficiency.
- Megestrol acetate, an appetite stimulant with progestational and antigonadotropic effects, has been shown to slightly improve appetite and increase weight but does not improve lean body mass or quality of life. Major complications include increased risk for thromboembolism, adrenal insufficiency, and hypogonadism in male patients.
- Dronabinol, a constituent of cannabis, has been studied for appetite stimulation in cancer patients, but results from large studies have revealed no major benefit.
- The psychiatric drugs mirtazapine and olanzapine both are potential therapies for cancer patients with anorexia-cachexia syndrome. Mirtazapine-treated patients gain weight and develop an improved appetite in some cases. Olanzapine treatment of cancer patients with cachexia who were receiving active chemotherapy showed a trend toward improved weight and may be useful for patients on chemotherapy who have difficult-to-control nausea and weight loss.
- Treatment with the NSAID celecoxib has resulted in weight gain, increased BMI, and improved quality of life. NSAIDs are frequently incorporated into combination drug therapy for cancer cachexia along with megestrol. A recent systematic review identified four studies that reported some evidence for the therapeutic benefits of NSAIDs in terms of weight gain, survival, quality of life, and inflammatory markers, but evidence was lacking for widespread use of NSAIDs in clinical practice.
- Anamorelin, a novel ghrelin-receptor agonist, has been evaluated in two large randomized trials in patients with advanced non–small cell lung cancer and cachexia. Although the trial failed to meet the primary endpoint, anamorelin significantly increased lean body mass, but not handgrip strength in these patients, and can be considered as an option.

CHRONIC Rx

- Nutritional supplements such as amino acids (l-glutamine, l-arginine, l-carnitine) have been evaluated with inconclusive results.
- Omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), which are found in fish oil, have been also investigated with inconclusive results.

- Ongoing exercise and rehabilitation programs need to be offered to all patients.

REFERRAL

- Nutritionists and cachexia clinics (if available).
- Palliative care specialists.

PEARLS & CONSIDERATIONS

- Cancer cachexia is an underrecognized problem present in up to half of all advanced cancer patients. Up to 1 in 5 cancer patients can die directly due to the effects of cancer cachexia.
- Multimodal intervention in early identified precachexia patients may prove to be beneficial.

AUTHOR: **Ritesh Rathore, MD**

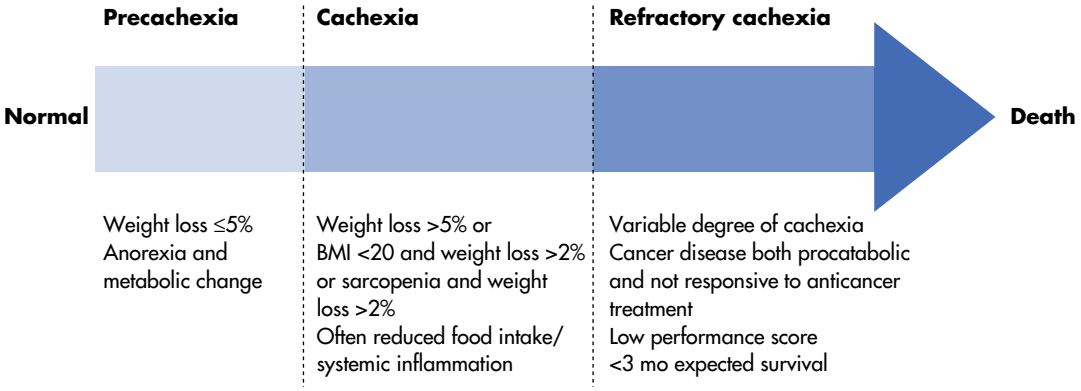

FIG. 1 Stages of anorexia-cachexia syndrome of malignancy. Cachexia represents a spectrum through which not all patients will progress. At present, there are no robust biomarkers to identify those precachectic patients who are likely to progress further or the rate at which they will do so. Refractory cachexia is defined essentially on the basis of the patient's clinical characteristics and circumstances. *BMI,* Body mass index. (From Fearon K et al: Definition and classification of cancer cachexia: an international consensus, *Lancet Oncol* 12(5):489-95, 2011.)

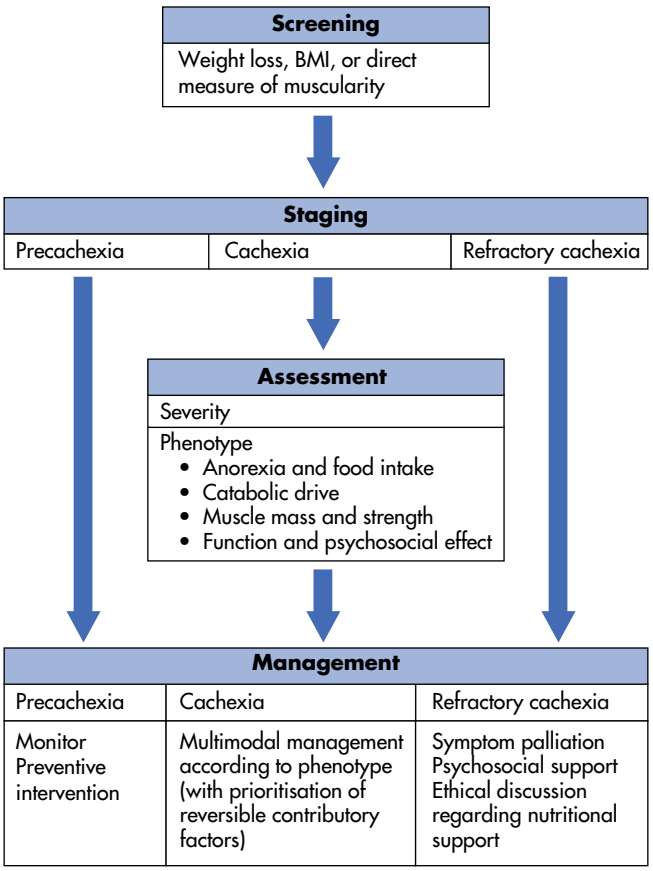

FIG. 2 Management of anorexia-cachexia syndrome of malignancy. Patients should be screened for cachexia, then undergo detailed assessment. All patients require optimum oncological and general medical management. Once patients with cachexia have been phenotyped, a detailed multimodal management plan (including nutrition, exercise, antiinflammatory strategies, and other adjuncts) can be established. *BMI,* Body mass index. (From Fearon K et al: Definition and classification of cancer cachexia: an international consensus, *Lancet Oncol* 12(5):489-95, 2011.)

SUGGESTED READINGS

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Zhou T et al: Development and validation of a clinically applicable score to classify cachexia stages in advanced cancer patients, *J Cachexia Sarcopenia Muscle* 9(2):306-314, 2018.

Anoxic Brain Injury

BASIC INFORMATION

DEFINITION

Anoxic brain injury occurs when a decrease in either blood flow or oxygen causes cerebral ischemia. The inadequate delivery of nutrients and oxygen to cerebral tissue commonly reflects defects in either cardiac circulation or respiratory function, or defects in both.

SYNONYMS

Hypoxic-ischemic injury
Anoxic encephalopathy
Cerebral hypoxia
Hypoxia of brain
Perinatal or intrapartum asphyxia (pediatric)

ICD-10CM CODE
G93.1 Anoxic brain damage, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:
- Variable based on diagnostic criteria.
- 424,000 out-of-hospital cardiac arrests per yr in the U.S.

PREVALENCE:
- Sequelae of anoxic brain injury may include vegetative state, which varies in prevalence from 40 to 168 per 1 million population, depending on definition used.
- Other sequelae may include death from either cardiac arrest or loss of whole-brain function (brain death) or progression to either minimally conscious state or dementia.
- Recovery is rare after 3 months of vegetative state, with life expectancy of 2 to 5 yr.

RISK FACTORS: Same as risk factors for cardiorespiratory arrest: age, race, hypertension, hyperlipidemia, tobacco use, drug or alcohol abuse, and physical inactivity.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Variable depending on degree of insult.
- Patient typically initially in coma and then may either recover awareness and wakefulness with variable degrees of cognitive or physical impairment, may progress to a vegetative state or a minimally conscious state, or may die due to cardiopulmonary arrest or loss of whole brain function (brain death).
- Coma: Eyes-closed state of both unconsciousness and unawareness with loss of sleep-wake cycles.
- Minimally conscious state: Altered state of awareness with normal sleep-wake cycles and intermittent interactivity with the environment; patient may intermittently follow simple commands and maintain visual tracking.
- Vegetative state (also known as unresponsive wakefulness): Altered state of awareness with normal sleep-wake cycles but with complete loss of both cognitive awareness and ability to interact with environment; persistent vegetative state is the term used for vegetative state after anoxic injury of between 1 and 3 months' duration, and permanent vegetative state is the term used for a vegetative state persisting beyond 3 months. A vegetative state due to traumatic brain injury is permanent only after 12 months.
- Brain death: Irreversible loss of both cortical and brainstem function manifesting as loss of awareness, cranial reflexes, and motor responses; brain death meets the legal criteria for death in U.S. jurisdictions. EEG is isoelectric; there is no intracerebral blood flow.

ETIOLOGY

- Ischemia (decreased cerebral perfusion): Myocardial infarction, hemorrhage, shock, high intracranial pressure
- Hypoxia (decreased oxygenation): Drowning, strangulation, aspiration, carbon monoxide poisoning
- Fig. E1 shows categories of mechanisms proposed to be involved in the evolution of secondary damage after severe traumatic brain injury in infants and children

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other causes of encephalopathy, including toxic, metabolic, infectious, or neoplastic causes; nonconvulsive status epilepticus; hypothermia
- Histotoxic hypoxia, the inability to utilize oxygen despite adequate delivery to cerebral tissue; i.e., cyanide poisoning

WORKUP

- Neurologic examination (coma examination) to ascertain level of encephalopathy
- Systemic evaluation for causes of cardiorespiratory failure
- Laboratory studies (listed in the following) to evaluate alternate causes of encephalopathy
- Imaging studies: MRI of brain or CT of head (if MRI cannot be obtained)

LABORATORY TESTS

Urine drug screen, serum metabolic profile, ammonia, complete blood count, coagulation panel, liver function test, arterial blood gas, blood alcohol panel, serum neuron-specific enolase (if available)

IMAGING STUDIES

- Imaging is usually not revealing within first 24 hr of an anoxic event
- Head CT without contrast (Fig. E2): Repeat 24 hr after anoxic event to evaluate for stroke, trauma, hemorrhage, or cerebral edema
- MRI of brain (Fig. E3): Obtain if head CT scan unrevealing; may show cortical necrosis and infarcts of the basal ganglia

OTHER STUDIES

- EEG: To assess for non-convulsive status epilepticus
- Somatosensory evoked potentials (SSEP; aka, N20 response): Obtain 24 to 72 hr after anoxic event

TREATMENT

NONPHARMACOLOGIC THERAPY

- Hypothermia: Evidence suggests that inducing hypothermia 32° C to 34° C (89.6° F to 93.2° F) for 24 hr following anoxic brain injury reduces metabolic demand and may improve prognosis for recovery. However, recent

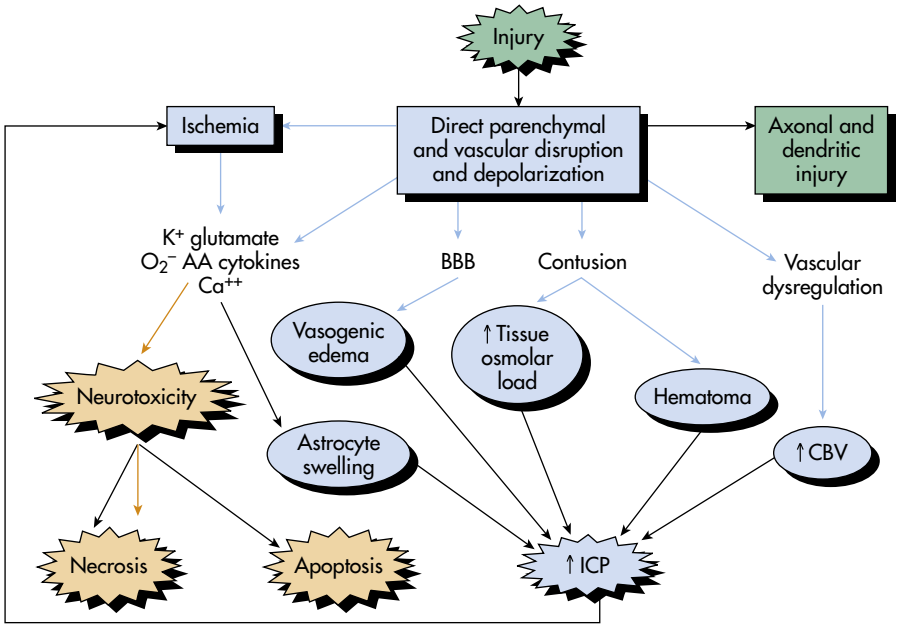


FIG. E1 Categories of mechanisms proposed to be involved in the evolution of secondary damage after severe traumatic brain injury in infants and children. Three major categories for these secondary mechanisms are (1) ischemia, excitotoxicity, energy failure, and cell death cascades; (2) cerebral swelling; and (3) axonal injury. *AA,* amino acid; *BBB,* blood-brain barrier; *CBV,* capillary blood volume; *ICP,* intracranial pressure. (From Fuhrman BP: *Pediatric critical care,* ed 4, St Louis, 2011, Mosby.)

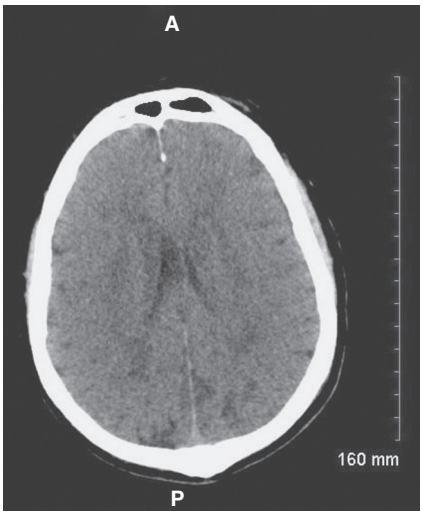


FIG. E2 Computed tomography without contrast of a patient 1 day after pulseless electrical activity showing diffuse sulci effacement and loss of gray-white matter differentiation indicating cerebral edema. Diffuse white and gray matter hypodensities are also present. The patient remained comatose and life support was eventually withdrawn.

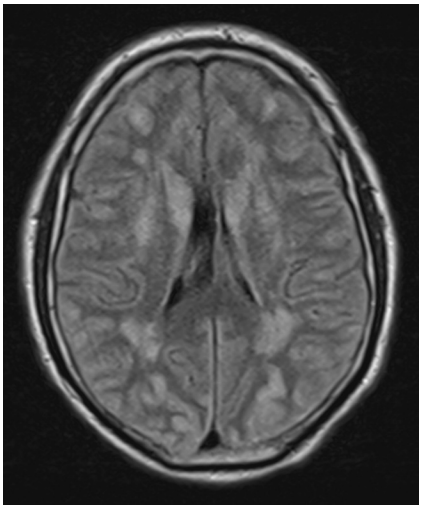


FIG. E3 Magnetic resonance image fluid-attenuated inversion recovery of a patient 1 day after pulseless electrical activity showing bilateral multiple cortical, subcortical, gray and white hyperintensities. The patient remained comatose and life support was eventually withdrawn.

meta-analysis suggests that the true risk-benefit of therapeutic hypothermia is unclear and is a topic of debate.
- Complications from hypothermia include bradycardia, hemodynamic instability, coagulopathy, infection, hyperglycemia, and hypokalemia.
- Contraindications for hypothermia: Active hemorrhage, hemodynamic instability, sepsis, or trauma.
- Indication for hypothermia: Patients who have been resuscitated from a cardiac arrest with VF/VT as the presenting rhythm.
- Hyperbaric oxygen is used in carbon monoxide poisoning.

ACUTE GENERAL Rx

- Supportive care: ABCs, secure airway, cardiopulmonary support in the critical care unit.
- Control seizures with antiepileptic medications (may need midazolam or propofol drip for severe, uncontrolled seizures).
- Treat myoclonus with clonazepam 8 to 12 mg daily in divided doses; levetiracetam and valproic acid may be used for myoclonic status epilepticus. Treatment of myoclonus due to cardiac arrest does not change neurologic prognosis.

CHRONIC Rx

- Maintain adequate nutrition, normothermia (if not utilizing therapeutic hypothermia) infection precautions; provide deep vein thrombosis and gastric ulceration prophylaxis
- Physical, occupational, and speech therapy as indicated per prognosis and patient ability
- May consider withdrawal of critical care and implementation of palliative care per prognosis, family consultation, and respect for autonomy and dignity of the patient

PROGNOSIS

- Out-of-hospital cardiopulmonary resuscitation (CPR) for cardiac arrest has a success rate of <10%.
- There is no standardized battery of testing to quantify anoxic injury and reliably predict outcomes.
- Anoxia time, duration of CPR, and cause of cardiac arrest are related to poor outcome after CPR but are not sufficient for prognosis.
- Strong predictors of poor outcome (evidence level A or B) (assuming patient did not undergo therapeutic hypothermia) are the following:
  1. Presentation with myoclonus status epilepticus within the first 24 hr following injury
  2. Absence of bilateral cortical SSEPs (N20 response) anytime
  3. Absent papillary or corneal reflexes, or absent or extensor motor responses after 72 hr following injury
  4. Serum neuron-specific enolase levels >33 μg/L 24 to 72 hr following injury
- Neuroimaging and EEG are sensitive but not specific predictors of outcome.
- Burst-suppression pattern or flat-line EEG carries bad prognosis, while reactive EEG to noxious stimuli predicts favorable outcome.
- The prognostic value of these findings and the timing of exam changes after therapeutic hypothermia. Timing should, at a minimum, be factored from the time the patient was fully rewarmed rather than from the time of initial cardiopulmonary arrest. The window for concluding poor prognosis based on examination after hypothermia may be extended further based on future studies. Furthermore, the reliability of NSE post-hypothermia has been called into question.

DISPOSITION

Varies per extent of insult from death to long-term care facility to acute rehabilitation to return to home

REFERRAL

Referral to a neurologist is appropriate for help with prognostication.

PEARLS & CONSIDERATIONS

COMMENTS

When assessing prognosis, use caution if patient is being treated with anesthetic agents or other depressants of consciousness, including anticonvulsants. Also, consider the impact of therapeutic hypothermia on the timing of prognostication. Thus serial neurologic exams are integral to best-practice care. When examining patients and determining prognosis, account for medications and illicit drugs that may depress consciousness and awareness as well as metabolic derangements that may affect the metabolism of pharmacologic agents or illicit drugs.

PREVENTION

CPR, risk factor modification, induced hypothermia

PATIENT & FAMILY EDUCATION

Consult with family members regularly and provide accurate assessment of prognosis.

SUGGESTED READINGS

Arrich J et al: Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation, *Cochrane Database Syst Rev* 15(2):CD004128, 2016.

AUTHORS: **Angad Jolly, PhD,** and **Joseph S. Kass, MD, JD, FAAN**

BASIC INFORMATION

DEFINITION

Anthrax is an acute infectious disease caused by the spore-forming bacterium *Bacillus anthracis.*

ICD-10CM CODES

A22.0	Cutaneous anthrax
A22.1	Pulmonary anthrax
A22.2	Gastrointestinal anthrax
A22.7	Anthrax sepsis

EPIDEMIOLOGY & DEMOGRAPHICS

- Anthrax most commonly occurs in hoofed animals and can only incidentally infect human beings who come in contact with infected animals or animal products. Between 20,000 and 100,000 cases of cutaneous anthrax occur worldwide annually. Twenty-three cases of anthrax were reported to the CDC from 1972 through 2000.
- Until the bioterrorism attack in 2001, most cases of anthrax occurred in industrial environments (contaminated raw materials used in manufacturing process) or in agriculture.
- There were 22 anthrax cases with five deaths (all inhalational) after a 2001 attack in which anthrax spores were sent through U.S. mail (Fig. E1).
- Traditionally, there are three major anthrax syndromes: cutaneous, inhalational, and gastrointestinal anthrax. A fourth type, injectional anthrax, was recognized after the 2009 to 2010 European outbreak from heroin-injecting drug users. This type of infection has not been reported in the United States.
- Direct person-to-person spread of anthrax is extremely unlikely, if it occurs at all; therefore, there is no need to immunize or treat contacts of persons ill with anthrax, such as household contacts, friends, or coworkers, unless they also were exposed to the same source of infection.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- **Inhalation anthrax** is the most lethal form. It begins with a brief prodrome resembling a viral respiratory illness without rhinorrhea. The incubation period may be as short as 1 day to 6 weeks. Host factors, dose of exposure, and chemoprophylaxis may affect the duration of the incubation period. A severe advanced phase of fever, shock, and respiratory distress follows the prodromal stage. Inhalational anthrax does not cause pneumonia but can progress to acute respiratory distress syndrome. Radiographic evidence of mediastinal widening and pleural and pericardial effusions can also occur. Mortality is higher when infection spreads to the meninges.
- **Cutaneous anthrax** (Fig. E2) is characterized by a skin lesion evolving from a papule, through a vesicular stage, to a depressed black eschar. The incubation period ranges from 1 to 12 days. The lesion is usually painless, but patients also may have fever, malaise, headache, and regional lymphadenopathy. The eschar dries and falls off in 1 to 2 wk with little scarring.
- **Gastrointestinal anthrax** usually follows eating raw or undercooked contaminated meat and can have an incubation period of 1 to 7 days. Disease presentation may be divided into two phases: oropharyngeal and lower gastrointestinal. Involvement of the pharynx is usually characterized by lesions at the base of the tongue, dysphagia, fever, and regional lymphadenopathy. Lower bowel inflammation typically causes nausea, loss of appetite, and fever followed by abdominal pain, hematemesis, and bloody diarrhea. Gastric ulcers may occur and may be associated with hematemesis.
- **Injectional anthrax** may have similar skin lesions present with IV drug users. These may progress rapidly with systemic dissemination. Unlike cutaneous anthrax, the injectional type is not associated with eschar formation on the skin.

ETIOLOGY

The disease is caused by *B. anthracis,* a gram-positive, spore-forming bacillus. It is aerobic, nonmotile, nonhemolytic on sheep's blood agar, and grows readily at a temperature of 37° C, forming large colonies with irregularly tapered outgrowths (a Medusa head appearance). In the host, it appears as single organisms or chains of two or three bacilli (Fig. E3).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Inhalation anthrax must be distinguished from influenza-like illness (ILI) and tularemia. Most cases of ILI are associated with nasal congestion and rhinorrhea, which are unusual in inhalation anthrax. Additional distinguishing factors are the usual absence of abnormal chest radiograph in ILI (see the following).

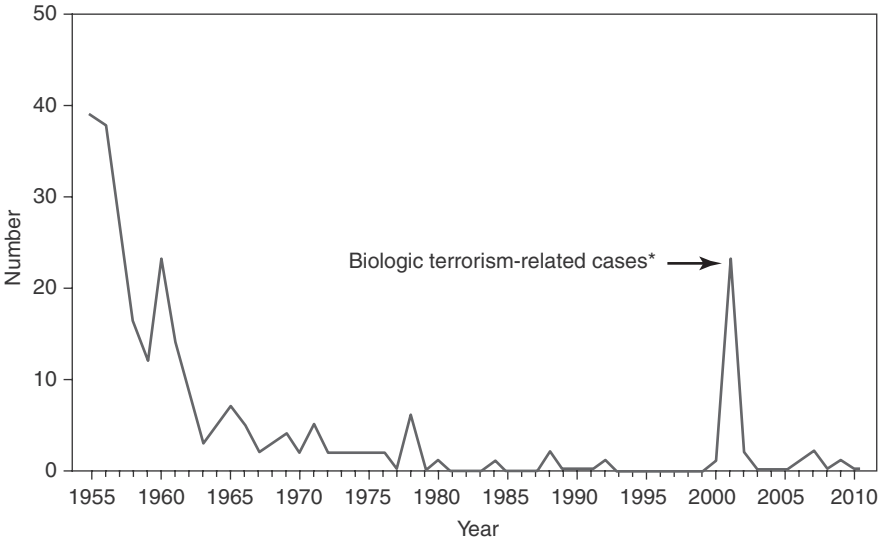


FIG. E1 Anthrax. Number of reported cases, by year—United States, 1955-2010. *One epizootic-associated cutaneous case was reported in 2001 from Texas. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59:1-111, 2012.)

FIG. E2 Cutaneous anthrax lesion on the skin of the forearm caused by the bacterium *Bacillus anthracis.* (From the Centers for Disease Control and Prevention Public Health Image Library. http://phil.cdc.gov/Phil/home.asp.)

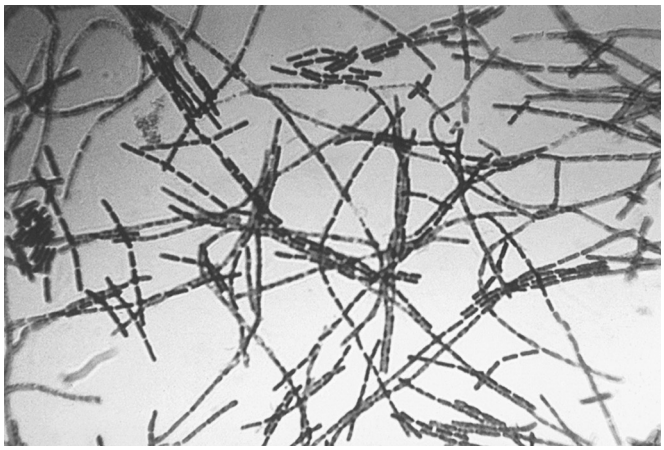


FIG. E3 A photomicrograph of *Bacillus anthracis* bacteria using gram stain technique. Anthrax is diagnosed by isolating *B. anthracis* from the blood, skin lesions, or respiratory secretions or by measuring specific antibodies in the blood of persons with suspected cases. (From the Centers for Disease Control and Prevention Public Health Image Library. http://phil.cdc.gov/Phil/home.asp.)

- Cutaneous anthrax should be distinguished from staphylococcal disease, ecthyma, ecthyma gangrenosum, plague, brown recluse spider bite, and tularemia.
- The differential diagnosis of gastrointestinal anthrax includes viral gastroenteritis, shigellosis, and yersiniosis.

LABORATORY TESTS

- Presumptive identification is based on Gram stain of material from skin lesion, cerebrospinal fluid (CSF), or blood showing encapsulated gram-positive bacilli.
- Confirmatory tests are performed at specialized laboratories. Virulent strains grow on nutrient agar in the presence of 5% CO_2. Susceptibility to lysis by gamma phage and direct fluorescent antibody (DFA) staining of cell-wall polysaccharide antigen are also useful confirmatory tests.
- Nasal swab culture to determine inhalation exposure is of limited diagnostic value. A negative result does not exclude the possibility of exposure. It may be used by public health officials to assist in epidemiologic investigations of exposed persons to evaluate the dispersion of spores.
- Serologic testing by enzyme-linked immunosorbent assay (ELISA) can confirm the diagnosis.
- A skin test (Anthracin test) that detects anthrax cell-mediated immunity is also available in specialized laboratories.
- Depending on disease severity, laboratory studies may also demonstrate hemoconcentration, elevated liver enzymes, anemia, thrombocytopenia, and coagulopathy.

IMAGING STUDIES

Chest radiographs usually reveal mediastinal widening. Additional findings include infiltrates and pleural effusion. An echocardiogram may reveal pericardial effusion.

Rx TREATMENT

NONPHARMACOLOGIC Rx

IV hydration and ventilator support may be necessary with inhalation anthrax.

ACUTE GENERAL Rx

- Uncomplicated cutaneous anthrax can be treated with an oral fluoroquinolone or doxycycline for 7 to 10 days. When inhalation of spores has occurred, the duration should be extended to 60 days.
- CDC recommendations (MMWR 64(4), 2015) for a clinical framework and medical countermeasure use during an anthrax mass-casualty incident are summarized in Figs. E4 through E6 and Boxes E1 through E3.
- If meningitis has not been ruled out, the IV antimicrobial regimen should include a fluoroquinolone plus a bactericidal with good CNS penetration (meropenem) plus a protein synthesis inhibitor (linezolid).
- If meningitis has been ruled out, a two-drug regimen that includes a fluoroquinolone plus linezolid or clindamycin is recommended. The addition of glucocorticoids should be in accordance with the bacterial meningitis protocol.
- Adjunct therapies for inhalation anthrax include the use of toxin-targeting monoclonal antibodies in combination with antibacterial drugs and prophylaxis. Raxibacumab and obiltoxaximab are currently available monoclonal antibodies from the Centers for Disease Control (CDC) and are not available for commercial sale. Drainage of toxin-laden fluids (pleural, pericardial effusions, and ascites) is also recommended.
- Initial postexposure prophylaxis therapy in adults is with ciprofloxacin, 500 mg PO bid, doxycycline 100 mg bid, or levofloxacin 500 mg daily. The total duration of treatment is 60 days. Administration of anthrax vaccine adsorbed (AVA), an inactivated cell-free filtrate of an avirulent strain available from the CDC in a series of three SC injections at 2-wk intervals, is also recommended for known or suspected inhalation exposure to anthrax in adults.
- A single dose of raxibacumab, a human monoclonal antibody directed against protective antigen, has been reported effective in animal studies with symptomatic inhalational anthrax. This can be used when no other option is available.

PROGNOSIS

- Case fatality estimates for inhalation anthrax are extremely high (>90%).
- During the 2001 bioterrorism attacks, the case fatality rate was lower at 45%. The decrease was linked to improvement in critical care management, drainage of effusions, and antimicrobial therapy.
- The case fatality rate for cutaneous anthrax when left untreated is less than 1%.
- The case fatality rate for gastrointestinal anthrax is estimated to be 25% to 60%.
- Even with treatment, the mortality rate for injectional anthrax is 34%.

REFERRAL

Consultation with an infectious disease specialist is recommended in all cases of anthrax. Local and state authorities should also be notified of suspected cases of anthrax.

PEARLS & CONSIDERATIONS

COMMENTS

- Postexposure prophylaxis: If the exposure to *B. anthracis* is confirmed and anthrax vaccine is available, three doses of the vaccine should be given at 0, 2, and 4 wk, and antibiotics should be continued throughout the 4-wk period. If vaccine is not available, antibiotics should be continued for 60 days.
- Preexposure vaccination is limited to groups at risk for repeated exposures to *B. anthracis* spores, such as bioterrorism level B laboratories and workers who will be making repeated entries into known *B. anthracis* spore-contaminated areas.
- The U.S. anthrax vaccine is an inactivated cell-free product licensed to be given in a six-dose series.

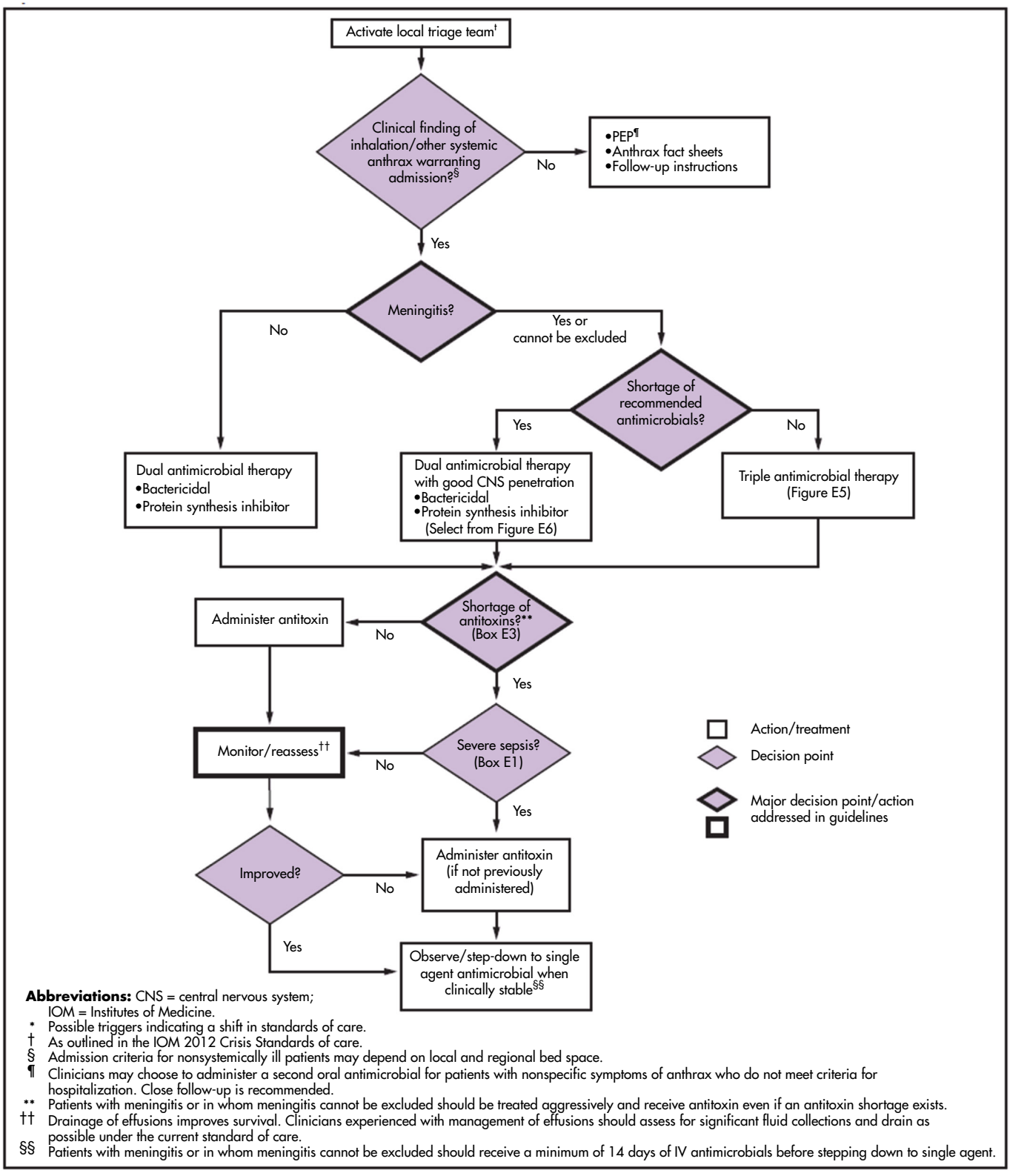
SUGGESTED READING

Adalja AA et al: Clinical management of potential bioterrorism-related conditions, *N Engl J Med* 372:954-962, 2015.

RELATED CONTENT

Anthrax (Patient Information)

AUTHOR: **Samaan Rafeq, MD**



Abbreviations: CNS = central nervous system; IOM = Institutes of Medicine.

* Possible triggers indicating a shift in standards of care.

† As outlined in the IOM 2012 Crisis Standards of care.

§ Admission criteria for nonsystemically ill patients may depend on local and regional bed space.

¶ Clinicians may choose to administer a second oral antimicrobial for patients with nonspecific symptoms of anthrax who do not meet criteria for hospitalization. Close follow-up is recommended.

** Patients with meningitis or in whom meningitis cannot be excluded should be treated aggressively and receive antitoxin even if an antitoxin shortage exists.

†† Drainage of effusions improves survival. Clinicians experienced with management of effusions should assess for significant fluid collections and drain as possible under the current standard of care.

§§ Patients with meningitis or in whom meningitis cannot be excluded should receive a minimum of 14 days of IV antimicrobials before stepping down to single agent.

FIG. E4 Crisis standards of care* framework for medical countermeasure prioritization among hospitalized persons with known or potential exposure to anthrax. (From Centers for Disease Control and Prevention: Clinical framework and medical countermeasure use during an anthrax mass-casualty incident, *MMWR* 64[RR04]:1-28, 2015.)

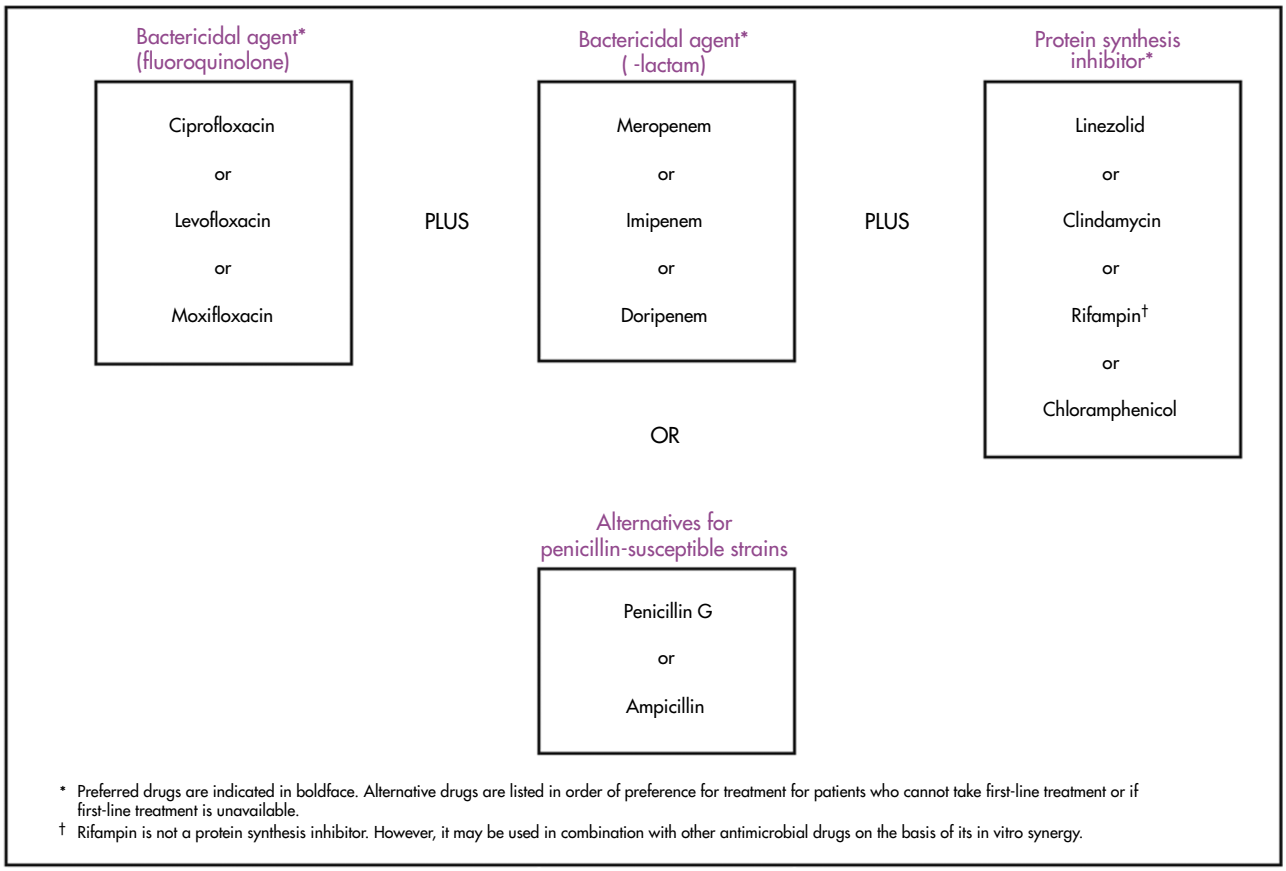


FIG. E5 Intravenous treatment for systemic anthrax with suspected, possible, or confirmed meningitis. (Adapted from Hendricks KA et al: Centers for Disease Control and Prevention expert panel meetings on prevention and treatment of anthrax in adults, *Emerg Infect Dis* 20[2], 2014. Available at https://doi.org/10.3201/eid2002.130687.)

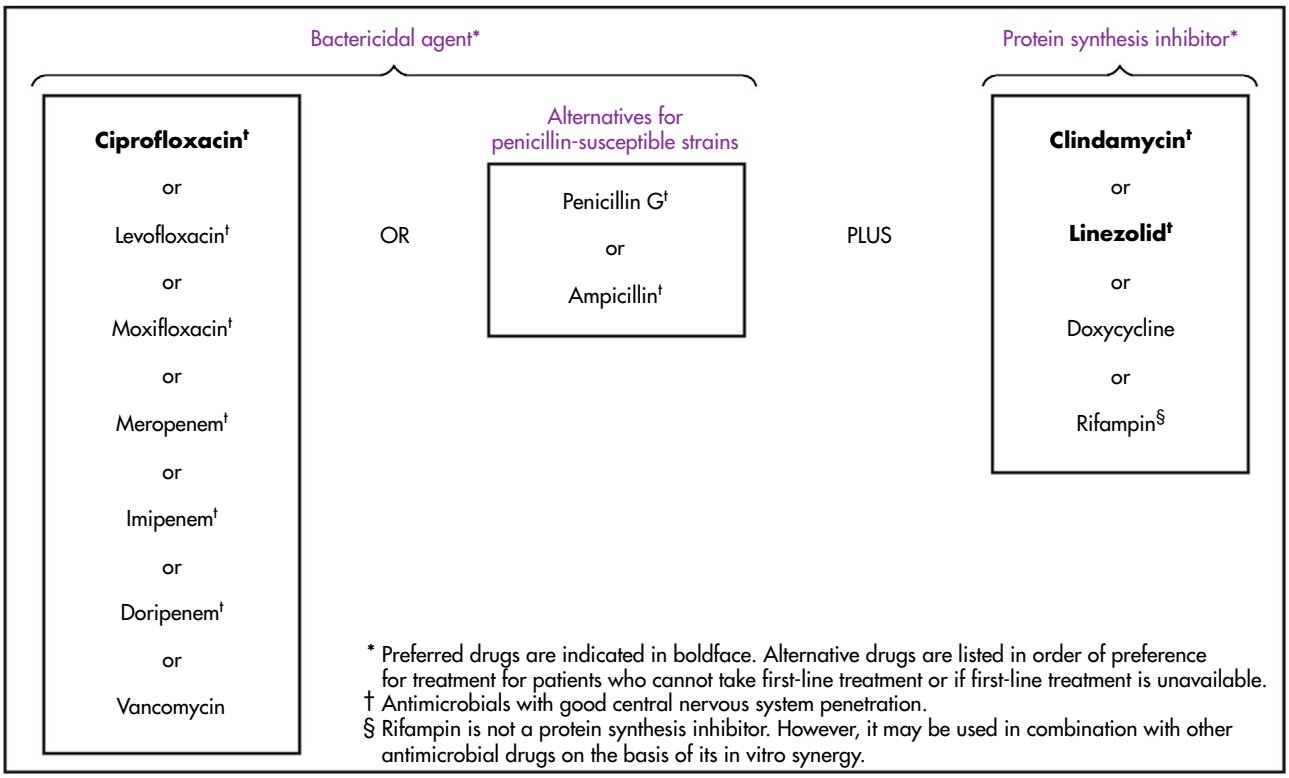


FIG. E6 Intravenous treatment for systemic anthrax when meningitis has been excluded. (Adapted from Hendricks KA et al: Centers for Disease Control and Prevention expert panel meetings on prevention and treatment of anthrax in adults, *Emerg Infect Dis* 20[2], 2014. Available at https://doi.org/10.3201/eid2002.130687.)

BOX E1 Diagnostic Criteria for Sepsis and Severe Sepsis*

Sepsis—documented or suspected infection plus one or more of the following:

General variables
- Fever (>38.3° C)
- Hypothermia (core temperature <36° C)
- Heart rate >90/min or >2 SD above normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (>20 ml/kg over 24 hr)
- Hyperglycemia (plasma glucose >140 mg/dl or 7.7 mmol/L) in the absence of diabetes

Inflammatory variables
- Leukocytosis (WBC count >12 × $10^3/\mu L$)
- Leukopenia (WBC count <4 × $10^3/\mu L$)
- Normal WBC count with greater than 10% immature forms
- Plasma C-reactive protein >2 SD above normal value
- Plasma procalcitonin >2 SD above normal value

Hemodynamic variables
- Arterial hypotension (SBP <90 mm Hg, MAP <70 mm Hg, or an SBP decrease >40 mm Hg in adults or <2 SD below normal value for age)

Organ dysfunction variables
- Arterial hypoxemia (PaO_2/FiO_2 <300)
- Acute oliguria (urine output <0.5 ml/kg/hr for at least 2 hours despite adequate fluid resuscitation)
- Creatinine increase >0.5 mg/dl or >44.2 μmol/L
- Coagulation abnormalities (INR >1.5 or aPTT >60 s)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count <100 × $10^3/\mu L$)
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or >70 μmol/L)

Tissue perfusion variables
- Hyperlactatemia (>1 mmol/L)
- Decreased capillary refill or mottling

Severe sepsis—documented or suspected infection resulting in tissue hypoperfusion or organ dysfunction documented by one or more of the following:
- Sepsis-induced hypotension
- Lactate above upper normal limits of laboratory
- Urine output <0.5 ml/kg/hr for >2 hours despite adequate fluid resuscitation
- Acute lung injury with $PaO2/FiO_2$ <250 in the absence of pneumonia as infection source
- Acute lung injury with $PaO2/FiO_2$ <200 in the presence of pneumonia as infection source
- Creatinine >2.0 mg/dl (176.8 μmol/L)
- Bilirubin >2 mg/dl (34.2 μmol/L)
- Platelet count <100 × $10^3/\mu L$
- Coagulopathy (international normalized ratio >1.5)

*Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyperthermia or hypothermia (rectal temperature >38.5° or <35° C), tachycardia (might be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.
aPTT, Activated partial thromboplastin time; *INR,* international normalized ratio; *MAP,* mean arterial pressure; *SBP,* systolic blood pressure; *SD,* standard deviation; *WBC,* white blood cell.
Adapted with permission from Dellinger RP et al: Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012, *Crit Care Med* 41:580-637, 2013; from Centers for Disease Control and Prevention: Clinical framework and medical countermeasure use during an anthrax mass-casualty incident, *MMWR* 64(RR04):1-28, 2015.

BOX E2 Parenteral Antimicrobial Choice for Treatment of Systemic Anthrax in Conventional, Contingency, and Crisis Standards of Care

Conventional setting
- Patients with probable, confirmed, or suspected meningitis should be treated with three recommended antimicrobials with good central nervous system penetration.
- Patients without evidence of meningitis should be treated with a minimum of one bactericidal agent plus one protein synthesis inhibitor.
- Parenteral combination treatment of systemic anthrax should be provided for at least 2 weeks or until the patient is clinically stable, whichever is longer; at that point, the patient may be transitioned to oral monotherapy for prophylaxis against ungerminated spores.

Contingency setting
- Same as conventional setting, except that alternatives to first-line antimicrobial treatment recommendations may be used.

Crisis setting
- If triple antimicrobial therapy is not available, patients with probable, confirmed, or suspected meningitis may be treated with two recommended antimicrobials (one bactericidal agent and one protein synthesis inhibitor, both with good central nervous system penetration).
- Patients without evidence of meningitis:
  1. Should be treated with a bactericidal antimicrobial combined with a protein synthesis inhibitor.
  2. Parenteral therapy may be stopped based on clinical judgment that the patient is clinically stable and improving; at that point, the patient may be transitioned to oral monotherapy for prophylaxis against ungerminated spores.
- Patients with confirmed or suspected meningitis are recommended to receive at least 14 days of antimicrobials and be clinically stable and improving, before considering transition to oral monotherapy for prophylaxis against ungerminated spores.

Centers for Disease Control and Prevention: Clinical framework and medical countermeasure use during an anthrax mass-casualty incident, *MMWR* 64(RR04):1-28, 2015.

BOX E3 Antitoxin Prioritization for Treatment of Systemic Anthrax in Conventional, Contingency, and Crisis Standards of Care

Conventional setting

- An antitoxin should be added to the combination antimicrobial treatment for patients for whom there is a high level of clinical suspicion for systemic anthrax.

Contingency setting

- Patients for whom there is a high level of clinical suspicion of systemic anthrax, with clinical symptoms or signs consistent with any of the general or inflammatory sepsis variables and in whom severe sepsis has not been diagnosed, should receive:
  1. Combination parenteral antimicrobial therapy.
  2. Short-term reevaluation and observation is recommended.
  3. Based on the clinical judgment of the local triage team, an antitoxin may be added to the antimicrobial regimen for patients who do not display rapid clinical improvement or who demonstrate any signs or symptoms of clinical deterioration.
- Patients for whom there is a high level of clinical suspicion for systemic anthrax, with clinical signs or symptoms consistent with severe sepsis or septic shock with a reasonable expectation of survival based on clinical judgment of the local triage team, should receive combination parenteral antimicrobial therapy plus antitoxin without delay.
- Patients with probable, confirmed, or suspected meningitis should receive combination parenteral antimicrobial therapy plus antitoxin without delay.
- Mechanisms should be in place to capture critical care and organ dysfunction measurements among septic anthrax patients, including measurements included in the sequential organ failure assessment (SOFA) score and other objective scoring systems.
- Disease-specific prognostic indicators should be defined based on real-time data and may inform and augment decisions of the local triage team regarding resource allocation.

Crisis setting

- Same as contingency setting.

Centers for Disease Control and Prevention: Clinical framework and medical countermeasure use during an anthrax mass-casualty incident, *MMWR* 64(RR04):1-28, 2015.

Antibody-Mediated Autoimmune Encephalitis

BASIC INFORMATION

DEFINITION

Antibody-mediated autoimmune encephalitis is a neurologic disease causing a spectrum of deficits, including subacute memory loss, changes in cognition, and depressed level of consciousness. Antibodies directed against membrane receptors and ion channel-associated proteins expressed on the surface of neurons in the central nervous system are responsible for these clinical manifestations.

SYNONYMS

Antibody-mediated encephalitis
Autoimmune encephalitis
Autoimmune encephalopathy
Anti-NMDAR encephalitis
Voltage-gated potassium channel antibody syndromes

CD-10CM CODE
G04.81 Other encephalitis and encephalomyelitis

EPIDEMIOLMOGY & DEMOGRAPHICS

INCIDENCE: It is difficult to estimate incidence as testing for encephalitis is relatively new. The most common form is anti-N-methyl-D-asparate receptor (anti-NMDAR) encephalitis. The incidence of anti-NMDAR encephalitis is 0.85 per million children annually. No data about incidence in adults is available.
PEAK INCIDENCE: It is difficult to estimate incidence because testing for these diseases is relatively new. The estimated annual incidence of all types of encephalitis is approximately five to eight cases per 100,000 persons. In nearly 50% of the cases the cause cannot be established.
PREVALENCE: It is difficult to estimate prevalence as testing for disease is relatively new.
PREDOMINANT AGE AND SEX: Anti-NMDAR predominantly affects young women, with a median age at presentation of 21 to 23 yr.
GENETICS: There are no known genetic risk factors for developing autoimmune encephalitis.
RISK FACTORS:

- Prior episode of autoimmune encephalitis, especially if not treated with immunotherapy.
- Tumors (particularly ovarian) have been associated with autoimmune encephalitis.
- Prior episode of herpes simplex virus encephalitis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typically presents with subacute (days to a few weeks) deficits of memory and cognition often followed by suppressed level of consciousness. If untreated, patients can progress to coma.
- Psychiatric manifestations are common early in the course of autoimmune encephalitis. These may include psychosis, panic attacks, aggression, inappropriate sexual behaviors, compulsive behaviors, euphoria, or fear, among many others.
- Physical examination can show neuromyotonia, hyperekplexia, psychosis, or dystonia.

ETIOLOGY

One category includes antibodies directed to intracellular antigens, such as anti-Hu. These disorders are strongly associated with cancer and involve T-cell responses targeting neurons. These disorders have a poor prognosis secondary to irreversible neuronal killing. Another category involves autoantibodies to extracellular epitopes of ion channels, receptors, and other associated proteins, such as the NMDA receptor. Cancer-associated autoimmune encephalitis tends to be variable but portends a less severe prognosis due to reversible neuronal damage.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infectious encephalitis (especially viral)
- Metabolic encephalopathy
- Wernicke encephalitis
- Neuroleptic malignant syndrome
- Serotonin syndrome
- Lymphoma
- Carcinomatous meningitis

WORKUP

Diagnostic testing to exclude other causes of encephalitis, including infectious and other autoimmune causes, should occur.

LABORATORY TESTS

Autoantibody testing is important for the diagnosis of autoimmune encephalitis. Tests for autoantibodies to NMDAR, LGI1, Caspr2, AMPAR (GluR1, GluR2 subunits), and GABA-B-R are available. These antibody tests are most sensitive and specific with CSF. CSF findings of leukocyte count, total protein, and the presence of oligoclonal bands (OCBs) can drastically differ among subtypes of autoimmune encephalitis. Serum testing may offer a low false-positive rate and a higher false-negative rate.

IMAGING STUDIES

Brain MRI in patients with NMDAR, AMPAR, LGI1, Caspr2, and GABA-B antibodies may be normal or show increased T2 signal, especially in the medial temporal lobes. Testing with MRI and EEG may also be helpful for excluding other causes.

TREATMENT

NONPHARMACOLOGIC THERAPY

Supportive care, including nutrition, is crucial in these patients.

ACUTE GENERAL Rx

Treatment for suspected autoimmune encephalitis is often begun empirically prior to specific antibody test results. This may include IVIG, plasmapheresis, and/or steroids. IVIG may be given early as it is less likely to worsen infectious encephalitis. If the patient does not respond in 2 wk or is critically ill, second-line therapies (rituximab or cyclophosphamide) should be considered.

CHRONIC Rx

No current chronic suppression is recommended for antibody-mediated autoimmune encephalitis, but relapse can occur and tends to follow a similar clinical course to the initial attack.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

No complementary or alternative medicine is known.

DISPOSITION

Patients require hospitalization during treatment but are often discharged home after resolution of disease process.

REFERRAL

Neurology and rheumatology evaluation may be beneficial to help exclude other causes of encephalitis.

PEARLS & CONSIDERATIONS

COMMENTS

Autoantibody tests may be used to diagnose or exclude particular causes, but these tests are complex, and not every positive result is definite evidence of an autoimmune disorder.

PREVENTION

Cancer screening should be completed for high-risk patients, as tumors can be associated with antibody-mediated autoimmune encephalitis. Known associations are HuD proteins in small cell lung cancer and NMDARs in ovarian teratoma.

PATIENT/FAMILY EDUCATION

The Autoimmune Encephalitis Alliance (https://aealliance.org/) is a resource that can be used by patients and their family for further information and support.

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SUGGESTED READINGS

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Stingl C et al: An update on the treatment of pediatric autoimmune encephalitis, *Curr Treat Options Rheum* 4(1):14-28, 2018 Mar.

BASIC INFORMATION

DEFINITION

Antiphospholipid antibody syndrome (APS), the most common acquired thrombophilia, is characterized by clinical features of arterial or venous thrombosis and/or pregnancy morbidity *and* the persistence of at least one type of antiphospholipid autoantibody (aPL). aPLs are antibodies directed against anionic phospholipids and phospholipid-binding protein cofactors. These autoantibodies lead to stimulation of procoagulant factors and inhibition of the fibrinolytic system. MTOR pathway upregulation, toll-like receptor signaling, and activation of vascular endothelium, monocytes, neutrophils, platelets, complement, pro-inflammatory cytokines, and various coagulation and fibrinolytic pathway targets have all been shown to play a role in this process.

Three types of aPLs have been characterized:

- Anticardiolipin antibodies (detected in approximately 23% to 44% of patients)
- Lupus anticoagulants (detected in approximately 34% of patients)
- Anti-β2-glycoprotein-I antibodies (detected in approximately 20% of patients)

APS can be primary or secondary to a rheumatic disease, with the most common being systemic lupus erythematosus (SLE). APS can affect all organ systems and includes venous and arterial thrombosis, recurrent fetal losses, and cytopenias, including thrombocytopenia and microangiopathic hemolytic anemia.

SYNONYM

Antiphospholipid syndrome

ICD-10CM CODE
D68.61 Antiphospholipid syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- Up to 5% of healthy individuals without a history of thrombosis have positive aPLs.
- Approximately 10% of patients with a deep venous thrombosis have aPLs.
- Nearly 20% of women under 50 who have a cerebrovascular accident (CVA) test positive for aPLs.
- 10% to 15% of women with recurrent miscarriages have aPLs.
- aPLs without APS can be seen in patients with certain medications, infections, malignancies, and autoimmune conditions.

PREDOMINANT AGE: Young to middle-aged adults

RISK FACTORS:

- Underlying SLE and collagen-vascular diseases; other autoimmune disorders, including rheumatoid arthritis, Sjögren syndrome, Behçet syndrome, primary immune thrombocytopenia (also known as idiopathic thrombocytopenic purpura), AIDS.
- Most individuals are otherwise healthy and have no underlying medical condition.
- Thrombotic risk is increased by the presence of other etiologies of systemic hypercoagulability, including oral contraceptives, pregnancy, smoking, prolonged immobilization, genetic thrombophilia, malignancy, and hyperlipidemia.

PROGNOSIS:

- 91% survival at 10 yr
- 71% success rate in pregnancy with recommended therapies; prematurity and intrauterine growth restriction are common complications

GENETICS: Some APS-positive families exist, and human leukocyte antigen (HLA) studies have suggested associations with HLA DR7, DR4, and Dqw7+Drw53.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

No pathognomonic findings on examination; Table 1 summarizes other features suggesting the presence of antiphospholipid antibodies, including abnormal findings consistent with ischemia or infarction.

- Thrombosis (Fig. E1):
  1. Patients with APS are at risk for both venous and arterial thromboses. Venous thromboses are more common, occurring as the initial manifestation of APS in approximately 30% of APS patients. Of all patients with deep venous thrombosis, approximately 10% have aPL. The most common site for deep vein thrombosis is the calf, but thromboses may also occur in the renal, hepatic, axillary, subclavian, vena cava, and retinal veins. The most common site of arterial thrombosis is the cerebral vessels, followed by the coronary, renal, mesenteric, and bypass arteries. Recurrent thrombosis is common with APS.
- Commonly involved organ systems include:
  1. Central nervous system: Stroke, transient ischemic attack, migraine, multi-infarct dementia, epilepsy, movement disorders, transverse myelopathy, retinal venous or arterial occlusion.
  2. Pulmonary: Pulmonary embolism and infarction, pulmonary hypertension, acute respiratory distress syndrome, diffuse alveolar hemorrhage.
  3. Cardiology: Libman-Sacks endocarditis, intracardiac thrombosis, coronary artery disease, myocardial infarction, valvulopathy, left ventricular diastolic dysfunction.
  4. Gastrointestinal: Abdominal pain, gastrointestinal bleed secondary to ischemia, splenic or pancreatic infarction, hepatic vein thrombosis, Budd-Chiari syndrome.
  5. Renal: Hypertension, renal infarct, renal artery or vein thrombosis, acute renal failure, glomerular damage including membranous nephropathy, minimal change disease, and pauci-immune glomerulonephritis.
  6. Hematology: Thrombocytopenia, hemolytic anemia.
  7. Endocrine: Addison disease secondary to adrenal hemorrhage and, less frequently, thrombosis.
  8. Cutaneous: Livedo reticularis, cutaneous necrosis, skin ulcerations, phlegmasia cerulea dolens, gangrene of digits (Fig. E2).
  9. Obstetric: Recurrent spontaneous abortion, premature delivery, or fetal growth restriction.
- **Catastrophic APS** (CAPS) (Table 2): CAPS is a rapidly progressive multi-organ thrombotic disease. Approximately 1% of APS is CAPS; approximately 45% of CAPS do not present as APS initially. CAPS is associated with a high mortality rate (50%). To make the diagnosis of catastrophic APS, four criteria must be satisfied:
  1. Evidence of involvement of three or more organs, systems, and/or tissues. The most common symptoms are abdominal pain, dyspnea, neurologic symptoms, chest pain, and skin rash.
  2. Development of manifestations simultaneously or in ≤1 wk.
  3. Confirmation by histopathology of small-vessel occlusion in at least one organ or tissue.
  4. Laboratory confirmation of the presence of aPL.

TABLE 1 Other Features Suggesting the Presence of Antiphospholipid Antibodies

Clinical
Livedo reticularis
Thrombocytopenia (usually 50,000-100,000 platelets/mm^3)
Autoimmune hemolytic anemia
Cardiac valve disease (vegetations or thickening)
Multiple sclerosis–like syndrome, chorea, or other myelopathy

From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, WB Saunders.

ETIOLOGY

- Endothelial cells are activated by aPLs causing upregulation of adhesion and procoagulant molecules such as tissue factor and von Willebrand factor.
- Table 3 and Box 2 summarize proposed pathogenic mechanisms of antiphospholipid syndrome. Mechanisms of pregnancy loss in antiphospholipid syndrome are summarized in Box 3.
- Monocyte activation by aPLs yields expression of inflammatory cytokines and additional tissue factor, contributing to the procoagulant state.
- Neutrophil activation by aPLs via complement is proposed to cause the release of neutrophil extracellular traps leading to increased thrombin.
- aPL binding to glycoprotein 1b and ApoE receptor 2 causes platelet activation and increased platelet adhesion.
- aPL binding decreases activation of antithrombin and protein C, while also reducing the ability of activated protein C to inactivate coagulation factors V and VIII.

TABLE 2 Differential Diagnosis of Catastrophic Antiphospholipid Syndrome (CAPS)

Laboratory Abnormalities	CAPS	TTP	DIC
Microangiopathic hemolytic anemia	–	+	+
Thrombocytopenia	+	+	+
Fibrinogen/FDP	Normal/Normal	Normal/Increased	Decreased/Increased
Anticardiolipin antibody	+	–	–
Lupus anticoagulant	+	–	–

DIC, Disseminated intravascular coagulation; *FDP,* fibrin degradation products; *TTP,* time to progression.

TABLE 3 Proposed Pathogenic Mechanisms of Antiphospholipid Syndrome

I. aPL-mediated promotion of tissue factor expression
  A. Direct injury and subsequent anti-β2 GPI binding on endothelial cells
  B. Signaling via annexin A2/TLR4/apoER2 inducing proadhesive prothrombotic phenotype
  C. Induction of adhesion molecules and tissue factor on endothelial cells and cytokine release

II. Activation of platelets and monocytes by aPL antibodies
  A. Activation of platelets via apoER2′, GPIbα, and/or β2 GPI-platelet factor 4 interaction
  B. Interference of β2 GPI in regulating vWF-mediated platelet adhesion
  C. Activation of monocytes results in increased tissue factor, VEGF, cytokine expression
  D. Activation of monocytes causes mitochondrial dysfunction and oxidative stress

III. Inhibition of endogenous anticoagulant and fibrinolytic mechanisms
  A. Disruption of the annexin A5 anticoagulant shield
  B. Interference with fibrinolysis via annexin A2, β2 GPI cofactor activity, autoactivation of XIIa, direct inhibition of plasmin and increase of PAI-1
  C. Inhibition of the protein C pathway: Decreased activation of protein C, barrier of APC proteolysis of factor Va and VIIIa, prevention of protein C and EPCR binding
  D. Interference with tissue factor pathway inhibitor

IV. aPL-mediated activation of complement
  A. Antibodies against β2 GP–HLA-DR7 complexes on cell surfaces trigger complement-mediated cytotoxicity

V. Direct activation of trophoblasts and endometrial cells by aPL antibodies
  A. Abnormal trophoblast proliferation, migration and invasiveness, increased trophoblast apoptosis, and reduced secretion of HCG and adhesion molecules
  B. Disruption in the differentiation of decidual endometrial cells
  C. Disruption of maternal spiral artery transformation and maturation

VI. Other mechanisms
  A. mTORC pathway–mediated vasculopathy
  B. Release in procoagulant microparticles by endothelial cells and platelets

APC, Activated protein C; aPL, antiphospholipid; apoER2, apolipoprotein E receptor 2; EPCR, endothelial cell protein C receptor; β2 *GPI,* β2-glycoprotein I; *HCG,* human chorionic gonadotropin; *HLA,* human leukocyte antigen; *mTORC,* mammalian target of rapamycin complex; *PAI-1,* plasminogen activator inhibitor 1; *TLR,* Toll-like receptor; *VEGF,* vascular endothelial growth factor; *vWF,* von Willebrand factor.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

- aPL binding to annexin A2 (tissue plasminogen activator receptor) contributes to the prothrombotic state seen in APS.
- The mammalian target of rapamycin complex (mTORC) has been shown to be involved in endothelial activation and in regulating expression of tissue factor and IL-8 in monocytes.
- Toll-like receptors 4 and 7 and triggering of the innate immune system are involved in endothelial activation and the development of the prothrombotic state.
- Autoantibodies against other antigens, such as phosphatidylserine, phosphatidyl ethanolamine, and other complexes have been identified in APS patients, but their clinical significance has yet to be elucidated.

DX DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other hypercoagulable states (inherited or acquired):

- Inherited: ATIII, protein C and protein S deficiencies, factor V Leiden, prothrombin gene mutation
- Acquired: Heparin-induced thrombocytopenia, myeloproliferative syndromes, malignancy
- Alternate causes of recurrent pregnancy loss should also be considered (e.g., anatomic or chromosomal abnormalities)

WORKUP

Diagnostic criteria of APS include at least one clinical criterion and at least one laboratory criterion.

- Clinical (Box 1):
  1. Venous, arterial, or small vessel thrombosis *or*
  2. Morbidity with pregnancy, defined as:
     a. Unexplained fetal death at ≥10 wks' gestation *or*
     b. ≥1 premature births before 34 wks' gestation secondary to eclampsia, preeclampsia, or severe placental insufficiency *or*
     c. ≥3 unexplained spontaneous abortions before 10 wks' gestation.
- Laboratory (see Table 4):
  1. Lupus anticoagulant present in plasma on two or more occasions at least 12 wk apart, *or*
  2. Anticardiolipin antibody, IgG or IgM present in serum or plasma at >40 MPL, GPL, or >99th percentile on two or more occasions at least 12 wk apart, *or*
  3. Anti-β2-glycoprotein-I antibodies present in serum or plasma at >99th percentile on two or more occasions at least 12 wk apart
- Screening tests:
  1. Partial thromboplastin time (PTT): Elevated, activated partial thromboplastin time prolongation indicating either the presence of a clotting factor deficiency, or the presence of an inhibitor such as a lupus anticoagulant.
  2. Mixing study: Elevated. Normal plasma is incubated with the patient's plasma. In cases of clotting factor deficiencies, the PTT will correct. If an inhibitor is present as in the case with APS, the PTT will not correct.
  3. Dilute Russell viper venom time: Elevated. Laboratory clotting requires the addition of phospholipids and calcium to plasma samples. Antiphospholipid antibodies bind the phospholipids in the test tube, thereby preventing clot formation. The addition of Russell viper venom to plasma results in immediate activation of Factor X (common pathway). Therefore, it will not be prolonged in intrinsic or extrinsic factor deficiencies but will be prolonged in the presence of an antiphospholipid antibody.
  4. The Lupus Anticoagulant screen is the addition of Russell viper venom to plasma. In the Lupus Anticoagulant confirmatory testing, massive doses of phospholipids are added to saturate the antiphospholipid antibody, thereby correcting the prolonged PTT.
- Initial testing for presence of aPL:
  1. Anticardiolipin (aCL) ELISA antibodies (IgG or IgM), *or*
  2. Lupus anticoagulant activity found, *or*
  3. Anti-beta2-glycoprotein (anti-β2GPI) ELISA antibodies (IgG or IgM).
- Confirmatory aPL testing (Table 5): Repeat testing after 12 wk is required to confirm the persistence of a positive aCL, anti-β2GPI, or LA test because transient aPL elevations can occur.

LABORATORY TESTS

Diagnostic evaluation of aPLs is indicated in:

- Patient with underlying SLE or collagen-vascular disease with thrombosis.
- Patient with recurrent, familial, or juvenile deep vein thrombosis (DVT) or thrombosis in an unusual location (mesenteric or cerebral).

BOX 1 Preliminary Criteria for Classification of Antiphospholipid Syndrome

Clinical criteria

Vascular thrombosis

One or more clinical events of arterial, venous, or small-vessel thrombosis in any tissue or organ. Thrombosis must be confirmed by Doppler ultrasonography, other imaging, or histopathologic analysis, with the exception of superficial venous thrombosis. The histopathologic study does not have to demonstrate significant evidence of inflammation of the blood vessel.

Pregnancy morbidity

- One or more unexplained deaths of morphologically normal fetuses at 10 or more wk of gestation, with a normal fetal morphology confirmed by ultrasound or direct examination of the fetus.
- One or more premature births of a morphologically normal newborn at 34 wk of gestation or before caused by
  - Severe preeclampsia or eclampsia defined according to current standards, or
  - Recognized placental insufficiency
- Three or more consecutive spontaneous abortions without explanation before 10 wk of gestation, excluding those associated with hormonal or anatomic alterations in the mother or chromosomal alterations inherited from either parent.

Laboratory criteria

The presence of at least one of the following test results:

- Lupus anticoagulant in the plasma on two or more separate occasions within a period of 12 wk, detected according to the guidelines of the International Society of Thrombosis and Haemostasis (Scientific Subcommittee on lupus anticoagulant/phospholipid-dependent antibodies).
- IgG or IgM anticardiolipin antibodies in plasma or serum in medium-high titers (more than 40 GPL or MPL units, respectively) on two or more separate occasions within a period of 12 wk, as measured by standardized ELISA.
- IgG or IgM anti–β_2-glycoprotein I antibodies in the serum or plasma (in titer above the 99th percentile) on two or more separate occasions within a period of 12 wk, as measured by standardized ELISA according to recommended procedures.

ELISA, Enzyme-linked immunosorbent assay; *Ig,* immunoglobulin.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE 4 Assays Used to Confirm Diagnosis of Antiphospholipid Syndrome

Assay	Methodology
"Criteria" aPL Assays	
aCL	ELISA
Anti-β2-GPI	ELISA
LAC	Clotting/functional assays
"Noncriteria" aPL Assays	
Assays to detect antibodies to other phospholipids (i.e., phosphatidylserine, phosphatidylinositol, phosphatidic acid, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylcholine)	ELISA
Annexin A5 resistance assay	Clotting/mechanistic assay
Assays to detect antibodies to prothrombin or prothrombin/phosphatidylserine	ELISA
Assays to detect antibodies to clotting proteins (i.e., protein C, protein S)	ELISA

aCL, Anticardiolipin; *aPL,* antiphospholipid antibody; *ELISA,* enzyme-linked immunosorbent assay; *β2 GPI,* β2 -glycoprotein I; *LAC,* lupus anticoagulant.
From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

- One or more unexplained thrombotic events. Do not test those at low risk, e.g., elderly patients with other thrombotic risk factors.
- One or more specific pregnancy events.
- Unexplained thrombocytopenia or microangiopathic hemolytic anemia.
- Patients with an unexplained elevation in PTT, or less commonly, in PT/INR.

Rx TREATMENT

ACUTE Rx

- Initial anticoagulation with heparin or low-molecular-weight heparin (LMWH), before transitioning to a vitamin K antagonist (VKA) such as warfarin, is recommended. DOACs are not recommended due to recent studies which have shown increased risk of recurrent thromboembolism, particularly in patients with high-risk APS (positivity for all three antiphospholipid antibodies) for patients on rivaroxaban compared to warfarin.
- Standard intensity (INR 2.0 to 3.0) anticoagulation with warfarin is preferred in venous thrombosis, as prior randomized trials failed to show a decrease in recurrent thromboses with high-intensity anticoagulation (INR 3.0 to 4.0). Task-force reports have not reached a consensus regarding intensity of anticoagulation in secondary thromboprophylaxis of arterial events.
- Unfractionated heparin (UFH) is preferred if quick reversibility is needed.

PRIMARY PREVENTION

- Although other cardiovascular risk factors, such as hypertension and hyperlipidemia, should be controlled, aspirin use for primary prevention remains controversial.
- Adding low-dose warfarin to aspirin for primary prevention seems to confer no benefit.
- Hydroxychloroquine may be useful in those patients with SLE and aPL; it has been shown to reduce the incidence of thrombotic complications in this population.
- Modifiable risk factors for thrombosis, such as smoking and immobility, should also be addressed when possible.
- For pregnant women with a positive test for aPL antibodies without a history of DVT or pregnancy morbidity, decision to treat with low-dose subcutaneous UFH or LMWH and/or low-dose aspirin, or to manage with surveillance should be made on an individual basis as there is no clear consensus data.

SECONDARY PREVENTION

- For men and nonpregnant women, long-term anticoagulation with warfarin, or with UFH or LMWH if warfarin is contraindicated, should be used.
- Modifiable risk factors for thrombosis should be reduced when possible.
- For pregnant women with previously diagnosed APS:
  1. Warfarin should be discontinued before pregnancy due to its teratogenic effects.
  2. For women with APS without prior thrombosis but with pregnancy morbidities of either unexplained fetal death at ≥10 wks' gestation or ≥3 unexplained spontaneous abortions before 10 wks' gestation, aspirin 81 mg in combination with subcutaneous UFH or LMWH is recommended to improve pregnancy outcomes.
  3. For women with APS without prior thrombosis but with pregnancy morbidity of ≥1 premature births before 34 wks' gestation secondary to eclampsia, preeclampsia, or severe placental insufficiency, aspirin 81 mg is recommended to improve pregnancy outcomes.

TABLE 5 Current Assays Used to Confirm the Diagnosis of Antiphospholipid Syndrome

Assay	Method
Criteria aPL assays	
Anticardiolipin	ELISA
Anti–β_2-glycoprotein I	ELISA
Lupus anticoagulant	Clotting or functional assays
Noncriteria aPL assays	
Assays to detect antibodies to other phospholipids (e.g., phosphatidylserine, phosphatidylinositol, phosphatidic acid, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylcholine)	ELISA
Annexin A5 resistance assay	Clotting or mechanistic assay
Assays to detect antibodies to prothrombin or prothrombin/phosphatidylserine	ELISA
Assays to detect antibodies to clotting proteins (e.g., protein C, protein S)	ELISA

aPL, Antiphospholipid antibody; *ELISA,* enzyme-linked immunosorbent assay.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

4. For pregnant women with APS and prior thrombosis, aspirin in combination with subcutaneous UFH or LMWH should be used.
5. Pregnant patients taking LMWH should be transitioned to unfractionated heparin before delivery for ease of reversibility.
6. Hypertension and hyperlipidemia, if present, should be controlled.

FOR CATASTROPHIC ANTIPHOSPHOLIPID ANTIBODY SYNDROME (CAPS)

- The combination of anticoagulation with heparin products, high-dose corticosteroids, and supportive care, including debriding necrotic tissue and treating underlying infections is the mainstay of therapy.
- Patients may be transitioned to oral anticoagulation with warfarin once clinically stable.
- Plasma exchange with or without IVIG has been shown to improve mortality; however, the decision to use IVIG should be made on an individual basis (e.g., avoid in patients in whom anticoagulation has been discontinued).
- Eculizumab (monoclonal antibody against complement protein C5) and rituximab (monoclonal antibody against CD20) have been used successfully in refractory cases.
- Immunosuppressant therapy with cyclophosphamide should be considered in patients with CAPS and SLE as it has been demonstrated to decrease mortality in this group.

CHRONIC Rx

- Anticoagulation with VKAs, such as warfarin, remains the standard of care. The potential role of new oral anticoagulants in APS remains uncertain. Trials involving rivaroxaban did not show non-inferiority to dose adjusted VKAs for thrombotic APS, and in fact showed a non-statistically significant near doubling of the risk for recurrent thrombosis.[1]
- Duration of treatment is unknown and should be determined on an individual basis. However, in the absence of any contraindication to anticoagulation, indefinite therapy is recommended, as the lifelong recurrence rate reached nearly 30% in some studies.
- Immunosuppressive agents such as corticosteroids and cyclophosphamide have not been shown to be effective for chronic treatment of APS.
- Limited data suggest that hydroxychloroquine may be effective in patients with APS and SLE, although efficacy in primary APS remains unproven.
- Recurrent thrombosis can occur even in the setting of "therapeutic" anticoagulation, and multiple assays have been studied to monitor the adequacy of anticoagulation in APS.
- In cases of recurrent thrombosis, hydroxychloroquine and statins (antiinflammatory and antithrombotic activity) may be considered as adjuvant therapies.
- Table 6 summarizes alternative therapies for antiphospholipid syndrome.

[1]Ordi-Ros J et al: Rivaroxaban versus vitamin K antagonist in antiphospholipid syndrome: a randomized noninferiority trial, *Ann Intern Med* 171(10):685-694, 2019.

DISPOSITION

- APS patients have a 20% to 70% risk for recurrent thrombosis. Positivity in more than one aPL assay is associated with increased thrombotic risk.
- Initial arterial thrombosis tends to be followed by arterial events, and initial venous thrombosis tends to be followed by venous events.
- Incidence of developing catastrophic APS is approximately 1.0% among APS patients.

REFERRAL

Referrals to hematology, rheumatology, and/or obstetric medicine should be placed when diagnosis is made.

PEARLS & CONSIDERATIONS

COMMENTS

- Cerebral features of SLE may be more related to thrombosis than inflammation and may respond better to anticoagulants than immunosuppression.
- False-positive lupus anticoagulant (LAC) tests have been reported in patients taking direct oral anticoagulants and heparin. For this reason, thrombophilia testing should be delayed until 2 to 4 wk after completion of anticoagulation.

PREVENTION

Prophylaxis for asymptomatic patients with positive aPL tests without previous thrombosis:

- No routine prophylaxis is recommended.
- Questionable whether low-dose aspirin is effective.
- Antithrombotic prophylaxis for major surgery, prolonged immobilization, and pregnancy is appropriate.
- Avoid combination oral contraceptive pills in women with positive aPL tests.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Antiphospholipid Antibody Syndrome (Patient Information)
Deep Vein Thrombosis (Related Key Topic)
Hypercoagulable State (Related Key Topic)
Pulmonary Embolism (Related Key Topic)

AUTHORS: **Jozal Waroich, MD,** and **John L. Reagan, MD**

TABLE 6 Alternative Therapies for Antiphospholipid Syndrome

Treatment	Target effect (in vitro and/or animal studies)	Results of human studies
Hydroxychloroquine	aPL-induced platelet activation Inhibition of aPL-mediated thrombosis in mice Protection of aPL-induced displacement of annexin A5 from phospholipin bilayers	Decreases thrombotic risk in SLE Increases survival in SLE Protective against thrombosis in aPL+ individuals Decreases aPL and/or LAC in SLE patients
Statins	Reversal of aPL-induced endothelial cell activation and TF upregulation Abrogation of enhanced thrombus formation in mice	Decrease proinflammatory and prothrombotic markers in APS Contraindicated in pregnancy
Rituximab	Blocking of B-cell activating factor, which can prevent disease onset in APS mouse model	Effective for aPL-related cytopenias Effective for catastrophic APS Increases response in APS (off-label use) RITAPS trial: Effective for some noncriteria manifestations of APS
Potential immunomodulatory approaches	Anticomplement peptides Inhibition of TF Inhibition of nuclear factor κB Inhibition of p38 MAPK Inhibition of TLR-4 Inhibition of TNF-α, or IL-6 Inhibition of apo ER2 Inhibition of mTORC Peptides mimicking domains of β_2-GPI or β_2-GPI receptor blockers Other biologics (Belimumab, Abatacept)	Experimental studies (MBB2: A single-chain fragment variable recognizing β_2-GP1) No human data
Experimental Tx	Autologous hematopoietic stem cell transplantation	Limited data; appears to be effective and safe in APS patients

aPL, Antiphospholipid antibody; *APS,* antiphospholipid syndrome; *β_2-GPI,* β_2-glycoprotein I; *IL-6,* interleukin-6; *LAC,* lupus anticoagulant; *MAPK,* mitogen-activated protein kinase; *mTORC,* mammalian target of rapamycin complex; *RITAPS,* rituximab in antiphospholipid syndrome; *SLE,* systemic lupus erythematosus; *TF,* tissue factor; *TLR,* Toll-like receptor; *TNF,* tumor necrosis factor.
Modified from Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

BOX 2 Mechanisms of Thrombosis in Antiphospholipid Syndrome

- Interaction between antiphospholipid antibodies and cells (endothelial cells, monocytes, platelets)
- Activation of cell signaling pathways
- Transcription of procoagulant factors (tissue factor) and adhesion molecules
- Complement activation
- Impaired nitric oxide production
- Antiphospholipid antibody inactivation of fibrinolysis
- Heightened release and decreased degradation of NETs

NET, Neutrophil extracellular trap.

BOX 3 Mechanisms of Pregnancy Loss in Antiphospholipid Syndrome

- Intraplacental thrombosis
- Impaired trophoblastic invasion and hormone production
- Activation of the complement system
- Defective placentation due to interference of anti–β_2-GPI with trophoblast growth and differentiation
- Displacement of annexin A5 by IgG antiphospholipid antibody–β_2-GPI complexes

β_2-GPI, β_2-Glycoprotein I; *Ig,* immunoglobulin.

SUGGESTED READINGS

Andrade D et al: 15th International Congress on Antiphospholipid Antibodies Task Force on Antiphospholipid Syndrome treatment trends report. In Erkan D, Lockshin MD, editors: *Antiphospholipid Syndrome*, New York, Springer, pp 317-338, 2017.

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Kearon C et al: Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism, *Blood* 131:2151-2160, 2018.

Pengo V et al: Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome, *Blood* 132:1365-1371, 2018.

Tektonidou M et al: EULAR recommendations for the management of antiphospholipid syndrome in adults, *Ann Rheum Dis* 78:1296-1304, 2019.

FIG. E1 Cutaneous thrombosis in antiphospholipid antibody syndrome. (From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, WB Saunders.)

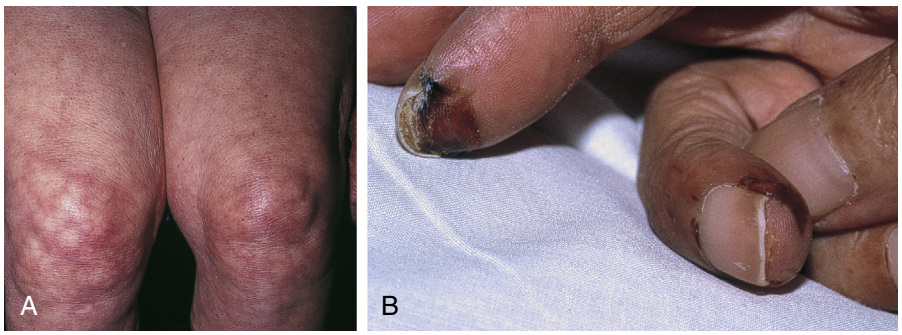

FIG. E2 Antiphospholipid syndrome. The clinical presentations of this disorder are protean and include those shown here. **A,** Broad bands of livedo around the knees in a patient with anticardiolipin antibodies. Physiologic livedo has a finer patterning and less obvious lesions. **B,** Digital infarcts, a nonspecific feature of several vascular occlusion disorders. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

Anxiety (Generalized Anxiety Disorder) PTG

BASIC INFORMATION

DEFINITION

Generalized anxiety disorder (GAD) is most likely to present in combination with other psychiatric and medical conditions. Individuals with GAD commonly present with excessive and disproportionately high levels of anxiety, fear, or worry for most days over at least a 6-mo period in a number of areas. The worrying must be greater than would be expected given the situation, and it must cause significant interference in functioning. The subjective anxiety must be accompanied by at least three somatic symptoms in adults and one in children (e.g., restlessness, irritability, sleep disturbance, muscle tension, difficulty concentrating, or fatigue). GAD cannot be diagnosed if it occurs only in the context of an active mood disorder, such as depression, or if the anxiety is better explained by another active anxiety disorder, such as PTSD or panic disorder.

SYNONYMS

Anxiety neurosis (former name for a subset of anxiety disorders)
Chronic anxiety
GAD

ICD-10CM CODE
F41.1 Generalized anxiety disorder300.02

DSM-5 CODE
300.02

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 6% to 9% per yr in adult primary care clinics; 1-yr incident rate per 100 persons/yr of 1.12

PEAK INCIDENCE: Peak incidence tends to occur later relative to other anxiety disorders, such as phobias; cumulative incidence of 4.3% by age 34 in a German community sample.

PREVALENCE (IN U.S.): In general population: Lifetime morbid risk of 9%; 12-month prevalence of 2.9%; lifetime prevalence in the National Comorbidity Survey-Replication was 5.7%.

- In primary care setting: 3% (the most common anxiety disorder in this setting)

PREDOMINANT SEX: Women are more frequently affected (2:1 ratio) but may present for treatment less often (3:2 female:male).

PREDOMINANT AGE:

- 30% report onset before age 11
- 50% have onset before age 18
- Median age of onset: 30 yr

GENETICS: Concordance rates in dizygotic twins and monozygotic twins are not different (0% to 5%)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Report of being "anxious" all of their lives
- Excessive worry, usually regarding family, finances, work, or health
- Sleep disturbance, particularly early insomnia
- Muscle tension (typically in the muscles of neck and shoulders) or headache
- Difficulty concentrating
- Daytime fatigue
- Gastrointestinal symptoms compatible with irritable bowel syndrome (one third of patients)
- Physical symptoms are the usual reason for seeking medical attention
- Comorbid psychiatric illness (e.g., dysthymia or major depression) and substance abuse (e.g., alcohol abuse) are frequent

ETIOLOGY

- Hypotheses include models based on neurotransmitters (catecholamines, indolamines) and developmental psychology (e.g., behavioral inhibition, neuroticism, and harm avoidance)
- Prevalence increased with a family history, increase in stress, history of physical or emotional trauma, and medical illness

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Wide range of psychiatric and medical conditions:
  1. Cardiovascular and pulmonary disease, such as cardiac arrhythmias or COPD
  2. Hyperthyroidism, hypoglycemia
  3. Substance abuse (e.g., cocaine, amphetamines, and PCP) or withdrawal (e.g., alcohol or benzodiazepines)
  4. Other anxiety disorders (e.g., social anxiety disorder), mood disorder
  5. Intrusive thoughts in obsessive-compulsive disorder or illness anxiety disorder

WORKUP

- Screening tests may enhance detection. A screening tool often used in primary care is the GAD-2. It asks, "During the past month, have you been bothered a lot by: (1) Nerves or feeling anxious or on edge? (2) Worrying about a lot of different things?" The response to each question is given a score of 0 (not at all), 1 (several days), 2 (more than half of the days), 3 (nearly every day). A score of ≥3 has a sensitivity of 86% and a specificity of 83% for detecting GAD. A simple 7-item in-office case finding instrument, the GAD-7, includes additional questions to assess symptom severity and can be used to monitor symptoms.
- Physical examination: Additional laboratory and radiologic workup depending on presenting symptoms.
- Iatrogenic cause should be suspected if anxiety follows recent changes in medication.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral therapy
- Acceptance and commitment therapy
- Relaxation training and meditative approaches
- Biofeedback
- Psychodynamic psychotherapy

PHARMACOLOGIC THERAPY

- Selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Azapirones (e.g., buspirone)
- Benzodiazepines (less favored)

ACUTE GENERAL Rx

- Acute treatment is rarely indicated because GAD is a chronic condition.
- If patients are in acute distress, the possibility of another cause, including another anxiety disorder such as panic disorder, should be considered.
- Caution in prescribing benzodiazepines because of the propensity for misuse and dependence. If used, the patient should be educated about the options and the risks.

CHRONIC Rx

- SSRIs and SNRIs (e.g., venlafaxine and duloxetine) are effective typical first-line treatment. Particularly useful if comorbid depression present.
- Buspirone can be effective with minimal potential for tolerance or abuse. May be less effective in patients with previous benzodiazepine exposure and may require a high-dose titration.
- Benzodiazepines can be effective under close supervision; however, they have fallen out of favor as a first-line treatment given their potential for functional impairment, abuse, and dependence.
- Sedating antidepressants, such as mirtazapine, may also be useful for initial insomnia secondary to anxious ruminations.

DISPOSITION

- GAD is chronic with periodic exacerbations.
- Treatment is given to reduce level of symptoms and improve functioning. Suicide risk is higher than in the general population.

REFERRAL

- For refractory symptoms
- For comorbid psychiatric conditions

PEARLS & CONSIDERATIONS

Since GAD is a risk factor for major depression, screening and early intervention for GAD (especially in women) may sometimes be helpful in reducing vulnerability to a mood disorder later in life.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Anxiety (Patient Information)
Panic Disorder, with or without Agoraphobia (Related Key Topic)
Social Anxiety Disorder (Related Key Topic)

AUTHOR: **Kristy L. Dalrymple, PhD**

SUGGESTED READINGS

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Aortic Coarctation

BASIC INFORMATION

DEFINITION

Coarctation of the aorta is a narrowing of the aorta that occurs near the ligamentum arteriosum just distal to the origin of the left subclavian artery. It causes an outflow obstruction proximal to the site of the stenosis, which leads to left ventricular pressure overload, hypertrophy, and potentially heart failure. The stenosis can be discrete or long and may have collateral vessels. It is commonly associated with other cardiac abnormalities such as a bicuspid aortic valve, patent ductus arteriosus, or ventricular septal defect.

SYNONYMS

Postductal coarctation of the aorta
Preductal coarctation of the aorta
Congenital hypoplasia of aortic arch
Coarctation of the aorta

ICD-10CM CODE
Q25.1 Aortic coarctation

EPIDEMIOLOGY & DEMOGRAPHICS

Aortic coarctation has a prevalence of approximately 4 per 10,000 live births and accounts for 4% to 6% of all congenital heart defects. It affects predominantly males, with a male to female ratio of 1.5:1.

GENETICS: Although most cases are sporadic and no specific genetic mutations have been identified, there have been case reports of coarctation occurring in families. Its association with a number of other conditions, such as Williams-Beuren and Sturge-Weber syndromes, also suggests a genetic predisposition. Most notably, up to 30% of patients with Turner syndrome also have coarctation of the aorta, and 5% to 15% of girls with coarctation have Turner syndrome.

RISK FACTORS: The cause for aortic coarctation among most patients is unknown. Genetic mutation and environmental causes are possibilities. It also can be acquired through inflammatory conditions such as Takayasu arteritis or severe atherosclerosis.

CLINICAL PRESENTATION & PHYSICAL FINDINGS

- Clinical presentation:
  1. The clinical manifestations of coarctation of the aorta depend on the age of discovery, severity of the aortic narrowing, and adequacy of collateral circulation.
  2. Neonates with severe coarctation may present with heart failure and/or shock when the ductus arteriosus closes. Neonates without severe aortic coarctation or with a persistent patent ductus arteriosus may be asymptomatic. Heart failure rarely occurs beyond the neonatal period.
  3. Beyond infancy, most patients are asymptomatic. Symptoms arise from severe hypertension, which may lead to epistaxis, headache, heart failure symptoms, or aortic dissection. Claudication of the lower extremities may also occur with physical exertion.
- Physical exam findings:
  1. "Brachial-femoral" delay characterized by diminished or delayed femoral pulses compared to the brachial pulses
  2. Upper extremity systolic hypertension
  3. Low or unobtainable blood pressure in the lower extremities
  4. Systolic ejection murmur at the left upper sternal border and left subscapular region
  5. A continuous murmur heard best posteriorly over the thoracic spine may be heard if there are large collaterals
  6. Systolic murmurs may be heard if there are coexisting cardiac defects (i.e., systolic ejection murmur with bicuspid aortic valve)

ETIOLOGY

- The exact pathogenesis is unknown. The two main theories for potential mechanisms are reduced antegrade intrauterine flow leading to underdevelopment of the fetal aortic arch and abnormal extension of tissue from the ductus arteriosus into the wall of the fetal thoracic aorta.
- In aortic coarctation, the arterial wall of the aorta has several pathologic abnormalities. There are cystic medial necrosis, increased stiffness and less distensibility, and increased collagen and less smooth muscle mass in the prestenotic segment.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hypoplastic left heart syndrome
- Interrupted aortic arch
- Pseudocoarctation
- Left ventricular outflow tract obstruction, including subaortic and supravalvular aortic stenosis
- Prior surgical ligation
- Critical aortic valve stenosis
- Obstructive peripheral arterial disease
- Aortic dissection

WORKUP

- Bilateral arm and leg blood pressures should be measured to search for a differential pressure.
- For patients with suspected aortic coarctation, the physical exam should include simultaneous palpation of the brachial and femoral pulses to assess for "brachial-femoral delay," which is characteristic of significant aortic coarctation.
- An electrocardiogram may show left ventricular hypertrophy, ST-T wave abnormalities, and RV conduction delay.
- Transthoracic echocardiogram, including suprasternal notch acoustic windows, should be performed.
- Every patient with coarctation should have at least one cardiovascular MRI or CT scan for a complete evaluation of the thoracic aorta and intracranial vessels.
- Cardiac catheterization is indicated when associated coronary artery disease is suspected or for therapeutic intervention of the coarctation.

LABORATORY TESTS

No specific laboratory tests are needed for coarctation of the aorta.

IMAGING STUDIES

- Box E1 summarizes important findings in the imaging evaluation of coarctation of the aorta. Anomalies associated with aortic coarctation are described in Box E2.
- Chest x-ray (Fig. E1):
  1. Posterior rib notching of ribs 3 to 8 is due to bony erosion by large collateral arteries.
  2. The "3" sign is formed by indentation of the aortic wall at the site of the coarctation with pre- and postcoarctation dilation.
- Echocardiography:
  1. Generally, echocardiography can establish the diagnosis and severity of coarctation of the aorta, but it is less useful for postoperative patients or for adult patients who may have less favorable acoustic windows compared with children.
  2. Aortic narrowing is visualized in the suprasternal notch view.
  3. Color flow imaging and pulsed Doppler localize the area of coarctation.
  4. Continuous wave Doppler estimates the severity of coarctation. The presence of collaterals may diminish the gradient across the coarctation; the gradient may be less severe than expected for the degree of the obstruction.
  5. Associated cardiac defects, chamber sizes, and left ventricular function can be evaluated.
- Magnetic resonance imaging and computed tomography:
  1. Per the ACC/AHA adult congenital heart disease guidelines, every adult patient with coarctation should have at least one cardiovascular MRI (Fig. E2, Fig. E3) or CT (Fig. E4) or a complete evaluation of the thoracic aorta.
  2. The modalities have very high diagnostic accuracy (>95%) in detecting coarctation of the aorta and its associated abnormalities.
  3. Both provide a large field of view and allow simultaneous visualization of the ascending aorta, aortic arch, descending aorta, aortic valve, and collaterals.
  4. CT and MRI are indicated for serial follow up imaging after surgical repair to assess for aortic dilatation or aneurysm formation.
  5. MRI is preferred to CT to decrease the lifetime exposure to radiation.
- Cardiac catheterization:
  1. Cardiac catheterization (Fig. E5) may be used to assess the peak gradient across the coarctation but is usually performed in conjunction with a therapeutic intervention (balloon angioplasty or stent placement).

TREATMENT

ACUTE GENERAL Rx

- Infants with critical coarctation are at risk for heart failure and death once the ductus arteriosus closes. Treatments include:
  1. Continuous intravenous infusion of prostaglandin E1 to keep the ductus arteriosus patent

BOX E1 Imaging Evaluation of Coarctation of the Aorta

Patency of the Ductus Arteriosus
Closed
Patent
Flow from aorta to pulmonary artery (typically postductal coarctation)
Flow from pulmonary artery to aorta (preductal coarctation or pulmonary hypertension)

Collateral Pathways
Scarce (typical of patients under 2 yr of age)
Abundant
Bridging the coarctated segment
Internal mammary to intercostal to distal aorta
Circumscapular pathways to distal aorta

Other Arch Anomalies and Stenoses
Arch interruption
Double aortic arch with stenosis in either or both arches
Coarctation proximal to left subclavian artery
Takayasu aortitis, rubella, Williams syndrome, neurofibromatosis, mucopolysaccharidosis, and other causes of stenoses not in the aortic isthmus

Subclavian Artery Anomalies
Atresia or stenosis of the left subclavian artery
Aberrant retroesophageal right subclavian artery
Proximal to the coarctation
Distal to the coarctation
Origin of both subclavian arteries distal to the coarctation

Associated Lesions
Cardiac, such as ventricular septal defect or bicuspid aortic valve
Aneurysms:
In aorta adjacent to coarctation
In the ductus
In the intercostal arteries
In the circle of Willis

Boxt LM, Abbara S: *Cardiac imaging: the requisites,* ed 4, Philadelphia, 2016, Elsevier.

BOX E2 Anomalies Associated with Aortic Coarctation

Common
Bicuspid aortic valve with stenosis and regurgitation
Patent ductus arteriosus
Ventricular septal defects
Turner syndrome

Rare:
Transposition of the great arteries
Double-outlet right ventricle
Shone syndrome (parachute mitral valve, supramitral ring, aortic valve stenosis, and aortic coarctation)

Boxt LM, Abbara S: *Cardiac imaging: the requisites,* ed 4, Philadelphia, 2016, Elsevier.

2. Dopamine and/or dobutamine to increase contractility for those with heart failure
3. Surgical repair once the patient is stabilized

CHRONIC Rx

- Systemic hypertension should be treated with angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, or beta-blockers.
- All patients with aortic coarctation should have long-term follow up with a congenital heart disease specialist.
- After repair, a CT or MRI of the repair site should be obtained at 1 yr postoperatively and then every 5 yr or less depending on anatomy to detect long-term complications.

NONPHARMACOLOGIC THERAPY

Aortic coarctation can be repaired surgically or percutaneously by balloon angioplasty and/or stent placement. The choice of intervention is made on an individual basis based on aortic morphology and should be determined by a multidisciplinary team including cardiologists, interventionalists, and cardiac surgeons who are experienced in treating patients with congenital heart disease.

- Repair should be performed in infancy or early childhood to prevent the common complications of unrepaired coarctation, including systemic hypertension, accelerated coronary artery disease, stroke, heart failure, and aortic dissection.
- The indications for intervention according to the ACC/AHA guidelines for the management of adults with congenital heart disease are:
  1. Peak-to-peak coarctation gradient ≥20 mm Hg (Level of evidence C).
  2. Peak-to-peak coarctation gradient <20 mm Hg in the presence of anatomic imaging evidence of significant coarctation (≥50% stenosis) with radiologic evidence of significant collateral flow (Level of evidence C).
- Surgery:
  1. Options include resection of coarctation and end-to-end anastomosis, a bypass graft across the area of coarctation, subclavian flap aortoplasty in long-segment coarctation, and prosthetic patch aortoplasty.
  2. Surgery compared with balloon angioplasty has been shown to be equally effective in reducing the peak systolic pressure gradient early after intervention.
  3. Surgery is indicated in the presence of a long re-coarctation segment, aortic aneurysm or pseudoaneurysm, or aortic arch hypoplasia.
- Balloon angioplasty and/or stent placement:
  1. Balloon angioplasty is the preferred intervention for patients with recurrent, discrete stenosis.
  2. Stent placement is not recommended in children <25 kg due to potential vascular complications from the large sheath size and the need for repeated interventions to expand the stent as they grow.
  3. Potential complications of percutaneous intervention include immediate residual pressure gradients, re-coarctation, aneurysm formation, dissection, and femoral artery complications.

COARCTATION AND PREGNANCY

Women with coarctation should receive prepregnancy counseling with input from an adult congenital heart disease specialist to determine maternal cardiac, obstetric, and fetal risks. Women with severe coarctation have an extremely high risk of maternal mortality and severe morbidity, and if pregnant, the option of pregnancy termination should be discussed.

REFERRAL

- All patients with coarctation of the aorta, with or without repair, should be referred to a congenital heart specialist.
- Intervention should involve a multidisciplinary team of cardiologists, interventionalists, and surgeons at an adult congenital heart disease center.

PEARLS & CONSIDERATIONS

COMMENTS

- Aortic coarctation is most commonly found distal to the origin of the left subclavian artery.
- The pathognomonic physical exam finding of aortic coarctation is the brachio-femoral delay.
- Systemic hypertension is the most common long-term complication of untreated aortic coarctation, but it is also associated with accelerated coronary artery disease, stroke, aortic dissection, and heart failure.
- An adult congenital heart disease specialist should monitor all patients with aortic coarctation.

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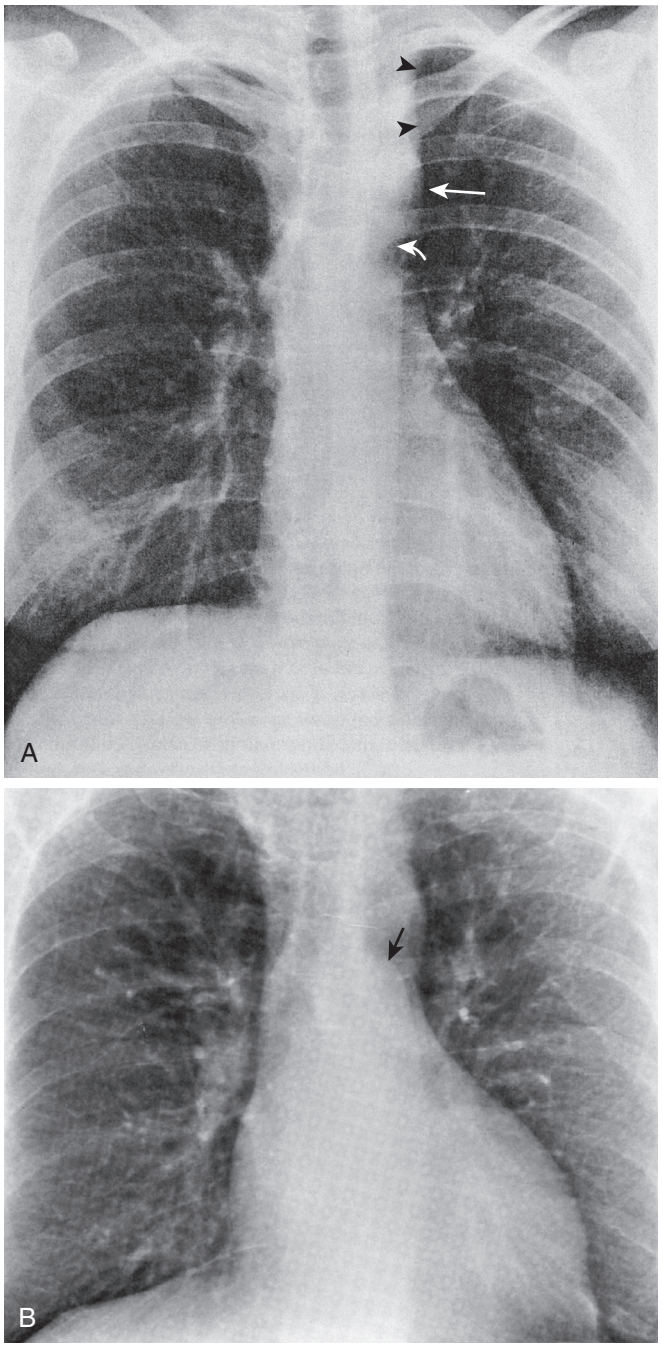

FIG. E1 Coarctation of the aorta. A, Minimal rib notching is present. The arch of the aorta *(straight arrow)* is unusually large, and the left subclavian artery *(arrowheads)* has elongated into the left apex. The site of the coarctation *(curved arrow)* is the deep concavity in the descending aorta. **B,** The para-aortic stripe has a deep indentation *(arrow)* posteriorly behind the pulmonary artery segment. (From Boxt LM, Abbara S: *Cardiac imaging: the requisites*, ed 4, Philadelphia, 2016, Elsevier.)

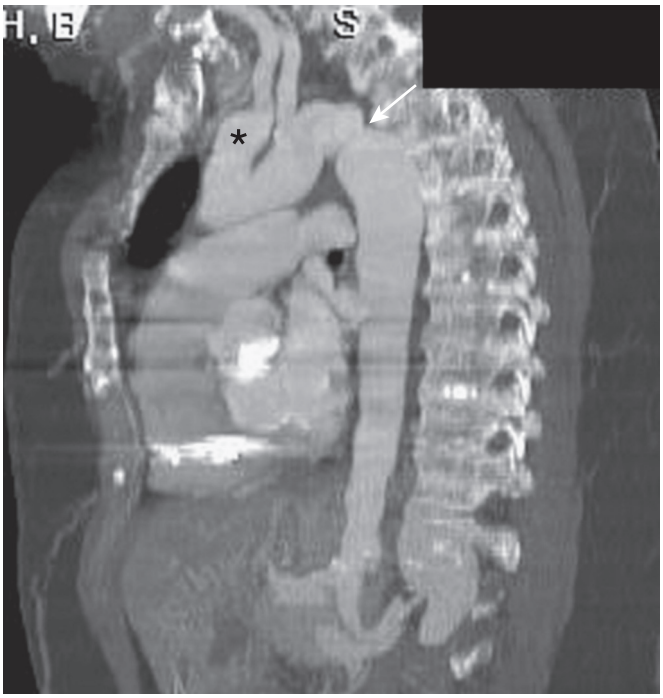

FIG. E2 Coarctation of the aorta. Reformatted computed tomography angiography of the thoracic and abdominal aorta demonstrating a coarctation *(arrow)* of the proximal thoracic aorta with prominent poststenotic dilatation. There is also aneurysmal enlargement of the brachiocephalic artery (*). (Courtesy Ruchira Garg, MD. From Boxt LM, Abbara S: *Cardiac imaging: the requisites*, ed 4, Philadelphia, 2016, Elsevier.)

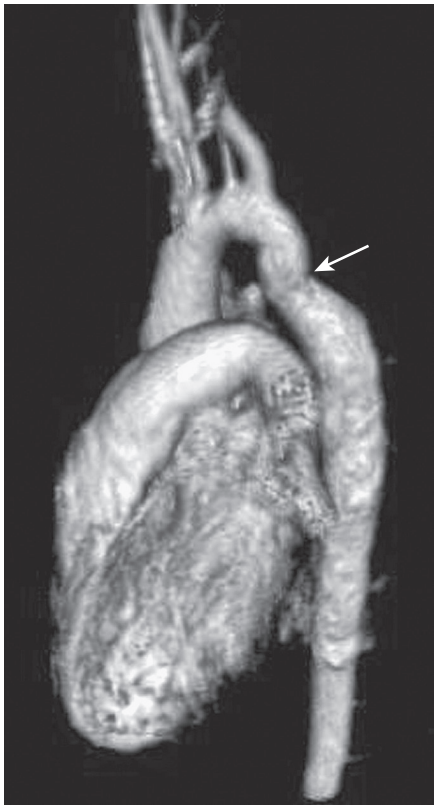

FIG. E3 Coarctation of the aorta. A gadolinium-enhanced 3D surface rendering of mild coarctation *(arrow)* with some tortuosity of the isthmus. There is no blood pressure gradient across this lesion at rest. (Courtesy Ruchira Garg, MD. From Boxt LM, Abbara S: *Cardiac imaging: the requisites*, ed 4, Philadelphia, 2016, Elsevier.)

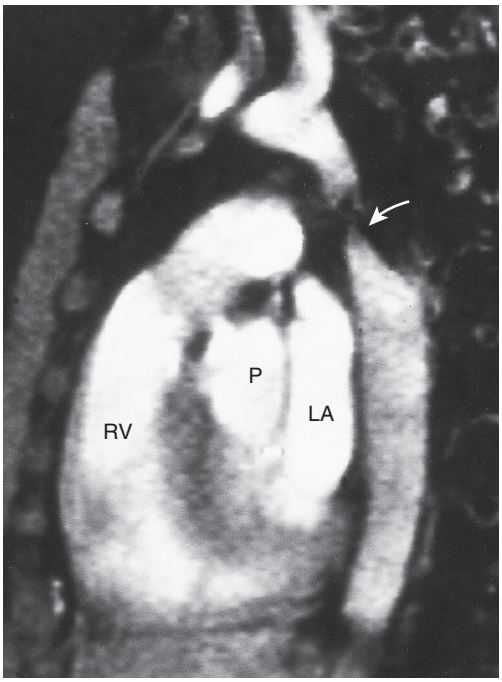

FIG. E4 Gradient echo image of an aortic coarctation. In the sagittal plane, which contains the right ventricle *(RV),* left pulmonary artery *(P),* and left atrium *(LA),* the aortic isthmus has a long stenosis *(curved arrow)* beginning distal to the left subclavian artery. (From Boxt LM, Abbara S: *Cardiac imaging: the requisites*, ed 4, Philadelphia, 2016, Elsevier.)

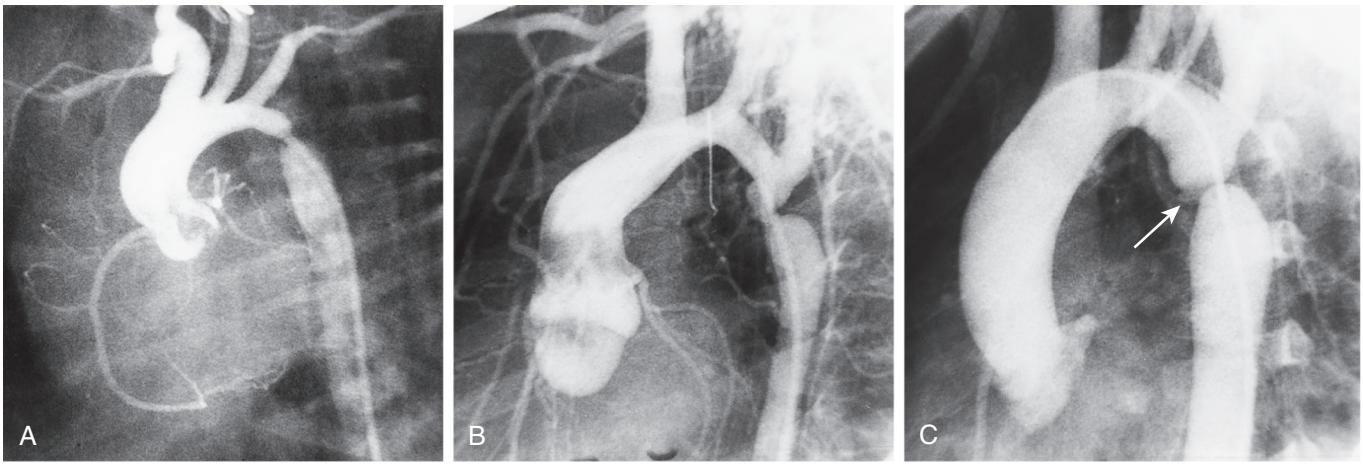

FIG. E5 Coarctation of the aorta. Aortography of three variations of aortic coarctation filmed in the left anterior oblique projection. **A,** Aortic valve stenosis is indicated by the domed leaflets of the bicuspid valve and the poststenotic dilatation of the ascending aorta. The transverse arch is frequently hypoplastic before the coarctation. **B,** The bicuspid aortic valve is oriented in an anteroposterior direction. There is pronounced poststenotic dilatation after the coarctation. Large internal mammary arteries and bridging mediastinal vessels are visible. **C,** The transverse arch has normal size. A small diverticulum *(arrow)* represents the obliterated ductus arteriosus. (From Boxt LM, Abbara S: *Cardiac imaging: the requisites*, ed 4, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Aortic dissection is part of a spectrum of aortic pathologies (acute aortic syndromes) that includes intramural hematomas and penetrating atherosclerotic ulcers. Aortic dissection occurs when blood passes through an intimal tear, separating the intima from the medial layers and creating a false lumen. Intramural hematoma (IMH) occurs when the vasa vasorum ruptures within the medial wall. IMH does not involve an intimal tearing unless a dissection develops. Seventeen percent of IMH will transform into aortic dissection. Penetrating atherosclerotic ulcers, which occur in the setting of extensive aortic atherosclerosis and hypertension, destroy the aortic intima and dissect into the aortic media. Rupture of atherosclerotic plaques with subsequent blood entry into the median wall forms a pseudoaneurysm. Fig. 1 illustrates acute aortic syndromes.

CLASSIFICATION

Aortic dissection is generally classified according to anatomic location (Fig. 2). Table 1 summarizes classification schemes of acute aortic dissection.

- Stanford (more commonly used classification system): Type A ascending aorta (proximal), type B descending aorta (distal)
- DeBakey: Type I ascending and descending aorta, type II ascending aorta, type III descending aorta
- Aortic dissection can also be classified by acuity of presentation: Hyperacute (<24 hr), acute (2 to 7 days), subacute (8 to 30 days), and chronic (>30 days). The overall survival rate is inversely related to time of presentation, with the highest survival rate in the hyperacute group and the lowest survival rate in the chronic group

SYNONYMS

Dissecting aortic aneurysm
Acute aortic syndrome
AAS

ICD-10CM CODES

I71.00	Dissection of unspecified site of aorta
I71.01	Dissection of thoracic aorta
I71.02	Dissection of abdominal aorta
I71.03	Dissection of thoracoabdominal aorta

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 2.6 to 3.5 per 100,000 person-yr; more frequent in winter as compared to other seasons, although no clear reason has been identified

PREDOMINANT SEX AND AGE: Males (65%) females (35%), ages 60 to 80 yr; mean = 63 yr

RISK FACTORS (TABLE 2):

- Hypertension (found in up to 77% of patients with aortic dissection)
- Atherosclerosis (found in up to 27% of patients with aortic dissection)
- Preexisting aortic aneurysm (found in up to 16% of patients with aortic dissection)
- Age (60 to 80 yr)
- Family history of aortic aneurysms/dissection
- History of cardiac surgery, aortic valve replacement, intraaortic catheterization
- Disorders of collagen (Marfan syndrome, Ehlers-Danlos syndrome)
- Vascular inflammation (giant cell arteritis, Takayasu arteritis, rheumatoid arthritis, syphilitic aortitis)
- Aortic coarctation, bicuspid aortic valve
- Turner syndrome
- Cocaine abuse (usually within 12 hours of last use of cocaine)
- Trauma
- Pregnancy and delivery
- Fluoroquinolone use
- Table 3 summarizes genetically triggered conditions associated with aortic dissection

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Sudden onset of severe sharp, tearing, or ripping chest pain. However, painless dissection occurs in approximately 6.4% of cases
- Anterior chest pain (79% type A, 63% type B)
- Back pain, abdominal pain (43% type A, 64% type B)
- Syncope (19% type A, 3% type B), generally secondary to cardiac tamponade or stroke
- Congestive heart failure (CHF)
- May present with hypertension (28% for type A, 66% in type B dissection), although 25% present with hypotension (systolic blood pressure <100 mm Hg), which can indicate bleeding, cardiac tamponade, or severe aortic regurgitation. Patients presenting with very high systolic blood pressure (>180 mm Hg for type A, >200 mm Hg for type B dissection), as well as in those with systolic blood pressure <=100 mm Hg, have significantly higher in-hospital mortality rates
- Pulse and blood pressure differentials (>20 mm Hg between arms) in 19% to 31% of cases caused by partial compression of subclavian arteries
- Aortic regurgitation in 18% to 50% of cases of proximal dissection, often with diastolic decrescendo murmur
- Myocardial ischemia caused by coronary artery occlusion, most commonly involving the right coronary artery
- Stroke in 5% to 10% of patients (secondary to dissection into or decreased blood flow to the carotids)
- Mesenteric ischemia occurs in 3% to 5% of cases, with external compression, flap prolapse, or involvement of arterial ostia
- Horner syndrome (ptosis, miosis, anhidrosis)
- Vocal cord paralysis or hoarse voice (caused by compression of the left recurrent laryngeal nerve)

ETIOLOGY

Genetics, in addition to other risk factors listed previously, contribute to the development of aortic dissection.

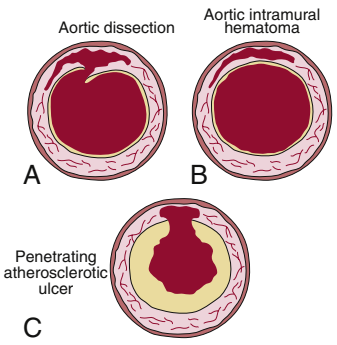

FIG. 1 Acute aortic syndromes. A, Classic aortic dissection. There is a tear in the intima with blood entering the media and a dissecting cleavage plane propagating for variable distances anterograde (and occasionally retrograde) throughout the aortic wall. **B,** Aortic intramural hematoma (IMH). A spontaneous hemorrhage of the vasa vasorum leads to bleeding within the media in the absence of an intimal tear or intimal flap. **C,** Penetrating atherosclerotic aortic ulcer (PAU). An ulcerated aortic plaque ruptures into the media, leading to an outpouching or ulceration in the aortic wall. This may be associated with IMH formation, pseudoaneurysm, or a focal, thick-walled aortic dissection. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Known as the great imitator: Pulmonary embolism, acute coronary syndrome, aortic stenosis/insufficiency, nondissecting aneurysm, pericarditis, cholecystitis, peptic ulcer disease, pancreatitis, musculoskeletal pain.
- Consider aortic dissection in patients with unexplained stroke, chest pain, syncope, acute-onset CHF, abdominal pain, back pain, and malperfusion of extremities or internal organs. Acute aortic syndromes may be associated with nonspecific signs and symptoms; a high clinical index of suspicion is necessary to detect the disease early in its course as nearly two thirds of patients under medical care are not diagnosed prior to death.
- In an emergency situation, a rapid yet comprehensive workup is crucial to reduce diagnostic time delay. This should include clinical assessment, laboratory data (D-dimer and troponin), chest x-ray, electrocardiogram (ECG), and aortic imaging in the appropriate patient.

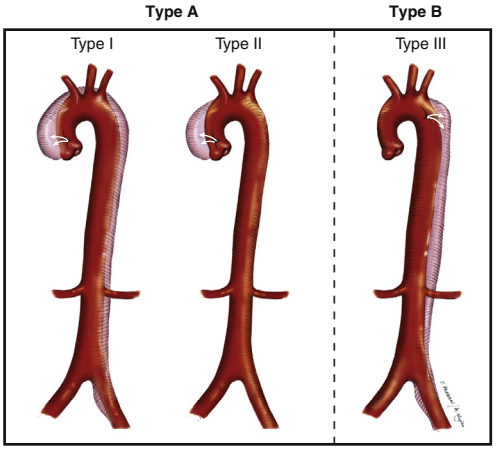

FIG. 2 Classification schemes of acute aortic dissection. (From Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.)

TABLE 1 Classification Schemes of Acute Aortic Dissection

DeBakey Classification	
Type I	Originates in the ascending aorta and extends at least to the aortic arch and often to the descending aorta (and beyond)
Type II	Originates in the ascending aorta and confined to this segment
Type III	Originates in the descending aorta, usually just distal to the left subclavian artery, and extends distally
Stanford Classification	
Type A	Dissections involving the ascending aorta (with or without extension into the descending aorta)
Type B	Dissections not involving the ascending aorta

From Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.

- The Aortic Dissection Detection Risk Score (ADD-RS) can be a useful tool in diagnosing aortic dissection in the emergency room setting. ADD-RS is based on the presence of one or more of the clinical risk markers outlined in Table 4. A high ADD-RS effectively stratifies the risk for acute aortic dissection (score 0 is low risk, score 1 is intermediate risk, and score ≥2 is high risk). Score 0 has 95.6% certainty in ruling out aortic dissection.
- The addition of D-dimer to ADD-RS may further improve diagnostic performance of each of these when used alone for ruling out acute aortic dissection or other acute aortic syndromes. Among low- to intermediate-risk patients (ADD-RS <2), a negative D-dimer (<500 mg/dl) can rule out aortic dissection with 99.7% certainty. Among high-risk patients (ADD-RS ≥2), D-dimer is not discriminatory and requires conclusive imaging.

WORKUP

ECG: Helpful to rule out MI, although dissection can lead to coronary ischemia.

LABORATORY TESTS

- D-dimer has a high negative predictive value in dissection, but lacks specificity in the setting of acute aortic dissection. However, a negative D-dimer does not rule out intramural hematoma or penetrating aortic ulcer.
- Soluble ST2, a novel biomarker, may have superior diagnostic performance over D-dimer in discriminating acute aortic dissection from other acute chest pain syndromes. At a cutoff level of 34.6 ng/ml, the sensitivity and specificity for acute aortic dissection were 99.1% and 84.9%, respectively.
- Several other biomarkers with different diagnostic windows can be used in the diagnosis of aortic dissection:
  1. Smooth muscle myosin heavy chain protein (released from damaged medial smooth muscle) can be used to detect proximal aortic dissections (91% sensitivity and 93% specificity). Myosin heavy chains will peak within 3 hr of dissection and clear within 24 hr of aortic injury.
  2. CK-BB isoenzyme also peaks within 6 hr of dissection.
  3. Calponin, a smooth muscle troponin counterpart, increases in aortic dissection with a wider diagnostic window when compared to smooth muscle myosin heavy chain and CK-BB.
  4. C-reactive protein, fibrinogen and soluble elastin fragments are under investigation.

IMAGING STUDIES

- Multidetector CT (Fig. E3 and Fig. E4) is considered the gold standard, but its use may be limited in patients with renal failure as it involves the use of intravenous contrast.

TABLE 2 Risk Factors for Aortic Dissection

- Hypertension
- Heritable or genetic thoracic aortic disease and syndromes
  - Marfan syndrome
  - Loeys-Dietz syndrome
  - Familial thoracic aortic aneurysm syndromes
  - Vascular Ehlers-Danlos syndrome
  - Turner syndrome
- Congenital diseases/syndromes
  - Bicuspid aortic valve
  - Coarctation of the aorta
  - Tetralogy of Fallot
- Atherosclerosis
  - Penetrating atherosclerotic ulcer
- Trauma, blunt or iatrogenic
  - Catheter/guidewire
  - Intra-aortic balloon pump
  - Aortic/vascular surgery
  - Motor vehicle accident
  - Coronary artery bypass grafting/aortic valve replacement/TAVR
  - Thoracic endovascular aneurysm repair (TEVAR)
- Cocaine/methamphetamine use
- Inflammatory/infectious diseases
  - Giant cell arteritis
  - Takayasu arteritis
  - Behçet syndrome
  - Aortitis
  - Syphilis
- Pregnancy (with underlying aortopathy)
- Weightlifting (with underlying aortopathy)

TAVR, Transcatheter aortic valve replacement.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

- Transesophageal echocardiography (TEE), multidetector CT, and MRI are all highly sensitive (98% to 100%) and specific (95% to 98%). Test of choice depends on clinical circumstances and hospital availability.
- TEE is study of choice in unstable patients with type A dissection but is operator dependent.
- MRI has high sensitivity and specificity but limited availability; not suitable for unstable patients; contraindicated with noncompatible pacemakers, metal devices.
- With medium or high pretest probability, a second diagnostic test should be done if the first is negative.
- Coronary computed tomographic angiography (CTA) may be an alternative and useful diagnostic study when evaluating for pulmonary embolism, acute coronary syndrome, and aortic dissection.
- Aortography rarely done, as less sensitive than TEE, CT, or MRI.
- Chest radiograph may show widened mediastinum (52% in type A dissections and 39% in type B dissections) and displacement of aortic intimal calcium. It is normal in 29% to 36% of patients with aortic dissection.
- Although the diagnostic sensitivity of transthoracic echocardiography is suboptimal (31% to 55%), it is useful in assessing potential high-risk features or complications, such as pericardial effusion, and making other

TABLE 3 Genetically Triggered Conditions Associated with Aortic Dissection

Marfan syndrome (MFS)	Autosomal dominant disorder of connective tissue caused by *FBN1* mutation; incidence of 1 in ≈5000 individuals; multisystem manifestations, including ectopia lentis; mitral valve prolapse, aortic root aneurysm, aortic dissection; skeletal features (pectus deformities, scoliosis, arachnodactyly, hyperflexibility, tall stature, elongated fingers and toes); dural ectasia; spontaneous pneumothorax
Loeys-Dietz syndrome (LDS)	Autosomal dominant disorder caused by mutations in *TGFBR1* and *TGFBR2*, associated with aneurysms and dissections involving the aorta and branch vessels, often at relatively small diameters and young age; manifestations include craniofacial features (hypertelorism, craniosynostosis, cleft palate, bifid or broad uvula), bluish sclera, arterial tortuosity, velvety and hyperlucent skin, easily visible veins, clubfeet, skeletal abnormalities; phenotypes may vary, including those with more pronounced craniofacial features and those with more cutaneous features; ectopia lentis has not been described in LDS; mutations in *TGFB2* lead to a syndrome with an overlap in clinical features of LDS and MFS
Familial thoracic aortic aneurysm (FTAA) syndromes	Autosomal dominant disorders with variable expression and penetrance leading to thoracic aortic aneurysms (TAAs) and dissections at variable ages in families; *ACTA2* mutations occur in 10%-15% of cases of FTAA and are associated with bicuspid aortic valve (BAV) disease, cerebral aneurysms, livedo reticularis, iris flocculi, PDA, moyamoya, and premature coronary artery disease; gene mutations causing familial thoracic aortic aneurysm and dissection (TAAD) include *ACTA2*, *TGFBR1*, *TGFBR2*, *FBN1*, *MYH11*, *MYLK*, *TGFB2*, *SMAD3*
Vascular Ehlers-Danlos syndrome (vEDS)	Autosomal dominant disorder of collagen synthesis caused by a gene mutation in *COL3A1* leading to rupture and dissection of the aorta (usually the descending and abdominal aorta) and branch vessels; manifestations include flexible digits, hyperlucent skin with visible veins, varicose veins, typical facial appearance, and spontaneous rupture of the uterus or bowel
Bicuspid aortic valve (BAV)	Congenital condition affecting ≈1% of the population, familial in ≈9% of cases; often associated with dilation of the ascending aorta and carries increased risk for aortic dissection; gene mutations include *NOTCH1* and loci at 15q, 18q, 5q, and 13q; may be associated with FTAA
Turner syndrome (TS)	Genetic disorder affecting 1 in 2000 live-born girls and caused by complete or partial loss of the second sex chromosome (XO, Xp); women with TS often have BAV and aortic coarctation; associated with ascending aortic dilation for body size and increased risk for aortic dissection, especially when associated with BAV, hypertension, and coarctation
Aneurysms-osteoarthritis syndrome	Autosomal dominant genetic disorder resulting from mutations in the *SMAD3* gene and associated with premature osteoarthritis, osteochondritis dissecans, skeletal features, aortic aneurysms, branch vessel aneurysms, and arterial tortuosity; overlap with LDS phenotype

From Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.

TABLE 4 Aortic Dissection Detection Risk Score (ADD-RS)

Clinical risk markers*	Score
High-risk condition such as Marfan syndrome, family history of aortic disease, known aortic valve disease, known thoracic aortic aneurysm, or previous aortic manipulation, including cardiac surgery.	1
Pain in the chest, back, or abdomen described as abrupt, of severe intensity, or a ripping/tearing sensation.	1
Physical examination findings of perfusion deficit, including pulse deficit, systolic blood pressure difference, or focal neurologic deficit, or with aortic diastolic murmur and hypotension/shock.	1

*Presence of ≥1 marker within each of these groups is given a score of 1 with a maximum cumulative score of 3 if all three are present.

Modified from Erbel R et al: 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC), *Eur Heart J* 35:2873-926, 2014; Hiratzka LF et al: 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease, *Circulation* 121:e266-369, 2010; and Hiratzka et al: Surgery for aortic dilatation in patients with bicuspid aortic valves: a statement of clarification from the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, *J Am Coll Cardiol* 67:724-31, 2016.

potential diagnoses. A negative transthoracic echocardiography, however, does not exclude aortic dissection.

Rx TREATMENT

- Urgent surgical consultation should be obtained for all thoracic aortic dissection regardless of anatomic location. Table 5 summarizes size threshold for prophylactic aortic root or ascending aortic aneurysm resection for various conditions.
- Proximal dissections (acute type A) require emergent surgery to prevent rupture or pericardial effusion.
- Distal dissections (Stanford type B) are usually treated medically unless distal organ involvement or impending rupture occurs.
  1. Surgical intervention for distal dissections is reserved for patients who have a complicated course, including occlusion of a major aortic branch, propagation of the dissection, enlarging aneurysm, and evidence of aortic rupture.
  2. Thoracic endovascular aortic repair (TEVAR) is a less invasive option for complicated type B aortic dissections and is associated with lower short- and midterm mortality than medical therapy. Indications for thoracic endovascular aortic repair for type B aortic dissection are summarized in Table 6.
  3. For acute type B dissections, in-hospital mortality in patients managed surgically has been reported to be 33.9% versus those managed with endovascular treatment at 10.6%.
  4. Independent predictors of complication and mortality in distal dissections include periaortic hematoma and descending aortic diameter >5.5 cm, partial false lumen thrombosis, primary tear >10 mm, one entry tear, and false lumen >22 mm.
  5. There is ongoing debate about a possible beneficial role of TEVAR for uncomplicated type B dissections. Data suggest that 30% of uncomplicated type B dissections will progress to an aneurysm.

ACUTE GENERAL Rx

- Admit to ICU for monitoring.
- Target systolic blood pressure 100 to 120 mm Hg; heart rate <60 beats/min to reduce aortic wall stress. Treatment with beta-blockers has been associated with improved survival in all patients with acute aortic dissections.
- IV beta-blockers are cornerstones of treatment, but multiple medications may be needed.
  1. Propranolol 1 mg every 3 to 5 min, metoprolol 5 mg IV every 5 min, or labetalol 20 mg IV, then 20 to 80 mg every 10 min, followed by nitroprusside 0.3 to 10 mcg/kg/min.
  2. Vasodilators should not be used without beta-blockade as they can induce reflex sympathetic stimulation and increase aortic shear stress.
  3. IV calcium channel blockers with negative inotropy (i.e., verapamil, diltiazem) may be used if beta-blockers are contraindicated.
- Pain control, often with morphine.

TABLE 5 Size Threshold for Prophylactic Aortic Root or Ascending Aortic Aneurysm Resection for Various Conditions

Condition	Size Threshold*
Degenerative aneurysm	≥5.5 cm
Bicuspid aortic valve	≥5.5 cm
Bicuspid aortic valve with risk factors or low surgical risk†	≥5.0 cm
Bicuspid aortic valve requiring aortic valve replacement	>4.5 cm
Marfan syndrome	≥5.0 cm
Marfan syndrome with risk factors‡	>4.5 cm
Loeys-Dietz syndrome§	4.0-4.5 cm
Familial thoracic aortic aneurysm syndromes¶	4.5-5.0 cm
Turner syndrome	>2.5 cm/m^2

*Lower thresholds for intervention may be considered according to body surface area in patients of small stature or in the case of rapid growth of the aorta. Age, body size, rapid growth, family history, risk of surgery, and patient and physician wishes may influence aortic size threshold.
†Family history of aortic dissection or aortic growth rate of 0.5 cm or more per yr or if the patient is at low surgical risk (<4%) and the surgery is performed by an experienced aortic surgical team in a center with established expertise in these procedures. Other risk factors for aortic dissection include coarctation of the aorta, hypertension, and the root phenotype of bicuspid aortic valve.
‡Family history of aortic dissection or rapid aortic growth (>3 mm/yr), or severe aortic or mitral regurgitation. If pregnancy desired, consider prophylactic aortic surgery for aortic diameter of 4.0 to 4.5 cm.
§It is reasonable to consider surgical repair of the aorta in adults with Loeys-Dietz syndrome or a confirmed *TGFBR1* or *TGFBR2* mutation with aortic diameter of 4.2 cm or more by transesophageal echocardiogram or 4.4 to 4.6 or more by CT or MRI. Aortic surgery at smaller diameters may be recommended when there are severe craniofacial features, rapid growth, or a family history of aortic dissection.
¶Surgical thresholds vary depending on the specific gene mutation involved. TAA caused by *ACTA2*, *SMAD3*, and *MYLK* may lead to aortic dissection at relatively small aortic diameters.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 6 Indications for Thoracic Endovascular Aortic Repair for Type B Aortic Dissection*

Rupture
Impending rupture
Malperfusion
Hemorrhagic pleural effusion
Refractory pain
Refractory hypertension
Aneurysmal dilation (>55 mm)
Rapid increase in diameter
Recurrent symptoms

*Or open surgical repair if anatomy is unsuitable for TEVAR.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

CHRONIC Rx

- Chronic aortic dissection (>2 wk) managed with aggressive blood pressure control; target <120/80 mm Hg in most patients
- Statin therapy to reduce low-density lipoprotein <70 mg/dl
- Tobacco cessation
- Minimize strenuous physical activity such as heavy lifting
- Serial imaging of the aorta, with multidetector CT or MRI should be performed at presentation, at 1, 3, 6, and 12 months given the higher risk of instability early on, followed by yearly clinical and imaging follow-up
- As stated above, endovascular repair should be considered in complicated chronic type B dissections, i.e., when the aortic diameter exceeds 5.5 cm, when there is uncontrolled pain or blood pressure, or when there is rapid growth of the dissecting aneurysm (>4 mm per yr)

TABLE 7 Suggested Imaging Surveillance of Asymptomatic Thoracic Aortic Aneurysms*

Initial Discovery of Aneurysm	Repeated Imaging at 6 Months to Document Stability
Degenerative aneurysm†	
3.5-4.4 cm	Annual imaging
4.5-5.4 cm	Annual to biannual imaging
MFS, BAV with TAA, and familial TAA	
3.5-4.4 cm	Annual imaging
4.5-5.0 cm	Biannual imaging
LDS‡	
<4 cm	At least annual imaging
>4 cm	Biannual imaging

BAV, Bicuspid aortic valve; *LDS,* Loeys-Dietz syndrome; *MFS,* Marfan syndrome; *TAA,* thoracic aortic aneurysm.
*For aneurysms growing rapidly, more frequent imaging is recommended. Management of TAA must take into account the family history, age, body size, sex, rate of aneurysm growth, and underlying disease.
†For relatively small degenerative aneurysms found by imaging to be stable from year to year, imaging may be performed every 2 to 3 yr (Hiratzka et al).
‡Some recommend surgery for aortic root dimensions larger than 4 cm in adults with LDS, whereas the American College of Cardiology/American Heart Association guidelines for thoracic aortic disease recommend prophylactic surgery at 4.2 cm by TEE and 4.4 to 4.6 cm by CT or MRI (Hiratzka et al).
From Hiratzka LF et al: 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine, *Circulation* 121:e266, 2010.; Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.

DISPOSITION

- 90% mortality rate within 2 wk for an untreated type A dissection.
- Proximal dissection is a surgical emergency. Time is critical; mortality rate is 1% to 3% per hour, approaching 70% after 48 hr.
- Overall, in-hospital mortality rate is 22% with proximal dissections (27% treated surgically and 56% treated medically) and 10% to 17% with distal dissections.
- Table 7 summarizes suggested imaging surveillance of asymptomatic thoracic aortic aneurysms.

REFERRAL

For ICU management and surgical intervention

PEARLS & CONSIDERATIONS

- Blood pressure control is essential; beta-blocker is first-line medication.
- Proximal dissection is a surgical emergency.
- Cardiac tamponade is not uncommon in patients with acute type A aortic dissection. Syncope, altered mental status, and a widened mediastinum on chest radiograph on presentation suggest tamponade, which warrants urgent operative therapy.
- Surgery for acute type A aortic dissection in patients ≥70 yr old can be performed with acceptable outcomes.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Aortic Dissection (Patient Information)

AUTHORS: **Marjan Mujib, MD,** and **Philip Stockwell, MD**

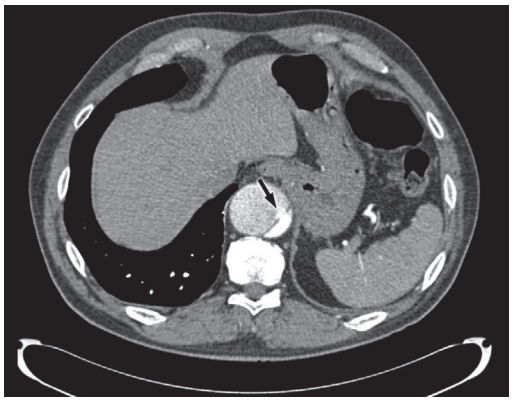

FIG. E3 Contrast-enhanced computed tomography scan of an aortic dissection demonstrating a fenestration in the intimal flap *(arrow)* with contrast material flowing from the small, densely opacified true lumen into the less opacified and larger false lumen of the aorta. (From Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.)

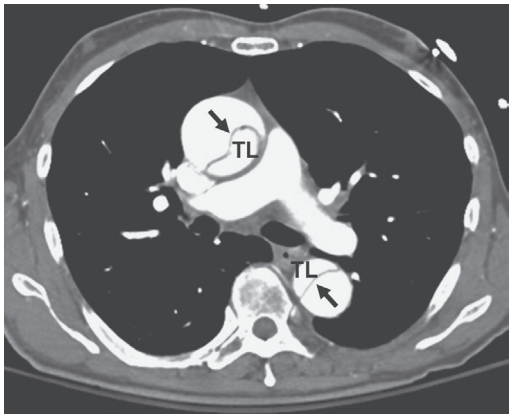

FIG. E4 Contrast-enhanced computed tomography scan demonstrating acute type A aortic dissection with enlargement of the ascending aorta and intimal flaps *(arrows)* in the ascending and descending aorta. Both the true lumen *(TL)* and the false lumen are opacified with contrast material in this example. (From Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.)

SUGGESTED READINGS

Erbel R et al: 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases, *Eur Heart J* 35(41):2873-2926, 2014.

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BASIC INFORMATION

DEFINITION

Aortic regurgitation (AR) is abnormal retrograde blood flow into the left ventricle from the aorta due to an inadequately closing aortic valve (AV). It can be acute or chronic in nature.

Stages of chronic aortic regurgitation:

- Stage A = at risk of aortic insufficiency (AI) without even trace AR (e.g., bicuspid AV, AV sclerosis, diseases of the ascending aorta, history of rheumatic heart disease, or infective endocarditis)
- Stage B = progressive AI with mild to moderate AR and preserved left ventricular ejection fraction (LVEF)
- Stage C = asymptomatic severe AR with preserved (stage C1) or reduced (stage C2) LVEF
- Stage D = symptomatic severe AR

SYNONYMS

Aortic insufficiency
AI
AR

ICD-10CM CODES	
I35.1	Nonrheumatic aortic (valve) insufficiency
I35.2	Nonrheumatic aortic (valve) stenosis with insufficiency
I06.2	Rheumatic aortic stenosis with insufficiency
Q23.1	Congenital insufficiency of aortic valve

EPIDEMIOLOGY & DEMOGRAPHICS

Prevalence varies with severity of AR, age, and gender, as summarized in Table 1.

- Most common cause in the developing world is rheumatic heart disease
- Most common causes in developed countries are aortic root dilation, congenital bicuspid aortic valve, and calcific valve disease
- Infectious endocarditis (IE) is the most frequent cause of acute AR

TABLE 1 Prevalence of Aortic Regurgitation (AR)

Mild AR Prevalence	Male	Females
Age 50-59	3.7 %	1.9%
Age 60-69	12.1%	6%
Age 70-83	12.2%	14.6%
Moderate-Severe AR Prevalence	**Male**	**Females**
Age 50-59	0.5%	0.2%
Age 60-69	0.6%	0.8%
Age 70-83	2.2%	2.3%

From Singh JP et al: Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study), *Am J Cardiol* 83:897, 1999.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical presentation varies depending on whether AR is acute or chronic. Chronic AR is well tolerated (except when secondary to IE), and patients remain asymptomatic for years. Common manifestations after significant deterioration of LVEF are dyspnea on exertion, syncope, chest pain, and congestive heart failure (CHF). The stages of chronic AR are summarized in Table 2. Acute severe AR manifests primarily with hypotension caused by a sudden fall in cardiac output and resultant cardiogenic shock. A rapid rise in left ventricular diastolic pressure results in a further decrease in coronary blood flow.

Physical findings in chronic AR:

- Widened pulse pressure (markedly increased systolic blood pressure with decreased diastolic blood pressure). Fig. E1 illustrates characteristics of the AR murmur
- Findings associated with widened pulse pressure:
  1. Bounding, "water hammer," or collapsing pulse **(*Corrigan* pulse)** can be palpated at the wrist or femoral artery and is caused by the rapid rise and sudden collapse of arterial pressure during late systole.
  2. Head "bobbing" with each heart beat **(*de Musset* sign).**
  3. "Pistol shot femorals" **(*Traube* sign)** describes a loud sound over the femoral artery with systole and diastole.
  4. Capillary pulsations **(*Quincke* sign)** may occur on the lips or at the base of the nail beds.
  - A to-and-fro intermittent femoral murmur **(*Duroziez* sign)** may be heard with slight compression of the femoral arteries. Popliteal systolic pressure increased >20 mm Hg over the brachial systolic pressure **(*Hill* sign);** a 40 to 60 mm difference represents moderate AR and >60 mm difference, severe AR
- Findings more of historical than practical interest, which are neither sensitive nor specific, include:
  1. ***Mueller* sign**—Systolic pulsations of the uvula
  2. ***Becker* sign**—Visible pulsations of the retinal arteries and pupils
  3. ***Mayne* sign**—More than a 15 mm Hg decrease in diastolic blood pressure with arm elevation from the value obtained with the arm in the standard position
  4. ***Rosenbach* sign**—Systolic pulsations of the liver
  5. ***Gerhard* sign**—Systolic pulsations of the spleen

Cardiac auscultation reveals:

- Displacement of cardiac impulse downward and to the patient's left
- S_3 heard over the apex
- Decrescendo, blowing diastolic murmur heard along left sternal border
- Low-pitched apical diastolic rumble **(*Austin Flint* murmur)**—the precise etiology is uncertain, but it is generally believed to be related to increased velocity of mitral inflow consequent to the AR
- Early systolic ejection sound and systolic ejection murmur

In patients with acute aortic insufficiency both the wide pulse pressure and the large stroke volume are absent. A short, blowing diastolic murmur may be the only finding on physical examination.

ETIOLOGY

- Leaflet abnormalities:
  1. Infective endocarditis
  2. Rheumatic fibrosis (most common cause in developing countries)
  3. Trauma with valvular rupture
  4. Congenital heart disease (bicuspid aortic valve—most common cause in the U.S., sinus of Valsalva aneurysm)
  5. Myxomatous degeneration
  6. Calcific AV disease
  7. Drug-induced (fenfluramine, dexfenfluramine, pergolide, cabergoline)
  8. Systemic rheumatic disorders (ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus)
- Aortic root or ascending aorta abnormalities:
  1. Annuloaortic ectasia
  2. Genetic syndromes (Ehlers-Danlos, Marfan)
  3. Trauma
  4. Ankylosing spondylitis
  5. Syphilitic aortitis
  6. Systemic hypertension
  7. Aortic dissection
- Postprocedural AR, usually due to a paravalvular leak, occurs in 10% to 20% of patients undergoing transcatheter aortic valve replacement (TAVR). Patients with more than mild AR after TAVR have worse outcomes than those without AR.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Patent ductus arteriosus, pulmonary regurgitation, and other valvular abnormalities.
- The differential diagnosis of cardiac murmurs is described in Sections II and III.

WORKUP

- Echocardiogram, chest radiograph, electrocardiogram (ECG), cardiac magnetic resonance (CMR) imaging, and cardiac catheterization (selected patients).
- Medical history and physical examination focused on dyspnea on exertion, syncope, chest pain, and CHF

IMAGING STUDIES

- Chest radiography:
  1. Left ventricular hypertrophy (LVH) (chronic AR)
  2. Aortic dilation
  3. Normal cardiac silhouette with pulmonary edema: Possible in patients with acute AR

TABLE 2 Stages of Chronic Aortic Regurgitation

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	**At risk of AR**	Bicuspid aortic valve (or other congenital valve anomaly) Aortic valve sclerosis Diseases of the aortic sinuses or ascending aorta History of rheumatic fever or known rheumatic heart disease IE	AR severity none or trace	None	None
B	**Progressive AR**	Mild to moderate calcification of a trileaflet valve bicuspid aortic valve (or other congenital valve anomaly) Dilated aortic sinuses Rheumatic valve changes Previous IE	***Mild AR:*** Jet width <25% of LVOT vena contracta <0.3 cm RVol <30 ml/beat RF <30% ERO <0.10 cm^2 Angiography grade 1+ ***Moderate AR:*** Jet width 25-64% of LVOT Vena contracta 0.3-0.6 cm RVol 30-59 ml/beat RF 30-49% ERO 0.10-0.29 cm^2 Angiography grade 2+	Normal LV systolic function Normal LV volume or mild LV dilation	None
C	**Asymptomatic severe AR**	Calcific aortic valve disease Bicuspid valve (or other congenital abnormality) Dilated aortic sinuses or ascending aorta Rheumatic valve changes IE with abnormal leaflet closure or perforation	***Severe AR:*** Jet width ≥65% of LVOT Vena contracta >0.6 cm Holodiastolic flow reversal in the proximal abdominal aorta RVol ≥60 ml/beat RF ≥50% ERO ≥0.3 cm^2 Angiography grade 3+ to 4+ In addition, diagnosis of chronic severe AR requires evidence of LV dilation	*C1:* Normal LVEF (≥50%) and mild-to-moderate LV dilation (LVESD ≤50 mm) *C2:* Abnormal LV systolic function with depressed LVEF (<50%) or severe LV dilation (LVESD >50 mm or indexed LVESD >25 mm/m^2)	None; exercise testing is reasonable to confirm symptom status
D	**Symptomatic severe AR**	Calcific valve disease Bicuspid valve (or other congenital abnormality) Dilated aortic sinuses or ascending aorta Rheumatic valve changes Previous IE with abnormal leaflet closure or perforation	***Severe AR:*** Doppler jet width ≥65% of LVOT Vena contracta >0.6 cm Holodiastolic flow reversal in the proximal abdominal aorta RVol ≥60 ml/beat RF ≥50% ERO ≥0.3 cm^2 Angiography grade 3+ to 4+ In addition, diagnosis of chronic severe AR requires evidence of LV dilation	Symptomatic severe AR may occur with normal systolic function (LVEF ≥50%), mild-to-moderate LV dysfunction (LVEF 40%–50%), or severe LV dysfunction (LVEF <40%)Moderate-to-severe LV dilation is present	Exertional dyspnea or angina, or more severe HF symptoms

AR, Aortic regurgitation; *ERO,* effective regurgitant orifice; *HF,* heart failure; *IE,* infective endocarditis; *LV,* left ventricle; *LVEF,* left ventricular ejection fraction; *LVESD,* left ventricular end-systolic dimension; *LVOT,* left ventricular outflow tract; *RF,* regurgitant fraction; *RVol,* regurgitant volume.

From Nishimura RA et al: 2014 AHA/ACCF guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 63:e57, 2014. In Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.

- ECG is not useful for diagnostic purposes but is commonly used in evaluation of patients with chronic AR to exclude associated arrythmia. Typical findings on an ECG are LVH as a result of volume overload.
- Echocardiography (Fig. E2) is the main imaging modality to diagnose AR and assess left ventricular size and function. Quantification of the severity of regurgitation can be made either qualitatively by Doppler vena contracta width (severe if >0.6 cm) or quantitatively by effective regurgitant orifice area (severe if >0.30 cm^2) and/or regurgitant volume (severe if >60 ml per/beat).
- CMR is indicated (class 1) in patients with moderate or severe AR and suboptimal echocardiographic images for the assessment of AR severity as well as LV systolic function and volumes.
- Cardiac catheterization is indicated in selected patients to assess the degree of left ventricular dysfunction and AR when echocardiographic parameters are inconclusive, and to determine if there is coexistent coronary artery disease.
- Serial evaluation of the size and morphology of the aortic sinuses and ascending aorta by echocardiography, CMR, or CT angiography is recommended in patients with a bicuspid

AV and an aortic diameter >4.0 cm, with the examination interval determined by the degree and rate of progression of aortic dilation and by family history. Patients with an aortic diameter >4.5 cm should be evaluated annually (Class 1).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of competitive sports and heavy weight lifting if: severe AR, patient is symptomatic, ejection fraction <50%, AR is associated with aortic root dilation
- Salt restriction
- Endocarditis prophylaxis is not recommended for chronic AR patients with native valves undergoing invasive procedures. However, antibiotic prophylaxis is recommended for patients with a prior history of infective endocarditis or a presence of prosthetic heart valve

ACUTE GENERAL Rx

- Emergent AV replacement (preferred) or repair for acute, severe AR
- Intraaortic balloon pump is contraindicated
- Afterload reduction: Angiotensin-converting enzyme (ACE) inhibitors and vasodilators (i.e., nitroprusside) in acute AR; diuretics for pulmonary edema
- Avoid beta-blockers that can prolong diastole
- Emergent surgical referral for cardiogenic shock

CHRONIC Rx

Management depends on whether patients are symptomatic and candidates for valve surgery. ACC/AHA guidelines for aortic valve replacement for chronic aortic regurgitation are summarized in Table 3.

- Symptomatic patients with severe AR who are candidates for valve surgery should proceed with valve replacement after medical optimization of heart failure. When surgery is contraindicated, TAVR is currently under assessment for treatment of native AR.
- Asymptomatic patients with severe AR and systolic dysfunction who are not surgical candidates should receive ACE/ARBs.
- Other medical treatments for AR are based on limited studies. Beta-blocker use is controversial but has been associated with a higher survival rate in severe AR. Vasodilatory therapies (nifedipine and enalapril) have failed to show benefit in reducing the need for or delaying AV replacement in asymptomatic, severe AR with normal systolic function, but ACE/ARB therapy may indeed benefit moderate to severe AR. Long-term vasodilator therapy with ACE inhibitors or nifedipine may be used in patients who have concomitant hypertension. There is no current definitive indication of medical therapy with afterload reduction for aortic regurgitation other than hypertension control.
- Beta-blockers in combination with ACE inhibitors are reasonable in patients with symptomatic severe AR or LV dysfunction when surgery cannot be performed because of concomitant comorbidities. In a retrospective cohort study of 756 patients with chronic AR, beta-blocker therapy was associated with decreased mortality. Patients treated with beta-blockers were more likely to be taking ACE inhibitors and dihydropyridine calcium channel blockers as well (53% vs. 40%). In the same study, patients treated with beta-blockers and undergoing AVR were also noted to have a mortality benefit.
- Diuretics and sodium restriction for CHF.
- Comparable efficacy of losartan and atenolol was shown in curbing aortic root dilatation growth in children and young adults (6 mo to 25 yr) with Marfan syndrome with similar outcomes of aortic regurgitation severity, surgery, aortic dissection, and death at 3 yr. Fig. 3 describes a management strategy for patients with chronic severe AR.

TABLE 3 American College of Cardiology/American Heart Association Guidelines for Aortic Valve Replacement (AVR) for Chronic Aortic Regurgitation (AR)

Class	Indication	Loe
I	AVR for symptomatic patients with severe AR regardless of LV systolic function (stage D).	B
	AVR for asymptomatic patients with chronic severe AR and LV systolic dysfunction (LVEF <50%) (stage C2).	B
	AVR for patients with severe AR (stage C or D) while undergoing cardiac surgery for other indications.	C
IIa	AVR is reasonable for asymptomatic patients with severe AR with normal LV systolic function (LVEF ≥50%), but severe LV dilation (stage C2, LVESD >50 mm).	B
	AVR is reasonable in patients with moderate AR (stage B) who are undergoing other cardiac surgery.	C
IIb	AVR may be considered for asymptomatic patients with severe AR and normal LV systolic function (stage C1, LVEF ≥50%) but severe LV dilation (LVEDD >65 mm) if surgical risk is low.*	C

*Particularly in the setting of progressive LV enlargement.
LOE, Level of evidence; *LV,* left ventricular; *LVEDD,* LV end-diastolic dimension; *LVEF,* LV ejection fraction; *LVESD,* LV end-systolic dimension.
From Zipes DP et al: *Braunwald's heart disease, a textbook of cardiovascular disease,* ed 11, Philadelphia, 2019, Elsevier.

REFERRAL

Surgical referral is reserved for the following patients:

- Patients with acute severe AR (i.e., infective endocarditis) and cardiogenic shock
- Symptomatic patients with severe AR regardless of LV systolic function (class I)
- Patients with hemodynamically stable severe AR undergoing CABG or surgery on the aorta or other heart valves
- Evidence of systolic dysfunction with left ventricular ejection fraction of less than 50% and asymptomatic patients with chronic severe AR
- Asymptomatic patients with severe AR and left ventricular ejection fraction >50%, but with left ventricular dilation:
  1. Echocardiographic end-systolic dimension >50 mm (Class IIa level of evidence) *or;*
  2. Echocardiographic end-diastolic dimension >65 mm with low surgical risk (Class IIb)

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Aortic Insufficiency (Patient Information)

AUTHORS: **Sarthak Khare, MD,** and **Argyro Papafilippaki, MD, FACC**

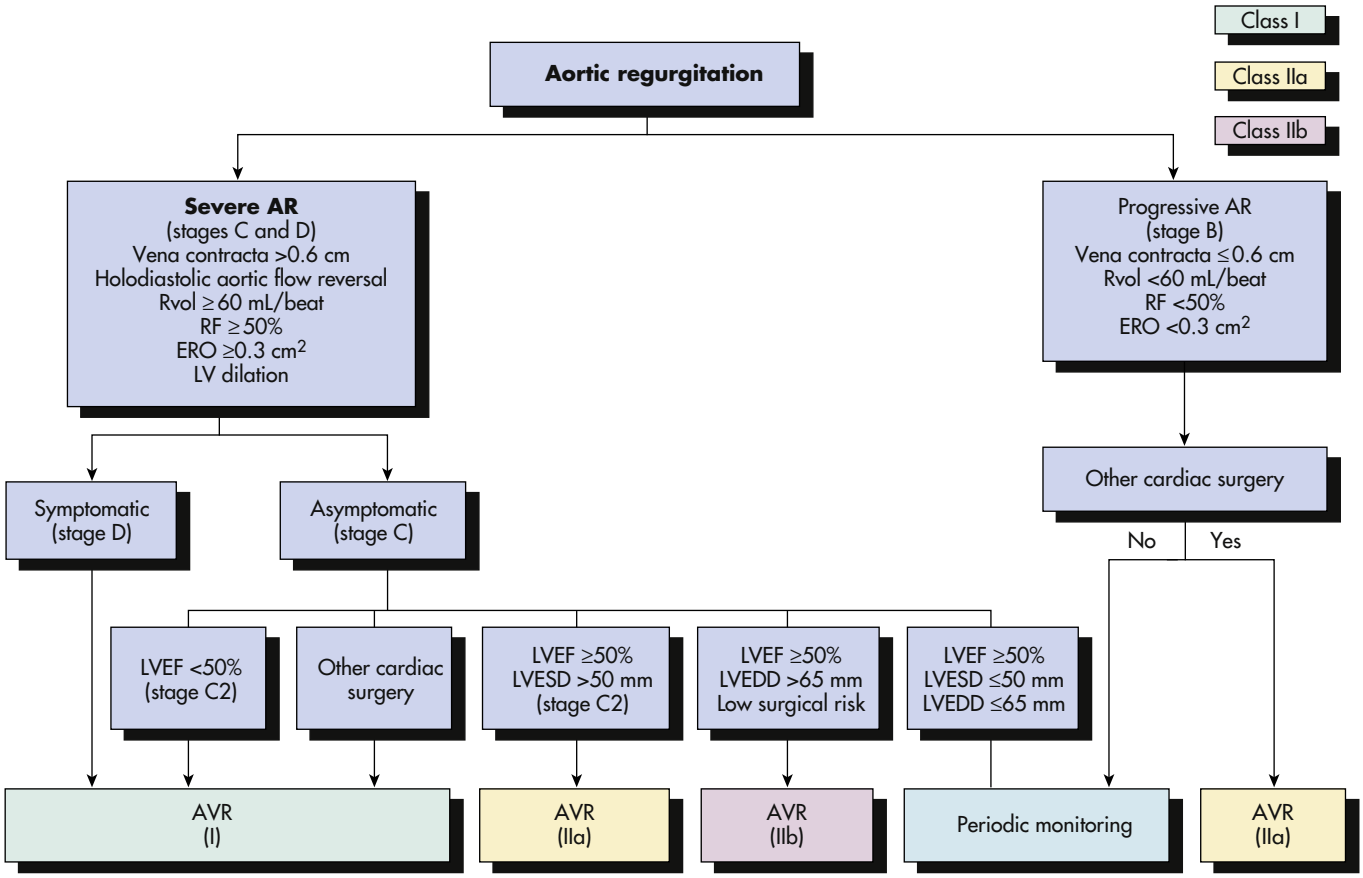

FIG. 3 Management strategy for patients with chronic severe aortic regurgitation (AR). *AVR,* Aortic valve replacement (valve repair may be appropriate in selected patients); *ERO,* effective regurgitant orifice; *LV,* left ventricle; *LVEDD,* left ventricular end-diastolic dimension; *LVEF,* left ventricular ejection fraction; *LVESD,* left ventricular end-systolic dimension; *RF,* regurgitant fraction; *RVol,* regurgitant volume. (From Zipes DP et al: *Braunwald's heart disease, a textbook of cardiovascular disease*, ed 11, Philadelphia, 2019, Elsevier.)

SUGGESTED READINGS

Enriquez-Sarano M, Tajik AJ: Clinical practice. Aortic regurgitation, *N Engl J Med* 351:1539, 2004.

Gilard M et al: Registry of transcatheter aortic valve implantation in high risk patients, *N Engl J Med* 366:1705-1715, 2012.

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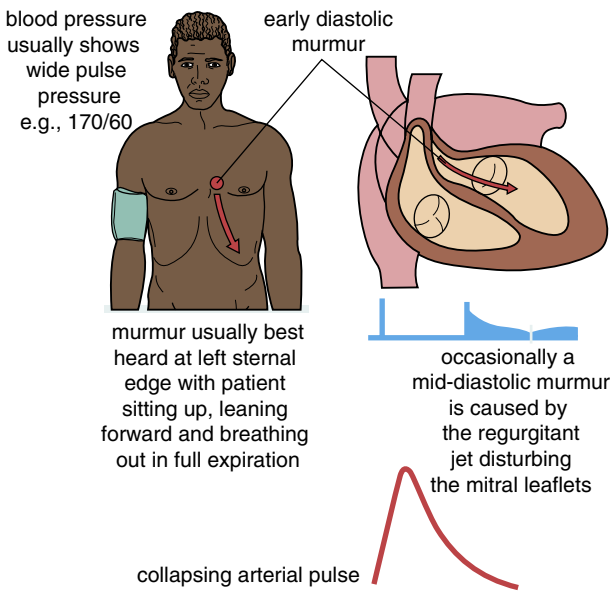

FIG. E1 Aortic regurgitation as an example of an early diastolic murmur. (From Epstein O et al: *Pocket guide to clinical examination,* ed 4, St Louis, 2009, Mosby.)

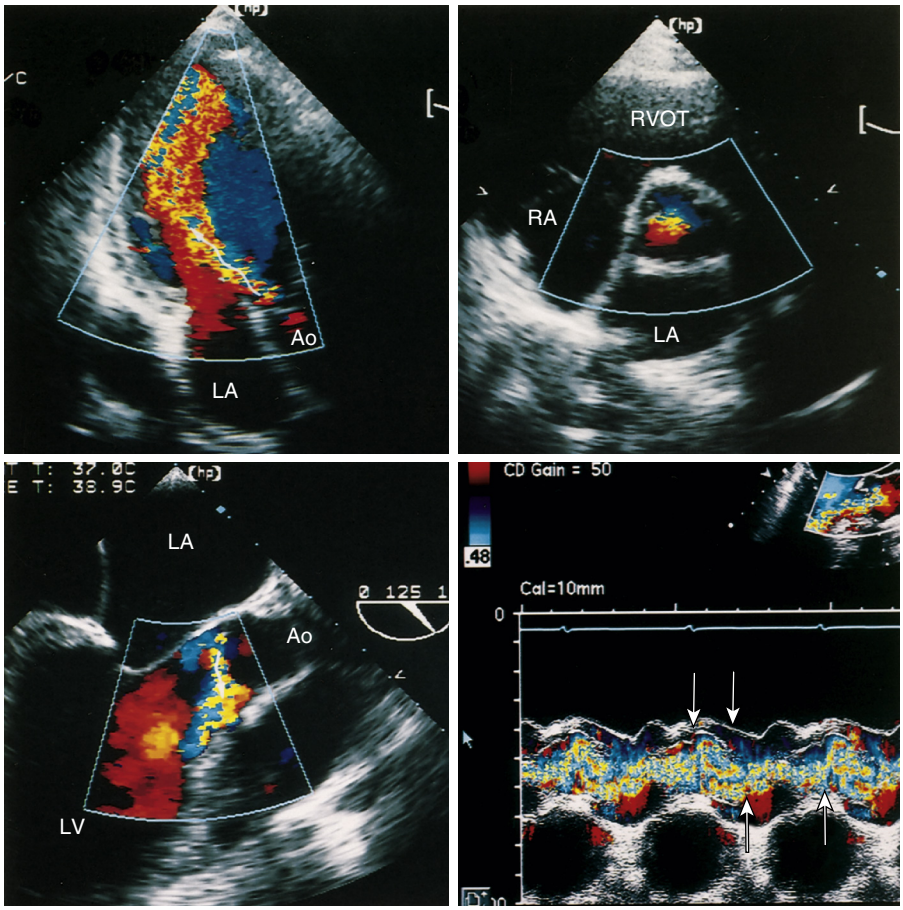

FIG. E2 Composite of echocardiograms recorded in patients with aortic regurgitation. The two top panels were recorded in the same patient and show, on the left, an apical long-axis view and, on the right, a parasternal short-axis view. In the apical long-axis view, note the fairly extensive confetti-like aortic regurgitation jet arising from the proximal aorta and traversing to the left ventricular apex. Note also that the aortic regurgitation jet velocities merge with the mitral inflow velocities, rendering quantitation problematic. The top right panel is recorded in the same patient and shows a central aortic regurgitation jet. The bottom left panel is a transesophageal echocardiogram recorded in a longitudinal view. Note the highly eccentric aortic regurgitation jet that appears to fill the entire width of the left ventricular outflow tract. This apparent filling of the left ventricular outflow tract is due to the posterior to anterior jet direction *(white arrow)* rather than to a substantial true width of the jet. The bottom right panel is a color M-mode echocardiogram recorded in a patient with aortic insufficiency in which the normal systolic flow can be appreciated as well as a continuous diastolic flow in the lumen of the aorta that represents aortic insufficiency. The two downward-pointing arrows denote the duration of systole, and the two upward-pointing arrows indicate the duration of diastole. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RVOT,* right ventricular outflow tract. (From Zipes DP et al [eds]: *Braunwald's heart disease,* ed 7, Philadelphia, 2005, Saunders.)

BASIC INFORMATION

DEFINITION

Aortic stenosis (AS) is obstruction of left ventricular systolic outflow due to aortic valve thickening/calcification generating a significant pressure gradient (aortic jet velocity of at least 2 m/sec). Symptoms typically appear when the valve orifice decreases to <1 cm^2 (normal orifice is 3 to 4 cm^2). Criteria for severe AS include a valve area <1.0 cm^2, a mean gradient >40 mm Hg, or a peak gradient >4 m/s. Doppler aortic jet velocities >5 m/sec is defined as very severe.

SYNONYMS

Aortic valve stenosis
AS

ICD-10CM CODES

I35.0	Nonrheumatic aortic (valve) stenosis
I35.2	Nonrheumatic aortic (valve) stenosis with insufficiency
Q23.0	Congenital stenosis of aortic valve

ETIOLOGY

- Idiopathic calcification of the aortic valve (most common cause in North America and Europe, presents at ages 60 to 80)
- Rheumatic heart disease: Characterized by commissural fusion leaving a small central orifice (most common cause worldwide)
- Progressive stenosis of congenital unicuspid or bicuspid valve (found in 1% to 2% of the population, presents at ages <30 yr for unicuspid and at ages 40 to 60 for bicuspid valves)
- Less common causes include rare metabolic disease (Fabry disease), systemic lupus erythematosus, radiation, end-stage renal disease, and obstructive vegetations/endocarditis may all cause early development of AS
- Genetic variation in the LPA locus, mediated by Lp(2) levels, is associated with aortic valve calcification across multiple ethnic groups and with incidental clinical aortic stenosis

EPIDEMIOLOGY & DEMOGRAPHICS

- Aortic stenosis is the most common valve lesion in adults in North America and Europe.
- The prevalence demonstrates a strong relationship with age, affecting 0.2% between ages 50 and 59 yr, 1.3% between 60 and 69 yr, 3.9% between 70 and 79 yr, and 9.8% between ages 80 and 89.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Harsh midsystolic, crescendo-decrescendo murmur (Fig. 1) best heard at base of heart and radiating into neck vessels; often associated with a thrill or ejection click; may also be heard well at the apex.
- Signs of severe AS include absent or diminished intensity of the second heart sound and/or slow-rising carotid upstroke with delayed amplitude (pulsus parvus et tardus), presence of S4, and a reverse splitting of the second heart sound.
- Early symptoms include decreased exercise tolerance, dyspnea on exertion, exertional dizziness or syncope, and exertional angina.
- Late symptoms include angina (secondary primarily to reduced coronary blood flow and increased total left ventricle [LV] oxygen demand), syncope, and heart failure.
- Table 1 summarizes the stages of valvular aortic stenosis.
- Pathophysiology: Antegrade velocities remain normal until the cross-sectional area of the left ventricular outflow tract (typically 3 to 4 cm^2) is reduced by roughly half. At this point, secondary to the increased resistance, the left ventricle systolic pressure starts to increase and the LV adapts with concentric hypertrophy. The hypertrophy allows for normalization of the wall stress and preservation of the ejection fraction, cardiac output, and left ventricular end diastolic pressures despite the LV/peripheral arterial system pressure gradient.
- LV hypertrophy eventually leads to LV diastolic dysfunction, which may herald early symptoms. That said, symptoms generally do not begin until stenosis becomes severe (valve area <1.0 cm^2, a mean gradient >40 mm Hg, or a peak gradient >4 m/s).
- For most patients, after becoming symptomatic, LV systolic function will begin to drop (decreased cardiac output and stroke volume) with development of signs and symptoms of overt heart failure. At this point, if a symptomatic severe AS patient does not

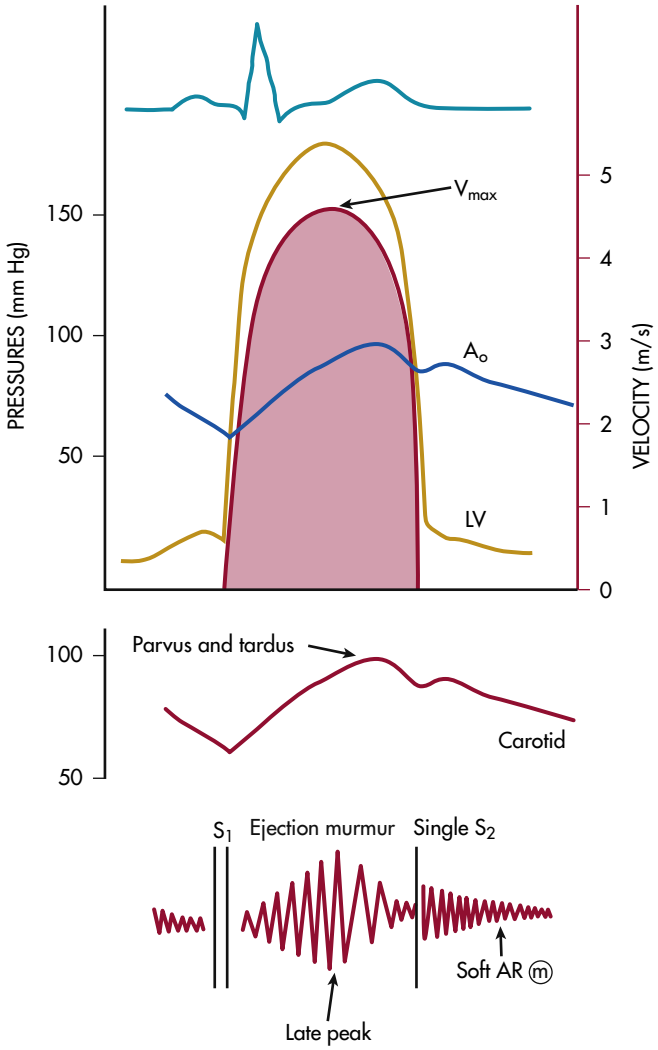

FIG. 1 Relationship between left ventricle (LV) and aortic (Ao) pressures and the Doppler aortic stenosis velocity curve *(in red)*. The pressure difference between the LV and aorta in systole is four times the velocity squared (the Bernoulli equation). Thus, a maximum velocity (Vmax) of 4.3 m/sec corresponds to a maximum LV to Ao pressure difference of 74 mm Hg and a mean systolic gradient of 44 mm Hg. On physical examination, the slow rate of rise and delayed peak in the carotid pulse (or parvus and tardus) matches the contour of the aortic pressure waveform. The murmur corresponds to the Doppler velocity curve with a harsh crescendo-decrescendo late-peaking systolic murmur, best heard at the aortic region (upper right sternal border). Often, a soft, high-pitched diastolic decrescendo murmur of aortic regurgitation also is appreciated. (From Bonow et al [eds]: *Braunwald's heart disease,* ed 9, Philadelphia, 2012, Saunders.)

TABLE 1 Stages of Valvular Aortic Stenosis

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	**At risk of AS**	Bicuspid aortic valve (or other congenital valve anomaly) Aortic valve sclerosis	Aortic Vmax <2 m/sec	None	None
B	**Progressive AS**	Mild to moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion or rheumatic valve changes with commissural fusion	***Mild AS:*** Aortic Vmax 2.0-2.9 m/sec or mean ΔP <20 mm Hg ***Moderate AS:*** Aortic Vmax 3.0-3.9 m/sec or mean ΔP 20-39 mm Hg	Early LV diastolic dysfunction may be presentNormal LVEF	None
C	**Asymptomatic severe AS**				
C1	Asymptomatic severe AS with preserved LVEF	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	***Severe AS:*** Aortic Vmax ≥4 m/sec or mean ΔP ≥40 mm Hg AVA typically is ≤1 cm^2 (or AVAi ≤0.6 cm^2/m^2) Very severe AS is an aortic Vmax ≥5 m/sec, or mean ΔP ≥60 mm Hg	LV diastolic dysfunction Mild LV hypertrophy Normal LVEF	None; exercise testing is reasonable to confirm symptom status
C2	Asymptomatic severe AS with LV dysfunction	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	Aortic Vmax ≥4 m/sec or mean ΔP ≥40 mm Hg AVA typically is ≤1 cm^2 (or AVAi ≤0.6 cm^2/m^2)	LVEF <50%	None
D	**Symptomatic severe AS**				
D1	Symptomatic severe high-gradient AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	***Severe AS:*** Aortic Vmax ≥4 m/sec, or mean ΔP ≥40 mm Hg AVA typically is ≤1 cm^2 (or AVAi ≤0.6 cm^2/m^2), but may be larger with mixed AS/AR	LV diastolic dysfunction LV hypertrophy Pulmonary hypertension may be present	Exertional dyspnea or decreased exercise tolerance Exertional angina Exertional syncope or presyncope
D2	Symptomatic severe low-flow/low-gradient AS with reduced LVEF	Severe leaflet calcification with severely reduced leaflet motion	AVA ≤1 cm^2 with resting aortic Vmax <4 m/sec, or mean ΔP <40 mm Hg Dobutamine stress echo shows AVA ≤1 cm^2 with Vmax ≥4 m/sec at any flow rate	LV diastolic dysfunction LV hypertrophy LVEF <50%	HF, angina, syncope or presyncope
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	Severe leaflet calcification with severely reduced leaflet motion	AVA ≤1 cm^2 with aortic Vmax <4 m/sec, or mean ΔP <40 mm HgAVAi ≤0.6 cm^2/m^2 Stroke volume index <35 ml/m^2 Measured when the patient is normotensive (systolic BP <140 mm Hg)	Increased LV relative wall thickness Small LV chamber with low-stroke volume. Restrictive diastolic filling LVEF ≥50%	HF, angina, syncope or presyncope

AR, Aortic regurgitation; *AS,* aortic stenosis; *AVA,* aortic valve area; *AVAi,* aortic valve area indexed to body surface area; *BP,* blood pressure; *HF,* heart failure; *LV,* left ventricle; *LVEF,* left ventricular ejection fraction; *ΔP,* pressure gradient; *Vmax,* maximum aortic velocity. From Nishimura RA et al: 2014 AHA/ACCF guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. In Mann DL et al (eds): *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.

undergo valve replacement, their mortality drastically increases.
- Acquired von Willebrand disease is seen in approximately 20% of severe AS, which can lead to GI bleeding from angiodysplasia (Heyde syndrome) that resolves after aortic valve replacement.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hypertrophic cardiomyopathy
- Mitral regurgitation
- Ventricular septal defect
- Aortic sclerosis. Aortic stenosis is distinguished from aortic sclerosis by the degree of valve impairment. In aortic sclerosis, the valve leaflets are abnormally thickened but obstruction to outflow is absent or minimal
- Subvalvular membrane or supravalvular AS
- Stages of valvular AS
  1. Stage A = at risk of AS
  2. Stage B = progressive AS (formerly known as mild and moderate AS)
  3. Stage C = asymptomatic severe AS
  4. Stage D = symptomatic severe AS

WORKUP

- Echocardiography: The primary test for diagnosis (see "Imaging Studies")
- ECG: May demonstrate left ventricular hypertrophy and/or left atrial abnormality
- Chest radiograph: May demonstrate cardiomegaly. Poststenotic dilation of the ascending aorta may also be evident
- Cardiac catheterization in selected patients (see "Imaging Studies")
- Dobutamine challenge (for low-gradient, low-flow AS)

IMAGING STUDIES

- Doppler echocardiography: Used to evaluate structure and anatomy of the valve. Hemodynamics can easily be assessed; allows calculation of both aortic valve area and estimation of pressure gradients to determine severity of AS (Fig. 2). Furthermore, allows evaluation of the LV size and function and pulmonary pressures.
- Chest x-ray:
  1. Poststenotic dilation of the ascending aorta
  2. Calcification of aortic cusps
  3. Rounding of left ventricle (LV) apex

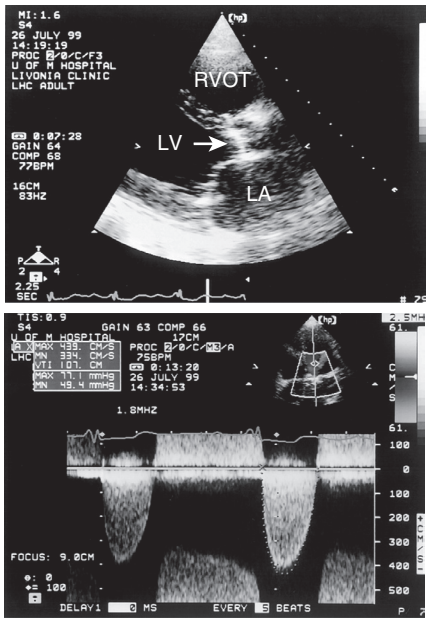

FIG. 2 Echocardiogram recorded in a patient with severe aortic stenosis. The *top panel* is a parasternal long-axis view recorded in systole. Left ventricular function is diminished. The aortic valve is markedly thickened and partially calcified. Its motion is markedly reduced, and in systole it appears that the valve occludes the orifice *(arrow)*. The *lower panel* is a continuous-wave Doppler recorded from the apex of the left ventricle along a line aimed through the stenotic aortic valve. Note the aortic stenosis signal below the zero crossing line. The peak velocity is 430 cm/sec, which corresponds to a maximum gradient of 77 mm Hg and a mean gradient of 49.4 mm Hg. *LA,* Left atrium; *LV,* left ventricle; *RVOT,* right ventricular outflow tract. (From Zipes DP et al [eds]: *Braunwald's heart disease,* ed 7, Philadelphia, 2005, Saunders.)

- ECG:
  1. Left ventricular hypertrophy (found in 80% of patients)
  2. Left atrial enlargement
  3. Atrial fibrillation (in late disease)
- Cardiac catheterization: Indicated in symptomatic patients awaiting aortic valve replacement (AVR) in order to detect coexisting coronary artery stenosis that may need bypass at the same time as aortic valve replacement. Previously, cardiac catheterization was used in symptomatic patients when noninvasive tests are inconclusive or when there is a discrepancy between noninvasive tests and clinical findings regarding severity of AS. Due to the increased risk of stroke when crossing the valve and with the advent of newer or improved imaging modalities (cardiac MR, PET-CT, TEE), there is rarely a role to directly measure the gradient across the valve.
- A CT with contrast for imaging the aorta may be needed for annular sizing, aortic measurements and if a transcatheter aortic valve replacement (TAVR) is planned, the CT scan is crucial to planning TAVR approach.
- Exercise testing: Strongly encouraged for any patient with stage C "asymptomatic" severe AS to evaluate exercise tolerance and to look for a fall in systemic blood pressure while exercising.

Rx TREATMENT

GENERAL Rx

MEDICAL:

- Once symptomatic, the mainstay of treatment is replacement of the valve. AS is a surgical disease. Fig. 3 summarizes a treatment strategy for patients with severe AS.
- Optimize loading conditions by keeping a normal volume status (gentle diuresis for volume overload as preload dependent) and controlling hypertension (HTN) but avoid vasodilators (nitrates); maintain sinus rhythm.
- In 2007, the AHA guidelines for prevention of infectious endocarditis were revised and routine antibiotic prophylaxis to undergo dental or other invasive procedures is no longer recommended, unless the patient has prior endocarditis.

INDICATIONS FOR AORTIC VALVE REPLACEMENT: Valve replacement is the treatment of choice in symptomatic patients because there is a 50% mortality rate at 2 yr with medical therapy alone. If a patient does not have a >1 yr life expectancy postprocedure or quality of life will not be improved by the aortic valve, then replacement should not be considered, but rather palliative therapies should be discussed. ACC/AHA guidelines for aortic valve replacement for aortic stenosis are summarized in Table 2.

Percutaneous aortic balloon valvuloplasty serves best as palliative therapy in severely symptomatic patients who are not surgical candidates and as a bridge to surgery in hemodynamically unstable adult patients. It is not an option in patients who are good candidates for valve replacement because restenosis occurs in most adult patients at 6 mo. Updated ACC /AHA guidelines for choice of surgical versus transcatheter treatment of aortic stenosis are summarized in Table 3.

If the patient does fulfill the intervention criteria (>1 yr life expectancy postprocedure and quality of life will be improved by the aortic valve), then replacement can be further considered.

Valve replacement is a **Class I Indication** for any patients with:

- Stage D1: Symptomatic severe AS
- Stage C2: Asymptomatic severe AS with LV ejection fraction (EF) <50%
- Stage C1 or C2: Asymptomatic severe AS undergoing CABG or surgery on the aorta or other heart valves

Valve replacement is a **Class IIa indication** for patients with:

- Stage D2: Low-flow/low gradient (with low ejection fraction <50%) with a positive low-dose dobutamine stress echo
- Stage D3: Symptomatic patients with low-flow/low gradient severe AS with a **normal LVEF** ≥50%, a valve area ≤1.0 cm^2, and a stroke volume index <35 ml/m^2
- (c) Stage C: Asymptomatic severe AS and abnormal blood pressure response (decrease in systolic blood pressure) or decreased exercise tolerance during exercise
- (d) Stage C: Asymptomatic patients with critical AS (peak velocity >5 m/s or mean pressure gradient >60 mm Hg) with low surgical risk
- (e) Stage B: Patients with moderate AS who are undergoing cardiac surgery for other indications

Valve replacement is a **Class IIb indication** for patients with:

- Stage C: Asymptomatic severe AS in a low-risk patient showing rapid progression of disease (Vmax >0.3m/s/yr).
- When deciding replacement strategy, surgical aortic valve replacement (SAVR) vs. transcatheter aortic valve replacement (TAVR), in all cases a heart team approach is a Class I indication. TAVR is a catheter-based technology that allows for implantation of a prosthetic valve without open heart surgery, decreasing recovery time and hospital stay. Historically, the replacement strategy has been driven by patient surgical risk. Primarily due to TAVR trial design, patients were classified by their STS-PROM score into four categories: extreme surgical risk (absolute surgical contraindication), high surgical risk (STS-PROM score >8), intermediate surgical risk (STS-PROM score 4 to 8), and low surgical risk (STS-PROM score <4).
- For the **extreme surgical risk** patients and **high surgical risk** patients (STS-PROM score >8), if a TAVR approach is feasible, then the recommendation is for a TAVR strategy. In a large meta-analysis of these high-risk patients with severe AS who were candidates for surgery, transfemoral TAVR (but not transthoracic TAVR) was associated with lower mortality at 2 yr. The surgical group had double the incidence of new-onset atrial fibrillation and major bleeding, but the TAVR group had a higher rate of paravalvular regurgitation and vascular complications.
- For **intermediate surgical risk** (STS-PROM 4 to 8), if TAVR approach is feasible and there is an absence of high-risk anatomical features that would increase the risk of a transcatheter approach, then the recommendation is for a TAVR strategy. In these intermediate-risk patients, transfemoral TAVR was associated with lower mortality rates, and nontransfemoral TAVR was similar to surgical aortic valve replacement with respect to death or disabling stroke rates, as demonstrated by the same large meta-analysis of four randomized trials. The notable differences were that TAVR resulted in larger aortic valve areas and had a lower rate of acute kidney injury, severe bleeding, and new-onset atrial fibrillation, whereas surgery resulted in fewer major vascular complications and less paravalvular aortic regurgitation.
- For **low surgical risk** patients (STS-PROM <4), if the patient meets the following four criteria: >65 yr old, transcatheter approach

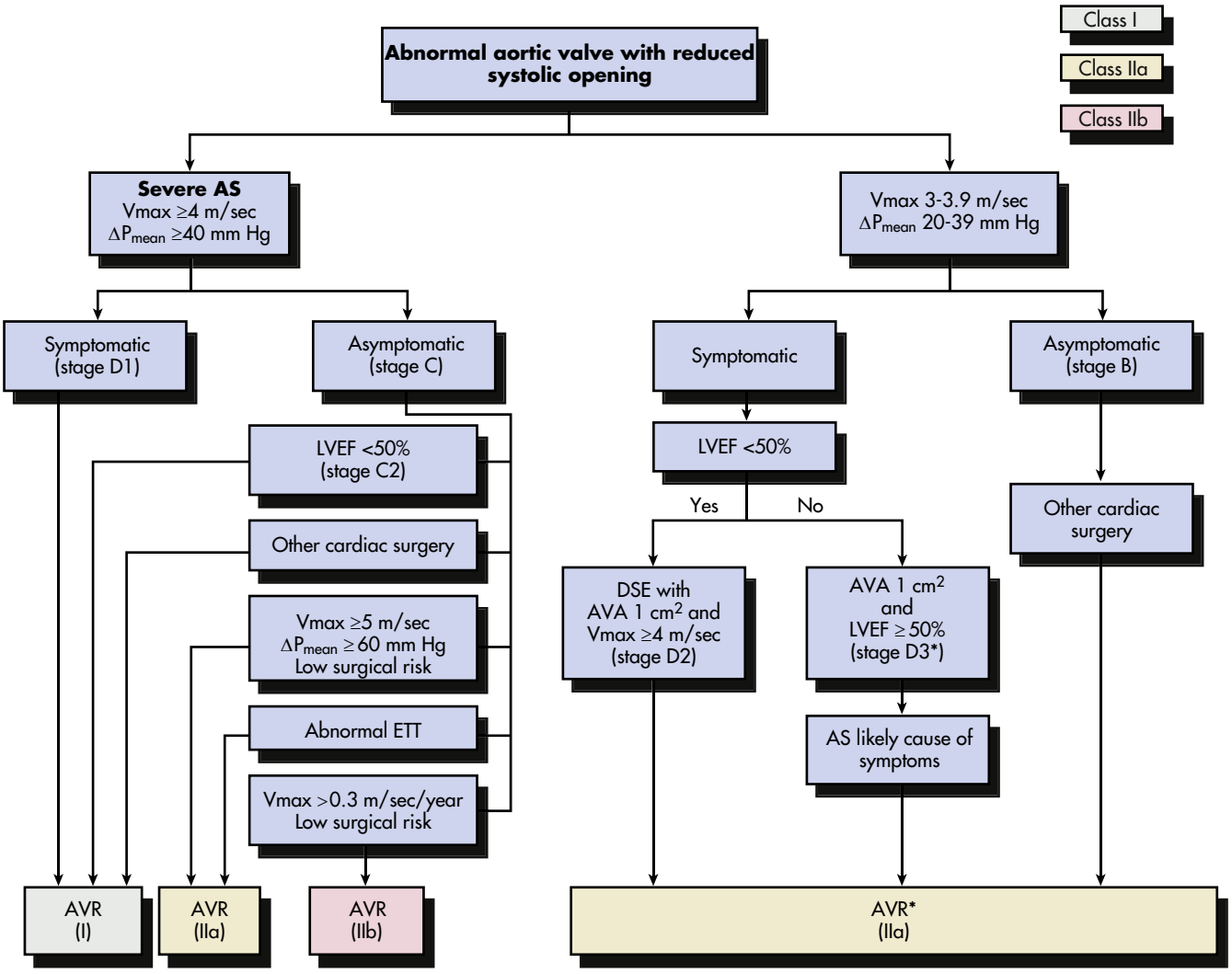

FIG. 3 Management strategy for patients with severe AS. Periodic monitoring is indicated for all patients in whom AVR is not yet indicated, including those with asymptomatic AS (stage B or C) and those with low-gradient AS (stage D2 or D3) who do not meet criteria for intervention. AVR should be considered with stage D3 AS only if valve obstruction is the most likely cause of symptoms, stroke volume index is <35 ml/m_2, indexed AVA is ≤0.6 cm_2/m_2, and data are recorded when the patient is normotensive (systolic BP <140 mm Hg). *AS,* Aortic stenosis; *AVA,* aortic valve area; *AVR,* aortic valve replacement; *BP,* blood pressure; *DSE,* dobutamine stress echocardiography; *ETT,* exercise treadmill test; *LVEF,* left ventricular ejection fraction; ΔP_{mean}, mean pressure gradient; *Vmax,* maximum velocity. (From Nishimura RA et al: 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology /American Heart Association Task Force on Practice Guidelines. In Mann DL et al [eds]: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.)

is feasible, aortic valve is trileaflet, and there is an absence of high-risk anatomic features that would increase the risk of transcatheter approach, then the recommendation is for a TAVR strategy. For these low-risk patients, from the PARTNER 3 trial, there was a significant lower primary endpoint (composite death, stroke, or rehospitalization at 1 yr).

DISPOSITION

- The presence of even mild symptoms is an indicator of poor survival for patients with AS. The average duration of symptoms before death is angina, 5 yr; syncope, 3 yr; CHF, 2 yr.
- Approximately 75% of patients with symptomatic AS will die within 3 yr of symptom onset unless the aortic valve is replaced.

REFERRAL

- A heart team referral for valve replacement in all symptomatic AS patients (Class I indication). There are studies that are examining the presence of moderate or severe valvular calcification, together with a rapid increase in aortic jet velocity and elevated BNP, to identify patients with a very poor prognosis who should be considered for early valve replacement rather than delayed until symptoms develop. Additionally, patients with severe AS who are asymptomatic should be considered for exercise stress test to see if they are truly without symptoms (low exercise tolerance) or if the BP drops with exercise, both which would be indications for a heart team referral.
- In asymptomatic patients, Doppler echocardiography is recommended every 6 to 12 months for severe aortic stenosis, every 1 to 2 yr for moderate disease, and every 2 to 3 yr for mild disease. Should have a low threshold to repeated echocardiogram for any change in symptoms or exam.
- Referral to cardiology should be considered in any patients with severe AS and in particular those with low-flow, low-gradient (low

TABLE 2 ACC/AHA Guidelines for Aortic Valve Replacement (AVR) for Aortic Stenosis (AS)

Class	Indication	LOE
I	AVR with severe high-gradient AS who have symptoms by history or on exercise testing (stage D1).	B
	AVR for asymptomatic patients with severe AS (stage C2) and LVEF less than 50%.	B
	AVR for patients with severe AS (stage C or D) when undergoing other cardiac surgery.	B
IIa	AVR is reasonable for asymptomatic patients with very severe AS (stage C1, aortic velocity ≥5 m/sec) and low surgical risk.	B
	AVR is reasonable in asymptomatic patients (stage C1) with severe AS and decreased exercise tolerance or an exercise fall in blood pressure.	B
	AVR is reasonable in symptomatic patients with low-flow/low-gradient severe AS with reduced LVEF (stage D2) with a low-dose dobutamine stress study that shows an aortic velocity of 4 m/sec or more (or mean pressure gradient ≥40 mm Hg) with a valve area of 1.0 cm^2 or less at any dobutamine dose.	B
	AVR is reasonable in symptomatic patients with low-flow, low-gradient severe AS (stage D3) who are normotensive and have LVEF of 50% or greater, if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms.	C
	AVR is reasonable for patients with moderate AS (stage B) (aortic velocity, 3.0 to 3.9 m/sec) who are undergoing other cardiac surgery.	C
IIb	AVR may be considered for asymptomatic patients with severe AS (stage C1) and rapid disease progression and low surgical risk.	C

LOE, Level of evidence; *LVEF,* left ventricular ejection fraction.
Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 3 Updated ACC/AHA Guidelines for Choice of Surgical Versus Transcatheter Treatment of Aortic Stenosis (AS)

Class	Indication	LOE
I	For patients in whom TAVR or high-risk surgical AVR is being considered, members of a heart valve team should collaborate to provide optimal patient care.	C
	Surgical AVR in symptomatic and asymptomatic patients with severe AS who meet an indication for AVR (listed in Table 2) when surgical risk is low or intermediate. (*Modified 2017*)	B
	TAVR in patients who meet an indication for AVR for AS who have a prohibitive surgical risk and a predicted post-TAVR survival >12 months. (*Modified 2017*)	A
	TAVR or surgical AVR in patients with severe AS who meet an indication for AVR and who have high surgical risk. (*Modified 2017*)	A
IIa	TAVR is a reasonable alternative to surgical AVR for symptomatic patients with severe AS and an intermediate surgical risk. (*New 2017*)	B
IIb	Percutaneous aortic balloon dilation may be considered as a bridge to surgical or transcatheter AVR in severely symptomatic patients with severe AS.	C
III	TAVR is not recommended in patients in whom the existing comorbidities would preclude the expected benefit from correction of AS.	B

LOE, Level of evidence; *AVR,* aortic valve replacement; *TAVR,* transcatheter AVR.
Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

ejection fraction) symptomatic aortic stenosis for further workup (dobutamine stress echo).
- Balloon valvuloplasty is useful in infants and children or poor surgical candidates who do not have calcified valve apparatus; it can be done as an intermediate procedure to stabilize high-risk patients before surgery.
- Role of palliative care:
  1. If life expectancy with aortic valve replacement (SAVR or TAVR) is <1 yr **or** the patient's quality of life is unlikely to improve after aortic valve replacement (due to coexisting significant comorbidities), palliative care consultation is extremely valuable as it focuses on shared decision making as well as improving quality of life without interruption of conservative medical therapy.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Aortic Stenosis (Patient Information)

AUTHOR: **GerardH. Daly, MD, MSc**

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Aphthous Ulcers

BASIC INFORMATION

DEFINITION

Small painful ulcers predominantly of the oral mucosa

SYNONYMS

Aphthae
Canker sores
Recurrent aphthous stomatitis (RAS)
Recurrent oral aphthae

ICD-10CM CODE
K12.0 Recurrent oral aphthae

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown
PEAK INCIDENCE: Adolescence
PREVALENCE: One in five individuals have been affected by aphthous ulcers in their lifetime.
PREDOMINANT SEX AND AGE: Most commonly affects women, adolescents, and young adults under the age of 40.
GENETICS: Up to 40% of patients have a family history of aphthous ulcers.
RISK FACTORS: Genetic factors, stress, trauma, tobacco, viral and bacterial infections, nutritional deficiencies, endocrine and immune disturbances

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Aphthous ulcers, also referred to as canker sores, are typically small round or oval-shaped lesions with a gray-white or yellow pseudomembranous base and erythematous halo (Fig. E1). Aphthous ulcers can affect any age group. However, they generally appear in childhood and subside by the third decade. The exact cause of aphthous ulcers is poorly understood, but multiple factors may play a role in their occurrence. These include, but are not limited to, trauma, nutritional deficiencies, viral and bacterial infections, medications, food hypersensitivities, hormonal or endocrine changes, and tobacco use. In the absence of systemic disease and in cases where aphthae reoccur, it is termed Recurrent Aphthous Stomatitis (RAS).
- **Recurrent aphthous stomatitis** has three subtypes including minor RAS (up to 80% of cases), major RAS (10% of cases), and herpetiform RAS (10%).
- **Minor RAS:** Classification of minor RAS depends on the number and size of the ulcers. Generally, 1 to 5 superficial aphthae less than 10 mm in size and localized to the lips, buccal mucosa, tongue, and floor of the mouth. Lesions tend to self-resolve in 4 to 14 days and leave no scarring.
- **Major RAS:** These lesions are similar in appearance to minor RAS except that their size, number, and location increase. Generally, they are greater than10 mm in diameter. They are deeper, extend to the gingiva and pharyngeal mucosa, last for weeks to months, and have a higher risk for scarring.
- **Herpetiform RAS:** Herpetiform lesions are often smaller, 1 to 3 mm. They are also deeper and in greater numbers (5 to 100). Ulcers are generally gray with irregular and nonerythematous borders. Smaller ulcers may cluster and coalesce to form larger ulcers. Ulcers are generally very painful, involve the floor of the mouth and ventral surface of the tongue, resolve within 14 days, and generally leave no visible scar.

ETIOLOGY

Both hereditary and environmental causes may contribute to the disease process.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Behçet syndrome
- Mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome
- Systemic lupus erythematosus
- Gluten-sensitive enteropathy
- Inflammatory bowel disease
- Human immunodeficiency virus infection
- Herpes simplex virus
- Cyclic neutropenia
- Periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA)
- Hyperimmunoglobulin D syndrome
- Agranulocytosis
- Autoimmune bullous disease
- Oral erosive lichen planus
- Drug-induced mucosal ulcers

Table E1 summarizes the etiologies and differential diagnosis of recurrent aphthae.

WORKUP

- Clinical history: A detailed history includes associated illness, family history, the frequency of ulceration, number and size of ulcers, duration of the outbreak, and location of ulcers including non-oral lesions.

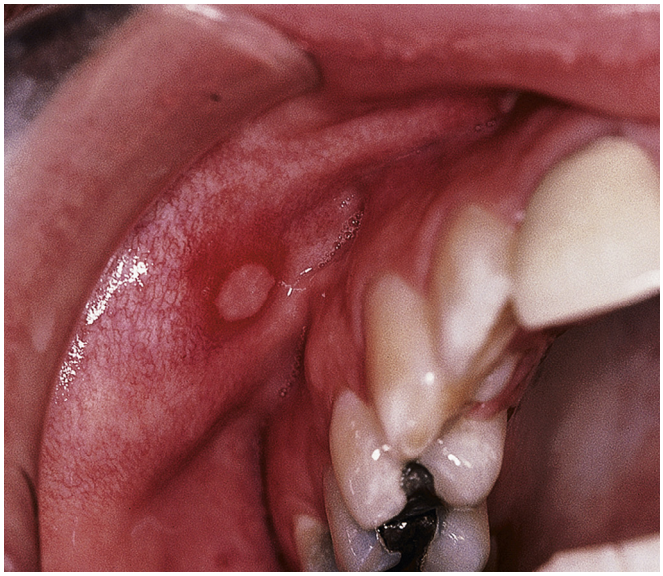

FIG. E1 Recurrent aphthous stomatitis. Minor aphthous ulcer. Shallow, creamy-white ulceration surrounded by an intensely red halo and located on non-keratinized mucosa, representing a classic presentation. (From Bolognia J et al: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.)

TABLE E1 Recurrent Aphthae—Etiologies and Differential Diagnosis

Etiologies

- Idiopathic (immune-mediated)
- Related to an underlying systemic disorder: Inflammatory bowel disease, systemic lupus erythematosus, HIV infection, Behçet syndrome, reactive arthritis*, cyclic neutropenia, PFAPA (*p*eriodic *f*ever, *a*phthous stomatitis, *p*haryngitis, and *a*denitis) syndrome, certain hereditary periodic fever syndromes (e.g., HIDS, NOMID)
- Possibly related to an underlying nutritional disorder (controversial): Vitamin B_{12}, folate, or iron deficiency

Differential Diagnosis

- Recurrent erosions and ulcerations due to an inflammatory disorder, e.g., erythema multiforme, fixed drug eruption, contact stomatitis: Less pain at onset, less peripheral erythema
- Recurrent herpes simplex viral infection: Only involves keratinized mucosa (hard palate, attached gingiva) in immunocompetent hosts.
- Trauma: Less pain at onset, less peripheral erythema, more ragged edges

HIDS, Hyperimmunoglobulinemia D with periodic fever syndrome; *HIV,* human immunodeficiency virus; *NOMID,* neonatal-onset multisystem inflammatory disease.
*Previously referred to as Reiter disease.
Modified from Bolognia J et al: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

TABLE E2 Recurrent Aphthous Stomatitis (RAS) Subtypes

	Minor RAS	Major RAS	Herpetiform RAS
DESCRIPTION	Round or oval lesions with gray, white, or yellow bases and erythematous border	Round or oval lesions with gray, white, or yellow bases and erythematous border	Small, deep ulcers, may cluster and coalesce to form larger irregular shaped ulcers
LOCATION	Lips, cheeks, tongue, the floor of mouth	Lips, pharynx	Lips, cheeks, tongue, the floor of mouth
SIZE OF ULCERS	<10 mm	>10 mm	1-3 mm
NUMBER OF ULCERS	1-5	1-10	10-100
DURATION	4-14 days; without scarring	>4 wk; possible scarring	<4 wk; without scarring

TABLE E3 Therapeutic Ladder for Complex Aphthosis

Local therapy (agents may be used in combination)

Local anesthetics (2)
Superpotent topical corticosteroids (1*/2) or corticosteroid inhalers (2)
Intralesional corticosteroids (2)
Topical tacrolimus (3)

Systemic therapy

Colchicine (1†/2)
Dapsone (1†/2)
Combination of colchicine and dapsone (2)
Thalidomide (1)

Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.
*Clobetasol propionate in an adhesive denture paste.
†In patients with Behçet syndrome.
Adapted from Letsinger JA et al: *J Am Acad Dermatol* 52:500-8, 2005, with permission. In Bolognia J et al: *Dermatology*, ed 4, Philadelphia, 2018, Elsevier.

- Physical examination: Aphthous ulcers are well-circumscribed small round or oval-shaped lesions with gray-white or yellow pseudomembranous bases with an erythematous halo. RAS may be further broken down into its subtypes as outlined in Table E2.
- RAS is generally a clinical diagnosis; however, if RAS is persistent, further laboratory testing may be considered.
- Biopsy: Typically not required; however, in more severe or persistent cases a biopsy may aid in ruling out other mucosal pathologies.

LABORATORY TESTS

If RAS is severe, persistent, or occurs at a later age of onset, it is reasonable to investigate further for other potential causes. Laboratory screening for other causes includes a complete blood count, inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein, and nutritional deficiency markers such as serum B^{12}, folate, and iron.

IMAGING STUDIES

There are no imaging studies indicated in the workup of aphthous ulcers.

Rx TREATMENT

The exact cause of aphthous ulcers and RAS is still largely unknown, and the first-line treatment modalities are aimed at supportive care and speeding up healing time. Treatment is based on low-quality studies, and there are no curative pharmacological treatments. If aphthae are secondary to an underlying disease, treatment of the primary disease may reduce the duration of the aphthae. Treatment is a stepwise approach (Table E3) and includes good oral hygiene, avoiding trauma (e.g., biting lips or cheeks, oral hardware including braces) and known drug or food triggers, topical anesthetics, topical corticosteroids, topical antimicrobials, and systemic medications.

ACUTE GENERAL Rx

- Topical anesthetics: Can be used before eating for temporary relief
  1. 2% viscous lidocaine applied directly or used as "swish and spit."
  2. Diphenhydramine liquid (12.5 mg/5 ml): Use 5 ml as "swish and spit."
- Topical corticosteroids: First-line treatment for mild to moderate RAS
  3. Dexamethasone elixir (0.5 mg/5 ml): Take 5 ml, swish for 5 min before spitting out. Repeat three to four times daily.
- Topical antimicrobial: Not typically necessary in mild cases but may be beneficial in preventing secondary infection in more severe cases or cases involving other immunosuppressive medications
  1. Chlorhexidine 0.12% mouth rinse: Use 15 ml as "swish and spit" twice daily.
  2. Nystatin suspension: "Swish and swallow" four times daily.

CHRONIC Rx

Oral options may be tried in patients reporting no benefit with topical treatment alone or in case of severe RAS.

- Oral prednisone 20 mg to 40 mg daily for 4 to 7 days is typically the first-line treatment of acute severe RAS.
- Montelukast 10 mg daily may be a safe alternative when severe RAS is not well controlled with oral corticosteroids.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Ascorbic acid 2000 mg/day may be considered as an adjunct to topical therapy in managing minor RAS.
- Zinc 50 mg/day may also be beneficial in wound healing.

NONPHARMACOLOGIC THERAPY

Laser therapy or chemical cauterization have been cited as an adjunct to the above therapies to help reduce acute pain; however, their ability to prevent recurrent episodes of aphthae is still unknown.

DISPOSITION

Although a painful condition, aphthous ulcers and RAS are generally self-resolving with an average healing time of 2 wk and carry an excellent prognosis. Consider an alternative etiology if the patient exhibits systemic symptoms or has other pertinent past medical history.

REFERRAL

Referral to a specialist is recommended if an alternative diagnosis is more likely. Severe or persistent cases of RAS may be referred to dermatology.

PREVENTION

Practice good oral hygiene.

PATIENT & FAMILY EDUCATION

Educate patients and parents of pediatric patients on pain control with the use of topical anesthetics before eating or drinking to prevent dehydration. Topical pain control is also beneficial before performing basic dental hygiene. Avoid citrus juices and spicy or salty foods. Educate regarding return precautions including worsening pain, the spread of ulcers (especially beyond oral mucocutaneous membranes), fever, decreased fluid intake, or other systemic symptoms.

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Appendicitis PTG

BASIC INFORMATION

DEFINITION

Appendicitis is the acute inflammation of the vermiform appendix.

ICD-10CM CODES

K35.2	Acute appendicitis with generalized peritonitis
K35.3	Acute appendicitis with localized peritonitis
K35.80	Unspecified acute appendicitis
K35.89	Other acute appendicitis
K36	Other appendicitis
K37	Unspecified appendicitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Appendicitis occurs in 10% of the population, most commonly between the ages of 10 and 30 yr. Median age is 22 yr. Lifetime risk is 7% to 14%.
- Approximately 300,000 appendectomies are performed in the U.S. each yr.
- It is the most common abdominal surgical emergency.
- Incidence of appendicitis has declined over the past 30 yr.
- Male:female ratio is 3:2 until mid-20s; it equalizes after age 30 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- In children with abdominal pain, fever is the single most useful sign associated with appendicitis. Vomiting, rectal tenderness, and rebound tenderness along with fever are more indicative of appendicitis in children than in adults.
- Abdominal pain: Initially the pain may be epigastric or periumbilical in nearly 50% of patients; it subsequently localizes to the right lower quadrant within 12 to 18 hr. Pain can be found in back or right flank if appendix is retrocecal or in other abdominal locations if there is malrotation of the appendix.
- Pain with right thigh extension *(psoas sign),* low-grade fever: Temperature may be >38° C if there is appendiceal perforation.
- Pain with internal rotation of the flexed right thigh *(obturator sign)* is present.
- Right lower quadrant (RLQ) pain on palpation of the left lower quadrant (LLQ) *(Rovsing sign):* Physical examination may reveal right-sided tenderness in patients with pelvic appendix.
- Point of maximum tenderness is in the RLQ *(McBurney point).*
- Nausea, vomiting, tachycardia, cutaneous hyperesthesias at the level of T12 can be present.

ETIOLOGY

Obstruction of the appendiceal lumen with subsequent vascular congestion, inflammation, and edema; common causes of obstruction are:

- Fecaliths: 30% to 35% of cases (most common in adults)
- Foreign body: 4% (fruit seeds, pinworms, tapeworms, roundworms, calculi)
- Inflammation: 50% to 60% of cases (submucosal lymphoid hyperplasia [most common etiology in children, teens])
- Neoplasms: 1% (carcinoids, metastatic disease, carcinoma)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Intestinal: Regional cecal enteritis, incarcerated hernia, cecal diverticulitis, intestinal obstruction, perforated ulcer, perforated cecum, Meckel diverticulitis
- Reproductive: Ectopic pregnancy, ovarian cyst, torsion of ovarian cyst, salpingitis, tuboovarian abscess, mittelschmerz, endometriosis, seminal vesiculitis
- Renal: Renal and ureteral calculi, neoplasms, pyelonephritis
- Vascular: Leaking aortic aneurysm
- Psoas abscess
- Trauma
- Cholecystitis
- Mesenteric adenitis
- Table 1 summarizes the differential diagnosis of appendicitis

WORKUP

Patients with RLQ pain, nausea, vomiting, anorexia, and RLQ rebound tenderness should undergo prompt clinical and laboratory evaluation. Imaging studies are generally not necessary in typical appendicitis and generally reserved for patients with an equivocal likelihood of appendicitis. They are useful when the diagnosis is uncertain. Laparoscopy may be useful as both a diagnostic and a therapeutic modality.

LABORATORY TESTS

- Complete blood count with differential reveals leukocytosis with a left shift in 90% of patients with appendicitis. Total white blood cell (WBC) count is generally lower than 20,000/mm^3. Higher counts may be

TABLE 1 Differential Diagnosis of Appendicitis

Diagnosis	Findings That Help Differentiate Entity from Appendicitis
Bacterial or viral enteritis	Nausea, vomiting, and diarrhea are severe; pain usually develops after vomiting.
Epiploic appendagitis	Focal abdominal pain and tenderness without migration or progression of the pain; patients have a paucity of other GI symptoms such as anorexia or nausea. Laboratory findings are usually normal.
Mesenteric adenitis	Duration of symptoms is longer; fever is uncommon; RLQ physical findings are less marked; WBC count is usually normal.
Pyelonephritis	Pain is more likely to be felt in the right flank; high fever and rigors are common; marked pyuria or bacteriuria and urinary symptoms are present; abdominal rigidity is less marked.
Renal colic	Pain radiates to the right groin; significant hematuria; character of the pain is clearly colicky.
Acute pancreatitis	Pain and vomiting are more severe; tenderness is less well localized; serum amylase and lipase levels are elevated.
Crohn disease	History of recurrent similar attacks; diarrhea is more common; palpable mass is more common; extraintestinal manifestations may have occurred or be present.
Cholecystitis	History of prior attacks is common; pain and tenderness are greater; radiation of pain is to the right shoulder; nausea is more marked; liver biochemical tests are more likely to be abnormal.
Meckel diverticulitis	Nearly impossible to distinguish preoperatively from appendicitis.
Cecal diverticulitis	Difficult to distinguish preoperatively from appendicitis; symptoms are milder and of longer duration; CT is helpful; patients are usually older.
Sigmoid diverticulitis	Usually occurs in older patients; changes in bowel habits are more common; radiation of the pain is to the suprapubic area, not RLQ; fever and WBC count are higher.
Small bowel obstruction	History of abdominal surgery; pain is colicky; vomiting and distention are more marked; RLQ localization is uncommon.
Ectopic pregnancy	History of menstrual irregularities; characteristic progression of symptoms is absent; syncope; positive pregnancy test.
Ruptured ovarian cyst	Occurs in the middle of the menstrual cycle; pain is of sudden onset; nausea and vomiting are less common; WBC count is normal.
Ovarian torsion	Vomiting is more marked and occurs at the same time as the pain; progression of symptoms is absent; abdominal or pelvic mass often is palpable.
Acute salpingitis or tuboovarian abscess	Longer duration of symptoms; pain begins in the lower abdomen; often there is a history of STDs; vaginal discharge and marked cervical tenderness often are present.

CT, Computed tomography; *GI,* gastrointestinal; *IV,* intravenous; *RLQ,* right lower quadrant; *STD,* sexually transmitted disease; *WBC,* white blood cell.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

indicative of perforation. Less than 4% have a normal WBC and differential. A WBC count <10,000/mm^3 decreases the likelihood of appendicitis. Low hemoglobin and hematocrit levels in an older patient should raise suspicion for gastrointestinal tract carcinoma.
- Microscopic hematuria and pyuria may occur in <20% of patients.
- Human chorionic gonadotropin to rule out pregnancy in females of reproductive age.

IMAGING STUDIES

- Multidetector computed tomography (Fig. E1) is a useful test for routine evaluation of suspected appendicitis in adults. CT of the abdomen/pelvis without contrast has a sensitivity of >90% and an accuracy >94% for acute appendicitis. A distended appendix, periappendiceal inflammation, and a thickened appendiceal wall are indicative of appendicitis. Table 2 describes CT findings of appendicitis. In children and young adults, exposure to CT radiation is of particular concern. Trials with low-dose CT (116 mGy cm) have shown that low-dose CT is not inferior to standard-dose CT (521 mGy cm) with respect to negative (unnecessary) appendectomy rates in young adults with suspected appendicitis.
- Ultrasonography (Fig. E2) has a sensitivity of 75% to 90% for the diagnosis of acute appendicitis, although it is highly operator dependent and difficult in patients with large body habitus. Ultrasound is useful, especially in pregnancy and in younger women when diagnosis is unclear. Normal ultrasonographic findings should not deter surgery if the history and physical examination are indicative of appendicitis.
- MRI of the abdomen and pelvis can also be used to accurately diagnose acute appendicitis in pregnant patients (100% sensitivity, 93.6% specificity) without exposure to ionizing radiation.

TABLE 2 Computed Tomography Findings of Appendicitis: SCALPEL Mnemonic

Term	Description
Stranding	Fat stranding suggests regional inflammation, possibly because of appendicitis.
Cecum	The appendix originates from the cecum, which should be identified first to help localize the appendix. The cecum may show wall thickening, suggesting appendicitis.
Air	Air outside of the lumen of the appendix is pathologic and suggests perforation. Air within the appendiceal wall is also abnormal.
Large	The normal appendix is <6 mm; an enlarged appendix >6 mm suggests appendicitis. Wall thickening >1 mm also suggests appendicitis.
Phlegmon	Inflammatory changes surrounding the appendix suggest a perforated appendix. A heterogeneous collection called a phlegmon may be seen. If the appendix has ruptured, a pericecal phlegmon may be the only remaining evidence, because the appendix itself may not be seen.
Enhancement	The wall of an abnormal appendix enhances with IV contrast and appears brighter than the normal bowel or the normal psoas muscle.
Lith	An appendicolith is a calcified stone sometimes found in the lumen of an inflamed appendix.

IV, Intravenous.
From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Nothing by mouth
- Do not administer analgesics until the diagnosis is made

ACUTE GENERAL Rx

- Urgent appendectomy (laparoscopic or open), correction of fluid and electrolyte imbalance with vigorous IV hydration, and electrolyte replacement
- IV antibiotic prophylaxis to cover gram-negative bacilli and anaerobes (ampicillin/sulbactam 3 g IV q6h or piperacillin/tazobactam 4.5 g IV q8h in adults)

PEARLS & CONSIDERATIONS

COMMENTS

- Perforation is common (20% in adult patients). Indicators of perforation are pain lasting >24 hr, leukocytosis >20,000/mm^3, temperature >102° F (38.9° C), palpable abdominal mass, and peritoneal findings.
- In general, prognosis is excellent. Mortality rate is <1% in young adults without complications; however, it exceeds 10% in elderly patients with ruptured appendix.
- In approximately 20% of patients who undergo exploratory laparotomy because of suspected appendicitis, the appendix is normal.
- An increasing amount of evidence supports the use of antibiotics instead of surgery for treating patients with uncomplicated appendicitis. A trial assessing the feasibility of nonoperative management for uncomplicated acute appendicitis in children using either IV piperacillin-tazobactam or ciprofloxacin metronidazole therapy for at least 24 hours followed by oral antibiotics for 10 days revealed that 90% of children managed nonoperatively had no progression within 30 days.[1] Another trial among patients with CT-proven, uncomplicated appendicitis revealed that antibiotic treatment did not meet the prescribed criterion for noninferiority compared with appendectomy. Most patients randomized to antibiotic treatment for uncomplicated appendicitis did not require appendectomy during the 1-yr follow-up period, and those who required appendectomy did not experience significant complications.[2] A 5-yr follow-up of antibiotic therapy for uncomplicated acute appendicitis in the APPAC randomized clinical trial revealed that among patients who were initially treated with antibiotics for uncomplicated acute appendicitis, the likelihood of late recurrence within 5 yr was 39.1%.[3] It remains to be determined whether the benefits of potentially avoiding an operation with antibiotics-first approach are outweighed by the burden to the patient related to future appendicitis episodes, more days of antibiotic therapy, lingering symptoms, and uncertainty that may affect quality of life.[4]

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Appendicitis (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

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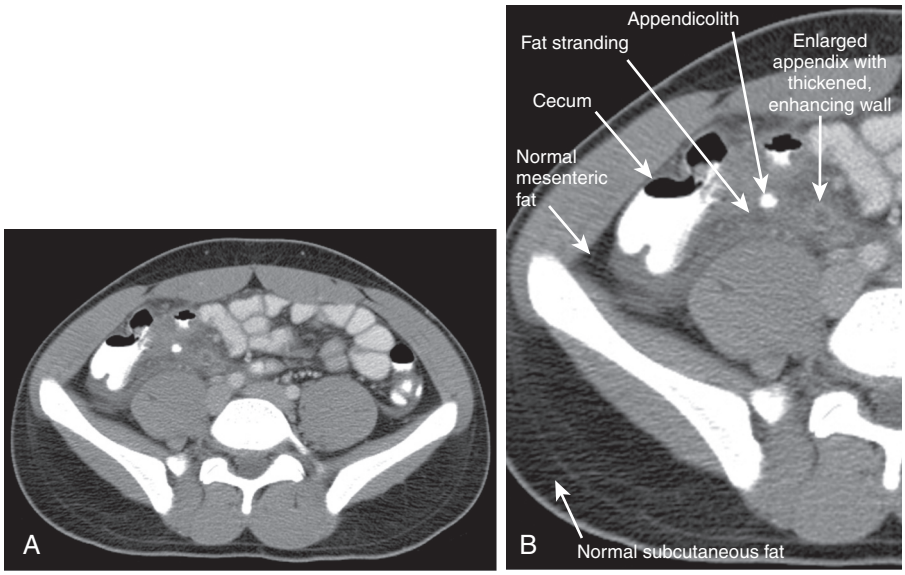

FIG. E1 Appendicitis, computed tomography (CT) with intravenous and oral contrast. This CT demonstrates classic findings of appendicitis in an 18-year-old male with right lower quadrant pain, as seen with CT with IV and oral contrast. Studies suggest that CT without contrast has similar sensitivity and specificity. An enlarged appendix is seen near the cecum as a right lower quadrant tubular structure in short-axis cross section, giving it a circular appearance. The surrounding fat shows stranding, a smoky appearance indicating inflammation (compare with normal mesenteric and subcutaneous fat, which is nearly black). The appendiceal wall shows enhancement, a brightening after administration of IV contrast. This slice also shows an appendicolith, an occasional finding of appendicitis. It does not appear to be within the appendix in this slice, because the appendix bends in and out of the plane of this slice. An appendicolith usually appears as a calcified (white) rounded structure, visible without any contrast. **A,** Axial CT image. **B,** Close-up. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

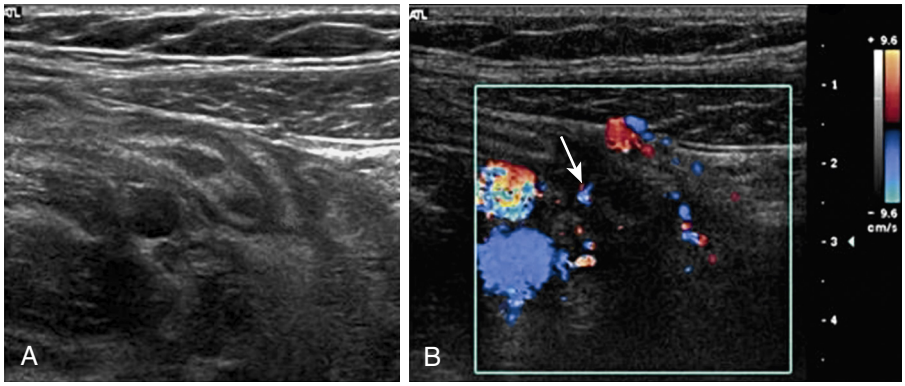

FIG. E2 Appendicitis. A, Transabdominal ultrasound using a linear transducer vdemonstrates a thick, tubular, noncompressible structure. **B,** Same imaging method with addition of color Doppler ultrasound shows increased vascularity within the luminal wall consistent with inflammation *(arrow).* (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

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Arrhythmogenic Right Ventricular Dysplasia ALG

BASIC INFORMATION

DEFINITION

Arrhythmogenic right ventricular dysplasia (ARVD) is a cardiomyopathy characterized by replacement of the normal myocardium with fibrofatty tissue, mainly of the right ventricle but also occasionally with involvement of the left ventricle. It is defined clinically by palpitations and syncope and potentially life-threatening ventricular arrhythmias.

SYNONYMS

Arrhythmogenic right ventricular cardiomyopathy
ARVC

ICD-10CM CODE
I42.8 Arrhythmogenic ventricular dysplasia

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 1:2000 to 5000 persons. It is one of the leading causes of arrhythmic cardiac arrest in young people and athletes.
PREDOMINANT SEX AND AGE: Mean age, 31 yr (range, 12 to 50 yr), predominantly male
RISK FACTORS: Family history of ARVD (present in nearly 50% of affected patients)
GENETICS:

- Autosomal dominant (most common) with variable penetrance and polymorphic phenotypic expression
- Autosomal recessive (rarely, e.g., Naxos disease)
- Several different gene mutations in desmosomal proteins
- Gene mutations can be identified in 50% of affected individuals

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- ARVD can present with palpitations, syncope, and chest discomfort and less commonly sudden cardiac arrest and signs of right ventricular failure such as dyspnea, edema, and fatigue. Patients may be clinically asymptomatic for many yrs.
- Cardiac arrest after physical exertion may be the initial presentation.
- Physical examination will be normal in most patients. Widely split S2 is an important diagnostic clue.

ETIOLOGY

ARVD is characterized by progressive replacement of mainly the right ventricular myocardium with fibrofatty tissue after apoptotic myocardial cell death caused by mutations of desmosomal protein.

DIAGNOSIS

A major criterion equals 2 points; a minor criterion equals 1 point. The diagnosis of ARVD is considered definite if the patient has 4 points and probable with 3 points. See Table 1 for diagnostic criteria.

DIFFERENTIAL DIAGNOSIS

- Cardiomyopathy with involvement of the right ventricle
- Uhl anomaly: Rare anomaly that presents mainly in childhood with signs and symptoms of right heart failure and characterized by a paper-thin right ventricle resulting from death of the myocytes throughout the right ventricle
- Idiopathic RV tachycardia
- Sarcoidosis
- Right ventricular infarction

WORKUP

- Initial workup includes history with focus on sudden death in the family, resting ECG, 24-Holter ECG, signal-averaged ECG, and imaging studies with echocardiography and MRI.
- ECG will have diagnostic findings in 50% to 90% of patients with ARVD, including T-wave inversions in anterior precordial leads V_1 to V_6, epsilon waves, and a QRS duration longer than 110 ms in V1 or >40 ms longer in V1 than V6 (Fig. 1).
- Ventricular tachycardia (VT) with left bundle branch block pattern and frequent PVCs (>500 in 24 h) might be detected by 24-hr Holter monitoring.
- An abnormal signal-averaged ECG is a minor diagnostic criteria.
- Echocardiography will show right ventricular dilation with regional wall motion abnormalities, aneurysms, and depressed RV function that varies with the severity of the disease.
- MRI (Fig. 2) is a noninvasive method to detect structural abnormalities (fibrofatty changes) and regional dysfunction. Cardiac MRI (CMR) is the most sensitive method to detect ARVD, but it has high false-positive rates. Cardiac CT angiogram (Fig. E3) will reveal thinning and aneurysmal dilation of the RV anterior wall and outflow tract.
- If the routine tests are not conclusive, endomyocardial biopsy and electrophysiologic testing can be considered. However, biopsies and radionuclide ventriculography are rarely performed in the U.S.

TREATMENT

No curative treatment is available. The treatment goal is focused on preventing sudden cardiac death, symptomatic treatment of right heart failure, and pharmacologic and invasive treatment of arrhythmias. Therapy with cardio-selective beta-blockers is recommended. Family members with a negative phenotype (either healthy gene carriers or those with an unknown genotype) do not need any specific treatment other than sports restriction; however, lifelong clinical assessment with the use of noninvasive tests at least every 2 yr is warranted.[1]

NONPHARMACOLOGIC THERAPY

- Avoidance of activity that may trigger ventricular tachycardia and may lead to disease progression.
- ICD implantation needs to be considered in patients who have the definite diagnosis of ARVD. Patients with unexplained syncope, advanced disease, documented ventricular arrhythmias, or a family history of sudden cardiac death or who have been resuscitated from cardiac arrest are at high risk. A subcutaneous ICD might be an alternative option instead of transvenous implantation.
- Radiofrequency catheter ablation is used in cases of refractory VT or frequent tachycardia after defibrillator placement.
- Cardiac transplantation.
- Fig. 4 describes a management algorithm for ARVD.

PHARMACOLOGIC TREATMENT

Antiarrhythmic therapy with sotalol (first-line treatment) or amiodarone, often in combination with beta-blockers, is used for tachycardia suppression.

REFERRAL

- Early cardiology and electrophysiology referral
- Consider referring for genetic counseling

PEARLS & CONSIDERATIONS

PREVENTION

All first-degree relatives should be tested if ARVD is confirmed. Sports activity increases the risk of sudden cardiac death among adolescents and young adults with ARVC. The estimated overall mortality ranges from 0.08% to 3.6% per yr.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Heiko Schmitt, MD, PhD**

[1]Corrado D et al: Arrhythmogenic right ventricular cardiomyopathy, *N Engl J Med* 376:61-72, 2017.

TABLE 1 Global or Regional Dysfunction and Structural Alterations

Major

2D echo criteria

Regional RV akinesia, dyskinesia, or aneurysm and one of the following measured at end diastole:

PLAX RVOT ≥32 mm or

PSAX RVOT ≥36

Fractional area change ≤33%

MRI criteria

Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and one of the following:

Ratio of RV end-diastolic volume to BSA >100, <110 ml/m^2 (male) or >100 ml/m^2

RV ejection fraction >40% ≤45%

RV angiography criteria

Regional RV akinesia, dyskinesia, or aneurysm

Minor

2D echo criteria

Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and one of the following measured at end diastole:

PLAX RVOT ≥29 <32 mm or

PSAX RVOT ≥32 <36

Fractional area change >33% ≤40%

MRI criteria

Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and one of the following:

Ratio of RV end-diastolic volume to BSA ≥110 ml/m^2 (male) or ≥100 ml/m^2

RV ejection fraction ≤40%

Tissue characterization of wall

Major

Residual myocytes <60% by morphometric analysis (or <50% if estimated) with fibrous replacement of the RV free wall myocardium in >1 sample, with or without fatty replacement of tissue on endomyocardial biopsy

Minor

Residual myocytes 60%-75% by morphometric analysis (or 50%-65% if estimated), with fibrous replacement of the RV free wall myocardium in >1 sample with or without fatty replacement of tissue on endomyocardial biopsy

Repolarization abnormalities

Major

Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 y of age (in the absence of complete RBBB QRS ≥120 ms)

Minor

Inverted T waves in V1 and V2 in individuals >14 y of age (in the absence of complete RBBB) or in V4, V5, and V6

Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 y of age in the presence of a complete RBBB

Depolarization or conduction abnormalities

Major

Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of T wave) in the right precordial leads (V1-V3)

Minor

Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRSd of ≥110 ms on standard ECG

Filtered QRS ≥114 ms

Duration of terminal QRS <40 mV ≥38 ms

Root-mean-square voltage of terminal 40 ms ≤20 μV

Terminal activation duration ≥55 ms measured from the nadir of the end of the QRS, including R', in V1, V2, or V3 in absence of complete RBBB

Arrhythmias

Major

Nonsustained or sustained VT of LBBB morph with superior axis

Minor

Nonsustained or sustained VT of RVOT configuration, LBBB morph with inferior axis or of unknown axis

>500 PVCs per 24 hr (Holter)

Family history

Major

ARVD/C in first-degree relative who meets Task Force criteria

ARVD/C confirmed pathologically at autopsy or surgery in first-degree relative

Identification of pathogenic mutation categorized as associated or probably associated with ARVD/C in the patient under evaluation

Minor

History of ARVD/C in first-degree relative in whom it is not possible to determine whether the family member meets Task Force criteria

Premature sudden death (<35 yr of age) caused by suspected ARVD/C in a first-degree relative

ARVD/C confirmed pathologically or by current Task Force criteria in second-degree relative

A major criterion equals 2 points, a minor criterion 1 point. The diagnosis of arrhythmogenic right ventricular dysplasia (ARVD) is considered definite if the patient has 4 points and probable with 3 points. *BSA,* Body surface area; *MRI,* magnetic resonance imaging; *PLAX,* parasternal long area; *PSAX,* parasternal short axis; *RBBB,* right bundle branch block; *RV,* right ventricle; *RVOT,* right ventricular outflow tract; *SAECG,* signal-averaged electrocardiogram; *2D,* two dimensional; *VT,* ventricular tachycardia.

From Marcus IM: Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia proposed modification of the Task Force criteria, *Circulation* 121:1533-1541, 2010.

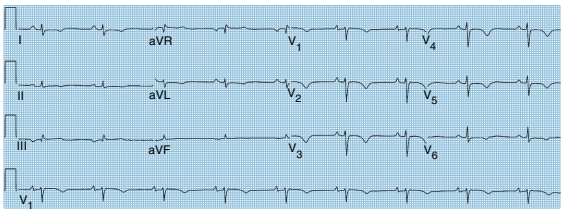

FIG. 1 Arrhythmogenic right ventricular cardiomyopathy—Epsilon wave. This 12-lead electrocardiogram tracing with lead Vfn11 rhythm strip shows sinus rhythm with T-wave inversion over the right precordial leads. In addition, there is an epsilon wave (small deflection at the end of the QRS complex), evident in lead V^1, which is characteristic of arrhythmogenic right ventricular cardiomyopathy. (From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

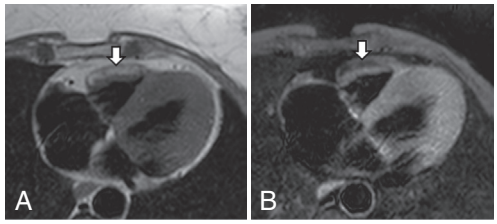

FIG. 2 Arrhythmogenic right ventricular cardiomyopathy. Spin-echo cardiovascular magnetic resonance without **(A)** and with **(B),** a fat-suppression prepulse. There is bright signal in the free wall of the right ventricle that suppresses with fat suppression *(arrows).* (From Sellke FW et al: *Sabiston & Spencer surgery of the chest,* ed 9, Philadelphia, 2016, Elsevier.)

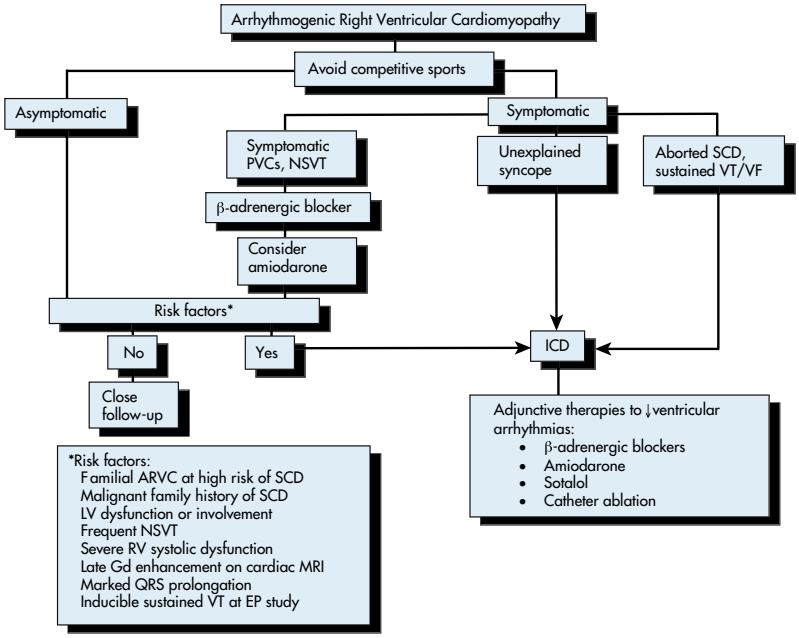

FIG. 4 Arrhythmogenic right ventricular cardiomyopathy. *ARVC,* Arrhythmogenic right ventricular cardiomyopathy; *EP,* electrophysiology; *Gd,* gadolinium; *ICD,* implantable cardiodefibrillator; *NSVT,* nonsustained ventricular tachycardia; *PVCs,* premature ventricular contractions; *SCD,* sequential compression device; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia. (From Olshansky B et al: *Arrhythmia essentials*, ed 2, Philadelphia, 2017, Elsevier.)

SUGGESTED READINGS

Bhonsale A et al: Incidence and predictors of implantable cardioverter-defibrillator therapy in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy undergoing implantable cardioverter-defibrillator implantation for primary prevention, *J Am Coll Cardiol* 58:1485-1496, 2011.

Calkins H: Arrhythmogenic right ventricular dysplasia, *Curr Probl Cardiol* 38:103-123, 2013.

Kim C et al: Studying arrhythmogenic right ventricular dysplasia with patient-specific iPSCs, *Nature* 6(494):105-110, 2013.

Peters S: QRS fragmentation and epsilon waves in Fontaine leads in arrhythmogenic right ventricular cardiomyopathy, *Int J Cardiol*, 2014.

Schinkel AF: Implantable cardioverter defibrillators in arrhythmogenic right ventricular dysplasia/cardiomyopathy: patient outcomes, incidence of appropriate and inappropriate interventions, and complications, *Circ Arrhythm Electrophysiol* 562-568, 2013.

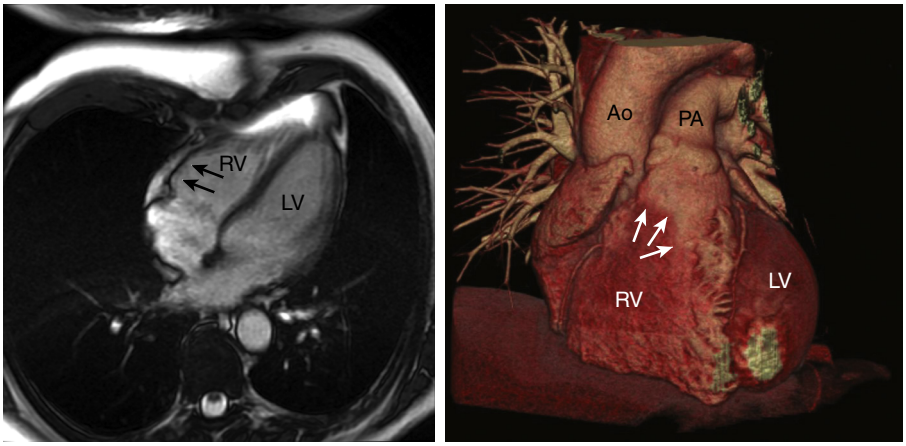

FIG. E3 Right ventricular aneurysm. This cardiac computed tomography angiogram shows thinning and aneurysmal dilation of the RV anterior wall and outflow tract *(arrows)* in a patient with arrhythmogenic right ventricular dysplasia, cardiomyopathy, and ventricular tachycardia. *Ao,* Aorta; *LV,* left ventricle; *PA,* pulmonary artery; *RV,* right ventricle. (Courtesy of Dr. Nasar Nallamothu, Prairie Cardiovascular Consultants, Springfield, IL. From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, Saunders.)

BASIC INFORMATION

DEFINITION

Asbestosis is a slow, progressive diffuse interstitial fibrosis as a consequence of dose-related inhalation exposure to fibers of asbestos in miners, millers, workers of asbestos textiles, and insulators. Clinically, the lung involvement is characterized by bilateral diffuse interstitial fibrosis, more pronounced in the lower lobes, and pleural thickening, leading to shortness of breath and dry cough.

Asbestos exposure can lead to the spectrum of pulmonary pathology, including pulmonary fibrosis; asbestos-related pleural plaque (ARPD), both focal and diffuse; and malignancies (small cell carcinoma, non–small cell carcinoma, or mesothelioma).

ICD-10CM CODE

J61 Pneumoconiosis due to asbestos and other mineral fibers

EPIDEMIOLOGY & DEMOGRAPHICS

- Five to 10 new cases per 100,000 persons per yr in the U.S.
- Prolonged interval (20 to 30 yr) between exposures to inhaled fibers and clinical manifestations of disease.
- Most common in workers over age 40 yr involved in the primary extraction of asbestos from rock deposits and in those involved in the fabrication and installation of products containing asbestos (e.g., naval shipyards in World War II; installation of floor tiles, ceiling tiles, acoustic ceiling coverings, wall insulation, and pipe coverings in public buildings).
- Smokers and heavy drinkers have the greatest risk of developing this disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Insidious onset of shortness of breath and dry cough with exertion is usually the first sign of asbestosis.
- Dyspnea becomes more severe as the disease advances; with time, progressively less exertion is tolerated.
- Cough is frequent and usually paroxysmal, dry, and nonproductive. Hemoptysis is rare but reported.
- Scant mucoid sputum may accompany the cough in the later stages of the disease.
- Fine end-respiratory crackles (rales, crepitations) are heard more predominantly in the lung bases.
- Digital clubbing, edema, jugular venous distention are present.
- Advanced cases may have signs of right heart failure.

ETIOLOGY/PATHOGENESIS

Inhalation of asbestos fibers. The pathogenesis of pulmonary interstitial inflammation and fibrosis is related to immune mechanisms. Asbestosis is known to be associated with positive serum antinuclear antibody (ANA) and rheumatoid factor (RF). Recently, an important role of interleukin-1beta (IL-1beta) in the pathogenesis of asbestosis and its systemic autoimmune manifestations have been reported.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Silicosis
- Siderosis, other pneumonoconioses
- Lung cancer
- Atelectasis

WORKUP

Documentation of exposure history, diagnostic imaging, pulmonary function testing

LABORATORY TESTS

- Generally not helpful
- Possible mild elevation of erythrocyte sedimentation rate (ESR), positive antinuclear antibody (ANA), and rheumatoid factor (RF) (these tests are nonspecific and do not correlate with disease severity or activity)
- Pulmonary function testing: With decreased vital capacity (VC), decreased total lung capacity (TLC), decreased carbon monoxide gas transfer (DLco)
- FEV1 might be reduced in concomitant smokers
- Arterial blood gases: Hypoxemia, hypercarbia in advanced stages

IMAGING STUDIES

- Chest radiograph (Fig. E1):
  1. Small, irregular shadows in lower lung zones.
  2. The imaging findings vary from benign pleural disease (including discrete plaques, pleural calcification, diffuse pleural thickening with blunting of costophrenic angles, and thickening of the interlobar fissure) to asbestosis (diffuse interstitial pulmonary fibrosis.
- Thickened pleura, calcified plaques (present under diaphragm and lateral chest wall).
- CT scan of chest (Fig. E2) confirms diagnosis. Typical findings on high-resolution CT of the chest include increased interstitial markings found mainly at the bases (Fig. E3). As the disease progresses, honeycombing is noted.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Smoking cessation, proper nutrition, exercise program to maximize available lung function
- Home oxygen therapy PRN
- Removal of patient from further asbestos fiber exposure

GENERAL Rx

- Prompt identification and treatment of respiratory infections
- Supplemental oxygen on a PRN basis
- Annual influenza vaccination, pneumococcal vaccination every 6 yr
- Pulmonary rehabilitation can be considered in advanced cases for improved cardiopulmonary capacity
- Some new data are coming out targeting IL-1 beta therapy on the progression of lung fibrosis that suggest a new perspective for the treatment of systemic autoimmune features of asbestosis and, possibly, of lung involvement.[1]

DISPOSITION

- There is no specific treatment for asbestosis.
- Death is usually from respiratory failure from cor pulmonale.
- Diffuse pleural thickening and asbestosis are associated with increased risks of malignant peritoneal mesothelioma beyond the risk calculated to be associated with the degree of asbestos exposure.[2]
- None of the benign pleural diseases or ARPD was associated with an increased risk of malignant pleural mesothelioma.
- Asbestos increases the risk for development of lung cancer regardless of smoking status. In patients with diffuse parenchymal disease secondary to asbestos, the risk of lung cancer is nearly 40 times higher than in those with no history of smoking.
- Asbestos exposure without asbestosis and smoking increases the risk of lung cancer. The joint effect of asbestos and smoking is additive and depends in part on the presence of asbestosis. Asbestos workers who stop smoking experience a dramatic decline in lung cancer risk, which approaches that of nonsmokers after 30 yr.
- Low-dose chest CT scanning offers an excellent opportunity to detect early-stage lung cancers in asbestos-exposed workers.
- Computed tomography is more sensitive than radiography, computed tomography without contrast generally suffices for evaluation, and PET scan (fluorodeoxyglucose-positron emission tomography) may have utility in patients with mesothelioma.
- Survival in patients after development of mesothelioma is 4 to 6 yr.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Asbestosis (Patient Information)

AUTHOR: **Imrana Qawi, MD**

[1]Niccoli L et al: Systemic autoimmune disease in asbestosis rapidly responding to anti-interleukin-1beta antibody canakinumab: a case report, *BMC Musculoskelet Disord* 14(16):146, 2015.

[2]Reid A et al: The additional risk of malignant mesothelioma in former workers and residents of Wittenoom with benign pleural disease or asbestosis, *Occup Environ Med* 62:665-669, 2005.)

SUGGESTED READINGS

American Thoracic Society: Diagnosis and initial management of nonmalignant diseases related to asbestos, *Am J Respir Crit Care Med* 170(691), 2014.

Expert Panel on Thoracic Imaging et al: ACR appropriateness criteria review ACR Appropriateness Criteria® occupational lung diseases, *J Thorac Imaging* 31(1), 2016.

FIG. E1 Asbestosis. Posteroanterior radiograph shows coarse linear opacities at both lung bases obscuring the cardiac borders. (From McLoud TC: *Thoracic radiology: the requisites*, St Louis, 1998, Mosby.)

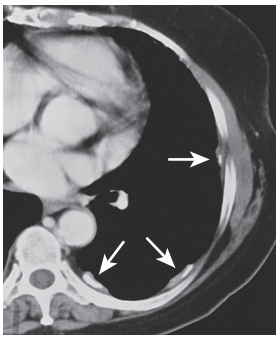

FIG. E2 Asbestos-related pleural plaques. Typical calcified pleural plaques (*arrows*) are visible. They are often internal to the ribs. (From Webb WR et al: *Fundamentals of body CT*, ed 4, Philadelphia, 2014, Saunders.)

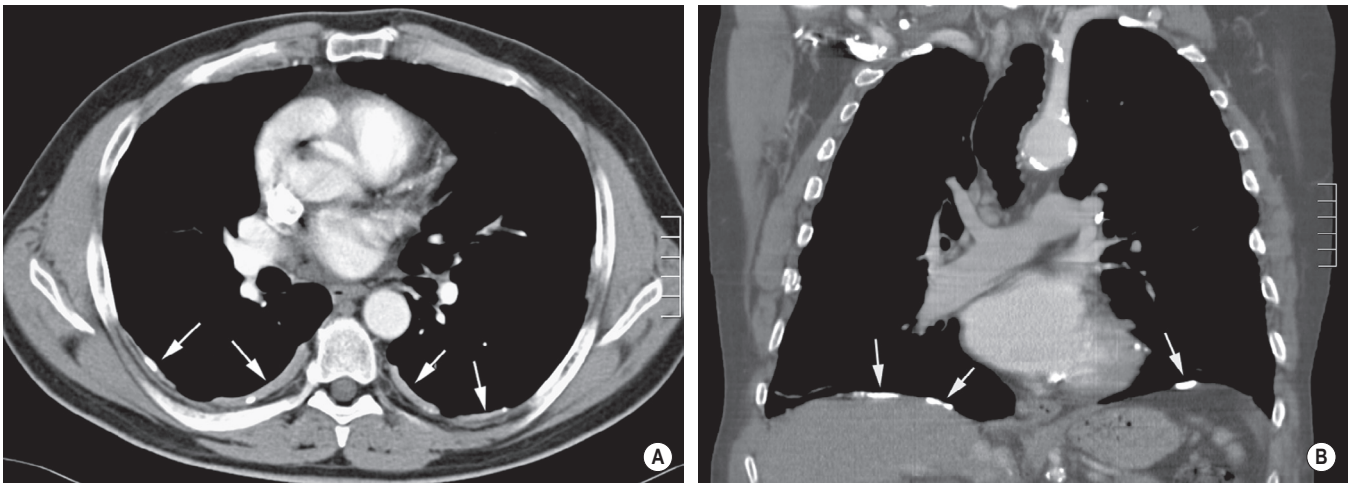

FIG. E3 Pleural plaques caused by asbestos exposure. (A) Axial and **(B)** coronal computed tomography. Pleural plaques are most commonly found along the lower thorax and on the diaphragmatic pleura *(arrows).* They can partially or completely calcify or ossify. (From Adam A et al: *Grainger & Allison's diagnostic radiology,* ed 5, 2007, Churchill Livingstone: In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Ascariasis is a parasitic infection caused by the nematode *Ascaris lumbricoides.* The majority of those infected are asymptomatic; however, clinical disease may arise from pulmonary hypersensitivity, intestinal obstruction, or nutrient depletion and other secondary complications.

SYNONYMS

Round worms
Worms

ICD-10CM CODES

B77.0	Ascariasis with intestinal complications
B77.81	Ascariasis pneumonia
B77.89	Ascariasis with other complications
B77.9	Ascariasis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Unknown. Worldwide, *A. lumbricoides* is the most common helminthic infection of humans, infecting as many as 1 billion or more persons. 71% of persons at risk for infection live in Asia and the Western Pacific.
- Three times the infection rates found in blacks as in whites.

PREVALENCE (IN U.S.): Estimated at 4 million, the majority of which live in the rural southeastern part of the country; ascariasis is associated with poor sanitation

PREDOMINANT SEX: Both sexes probably equally affected, with a possible slight female preponderance

PREDOMINANT AGE: Most common in children from ages 2 to 10 yr old and decreases after age 15; infections tend to cluster in families

PEAK INCIDENCE: Unknown

NEONATAL INFECTION: Probable transmission, though not specifically studied

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most people infected with *Ascaris* are asymptomatic
- Occurs approximately 9 to 12 days after ingestion of eggs (corresponding to the larval migration through the lungs)
- Nonproductive cough
- Substernal chest discomfort
- Fever
- In patients with large worm burdens, especially children, intestinal obstruction associated with perforation, volvulus, and intussusception
- Migration of worms into the biliary tree giving clinical appearance of biliary colic and pancreatitis as well as acute appendicitis with movement into that appendage
- Rarely, infection with *A. lumbricoides* producing interstitial nephritis and acute renal failure
- In endemic areas in Asia and Africa, malabsorption of dietary proteins and vitamins as a consequence of chronic worm intestinal carriage; 1 billion people worldwide are infected with this nematode

ETIOLOGY

- Transmission is usually hand to mouth, but eggs may be ingested via transported vegetables grown in contaminated soil.
- Eggs are hatched in the small intestine, with larvae penetrating intestinal mucosa and migrating via the circulation to the lungs.
- Larval forms proceed through the alveoli, ascend the bronchial tree, and return to the intestines after swallowing, where they mature into adult worms.
- Estimated time until the female adult worm begins producing eggs is 2 to 3 mo.
- Eggs are passed out of the intestines with feces and can survive for years in warm, moist, shaded soil.
- Within human host, adult worm life span is 1 to 2 yr.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Radiologic manifestations and eosinophilia to be distinguished from drug hypersensitivity and Löffler syndrome.
- Table E1 compares features of major intestinal nematodes.

LABORATORY TESTS

- Examination of the stool for *Ascaris* ova (Fig. E1)
- The World Health Organization (WHO) recommends the Kato-Katz thick smear kit for soil-transmitted helminths
- Expectoration or fecal passage of adult worm
- Adult male worms: 10 to 30 cm long; adult female worms: Larger than male, up to 40 cm
- Eosinophilia: Most prominent early in the infection and subsides as the adult worm infestation established in the intestines; usually in 5% to 12% range but can be up to 50%
- Serology: Patients develop immunoglobulin G (IgG) antibodies, but they cross react with antigens from other helminths and are not protective; thus, serology is used more for epidemiologic purposes than for individual diagnosis
- Polymerase chain reaction (PCR) on stool samples; multiplex PCR can differentiate multiple different parasite species (*A. lumbricoides, T. trichiura,* and *N. americanus*)

IMAGING STUDIES

- Chest x-ray to reveal bilateral oval or round infiltrates of varying size (Löffler syndrome); NOTE: Infiltrates are transient and eventually resolve.
- Plain films of the abdomen and contrast studies to reveal worm masses in loops of bowel.
- Ultrasonography and endoscopic retrograde cholangiopancreatography (ERCP) to identify worms in the pancreaticobiliary tract.
- CT scan with oral contrast can also assist in the detection of GI foreign bodies such as parasites.

TREATMENT

NONPHARMACOLOGIC THERAPY

Aggressive IV hydration, especially in children with fever, severe vomiting, and resultant dehydration

ACUTE GENERAL Rx

- All infected patients, including asymptomatic ones, should be treated.
  1. Albendazole: 400 mg PO × 1 dose is the first-line agent
  2. Mebendazole 100 mg PO bid × 3 days for persons >1 yr of age or mebendazole 500 mg PO × 1 dose for persons >1 yr of age (not available as 500 mg in the U.S.)
- Cure rate with these agents is 95% to 100%, but they are contraindicated in pregnancy.
- Side effects: GI discomfort, headache, and rarely leukopenia
- Alternative agent or for use in pregnancy: Pyrantel pamoate (Antiminth)
  1. Given at a dose of 11 mg/kg PO (maximum dose of 1 g/day)
  2. Considered safe for use in pregnant women
- Other alternative agents:
  1. Ivermectin: 150 to 200 mcg/kg orally once
  2. Nitazoxanide: Ages 2 to 3 yrs: 100 mg/5 ml bid × 3 days, and ages 4 to 11 yrs: 200 mg/10 ml bid × 3 days. Cure rates in heavy worm burden are only 50% to 80%
  3. Piperazine citrate: No longer first-line agent due to toxicity but still used in cases of intestinal or biliary obstruction, as drug paralyzes the worm, helping its expulsion. Dose: 50 to 75 mg/kg once daily up to maximum of 3.5 g for 2 days
  4. Levamisole: 2.5 mg/kg once orally is recommended by the WHO as alternative therapy, but not available in the U.S.
- Complete obstruction should be managed surgically.

DISPOSITION

Overall prognosis is good. Patients should be reevaluated in 2 to 3 mo. Reinfection is common.

REFERRAL

- To gastroenterologist in cases of visualized pancreaticobiliary tract or appendiceal obstruction

- To surgeon in cases of complete obstruction or suspected secondary complication (e.g., perforation or volvulus)

PEARLS & CONSIDERATIONS

COMMENTS

- Hepatic abscess, containing both viable and dead worms, complicating *Ascaris*-induced biliary duct disease has been documented.
- Given the known transmission of the parasite, routine hand washing with soap and proper disposal of human waste would significantly decrease the prevalence of this disease.
- Other protective measures to avoid ingestion of worm eggs:
  1. Peel or cook food.
  2. Boil drinking water.
  3. Do not place small children directly on soil.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Ascariasis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Das AK: Hepatic and biliary ascariasis, *J Glob Infect Dis* 6:65-72, 2014.
Dold C, Holland CV: Ascaris and ascariasis, *Microbes Infect* 13:632-637, 2011.
Jourdan PM et al: Soil-transmitted helminths in infections, *Lancet* 391:252-265, 2018.
Lamberton PH, Jourdan PM: Human ascariasis: diagnostic update, *Curr Trop Med Rep* 2:189-200, 2015.

TABLE E1 Features of Major Intestinal Nematodes

Nematode	Transmission	Direct Person-to-Person Transmission	Geographic Distribution	Duration of Infection	Location of Adult Worm(s)	Treatment*
Ascaris lumbricoides	Ingestion of infective eggs	No	Warm, humid areas; temperate zones in warmer months	1-2 yr	Free in lumen of small bowel, primarily jejunum	Albendazole Mebendazole Pyrantel Ivermectin Levamisole Piperazine
Trichuris trichiura (whipworm)	Ingestion of infective eggs	No	Warm, humid areas; temperate zones in warmer months	1-3 yr	Anchored in superficial mucosa of cecum and colon	Albendazole Mebendazole
Necator americanus, Ancylostoma duodenale (hookworm)	Penetration of skin by filariform larvae	No	Warm, humid areas; temperate zones in warmer months	3-5 yr *(Necator);* 1 yr *(Ancylostoma)*	Attached to mucosa of mid to upper portion of small bowel	Albendazole Mebendazole Levamisole Pyrantel
Strongyloides stercoralis	Penetration of skin or bowel mucosa by filariform larvae	Yes	Primarily warm, humid areas but can be worldwide	Lifetime of host	Embedded in mucosa of duodenum, jejunum	Ivermectin† Albendazole Thiabendazole
Enterobius vermicularis (pinworm)	Ingestion of infective eggs	Yes	Worldwide	1 mo	Free in lumen of cecum, appendix, adjacent colon	Albendazole Mebendazole Pyrantel Ivermectin Levamisole Piperazine

*Nitazoxanide has been shown to be effective in the treatment of ascariasis, trichuriasis, and enterobiasis in several trials in Mexico. Tribendimidine, which is licensed in China, was shown to be efficacious against *Ascaris* spp. and had moderate efficacy against *Strongyloides* spp. in a randomized trial.
†Drug of choice.
From Bennett et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

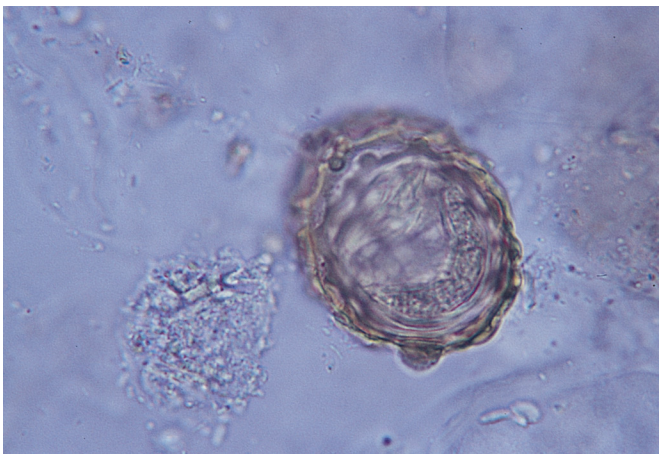

FIG. E1 ***Ascaris lumbricoides*** **ovum in feces.** The ovum measures 50 to 70 mm × 40 to 50 mm and is elliptical. The rough albuminous coat gives it a mammillated appearance. (From Cohen J, Powderly WG: *Infectious diseases*, ed 2, St Louis, 2004, Mosby.)

BASIC INFORMATION

DEFINITIONS

Ascites refers to a pathologic accumulation of fluid in the peritoneal cavity, most commonly caused by liver cirrhosis.

- **Diuretic-resistant ascites:** Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of lack of response to dietary sodium restriction and maximal doses of diuretics.
- **Diuretic-intractable ascites:** Ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that precludes the use of effective doses of diuretics.

SYNONYMS

Peritoneal cavity fluid
Hydroperitoneum
Hydroperitonia
Hydrops abdominis

ICD-10CM CODES

R18	Ascites
C78.6	Malignant ascites
K70.11	Alcoholic hepatitis with ascites
K70.31	Alcoholic cirrhosis of liver with ascites
K71.51	Toxic liver disease with chronic active hepatitis with ascites
R18.8	Other ascites

EPIDEMIOLOGY & DEMOGRAPHICS

Ascites is the most common complication of cirrhosis and signifies decompensation of chronic liver disease. Ascites occurs at a rate of 7% to 10% annually in cirrhotic patients. Ascites occurs in ~60% of individuals with cirrhosis within 10 yr of diagnosis. Cirrhosis is the cause of 85% of cases of ascites.

CLINICAL PRESENTATION & PHYSICAL FINDINGS

- Important information to elicit within history:
  1. History of viral hepatitis
  2. Alcoholism
  3. Intravenous drug use, intranasal cocaine use
  4. Sexual history (i.e., men who have sex with men)
  5. History of transfusions, tattoos, piercings, imprisonment
  6. Travel history and time spent in endemic regions for hepatitis
  7. Symptoms suggestive of peritoneal malignancy (e.g., weight loss, pain, palpable masses, rectal/vaginal bleeding)
  8. Other liver disease symptoms (e.g., increasing abdominal girth, jaundice, pruritus, confusion, pedal edema)
  9. Cardiac symptoms (e.g., pedal edema, shortness of breath, orthopnea, chest pain)
  10. Hypothyroid disease (fatigue, weight gain, constipation)
  11. History of ascites, prior treatment, LVP requirements and frequency
- Important physical exam findings:
  1. Protuberant abdomen (Fig. E1)
  2. Bulging flanks (can be present in obesity)
  3. Flank dullness to percussion (requires ~1500 ml of fluid)
  4. Fluid wave on abdominal exam
  5. Lower extremity edema
  6. Shifting dullness on abdominal exam
  7. Physical signs associated with liver cirrhosis: Spider angiomas, jaundice, loss of body hair, skeletal muscle wasting (sarcopenia), Dupuytren contracture, bruising, palmar erythema, gynecomastia, testicular atrophy, rectal varices, and caput medusae

ETIOLOGY

Pathophysiology of ascites (Fig. E2): Increased hepatic resistance to portal flow leads to portal hypertension. A portal pressure >12 mm Hg appears to be required for fluid retention. The splanchnic vessels respond by increased secretion of nitric oxide, causing splanchnic artery vasodilation. Vasodilation appears also to be mediated by the translocation of enteric bacteria and bacterial products. Early in the disease increased plasma volume and increased cardiac output compensate for this vasodilation. However, as the disease progresses the effective arterial blood volume decreases, causing sodium and fluid retention through activation of the renin-angiotensin system. Over time activation of the sympathetic system causes renal vascular perfusion to decrease and may lead to hepatorenal syndrome. The change in capillary pressure causes increased permeability and retention of fluid in the abdomen.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Chronic parenchymal liver disease, leading to portal hypertension
- Acute liver failure
- Noncirrhotic portal hypertension (e.g., portal vein clot)
- Peritoneal carcinomatosis
- Cardiac disease (e.g., heart failure, constrictive pericarditis)
- Hepatic venous outflow obstruction (e.g., Budd-Chiari syndrome, IVC webs)
- Protein losing enteropathy
- Peritoneal tuberculosis
- Nephrotic syndrome
- Pancreatitis

LABORATORY TESTS

- Initial evaluation should always include:
  1. Diagnostic paracentesis. Laboratory tests on this fluid should include a cell count and differential, cytology, albumin, total protein, culture, and Gram stain. A serum-ascites albumin gradient (SAAG) should be calculated in all patients. The SAAG is measured by subtracting the level of albumin in the ascitic fluid from a concurrent serum albumin measurement: SAAG = serum albumin – ascites albumin
     a. If the SAAG is greater than 1.1, the cause of ascites can be attributed to portal hypertension (from Cirrhosis, Budd-Chiari syndrome) or heart failure.
     b. If SAAG is less than 1.1, a non-portal hypertension etiology of ascites must be sought. Optional tests on paracentesis fluid include amylase, LDH, acid-fast bacilli, and glucose levels.
     c. Total ascitic fluid protein assess the risk of spontaneous bacterial peritonitis (SBP). Patients with protein concentration <1.5 g/dl have an increased risk of SBP.
  2. AST, ALT, total and direct bilirubin, albumin, alkaline phosphatase, GGTP
  3. CBC, coagulation studies
  4. Electrolytes, BUN, creatinine
- Causes of ascites in the normal or diseased peritoneum by SAAG are summarized in Table 1.
- Fig. 3 illustrates an algorithm for the approach to the differential diagnosis of ascites.

IMAGING STUDIES

- Abdominal ultrasound (Fig. 4) is the most sensitive measure for detecting ascitic fluid; a CT or MRI scan is a viable alternative. Doppler studies of portal and hepatic veins should be added to rule out vascular etiology.
- Endoscopy of the upper GI tract to evaluate for esophageal varices if ascites is secondary to portal hypertension.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Sodium-restricted diet (88 mmol, <2 g/day).
- Fluid restriction to 1 L/day in patients with severe hyponatremia (sodium <120 mEq/L).
- Counsel on avoiding NSAIDs and discontinuation of ACE inhibitors and ARBs.
- Consider discontinuing or not initiating propranolol in patients with refractory ascites.

ACUTE GENERAL Rx

- Patients with moderate-volume ascites causing only moderate discomfort may be treated on an outpatient basis with the following diuretic regimen:
  1. Spironolactone: Start at 50 to 100 mg/day and titrate up to 400 mg day every 3 to 4 days (monotherapy or combination therapy with furosemide).
  2. Furosemide: Start at 40 mg/day and titrate up to 160 mg/day maximum. Monitor renal function and sodium levels carefully for signs of prerenal azotemia (in patients without edema. Goal weight loss is 300 to 500 g/day; in patients with edema, goal weight loss is 800 to 1000 g/day). Furosemide alone is not recommended.

TABLE 1 Causes of Ascites in the Normal or Diseased Peritoneum by Serum-to-Ascites Albumin Gradient (SAAG)

Normal Peritoneum	
Portal Hypertension (SAAG >1.1 G/dl)	**Hypoalbuminemia (SAAG <1.1 g/dl)**
Hepatic congestion	Nephrotic syndrome
Congestive heart failure	Protein-losing enteropathy
Constrictive pericarditis	Severe malnutrition with anasarca
Tricuspid insufficiency	
Budd-Chiari syndrome	
Liver Disease	**Miscellaneous Conditions (SAAG <1.1 g/dl)**
Cirrhosis	Chylous ascites
Alcoholic hepatitis	Pancreatic ascites
Fulminant hepatic failure	Bile ascites
Massive hepatic metastases	Nephrogenic ascites
	Urine ascites
	Ovarian disease
Diseased Peritoneum (SAAG <1.1 g/dl)	
Infections	**Other Rare Conditions**
Bacterial peritonitis	Familial Mediterranean fever
Tuberculous peritonitis	Vasculitis
Fungal peritonitis	Granulomatous peritonitis
HIV-associated peritonitis	Eosinophilic peritonitis
Malignant Conditions	
Peritoneal carcinomatosis	
Primary mesothelioma	
Pseudomyxoma peritonei	
Hepatocellular carcinoma	

From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.

- Patients with large-volume ascites causing marked discomfort or decrease in activities of daily living may also be treated as outpatients if there are no complications. There are two options for treatment in these patients:
  1. Large-volume paracentesis or
  2. Diuretic therapy until loss of fluid is noted (maximum spironolactone 400 mg daily and furosemide 160 mg daily).
     a. No difference in long-term mortality rate was found; however, paracentesis is faster, more effective, and associated with fewer adverse effects.
     b. Patients receiving large-volume paracentesis should receive albumin replacement therapy at the dose of 7 to 9 g/L of fluid removed if more than 5 L are taken out to prevent paracentesis-induced circulatory dysfunction (PICD). Patients with renal dysfunction or hyponatremia should receive albumin for lower volumes as well.
- Table 2 summarizes primary medical therapy and adjunctive medications used to increase the efficacy of primary therapy in the treatment of ascites.

CHRONIC Rx

- 5% to 10% of patients with large-volume ascites will be refractory to high-dose diuretic treatment. Treatment strategies include repeated large-volume paracentesis with infusion of albumin every 2 to 4 wk or placement of a transjugular intrahepatic portosystemic shunt (TIPS).
- TIPS evaluation should include echocardiogram, assessment for hepatic encephalopathy, and characterization of liver impairment.
- Discuss referral to transplant-capable center.
- Patients known to have ascites should receive a diagnostic tap if they develop any signs of SBP or on any admission to the hospital even in the absence of these signs.
- Primary prophylaxis for SBP is recommended in patients with ascitic fluid protein <1.5 g/dl along with impaired renal function (creatinine ≥1.2 mg/dl or 106 micromol/L), BUN ≥25 mg/dl or 8.9 mmol/L or Na ≤130 mEq/L or 130 mmol/L, or liver failure (Child-Pugh score ≥9 and bilirubin ≥3 mg/dl or 51 micromol/L).
- Secondary prophylaxis should be instituted in all patients who were diagnosed with SBP in the form of a daily fluoroquinolone, ciprofloxacin or norfloxacin, or double strength trimethoprim-sulfamethoxazole
- Patients with known ascites who develop gastrointestinal bleeding should receive intravenous ceftriaxone for 7 days to prevent bacterial infections.
- Clinical use of Vaptan agents is not currently recommended in cirrhotic patients.
- Oral midodrine 7.5 mg three times daily has been shown to increase urine volume, urine sodium, mean arterial pressure, and survival.
- Peritoneovenous shunts or surgical portosystemic shunts have poor evidence and are not recommended.
- The Alfapump system (not approved in North America) works by transporting small amounts of fluid from the peritoneal cavity to the bladder. Studies have shown improved symptoms and reduced LVP requirements.
- Liver transplantation remains definitive management for cirrhosis with refractory ascites.
- Table 3 summarizes the management of refractory ascites.
- A treatment approach to patients with malignant ascites is described in Fig. E5.

DISPOSITION

- Development of ascites signals a shift to decompensated cirrhosis and close follow-up is required.
- Monitor closely for worsening liver function and development of spontaneous bacterial peritonitis (SBP).

REFERRAL

Referral to hepatology at a transplant-capable center.

PEARLS & CONSIDERATIONS

COMMENTS

- Prevalence of SBP in patients with ascites ranges between 10% and 30%.
  1. Presence of at least 250 neutrophils per cubic millimeter of ascitic fluid is diagnostic.
  2. Gram-negative bacteria such as *E. coli* are the most common isolates.
  3. Third-generation cephalosporins are the treatment of choice.
  4. By 1 yr, 70% of patients have recurrence of SBP and may be prophylaxed with ciprofloxacin 750 mg PO once/wk.

PREVENTION

- Prevention of liver cirrhosis through avoidance of long-term use of alcohol, immunization against hepatitis A and B, and treatment of hepatitis C
- In cirrhotic patients, following a low-sodium diet (<2 g daily)

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Ascites (Patient Information)
Cirrhosis (Related Key Topic)

AUTHORS: **Marc Monachese, MD, Roxana Chis, MD,** and **Talia Zenlea, MD**

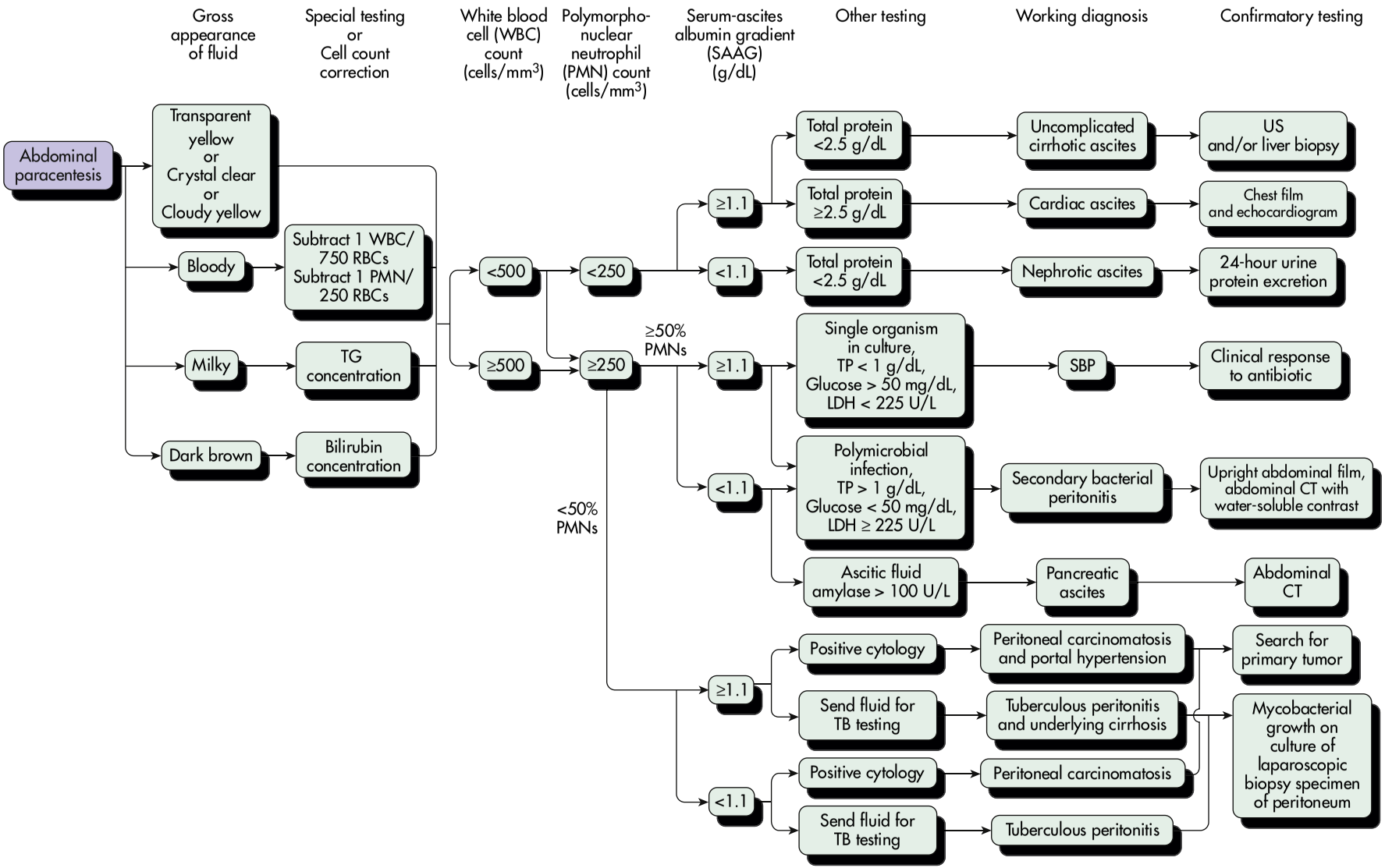

FIG. 3 Algorithm for the approach to the differential diagnosis of ascites. *LDH,* Lactic dehydrogenase; *PMN,* polymorphonuclear neutrophil; *RBC,* red blood cell; *TP,* total protein. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

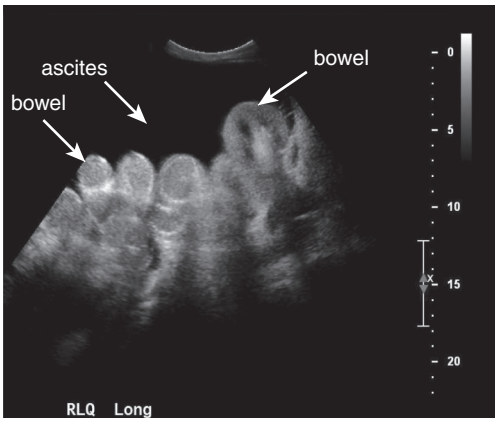

FIG. 4 Ascites, ultrasound. Ultrasound is useful for detection of ascites. Simple fluids such as ascites are excellent sound transmission media, reflecting almost no sound waves. As a consequence, they appear quite hypoechoic *(black)* on ultrasound. This view of the right lower quadrant shows loops of bowel surrounded by fluid. During the ultrasound, the bowel loops would be seen to undergo peristalsis and drift back and forth in the ascitic fluid with patient movement. Ultrasound cannot distinguish the composition of the fluid; ascites, liquid blood, liquid bile, urine, and infectious fluids have a similar appearance, with a few exceptions. Blood may coagulate and form septations within the fluid collection. Infectious fluids also frequently form loculated fluid collections that may be recognized on ultrasound, although the exact composition cannot be determined. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

TABLE 2 Primary Medical Therapy and Adjunctive Medications Used to Increase the Efficacy of Primary Therapy in the Treatment of Ascites

Class	Medication	Dosing	Relevant Action	Notes
Diuretics	Spironolactone	400 mg + daily*	Aldosterone receptor antagonist	Primary therapy
	Furosemide	160 mg + daily*	Inhibits Na-K-2Cl symporter	Primary therapy
Vasoconstrictors	Octreotide	300 mcg bid*	Splanchnic vasoconstriction, inhibits RAAS	Also used in combination with midodrine to treat hepatorenal syndrome; given for first 5 days following variceal bleeding to decrease recurrence
	Midodrine	7.5 mg tid*	Inhibits RAAS	Also used in combination with octreotide and albumin to treat hepatorenal syndrome
α2-Agonist	Clonidine	0.075 mg bid*	Inhibits sympathetic outflow, inhibits RAAS	Increases sensitivity to spironolactone
Colloid	Albumin	25 g*	Increased oncotic pressure	Also utilized with large-volume paracentesis and in the treatment of hepatorenal syndrome

RAAS, Renin-angiotensin-aldosterone system
*The above doses have been derived from various studies and may not be suitable for all patients. Titration is always recommended.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

TABLE 3 Management of Refractory Ascites

Definitions	Ascites that is not eliminated even with maximum diuretic therapy
	Ascites that is not eliminated because maximum dosages of diuretics cannot be attained, given the development of diuretic-induced complications
Recommended therapy	Total paracentesis + IV albumin (7-9 g/L of ascites removed) if >5 L removed
	Continue with salt restriction and diuretic therapy as tolerated
Alternative therapy	TIPS for patients who require frequent paracenteses (every 1-2 weeks) and whose CTP score is ≤11 or MELD <17
Peritoneovenous shunt for patients who are not candidates for TIPS or transplant	

CTP, Child-Turcotte-Pugh; *IV,* intravenous; *MELD,* model for end-stage liver disease; *TIPS,* transjugular intrahepatic portosystemic shunt.
Data from Garcia-Tsao G, Lim JK; Members of the Veterans Affairs Hepatitis C Resource Center Program: management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program, *Am J Gastroenterol*, 104:1802-1829, 2009.
From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.

SUGGESTED READINGS

Adebayo D et al: Refractory ascites in liver cirrhosis, *Am J Gastroenterol* 114, 2019.

Fukui H et al: Evidence-based clinical practice guidelines for liver cirrhosis 2015, *J Gastroenterol* 51(7):629-650, 2016.

Hudson B et al: Cirrhosis with ascites in the last year of life: a nationwide analysis of factors shaping costs, health-care use, and place of death in England, *Lancet Gastroenterol Hepatol* 3:95-103, 2018.

Møller S et al: The pathophysiology of arterial vasodilatation and hyperdynamic circulation in cirrhosis, *Liver Int* 38:570-580, 2018.

Pederson et al: Management of cirrhotic ascites, *Ther Adv Chronic Dis* 6(3):124-137, 2015.

Pose E et al: Translating our current understanding of ascites management into new therapies for patients with cirrhosis and fluid retention, *Dig Dis* 35:402-410, 2017.

Runyon B: *Management of adult patients with ascites due to cirrhosis: update*, AASLD Practice Management Guidelines, 2012. Available at www.aasld.org/publications/practice-guidelines.

FIG. E1 Ascites. (From Swartz MH: *Textbook of physical diagnosis, history, and examination,* ed 7, Philadelphia, Elsevier, 2014.)

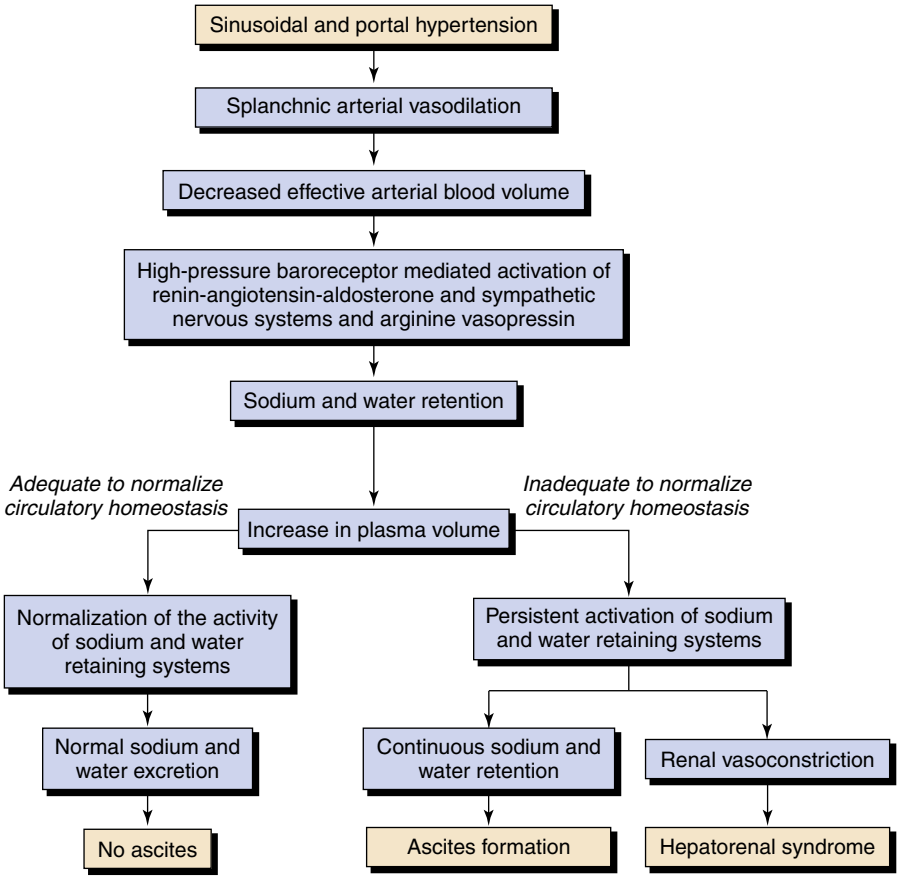

FIG. E2 Pathogenesis of functional renal abnormalities and ascites formation in liver cirrhosis. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

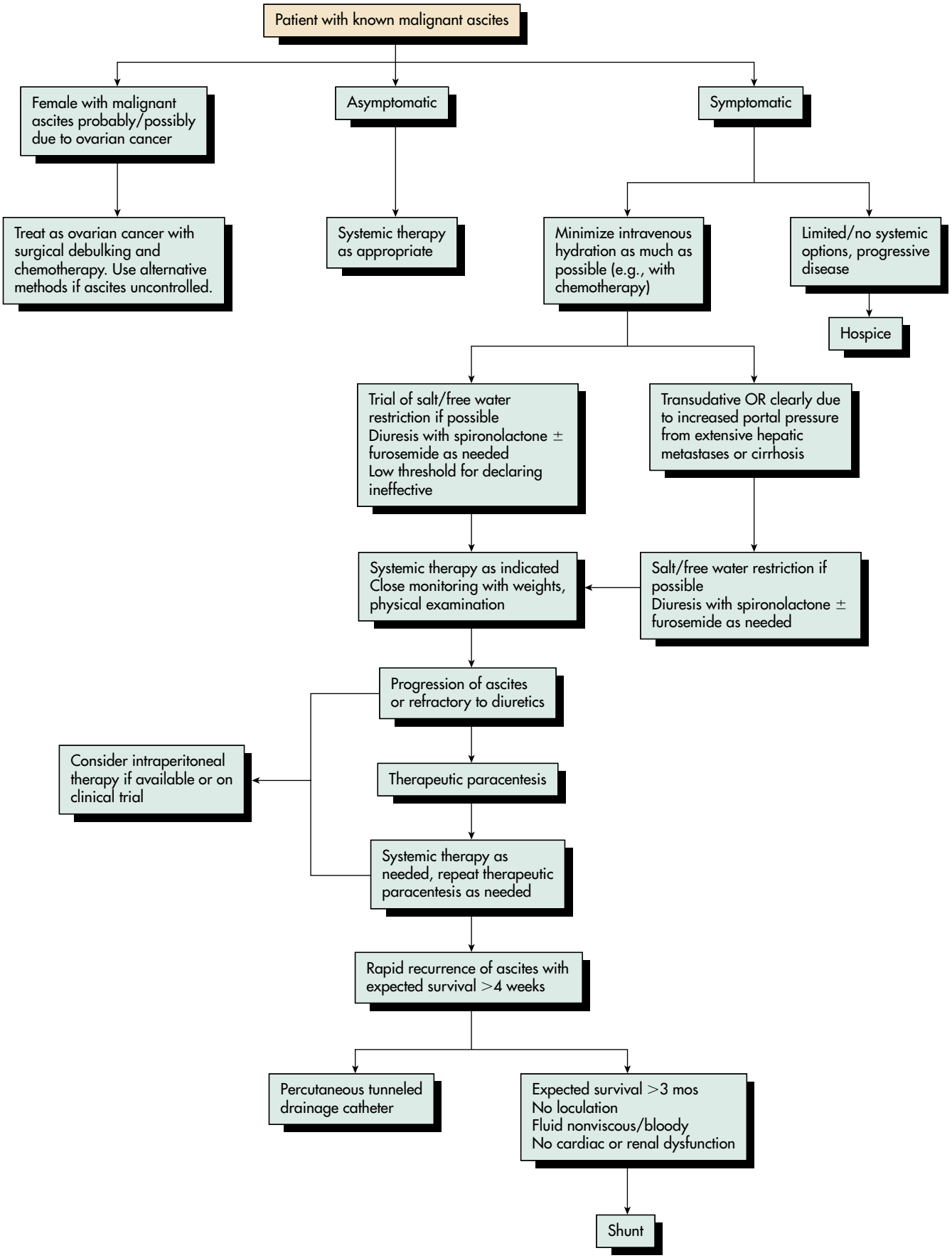

FIG. E5 Malignant ascites, treatment approach. (From Abeloff MD: *Clinical oncology,* ed 3, Philadelphia, 2004, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Aspergillosis refers to several forms of a broad range of illnesses caused by infection with *Aspergillus* species. Fig. 1 illustrates the spectrum of *Aspergillus* infection.

ICD-10CM CODES

B44.0	Invasive pulmonary aspergillosis
B44.1	Other pulmonary aspergillosis
B44.2	Tonsillar aspergillosis
B44.7	Disseminated aspergillosis
B44.81	Allergic bronchopulmonary aspergillosis
B44.89	Other forms of aspergillosis
B44.9	Aspergillosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE & PREVALENCE:

- *Aspergillus* species are ubiquitous in the environment internationally and occur as a mold found in soil. *Aspergillus fumigatus* is the most common human pathogen.
- Cause a variety of illness from hypersensitivity pneumonitis to disseminated overwhelming infection in immunosuppressed patients.
- Frequently cultured from hospital wards from unfiltered outside air circulating through open windows as well as water sources.
- Reach the patient by airborne conidia (spores) that are small enough (2.5 to 3 μm) to reach the alveoli on inhalation.
- Can invade the nose, paranasal sinuses, external ear, or traumatized skin.

RISK FACTORS:

- The clinical syndrome depends on the underlying lung architecture, the host's immune response, and the degree of inoculum.
- Incidence of invasive aspergillosis is increasing with advances in the treatment of life-threatening diseases, such as aggressive chemotherapy or bone marrow and organ transplantation. It also can rarely occur in normal hosts, especially associated with influenza A. Liver and lung transplant recipients are at highest risk for pulmonary disease. Genetic deficiency of the soluble-pattern-recognition receptor known as long pentraxin 3 (PTX3) affects the antifungal capacity of neutrophils and may contribute to the risk of invasive aspergillosis in patients treated with hematopoietic stem-cell transplantation (HSCT).
- Patients with AIDS and a CD4 count <50/mm^3 have an increased susceptibility to invasive aspergillosis, but it is otherwise uncommon in patients with HIV.
- Pandemic influenza A (H1N1) infection may predispose immunocompromised patients to invasive aspergillosis.
- Patients with chronic granulomatous disease are at higher risk for infections with *Aspergillus* species.

ETIOLOGY

- *A. fumigatus* is the usual cause.
- *A. flavus* is the second most important species, particularly in invasive disease of immunosuppressed patients and in lesions beginning in the nose and paranasal sinuses. *A. niger* can also cause invasive human infection.

ALLERGIC ASPERGILLOSIS:

- Is a hypersensitivity pneumonitis.
- Presents as cough, dyspnea, fever, chills, and malaise typically 4 to 8 hr after exposure.
- Repeated attacks can lead to granulomatous disease and pulmonary fibrosis.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA):

- Symptoms occur most commonly in atopic individuals during the third and fourth decades of life.
- Hypersensitivity reaction to *Aspergillus* fungal antigens present in the bronchial tree.
- Results from an initial type I (immediate hypersensitivity) and type III reactions (immune complexes).
- Underdiagnosed pulmonary disorder in patients with asthma and cystic fibrosis (reported prevalence in asthmatic patients varies from 6% to 28% and in cystic fibrosis 6% to 25%).

ASPERGILLOMAS ("FUNGUS BALLS"):

- In the absence of invasion or significant immune response, *Aspergillus* can colonize a preexisting cavity, causing pulmonary aspergilloma.
- Forms masses of tangled hyphal elements, fibrin, and mucus.
- Patients typically have a history of chronic lung disease, tuberculosis, sarcoidosis, or emphysema.
- Manifests commonly as hemoptysis.
- Many are asymptomatic.

INVASIVE ASPERGILLOSIS:

- Patients with prolonged and profound granulocytopenia or impaired phagocytic function are predisposed to rapidly progressive *Aspergillus* pneumonia.
- Typically a necrotizing bronchopneumonia, ranging from small areas of infiltrate to intensive bilateral hemorrhagic infarction.
- Most common presentation: Unremitting fever and a new pulmonary infiltrate despite broad-spectrum antibiotic therapy in an immunosuppressed patient.
- Dyspnea and nonproductive cough are common; sudden pleuritic pain and tachycardia, sometimes with a pleural rub, may mimic pulmonary embolism; hemoptysis is uncommon.
- Chest radiograph (CXR) may reveal patchy bronchopneumonic, nodular densities, consolidation, or cavitation. High-resolution CT scan is more sensitive and specific than CXR in neutropenic patients.
- Immunocompromised patients: Invasive pulmonary *Aspergillus* (IPA) generally is acute and evolves over days to weeks; less commonly, patients with normal or only mild abnormalities of the immune system may develop a more chronic, slowly progressive form of IPA.

EXTRAPULMONARY DISSEMINATION:

- Cerebral infarction from hematogenous dissemination may occur in immunosuppressed individuals.
- Abscess formation from direct extension or invasive disease in the sinuses.
- Esophageal or gastrointestinal ulcerations may occur in the immunosuppressed host.
- Fatal perforation of the viscus or bowel infarction may occur.
- Necrotizing skin ulcers (Fig. E2).
- Osteomyelitis.
- Endocarditis in patients who have recently undergone open heart surgery.
- Infection of an implantable cardioverter-defibrillator has been reported.

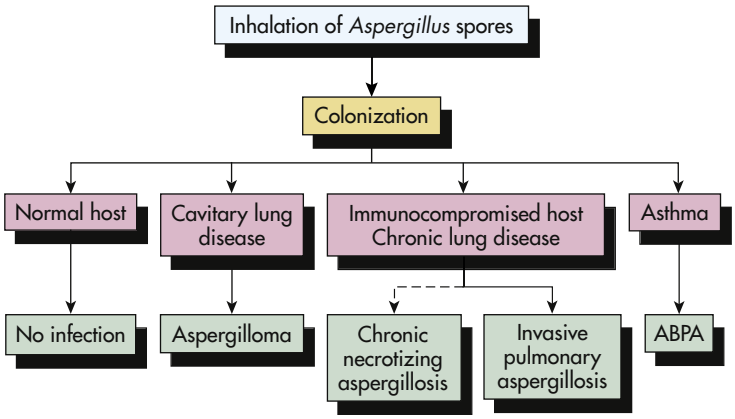

FIG. 1 The spectrum of *Aspergillus* infection. *ABPA,* Allergic bronchopulmonary aspergillosis. (From Sellke FW, del Nido PJ, Swanson SJ: *Sabiston & Spencer surgery of the chest,* ed 9, Philadelphia, 2016, Elsevier.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Tuberculosis
- Cystic fibrosis
- Carcinoma of the lung
- Eosinophilic pneumonia
- Bronchiectasis
- Sarcoidosis
- Lung abscess

WORKUP

Physical examination and laboratory data

LABORATORY TESTS

ABPA:

- Peripheral blood eosinophilia and an elevated total serum immunoglobulin E (IgE) level.
- Skin test with *Aspergillus* antigenic extract is usually positive but nonspecific.
- *Aspergillus* serum precipitating antibody is present in 70% to 100% of cases.
- Sputum cultures may be positive for *Aspergillus* spp. but are nonspecific.

ASPERGILLOMAS:

- Sputum culture
- Serum precipitating antibody

INVASIVE ASPERGILLOSIS:

- Definitive diagnosis requires the demonstration of tissue invasion (i.e., septate, acute angle branching hyphae) or a positive culture from the tissue obtained by an invasive procedure such as transbronchial biopsy.
- Sputum and nasal cultures: In high-risk patients a positive culture is strongly suggestive of invasive aspergillosis.
- Serology: The *Platelia Aspergillus* ELISA assay detects a circulating fungal antigen, galactomannan. The **Galactomannan antigen immunoassay** is often used for diagnosis. Galactomannan is a polysaccharide contained in the cell wall of *Aspergillus.* Its presence in serum or other body fluids is indicative of invasive infection, and it is recommended as an accurate marker for diagnosis in certain patient subpopulations (hematologic malignancy and hematopoietic stem cell transplantation). The sensitivity of the Galactomannan antigen immunoassay can be impaired by antifungal therapy. The β-D glucan assay can also be used to detect early infection, but is not specific for *Aspergillus* species.[1]
- Blood cultures: Usually negative.
- Lung biopsy is necessary for definitive diagnosis.
- Biopsy and culture of extrapulmonary lesions.
- Polymerase chain reaction assays may be employed, but their results should be interpreted in conjunction with other diagnostic tests and the clinical context.

IMAGING STUDIES

ABPA:

- CXRs show a variety of abnormalities, from small, patchy, fleeting infiltrates (commonly in the upper lobes) to lobar consolidation or cavitation.
- A majority of patients eventually develop central bronchiectasis.

ASPERGILLOMAS: CXR or CT scans usually show the characteristic intracavity mass (Figs. E3 and E4) partially surrounded by a crescent of air ("halo sign").

INVASIVE ASPERGILLOSIS: CXR and CT scanning may also reveal cavity formation and the halo sign. Air bronchograms typically disappear as they are filled with hemorrhagic fluid.

Rx TREATMENT

ACUTE GENERAL Rx

ABPA:

- Prednisone (0.5 to 1 mg/kg PO) until the CXR has cleared, followed by alternate-day therapy at 0.5 mg/kg PO (3 to 6 mo) plus itraconazole oral solution 2.5 mg/kg PO bid or 200 mg capsules bid for 16 weeks.
- If a patient is corticosteroid dependent, prophylaxis for the prevention of *Pneumocystis jiroveci* infection and maintenance of bone mineralization should be considered.
- Bronchodilators and physiotherapy.
- Serial CXR and serum IgE is useful in guiding treatment.

ASPERGILLOMAS:

- Controversial and problematic; the optimal treatment strategy is unknown.
- Up to 10% of aspergillomas may resolve clinically without overt pharmacologic or surgical intervention.
- Observation for asymptomatic patients.
- Surgical resection/arterial embolization for those patients with severe hemoptysis or life-threatening hemorrhage.
- For those patients at risk for marked hemoptysis with inadequate pulmonary reserve, consider itraconazole 200 to 400 mg/day PO. Voriconazole and posaconazole are also effective.

INVASIVE ASPERGILLOSIS:

- Voriconazole 6 mg/kg IV/PO bid on day 1 followed by 4 mg/kg IV/PO bid. Voriconazole serum concentrations need to be monitored to achieve a target range of 1.0 to 5.5 mg/L (trough on day 4).
- Isavuconazonium sulfate (prodrug of Isavuconazole) 372 mg IV/PO tid for six doses and then 372 mg IV/PO daily.

Alternative treatment:

- Amphotericin B lipid complex (ABLC) 5 mg/kg IV daily.
- Liposomal amphotericin B (L-AMB) 3 to 5 mg/kg IV daily.
- Posaconazole delayed-release tabs 300 mg PO for two doses, then 300 mg PO daily or posaconazole suspension 200 mgs qid, then 400 mg po bid after stabilization of disease or posaconazole 300 mg IV over 90 minutes bid for one day, then 300 mg IV daily.
- Because azoles and echinocandins target different cellular sites, combination therapy may have additive activity against *Aspergillus* species.

REFERRAL

To an infectious diseases specialist

PEARLS & CONSIDERATIONS

- Unlike fluconazole, the potential for drug-drug interactions with voriconazole is high. Azoles may interact with drugs used for chemotherapy by increasing toxicity and/or by reducing efficacy.
- Azole resistance has appeared in *Aspergillus fumigatus*; the main resistance mechanism is a point mutation of CYP51A, the gene coding for 14 alpha-sterol demethylase, the target enzyme of antifungal drugs. Global prevalence of azole resistance in *Aspergillus* is estimated to be approximately 3% to 6%.
- Agitation of hospital buildings by renovations or repairs may increase the incidence of *Aspergillus* infections in immunosuppressed individuals.
- Echinocandins should never be used as primary treatment of aspergillosis.
- *Aspergillus and Nocardia* species may co-infect.
- Use of antifungal agents in combination is discussed in Box 1.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Aspergillosis (Patient Information)

AUTHOR: **Sajeev Handa, MD, SFHM**

[1] False-negative results occur in patients who are receiving antifungal agents other than fluconazole. The sensitivity of the galactomannan assay for invasive pulmonary aspergillosis is higher in brochoalveolar lavage fluid than in serum. In patients with risk factors and radiologic findings suggestive of invasive aspergillosis, a positive galactomannan confirms the diagnosis of probable invasive pulmonary aspergillosis.

BOX 1 Use of Antifungal Agents in Combination

The development of new antifungal drugs gives the clinician more options for prophylaxis and therapy than in previous years. There is an overall level of simplicity to the drug choices once their mechanisms of action are understood. The polyenes, including amphotericin products and the topical agent nystatin, attach onto ergosterol in the fungal cell membrane and are considered fungicidal, because cytoplasm leaks out, and individual cells die. The azoles, including fluconazole, itraconazole, voriconazole, and posaconazole, prevent the formation of new ergosterol. Azoles are considered fungistatic, because removal of the drug permits cell regrowth. Theoretically, use of an azole together with a polyene may have an overall static effect for an established infection as the ergosterol target for the fungicidal polyene is depleted. However, this combination may have advantages in terms of enhanced spectrum of activity. The echinocandins, including caspofungin, micafungin, and anidulafungin, prevent interaction of the catalytic and regulatory subunits of the β-glucan synthesis enzyme, so less β-glucan is formed for the cell wall. The scaffolding for the fungal cell wall is not maintained, and a dividing cell may burst open when trying to extend the new cell wall over daughter cells. The echinocandins are considered fungicidal for yeasts but fungistatic for molds, because drug activity is concentrated at only the tips of the extending hyphae with little effect on less metabolically active subapical compartments of the fungus. Combination therapy may have the most effect when a cell wall agent (an echinocandin) is used together with a cell membrane agent (a polyene or an azole). There is no role for three-drug therapy (an echinocandin, a polyene, and an azole). Aside from cases of cryptococcal meningitis, in which the importance of combination therapy is well established, the benefits of frontline use of combination antifungal for molds remain controversial, although active investigation continues in clinical trials. The value of combination regimens as salvage therapy for refractory mold infections remains uncertain.

From Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

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Marr KA et al: Combination antifungal therapy for invasive aspergillosis, a randomized trial, *Ann Intern Med* 162:81-89, 2015.

Miceli MH, Kauffman CA: Aspergillus galactomannan for diagnosing invasive aspergillosis, *JAMA* 318(12):1175

Patterson TF et al: Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America, *Clin Infec Dis 2016* 63, 2016.

FIG. E2 Cutaneous aspergillosis. Erythematous plaque with necrosis and eschar formation in a young female with immunosuppression and disseminated *Aspergillus fumigatus* infection. (From Paller AS, Mancini, AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

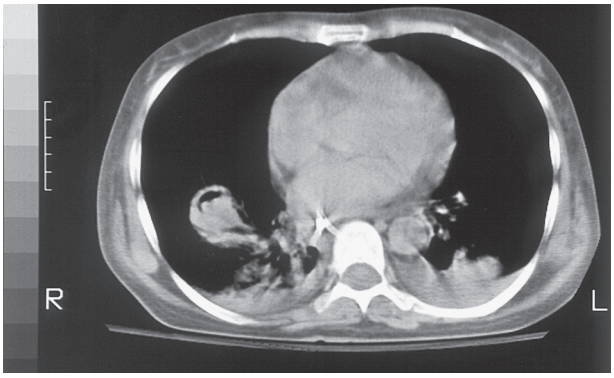

FIG. E3 Computed tomography scan demonstrating an aspergilloma involving the right lower lobe. (From Sellke FW, del Nido PJ, Swanson SJ: *Sabiston & Spencer surgery of the chest*, ed 9, Philadelphia, 2016, Elsevier.)

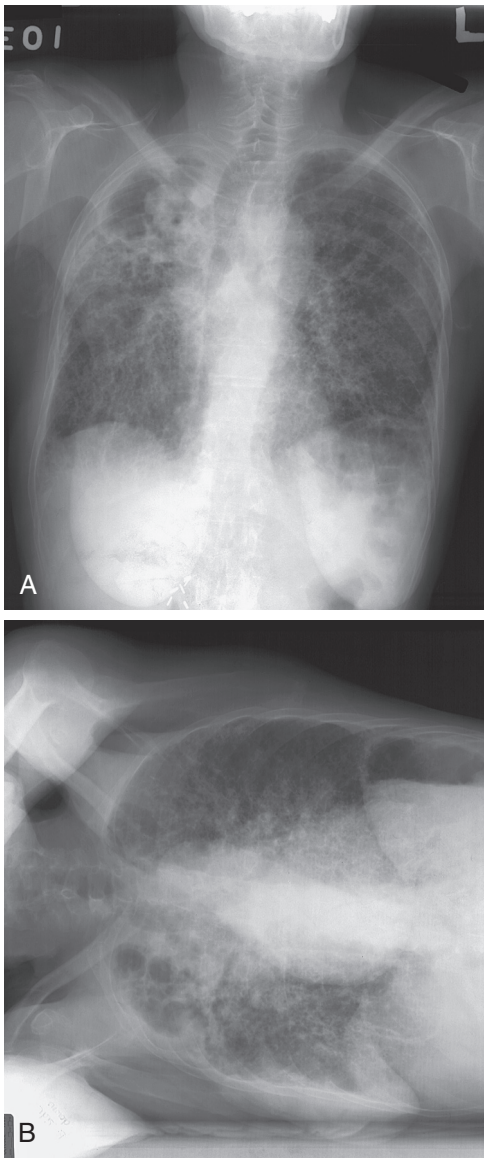

FIG. E4 Posteroanterior **(A)** and decubitus **(B)** chest radiographs demonstrating an aspergilloma within a right upper lobe cavity. The fungus ball "moves" with change in patient position. (From Sellke FW, del Nido PJ, Swanson SJ: *Sabiston & Spencer surgery of the chest*, ed 9, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Aspiration pneumonia is a vague term that refers to pulmonary abnormalities following abnormal entry of endogenous or exogenous substances in the lower airways. It can be considered part of the continuum that also includes community- and hospital-acquired pneumonias. It is generally classified as:

- Aspiration (chemical pneumonitis)
- Primary bacterial aspiration pneumonia
- Secondary bacterial infection of chemical pneumonitis

SYNONYM

Pneumonia, aspiration

ICD-10CM CODE

J69.0 Pneumonitis due to inhalation of food and vomit

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- 20% to 35% of all pneumonias
- 5% to 15% of all community-acquired pneumonias

PEAK INCIDENCE: Elderly patients in hospitals or nursing homes

PREVALENCE (IN U.S.): Unknown (unreliable data)

PREDOMINANT SEX: Males and females affected equally

PREDOMINANT AGE: Elderly

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Shortness of breath, tachypnea, cough, sputum, fever after vomiting, or difficulty swallowing
- Rales, rhonchi, often diffusely throughout lung

ETIOLOGY

Complex interaction of etiologies, ranging from chemical (often acid) pneumonitis after aspiration of sterile gastric contents (generally not requiring antibiotic treatment) to bacterial aspiration. Risk factors for aspiration pneumonia include vomiting, decreased consciousness, poor dentition, ineffective cough reflex, and gastroesophageal reflux disease. Table 1 summarizes risk factors for aspiration pneumonia.

COMMUNITY-ACQUIRED ASPIRATION PNEUMONIA:

- Generally results from predominantly anaerobic mouth bacteria (anaerobic and microaerophilic streptococci, fusobacteria, gram-positive anaerobic non–spore-forming rods), *Bacteroides* species (*melaninogenicus*, *intermedius*, *oralis*, *ureolyticus*), *Haemophilus influenzae,* and *Streptococcus pneumoniae*
- Rarely caused by *Bacteroides fragilis* (of uncertain validity in published studies) or *Eikenella corrodens*
- High-risk groups: The elderly; alcoholics; IV drug users; patients who are obtunded; stroke victims; and those with esophageal disorders, seizures, poor dentition, or recent dental manipulations

HOSPITAL-ACQUIRED ASPIRATION PNEUMONIA:

- Often occurs among elderly patients and others with diminished gag reflex; those with nasogastric tubes, intestinal obstruction, or ventilator support; and especially those exposed to contaminated nebulizers or unsterile suctioning.
- High-risk groups: Seriously ill hospitalized patients (especially patients with coma, acidosis, alcoholism, uremia, diabetes mellitus, nasogastric intubation, or recent antimicrobial therapy, who are frequently colonized with aerobic gram-negative rods); patients undergoing anesthesia; those with strokes, dementia, or swallowing disorders; the elderly; and those receiving antacids or H_2 blockers, or proton pump inhibitors (but not sucralfate).
- Hypoxic patients receiving concentrated O_2 have diminished ciliary activity, encouraging aspiration.
- Causative organisms:
  1. Anaerobes listed above, although in many studies gram-negative aerobes (60%) and gram-positive aerobes (20%) predominate.
  2. *E. coli, P. aeruginosa, S. aureus* including MRSA, *Klebsiella, Enterobacter, Serratia, Proteus* spp., *H. influenzae, S. pneumoniae, Legionella,* and *Acinetobacter* spp. (sporadic pneumonias) in two thirds of cases.
  3. Fungi, including *Candida albicans,* in <1%.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other necrotizing or cavitary pneumonias (especially tuberculosis, gram-negative pneumonias)
- See "Tuberculosis, Pulmonary"

WORKUP

- Chest x-ray
- Complete blood count (CBC), blood cultures
- Sputum gram stain and culture
- Consideration of tracheal aspirate

LABORATORY TESTS

- CBC: Leukocytosis often present.
- Sputum gram stain:
  1. Often useful when carefully prepared immediately after obtaining suctioned or expectorated specimen, examined by experienced observer.
  2. Only specimens with multiple white blood cells and rare or absent epithelial cells should be examined.
  3. Unlike nonaspiration pneumonias (e.g., pneumococcal), multiple organisms may be present.
  4. Long, slender rods suggest anaerobes.
  5. Sputum from pneumonia caused by acid aspiration may be devoid of organisms.
  6. Cultures should be interpreted in light of morphology of visualized organisms.

IMAGING STUDIES

- Chest x-ray often reveals bilateral, diffuse, patchy infiltrates and posterior segment upper lobes (Fig. 1). Chemical pneumonitis typically affects the most dependent regions of the lungs. The chest x-ray may be negative early in the course of aspiration pneumonia.
- Aspiration pneumonia of several days' or longer duration may reveal necrosis (especially community-acquired anaerobic pneumonias) and even cavitation with air-fluid levels, indicating lung abscess.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Airway management to prevent repeated aspiration
- Ventilatory support if necessary
- Rehabilitative management: Physical, pulmonary, and dysphagia therapy combined with appropriate nutrition can reduce length of stay and mortality

ACUTE GENERAL Rx

- **Chemical pneumonitis:** Acute aspiration of acidic gastric contents without bacteria may not require antibiotic therapy; initial treatment involves airway maintenance and management of bronchospasm and airway edema. Routine adjunctive treatment with glucocorticoids is not recommended. Consultation with an infectious disease or pulmonary expert is recommended.
- **Aspiration pneumonia:** Antibiotic selection depends on the site of acquisition (long-term care facility, hospital, community), which modifies risk factors for infection with multidrug-resistant pathogens.

TABLE 1 Risk Factors for Dysphagia and Aspiration Pneumonia

Cerebrovascular disease
Ischemic stroke
Hemorrhagic stroke
Subarachnoid hemorrhage
Degenerative neurologic disease
Alzheimer disease
Multi-infarct dementia
Parkinson disease
Amyotrophic lateral sclerosis (motor neuron disease)
Multiple sclerosis
Head and neck cancer
Oropharyngeal malignancy
Oral cavity malignancy
Esophageal malignancy
Other
Scleroderma
Diabetic gastroparesis
Reflux esophagitis
Presbyesophagus
Achalasia

From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.

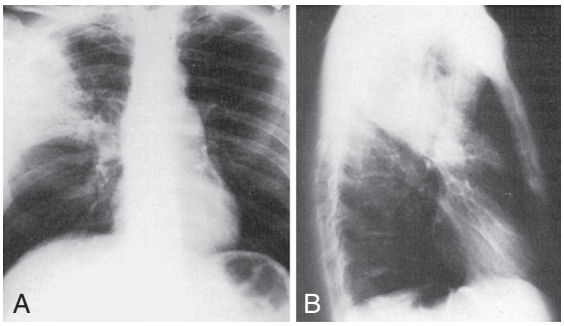

FIG. 1 Anaerobic necrotizing pneumonia following aspiration of oropharyngeal secretions. Multiple, small (<2 cm) radiolucencies are seen throughout the posterior segment of the right upper lobe on the postero-anterior **(A)** and lateral **(B)** projections. (Courtesy Michael Gotway, MD. From Mason RJ et al: *Murray & Nadel's textbook of respiratory medicine*, ed 5, Philadelphia, 2010, Saunders.)

- Community-acquired aspiration pneumonia or hospital-acquired cases with low risk of multidrug-resistant pathogens: Ampicillin-sulbactam 1.5 to 3 g every 6 hours IV, or amoxicillin-clavulanate PO 875 mg twice daily, or a fluoroquinolone (levofloxacin 750 mg IV or PO) is effective. Clindamycin (450 mg oral qid or 600 mg IV every 8 hours) can be added to the other agent when the risk of predominantly anaerobic infection is high.
- Nursing home aspirations or hospital-acquired aspiration pneumonias with concerns for resistance: Broad-spectrum treatment with piperacillin-tazobactam 3.375 g q6h or cefepime 2 g q8h ± vancomycin (15 mg/kg q12h IV) or linezolid (600 mg q12h PO or IV) if MRSA is suspected or known (e.g., documented nasal or respiratory colonization with MRSA).
  1. Knowledge of resident flora in the micro-environment of the aspiration within the hospital is crucial to intelligent antibiotic selection; consult infection control nurses or hospital epidemiologist.
  2. Confirmed *Pseudomonas* pneumonia should be treated with antipseudomonal beta-lactam agent (piperacillin/tazobactam, cefepime, meropenem) plus an aminoglycoside until antimicrobial sensitivities confirm that less toxic agents may replace the aminoglycoside.

DISPOSITION

Repeat chest x-ray in 6 to 8 wk in most patients.

REFERRAL

For consultation with infectious disease and/or pulmonary experts for patients with respiratory distress, hypoxia, ventilatory support, pneumonia in more than one lobe, or necrosis or cavitation on x-ray examination or for those not responding to antibiotic therapy within 2 to 3 days.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Aspiration Pneumonia (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Daoud E, Guzman J: Are antibiotics indicated for the treatment of aspiration pneumonia? *Cleve Clin J Med* 77(9):573, 2010.

DiBardino DM, Wunderink RG: Aspiration pneumonia: a review of modern trends, *J Crit Care* 30:40-48, 2015.

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Momoski R: Rehabilitative management for aspiration pneumonia in elderly patients, *J Gen Fam Med* 18:12-15, 2017.

Teramoto S et al: Update on the pathogenesis and management of pneumonia in the elderly–roles of aspiration pneumonia, *Respir Investig* 53:178-184, 2015.

BASIC INFORMATION

DEFINITION

The National Asthma Education and Prevention Program (NAEPP) guidelines define asthma as "a chronic inflammatory disease of the airways in which many cells and cellular elements play a role: in particular mast cells, neutrophils, eosinophils, T lymphocytes, macrophages, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. The episodes are usually associated with widespread but variable airflow obstruction that is reversible either spontaneously or as a result of treatment." **Status asthmaticus,** or acute severe asthma, is a refractory state that does not respond to standard therapy such as inhaled beta-agonists or subcutaneous epinephrine. It may persist for several hours.

SYNONYMS

Bronchospasm
Reactive airway disease
Asthmatic bronchitis

ICD-10CM CODES

J45.20	Mild intermittent asthma, uncomplicated
J45.21	Mild intermittent asthma with (acute) exacerbation
J45.22	Mild intermittent asthma with status asthmaticus
J45.30	Mild persistent asthma, uncomplicated
J45.31	Mild persistent asthma with (acute) exacerbation
J45.32	Mild persistent asthma with status asthmaticus
J45.40	Moderate persistent asthma, uncomplicated
J45.41	Moderate persistent asthma with (acute) exacerbation
J45.42	Moderate persistent asthma with status asthmaticus
J45.50	Severe persistent asthma, uncomplicated
J45.51	Severe persistent asthma with (acute) exacerbation
J45.52	Severe persistent asthma with status asthmaticus
J45.901	Unspecified asthma with (acute) exacerbation
J45.902	Unspecified asthma with status asthmaticus
J45.909	Unspecified asthma, uncomplicated
J45.991	Cough variant asthma
J45.998	Other asthma

EPIDEMIOLOGY & DEMOGRAPHICS

- Asthma has been diagnosed in 7.5% of the population in the U.S., and its prevalence is steadily rising among patients older than 65 yr, African Americans, women, and persons below the poverty level.
- It accounts for around 440,000 hospitalizations and 1.8 million emergency department visits yearly in the U.S.
- It is more common in children, but the gap is closing because of a rapid increase in adult-onset asthma (9.5% of children vs. 8.2% of adults).
- 50% to 80% of children with asthma develop symptoms before 5 yr of age. Early childhood risk factors for asthma are described in Table 1.
- The overall asthma mortality rate in the U.S. has slightly improved to 11 per 1 million persons.
- It is estimated that 300 million people have asthma. An increase in prevalence to 400 million is anticipated by 2025.
- Box 1 summarizes risk factors for severe and fatal asthma in adults.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Physical examination varies with the stage and severity of asthma and may reveal normal lung examination results in many patients. However, some degree of wheezing and prolonged expiratory phases of respiration are seen with persistent or acute disease. Box 2 summarizes signs and symptoms of severe asthma. Physical examination during status asthmaticus may reveal:

- Tachycardia and tachypnea
- Use of accessory respiratory muscles
- Pulsus paradoxus (inspiratory decline in systolic blood pressure >10 mm Hg)
- Absence of wheezing (silent chest) or decreased wheezing can indicate worsening obstruction
- Mental status changes: Generally secondary to hypoxia and hypercapnia and constitute an indication for urgent intubation
- Paradoxic abdominal and diaphragmatic movement on inspiration (detected by palpation over the upper part of the abdomen in a semirecumbent position) indicates diaphragmatic fatigue, another sign of impending respiratory crisis

TABLE 1 Early Childhood Risk Factors for Persistent Asthma

Parental asthma
Allergy:
Atopic dermatitis (eczema)
Allergic rhinitis
Food allergy
Inhalant allergen sensitization
Food allergen sensitization
Severe lower respiratory tract infection:
Pneumonia
Bronchiolitis requiring hospitalization
Wheezing apart from colds
Male gender
Low birthweight
Environmental tobacco smoke exposure
Possible use of acetaminophen (paracetamol)
Exposure to chlorinated swimming pools
Reduced lung function at birth

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, WB Saunders.

BOX 1 Risk Factors for Severe and Fatal Asthma in Adults

- History of prior nonfatal asthma attack
- Prior intubation
- Female gender
- Age >65 yr
- African American ethnicity
- Obesity
- Tobacco use
- Inhalational drug abuse
- Poorly controlled disease
- Poor recognition of dyspnea and other symptoms
- Steroid dependence
- H1N1 viral infection
- Misuse or lack of proper use of maintenance medications
- Psychiatric illness
- Lack of access to medical care
- Lack of ability to limit triggers (i.e., persistent exposure to pollutants, dust)
- Comorbid heart disease, obesity, and/or diabetes
- Bronchoalveolar lavage predominance of neutrophils, interleukin 8, and matrix metalloproteinase

From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

BOX 2 Signs and Symptoms of Severe Asthma

- "Tripoding"—sitting upright and leaning forward
- Diaphoresis
- Use of accessory muscles
- Asynchronous accessory muscle use
- Air trapping and hyperinflation manifesting as decreased inspiratory stroke volume and pulsus paradoxus
- Peak flow <200 L/min and/or <30% predicted*
- FEV_1 <1 L/min and/or <20% predicted*
- Evidence of barotrauma:
  - Unilateral diminution in breath sounds
  - Tracheal deviation
  - Thoracic crepitus
- Signs of impending respiratory arrest:
  - Altered mentation
  - Cyanosis
  - Hypoxia
  - Hypercarbia
  - Hemodynamic instability
  - Silent chest

*These values are estimations because both peak expiratory flow rate and forced expiratory volume in 1 second (FEV_1) vary with age, gender, and height.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

- The following abnormalities in vital signs are indicative of severe asthma:
  1. Pulsus paradoxus >18 mm Hg
  2. Respiratory rate >30 breaths/min
  3. Tachycardia with heart rate >120 beats/min

ETIOLOGY

- The pathophysiology of asthma involves a complex interaction among various environmental and genetic factors. Genetic and phenotypic associations in asthma are described in Box 3.
- Allergic (extrinsic) asthma is triggered by various aeroallergens or nonspecific (e.g., dust, cigarette smoke, fumes, cold air, exercise) exposures in patients who are prone to develop IgE antibodies in response to various exposures. The pathogenesis of antigen-induced asthma is illustrated in Fig. 1.
- A recent study of a prebirth cohort observed that maternal intake of foods commonly considered allergenic (peanut and milk) was associated with a decrease in allergy and asthma in the offspring. No dietary changes during pregnancy are therefore recommended for prevention of allergies or asthma.
- A recent trial revealed that supplementation with n-3 long-chain polyunsaturated fatty acids (LCPUFAs, fish oil-derived fatty acids) in the third trimester of pregnancy reduced the absolute risk of persistent wheeze or asthma and infections of the lower respiratory tract in offspring by approximately 7 percentage points, or one third.[1]
- Nonallergic (intrinsic) asthma commonly manifests as adult-onset asthma in response to respiratory tract infection or psychological stress.
- Occupation exposure to certain organic or nonorganic agents can trigger asthma.
- Evidence suggests that dampness and mold contribute to the risk of developing asthma and that remediation of these in homes reduces asthma symptoms and medication use in adults.
- Exercise-induced asthma is seen most frequently in adolescents and manifests with bronchospasm after beginning of exercise and improves with discontinuation of exercise.
- Drug-induced asthma is associated with use of NSAIDs, β-blockers, sulfites, and certain foods and beverages.
- There is a strong association of the *ADAM 33* gene with asthma and bronchial hyperresponsiveness. Experimental, genetic, and clinical studies support an important role for Th2 immune pathways in the pathogenesis of severe asthma. Th2 cells are stimulated by dendritic cells to produce IL-5, IL-13, and IL-4, the latter driving IgE synthesis. This group is characterized by eosinophilia, and IL-5 is felt to be the most specific cytokine in eosinophil regulatory pathways.

BOX 3 Genetic and Phenotypic Associations in Asthma

- ***ADAM33:*** gene bronchoconstriction
- ***ORMDL3/GSDMB*** locus, chromosome 17q21: childhood onset
- CpG portion of ***ACSL3:*** associated with maternal exposure to automobile pollution
- ***IL33*** on chromosome 9
- ***IL2RB*** on chromosome 22

From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

[1]Bisgaard H et al: Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring, *N Engl J Med* 375:2530-2539, 2016.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Postinfectious bronchitis
- Rhinitis with postnasal drip
- COPD
- GERD
- Pneumonia and other upper respiratory infections
- Foreign body aspiration (most frequent in younger patients)
- Anxiety disorder
- Diffuse interstitial lung disease
- Hypersensitivity pneumonitis
- CHF
- Pulmonary embolism (in adult and elderly patients)

WORKUP

- Diagnosis of asthma requires documentation of airway obstruction and some degree of reversibility of the obstruction, if and when patient can participate.
- For symptomatic adults and children age >5 yr who can perform spirometry, pre- and postbronchodilator spirometry is the recommended test of choice.
- Airflow reversibility is defined as increase in forced expiratory volume in 1 sec (FEV_1 by at least 12% increase and 200 ml) after inhaling a short bronchodilator.
- The degree of reversibility measured by spirometry correlates with airway inflammation, and patients with a high degree of reversibility have a greater risk of irreversible airflow obstruction in subsequent years.

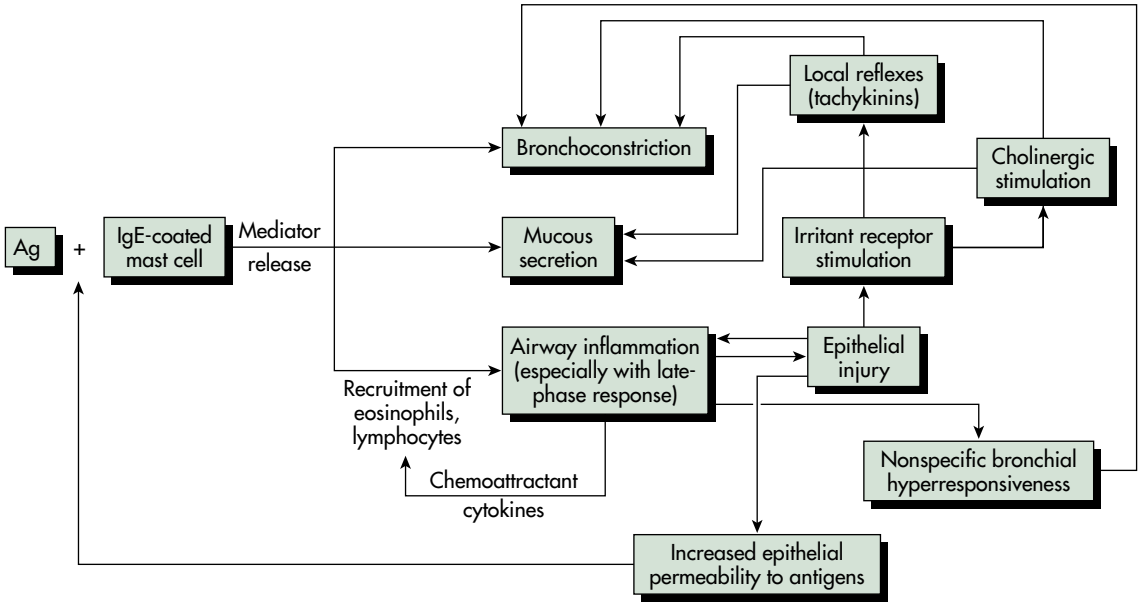


FIG. 1 Schematic diagram of events in pathogenesis of antigen-induced asthma. A hypothetical series of complex interactions is shown, focusing on bronchoconstriction, mucus secretion, and airway inflammation. *Ag,* Antigen; *IgE,* immunoglobulin E. (From Weinberger SE: *Principles of pulmonary medicine,* ed 7, Philadelphia, 2019, Elsevier.)

- For children age <5 yr, spirometry is generally not feasible. Young children with asthma symptoms should be treated as having suspected asthma after alternative diagnoses are ruled out.
- Negative spirometry results do not rule out asthma. Patients with high clinical suspicion should undergo bronchial challenge test using methacholine or other specific agents.
- The clinician should evaluate for environmental causes (e.g., house dust mites, indoor pets) and exposure to other allergens such as tobacco smoke. The degree of reversibility measured by spirometry correlates with airway inflammation, and patients with a high degree of reversibility have a greater risk of irreversible airflow obstruction in subsequent years.
- In the absence of spirometry testing, variability of peak flow measurements by a handheld device can be used to diagnose asthma.
- Fig. E2 describes an algorithm for diagnosing asthma.

After diagnosis, the severity of asthma should be classified during the initial assessment before initiating therapy. Patients are divided into four groups based on the severity of their asthma symptoms and number of exacerbations (see Table 2).

- Once therapy is initiated, the emphasis for clinical management should gear toward achievement of asthma control. The level of asthma control should be used to guide decisions either to maintain or adjust therapy.
- Schedule visits at 2- to 6-wk intervals for patients who are just starting therapy or who require a step up in therapy to achieve or regain asthma control. Schedule visits at 6- to 12-mo intervals, after asthma control is achieved, to monitor whether asthma control is maintained. The interval will depend on factors such as the duration of asthma control or the level of treatment required. Consider scheduling visits at 3-mo intervals if step-down therapy is anticipated.

LABORATORY TESTS

Laboratory tests are usually not necessary and the results can be normal if obtained during a stable period.

- Arterial blood gases (ABGs) can be used during acute bronchospasm in staging the severity of an asthmatic attack:
  1. Mild: Decreased Pa_{O_2} and Pa_{CO_2}, increased pH
  2. Moderate: Decreased Pa_{O_2}, normal Pa_{CO_2}, normal pH
  3. Severe: Marked decreased Pa_{O_2}, increased Pa_{CO_2}, and decreased pH
- Complete blood count: Leukocytosis with left shift may indicate the existence of bacterial infection. Elevated eosinophils point toward allergic component of asthma.
- Spirometry is recommended at the initial assessment and at least every 1 to 2 yr after treatment is initiated and when the symptoms and peak expiratory flow have stabilized. Spirometry as a monitoring measure may be performed more frequently, if indicated, based on severity of symptoms and the disease's lack of response to treatment.
- Peak expiratory flow rate (PEFR) can be used to assess severity of an acute exacerbation episode. Value should be compared with individual's personal best number (see asthma action plan).
- Serum IgE levels help guide treatment for patients with severe persistent asthma, and they also help monitor response to treatment in the same group.
- Specific allergy testing may be helpful in a subgroup of patients.

IMAGING STUDIES

- Chest x-ray: Usually normal, may show evidence of thoracic hyperinflation (e.g., flattening of the diaphragm, increased volume over the retrosternal air space).

TABLE 2 Classifying Asthma Severity and Initiating Treatment in Youths ≥12 Yr and Adults (Assessing severity and initiating treatment for patients who are not currently taking long-term control medications)

Components of Severity		CLASSIFICATION OF ASTHMA SEVERITY (≥12 YR)			
			PERSISTENT		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
Normal FEV_1/FVC: yr85% yr80% yr75% yr70%	Nighttime awakenings	≤2x/mo	3-4x/mo	>1x/wk but not nightly	Often 7x/wk
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/wk	>2 days/wk but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	Normal FEV_1 between exacerbations			
		FEV_1 >80% predicted	FEV_1 >80% predicted	FEV_1 >60% but <80% predicted	FEV_1 <60% predicted
		FEV_1/FVC normal	FEV_1/FVC normal	FEV_1/FVC reduced 5%	FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1 per yr	≥2 per yr		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.			
		Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Therapy		Step 1	Step 2	Step 3	Step 4 or 5
				and consider short course of oral systemic corticosteroids	
		In 2-6 wk, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.

Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2 to 4 wk and spirometry. Assign severity to the most severe category in which any feature occurs.

At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

To access the complete *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma,* go to www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.

EIB, Exercise-induced bronchospasm; *FEV_1,* forced expiratory volume in 1 second; *FVC,* forced vital capacity; *ICU,* intensive care unit.

From National Asthma Education and Prevention Program: *Expert panel report 3: guidelines for diagnosis and management of asthma,* National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

- ECG: Tachycardia, nonspecific ST-T wave changes are common during an asthma attack; may also show cor pulmonale, right bundle branch block, right axial deviation, counterclockwise rotation.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of triggering factors (e.g., salicylates, sulfites), environmental or occupational triggers
- Encouragement of regular exercise (e.g., swimming)
- Patient education regarding warning signs of an attack and proper use of medications (e.g., correct use of inhalers)
- Assess asthma control with use of validated questionnaires

GENERAL Rx

The 2007 NAEPP guidelines (see Tables 2 to 10) provide treatment options by age groups: 0 to 4 yr, 5 to 11 yr, and >12 yr. A step-up approach is described based on the severity of symptoms.

An approach to home management of acute asthma is described in Fig. E3. Short-acting beta-selective adrenergic agonists (SABAs) administered by inhalation is the most effective therapy for quick relief of asthmatic symptoms. They are recommended for use only as needed for relief of symptoms or before anticipated exposure to known triggers such as exercise. They should not be use as a single agent except for intermittent asthma symptoms. When symptoms become more frequent or more severe, step-up treatment with maintenance inhalers is recommended (see Table 4). Inhaled steroid is the mainstay of treatment for maintenance therapy. Other treatment options include long-acting beta-agonist (LABA), combination of inhaled steroids and LABA, leukotriene receptor antagonist (LTRA), cromolyn, zileuton, and theophylline. Oral corticosteroids are reserved as a last resort for maintenance therapy for recalcitrant cases. Various studies have showed some degree of benefit when adding LAMA to ICS + LABA in moderate to severe asthma. There are several corticosteroid/LABA combination inhalers available (fluticasone/salmeterol [Advair], budesonide/formoterol [Symbicort], mometasone/formoterol [Dulera], and ICS/LABA fluticasone furoate 200 mcg and vilanterol 25 mcg inhalation powder [Breo Ellipta]) on the market. None of these combinations is indicated for the initial treatment of asthma or for acute therapy of asthma symptoms. There is no evidence that one product is more effective than the others. A large study investigating the safety of LABA and ICS combination inhalers confirmed their

TABLE 3 Assessing Asthma Control and Adjusting Therapy in Youths ≥12 Yr and Adults

Components of Control		CLASSIFICATION OF ASTHMA CONTROL (≥12 YR)		
		Well Controlled	**Not Well Controlled**	**Very Poorly Controlled**
Impairment	Symptoms	≤2 days/wk	>2 days/wk	Throughout the day
	Nighttime awakenings	≤2×/mo	1-3x/wk	≥4/wk
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/wk	>2 days/wk	Several times per day
	FEV_1 or peak flow	>80% predicted/personal best	60%-80% predicted/personal best	<60% predicted/personal best
	Validated questionnaires			
	ATAQ	0	1-2	3-4
	ACQ	≤0.75*	≥1.5	N/A
	ACT™	≥20	16-19	≤15
Risk	Exacerbations requiring oral systemic corticosteroids	0-1 per yr	≥2 per yr	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term follow-up care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment		Maintain current step. Regular follow-up every 1-6 mo to maintain control. Consider step down if well controlled for at least 3 mo.	Step up 1 step and reevaluate in 2-6 wk. For side effects, consider alternative treatment options.	Consider short course of oral systemic corticosteroids. Step up 1-2 steps. Reevaluate in 2 wk. For side effects, consider alternative treatment options.

The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's recall of previous 2 to 4 wk and by spirometry or peak flow measures.
Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.
At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.
Validated questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain):

- ATAQ = Asthma Therapy Assessment Questionnaire
- ACQ = Asthma Control Questionnaire (user package may be obtained at www.qoltech.co.uk or juniper@qoltech.co.uk)
- ACT = Asthma Control Test™
- Minimal Important Difference: 1.0 for the ATAQ; 0.5 for the ACQ; not determined for the ACT

Before step up in therapy:

- Review adherence to medication, inhaler technique, environmental control, and comorbid conditions
- If an alternative treatment option was used in a step, discontinue and use the preferred treatment for that step

EIB, Exercise-induced bronchospasm; *FEV_1,* forced expiratory volume in 1 second; *ICU,* intensive care unit.
The Asthma Control Test is a trademark of QualityMetric Incorporated.
*ACQ values of 0.76-1.4 are indeterminate regarding well-controlled asthma.
From National Asthma Education and Prevention Program: *Expert panel report 3: guidelines for diagnosis and management of asthma,* National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

long-term safety and demonstrated a reduced risk of exacerbations and improved lung function, when compared with an equivalent dose of ICS alone.

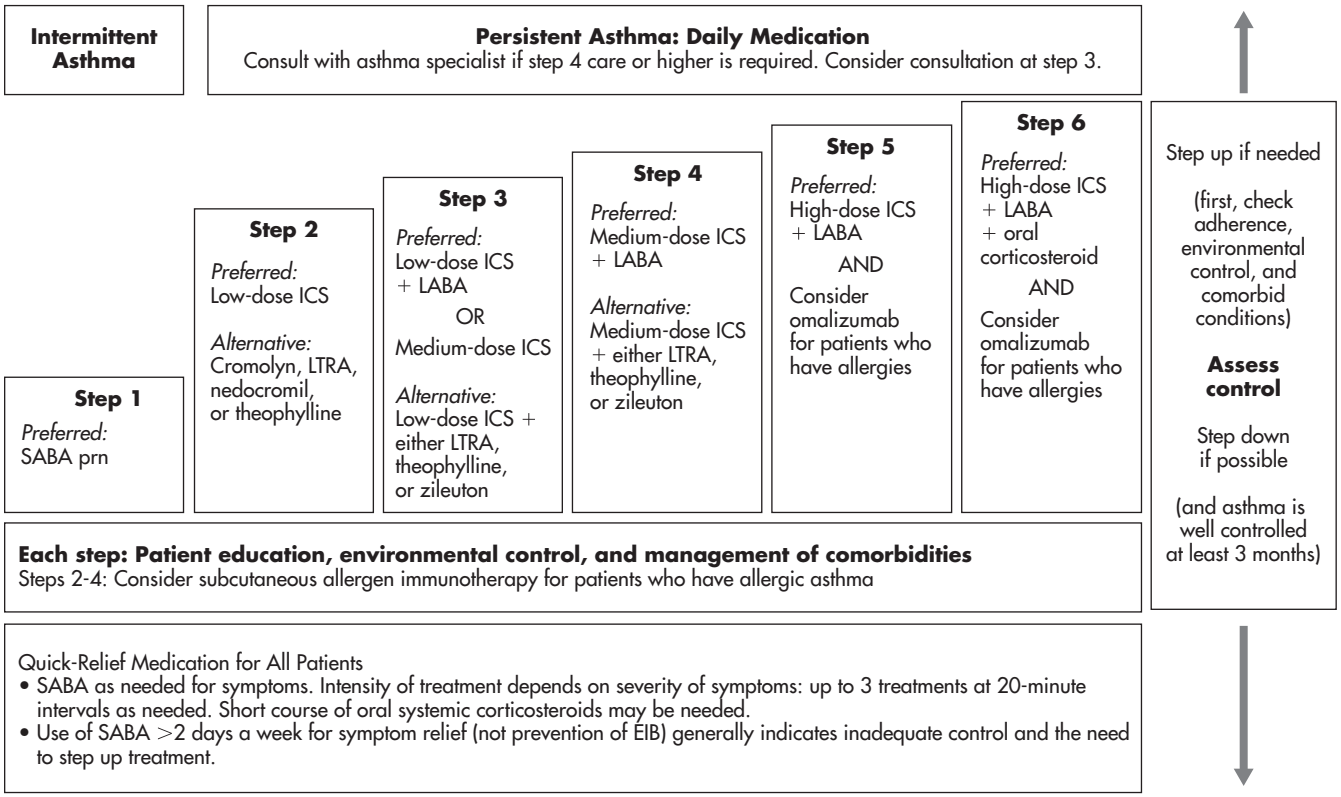
IMMUNOLOGIC TARGETS

- Dupilumab is a human monoclonal antibody to IL-4 and IL-13 FDA approved in patients 12 yr or older with moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid–dependent asthma.
- Mepolizumab (Nucala), an anti-interleukin-5 treatment, is approved by the FDA as an add-on for patients aged ≥12 yr with severe eosinophilic asthma that is uncontrolled on Step 4 treatment. Mepolizumab is a monoclonal antibody to IL-5 that has been shown to reduce exacerbations in patients with severe asthma who have blood eosinophil counts of 150/μL or greater. Mepolizumab is administered subcutaneously into the upper arm, thigh, or abdomen, 100 mg every 4 weeks. Hypersensitivity reactions have been reported with mepolizumab. In addition, herpes zoster infections have led to the recommendation of the administration of the varicella zoster vaccine to adults ages 50 or older 4 weeks prior to initiation of mepolizumab (unless they are at risk for disseminated zoster).
- Reslizumab, another anti-IL-5 monoclonal antibody, has a similar indication for eosinophilic asthma and uses a higher eosinophil cutoff (400) based on a greater predictive value for sputum eosinophilia. Benralizumab, a monoclonal anti-IL5 receptor alpha antibody, is an additional FDA-approved add-on treatment to consider for patients 12 yr or older with persistent severe eosinophilic asthma. It is administered as a subcutaneous injection every 4 wk for the first 3 doses then every 8 wk after that. Hypersensitivity reactions are more common than other anti-IL-5 antibodies and occur in about 3% of patients. Other adverse events include headache and pharyngitis.
- Omalizumab, an anti-IgE monoclonal antibody, is indicated for the treatment of moderate and severe persistent asthma with elevated IgE level, which is refractory to other treatment noted earlier. It is administered subcutaneously every 2 or 4 wk.

BRONCHIAL THERMOPLASTY

Selected patients with severe persistent asthma who have failed medical treatment may benefit from bronchial thermoplasty. This requires the insertion of a catheter via bronchoscopy and use of radiofrequency heat to reduce bronchial smooth muscle. Long-term follow-up data showed persistent reduction in asthma exacerbation and fewer ED visits over a period of 5 yr. FDA labeling is for "severe persistent asthma inadequately controlled on ICS + LABA."

TABLE 4 Stepwise Approach for Managing Asthma in Youths ≥12 Yr and Adults



The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.

If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.

Zileuton is a less desirable alternative due to limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels. In step 6, before oral systemic corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.

Steps 1, 2, and 3 preferred therapies are based on Evidence A; step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on (EPR-2 1997) and Evidence B for omalizumab.

Immunotherapy for steps 2 to 4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.

Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

This information is directly abstracted from the 2007 NAEPP *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* and is not intended to promote or endorse any of the listed products.

To access the complete *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma,* go to www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.

EIB, Exercise-induced bronchospasm; *ICS,* inhaled corticosteroid; *LABA,* inhaled long-acting beta$_2$-agonist; *LTRA,* leukotriene receptor antagonist; *prn,* as necessary; *SABA,* inhaled short-acting beta$_2$-agonist.

From National Asthma Education and Prevention Program: *Expert panel report 3: guidelines for diagnosis and management of asthma,* National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

TABLE 5 Classifying Asthma Severity and Initiating Treatment in Children 5-11 Yr (Assessing severity and initiating treatment in children who are not currently taking long-term control medications)

Components of Severity		CLASSIFICATION OF ASTHMA SEVERITY (5-11 YR OF AGE)			
			PERSISTENT		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
	Nighttime awakenings	≤23/mo	3-4×/mo	>1×/wk but not nightly	Often 7×/wk
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/wk	>2 days/wk but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	Normal FEV_1 between exacerbations			
		FEV_1 >80% predicted	FEV_1 = >80% predicted	FEV_1 60%-80% predicted	FEV_1 <60% predicted
		FEV_1/FVC >85%	FEV_1/FVC >80%	FEV_1/FVC 75%-80%	FEV_1/FVC <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1 per yr	≥2 per yr		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.			
		Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Therapy		Step 1	Step 2	Step 3, medium-dose ICS option	Step 3, medium-dose ICS option, or Step 4
				and consider short course of oral systemic corticosteroids	
		In 2-6 wk, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.

Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2 to 4 wk and spirometry. Assign severity to the most severe category in which any feature occurs.

At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

EIB, Exercise-induced bronchospasm; *FEV_1,* forced expiratory volume in 1 second; *FVC,* forced vital capacity; *ICS,* inhaled corticosteroid; *ICU,* intensive care unit.

From National Asthma Education and Prevention Program: *Expert panel report 3: guidelines for diagnosis and management of asthma,* National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

TABLE 6 Assessing Asthma Control and Adjusting Therapy in Children 5-11 Yr

Components of Control		CLASSIFICATION OF ASTHMA CONTROL (5-11 YR OF AGE)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/wk but not more than once on each day	>2 days/wk or multiple times on ≤2 days/wk	Throughout the day
	Nighttime awakenings	≤1×/mo	≥2×/mo	≥2×/wk
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/wk	>2 days/wk	Several times per day
	Lung function			
	FEV_1 or peak flow	>80% predicted/personal best	60%-80% predicted/personal best	<60% predicted/personal best
	FEV_1/FVC	>80% predicted	75%-80%	<75% predicted
Risk	Exacerbations requiring oral systemic corticosteroids	0-1 per yr	≥2 per yr	
		Consider severity and interval since last exacerbation		
	Reduction in lung growth	Evaluation requires long-term follow-up care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment		Maintain current step. Regular follow-up every 1-6 mo. Consider step down if well controlled for at least 3 mo.	Step up 1 step and reevaluate in 2-6 wk. For side effects, consider alternative treatment options.	Consider short course of oral systemic corticosteroids. Step up 1-2 steps. Reevaluate in 2 wk. For side effects, consider alternative treatment options.

The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.

The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's/caregiver's recall of previous 2 to 4 wk and by spirometry or peak flow measures. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.

At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

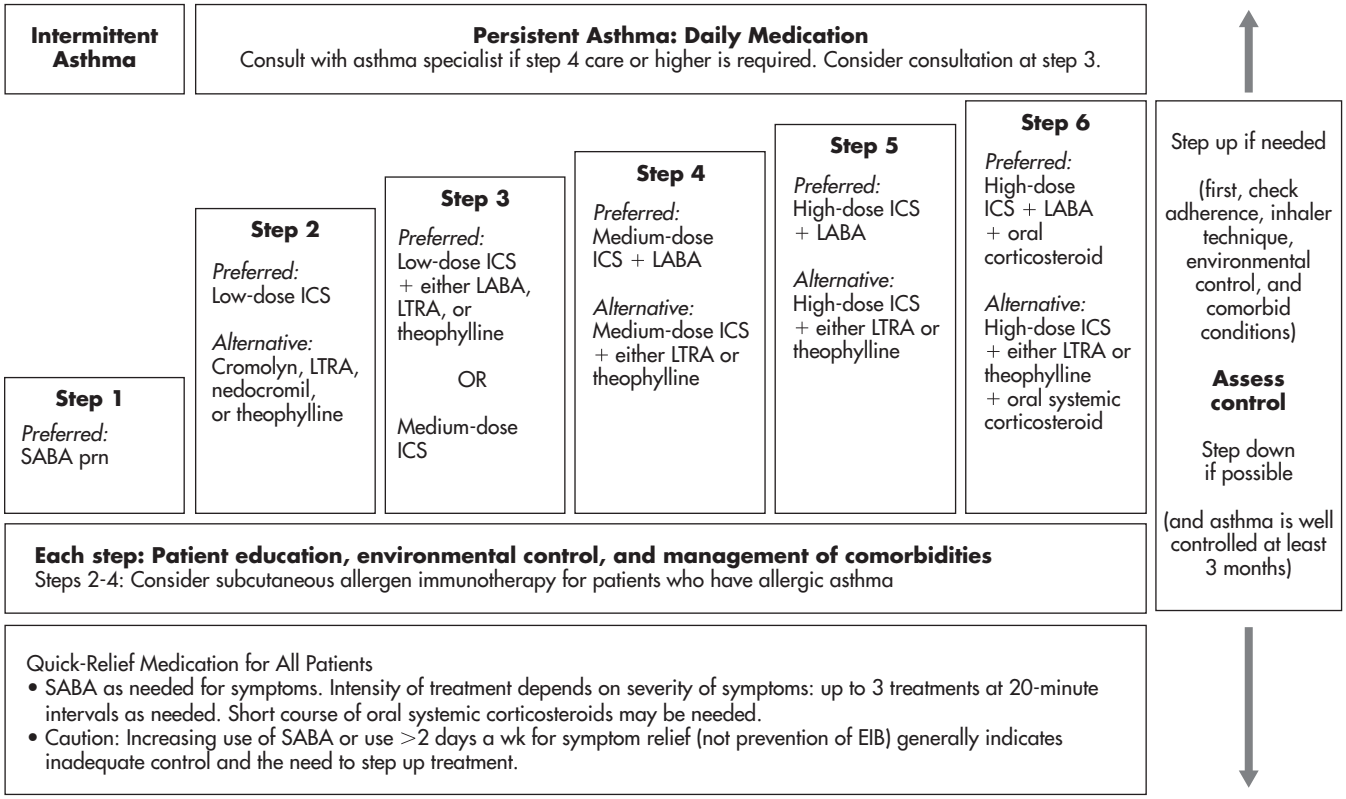
Before step up in therapy:

- Review adherence to medications, inhaler technique, environmental control, and comorbid conditions.
- If an alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

EIB, Exercise-induced bronchospasm; *FEV_1,* forced expiratory volume in 1 second; *FVC,* forced vital capacity; *ICU,* intensive care unit.

From National Asthma Education and Prevention Program: *Expert panel report 3: guidelines for diagnosis and management of asthma,* National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

TABLE 7 Stepwise Approach for Managing Asthma in Children 5-11 Yr



The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
Step 1 and step 2 medications are based on Evidence A. Step 3 ICS 1 adjunctive therapy and ICS are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; steps 4-6 are based on expert opinion and extrapolation from studies in older children and adults. Immunotherapy for steps 2 to 4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.
This information is directly abstracted from the 2007 NAEPP *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* and is not intended to promote or endorse any of the listed products.
EIB, Exercise-induced bronchoconstriction; *ICS,* inhaled corticosteroid; *LABA,* inhaled long-acting beta$_2$-agonist; *LTRA,* leukotriene receptor antagonist; *prn,* as necessary; *SABA,* inhaled short-acting beta$_2$-agonist.
From National Asthma Education and Prevention Program: *Expert panel report 3: guidelines for diagnosis and management of asthma,* National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

OTHER MEDICATIONS

Tiotropium (Spiriva) has been used for decades as first-line treatment for COPD. This LAMA is now approved for a second indication for the treatment of asthma and is included in the most recent (2018) Global Initiative for Asthma (GINA) guidelines as a possible add-on at step 4. A systematic review including over 7000 patients demonstrated the use of LAMA compared with placebo as an add-on to inhaled corticosteroids was associated with lower risk of exacerbation. Adding LAMA to a dual LABA-ICS regimen was not shown to reduce exacerbation rates but can improve lung function.

Azithromycin: The AZISAST Trial randomized 109 patients on high-dose ICS/LABA (step 4 or 5 per GINA guidelines) to maintenance therapy with azithromycin or placebo. Overall, there was no benefit seen with azithromycin therapy with regard to any of the outcomes tested. However, subgroup analysis showed that patients with noneosinophilic asthma had fewer exacerbations. More data are needed, but this result suggests azithromycin may be an effective option for the neutrophilic/Th-1 phenotype (COPD is also neutrophilic).

Immunosuppressants such as methotrexate can decrease long-term steroid requirements; however, they have significant side effects, and there is no evidence of persistent therapeutic effect after discontinuing them.

TREATMENT OF SEVERE ASTHMA (ETS/ETA GUIDELINES)

- The American Thoracic Society (ATS) classification of "severe asthma" refers to patients who require high-dose inhaled or near-continuous oral glucocorticoid treatment to maintain asthma control.
- In patients who do not achieve adequate control with the combination of a high-dose inhaled glucocorticoid and LABA, an additional controller medication such as an antileukotriene agent is recommended (tiotropium or theophylline).
- For patients with atopic severe asthma who have a serum IgE level of 30 to 700 IU/ml and documented sensitivity to a perennial allergen, recommend adding omalizumab.
- For patients with severe asthma, frequent exacerbations, and an eosinophilic phenotype despite guideline-based therapy, consider add-on therapy with one of the anti-interleukin (IL)-5 antibodies, mepolizumab, reslizumab, or benralizumab.
- Bronchial thermoplasty is approved for use in selected adults with severe asthma that is not well controlled with inhaled glucocorticoids and LABAs.
- Potential alternative and experimental therapies include immunomodulatory therapy and macrolide antibiotics.[a]

[a]Recent trials (AMAZES) in patients who have symptomatic asthma despite inhaled maintenance therapy have shown that azithromycin 500 mg 3 times/week reduced exacerbations and improved quality of life.

TABLE 8 Classifying Asthma Severity and Initiating Treatment in Children 0-4 Yr (Assessing severity and initiating treatment in children who are not currently taking long-term control medications)

Components of Severity		CLASSIFICATION OF ASTHMA SEVERITY (0-4 YR OF AGE)			
			PERSISTENT		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1-2×/mo	3-4×/mo	>1×/wk
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/wk	>2 days/wk but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic corticosteroids	0-1 per yr	≥2 exacerbations in 6 mo requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 yr lasting >1 day AND risk factors for persistent asthma.		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time.			
		Exacerbations of any severity may occur in patients in any severity category.			
Recommended Step for Initiating Therapy		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	
		In 2-6 wk, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4-6 wk, consider adjusting therapy or alternative diagnoses.			

The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.

Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.

At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past six months, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

To access the complete *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*, go to www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.

EIB, Exercise-induced bronchospasm.

From National Asthma Education and Prevention Program: *Expert panel report 3: guidelines for diagnosis and management of asthma,* National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

TABLE 9 Assessing Asthma Control and Adjusting Therapy in Children 0-4 Yr of Age

Components of Control		CLASSIFICATION OF ASTHMA CONTROL (0-4 YR OF AGE)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/wk	>2 days/wk	Throughout the day
	Nighttime awakenings	≤13/mo	>1×/mo	>1×/wk
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/wk	>2 days/wk	Several times per day
Risk	Exacerbations requiring oral systemic corticosteroids	0-1 per yr	2-3 per yr	>3 per yr
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment		Maintain current step. Regular follow-up every 1-6 mo. Consider step down if well controlled for at least 3 mo.	Step up 1 step. Reevaluate in 2-6 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative treatment options.	Consider short course of oral systemic corticosteroids. Step up 1-2 steps. Reevaluate in 2 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative treatment options.

The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.

The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2 to 4 wk. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.

At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

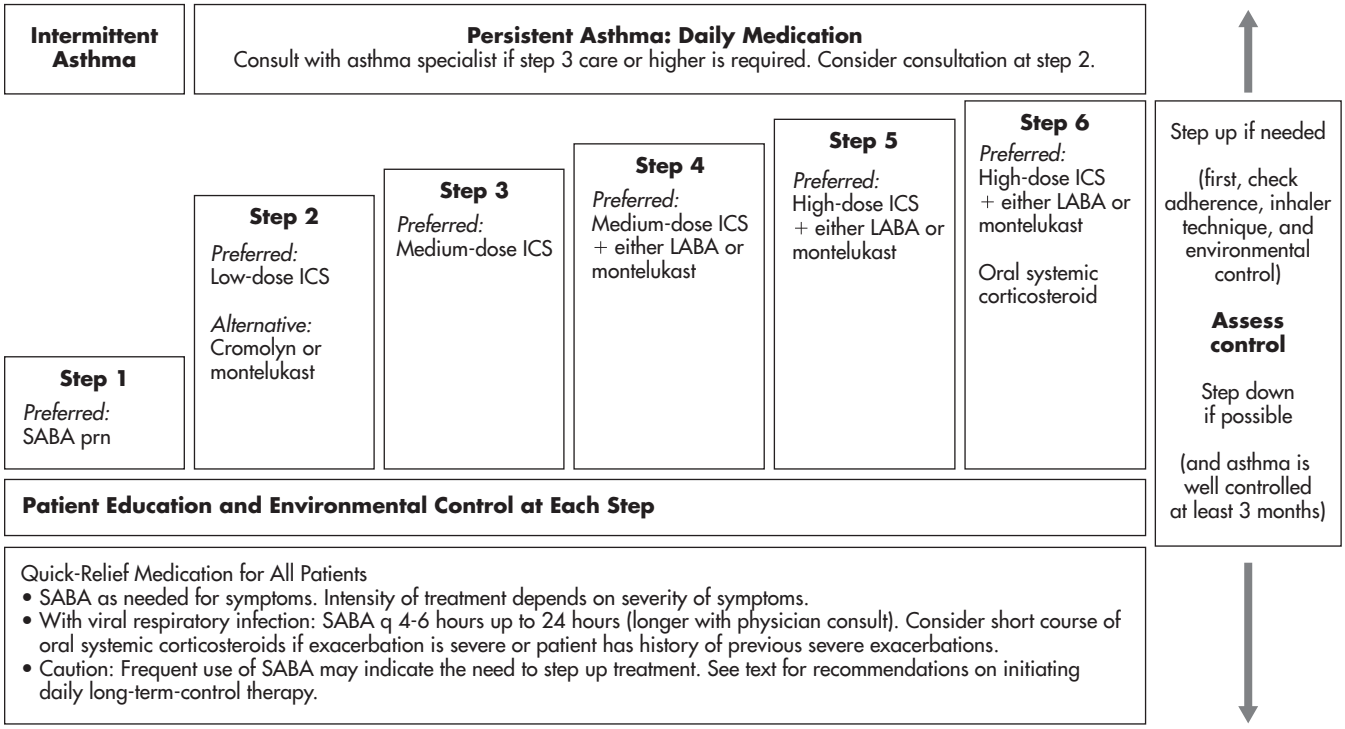
Before step up in therapy:

- Review adherence to medications, inhaler technique, and environmental control.
- If an alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

EIB, Exercise-induced bronchospasm; *ICU,* intensive care unit.

From National Asthma Education and Prevention Program: *Expert panel report 3: guidelines for diagnosis and management of asthma,* National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

TABLE 10 Stepwise Approach for Managing Asthma in Children 0-4 Yr



The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs. If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
If clear benefit is not observed within 4 to 6 wk and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
Studies on children 0 to 4 yr are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in other children.
This information is directly abstracted from the 2007 NAEPP *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* and is not intended to promote or endorse any of the listed products.
ICS, Inhaled corticosteroid; *LABA,* inhaled long-acting beta$_2$-agonist; *prn,* as necessary; *SABA,* inhaled short-acting beta$_2$-agonist.
From National Asthma Education and Prevention Program: *Expert panel report 3: guidelines for diagnosis and management of asthma,* National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

- In the future, treatments tailored to asthma phenotypes may improve asthma outcomes.

Treatment of status asthmaticus is as follows:

- Oxygen generally started at 2 to 4 L/min by nasal cannula or Venti-Mask at 40% Fio_2; further adjustments are made according to oxygen saturations.
- Bronchodilators: Initiate treatment with high-dose SABA plus ipratropium bromide administered by means of a nebulizer every 20 min. Use of a metered-dose inhaler with valved holding chamber may be acceptable for patients with mild-to-moderate exacerbations.
- Albuterol nebulizer solution (0.63 mg/3 ml, 1.25 mg/3 ml, 2.5 mg/3 ml, or 5.0 mg/ml): 2.5 to 5 mg every 20 min over the first hr, then 2.5 to 10 mg every 1 to 4 hr as needed or 10 to 15 mg/hr continuously. Other useful medications are levalbuterol nebulizer solution (0.31 mg/3 ml, 0.63 mg/3 ml, 1.25 mg/3 ml) and ipratropium nebulizer solution (0.25/ml [0.025%]).
- Corticosteroids:
  1. Early administration is advised, particularly in patients using steroids at home.
  2. Patients may be started on systemic corticosteroids; methylprednisolone, prednisone, or prednisolone may be used. Dose range is from 40-80 mg/day in one or two divided doses, generally given until peak expiratory flow reaches 70% of predicted value.
  3. Generally for corticosteroid courses <1 wk there is no need to taper the dose.
- IV hydration: Judicious use is necessary to avoid congestive heart failure in elderly patients. Aggressive IV hydration is not recommended.
- IV antibiotics are indicated when there is suspicion of bacterial infection (e.g., infiltrate on chest radiograph, fever, or leukocytosis).
- Intubation and mechanical ventilation are indicated when previous measures fail to produce significant improvement. Table 11 summarizes treatment of life-threatening asthma.
- Discharge home from the emergency department is appropriate if the FEV_1 or PEF after treatment is 70% or greater of the personal best or predicted value and if there is sustained improvement in lung function and symptoms for at least 1 hr.

REFERRAL

Box 4 describes indications for referral to an asthma specialist.

PEARLS & CONSIDERATIONS

COMMENTS

- The differentiation of asthma from COPD can be challenging. A history of atopy and intermittent, reactive symptoms points toward a diagnosis of asthma, whereas smoking and advanced age are more indicative of COPD. Spirometry is useful in distinguishing asthma from COPD.
- In all asthma patients it is important to treat or prevent comorbid conditions (e.g., rhinosinusitis, vocal cord dysfunction, gastroesophageal reflux disease). However, despite the presumed association between asthma and GERD, trials of PPIs in patients with poorly controlled asthma did not reveal any beneficial effects.
- Inhaled low-dose corticosteroids are the single most effective therapy for adult patients with asthma who require more than an occasional use of SABAs to control their asthma.
- Stepping down inhaled corticosteroids after asthma is well controlled now has level A evidence.
- Leukotriene modifiers/receptor agonists represent a reasonable alternative in adults

TABLE 11 Summary of Treatment for Life-Threatening Asthma

Treatment	Dose and Frequency	Comments
Oxygen	1-3 L/min by nasal cannula Goal is to maintain oxygen saturation (Spo_2) >92% Use heated cascade humidifier to avoid dry air–induced bronchoconstriction	Transient drop in O_2 tension with beta-adrenergic therapy Avoid hyperoxia (may be associated with hypercarbia)
Bronchodilators		
$Beta_2$-selective agonists: Albuterol or salbutamol, levalbuterol	*Albuterol*: 2.5-5 mg (0.5-1 ml of 0.5% solution in 5 ml of normal saline) by nebulizer every 20 min for 3 doses total (for optimal delivery, dilute aerosols to a minimum of 3 ml at gas flow of 6-8 L/min), followed by 2.5-10 mg q1-4h as needed, or 10-15 mg/h continuously; titration based on response and severity of symptoms *Albuterol MDI*, delivered with a spacer (each spacer dose takes 1-2 min; 90 μg/puff), 4-8 puffs every 20 min for 4 h, then q4h as needed *Albuterol*: 5-7.5 mg by jet nebulizer (each treatment takes 15-20 min) *Levalbuterol* (0.63 mg/3 ml and 1.25 mg/3 ml nebulizer): 1.25-2.5 mg every 20 min for 3 doses total, then 1.25-5 mg q1-4h as needed, or 5-7.5 mg/h continuous nebulization *Levalbuterol MDI* (45 μg/puff): 4-8 puffs every 20 min for 4 h, followed by q1-4h as needed	$Beta_2$-selective agonists are the cornerstone of therapy Continuous nebulization used for a majority of severely ill patients In study of continuous vs. intermittent therapy in severe exacerbations (excluding life-threatening asthma), no difference noted in pulmonary function improvement or need for hospitalization Lower frequency of side effects with continuous treatment Watch for hypokalemia, tremors, tachycardia, and lactic acidosis Oral or parenteral route: Loss of $beta_2$-selectivity MDI: 4 puffs of albuterol (0.36 mg) = 2.5 mg of albuterol nebulization Levalbuterol 0.63 mg = racemic albuterol 1.25 mg for efficacy and side effects *Intubated patients*: Nebulizers are less efficient in delivering doses to lower airways (6-10%) than MDIs (11%)
Epinephrine	*Subcutaneous epinephrine* dose for adults: 0.3-0.5 ml of a 1:1000 dilution (1 mg/ml), depending on age and weight; repeat every 20 min for 3 doses total	
Terbutaline	*Subcutaneous terbutaline*, 0.25 mg; repeat every 20 min for 3 doses total	Terbutaline is the parenteral agent of choice in pregnancy For refractory life-threatening asthma: Intravenous epinephrine (high risk for cardiac events, infarction, and arrhythmias) or racemic epinephrine may be considered
Anticholinergics		
Ipratropium (for acute severe asthma warranting visit to emergency department)	*Ipratropium bromide*: 0.5 mg by nebulizer (0.25 mg/ml) every 20 min for 3 doses, then q2-4h as needed *Ipratropium MDI* (0.018 mg/puff): 4-8 puffs per treatment every 20 min for up to 3 h *Combinations*: Albuterol (2.5 mg/3 ml) + ipratropium (0.5 mg/3 ml): 3 ml every 20 min for 3 doses total, then as needed MDI delivering albuterol 90 μg + ipratropium 18 μg: 8 puffs every 20 min for up to 3 h	Ipratropium: Onset of action is slow (20 min), peak effectiveness at 60-90 min, no systemic side effects, improved lung function and reduced recovery time Use a handheld mouthpiece nebulizer (contamination of the ocular area with precipitation of narrow-angle glaucoma may occur if facemask is used for delivery of anticholinergic agent) Ipratropium may be combined with nebulized albuterol dose in the emergency room; no proven benefit shown in hospitalized patients
Corticosteroids: Prednisone, prednisolone, methylprednisolone	40-80 mg/day in 1 or 2 divided doses until peak expiratory flow reaches 70% of predicted or personal best FEV_1 or PEFR <50% Methylprednisolone 40 mg IV q6h OR Hydrocortisone 200 mg IV	No advantage of higher doses No advantage of IV therapy over oral if absorption and gut transit are not impaired Total steroid course: 3-10 days, <1 wk; no need to taper steroids Inhaled steroids can be started at any time
Heliox	Helium-oxygen mixture (80-20 or 70-30) Routine use cannot be recommended at this time	Improves O_2 and aerosolized medication delivery to distal lung Decreases flow turbulence and resistance Lower gas density facilitates exhalation, reduces air trapping and intrinsic PEEP Improves pulmonary function in subgroup of patients with most severe airflow obstruction
Magnesium sulfate	2 g IV given over 20 min; may repeat Monitor magnesium levels Avoid in renal insufficiency	Bronchodilatation from inhibition of the calcium channel and decreased acetylcholine release IV and inhaled or nebulized magnesium sulfate improves pulmonary function in acute severe asthma IV magnesium widely used as adjunct therapy

FEV_1, Forced expiratory flow in 1 second; *IV*, intravenous; *MDI*, metered-dose inhaler; *PEEP*, positive end-expiratory pressure; *PEFR*, peak expiratory flow rate.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Elsevier.

unable or unwilling to use corticosteroids; however, these agents are less effective than monotherapy with inhaled corticosteroids.
- Use of LABAs alone without use of a long-term asthma medication, such as an inhaled corticosteroid, is contraindicated. LABAs should also not be used in patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids. Continued use of LABAs may cause down-regulation of the beta-2 receptor with loss of the bronchoprotective effect from rescue therapy with a SABA.
- Patients who remain symptomatic despite inhaled corticosteroids benefit from the addition of LABAs. Trials in patients with poorly controlled asthma despite the use of inhaled glucocorticoids and LABAs have shown that the addition of tiotropium, a long-acting anticholinergic bronchodilator approved for treatment of COPD, increased the time to the first severe exacerbation and provided modest sustained bronchodilation.
- Therapy with systemic corticosteroids accelerates the resolution of acute asthma and reduces the risk of relapse. There is no evidence that doses >50-100 mg prednisone equivalent are beneficial.
- In patients with allergies and elevated serum immunoglobulin (Ig) E levels, use of anti-IgE therapy is beneficial.
- Bronchial thermoplasty should be considered in selective patients with severe persistent asthma with recurrent exacerbations or ED visits. Biologic modifiers of the Th2 immune pathways (neutralizing monoclonal antibodies, receptor antagonists, soluble receptors) are potential options for the development of new treatments of severe asthma. Adjunct therapies for bronchospasm are summarized in Table 12.
- The response to treatment for asthma is characterized by wide individual variability. A functional glucocorticoid-induced transcript 1 gene *(GLCCI1)* variant is associated with substantial decrements in the response to inhaled glucocorticoids in patients with asthma. Another potential cause of the variability in response to treatment is heterogeneity in the role of interleukin-13 expression in the clinical asthma phenotype. Patients with asthma who have a certain biochemical signature are more likely to respond to an anti–interleukin-13 monoclonal antibody than those without such a signature. Identification of genetic variants can eventually lead to personalized asthma treatment. Failure of pharmacologic treatment is often due to uncontrolled comorbid conditions (tobacco, allergic rhinitis, pollutants), poor inhaler technique, or lack of adherence to prescribed medication.

BOX 4 Possible Indications for Referral to an Asthma Specialist

- Severe, acute asthma that has caused loss of consciousness, hypoxia, respiratory failure, convulsions, or near death
- Poorly controlled asthma as indicated by admission to a hospital, frequent need for emergency care, need for oral corticosteroids, absence from school or work, disruption of sleep, interference with quality of life
- Severe, persistent asthma requiring step 4 care (consider for patients who require step 3 care)
- Patient <3 yr who requires step 3 or 4 care (consider for patient <3 yr who requires step 2 care)
- Requirement for continuous oral corticosteroids or high-dose inhaled corticosteroids or more than two short courses of oral corticosteroids within 1 yr
- Need for additional diagnostic testing such as allergy skin testing, rhinoscopy, provocative challenge, complete pulmonary function testing, bronchoscopy
- Consideration for immunotherapy
- Need for additional education regarding asthma, complications of asthma and treatment of asthma, problems with adherence to management recommendations, or allergen avoidance
- Uncertainty of diagnosis
- Complications of asthma, including sinusitis, nasal polyposis, aspergillosis, severe rhinitis, vocal cord dysfunction, gastroesophageal reflux

Modified from National Asthma Education and Prevention Program, National Heart, Lung, and Blood Institute: *Expert Panel Report 2: guidelines for the diagnosis and management of asthma,* Bethesda, MD, 1997, National Institutes of Health, NIH publication No 97-4051.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Asthma (Patient Information)
Asthma-COPD Overlap Syndrome (Related Key Topic)

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TABLE 12 Adjunct Therapies for Bronchospasm

Nontraditional Therapy for Severe Bronchospasm	Comments
Intravenous beta$_2$-agonists	No data show any benefit in adding IV agent to nebulization Avoid IV isoproterenol owing to danger of myocardial toxicity
Oral or IV leukotriene receptor antagonists (LTRAs): Montelukast 10 mg oral daily, zafirlukast	Rapid bronchodilation in impending respiratory failure Improves pulmonary function within 10 min Oral LTRAs can be added as an adjunct in severe asthma
Noninvasive positive-pressure ventilation (NPPV)	NPPV reduces the need for endotracheal intubation in severe asthma exacerbation
Inhaled nitric oxide (NO) (adding 15 ppm to the inspiratory circuit)	Rapid improvement in ventilated patients with asthma refractory to medical treatment
Omalizumab (anti-IgE antibody)	Role in acute asthma is unstudied Improves asthma control in allergic asthmatics
General anesthetic agents: Isoflurane or halothane anesthesia IV thiopental, IV propofol, IV ketamine	Propofol relaxes the smooth muscles in arteries and veins and has bronchodilator effect
Plasma exchange (during pregnancy) Pumpless extracorporeal carbon dioxide removal Extracorporeal life support (ECLS)	Case reports of adjunct therapies; used as salvage therapy for life-threatening asthma
Glucagon	Rapid smooth muscle relaxant, short half-life; small study report
Nebulized DNase (dornase 2.5 mg via tracheal tube)	Case report of use in pregnant patient with rapid improvement
Bronchial lavage	Anecdotal reports: Exacerbates auto-PEEP, decreases oxygenation

IgE, Immunoglobulin E; *IV,* intravenous; *PEEP,* positive end-expiratory pressure.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Elsevier.

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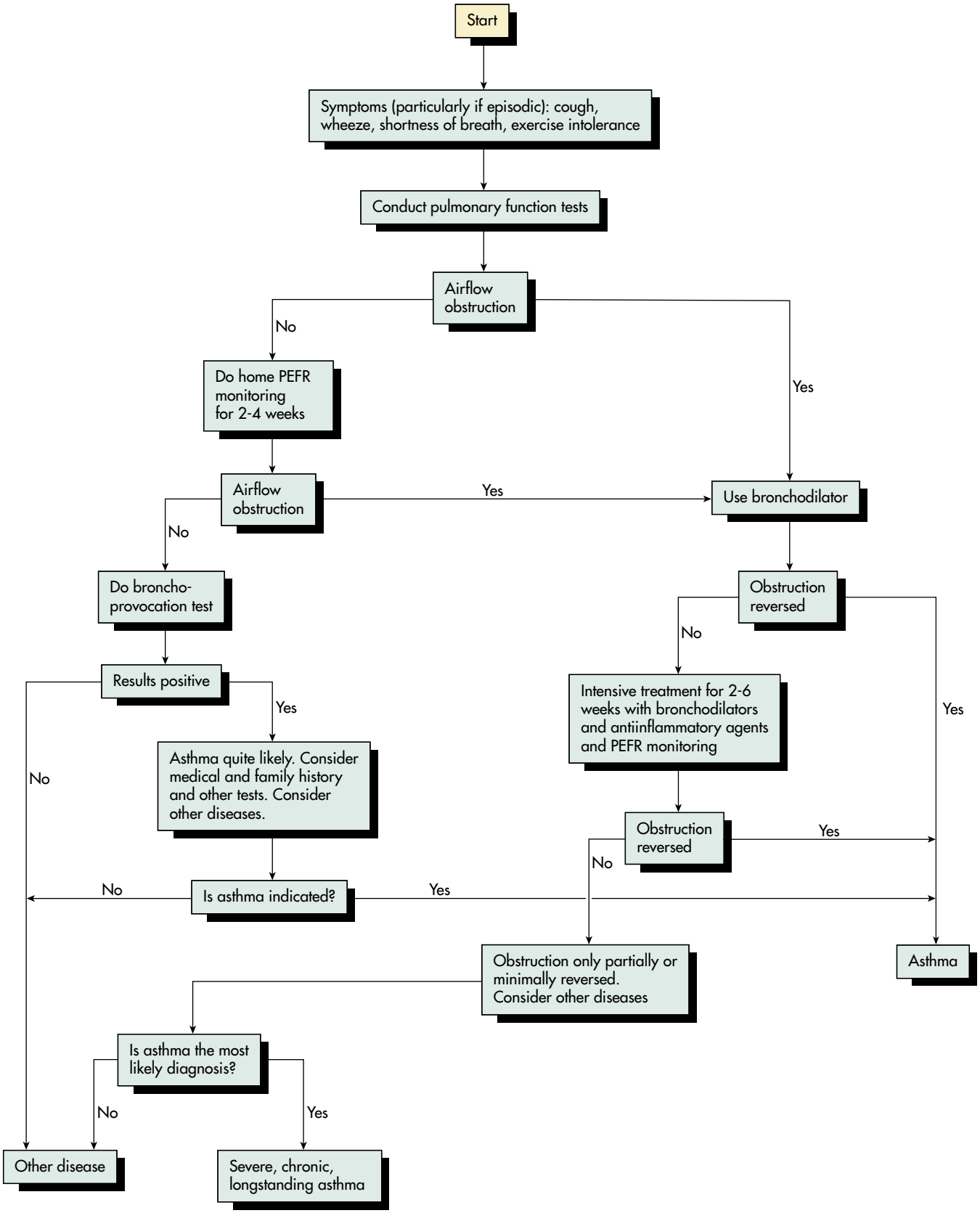

FIG. E2 Algorithm for diagnosing asthma. *PEFR,* Peak expiratory flow rate. (From Fireman P: *Atlas of allergies and immunology,* ed 3, St Louis, 2006, Mosby.)

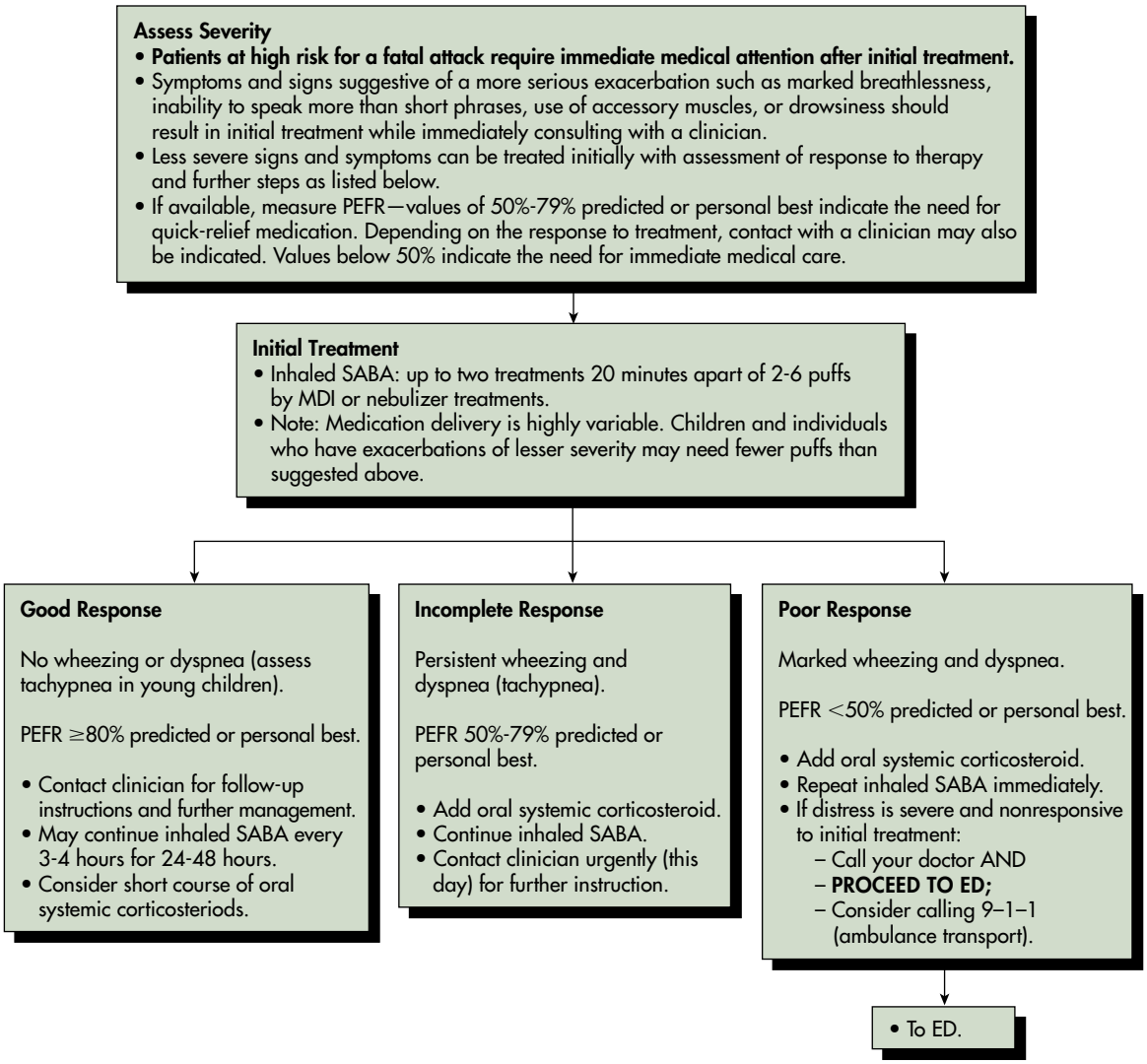

FIG. E3 Home management of acute asthma. *ED,* Emergency department; *MDI,* metered-dose inhaler; *PEFR,* peak expiratory flow rate; *SABA,* short-acting beta$_2$-agonist (quick-relief inhaler). (Modified from National Asthma Education and Prevention Program, National Heart, Lung, and Blood Institute, *Expert Panel Report 3: guidelines for the diagnosis and management of asthma,* 2007.)

Asthma-COPD Overlap Syndrome

BASIC INFORMATION

DEFINITION

The asthma and chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) is a recently recognized clinical entity of important significance. It identifies a subgroup of smokers with COPD that shares some pathogenic and inflammatory characteristics with asthma and that tends to have a more severe disease phenotype than just COPD alone. It has been defined as either:

- Asthma with partially reversible airflow obstruction with or without emphysema or reduced carbon monoxide diffusing capacity (DLco) to <80% predicted
- Chronic obstructive pulmonary disease (COPD) with emphysema accompanied by reversible or partially reversible airflow obstruction, with or without environmental allergies or reduced DLco

SYNONYMS

Bronchospasm
Reactive airway disease
Asthmatic bronchitis
Hyperreactive airways
Chronic obstructive pulmonary disease

ICD10-CM CODES

J45	Asthma
J42	Unspecified chronic bronchitis
J43	Emphysema
J44	COPD
J44.9	COPD, unspecified
M35.1	Other overlap syndromes

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- COPD afflicts 14.2 million adults (a prevalence of 1 in 5) in the U.S.
- Twenty-five million Americans (18 million adults and 7 million children) have asthma (prevalence of 1 in 12 adults).
- The prevalence of bronchial hyperresponsiveness among patients with COPD has been reported to be 60%.
- Reversibility of airway obstruction is frequently present in COPD as well; in two studies, reversibility was observed in up to 44% and 50% of patients with COPD.
- Among published studies, persons with ACOS have worse lung function, more respiratory symptoms, and a lower health-related quality of life than those with either disease alone. Those with ACOS are reported to experience more frequent health care utilization and more severe impairment than persons with COPD or asthma alone.
- In a recent study, 15-yr mortality for ACOS was similar to that for COPD and worse than that for asthma and healthy controls. ACOS had a significant impact on physical performance, functional ability, and health-related quality of life.
- The prevalence of ACOS is between 15% and 25% in an adult population of obstructive airway diseases. ACOS is also more prevalent in the elderly, African Americans, and among individuals with greater disease severity.
- Epidemiologic studies report an estimated prevalence of 20%.

PREDOMINANT SEX AND AGE:

- Sex: In a large, population-based sample, women were more likely than men to report ACOS.
- Age: The prevalence of overlap syndrome has been shown to increase with age (>60-70), which may reflect that with time asthmatics may develop fixed airway obstruction.
- Race: No published predilection for race/ethnicity noted.

GENETICS:

- No known genetic basis described. Genetic linkage studies and genome-wide association (GWA) studies have been of limited value in characterizing a link between asthma and COPD.
- Postma, et al. (2015) evaluated the paucity of GWA studies, assessing overlap syndrome and the focus on clearly defined outcomes that do not include overlap and that hamper the current insight that genetic studies provide. However, Hardin et al (2014) showed that the two most significant associations among non-Hispanic white overlap subjects include variants from the *CSMD1* gene, which has been associated with emphysema, and within the *SOX5* gene, which has previously been associated with COPD and may play a role in lung development.
- In a meta-analysis across the non-Hispanic white and African American groups, several variants in the *GPR65* gene were identified that were associated with the overlap syndrome.

RISK FACTORS:

- Smoking
- Atopy
- Genetics
- Childhood asthma
- Older age
- Allergies
- Infections (rhinovirus, influenza, mycoplasma)
- Higher body mass index (BMI)
- Patients with ACOS have the combined risk factors of smoking and atopy and are generally younger than patients with COPD

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Physical examination:

- May be normal
- Wheezing, rhonchi
- Hoover sign
- In severe cases, decreased airway entry, abdominal retractions, accessory muscle use, abdominal muscle use

Clinical presentation:

- Wheezing
- Shortness of breath
- Chest tightness
- History of repeated respiratory infections
- Chronic cough (typically productive)
- Episodic symptoms instigated by certain triggers (odors, temperatures, allergens)
- Decreased exercise tolerance

ETIOLOGY

- The pathophysiology of asthma involves a complex interaction among various environmental and genetic factors.
- Cigarette smoking interacts with the inflammation and remodeling that occur in asthma and COPD.
- No genetic basis identified thus far.

DIAGNOSIS

ACOS should be considered when "a similar number of features listed for asthma and COPD are present." This definition for ACOS is not yet very specific because it is recognized that a more detailed classification of patients with overlapping features of asthma and COPD is needed. Studies performed so far have generally based the diagnosis of ACOS on the pattern of symptoms, the presence of incompletely reversible airflow obstruction in ex- or current smokers or patients with asthma, the degree of bronchodilator reversibility, and bronchial hyperresponsiveness.

DIFFERENTIAL DIAGNOSIS

- COPD
- Asthma
- Central airway obstruction
- Bronchiectasis
- Heart failure
- Obliterative bronchiolitis

WORKUP

- Patients must have demonstrated either one of these to be diagnosed with "overlap syndrome":
  1. Reversible airflow: Increase in FEV1 or forced vital capacity (FVC) by ≥200 ml and 12% postbronchodilator challenge
  2. Airway hyperresponsiveness (AHR): A positive methacholine challenge test
- Asthma defined by the Global Initiative for Asthma (GINA) executive summary criteria, as a clinical syndrome with "variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment"
- COPD according to the American Thoracic Society/European Respiratory Society (ATS/ERS) joint task force: "a preventable and treatable disease state characterized by airflow limitation that is not fully reversible"

LABORATORY TESTS

- Arterial blood gas (ABG)
- Complete blood count (CBC)
- Spirometry
- Methacholine challenge
- Peak expiratory flow rate (PEFR)
- Serum immunoglobulin E
- Sputum
- Allergy testing

IMAGING STUDIES

- Chest x-ray
- Chest CT scan
- ECG

Rx TREATMENT

There is little information about the response of ACOS patients to most of the current pharmacologic therapies because they have been systematically excluded from both COPD and asthma pharmacologic trials. The main interest in differentiating ACOS from COPD lies in the different response to inhaled corticosteroids (ICS). Some studies demonstrate that patients with COPD and eosinophilic inflammation treated with ICS present a significant improvement clinically and objectively by spirometry.

NONPHARMACOLOGIC THERAPY

- Avoidance of environmental or occupational trigger factors
- Patient education regarding warning signs of an attack and proper use of medications (e.g., correct use of inhalers)
- Pulmonary rehabilitation

ACUTE GENERAL Rx

- At present, there are no randomized clinical trial data to help guide therapeutic interventions in overlap syndrome.
- Treatment typically is directed toward management of symptoms.
- For dynamic obstruction and/or hyperinflation, bronchodilators may provide the greatest benefit.
- Whether long-acting muscarinic antagonists (LAMAs) alone or in combination with long-acting beta-agonists (LABAs) are appropriate in overlap syndrome remains to be elucidated.
- For patients in whom bronchospasm is demonstrated, bronchodilators and ICSs are reasonable options.
- Clinical trials have shown efficacy for fluticasone furoate/vilanterol combination (the first once-daily ICS/LABA) versus twice-daily fluticasone propionate/salmeterol; it can provide substantial improvement in lung functions in a population of ACOS, indicating that this combination should be considered for the regular treatment of ACOS.
- The 2018 GINA guideline supports consideration of including an ICS in treatment regimens of patients with ACOS. A well-designed case-control trial demonstrated newly prescribed ICS+LABA combination therapy in patients with a history of COPD and asthma was associated with lower composite risk of hospitalization or death compared with LABA treatment alone.
- A more recent study showed some efficacy with the use of omalizumab as an effective and safe therapy for patients with ACOS. However, this study included only three patients; therefore, larger randomized trials are needed.

CHRONIC Rx

- Earlier screening of the overlap syndrome is important in current or former smokers in their fifth decade of life who have partially reversible airway obstruction and progressive exercise intolerance and who have variable or no response to guideline-recommended asthma treatments. Smoking cessation, oxygen supplementation, pulmonary rehabilitation, and vaccines are all reasonable interventions.
- As the prevalence of overlap syndrome increases with age, targeting nonrespiratory age-related changes that may influence respiratory disease is paramount. This includes targeting nasal obstruction symptoms (due to nonallergic or allergic rhinitis, mucosal dryness, or vasomotor symptoms) with nasal irrigation, nasal steroids, and/or nasal anticholinergics.
- Treating comorbidities such as chronic aspiration, gastroesophageal reflux disease (GERD), or vocal cord dysfunction (VCD) is important.
- Evaluation for cardiovascular disease is important given the higher risk of cardiovascular disease in patients with asthma-COPD overlap syndrome even without the presence of comorbidities.

COMPLEMENTARY & ALTERNATIVE MEDICINE

None

REFERRAL

Referral for expert advice and further diagnostic evaluation is necessary in the following contexts:

- Persistent symptoms and/or exacerbations
- Diagnostic uncertainty
- Patients with asthma/COPD with atypical/additional symptoms such as hemoptysis, weight loss, night sweats, fevers, signs of bronchiectasis
- Comorbidities that may interfere with assessment and management
- No response to treatment

PEARLS & CONSIDERATIONS

PREVENTION

- Smoking cessation
- Avoidance of triggers

RELATED TOPICS

Asthma (Related Key Topic)
Chronic Obstructive Pulmonary Disease (Related Key Topic)

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SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Astrocytoma is a type of neuroepithelial tumor that arises from astrocytes, which are glial precursor cells. The distinction of different grades of astrocytoma provides important clinical prognostic information (Table 1). According to the World Health Organization (WHO) classification astrocytoma is classified as below based on the histopathology:

- Grade I: Pilocytic astrocytoma
- Grade II: Diffuse astrocytoma
- Grade III: Anaplastic astrocytoma
- Grade IV: Glioblastoma
- Grades III and IV are considered high-grade astrocytomas (HGAs) or malignant

SYNONYM

Astroglial neoplasms

ICD-10CM CODE

C71.9 Malignant neoplasm of brain, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

According to Surveillance, Epidemiology, and End Results (SEER) registry, the incidence of primary CNS tumor is 6.4 cases per 100,000 persons per yr with age-adjusted death rate of 4.4 per 100,000. According to the Central Brain Tumor Registry of the United States (CBTRUS), astrocytomas constitute about 10% of the central nervous system neoplasms.

ETIOLOGY

- No agent has been definitely implicated in the causation of CNS tumors, and risk factors can be identified only in minority of patients. Farmers and petrochemical workers have been shown to have a higher incidence of primary brain tumors. Exposure to ionizing radiation is a known risk factor for a small percentage of astrocytomas.
- Different hereditary syndromes are associated with increased risk and high frequency of astrocytoma.
  1. Neurofibromatosis type 1 is associated with increased frequency of astrocytoma.
  2. Li-Fraumeni syndrome (germ line mutation in one of p53 allele) is associated with increased frequency of malignant gliomas.

GENE AND CHROMOSOMAL ALTERATIONS IN ASTROCYTOMA:

- Alteration in p53, a tumor suppressor encoded by the *TP53* gene on chromosome 17p, plays a key role in the development of at least one third of all grades of astrocytoma. In addition, in high-grade astrocytomas, p53 function may be deregulated by alteration of other genes, including amplification of MDM2 or MDM4 and 9p deletions that result in loss of the p14 product of the *CDKN2A* gene.
- Mutations of isocitrate dehydrogenase 1 gene (*IDH1*) occur in a large fraction of grade II and grade III astrocytomas as well as in other gliomas. IDH-mutated tumors have a better prognosis compared with those with IDH-wild type status.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The presenting symptoms of astrocytoma depend, in part, on the location of the lesion and its rate of growth. Astrocytomas classically present with any one or more of the following features:

- Headache (less frequent)
- New-onset partial or generalized seizures (>50%)
- Nausea and vomiting
- Focal neurologic deficit (cranial nerve palsy, hemiplegia, ataxia)
- Change in mental status
- Papilledema (rare)

DIAGNOSIS

A provisional diagnosis of astrocytoma is made on clinical grounds and radiographic imaging studies. Tissue pathology is needed to establish the diagnosis and to grade the astrocytoma.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is vast and includes any cause of headache, seizures, change in mental status, and focal neurologic deficits.

WORKUP

- The imaging modality of choice is contrast-enhanced MRI, which can demonstrate anatomy and pathological process in detail. CT scanning is reserved for patients who are unable or unwilling to get MRI. Biopsy with histological confirmation is required to establish a diagnosis of astrocytoma.
- Stereotactic biopsy under CT or MRI guidance has been reserved for tumors that are deeply seated, multicentric tumors or diffuse nonfocal tumors where surgical resection is not practical. Major objectives of surgical resection are to maximally remove the tumor bulk, reduce tumor-associated mass effect and elevated intracranial pressure and provide tissue for pathological analysis. The surgical resection is carried out in a manner that minimizes the risk to neurological functioning. Surgery can also rapidly reduce the tumor bulk with potential benefits in terms of mass effect, edema, and hydrocephalus.

LABORATORY TESTS

There are no diagnostic or supportive blood tests for astrocytoma.

IMAGING STUDIES

MRI (Fig. 1) is the diagnostic imaging study of choice. MRI with contrast and magnetic resonance angiography are used to locate the margins of the tumor, distinguish vascular masses from tumors, detect low-grade astrocytomas (LGAs) not seen by CT scan, and provide clear views of the posterior fossa.

TREATMENT

ACUTE GENERAL Rx

- Corticosteroids (usually dexamethasone) need to be started immediately preoperatively in all primary CNS tumors unless CNS lymphoma is being suspected. Corticosteroids reduce cerebral edema and thus minimize secondary brain injury from cerebral retraction. Corticosteroids needs to be continued in the immediate postoperative period and tapered as quickly as possible. If there is increased intracranial pressure and impending herniation, patient should be started

TABLE 1 Comparison of Astrocytoma Histopathology

	Pilocytic Astrocytoma	Diffuse Astrocytoma	Anaplastic Astrocytoma	Glioblastoma Multiforme
Malignant potential	Benign	Low grade	High grade	Very malignant
Age (approximate)	Children	Third or fourth decade	Fifth decade	Sixth decade
Location	Optic chiasm or hypothalamus > cerebellum > brainstem*	Hemispheres (cortex + white matter)	Hemispheres (cortex + white matter)	Hemispheres (cortex + white matter)
Enhancement	Mild	Mild	Moderate (ring)	Intense
Vasogenic edema	Minimal	Minimal	Moderate	Significant
Calcification	Common	Up to 20%	Occasional	Rare

*It is typically cystic with a mural nodule and located within the posterior fossa—it tends to be solid or lobulated when seen elsewhere.
From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.

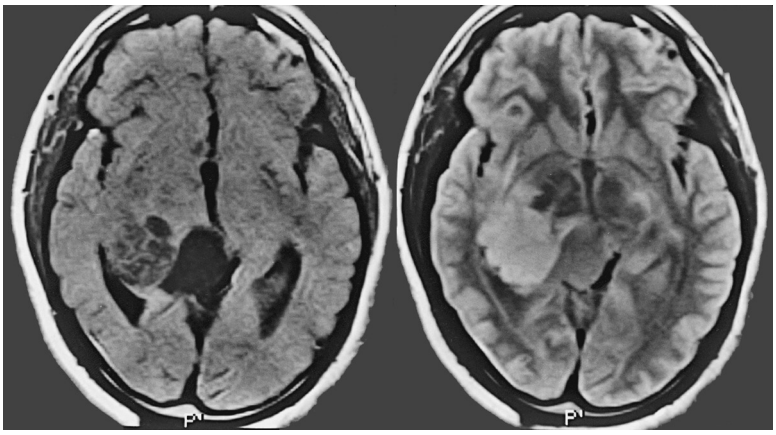

FIG. 1 Magnetic resonance image of a low-grade astrocytoma, demonstrating a hypointense right temporal lesion without contrast enhancement on T1 and hyperintense signal on T2. (From Goetz CG, Pappert EJ: *Textbook of clinical neurology,* Philadelphia, 1999, WB Saunders.)

on IV mannitol, and mechanical ventilation with hyperventilation should be considered if there is depressed consciousness.
- The use of preoperative prophylactic anticonvulsants is less commonly indicated. The practice pattern in the U.S. seems to indicate its widespread use.

STAGE-SPECIFIC Rx

- Grade I astrocytomas are usually indolent and circumscribed tumors. Complete surgical resection is the mainstay of therapy whenever feasible and is curative for these tumors. If complete surgical resection is not feasible due to location of tumor such as when the tumor is in optic pathway, hypothalamus, and in deep midline structures, asymptomatic patients can be observed in these cases until maximally safe resection is feasible upon progression. Unfortunately, despite aggressive near-total resection, delayed recurrence and eventual malignant transformation are common.
- In grade II astrocytoma, the extent of postoperative residual disease is an important variable for time to first relapse. Postoperative use of PCV chemotherapy (procarbazine, lomustine, and vincristine regimen) concurrent with radiotherapy improves progression-free survival and overall survival.
- In grade III anaplastic astrocytoma, surgical resection has shown to prolong survival and postoperative chemotherapy and radiotherapy is routinely used. Recent randomized clinical trials have established a survival benefit with the use of concurrent chemotherapy (temozolomide) for 6 to 12 mo.
- In grade IV glioblastoma, surgical resection improves median survival. Randomized trials have demonstrated survival benefit with use of concurrent chemotherapy with radiotherapy followed by further 6 mo of temozolomide chemotherapy alone. Unfortunately, even with chemotherapy and radiation therapy, the 2-yr survival in these patients is only 16%.

TREATMENT OF RECURRENT DISEASE

- For grade 1 astrocytoma, re-resection should be considered. For patients who have tumors that are not amenable to resection, chemotherapy or radiotherapy can improve recurrence-free survival, although role of chemotherapy in adults remain controversial.
- For grade 2 astrocytoma, radiation therapy can be considered in the relapsed setting if not given in the adjuvant setting. Data on use of chemotherapy in low-grade gliomas in adults is sparse. Although the results are encouraging, number of patients treated in these studies is small and there were a lot of methodological flaws in the studies. For recurrent grade III anaplastic astrocytoma treated with radiation therapy in the past, there is a role for chemotherapy. Nitrosoureas-based regimen and temozolomide (alkylating agent) have shown efficacy in this setting.
- Various targeted therapies are currently being studied in patients with recurrent glioblastoma. Irinotecan with bevacizumab or bevacizumab alone have been studied in a phase 2 trial, and a response rate of 38% and 28% respectively was reported in that study. Median survival was 8.7 mo and 9.2 mo, respectively. The PD-1 checkpoint inhibitors are currently being evaluated and have shown promising early results in relapsed patients.
- In the case of both recurrent and newly diagnosed glioblastoma, the use of tumor-treatment fields (TTF) devices in conjunction with the use of temozolomide chemotherapy has demonstrated a survival benefit and is approved by the FDA.

PROGNOSIS

- Grade 1 astrocytoma has a good prognosis and is usually cured with surgical resection.
- Grade 2 astrocytoma has a median survival of about 7.5 yr with treatment.
- Grade 3 anaplastic astrocytoma has a median survival of approximately 5 yr. The patients with 1p and 19q co-deletion have superior survival compared with patients without deletion.
- Median survival of glioblastoma is approximately 14 mo.

REFERRAL

A multidisciplinary consultation with a neurosurgeon, radiation oncologist, and neurooncologist is required to assist in the diagnostic workup and to provide immediate and follow-up treatment.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Astrocytoma (Patient Information)
Brain Cancer (Patient Information)
Brain Neoplasm, Benign (Related Key Topic)
Brain Neoplasm, Glioblastoma (Related Key Topic)

AUTHOR: **Bharti Rathore, MD**

SUGGESTED READINGS

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Ataxia

BASIC INFORMATION

DEFINITION

Although ataxia typically is used to describe an unbalanced, incoordinated gait, the term is commonly used more expansively to refer to a general incoordination of movement that can affect movements of the limbs, the trunk, the oropharyngeal apparatus used for swallowing and speaking, and eye movements. The most common presentation is a complaint of imbalance when walking, leading to falls or walking into walls. People with gait ataxia have a broad-based gait and have difficulty with tandem walking.

SYNONYMS

Gait instability
Loss of balance
Functional impairment

ICD-10CM CODES

R27.0	Ataxia, unspecified
G11.0	Congenital nonprogressive ataxia
G11.1	Early-onset cerebellar ataxia
G11.2	Late-onset cerebellar ataxia
G11.3	Cerebellar ataxia with defective DNA repair
G11.8	Other hereditary ataxias
G11.9	Hereditary ataxia, unspecified
G32.81	Cerebellar ataxia in diseases classified elsewhere
G60.2	Neuropathy in association with hereditary ataxia
I69.093	Ataxia following nontraumatic subarachnoid hemorrhage
I69.193	Ataxia following nontraumatic intracerebral hemorrhage
I69.293	Ataxia following other nontraumatic intracranial hemorrhage
I69.393	Ataxia following cerebral infarction
I69.893	Ataxia following other cerebrovascular disease
I69.993	Ataxia following unspecified cerebrovascular disease

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Hereditary ataxia can affect 1 in 50,000 people in the U.S.
PEAK INCIDENCE: Can affect all age groups. Hereditary ataxias peak in young adulthood. Ataxia after age 65 is commonly secondary to stroke.
PREVALENCE: 13.9 per 10,000
PREDOMINANT SEX AND AGE: Ataxia can affect both sexes in equal proportions.
GENETICS: The most common type of inherited ataxia in the U.S. is Friedreich ataxia (FA), which is autosomal recessive. The second most inherited ataxia is autosomal dominant spinocerebellar ataxia (SCA) type 3.
RISK FACTORS:

- A positive family history of ataxia
- Excessive alcohol use
- Hypothyroidism
- Chronic anticonvulsant use
- A history of celiac disease
- A history of cerebrovascular disease

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most individuals will complain of unsteadiness and eventually frequent falls. They may also experience double vision or a sense of the environment moving. Speech may become unintelligible, and they are frequently asked to repeat themselves. A history of difficulty cycling or performing physical activities may be present.
- Physical exam findings include slurred speech, nystagmus, square wave jerks, dysconjugate gaze, and ocular bobbing. Dysmetria and past pointing may be noted in the finger to nose and heel to shin testing. Dysdiadochokinesia may be noted on exam.
- Gait is notable for having a wide base and for difficulty turning with easy falling to one side. Frequent truncal swaying and veering is present. Tandem gait is abnormal.

ETIOLOGY

- Ataxia can be caused by a variety of diseases.
- Genetic causes of ataxia include Friedreich ataxia, the many spinocerebellar ataxias, ataxia telangiectasia, the episodic ataxias, ataxia with oculomotor apraxia, abetalipoproteinemia, and diseases such as MELAS (mitochondrial encephalopathy, lactic acidosis, stroke-like episodes) or MIRAS (mitochondrial recessive ataxic syndrome).
- Strokes of the cerebellum or of the cerebellar inflow or outflow tracks.
- Infections of the cerebellum such as cerebellar brain abscesses or meningitis involving the cerebellar meninges.
- Tumors of the cerebellum, as well as carcinomatosis and lymphomatosis.
- Arnold-Chiari malformation.
- Metabolic causes include hypothyroidism, chronic alcohol use, chronic phenytoin use, and deficiencies of vitamin E, B_1, and B_{12}.
- Immune causes include multiple sclerosis, postinfectious cerebellitis, gluten ataxia due to celiac disease, Hashimoto encephalopathy, Miller Fisher variant of Guillain-Barré syndrome, anti-GAD65 associated cerebellar ataxia, and paraneoplastic syndromes, most commonly subacute cerebellar degeneration associated with anti-Yo antibodies due to breast, ovarian, or uterine malignancies, but also including other paraneoplastic syndromes that can manifest with cerebellar ataxia, such as anti-Hu associated with small cell lung cancer.
- Genetic disorders such as Friedreich ataxia (autosomal recessive) or the many numbered spinocerebellar ataxias (autosomal dominant)
- Severe large-fiber neuropathy
- Ganglionopathy
- Epilepsy
- Celiac disease
- Wilson disease
- Cerebral anoxia
- Cerebellar tumors
- Stroke
- Postinfectious cerebellitis
- Miller-Fisher variant of Guillain-Barré syndrome
- Paraneoplastic subacute cerebellar degeneration
- Anti-GAD65-associated cerebellar ataxia
- Leptomeningeal diseases affecting the cerebellum
- Conversion disorder

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Vitamin deficiency: B_1 (thiamine), B_6 (pyridoxine), B_{12} (cobalamin), copper
- Vitamin excess: B_6 (pyridoxine)
- Alcoholism
- Anticonvulsant use, such as phenytoin

WORKUP

- The workup for ataxia should be systematic and should always look for easily reversible disorders.
- Always start with a family history and investigate for any family members that were affected. This may guide genetic testing.
- Acute-onset ataxia warrants consideration of an acute stroke with appropriate brain imaging.
- Brain imaging, preferably magnetic resonance imaging (MRI), is highly recommended.
- A lumbar puncture may be necessary if infectious, immune-mediated, or neoplastic leptomeningeal disease is suspected.
- If a malignancy is present, then consider an appropriate paraneoplastic panel. However, the paraneoplastic syndrome may precede the appearance of a malignancy on imaging, and a paraneoplastic panel for cerebellar degeneration may be appropriate once other more common etiologies have been ruled out.

LABORATORY TESTS

- Complete metabolic panel, including liver function tests
- Complete blood count with differential and peripheral smear
- Thyroid function tests
- HIV and RPR
- Vitamin B_{12} and vitamin E
- Anti-tissue transglutaminase
- Serum copper and ceruloplasmin
- In selected cases: Genetic testing for spinocerebellar ataxias, paraneoplastic panel for cerebellar degeneration, anti-GAD65 antibodies, anti-TPO antibodies, and lumbar puncture for cytology if leptomeningeal carcinomatosis or lymphomatosis is suspected
- Notes about laboratory testing:
  1. Thiamine levels are not reliable for detecting thiamine deficiency. Thiamine pyrophosphate or erythrocyte transketolase activation may be better, but neither the sensitivity nor specificity of these tests has been established.

2. Total cholesterol must be measured concomitantly with vitamin E levels to interpret result of vitamin assay.
3. Low normal vitamin B_{12} levels of up to 400 pg/ml range can still result in neurological dysfunction. Measuring methylmalonic acid and homocysteine levels is more sensitive in patients with low normal vitamin B_{12} levels, with a high level suggesting vitamin B_{12} deficiency.
4. Electromyography and nerve conduction studies are warranted when the ataxia is thought to be due to peripheral nerve demyelination or part of a myeloneuropathy causing both peripheral neuropathy and dorsal column dysfunction, leading to proprioceptive loss from a sensory ataxia.

IMAGING STUDIES

- MRI of the brain with and without contrast is preferable.
- Computed tomography (CT) scan of the head if MRI is not feasible.
- Cardiac echocardiogram is recommended for the inherited ataxias.

Rx TREATMENT

Treatment of ataxia is highly variable. The best way to treat ataxia is to investigate the cause and, if treatable, then treat the underlying condition. For example, if there is a vitamin deficiency, then vitamin replacement is recommended. Table E1 summarizes treatable causes of inherited ataxia.

However, sometimes the cause is genetic or unknown, and treatment is directed at minimizing complications, such as neuropathy or cardiac disease, and rehabilitative therapy for the ataxia and motor complications.

NONPHARMACOLOGIC THERAPY

Rehabilitative services such as physical, occupational, and speech therapy are a necessary part of the treatment of all ataxias, and evidence suggests it does improve functional status for individuals affected by ataxia.

ACUTE GENERAL Rx

Abrupt and sudden ataxia should always be worked up for stroke, which includes following an established acute stroke protocol.

CHRONIC Rx

Search for the underlying cause and focus on symptomatic management to prevent future disabilities. Rehabilitative services are integral to long-term care. Always evaluate cardiac and renal function and check for signs of developing neuropathy.

COMPLEMENTARY & ALTERNATIVE MEDICINE

There are currently no widely accepted or evidence-based forms of complementary medicine for ataxia.

DISPOSITION

Reversible causes of ataxia may see rapid improvement in symptoms. Genetic ataxias tend to be progressive.

REFERRAL

Always refer to a neurologist.

PEARLS & CONSIDERATIONS

COMMENTS

Look for reversible causes.

PREVENTION

A gluten-free diet would be preferable for people with celiac sprue disease.

PATIENT & FAMILY EDUCATION

Educate families on the need to be supportive and make the home environment safe.

RELATED CONTENT

Friedreich Ataxia (Related Key Topic)
Ataxia Telangiectasia (Related Key Topic)

AUTHORS: **Nawaz K.A. Hack, MD,** and **Joseph S. Kass, MD, JD, FAAN**

TABLE E1 Treatable Causes of Inherited Ataxia

Disorder	Metabolic Abnormality	Distinguishing Clinical Features	Treatment
Acute disseminated encephalomyelitis	Demyelination	Positive MRI findings	Steroids, IVIG, rituximab
Ataxia with vitamin E deficiency	Mutation in α-tocopherol transfer protein	Ataxia, areflexia, retinopathy	Vitamin E
Bassen-Kornzweig syndrome	Abetalipoproteinemia	Acanthocytosis, retinitis pigmentosa, fat malabsorption	Vitamin E
Hartnup disease	Tryptophan malabsorption	Pellagra rash, intermittent ataxia	Niacin
Familial episodic ataxia type 1 and type 2	Mutations in potassium channel (KCNA1) and α_{1A} voltage-gated calcium channel, respectively	Episodic attacks, worse with pregnancy or birth control pills	Acetazolamide
Multiple carboxylase deficiency	Biotinidase deficiency	Alopecia, recurrent infections, variable organic aciduria	Biotin
Mitochondrial complex defects	Complexes I, III, IV	Encephalomyelopathy	Possibly riboflavin, CoQ10, dichloroacetate
Opsoclonus-myoclonus-ataxia syndrome	Paraneoplastic or spontaneous autoimmune	Underlying neuroblastoma or autoantibodies	Steroids, IVIG, rituximab
Pyruvate dehydrogenase deficiency	Block in E-M and Krebs cycle interface	Lactic acidosis, ataxia	Ketogenic diet, possibly dichloroacetate
Refsum disease	Phytanic acid, α-hydroxylase	Retinitis pigmentosa, cardiomyopathy, hypertrophic neuropathy, ichthyosis	Dietary restriction of phytanic acid
Urea cycle defects	Urea cycle enzymes	Hyperammonemia	Protein restriction, arginine, benzoate, α-ketoacids

CoQ10, Coenzyme Q10; *E-M,* mitochondrial electron transport; *IVIG,* intravenous immunoglobulin.
Modified from Stumpf DA: The inherited ataxias, *Pediatr Neurol* 1:129-133, 1985, Table 1; and from Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF et al (eds): *Swaiman's pediatric neurology*, 5e, Philadelphia, 2912, WB Saunders, 2012, Table 67-1; in Kliegman RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

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BASIC INFORMATION

DEFINITION

Ataxia telangiectasia (AT) is a rare autosomal recessive disorder of childhood that results from defective DNA repair mechanisms. AT is a multisystem disease characterized by progressive cerebellar ataxia, choreoathetosis, oculocutaneous telangiectasias (Fig. E1), frequent infections, increased sensitivity to ionizing radiation, and predisposition to malignancies.

ICD-10CM CODE
G11.3 Cerebellar ataxia with defective DNA repair

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1/40,000 live births; it is estimated that 1.4% to 2% of whites in the U.S. carry one defective AT gene. It is the second most common cause of autosomal recessive ataxia after Friedreich ataxia.
PEAK INCIDENCE: Childhood (onset at age 1 to 5 yr)
PREDOMINANT SEX: Males and females are equally affected.
GENETICS: Condition is autosomal recessive and progressive. The defective gene, designated *ATM* (for AT mutated), has been mapped to chromosome 11q22-23. More than 100 mutations have been discovered. The gene product, expressed in all tissues, encodes a large nuclear and cytoplasmic protein kinase that is a member of the phosphatidylinositol-3 kinases and another region similar to DNA repair genes. It becomes recruited and activated by double-stranded DNA breaks and phosphorylates several downstream proteins, which lead to cell cycle arrest, DNA repair, or apoptosis. Developing lymphocytes also require the *ATM* gene product for V(D)J recombination, an essential step in the diversification of lymphocyte antigen receptors.

FIG. E1 Ataxia telangiectasia. (From Callen JP [ed]: *Color atlas of dermatology,* ed 2, Philadelphia, 2000, Saunders.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Children show normal early development until they start to walk, when gait and truncal ataxia become apparent. Thereafter, children develop polyneuropathy, progressive apraxia of eye movements, slurred speech, choreoathetosis, mild diabetes mellitus, delayed physical and sexual development, and signs of premature aging (graying of the hair, loss of skin elasticity and subcutaneous fat).
- Progression, at times, may be so indolent that the condition is misdiagnosed as cerebral palsy.
- Children with AT experience deterioration of motor skills. By the second decade of life, most patients rely on wheelchairs for at least part of the day. Progressive oromotor difficulties also develop over time, placing patients at risk for aspiration.
- Typically, individuals with AT initially have normal intelligence that deteriorates over time until it plateaus at approximately 10 yr of age. As deterioration of motor skills occurs much more aggressively, scholastic skills can become impeded, leading to inaccurate results on traditional timed neuropsychological assessments. Deterioration of speech is typically noted after 5 to 8 yr of age.
- Telangiectasias are virtually pathognomonic for AT and can aid in diagnosis, but they typically appear after 6 yr of age. Sometimes either a complete absence of telangiectasias or a delay in the appearance of telangiectasias results in a delayed diagnosis. Telangiectasias occur primarily in the bulbar conjunctivae and have been misdiagnosed as conjunctivitis. The telangiectasias can progress over the surface of the ears and cheeks, in the corners of the eyes, on exposed parts of the neck, on the bridge of the nose, and in the flexor creases of the forearms. Children with AT may also have café-au-lait macules, hypopigmented macules, or melanocytic nevi.
- Immunodeficiencies occur in 60% to 80% of individuals with AT due to B-cell and T-helper cellular dysfunction and defective V(D)J recombination, leading to abnormal immunoglobulin subclasses. Serum and saliva IgA is absent in 70% to 80%. Serum IgE is low or absent in 80% to 90%, and serum IgM may be elevated. Thymic and other lymphoid tissue frequently have hypoplastic and embryonic appearance. Impaired humoral and cellular immunities lead to recurrent sinopulmonary infections. The severity of immunodeficiency is unrelated to the severity of neurologic phenotype and is also not progressive. Recurrent sinopulmonary infections and aspirations, however, can lead to bronchiectasis later in life.
- In the central nervous system, there is loss of Purkinje cells in the cerebellum, and surviving Purkinje cells may contain eosinophilic cytoplasmic inclusions. Older individuals experience demyelination of the posterior columns and dorsal spinocerebellar tracts. There are also reports of anterior horn cell loss. Peripheral nerves can develop lipid inclusions in Schwann cells, resulting in secondary axonal degeneration.
- Malignancy: Beyond 10 yr of age, the incidence rate is 1% per yr; the overall risk rate is approximately 30% to 40%, of which 85% of cases are leukemia and lymphoma. Predisposition to other cancers (e.g., breast cancer) may also exist, thought to be caused by the phosphorylation of the tumor-suppressor/breast cancer susceptibility gene *BRCA1* by *ATM*.
- Up to 2% of the U.S. population may be carriers of AT. Heterozygote/carriers of the *ATM* gene are thought to have none of the classic manifestations of AT; however, they may have a greater incidence of malignancy at a younger age.

ETIOLOGY

- Cytogenetics show a 7;14 translocation in 5% to 15% of individuals with AT. Cloning and sequencing has identified the ATM (Ataxia Telangiectasia, Mutated, Mapped to chromosome 11q22.3) gene, a protein kinase that is either missing or defective. The ATM mutation delays accumulation of the tumor-suppressor p53 in response to DNA damage, thereby increasing cancer risk. Cells are susceptible to damage by both ionizing radiation and chemotherapeutic agents that cause double-stranded DNA breakages (also see "Genetics" section of this topic).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Early-onset ataxia:
- Friedreich ataxia
- Abetalipoproteinemia (Bassen-Kornzweig syndrome)
- Acquired vitamin E deficiency
- Early-onset cerebellar ataxia with retained reflexes (EOCA)
- Ataxia-ocular apraxia type 1 (AOA1)
- Ataxia-ocular apraxia type 2 (AOA2)
- Ataxia telangiectasia-like disorder (ATLD)
- Spinocerebellar ataxia
- Juvenile GM2 gangliosidosis
- Juvenile sulfatide lipidosis
- Marinesco-Sjögren syndrome
- Hartnup disease and maple syrup urine disease
- Infantile adrenoleukodystrophy (X-linked)

WORKUP

Diagnosis relies on the constellation of clinical findings, including ataxia and speech changes, as well as family history and neuroimaging studies.

LABORATORY TESTS

- Acanthocytes are frequently seen on smear.
- Serum immunoglobulin levels (IgA, IgG, IgE, and IgG subclasses) should be measured to evaluate for immunoglobulin deficiency and oligoclonal gammopathy.

- Serum α-fetoprotein is increased in more than 95% of patients with AT older than the age of 8 mo.
- Prenatal testing is available. Fibroblasts can be screened for abnormal sensitivity to ionizing radiation.
- Immunoblotting is the most sensitive and specific way to detect the ATM protein. Approximately 90% of individuals have no detectable ATM protein.

IMAGING STUDIES

CT or MRI scans will show cerebellar atrophy in nearly all children with ATM between 2 and 8 yr of age. Telangiectasias may be observed as punctate hemosiderin deposits.

Rx TREATMENT

- No proven disease-specific treatment is currently available. Treatment is focused on amelioration of disease manifestations.
- Surveillance for infections and neoplasms is necessary. Individuals with frequent and severe infections may benefit from intravenous immunoglobulin. Some have been placed on prophylactic antibiotics. Children should be immunized with pneumococcal and influenza vaccines.
- The cloning and sequencing of the gene for AT have opened several avenues for intervention, including gene therapy, targeted pharmacologic intervention to correct the function of the altered protein, and direct replacement of the functional protein.
- Recent studies suggest symptomatic improvement with glucocorticoids, which are postulated to induce alternative splicing of the ATM protein and result in retained protein kinase activity.

NONPHARMACOLOGIC THERAPY

- Minimize radiation because it may induce further chromosomal damage and lead to neoplasms. Even diagnostic radiographs should be limited because of the theoretical risk that radiation may lead to chromosomal breakages.
- Monitor swallowing as needed to evaluate for aspiration.
- Physical and occupational therapy to maintain flexibility and minimize contractures.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Antioxidant treatment with vitamin E is often given empirically, though it has not been formally tested. α-Lipoic acid crosses the blood-brain barrier and may therefore have some advantage.

DISPOSITION

AT has a poor prognosis given the multisystem involvement; however, the expected life span has increased considerably. Most individuals now live beyond 25 yr of age and some into the fourth and fifth decades of life. Morbidity is typically related to either infection or neoplasm.

REFERRAL

- Immunology
- Neurology
- Gastroenterology and nutrition
- Physical and occupational therapy
- Genetic counselor

PEARLS & CONSIDERATIONS

COMMENTS

- Most common cause of hereditary ataxia
- Defect in DNA repair
- Predisposition to frequent infections, malignancies, and sensitivity to ionizing radiation

PATIENT/FAMILY EDUCATION

Ataxia Telangiectasia Children's Project: www.atcp.org

National Ataxia Foundation (NAF): www.ataxia.org

RELATED CONTENT

Ataxia (Related Key Topic)

AUTHORS: **Chloe Mander Nunneley, MD, Joseph S. Kass, MD, JD, FAAN,** and **Nicole J. Ullrich, MD, PhD**

BASIC INFORMATION

DEFINITION

Atelectasis describes collapse of lung with some degree of volume loss. There are two major types of atelectasis. Obstructive atelectasis is the most common type due to reabsorption of gas from alveoli when communication between alveoli and the trachea is obstructed. Nonobstructive atelectasis is usually due to loss of contact between parietal and visceral pleura, compression (pleural effusion), or loss of surfactant.

ICD-10CM CODE
J98.11 Atelectasis

EPIDEMIOLOGY & DEMOGRAPHICS

- Postoperative patients and patients with lung or chest wall injury are at increased risk of atelectasis.
- Asbestos exposure increases risk for an entity called "rounded atelectasis."
- Occurs frequently in patients receiving mechanical ventilation.
- There is no known racial or sexual predilection for atelectasis.
- Dependent regions of the lung are more prone to atelectasis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Decreased or absent breath sounds
- Abnormal chest percussion
- Cough, dyspnea, decreased vocal fremitus, and vocal resonance
- Diminished chest expansion, tachypnea, tachycardia

ETIOLOGY

- Trauma caused by shear force generated by repetitive expansion and collapse during positive-pressure ventilation (e.g., mechanical ventilation)
- Airway obstruction (e.g., endobronchial tumor, a lymph node, foreign bodies, mucus plug)
- Extrinsic bronchial compression (e.g., neoplasms, aneurysms of ascending aorta, enlarged left atrium)
- Pleural disease (e.g., pleural effusion, mesothelioma, rounded atelectasis, pneumothorax)
- Alveolar injury (e.g., toxic fumes, aspiration of gastric contents, infections, acute respiratory distress syndrome)
- Chest wall abnormalities (e.g., trauma, scoliosis, rib fracture, obesity)
- Impaired respiratory mechanics or decreased cough response (e.g., pain, postanesthetic effect, abdominal distention, neuromuscular disease)
- Table 1 summarizes anatomic causes of atelectasis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Neoplasm (Bronchogenic carcinoma must be excluded)
- Pneumonia
- Pleural effusion
- Abnormalities of brachiocephalic vein and the left pulmonary ligament

WORKUP

- Chest x-ray (Fig. 1)
- Thoracic ultrasonography
- CT scan (Prone positioning CT scan with improvement or reduction in atelectasis may be used to differentiate from other etiology)
- Fiberoptic bronchoscopy (selected patients)

IMAGING STUDIES

- Chest radiograph suggests the diagnosis but fails to confirm the diagnosis in many cases.
- Ultrasonography helps differentiate atelectasis from effusion or consolidation.
- CT scan is useful in patients with suspected endobronchial neoplasm or extrinsic bronchial compression.
- Prone images help differentiate true consolidation from dependent atelectasis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Deep breathing, mobilization of the patient
- Incentive spirometry
- Handheld positive end-expiratory pressure (PEEP) devices (e.g., PEEP valve, Acapella)
- Tracheal suctioning in select patients (e.g., mechanical ventilation and tracheostomy)
- Humidification
- Therapies for improving cough and clearance of secretions from airways (chest physiotherapy, chest wall percussion, and postural drainage)
- Fiberoptic bronchoscopy (selected patients) might be helpful with mucous plug, removal of foreign body, or evaluation of endobronchial and peribronchial lesions

ACUTE GENERAL Rx

- Positive-pressure breathing (continuous positive airway pressure by face mask, positive end-expiratory pressure for patients on mechanical ventilation)
- Use of mucolytic agents (e.g., acetylcysteine [Mucomyst])
- Recombinant human DNase (dornase alpha) in patients with cystic fibrosis
- Bronchodilator therapy in selected patients
- Pain control in postoperative and trauma cases
- Pleural drainages in cases of large effusions, hemothorax, or empyema
- Treatment of atelectasis is summarized in Table 2

CHRONIC Rx

- Chest physiotherapy
- Humidification of inspired air
- Frequent nasotracheal suctioning

DISPOSITION

Prognosis varies with the underlying etiology

REFERRAL

- Bronchoscopy for removal of foreign body or plugs unresponsive to conservative treatment
- Surgical referral for removal of obstructing neoplasm

PEARLS & CONSIDERATIONS

COMMENTS

Patients should be educated that frequent changes of position are helpful in clearing secretions. Sitting the patient upright in a chair is recommended to increase both volume and vital capacity relative to the supine position. Adequate pain control is paramount after surgical intervention or rib fractures.

RELATED CONTENT

Atelectasis (Patient Information)

AUTHORS: **Harinder P. Singh, MD,** and **Samaan Rafeq, MD**

TABLE 1 Anatomic Causes of Atelectasis

Cause	Clinical Examples
External compression on the pulmonary parenchyma	Pleural effusion, pneumothorax, intrathoracic tumors, diaphragmatic hernia
Endobronchial obstruction completely obstructing the ingress of air	Enlarged lymph node, tumor, cardiac enlargement, foreign body, mucoid plug, broncholithiasis
Intraluminal obstruction of a bronchus	Foreign body, asthma, granulomatous tissue, tumor, secretions including mucous plugs, bronchiectasis, pulmonary abscess, chronic bronchitis, acute laryngotracheobronchitis, plastic bronchitis
Intrabronchiolar obstruction	Bronchiolitis, interstitial pneumonitis, asthma
Respiratory compromise or paralysis	Neuromuscular abnormalities, osseous deformities, overly restrictive casts and surgical dressings, defective movement of the diaphragm, or restriction of respiratory effort

From Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

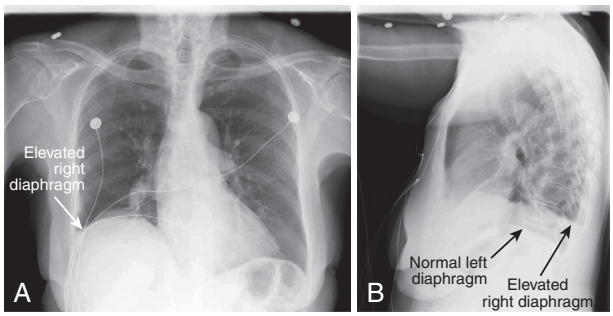

FIG. 1 Atelectasis with elevated diaphragm: An example of volume loss. The right hemidiaphragm in this patient appears elevated on both the posterior-anterior **(A)** and the lateral **(B)** views. Is this the correct interpretation of the x-ray, and if so, what is the cause? Consider the alternative interpretations. A subpulmonic pleural effusion would appear similar, as it would have the same density as liver, heart, and diaphragm and would layer over the diaphragm with the patient upright. This appears less likely in that a meniscus might be seen along the lateral chest wall with a pleural effusion but is not present here. In addition, a pleural effusion occupies space and might be expected to push the heart to the left, whereas in this case the heart may be slightly deviated to the right. Atelectasis of the lower right lung would result in volume loss, pulling the heart and hemidiaphragm into the space normally occupied by lung. This is consistent with the observed features. An infiltrate in this location could explain the x-ray findings but appears less likely for similar reasons to those cited for effusion. Some simple maneuvers could narrow the differential diagnosis. Chest ultrasound, decubitus x-ray views, or CT could identify an effusion. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

TABLE 2 Treatment for Atelectasis

Cause of Atelectasis	Treatment
Pleural effusion or pneumothorax	Relieve compression
Mucus plug	Tracheal or bronchoscopic aspiration Continuous positive airway pressure
Foreign body	Bronchoscopic examination
Asthma	Bronchodilator and corticosteroid treatment Recombinant human deoxyribonuclease (off label use) Hypertonic saline with or without bronchodilator
Neuromuscular diseases	Intermittent positive pressure breathing Mechanical insufflator–exsufflator Noninvasive bilevel positive pressure ventilation
Cystic fibrosis	Airway clearance therapies Hypertonic saline with or without bronchodilator

From Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

Atopic Dermatitis PTG

BASIC INFORMATION

DEFINITION

Atopic dermatitis is a genetically determined eczematous eruption that is pruritic, symmetric, and associated with personal family history of allergic manifestations (atopy). Box 1 summarizes criteria for atopic dermatitis. Modified criteria for children with atopic dermatitis are described in Box 2.

SYNONYMS

Eczema
Atopic neurodermatitis
Atopic eczema

ICD-10CM CODES	
L20.9	Atopic dermatitis, unspecified
L20.89	Other atopic dermatitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence is between 5 and 25 cases/1000 persons.
- Highest incidence is among children (10% to 20%). It accounts for 4% of acute care pediatric visits. It affects 1% to 3% of the adult population.
- Onset of disease before age 5 yr in 85% of patients.
- More than 50% of children with generalized atopic dermatitis develop asthma and allergic rhinitis by age 13 yr.
- Concordance in monozygotic twins is 77%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Atopic dermatitis presentation can be subdivided into three phases:
  1. Acute: Vesicular, crusting, weeping eruption.
  2. Subacute: Dry, scaly, erythematous papules and plaques.
  3. Chronic: Lichenification from repeated scratching.
- The lesions are typically on the neck, face, upper trunk, and bends of elbows and knees (symmetric on flexural surfaces of extremities) (Fig. 1, *A*, and Fig. E2). Atopic dermatitis lesions are usually discrete but vaguely delineated, scaly, and erythematous.
- There is dryness, thickening of the involved areas, discoloration, blistering, and oozing.
- Papular lesions are frequently found in the antecubital and popliteal fossae.
- In children, red scaling plaques are often confined to the cheeks and the perioral and perinasal areas.
- ***Hertoghe sign:*** Loss of the outer eyebrow from chronic rubbing (Fig. 1, *B*).
- Constant scratching may result in areas of hypopigmentation or hyperpigmentation (more common in blacks).
- In adults, redness and scaling in the dorsal aspect of the hands or about the fingers are the most common expression of atopic dermatitis; oozing and crusting may be present.
- Secondary skin infections may be present (*Staphylococcus aureus,* dermatophytosis, herpes simplex).

ETIOLOGY

Unknown; elevated T-lymphocyte activation, defective cell immunity, and B-cell IgE overproduction may play a significant role.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Scabies
- Psoriasis
- Dermatitis herpetiform
- Contact dermatitis
- Photosensitivity
- Seborrheic dermatitis
- Candidiasis, tinea
- Lichen simplex chronicus
- Other: Xerosis, impetigo, Wiskott-Aldrich syndrome, phenylketonuria, ichthyosis, HIV dermatitis, nonnummular eczema, histiocytosis X, malignancies (T-cell lymphoma/mycosis fungoides, Letterer-Siwe disease), graft-versus-host disease, metabolic and nutritional deficiencies (zinc, niacin, pyridoxine deficiencies)

BOX 1 Criteria for Atopic Dermatitis

Major criteria
Must have three of the following:
- Pruritus
- Typical morphology and distribution
  - Flexural lichenification in adults
  - Facial and extensor involvement in infancy
- Chronic or chronically relapsing dermatitis
- Personal or family history of atopic disease (e.g., asthma, allergic rhinitis, atopic dermatitis)

Minor criteria
Must also have three of the following:
- Xerosis
- Ichthyosis or hyperlinear palms or keratosis pilaris
- IgE reactivity (immediate skin test reactivity, RAST test positive)
- Elevated serum IgE
- Early age of onset
- Tendency for cutaneous infections (especially *Staphylococcus aureus* and HSV)
- Tendency to nonspecific hand/foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie-Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor or facial erythema
- Pityriasis alba
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food hypersensitivity
- Course influenced by environmental or emotional factors
- White dermatographism or delayed blanch to cholinergic agents

HSV, Herpes simplex virus; *IgE,* immunoglobulin E; *RAST,* radioallergosorbent assay.
From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Saunders.

BOX 2 Modified Criteria for Children with Atopic Dermatitis

Essential features
- Pruritus
- Eczema
  - Typical morphology and age-specific pattern
  - Chronic or relapsing history

Important features
- Early age at onset
- Atopy
- Personal or family history
- IgE reactivity
- Xerosis

Associated features
- Atypical vascular responses (e.g., facial pallor, white dermatographism)
- Keratosis pilaris, ichthyosis, or hyperlinear palms
- Orbital or periorbital changes
- Other regional findings (e.g., perioral changes, periauricular lesions)
- Perifollicular accentuation, lichenification, or prurigo lesions

IgE, Immunoglobulin E.
From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Saunders.

FIG. 1 A, Flexural atopic dermatitis with lichenification. Many of the skin changes are secondary to scratching. Linear lichenification, as shown here, and excoriations are typical. **B,** Hertoghe sign: Loss of the outer eyebrow may occur in the atopic patient as a result of chronic rubbing. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

- Table 1 summarizes characteristics and clinical features of disorders in the differential diagnosis of atopic dermatitis

WORKUP

Diagnosis is based on the presence of three of the following major features and three minor features.

MAJOR FEATURES:

- Pruritus
- Personal or family history of atopy: Asthma, allergic rhinitis, atopic dermatitis
- Facial and extensor involvement in infants and children
- Flexural lichenification in adults

MINOR FEATURES:

- Elevated IgE
- Eczema-perifollicular accentuation
- Recurrent conjunctivitis
- Ichthyosis
- Nipple dermatitis
- Wool intolerance
- Cutaneous S. *aureus* infections or herpes simplex infections
- Food intolerance
- Hand dermatitis (nonallergic irritant)
- Facial pallor, facial erythema
- Cheilitis
- White dermographism
- Early age of onset (after 2 mo of age)

LABORATORY TESTS

- Lab tests are generally not helpful.
- Elevated IgE levels are found in 80% to 90% of atopic dermatitis.
- Consider skin biopsy only in cases unresponsive to treatment.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Clip nails to decrease abrasion of skin
- Avoidance of triggering factors:
  1. Sudden temperature changes, sweating, low humidity in the winter
  2. Contact with irritating substance (e.g., wool, cosmetics, some soaps and detergents, tobacco)
  3. Foods that provoke exacerbations (e.g., eggs, peanuts, fish, soy, wheat, milk)
  4. Stressful situations
  5. Allergens and dust
  6. Excessive hand washing
- Phototherapy in moderation may be effective in resistant cases

ACUTE GENERAL Rx

- Emollients can be used to prevent dryness. Severely affected skin can be optimally hydrated by occlusion in addition to application of emollients.
- Low-potency topical corticosteroids (e.g., 1% to 2.5% hydrocortisone) may be helpful and are generally considered first-line therapy. Use intermediate-potency steroids (e.g., triamcinolone, fluocinolone) for more severe cases and limit potent corticosteroids (e.g., betamethasone, desoximetasone, clobetasol) to severe cases. Table 2 summarizes relative potencies of topical corticosteroids.
- Crisaborole 2% ointment is a phosphodiesterase type-4 (PDE4) inhibitor modestly effective for short-term treatment of mild to moderate atopic dermatitis.
- Oral antihistamines (e.g., hydroxyzine, diphenhydramine) are effective in controlling pruritus and inducing sedation, restful sleep, and prevention of scratching during sleep. Doxepin and other tricyclic antidepressants also have antihistamine effect, induce sleep, and reduce pruritus.
- The topical immunomodulators pimecrolimus and tacrolimus are especially useful for treatment of the face and intertriginous sites, where steroid-induced atrophy may occur. However, due to concerns about carcinogenic potential, the FDA recommends limiting their use for short periods in patients who are intolerant or unresponsive to other treatments. Pimecrolimus cream 1% is applied bid and has antiinflammatory effects secondary to blockage of activated T-cell cytokine production. Tacrolimus ointment (0.03% or 0.1%) applied bid is a macrolide that suppresses humoral and cell-mediated immune responses.
- Oral prednisone, intramuscular triamcinolone, Goeckerman regimen, psoralen and ultraviolet A light therapy are generally reserved for severe cases.
- Cyclosporine, azathioprine, mycophenolate, and interferon gamma are sometimes tried for recalcitrant disease in adults by physicians who specialize in severe inflammatory skin conditions.
- The human monoclonal antibody dupilumab is effective in adults with moderate to severe atopic dermatitis that have not responded to topical therapies. It can be used with or without corticosteroids. It is injected subcutaneously. Cost is a limiting factor.
- Table 3 summarizes the management of atopic dermatitis.

DISPOSITION

- Resolution occurs in approximately 70% of patients by adulthood.
- Most patients have a course characterized by remissions and intermittent flares.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Dermatitis (Patient Information)
Eczema (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

TABLE 1 Differential Diagnosis of Atopic Dermatitis (AD)

	Main Age Group Affected	Frequency*	Characteristics and Clinical Features
Other Types of Dermatitis			
Seborrheic dermatitis	Infants	Common	Salmon-red greasy scaly lesions, often on the scalp (cradle cap) and napkin area; generally presents in the first 6 wk of life; typically clears within weeks
Seborrheic dermatitis	Adults	Common	Erythematous patches with yellow, white, or grayish scales in seborrheic areas, particularly the scalp, central face, and anterior chest
Nummular dermatitis	Children and adults	Common	Coin-shaped scaly patches, mostly on legs and buttocks; usually no itch
Irritant contact dermatitis	Children and adults	Common	Acute to chronic eczematous lesions, mostly confined to the site of exposure; history of locally applied irritants is a risk factor; might coexist with AD
Allergic contact dermatitis	Children and adults	Common	Eczematous rash with maximum expression at sites of direct exposure but might spread; history of locally applied irritants is a risk factor; might coexist with AD
Lichen simplex chronicus	Adults	Uncommon	One or more localized, circumscribed, lichenified plaques that result from repetitive scratching or rubbing because of intense itch
Asteatotic eczema	Adults	Common	Scaly, fissured patches of dermatitis overlying dry skin, most often on lower legs
Infectious Skin Diseases			
Dermatophyte infection	Children and adults	Common	One or more demarcated scaly plaques with central clearing and slightly raised reddened edge; variable itch
Impetigo	Children	Common	Demarcated erythematous patches with blisters or honey-yellow crusting
Scabies	Children	Common†	Itchy superficial burrows and pustules on palms and soles, between fingers, and on genitalia; might produce secondary eczematous changes
HIV	Children and adults	Uncommon	Seborrhea-like rash
Keratinization Disorders			
Ichthyosis vulgaris	Infants and adults	Uncommon	Dry skin with fine scaling, particularly on the lower abdomen and extensor areas; perifollicular skin roughening; palmar hyperlinearity; full form (i.e., 2 *FLG* mutations) is uncommon; often coexists with AD
Nutritional Deficiency–Metabolic Disorders			
Zinc deficiency (acroder-matitis lenteropathica)	Children	Uncommon	Erythematous scaly patches and plaques, most often around the mouth and anus; rare congenital form accompanied by diarrhea and alopecia
Biotin deficiency (nutritional or biotinidase deficiency)	Infants	Uncommon	Scaly periorofacial dermatitis, alopecia, conjunctivitis, lethargy, hypotonia
Pellagra (niacin deficiency)	All ages	Uncommon	Scaly crusted epidermis, desquamation, sun-exposed areas, diarrhea
Kwashiorkor	Infants and children	Geographic dependent	Flaky scaly dermatitis, swollen limbs with cracked peeling patches
Phenylketonuria	Infants	Uncommon	Eczematous rash, hypopigmentation, blonde hair, developmental delay
Neoplastic Disease			
Cutaneous T-cell lymphoma	Adults	Uncommon	Erythematous pink-brown macules and plaques with a fine scale; poorly responsive to topical corticosteroids; variable itch (in early stages)
Langerhans cell histiocytosis	Infants	Uncommon	Scaly and purpuric dermatosis, hepatosplenomegaly, cytopenias

FLG, Filaggrin gene; *HIV*, human immunodeficiency virus.
*Common = approximately 1 in 10 to 1 in 100; uncommon = 1 in 100 to 1 in 1000; rare = 1 in 1000 to 1 in 10,000; very rare ≤ 1 in 10,000.
†Especially in developing countries.
From Kliegman RM: *Nelson Textbook of Pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

TABLE 2 Relative Potencies of Topical Corticosteroids (from Most Potent to Weakest)

Class	Drug	Dosage Form(s)	Strength (%)
I. Very high potency			
	Augmented betamethasone dipropionate	Ointment	0.05
	Clobetasol propionate	Cream, ointment, foam	0.05
	Diflorasone diacetate	Ointment	0.05
	Halobetasol propionate	Cream, ointment	0.05
II. High potency			
	Amcinonide	Cream, lotion, ointment	0.1
	Augmented betamethasone dipropionate	Cream	0.05
	Betamethasone dipropionate	Cream, ointment, foam, solution	0.05
	Desoximetasone	Cream, ointment	0.25
	Desoximetasone	Gel	0.05
	Diflorasone diacetate	Cream	0.05
	Fluocinonide	Cream, ointment, gel, solution	0.05
	Halcinonide	Cream, ointment	0.1
	Mometasone furoate	Ointment	0.1
	Triamcinolone acetonide	Cream, ointment	0.5
III-IV. Medium potency			
	Betamethasone valerate	Cream, ointment, lotion, foam	0.1
	Clocortolone pivalate	Cream	0.1
	Desoximetasone	Cream	0.05
	Fluocinolone acetonide	Cream, ointment	0.025
	Flurandrenolide	Cream, ointment	0.05
	Fluticasone propionate	Cream	0.05
	Fluticasone propionate	Ointment	0.005
	Mometasone furoate	Cream	0.1
	Triamcinolone acetonide	Cream, ointment	0.1
V. Lower-medium potency			
	Hydrocortisone butyrate	Cream, ointment, solution	0.1
	Hydrocortisone probutate	Cream	0.1
	Hydrocortisone valerate	Cream, ointment	0.2
	Prednicarbate	Cream	0.1
VI. Low potency			
	Alclometasone dipropionate	Cream, ointment	0.05
	Desonide	Cream, gel, foam, ointment	0.05
	Fluocinolone acetonide	Cream, solution, oil	0.01
VII. Lowest potency			
	Dexamethasone	Cream	0.1
	Hydrocortisone	Cream, ointment, lotion, solution	0.25, 0.5, 1
	Hydrocortisone acetate	Cream, ointment	0.5-1

From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.

TABLE 3 Management of Mild, Moderate, and Severe Forms of Atopic Dermatitis

Mild	Moderate	Severe
Bathing and barrier repair*	Bathing and barrier repair*	Bathing and barrier repair*
Avoidance of irritant and allergic triggers	Avoidance of irritant and allergic triggers	Avoidance of irritant and allergic triggers
Intermittent, short-term use of class VI or VII topical steroids ± topical calcineurin inhibitors	Intermittent, short-term use of class III–V topical steroids ± topical calcineurin inhibitors	Class II topical steroids for flares; class III–V topical steroids ± tacrolimus ointment for maintenance
Treatment of superinfection	Treatment of superinfection	Treatment of superinfection
	Oral antihistamines	Oral antihistamines
		Systemic antiinflammatory agents, ultraviolet light therapy

*Barrier repair may be accomplished by application of effective emollients or from barrier-repair agents.
From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.

SUGGESTED READINGS

Beck LA et al: Dupilumab treatment in adults with moderate to severe atopic dermatitis, *N Engl J Med* 371:130-139, 2014.
Berke R et al: Atopic dermatitis: an overview, *Am Fam Physician* 86:35-42, 2012.
Bershad SV: In the clinic: atopic dermatitis (eczema), *Ann Intern Med* 155:ITC 5-1, 2011.

FIG. E2 Flexural involvement in childhood atopic dermatitis. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Saunders.)

Atrial Fibrillation ALG PTG

BASIC INFORMATION

DEFINITION

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by disorganized and rapid atrial activation and uncoordinated atrial contraction. AF occurs when structural and/or electrophysiologic abnormalities alter atrial tissue to promote abnormal impulse formation and/or propagation. The ventricular rate is dependent on the conduction properties of the atrioventricular (AV) node, which can be influenced by vagal/sympathetic tone, medications, or disease of the AV node.

Multiple classification schemes have been used in the past to characterize AF. The current classification scheme (divided into three major types) used by the American College of Cardiology (ACC)/American Heart Association (AHA) guideline committee is as follows:

- Paroxysmal AF: More than one episode of AF that terminate spontaneously or with intervention within 7 days
- Persistent AF: Episodes of AF that last longer than 7 days
  1. Early-persistent AF: AF that has been continuous for longer than 7 days but fewer than 3 mo
  2. Long-standing persistent AF: AF that has persisted for longer than 1 yr, either because cardioversion has failed or because cardioversion has not been attempted
- Permanent AF: When patient and physician decide to stop pursuing restoring sinus rhythm
- In addition to the previous AF categories, which are mainly defined by episode timing and termination, the ACC/AHA/European Society of Cardiology (ESC) guidelines describe additional AF categories in terms of other characteristics of the patient:
  1. Lone atrial fibrillation (LAF): Generally refers to AF in younger patients without clinical or echocardiographic evidence of cardiopulmonary disease, diabetes, or hypertension
  2. Nonvalvular AF: Atrial fibrillation in the absence of moderate-to-severe mitral stenosis or in the presence of a mechanical heart valve
  3. Secondary AF: Occurs in the setting of a primary condition that may be the cause of the AF, such as acute myocardial infarction, cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia, or other acute disease. It is considered separately because AF is less likely to recur once the precipitating condition has resolved
  4. Silent AF: Asymptomatic AF diagnosed by an ECG or rhythm strip

SYNONYMS

AF
Paroxysmal atrial fibrillation (PAF)
AFib

ICD-10CM CODES

I48.0 Paroxysmal atrial fibrillation
I48.1 Persistent atrial fibrillation
I48.2 Chronic atrial fibrillation
I48.91 Unspecified atrial fibrillation

EPIDEMIOLOGY & DEMOGRAPHICS

- The prevalence of AF increases with age, from 2% in adults <65 yr to 9% of those >65 yr.
- AF affects over 3 million people in the United States. AF is uncommon in infants and children and, when present, almost always occurs in association with structural heart disease.
- The incidence of AF is significantly higher in men than in women in all age groups (1.1% versus 0.8%). AF appears to be more common in whites than in blacks, who may have lower awareness of the disease.
- Stroke due to thromboembolism is the most common and dreaded complication of AF. The rate of ischemic stroke in patients with non-rheumatic AF averages 5% a yr, which is somewhere between 2 and 7× the rate of stroke in patients without AF. The risk of stroke is not due solely to AF; changes in the endothelium and elevated markers of inflammation that may contribute to thrombosis are found in patients with AF, regardless of their rhythm at the time. The attributable risk of stroke from AF is estimated to be 1.5% for those aged 50 to 59 yr, and it approaches 36% for those aged 80 to 89 yr.
- Table 1 summarizes the thromboembolic risk score.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical presentation is variable:

- Palpitations, dizziness, or lightheadedness
- Fatigue, weakness, or impaired exercise tolerance

TABLE 1 Thromboembolic Risk Score

CHA_2DS_2-VASc Risk factors	Score
Congestive heart failure	1
Hypertension	1
Age ≥75	2
Diabetes	1
Previous stroke, TIA, or thromboembolism	2
Vascular disease	1
Age 65-75	1
Female	1

European Society of Cardiology (ESC), American Heart Association (AHA), and American College of Cardiology (ACC) Guidelines recommend to use CHA2DS2-VASc Score to assess the risk of stroke in patients with atrial fibrillation. ESC Guidelines recommend patients with risk factor(s) ≥1 to receive effective stroke prevention therapy. Antithrombotic therapy is not recommended in patients with AF (irrespective of gender) who are aged <65 and with lone AF as they have very low absolute event rates. AHA/ACC Guidelines recommend oral anticoagulation for patients with CHA2DS2-VASc ≥2; for patients with nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered.
CHA2DS2-VASc, Congestive heart failure, hypertension, age, diabetes, stroke/TIA, and vascular disease; *TIA,* transient ischemic attack.
From Ronco C et al: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.

- Angina
- Dyspnea
- Some patients are asymptomatic
- Cardiac auscultation revealing irregularly irregular rhythm
- Thromboembolic phenomenon such as stroke

ETIOLOGY

- The most frequent change in AF is the loss of atrial muscle mass and atrial fibrosis
- Fibrillation is presumed to be caused by multiple wandering wavelets, usually originating from the pulmonary veins. Both reentrant and focal mechanisms have been proposed (Fig. 1)
- Vascular causes: Hypertensive heart disease
- Valvular heart disease
- Pulmonary causes: Pulmonary embolism, chronic obstructive pulmonary disease, obstructive sleep apnea, carbon monoxide poisoning
- Structural cardiac disease: Hypertrophic cardiomyopathy, congestive heart failure, coronary artery disease, myocardial infarction, congenital heart disease (especially those that lead to atrial enlargement such as atrial septal defect)
- Pericarditis and myocarditis
- Arrhythmias: Atrial tachycardias and atrial flutters have been associated with atrial fibrillation, as has Wolff-Parkinson-White syndrome
- Endocrine: Thyrotoxicosis, hyperthyroidism or subclinical hyperthyroidism, pheochromocytoma, obesity
- Surgery: Both cardiac and noncardiac
- Electrolytes: Hypokalemia, hypomagnesemia
- Systemic stress: Fever, anemia, hypoxia, sepsis, infections (e.g., pneumonia)
- Medications/toxins: Digitalis, adenosine, theophylline, amphetamines, cocaine, antihistamines, alcohol abuse and/or withdrawal, caffeine, steroidal antiinflammatory drugs (SAIDs), nonsteroidal antiinflammatory drugs (NSAIDs)
- Frequency of vigorous exercise is associated with an increased risk of developing AF in young men and joggers
- Porphyrias have been associated with autonomic dysfunction and increased risk of AF
- Patients with metabolic syndrome, excessive vitamin D intake, or excessive niacin intake have a higher risk of AF

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Multifocal atrial tachycardia
- Atrial flutter
- Frequent atrial premature beats
- Atrial tachycardia
- AV nodal reentry tachycardia (AVNRT)
- Wolff-Parkinson-White syndrome

WORKUP

The evaluation of atrial fibrillation involves diagnosis, determination of the etiology, and classification of the arrhythmia. A minimal evaluation

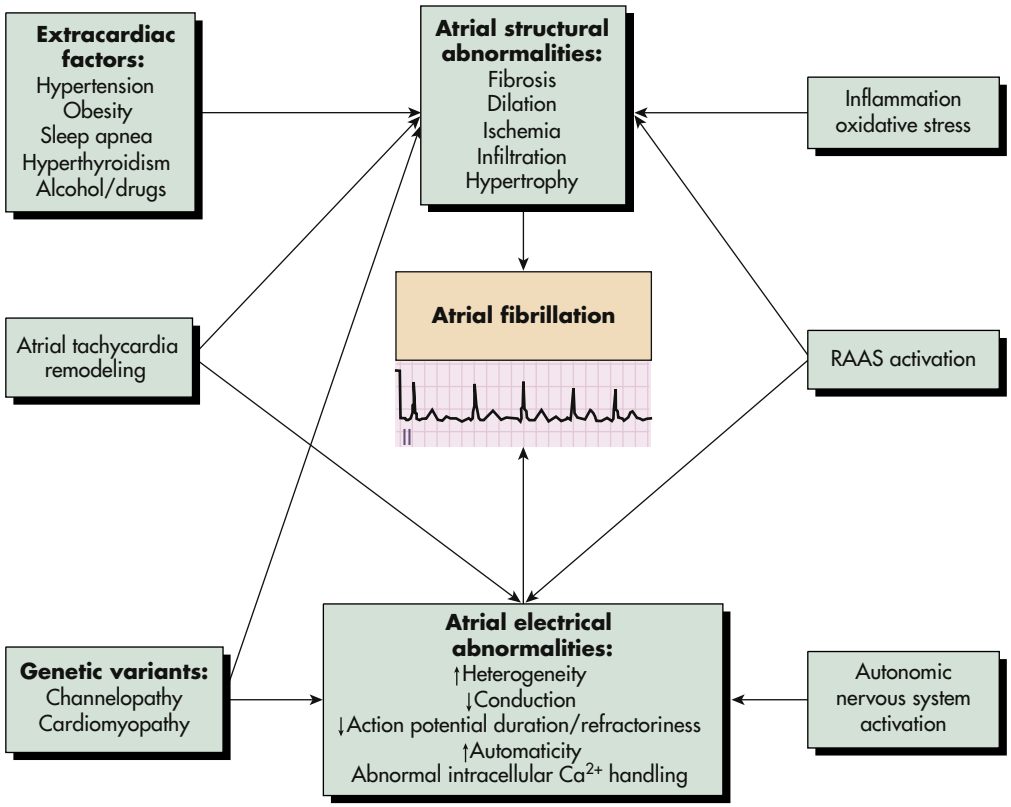

FIG. 1 Mechanisms of atrial fibrillation. *Ca^{2+},* Ionized calcium; *RAAS,* renin-angiotensin-aldosterone system. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.)

includes a history and physical examination, ECG, transthoracic echocardiogram, and case-specific laboratory work to rule out secondary AF.

LABORATORY TESTS

- Thyroid-stimulating hormone, free T_4
- Serum electrolytes
- Toxicity screen
- CBC count (looking for anemia, infection)
- Renal and hepatic function tests
- D-dimer/CT scan of chest pulmonary embolism protocol (if the patient has risk factors to merit a pulmonary embolism workup)

IMAGING STUDIES

- ECG (Fig. 2)
- Absence of P waves
- Fibrillatory or F waves at the isoelectric baseline with varying amplitude, morphology, and intervals (Fig. 3)
- Irregular ventricular rate
- Echocardiography to rule out structural heart disease (evaluate ventricular size, thickness, and function, atrial size, pericardial disease, and valve function)
- Chest radiography (if pulmonary disease or congestive heart failure [CHF] is suspected)
- Transesophageal echocardiography (TEE): Helpful to evaluate for left atrial thrombus (particularly in the left atrium appendage) to guide cardioversion or ablation (if thrombus is seen, cardioversion should be delayed)

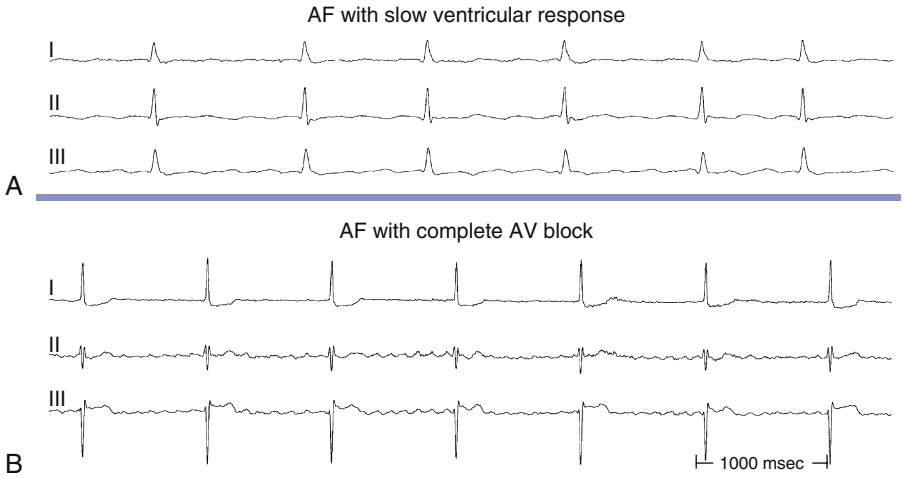

FIG. 2 Atrial fibrillation *(AF)* with slow ventricular rate. **A,** The ventricular rhythm is irregular, indicating that it is the result of conducted atrial beats. **B,** The ventricular rhythm is regular, consistent with the presence of complete atrioventricular *(AV)* block and a regular junctional escape rhythm. (From Issa Z et al: *Clinical arrhythmology and electrophysiology*, ed 2, Philadelphia, 2012, Saunders Elsevier.)

- CT and MRI: In patients with a positive D-dimer result, chest CT angiogram may be necessary to rule out pulmonary embolus. 3D imaging technologies (CT scan or MRI) are often helpful to evaluate atrial anatomy if AF ablation is planned
- 6-minute walk test or exercise test: 6-minute walk or exercise testing can help assess the adequacy of rate control. Exercise testing can also exclude ischemia prior to treatment of patients with class Ic antiarrhythmic drugs and can be used to reproduce exercise-induced AF
- Sleep study (if sleep apnea is suspected)
- Holter monitor or event recorder if the diagnosis of AF is in question and to assess AF burden
- Electrophysiologic study: When initiation of AF is secondary to a supraventricular tachycardia, such as AVNRT or Wolff-Parkinson-White syndrome

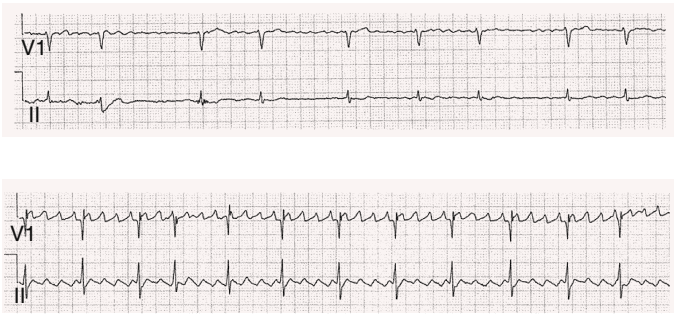

FIG. 3 Comparison between the F waves of atrial fibrillation *(top panel)* and the flutter waves of atrial flutter *(bottom panel).* Note that F waves are variable in rate, shape, and amplitude, whereas flutter waves are constant in rate and all aspects of morphology. Shown are leads V1 and II. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

Rx TREATMENT

ACUTE GENERAL Rx: New-onset AF:

- If the patient is hemodynamically unstable (hypotension, congestive heart failure, or angina), perform synchronized cardioversion after immediate conscious sedation with a rapid short-acting sedative (e.g., midazolam). The ACC/AHA recommendations for cardioversion of atrial fibrillation are summarized in Table 2. The likelihood of cardioversion-related clinical thromboembolism is low in patients with AF lasting <48 hr. Patients with AF lasting >2 days have a 5% to 7% risk for clinical thromboembolism if cardioversion is not preceded by several weeks of anticoagulation therapy. However, if transesophageal echocardiography reveals no atrial thrombus, cardioversion may be performed safely after therapeutic anticoagulation has been achieved. Alternatively, patients can be safely anticoagulated for approximately 1 mo and then undergo cardioversion without transesophageal echocardiogram. Anticoagulant therapy should be continued for at least 1 mo after cardioversion to minimize the incidence of adverse thromboembolic events. It can be stopped after 1 mo as long as AF has not recurred if the patient is deemed low risk of stroke using the Congestive heart failure, hypertension, age, diabetes, stroke/TIA, and vascular disease (CHA_2DS_2-VASc) scoring system (Table 1).
- If the patient is hemodynamically stable, a rate-control strategy is typically pursued initially. ACC/AHA recommendations for pharmacologic rate control of atrial fibrillation are summarized in Table 3.
- Treatment options for rate control include the following:
  1. Diltiazem 0.25 mg/kg (maximum of 25 mg) given intravenously (IV) over 2 min followed by a second dose of 0.35 mg/kg (maximum of 25 mg) 15 min later if the rate is not slowed to <100 beats/min. May then follow with IV infusion 10 mg/hr (range, 5 to 15 mg/hr) to achieve a resting heart rate of <100 beats/min. Onset of action after IV administration is usually within 3 min, with peak effect most often occurring within 10 min. After the ventricular rate is slowed, the patient can be changed to oral diltiazem 60 to 90 mg q4 to 6h. High doses of calcium channel blockers can exacerbate heart failure and thus should be used with caution in patients presenting with symptoms of heart failure or depressed ejection fraction.
  2. Verapamil 2.5 to 5 mg IV initially, then 5 to 10 mg IV 10 min later if the rate is still not slowed to <100 beats/min. After the ventricular rate is slowed, the patient can be changed to oral verapamil 80 to 120 mg q6 to 8h. Main concern is hypotension and heart failure with this medication, and it should not be used in patients with CHF.
  3. Esmolol and metoprolol are beta-blockers available in IV preparations that can be used. High doses of beta-blockers can have negative inotropic effects in heart failure and should be used with caution.
  4. Digoxin is not a potent AV nodal blocking agent and has a potential for toxicity and therefore cannot be relied on for acute control of the ventricular response, but it may be used in conjunction with beta-blockers and calcium channel blockers. It may be a useful adjunct to a beta-blocker in the hypotensive or heart failure patient, which is not infrequent. When used, give 0.5 mg IV loading dose (slow) and then 0.25 mg IV 6 hr later. A third dose may be needed after 6 to 8 hr; the daily dose varies from 0.125 to 0.25 mg (decrease dosage in patients with renal insufficiency and elderly patients) depending on the heart rate and signs or symptoms of digoxin toxicity. Toxicity is manifested by GI and visual complaints, atrial tachyarrhythmias, heart block, and ventricular tachycardia.
  5. Amiodarone has a class IIa recommendation from the ACC/AHA/ESC for use as a rate-controlling agent for patients who are intolerant of or unresponsive to other agents, such as patients with heart failure who may otherwise not tolerate diltiazem or metoprolol. Caution should be exercised in those who are not receiving anticoagulation because amiodarone can promote cardioversion, thereby posing a thromboembolic risk.
- AV nodal blocking agents, particularly calcium channel blockers and digoxin, should be avoided in patients with Wolff-Parkinson-White syndrome and AF because, by blocking the AV node, AF impulses may be transmitted exclusively down the accessory pathway, which can result in ventricular fibrillation. If this happens, the patient will require immediate defibrillation. Procainamide, flecainide, or amiodarone can be used instead if Wolff-Parkinson-White syndrome is suspected.
- In the acute setting, pharmacologic cardioversion (e.g., ibutilide, dofetilide) is less commonly used than electrical cardioversion. A major disadvantage with pharmacologic cardioversion is the risk of development of ventricular tachycardia and other serious arrhythmias, especially due to acute prolongation of the QT interval.
- ACC/AHA recommendations for maintenance of sinus rhythm in patients with atrial fibrillation are summarized in Table 4.

CHRONIC THERAPY

- Avoidance of alcohol in patients with suspected excessive alcohol use.
- Treatment of underlying source or cause, if any found.
- Treatment of modifiable risk factors such as obstructive sleep apnea, hypertension, and obesity have been shown to decrease AF burden in patients.
- Per the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and Rate Control versus Electrical Cardioversion (RACE) trials, either rate control or rhythm control strategies show no difference in composite cardiovascular end points of death, CHF, bleeding, drug side effects, or thromboembolism. Both approaches have similar outcomes as long as appropriate anticoagulation is maintained based on the individual's stroke risk.

TABLE 2 ACC/AHA Recommendations for Cardioversion of Atrial Fibrillation

Class	Indication	Level of Evidence
Pharmacologic Cardioversion		
Class I (indicated)	Administration of flecainide, dofetilide, propafenone, or ibutilide is recommended for pharmacologic cardioversion of AF.	A
Class IIa (reasonable)	Administration of amiodarone is a reasonable option for pharmacologic cardioversion of AF.	A
	A single oral bolus dose of propafenone or flecainide ("pill-in-the-pocket") can be administered to terminate persistent AF outside the hospital once treatment has proved safe in the hospital for selected patients without sinus or AV node dysfunction, bundle branch block, QT interval prolongation, the Brugada syndrome, or structural heart disease. Before antiarrhythmic medication is initiated, a beta-blocker or nondihydropyridine calcium channel antagonist should be given to prevent rapid AV conduction in the event atrial flutter occurs.	C
	Administration of amiodarone can be beneficial on an outpatient basis in patients with paroxysmal or persistent AF when rapid restoration of sinus rhythm is not deemed necessary.	C
Class IIb (may be considered)	Administration of quinidine or procainamide might be considered for pharmacologic cardioversion of AF, but the usefulness of these agents is not well established.	C
Class III (not indicated)	Digoxin and sotalol may be harmful when used for pharmacologic cardioversion of AF and are not recommended.	A
	Quinidine, procainamide, disopyramide, and dofetilide should not be started out of the hospital for conversion of AF to sinus rhythm.	B
Direct-Current Cardioversion		
Class I (indicated)	When a rapid ventricular response does not respond promptly to pharmacologic measures for patients with AF with ongoing myocardial ischemia, symptomatic hypotension, angina, or heart failure, immediate R wave–synchronized direct-current cardioversion is recommended.	C
	Immediate direct-current cardioversion is recommended for patients with AF involving preexcitation when very rapid tachycardia or hemodynamic instability occurs.	B
	Cardioversion is recommended in patients without hemodynamic instability when symptoms of AF are unacceptable to the patient. In case of early relapse of AF after cardioversion, repeated direct-current cardioversion attempts may be made after administration of antiarrhythmic medication.	C
Class IIa (reasonable)	Direct-current cardioversion can be useful to restore sinus rhythm as part of a long-term management strategy for patients with AF.	B
	The patient's preference is a reasonable consideration in the selection of infrequently repeated cardioversions for the management of symptomatic or recurrent AF.	C
Class III (not indicated)	Frequent repetition of direct-current cardioversion is not recommended for patients who have relatively short periods of sinus rhythm between relapses of AF after multiple cardioversion procedures despite prophylactic antiarrhythmic drug therapy.	C
	Electrical cardioversion is contraindicated in patients with digitalis toxicity or hypokalemia.	C
Pharmacologic Enhancement of Direct-Current Cardioversion		
Class IIa (reasonable)	Pretreatment with amiodarone, flecainide, ibutilide, propafenone, or sotalol can be useful to enhance the success of direct-current cardioversion and to prevent recurrent AF.	B
	In patients who relapse to AF after successful cardioversion, it can be useful to repeat the procedure after prophylactic administration of antiarrhythmic medication.	C
Class IIb (may be considered)	For patients with persistent AF, administration of beta-blockers, disopyramide, diltiazem, dofetilide, procainamide, or verapamil may be considered, although the efficacy of these agents to enhance the success of direct-current cardioversion or to prevent early recurrence of AF is uncertain.	C
	Out-of-hospital initiation of antiarrhythmic medications may be considered in patients without heart disease to enhance the success of cardioversion of AF.	C
	Out-of-hospital administration of antiarrhythmic medications may be considered to enhance the success of cardioversion of AF in patients with certain forms of heart disease once the safety of the drug has been verified for the patient.	C
Prevention of Thromboembolism in Patients with Atrial Fibrillation Undergoing Cardioversion		
Class I (indicated)	For patients with AF of 48-hr duration or longer, or when the duration of AF is unknown, anticoagulation (INR 2.0-3.0) is recommended for at least 3 wk before and 4 wk after cardioversion, regardless of the method (electrical or pharmacologic) used to restore sinus rhythm.	B
	For patients with AF of more than 48-hr duration requiring immediate cardioversion because of hemodynamic instability, heparin should be administered concurrently (unless contraindicated) by an initial intravenous bolus injection, followed by a continuous infusion in a dose adjusted to prolong the activated partial thromboplastin time to 1.5 to 2× the reference control value. Thereafter, oral anticoagulation (INR, 2.0-3.0) should be provided for at least 4 wk, as for patients undergoing elective cardioversion. Limited data support subcutaneous administration of low-molecular-weight heparin in this indication.	C
	For patients with AF of less than 48-hr duration associated with hemodynamic instability (angina pectoris, myocardial infarction, shock, or pulmonary edema), cardioversion should be performed immediately, without delay, for prior initiation of anticoagulation.	C

Continued

TABLE 2 ACC/AHA Recommendations for Cardioversion of Atrial Fibrillation—cont'd

Class	Indication	Level of Evidence
Class IIa (reasonable)	During the 48 hr after onset of AF, the need for anticoagulation before and after cardioversion may be based on the patient's risk of thromboembolism.	C
	As an alternative to anticoagulation before cardioversion of AF, it is reasonable to perform transesophageal echocardiography in search of thrombus in the left atrium or left atrial appendage.	B
	a. For patients with no identifiable thrombus, cardioversion is reasonable immediately after anticoagulation with unfractionated heparin (e.g., initiated by intravenous bolus injection and an infusion continued at a dose adjusted to prolong the activated partial thromboplastin time to 1.5-2× the control value until oral anticoagulation has been established with an oral vitamin K antagonist [e.g., warfarin] as evidenced by an INR ≥2.0).	B
	Thereafter, continuation of oral anticoagulation (INR, 2.0-3.0) is reasonable for a total anticoagulation period of at least 4 wk, as for patients undergoing elective cardioversion.	B
	Limited data are available to support the subcutaneous administration of a low-molecular-weight heparin in this indication.	C
	b. For patients in whom thrombus is identified by transesophageal echocardiography, oral anticoagulation (INR, 2.0-3.0) is reasonable for at least 3 wk before and 4 wk after restoration of sinus rhythm, and a longer period of anticoagulation may be appropriate even after apparently successful cardioversion because the risk of thromboembolism often remains elevated in such cases.	C
	For patients with atrial flutter undergoing cardioversion, anticoagulation can be beneficial according to the recommendations as for patients with AF.	C

ACC, American College of Cardiology; *AF,* atrial fibrillation; *AHA,* American Heart Association; *INR,* international normalized ratio.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 3 ACC/AHA Recommendations for Pharmacologic Rate Control of Atrial Fibrillation

Class	Indication	Level of Evidence
Class I (indicated)	Measurement of the heart rate at rest and control of the rate with pharmacologic agents (either a beta-blocker or nondihydropyridine calcium channel antagonist, in most cases) are recommended for patients with persistent or permanent AF.	B
	In the absence of preexcitation, intravenous administration of beta-blockers (esmolol, metoprolol, or propranolol) or nondihydropyridine calcium channel antagonists (verapamil, diltiazem) is recommended to slow the ventricular response to AF in the acute setting, exercising caution in patients with hypotension or heart failure.	B
	Intravenous administration of digoxin or amiodarone is recommended to control heart rate in patients with AF and heart failure who do not have an accessory pathway.	B
	In patients who experience symptoms related to AF during activity, the adequacy of heart rate control should be assessed during exercise, adjusting pharmacologic treatment as necessary to keep the rate in the physiologic range.	C
	Digoxin is effective after oral administration to control the heart rate at rest in patients with AF and is indicated for patients with heart failure or left ventricular dysfunction and for sedentary individuals.	C
Class IIa (reasonable)	A combination of digoxin and either a beta-blocker or nondihydropyridine calcium channel antagonist is reasonable to control the heart rate both at rest and during exercise in patients with AF. The choice of medication should be individualized and the dose modulated to avoid bradycardia.	B
	It is reasonable to use ablation of the AV node or accessory pathway to control heart rate when pharmacologic therapy is insufficient or associated with side effects.	B
	Intravenous amiodarone can be useful to control heart rate in patients with AF when other measures are unsuccessful or contraindicated.	C
	When electrical cardioversion is not necessary in patients with AF and an accessory pathway, intravenous procainamide or ibutilide is a reasonable alternative.	C
Class IIb (may be considered)	When the ventricular rate cannot be adequately controlled both at rest and during exercise in patients with AF by a beta-blocker, nondihydropyridine calcium channel antagonist, or digoxin, alone or in combination, oral amiodarone may be administered to control the heart rate.	C
	Intravenous procainamide, disopyramide, ibutilide, or amiodarone may be considered for hemodynamically stable patients with AF involving conduction over an accessory pathway	B
	When the rate cannot be controlled with pharmacologic agents or tachycardia-mediated cardiomyopathy is suspected, catheter-directed ablation of the AV node may be considered in patients with AF to control the heart rate.	C
Class III (not indicated)	Strict rate control (<80 beats/min at rest or <110 beats/min during 6-minute walk) is not beneficial compared to a resting rate <110 beats/min in asymptomatic patients with persistent AF and an ejection fraction >40%, although uncontrolled tachycardia can lead to reversible left ventricular dysfunction over time.	B
	Digitalis should not be used as the sole agent to control the rate of ventricular response in patients with paroxysmal AF.	B
	Catheter ablation of the AV node should not be attempted without a prior trial of medication to control the ventricular rate in patients with AF.	C
	In patients with decompensated heart failure and AF, intravenous administration of a nondihydropyridine calcium channel antagonist may exacerbate hemodynamic compromise and is not recommended.	C
	Intravenous administration of digitalis glycosides or nondihydropyridine calcium channel antagonists to patients with AF and a preexcitation syndrome may paradoxically accelerate the ventricular response and is not recommended.	C

ACC, American College of Cardiology; *AF,* atrial fibrillation; *AHA,* American Heart Association; *AV,* atrioventricular.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 4 ACC/AHA Recommendations for Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation

Class	Indication	Level of Evidence
Class I (indicated)	Before initiation of antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended.	C
	Catheter ablation by an experienced operator is useful in selected patients with symptomatic paroxysmal AF who have failed treatment with an antiarrhythmic drug and have a normal or mildly dilated left atrium and normal or mildly reduced left ventricular function.	A
Class IIa (reasonable)	Pharmacologic therapy can be useful in patients with AF to maintain sinus rhythm and to prevent tachycardia-induced cardiomyopathy.	C
	Infrequent, well-tolerated recurrence of AF is reasonable as a successful outcome of antiarrhythmic drug therapy.	C
	Outpatient initiation of antiarrhythmic drug therapy is reasonable in patients with AF who have no associated heart disease when the agent is well tolerated.	C
	In patients with lone AF without structural heart disease, initiation of propafenone or flecainide can be beneficial on an outpatient basis in patients with paroxysmal AF who are in sinus rhythm at the time of drug initiation.	B
	Sotalol can be beneficial in outpatients in sinus rhythm with little or no heart disease, prone to paroxysmal AF, if the baseline uncorrected QT interval is shorter than 460 milliseconds, serum electrolyte values are normal, and risk factors associated with class III drug–related proarrhythmia are not present.	C
	Catheter ablation is a reasonable for treatment of symptomatic persistent AF.	A
Class IIb (may be considered)	Catheter ablation may be reasonable for patients with symptomatic paroxysmal AF and significant left atrial dilation or significant left ventricular dysfunction.	A
Class III (not indicated)	Antiarrhythmic therapy with a particular drug is not recommended for maintenance of sinus rhythm in patients with AF who have well-defined risk factors for proarrhythmia with that agent.	A
	Pharmacologic therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or AV node dysfunction unless they have a functioning electronic cardiac pacemaker.	C

ACC, American College of Cardiology; *AF,* atrial fibrillation; *AHA,* American Heart Association.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

- For patients without symptomatic AF, a rate-control strategy with calcium channel blockers, beta-blockers, or digoxin is a reasonable option. The RACE 2 trial indicates that a lenient rate control strategy, with a target resting heart rate of <110 beats/min, is noninferior to a strict control strategy, with a target resting heart rate of <80 beats/min and an exercise heart rate of <110 beats/min. Most recent ACC/AHA guidelines, however, recommend targeting a heart rate <80 beats/min over a target of <110 beats/min.
- In patients with symptomatic AF, younger patients, or those with difficult to control heart rate, an attempt should be made to maintain sinus rhythm with antiarrhythmic agents. Options of antiarrhythmic agents include amiodarone, dronedarone, (paroxysmal atrial fibrillation only without heart failure), dofetilide, flecainide, propafenone (contraindicated with structural heart disease), or sotalol. The decision of which strategy to follow should be best made in consultation with a cardiologist. Use of dronedarone should be avoided in patients with persistent or permanent atrial fibrillation because of worsened cardiovascular outcomes, especially in those with concomitant symptomatic heart failure (see Fig. 4 for a proposed algorithm to guide maintenance of sinus rhythm).

NONPHARMACOLOGIC THERAPY

- Catheter ablation of AF has become a common procedure for symptomatic drug-refractory or drug-intolerant patients. Sinus rhythm can be maintained long term in the majority of patients with paroxysmal atrial fibrillation (PAF) by circumferential pulmonary vein ablation performed in experienced centers. Established centers have reported success rates of 70% to 85% in patients with paroxysmal AF, but up to 50% of patients may require more than one ablation to achieve success. Complication rates are 4.5% in the largest international survey of hospitals performing this procedure. Success with persistent AF is much lower, with long-term success rates of 40% to 50% in many studies, and such patients often require more than one procedure. The most common techniques used to isolate the pulmonary veins are radiofrequency ablation and cryoballoon ablation, which have shown similar results for patients with PAF.
- Pulmonary vein isolation is being increasingly used to treat AF in patients with heart failure. Trials have shown that pulmonary vein isolation is superior to AV node ablation with biventricular pacing in patients with heart failure who have drug-refractory AF.
- AV nodal ablation with permanent pacemaker implantation may become necessary in some patients in whom rate and rhythm are difficult to control despite drugs and cardioversion, although it is generally used as a therapy of last resort.
- The Cox-Maze III surgical procedure, with its modifications creating electrical barriers to the macroreentrant circuits that are believed to underlie AF, is being performed with good results in some medical centers (preservation of sinus rhythm in 70% to 95% of patients without the use of long-term antiarrhythmic medication). Success rates are higher in paroxysmal than in persistent or permanent atrial fibrillation. Surgical ablation is often used for patients undergoing aortic or mitral valve surgery. As a stand-alone procedure, it is a Class IIb recommendation per ACC/AHA Guidelines in 2017. Some centers perform surgical pulmonary vein isolation similar to this procedure using a mini-thoracotomy or video thoracoscopic "Mini-Maze" approach. Another surgical method is a pericardioscopic approach that allows extensive posterior wall ablation and, when combined with catheter ablation in a "hybrid" approach, has shown promising results for patients with persistent AF.
- It is important to understand that ablation therapy will not eliminate the need to take anticoagulant drugs. Even after ablation,

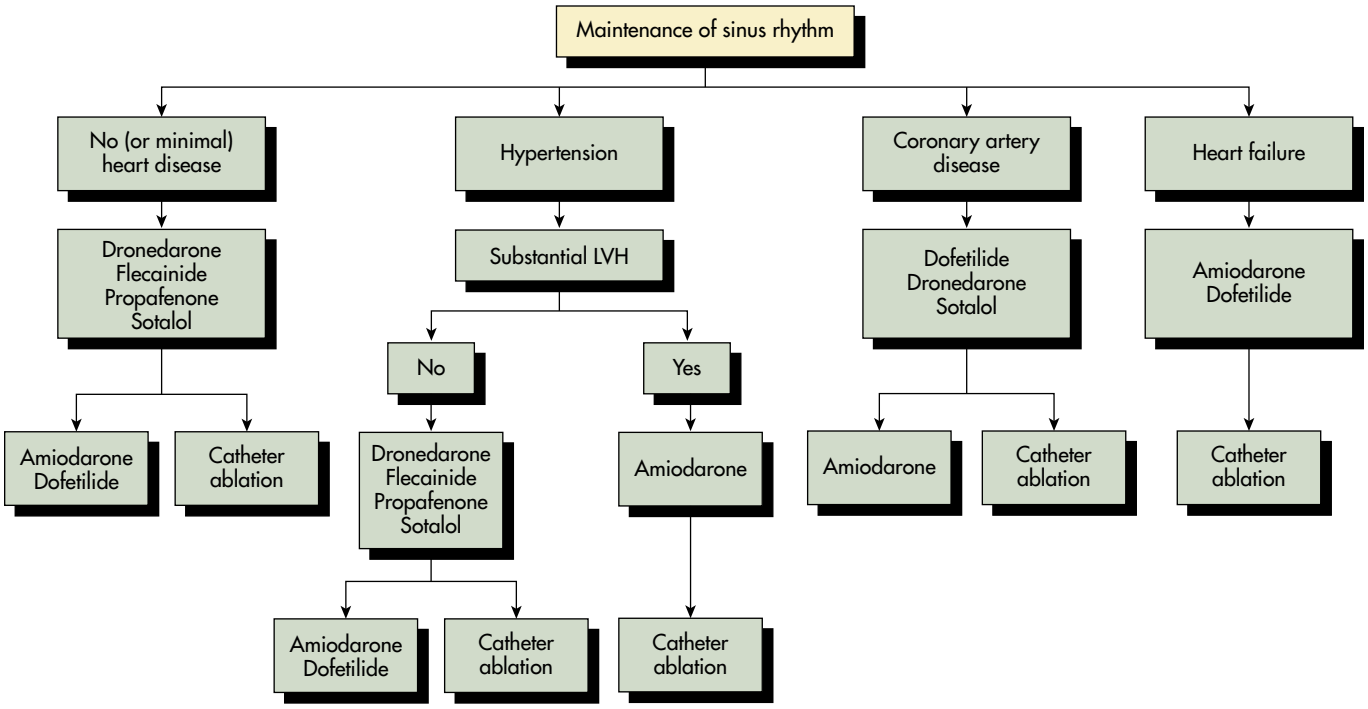

FIG. 4 Therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. Drugs are listed alphabetically and not in order of suggested use. The seriousness of heart disease progresses from left to right, and selection of therapy in patients with multiple conditions depends on the most serious condition present. *LVH,* Left ventricular hypertrophy. (From Wann LS et al: 2011 ACCF/AHA/HRS Focused update on the management of patients with atrial fibrillation [updating the 2006 guideline]: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 57[2]:223-242, 2011.)

patients with AF face increased risk of thromboembolic events and most electrophysiologists suggest lifelong anticoagulation for patients with elevated stroke risk score. Due to the increasing success rate of ablation, catheter-based therapy is considered the first-line treatment for paroxysmal AF patients intolerant or refectory to one medication or IIa for persistent patients in the ACC/AHA AF Ablation Guidelines in 2017. It remains a IIb indication for patients in long-standing persistent atrial fibrillation.

STROKE PREVENTION

- The decision whether to pursue long-term anticoagulation must be made in light of the patient's risk for a cardioembolic event versus risk for a bleeding event. ACC/AHA recommendations for prevention of thromboembolism in atrial fibrillation are summarized in Table 5. In nonvalvular AF, CHA2DS2-VASc has superseded the CHADS2 scoring system (C = congestive heart failure; H = hypertension; A = age [>75 yr is 2 points]; D = diabetes; S = stroke, transient ischemic attack, or thromboembolic disease [2 points]; V = vascular disease, A = age 65-74 yr; and Sc = sex category, with females getting 1 extra point). Patients with a CHA2DS2-VASc score of 0 are considered low risk, 1 to 2 are considered moderate risk, and >2 are considered high risk. Per guidelines, patients with a score of 0 do not merit anticoagulation. Patients with a score of 1 can be treated at the discretion of the physician with either aspirin or an oral anticoagulant (warfarin or a novel oral anticoagulant). Anticoagulation with either warfarin or a novel oral anticoagulant is recommended for all men with a CHADS2-VASc score of 2 or above and women with a CHADS2-VASc score of 3 or above. The available direct-acting oral anticoagulants (DOACs) are recommended over warfarin in DOAC-eligible patients with atrial fibrillation in the new 2019 AHA/ACC/Heart Rhythm Society (HRS) Focused Update of the 2014 AHA/ACC/HRS Guidelines.
- Increasing amounts of evidence now show that aspirin likely does not protect a person from stroke in AF and has recently been dropped from most of the ACC/AHA and European Atrial Fibrillation guidelines. Target INR for patients on warfarin with an indication for anticoagulation is 2 to 3 and should be diligently monitored to avoid risk of stroke versus bleeding. Patients with hypertrophic cardiomyopathy or thyrotoxicosis with AF also have a high risk of stroke and should be anticoagulated irrespective of their CHADS2-VASc score.
- The DOACs include several factor Xa inhibitors (Table 6) and a direct thrombin inhibitor.
  1. Dabigatran is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. In the RE-LY trial of 18,113 patients with mean CHADS2 score of 2.1, dabigatran 110 mg bid was noninferior to warfarin, and 150 mg bid was superior to warfarin in prevention of thromboembolic events. Bleeding risk was similar to that of warfarin for both doses. Idarucizumab has been approved as a dabigatran reversal agent. Onset is immediate, and it provides full reversal for at least 24 hr in most patients.
  2. Factor Xa inhibitors (apixaban, rivaroxaban, edoxaban) are also effective in reducing stroke and systemic embolism in patients with atrial fibrillation. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial in patients at high risk for stroke (mean CHADS2 score 2.1) using apixaban, the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial using rivaroxaban in patients with

TABLE 5 ACC/AHA Recommendations for Prevention of Thromboembolism in Atrial Fibrillation

Class	Indication	Level of Evidence
Class I (indicated)	Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except those with lone AF or contraindications.	A
	The selection of the antithrombotic agent should be based on the absolute risks of stroke and bleeding and the relative risk and benefit for a given patient.	A
	For patients without mechanical heart valves at high risk of stroke, chronic oral anticoagulant therapy with a vitamin K antagonist is recommended in a dose adjusted to achieve the target intensity international normalized ratio (INR) of 2.0-3.0 unless contraindicated. Factors associated with highest risk for stroke in patients with AF are prior thromboembolism (stroke, transient ischemic attack, or systemic embolism) and rheumatic mitral stenosis.	A
	Anticoagulation with a vitamin K antagonist is recommended for patients with more than one moderate risk factor. Such factors include age ≥75 yr, hypertension, heart failure, impaired left ventricular systolic function (ejection fraction ≤35% or fractional shortening <25%), and diabetes mellitus.	A
	INR should be determined at least weekly during initiation of therapy and monthly when anticoagulation is stable.	A
	Dabigatran is a useful alternative to warfarin in patients with AF and risk factors for stroke who do not have a prosthetic heart valve or significant valve disease, a creatinine clearance <15 ml/min, or advanced liver disease.	B
	Aspirin, 81-325 mg daily, is recommended as an alternative to vitamin K antagonists in low-risk patients or in those with contraindications to oral anticoagulation.	A
	For patients with AF who have mechanical heart valves, the target intensity of anticoagulation should be based on the type of prosthesis, maintaining an INR of at least 2.5.	B
	Antithrombotic therapy is recommended for patients with atrial flutter as for those with AF.	C
Class IIa (reasonable)	For primary prevention of thromboembolism in patients with nonvalvular AF who have just one of the following validated risk factors, antithrombotic therapy with either aspirin or a vitamin K antagonist is reasonable, based on an assessment of the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation, and the patient's preferences: Age ≥75 yr (especially in female patients), hypertension, heart failure, impaired left ventricular function, or diabetes mellitus	A
	For patients with nonvalvular AF who have one or more of the following less well-validated risk factors, antithrombotic therapy with either aspirin or a vitamin K antagonist is reasonable for prevention of thromboembolism: Age 65-74 yr, female gender, or coronary artery disease. The choice of agent should be based on the risk of bleeding complications, ability to sustain adjusted chronic anticoagulation, and the patient's preferences.	B
	It is reasonable to select antithrombotic therapy by the same criteria irrespective of the pattern (i.e., paroxysmal, persistent, or permanent) of AF.	B
	In patients with AF who do not have mechanical prosthetic heart valves, it is reasonable to interrupt anticoagulation for up to 1 wk without substituting heparin for surgical or diagnostic procedures that carry a risk of bleeding.	C
	It is reasonable to reevaluate the need for anticoagulation at regular intervals.	C
Class IIb (may be considered)	In patients ≥75 yr at increased risk of bleeding but without frank contraindications to oral anticoagulant therapy, and in other patients with moderate risk factors for thromboembolism who are unable to safely tolerate anticoagulation at the standard intensity of INR 2.0-3.0, a lower INR target of 2.0 (range, 1.6-2.5) may be considered for prevention of ischemic stroke and systemic embolism.	C
	When surgical procedures require interruption of oral anticoagulant therapy for longer than 1 wk in high-risk patients, unfractionated heparin may be administered or low-molecular-weight heparin given by subcutaneous injection, although the efficacy of these alternatives in this situation is uncertain.	C
	After percutaneous coronary intervention or revascularization surgery in patients with AF, low-dose aspirin (<100 mg/day) and/or clopidogrel (75 mg/day) may be given concurrently with anticoagulation to prevent myocardial ischemic events, but these strategies have not been thoroughly evaluated and are associated with an increased risk of bleeding.	C
	In patients undergoing percutaneous coronary intervention, anticoagulation may be interrupted to prevent bleeding at the site of peripheral arterial puncture, but the vitamin K antagonist should be resumed as soon as possible after the procedure and the dose adjusted to achieve an INR in the therapeutic range. Aspirin may be given temporarily during the hiatus, but the maintenance regimen should then consist of the combination of clopidogrel, 75 mg daily, plus warfarin (INR, 2.0-3.0). Clopidogrel should be given for a minimum of 1 mo after implantation of a bare-metal stent, at least 3 mo for a sirolimus-eluting stent, at least 6 mo for a paclitaxel-eluting stent, and 12 mo or longer in selected patients, following which warfarin may be continued as monotherapy in the absence of a subsequent coronary event. When warfarin is given in combination with clopidogrel or low-dose aspirin, the dose intensity must be carefully regulated.	C
	In patients with AF younger than 60 yr without heart disease or risk factors for thromboembolism (lone AF), the risk of thromboembolism is low without treatment, and the effectiveness of aspirin for primary prevention of stroke relative to the risk of bleeding has not been established.	C
	In patients with AF who sustain ischemic stroke or systemic embolism during treatment with low-intensity anticoagulation (INR, 2.0-3.0), rather than add an antiplatelet agent, it may be reasonable to raise the intensity of the anticoagulation to a maximum target INR of 3.0-3.5.	C
	Clopidogrel plus aspirin may be considered in patients who cannot tolerate or who refuse an oral anticoagulant.	B
Class III (not indicated)	Long-term anticoagulation with a vitamin K antagonist is not recommended for primary prevention of stroke in patients younger than 60 yr without heart disease (lone AF) or any risk factors for thromboembolism.	C

ACC, American College of Cardiology; *AF,* atrial fibrillation; *AHA,* American Heart Association.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 6 Comparison of the Features of the Direct Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin (IIa)	Factor Xa	Factor Xa	Factor Xa
Active Drug	No	Yes	Yes	Yes
Onset Time (h)	0.5-2	2-4	3-4	1-3
Half-Life (h)	12-17	5-13	~12	9-11
Renal Excretion (%)	80	33	27	50
Reversal Agent	Idarucizumab 5 g IV bolus	Andexanet alfa or PCC	Andexanet alfa or PCC	Andexanet alfa or PCC

IV, Intravenous; *PCC,* prothrombin complex concentrate.
From Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 7 Bleeding Risk Score

HAS-BLED Risk factors	Score
Hypertension	1
Abnormal liver function	1
Abnormal renal function	1
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (age >65)	1
Drugs	1
Alcohol	1

HAS-BLED is the most validated bleeding score for patients with AF in whom antithrombotic therapy is indicated. When HAS-BLED score ≥3, caution and regular review are appropriate, as well as efforts to correct the potentially reversible risk factors for bleeding.
INRs, International normalized ratio.
From Ronco C et al: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.

CHADS2 score 3.5, and the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation (ENGAGE-AF) trial using edoxaban in patients with a CHADS2 score of at least 2, showed that these anticoagulants reduce the risk of stroke, systemic embolism, and serious bleeding compared with warfarin. Rivaroxaban showed noninferior efficacy to warfarin in prevention of thromboembolism. Apixaban showed superior stroke reduction, reduced bleeding events, and an overall mortality benefit when compared with warfarin. Edoxaban showed noninferiority to warfarin with respect to stroke and systemic embolism prevention, with lower rates of bleeding and death from cardiovascular causes, but benefit was limited to patients with moderately impaired renal function. Rivaroxaban and edoxaban are dosed once a day, and apixaban is dosed twice a day. A factor Xa reversal agent, andexanet alfa, has received FDA approval as a reversal for the anticoagulant effect of these agents.

- The decision to anticoagulate should be made irrespective of whether the atrial fibrillation is paroxysmal, persistent, or permanent.
- For patients in whom anticoagulation with warfarin or other anticoagulants is contraindicated due to high bleeding risk (Table 7), left atrial appendage exclusion is an alternative. Several methods can be used, including the Lariat procedure and the AtriClip, but these are still considered unproven for stroke prevention in AF. The Watchman device is a left atrial appendage occlusion device and is the only device approved by the FDA for stroke prevention specifically for patients with AF that require anticoagulation but have an appropriate reason to seek an alternative. Patients with surgical ligation of the left atrial appendage still have an indication for anticoagulation due to lack of clinical trials showing a stroke risk reduction and inconsistent techniques.
- Perioperative bridging anticoagulation in patients with AF: Current guidelines advise perioperative continuation of warfarin in low-risk patients (CHADS2 score 0 to 2) and bridging anticoagulation only in those at highest risk of thromboembolism (CHADS2 score 5 to 6). The recent Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) Study found that for patients who require procedure-related warfarin interruption, forgoing bridging anticoagulation was noninferior to perioperative bridging with low molecular weight heparin and decrease the risk of major bleeding. Based on this study, a no-bridging strategy is appropriate for lower-risk AF and minor procedures but in high-risk patients having major surgery the answer remains debatable.

PROGNOSIS

- AF is associated with a 1.5- to 1.9-fold higher risk of death, which is in part due to the strong association between AF and thromboembolic events.
- AF is also independently associated with an increased risk of incident myocardial infarction, especially in women and blacks.
- Development of AF predicts heart failure and is associated with a worse New York Heart Association Heart Failure classification. AF may also worsen heart failure in individuals who are dependent on the atrial component of the cardiac output.
- AF in the setting of acute myocardial infarction was associated with a 40% increase in mortality compared to patients in sinus rhythm.
- ACC/AHA recommendations for special considerations in atrial fibrillation are summarized in Table 8.

DISPOSITION

Factors associated with maintenance of sinus rhythm after cardioversion include:
- Left atrium diameter <60 mm
- Absence of mitral valve disease
- Short duration of AF

REFERRAL

Refer to a cardiologist those patients in whom antiarrhythmic therapy or catheter-based/surgical intervention is being considered.

PEARLS & CONSIDERATIONS

COMMENTS

The number of patients anticoagulated in the United States is approximately half the amount that should be anticoagulated for AF, resulting in a large burden of stroke. The exact burden of AF needed to trigger the need for anticoagulation is not known, though recent pacemaker trials have suggested that as little as 6 min confers significant stroke risk. Reversal agents for the new class of anticoagulation are now available: Idarucizumab for reversal of dabigatran; andexanet alfa for reversal of apixaban and rivaroxaban (pending FDA approval).

The American Academy of Family Physicians and the American College of Physicians provide the following recommendations for the management of newly detected AF:
- Rate control with chronic anticoagulation is the recommended strategy for the majority

TABLE 8 ACC/AHA Recommendations for Special Considerations in Atrial Fibrillation

Class	Indication	Level of Evidence
Postoperative Atrial Fibrillation		
Class I (indicated)	Unless contraindicated, treatment with an oral beta-blocker to prevent postoperative AF is recommended for patients undergoing cardiac surgery.	A
	Administration of AV nodal blocking agents is recommended to achieve rate control in patients who develop postoperative AF.	B
Class IIa (reasonable)	Preoperative administration of amiodarone reduces the incidence of AF in patients undergoing cardiac surgery and represents appropriate prophylactic therapy for patients at high risk for postoperative AF.	A
	It is reasonable to restore sinus rhythm by pharmacologic cardioversion with ibutilide or direct-current cardioversion in patients who develop postoperative AF, as advised for nonsurgical patients.	B
	It is reasonable to administer antiarrhythmic medications in an attempt to maintain sinus rhythm in patients with recurrent or refractory postoperative AF, as recommended for other patients who develop AF.	B
	It is reasonable to administer antithrombotic medication in patients who develop postoperative AF, as recommended for nonsurgical patients.	B
Class IIb (may be considered)	Prophylactic administration of sotalol may be considered for patients at risk for development of AF after cardiac surgery.	B
Acute Myocardial Infarction		
Class I (indicated)	Direct-current cardioversion is recommended for patients with severe hemodynamic compromise or intractable ischemia, or when adequate rate control cannot be achieved with pharmacologic agents in patients with acute myocardial infarction and AF.	C
	Intravenous administration of amiodarone is recommended to slow a rapid ventricular response to AF and to improve left ventricular function in patients with acute myocardial infarction.	C
	Intravenous beta-blockers and nondihydropyridine calcium antagonists are recommended to slow a rapid ventricular response to AF in patients with acute myocardial infarction who do not display clinical left ventricular dysfunction, bronchospasm, or AV block.	C
	For patients with AF and acute myocardial infarction, administration of unfractionated heparin by either continuous intravenous infusion or intermittent subcutaneous injection is recommended in a dose sufficient to prolong the activated partial thromboplastin time to 1.5-2× the control value, unless contraindications to anticoagulation exist.	C
Class IIa (reasonable)	Intravenous administration of digitalis is reasonable to slow a rapid ventricular response and to improve left ventricular function in patients with acute myocardial infarction and AF associated with severe left ventricular dysfunction and heart failure.	C
Class III (not indicated)	The administration of class IC antiarrhythmic drugs is not recommended in patients with AF in the setting of acute myocardial infarction.	C
Management of Atrial Fibrillation Associated with Wolff-Parkinson-White (WPW) Preexcitation Syndrome		
Class I (indicated)	Catheter ablation of the accessory pathway is recommended for symptomatic patients with AF who have WPW syndrome, particularly those with syncope due to rapid heart rate or those with a short bypass tract refractory period.	B
	Immediate direct-current cardioversion is recommended to prevent ventricular fibrillation in patients with a short anterograde bypass tract refractory period in whom AF occurs with a rapid ventricular response associated with hemodynamic instability.	B
	Intravenous procainamide or ibutilide is recommended to restore sinus rhythm in patients with WPW in whom AF occurs without hemodynamic instability in association with a wide QRS complex on the electrocardiogram (≥120-msec duration) or with a rapid preexcited ventricular response.	C
Class IIa (reasonable)	Intravenous flecainide or direct-current cardioversion is reasonable when very rapid ventricular rates occur in patients with AF involving conduction over an accessory pathway.	B
Class IIb (may be considered)	It may be reasonable to administer intravenous quinidine, procainamide, disopyramide, ibutilide, or amiodarone to hemodynamically stable patients with AF involving conduction over an accessory pathway.	B
Class III (not indicated)	Intravenous administration of digitalis glycosides or nondihydropyridine calcium channel antagonists is not recommended in patients with WPW syndrome who have preexcited ventricular activation during AF.	B
Hyperthyroidism		
Class I (indicated)	Administration of a beta-blocker is recommended to control the rate of ventricular response in patients with AF complicating thyrotoxicosis, unless contraindicated.	B
	In circumstances when a beta-blocker cannot be used, administration of a nondihydropyridine calcium channel antagonist (diltiazem or verapamil) is recommended to control the ventricular rate in patients with AF and thyrotoxicosis.	B
	In patients with AF associated with thyrotoxicosis, oral anticoagulation (INR, 2.0-3.0) is recommended to prevent thromboembolism, as recommended for AF patients with other risk factors for stroke.	C
	Once a euthyroid state is restored, recommendations for antithrombotic prophylaxis are the same as for patients without hyperthyroidism.	C

TABLE 8 ACC/AHA Recommendations for Special Considerations in Atrial Fibrillation—cont'd

Class	Indication	Level of Evidence
Management of Atrial Fibrillation during Pregnancy		
Class I (indicated)	Digoxin, a beta-blocker, or a nondihydropyridine calcium channel antagonist is recommended to control the rate of ventricular response in pregnant patients with AF.	C
	Direct-current cardioversion is recommended in pregnant patients who become hemodynamically unstable because of AF.	C
	Protection against thromboembolism is recommended throughout pregnancy for all patients with AF (except those with lone AF and/or low thromboembolic risk). Therapy (anticoagulant or aspirin) should be chosen according to the stage of pregnancy.	C
Class IIb (may be considered)	Administration of heparin may be considered during the first trimester and last month of pregnancy for patients with AF and risk factors for thromboembolism. Unfractionated heparin may be administered either by continuous intravenous infusion in a dose sufficient to prolong the activated partial thromboplastin time to 1.5-2× the control value or by intermittent subcutaneous injection in a dose of 10,000-20,000 units every 12 hr, adjusted to prolong the midinterval (6 hr after injection) activated partial thromboplastin time to 1.5× control.	B
	Despite the limited data available, subcutaneous administration of low-molecular-weight heparin may be considered during the first trimester and last month of pregnancy for patients with AF and risk factors for thromboembolism.	C
	Administration of an oral anticoagulant may be considered during the second trimester for pregnant patients with AF at high thromboembolic risk.	C
	Administration of quinidine or procainamide may be considered to achieve pharmacologic cardioversion in hemodynamically stable patients who develop AF during pregnancy.	C
Management of Atrial Fibrillation in Patients with Hypertrophic Cardiomyopathy (HCM)		
Class I (indicated)	Oral anticoagulation (INR, 2.0-3.0) is recommended in patients with HCM who develop AF, as for other patients at high risk of thromboembolism.	B
Class IIa (may be considered)	Antiarrhythmic medications can be useful to prevent recurrent AF in patients with HCM. Available data are insufficient to recommend one agent over another in this situation, but (a) disopyramide combined with a beta-blocker or nondihydropyridine calcium channel antagonist or (b) amiodarone alone is generally preferred.	C
Management of Atrial Fibrillation in Patients with Pulmonary Disease		
Class I (indicated)	Correction of hypoxemia and acidosis is the recommended primary therapeutic measure for patients who develop AF during an acute pulmonary illness or exacerbation of chronic pulmonary disease.	C
	A nondihydropyridine calcium channel antagonist (diltiazem or verapamil) is recommended to control the ventricular rate in patients with obstructive pulmonary disease who develop AF.	C
	Direct-current cardioversion should be attempted in patients with pulmonary disease who become hemodynamically unstable as a consequence of AF.	C
Class III (not indicated)	Theophylline and beta-adrenergic agonist agents are not recommended for patients with bronchospastic lung disease who develop AF.	C
	Beta-blockers, sotalol, propafenone, and adenosine are not recommended in patients with obstructive lung disease who develop AF.	C

ACC, American College of Cardiology; *AF,* atrial fibrillation; *AHA,* American Heart Association; *AV,* atrioventricular; *INR,* international normalized ratio.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

of asymptomatic patients with chronic AF. Rhythm control has not been shown to be superior to rate control (with chronic anticoagulation) in reducing morbidity and mortality, and may be inferior in some patient subgroups to rate control. Rhythm control is appropriate when based on other special considerations, such as patient symptoms, exercise tolerance, and patient preference.

- Patients with AF should receive chronic anticoagulation, unless they are at low risk for stroke as stated earlier or have specific contraindications.
- For patients with AF, the following drugs are recommended for their demonstrated efficacy in rate control during exercise and while at rest: Atenolol, metoprolol, diltiazem, and verapamil (drugs listed alphabetically by class). Digoxin is effective only for rate control at rest and, therefore, should be used only as a second-line agent for rate control in AF.
- For patients who elect to undergo acute cardioversion to achieve sinus rhythm in AF, both direct-current cardioversion and pharmacologic conversion are appropriate options in an otherwise healthy patient.
- Both transesophageal echocardiography with short-term prior anticoagulation followed by early acute cardioversion (in absence of intracardiac thrombus) with postcardioversion anticoagulation vs. delayed cardioversion with preanticoagulation and postanticoagulation are appropriate management strategies for patients who elect to undergo cardioversion.
- Among patients with paroxysmal AF without previous antiarrhythmic drug treatment, ablation compared with antiarrhythmic drugs resulted in a lower rate of recurrent atrial tachyarrhythmias at 2 yr. However, recurrence was frequent in both groups.
- Among patients with atrial fibrillation who undergo packed cell volume, the risk of bleeding is lower among those who receive dual therapy with dabigatran and a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) than among those who receive triple therapy with warfarin, a $P2Y_{12}$ inhibitor, and aspirin. Dual therapy has been shown to be noninferior to triple therapy with respect to the risk of thromboembolic events.[1]
- In patients with atrial fibrillation and stable coronary artery disease, rivaroxaban

[1]Cannon CP et al: Dual antithrombotic therapy with dabigatran after PCV in atrial fibrillation, *N Engl J Med* 377:1513-1524, 2017.

monotherapy is noninferior to combination therapy with rivaroxaban plus a single antiplatelet agent for efficacy and superior for safety.[2]

- In patients presenting to the ED with recent-onset, symptomatic atrial fibrillation, a wait-and-see approach is noninferior to early cardioversion in achieving a return to sinus rhythm at 4 weeks.[3]

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Atrial Fibrillation (Patient Information)

AUTHOR: **Tania B. Babar, MD**

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Atrial Flutter PTG

BASIC INFORMATION

DEFINITION

Typical atrial flutter is the term commonly applied to the atrial macroreentrant circuit that circulates around the tricuspid annulus in the right atrium. The critical isthmus of the circuit is the tissue between the inferior vena cava and the tricuspid annulus, and a more precise name for this arrhythmia is *cavotricuspid isthmus-dependent atrial flutter*, or CTI flutter. Because of its anatomic and physiologic stability, the result is regular atrial depolarizations, typically at a rate of 250 to 350 beats/min. Regular, macroreentrant atrial arrhythmias at this rate that do not use the CTI are referred to as *atypical atrial flutter*. Because of the circuit's stability, conduction through the atrioventricular node (AVN) is often predictable at a common mathematical denominator. For example, when the flutter rate is 300 beats/min, 2:1 conduction results in a ventricular rate of 150 beats/min. By extension, 3:1 conduction results in a ventricular rate of 100 beats/min, 4:1 in a rate of 75 beats/min, and 5:1 in a rate of 60 beats/min. If the regular atrial impulses conduct at a variable rate through the AVN, the result may be an irregular QRS pattern. Table E1 summarizes the different types of atrial flutter and distinguishing features on scalar electrocardiography.

ICD-10CM CODES

I48.3	Typical atrial flutter
I48.4	Atypical atrial flutter
I48.92	Unspecified atrial flutter

EPIDEMIOLOGY & DEMOGRAPHICS

- Atrial flutter is the second most common atrial tachyarrhythmia after atrial fibrillation, with an estimated 200,000 new cases annually in the U.S.
- Atrial flutter is common in patients with congestive heart failure, chronic obstructive pulmonary disease (COPD), or during the first wk after open heart surgery.
- Atrial flutter occurs more frequently with advancing age (5/10,0000 age <50 vs. 587/100,000 age >80 yr) and 2.5 times more frequently in men than in women.
- Patients taking antiarrhythmics for chronic suppression of atrial fibrillation may convert to atrial flutter.
- Atrial flutter is typically seen in patients with underlying structural heart disease and is uncommon in children or young adults.
- More than 50% of patients with atrial flutter will develop atrial fibrillation in 3 yr, and more than 80% will develop atrial fibrillation within 5 yr. This is important when considering treatment options for atrial flutter and future considerations around anticoagulation.

CLASSIFICATION

Historically, the Wells classification designated atrial flutter as type I and type II. However, it is now recognized that tachycardias satisfying either of the definitions for type I or type II can be caused by reentrant circuits or by rapid focal atrial tachycardia, and this classification is infrequently used. Designating atrial flutter based on whether or not it is CTI dependent is more useful because of the management (i.e., ablation) options. Type I CTI-dependent atrial flutter, also known as common atrial flutter or typical atrial flutter, has an atrial rate of 240 to 350 beats/min. The reentrant loop circles the right atrium, passing through the CTI, a body of fibrous tissue in the lower atrium between the inferior vena cava and the tricuspid valve. CTI flutter can revolve around the tricuspid annulus in either direction (counterclockwise or clockwise) when viewing the tricuspid annulus *en face*.

- Counterclockwise atrial flutter is the more common type (~75%). The flutter waves are "sawtooth" and negative on the surface ECG leads II, III, and aVF; positive in V1; and negative in V6. (Fig. 1)
- Clockwise atrial flutter is less common (~25%): The reentry loop cycles in the opposite direction; thus, the flutter waves are upright in leads II, III, and aVF; negative in V1; and positive in V6. (Fig. 2)

Atypical atrial flutter is defined by absence of CTI dependence and may occur in patients with prior cardiac surgery, congenital heart disease, or prior radiofrequency ablation (especially left atrial ablation for atrial fibrillation) or may be idiopathic. One ECG feature is the lack of discordance between the inferior leads (leads II, III, and aVF) and V1. Flutter circuits in the left atrium often have upright flutter waves in all precordial leads.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Palpitations
- Dizziness, lightheadedness, syncope, or near syncope
- Angina
- Congestive heart failure
- Embolic phenomena from intracardiac thrombus

ETIOLOGY

- Age-related degenerative changes
- Rheumatic heart disease
- Congenital heart disease
- Left ventricular dysfunction or congestive heart failure
- Acute myocardial infarction (rarely)
- Thyrotoxicosis
- Pulmonary embolism
- Mitral valve disease
- Cardiac surgery
- Chronic obstructive pulmonary disease
- Obesity
- Pericarditis
- Pulmonary hypertension
- Antiarrhythmic therapy use in patients with atrial fibrillation

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Atrial fibrillation
- Atrial tachycardia
- Supraventricular tachycardia:
  1. Atrioventricular node reentry
  2. Orthodromic reciprocating tachycardia (using a concealed bypass tract)
  3. Junctional ectopic tachycardia
  4. Wolff-Parkinson-White syndrome
- Sinus tachycardia

WORKUP

- ECG
- Laboratory evaluation
- Assessment of CHA_2DS_2-VaSc score

LABORATORY TESTS

- Thyroid function studies
- Serum electrolytes, including renal and hepatic tests (anticipating antiarrhythmic therapy use)

IMAGING STUDIES

- ECG:
  1. Absence of P waves
  2. Regular, "sawtooth," or "F" (flutter) wave pattern without an isoelectric baseline in leads II, III, and aVF (seen most commonly with counterclockwise typical CTI-flutter)
  3. There is rarely 1:1 atrioventricular (AV) conduction in atrial flutter (unless preexcitation is present). Rather, AV conduction is usually in a 2:1 (Fig. 1), 3:1, or 4:1 fashion, with corresponding usual ventricular rates of 150, 100, or 75 beats/min, respectively (assuming an atrial rate of 300 beats/min). With high vagal tone or AV block, ventricular rates may be slow in atrial flutter.
- Echocardiography (for new diagnoses) to evaluate for structural heart disease (ventricular size, thickness, and function; atrial size, and valve function).
- Transesophageal echocardiography: Consider in patients with associated structural or functional heart disease to ascertain the presence of intracardiac thrombi, in the absence of an appropriate duration of anticoagulation.
- Holter monitoring or event recorder to assess for paroxysmal atrial flutter or rate control or to identify the arrhythmia if symptoms are nonspecific or to identify triggering events.
- Electrophysiologic studies: Required for a precise diagnosis, for mapping pathway, and for ablation.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Vagal maneuvers (e.g., the Valsalva maneuver or carotid sinus massage) may transiently slow the ventricular rate (by increasing AV block) and may make flutter waves more

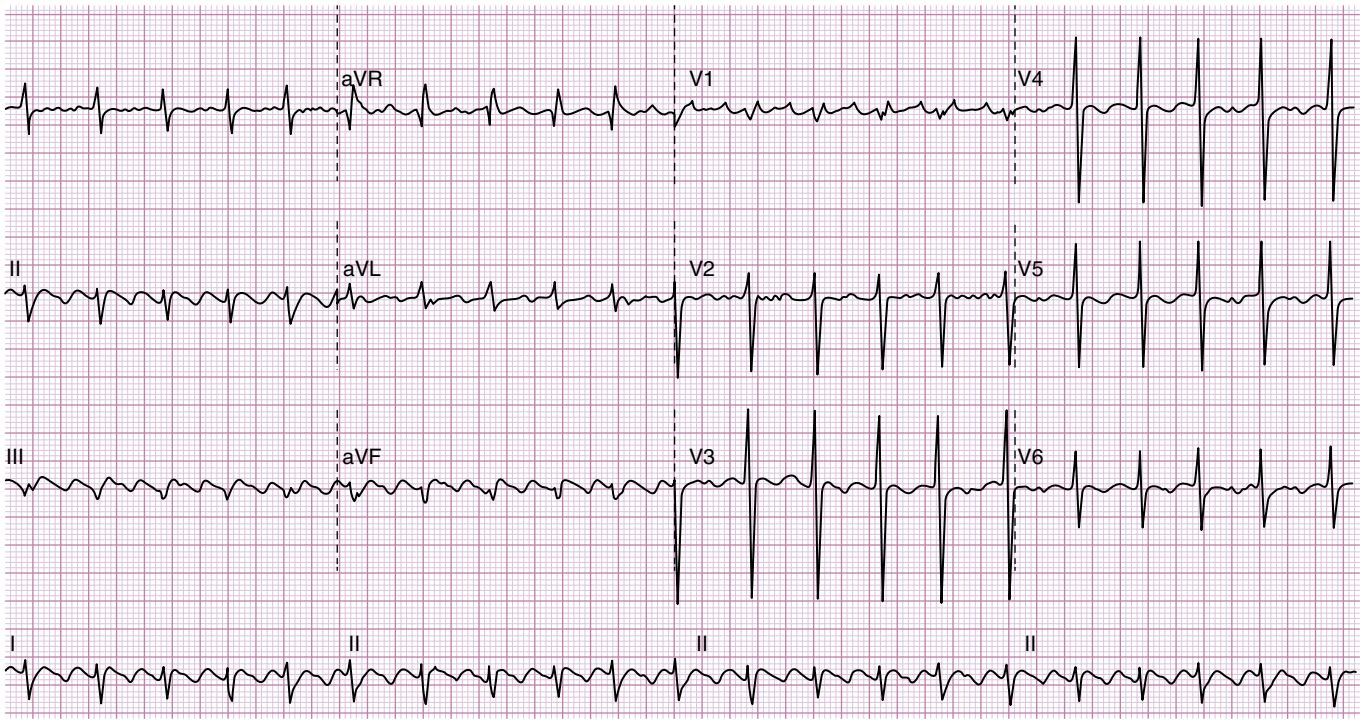


FIG. 1 Counterclockwise atrial flutter with 2:1 atrioventricular conduction. Note the negative flutter waves in leads II, III, and F, positive in V1 and negative in V6. The second flutter wave can be seen overlying the QRS in the inferior leads and at the end of the QRS in lead V1. *aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right.

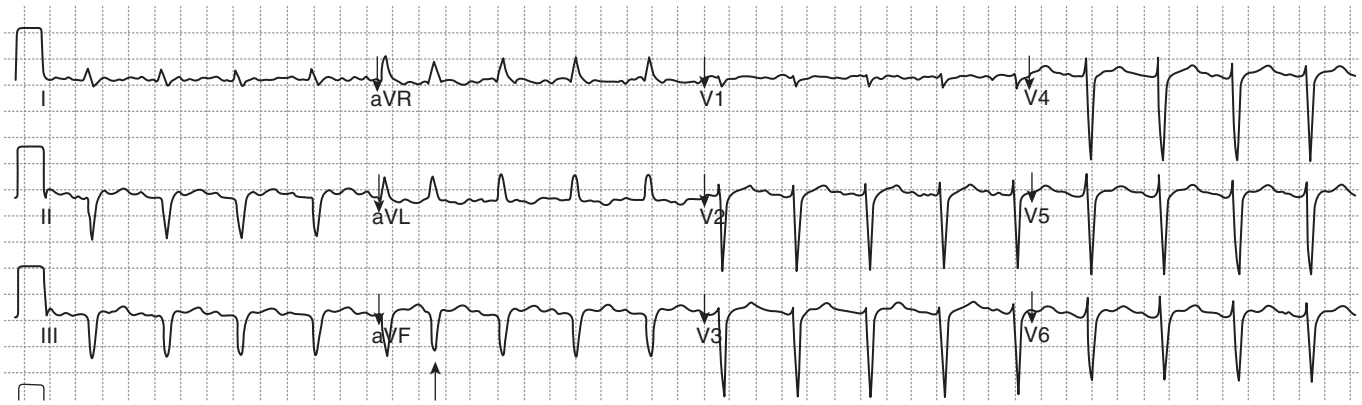


FIG. 2 Clockwise atrial flutter with predominant 2:1 atrioventricular conduction. Note the positive flutter waves in leads II, III, and F, negative in V1 and positive in V6. The overall ventricular rate is slower than in Fig. 1 due to a slow flutter rate of approximately 200 bpm. One beat is conducted 1:1 *(arrow). aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right.

evident. Adenosine may be similarly helpful for diagnostic purposes, allowing the unmasking of the atrial rhythm in the absence of ventricular activity. Maneuvers that affect AV conduction are unlikely to terminate atrial flutter.

- Direct current cardioversion is the treatment of choice for acute management of atrial flutter associated with hemodynamic instability or debilitating symptoms such as angina, congestive heart failure, or hypotension. Electrical cardioversion may be successful with energies as low as 25 joules, but because 100 joules is virtually always successful, this may be a reasonable initial shock strength. If the electrical shock results in atrial fibrillation, a second shock at a higher energy level is used to restore normal sinus rhythm. Sedation of a conscious patient is highly recommended before cardioversion is performed. Patients should be therapeutically anticoagulated for at least a mo or longer depending on their stroke risk (CHA_2DS_2-VASc score; Table 2).
- Overdrive pacing in the atrium may also terminate atrial flutter. This method is especially useful in patients who have recently undergone cardiac surgery and still have temporary atrial pacing wires and in patients who have an implanted pacemaker or defibrillator with an atrial lead.
- Radiofrequency ablation to interrupt the atrial flutter is highly effective for patients with chronic or recurring atrial flutter and is generally considered first-line therapy in those with recurrent episodes of atrial flutter and may be offered for a first-ever episode of atrial flutter. It has been shown to improve health-related quality of life. Despite successful ablation of atrial flutter, however, the risk of future atrial fibrillation remains.

ACUTE Rx

- Treatment choices are based on clinical circumstances. Fig. 3 describes an acute treatment of atrial flutter algorithm. Table 3 summarizes atrial flutter therapy.
- If the patient is unstable, proceed directly to electrical cardioversion.
- In the hemodynamically stable patient, proceed with rate control or rhythm control strategy.
- AV blocking agents such as calcium channel blockers, beta-blockers, and digitalis (second-line treatment) may all be used for rate control. Atrial flutter may spontaneously convert to normal sinus rhythm with this strategy.
- In general, atrial flutter is more difficult to rate-control than atrial fibrillation.
- The rate of recurrence of atrial flutter with cardioversion alone is difficult to determine because most published data combine atrial flutter with atrial fibrillation. However, the recurrence rate is substantial, perhaps 50% at 1 yr.
- Intravenous ibutilide is a first-line medication for pharmacologic cardioversion of atrial flutter in patients with normal systolic function and QT intervals. The success rate is approximately 60%, and it is more effective than procainamide, sotalol, or amiodarone.

CHRONIC Rx

- Few data exist to decide on the choice of rate control versus rhythm control in patients with atrial flutter. However, rate control may be difficult in atrial flutter, and ablation success exceeds 90%. Although ablation results in more durable freedom from atrial flutter recurrence, there are several pharmacologic options to help maintain sinus rhythm after cardioversion of atrial flutter, such as dofetilide, amiodarone, flecainide, propafenone, or sotalol. The choice of antiarrhythmic therapy is, in part, dictated by the presence or absence of underlying structural heart disease.
- Elective outpatient cardioversion or ablation can be performed either immediately preceded by transesophageal echocardiography (TEE) to evaluate the left atrium and the left atrial appendage for thrombus or after a period of at least 3 wk of documented therapeutic anticoagulation before cardioversion. At least 4 wk of anticoagulation should be administered after cardioversion, if not longer, depending on the overall thromboembolic risk of the patient as determined by the CHA_2DS_2-VASc score.

DISPOSITION

More than 85% of patients convert to regular sinus rhythm after cardioversion. Ablation success rates exceed 90%.

REFERRAL

Refer patients who are considered for rhythm control of atrial flutter to cardiologists, especially patients who are candidates for radiofrequency ablation.

TABLE 2 CHA_2DS_2-VASc Risk Score for Prediction of Stroke Risk in Atrial Fibrillation

Risk Factor	Points
CHF/LV dysfunction	1
Hypertension	1
Age ≥75 yr	2
Diabetes mellitus	1
Stroke/TIA/embolism	2
Vascular disease	1
Age 64-74 yr	1
Sex category (female)	1
Maximum score	9

CHF, congestive heart failure; *LV,* left ventricular; *TIA,* transient ischemic attack.

PEARLS & CONSIDERATIONS

COMMENTS

- The surface ECG is the best tool for recognizing atrial flutter and distinguishing atrial flutter from atrial fibrillation.
- Ablation for typical atrial flutter is highly effective, straightforward, and relatively safe. It should be considered for patients with recurrent episodes and even for a first-ever episode.

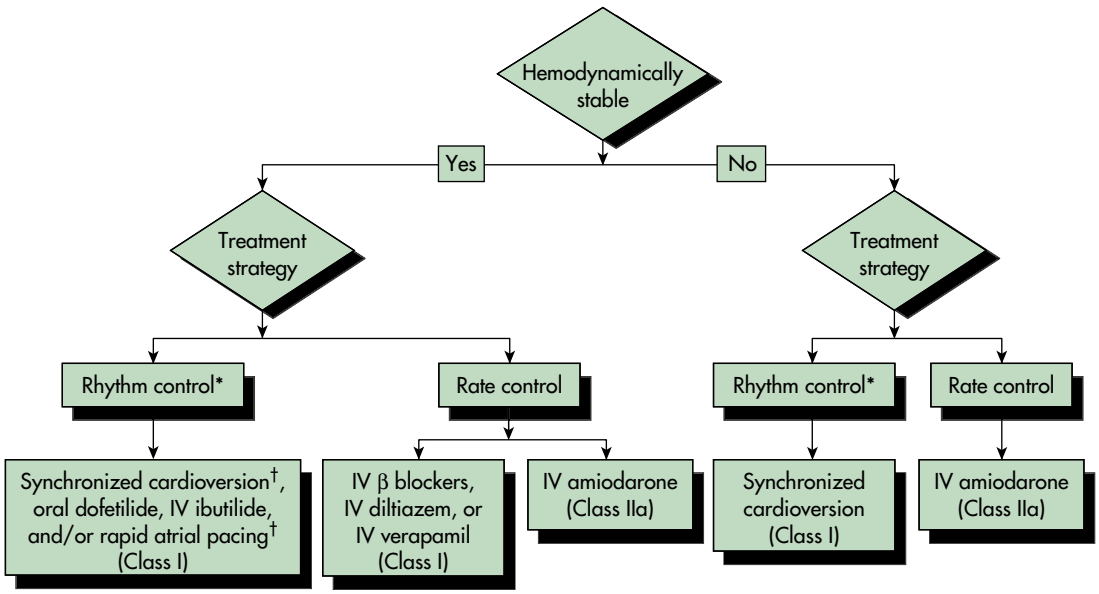


FIG. 3 Acute treatment of atrial flutter. *Anticoagulation as per guideline is mandatory. †For rhythms that break or recur spontaneously, synchronized cardioversion, or rapid atrial pacing is not appropriate. *IV,* Intravenous. (Reproduced with permission from Page RL et al: 2015 ACC/AHA/HRS Guideline for the management of adult patients with supraventricular tachycardia, *JACC* 67(13):e27-e115, 2016. In Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

TABLE 3 Atrial Flutter Therapy

Acute therapy for poorly tolerated AFL or continuous rapid ventricular rate	• If prolonged (i.e., >48 to 72 hr), anticoagulation with heparin followed by therapeutic warfarin or NOAC as cardioversion may be associated with thromboembolic risk. Anticoagulation guidelines for cardioversion are the same as for atrial fibrillation and may indicate need for a TEE for prolonged episodes. Adenosine and carotid massage can be used to help to diagnose AFL masquerading as sinus rhythm. • **First line:** DCC under anesthesia with anticoagulation as necessary. Consider the length of the episode. • **Second line:** Ibutilide or procainamide may be attempted for conversion prior to DCC attempts. Ibutilide may be 70% effective if AFL has been present for <48 hr, although often this is not known with certainty. Procainamide may help maintain sinus rhythm. • **Alternate:** Rapid atrial pacing (esophageal, epicardial, or endocardial, depending on the situation). To pace terminate, pace for 10 to 15 s at a rate of 10% to 20% faster than rate of flutter. If ineffective, burst pace 10 bpm faster at a time for 10 to 15 s at a time until conversion to AF or sinus rhythm. Adding procainamide may help pace termination efficacy; however, it may speed AV conduction if the ventricular response is not adequately controlled with AV nodal blocker drugs (see Chronic prevention, later); 20% to 30% will pace to AF and 10% to 20% will have no effect from pacing, depending on patient selection for the procedure. When AF occurs, it is usually short lived and terminates spontaneously within 24 hr. If persistent, DCC can be attempted with or without antiarrhythmic drugs. Rapid AFL (atrial rate >350) and atrial fib/flutter usually cannot be pace terminated. However, slower AFL (rate <350) of any flutter wave morphology can often be pace terminated. • Oral drug loading alone to terminate AFL is rarely useful. • If recurrent episodes, use class IC or III antiarrhythmic drugs until steady state is achieved, then attempt cardioversion. These drugs (particularly 1C drugs) may stabilize the flutter circuit. It may also create another form of AFL—"IC" AFL—from AF. Ablation remains first-line therapy, especially if AFL is isthmus dependent. • Consider ablation for all persistent, refractory, or symptomatic AFL. However, despite AFL ablation, AF may occur, especially in individuals with underlying structural heart disease. • AV nodal ablation, although not preferable, could be considered when ventricular rate control cannot be achieved and flutter cannot be ablated, or if symptomatic, refractory, and/or if associated with tachycardia-induced cardiomyopathy. This option may be considered in cases where individuals have multiple forms of nonablatable AFL or AF and especially for those who do have non–isthmus-dependent AFL.
Chronic prevention	• If structural heart disease without CHF: sotalol (initiate in the hospital), dofetilide, amiodarone. • If structural heart disease with CHF: amiodarone, dofetilide. • If no structural heart disease: propafenone, flecainide, sotalol, dofetilide, or amiodarone, but propafenone or flecainide may need concomitant AV nodal blocking drugs to prevent 1:1 conduction. • If class I or III drugs are used, first control the ventricular response rate with an AV nodal blocking drug. Otherwise, the vagolytic effects of class IA drugs can enhance AV nodal conduction, and both 1A and 1C drugs can lead to AFL with 1:1 AV conduction. • Drug therapy alone for pure AFL flutter is usually not effective. • Consider radiofrequency catheter ablation early; it has become first-line therapy.
Nonresponders with severe symptoms	• If type I AFL, radiofrequency ablation of the right atrial isthmus. • Atypical AFL is more difficult to ablate and depends on the location of reentrant circuit. Success rates are lower than that for typical AFL. It is more difficult when there is congenital heart disease, valve disease, or prior surgery in which significant areas of scar are present. • Ventricular rate control, antiarrhythmic drugs, or AV node ablation (less preferable) can be performed for atypical, nonablatable AFL. • If AV node ablation and pacing is performed and AFL is intermittent, mode-switching function should be programmed "ON."
MI	• If hemodynamic intolerance or ongoing refractory myocardial ischemia, emergent cardioversion. AFL may increase MVO_2 due to rapid ventricular rate, causing further ischemia, diastolic dysfunction, and pulmonary congestion and edema. • If recurrent, IV amiodarone or procainamide. • Consider temporary antitachycardia pacing if recurrent and poorly tolerated.
Preoperative	• For cardiac surgery, convert AFL to NSR if adequate anticoagulation has been achieved, or ensure that ventricular response is well controlled. • If surgery is elective and AFL is chronic, antiarrhythmic drugs or catheter ablation may be considered. However, anticoagulation should be continued at least 3 wk after conversion of longer-term (>48 hr) AFL prior to elective surgery. • For more urgent surgery in which anticoagulation cannot be used, consider rate control without cardioversion. • For short-duration (<48 hr) AFL, DCC can be performed (may consider heparin prior to DCC with surgical consultation as to risk).
Postoperative	• AFL occurs in 10%-20% of all patients after cardiac surgery; it typically occurs with AF. Incidence peaks at days 2-3. It is more common in older patients. It rarely occurs after other types of surgery. The AFL may resolve spontaneously; however, the rhythm can increase the length of hospital stay, exacerbate heart failure, slow the recovery process, and cause symptoms. • Control rate with β-adrenergic blocker if no CHF or bronchospastic disease and good LVEF (>40%). Diltiazem is often successful as a second-line drug, but use with caution in patients with poor LVEF. Digoxin for rate control is less effective but may be considered, particularly in patients with poor LV function. • IV amiodarone may be useful for persistent and poorly tolerated AFL; amiodarone or other antiarrhythmic drugs may be helpful for recurrent episodes. • DCC or atrial pace termination (if atrial pacing leads are present) is often successful, especially when employed early after the AFL onset. • Discontinue inotropic drugs, if possible.

AF, Atrial fibrillation; *AFL,* atrial flutter; *AV,* atrioventricular; *CHF,* congestive heart failure; *DCC,* direct current cardioversion; *IV,* intravenous; *LV,* left ventricle; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction; *MVO_2,* myocardial oxygen consumption; *NOAC,* non–vitamin K oral anticoagulants; *NSR,* normal sinus rhythm; *TEE,* transesophageal echocardiography.

From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.

- Patients with atrial flutter carry a significant risk for subsequent development of atrial fibrillation.
- Anticoagulation should be considered for all patients whose CHA_2DS_2-VaSc score is ≥2. Anticoagulation is generally not recommended in patients with a CHA_2DS_2-VaSc score of zero. For patients with a CHA_2DS_2-VaSc score of 1, low-dose aspirin or oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) are appropriate options.
- Although anticoagulation recommendations for atrial flutter are identical to those for atrial fibrillation, studies suggest that the absolute risk of stroke is lower from atrial flutter than from fibrillation.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Atrial Flutter (Patient Information)
Atrial Fibrillation (Related Key Topic)

AUTHOR: **Daniel R. Frisch, MD**

TABLE E1 Characteristics of Different Types of Atrial Flutter and Distinguishing Features on Scalar Electrocardiography

Type	Reentrant Circuit	ECG Pattern	Lead V1/V6
Typical counterclockwise	Tricuspid annulus dependent on the CTI	Sawtooth flutter wave; negative in II, III, and aVF	Positive V1 Negative V6
Typical clockwise	Tricuspid annulus dependent on the CTI	"Inverse sawtooth"; positive and often notched in II, III, and aVF	Broad and negative in V1 (often notched) Positive in V6
Lower loop reentry	CTI	Usually similar to typical counterclockwise CTI flutter except subtle loss of terminal positive deflection in leads II, III, and aVF	Usually similar to typical counterclockwise
Upper loop reentry	Superior vena cava and upper crista terminalis	Similar to typical clockwise flutter	Similar to typical clockwise flutter
Right atrial free wall	Around areas of scar in lateral or posterior right atrium (caused by previous atrial surgery or spontaneously)	Variable	Typically negative or biphasic with terminal negative deflection in V1
Septal atrial flutter	Atrial septum, typically after previous surgery	Variable	Usually biphasic or isoelectric in V1
Mitral annular flutter	Around mitral annulus, often slow zone of block around PV interval; frequently occurs in setting of left atrial surgery or ablation	Variable; I, III, and aVF, often positive but low amplitude	Usually positive in V1 (or rarely isoelectric) and often broad
Postatrial fibrillation ablation/maze flutter	Variable; circuit involves previous ablations or scar in left atrium	Variable	Variable

aVF, Augmented vector foot; *CTI,* cavotricuspid isthmus.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

SUGGESTED READING

AHA/ACC/HRS 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: 2016 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society, *J Am Coll Cardiol* 36:2242-2246, 2016.

BASIC INFORMATION

DEFINITION

Atrial myxoma is a benign neoplasm of mesenchymal origin and is the most common primary tumor of the heart.

SYNONYM

Cardiac myxoma

ICD-10CM CODE
D15.1 Benign neoplasm of heart

EPIDEMIOLOGY & DEMOGRAPHICS

- Primary cardiac tumors are extremely rare, with an autopsy frequency of 0.001% to 0.3%. The most frequent cardiac tumors are metastases, occurring 30 times more frequently than primary tumors.
- Myxomas are the most common primary cardiac tumors, accounting for 30% to 50% of all benign neoplasms of the heart.
- 65% of cardiac myxomas occur in females. 4.5% to 10% of cardiac myxomas are familial (Carney syndrome).
- Median age of incidence is 49 yr but can occur at any age.
- Average age of incidence of familial cases is 25 yr.
- Most arise in the left atrium (75%), but myxomas can also be found in the right atrium (18%), right ventricle (4%), and left ventricle (3%). They are usually pedunculated and attached to the intraatrial septum (Fig. E1).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with atrial myxomas, when symptomatic, characteristically present in one of three ways:

1. Atrioventricular valve obstruction (e.g., mitral or tricuspid valve): May present with dyspnea, orthopnea, paroxysmal nocturnal dyspnea, wheezing, edema, dizziness, syncope, chest pain, atrial fibrillation, and sudden death (rare). A marked change in the severity of any symptom caused by a change in position of the patient, especially if recumbency relieves dyspnea, is suggestive of myxoma.
2. Systemic embolization: Leading to cerebrovascular accidents, pulmonary embolism, paradoxical embolism and acute coronary syndrome. This is present in 29% of patients with atrial myxomas.
3. Constitutional symptoms: Fever, weight loss, arthralgias, and Raynaud phenomenon.
4. Other rare manifestations include peripheral neuropathy, typical angina caused by coronary steal phenomenon (especially large vascularized atrial myxomas), and paraneoplastic syndromes.

- On exam there may be widely split loud S1, secondary pulmonary hypertension, murmurs of regurgitation (holosystolic) or stenosis (rumbles), an early diastolic sound 80 to 120 milliseconds after A2 called "tumor plop" which may resemble an opening snap.

ETIOLOGY:

- Most cases (90%) of atrial myxomas are sporadic with no known cause.
- Carney complex, transmitted in an autosomal dominant pattern, accounts for the majority of familial myxomas and as much as 7% of cardiac myxomas. Carney syndrome manifests as cardiac and extracardiac myxomas, pigmented skin discoloration, endocrine hyperactivity, and other tumors, such as schwannomas. There are at least three different genetic loci with two identified genes for this complex.

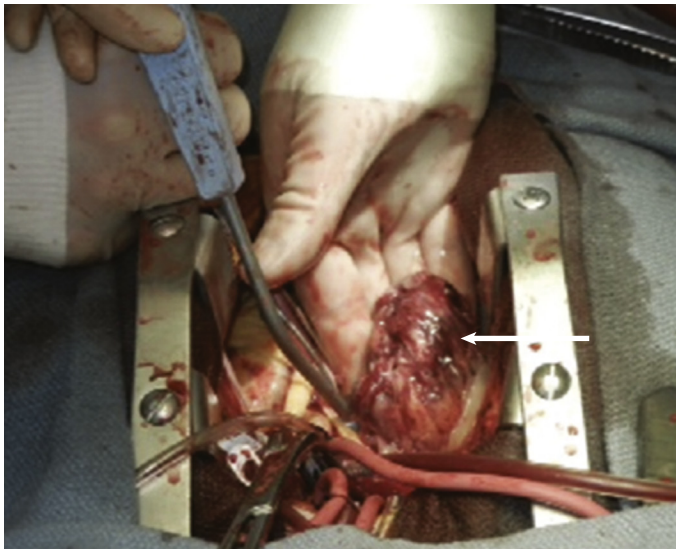


FIG. E1 Gross appearance of a left atrial myxoma. Note the thrombus-appearing material on the surface *(arrow),* which is likely a mechanism for embolic events associated with cardiac myxomas. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary valvular diseases: Mitral stenosis, mitral regurgitation, tricuspid stenosis, tricuspid regurgitation
- Pulmonary hypertension
- Endocarditis
- Vasculitis
- Atrial thrombus (Table E1 summarizes distinguishing characteristics of thrombus from atrial myxoma.)
- Pulmonary embolism
- Cerebrovascular accidents
- Collagen-vascular disease
- Carcinoid heart disease
- Benign tumors of the heart (papillary fibroelastoma, rhabdomyoma, fibroma, teratoma, and lipoma)
- Malignant tumors of the heart (angiosarcoma, rhabdosarcoma, fibrosarcoma, and leiomyosarcoma)
- Metastatic tumors to the heart (melanoma, lung, breast, renal, esophageal, and sarcomas)

WORKUP

A high index of suspicion is needed because the clinical manifestations are nonspecific and similar to many common cardiovascular and pulmonary diseases.

LABORATORY TESTS

Although not very specific, the following laboratory findings may be abnormal in patients with atrial myxomas:

- Complete blood count: Anemia, polycythemia, thrombocytopenia may occur
- Erythrocyte sedimentation rate, C-reactive protein, and serum immunoglobulins are commonly elevated
- Cardiac biomarker levels (troponin and CK-MB) can be elevated
- Electrocardiogram: Nonspecific findings including left or right atrial enlargement, atrial fibrillation, premature ventricular depolarizations, or ventricular tachycardia

IMAGING STUDIES (Fig. E2)

- Transthoracic echocardiography (Fig. E3): With 95% diagnostic sensitivity, it is the initial test of choice in suspected cases of atrial myxoma.
- Chest radiograph: About one third of patients have normal findings. Evidence of altered cardiac contour, pulmonary edema, and chamber enlargement may be present.
- Transesophageal echocardiography: Nearly 100% sensitive and may better define cardiac masses not clearly visualized by transthoracic echocardiography.
- CT: Often used for diagnosis; defines tumor extension and evaluates adjacent cardiac structures.
- MRI (Fig. E3): Delineates size, shape, and tissue characteristics, helping distinguish thrombus from tumor.

TABLE E1 Distinguishing Thrombus from an Atrial Myxoma

	Myxoma	Thrombus
Contrast enhancement	Yes	No
Morphology	Sessile or pedunculated	Usually sessile
Atrial fibrillation	Uncommon	Likely to be present
Atrial location	Commonly attached to the intraatrial septum	Usually occurs in an enlarged chamber and the atrial appendage is commonly involved

From Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.

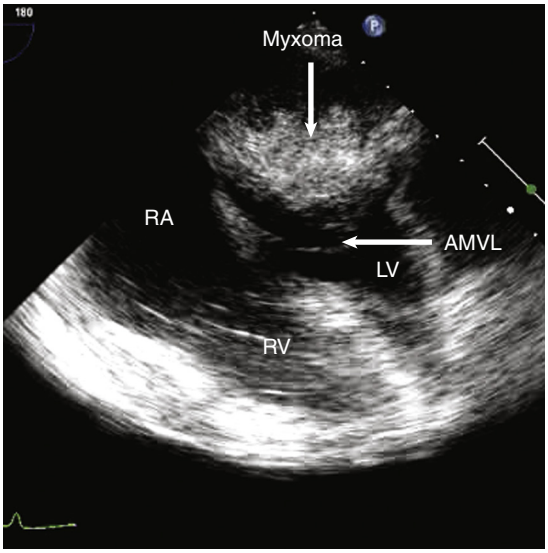


FIG. E2 A large left atrial myxoma prolapsing across the mitral valve, resulting in heart failure symptoms. *AMVL,* Anterior mitral valve leaflet; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.)

- Cardiac catheterization: Will show neovascularization in 50% of the cases and may be required to rule out concomitant coronary artery disease in anticipation of surgical excision.

Rx TREATMENT

ACUTE GENERAL THERAPY

- Surgical excision is the treatment of choice.
- Surgery should be done promptly because systemic embolization and/or sudden death can occur while waiting for the procedure.

CHRONIC Rx

Postoperative arrhythmias and conduction abnormalities were present in 26% of patients and can be treated accordingly.

DISPOSITION

- Surgical results have reported a 95% survival rate after a follow-up of 3 yr.
- Careful follow-up is necessary because up to 5% of sporadic cases and 20% of familial cases of atrial myxoma may recur within the first 6 yr after surgery. A family history of myxomas, atypical location and multicentric features are risk factors for myxoma recurrence after resection.
- Sudden death in untreated patients may occur in up to 15%, resulting from coronary or systemic embolization or obstruction of the mitral or tricuspid valve.

REFERRAL

- Consultation with a cardiologist is recommended.
- Once the presence of cardiac tumor is confirmed, consultation with a cardiovascular surgeon is needed for prompt surgical excision.

! PEARLS & CONSIDERATIONS

- Approximately two thirds of patients present with cardiovascular symptoms, specifically dyspnea, often suggestive of valvular obstruction.
- Nearly one third of patients have evidence of systemic embolization.

COMMENTS

Annual echocardiograms should be performed to monitor for recurrence of atrial myxomas after surgical excision.

RELATED CONTENT

Atrial Myxoma (Patient Information)

AUTHOR: **John Wylie, MD, FACC**

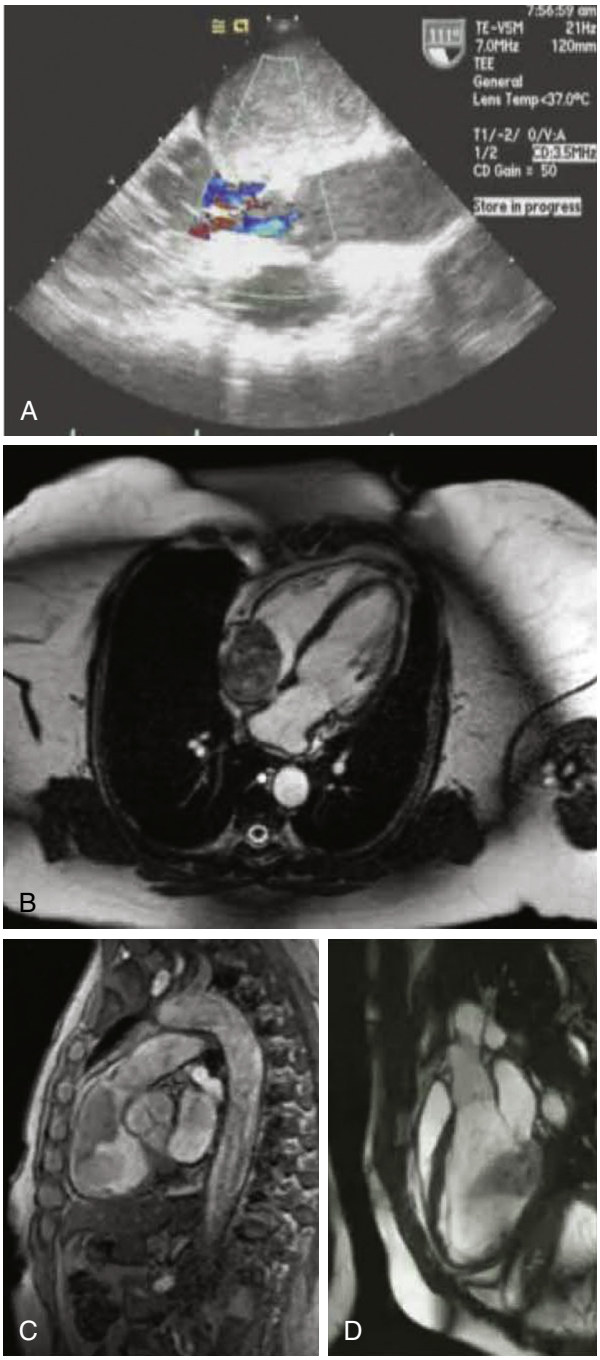


FIG. E3 Myxomas of the heart. A, Echocardiography of giant left atrial myxoma. **B,** Magnetic resonance imaging of right atrial myxoma. **C,** Magnetic resonance imaging of right ventricular myxoma. **D,** Magnetic resonance imaging of left ventricular myxoma. (From Sellke FW et al: *Sabiston & Spencer surgery of the chest*, ed 9, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

An atrial septal defect (ASD) is a true defect in the interatrial septum that allows blood flow between the atria. Fig. 1 illustrates the physiology of ASD. The five forms of ASD are described below and illustrated in Fig. 2.

- Primum: This type of ASD occurs when the anterior and posterior endocardial cushions do not fuse with the septum primum creating a deficiency in the inferior portion of the septum primum. This defect is frequently associated with a cleft anterior mitral leaflet and with left ventricular outflow obstruction.
- Secundum: This is the most common form of ASD. It is caused by failure of the septum primum to fuse with the septum secundum. This defect can form anywhere along the septum, but it is most commonly found near the fossa ovalis.
- Sinus venosus defect: This defect is located at the junction of the right atrium and the superior vena cava or inferior vena cava. In a sinus venosus defect, a left-to-right shunt develops through an opening in the wall between the pulmonary veins and the right atrium. Most commonly this defect involves an anterior wall deficiency in the right upper pulmonary vein, which allows it to drain into the right atrium while remaining anatomically connected to the left atrium. Less commonly, the right lower pulmonary vein is involved. The left pulmonary veins can also drain into a vertical vein that communicates with the superior vena cava.
- Coronary sinus septal defect (unroofed coronary sinus): This is a defect between the wall of the coronary sinus and the left atrium that results in a left-to-right shunt. This defect is often associated with a persistent left superior vena cava.
- Iatrogenic atrial septal defect (iASD) is a complication of electrophysiology and structural interventional procedures that require transseptal puncture.

ASD should be distinguished from a patent foramen ovale (PFO), a flaplike opening between the two atria, caused by failure of the septum primum to fuse to the superior limb of the septum secundum in postnatal life. Whereas ASDs represent a congenital defect established in utero due to failure of normal atrial septal development, a persistent PFO in postnatal life represents the failure of an anatomically necessary defect to close. PFO occurs in approximately 20% to 25% of the normal adult population.

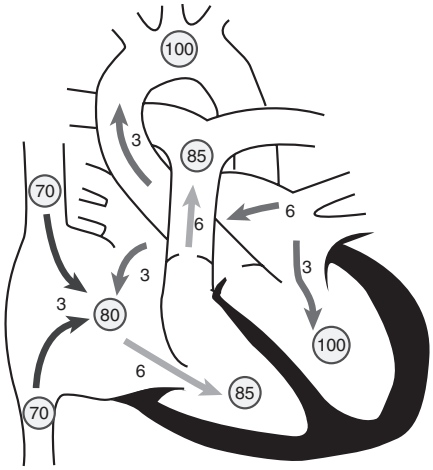


FIG. 1 Physiology of atrial septal defect (ASD). Circled numbers represent oxygen saturation values. The numbers next to the arrows represent volumes of blood flow (in L/min/m^2). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Qp/Qs) of 2:1. Desaturated blood enters the right atrium from the venae cavae at a volume of 3 L/min/m^2 and mixes with an additional 3 L of fully saturated blood shunting left to right across the ASD; the result is an increase in oxygen saturation in the right atrium. Six liters of blood flow through the tricuspid valve causing a mid-diastolic flow rumble. Oxygen saturation may be slightly higher in the RV because of incomplete mixing at the atrial level. The full 6 L of blood flows across the RV outflow tract and causes a systolic ejection flow murmur. Six liters return to the left atrium, with 3 L shunting left to right across the defect and 3 L crossing the mitral valve to be ejected by the left ventricle into the ascending aorta (normal cardiac output). (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

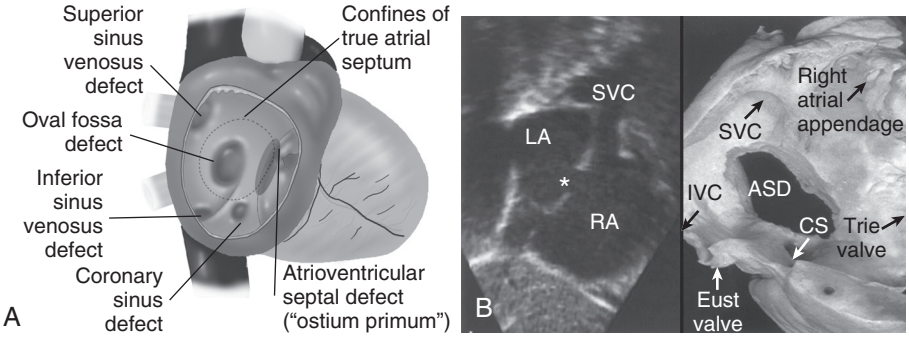


FIG. 2 A, Schematic diagram outlining the different types of interatrial shunting that can be encountered. Note that only the central defect is suitable for device closure. **B,** Subcostal right anterior oblique view of a secundum atrial septal defect *(ASD) (asterisk)* that is suitable for device closure. The right panel is a specimen as seen in a similar view, outlining the landmarks of defect. *CS,* Coronary sinus; *IVC,* inferior vena cava; *LA,* left atrium; *RA,* right atrium; *SVC,* superior vena cava. (From Zipes DP et al [eds]: *Braunwald's heart disease*, ed 7, Philadelphia, 2005, Saunders.)

SYNONYMS

ASD
Interatrial septal defect

ICD-10CM CODES

Q21.1	Atrial septal defect
I23.1	Atrial septal defect as current complication following acute myocardial infarction

EPIDEMIOLOGY & DEMOGRAPHICS

- Secundum, 75%; primum, 15% to 20%; sinus venosus, 5% to 10%; coronary sinus, <1%
- Incidence of ASD is greater in females and in patients with Down syndrome
- Accounts for 8% to 10% of congenital heart abnormalities
- Prevalence is 1.6 per 1000 live births
- Holt-Oram syndrome is an autosomal dominant disorder that involves skeletal anomalies, ASD, and cardiac conduction disease (most commonly atrioventricular [AV] blocks)
- Secundum defects are associated with multiple genetic syndromes including Noonan syndrome, Treacher Collins syndrome, thrombocytopenia–absent radii syndrome, and Down syndrome (trisomy 21)
- ASD may occur as an isolated defect or as part of other congenital cardiac syndromes such as Ebstein anomaly, Lutembacher syndrome, or fetal alcohol syndrome

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Small ASDs or PFOs may close spontaneously during infancy whereas infants with large ASDs may develop heart failure, recurrent respiratory infections, or failure to thrive. The majority of ASDs are small and do not cause any symptoms during infancy. Patients with small ASDs are usually diagnosed by the presence of a cardiac murmur auscultated during routine physical examination.
- Exertional fatigue and dyspnea are usually the main presenting symptoms.

- On rare occasions, young adults may present with ischemic stroke caused by paradoxical embolism through the ASD or PFO.
- Platypnea-orthodeoxia (characterized by dyspnea and deoxygenation when changing from a recumbent position to sitting or standing).
- Patients with ASDs caused by congenital syndromes may present with clinical features to the underlying syndrome.
- Atrial arrhythmias such as atrial fibrillation and atrial flutter are significantly increased in patients with ASDs.

CLINICAL FEATURES

- Cyanosis and clubbing (due to right-to-left shunting)
- Increased jugular venous pressure (may be due to RV failure from left-to-right shunting through a small ASD, or elevated left atrial pressures when a large ASD is present)
- Prominent RV impulse
- Visible and palpable pulmonary artery pulsations
- Wide fixed splitting of S_2
- An accentuated pulmonic component of S_2 (if the patient has pulmonary hypertension)
- Pansystolic murmur best heard at the apex (secondary to mitral regurgitation associated with the ostium primum defect)
- Ejection systolic flow murmur (pulmonary valve flow murmur; Fig. E3)
- Diastolic rumble (atrioventricular valve flow murmur)

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary pulmonary hypertension
- Pulmonary stenosis
- Rheumatic heart disease
- Mitral valve prolapse
- Cor pulmonale
- Anomalous pulmonary venous connection

WORKUP

- ECG:
  1. Ostium primum defect: Extreme left axis deviation, incomplete or total right bundle branch block, prolongation of PR interval
  2. Sinus venosus defect: Right axis deviation, abnormal P axis (suggesting an absent or deficient sinus node)
  3. Ostium secundum defect: Right axis deviation, incomplete or total right bundle branch block, right atrial enlargement

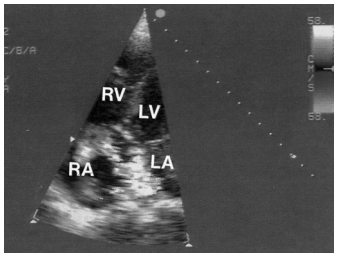


FIG. 4 Color flow Doppler apical four-chamber view showing blood flow from the left atrium *(LA)* to the right atrium *(RA)* through a moderately sized atrial septal defect. *LV,* Left ventricle; *RV,* right ventricle. (From Zipes DP: *Braunwald's heart disease: a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

IMAGING STUDIES

- Chest x-ray: Cardiomegaly, right heart enlargement, increased pulmonary vascular pattern.
- Echocardiography (Fig. 4): Transthoracic echocardiography (TTE) has a high degree of sensitivity for diagnosing secundum and primum ASDs. Echocardiography with saline bubble contrast and Doppler flow studies can measure the size of the defect, the direction of shunting, right heart volume overload, and elevated pulmonary artery pressures. However, sinus venosus defects are frequently missed.
- Transesophageal echocardiography (TEE): TEE is much more sensitive than TTE in identifying and locating pulmonary venous return in sinus venosus defects and can be helpful identifying all forms of ASD when TTE is nondiagnostic. TEE can determine defect size, defect proximity to other cardiac structures, and the size of the defect rims. Measurements generated by TEE are used in the catheterization laboratory to determine whether a patient is suitable for device closure.
- Cardiac catheterization: Left heart catheterization is not used to diagnose ASDs; it is used to assess the coronary arteries before ASD repair. Right-sided heart catheterization is used to assess the severity of the shunt, the extent of pulmonary hypertension, pulmonary vascular resistance (PVR), and pulmonary artery vasoreactivity to vasodilators. In ASD, right-sided heart catheterization will often reveal a "step-up" in arterial oxygen saturation in the right atrium compared with the superior vena cava due to left-to-right shunting from primum or secundum defects. This may not be the case in patients with ASDs from sinus venous defects who develop only partial anomalous pulmonary venous return.
- Cardiac MRI and CT: MRI is the gold standard for assessing RV size and function. MRI is also useful for assessing anomalous pulmonary venous return and persistent left superior vena cava. Cardiac CT can offer similar information. This imaging is useful when echocardiography is not diagnostic.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Asymptomatic patients with small defects, shunts with a pulmonary to systemic flow ratio (Qp/Qs) of <1.5:1, normal RV size, and without pulmonary artery hypertension (PAH) do not require medical therapy. However, they should be routinely assessed for development of clinical symptoms, arrhythmias, embolic events, and progression of structural disease with serial echocardiography.
- Patients should undergo echocardiography every 2 to 3 yr to monitor RV size and function and pulmonary pressure. Left-to-right shunting is expected to increase with age due to progressive noncompliance of the left ventricle and age-acquired heart disease.

GENERAL Rx

- Children and infants: ASD closure is indicated before age 10 if Qp/Qs is >2:1 (many experts advocate closure for Qp/Qs >1.5:1), if ASD size is >5 mm, or if there is evidence of RV dilation.
  1. ASDs with a diameter of <5 mm and no evidence of RV volume overload do not require closure unless associated with paradoxic embolism.
  2. ASD closure (either percutaneously or surgically) is indicated for either right atrial or right ventricular enlargement even if the patient is asymptomatic.
  3. Sinus venosus, coronary sinus, or primum variant ASDs should be repaired surgically rather than by percutaneous closure.
  4. Surgical closure of a secundum variant ASD is appropriate when other defects exist that require surgical intervention, or when the anatomy of the defect precludes the use of a percutaneous device.
- Adults: ASD closure should be considered if any of the following are present: Left-to-right shunting with Qp/Qs >1.5:1, right-sided chamber enlargement, clinical symptoms, pulmonary hypertension with pulmonary artery pressure less than two-thirds systemic levels, PVR less than two-thirds systemic vascular resistance, or pulmonary hypertension that responds to vasodilation therapy. These patients should be managed by specialists in adult congenital heart disease and pulmonary hypertension.
- Patients with severe, irreversible PAH and no evidence of a left-to-right shunt should not undergo ASD closure.
- ASD closure is reasonable in the presence of:
  1. Paradoxic embolism (Class 2a indication).
  2. Documented orthodeoxia-platypnea (Class 2a indication).
- The majority of iASDs close spontaneously. However, ASD closure should be actively pursued if high risk features are present such as iASD >8 mm, right-to-left shunting, large left-to-right shunt, a predisposition to thromboembolism, or right ventricular dysfunction.
- Percutaneous catheter device closure has >95% success rate in appropriate candidates. Early complications include device thrombus formation, atrial arrhythmias, erosion, and device dislodgement. Potential mid- and long-term complications include late device erosion into the aortic root or pericardium, atrial dysrhythmias, and infective endocarditis. A combination of low-dose aspirin and clopidogrel is required for 3 to 6 mo after the procedure to prevent thrombus formation. Close clinical follow-up that includes echocardiogram is recommended before discharge, then at 1 wk, 6 mo, and 12 mo postintervention.

- Percutaneous closure is contraindicated in patients with sinus venosus, primum, or unroofed coronary sinus variant ASDs. Successful percutaneous ASD closure in patients with secundum defects depends on the anatomy of the defect. Percutaneous closure is not indicated for secundum defects if the defect is too large; too close to the coronary sinus, AV valves, or pulmonary veins; or if there are inadequate rims. Percutaneous closure of secundum ASD may be successful if the stretched diameter is <41 mm with adequate rims. The procedure should not be performed in the presence of sepsis, bleeding disorder, or intracardiac thrombi.
- Surgical closure involves the placement of a pericardial or Dacron patch through a minimally invasive approach (with or without robotic assistance). Surgical closure of ASD improves function status, exercise capacity, and patient survival; however, it does not prevent atrial fibrillation or stroke, especially if patients pursue ASD repair after age 40.
- Cox maze procedure should be considered for patients with intermittent or chronic atrial fibrillation when they undergo ASD closure.

DISPOSITION

- Mortality rate increases in patients with large ASDs that go untreated. Complications of longstanding ASD include RV failure, arrhythmias, paradoxic embolism, and PAH leading to right-to-left shunting (Eisenmenger syndrome).
- Patients with small shunts (<1.5:1) have a normal life expectancy.
- Spontaneous closure or size reduction is more likely in younger patients with defects <10 mm in diameter.
- A basic assessment for adults with congenital heart disease should include systemic arterial oximetry, ECG, chest radiograph, transthoracic echocardiography, and blood tests for complete blood count and coagulation screen.
- Intracardiac shunts constitute moderate risk for noncardiac procedures. High-risk features include severe systolic dysfunction (ejection fraction <35%), severe pulmonary hypertension, cyanotic heart disease, and severe left-side outlet obstruction.
- Annual postoperative clinical follow-up is recommended for patients who pursue ASD repair as adults in order to monitor for PAH, atrial arrhythmias, RV or LV dysfunction, and coexisting valvular lesions.
- Preoperative atrial fibrillation is a risk factor for both postoperative and long-term atrial fibrillation. The older the patient undergoing ASD repair, the more likely that patient is to develop atrial fibrillation, even after the ASD is repaired.
  1. The benefits of ASD repair include improved functional status and exercise capacity, improved survival (if closed in childhood), improved quality of life, prevention of right-sided heart failure, and prevention of PAH.
  2. Potential mid- to long-term complications of ASD closure in adulthood include tachyarrhythmias (atrial fibrillation or atrial flutter), bradyarrhythmias (sinus node dysfunction or heart block), stroke (greater risk in older patients), residual ASDs (due to incomplete initial closure or patch dehiscence), right-sided heart failure, PAH (risk is correlated with the size of the original defect and inversely related to age at time of closure), mitral valve regurgitation or subaortic stenosis (associated with primum ASDs), device migration/erosion, and pulmonary venous congestion.
  3. Women with ASD have an increased risk of paradoxic embolus, stroke, arrhythmia, and heart failure during pregnancy. ASD repair before pregnancy reduces these risks. However, if ASD is undiagnosed before pregnancy, close monitoring for the duration of pregnancy is sufficient. The only contraindication to pregnancy in women with ASD is severe PAH.
  4. Scuba diving is contraindicated in patients with unrepaired ASDs because the pressure from deep sea diving increases the risk of paradoxic emboli. In addition, high-altitude climbing should be avoided because it can lead to right-to-left shunting and oxygen desaturation.
- In regard to infective endocarditis prophylaxis for dental procedures:
  1. Prophylaxis is not indicated for an unrepaired ASD.
  2. Prophylaxis is indicated for 6 mo following ASD repair if prosthetic material was used to repair the defect.
  3. Prophylaxis is indicated for a repaired ASD (or any congenital heart defect) if residual defects remain either at or near the site of the prosthetic material or device used for repair.

The estrogen-containing oral contraceptive pill is not recommended in acute congenital heart disease patients at risk for thromboembolism. This includes patients with atrial fibrillation, severe PAH, Fontan repair, or cyanosis related to an intracardiac shunt.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Atrial Septal Defect (ASD) (Patient Information)

AUTHORS: **Craig L. Basman, MD,** and **Rebecca Jonas, MD**

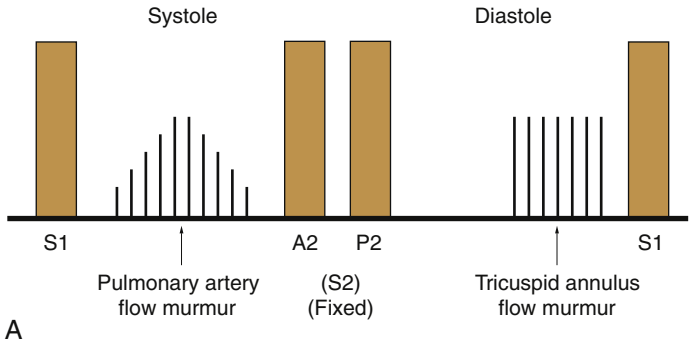
SUGGESTED READINGS

Mohamad Alkhouli et al: Iatrogenic atrial septal defect following transseptal cardiac interventions, *Int J Cardiol* 209:142-148, 2016.

Chubb H et al: Pathophysiology and management of arrhythmias associated with atrial septal defect and patent foramen ovale, *Arrhythm Electrophysiol Rev* 3(3):168-172, 2014.

Moake L: Transcatheter device closure for atrial septal defects: safety, efficacy, complications, and costs, *Crit Care Nurs Clin North Am* 23(2):339-348, 2011.

Warnes CA et al: ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to develop guidelines for the management of adults with congenital heart disease), *J Am Coll Cardiol* 52:e143-e263, 2008.



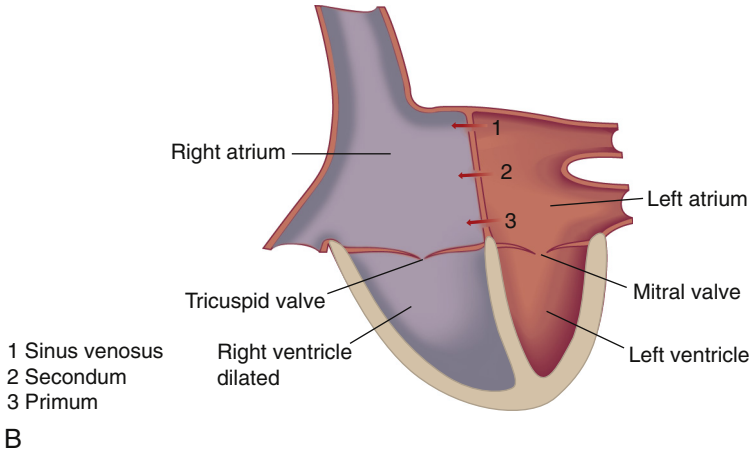


FIG. E3 Atrial septal defect. A, Murmur at the left sternal edge. **B,** Anatomy. (From The patient with a murmur. In Baker T, Nikolic G, O'Connor S [eds]: *Practical cardiology,* Philadelphia, 2008, Elsevier.)

Atrioventricular Dissociation

BASIC INFORMATION

DEFINITION

Atrioventricular (AV) dissociation is defined as a lack of association between the atria and the ventricles or independent function of the atria and ventricles. This simple definition will serve as a reminder that AV dissociation should be considered an umbrella rather than a diagnosis. AV dissociation may occur in the setting of bradycardic rhythms (Fig. E1 and Fig. E2), complete heart block (Fig. E3), as well as tachycardic rhythms (ventricular tachycardia, atrial rhythm with associated accelerated junctional rhythm or AV nodal reentrant tachycardia).

SYNONYMS

Third-degree AV block
CHB
Complete AV block

ICD-10CM CODE

I44.2 Atrioventricular block, complete

EPIDEMIOLOGY & DEMOGRAPHICS

The prevalence is the sum of the diagnoses that are characterized by AV dissociation.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Physical examination findings may be normal unless the arrhythmia is causing hemodynamic compromise. If the right atrium contracts against a closed tricuspid valve during ventricular systole, Cannon A waves may be seen in the jugular vein. Patients may present with the following clinical manifestations:

- Dizziness, palpitations
- Syncope or presyncope (caused by reduced cardiac output)
- Fatigue, impaired exercise tolerance
- Mental status changes
- Congestive heart failure
- Angina pectoris
- Some patients may be asymptomatic

ETIOLOGY

- Slow rate of firing from sinus node
- Inappropriately fast pacemaker from the ventricle
- Iatrogenic: Anesthesia, inotrope infusion, ventricular pacing, radiofrequency ablation of slow pathway, digoxin toxicity
- Sinus node disease, ischemia, hyperkalemia, overactive vagal drive
- Complete heart block: Progressive fibrosis of the His-Purkinje system, medications, Lyme disease

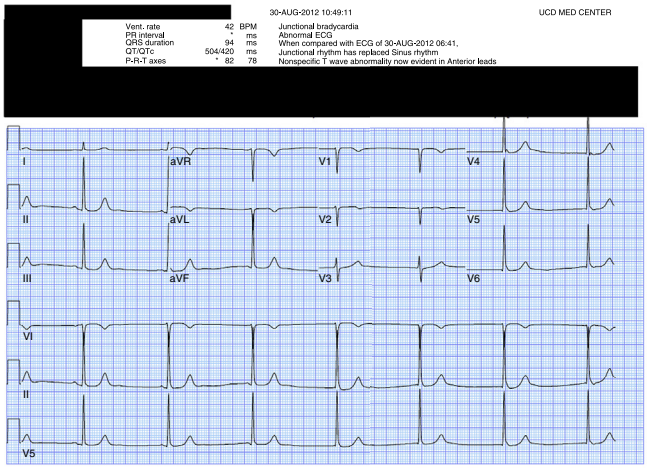


FIG. E1 An electrocardiogram was obtained at the primary care practitioner's office. Computer interpretation indicated junctional bradycardia at a rate of 42 beats per min. While the rate was regular, not every QRS complex was preceded by a P wave. There were no acute ST- or T-wave changes consistent with ischemia. (From Singh GD et al: Food for thought: atrioventricular dissociation, *Am J Med* 126(12):1050-1053, 2013.)

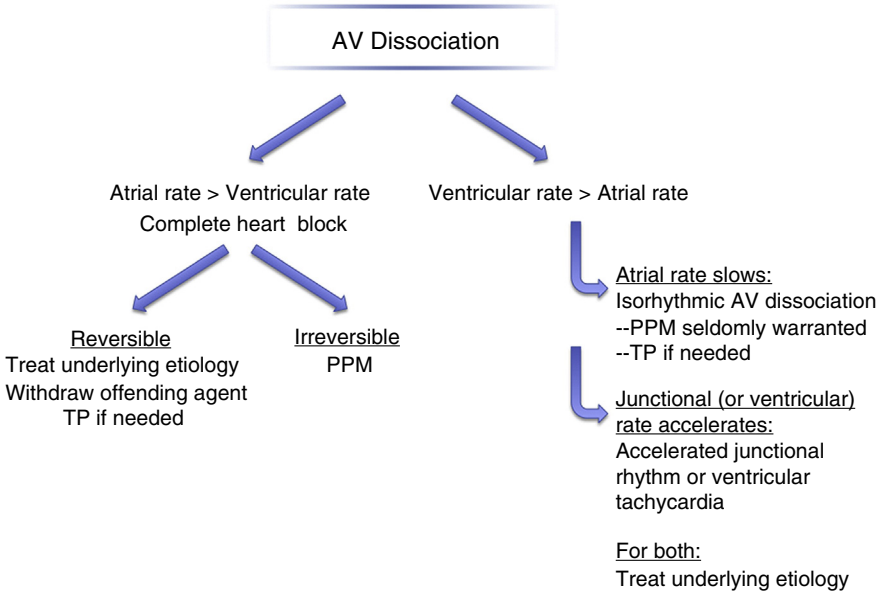


FIG. E2 This flow chart demonstrates the relationship between atrioventricular dissociation due to complete heart block vs. atrioventricular dissociation from a ventricular rate that is greater than the atrial rate. *AV*, atrioventricular; *PPM*, permanent pacemaker; *TP*, temporary pacemaker. (From Singh GD et al: Food for thought: atrioventricular dissociation, *Am J Med* 126(12):1050-1053, 2013.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis should be targeted toward the diagnoses that include AV dissociation.
- NOTE: The atrium does not need to be faster than the ventricular rate in AV dissociation, as is the case in the definition of complete heart block.
  1. Isorhythmic AV dissociation: Atrial and ventricular rates are the same but dissociated.
  2. Interference dissociation: Similar atrial and ventricular rates but conduction occurs sometimes.

WORKUP

- Workup such as routine laboratory studies, cardiac biomarkers, and cardiac imaging should be dictated by the clinical circumstances.
  1. Laboratory studies: Particular attention to electrolyte abnormalities (potassium) and digoxin level
  2. Lyme antibody titer in the case of complete heart block, particularly in the Northeastern U.S.

TREATMENT

ACUTE GENERAL Rx

- Initial treatment should focus on the hemodynamic stability and symptoms of the patient.
- Bradycardic rhythms:
  1. If necessary (i.e., symptoms or hemodynamic compromise), a temporary pacemaker is the most reliable therapy.
  2. Hold AV-nodal blocking agents.
  3. Chronotropic medications: Atropine, dopamine, dobutamine, or isoproterenol may be used as second-line agents while preparing for a temporary pacemaker.

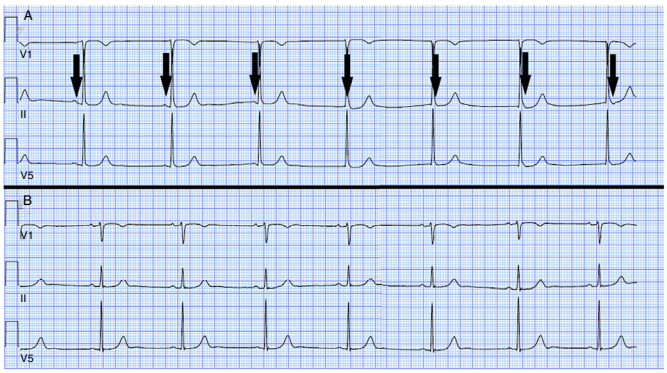


FIG. E3 A, In the initial rhythm strip—also shown in Fig. E1—solid black arrows indicate atrial complexes initiated by the sinus node. Note that for each beat, the sinus impulse is progressively closer to the QRS complex, then becomes obscured within the QRS complex, and finally is seen beginning to emerge on the downstroke of the R wave in the last three QRS complexes. The junctional pacemaker, at 42 beats per min, is slightly faster than the atrial rate of 41 beats per min. **B,** Another echocardiogram was performed after the patient was treated for dyspepsia. The rhythm strip shows sinus bradycardia with a rate of 45 beats per min. (From Singh GD et al: Food for thought: atrioventricular dissociation, *Am J Med* 126(12):1050-1053, 2013.)

- Tachycardic rhythms (ventricular tachycardia):
  1. In the setting of hemodynamic compromise, cardioversion is the first-line therapy
  2. IV antiarrhythmic drugs: Amiodarone or lidocaine to suppress the arrhythmia
  3. Treatment of the underlying cause of ventricular tachycardia: Coronary angiogram if ischemia vs. electrophysiology (EP) study +/– ablation

REFERRAL

All patients with AV dissociation should be referred to a cardiologist for diagnostic evaluation of the rhythm.

PEARLS & CONSIDERATIONS

COMMENTS

- Recall that AV dissociation is merely an umbrella that includes multiple diagnoses, including both bradycardic and tachycardic arrhythmias.
- Specific considerations regarding etiology, treatment, and disposition should be directed toward the rhythm that has caused AV dissociation.

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Attention Deficit Hyperactivity Disorder PTG

BASIC INFORMATION

DEFINITION

Attention deficit hyperactivity disorder (ADHD) is a chronic disorder of attention and/or hyperactivity-impulsivity. Symptoms must be present before 12 yr of age, last at least 6 mo, and cause functional impairment in multiple settings. The diagnostic keys for ADHD are described in Table 1.

SYNONYMS

Hyperactivity
Hyperkinetic disorder
Attention deficit disorder (ADD)
ADHD

ICD-10CM CODES

F90.0	Attention-deficit hyperactivity disorder, predominantly inattentive type
F90.1	Attention-deficit hyperactivity disorder, predominantly hyperactive type
F90.2	Attention-deficit hyperactivity disorder, combined type
F90.8	Attention-deficit hyperactivity disorder, other type
F90.9	Attention-deficit hyperactivity disorder, unspecified type

DSM-5 CODES
314.00, 314.01

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Diagnosis is usually first made in school-aged children (6 to 9 yr).
PREVALENCE: Five percent to 10% of school-aged children (most prevalent neurodevelopmental disorder among children); up to 5% of adolescents and 2% to 4% of adults. Children from families with low socioeconomic status and children with public insurance are diagnosed with ADHD at higher rates than their peers.
PREDOMINANT SEX: Among children, male predominance with ratio of 2:1 to 4:1. Among adults, ratio is closer to 1:1 (sex difference may reflect referral bias).
PREDOMINANT AGE: Some symptoms must occur before age 12 yr. Symptoms (especially motoric hyperactivity) tend to diminish with age. Up to 70% continue to meet criteria in adolescence, and an estimated 40% to 65% have some symptoms in adulthood.
GENETICS: Strong polygenetic component. First-degree relatives of ADHD patients have 5 times greater risk of ADHD relative to controls. Studies suggest potential involvement of several genes, including those associated with serotonin and glutamate transporters as well as dopamine metabolism in addition to neuronal development.
RISK FACTORS: Possible risk factors include in utero tobacco/drug exposure or hypoxia, low birth weight, prematurity, pregnancy, lead exposure (though most children with elevated lead levels do not develop ADHD), head trauma in young children, family dysfunction, low socioeconomic status. Evidence supports possible association between dietary factors (e.g., refined sugar, food additives) and ADHD in a small percentage of patients. A causal link between environmental toxins and ADHD has not been clearly established.

TABLE 1 Diagnostic Keys for Attention Deficit Hyperactivity Disorder

1. Inattention
   a. Careless mistakes in schoolwork, work, or other activities
   b. Seems not to listen when spoken to directly
   c. Poor follow-through on schoolwork or chores
   d. Difficulty organizing
   e. Easily distracted by extraneous stimuli and is forgetful
2. Hyperactivity
   a. Trouble sitting still
   b. May act as if "driven by a motor"
   c. May talk excessively
3. Impulsivity
   a. Trouble holding back in class
   b. Trouble taking turns
   c. Interrupts

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Three types:
  1. Predominantly inattentive: Difficulty organizing, planning, remembering, concentrating, starting/completing tasks; symptoms may not be present during preferred activities.
  2. Predominantly hyperactive-impulsive: Edgy/restless, talkative, disruptive/intrusive, disinhibited, impatient.
  3. Combined.
- Usually diagnosed in elementary school when achievement is compromised and behavioral problems are not tolerated. Children with academic underproductivity, problems with peer and family relations, or discipline issues are often referred for evaluation. Of the more than 4 million children in the U.S. who have ADHD, most have comorbid conditions (see the following) and nearly half use special education and mental health services.
- Up to 50% may have associated disorders such as psychiatric diagnoses (oppositional defiant disorder, conduct disorder, depression, anxiety, eating disorders), learning disabilities, or substance abuse.
- In adults, motoric hyperactivity is less common, but restlessness, edginess, and difficulty relaxing are often seen. Disorganization and difficulty completing tasks are other common complaints.

ETIOLOGY

Strongest evidence exists for genetic inheritance. Other theories include abnormal metabolism of brain catecholamines, structural brain abnormalities, reduced activation in the basal ganglia and anterior frontal lobe, as well as environmental factors (see earlier).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Medical: Visual/hearing impairment, seizure disorder, head injury, sleep disorder, medication interactions, mental retardation/intellectual disability, specific learning disorder, autism spectrum disorder/development delay, thyroid abnormalities, lead toxicity, movement disorders.
- Psychiatric: Depression, bipolar disorder, disruptive mood, dysregulation disorder, anxiety, obsessive-compulsive disorder, oppositional defiant disorder, intermittent explosive disorder, conduct disorder, posttraumatic stress disorder, reactive attachment disorder, and substance abuse.
- Psychosocial: Mismatch of learning environment with ability, family dysfunction, abuse/neglect.

WORKUP

- Clinical interview should include assessment of symptoms and impact on work/school and relationships; developmental history; personal and family psychiatric history, including substance abuse; social history, including family dysfunction; medical history.
- Physical examination should be performed to investigate medical causes for symptoms, coexisting conditions, and contraindications to treatment. Special focus should be paid to evaluation of dysmorphic features; neurologic examination, including assessment for neurocutaneous findings; and assessment of hearing and vision.
- Information from collateral sources (parents, partners, teachers) is crucial to diagnosis. Many patients will not display symptoms during an office visit and may underreport or overreport symptoms.
- Self-rating scales and standardized symptom-specific questionnaires from collateral sources can help diagnose and assess response to treatment. The use of ADHD-specific rating scales over broadband behavioral scale is associated with improved sensitivity and specificity.
- Laboratory or imaging studies should be undertaken only if indicated by history or physical examination.
- The FDA has approved a quantitative electroencephalogram test to aid in the diagnosis of ADHD in children, but sufficient evidence to support its routine use is lacking.
- Ancillary testing (e.g., neuropsychological testing including verbal and performance IQ/achievement testing and language evaluation, and mental health assessment) may be indicated based on clinical findings and may require referral.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- The majority of studies comparing the efficacy of pharmacologic vs. nonpharmacologic interventions demonstrate the superiority of pharmacologic treatments.
- Studies on combined treatments have not shown significant improvements in core ADHD symptoms when behavioral treatments are added to stimulant medications. However, improvements in related areas of concern such as parent-child relations, aggressiveness, teacher-rated social skills, and reaching achievement have been seen in combined treatment groups.
- Prevailing opinion favors a multimodal approach in which nonpharmacologic behavioral therapies including parent-child behavioral therapy and social skills training can be used to target comorbid conditions or behaviors that have not responded to medication.
- Behavioral therapy alone is often considered when children are under 6 yr, symptoms and impairment are mild, if parents are opposed to or patients cannot tolerate medications, or if there is uncertainty or disagreement about the diagnosis (e.g., between parents and teachers).
- Educational interventions are recommended, particularly in the setting of learning disabilities. Children with ADHD are entitled to reasonable educational accommodations under a 504 Plan or the Individuals with Disabilities Education Act.
- Behavioral interventions (e.g., goal setting and rewards systems) show short-term efficacy and are endorsed by most national organizations. Time management and organizational skills appear useful. Social skills training may also be useful.
- Psychotherapy such as cognitive therapy, play therapy, or insight-oriented therapy are unlikely to be useful in addressing the core symptoms of ADHD. However, it may be beneficial in treating comorbid psychiatric conditions.
- Preliminary research concentrating on improving diagnosis, treatment outcomes, and medication compliance using eHealth (telemedicine, mobile apps, text reminders) have been promising.
- Elimination diets are not routinely recommended.
- Many support and advocacy groups provide education and other resources (e.g., Children and Adolescents with ADHD, National ADD Association, American Academy of Child and Adolescent Psychiatry).

ACUTE GENERAL Rx

- Most studies on treatment of ADHD are performed in children; limited data available on adults.
- Mainstay of treatment is stimulant medication. Second-line therapies include antidepressants and alpha-agonists. Table 2 summarizes FDA-approved treatments for ADHD.
- Stimulants:
  1. Release or block uptake of dopamine and norepinephrine.
  2. Include short- and long-acting methylphenidate, dextroamphetamine, and dextroamphetamine/amphetamine combinations (mixed amphetamine salts). A methylphenidate patch (Daytrana) is available, as is a pro-drug form of dextroamphetamine, lisdexamfetamine (Vyvanse), which is designed to limit the abuse potential. A long-acting oral suspension of methylphenidate (Quillivant XR), a long-acting chewable tablet of methylphenidate

TABLE 2 FDA-Approved Treatments for Attention Deficit Hyperactivity Disorder

Generic Name	Brand Name	Formulations and Strengths	Duration of Behavioral Effect (h)	Comments
Amphetamines				
D-amphetamine	Dexedrine	Tablets: 5, 10 mg	3-6	
	Dexedrine Spansule	Spansules: 5, 10, 15 mg		
	ProCentra	Oral solution: 5 mg/5 ml		
Mixed amphetamine /dextroamphetamine	Adderall	Tablets: 5, 7.5, 10, 12.5, 15, 20, 30 mg	4-6	
	Adderall XR	Capsules: 5, 10, 15, 20, 25, 30 mg	8-10	Capsule with 1:1 ratio of IR to DR beads
	Evekeo	Tablets: 5, 10 mg	10	Racemic amphetamine sulfate, 1:1 D-amphetamine and L-amphetamine
	Dyanavel	Oral suspension: 2.5 mg/ml	8-13	Shake the bottle before administering the dose
Lisdexamfetamine dimesylate	Vyvanse	Capsules: 20, 30, 40, 50, 60, 70 mg	8–12	Inactive prodrug in which L-lysine is chemically bonded to D-amphetamine
Methylphenidates				
Methylphenidate	Ritalin	Tablets: 5, 10, 20 mg	3-4	
	Methylin	Tablets, chewable: 2.5, 5, 10 mg	3-4	
		Oral solution: 5 mg/5 ml, 10 mg/5 ml (500 ml)	3-4	
	Ritalin LA	Capsules: 10, 20, 30, 40 mg	8-9	Capsule with 1:1 ratio of IR beads to DR beads
	Metadate ER	Tablets: 10, 20 mg	5-8	
	Metadate CD	Capsules: 10, 20, 30 mg	8-9	Capsule with 3:7 ratio of IR beads to DR beads
	Concerta	Tablets: 18, 27, 36, 54 mg	8-12	Ascending profile, OROS technology
	Daytrana	Transdermal patch: 10, 15, 20, 30 mg/9 h	9	Delivery rate of 1.1, 1.6, 2.2, 3.3 mg/h for the patches, respectively, based on 9-h wear times in patients ages 6-12 yr
	Quillivant XR	Oral suspension: 25 mg/ 5 ml	8-12	Shake the bottle before administering the dose
	QuilliChew ER	Chewable tablets: 20, 30, 40 mg	8	
	Aptensio XR	Capsules: 10, 15, 20, 30, 40, 50, 60 mg	9-12	May be swallowed or opened and contents mixed into food.
Dexmethylphenidate	Focalin	Tablets: 2.5, 5, 10 mg		*d-threo*-enantiomer of methylphenidate, twice as potent as racemic methylphenidate
	Focalin XR	Capsules: 5, 10, 20 mg		

DR, Delayed-release; *IR,* immediate-release; *OROS,* osmotic-controlled release oral delivery system.
From Stern TA et al: *Massachusetts General Hospital handbook of general hospital psychiatry,* ed 7, Philadelphia, 2018, Elsevier.

(QuilliChew ER), a long-acting orally disintegrating tablet of mixed amphetamine preparation (Adzenys XR-ODT), and a long-acting liquid amphetamine preparation (Dyanavel XR) are also available.

3. All stimulants equally effective; however, not all patients improve with stimulants. Patients who do not respond well to one stimulant may respond to another.
4. Do not cause euphoria or lead to addiction when taken as directed.
5. Improve cognition, inattention, impulsiveness/hyperactivity, and driving skills. Limited impact on academic performance, learning, and emotional problems.
6. Side effects are usually mild, reversible, and dose dependent, including anorexia, weight loss, sleep disturbances, increased heart rate and blood pressure, irritability, moodiness, headache, onset or worsening of motor tics, reduction of growth velocity (but not adult height). Do not worsen seizures in patients on adequate anticonvulsant therapy. Rebound of symptoms can occur with withdrawal of medication.
7. Stimulants are associated with an increased risk of cardiovascular events and death. Patients should be carefully evaluated for cardiovascular disease before beginning therapy and be periodically monitored, including blood pressure checks, while they are treated. However, despite concerns regarding cardiovascular risk, these medications are generally safe. Recent studies have shown that among young and middle-aged adults, current or new use of ADHD medications, compared with nonuse or remote use, is not associated with an increased risk of serious cardiovascular events. Routine, pre-treatment screening with ECGs is not currently recommended by the American Academy of Pediatrics or the American Academy of Child and Adolescent Psychiatry.
8. There are reports of psychotic or manic symptoms (particularly hallucinations) associated with stimulant use in children and adolescents, with a 2006 report revealing that these symptoms might emerge in 0.25% of treated children (1 in 400) (Ross RG: *Am J Psychiatry* 163:1149-1152, 2006).

- Atomoxetine (Strattera):
  1. Selective norepinephrine reuptake inhibitor.
  2. Generally felt to be less effective than stimulants, but a useful alternative in patients who have not tolerated or responded to stimulants or in the setting of patient or family substance abuse.
  3. Efficacy and safety of use beyond 2 yr of treatment have not been studied. There have been reports of behavioral abnormalities and increased suicidality in children and adolescents.
  4. Side effects: Gastrointestinal upset, sleep disturbance, decreased appetite, dizziness, sexual side effects in men. Cardiovascular side effects have also been reported.
  5. There have been rare reports of severe liver injury in adults and children.
- Antidepressants (bupropion, imipramine, desipramine, nortriptyline):
  1. May be useful in patients with coexisting psychiatric disorders.
  2. Studies comparing efficacy versus stimulants are inconclusive.
  3. Side effects: Arrhythmias, anticholinergic effects, lowering of seizure threshold.
- Alpha-2-adrenergic agonists (clonidine, guanfacine):
  1. Appear to be less effective than stimulants, but may be particularly useful as an adjunctive treatment to stimulants, particularly in patients with a partial stimulant response or who experience side effects such as sleep disturbance or concurrent symptoms of overarousal, irritability, or aggression.
  2. Extended-release formulations of guanfacine (Intuniv) and clonidine (Kapvay) have been approved by the FDA for treatment of ADHD in children ages 6 to 17 yr. A transdermal clonidine patch is also available.
  3. Potential side effects include sedation, fatigue, headache, bradycardia, hypotension, and depression.
- Use of medications, particularly stimulants (which are monitored under the Controlled Substance Act), requires frequent monitoring.

DISPOSITION

- Although symptoms may change over time, for many patients ADHD represents a chronic condition that requires lifelong management.
- Patients are at higher risk for academic underachievement, lower socioeconomic status, work and relationship difficulties, high-risk behavior, and psychiatric comorbidities.

REFERRAL

- Diagnosis complicated by difficult-to-treat comorbid psychiatric conditions, developmental disorders, or mental retardation
- Lack of adequate response to stimulants/atomoxetine/alpha-adrenergic agents

PEARLS & CONSIDERATIONS

- The World Health Organization's Adult Self-Report Scale (ASRS) v1.1 has good sensitivity and adaptability to the primary care setting.
- Among adults with persistent ADHD symptoms treated with medication, trials have shown that the use of cognitive behavioral therapy compared with relaxation with educational support resulted in improved ADHD symptoms, which were maintained at 12 mo.
- ADHD has been associated with criminal behavior in some studies. Data analysis has shown that among patients with ADHD, rates of criminality are lower during periods when they receive ADHD medication.
- Recommendations for the diagnosis and management of ADHD have been published by the Centers for Disease Control and Prevention (www.cdc.gov/ncbddd/adhd/guidelines.html).

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Attention Deficit Hyperactivity Disorder (ADHD) (Patient Information)

AUTHORS: **Pamela E. Hoffman, MD,** and **Emily R. Katz, MD**

SUGGESTED READINGS

Chan E et al: Treatment of attention-deficit/hyperactivity disorder in adolescents, a systematic review, *J Am Med Assoc* 315(18):1997-2008, 2016.

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Habel LA et al: ADHD medications and risk of serious cardiovascular events in young and middle-aged adults, *J Am Med Assoc* 306(24):2673-2683, 2011.

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McGough JJ: Treatment controversies in adult ADHD, *Am J Psychiatry* 173(10):960-966, 2016.

Olsen MR, Casado-Lumbreras C, Colomo-Palacios R: ADHD in eHealth—a systematic literature review, *Procedia Comput Sci* 100:207-214, 2016.

Punja S et al: Amphetamines for attention deficit hyperactivity disorder (ADHD) in children and adolescents, *Cochrane Database Syst Rev* 2:CD009996, 2016.

BASIC INFORMATION

DEFINITION

Autism spectrum disorder (ASD) encompasses a continuum of developmental disabilities characterized by marked social impairment. Box 1 describes the diagnostic keys and case determination criteria under *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5). There is usually impairment in several additional domains integral to social functioning, including communication, language, and social interactions. Repetitive/stereotyped behaviors and interests as well as sensory issues (i.e., hypersensitivity, hyposensitivity) also are prominent. Comorbid intellectual disability, neurological and medical problems, and an increased risk of psychiatric disorders are frequently present in ASD. Both core and associated features can vary dramatically among individuals. In addition, timing of onset can differ, as about one quarter of children with ASD are noted to lose skills after developing normally for as long as 2 yr, whereas others present with delays across most developmental domains within the first year of life. The diagnosis of ASD can accurately be made by 3 yr of age. However, gender and cognitive, linguistic, and adaptive functioning impact ASD presentation and can affect age of diagnosis. DSM-5 criteria no longer differentiate separate disorders. Instead, an overarching diagnosis of ASD is given; severity levels (1, 2, or 3) have been introduced to identify the magnitude of social and behavioral impairment and the support required to ensure the safety and well-being of the individual. Specifiers have been added to capture associated features (e.g., intellectual disability, language impairment, medical or genetic conditions, and catatonia).

SYNONYMS

ASD
Autism
Autistic disorder
Early infantile autism
Childhood autism
Kanner autism
Asperger disorder
Pervasive developmental disorder
Pervasive developmental disorder–not otherwise specified (PDD-NOS)

ICD-10CM CODES
F84.0 Autism spectrum disorder
DSM-5 CODES
299.00 Autism spectrum disorder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Autism spectrum disorder afflicts up to 3% of children in the United States.
PREVALENCE: 1:68 (1:42 for boys, 1:189 for girls). It is unclear whether the increase in prevalence reflects an expansion of the diagnosis to include subthreshold cases, increased awareness of the disorder, improvement in diagnostic accuracy, changes in public policy related to service eligibility, or a true increase in the frequency of autism spectrum disorder.
PREDOMINANT SEX AND AGE: Male:female ratio of 2 to 5:1. Lifelong.
PEAK INCIDENCE: Before age 3 yr
RISK FACTORS: Prenatal and perinatal risk factors identified include hypoxia-related obstetric complications, use of valproic acid during pregnancy, use of thalidomide during pregnancy, advanced parental age, multiple birth, prematurity, congenital sensory deficits, and significant exposure to air pollutions (during pregnancy and in the postnatal period). However, it is not established whether these are causal factors.
GENETICS:

- Autism spectrum disorder is highly inheritable with a heritability index of 82% to 90%.
- The concordance rate for ASD varies across studies and ranges from 36% to 95% for monozygotic twins; the concordance rate is estimated between 20% and 40% for dizygotic twins and between 10% and 20% for non-twin siblings.
- Copy number variants (CNVs) account for 10% to 20% of autism spectrum disorder cases, but each CNV is rare (no more than 1% of cases). Rare chromosomal abnormalities account for about 10% of cases, but each type is rare (no more than 1% of cases).
- Common genetic variants acting in an additive manner account for approximately 35% of cases. Research has identified approximately 1000 gene mutations as being possibly contributory, but only about 20 of them have been associated with ASD with "high confidence."
- In the remaining cases, ASD is suggested to arise from a combination of unknown genetic variations, environmental influences, and epigenetic factors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Common triad of marked impairment in social interactions (poor social-emotional reciprocity), impaired and atypical verbal and nonverbal communication, and repetitive and unusual behavior or play
- Marked impairment in the understanding and use of both verbal and nonverbal communication, including unchanging facial expression and lack of gestures during interactions
- Stereotypic behavior (i.e., hand flapping, body rocking) or language (i.e., echolalia, palilalia)
- Perceptual hypersensitivity (i.e., auditory, tactile, olfactory, gustatory) and avoidance of novel stimuli; or perceptual hyposensitivity (e.g., abnormally high threshold for pain)
- Brain abnormalities have been identified at anatomical and functional levels; abnormalities are detected as early as the first year of

BOX 1 Autism Spectrum Disorder (ASD) Case Determination Criteria under DSM-5

DSM-5 Behavioral Criteria	
A. Persistent deficits in social communication and social interaction	A1: Deficits in social emotional reciprocity A2. Deficits in nonverbal communicative behaviors A3. Deficits in developing, maintaining, and understanding relationships
B. Restricted, repetitive patterns of behavior, interests, or activities, currently or by history	B1: Stereotyped or repetitive motor movements, use of objects or speech B2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior B3. Highly restricted interests that are abnormal in intensity or focus B4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment
Historical PDD diagnosis	Any ASD diagnosis documented in a comprehensive evaluation, including a DSM-IV diagnosis of autistic disorder, Asperger disorder, or pervasive developmental disorder–not otherwise specified (PDD-NOS)
DSM-5 case determination	All three behavioral criteria coded under part A, and at least two behavioral criteria coded under part B OR Any ASD diagnosis documented in a comprehensive evaluation, whether based on DSM-IV-TR or DSM-5 diagnostic criteria NOTE: A child might be disqualified from meeting the DSM-5 surveillance case definition for ASD if, based on the clinical judgment of one or more reviewers, there is insufficient or conflicting information in support of ASD, sufficient information to rule out ASD, or if one or more other diagnosed conditions better account for the child's symptoms.

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; *PDD*, pervasive developmental disorder.

Baio J et al: Prevalence of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014. *MMWR Surveill Summ* 67(No. SS-6):1-23, 2018. https://dx.doi.org/10.15585/mmwr.ss6706a1.

BOX 2 Red Flags for Social Communication Development

Prompt evaluation should occur for any of the following: **No vocalizations by 6 months:** *A parent should be able to have a reciprocal "conversation" by this age, consisting of at least several volleys back and forth.* **No polysyllabic consonant babbling by 12 months:** *At least some of these vocalizations should be directed at someone with communicative intent.* **No gestures by 12 months:** *The earliest gesture an infant learns is to raise his/her arms to request to be picked up, usually once sitting independently. Pointing should be with an isolated index finger, not the whole hand, and should be used "to request" or "to show," not just pointing at pictures in a book or pointing to have an adult label items. Any use of hand-over-hand by the child (e.g., putting a parent's hand on the cabinet door where the cookies are kept or using the parent's hand to point at pictures in a book) is a hallmark of ASD.* **No spontaneous (not echoed) single words by 16 months other than mama or dada:** *Spontaneous words must be beyond those used to simply label items and must be used by the child to communicate, to request, to show, or to share.* **No spontaneous (not echoed) phrases by 24 months or sentences by 36 months:** *Spontaneous phrases and sentences must be used by the child to communicate, to request, to show, or to share.* **Any loss of social communication abilities, including babbling, single words, phrases, response to name, social engagement, or gestures:** *If a parent reports their infant has decreased or stopped any social communication milestones, this is usually the hallmark of the onset of regression.*

Swaiman KF et al: *Swaiman's pediatric neurology, principles and practice*, ed 6, Philadelphia, 2017, Elsevier.

life and are accompanied by atypical brain maturation trajectories
- No biomarkers have been identified

ETIOLOGY

- Majority of cases are not associated with a comorbid medical condition
- High prevalence of comorbid seizure disorder (25%) and/or intellectual disability (up to 75%)
- Sometimes present in the context of medical conditions (e.g., encephalitis, cytomegalovirus, toxoplasmosis, phenylketonuria [PKU], fragile X syndrome, tuberous sclerosis complex, neurofibromatosis)
- Numerous studies have shown **no** association between immunizations (specifically MMR vaccine) or thimerosal-containing vaccines (i.e., diphtheria, pertussis, and tetanus) and autism spectrum disorder

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Several genetic syndromes manifest with a phenotype similar to ASD (e.g., 22q11.2 deletion syndrome, Angelman syndrome, Aicardi syndrome, Cornelia de Lange syndrome, Christianson syndrome, fragile X syndrome, Landau-Kleffner syndrome, Klinefelter syndrome, neurofibromatosis, Prader-Willi syndrome, Rett syndrome, tuberous sclerosis complex, Williams syndrome).
- Several psychiatric or neurodevelopmental disorders present with symptoms similar to ASD (e.g., Tourette syndrome, selective mutism, catatonia, social phobia, obsessive/compulsive disorder, expressive language disorder, mixed receptive-expressive language disorder, stereotypic movement disorder, intellectual disability). Differences are notable in onset of symptoms and developmental trajectories.
- Social (pragmatic) communication disorder, introduced in DSM-5 and characterized by significant difficulties with verbal and nonverbal communication.
- Childhood-onset schizophrenia: Follows period of normal development.
- Attachment disorders (reactive attachment disorder, disinhibited social engagement disorder); individuals with these disorders can present with language delays, cognitive delays, social difficulties, and stereotypies. Differences are notable before 5 yr of age.

WORKUP

- Rule out underlying medical condition, including genetic syndromes.
- "Red flags" for critical delays in social communication development should be recognized or queried and should initiate evaluation for an ASD (Box 2). Validated autism spectrum disorder–specific screening tools are available for children age ≥18 mo. All children should be screened specifically for ASD at 18 and 24 mo. General developmental screening tools are currently used in children 9 to 18 mo.
- Gold standard assessment includes detailed developmental and family history, assessment of developmental/intellectual functioning, assessment of ASD symptomatology, and assessment of adaptive behaviors.
- Additional workup may include assessment of language functioning, neuropsychological functioning, and psychiatric presentation.

LABORATORY TESTS

- PKU screen (usually done at birth in the United States)
- Lead exposure screening
- Audiology testing for young children with ASD; school-based hearing screening may be sufficient in older children with autism spectrum disorders and without significant language or learning deficits
- Karyotype, chromosome microarray analysis, and DNA testing for fragile X syndrome in both boys and girls, as well as for different de novo copy number variants or mutations in specific genes associated with the disorder

IMAGING STUDIES

- Electroencephalogram to diagnose coexisting seizure disorder if seizures are suspected or if language regression is present (i.e., Landau-Kleffner syndrome)
- Brain MRI if tuberous sclerosis complex or Aicardi syndrome (callosal agenesis) is suspected

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Consistent behavioral training program in both the home and school environments
- A number of treatment programs have been developed; many are based on applied behavioral analysis (ABA) (e.g., Discrete Trial Training); others combine ABA procedures with social-emotional development (e.g., Pivotal Response Training, Floortime, Early Start Denver Model)
- Special educational program focused on language and communication skills, social and life skills development (e.g., TEACCH)
- Cognitive-Behavioral Therapy (CBT) has proven effective to ameliorate symptoms of anxiety in higher functioning individuals with ASD
- Highly structured home environment
- Education for families and teachers; the Autism Speaks™ website may be helpful in this regard: www.autismspeaks.org

ACUTE GENERAL Rx

- Obsessive or ritualistic behaviors: Selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics, valproic acid
- Aggression, irritability, self-injury: Atypical antipsychotic agents (e.g., risperidone), anticonvulsant mood stabilizers, SSRIs, beta-blockers, opiate antagonist (self-injury only)
- Hyperactivity, impulsivity, inattention: Stimulants, α-2 adrenergic agonists, atypical antipsychotics
- Anxiety: SSRIs, buspirone, mirtazapine
- Mood lability: Valproic acid, carbamazepine, lithium, aripiprazole
- Depression: SSRIs, mirtazapine
- Catatonia: Avoid antipsychotics, which make catatonia worse and potentially malignant, and use lorazepam; if unsuccessful, electroconvulsive therapy may be indicated
- Only risperidone and aripiprazole are FDA-approved for the management of symptoms associated with ASD
- Medications used to decrease specific symptoms associated with Autism Spectrum Disorder are summarized in Table 1

CHRONIC Rx

- Extended use of medications for acute management of comorbid psychiatric disorder
- Use of medications for comorbid medical conditions, including sleep problems and gastrointestinal problems
- Pharmacotherapy is palliative, not curative, of autism spectrum disorder

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Preliminary evidence is available for effectiveness of melatonin in ameliorating sleep problems.

TABLE 1 Medications Used to Decrease Specific Symptoms Associated with Autism Spectrum Disorder *

Drug	Dose	Age†	N	Efficacy	Side Effects
Neuroleptic Agents					
Risperidone	0.25-2.5 mg/d <20 kg 0.5-2.5 mg/d 20-45 kg 0.5-3.5 mg/d >45 kg Mean = 2.4 mg/d	5-17	101	Decreased tantrums, aggression, self-injury, hyperactivity	Weight gain, increased appetite, transient sedation
Risperidone	1.2-2.9 mg/d child Mean = 2.0 mg/d 2.4-5.3 mg/d adult Mean = 3.6 mg/d	8-56	36	Decreased irritability, hyperactivity	Increased appetite, weight gain, sedation
Risperidone	0.125-0.175 vs. 1.25-1.75 vs. placebo	5-17	96	Higher dose improves global function and irritability	Somnolence sedation increased appetite
Risperidone	0.01-0.06 mg/kg/d Mean = 1.17 mg/d	5-12	79	Decreased irritability, hyperactivity, noncompliance, conduct problems	Weight gain, transient somnolence, mildly increased heart rate and blood pressure
Risperidone	0.5-1.5 mg/d Mean = 1.14 mg/d	2.5-6	24	Minimal improvement in global autism severity scores	Weight gain, increased prolactin levels
Risperidone	1.0-10.0 mg/d	18-43	n =?	Reduced repetitive behavior, aggression, self-injury, property destruction	Transient sedation
Aripiprazole	5 mg/d, 10 mg/d, or 15 mg/d	6-17	218	Reduced irritability, hyperactivity, stereotypy at all doses	Sedation, EPS, weight gain
Aripiprazole	2-15 mg/d	6-17	98	Reduced irritability, hyperactivity, stereotypy, inappropriate speech, global improvement	Decreased prolactin level, weight gain, EPS
Aripiprazole	2-15 mg/d continuation active tx vs. placebo	6-17	85	No difference in time to relapse	
Opiate Antagonists					
Naltrexone	1.0 mg/kg/d	3-8	41	No improvement over placebo in behavior and learning; improved hyperactivity	None greater than placebo
Naltrexone	1.0 mg/kg/d 2 weeks only	3-8	24	No improvement in communication skills	Transient sedation
Naltrexone	40 mg/d Single dose	3-7	23	Decreased hyperactivity, improved attention	Not reported
Naltrexone	1 mg/kg/dose	3-7	23	Decreased hyperactivity and improved attention by teacher, but not parent, report	No side effects
Serotonin Reuptake Inhibitors					
Fluvoxamine	Mean dose = 276.7 mg/d	18-53	n = 30	Reduced repetitive thoughts and behavior, and aggression; improved social communication	Transient nausea and sedation
Buspirone	2.5 mg or 5 mg/d	2-6	166	Improvement in repetitive behaviors not total ADOS	
Clomipramine	5-10 mg/d	8-17	34	No improvement executive function	Diarrhea, headache, fatigue
Fluoxetine	4.8-20 mg/d Mean = 10.6 mg/d; 0.38 mg/kg/d	5-17	39	Modest reduction in repetitive behaviors, but no improvement in global functioning	Agitation requiring dose reduction
Citalopram	2.5-20 mg/d Mean = 16.5 mg/d	5-17	149	No improvement in repetitive behavior or global functioning	Increased energy, inattention, impulsivity, hyperactivity, stereotypy, diarrhea, insomnia, dry skin
Stimulants					
Methylphenidate	0.125, 0.25, or 0.5 t.i.d. mg/kg/day	5-14	72	Reduced inattention, distractibility, hyperactivity, and impulsivity	Irritability, decreased appetite, difficulty falling asleep, emotional outbursts
Methylphenidate	0.25, 0.5 mg/kg/dose	5-13	33	Positive efforts on social behavior	None discussed
Methylphenidate	10-40 LA AM, 2.5-10 mg afternoon	7-13	24	Decreased hyperactive and impulsive behavior	Loss of appetite, insomnia
Atomoxetine	20-100 mg/d Mean = 44.2 mg/d	5-15	16	Reduced hyperactivity, impulsivity, social withdrawal	Transient nausea and fatigue
Antiseizure Drugs					
Lamotrigine	Mean = 5.0 mg/kg/d	3-11	28	No improvement greater than placebo in disruptive behavior and autism symptoms	Aggression, insomnia, echolalia
Levetiracetam	20-30 mg/kg/d	5-17	20	No improvement in disruptive behavior or irritability	Aggression, agitation
Divalproex sodium	500-1500 mg/d	5-17	13	Reduction in compulsive-type repetitive behavior	Irritability, weight gain, aggression
Divalproex sodium	125 mg QD titrated up to 500 bid	5-17	27	Reduction in irritability	Irritability
Bumetanide	0.5 mg bid	3-11	60	Improved autistic behaviors and global function	Diarrhea, increased irritability

ADOS, Autism Diagnostic Observation Schedule; *EPS,* extrapyramidal symptoms; *LA AM,* L-alpha-acetylmethadol; *QD,* every day; *t.i.d.,* three times per day; *tx,* treatment.
*Includes only double-blind, randomized, placebo-controlled trials.
†Age in years.
Swaiman KF et al: *Swaiman's pediatric neurology, principles and practice*, ed 6, Philadelphia, 2017, Elsevier.

- Very limited rigorous evidence is available on the effectiveness of complimentary and alternative medicine, including nutritional interventions.

DISPOSITION

- Most children will require some degree of assistance as adults.
- DSM-5 identifies three severity levels based on social communication and restricted, repetitive behaviors: Level 1 (requiring support), Level 2 (requiring substantial support), and Level 3 (requiring very substantial support).
- With early diagnosis and proper treatment/support, the prognosis for children without language and intellectual impairment is fair to very good despite lifelong symptoms.
- Poorer outcomes include a lack of joint attention by age 4 yr, a lack of functional speech by age 5 yr, intellectual disability, seizures, comorbid medical or psychiatric syndromes, and a pervasive lack of social relatedness.
- Best outcomes are associated with early identification and treatment, the development of oral communication skills, and the cognitive and behavioral capacity for inclusion in regular education settings with typically developing peers.

REFERRAL

Assistance may be needed in diagnosis (child psychiatrist, clinical psychologist, geneticist, pediatric neurologist, developmental pediatrician), symptom management (speech language pathologist, occupational therapist, clinical psychologist), parental teaching (clinical psychologist, psychiatric social worker), and intervention with the school system (educational advocate, attorney).

PEARLS & CONSIDERATIONS

- There is no scientific evidence of a relation between childhood vaccination and the development of autism spectrum disorder.
- Evidence suggests that a disproportionate number of children with autism spectrum disorder suffer from a variety of medical problems including sleep difficulties, gastrointestinal problems, and oral health problems.
- Psychiatric comorbidities are very prominent across the life span, with estimated prevalence ranging from 30% to 70%.
- The new U.S. Preventive Services Task Force (USPSTF) recommendation on screening for ASD in young children concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for ASD in young children for whom no concerns of ASD have been raised by their parents or a clinician.
- A recent trial has shown that daily intranasal oxytocin improves social behavior in kids with ASD whose baseline endogenous blood oxytocin levels are low.[1]

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Autism (Patient Information)

AUTHOR: **Giulia Righi, PhD**

[1]Parker KJ et al: Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism. *Proc Natl Acad Sci USA* 114:8119, 2017.

SUGGESTED READINGS

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Young N, Findling RL: An update on pharmacotherapy for autism spectrum disorder in children and adolescents, *Curr Opin Psychiatry* 28(2):91-101, 2015.

BASIC INFORMATION

DEFINITION

Autoimmune hepatitis (AIH) is a chronic inflammatory condition of the liver characterized by elevated serum globulin levels (IgG), presence of circulating autoantibodies, interface hepatitis on histology, and plasma cell rich infiltrate. Three types have been described:

- Type 1, or "classic," autoimmune hepatitis is the most predominant form in the U.S. and worldwide (80%) and has a bimodal age distribution with peaks between 10 and 20 and 45 and 70 yr of age. Patients are positive for antinuclear antibodies (ANA) and/or anti-smooth muscle antibodies (ASMA) and have specific associated human leukocyte antigen (HLA) haplotypes: DR3, DR4, DR13. Usually excellent treatment response, but variable relapse rates after drug withdrawal; usually need for long-term maintenance therapy.
- Type 2, up to 10% of AIH cases, primarily affects young children between 2 and 14 yr of age, and is characterized by the presence of antibodies to liver/kidney microsomes (anti-LKM-1) or liver cytosol 1. Patients have associated HLA haplotypes: DR3 and DR7. This form is generally more advanced at presentation and is more difficult to treat; need for long-term maintenance therapy is very common.
- Type 3, up to 10% of AIH cases, only soluble liver antigen/liver pancreas antigen (SLA/LP) positive, otherwise very similar to AIH-1. Often Ro52-antibody positive. Lifelong immunosuppression in most, if not all patients.

SYNONYMS

Autoimmune chronic active hepatitis
AIH
Chronic active hepatitis
Lupoid hepatitis
Plasma cell hepatitis

ICD-10CM CODES

K75.4 Autoimmune hepatitis
K73.2 Chronic active hepatitis, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

- Annual incidence (estimated): 0.2 to 2.0 cases per 100,000, similar to primary biliary cirrhosis (PBC), more common than primary sclerosing cholangitis (PSC).
- Point prevalence (estimated): 16.9 per 100,000.
- Type 1: Age of onset has a bimodal distribution with peaks between 10 and 20 and 45 and 70 yr.
- Type 2: More common in young children 2 to 14 yr of age.
- Female:male ratio is 3.6:1; type 1 has an 80% female predominance, whereas type 2 has a 90% female predominance.
- Approximately 100,000 to 200,000 persons affected in the U.S.
- Accounts for 4% to 6% of liver transplants in the U.S.
- Associated with HLA-DRB1*0301 and HLA-DRB1*0401 alleles.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Varies from intermittent asymptomatic elevations of liver enzymes to advanced cirrhosis. One third of adults and one half of child patients with AIH have cirrhosis at presentation. AIH can also present initially as a fulminant hepatitis.
- Symptoms may include fatigue, anorexia, nausea, abdominal pain, pruritus, and arthralgia.
- Autoimmune findings may include arthritis, xerostomia, keratoconjunctivitis, cutaneous vasculitis, and erythema nodosum.
- Patients with advanced disease can show hepatosplenomegaly, ascites, peripheral edema, abnormal bleeding, and jaundice.

ETIOLOGY

- Exact etiology is unknown; liver histology demonstrates cell-mediated immune attack against hepatocytes.
- Presence of a variety of autoantibodies suggests an autoimmune mechanism.
- Observational studies have supported the idea of the main inflammatory activity being driven by T cells recognizing antigens expressed in the liver.
- There are likely two components involved: genetic predisposition and an inciting environmental trigger.
- Potential triggering agents such as viruses (hepatitis A, B, C) or drugs (minocycline, nitrofurantoin, biological agents, tumor necrosis factor [TNF] blockade) likely possess some homology similar to liver-specific antigens.

DIAGNOSIS

- A simplified diagnostic criteria for routine clinical practice has been developed by the International Autoimmune Hepatitis Group (see Table 1).
- Suggestive findings on histology: Lymphoplasmacytic infiltrate invading the hepatocyte boundary surrounding the portal triad (limiting plate). Also, a periportal infiltrate may be seen (interface hepatitis). Pericentric necrosis may be present in acute-onset AIH, indistinguishable from drug-induced liver injury (DILI).
- If coexistent findings of cholestatic liver disease on histology, rule out PSC and PBC, consider magnetic resonance cholangiography.
- The European Association for the Study of the Liver guidelines require liver biopsy as part of the diagnostic evaluation.
- The American Association for the Study of Liver Disease (AASLD) approach is to obtain a liver biopsy if the diagnosis is unclear or to assess disease activity prior to initiating treatment.

DIFFERENTIAL DIAGNOSIS

AIH should be considered in any patient with acute or chronic liver disease.

- Acute viral hepatitis (A, B, C, D, E, cytomegalovirus, Epstein-Barr, herpes)
- Chronic viral hepatitis (B, C)
- Toxic hepatitis (alcohol, drugs)
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Hemochromatosis
- Nonalcoholic steatohepatitis
- Systemic lupus erythematosus
- Wilson disease
- Alpha-1 antitrypsin deficiency

WORKUP

- History and physical examination with attention to the presence of autoimmune abnormalities such as autoimmune thyroiditis, Graves disease, inflammatory bowel disease, celiac sprue, and rheumatoid arthritis. Fig. 1 illustrates a diagnostic algorithm for autoimmune hepatitis
- Liver function tests and serum gamma-globulins
- Tests for autoantibodies: ANA, ASMA, anti-LKM, SLA/LP
- Liver biopsy for establishing diagnosis and disease severity

LABORATORY TESTS

- Aminotransferases generally elevated and may fluctuate, generally alanine aminotransferase (ALT) > aspartate aminotransferase (AST)
- Bilirubin and alkaline phosphatase moderately elevated or normal
- Elevation of gamma globulin (>2.0 g/dl [20 g/L]) and immunoglobulin G seen in 90% of patients, seen as markers of activity
- Circulating autoantibodies (Table E2) often present:
  1. Rheumatoid factor
  2. ANA:
     a. Present in two thirds of patients
     b. Typical pattern is homogeneous or speckled
     c. Titer does not correlate with the stage, activity, or prognosis

TABLE 1 Simplified Diagnostic Criteria for Autoimmune Hepatitis

Variable	Cutoff	Points	Cutoff	Points
ANA or SMA	≥1:40	1	≥1:80	2
LKM			≥1:40	2
SLA			Positive	2
IgG	≥ULN	1	≥1.1 × ULN	2
Histology	Compatible with AIH	1	Typical of AIH	2
Absence of viral hepatitis			Yes	2

Maximum number of points for all antibodies = 2, total = 8. Probable AIH ≥6 points, definite AIH ≥7 points. 88% sensitivity and 97% specificity. *AIH,* Autoimmune hepatitis; *ANA,* antinuclear antibody; *IgG,* immunoglobulin G; *LKM,* liver/kidney microsomes; *SLA,* soluble liver antigen; *SMA,* smooth muscle antibody; *ULN,* upper limit of normal.

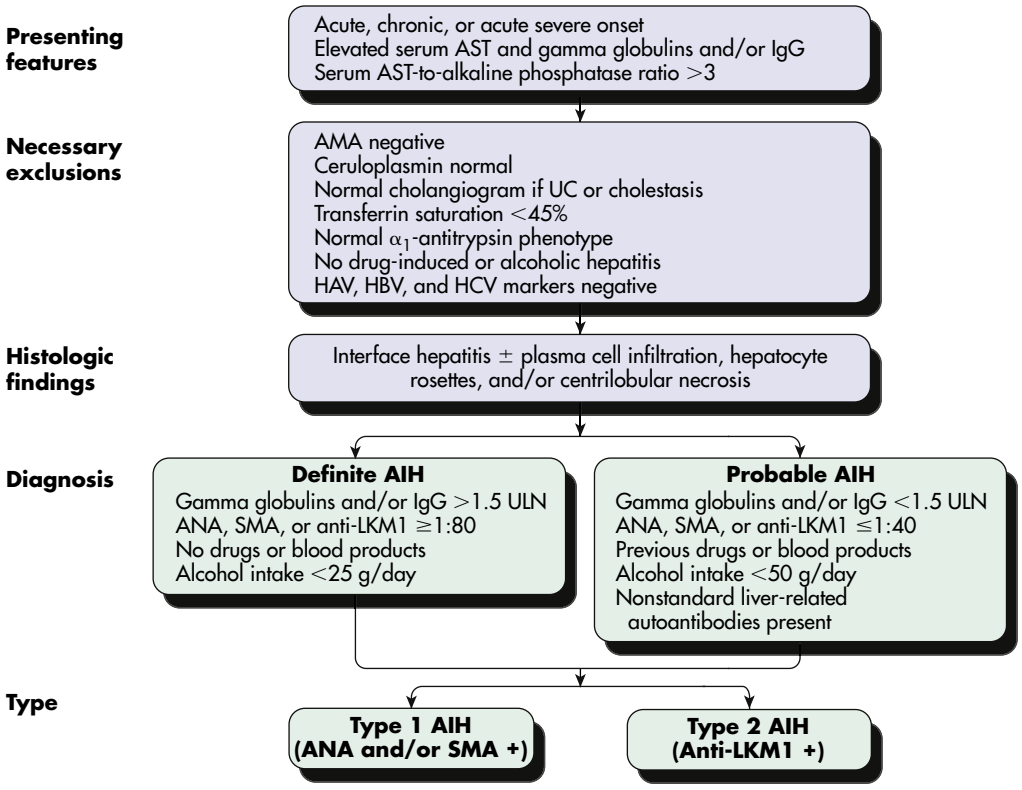

FIG. 1 Diagnostic algorithm for autoimmune hepatitis *(AIH)*. The diagnosis requires predominant elevation of the serum AST level and exclusion of other hepatic diseases (especially primary biliary cirrhosis, primary sclerosing cholangitis, Wilson disease, hemochromatosis, α1-antitrypsin deficiency, drug-induced or alcoholic hepatitis, and viral hepatitis). Antimitochondrial antibodies *(AMA)* should be absent; cholangiography should be negative in patients with concurrent UC or cholestasis; and the serologic markers of HAV, HBV, and HCV should be negative. Interface hepatitis should be present on histologic examination, and laboratory manifestations of immune reactivity should be evident by abnormal elevation of the serum gamma globulin and/or immunoglobulin G *(IgG)* level and the presence of antinuclear antibodies *(ANA)*, smooth muscle antibodies *(SMA)*, or antibodies to liver kidney microsome type 1 *(anti-LKM1)*. The degree of immune reactivity and the presence of confounding etiologic factors, such as alcohol and drug or blood product exposure, distinguish definite from probable AIH. Classification as type 1 AIH or type 2 AIH is based on the type of autoantibodies that predominate in the disease. *AST*, Aspartate aminotransferase; *HAV*, hepatitis A virus; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *UC,* ulcerative cholitis; *ULN*, upper limit of normal. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

3. Anti-SMA:
   a. Present in 87% of patients
   b. Titer does not correlate with course or prognosis
4. Anti-LKM antibodies:
   a. Typically found in patients who are ANA negative and SMA negative
   b. Characterizes type 2 AIH
   c. Present in pediatric population and up to 20% of adults in Europe; also present in patients with drug-induced hepatitis
5. Autoantibodies against soluble liver antigen and liver-pancreas antigen (anti-SLA/LP):
   a. Present in 10% to 30% of patients
   b. Associated with higher rate of relapse after corticosteroid therapy
   c. Several studies suggest that patients with anti-SLA/LP have a more severe course

Serum perinuclear anti-neutrophil cytoplasmic antibodies levels are useful for diagnosis of the 10% to 15% of patients with negative ASMA, negative ANA, and low gamma globulin levels.

- Hypoalbuminemia and prolonged prothrombin time with advanced disease
- There is a well-described overlap syndrome with primary biliary cirrhosis (7%), primary sclerosing cholangitis (6%), and autoimmune cholangitis (11%). In patients who do not respond to therapy after 3 mo, consider cholangiographic studies to evaluate for primary sclerosing cholangitis

IMAGING STUDIES

- Ultrasound of liver and biliary tree to rule out obstruction or hepatic mass.
- MR cholangiography if signs of concurrent cholestatic liver disease.
- Cirrhosis secondary to AIH is a risk factor for development of hepatocellular carcinoma (although less so than viral hepatitis). Patients with cirrhosis should get ultrasonography and AFP every 6 mo.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid alcohol and hepatotoxic medications.
- Liver transplantation is an option for end-stage disease or fulminant hepatic failure.

PHARMACOLOGIC THERAPY

- Initial treatment:
  1. Predniso(lo)ne 0.5 to 1 mg/kg/day followed by addition of azathioprine when bilirubin levels are <6 mg/dl, ideally 2 wk after initiation of steroid treatment. Initial dose 50 mg/day, increase depending on toxicity and response up to 1 to 2 mg/kg. A combination of oral budesonide (6 to 9 mg/day) and azathioprine (1 to 2 mg/kg/day) can be used to induce and maintain remission in patients with non-cirrhotic AIH, with a lower rate of steroid-specific side effects. Treatment of AIH should be response-guided, and regimens should be individualized. Steroids are contraindicated in brittle diabetes mellitus, uncontrolled hypertension, prior steroid intolerance, severe osteopenia, and psychosis. Azathioprine is contraindicated by thiopurine S-methyltransferase (TPMT) deficiency, leukopenia, or thrombocytopenia. Budesonide is contraindicated in cirrhosis because portal systemic shunting and abnormal hepatic metabolism prevent complete hepatic first-pass extraction, reducing therapeutic efficacy and causing systemic steroid side effects.
  2. The azathioprine metabolite, 6-mercaptopurine, has shown promise via small studies in maintaining remission for patients intolerant of azathioprine.

3. Combination therapy allows lower prednisone doses, fewer steroid side effects, and faster normalization of liver function tests.

- The primary goal of therapy in AIH is to achieve remission. The 2015 European Association for the Study of the Liver (EASL) Practice Guideline define biochemical remission as normalization of IgG and aminotransferases. Histologic remission is defined as normal histology or minimal hepatitis (HAI <4 or equivalent) based on the hepatic activity index (HAI). Secondary goals of therapy are the prevention of progression of fibrosis to cirrhosis and reversion of cirrhosis to a lower stage of fibrosis, which has been documented.
- Indications for treatment:
  1. Advanced fibrosis/cirrhosis
  2. Active disease (HAI >4) on histology
- Treatment not indicated:
  1. Mild disease with ALT <3× ULN; HAI <4 and no advanced fibrosis (in these cases treatment is optional)
  2. Patients can be monitored every 3 months with laboratory tests (ALT, IgG)
- Evaluation of treatment response:
  1. Goals are the absence of symptoms, normalization of liver function tests, and absence of inflammatory activity on liver biopsy. Generally, this is a steroid-responsive condition, but up to 20% do not respond.
  2. Patients whose transaminase levels normalize may continue to have ongoing active hepatitis involving inflammation and fibrosis.
  3. Histologic improvement may lag behind clinical and laboratory improvement by as much as 6 mo. Because of this, repeat liver biopsy should be considered after normalization of transaminase levels and before stopping treatment. A review of AIH studies between 1972 and 2013 shows that hepatic fibrosis improves in 53% to 57% of cases and that progressive fibrosis is slowed or prevented in 79% of patients.
  4. After initial remission is achieved and azathioprine has been added, steroid taper can be initiated as long as liver tests are normal. About 50% to 86% of patients will relapse after this and require long-term maintenance medications.
  5. Complete normalization on biopsy is associated with a 15% to 20% risk of relapse, whereas persistent interface hepatitis is associated with a 90% risk of relapse. Do not attempt multiple treatment withdrawals. The risk of developing cirrhosis with single relapse is 9.5%, whereas multiple relapses are associated with 37.5% risk of developing cirrhosis. The patient with sustained remission has a risk of cirrhosis of 4.5%.
  6. Suboptimal response: A failure to adequate response should lead to a reconsideration of the diagnosis or re-evaluation of adherence to treatment. In patients with suboptimal response despite reconfirmation of diagnosis and adherence, doses of prednisolone and azathioprine should be increased, or alternative medications should be used. Patients with acute severe AIH should be treated with high doses of intravenous corticosteroids (>1 mg/kg) as early as possible. Lack of improvement within 7 days should lead to consideration of emergency liver transplantation.

DISPOSITION

- Long-term treatment may be necessary for sustained remission in individuals who relapse after initial immunosuppression withdrawal and in partial responders.
- 65% of patients achieve remission by 18 mo; 80% achieve remission by 3 yr.
- Approximately 10% to 15% of patients do not respond to conventional therapy. The risk factors for nonresponse include presence of underlying cirrhosis, younger age, or longer duration of disease, HLA-B8 or DR3. High-dose therapy can achieve remission in 70%: Prednisone 60 mg or dual therapy with prednisone 30 mg and AZA 150 mg. Other alternatives such as mycophenolate, the calcineurin inhibitors (CNIs), tacrolimus (TAC) and cyclosporine (CSA), sirolimus (SIR), everolimus (EVR), rituximab, and infliximab, have been used successfully. However, none of the alternative therapies has been studied in multicenter, randomized, controlled trials.
- Orthotopic liver transplantation (OLT) is a lifesaving option for AIH patients with acute liver failure, decompensated cirrhosis, or HCC. Allograft and patient survival are excellent; however, AIH recurs in the allograft in a minority (25% probability in first 5 yr, 50% in 10 yr).

REFERRAL

Patients with advanced cirrhosis or who progress to end-stage liver disease are candidates for liver transplantation and should be referred to appropriate medical centers that provide liver transplantation services.

PEARLS & CONSIDERATIONS

COMMENTS

- ANA and SMA are observed together in 60% of cases. Serum titers >1:40 suggest autoimmune hepatitis.
- A variety of autoimmune conditions can be seen in association with autoimmune hepatitis, including thyroiditis, Graves disease, ulcerative colitis, rheumatoid arthritis, uveitis, pernicious anemia, Sjögren syndrome, mixed connective tissue disease, CREST syndrome, and vitiligo.
- Variant forms of autoimmune hepatitis (overlap syndrome) have clinical and serologic findings of autoimmune hepatitis plus features of other forms of chronic liver disease such as PBC or PSC.

PREVENTION

None

PATIENT & FAMILY EDUCATION

- American Liver Foundation (ALF): Phone: 800-GO-LIVER (465-4837); Internet: www.liverfoundation.org
- National Digestive Diseases Information Clearinghouse: www.niddk.nih.gov/health-information/digestive-diseases

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Autoimmune Hepatitis (Patient Information)

AUTHORS: **Jaspreet S. Suri, MD,** and **Andreea M. Catana, MD**

TABLE E2 Serologic Markers of Autoimmune Hepatitis

Autoantibodies	Antigenic Target	Clinical Implications
ANA	Multiple nuclear antigens	Type 1 AIH Variably expressed with SMA
SMA	Actin (F and G) Nonactin components (14%)	Type 1 AIH Variably expressed with ANA
Anti-LKM1	CYP2D6 (main epitope, 193-212 amino acid sequence)	Type 2 AIH Usually exclusive of ANA, SMA Mainly in children Associated with HLA DRB1*07
Anti-SLA	Transfer ribonucleoprotein ($tRNP^{(ser)sec}$); renamed Sep [O-phosphoserine] tRNA:Sec [selenocysteine] tRNA synthase (SEPSECS)	Diagnostic specificity of 99% for AIH Associated with HLA DRB1*0301 and anti-Ro/SSA Of prognostic value (severe disease, relapse, treatment dependence)
Atypical pANCA	Nuclear lamina proteins	Present in 50%-92% of type 1 AIH Absent in type 2 AIH Associated with PSC and UC
Anti-actin	Actin (F and G)	Present in 86% of AIH with SMA Of possible prognostic value (assay dependent) Double reactivities to actin and α-actinin are associated with severe disease
Anti-asialoglycoprotein receptor	Asialoglycoprotein receptor (recombinant H1 subunit in investigational EIA)	Associated with histologic activity and relapse after drug withdrawal Disappears with effective treatment
Anti-liver cytosol type 1	Formiminotransferase cyclodeaminase	Frequently concurrent with anti-LKM1 (32%) Mainly in young patients (≤20 yr of age) Associated with concurrent immune diseases, severe liver inflammation, and rapid progression to cirrhosis Rare in North American patients

Anti-LKM1, Antibodies to liver kidney microsome type 1; *anti-SLA,* antibodies to soluble liver antigen; *AIH,* autoimmune hepatitis; *ANA,* antinuclear antibodies; *CYP2D6,* cytochrome P450 2D6; *EIA,* enzyme immunoassay; *pANCA,* perinuclear antineutrophil cytoplasmic antibodies; *PSC,* primary sclerosing cholangitis; *Ro/SSA,* ribonucleoprotein/Sjögren syndrome A protein; *SMA,* smooth muscle antibodies.

From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

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Autosomal Dominant Polycystic Kidney Disease (ADPKD)

BASIC INFORMATION

DEFINITION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease. ADPKD is a systemic, inherited disorder due to mutations in either the *PKD1* or *PKD2* genes. These mutations lead to continual, fluid-filled cyst formation and growth in multiple organs including the kidneys, liver, and pancreas. ADPKD is also associated with multiple gastrointestinal and cardiovascular abnormalities.

SYNONYMS

Polycystic kidney disease
ADPKD
PKD

ICD-10CM CODES

Q61.3	Polycystic kidney, unspecified
Q61.2	Polycystic kidney, adult type
Q61.19	Other polycystic kidney, infantile type
Z82.71	Family history of polycystic kidney

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common, single, genetic cause of chronic kidney disease (CKD).
- Mendelian dominant disorder.
- Affects all ethnic groups equally worldwide.
- Autosomal dominant polycystic kidney disease type 1: Approximately 78% of affected individuals with genetically resolved cases have a gene mutation on chromosome 16 (*PKD1* gene).
- Autosomal dominant polycystic kidney disease type 2: Approximately 15% of affected individuals with genetically resolved cases have a gene mutation located on chromosome 4 (*PKD2* gene).
- Autosomal dominant polycystic kidney disease type 3: An increasing number of cases have been linked to mutations of the alpha glucosidase II gene (*GANAB*) located on chromosome 11q12.3.
- Each child of an affected parent has a 50% chance of inheriting the mutated gene.
- The disease has 100% penetrance and does not skip generations.

INCIDENCE: ADPKD prevalence was reported to be between 1 in 400 and 1 in 1000 live births based on earlier studies from Denmark and U.S. ADPKD prevalence reported in subsequent studies from Europe and Japan is between 1 in 2525 and 1 in 4000.

GENETICS: The bulk of ADPKD cases stem from a mutation in the *PKD1* gene, located on the short arm of chromosome 16. The gene encoding polycystin-1 (PC1) plays a vital role in cell-cell and cell-matrix interactions and primary ciliary function. Mutations in the *PKD1* gene lead to altered differentiation of epithelial cells and the abnormal phenotypic expression that characterizes ADPKD. ADPKD is less commonly caused by a mutation in the *PKD2* gene located on chromosome 4. The *PKD2* gene encodes the protein polycystin-2 (PC2) that is involved in intracellular calcium signaling. *PKD2* patients typically have milder disease with later onset of end-stage renal disease (ESRD), death, and hypertension. Polycystins 1 and 2 form a single functional protein complex via interactions of their intracellular carboxy termini. Consequently, a mutation of either the *PKD1* or *PKD2* gene produces a similar phenotype that cannot be distinguished.

ADPKD is also caused by mutations in the *GANAB* gene in up to 3% of ADPKD patients. This gene is located on chromosome 11q12.3 and is expressed in kidney and liver. The gene product plays an important role in PC1 maturation. Typically, ADPKD patients with *GANAB* gene mutations have mild PKD and mild-to-severe polycystic liver disease.

CLINICAL PRESENTATION

ADPKD is a systemic disorder, and symptoms relate primarily to kidney cyst burden and extrarenal involvement, including polycystic liver disease and vascular complications (Fig. E1). Total kidney volume (TKV) and cyst volume in ADPKD increase exponentially over time in patients with ADPKD.

RENAL MANIFESTATIONS

Many patients with ADPKD are relatively asymptomatic, particularly in the first three decades of life. A diagnosis of ADPKD is typically established by identification of an afflicted family member with asymptomatic screening (approximately 40% of cases), or renal imaging performed for clinical indications. Patients may present with gross hematuria, flank mass/pain, polyuria/nocturia, fever due to a kidney or lower urinary tract infection, nephrolithiasis, or blood pressure elevation. Typically more than half of patients will have one of these complications by age 30. Importantly, all of these complications are manifested through increased cyst burden or TKV.

Gross hematuria occurs in 35% to 50% of patients with ADPKD and is associated with greater TKV. Gross hematuria may also result from spontaneous or traumatic cyst rupture into the collecting system and more typically microscopic hematuria is secondary to nephrolithiasis. Nephrolithiasis occurs in approximately 27% of ADPKD patients, due in part to low levels of urinary citrate, increased serum uric acid concentrations, and alterations in calcium oxalate and calcium phosphate supersaturation. Nephrolithiasis may present with acute flank pain with radiation to the groin, often with a fever and hematuria, commonly microscopic.

Polyuria, nocturia, and increased thirst in ADPKD occur from impaired urinary concentrating ability and increase in circulating vasopressin levels.

Proteinuria is not a common feature of ADPKD and is usually less than 1 g/day. However, the presence of detectable proteinuria and microalbuminuria is correlated with increased TKV and more severe kidney disease.

Lower urinary tract infections are common in patients with ADPKD but may not occur more frequently than in the general population. Renal cyst infections are specific to ADPKD, and patients typically present with localized flank pain, fevers, and nausea and vomiting, similar to pyelonephritis.

Acute flank pain can be caused by a kidney stone, kidney or liver cyst rupture, or hemorrhage. Chronic pain is typically due to enlarged kidneys, unilaterally or bilaterally.

CARDIAC MANIFESTATIONS

Hypertension occurs in 60% of patients with ADPKD before any substantial decline in kidney function, and appears earlier in males than in females. Hypertension in ADPKD is due to upregulation of the renin-angiotensin-aldosterone system (RAAS). Hypertension is a predictor of worse renal outcome and is associated with cardiovascular morbidity and mortality. Cardiac valvular abnormalities occur in 25% to 30% of patients and include mitral valve prolapse and aortic regurgitation.

EXTRARENAL MANIFESTATIONS

- The prevalence of intracranial aneurysms (ICAs) in ADPKD is approximately 5% and increases to as high as 20% in patients who have a first-degree relative with a known intracranial aneurysm rupture.
- Rupture of an ICA is a serious complication of PKD and may produce significant permanent morbidity or death. Routine screening for ICA is recommended for patients with a family history of ICA or intracerebral bleed. Recently, smoking exposure and the presence of hypertension have been shown to associate with ICA in ADPKD. Screening is also recommended for ADPKD patients before major elective surgery, patients employed in high-risk occupations that would potentially place the lives of others at risk from a ruptured aneurysm (e.g., pilots, heavy machine operators), or patients with warning symptoms such as a sentinel headache.
- In addition to kidney cysts, cysts can develop in the liver, pancreas, and seminal vesicles. Hepatic cysts are common and occur in nearly 85% of ADPKD patients by age 30 yr. Hepatic cysts represent the most common extrarenal manifestation of ADPKD. Liver cystic disease is typically asymptomatic and develops slightly later than kidney cysts in ADPKD. However, hepatic cysts can cause serious complications including pain, infection, bleeding, and biliary obstruction. Liver cysts continue to grow and expand after patients reach kidney failure.
- Colonic diverticula and abdominal or inguinal hernias occur more frequently in ADPKD patients.
- Seminal vesical cysts have been reported to occur in up to 40% of men with ADPKD, but are not associated with reduced fertility.
- Patients with ADPKD may be at an increased risk of developing liver, colon, and kidney cancer. However, there is sparse evidence on which to recommend any change in current cancer-screening guidelines for ADPKD patients.

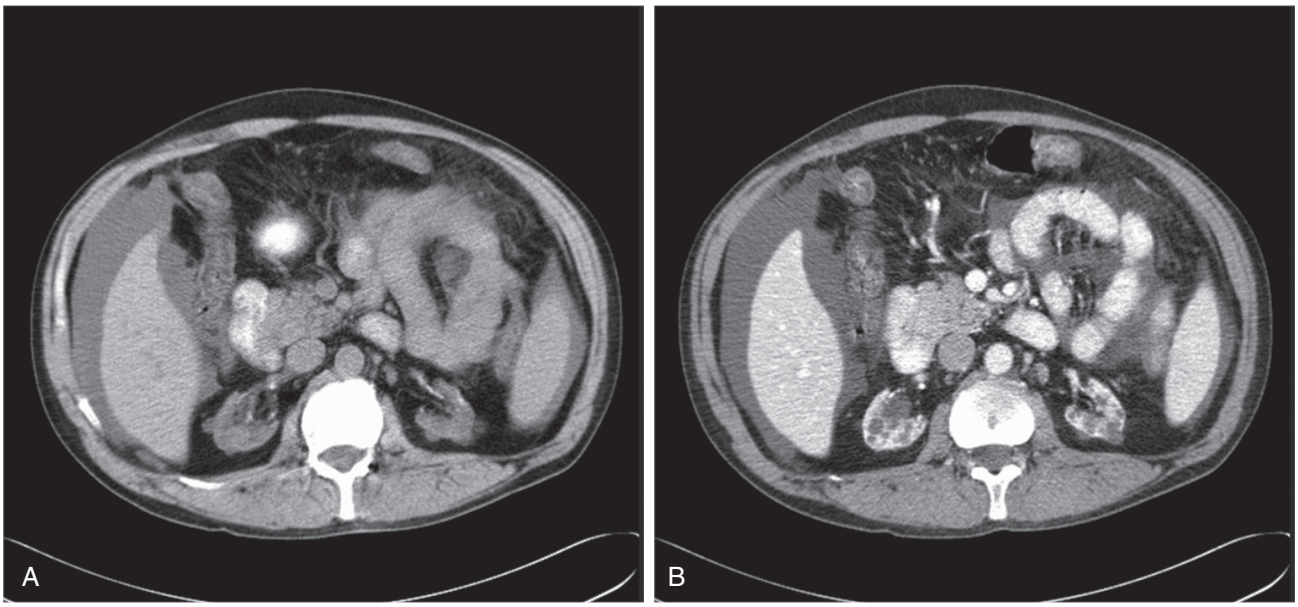

FIG. 3 Adulthood-acquired polycystic kidney disease: computed tomography scan, axial image without contrast material **(A),** and axial image after administration of contrast material **(B).** The kidneys are small bilaterally with multiple 1-cm cysts primarily in the cortex. (From Skorecki K et al: *Brenner & Rector's the kidney*, ed 10, Philadelphia, 2016, Elsevier.)

NATURAL HISTORY

- Patients with *PKD1* gene mutations have faster disease progression than patients with *PKD2* gene mutations. The median age of onset of ESRD is 54 yr in *PKD1* gene patients and 74 yr in *PKD2* patients.
- Patients with truncating *PKD1* gene mutations have faster disease progression than patients with nontruncating *PKD1* gene mutations. The median age of onset of ESRD is 55 yr in *PKD1* patients with truncating mutations and 67 yr in patients with nontruncating mutations.
- Other clinical risk factors associated with progressive kidney disease in ADPKD include male sex, onset of hypertension before 35 yr of age, gross hematuria before age 40, presence of proteinuria or microalbuminuria, increased urinary sodium excretion, and increased circulatory low-density lipoprotein cholesterol levels. However, all of these risk factors are mediated through cyst burden or TKV.
- Data from the Consortium of Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) indicate that a decline in renal blood flow and increases in TKV and cyst volume are strong predictors of future renal functional decline and progression to CKD stage 3. A baseline height-adjusted TKV (htTKV) of 600 ml/m predicts the risk of developing CKD stage 3 within 8 yr. Patients with ADPKD may be classified as 1A to 1E based on the Mayo Clinic Imaging Classification of ADPKD (https://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754). This classification is based on growth rates estimated from age-based htTKV (<1.5%, 1.5% to 3%, 3% to 4.5%, 4.5% to 6%, >6%/yr). This classification should only be applied to patients previously classified as having typical ADPKD (i.e., large kidneys with extensive cysts scattered throughout both kidneys at ages 15 to 80 yr). Patients in class 1A are at a low risk for renal function decline. Patients in classes 1C to 1E are at a high risk for progressive disease. This classification helps physicians identify patients with severe disease.

Dx DIAGNOSIS

- Ultrasound of the kidneys is the most commonly used imaging modality for screening and diagnosis. It is inexpensive, readily available, noninvasive, and free of radiation. CT and MRI are also used, but typically in the setting of acute complications. CT scans (Fig. E2) and MRI are more sensitive than ultrasound, with cyst detection at <1 cm in size.
- The following diagnostic criteria are used for diagnosis of ADPKD in asymptomatic individuals at risk for development of ADPKD (i.e., those with positive family history of ADPKD):
  1. Individuals 15 to 39 yr of age: At least three unilateral or bilateral kidney cysts.
  2. Individuals 40 to 59 yr of age: At least two cysts in each kidney.
  3. Individuals older than 60 yr of age: At least four cysts in each kidney.
- With no family history of ADPKD, there is no definitive number of cysts and/or cyst location that provides an unequivocal diagnosis. The diagnosis is strongly suspected when multiple and bilateral kidney cysts are present along with hepatic cysts.
- Genetic testing can be done to diagnose ADPKD when imaging results are equivocal and when a definitive diagnosis is required in a young individual such as a potential living donor.

DIFFERENTIAL DIAGNOSIS

- Multiple benign simple cysts
- Autosomal recessive PKD
- Familial juvenile nephronophthisis
- Medullary cystic or UMOD (uromodulin) disease
- Medullary sponge kidney
- Tuberous sclerosis
- von Hippel-Lindau syndrome
- Acquired cystic kidney disease (Fig. 3)
- Table 1 compares renal cystic diseases

LABORATORY TESTS

- Hemoglobin and hematocrit may be elevated because of increased erythropoietin production but are typically similar to levels in other patients with CKD.
- Urinalysis can show microscopic hematuria and proteinuria (rarely >1 g per day).
- With decreased kidney function, blood urea nitrogen and creatinine are elevated.
- Platelet counts can be mildly reduced in patients with extensive polycystic liver disease.
- Metabolic acidosis, hyperparathyroidism, and hyperphosphatemia are all associated with CKD in ADPKD.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Dietary intervention should be prescribed to all ADPKD patients.

- Restriction of dietary salt (<2 g sodium per day) and calories is recommended. Post hoc analysis of the HALT-PKD trial in which all patients were instructed to follow a sodium-restricted diet (2.4 g per day) showed that greater urine sodium excretion was

TABLE 1 Comparison of Renal Cystic Diseases

	ADPKD	Tuberous Sclerosis	ARPKD	MCDK	Simple Cyst
Inheritance	AD	AD	AR	None	None
Distribution	Bilateral unequal	Bilateral	Bilateral equal	Unilateral or bilateral	Unilateral
Kidney size	Normal or large	Normal or large	Very large (>90th percentile)	Small or large	Normal
Extrarenal manifestations	Cysts in the liver, spleen, pancreas	Cardiac rhabdomyomas, intracranial tubers	Congenital hepatic fibrosis	None	None
Age at presentation	Third decade	Often <18 mo	Neonate and childhood	Antenatal, rare in childhood	Onset in adult life
Cyst size	Visible cysts of variable size	Similar to ADPKD, ± angiomyolipomas	Generally small	Large then often involute	Variable
Diagnosis	US, genetic	US, cardiac echo, cranial MRI	US, IVU, liver biopsy	US, MAG3	US, IVU
Malignancy risk	No	Yes	No	Rare	No

AD, Autosomal dominant; *ADPKD,* autosomal dominant polycystic kidney disease; *AR,* autosomal recessive; *ARPKD,* autosomal recessive polycystic kidney disease; *IVU*, intravenous urography; *MCDK,* multicystic dysplastic kidney; *MRI,* magnetic resonance imaging; *US,* ultrasound.
From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.

associated with kidney growth and faster renal function decline.
- Cyclic adenosine monophosphate (cAMP) contributes to cyst formation and growth in ADPKD. Circulating vasopressin stimulates renal cAMP production. Increasing water intake to greater than 3 L per day can suppress vasopressin. Consequently, increasing water intake is recommended for all ADPKD patients with preserved renal function. However, serum sodium should be monitored carefully in patients with advanced CKD because these individuals are vulnerable to the development of hyponatremia.

CHRONIC GENERAL Rx

- Data from the HALT-PKD trial showed that in young individuals with preserved kidney function, strict BP control of <110/75 mm Hg was associated with slower increase in TKV, reduced urinary albumin excretion, and a greater reduction of left ventricular mass index.
- For all ADPKD patients, the goal BP is <130/80 mm Hg. For young, healthy patients with ADPKD and with intact kidney function, the goal BP target can be <110/75 mm Hg.
- ACE inhibitors or angiotensin II receptor blockers are the drugs of first drug for treatment of hypertension.
- Hyperlipidemia should be aggressively treated, and LDL-cholesterol targets are <80 mg/dl.
- Pravastatin was found to have a beneficial effect on htTKV, left ventricular mass index, and urinary albumin excretion in a randomized, double-blind, placebo-controlled phase 2 trial involving 91 children and young adults with ADPKD. A 23% change in htTKV was observed in the pravastatin group compared to 31% in the placebo group.
- Statin therapy did not show any benefit in a post hoc analysis of the HALT-PKD trials. However, this study was not randomized, different statin drugs and doses were used, and only a small number of statin users were in that study.
- Use of statins in the management of patients with ADPKD is a personal physician choice. A larger, randomized controlled trial is required to study the effect of statins on cyst growth.
- Patients who progress to ESRD require renal replacement therapy. Both peritoneal dialysis and hemodialysis can be used as a bridge to kidney transplantation.

The complication rates after nephrectomy are higher with pre–kidney transplant nephrectomy compared with posttransplant nephrectomy. Blood transfusion during pre–kidney transplant nephrectomy my cause allosensitization and can delay kidney transplantation evaluation. Consequently, routine pre–kidney transplant nephrectomy is not recommended. Pre–kidney transplant unilateral or bilateral nephrectomy is recommended only in select patients with recurrent infections, recurrent or severe bleeding, renal cell carcinoma, and significant kidney enlargement causing limitation of daily activities, and malnutrition.

ACUTE GENERAL Rx

- The treatment of gross hematuria is typically supportive with bed rest, hydration, and analgesics. Antihypertensive medications should be stopped during this time.
- Extracorporeal shock wave lithotripsy (ESWL) has been used in patients with small obstructing kidney stones (<2 cm diameter) in the renal pelvis or calyces. Percutaneous nephrolithotomy is another potential option.
- Infections are treated with antibiotics that penetrate cysts, such as fluoroquinolones, trimethoprim/sulfamethoxazole, vancomycin, and chloramphenicol.
- New therapies affecting cyst growth
- Tolvaptan
- In a phase 3, double-blind, placebo-controlled, randomized trial (TEMPO 3:4 trial) involving 1450 patients with PKD and preserved kidney function, the vasopressin-receptor 2 antagonist, tolvaptan, significantly decreased kidney volume and slowed the decline in kidney function. The benefits of tolvaptan on TKV rate of increase and decline of kidney function are greater in patients with increased albuminuria. The benefits of tolvaptan on TKV were seen across CKD stages 1 to 3.
- The effect of tolvaptan on delaying renal function decline was maintained for additional 2 yr in an extension study TEMPO 4:4 trial, where all TEMPO 3:4 participants were offered treatment with tolvaptan for an additional 2 yr.
- A second tolvaptan trial (REPRISE) was conducted and examined the safety and efficacy of tolvaptan in patients with more advanced ADPKD. This was a 12-mo phase III, randomized withdrawal, multicenter, placebo-controlled double-blind trial that included 1370 patients with eGFR between 25 and 65 ml/min/1.73 m^2. Tolvaptan-treated patients demonstrated a reduction in eGFR decline of 35% compared to placebo. Those receiving placebo lost 3.61 ml/min per 1.73 m^2 per yr. Tolvaptan-treated patients demonstrated an eGFR decline of 2.34 ml/min per 1.73 m^2 per yr, a difference of 1.27 ml/min per 1.73 m^2 per yr, which was statistically significant. The beneficial effect of tolvaptan on renal function decline was established in all subgroups (<55 yr of age, men and women, and patients with CKD stages 3A, 3B, and 4). This beneficial effect was not observed in patients older than 55 yr of age. However, firm conclusions cannot be made in this subgroup due to relatively smaller numbers.
- Based on the above studies, the FDA approved tolvaptan for treatment of ADPKD in adult patients at risk for rapidly progressing ADPKD on April 24, 2018.
- Patients at Mayo classes 1C–1E levels of cyst burden (faster rates of cyst growth) likely have rapidly progressive disease and should be considered for treatment with tolvaptan. Treated individuals may experience polyuria, nocturia, abnormally frequent urination, and polydipsia. Post-hoc analysis of TEMPO 3:4 and TEMPO 4:4 trials suggests that the drug effects are more pronounced early after drug initiation and in patients with better kidney function. Appropriate hydration

is essential to prevent thirst, dehydration, and hypernatremia.

A minor reversible eGFR reduction of 5% to 10% is anticipated after initiation of tolvaptan. Tolvaptan dose reduction or withholding of the agent is recommended if a significant decline of GFR of >20% is observed. Renal function testing should be carried out 2 and 4 wk after initiation, then monthly for the first 18 mo, and every 3 mo thereafter. To ensure that patients are maintaining hydration while on tolvaptan, plasma sodium concentration measurements must be obtained.

- Another important adverse event associated with tolvaptan is liver toxicity. Two patients in the TEMPO 3:4 trial and 1 patient in the TEMPO 4:4 trial developed serious drug-induced liver injury. In the REPRISE trial, liver adverse effects were greater in the tolvaptan group compared to placebo (5.6% vs. 1.2%). Because of the risks of serious liver injury, tolvaptan prescriptions are only available through a restricted distribution program called the Risk Evaluation and Mitigation Strategy (REMS). Under this program, liver function testing is done before initiation of treatment, at 2 wk and 4 wk after initiation, then monthly for the first 18 mo, and every 3 mo thereafter.

Other therapies affecting cyst growth:

- A small trial involving the somatostatin analogue, octreotide long-acting repeatable depot, showed that there was significantly less increase in TKV in the octreotide group compared with placebo. Another randomized phase III trial involving 100 ADPKD patients with eGFRs between 15 and 40 ml/min per 1.73 m^2 demonstrated that a 3-yr treatment with octreotide long-acting release (octreotide LAR) significantly slowed kidney volume growth. Octreotide LAR did not affect GFR decline compared with placebo. However, fewer patients in the octreotide group progressed to the combined end point of doubling of serum creatinine or ESRD when compared with placebo (19% vs. 43%).
- In a phase 2, randomized, double-blind, placebo-controlled study, the oral tyrosine kinase inhibitor bosutinib reduced kidney growth and preserved kidney function. However, medication-related adverse events (diarrhea, rash, and pancreatitis) and acute declines in kidney function have limited development of this agent.
- Two randomized, double-blind trials investigating the mammalian target of rapamycin inhibitors, sirolimus and everolimus, did not show any effect on renal function in these patients. The shorter duration of these trials and inadequate dosing of the medications may have affected the outcome.

REFERRAL

- Patients with ADPKD should be referred at time of diagnosis to a nephrologist for ongoing care. Urology can also be consulted in patients with nephrolithiasis for recurrent episodes of gross hematuria, or consideration for nephrectomy before transplantation.

Genetic counseling should be offered if patients plan to start a family or are considering having their children undergo screening examinations. Individuals at risk for ADPKD should undergo pretest and posttest counseling if they are found to have ADPKD.

PEARLS & CONSIDERATIONS

- ADPKD is the most common, single, genetic cause of CKD.
- TKV increases exponentially over time, and the increase in TKV is a strong predictor of future kidney functional decline.
- Increasing water intake to >3 L per day is recommended in patients with ADPKD and preserved kidney function.
- Tolvaptan is recommended for patients with rapidly progressing ADPKD.
- Strict blood pressure control is recommended for all ADPKD patients.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Polycystic Kidney Disease (Patient Information)

AUTHOR: **Bharathi V. Reddy, MD**

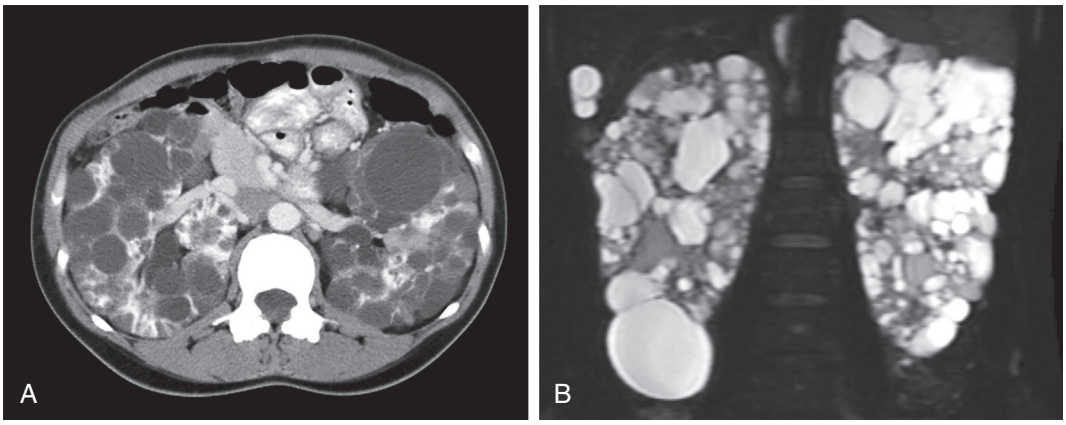

FIG. E1 A, Axial contrast-enhanced computed tomography (CT) image and **B,** coronal T2-weighted single-shot fast spin echo magnetic resonance imaging (MRI) in a 39-yr-old woman with autosomal polycystic kidney disease. Contrast administration is necessary to differentiate the cystic tissue from preserved parenchyma and detect small cysts using CT, but it is not necessary using MRI. (From Chebib FT et al: Autosomal dominant polycystic kidney disease: core curriculum 2016, *Am J Kidney Dis* 67(5):792-810, 2016.)

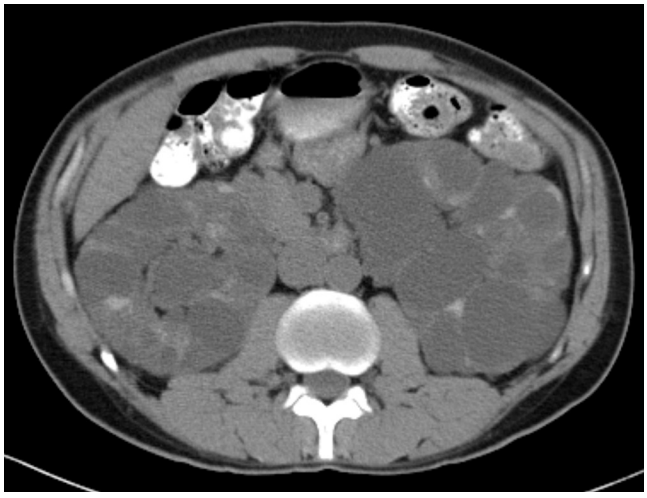

FIG. E2 Autosomal dominant polycystic kidney disease: Computed tomography scan without contrast material. This image demonstrates the markedly enlarged kidney bilaterally with multiple low-density cysts throughout both kidneys. The little remaining renal parenchyma is noted by the sparse, higher density material squeezed by the cysts. (From Skorecki K et al: *Brenner & Rector's the kidney*, ed 10, Philadelphia, 2016, Elsevier.)

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BASIC INFORMATION

DEFINITION

Cerebral arteriovenous malformations (AVMs) are congenital vascular lesions that are characterized by blood flow from high-pressure arterial vessels directly into thin-walled veins without passing through an intervening capillary/venule system (Fig. 1).

SYNONYMS

Arteriovenous malformations of the brain
AVM
Brain AVM

ICD-10CM CODE
Q28.2 Arteriovenous malformations of cerebral vessels

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:
- Detection rates in large prospective studies range from 1.1 to 1.4 per 100,000 person-yr.
- Incidence of hemorrhage, the most common and often most clinically dangerous presentation, is estimated to be 2% to 4% per yr.

PREVALENCE: Estimated about 1.3 per 100,000
PREDOMINANT SEX AND AGE:
- There is a slight male preponderance; studies of varying populations show 1.04:1 to 1.2:1 male:female ratio.
- Peak age at time of hemorrhage occurrence is about 20 yr, but it can occur in younger and older patients.

RISK FACTORS:
- Male sex and presence of HHT are risk factors for AVM.
- The risk of hemorrhage is increased with prior hemorrhage, presence of a single draining vein, and diffuse nidus morphology.

GENETICS:
- Cerebral AVMs are sporadic in most cases.
- AVMs are present in about 20% of cases of Osler-Weber-Rendu syndrome (also known as hereditary hemorrhagic telangiectasia [HHT]), an autosomal dominant disorder that results in abnormal blood vessel formation in the skin, lungs, liver, brain, and other organs.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The most common presentation is hemorrhage; symptoms vary based on location and magnitude of hemorrhage.
- Patients may present with seizures or neurologic deficits related to mass effect of the AVM nidus.
- Headache and pulsatile tinnitus may be present.
- In infants, AVM may present as cyanotic heart failure, macrocephaly, or hydrocephalus.
- A bruit may be auscultated through the scalp or orbit.
- AVMs may also present with associated intracranial aneurysms that occur on distant, unrelated vessels, on a proximal artery that feeds the aneurysm (flow-related aneurysm), or within the AVM nidus itself (intranidal aneurysm). Patients may present with a subarachnoid hemorrhage related to the aneurysm rather than to the AVM.

ETIOLOGY

In most cases, AVMs are congenital abnormalities caused by failure of formation of a capillary bed between embryonic arterial and venous vascular plexuses during the first trimester of gestation; however, de novo sporadic AVMs have been reported.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of cerebral AVMs includes other vascular lesions such as cavernous malformations, dural arteriovenous fistulas, and intracranial aneurysms. Table E1 compares vascular malformations, and Table E2 describes major differences between hemangiomas and vascular malformations.

LABORATORY TESTS

- CBC and basic metabolic panel (BMP) with renal function panel prior to contrast dye administration with CT angiography/cerebral angiogram.
- Prothrombin time/international normalized ratio/partial thromboplastin time (PT/INR/PTT) should be drawn and corrected in the case of bleeding diathesis.

IMAGING STUDIES

- In the acute setting, a CT scan of the head to check for hemorrhage and a CT angiogram of the head for characterization of the lesion may be helpful (although calcification may be present and potentially pose as small acute blood).
- MRI of the brain delineates the nidus and its relationship to surrounding soft tissue structures better than a CT scan; however, in the setting of an acute hemorrhage these details will be obscured.
- Four-vessel cerebral angiogram (arteriogram) is the best study to evaluate AVM. Angiography in multiple projections helps identify the number and location of feeding and draining vessels for treatment planning (Fig. 2). High-resolution images of the nidus may also reveal other irregularities such as aneurysms that often arise given the abnormal histology of the vessel walls and the high-pressure blood flow traversing them.

TREATMENT

Pharmacologic management of seizures with antiepilepsy drugs and of headaches with oral analgesics can provide symptomatic relief.

NONPHARMACOLOGIC THERAPY

- Nonemergent outpatient setting: Cerebral angiogram provides characterization of the lesion. Based on angiographic characteristics, the Spetzler-Martin AVM grading system may be used to help guide treatment. In general, grade 5 AVMs are considered unresectable; they are not treated because the risks of treatment likely outweigh the risk of hemorrhage. Current tools for the treatment of AVMs include surgical resection, radiosurgery, and endovascular embolization (with liquid glues or embolic agents).
- Surgical resection: In low-grade lesions by an experienced neurosurgeon yields a high cure rate (~95% in published studies). Resection should include removal of all of the nidus of the AVM; failure to remove the complete nidus may increase the risk of recurrence. An increasing Spetzler-Martin grading scale increases risk of neurologic complications. Intraoperative imaging techniques such as indocyanine-green in-field angiography and conventional digital subtraction angiography are used to verify complete resection.
- Radiosurgery: Alternative definitive treatment for AVMs. Traditionally employed to treat

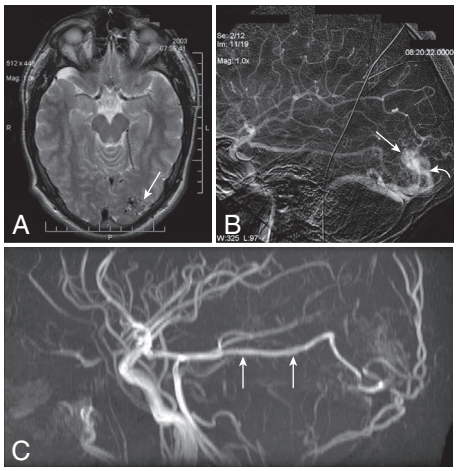

FIG. 1 A 14-year-old child with a left occipital arteriovenous malformation (AVM). A, Magnetic resonance image shows multiple flow voids in the left occipital lobe *(arrow).* **B,** Lateral view from catheter angiogram confirms the presence of an AVM *(arrow)* and early draining veins *(curved arrow).* **C,** Lateral maximum intensity projection image from a magnetic resonance angiogram shows an enlarged posterior cerebral artery branch *(arrows),* which feeds the tangle of abnormal vessels. (From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, WB Saunders.)

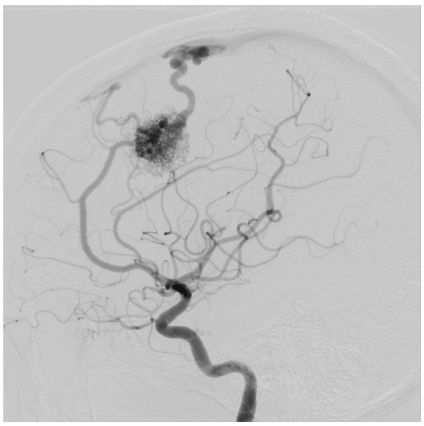

FIG. 2 Arteriovenous malformation of the frontal lobe. The anterior cerebral artery provides primary arterial supply with venous drainage superficially into the superior sagittal sinus.

AVMs in eloquent areas (e.g., brainstem); stereotactic radiosurgery is increasingly used for higher Spetzler-Martin grade AVM. Reported rates of confirmed radiographic obliteration after AVM radiosurgery range from 47% to 90%.

- Endovascular embolization involves transarterial superselective blockage of the AVM. It has become an important adjunctive tool. Currently recommended and approved for use before resection, preoperative embolization can reduce arterial flow and pressure within the AVM, assisting in speed and safety of surgical resection. In addition, embolization may often be used to treat intranidal or flow-related aneurysms in coordination with either resection or radiosurgery. Embolization alone in obliterating an AVM is not routinely recommended.
- Treatment decisions should take into consideration the morbidity associated with the treatment modality versus the risk of future hemorrhage or neurologic deterioration. Disability stemming from intractable seizures or severe headaches may make invasive definitive treatment a more attractive option.
- Acute cerebral hemorrhage: In the case of an acute hemorrhage, airway and breathing must be maintained, with intubation if necessary. Acute neurosurgical intervention for clot evacuation may be warranted. Microsurgical resection of the AVM may or may not be feasible in the acute setting and is controversial.

DISPOSITION

Whether the patient is receiving elective treatment of a known lesion or presenting with an acute hemorrhage, the patient should receive care in a progressive or intensive care unit with experience dealing with cerebrovascular disease. Once the patient is stabilized, appropriate rehabilitation should be arranged.

REFERRAL

- Cerebral AVMs should be managed by a qualified neurosurgeon.
- Referral to radiation medicine for adjuvant radiosurgery should be made when indicated.
- Referral to an interventional radiologist for endovascular treatment may be warranted.
- Treatment in a primary stroke center or other specialized center that offers all treatment modalities is recommended.

PEARLS & CONSIDERATIONS

COMMENTS

- No two AVMs are exactly the same; individualization of treatment decisions is the mainstay. Additionally, many AVMs could be effectively treated through one of several modalities or a combination thereof. Factors such as patient age, overall health status, radiographic characteristics, route of surgical access, and potential morbidities of each treatment modality are vital variables in consideration for treatment. The advisability of intervention for unruptured AVMs remains controversial. In a recent randomized trial comparing medical management with specific interventions to obliterate AVMs (neurosurgery, embolization, radiotherapy, or a combination) the rates of neurological disability were higher in the intervention group than with conservative treatment.[1]
- The annual risk of hemorrhage from a cerebral AVM is approximately 3%, but depending on the clinical and anatomical features of the malformations, the risk may be as low as 1% or as high as 33%. The risk of bleeding is increased if the patient has had previous episodes of bleeding, if there is a berry aneurysm on an artery feeding the AVM, and if there is a restriction of venous drainage from the AVM.[2]

PATIENT & FAMILY EDUCATION

If a patient with a known AVM suffers from acute-onset neurologic deficits or stroke-like symptoms, emergency medical attention is warranted for potential hemorrhage. Presence of AVMs, cerebral or otherwise, in family members should be disclosed to the patient's primary care physician because the presence of a genetic condition predisposing to cerebral AVMs should be considered.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Stephen L. Grupke, MD, MS,** and **Justin F. Fraser, MD**

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TABLE E1 Vascular Malformations

Type	Example(s)
Capillary	Port-wine stain
Venous	Venous malformation Angiokeratoma circumscriptum (hyperkeratotic venule) Cutis marmorata telangiectasia congenita (congenital phlebectasia)
Arterial	Arteriovenous malformation
Lymphatic	Superficial lymphatic malformation (lymphangioma circumscriptum) Deep lymphatic malformation with macrocysts and/or microcysts (cystic hygroma)

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, WB Saunders.

TABLE E2 Major Differences Between Hemangiomas and Vascular Malformations

	Hemangiomas	Vascular Malformations (Capillary, Venous, Lymphatic, Arterial, and Arteriovenous, Pure, or Complex-Combined)
Clinical	Variably visible at birth	Usually visible at birth (AVMs may be quiescent)
	Subsequent rapid growth	Growth proportionate to the skin's growth (or slow progression); present lifelong
	Slow, spontaneous involution	
Sex ratio F:M	3:1-5:1; 7:1 in severe cases	1:1
Pathology	Proliferating stage: Hyperplasia of endothelial cells and smooth muscle cell actin–positive cells	Flat endothelium
	Multilaminated basement membrane	Thin basement membrane
	Higher mast cell content in involution	Often irregularly attenuated walls (VM, LM)
Radiology	Fast-flow lesion on Doppler sonography	Slow-flow (CM, LM, VM) or fast-flow (AVM) on Doppler ultrasonography
	Tumoral mass with low voids on MRI	MRI: Hyperintense signal on T2-weighted images when slow-flow (LM, VM); flow voids on T1- and T2-weighted images when fast-flow (AVM)
	Lobular tumor on arteriogram	Arteriography of AVM demonstrates AV shunting
Bone changes	Rarely mass effect with distortion but no invasion	*Slow-flow VM:* Distortion of bones, thinning, underdevelopment *Slow-flow CM:* Hypertrophy *Slow-flow LM:* Distortion, hypertrophy, and invasion of bones *High-flow AVM:* Destruction, rarely extensive lytic lesions *Combined malformations* (e.g., slow-flow [capillary lymphatic venous malformation, Klippel-Trenaunay syndrome] or fast-flow [capillary arteriovenous malformation, Parkes Weber syndrome]): Overgrowth of limb bones, gigantism
Immunohistochemistry on tissue samples	*Proliferating hemangioma:* High expression of PCNA, type IV collagenase, VEGF, urokinase, and bFGF, glucose transporter-1	Lack expression of PCNA, type IV collagenase, urokinase, VEGF, and bFGF
	Involuting hemangioma: High levels of tissue inhibitor of metalloproteinase-1, bFGF	One familial (rare) form of VM linked to a mutated gene on 9p *(VMCM1)*
Hematology	No coagulopathy (Kasabach-Merritt syndrome is a complication of other vascular tumors of infancy, e.g., kaposiform hemangioendothelioma and tufted angioma)	Slow-flow VM, LM, or LVM may have an associated localized intravascular coagulopathy with risk of bleeding (disseminated intravascular coagulation)

AV, Atrioventricular;*AVM,* arteriovenous malformation; *bFGF,* basic fibroblast growth factor; *CM,* capillary malformation/port-wine stain; *F:M,* female:male; *LM,* lymphatic malformation; *LVM,* lymphovenous malformation; *MRI,* magnetic resonance imaging; *PCNA,* proliferating cell nuclear antigen; *VEGF,* vascular endothelial growth factor; *VM,* venous malformation.

From Eichenfeld LF et al: *Textbook of neonatal dermatology,* Philadelphia, 2001, WB Saunders.

BASIC INFORMATION

DEFINITION

Babesiosis is a tick-transmitted protozoan disease of animals, caused by intraerythrocytic parasites of the genus *Babesia.* Humans are incidentally infected, resulting in a nonspecific febrile illness. The disease can be severe in immunocompromised hosts.

ICD-10CM CODE
B60.0 Babesiosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): From 2011 to 2015 the CDC was notified of 7612 cases of babesiosis. Cases were reported in 27 states, with 94.5% of cases occurring in 7 states (Fig. 1).

PREVALENCE (IN U.S.):

- In areas of high endemicity, seropositivity ranging from 9% (Rhode Island) to 21% (Connecticut)
- Highest number of reported cases in New York

PREDOMINANT SEX: Males (most likely through increased exposure to vectors during recreational or occupational activities)

PREDOMINANT AGE: Severity apparently increasing with age greater than 50 yr or neonate

PEAK INCIDENCE: Spring and summer months, May through September

GENETICS: None known

CONGENITAL INFECTION: Definite evidence of vertical transmission

NEONATAL INFECTION: Many cases of perinatal transmission

BLOOD TRANSFUSION: Many instances. Blood donation screening for antibodies to and DNA from *B. microti* has been shown to significantly decrease the risk of transfusion-transmitted babesiosis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation period is 1 to 4 wk, or 6 to 9 wk, occasionally longer in transfusion-associated disease.
- Gradual onset of irregular fever, chills, diaphoresis, headache, myalgia, arthralgia, fatigue, and dark urine. Symptoms usually begin within 1 mo after tick bite and within 6 mo after transfusion of infected blood products. Fever is the most frequently reported clinical manifestation.
- On physical examination: Petechiae, frank or mild hepatosplenomegaly, and jaundice. Most patients have a normal physical examination.
- Infection with *B. divergens* (Europe) produces a more severe illness with a rapid onset of symptoms and increasing parasitemia progressing to massive intravascular hemolysis and renal failure.

ETIOLOGY

- Vector: Deer tick, *Ixodes scapularis* (also known as *I. dammini*).
  1. Feeds on rodents during the spring and summer while in its larval and nymphal stages and on deer as an adult
  2. Requires a blood meal to mature to each stage, hence human infection
  3. During the warmer months in endemic areas, humans are readily infected while engaging in outdoor activities
  4. Tick must attach for 36 to 72 hours to transmit infection
- *B. microti* and *B. divergens* account for most human infections. Table 1 compares causal agents and clinical manifestations of babesiosis.
- In the U.S., cases caused by *B. microti* are acquired on offshore islands of the northeastern coast, including Nantucket Island, Cape Cod, and Martha's Vineyard in Massachusetts; Block Island in Rhode Island; and Long Island, Fire Island, and Shelter Island in New York; as well as the nearby mainland including Connecticut, Rhode Island, Massachusetts, New York, and New Jersey.
- Sporadic cases reported from California, Georgia, Maryland, Minnesota, Virginia, Wisconsin, and most recently the WA-1 strain from Washington State and the MO-1 strain from Missouri.
- *B. divergens* is implicated in human disease in Europe, where the disease remains rare and predominantly associated with asplenia.
- *B. venatorum* is emerging as an important pathogen in mainland China.
- Majority of cases of *B. microti* are asymptomatic.
- Is transmissible by transfusion of erythrocytes, or through red cell-contaminated platelets.
- Mixed infections (*B. microti* and *Borrelia burgdorferi,* the causative agent of Lyme disease) are estimated to occur in 30% (Rhode Island and Connecticut) to 60% (New York) of cases.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Malaria
- Ehrlichiosis
- Leptospirosis
- Salmonellosis, including typhoid fever
- Acute viral hepatitis
- Hemorrhagic fevers
- Subacute bacterial endocarditis

WORKUP

Should be suspected in any febrile patient living or traveling in an endemic area, irrespective of exposure history to ticks or tick bites, especially if asplenic. The hallmark of babesiosis is hemolysis with resulting anemia. Elevated liver enzymes, thrombocytopenia, and acute kidney injury may occur.

LABORATORY TESTS

- The preferred method for diagnosing babesiosis is polymerase chain reaction (PCR) using whole blood specimens.
- In experienced hands, sequential examination of Giemsa stained thin smears is equally effective.

FIG. 1 Reported cases of babesiosis, by patient's county of residence*—33 states, 2015.† *N = 2070; county of residence was known for all but four (<1%) of the 2074 total patients. Each dot represents one case; dots were placed randomly within the patient's county of residence. †Year as reported by the health department. (From Gray EB, Herwaldt BL: Babesiosis Surveillance—United States, 2011-2015. *MMWR Surveill Summ* 2019;68(No. SS-6):1-11. DOI: http://dx.doi.org/10.15585/mmwr.ss6806a1external icon.)

TABLE 1 Causal Agents and Clinical Manifestations of Babesiosis

Babesia Species	Geographic Distribution	Tick Vectors	Animal Reservoirs	Epidemiology	Clinical Manifestations
B. divergens	United Kingdom, Western Europe, Eastern Europe, Sweden, Russia; not reported in United States	*Ixodes ricinus*	Cattle, reindeer	Incubation, 1-4 wk. Occurs during summer months in cattle-raising regions Targets splenectomized or immunocompromised patients primarily	Fulminant course with high case-fatality rate Fever, rigors, headache, myalgia, jaundice, hemoglobinuria, hemolytic anemia, acute renal failure, multiorgan failure
B. microti	Parallels the U.S. Northeast endemic regions for *Borrelia burgdorferi*, especially the islands off New York, Massachusetts, Connecticut, and Rhode Island and focal areas in Connecticut, New Jersey, Wisconsin, and Minnesota	Deer ticks: *Ixodes dammini* and *Ixodes scapularis*	White-footed mouse *(Peromyscus leucopus)*	Incubation, 1-4 wk after tick bites or 4-9 wk after blood transfusions Transmission primarily by nymphal ticks Targets older, not necessarily immunocompromised patients, particularly severe in those immunocompromised by HIV infection, advanced age, coinfections with *B. burgdorferi* Seasonality parallels tick nymph activity; 80% of cases occur from May to August	Often asymptomatic in young, healthy patients Self-limited influenza-like febrile illness with onset of anorexia, malaise, and lethargy followed in 1 wk by high fever, diaphoresis, myalgias; mild splenomegaly and rarely hepatomegaly Later hemolysis, hemolytic anemia, thrombocytopenia, jaundice, acute renal failure, especially in the splenectomized, older adults, or the immunocompromised Complications include ARDS and DIC Case-fatality rate, 5%
MO-1 (a relative or subspecies of *B. divergens*)	Rural Missouri and Kentucky	*Ixodes dentatus* (rabbit tick)	Rabbits, birds	Incubation, 1-4 wk after tick bites Spring to autumn seasonality Targets the splenectomized, like *B. divergens*	Same as above—often asymptomatic, except in the splenectomized, who will develop high parasitemia and multiorgan failure
WA-1 (a relative or subspecies of *B. gibsoni*)	Rural Washington state	Ixodid ticks, including *Ixodes dentatus*	Unknown—wild canids and ungulates suspected	Incubation, 1-4 wk Targets the splenectomized, older adults, immunocompromised, premature infants May be transmitted by blood transfusion	Same as above—often asymptomatic, except in the splenectomized, who will develop high parasitemia and multiorgan failure
CA-1, CA-2, etc. subspecies (relatives or subspecies of mule deer and bighorn sheep *Babesia* species)	U.S. Pacific coast, primarily rural and semirural areas of California	Ixodid ticks	Unknown—mule deer and bighorn sheep suspected	Incubation, 1-4 wk Targets the splenectomized, elderly, immunocompromised, and premature infants	Same as above—often asymptomatic, except in the splenectomized, who will develop high parasitemia and multiorgan failure

ARDS, Acute respiratory distress syndrome; *DIC,* disseminated intravascular coagulation.
From Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.

- Babesial DNA by PCR has comparable sensitivity and specificity to microscopic analysis of thin blood smears. PCR is more sensitive than smears at the onset of infection when parasite load may be minimal.
- Diagnosis achieved serologically by indirect immunofluorescence assay (IFA) is specific for *B. microti.*
  1. Assay is hampered by the inability to distinguish between exposed patients and those who are actively infected.
  2. Immunoglobulin G titer of ≥1:64 is indicative of seropositivity, whereas one ≥1:1024 is considered diagnostic of acute infection. Immunoglobulin M (IgM) titer of 1:64 is considered indicative of acute infection.
  3. IgM indirect immunofluorescent-antibody test may be highly sensitive and specific for diagnosis. IgM titer of 1:64 is considered indicative of acute infection.
- CBC to reveal mild to moderate thrombocytopenia and anemia. The white blood cell (WBC) count may be normal, elevated, or low. Abnormally elevated serum chemistries, including creatinine, liver function profile, lactate dehydrogenase, and indirect and total bilirubin levels; haptoglobin is low.
- Urinalysis to reveal proteinuria and hemoglobinuria.
- Examination of Giemsa- or Wright-stained thin blood films for intraerythrocytic parasites (Fig. 2):
  1. In its classic, though infrequently seen, form a "tetrad" or "Maltese cross" composed of four daughter cells attached by cytoplasmic strands is observed.
  2. More commonly, smaller forms composed of a single chromatin dot are eccentrically located within bluish cytoplasm.
  3. Parasitized erythrocytes may be multiply infected but not enlarged.
  4. Extra-erythrocytic forms may be seen.
  5. Gametocytes are *not* seen; this is a characteristic of malaria.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Supportive care with adequate hydration

ACUTE GENERAL Rx

- In patients with intact spleens: Predominantly asymptomatic or if symptomatic, generally self-limited

- Therapy may be offered to any symptomatic patient. Table 2 summarizes treatment recommendations.
- Therapy is mandatory for the severely ill patient, especially if asplenic, elderly, or immunosuppressed. Combination of atovaquone 750 mg q12h and azithromycin 500 mg on day 1 and 250 mg per day thereafter for 7 to 10 days appears to be as effective as a regimen of clindamycin and quinine with fewer adverse reactions. This is the preferred regimen for mild disease.
- Combination of quinine sulfate 650 mg PO tid plus clindamycin 600 mg PO tid (600 mg parenterally qid) taken for 7 to 10 days. Severely ill patients are hospitalized and treated with clindamycin and quinine or azithromycin plus atovaquone.
- Exchange transfusions in addition to antimicrobial therapy: Successful treatment for severe infections in asplenic patients associated with high levels of *B. microti* or *B. divergens* parasitemia. Exchange transfusion is recommended for patients with >10% parasitemia, but may be considered for any severely ill patient.
- Relapsed and immunocompromised patients may require a longer duration of therapy.

DISPOSITION

Prognosis is usually good and fatal outcomes are rare.

REFERRAL

- For prompt consultation with an infectious disease specialist if the diagnosis is acutely suspected, especially in the asplenic, elderly, or immunocompromised patient
- For hospitalization for the severely ill patient who may require exchange transfusions in addition to antibiotic therapy

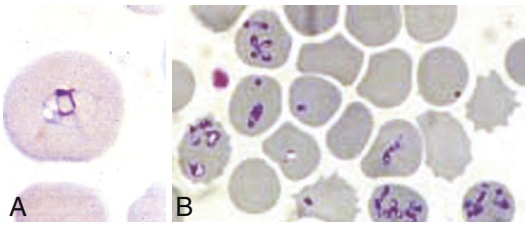

FIG. 2 Babesia parasites. Human infection with species of piroplasm transmitted by the bite of the tick *Ixodes ricinus* infected from cattle is a rare occurrence. Infection in normal people with this piroplasm may give rise to a self-limiting fever and parasitemia, as in the case of infection with the rodent parasite *Babesia microti* on the northeastern seaboard of the United States via the tick *Ixodes scapularis* **(A).** Heavy red-cell infection may develop, however, in splenectomized patients, leading to fatal hemolytic anemia. This patient died as a result of an infection acquired from the cattle parasite *Babesia divergens* in Scotland **(B).** Other species of *Babesia* that occasionally infect humans, for example, the WA1, CA1, and MO1 isolates from the United States, are distinguished by molecular means. (Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.)

TABLE 2 Treatment of Human Babesiosis

Organism	Severity	Adults	Children
Babesia microti *	Mild†	Atovaquone 750 mg q12h PO plus azithromycin 500 mg PO on day 1 and 250 mg/day PO from day 2 on	Atovaquone 20 mg/kg q12h PO (maximum 750 mg/dose) plus azithromycin 10 mg/kg PO on day 1 (maximum 500 mg/dose) and 5 mg/kg/day PO from day 2 on (maximum 250 mg/dose)
	Severe‡,§	Clindamycin 300-600 mg q6h IV or 600 mg q8h PO plus quinine 650 mg q8h PO	Clindamycin 7-10 mg/kg q6-8h IV or 7-10 mg/kg q6-8h PO (maximum 600 mg/dose) plus quinine 8 mg/kg q8h PO (maximum 650 mg/dose)
*Babesia divergens**		Immediate complete RBC exchange transfusion plus clindamycin 600 mg q6-8h IV plus quinine 650 mg q8h PO	Immediate complete RBC exchange transfusion plus clindamycin 7-10 mg/kg q6-8h IV (maximum 600 mg/dose) plus quinine 8 mg/kg q8h PO (maximum 650 mg/dose)

IV, Intravenously; *PO,* orally; *RBC,* red blood cell.
NOTE: Monitor patients on quinine with electrocardiography; monitor quinine serum levels in the setting of hepatic or renal disease.
*Treatment for 7 to 10 days, but duration may vary.
†Atovaquone (750 mg twice daily) combined with higher doses of azithromycin (600 to 1000 mg/day) has been used in immunocompromised patients. With this regimen, symptoms and parasitemia resolve faster.
‡Consider partial or complete RBC exchange transfusion in cases of high-grade parasitemia (≥10%), severe anemia (<10 g/dl), or pulmonary, renal, or hepatic compromise. Even when parasitemia is less than 10%, consider exchange transfusion if acute respiratory distress syndrome or syndrome resembling a systemic inflammatory response syndrome is present.
§In asplenic individuals and in immunocompromised patients, persistent or relapsing babesiosis should be treated for at least 6 wk, including 2 wk during which parasites are no longer detected.
From Bennet et al: *Principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.

PEARLS & CONSIDERATIONS

COMMENTS

- Prevention of babesiosis in asplenic or immunocompromised hosts is best achieved by avoidance of areas where the vector is endemic, especially May through September.
- If residence or travel in endemic areas is unavoidable, advise patients to perform daily cutaneous self-examination, wear light-colored clothing (to facilitate removal of ticks), tuck pants into socks, and apply tick repellent (diethyltoluamide and dimethyl phthalate) to skin or clothing.
- Advise a daily inspection for ticks in family pets (e.g., cats and dogs).
- Infection with *B. divergens,* especially in the asplenic patient, is often fatal.
- Concurrent cases of babesiosis and Lyme disease, anaplasma, *Borrelia miyamotoi*, and Powassan virus have been documented—check for combined infection in severely ill patients.
- A combination of clindamycin and quinine has been successfully used to treat babesiosis during the third trimester of pregnancy without incurring apparent adverse effect on the fetus.
- In 2011 the CDC added babesiosis to the list of nationally notifiable diseases.
- Tick avoidance is paramount in prevention of babesiosis.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Babesiosis (Patient Information)

AUTHOR: **Patricia Cristofaro, MD**

SUGGESTED READINGS

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Baker Cyst (PTG)

BASIC INFORMATION

DEFINITION

Baker cyst is a fluid-filled popliteal bursa located along the medial border of the popliteal fossa. It is an extension of the semimembranosus bursa posteriorly (see Fig. E1).

SYNONYM

Popliteal synovial cyst

ICD-10CM CODES

M71.2	Synovial cyst of popliteal space [Baker], unspecified knee
M71.21	Synovial cyst of popliteal space [Baker], right knee
M71.22	Synovial cyst of popliteal space [Baker], left knee

EPIDEMIOLOGY & DEMOGRAPHICS

- Most are asymptomatic and incidentally found on imaging exams.
- Occurs at all ages, most commonly between age 35 to 70 yr, increasing with age.
- The prevalence of popliteal cysts varies based on the imaging technique used and the age of the patient population.
- Between 2% and 6% of all patients believed to have clinical deep venous thrombosis (DVT) have symptomatic Baker cysts.
- Approximately 5% to 40% of MRIs performed for osteoarthritis or internal derangement reveal popliteal cysts.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms associated with associated joint pathology (knee swelling or stiffness)
- Pain in the popliteal space
- Leg edema
- Prominence of the popliteal fossa
- Decreased range of motion of the knee
- Locking of the knee
- Foucher sign: The cyst becomes hard with knee extension and soft with knee flexion
- Neuropathic lancinating pains radiating from the knee down the back of the leg

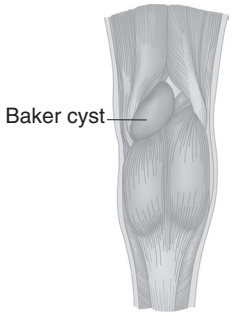

FIG. E1 Baker cyst is an extension of the semimembranosus bursa posteriorly. This bursa is often connected with a joint cavity. (From Marx J: *Rosen's emergency medicine: concepts and clinical practice,* ed 6, Philadelphia, 2006, Saunders.)

- Pain or discomfort with prolonged standing and hyperflexion of the knee
- Presence of associated DVT

ETIOLOGY

- Believed to be fluid distention of bursal sac separating semimembranous tendon from medial head of gastrocnemius
- May represent a true cyst but more often a degenerative or inflammatory joint disease or injury; they usually communicate with adjacent knee joint space. Thus, a Baker cyst usually denotes increased intraarticular pressure from underlying joint disease. Sequestration of synovial fluid in the popliteal fossa can result from a valve-like effect between joint space and cyst controlled by gastrocnemius-semimembranosus muscle changes with knee flexion and extension
- In children, popliteal cysts are usually a primary process arising from the gastrocnemius-semimembranosus bursa without direct communication with the joint space
- In adults, Baker cysts are usually associated with pathologic changes of the knee joint, such as the following:
  1. Rheumatoid arthritis (RA)
  2. Osteoarthritis of the knee
  3. Meniscal tears
  4. Patellofemoral chondromalacia
  5. Fracture
  6. Gout
  7. Pseudogout
  8. Infection (tuberculosis)

DIAGNOSIS

Baker cyst frequently mimics DVT and is sometimes referred to as *pseudothrombophlebitis syndrome.*

DIFFERENTIAL DIAGNOSIS

- DVT
- Popliteal artery aneurysm
- Abscess
- Tumor (sarcomas/lymphomas)
- Lymphadenopathy
- Varicosity
- Synovial or ganglion cysts

WORKUP

The diagnosis can be made by physical examination alone. However, anyone suspected of having a popliteal cyst should undergo imaging studies to exclude other causes.

LABORATORY TESTS

Blood tests are not specific.

IMAGING STUDIES

- Plain radiographs (anteroposterior and lateral views) may show calcification in a solid tumor or in the posterior meniscal area.
- Ultrasound (Fig. E2) is safe, portable, and cost effective and excludes other clinically important causes of popliteal fossa pathology, including DVT.

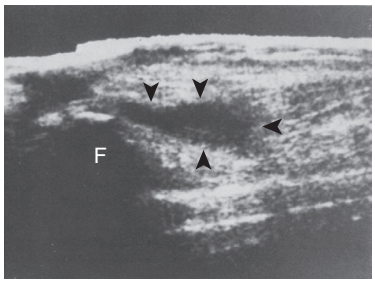

FIG. E2 Sonography of a popliteal cyst. Sagittal sonographic section through the popliteal space in this patient demonstrates a sonolucent fluid collection *(arrowheads)* posterior and inferior to the medial femoral condyle *(F).* (From DeLee D, Drez D [eds]: *DeLee and Drez's orthopaedic sports medicine,* ed 2, Philadelphia, 2003, Saunders.)

- MRI if internal derangement is suspected, surgery being considered, or diagnosis unclear after ultrasound.

TREATMENT

Asymptomatic cysts found incidentally do not require treatment.

NONPHARMACOLOGIC THERAPY

- Rest
- Strenuous activity avoidance
- Knee immobilization sometimes necessary

ACUTE GENERAL Rx

- NSAIDs can be used to treat underlying joint pathology (RA, gout, and pseudogout).
- Arthrocentesis with intraarticular injection or injection of the cyst (Fig. E3) with corticosteroids (triamcinolone acetonide 40 mg).

CHRONIC Rx

- The majority of Baker cysts are successfully treated conservatively
- If refractory symptoms, surgical procedures addressing the underlying cause include:
  1. Arthroscopic surgery to remove loose cartilaginous fragment
  2. Partial or total meniscectomy
  3. Open excision of the cyst

DISPOSITION

- Baker cysts may spontaneously resolve without treatment
- Complications of Baker cysts include:
  1. Rupture
  2. DVT
  3. Nerve impingement resulting in posterior tibial nerve entrapment, anterior compartment syndrome, or posterior compartment syndrome
  4. Popliteal artery occlusion

REFERRAL

Orthopedic surgeon if surgery is contemplated

RELATED CONTENT

Baker Cyst (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

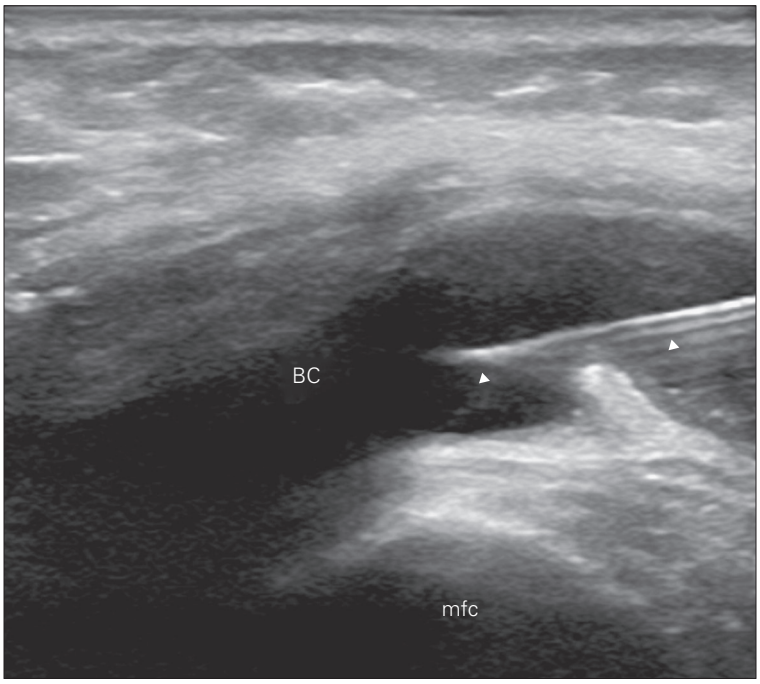

FIG. E3 Ultrasound-guided injection of a Baker cyst. The needle *(arrowheads)* has a hyperechoic appearance inside the Baker cyst *(BC).* *mfc,* Posterior aspect of the medial femoral condyle. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Balanitis is an inflammation of the superficial tissues of the penile head (glans penis). If the foreskin (prepuce) is involved, it is called *balanoposthitis*.

ICD-10CM CODES

B37.42 Candidal balanitis
N48.1 Balanitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): More common in uncircumcised males and in diabetic patients
PREVALENCE (IN U.S.): One study reports that 11% of adult men seen in a urology clinic and 3% of male children (mostly uncircumcised) have balanitis.
PREDOMINANT SEX: Almost exclusive to males but can affect clitoris.
PEAK INCIDENCE: All ages, especially in sexually active men. It occurs in one quarter of male sex partners of women infected with *Candida.*

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Itching and tenderness
- Pain, dysuria, and local edema and erythema
- Rarely, ulceration and lymph node enlargement
- Severe ulcerations leading to superimposed bacterial infections
- Inability to void: Unusual, but a more distressing and serious complication

ETIOLOGY

- Causes include infectious agents, skin disorders, or miscellaneous
- Infectious diseases: *Candida species (40%), Neisseria gonorrhoeae,* human papillomavirus, herpes simplex, *Gardnerella vaginalis, Treponema pallidum* (syphilis), HIV, *Trichomonas, Staphylococcus aureus,* group A streptococcus, anaerobic bacteria
- Skin disorders: Circinate balanitis of Reiter syndrome, lichen sclerosis (balanitis xerotica obliterans)
- Miscellaneous: Poor hygiene, causing erosion of tissue with erythema and promoting growth of *Candida albicans* (Fig. E1), trauma (zippers, urinary catheters), allergic reactions to condoms or medications

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Leukoplakia
- Nummular eczema
- Balanitis xerotica obliterans
- Psoriasis
- Carcinoma of the penis
- Plasma cell balanitis (noninfectious)
- Erythroplasia of Queyrat
- Nodular scabies
- Circinate balanitis (Reiter syndrome)

WORKUP

- Sexually active males: Assessment for evidence of other sexually transmitted diseases
- Biopsy if lesions do not heal

LABORATORY TESTS

- Venereal disease research laboratory, HIV, and nucleic acid amplification tests for chlamydia and gonorrhea
- Fasting blood sugar and hemoglobin A_{1C} to rule out diabetes
- Wet mount for *Trichomonas*
- Potassium hydroxide preparation for yeast

TREATMENT

NONPHARMACOLOGIC THERAPY

- Maintenance of meticulous hygiene
- Retraction and bathing of prepuce several times a day
- Warm sitz baths to ease edema and erythema
- Consideration of circumcision, especially when symptoms are severe or recurrent
- With Foley catheters, strict catheter care strongly advised

ACUTE GENERAL Rx

- Metronidazole 2 g PO as a single dose for *Trichomonas* or fluconazole 150 mg PO × 1 or itraconazole 200 mg PO bid × 1 day for suspected fungal infection
- Clotrimazole 1% cream applied topically twice daily to affected areas for suspected fungal infection
- Bacitracin or Neosporin ointment applied topically four times daily for bacterial infection
- With more severe bacterial superinfection: Cephalexin 500 mg PO qid
- Topical corticosteroids added four times daily if dermatitis severe
- Patients with suspected urinary tract infections: Trimethoprim-sulfa DS twice daily or ciprofloxacin 500 mg PO bid after obtaining appropriate cultures

DISPOSITION

Balanitis is often self-limited and usually responds to conservative therapy; if it does not improve, consider circinate balanitis of Reiter syndrome, nodular scabies, and primary skin lesions including skin carcinoma.

PEARLS & CONSIDERATIONS

Don't forget about nodular scabies involving the prepubic area—examine the region carefully for burrows and tracks of *Sarcoptes scabiei.*

REFERRAL

- For surgical evaluation for circumcision if symptoms are recurrent, especially if phimosis or meatitis occurs (NOTE: Severe phimosis with an inability to void may require prompt slit drainage.)
- For biopsy to rule out other diagnoses such as premalignant or malignant lesions if lesions are not healing

SUGGESTED READINGS

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RELATED CONTENT

Balanitis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

FIG. E1 Candidal balanitis. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

BASIC INFORMATION

DEFINITION

Barrett esophagus occurs when the squamocolumnar junction is displaced ≥1 cm proximal to the gastroesophageal junction and the squamous lining of the lower esophagus is replaced by metaplastic columnar epithelium, which predisposes to the development of esophageal adenocarcinoma. While cardia-type epithelium has been shown to predispose to esophageal cancer, the presence of intestinalized epithelium is still considered essential for the diagnosis. Recent data show that the absolute annual risk for esophageal carcinoma in Barrett esophagus is 0.12%, which is much lower than the assumed risk of 0.5% that is the basis for current surveillance guidelines.

SYNONYMS

Esophagus, Barrett
Esophagus, columnar-lined
Ulcer, Barrett

ICD-10CM CODES

K22.70	Barrett esophagus without dysplasia
K22.710	Barrett esophagus with low grade dysplasia
K22.711	Barrett esophagus with high grade dysplasia
K22.719	Barrett esophagus with dysplasia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Male/female ratio of 4:1.
- Mean age of onset is 40 yr, with a mean age range of diagnosis of 55 to 60 yr.
- Occurs more frequently in white and Hispanic individuals than in African American individuals, with a ratio of 10 to 20:1.
- Mean prevalence of 5% to 15% in patients undergoing endoscopy (EGD) for symptoms of gastroesophageal reflux disease (GERD). It is estimated that 5.6% of adults in the United States have Barrett esophagus. The prevalence rate may be as low as ~1% in patients without risk factors and varies based on patient location (Western vs. non-Western countries) and number of risk factors.
- Independent risk factors include chronic reflux (>5 yr), hiatal hernia, age >50 yr, male gender, white ethnicity, smoking history, and intraabdominal obesity. A family history with at least one first-degree relative with Barrett esophagus or adenocarcinoma of the esophagus is a significant risk factor.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

SYMPTOMS:

- Chronic heartburn
- Dysphagia with solid food
- May be an incidental finding on EGD in patients without reflux symptoms
- Less frequent: Chest pain, hematemesis, melena
- Patients may be asymptomatic

PHYSICAL FINDINGS:

- Nonspecific; can be completely normal
- Epigastric tenderness on palpation

ETIOLOGY

- Metaplasia is thought to result from reepithelialization of esophageal tissue injured as a result of chronic GERD.
- Patients with Barrett esophagus tend to have more severe esophageal motility disturbances (decreased lower esophageal sphincter pressure, ineffective peristalsis) and greater esophageal acid exposure on 24-hour pH monitoring. Table 1 lists some physiologic abnormalities that have been reported in Barrett patients and suggests how these abnormalities may contribute to GERD severity.
- Bile salts in the presence of acid may produce oxidative stress, induce reactive oxygen species, and alter transcriptional factor activity, all of which may induce the formation of Barrett epithelium, DNA damage, and dysplastic progression.
- Familial clustering of GERD and Barrett esophagus suggests a genetic predisposition, but no gene has yet been identified. Early data suggest that patients who develop Barrett are genetically predisposed to a severe inflammatory response to GERD. Candidate susceptibility loci include *CRTC1*, *BARX1*, and *FOXP1*.
- Progression from metaplasia to dysplasia to carcinoma is associated with changes in gene structure and expression, including the caudal-related homeobox family of transcription factors *(CDX1* and *CDX2),* the embryonic transcription factor SOX2, and the tumor suppressors p16 *(CDKN2A)* and *TP53.*
- Transcriptionally active high-risk human papillomavirus has been described in cohorts of patients with Barrett esophagus with dysplasia and esophageal adenocarcinoma.
- Patients with Barrett esophagus and esophageal adenocarcinoma may have a shift in the esophageal microbiome toward a gram-negative population, which may play a role in oncogenesis through the release of proinflammatory cytokines and activation of oncogenic transcriptional regulators such as nuclear factor-κB (NF-κB).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- GERD, uncomplicated
- Erosive esophagitis
- Gastritis
- Peptic ulcer disease
- Angina
- Malignancy
- Stricture or Schatzki ring

WORKUP

- The American Gastroenterological Association Medical Position Panel gave a weak recommendation for screening patients with multiple risk factors, including age over 50, male sex, white race, chronic GERD, hiatal hernia, elevated body mass index, and intraabdominal distribution of body fat. An international consensus group suggested screening men over 60 with GERD symptoms for more than 10 yr. An American College of Gastroenterology (ACG) Clinical Guideline suggested screening men with >5 yr and/or frequent symptoms of GERD and two or more risk factors including age >50, Caucasian race, presence of central obesity, current or past history of smoking, and a confirmed family history of Barrett or esophageal adenocarcinoma. An American Society for Gastrointestinal Endoscopy (ASGE) guideline stated that although there was insufficient evidence on the effectiveness of screening, if done, it should be performed for high-risk individuals, who were defined as patients with a family history of esophageal adenocarcinoma or Barrett esophagus, or moderate-risk patients with GERD and one of the earlier-defined risk factors. General population screening is not currently recommended. Although screening has become standard of practice in some communities, the effectiveness of screening using current techniques is controversial because it may not improve mortality rates from adenocarcinoma.
- EGD with biopsy is necessary for diagnosis. Ideally, this should be done via high-resolution white-light endoscopy with at least four biopsies for every 2-cm segment. If erosive

TABLE 1 Proposed Physiologic Abnormalities Contributing to Gastroesophageal Reflux Disease in Patients with Barrett Esophagus

Abnormality	Potential Consequences
Extreme hypotension of the lower esophageal sphincter	Gastroesophageal reflux
Ineffective esophageal motility	Defective clearance of refluxed material
Gastric acid hypersecretion	Reflux of highly acidic gastric juice
Duodenogastric reflux	Esophageal injury caused by reflux of bile acids and pancreatic enzymes
Decreased salivary secretion of EGF	Delayed healing of reflux-damaged esophageal mucosa
Decreased esophageal pain sensitivity to refluxed caustic material	Failure to initiate therapy

EGF, Epidermal growth factor.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, WB Saunders.

esophagitis is present, patients should be treated to heal esophagitis with repeat endoscopy and biopsies 8 to 12 wk later to determine if underlying Barrett esophagus is present. ASGE recommends concurrent use of chromoendoscopy or virtual chromoendoscopy if available.

- Unsedated transnasal endoscopy and an esophageal cytology device (Cytosponge®) may be acceptable alternatives to conventional endoscopy. Wireless esophageal capsule endoscopy may detect Barrett esophagus but with too low a sensitivity and specificity to be recommended. Imaging studies are not useful.
- Diagnosis requires the presence of metaplastic columnar epithelium at least 1 cm proximal to the gastroesophageal junction (Figs. 1 and E2). Longer-segment (≥3 cm) Barrett esophagus is more readily diagnosed. Barrett esophagus may be described using the Prague criteria, documenting the circumferential and maximal length via a C and M score. The Paris classification may be used to report associated visible lesions. At least two expert gastrointestinal pathologists should concur if any grade of dysplasia is diagnosed.
- Intestinal metaplasia of the gastric cardia is not Barrett esophagus and does not have the same risk for malignancy.
- Biomarkers using tissue samples and, more recently, blood tests involving whole genome sequencing and even breath tests for volatile organic compounds, and advanced imaging techniques, such as mutational load, fluorescence in situ hybridization, autofluorescence imaging, white light postprocessing algorithms, confocal laser endomicroscopy, and optical coherence tomography (recently incorporated into volumetric laser endomicroscopy), are being evaluated to assist with diagnosis and to better understand progression of disease, prediction of response to therapy, or prognosis.
- Screening for *Helicobacter pylori* infection in patients with GERD and Barrett esophagus is not recommended.

Rx TREATMENT

The goal is to control GERD symptoms and maintain healed mucosa.

NONPHARMACOLOGIC THERAPY

Nonpharmacologic therapy includes lifestyle modifications; elevating head of bed; and avoiding chocolate, tobacco, caffeine, mints, and certain drugs (see "Gastroesophageal Reflux Disease").

ACUTE GENERAL Rx

- Proton pump inhibitors are the most effective treatment for GERD. Therapy should be titrated to control symptoms and/or to promote healing of endoscopic signs of disease.
- If patient is asymptomatic and incidentally found to have Barrett esophagus, once-daily proton pump inhibitors should be prescribed, as they may reduce the risk of neoplastic progression.

CHRONIC Rx

- Chronic acid suppression is recommended to control symptoms, maintain healing, and reduce neoplastic progression. For patients with Barrett esophagus, the benefits of the use of proton-pump inhibitors is thought to outweigh the potential risks.
- Antireflux surgery may be considered for management of GERD and associated sequelae, but it has not been proven to be superior to medical therapy. Patients continue to require endoscopic surveillance of their esophagus.
- When GERD is controlled by either medical or surgical therapy, ablation of metaplastic epithelium usually leads to replacement by normal squamous epithelium. Because only a minority of patients with Barrett esophagus progress to high-grade dysplasia or carcinoma, endoscopic eradication therapy is not recommended for the general population of patients with nondysplastic Barrett esophagus.
- Endoscopic eradication therapy is becoming the treatment of choice for low-grade dysplasia and is the treatment of choice for high-grade dysplasia. Radiofrequency ablation or photodynamic therapy, combined with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) of visible mucosal irregularities, should be performed in conjunction with aggressive surveillance and eradication of all remaining Barrett epithelium. Endoscopic therapy is preferred over surgical treatment in properly staged individuals. These therapies may even be considered for patients with focal intramucosal carcinoma, if properly staged (T1 SM1 or lower). Cryotherapy is being evaluated for the complete eradication of both dysplasia and intestinal metaplasia and reduced risk for disease progression. All these options run the risk for residual or buried metaplasia. Ultimate goals of therapy include both complete eradication of dysplasia (CE-D) and complete eradication of intestinal metaplasia (CE-IM). Even with CE-IM, recurrence has been documented in 5% to 39.5% of patients. Modalities for endoscopic treatment of Barrett esophagus are summarized in Table 2.
- Surgical resection is definitive therapy and may be offered for multifocal high-grade dysplasia, carcinoma that has extended into the submucosa (T1 SM2 or 3), or patients with poorly differentiated carcinomas or with evidence of lymphovascular invasion. Mortality appears to be lower with experienced surgeons operating in high-volume centers.
- Patients with cardiovascular risk factors may be considered for low-dose aspirin therapy for chemoprevention of esophageal adenocarcinoma. NSAIDs or NSAIDs combined with statins are potentially effective at reducing

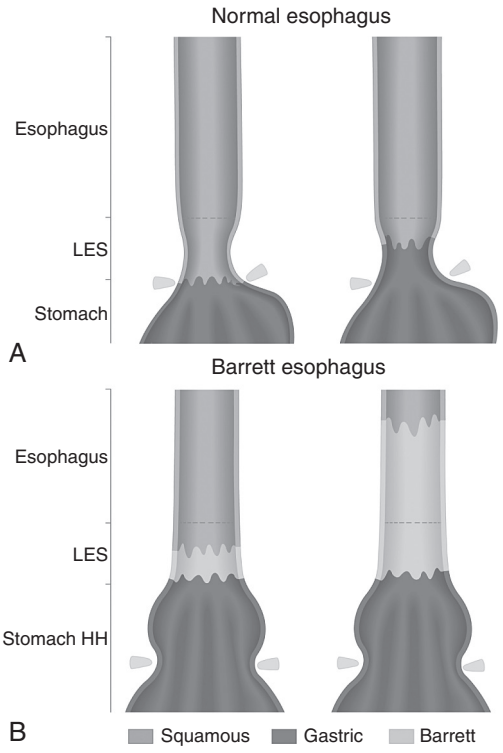

FIG. 1 Anatomic landmarks of the normal LES region (A) and of Barrett esophagus (B). Note that gastric mucosa is very common and normal in the LES region and that in Barrett esophagus, the squamocolumnar junction is not only proximally displaced within the tubular esophagus, but that the intervening mucosa is composed of intestinalized Barrett metaplastic epithelium. *HH,* Hiatal hernia; *LES,* lower esophageal sphincter. (From Silverburg SG: *Principles of practice of surgical pathology and cytopathology,* ed 4, New York, 2006, Churchill Livingstone.)

TABLE 2 Modalities for Endoscopic Treatment of Barrett Esophagus

Modality	HGD Resolved	BE Resolved	Recurrence Rate	Subsquamous BE Rate	Stricture Rate	Complication Rate	Advantages	Disadvantages
APC	67%-98.6%	38%-98%	33%-68% low power	25%-45% low power 0-30% high power	4%-10%	24% low power 40%-60% high power	Noncontact, technically simple	Requires several treatment sessions
MPEC	–	25%-88%	7%	7%	2%	41%-43%	Noncontact, technically simple, relatively inexpensive, readily available	Requires several treatment sessions
PDT	77%-88%	13%	5%-11%	2%-24%	4.8%-53%	4.8%-53%	Easy to perform; only FDA-approved ablation method for treatment of precancerous lesions in BE	Photosensitivity, relatively high stricture rate
EMR	59%-97%	53%	4%-30%	–	3%-30%	12%-60%	Histologic assessment; complete removal of circumferential short-segment BE; 1-2 sessions	Difficulty treating long-segment BE

APC, Argon plasma coagulation; *BE,* Barrett esophagus; *EMR,* endoscopic mucosal resection; *FDA,* U.S. Food and Drug Administration; *HGD,* high-grade dysplasia; *MPEC,* multipolar electrocoagulation; *PDT,* photodynamic therapy.
From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.

the risk of esophageal adenocarcinoma but are not currently recommended for use because of the risk of adverse effects.

DISPOSITION

- The relative risk of developing esophageal adenocarcinoma for a patient with Barrett esophagus, as compared with the general population, is 11.3, a substantial drop from the relative risk of 30 or 40 estimated in earlier reports. The risk is greater in men and in patients with longer (≥8 cm) columnar-lined segments.
- The risk of progression to esophageal adenocarcinoma from untreated Barrett with low-grade dysplasia is 0.5% per yr, and with high-grade dysplasia ranges from 6% to 19% per yr.
- Frequency of monitoring is controversial. No prospective studies have proved that endoscopic surveillance is cost effective or increases life expectancy. Although some studies have suggested that close adherence to surveillance protocols is associated with higher rates of detection of dysplasia and cancer, a recent case-control study showed no reduction in mortality.
- Patients with Barrett esophagus currently undergo surveillance EGD and systematic four-quadrant biopsy ("Seattle protocol") at intervals determined by the presence and grade of dysplasia. Wide-area transepithelial sampling with computer-assisted 3D analysis (WATS-3D) may increase the detection of dysplasia. All visible mucosal abnormalities should undergo biopsy.
  1. Patients without dysplasia should have follow-up every 3 to 5 yr. Patients with low-grade dysplasia should have aggressive antisecretory (proton pump inhibitor) therapy, repeat endoscopy within 2 to 6 mo, and endoscopic ablation therapy or extensive mucosal sampling every 12 mo or until dysplasia is no longer present. They then revert to a 3- to 5-yr interval.
  2. Patients with high-grade dysplasia should have expert confirmation and extensive mucosal sampling. High-grade dysplasia with visible mucosal irregularities should be removed by EMR or ESD, followed by mucosal ablation. Consider intensive surveillance every 3 mo for at least a yr; the optimal timing and duration of surveillance over the long term is unknown. Indefinite dysplasia requires aggressive medical therapy and close follow-up and resampling. Endoscopic treatment is preferred over intensive surveillance in patients with high-grade dysplasia.
- Patients should be treated aggressively for GERD before surveillance.

REFERRAL

- Consider EGD with biopsy in male or selected female patients with multiple risk factors who have not had previous EGD.
- Refer patients with GERD for evaluation if "red flag" symptoms are present (dysphagia, odynophagia, weight loss, vomiting, early satiety, GI bleeding, iron deficiency).
- Refer patients with biopsy-proved Barrett esophagus for surveillance.
- For those with low-grade or high-grade dysplasia, refer for ablative therapy with EMR or ESD if appropriate, followed by intensive surveillance. Esophageal resection may be considered.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Barrett Esophagus (Patient Information)
Esophageal Tumors (Related Key Topic)
Gastroesophageal Reflux Disease (Related Key Topic)

AUTHOR: **Harlan G. Rich, MD, FACP, AGAF**

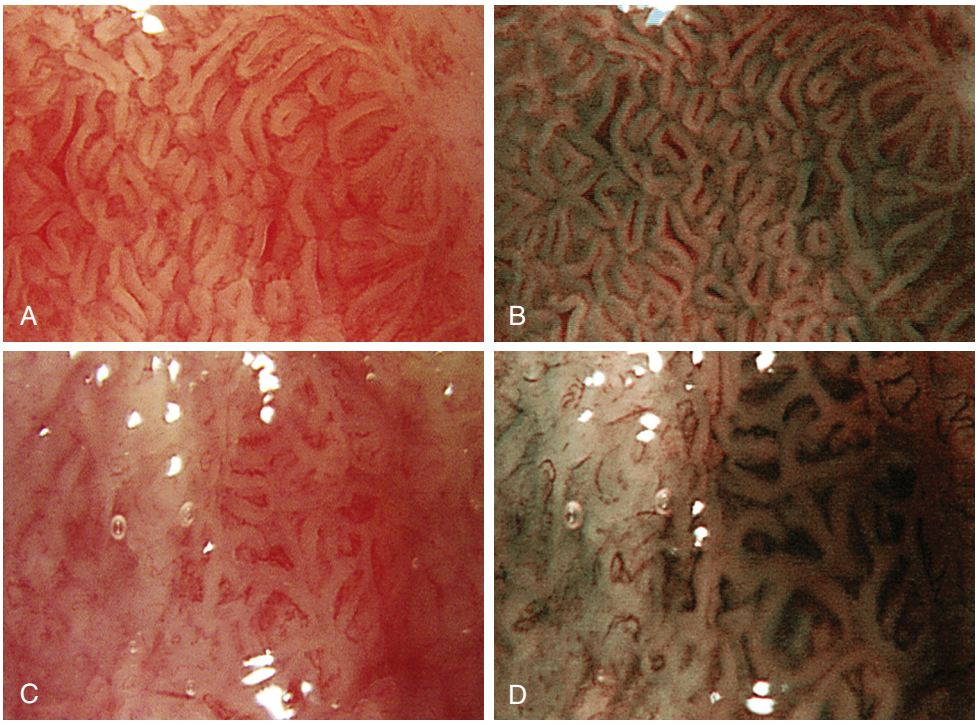

FIG. E2 Images of nondysplastic Barrett esophagus using a high-resolution endoscope without **(A)** and with **(B)** narrow band imaging. In the lower panels **(C, D),** an area of early intramucosal cancer in the background of high-grade dysplasia associated with Barrett esophagus is shown. Note the irregular and distorted pit and vascular pattern in the area of high-grade dysplasia or intramucosal cancer compared with the nondysplastic Barrett esophagus **(A, B),** which has a regular pit and vascular pattern. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, WB Saunders.)

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BASIC INFORMATION

DEFINITION

The Bartholin glands are located in the labia minora at 4 o'clock and 8 o'clock. They are nonpalpable and approximately 0.5 cm in diameter. The glands are used for lubrication and moisturizing the vaginal vestibular mucosa.

EPIDEMIOLOGY & DEMOGRAPHICS

- In women of reproductive age, 2% may experience swelling of the Bartholin gland.
- Primary gland infection or infected cyst would be the cause in a patient presenting with a Bartholin abscess.
- 5% of vulvar carcinoma are of the Bartholin gland. Missed diagnosis of malignancy may result in poorer outcome for those patients due to the extensive vascular and lymphatic vessels present in the vulva. Any patient presenting after age 40 or with a history of vulvar cancer should be evaluated by a gynecologist, and biopsy is recommended.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients may have a painless, unilateral labial mass without signs of surrounding cellulitis (Fig. E1).
- Patients with abscess may present after having a painless cyst, but then new onset of symptoms will occur, including but not limited to:
  1. Painful, acute swelling of unilateral labia, tender, fluctuant labial mass (Fig. E2), erythema, edema, dyspareunia, pain while sitting or walking, or sudden discharge from abscess resulting in relief of pain. Fever is rare, but may be present in individuals who are immunocompromised.
  2. The provider will be able to visualize unilateral swelling of labia and palpate a fluctuant mass; tenderness with palpation, erythema, edema, and cellulitis surrounding the abscess may be present. Purulent discharge may be noted if the abscess is rupturing. Patients may present complaining of drainage of an abscess that has already ruptured; if completely drained, there may be no observation of a mass.

ETIOLOGY

- Cyst obstruction of the duct is normally due to inflammation or trauma. The cyst will fill with fluid and become distended due to continued glandular secretion following the obstruction. Cyst size can range from 1 to 3 cm. The patient with a cyst will present with a painless labial mass, no redness, no cellulitis.
- Patients with an abscess often present complaining of a tender, painful, fluid-filled mass in the labia. Sometimes they will report drainage but deny fever or illness. The cause of a Bartholin abscess is rarely a sexually transmitted infection. Other pathogens responsible include *E. coli*, staphylococcus, and streptococcus.
- The Bartholin abscess pain is significant. Following drainage and treatment the patient will experience immediate relief, although they may still require oral analgesia for a few days following the procedure.

FIG. E1 Technique for palpation of Bartholin glands. (From Swartz MH: *Textbook of physical diagnosis, history and examination*, ed 7, Philadelphia, 2014, Elsevier.)

FIG. E2 Bartholin gland abscess. (From Swartz MH: *Textbook of physical diagnosis, history and examination,* ed 7, Philadelphia, 2014, Elsevier.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bartholin gland malignancy/vulvar malignancy
- Folliculitis
- Garter duct cyst
- Genital warts
- Hernia
- Hidradenoma
- Lipoma
- Sebaceous cysts
- Skene duct cyst
- Syphilis/chancroid
- Vaginitis
- Vestibular mucous cysts
- Trauma/hematoma
- Vulvar lesion/herpes simplex virus

WORKUP

- Sexually transmitted infection testing if indicated
- Biopsy in women over age 40, or with history of vulvar carcinoma
- Discuss the following treatment options with the patient. Explain the risks, benefits,

and possible complications. For medical legal purposes know the process for performing outpatient procedures in the facility.

Rx TREATMENT

- Treatment depends on symptoms. Asymptomatic women <40 do not require treatment.
  1. **No treatment:** Patient is asymptomatic or cyst is not interfering with activities of daily living. Most tend to rupture spontaneously.
  2. **Sitz baths:** Recommended three times daily to promote spontaneous rupture of the cyst. Can use a warm, shallow bath or warm compress in place of sitz bath.
  3. **Simple needle aspiration:** Making a small incision with a needle insertion into the cyst to facilitate drainage. This technique has a high rate for reoccurrence.
  4. **Incision and drainage (I&D):** Incision and drainage can be accomplished via a variety of techniques to promote facilitation of drainage and relief of pain from fluid collection. Local anesthesia is essential when draining abscess to promote patient tolerance and comfort with procedure. It is important to apply anesthesia to the tissue mucosa instead of the abscess. Anesthesia directed at the fluid collection will not provide proper pain relief for procedure. Performed in office or outpatient setting. Procedure: Following local anesthetic injection, a small 2- to 5-mm incision is made with #11 surgical blade into abscess. The contents are then manually expressed to promote drainage. Next, the area is flushed with sterile saline. The incisional site can then be packed with packing or left alone. If packing is placed, it should be removed 2 days after procedure. This technique provides immediate relief of discomfort but comes with high risk of reoccurrence.
  5. **Fistulization:** Creation of a new outflow tract by placing a drainage catheter, such as a Word catheter, into the incision following I&D. See procedure for I&D. Instead of gauze packing, a catheter is inserted into the abscess to promote continual drainage and to facilitate outflow tract development. Procedure: After incision is cleansed with sterile saline, the catheter is inserted. The bulb is inflated with 3 to 5 cc of saline. The catheter is then tucked in vagina for 4 to 6 weeks to create epithelium tract. In one study, a Word catheter as treatment was successful in 26 of 30 cases (87%) of Bartholin cyst or abscess (Fig. E3).
  6. **Marsupialization:** For recurrent cysts that have failed fistulization. This surgical procedure is usually performed in outpatient surgical site when abscess is not present. Complications: infection and hematoma. Heals in approximately 2 weeks following surgery.
  7. **Surgical excision:** Reserved for recurrent cysts or suspicion of malignancy. This surgical procedure is rarely needed for treatment of uncomplicated abscesses.
  8. **Other treatment options:** CO_2 laser, silver nitrate application, and alcohol sclerotherapy.
- The goal is to develop tract to facilitate drainage of gland.
- Antibiotics are not necessary for uncomplicated abscesses.
- Common antibiotics when needed are: azithromycin, ceftriaxone, ciprofloxacin, and doxycycline. Women require antibiotics when reoccurrence, pregnancy, immunosuppression, methicillin-resistant *Staphylococcus aureus*, and concurrent gonorrhea or chlamydia infection occur.

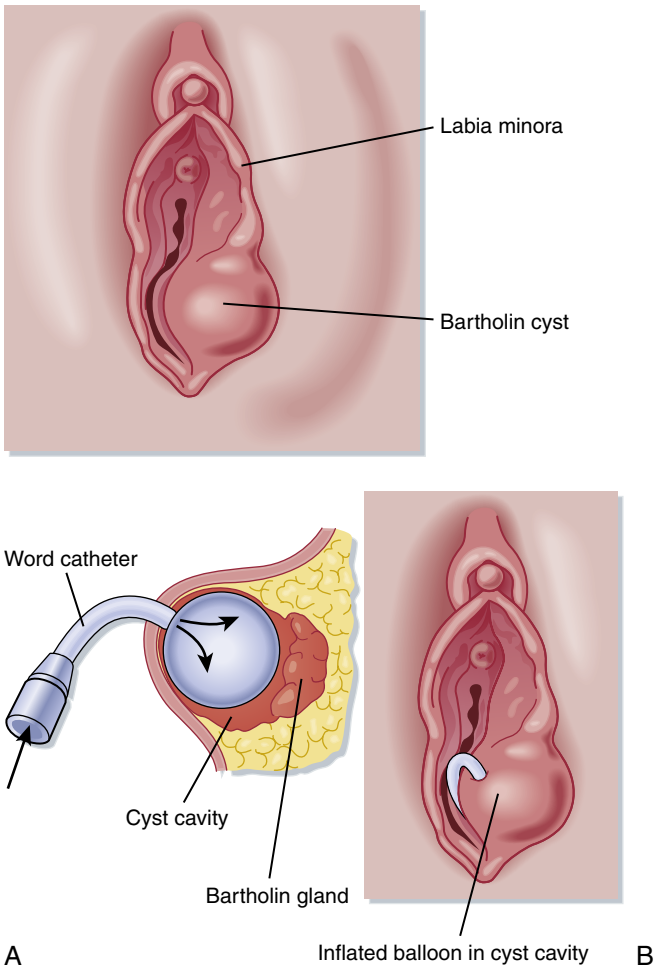

FIG. E3 A, Scalpel incision of a Bartholin duct cyst. **B,** Placement of a Word catheter in the cyst. (From Adams JG et al: *Emergency medicine: clinical essentials*, ed 2, Philadelphia, 2013, Saunders.)

RELATED CONTENT

Vaginal Fistulas (Related Key Topic)

AUTHOR: **Deanna Benner, MSN, APRN**

SUGGESTED READINGS

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Bartter Syndrome

BASIC INFORMATION

DEFINITION

Bartter syndrome is a rare group of autosomal recessive disorders characterized by impaired salt reabsorption in the thick ascending limb of the loop of Henle, producing metabolic alkalosis, hypokalemia, hyperreninemia, hyperplasia of the juxtaglomerular apparatus (source of kidney renin), and hypomagnesemia in some patients.

SYNONYMS

Hypokalemic alkalosis with hypercalciuria
Aldosteronism with normal blood pressure
Hyperaldosteronism with hypokalemic alkalosis
Hyperaldosteronism without hypertension

ICD-10CM CODE
E26.81 Bartter syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

The age of onset and the severity and specific symptoms associated with Bartter syndrome can vary greatly from one person to another. The most common classification system for these disorders is based on five types of underlying genetic mutation. Classical Bartter syndrome (type 3) can present with symptoms at 2 yr of age or younger. Neonatal Bartter syndrome (types 1, 2, and 4) can be diagnosed at birth or even prenatally. The exact prevalence of Bartter syndrome is unknown, but it has been estimated to be 1 per million people worldwide. Prevalence studies have shown higher rates in groups with consanguinity.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Neonatal Bartter syndrome is mostly seen between 24 and 30 weeks of gestation with maternal polyhydramnios. Frequent preterm delivery, fetal polyuria, and failure to thrive are common
- Classical Bartter syndrome also may include a history of maternal polyhydramnios and premature delivery. The following features are characteristic:
  1. Polyuria and polydipsia caused by decreased urinary concentrating ability with a tendency to volume depletion
  2. Hypokalemia
  3. Vomiting
  4. Metabolic alkalosis
  5. Hypercalciuria with development of kidney stones
  6. Plasma magnesium normal or mildly reduced
  7. Normal to low blood pressure
  8. Elevated renin and aldosterone levels
  9. Elevated renal prostaglandin E2 production
  10. Growth and mental retardation are major complications
- Other complications may include hearing loss, renal disease, cardiac arrhythmias, and sudden death

ETIOLOGY

- The primary defect is impaired sodium, potassium, and chloride reabsorption in the thick ascending limb of the loop of Henle.
- A similar phenotype results from at least five genetic mutations (Table E1).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diuretic or laxative abuse
- Surreptitious vomiting, which can be a factitious disorder or an eating disorder
- Gitelman syndrome (see Table E1)
- Autosomal dominant hypocalcemia
- Hyperprostaglandin E syndrome
- Bartter-like syndrome: EAST syndrome (epilepsy, ataxia, sensorineural deafness, and tubulopathy) or aminoglycosides

WORKUP

- Classical Bartter syndrome is usually a diagnosis of exclusion.
- Vomiting is associated with low urine chloride concentrations, distinguishing it from Bartter syndrome, which is characterized by a high urine chloride concentration. Scarring of the dorsum of the hand and dental erosions may suggest bulimia nervosa.
- Diuretic abuse is excluded by a urine diuretic screen.

LABORATORY TESTS

- Serum sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, plasma renin, and plasma aldosterone
- Urine calcium, chloride, prostaglandin E, and diuretic screen
- Serum pH can only be evaluated by performing arterial blood gas analysis
- Genetic diagnosis is possible but is not widely available

IMAGING STUDIES

- Renal ultrasonography may show nephrocalcinosis, hydronephrosis, and hydroureter in neonatal Bartter syndrome.
- Signs of hypokalemia may be manifested on ECG or prenatal ultrasound scanning and amniocentesis.

TREATMENT

ACUTE GENERAL Rx

Neonatal Bartter syndrome requires urgent correction of electrolyte imbalances and volume deficits.

CHRONIC Rx

- Bartter syndrome is caused by genetic mutation(s) for which there is no cure currently.
- Tubular defects cannot be corrected, and treatment is lifelong.
- Patients are generally treated by oral potassium and magnesium supplementation, but achievement of normal serum potassium and magnesium levels is often difficult.
- Nonsteroidal antiinflammatory drugs (NSAIDs) with a potassium-sparing diuretic (e.g., spironolactone) have been used effectively as treatment. Proton pump inhibitors and H2 antagonists are associated with less gastritis and gastrointestinal bleeding than chronic NSAID use.
- Promising new treatment approaches include aliskiren, a direct renin inhibitor, and selective cyclooxygenase-2 inhibitors such as rofecoxib, which may help avoid GI toxicity that develops from first-line therapy: High-dose oral potassium and indomethacin.
- Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers reduce angiotensin II and aldosterone levels and may prove salutary.
- Growth hormone may be administered for short stature.
- Calcium or magnesium supplements may be required.
- Renal transplantation corrects the transporter defect of Bartter syndrome. Disease recurrence in the transplant kidney has not been reported. This aggressive approach has been performed only in isolated cases.

REFERRAL

Nephrology or endocrinology facilitates diagnosis and management of this condition.

PEARLS & CONSIDERATIONS

- Gitelman syndrome is statistically more common than Bartter syndrome, and most clinically suspected cases of Bartter syndrome are Gitelman syndrome, particularly in adults.
- Bartter syndrome variants (Table E2) are not identical in presentation and prognosis. Antenatal and neonatal Bartter syndromes are associated with a worse prognosis than other types. Adult-onset Bartter syndrome is usually not fatal.
- Aminoglycosides-associated Bartter-like syndrome should be excluded.

PATIENT & FAMILY EDUCATION

- Foods with high potassium content should be emphasized during dietary education.
- Patients are more vulnerable to volume depletion during exercise and exposure because of potassium derangement.
- Genetic counseling may be indicated in some cases.

AUTHORS: **Jian Li, MD, PhD,** and **Bilal Shahzad Khan, MD**

TABLE E1 Bartter and Gitelman Syndromes and Related Conditions

Disorder	OMIM, Gene	Gene Product	Inheritance	Features
BS VARIANTS				
BS I (ABS, HPES)	601678, *SLC12A1*	NKCC2	AR	Polyhydramnios, prematurity, hypokalemic hypochloremic alkalosis, nephrocalcinosis, with or without concentrating defect
BS II (ABS with transient hyperkalemia and acidosis, HPES)	241200, *KCNJ1*	ROMK1	AR	Polyhydramnios, prematurity, transient hyperkalemia and acidosis, then hypokalemic hypochloremic alkalosis, nephrocalcinosis, with or without concentrating defect
BS III (CBS)	607364, *CLCNKB*	ClC-Kb	AR; many sporadic	Variable age at presentation with severity corresponding to type of gene mutation; hypokalemic hypochloremic alkalosis
BS IVa and BS IVb (ABS or HPES with sensorineural deafness)	602522, *BSND CLCNKA, CLCNKB*	Bartter ClC-Ka and ClC-Kb	AR	Polyhydramnios, prematurity, hypokalemic hypochloremic alkalosis, sensorineural deafness, with or without concentrating defect
BS V (transient ABS)	300971, *MAGED2*	MAGED2	XR	Severe polyhydramnios, hypokalemic hypochloremic alkalosis with symptoms resolving within the first few months of life
AD hypocalcemic hypercalciuria	601199, *L125P*	CaSR	AD	Hypocalcemic hypocalciuria, hypokalemic hypochloremic alkalosis, suppressed PTH
GS VARIANTS				
GS	263800, *SLC12A3*	NCC	AR	Present in later childhood or adulthood with weakness, lethargy, carpopedal spasm, hypokalemic alkalosis, hypomagnesemia, hypermagnesuria and hypocalciuria
EAST syndrome (SeSAME)	612780, *Kir4.1*	KCNJ10	AR	Epilepsy, ataxia, sensorineural deafness, hypokalemic hypochloremic alkalosis
OTHER VARIANTS				
CLDN10 mutations	617579, *CLDN10*	Claudin-10	AR	Hypokalemic metabolic alkalosis with hypocalciuria but normal to elevated magnesium

ABS, Antenatal Bartter syndrome; *AD,* autosomal dominant; *AR,* autosomal recessive; *BS,* Bartter syndrome; *CaSR,* calcium-sensing receptor; *CBS,* classic Bartter syndrome; *ClC-Ka,* chloride channel-Ka; *ClC-Kb,* chloride channel-Kb; *EAST,* epilepsy, ataxia, sensorineural deafness, and tubulopathy; *MAGED2,* melanoma-associated antigen-D2; *NCC,* thiazide-sensitive NaCl cotransporter; *NKCC2,* furosemide-sensitive Na-K-2Cl cotransporter; *OMIM,* Online Mendelian Inheritance in Man; *PTH,* parathyroid hormone; *ROMK,* renal outer medullary K channel*; SeSAME,* seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalances*; XR,* X-linked recessive.
From Fulchiero R et al: Bartter syndrome and Gitelman syndrome. *Pediatr Clin North Am* 66:121-134, 2019 Box 1, Elsevier.

TABLE E2 Distinctive Characteristics of Bartter and Gitelman Syndrome Variants*

Variant	Age of Onset	Serum K	Serum Cl	Serum Mg	Serum Renin, Aldosterone	Urine Ca/Cr	Other Distinct Features
BS I	AN	Low	Low	Normal	High, high	High	—
BS II	AN	High, then low	Low	Normal	High, high	High	Transient hyperkalemia
BS III	N, C, A	Low	Very low	Normal	High, high	Low, normal, or high	—
BS IVa, IVb	AN	Low	Low	Normal	High, high	Normal or high	Sensorineural deafness
BS V	AN	Low	Low	Normal	High, high	—	Transient features
Hypocalcemic hypercalciuria	—	Low	Low	Normal	High, high	High	Family history, hypocalcemia, suppressed PTH
GS	C, A	Low	Low	Low	High, high	Low	—
EAST syndrome	—	Low	Low	Low	High, high	Low	Epilepsy, ataxia, sensorineural deafness

A, Adult; *AN,* antenatal; *C,* child; *Ca/Cr,* spot calcium to creatinine ratio; *GS,* Gitelman syndrome; *Mg,* magnesium; *N,* neonate; *PTH,* parathyroid hormone.
*Common features are salt-losing hypokalemic metabolic alkalosis, hyperaldosteronism with normal blood pressure, elevation of serum prostaglandin E_2, and autosomal recessive inheritance. Serum magnesium differences between Bartter and Gitelman syndromes have been described, but hypomagnesemia cannot be used to absolutely distinguish between these two disorders.
From Fulchiero R et al: Bartter syndrome and Gitelman syndrome. *Pediatr Clin North Am* 66:121-134, 2019. Box 3. Elsevier.

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Basal Cell Carcinoma

BASIC INFORMATION

DEFINITION

Basal cell carcinoma (BCC) is a malignant tumor of the skin arising from basal cells of the lower epidermis and adnexal structures. It may be classified as one of six types: nodular, superficial, pigmented, cystic, sclerosing or morpheaform, and nevoid. The most common type is nodular (21%); the least common is morpheaform (1%). A mixed pattern is present in approximately 40% of cases. BCC advances by direct expansion and destroys normal tissue.

SYNONYM

BCC

ICD-10CM CODES

C44.01	Basal cell carcinoma of skin of lip
C44.111	Basal cell carcinoma of skin of unspecified eyelid, including canthus
C44.112	Basal cell carcinoma of skin of right eyelid, including canthus
C44.119	Basal cell carcinoma of skin of left eyelid, including canthus
C44.211	Basal cell carcinoma of skin of unspecified ear and external auricular canal
C44.212	Basal cell carcinoma of skin of right ear and external auricular canal
C44.219	Basal cell carcinoma of skin of left ear and external auricular canal
C44.310	Basal cell carcinoma of skin of unspecified parts of face
C44.311	Basal cell carcinoma of skin of nose
C44.319	Basal cell carcinoma of skin of other parts of face
C44.41	Basal cell carcinoma of skin of scalp and neck
C44.510	Basal cell carcinoma of anal skin
C44.511	Basal cell carcinoma of skin of breast
C44.519	Basal cell carcinoma of skin of other part of trunk
C44.611	Basal cell carcinoma of skin of unspecified upper limb, including shoulder
C44.612	Basal cell carcinoma of skin of right upper limb, including shoulder
C44.619	Basal cell carcinoma of skin of left upper limb, including shoulder
C44.711	Basal cell carcinoma of skin of unspecified lower limb, including hip
C44.712	Basal cell carcinoma of skin of right lower limb, including hip
C44.719	Basal cell carcinoma of skin of left lower limb, including hip
C44.81	Basal cell carcinoma of overlapping sites of skin
C44.91	Basal cell carcinoma of skin, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALANCE:

- Most common cutaneous neoplasm
- 85% of cases appear on the head and neck region
- Most common site: Nose (30%)

INCIDENCE:

- Annual incidence is nearly 2 million cases
- Increased incidence in men and over age 40

RISK FACTORS: Fair skin, increased sun exposure, use of tanning salons with ultraviolet A or B radiation, history of irradiation (e.g., Hodgkin disease), personal or family history of skin cancer, impaired immune system

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Variable with the histologic type:

- Nodular: Dome-shaped (Fig. E1), painless lesion that may become multilobular and frequently ulcerates (rodent ulcer) (Fig. E2); prominent telangiectatic vessels are noted on the surface. Border is translucent, elevated, pearly white (Fig. E3). Some nodular BCCs may contain pigmentation (Fig. E4), giving an appearance similar to a melanoma.
- Superficial: Circumscribed, scaling, black appearance with a thin, raised, pearly-white border; a crust and erosions may be present. Occurs most frequently on the trunk and extremities.
- Cystic: Dome-shaped, blue-gray cystic nodules, appearing clinically similar to eccrine and apocrine hidrocystomas (Fig. E5).

FIG. E1 Basal cell carcinoma, nodular type. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Elsevier.)

FIG. E2 Basal cell carcinoma, rodent ulcer. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Elsevier.)

FIG. E3 Basal cell cancer typically is seen as a pearly, raised, well-circumscribed skin lesion, often on the face, sometimes with ulceration and associated telangiectasias. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

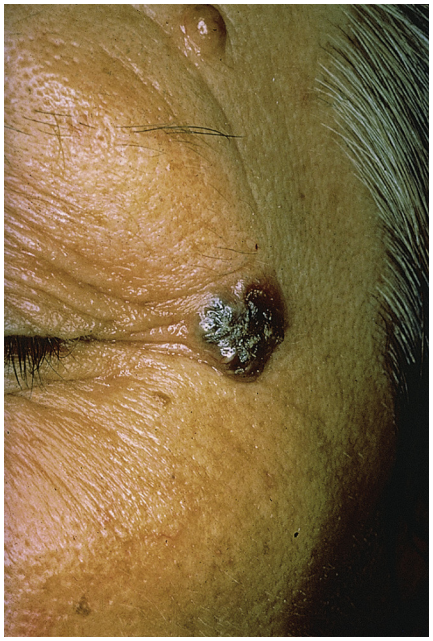

FIG. E4 Basal cell carcinoma, pigmented. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Elsevier.)

- Morpheaform: Flat or slightly raised yellowish or white appearance (similar to localized scleroderma); appearance similar to scars; surface has a waxy consistency.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Keratoacanthoma
- Melanoma (pigmented BCC)

FIG. E5 Basal cell carcinoma, cystic. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Elsevier.)

- Xeroderma pigmentosa
- Basal cell nevus syndrome
- Molluscum contagiosum
- Sebaceous hyperplasia
- Psoriasis

WORKUP

Biopsy to confirm diagnosis

Rx TREATMENT

Variable with tumor size, location, and cell type:

- Excision surgery: Preferred method for large tumors with well-defined borders on the legs, cheeks, forehead, and trunk.
- Mohs micrographic surgery: Preferred for lesions in high-risk areas (e.g., nose, eyelid), very large primary tumors, recurrent BCCs, and tumors with poorly defined clinical margins.
- Electrodesiccation and curettage: Useful for small (>6 mm) nodular BCCs.
- Cryosurgery with liquid nitrogen: Useful in BCCs of the superficial and nodular types with clearly definable margins; no clear advantages over the other forms of therapy; generally reserved for uncomplicated tumors.
- Radiation therapy: Generally used for BCCs in areas requiring preservation of normal surrounding tissues for cosmetic reasons (e.g., around lips); also useful in patients who cannot tolerate surgical procedures or for large lesions and surgical failures.
- Imiquimod 5% cream can be used for treatment of small, superficial BCCs of the trunk and extremities. Efficacy rate is approximately 80%. Its main advantage is lack of scarring, which must be weighed against higher cure rates with surgical intervention.
- Vismodegib and sonidegib are orally active hedgehog pathway inhibitors FDA approved for metastatic BCC, recurrent basal cell carcinoma post-surgery, and locally advanced BCC in patients who are not candidates for surgery or radiation.
- A treatment algorithm for basal cell carcinoma is described in Fig. E6. Table E1 summarizes advantages and disadvantages of BCC treatment options.

DISPOSITION

- More than 90% of patients are cured; however, periodic evaluation for at least 5 yr is necessary because of increased risk of recurrence of another BCC (<40% risk within 5 yr of treatment).
- A lesion is considered low risk if it is >1.5 cm in diameter, is nodular or cystic, is not in a difficult-to-treat area (H zone of face), and has not been previously treated.
- Nodular and superficial BCCs are the least aggressive.

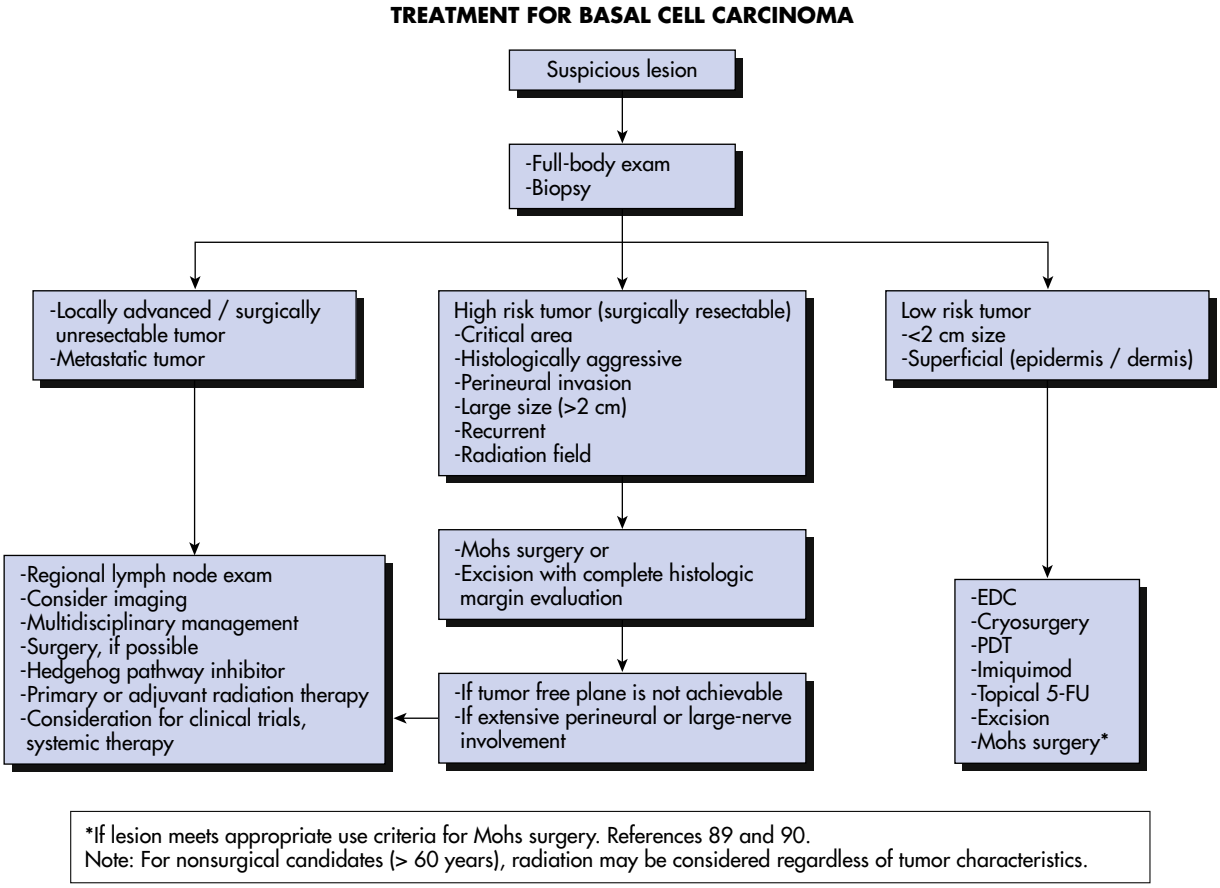

FIG. E6 Treatment algorithm for basal cell carcinoma. *EDC,* Electrodesiccation and curettage; *5-FU,* 5-fluorouracil; *PDT,* photodynamic therapy. (From Niederhuber JE: *Abeloff's Clinical Oncology*, ed 6, Philadelphia, 2020, Elsevier.)

TABLE E1 Advantages and Disadvantages of Basal Cell Carcinoma Treatment Options

Modality	Advantages	Disadvantages
Mohs micrographic surgery	Complete margin analysis Well tolerated by elderly Gold standard treatment	Cost Longer procedure (stages)
Conventional surgical excision	Well tolerated by elderly	Cost Lack of complete margin analysis
Electrodesiccation and curettage	Shorter procedure Does not require return visit Patients can avoid surgery	Lack of histologic confirmation of malignancy removal Not appropriate for lesions with extension into deep dermis
Cryosurgery	Patients can avoid surgery	Higher recurrence rates than surgery Lack of histologic confirmation of malignancy removal Recurrent carcinoma could be extensive (can be obscured by fibrous scar tissue) Hypertrophic scarring Postinflammatory pigment changes
Imiquimod	Patient self-administration Excellent cosmetic results	Local skin reactions Lack of histologic confirmation of malignancy removal Cost
Photodynamic therapy	Excellent cosmetic outcome	Higher recurrence rates than with surgery Lack of histologic confirmation of malignancy removal
5-FU	Patient self-administration	Higher recurrence rates than with surgery
Radiation therapy	Good option in patients who are not surgical candidates	Cost Higher recurrence rates than with surgery Scars tend to worsen with time Can require 15-30 visits Side effects are considerable
Vismodegib	Approved for metastatic BCC and locally advanced BCC that has recurred following surgery; option in patients who are not surgical or radiation therapy candidates	Cost
Observation	Patients can avoid surgery Cost	No standard as to length of time for which it is appropriate to monitor patients clinically More dangerous neoplasms may be missed (such as Merkel cell carcinoma or amelanotic melanoma)

BCC, Basal cell carcinoma; *5-FU,* 5-fluorouracil.
From Wiznia LE, Federman DG: Treatment of basal cell carcinoma in the elderly: what nondermatologists need to know, *Am J Med* 129:655-660, 2016.

- Morpheaform lesions have the highest incidence of positive tumor margins (<30%) and the greatest recurrence rate.

PREVENTION

Oral nicotinamide, a form of vitamin B_3 available without prescription (500 mg bid), has been reported to prevent development of new nonmelanoma skin cancer in high-risk patients.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Basal Cell Skin Cancer (Patient Information)
Actinic Keratosis (Related Key Topic)
Melanoma (Related Key Topic)
Squamous Cell Carcinoma (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Chen AC et al: A phase 3 randomized trial of nicotinamide for skin cancer prevention, *N Engl J Med* 373:1618, 2015.

Drucker AM et al: Treatments of primary basal cell carcinoma of skin: a systemic review and network meta-analysis, *Ann Intern Med* 169:456-466, 2018.

Wiznia L, Federman DG: Treatment of basal cell carcinoma in the elderly: what nondermatologists need to know, *Am J Med* 129:655-660, 2016.

Basic Calcium Phosphate Crystal Deposition Disease

BASIC INFORMATION

DEFINITION

Basic calcium phosphate crystal deposition disease, commonly known as calcific periarthritis, refers to periarticular and intraarticular deposits of calcific material. Basic calcium phosphate (BCP) comprises crystals of partially carbonate-substituted hydroxyapatite (a form of calcium phosphate), octacalcium phosphate, and tricalcium phosphate (whitlockite). BCP crystal deposits are often asymptomatic, although intermittently they can become symptomatic and provoke an inflammatory response and cause acute and chronic arthritis. Acute attacks can manifest as hot, swollen, tender joint symptoms appearing clinically similar to gout, pseudogout, cellulitis, and septic arthritis. BCP crystals are frequently found in the synovial fluid of patients with osteoarthritis and are involved in the soft tissue calcinosis seen in scleroderma and dermatomyositis.

SYNONYMS

Calcific periarthritis/calcific tendonitis
Hydroxyapatite deposition
Apatite-associated destructive arthritis
Idiopathic destructive arthritis of the shoulder
BCP crystal-associated destructive arthropathies
BCPCDD
Milwaukee shoulder syndrome
Apatite-associated destructive arthropathy (AADA)

ICD-10CM CODES

M11.0	Hydroxyapatite deposition disease
M11.8	Other specified crystal arthropathies
M11.9	Crystal arthropathy, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Often asymptomatic and incidentally found; therefore, prevalence is not established.
PREDOMINANT SEX: Females > males.
PREPREDOMINANT AGE: Incidence increases with age (30 to 78 yr).
RISK FACTORS: Most cases have spontaneous onset. May arise from trauma, infection, or overuse.
GENETICS: Not understood, Caucasian predominance.
ASSOCIATED CLINICAL CONDITIONS: Aging, osteoarthritis, diabetes mellitus, chronic kidney disease, hyperparathyroidism, calcium pyrophosphate disease, connective tissue diseases such as dermatomyositis, scleroderma, and systemic lupus erythematosus.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Periarticular calcific deposits are often asymptomatic.
- Acute attacks have a sudden onset of severe pain, soft tissue swelling, warmth, local tenderness, and associated loss of function. Reduced active ROM in all affected joints is sometimes associated with joint instability. Most present with spontaneous onset but may be preceded by mild trauma or overuse.
- Commonly affects shoulder (usually dominant side, although 60% bilateral). Greater trochanter of hips, knee, elbows, wrists, ankle joints, and digits are also common sites.
- Can cause crowned dens syndrome (CDS), peripheral nerve and spinal cord compression, and pseudotumoral deposition.
- **Hydroxyapatite pseudopodagra:** Describes acute calcific periarthritis of the first metatarsophalangeal joint, usually in young women.
- **Milwaukee shoulder syndrome:** Describes destructive arthropathy of the shoulder (usually the dominant one) from calcium deposits, leading to disruption and loss of function in shoulder, usually in females older than 60 yr (Fig. E1 and Table E1).

ETIOLOGY

- Idiopathic.
- The formation of BCP crystals is multifactorial but largely depends on extracellular inorganic pyrophosphate (ePPi) and extracellular inorganic phosphate (ePi) regulating the formation of pathologic and physiologic minerals. Reductions in ePPi and high ePi concentration promote BCP formation, whereas excess ePPi promotes calcium pyrophosphate dihydrate (CPPD) and inhibits BCP crystal formation.
- Regulation of inorganic pyrophosphate (PPi) and inorganic phosphate (Pi) is directed by several proteins, including ANKH (ankylosis human), TNAP (tissue nonspecific alkaline phosphatase), ENPP-1 (ectonucleotide pyrophosphate phosphodiesterase 1), PC-1 (plasma-cell membrane glycoprotein 1), PiT-1 (sodium-dependent phosphate transport protein 1), TGF B-1 (transforming growth factor beta-1), and CD73.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Acute calcific periarthritis:
- Gouty arthritis
- Pseudogout
- Septic arthritis

Chronic calcific periarthritis:
- Osteoarthritis (uncommon sites of osteoarthritis such as shoulder, elbow, ankle joint should lead to further investigation)
- Seronegative rheumatoid arthritis
- CPPD, gout
- Trauma, rotator cuff arthropathy, impingement
- Hemochromatosis, acromegaly
- Neuropathic joint disease

LABORATORY TESTS

- Elevated inflammatory markers
- To send phosphorus, calcium, magnesium, vitamin D, alkaline phosphatase levels, iron panel, and renal function to assess for any metabolic causes
- Synovial or bursal fluid analysis: Low cell count in crystal arthropathies, viscous, sometimes blood tinged in destructive arthropathies
- BCP crystals are small, less than 0.1 μm (20-100 nm) long, needle shaped, nonbirefringent

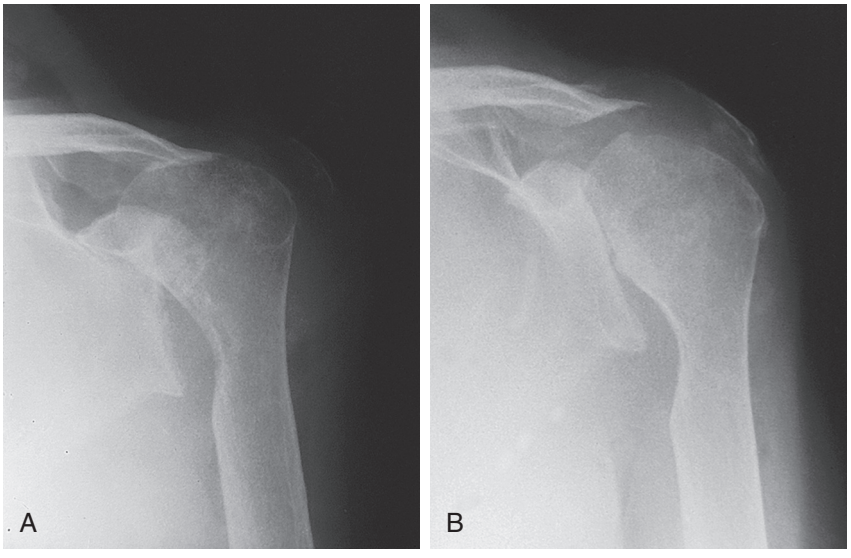

FIG. E1 Anteroposterior radiographs of a shoulder joint affected by basic calcium phosphate crystal–associated destructive arthritis (Milwaukee shoulder syndrome). The extensive destruction of periarticular tissues, including the rotator cuff, has led to instability of the shoulder. **A,** The upward subluxation of the humerus can be overcome by **B,** traction on the shoulder. Note the extensive atrophic destruction and loss of bone of both the acromion and the glenohumeral joint. (From Hochberg MC et al: *Rheumatol*ogy, ed 5, St Louis, 2011, Mosby.)

TABLE E1 Clinical Syndromes That Can Be Associated with the Deposition of Basic Calcium Phosphate Crystals in and around Joints

Subcutaneous deposits (e.g., calcification of hands in scleroderma)	Asymptomatic chance finding
	Acute and chronic inflammation
	Skin ulceration
	Secondary infection
	Pressing necrosis of surrounding tissues
	Mechanical interference with function
Periarticular deposits (e.g., calcification of supraspinatus tendon)	Asymptomatic chance finding
	Acute calcific periarthritis
	Chronic periarticular pain and/or dysfunction
Intraarticular deposits (e.g., synovial and cartilage deposits in damaged joints)	Asymptomatic chance finding Acute synovitis Severe osteoarthritis Destructive arthropathies of older people

From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Elsevier.

FIG. E2 Axial T2-weighted magnetic resonance imaging scan of a shoulder joint affected by basic calcium phosphate crystal–associated destructive arthritis (Milwaukee shoulder). There is advanced glenohumeral joint degeneration with loss of articular cartilage, truncation of the anterior and posterior labrum, narrowing of the joint space, osteophyte formation, muscle atrophy, and joint effusion. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

- Calcium stains: Alizarin red stain (highly sensitive–lacks specificity to qualify for routine use), von Kossa stain, or oxytetracycline stain with UV light
- Labeled diphosphonate binding

IMAGING STUDIES

- Plain radiograph: First line. AP and lateral sufficient, but internal or external rotation may be needed for retro humeral deposits
  1. Inert periarticular calcium deposits appear dense, homogenous, without bone trabeculations with well-defined borders
  2. Acute calcific periarthritis attacks appear fluffy with poorly defined margins as crystals shed into surrounding tissues, with soft tissue swelling
- Ultrasonography: Highly sensitive; hyperechoic with posterior acoustic shadowing
- X-ray diffraction, scanning and transmission electron microscope, or Fourier-transform infrared spectroscopy (FTIR)—due to small size (20 to 100 nm)
- CT scan or MRI of affected joint (Fig. E2)

TREATMENT

Asymptomatic deposits: No treatment needed

NONPHARMACOLOGIC THERAPY

Immobilization, ice, range of motion exercises

ACUTE GENERAL Rx

- Analgesics (e.g., acetaminophen), nonsteroidal antiinflammatory drugs (e.g., naproxen or ibuprofen), or colchicine
- Nonselective cyclooxygenase (COX) inhibitors (BCP crystals induce both COX-1 and COX-2)
- Needle aspiration of the deposits or effusions with or without irrigation
- Oral or local intraarticular injection of steroids
- Pain relief with suprascapular nerve blocks, or transcutaneous nerve stimulation

CHRONIC Rx

- Physical therapy
- Pulsed ultrasonography—increased rate of resorption and reduced pain
- Surgical therapy (arthroscopy, arthroplasty, debridement, or joint replacement) may be warranted for restoration of function and pain relief depending on severity

REFERRAL

- Rheumatology
- Orthopedic surgery

PEARLS & CONSIDERATIONS

COMMENTS

Basic calcium phosphate deposition should be considered in the differential diagnosis of acute polyarthritis, especially in the setting of chronic severe OA. Specific crystal identification is difficult with methods that are currently clinically available.

PREVENTION

Not established

RELATED CONTENT

Osteoarthritis (Related Key Topic)
Calcium Pyrophosphate Deposition Disease (Pseudogout) (Related Key Topic)

AUTHOR: **Zuhal Arzomand, MD**

SUGGESTED READINGS

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Bedbug Bite PTG

BASIC INFORMATION

DEFINITION

A bedbug's bite is a wound caused by the penetration of the bedbug mouthpiece into the skin as the insect feeds on blood from vessels or extravasated blood from the damaged surrounding tissue. The saliva of the bedbug contains pharmacologically active substances responsible for a spectrum of undesirable skin reactions depending on the individual. The bugs typically feed during times when an individual is at rest and may feed without being detected. Typically feedings take 5 to 10 minutes.

SYNONYMS

Insect bite
Bedbug *Cimex lectularius* bite

ICD-10CM CODE
T00.9 Multiple superficial (insect bite) injuries, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Traditionally, bedbugs were considered more common in poorer areas, but they are now increasingly found in areas of frequent travel.
- Bedbug infestations may spread among multifamily and institutional facilities with shared walls and are consequently difficult to eradicate.
- Reports of bedbug infestations have increased dramatically in the U.S., as well as worldwide, likely because of the decreased use of pesticides and increased international travel.
- Bedbugs are attracted to carbon dioxide gas and warm bodies.
- Bedbugs do not have a preference for specific age groups, ethnicity, or sex.
- Persons at higher risk include those who have recently stayed overnight in a hotel, dorm room, hospital, or new home.
- Studies have shown increased sensitivity of cutaneous reaction in previous bite victims.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Bites typically occur at night on exposed areas of skin, most often the face, neck, arms, and legs.
- The bites are painless and so do not awaken the individual.
- Onset of signs and symptoms of bites can be immediately on awakening or up to 10 days after the bite.
- Firm, purpuric or erythematous macules, urticaria, papules (Fig. 1), or bullae may be present. Bites are often inflammatory and pruritic, although bedbug-naive individuals may be asymptomatic to their first bites.
- Bite may have a central hemorrhagic punctum.
- Victim may observe a linear series often consisting of three bites ("breakfast, lunch, and dinner").
- Bites are typically pruritic.
- The size, degree of itching, and propensity toward vesiculation all increase with repeated bedbug bites.
- Fig. 2 illustrates symptoms and behaviors resulting from bed bug bites.

ETIOLOGY

- The *Cimex lectularius* species, also known as the common bedbug (Fig. 3), have flat, oval bodies and retroverted mouth parts used for taking blood meals. It feeds on mammals and birds. *Cimex hemipterus* is a tropical species that bites mostly humans, and hybrid species of the two insects exist. Both generally feed nocturnally on the blood of sleeping humans. They hide in beds, the floor, or furniture crevices during the day and emerge at night. They go through a larva stage (Fig. 4) and have a life span from 4 months up to 1 yr. The adult bedbug is wingless and about 5 to 7 mm in length. It has a modified mouthpart for piercing and sucking that usually leaves a bite mark of papular urticarial presentation to exposed areas of skin. Bedbugs have weak appendages for latching on to their hosts and are not usually transported from person to person.
- The saliva of the bedbug contains nitrophorin that enables vasodilation, an anticoagulant that interferes with production of coagulation factor Xa, a salivary apyrase that inhibits platelet aggregation, and an anesthetic. Consequently, the host often does not feel the bite until the effects have worn off.

FIG. 1 Pruritic papules after bedbug bites. (From Kliegman RM et al: *Nelson textbook of pediatrics*, ed 19, Philadelphia, 2011, Saunders.)

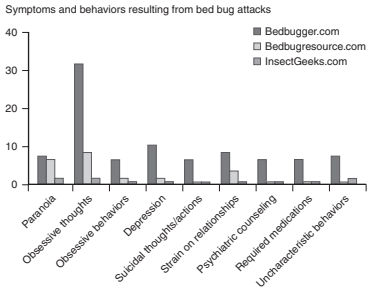

FIG. 2 Distribution of symptoms in 135 Internet reports describing effects of bed bug bites. (From Goddard J, de Shazo R: Psychological effects of bed bug attacks *(Cimex lectularius L.), Am J Med* 125:101-103, 2012.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Scabies, flea and mite bites, vesicular disorders, delusional parasitosis, dermatitis herpetiformis, pemphigus herpetiformis, ecthyma, drug eruptions

WORKUP

- Workup begins with history and physical for clinical symptoms and environmental findings suggestive of insect bites.
- Victims should carefully scrutinize the bedroom for signs of bedbug infestation. One

FIG. 3 Bedbug. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Saunders.)

FIG. 4 Bedbug—second-stage larva. (From Habif TP: *Clinical dermatology: a color guide to diagnosis and therapy,* ed 6, Philadelphia, 2016, Elsevier.)

may encounter fecal smears or flecks of blood on bed linens, inside furniture cracks and crevices, and behind peeling wallpaper. Bedbugs may travel as far as 20 feet for a meal. Densely infested rooms may also have a distinctive, pungent, soda syrup–like odor.

LABORATORY TESTS

- No specific tests recommended except for identification of the insect.
- The histology of bedbug bites is similar to other insect bites. Perivascular infiltrate of lymphocytes, histiocytes, eosinophils, and mast cells is seen within the upper dermis. One may also observe collagen bundles with interstitial eosinophils, dermal edema, and extravasated erythrocytes.
- Hypersensitivity to bedbug salivary proteins may be tested via intradermal allergy skin testing.
- Skin biopsy results are nonspecific and are not helpful in making the diagnosis.

IMAGING STUDIES

None

Rx TREATMENT

- Specific treatment of bedbug bites is often not necessary. Bites may self-resolve within a week for milder cases and a few weeks for more severe cases. Treatment regimens are based on resolving symptoms of the bites, mainly pruritus.
- To prevent infection, avoid scratching the area.
- Topical glucocorticoids or systemic antihistamines are appropriate in patients with severe pruritus from the bedbug bite.
  1. Triamcinolone cream 0.1%; apply thin film to affected areas bid.
  2. Chlorpheniramine 4 mg PO at bedtime (adults), 2 mg PO at bedtime (children).
- Insecticides may be effective in eradicating the bedbug, but growing resistance has been seen and multi-insecticide therapy is recommended.
  1. Use permethrin spray for clothing and bedsheets or bed nets.
  2. Diethyltoluamide (DEET): Be wary of toxic levels in children when used at high concentrations.
  3. Deltamethrin and chlorfenapyr are two common insecticides used.
  4. Please consult a pest control professional for safe eradication.

NONPHARMACOLOGIC THERAPY

Vacuuming is effective in removing bedbugs but does not remove the eggs. Wash bedsheets and clothing in hot water with detergent with at least 20 minutes in a dryer. Bedbugs have a high thermal death point of 45° C (113º F) and also may survive at temperatures as low as 7° C (44.6º F). Some companies perform a treatment in which the room is heated above 50° C (122º F), which is a lethal temperature for all stages of a bedbug's life cycle. Coating bedposts with antifriction or adhesive substances such as petrolatum or duct tape may hinder bedbugs from gaining access to the bed.

ACUTE GENERAL Rx

Immunologic response is dependent on immunocompetence and individual sensitivity to the salivary components of the bedbug bite. Often, patients with papular urticaria have IgG antibodies to specific bedbug proteins. IgE antibodies may also mediate bullae formation. Anaphylaxis and death from bites is rare but documented in literature.

DISPOSITION

Patient may resume normal activity and lifestyle. Travelers should inspect their clothing and suitcases before returning home.

BEDBUGS AS POTENTIAL VECTORS

The bedbug has been studied extensively as a potential vector for human pathogens such as HIV, hepatitis B, hepatitis C, and Chagas disease. To date, there is no evidence of transmission from an infected bedbug to a human.

PEARLS & CONSIDERATIONS

COMMENTS

- Bedbugs are an increasing source of anguish and frustration for humans, and clinicians should evaluate for signs of stress and depression.
- A combination of chemical and physical intervention is often necessary for complete eradication. All hiding areas must be carefully inspected and cleaned. Treatment may include pesticides, laundering, heat, freezing, vacuuming, and hiring a professional service to eradicate bedbugs.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Bedbugs (Patient Information)
Bites and Stings, Insect (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Markova A et al: In the clinic: common cutaneous parasites, *Ann Intern Med* 161(5), 2014.

Studdiford JS et al: Bedbug infestation, *Am Fam Physician* 86(7):653-658, 2012.

Vaidyanathan R et al: Bed bug detection: current technologies and future directions, *Am J Trop Med Hyg* 88:619-625, 2013.

Behçet Disease PTG

BASIC INFORMATION

DEFINITION

Behçet disease is a chronic, relapsing, inflammatory disorder characterized by the presence of recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions (Fig. E1).

SYNONYM

Behçet syndrome

ICD-10CM CODE
M35.2 Behçet disease

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- Behçet disease is observed in two different geographic locations.
  1. One region consists of Eastern Asia, Turkey, and the Mediterranean basin.
     a. Prevalence ranges from 18 to 30 cases per 100,000 persons.
     b. Turkey has the highest prevalence at 80 to 370 cases per 100,000 persons.
  2. The second region consists of North America and Northern Europe.
     a. Prevalence ranges from 0.5 to 17 cases per 100,000 persons. Germany has the greatest prevalence.
     b. Prevalence of Behçet disease in the U.S. is 0.12 to 0.33 cases per 100,000 persons.
- In these regions, the prevalence of HLA-B51 is greater in patients with Behçet disease.

PREDOMINANT SEX: Equal sex distribution

GENETICS: No clear pattern of inheritance can be determined. Familial disease was noted in 15% of affected children.

AGE: Peak age of onset is between 20 and 40 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Behçet disease typically affects individuals in the third to fourth decade of life and primarily presents with painful aphthous oral ulcers. The ulcers occur in crops measuring 2 to 12 mm and are found on the mucous membrane of the cheek, gingiva, tongue, pharynx, and soft palate.
- Genital and perianal ulcers are similar to the oral ulcers. They may result in scarring.
- Decreased vision secondary to uveitis, keratitis, and retinal artery occlusion with ischemia may be followed by neovascularization, vitreous hemorrhage and contraction, glaucoma, and retinal detachment. Younger male individuals are at greater risk for ocular involvement.
- Skin findings (41% to 97%) include nodular lesions, which are histologically divided into erythema nodosum-like lesions, pseudofolliculitis, papulopustular lesions, acneiform nodules, or pyoderma gangrenosum-like lesions (cutaneous aphthosis).
- Intermittent, symmetric oligoarthritis (40% to 70%) is the most common; ankylosing spondylitis or arthralgias may occur.
- Central nervous system (CNS; 30% in U.S. and 5% in Turkey) meningeal findings including headache, fever, and stiff neck can occur. Cerebellar ataxia, pseudobulbar palsy, and dementia occur with involvement of the brainstem. Vascular involvement (25% to 30%), unique in that it is both arterial and venous, involves vessels of all sizes and may cause systemic arterial vasculitis (aneurysms and occlusions), pulmonary artery vasculitis, venous occlusions (including superficial, deep, cerebral, portal, and mesenteric veins),

FIG. E1 Mucocutaneous manifestations of Behçet disease. A, Oral aphthous ulcers. **B,** Genital ulcers in the scrotum and skin of the shaft of the penis. **C,** Ulcers in the groin *(arrow)* and scars of previous ulcers in the scrotum *(asterisks).* **D,** Skin pathergy response in the forearm as erythematous pustule *(asterisk)* or papule at the needle prick sites at 48 hours. **E,** Pathergic tongue ulcer *(arrow)* induced by dental trauma. **F,** Papulopustular lesions in the calf. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

TABLE E1 Frequencies of Clinical Manifestations of Behçet Disease

Manifestation	Frequency (%)
Mucocutaneous	
Oral aphthous ulcers	97-100*
Genital ulcers	70-90
Papulopustular lesions	70-90
Erythema nodosum–like lesions	40-60
Superficial thrombophlebitis	15-30
Skin pathergy reaction	30-80
Ocular	
Uveitis (bilateral, 80%; unilateral, 20%)	30-50
Musculoskeletal	
Arthritis	40-50
Vascular	
Deep vein thrombosis	10-15
Arterial aneurysms	5
Neurologic involvement	5-10
Parenchymal involvement	80-90
Cerebral sinus thrombosis	10-20
Intestinal involvement	2-30
Family history	3-20

*Frequency may be 80% at disease onset.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

pulmonary embolus, right ventricle thrombosis, and Budd-Chiari syndrome.
- GI involvement is more common in Japanese individuals; ulcerative lesions primarily involve distal ileum and cecum, but any region can be affected. GI lesions tend to perforate or bleed and may recur after surgery.
- Table E1 summarizes frequencies of clinical manifestations of Behçet disease.

ETIOLOGY

The etiology of Behçet disease is unknown. An immune-related vasculitis, a perivascular inflammation, or both are thought to lead to many of the manifestations of Behçet disease. Multiple triggers for this process have been investigated, including herpes simplex virus infection, streptococcal antigen, and others.

Dx DIAGNOSIS

According to the International Study Group for Behçet Disease, the diagnosis of Behçet disease is established when oral ulcerations recur at least three times in one 12-mo period plus at least two of the following conditions in the absence of other systemic diseases:
- Recurrent genital ulceration
- Eye lesions
- Skin lesions
- Positive pathergy test (erythematous papules or pustules [>2 mm in diameter] at sterile needle injection sites after 24 to 48 hours)

DIFFERENTIAL DIAGNOSIS

- Inflammatory bowel disease (ulcerative colitis and Crohn disease)
- Sprue disease
- Herpes simplex infection
- Benign aphthous stomatitis
- Cyclic neutropenia
- Acquired immune deficiency syndrome (AIDS)
- Systemic lupus erythematosus
- Reiter syndrome
- Ankylosing spondylitis
- Hypereosinophilic syndrome
- Sweet syndrome
- Lichen planus
- Pemphigoid

WORKUP

The diagnosis of Behçet disease is a clinical diagnosis. Laboratory tests and x-ray imaging may be helpful in working up the complications of Behçet disease or excluding other diseases in the differential. Commonly used criteria for classification of Behçet disease are summarized in Box E1.

LABORATORY TESTS

No diagnostic laboratory tests for Behçet disease exist. The measurements of T-cell proliferative response to heat shock protein (HSP) and impaired fibrinolytic activity have been proposed for the diagnosis of Behçet disease, but the value of testing has not been confirmed.

IMAGING STUDIES

CT scan, MRI, and angiography are useful for detecting CNS and vascular lesions.

Rx TREATMENT

Treatment is directed at the patient's clinical presentation and complications (e.g., mucocutaneous lesions, ocular lesions, arthritis, GI, CNS, or vascular lesions).

NONPHARMACOLOGIC THERAPY

Supportive care and rest during flares, and moderate exercises such as swimming or walking when symptoms improve or disappear

ACUTE GENERAL Rx

- Oral and genital ulcers:
  1. Topical and intralesional corticosteroids (e.g., triamcinolone acetonide ointment applied tid)
  2. Tetracycline tablets 250 mg dissolved in 5 cc water and applied to the ulcer for 2 to 3 min
  3. Colchicine 0.5 to 1.5 mg/day PO
  4. Thalidomide 100 to 300 mg PO daily
  5. Dapsone 100 mg PO daily
  6. Pentoxifylline 300 mg/day PO
  7. Azathioprine 1 to 2.5 mg/kg/day PO
  8. Methotrexate 7.5 to 25 mg/wk PO or intravenously
  9. Interferon alfa-2a and interferon alfa-2b (generally given 3 to 19 million units three times weekly)
  10. Recent trials have shown that apremilast, an oral phosphodiesterase-4 inhibitor that modulates several inflammatory pathways may be effective in treating oral ulcers (NJEM 372:1510-1518, 2015)
- Ocular lesions:
  1. Anterior uveitis is treated by an ophthalmologist with topical corticosteroids (e.g., betamethasone drops 1 to 2 drops tid); topical injection with dexamethasone 1 to 1.5 mg has also been tried
  2. Infliximab 5 mg/kg single dose
  3. Cyclosporine A (5 mg/kg/day) with or without prednisone or azathioprine 1 to 2.5 mg/kg/day PO
- CNS disease:
  1. Chlorambucil 0.1 mg/kg/day is used in the treatment of posterior uveitis, retinal vasculitis, or CNS disease; patients not responding to chlorambucil can be tried on cyclosporine 5 to 7 mg/kg/day
  2. In CNS vasculitis, cyclophosphamide 2 to 3 mg/kg/day is used. Prednisone can be used as an alternative
- Arthritis:
  1. NSAIDs (e.g., ibuprofen 400-800 mg tid PO or indomethacin 50-75 mg/day PO)
  2. Sulfasalazine 1 to 3 g/day PO is an alternative treatment
- GI lesions:
  1. Sulfasalazine 1 to 3 g/day PO
  2. Prednisone 40 to 60 mg/day PO
- Vascular lesions:
  1. Prednisone 40 to 60 mg/day PO
  2. Cytotoxic agents as mentioned previously
  3. Heparin 5000 to 20,000 U/day followed by oral warfarin

CHRONIC Rx

- Chronic therapy is usually continued for approximately 1 yr after remission.
- Surgery may be indicated in patients with complications of bowel perforation, vascular occlusive disease, and aneurysm formation.
- Mortality is associated with early age of onset, arterial involvement, male gender, and frequent disease flares.

DISPOSITION

- The aphthous oral ulcers last 1 to 2 wk, recurring more frequently than genital ulcers.
- 25% of Japanese patients with ocular lesions become blind.
- The disease course is unpredictable.
- The morbidity of Behçet disease comes primarily from ocular and cutaneous involvement; however, mortality relates primarily to large-size vessel involvement and CNS diseases.

REFERRAL

If the diagnosis of Behçet disease is suspected, a referral to dermatology, rheumatology, and ophthalmology is indicated because the disease is so rare.

PEARLS & CONSIDERATIONS

COMMENTS

- The pathergy test refers to the formation of an erythematous papule or pustule of ≥2 mm

BOX E1 Commonly Used Criteria for Classification of Behçet Disease

Japanese Criteria*

Major Symptoms	Minor Symptoms
Recurrent aphthous oral ulcers	Arthritis
Skin lesions	Intestinal ulcers
Ocular inflammation	Epididymitis
Genital ulcers	Vascular lesions
	Neuropsychiatric disease

Complete patients:
Patients with all four major symptoms during the clinical course

Incomplete patients:
Three major symptoms
Two major and two minor symptoms
Typical recurrent ocular inflammation and one or more major symptoms
Typical recurrent ocular inflammation and two minor symptoms

International study group criteria†:
For a clinical diagnosis of Behçet disease, the patient must have recurrent oral ulceration plus at least two of these additional findings in the absence of any other clinical explanation:

Recurrent oral ulceration:
Minor aphthous, major aphthous, or herpetiform ulcers observed by the physician or reliably described by the patient, which recurred at least three times over a 12-mo period

Recurrent genital ulceration:
Aphthous ulceration or scarring observed by the physician or reliably described by the patient

Eye lesions:
Anterior or posterior uveitis or cells in the vitreous body on slit-lamp examination or retinal vasculitis detected by an ophthalmologist

Skin lesions:
Erythema nodosum, pseudofolliculitis, papulopustular lesions, or acneiform nodules not related to glucocorticoid treatment or adolescence

Positive pathergy test:
Test interpreted as positive by the physician at 24-48 hours

International criteria for Behçet disease‡
Point score system: Scoring 4 indicates diagnosis of Behçet disease

Sign or Symptom	Points
Ocular lesion	2
Genital aphthosis	2
Oral aphthosis	2
Skin lesions	1
Neurologic manifestations	1
Vascular manifestations	1
Positive pathergy test result§	1

*Data from Kirino Y, Ideguchi H, Takeno M, et al: Continuous evolution of clinical phenotype in 578 Japanese patients with Behçet's disease: a retrospective observational study. *Arthritis Res Ther* 18:217, 2016.
†Modified from Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet* 335:1078–1080, 1990.
‡From International Team for the Revision of the International Criteria for Behçet's Disease. The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. *J Eur Acad Dermatol Venereol* 28:338–347, 2014.
§Pathergy test is optional. When pathergy testing is done, 1 additional point is given for a positive result.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

SUGGESTED READINGS

Hatemi G et al: Apremilast for Behçet syndrome, a phase 2 placebo-controlled study, *N Engl J Med* 372L:1510-1518, 2015.
Hatemi G et al: 2018 Update of the EULAR recommendations for the management of Behçet syndrome, *Ann Rheum Dis* 77:808-818, 2018.

after oblique insertion of a sterile 20- or 25-gauge needle into the skin after 24 to 48 hours.
- Because of the rarity of this disease, data from controlled, prospective, randomized clinical trials are lacking.

RELATED CONTENT

Behçet Syndrome (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

Bell Palsy ALG PTG

BASIC INFORMATION

DEFINITION

Acute peripheral facial nerve (cranial nerve VII) palsy

SYNONYMS

Idiopathic facial paralysis
Facial nerve palsy

ICD-10CM CODE
G51.0 Bell palsy

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 20 to 30 cases per 100,000
PEAK INCIDENCE: Patients less than 70 yr old and pregnant females, especially during the third trimester and first postpartum wk
PREDOMINANT SEX AND AGE: Sexes are equally affected. The median age is 40.
RISK FACTORS: Diabetes and pregnancy

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients present with acute or subacute (hours to days) onset of unilateral facial paralysis with maximal weakness at 3 wk. Clinical findings are dependent on the location of facial nerve injury and involvement of associated branches (Fig. 1). One third of patients demonstrate incomplete paralysis, and the remaining two thirds have complete paralysis. Recovery usually occurs within the first 6 mo.
- Patients may also present with variable involvement of taste over the anterior two thirds of the tongue and/or altered secretion of the lacrimal and salivary glands.

ETIOLOGY

Most cases of Bell palsy are thought to be secondary to either a viral inflammatory or immune injury. Herpes simplex virus is thought to be the most common viral pathogen followed by herpes zoster. Other infectious causes include Epstein-Barr virus, cytomegalovirus, adenovirus, rubella, and mumps.

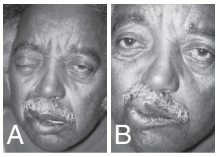

FIG. 1 A patient with a lesion of the facial nerve. A, The patient has difficulty in closing his left eye, and the left corner of his mouth droops. **B,** The latter defect is especially evident when the patient attempts to purse his lips. (From Haines DE: *Fundamental neuroscience for basic and clinical applications,* ed 3, Philadelphia, 2006, Churchill Livingstone.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cortical stroke: Forehead and periorbital muscles are spared in stroke patients because of bilateral innervation of the upper face
- Brain stem stroke: Ipsilateral weakness in the upper and lower muscles of facial expression due to a stroke affecting the nucleus or fascicle of the seventh nerve
- Lyme disease: Facial nerve palsy is the most common cranial neuropathy associated with Lyme disease. In Lyme meningitis, facial nerve palsy may be unilateral or bilateral
- HIV
- Ramsay Hunt syndrome: Facial nerve paralysis associated with ipsilateral zoster oticus
- Parotid gland tumors
- Trauma/temporal bone fracture
- Meningeal processes:
  1. Infectious: Lyme disease, HIV, syphilis, leprosy, tuberculosis meningitis, fungal meningitis
  2. Inflammatory: Sarcoidosis, Sjögren syndrome, and Guillain-Barré syndrome and its variants
  3. Leptomeningeal carcinomatosis or lymphomatosis: Breast cancer, lung cancer, and lymphoma are most common
- Möbius syndrome
- Melkersson-Rosenthal syndrome

WORKUP

- Bell palsy is a clinical diagnosis.
- Additional workup may be necessary in patients with an uncertain diagnosis, complete seventh nerve injury, evidence of neurologic dysfunction in addition to seventh nerve injury, and lack of recovery.

LABORATORY TESTS

Laboratory tests are not typically recommended. However, if the diagnosis of Bell palsy is in question (e.g., bilateral facial nerve palsy, concern for a secondary etiology), then it is reasonable to pursue the following tests:

- Lyme antibody followed by Western blot for positive cases for confirmation. Consider lumbar puncture for CSF analysis for Lyme serologies
- ACE level
- Glycosylated hemoglobin (HgA1C)
- HIV
- RPR and VDRL in CSF
- ESR

ELECTRODIAGNOSTIC TESTING

Electrodiagnostic testing may be performed 2 wk after the onset of symptoms to assess the integrity of a motor unit and the degree of nerve damage. Facial motor response remains normal for the first 3 days following an injury and then rapidly decreases depending on the severity of the lesion. A facial motor study may be performed at 10 days and compared to the contralateral side. A motor response that is 10% the amplitude of the unaffected side on electrodiagnostic testing corresponds with 90% motor axon degeneration. One study found that patient recovery was poor when this critical value was reached.

IMAGING STUDIES

Imaging studies are not usually indicated.

- Brain MRI is indicated in certain cases, such as an upper motor neuron pattern (able to wrinkle forehead) where the temporalis branch of the facial nerve is spared.
- Brain MRI with gadolinium is indicated either when other cranial nerve palsies are present or when a meningeal process is suspected.
- CT temporal bone is indicated in cases of either trauma or complete facial paralysis in which the surgeon is considering decompression.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Reassurance that most patients will have a full recovery and that the patient did not sustain a stroke.
- Eye patch to prevent corneal drying/abrasion and subsequent ulceration. Patients may protect their eyes with Lacri-Lube at night and artificial tears during the day.
- Acupuncture with needle manipulation and strong stimulation has been shown to improve recovery after Bell palsy when compared to acupuncture without needle manipulation.[1]

ACUTE GENERAL Rx

- Corticosteroids started within 72 hr will expedite speed and rate of recovery in most patients. Antiviral therapy alone has no benefit.
  1. Two high-quality randomized trials assessed efficacy of early (<72 hr) treatment with glucocorticoids alone, antiviral therapy alone, and combination therapy in the treatment of Bell palsy. Glucocorticoids alone were effective, while antiviral therapy showed no benefit when given either alone or with concomitant glucocorticoid therapy.
  2. The largest study compared groups receiving the following treatments: (a) 60 mg prednisolone daily, (b) 1000 mg valacyclovir three times daily for 1 wk, (c) combination therapy, and (d) placebo. All interventions were administered within 72 hr of presentation.
  3. Time to recovery, determined at a 1-yr follow-up appointment, was shortest in the group treated with prednisolone monotherapy. The efficacy of valacyclovir

[1]Xu SB et al: Effectiveness of strengthened stimulation during acupuncture for the treatment of Bell palsy: a randomized controlled trial, *CMAJ* 185:473-479, 2013.

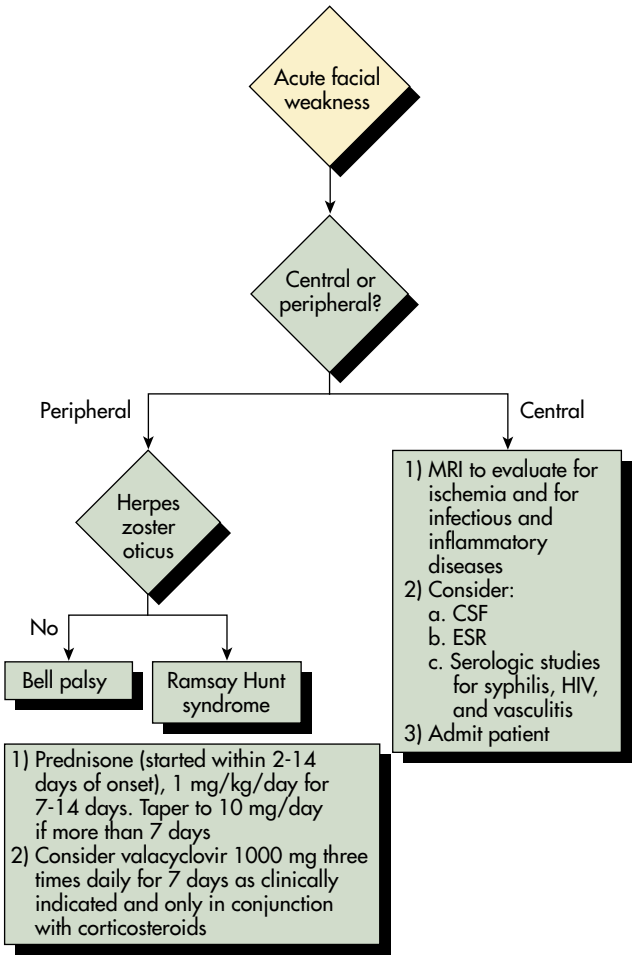

FIG. 2 Algorithm outlining the treatment of patients with Bell palsy. *CSF,* Cerebrospinal fluid; *ESR,* erythrocyte sedimentation rate; *HIV,* human immunodeficiency virus; *MRI,* magnetic resonance imaging. (Modified from Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, St Louis, 2013, Elsevier.)

monotherapy did not differ from placebo, and no added benefit was seen with combination therapy.

- Treatment guidelines recommend prednisone 60 to 80 mg daily for 1 wk.
  1. Despite the lack of strong clinical evidence, some authors still recommend treatment with valacyclovir (1000 mg 3 times daily for 1 wk) in severe cases (i.e., level IV or greater on the House-Brackmann grading system).
- Surgical decompression is not currently recommended.
  1. The 2001 American Academy of Neurology Practice Parameter concluded there was insufficient evidence to make any recommendation regarding surgical decompression for Bell palsy.
  2. This conclusion was further substantiated by a 2011 Cochrane systematic review, which looked at two additional studies, again citing insufficient evidence regarding surgical decompression for Bell palsy.
- Fig. 2 describes an algorithm for the treatment of patients with Bell palsy.

CHRONIC Rx

Botulinum toxin may be used in cases of hemifacial spasm that may follow recovery from Bell palsy.

DISPOSITION

- Between 70% and 90% of patients with Bell palsy have a complete recovery within a few weeks.
- 85% show recovery after 3 wk. Prognosis is favorable if recovery is seen during this timeframe.
- 13% have slight sequelae, and 16% have residual weakness, synkinesis, or contracture.

FIG. 3 Bell palsy. The patient with Bell palsy (facial nerve palsy) will demonstrate an unwrinkled forehead, widely opened eyes (with weakness of eyelid closure), flattening of the nasolabial fold, and a droop of the corner of the mouth. (From Remmel KS et al: *Handbook of symptom-oriented neurology,* ed 3, St Louis, 2002, Mosby.)

- Recurrence rate is 7%, and the average time to recurrence is 10 yr.

REFERRAL

- Neurologist if clinical diagnosis is in question
- Ophthalmologist if concern for corneal abrasion or ulceration

PEARLS & CONSIDERATIONS

COMMENTS

- Assess wrinkling of forehead (Fig. 3). If present on affected side, ensure that the facial weakness is not central.
- Assess for strength of eye closure. A patient with Bell palsy will have difficulty with ipsilateral eye closure, whereas a patient with a central lesion with have equal eye closure strength bilaterally.
- Assess for other cranial nerve deficits or long-tract signs because brain stem fascicular lesions of the seventh nerve can show peripheral facial pattern of weakness.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Bell Palsy (Facial Palsy) (Patient Information)

AUTHORS: **Alexandra Buffie, MD, Joseph S. Kass, MD, JD, FAAN,** and **John Sladky, MD**

SUGGESTED READINGS

Albers JR, Tamang S: Common questions about Bell palsy, *Am Fam Phys* 89(3):209-212, 2014.

Lee HY et al: Steroid antiviral treatment improves the recovery rate in patients with severe Bell's palsy, *Am J Med* 126:336-341, 2013.

Benign Paroxysmal Positional Vertigo ALG

BASIC INFORMATION

DEFINITION

Benign paroxysmal positional vertigo (BPPV) is a labyrinthine disorder and is the most common cause of vertigo. It is characterized by paroxysms of brief spinning sensation accompanied by nystagmus that usually last less than a minute. These paroxysms are generally induced by changes in head position with respect to gravity.

SYNONYM

BPPV

ICD-10CM CODE
H81.1 Benign paroxysmal vertigo

EPIDEMIOLOGY & DEMOGRAPHICS

Higher prevalence seen in elderly and women.
INCIDENCE: Incidence increases with advancing age. Unrecognized BPPV can be found in about 10% of certain geriatric populations, and there is a cumulative incidence of nearly 10% by age 80 yr.
PREVALENCE: Lifetime prevalence is 2.4%. Reported prevalence is 10.7 and 64 cases per 100,000 population. BPPV is by far the most common type of vertigo.
PREDOMINANT SEX AND AGE: Female (2:1 to 3:1 ratio); peak onset: 50 to 60 yr.
GENETICS: Unknown
RISK FACTORS: Head trauma, inner ear surgery, viral labyrinthitis, Ménière disease, migraine. The majority are idiopathic.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Brief paroxysms of vertigo and nystagmus with certain head positions are seen in 70%.
- Episodes are typically triggered by head position changes such as while getting in or out of bed, rolling over in bed, tilting the head forward, or bending forward.
- Episodes are brief, usually lasting 30 to 40 seconds but can recur for several days or months.
- Usually no hearing abnormalities are present.
- Direction of nystagmus depends on the canal affected with reversal of direction being seen while sitting up, and fatigability with repeated testing.
- Rarely persistent vertigo and disequilibrium may be seen.

POSTERIOR SEMICIRCULAR CANAL (PSC)

While posterior, horizontal or superior semicircular canal can be affected as isolated or in different combinations, PSC involvement is most common (60% to 90%) and will be discussed in the following sections. Nystagmus is up-beating and torsional and can be elicited by the Dix-Hallpike maneuver.
DIX-HALLPIKE MANEUVER: With head turned to one side at an angle of 45 degrees, patient is moved rapidly from sitting to supine position with head hanging below the end of the table at an angle of 15-20 degrees. The posterior semicircular canal comes into the sagittal plane and the free floating otolith debris moves down and away from the ampulla. An up-beating and torsional nystagmus will be seen with the top poles of the eye beating towards the lower ear.

HORIZONTAL SEMICIRCULAR CANAL

Involvement may be underestimated as it may remit spontaneously. It produces either geotropic nystagmus beating towards the ground or apogeotropic nystagmus beating towards the ceiling when the head is turned to either side in the supine position. The nystagmus beats stronger towards the affected ear.
HEAD ROLL TEST FOR THE RIGHT HORIZONTAL SEMICIRCULAR CANAL (INDUCING GEOTROPIC NYSTAGMUS): Patient is moved from sitting to supine position, then head is rolled 90 degrees to the left. The otolithic debris moves away from the cupula of horizontal semicircular canal, a left beating geotropic nystagmus (towards the ground) is seen. Next the head is turned 90 degrees to the right—a right-beating stronger geotropic nystagmus is seen as otolithic debris moves towards the cupula of the right horizontal semicircular canal.
SUPINE HEAD ROLL TEST FOR THE RIGHT HORIZONTAL SEMICIRCULAR CANAL (INDUCING APOGEOTROPIC NYSTAGMUS): Patient is moved from sitting to supine position, then head is rolled 90 degrees to the left. This induces deflection of the cupula of the right horizontal semicircular canal due to otolithic debris near or attached to the cupula. A strong, right-beating apogeotropic nystagmus (towards the ceiling) is induced. Next, the head is turned 90 degrees in the opposite direction. Now the right horizontal semicircular canal cupula is deflected in the opposite direction and a weak, left-beating apogeotropic nystagmus results.

ANTERIOR SEMICIRCULAR CANAL

Involvement is rare as it is located uppermost in the labyrinth and so otolithic debris is unlikely to become trapped. A downbeat and torsional nystagmus where the top poles of the eye beat towards the lower ear is seen. Evaluating for central lesions is a must in these cases.

ETIOLOGY

The fundamental pathologic process is believed to be the movement of otolithic debris in the endolymph of the inner ear. The debris may be present in the cupula (cupulolithiasis) or free floating within the semicircular canal near the cupula (canalithiasis). Static head position changes with respect to gravity, causing the debris to move within the semicircular canal and creating a false sense of rotation.

DIAGNOSIS

Elicitation of a typical nystagmus with Dix-Hallpike is the standard for diagnosing posterior canal BPPV. However, 25% of symptomatic patients may not exhibit nystagmus. Appropriate referral to a neurologist or neuro-otologist should be considered in these cases.

Fig. E1 shows a diagnostic algorithm for vertigo and dizziness.

DIFFERENTIAL DIAGNOSIS

- Vestibular neuritis
- Vestibular migraine
- Ménière disease
- Stroke
- Box 1 lists causes of vertigo with and without hearing loss
- Table 1 describes the differential diagnosis of true vertigo

WORKUP

None; BPPV is a clinical diagnosis.

IMAGING STUDIES

To be obtained only when stroke remains high in the differential diagnosis

TREATMENT

- BPPV usually resolves without treatment in 2 to 4 wk. Recurrences are common in the first yr, and long-term recurrence rates range from 30% to 50%.
- Nausea and vomiting may be treated symptomatically with medications.
- Canalith repositioning maneuvers (Epley and Semont maneuvers for the posterior canal) are effective. They are designed to "flush" otolithic debris out of the semicircular canals into the vestibule where they are resorbed. Epley maneuver for BPPV of the posterior canal is recommended as standard of care by the American Academy of Neurology and American Academy of Otolaryngology-Head and Neck Surgery. When patients do not respond, it may be related to the technique,

BOX 1 Causes of Vertigo with and without Hearing Loss

Hearing Loss
Conductive
- Otitis media with effusion
- Chronic suppurative otitis media or cholesteatoma should be considered

Sensorineural
- Perilymphatic fistula
- Tumor
- Ménière disease
- Migraine headache
- Genetic syndromes
- Temporal bone fracture
- Vestibular concussion

No Hearing Loss
Acute Vertigo
- Perilymphatic fistula
- Benign positional vertigo
- Seizure
- Labyrinthitis

Recurrent or Chronic Vertigo
- Acoustic neuroma
- Multiple sclerosis

From Marx JA et al: *Rosen's emergency medicine: concepts and clinical practice*, ed 7, Philadelphia, 2010, Elsevier.

TABLE 1 Differential Diagnosis of Patients with True Vertigo

Cause	History	Associated Symptoms	Physical
Peripheral			
1. Benign paroxysmal positional vertigo	Short-lived, positional, fatigable episodes	Nausea, vomiting	Single position can precipitate vertigo. Horizontorotary nystagmus often can be induced at bedside
2. Labyrinthitis			
• Serous	Mild to severe positional symptoms. Usually coexisting or antecedent infection of ear, nose, throat, or meninges	Mild to severe hearing loss can occur	Usually nontoxic patient with minimal fever elevation
• Acute suppurative	Coexisting acute exudative infection of the inner ear. Severe symptoms	Usually severe hearing loss, nausea, vomiting	Febrile patient showing signs of toxicity. Acute otitis media
• Toxic	Gradually progressive symptoms: Patients on medication causing toxicity	Hearing loss that may become rapid and severe, nausea and vomiting	Hearing loss. Ataxia common feature in chronic phase
3. Ménière disease	Recurrent episodes of severe rotational vertigo usually lasting hours. Onset usually abrupt. Attacks may occur in clusters. Long symptom-free remissions	Nausea, vomiting, tinnitus, hearing loss	Positional nystagmus not present
4. Vestibular neuronitis	Sudden onset of severe vertigo, increasing in intensity for hours, then gradually subsiding over several days. Mild positional vertigo often lasts weeks to months. Sometimes history of infection or toxic exposure that precedes initial attack. Highest incidence is found in third and fifth decades	Nausea, vomiting. Auditory symptoms do not occur	Spontaneous nystagmus toward the involved ear may be present
5. Acoustic neuroma	Gradual onset and increase in symptoms. Neurologic signs in later stages. Most occur in women between 30 and 60	Hearing loss, tinnitus. True ataxia and neurologic signs as tumor enlarges	Unilateral decreased hearing. True truncal ataxia and other neurologic signs when tumor enlarges. May have diminution or absence of corneal reflex. Eighth cranial nerve deficit may be present
Central			
1. Vascular disorders			
• Vertebrobasilar insufficiency	Should be considered in any patient of advanced age with isolated new-onset vertigo without an obvious cause. More likely with history of atherosclerosis. Initial episode usually seconds to minutes	Often headache. Usually neurologic symptoms including dysarthria, ataxia, weakness, numbness, double vision. Tinnitus and deafness uncommon	Neurologic deficits usually present, but initially neurologic examination can be normal
• Cerebellar hemorrhage	Sudden onset of severe symptoms	Headache, vomiting, ataxia	Signs of toxicity. Dysmetria, true ataxia. Ipsilateral sixth cranial nerve palsy may be present
• Occlusion of posterior inferior cerebellar artery (Wallenberg syndrome)	Vertigo associated with significant neurologic complaints	Nausea, vomiting, loss of pain and temperature sensation, ataxia, hoarseness	Loss of pain and temperature sensation on the side of the face ipsilateral to the lesion and on the opposite side of the body, paralysis of the palate, pharynx, and larynx. Horner syndrome (ipsilateral ptosis, miosis, and decreased facial sweating)
• Subclavian steal syndrome	Classic picture is syncopal attacks during exercise, but most cases present with more subtle symptoms	Arm fatigue, cramps, mild lightheadedness may be only other symptoms than vertigo	Diminished or absent radial pulses in affected side or systolic blood pressure differentials between the two areas occur in most patients
2. Head trauma	Symptoms begin with or shortly after head trauma. Positional symptoms most common type after trauma. Self-limited symptoms that can persist weeks to months	Usually mild nausea	Occasionally, basilar skull fracture
3. Neck trauma	Usual onset 7-10 days after whiplash injury. Symptoms may last weeks to months. Episodes seconds to minutes when turning head	Neck pain	Neck tenderness, pain on movement, and positional nystagmus and vertigo when head is turned to side of the whiplash
4. Vertebrobasilar migraine	Vertigo almost always followed by headache. Patient has usually had similar episodes in past. Most patients have a family history of migraine. Syndrome usually begins in adolescence	Dysarthria, ataxia, visual disturbances, or paresthesias usually precede headache	No residual neurologic or otologic signs are present after attack

TABLE 1 Differential Diagnosis of Patients with True Vertigo—cont'd

Cause	History	Associated Symptoms	Physical
5. Multiple sclerosis	Vertigo presenting symptoms in 7%-10% and appears in the course of the disease in a third. Onset may be severe and suggest labyrinth disease. Disease onset usually between ages 20 and 40. Often history of other attacks with varying neurologic signs or symptoms	Nausea and vomiting, which may be severe	May have horizontal, rotary, or vertical nystagmus. Nystagmus may persist after the vertiginous symptoms have subsided. Bilateral internuclear ophthalmoplegia and ataxic eye movements suggest multiple sclerosis
6. Temporal lobe epilepsy	Can be initial or prominent symptom in some patients with the disorder	Memory impairment, hallucinations, trancelike states, seizures	May have aphasia or convulsions
7. Hypoglycemia	Should be considered in diabetics and any other patient with unexplained symptoms	Sweating, anxiety	Tachycardia, mental status change may be present

From Marx JA et al: *Rosen's emergency medicine: concepts and clinical practice,* ed 7, Philadelphia, 2010, Elsevier.

or they may be refractory. There is no clear consensus on how many times the maneuver should be performed at a single visit. Many prefer to do it two or three times if nystagmus is still present with the second maneuver. Other maneuvers such as Barbecue, Vannucchi, and Gufoni are used to reposition debris in the horizontal semicircular canal and will not be discussed here.

EPLEY MANEUVER:

- Head is turned 90 degrees towards unaffected side. The head and trunk are then turned an additional 90 degrees in the same direction, so that the patient lies on the unaffected side with head pointing towards the floor. The otolithic debris moves in the same direction, producing a brief nystagmus. The patient is then moved to a sitting position, which allows the debris to fall out of the canal into the utricle through the common crus.
- Each position should be maintained for 30 seconds or until the nystagmus or vertigo resolves. Sometimes nystagmus in the opposite direction is seen. It is prudent for patients to sit still in the upright position for about 15 minutes and then to walk cautiously.

NONPHARMACOLOGIC THERAPY

Transection of the ampullary nerve (singular nerve) and plugging of the involved canal are rarely performed for intractable and treatment-resistant cases.

ACUTE GENERAL Rx

Canalith repositioning

CHRONIC Rx

If multiple treatments are needed, patients should be instructed to perform the maneuvers at home.

REFERRAL

To a neuro-otologist, otolaryngologist, neurologist

PEARLS & CONSIDERATIONS

- BPPV is a benign and self-limiting condition but can be disabling.
- Diagnosis is clinical and canalith repositioning maneuvers are effective.

PATIENT & FAMILY EDUCATION

- Reassurance
- Fall precautions

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Ménière Disease (Related Key Topic)
Vestibular Neuronitis (Related Key Topic)

AUTHORS: **Padmaja Sudhakar, MBBS,** and **Sachin Kedar, MBBS, MD**

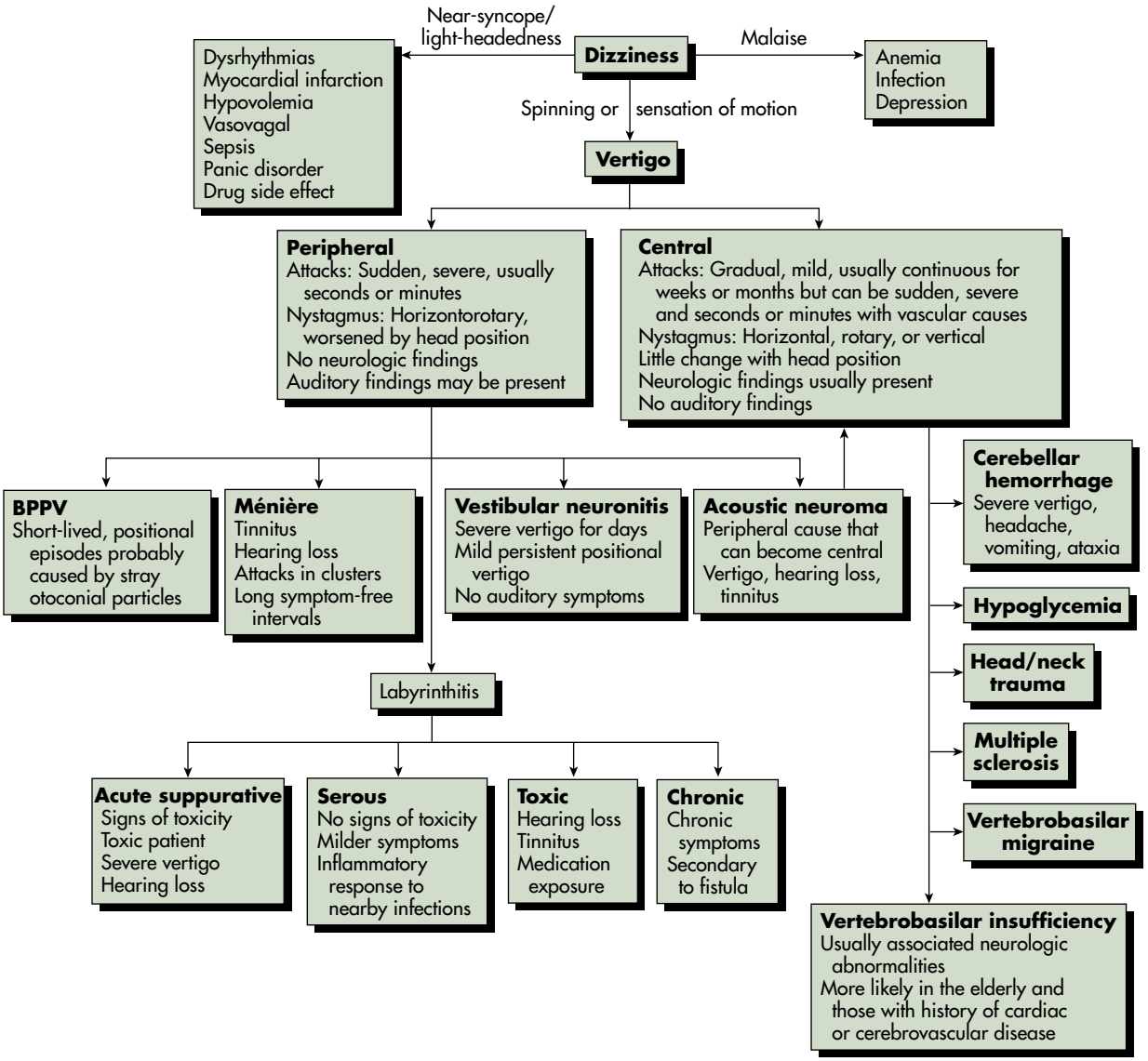

FIG. E1 Diagnostic algorithm for dizziness and vertigo. *BPPV*, Benign paroxysmal positional vertigo. (From Marx JA et al: *Rosen's emergency medicine: concepts and clinical practice*, ed 7, Philadelphia, 2010, Elsevier.)

SUGGESTED READING

Kim JS, Zee DS: Clinical practice. Benign paroxysmal positional vertigo, *N Engl J Med* 370(12):1138-1147, 2014.

BASIC INFORMATION

DEFINITION

Benign prostatic hyperplasia (BPH) is the benign growth of the prostate, generally originating in the periureteral and transition zones, with subsequent obstructive and irritative voiding symptoms. Histologically, BPH refers to the proliferation of smooth muscle, epithelium, and stromal cells within the transition zone of the prostate that surrounds the proximal urethra.

SYNONYMS

Benign prostatic hypertrophy
BPH
Prostatic hypertrophy

ICD-10CM CODES

N40.0	Enlarged prostate without lower urinary tract symptoms
N40.1	Enlarged prostate with lower urinary tract symptoms
N40.2	Nodular prostate without lower urinary tract symptoms
N40.3	Nodular prostate with lower urinary tract symptoms

EPIDEMIOLOGY & DEMOGRAPHICS

- 80% of men have evidence of BPH by age 80 yr.
- Medical and surgical intervention for problems caused by BPH is required in <20% of males by age 75 yr.
- Transurethral resection of the prostate (TURP) is the tenth most common operative procedure (<400,000/yr in U.S.).
- 10% to 30% of men with BPH have occult prostate cancer.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Digital rectal examination (DRE) reveals enlargement of the prostate.
- Focal enlargement may be indicative of malignancy.
- There is poor correlation between size of prostate and symptoms (BPH may be asymptomatic if it does not encroach on the urethral lumen).
- Most patients with BPH report difficulty in initiating urination (hesitancy), decrease in caliber and force of stream, incomplete emptying of bladder often resulting in double voiding (need to urinate again a few minutes after voiding), postvoid "dribbling," and nocturia.

ETIOLOGY

Multifactorial (Fig. E1); a functioning testicle is necessary for development of BPH (as evidenced by the absence in males who were castrated before puberty).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Prostatitis
- Prostate cancer
- Strictures (urethral)
- Medications interfering with the muscle fibers in the prostate and also with bladder function:
  1. Opiates: Impaired autonomic function
  2. Decongestants: Increased sphincter tone
  3. Antihistamines: Decreased parasympathetic tone
  4. Tricyclic antidepressants: Anticholinergic effects
- Neurogenic bladder
- Bladder cancer

WORKUP

Symptom assessment (use of American Urological Association [AUA] Symptom Index for BPH [Table 1]), laboratory tests, and imaging studies. Fig. E2 describes a diagnostic approach to patients with BPH.

LABORATORY TESTS

- Prostate-specific antigen (PSA): Protease secreted by epithelial cells of the prostate; elevated in 30% to 50% of patients with BPH. Testing for PSA increases detection rate for prostate cancer and tends to detect cancer at an earlier stage. However, the PSA test does not discriminate well between patients with symptomatic BPH and those with prostate cancer, particularly if the cancer is pathologically localized and curable. The test may also trigger additional evaluation, including ultrasound biopsy of the prostate. Asymptomatic men with PSA levels >2 ng/ml do not need annual testing. According to the AUA, PSA testing and DRE should be offered to any asymptomatic man <50 yr with a life expectancy of 10 yr. PSA testing can also be offered at an earlier age in men at higher risk of prostatic cancer (e.g., first-degree relatives with prostate cancer; African American race).
- Measurement of "free" PSA is useful to assess the probability of prostate cancer in patients with normal DRE and total PSA between 4 and 10 ng/ml. In these patients

TABLE 1 International Prostate Symptom Score (I-PSS)

	Score						
Symptom	**Not at All**	**Less Than 1 Time in 5**	**Less Than Half the Time**	**About Half the Time**	**More Than Half the Time**	**Almost Always**	**Total Score**
Incomplete emptying: Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
Frequency: Over the past month, how often have you had to urinate again <2 hr after you finished urinating?	0	1	2	3	4	5	
Intermittency: Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
Urgency: Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
Weak stream: Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
Straining: Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 Time	2 Times	3 Times	4 Times	5 or More Times	
Nocturia: Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	
Total I-PSS score =							

the global risk of prostate cancer is 25%. However, if the free PSA is >25%, the risk of prostate cancer decreases to 8%, whereas if the free PSA is <10%, the risk of cancer increases to 56%. Free PSA is also useful to evaluate the aggressiveness of prostate cancer. A low free PSA percentage generally indicates a high-grade cancer, whereas a high free PSA percentage is generally associated with a slower-growing tumor.
- Elevated measurement of prostate cancer gene 3 (*PCA3*) in urine specimens collected after digital exam is helpful in deciding about prostate biopsy in men with elevated PSA (increased *PCA3* = increased likelihood of prostate cancer).
- Urinalysis, urine culture, and sensitivity to rule out infection (if suspected).
- Blood urea nitrogen and creatinine to rule out postrenal insufficiency.

IMAGING STUDIES

- Transrectal ultrasound may be indicated in patients with palpable nodules or significant elevation of PSA. It is also useful to estimate prostate size. BPH may also be evident in suprapubic ultrasound and MRI (Fig. E3).
- Uroflowmetry may be used to determine relative impact of obstruction on urine flow. Urethral pressure profile is useful to predict prostatic hypertrophy within the urethral lumen.
- Pressure flow studies, although invasive, are particularly helpful in patients whose history and/or examination suggest primary bladder dysfunction as a cause of symptoms of prostatism. They are also useful in patients for whom a distinction between prostatic obstruction and impaired detrusor contractility may affect the choice of therapy. However, pressure flow studies may not be useful in the workup of the usual patient with symptoms of prostatism.
- Postvoid residual urine measurement has not been proved useful in predicting the need for or response to treatment; it may be useful in monitoring the course of the disease in patients who elect nonsurgical treatment.
- Urethral cystoscopy is an option during later evaluation if invasive treatment is being planned.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of caffeine or any other foods that may exacerbate symptoms
- Avoidance of medications that may exacerbate symptoms (e.g., most cold and allergy remedies)

GENERAL Rx

- Asymptomatic patients with prostate enlargement caused by BPH generally do not require treatment. Patients with mild to moderate symptoms are candidates for pharmacologic treatment (see the following). For patients who have specific complications from BPH, prostate surgery is usually the most appropriate form of treatment. However, surgery may result in significant complications (e.g., incontinence, infection).
- Alpha-blockers (e.g., tamsulosin, alfuzosin, doxazosin, prazosin, terazosin) relax smooth muscle of the bladder neck and prostate and can increase peak urinary flow rate. They have no effect on the size of the prostate. Alpha-1 blockers are useful in symptomatic patients to relieve symptoms of obstruction by causing relaxation of smooth muscle tone in the prostatic capsule, urethra, and bladder neck.
- Hormonal manipulation with finasteride, a 5-alpha-reductase inhibitor that blocks conversion of testosterone to dihydrotestosterone, can reduce the size of the prostate. Usual dose is 5 mg qd. Treatment requires ≥6 mo for maximal effect.
- Dutasteride is also a 5-alpha-reductase inhibitor useful to decrease prostate size and improve urinary flow. In addition to inhibiting the isoform of 5-alpha-reductase located in the prostate, the medication inhibits a second isoform and reduces dihydrotestosterone formation in the skin and liver. Usual dose is 0.5 mg qd.
- Tadalafil 2.5 to 5 mg qd has been FDA-approved to treat patients with signs and symptoms of BPH and patients with both ED and signs and symptoms of BPH. Tadalafil can potentiate the hypotensive effect of alpha-blockers and should not be used in combination with alpha-blockers.
- The dietary supplement saw palmetto is commonly used for relief of symptoms of BPH. Recent trials using 160 mg of saw palmetto bid did not improve symptoms of BPH. This contrasts with the positive findings of many previous studies. Trials with higher dose-ranging protocols are currently in progress.
- TURP is the most commonly used surgical procedure for BPH. It is recommended for patients unresponsive to medical therapy who have renal insufficiency, recurrent UTIs, bladder stones, or gross hematuria. Transurethral incision of the prostate (TUIP), a procedure almost equivalent in efficacy, is limited to patients whose estimated resection tissue weight would be 30 g or less. TUIP can be performed in an ambulatory setting or during a 1-day hospitalization. Open prostatectomy is typically performed on patients with very large prostates. A prostatic urethral lift implant (UroLift) is now available for BPH. It is placed transurethrally at the site of obstruction to open the urethra by compressing the obstructing prostatic lobes and holding them permanently retracted with suture-based implants.
- Laser therapy for BPH is a less invasive alternative to TURP; YAG laser enucleation has minimal effect on potency, libido, or patient satisfaction with his sex life and is associated with retrograde ejaculation. However, recent studies indicate that at least in the initial 7 mo after surgery, TURP is moderately more effective than laser therapy in relieving symptoms of BPH.
- Transurethral needle ablation with radiofrequency to remove periurethral prostate tissue is being increasingly used in patients with prostate volume >60 ml and moderate symptoms. It has a low morbidity rate, but treatment failure is approximately 25% at 5 yr and <80% at 10 yr.
- Balloon dilation of the prostatic urethra is less effective than surgery for relieving symptoms but is associated with fewer complications. It is a reasonable treatment option for patients with smaller prostates and no middle lobe enlargement.
- Surgery need not be the treatment of last resort for most patients; that is, patients need not undergo other treatments for BPH before they can have surgery. However, recommending surgery on the grounds that a patient's surgical risk will "only increase with age" is generally inappropriate.

DISPOSITION

With appropriate therapy, symptoms improve or stabilize in <70% of patients with BPH.

REFERRAL

Urology referral for patients with severe or intolerable symptoms and for any patient suspected of having prostate cancer (10% to 30% of men with BPH)

PEARLS & CONSIDERATIONS

COMMENTS

- Emerging technologies for treating BPH, including prostatic artery embolization, transurethral holmium laser enucleation, transurethral electrovaporization, and transurethral microwave thermotherapy of the prostate, appear promising; however, long-term effectiveness has not yet been demonstrated.
- The increase in the use of pharmacologic management has resulted in <30% reduction in the total number of TURP procedures.
- Combined drug therapy for BPH with an alpha-blocker and a 5-alpha-reductase inhibitor is superior to monotherapy with either agent. After 1 yr of combination therapy, withdrawal of the alpha-blocker will usually not exacerbate symptoms.
- Treatment with 5-alpha-reductase inhibitors (finasteride, dutasteride) is associated with approximately 30% higher risk for developing type 2 diabetes.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Enlarged Prostate (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Abt D et al: Comparison of prostatic artery embolisation (PAE) versus transurethral resection of the prostate (TURP) for benign prostatic hyperplasia: randomised, open label, non-inferiority trial, *BMJ*, 2018.

Barry MJ et al: Effect of increasing saw palmetto extract on lower urinary tract symptoms: a randomized trial, *J Am Med Assoc* 306(12):1344-1351, 2012.

Crawford ED et al: Diagnostic performance of PCA3 to detect prostate cancer in men with increased prostate specific antigen: a prospective study of 1,962 cases, *J Urol* 188:1726-1731, 2012.

Fullhase J et al: Systematic review of combination drug therapy for non-neurogenic male lower urinary tract symptoms, *Eur Urol* 64:228-243, 2013.

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Sarma AV, Wei JT: Benign prostatic hyperplasia and lower urinary tract symptoms, *N Engl J Med* 367:248-257, 2012.

Wei L et al: Incidence of type 2 diabetes mellitus in men receiving steroid 5-alpha reductase inhibitors: population based cohort study, *BMJ* 365:L1204, 2019.

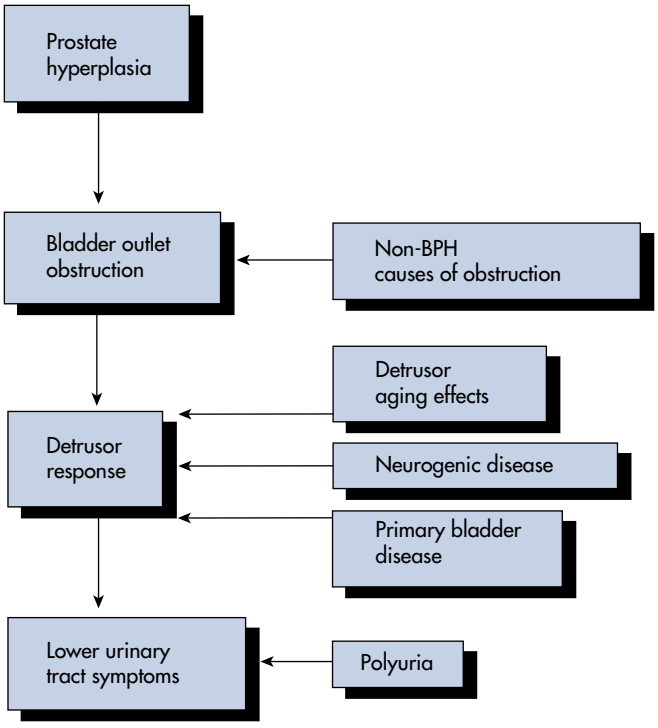

FIG. E1 The pathophysiology of benign prostatic hyperplasia *(BPH)* involves complex interactions between urethral obstruction, detrusor function and dysfunction, and urine production. (From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.)

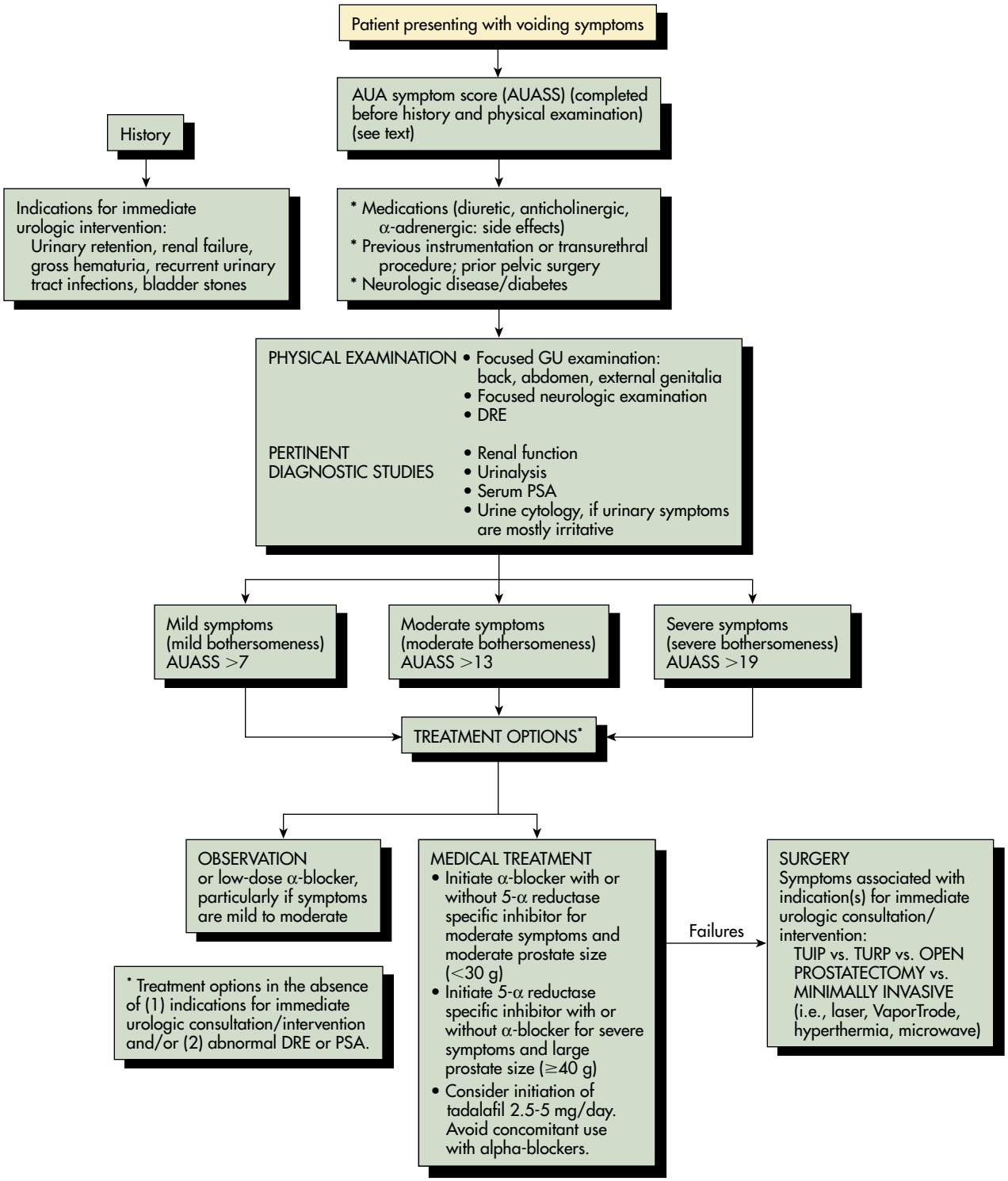

FIG. E2 Critical pathway for patients with benign prostatic hypertrophy. *AUA,* American Urological Association; *DRE,* digital rectal examination; *GU,* genitourinary; *PSA,* prostate-specific antigen; *TUIP,* transurethral incision of the prostate; *TURP,* transurethral resection of the prostate. (Modified and updated from Nseyo UP [ed]: *Urology for primary care physicians,* Philadelphia, 1999, Saunders.)

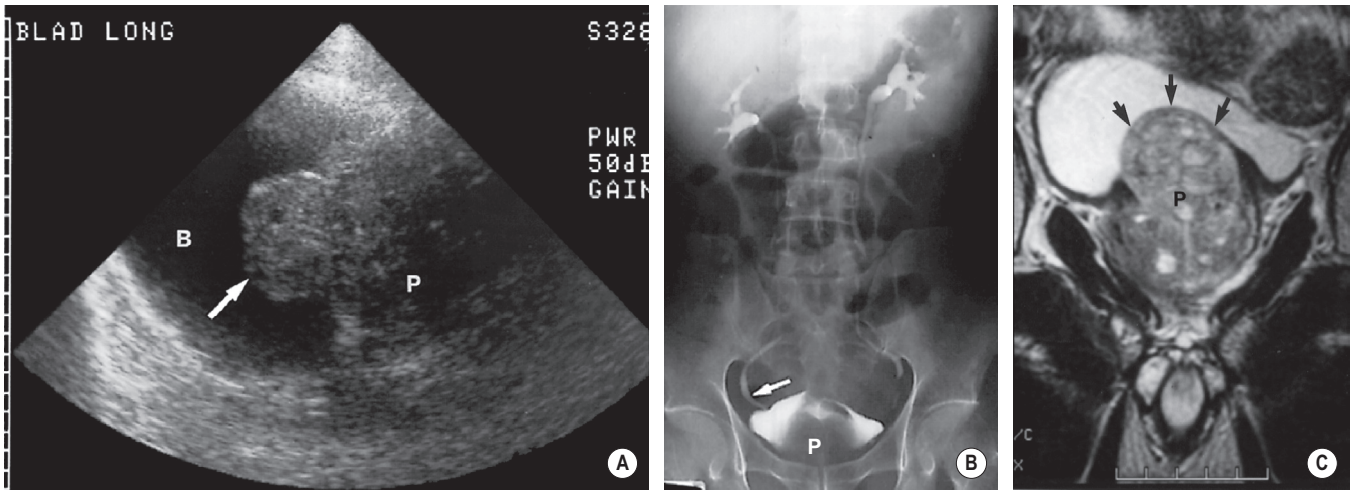

FIG. E3 Benign nodular hyperplasia demonstrated on **(A)** a suprapubic US scan: markedly enlarged prostate gland *(P)* with enlargement of the intravesical portion *(arrow),* which protrudes into the urinary bladder *(B).* Benign nodular hyperplasia on **(B)** IVU and **(C)** coronal plane T2WI. On the intravenous urogram study the enlarged prostate gland *(P)* elevates the bladder floor and causes a J-hooking (fish-hooking) deformity of the distal ureters *(arrow).* No obstruction is seen. The magnetic resonance image provides direct visualization of the prostate *(P)* and its impression on the bladder floor *(arrows).* (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

Biceps Tendonitis

BASIC INFORMATION

DEFINITION

Biceps tendonitis, a frequent cause of shoulder pain, refers to the irritation of the long head of the biceps brachii. The tendon originates at the glenoid, attaching to the glenoid labrum, passing intraarticularly, and entering the biceps groove between the greater and lesser tuberosities of the proximal humerus (Fig. E1). Irritation of the tendon can occur anywhere along the tendon. Degeneration of the tendon may be due to repetitive stress, such as in overhead-throwing athletes, or may result from cumulative effects of traction, friction, shear, and compression of the tendon over time.

SYNONYMS

Bicipital tendonitis
Bicipital tenosynovitis
Biceps tendinosis

ICD-10CM CODES	
M75.20	Bicipital tendinitis of unspecified shoulder
M75.21	Bicipital tendinitis of right shoulder
M75.22	Bicipital tendinitis of left shoulder

EPIDEMIOLOGY & DEMOGRAPHICS

- Prevalence of degenerative biceps tendinopathy in older adults is approximately 0.5 per 100,000 in a 5-yr period.
- Degenerative tendinopathy is more common in male patients than in female patients, at a ratio of 3:1.
- 41% of complete rotator cuff tears have concomitant biceps tendonitis.

RISK FACTORS: Athletes involved in throwing sports, swimming, contact sports, weight lifting, gymnastics, and martial arts are at higher risk, as well as nonathletes performing repetitive overhead movements such as carpenters, electricians, and mechanical wheelchair users.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Biceps tendinopathy is associated with additional shoulder pathology more often than it presents as an isolated pathology, and therefore the diagnosis can be challenging.

- Patients typically complain of progressively worsening pain over the anterior shoulder.
- Pain may radiate from the anterior shoulder down the anterior arm.
- In some patients, the tendon may subluxate or dislocate from the bicipital groove, which is often felt as an uncomfortable "click" in the anterior shoulder.
- Point tenderness over the bicipital groove is commonly present, especially with 10 degrees of internal rotation of the shoulder.
- A positive Yergason test (pain with resisted supination with the elbow at 90 degrees) is suggestive.
- A positive Speed test (pain in the bicipital groove on resisted forward flexion of the arm with the palm up and the elbow straight with resolution with the palm down) is suggestive.
- Uppercut and bear-hug tests may also increase the sensitivity of diagnosis.
- A "Popeye" sign (distal migration and bunching of the biceps muscle) suggests rupture of the tendon (Fig. E2).

ETIOLOGY

- A combination of traction, friction, shear, and compression of the tendon may lead to inflammation of the synovial lining covering the tendon.
- In overhead athletes, biceps tendinopathy is more frequently isolated.
- In the older adult population, tendinopathy is frequently associated with impingement and rotator cuff pathology.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rotator cuff tear: Frequently associated, both pathologies may exist
- Calcific tendonitis of the rotator cuff: Acute, intractable pain is more frequently over the lateral shoulder, and calcified inclusions of the cuff tendons may be visible on x-ray
- Glenohumeral osteoarthritis: May be diagnosed by degenerative changes on x-ray
- Septic arthritis: Often acute and associated with effusion, pain with small movements, and elevated inflammatory markers
- Cervical radiculopathy: Typically presents with weakness and/or sensory changes; radicular pain may radiate to the shoulder
- Superior lesion from anterior to posterior or labral tears
- Subacromial bursitis/impingement syndrome
- Acromioclavicular joint arthritis

WORKUP

Diagnosis of biceps tendinopathy may be suspected from history and physical examination

IMAGING STUDIES

- X-rays are important in identifying other causes of pain such as fractures and arthritis. Generally, they should be ordered initially when working up shoulder pain.
- MRI is frequently used to assist in the diagnosis and may demonstrate thickening and increased signal within the tendon. MRI should be obtained with acute trauma to rule out pathologies (e.g., acute rotator cuff tears) that should be addressed immediately for improved outcomes (Fig. E3).

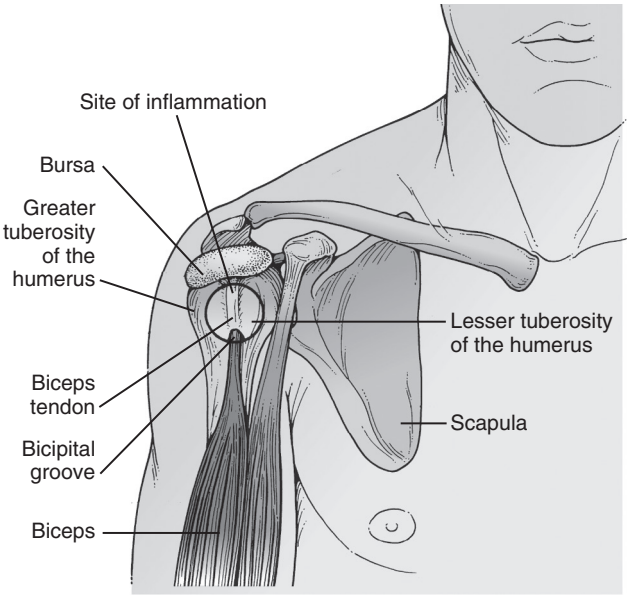

FIG. E1 Anatomic location of the long head of the biceps tendon with surrounding structures of the shoulder. (From Roberts JR et al: *Clinical procedures in emergency medicine,* ed 5, Philadelphia, 2009, WB Saunders.)

FIG. E2 Clinical photograph showing the "Popeye" deformity. (From Hochberg MD: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

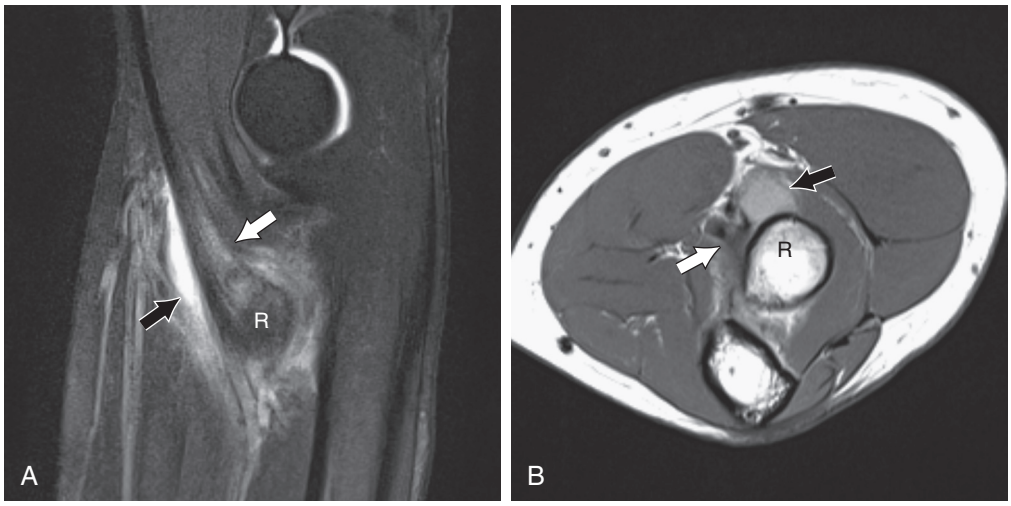

FIG. E3 Distal biceps partial tear. A, Sagittal fat suppressed T2-weighted and **B,** axial proton-density magnetic resonance images demonstrate marked thickening of the discontinuity of the distal biceps tendon short-head fibers associated with increased intrasubstance signal consistent with severe tendinosis *(white arrows).* A distended bicipitoradial bursa is noted *(black arrows). R,* Radial tuberosity. (From Pope TL et al: *Musculoskeletal imaging*, ed 2, Philadelphia, 2014, WB Saunders.)

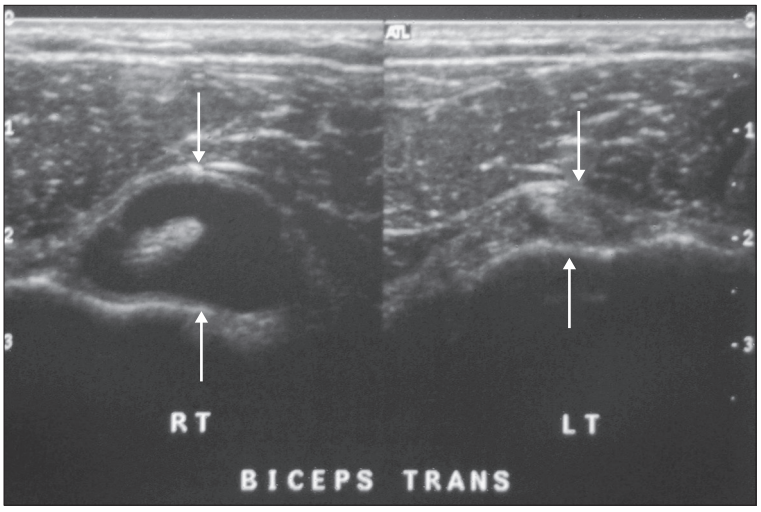

FIG. E4 Ultrasound image of bicipital tendinitis. A transverse image shows a large effusion *(arrows)* in the long head of the biceps tendon sheath. (From Hochberg MD: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

- Ultrasound may reveal the presence of an effusion or absence of the biceps tendon in the intertubercular groove (Fig. E4).
- Subluxation of the tendon may also be seen on MRI or ultrasound.
- Suspicion of tendinopathy can be confirmed with arthroscopy.

Rx TREATMENT

It is often necessary to establish whether the tendonitis is primary or secondary to determine the optimal treatment modalities. Initial conservative treatment is usually very successful.

NONSURGICAL THERAPY

Nonsurgical treatment is typically appropriate in cases not involving acute trauma or other concomitant pathologies requiring immediate intervention. Rest and activity modification, NSAIDs, and physical therapy benefit many patients.

Patients who experience insufficient improvement after a 6- to 8-wk period of conservative treatment may be considered for corticosteroid injection into either the glenohumeral joint or the tendon sheath itself. The tendon should never be directly injected, and ultrasound is recommended as an adjunct to improve accuracy of injections.

SURGICAL TREATMENTS

Surgical management of the biceps tendon may include tenodesis (cutting the tendon and reattaching it at a more distal location along its course) or tenotomy (cutting the tendon without reattaching it distally).

ACUTE GENERAL Rx

Nonsteroidal antiinflammatory drugs (NSAIDs) are good adjuncts to treatment that expedite the recovery process by decreasing edema, inflammation, and pain.

REFERRAL

Consider referral to a physical therapist early in treatment. Patients who do not improve with conservative management over 2 to 3 mo or with acute concomitant pathologies (e.g., acute rotator cuff tear) should be considered for consult to an orthopedic surgeon.

PEARLS & CONSIDERATIONS

COMMENTS

Improved outcomes are noted from surgical fixation of acute tears of the rotator cuff within 6 wk, so prompt workup and referral for these patients is important.

AUTHORS: **Stephen E. Marcaccio, MD,** and **Brett D. Owens, MD**

SUGGESTED READINGS

Erickson BJ et al: Biceps tenodesis: an evolution of treatment, *Am J Orthop* 46(4):E219-E223, 2017.

Frank RM et al: Management of biceps tendon pathology: from the glenoid to the radial tuberosity, *J Am Acad Orthop Surg* 26(4):e77-e89, 2018, https://doi.org/10.5435/JAAOS-D-17-00085.

Rosas S et al: A practical, evidence-based, comprehensive (PEC) physical examination for diagnosing pathology of the long head of the biceps, *J Shoulder Elbow Surg* 26(8):1484-1492, 2017.

BASIC INFORMATION

DEFINITION

Bicuspid aortic valves (BAVs) are the most common congenital disorder of the heart. It is a result of partial or complete fusion of two of the aortic valve leaflets. Most commonly, fusion of leaflets forms a central raphe, and right and left coronary cusps fuse together. BAV aortopathy results in aortic root and ascending aorta dilation. Aortopathy of the BAV is probably related to rheologic force and shear stress on the aortic wall. It results in cystic medial degeneration of the aortic wall.

SYNONYM

Bicommissural aortic valve

ICD-10CM CODE
Q23.1 Bicuspid aortic valve

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:
- Approximately 1% to 2% of the general population has BAV.
- BAV is the most common cause for valvular aortic stenosis in persons ≤65 yr of age.

PREDOMINANT SEX & AGE: Predominant in males with 2:1 male-to-female ratio.

RISK FACTORS: BAV can be sporadic (more common) and familial. No clear risk factors have been defined. However, multiple clinical conditions are associated with it.
- Coarctation of the aorta
- Turner syndrome
- Shone complex (supravalvular mitral ring, subvalvular aortic membrane, parachute mitral valve, coarctation of the aorta)
- Supravalvular aortic stenosis
- Sinus of Valsalva aneurysm
- Ventricular septal defect

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms and signs:
- Usually asymptomatic in the young. However, the bicuspid valve degenerates more rapidly than the native tricuspid aortic valve due to rheologic force and shear stress, and causes rapid progression of aortic stenosis. Similar forces on the aortic wall cause aortic root and ascending aorta dilation, which results in aortic aneurysm formation and aortic regurgitation
- Ejection click
- Early peaking ejection systolic murmur
- Early diastolic murmur if aortic root dilated and aortic regurgitation present

ETIOLOGY

It is a common congenital disorder. Embryologically, aortic valve cusps fail to separate, which results in a larger and a smaller cusp.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Subvalvular aortic membrane
- Aortic valvular stenosis
- Supravalvular stenosis

LABORATORY TESTS

No laboratory tests are recommended for diagnosing BAV.

IMAGING STUDIES

- Transthoracic echocardiogram
- Transesophageal echocardiogram
- Cardiac computed tomography angiogram (CCTA)
- Cardiac magnetic resonance angiogram

TREATMENT

- Echocardiographic surveillance is needed to assess progression of bicuspid valve aortic stenosis, regurgitation, and aortic root dilation. If echocardiogram is not optimal to measure aortic root and ascending aorta diameters, consider aortic magnetic resonance angiography or CT angiography. Surveillance interval is determined by the degree and rate of progression of aortic dilation and by family history. Annual surveillance is needed if the aortic diameter is greater than 4.5 cm.
- Surgical aortic valve replacement (SAVR) is indicated for symptomatic BAV disease without aortopathy in low- to intermediate-risk patients.
- Surgical aortic root and/or ascending aorta repair is recommended in patients with BAV disease and aortic aneurysm diameter ≥5.5 cm. SAVR can be considered for moderate to severe BAV stenosis.
- Surgical aortic root and/or ascending aorta repair with valve replacement is recommended in patients with BAV disease and aortic aneurysm diameter of 5.0 cm if there is a family history of dissection or rapid aortic growth (3 to 5 mm/yr) or aortic coarctation, or small stature. SAVR can be considered for moderate to severe BAV stenosis.
- It is reasonable to surgically repair a 4.5 cm aortic root and/or ascending aorta if patient is undergoing SAVR for moderate to severe BAV disease.
- Transcatheter aortic valve replacement (TAVR) is a reasonable option for symptomatic BAV stenosis with reasonable anatomy (no aortopathy) in intermediate and high surgical risk patients. However, Transcatheter Valve Registry data showed higher rates of stroke, annular rupture, and need for permanent pacemakers with TAVR in BAV stenosis compared with tricuspid aortic valve stenosis.
- In 2019 the PARTNER III trial showed significantly lower risk of annual mortality, stroke, or rehospitalization with TAVR compared with SAVR. However, this trial excluded BAV stenosis patients.

REFERRAL

- If BAV disease present, refer to general cardiologist for surveillance
- Heart team approach for management of BAV aortopathy with BAV disease

PEARLS & CONSIDERATIONS

- Most common congenital cardiac abnormality in general population
- Most commonly associated with aortic root and ascending aorta aneurysm
- Close surveillance needed for early diagnosis of disease progression and referral to a cardiac surgeon or formal heart valve team if regurgitation or stenosis becomes severe or symptomatic

PREVENTION

- No clear data on prevention of BAV
- PROCAS and ASTRONOMER trials showed no effect of statin on delay in progression of aortic valve degeneration

PATIENT & FAMILY EDUCATION

Close follow-up with PCP and cardiologist

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Aortic Stenosis (Related Key Topic)

AUTHOR: **Maheswara Satya Gangadhara Rao Golla, MD**

SUGGESTED READINGS

Nishimura et al: AHA/ACC guideline for the management of patients with valvular heart disease, *J Am Coll Cardiol* 63(22):e57-e185, 2014.

Yacoub et al: Importance of stress mapping of aortic wall in aortic valve disease, *J Am Coll Cardiol* 67(14):1755-1756, 2016.

Binge Eating Disorder (BED)

BASIC INFORMATION

DEFINITION

Binge eating disorder (BED) is characterized by recurrent binge eating episodes, during which an abnormally large amount of food is consumed in a short period of time, accompanied by a sense of loss of control. At least 3 of the following features need to be present in a binge eating episode:

1. Consuming food faster than normal
2. Consuming food until uncomfortably full
3. Consuming large amounts of food when not hungry
4. Consuming food alone due to embarrassment
5. Feeling disgusted, depressed, or guilty after eating a large amount of food

In order to meet criteria for BED, individuals must engage in binge eating episodes at least once per week for 3 months, feel significant distress with regard to their binge eating behaviors, and not utilize compensatory behaviors (e.g., induced vomiting, laxative misuse, overexercising) seen in other eating disorders like bulimia nervosa.

SYNONYMS

Compulsive overeating
BED

ICD-10CM CODE
F50.81 Binge eating disorder
DSM-5 CODE
307.51

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: To our knowledge, no incidence studies on BED yet exist.

PREVALENCE (IN U.S.): Approximately 2% lifetime prevalence in adult community samples was found (women 3.5%; men 2.0%). BED was found to be the most common eating disorder in males—the female:male ratio being more balanced (about 3:2) compared with other eating disorders (about 9:1). Lower lifetime prevalence rates among 13- to 18-yr-old adolescents (girls 2.3%; boys 0.8%) were found. The 12-month prevalence among adult women and men is 1.6% and 0.8%, respectively.

PREDOMINANT AGE (IN U.S.): Higher prevalence rates in females (1.75:1) were found among adults.

GENETICS:

- BED appears to aggregate in families and have a sizable genetic component.
- Family studies report odds ratios between 1.9 and 2.2 for the risk of BED in a relative of a proband with BED compared with relatives of controls.
- Twin studies of BED have reported heritability estimates ranging from 41% to 57% for varying definitions of this disorder.

RISK FACTORS:

- Mental health concerns and psychopathology (mood disorders, anxiety disorders, personality disorders, conduct problems, negative affectivity, substance abuse)
- Temperament and coping style (e.g., high avoidance motivation, low distress tolerance, low extraversion, and self-directedness)
- Severe childhood obesity
- Experience of bullying/weight-related stigmas
- Lifestyle disruptions and deprivation
- Family weight and eating concerns (family dieting, family history of bulimia nervosa, family overeating)
- Quality of parenting (family discord, maternal/paternal problem parenting, parental separation/absence/death)
- Sexual and physical abuse

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Although not necessary for a diagnosis, individuals presenting with BED are often overweight or obese.
- BED is highly comorbid with other forms of psychopathology, especially mood and anxiety disorders. Individuals seeking treatment with acute symptoms of other disorders might not initially report binging episodes, which underscores the importance of thorough initial assessment.
- Males with BED are more likely to underreport symptoms.
- Among individuals with BED, men tend to have significantly higher BMI, whereas women tend to have significantly higher eating-disorder psychopathology.
- Disordered eating symptoms can improve or worsen over time, and diagnostic labels might transition from BED to other eating disorders over time.
- There is potential for higher suicide risk among individuals with BED, possibly because of comorbid psychopathology, and suicidal ideation/intent should be monitored.
- General difficulty to cope with negative emotions and avoidance of aversive experiences/feelings might be apparent.
- Significant shame and self-conscious emotions regarding bingeing behaviors might be present, often resulting in underreporting of binge-eating behaviors.

ETIOLOGY

Research suggests that individual factors (e.g., genetic, biologic, temperamental), environmental factors (e.g., family environment, social network, external sources of stress), and their interactions each contribute.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Important to establish the presence of objective binge eating episodes versus subjective binge eating episodes and nonbinge forms of overeating
- Important to establish that binge eating episodes are not associated with the recurrent use of inappropriate compensatory behaviors (e.g., purging, overexercising)
- Important to establish that binge eating episodes do not occur exclusively during the course of anorexia nervosa, bulimia nervosa, or avoidant/restrictive food intake disorder

WORKUP

- Careful medical and psychosocial history
- Physical examination reveals no specific diagnostic signs of BED
- Mental status examination

LABORATORY TESTS

No laboratory tests are diagnostic. However, given that BED is frequently associated with overweight and obesity, tests examining associated medical problems (e.g., type II diabetes, high triglycerides) might benefit an individual's overall treatment plan.

IMAGING STUDIES

Neuroimaging studies suggest there are corticostriatal circuitry alterations in BED similar to those observed in substance abuse, including altered function of prefrontal, insular, and orbitofrontal cortices and the striatum. Imaging is not recommended as part of routine evaluation.

TREATMENT

NONPHARMACOLOGIC THERAPY

- The primary goal of therapeutic approaches to BED is reduction and/or elimination of binge eating episodes and the associated symptoms of distress.
- Variations of cognitive behavior therapy (CBT) and interpersonal psychotherapy (IPT) remain the most established treatments for BED.
- Growing literature on other psychotherapeutic approaches to BED has also yielded empirical support for dialectical behavior therapy (DBT) and mindfulness-based therapies.
- Combining different interventions at the same time does not add significant advantages. Planning sequential treatments, with more specific interventions for nonresponders, seems to be a more promising strategy.
- Behavioral weight loss (BWL) and self-help interventions evidenced some efficacy in patients with lower psychopathological features. Moreover, BWL approaches have not fared as well as CBT and IPT approaches in ameliorating disordered eating patterns.
- Morbidly obese patients with BED might be well-served by weight loss (bariatric) surgery, which has been found to be associated with sustained, substantial weight loss, as well as reduction in binge eating episodes.
- Preliminary findings regarding electronically delivered psychotherapeutic interventions (e.g., Internet-based CBT) for BED have yielded some empirical support.
- One of the limitations of extant literature is the predominant inclusion of female participants in RCTs.

ACUTE GENERAL Rx

- The pharmacotherapy literature on treating BED in the short-term has focused on

achieving the following objectives: Reducing the frequency of binge eating episodes, reducing weight, and improving associated psychopathology (e.g., depression/anxiety symptoms).
- Preliminary support for specific medications within the classes of antidepressants, anticonvulsants, and antiobesity agents has been found for treating symptoms associated with BED.
- Antidepressants are thought to influence treatment outcomes by addressing the mood and anxiety symptoms that often co-occur with BED. Anticonvulsants have been examined in the treatment of BED because of their success in treating other impulse control disorders. Antiobesity agents have been used to address the overweight and obesity that usually accompanies BED.
- Lisdexamfetamine dimesylate (Vyvanse) is the only medication that has been approved by the Food and Drug Administration (FDA) for the treatment of BED. Two studies found that participants taking the medication experienced a decrease in the number of binge-eating days per week and had fewer obsessive-compulsive binge eating behaviors compared with those on placebo. Longer-term maintenance studies examining the treatment of BED have not yet been published.
- Exploratory work using substance use treatment agents to address BED symptoms is currently under way.
- The existing literature on pharmacotherapy approaches to BED has several limitations, including short duration of RCTs and lack of adequately sized RCTs.

CHRONIC Rx

The long-term treatment of BED using pharmacotherapy has not as yet been systematically investigated.

COMPLEMENTARY & ALTERNATIVE MEDICINE

One study found that hour-long, weekly yoga sessions were associated with reductions in binge eating, BMI, and hip and waist measurements, and an increase in physical activity. More follow-up research is needed in this area.

DISPOSITION

- Data on the long-term outcome of BED, including mortality, are scarce.
- Most outcome data on BED are derived from RCTs. In studies on the outcome of binge eating disorder with a follow-up duration over 3 yr, remission rates in the samples treated with psychotherapy ranged from 19% to 65% across the studies.
- Prospective longitudinal studies with adolescents have found that girls with BED had a twofold risk of becoming overweight or obese, or developing high depressive symptoms compared with nondisordered girls. Among boys, weekly binges predicted drug use as well.
- Various factors may affect treatment response to BED. For instance, higher frequency of binges, increased comorbid psychopathology, and decreased social/family support have been found to be associated with worse treatment outcomes.

REFERRAL

- Referral to mental health specialists: For diagnosis and symptom management (using psychotherapy, pharmacotherapy)
- Referral to nutrition, exercise specialist and/or bariatric surgeon: If patient with BED is morbidly obese and has associated medical problems

PEARLS & CONSIDERATIONS

COMMENTS

- Individuals with BED who are overweight or obese and are interested in weight loss, should also be encouraged to engage in treatment for disordered eating. Although the psychological treatments for BED do not produce substantial weight loss, the elimination of binge eating protects against future weight gain.
- If possible, including family in treatment can be helpful for building social and environmental supports, especially for adolescent and young adult clients.

PREVENTION

There are no known ways to prevent BED (or other eating disorders). However, research suggests that involving education on weight stigma, healthy eating, and body confidence in interventions among school children might ameliorate future body dissatisfaction and disordered eating.

PATIENT & FAMILY EDUCATION

- National Eating Disorders Association (NEDA, www.nationaleatingdisorders.org/) provides patient, family, and professional information on eating disorders, including BED.
- Additional, local and/or online support groups for BED are common and should be investigated.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED TOPICS

Anorexia Nervosa (Related Key Topic)
Bulimia Nervosa (Related Key Topic)

AUTHORS: **Eishita Manjrekar, PhD,** and **Mark Zimmerman, MD**

SUGGESTED READINGS

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Lydecker J et al: Comparing men and women with binge-eating disorder and comorbid obesity, *Int J Eat Disord* 51:411-417, 2018.

McCuen-Wurst C et al: Disordered eating and obesity: associations between binge-eating disorder, night-eating syndrome, and weight-related comorbidities, *Ann N Y Acad Sci* 1411:96-105, 2018.

Bipolar Disorder PTG

BASIC INFORMATION

DEFINITION

Bipolar disorder is an episodic, recurrent, and frequently progressive condition in which the afflicted individual experiences at least one episode of mania, characterized by at least 1 wk of continuous symptoms of elevated, expansive, or irritable mood, in association with three or more of the following symptoms (four if irritability is the presenting mood):

- Decreased need for sleep
- Grandiosity or inflated self-esteem
- Pressured speech
- Flight of ideas or subjective sense of racing thoughts
- Distractibility
- Increased level of goal-directed activity
- Problematic behavior with a high potential for painful consequences

Most individuals with bipolar disorder also experience one or more episodes of major depression over their lifetimes or have symptoms of a depressive episode commingled with those of mania (mixed episode). Hypomanic episodes may also occur.

SYNONYMS

Manic-depression
Cycloid psychosis

ICD-10CM CODES	
F42.0	Bipolar affective disorder, current episode hypomanic
F31.1	Bipolar affective disorder, current episode manic without psychotic symptoms
F31.2	Bipolar affective disorder, current episode manic with psychotic symptoms
F31.3	Bipolar affective disorder, current episode mild or moderate depression
F31.4	Bipolar affective disorder, current episode severe depression without psychotic symptoms
F31.5	Bipolar affective disorder, current episode severe depression with psychotic symptoms
F31.6	Bipolar affective disorder, current episode mixed
F31.8	Bipolar II disorder
DSM-5 CODES	
296.41-296.80	Depends on specific diagnosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.016% to 0.021%
PREVALENCE (IN U.S.): 0.4% to 1.6% (lifetime); bipolar spectrum disorders: 2.8%; approximately 25% attempt suicide, and suicide deaths occur 20× more frequently than in the general population
PREDOMINANT SEX: Equal distribution among male and female
PREDOMINANT AGE: Lifelong condition with age of onset 14 to 30 yr
PEAK INCIDENCE: Onset in 20s
GENETICS:

- Concordance rates for monozygotic twins: 0.7 to 0.8; for dizygotic twins: 0.2
- Risk of affective disorder in offspring with one affected parent with bipolar disorder: 27% to 29%; with two affected parents: 50% to 74%
- Heritability estimate of 0.85
- No specific causal mutations have been identified, but cross-disorder studies indicate an overlap with genes associated with a risk for autism or schizophrenia. Genome-wide association analyses and exome sequencing have suggested a role for *CACNA1C, ANK3, TRANK1, ODZ4, ZNF804A,* and *KDM5B,* among others, and have implicated ion channelopathies, immune and neuronal signaling, and histone methylation in pathogenesis of bipolar disorder. It is hypothesized that heritability derives from the additive effect of a number of common risk alleles in association with a few higher-risk deleterious variants

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Mania associated with:
  1. Psychomotor activation that is usually goal directed but not necessarily productive
  2. Increase in goal-directed activity and excessive involvement in activities leading to unexpected adverse outcomes
  3. Elevated, euphoric, and frequently labile mood
  4. Decreased need for sleep
  5. Flight of ideas with rapid, loud, pressured speech
- Psychosis often occurs (75%), with delusions, hallucinations, and/or formal thought disorder
- Depressive episodes resembling major depressive disorder (see "Depression, Major"), although usually of shorter duration and more frequent; atypical features (hypersomnia, prominent anxiety, weight gain) may be present
- Mixed states, characterized by activation, irritability, and dysphoria, also possible.

KEY DIAGNOSTIC CRITERIA DISTINGUISHING BIPOLAR I DISORDER FROM BIPOLAR II DISORDER:

[1]**Manic episode (Bipolar I Disorder)**

- Distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy lasting at least 1 wk (or less if hospitalization is required)
- Must be accompanied by at least three of the following symptoms (four if mood is only irritable): Inflated self-esteem or grandiosity, decreased need for sleep, pressured speech, racing thoughts, distractibility, increased involvement in goal-directed activity or psychomotor agitation, excessive involvement in pleasurable activities with a high potential for painful consequences
- Symptoms do not meet criteria for a mixed episode
- Disturbance must be sufficiently severe to cause marked impairment in social or occupational functioning or to require hospitalization, or it is characterized by the presence of psychotic features
- Symptoms not due to direct physiologic effect of medication, general medication condition, or substance abuse, although if they persist after a direct condition is addressed, a primary bipolar condition should be considered

Hypomanic episode (Bipolar II Disorder)

- Distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently elevated activity or energy lasting at least 4 consecutive days
- Must be accompanied by at least three of the following symptoms (four if mood is only irritable): Inflated self-esteem or grandiosity, decreased need for sleep, pressured speech, racing thoughts, distractibility, increased involvement in goal-directed activity or psychomotor agitation, excessive involvement in pleasurable activities with a high potential for painful consequences
- Hypomanic episodes must be clearly different from the person's usual nondepressed mood, and there must be a clear change in functioning that is not characteristic of the person's usual functioning; consider using checklist (HCL-32) for accuracy
- Changes in mood and functioning must be observable by others. In contrast to a manic episode, a hypomanic episode is not severe enough to cause marked impairment in social or occupational functioning or to require hospitalization, and there are no psychotic features
- Symptoms not due to direct physiologic effect of medication, general medication condition, or substance abuse

ETIOLOGY

Hypotheses:

- Abnormalities of GABAA and G protein–coupled receptor and membrane function, calcium dysregulation
- Alteration of cAMP, MAP kinase, protein kinase C, arachidonic acid cascade, and glycogen synthase kinase-3 signal transduction pathways; mitochondrial dysfunction
- Alteration in cell survival pathways, glial and neuronal death and loss of neuroplasticity; proposed biomarkers include BDNF and measures of inflammation, oxidative stress, and endothelial function

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Secondary manias caused by medical disorders (e.g., hyperthyroidism, AIDS, early dementia, stroke and nondominant frontal lobe lesions, Cushing's syndrome) or

[1]Criteria are from the American Psychiatric Association: *Diagnostic and statistical manual of mental disorders, fifth edition,* Washington, DC, 2013, American Psychiatric Association.

pharmacologic treatment (e.g., steroids, stimulants)
- First onset of mania after age 50 yr suggestive of secondary mania
- Less severe, and possibly distinct, conditions of bipolar type II and cyclothymia
- Comorbid substance abuse or dependency occurs in 60% to 75% of patients and may confound diagnosis and treatment
- Presentation can be confused with schizophrenia or paranoid psychosis

WORKUP
- History
- Physical examination
- Mental status examination
- Mood Disorder Questionnaire (MDQ); Composite International Diagnostic Interview (CIDI) (3.0)

LABORATORY TESTS
Because of high rate of secondary manias, initial evaluation to confirm health of all major organ systems (routine chemistries, complete blood count, urinalysis, sedimentation rate)

IMAGING STUDIES
- Consider brain imaging if late onset or if neurologic examination is abnormal.
- Neuroimaging may show evidence of ventricular enlargement or increased white matter hyperintensities; decrements in prefrontal and temporal lobe cortical thickness also reported. Corresponding changes in neurocognition, including changes in executive function, verbal memory, and processing speed, may occur.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY
- Cognitive-behavioral and family-focused psychoeducational psychotherapy to help patients cope with consequences of the disease, improve adherence with medications, and identify possible environmental triggers; consider life charting
- Bright light therapy in the northern latitudes in individuals exhibiting a seasonal pattern of winter depression
- Lifestyle "regularization"; effective sleep hygiene; interpersonal and social rhythm therapy; integrated care management for chronic conditions
- Many smartphone mobile apps for bipolar disorder are available to provide information, help monitor symptoms, and deliver interventions

ACUTE GENERAL Rx
- First-line agents for acute mania and mixed states: Lithium 1500 to 1800 mg/day (0.8 to 1.2 mEq/L), valproate 1000 to 1500 mg/day (50 to 125 ng/ml), carbamazepine 600 to 800 mg/day (4 to 12 micrograms/ml), oxcarbazepine 900 to 2400 mg/day, olanzapine 10 to 20 mg/day, risperidone 2 to 4 mg/day, quetiapine 350 to 800 mg/day, ziprasidone 80 to 120 mg/day, asenapine 10 to 20 mg/day, or aripiprazole 10 to 30 mg/day. Treatment-resistant cases may respond to varying combinations of these agents or to the addition of clozapine.
- Useful adjuncts to acute treatment of mania: Benzodiazepines: lorazepam 1 to 2 mg q4h, clonazepam 1 to 2 mg q4h.
- Traditional antidepressants can induce manic episodes and exacerbate mania in mixed episodes and may be less effective than in treatment of unipolar depression.
- First-line options for bipolar depression include lithium, lurasidone, quetiapine, lamotrigine, and olanzapine/fluoxetine combination. Bupropion may have a lower risk for triggering mania, and monoamine oxidase inhibitors or electroconvulsive therapy may be efficacious in treatment-resistant cases. Off-label agents with possible efficacy include modafinil, pramipexole, and intravenous ketamine.

CHRONIC Rx
- Goal of long-term treatment: Prevention of relapse or episode recurrence
- Best agents for prophylaxis of mania: Lithium, quetiapine, aripiprazole, and olanzapine (valproate, carbamazepine/oxcarbazepine possibly beneficial)
- Best agents for prophylaxis of depression: Lamotrigine and lithium
- Risk/benefit of atypical antipsychotics versus traditional mood stabilizers in maintenance unclear
- Long-term use of antidepressants: Frequently destabilizes patient and leads to more frequent relapses; depression outweighs mania as the most debilitating dimension over the life span; bipolar disorder accounts for 7% of all disease-related disability-adjusted life yrs

DISPOSITION
- Course is variable.
- More than 90% of patients having a single manic episode are likely to experience others.
- Uncontrolled manic or depressive episodes can lead to additional episodes.
- Lithium, in comparison to other mood stabilizers or atypical antipsychotic agents, has been shown to specifically decrease suicidal risk.
- Socioeconomic consequences of both mania and depression can be severe and disabling.
- Mortality rate from all causes is 15× that of the general population.

REFERRAL
- If use of antidepressant contemplated or in cases of pediatric bipolar disorder
- If patient is severely manic, rapid cycling, pregnant, or suicidal or is in a bipolar, mixed episode

! PEARLS & CONSIDERATIONS

COMMENTS
- All patients presenting with depression should be asked about past personal and family history of mania and hypomania; 70% of bipolar patients have previously been misdiagnosed. Onset before age 25, postpartum onset, and poor prior response to antidepressants are additional clues.
- Prompt recognition of the earliest signs of mania in a given individual (e.g., decreased need for sleep, increased rate of speech) allows earlier intervention and a better likelihood of preventing a full episode.
- Bipolar disorder in children frequently manifests as episodic behavioral disinhibition, affective lability, and temper dysregulation, but current consensus indicates that the condition is overdiagnosed in this age group. Disruptive mood dysregulation disorder (DMDD) describes children who exhibit persistent irritability and severe temper outbursts on a frequent basis (at least three times/wk for a yr or more).
- Rapid cycling (greater than three episodes/yr) and mixed states are associated with a poorer prognosis, including a longer course, more treatment resistance, more substance use comorbidity, and increased suicidal risk.
- Patients treated with atypical antipsychotic agents should be carefully monitored for development of metabolic syndrome. Independent of medication effect, there is a higher prevalence of metabolic syndrome and abdominal obesity in those with bipolar disorder.
- Despite some variation in prevalence, the severity, impact, and patterns of comorbidity of bipolar disorder are similar in different countries in world health surveys.
- Bipolar disorder often co-occurs with anxiety disorders and attention deficit hyperactivity disorder (ADHD), making attribution of specific symptoms difficult.
- Patients receiving anticonvulsants or antidepressants should be monitored for a possible increase in suicidal thoughts or behavior.
- There is preliminary evidence that nutraceutical agents like omega-3 fatty acids and *N*-acetyl cysteine (NAC) may have efficacy in the treatment of bipolar disorder.
- Multiple studies show a correlation between bipolar disorder and heightened creativity.
- Patients with bipolar disorder are at risk for catatonic syndrome including manic delirium.

PATIENT/FAMILY EDUCATION
Information available at www.NMHA.org/ and www.dbsalliance.org/.

SUGGESTED READINGS
Available at ExpertConsult.com

RELATED CONTENT
Bipolar Disorder (Patient Information)
Depression, Major (Related Key Topic)

AUTHOR: **Victor I. Reus, MD**

SUGGESTED READINGS

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Bite Wounds PTG

BASIC INFORMATION

DEFINITION

A bite wound can be animal or human, accidental, or intentional.

ICD-10CM CODES

T14.1	Open wound of unspecified body region
T01.9	Multiple open wounds, unspecified
S31.000A	Unspecified open wound of lower back and pelvis without penetration into retroperitoneum, initial encounter
S41.159A	Open bite of unspecified upper arm, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

- Bite wounds account for 1% of emergency department visits, and about 2% of patients need hospitalization.
- More than 1 million bites occur in human beings annually in the U.S.
- Dog bites account for 85% to 90% of all bites and result in 10 to 20 fatalities yearly in the U.S.; most dog bite victims are children. Cat bites account for 10% to 20%. The animal typically is owned by the victim.
- Infection rates are highest for cat bites (30% to 50%), followed by human bites (15% to 30%) and dog bites (5%).
- The extremities are involved in 75% of bites.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The appearance of the bite wound is variable (e.g., puncture wound, tear, avulsion).
- Cellulitis, lymphangitis, and focal adenopathy may be present in infected bite wounds.
- Patient may have fever and chills.

ETIOLOGY

- Increased risk of infection: Human and cat bites, closed-fist injuries, wounds involving joints, puncture wounds, face and lip bites, bites with skull penetration, bites in immunocompromised hosts
- Mixed aerobes and anaerobes typically compose the bacteria in bite wounds. Most frequent infecting organisms:
  1. *Pasteurella* spp.: Responsible for majority of infections within 24 hr of dog *(P. canis)* and cat *(P. multocida, P. septica)* bites
  2. *Capnocytophaga canimorsus* (formerly DF-2 bacillus): A gram-negative organism responsible for late infection, usually after dog bites
  3. Gram-negative organisms *(Pseudomonas, Haemophilus)*: Often found in human bites
  4. *Streptococcus* spp., *Staphylococcus aureus*
  5. *Eikenella corrodens* in human bites

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bite from a rabid animal (often the attack is unprovoked)
- Factitious injury

WORKUP

- Determination of the time elapsed since the patient was bitten, status of rabies immunization of the animal, and underlying medical conditions that might predispose the patient to infection (e.g., DM, immunodeficiency)
- Documentation of bite site, notification of appropriate authorities (e.g., police department, animal officer)
- Box 1 summarizes management procedures for bite wounds

LABORATORY TESTS

- Generally not necessary
- Hematocrit if there has been significant blood loss
- Wound cultures (aerobic and anaerobic) if there is evidence of sepsis or victim is immunocompromised; cultures should be obtained before irrigation of the wound but after superficial cleaning

IMAGING STUDIES

Radiographs are indicated when bony penetration is suspected or if there is suspicion of fracture or significant trauma; they are also useful for detecting foreign bodies (when suspected).

BOX 1 Management Procedures for Bite Wounds

Obtain history from patient:
- Situation leading to injury
- Place of occurrence
- Patient allergies
- Other medications (potential interactions)

Perform evaluation of patient:
- Nerve function
- Tendon function
- Vascular integrity
- Range of motion
- Potential bone and joint involvement

Diagram or photograph wound
Mark leading edge of cellulitis
Culture wound (if infected)
Irrigate wound (do not irrigate puncture wounds)
Debride wound cautiously
Obtain diagnostic imaging for penetrating injuries overlying bones or joints, if fracture suspected or foreign body suspected
Drain abscesses
Operative debridement (for removal of devitalized tissue and for severe bites, as indicated)
Administer antimicrobial agents (prophylactic therapy, 3 to 5 days; longer duration for established infection)
Elevate injured area
Close the wound (see text)
Immobilize wound area (3 days for hands)
Have the patient exercise the injured area (if previously immobilized)
Administer tetanus toxoid
Submit health department report (if required)

Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Local care with debridement, vigorous cleansing, and saline irrigation of the wound; debridement of devitalized tissue
- High-pressure irrigation to clean bite wound and ensure removal of contaminants (e.g., use saline solution with a 30- to 35-ml syringe equipped with a 20-gauge needle or catheter with tip of syringe placed 2 to 3 cm above the wound)
- Avoid blunt probing of wounds (increased risk of infection)
- If the animal is suspected to be rabid: Infiltrate wound edges with 1% procaine hydrochloride, swab wound surface vigorously with cotton swabs and 1% benzalkonium solution or other soap, and rinse wound with normal saline

ACUTE GENERAL Rx

- Avoid suturing of hand wounds and any wounds that appear infected.
- Clenched fist injuries that develop after a punch to another's mouth usually require hospitalization, IV antibiotics, and evaluation by a hand specialist.
- Puncture wounds should be left open.
- Give antirabies therapy and tetanus immune globulin (250 to 500 units IM in limb contralateral to toxoid) and toxoid (adult or child older than 5 yr: 0.5 ml DT given IM, child <5 yr 0.5 ml DPT IM) as needed.
- Use empiric antibiotic therapy in high-risk wounds (e.g., cat bite, hand bites, face bites, genital area bites, bites with joint or bone penetration, human bites, immunocompromised host): Amoxicillin-clavulanate 875 to 1000 mg bid for 7 days or cefuroxime 500 mg bid for 7 days.
- In hospitalized patients, IV antibiotics of choice are cefoxitin 1 to 2 g q6h, ampicillin-sulbactam 1.5 to 3 g q6h, ticarcillin-clavulanate 3 g q6h, cefoxitin 2 g IV q8h, or ceftriaxone 1 to 2 g q24h.
- Penicillin allergy: Animal bite (doxycycline or moxifloxacin or trimethoprim/sulfamethoxazole with either clindamycin or metronidazole); human bite (moxifloxacin plus clindamycin, trimethoprim/sulfamethoxazole plus metronidazole).
- Prophylactic therapy for persons bitten by others with HIV and hepatitis B (see Section V).
- Table 1 summarizes the treatment of mammalian bites. The comparative in vitro antimicrobial activity of selected oral antimicrobial agents against common bite wound pathogens is summarized in Table 2.

DISPOSITION

- Prognosis is favorable with proper treatment.
- Important prognostic factors are type and depth of wound, which compartments are

TABLE 1 Treatment of Mammalian Bites

Type	Wound Care	Antibiotic PR	Tetanus PR	Rabies PR	HIV PR	Hepatitis PR
Human	High-pressure irrigation of the wound with normal saline or dilute (<1%) povidone-iodine solution; débride devitalized tissue or ragged edges	Amoxicillin-clavulanate, second-generation cephalosporin with anaerobic activity, penicillin plus dicloxacillin, clindamycin plus ciprofloxacin or trimethoprim-sulfamethoxazole	Tetanus immunoglobulin (250 units IM) and tetanus toxoid (0.5 mg IM) if never had a tetanus vaccine or have not had 3 doses of tetanus toxoid; tetanus toxoid (0.5 mg IM) if >5 yr since previous tetanus booster	None	ART therapy started within the first 48-72 hr and continued for 28 days or bite source tested HIV negative; refer to the hospital for the specific drugs used in ART therapy	HBIG (0.06 ml/kg IM); HBV given at separate site from HBIG
Cat	High-pressure irrigation of the wound with normal saline or dilute (<1%) povidone-iodine solution; débride devitalized tissue or ragged edges	Amoxicillin-clavulanate, second-generation cephalosporin with anaerobic activity, penicillin plus a first-generation cephalosporin, clindamycin plus a fluoroquinolone or trimethoprim-sulfamethoxazole	Tetanus immune globulin (250 units IM) and tetanus toxoid (0.5 mg IM) if never had a tetanus vaccine or have not had 3 doses of tetanus toxoid; tetanus toxoid (0.5 mg IM) if >5 yr since previous tetanus booster	HRIG (20 IU/kg) injected IM and/or around the bite site; rabies vaccine (1 ml IM) given in the deltoid in adults and in the thigh in children, on days 0, 3, 7, 14, and 28	None	None
Dog	High-pressure irrigation of the wound with normal saline or dilute (<1%) povidone-iodine solution; débride devitalized tissue or ragged edges	Amoxicillin-clavulanate, second-generation cephalosporin with anaerobic activity, penicillin plus a first-generation cephalosporin, clindamycin plus a fluoroquinolone or trimethoprim-sulfamethoxazole	Tetanus immune globulin (250 units IM) and tetanus toxoid (0.5 mg IM) if never had a tetanus vaccine or have not had 3 doses of tetanus toxoid; tetanus toxoid (0.5 mg IM) if >5 yr since previous tetanus booster	HRIG (20 IU/kg) injected IM and/or around the bite site; rabies vaccine (1 ml IM) given in the deltoid in adults and in the thigh in children, on days 0, 3, 7, 14, and 28	None	None

ART, Antiretroviral therapy; *HBIG,* hepatitis B immune globulin; *HBV,* hepatitis B vaccine; *HIV,* human immunodeficiency virus; *HRIG,* human rabies immune globulin; *IM,* intramuscularly; *PR,* prophylaxis.
From Adams JG et al: *Emergency medicine: clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

TABLE 2 Comparative in Vitro Antimicrobial Activity of Selected Oral Antimicrobial Agents against Common Bite Wound Pathogens

	Staphylococcus aureus[a]	*Eikenella corrodens*	*Streptococcus*	*Haemophilus*	*Pasteurella*	Anaerobes
Amoxicillin	–	+	v	v	v	v
Amoxicillin–clavulanic acid	v	+	+	+	+	+
Cephalexin	v	–	v	–	v	–
Cefaclor	v	–	v	v	v	–
Cefuroxime	v	v	v	v	v	–
Meropenem	v	+	+	+	+	+
Dicloxacillin	v	–	v	–	–	–
Erythromycin	v	–	v	–	v	–
Azithromycin	v	v	v	–	v	v
Clarithromycin	v	v	v	–	v	–
Trimethoprim-sulfamethoxazole	+	+	v	+	+	–
Moxifloxacin	+	+	+	+	+	+
Clindamycin	+	–	+	–	–	+

+, Active; *–,* poorly active or inactive; *v,* variable.
[a]Methicillin-resistant *S. aureus* can be a pathogen in bite wounds.
Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.

BOX 2 Advice for Avoiding the Bites and Attacks of Common Pets

Dogs
- Do not leave a young child alone with a dog.
- Never approach or try to pet an unfamiliar dog, especially if it is tied up or confined.
- Always ask the dog's owners if you can pet the dog.
- Do not lean over a dog or pet it directly on the head.
- Do not kiss a dog.
- Avoid quick or sudden movements that may startle a dog.
- Never pet or step over a sleeping dog.
- Never try to take a bone or toy away from a dog (other than your own dog).
- Know the appearance of an angry dog: barking, growling, snarling with teeth showing, ears laid flat, legs stiff, tail up, and hair on the back standing up.
- Never step between two fighting dogs; if you need to separate them, use a bucket of water or a hose.
- Do not approach a female dog that is nursing her pups.
- Teach injury prevention advice to children from an early age.

Cats
- Be aware that some cats do not like prolonged petting.
- Know warning signs of an impending bite: twitching of the tail, restlessness, and "intention" bites (i.e., the cat moves to bite but does not bite).

Ferrets
- Do not sell or adopt a ferret that is known to bite.
- Do not push your fingers through the wires of a ferret cage.
- Reach for a ferret from the side with the palm upward rather than from above.
- Do not handle food and then handle young ferrets without washing your hands first.
- Do not poke a ferret or pull on its tail or ears.
- Never leave a ferret alone with a child or infant.
- If a ferret bites and locks on very tightly, pour cold and fast-running water over its face.

From Auerbach P: *Wilderness medicine, expert consult,* premium edition—enhanced online features and print, Philadelphia, 2012, Elsevier.

entered, and pathogenicity of inoculated bacteria.
- Punctures that are difficult to irrigate adequately, carnivore bites over vital structures (arteries, nerves, joints), and tissue crushing that cannot be debrided have a worse prognosis.
- In general, human bites have a higher complication and infection rate than do animal bites.
- Nearly 50% of the anaerobic gram-negative bacilli isolated from human bite wounds may be penicillin resistant and beta-lactamase positive.

PREVENTION

Box 2 provides advice for avoiding the bites and attacks of common pets.

REFERRAL

- Hospitalization and IV antibiotic therapy for infected human bites; bites with injury to joints, nerves, or tendons; or any animal bites unresponsive to oral therapy.
- Human bites with tendon involvement should go to operating room for washout.
- In the outpatient setting, bite wounds should be reevaluated within 48 hr to assess for signs of infection.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Animal and Human Bites (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READING

Ellis R, Ellis C: Dog and cat bites, *Am Fam Physician* 90(4):239-243, 2014.

BASIC INFORMATION

DEFINITION

There are two major classes of arthropods: insects and Arachnida. This chapter focuses on the class Arachnida. Arachnid bites consist of bites caused by:

- Spiders
- Scorpions
- Ticks

ICD-10CM CODES

T63.301	Toxic effect of unspecified spider venom, accidental (unintentional), initial encounter
T63.2	Toxic effect of venom of scorpion, accidental (unintentional), initial encounter
E906	Bite of nonvenomous arthropod; insect bite, not otherwise specified

EPIDEMIOLOGY & DEMOGRAPHICS

- Spiders—ubiquitous; only three types potentially significantly harmful:
  1. Sydney funnel web spider—Australia
  2. Black widow (Fig. E1)—worldwide (excluding Alaska)
  3. Brown recluse (Fig. E2)—most common (South Central U.S.)
- Scorpions—various warm climates: Africa, Central South America, Middle East, India; Texas, New Mexico, California, and Nevada in the U.S.
- Ticks—woodlands

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Spiders:

- Sydney funnel web—atracotoxin toxin
  1. Piloerection, muscle spasms leading to tachycardia, hypertension, increased intracranial pressure, coma
- Black widow—females toxic
  1. Initial reaction: Local swelling, redness (two fang marks) leading to local piloerection, edema, urticaria, diaphoresis, lymphangitis
  2. Pain in limb leading to rest of body (chest pain, abdominal pain), compartment syndrome
- Brown recluse
  1. Minor sting or burn
  2. Wound may become pruritic and red with a blanched center with vesicle (Fig. E3). Can necrose, especially in fatty areas (Fig. E4). Leaves eschar, which sloughs and leaves ulcer; can take months to heal
  3. Systemic symptoms: Headache, fever, chills, gastrointestinal upset, hemolysis, renal tubular necrosis, disseminated intravascular coagulation possible

Scorpions:

- Sting leading to sympathetic and parasympathetic stimulation: Hypertension, bradycardia, vasoconstriction, pulmonary edema, reduced coronary blood flow, priapism, inhibition of insulin
- Also possible: Tachycardia, arrhythmia, vasodilation, bronchial relaxation, excessive salivation, vomiting, sweating, bronchoconstriction, pancreatitis
- Clinically significant scorpion envenomation by *Centruroides sculpturatus* produces a severe neuromotor syndrome and respiratory insufficiency that often requires ICU admission

Ticks: U.S., Europe, Asia

- Very small (<1 mm). Must be attached >36 hr to transmit disease
- Lyme disease—most common (see "Lyme Disease"). Caused by the bacterium *Borrelia burgdorferi* and is transmitted to humans through the *Ixodes scapularis* tick
  1. Early localized (days): Erythema migrans in 60% to 80% of cases
  2. Early disseminated (weeks): Mild to moderate constitutional symptoms, secondary skin lesions, fever, adenopathy, facial palsy, peripheral neuropathy, lymphocytic meningitis, meningoencephalitis, cardiac manifestations (heart block)
  3. Late (months to yrs): Chronic arthritis, dermatitis, neuropathy, keratitis
- Babesiosis (see "Babesiosis")
- Ehrlichiosis/anaplasmosis (see "Ehrlichiosis and Anaplasmosis")

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cellulitis
- Urticaria

Other tick-borne illnesses:

- Babesiosis
- Tick-borne relapsing fever/*Borrelia miyamotoi*
- Tularemia
- Rocky Mountain spotted fever
- Ehrlichiosis/anaplasmosis
- Colorado tick fever
- Tick paralysis, Powassan disease
- Community-acquired cutaneous methicillin-resistant *Staphylococcus aureus*

WORKUP

Physical examination: Thorough skin examination may reveal fang marks, attached ticks, black eschar.

TREATMENT

ACUTE GENERAL Rx

Spiders:

- Sydney funnel web
  1. Pressure, immediate immobilization, supportive care, antivenin
- Black widow
  1. Treatment based on severity of symptoms; bite is rarely fatal
  2. All should receive oxygen, IV, cardiac monitor, tetanus prophylaxis
  3. Symptomatic/supportive therapy
  4. 10% calcium gluconate for muscle cramps (controversial)
  5. Antivenin only for more severe reactions; it carries a risk of anaphylaxis
     a. Dose: One vial in 100 ml 0.9% saline over 20 to 30 min
     b. Skin test before use
     c. Give antihistamines with use
- Brown recluse
  1. Pain management, tetanus, supportive treatment
  2. No consensus regarding best treatment; some evidence for hyperbaric oxygen

Scorpions:

- Fluids, supportive care, species-specific antivenin (equine based, risk of serum sickness) is controversial.
- IV administration of scorpion-specific F(ab')2 antivenin has been reported effective in resolving the clinical syndrome within 4 hours and reducing the need for concomitant sedation with midazolam and reducing the levels of circulating unbound venom.

Ticks:

- Prophylactic: Tick >36 hr: Single dose of doxycycline 200 mg
- Early localized disease
  1. Duration of antibiotics: 10 to 21 days
  2. Doxycycline preferred in patients with possible concurrent ehrlichiosis
  3. Treatment of choice in children: Amoxicillin for 14 days
- Early disseminated: Treatment depends on manifestation
- Late disease: May require longer-term or IV therapy; controversial for neurologic disease (see "Lyme Disease")

DISPOSITION

- For patients with systemic reactions, send home with emergency epinephrine kit.
- If severe or anaphylactic reaction, admit and observe for 48 hr for cardiac, renal, or neurologic problems.

REFERRAL

For patients with systemic reactions, refer to allergist for immunotherapy; 95% to 98% effective in preventing anaphylaxis.

PEARLS & CONSIDERATIONS

Actual spider bites rare; need witnessed bite. Patient should bring spider, if possible, for confirmation. Bites usually occur in settings of unusually close contact with spider. Bedbugs becoming more prevalent; repeated exposure increases severity of reaction.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Bites and Stings (Patient Information)
Bites and Stings, Insect (Related Key Topic)

AUTHOR: **Gail M. O'Brien, MD**

SUGGESTED READINGS

Choi E, Pyzocha NJ, Maurer DM: Tick-borne illnesses, *Curr Sports Med Rep* 15(2):98-104, 2016.

Diaz JH, LeBlanc KE: Common spider bites, *Am Fam Physician* 75:869-873, 2007.

Isbister GK, Bawaskar HS: Scorpion envenomation, *N Engl J Med* 371:457-463, 2014.

Warrell DA: Venomous bites, stings, and poisoning: an update, *Inf Dis Clin N Am* 33(1):17-38, 2019.

FIG. E1 Black widow spider *(Latrodectus hesperus)*. (Courtesy Sean Bush, MD)

FIG. E3 Brown recluse spider bite after 24 hours, with central ischemia and rapidly advancing cellulitis. (From Ignatavicius DD, Workman LM: *Medical surgical nursing,* ed 6, Philadelphia, 2010, Elsevier, pp 147.)

FIG. E2 *Loxosceles* sp. (brown recluse spider). (Courtesy Katia C. Barbaro, Sao Paulo, Brazil.)

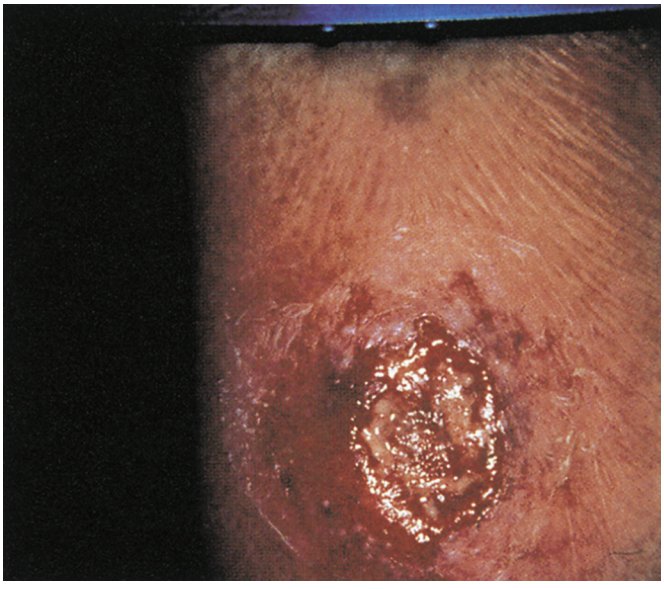

FIG. E4 Brown recluse spider bite after 48 hours of treatment. (From Hill MJ: *Skin disorders—Mosby's clinical nursing series,* St Louis, 1994, Mosby. Courtesy Dr. William N. New, Dallas.)

BASIC INFORMATION

DEFINITION

Most stinging insects belong to the Hymenoptera order and include the winged: honey bees, hornets, bumblebees, sweat bees, wasps (including yellow jackets), and the unwinged: harvester ants, fire ants, and the Africanized honey bee ("killer bee"). Thousands of species can sting or bite. Wasps cause 70% of all reactions to stings. Spiders, which are arachnids, not insects, are another cause of bites (Fig. 1) (see "Bites and Stings, Arachnids"). The venom of the Hymenoptera order (Fig. 2) contains vasoactive and proinflammatory mediators that can cause local reactions. A small number of those stung can develop a systemic hypersensitivity reaction. Bites differ from stings due to the injection of venom. The usual local effect of a sting is intense pain, immediate erythema, edema, and pruritus from the injecting venom. Allergic reactions can be either local or generalized. Generalized reactions can lead to anaphylactic shock. This is a rapid-onset event and can cause death. The majority of reactions occur within the first 6 hr after the sting or bite, but a delayed reaction may occur up to 24 hr after the sting. Delayed reactions are rare and include serum sickness (fever, malaise, urticaria, and arthralgias). A biphasic reaction can occur.

SYNONYM

Venom allergy

ICD-10CM CODES

T63.424	Toxic effect of venom of ants, undetermined, initial encounter
T63.444	Toxic effect of venom of bees, undetermined, initial encounter
T63.464	Toxic effect of venom of wasps, undetermined, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (OF BEE STINGS AND INSECT BITES):

- Unknown prevalence, very underreported; can be cause of outdoor sudden death; 56% to 94% of the population has been stung at least once.
- Account for 2.3% of ED visits; 5% to 7.5% of the population is hypersensitive, with large local or systemic reactions to the venom of one or more stinging insects.
- Insect bites are the most common cause of anaphylaxis reactions and account for 20% of all anaphylaxis-related deaths.
- Most anaphylactic reactions occur during summer months in those most likely to be exposed, including children, males, and outdoor workers. There are no tests to predict reaction accurately; the reaction to a prior sting is still the best predictor. Anaphylaxis can occur after a number of uneventful stings.
- Approximately half of fatal reactions occur without prior allergic response.
- Bites by fire ants are less likely to cause systemic disease.
- Spider bites are rare; only a few of the thousands of spider species cause a reaction in humans. Observation and collection of the spider inflicting the bite is necessary (see Bites and Stings, Arachnids).
- Well syndrome, a rare eosinophilic inflammatory skin disorder, can be triggered by a bite or sting.

INCIDENCE (IN U.S.): 40 to 100 people die each yr from insect sting anaphylaxis; anaphylaxis occurs most often within 10 to 30 min of a sting. Delayed reactions are rare, occurring only in <0.3% of stings.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Stings:
  1. Local reactions:
     a. Cutaneous: The skin is the most common site of a local allergic reaction. Manifestations include flushing, urticaria, pruritus, and angioedema. Local reactions may last several days. Location of sting does not increase risk of a systemic reaction.
  2. Systemic reactions:
     a. Local swelling greater than 10 cm is associated with increased risk of a systemic reaction with repeat exposure.
     b. Respiratory: This is the leading cause of anaphylactic death. Anaphylaxis as defined by consensus of the National Institutes of Health (NIH) 2006 is a severe life-threatening hypersensitivity reaction. Symptoms of upper or lower airway obstruction including hoarseness, choking, throat tightness or tingling that may progress to stridor, laryngeal edema, laryngospasm, and bronchoconstriction.
     c. Cardiovascular: Cardiac manifestations are the second leading cause of death from anaphylaxis; the most common reaction is hypotension that can progress to profound hypovolemic shock. Tachycardia and arrhythmia may occur. Myocardial infarction is rare.
     d. General symptoms: Abdominal pain, nausea, vomiting, lightheadedness, and diarrhea.

Fire ant bites:

- Initial wheal and flare response
- Subsequent development of circularly arrayed blisters within 24 hr (Fig. E3)
- Blisters may develop the appearance of pustules, but they are not infected

Flea bites:

- Classic linear configuration (Fig. E4)
- Multiple excoriated, clustered red papules (Fig. E5)

ETIOLOGY

Stings:

- Most systemic reactions to insect stings are classic immunoglobulin E (IgE)–mediated reactions. Anaphylaxis can be the presenting sign of indolent mastocytosis.
- Reactions occur in previously sensitized patients who have produced high titers of IgE antibody to insect venom antigens.
- Sensitization to wasp venom can occur after a single sting but is more common after a few stings.
- Sensitization to bee venom occurs mainly in people who have been stung frequently by bees.

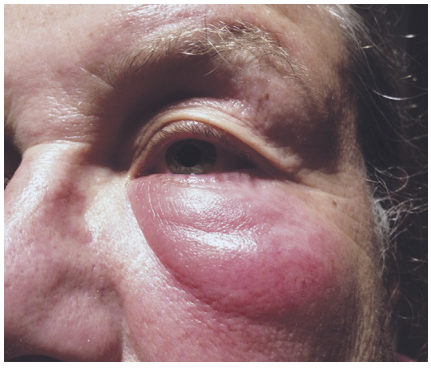

FIG. 1 Spider bite to lower eyelid. (From Swartz MH: *Textbook of physical diagnosis,* ed 7, Philadelphia, 2014, Elsevier.)

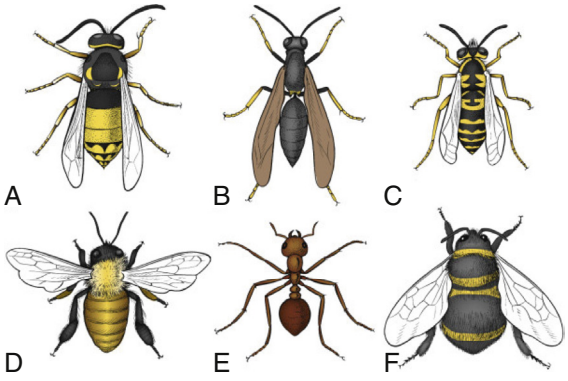

FIG. 2 Representative venomous Hymenoptera. A, Hornet (*Vespula maculata*). **B,** Wasp (*Chlorion ichneumerea*). **C,** Yellowjacket (*Vespula maculiforma*). **D,** Honeybee (*Apis mellifera*). **E,** Fire ant (*Solenopsis invicta*). **F,** Bumblebee (*Bombus* species). (From Erickson TB, Marquez A: Arthropod envenomation and parasitism. In Auerbach PS et al (eds)*: Auerbach's wilderness medicine,* ed 7, Philadelphia, 2017, Elsevier, Fig 41-1, p 937. In Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.)

Bites:
- Fire ant venom contains proteins toxic to the skin.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS
- Stings: Cellulitis, bites, rash
- Bites: Stings, cellulitis

WORKUP
The history is essential for accurate diagnosis including timing of sting or bite and type of insect (bee, wasp, spider, or ant) if known.

LABORATORY TESTS (FOR HYPERSENSITIVITY REACTION)
- Skin test: Either skin prick test or intradermal method with fire ant or hymenoptera venom
- Venom skin tests and occasionally radioallergosorbent tests (RAST) to provide additional information, only for those with history of a systemic reaction
- Venom-specific IgE tests
- Basophil activation tests and mast cell mediator testing are being developed to identify those with allergy and predict those who will have more severe reactions
- Measuring baseline serum tryptase can identify patients as high risk for anaphylaxis and those with mastocytosis

Rx TREATMENT

ACUTE GENERAL Rx
Sting:
- Local Poison Control Center can be contacted.
- Removal of the stinger most easily performed with a flat tool such as a credit card within 30 seconds of the sting, followed by cleansing and application of ice.
- Venom may all be released within 20 seconds of bite or sting.
- Avoid squeezing, which may push venom out of the venom sac and into the tissue.
- Supportive care with oral antihistamines, nonsteroidal antiinflammatory medications/pain medications, topical corticosteroids for 5 to 7 days, and cold compresses for limited reactions.
- Large local reactions (LLR>10 cm) may benefit from oral steroids. 50 mg/day prednisone for 5 to 7 days. Oral second-generation antihistamine can treat and prevent this reaction as well as high potency topical steroids. Unknown if future reactions will be severe.
- Patients with previous reactions or multiple stings to the mouth or neck should be evaluated in an emergency department.
- Unusual reactions to multiple stings include cerebrovascular accident or acute kidney injury due to many causes, including hypotension or direct toxicity from venom.
- Systemic reactions = Anaphylaxis: Treat quickly with intramuscular epinephrine (no contraindication for use). Increased risk of death if epinephrine delayed. The patient should be supine with 0.30 mg IM in anterior/lateral thigh. Patient should be observed for 4 to 8 hr. Adults with preexisting cardiovascular (CV) disease are at greater risk due to challenges handling the stress.
  1. H1- and H2-blockers, oxygen, IV glucocorticoids, beta-agonists, pressors, and IV fluids may also be beneficial for anaphylaxis. No data that glucocorticoids improve clinical outcomes.
  2. Patients should be given 2 units of self-injectable epinephrine pens for home use and referral to allergy indicated after a systemic reaction. Patients should be transported to ED if epinephrine is used, due to 20% risk of recurrence of symptoms.
- Tetanus not needed.

Bite:
- Supportive care—wash with soap and water
- Application of ice or cooling. Calamine lotion may be helpful
- Surveillance for secondary cellulitis—more common with yellow jacket bites

DISPOSITION
Sting:
- Prognosis for a limited reaction is excellent.
- Subsequent anaphylaxis may occur in up to 65% of patients stung again with history of prior systemic reaction. Large local reaction does not predict a systemic reaction.
- There is no evidence that the next sting will necessarily cause a more severe reaction. Variable outcome is due to the patient's age, comorbidities, time elapsed since prior exposure, dose of venom injected, and site of sting.
- Watch for secondary cellulitis.
- Patients who have a history of a severe systemic reaction should:
  1. Be educated to avoid stinging insects.
  2. Carry two syringes preloaded with epinephrine for self-administration.
  3. Undergo testing for serum levels of venom-specific IgE.
  4. Be referred to allergist for venom immunotherapy (VIT), which reduces chance of serious allergic reaction from 60% to <5%. VIT is typically needed for 3 to 5 yr.
  5. Carry medical identification for stinging insect hypersensitivity.
  6. Have a baseline tryptase level checked if an anaphylactic reaction to a sting has been experienced in the past to evaluate the possibility of an underlying mast cell disorder. Patients with levels >20 ng/ml need further evaluation. VIT may benefit those with mastocytosis and wasp venom allergy.
  7. Strategies to avoid bites and stings: No food outside, no garbage or open doors/windows near home, no fragrances or use of public outdoor toilets.

Bite:
- Prognosis for fire ant bite is excellent.
- Large lesions from brown recluse spider bites may take months to heal.
- Watch for secondary cellulitis.

REFERRAL
- Consider referral to an allergist for VIT. All patients with severe systemic reactions should be referred for testing and, if positive, should receive VIT for 5 yr.
- Risk of subsequent anaphylaxis with immunotherapy falls to <5%.
- VIT for 5 yr induces long-term protection in most patients.

! PEARLS & CONSIDERATIONS

Hypersensitivity to stings is common. Reactions range from local nonallergic reaction to venom to life-threatening systemic reaction with anaphylaxis. This could indicate underlying mast cell disorder; tryptase level is indicated. Venom-specific immunotherapy is highly effective in decreasing subsequent anaphylaxis. Venom immunotherapy is currently indicated for systemic reactions, and there is efficacy for prevention of large local reactions, which can result in significant morbidity.

SUGGESTED READINGS
Available at ExpertConsult.com

RELATED CONTENT
Bites and Stings (Patient Information)
Bites and Stings, Arachnids (Related Key Topic)

AUTHOR: **Lynn A. Bowlby, MD**

SUGGESTED READINGS

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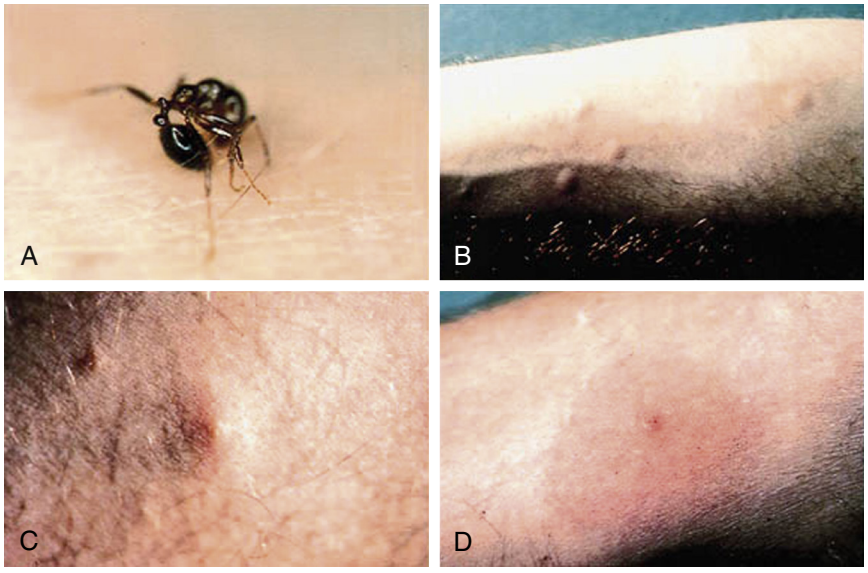

FIG. E3 A, Stinging fire ant (*Solenopsis invicta*). **B,** Wheal-and-flare reactions 5 min after multiple fire ant stings. **C,** Sterile pustule 24 hours after fire ant sting. **D,** Cutaneous late-phase allergic reaction 24 hours after fire ant sting. Excoriated sterile pustule in center of lesion. (From Kemp SF et al: Expanding habitat of the imported fire ant (Solenopsis invicta): a public health concern, *J Allergy Clin Immunol* 105[4]:683-691, 2000.)

FIG. E4 Flea bites. The classic linear configuration of flea bites (the breakfast, lunch, and dinner sign) caused by the tendency of fleas to jump and crawl rather than fly. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E5 Flea bites. Multiple excoriated, clustered red papules. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Injury resulting from a snake biting a human.

ICD-10CM CODES

T63.0	Toxic effect of snake venom
T63.001A	Toxic effect of unspecified snake venom, accidental (unintentional), initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

- The CDC reports that, between 1950 and 2010, there were on average 5000 snakebites annually, which correlates to 1.56 bites per 100,000 people. In the U.S. alone, there are five cases of snake bites resulting in death per yr. Data from the National Electronic Injury Surveillance System reveals that the number of snakebites (including from nonvenomous snakes) between 2001 and 2010 was close to 9200 on average per yr, with more than 2800 venomous bites per yr.
- The highest incidence is reported in southern states, especially Texas and Florida.
  1. Snakebites peak during the warmer months of April through November.
  2. Worldwide, farm workers have the highest incidence of snakebites. In the U.S., most snakebites result from intentional provocation of wild snakes or in the setting of handling captive snakes.
  3. In the U.S., 13.9% of bites occurred predominantly in landscapers, snake handlers, and outdoor professionals, with 76% of the envenomations involving the upper extremity.
  4. The sex ratio (male:female) is 2.7.
  5. Incidence peaks in those between 10 and 14 yr of age and then steadily decreases in adults to about 2 bites per 100,000. Alcohol use and drug intoxication are implicated in many snakebites. The risk of death is highest in children, the elderly, and in those with delayed presentation to care.
  6. Exotic, nonnative pets also account for 1% to 2% of snake envenomations.
- In the U.S., at least one species of poisonous snake (Fig. E1) has been identified in every state, with the exception of Alaska, Hawaii, Rhode Island, and Maine. Table E1 summarizes medically important snake families.
- The Viperidae family includes the Crotalinae subfamily which is the only subfamily native to North America. These are commonly referred to as crotalids or pit vipers and include rattlesnakes, copperheads, and cottonmouths (water moccasins).
  1. Crotalids are responsible for 98% of snake envenomations in the U.S.
  2. Crotalids are characterized by a prominent, diamond-shaped head, a heat-sensing pit between the eye and nostril, long retractable fangs, and, in the case of rattlesnakes, the telltale rattler.
  3. Crotalid bites are typically very painful. Their venom contains a hemotoxin, a neurotoxin, a cardiotoxin, and necrotizing factors leading to direct tissue damage and necrosis. Dry bites (when envenomation does not occur) make up approximately 3 to 25% of pit viper bites.
- The Elapidae family includes mambas, cobras, and coral snakes.
  1. Coral snakes are the only member of the Elapidae family found in the U.S.
  2. Coral snakes are much less common than crotalids, are innately less aggressive, and represent only 2% of reported snakebites in the U.S.
  3. Elapids have smaller heads and shorter fangs, and they are identified by vibrant bands of yellow, red, and black. The popular saying "Red on yellow, kill a fellow; red on black, venom lack" is used to distinguish between venomous and nonvenomous snakes in the U.S. Caution should be used when applying this axiom internationally, as some coral snakes within South America display red-on-black coloring and are in fact venomous.
  4. Because of their shorter fangs, elapids rely on a longer bite time to inject their venom. Less than 40% of coral bites result in envenomation.
  5. The elapid venom competitively blocks the acetylcholine receptor leading to a delayed onset of systemic symptoms. The venom lacks proteolytic enzymes so there is minimal soft tissue destruction. In the last 40 yr, there has only been 1 fatality from a coral snake bite, and this was because the patient did not seek treatment.

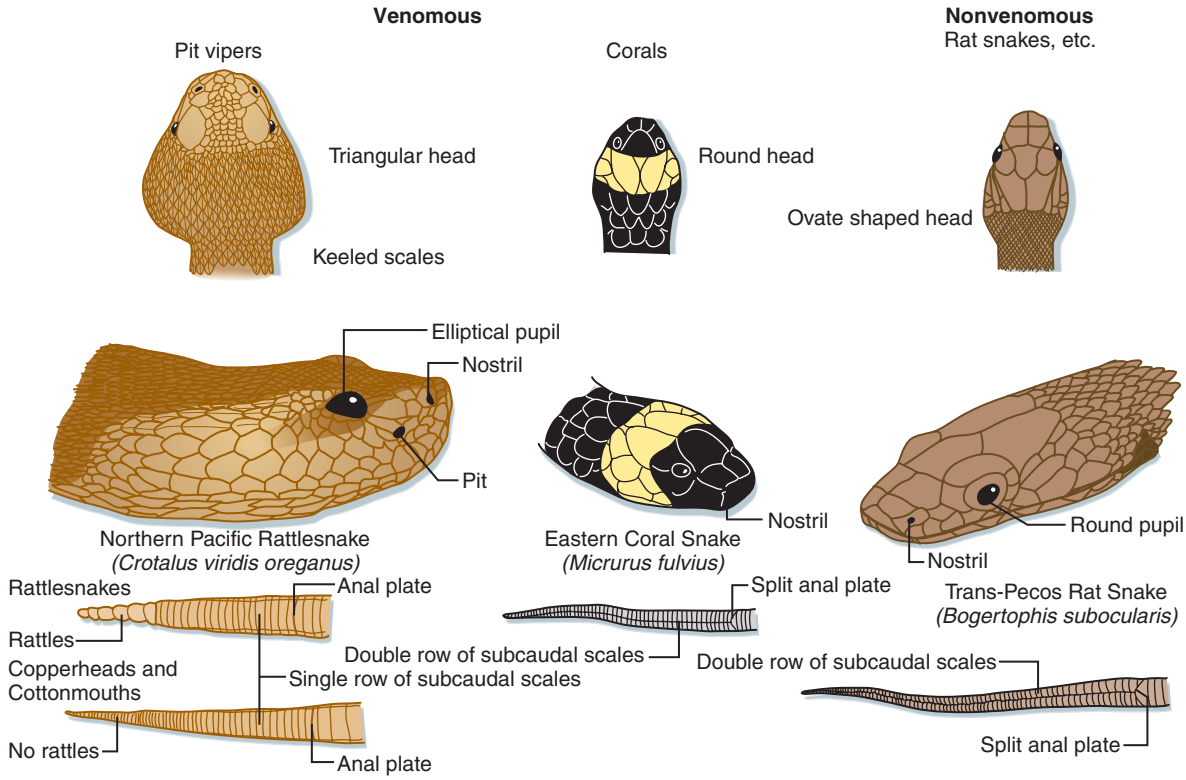

FIG. E1 Anatomic comparison of pit vipers, coral snakes, and nonvenomous snakes of the United States. (Modified from Adams JG et al [eds]: *Emergency medicine,* Philadelphia, 2008, WB Saunders. Drawing by Marlin Sawyer. In Kliegman, RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2019, Elsevier.)

TABLE E1 Medically Important Snake Families

Family	Venomous?	Location	Examples	Toxin Effects/Other Comments
Colubridae	Some species	Most parts of the world	Garter snakes (*Thamnophis* spp.), king snakes, and milk snakes (*Lampropeltis* spp.)	Largest family of snakes; most are considered harmless to humans; a few species are dangerously toxic (e.g., African boomslang [*Dispholidus typus*])
Boidae	None	Most parts of the world	*Boa* sp., *Python* sp.	Constrictors; unsupervised children should not be allowed access to large constrictors
Viperidae				
Subfamily Crotalinae (pit vipers)	All	Americas, Asia	Rattlesnakes (*Crotalus* spp.), cottonmouths, and copperheads (*Agkistrodon* spp.), Lancehead pit vipers (*Bothrops* spp.)	Heat-sensing "pit" between each eye and nostril
Subfamily Viperinae (true vipers)	All	Europe, Africa, Middle East, Asia	Puff adder (*Bitis arietans*), Gaboon viper (*Bitis gabonica*)	No heat-sensing pits
Elapidae	All	Americas, Africa, Middle East, Asia	Cobras (*Naja* spp.), mambas (*Dendroaspis* spp.), kraits (*Bungarus* spp.), coral snakes (*Micrurus* spp.), and the venomous snakes of Australia	Highly variable venom effects—some largely neurotoxic, others causing severe local tissue damage
Hydrophiidae	All	Warm waters of the Pacific Ocean, Indian Ocean, and Oceania (none in the Atlantic Ocean)	Sea snakes including the pelagic sea snake (*Pelamis platurus*)	Neurotoxins and myotoxins; rarely bite humans unless provoked

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

- The degree of envenomation correlates to the size of the snake, with envenomation from larger snakes producing significantly worse local and systemic symptoms than bites from smaller animals.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The effects of envenomation vary by the type of snake but typically includes local tissue injury, coagulopathy, neurotoxicity, and cardiovascular instability, as well as renal failure. Crotalids typically cause more severe local effects as well as hematologic symptoms including primary consumptive coagulopathies and, less commonly, neurologic complications. The exception is the Mohave rattlesnake bite, where local tissue destruction following envenomation is minimal, but severe neurologic symptoms can occur up to 12 hours after the bite. This is similar to elapid bites, which cause less localized tissue damage but have more severe and often delayed neurotoxic manifestations.

CROTALINAE (PIT VIPERS): Local signs and symptoms:

- Intense pain within 5 min.
- Localized edema within 30 min.
- Erythema, ecchymosis, and serous/hemorrhagic bullae can develop over hours (Fig. E2).
- Compartment syndrome is rare but can develop around the site of the bite due to significant amounts of soft tissue swelling and subcutaneous tissue fluid accumulation.
- If edema or erythema does not occur within 8 hours of a confirmed crotalid snakebite, it is assumed envenomation did not occur ("dry bite"). Roughly 25% of crotalid bites are "dry bites."

Systemic manifestations:

- Nonspecific: Nausea, vomiting, diarrhea, lightheadedness, weakness, diaphoresis, chills
- Coagulopathy: Epistaxis, bleeding from gums, internal hemorrhage
- Neurotoxicity: Perioral paresthesias, metallic taste, tingling of fingers or toes (especially with rattlesnake bites), localized/generalized fasciculations, mental status change
- Nephrotoxicity: Secondary to rhabdomyolysis

FIG. E2 Southern Pacific rattlesnake *(Crotalus helleri)* bite wounds. (Courtesy Sean Bush, MD)

- Increased vascular permeability: Severe hypotension, tachycardia, respiratory distress

ELAPIDAE (CORAL SNAKES): Local signs and symptoms:

- Absent or minimal local effects, such as mild pain, swelling, or paresthesias at site of bite

Systemic manifestations:

- May be delayed for up to 12 hours.
- Nonspecific: Nausea, vomiting, abdominal pain, dizziness.
- Neurotoxic: Cranial neuropathies typically appear first, including ptosis, ophthalmoplegia, dysphagia, drooling, and mydriasis with absent or prolonged pupillary light reflex. Descending paralysis and respiratory failure (due to diaphragmatic weakness) can be delayed many hours.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bite: Nonvenomous snakebite, "dry bite," scorpion bite, insect bite, cellulitis, laceration, puncture wound, necrotizing fasciitis
- Descending paralysis: Myasthenia gravis, botulism, shellfish poisoning
- Rhabdomyolysis: Crush injury, prolonged immobilization, marked exercise, hyperthermia, metabolic myopathies, drugs or toxins, infections, electrolyte disorders
- Coagulopathy: Sepsis, multiple trauma, obstetrical complications, malignancy

TABLE E2 Indications for Snake Antivenom Administration

Evidence of Systemic Toxicity:	
Hemodynamic or respiratory instability	Hypotension, respiratory distress
Hemotoxicity	Clinically significant bleeding or abnormal coagulation studies
Neurotoxicity	Any evidence of toxicity: Usually beginning with cranial nerve abnormalities and progressing to descending paralysis including the diaphragm
Evidence of local toxicity	*Progressive* soft tissue swelling

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

WORKUP

- Stabilize and resuscitate unstable patients.
- Initial evaluation of the bite (see details below):
  1. Complete physical and neurologic examination.
  2. Obtain past medical history, including any history of allergic reaction to horse serum, sheep serum, or papaya in those previously treated for snakebite (see antivenom treatment). Patients with allergies to papain, chymopapain, or other papaya extracts may be at risk of an allergic reaction to crotalid antivenom.
- Labs and imaging (see details below).
- Determine need for antivenom (see the following and Table E2).
- Call Poison Control Hotline: 1-800-222-1222.
- Call local zoo when treating patients with envenomations from exotic pets or nonnative snakes.
- Serially reassess, including serial neurologic exams, all cases of suspected envenomation for 8 hours, longer if clinical status deteriorates.

LABORATORY TESTS

- Complete blood count with peripheral smear, electrolytes, blood urea nitrogen, creatinine, prothrombin time, partial prothrombin time, fibrinogen, D-dimer, creatine kinase, liver function tests, sedimentation rate, arterial blood gas, type and crossmatch, urinalysis, and electrocardiogram.
- Repeat labs every 4 to 6 hours to monitor trend.

IMAGING STUDIES

- Consider chest x-ray in cases of severe envenomation or in patients with underlying cardiopulmonary disease to rule out pulmonary edema.
- Plain films of bite site for retained fangs (poor sensitivity). Bedside ultrasound is another option to rule out a retained foreign body in the setting of snakebite (negative predictive value of 96%).
- Computed tomography (CT) of head if concern for intracranial hemorrhage or if any cognitive/neurologic deficit is recognized on exam.
- CT abdomen or focused assessment with sonography in trauma (FAST) if concern for intraabdominal bleeding exists or if patient complains of abdominal pain or distention.

Rx TREATMENT

ACUTE GENERAL Rx

IN THE FIELD:

- There is no field first aid that will significantly treat the envenomation; therefore, the most important intervention is to transport the patient quickly to the nearest medical facility.
- Remove any constricting items including rings, watches, jewelry, or tight clothing.
- The affected part should be kept at the level of the heart and neutral. Keep the joint in a functional position to minimize disability should the limb or joint become severely swollen or immobile.
- Do *not* apply a tourniquet, incise wound, apply mechanical or oral suction, attempt electrotherapy, or apply ice. These interventions have not been shown to provide any benefit and have the potential to cause further harm, including tissue damage, infection, and caregiver envenomation.
- A loose tourniquet, applied to occlude only lymphatic drainage and loosened every 60 to 90 seconds, can be applied for 10 min if the patient was bitten by a coral snake or other species with neurotoxic venom and the patient is exhibiting neurologic symptoms or there is a prolonged transport time. A properly applied pressure bandage should produce a pressure of 40 to 70 mm Hg and 55 to 70 mm Hg in the upper and lower extremity, respectively. Overall, this is not a recommended technique.
- Avoid alcohol, stimulants (caffeine), or agents that can suppress mental status.
- Do *not* pick up a dead snake, as the strike reflexes remain intact and can still envenomate.
- When possible, a picture can be taken from a safe distance for later classification of the snake.

IN THE HOSPITAL:

- Assess airway, breathing, and circulation and intervene as needed. Patients with neurotoxic envenomation from elapids or Mohave rattlesnakes can develop respiratory failure (from diaphragmatic paralysis) and may require intubation. Perform pulmonary function tests (PFTs) and place end tidal CO_2 monitoring. Be cautious and repeat the examination as neurotoxic symptoms may be delayed for many hours.
- Place on monitor, obtain vital signs, place 2 large-bore IVs and give crystalloid.
- Unstable patients should be given antivenom immediately. Administration should not be delayed for wound care of the bite.
- In stable patients, obtain a history, including the time of bite and description of snake.
- Inspect bite site for fang marks and local tissue injury. Clean bite site and remove any retained fangs. Bite may appear like two distinct puncture wounds or small scratches.
- Mark leading edge of erythema and edema, and obtain circumferential measurements every 15 min to assess for progression.
- Obtain initial labs and repeat every 4 to 6 hours.
- Determine need for antivenom and begin preparation. It can take up to 1 hour to reconstitute antivenom, so this process should be started as early as possible.
- Contact Poison Control at 1-800-222-1222, which will connect you to your local poison control center. They will provide guidance for treatment and use of antivenom and also track snakebite incidence.
- Immunize against tetanus if no booster within the past 5 yr. If never immunized, give immunoglobulin as well as toxoid.
- Prophylactic antibiotics are not recommended. Antibiotics should be given only if purulence or other signs of infection are identified, at which time the patient should be given broad-spectrum antibiotics that cover gram-negative bacteria (i.e., ampicillin-sulbactam or quinolone derivatives).
- Aggressive pain control with opioids. Avoid NSAIDs as they increase risk of bleeding, platelet dysfunction, and nephrotoxicity.

ANTIVENOM TREATMENT

CROTALID (RATTLESNAKE, COPPERHEAD, COTTONMOUTH) ENVENOMATIONS:

- CroFab (Crotalinae polyvalent ovine immune Fab), made from sheep serum, is the antivenom commercially available in the U.S. for crotalid envenomations.
- Indications for antivenom administration include swelling, pain, and/or ecchymosis extending beyond area immediately adjacent to bite, any progression of local symptoms (≥2 cm of erythema spread), any systemic symptoms, any development of coagulation lab abnormalities, or abnormal bleeding.
- Patients with crotalid envenomation who have minimal or nonprogressive symptoms should *not* be given CroFab and instead should be monitored for 8 to 12 hours.
- Dosing:
  1. For moderate symptoms, reconstitute 4 to 6 vials of antivenom (CroFab). Each vial should be mixed in 25 ml of normal saline. The 4 to 6 reconstituted vials should then be mixed in 250 ml normal saline and infused over 60 min. Infuse the first 25 ml slowly over the first 10 min to monitor for allergic reaction.
  2. For patients with shock or serious active bleeding, give an initial dose of 8 to 12 vials.

3. If no improvement after first round (defined as progression of local symptoms, persistent systemic symptoms, derangement of laboratory values, or continued bleeding), repeat the initial dose of antivenom after 1 hour.
4. Between 4 and 18 vials of antivenom may be necessary to control initial symptoms.

- After initial control of symptom progression, give maintenance dose of 2 vials every 6 hours for 3 doses to prevent recurrent toxicity. This is because the half-life of CroFab is shorter than the venom's half-life.
- Hematologic labs (fibrinogen, platelet levels, and coagulation studies) should be repeated within an hour of antivenom administration.
- The manufacturer of CroFab maintains a 24/7 hotline: 1-877-377-3784.
- A new Crotalinae antivenom, Anavip, was approved by the FDA in May 2015 and became available in October 2018. It is only approved for rattlesnake envenomation. Anavip is an equine antivenom that has venom specific $F(ab')_2$ fragments of immunoglobulin G (IgG), as opposed to two separate Fab fragments, increasing the half-life in the blood and leading to greater binding and therefore greater elimination of the venom. Because of the longer half-life, dosing with Anavip also eliminates the need for repeat outpatient antivenom dosing, as is required with CroFab. There is a lower risk of adverse coagulopathic reactions and serum sickness because, similar to CroFab, these antivenoms lack the Fc component of the IgG.
- Dosing:
  1. For moderate symptoms, reconstitute 10 vials of antivenom (Anavip). Each vial should be mixed in 10 ml of normal saline. The 10 reconstituted vials should then be mixed in 250 ml normal saline and infused over 60 min. Infuse the first 8 ml slowly over the first 10 min to monitor for allergic reaction.
  2. If no improvement after first round (defined as progression of local symptoms, persistent systemic symptoms, derangement of laboratory values, or continued bleeding), repeat the initial dose of antivenom after 1 hour and repeat every hour as needed.
  3. Re-emerging symptoms should be given an additional 4 vials as needed.
  4. There is no known maximum dose.

ELAPID (CORAL SNAKE) ENVENOMATIONS:

- In the U.S., production of coral snake antivenom by Pfizer/Wyeth was discontinued and only one lot of Antivenin still exists (Lot #L67530). The antivenom's expiration date was extended to January 31, 2020. The use of expired antivenom may be considered in a patient with life-threatening symptoms but should only be administered in conjunction with Poison Control and/or a medical toxicologist. If coral snake antivenom is not available, providers may consider contacting their local zoo to determine whether a provisional antivenom is available. Small-animal studies support the use of black-banded coral snake (Coralmyn), tiger snake, Australia/New Guinea polyvalent antivenom, or anticoral antivenom for neutralization of North American coral snake venom. Many zoos caring for wild snake species stock these specific antivenoms. It is important to note that the effectiveness of these particular antivenoms in human snakebites by the North American coral snake has not been studied. If considering administering alternate antivenom, the provider should contact Poison Control to help orchestrate acquisition.
- In the U.S., only symptomatic patients with confirmed coral snake bites should receive antivenom. The initial dose is 3 to 5 vials given by slow intravenous push, although a higher dose may be necessary in children or in envenomations from large coral snakes.
- There is a high risk of allergic reaction with horse serum-based elapid antivenom so epinephrine, diphenhydramine, IV corticosteroids, and albuterol should be readily available prior to giving antivenom.
- If antivenom administration will be delayed, can consider anticholinesterase therapy (neostigmine) 0.5 to 2 mg by slow IV push with atropine pretreatment.

NONNATIVE OR EXOTIC SNAKE ENVENOMATIONS: Contact the Poison Control Center or your local zoo, as zoos with exotic snakes are required to maintain a supply of snake-specific antivenom on their premises.

DISPOSITION

- All patients who are given antivenom must be admitted and monitored in an ICU for further observation and supportive care. Patients should be observed for a minimum of 18 to 24 hours after initial control of symptom progression, and they are safe for discharge when symptom progression has resolved and laboratory values have normalized.
- Victims of crotalid envenomations with minimal to no toxicity and normal serial lab values should be observed for 8 to 12 hours.
- Suspected Mohave rattlesnake bites, a subset of crotalids, should be observed 12 to 24 hours, as their venom predominantly causes neurotoxicity and symptoms may be delayed (similar to elapids).
- Asymptomatic patients with coral snakebites should be observed for 12 to 24 hours because neurotoxicity may be delayed.
- Children, the elderly, those with significant comorbidities, and patients who sustain bites to the legs, face, or neck may require observation for 24 hours.

FOLLOW-UP:

- All patients who receive antivenom should have repeat labs at 2 to 3 days and 5 to 7 days after the last administered antivenom dose to evaluate for delayed hematologic complications or serum sickness.
- Return for worsening, nondependent swelling, abnormal bleeding, or signs of serum sickness, which include fatigue, rash, or arthralgias. If serum sickness develops, give prednisone 1 mg/kg/day, then once symptoms resolve taper dose over 1 week.
- Patients should adhere to bleeding precautions (no contact sports, dental extractions, elective surgery, etc.) for 2 weeks.

REFERRAL

Refer to a medical facility with an ICU for administration of antivenom. The approach to snakebites should be multidisciplinary and should include medical toxicology or other physician snakebite specialists, as well as hematology or nephrology if needed. All snakebites should be reported to Poison Control and the local health department for surveillance.

PEARLS & CONSIDERATIONS

OTHER CONSIDERATIONS

- Frequent assessment and clinical judgment is essential in the treatment of snakebites, as patients do not have a uniform response to envenomation and treatment.
- Dosage of antivenom is based on typical envenomation rather than age or weight, so the dose is the same for children and adults.
- Antivenom is most effective when given within 4 hours of the bite and least effective if delayed beyond 12 hours. Systemic symptoms (coagulopathy, CNS effects, etc.) respond better to treatment than do local symptoms (erythema/edema, bullae, etc.).
- Antivenom is not contraindicated in pregnancy. There have been no adverse reactions to mother or to fetus reported secondary to antivenom treatment. The potential coagulopathy associated with envenomation may place the fetus at higher risk for placental abruption, so prompt treatment with antivenom is prudent. Pregnant victims of snakebites who are treated with antivenom have a significantly lower rate of miscarriage when compared with those who did not receive antivenom.
- Although local wound effects can be severe, wound management should not take precedence over antivenom administration. Some studies suggest that even in the case of compartment syndrome, antivenom may be more effective than fasciotomy, although both may be necessary.

COMPLICATIONS

- Hypersensitivity reactions and serum sickness can occur following antivenom administration. These reactions are much more common with equine-derived antivenom than with ovine-derived antivenom. CroFab derived from sheep serum should be used preferentially over equine serum if available, given the decreased risk for adverse reaction. Elapid antivenom is derived from horse serum, so the risk for allergic reaction and anaphylaxis remains high.
- Anaphylaxis to antivenom can occur within 30 min and should be treated by immediately stopping the infusion and managing the symptoms. Epinephrine, diphenhydramine, and hydrocortisone should be administered

as needed. If the anaphylaxis is well-controlled and the envenomation is severe, the antivenom infusion can then be resumed.
- In patients with a known hypersensitivity to antivenom, prophylactic epinephrine has been found to reduce the rate of adverse effects.
- Delayed or recurrent hematologic complications are common and can manifest up to 2 weeks post treatment. Most bleeding is self-limited but can rarely be severe, necessitating close follow-up and occasionally repeat doses of antivenom.
- Serum sickness occurs 7 to 14 days after antivenom administration and is characterized by fever, rash, arthralgias, and lymphadenopathy. It can be treated with prednisone 60 mg PO daily, tapered over 7 to 10 days.

SUGGESTED READINGS

ANAVIP: *Crotalidae Immune F(ab')$_2$ (Equine) [package insert]*, Mexico D.F., Mexico, 2015, Instituto Bioclon S.A. de C.V.

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SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Snakebites (Patient Information)

AUTHORS: **Ashley A. Jacobson, MD,** and **Neha P. Raukar, MD, MS**

BASIC INFORMATION

DEFINITION

Bladder cancer is a field change disease in which the entire urothelium from the renal pelvis to the urethra is susceptible to malignant transformation. The disease stages include non–muscle-invasive bladder cancer, muscle-invasive bladder cancer, and metastatic urothelial carcinoma. The three types of bladder cancer are transitional cell carcinoma, squamous cell carcinoma, and adenocarcinoma.

ICD-10CM CODES

C67.9	Malignant neoplasm of bladder, unspecified
C79.11	Secondary malignant neoplasm of bladder
D09.0	Carcinoma in situ of bladder
D30.3	Benign neoplasm of bladder
D41.4	Neoplasm of uncertain behavior of bladder
D49.4	Neoplasm of unspecified behavior of bladder

EPIDEMIOLOGY & DEMOGRAPHICS

In 2019, an estimated 80,470 new cases and 17,670 deaths in the U.S. were attributed to bladder cancer. It is the sixth commonest malignancy in the U.S., with a median age of diagnosis of 73 yr.

PREDOMINANT SEX: It is 3 to 4 times more common in men than in women; lifetime risks are 1 in 26 for men and 1 in 88 for women.

RISK FACTORS:

Smoking:

- More than half of bladder cancers are related to smoking.
- Smoking risk is based on consumption; there is a two- to three-fold increase for subjects smoking >10 cigarettes per day.
- Smokers of low-tar and low-nicotine cigarettes have a lower risk when compared with higher tar and nicotine cigarettes.
- Those who smoke unfiltered cigarettes have a 50% increased risk of bladder cancer compared with those who smoke filtered cigarettes.
- Pipe smokers have a lower risk of bladder cancer compared with cigarette smokers.
- Cigars, snuff, and chewing tobacco, although implicated in nonurologic cancers, are not thought to influence bladder cancer risk.

Diet:

- Diets rich in beef, pork, and animal fat increase risk of bladder cancer.
- Beer consumption has been linked to bladder cancer development as a result of the presence of nitrosamines in the beer. Drinking coffee is not thought to contribute to bladder cancer risk.
- Medications: Long-term (>1 yr) use of pioglitazone and rosiglitazone.

PEAK INCIDENCE: Incidence increases with age: Higher after age 60 yr, uncommon in those younger than 40 yr.

GENETICS: It is thought to be multifactorial in etiology, involving both genetic and environmental interactions. Overall, approximately 20% to 25% of the male population in the U.S. with bladder cancer is estimated to have the disease as a result of occupational exposure.

DISTRIBUTION: In North America, transitional cell carcinomas (TCC) account for 93%, squamous cell carcinomas account for 6%, and adenocarcinomas account for 1% of bladder cancers.

PATHOGENESIS: Two pathways exist for bladder cancer (TCC):

- Papillary superficial disease occasionally leading to invasive cancer (75%)
- Carcinoma in situ (CIS) and solid invasive cancer with high risk of disease progression (25%)

Two distinct forms of "superficial cancer" exist:

- T_a: Papillary low-grade tumor with a high rate of recurrence; disease progression occurs in 5%
- T_1: Higher-grade papillary tumor that infiltrates the lamina propria; often associated with flat CIS that may involve the urothelium diffusely. Disease progression occurs in 30% to 50%. This is subdivided into:
  1. T_{1a}: Penetration up to the muscularis mucosa; disease progression in 5%
  2. T_{1b}: Penetration through the muscularis mucosa; disease progression in 53%

Flat CIS:

- Entirely different and separate pathway of cancer development whose mechanism is manifested by dysplasia, which leads to the occurrence of poorly differentiated malignant cells that replace or undermine the normal urothelium and extend along the plane of the bladder wall. It penetrates the basement membrane and lamina propria in 20% to 30% of cases and is associated with the development of solid tumor growth. A p53 defect occurs in 50% of these cases.

At presentation, 50% to 51%% of cancers are in situ, 34% to 35% are localized to the bladder, 17% are regionally spread to the lymph nodes, and 4% to 5% present with distant metastases. Eighty percent of superficial TCC recur, with up to 30% progressing to a higher stage or grade. Younger patients most commonly develop low-grade papillary noninvasive TCC and are less likely to have recurrences when compared with older patients with similar lesions. Involvement of the upper tracts with tumor occurs in 25% to 50% of cases (see Table 1 and E2).

MOLECULAR EPIDEMIOLOGY: TCC is usually a field change disease with tumors arising at different times and sites in the urothelium, suggesting a polyclonal etiology of bladder cancer. Non–muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) are genetically different. NMIBC is characterized by a high frequency of mutations in the *FGFR* oncogene, leading to constitutive activation of the RAS/MAPK pathway. In MIBC, mutations in the *TP53* gene prevail. In general, mutations in *FGFR* and *TP53* are mutually exclusive, suggesting that NMIBC and MIBC develop along different oncogenetic pathways. However, these mutations often occur simultaneously in stage pT_1 tumors that invade the connective tissue layer underlying the urothelium. Recently, somatic mutations in the *PIK3CA* oncogene, which encodes the catalytic subunit p110α of class-IA PI3 kinase, were described in 13% to 27% of bladder tumors. These mutations often coincided with *FGFR3* mutations. Mutations in the *RAS* oncogenes (*HRAS*, *KRAS*, and *NRAS*) have also been found in 13% of bladder tumors and in all stages and grades; they are mutually exclusive with *FGFR3* mutations.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Gross, painless hematuria
- Microhematuria
- Frequency, urgency, occasional dysuria
- With locally invasive to distant metastatic disease, the presentation can include:
  1. Abdominal pain
  2. Flank pain
  3. Lymphedema
  4. Renal failure
  5. Anorexia
  6. Bone pain

ETIOLOGY

Bladder cancer is a potentially preventable disease associated with specific etiologic factors:

- Cigarette smoking is associated with 45% to 65% of cases. The risk of developing a TCC is two to four times higher in smokers than in nonsmokers, and that risk persists for many yrs, being equal to nonsmokers only after 12 to 15 yr of smoking abstinence. Smoking is associated with higher histologic grade and stage, increase in the numbers of tumors, and increased size
- Occupational exposures: Dye workers, textile workers, tire and rubber workers, petroleum workers
- Chemical exposure: O-toluidine, 2-naphthylamine, benzidine, 4-amino-biphenyl, and nitrosamines
- Exposure to herpes papilloma virus type 16

Squamous carcinomas are associated with:

- Schistosomiasis
- Urinary calculi
- Indwelling catheters
- Bladder diverticula

Miscellaneous causes:

- Phenacetin abuse
- Cyclophosphamide
- Pelvic irradiation
- Tuberculosis

Adenocarcinomas are associated with:

- Exstrophy
- Endometriosis
- Neurogenic bladder
- Urachal abnormalities
- As a secondary site for distant metastases from other organs (e.g., colon cancer)

DIAGNOSIS

- History and physical examination.
- Urinalysis.

TABLE 1 2018 TNM Bladder Cancer Stage Classification

T stage	Description
T_X	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_a	Noninvasive papillary carcinoma
T_{is}	Carcinoma in situ
T_1	Tumor invades lamina propria
T_2	Tumor invades muscularis propria
pT_{2a}	Tumor invades superficial muscularis propria (inner half)
pT_{2b}	Tumor invades deep muscularis propria (outer half)
T_3	Tumor invades perivesical tissue
pT_{3a}	Microscopic invasion
pT_{3b}	Macroscopic invasion (extravesical mass)
T_4	Tumor invades any of the following: Prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T_{4a}	Tumor invades prostatic stroma, uterus, vagina
T_{4b}	Tumor invades pelvic wall, abdominal wall
Regional lymph nodes (N)	
N_0	No lymph node metastasis
N_1	Single lymph node metastasis in true pelvis (perivesical, obturator, internal/external iliac, or sacral lymph node)
N_2	Multiple lymph node metastases in true pelvis (perivesical, obturator, internal/external iliac, or sacral lymph node metastasis)
N_3	metastasis to the common iliac lymph nodes
Distant metastasis (M)	
M_0	No distant metastasis
M_1	Distant metastasis
M_{1a}	Distant metastasis limited to lymph nodes beyond the common iliacs
M_{1b}	Non–lymph-node distant metastases

- Cystoscopy with bladder barbotage and biopsy. Fluorescence cystoscopy offers improvement in the detection of flat neoplastic lesions such as carcinoma in situ.
- Transurethral resection of bladder tumor (TURBT).
- There is insufficient evidence to determine whether a decrease in mortality rate from bladder cancer occurs with hematuria testing, urinary cytology, or a variety of other tests on exfoliated urinary cells or other substances.
- In addition to urinary cytology and bladder barbotage, BTA, NMP22, and fibrin degradation products have been approved by the FDA as bladder cancer tumor markers. No marker has general, widespread acceptance because the results are affected by the presence of stents, recent urologic manipulation, stones, infection, bowel interposition, and prostatitis, creating false-positive results.
- Urinary biomarkers: Six urinary biomarkers have been approved by the FDA for diagnosis on surveillance of bladder cancer.
  1. Quantitative nuclear matrix protein 22 (Alere NMP22)
  2. Qualitative NMP22 (BladderChek)
  3. Qualitative bladder tumor antigen (BTA stat)
  4. Quantitative BTA (BTA TRAK)
  5. Fluorescence in situ hybridization (FISH)
  6. Fluorescent immunohistochemistry (ImmunoCyt)
- Generally, urinary biomarkers miss a substantial proportion of patients with bladder cancer and are subject to false-positive results in others. Accuracy is poor for low-stage and low-grade tumors.[1]

DIFFERENTIAL DIAGNOSIS

- Urinary tract infection
- Frequency-urgency syndrome
- Interstitial cystitis
- Stone disease
- Endometriosis
- Neurogenic bladder

WORKUP

Fig. 1 illustrates a diagnostic and treatment algorithm for bladder cancer.

LABORATORY TESTS

- Urine cytology.
- Urine telomerase: Telomerase activity in voided urine or bladder washings determined by the telomeric repeat amplification protocol (TRAP) assay. This test has been reported to accurately detect the presence of bladder tumors in men. It represents a potentially useful noninvasive diagnostic innovation for bladder cancer detection in high-risk groups such as habitual smokers or in symptomatic patients.

[1] Chou R et al: Urinary biomarkers for diagnosis of bladder cancer: a systematic review and meta-analysis, *Ann Intern Med* 163:922-931, 2015.

RADIOLOGIC TESTS

- Renal ultrasound, retrograde pyelography, CT scan, and MRI.
- One or a combination of studies can be used. In the absence of skeletal symptoms, bone scan is not recommended.

Rx TREATMENT

SURGICAL APPROACHES

- The goal of any resection should be the visual eradication of any tumor burden and the assurance of an adequate depth of resection
- Initially, transurethral resection of bladder tumor (TURBT). Using cutting current, a loop electrode is used to resect the tumor inclusive of muscularis propria (Fig. E2). Histologically, bladder tumors frequently exhibit growth beyond the visible edge, and, as such, resection should include an approximate 2-cm margin of normal-appearing tissue. Wide resection of tumors will ensure completeness, whether the tumor has a broad base or a tentacular growth pattern (Fig. E3)
- Loop biopsy of the prostatic urethra if high-grade TCC is suspected
- If superficial disease, follow-up protocol with repeat TURBT and/or the use of intravesical agents is recommended
- For advanced bladder cancer, radical cystectomy with urethrectomy (unless orthotopic diversion is planned), and either ileal loop conduit or orthotopic diversion

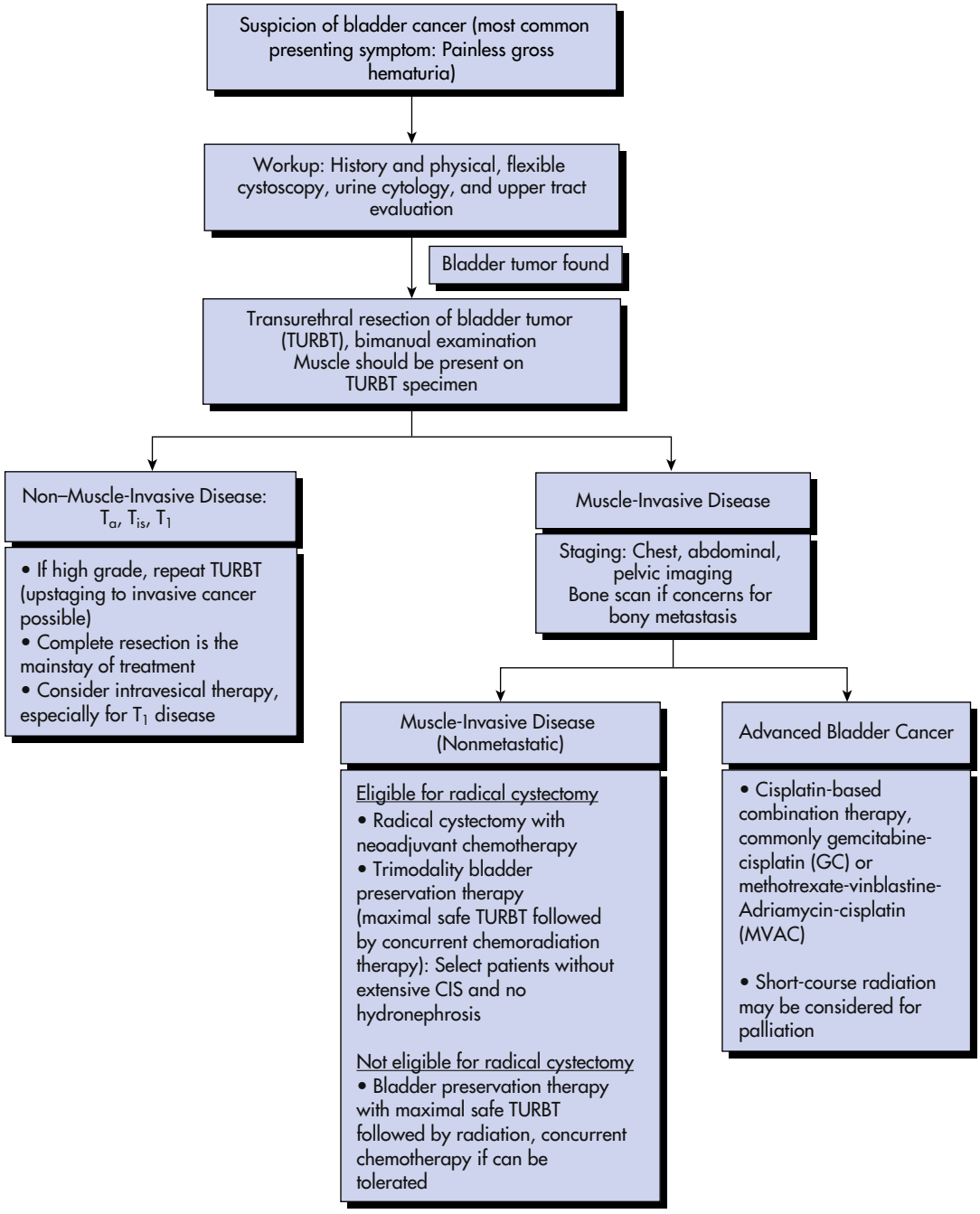

FIG. 1 Diagnostic and treatment algorithm for bladder cancer. *CIS,* Carcinoma in situ. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

BLADDER PRESERVATION APPROACHES: After cystectomy for muscle-invasive disease, 50% or more of the patients will develop metastases. Most patients develop metastases at distant sites; a third relapse locally. Bladder preservation management is offered in individuals who refuse surgery or who might not be suitable radical cystectomy patients. Bladder-sparing protocols include extensive TURBT or partial cystectomy with external-beam or interstitial radiotherapy and systemic chemotherapy. Radiotherapy as a single treatment modality is not effective. The best predictor of successful bladder preservation is a complete response after the combination of initial TURBT and neoadjuvant chemotherapy with stages T_2 to T_{3a}.

INDICATIONS FOR PARTIAL CYSTECTOMY:
- Tumor within a bladder diverticulum
- Solitary, primary, and muscle-invasive or high-grade lesion of a region of the bladder that allows complete excision with adequate surgical margins
- Inability to adequately resect tumor by TURBT alone because of size or location
- Tumor overlying a ureteral orifice requiring ureteral reimplantation
- Biopsy of a radiation-induced ulceration
- Palliation of severe local symptoms
- Patient refusal of urinary diversion
- Poor-risk patient who is not a diversion candidate

CONTRAINDICATIONS:
- Multiple tumors
- CIS
- Cellular atypia on biopsy
- Prostatic invasion
- Invasion of the trigone
- Inability to achieve adequate surgical margins
- Prior radiotherapy
- Inability to maintain adequate bladder volume after resection
- Evidence of extravesical tumor extension
- Poor surgical risk

BOX 1 American Urological Association Guideline Recommendations

For all index patients:
- Standard: Physicians should discuss with the patient the treatment options and the benefits and harms, including side effects, of intravesical treatment.

For a patient who presents with an abnormal growth on the urothelium but who has not yet been diagnosed with bladder cancer:
- Standard: If the patient does not have an established histologic diagnosis, a biopsy should be obtained for pathologic analysis.
- Standard: Under most circumstances, complete eradication of all visible tumors should be performed.
- Standard: If bladder cancer is confirmed, periodic surveillance cystoscopy should be performed.
- Option: An initial single dose of intravesical chemotherapy may be administered immediately postoperatively.

For a patient with small volume, low-grade T_a bladder cancer:
- Recommendation: An initial single dose of intravesical chemotherapy may be administered immediately postoperatively.

For a patient with multifocal and/or large volume, histologically confirmed, low-grade T_a or a patient with recurrent low-grade T_a bladder cancer:
- Recommendation: An induction course of intravesical therapy with bacillus Calmette-Guérin or mitomycin C is recommended for the treatment of these patients with the goal of preventing or delaying recurrence.
- Option: Maintenance bacillus Calmette-Guérin or mitomycin C may be considered.

For a patient with initial histologically confirmed high-grade T_a, T_1, and/or carcinoma in situ bladder cancer:
- Standard: For patients with lamina propria invasion (T_1) but without muscularis propria in the specimen, repeat resection should be performed prior to additional intravesical therapy.
- Recommendation: An induction course of bacillus Calmette-Guérin followed by maintenance therapy is recommended for treatment of these patients.
- Option: Cystectomy should be considered for initial therapy in select patients.

For a patient with high-grade T_a, T_1, and/or carcinoma in situ bladder cancer that has recurred after prior intravesical therapy:
- Standard: For patients with lamina propria invasion (T_1) but without muscularis propria in the specimen, repeat resection should be performed prior to additional intravesical therapy.
- Recommendation: Cystectomy should be considered as a therapeutic alternative for these patients.
- Option: Further intravesical therapy may be considered for these patients.

ACUTE GENERAL Rx

INDICATIONS FOR INTRAVESICAL CHEMOTHERAPY:
- High-grade tumor
- Tumor size <5 cm
- Multiple tumors
- Presence of CIS
- Positive urinary cytologic findings after a resection
- Incomplete tumor resection

Intravesical agents: Thiotepa, doxorubicin, mitomycin C, BCG, interferon, interleukin-2, and keyhole-limpet hemocyanin. Photodynamic therapy with hematoporphyrin derivatives has also been used.

INDICATIONS FOR CYSTECTOMY:
- Large tumors not amenable to complete TURBT
- High-grade tumor
- Multiple tumors with frequent recurrences
- Diffuse CIS not responsive to intravesical chemotherapy
- Prostatic urethra involvement
- Irritative bladder symptoms with upper tract deterioration
- Muscle-invasive disease
- Disease outside the bladder

SYSTEMIC THERAPY:
- Cisplatin-based chemotherapy is used concurrently with radiotherapy in bladder preservation or neoadjuvant therapy approaches for resectable cases.
- Combination chemotherapy regimens are used as perioperative (neoadjuvant and adjuvant) therapy for locally advanced disease in conjunction with bladder resection.
- In fit patients with metastatic cancers, combination cisplatin-based chemotherapy regimens are used as palliative therapy. The most effective combination regimens include MVAC (cisplatin, methotrexate, vinblastine, doxorubicin) and GC (gemcitabine, cisplatin), which provide palliation and modest survival benefit.
- In patients with metastatic cancers who are unfit to receive cisplatin-based chemotherapy regimens, the use of immune checkpoint inhibitors is the preferred therapy option. Available agents include the PD-1 inhibitors (nivolumab, pembrolizumab) and PDL-1 inhibitors (atezolizumab, durvalumab, avelumab). These are also used as salvage therapy in patients who have failed prior chemotherapy approaches.
- Alterations in the gene encoding fibroblast growth factor receptor (FGFR) are detected in 15% to 20% of cases of locally advanced or metastatic urothelial carcinoma. Erdafitinib, a tyrosine kinase inhibitor of FGFR1-4, has shown response rates of 40% in previously treated patients with FGFR alterations, and median survival was reported at approximately 14 mo.

RADIOTHERAPY: Conflicting reports suggest that superficial bladder cancer is more sensitive to radiotherapy. Only 20% to 30% of patients with invasive bladder cancer can be cured by external-beam radiation therapy alone. It is used in combination with surgery or with systemic agents to treat bladder cancer primarily in patients who are not surgical candidates or who refuse surgery. Combination chemotherapy (cisplatin) given concurrently with radiotherapy has shown significant improved locoregional control of bladder cancer in bladder-preservation strategies.

CHRONIC Rx

FOLLOW-UP RECOMMENDATIONS FOR SUPERFICIAL BLADDER CANCER:
- Cystoscopy, bladder barbotage, and bimanual examination every 3 mo for 2 yr, then every 6 mo for 2 yr, and annually thereafter.
- Upper tract studies are based on the risk of upper tract tumor development, generally every 2 to 5 yr.

PEARLS & CONSIDERATIONS

COMMENTS
- Useful prognostic parameters for bladder tumor recurrence and subsequent progression are tumor grade, tumor depth, multifocal tumors, frequency of recurrence, tumor size, CIS, lymphatic invasion, papillary or solid tumor configuration.
- Currently, the incidence of occupational bladder cancer seems to be increasing faster in women than in men. Workers with aromatic amine exposure have the highest incidence, whereas those exposed to polycyclic aromatic hydrocarbons and heavy metals have the greatest mortality.
- The 5-yr survival for bladder cancer is 76%; it ranges from 96% for in situ, 70% for localized, 35% for regional, and 5% for distant cancers.
- Box 1 describes the American Urological Association Guideline Recommendations for bladder cancer.

SUGGESTED READINGS
Available at ExpertConsult.com

RELATED CONTENT
Bladder Cancer (Patient Information)

AUTHOR: **Bharti Rathore, MD**

SUGGESTED READINGS

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TABLE E2 2018 TNM Bladder Cancer Stage Groupings

Stage	T	N	M
Stage 0_a	T_a	N_0	M_0
Stage 0_{is}	T_{is}	N_0	M_0
Stage I	T_1	N_0	M_0
Stage II	T_{2a-2b}	N_0	M_0
Stage III_A	T_{3a-3b}, T_{4a}	N_0	M_0
	T_1-T_{4a}	N_1	M_0
Stage III_B	T_1-T_{4a}	N_{2-3}	M_0
Stage IV_A	T_{4b}	Any N	M_0
	Any T	Any N	M_{1a}
Stage IV_B	Any T	Any N	M_{1b}

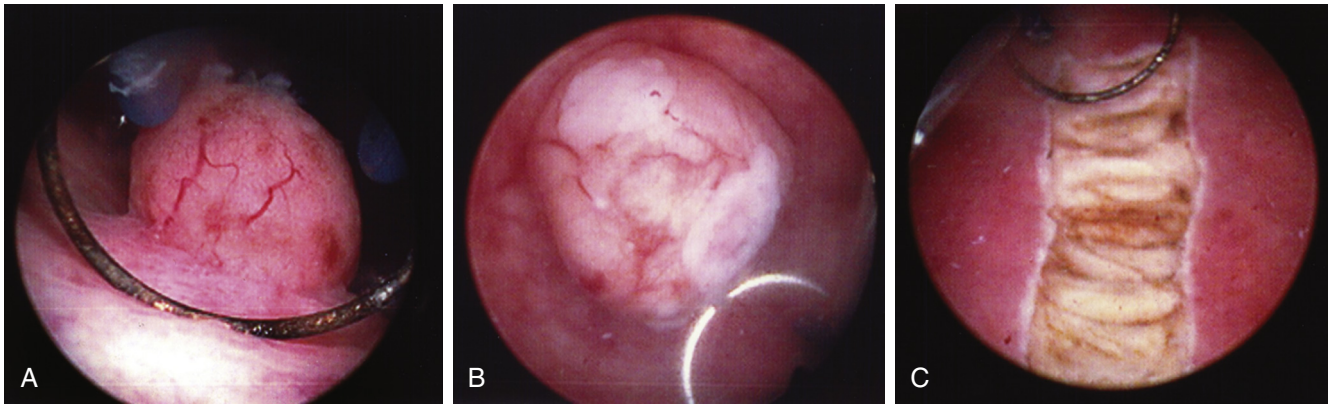

FIG. E2 A, Broad-based papillary lesion. **B,** Resection of lesion with loop electrocautery. **C,** Depth of resection to detrusor muscle. (From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.)

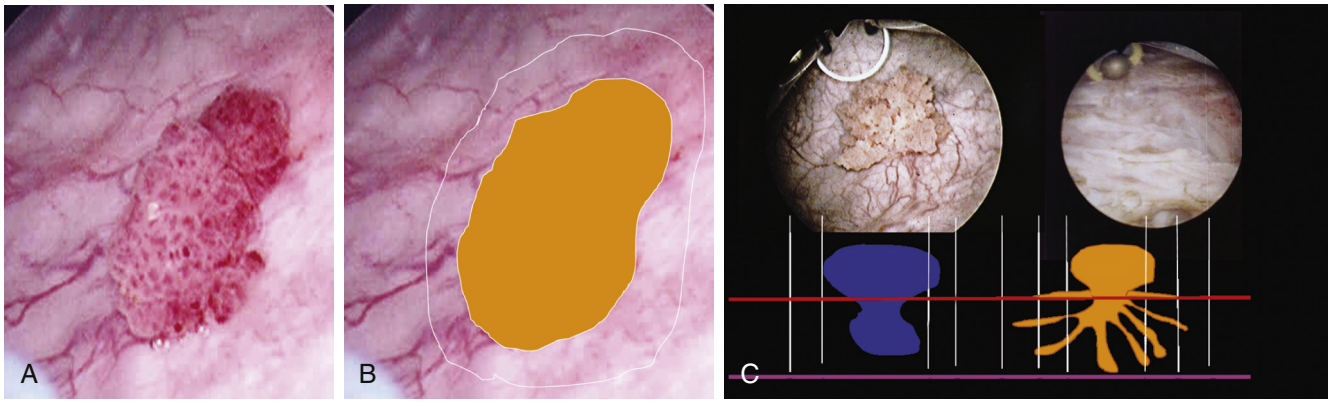

FIG. E3 A, Papillary bladder lesion. **B,** Visual boundary of tumor and margin of resection to optimize tumor destruction. **C,** Deep invasion of tumor in broad-based and tentacular pattern. (From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

The International Continence Society defines bladder pain syndrome, otherwise known as interstitial cystitis (IC), as a clinical syndrome consisting of suprapubic pain related to bladder filling and accompanied by other symptoms, such as increased daytime and nighttime frequency in the absence of proven infection or other obvious pathology. The American Urological Association defines interstitial cystitis/bladder pain syndrome (IC/BPS) as an unpleasant sensation perceived to be related to the urinary bladder that is associated with lower urinary tract symptoms >6 wk duration, in the absence of infection or other unidentifiable causes.

SYNONYMS

Interstitial cystitis
Interstitial cystitis/bladder pain syndrome (IC/BPS)
Painful bladder syndrome
Tic douloureux of bladder

ICD-10CM CODES

N30.1	Interstitial cystitis (chronic)
N30.9	Cystitis, unspecified
N30.10	Interstitial cystitis (chronic) without hematuria
N30.11	Interstitial cystitis (chronic) with hematuria

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 21 cases per 100,000 women and four cases per 100,000 men annually

PREVALENCE:

- 197 per 100,000 women and 41 per 100,000 men in the U.S.
- Because the disease is substantially underdiagnosed, it may actually affect one in five women and one in 20 men.
- More than 81% of women diagnosed with chronic pelvic pain and up to 84% of men initially diagnosed with chronic prostatitis actually have IC.
- More than 90% of patients diagnosed with overactive bladder who do not respond to anticholinergics are subsequently diagnosed with IC.

PREDOMINANT SEX AND AGE:

- White women constitute 95% of patients with IC
- Female:male ratio of 5 to 10:1
- Most prevalent in fourth and fifth decades of life

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Urinary urgency, frequency (>8 in daytime), nocturia (>2 at night), and suprapubic pain are the most common symptoms
- Suprapubic pain is worse with bladder filling or urinating and relieved after emptying
- Dyspareunia
- Symptoms lasting longer than 6 mo
- Intensity of symptoms waxes and wanes
- Insidious onset and worsens to the final stage within 5 to 15 yr
- Exercise, stress, sexual activity, ejaculation, certain foods with high potassium and acids (beer, spices, bananas, tomatoes, chocolate, strawberries, artificial sweeteners, oranges, cranberries, caffeine), menstruation, prolonged sitting, and activation of allergies exacerbate the symptoms
- Often associated with irritable bowel syndrome, migraine, endometriosis, skin sensitivities, multiple drug allergies, other allergies, vulvodynia, fibromyalgia, chronic fatigue syndrome, systemic lupus erythematosus, and mood disorders
- Dysphoric mood
- Lower abdominal tenderness
- Tender prostate in digital rectal examination
- Levator ani tenderness in female
- Tenderness of anterior vaginal wall/bladder neck in female

ETIOLOGY

Unknown. Fig. 1 illustrates a hypothesis for etiologic cascade of painful bladder syndrome/interstitial cystitis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Chronic pelvic pain
- Overactive bladder
- Recurrent urinary tract infection
- Endometriosis
- Pelvic adhesions
- Vulvar vestibulitis
- Vulvodynia
- Urethral pain syndrome
- Chronic nonbacterial prostatitis
- Frequent vaginitis
- Benign prostatic hyperplasia

WORKUP

- IC can be considered a diagnosis of exclusion when no known cause of painful bladder can be identified.
- There is no definite diagnostic test.

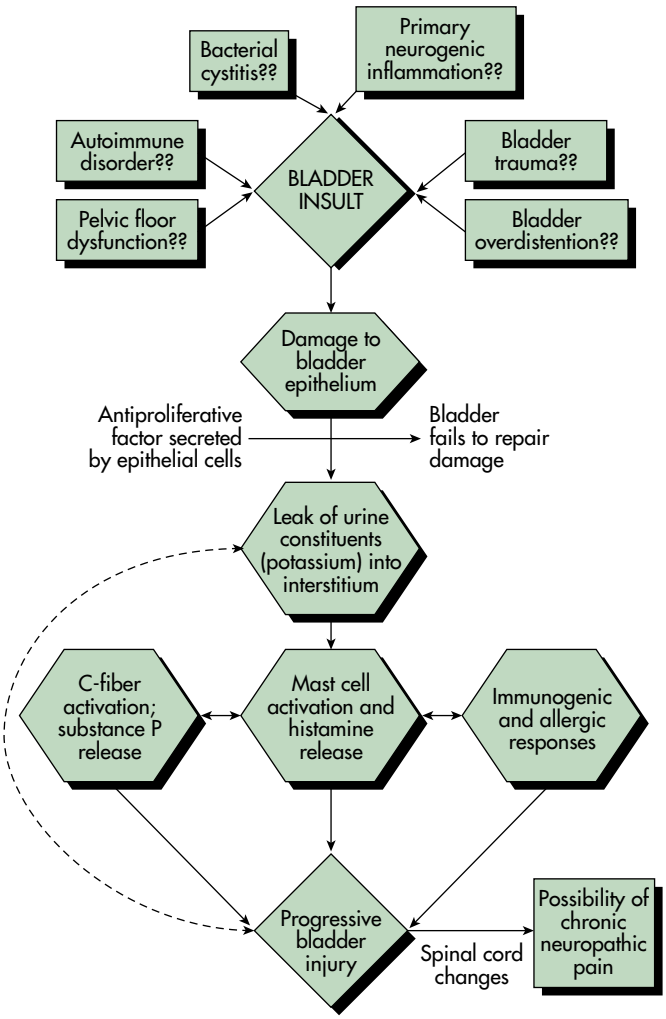

FIG. 1 Hypothesis for etiologic cascade of painful bladder syndrome/interstitial cystitis. (From Wein AJ: Painful bladder syndrome/interstitial cystitis and related disorders. In Wein AJ et al [eds]: *Campbell-Walsh urology*, ed 11, Philadelphia, 2007, Elsevier.)

- Validated questionnaires such as Pelvic Pain and Urgency/Frequency scale (PUF), O'Leary-Sant symptoms and problem index, and Wisconsin IC scale. PUF is the most commonly used.
- Voiding diary shows low-volume (<100 ml) and high-frequency voiding pattern.
- National Institute of Diabetes and Diseases of the Kidney diagnostic criteria misses 60% of IC patients and is not clinically used anymore.
- Anesthetic bladder challenge: With this test the symptoms dissipate on instillation of an anesthetic cocktail into the bladder.
- Cystoscopy and hydrodistention under general anesthesia may show terminal hematuria (Fig. E2), glomerulation, Hunner ulcers (Fig. E3), and small bladder capacity of less than 350 ml. Cystoscopy and/or urodynamic testing should be considered when the diagnosis is in doubt, but the tests are not necessary to confirm an IC/BPS diagnosis in uncomplicated cases.
- Bladder biopsy is not essential for diagnosis of IC.
- Parson potassium sensitivity test (PST).
- Urodynamics are unnecessary in diagnosis of IC.

LABORATORY TESTS

- Urine analysis and culture.
- Urine cytology should be performed if microscopic or gross hematuria is present, or with other risk factors such as smoking, age >40 yr, and other bladder cancer risk factors.
- Culture of sexually transmitted diseases if clinically indicated. Nonbacteriuric patients with pyuria should be screened for *Chlamydia.*
- Urine biomarkers (e.g., antiproliferative factor) are promising but not ready for clinical use.

IMAGING STUDIES

CT or ultrasound of abdomen and pelvis may be considered to rule out other pathology.

Rx TREATMENT

- There is no consensus for optimal management.
- There is no cure for this disease.

NONPHARMACOLOGIC THERAPY

- Avoidance of activities associated with flare-ups
- Avoidance of smoking
- Dietary restriction, avoiding common irritants (e.g., coffee, citrus fruits)
- Physical therapy
- Exercise
- Behavioral therapy
- Bladder retraining
- Biofeedback
- Warm sitz bath, ice, heating pad
- Thiele massage (transrectal and transvaginal manual therapy of pelvic floor muscle) in presence of pelvic floor muscle tenderness and spasm
- Hydrodistention only gives temporary relief, so it is not commonly used anymore

ACUTE AND CHRONIC Rx

- A course of empiric antibiotics if not tried yet. Long-term oral antibiotics are not recommended.
- Oral therapy is tried first.
- Pentosan polysulfate sodium (Elmiron) is the only FDA-approved and most effective oral therapy.
- Most treatment takes 3 to 6 mo before maximum benefit is seen.
- Adjunct oral therapy includes tricyclic antidepressants (amitriptyline), cimetidine, antihistaminics (hydroxyzine, montelukast), neuroleptics (gabapentin, topiramate), analgesics (NSAIDs, opioid analgesics), and occasionally antimuscarinics.
- Oral therapies can be used in combination.
- Antihistaminics are preferred for patients with an allergy history or those who show mast cells in bladder biopsy.
- Oral prednisone is used in presence of Hunner ulcers.
- Other drugs rarely used for IC are cyclosporin A, interleukin-10, imatinib, methotrexate, suplatast, misoprostol, and quercetin.
- Growth factor inhibitors, gene therapy, RDP 58, and vitamin B_3 analogue (BXL 628) may represent future therapies.
- Intravesical treatment is used when oral medications fail, for acute flare-ups, or before the oral medications take full effect.
- Dimethyl sulfoxide (DMSO), heparin, lidocaine, hyaluronic acid, capsaicin, botulinum toxin A, chondroitin sulfate, steroids, and Elmiron are drugs used for intravesical treatment.
- DMSO is the only FDA-approved intravesical treatment.
- DMSO is used less often now because of its side effects, specifically a garlic-like odor or taste on breath or skin that lasts 72 hr after treatment.
- Intravesical therapy typically involves mixture of heparin or Elmiron with lidocaine and sodium bicarbonate.
- Silver nitrate and clorpactin have fallen out of favor.

SURGERY

- Major surgical intervention is not the mainstay of treatment.
- Patients whose condition is extreme and who are miserable may consider surgery if medications fail.
- Sacral neuromodulation (InterStim) is the current preferred surgical intervention.
- Laser ablation, fulguration, or resection is offered when Hunner ulcers are seen in cystoscopy.
- Augmentation cystoplasty is not recommended.
- Cystourethrectomy with urinary diversion is rarely done.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Transcutaneous electric nerve stimulation
- Intravaginal electric nerve stimulation
- Acupuncture
- Urinary chelating agents such as Polycitra-K crystals, Urocit-K
- Prelief, an over-the-counter food additive
- Herbal remedies such as Algonot Plus, CystoProtek, Cysta-Q, aloe vera

DISPOSITION

Voiding diary and symptom questionnaire are helpful to monitor response to treatment.

REFERRAL

- Urologist
- Pain specialist
- Physical therapist

! PEARLS & CONSIDERATIONS

COMMENTS

- On average, these patients see five physicians and endure irritating voiding symptoms for 5 yr before the disease is identified.
- Besides symptom questionnaire and urine analysis, all other diagnostic tests are optional.
- PST is well tolerated.
- Negative cystoscopy does not rule out IC.

PREVENTION

Early identification and timely intervention improve patient outcome.

PATIENT & FAMILY EDUCATION

- IC support groups
- Interstitial Cystitis Association
- Interstitial Cystitis Network

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

French LM, Bhambore N: Interstitial cystitis/painful bladder syndrome, *Am Fam Phys* 83(10):1175-1181, 2011.

Randel A: American Urological Association approach to the diagnosis and management of IC/BPS, *Am Fam Physician* 86:97-103, 2012.

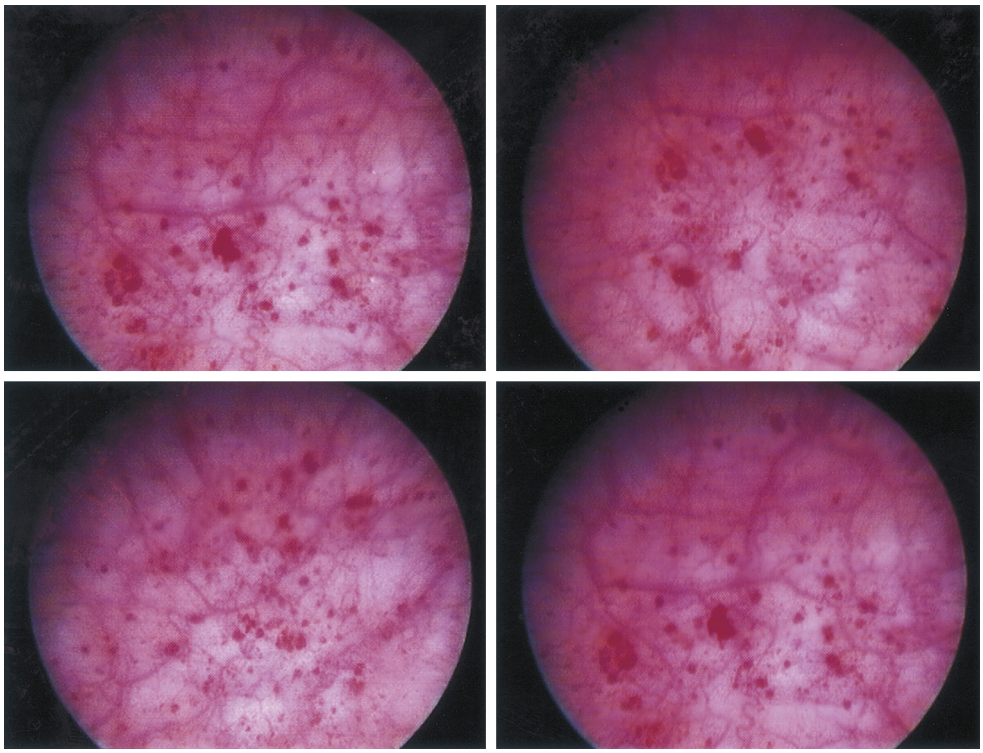

FIG. E2 Typical appearance of glomerulations after bladder distention in a patient with nonulcerative bladder pain syndrome. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

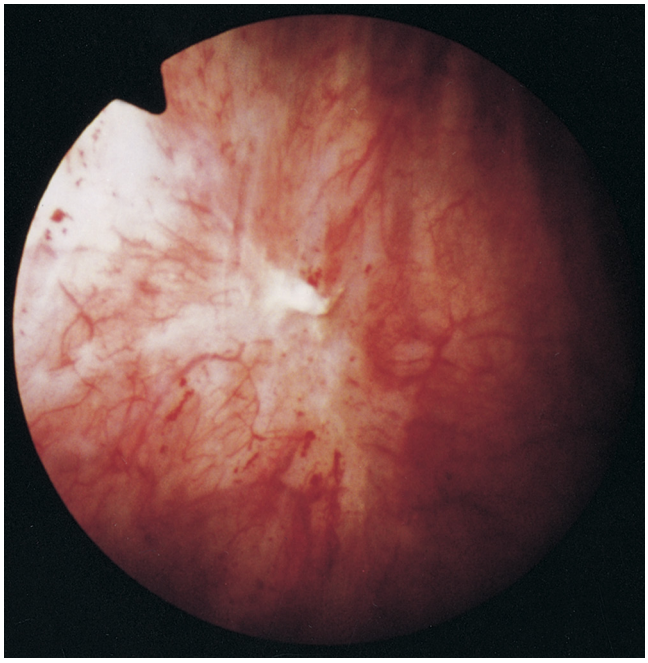

FIG. E3 Typical appearance of Hunner ulcer in a patient with bladder pain syndrome before bladder distention. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

Blastomycosis

BASIC INFORMATION

DEFINITION

Blastomycosis is a systemic pyogranulomatous disease caused by a dimorphic fungus, *Blastomyces dermatitidis.* Since 2013, another variant, *Blastomyces gilchristii*, has been described in the literature.

ICD-10CM CODES

B40.9	Blastomycosis, unspecified
B40.0	Acute pulmonary blastomycosis
B40.1	Chronic pulmonary blastomycosis
B40.2	Pulmonary blastomycosis, unspecified
B40.3	Cutaneous blastomycosis
B40.7	Disseminated blastomycosis
B40.89	Other forms of blastomycosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE & PREVALENCE:

- Most patients reside primarily in North America in the southeastern and south central U.S., especially those bordering the Mississippi and Ohio River valleys, the Midwestern U.S., and Canadian provinces bordering the Great Lakes.
- Point source outbreaks usually occur.
- Rare cases reported outside the U.S.

RISK FACTORS:

- Widely disseminated disease is most common in immunocompromised hosts, especially those with acquired immunodeficiency syndrome (AIDS).
- Initial infections result from inhalation of conidia into the lungs, although primary cutaneous blastomycosis has been reported after dog bites.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute infection: <50% symptomatic, median incubation 30 to 45 days. Symptoms are nonspecific: Mimic influenza or bacterial infection with abrupt onset of myalgias, arthralgias, chills, and fever; transient pleuritic pain, cough that is initially nonproductive. Resolution within 4 wk is usual.
- Chronic or recurrent infection: Indolent, progressive; includes pulmonary or extrapulmonary disease.

PULMONARY MANIFESTATIONS: Symptoms and signs of chronic pneumonia: Productive cough, hemoptysis, pleuritic chest pain, weight loss, low-grade pyrexia

- *B. gilchristii* infection has been linked to fatal acute respiratory distress syndrome in adults.

EXTRAPULMONARY MANIFESTATIONS:

- Cutaneous: Most common; may occur with or without pulmonary disease (Fig. E1). Two different lesions:
  1. *Verrucous:* Beginning as a small papulopustular lesion on exposed body areas that may develop into an eschar with peripheral microabscesses (Fig. E2).
  2. *Ulcerative:* Subcutaneous nodules (cold abscesses) and rarely cutaneous inoculation blastomycosis may occur.
- Bone and joint: 10% to 50% have osteolytic lesions (Fig. E3); affects long bones, vertebrae, and ribs; lesions may present with contiguous soft tissue abscess or draining sinus that spreads to a joint, resulting in pyarthrosis.
- Genitourinary: 10% to 30%; prostatic involvement is most common and may present as obstruction; epididymis and testes may also be affected.
- Central nervous system: 5% normal host; 40% AIDS patients; meningitis and abscess formation.

ETIOLOGY

B. dermatitidis exists in warm, moist soil that is rich in organic material. When these microfoci are disturbed, the aerosolized spores or conidia are inhaled into the lungs. Disease at other sites is a result of dissemination from the initial pulmonary infection; the latter may be acute or chronic.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

PULMONARY INFECTION:

- Bacterial pneumonia
- Histoplasmosis
- Coccidioidomycosis
- Tuberculosis
- Bronchogenic carcinoma

CUTANEOUS INFECTION:

- Bromoderma
- Pyoderma gangrenosum
- *Mycobacterium marinum* infection
- Squamous cell carcinoma
- Giant keratoacanthoma

WORKUP

- Physical examination and laboratory data
- Definitive diagnosis established by culture or by visualization of organisms by fungal stains
- Antibody tests lack sensitivity

LABORATORY TESTS

- Presumptive diagnosis can be made by visualizing the distinctive yeast forms in clinical specimens
- Culture: On Sabouraud medium or more enriched media
  1. Aspirated material from abscesses
  2. Skin scrapings
  3. Prostatic secretions (urine culture with prostatic massage)

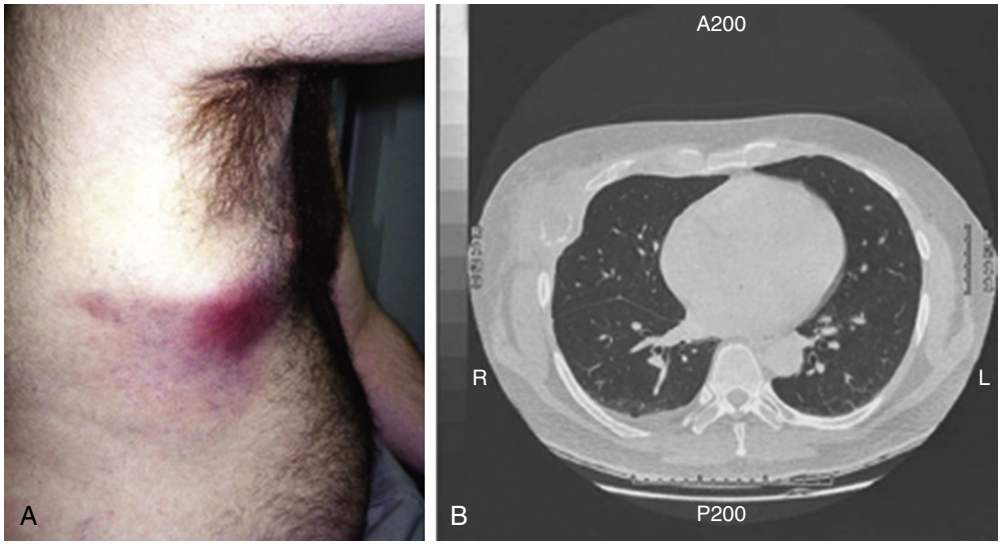

FIG. E1 A, Blastomycosis osteomyelitis of a rib and chest wall. **B,** Computed tomography scan appearance. Primary infection in the blood may spread to the skeleton. (From Firestein GS et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, WB Saunders, Elsevier.)

FIG. E2 The typical verrucous skin lesion of blastomycosis on the cheek. Note the circumscribed edges. (From Mandell GL et al: *Principles and practice of infectious diseases,* ed 6, Philadelphia, 2005, Churchill Livingstone.)

- Direct examination of specimens
  1. Wet preparation with 10% KOH (Fig. E4)
  2. Histopathology: Typically demonstrates pyogranulomas; yeast identification requires special stains
- A commercial test for *Blastomyces* antigen in specimens of urine, blood, and other fluids is available
- Serologic tests: A negative test result cannot exclude blastomycosis, and a positive titer should not be an indication to start treatment; therefore, current serologic assays serve no role

IMAGING STUDIES

In chronic disease, chest radiographic findings are nonspecific, but lobar or segmental alveolar infiltrates, especially of the upper lobes, are most common and may progress to cavitation.

Rx TREATMENT

- Treatment remains controversial for acute pulmonary blastomycosis. Generally, all immunocompromised patients and patients with moderate to severe pneumonia or disseminated infection require therapy.
- Because the acute form may be benign and self-limited, some patients may be closely observed.
- Resolution of chronic blastomycosis without antifungal therapy is uncommon, and untreated blastomycosis has been associated with mortality rates approaching 60%.

NON–CENTRAL NERVOUS SYSTEM BLASTOMYCOSIS

Moderately severe to severe:

- Liposomal amphotericin B (L-AmB) 3 to 5 mg/kg/day or L-AmB 0.7 to 1 mg/kg/day × 1 to 2 wk or until clinical response, then itraconazole oral solution 2.5 mg/kg po tid for 3 days, then once daily or bid for 6 to 12 mo

Mild to moderate:

- Itraconazole 200 mg PO tid for 3 days and then once or bid for 6 to 12 mo

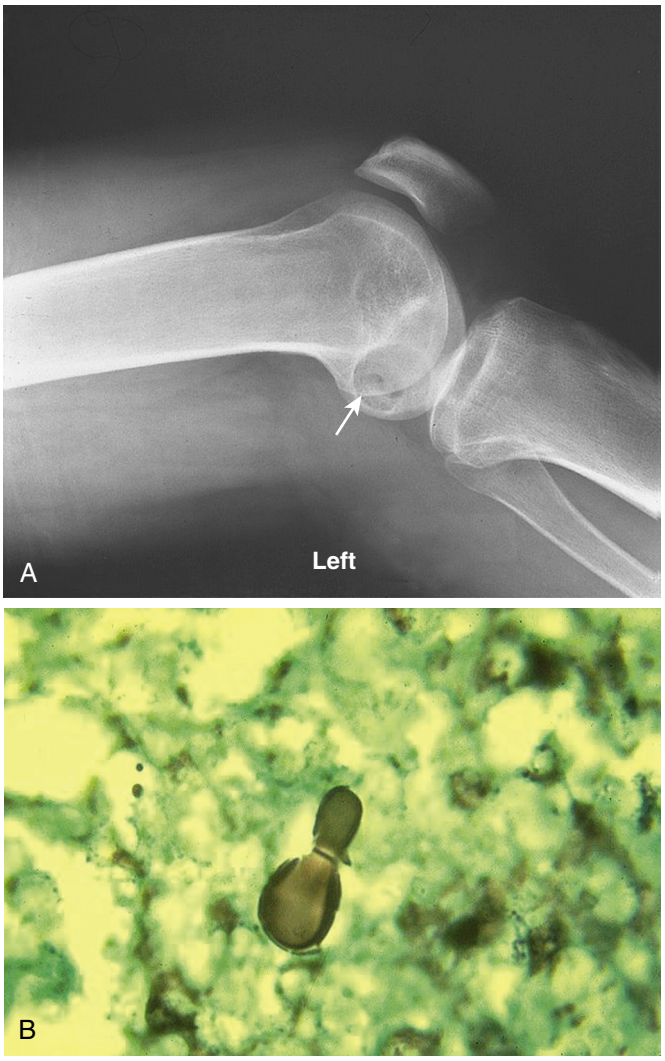

FIG. E3 Blastomycosis joint infection. A, Radiographs commonly show punched-out bone lesions *(arrow)*. **B,** Synovial histology shows epithelioid granulomas with budding yeast forms. (From Firestein GS et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, WB Saunders, Elsevier.)

Alternative regimens:

- Posaconazole delayed-release tabs 300 mg PO bid for 2 doses and then 300 mg PO daily; suspension 200 mg 4x daily and then 400 mg po bid after stabilization of disease or 300 mg IV over 90 min bid for 1 day and then 300 mg IV daily
- Voriconazole 4 mg/kg po bid
- Isavuconazonium sulfate 372 mg po/IV tid for 6 doses then 372 mg po/IV daily
- Fluconazole 400 to 800 mg PO once a day (less effective than Itraconazole)

CENTRAL NERVOUS SYSTEM BLASTOMYCOSIS

Liposomal amphotericin B at a dosage of 5 mg/kg/day over 4 to 6 wk, followed by either fluconazole 800 mg/day or voriconazole 6 mg/kg bid for two doses and then 4 mg/kg bid for at least 12 mo and until resolution of cerebrospinal fluid abnormalities

NOTE:

- Lifelong suppressive therapy with oral itraconazole 200 mg/day may be required, especially in immunocompromised individuals.

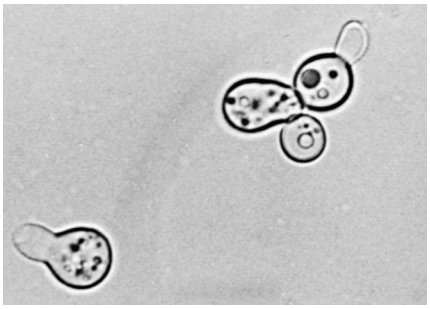

FIG. E4 Yeast cells of *Blastomyces dermatitidis* in wet smear (×1000). (From Mandell GL et al: *Principles and practice of infectious diseases,* ed 6, Philadelphia, 2005, Churchill Livingstone.)

- Serum itraconazole levels should be determined in all patients after they have received treatment with this agent for 2 wk.
- Surgery may be indicated for drainage of large abscesses.

DISPOSITION

- Before antifungal therapy, the disease had a progressive course with eventual extrapulmonary disease and a mortality rate approaching 60%.
- Relapse rate for patients treated with AmB is 5%; relapse is more common in AIDS patients.

PEARLS & CONSIDERATIONS

- *Blastomyces dermatitidis* may mimic other diseases.
- Colonization does not occur as with *Candida* and *Aspergillus* species.

AUTHOR: **Sajeev Handa, MD, SFHM**

SUGGESTED READINGS

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Dalcin D et al: *Blastomyces gilchristii* as cause of fatal acute respiratory distress syndrome, *Emerg Infect Dis* 22(2):306-308, 2016, https://doi.org/10.3201/eid2202.151183.

Roy M et al: A large community outbreak of blastomycosis in Wisconsin with geographic and ethnic clustering, *Clin Infec Dis* 57:655-662, 2013.

BASIC INFORMATION

DEFINITION

Blepharitis is a chronic inflammation of the eyelid margins that is often refractory to treatment with infectious and noninfectious etiologies.

SYNONYMS

Eyelid infection or inflammation
Eczema of the eyelids
Dermatoblepharitis
Angular blepharitis

ICD-10CM CODES

H01.009	Unspecified blepharitis unspecified eye, unspecified eyelid
H01.019	Ulcerative blepharitis unspecified eye, unspecified eyelid
H01.029	Squamous blepharitis unspecified eye, unspecified eyelid

EPIDEMIOLOGY & DEMOGRAPHICS

- Common in children, particularly those with atopic dermatitis and eczema.
- Adults with seborrhea involving the eyelids.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Common symptoms: Red eyes, burning sensation, excessive tearing, blurred vision, pruritic eyelids.
- Chronically infected lids are usually diffusely erythematous with collarettes (fibrin exudate) at the base of the lashes.
- Lid margins thicken over time, with associated loss of eyelashes (madarosis), misdirected growth of lashes (trichiasis), and overflow or inspissation of the meibomian glands (Fig. E1).
- Associated conjunctivitis with erythema and edema but no discharge.
- Chalazion: Chronic sterile inflammation of an oil gland of the eyelid.
- Superficial punctate erosions of the inferior corneal epithelium are common.
- More severe findings, such as corneal pannus, ulcerative keratitis, or lid ectropion, are less common.

ETIOLOGY

Multiple: Bacterial and nonbacterial causes:

- Staphylococcal infection most common but streptococcal, Moraxella, and other bacterial infections; viral infections (e.g., herpes simplex, herpes zoster, *Molluscum contagiosum*); and a number of ecoparasites (Fig. E2), including pediculosis, may cause blepharitis
- Seborrheic dermatitis
- Rosacea
- Dry eye (keratoconjunctivitis sicca): Decrease in tear volume
- Meibomian gland dysfunction
- Contact lens intolerance
- Two categories of blepharitis (Table E1):
  1. Anterior blepharitis, most often associated with staphylococcal infection
  2. Posterior blepharitis, associated with meibomian gland dysfunction and seborrheic dermatitis or rosacea

NOTE: Blepharitis patients have normal skin microflora in greater amounts (mostly *S. epidermidis* and *Propionibacterium acnes*). (*S. aureus* and *S. epidermidis* can be cultured in 10% to 35% and 90% to 95% of healthy persons, respectively.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Keratoconjunctivitis sicca
- Eyelid malignancies

FIG. E1 Chronic posterior blepharitis. A, Capping of meibomian gland orifices by oil globules; **B,** hyperemic, telangiectatic lid margin; **C,** expressed toothpaste-like material; **D,** froth on the eyelid margin. (From Bowling B: *Kanski's clinical ophthalmology, a systemic approach*, ed 8, Philadelphia, 2016, Elsevier. Fig C, Courtesy of J Silbert, from Silbert J: *Anterior segment complications of contact lens wear*, Boston, 1999, Butterworth-Heinemann.)

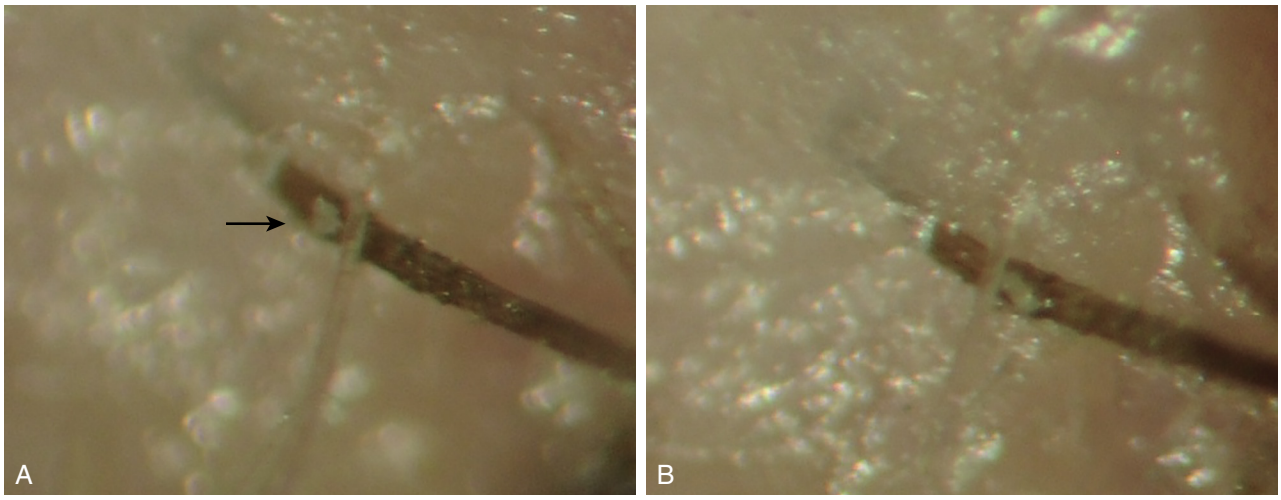

FIG. E2 ***Demodex*** **mite. A,** Mite visible at eyelash base as a whitish lesion *(arrow)* after lash manipulation following clearance of collarette; **B,** photograph taken 2 seconds later showing rapid migration. (From Bowling B: *Kanski's clinical ophthalmology, a systemic approach,* ed 8, Philadelphia, 2016, Elsevier.)

TABLE E1 Summary of Characteristics of Chronic Blepharitis

Feature	Anterior Blepharitis	Staphylococcal	Seborrhoeic	Posterior Blepharitis
Lashes	Deposit	Hard	Soft	
	Loss	++	+	
	Distorted or trichiasis	++	+	
Lid margin	Ulceration	+		
	Notching	+		++
Cyst	Hordeolum	++		
	Meibomian			++
Conjunctiva	Phlyctenule	+		
Tear film	Foaming			++
	Dry eye	+	+	++
Cornea	Punctate erosions	+	+	++
	Vascularization	+	+	++
	Infiltrates	+	+	++
Commonly associated skin disease		Atopic dermatitis	Seborrhoeic dermatitis	Acne rosacea

From Bowling B: *Kanski's clinical ophthalmology, a systemic approach*, ed 8, Philadelphia, 2016, Elsevier.

- Herpes simplex blepharitis
- Molluscum contagiosum
- Phthiriasis palpebrarum
- *Phthirus pubis* (pubic lice)
- *Demodex folliculorum* (transparent mites)
- Allergic blepharitis

WORKUP

Scrapings of the eyelids to show polymorphonuclear leukocytes and gram-positive cocci

LABORATORY TESTS

Eyelid cultures and antibiotic sensitivity testing (usually not done unless patient fails to respond to initial treatment regimen)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Alkaline soaps may be beneficial; alcohol and some detergents remove surface lipids and microflora.
- Hot compresses applied to closed lids for 5 to 10 min: Heat loosens debris from lid margins and increases meibomian gland fluidity.
- Firm massage of the lid margins to enhance the flow of secretions from glands, followed by cleansing of the lids with cotton-tipped applicators dipped in a 50:50 mixture of baby shampoo and water.
- Lashes and lid margins scrubbed vigorously while the eyelids are closed, followed by thorough rinsing.
- Following local massage and cleansing, the mainstay of treatment is application of topical antibiotic ointment to the eyelid margins.
  1. Most effective topical antibiotics include bacitracin, erythromycin or 1% azithromycin solution, aminoglycoside and fluoroquinolone ophthalmic ointments.
  2. Ointment is applied 1 to 4 times daily, depending on the severity, for 1 to 2 wk, followed by once daily, at bedtime, for another 4 to 8 wk until all signs of inflammation have disappeared.
- Oral antibiotics: Long-term use of doxycycline or tetracycline in a tapering dose may be helpful in severe cases for patients older than 12 yr of age.
- Topical glucocorticoids: Short-term use in acute exacerbations of blepharitis.
- For patients with rosacea: Tetracycline 250 mg orally 4 times daily or doxycycline 100 mg orally bid along with local treatment for several months.
- Recalcitrant cases with antibiotic resistance:
  1. Vancomycin eye drops 1%
  2. Ciprofloxacin or ofloxacin eye drops

CHRONIC Rx

- By definition, this is a chronic condition for which there is frequently no cure.
- Some newer agents being evaluated are topical cyclosporine 0.05% eye drops, thermal pulsation systems to break up material in meibomian glands, topical metronidazole and topical tacrolimus, and tear lipid substitutes.

DISPOSITION

This condition may be refractory to treatment.

REFERRAL

To an ophthalmologist if patient fails to respond to local therapy

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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Pflugfelder SC, Karpecki PM, Perez VL: Treatment of blepharitis: most recent clinical trials, *Ocul Surf* 12:273-284, 2014.

BASIC INFORMATION

DEFINITION

Blepharospasm (BSP) is a movement disorder characterized by hyperactivity of the orbicularis oculi and other muscles around the eyes.

SYNONYMS

BSP
Orbicularis oculi spasms
Focal dystonia

ICD 10-CM CODE
G24.5 Blepharospasm

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Not applicable.
PEAK INCIDENCE: Not applicable.
PREVALENCE: Prevalence is between 20 and 133 cases per million depending on geographic area.
PREDOMINANT SEX AND AGE: Female preference, peak age at onset between the fifth and seventh decade.
GENETICS: Predominantly a sporadic disorder, however 25% of patients have one or more family members affected by dystonia. No specific genetic association specific to BSP is known.
RISK FACTORS: Risk of primary BSP increases with diseases of the anterior segment of the eye and preceding head trauma. Risk of secondary BSP increases with focal lesions in multiple brain regions, comorbid Parkinson disease, tardive dyskinesia, or conditions associated with eyelid weakness such as facial palsy and myasthenia.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Motor manifestations include orbicularis oculi (OO) spasms (Fig. E1), apraxia of eyelid opening, increased blinking rate, and dystonia at other body sites (most commonly oromandibular and cervical regions).
- OO spasms are stereotyped, bilateral, and synchronous. Spasms may be brief or sustained, and may induce narrowing or closure of the eyelids.
- Apraxia of eyelid opening is transient failure to voluntarily reopen the eyes without an apparent spasm of the OO muscle and despite sustained frontalis muscle contraction.
- Nonmotor manifestations include the presence of a so-called "sensory trick" (certain actions involving gentle stimulation to the face alleviate symptoms and allow patients with BSP to keep eyes open, e.g., light touch to certain areas of the face, wearing tinted lenses, talking, singing, or chewing/eating); other sensory symptoms (burning sensation and grittiness in the eye, dry eye, and photophobia); psychiatric disturbances (depression and obsessive/compulsive symptoms); sleep abnormalities, and cognitive dysfunction.

ETIOLOGY

- Primary BSP is predominantly sporadic, although up to 25% of patients have one or more family members with dystonia. Several genes are associated with adult-onset dystonia, though none have been associated with pure BSP.
- Secondary BSP is associated with several different focal lesions of the brain (thalamus, basal ganglia, lower brain stem, cerebellum, midbrain, and cortex) or may be associated with other movement disorders including PD, TD, facial palsy, or myasthenia.
- A proposed mechanism involves loss of striatal dopamine leading to reduced tonic inhibition of trigeminal reflex circuits combined with weakening of lid closure by the OO muscle. This leads to an adaptive increase in activity of trigeminal sensory-motor blink circuits.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pure apraxia of eyelid opening, a common feature of lesions of the nondominant parietal lobe (among other regions)
- Bell palsy (unilateral facial weakness involving both the upper and lower face due to lower-motor-neuron facial nerve palsy; etiology may be viral, inflammatory, autoimmune, or ischemic)
- Eyelid myokymia (typically unilateral, spontaneous, fine fascicular contractions of the lower orbicularis oculi without atrophy or weakness)
- Hemifacial spasm (brief clonic movements of OO typically spreading to other facial regions, often associated with chronic irritation of the facial nerve or nucleus)
- Dry eye, or conjunctivitis/keratitis with frequent blinking
- Myasthenia gravis with eyelid ptosis

WORKUP

BSP is a clinical diagnosis that relies on thorough neuropsychiatric and ophthalmologic evaluation.

LABORATORY TESTS

No tests are diagnostic. However, certain findings on electromyography (evaluation of blink reflex excitability recovery curve) present in dystonia and BSP, but not in psychogenic BSP, may reinforce clinical suspicion.

IMAGING STUDIES

Standard brain imaging has not consistently demonstrated clinical utility for BSP.

TREATMENT

ACUTE GENERAL Rx

- Botulinum neurotoxin type A is first-line treatment for BSP. Side effects such as transient ptosis, blurred vision, and diplopia are uncommon and tend to improve spontaneously within weeks.
- Modest improvement has come with anticholinergics (e.g., trihexyphenidyl), benzodiazepines, baclofen, and tetrabenazine. However, side effects may be too problematic.

CHRONIC Rx

Long-term efficacy of Botulinum neurotoxin type A treatment in BSP has been documented. However, this has not led to significant improvements upon quality of life, indicating non-motor manifestations of BSP require individual attention. More literature is needed in this regard.

REFERRAL

Movement disorder specialist consultation is common.

AUTHOR: **Jordan Anderson, MD**

FIG. E1 Essential blepharospasm. (From Bowling B: *Kanski's clinical ophthalmology, a systemic approach*, ed 8, 2016, Philadelphia, Elsevier.)

SUGGESTED READINGS

Defazio G et al: Development and validation of a clinical guideline for diagnosing blepharospasm, *Neurology* 81(3):236-240, 2013.

Defazio G et al: Blepharospasm 40 years later, *Mov Disord* 32(4):498-509, 2017.

Valls-Sole J, Defazio G: Blepharospasm: update on epidemiology, clinical aspects, and pathophysiology, *Front Neurol* 7:45, 2016.

Body Dysmorphic Disorder (PTG)

BASIC INFORMATION

DEFINITION

Body dysmorphic disorder (BDD) is classified as an obsessive-compulsive and related disorder. It is characterized by preoccupation with one or more perceived defects or flaws in physical appearance that are not observable or appear only slight to others, as well as repetitive behaviors (e.g., excessive grooming, mirror checking, skin picking, reassurance seeking) in response to the appearance concerns. The preoccupations cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (usually both). The preoccupations are not better explained by concerns with body fat or weight in a person whose symptoms meet diagnostic criteria for an eating disorder.

SYNONYMS

Dysmorphophobia
BDD

ICD-10CM CODES
F45.22 Body dysmorphic disorder
DSM-5 CODE
300.50

EPIDEMIOLOGY & DEMOGRAPHICS

- Affects 1.7% to 2.9% of the general population (in nationwide epidemiologic studies)
- Prevalence among general cosmetic surgery patients is 13% to 15%
- Weighted prevalence in rhinoplasty surgery settings is 20.1%
- Weighted prevalence among dermatology outpatients is 11.3%
- Slightly higher prevalence among females (but not in cosmetic surgery or dermatology settings)
- Onset most commonly in early adolescence (two thirds have onset before age 18)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Excessive preoccupation (obsession) with one or more perceived defects in appearance that are not observable or appear only slight to others. Patients believe they look abnormal, ugly, unattractive, or deformed, whereas in reality they look normal. Any part of the body may be a focus of concern; skin (e.g., perceived acne or scarring), hair (e.g., perceived thinning or excessive body or facial hair), and nose (e.g., size or shape) concerns are most common. Muscle dysmorphia is a form of BDD that occurs primarily in men and focuses on excessive concern that one's body build is too small or is insufficiently muscular. Most patients are preoccupied with multiple body areas.
- The body areas with which the patient is concerned appear physically normal; if a physical defect is present, it is slight, and the patient's reaction to it is excessive.
- Most patients have poor insight (i.e., are mostly convinced) or absent insight (i.e., delusional beliefs; are completely convinced) regarding the accuracy of their beliefs about the appearance of the perceived defects.
- At some point during the course of the disorder, all patients engage in repetitive behaviors such as frequent mirror checking, excessive grooming, skin picking to try to fix perceived skin flaws, reassurance seeking, and repeatedly measuring or feeling the perceived defect. The intent of these behaviors is to check, try to improve, or gain reassurance about the appearance of the perceived flaws. Nearly all patients attempt to camouflage or hide the perceived defects—e.g., with makeup, a hat, hair, or body position.
- Nearly all experience impairment in psychosocial functioning and quality of life as a result of their appearance concerns; impairment is usually substantial.
- Suicidal ideation, suicide attempts, and completed suicide appear common.
- Commonly co-occurring mental disorders are major depressive disorder, substance use disorders (including abuse of anabolic androgenic steroids in muscle dysmorphia), social anxiety disorder, obsessive-compulsive disorder (OCD), and personality disorder.

ETIOLOGY

Likely multifactorial, with both genetic and environmental risk factors (e.g., teasing). Has shared genetic vulnerability with obsessive-compulsive disorder plus BDD-specific genetic influences. Neuropsychological and fMRI studies indicate abnormalities in visual processing consisting of excessive focus on details rather than on larger global and configural elements of visual stimuli (with some similarities to anorexia nervosa). Information processing deficits and biases also characterize BDD, which may also play a role in the disorder's development and/or maintenance.

DIAGNOSIS

Psychiatric interview: Ask:

- Are you very worried about your appearance in any way? *OR:* Are you unhappy with how you look?
- Does this concern with your appearance preoccupy you? If you add up all the time you spend each day thinking about your appearance, how much time would you estimate it takes (at least an hour a day)?
- How much distress does this concern cause you?
- What effect does this concern have on your life?
- Is there anything you feel an urge to do over and over again in response to your appearance concerns? (Give examples, such as mirror checking, comparing with others, skin picking to remove perceived skin flaws)
- Determine that the perceived appearance defects are actually nonexistent or only slight.

DIFFERENTIAL DIAGNOSIS

- Often undiagnosed because of patient's reluctance to divulge symptoms due to shame and fear of being misunderstood (e.g., considered vain)
- OCD
- Eating disorder
- Social anxiety disorder
- Major depressive disorder

WORKUP

Clinical evaluation focused on BDD symptoms and associated impairment in functioning.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive behavioral therapy (CBT) with a focus on cognitive restructuring, exposure, perceptual retraining, and response (ritual) prevention; CBT must be specifically tailored to BDD's unique symptoms.
- Do not try to talk patients out of their concern; it is ineffective.
- Avoid cosmetic procedures; a majority of patients with BDD receive them, but such treatments do not appear effective for BDD. Dissatisfied patients may sue or even become violent toward the treating clinician.

CHRONIC Rx

- Serotonin reuptake inhibitors (SRIs) are medication of choice both acutely and chronically; high doses (similar to those for OCD) often needed
- Other agents (e.g., neuroleptics, tricyclic antidepressants other than clomipramine) do not appear as beneficial, although limited evidence suggests that atypical neuroleptics and buspirone may be helpful as SRI augmentation agents
- CBT tailored specifically to BDD is recommended, with an SRI if BDD symptoms are moderate to severe, the patient is suicidal because of BDD symptoms, or comorbidity is present that may benefit from an SRI
- Support groups if available
- More intensive BDD-focused treatment (e.g., intensive outpatient, residential treatment) if outpatient care is insufficient

DISPOSITION

- Untreated BDD tends to be chronic and can lead to social isolation; school dropout; loss of employment; major depression; abuse of drugs or alcohol; unnecessary surgery, dermatologic treatment, or other cosmetic treatment; and suicide.
- With correct diagnosis and treatment, a majority improve.

PEARLS & CONSIDERATIONS

- In clinical settings, approximately three quarters have lifetime co-occurring major depressive disorder; suicidal ideation is common.

- Reassurance that the patient looks normal is rarely helpful.
- Patients often have an unrealistic expectation of improvement with plastic surgery, dermatologic treatment, and other cosmetic procedures; these treatments do not appear to be effective.
- All patients should be screened and monitored for suicidality.

PATIENT/FAMILY EDUCATION

- Family support and encouragement of appropriate treatment is important.
- Phillips KA: *Understanding body dysmorphic disorder: an essential guide.* Oxford University Press, 2009.
- www.KatharinePhillipsMD.com
- https://bdd.iocdf.org/

RELATED CONTENT

Body Dysmorphic Disorder (Patient Information)
Obsessive-Compulsive Disorder (Related Key Topic)

AUTHOR: **Katharine A. Phillips, MD**

SUGGESTED READINGS

Ishii LE et al: Clinical practice guideline: improving nasal form and function after rhinoplasty executive summary, *Otolaryngol Head Neck Surg* 156:205-219, 2017. supplement: 156(2S):S1-S30, 2017.

National Institute for Health and Clinical Excellence (National Health Service) Obsessive Compulsive Disorder (OCD) and body dysmorphic disorder (BDD) Practice Guideline (website) www.nice.org.uk/CG31.

Phillips KA: Body dysmorphic disorder: common, severe, and in need of treatment research (Invited Editorial), *Psychother Psychosom* 83:325-329, 2014.

Phillips KA, editor: *Body dysmorphic disorder: advances in research and clinical practice*, New York, 2017, Oxford University Press.

Wilhelm S et al: *Cognitive-behavioral therapy for body dysmorphic disorder*, New York, 2013, Guilford Press.

Bone Tumor, Primary Malignant (ALG) (PTG)

BASIC INFORMATION

DEFINITION

Primary malignant bone tumors are invasive and anaplastic and have the ability to metastasize. These neoplasms can arise from the marrow (myeloma), but may also develop from bone, cartilage, fat, and fibrous tissues (Fig. E1). Leukemia and lymphoma are excluded from this discussion.

FIBROSARCOMA AND LIPOSARCOMA: They are extremely rare and similar to tumors arising in soft tissue.

OSTEOSARCOMA: A rare primary malignant tumor of bone characterized by malignant tumor cells that produce osteoid or bone. Several variants have been described: Parosteal sarcoma, periosteal sarcoma, multicentric, and telangiectatic forms.

CHONDROSARCOMA: A malignant cartilage tumor that may develop primarily or secondarily from transformation of a benign osteocartilaginous exostosis or enchondroma.

EWING SARCOMA: A malignant tumor of the bone or soft tissues characterized by the presence of small, round, blue cells on immunohistochemical evaluation.

MULTIPLE MYELOMA: A neoplastic proliferation of plasma cells in the bone marrow.

SYNONYMS

Multiple myeloma:
- Plasma cell myeloma
- Plasmacytoma

ICD-10CM CODES

C41.9	Malignant neoplasm of bone and articular cartilage, unspecified
C40.00	Malignant neoplasm of scapula and long bones of unspecified upper limb
C40.01	Malignant neoplasm of scapula and long bones of right upper limb
C40.02	Malignant neoplasm of scapula and long bones of left upper limb
C40.10	Malignant neoplasm of short bones of unspecified upper limb
C40.11	Malignant neoplasm of short bones of right upper limb
C40.12	Malignant neoplasm of short bones of left upper limb
C40.20	Malignant neoplasm of long bones of unspecified lower limb
C40.21	Malignant neoplasm of long bones of right lower limb
C40.22	Malignant neoplasm of long bones of left lower limb
C40.30	Malignant neoplasm of short bones of unspecified lower limb
C40.31	Malignant neoplasm of short bones of right lower limb
C40.32	Malignant neoplasm of short bones of left lower limb
C40.80	Malignant neoplasm of overlapping sites of bone and articular cartilage of unspecified limb
C40.81	Malignant neoplasm of overlapping sites of bone and articular cartilage of right limb
C40.82	Malignant neoplasm of overlapping sites of bone and articular cartilage of left limb
C40.90	Malignant neoplasm of unspecified bones and articular cartilage of unspecified limb
C40.91	Malignant neoplasm of unspecified bones and articular cartilage of right limb
C40.92	Malignant neoplasm of unspecified bones and articular cartilage of left limb
C41.0	Malignant neoplasm of bones of skull and face
C41.4	Malignant neoplasm of pelvic bones, sacrum and coccyx
C41.9	Malignant neoplasm of bone and articular cartilage, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

Table E1 summarizes incidence, in decreasing order, of lesions that may present as a primary bone tumor.

MULTIPLE MYELOMA:
- The most common tumor in bone
- Age at onset: Usually >40 yr
- Male/female ratio of 2:1

OSTEOGENIC SARCOMA:
- Average age at onset: 10 to 20 yr
- Males afflicted more often than females
- Parosteal sarcoma in older patients

CHONDROSARCOMA:
- Age at onset: 40 to 60 yr
- Male/female ratio of 2:1

EWING SARCOMA: Age at onset: 10 to 15 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

MULTIPLE MYELOMA:
- May present as a systemic process or, less commonly, as a "solitary" extramedullary lesion
- Early manifestations: Anorexia, weight loss, and bone pain; majority of cases present initially with back pain that often leads to the detection of a destructive skeletal lesion
- Other organ systems eventually become involved, resulting in more bone pain, anemia, renal insufficiency, and/or bacterial infections, usually as a result of the dysproteinemia typical of this disorder
- Possible secondary amyloidosis, leading to cardiac failure or nephrotic syndrome

OSTEOSARCOMA:
- Most originating in the metaphysis
- 50% to 60% around the knee
- Possible pain and swelling, but otherwise healthy patient
- Osteosarcoma in conjunction with Paget disease, manifested primarily as a sudden increase in bone pain

CHONDROSARCOMA:
- Tumor most commonly involving the pelvis, upper femur, and shoulder girdle
- Painful swelling

EWING SARCOMA:
- Painful soft tissue mass often present
- Possibly increased local heat
- Midshaft of a long bone usually affected (in contrast to other tumors)
- Weight loss, fever, and lethargy

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Osteomyelitis
- Metastatic bone disease

LABORATORY TESTS

- Slightly elevated alkaline phosphatase in osteosarcoma
- In Ewing sarcoma: Reflective of systemic reaction; includes anemia, an increase in white blood cell count, and an elevated sedimentation rate
- In multiple myeloma:
  1. Bence Jones protein in the urine
  2. Anemia and elevated erythrocyte sedimentation rate
  3. Characteristic dysproteinemia on serum protein electrophoresis showing a monoclonal spike
  4. Elevated quantitative immunoglobulins, beta-2 microglobulin, and elevated kappa:lambda ratio upon serum-free light chain assay
  5. Rouleaux formation in the peripheral blood smear

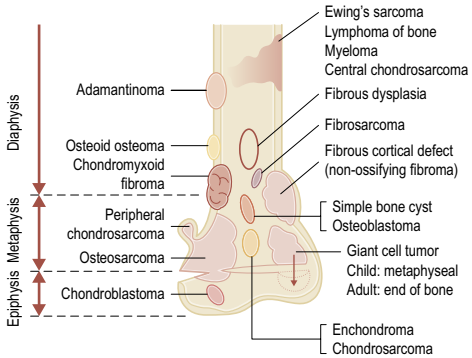

FIG. E1 Site of origin of bone tumors. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.)

TABLE E1 Incidence, in Decreasing Order, of Lesions That May Present as a Primary Bone Tumor

Lesion	Incidence of All Tumors (%)†,‡
Osteosarcoma	17
Chondrosarcoma	11
Enchondroma*	6
Fibrous dysplasia*	6
Giant cell tumor	6
Nonossifying fibroma/fibrous cortical defect*	5
Ewing sarcoma	5
Malignant fibrous histiocytoma/fibrosarcoma	5
Osteochondroma*	4
Aneurysmal bone cyst	4
Metastasis	4
Osteomyelitis	4
Solitary bone cyst	3
Osteoid osteoma	3
Langerhans cell histiocytosis (eosinophilic granuloma)	3
Chondroblastoma	2
Others	12

*Lesions are often asymptomatic and therefore much more frequent than the table suggests.
†Benign tumors and tumor-like lesions in general are underreported in these frequency distributions.
‡Data are based on 6873 tumors on file in the Netherlands Committee on Bone Tumors.
From Pope TL et al: *Musculoskeletal imaging*, ed 2, Philadelphia, 2015, Elsevier.

TABLE E2 Systemic Approach in Diagnosing Osseous Tumors or Tumor-Like Lesions

1. Categorize the radiograph (normal, variant, tumor-like lesion, tumor).
2. Determine the prevalence of lesions in relation to the age of the patient.
3. Determine the prevalence of lesions in the affected bone.
4. Is the lesion solitary, or are there multiple lesions?
5. Determine the prevalence of osseous lesions in the affected part of the bone.
6. Analyze the radiograph in detail.
7. Analyze additional information (MR, CT, clinical and laboratory data, and so on).
8. Perform a biopsy, if needed, based on the comprehensive imaging findings.

From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, Elsevier.

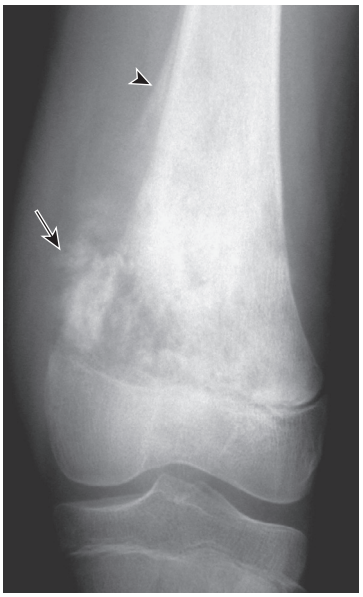

FIG. E2 Conventional central osteosarcoma. AP radiograph of the distal femur showing a classic osteosarcoma with mixed lytic and sclerotic areas, tumor bone formation in the extraosseous mass *(arrow)*, and a proximal Codman's triangle *(arrowhead)*. (From Adam A et al: *Grainger & Allison's diagnostic radiology,* ed 5, Philadelphia, 2008, Churchill Livingstone.)

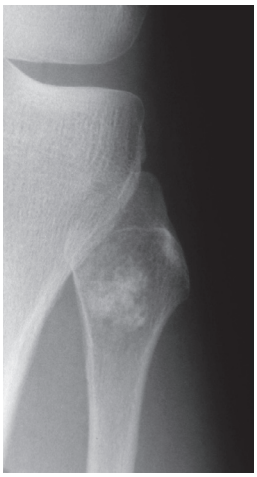

FIG. E3 Chondrosarcoma. AP XR showing a mineralized lesion of the fibula due to low-grade chondrosarcoma. The lesion cannot be radiologically differentiated from a chondroma. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.)

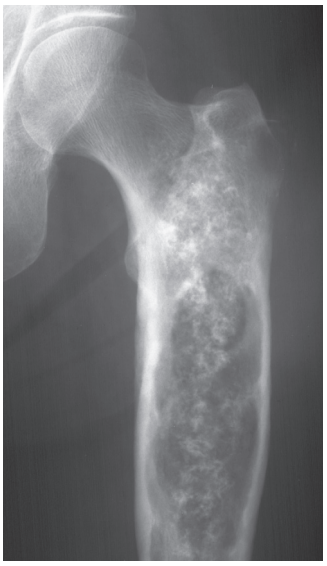

FIG. E4 AP radiograph of the femur showing an extensive central chondrosarcoma with typical chondroid matrix, cortical expansion and thickening with endosteal scalloping. (From Grant, LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.)

6. Often presence of hypercalcemia
7. Elevated serum lactate dehydrogenase (LDH)

IMAGING STUDIES

- Table E2 summarizes a systemic approach in diagnosing osseous tumors or tumor-like lesions.
- Classic osteogenic sarcoma penetrates the cortex early in many cases.
  1. A blastic (dense), lytic (lucent), or mixed response may be seen in the affected bone (Fig. E2).
  2. An aggressive perpendicular sunburst pattern may be present as a result of periosteal reaction, and peripheral Codman triangles are often noted.
  3. Margins of the tumor are poorly defined.
- Speckled calcifications in a destructive radiolucent lesion are usually suggestive of chondrosarcoma (Figs. E3, E4, and E5).
- Ewing sarcoma is characterized radiographically by mottled, irregular destructive changes with periosteal new bone formation. The latter may be multilayered, producing the typical "onion skin" appearance.
- Typical x-ray finding in multiple myeloma is the "punched out" lesion with sharply demarcated edges.
  1. Multiple lesions are usual.
  2. Diffuse osteoporosis may be the only finding in many cases.
  3. Pathologic fractures are common.
- In multiple myeloma, MRI scans or PET are routinely utilized for the purposes of staging

FIG. E5 Dedifferentiated chondrosarcoma. AP XR showing a proximal femoral chondrosarcoma with an adjacent area of lytic destruction and a pathological fracture. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.)

extent of disease and also for monitoring for response and/or disease progression.

Rx TREATMENT

The evaluation and treatment of malignant bone tumors are complicated. Diagnostic studies and treatment should be supervised by an orthopedic cancer specialist and oncologist.

DISPOSITION

- In the past 20 yr, dramatic improvements have been made in the treatment protocols for osteosarcoma with the use of adjuvant multidrug regimens and limb-sparing surgery.
- Prognosis of multiple myeloma has markedly improved with introduction of several newer therapies, including proteasome inhibitors, immunomodulatory drugs, histone deacetylase inhibitors, and monoclonal antibodies. Additionally, immunotherapy approaches with checkpoint inhibitors are under investigation with promising initial results.
- Prognosis for Ewing sarcoma has improved with a combination of chemotherapy, local resection, and radiation therapy.
- Chondrosarcomas are not sensitive to chemotherapy or radiation, and prognosis depends on the grade of the tumor and the ability to obtain an adequate resection.

PEARLS & CONSIDERATIONS

Early diagnosis is important because most bone tumors are initially localized and have not metastasized at the time of initial presentation. In multiple myeloma, early utilization of autologous stem cell transplantation confers a survival benefit in eligible patients.

RELATED CONTENT

Multiple Myeloma (Related Key Topic)
Sarcoma (Related Key Topic)

AUTHOR: **Bharti Rathore, MD**

BASIC INFORMATION

DEFINITION

Borderline personality disorder (BPD) is characterized by a pervasive pattern of instability in interpersonal relationships, self-image, affect regulation, and impulse control that causes significant subjective distress or impairment of functioning. The individual must meet five or more of the following criteria:

1. Frantic efforts to avoid real or imagined abandonment
2. Unstable and intense personal relationships characterized by alternating between extremes of idealization and devaluation
3. Identity disturbance characterized by an unstable self-image
4. Impulsivity in at least two areas that are potentially self-damaging (e.g., overspending, sex, substance abuse, binge eating, reckless driving)
5. Recurrent suicidal behavior, gestures, threats, or self-mutilating behavior
6. Affective instability due to a marked reactivity of mood
7. Chronic feelings of emptiness
8. Inappropriate, intense anger or difficulty controlling anger
9. Transient, stress-related paranoid ideation or severe dissociative symptoms

SYNONYM

BPD

ICD-10CM CODES
F60.3 Emotionally unstable personality disorder
F60.3 Borderline personality disorder
DSM-5 CODE
301.83

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Affects approximately 1% to 3% of the general population and up to 10% of psychiatric outpatients
PREDOMINANT SEX: Female (3:1) historically, although recent studies indicate fewer gender disparities
PREDOMINANT AGE: 20s
GENETICS: BPD is five times as likely if disorder is present in a first-degree relative. Increased prevalence of mood disorders and substance abuse disorders also found in first-degree relatives
RISK FACTORS: Association with childhood physical, sexual, or emotional abuse and/or neglect

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination may reveal scarring from self-injury on arms, legs, or other areas of the body. Mental status examination may reveal affective lability.
- Clinical presentation may reveal the following:
  1. A pervasive sense of loneliness and emptiness
  2. Underlying negative affect with dysphoria
  3. High frequency of comorbid psychiatric disorders, especially posttraumatic stress disorder (PTSD), anxiety disorders generally, mood disorders, attention-deficit/hyperactivity disorder, and substance use disorders
  4. Intense emotions with difficulty returning to emotional baseline
  5. All-or-nothing, either/or cognitive style that is represented by a phenomenon known as "splitting," in which patient sees situations or people as all good or all bad
  6. Difficulty in maintaining commitment to long-term goals; history of numerous stormy relationships and multiple jobs
  7. Reports a high number of sexual partners due to either/both impulsivity and victimization
  8. Reacts with rage, panic, despair to actual or perceived abandonment; may present with suicidality or self-mutilating behavior in response to recent stressor
  9. Attempts to block the experience of pain, which may induce feelings of derealization, depersonalization, changes in consciousness, and/or brief psychotic reactions with delusions and hallucinations
  10. Substance use, gambling, overspending, eating binges, and/or self-injury as a way to escape intensely painful affect

ETIOLOGY

- Interaction of psychosocial adversity plus genetic factors
- Hypotheses:
  1. Genetic: Increased risk if first-degree relative with BPD
  2. Biologic: Abnormalities in limbic system and other areas of the brain cause emotional dysregulation. Serotonergic functioning appears to be disturbed
  3. Environmental: History of childhood abuse (most commonly sexual), invalidation, or neglect

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Histrionic, antisocial, and narcissistic personality disorders share some common features.
- Persistent depressive disorder and other depressive disorders: Requires a stability of affective symptoms not seen in BPD.
- Bipolar disorder: Mood changes in BPD often triggered by stressors and less sustained than in bipolar disorder.
- Substance abuse or dependence: Often induces impulsive, emotionally labile behavior.
- PTSD: Individuals with BPD often have history of trauma but do not avoid the feared stimulus or reexperience the trauma, as with PTSD.
- Mild cases of schizophrenia may superficially resemble BPD.

UNDERDIAGNOSIS AND MISDIAGNOSIS

- BPD may be underdiagnosed, particularly in outpatient settings that do not permit long-term observation.
- Screening for BPD should include assessment of the most common features of affective instability and chronic anger, particularly in young adults.
- Many patients with BPD are incorrectly diagnosed with bipolar disorder. Cyclothymia, which is a subtype of bipolar disorder in DSM-5, is characterized by separation-related affective sensitivity and frequent depressive and hypomanic episodes, may be most difficult to distinguish from BPD.
- Onset usually occurs in adolescence. Features should not be dismissed as normal adolescent behavior.

WORKUP

- History (helpful to gather collateral information from family and friends)
- Physical examination: Neurological soft signs may reflect a vulnerability to impulsivity and affect storms
- Mental status examination

LABORATORY TESTS

- Toxicology screen; substance use is common and can mimic features of personality disorders.
- Screen for HIV and other sexually transmitted illnesses.

IMAGING STUDIES

Structural and functional MRI demonstrate amygdala hyperactivity, reduced hippocampus and amygdala volume, greater activation within the insula and posterior cingulate cortex, and less activation in regions extending from the amygdala to the cingulate and prefrontal cortex. Positron emission tomography (PET) scans reveal reduced metabolism in prefrontal cortex. Recent PET research reveals dysregulation of endogenous opioid function. Lower cortical gray matter density may be noted on MRI. Imaging is not recommended as part of routine evaluation.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Psychotherapy is the recommended primary treatment for BPD.
- Dialectical behavior therapy (DBT), mentalization-based therapy, variations of cognitive behavior therapy (CBT), and psychodynamic therapies (including transference-focused therapy) have the most empirical support from randomized trials and recent meta-analyses. Nonetheless, effects are small and unstable at long-term follow-up.
- The goal of DBT and most CBT variations is to help patients improve mindful awareness of emotions, control impulsive behaviors and angry outbursts, and develop social skills. In mindfulness treatment, the emphasis is on teaching patients to stand outside of their

feelings and observe emotions in themselves and others. The focus of transference-focused psychotherapy is on examining the affect-laden themes that emerge in the relationship between patient and therapist. Preliminary evidence exists for effectiveness of more integrative treatment models, such as the unified protocol and mindfulness-based therapies generally. Positive outcomes are also reported using "good psychiatric management" (GPM), which combines principles from various therapies and emphasizes psychoeducation and goal-setting. Effective therapeutic treatments typically combine weekly group and individual therapy meetings.
- Treatment may also include inpatient and partial hospitalization in more severe cases.

ACUTE GENERAL Rx

Low-dose antipsychotics to control impulsivity, brief psychotic episodes.

CHRONIC Rx

- Medications have low to moderate effectiveness and are most effective in improving symptoms of impulsivity, mood instability, and self-destructive behavior. Effectiveness only studied for the first 3 mo of treatment.
- SSRIs if concurrent mood disorder. Higher doses may be required than for major depression.
- Low-dose antipsychotics.
- Mood stabilizers (lithium, valproate, carbamazepine, topiramate).
- Lamotrigine is not effective in the treatment of BPD in placebo-controlled trials.
- In preliminary studies, omega-3 fatty acids improve irritability.

DISPOSITION

- Course is variable. The most unstable period is typically in early adulthood; the majority achieve greater stability in social/occupational functioning later in life but often continue with difficulty maintaining intimate relationships.
- Clinically salient features such as alcohol/substance use and self-injury may be less common in older adults.
- Often presents in emergency room when in acute distress.
- No evidence of progression to schizophrenia, but there is a high incidence of concurrent major depression and other psychiatric disorders.
- Patients with high pretreatment symptom severity who report and maintain a strong therapeutic alliance with their providers report highest treatment benefits.
- Drop-out rates are variable in research studies and may be high for individual patients.

REFERRAL

- Referral to mental health specialist:
  1. For diagnosis and management
  2. Use of pharmacotherapy
  3. Patient is severely impaired or suicidal

PEARLS & CONSIDERATIONS

COMMENTS

- Negative perceptions of patients with BPD among health care providers have potential to limit accurate diagnosis, access to care, and quality of treatment provided.
- Approach making the diagnosis of BPD in the same clear, straightforward way you would any other psychiatric diagnosis. Patients who are and are not diagnosed with BPD report equal satisfaction with their doctors regardless of diagnosis received.
- Consider frequent, brief, scheduled visits for needy, demanding, or somaticizing patients with BPD.
- Validate the patient's feelings while stating the expectation of behavior control.
- Be matter-of-fact; avoid expressing extreme emotions.
- Be alert to the risk of suicide and assess suicide risk often.
- Be alert to the risk of nonsuicidal self-harm, such as cutting.
- Convey a demeanor of competence but openly acknowledge minor errors.
- Have a low threshold for seeking psychiatric consultation.
- Patients commonly present with high functional impairment across multiple settings. Psychosocial impairment as great as, or even greater than, that of bipolar disorder.
- An alternative model of diagnosing borderline personality disorder exists in the DSM-5 section III, consisting of: (1) impairment in personality functioning (identity, self-direction, empathy, or intimacy) and (2) four or more of seven maladaptive personality traits (emotional lability, anxiousness, separation insecurity, depressivity, impulsivity, risk-taking, and hostility).

PREVENTION

- There are no known ways to prevent BPD (or other personality disorders).
- Suicidality should be actively and consistently monitored.
- Benzodiazepines, narcotic analgesics, and other drugs with potential for dependency should be used rarely and with great caution, due to impaired impulse control and risk of addictive behavior.
- Patients should be asked frequently and in detail about parenting practices. Low frustration tolerance, externalization of blame for psychological distress, and impaired impulse control put children at risk for neglect or abuse.

PATIENT & FAMILY EDUCATION

- National Alliance for the Mentally Ill (NAMI; www.nami.org) provides patient information, online chat groups, and information on support groups throughout the U.S. for people with BPD and their families.
- National Education Alliance for Borderline Personality Disorder (NEA BPD) provides online patient, family, and professional information on BPD.
- Additional, local and/or online support groups for BPD are common and should be investigated.

RELATED CONTENT

Borderline Personality Disorder (Patient Information)

AUTHORS: **Mark Zimmerman, MD,** and **Theresa A. Morgan, PhD**

SUGGESTED READINGS

American Psychiatric Association: Practice guidelines for the treatment of patients with borderline personality disorder. Available at www.psychiatryonline.com/pracGuide/pracGuideTopic_13.aspx, https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/bpd.pdf.

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BASIC INFORMATION

DEFINITION

Botulism is an illness caused by a neurotoxin produced primarily by *Clostridium botulinum.* Five types of disease can occur: Foodborne botulism, wound botulism, infant intestinal botulism, adult enteric botulism (similar to infant botulism), and inhalational botulism. Of note, inhalational botulism is exceedingly rare, but could occur as a result of bioterrorism.

SYNONYMS

Clostridium botulinum food poisoning
Botulinum toxin food poisoning
Wound botulism
Infantile botulism

ICD-10CM CODES	
A05.1	Botulism food poisoning
A48.51	Infant botulism
A48.52	Wound botulism

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): In 2016, 205 cases of botulism were reported in the U.S. Foodborne botulism accounts for 20% of cases; over 70% of cases are infant botulism. Systemic botulism toxicity resulting from cosmetic use of botulinum toxin is exceedingly rare and has only been reported with unlicensed use.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms usually begin 12 to 36 hr following ingestion of the toxin
- Severity of illness is related to the quantity of toxin ingested
- Significant findings:
  1. Acute, bilateral cranial nerve palsies, with ocular and bulbar manifestations being most frequent (diplopia, ophthalmoplegia, ptosis, dysphagia, dysarthria, fixed and dilated pupils, and dry mouth)
  2. Bilateral motor nerve involvement that may progress to a descending flaccid paralysis
  3. No sensory deficits aside from possible blurred vision
  4. GI symptoms (dry mouth, nausea, vomiting, diarrhea, or cramps)
  5. Normal heart rate, blood pressure, and temperature
  6. Normal mental status
- Wound botulism:
  1. Occurs primarily in injection drug users (subcutaneous "black tar" heroin injection—"skin popping") or with traumatic injury
  2. Presentation is similar to that of foodborne disease, except for a longer incubation period (4 to 14 days) and absence of GI symptoms
  3. Fever is uncommon and if present may be due to wound infection, which is not always apparent

ETIOLOGY

- Botulism is caused by one of several neurotoxins (usually A, B, E, or F) produced by *C. botulinum,* an anaerobic, gram-positive bacillus. Spore production guarantees survival of the organism in extreme conditions; it is found worldwide. Botulinum toxin blocks acetylcholine-mediated neurotransmission and is the most powerful neurotoxin known.
- Disease results from absorption of toxin into the circulation from a mucosal surface or wound. Botulinum toxin does not penetrate intact skin.
- In foodborne botulism, disease is caused by ingestion of preformed toxin. Although rapidly inactivated by heat, the toxin can survive the proteolytic environment of the stomach.
- In wound botulism, toxin is elaborated by organisms that contaminate a wound.
- In infant botulism (and probably adult botulism of unknown etiology), toxin is produced by organisms in the GI tract. Antibiotic use and achlorhydria can predispose to colonization by *C. botulinum* and elaboration of toxin.
- Inhalational botulism has been demonstrated experimentally in primates. Rare case reports of inhalational botulism from snorting contaminated cocaine have been reported, and there is concern for the potential use of manufactured aerosolized toxin as a bioterrorism agent.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Myasthenia gravis, Lambert-Eaton myasthenic syndrome
- Guillain-Barré syndrome or other acute inflammatory demyelinating polyneuropathy
- Tick paralysis
- Stroke
- Polio
- Acute flaccid myelitis
- Heavy metal intoxication
- Shellfish poisoning

LABORATORY TESTS

- Treatment should start *before* laboratory confirmation in suspected cases, as laboratory testing may take several days.
- Serum, food, and/or stool should be sent for anaerobic cultures and toxin assay.
- Public health laboratories may perform mouse bioassay testing, which confirms toxin type in 75% of cases. Immunoassays and PCRs are under investigation for rapid source tracking.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive care with intubation if respiratory failure occurs; ventilation may need to continue for some time, as pharmacologic therapy halts only short-term disease progression.
- Debridement of the wound in wound botulism.

ACUTE GENERAL Rx

- **For non-infants:** Give equine heptavalent botulinum antitoxin (HBAT), which contains antibodies for seven known botulism types (A through G), as early as possible. Antitoxin should be administered before laboratory confirmation if botulism is suspected.
  1. The antitoxin (BAT, Cangene Corporation) is available from the Centers for Disease Control and Prevention (1-404-639-2206 Monday through Friday or 1-404-639-2888 evenings/weekends); it is derived from horse serum, so there is a significant incidence of serum sickness.
  2. Skin testing (conjunctival instillation and observation for 15 min), and possible desensitization, is recommended before treatment. Reported hypersensitivity rates range from 9% to 20%.
- Give wound botulism patients penicillin 3 million U IV q4h after antitoxin has been administered. Use metronidazole 500 mg IV q8h as an alternative for penicillin-allergic patients. Avoid aminoglycosides and tetracyclines, as they are ineffective and can worsen neuromuscular blockade.
- **For infants:** Give human botulinum immunoglobulin (BabyBIG) IV as a single dose as early as possible. Immune globulin should be administered before laboratory confirmation if botulism is suspected. Call 1-510-231-7600 to begin the process of drug acquisition and for administration instructions. Do not use equine antitoxin. Babies with infantile intestinal botulism may benefit from a cathartic to mechanically clear the number of *C. botulinum* vegetative forms and spores residing in the gastrointestinal tract. Avoid antibiotics in infant botulism because antimicrobials may lyse *C. botulinum* in the gut and increase toxin load.

DISPOSITION

- Highest mortality in the first cases in an outbreak, with subsequent cases receiving rapid treatment.
- Complete recovery for most individuals (may take up to 1 yr).

PEARLS & CONSIDERATIONS

COMMENTS

- Routine cooking inactivates the toxin, but spores are resistant to environmental factors. At room temperature, spores can germinate and produce toxin. Pressure cooking can kill spores.
- Most outbreaks are associated with home-canned foods, including fruits, vegetables, and fish. Botulinum spores can be found in honey and corn syrup, and thus children under 12 months of age should not eat honey or foods with honey in them.
- Patients must be closely monitored for progression to respiratory failure.

- Notify public health authorities immediately to alert other health care services of possible additional cases and to initiate investigation into cause and scope of outbreak.
- Immunity to botulism does not occur after toxin exposure/infection, and repeated botulism can occur.

SUGGESTED READINGS

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RELATED CONTENT

Botulism (Patient Information)

AUTHORS: **Stephen Dolter, MD,** and **Russell J. McCulloh, MD**

BASIC INFORMATION

DEFINITION

A brain abscess is a focal intracerebral infection that can arise as a complication of a bacterial, mycobacterial, fungal, or parasitic infection, or as a sequelae after surgery or trauma.

ICD-10CM CODE
G06.0 Intracranial abscess and granuloma

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Uncommon (reported incidence 0.4 to 0.9 cases per 100,000 population; occurs about 2% as commonly as brain tumors)
PEAK INCIDENCE: Preadolescence and middle age (and depends on predisposing condition); increased rates in the immunocompromised host
PREDOMINANT AGE: Occurs at any age
PREDOMINANT SEX: Men affected more than women (ratio 2:1 to 3:1)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Classic triad: Fever, headache, and focal neurologic deficit (present in approximately 20% of cases).
- Clinical presentation is often due to the manifestations of the space-occupying lesion rather than to signs of systemic infection.
- Fever is present in only 32% to 79% of patients.
- Headache is usually localized to the side of the abscess; onset can be gradual or severe; present in an average of 70% to 75% of cases.
- Focal neurologic findings (e.g., seizures, hemiparesis, aphasia, ataxia) depend on the location of the abscess and are seen in 23% to 66% of cases.
- Papilledema is present in 9% to 51% of cases.
- Presence of adjacent infections (dental abscess, otitis media, sinusitis, or postneurosurgical infection) may be a clue to the underlying diagnosis and should be sought in any suspected case.
- Time course from symptom onset to presentation ranges from hours in fulminant cases to more than 1 month; 75% present in the first 2 weeks.
- The nonspecific presentation of a brain abscess warrants that clinicians maintain a high index of suspicion. Table 1 describes common initial features of brain abscess.

ETIOLOGY

- Brain abscesses are classified based on the likely portal of entry and can arise from:
  1. Contiguous infection (e.g., dental abscess, otitis media, sinusitis, or post neurosurgical infection)
  2. Hematogenous spread from a remote site (e.g., endocarditis, bacteremia), which typically causes multiple lesions

TABLE 1 Brain Abscess: Initial Features in 123 Cases

Headache	55%
Disturbed consciousness	48%
Fever	58%
Nuchal rigidity	29%
Nausea, vomiting	32%
Seizures	19%
Visual disturbance	15%
Dysarthria	20%
Hemiparesis	48%
Sepsis	17%

From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.

- Likely source of abscess and common organisms involved:
  1. Contiguous focus or primary infection (55% of all brain abscesses):
     a. Paranasal sinus: Occur in frontal lobe; streptococci (especially microaerophilic and anaerobic streptococci), *Bacteroides*, *Haemophilus*, and *Fusobacterium* spp.
     b. Otitis media/mastoiditis: Occur in temporal lobe and cerebellum; aerobic and anaerobic streptococci, *Enterobacteriaceae*, *Bacteroides*, and *Pseudomonas* spp.
     c. Dental infection: Occur in frontal lobe; mixed *Fusobacterium*, *Bacteroides*, and *Streptococcus* spp. (especially *S. viridans* and anaerobic streptococci)
     d. Penetrating head injury: Site of abscess depends on site of wound; *Staphylococcus aureus*, aerobic streptococci, *Clostridium* spp., *Enterobacteriaceae*
     e. Postoperative: *Staphylococcus epidermidis* and *S. aureus, Enterobacteriaceae,* and *Pseudomonas aeruginosa*
  2. Hematogenous spread from a distant site of infection (25% of all brain abscesses): Abscesses most commonly multiple, especially in middle cerebral artery distribution; infecting organism(s) depend on source
     a. Congenital heart disease: Streptococci, *Haemophilus* spp.
     b. Endocarditis: *S. aureus*, viridans streptococci
     c. Urinary tract: Enterobacteriaceae, Pseudomonadaceae
     d. Intraabdominal: Streptococci, *Enterobacteriaceae*, anaerobes
     e. Lung: streptococci, *Actinomyces* spp., *Fusobacterium* spp.
     f. Immunocompromised host: *Toxoplasma* spp., *Enterobacteriaceae*, *Nocardia* spp., listeriosisi, other fungi, tuberculosis
        (1) Fungi are responsible for up to 90% of cerebral abscesses in solid organ transplant recipients
  3. Cryptogenic (unknown source): 20% of all brain abscesses

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other parameningeal infections: Subdural empyema, epidural abscess, thrombophlebitis of the major dural venous sinuses and cortical veins
- Embolic strokes in patients with bacterial endocarditis
- Mycotic aneurysms with leakage
- Acute hemorrhagic leukoencephalitis
- Parasitic infections: Toxoplasmosis, echinococcosis, cysticercosis
- Metastatic or primary brain tumors
- Cerebral infarction
- CNS vasculitis
- Chronic subdural hematoma

WORKUP

Physical examination, laboratory tests, and imaging studies

LABORATORY TESTS

- White blood cell counts are elevated in 60% of patients.
- Erythrocyte sedimentation rate is usually elevated but may be normal.
- Lumbar puncture is contraindicated because of the potential for increased intracranial pressure and the risk for herniation due to the space-occupying abscess. Lumbar puncture may be helpful only in those with suspicion for meningitis or abscess rupture into the ventricular system; however, the risk of herniation must be considered.
- The yield of gram stain and culture of material aspirated at time of surgical drainage is very high.
- Cultures of contiguous sites of infection should be considered (e.g., paranasal sinus, otitis, skin site abscess from a neurosurgical procedure). These sites of infection may need surgical drainage in order to control the infection.
- Blood cultures and cerebrospinal fluid cultures may identify the causative organism in up to 25% of patients.
- Based on the appearance of lesions on imaging, then antitoxoplasma IgG antibodies from the blood and anticysticercal antibodies in the CSF can aid in the diagnosis of CNS toxoplasma and neurocysticercosis infections, respectively.

IMAGING STUDIES

- CT scan with contrast enhancement or MRI with gadolinium can be used to detect brain abscess. CT is rapid and available in most medical settings. An MRI with gadolinium (Fig. E1) is able to provide more detailed images in order to differentiate between abscess and tumor or other mass.
- CT scan (Fig. 2) with intravenous contrast enhancement is still an excellent test (sensitivity 95% to 99%).
- Serial CT or MRI scanning is recommended to follow the response to therapy.

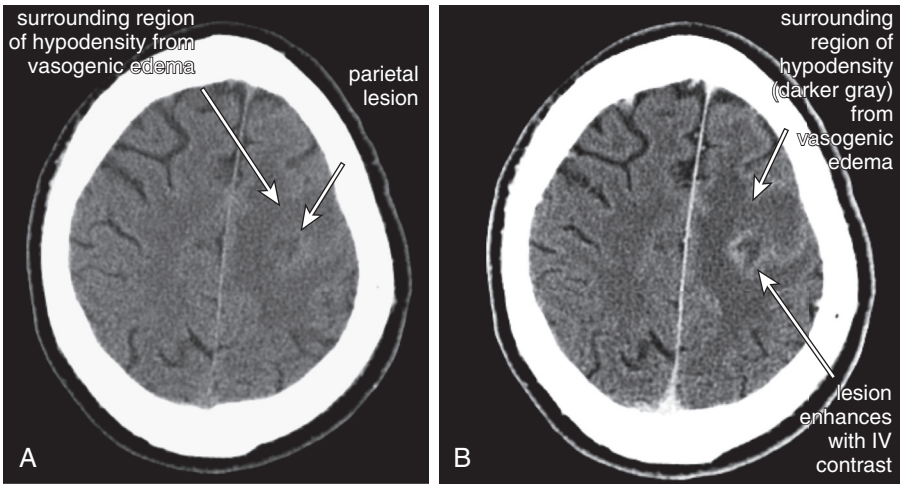

FIG. 2 Brain abscess. This 48-yr-old male presented with status epilepticus. Computed tomography (CT) of the brain showed a parietal mass, which at brain biopsy was found to be an abscess. Cultures grew mixed gram-positive and gram-negative organisms and anaerobes. The patient was subsequently found to be human immunodeficiency virus positive. **A,** Noncontrast head CT, brain windows. **B,** CT with intravenous (IV) contrast moments later, brain windows. Abscesses and other infectious, inflammatory, or neoplastic lesions typically have surrounding hypodense regions representing vasogenic edema. When IV contrast is administered **(B),** the lesion may enhance peripherally, often referred to as ring enhancement. (From Broder JS: *Diagnostic imaging for the emergency physician*, Philadelphia, 2011, Saunders.)

Rx TREATMENT

ACUTE GENERAL Rx

- Effective treatment involves a combination of empiric antibiotic therapy and timely excision or aspiration of the abscess.
- If evidence of edema or mass effect, treatment of elevated intracranial pressure is paramount.
  1. Hyperventilation of mechanically ventilated patient.
  2. Dexamethasone initially in a dosage of 10 mg IV followed by 4 mg IV q6h until symptoms of cerebral edema subside. Steroids should be discontinued as soon as possible.
  3. Mannitol 0.25 to 1 g/kg IV over 20 to 30 min q6 to 8h; maximum of 6 g/kg in 24 hr.
- Medical therapy is never a substitute for surgical intervention to relieve increased intracranial pressure. Neurologic deterioration usually mandates surgical intervention.
- Steroids should be limited to patients with severe cerebral edema or midline shift.

MEDICAL Rx

If abscess <2.5 cm and patient is neurologically stable and conscious, may start antibiotics and observe. Empiric antibiotic therapy guided by:

- Abscess location
- Suspicion of primary source
- Presence of single or multiple abscesses
- Patient's underlying medical conditions (e.g., HIV, immunocompromised)

Selection of empiric antibiotic therapy:

- Primary infection or contiguous source:
  1. Otitis media/mastoiditis, sinusitis: Third-generation cephalosporin (cefotaxime 2 g q4h IV or ceftriaxone 2 g q12h IV) plus metronidazole 15 mg/kg IV as a loading dose, then 7.5 mg/kg q8h IV, not to exceed 4 g per day
  2. Dental infection: Penicillin G (20 million to 24 million units per day IV in six divided doses) plus metronidazole (dose as above)
  3. Head trauma: Third- or fourth-generation cephalosporin (cefotaxime 2 g IV q4h or ceftriaxone 2 g IV q12h or cefepime 2 g IV q8h) plus vancomycin (30 mg/kg IV in two divided doses adjusted for renal function)
  4. Postoperative neurosurgery: Vancomycin (dose as above) plus ceftazidime (2 g IV q8h) or cefepime (2 g IV q8h), or meropenem (1 g IV q8h). Replace vancomycin with nafcillin (2g IV q4h) if susceptibility testing reveals methicillin-sensitive *S. aureus*
- Hematogenous spread (congenital heart disease, endocarditis, urinary tract, lung, intraabdominal): Vancomycin (empiric therapy, dose as above) or nafcillin (if susceptibility testing reveals methicillin-sensitive *S. aureus*, dose as above) plus metronidazole plus third-generation cephalosporin (cefotaxime 2 g IV q4h or ceftriaxone 2 g IV q12h). Antibiotic therapy can be adjusted based on the etiology of the underlying infection, if known. Depending on the source, many experts advocate for anaerobic coverage, even with no documentation given suboptimal sensitivity of current techniques
- HIV-infected or immunocompromised patient: Metronidazole plus a third-generation cephalosporin, antifungal, or antiparasitic agent. Duration of antibiotic therapy is guided by the clinical course and by whether the abscess was surgically aspirated or excised; it is usually prolonged. Most recommend parenteral treatment for at least 4 to 8 weeks, with serial neuroimaging to ensure adequate resolution. (Imaging weekly could be considered for first 2 weeks of therapy, then every 2 weeks until resolution.) Surgical therapy may be required for clinical failure (i.e., increasing size of abscess on imaging despite antibiotic therapy).

SURGICAL Rx

- Three indications for surgical intervention:
  1. Collect specimens for culture and sensitivity
  2. Reduce mass effect
  3. Clinical failure with antibiotic therapy alone
- Stereotactic biopsy or aspirate of the abscess if surgically feasible
- Essential to selection of targeted antimicrobial coverage
- Timing and choice of surgery depend on:
  1. Primary infection source
  2. Number and location of the abscesses
  3. Whether the procedure is diagnostic or therapeutic
  4. Neurologic status of the patient

DISPOSITION

- Prompt diagnostic consideration, early institution of appropriate antimicrobial therapy, and advanced neuroradiologic imaging have reduced the mortality rate from brain abscesses from 40% to 80% in the preantibiotic era to 10% to 20% at present.
- Morbidity is usually manifest as persistent neurologic sequelae (seizures, intellectual or behavioral impairment, motor deficits).

REFERRAL

Consultation with infectious disease and neurosurgery

PEARLS & CONSIDERATIONS

COMMENTS

- It is important to maintain a high index of suspicion because a brain abscess often presents with nonspecific symptoms.
- Rapid imaging and early institution of appropriate antimicrobial therapy improve patient morbidity and mortality.
- Neurosurgical consultation is mandatory.

PREVENTION

Because brain abscesses arise from either contiguous infections or hematogenously from a remote site, early and appropriate treatment of predisposing infections is paramount to prevent brain abscess.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Brain Abscess (Patient Information)

AUTHOR: **Erica Hardy, MD, MMS**

SUGGESTED READINGS

Bodilsen J et al: Risk factors for brain abscess: a nationwide, population-based, nested case-control study: *Clin Infect Dis.* 2019 Oct 23. pii: ciz890. doi: 10.1093/cid/ciz890.E pub ahead of print.

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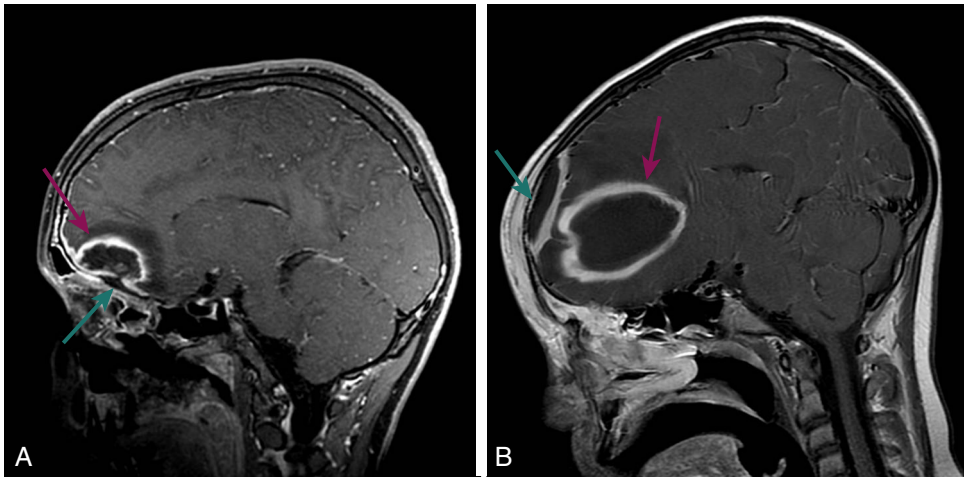

FIG. E1 Magnetic resonance sagittal T1-weighted images with gadolinium contrast, from two different patients with cerebral abscess *(red arrows).* Each abscess has a hypointense core with a rim of contrast enhancement. In addition, each patient exhibits an epidural empyema *(green arrow),* developing from a contiguous area between the abscess and epidural space. (Swaiman KF et al: *Swaiman's pediatric neurology, principles and practice,* ed 6, Philadelphia, 2017, Elsevier.)

BASIC INFORMATION

DEFINITION

Brain metastases result from a spread of cancers originating in other organs to the brain and are devastating complications of cancer. Brain metastases are the most common intracranial tumors in adults and account for more than one half of brain tumors.

ICD-10CM CODES

C79.89	Secondary malignant neoplasm of other specified sites
C80.0	Disseminated malignant neoplasm, unspecified
C80.9	Malignant neoplasm, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Accurate data on the incidence of metastatic brain disease are not available. Population studies based on review of epidemiological data show an overall incidence of 8.3 to 14.3 per 100,000 population per yr. However, these studies underestimate the true incidence of brain metastases because they rely on historical data from times when diagnostic imaging was poor. Autopsy-based studies are thought to show higher incidence of brain metastases because they identify asymptomatic brain metastases. However, autopsy-based data are now more than 20 yr old. Ultimately, the incidence of metastatic brain malignancy is rising, likely due to improved detection and better control of extracerebral disease.
- In the U.S., an estimated 98,000 to 170,000 new cases occur each yr, representing 24% to 45% of all cancer patients. The incidence is higher in autopsy series, where 20% of patients with systemic disease have brain metastases.

PREDOMINANT SEX AND AGE:

- In patients with systemic malignancies, brain metastases occur in 10% to 30% of adults and 6% to 10% of children. Of these, about 60% of patients are between the ages of 50 and 70 yr.
- There is no definite gender predilection. Some data indicate that metastatic brain malignancy has a higher incidence in men because men have a higher incidence of primary lung cancer.

RISK FACTORS

- In adults, the cumulative incidence (CI) of metastases to the brain depends on the type of primary cancer as follows: Lung cancer (16% to 20% CI), renal cell carcinoma (7% to 10% CI), melanoma (7% CI), breast cancer (5% CI), and colorectal cancers (1% to 2% CI). Lymphoma is also known to metastasize to the brain. These metastatic lesions may or may not be present at the patient's initial presentation. The majority of patients with metastases to the brain have greater than one metastasis. The cancers with the highest association of intracranial hemorrhage include renal cell carcinoma, melanoma, and the less common malignancies of thyroid carcinoma and choriocarcinoma.
- The most common primary pediatric solid tumors associated with metastatic spread include sarcomas, neuroblastoma, and germ cell tumors. Leukemias are well known to seed the CNS. Metastatic disease is usually never seen when a child first presents with malignancy, with the occasional exception of leukemia. For solid tumors, metastatic disease is seen at the time of disease recurrence. Neuroblastoma CNS lesions have a high propensity to hemorrhage.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical presentations vary depending on where the lesion is located. Brain metastases should be suspected in any cancer patient developing acute neurologic signs or symptoms. Neurologic symptoms, however, are common in patients with systemic cancer. In an analysis of more than 800 patients with neurologic symptoms, brain metastases were found in only 16%.
- Symptoms:
  1. Headache occurs in 40% to 50% of patients with brain metastases. Frequency is higher with metastases located in the posterior fossa, which may result in obstructive hydrocephalus. The headache can be accompanied by nausea, vomiting, focal neurologic signs, and postural variation.
  2. Focal neurologic signs/symptoms are the presenting symptom in 20% to 40% of patients. Hemiparesis is the most frequent complaint. However, the specific neurologic dysfunction depends on the location of the brain metastasis.
  3. Cognitive dysfunction, including memory problems or mood or personality changes, is the presenting problem in 30% to 45% of patients.
  4. Seizures are the presenting symptom for 10% to 20% of patients with metastatic brain tumors and indicate supratentorial metastases.
  5. Acute stroke secondary to hemorrhage into a metastasis, hypercoagulability, or local vascular invasion occurs in 5% to 10% of patients.

ETIOLOGY

The most common mechanism of metastasis to the brain is by hematogenous spread. The most common location is at the junction of the gray matter and white matter of the cerebral hemispheres (almost 80%). The blood vessels decrease in diameter in these regions, which is thought to act like a trap for clumps of tumor cells. Different tumor types have a tendency to metastasize to different regions of the brain. For example, metastases of small cell lung carcinoma are equally distributed in all regions, whereas pelvic (prostate and uterine) and gastrointestinal tumors more commonly metastasize to the posterior fossa.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary brain tumor
- Infection: Bacterial abscess or fungal disease
- Progressive multifocal leukoencephalopathy
- Demyelinating disease: Multiple sclerosis, post-infectious encephalomyelitis
- Cerebral infarction or bleeding
- Effects of treatment, such as radiation necrosis

LABORATORY TESTS

- Routine laboratory studies are not typically helpful.
- Lumbar puncture is generally contraindicated due to increased intracranial pressure and risk of herniation.
- Brain biopsy is necessary in some cases for a definitive diagnosis, particularly in the case of unknown primary tumor. Illustrating this situation is a study of cancer patients with solitary brain lesions that were presumed to be metastatic disease; in about 10% of study participants, the lesions were proved to be a different pathology.

IMAGING STUDIES

- MRI (Fig. 1) with and without contrast is the imaging study of choice. Important features on MRI suggesting brain metastases include: Presence of multiple lesions, localization at the junction of the gray and white matter, circumscribed margins, or large amounts of vasogenic edema. CT of the head with contrast (Fig. 2) can be used when MRI is contraindicated.

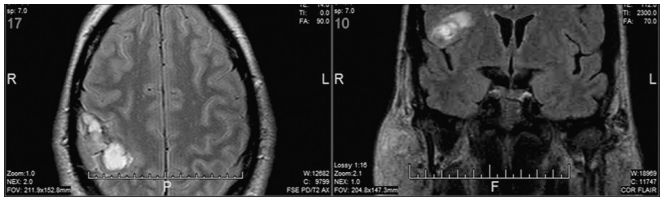

FIG. 1 Brain magnetic resonance imaging (axial and coronal fluid-attenuated inversion recovery sequences) showing hemorrhagic metastatic deposition in the inferior right frontoparietal lobe (lobulated high signal focus) in a 40-yr-old woman with metastatic choriocarcinoma to the brain. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, WB Saunders.)

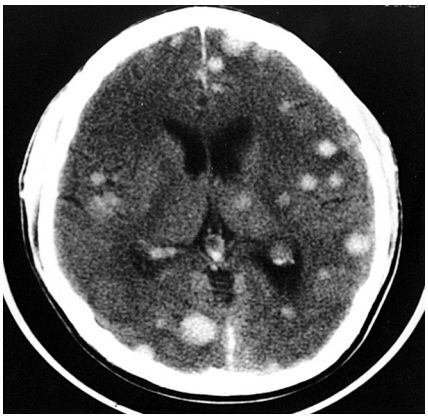

FIG. 2 Intracranial metastatic disease. Axial contrast-enhanced CT scan of head reveals multiple enhancing nodules throughout gray and white matter structures consistent with metastatic disease. (From Vincent JL et al [eds]: *Textbook of critical care*, ed 6, Philadelphia, 2011, WB Saunders.)

- MR spectroscopy and PET are useful to differentiate tumor from either other space-occupying lesions or radiation necrosis.
- Newer experimental imaging studies, such as receptor-targeted and ligand-based molecular imaging, are on the horizon.
- In about 80% of patients, brain metastases develop after the diagnosis of systemic cancer. In the remaining patients, brain metastases are diagnosed either simultaneously or before the primary tumor is found. In patients without a known primary tumor, the lung should be the primary focus of evaluation. Other frequent primary cancer types include melanoma, colon cancer, and breast cancer. PET scan may be useful in these patients to help identify either the primary tumor or other sites of metastatic disease, which may be more amenable to biopsy.

Rx TREATMENT

- Management of patients with brain metastases is influenced by the overall prognosis and may include treatments targeted at the metastases, management and prevention of complications (seizures, edema), and treatment of systemic malignancy.
- In patients considered to have a favorable prognosis (i.e., one to three metastases, good Karnofsky performance score, and controlled or absent systemic disease), treatment focuses on surgical resection and stereotactic radiation either to eradicate or control the brain metastases. Whole-brain radiation (WBRT) is widely used but has significant side effects. A study through the European Organisation for Research and Treatment of Cancer (EORTC), along with prior randomized studies, has shown the addition of WBRT did not improve overall survival but seemed to reduce the rates of disease relapse. A meta-analysis of five randomized controlled trials found that WBRT decreased the relative risk of intracranial disease progression at 1 yr by 53% but did not improve survival. Additionally, the individuals who did not receive WBRT after stereotactic radiosurgery or surgery had better quality-of-life scores. Unfortunately, few patients with metastatic disease are able to meet inclusion criteria for such studies.
- In patients with poor prognosis, treatment focuses on symptom control and WBRT.

ACUTE GENERAL Rx

- Steroids are used to reduce peritumoral edema and intracranial pressure.
- Antiepileptics are started for patients who present with seizures. Prophylactic treatment for seizures is not indicated in patients without a prior history of seizure.
- Anticoagulants are sometimes used to prevent venous thromboembolic disease but should be used with caution in patients with brain metastases that are at increased risk of hemorrhage.

CHRONIC Rx

- Radiation therapy has become the mainstay of treatment for brain metastases, including whole brain radiation therapy and stereotactic radiosurgery (SRS).
- For highly chemosensitive tumors, chemotherapy has been integrated into the primary management of patients with disseminated disease.
- For other tumors (e.g., small cell and non–small cell lung cancers, breast cancer, melanoma) systemic chemotherapy or molecularly targeted agents may be of palliative value when surgery, whole brain radiation therapy, and SRS have failed or are inappropriate. In most cases, two to three agents in combination are used in conjunction with whole brain radiation therapy. A phase II trial has shown combination treatment of lapatinib, an epidermal growth factor receptor inhibitor (EGFR-inhibitor), and capecitabine, an antimetabolite prodrug that is converted to 5-fluorouracil, as active for first-line treatment of *HER2*-positive breast brain metastases. Another phase II trial showed sagopilone (low-molecular-weight epothilone B analogue) as showing modest activity in patients with metastatic breast cancer. Additionally, dabrafenib, a tyrosine kinase inhibitor of *BRAF,* had some activity and an acceptable safety profile for metastatic melanoma with $BRAF^{V600E}$ mutations. Ipilimumab, a monoclonal antibody against cytotoxic T-lymphocyte antigen 4, was used for patients with metastatic melanoma and showed an improved median overall survival of 7 mo in clinically asymptomatic lesions and 3.7 mo in patients with neurologic symptoms. There are also other reports of its efficacy.

DISPOSITION

- The median survival of patients who receive supportive care and are treated with corticosteroids only is approximately 1 to 2 mo.
- Key prognostic factors are performance status, extent of systemic disease, and age. Most favorable outcome is found in patients with Karnofsky performance score ≥70, age younger than 70 yr, no systemic disease or local control of primary tumor without extracranial metastases, and female gender. In this group, median survival is estimated at 7.1 mo.

REFERRAL

Treatment involves a multispecialty team. Consultations from oncology, neurosurgery, neurology, radiation oncology, psychiatry, and physical therapy are all warranted.

! PEARLS & CONSIDERATIONS

COMMENTS

- Brain metastases are the most common intracranial tumors in adults, accounting for more than half of all brain tumors.
- Lung cancer, melanoma, renal cell carcinoma, and breast cancer are the most common primary tumors that metastasize to the brain.
- MRI of the brain with and without contrast is the most reliable imaging study.
- Treatment depends upon the patient's overall prognosis.

PATIENT & FAMILY EDUCATION

- American Brain Tumor Association (http://www.abta.org)
- National Brain Tumor Society (http://www.braintumor.org)

RELATED CONTENT

Brain Cancer (Patient Information)

AUTHORS: **A. Basit Khan, MD, Joseph S. Kass, MD, JD, FAAN,** and **Nicole J. Ullrich, MD, PhD**

BASIC INFORMATION

DEFINITION

Brain neoplasms are a diverse group of primary (nonmetastatic) tumors arising from one of many different cell types within the central nervous system (CNS). Specific tumor subtypes and prognosis depend on the tumor cell of origin, certain genetic markers, and pattern of growth. The diffuse low-grade gliomas (LGGs) include World Health Organization grade II astrocytomas, oligodendrogliomas, and oligoastrocytomas.

SYNONYMS

Low-grade glioma (LGG)
Glioneuronal tumor
Meningioma
Primary brain tumor

ICD-10CM CODE
D33.2 Benign neoplasm of brain, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: U.S. incidence rate of a new brain tumor is approximately 6.4/100,000 persons per yr for all primary brain tumors (Table 1). One third of these are considered malignant and the remainder benign or borderline malignant. The incidence rate in children aged 0 to 19 yr is lower (5.6 per 100,000 children). Primary brain neoplasms account for ~2% of all cancers, with a disproportionate share of cancer morbidity and mortality. It is the most common cause of cancer death in children up to 15 yr.

PEAK INCIDENCE: Depends on histology, though highest peak at ~age 50 yr.

PREDOMINANT SEX AND AGE: Slight male predominance of malignant brain tumors (8.0 vs. 5.5/100,000 person/yr). Men account for slightly less than half of cases of both benign and malignant brain tumors, as meningiomas have a higher incidence in women.

GENETICS: Most primary CNS neoplasms are sporadic; 5% are associated with hereditary syndromes that predispose to neoplasia. The most common of these include:

- Li-Fraumeni syndrome: *p53* mutation on chromosome 17q13, gliomas
- Von Hippel-Lindau: VHL, chromosome 3p25, hemangioblastoma
- Tuberous sclerosis: *TSC1/TSC2* (chromosome 9q34/16p13), subependymal giant cell astrocytoma
- Neurofibromatosis type 1: NF1, chromosome 17q11, neurofibroma, optic nerve glioma, low-grade glioma
- Neurofibromatosis type 2: NF2, chromosome 22q12, schwannoma, meningioma, ependymoma
- Retinoblastoma: pRB, chromosome 13q, retinoblastoma
- Gorlin syndrome: PTCH, chromosome 9q31, desmoplastic medulloblastoma
- Hereditary nonpolyposis colorectal cancer (HNPCC): Mismatch repair deficiency, high-grade gliomas

RISK FACTORS: Exposure to ionizing radiation has been implicated in meningiomas, gliomas, and nerve sheath tumors. No convincing evidence has shown a link with trauma, occupation, cellular phone use, diet, or electromagnetic fields.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- In general, the location, size, and rate of growth will determine the symptoms and signs of a brain tumor.
- Headache is common and is the worst symptom in nearly half of all patients. The headaches are usually a dull, constant pain that is often worse at night. Symptoms of increased intracranial pressure may also be present, including nausea and vomiting, and may worsen with changes in body position that increase thoracic pressure (coughing, sneezing, Valsalva maneuver). Papilledema is suggestive of obstructive hydrocephalus.
- Seizures occur in 33% of patients and are among the most common symptoms, particularly with brain metastases and low-grade gliomas. The type of seizure and clinical presentation depend on the location of the brain tumor. Tumor-related seizures are typically repetitive and have similar presentation patterns. It is thought that patients with seizures typically have smaller tumors at the time of diagnosis compared with those with other symptoms, because the onset of seizures prompts an imaging study, leading to an earlier diagnosis.
- Focal neurologic signs and symptoms, including muscle weakness, sensory changes, or visual disturbances are also quite frequent. In addition, cognitive dysfunction, accompanied by changes in memory or personality change, may be recounted, often in retrospect.

ETIOLOGY

Most cases are idiopathic, though specific chromosomal abnormalities have been implicated in some tumor types.

TABLE 1 Frequency of Primary Central Nervous System Tumors

Children (0-14 Yr)		Adults (≥15 Yr)	
Type	**Percentage**	**Type**	**Percentage**
Glioblastoma	20	Glioblastoma	50
Astrocytoma	21	Astrocytoma	10
Ependymoma	7	Ependymoma	2
Oligodendroglioma	1	Oligodendroglioma	3
Medulloblastoma	24	Medulloblastoma	2
Neuroblastoma	3	Neurilemmoma	2
Neurilemmoma	1	Pituitary adenoma	4
Craniopharyngioma	5	Craniopharyngioma	1
Meningioma	5	Meningioma	17
Teratoma	2	Pinealoma	1
Pinealoma	2	Hemangioma	2
Hemangioma	3	Sarcoma	1
Sarcoma	1	Others	5
Others	5	TOTAL	100
TOTAL	100		

From Goetz CG, Pappert EJ: *Textbook of clinical neurology,* Philadelphia, 1999, WB Saunders.

DIAGNOSIS

- Diagnosis is typically based on clinical presentation and imaging characteristics. Specifically, neuroimaging is critical for preoperative planning and tumor etiology.
- Tumors are best seen on brain MRI with and without contrast; calcifications are sometimes present.
- Benign and low-grade tumors, typically in the glioma family, are heterogeneous and are generally seen as an infiltrating hemispheric lesion.

LABORATORY TESTS

- Ultimately, only histologic examination can provide the exact diagnosis. Additional features such as proliferative index, immunohistochemical stains, and electron microscopy can also be used to aid in diagnosis.
- The current classification schema for gliomas is based on molecular genetic and histologic criteria. Tumor histology/histologic diagnosis (World Health Organization [WHO] grading system) includes number of mitoses, capillary endothelial proliferation, and necrosis.
- Molecular genetic analysis of tumors is critical to classification of tumor type, stratification of treatments, and prognosis. Low-grade gliomas are divided into three categories based on molecular genetic findings based on the presence of an isocitrate dehydrogenase (IDH) mutation or 1p/19q codeletion. The presence of both a 1p/19q codeletion and an IDH mutation indicates an oligodendroglioma. A glioma with an IDH mutation but lacking an 1p/19q codeletion typically has *T53* and *ATRX* mutations and represents an astrocytoma. The other category of glioma lacks both an IDH mutation and a 1p/19q codeletion.

- A codeletion of 1p/19q bestows a favorable prognosis. Low-grade gliomas lacking an IDH mutation have a poor prognosis, one comparable to glioblastoma.
- However, even tumors with benign histology can cause significant morbidity due to their location and effect on surrounding structures.

DIFFERENTIAL DIAGNOSIS

- Stroke/cerebral hemorrhage
- Abscess/parasitic cyst
- Demyelinating disease: Multiple sclerosis, postinfectious encephalomyelitis
- Metastatic tumors
- Primary CNS lymphoma

WORKUP

Neuroimaging studies and pathologic sampling are the most important diagnostic modalities in evaluation of brain tumors and may be critical for preoperative planning.

IMAGING STUDIES

- MRI with gadolinium enhancement is highly sensitive and permits visualization of the tumor with relation to the surrounding tissue. Specifically, enhancing tumor can be distinguished from surrounding edema. Low-grade tumors often present as an infiltrating lesion without mass effect. MRI is superior to CT scanning for evaluating the meninges, subarachnoid space, and posterior fossa, and for defining relation to major intracranial vessels, although CT scanning is useful if calcification or hemorrhage is suspected (Fig. E1). Fig. E2 shows the appearance of astrocytoma in imaging studies.
- Magnetic resonance spectroscopy is increasingly being used as a diagnostic tool to help differentiate intracranial tumors from other intracranial processes using different chemical markers. For example, *N*-acetylaspartate is often decreased in brain tumors, whereas choline, a component of cell membranes, is often increased in brain tumors because of high cellular turnover.
- PET scan is helpful to distinguish neoplastic lesions (with high rate of metabolism) from other lesions such as demyelination or radiation necrosis (with a much lower metabolic rate). Such lesions take up greater amounts of glucose than surrounding tissues or tumors with slower metabolic rates. May be useful to help map functional areas of the brain before surgery or radiation.
- Functional MRI is now used as an adjunct in perioperative planning for patients whose lesion is in vital regions, such as those responsible for speech, language, and motor control.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Maximal surgical removal or debulking is the initial treatment of choice and provides tissue for diagnosis and molecular characterization. Maximal safe resection is often favored with a trend toward improved survival with this approach.
- Biopsy alone is performed if the tumor is located in eloquent regions of brain or is inaccessible; this is essential for histopathologic diagnosis. Biopsy can be performed under CT or MRI guidance using stereotactic localization.
- If the tumor is benign (e.g., meningioma, acoustic neuroma), often no further therapy is required.

ACUTE GENERAL Rx

Antiseizure medications have been used perioperatively and to control seizures resulting from focal lesions. Prophylactic use of anticonvulsants is not typically recommended without clear history of seizures.

CHRONIC Rx

- Chemotherapy (combination or single agent) may be used before, during, or after surgery and radiation therapy. In children, chemotherapy is often used to delay radiation therapy. A recent trial in patients with grade 2 glioma who were younger than 40 yr of age and had undergone subtotal tumor resection or who were 40 yr of age or older, progression-free survival and overall survival were longer among those who received combination chemotherapy in addition to radiation therapy than among those who received radiation therapy alone.[1]
- Radiation is useful for certain types of tumors and is often used if there is residual tumor after surgery; conventional radiation uses external beams over a period of weeks, whereas stereotactic radiosurgery delivers a single, high dose of radiation to a well-defined area (usually <1 cm). Long-term effects of radiation therapy include radiation necrosis (particularly of white matter), blood vessel hyalinization, and secondary tumors (usually meningiomas, sarcomas, and malignant astrocytomas). Radiosensitizers may help increase the therapeutic effect of radiation therapy.
- Experimental therapies are continually in development and target molecular characterization of tumors and small molecule blockers of signal transduction cascades involved in tumor growth. Some of these therapies involve antisense molecules, biologic agents, immunotherapies, or angiogenesis inhibitors. Intratumoral drug infusions and convection-enhanced delivery of novel agents are currently under study.

[1] Buckner JC et al: Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma, *N Engl J Med* 374:1344-1355, 2016.

DISPOSITION

In general, younger age, high performance status, lower pathologic grade, the presence of an IDH mutation, and a 1p/19q codeletion have more favorable prognosis. For all histologic subtypes of brain tumors, pediatric and young adult patients have a better survival rate.

REFERRAL

- All cases warrant evaluation by an oncologist and neurosurgeon. Referral to a neurologist is indicated for management of seizures and headaches related to the tumor.
- Patients should be evaluated for physical and occupational therapy.
- Children should undergo neuropsychologic evaluations and screening for learning disabilities.

! PEARLS & CONSIDERATIONS

COMMENTS

Molecular genetic characterization is important for diagnosis, therapeutic approach, and prognosis, for which mutations in IDH and the presence of a 1p/19q codeletion represented some of the critical genetic determinations. In general, younger age, high performance status, and lower pathologic grade have more favorable prognosis. For all histologic subtypes of brain tumors, pediatric and young adult patients have a better survival.

PATIENT & FAMILY EDUCATION

American Brain Tumor Association (www.abta.org)
National Brain Tumor Society (www.braintumor.org)
Pediatric Low Grade Astrocytoma (PLGA) (https://akidsbraintumorcure.org)

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Brain Cancer (Patient Information)
Astrocytoma (Related Key Topic)
Meningioma (Related Key Topic)

AUTHORS: **Emma H. Weiss, MD, Nicole J. Ullrich, MD, PhD,** and **Joseph S. Kass, MD, JD, FAAN**

SUGGESTED READINGS

Buckner JC et al: Radiation plus procarbazine, ccnu, and vincristine in low-grade glioma, *N Engl J Med* 374:1344-1355, 2016.

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Wen PY, Huse JT: 2016 World Health Organization classification of central nervous system tumors, *Continuum (Minneap Minn)* 23(6):1531-1547, 2017.

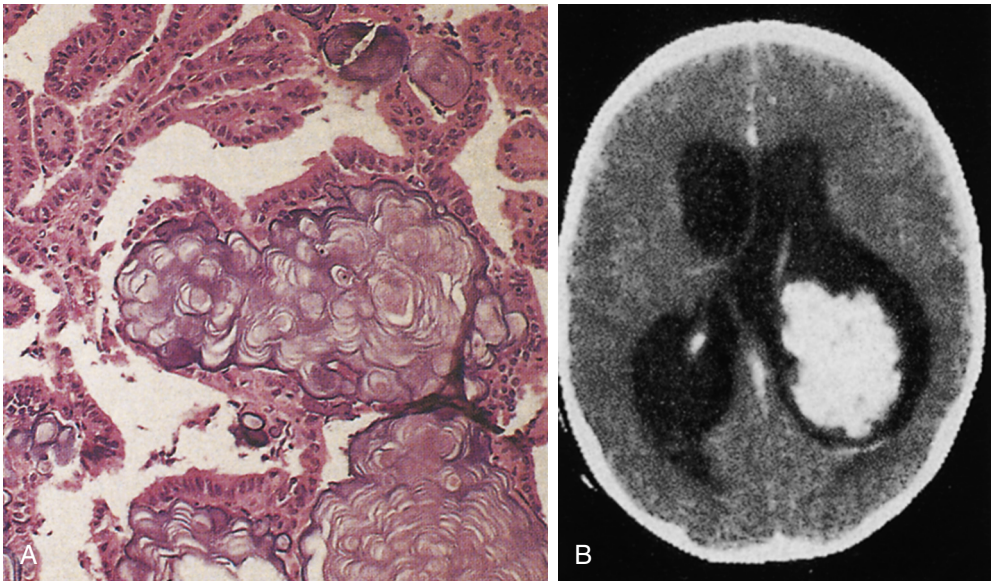

FIG. E1 Choroid plexus papilloma. A, Calcification is common both in normal aging choroid plexus and in choroid plexus papillomas and is associated with **B,** hyperdensity on computed tomography scan. (From Skarin AT: *Atlas of diagnostic oncology*, ed 4, Philadelphia, 2010, Mosby.)

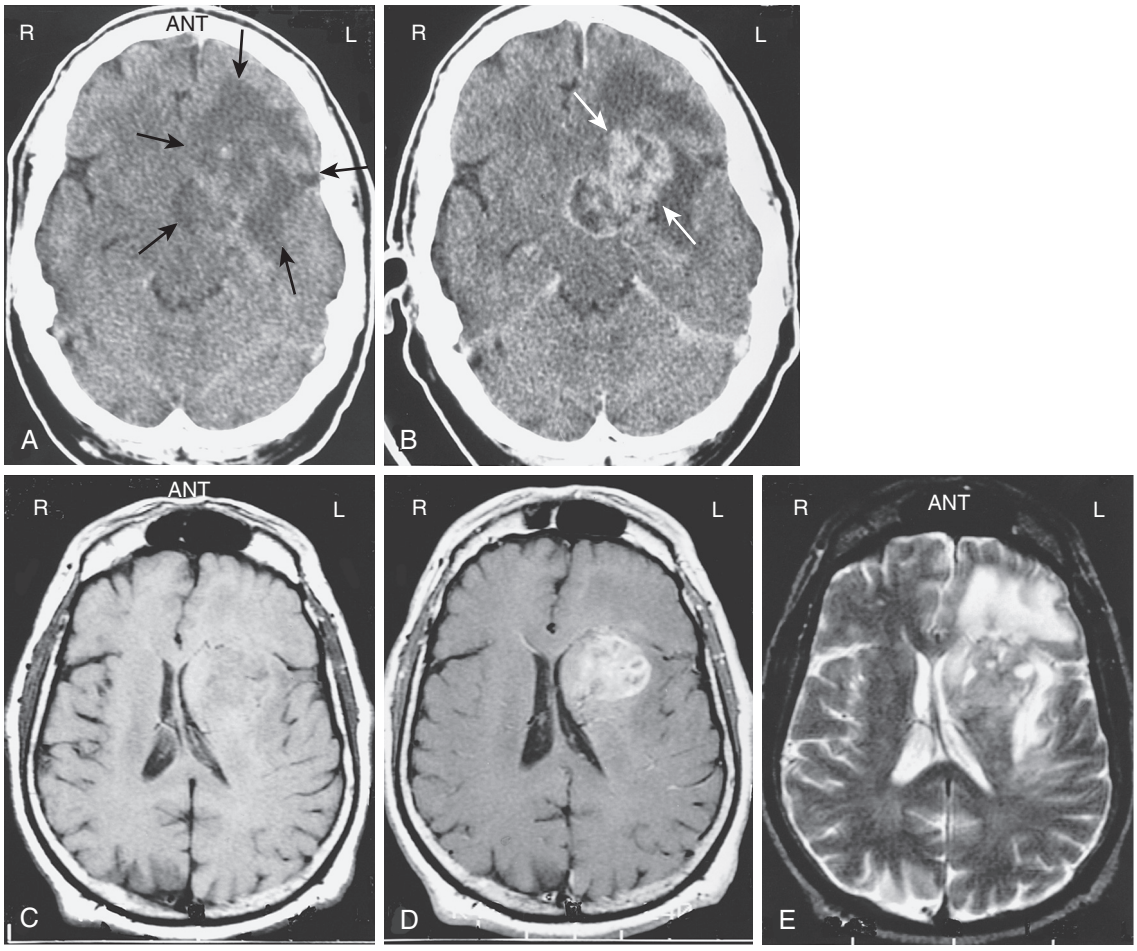

FIG. E2 Astrocytoma. These contrasted and noncontrasted computed tomography (CT) and magnetic resonance (MR) images were obtained from the same patient and demonstrate a left astrocytoma with a large amount of surrounding edema. The noncontrasted CT scan **(A)** shows only a large area of low density that represents the tumor and edema *(arrows).* A contrasted CT scan **(B)** shows enhancement of the tumor *(arrows)* surrounded by the dark or low-density area of edema. A noncontrasted T1 MR image **(C)** clearly shows a mass effect due to impression of the tumor on the left lateral ventricle and some midline shift. A gadolinium-enhanced T1 MR image **(D)** clearly outlines the tumor, but the edema is difficult to see. A T2 MR image **(E)** shows the tumor rather poorly, but the surrounding edema is easily seen as an area of increased signal *(white).* (From Mettler FA Jr: *Essentials of radiology,* ed 3, Philadelphia, 2014, Elsevier.)

BASIC INFORMATION

DEFINITION

Glioblastoma (GBM) is the most aggressive diffuse glioma of astrocytic lineage and corresponds to grade IV in the World Health Organization's (WHO) classification system. GBM is the most common brain and central nervous system (CNS) malignancy, accounting for 45.2% of malignant primary brain and CNS tumors, 54% of all gliomas, and 16% of all primary brain and CNS tumors.

GBM represents a molecularly heterogeneous disease with numerous subclassifications. GBMs comprise primary and secondary subtypes that evolve through different genetic pathways, affect patients at different ages, and have differences in outcomes. Primary (*de novo*) GBMs account for 80% of GBMs and occur in older patients (mean age 62 yr). Secondary GBMs develop from lower-grade astrocytomas or oligodendrogliomas and occur in younger patients (mean age 45 yr).

ICD-10CM CODE

C71.9 Malignant neoplasm of brain, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Based on the 2014 CBTRUS report, the average annual age-adjusted incidence rate (IR) of GBM is 3.19/100,000 population.

PREDOMINANT SEX AND AGE: GBM is primarily diagnosed at older ages, with the median age of diagnosis at 64 yr. It is uncommon in children, accounting for ~3% of all brain and CNS tumors reported among infants to 19-yr-olds. A higher incidence of GBM has been reported in men compared with women; the incidence rate is 1.6 times higher in males [3.97 vs. 2.53]. Whites have the highest incidence rates for GBM compared with any other race in the U.S.

RISK FACTORS: Many genetic and environmental factors have been studied in GBM, but no risk factor that accounts for a large proportion of GBM has been identified. Like many cancers, the causes are sporadic. Factors associated with GBM risk are prior therapeutic radiation, decreased susceptibility to allergy, immune factors and immune genes, and some single nucleotide polymorphisms (SNPs) detected by genome-wide association studies (GWAS). There is no substantial evidence of GBM association with lifestyle characteristics such as cigarette smoking, alcohol consumption, drugs, or dietary exposure to N-nitroso compounds (cured or smoked meat or fish). Inconsistent and nondefinitive results have been published regarding the risk of glioma with use of mobile phones.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients present with a variety of symptoms, including headache, seizures, symptoms of increased intracranial pressure, and cognitive disturbances.

DIAGNOSIS

IMAGING STUDIES

Initial workup includes imaging studies. Brain MRI with and without contrast is the study of choice, and demonstrates a contrast-enhancing tumor. Functional MRI is now used as an adjunct modality in perioperative planning for patients whose lesion is in vital regions (eloquent regions), such as those responsible for speech, language, and motor control. Pathologically, GBM is a high-grade astrocytoma characterized by hypercellularity, mitotic activity, nuclear atypia, pseudopalisading necrosis, and microvascular proliferation. Various molecular markers have been identified distinguishing GBM from other lower grade astrocytomas, as well as differentiating primary and secondary subtypes of GBM.

TREATMENT

- GBM is an aggressive neoplasm with a median survival of 3 mo if untreated.
- Combined modality therapy with surgery, RT, and chemotherapy has significantly improved survival of GBM patients. Treatment is complex and initially consists of maximal-safe surgical resection followed by RT with concurrent temozolomide (TMZ) chemotherapy followed by six cycles of maintenance TMZ with tumor-treating fields.
- Surgical intervention has decompressive and cytoreductive effects, and there is increasing evidence of a significant survival advantage with complete resection.
- Various emerging treatment modalities under investigation seem promising, including immunotherapy. Regression of glioblastoma after chimeric antigen receptor T-cell therapy has been reported (see Brown CE et al, in Suggested Readings). Intratumoral infusion of recombinant nonpathogenic polio-rhinovirus chimera (PVSRIPO) has improved survival rate in advanced stage glioblastoma (see Desjardins et al in Suggested Readings).
- Symptomatic treatment includes corticosteroids to reduce cerebral edema, antiepileptic drugs for seizures, and painkillers for headache.

REFERRAL

Treatment involves a multidisciplinary team approach including oncology, neurosurgery, neurology, and radiation oncology.

PROGNOSIS

Survival: GBM has a poor prognosis with a low relative survival estimate; only a few patients reach long-term survival status of 2.5 yr, and less than 5% of patients survive 5 yr post-diagnosis. The relative survival for the first yr after diagnosis is 35%, falls in the second yr post-diagnosis to 13.7%, and continues to fall thereafter. Median survival of GBM post-diagnosis is 15 mo following standard therapy. Several variables affect the prognosis of GBM patients, including age, preoperative performance status, tumor location, preoperative imaging characteristics of the tumor, and the extent of resection.

Prognostic molecular markers in GBM: All GBMs are WHO grade IV but exhibit significant genetic heterogeneity. Tumor subtypes, based on genetic alterations, exist within this larger homogeneous histologic category and carry prognostic significance. These markers include methylation status of the gene promoter for O^6-methylguanine-DNA methyltransferase (MGMT), isocitrate dehydrogenase enzyme 1/2 *(IDH1/2)* mutation, epidermal growth factor receptor (EGFR) overexpression and amplification, tumor protein *(TP53)* mutation, *ATRX* mutation and genetic losses of chromosomes.

- Primary GBMs show EGFR overexpression, phosphatase and tensin homolog gene (*PTEN*) mutations, and loss of heterozygosity (LOH) 10q, p16 deletions; less frequently shown are mouse double-minute 2 (MDM2) amplification, high frequency of telomerase reverse transcriptase (hTERT) promoter mutations, and absence of *IDH1* mutation.
- The hallmark of secondary GBMs is *TP53,* alpha thalassemia/mental retardation syndrome X-linked *(ATRX)* and *IDH1* mutations; additionally, they show LOH 10q.
- The MGMT promoter is methylated in approximately 50% of newly diagnosed GBMs. MGMT methylation is more common in secondary than primary GBM (75% vs. 36%, respectively) and has prognostic and predictive significance of better overall survival in patients with GBM, irrespective of treatment choices.
- *IDH1/2* mutations are far more common in grades II and III astrocytomas and oligodendrogliomas compared with GBMs, and more than 90% of the mutations involve *IDH1. IDH1/2* mutations are a selective molecular marker of secondary GBMs, help distinguish them from primary GBMs, and are a marker of more favorable prognosis in high-grade gliomas.
- In GBMs, EGFR signaling promotes cell division, tumor invasiveness, and resistance to radiation therapy (RT) and chemotherapy. About 40% of all GBMs have EGFR amplification, and it is more common in primary as compared with secondary GBMs.
- Mutation of the *TP53* gene has been found in 60% to 70% of secondary GBMs and 25% to 30% of primary GBMs, and it occurs more frequently in younger patients. Studies of *TP53* mutations as a prognostic marker have not been definitive.
- *ATRX* is frequently mutated in grade II-III astrocytomas (71%), oligoastrocytomas (68%), and secondary GBMs (57%), but is infrequent in primary (4%) and pediatric GBMs (20%) as well as pure oligodendroglial tumors (14%). In a prospective cohort of patients with astrocytic tumors, those harboring *ATRX* loss had a significantly better prognosis than the ones that expressed *ATRX* and had IDH mutation.
- *TERT* mutation is one of the most frequent genetic alterations in primary adult GBMs and is significantly higher in these tumors as compared with secondary adult or any pediatric GBMs. GBMs with *TERT* mutation have a shorter survival than those without *TERT* mutations. However, when adjusted for GBM subtype (primary and secondary), they do not have a significant impact on survival.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Jigisha P. Thakkar, MD**

SUGGESTED READINGS

Brown CE et al: Regression of glioblastoma after chimeric antigen receptor T-cell therapy, *N Engl J Med* 375:2561-2569, 2016.

Desjardins A et al: Recurrent glioblastoma treated with recombinant poliovirus, *N Engl J Med* 379(2):150-161, 2018.

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Breast Abscess PTG

BASIC INFORMATION

DEFINITION

Breast abscess is an acute inflammatory process resulting in the formation of a collection of purulent material (pus) in breast tissue. Typically, there is painful, erythematous mass formation in the breast, occasionally draining through the overlying skin or nipple duct.

SYNONYMS

Subareolar abscess
Lactational or puerperal abscess

ICD-10CM CODES

O91.111	Abscess of breast associated with pregnancy, first trimester
O91.112	Abscess of breast associated with pregnancy, second trimester
O91.113	Abscess of breast associated with pregnancy, third trimester
O91.119	Abscess of breast associated with pregnancy, unspecified trimester
O91.12	Abscess of breast associated with the puerperium
O91.13	Abscess of breast associated with lactation

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 10% to 30% of all breast abscesses are lactational; acute mastitis occurs in 10% of nursing mothers, with one in 15 of these women developing abscess. A recent Cochrane review, however, found that as many as 30% of nursing mothers may have evidence of mastitis. Smoking, obesity, and diabetes may be risk factors for nonpuerperal mastitis with abscess. More recently, nipple piercing may also be associated with infection.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Painful, erythematous induration involving breast and leading to fluctuant, possibly palpable abscess
- Systemic symptoms: Fever and malaise

ETIOLOGY

- Lactational abscess: Milk stasis and bacterial infection leading to mastitis and then abscess, with *Staphylococcus aureus* (commonly MRSA) the most common causative agent
- Subareolar abscess:
  1. Central ducts involved, with obstructive nipple duct changes leading to bacterial infection
  2. Cultured organisms mixed, including anaerobes, staphylococci, streptococci, and others

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Inflammatory carcinoma
- Advanced carcinoma with erythema, edema, and/or ulceration
- Tuberculous abscess (rare in the U.S.)
- Hidradenitis of breast skin
- Sebaceous cyst with infection

WORKUP

- Clinical examination. Fig. 1 illustrates the various areas where breast abscesses can develop
- Ultrasound to identify fluid collection, which can be used to guide treatment options
- If abscess suspected, referral to surgeon for incision, drainage, and biopsy

LABORATORY TESTS

- Perform culture and sensitivity test of abscess contents.
- If mammogram or ultrasound is required but prevented by discomfort, perform after treatment and subsequent resolution of abscess.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Established abscess: Incision and drainage vs. needle aspiration
- Biopsy of abscess cavity wall to exclude carcinoma

ACUTE GENERAL Rx

- Antibiotics: Generally staphylococci (*S. aureus)* in lactational abscess. Recommended initial antibiotic therapy is nafcillin or oxacillin 2 g q4h IV or cefazolin 1 g q8h IV for 10 to 14 days. Alternative includes vancomycin 1 g IV q12h.
- If acute mastitis is identified and treated early without the development of an abscess, resolution without drainage is possible.
- Subareolar abscess: Broad-spectrum antibiotic treatment (e.g., cephalexin 500 mg PO qid or cefazolin 1 g q8h IV for 10 to 14 days for more severe infection) and drainage (Fig. 1) are needed to control acute phase. If abscess is odoriferous, consider anaerobes as most likely etiology and add metronidazole 500 mg PO/IV tid.

CHRONIC Rx

Further surgical treatment for recurrences or fistula

DISPOSITION

- Lactational abscess: Possible to continue breastfeeding without risk of infection to the infant
- Subareolar abscess:
  1. High risk for recurrence or complication of fistula formation
  2. Patient informed and referred to General Surgery for evaluation and treatment

REFERRAL

- If abscess drainage required.
- If subareolar abscess involved, refer to surgery.

RELATED CONTENT

Breast Abscess (Patient Information)
Breast Cancer (Related Key Topic)
Mastodynia (Related Key Topic)

AUTHOR: **Anthony Sciscione, DO**

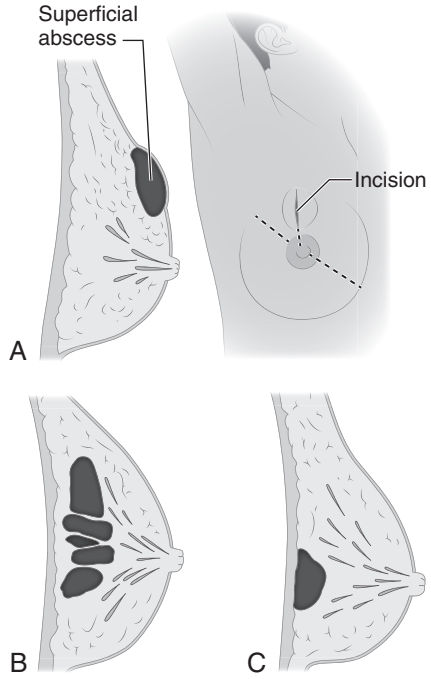

FIG. 1 A, A superficial breast abscess may be drained with a linear incision that radiates from the nipple. **B** and **C,** Diagrams of intramammary abscess **(B)** and retromammary abscess **(C)**. Both require drainage under general anesthesia. The abscess itself may not be fully appreciated if it is deep seated, and the mistaken diagnosis of cellulitis may be made. (Redrawn from Wolcott MW: *Ferguson's surgery of the ambulatory patient*, 5th ed, Philadelphia, 1974, JB Lippincott. Reprinted with permission.)

BASIC INFORMATION

DEFINITION

Breast cancer refers to both in situ and invasive carcinoma of the breast. Breast cancer can be of either ductal or lobular types.

SYNONYM

Carcinoma of the breast

ICD-10CM CODES

C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male breast

EPIDEMIOLOGY & DEMOGRAPHICS

- In the U.S., there will be an estimated 271,270 new patients and an estimated 42,260 deaths in 2019.
- The most common form of breast cancer is hormone-receptor positive; its incidence has increased particularly among young women. Breast cancer is nearly exclusively the disease of women, with only 1% of breast cancers occurring in males.
- Table 1 enumerates risk factors for breast cancer.
- Genetically defined group of women with *BRCA1* or *BRCA2* genes identified to carry lifetime risk as high as 85%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Increasing number of small breast cancers are found by mammograms in which case patients are usually completely free of symptoms or physical findings.
- Palpable lump or mass which can be self-detected or physician-detected.
- Skin and/or nipple retraction and skin edema, erythema, ulcer, satellite nodule.
- Nodal enlargement in axilla and supraclavicular areas.
- Nipple discharge may be serous or bloody.
- Generalized symptoms and signs, including fatigue, weight loss, jaundice, and anorexia, may be present in metastatic cases.

ETIOLOGY

- The precise mechanism of carcinogenesis is not understood. Endogenous and exogenous estrogen exposure is key to the development of receptor-positive breast cancer.
- Breast cancer is no longer perceived as a single disease. Molecular classification based on gene expression profiling has shown breast cancer to be of the following types:
  1. Luminal A type: Endocrine responsive with favorable prognosis.
  2. Luminal B type: Endocrine responsive with less favorable prognosis.
  3. Normal type: Resemble normal epithelium and prognosis similar to luminal B type.
  4. *HER2* amplified type: *HER2* gene amplification.
  5. Basal type: Hormone receptor and *HER2* negative cancers with poor prognosis.
- Approximately 10% of all women with breast cancer have a germline mutation of *BRCA1, BRCA2, P53*, or other mutations.
- Possibly interaction of ovarian estrogen, non-ovarian estrogen, estrogens of exogenous origin with breast tissue of varied carcinogenic susceptibility to develop cancer.
- Other known or suspected variables: Childbearing, breastfeeding practice, diet, physical activity, body mass, alcohol intake.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Benign disease is summarized in Table 2. The following nonmalignant breast lesions can simulate breast cancer on both physical and mammogram examinations:

- Fibrocystic changes
- Fibroadenoma
- Hamartoma

TABLE 1 Risk Factors for Breast Cancer

Risk Factor	Relative Risk
Any benign breast disease	1.5
Postmenopausal hormone replacement	1.5
Menarche at <12 yr	1.1-1.9
Moderate alcohol intake (2-3 drinks/day)	1.1-1.9
Menopause at >55 yr	1.1-1.9
Increased bone density	1.1-1.9
Sedentary lifestyle and lack of exercise	1.1-1.9
Proliferative breast disease without atypia	2
Age at first birth >30 yr or nulliparous	2-4
First-degree relative with breast cancer	2-4
Postmenopausal obesity	2-4
Upper socioeconomic class	2-4
Personal history of endometrial or ovarian cancer	2-4
Significant radiation to chest	2-4
Increased breast density on mammogram	2-4
Older age	>4
Personal history of breast cancer (in situ or invasive)	>4
Proliferative breast disease with atypia	>4
Two first-degree relatives with breast cancer	5
Atypical hyperplasia and first-degree relative with breast cancer	10

(From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.)

WORKUP

- Initial workup:
  1. Mass assessment by medical professional.
  2. Diagnostic mammogram followed by breast ultrasound for suspicious lesions.
  3. MRI (Fig. 1) may detect suspicious lesions better than mammography alone in women with dense breasts or inherited predisposition to breast cancer.
  4. Table 3 summarizes guidelines for evaluation and treatment of nonpalpable ductal carcinoma in situ.
- Diagnosis:
  1. Positive aspiration cytology on a clinically and mammographically suspicious mass is highly accurate, but it requires open biopsy confirmation.
  2. Stereotactic, ultrasound-guided core-needle biopsy procedures are accurate and have low complication rates. Indications for stereotactic core biopsy are summarized in Box 1. Box 2 describes contraindications to stereotactic core biopsy.
  3. Excisional surgical biopsy establishes diagnosis.
- Breast radiologic evaluation and an algorithm for breast cancer screening and evaluation are described in Section III. The differential diagnosis of breast lumps is described in Section II.

TABLE 2 American Board of Pathology Histologic Classification of Benign Disease

Histopathologic Findings	Approximate Relative Risk
Nonproliferative	No added risk
Cysts	
Duct ectasia	
Calcification	
Fibroadenoma	
Milk ductal epithelial hyperplasia	
Sclerosing adenosis	No added risk
Papillomatosis	Slight added risk
Radial scars	
Complex sclerosing lesions	?
Moderate florid hyperplasia	1.5:1-2:1
Atypical hyperplasia (ductal and lobular)	4:1
Extensive ductal involvement of atypical hyperplasia	7:1
Lobular carcinoma in situ	10:1
Ductal carcinoma in situ	10:1

(From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

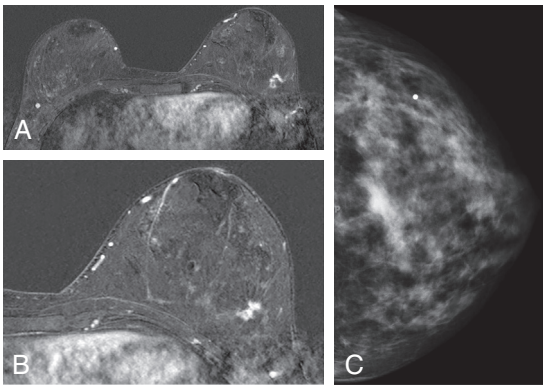

FIG. 1 A 42-yr-old woman with *BRCA2* mutation. Magnetic resonance imaging (MRI) screening showed a 1.2-cm invasive ductal cancer in the lower outer left breast seen only on MRI **(A** and **B)** and subsequently on second-look ultrasound. **C,** The mammogram showed only dense breast tissue. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

TABLE 3 Guidelines for Evaluation and Treatment of Nonpalpable Ductal Carcinoma In Situ

1. Careful multiview mammography with or without ultrasound and including magnification views
   - Document extent of disease
   - Identify other areas of microcalcification
2. Suspicious microcalcifications and densities cleared with needle localization biopsy
3. Specimen radiography with magnification techniques
4. Radiograph-directed histopathologic evaluation with orientation of specimen by surgeon using multicolored inked margins
5. Complete pathologic description to include:
   - Type of DCIS and size of tumor
   - Relation to microcalcifications
   - Distance of lesion from inked margins
   - Presence of multifocality
   - Presence or risk of microinvasion
6. Repeat mammography with magnification to confirm successful clearing of suspicious areas
7. Repeat breast excision if:
   - Residual microcalcifications are found
   - Margins are unacceptable

DCIS, Ductal carcinoma in situ.
(From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

BOX 1 Indications for Stereotactic Core Biopsy

- Certain probably benign lesions, BI-RADS 3, depending on clinical suspicion, patient or physician preference, or when short-term follow-up is not practical
- Lesions suspicious, BI-RADS 4
- Lesions highly suspicious, BI-RADS 5
- New suspicious microcalcifications, developing asymmetries, or architectural distortions
- Nonpalpable asymmetry, focal asymmetry, or solid mass on mammogram not seen on ultrasound
- Mammographic lesions corresponding to suspicious areas of enhancement on MRI

BI-RADS, Breast Imaging-Reporting and Data System; *MRI,* magnetic resonance imaging.
(From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

BOX 2 Contraindications to Stereotactic Core Biopsy

- Patient unable to lie prone or cooperate
- Patient's weight
- Lesion location near nipple, too superficial to skin, or too posterior to chest wall
- Lesion mammographically occult
- Patient has severe kyphosis or movement disorders
- Lack of breast tissue thickness for adequate compression

(From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

STAGING

Table 4 describes the pathologic staging of breast cancer.

IMAGING STUDIES

Mammograms (Fig. E2, Fig. E3): 30% to 50% of breast cancers are detected by screening mammograms as a spiculated mass, a mass with or without microcalcifications, or a cluster of microcalcifications. MRI is a modality that is particularly useful in patients with breast implants and when there is a strong family history of breast cancer. MRI is also better for assessing the response to neoadjuvant chemotherapy and is useful in identifying the primary tumor in patients who present with axillary adenopathy.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- These approaches include various types of surgical resection and reconstruction as well as adjuvant radiotherapy.
- For early breast cancer, the primary therapy is typically surgical. The choice is between modified radical mastectomy and breast-conserving treatment, which consists of lumpectomy, axillary staging with sentinel node biopsy, or axillary dissection.
- Table 5 compares ductal versus lobular carcinoma in situ. Adjuvant treatment guidelines for patients with early-stage invasive breast cancer are described in Table 6.
- Among patients with limited sentinel lymph nodes (SLN) who are treated with breast conservation and systemic therapy, sentinel lymph node dissection (SLND) alone compared with axillary lymph node dissection (ALND) did not result in inferior survival.
- DCIS: Local breast-conserving therapy (lumpectomy plus radiation therapy) or mastectomy followed by endocrine therapy in estrogen receptor-positive cases.
- Invasive breast cancer: Mastectomy or lumpectomy, along with sentinel lymph node evaluation followed by radiation therapy for large tumors.
- Invasive breast cancer may require adjuvant endocrine therapy and chemotherapy. Endocrine therapy is recommended alone or after chemotherapy in patients with hormone-receptor positive tumors. Breast cancer intrinsic subtypes are summarized in Table 7. Treatment according to breast cancer subtypes is described in Table 8. Adjuvant hormone therapy with antiestrogen drugs reduces disease recurrence and mortality in women with breast cancer. Aromatase inhibitors (anastrozole, letrozole, exemestane, fulvestrant) decrease the agonist effect of estrogen by inhibiting estrogen synthesis and have become preferred first-line hormonal treatment agents over the selective estrogen receptor modulator tamoxifen.
- Standard *adjuvant chemotherapy* regimens in current use in the U.S. include AC (cyclophosphamide plus doxorubicin), AC-T (doxorubicin and cyclophosphamide followed by a taxane),

TABLE 4 Pathological Staging of Breast Cancer

T_X	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_{is}	Carcinoma in situ
T_{is} (DCIS)	Ductal carcinoma in situ
T_{is} (LCIS)	Lobular carcinoma in situ
T_{is} (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted
T_1	Tumor ≤20 mm in greatest dimension
T_{1mi}	Tumor ≤1 mm in greatest dimension
T_{1a}	Tumor >1 mm but ≤5 mm in greatest dimension
T_{1b}	Tumor >5 mm but ≤10 mm in greatest dimension
T_{1c}	Tumor >10 mm but ≤20 mm in greatest dimension
T_2	Tumor >20 mm but ≤50 mm in greatest dimension
T_3	Tumor >50 mm in greatest dimension
T_4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T_{4a}	Extension to chest wall, not including only pectoralis muscle adherence/invasion
T_{4b}	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T_{4c}	Both T_{4a} and T_{4b}
T_{4d}	Inflammatory carcinoma
N_X	Regional lymph nodes cannot be assessed (e.g., previously removed)
N_0	No regional lymph node metastasis
N_1	Metastasis to movable ipsilateral level I, II axillary lymph node(s)
N_2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted or in clinically detected ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis
N_{2a}	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N_{2b}	Metastases only in clinically detected ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases
N_3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s), with or without level I, II axillary node involvement, or in clinically detected ipsilateral internal mammary lymph node(s) and in the *presence* of clinically evident level I, II axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s), with or without axillary or internal mammary lymph node involvement
N_{3a}	Metastasis in ipsilateral infraclavicular lymph node(s)
N_{3b}	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N_{3c}	Metastasis in ipsilateral supraclavicular lymph node(s)
M_0	No clinical or radiographic evidence of distant metastasis
$cM_{0(i+)}$	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M_1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm
G_X	Grade cannot be assessed
G_1	Low combined histologic grade (favorable)
G_2	Intermediate combined histologic grade (moderately favorable)
G_3	High combined histologic grade (unfavorable)

Stage Groupings in Breast Cancer

Stage	T	N	M
0	T_{is}	N_0	M_0
I_A	T_1	N_0	M_0
I_B	T_0-T_1	N_{1mi}	M_0
II_A	T_0-T_1	N_1	M_0
	T_2	N_0	M_0
II_B	T_2	N_1	M_0
	T_3	N_0	M_0
III_A	T_0-T_2	N_2	M_0
	T_3	N_1-N_2	M_0
III_B	T_4	N_0-N_2	M_0
III_C	Any T	N_3	M_0
IV	Any T	Any N	M_1

(From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.) (AJCC 8th ed., 2018)

and TC (docetaxel and cyclophosphamide). Fig. E4 illustrates considerations for adjuvant chemotherapy in breast cancer.

- *Neoadjuvant chemotherapy* (same regimens as used in the adjuvant setting) results in pathologic complete responses in significant number of cases, causes downstaging, provides an assessment of chemosensitivity, and provides no deleterious effect on survival.
- The benefit of adjuvant chemotherapy or hormone therapy can be assessed by commercially available *multigene assays* (OncotypeDx, Mammaprint) that have demonstrated utility in determining prognostic and predictive benefit with both hormonal therapy and chemotherapy in breast cancer. Recently published results from the prospective TAILORx trial support the routine use of multigene assays so as to identify intermediate-risk score patients in which chemotherapy can be safely omitted.
- *Metastatic breast cancer* is approached based on the extent of bone-only or visceral disease sites as well as the rate of symptomatic progression. Typically, bone-only metastatic disease is approached with upfront, sequential hormonal therapy. The combination of mTOR inhibitors (everolimus) or CDK4/CDK6 inhibitors (palbociclib, ribociclib, abemaciclib) with aromatase inhibitors has been associated with improved overall survival. Among patients with *PIK3CA*-mutated, hormone-receptor-positive, *HER2*-negative advanced breast cancer who had received endocrine therapy previously, treatment with the combination of alpelisib plus fulvestrant prolonged progression-free survival, leading to the approval of this combination approach. Commonly used cytotoxic chemotherapy and anti-*HER2* therapy drugs in metastatic breast cancer are summarized in Table 9.
- Patients with progressive bone disease or those with visceral disease are treated with typically single-agent chemotherapy and occasionally with combination chemotherapy regimens. The chemotherapy agents are the same as those used in early stages of disease. Sequential chemotherapy with different classes of chemotherapy agents are usually used to provide palliation with improvement in survival and symptoms.
- Patients whose tumors have germline *BRCA1*/2 mutations can be treated with the PARP inhibitors olaparib or talazoparib.
- Patients with triple-negative breast cancer whose tumors express the program death ligand-1 receptor derive a survival benefit with the use of the combination of albumin-bound paclitaxel and the immune inhibitor atezolizumab.
- In patients with metastatic *HER2/neu*-positive breast cancer, the addition of the monoclonal antibody pertuzumab to the standard regimen of trastuzumab and docetaxel significantly improves the median overall survival. Also, the antibody-drug conjugate TDM-1 improves survival in this group of patients.

TABLE 5 Carcinoma In Situ: Lobular Versus Ductal

Feature	Lobular Carcinoma In Situ	Ductal Carcinoma In Situ
Age	Younger	Older
Palpable mass	No	Uncommon
Mammographic appearance	Not detected on mammography	Microcalcifications, mass
Immunophenotype	E-cadherin negative	E-cadherin positive
Usual manifestation	Incidental finding on breast biopsy	Microcalcifications on mammography or breast mass
Bilateral involvement	Common	Uncertain
Risk and site of subsequent breast cancer	25% risk for invasive breast cancer in either breast over remaining lifespan	At site of initial lesion; 0.5% risk/yr of invasive breast cancer in opposite breast
Prevention	Consider tamoxifen or raloxifene	Consider tamoxifen or raloxifene if estrogen-receptor positive
Treatment	Yearly mammography and breast examination	Lumpectomy ± radiation; mastectomy for large or multifocal lesions

(From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.)

TABLE 6 Adjuvant Treatment Guidelines for Patients with Early-Stage Invasive Breast Cancer

Patient Group	Treatment
Hormone Receptor-Positive and *HER2* Positive Breast Cancer	
<0.5 cm	Consider adjuvant endocrine therapy
0.6-1 cm	Adjuvant endocrine therapy Consider adjuvant chemotherapy and trastuzumab
>1 cm	Adjuvant endocrine therapy Adjuvant chemotherapy and trastuzumab
Node positive	Adjuvant endocrine therapy Adjuvant chemotherapy with pertuzumab and trastuzumab
Hormone Receptor-Positive and *HER2* Negative Breast Cancer	
<0.5 cm	No adjuvant therapy
>0.5 cm	Adjuvant hormonal therapy Consider adjuvant chemotherapy based on 21-gene recurrence score
Node-positive	Adjuvant hormonal therapy + adjuvant chemotherapy
Hormone Receptor-Negative and *HER2* Positive Breast Cancer	
<0.5 cm	Consider adjuvant chemotherapy and trastuzumab
0.6-1 cm	Consider adjuvant chemotherapy and trastuzumab
>1 cm	Adjuvant chemotherapy and trastuzumab
Node positive	Adjuvant endocrine therapy Adjuvant chemotherapy with pertuzumab and trastuzumab
Hormone Receptor-Negative and *HER2* Negative Breast Cancer	
≤0.5 cm	No adjuvant therapy
0.6-1.0 cm	Consider adjuvant chemotherapy
>1 cm or node positive	Adjuvant chemotherapy

HER2, human epidermal growth factor receptor 2.
(Modified from National Comprehensive Cancer Network Guidelines. Available at www.nccn.org.)

CHRONIC Rx

Follow-up after treatment of early breast cancer stages includes:

- Regular clinical evaluations as delineated by medical oncologist or surgeon.
- Annual mammograms and breast MRI as indicated.
- Laboratory tests as indicated.
- Tumor markers and CT scans for surveillance are not recommended.
- Patient instruction in monthly breast self-examination.
- Prognosis after curative therapy: Depends on size of tumor, extent of nodal metastasis, and pathologic grade of tumor.
- Systemic adjuvant therapy: Improves prognosis significantly. Women who take tamoxifen for 10 yr lower their recurrence risk by 25% and their dying of breast cancer risk by 27% compared with those who took it for just 5 yr. Adjuvant therapy with an aromatase inhibitor improves survival outcomes, compared with tamoxifen, in postmenopausal women with hormone receptor–positive breast cancer. Recent trials have shown that in premenopausal women with hormone receptor–positive early breast cancer, adjuvant treatment with the aromatase inhibitor exemestane plus ovarian suppression, compared with tamoxifen plus ovarian suppression, significantly reduced recurrence.
- Isolated tumor cells or micrometastases in regional lymph nodes are associated with a reduced 5-yr rate of disease-free survival among women with favorable early-stage breast cancer who do not receive adjuvant therapy. Survival is improved in patients with isolated tumor cells or micrometastases who received adjuvant therapy.
- Retrospective analyses suggest that occult lymph-node metastases are an important prognostic factor for disease recurrence or survival among patients with breast cancer; however, recent trials indicate that the magnitude of the difference in outcome at 5 yr is small (1.2 percentage points). These data do not favor a clinical benefit of additional evaluation (including immunohistochemical analysis) of initially negative sentinel nodes in patients with breast cancer.
- The addition of zoledronic acid to adjuvant endocrine therapy improves disease-free survival in premenopausal patients with estrogen-responsive early breast cancer.

REFERRAL

Referral to a multidisciplinary team consisting of a breast surgeon, reconstructive surgeon, medical oncologist, and radiation oncologist is necessary as soon as breast cancer is suspected.

PEARLS & CONSIDERATIONS

BREAST CANCER IN PREGNANCY AND LACTATION

- Frequency in women 40 yr or younger reported to be 15%
- May carry worse prognosis because disease discovery delayed by engorged and nodular breast changes and/or because disease progression more rapid in pregnancy
- Survival rates similar to those for nonpregnant early-stage patients in same age group
- Expedient workup recommended, including mammography and sonography
- Choice of mastectomy or lumpectomy with axillary dissection for treatment
- Adjuvant chemotherapy delayed until third trimester or after delivery
- Irradiation to breast after lumpectomy delayed until after delivery

DUCTAL CARCINOMA IN SITU (DCIS, INTRADUCTAL CARCINOMA) (SEE TABLE 5)

- Discovered by mammogram as cluster of microcalcifications and/or density
- Presents less often as a palpable mass or nipple discharge
- Before mammogram screening, DCIS accounted for 1% of all breast cancers

TABLE 7 Breast Cancer Intrinsic Subtypes

Subtype	Characteristics	Markers
Luminal A	Low grade High ER ~40% of all breast cancer Good prognosis	ER+, PR+, *HER2*– Low Ki-67 (<14%)
Luminal B	Higher grade Lower ER ~20% of all breast cancer Poorer prognosis than luminal A	ER+, PR+/–, *HER2*+/– High Ki-67 (>14%)
HER2-enriched	High grade Often node positive *P53* mutations ~10%-15% of all breast cancer	ER–, PR–, *HER2*+
Basal-like	High proliferation *BRCA* dysfunction ~15%-20% of all breast cancer Poor prognosis	ER–, PR–, *HER2*– CK5/6 Or EGFR+

CK, Cytokeratin; *EGFR*, epidermal growth factor receptor; *ER*, estrogen receptor; *HER2*, human epidermal growth factor receptor 2; *PR*, progesterone receptor.
(From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

TABLE 8 Treatment According to Breast Cancer Subtype

Subtype	Treatment Response and Prognosis
Luminal A	Respond to endocrine therapy • Premenopausal: SERMs (tamoxifen) • Postmenopausal: AIs (exemestane, anastrozole, letrozole)
Luminal B	Response to endocrine therapy lower Response to chemotherapy greater than luminal A
HER2-enriched	Respond to anti-*HER2* agents (trastuzumab, pertuzumab, lapatinib)
Basal-like	No response to endocrine therapy or anti-*HER2* agents Chemotherapy only treatment outside of a clinical trial

AIs, Aromatase inhibitors; *HER2*, human epidermal growth factor receptor 2; *SERMs*, selective estrogen receptor modulators.
(From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

TABLE 9 Commonly Used Cytotoxic Chemotherapy and Anti-*HER2* Therapy Drugs in Metastatic Breast Cancer

Cytotoxic Chemotherapy
Albumin-bound paclitaxel
Capecitabine
Cisplatin
Carboplatin
Docetaxel
Doxorubicin
Epirubicin
Eribulin
Gemcitabine
Ixabepilone
Vinorelbine

Anti-*Her2* Therapy
Ado-trastuzumab emtansine
Lapatinib
Pertuzumab
Trastuzumab

(From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

- Now 15% to 20% or even higher proportion have DCIS
- Treated with lumpectomy with cure rates 98% to 99%
- Higher-risk cases require breast radiation and adjuvant hormone therapy
- Mastectomy possibly required with multifocal and/or high-grade DCIS

INFLAMMATORY CARCINOMA

- Rare, rapidly progressive and often lethal form of breast cancer
- Presents as erythematous and edematous breast resembling mastitis
- Biopsy required, including that of the skin
- Treatment with upfront combination chemotherapy followed by surgery and radiotherapy
- Prognosis once dismal; now 5-yr disease-free survival approaches 50% (Fig. E5)

COMMENTS

- The U.S. Preventive Services Task Force (USPSTF) now recommends against automatic "routine" screening of younger women (age range 40 to 49). The task force recommends biennial screening mammography for all middle-aged women (age range 50 to 74). It also states that current evidence is insufficient to assess the benefits and harms of screening mammography in older women (aged 75 and older). The task force also discourages women from performing breast self-examination. Several other U.S. organizations, such as the American Congress of Obstetricians and Gynecologists, however, still recommend annual screening beginning at age 40 yr. Breast cancer screening recommendations by organization are summarized in Table 10.
- The American Cancer Society guidelines for breast cancer screening are summarized in the following:
  1. Women with an *average risk* of breast cancer should undergo regular screening mammography as below:
     a. Women should have the opportunity to begin annual screening between the ages of 40 and 44 yr. (Qualified recommendation)
     b. Women aged 45 to 54 yr should be screened annually. (Qualified recommendation)
     c. Women 55 yr and older should transition to biennial screening or have the opportunity to continue screening annually. (Qualified recommendation)
  2. Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 yr or longer. (Qualified recommendation)
  3. Women who are at *high risk* for breast cancer based on certain factors should get an MRI and a mammogram every yr, typically starting at age 30 yr. This includes women who:
     a. Have a lifetime risk of breast cancer of about 20% to 25% or greater, according to risk assessment tools that are based mainly on family history.
     b. Have a known *BRCA1* or *BRCA2* gene mutation (based on genetic testing).
     c. Have a first-degree relative (parent, brother, sister, or child) with a *BRCA1* or *BRCA2* gene mutation and have not had genetic testing themselves.
     d. Had radiation therapy to the chest between the ages of 10 and 30 yr.
     e. Have Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome, or have first-degree relatives with one of these syndromes.
- Physicians should be familiar with the risks and benefits of various competing recommendations in order to better counsel patients.
- Breast radiologic evaluation, evaluation of nipple discharge, and evaluation of palpable mass are described in Section III.
- Exposure of the heart to ionizing radiation during breast cancer radiotherapy increases risk of ischemic heart disease. The increased rate of ischemic heart disease begins within a few yrs of exposure and continues for at least 20 yr. The increase is proportional to the mean radiation dose to the heart.

RISK REDUCTION STRATEGIES

- Prophylactic bilateral mastectomy reduces the risk for invasive breast cancer by >90%.
- Counseling points for women with average risk interested in contralateral prophylactic mastectomy (CPM) are summarized in Box 3.
- Selective estrogen receptor modulators (SERM) reduce the incidence of hormone receptor-positive invasive breast cancer by 50%.
- Ovarian failure is a common toxic effect of chemotherapy. Administration of the gonadotropin-releasing hormone (GnRH) agonist Goserelin appears to protect against ovarian failure, reducing the risk of early menopause and improving prospects for fertility.

TABLE 10 Breast Cancer Screening Recommendations by Organization

Organization	When to Initiate Screening	Frequency of Screening	When to Stop Screening
American Academy of Family Physicians (AAFP)	Follow U.S. Preventive Services Task Force (USPSTF) recommendations	Follow USPSTF recommendations	Follow USPSTF recommendations
American Cancer Society (ACS)	Opportunity to begin screening at ages 40-44 Regular screening starting at age 45	Annually from age 45-54 Biennially starting at age 55 with opportunity to continue annually	Continue screening mammography as long as overall health is good and life expectancy is 10 yr or longer
American College of Obstetricians and Gynecologists (ACOG)	Annual screening starting at age 40	Annually	Not specified
American College of Physicians (ACP)	Individualized for women ages 40-49 Regular screening starting at age 50	Biennially	Age 75 yr or older Women of any age with life expectancy <10 yr
American College of Radiology (ACR)	Annual screening starting at age 40	Annually	Should be considered as long as the patient is in good health and is willing to undergo additional testing if an abnormality is detected
National Comprehensive Cancer Network (NCCN)	Annual screening starting at age 40	Annually	Upper age limit is not yet established Consider comorbid conditions limiting life expectancy (e.g., ≤10 yr) and whether therapeutic interventions are planned
U.S. Preventive Services Task Force (USPSTF)	Individualized for women ages 40-49 Regular screening beginning at age 50	Biennially	Insufficient evidence to recommend for or against screening at age 75 or older

(From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

BOX 3 Counseling Points for Women with Average Risk Interested in Contralateral Prophylactic Mastectomy (CPM)

- There is a low annual contralateral breast cancer risk in women with average risk factors.
- Risk of contralateral breast cancer is decreasing with use of adjuvant therapy.
- Removing the contralateral breast does not decrease the risk for developing distant metastases.
- Breast cancer does not commonly metastasize from one breast to the other.
- CPM does not improve breast cancer–specific survival.
- CPM does not decrease local recurrence.
- Contralateral breast cancers tend to be at a lower stage than the initial primary cancer.
- CPM increases the surgical complication risk.
- Choice of CPM may influence reconstruction options.
- There are alternatives to CPM, including chemoprevention and surveillance.

(From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Breast Cancer (Patient Information)
Breast Cancer: For Men (Patient Information)
Breast Abscess (Related Key Topic)
Fibrocystic Breast Disease (Related Key Topic)

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SUGGESTED READINGS

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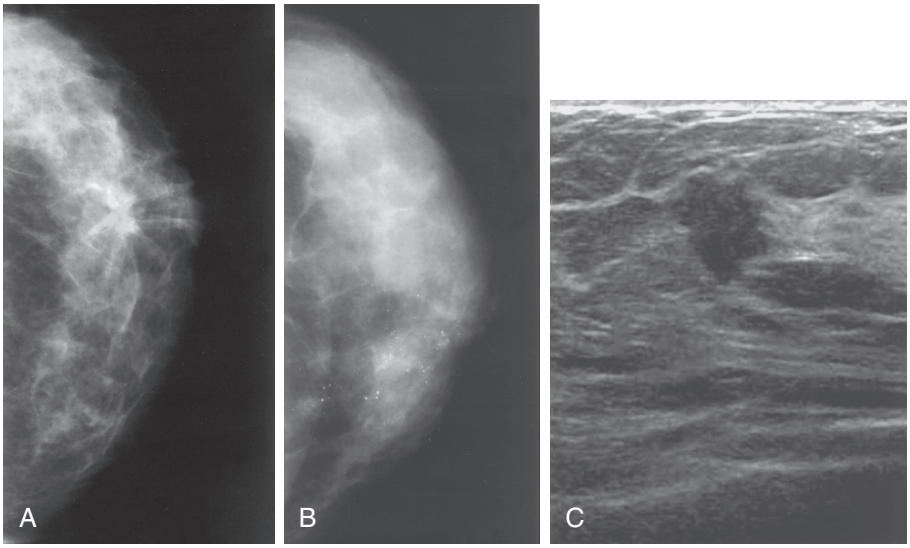

FIG. E2 Mammogram and ultrasound findings of breast disease. A, A stellate mass in the breast. The combination of a density with spiculated borders and distortion of surrounding breast architecture suggests a malignancy. **B,** Clustered microcalcification. Fine, pleomorphic, and linear calcifications that cluster together suggest the diagnosis of ductal carcinoma in situ (DCIS). **C,** An ultrasound image of breast cancer. The mass is solid, containing internal echoes, and displaying an irregular border. Most malignant lesions are taller than they are wide. (From Townsend CM et al [eds]: *Sabiston textbook of surgery*, ed 17, Philadelphia, 2004, WB Saunders.)

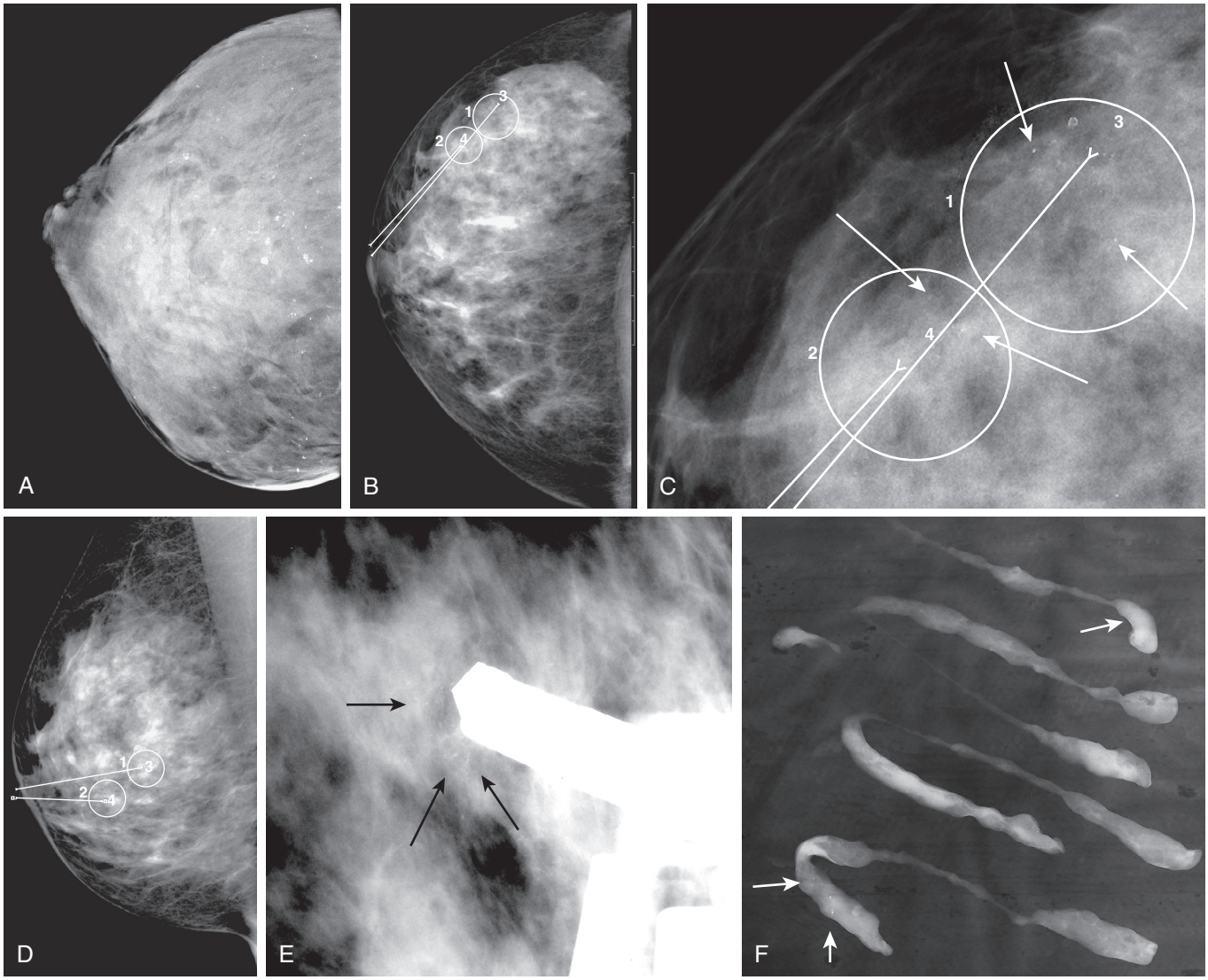

FIG. E3 Digital mammography and workup of breast calcifications. A, Craniocaudal (CC) view in a routine screening of a 43-yr-old woman. Digital mammography penetrates dense breast tissue better than film-screen mammography, clearly showing diffuse benign pattern of large and small calcifications throughout the breast. **B,** CC view in a routine screening of a 46-yr-old woman. Digital mammography shows two areas of very faint calcification in the outer breast that require further workup. **C,** Close-up view of **B,** showing the calcifications (*arrows*) to be variable in size and shape, which is worrisome for malignancy, particularly ductal carcinoma in situ. Such tiny calcifications in a background of dense breast stroma are easier to see on digital mammography than on film-screen mammography. Computer-assisted diagnosis programs also help the radiologist to locate even tiny groups of faint calcifications such as these. **D,** Mediolateral view in the same patient as in **B,** showing that the calcifications are in the lower breast. **E,** Image from stereo core biopsy procedure in the same patient as in **B,** showing the core needle immediately proximal to one of the groups of calcifications. Stereo core biopsy allows histologic sampling of tiny groups of calcifications, which can be very helpful in planning surgical approach. This interventional procedure can decrease the total number of surgeries that a patient must undergo to achieve definitive treatment. **F,** Radiograph of specimen from stereo core biopsy procedure on the same patient as in **B,** showing that there are several tiny calcifications (*arrows*) within some of the core samples. Pathologic analysis of the core biopsy revealed ductal carcinoma in situ, high grade, with comedo features. (From Skarin AT: *Atlas of diagnostic oncology*, ed 4, Philadelphia, 2010, Elsevier.)

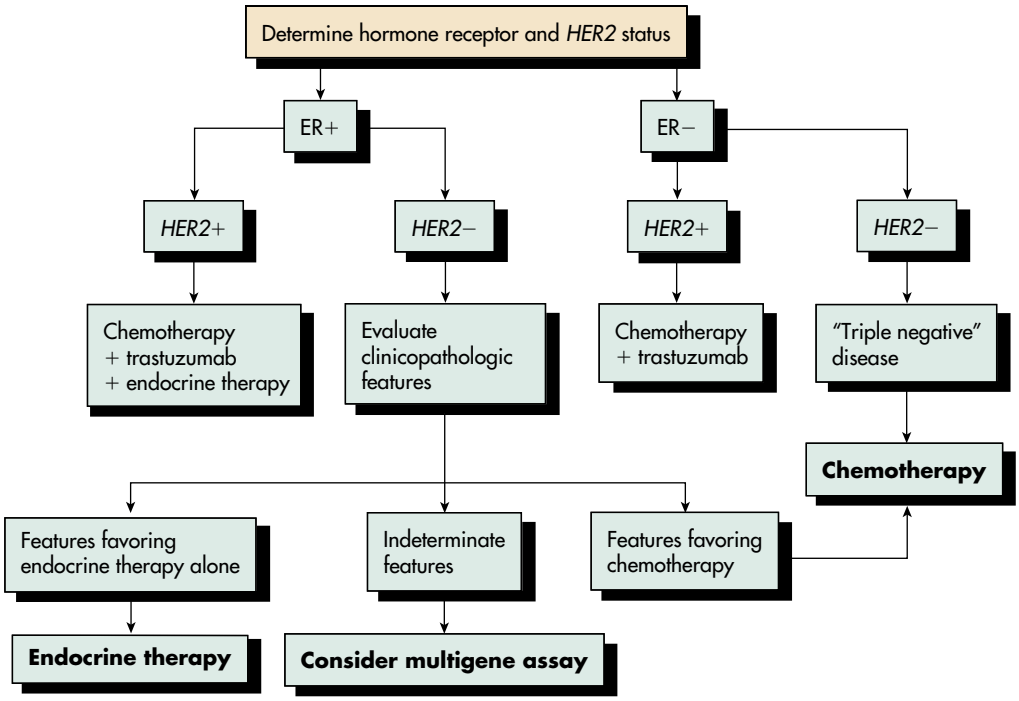

FIG. E4 Management of recurrent and metastatic breast cancer. Considerations for adjuvant chemotherapy. *ER,* Estrogen receptor; *HER2,* human epidermal growth factor receptor 2. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, WB Saunders.)

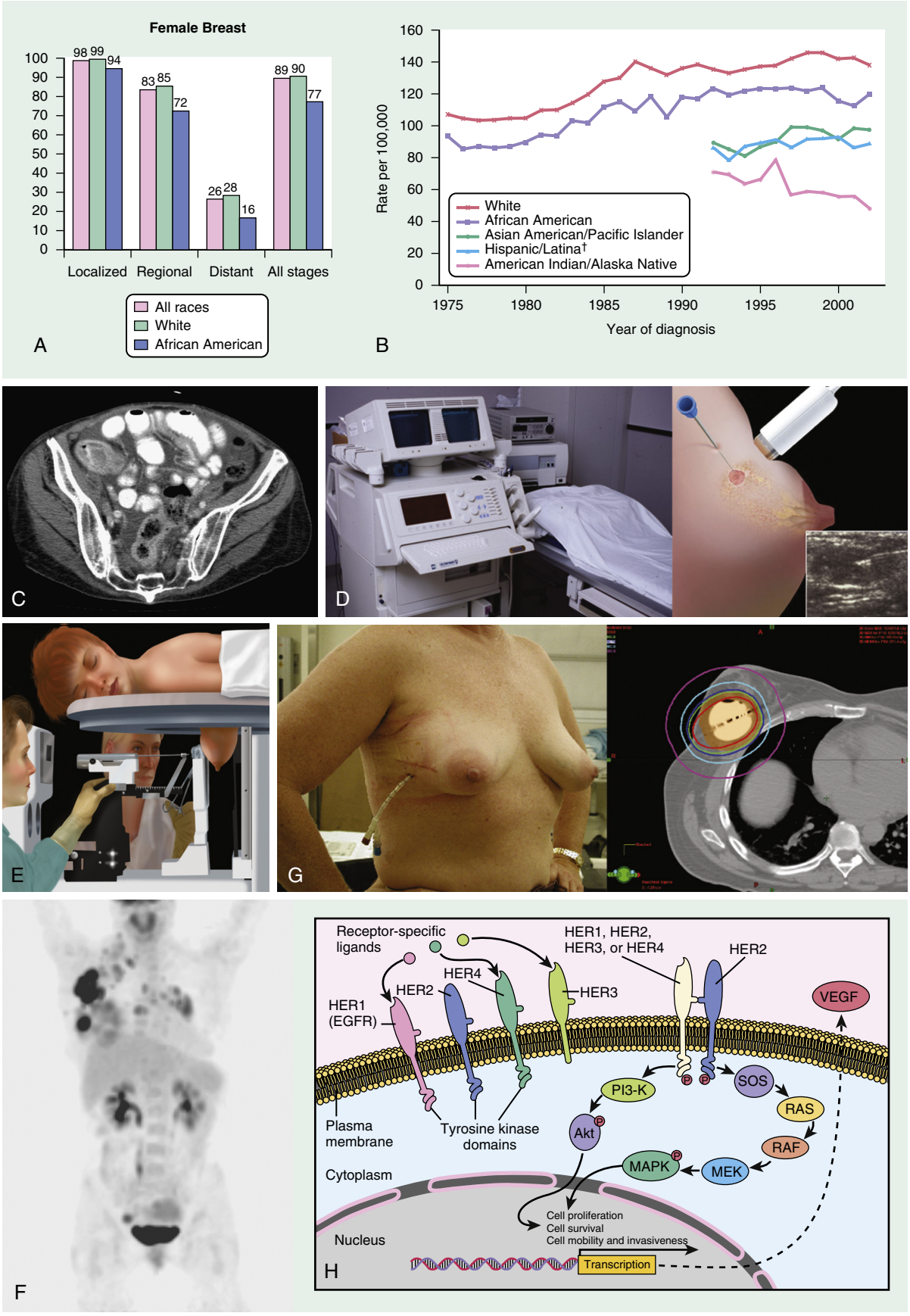

FIG. E5 A, 5-yr relative survival by race and stage at diagnosis of breast cancer (SEER data, 1996-2002). **B,** Female breast cancer incidence by race and ethnicity (SEER data). **C,** When lobular breast cancer metastasizes, it can often infiltrate serosal surfaces, mimicking ovarian cancer. This patient presented with abdominal

Continued

FIG. E5 (Continued)
bloating, tightness, and narrowing in her stool caliber 9 yr after the diagnosis of a stage I breast cancer. Note the diffuse thickening of the rectal and colonic wall, peritoneal carcinomatosis, and ascites. A colonoscopy was performed, and biopsy confirmed diffuse involvement with metastatic adenocarcinoma consistent with a breast primary. On restaging, she was also noted to have multiple osseous metastases. **D,** In an ultrasound-guided needle biopsy, the ultrasound probe is used to localize the lesion that was identified either on physical examination or on mammogram. A biopsy needle is passed through the lesion several times to obtain tissue. Compared to a stereotactic biopsy, an ultrasound-guided biopsy is faster and better tolerated by most patients. However, not all lesions may be amenable to an ultrasound-guided biopsy. **E,** The premise behind stereotactic needle biopsy is that a lesion can be localized in 3D by evaluating its changes in position in a series of angled radiographic views. First, a radiograph localizes the suspicious area; then two additional views, angled 15 degrees to either side of the lesion, are obtained. A computer calculates how much the lesion's position appears to have changed on each of the angled views and uses these data to estimate the lesion's location within 3D space. With the advent of digital mammography, these images are commonly acquired digitally. **F,** Positron emission tomography (PET) involves injection of a substance labeled with a positron-emitting isotope (commonly, fluorine-18 bound to D-glucose, called FDG for 2-([18F]fluoro-2-deoxy-D-glucose)). Metabolically active cells, especially malignant ones, preferentially take up glucose and therefore FDG, as compared with nonneoplastic tissue. Sensitivity of PET can vary considerably by tumor type and size. False-positive results can occur in areas of inflammation or infection. Many machines now acquire CT images in tandem with PET images, which can then be fused together to provide anatomic correlation by CT with metabolic activity measurements by PET. This patient presented with palpable axillary adenopathy and a large breast mass with associated erythema, skin edema, and nipple retraction. Note the extremely intense areas of uptake within the right breast and axilla corresponding to the patient's known locally advanced breast cancer. Also note the intense uptake in the right supraclavicular, paratracheal, prevascular, precarinal, and hilar lymph nodes suspicious for metastatic disease. Uptake in the kidney, bladder, and ureters is physiologic and due to FDG excretion. Uptake in the right adnexa and jaw is most likely physiologic and benign. **G,** Panels 1 and 2: Accelerated partial breast irradiation (APBI) encompasses techniques including intracavitary and interstitial brachytherapy as well as 3D-conformal, intensity-modulated, and intraoperative external-beam radiation therapy. One of the more commonly used brachytherapy methods in the U.S., the MammoSite Brachytherapy System (Hologic, Massachusetts), involves insertion of a catheter with a balloon tip into the lumpectomy cavity at the time of surgery or shortly thereafter (panel 1). The balloon is filled with saline, and a high-dose-rate radioactive source is introduced twice per day for 5 days by computed axial tomography scan–based treatment planning, permitting a highly conformal dose to be delivered to the first centimeter of remaining breast tissue with optimal sparing of the remaining tissue and other regional organs (panel 2). The balloon catheter is removed upon completion. APBI is an option only for selected patients, mainly older women with smaller, node-negative "low-risk" tumors and with negative margins. **H,** The *HER* family of receptors (human epidermal growth factor receptor, also called ErbB) is a group of transmembrane tyrosine kinase receptors that regulate cell growth, survival, and differentiation via a variety of pathways, including RAS (rat sarcoma), RAF (receptor activation factor), MAPK (mitogen-activated protein kinase), and MEK (mitogen extracellular signal kinase). The tyrosine kinase domains are activated by dimerization. Current therapeutics involve tyrosine kinase inhibitors (e.g., lapatinib) and antibodies directed against the *HER2* protein and VEGF (vascular endothelial growth factor) (e.g., trastuzumab and bevacizumab). *Akt,* protein kinase B; *PI3-K,* phosphatidylinositol 3-kinase; *SOS,* Son of sevenless. (Skarin AT: *Atlas of diagnostic oncology*, ed 4, Philadelphia, 2010, Elsevier.)(Image courtesy of Drs. Pamela Dipiro and Wendy Chen, Dana Farber Cancer Institute, Boston, MA.) (Image courtesy of Robyn L. Birdwell, MD, Brigham and Women's Hospital, Boston, MA, and Diagnostic Imaging Breast, Amirsys, Inc., Salt Lake City, UT, 2006.) (Image courtesy of Robyn L. Birdwell, MD, Brigham and Women's Hospital, Boston, MA, and Diagnostic Imaging Breast, Amirsys, Inc., Salt Lake City, UT, 2006). (Courtesy of Phillip M. Devlin, MD, Dana Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA.)

BASIC INFORMATION

DEFINITION

Breech presentation occurs when fetal longitudinal axis is such that the cephalic pole occupies the uterine fundus (Fig. E1). Three types exist: Frank (48% to 73%, flexed hips, extended knees), complete (4.6% to 11.5%, flexed hips and knees), and footling (12% to 38%, hips extended).

ICD-10CM CODES

O83	Breech extraction
O83.1	Other assisted breech delivery
O83.2	Other manipulation assisted delivery (version with extraction)
O32.	Maternal care for malpresentation
O32.1	Maternal care for breech presentation
O32.8	Maternal care for footling, incomplete, prolapsed breech
P03.0	Newborn affected by breech delivery and extraction

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Gestational age dependent: 3% to 4% overall, 14% at 29 to 32 wk, 33% at 21 to 24 wk

PERINATAL MORTALITY: Three to five times increase over vertex presentation at term, regardless of delivery route. When corrected for associated increase in congenital anomalies and complications of prematurity, morbidity and mortality rates approach those of vertex presentation at term regardless of delivery route.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Lack of presenting part on vaginal examination
- Fetal heart tones heard above the umbilicus
- Leopold maneuvers revealing mobile fetal part in the uterine fundus

ETIOLOGY

- Abnormal placentation (fundal), uterine anomalies (fibroids, septa), pelvic or adnexal masses, alterations in fetal muscular tone, or fetal malformations
- Associated conditions: Trisomy 13, 18, 21; Potter syndrome; myotonic dystrophy; prematurity

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Vertex, oblique, or transverse lie

WORKUP

- Determine if any etiology for breech presentation exists that may affect mode of delivery selection: Presence of uterine anomalies (fibroids, septum, Mullerian anomaly), placentation issues, estimated gestational age of fetus, fetal congenital anomalies, fetal aneuploidy.
- If fetus viable and it is clinically indicated, assess fetal status by continuous FHR monitoring.
- Perform ultrasound to confirm position and presenting part (see "Imaging Studies").
- Assess pelvis to determine feasibility of vaginal delivery.
- Assess other comorbidities in regards to safety of vaginal versus abdominal delivery.

IMAGING STUDIES

Ultrasound to evaluate for:

- Fetal anomalies
- Placental location
- Position of fetal head relative to spine (check for hyperextension)
- Estimated fetal weight (2500-3800 g for attempt of vaginal delivery)
- Type of breech (frank, complete, footling)
- Gestational age

TREATMENT

ACUTE GENERAL Rx

- Vaginal delivery in breech position.
  1. Vaginal delivery in selected patients (see "Comments" section): Allow maternal expulsive forces to deliver fetus until scapula visible (avoiding traction); with flexion and/or Piper forceps, deliver fetal head
- Cesarean delivery.
  1. Perform cesarean section (see "Comments").
- External cephalic version followed by induction of labor and attempt at vaginal delivery in vertex position.
  1. Improved success if >37 wk. Success rates range from 16% to 100%. Adequate uterine relaxation is essential. Use of terbutaline and/or epidural anesthesia improves success rates. Data are not adequate to establish absolute or relative contraindications; must individualize. Contraindicated if vaginal delivery is not appropriate. In general, contraindicated with active placental abruption, placenta previa, certain fetal anomalies, version of a first breech presenting multiple gestation, or nonreassuring fetal status. Other relative contraindications: Perform with caution with low-lying placenta, prior uterine incision, and preterm gestation. Informed consent includes risks of abruption, cord prolapse, rupture of membranes, stillbirth, and hemorrhage (<1%).

COMPLICATIONS

- Head entrapment: Leading cause of death (with the exception of anomalous fetuses); 88 cases per 1000 deliveries; avoid by maintaining flexion of fetal head (Mauriceau Smellie Veit maneuver), use of Piper forceps or Dührssen incisions. Avoid hyperextension of head during delivery.
- Cord prolapse: Usually occurs late in labor. Incidence depends on type of breech: Frank (0.5%), complete (4%-5%), footling (10%).
- Nuchal arm: Arm extended above fetal head; occurs when there is undue traction before delivery of fetal scapulas. Treatment: Bring trapped arm across infant's face (Lovset maneuver).

DISPOSITION

If confounding variables are corrected for (prematurity, associated congenital anomalies [6.3% of breeches vs. 2.4% in general population]), route of delivery plays less important role in fetal outcome than previously believed if the obstetrician performing the delivery is experienced in breech delivery. Since the publication of the Term Breech Trial in 2000, planned cesarean is becoming the preferred mode of birth for women with a breech fetus. In addition,

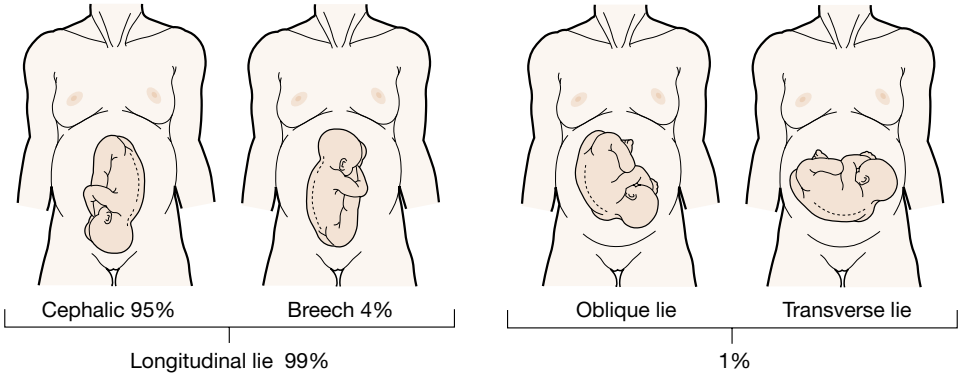

FIG. E1 Fetal lie at term. (From Magown BA: *Clinical obstetrics & gynaecology,* ed 4, 2019, Elsevier.)

as seasoned obstetricians retire, and fewer new physicians are taught the technique of breech delivery, despite relative safety, this modality as an option for delivery has decreased over time.

REFERRAL

An obstetrician trained in vaginal breech delivery is prerequisite for attempt; explain to the patient that with cesarean section, certain risks (i.e., hyperextension of the fetal head with resultant spinal cord injury) may be minimized but not eliminated. Cesarean section also comes with its own risks and requires informed consent as well.

PEARLS & CONSIDERATIONS

COMMENTS

Since the publication of the Term Breech Trial in 2000, little evidence has proven conclusively that cesarean birth is safer than vaginal birth of a fetus in a breech presentation when certain criteria are met. For a planned vaginal delivery of the breech presentation, mortality rate increased thirteenfold and morbidity sevenfold, mainly because of an increase in congenital anomalies, perinatal hypoxia, birth injury, and prematurity. Based on the 2015 Cochrane Review, planned cesarean section compared with planned vaginal birth reduced perinatal or neonatal death as well as the composite outcome death or serious neonatal morbidity, at the expense of increased maternal morbidity. In a subset with 2-yr follow-up, infant medical problems were increased following planned c-section, and no difference in long-term neurodevelopmental delay was found. There is no contraindication to induction of labor in breech presentation or planned breech delivery in primigravidas. Many obstetric organizations support the option of a planned vaginal birth for women with a breech presentation. The benefits need to be weighed against factors such as mother's preference for vaginal birth and risks such as future pregnancy complications. Planned vaginal delivery of term singleton breech fetus is reasonable under a hospital-specific strict prelabor selection criteria with intrapartum management guidelines/protocols, and with an experienced provider and informed consent of the patient.

CRITERIA FOR TRIAL OF LABOR WITH A PLANNED BREECH DELIVERY

- Gestational age >37 wk (proceed with caution in preterm delivery of the breech fetus; consider Maternal-Fetal Medicine consultation in these situations)
- Estimated fetal weight, 2500 to 4000 g—recognizing inherent error in estimated fetal weight approximations; actual fetal weight may be substantially smaller or larger (proceed with caution in fetuses weighing 1500-2500 g; consider Maternal-Fetal Medicine consultation in these situations)
- Adequate pelvis
- Flexed fetal head
- Frank or complete breech preferred if planning induction, although in active spontaneous unplanned labor, footling breech can be delivered safely if no cord prolapse
- No known fetal anomalies
- Normal amniotic fluid index (consider at minimum presence of mean vertical pocket >2 cm)
- Bedside availability of anesthesia and capability for immediate cesarean section (consider epidural placement; consider delivery in operating room in the event of need for emergent cesarean section)
- Informed consent
- Obstetrician trained in vaginal breech delivery

SUGGESTIONS FOR WHEN TO CONSIDER A PLANNED CESAREAN SECTION FOR BREECH

- Estimated fetal weight <1500 g or >4000 g
- Footling presentation (20% risk of cord prolapse, usually late in course of labor)
- Inadequate pelvis
- Hyperextended fetal head (21% risk of spinal cord injury)
- Nonreassuring fetal status
- Abnormal progress of labor
- Lack of trained obstetrician

RELATED CONTENT

Breech Birth (Patient Information)
Preterm Labor (Related Key Topic)

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SUGGESTED READINGS

American College of Obstetricians and Gynecologists: *ACOG practice bulletin number 161, External cephalic version*, February 2016.

American College of Obstetricians and Gynecologists: *ACOG Committee Opinion Number 745. Mode of Term Singleton Breech Delivery.* Replaces Committee Opinion Number 340 July 2006. Interim update August 2018.

American College of Obstetricians and Gynecologists: *ACOG & SMFM Joint Obstetric Care Consensus Statement. Safe Prevention of the Primary Cesarean Delivery Number 1,* reaffirmed 2019.

American College of Obstetricians and Gynecologists: *ACOG Patient Education Pamphlet AP079. If your baby is breech,* February 2019.

Hofmeyr GJ et al: Planned caesarean section for term breech delivery, *Cochrane Database Syst Rev* 7:CD000166, 2015.

BASIC INFORMATION

DEFINITION

Bronchiectasis is an irreversible pathologic dilatation of the bronchi or bronchioles resulting from a variety of causes through an interplay of host factors (either anatomic or immune defense abnormality), respiratory pathogens, and environmental factors. Radiographically, it is often divided into cylindrical, varicose, and cystic varieties, although these variants have no significant etiologic or prognostic relevance.

ICD-10CM CODES

J47.0	Bronchiectasis with acute lower respiratory infection
J47.1	Bronchiectasis with (acute) exacerbation
J47.9	Bronchiectasis, uncomplicated
Q33.4	Congenital bronchiectasis

EPIDEMIOLOGY & DEMOGRAPHICS

- The exact prevalence of bronchiectasis is unknown.
- Cystic fibrosis is responsible for nearly 50% of all cases of bronchiectasis.
- Acquired primary bronchiectasis is uncommon because of rapid diagnosis of pulmonary infections and frequent use of antibiotics.
- Effective childhood immunizations have led to a significant decrease in the incidence of bronchiectasis resulting from pertussis.
- Declining incidence of pulmonary tuberculosis has also resulted in a decline in bronchiectasis without apparent causes.
- In developed countries, an increasing proportion of patients with an identifiable cause of bronchiectasis is being seen.
- Data on morbidity and mortality from bronchiectasis are limited because patients with the highest morbidity typically are not adequately represented in randomized controlled studies.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Moist crackles at lung bases
- Chronic cough, typically with expectoration of large amount of purulent sputum
- Fever, night sweats, generalized malaise, weight loss
- Hemoptysis
- Halitosis, skin pallor
- Clubbing (infrequent)

ETIOLOGY

- Cystic fibrosis
- Lung infections (pneumonia, lung abscess, TB, nontubercular mycobacterial infections, fungal infections, viral infections)
- Impaired host defense (panhypogammaglobulinemia, primary ciliary dyskinesia/Kartagener syndrome, AIDS, chemotherapy)
- Localized airway obstruction (congenital structural defects, foreign bodies, neoplasms)
- Inflammation (inflammatory pneumonitis, granulomatous lung disease, allergic aspergillosis)
- Rheumatoid arthritis, ulcerative colitis, and so on
- Congenital disorders such as tracheobronchomegaly (Mounier Kuhn syndrome), cartilage deficiency (Williams-Campbell syndrome)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- TB
- Asthma
- Chronic bronchitis or chronic rhinosinusitis
- Interstitial fibrosis
- Chronic lung abscess
- Foreign body aspiration
- Cystic fibrosis
- Lung carcinoma
- GERD

LABORATORY TESTS

- Sputum for Gram stain, culture and sensitivity, and acid-fast bacteria
- Complete blood count with differential (leukocytosis with left shift, anemia)
- Serum protein electrophoresis to evaluate for hypogammaglobulinemia
- Antibody test for aspergillosis
- Testing for allergic bronchopulmonary aspergillosis
- Serum immunoglobulins (total IgG, IgA, IgM)
- Sweat test in patients with suspected cystic fibrosis
- Pulmonary function tests: Mild to moderate airflow obstruction
- Serum anti-*Pseudomonas aeruginosa* (PA) IgG antibody testing is highly accurate to detect chronic PA colonization in bronchiectasis patients

IMAGING STUDIES

- Chest x-ray (Fig. E1 and Fig. E2): Hyperinflation, crowded lung markings, small cystic spaces at the base of the lungs.
- High-resolution CT scan of the chest (Figs. E3 to E6) has become the best tool to detect cystic lesions and exclude underlying obstruction from neoplasm with a sensitivity and specificity exceeding 90%. The CT study should be a noncontrast study with the use of 1- to 1.5-mm window every 1 cm with acquisition time of 1 sec. Typical findings on CT include enlarged internal bronchial diameter, bronchi appearing larger than accompanying artery, lack of tapering of an airway toward periphery, ballooned cysts at the end of bronchus, and varicose constrictions along airways.
- Bronchoscopy may be helpful to evaluate hemoptysis, rule out obstructive lesions, remove mucus plugs, and also obtain microbiologic data on respiratory pathogens.
- Table 1 summarizes diagnostic studies for the classification and management of patients with bronchiectasis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Postural drainage (reclining prone on a bed with the head down on the side) and chest percussion with use of inflatable vests/high-frequency chest wall oscillation or mechanical vibrators applied to the chest may enhance removal of respiratory secretions.
- Adequate hydration.
- Supplemental oxygen for hypoxemia.
- Inhaled hypertonic saline in conjunction with chest physiotherapy improves airway clearance.

ACUTE GENERAL Rx

- Antibiotic therapy is based on the results of sputum, Gram stain, and culture and sensitivity; in patients with inadequate or inconclusive results, empiric therapy with amoxicillin/clavulanate 500 to 875 mg q12h, TMP-SMX q12h, doxycycline 100 mg bid, a fluoroquinolone, or cefuroxime 250 mg bid for 14 to 21 days is recommended.
- There is strong consideration for intravenous antibiotics in patients who require hospitalizations for acute exacerbation with signs of respiratory distress.
- Bronchodilators are useful in patients with demonstrable airflow obstruction.

CHRONIC Rx

- Avoidance of tobacco.
- Maintenance of proper nutrition and hydration.
- Prompt identification and treatment of infections.
- Pneumococcal vaccination and annual influenza vaccination.
- In patients with cystic fibrosis, using rhDNase and aerosolized antipseudomonal antibiotics should be considered. This should not be offered to patients with non–cystic fibrosis related bronchiectasis.
- Specific immunoglobulin replacement in patients with selective immunoglobulin deficiency.
- Adults with bronchiectasis with a new isolation of *P. aeruginosa* should be offered eradication antibiotic treatment. This should not be offered to adults with bronchiectasis following new isolation of pathogens other than *P. aeruginosa.*
- Inhaled corticosteroids should not be offered to adults with isolated bronchiectasis. However, the diagnosis of bronchiectasis should not affect the use of inhaled corticosteroid in patients with comorbid asthma of chronic obstructive pulmonary disease.
- Long-term antibiotics should be offered for adults with bronchiectasis who have three or more exacerbations per yr.
- Long-term mucoactive treatment (≥3 mo) should be considered in patients who have difficulty in expectorating sputum and poor quality of life and where standard airway clearance techniques such as chest physiotherapy have failed to control symptoms.
- Bronchodilators should be used before physiotherapy, including inhaled mucoactive drugs, as well as before inhaled antibiotics, as this increases tolerability and optimizes delivery of medications in diseased areas of the lungs.

TABLE 1 Diagnostic Studies for the Classification and Management of Patients with Bronchiectasis

Test	Comments
Routine, Universal Studies	
Computed tomography lung scan (CTLS)	If bronchiectasis (BXSIS) is suspected, CTLS is the definitive test. Thin-section, high-resolution images may help detect subtle airway dilation before bronchial walls are grossly thickened. Contrast is generally not helpful and may, in fact, compromise the overall resolution of the study. CTLS may also identify esophageal abnormalities.
Pulmonary function tests (PFTs)	For patients with significant bronchiectasis, comprehensive PFTs, including spirometry, bronchodilator responsiveness, lung volumes, and diffusion capacity, are important studies that aid in management and prognosis. PFTs may also provide useful hints regarding predisposing conditions.
Complete blood count	Anemia may reflect effects of chronic infection or blood loss (consider inflammatory bowel disorders). Leukocytosis may mark severity of infection. Eosinophilia may suggest ABPA/M.
ESR, C-reactive protein	Nonspecific markers of inflammation; very high levels may suggest underlying connective tissue disease or vasculitis.
Routine sputum culture	Antibiotic therapy in bronchiectasis should generally be directed against specific pathogens and guided by in vitro susceptibility. The presence of mucoid strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus* may raise suspicions for CF. *Stenotrophomonas maltophilia*, *Alcaligenes xylosoxidans*, and *Burkholderia cepacia* are gram-negative bacilli that may prove problematic pathogens in patients with long-standing bronchiectasis. Isolation of *B. cepacia* and *Helicobacter pylori* requires special laboratory techniques.
Mycobacterial sputum culture	Environmental mycobacteria such as *Mycobacterium avium* complex, *M. chelonae*, and *M. abscessus* appear to be increasingly common in contemporary bronchiectasis. May be commensal but often are pathogenic.
Fungal sputum culture	In patients with an asthmatic component, the presence of *Aspergillus* species (or other molds including Pseudallescheria or penicillium) may be suggestive of etiology.
CT scan of sinuses	Many patients with bronchiectasis also suffer chronic rhinosinusitis. The presence of extensive sinus involvement suggests possible CF, immunoglobulin deficiencies, or ciliary disorders. Also, optimal management often entails aggressive sinus care.
Specific, Directed Studies	
Sweat chloride, CF genotyping, and nasal potential differences	For bronchiectasis patients with bilateral disease, recurrent sinusitis, and no other identified risk factor, mild variants of CF appear to be relatively common. Sweat chloride is regarded as the primary screening test for CF, but a considerable portion of adults with CF have borderline or normal results. Nasal potential difference may be useful for identifying CF in equivocal cases.
$Alpha_1$-antitrypsin (AAT) levels and phenotype	AAT anomalies appear to be a substantial risk factor for bronchiectasis, especially with white females. Abnormal proteinase inhibitor (Pi) phenotypes, even heterozygous patterns such as MS, appear to confer risk even with normal levels of AAT. Repletion of AAT may enhance resistance to lower respiratory tract infections.
Immunoglobulin (Ig) levels	Deficiencies of IgG or IgA may promote bronchiectasis; IgG subclass deficiencies may also be a factor. Elevated levels of IgE may suggest ABPA/M or Job syndrome. Hyper-IgM may be associated, as well, with chronic infections.
Ciliary morphology or function	For individuals with suggestive stories, a nasal ciliated epithelium biopsy with transmission electron microscopy may identify primary ciliary dyskinesia. Other studies including ex vivo ciliary activity, the saccharine test, or spermatozoa analysis may aid in this diagnosis.
Nasal nitric oxide (NNO) levels	Patients with documented PCD have significantly lower levels of NNO than normal or patients with CF. Although not universally available, such testing may prove highly useful in identifying PCD. Paradoxically, exhaled NO levels have been elevated in bronchiectasis of diverse etiologies except CF.
Barium swallow (BaS)	The BaS may detect disturbed deglutition, esophageal diverticula, obstructing lesions (tumors or strictures), hypomotility, achalasia, hiatal hernias, or lower esophageal sphincter (LES) incompetence with reflux. The absence of reflux on a BaS, however, does not exclude this problem (see pH probe).
pH probe	For patients suspected of gastroesophageal reflux, an 18- to 24-hour study with a transnasal pH probe may identify, quantitate, and characterize reflux. Medications that inhibit acid production must be stopped before such tests.
Esophageal manometry	For patients being considered for surgical repair of the LES, manometry should be performed to determine that the esophagus generates sufficient pressure to propel food and liquids through the tightened sphincter.
Tailored hypopharyngography (TH)	TH is useful in detecting abnormalities of the initial phase of swallowing, deglutition. Persons particularly prone to problems include those with prior strokes, Parkinson disease, bulbar disorders including postpolio syndrome, and those with prior laryngeal or pharyngeal surgery. Note that some patients have gross aspiration without clinical manifestations (choking, coughing); this may occur in individuals with none of the above risk factors.
Less Common, Exotic Studies	
Collagen vascular disease (CVD) serologies	Various CVDs may contribute to the risk for bronchiectasis, including RA, ankylosing spondylitis, and systemic lupus erythematosus. Thus, for patients with compatible histories or physical findings, assays for rheumatoid factor, HLA-B27, and ANA may provide insight into predisposing conditions. CVD serologies may also suggest the diagnosis of Sjögren syndrome, particularly SSA/Ro and/or SSB/La.
Schirmer test	For patients with histories suggestive of "sicca syndrome" (dry eyes, dry mouth, oral ulcers), a positive Schirmer test may indicate the presence of either primary or secondary (associated with a CVD) Sjögren syndrome.

ABPA/M, Allergic bronchopulmonary aspergillosis/other mycoses; *ANA*, antinuclear antibody; *CF*, cystic fibrosis; *ESR*, erythrocyte sedimentation rate; *HLA*, human leukocyte antigen; *MS,* multiple sclerosis; *NO,* nitric oxide; *PCD*, primary ciliary dyskinesia; *RA*, rheumatoid arthritis.
From Mason RJ: *Murray & Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, Saunders.

DISPOSITION

- Prognosis is variable with severity of the disease and underlying etiology of bronchiectasis.
- In overlap syndrome of bronchiectasis with rheumatoid arthritis, worse outcomes occurred compared with other bronchiectasis etiologies.

REFERRAL

- Surgical referral for partial lung resection in patients with localized, severe disease unresponsive to medical therapy or in patients with massive hemoptysis. Surgical resection of localized bronchiectasis is safe and improves quality of life.
- Lung transplantation for bronchiectasis accounts for about 2% to 3% of all lung transplant candidates (*The Registry of the International Society for Heart and Lung Transplantation*).

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Bronchiectasis (Patient Information)

AUTHORS: **Aline N. Zouk, MD,** and **Samaan Rafeq, MD**

FIG. E1 Bronchiectasis. Multiple ring shadows, many containing air-fluid levels, are present throughout the lower zones of this patient with cystic bronchiectasis. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

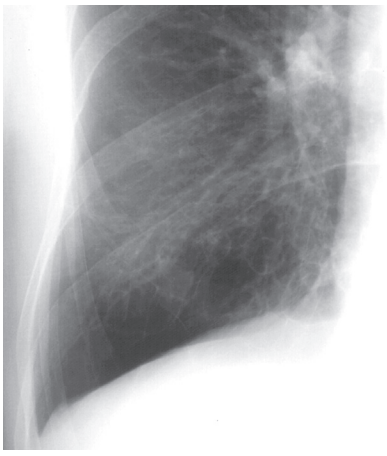

FIG. E2 Bronchiectasis. Targeted image of a right lower lung base shows tramlines and ring opacities. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

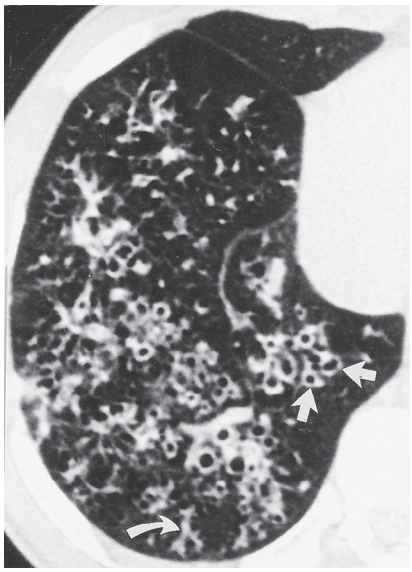

FIG. E3 Bronchiectasis. CT demonstrating dilated subsegmental bronchi. The bronchi are larger than the accompanying vessels with some demonstrating the "signet ring" sign *(arrows).* Plugging of peripheral smaller bronchi is also evident *(curved arrow).* (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

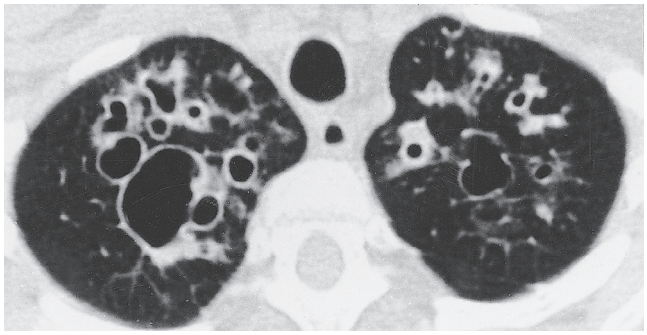

FIG. E4 Cystic bronchiectasis. CT demonstrates multiple ring shadows due to irregularly dilated bronchi. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

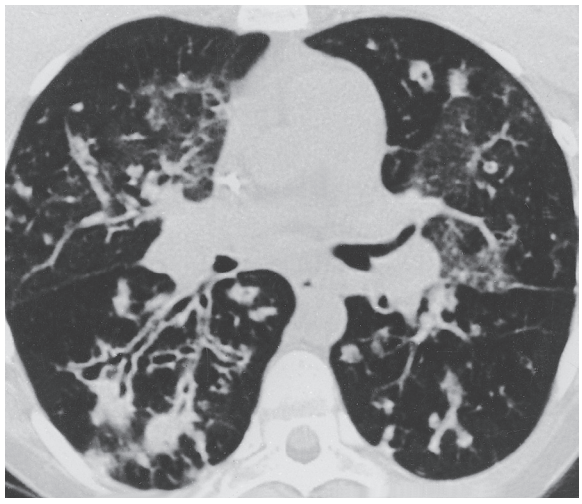

FIG. E5 Cylindrical bronchiectasis. The bronchi fail to taper and have irregular thickened walls. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

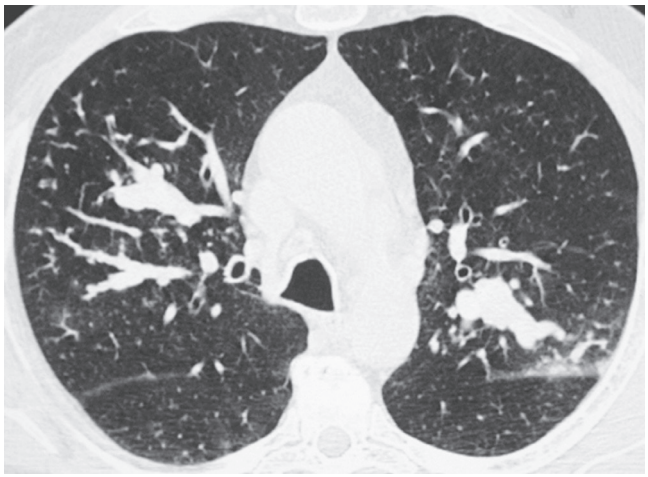

FIG. E6 ABPA. HRCT demonstrating mucoid impactions within segmental and subsegmental dilated bronchi in the upper lobes. Small centrilobular linear branching opacities are seen in the periphery of the right upper lobe. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Brucellosis is a zoonotic infection caused by one of four species of *Brucella*. It commonly presents as a nondescript febrile illness. It is the most common zoonosis worldwide.

SYNONYMS

Malta fever, undulant fever
Bang disease

ICD-10CM CODE
A23.9 Brucellosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): About 100 to 200 cases/yr (may be underreported) (Fig. E1), predominantly *B. melitensis*. The number of cases is increasing worldwide due to travel and globalization.
PREDOMINANT SEX: Male
PREDOMINANT AGE: Adult
CONGENITAL INFECTION: Recent evidence suggests a high rate of spontaneous abortions in untreated pregnant women during the first and second trimesters.
NEONATAL INFECTION: Can occur if mother is infected during pregnancy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation period is 1 wk to 3 mo.
- Patients may be asymptomatic or have nonspecific symptoms such as fever, sweats, malaise, weight loss, depression, arthralgia, and arthritis.
- Fever is the most common finding (Fig. E2).
- Hepatomegaly, splenomegaly, or lymphadenopathy is possible.
- Localized disease includes endocarditis, meningitis, spondylitis, sacroiliitis, and osteomyelitis (especially vertebral).
- Chronic hepatosplenic suppurative brucellosis (CHSB) presents with hepatic or splenic abscesses. This form is thought to be a reactivation and can occur years after the acute infection.
- Table E1 describes a clinical classification of human brucellosis.

ETIOLOGY

- Caused by infection with *Brucella* species:
  1. Most commonly *B. melitensis* but also *B. suis, B. abortus*, or *B. canis*.
  2. A small, gram-negative coccobacillus.
- Acquired through ingestion of organisms (unpasteurized goat's or cow's milk, cheese, or ice cream) or breaks in the skin or by inhalation.
- Most cases occur after exposure to animals (sheep, goats, swine, cattle, or dogs) or animal products (i.e., milk, cheese, hides, tissue).
- Most cases (in the U.S.) occur in men with occupational exposure to animals (e.g., farmers, ranchers, laboratory workers, veterinarians, abattoir workers). Accidental animal vaccine exposure warrants evaluation for a full therapeutic antibiotic regimen.
- Laboratory workers, especially those in microbiology, are also at increased risk. Guidelines for postexposure prophylaxis are available from *MMWR Surveill Summ* 57:39, 2009.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Many febrile conditions without localizing manifestations (i.e., tuberculosis, endocarditis, typhoid fever, malaria, autoimmune diseases)

WORKUP

- Cultures of blood, bone marrow, or other tissue (e.g., lymph node, liver) should be sent and held for 4 wk because *Brucella* spp. grow slowly in vitro.
- Granulomas on biopsy are suggestive of diagnosis.
- Serum agglutination test (see the following).

LABORATORY TESTS

- WBC count: Normal or low.
- Serology:
  1. Serum agglutination test (SAT) to detect antibodies to *B. abortus, B. melitensis,* and *B. suis.* An elevated initial titer of ≥1:160 or demonstration of a fourfold increase from acute to convalescent titers is considered diagnostic. Positive test results warrant confirmatory testing with specific *Brucella* agglutination tests.
  2. Specific antibody test to identify antibodies to *B. canis.*
  3. False-negative SAT possibly resulting from a prozone effect.
  4. PCR (polymerase chain reaction) for *Brucella* spp. specific 16S rRNA or DNA sequences are increasingly used for the

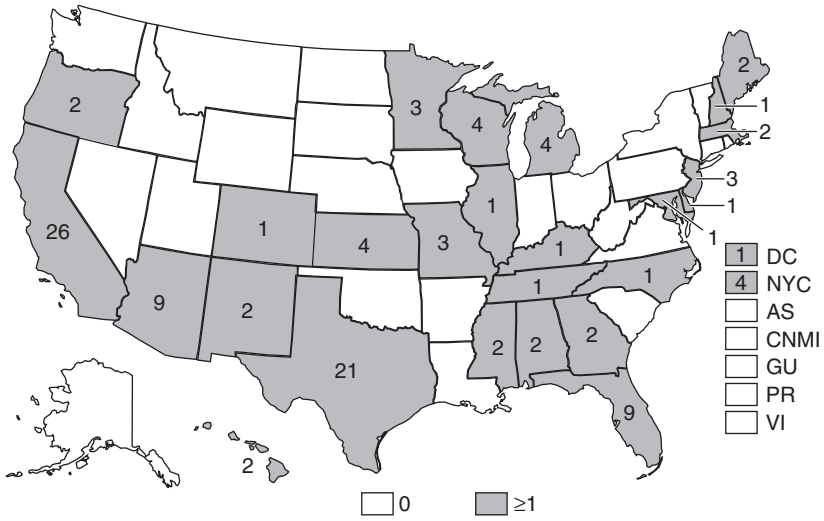

FIG. E1 Brucellosis. Number of reported cases—United States and U.S. territories, 2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59:1-111, 2012.)

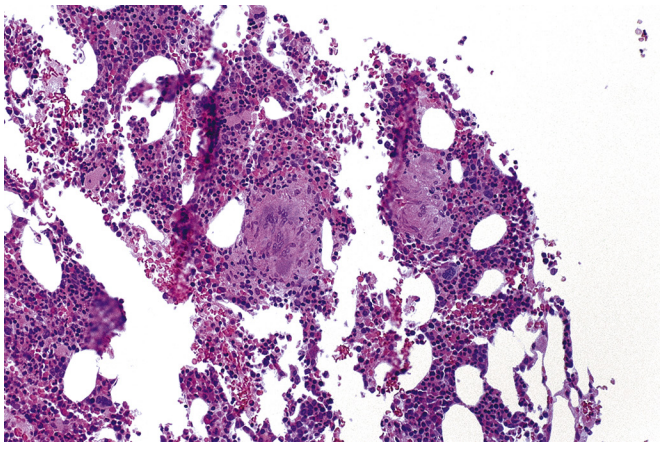

FIG. E2 Brucellosis. Several small noncaseating granulomas are present in the bone marrow of a patient with an unexplained febrile disease. He was not aware of exposure to *Brucella* in over 30 yr (HANDE, ×40, *Brucella suis* isolated from blood cultures). (From Scott MA et al: Infectious disease pathology. Silverberg SG [ed]: *Principles and practice of surgical pathology and cytopathology,* ed 4, Philadelphia, 2006, Churchill Livingstone, p 101.)

TABLE E1 Clinical Classification of Human Brucellosis

Classification	Duration of Symptoms Before Diagnosis	Major Symptoms and Signs	Diagnosis	Comments
Subclinical	—	Asymptomatic	Positive (low titer) serology, negative cultures	Occurs in abattoir workers, farmers, and veterinarians
Acute and subacute	Up to 2-3 mo and 3 mo to 1 yr	Malaise, chills, sweats, fatigue, headache, anorexia, arthralgias, fever, splenomegaly, lymphadenopathy, hepatomegaly	Positive serology, positive blood or bone marrow cultures	Presentation can be mild, self-limited *(B. abortus)* or fulminant with severe complications *(B. melitensis)*
Localized	Occurs with acute or chronic untreated disease	Related to involved organs	Positive serology, positive cultures in specific tissues	Bone or joint, genitourinary, hepatosplenic involvement most common
Relapsing	2-3 mo after initial episode	Same as acute illness but may have higher fever and more fatigue, weakness, chills, and sweats	Positive serology, positive cultures	May be extremely difficult to distinguish relapse from reinfection
Chronic	>1 yr	Nonspecific presentation but neuropsychiatric symptoms and low-grade fever most common	Low titer or negative serology, negative cultures	Most controversial classification; localized disease may be associated

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

diagnosis of brucellosis from blood, tissue samples, and bone marrow.

IMAGING STUDIES

- Radiographs to show splenic or hepatic calcifications in chronic disease
- Bone scan, MRI, and radiographs of the spine to suggest osteomyelitis
- Ultrasound or CT scan of the abdomen to show an enlarged liver or spleen
- Echocardiogram to reveal vegetations in endocarditis

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Drainage of abscesses
- Valve replacement for endocarditis

ACUTE GENERAL Rx

Combination antibiotics required:

- Major options:
  1. Doxycycline 100 mg PO bid for 6 wk plus rifampin plus gentamycin 5 mg/kg qd for 7 days.
- Alternative therapies:
  1. Doxycycline 100 mg PO bid plus rifampin 600 to 900 mg PO qd for 6 wk plus streptomycin.
  2. Sulfamethoxazole 800 mg/trimethoprim 160 mg one DS tablet PO qid, ciprofloxacin 500 mg bid for 6 wk along with doxycycline or rifampin as an alternative regimen.
  3. Courses <6 wk are associated with higher relapse rates; longer courses are recommended for complicated disease (e.g., osteomyelitis, endocarditis, and neurobrucellosis).

DISPOSITION

- Relapse is possible weeks to months after the completion of therapy.
- Reactivation with CHSB has been reported up to 35 yr after initial illness.

REFERRAL

For all cases to an infectious disease specialist

PEARLS & CONSIDERATIONS

COMMENTS

- Alert the microbiology laboratory to the possibility of *Brucella* spp. (prolonged incubation needed and biohazard for laboratory personnel).
- Do not use doxycycline in children or pregnant women.
- Avoid aminoglycosides in pregnant women.
- Fluoroquinolones have good in vitro activity against *Brucella* spp. and are under study as components of complex regimens. However, they do not perform well in the requisite acidic environment.
- Monotherapy is not effective.

AUTHOR: **Patricia Cristofaro, MD**

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BASIC INFORMATION

DEFINITION

Brugada syndrome (BRS) is an inherited disorder involving cardiac sodium channels characterized by typical electrocardiographic abnormalities. Patients with a Brugada pattern on ECG and symptoms such as palpitations, syncope, or sudden death are deemed to have BRS. BRS predisposes one to sudden cardiac death (SCD) secondary to polymorphic ventricular tachycardia (PVT) or ventricular fibrillation (VF) in the absence of structural heart disease.

SYNONYMS

BRS
Sudden unexpected nocturnal death syndrome (SUNDS)

ICD-10CM CODES
I49.9 Cardiac arrhythmia, unspecified
I47.2 Ventricular tachycardia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The incidence ranges from 1 to 5:10,000 people in Europe and 12:10,000 in Southeast Asia.
PREVALENCE: It comprises 4% of SCD and 20% of SCD in structurally normal hearts. Although found in every population, the prevalence is much higher in Asian and Southeast Asian countries; in some Southeast Asian countries, such as Laos and Thailand, it may be the most common form of natural death in younger males.
PREDOMINANT SEX AND AGE: BRS is more common in males (58% to 80% of patients). Mean age at presentation is 40 to 45.
GENETICS: The disease is autosomal dominant with variable expression (Table 1).

- *SCN5A,* the gene that encodes for the alpha subunit of the cardiac sodium channel, accounts for about 20% to 30% of cases of BRS.
- *SCN10a,* the gene that encodes the Nav1.8 subunit of the sodium channel, has been found in 17% of BRS patients, making it the second most-common-known mutation.
- Known genetic abnormalities are only found in half of patients; thus the impact of genetic testing is limited. When available, it may be useful in identifying silent carriers.
- In all genotypes, the basic abnormality is either a decrease in the inward sodium or calcium current or an increase in the outward potassium current.

RISK FACTORS: First-degree relatives with sudden death or known BRS

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical exam is usually benign
- Classic ECG finding is a pattern of atypical right bundle branch block (RBBB) with persistent ST elevation of cove-like morphology and T-wave inversion in the anterior leads (V1 to V2)
- Often an incidental finding diagnosed from a typical ECG pattern
- Palpitations
- Nocturnal agonal respirations
- Syncope
- Sudden cardiac arrest (SCA)/SCD secondary to rapid PVT that frequently degenerates into VF more often at night
- Fig. 1 illustrates Brugada ECG patterns. Type 1 is the most common and characteristic (Fig. 2)
- Type 1 ECG pattern is defined as an elevated ST segment ≥2 mm that descends in a coved pattern to an inverted T wave. This finding can be transient and may be provoked (sodium channel blockers, vagal maneuvers, increased alpha-adrenergic tone, beta-blockers, tricyclic or tetracyclic antidepressants, fever, hypokalemia, hyperkalemia, hypercalcemia, and alcohol and cocaine toxicity)
- Type 2 ECG pattern (Fig. 3) is not diagnostic of BRS but may be suggestive and warrant further testing. This pattern is a "saddle back" ST-T wave morphology with an upright or biphasic T wave. Type 2 (formerly known as types 2 and 3) can change to a type 1 pattern with the triggers noted above. Table 2 describes drugs used to unmask Brugada ECG pattern

ETIOLOGY

Autosomal dominant inheritance with variable penetration

DIAGNOSIS

Diagnosis is made by the presence of a type 1 ECG *and* symptoms.

- ST segment elevation with type 1 morphology ≥2 mm in one or more right-sided leads (V_1 to V_2), occurring either spontaneously or after provocative drug testing
- Type 2 ECG that converts into type 1 following sodium channel blocker (procainamide/flecainide/ajmaline) challenge (Fig. 2)

TABLE 1 Molecular Basis of the Brugada Syndrome

Disease	Gene	Protein	Ionic Current	Function	Inheritance
BRS type 1	*SCN5A*	$Na_v1.5$	Subunit alpha I_{Na}	Loss	Autosomal dominant
BRS type 2	*GPD1L*	G3PD1L	Interaction subunit alpha I_{Na}	Loss	Autosomal dominant
BRS type 3	*CACNA1C*	$Ca_v1.2$	Subunit alpha I_{CaL}	Loss	Autosomal dominant
BRS type 4	*CACNB2B*	$Ca_v\beta_2$	Subunit beta I_{CaL}	Loss	Autosomal dominant
BRS type 5	*SCN1B*	$Na_v\beta_1/\beta_{1b}$	Subunit beta I_{Na}	Loss	Autosomal dominant
BRS type 6	*KCNE3*	MiRP2	Subunit beta I_{Ks}/I_{to}	Gain	Autosomal dominant
BRS type 7	*SCN3B*	$Na_v\beta_3$	Subunit beta I_{Na}	Loss	Autosomal dominant

From Issa ZF et al: *Clinical arrhythmology and electrophysiology: a companion to Braunwald's heart disease,* ed 2, Philadelphia, 2012, Saunders.

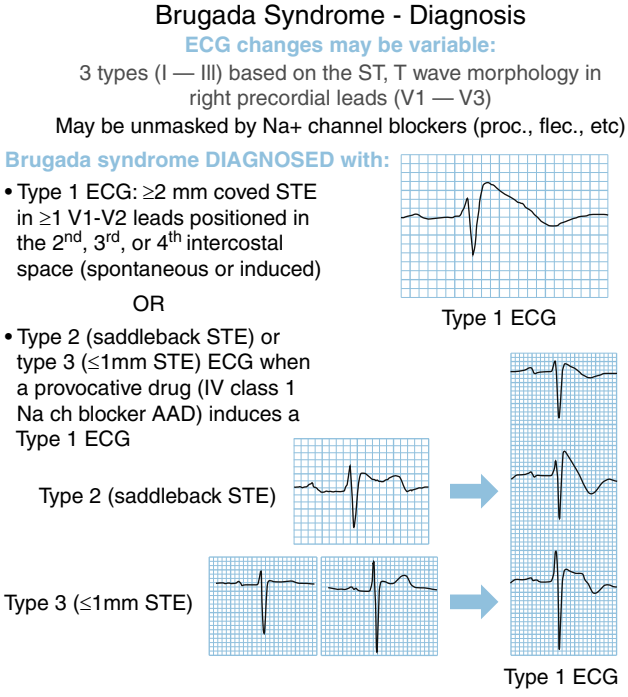

FIG. 1 Brugada electrocardiogram *(ECG)* patterns. A type 1 ECG pattern supports diagnosis of Brugada syndrome. Brugada syndrome can be considered for type 2 or 3 ECG patterns if ECG pattern converts to a type 1 pattern after challenge with a sodium channel *(Na ch)* blocker. *AAD,* Antiarrhythmic drugs; *STE,* ST-segment elevation; *IV,* intravenous. (From Olshansky B et al: *Arrhythmia essentials*, ed 2, Philadelphia, 2017, Elsevier.)

DIFFERENTIAL DIAGNOSIS

A number of diseases can lead to a BRS-like abnormality on the surface ECG, including the following:

- Atypical RBBB
- Early repolarization
- Acute pericarditis
- Acute myocardial infarction or ischemia
- Pulmonary embolism
- Various central and autonomic system abnormalities
- Duchenne muscular dystrophy
- Electrolyte abnormalities such as hyperkalemia and hypercalcemia
- Arrhythmogenic right ventricular cardiomyopathy
- Pectus excavatum

WORKUP

- Clinical history with special emphasis on syncope, palpitations, nocturnal agonal respirations, and family history.
- Echocardiography to rule out structural heart disease. While no structural heart disease is usually apparent, there are some recent reports indicating mild abnormalities in the right ventricle (RV) and left ventricle (LV).
- MRI, especially to rule out ARVC (arrhythmogenic right ventricular cardiomyopathy).
- Electrophysiology study. No consensus exists on the value of arrhythmia induction in predicting future clinical events in individual patients. However, findings such as HV (His ventricular) conduction interval >60 ms and VERP (ventricular effective refractory period) <200 ms during electrophysiology study can help in supporting a diagnosis. Repeated trials have failed to show a predictive power of electrophysiology study, and it still exists as a IIb recommendation. A recent meta-analysis has suggested it may have some utility, and its use in risk stratification remains controversial.
- Laboratory tests are unhelpful. Genetic testing may be helpful for prognosis and family evaluation, but it is not necessary for diagnostic purposes.
- First-degree relatives should obtain ECG and be evaluated for symptoms.
- The following are considered indicators of high risk in an asymptomatic patient:
  1. Spontaneous type 1 ECG at baseline
  2. Presence of fragmented QRS on ECG
  3. RVERP (right ventricular effective refractory period) <200 ms on EPS
  4. Male sex
  5. Spontaneous atrial fibrillation

  Note that family history of sudden death is not considered a high-risk feature in BRS.

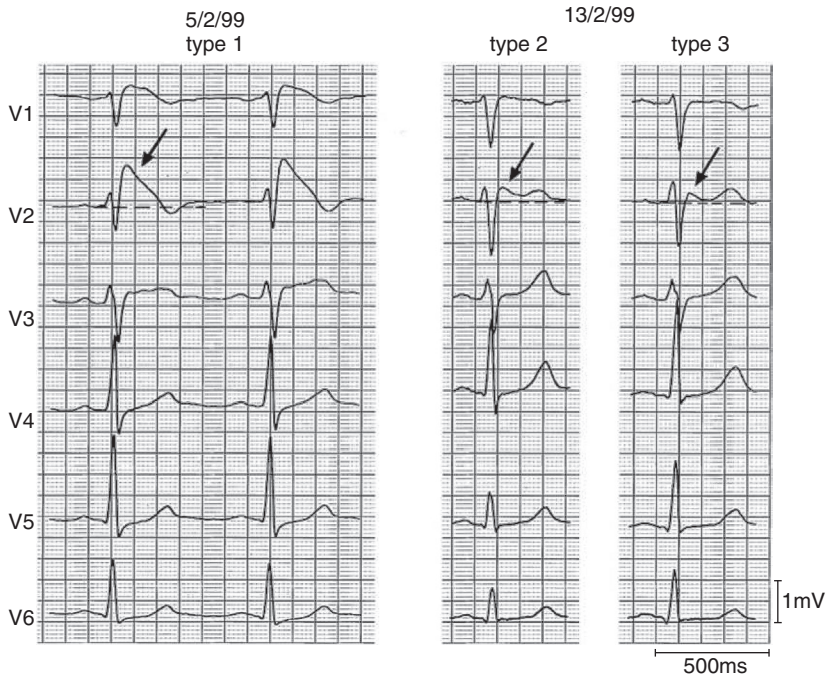

FIG. 2 Electrocardiogram (ECG) changes in Brugada syndrome. ST elevation occurs in the anterior precordial leads, leads V1 and V2. Type 1 (coved) ECGs with 1 mV of ST elevation have the most prognostic significance. (From Strickberger SA et al: AHA/ACCF scientific statement on the evaluation of syncope, *J Am Coll Cardiol* 47:473-484, 2006.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- The only effective strategy that prevents sudden cardiac death in BRS is implantable cardioverter-defibrillator (ICD). Currently there are no class I recommendations for primary prevention because clinical events are extremely rare, even in high-risk patients. Fig. 4 depicts the algorithm for clinical decision making regarding recommendation of an ICD.
- Definitive candidates for ICD (class I) are patients who survived SCD or have had sustained VT (secondary prevention).
- ICD can be useful (class IIa) for patients who have type 1 ECG pattern (either spontaneous or after class IC drug test) associated with history of syncope.
- ICD may be considered (class IIb) if there is inducible VF on electrophysiologic (EP) study, but this remains controversial.
- Patients with spontaneous type 1 ECG without syncope or inducible VF on EP study or

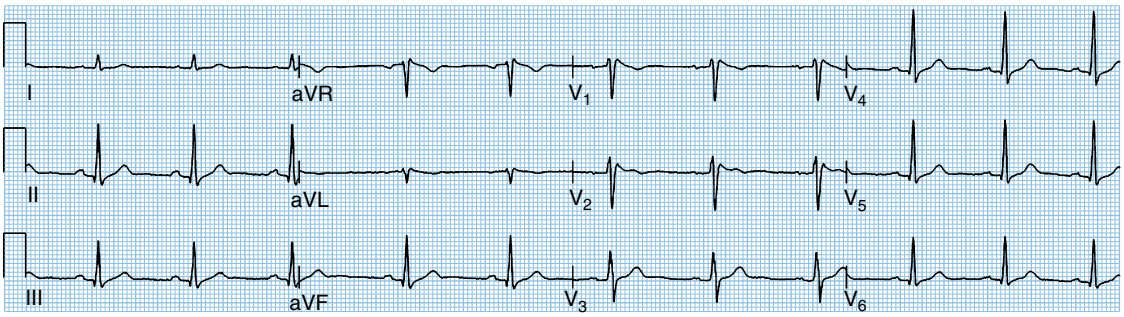

FIG. 3 Type II Brugada pattern electrocardiogram (ECG). This 12-lead ECG shows a type II Brugada pattern in leads V1 and V2. Whereas a type I ECG pattern supports a diagnosis of Brugada syndrome, Brugada syndrome can be considered for type 2 or 3 ECG patterns (see Fig. 1) if the ECG pattern converts to a type 1 pattern after challenge with a sodium channel blocker. *aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right. (From Olshansky B et al: *Arrhythmia essentials*, ed 2, Philadelphia, 2017, Elsevier.)

TABLE 2 Drugs Used to Unmask Brugada ECG Pattern

Drug	Dose
Ajmaline	1-mg/kg IV infusion over 5 min
Flecainide	2-mg/kg IV infusion over 10 min, maximum 150 mg; or 400 mg PO
Procainamide	10-mg/kg IV infusion over 10 min
Pilsicainide	1-mg/kg IV infusion over 10 min

asymptomatic patients with drug-induced type 1 ECG pattern are considered a lower risk group for SCD, and ICD is not indicated in these patients.

- Radiofrequency catheter ablation of the RV epicardium may be performed for patients with recurrent ventricular arrhythmias and may eliminate the Brugada ECG phenotype. It has also been associated with very low recurrence of arrhythmia in small studies. This has become an accepted therapy for patients with ICD shocks and requires referral to specialized centers.

ACUTE GENERAL Rx

- Isoproterenol (class IIa) may be used for electrical storm.
- Quinidine, which blocks both Ito and IKr currents in the RV epicardium, is used in patients with a history of multiple appropriate ICD shocks, as well as for electrical storms and treatment of supraventricular tachycardia (SVT) in these patients. It is also useful in cases where the patient refuses an ICD implant or when an ICD implant is contraindicated.

REFERRAL

Consultation with a cardiac electrophysiologist is strongly recommended if BRS is suspected.

PEARLS & CONSIDERATIONS

COMMENTS

- The clinical manifestations, such as syncope and SCD, are rare in the pediatric group, but fever can acutely predispose to cardiac arrest. Mean age of presentation is 40 to 45 yr.
- Cardiac events may occur during sleep, at rest, or after a large meal.
- BRS patients should be advised to avoid all drugs that may induce a type 1 ECG pattern and/or be known to trigger ventricular arrhythmias and avoid unnecessary use of drugs (a drug that is not yet identified as potentially dangerous for these patients does not make its use safe). For up-to-date information on this matter, a full list can be found at www.brugadadrugs.org.
- Fever may induce the appearance of a type 1 BRS ECG pattern and may trigger episodes of PVT/VF in BRS patients. In the case of fever, close ECG monitoring is appropriate in combination with lowering of the body temperature.
- The classic ECG changes in BRS can be transient with patients having normal ECGs in between highly abnormal ones.
- The appearance of syncope, seizures, or nocturnal agonal respiration must lead to prompt medical evaluation.
- Family screening for BRS in first-degree relatives is strongly recommended.
- Although participation in sports is not strictly prohibited, competitive training can lead to development of strong vagal tone and subsequent higher risk of clinical events. Hence, participation in sports at a competitive or professional level is not advised.
- Once diagnosed initially by an ECG pattern, all patients must be followed up on a regular basis by an electrophysiologist.

PREVENTION

Identification of patients with BRS, risk stratification, and appropriate screening of family members are paramount to the prevention of SCD. Patients with known BRS should have fevers aggressively treated with antipyretics and avoid drugs associated with drugs that induce a type 1 pattern.

PATIENT & FAMILY EDUCATION

Immediate family members should be notified and be screened for BRS.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **John Wylie, MD, FACC**

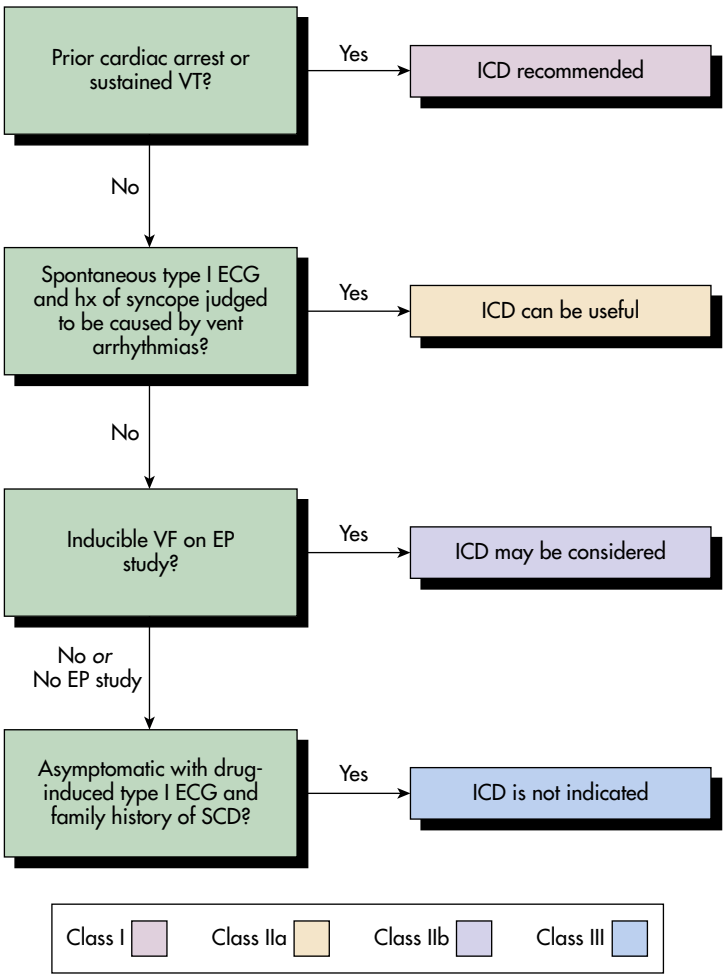

FIG. 4 Consensus recommendations for ICDs in patients diagnosed with Brugada syndrome. (*hx,* History; *ICD,* implantable cardioverter-defibrillator; *SCD,* sequential compression device; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia.) (From Priori SG et al: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes, *Heart Rhythm* 10:1932-1963, 2013.)

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Forcible clenching or grinding of the teeth during sleep or wakefulness, often leading to damage of the teeth.

ICD-10CM CODES
G47.63 Sleep related bruxism
F45.8 Other somatoform disorders

EPIDEMIOLOGY & DEMOGRAPHICS

- Occurs in 15% of children and 75% of adults.
- Familial cases have occasionally been described.
- Bruxism often presents between age 10 and 20 yr but may persist throughout life.
- Nocturnal bruxism is noted most often during stages I and II NREM sleep and REM sleep.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Complaints of grinding of teeth from a sleep partner or members of the family are common. In many cases the masticatory system will adapt to the phenomenon, but in severe cases nearly every part of the masticatory system may be damaged. Excessive wearing of dentition is the most common physical finding (Fig. E1). Tender or hypoatrophied masticatory muscles may also be observed.

ETIOLOGY:

- Cause is controversial. Fig. E2 illustrates the cascade of physiologic events in the genesis of sleep bruxism and rhythmic masticatory muscle activity and course of action for management.
- Possible causes include occlusal discrepancies, anatomy of the bony structures of the orofacial region, part of the sleep arousal response, disturbances of the central dopaminergic system, smoking, alcohol, drugs, stress, and personality.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Dental compression syndrome
- Temporomandibular joint disorders
- Chronic orofacial pain disorders
- Oral motor disorders
- Malocclusion

WORKUP

- History should have an emphasis on sleep habits, including excessive snoring, pain in the temporal mandibular region, interview with close family members, health habits, personality quirks.
- Physical examination of the teeth and masticatory muscles is mandatory.
- Sleep studies in selected cases may be helpful.

LABORATORY TESTS

None indicated unless a systemic disease is suspected (e.g., infection, autoimmune disorder)

IMAGING STUDIES

X-ray studies of teeth and temporomandibular joints

TREATMENT

NONPHARMACOLOGIC THERAPY

Biofeedback, psychological counseling, and elimination of harmful health habits have been used with limited success.

GENERAL Rx

- Oral splints (Fig. E3); night guard to protect teeth may be useful
- Correction of malocclusion
- Pain management (e.g., gabapentin, ibuprofen)
- Medication to relieve anxiety and improve sleep (e.g., benzodiazepine or trazodone at bedtime)
- Local injections of botulinum toxin into masseter muscles to prevent dental and temporomandibular joint complications

DISPOSITION

Referral to dentist mandatory if damage to teeth evident

PEARLS & CONSIDERATIONS

- Like any poorly understood disease, treatment is often unsatisfactory and subject to quackery.
- Both diurnal and nocturnal bruxism may be associated with various movement and degenerative disorders (e.g., Huntington disease, oromandibular dystonia) and are quite common in children with cerebral palsy and mental retardation.

RELATED CONTENT

Bruxism (Tooth Grinding) (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

FIG. E1 Example of sleep-related grinding damage. A, Frontal view. **B,** Occlusal view on the lower jaw. (From Kryger M, Roth T, Dement WC: *Principles and practice of sleep medicine*, ed 6, Philadelphia, 2017, Elsevier.)

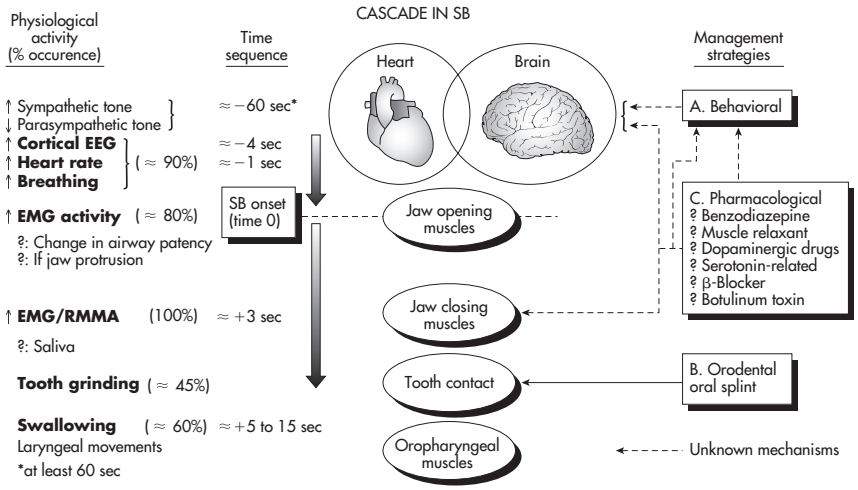

FIG. E2 Cascade of physiologic events in genesis of sleep bruxism and rhythmic masticatory muscle activity (*left*) and courses of action for management (*right*). (From Lavigne G et al: Sleep bruxism. In Kryger MH, Roth T, Dement WC [eds]: *Principles and practice of sleep medicine*, ed 5, Philadelphia, 2011, Elsevier, pp. 1128-1139.)

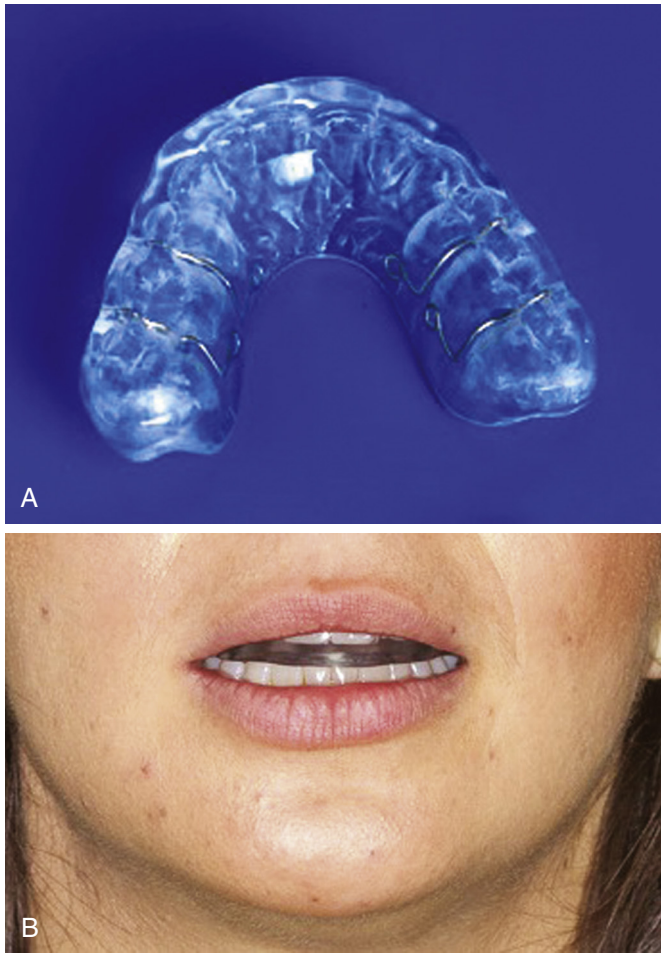

FIG. E3 A, Example of a hard occlusal stabilization appliance, indicated for the management of sleep bruxism and commonly used to assess the presence and progression of the condition based on wear patterns on the occlusal surface. **B,** In situ on the upper jaw. (From Kryger M, Roth T, Dement WC: *Principles and practice of sleep medicine*, ed 6, Philadelphia, 2017, Elsevier.)

Budd-Chiari Syndrome PTG ALG

BASIC INFORMATION

DEFINITION

Budd-Chiari syndrome (BCS) is a rare disorder defined by the obstruction of hepatic venous outflow anywhere from the small hepatic veins to the junction of the inferior vena cava (IVC) and the right atrium. Primary BCS is defined by endoluminal obstruction as seen in thromboses, phlebitis, or webs. Secondary BCS occurs when the obstruction is caused by compression or invasion by a lesion originating outside of the veins (tumor, abscess, cyst, etc.). It can also be a postoperative complication of orthotopic liver transplantation (OLT).

SYNONYMS

BCS
Hepatic vein thrombosis
Obliterative endophlebitis of the hepatic veins
IVC thrombosis
Chiari-Budd syndrome
Budd syndrome
Chiari disease
Rokitansky disease

ICD-10CM CODE
I82.0 Budd-Chiari syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Males: 2.0/1 million persons per yr
Females: 2.2/1 million persons per yr

PREDOMINANT SEX:

- In Western countries, women are more commonly affected (approximately 2/3 of cases).
- In Asia, men are slightly more affected (approximately 1.5/1).

PREDOMINANT AGE:

- In Western countries, presentation is usually in the third and fourth decades of life, with the median age being 35 to 50 yr.
- In Asia, presentation is usually at a median age of 36 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical presentation and characteristics vary with geography. The classic presentation of Budd-Chiari syndrome includes hepatomegaly, ascites, and right upper quadrant pain. In Africa and South Asia, intravascular webs are more often associated with IVC thrombosis with a stronger association with subsequent liver cirrhosis and hepatocellular carcinoma. In the U.S., BCS is more commonly associated with primary myeloproliferative disorders and underlying hypercoagulable states. Underlying factors that contribute to BCS can be identified in more than 80% of cases; multiple causative factors are identified in up to 50% of cases.

- Clinical manifestations can be caused by complete or partial occlusion of any or all of the three major hepatic veins or the inferior vena cava.
- Presentation is variable according to the degree, location, acuity of obstruction, and presence of collateral circulation:
  1. Fulminant/acute (25%): Severe right upper quadrant abdominal pain, fever, nausea, vomiting, mild jaundice, hepatomegaly, transudative and intractable ascites, marked elevation in serum aminotransferases (AST/ALT >5 times the upper limit of normal), elevation of alkaline phosphatase to 300 to 400 IU/L, serum-ascites albumin gradient ≥1.1 with total protein >2.5 g/dl, coagulopathy (usually international normalized ratio [INR] >1.5), variceal bleeding, encephalopathy within 8 wk of onset of jaundice, renal failure. Biopsy, if performed, would reveal hepatic necrosis. Early recognition and treatment are essential for survival; a slow decrease in ALT is associated with poor survival.
  2. Subacute/chronic (60%): Vague abdominal discomfort, gradual progression to caudate lobe hypertrophy with atrophy of the rest of the liver, portal hypertension with or without cirrhosis and its sequelae, transudative ascites, lower-extremity edema, esophageal varices, splenomegaly, coagulopathy, mild to moderate elevation in aminotransferases, bilirubin and alkaline phosphatase, hepatorenal syndrome, hepatopulmonary syndrome, and rarely, encephalopathy; biopsy, if performed, could reveal minimal hepatic necrosis.
  3. Asymptomatic (up to 20%): Usually discovered incidentally by abnormal liver function tests or imaging attained for other reasons.

ETIOLOGY:

Approximately 80% to 87% of patients have one prothrombotic risk factor, and approximately 50% have multiple.

- Primary myeloproliferative diseases: Up to 53% of BCS patients have a primary myeloproliferative disease and polycythemia vera is responsible for 10% to 40% of these cases.
  1. Essential thrombocythemia and idiopathic myelofibrosis are less common causes.
  2. *JAK2* mutations are implicated in cases of idiopathic BCS (identified in 25% to 60% of cases).
- Hypercoagulable states (inherited and acquired) often coexist with other causes.
  1. Anticardiolipin antibodies (up to 25%)
  2. Hyperhomocysteinemia (22%)
  3. Paroxysmal nocturnal hemoglobinuria (5% to 19%)
  4. Factor V Leiden (25%)
  5. Factor II gene mutation (5%)
- Protein C, protein S, and antithrombin III deficiency are difficult to interpret because the presence of liver disease may confound results. However, they account for 4.0%, 3.0%, and 3.0% of BCS, respectively.
- Heterozygosity for *G20210A* prothrombin gene mutation, methylenetetrahydrofolate reductase (MTHFR) mutation, Tet methylcytosine dioxygenase 2 mutation, and calreticulin mutation may be seen in BCS.
- Pregnancy and oral contraceptive pills are also predisposing factors to develop BCS.
- Malignancy causing external compression or invasion of vascular structures (up to 10% of cases).
  1. Most commonly due to hepatocellular carcinoma but also can be due to neoplasms of the kidney, adrenal gland, pancreas, stomach, lung and sarcomas of the right atrium, inferior vena cava, and hepatic veins.
- Rare but reported: Sickle cell anemia, infections with liver abscess, hydatid cyst (echinococcosis), schistosomiasis, sarcoidosis, Behçet disease, membranous webs of IVC or hepatic veins (more common in Africa and South Asia, can be congenital or acquired secondary to underlying myeloproliferative disorder), abdominal trauma, liver torsion, granulomatous venulitis, ulcerative colitis, celiac disease, systemic lupus erythematous, minimal change nephrotic syndrome, neurofibromatosis, α-1 antitrypsin deficiency, hypereosinophilic syndrome, idiopathic (10% to 25%).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hepatitis from ischemia, viral infection, toxin, alcohol
- Cholecystitis
- Hepatic veno-occlusive disease (sinusoidal obstruction syndrome)
- Congestive hepatopathy, also known as *cardiac cirrhosis*, from tricuspid regurgitation, right atrial myxoma, constrictive pericarditis
- Cirrhosis from any etiology

LABORATORY TESTS

- Assessment of liver injury and function: Serum aminotransferases, alkaline phosphatase, prothrombin time (PT), albumin, bilirubin.
- Exclusion of another form of liver disease: Viral hepatitis panel, autoantibodies (antinuclear antibody, anti–smooth muscle antibody, anti-mitochondrial antibody), iron studies, ceruloplasmin, and α-1 antitrypsin.
- Ascites protein content ≥2.5 g/dl and serum ascites albumin gradient >1.1 g/dl are suggestive of transudative ascites from BCS or cardiac ascites.
- Evaluation for underlying myeloproliferative disorder and hypercoagulable state: CBC, bone marrow biopsy, tests for hypercoagulable states (Factor V Leiden, prothrombin gene *G20210A* mutation, protein C, protein S, antithrombin deficiencies, antiphospholipid syndrome, and paroxysmal nocturnal hemoglobinuria). Protein C, protein S, and antithrombin deficiencies may be difficult to

interpret in the setting of liver dysfunction, but levels <20% of normal are suggestive of a true deficiency; thrombophilia screening for the JAK2 V617F mutation, hyperhomocysteinemia, and MTHFR C677T mutation may be useful if no other cause for myeloproliferative disorders or hypercoagulable states are identified.

IMAGING STUDIES

- Diagnosis of BCS is made by radiographic imaging (Figs. E1, E2, and E3).
- Doppler ultrasonography is the first-line test. Diagnostic sensitivity and specificity are 85% to 90%. Findings include large hepatic vein with an absent flow signal, or with reversed or turbulent flow; large intrahepatic or subcapsular collateral vessels; enlarged, stenotic, thickened, or tortuous hepatic veins; spider web pattern near hepatic vein ostia and associated absent flow in that region; caudate lobe hypertrophy (as the caudate lobe has an alternate blood supply through anastomoses); flattened or absent hepatic venous waveform without fluttering; hyperechoic cord replacing a normal vein.
- MRI with gadolinium contrast is the second-line test. It is superior to contrast-enhanced CT (Fig. E4) with a sensitivity and specificity of approximately 90%, and it is preferred in younger patients due to the lack of radiation. Findings include obstructed hepatic veins or IVC, large intrahepatic or subcapsular collaterals, and caudate lobe hypertrophy. MRI is beneficial to visualize the entire length of the IVC and distinguish between acute, subacute, and chronic BCS. Three-dimensional contrast-enhanced magnetic resonance angiography (MRA; see Fig. 5) rivals hepatic venography in sensitivity.
- Contrast-enhanced CT may reveal similar findings as Doppler ultrasound as well as delayed or absent filling of the hepatic veins, parenchymal opacification of the liver, narrowing and/or compression of the inferior vena cava, and caudate lobe hypertrophy. Contrast enhancement localizes more centrally than peripherally and has a patchy and flea-bitten appearance. The use of CT is limited given that in almost 50% of patients, the test is indeterminate or a false-positive. Ultrasonography is more accurate than CT for detecting lesions in the hepatic veins and IVC.
- CT image reconstruction of vasculature is becoming more available.
- Venography: Although it is the gold standard, it is not essential for diagnosis, and it should be performed when other noninvasive imaging tests are nondiagnostic in the setting of strong clinical suspicion for BCS. Measurement of pressure gradients can help predict success of percutaneous or surgical shunt intervention. Confirms the pathognomonic web pattern caused by collateral venous flow.
- Liver biopsy: Not necessary to diagnose BCS but may be helpful in patients with cirrhosis in whom the diagnosis remains uncertain and is critical for differentiating from hepatic venoocclusive disease or congestive hepatopathy. Findings include hepatic congestion, hepatocyte necrosis and fibrosis in centrilobular areas, and compensatory nodular regenerative hyperplasia with progression to fibrosis and cirrhosis. In advanced BCS, infarction caused by concomitant thrombosis of the intrahepatic, extrahepatic, and portal veins may be seen. There are conflicting studies regarding the association of histologic findings and prognosis.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Goal of therapy is decompression of hepatic congestion.
- In general, therapeutic procedures should be introduced by order of increasing invasiveness based on response/failure to therapy rather than disease severity. Fig. 6 illustrates a treatment algorithm for patients with Budd-Chiari syndrome.
- Hypercoagulable states should be investigated in all patients.

ACUTE GENERAL Rx

- Anticoagulation, first with low-molecular-weight heparin (LMWH), followed by warfarin, even in the absence of an underlying hypercoagulable disorder. Recent research also suggests that using direct-acting oral anticoagulants in BCS is safe and effective.
- In situ thrombolysis: Can be successful when performed in patients with recently thrombosed veins (within 2 to 3 wk after symptom onset) that are well defined on venography. Mature clots are nonresponsive to thrombolysis, and bleeding risk is high if portal hypertension has developed.
- Balloon angioplasty: Complicated by 50% restenosis rate within 2 yr; effective when membranous webs or short segment hepatic vein stenosis are the etiology.
- Stenting: May improve long-term patency rates to 90%, but if placed above the intrahepatic IVC, may complicate future liver transplantation.
- Transjugular intrahepatic portosystemic shunt (TIPS) (Fig. 7): Indicated with diffuse

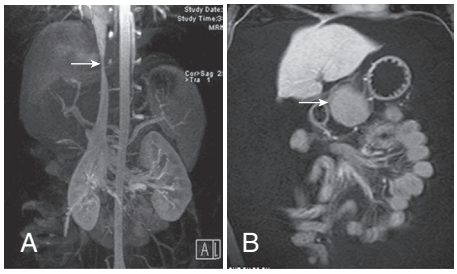

FIG. 5 Magnetic resonance venogram. A, Intravenous cholangiography (IVC) obstruction *(arrow)* at the level of the caudate. **B,** Hypertrophic caudate lobe *(arrow)*. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, WB Saunders.)

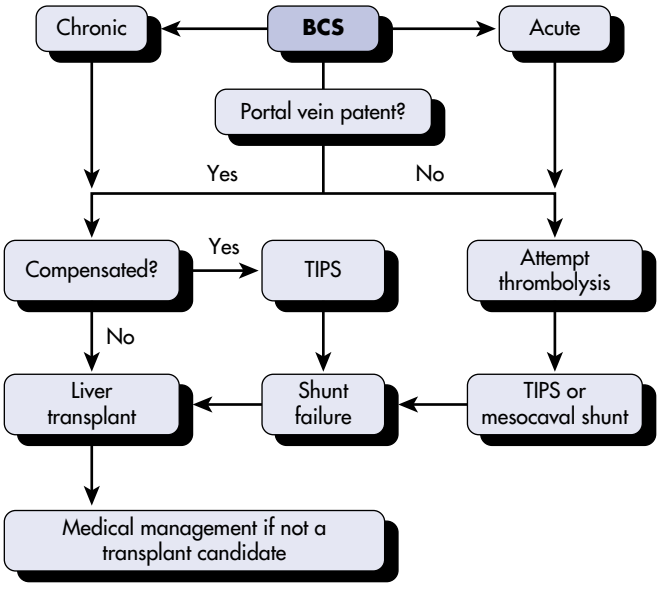

FIG. 6 Treatment algorithm for patients with Budd-Chiari syndrome (BCS). *TIPS,* Transjugular intrahepatic portosystemic shunt. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

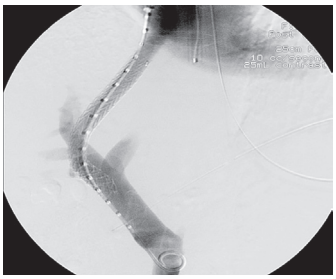

FIG. 7 Transjugular intrahepatic portosystemic shunt extending from the right portal vein into the right atrium. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

hepatic vein thrombosis, refractory ascites, recurrent variceal bleeding and progressive liver failure. Polytetrafluoroethylene (ePTFE)-coated stents have improved TIPS-patency rates, especially in patients with underlying hypercoagulable defects with a 76% 10-yr survival rate.
- Surgical portal systemic shunts: Indicated when angioplasty and stenting have failed and when complications from portal hypertension are also present. This option is no longer common practice and provides no survival benefit.
- Liver transplant may be indicated in patients with cirrhosis or fulminant hepatic failure and in patients who fail to respond to TIPS; 10-yr survival is reported to range between 69% and 84%.
- Supportive measures.

CHRONIC Rx

- Lifelong anticoagulation: Warfarin therapy, with a target INR of 2 to 3 or low-molecular-weight heparin, lessens, but does not completely prevent, recurrence. Anticoagulation should be continued permanently unless the patient has an adverse event to anticoagulation, the obstruction is because of an anatomic cause that has been corrected, or anticoagulation is contraindicated.
- In patients with an underlying myeloproliferative disorder, first-line treatment is with hydroxyurea and aspirin.
- Treat liver dysfunction and complications related to portal hypertension such as ascites and variceal bleeding.
- Invasive interventions should be reserved for symptomatic patients who do not improve with medical therapy.
- Manage shunt thrombosis; which is a common complication.
- Liver transplantation is another treatment option with a 71% to 89% survival rate at 5 yr; up to 27% recurrence of BCS after transplant has been recognized.
- Monitor for development of hepatocellular carcinoma and transformation of myeloproliferative disease in patients with long-standing, well-controlled BCS and post-transplant lymphoma in orthotopic liver transplantation (OLT) recipients.

DISPOSITION

Prognosis is variable and depends on multiple factors, including time to recognition and treatment, etiology, acuity, the type of intervention, and the condition of the patient at the time of treatment. Overall mortality rates are decreasing with the use of anticoagulation and early diagnosis of asymptomatic cases. Given numerous therapeutic options, the survival rate is 90%, 83%, and 72% at 1, 5, and 10 yr from diagnosis.

- A prognostic index called the *Rotterdam BCS Index* has been described: 1.27 × Encephalopathy + 1.04 × Ascites + 0.72 × PT + 0.004 × Bilirubin.
  1. Encephalopathy and ascites are scored as 1 for present or 0 as absent, and PT is scored as greater (1) or less than (0) an INR of 2.3.
  2. An index of <1.1 correlates to low risk (5-yr survival rate, 89%), 1.1 to 1.5 with intermediate risk (5-yr survival rate, 74%), and >1.5 with high risk (5-yr survival rate, 42%).
- There is also the *BCS-TIPS PI score*, which is a prognostic index for survival 1 yr after TIPS: Age (yr) × 0.08 + bilirubin × 0.16 + INR × 0.63.
  1. Seven is the most specific discriminative factor, with those scoring above 7 necessitating emergent OLT as the first-line treatment.

REFERRAL

Fulminant presentations should immediately be referred to a center capable of liver transplantation. All cases benefit from referral to a hepatologist, a hematologist, an interventional radiologist, and a surgeon specializing in hepatobiliary disease.

PEARLS & CONSIDERATIONS

COMMENTS

- Look for one or more underlying causes, especially hypercoagulable or hematologic disorders, and malignancies or space-occupying lesions that may compress or invade the hepatic outflow tract.
- Myeloproliferative disorders are most common.
- Diagnosis relies on imaging; beginning with Doppler ultrasound.
- Treatment with anticoagulation comes first; followed by invasive interventions as needed. Prophylaxis of portal hypertension can reduce the risk of major bleeding associated with anticoagulation therapy.
- Referral for liver transplantation may be necessary.
- Prognostic indices can assist in management and estimate survival rates.

PREVENTION

In the setting of known risk factors, such as a hypercoagulable state or myeloproliferative disorder, any additional risks, such as smoking or oral contraceptive therapy, should be avoided.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Budd-Chiari Syndrome (Patient Information)
Hypercoagulable State (Related Key Topic)

AUTHORS: **Jeanette G. Smith, MD,** and **Dina A. Ibrahim, MD**

SUGGESTED READINGS

Copelan A et al: Diagnosis and management of Budd-Chiari syndrome: an update, *Cardiovasc Intervent Radiol* 38(1):1-12, 2015.

Fox MA et al: Budd-Chiari syndrome—a review of the diagnosis and management, *Acute Medicine* 10(1)5-9, 2011.

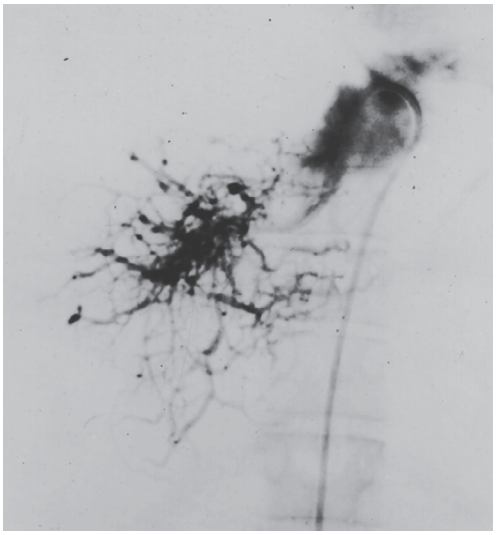

FIG. E1 Budd-Chiari syndrome. A catheter has been passed retrogradely into a right hepatic vein. Injection of contrast medium has outlined an extensive fine network of collateral vessels. This "spider web" appearance is pathognomonic of Budd-Chiari syndrome. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.)

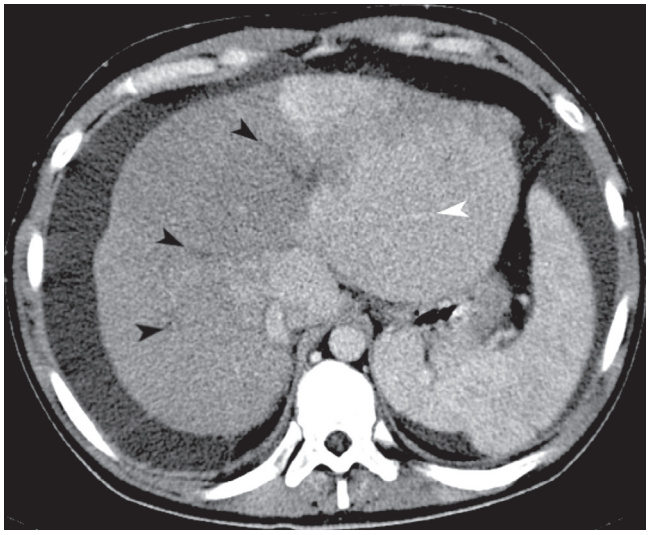

FIG. E2 Acute Budd-Chiari syndrome. On portal phase CT, most of the caudate and left lobe of the liver has enhanced normally and the left hepatic vein can just be seen *(white arrowhead)*, but the right lobe has abnormally low attenuation, and the middle and right hepatic vein branches are attenuated and have failed to opacify *(black arrowheads)*. Ascites is present. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.)

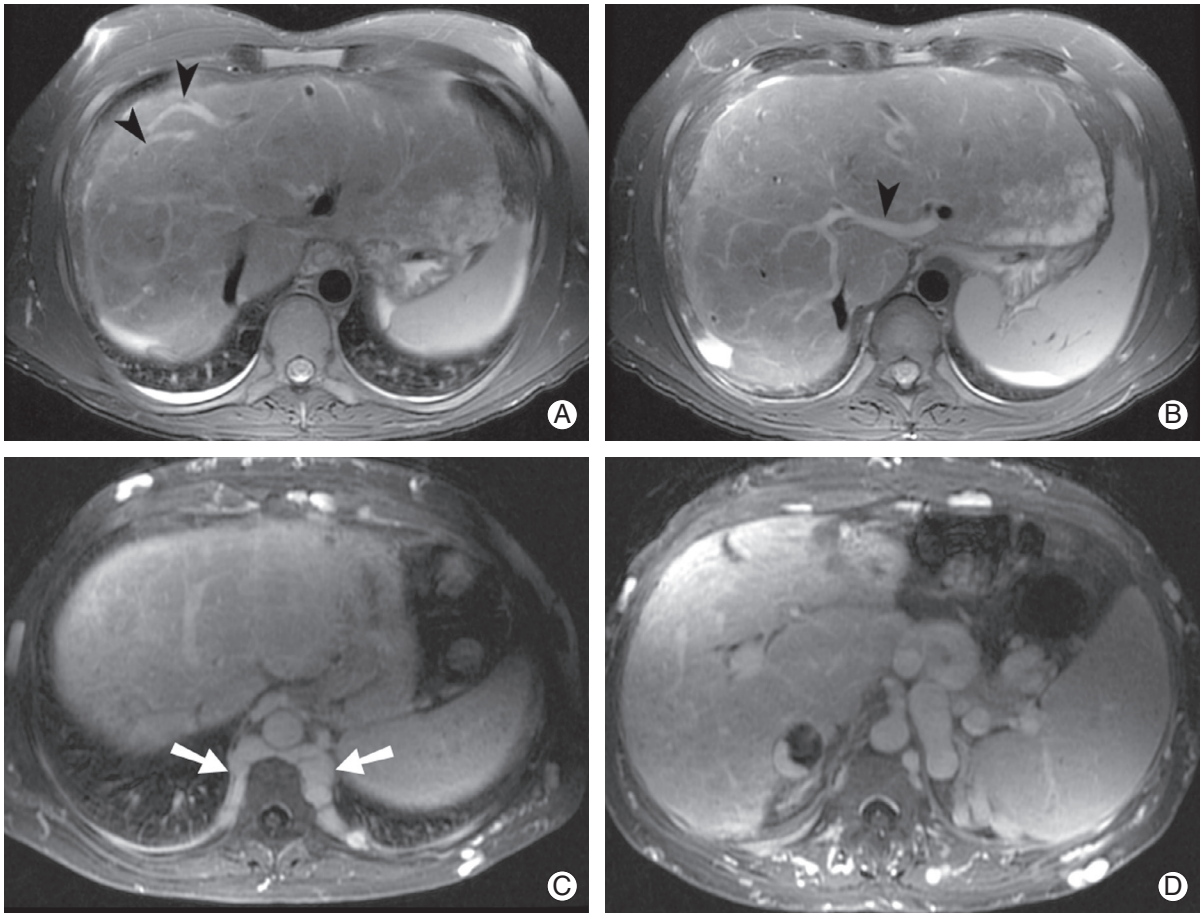

FIG. E3 Chronic Budd-Chiari syndrome. Changes in a patient with previous occlusion of the right and middle hepatic veins include hypertrophy of the left lobe and numerous abnormal curved venous channels *(arrowheads)* shown on multishot T2-weighted (T2W) fast spin echo (FSE) imaging at two different levels **(A, B).** In a separate patient after occlusion of the inferior vena cava (IVC) by thrombus **(C, D),** there are enlarged retroperitoneal and azygos system veins *(arrows)*, as well as numerous superficial collateral veins, shown on postgadolinium T1-weighted (T1W) MRI. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.)

FIG. E4 Computed tomography scan of Budd-Chiari syndrome. The appearances are not immediately diagnostic for the nonexpert, and infiltrative disease is sometimes suspected. (From Forbes A et al [eds]: *Atlas of clinical gastroenterology*, ed 3, St Louis, 2005, Mosby.)

BASIC INFORMATION

DEFINITION

Bulimia nervosa is a prolonged illness characterized by a specific psychopathology. According to the *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition (DSM-5), bulimia nervosa can be diagnosed by:

- (A) Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
  1. Eating, in a discrete period of time, an amount of food that is definitely larger than what most individuals would eat in a similar period of time under similar circumstances.
  2. A sense of lack of control over eating during the episode.
- (B) Recurrent inappropriate compensators/behaviors in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise. (C) The binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 mo. (D) Self-evaluation is unduly influenced by body shape and weight. (E) The disturbance does not occur exclusively during episodes of anorexia nervosa.

ICD-10CM CODE
F50.2 Bulimia nervosa

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE: Affects 1% to 3% of female adolescents and young adults
PREDOMINANT SEX: Female:male ratio of 10:1
PREDOMINANT AGE: Adolescence to young adulthood; mean age of onset 17 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Parotid and salivary gland swelling
- Scars on the back of the hand and knuckles (Russell sign) from rubbing against the upper incisors when inducing vomiting
- Eroded enamel, particularly on the lingual surface of the upper teeth; pyorrhea and other gum disorders possible
- Petechial hemorrhages of the cornea, soft palate, or face possibly noted after vomiting
- Loss of gag reflex, well-developed abdominal musculature
- Often no emaciation; normal physical examination possible

ETIOLOGY

- Etiology is unknown but likely multifactorial (sociocultural, psychological, familial factors).
- Bulimia is much more common in Western societies, where there is a strong cultural pressure to be slender.
- According to the American Psychiatric Association, patients with eating disorders display a broad range of symptoms that occur along a continuum between those of anorexia nervosa and bulimia.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Schizophrenia
- Gastrointestinal disorders
- Neurologic disorders (seizures, Kleine-Levin syndrome, Klüver-Bucy syndrome)
- Brain neoplasms
- Psychogenic vomiting

WORKUP

- The following questions are useful to screen patients for bulimia:
  1. "Are you satisfied with your eating habits?"
  2. "Do you ever eat in secret?"
- Answering "no" to the first question and/or "yes" to the second question has 100% sensitivity and 90% specificity for bulimia. The SCOFF questionnaire can also be used as a screening tool for eating disorders (see "Anorexia Nervosa").
- According to the DSM-5, the level of severity is based on the frequency of inappropriate compensatory behaviors and may be increased to reflect other symptoms and degree of functional disability, as noted below:
  1. Mild: An average of 1 to 3 episodes of inappropriate compensatory behaviors per week
  2. Moderate: An average of 4 to 7 episodes of inappropriate compensatory behaviors per week
  3. Severe: An average of 8 to 13 episodes of inappropriate compensatory behaviors per week
  4. Extreme: An average of ≥14 inappropriate compensatory behaviors per week
- Table E1 describes eating and weight control habits commonly found in children and adolescents with an eating disorder.

LABORATORY TESTS

- Electrolyte abnormalities from vomiting (hypokalemia and metabolic alkalosis) or diarrhea from laxative abuse (hypokalemia and hyperchloremic metabolic acidosis)
- Hyponatremia, hypocalcemia, hypomagnesemia (caused by laxative abuse)
- Elevated cortisol, decreased luteinizing hormone, decreased follicle-stimulating hormone

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive behavioral therapy, particularly interpersonal therapy to control abnormal behaviors
- Use of food diaries, nutritional counseling, and planning meals at least 1 day in advance are useful measures to counter abnormal eating behaviors
- Correction of electrolyte abnormalities

ACUTE GENERAL Rx

- Selective serotonin reuptake inhibitors are generally considered to be the safest medication option in these patients. They are useful in severely depressed patients and in those who do not benefit from cognitive behavioral therapy.
- Prompt recognition and treatment of complications:
  1. Ipecac cardiotoxicity from laxative abuse
  2. Electrolyte abnormalities (see "Laboratory Tests")
  3. Esophagitis and Mallory-Weiss tears; esophageal rupture from repeated vomiting
  4. Aspiration pneumonia and pneumomediastinum
  5. Menstrual irregularities (including amenorrhea)
  6. Gastrointestinal abnormalities: Acute gastric dilation, pancreatitis, abdominal pain, constipation

CHRONIC Rx

- Psychotherapy continued for years and focused specifically on self-image and family and peer interactions is an integral part of successful recovery.
- Family therapy is also recommended, especially in younger patients.

DISPOSITION

Course is variable and marked by frequent recurrence of exacerbations.

REFERRAL

- In addition to the primary care physician, the multidisciplinary team should include a dietician, a psychiatrist, and a family therapist.
- Hospitalization should be considered for patients with severe electrolyte abnormalities or those with suicidal thoughts.

PEARLS & CONSIDERATIONS

COMMENTS

- Bulimia has a close association with depression, bipolar disorder, obsessive-compulsive disorder, alcoholism, and substance abuse.
- Bulimia should be considered in all patients (especially adolescents) with unexplained hypokalemia and metabolic alkalosis.

RELATED CONTENT

Bulimia (Patient Information)
Anorexia Nervosa (Related Key Topic)
Binge Eating Disorder (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

TABLE E1 Eating and Weight Control Habits Commonly Found in Children and Adolescents with an Eating Disorder

	Prominent Features		Clinical Comments Regarding Eating Disorder Habits	
Habit	**Anorexia Nervosa**	**Bulimia Nervosa**	**Anorexia Nervosa**	**Bulimia Nervosa**
Overall intake	Inadequate energy (calories), although volume of food and beverages may be high due to very low caloric density of intake due to "diet" and nonfat choices	Variable, but calories normal to high; intake in binges often "forbidden" food or drink that differs from intake at meals	Consistent inadequate caloric intake leading to wasting of the body	Inconsistent balance of intake, exercise, and vomiting, but severe caloric restriction is short-lived
Food	Counts and limits calories, especially from fat; emphasis on "healthy food choices" with reduced caloric density; monotonous, limited "good" food choices, often leading to vegetarian or vegan diet; strong feelings of guilt after eating more than planned leads to exercise and renewed dieting	Aware of calories and fat, but less regimented in avoidance than AN; frequent dieting interspersed with overeating, often triggered by depression, isolation, or anger	Obsessive-compulsive attention to nutritional data on food labels and may have "logical" reasons for food choices in highly regimented pattern, such as sports participation or family history of lipid disorder	Choices less structured, with more frequent diets
Beverages	Water or other low- or no-calorie drinks; nonfat milk	Variable, diet soda common; may drink alcohol to excess	Fluids often restricted to avoid weight gain	Fluids ingested to aid vomiting or replace losses
Meals	Consistent schedule and structure to meal plan; reduced or eliminated caloric content, often starting with breakfast, then lunch, then dinner; volume can increase with fresh fruits, vegetables, and salads as primary food sources	Meals less regimented and planned than in AN; more likely impulsive and unregulated, often eliminated following a binge-purge episode	Rigid adherence to "rules" governing eating leads to sense of control, confidence, and mastery	Elimination of a meal following a binge-purge only reinforces the drive for binge later in the day
Snacks	Reduced or eliminated from meal plan	Often avoided in meal plans, but then impulsively eaten	Snack foods removed early because "unhealthy"	Snack "comfort foods" can trigger a binge
Dieting	Initial habit that becomes progressively restrictive, although often appearing superficially "healthy"; beliefs and "rules" about the patient's idiosyncratic nutritional requirements and response to foods are strongly held	Initial dieting gives way to chaotic eating, often interpreted by the patient as evidence of being "weak" or "lazy"	Distinguishing between healthy meal planning with reduced calories and dieting in ED may be difficult	Dieting tends to be impulsive and short-lived, with "diets" often resulting in unintended weight gain
Binge eating	None in restrictive subtype, but an essential feature in binge-purge subtype	Essential feature, often secretive; shame and guilt prominent afterward	Often "subjective" (more than planned but not large)	Relieves emotional distress, may be planned
Exercise	Characteristically obsessive-compulsive, ritualistic, and progressive; may excel in dance, long-distance running	Less predictable; may be athletic, or may avoid exercise entirely	May be difficult to distinguish active thin vs. ED	Males often use exercise as means of "purging"
Vomiting	Characteristic of binge-purge subtype; may chew then spit out, rather than swallow, food as a variant	Most common habit intended to reduce effects of overeating; can occur after meal as well as a binge	Physiologic and emotional instability prominent	Strongly "addictive" and self-punishing, but does not eliminate calories ingested—many still absorbed
Laxatives	If used, generally to relieve constipation in restrictive subtype, but as a cathartic in binge-purge subtype	Second most common habit used to reduce or avoid weight gain, often used in increasing doses for cathartic effect	Physiologic and emotional instability prominent	Strongly "addictive," self-punishing, but ineffective means to reduce weight (calories are absorbed in the small intestine, but laxatives work in the colon)
Diet pills	Very rare, if used; more common in binge-purge subtype	Used to either reduce appetite or increase metabolism	Use of diet pills implies inability to control eating	Control over eating may be sought by any means

AN, Anorexia nervosa; *BN,* bulimia nervosa; *ED,* eating disorder.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

BASIC INFORMATION

DEFINITION

Bullous pemphigoid (BP) is a chronic, autoimmune, subepidermal blistering disease commonly seen in the elderly. It is the most common of the acquired bullous autoimmune dermatoses. Other related diseases in the pemphigoid nosology include mucous membrane or cicatricial pemphigoid (MMP), anti-laminin 332 pemphigoid, Brusting-Perry pemphigoid, anti-laminin gamma-1 (anti-p200) pemphigoid, and dermatitis herpetiformis. Some consider linear IgA bullous dermatosis (LABD) and epidermolysis bullosa acquisita (EBA) to be forms of MMP. These diseases are all characterized by subepidermal loss of adhesion in hemidesmosomes of the basement membrane zone.

SYNONYMS

BP
Pemphigoid

ICD-10CM CODE
L12.0 Bullous pemphigoid

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common of the autoimmune bullous dermatoses in developed countries.
- Median age of onset is 75 to 80 yr, with rate of incidence increasing above age 70 yr and reaching a maximum above age 90 yr.
- Incidence varies depending on geographic location: Estimated at 24 cases per 1 million person-yr in the U.S. and ranging from 2.4 to 42.8 cases per 1 million person-yr in Europe.
- Bullous pemphigoid is very rare in children.
- Sex predilection varies by study, with some demonstrating no significant difference in incidence and others showing a general trend of female predilection in patients under age 75 but increased frequency in males over age 80.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

HISTORY:

- Two stages:
  1. Non-bullous phase: Starts as excoriated, eczematous, papular, or **urticarial plaques** characterized by extreme pruritus
  2. Bullous phase: Occurs days to months later and is characterized by formation of **tense blisters** (Fig. E1) that only become flaccid after rupture

PHYSICAL FINDINGS:

- Anatomic distribution:
  1. Flexor surfaces of the arms and legs, groin, axilla, chest, and abdomen; generally spares the head and neck
  2. Mucosal membrane involvement seen in 10% to 40% of patients (when present, typically involves the oral mucosa with sparing of the lips)
- Lesion configuration:
  1. May be localized in up to 30% of cases (extremities most common) or become generalized
  2. Lesions can have an annular or figurate pattern and may resemble erythema multiforme
- Lesion morphology:
  1. Tense blisters (bullae) measuring 1 to 3 cm in diameter and filled with clear or bloody fluid (Fig. E1) on either normal or urticarial skin are characteristic
  2. Absoe Hansen negative: No spread of eroded bases as blisters rupture; and also Nikolsky sign negative
  3. Heal without scarring but may leave postinflammatory hyperpigmentation or, more rarely, milia

ETIOLOGY

- Autoimmune disease with immunoglobulin (Ig) G and/or C3 complement targeting hemidesmosomal antigens (BP180 or BP230) located in the epidermal basement membrane zone
- Drug-induced pemphigoid, although uncommon, can occur in patients taking penicillamine, captopril (and rarely other angiotensin-converting enzyme inhibitors), penicillin and its derivatives, furosemide, sulfhydryl- or phenol-containing cephalosporins, sulfasalazine, acetylsalicylic acid, nonsteroidal antiinflammatory drugs (NSAIDs), dipeptidyl peptidase IV inhibitors (gliptins), TNF-α inhibitors, and vaccines
- Additionally, there are several reports of UV- or radiation therapy-induced BP
- BP patients are significantly more likely to have neurologic disease, with multiple sclerosis having the strongest association; unipolar or bipolar disorder, dementia, stroke and Parkinson disease are also associated with BP

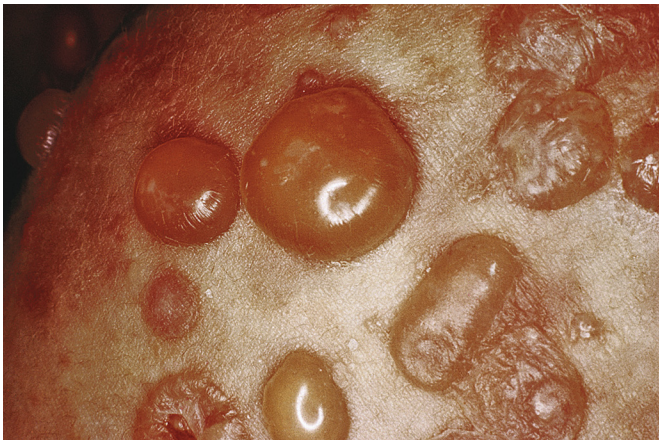

FIG. E1 Bullous pemphigoid. Large, tense bullae are seen on the lower region of the abdomen in this 13-year-old boy. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, 2016, Philadelphia, Elsevier.)

DIAGNOSIS

Diagnosis is based on a combination of clinical, histologic, and immunofluorescence findings. Direct immunofluorescence (DIF) microscopy is the gold standard. A detailed medical history, including date of onset, evolution of lesions, presence of pruritus, associated neurologic or psychiatric diseases and malignancies, and medication history over the past 6 months, should be obtained. BP should be high on the differential for an elderly patient presenting with generalized itch or nonscarring lesions without mucosal involvement and sparing the head and neck. The diagnosis can be confirmed with the following steps:

1. Validated BP criteria: Three of four clinical features (age >70, nonscarring, no mucosal involvement, absence of bullous lesions on head and neck) plus evidence of linear IgG and/or C3 deposits along basement membrane on DIF microscopy
2. Skin biopsy: Evidence of IgG anti-basement membrane autoantibodies on indirect immunofluorescence (IIF) microscopy
3. Skin biopsy: Evidence of anti-BP180 IgG and/or anti-BP230 IgG autoantibodies on enzyme-linked immunosorbent assay (ELISA)

DIFFERENTIAL DIAGNOSIS

- Bullous arthropod bites
- Linear IgA bullous dermatosis
- Dermatitis herpetiformis
- Anti-laminin gamma-1 (anti-p200) pemphigoid
- Brunsting-Perry pemphigoid
- Bullous systemic lupus erythematosus
- Mucous membrane or cicatricial pemphigoid
- Epidermolysis bullosa acquisita
- Pemphigoid gestationis
- Bullous erythema multiforme
- Generalized fixed drug eruption
- Impetigo
- Porphyria cutanea tarda
- Bullous lichen planus
- Pemphigus vulgaris
- Paraneoplastic pemphigus
- Table E1 compares some of these immunobullous diseases

LABORATORY TESTS

- Histology of lesional skin

TABLE E1 Immunobullous Skin Diseases

Immunobullous Disease	Clinical Presentation	Serum Autoantibodies	Targeted Protein or Structure	Tissue Immunofluorescence*
Pemphigus Dermatoses				
Pemphigus vulgaris	Flaccid bullae on noninflamed skin, crusting, positive Nikolsky sign;† commonly affects scalp, chest, intertriginous areas, and oral mucosa	IgG epithelial cell surface; correlates with disease activity	Desmoglein 3 and desmoglein 1 of the desmosome	Epidermal IgG and C3 cell surface staining
Pemphigus foliaceous	Superficial bullae, erosions, and scale with crusting, positive Nikolsky sign†	IgG epithelial cell surface; correlates with disease activity	Desmoglein 1 of the desmosome	Epidermal IgG and C3 cell surface staining
Paraneoplastic pemphigus	Flaccid bullae, lichenoid or erythema multiforme-like, usually involves mucosa, often extensively includes esophageal and respiratory areas	IgG epithelial cell surface and basement membrane zone (staining on rodent bladder epithelium is characteristic); correlates with disease activity	Desmoglein 3, desmoplakin 1, desmoplakin 2, BPAG1, envoplakin, periplakin, other proteins of the desmosome and hemidesmosome	Epidermal IgG and C3 cell surface and basement membrane zone staining
IgA pemphigus	Flaccid bullae, similar to pemphigus vulgaris	IgA epithelial cell surface; correlates with disease activity	Desmocollin 1 of the desmosome	Epidermal IgA cell surface staining
Pemphigoid Dermatoses				
Bullous pemphigoid	Tense bullae, often on urticarial base, prominent pruritus	IgG basement membrane zone, epidermal	BPAG2, BPAG1, hemidesmosome, lamina lucida	Linear basement membrane zone IgG and C3
Mucous membrane or cicatricial pemphigoid	Tense bullae and erosions, scarring sequelae	IgG basement membrane zone, epidermal	BPAG2, laminin 332 (previously known as laminin 5 or epiligrin), hemidesmosome, lamina lucida	Linear basement membrane zone IgG and C3
Pemphigoid gestationis	Tense bullae, similar to bullous pemphigoid; onset during or immediately after pregnancy	Complement fixing, basement membrane zone, epidermal	BPAG2, BPAG1, hemidesmosome, lamina lucida	Linear basement membrane zone C3
Epidermolysis bullosa acquisita	Tense bullae; commonly occurs in areas of trauma and in oral mucosa	IgG basement membrane zone, dermal‡	Type VII collagen, anchoring fibrils	Linear basement membrane zone IgG and C3; may show linear IgA and IgM
Linear IgA bullous dermatosis and chronic bullous disease of childhood	Tense bullae, similar to bullous pemphigoid; oral involvement common in adult disease	IgA basement membrane zone, epidermal (rarely dermal)	97-kD portion of BPAG2, hemidesmosome, lamina lucida	Linear basement membrane zone IgA
Dermatitis herpetiformis	Small bullae on extensor surfaces (elbows and knees); markedly pruritic; associated with intestinal gluten sensitivity	IgA endomysial and transglutaminase antibodies; correlates with disease activity and compliance with gluten-free diet	Epidermal transglutaminase	Granular basement membrane zone IgA with stippling in dermal papillae
Bullous lupus erythematosus§	Tense bullae, photodistributed	IgG basement membrane zone, dermal	Type VII collagen, anchoring fibrils	Linear basement membrane zone IgG; may show granular IgM and C3 basement membrane zone as in lupus band

BPAG1, 230-kD bullous pemphigoid antigen 1; *BPAG2,* 180-kD bullous pemphigoid antigen 2; *C3,* complement component 3, *cell surface,* intercellular substance; *Ig,* immunoglobulin.
*In all suspected immunobullous disease, the biopsy for diagnosis should be obtained from perilesional tissue because immunoreactants may not be present in lesional tissue; perilesional skin is the area immediately adjacent to but not involving a lesion. Serum studies are also essential to differentiate diseases.
†The Nikolsky sign is the formation of a new blister or extension of a blister from shearing pressure applied on normal-appearing skin or at the edge of an existing blister.
‡*Dermal* and *epidermal* refer to localization of antibodies on human split skin by indirect immunofluorescence of serum.
From Adkinson NF et al: *Middleton's allergy principles and practice,* ed 8, Philadelphia, 2014, Saunders.

1. Light microscopy: Subepidermal bullae with eosinophils and/or neutrophils with associated eosinophil and/or neutrophil dermal infiltrate
2. Direct immunofluorescence (DIF) microscopy (gold standard): Linear IgG and or C3 deposits along dermoepidermal junction

- Immune serological tests. NOTE: Only confirmatory with DIF microscopy findings
  1. Indirect immunofluorescence (IIF): Circulating IgG anti-basement antibodies using 1 mol/L NaCl-separated normal skin as substrate
  2. ELISA: Test for anti-BP180 IgG; if negative, test for anti-BP230 IgG

Rx TREATMENT

Bullous pemphigoid may be a self-limited disease, but its course may last from months to yrs. Treatment is based on the degree of disease involvement and the rate of disease

progression; however, there is no general consensus on how to determine disease severity. A European guideline defines severity by percent skin involvement, with less than 10% defined as mild, between 10% and 30% defined as moderate, and greater than 30% defined as severe.

NONPHARMACOLOGIC THERAPY

- Mild soaps with emollients to wet skin after bathing
- Use of nonadherent dressings in the case of extensive erosive lesions to prevent bacterial superinfection, minimize pain, and promote healing
- Only drain larger blisters and leave the blister roof intact as a natural dressing; remove fluttering skin only in broken blisters
- Avoid mechanical trauma to the skin

STAGE-SPECIFIC THERAPY

- Mild: Topical class I steroids daily
- Moderate: Class I topical steroids daily; systemic therapy may be added as needed
- Severe: Class I topical steroids daily in combination with systemic immunosuppressants
- Intralesional triamcinolone acetonide to isolated lesions
- Oral antihistamines to control pruritus

TETRACYCLINES

- Doxycycline 100 mg twice daily is similar in effectiveness to oral prednisolone, with decreased side effects compared with oral steroids.
- Tetracycline 500 mg four times daily plus nicotinamide 500 mg three times daily had similar effectiveness as prednisone 40 to 80 mg daily.

SYSTEMIC STEROID INDUCTION THERAPY

- Prednisolone (or equivalent) 0.5 mg/kg per day, which can be combined with adjuvant immunosuppressive therapy, including azathioprine, dapsone, doxycycline, methotrexate, and mycophenolate mofetil
- Initial doses greater than 1.0 mg/kg of prednisolone show little added benefit

TREATMENT-RESISTANT THERAPY

- Intravenous immunoglobulin therapy 2 g/kg per cycle (4- to 6-week intervals)
- Immunoadsorption or plasmapheresis
- Rituximab (anti-CD20) 1000 mg IV on day 1 then day 14 *or* 375 mg/m^2 IV administered four times at weekly intervals

SYSTEMIC CONSOLIDATION THERAPY

- Once disease control is achieved with oral steroids, begin tapering corticosteroids by 25% at 7- to 14-day intervals; if induction dose is less than 20 mg/day, taper over 2- to 4-week intervals.
- If relapse occurs, return to dose given two reduction intervals prior; can resume taper after 14 days of disease control.
- May add or switch to adjuvant agents as needed.
- Disease control is defined as no new lesion formation concurrent with healing of existing lesions.
- Relapse is defined as greater than three new lesions per month or one lesion greater than 10 cm that does not heal spontaneously in one week or progression of the existing lesions or reemergence of daily pruritus.

DISPOSITION

In the United States, mortality rates are estimated at between 11% to 23% after 1 yr. Standardized mortality ratios range from 1.90 to 6.6. BP is a chronic disease; exacerbations and relapses are not uncommon, even in successfully treated individuals. A recent prospective study reported a 45% relapse rate of the evaluable patients at 12 months, with the majority of relapses occurring in the first 6 months after cessation of therapy. In this study, an ELISA titer score three times higher than the normal cutoff value at time of therapy cessation was the main predicting factor for BP relapse within the next yr. Dementia and initial extensive disease may be two additional independent risk factors associated with relapse during the first yr of therapy.

REFERRAL

Dermatology

PEARLS & CONSIDERATIONS

COMMENTS

- Pruritus can be the presenting complaint and can precede the appearance of any skin lesions.
- Bullous pemphigoid should be high on the differential in patients over 70 yr old with tense bullae.
- Extremely pruritic urticarial plaques can precede onset of tense bullae by months.
- Doxycycline 100 mg twice daily is equally effective to oral prednisolone.

RELATED CONTENT

Bullous Pemphigoid (Patient Information)

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SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

- Delayed conduction in the His-Purkinje system that meets criteria for right bundle branch block (RBBB), left bundle branch block (LBBB), or hemifascicular block. The latter can be either left anterior fascicular block (LAFB) or left posterior fascicular block (LPFB). Bifascicular block is a combination of RBBB and either LAFB or LPFB. All of these are categories of bundle branch block. Any delayed conduction that does not meet these criteria is not considered bundle branch block but rather categorized as intraventricular conduction delay (IVCD) (see also topic "Intraventricular Conduction Delay"). Repolarization abnormalities may be seen in multiple leads with LBBB and in leads V1-V3 in RBBB. These include T wave inversions and ST segment depression in the opposite direction from the QRS complex. Fig. 1 illustrates a diagrammatic representation of fascicular blocks in the left ventricle. Table 1 and Table 2 summarize common diagnostic criteria for fascicular blocks and bundle branch blocks.
- The bundle branch block can be persistent or intermittent. The latter is predominantly rate-related, usually RBBB, during tachycardia or acute shortening of the R-R interval, which is common during atrial fibrillation. Bradycardia-dependent aberrancy can also be seen. Alternating bundle branch block between RBBB and LBBB is a sign of conduction system disease and will often progress to complete heart block.

SYNONYMS

- Fascicular block
- Aberrancy
- Conduction disturbance
- Conduction delay
- Conduction defect

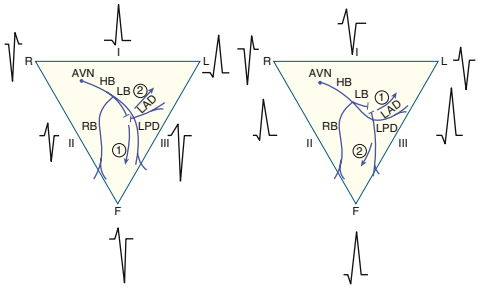

FIG. 1 Diagrammatic representation of fascicular blocks in the left ventricle. *Left,* Interruption of the left anterior fascicle or division (here labeled LAD) results in an initial inferior (1) followed by a dominant superior (2) direction of activation. *Right,* Interruption of the left posterior fascicle or division (here labeled LPD) results in an initial superior (1) followed by a dominant inferior (2) direction of activation. *AVN,* Atrioventricular node; *HB,* His bundle; *LB,* left bundle; *RB,* right bundle. (Courtesy Dr. C. Fisch.) (From Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.)

TABLE 1 Common Diagnostic Criteria for Fascicular Blocks

Left Anterior Fascicular Block

Frontal plane mean QRS axis between −45 and −90 degrees qR pattern in lead aVLQRS duration <120 msec
Time to peak R wave in aVL ≥45 msec

Left Posterior Fascicular Block

Frontal plane mean QRS axis between +90 and +180 degrees rS pattern in leads I and aVL with qR patterns in leads III and aVF
QRS duration <120 msec
Exclusion of other factors causing right axis deviation (e.g., right ventricular overload patterns, lateral infarction)

aVF, Augmented vector foot; *aVL,* augmented vector left.
From Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.

TABLE 2 Common Diagnostic Criteria for Bundle Branch Blocks

Complete Left Bundle Branch Block

QRS duration ≥120 msec
Broad, notched, or slurred R waves in leads I, aVL, V5, and V6
Small or absent initial r waves in right precordial leads (V1 and V2) followed by deep S waves
Absent septal q waves in leads I, V5, and V6
Prolonged time to peak R wave (>60 msec) in V5 and V6

Complete Right Bundle Branch Block

QRS duration ≥120 msec rsr′, rsR′, or rSR′, patterns in leads V1 and V2
S waves in leads I and V6 ≥40 msec wide
Normal time to peak R wave in leads V5 and V6 but >50 msec in V1

aVF, Augmented vector foot; *aVL,* augmented vector left.
From Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.

ICD-10CM CODES
Bundle branch block (fascicular block):
I44.4 Anterior
I44.5 Posterior
I44.60 Hemiblock (hemifascicular block)
I44.7 Left
I45.10 Right
I45.2 Bilateral (bifascicular)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The cumulative incidence of any type of bundle branch block increases with age (1.5% at age 50, 18% at age 80)
PEAK INCIDENCE: Cumulative incidence of 18% at age 80 for any type of bundle branch block
PREVALENCE: The estimated prevalence in the general population for any type of bundle branch block ranges between 0.2% and 3.4% and increases with age.

- Complete LBBB: 0.4% men age 50, 5.7% men age 80, 1.1% women age 50 to 80
- Complete RBBB: 0.2% men before age 30, 0.8% men age 50, 1.3% men age 80, 1.3% women age 50 to 80, 2.3% in men and women age 60
- Incomplete RBBB: 13.5% age 20, 3.4% age 50

PREDOMINANT SEX AND AGE: More common in men, incidence increases with age
GENETICS: Most cases of bundle branch block are not hereditary. The Brugada syndrome is an autosomal dominant genetic disorder with pseudo-RBBB but is not a true bundle branch block (see section on Brugada Syndrome). The hereditary bundle branch defect is an autosomal dominant genetic disease that has been described in Lebanon and was mapped to the long arm of chromosome 19.
RISK FACTORS: Male gender, elder age, structural heart disease, cardiomyopathy, hypertension

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- RBBB can cause wide splitting of the second heart sound (S_2). Either LBBB or RBBB can cause continuous splitting of S_2 during respiration.
- Isolated bundle branch block does not cause symptoms. Nevertheless, it is usually a result of heart disease, either in the conduction system or the surrounding cardiac tissues, and its existence can aggravate the clinical picture of the causal entity.
- In patients with heart failure, the presence of LBBB can cause ventricular dyssynchrony and worsen heart failure. LBBB or RBBB, when coexistent with coronary artery disease, diabetes, or heart failure, are markers for increased mortality.
- RBBB can be seen in pulmonary hypertension or acute pulmonary embolism, generally in entities that increase the right ventricular afterload. The presence of bundle branch block can be associated with other conduction defects such as second or third degree AV block.

Bundle Branch Block

ETIOLOGY

- Bundle branch block can be a result of disease in the His-Purkinje conduction system but can also result from disease or fibrosis surrounding the conduction system (i.e., myocardial infarction), antiarrhythmic drugs, or hyperkalemia. Selected causes of bundle branch block are the following: intracardiac catheter manipulation, myocardial ischemia or infarction, myocarditis, cardiomyopathy, and Lenegre or Lev disease. RBBB in particular is associated with pulmonary hypertension and pulmonary embolism, whereas LBBB can be caused by an anterior myocardial infarction.
- Rate-related branch block in normal hearts is usually seen in tachycardia or in atrial fibrillation where a long R-R interval is followed by a shorter one. This is due to Ashman phenomenon, where a long cycle length interval causes prolongation in the refractory period resulting in bundle branch block on the subsequent early beat. This is a common property of all cardiac tissues but more evident in the conduction system. The rate-related bundle block is usually RBBB since the right bundle has a longer refractory period than the left bundle for the same heart rate. Another phenomenon is bradycardia-dependent aberrancy. This may be due to automaticity in a bundle branch block during diastole leading to BBB on a subsequent beat. Other explanations include vagal tone inhibition or phase 4 block. In phase 4 block, the cells have depleted sodium reserves resulting in low resting membrane potentials that impose difficulty in cell excitability resulting in conduction block.
- In patients with LBBB, detailed mapping has demonstrated that the site of block is in the proximal left conduction system in 64% of cases.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Refer to Table 3.
- An accessory pathway can cause an appearance of RBBB or LBBB. If lead V1 is placed higher than the fourth intercostal space or more right than the parasternal area, the EKG can resemble incomplete RBBB.
- An inferior myocardial infarction can resemble left anterior fascicular block, but in the inferior myocardial infarction, the inferior leads (II, III, aVF) will have qR instead of QS morphology. Left posterior fascicular block can resemble lateral myocardial infarction, right ventricular hypertrophy, dextrocardia, or lateral accessory pathway. Accelerated idioventricular rhythm can resemble LBBB or RBBB, depending on the origin of the ventricular pacemaker site.

WORKUP

- Resting, ambulatory, and exercise electrocardiogram
- Investigation of coexistent comorbidities such as heart failure, myocardial infarction, and cardiomyopathies
- Acute LBBB should prompt investigation for anterior myocardial infarction (Fig. 2) whereas acute RBBB for pulmonary hypertension, or pulmonary embolism (Fig. 3)
- Figs. 2 and 3 illustrate diagnostic evaluations for bundle branch block.

LABORATORY TESTS

- Standard laboratory testing appropriate for age, gender, and metabolic abnormalities
- Electrolyte abnormalities and especially hyperkalemia should be excluded

IMAGING STUDIES

Electrocardiogram (Figs. 4 and 5)

Rx TREATMENT

- Treat the underlying cause (Tables 4 and 5)
- In asymptomatic patients with an isolated bundle branch block, no therapy is required

NONPHARMACOLOGIC THERAPY

Cardiac resynchronization therapy (CRT) with biventricular or His-bundle devices can benefit selected patients with LBBB and depressed EF, if heart failure is present. Permanent pacemaker is appropriate for patients with cardiac syncope or coexisting third degree, or Mobitz type II second degree AV block, when not due to a reversible cause.

ACUTE GENERAL Rx

In acutely established bundle branch block, investigate the cause. In acute LBBB, anterior myocardial infarction should be investigated whereas in acute RBBB investigation should target pulmonary embolism.

CHRONIC Rx

Optimization of potential coexisting comorbidities such as coronary artery disease, heart failure, hyperkalemia, diabetes

DISPOSITION

There is no specific disposition plan for isolated bundle branch block. Entities such as myocardial ischemia or infarction, myocarditis, and cardiomyopathy should be investigated prior to disposition in a new bundle branch block with associated symptoms. Pulmonary embolism should also be investigated in a new RBBB with suspecting symptoms.

REFERRAL

In selected patients at risk for sudden cardiac death such as Brugada syndrome, or in cases of new bundle branch block associated with acute symptoms, referral is indicated.

! PEARLS & CONSIDERATIONS

COMMENTS

Acute LBBB can be caused by anterior myocardial infarction. Acute RBBB can be due to pulmonary embolism. Bundle branch block is a normal variant, especially in young individuals. History and physical exam are needed to identify associated cardiac abnormalities. In patients with heart failure, and depressed ejection fraction, cardiac resynchronization is beneficial in the presence of LBBB but not in the presence of RBBB.

TABLE 3 Differential Diagnosis of Bundle Branch Block

	Right Bundle Branch Block		Left Bundle Branch Block		Hemifascicular Block	
	Incomplete	**Complete**	**Incomplete**	**Complete**	**Left Anterior Fascicular Block**	**Left Posterior Fascicular Block**
QRS Axis	Normal	Normal	Normal or left	Normal or left	Left and >–45°	Right and >+90°
QRS Duration	<120 msec	>120 msec	<120 msec	>130 msec	<120 msec	<120 msec
I	qRs	Deep S	No q wave	Tall R wave, no q wave, no S wave	Positive QRS	rS
aVL	qRs	Deep S		Tall R wave, no q wave, no S wave	qR	rS
II, III, aVF					rS	qR
Precordial Leads	rSR' in V1-V2, qRs in V5-V6	RsR' in V1-V2, deep S in V5-V6	No q wave in V5-V6	QS or rS in V1-V2, tall R wave and no q wave or S wave in V5-V6	Poor R wave progression in V1-V3	
aVR	rsR'				Often tall R wave	

aVF, Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right.

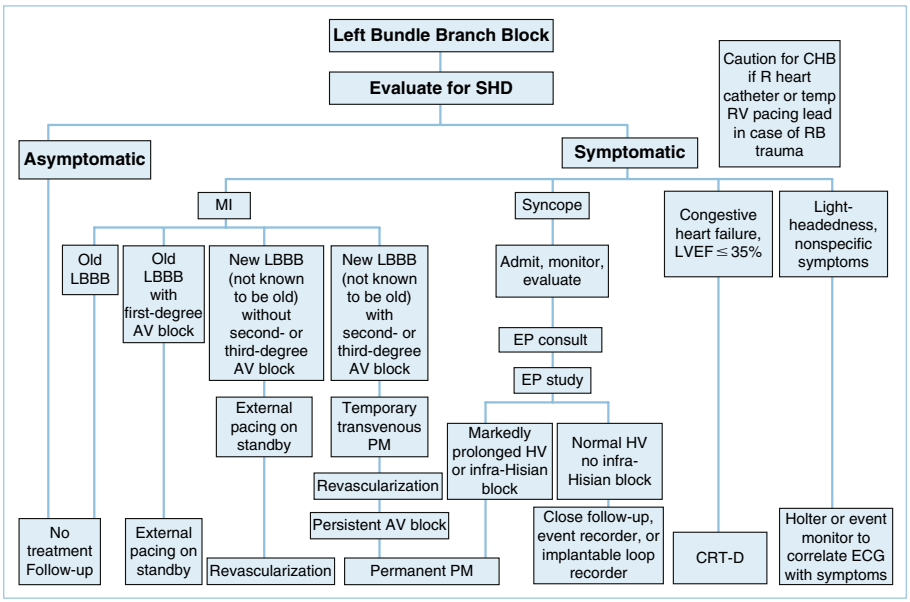

FIG. 2 Left bundle branch block *AV,* Atrioventricular; *CHB,* complete heart block; *CRT-D,* cardiac resynchronization therapy combined with a defibrillator; *ECG,* electrocardiogram; *EP,* electrophysiology; *LBBB,* left bundle branch block; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction; *PM,* pacemaker; *RB,* right bundle; *RV,* right ventricular; *SHD,* structural heart disease (no overt evidence of myocardial, valvular, congenital, or coronary heart disease). (From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

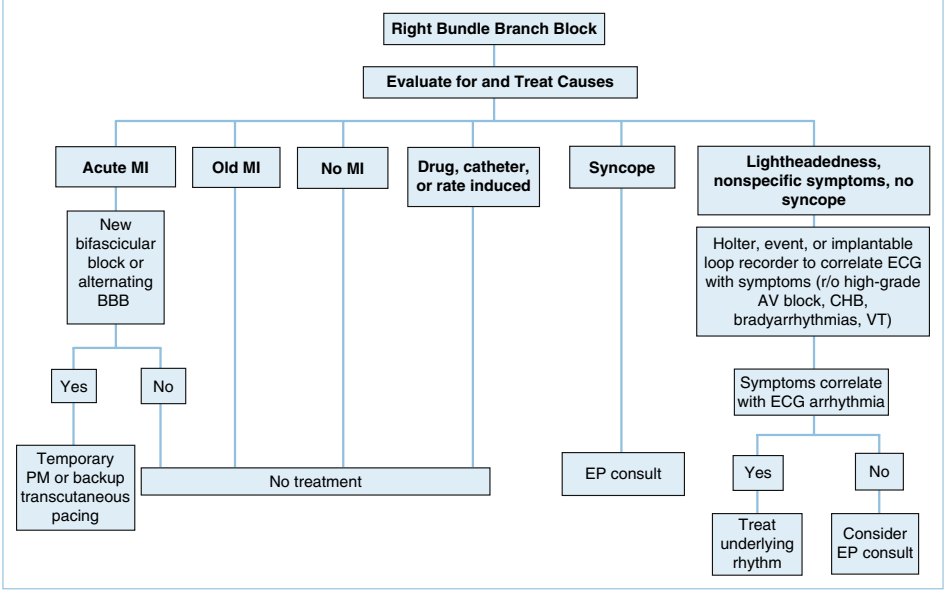

FIG. 3 Right bundle branch block. *AV,* Atrioventricular; *BBB,* bundle branch block; *CHB,* complete heart block; *ECG,* electrocardiogram; *EP,* electrophysiology; *MI,* myocardial infarction; *PM,* pacemaker; *VT,* ventricular tachycardia. (From Olshansky B,et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

PREVENTION

Modification of associated comorbidities such as optimization of heart failure, coronary artery disease, hypertension, and diabetes.

PATIENT & FAMILY EDUCATION

Bundle branch block is a problem in the heart's electrical system. There are several types, but clinically the most important is the left bundle branch block in which one of the two main "wires" in the heart is not functioning correctly. As a result, the heart's pumping chambers are squeezing out of sync and can worsen the heart's ability to pump in people with heart failure. It is more common in older adults and people with serious heart disease.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Atrioventricular Dissociation (Related Key Topic)
Brugada Syndrome (Related Key Topic)
Heart Failure (Related Key Topic)
Intraventricular Conduction Delay (Related Key Topic)
Myocardial Infarction (Related Key Topic)
Pulmonary Embolism (Related Key Topic)

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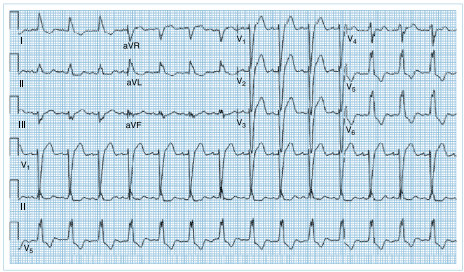

FIG. 4 Left bundle branch block. This 12-lead electrocardiogram shows LBBB that is characterized by a wide (>0.12 seconds) QRS complex; broad monophasic R waves in leads V5, V6, and I that are commonly slurred or notched; rS or QS complexes in the right precordial leads; and secondary ST- and T-wave changes that are opposite in direction to the major QRS deflections. The mean frontal plane QRS axis is normal, but left-axis deviation may be present. aVF, Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right; *LBBB,* left bundle branch block. (From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

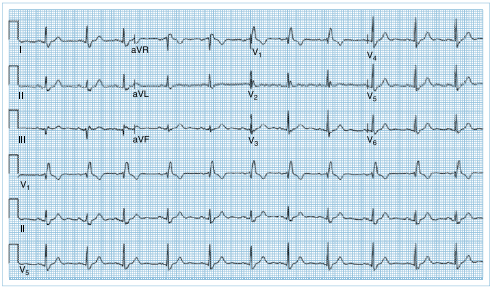

FIG. 5 Right bundle branch block. This 12-lead electrocardiogram shows RBBB that is characterized by a wide (≥0.12 seconds) QRS complex; a secondary R wave (R′) in V1 and V2 (rsR′ or rSR′) with R′ usually taller than the initial R wave; a wide, slurred S wave in leads V5, V6, and I; and secondary ST- and T-wave changes that are opposite in direction to the terminal QRS deflections over the right precordial leads. The mean frontal plane QRS axis is normal. *aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right; *RBBB,* right bundle branch block. (From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

TABLE 4 Left Bundle Branch Block Management

Setting	Therapy
Asymptomatic normal LV function	• No therapy—rule out structural heart disease, ischemic heart disease. • Requires long-term follow-up. • If instrumentation of the right ventricle is planned, be ready to temporarily pace (preferably externally or via a temporary pacemaker wire) if transient traumatic RBBB with resultant complete AVB is induced. • Trauma to the right bundle can last from minutes to more than 24 hours.
Symptomatic (syncope, lightheadedness)	• Admit, monitor, and evaluate for structural heart disease. • If syncope occurs, EP consultation and possible EP testing is indicated. • If HV interval is 100 msec or more or if infra-Hisian block is provoked with atrial pacing at rates of <160 bpm with or without procainamide challenge, implant a permanent pacemaker.
Symptomatic cardiomyopathy (CHF)	• If LVEF is 35% or less, NYHA class II, III, or IV heart failure symptoms are present with LBBB with QRS duration of more than 130 ms: CRT-D ICD implantation is indicated (may improve LV function, reduce heart failure symptoms, and reduce the risk of sudden death).
Myocardial infarction	• New (or not known to be old) LBBB: revascularization with direct PTCA with or without stent. • Temporary pacemaker if second-degree or third-degree AVB is present. • New onset LBBB indicates extensive myocardial ischemia or infarction and is associated with worse prognosis. • Have external (transcutaneous) pacing on standby if no AVB is present.
Preoperative	• No therapy is required if the patient is asymptomatic, whether or not coronary artery disease or systolic dysfunction is present. • Cardiac workup (stress test, echocardiogram) to exclude structural heart disease if symptomatic. • LBBB is not per se an indication for treadmill testing. If stress testing is performed, imaging must accompany the test if the aim is to document the presence of obstructive coronary artery disease; imaging is not required if the aim of the stress test is the assessment of effort tolerance.
Postoperative	• No therapy if asymptomatic. • Common after aortic valve replacement (usually persistent) and after CABG (transient due to cardioplegia).
Alternating LBBB and RBBB	• Alternating BBB may be due to trifascicular disease • Because of the high rate of progression to CHB, permanent pacemaker implantation is advised. • Alternating BBB may also be seen as a digitalis toxic rhythm, although in current practice this occurs only rarely.

AVB, Atrioventricular block; *BBB,* bundle branch block; *CABG,* coronary artery bypass graft; *CHB,* complete atrioventricular block; *CHF,* congestive heart failure; *CRT-D,* cardiac resynchronization and defibrillation therapy; *EP,* electrophysiology; *HV,* histoventricular; *ICD,* implantable cardioverter defibrillator; *LBBB,* left bundle branch block; *LV,* left ventricular; *LVEF,* left ventricular ejection fraction; *NYHA,* New York Heart Association; *PTCA,* percutaneous transluminal coronary angioplasty; *RBBB,* right bundle branch block.
From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.

TABLE 5 Right Bundle Branch Block Management

Setting	Therapy
Outpatient asymptomatic	• No therapy. • May occur with instrumentation of the right ventricle (e.g., Swan-Ganz catheter) and trauma to the right bundle. • Can last up to 24 h.
Symptomatic (syncope)	• Admit the patient with RBBB who has syncope. • If symptoms of syncope occur (may be related to AVB or VT), attempt to correlate symptoms with rhythm by Holter or event monitoring. • Evaluate for underlying structural cardiac disease. • Consider EP testing to assess AV conduction and the presence of inducible VT (present in up to 30% of symptomatic RBBB patients) if the patient is syncopal.
MI	• Isolated RBBB: No therapy. • RBBB with LAFB or LPFB (that is new or not known to be old) or alternating BBB: • Temporary pacemaker • Alternatively, placement of a transcutaneous pacing system • RBBB occurs in 3%-7% of MIs, often with LAFB, and usually because of anterior or anteroseptal infarction. • The combination is less common in the current era of early revascularization via percutaneous techniques.
Preoperative	• No therapy—temporary pacemaker not required. • Perform cardiac evaluation to exclude other cardiovascular disease.
Postoperative	• No treatment. • Most common conduction disturbance in this setting.
Alternating LBBB and RBBB	• Permanent pacemaker if not due to reversible cause.

AV, Atrioventricular; *AVB,* atrioventricular block; *BBB,* bundle branch block; *EP,* electrophysiology; *LAFB,* left anterior fascicular block; *LBBB,* left bundle branch block; *LPFB,* left posterior fascicular block; *MI,* myocardial infarction; *RBBB,* right bundle branch block; *VT,* ventricular tachycardia.

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Burning Mouth Syndrome

BASIC INFORMATION

DEFINITION

Burning mouth syndrome (BMS) is an uncommon disorder characterized by continuous burning pain in the tongue or oral mucous membranes where no underlying dental or medical cause can be identified and no oral signs are found. BMS may be accompanied by subjective xerostomia (dry mouth sensation in which no cause can be found), dysgeusia (altered taste), dysosmia (altered smell), and oral paresthesia (e.g., tingling).

Diagnostic criteria:

- Oral pain fulfilling criteria B and C
- Recurring daily for >2 hours per day for >3 months
- Pain has both of the following characteristics:
  1. Burning quality
  2. Felt superficially in the oral mucosa
- Oral mucosa is of normal appearance, and clinical examination including sensory testing is normal.
- Not better accounted for by another ICHD-3 (the *International Classification of Headache Disorders, 3rd edition*) diagnosis

SYNONYMS

BMS
Glossodynia
Oral dysesthesia
Glossopyrosis
Stomatodynia

ICD-10CM CODE
K14.6 Glossodynia

EPIDEMIOLOGY & DEMOGRAPHICS

- 5 per 100,000 general population.
- Women 3 to 7 times more likely than men of a similar age; most prevalent in postmenopausal women.
- Typically occurs in middle-aged or older adults. The prevalence may increase from three- to twelvefold with increasing age.
- Asian and Native Americans have considerably higher risk.
- 30% to 50% of patients improve spontaneously.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Sensation is usually bilaterally located on the tongue, most frequently on the anterior two thirds of the tongue, the anterior hard palate, and the lower lip mucosa.
- Sensation most typically described as burning, scalded, or tingling. Sometimes described as "discomfort," "tender," or "annoying" rather than pain or burning.
- The oropharyngeal exam may show atrophy, erythema, leukoplakia, erosion, or ulceration.
- May present with oral parafunctional habits such as bruxism, jaw clenching, and tongue thrusting, which are increased with anxiety.
- Pain is chronic and often lasts at least 4 to 6 months.
- Up to two thirds of patients report a spontaneous partial recovery within 6 to 7 yr from onset, with the pain changing from constant to intermittent.

ETIOLOGY

More than 50% of cases have no identifiable cause (primary BMS). Many of the currently proposed etiologies of secondary BMS include:

- Psychological dysfunction: Many patients concomitantly have personality or mood changes, report more adverse life events, somatization, anxiety, and depression. A proportion of patients have anxiety centered around concerns of cancer (cancerphobia).
- Neurologic: Decreased levels of dopamine likely contribute to the painful clinical conditions, including burning mouth syndrome.
- Endocrine: Hormonal alterations, especially in menopause, lead to a deficit in neuroprotective steroids that can cause atrophic changes in oral mucosa.
- Immunologic: Observational studies have shown elevation of serum erythrocyte sedimentation (ESR) rate and salivary immunoglobulin A compared with control patients.
- Infectious: Fusospirochetes, *Candida, Enterobacter, Helicobacter pylori,* and *Klebsiella* infection. *Candida* may not always produce visible lesions.
- Local irritants, such as smoking, and dental materials, such as mercury.
- Medications, such as angiotensin-converting enzyme (ACE) inhibitors and protease inhibitors.
- Trigeminal small-fiber sensory neuropathy.
- Nutritional deficiencies: Iron, zinc, folate, and vitamin B.

There may be an association between supertasters (those with enhanced ability to taste) and those with BMS caused by their increased density of taste buds that are surrounded by bundles of trigeminal nerve neurons.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Mucosal disease such as lichen planus, candidiasis, xerostomia, pemphigoid, and allergic contact stomatitis
- Nutritional deficiency in zinc, iron, folate, or vitamins B_1, B_2, B_6, B_9, B_{12}
- Dry mouth from Sjögren syndrome or after chemo/radiation therapy
- Cranial nerve injury
- Medication effect
- Systemic factors such as diabetes, abnormal thyroid, autoimmune conditions, Parkinson disease

WORKUP

- Clinical history is the most important in diagnosing BMS.
- Very important to rule out other pathologic conditions first.

LABORATORY TESTS

There is no diagnostic test for BMS but consider testing for vitamin B, folate, ferritin, or zinc deficiency as well as CBC, luteinizing hormone, follicle-stimulating hormone, hemoglobin A1c, thyroid function (T_3/T_4), and ESR.

TREATMENT

NONPHARMACOLOGIC THERAPY

Consider discontinuation of medications that may cause xerostomia (e.g., anticholinergics, psychotropics) and substitution for medications that may cause oral burning (e.g., ACE inhibitors, angiotensin-receptor blockers, antiretrovirals). Formal psychotherapy and cognitive behavioral therapy have been helpful for some patients.

- Capsaicin (hot pepper powder) can be used as a topical desensitizing agent.
- Rinse mouth with 1 tsp of a 1:2 solution of hot pepper and water; increase strength of capsaicin as tolerated to a maximum 1:1 dilution.

ACUTE GENERAL Rx

No definitive cure exists. Attempting combinations of therapies may be appropriate. Interestingly, cognitive therapy may be synergistic with other agents.

Treatment options currently include:

- Low-dose benzodiazepines:
  1. Clonazepam 0.25 to 2 mg/day; start with 0.25 mg at bedtime and increase dose q4 to 7 days until oral burning is relieved or side effects.
  2. Topical clonazepam solution 0.1 to 0.5 mg/ml; swish with 5 ml for 5 minutes and spit two to four times daily.2.
- Low-dose tricyclic antidepressants:
  1. Amitriptyline or nortriptyline 10 to 150 mg/day; start with 10 mg at bedtime and increase dose by 10 mg q 4 to 7 days.
- Low-dose gabapentin 300 to 1600 mg/day; start with 100 mg at bedtime and increase dose by 100 mg q 4 to 7 days (take in divided doses).
  1. Oral nystatin
- Capsaicin (topical oral) dopaminergic D2 agonists: Pramipexole
  1. Based on the dopaminergic dysfunction in BMS, a case report described the use of pramipexole 0.125 mg at night with improvement with symptoms in 4 weeks. A case series of 6 patients with BMS also demonstrated clear improvement of symptoms in all cases with the doses between 0.36 mg and 1.05 mg per day.
- Low-level laser therapy:
  1. Clinical trials have shown improved symptom control when given over two sessions weekly for 4 to 5 wk and can be an alternative treatment to psychoactive drugs.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Antioxidant alpha lipoic acid
- Acupuncture may be effective
- Relaxation programs and massage

REFERRAL

Consider referral to a subspecialist in this area, such as a dentist or ENT if initial therapy fails to resolve symptoms. Surgery is not recommended.

PEARLS & CONSIDERATIONS

COMMENTS

BMS is a rare but possibly debilitating disease that can be highly frustrating to the patient and the practitioner. The patient often experiences an unremitting burning pain in the mouth without any apparent clinical signs, and the practitioner is unable to definitively diagnose symptoms even with the use of laboratory testing or imaging. Other diseases should be ruled out.

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BASIC INFORMATION

DEFINITION

- Cutaneous burns can be classified by type of injury (e.g., thermal vs. chemical), burn depth (e.g., first, second, third degree), extent of burn (total burn surface area [TBSA]), and burn severity (e.g., minor vs. major). Types of burn injury include thermal (flames, scalds, hot contactants), chemical, electrical, and radiation burns. This chapter will focus on thermal and electrical burns.
- Burns can affect skin and respiratory, ocular, oral, and genital mucosa.

SYNONYMS

Thermal injury
Chemical injury
Electrical injury
Radiation injury

ICD-10CM CODES

T29.0 Burns of multiple regions, unspecified degree
T30.0 Burn of unspecified body region, unspecified degree
T30.1 Burn of first degree, body region unspecified
T30.2 Burn of second degree, body region unspecified
T30.3 Burn of third degree, body region unspecified
T31.0 Burns involving less than 10% of body surface
T31.1 Burns involving 10%-19% of body surface
T31.2 Burns involving 20%-29% of body surface
T31.3 Burns involving 30%-39% of body surface
T31.4 Burns involving 40%-49% of body surface
T31.5 Burns involving 50%-59% of body surface

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.):

- More than 1.2 million individuals experience burns in the U.S., and burn injuries account for approximately 500,000 emergency department visits, with 9% (45,000) requiring hospitalization and 0.8% (4000) resulting in death annually.
- Of thermal injury, scald burn from liquid is most common—followed by flame, flash burn, and then contact burn.

PREDOMINANT AGE & SEX: Children ages 2 to 4 yr have the greatest frequency of burns (most commonly scald burns), with male adolescent and young adults ages 17 to 25 with second greatest frequency (most commonly from flammable liquids).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- It is important to note that burns occur unevenly, often with various depths (Table 1)
- First-degree (superficial) burns: penetrate epidermis only (minimal barrier loss)
  1. Very painful, intact, erythematous skin with minimal to no edema and no blistering
- Second-degree (partial-thickness) burns: epidermis and part of dermis is affected
  1. Moist, very painful skin with edema and blistering/blebs
  2. Superficial partial-thickness burns: cherry red with two-point discrimination intact, incredibly painful
  3. Deep partial-thickness burns: mottled white and cherry red; only the sensation of pressure is intact in these areas
- Third-degree (full-thickness) burns: entire epidermis and dermis are affected, with destruction of hair follicles and sweat glands
  1. The skin is dry, charred, pale, painless, and leathery; charred vessels may be visible beneath, little or no pain, and hair pulls out easily

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Cultural practices leading to burnlike lesions in distinctive patterns (e.g., cupping, coining, moxibustion), cellulitis, Stevens-Johnson syndrome/toxic epidermolytic necrolysis

CLASSIFICATION

- Burns are classified by (1) depth of injury, (2) extent of injury, and (3) severity, according to the American Burn Association.
- Depth of injury (see Table 1):
  1. Indicates how the wound will heal and whether grafting will be needed.
- Extent of TBSA:
  1. The TBSA is best classified by using age-specific burn charts and the "rule of nines" (Fig. 1).
  2. For scattered burns, utilizing patient's palm including fingers to equate 1% body surface area can be helpful.
  3. TBSA indicates how aggressively the patient will need to be resuscitated.
- Severity: Determined by burn depth, TBSA, age, location, type of injury, and presence/absence of coexisting conditions. Severity classification helps triage patients to outpatient, inpatient, or burn unit care (see Table 2).
  1. Minor burns: outpatient management
  2. Moderate burns: admission to hospital with experience managing burns or burn center referral
  3. Major burns: referral to burn center

LABORATORY STUDIES (MODERATE OR MAJOR BURNS)

- CBC, electrolytes, BUN, creatinine, glucose, liver function tests, venous blood gas, blood coagulation, and type and screen in anticipation of blood transfusion
- *If smoke inhalation expected:* Serial ABG carboxyhemoglobin and continuous ECG
- *If electrical burn or if concern for rhabdomyolysis:* Urinalysis, urine myoglobin, and CPK levels

TABLE 1 Categorization of Burn by Depth

Burn Type	Histologic Depth	Clinical Presentation	Treatment	Healing Time/Prognosis
1st degree	Epidermis	Erythematous but intact skin, no blisters, pain may range in severity	Topical salves, cold compresses, NSAIDs for pain control	2-5 days with no scarring
Superficial 2nd degree (partial thickness)	Papillary dermis	Erythematous with superficial blisters, intense pain	Topical antimicrobials with gauze dressing or biosynthetic dressing (if widespread), pain control	5-21 days with no grafting
Deep 2nd degree (partial thickness)	Reticular dermis	Erythematous with superficial/deep blisters, range of pain depending on nerve involvement	Same	21-35 days with no infection; if infected, converts to full-thickness burn
3rd degree (full thickness)	Through dermis to subcutaneous tissue. Can involve fascia, muscle, and bone.	White or black, possible eschar, may or may not be painful depending on nerve damage	Usually requires grafting, may require resuscitation depending on TBSA affected, pain control	Large areas require grafting, but small areas may heal from the edges after wks

NSAID, Nonsteroidal antiinflammatory drug; *TBSA,* total body surface area.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, WB Saunders; and Kessides MC, Skelsey MK: Management of acute partial-thickness burns, *Cutis* 86:249-257, 2010.

- *If severe lactic acidosis:* Consider checking cyanide level

IMAGING STUDIES

- If smoke inhalation suspected: Chest radiograph and bronchoscopy
- If high-voltage electrical burn: Cardiac monitoring first 24 hours

Rx TREATMENT

ACUTE GENERAL Rx

MINOR BURNS (FIRST-DEGREE BURNS AND SECOND/THIRD-DEGREE BURNS OF LIMITED TBSA):

- Outpatient management: "6 Cs"
  1. Clothing: Remove hot or burned clothing.
  2. Cooling: Cool (approximately 54° F [12.22° C]) for 10 to 30 min (under faucet or compress) to reduce edema/pain by conducting heat away from skin. Not recommended with extensive burns due to theoretical risk of hypothermia and shock. No ice packs.
  3. Cleaning: Wash gently with mild alcohol-free soap, then normal saline daily. Remove all old ointment and any loose skin. Blot dry. No evidence supports vigorous cleansing with antiseptic solutions. Embedded materials should be removed by copious irrigation using a large-gauge syringe.
  4. Chemoprophylaxis: Tetanus immunization (all deep second- and third-degree burns). Routine skin cultures are NOT recommended except when wound infection suspected, and prophylactic systemic antibiotics are NOT recommended. All second- and third-degree burns are treated with a topical antimicrobial agent. This may include silver sulfadiazine, bacitracin, bismuth-impregnated Vaseline gauze, or silver-impregnated synthetic dressings.
  5. Covering: All second- and third-degree burns should be covered with sterile dressing. If financial resources are limited, instead of gauze, can purchase cotton gloves, T-shirts, or similar at discount stores, wash, and reuse.
  6. Comfort: Analgesics (Tylenol and NSAIDs—alone or in combination with opioids) around the clock are recommended. Additional "rescue" analgesics before dressing changes and physical activity recommended.

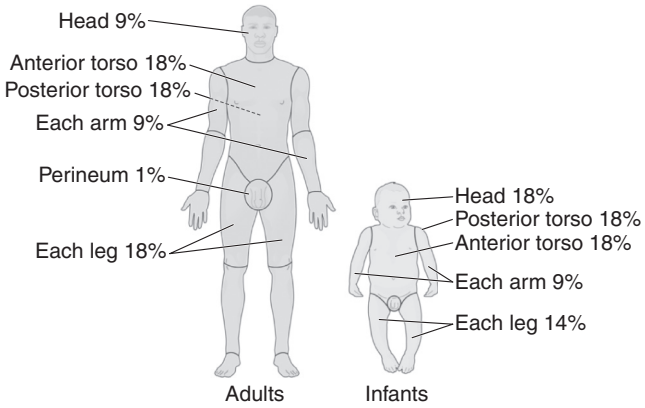

FIG. 1 The "rule of nines" for estimating second-degree and third-degree burns. Because infants have significantly larger heads and smaller legs than do adults, different rules must be used in evaluating these patients. A simple, practical rule is that the palm of the patient's hand, with fingers, equals 1% of the total body area. (From Ferri F: *Practical guide to the care of the medical patient,* ed 9, St Louis, 2014, Elsevier.)

MODERATE AND MAJOR BURNS (SECOND/THIRD-DEGREE BURNS OF EXTENSIVE TBSA):

- Patients with moderate/major burns (Fig. 1) should be admitted to the hospital or referred to a burn center. Indications for hospitalization for burns are described in Table 2. Burn care can be compartmentalized into four main phases: initial assessment and triage (phase I), resuscitation (phase II), burn wound coverage and critical care (phase III), and rehabilitation (phase IV) (Fig. 2).
  1. Assessment of ABCs: Establish airway and assess breathing (inspect for inhalation injury and intubate for suspected airway edema, often seen 12 to 24 hours later); O_2; establish circulation (place two large-bore peripheral IV lines, ECG).
  2. IV fluid resuscitation: Various fluid resuscitation formulas have been proposed and used to guide burn providers. These formulas each estimate the amount each patient may require during the course of a 24- to 48-hour postburn resuscitation period. The goal is to maintain optimal end-organ perfusion during this time with volume replacement at the lowest physiologic cost. Parkland formula (Ringer lactate at 2 to 4 ml/kg per % TBSA per 24 hours with half the calculated fluid given in the first 8 hours) is an effective modality in severe burns (Fig. 3) and has been commonly used. Once fluid resuscitation is initiated, the crystalloid rate should be titrated up or down on a regular basis while maintaining a urine output of around 0.5 to 1.0 ml/kg/h in adults. Various algorithms and clinical protocols have been proposed. One such algorithm is depicted in Fig. 4. The goal of burn resuscitation is to provide adequate fluid necessary to avoid end-organ failure while avoiding "fluid creep." Rescue therapy in the form of colloid infusion with albumin has been described as "colloid rescue." The military's Joint Trauma System Clinical Practice Guidelines recommend that 5%

TABLE 2 Classification of Burns by Severity and Indications for Hospitalization or Burn Center Referral

Criteria	Minor Burn	Moderate Burn	Major Burn
Total body surface area (%)	All 1st degree burns <10% adults <5% children or elderly <2% for 3rd degree	2nd degree burns 10%-20% adults 5%-10% in children or elderly 2%-5% 3rd degree	All 1st degree burns >20% adults >10% children and elderly >5% 3rd degree
Type of burn injury		Low-voltage burn Suspected inhalation injury	High-voltage burn Chemical burn Known
Location		Circumferential burn	Clinically significant burn to face, eyes, ears, genitalia, over joints
Coexisting conditions		Concomitant medical problem predisposing to infection (e.g., diabetes, sickle cell anemia)	Significant associated injuries (e.g., fracture, other major trauma)
	Outpatient management	Inpatient management—consider referral to burn center*	Referral to burn center

*Per the American Burn Association (ABA), any partial-thickness burn >10% total body surface area or any factors listed in moderate or major burn category warrant referral to burn center. Additional factors per the ABA include burned children in a hospital without qualified personnel or equipment for the care of children and burn injury in a patient who will require special social, emotional, or rehabilitative intervention (including suspected child abuse).

Modified from Singer AJ, Dagum AB: Current management of acute cutaneous wounds, *N Engl J Med* 359 (10):1037-1046, 2008.

albumin should be initiated as early as 8 hours after a burn if certain conditions are met. These conditions include that the hourly IV fluid rate exceeds 1500 ml/h or the projected 24-hour total fluid volume approaches 250 ml/kg.

3. Baseline neurologic and vascular assessment.
4. Foley catheter and NG tube (20% of patients develop an ileus): Urine output 30 ml/h.
5. Optimize nutritional support: Mayes equations to calculate energy requirements after burn (Box 1).

- Frequent reassessment in the first 24 to 72 hours, as wound depth can change significantly.

Phase I

Initial Assessment and Triage

- Stop the burning process. Remove patient and providers from harm.
- **Primary Survey**
  - **Airway**—Assess for ability to maintain patent
  - **Breathing**—Evaluate for inhalation injury/carbon monoxide
  - **Circulation**—Evaluate adequacy of perfusion
- **Begin Resuscitation**
  - Secure intravenous or intraosseous access and begin judicious fluids (lactated Ringer)
- **Secondary Survey**
  - Evaluate for other traumatic injuries
  - Use Rule of 9's for TBSA estimate, and Rule of 10's to calculate initial fluid rate

Phase II

Fluid Resuscitation: 0–48 h

- Titrate IV rate hourly based on a compilation of various endpoints centered on urine output
  - Urine output goal—30–50 mL/h (or approximately 0.5 mL/kg per hour)
  - Use other endpoints to guide resuscitation (lactate, base deficit, $ScvO_2$, CVP, MAP, etc.)
- Albumin early for "runaway" resuscitation. Consider other adjuncts such as plasma, high-dose vitamin C, and plasmapheresis
- Serial evaluation for resuscitation morbidity
  - Abdominal compartment syndrome, extremity compartment syndrome, pulmonary edema, cerebral edema

Phase III

Burn Wound Coverage and Critical Care—Continue Until Definitive Coverage Has Been Attained

- Surgical debridement (if indicated) via burn wound excision and autografting (definitive coverage)
  - Temporary coverage with skin substitutes if inadequate availability of autograft
- Optimize conditions for wound healing—Optimize hemodynamics, organ support, nutrition support
- Prevent and treat infectious complications (wounds, blood, lung, bladder, etc.)
- Prevent hospital complications (DVT, stress ulcers, decubitus)

Phase IV

Rehabilitation/Resilience—Begin Early and Continue Through Discharge and Beyond

- Proper limb positioning to prevent contractures
- Aggressive rehabilitation—Active range of motion, exercise
- Anabolic agents (propranolol, oxandrolone)
- Psychosocial support

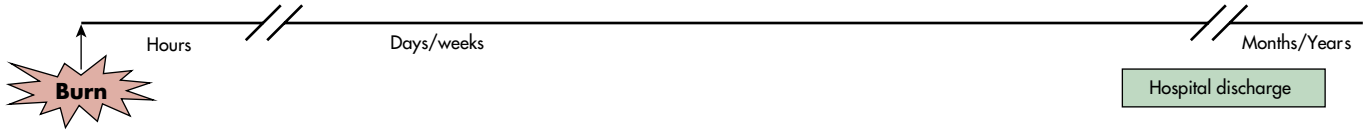

FIG. 2 The four major phases of burn care. Initial assessment and triage (phase I), resuscitation (phase II), burn wound coverage and critical care (phase III), and rehabilitation (phase IV). *CVP,* Central venous pressure; *DVT,* deep vein thromboses; *IV,* intravenous; *MAP,* mean arterial pressure; *Scv_{02},* central venous oxygen saturation; *TBSA,* total body surface area. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.)

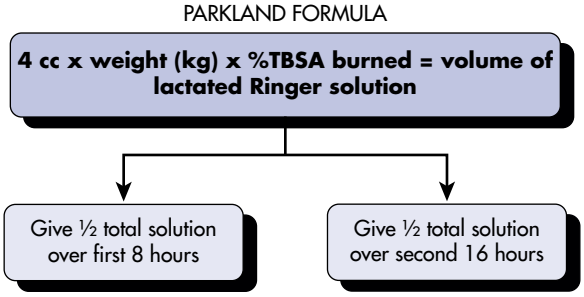

FIG. 3 Parkland formula. *TBSA,* Total body surface area. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

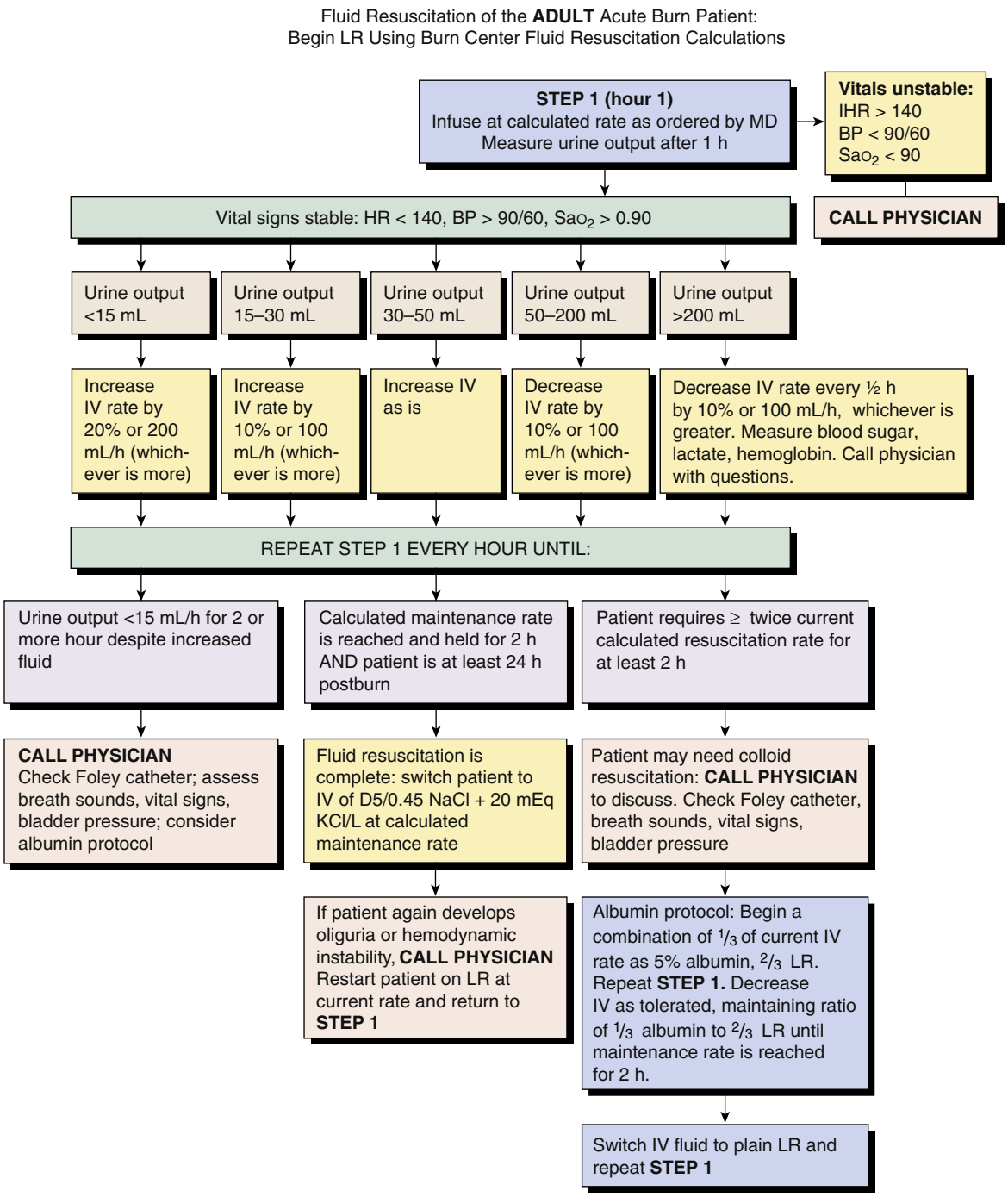

FIG. 4 Burn fluid resuscitation protocol used at the University of Utah. Physicians order an initial infusion rate of lactated Ringer solution based on Parkland formula calculations and indicate the target maintenance rate. The nursing staff measures hourly urine output and increases or decreases fluids based on this response. If patients experience unexpected changes in vital signs or do not respond appropriately, physicians are contacted. An option for the use of colloid-containing resuscitation is included for patients whose requirements fail to decline. This regimen permits close titration of fluids without requiring hourly physician input. *BP,* Blood pressure; *D5/0.45,* glucose 5.0% and sodium chloride 0.45%; *HR,* heart rate; *IHR,* intrinsic heart rate; *IV,* intravenous; *LR,* lactated Ringer solution; *MD,* physician; *Sao_2,* oxygen saturation. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

BOX 1 Mayes Equations to Calculate Energy Requirement after a Burn

Mayes equation for a 5- to 10-yr-old burn patient with injury <50% TBSA:

$$818 + 37.4\ (\text{weight in kilograms}) + 9.3 \times \text{TBSA burn}$$

Mayes equation for a 5.5-yr-old patient with a 45% TBSA scald burn weighing 20 kg:

$$818 + 37.4\ (20\ \text{kg}) + 9.3 \times 45\ \text{TBSA scald}$$

$$818 + 748 + 481.5 = 2047.5\ \text{calories/day}$$

TBSA, Total body surface area.
From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, WB Saunders.

BURN WOUND CARE BY BURN DEPTH Rx

GENERAL:

- Vigilant wound care with dressings to prevent evaporation and minimize threat of wound colonization and infection of nonintact skin
- Daily activity necessary to maintain function of burned extremity, decrease pain and swelling, and promote healing
- First-degree burns (skin intact):
  1. *Dressing:* None required (except to protect from injury); topical antibacterial agents NOT recommended
  2. *Other:* Emollients, cool compresses (avoid ice), if pruritic, trial of antihistamines
  3. *Prognosis:* Heals within 1 wk without scarring; may heal with pigmentary changes (limit by sunscreen and sun avoidance of area for 1 yr)
- Second-degree (superficial partial-thickness) burns without adherent exudate or eschar:
  1. *Blisters:* Sharp debridement of ruptured blisters; leave intact blisters. Quicker healing and reduced infections when intact blisters are not disturbed. Consider unroofing blisters that show no sign of resorption over several wks or contain cloudy fluid.
  2. *Dressing:* Topical antimicrobial ointment (e.g., Bactroban) or A&D ointment with nonadherent dressing twice a day. Alternate: Biosynthetic dressing (alginates, hydrofibers, or foam dressings)—many with silver as antimicrobial (absorb exudates, maintain moist environment, require fewer dressing changes, which reduces pain/anxiety).
  3. *Prognosis:* Heals with minimal scarring in 10 to 14 days. May heal with pigmentary changes (reduced with sunscreen and sun avoidance of area × 1 yr).
- Second-degree (deep partial-thickness) burns with adherent exudates; localized third-degree burns; cellulitic wounds:
  1. *Dressing:* Silver sulfadiazine 1%: Broader spectrum, better penetration of necrotic tissue than Bactroban, but inhibits epithelialization and promotes hypertrophic scarring in studies. Must stop use once exudates and eschar have separated from wound. Alternative: Enzymatic debrider (e.g., Santyl or Accuzyme)—chemically debrides devitalized tissue without harming healthy tissue.
  2. *Referral:* Burn specialist for consultation regarding need for excision and grafting.
  3. *Prognosis:* Deep second-degree burns heal with significant scarring, often take 3 to 4 wk to heal. If infected, convert to third-degree burns. Third-degree burns typically require skin graft, but small areas may heal from edges after wks.

DISPOSITION/FOLLOW-UP CARE

- Outpatient: Evaluate next day to assess level of injury, level of pain, and ability to manage dressing changes on own. If insufficient, daily evaluation until complete wound epithelialization recommended. Epithelialization: Tiny islands of epithelialization throughout wound. If no epithelialization after 2 wk, or subsequent evaluation reveals third-degree burn, referral to burn surgeon recommended. Box E2 describes common complications in burn patients.
- Following re-epithelialization, visits every 4 to 6 wk to monitor for hypertrophic scar formation (early referral to burn/scar specialist if occurs).
- Mortality rates higher in patients >60 yr of age, with burns >40% TBSA, or with inhalation injury. Long-term risk of developing squamous cell carcinoma of the skin within burn injury. Long-term skin monitoring necessary.

REFERRAL

Consultation of burn specialist or burn center referral per Table 2.

PEARLS & CONSIDERATIONS

COMMENTS

- In circumferential skin burns, look for compartment syndrome of limbs (e.g., tightening, progressive deterioration of peripheral motor and sensory exam findings, severe pain, and loss of arterial Doppler signals). Escharotomy may be necessary.
- If child abuse is suspected, social services at the hospital or child protective services must be contacted.
- Fig. E5 describes an algorithm for the treatment of chemical burns.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Burns (Patient Information)
Electrical and Lightning Injury (Related Key Topic)

AUTHOR: **Lisa Pappas-Taffer, MD**

SUGGESTED READINGS

Kessides MC, Skelsey MK: Management of acute partial-thickness burns, *Cutis* 86:249-257, 2010.

Moss L: Treatment of the burn patient in primary care, *Adv Skin Wound Care* 23(11):517-524, 2010.

BOX E2 Common Complications in Burn Patients

Cardiovascular

- Endocarditis and suppurative thrombophlebitis are intravascular infections that typically present as fever and bacteremia without signs of local infection.
- Hypertension occurs in up to 20% of children and is best managed with β-adrenergic blockers.
- Venous thromboembolic complications are so infrequent in patients with large burns that routine prophylaxis is not routine in all programs. Iatrogenic catheter insertion complications are minimized by meticulous technique.

Pulmonary

- Carbon monoxide intoxication, best managed acutely with effective ventilation with pure oxygen, can be associated with delayed neurologic sequelae.
- Pneumonia may occur with or without antecedent inhalation injury and is treated with pulmonary toilet and antibiotics.
- Respiratory failure may occur early postinjury secondary to inhalation of noxious chemicals or later in the course (secondary to sepsis or pneumonia).

Neurologic

- Transient delirium occurs in up to 30% of patients and generally resolves with supportive therapy when the possibility of anoxia, metabolic disturbance, and structural lesions is eliminated by appropriate studies.
- Seizures most commonly result from hyponatremia or abrupt benzodiazepine withdrawal.
- Peripheral nerve injuries occur from direct thermal injury, compression from compartment syndrome or overlying inelastic eschar, major metabolic disturbances, or improper splinting techniques.
- Delayed peripheral nerve and spinal cord deficits develop wks or mos after high-voltage injury secondary to small vessel injury and demyelinization.

Hematologic

- Neutropenia and thrombocytopenia, as well as disseminated intravascular coagulation, are common indicators of impending sepsis and should prompt appropriate investigations.
- Global immunologic deficits associated with burn injury contribute to a high rate of infectious complications.

Renal

- Early acute renal failure follows inadequate perfusion during resuscitation or myoglobinuria.
- Late renal failure complicates sepsis and multi-organ failure or the use of nephrotoxic agents.

Adrenal

- Acute adrenal insufficiency secondary to hemorrhage into the gland presents as hypotension, fever, hyponatremia, and hyperkalemia.

Otolaryngologic

- Auricular chondritis secondary to bacterial invasion of cartilage results in rapid loss of viable tissue and is prevented by routine use of topical mafenide acetate on burned ears.
- Sinusitis and otitis media can be caused by transnasal instrumentation and are treated by relocation of tubes, antibiotics, and judicious surgical drainage.
- Complications of endotracheal intubation include nasal alar and septal necrosis, vocal cord erosions and ulcerations, tracheal stenosis, and tracheoesophageal and tracheoinnominate artery fistulas. The occurrence of such complications is minimized by compulsive attention to tube position, avoidance of oversized tubes, and attention to cuff pressures.

Gastrointestinal

- Hepatic dysfunction secondary to transient hepatic blood flow deficits and manifested as transaminase elevations is common during resuscitation from large burns and resolves with volume restitution. Late hepatic failure, beginning with elevations of cholestatic chemistries and progressing through coagulopathy and frank failure, complicates sepsis and multiorgan failure.
- Pancreatitis, beginning with amylase and lipase elevations and ileus and progressing through hemorrhagic pancreatitis, is generally coincident with splanchnic flow deficits early and sepsis-induced organ failures later in the hospital course.
- Acalculous cholecystitis can present as sepsis without localized symptoms or signs accompanied by rising cholestatic chemistries. A standard radiographic evaluation can be followed by bedside percutaneous cholecystostomy in unstable patients.
- Gastroduodenal ulceration secondary to splanchnic flow deficits that degrade mucosal defenses is extremely common and often life threatening if routine histamine-receptor blockers and antacids are not administered.
- Intestinal ischemia, which can progress to infarction, is secondary to inadequate resuscitation and splanchnic flow deficits.

Ophthalmologic

- Ectropia from progressive contraction of burned ocular adnexa results in exposure of the globe. This requires acute eyelid release. Tarsorrhaphy is rarely helpful, more often resulting in injury to the tarsal plate as contraction forces pull out tarsorrhaphy sutures.
- Corneal ulceration, which develops after initial epithelial injury or later exposure due to ectropion, can progress to full-thickness corneal destruction if secondary infection occurs. This is prevented by careful globe lubrication with topical antibiotics in the former case and acute lid release in the later.
- Symblepharon, or scarring of the lid to the denuded conjunctiva after chemical burns or corneal epithelial defects complicating toxic epidermal necrolysis, is prevented by daily examination and adhesion disruption with a fine glass rod.

Genitourinary

- Urinary tract infections are minimized by maintaining bladder catheters only when absolutely required and are treated with appropriate antibiotics. Neither catheterization nor colonic diversion is usually required for management of perineal and genital burns.
- Candida cystitis occurs in those patients treated with bladder catheters and broad-spectrum antibiotics. Catheter change and amphotericin irrigation for 5 days is generally successful. If infections are recurrent, the upper tracts should be screened ultrasonographically.

Musculoskeletal

- Burned-exposed bone is generally debrided with a dental drill until viable cortical bone is reached, which is then allowed to granulate and is autografted. Patients whose overall condition and wounds are appropriate are managed with local or distant flaps.
- Fractured and burned extremities are best immobilized with external fixators while overlying burns are grafted. Burn patients with coincident fractures in unburned extremities benefit from prompt internal fixation.
- Heterotopic ossification develops wks after injury, is seen most commonly around deeply burned major joints such as

BOX E2 Common Complications in Burn Patients—cont'd

the triceps tendon, and presents as pain and decreased range of motion. Most patients respond to physical therapy, but some require excision of heterotopic bone to achieve full function.

Soft Tissue

- Hypertrophic scar formation is a major cause of long-term functional and cosmetic deformities seen in burn patients. This poorly understood process is heralded by a secondary increase in neovascularity between 9 and 13 wk after epithelialization. Management options include grafting of deep dermal and full-thickness wounds, compression garments, judicious steroid injections, topical silicone products, and scar release and resurfacing procedures. NOTE: Systematic reassessment of seriously ill burn patients facilitates timely detection of complications. It is the very rare burn patient who does not experience complications during their care, particularly while in the intensive care unit. Unfortunately, many common burn complications are obscured by the fevers and hyperdynamic physiology that accompany a large burn.

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.

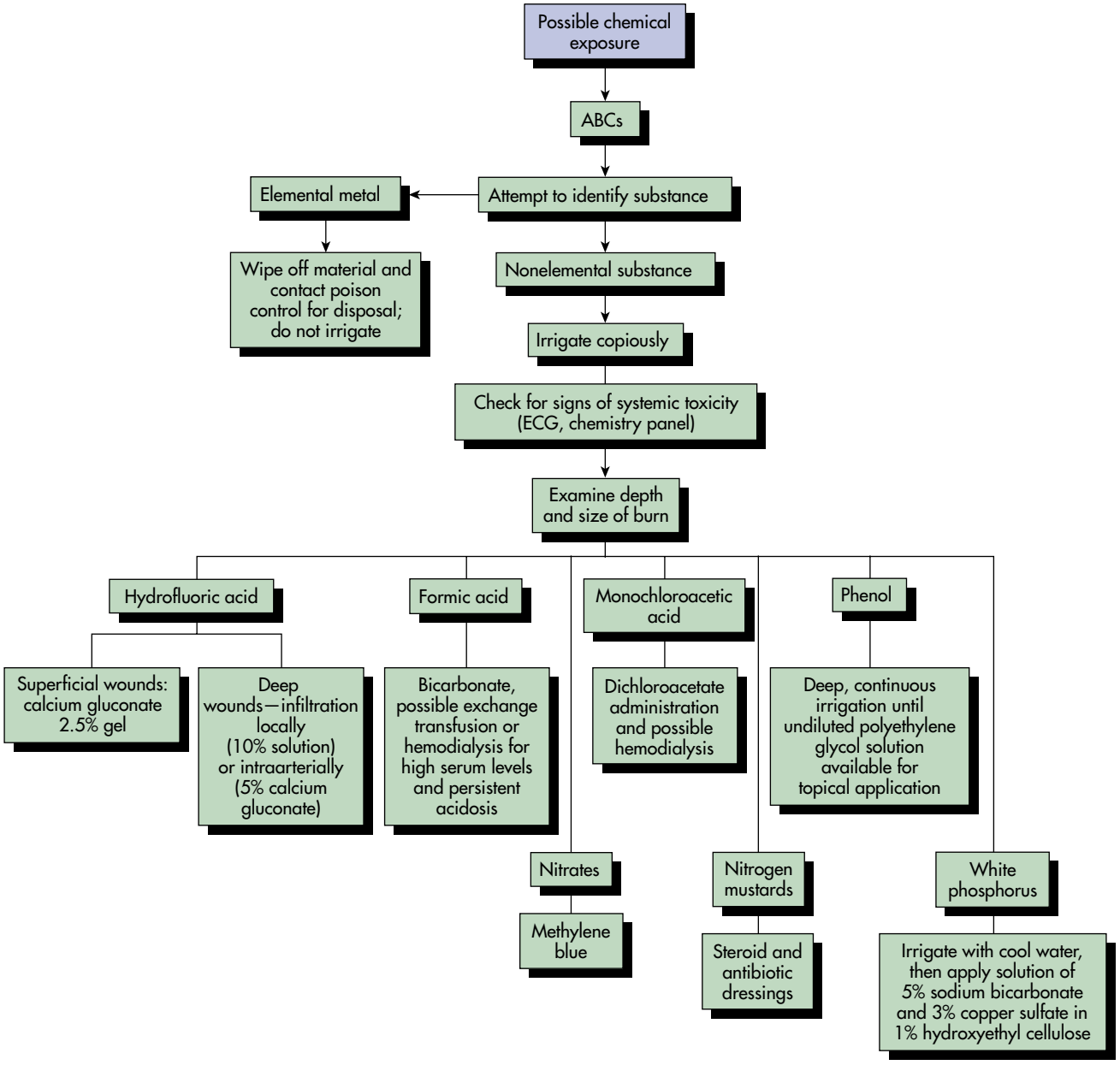

FIG. E5 Algorithm for the treatment of chemical burns. *ABC,* Airway, breathing, circulation; *ECG,* electrocardiogram. (From Adams JG et al: *Emergency medicine: clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

BASIC INFORMATION

DEFINITION

Bursitis is an inflammation of a bursa, which is a thin-walled, synovial-lined sac. A bursa functions as a cushion to reduce friction while also facilitating movement of tendons and muscles over bony prominences. Olecranon bursitis and prepatellar bursitis are the most common, usually due to chronic microtrauma from repetitive pressure or activity.

SYNONYMS

Student elbow, miner elbow, draftsman elbow (olecranon bursitis)
Housemaid knee, carpet-layer knee (prepatellar bursitis)
Weaver bottom (ischial gluteal bursitis)
Baker cyst (gastrocnemius-semimembranosus bursa)
Pump bumps (subcutaneous calcaneal bursitis)
Pes anserine bursitis (goose foot, insertion of conjoined tendon into medial knee)

ICD-10CM CODES

M70.20	Other shoulder lesions, unspecified shoulder
M70.40	Olecranon bursitis, unspecified elbow
M70.60	Trochanteric bursitis, unspecified hip
M70.70	Other bursitis of hip, unspecified hip
M71.20	Other specified enthesopathies of unspecified lower limb, excluding foot
M75.80	Prepatellar bursitis, unspecified knee
M76.899	Synovial cyst of popliteal space [Baker], unspecified knee
M77.50	Other enthesopathy of unspecified foot

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Local swelling, tenderness, erythema, warmth over the site of bursa is common with prepatellar and olecranon bursitis.
- Subacromial bursitis may present with chronic shoulder pain, worse with overhead and repetitive activities, without weakness or stiffness.
- Range of motion may be markedly limited in septic arthritis, whereas ROM is relatively preserved in nonseptic bursitis.
- Subacromial/subdeltoid bursitis and trochanteric bursitis may also be found in polymyalgia rheumatica (PMR), thus can present with symptoms of PMR.

ETIOLOGY

- Acute traumatic
- Chronic microtrauma from repetitive activity or pressure
- Infection (septic bursitis)—spread from contiguous skin or soft tissue infection (*Staphylococcus aureus* causative in >80%)
- Crystal diseases (e.g., gout, pseudogout)
- Systemic inflammatory arthritis, particularly rheumatoid arthritis
- Bleeding (from diathesis, anticoagulation, or trauma)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute monoarthritis caused by septic arthritis or crystal arthritis (gout, pseudogout)
- Tendinitis, tenosynovitis
- Cellulitis

WORKUP

Bursal fluid aspiration: Send for Gram stain, culture and sensitivity, cell count, and crystal analysis

IMAGING STUDIES

- Plain radiography can rule out foreign body penetration and other bone or joint problems such as fracture (Fig. E1)
- MRI to define soft tissue involvement
- Musculoskeletal ultrasound to visualize superficial and deep bursae; assess inflammatory activity with Doppler and directly guide aspiration/injection

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid direct pressure or repetitive irritation
- Joint protection (e.g., kneeling pads, compression wraps)
- Rest, ice, elevation for acute phase
- Physical therapy
- Activity modification

ACUTE GENERAL Rx

- Septic:
  1. Appropriate antibiotic coverage and drainage. If MSSA, use nafcillin or oxacillin 2 g IV q4h or dicloxacillin 500 mg PO qid. If MRSA, use vancomycin 15 to 20 mg/kg IV q8-12h or linezolid 600 mg PO bid
  2. Serial aspirations of purulent fluid or surgical drainage may be indicated
- Nonseptic:
  1. Aspiration of bursal fluid or blood from acute trauma
  2. Nonpharmacologic therapy
  3. Traumatic bursitis may respond well to aspiration and corticosteroid injection
  4. Inflammatory arthritis such as gout or RA: Treat underlying condition with specific therapies and with systemic antiinflammatory medications for active disease; can consider intrabursal injection of steroids

CHRONIC Rx

- Aspiration and drainage of fluid can provide symptomatic improvement if large fluid collection, followed by compression dressing to prevent fluid reaccumulation
- Steroid injection into nonseptic bursa if inflammatory, recurrent, or persistently symptomatic (40 mg triamcinolone mixed with 1 to 3 ml lidocaine, depending on size of bursa)
- Oral NSAIDs, over-the-counter analgesics
- Patients in whom conservative therapy fails to resolve symptoms of chronic inflammatory may be considered for surgical bursectomy

DISPOSITION

- Conservative nonsurgical treatment is effective in most cases. Surgical drainage may be indicated for loculated bursitis or if septic. Recurrent bursitis affecting function may require surgical bursectomy.

REFERRAL

Orthopedic consultation may be needed as part of treatment of septic bursitis, or for persistent or recurrent bursitis that interferes with daily function.

PEARLS & CONSIDERATIONS

Bursae in patients with RA are not usually the sole site of active flare. Therefore, in patients with RA, acute bursitis should be considered septic bursitis until proven otherwise.

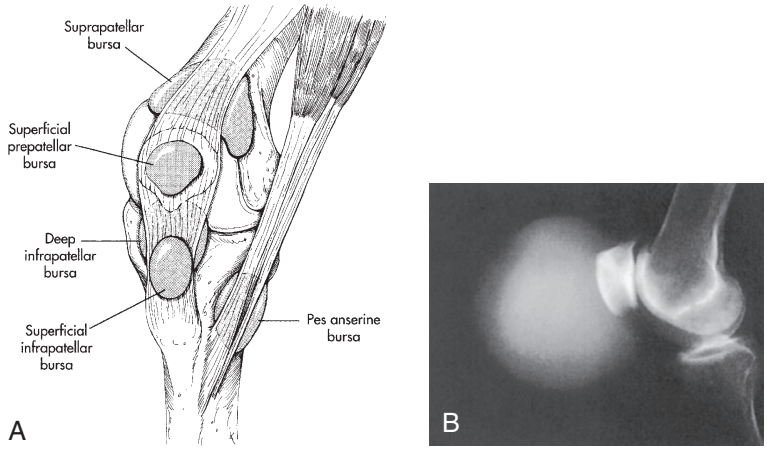

FIG. E1 A, Bursae around the knee. **B,** Markedly swollen prepatellar bursa. (From Scudieri G [ed]: *Sports medicine principles of primary care,* St Louis, 1997, Mosby.)

COMMENTS

- Scapulothoracic bursitis is underrecognized and undertreated. It results from friction between superomedial angle of scapula and adjacent second and third ribs. Crepitus, snapping, and tenderness are suggestive findings; it can also cause chest wall pain.
- Do not incise and drain sterile bursae because chronic draining sinus tract may develop and risk iatrogenic septic bursitis.
- In bursitis caused by infectious or systemic inflammatory disorders, the leukocytosis in bursal fluid may be substantially less intense than the elevations in the joint fluid.
- Investigate crystal-induced bursitis for underlying metabolic or hematologic diseases (hemochromatosis, hyperparathyroidism [calcium pyrophosphate deposition disease]), and for hyperuricemia (gout).

SUGGESTED READINGS

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RELATED CONTENT

Bursitis (Patient Information)

AUTHORS: **Shashank Dwivedi, MD,** and **Manuel F. DaSilva, MD**

BASIC INFORMATION

DEFINITION

Calcium pyrophosphate dihydrate crystal deposition (CPPD) disease refers to the precipitation of calcium pyrophosphate dihydrate (CPP) in connective tissues that may be asymptomatic or may be associated with several clinical syndromes, including acute and chronic arthritis. CPP was formerly abbreviated and commonly referred to as "CPPD," but the abbreviation is now reserved for "CPP deposition." Alternative names (Table 1) representing specific clinical or radiographic features of CPPD disease include pseudogout, chondrocalcinosis, and pyrophosphate arthropathy.

Pseudogout/acute CPP crystal arthritis is used to describe acute attacks of CPP crystal-induced arthritis that clinically resembles the arthritis that is commonly encountered in gout. The term *acute CPP crystal arthritis* is now preferred in place of *pseudogout*.

Chondrocalcinosis (CC) refers to radiographic calcification in hyaline cartilage and/or fibrocartilage and does not confirm the diagnosis of CPP-related arthritis as it can be present in other types of crystal deposition diseases or be asymptomatic.

Pyrophosphate arthropathy is the term used for a chronic structural arthropathy related to CPP deposition.

SYNONYMS

Calcium pyrophosphate dihydrate crystal deposition disease
CPP crystal deposition disease
CPPD
Chondrocalcinosis (CC)
Pseudogout
Pyrophosphate arthropathy

ICD-10CM CODES

M11.2	Other chondrocalcinosis
M11.9	Crystal arthropathy, unspecified
M11.8	Other specified crystal arthropathies
M11.1	Familial chondrocalcinosis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- The epidemiology of CPPD crystal deposition is described in Table 2.
- Most linked with advancing age (average age of 72).

GENETICS: Familial forms

- Associated with *ANKH* (ankylosis human) gene, which functions to transport inorganic pyrophosphate (PPi) out of cells, or the osteoprotegerin gene (TNFRSF11B).
- Familial mutations can increase extracellular PPi levels and lead to onset of CPPD disease in the third or fourth decade of life.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- *Acute* CPP *crystal arthritis/pseudogout:* Monoarticular attacks most commonly involve the knee and wrist but can be polyarticular (Fig. E1). Patients, especially the elderly, can have systemic manifestations such as fever and altered mental status. Situations that may trigger acute CPPD crystal arthritis are described in Box E1
- Asymptomatic disease ("asymptomatic CPPD")
- Pseudogout (acute CPP crystal arthritis)
- Pseudo-RA (chronic CPP crystal inflammatory arthritis): Symmetric polyarthritis
- Pseudo-OA, with or without superimposed acute attacks (OA with CPPD)
- Pseudo-neuropathic joint disease
- Crowned-dens syndrome caused by crystal deposition in the ligamentum flavum of the cervical spine, either asymptomatic or causing acute neck pain
- Pseudo-polymyalgia rheumatica (pseudo-PMR): Pain and stiffness in the neck and shoulder girdle mimicking PMR

ETIOLOGY

- Idiopathic
- Familial
- Trauma
- Metabolic and endocrine disorders (Table 3): Hyperparathyroidism, hypophosphatasia, hemochromatosis, hypomagnesemia, Gitelman syndrome, Bartter syndrome, gout, ochronosis, acromegaly, Wilson disease, familial hypocalciuric hypercalcemia, X-linked hypophosphatemic rickets

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gouty arthritis (Table 4)
- Septic arthritis
- RA
- Spondyloarthritis (ReA, PsA)
- PMR

Table 5 describes metabolic diseases predisposing to CPPD disposition. Section II describes the differential diagnosis of acute monoarticular and oligoarticular arthritis and crystal-induced arthritides. An algorithm for evaluation and treatment of CPPD is shown in Fig. 2.

LABORATORY TESTS

- Arthrocentesis with presence of weakly positive birefringent rhomboid-shaped crystals by compensated polarized light microscopy (Fig. E3).
- Synovial fluid should always be analyzed for cell count with differential, crystals, Gram stain, and culture because acute CPP crystal arthritis/pseudogout and septic arthritis can co-exist.
- Evaluate for possible metabolic causes, especially in younger patients aged <55 yr or patients with florid polyarticular disease. Box 2 describes screening blood tests for metabolic diseases associated with CPPD crystal deposition.

IMAGING STUDIES

- Plain radiographs (Figs. E4, E5, and E6) often reveal CC located parallel to subchondral bone.
  1. Classic locations for CC (Fig. E1) include knee menisci (Fig. E7), wrist triangular fibrocartilage, symphysis pubis, and glenoid and acetabular labra.
- Musculoskeletal ultrasound can detect deposition of CPP crystals within the hyaline

TABLE 1 Nomenclature of Calcium Pyrophosphate and Associated Syndromes

Definition	Old Terms	EULAR Recommendations	Preferred Term (Abbreviation)
Radiographic correlate of CPPD	Chondrocalcinosis, chondrocalcinosis articularis	Chondrocalcinosis	Chondrocalcinosis (CC)
Acute inflammatory arthritis caused by CPP crystals	Pseudogout	Acute CPP crystal arthritis	Acute CPP crystal arthritis
Calcium pyrophosphate dihydrate crystals	Calcium pyrophosphate dehydrate; calcium pyrophosphate dihydrate	Calcium pyrophosphate crystals	Calcium pyrophosphate crystals (CPP crystals)
All clinical syndromes associated with CPP crystals	Calcium pyrophosphate dehydrate deposition disease	None	Calcium pyrophosphate deposition disease (CPPD)
Chronic arthritis caused by CPP crystals ± inflammation	Calcium pyrophosphate dihydrate deposition disease: Pyrophosphate arthropathy; pseudorheumatoid arthritis; pseudoosteoarthritis	Chronic CPP crystal arthritis, OA with CPPD	Chronic CPP crystal arthritis, OA with CPPD
Deposition of calcium pyrophosphate crystals in joints or tissue with or without clinical symptoms	Calcium pyrophosphate dihydrate deposition	CPPD	Calcium pyrophosphate deposition (CPPD)

CPP, Calcium pyrophosphate; *CPPD,* calcium pyrophosphate dihydrate crystal deposition disease; *EULAR,* European League Against Rheumatism; *OA,* osteoarthritis.
From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

TABLE 2 Epidemiology of Calcium Pyrophosphate Dihydrate Crystal Deposition

Age Association	Rises with Age
Sex distribution	(F:M) 1:1
Chondrocalcinosis prevalence	8.1% (age range 63 to 93)
Pyrophosphate arthropathy prevalence	3.4% (age range 40 to 89)
Geography	Appears ubiquitous
Genetic associations	Mutations of *ANKH* gene on chromosome 5p (CCAL2) and unknown genes on chromosome 8q (CCAL1)

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

cartilage and/or fibrocartilage. In contrast to urate crystal deposits in gout, CPP crystals often deposit within the substance of the hyaline cartilage and fibrocartilage, providing a means to distinguish CPP from urate deposition that occurs on the surface of the hyaline cartilage as seen in gout (Fig. E8).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

General measures such as immobilization of inflamed joint

ACUTE GENERAL Rx

- Monoarticular pseudogout:
  1. Aspiration followed by intraarticular corticosteroid injection (often superior to systemic treatment in the elderly)
- Polyarticular pseudogout:
  1. Oral corticosteroids, colchicine, or NSAIDs, if not contraindicated

CHRONIC GENERAL Rx

Prophylaxis: Daily low-dose colchicine 0.6 mg twice daily or once daily as tolerated

- Pseudo-RA or refractory disease: Hydroxychloroquine or methotrexate
- Anakinra (Interleukin-1 receptor antagonist): Treatment and prophylaxis of polyarticular acute CPP crystal arthritis unresponsive to oral corticosteroids
- Treat underlying metabolic disease
- Management options for CPPD are summarized in Boxes E3 and E4

DISPOSITION

Structural joint damage may occasionally occur, requiring arthroplasty in rare cases.

REFERRAL

Rheumatology

TABLE 3 Diseases Associated with Calcium Pyrophosphate Dihydrate Crystal Deposition Disease

Disease	Strength of Evidence for a Link with CPPD	Recommended Testing
Hyperparathyroidism	Strong	Calcium, parathyroid hormone level
Hemochromatosis	Strong	Fe, TIBC, ferritin, C282Y
Hypophosphatasia	Strong	Alkaline phosphatase
Hypomagnesemia	Strong	Magnesium
Gout	Strong	Synovianalysis
Rheumatoid arthritis	Moderate	Clinical judgement
Osteoporosis	Moderate	Bone density if warranted

CPPD, Calcium pyrophosphate dihydrate crystal deposition disease; *TIBC,* total iron-binding capacity.
From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

TABLE 4 Differences Between Acute Gouty Arthritis and Acute Calcium Pyrophosphate Crystal Arthritis

Symptom or Sign	Acute Gout	Acute CPP Crystal Arthritis
Pattern of joint involvement	First MCP joint, other lower extremity joints	Knee, wrist, ankle, spine
Response to colchicine	Excellent in early attack	Variable
Blood in joint fluid	Unusual	Not unusual
Duration of attack	7-10 days	Days to weeks

CPP, Calcium pyrophosphate dihydrate; *MCP,* metacarpophalangeal.
From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

TABLE 5 Metabolic Diseases Predisposing to Calcium Pyrophosphate Dihydrate Crystal Deposition

	CC	Pseudogout	Chronic PA
Hemochromatosis	Yes	Yes	Yes
Hyperparathyroidism	Yes	Yes	No
Hypophosphatasia	Yes	Yes	No
Hypomagnesemia	Yes	Yes	No
Gout	Possibly	Possibly	No
Acromegaly	Possibly	No	No
Ochronosis	Yes	Yes	No
Familial hypocalciuric hypercalcemia	Possibly	No	No
X-linked hypophosphatemic rickets	Possibly	Possibly	Possibly

CC, Chondrocalcinosis; *PA,* pyrophosphate arthropathy.

! PEARLS & CONSIDERATIONS

COMMENTS

Acute CPP crystal arthritis/pseudogout attacks have been reported to occur in the setting of surgical procedures, diuresis, bisphosphonate administration, and hyaluronate joint injections.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pseudogout (Patient Information)
Gout (Related Key Topic)

AUTHORS: **Nicole B. Yang, MD,** and **Anthony M. Reginato, PhD, MD**

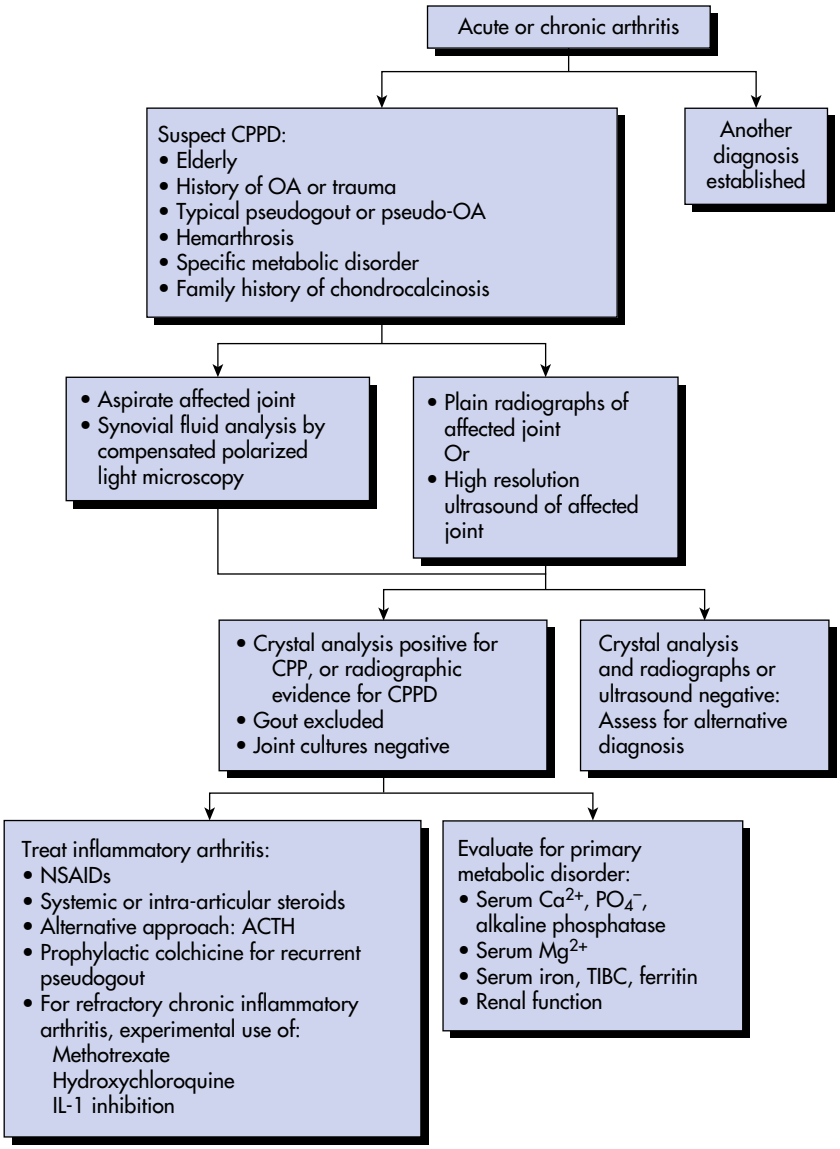

FIG. 2 Algorithm for evaluation and treatment of calcium pyrophosphate dihydrate disease. *ACTH,* Adrenocorticotropic hormone; *CPP,* calcium pyrophosphate dihydrate; *CPPD,* calcium pyrophosphate dihydrate crystal deposition; *IL,* interleukin; *NSAIDs,* nonsteroidal antiinflammatory drugs; *OA,* osteoarthritis; *TIBC,* total iron-binding capacity. (From Firestein GS et al: *Kelley and Firestein's textbook of rheumatology,* ed 10, Philadelphia, 2017, Elsevier.)

BOX 2 Screening Blood Tests for Metabolic Diseases Associated with Calcium Pyrophosphate Dihydrate Crystal Deposition

Calcium
Alkaline phosphatase
Magnesium
Ferritin, iron, transferrin
Liver function
Thyroid-stimulating hormone

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

SUGGESTED READINGS

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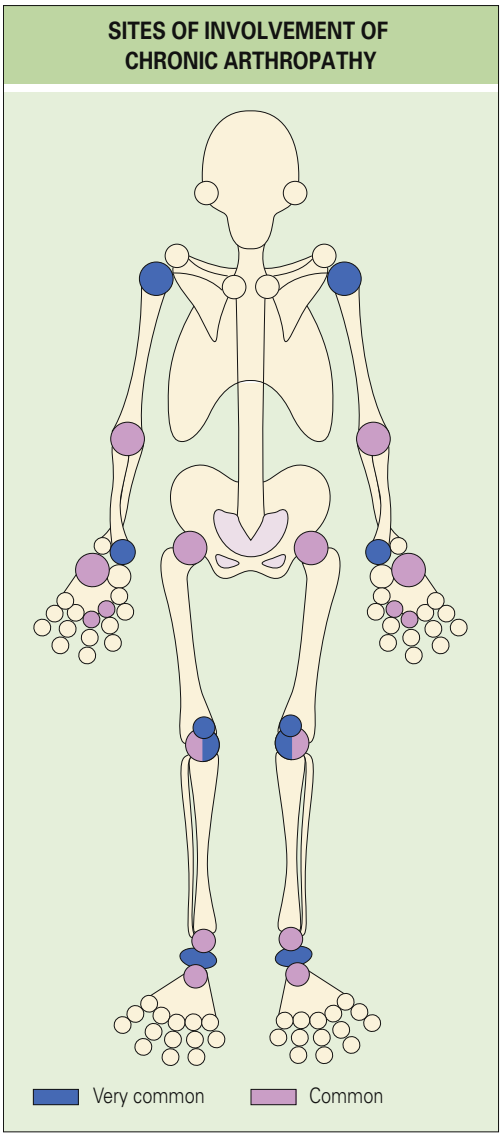

FIG. E1 Distribution of joint involvement with calcium pyrophosphate dihydrate crystal deposition (CPPD) disease. CPPD often involves joints not typically involved in osteoarthritis. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

BOX E1 Situations that May Trigger Acute Calcium Pyrophosphate Dihydrate Crystal Arthritis

Definite

Direct trauma to joint

Intercurrent medical illness (e.g., chest infection, myocardial infarction)

- Surgery (especially parathyroidectomy)
- Blood transfusion, parenteral fluid administration
- Joint lavage

Possible

Institution of thyroxin replacement therapy

- Intraarticular injection of hyaluronan
- Bisphosphonate treatment
- Note: Most cases of pseudogout develop spontaneously

From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.

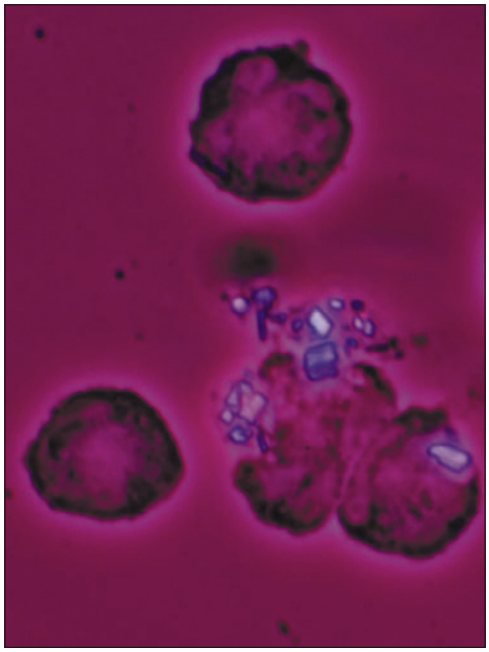

FIG. E3 Calcium pyrophosphate dihydrate (CPP) crystals. Typical CPP crystals as seen with compensated polarizing light microscopy (40×). (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier).

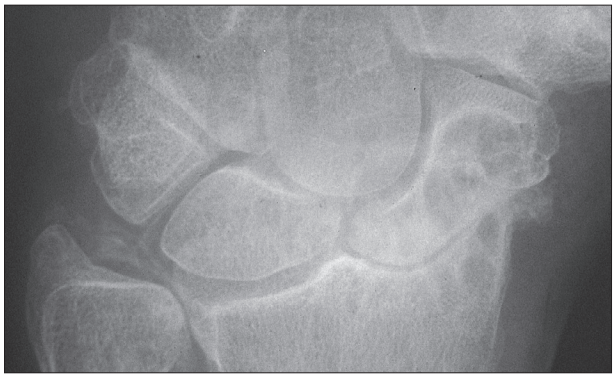

FIG. E4 Chondrocalcinosis in the wrist. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

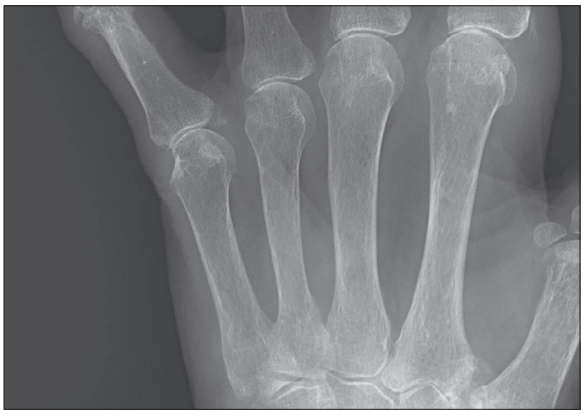

FIG. E5 Chondrocalcinosis around the finger joints in calcium pyrophosphate deposition disease. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

FIG. E6 Linear calcification in Achilles tendons in calcium pyrophosphate deposition disease. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

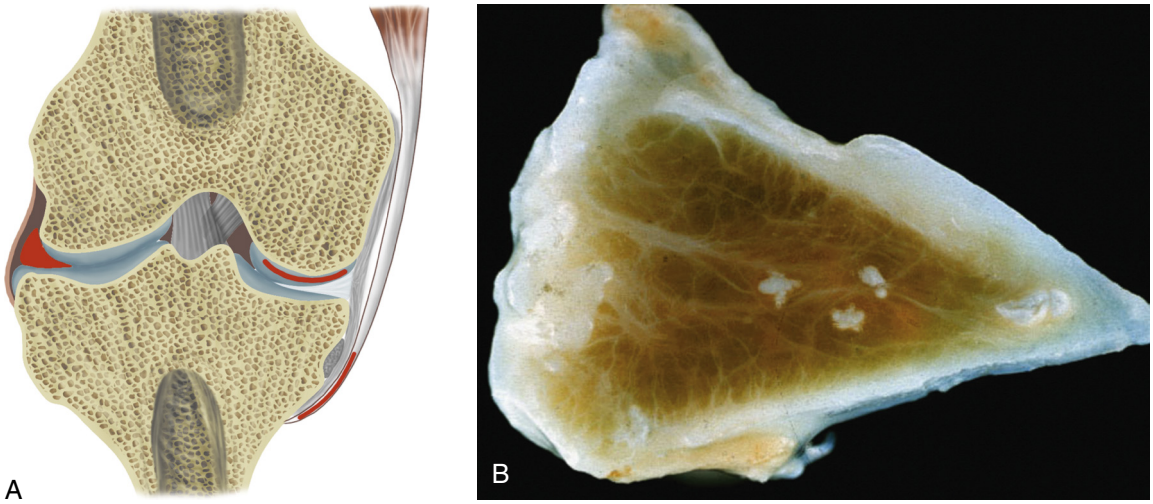

FIG. E7 A, Typical distribution of intraarticular deposition of calcium pyrophosphate. Shown are the meniscal, hyaline cartilage, and entheseal sites of deposition. **B,** A section through a meniscus confirms the linear superficial deposition as well as the deeper granular foci. (From Pope TL et al: *Musculoskeletal imaging*, ed 2, Philadelphia, 2014, WB Saunders.)

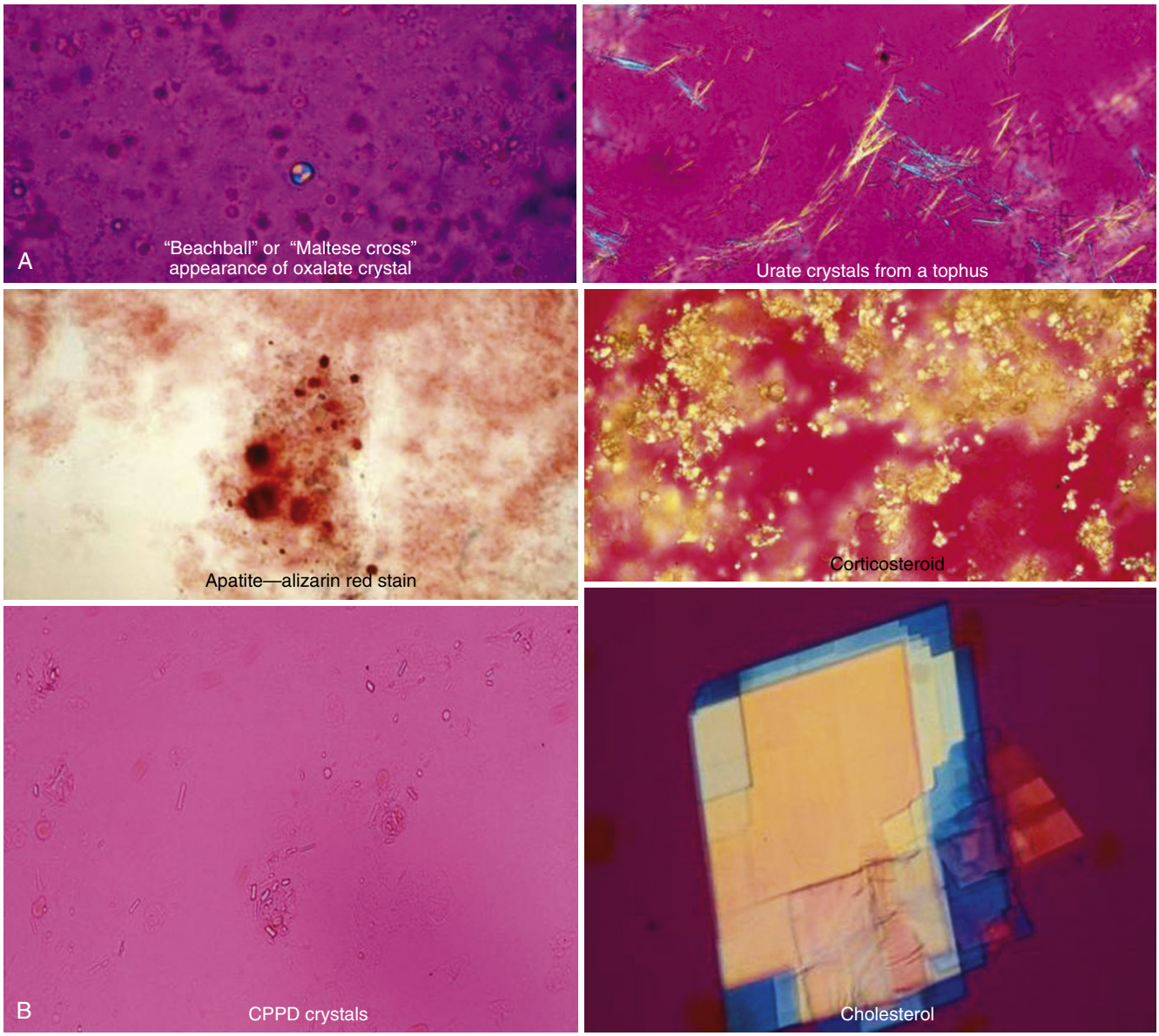

FIG. E8 Example of crystals as seen in the crystal laboratory. A, Typical oxalate *(left)* and urate *(right)* crystals. **B,** Examples of hydroxyapatite, cholesterol, intraarticular corticosteroid injection material, and calcium pyrophosphate. *CPPD*, Calcium pyrophosphate dihydrate crystal deposition. (From Pope TL et al: *Musculoskeletal imaging*, ed 2, Philadelphia, 2014, WB Saunders.)

BOX E3 Management Options for Chronic Calcium Pyrophosphate Crystal Arthritis with Inflammatory Symptoms

Colchicine
Low-dose prednisone (<10 mg/day)
Nonsteroidal antiinflammatory drugs
Hydroxychloroquine
Methotrexate
Interleukin-1β antagonists
Combinations of drugs listed above

From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

BOX E4 Management Options for Chronic Calcium Pyrophosphate Crystal Arthritis without Inflammatory Symptoms

Colchicine
Low-dose prednisone
Nonsteroidal antiinflammatory drugs
Pain medications
Combinations of drugs listed above

From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

BASIC INFORMATION

DEFINITION

Calcium-alkali syndrome is the triad of hypercalcemia, metabolic alkalosis, and renal insufficiency due to consumption of large amounts of calcium and absorbable alkali. For conventional diagnostic purposes, only hypercalcemia with an appropriate history of ingestions must be present.

SYNONYM

Milk-alkali syndrome

PRESENTATIONS

Calcium-alkali syndrome presents in one of three patterns:

1. Acute: This stage occurs after approximately 1 week of excessive calcium and alkali intake. Symptoms are attributable to hypercalcemia and may include nausea, vomiting, weakness, mental status depression, and confusion. Metabolic alkalosis is present with a normal or elevated serum phosphorus level. An elevated serum creatinine reflects acute kidney injury. Cessation of exogenous calcium and alkali leads to resolution of signs and symptoms.
2. Subacute or intermediate ***(Cope syndrome):*** Patients typically are encountered after milk and alkali have been ingested intermittently for yrs. Affected patients demonstrate symptoms of acute and chronic hypercalcemia and respond to medication withdrawal with gradual improvement. Kidney function is often mildly and chronically impaired.
3. Chronic form ***(Burnett disease):*** Symptoms of chronic hypercalcemia present after prolonged high calcium and alkali intake and include polyuria, polydipsia, myalgias, and pruritus. Physical evidence of metastatic calcification is detectable as nephrocalcinosis and band keratopathy. Laboratory findings are like those of the acute syndrome. Muscle aches and pruritus improve slowly as the plasma calcium concentration gradually improves. Minimal or no improvement in kidney function occurs due to irreversible damage.

ICD-10CM CODE
E83.52 Disorders of calcium metabolism

EPIDEMIOLOGY & DEMOGRAPHICS

In the early twentieth century, the calcium-alkali syndrome was associated with the Sippy antacid regimen for peptic ulcer disease that entailed ingestion of large amounts of calcium salts, particularly from milk and absorbable bicarbonate compounds. Kidney injury and alkalosis were followed by hypercalcemia. Following the developments of type 2 histamine receptor blockers and proton pump inhibitors, the syndrome virtually disappeared. However, since the 1980s, a resurgence of hypercalcemia associated with calcium-containing product use for osteoporosis prevention occurred. In chronic kidney disease patients, calcium carbonate use as a phosphate binder instead of aluminum hydroxide produced the "calcium-alkali" syndrome. This updated term supplants "milk-alkali syndrome," as milk is no longer the source of calcium. The calcium-alkali syndrome was the third-most cause of hypercalcemia (12%) in hospitalized patients from 1990 to 1993, following hypercalcemia of malignancy and primary hyperparathyroidism.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Asymptomatic hypercalcemia:
  1. Less than half of all cases are incidental findings of hypercalcemia on random laboratory testing.
- Symptomatic hypercalcemia:
  1. Symptoms: Nausea, vomiting, anorexia, fatigue, vague abdominal pain, nephrolithiasis- and pancreatitis-related pain, constipation, myalgia, confusion, and psychosis. In chronic cases, polyuria and polydipsia may be reported.
  2. Physical examination and other testing: Mental status changes include anxiety, depression, and cognitive dysfunction; also shortened QT segment interval.

ETIOLOGY

Overconsumption of supplemental calcium of 3 to 20 g daily in association with volume depletion, renal impairment, or thiazide diuretic use is the most common etiology. The resulting hypercalcemia reduces glomerular filtration of calcium and induces salt-wasting reducing extracellular fluid volume that further lowers glomerular filtration and increases bicarbonate reabsorption with metabolic alkalosis. Vomiting or diuretic-induced volume depletion worsen hypercalcemia and alkalosis. The paradigm of demographics has shifted from young males with peptic ulcer disease in the nineteenth century to postmenopausal women, solid organ transplant recipients, bulimic patients, pregnant women, dialysis patients, and elderly individuals who experience greater bone loss and are prone to developing hypercalcemia in the presence of excess calcium supplements. Betel nut chewing, a practice in Asia and the South Pacific, is associated with calcium-alkali syndrome. The nuts are bitter and coated with a compound that is converted to bicarbonate, fostering metabolic alkalosis.

PATHOGENESIS

Calcium alkali syndrome has a generation and maintenance phase. Generation phase of hypercalcemia is due to the increased calcium absorption, decreased renal excretion, and saturation of bone buffering of calcium. Maintenance phase is promoted by hypercalcemia-induced volume depletion from diuresis and natriuresis by activation of CaSR in the thick ascending loop of Henle, a decrease in GFR which decreases filtration of calcium, and an increase in renal absorption of calcium as a result of volume depletion and metabolic alkalosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Hypercalcemia from other causes includes primary hyperparathyroidism, certain malignancies, and granulomatous disorders including tuberculosis, sarcoidosis, and silicosis.

LABORATORY TESTS

- Elevated serum ionized calcium (wide variation reported)
- Elevated BUN and serum creatinine from acute kidney injury or chronic kidney disease
- Elevated serum bicarbonate and arterial pH from metabolic alkalosis
- Parathyroid hormone, usually suppressed by hypercalcemia in calcium-alkali syndrome, may be elevated, particularly if evaluated after treatment initiation
- Serum phosphorus level is variable (historically high with milk ingestion but low with calcium carbonate ingestion due to gut phosphate binding)
- Hypomagnesemia occasionally

TREATMENT

NONPHARMACOLOGIC THERAPY

Hemodialysis is indicated rarely for severe renal dysfunction or markedly symptomatic hypercalcemia.

ACUTE GENERAL Rx

- Discontinuation of all calcium and bicarbonate supplementation.
- Volume repletion by intravenous saline, followed by loop diuretic administration to increase urinary calcium excretion.
- Transient hypocalcemia can be seen when patients are treated with loop diuretic followed by rebound rise in PTH, which is something unique to calcium alkali syndrome as the hypercalcemic stimulus is suddenly removed.
- Bisphosphonates are avoided as they cause prolonged suppression of serum calcium in calcium alkali syndrome.
- Patient education to limit future calcium supplementation from over-the-counter calcium supplements (TUMS) and antacids containing calcium carbonate (Calcarb, CitraCal, Caltrate).

PROGNOSIS

Hypercalcemia and associated symptoms resolve with withdrawal of excess calcium supplementation and treatment of hypercalcemia. Acute cases typically resolve in 1 to 2 days while chronic cases take longer. Patients initially presenting with kidney failure may incur residual kidney damage.

DISPOSITION

Treatment is determined by degree of hypercalcemia and symptoms. Hospitalization is required for symptomatic patients or for patients whose

total serum calcium is >11.5 mg/dl and who may require IV volume repletion and other intensive treatments for hypercalcemia.

REFERRAL

- Endocrinology
- Nephrology

PEARLS & CONSIDERATIONS

COMMENTS

Detailed history of dietary supplements and over-the-counter medications (see Table E1) can provide important clues. Many patients do not list dietary supplements as a medication.

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TABLE E1 Potential Sources of Alkali

Alkali/Alkali Precursor	Source
Bicarbonate	Sodium bicarbonate: Pills, intravenous solutions Proprietary brands, e.g., Alka-Seltzer baking soda Potassium bicarbonate: Pills, oral solutions
Lactate	Lactated Ringer solution, peritoneal dialysis solutions
Acetate, glutamate, propionate	Parenteral nutrition
Citrate	Blood products, plasma exchange, potassium supplements, alkalinizing agents
Calcium compounds (alkalinizing effect minimal when given by mouth), acetate, citrate, and carbonate	Calcium supplements, phosphate binders

From Johnson RJ, Feehally J: *Comprehensive clinical nephrology*, ed 2, St Louis, 2000, Mosby.

BASIC INFORMATION

DEFINITION

Carcinoma of unknown primary (CUP) refers to a diverse group of malignancies for which the anatomic site of origin cannot be determined despite extensive investigations.

SYNONYMS

Cancer NOS
Cancer unspecified site
Malignancy unspecified site
CUP

ICD-10CM CODE
C80.1 Malignant (primary) neoplasm, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- CUP accounts for about 4% of all cancers, and the annual incidence in the United States is 7 to 12 cases per 100,000 persons.
- It is the seventh most frequent common cause of cancer and the fourth most common cause of cancer death. It predominantly occurs in adults and is more common in males.
- In the United States, an estimated 31,810 new cases are expected in 2018. CUP incidence rates have been decreasing since the early 1980s, 3.6 % per yr in the last two decades.
- Most cases of CUP are carcinomas, which are divided into adenocarcinomas (90%), squamous cell carcinomas (5%), and undifferentiated carcinomas (5%).
- Recent data suggest that the risk of CUP is substantially increased in heavy smokers and to a lesser degree increased in obese patients.
- There is a variable rate of mutations detected in CUP (18%-30%). The tumor suppressor gene *p-53* has overexpression rates (40% to 50%) or mutation rates (25% to 40%) that are comparable to that seen in other solid tumors. The evaluation of VEGF-A (vascular endothelial growth factor-A, angiogenesis factor) and matrix metalloproteinases (enzymes that degrade stroma) showed that these are universally expressed and active angiogenesis is present in CUP.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical findings can be variable and include generalized and organ-specific findings.
- General findings can include cachexia, pallor, edema, icterus, edema, skin rash, muscle wasting among others.
- Organ-specific findings are related to the dysfunction of the underlying organ(s) involved with CUP.
- The clinical course is often highlighted by a short presentation history, with symptoms and signs associated with metastatic sites, early dissemination, aggressive clinical course, and occasionally an unpredictable metastatic pattern.
- Multiple organs are involved at diagnosis in up to half of patients.
- The clinicopathologic subsets comprising CUP are shown in Table 1.

DIAGNOSIS

WORKUP

- Comprehensive medical history
- Complete physical examination with particular attention to skin, lymph node sites, organ enlargement, and testes; also rectal examination and pelvic examination (in women) (Table 2)
- Histopathology review of biopsy specimens

LABORATORY TESTS

- Complete blood count.
- Comprehensive chemistry panel.
- Urine analysis.
- Stool for occult blood.
- Tumor markers (in selected cases): Prostate-specific antigen (PSA), β-human chorionic gonadotrophin, α-fetoprotein.
- Adequate tissue biopsy with immunohistochemical (IHC) staining is done to guide broad diagnostic category assignments—carcinoma, melanoma, sarcoma, or lymphoma. Commonly used immunoperoxidase stains to assist in the differential diagnosis of carcinoma of unknown primary cancer are summarized in Table 3.
- Subtyping with IHC panels helps further classifying into adenocarcinoma, squamous carcinoma, germ cell tumor, neuroendocrine, thyroid, hepatocellular, or renal origin.
- Stepwise approach for IHC-derived diagnosis of likely site of origin is depicted in Table 4.
- In up to 25% cases, a single site of origin can be narrowed down by IHC staining (e.g., TTF-1 positive and CK-1 positive lung cancer profile).
- Molecular diagnosis is carried out by commercially available multi-gene assays that utilize micro-array or polymerase chain reaction assays and can assist in finalizing diagnosis in up to 80% to 90% of cases in which initial IHC staining has been inconclusive.

IMAGING STUDIES

- CT scans of the chest, abdomen, and pelvis; also CT of the neck in case of neck lymphadenopathy
- For selected cases
  1. PET scan
  2. Mammography and/or breast MRI
  3. Testicular ultrasonography

TABLE 1 Clinicopathologic Subsets of Patients with CUP

	Median Age (Yrs)	Sex of Patients (M/F)	Histopathology
Lymph Nodes			
Mediastinal retroperitoneal	<50	70%/30%	UDF or PDF
Axillary	52	0%/100%	Adenocarcinoma (WDF, MDF, or PDF)
Cervical	57-60	80%/20%	SCC
Inguinal	58	50%/50%	UDF, SCC, mixed SCC and adenocarcinoma
Peritoneal Cavity			
Primary peritoneal in women	55-65	0%/100%	Adenocarcinoma (serous papillary)
Ascites of other unknown origin	–	–	Adenocarcinoma (MDF or PDF; mucin; with or without signet ring cells)
Neuroendocrine tumors	63	60%/40%	PDF with neuroendocrine features; low-grade neuroendocrine cancers; small-cell anaplastic cancers
Liver (mainly) or other organs, or both	62	61%/39%	Adenocarcinoma (MDF or PDF)
Lungs			
Pulmonary metastases	–	–	Adenocarcinoma (WDF, MDF, or PDF)
Pleural effusions	–	–	Adenocarcinoma (MDF or PDF)
Bones (one or more)	–	–	Adenocarcinoma (WDF, MDF, or PDF)
Brain (one or more)	51-55	M>F	Adenocarcinoma (WDF, UDF, or PDF); SCC

CUP, Cancer of unknown primary; *F,* women; *M,* men; *MDF,* moderately differentiated; *PDF,* poorly differentiated; *SCC,* squamous cell carcinoma; *UDF,* undifferentiated; *WDF,* well differentiated.
From Pavlidis N, Pentheroudakis G: Cancer of unknown primary site, *Lancet* 379(9824):1428-1435, 2012.

TREATMENT

- CUP patients often require early supportive care for their advanced cancer; also there is elevated psychosocial distress with the uncertainties of diagnosis and treatment options. Anxiety and depression are more common in CUP patients compared to patients with known primaries.
- Treatment is based according to the most likely site of origin for the cancer, with systemic chemotherapy typically being the mainstay of therapy.
- Treatment is typically palliative, and standard chemotherapy consists of platinum plus taxane combinations. In addition, gemcitabine-based regimens can be used.
- Next-generation gene sequencing and in situ hybridization techniques in a large study of 1806 CUP cases were able to identify potential biomarkers predictive of therapeutic efficacy in 96% of cases. Additionally, biomarkers associated with a potential lack of benefit were identified in numerous cases, which could further refine the management of patients with CUP.

TABLE 2 Recommended Evaluation Following Initial Light Microscopic Diagnosis

Diagnosis	Clinical Evaluation*	Special Pathologic Studies
Adenocarcinoma (or poorly differentiated adenocarcinoma)	PET CT of chest, abdomen; men: Serum psa; women: Mammogram; additional directed radiologic or endoscopic studies to evaluate abnormal symptoms, signs, laboratory values	Men: PSA stain; women: Estrogen and progesterone receptor stains (if clinical features suggest metastatic breast cancer)
Poorly differentiated carcinoma	PET CT of chest, abdomen; serum hCG, AFP; additional directed radiologic or endoscopic studies to evaluate abnormal symptoms, signs, laboratory values	Immunoperoxidase staining; electron microscopy (if immunoperoxidase stains indeterminate)
Squamous carcinoma, cervical nodes	PET direct laryngoscopy with visualization; biopsy of nasopharynx, pharynx, hypopharynx, larynx; fiberoptic bronchoscopy (if laryngoscopy is negative)	—
Squamous carcinoma, inguinal nodes	PET complete examination of perineal area (including pelvic examination); anoscopy cystoscopy	—

*In addition to a history, physical examination, complete blood cell counts, chemistry profile, and chest radiograph.
AFP, α-Fetoprotein; *CT*, computed tomography; *hCG*, human chorionic gonadotropin; *PET*, positron emission tomography; *PSA*, prostate-specific antigen.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 25, Philadelphia, 2016, Saunders.

TABLE 3 Commonly Used Immunoperoxidase Stains to Assist in the Differential Diagnosis of Carcinoma of Unknown Primary Cancers

Primary Tissue Stain	Immunoperoxidase Stain
Lung cancer	Thyroid transcription factor (TTF-1), surfactant protein A precursor (SP-A1)
Breast cancer	Estrogen receptor (ER), gross cystic disease fibrous protein-15 (GCDFP-15), mammaglobin, Her-2/neu, GATA3
Lymphoma	Leukocyte common antigen (LCA), CD3, CD4, CD5, CD20, CD45
Gastrointestinal cancers	CK7, CK20, CDX-2, carcinoembryonic antigen (CEA)
Müllerian or ovarian	CK7, estrogen receptor (ER), WT-1, PAX-8, PAX2
Prostate cancer	PSA, alpha-methylacyl CoA racemase/P504S (AMACR/P504S), P501S (prostein), and prostate-specific membrane antigen (PSMA), NKX3-1
Germ cell tumor	β-hCG, αFP, OCT3/4, CKIT, CD30 (embryonal), SALL4
Hepatocellular cancers	Hep Par-1, arginase-1 (Arg-1), Glypican-3
Sarcoma	Desmin1, factor VIII, CD31, smooth muscle actin for leiomyosarcoma, MyoD1 for rhabdomyosarcoma
Renal cell cancer	RCC, CD10, PAX-8
Neuroendocrine tumor	Chromogranin, synaptophysin, CD56
Melanoma	S100, vimentin, HMB-45, tyrosinase and Melan-A, SOX-10
Urothelial	CK7, CK20, thrombomodulin, uroplakin III
Mesothelioma	Calretinin, WT-1, D2-40, mesothelin

From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

- In another study of 442 patients with CUP, the use of targeted clinical-grade, next-generation sequencing resulted in the detection of alterations in circulating tumor DNA in 80% of patients. Among the patients harboring characterized alterations, distinct genomic profiles were observed in the majority of cases exhibited potentially targetable alterations with currently available biologic therapies.
- Favorable and unfavorable CUP subsets are shown in Table 5.
- ***Favorable CUP:***
  1. Women with peritoneal adenocarcinoma when treated as advanced ovarian cancer with surgical cytoreduction and adjuvant systemic chemotherapy can have median survivals in the 36-mo range.
  2. Patients with a midline tumor characteristically treated as germ cell tumors have median survivals of 12 mo.
  3. Patients with poorly differentiated neuroendocrine cancers are treated with combination platinum-containing chemotherapy and median survivals are in the 15-mo range.
  4. Women with axillary nodal adenocarcinoma are approached as breast cancers with treatment plans incorporating axillary and breast surgery followed by adjuvant chemotherapy, hormone therapy and radiotherapy; survival rates are comparable to similarly staged breast cancers.
  5. Patients with metastatic squamous neck nodal cancer are treated as head–neck cancers with chemoradiotherapy and/or neck dissection.
  6. Patients with a colon adenocarcinoma profile are treated with systemic regimens as in metastatic colorectal cancers with median survivals in the 24-mo range.
  7. Men with blastic bone metastases and elevated prostate specific antigen are treated with initial androgen deprivation therapy and later on with systemic chemotherapy.
- ***Unfavorable CUP:***
  1. Account for 75% to 80% of all CUP patients.
  2. The most common presentation is advanced visceral disease, often with liver metastases; median survivals with systemic platinum and taxane-containing chemotherapy are typically in the range of 6 to 7 mo.

DISPOSITION

Newer clinical practice guidelines recommend that gene panel testing be routinely undertaken to support diagnosis based on the findings of genomic mutations and to select a therapeutic drug that is likely to be effective.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Ritesh Rathore, MD**

TABLE 4 Immunohistochemical Approaches for Diagnosis of CUP

	Diagnosis
Step One	
AE1 or AE3 pan-cytokeratin	Carcinoma
Common leukocyte antigen	Lymphoma
S100; HMB-45	Melanoma
S100; vimentin	Sarcoma
Step Two	
CK7 or CK20; PSA	Adenocarcinoma
PLAP; OCT4; AFP; human chorionic gonadotropin	Germ cell tumors
Hepatocyte paraffin1; canalicular pCEA, CD10, or CD13	Hepatocellular carcinoma
RCC; CD10	Renal cell carcinoma
TTF1; thyroglobulin	Thyroid carcinoma
Chromogranin; synaptophysin, PGP9.5; CD56	Neuroendocrine carcinoma
CK5 or CK6; p63	Squamous cell carcinoma
Step Three	
PSA; PAP	Prostate
TTF1	Lung
GCDFP-15; mammaglobin; ER	Breast
CDX2; CK20	Colon
CDX2 (intestinal epithelium); CK20; CK7	Pancreas or biliary
ER; CA-125; mesothelin; WT1	Ovary

Step one detects broad type of cancer. Step two detects subtype. Step three detects origin of adenocarcinoma. Positive results with any of these stains indicates a tumor is present, but without absolute certainty.

AFP, α-Fetoprotein; *CA-125,* cancer antigen 125; *ER,* estrogen receptor; *GCDFP-15,* gross cystic disease fluid protein 15; *OCT4,* octamer-binding transcription factor 4; *PAP,* prostatic acid phosphatase; *pCEA,* polyclonal carcinoembryonic antigen; *PLAP,* placental alkaline phosphatase; *PSA,* prostate-specific antigen; *RCC,* renal cell carcinoma antigen *TTF1,* thyroid transcription factor 1; *WT1,* Wilms tumor 1.

From Pavlidis N, Pentheroudakis G: Cancer of unknown primary site, *Lancet* 379:1428-1435, 2012.

TABLE 5 Prognostic Classification of CUP Patients

Favorable Subset
Women with papillary adenocarcinoma of the peritoneal cavity
Women with adenocarcinoma involving the axillary lymph nodes
Poorly differentiated carcinoma with midline distribution
Poorly differentiated neuroendocrine carcinoma
Squamous cell carcinoma involving cervical lymph nodes
Adenocarcinoma with a colon-cancer profile (CK20+, CK7−, CDX2+)
Men with blastic bone metastases and elevated prostate-specific antigen (adenocarcinoma)
Isolated inguinal adenopathy (squamous carcinoma)
Patients with one small, potentially resectable tumor
Unfavorable Subset
Adenocarcinoma metastatic to the liver or other organs
Nonpapillary malignant ascites (adenocarcinoma)
Multiple cerebral metastases (adenocarcinoma or squamous carcinoma)
Several lung or pleural metastases (adenocarcinoma)
Multiple metastatic lytic bone disease (adenocarcinoma)
Squamous cell carcinoma of the abdominopelvic cavity

From Pavlidis N, Pentheroudakis G: Cancer of unknown primary site, *Lancet* 379:1428-1435, 2012.

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Infection caused by the species of the genus *Candida.* All the different *Candida* species can cause disease, but infections caused by *Candida albicans* are the most common. *Candida* species are ubiquitous and are the most common fungal pathogens affecting mankind. Cutaneous candidiasis comprises superficial *Candida* infections of the skin and mucosal membranes.

Cutaneous candidiasis can be classified into two subgroups: Cutaneous candidiasis syndromes and chronic mucocutaneous syndromes. Cutaneous candidiasis syndromes include:

- Generalized cutaneous candidiasis
- Intertrigo
- *Candida* folliculitis
- Paronychia/onychomycosis
- Perianal candidiasis
- Erosio interdigitalis blastomycetica
- Balanitis

Chronic mucocutaneous syndromes include:

- Oropharyngeal candidiasis
- Esophageal candidiasis
- Vulvovaginal candidiasis
- GI candidiasis (gastric/intestines/perianal)
- *Candida* cystitis

SYNONYMS

Yeast infection
Candidosis
Moniliasis
Oidiomycosis

ICD-10CM CODES	
B37.2	Candidiasis of skin and nail
B37.8	Candidiasis, unspecified
B37.89	Other sites of candidiasis

EPIDEMIOLOGY & DEMOGRAPHICS

- *Candida* species: It is the most common fungal infection in immunocompromised people.
- Most females (75%) experience an episode of vulvovaginal candidiasis in their lifetime.

INCIDENCE: Estimated to be 50 cases per 100,000 persons

PREVALENCE: Colonizes more than 50% of U.S. population

PREDOMINANT SEX AND AGE:

- Female > male
- No predominant age, but neonates and the elderly (adults >65 yr) are susceptible to *Candida* colonization and to getting mucocutaneous candidiasis

RISK FACTORS: Risk factors that allow *Candida* infection include:

- Age >65 yr
- Females in the third trimester
- Defects in the mucocutaneous barrier (e.g., wounds, burns, ulcerations)
- Decreased/defective granulocytes/monocytes
- Diseases of white blood cells (e.g., chronic granulomatous disease)
- Complement deficiency
- Certain diseases associated with cell-mediated immunity (e.g., HIV, DM)
- Use of certain medications (e.g., broad-spectrum antibiotics, high doses of corticosteroids)
- Increased skin pH due to panty liners and occlusive attire
- Chronic mucocutaneous candidiasis: (CMC) is characterized by susceptibility to *Candida* infection of skin, nails (Fig. E1), and mucous membranes. Patients with recessive CMC and autoimmunity have mutations in the autoimmune regulator *AIRE.* Mutations in the CC domain of *STAT1* underlie autosomal-dominant CMC and lead to defective Th1 and Th17 responses, which may explain the increased susceptibility to fungal infections (van de Veerdonk et al). Some patients have autosomal recessive polyglandular autoimmune syndrome type 1 (also autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED] syndrome)

Anatomical sites predisposed to *Candida* infection include:

- Axilla
- Beneath the breast, abdominal fold, intertriginous areas
- Periungual creases
- Inguinal creases
- Back and buttocks of bedridden persons

PHYSICAL FINDINGS & CLINICAL PRESENTATION

There are several clinical presentations of cutaneous candidiasis. A few are presented here.

- Cutaneous candidiasis
  1. Presents as erythematous, sometimes shiny with flakes and fluid lesions at the edge of the redness (satellite pustules). It is itchy, and the skin becomes inflamed. Pustules may be present in candidiasis of the scrotal and perineal skin
- Gastrointestinal tract candidiasis
  1. Oropharyngeal candidiasis [thrush]
     a. Usually seen in diabetics, after exposure to inhaled steroids, broad-spectrum antibiotics, chemotherapy, radiation to head and neck, and in immunosuppressed individuals (e.g., patients with a history of HIV infection). It is also seen in some patients who wear dentures
        Symptoms include:
        (1) White, thick patches on the oral mucosa (Fig. E2), tongue, palate, or oropharynx or under dentures
        (2) Dysphagia, mouth soreness, and pain on eating and swallowing
        (3) Tongue burning
     b. Physical examination shows:
        (1) Erythema of the buccal mucosa
        (2) White patches on buccal cavity surfaces (described previously)
        (3) Transverse fissuring
  2. Esophageal candidiasis:
     a. Most common in patients with:
        (1) Hematologic cancers
        (2) HIV/AIDS
     b. History of oropharyngeal candidiasis. Symptoms include:
        (1) Odynophagia (pain on swallowing), hallmark of the disease
        (2) Dysphagia
        (3) Epigastric pain
        (4) Retrosternal pain
     c. Physical examination shows:
        (1) Affects mainly the distal one third of the esophagus. Endoscopy shows areas of the erythema and edema; scattered white patches or ulcers
  3. Perianal candidiasis:
     a. Skin maceration
     b. Itching
     c. Frequently extends to the perineum
- Paronychia/onychomycosis
  1. Fungal infection of the nail and surrounding tissues
  2. Associated with diabetes mellitus and immersion of hands or feet in water
  3. History: Pain and redness around and beneath the nail and nail bed
  4. Physical exam: Inflammation around the toe nail. There may also be nail thickening and discoloration (dystrophic nails). Nail loss may also occur
- Respiratory tract candidiasis
  1. Usually seen in hospitalized patients
  2. About 25% of outpatients have their respiratory tract colonized by *Candida* species
- Genitourinary tract candidiasis
  1. Vulvovaginal candidiasis
     a. Most common form of mucosal candidiasis.
     b. Risk factors include increased estrogen level (e.g., contraceptive pill), steroid or antibiotic use, diabetes, HIV infection, IUD, and diaphragm use.
     c. It causes itching, curdy white discharge, and occasionally dysuria, dyspareunia, and vaginal irritation.
     d. On examination the mucosa may be inflamed with vulvar and vaginal erythema, and vaginal discharge, classically described as white and curdy.
     e. Painful erythema or itchy penile inflammation may occur in male sexual partners of affected females.
  2. *Candida* balanitis
     a. Usually acquired through sexual contact with a partner who has vulvovaginal candidiasis. Common in diabetic patients and uncircumcised individuals. The dominant species is *C. albicans.*
     b. Symptoms include penile pruritus and white patches on penis. There could be severe burning and itching. Infection could also spread to the perineum.
     c. Physical exam: Dry, erythematous, and scaly patches on penis and sometimes on the thighs, scrotum, and buttocks. Papules, vesicles or pustules and ulceration may also be present.

- **Others**
  1. Erosio interdigitalis blastomycetica: Denudating/macerating area commonly seen in third web space.
  2. Mastitis: Injured nipples in lactating women can lead to infections, including *Candida* infections.
  3. *Candida* folliculitis: Pustulous nodules in hairy areas.
  4. Intertrigo: This occurs in folds of the skin and creases (Fig. E3). It is characterized by erosions, exudation, oozing, and maceration.

ETIOLOGY

The most common cause of cutaneous candidiasis is *Candida albicans.*

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Intertrigo
Seborrheic dermatitis
Psoriasis
Bacterial vaginosis
Contact dermatitis

WORKUP

- Mucocutaneous and cutaneous candidiasis
  1. Obtain scrapings from the skin, oral, and vaginal mucosa or nails.
  2. The presence of hyphae/pseudohyphae or budding yeast cells on wet smear, as well as confirmation by culture, is the recommended procedure to diagnose cutaneous candidiasis.
  3. KOH smears are helpful.
- Respiratory candidiasis
  1. Sputum gram stain: Shows yeast cells
  2. Sputum cultures
  3. Lung biopsy: Establishes the diagnosis
- Gastrointestinal candidiasis
  1. Upper endoscopy with or without biopsy (Fig. 4)

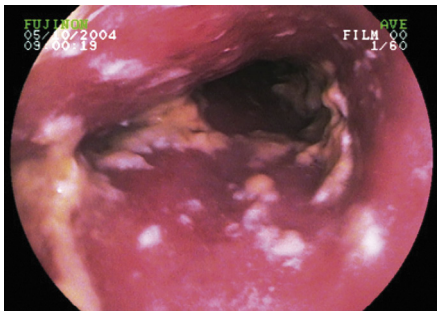

FIG. 4 Endoscopic appearance of esophageal candidiasis. (Courtesy Dr. B. Rembacken, Leeds, U.K.)

Rx TREATMENT

PHARMACOLOGIC THERAPY

- Cutaneous candidiasis
  1. Decrease/prevent moisture in area
  2. Apply antifungal agents (nystatin powder or cream with an azole or ciclopirox [e.g., clotrimazole, econazole, miconazole])
- Gastrointestinal candidiasis
  1. Oropharyngeal candidiasis
     a. Treat with either
        (1) Oral topical antifungal agent (e.g., nystatin 1:100,000 U/ml, 5 ml swish and swallow qid) OR
        (2) Systemic oral azoles (e.g., fluconazole 100 mg qd ×14 days)
  2. In HIV-positive patients, use high doses of fluconazole (100 to 200 mg PO qd for 7 to 14 days), itraconazole, or posaconazole
- *Candida* esophagitis
  1. Treat with systemic fluconazole for 2 to 3 wk
  2. Treat with IV fluconazole if patient is unable to take oral medication
- Genitourinary tract candidiasis
  1. Vulvovaginal candidiasis: Treatment options for acute cases include:
     a. A single dose of oral fluconazole (fluconazole 150 mg PO × 1 dose) OR
     b. Topical antifungal agent
  2. For chronic or recurrent cases, treat with fluconazole 150 mg qd × 3 doses and then 150 mg/wk for 6 mo
- Chronic mucocutaneous candidiasis
  1. Treatment with azoles is effective (e.g., fluconazole 100 to 400 mg daily)
  2. When patient improves, follow with maintenance treatment with same azole for life

FOLLOW-UP CARE

- Mucocutaneous candidiasis
  1. Patient should be instructed to call or follow up if symptoms persist, recur, or worsen.
  2. For recurrent infections:
     a. Check HIV antibodies.
     b. Check FBS, HbA_{1c}.
     c. Rule out hematologic malignancy or solid organ malignancy.
     d. Refer to infectious disease specialist if no etiology is found.

PREVENTION

- Maintaining dry environment (e.g., by wearing cotton underwear)
- Decreased use of antibiotic
- No douching

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Candidiasis (Patient Information)

AUTHOR: **Daniel K. Asiedu, MD, PhD, FACP**

FIG. E1 Hand and nail involvement in chronic mucocutaneous candidiasis. (From James WD et al: *Andrews' diseases of skin*, ed 12, Philadelphia, 2016, WB Saunders.)

FIG. E2 Oral candidiasis. (From Swartz, MH: *Textbook of physical diagnosis,* ed 7, Philadelphia, 2014, Elsevier.)

FIG. E3 Intertriginous candidiasis of the neck. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, WB Saunders.)

SUGGESTED READING

van de Veerdonk FL et al: STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis, *N Engl J Med* 365:54-61, 2011.

BASIC INFORMATION

DEFINITION

Severe and invasive diseases are caused by *Candida* infection. More than 15 different *Candida* species cause disease in humans, but at least 95% of invasive disease is caused by *C. albicans, C. glabrata, C. tropicalis, C. parapsilocis,* and *C. krusei*. These organisms cause serious disease referred to as invasive candidiasis. Invasive candidiasis embodies a variety of diseases caused by hematogenous spread of *Candida* to multiple viscera (e.g., kidney, brain, heart). These diseases include candidemia, disseminated candidiasis, meningitis, and endophthalmitis. Invasive candidiasis is a significant cause of morbidity and mortality for certain groups of patients.

SYNONYM

Systemic candidiasis

ICD-10CM CODES	
B37.89	Other sites of candidiasis
B37.1	Pulmonary candidiasis
B37.2	Candidiasis of skin and nail
B37.5	Candidal meningitis
B37.6	Candidal endocarditis
B37.7	Candidal sepsis
B37.9	Candidiasis unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Invasive candidiasis is the most common fungal disease among hospitalized patients in the developed world. It is an important nosocomial infection. It affects over 250,000 people worldwide each yr and causes more than 50,000 deaths.

In the U.S., *Candida* species cause 8% to 10% of nosocomial bloodstream infections (fourth most common bloodstream infection). *C. albicans* is the most common cause of candidemia, but other non-*albicans* species have been implicated in recent yrs. These include *C. glabrata, C. parapsilosis, C. tropicalis,* and *C. krusei.* Incidence rates of candidemia are between 2 and 14 cases/100,000 persons.

PREVALENCE: No data available

PREDOMINANT SEX AND AGE: Equal between males and females; all ages are susceptible.

RISK FACTORS: Prolonged hospitalization and ICU stay, use of broad-spectrum antibiotics, prolonged indwelling of catheters (especially central venous catheters), acute and chronic renal failure, surgery requiring general anesthesia, cancer (e.g., solid neoplasms), transplantation (bone marrow or solid organ), recent chemotherapy/radiation therapy, use of immunosuppressive drugs, parenteral alimentation, use of internal prosthetic devices, organ transplant, hemodialysis, mechanical, surgical procedures

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History
  1. Fever unresponsive to broad-spectrum antibiotics
  2. History of prolonged indwelling IV catheter
  3. A personal history of any of the risk factors listed earlier
- Physical findings (general)
  1. Fever
  2. Hypotension
  3. Generalized malaise
  4. Tachycardia
  5. Change in mental status
  6. Signs of multiorgan system failure
- Specific diseases
  1. Candidemia
     a. A positive blood culture is the gold standard for the diagnosis of candidemia. Obtain blood cultures in patients suspected to have candidemia. *Candida* species must be isolated from at least one blood culture. A positive culture for *Candida* should be investigated thoroughly because of the increased risk of morbidity and mortality. Attributable mortality to candidemia in adults is 15% to 20%.
     b. Most common manifestation of invasive candidiasis.
     c. Physical exam may include fever, macronodular skin lesions, septic shock, *Candida* endophthalmitis.
  2. Disseminated candidiasis
     a. Seen in patients with neutropenia who have undergone cytotoxic chemotherapy for a hematologic malignancy
     b. Associated with multiple deep-organ infections or failure
     c. Blood culture positive
     d. Fever not responding to broad-spectrum antibiotics
     e. Physical exam: Discrete erythematous or palpable rash, sepsis/septic shock
  3. Endophthalmitis
     a. Iatrogenic/accidental or traumatic fungal infection of the eye (exogenous) or hematogenous seeding of the eye (endogenous); *C. albicans* accounts for about 90% of cases of endogenous endophthalmitis
     b. Starts as choroidal lesion, progresses to vitreitis and endophthalmitis and eventually blindness
     c. Physical exam shows fever. An early funduscopic exam by an ophthalmologist should be performed in all patients with candidemia. Funduscopic examination may show large and off-white cotton ball–like lesions with indistinct borders. Patients usually present with decreased visual acuity and occasional pain
  4. *Candida* infection of the CNS
     a. Exogenous and endogenous forms
     b. Usually invades the meninges
     c. Commonly found in long-term ICU patients
     d. May present as meningitis, mycotic aneurysms, change in mental status
     e. Physical examination reveals fever, neck rigidity, confusion, headache, and coma
  5. Candidal musculoskeletal infections
     a. Candida infect the skeletal system, especially the joints as a result of trauma, joint injections, and other surgical interventions, such as IV drug use (hematogenous seeding)
     b. Previously uncommon; now relatively common probably due to increased frequency of candidemia and disseminated candidiasis
     c. Knee and vertebral column (especially lumbosacral vertebral disks and vertebral bodies, which can lead to vertebral osteomyelitis, with or without discitis) are involved
     d. Physical exam is usually unremarkable but may show tenderness over involved area, fever, erythema, bone deformity, weight loss, and sometimes a draining fistulous tract
  6. Candidal infections of the heart
     a. Usually found in patients with artificial heart valves, IV drug users, and patients with an indwelling central venous catheter
     b. May present as infective endocarditis, myocarditis, or pericarditis
     c. Physical examination reveals fever, hypotension, tachycardia, new or changing murmur, and signs and symptoms of heart failure
  7. Hepatosplenic candidiasis (chronic systemic candidiasis)
     a. Seen in patients with hematologic malignancy and neutropenia; usually develops during recovery from a neutropenic state (normally after undergoing myeloablative chemotherapy)
     b. On examination, patients have low-grade fever, right upper quadrant pain, palpable/tender liver, splenomegaly, and rarely jaundice
     c. MRI/CT/US may reveal multiple focal abnormalities in the liver, spleen, and kidneys
  8. *Candida* peritonitis
     a. Associated with GI surgery: Perforations, acute necrotizing pancreatitis, peritoneal dialysis
     b. Clinical manifestations include fever, chills, abdominal pain; nausea, vomiting, constipation
     c. Physical examination reveals abdominal distention, abdominal pain, absent bowel sounds
  9. Other forms of invasive candidiasis
     a. *Candida* splenic abscess
     b. *Candida* cholecystitis
     c. Renal candidiasis
     d. Mediastinitis
     e. Empyema
     f. Pneumonia (rare)
     g. Meningitis
     h. Septic arthritis

ETIOLOGY

- Several species of *Candida* exist in nature
- Medically significant include:
  1. *C. albicans:* Together with *C. glabrata,* they account for 70% to 80% of *Candida* in invasive candidiasis.
  2. *C. glabrata:* Together with *C. albicans,* they account for 70% to 80% of *Candida* in invasive candidiasis.

3. *C. parapsilosis:* Associated with indwelling vascular catheters and prosthetic devices
4. *C. tropicalis:* Especially in leukemic patients
5. *C. krusei:* Resistant to fluconazole and ketoconazole

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Sepsis (bacterial)
- Septic shock
- Cryptococcosis
- Aspergillosis

LABORATORY TESTS

- Laboratory studies are nonspecific. It is often necessary to perform several diagnostic tests to achieve maximum accuracy.
- High index of suspicion is needed.
- Candidemia/disseminated candidiasis: Candidemia represents the tip of the iceberg with respect to the more invasive forms of candidiasis. Central lines often contribute to the propagation of candidemia. From the blood, infection can spread to almost any organ.
  1. Blood culture is the gold standard of diagnosis. They are helpful but have low positive yield. Only 40% to 60% of patients with infection have positive culture. 95% of blood cultures that are positive for *Candida* species become positive within 96 hours. Candida in a blood culture is NOT a contamination, and the source of the infection should be sought.
  2. Diagnosis can also be made from normally sterile sites. Specific species identification is necessary since only 10% of known *Candida* species produce disease in humans.
  3. The T2 magnetic resonance assay of whole blood can be performed on blood samples even after initiation of antifungal therapy.
  4. Serum (1,3) beta-D-glucan detection assay: High specificity and high positive predictive value. It can also be used for diagnosing invasive candidiasis when blood cultures are negative.
  5. New techniques allow for quick identification of *Candida* species in blood. These include:
     a. Peptide nucleic acid fluorescence in-situ hybridization (PAN-FISH)
     b. Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS)
- Hepatosplenic candidiasis (focal):
  1. Elevated serum alkaline phosphatase.

IMAGING STUDIES

- Imaging studies are generally not required or useful.
- Ultrasound is useful for diagnosing hepatosplenic abscess. "Bull's eye or target lesions" are observed in the liver and spleen.
- CT scanning may be used to diagnose hepatosplenic candidiasis, as well as intraabdominal/renal abscesses.
- ECHO is useful to rule in or rule out *Candida* endocarditis.

Rx TREATMENT

- To successfully treat invasive *Candida* infection, it is important to start antifungal medication as early as possible. A small delay (approximately 12 to 24 hr) in starting treatment may result in a significantly excessive mortality rate.
  1. Do not dismiss *Candida* spp. as a contaminant when it is isolated in blood cultures or other sterile sites.
  2. Before treatment, also consider removal of an intravenous catheter.
- Antifungals available include:
  1. Azoles (e.g., fluconazole, posaconazole, itraconazole, voriconazole). They inhibit the synthesis of ergosterol, a fungal cell component.
  2. Echinocandins (e.g., caspofungin, micafungin, anidulafungin). These are glucan synthesis inhibitors. Glucan is an important component of fungal cell walls. Most studies have provided reasonable support for echinocandins as treatment of choice for the majority of patients with invasive candidiasis.
  3. Polyenes (e.g., amphotericin B, lipid formulation of amphotericin, nystatin). Broad spectrum. Their mechanism of action is to increase cytoplasmic permeability.
  4. Antimetabolites (e.g., flucytosine). Flucytosine is deaminated to 5-fluorouracil in fungal cell. 5-Fluorouracil inhibits RNA and protein synthesis.

TREATMENT PLANS

CANDIDEMIA: General principles:

- For documented candidemia, 2 weeks of antifungal treatment after the first negative blood culture is recommended.
- In nonneutropenic patients, a dilated funduscopic examination in the first week of treatment is recommended.
- In neutropenic patients, delay (b) above until neutrophil recovery because characteristic ocular findings may be delayed.
- Treatment depends on whether the patient is neutropenic or not.
  1. **Nonneutropenic adult patients:** The initial treatment is with an Echinocandin, e.g., caspofungin 70 mg loading dose, then 50 mg IV daily *or* micafungin 100 mg IV daily. Alternatives include fluconazole 800 mg as loading dose, then 400 mg/day for at least 2 wk after clinical improvement or negative blood culture. Amphotericin B is equally efficacious.
  2. **Neutropenic adult patients:** An echinocandin is the drug of choice (e.g., caspofungin) 70 mg IV loading dose then 50 mg/day IV or micafungin 100 mg/day IV or anidulafungin 200 mg IV loading dose then 100 mg IV all for at least 2 wk after clear blood culture and after clinical improvement. An alternative is fluconazole.
  3. **Preferred oral step-down therapy:** Neutropenic and nonneutropenic clinically stable patients who have
     a. *Candida*-susceptible fluconazole
     and
     b. Negative blood cultures can be transitioned to oral fluconazole (400 mg [6 mg/kg] daily) after about 5 to 7 days.

DISSEMINATED CANDIDIASIS: Fluconazole is the drug of choice.

DISSEMINATED CANDIDIASIS WITH END-ORGAN INFECTION:

- Treatment is the same as for candidemia of nonneutropenic patients. In most cases, therapy is prolonged for at least 4 to 6 wk.
- The echinocandins are the first-line therapy.

OSTEOMYELITIS OR SEPTIC ARTHRITIS:

- Fluconazole 400 mg IV or PO *or*
- Caspofungin 50 mg IV daily *or*
- Micafungin 100 mg IV daily

ENDOCARDITIS:

- Caspofungin 50 to 150 mg/day *or*
- Micafungin 100 to 150 mg/day *or*
- Anidulafungin 100 to 200 mg/day

MYOCARDITIS:

- Lipid-based amphotericin B 3 to 5 mg/kg daily *or*
- Caspofungin 150 mg/d *or* micafungin 100 mg/d.

ESOPHAGITIS:

- Caspofungin 50 mg IV daily
- Fluconazole 200 to 400 mg/day

PERICARDITIS: Lipid-based amphotericin B 3 to 5 mg/kg daily

SURGICAL CARE: Includes:

- Drainage
- Removal of any foreign bodies
- Surgical debridement
- Organ-specific care (e.g., valve replacement for endocarditis, splenectomy for splenic abscess, or vitrectomy for fungal endophthalmitis)

DISPOSITION

- Several factors affect prognosis: Infection site, degree of immune suppression, and how quickly diagnosis and therapy are initiated
- Overall mortality rate: 30% to 40%

REFERRAL

- Always involve an infectious disease specialist.
- Referral to specialist will depend on the organ involved. For example:
  1. Endocarditis will require a cardiothoracic surgeon.
  2. Endophthalmitis will require an ophthalmologist.

FOLLOW-UP CARE

- Prolonged periods, mainly in the hospital, of antifungal treatment may be necessary.
- Closely monitor patients on amphotericin B because of the high incidence of side effects. Check basic metabolic panel, magnesium, and CBC at least twice a week.

PEARLS & CONSIDERATIONS

PREVENTION

Basic preventive measures are similar to those used for nosocomial infections. This includes:

- Maximizing hand hygiene recommendations:
  1. Hand washing.
  2. Using alcohol/chlorhexidine solution.
- Adhering strictly to recommendations for placement and care of central lines and catheters.
- Judicious use of antimicrobials
  1. Notes on *C. auris*:
     a. CDC issued warnings in 2016 about the emergence of *C. auris*, a multidrug-resistant *Candida* species. It is resistant to fluconazole and amphotericin B in 93% and 35% of patients, respectively.
     b. It has caused invasive health care–associated infections in many countries and has high mortality rates.
     c. Initial treatment is with echinocandin. Patient should be closely followed with cultures.
     d. Special infection control precautions should be followed for patients infected with or colonized by *C. auris.*

PROPHYLAXIS

Antifungal prophylaxis should be limited to patients in whom it has proved beneficial: patients with gastrointestinal anastomotic leakage, patients undergoing transplantation of the pancreas or small bowel, selected patients undergoing liver transplantation who are at high risk for candidiasis, and extremely low-birth-weight neonates in settings with a high incidence of neonatal candidiasis.

PATIENT/FAMILY EDUCATION

- Inform them about the risk factors for invasive candidiasis.
- Inform them of the seriousness of the disease and the associated high morbidity/mortality rates, thus requiring aggressive treatment.
- Side effects and toxicities associated with treatment.

RELATED CONTENT

Candidiasis (Patient Information)
Candidiasis, Cutaneous (Related Key Topic)

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Daniel K. Asiedu, MD, PhD, FACP**

SUGGESTED READINGS

Pappas PG et al: Invasive candidiasis, *Nature Reviews/Disease Primers* 4, Article number 18026, 2018 .

Pappas PG et al: Clinical practice guidance for the management of candidiasis: 2016 Update by infectious disease Society of America, *Clin Infect Dis* 62:e1, 2016.

Carbon Monoxide Poisoning PTG

BASIC INFORMATION

DEFINITION

Carbon monoxide (CO) is a colorless, odorless, tasteless, nonirritating gas. When inhaled, it produces toxicity by causing cellular hypoxia and damage.

ICD-10CM CODES

T68	Toxic effect of carbon monoxide
T58.01	Toxic effect of carbon monoxide from motor vehicle exhaust, accidental (unintentional), initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

- A leading cause of accidental and intentional poisoning in the U.S.
- Can occur because of acute toxicity or chronic exposure.
- CO poisoning is seen more frequently during the fall and winter months in cold climates. Frequently seen after storm-related power outages, mostly due to the use of portable gasoline-powered electrical generators.
- Most fatal cases of CO poisoning occur in the home.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Depends on the severity and duration of exposure. The brain and heart are most sensitive to CO poisoning. Table 1 summarizes carboxyhemoglobin concentration and related symptoms.
- Presentation is often nonspecific and may be mistaken for a flulike illness.
- Severity of poisoning does not correlate with carboxyhemoglobin (COHb) levels.
- Mild to moderate poisoning may present with headache, malaise, dizziness, nausea, dyspnea, difficulty concentrating, confusion, and blurred vision. Patients may have tachypnea and tachycardia.
- Severe poisoning may present with hypotension, arrhythmias, myocardial ischemia, pulmonary edema, lethargy, ataxia, loss of consciousness, seizure, coma, or, rarely, cherry-red skin.
- Delayed neurologic sequelae may develop days to weeks after apparent recovery from acute poisoning. Patients may present with neurologic or psychiatric symptoms (cognitive deficits, memory loss, personality changes, movement disorders, Parkinson, psychosis, neurologic deficits).

ETIOLOGY

- CO results from the incomplete combustion of carbon-containing compounds. CO poisoning occurs from inhaling smoke from fires, motor vehicle/motor boat exhaust, or the burning of fuel (oil, wood, coal, gasoline, natural gas) in poorly functioning or improperly ventilated devices (heating systems, stoves/grills, portable generators, etc.). Methylene chloride (paint stripper) fumes are converted to CO by the liver.
- CO toxicity results from tissue hypoxia and direct CO-mediated damage at the cellular level. This may explain why COHb levels alone are not predictive of clinical toxicity. The mechanisms of CO toxicity are not completely understood.
- CO impairs oxygen delivery. CO reversibly binds hemoglobin with an affinity 250 times greater than oxygen, displacing oxygen from hemoglobin and decreasing the oxygen-carrying capacity of blood. By binding to hemoglobin, CO changes the structure of the hemoglobin molecule and decreases oxygen release to tissue.
- CO may also interfere with peripheral oxygen utilization by binding to other heme-containing proteins including cytochromes and myoglobin. Cellular respiration may be depressed by inhibition of mitochondrial function.
- Neurologic toxicity is not explained by hypoxia alone and is related to the complex intracellular actions of CO. CO precipitates an inflammatory cascade that results in oxidative damage and brain lipid peroxidation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Viral syndromes
- Cyanide, hydrogen sulfide
- Methemoglobinemia
- Amphetamines and derivatives
- Cocaine, phencyclidine (PCP)
- Cyclic antidepressants
- Phenothiazines
- Theophylline

WORKUP

History (duration and source of CO exposure, loss of consciousness), physical examination (detailed neurologic examination), laboratory and imaging tests

LABORATORY TESTS

- COHb level (measured by CO-oximetry on arterial or venous blood). COHb level >3% in nonsmokers confirms exposure. Heavy smokers may have baseline levels up to 10% to 15%. Levels may be low if the patient has already received supplemental oxygen or if delays occur between exposure and testing.
- NOTE: Pulse oximetry and arterial blood gas (ABG) may be falsely normal because neither measures oxygen saturation of hemoglobin directly. Pulse oximetry is inaccurate because of the similar absorption characteristics of oxyhemoglobin and COHb. An ABG is inaccurate because it measures oxygen dissolved in plasma (which is not affected by CO) and then calculates oxygen saturation of hemoglobin.
- Electrolytes, glucose, BUN, creatinine, cardiac biomarkers, ABG (lactic acidosis and rhabdomyolysis may develop), CBC (polycythemia from hypoxia in chronic CO poisoning).
- ECG (ischemia, arrhythmia).
- Pregnancy test (fetus at high risk).
- Consider toxicology screen.
- Table 2 summarizes treatment strategies for acute smoke inhalation.

IMAGING STUDIES

- Chest x-ray (noncardiogenic edema)
- Brain CT, MRI if neurologic abnormalities are present, to exclude other causes

TREATMENT

ACUTE GENERAL Rx

- Remove from site of CO exposure
- Ensure adequate airway
- Continuous ECG monitor
- Fetal monitoring if pregnant
- 100% oxygen by nonrebreather mask or endotracheal tube (decreases half-life of COHb from 4 to 6 hr to 60 to 90 min) until COHb level is <5% and patient is asymptomatic. Table 3 describes the half-life of COHb
- Hyperbaric oxygen (2.5 to 3 atm)
  1. Questionable beneficial effect over normobaric oxygen. Disparate findings in various studies: Some suggest hyperbaric oxygen treatment reduces the incidence of neurologic sequelae, and others have found it worsens neurologic outcomes compared to normobaric oxygen treatment. A large retrospective study suggests it may decrease short-term

TABLE 1 Carboxyhemoglobin Concentration and Related Symptoms

COHb (%)	Symptoms
<20	Slight headache and dilation of peripheral blood vessels
21-40	Severe headache and pulsating in temporal blood vessels, vertigo, dizziness, nausea and vomiting, circulatory collapse
41-60	Symptoms as above, syncope, tachycardia, hyperventilation, intermittent seizures, cyanosis, coma, shock, Cheyne-Stokes respiration
61-80	Coma, intermittent seizures, impaired heart and lung function, weak pulses, slow breathing, death within hours
>81	Death occurs within minutes

COHb, Carboxyhemoglobin.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

TABLE 2 Treatment Strategies for Acute Smoke Inhalation

Current	Under Investigation
Rescue victim from source	Activated protein C
High-flow 100% O_2	Antiinflammatory drugs: • Methylprednisolone • Phenytoin
Body check	Nitric oxide synthase inhibitors
Intravenous access	Antioxidants: • Gamma-tocopherol • 21-aminosteroid
± Intubation	Endothelin-I-receptor antagonist tezosentan
If upper airway edema: • Nebulized adrenaline • Nebulized corticosteroids	P-selectin blockade
If bronchospasm: • Nebulized alpha$_2$-agonists	Nebulized deferoxamine-pentastarch complex
If elevated COHb: • High-flow 100% O_2 • Hyperbaric oxygen	Mechanical ventilation: • High-frequency percussive ventilation • Airway pressure release ventilation • Volumetric diffuse ventilator
If cyanide intoxication: • Amyl nitrate • Sodium thiosulfate • Hydroxocobalamin (Cyanokit)	Extracorporeal membrane oxygenation
Mechanical ventilation, Low tidal volume	Arteriovenous carbon dioxide removal
Nebulized heparin	Pulmonary decontamination with nebulized amphoteric chelating agents
Nebulized *N*-acetylcysteine	

COHb, Carboxyhemoglobin.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 4, Philadelphia, 2014, Elsevier.

TABLE 3 Half-Life of COHb

Oxygen Concentration	Half-Life
21% (room air)	4-5 hr
100% (mask or endotracheal)	60-90 min
100% (hyperbaric molecular oxygen)	20-30 min

COHb, Carboxyhemoglobin.
From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

and long-term mortality, especially in individuals <20 yr old and those with acute respiratory failure. Multiple sessions were associated with lower mortality than a single session
2. Decreases half-life of COHb to 20 to 30 min; increases amount of oxygen dissolved in plasma. It also reduces CO binding to other heme-containing proteins
3. Consider for:
   a. Severe intoxication (COHb >25%, history of loss of consciousness, neurologic symptoms or signs, cardiovascular compromise, severe metabolic acidosis)
   b. Pregnant women with COHb >20% or signs of fetal distress. CO elimination is slower in fetus than mother, fetal Hgb has greater affinity for CO than adult Hgb
   c. Should be instituted quickly if deemed necessary
- Consider concomitant poisoning with other toxic/irritant gases that may be present in smoke (e.g., cyanide) or thermal injury to airway. Toxic effects of CO and cyanide are synergistic
- Identify source of exposure and determine if poisoning was accidental

DISPOSITION

- Patients with mild accidental poisoning can be treated in an ambulatory setting. Those with moderate/severe poisoning or coexisting illness require hospitalization.
- About 35% of patients with moderate to severe poisoning have cardiac dysfunction (arrhythmia, LV systolic dysfunction, ischemia).
- Survivors of severe poisoning are at 14% to 40% risk for neurologic sequelae.
  1. Deficits are usually apparent within 3 wk of poisoning but may present months later.
  2. Risk of developing sequelae is greater if patient lost consciousness during acute poisoning and with older age.
  3. Brain MRI and functional CT may reveal changes; damage is seen most often in the globus pallidus and deep white matter.
  4. Recovery may occur over months to years.
- Severe CO poisoning is associated with increased long-term morbidity and mortality.
- High risk of fetal demise.

REFERRAL

- American Association of Poison Control Centers: 1-800-222-1222
- Hyperbaric unit; accredited facilities are listed on the Undersea & Hyperbaric Medical Society website (www.uhms.org)
- Psychiatric evaluation if intentional poisoning

PEARLS & CONSIDERATIONS

- Hookah smoking is increasingly being recognized as a cause of CO poisoning, especially among young adults.
- Severity of poisoning and prognosis do not correlate with COHb levels because hypoxia represents only a component of CO's toxic effect. New therapies to address CO toxicity are being proposed.
- Neuropsychometric testing is an objective measure of cognitive function but is not universally used.
- Imaging techniques and biomarkers to define severity of CO poisoning, early prediction of CNS damage and prognosis are being studied, but are not ready for application.
- Pulse CO-oximetry measurement of CO saturation has limited clinical use.
- Treatment with hydroxocobalamin (for cyanide toxicity) may make subsequent COHb testing unreliable.
- Contact local fire department to assess environment and identify source of CO.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Carbon Monoxide Poisoning (Patient Information)

AUTHOR: **Sudeep K. Aulakh, MD**

SUGGESTED READINGS

Annane D et al: Hyperbaric oxygen therapy for acute domestic carbon monoxide poisoning: two randomized controlled trials, *Intensive Care Med* 37:486, 2011.

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Weaver LK et al: False positive rate of carbon monoxide saturation by pulse oximetry of emergency department patients, *Respir Care* 58:232, 2013.

Wolf SJ et al: Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with acute carbon monoxide poisoning, *Ann Emerg Med* 69:98, 2017.

Wong CS et al: Increased long-term risk of dementia in patients with carbon monoxide poisoning, *Medicine (Baltimore)* 95(3):e2549, 2016.

Carcinoid Syndrome ALG PTG

BASIC INFORMATION

DEFINITION

Carcinoid syndrome is a symptom complex characterized by paroxysmal vasomotor disturbances, diarrhea, and bronchospasm. It is caused by the action of amines and peptides (serotonin, bradykinin, histamine) produced by tumors arising from neuroendocrine cells.

SYNONYMS

Flush syndrome
Argentaffinoma syndrome

ICD-10CM CODE
E34.0 Carcinoid syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Carcinoid tumors are found incidentally in 0.5% to 0.75% of autopsies.
- Carcinoid tumors are principally found in the following organs: Appendix (40%); small bowel (20%; 15% in the ileum); rectum (15%); bronchi (12%); esophagus, stomach, and colon (10%); and ovary, biliary tract, and pancreas (3%). Table E1 summarizes the relative frequencies of selected carcinoid tumors and their prevalence of metastases and carcinoid syndrome.
- The incidence of carcinoids is 2.47 to 4.48/100,000, depending on race and sex, and is highest in black men. The overall incidence has increased over the last 30 yr due in part to improved diagnostic modalities.
- Carcinoid tumors can be classified using the WHO classification as follows:
  1. WHO I: Well-differentiated, <2 cm diameter, low proliferation index (<2%), confined to mucosa and submucosa.
  2. WHO II: Differentiated, >2 cm diameter, invasive growth, high proliferation index (2% to 15%).
  3. WHO III: Poorly differentiated carcinomas with metastases and proliferation index >15%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Cutaneous flushing (75% to 90%):
  1. The patient usually has red-purple flushes starting in the face, then spreading to the neck and upper trunk (Fig. E1).
  2. The flushing episodes last from a few minutes to hours (longer-lasting flushes may be associated with bronchial carcinoids).
  3. Flushing may be triggered by emotion, alcohol, or foods or may occur spontaneously.
  4. Dizziness, tachycardia, and hypotension may be associated with the cutaneous flushing.
- Diarrhea (>70%): Often associated with abdominal bloating and audible peristaltic rushes.
- Intermittent bronchospasm (25%): Characterized by severe dyspnea and wheezing.
- Facial telangiectasia.
- Tricuspid insufficiency, pulmonic stenosis from carcinoid heart lesions.

ETIOLOGY

- Carcinoid syndrome is caused by neoplasms originating from neuroendocrine cells.
- Carcinoid tumors do not usually produce the syndrome unless liver metastases are present or the primary tumor does not involve the gastrointestinal tract.

DIAGNOSIS

- See Fig. E2 for diagnostic algorithm.

DIFFERENTIAL DIAGNOSIS

- Flushing: Carcinoid syndrome must be distinguished from idiopathic flushing (IF); patients with IF more often are female, are younger, and have a longer duration of symptoms; palpitations, syncope, and hypotension occur primarily in patients with IF. Additional causes of flushing that need to be ruled out are menopause, medications (niacin, nitrates), alcohol, renal cell carcinoma, medullary cancer of thyroid, VIPoma, mastocytosis, and chronic use of food additives (nitrites, sulfites)
- Diarrhea: irritable bowel syndrome, inflammatory bowel disease, laxative abuse, infectious colitis
- Bronchospasm: Asthma, foreign body, gastroesophageal reflux disease, lung neoplasm

LABORATORY TESTS

- The biochemical marker for carcinoid syndrome is increased 24-hr urinary 5-hydroxyindoleacetic acid, a metabolite of serotonin (5-hydroxytryptamine).
- False elevations can be seen with ingestion of certain foods (bananas, pineapples, eggplant, avocados, walnuts) and certain medications (acetaminophen, caffeine, guaifenesin, reserpine); therefore patients should be on a restricted diet and avoid these medications when the test is ordered.
- Falsely low results can occur with use of alcohol, aspirin, monoamine oxidase inhibitors, and St. John's wort.
- Liver function studies are an unreliable indicator of liver involvement.

IMAGING STUDIES

- CT scan of chest is useful to detect bronchial carcinoids.
- CT scan or MRI of abdomen (Fig. E3) is useful to detect liver metastases (palpable in >50% of cases).
- Iodine-123–labeled somatostatin can detect carcinoid endocrine tumors with somatostatin receptors.
- Scanning with radiolabeled octreotide (Fig. E4) can visualize previously undetected or metastatic lesions.
- Positron emission tomography scan.

TABLE E1 Relative Frequencies of Selected Carcinoid Tumors and Their Prevalence of Metastases and Carcinoid Syndrome

	% of all Carcinoids[a]	% with Metastases	% with Carcinoid Syndrome
Gastric	2-6	22-31	10
Small intestinal[b]	10-28	14-71	3-13
Appendiceal	2-38	2-35	<1
Colonic	4-10	60-71	5
Rectal	10-19	3-14	<1
Pancreatic	<1	66-100	Up to 100
Tracheal/bronchial/pulmonary	85	13	13

[a]Other less-common sites for carcinoids not included here include esophagus, liver, gallbladder, biliary tract, larynx, cervix, ovary, and testis.
[b]Small intestine includes duodenum, ampulla, jejunum, ileum, and Meckel diverticulum.
From Feldman M et al: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

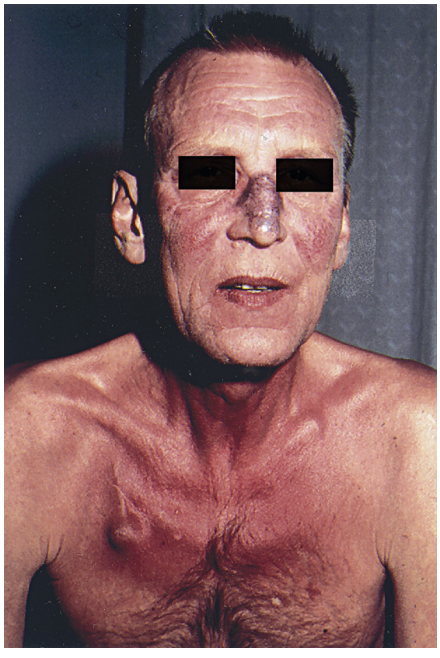

FIG. E1 Long-lasting, chronic flushing in a patient with long-standing carcinoid disease. Note the telangiectases. (From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.)

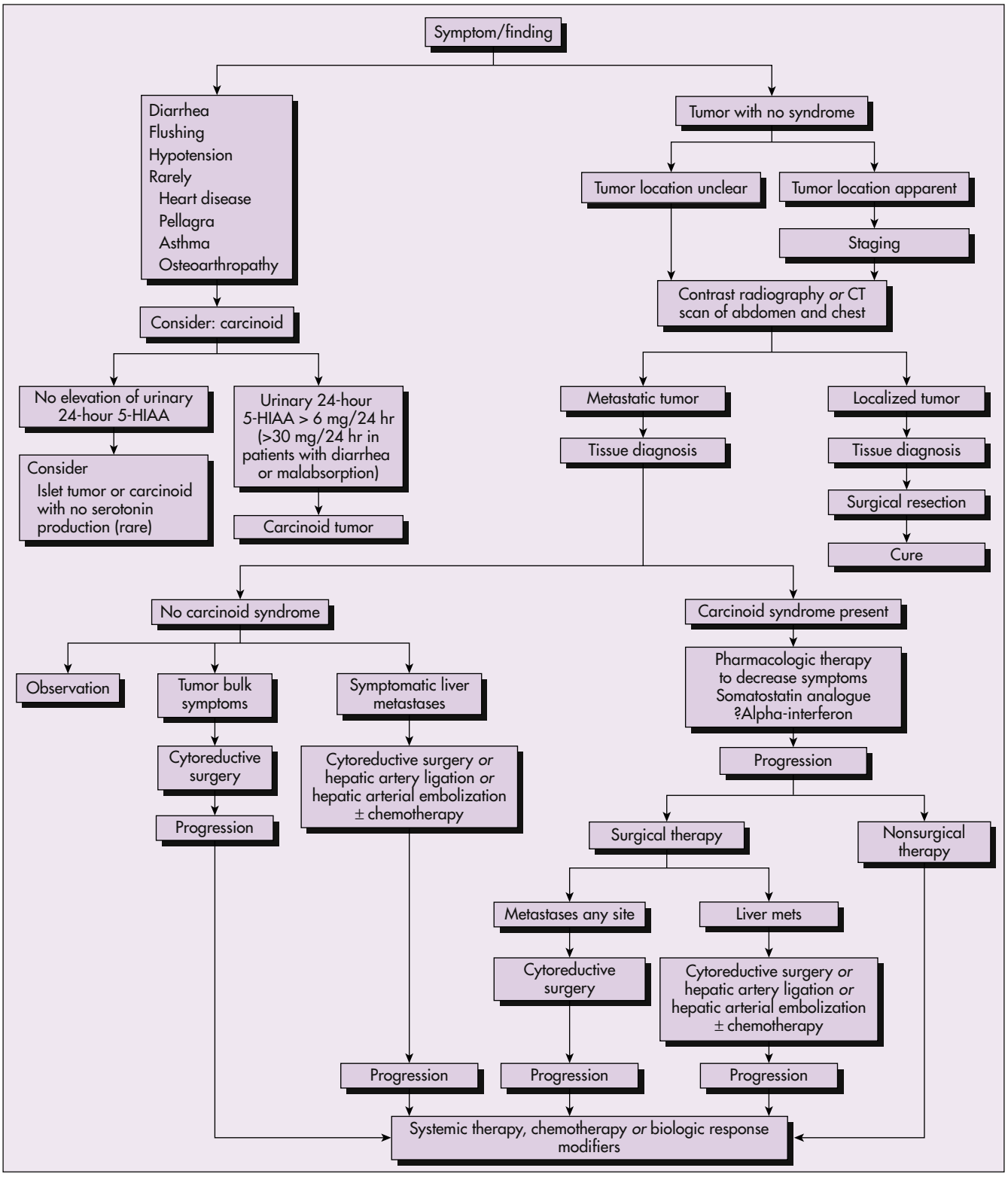

FIG. E2 Algorithm of diagnosis and treatment of carcinoid tumors. *CT,* Computed tomography; *mets,* metastasis. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Avoidance of ethanol ingestion (may precipitate flushing)

GENERAL Rx

- Surgical resection of the tumor can be curative if the tumor is localized or palliative and results in prolonged asymptomatic periods if metastases are present. Surgical manipulation of the tumor can, however, cause severe vasomotor abnormalities and bronchospasm (carcinoid crisis).
- Percutaneous embolization and ligation of the hepatic artery can decrease the bulk of the tumor in the liver and provide palliative treatment of tumors with hepatic metastases.
- Cytotoxic chemotherapy: Combination chemotherapy with 5-fluorouracil and streptozocin can be used in patients with unresectable or recurrent carcinoid tumors; however, it has only limited success. Control of clinical manifestations:
  1. Somatostatin analogues (octreotide and lanreotide) are effective for both flushing and diarrhea in most patients. Telotristat ethyl, a tryptophan hydroxylase inhibitor is FDA approved for use in combination with somatostatin analogues (SSA) for diarrhea inadequately controlled with SSA.
  2. Flushing may be controlled by the combination of H_1- and H_2-receptor antagonists (e.g., diphenhydramine 25 to 50 mg PO q6h and ranitidine 150 mg bid).
  3. Diarrhea may respond to diphenoxylate with atropine (Lomotil).
  4. Bronchospasm can be treated with aminophylline and/or albuterol.
- Nutritional support: Supplemental niacin therapy may be useful to prevent pellagra because the tumor uses dietary tryptophan for serotonin synthesis, resulting in a nutritional deficiency in some patients.
- Interferon alfa may be useful as an additive to control symptoms unresponsive to somatostatin analogues.

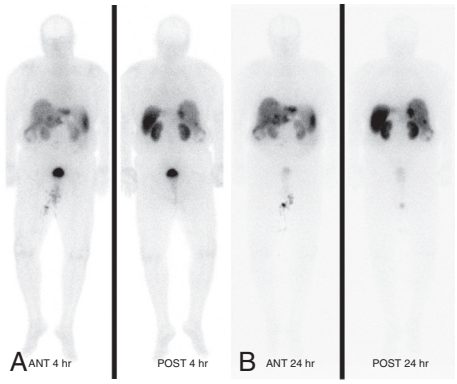

FIG. E3 A and **B,** Octreoscan illustrating uptake pattern in liver metastases from a small bowel carcinoid. *ANT,* Anterior; *POST,* posterior. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

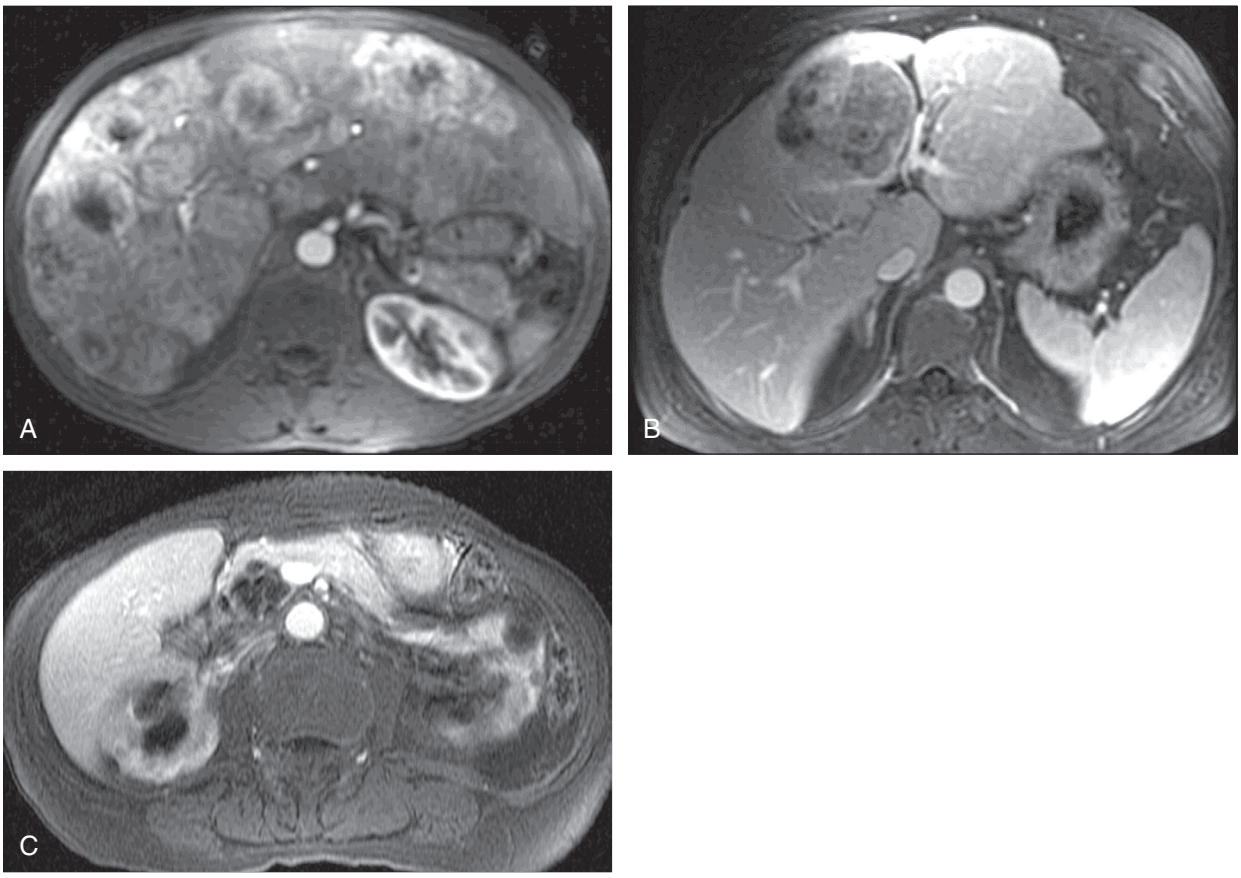

FIG. E4 (A) Carcinoid metastases to the liver. Axial magnetic resonance image with gadolinium shows multiple enhancing masses in both lobes of the liver. **(B)** Hepatoma. Axial magnetic resonance image with gadolinium shows a solid mass in the left lobe of the liver. **(C)** Intraductal papillary mucinous tumor of the pancreas. Axial T1-weighted magnetic resonance image of the abdomen shows a low–signal intensity cystic mass in the head of the pancreas. (Courtesy Dr. Ihab Kamel, The Johns Hopkins University in Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

- Echocardiography and monitoring for right-sided congestive heart failure are recommended for patients with unresectable disease because endocardial fibrosis, involving predominantly the endocardium, chordae, and valves of the right side of the heart, can occur.

DISPOSITION

Carcinoids of the appendix and rectum have a low malignancy potential and rarely produce the clinical syndrome; metastases are also uncommon if the size of the primary lesion is <2 cm in diameter. Table E2 summarizes the 5-yr survival rates of selected carcinoid tumors by stage.

RELATED CONTENT

Carcinoid Syndrome (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

TABLE E2 Five-Year Survival Rates (%) of Selected Carcinoid Tumors by Stage

	Localized Stage	Regional Stage	Distant Stage	Unstaged	All Stages
Gastric	64	40	10	66	49
Small intestinal	65	66	36	53	55
Appendiceal	94	85	34	78	86
Colonic	71	44	20	68	42
Rectal	81	47	18	75	72
Pancreatic	N/A	0	26	57	34
Tracheal/bronchial/ pulmonary	85	70	14	65	77

From Feldman M et al: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

BASIC INFORMATION

DEFINITION

Cardiac tamponade is a life-threatening condition in which an accumulation of fluid within the pericardial space causes impaired diastolic filling and cardiac output as well as arterial hypotension due to elevated pericardial pressure.

ICD-10CM CODE
I31.4 Cardiac tamponade

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Tachypnea/dyspnea
- Chest pain may be present
- Beck triad:
  1. Absolute or relative hypotension
  2. Elevated jugular venous pressure (with prominent *x* descent and blunted *y* descent)
  3. Muffled heart sounds
- Tachycardia (except in uremia or hypothyroid patients)
- Pulsus paradoxus (decrease in systolic arterial pressure of 10 mm Hg or more during normal inspiration while in normal sinus rhythm). Tamponade settings in which pulsus paradoxus may not be present are summarized in Box 1
- Pericardial friction rub may be heard in patients with cardiac tamponade due to inflammatory pericarditis
- Reduced or absent apical cardiac impulse
- Signs of hypoperfusion from reduced cardiac output (diaphoresis, cool extremities, peripheral cyanosis, and depressed sensorium)

ETIOLOGY

- Acute (rapidly accumulating pericardial effusion leading to cardiac tamponade): Does not need a large amount of effusion to cause tamponade; rather, it is the rapidity of fluid accumulation that leads to clinical tamponade. It requires urgent reduction of pericardial pressure. Causes for acute cardiac tamponade include:
  1. Penetrating chest trauma
  2. Aortic dissection (more commonly in Type A)
  3. Postinfarction myocardial rupture and/or hemorrhagic pericarditis (Dressler syndrome)
  4. Iatrogenic (right ventricular perforation during central line and pacemaker insertions, endomyocardial biopsy, cardiac ablation, post–coronary bypass surgery or post–percutaneous coronary intervention)
- Subacute or chronic: Occurs over days to weeks, and the effusion is usually large; causes include the following:
  1. Malignancy (e.g., lung, breast, lymphoma)
  2. Viral pericarditis (e.g., Coxsackie, human immunodeficiency virus, enterovirus, HSV 6, parvovirus, etc.)
  3. Bacterial, fungal, or tuberculous pericarditis
  4. Uremia
  5. Hypothyroidism/myxedema (rare)
  6. Collagen vascular disease (e.g., lupus, rheumatoid arthritis, scleroderma)
  7. Radiation
  8. Post–myocardial infarction or post–cardiac ablation inflammation
  9. Idiopathic
- Regional cardiac tamponade occurs when the localized or loculated hematoma compresses only selected cardiac chambers

BOX 1 Tamponade Settings in Which Pulsus Paradoxus May Not Be Present

- Nonrestrictive (large) atrial septal defect
- Severe aortic insufficiency
- Loculated effusion
- LV hypertrophy and other causes of elevated LV diastolic pressure
- Shock caused by hypovolemia, or profound circulatory collapse with tamponade
- Severe left ventricular dysfunction
- Low-pressure tamponade
- RV hypertrophy or other cause of impaired RV filling
- Positive-pressure ventilation
- Arrhythmias

LV, Left ventricular; *RV,* right ventricular.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

DIAGNOSIS

Cardiac tamponade is a clinical diagnosis made at the bedside using patient history and physical examination. The echocardiogram can help confirm or reject the clinical diagnosis. Tamponade can be confirmed invasively by the measurement of elevated intrapericardial pressures with an intrapericardial catheter and right heart catheterization. Typical findings are diastolic equalization of pressures, usually ranging from 10 to 30 mm Hg (diastolic pulmonary artery pressure = right ventricular diastolic pressure = right atrial pressure = intrapericardial pressure), and lowering of the intrapericardial pressure with fluid drainage. Thereafter, the underlying etiology must be determined with specific laboratory work (see "Laboratory Tests").

DIFFERENTIAL DIAGNOSIS

Other conditions that can also lead to elevated jugular venous pressure, decreased systemic pressure, and pulsus paradoxus include:

- Chronic obstructive pulmonary disease and asthma exacerbations
- Constrictive pericarditis (Table 1)
- Effusive-constrictive pericarditis
- Restrictive cardiomyopathy
- Right ventricular infarction
- Pulmonary embolism
- Chronic biventricular heart failure

LABORATORY TESTS

- Electrolytes, blood urea nitrogen, creatinine, erythrocyte sedimentation rate, thyroid function tests, antinuclear antibody, rheumatoid factor, PPD, blood cultures, viral titers, and pericardial fluid analysis including cytology and cultures
- Possible 12-lead ECG findings:
  1. Sinus tachycardia
  2. PR depression and/or diffuse ST elevations if acute pericarditis is present
  3. Electrical alternans (beat to beat alternations in the QRS complex heights) (Fig. E1)
  4. Low QRS voltage in patients with a pericardial effusion may be a specific manifestation of cardiac tamponade, not of the effusion (QRS complex <0.5 mV in the limb leads and <1.0 mV in precordial leads)

IMAGING STUDIES

- Chest radiograph (enlarged cardiac silhouette with clear lung fields) (Fig. 2)
- Chest CT (may overestimate size of the effusion) (Fig. 3)
- Cardiac MRI (as an adjunct to echocardiography)
- Echocardiogram findings (Fig. 4):
  1. Pericardial effusion
  2. Right atrial inversion for greater than one third of systole has a sensitivity of 94% and a specificity of 100% for the diagnosis of tamponade
  3. Diastolic collapse of the right ventricle (early diastole) is pathognomonic and very specific
  4. >25% mitral and >50% tricuspid valve inflow variation on the first beat of inspiration and expiration, respectively
  5. Plethoric inferior vena cava (IVC dilation and <50% decrease in the diameter of the IVC during inspiration)
  6. Left atrial collapse (high specificity)
- Cardiac catheterization as discussed earlier will see equalization of intracardiac diastolic pressures and increase of right-sided pressures and reduction of left-sided pressures, which subsequently causes pulsus paradoxus (the pathognomonic finding on physical examination)

TABLE 1 Hemodynamics in Cardiac Tamponade and Constrictive Pericarditis

	Tamponade	Constriction
Paradoxical pulse	Usually present	Present in ~1/3
Equal left- and right-sided filling pressures	Present	Present
Systemic venous wave morphology	Absent *y* descent	Prominent *y* descent (M or W shape)
Inspiratory change in systemic venous pressure	Decrease (normal)	Increase or no change (Kussmaul sign)
"Square root" sign in ventricular pressure	Absent	Present

From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, WB Saunders.

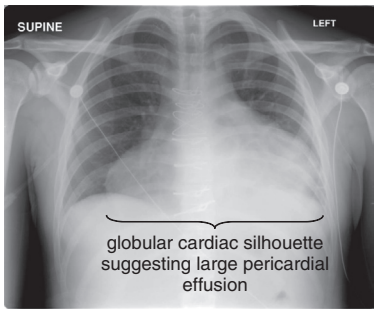

FIG. 2 Massive pericardial effusion and tamponade. This 23-yr-old male has a history of aortic valve replacement for infective endocarditis. He presented with increased chest pain and dyspnea. His chest x-ray shows a globular cardiac silhouette, suggesting a large pericardial effusion. The lung fields and right costophrenic angle appear clear, although the left costophrenic angle is hidden behind the heart and cannot be assessed. The patient underwent chest computed tomography to evaluate his aorta, as he complained of severe interscapular pain as well (see Fig. 3). (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, WB Saunders.)

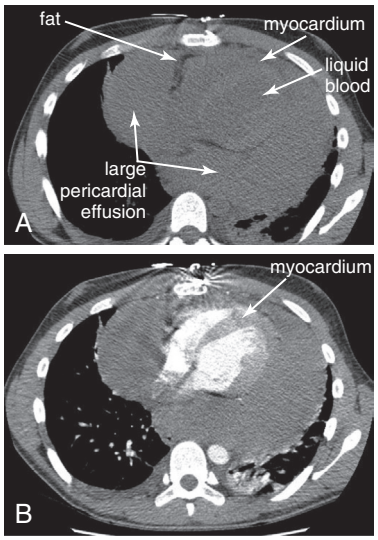

FIG. 3 Massive pericardial effusion. Same patient as Fig. 2. The patient underwent chest computed tomography (CT) without **(A)** and then with **(B)** intravenous contrast to evaluate his aorta, which was normal. However, the CT confirmed a massive pericardial effusion surrounding a normal-appearing heart. Without contrast, note that fluid blood within the chambers of the heart has a slightly lower density than the pericardial effusion, which has a density more similar to that of myocardium. When contrast is administered, the ventricular chambers fill completely, and the myocardium enhances and becomes somewhat brighter than the surrounding pericardial effusion. The heart itself is outlined by a thin stripe of fat, which appears nearly black on soft tissue windows. The patient developed hypotension, suggesting cardiac tamponade, and pericardial window was performed for drainage of the effusion. In the operating room, the effusion was found to be coagulated blood. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, WB Saunders.)

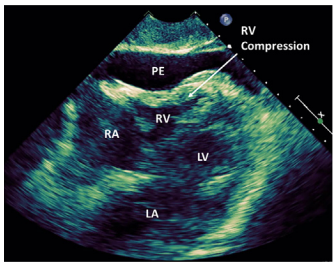

FIG. 4 Cardiac tamponade on echocardiography. Echo shows large pericardial effusion which is compressing the right ventricle. *LA,* Left atrium; *LV,* left ventricle; *PE,* pericardial effusion; *RA,* right atrium; *RV,* right ventricle. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Cardiac tamponade should be treated emergently with removal of the pericardial fluid (Fig. E5).
- Avoid drugs that reduce preload (e.g., nitrates, diuretics).
- Large pericardial effusions (>20 mm) without hemodynamic compromise (tamponade) can be managed conservatively with careful monitoring, IV fluids, treatment of the underlying cause, clinical follow-up, and frequent serial surveillance echocardiography.

ACUTE GENERAL Rx

- Aggressive intravascular volume expansion (saline or blood)
- Emergency pericardial fluid removal by pericardiocentesis or surgical pericardiotomy by way of the subxiphoid pericardial window
- Pericardiocentesis should be performed under echocardiographic and fluoroscopic guidance when available
- Pericardiocentesis is an absolute contraindication if the etiology of the pericardial effusion is aortic dissection, wherein emergent surgical management is indicated
- Inotropic or vasopressor support if above measures cannot be performed immediately

CHRONIC Rx

- Depends on etiology. Patients with inflammatory causes of pericarditis leading to effusion should be treated with antiinflammatory therapy (NSAIDs) for an extended 3-mo course of colchicine
- Pericardiocentesis with draining catheter: The catheter can be left inside the pericardium to allow continued drainage for 24 to 48 hr. If residual fluid still persists with hemodynamic compromise, surgical drainage should be considered. In the absence of significant residual fluid (output <50 ml in 24-hr period), discontinuation of the draining catheter can be done with periodic postprocedure echocardiographic monitoring for reaccumulation (e.g., 24 hr, 7 days, 30 days, 3 mo, 6 mo, 12 mo) depending on the etiology and the rate of reaccumulation
- Other surgical drainage procedures include:
  1. Subxiphoid pericardiotomy drainage
  2. Pericardial window; draining the pericardial fluid into the left hemithorax
  3. Limited pericardiectomy
  4. Complete pericardiectomy, especially in patients with effusive-constrictive pericarditis, bacterial pericarditis, or tuberculous pericarditis (See "Pearls & Considerations")

DISPOSITION

The prognosis of cardiac tamponade depends on the underlying cause.

REFERRAL

- Emergent cardiology consultation along with thorough echocardiographic exam should be made if cardiac tamponade is suspected.
- Cardiothoracic surgery or interventional cardiology consultation should also be considered if pericardial drainage is indicated.

PEARLS & CONSIDERATIONS

- Cardiac tamponade should always be considered during pulseless electrical activity arrest and may require emergent pericardiocentesis at the bedside.
- Evaluation for pulsus paradoxus should always be performed during normal respiration because deep inspiration may render a false-positive finding.
- Strong consideration should be given to performing early pericardiocentesis in patients who have pericardial effusion associated with bacterial pneumonia or empyema because the incidence of bacterial pericarditis is especially high in this clinical situation and the subsequent development of cardiac tamponade and severe chronic constrictive pericarditis are ominous complications.
- Pericardiocentesis is an absolute contraindication if the etiology of the pericardial effusion is due to aortic dissection extending into the pericardial sac.
- As little as 100 ml of fluid can lead to acute cardiac tamponade if the rate of accumulation is rapid, whereas with gradual accumulation, the pericardial sac can hold up to 5 L of fluid before tamponade occurs.
- With effusions that are small, organized, and/or loculated, needle aspiration should generally be avoided. An exception is acute cardiac tamponade complicating a cardiac procedure (e.g., percutaneous coronary intervention) with anticoagulation. In this setting, the effusion is often small, but pericardial pressure rises very quickly, resulting in hemodynamic compromise.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Cardiac Tamponade (Patient Information)
Pericarditis (Related Key Topic)

AUTHORS: **Vrinda Trivedi, MBBS,** and **Aravind Rao Kokkirala, MD, FACC**

SUGGESTED READINGS

Klein AL et al: American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease: endorsed by the Society for Cardiovascular Magnetic Resonance and Society of Cardiovascular Computed Tomography, *JASE* 26(9):965, 2013.

Weaver LK et al: False positive rate of carbon monoxide saturation by pulse oximetry of emergency department patients, *Respir Care* 58(2):232-240, 2013.

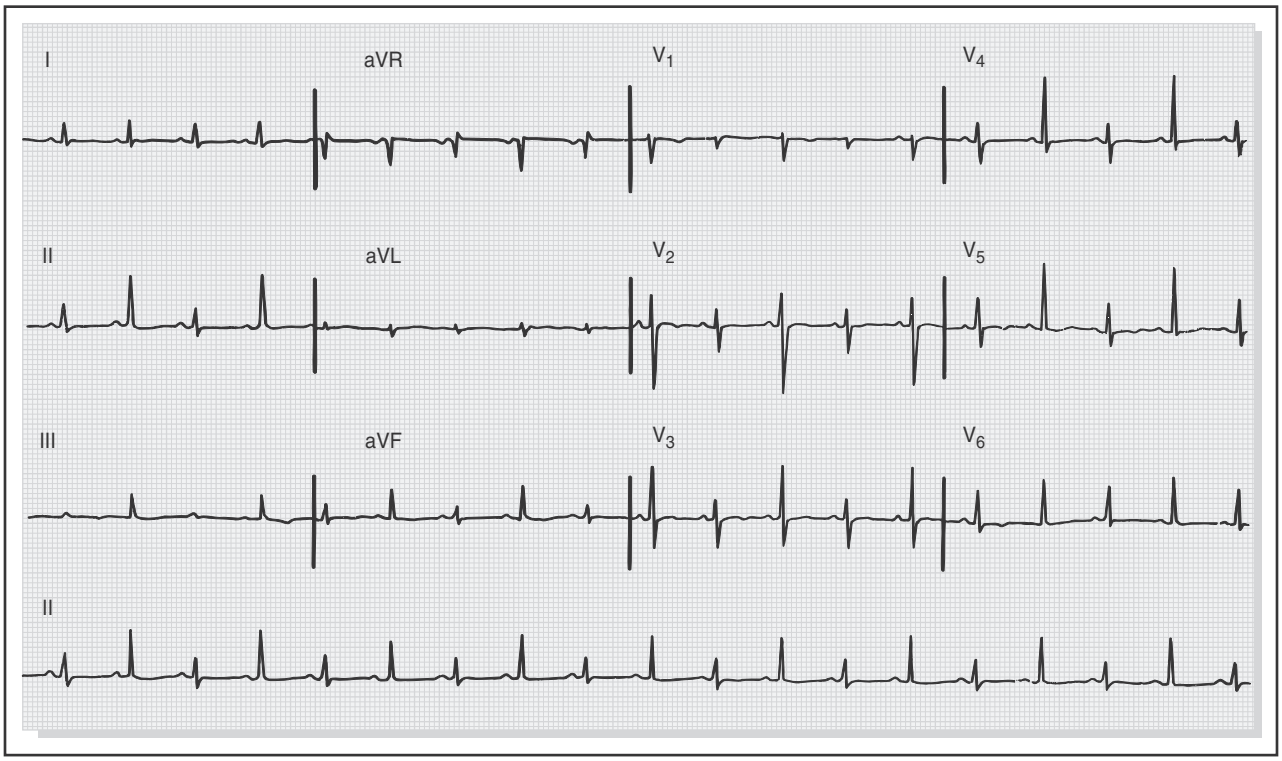

FIG. E1 Total electrical alternans (P-QRS-T) caused by pericardial effusion with tamponade. This finding, particularly in concert with sinus tachycardia and relatively low voltage, is a highly specific, although not sensitive, marker of cardiac tamponade. *aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right. (From Bonow RO: *Heart disease,* ed 9, Philadelphia, 2012, WB Saunders.)

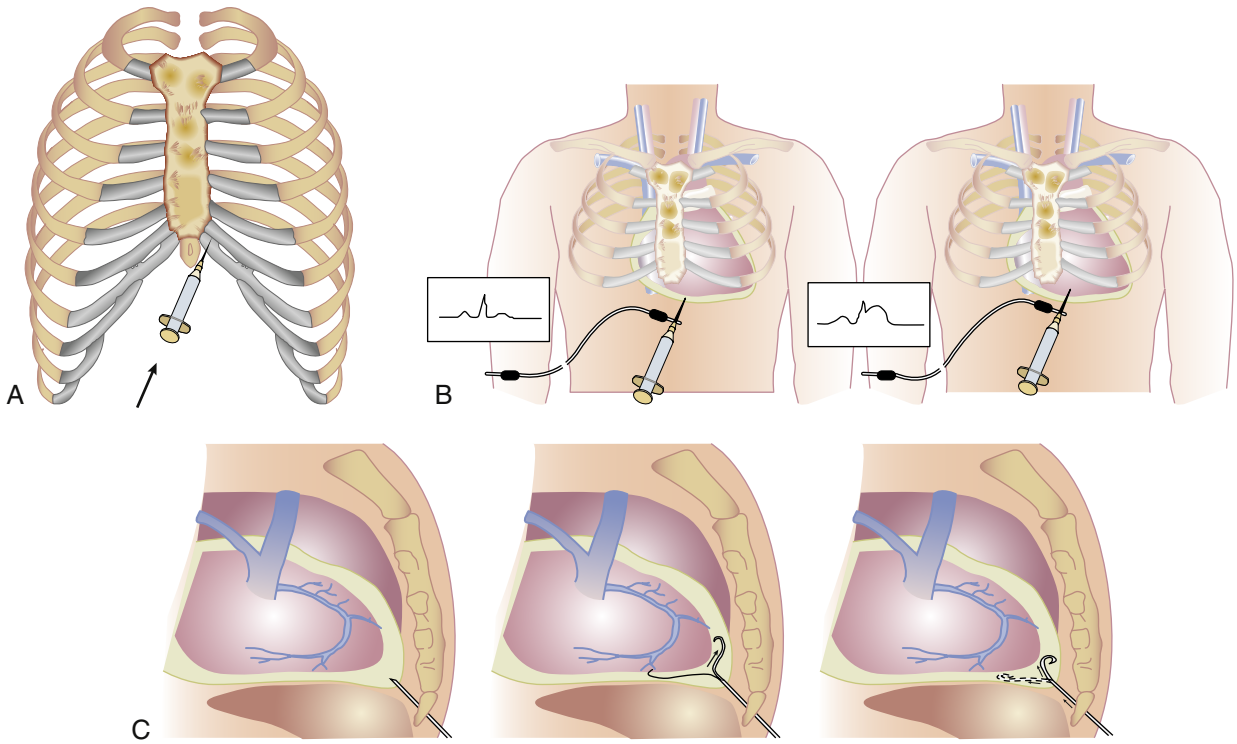

FIG. E5 Diagrammatic representation of a pericardiocentesis procedure via subxiphoid approach. **A,** A subxiphoid approach is used. **B,** A pericardial needle is connected to an electrocardiogram (ECG) lead and is advanced left, lateral to the subxiphoid area, aiming toward the left shoulder. ST-segment elevation is seen on the ECG lead tracing when the needle touches the epicardium. The needle should be retracted slightly until the ST-segment elevation disappears. **C,** After the pericardial space is entered with the pericardial needle, a guidewire is introduced in the pericardial space through the needle. The needle is removed, and a catheter is inserted in the pericardial sac over the guidewire (either anteriorly or inferiorly in the pericardial sac). (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

Cardiomyopathy, Chemical-Induced

BASIC INFORMATION

DEFINITION

Cardiomyopathy, chemical-induced (CMc), is a change in myocardial structure and/or function caused by chemical compounds. Many chemicals, including environmental toxins prescription drugs, and illicit drugs, are associated with cardiomyopathy (CM). These include (but are not limited to) alcohol, cocaine, amphetamines, chloroquine, anabolic steroids, anthracyclines, 5-fluorouracil (5-FU), zidovudine, tyrosine kinase inhibitors, and trastuzumab.

SYNONYMS

Alcoholic cardiomyopathy (ACM)
Cocaine-induced CM
Anabolic steroid-induced CM
Anthracycline-induced CM
Chemotherapy-induced CM
CMc

ICD-10CM CODE
I42.7 Cardiomyopathy due to drug and external agent

EPIDEMIOLOGY & DEMOGRAPHICS

- ACM occurs in about 5% to 10% of alcoholics and accounts for 21% to 36% of dilated cardiomyopathy in high-income countries. Most patients in whom alcoholic cardiomyopathy develops have been drinking more than 80 to 90 g of ethanol per day for more than 5 yr. A key factor for diagnosing ACM is a history of heavy alcohol consumption in the absence of coronary artery disease.
- The risk of doxorubicin-induced cardiotoxicity is dose dependent: 3% to 5% with 400 mg/m^2, 7% to 26% at 550 mg/m^{22}, and 18% to 48% at 700 mg/m^2.
- The addition of trastuzumab to an anthracycline-based chemotherapy regimen markedly increases the incidence of heart failure (28% vs. 1.7% to 21% with trastuzumab alone). The incidence can be significantly reduced by introducing a drug-free interval between the agents. Long-term follow-up data regarding trastuzumab cardiotoxicity are favorable, as the cardiotoxic effects generally manifest during treatment and are reversible.
- Other chemotherapeutic agents known to cause cardiomyopathy include idarubicin (>90 mg/m^2, 5% to 18%), epirubicin (>900 mg/m^2, 0.9% to 11.4%), docetaxel (2.3% to 13%), cyclophosphamide (7% to 28%), bortezomib (2% to 5%), sunitinib (2.7% to 19%), 5-fluorouracil [5-FU] (6% to 7%), and carfilzomib (11% to 25%). Table 1 summarizes chemotherapeutic agents implicated in clinical syndromes of cardiotoxicity.

PREDOMINANT SEX AND AGE: The prevalence of ACM appears to be similar among alcoholic men and women, with women developing left ventricular (LV) dysfunction at a lower ethanol dose than men. Significant racial differences exist, with blacks having higher mortality rates than non-Hispanic whites. Anthracycline- and trastuzumab-induced cardiomyopathy is more common in those aged >50 yr.

RISK FACTORS:

- Consumption of more than 80 to 100 g/day of alcohol for more than 10 yr significantly increases the risk of ACM.
- The occurrence of chronic anthracycline-induced CM is correlated to cumulative dose, age, preexisting heart disease, concomitant chemotherapy, and history of mediastinal radiation therapy. Children are more susceptible to anthracycline-induced CM.
- Additional risk factors for anthracycline-induced CM include radiation therapy involving the cardiac silhouette as well as use of trastuzumab.
- Infusional dosing may reduce the risk for cardiotoxicity compared to bolus regimens.

GENETICS:

- In patients with ACM, the deletion (DD) genotype of angiotensin-converting-enzyme (ACE) is more common than insertion (II) and deletion, insertion (DI) genotypes. The underlying mechanism involves direct toxicity of ethanol to the myocardium through uncoupling of adenosine triphosphate.
- Anthracycline-induced CM is linked to an increase in cardiac oxidative stress via the pathways of mitochondrial nitric oxide synthesis, and nicotinamide adenine dinucleotide phosphate reduction.
- One study suggests that polymorphisms in the carbonyl reductase genes could be related to anthracycline-induced CM.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The majority of clinical characteristics of CMc are similar to dilated cardiomyopathy of other etiologies. Symptoms may be insidious or acute in onset.

- Acute anthracycline-induced CM can start at any time after the first dose and may present with arrhythmias (most commonly supraventricular tachycardia), left ventricular (LV) dysfunction, or pericardial disease. Typically the first manifestation of anthracycline-induced cardiotoxicity is subtle diastolic dysfunction noted on tissue Doppler. The subacute and chronic symptoms may occur 3 mo to 10 yr after the last dose. Patients usually present with heart failure. More recently, mortality has improved as a result of medical therapy with ACE inhibitors and beta-blockers. In fact, recent trials, including the OVERCOME trial, have demonstrated a benefit in preemptively treating low-cardiac-risk patients undergoing anthracycline therapy with beta-blockers and ACE-inhibitors to prevent the development of CM.
- Cardiac symptoms after 5-FU treatment include angina (most common), myocardial infarction, arrhythmia, acute pulmonary edema, cardiac arrest, and pericarditis. The mechanism of angina and myocardial infarction is coronary vasospasm and endothelial injury. The overall incidence of angina is approximately 10%.
- ACM typically occurs after yr of heavy drinking. Concurrent cirrhosis may be present. The presentation is typically heart failure with or without arrhythmia. Atrial fibrillation is the most common arrhythmia associated with chronic alcohol abuse and can also be seen with acute intoxication (holiday heart syndrome).
- Patients with cocaine-induced CM may present with adrenergic symptoms (palpitations, pallor, diaphoresis, and anxiety), hypertension, angina, atrial and ventricular arrhythmias, and heart failure.
- Anabolic steroids can cause LV hypertrophy and dilation, and lead to heart failure, arrhythmia, myocardial infarction, hypertension, and sudden death.

ETIOLOGY

- The underlying mechanism of chemotherapy-induced cardiotoxicity is not well established. Several pathways have been proposed (Fig. 1), including an increase in oxidative stress, free radical production, apoptosis, disturbance of DNA, RNA and protein synthesis, and vasospasm.
- Nutritional deficiencies, such as thiamine deficiency, also play a role in ACM.
- Table 2 describes mechanisms of ethanol-induced myocardial injury. Table 3 summarizes the effects of light-to-moderate and heavier alcohol intake on cardiovascular risk factors and outcomes.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infectious cardiomyopathy: Viral, HIV related, Lyme disease, Chagas disease
- Ischemic cardiomyopathy
- Dilated cardiomyopathy, related to valvular disease or hypertension
- Cirrhotic cardiomyopathy
- Tachycardia-induced cardiomyopathy
- Stress-related (takotsubo) cardiomyopathy
- Peripartum cardiomyopathy
- Genetic causes of dilated cardiomyopathy

WORKUP

- Chemical exposure history
- Electrocardiogram, serum electrolytes, renal function, and hepatic function
- Serum troponin and brain natriuretic peptide (BNP) levels
- Transthoracic echocardiogram for the evaluation of heart structure and function
- Rule out the diagnosis of coronary artery disease by coronary angiography
- Cardiac magnetic resonance (CMR) imaging can be used to evaluate for myocardial scar and fibrosis

LABORATORY TESTS

- There are no specific diagnostic tests to help differentiate CMc from other forms of

TABLE 1 Chemotherapeutic Agents Implicated in Clinical Syndromes of Cardiotoxicity

Agent	Frequency of Cardiotoxicity*	Comments
Left Ventricular Dysfunction–Heart Failure		
Chemotherapeutics		
Anthracyclines		
Doxorubicin	+++	Highly dose-dependent
Epirubicin	+	Risk factors include age (old and young), prior mediastinal radiation, history of heart disease, decreased ejection fraction; drop in ejection fraction on drug therapy, female sex (for children), and other agents (especially trastuzumab)
Idarubicin	++	Risk decreased by liposomal encapsulation or dexrazoxane
Alkylating agents		
Cyclophosphamide	+++	Primarily seen with high-dose "conditioning" regimens
Ifosfamide	+++	Risk factors are previous mediastinal irradiation and anthracycline drug therapy Also can have myocarditis, pericarditis, myocardial necrosis
Taxanes		
Paclitaxel	+/++	Also employed in paclitaxel-eluting stent
Docetaxel	+	
Proteasome inhibitor		
Bortezomib	+/++	Moderately high rates of HF seen in trials (5%), but rates only minimally higher than in patients receiving dexamethasone
Targeted Therapeutics		
Monoclonal antibodies		
Trastuzumab	++	Not common as single agent Increased risk with anthracyclines, paclitaxel, cyclophosphamide
Pertuzumab	+/++	Targets HER2 Rates of LV dysfunction as high as ~25% in one series
Bevacizumab	+/++	Targets VEGF-A (ligand for VEGFRs) and serves as a trap, preventing interaction with its receptor HF can be seen in setting of severe hypertension, which occurs in 10%-25% of patients, depending on dose; anthracyclines may increase HF risk
Tyrosine kinase inhibitors		
Imatinib, nilotinib	+	Can cause severe fluid retention with peripheral edema, pleural and pericardial effusion not secondary to LV dysfunction
Dasatinib	++	Same as above regarding fluid retention Can cause severe pulmonary hypertension; mechanism unclear
Sunitinib	+++	LV dysfunction common; hypertension likely plays role
Sorafenib	++	Rate of cardiotoxicity not clear as of yet
Ischemic Syndromes		
Fluorouracil, capecitabine	++	ACS; patients with CAD at increased risk Recurs with rechallenge; multiple mechanisms proposed; etiology remains unknown
Cisplatin, carboplatin	+	ACS caused by vasospasm or vascular injury Hypertension common; thromboembolism more common (see below)
Interferon-α	+	Risk of ischemia increased in patients with CAD; hypertension common
Paclitaxel	+	Myocardial ischemia in 1%-5%; serious ischemic cardiac events not common
Docetaxel	+	Limited data, but rate probably ~1%
Bevacizumab	++	Arterial thrombotic events including MI and stroke
Vinca alkaloids	+	~1% risk of cardiac events; ischemia possibly caused by coronary spasm
Sorafenib	+/++	~2.5% risk of ACS
Erlotinib, nilotinib	+/++	Limited data, but rate ~2%; concern over possible increase in peripheral vascular events
Hypertension		
Cisplatin	++++	
Bevacizumab	++++	Extremely common with all anti-VEGF therapeutics to date
Sunitinib	++++	Intrinsic in mechanism of action of these agents
Sorafenib	+++	
Venous Thrombosis		
Cisplatin	+++	Deep vein thrombosis or pulmonary embolism in 8.5%; most occur early in treatment Additional risk factors for deep vein thrombosis often present
Thalidomide	++++	Uncommon with monotherapy, but risk rises with concurrent chemotherapy
Lenalidomide	+++	See comments for thalidomide
Erlotinib	++	Rate with erlotinib plus gemcitabine ~2% over that with gemcitabine alone

ACS, Acute coronary syndrome; *CAD,* coronary artery disease; *HER2,* human epidermal growth factor receptor 2; *HF,* heart failure; *LV,* left ventricular; *MI,* myocardial infarction; *VEGF,* vascular endothelial cell growth factor; *VEGFR,* vascular endothelial cell growth factor receptor.

*Relative frequency of cardiotoxicity is scored as follows: + = ≤1%; ++ = 1% to 5%; +++ = 6% to 10%; ++++ = >10%.

From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

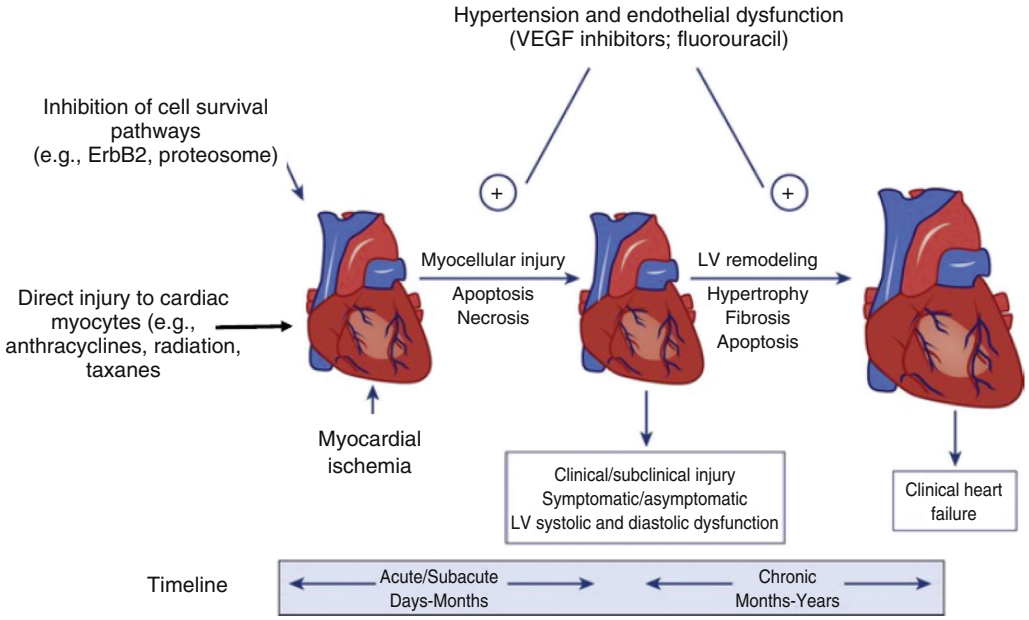

FIG. 1 Pathophysiology of chemotherapy-induced cardiotoxicity. The specific mechanisms and clinical manifestations of cardiac injury may vary according to each chemotherapy class, but the final common pathway linking the initial injury to acute, subacute, and chronic manifestations are often overlapping. Acute and subacute injury are often asymptomatic and may or may not be associated with a measurable change in ejection fraction. Chronic cardiac injury usually is associated with left ventricular *(LV)* remodeling characterized by LV enlargement, reduced ejection fraction, and eventually symptomatic heart failure. Hypertension associated with inhibitors of the vascular endothelial growth factor *(VEGF)* signaling pathway can exacerbate myocardial injury and cardiac disease progression in the acute, subacute, and chronic settings. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

TABLE 2 Mechanisms of Ethanol-Induced Myocardial Injury

Direct Toxic Effects
Uncoupling of the excitation/contraction system
Reduced calcium sequestration in the sarcoplasmic reticulum
Inhibition of the sarcolemmal adenosine triphosphate–dependent Na^+/K^+ pump
Reduction in the mitochondrial respiratory ratio
Altered substrate uptake
Increased interstitial/extracellular protein synthesis
Toxic Effect of Metabolites
Acetaldehyde
Ethyl esters
Nutritional or Trace Metal Deficiencies
Thiamine
Selenium
Electrolyte Disturbances
Hypomagnesemia
Hypokalemia
Hypophosphatemia
Toxic Additives
Cobalt
Lead
Arsenic

K, Potassium; *Na,* sodium.
From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

CM, but the following laboratory tests are generally helpful; serum electrolytes, renal function, hepatic function, thyroid-stimulating hormone, iron profile, and inflammatory markers.

- Recent studies have suggested that early elevation of troponin levels, BNP, and myeloperoxidase following chemotherapy may be a predictor of future development of cardiomyopathy.

IMAGING STUDIES

- ECG
- Nonspecific findings of a cardiomyopathy may be present, including sinus tachycardia, nonspecific ST-T wave changes, decreased QRS voltage, interventricular conduction delay or bundle branch block, and QT interval abnormalities. In 5-FU toxicity, significant ST segment deviations may present.
- Echocardiogram
  1. Asymptomatic alcoholics may present with mild LV hypertrophy, diastolic dysfunction, LV dilation, and decrease in left ventricular ejection fraction (LVEF).
  2. Baseline LVEF should be performed before initiation of anthracycline-based chemotherapy, preferably with an echocardiogram or multigated acquisition (MUGA) scan.
     a. Anthracycline-based chemotherapy should generally be avoided for patients with an LVEF ≤40, or LVEF >40 but <50 with prior heart failure.
     b. Total doxorubicin dose should be limited to 450 mg/m^2.
     c. If baseline LVEF is ≥55%, then subsequent evaluation should be at the end of treatment if the doxorubicin dose is <200 mg/m^2 or serially at 200, 300, 350, and 400 mg/m^2 for higher doses. Doxorubicin therapy should be discontinued if there is a >15% absolute drop in LVEF, decease

TABLE 3 Qualitative Effects of Light-to-Moderate and Heavier Alcohol Intake on Cardiovascular Risk Factors and Outcomes

Cardiovascular Risk Factors and Outcomes	Light-to-Moderate Alcohol Intake (<2 Drinks per Day)	Heavier Alcohol Intake (>2 Drinks per Day)
Blood pressure	↔	↑↑
HDL cholesterol	↑↑	↑↑↑
Triglycerides	↑	↑↑
LDL cholesterol	↔ or ↓	↑
Platelet aggregability/coagulability	↓	↓↓
Systemic inflammation	↓	↑
Congestive heart failure	↓	↑↑
Coronary artery disease (angina, nonfatal MI)	↓↓	↓
Atrial fibrillation	↔	↑↑
Stroke	↓	↑↑
Sudden cardiac death	↓↓	↑

HDL, High-density lipoprotein; *LDL*, low-density lipoprotein; *MI*, myocardial infarction.
From Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.

in LVEF to ≤40%, or symptomatic congestive heart failure with an LVEF <50. There has been no direct causal link between anthracyclines and the development of heart failure with a preserved ejection fraction.

d. Peak systolic global longitudinal strain imaging (GLS) is an emerging echocardiographic measurement. A 10% to 15% early decrease in GLS by speckle tracking echocardiography during treatment seems to be the most useful parameter for the early detection of cardiotoxicity. Echocardiographic strain and strain rate imaging are sensitive, noninvasive methods for assessment of myocardial function.

- Radionuclide imaging (Fig. E2).
  1. If baseline LVEF is <50% with no prior history of heart failure, the cardiac risks vs. oncological benefits should be discussed with the patient, cardiologist, and oncologist before initiating therapy. Optimization of cardiovascular status, including hypertension control, is recommended. Cardio-protective agents such as ACE inhibitors and beta-blockers should be initiated and serial LVEF measurements done after each dose.
  2. Even after chemotherapy, periodic screening with echocardiography and/or biomarkers should be considered for up to 10 yr for those with high cumulative anthracycline doses or a history of reversible LV dysfunction during treatment.

Rx TREATMENT

ACUTE GENERAL Rx

- Treat decompensated heart failure with diuresis and inotropes if there is a low cardiac output state.
- For angina in acute cocaine intoxication or induced by 5-FU, benzodiazepines, nitrites, and calcium channel blockers are first-line therapy. If ECG provides evidence of acute myocardial infarction, patients should proceed to emergent cardiac catheterization and coronary angiography.

CHRONIC Rx

- Dexrazoxane is an ethylenediaminetetraacetic acid-like chelator that acts by binding to iron, which prevents anthracycline cardiotoxicity. Cardiooncology experts suggest a 10:1 ratio of dexrazoxane to anthracycline, given 15 to 30 min before doxorubicin administration. However, its routine use is not currently recommended in adults except in cases of a cumulative doxorubicin dose of 300 mg/m^2 or greater with an ongoing indication to receive doxorubicin-based chemotherapy.
- Those developing anthracycline-induced CM generally should not be rechallenged with the drug, as the cardiac damage is usually irreversible due to cell death.
- Beta-blocker: Carvedilol and nebivolol have been shown to have protective effects on LV systolic function during anthracycline therapy. Larger trials with metoprolol have shown no benefit.
- The following ACE inhibitors and angiotensin receptor blocker (ARB) have been shown to protect against anthracycline cardiotoxicity: Enalapril, ramipril, and telmisartan. Results from the PRADA trial suggest that use of the ARB candesartan mitigates anthracycline-induced decline in LVEF.
- There is growing interest in the use of statins for primary prevention of anthracycline-mediated cardiotoxicity based on their antioxidant and anti-inflammatory properties, although a cardioprotective effect has not been established.
- Thiamine, folic acid, and multivitamins are adjunctive treatments for ACM. Abstinence can usually reverse the cardiomyopathy.

DISPOSITION

Prognosis depends on the dosage of chemicals and the severity of LV dysfunction.

REFERRAL

Close follow-up with a cardiooncologist.

PEARLS & CONSIDERATIONS

The presentation of chemotherapy-induced cardiac toxicity ranges from an asymptomatic decline in LVEF to overt heart failure. The incidence is dose-dependent in the case of anthracyclines and may manifest up to 10 yr after the initial exposure. Therefore, regular clinical follow-up with echocardiographic surveillance is advised.

PREVENTION

- Noninvasive assessment of LV function before, during, and after anthracycline-containing chemotherapy with echocardiography or MUGA scan.
- To reduce the risk of doxorubicin cardiotoxicity, the lifetime cumulative dosage should be limited to <450 mg/m^2 in adults.
- Other approaches include the use of infusion rather than bolus dosing, liposomal encapsulated doxorubicin, less cardiotoxic analogs of doxorubicin such as epirubicin, and co-administration of protective agents such as dexrazoxane.
- 5-FU treatment should be terminated if cardiac symptoms develop. Readministration is not recommended.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Vrinda Trivedi, MBBS,** and **Aravind Rao Kokkirala, MD, FACC**

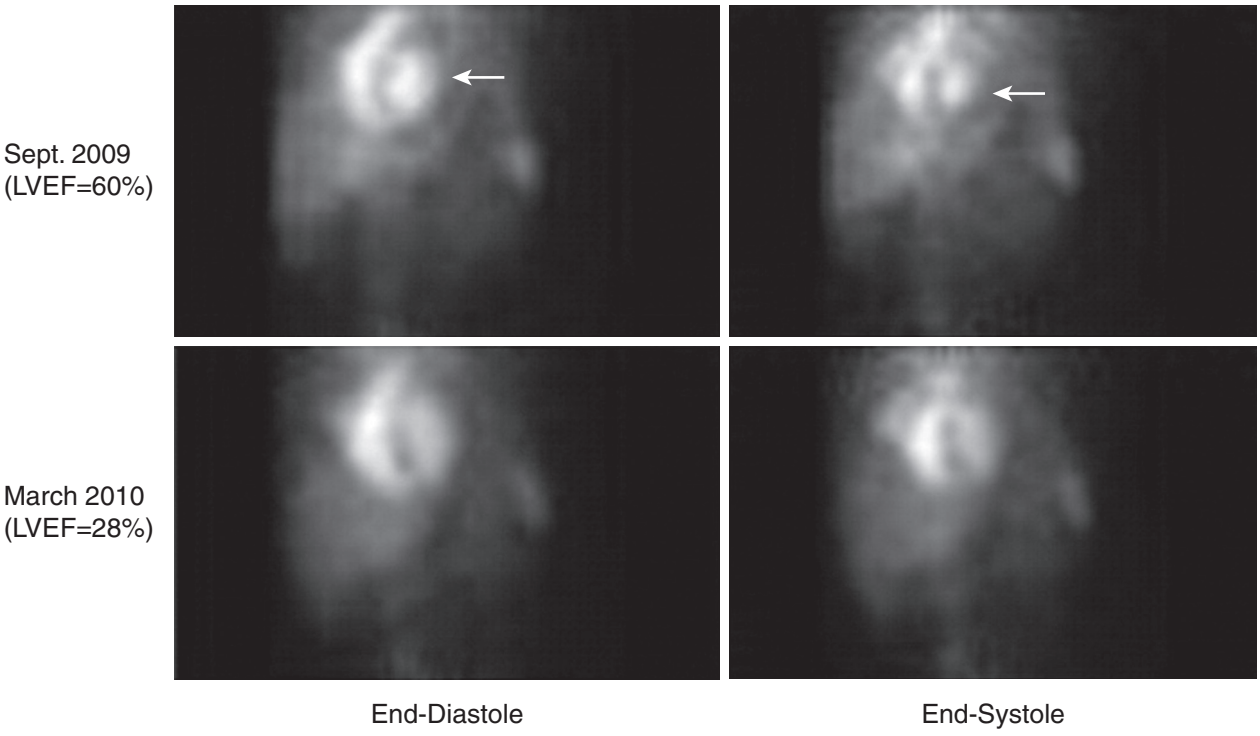

FIG. E2 Technetium-99m-pertechnetate multigated acquisition scans in a 47-year-old woman with breast cancer treated with doxorubicin. The top scan was taken before initiation of doxorubicin and cyclophosphamide therapy in September 2009. The left ventricular ejection fraction *(LVEF)* (left ventricular end-diastolic counts minus left ventricular end-systolic counts/left ventricular end-diastolic counts 100) was calculated at 60%. The bottom scan was taken in March 2010 after treatment with a total doxorubicin dose of 451 mg/m^2. Left ventricular ejection fraction was calculated at 28%. Left ventricle (*white arrows*) during end-diastole and end-systole. (From Figueredo VM: Chemical cardiomyopathies: the negative effects of medications and nonprescribed drugs on the heart, *Am J Med* 124:480-488, 2011.)

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Cardiomyopathy, Dilated PTG

BASIC INFORMATION

DEFINITION

Dilated cardiomyopathy (DCM) describes a group of diseases involving the myocardium and characterized by dilation and impaired contraction of one or both ventricles that is not wholly the result of hypertension, coronary atherosclerosis, valvular dysfunction, congenital, or other structural heart disease. As a result, the systolic function of the heart is impaired, and the patient may develop overt heart failure, atrial and/or ventricular arrhythmias, and sudden death. The disease is considered idiopathic if primary and secondary causes of heart disease are excluded.

SYNONYMS

Congestive cardiomyopathy
Idiopathic cardiomyopathy

ICD-10CM CODES

B33.24	Viral cardiomyopathy
I11.0	Hypertensive heart disease with heart failure
I42.0	Dilated cardiomyopathy (includes congestive cardiomyopathy)
I42.9	Cardiomyopathy, unspecified (includes cardiomyopathy [primary] [secondary] NOS)
I43	Cardiomyopathy in diseases classified elsewhere
I50.20 to I50.9	(Unspecified, acute, chronic, or acute on chronic) + (systolic, diastolic, or combined) (congestive) heart failure
O90.3	Peripartum cardiomyopathy

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: DCM is the most common form of cardiomyopathy, comprising approximately 60% of all cases.

PREVALENCE: The estimated age-adjusted prevalence of DCM in the U.S. in general is approximately 36 per 100,000 or 1:2500. The incidence is approximately 5 to 8 per 100,000 persons per yr.

PREDOMINANT AGE: Although DCM can occur at any age, the incidence is greatest in the third and fourth decades of life in men.

GENETICS: African Americans have a three-fold increased risk for developing DCM, irrespective of comorbidities or socioeconomic factors, compared with whites.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Affected patients may present in a number of ways and the etiology most often is elucidated by obtaining a focused history. The patient may display common symptoms of congestive heart failure, which may be of insidious or sudden onset. The patient may also be asymptomatic and the diagnosis made by the incidental finding of cardiomegaly on a chest x-ray. Classical signs of heart failure may be absent. When present, findings are indistinguishable from other heart failure syndromes, including:

- Increased jugular venous pressure
- Narrow pulse pressure
- Pulmonary rales, hepatomegaly, peripheral edema
- S3, S4
- Mitral regurgitation, tricuspid regurgitation (less common)

ETIOLOGY

DCM can be attributed to genetic and nongenetic causes, including hypertension, valve disease, inflammatory/infectious processes, and toxins.

- Idiopathic (often a viral infection that cannot be confirmed)
- Infections (viral [human herpesvirus 6, influenza, echovirus, cytomegalovirus, Coxsackie B, adenovirus, parvovirus, HIV], rickettsial, mycobacterial, toxoplasmosis, trichinosis, Chagas disease)
- Ischemic heart disease
- Alcoholism (15% to 40% of all cases in Western countries)
- Uncontrolled tachyarrhythmia ("tachycardia-mediated")
- Sleep apnea–obstructive or nonobstructive
- Cirrhotic (not necessarily alcohol-induced)
- End-stage renal disease–related
- Nutritional deficiencies (selenium, L-carnitine, thiamine)
- Peripartum (greatest risk from last trimester of pregnancy to 6 mo postpartum)
- Chemotherapeutic (anthracycline, doxorubicin, daunorubicin) or pharmacologic agents (antiretrovirals, phenothiazines) (see "Cardiomyopathy, Chemical-Induced")
- Substance abuse (cocaine, heroin, organic solvents, "glue-sniffer's heart")
- Postmyocarditis
- Toxins (cobalt, lead, phosphorus, carbon monoxide, mercury) Collagen-vascular disease (systemic lupus, rheumatoid arthritis, polyarteritis, dermatomyositis, sarcoidosis)
- Hereditary familial neuromuscular disorders (e.g., muscular dystrophy, myotonic dystrophy)
- Endocrine dysfunction (acromegaly, osteogenesis imperfecta, myxedema, thyrotoxicosis, diabetes)
- Hematologic (e.g., sickle cell anemia, hereditary sideroblastic anemias and thalassemias, hypereosinophilia, hereditary hemochromatosis)
- Stress-induced (i.e., takotsubo or broken heart syndrome)
- Left ventricular (LV) noncompaction
- Autoimmunity ("anti-heart antibodies" [AHAs; beta-1 adrenoceptor, alpha-myosin heavy chain, beta-myosin heavy chain, myosin light chain] are hypothesized to cause DCM based on animal studies) appears to be applicable to humans, as AHAs can be detected in 38% of patients with an idiopathic DCM
- *TTN* truncating mutations (mutations in *TTN*, the gene encoding the sarcomere protein titin) are a common cause of DCM, occurring in approximately 25% of familial cases of idiopathic DCM and in 18% of sporadic cases

DIAGNOSIS

DCM is a diagnosis of exclusion, made after ruling out other potential causes of myocardial dysfunction.

DIFFERENTIAL DIAGNOSIS

- Coronary atherosclerosis, that is, left ventricular dysfunction secondary to ischemia and/or myocardial infarction
- Valvular dysfunction (especially aortic and mitral regurgitation)
- Other cardiomyopathies (restrictive, hypertrophic)
- Pulmonary disease (embolism, obstructive, restrictive)
- Pericardial abnormalities (constrictive pericarditis, tamponade)
- Hypothyroidism/myxedema
- Athlete heart

WORKUP

- Medical history: Emphasis on symptoms of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, weight gain, palpitations, fatigue, or signs of systemic and pulmonary embolism, substance abuse history, possible toxin exposures (especially occupational)
- Physical exam (see "Physical Findings & Clinical Presentation")
- Testing (see "Laboratory Tests" and "Imaging Studies" for more detail): Laboratory, chest x-ray, ECG, echocardiogram, cardiac catheterization; myocardial biopsy is not routinely recommended, unless acute myocarditis requiring immunosuppressive therapy is considered (e.g., giant cell myocarditis)

LABORATORY TESTS

- Chemistries/metabolites (deficiencies), renal function tests (renal dysfunction)
- Cardiac biomarkers (elevation of cardiac troponin or brain natriuretic peptide)
  1. Persistently increased cardiac troponin T levels are a marker of poor outcome in cardiomyopathy patients
- Endocrine (particularly thyroid)
- Iron studies (hemochromatosis, deficiency)
- Rheumatologic and inflammatory (antinuclear antibody, erythrocyte sedimentation rate, and C-reactive protein tests)
- Others as indicated (HIV, Lyme, neurohormonal)

IMAGING STUDIES

Chest x-ray:

- Cardiac silhouette enlargement (particularly left ventricle)
- Pulmonary vascular redistribution and congestion (Kerley B lines, cephalization of vasculature), pleural effusion (may appear as unilateral, most often on the right side)

ECG:

- ECG findings are typically nonspecific, and sinus tachycardia is usually a reflection of underlying heart failure. Large voltage in precordial leads and low voltage in limb leads may be seen in advanced disease
- Intraventricular conduction defects and left bundle branch block

- Arrhythmias (atrial fibrillation, premature ventricular or atrial contractions, ventricular tachycardia)

Echocardiogram (Fig. 1):

- Low ejection fraction with global hypokinesis
- Four-chamber enlargement (LV enlargement usually predominates)
- Mitral or tricuspid regurgitation ("secondary" regurgitation from tethering due to incomplete leaflet closure caused by ventricular dilation)

Cardiac catheterization:

- On initial presentation to exclude obstructive epicardial coronary artery disease

Cardiac magnetic resonance imaging (CMRI):

- Particularly if infiltrative or inflammatory etiology suspected

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Treatment of underlying disease (systemic lupus, alcoholism)
- Dietary sodium restriction (<2 g/day)
- Exercise training has been shown to be associated with reduced risk for hospitalization and death in patients with history of heart failure in limited trials; enrollment in a formal cardiac rehabilitation program may be beneficial in improving patient's functional status

ACUTE GENERAL Rx

- Identify and treat the etiology of the acute exacerbation, when able. A helpful mnemonic is FAILURE: **F**ailure to take medications, **a**nemia/**a**rrhythmia, **i**schemia/**i**nfection/**i**nfarction, **l**ifestyle (dietary indiscretion), **u**pregulation of cardiac output (hyperthyroidism or pregnancy), **r**enal failure, **e**mbolus (pulmonary).
- Diuretics are indicated for all patients with current symptoms or history of heart failure and reduced left ventricular ejection fraction (LVEF) with evidence of volume overload (see "Physical Findings & Clinical Presentation") to improve symptoms. It is important to note that diuretics have not been shown to improve mortality rates.
- Patients with associated coronary atherosclerosis (angina, ECG changes, reversible defects on myocardial perfusion imaging) may benefit from percutaneous or surgical revascularization.

CHRONIC Rx

- Diuretics as noted in "Acute General Rx."
- ACE inhibitors (and angiotensin receptor blockers) have been shown to have favorable effects on ventricular remodeling in patients with cardiomyopathy and a demonstrable mortality benefit in these patients. They also reduce afterload and improve cardiac output. Recommended in all patients with reduced LV systolic function (ejection fraction [EF] ≤40%), regardless of symptoms unless specific contraindications exist.
- Beta-blockers work by inhibiting the adverse effects of the sympathetic nervous system in patients with ventricular systolic dysfunction (EF ≤40%). *Only* carvedilol, long-acting metoprolol succinate, and bisoprolol have shown a mortality benefit in patients with LV systolic dysfunction. Unless specifically contraindicated, they should be started after the acute exacerbation has resolved and titrated to the maximum tolerated dose.
- Aldosterone antagonists (spironolactone and eplerenone) have shown mortality benefit along with a decreased rate of hospitalization for heart failure in patients with symptomatic heart failure and reduced LV systolic function (EF ≤35%). They should be used following label guidelines and with close monitoring of renal function and potassium.
- Hydralazine/nitrates improve both morbidity and mortality, and should be considered in the following populations: African Americans with persistent New York Heart Association (NYHA) class III or IV heart failure with an EF <40%, on optimal medical therapy (beta-blocker and angiotensin-converting enzyme [ACE] or angiotensin II receptor blockers [ARB]); and those unable to take ACE inhibitors or ARBs due to intolerance, hypotension, or renal insufficiency.

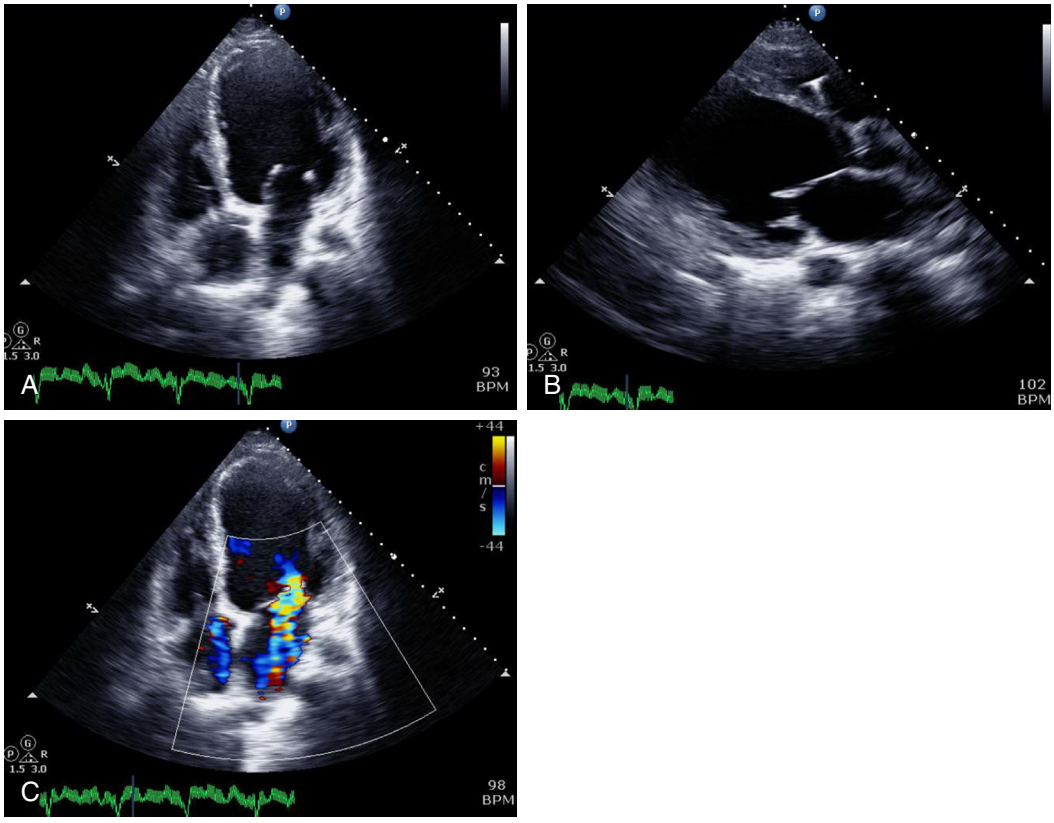

FIG. 1 2-Dimensional echocardiogram in a 37-year-old male with non-ischemic dilated cardiomyopathy showing a dilated, thinned left ventricle (LV). **A,** Apical four chamber. **B,** Parasternal long axis of the left ventricle. **C,** Mitral regurgitation ("secondary" regurgitation due to incomplete coaptation of the mitral valve leaflets). (Courtesy of J. Bell, MD.)

TABLE 1 Factors Associated with an Adverse Outcome in Dilated Cardiomyopathy

Clinical	Noninvasive	Invasive
NYHA Class III/IV	Low LV ejection fraction	High LV filling pressures
Increasing age	Marked LV dilation	
Low exercise peak oxygen consumption	Low LV mass	
Marked intraventricular conduction delay	≥Moderate mitral regurgitation	
Complex ventricular arrhythmias	Abnormal diastolic function	
Abnormal signal-averaged ECG	Abnormal contractile reserve	
Evidence of excessive sympathetic stimulation	Right ventricular dilation or dysfunction	
Protodiastolic gallop (S_3)		
Elevated serum BNP		
Elevated uric acid		
Decreased serum sodium		

BNP, Brain natriuretic peptide; *ECG,* electrocardiogram; *LV,* left ventricular; *NYHA,* New York Heart Association.
From Hare JM: The dilated, restrictive, and infiltrative cardiomyopathies. In Bonow RO et al (eds): *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 9, St Louis, 2011, Saunders.

- Digoxin is used for its positive inotropic effects in heart failure due to systolic dysfunction. It has no mortality benefit but has been shown to improve quality of life in appropriately selected patients.
- Angiotensin receptor-neprilysin inhibitor (ARNI), sacubitril-valsartan, approved in the U.S in 2015, was developed to block harmful effects of renin-angiotensin-aldosterone system (RAAS) activation while raising levels of endogenous vasoactive peptides degraded by neprilysin, such as natriuretic peptides, bradykinin, and adrenomedullin. Used in place of an ACE inhibitor or angiotensin receptor blocker and on top of optimal medical therapy in patients with class II-IV heart failure and an EF of 40% or less was found to significantly reduce multiple heart failure end points, including death, hospitalizations, and cardiovascular death in comparison to enalapril.
- Ivabradine was FDA approved in 2015 for patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤35% who are in sinus rhythm with resting heart rates ≥70 beats/min and either of the following: (1) Are on maximally tolerated doses of beta-blockers or (2) have a contraindication to beta-blocker use. It acts by blocking the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel responsible for the cardiac pacemaker I_f current, which regulates heart rate.

DISPOSITION

- Annual mortality rate is 20% in patients with moderate heart failure, and it exceeds 50% in patients with severe heart failure. Once symptomatic, hospitalizations are frequent and readmission rates are high (>50% at 3 mo). A multispecialty treatment approach (e.g., primary care, cardiology, nutrition, cardiac rehabilitation) is recommended.
- Factors associated with an adverse outcome in DCM are described in Table 1.

REFERRAL

- Implantation of a cardiac defibrillator for primary prevention of sudden cardiac death can be considered for patients with LVEF ≤35% and on optimal medical therapy regardless of symptom status.
- Patients with LVEF <35%, left bundle branch block on ECG (QRS ≥0.13 sec), and persistent heart failure symptoms may benefit from cardiac resynchronization therapy via a biventricular pacemaker.
- Consider heart transplantation for relatively young patients (there is no precise age threshold) free of other significant comorbid conditions who are unresponsive to medical therapy. DCM is the reason for 45% of all heart transplantations in the U.S.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients should be encouraged to restrict or eliminate alcohol and reduce sodium intake (<2 g daily).
- Patients may benefit from daily weight checks as a means of early detection of volume overload and decompensated heart failure.
- Vulnerability to cardiomyopathy among chronic alcohol abusers is partially genetic and related to the presence of the ACE DD genotype.
- Idiopathic DCM is often familial, and apparently healthy relatives may have latent, early, or undiagnosed disease. Echocardiographic evaluation of family members is recommended.
- Incorporation of sequencing approaches that detect *TTN* truncations into genetic testing for DCM may substantially increase test sensitivity and allow earlier diagnosis of DCM.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Dilated Cardiomyopathy (Patient Information)
Cardiomyopathy, Chemical-Induced (Related Key Topic)

AUTHORS: **Christopher P. Blomberg, DO,** and **Jennifer Bell, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Hypertrophic cardiomyopathy (HCM) is most commonly an autosomal dominant myocardial disorder characterized by disorganized myocyte architecture and marked thickening (hypertrophy) of the left ventricular wall (≥15 mm), without dilation, *not explained by another cardiac or systemic disorder*. The interventricular septum is the most common site of enlargement, though hypertrophy may involve other focal regions or may be concentric. HCM may result in hemodynamically significant obstruction within the left ventricular outflow tract (LVOT) and/or impairment of the diastolic function of the left ventricle. However, about one third of patients have no obstruction at rest or with provocation.

SYNONYMS

HCM
Hypertrophic cardiomyopathy
Idiopathic hypertrophic subaortic stenosis (IHSS)
Hypertrophic obstructive cardiomyopathy (HOCM)
Hypertrophic nonobstructive cardiomyopathy
Asymmetric septal hypertrophy (ASH)
Familial hypertrophic cardiomyopathy

ICD-10CM CODES

I42.1	Obstructive hypertrophic cardiomyopathy (includes hypertrophic subaortic stenosis)
I42.2	Other hypertrophic cardiomyopathy (includes nonobstructive hypertrophic cardiomyopathy)
I42.8	Other cardiomyopathies
I42.9	Cardiomyopathy, unspecified (includes cardiomyopathy [primary] [secondary] not otherwise specified)

EPIDEMIOLOGY & DEMOGRAPHICS

- Prevalence in the general population in the U.S., China, and Japan is estimated to be between 1/500 to 1/200 (the most common genetically transmitted cardiovascular disease).
- HCM is the most common cause of sudden cardiac death in young athletes (more commonly among blacks).
- There is equal prevalence in men and women (probably underdiagnosed in women).
- It occurs across ethnicities, perhaps underdiagnosed among blacks.
- Mortality rate is approximately 1%/yr, as high as to 2%/yr in children.
- The most common form of the disease is familial (60% to 70% of cases), and it follows an autosomal dominant inheritance pattern with variable expression.
- Spontaneous mutations can also occur, accounting for approximately 20% of cases. It is otherwise indistinguishable from the familial form.
- A variant form seen in the elderly (5% to 10% of cases) has a better prognosis, and it is not typically associated with sudden cardiac death.
- The familial form is usually diagnosed in young patients. It is most often caused by a mutation in one of the contractile protein genes of the cardiac sarcomere. See "Etiology" for more details.
- Nonsarcomeric genetic mutations that cause storage disease (e.g., Fabry disease) have a very similar clinical presentation.
- Apical HCM is a variant more common among Asians: As many as 41% of Chinese HCM and 15% of Japanese HCM patients. Clinically there is no LVOT obstruction.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients may have subtle symptoms of progressive congestive heart failure (CHF). At the time of diagnosis, most patients are asymptomatic, referred and diagnosed based on family history. HCM may be suspected on the basis of abnormalities found on physical examination. Classic findings include:

- Harsh, systolic, crescendo–decrescendo murmur at the left sternal border or apex. The murmur increases with maneuvers that decrease venous return or LV size (Valsalva, standing), and decreases with those that increase venous return or afterload (squatting, hand grip, post-Valsalva release).
- Paradoxical splitting of S2 (if left ventricular obstruction is present).
- S4 may be present.
- Double or triple LV apical impulse ("triple ripple": Atrial contraction, early rapid ejection, and late slow ejection).
- Pulsus bisferiens (double pulsation on palpation of the carotid pulse).

Increased obstruction can occur with:

- Drugs: Digitalis, β-adrenergic stimulators (isoproterenol, dopamine, epinephrine), nitroglycerin, vasodilators, diuretics, alcohol, inhalation of amyl nitrate
- Hypovolemia
- Tachycardia
- Valsalva maneuver
- Standing position

Decreased obstruction is seen with:

- Drugs: β-adrenergic blockers, calcium channel blockers, disopyramide, α-adrenergic stimulators
- Volume expansion
- Bradycardia
- Hand-grip exercise
- Squatting position
- Release phase of the Valsalva maneuver

Clinical manifestations are as follows:

- Syncope or presyncope (usually seen with exercise)
- Angina
- Palpitations
- Sudden cardiac death
- Heart failure (typically with advanced stages): Dyspnea on exertion, orthopnea, edema, increased jugular venous pressure, paroxysmal nocturnal dyspnea

ETIOLOGY

- Genetic: Autosomal dominant trait with variable penetrance caused by mutations in multiple genes encoding proteins of the cardiac sarcomere and calcium regulation. To date, >1400 mutations have been identified among at least 13 genes, with variable phenotypes, expressivity, and penetrance. The most vigorous evidence indicates that eight genes are known to definitively cause HCM: Beta myosin heavy chain, myosin binding protein C, troponin T, troponin I, tropomyosin alpha-1 chain, actin, regulatory light chain, and essential light chain. HCM may be caused by a single mutation in one of two alleles; however, 5% of patients have at least two mutations. Sarcomeric protein gene mutations account for up to 60% of cases of HCM.
- Metabolic: Most are autosomal recessive, but some are X-linked. Most commonly, they are due to Anderson-Fabry disease (a lysosomal storage disease). Other metabolic etiologies include the glycogen storage diseases Pompe and Danon, AMP-kinase (PRKAG2), and carnitine disorders.
- Mitochondrial: These comprise autosomal dominant, autosomal recessive, X-linked, and maternally inherited traits. Most frequently, they are due to mutations in the respiratory chain protein complexes. The age of onset and severity of involvement are variable.
- Neuromuscular: These are most commonly associated with Friedreich ataxia, but they are also associated with *FHLI*.
- Malformation syndromes: These etiologies include Noonan (formerly referred to as LEOPARD), Costello, and cardiofaciocutaneous.
- Amyloidosis: These include familial ATTR, wild-type TTR (senile), and amyloid light-chain (AL) amyloidosis.
- Drug-induced: Tacrolimus, hydroxychloroquine, and steroids.
- Sporadic occurrence.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hypertensive heart disease
- Aortic stenosis
- Subaortic stenosis
- Athlete heart
- Volume depletion

WORKUP

- Medical history: Unexplained clinical manifestations and/or family history of sudden death.
- Physical exam: See "Physical Findings & Clinical Presentation."
- Genetic counseling with or without testing.
- ECG is abnormal in 75% to 95% of patients, although there are no pathognomonic findings. Typical findings include:
  1. Left ventricular (LV) hypertrophy (abnormally tall R waves in the precordial leads) in up to 80% of patients (Fig. E2).

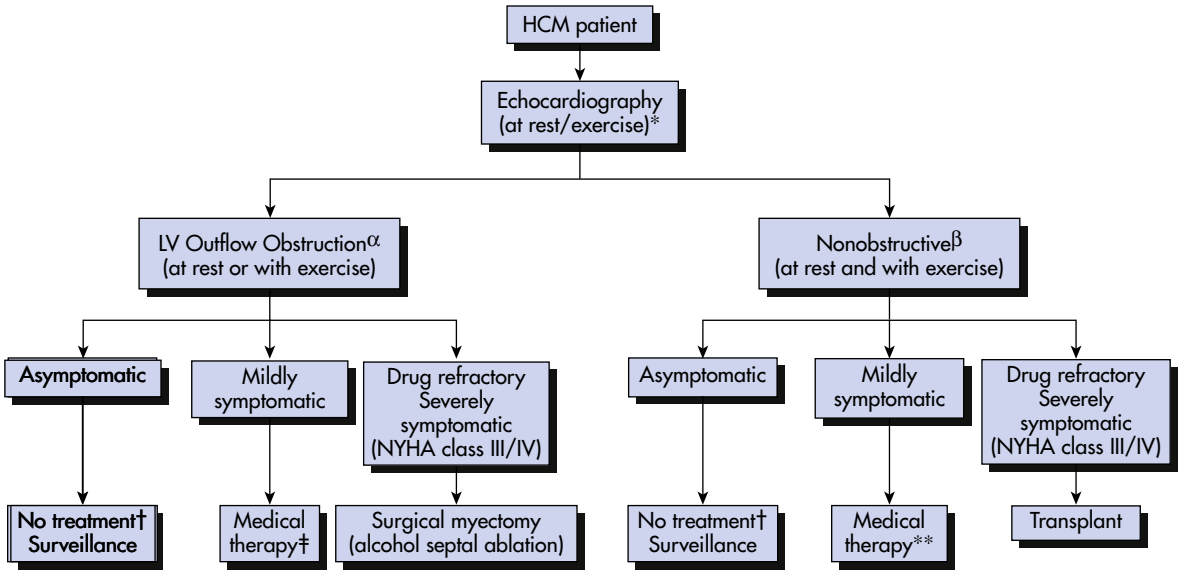

FIG. 1 Heart failure management strategies starting with echocardiography. *Patients without LV outflow tract gradient (<30 mm Hg) at rest should undergo stress (exercise) echocardiography. †No data on benefit of pharmacologic therapy, although beta-blockers often are administered prophylactically in clinical practice. **Beta-blockers, calcium channel antagonists, and possibly diuretics administered judiciously. ‡Usually, beta-blockers or calcium channel antagonists (verapamil), or disopyramide. α, generally regarded, by definition, as ≥30 mm Hg outflow gradient, but ≥50 mm Hg when septal reduction intervention is considered (i.e., septal myectomy; alcohol ablation). β, no or trivial (<30 mm Hg) outflow gradient at rest and with exercise. *HCM,* Hypertrophic cardiomyopathy; *LV,* left ventricle; *NYHA,* New York Heart Association. (From Maron BJ et al: State-of the art review: hypertrophic cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine. *J Am Coll Cardiol* 2014;64:83, in Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

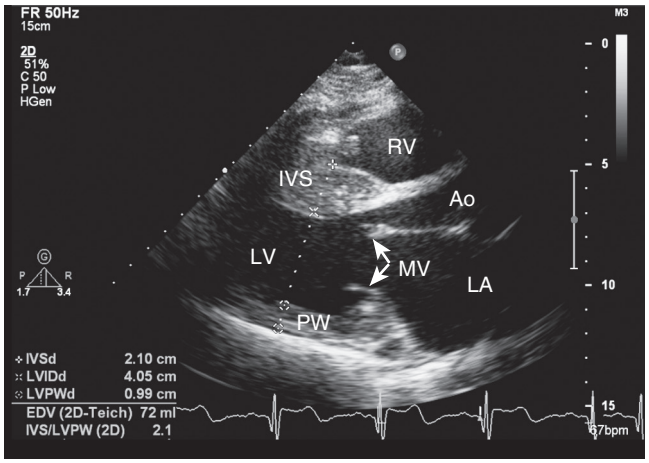

FIG. 3 Echocardiographic appearance of hypertrophic cardiomyopathy. Parasternal long-axis view from a patient with hypertrophic cardiomyopathy demonstrating asymmetrical septal hypertrophy. The interventricular septum (marked by *arrow*) measures 2.1 cm; the posterior wall measures 0.99 cm. *Ao,* Aorta; *IVS,* interventricular septum; *LA,* left atrium; *LV,* left ventricle; *MV,* mitral valve; *PW,* posterior wall; *RV,* right ventricle. (From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, Saunders.)

2. Abnormal Q waves in lateral and inferior leads.
3. T wave inversions (associated with the apical hypertrophy predominant variant).

- Echocardiography (Fig. 3) is usually diagnostic as the majority of patients have significant LV hypertrophy (See "Imaging Studies" for details) and should be repeated every 12 to 24 months or as clinically needed.
- 24-hour Holter monitor to screen for potentially lethal ventricular arrhythmias (principal cause of syncope or sudden death in obstructive cardiomyopathy) should be performed at the initial diagnosis and in patients that subsequently develop palpitations, lightheadedness, or syncope. The presence of these arrhythmias identifies patients who are candidates for implantable cardioverter-defibrillator (ICD) therapy.
- In the absence of significant LVOT obstruction, exercise testing is indicated at diagnosis and annually thereafter to evaluate for symptoms and response to exercise. A drop in systolic blood pressure by at least 20 mmHg or failure to augment by at least 20 mmHg with exercise are markers of poor prognosis and are indicators for referral for myotomy/myomectomy. Cardiopulmonary exercise testing can provide objective evidence for worsening diseases, but need only be performed every 2 to 3 yr.
- Biomarkers of myocardial fibrosis in HCM include brain natriuretic peptide and high-sensitivity cardiac troponin T and I. Other labs include complete blood count, basic metabolic panel, liver function test, thyroid stimulating hormone, serum protein electrophoresis, urine protein electrophoresis free light chain ratio (Kappa/Lambda).

- Screening for sarcomere protein gene mutations in family members of patients with HCM can identify a broad subgroup of patients with increased propensity toward long-term impairment of left ventricular function and adverse outcome, irrespective of the myofilament (thick, intermediate, or thin) involvement.
- In individuals with pathogenic mutations who do not express the HCM phenotype, it is recommended to perform serial electrocardiogram (ECG), transthoracic echocardiogram (TTE), and clinical assessment at periodic intervals (12 to 18 months in children and adolescents and about every 5 yr in adults), based on the patient's age and change in clinical status.
- Endomyocardial biopsy may be helpful to rule out diseases other than HCM if a diagnosis remains inconclusive after extensive testing.

IMAGING STUDIES

- Chest x-ray may be normal or show cardiomegaly.
- Two-dimensional echocardiography is used to establish the diagnosis and assess the severity of obstruction when present. LV wall thickness will usually be ≥15 mm (although some may be genetically positive but phenotype negative), and most patients (up to 95%) will have asymmetric (ratio of septum thickness to left ventricular wall thickness >1.3:1) LV wall hypertrophy. Symmetric LV hypertrophy is less common. The septum is most often affected, followed by the left ventricular midcavity and apex. In addition, 25% to 30% of patients will manifest systolic anterior motion (SAM) of the anterior leaflet of the mitral valve, causing obstruction of the LVOT and mitral regurgitation. Two-dimensional strain imaging echocardiography is useful for differentiation of HCM and cardiac amyloidosis from other causes of ventricular wall thickening. Up to 80% of HCM patients will also have diastolic dysfunction as evidenced by pulsed mitral valve inflow pattern and tissue Doppler.
- Cardiac MRI or cardiac CT may be of diagnostic value when echocardiographic studies are technically inadequate. MRI is also useful in identifying unusual segmental hypertrophy undetectable by standard echocardiography and can detect myocardial replacement fibrosis (an independent predictor of adverse cardiac outcomes and ventricular arrhythmias) using late gadolinium enhancement. cardiac magnetic resonance evaluation may be considered every 5 yr or every 2 to 3 yr in patients with progressive disease.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid volume depletion: An underfilled left ventricle causes closer approximation of the hypertrophic interventricular septum and anterior mitral valve leaflet, worsening the outflow tract obstruction and mitral regurgitation, potentially leading to dizziness, hypotension, and/or syncope.
- Exercise restriction: The risk of sudden cardiac death is increased by exercise in HCM patients and rapid heart rates may cause LV underfilling as described above; therefore, participation in competitive sports and intense physical activity should be avoided. As a part of a healthy lifestyle, low-intensity aerobic exercise is reasonable.
- Avoidance of alcohol: Alcohol use (even in small amounts) may result in increased obstruction of the left ventricular outflow tract. Other stimulants such as cocaine and other sympathomimetic recreational drugs should also be avoided.

ACUTE GENERAL Rx

- Therapy for HCM is directed at blocking the effect of catecholamines and generally avoiding vasodilator or diuretic agents that can exacerbate the dynamic left ventricular outflow tract obstruction.
- Beta-blockers' beneficial effects on symptoms (principally dyspnea and chest pain) and exercise tolerance appear to be largely a result of a decrease in the heart rate with consequent prolongation of diastole and increased passive ventricular filling. By reducing the inotropic response, beta-blockers may also reduce myocardial oxygen demand and decrease the outflow gradient during exercise, when sympathetic tone is increased. Dose titration to a resting heart rate of less than 65 bpm is recommended.
- Nondihydropyridine calcium channel blockers (e.g., verapamil [preferred], diltiazem) can also decrease left ventricular outflow obstruction through a mechanism similar to beta-blockers. However, they are mainly second-line agents used in patients who cannot tolerate beta-blockers as they also theoretically have vasodilatory properties that may worsen severe outflow tract gradients.
- Disopyramide is an antiarrhythmic that is also a negative inotrope, resulting in further decrease in outflow gradient. It is sometimes used in combination with beta-blockers.
- Prophylactic antibiotics before dental, GI, and genitourinary procedures are no longer recommended according to the American Heart Association (AHA) guidelines.
- Avoid use of digitalis, intravenous inotropes, dihydropyridine calcium channel blockers (e.g., nifedipine, amlodipine), nitrates, and vasodilators.
- Diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers should be used with caution.
- Intravenous phenylephrine (or another pure vasoconstricting agent) is recommended for the treatment of acute hypotension in patients with obstructive HCM who do not respond to fluid administration.
- ICDs are a safe and effective therapy in HCM patients prone to ventricular arrhythmias. In their practice guidelines, the major cardiology societies (AHA/ACC/HRS) give a strong recommendation (Class I) for ICD implantation in all patients with HCM who have had an episode of sustained ventricular tachycardia or fibrillation. In addition, they endorse the prophylactic placement of an ICD (Class IIa recommendation) for patients with one or more of the major risk factors for sudden cardiac death (outlined in "Disposition"). In patients with New York Heart Association (NYHA) functional class III or IV heart failure symptoms on maximal medical therapy, an ICD also may be considered when ejection fraction (EF) is less than or equal to 50%.
- Dual-chamber pacing may provide symptomatic relief of symptoms attributable to LVOT obstruction and refractory to medical therapy.
- Systolic dysfunction in patients with HCM is defined as an EF of less than or equal to 50%, at which point medical therapy should follow guidelines for heart failure with reduced EF (ACE inhibitors, angiotensin II receptor blockers, beta-blockers, etc.).
- HCM patients are at an increased risk of atrial fibrillation (AF) as well as systemic thromboembolism. AF occurs in over 20% of the HCM population. AF is an important source of symptoms, morbidity, and mortality and correlates to a worse prognosis. Anticoagulation for AF is indicated independent of CHA_2DS_2-VASc score and should aim for thromboembolic risk mitigation with a vitamin K antagonist (unless contraindicated) and symptom alleviation via rhythm (generally preferred due to poor tolerance of AF with HCM) or rate control. If a vitamin K antagonist cannot be used in a patient (due to inability to maintain a therapeutic INR, inability to adequately perform INR monitoring, or other side effects), the 2014 ESC HCM (Class Ib) and 2014 ACC/AHA/HRS AF (Class Ic) guidelines recommend the use of direct thrombin or factor Xa inhibitors, even though there is no data on their use in patients with HCM.
- Fig. 1 summarizes heart failure management strategies.

DISPOSITION

HCM is not a static disease. Some adults may experience subtle regression in wall thickness, whereas others (~5% to 10%) paradoxically evolve into an end-stage cardiomyopathy resembling dilated cardiomyopathy, characterized by cavity enlargement, left ventricular wall thinning, and systolic dysfunction. Patients with HCM are at increased risk for sudden death, especially if the onset of symptoms began during childhood. Severe left ventricular outflow obstruction at rest is also a strong, independent predictor of severe symptoms of heart failure and death. ICD implantation for primary prevention should be considered if patients (particularly the young) have any of the following high-risk features:

- Personal history of sudden cardiac death or out of hospital cardiac arrest (major risk factor)
- Spontaneous sustained ventricular tachycardia or ventricular fibrillation (major risk factor)
- Family history of premature death in a first-degree relative possibly caused by HCM
- Unexplained syncope
- Nonsustained ventricular tachycardia during Holter monitoring
- Substantial septal hypertrophy (>30 mm)
- Abnormal blood pressure response during exercise

- Increased delayed gadolinium enhancement on cardiac magnetic resonance imaging is suggested in some recent studies as a marker of increased sudden cardiac death risk

REFERRAL

- Surgical treatment (septal myectomy involving resection of the basal septum) is now the gold standard for relieving outflow tract obstruction in patients with large outflow gradient (≥50 mm Hg) and moderate to severe symptoms unresponsive to medical therapy. The risk for sudden death from arrhythmias is not altered by surgery. When this operation is performed by experienced surgeons in tertiary referral centers, the operative mortality rate is <1%, and many patients are able to achieve near-normal exercise capacity after surgery. Mitral valvuloplasty or plication in combination with myectomy may be necessary in <5% of patients. Risks of surgery include AV nodal block, ventricular septal defect, and aortic regurgitation (AR).
- Alcohol septal ablation is a nonsurgical alternative to reduce the size of the interventricular septum. This can be done in patients with HCM refractory to pharmacologic treatment, particularly in those who are not candidates for myectomy due to high surgical risk or patient preference. This technique involves the injection of ethanol in a septal perforator branch of the left anterior descending coronary artery (Fig. E4), producing a controlled myocardial infarction of the interventricular septum, and thereby reducing septal mass and consequently the left ventricular outflow tract gradient. This method may lead to improvement in both subjective and objective measures of exercise capacity, but results are not as effective as surgery because they are associated with a high incidence of heart block, requiring permanent pacing in approximately 25% of patients, and/or recurrence of obstruction and symptoms. This should be done only at centers with experienced operators.
- Refractory end-stage heart failure symptoms can be treated with left ventricular assist device, biventricular assist device, or heart transplant.

PEARLES & CONSIDERATIONS

COMMENTS

- Clinical screening of first-degree relatives with two-dimensional echocardiography and ECG is indicated. Starting at the age of 12, periodic screening at 12- to 18-month intervals is recommended for children of patients with HCM and in competitive athletes. Periodic screening of first-degree adult family members not in competitive athletics is recommended at 5-yr intervals because hypertrophy may not be detected until the sixth decade of life. If the index patient does not have a definite pathogenic mutation, then genetic testing of relatives is not indicated.
- Genetic counseling and screening (Fig. E5, Table 1) is recommended in first-degree relatives of patients with HCM. Genetic screening of first-degree relatives can refine or eliminate the need for periodic clinical screening. At least 13 genes are known to cause HCM, among them: Cardiac myosin binding protein-C, beta-myosin heavy chain, troponin T, troponin I, alpha tropomyosin, actin regulatory light chain, and essential light chain. Clinical predictors of positive genotype, such as the presence of ventricular arrhythmias, age at diagnosis, degree of left ventricular wall hypertrophy, and family history of HCM, may aid in patient selection for genetic testing and increase the yield of cardiac sarcomere gene screening. Currently a mutation can be identified in 40% to 60% of all cases, sporadic or familial.
- All HCM patients who wish to become pregnant should be given prenatal counseling about the risk of transmission (about 50%) to their offspring and should be followed at a tertiary care center that specializes in high-risk pregnancies. Most patients with HCM tolerate pregnancy well due to the higher circulating blood volume.
- The mortality rate in HCM is approximately 1% to 2% per yr.
- About one third of HCM patients will not have a resting or labile outflow gradient (i.e., nonobstructive form of HCM), but it is important to note that lethal ventricular arrhythmias can occur in the absence of obstruction or symptoms.
- Myocardial fibrosis is a hallmark of hypertrophic cardiomyopathy. Biomarkers of collagen metabolism such as serum C-terminal propeptide of type I procollagen (PICP) are significantly higher in mutation carriers without left ventricular hypertrophy and in subjects with overt hypertrophic cardiomyopathy than in controls, indicating that a probiotic state precedes the development of hypertrophy of fibrosis identifiable with cardiac MRI.

TABLE 1 Proposed Clinical Family Screening Strategies with Echocardiography or Cardiovascular Magnetic Resonance (and 12-Lead Electrocardiography) for Detection of HCM with Left Ventricular Hypertrophy*

Age <12 yr
Optional unless:
Malignant family history of premature death from HCM, or other adverse complications
Competitive athlete in an intense training program
Onset of symptoms
Other clinical suspicion of early left ventricular hypertrophy
Age 12-21 yr†
Every 12-18 months
Age >21 yr
Imaging at onset of symptoms, or possibly at 5-yr intervals at least through midlife; more frequent intervals for imaging are appropriate in families with malignant clinical course or history of late-onset HCM

*In family members who had not undergone genetic testing, or in whom testing was unresolved or indeterminant.
†Age range takes into consideration individual variability in achieving physical maturity, and in some patients, screening may be justified at an earlier age; initial evaluation should be performed no later than early pubescence.
From Maron BJ, Maron MS, Semsarian C: Genetics of hypertrophic cardiomyopathy after 20 years: Clinical perspectives. *J Am Coll Cardiol* 60:705, 2012, in Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hypertrophic Cardiomyopathy (Patient Information)

AUTHOR: **Christopher P. Blomberg, DO**

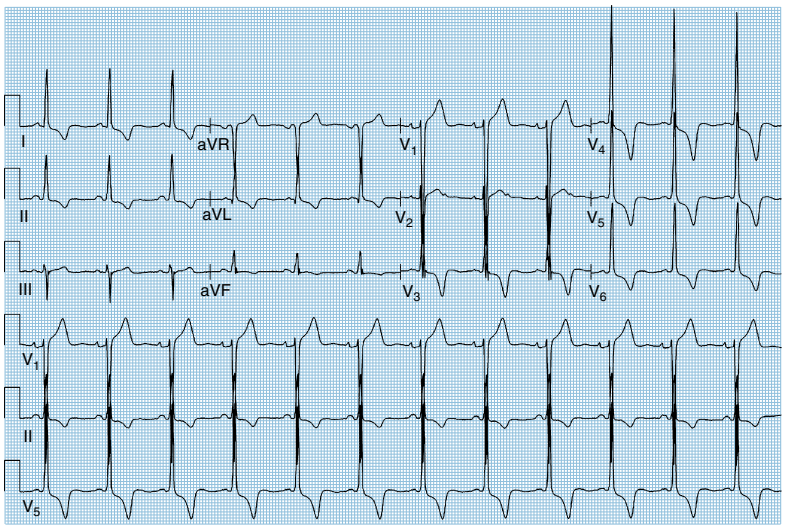

FIG. E2 Hypertrophic cardiomyopathy. This 12-lead electrocardiogram with rhythm strips shows sinus rhythm with marked left ventricular hypertrophy and associated ST-T abnormalities. These findings in a young patient with syncope suggest the diagnosis of hypertrophic cardiomyopathy, which was confirmed by echocardiography. *aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right. (From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

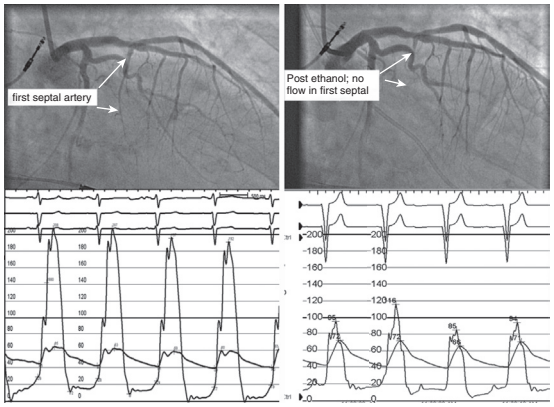

FIG. E4 Septal ablation for obstructive hypertrophic cardiomyopathy. *Left,* Large pressure gradient between the left ventricle and aorta. A large proximal septal perforating artery is identified. *Right,* Following selective injection of ethanol, there is no flow within the septal artery, and the gradient is dramatically reduced. (From Bonow RO et al: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 9, St Louis, 2011, Saunders.)

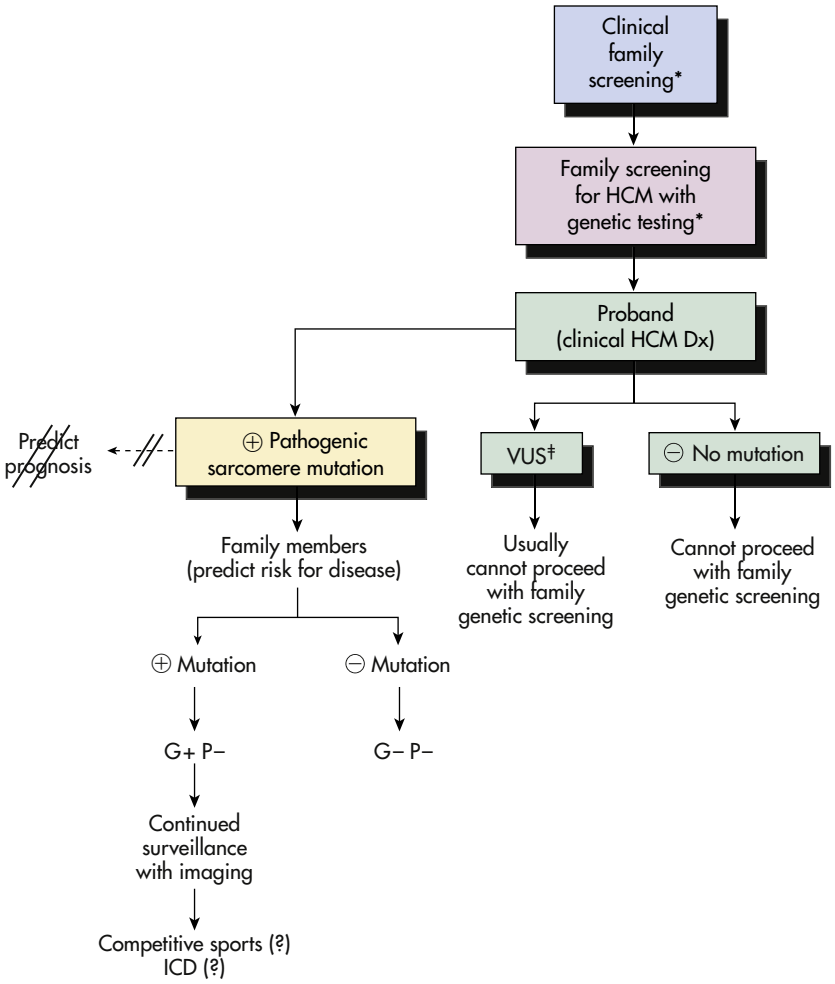

FIG. E5 Role of genetic testing in family screening strategies in hypertrophic cardiomyopathy *(HCM).* Some form of family screening for HCM in family members of the proband is universally recommended. The preferred first option (*) for clinical testing family members is usually with cardiac imaging and electrocardiography to identify phenotype-positive relatives. The predominant role for genetic testing in this setting is to identify those family members who are at risk for developing disease who do not have left ventricular (LV) hypertrophy. This strategy is initiated by successfully genotyping the proband with a clinically expressed HCM phenotype. Failure to identify the causative mutation in the proband is an indeterminate result that provides no useful information and precludes predictive testing in family members. The likelihood of obtaining a positive test result in the proband is less than 50%, insofar as all genes causing HCM have not yet been identified. Furthermore, many of the detected mutations will not be judged to be pathogenic, thereby eliminating substantially more than 50% of families from the option of genotyping for identification of relatives at risk for HCM. Accordingly, the genetic test results in the proband will be actionable in terms of family screening in only a minority of cases. *Dx,* Diagnosis; *G+ P–,* genotype-positive, phenotype-negative; *G– P–,* genotype-negative, phenotype-negative; *ICD,* implantable cardioverter-defibrillator; *VUS,* variant of uncertain significance. (Modified from Maron BJ, Maron MS, Semsarian C: Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives, *J Am Coll Cardiol* 60:705, 2012. In Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015. Elsevier.)

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BASIC INFORMATION

DEFINITION

Restrictive cardiomyopathy refers to either an idiopathic or a secondary myocardial disorder (in the absence of ischemic, hypertensive, valvular, or congenital heart disease) characterized by restrictive filling (Fig. E1), normal or reduced left ventricular (LV) and right ventricular (RV) volumes, and normal or near normal systolic LV and RV function. Pathophysiologically, the myocardium is abnormally stiff, resulting in decreased compliance, abnormal relaxation in diastole, and increased filling pressures leading to enlarged left atria.

SYNONYMS

Idiopathic restrictive cardiomyopathy
Infiltrative cardiomyopathy

ICD-10CM CODES	
D86.XX	Sarcoidosis-related codes
E83.11X	Hemochromatosis-related codes
E85.X	Amyloidosis-related codes
I42.5	Other restrictive cardiomyopathy
I42.8	Other cardiomyopathies
I43.1	Cardiomyopathy in metabolic diseases
I42.9	Cardiomyopathy, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- A relatively uncommon cardiomyopathy, accounting for 5% of all primary myocardial diseases.
- Most frequently caused by amyloidosis or myocardial fibrosis (following open heart surgery, transplantation or radiation).
- Patients classified as having "idiopathic" restrictive cardiomyopathy may have mutations in the gene for cardiac troponin I, and restrictive cardiomyopathy may represent an overlap with hypertrophic cardiomyopathy in many familial cases.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Restrictive cardiomyopathy presents with symptoms of progressive left-sided and right-sided heart failure:

- Fatigue, weakness (caused by low output as patients are unable to augment cardiac output by increasing heart rate without compromising ventricular filling).
- Progressively worsening exercise intolerance and dyspnea.
- Anginal chest pain can be seen (particularly in patients with amyloidosis) from myocardial compression of small coronaries.
- Palpitations (atrial fibrillation is common), dizziness or syncope (from orthostasis, heart block, or malignant arrhythmia).
- Edema, ascites, hepatomegaly, distended neck veins (from elevated right heart pressures).
- Kussmaul sign may be present (rise, or failure to fall, of the jugular veins on inspiration).
- On auscultation: Murmurs of mitral or tricuspid regurgitation may be heard; an S3 may be present.
- Apical impulse may be palpable (can help distinguish it from constrictive pericarditis) and nondisplaced.

ETIOLOGY

Disease may be classified according to pathophysiologic processes:

- Infiltrative:
  1. Amyloidosis (most common overall): The main types include AA, AL, Aß (ß amyloid), and ATTR (transthyretin-mutated or wild type [commonly known as senile systemic])
  2. Sarcoidosis (more commonly causing a dilated cardiomyopathy with regional wall motion abnormalities)
- Noninfiltrative:
  1. Idiopathic (familial subtypes may have genetic overlap with hypertrophic cardiomyopathy)
  2. Scleroderma
  3. Diabetic cardiomyopathy
  4. Pseudoxanthoma elasticum
- Storage diseases:
  1. Hemochromatosis (more commonly associated with a dilated cardiomyopathy)
  2. Glycogen or other storage diseases (Gaucher, Hurler, Fabry—all rare)
- Endomyocardial:
  1. Endomyocardial fibrosis
  2. Hypereosinophilic syndrome (Loeffler syndrome)
- Carcinoid heart disease
- Radiation
- Metastatic cancers
- Drug related (anthracyclines, serotonin, ergotamine, busulfan, methysergide)

DIAGNOSIS

The diagnosis of idiopathic or primary restrictive cardiomyopathy is rare and is a diagnosis of exclusion.

DIFFERENTIAL DIAGNOSIS

- Constrictive pericarditis (see Table E1)
- Valvular dysfunction (especially aortic stenosis)
- Hypertrophic cardiomyopathy
- Hypertensive heart disease

WORKUP

- Complete blood count with differential (to identify eosinophilia), iron studies, serum renal function studies, chest x-ray, ECG, echocardiogram
- Right and left heart catheterization, magnetic resonance imaging, and computed tomography (in select cases)
- Aspiration biopsy of subcutaneous fat to detect amyloidosis
- Endomyocardial biopsy if diagnostic confirmation needed
- Brain natriuretic peptide (BNP) serum levels (>400 pg/ml): There are data suggesting that BNP levels are markedly elevated in restrictive cardiomyopathy but near normal in constrictive pericarditis, most likely resulting from the lack of myocardial stretching in constriction that is required for BNP release
- Genetic testing, including testing for transthyretin mutation in amyloidosis

IMAGING STUDIES

- Chest x-ray:
  1. Ranges from normal cardiomediastinal silhouette to moderate cardiomegaly (primarily because of biatrial enlargement).
  2. Evidence of heart failure may be present.
  3. Presence of pericardial calcification favors alternative diagnosis of constrictive pericarditis.
- ECG:
  1. Nonspecific ST-T wave abnormalities are the most common finding. Voltage may be low in infiltrative etiologies such as amyloidosis.
  2. Frequent atrial and ventricular ectopy are often present. Atrial fibrillation may be present.
  3. High-degree atrioventricular block, intraventricular conduction delay may be seen in advanced cases.
- Echocardiogram (Fig. 2):
  1. Biatrial enlargement almost always present.
  2. Wall thickness depends on etiology; often thickened in infiltrative disease.

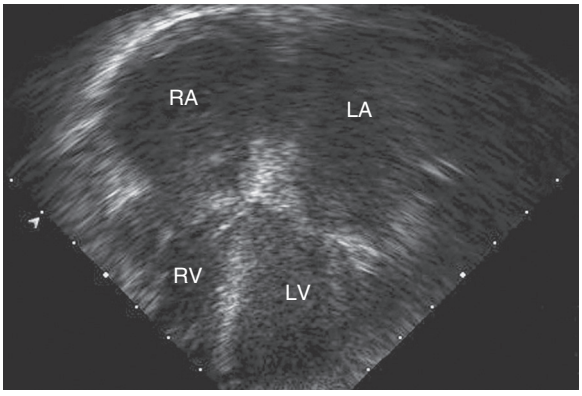

FIG. 2 Echocardiogram of a patient with restrictive cardiomyopathy. The optical four-chamber view shows the markedly enlarged right and left atria, compared to the normal-sized left and right ventricular chambers. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

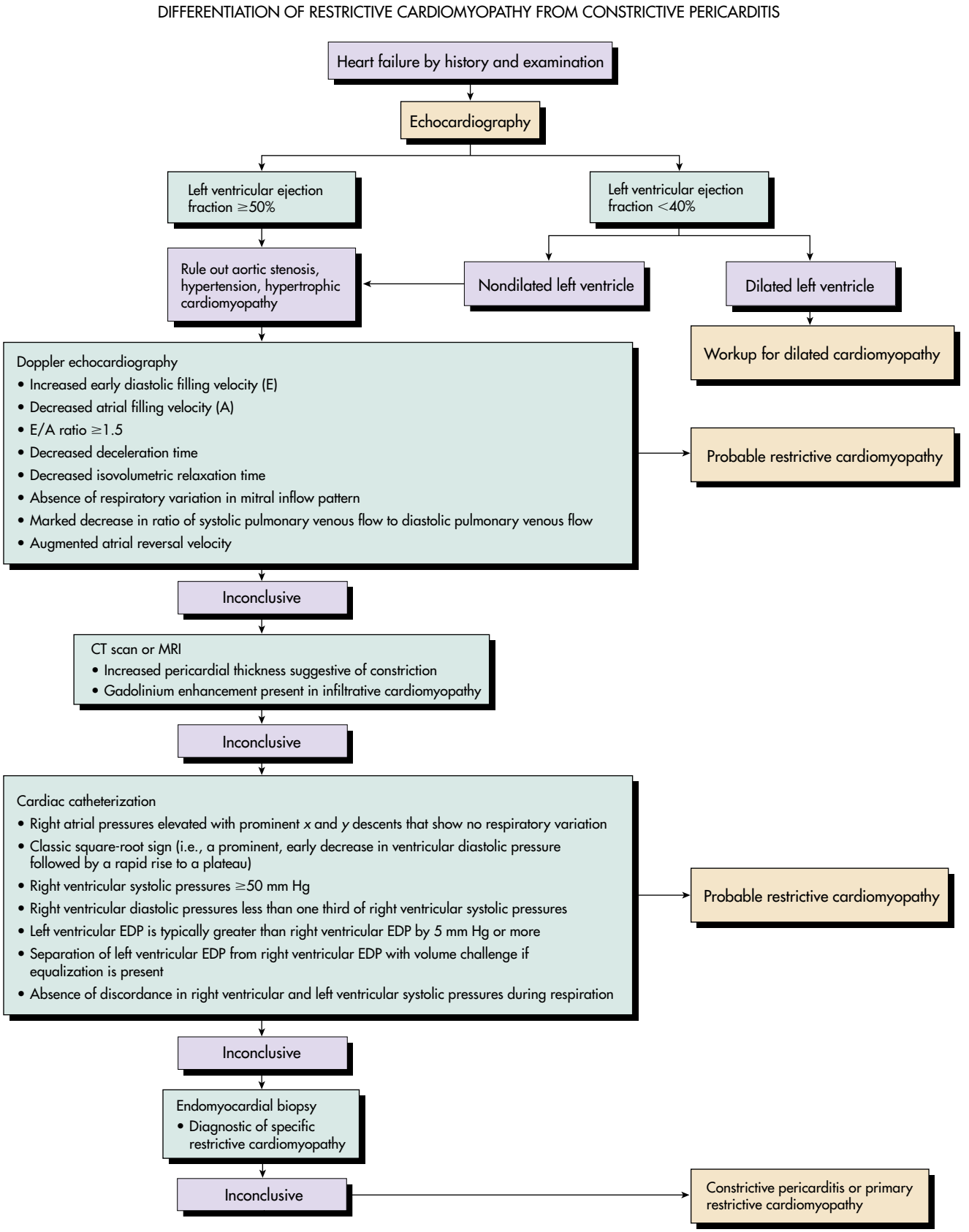

FIG. 3 Differentiation of restrictive cardiomyopathy from constrictive pericarditis. *CT,* Computed tomography; *EDP,* end-diastolic pressure; *MRI,* magnetic resonance image. (From Pereira NL, Dec GW: Restrictive and infiltrative cardiomyopathies. In Crawford MH et al: *Cardiology,* Philadelphia, 2010, Elsevier.)

3. Myocardial appearance may be altered (speckled pattern with apical sparing suggestive of amyloidosis).
4. Ventricular chamber sizes and systolic function are often normal or reduced.
5. Echo Doppler shows evidence of diastolic dysfunction. Tissue Doppler demonstrates low mitral annular velocities.

- Cardiac catheterization:
  1. Characteristic hemodynamic findings are a dip and plateau, or square-root sign, in the left ventricular tracing where a deep and rapid decline in ventricular pressure at the onset of diastole is immediately followed by rapid rise and plateau in early diastolic phase.
  2. To distinguish restrictive cardiomyopathy from constrictive processes (Fig. 3):
     a. Constrictive: Usually involves both ventricles and leads to equalization of diastolic pressures between all four cardiac chambers to within 5 mm Hg. There is discordance in RV and LV pressures generated during inspiration, which is due to increased ventricular interdependence and decreased left atrial filling (caused by a decreased gradient in inspiration between the pulmonary veins, which are outside the constrictive process and the left atrium).
     b. Restrictive cardiomyopathy: Impairs the left ventricle more than the right, often with left-sided end-diastolic pressures of 5 mm Hg greater than the right. The presence of increased pulmonary arterial systolic pressures is also suggestive of restrictive disease. Simultaneous RV and LV pressure tracings demonstrate concordant patterns during the respiratory cycle.
- Cardiac computed tomographic scan may be helpful to identify a thickened and calcified pericardium, consistent with constrictive pericarditis.
- Cardiac magnetic resonance imaging (CMRI) may also be useful to distinguish restrictive cardiomyopathy from constrictive pericarditis (thickness of the pericardium greater than 4 mm in the latter). CMRI is particularly helpful in the diagnosis of the amyloid or sarcoid variants and may have value in other variants as well. Late gadolinium enhancement can be seen with infiltrative diseases.
- Technetium pyrophosphate bone scintigraphy is useful in diagnosis of transthyretin cardiac amyloidosis and differentiates it from light chain amyloidosis.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Congestive symptoms may respond to dietary sodium restriction (<2 g/day).

ACUTE GENERAL Rx

Treatment of volume overload and heart failure symptoms with diuretic therapy.

CHRONIC Rx

- Treatment involves management of the underlying disease if it exists:
  1. Hemochromatosis may respond to repeated phlebotomy and iron chelators to decrease iron deposition in the heart.
  2. Sarcoidosis may respond to corticosteroid therapy.
  3. Primary amyloidosis may respond to chemotherapy (high-dose melphalan with autologous stem cell therapy or bortezomib-based regimens). ATTR may be treated with liver transplant or other promising novel therapeutic agents that are currently being tested in clinical trials.
  4. Eosinophilic cardiomyopathy may respond to corticosteroid and cytotoxic drugs.
  5. There is no effective therapy for other causes of restrictive cardiomyopathy.
- Overall, the goal of treatment is to reduce symptoms by decreasing filling pressures while preserving cardiac output. Since there is currently no drug available to specifically act on myocardial relaxation, therapy centers on low-dose diuretics to lower the preload.
- Beta-blockers or calcium channel blockers have not been demonstrated to improve symptoms or alter the course of disease. Must be careful not to decrease HR too far, as this will affect cardiac output (CO = HR × stroke volume).
- ACE inhibitors (or angiotensin receptor blockers [ARBs]) and vasodilators should be avoided in patients with amyloidosis as they are poorly tolerated. Even small doses can trigger profound hypotension (probably due to associated autonomic neuropathy). Adequate preload is necessary for LV filling and ultimately cardiac output.
- Atrial fibrillation is common and patients with it or with a history of embolization should be anticoagulated. Tachycardia (of any cause) is poorly tolerated and a common cause of decompensation. Rate control is of paramount importance. Cardioversion in case of rapid atrial fibrillation should be considered. Of note, digoxin should be used with caution as it is potentially arrhythmogenic (particularly in patients with amyloidosis).
- Fibrosis of the cardiac conduction system may result in complete heart block presenting as dizziness or syncope (especially in amyloidosis) and pacemaker implantation may be required. The course of restrictive cardiomyopathy is variable and depends on the underlying etiology. Death usually results from heart failure or arrhythmias, and interventions aimed at addressing these are recommended.
  1. For the amyloid variant, an implantable cardiac defibrillator offers little prophylactic benefit beyond the ability to pace because the cause of sudden cardiac death is usually electromechanical disassociation.

DISPOSITION

Prognosis varies with the etiology of the cardiomyopathy but is poor overall as disease is rarely detected before advanced stages.

REFERRAL

Cardiac transplantation can be considered in patients with refractory symptoms and idiopathic or familial restrictive cardiomyopathies.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Restrictive Cardiomyopathy (Patient Information)

AUTHOR: **Nathan Riddell, MD**

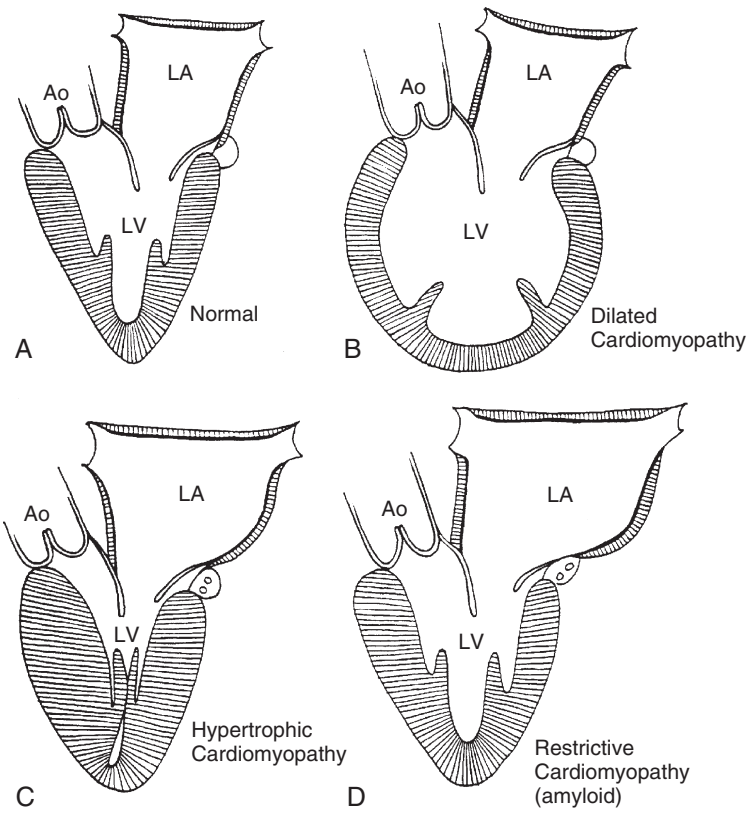

FIG. E1 Cardiomyopathies. A, Normal. **B,** Dilated. **C,** Hypertrophic. **D,** Restrictive. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle. (Modified from Roberts WC, Ferrans VJ: Pathologic anatomy of the cardiomyopathies. *Hum Pathol* 6:289-342, 1975.)

TABLE E1 Differentiation between Restrictive Cardiomyopathy and Constrictive Pericarditis

Type of Evaluation	Restrictive Cardiomyopathy	Constrictive Pericarditis
Physical examination	Kussmaul sign present Apical impulse may be prominent Regurgitant murmurs are common	Kussmaul sign may be present Apical impulse usually not palpable Pericardial knock may be present Pulsus paradoxus may be present
Electrocardiography	Low QRS voltage (especially in amyloidosis) Pseudoinfarction pattern Bundle branch blocks AV conduction disturbances Atrial fibrillation	Low QRS voltage Repolarization abnormalities
Chest radiography		Calcification of the pericardium may be present
Echocardiography	Marked enlargement of the atria Increased wall thickness (especially in amyloidosis) Valvular thickening (especially in hypereosinophilia)	Atria usually of normal size Normal wall thickness Pericardial thickening may be seen
Doppler echocardiography	Restrictive mitral inflow (dominant E wave with short deceleration time) No significant variation of transvalvular velocities with respiration (<10%) Reversal of forward flow in hepatic veins during inspiration Low tissue Doppler velocities	Restrictive mitral inflow (dominant E wave with short deceleration time) Increased velocity of RV filling and decreased velocity of LV filling with inspiration; opposite with expiration; variation in velocity exceeds 15% Reversal of forward flow in hepatic veins during expiration Increased septal tissue Doppler velocities with below normal lateral velocities
Cardiac catheterization	Prominent atrial x and y descents (w sign) Dip-and-plateau appearance of ventricular diastolic pressure Diastolic pressures increased but not equalized (LV diastolic pressure higher than RV diastolic pressure)	Prominent atrial x and y descents (w sign) Dip-and-plateau appearance of ventricular diastolic pressure Increase and equalization of diastolic pressures Discordance of RV and LV peak systolic pressures (with inspiration, RV systolic pressure increases and LV systolic pressure decreases)
Endomyocardial biopsy	May reveal specific cause of restrictive cardiomyopathy	No specific findings on endomyocardial biopsy Pericardial biopsy may reveal abnormality
Computed tomography, magnetic resonance imaging	Late gadolinium myocardial enhancement in certain conditions	Pericardial thickening >4 mm
Laboratory testing	BNP is elevated	BNP may be normal to slightly elevated

AV, Atrioventricular; *BNP,* brain natriuretic peptide; *LV,* left ventricular; *RV,* right ventricular.
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Maron BJ et al: Contemporary definitions and classification of the cardiomyopathies: an American heart association Scientific Statement from the Council on clinical Cardiology, heart failure and transplantation committee; quality of care and outcomes research and functional genomics and translational biology interdisciplinary working groups; and council on epidemiology and prevention, *Circulation* 113:1807, 2006.

Mazen H: Novel drugs targeting transthyretin amyloidosis, *Curr Heart Fail Rep* 11:50-57, 2014.

BASIC INFORMATION

DEFINITION

- The term *cardiorenal syndrome (CRS)* refers to disorders of the heart and kidneys in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other.
- According to the recent definition proposed by the consensus conference of the Acute Dialysis Quality Initiative Group (September 2008), CRS has been used to define different clinical conditions in which heart and kidney dysfunction overlap.
- There are five types of CRS (Fig.E1).
- This section focuses on CRS types 1 and 2.

SYNONYM

CRS

ICD-10CM CODES

I13	Hypertensive heart and chronic kidney disease
I13.0	Hypertensive heart and chronic kidney disease (unspecified or stages 1-4) with heart failure
I13.2	Hypertensive heart and chronic kidney disease (stage 5 or ESRD) with heart failure

EPIDEMIOLOGY & DEMOGRAPHICS

- The prevalence of congestive heart failure (CHF) in the United States exceeded 6.2 million people from 2013 to 2016.
- Chronic kidney disease (CKD) is present in 20% to 67% of patients with CHF.
  1. Women, the elderly, Caucasians, and patients with diabetes mellitus or treatment-resistant hypertension have an increased incidence of CHF.
  2. In general, mortality is increased in patients with HF and reduced glomerular filtration rate (GFR).
  3. CKD patients have an increased risk of atherosclerotic heart disease and HF.
  4. Cardiovascular disease is responsible for up to 50% of deaths in patients with CKD.
- 20% to 30% of patients treated for acute or chronic CHF will develop acute kidney injury (AKI).
  1. In patients with acute CHF, the severity of AKI is increased with decreased left ventricular systolic function and baseline CKD.
  2. Only 9% of patients hospitalized with acute HF in the Acute Decompensated Heart Failure National Registry database (ADHERE) had normal renal function with GFR >90 ml/min per 1.73 m^2 on admission.
- Patients with acute HF experienced the highest frequency of CRS, but the impact on mortality was greatest in patients who developed CRS in the setting of cardiac surgery.

Cardiorenal syndrome (CRS) general definition:
A pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ

CRS type I (acute cardiorenal syndrome)
Abrupt worsening of cardiac function (e.g., acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury

CRS type II (chronic cardiorenal syndrome)
Chronic abnormalities in cardiac function (e.g., chronic congestive heart failure) causing progressive and permanent chronic kidney disease

CRS type III (acute renocardiac syndrome)
Abrupt worsening of renal function (e.g., acute kidney ischemia or glomerulonephritis) causing acute cardiac disorder (e.g., heart failure, arrhythmia, ischemia)

CRS type IV (chronic renocardiac syndrome)
Chronic kidney disease (e.g., chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events

CRS type V (secondary cardiorenal syndrome)
Systemic condition (e.g., diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

FIG. E1 Definitions of cardiorenal syndromes. (From Ronco C et al: Cardiorenal syndrome, *J Am Coll Cardiol* 52(19):1527–1539, 2008.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute/subacute decompensated heart failure (ADHF)
  1. Clinical symptoms
     a. Dyspnea with exertion or at rest
     b. Orthopnea
     c. Paroxysmal nocturnal dyspnea
     d. Right upper quadrant pain
  2. Vital signs
     a. Sinus tachycardia
     b. Hypertension or hypotension
     c. Elevated respiratory rate
     d. Narrow pulse pressure
     e. Pulsus alternans: Poor prognostic indicator
  3. Physical exam findings
     a. Elevated jugular venous pressures
     b. Peripheral edema
     c. Third heart sound (S3)
     d. Respiratory crackles
     e. Abdominal ascites
     f. Hepatomegaly and splenomegaly
- Chronic heart failure
  1. Clinical symptoms
     a. Dyspnea
     b. Fatigue
     c. Anorexia is a poor prognostic feature
  2. Vital signs
     a. Hypotension may be present with a low cardiac output state; sinus tachycardia may be absent
     b. Physical exam findings
        (1) Like findings in ADHF, but rales may be absent, reflecting the rapidity of the collection of fluid. In chronic HF, the pulmonary vasculature may store large alveolar fluid volumes instead of total body intravascular volume
- Findings of HF will be associated with laboratory findings of kidney disease (discussed later). In extreme cases, physical exam findings of severe kidney disease such as asterixis, uremic frost, uremic smell, and uremic pericarditis may be present

ETIOLOGY

The major mechanism of acute CRS is believed to be systemic congestion leading to increased renal venous pressure that in turn reduces renal perfusion. The etiology of CRS can be divided into various categories (Figs. E2, E3, and E4):

- Increased renal venous pressure.
  1. Secondary to elevated central venous pressure or elevated intraabdominal pressure.
  2. Frequency of worsening kidney function is lowest in patients with central venous pressure (CVP) <8 mm Hg.
  3. GFR increase may occur following diuretic therapy, which is most likely mediated by a reduction in renal venous pressure and/or a reduction in right ventricular dilation.
- Reduced renal perfusion.
  1. Common cause of CRS type 1 (acute CHF results in AKI).

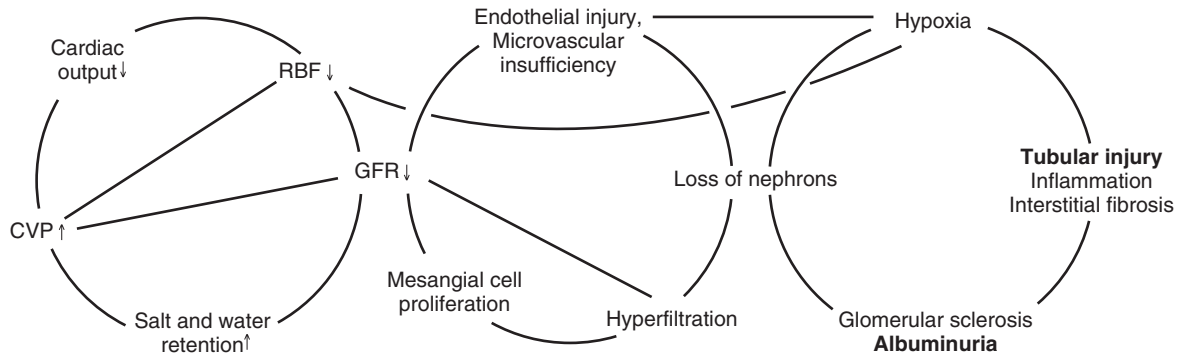

FIG. E2 Integrated pathways of the cardiorenal syndrome in heart failure. *CVP,* Central venous pressure; *GFR,* glomerular filtration rate; *HF,* heart failure; *RBF,* renal blood flow. (From Damman K et al: The cardiorenal syndrome in heart failure, *Prog Cardiovasc Dis* 54:144-153, 2011.)

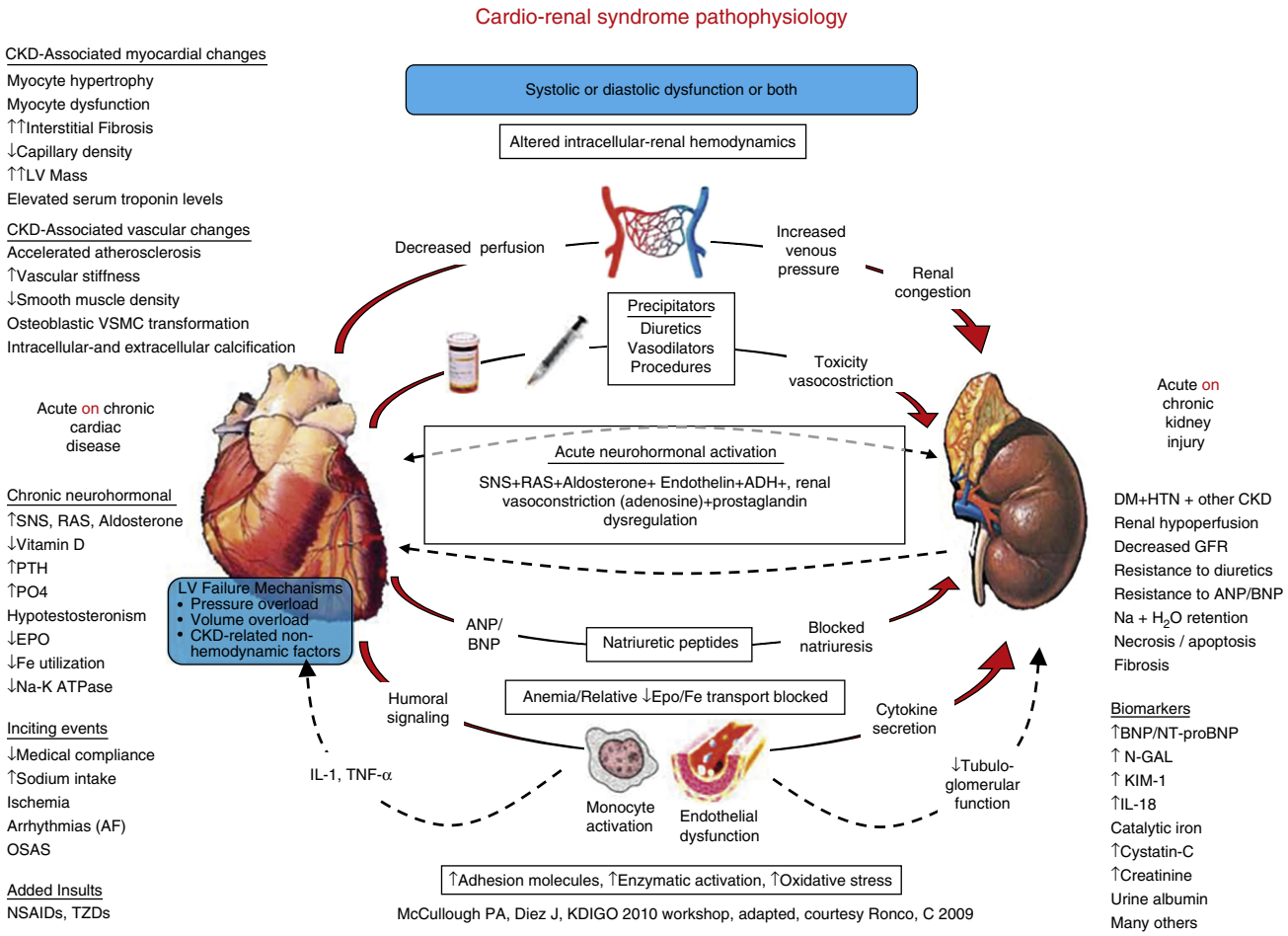

FIG. E3 Pathophysiology of type 1 cardiorenal syndrome or worsening renal function after hospitalization for acutely decompensated HF. *ADH,* Antidiuretic hormone; *AF*, atrial flutter; *ANP/BNP*, atrial natriuretic protein/B-type natriuretic peptide; *BNP*, B-type natriuretic peptide; *CKD*, chronic kidney disease; *DM*, diabetes mellitus; *EPO*, erythropoietin; *GFR*, glomerular filtration rate; *HTN*, hypertension; *IL*, interleukin; *KIM*, kidney injury molecule; *LV*, left ventricular; *N-GAL*, neutrophil gelatinase-associated lipocalin; *NSAIDs*, nonsteroidal antiinflammatory drugs; *NT-proBNP*, N-terminal pro B-type natriuretic peptide; *OSAS*, obstructive sleep apnea syndrome; *PTH*, parathyroid hormone; *RAS*, renin-angiotensin system; *SNS*, sympathetic nervous system; *TNF*, tumor necrosis factor; *TZDs*, thiazolidinediones; *VSMC*, vascular smooth muscle cell. (From Herzog CA et al: Cardiovascular disease in chronic kidney disease: a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO), *Kidney Int* 80:572, 2011.)

2. Loop diuretic therapy can reduce ventricular preload and reduce cardiac output by as much as 20%.

- Right ventricular dilation and dysfunction.
  1. Increases central venous pressure that increases renal venous pressure and reduces GFR.
  2. Right ventricular dilation and dysfunction reduce left ventricular filling and renal blood flow.
- Neurohormonal.
  1. Activation of the renin-angiotensin-aldosterone system, sympathetic nervous system, antidiuretic hormone, and endothelin-1 increases salt and water retention. Systemic vasoconstriction decreases renal perfusion.
  2. Activation of the above neurohormonal systems supersedes vasodilatory effects of natriuretic peptides, nitric oxide, prostaglandins, and bradykinin.

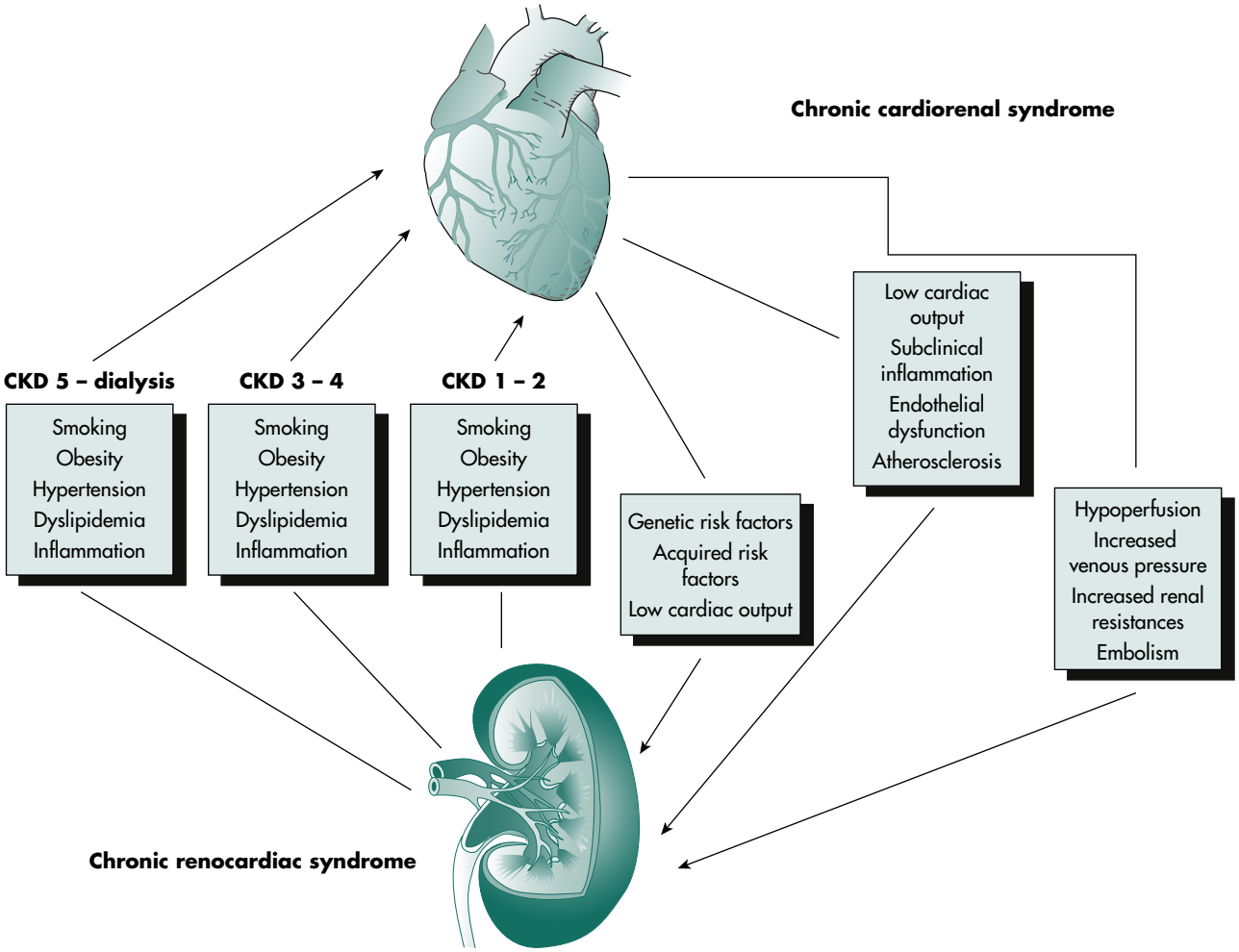

FIG. E4 Pathophysiology of type 2 cardiorenal syndrome. *CKD,* Chronic kidney disease. (Ronco C et al: *Critical care nephrology*, ed 3, Philadelphia, 2019, Elsevier.)

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Before establishing a diagnosis of CRS, rule out other causes of kidney failure
  1. Prerenal causes:
     a. Volume depletion (overdiuresis, gastrointestinal losses, or vomiting)
     b. Fluid overload states, excluding CHF (cirrhosis, nephrotic syndrome)
  2. Intrinsic renal disease:
     a. Acute tubular necrosis
     b. Glomerular disease: Nephrotic and nephritic syndromes
  3. Postrenal causes:
     a. Obstruction

WORKUP

- Medical history consistent with CHF symptoms including dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, increasing abdominal girth, or weight gain. Laboratory results demonstrate signs of kidney injury.
- Diagnostic workup includes chest radiograph, echocardiogram, kidney ultrasound, and laboratory tests.

LABORATORY TESTS

- Serum creatinine:
  1. Patients with CRS had a mortality odds ratio of 1.48 for even mild increases in serum creatinine levels (0.3 to 0.5 mg/dl above baseline), with higher odds ratio for mortality with increases of serum creatinine >0.5 mg/dl
     a. For serum creatinine level increases of >0.5 mg/dl, the odds ratio for mortality increases to 3.22
- Glomerular filtration rate (GFR):
  1. Evaluation of GFR using estimated GFR (eGFR) or calculated GFR
- Blood urea nitrogen:
  1. Admission levels >43 mg/dl are associated with higher in-hospital mortality rate
- Brain natriuretic peptide (BNP):
  1. Initial admission values >480 pg/ml are associated with a 51% chance of death, hospital readmission, or an emergency department visit within 6 months versus levels <230 pg/ml
- It may be difficult to distinguish between CKD and impaired kidney function due to CRS, especially when prior renal function is unknown. Some patients have underlying CKD and CRS. Findings that support underlying CKD include significant proteinuria (>1000 mg/day), urine sediment with hematuria and/or pyuria, cellular casts, and/or small echogenic kidneys on ultrasound

IMAGING STUDIES

- Chest radiograph:
  1. May demonstrate signs of fluid overload, including pulmonary edema, effusions, or fluid in the fissures
- Echocardiogram:
  1. Determines presence of underlying systolic or diastolic dysfunction and/or significant valvular disease
- Kidney ultrasound:
  1. Kidney ultrasound can help distinguish between acute and chronic kidney disease and determine whether obstruction may be worsening kidney function

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Sodium and fluid restriction with sodium less than 2 g (87 mmol) daily is recommended for CHF patients
- Hemodialysis/ultrafiltration

1. Used when there is insufficient response to pharmacologic treatment or when pharmacologic agents are limited by hemodynamics or worsening laboratory values

- Left ventricular assist device/cardiac resynchronization therapy (CRT)
  1. Improves cardiac output by improving ejection fraction by 7% and HF symptoms in patients with New York Heart Association (NTHA) Class II to IV HF with left ventricular ejection fractions ≤35% and left bundle branch block with QRS duration >150 msec

ACUTE GENERAL Rx

No medical treatment directly improves GFR in the setting of CRS. Enhancing cardiac function may improve kidney function by alleviating any of the mechanisms of CRS listed.

- Diuretics:
  1. Extracellular fluid volume reduction improves the left ventricular Frank-Starling relationship.
  2. Reducing volume overload decreases central venous pressure, renal venous pressure, and right ventricular dilation. Consequently, right ventricular function and left ventricular performance improve.
  3. Twice-daily intravenous furosemide initiated at 2.5 times the daily oral furosemide equivalent dose is a recommended initial dosing strategy.
  4. High-dose intravenous bolus loop diuretic therapy improves cardiopulmonary congestion more effectively than low-dose loop diuretics. Continuous loop diuretic infusions are not more effective than frequently administered bolus loop diuretic regimens for fluid removal in non-oliguric patients.
  5. Diuretic resistance is frequently encountered. Common causes are inadequate dose of diuretic, nonadherence to the medical regimen, and/or high sodium intake. Pharmacokinetic factors include slow absorption of diuretic due to gut edema, impaired secretion of diuretic into the tubular lumen due to low renal plasma flow, CKD, hypoalbuminemia, hypotension, and antinatriuretic drugs.
  6. Combination diuretic regimes may optimize treatment (e.g., furosemide and metolazone).
- Blockade of the renin-angiotensin-aldosterone system:
  1. Angiotensin–converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers, aldosterone receptor antagonists, and direct renin inhibitors
     a. Use limited by worsening kidney function, particularly if serum creatinine is greater than 2.5 mg/dl
     b. Permits reduced diuretic dosages
     c. Efficacy of anti-renin-angiotensin-aldosterone system therapy in the management of decompensated HF is well established, but its role in CRS is unproven
- Vasodilators:
  1. Nitroglycerin and nitroprusside
     a. Increase renal perfusion pressure by improving Frank-Starling relationships and cardiac output
- Inotropic agents:
  1. Dobutamine, dopamine, and milrinone
  2. Improve cardiac output and renal perfusion by vasodilation. Used to treat cardiogenic shock and low cardiac output states with normal blood pressure
  3. Dobutamine and milrinone may lower systemic blood pressure, limiting therapeutic efficacy
- Mechanical fluid removal such as extracorporeal ultrafiltration (UF) may be required to achieve control of fluid balance, particularly in patients resistant to diuretic therapy. UF removes plasma salt and water isotonically via convection through a highly permeable filter in an extracorporeal circuit. With slow continuous UF, the intravascular fluid volume remains stable as fluid shifts from the extravascular to intravascular space without inducing hypotension. UF may be indicated in highly refractory HF patients with diuretic resistance
- Sodium-glucose cotransporter-2 (SGLT-2) inhibitors may positively influence cardiovascular outcomes in patients with CKD. The EMPEROR heart failure trial will investigate the safety and efficacy of empagliflozin in patients with chronic HF and, respectively, preserved and reduced cardiac function

DISPOSITION

Based on improvements in heart failure and kidney function.

REFERRAL

Consultations by a cardiologist and nephrologist are recommended.

RELATED CONTENT

Acute Kidney Injury (Related Key Topic)
Heart Failure (Related Key Topic)

AUTHORS: **Chandrika Chitturi, MD,** and **Sandeep Soman, MD**

SUGGESTED READINGS

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Carotid Artery Stenosis PTG

BASIC INFORMATION

DEFINITION

Carotid artery stenosis is narrowing of the carotid arterial lumen, typically as a result of atherosclerosis.

SYNONYM

Atherosclerotic disease of the carotid artery

ICD-10CM CODES

I65.29	Occlusion and stenosis of unspecified carotid artery
I65.21	Occlusion and stenosis of right carotid artery
I65.22	Occlusion and stenosis of left carotid artery
I65.23	Occlusion and stenosis of bilateral carotid arteries

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 2.2 to 8/1000 persons per yr
PREVALENCE: 11 to 77/100,000 persons; it is estimated that 5/1000 persons aged 50 to 60 yr and 100/1000 persons >80 yr have carotid stenosis >50%. (NOTE: The incidence of carotid artery stenosis is unknown as screening is not routine. However, the incidence of transient ischemic attack [TIA], a common presenting symptom of carotid stenosis, is well known.)
PREDOMINANT SEX AND AGE: Male:female ratio of 2:1; more common in whites than African Americans and Asians
PEAK INCIDENCE: Peak incidence is between 50 and 60 yr.
GENETICS: Multifactorial; twin studies (monozygotic versus dizygotic) suggest a familial influence.
RISK FACTORS: Hypertension, dyslipidemia, diabetes mellitus, and smoking are the four major risk factors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients with carotid artery stenosis are often asymptomatic, but many either have a carotid bruit or experience a TIA.

- Carotid bruit: The presence of a carotid bruit is a better indicator of generalized atherosclerosis and is thus a better predictor of ischemic heart disease than future stroke.
- TIA: Carotid artery stenosis is classically heralded by ipsilateral transient monocular blindness (amaurosis fugax), contralateral numbness or weakness, contralateral homonymous hemianopsia, or aphasia.

ETIOLOGY

- Atherosclerosis (most common by far)
- Aneurysm
- Arteritis
- Carotid dissection
- Fibromuscular dysplasia
- Post-radiation necrosis
- Vasospasm

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Aneurysm, arteritis, and carotid dissection

WORKUP

Systematic history, examination, and diagnostic studies to assess for carotid stenosis and other risk factors of TIA and stroke. Carotid artery stenosis is responsible for approximately 10% of all ischemic strokes.

LABORATORY TESTS

CBC, comprehensive metabolic panel, fasting lipid profile, PT/international normalized ratio, APTT, HgA1C

IMAGING STUDIES

- Four imaging modalities are available for the evaluation of carotid artery stenosis (Table 1).
- Patients with transient ischemic attack or stroke should be evaluated for carotid artery stenosis via carotid duplex, magnetic resonance angiography, or computed tomography angiography. Conventional angiography may be obtained to confirm the degree of stenosis and plan for interventional (Fig. 1).
- The U.S. Preventive Services Task Force recommends against screening for asymptomatic carotid artery stenosis in the general adult population.
- Screening with carotid duplex may be considered in asymptomatic patients with carotid bruit, in those with multiple risk factors for atherosclerosis, or those with known atherosclerotic disease at other sites such as coronary artery disease, peripheral arterial disease, or abdominal aortic aneurysms.
- Patients identified to have >50% stenosis on carotid duplex may be re-imaged annually to assess progression and should have intensive medical management of vascular risk factors.

TREATMENT

ACUTE GENERAL Rx

- General medical therapy should be aimed at risk factor reduction. The major risk factors for carotid artery stenosis are hypertension, diabetes mellitus, dyslipidemia, and smoking (see "Stroke, Secondary Prevention").
- Antiplatelet therapy: Three antiplatelet options are available for patients with carotid artery stenosis: ASA, ASA plus dipyridamole, or clopidogrel.

TABLE 1 Imaging Modalities for Carotid Stenosis

Imaging Modality	Benefit	Drawback
Cerebral angiography	• Gold standard • Assesses plaque morphology • Assesses presence of collaterals	• Invasive • High cost • 4% incidence rate of complications • 1% incidence rate of serious complications or death
Carotid duplex	• Sensitive in detecting high-grade stenosis (>70%) • Less invasive • Lower cost	• Can be limited by body habitus • Technician dependent • Overestimates degree of stenosis • May not distinguish high grade stenosis from complete occlusion
Magnetic resonance angiography (MRA)	• Sensitive in detecting high-grade stenosis (>70%) • Less operator dependent	• Overestimates degree of stenosis • Cannot be performed in patients who are critically ill, unable to tolerate supine positioning, have pacemaker or other ferromagnetic hardware, or are claustrophobic* • Expensive • Takes much longer to obtain compared with other modalities
Computed tomography angiography (CTA)	• Sensitive for high-grade stenosis	• Contraindicated in patients with serum creatinine concentration >1.5 mg/dl • Uses ionizing radiation

*One study revealed that ~17% of patients are unable to tolerate MRA secondary to claustrophobia or are unable to lie still for procedure.

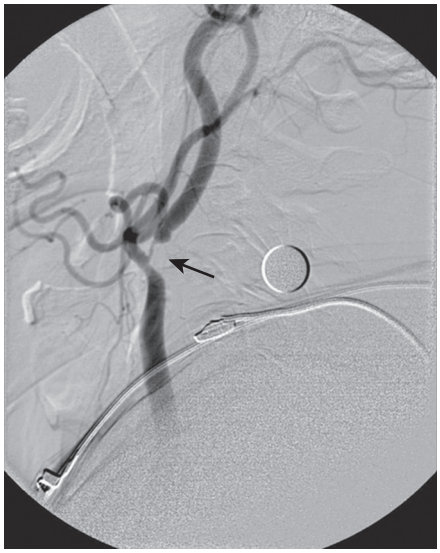

FIG. 1 Conventional angiography demonstrating severe stenosis of the internal carotid artery at the bifurcation.

NONPHARMACOLOGIC THERAPY

Carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS) (Fig. 2) are the two nonpharmacologic options available. The decision on which revascularization procedure to favor is dependent upon the presence or absence of symptoms, degree of stenosis, medical comorbidities, operative risk of the patient, and experience and outcomes data of the proceduralist. Factors associated with increased risk from carotid artery surgery are summarized in Table 2.

In a trial involving asymptomatic patients with severe carotid stenosis who were not at high risk for surgical complications, stenting was noninferior to endarterectomy with regard to the rate of the primary composite end point at 1 yr. In analyses that included up to 5 yr of follow-up, there were no significant differences between the study groups in the rates of nonprocedure-related stroke, all stroke, and survival.[1]

ASYMPTOMATIC CAROTID STENOSIS

The benefit of surgical revascularization of the carotids (CEA or CAS) in asymptomatic patients is not well established. In the U.S., more than 90% of carotid artery interventions are performed in asymptomatic patients, even though evidence suggests that up to 90% of these patients are undergoing an ultimately unnecessary and potentially harmful procedure. In contrast, the percentage of interventions performed for asymptomatic stenosis is approximately 60% in Germany and Italy, 15% in Canada and Australia, and 0% in Denmark.[2]

According to the most recent guidelines, revascularization procedures may be considered in asymptomatic patients with >70% stenosis if the anticipated perioperative risk is less than 3%, but surgery should only be recommended after considering medical comorbidities and life expectancy and after discussing the risks and benefits in detail with the patients. It is important to note that trials of CEA for asymptomatic carotid stenosis were performed prior to the era of aggressive medical management of vascular risk factors. Recently launched studies of asymptomatic carotid stenosis versus aggressive contemporary medical management will answer lingering questions from older studies.

SYMPTOMATIC CAROTID STENOSIS

In patients who have suffered a non-disabling ischemic stroke or TIA in the preceding 6 mo, surgical revascularization by CEA is recommended if the degree of carotid stenosis is severe (70% to 99%) and if the anticipated rate of perioperative stroke or mortality is <6%. The number needed to treat to prevent 1 stroke in 2 yr is 6.

In patients who have suffered a non-disabling ischemic stroke or TIA in the preceding 6 mo, and who have moderate carotid stenosis (50 to 69%), CEA is recommended based on an assessment of the patient's age, sex, and comorbidities. To prevent 1 stroke in 5 yr, 15 patients with moderate carotid stenosis would have to undergo CEA. Factors to consider in recommending CEA for patients with moderate symptomatic carotid stenosis are age, sex, and comorbidities. The NASCET trial, which studied the efficacy of CEA versus medical management, suggested that women experienced higher complication rates from CEA than men. However the CREST trial, which compared CEA to carotid stenting, did not find a sex-related outcome difference between the two interventions. It did find that patients older than 70 did better with CEA than with carotid stenting. All patients undergoing CEA should be started on aspirin (ASA; 81 or 325 mg daily) and a high dose statin before surgery. This therapy, along with blood pressure control and aggressive management of other vascular risk factors, should be continued indefinitely.

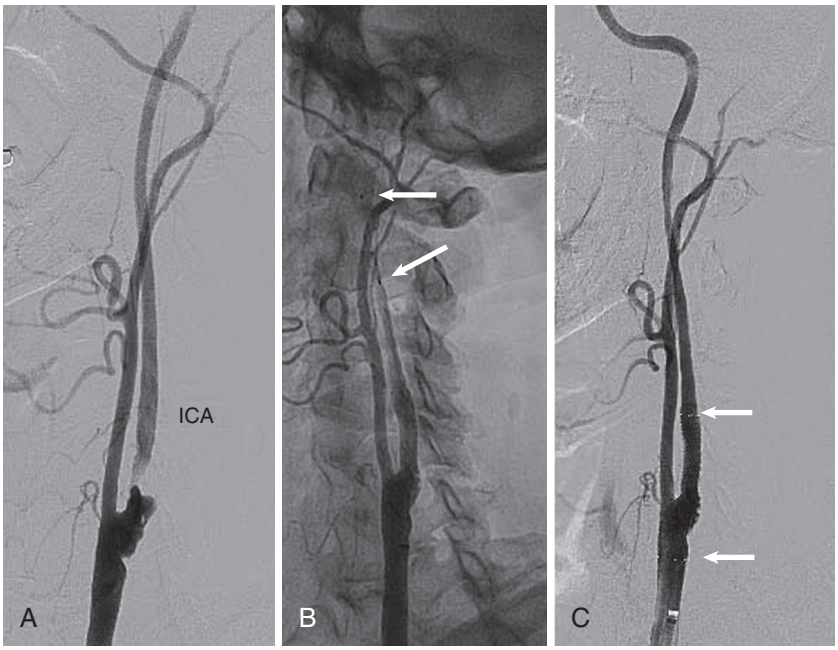

FIG. 2 Carotid stenting for symptomatic carotid stenosis. A, Stenosis at origin of left internal carotid artery. **B,** Stent deployed. Arrows indicate markers of embolic protection filter. **C,** Final angiogram with arrows indicating the margins of the stent. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.)

TABLE 2 Factors Associated with Increased Risk from Carotid Artery Surgery

Anatomic Criteria
High cervical or intrathoracic lesion
Previous neck surgery or radiation therapy
Contralateral carotid artery occlusion
Previous ipsilateral carotid endarterectomy
Contralateral laryngeal nerve palsy
Tracheostomy
Medical Comorbidities
Age >80 yr*
Class III or IV congestive heart failure
Class III or IV angina pectoris
Left main coronary disease
Two- or three-vessel coronary artery disease
Need for open heart surgery
Ejection fraction ≤30%
Recent myocardial infarction
Severe chronic obstructive lung disease

*The risk for a cerebrovascular accident (stroke) with carotid artery stent placement is increased, and the risk for myocardial infarction with carotid endarterectomy is increased.

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.

[1] Rosenfield K et al, for the ACT I Investigators: Randomized trial of stent versus surgery for asymptomatic carotid stenosis, *N Engl J Med* 374:1011-1020, 2016.

[2] Spence DJ, Naylor AR: Endarterectomy, stenting, or neither for asymptomatic carotid artery stenosis, *N Engl J Med* 374:1087-1088, 2016.

CAS can be an alternative to CEA in select patients considered to be at high surgical risk or with unfavorable neck anatomy for surgery.

CEA is preferred over CAS in older patients.

For patients undergoing CAS, dual antiplatelet therapy is recommended for a minimum of 30 days.

When feasible, early revascularization within 14 days after incident event should be undertaken unless there are definite contraindications. For patients undergoing early intervention, CEA is associated with lower periprocedural complication rate than CAS.

Surgical revascularization is not recommended in <50% stenosis, total occlusion, or in patients with major disabling strokes.

In patients who are considered high surgical risk for either CEA or CAS, the role of medical therapy alone compared with surgical revascularization is not well established.

DISPOSITION

Disposition and prognosis depend on several variables (Table 3): The degree of stenosis, the presence of symptoms, medication compliance, and the type of intervention (if any).

PEARLS & CONSIDERATIONS

The results of ongoing studies concerning the best treatment of patients with carotid artery stenosis may result in guideline changes.

SPECIAL CONSIDERATION

Some studies have shown that in patients with bilateral hemodynamically significant stenosis (>70%), blood pressure reduction resulted in worsened outcomes for stroke. These patients would likely be candidates for CEA.

Carotid artery occlusion (100% blockage), for which there is no routine treatment, was reexamined in the national Carotid Occlusion Surgery Study (www.cosstrial.org). Recently published results from the COSS trial demonstrate that superficial temporal artery to middle cerebral artery anastomosis does not provide an overall benefit for ipsilateral 2-yr stroke recurrence when compared to medical therapy alone.

PREVENTION

Prevention of carotid stenosis should include pursuit of a healthy lifestyle and management of risk factors for atherosclerosis.

PATIENT & FAMILY EDUCATION

Patients should be counseled to pursue a healthy lifestyle including exercise and smoking cessation. In addition, patients should take an active role in controlling blood pressure and blood glucose. Further educational materials can be found online at: www.strokecenter.org/education.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Carotid Stenosis (Patient Information)
Transient Ischemic Attack (Related Key Topic)

AUTHORS: **Saagar N. Patel, MD, Joseph S. Kass, MD, JD, FAAN,** and **Prashanth Krishnamohan, MBBS, MD**

TABLE 3 Carotid Stenosis Management

Degree of Carotid Artery Stenosis	<50%	50%-69%	70%-99%
Asymptomatic	• Medical management	• Medical management • Inconclusive evidence base to favor surgical treatment. May be considered in select patients with >60% stenosis.*	• Medical management • CEA in highly selected patients*
Symptomatic	• Medical management	• CEA • CAS can be an alternative	• CEA • CAS can be an alternative

CAS, Carotid artery stenting; *CEA,* carotid endarterectomy.

*CEA can be considered in asymptomatic patients with >70% stenosis if the anticipated rate of perioperative complications (stroke, myocardial infarction, and death) is <3%, life expectancy is greater than 5 yr, and the risks, and benefits (including medical comorbidities) have been discussed thoroughly with the patients and their families

SUGGESTED READINGS

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Grotta JC: Carotid stenosis, *N Engl J Med* 369:1143-1150, 2013.

Meschia JF et al: Evaluation and management of atherosclerotic carotid stenosis, *Mayo Clin Proc* 92(7):1144-1157, 2017.

Rantner B et al: Early endarterectomy carries a lower procedural risk than early stenting in patients with symptomatic stenosis of the internal carotid artery: results from 4 randomized controlled trials, *Stroke* 48:1580, 2017.

Rosenfield K, Matsumura JS, Chaturvedi S: For the ACT I Investigators: randomized trial of stent versus surgery for asymptomatic carotid stenosis, *N Engl J Med* 374:1011-1020, 2016.

Spence DJ, Naylor AR: Endarterectomy, stenting, or neither for asymptomatic carotid artery stenosis, *N Engl J Med* 374:1087-1088, 2016.

BASIC INFORMATION

DEFINITION

Light-headedness, dizziness, presyncope, or syncope in a patient with carotid sinus hypersensitivity is defined as carotid sinus syndrome (CSS). Carotid sinus hypersensitivity is the exaggerated response to carotid stimulation resulting in bradycardia, hypotension, or both. CSS is often considered a variant of neurocardiogenic syncope. The 2013 European Guidelines (ESC) defines CSS as syncope with reproduction of symptoms during carotid sinus massage of 10-second duration. There are two components of CSS: cardioinhibitory and vasodepressor.

SYNONYMS

Carotid sinus syncope
CSS
Carotid sinus hypersensitivity

ICD-10CM CODES

G90.01	Carotid sinus syncope
R55	Syncope and collapse

EPIDEMIOLOGY & DEMOGRAPHICS

- Carotid sinus hypersensitivity accounts for 1% of syncopal episodes (Fig. 1).
- Carotid sinus hypersensitivity is frequently associated with atherosclerosis and diabetes mellitus.
- Incidence increases with age, with an average age of onset at 61 to 74 yr. Fig. 2 illustrates age distribution of the patients with carotid sinus syndrome.
- Men are affected more often than women (2:1).
- CSS is rarely found in patients younger than 50 yr.

MECHANISM

- The carotid sinus is located in the internal carotid artery.
- There is a reflex loop between the mechanoreceptors of the carotid sinus and the vagal nucleus in the midbrain.
- There is an exaggerated cardioinhibitory and vasodepressor reaction caused by decreased sympathetic and increased parasympathetic outflow to the heart and vasculature, respectively.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Often associated with sudden neck movements, especially rotation, neck palpation, shaving, or tight-fitting collars, but can occur in the absence of clear provocation.
- Mild form has symptoms such as fatigue, lightheadedness, nausea, warmth, pallor, or diaphoresis.
- More severe form of the condition has sudden abrupt loss of consciousness without prodrome.

Properly performed carotid sinus massage (CSM) at the bedside is diagnostic. The European Society of Cardiology recommends carotid sinus massage as part of the exam in patients with syncope of unknown etiology and age over 40. This maneuver can elicit three types of responses in patients with carotid sinus hypersensitivity (see "Diagnosis").

- CSM should be performed with the patient in the supine and upright positions while monitoring the patient's blood pressure by cuff and heart rate by ECG.
- CSM should be performed on both the right and left sides but on only one carotid artery at a time.
- Vigorous pressure is applied over the carotid artery, directed posterior to compress the artery against the spinous process of the vertebrae, at the level of the cricoid cartilage for 10 to 30 seconds. Repeat on the opposite side if no effect is produced.
- Contraindications to CSM include the presence of carotid artery bruits, documented carotid artery stenosis >70%, history of stroke or transient ischemic attack <3 mo, history of myocardial infarction <6 mo, history of serious ventricular arrhythmia, or prior carotid endarterectomy.
- Complications of CSM are rare (0.1% to 1%) and may include transient visual disturbance, transient paresis, tachyarrhythmias, or bradyarrhythmias.
- False-positive results with carotid sinus massage may be relatively common in the elderly population. Thus alternative explanations for syncope should be investigated prior to attribution of symptoms to carotid sinus hypersensitivity.

ETIOLOGY

- Idiopathic
- Head and neck tumors (e.g., thyroid)
- Significant lymphadenopathy
- Carotid body tumors
- Prior neck surgery

DIAGNOSIS

- The diagnosis of CSS is made in a patient with a history of syncope when carotid sinus hypersensitivity is demonstrated by CSM and no other cause of syncope is identified.
- CSM can elicit three types of responses diagnostic of carotid sinus hypersensitivity:
  1. Cardioinhibitory type: CSM producing (1) asystole for at least 3 sec in the absence of symptoms or (2) reproduction of symptoms occurring with a decline in heart rate of 30% to 40% or asystole of up to 2 sec in duration. Symptoms should not recur when CSM is repeated after atropine infusion.
  2. Vasodepressor type: CSM producing (1) a decrease in systolic blood pressure of 50 mm Hg in the absence of symptoms or 30 mm Hg in the presence of neurologic symptoms; (2) no evidence of asystole; or (3) neurologic symptoms that persist after infusion of atropine.
  3. Mixed type: CSM producing both types of responses.

DIFFERENTIAL DIAGNOSIS

All causes of syncope

WORKUP

- Evaluation for structural heart disease and other arrhythmias.
- Exclude other causes of syncope or presyncope: Detailed history, physical examination including orthostatic vital signs, ECG.
- Evaluation for vasovagal syncope which may include tilt table testing.

TREATMENT

NONPHARMACOLOGIC THERAPY

Reassurance and education are important. Avoid applying neck pressure from tight collars, shaving, or rapid head turning.

ACUTE GENERAL Rx

Treatment will vary according to the type of carotid hypersensitivity response and symptoms present (see "Chronic Rx").

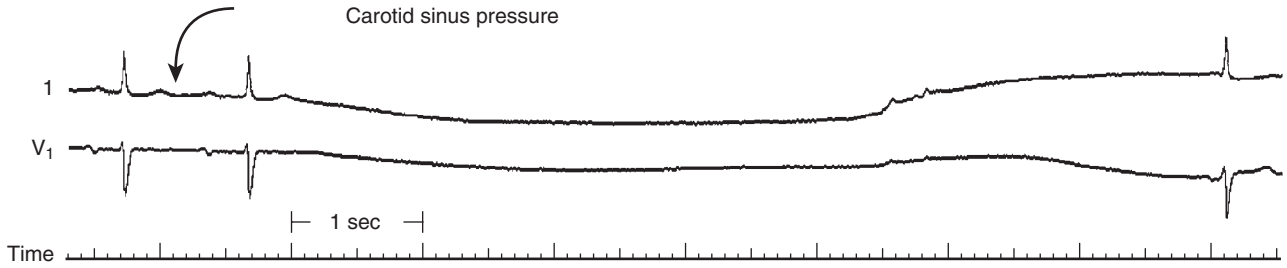

FIG. 1 Carotid sinus hypersensitivity. Two surface electrocardiogram leads are shown during carotid sinus pressure, as indicated. The PR interval is prolonged and followed by a 7.5-second sinus pause ended by a P wave and probable junctional escape complex. The patient was nearly syncopal during this period. (From Issa ZF et al: *Clinical arrhythmology and electrophysiology: a companion to Braunwald's heart disease*, ed 2, Philadelphia, 2012, Saunders.)

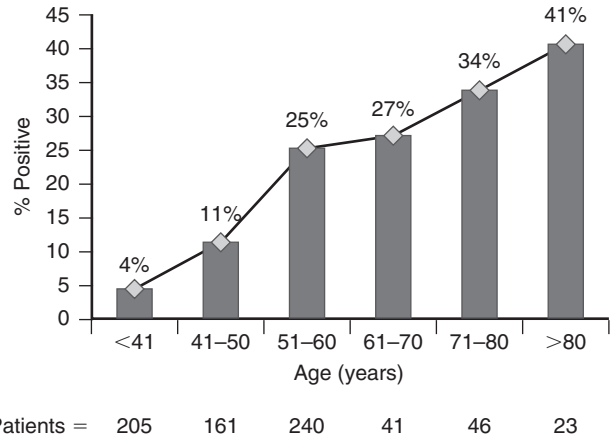

FIG. 2 Age distribution of patients with carotid sinus syndrome. (From Puggioni E et al: Results and complications of the carotid sinus massage performed according to the "method of symptoms," *Am J Cardiol* 89:599-601, 2002.)

CHRONIC Rx

Therapy is divided into three classes: medical, surgical (carotid denervation), and cardiac pacing.

- Surgical therapy has been largely abandoned except in cases of compressing tumors or masses responsible for CSS.
- For infrequent and mildly symptomatic carotid sinus hypersensitivity of either the cardioinhibitory or vasodepressor type, treatment is generally not necessary.
- Cardiac pacing is indicated in patients with recurrent syncope in whom CSM induces ventricular asystole of more than 6 seconds and accompanied by syncope. Dual chamber pacing is recommended as there is evidence that single-chamber pacing worsens syncope recurrence.

Permanent pacing is not indicated for carotid sinus hypersensitivity with no, or only vague, symptoms.

For symptomatic patients with a vasodepressor response to CSM:

- No medical treatment is proven to be effective
- Drugs, such as vasodilators, that would worsen the response should be discontinued or reduced if feasible
- Permissive hypertension
- Increased fluids (≥2 L) and salt intake (>6 g/day)
- Sympathomimetics: Midodrine, titrate from 2.5 to 10 mg tid based on BP and therapeutic response (major side effect in urinary retention in elderly males)
- Serotonin-specific reuptake inhibitors
- Fludrocortisone
- Elastic knee-high or thigh-high stockings
- Carotid sinus denervation

For symptomatic patients with CSS with a mixed response to CSM:

- Combination of dual-chamber permanent pacemaker and agents used to treat vasodepressor response

DISPOSITION

- Up to 50% of the patients have recurrent symptoms.
- No increased mortality rate in patients with idiopathic CSS compared with the general population.

REFERRAL

Cardiology referral is indicated if pacemaker placement is being considered.

PEARLS & CONSIDERATIONS

- The most common type of CSS is cardioinhibitory, followed by mixed and vasodepressor responses.
- Driving restrictions in the 2009 ESC syncope update and 2006 AHA/ACCF consensus document on syncope are stratified according to whether patients have mild or severe syncope.
- Mild carotid sinus syndrome is defined as infrequent mild symptoms (without syncope), with clear precipitating causes (usually standing), warning signs, and infrequent occurrence. For patients with mild sinus hypersensitivity, no driving restrictions are recommended for private or commercial driving.
- Severe carotid sinus syndrome is marked by syncope without warning occurring in any position, without precipitating causes and frequent occurrences. For patients with severe hypersensitivity, all driving is prohibited. If symptoms are controlled, driving is permitted 1 to 6 months after, based on the modality of treatment.

COMMENTS

Prognosis depends on the underlying cause.

RELATED CONTENT

Syncope (Patient Information)
Orthostatic Hypotension (Related Key Topic)
Syncope (Related Key Topic)

AUTHOR: **John Wylie, MD**

BASIC INFORMATION

DEFINITION

Carpal tunnel syndrome (CTS) is a compression neuropathy of the median nerve as it passes under the transverse carpal ligament at the wrist (Figs. E1 and E2). It is the most common entrapment neuropathy.

SYNONYM

CTS

ICD-10CM CODES

G56.0	Carpal tunnel syndrome, unspecified upper limb
G56.01	Carpal tunnel syndrome, right upper limb
G56.02	Carpal tunnel syndrome, left upper limb

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 3.8% of the general population (the most common entrapment neuropathy)
PREVALENT AGE: 30 to 60 yr
PREVALENT SEX: Females are affected two to five times as often as males.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain, paresthesia in 1st, 2nd, 3rd, and lateral half of 4th fingers, worse at night, with awakenings from sleep due to pain and paresthesias being common.
- ***Tinel sign*** at wrist (Fig. 3): Tapping lightly over the median nerve on the volar surface of the wrist produces a tingling sensation radiating from the wrist to the hand.
- ***Phalen sign*** (Fig. 4): Reproduction of symptoms after 1 min of gentle, unforced wrist flexion.

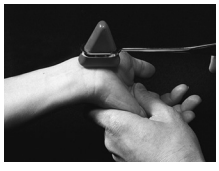

FIG. 3 Tinel sign. The wrist is held in extension while gentle percussion is performed over and just proximal to the transverse carpal ligament. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

FIG. 4 Phalen (wrist flexion) test. With the wrists held in unforced flexion for 30 to 60 seconds, a positive test reproduces or worsens the patient's symptoms. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

- Carpal compression (Durkan) test: Direct pressure over the patient's carpal tunnel for 30 sec elicits symptoms.
- Thenar atrophy in long-standing cases with weakness of thumb abduction and opposition.
- Findings may be bilateral in up to 65% of patients.

ETIOLOGY

- Idiopathic in most cases—caused by increased pressure within the carpal tunnel leading to nerve ischemia
- Commonly associated with diabetes, obesity, female gender, advancing age, pregnancy, hypothyroidism, rheumatologic disorders, autoimmune disorders
- Specific occupations with repetitive strain or job-related mechanical overuse
- May also occur due to mass occupying lesions (tenosynovitis, gout, ganglion) or as a result of trauma (distal radius fractures, perilunate and lunate dislocations, etc.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cervical radiculopathy
- Chronic tendinitis
- Pronator teres syndrome
- Anterior interosseous syndrome
- Complex regional pain syndrome
- Brachial plexopathy, thoracic outlet syndrome
- Polyneuropathy
- Other entrapment neuropathies
- Traumatic wrist injuries
- Vascular disorders (Raynaud syndrome)
- Cervical myelopathy

IMAGING STUDIES

Carpal tunnel syndrome is a clinical diagnosis, but imaging may assist workup in uncertain situations. Accumulating evidence suggests that diagnostic ultrasound may be almost as sensitive as nerve conduction velocity tests and may help identify the structural cause of nerve compression. X-ray or MRI may be helpful in ruling out other conditions.

ELECTRODIAGNOSTIC STUDIES

Nerve conduction velocity tests (NCS) demonstrate impaired sensory conduction across the carpal tunnel and may help guide treatment based on the severity of median nerve compression. Electromyography may show active denervation muscle potentials. Specificity of NCS and electromyography for CTS is >95%, and sensitivity is >85%.

TREATMENT

ACUTE GENERAL Rx

- Activity modification and ergonomic optimization (desk, keyboard).
- Nocturnal wrist splint has been shown to be effective.
- No evidence for effectiveness of NSAIDs.
- Corticosteroid injection of carpal canal on ulnar side of palmaris longus tendon proximal to wrist crease (Figs. E5 and E6): Can be done with palpation guidance or under ultrasound guidance. In different clinical studies, injections have increased patient satisfaction and improved clinical symptoms, albeit temporarily.
- Low-dose oral corticosteroids are optional but usually not effective.
- Short-term benefit from ultrasound therapy (physical therapy modality).
- Carpal tunnel release if no response from nonoperative treatment.

DISPOSITION

Clinical course may have remissions and exacerbations. Some may progress from intermittent to persistent sensory complaints (numbness, tingling, paresthesia) and then to motor symptoms. In pregnancy, symptoms usually resolve spontaneously weeks after delivery.

REFERRAL

Surgical referral is needed if conservative treatment fails. Surgery (sectioning of transverse carpal ligament) is performed by open, endoscopic, or minimal incision techniques, with good long-term results. Carpal tunnel release is one of the most common surgeries performed, with approximately 400,000 conducted per yr. Recurrence and complication rates range from 3% to 19% in some series, with revision required in up to 12% of patients.

PEARLS & CONSIDERATIONS

- The sensory changes of carpal tunnel syndrome spare the thenar eminence. This distinctive pattern occurs because the palmar sensory cutaneous branch of the median nerve arises proximal to the wrist, passing superficial to the tunnel.
- Role of repetitive hand or wrist use and workplace factors in the development of carpal tunnel syndrome remains controversial.
- Recent trials from the Mayo Clinic using ultrasound-guided perineural injection therapy (PIT) using 5% dextrose (D_5W) have shown promising results in patients with mild-to-moderate CTS.[1]

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Carpal Tunnel Syndrome (Patient Information)

AUTHORS: **Shashank Dwivedi, MD,** and **Manuel F. DaSilva, MD**

[1] Wu YT et al: Six-month efficacy of perneural dextrose for carpal tunnel syndrome: a prospective, randomized, double-blind, controlled trial, *Mayo Clin Proc* 92(8):1179-1189, 2017.

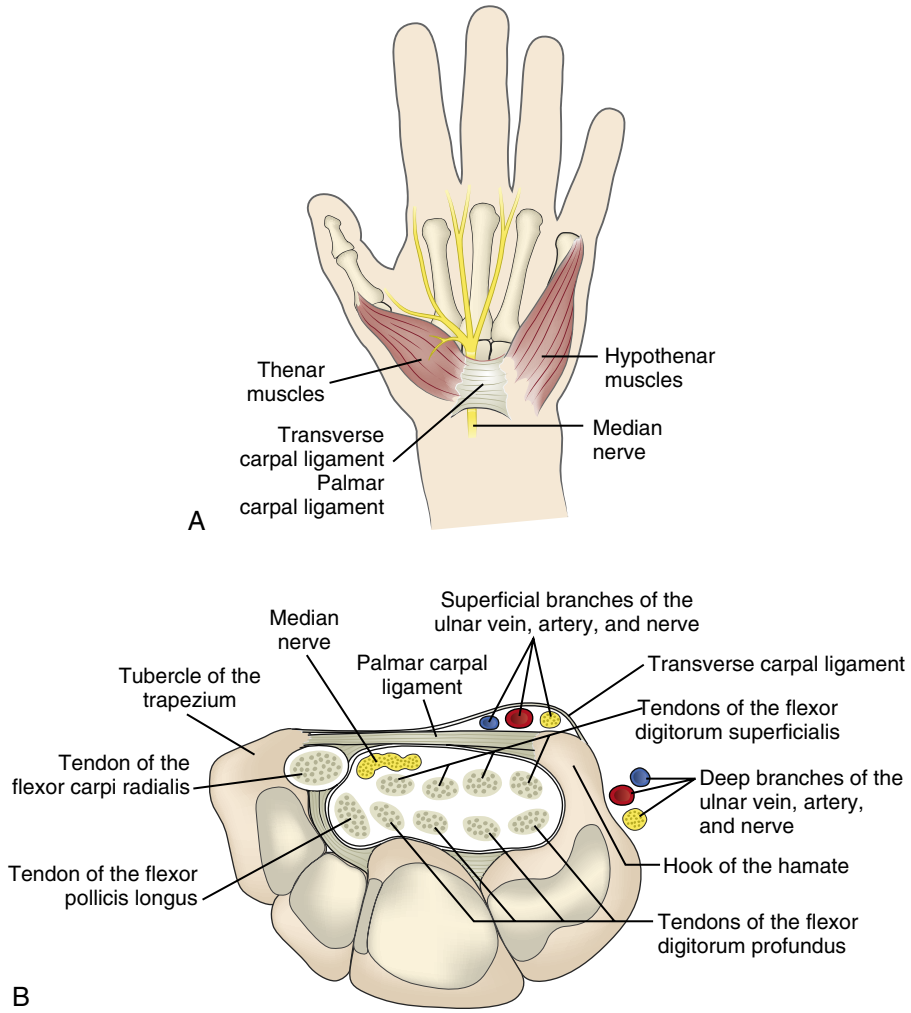

FIG. E1 Anatomic basis of carpal tunnel syndrome. A, General view of the relationship between the median nerve and the flexor retinaculum. **B,** Cross section at the distal carpal row showing the structures in the carpal tunnel. (Redrawing based on an illustration by Li-Guo Liang, in Yu HL et al: *Atlas of hand anatomy and clinical implications,* Philadelphia, 2004, Mosby. From Auerbach P: *Wilderness medicine,* ed 5, Philadelphia, 2007, Mosby.)

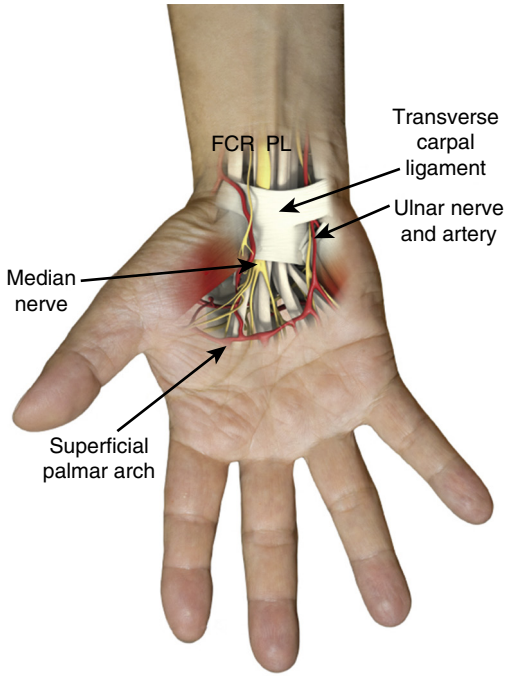

FIG. E2 Carpal tunnel anatomy. (Original artwork by Manuel F. DaSilva, MD)

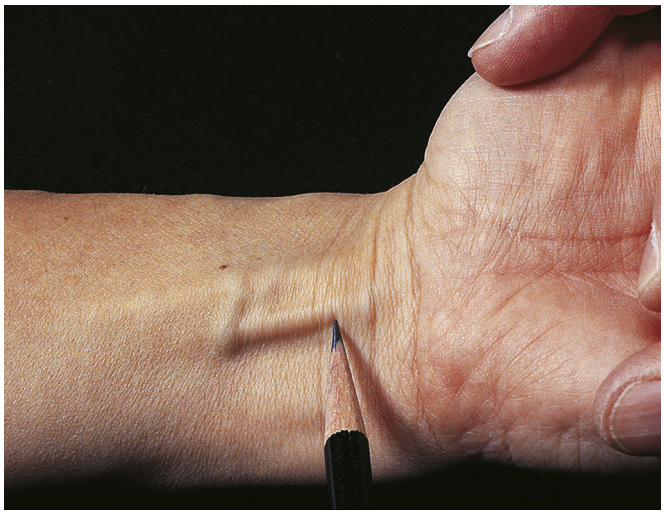

FIG. E5 Palmaris longus tendon. The pencil point identifies the tendon of the palmaris longus muscle, an important landmark in determining the site of injection for carpal tunnel syndrome. The tendon of the flexor carpi radialis can be seen just to the radial side of the palmaris longus tendon. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

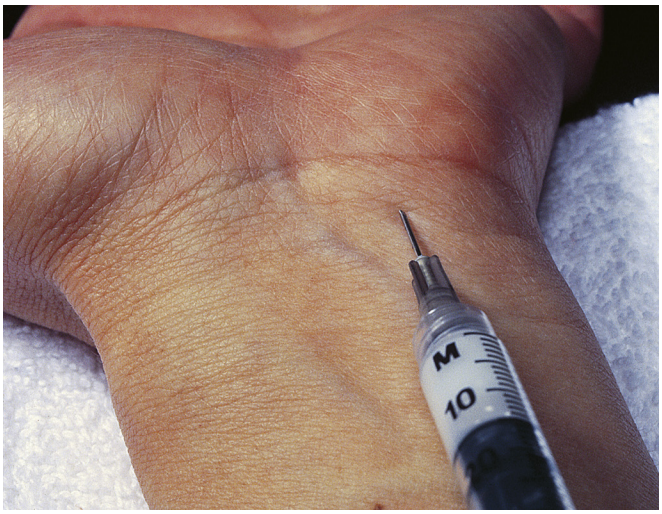

FIG. E6 Carpal tunnel injection. The needle is inserted just proximal to the wrist crease and to the ulnar side of the palmaris longus tendon. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

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Burton CL et al: Clinical course and prognostic factors in conservatively managed carpal tunnel syndrome: a systematic review, *Arch Phys Med Rehabil* 97(5):836-852, 2016.

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Stütz N et al: Revision surgery after carpal tunnel release--analysis of the pathology in 200 cases during a 2 year period, *J Hand Surg Br* 31(1):68-71, 2006.

Ting BL et al: Median nerve ultrasonography measurements correlate with electrodiagnostic carpal tunnel syndrome severity, *J Am Acad Orthop Surg* 27(1):e17-e23, 2019.

Wessel LE et al: Sonographic findings are associated with carpal tunnel symptom severity, *Hand Surg Am* S0363- 5023(17):31113-31119, 2018.

BASIC INFORMATION

DEFINITION

Cataracts are the clouding and opacification of the normally clear crystalline lens of the eye. The opacity may occur in the cortex, the nucleus of the lens, or the posterior subcapsular region, but it is usually in a combination of areas.

SYNONYMS

Congenital cataracts (e.g., from rubella)
Metabolic cataracts (e.g., caused by diabetes)
Hereditary cataracts
Age-related senile cataracts (nuclear sclerotic and cortical cataracts)
Traumatic cataracts
Toxic or drug-induced cataracts (e.g., caused by steroids)
Lenticular opacities

ICD-10CM CODES

H26.9	Cataract, unspecified
H25.0	Senile incipient cataract
H25.1	Senile nuclear cataract
H26.0	Infantile, juvenile and presenile cataract
E11.36	Type 2 diabetes mellitus with diabetic cataract
E13.36	Other specified diabetes mellitus with diabetic cataract
H25.011	Cortical age-related cataract, right eye
H25.012	Cortical age-related cataract, left eye
H25.013	Cortical age-related cataract, bilateral
H25.019	Cortical age-related cataract, unspecified eye
H25.039	Anterior subcapsular polar age-related cataract, unspecified eye
H25.049	Posterior subcapsular polar age-related cataract, unspecified eye
H25.099	Other age-related incipient cataract, unspecified eye
H25.10	Age-related nuclear cataract, unspecified eye
H25.9	Unspecified age-related cataract
H26.019	Infantile and juvenile cortical, lamellar, or zonular cataract, unspecified eye
H26.039	Infantile and juvenile nuclear cataract, unspecified eye
H26.041	Anterior subcapsular polar infantile and juvenile cataract, right eye
H26.042	Anterior subcapsular polar infantile and juvenile cataract, left eye
H26.043	Anterior subcapsular polar infantile and juvenile cataract, bilateral
H26.069	Combined forms of infantile and juvenile cataract, unspecified eye
H26.09	Other infantile and juvenile cataract
H26.101	Unspecified traumatic cataract, right eye
H26.102	Unspecified traumatic cataract, left eye
H26.103	Unspecified traumatic cataract, bilateral
H26.109	Unspecified traumatic cataract, unspecified eye
H26.8	Other specified cataract
H26.9	Unspecified cataract

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Most common cause of treatable blindness; cataract removal is one of the most frequent surgical procedure in patients >65 yr (3.5 million cataract operations per yr). By 2020 more than 30 million Americans will have cataracts. Of Americans >40 yr, 20.5 million (17.2%) have cataracts. Of these, 5% have had surgery.

PEAK INCIDENCE:

- In early life: Congenital and hereditary causes predominant; consider drug related, diabetes, and trauma
- In older age group: Nuclear sclerotic, cortical, and posterior subcapsular cataracts (after 40 yr)

PREDOMINANT AGE: Elderly; some stage of cataract development is present in >50% of persons 65 to 74 yr and in 65% of those >75 yr. Lens opacification and sclerosis begins around age 40 yr and then usually progresses either slowly or rapidly depending on individual and health.

GENETICS: Hereditary with syndromes such as galactosemia, homocystinuria, diabetes

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Cloudiness and opacification of the crystalline lens of the eye (Fig. E1, Fig. E2)
- Decrease or absence of the red reflex (important in pediatric ages, since visual acuity is more difficult to assess)
- Painless decreased visual acuity (difficulty reading, seeing road signs: usually gradual, over mo to yr)
- Glare and decreased night vision (early symptom: difficulty with night driving)

ETIOLOGY

- Heredity
- Trauma (may develop cataract quickly with significant trauma)
- Age related
- Drug related (e.g., corticosteroids, smoking)
- Radiation (UV B and ionizing)
- Congenital (genetic, metabolic, or infections)
- Inflammatory (e.g., history of uveitis or previous ocular surgery)
- Diabetes
- Collagen vascular disease

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Corneal lesions
- Retinal lesions, detached retina, tumors
- Vitreous disease, chronic inflammation

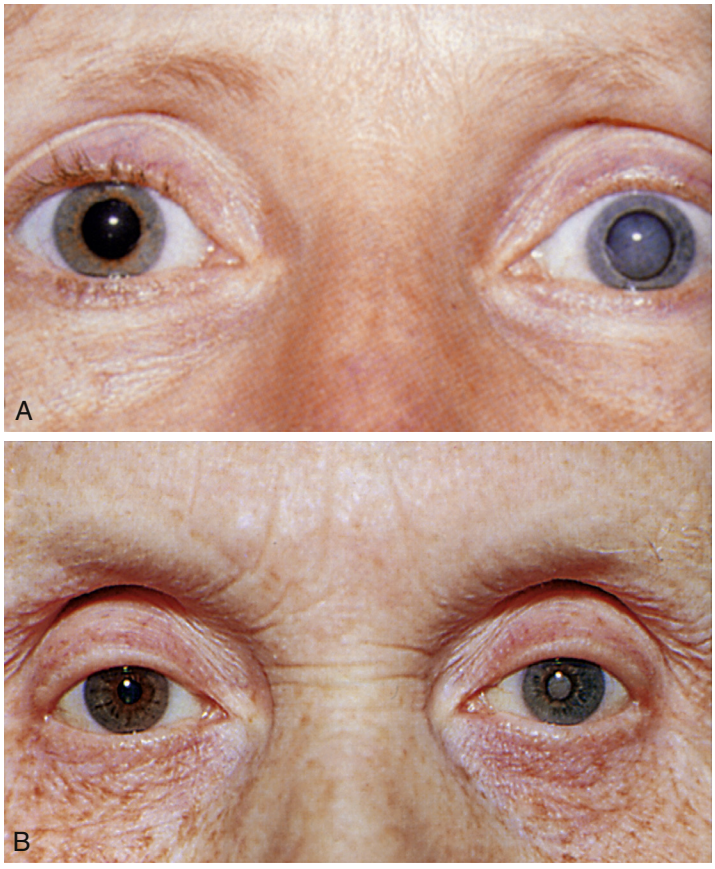

FIG. E1 A and B, Cataract of the left eye. (From Swartz, MH: *Textbook of physical diagnosis, history and examination*, ed 7, Philadelphia, 2014, Elsevier.)

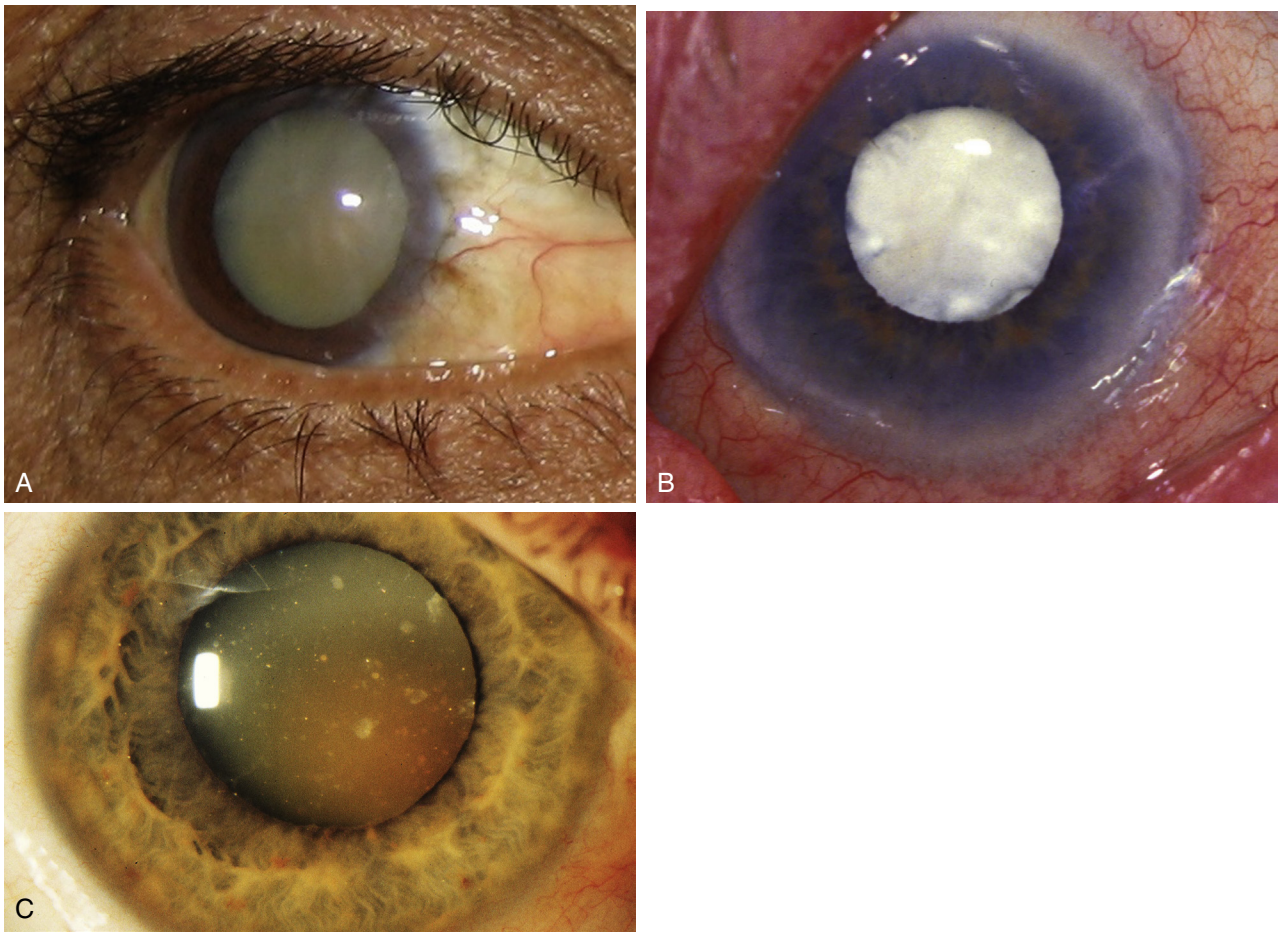

FIG. E2 Cataract maturity. A, Mature cataract—secondary divergent squint is present; **B,** Hypermature cataract with wrinkling of the anterior capsule; **C,** Morgagnian cataract with liquefaction of the cortex and inferior sinking of the nucleus. (Courtesy S Chen, Part A; C Barry, Parts B and C; In Bowling B: *Kanski's clinical ophthalmology, a systemic approach*, ed 8, Philadelphia, 2016, Elsevier.)

WORKUP

- Complete eye examination, including visual acuity and measurement of refractive error, slit lamp examination, dilated funduscopic examination, and brightness acuity testing
- Complete physical examination for other underlying causes

LABORATORY TESTS

- Rarely, urinary amino acid screening and central nervous system imaging studies with congenital cataracts
- Fasting glucose in young adults with cataracts, particularly posterior subcapsular type (PSC)
- Diabetes, collagen vascular disease, other metabolic diseases in younger patients
- Genetic and hereditary evaluation

Rx TREATMENT

There is no evidence that antioxidants or drugs will slow or treat cataracts.

NONPHARMACOLOGIC THERAPY

- Wait until vision is compromised before doing surgery.
- Plan cataract removal with intraocular lens (Fig. E3) implantation when vision is compromised and limiting activities of daily living, such as driving at night or reading. Removal of the cataract should be expected to improve the ability of the patient to perform these activities. Another indication to remove cataracts might be to improve the examination view for treatment and assessment of retinal diseases.
- Decision for timing of surgery depends upon patient complaints, best corrected visual acuity (e.g., 20/50), and glare measurements (brightness acuity test decreases vision significantly).

ACUTE GENERAL Rx

None necessary except when acute glaucoma or inflammation occurs with the rare hypermature cataracts

CHRONIC Rx

- Change glasses as cataracts develop.
- Myopia (near-sighted shift in prescription) is common, and glasses can be adjusted until surgery is contemplated.

DISPOSITION

Refer if sight is compromised or the eye is red or inflamed.

REFERRAL

Refer to ophthalmologist for evaluation for extraction (Fig. E4, Fig. E5) when vision is compromised (see "Nonpharmacologic Therapy").

PEARLS & CONSIDERATIONS

- Patients want to know five things about cataracts:
  1. Chance for vision improvement (other eye conditions often coexist, such as macular degeneration, diabetic retinopathy, corneal diseases, etc., any of

which may limit the expected visual outcome of cataract removal)
2. When vision will improve
3. Risk from surgery (such as infection, hemorrhage, retinal detachment, corneal problems)
4. Effect of surgery, including reduction of refractive errors
5. Types of complications

- Men planning cataract surgery should, if feasible, delay the use of alpha-blockers until after surgery has been completed. The risk of intraoperative floppy iris syndrome is substantial among men taking tamsulosin and similar alpha-blockers. This is often unavoidable, and discontinuation of alpha-blockers does not help, although intraoperative techniques have improved to make floppy iris syndrome less complicated.

RELATED CONTENT

Cataracts (Patient Information)

AUTHOR: **R. Scott Hoffman, MD**

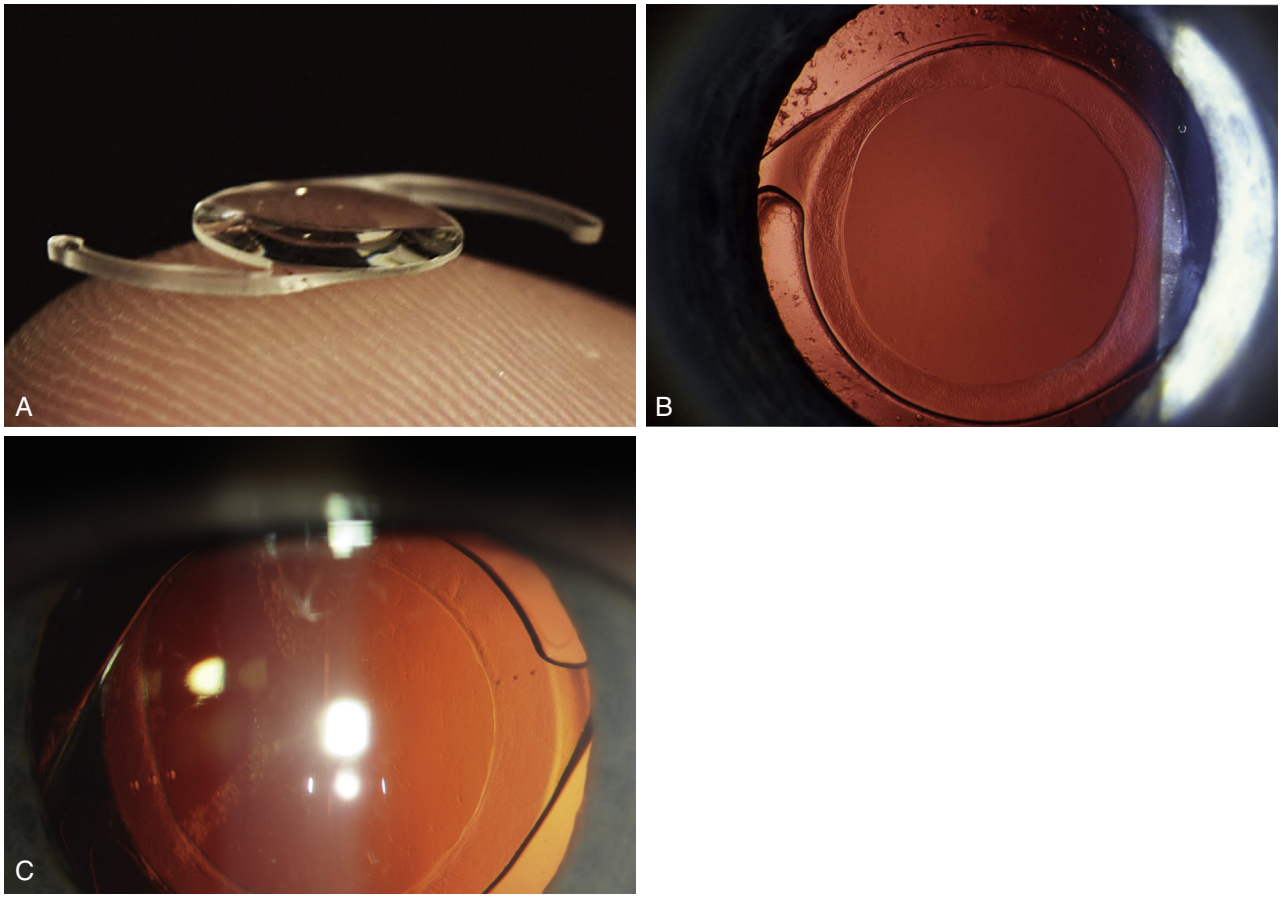

FIG. E3 Intraocular lens (IOL). A, One-piece flexible IOL—note the square-edged optic; **B,** IOL *in situ* in the capsular bag; **C,** Implanted toric IOL showing diametrically opposite sets of three dots marking the lens axis (From Bowling B: *Kanski's clinical ophthalmology, a systemic approach,* ed 8, Philadelphia, 2016, Elsevier. Part A, courtesy C Barry.)

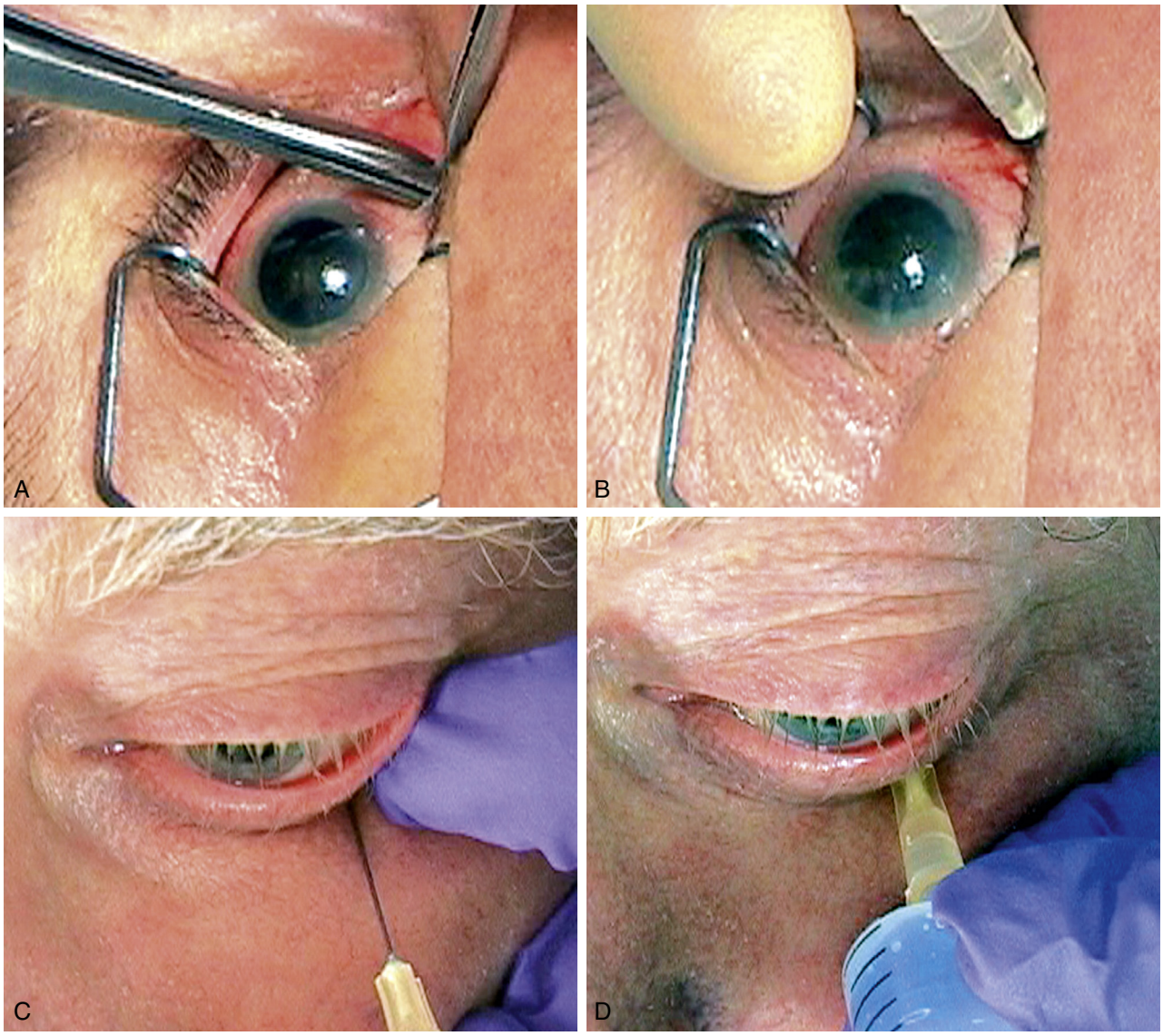

FIG. E4 Local anesthesia for cataract surgery. A, Conjunctival dissection for sub-Tenon anesthesia; **B,** Sub-Tenon infiltration with a blunt cannula; **C,** Insertion of needle for peribulbar anesthesia; **D,** Peribulbar infiltration of anesthetic agent. (From Bowling B: *Kanski's clinical ophthalmology, a systemic approach,* ed 8, Philadelphia, 2016, Elsevier.)

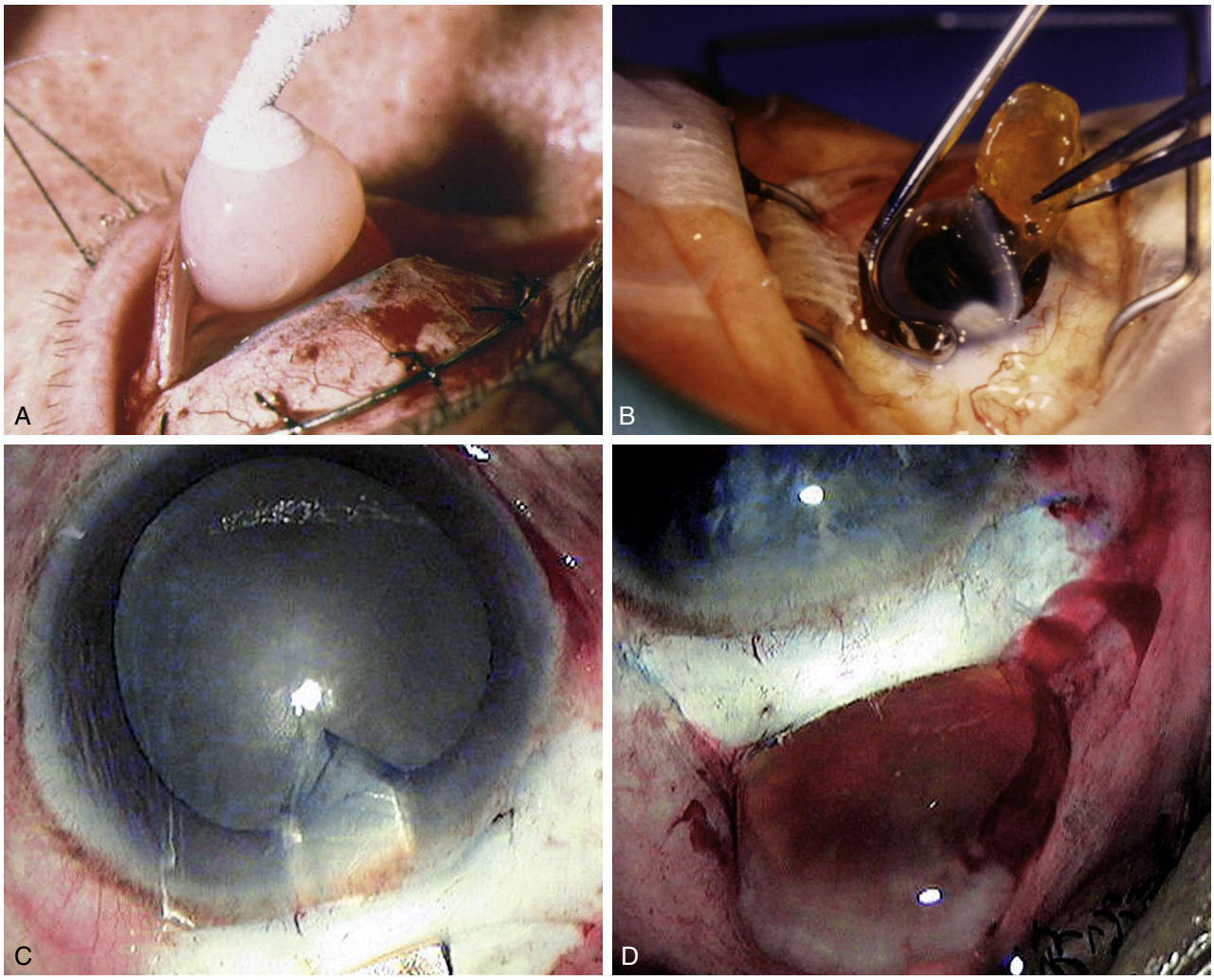

FIG. E5 Manual cataract surgery. A, Intracapsular extraction; **B,** Extracapsular extraction; **C** and **D,** Manual small-incision cataract surgery. (Courtesy C Barry, Parts A and B; A Hennig, Parts C and D. In Bowling B: *Kanski's clinical ophthalmology, a systemic approach,* ed 8, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Catatonia is a psychomotor syndrome of disordered volition characterized by catalepsy, waxy flexibility, stupor or psychomotor agitation, mutism and negativism (oppositionalism), motor signs such as posturing, mannerisms, grimaces, stereotypies, and echophenomena. Screening and severity rating scales, such as the Bush-Francis Catatonia Rating Scale (BFCRS), are often used to define the condition, as are *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (DSM-5) criteria. Catatonia is an independent syndrome that co-occurs with several mental and medical conditions.

SYNONYMS

Catatonic stupor
Catatonic excitement
Schizophrenic catalepsy
Schizophrenic catatonia
Schizophrenic flexibilitas cerea

ICD-10CM CODES	
F06.1	Catatonic disorder due to known physiological condition; catatonia associated with another mental disorder
F20.2	Catatonic schizophrenia
R40.1	Catatonia, not otherwise specified; catatonic stupor
DSM-5 CODE	
293.89	Catatonia due to a general medical condition

In DSM-5, the specifier "with catatonia" is used for schizophrenia, schizoaffective, schizophreniform, and brief psychotic and substance-induced psychotic disorders. The specifier "with catatonia" is also used for current or most recent major depressive or manic episode in major depressive disorder and in bipolar I and II disorders. Catatonia NOS can also be diagnosed in DSM-5.

In DSM-5, 3 out of the following 12 symptoms must be present to diagnose catatonia:

- Stupor: No or very little psychomotor response
- Catalepsy: Passive rigidity of posture held against gravity
- Mutism: No or very little verbal response
- Waxy flexibility: Persistence of body part positioning after slight resistance
- Negativism: Oppositional nonresponse to instructions
- Posturing: Active spontaneous holding of a position against gravity
- Mannerisms: Caricatured odd movements
- Stereotypy: Frequent repetitive non–goal-directed movements
- Agitation: Nonprovoked heightened psychomotor activity
- Grimacing: Distortions of facial affect
- Echolalia: Repetition of others' words
- Echopraxia: Repetition of others' movements

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The incidence of catatonia has been studied primarily in acutely ill psychiatric inpatients and is present in approximately 10% of patients, with estimates ranging from 5% to 20%, based on prospective studies of psychiatric unit admissions over a span of 1 yr.

PREVALENCE: Catatonia has a 9% to 17% prevalence rate in patients with acute psychiatric disorders, with stuporous catatonia the most common subtype. Catatonic excitement occurs in 15% to 25% of acutely ill hospitalized manic patients. Signs of catatonia occur in up to 17% of adults with autism-spectrum disorders and 30% of patients with delirium. The catatonia prevalence rate was 23.9% in patients undergoing electroconvulsive therapy (ECT) or having elevated creatinine phosphokinase.

GENETICS: Familial clustering of catatonia suggests a genetic component that lacks classic Mendelian inheritance. Studies of periodic catatonia show familial aggregation and evidence for genetic linkage to chromosome 15. Individuals with chromosome 22q11.2 deletion syndrome (DS), which includes conditions such as DiGeorge syndrome and velocardiofacial syndrome, are at risk for catatonia. The 22q11.2DS is associated with disrupted dopamine (DA), γ-aminobutyric acid (GABA), and glutamate systems, which are thought to be dysfunctional in catatonia. Myelin basic protein *Mbp*$^{+/-}$ mice developed late-onset catatonia, and mice lacking 2′ 3′-cyclic nucleotide 3′-phosphodiesterase (*Cnp)* produced defective myelin that leads to degeneration, neuroinflammation, and subsequent catatonia. In the human *Cnp* model, homozygotes for the SNP rs2070106 A allele showed decreased mRNA expression of *Cnp* and a predisposition to catatonia, suggesting that oligodendrocytic dysfunction related to microglial activation may produce a vulnerability to catatonia as in individuals with schizophrenia with *Cnp* rs2070106-AA.

RISK FACTORS: See Table 1 for a list of risk factors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Catatonia is a neuropsychiatric syndrome whose cluster of psychomotor signs and symptoms results in aberrations of movement and behavior. Following Kraepelin, catatonia was generally synonymous with schizophrenia until the 1990s. Under DSM-5, catatonia is recognized as due to a medical or psychiatric condition, or unspecified, as, for example, in recurrent idiopathic catatonia. Mood disorders such as major depressive disorder and bipolar disorder are now recognized as more commonly associated with catatonia.

Subtypes of catatonia include **catatonic withdrawal** or **stuporous catatonia,** marked by motoric immobility, staring, mutism, rigidity, withdrawal and refusal to eat, along with more bizarre features, such as posturing, grimacing, negativism, waxy flexibility, echophenomena, stereotypy, verbigeration, and automatic obedience; **excited catatonia,** characterized by purposeless and excessive motor activity, which may include disorganized pressured speech, flight of ideas, verbigeration, disorientation/confusion, and confabulation; and **malignant catatonia,** where catatonic signs are accompanied by fever and dysautonomia. Some experts delineate the catatonia symptom profile into decreased (stupor), increased (excitement), or abnormal psychomotor patterns. Malignant catatonia is associated with increased morbidity and mortality. A specific example of malignant catatonia is neuroleptic malignant syndrome (NMS), induced by dopamine-blocking agents or withdrawal of a dopamine or GABA-A agonist. Another variant, known as manic delirium or delirious mania, exists with features of both excited and malignant catatonia. Periodic catatonia can present with alternating stuporous and excited forms.

ETIOLOGY

Although catatonia is a heterogeneous condition with multiple etiologies and pathophysiologies, myelin changes may indicate a final common pathway, setting in motion an innate neuroinflammatory cascade involving microgliosis in cingulo-frontoparietal regions that then may affect motor functioning in basal ganglia.

See Table 2 for a listing of etiologies.

DIAGNOSIS

Catatonia can lead to medical complications resulting in significant morbidity and mortality, making rapid diagnosis and treatment a priority. Medical complications abound, and the mortality rate for malignant catatonia despite better recog-

TABLE 1 Risk Factors for Catatonia

- Prior episodes of catatonia
- History of or current extrapyramidal symptoms
- Mood disorder with psychomotor retardation or excitement
- Autism-spectrum disorder
- Epilepsy, migraine, and epileptiform activity on EEG
- Frontal, basal ganglia, brain stem, pontine, or cerebellar disease
- Dehydration
- Recent weight loss
- Medications that lower seizure threshold
- Use of dopamine-blocking agents
- Serotonergic medications
- Cocaine use
- Withdrawal from alcohol, benzodiazepines, or other GABA-ergic agents
- Long-term anticholinergic use with recent withdrawal or decrease in dose
- Hyponatremia, hypomagnesemia
- Low serum iron
- Perinatal infectious disease
- MRI findings of cingulo-frontal-parietal cortico-striato-thalamo-cortical circuit lesions

EEG, Electroencephalogram*; GABA*, γ-aminobutyric acid.
Adapted from Fink M, Taylor MA: *Catatonia: a clinician's guide to diagnosis and treatment.* New York, 2003, Cambridge University Press.

TABLE 2 Etiologies

Primary Psychiatric

- Mood disorders
- Schizophrenia
- Autism
- Acute psychoses
- Conversion disorder
- Dissociative disorder
- Obsessive-compulsive disorder
- Personality disorders

Secondary Neuromedical

- Cerebrovascular
- Other CNS disorders
- Neoplasms
- Poisonings
- Infections
- Paraneoplastic and autoimmune encephalitides (especially anti-NMDA receptor antibody encephalitis)
- Metabolic and other medical causes
- Drug related: Induced with dopamine-blocking agents, tacrolimus, disulfiram, and phencyclidine, among many others; Discontinuation of dopamine agonist medications and other antiparkinsonians and of GABA-A agonists and of clozapine can precipitate a catatonia
- Idiopathic

CNS, Central nervous system; *GABA,* gamma aminobutyric acid; *NMDA, N*-methyl-D-aspartate.

nition and treatment is still 9% to 10%. For a list of potential medical complications, see Table 3.

DIFFERENTIAL DIAGNOSIS

- **Locked-in syndrome,** linked to pontine lesions, can be distinguished because patients will generally attempt to communicate with their eyes. Patients in a **persistent vegetative state** may also appear to be catatonic.
- **Stiff person syndrome** is an autoimmune disorder that presents during severe stress with intense lower-extremity spasmodic stiffness that may appear like catatonic posturing, but these patients speak and describe their pain.
- **Extrapyramidal parkinsonism** or **tardive dystonia:** These may have a distinctive tremor but are not negativistic and lack bizarre catatonic psychomotor symptoms.
- **Nonconvulsive status epilepticus** can also produce a catatonic-like state where electroencephalography is essential for accurate diagnosis and prompt management that may minimize cognitive damage.
- **Akinetic mutism,** an extreme form of the abulic syndrome caused by neurologic injury, can be conceptualized as a version of catatonia.
- **Hypoactive delirium** may overlap or coexist with catatonia. It is extremely important to confirm a delirious patient is not also suffering from a catatonic episode, because neuroleptics can worsen simple catatonia, resulting in malignant catatonia.

WORKUP

See Table 4 for evaluation and Table 5 for workup.

TABLE 3 Medical Complications of Catatonia

Simple Nonmalignant Catatonia

- Aspiration
- Burns
- Cachexia
- Dehydration
- Pneumonia
- Pulmonary emboli
- Deep vein thromboses
- Urinary retention and sequelae

Malignant Catatonias

- Acute renal failure
- Acute respiratory distress syndrome
- Cardiac arrest
- Cheyne-Stokes breathing
- Death
- Dysphagia secondary to muscle spasm
- Diffuse intravascular coagulation
- ECG changes
- Gait abnormalities
- Gastrointestinal bleed
- Hepatocellular damage
- Hypoglycemia
- Intestinal pseudoobstruction
- Laryngospasm
- Myocardial infarction
- Necrotizing enterocolitis
- Respiratory arrest
- Rhabdomyolysis
- Seizures
- Sepsis
- Unresponsiveness to pain

ECG, Electrocardiogram.

LABORATORY TESTS

Fever and hyperautonomia, leukocytosis, low sodium, loss of body weight (>5% in 3 wk, >20% in 6 mo), low serum iron, elevated creatinine phosphokinase, cerebrospinal fluid pleocytosis, low serum ceruloplasmin level, myoglobinuria, EEG findings consistent with catatonia, for example, generalized or focal slowing, epileptiform activity

IMAGING STUDIES

- MRI: Mesoencephalofrontal dissolution related to lesions in the frontal cortex, particularly orbitofrontal cortex and anterior cingulate cortex and its basal ganglia thalamo-cortical circuit, parietal cortex, pons, and medial cerebellum
- SPECT: Frontoparietal hypoperfusion—left > right

Rx TREATMENT

NONPHARMACOLOGIC THERAPY AND MANAGEMENT

- Managements includes early recognition, close observation, and frequent vital signs.
- Supportive care is essential: Hydration; nutrition; mobilization; anticoagulation; and pulmonary embolus, and deep vein thrombosis, and aspiration precautions.

TABLE 4 Catatonia Examination Based on Bush-Francis Catatonia Rating Scale

1. Observe while trying to engage in conversation (mutism).
2. Scratch your head or rub nose in exaggerated manner (echopraxia).
3. Examine for rigidity, attempt to reposture (waxy flexibility), and instruct patient to "keep your arm loose" while moving it with lighter and heavier force (gegenhalten).
4. Ask patient to extend arm; place your finger beneath patient's hand and try to raise it slowly after stating: "Do NOT let me raise your arm" (mitgehen-anglepoise lamp).
5. Extend your hand stating: "Do NOT shake my hand" (ambitendency).
6. Reach into your pocket and state: "Stick your tongue out, I want to stick a pin in it (or I want to write on it with my pen)" (automatic obedience).
7. Check for grasp reflex.
8. Check the chart for reports from previous 24 h. Check for PO intake, vital signs, and any behavior changes or incidents.
9. Observe patient each day for activity, abnormal movements, abnormal speech, echopraxia, rigidity, negativism, waxy flexibility, gegenhalten, mitgehen, ambitendency, automatic obedience, and grasp.

PO, By mouth.

Adapted from Bush G, Fink M, Petrides G, Dowling F, Francis A: Catatonia I: rating scale and standardized examination. *Acta Psychiatr Scand* 93:129-136, 1996.

TABLE 5 Workup for Catatonia

- EEG
- Neuroimaging
- Routine blood work including creatine phosphokinase and serum iron level and other blood work as indicated
- Urine for myoglobinuria
- Ceruloplasmin for Wilson disease as indicated
- Cerebrospinal fluid analysis including antibody titers for autoimmune limbic encephalitides as indicated

EEG, Electroencephalogram.

- Discontinue antipsychotics or other drugs such as metoclopramide, which can cause or worsen catatonia.
- Restart recently withdrawn dopamine agonists, antiparkinsonians, and benzodiazepines, especially in patients with parkinsonism.
- Institute supportive measures (e.g., cooling blankets, parenteral fluids, antihypertensives) if malignant catatonia emerges.

ACUTE GENERAL Rx (SEE TABLE 6)

CHRONIC RX: Maintenance medications or ECT and close psychiatric follow-up for recurrence

DISPOSITION

Disposition will vary depending on response. Because response rate to lorazepam and ECT is high, ranging from 65% to 85%, many patients can return home. Some patients with chronic catatonia who do not respond well need long-term care in facilities.

TABLE 6 A Treatment Approach for Catatonic States

- Lorazepam treatment trial, if there are no contraindications, can give 2 mg IV and observe for effect; if none, come back in 3 h and do it again; if no effect, can do it again in 3 h for a total of 6 mg over 24 h. Can go up to 20 mg/d in divided doses before saying the patient has failed to be lysed, especially if partial improvement has been seen.
- For those who show partial improvement on day 1, can continue 2 mg IV q8h for 3-4 days and may continue it longer if benefit is greater than risk, to maintain the level of improvement achieved, especially if the catatonia has been present >1 mo.
- After lysis of the catatonia, can switch to sublingual or oral in divided doses. This usually maintains the effect, although an occasional patient needs IV dose reinstituted.
- After lysis, psychosis depending on etiology may continue, and sometimes patients will need cautious use of an atypical antipsychotic medication. Most often if circumstances warrant it, one can use a low-potency, atypical antipsychotic such as olanzapine or aripiprazole while continuing lorazepam to buffer against re-emergence of catatonia and NMS.
- It is important to have patients with catatonia diathesis who need a neuroleptic on a benzodiazepine until there is more confidence that the patient is less in danger of catatonia.
- If patient is not improving: Trial of adjunctive amantadine: 100 mg/d titrating up every 3 days to 400 mg/d in divided doses. Trial of adjunctive memantine: 10 mg/d for 3 or 4 days, then increase to 10 mg bid if ineffective. Trial of adjunctive topiramate: 100 mg bid up to 200 mg bid. Trial of dopamine agonists (bromocriptine 2.5 mg bid-tid up to 45 mg/d, Sinemet, lisuride, and pramipexole have all been used with anecdotal success). Zolpidem 5-10 mg PO, if feasible, can be used as a test for catatonia response.
- For malignant catatonia, use lorazepam trial as described earlier. If still catatonic, ECT is often lifesaving and should be instituted prior to day 5 of syndrome. If ECT is not available or refused by surrogate decision-maker, can try a dopamine agonist with or without dantrolene 100-300 mg/d in divided doses starting with 1-2.5 mg/kg IV; when acidosis, rigidity, and fever resolve, then 1 mg/kg IV q6h × 48 h; with further improvement, taper to q12h, then 1 mg/kg each day × 8 days.
- For catatonic excitement (delirious mania): Consider lorazepam and ECT first; then lorazepam and olanzapine, lorazepam and Depakote, or carbamazepine.
- For catatonia secondary to autoimmune encephalitides (e.g., anti-NMDA receptor encephalitis), use of anti-inflammatory strategies is indicated: steroids, intravenous Ig, rituximab, cyclophosphamide, plasmapheresis.

bid, Twice daily; *ECT,* electroconvulsive therapy; *Ig*, immunoglobulin; *IV,* intravenous; *NMDA, N*-methyl-D-aspartate; *NMS,* neuroleptic malignant syndrome; *PO,* by mouth; *tid,* three times daily.

Adapted from Fricchione G, Beach S: Cingulate aspects of catatonia and treatment. In Vogt B (ed): *Cingulate cortex*. New York, 2019, Elsevier.

PEARLS & CONSIDERATIONS

- Simple catatonias treated with neuroleptics often develop NMS.
- Once malignant (catatonia with autonomic instability and hyperthermia), mortality risk increases.
- Patients with malignant catatonia who are receiving neuroleptics have an even higher mortality risk.
- Catatonia that has been present for <1 mo is often easier to treat.
- While attempting pharmacotherapy, it is prudent to introduce the potential need for ECT by seeking surrogate approval and consent.

PREVENTION

Use of dopamine blocking and GABA-A blocking medications in high-risk groups requires caution.

PATIENT & FAMILY EDUCATION

Patient and family education is available at the Penn State University Catatonia Information Center website (http://www.catatonia.org; Andrew Francis, PhD, MD, Director).

RELATED CONTENT

Serotonin Syndrome (Related Key Topic)
Neuroleptic Malignant Syndrome (Related Key Topic)

AUTHOR: **Gregory L. Fricchione, MD**

SUGGESTED READINGS

American Psychiatric Association: In *Diagnostic and statistical manual of mental disorders*, ed 5, Arlington, 2013, American Psychiatric Association (DSM-5).

Bush G, Fink M, Petrides G, Dowling F, Francis A: Catatonia I: rating scale and standardized examination, *Acta Psychiatr Scand* 93:129-136, 1996.

Caroff SN, Mann SC, Francis A, Fricchione GL, editors: *Catatonia. from psychopathology to neurobiology*, Washington, DC, 2004, American Psychiatric Publishing Inc.

Fink M, Taylor MA: *Catatonia: a clinician's guide to diagnosis and treatment*, NY, 2003, Cambridge University Press.

Fricchione G, Beach S: Cingulate aspects of catatonia and treatment. In Vogt B, editor: *Cingulate Cortex*, NY, 2019, Elsevier (in press).

Rosebush PI, Mazurek MF: Catatonia and its treatment, *Schizophr Bull* 36:239-242, 2010.

Walther S, Stegmayer K, Wilson JE, Heckers S: Structure and neural mechanisms of catatonia, *Lancet Psychiatry* 6:610-619, 2019.

BASIC INFORMATION

DEFINITION

Cat-scratch disease (CSD) is an infectious disease consisting of gradually enlarging regional lymphadenopathy occurring after contact with a feline. Atypical presentations are characterized by a variety of neurologic manifestations as well as granulomatous involvement of the eye, liver, spleen, and bone. The disease is usually self-limiting, and recovery is complete; however, patients with atypical presentations, especially if immunocompromised, may suffer significant morbidity and mortality.

SYNONYMS

CSD
Cat-scratch fever
Benign inoculation lymphoreticulosis
Nonbacterial regional lymphadenitis

ICD-10CM CODE
A28.1 Cat-scratch disease

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Unknown
INCIDENCE (IN U.S.)
- 9 to 10 cases per 100,000 persons per yr (22,000 cases per yr)
- Majority of reported cases occur in persons <21 yr

PEAK INCIDENCE: August through January

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Classic, most common finding: Regional lymphadenopathy occurring within 2 wk of a scratch or contact with felines; usually a new kitten in the household
- Tender, swollen lymph nodes most commonly found in the head and neck (Fig. E1), followed by the axilla and the epitrochlear, inguinal, and femoral areas
- Erythematous overlying skin, showing signs of suppuration from involved lymph nodes
- On careful examination, evidence of cutaneous inoculation in the form of a nonpruritic, slightly tender pustule or papule
- Fever in most patients
- Malaise and headache in fewer than a third of patients
- Atypical presentations in less than 15% of cases
  1. Usually in association with lymphadenopathy and a low-grade or frank fever (>101° F, >38.3° C)
  2. Include granulomatous involvement of the conjunctiva (Parinaud oculoglandular syndrome) and focal masses in the liver, spleen, and mesenteric nodes
- CNS involvement: Neuroretinitis, encephalopathy, encephalitis, transverse myelitis, seizure activity, and coma
- Osteomyelitis in adults and children
- Can be a cause of culture-negative endocarditis
- In HIV-infected and other immunocompromised patients, *Bartonella henselae* is the cause of bacillary angiomatous and peliosis hepatis

ETIOLOGY

- Major cause: *Bartonella henselae*, possibly *Afipia felis* and *Bartonella clarridgeiae*
- Mode of transmission: Predominantly by direct inoculation through the scratch, bite, or lick of a cat, especially a kitten
- Also can be transmitted by flea bite (with the flea obtaining the bacteria from a bacteremic cat); rarely after exposure to a dog, probably secondary to flea bites
- Approximately 2 wk after introduction of the bacteria into the host, regional lymphatic tissues displaying granulomatous infiltration associated with gradual hypertrophy
- Possible dissemination to distant sites (e.g., liver, spleen, and bone), usually characterized by focal masses or discrete parenchymal lesions

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Granulomas of this syndrome must be differentiated from those associated with:
- Tularemia
- Tuberculosis or other mycobacterial infections
- Brucellosis
- Sarcoidosis
- Sporotrichosis or other fungal diseases
- Toxoplasmosis
- Lymphogranuloma venereum
- Benign and malignant tumors such as lymphoma

WORKUP

Diagnosis should be considered in patients who present with a predominant complaint of gradually enlarging regional (focal) lymphadenopathy, often with fever and a recent history of having contact with a cat. A primary ulcer at the site of the cat scratch may or may not be present at the time lymphadenopathy becomes manifest.

LABORATORY TESTS

- Serologies: An IFA *Bartonella* serology (titer ≥1:64) is strongly suggestive of infection. An IFA titer >1:256 is diagnostic.
- A PCR assay on tissue, blood or intraocular fluid is also available but sensitivity is not high.
- Lymph node biopsy: Granulomatous inflammation consistent with CSD.
- Warthin-Starry silver stain on biopsy can identify the bacteria.
- Histopathologically, Warthin-Starry silver stain has been used to identify the bacillus.
- Culture: *B. henselae* is a fastidious, slow-growing, gram-negative rod that requires specific culture techniques for tissue or blood.
- Routine laboratory findings:
  1. Mild leukocytosis or leukopenia
  2. Infrequent eosinophilia
  3. Elevated ESR or CRP
- Abnormalities of bilirubin excretion and elevated hepatic transaminases are usually secondary to hepatic obstruction by granuloma, mass, or lymph node.
- In patients with neurologic manifestations, lumbar puncture usually reveals normal CSF, although there may be a mild pleocytosis and modest elevation in protein.
- CSD skin test is no longer used for clinical purposes.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Warm compresses to the affected nodes
- In cases of encephalitis or coma: Supportive care

ACUTE GENERAL Rx

- This disease is typically self-limited and generally resolves within 2 to 6 months. Most studies show no additional benefit from antibiotic therapy.
- It would be prudent to treat severely ill patients, especially if immunocompromised, with antibiotic therapy, because these patients tend to suffer dissemination of infection and increased morbidity.
- *Bartonella* is usually sensitive to a 5-day course of azithromycin (500 mg on day 1 followed by 250 mg for 4 days for weight >45.5 kg; 10 mg/kg on day 1 followed by 5 mg/kg for 4 days for weight <45.5 kg) or alternatively tetracycline, sulfa, and the quinolones can be used for 7 to 10 days.
- Hepatosplenic disease, neuroretinitis, and endocarditis require longer courses of therapy.
- Antipyretics and NSAIDs may also be used for lymphadenitis.

DISPOSITION

- Overall prognosis is good.
- Surgical drainage is generally not recommended. Excision of the entire lymph node may be necessary if not responding after prolonged treatment.

REFERRAL

- For diagnostic aspiration or excision in presence of regional lymphadenopathy, bone lesions, and mesenteric lymph nodes and organs
- Infectious diseases specialist for organ involvement including endocarditis
- To ophthalmologist for ocular granulomas

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Cat-Scratch Disease (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Cheslock MA, Embers ME: Human bartonellosis: an underappreciated public health problem? *Trop Med Infect Dis* 4(2), 2019.

Klotz SA et al: Cat-scratch disease, *Am Fam Physician* 83(2):152-155, 2011.

Psarros G et al: Bartonella henselae infections in solid organ transplant patients: report of 5 cases and review of the literature, *Medicine* 91:111-121, 2012.

Zangwill KM: Cat scratch disease and other Bartonella infections, *Adv Exp Med Biol* 764:159-166, 2013.

FIG. E1 Cat-scratch disease. A, Ulcerated papule on the cheek caused by a cat scratch 2 weeks previously and enlargement of submandibular lymph nodes. **B,** Line of papules on the forearm of another patient at the site of a cat scratch. **C,** Marked enlargement of the ipsilateral axillary lymph nodes. (Courtesy B.J. Zitelli and H.W. Davis. From Zitelli BJ: *Atlas of pediatric physical diagnosis,* St Louis, 2002, Mosby.)

Cavernous Sinus Thrombosis PTG

BASIC INFORMATION

DEFINITION

Cavernous sinus thrombosis (CST) is a late complication of either facial or paranasal sinus infection, resulting in thrombosis of the cavernous sinus and inflammation of its surrounding anatomic structures, including cranial nerves III, IV, V (ophthalmic and maxillary branch), and VI, and the internal carotid artery.

SYNONYMS

CST
Intracranial venous sinus thrombosis or thrombophlebitis
Dural sinus thrombosis

ICD-10CM CODE
G08 Intracranial and intraspinal phlebitis and thrombophlebitis

EPIDEMIOLOGY & DEMOGRAPHICS

- CST is rare in the post-antibiotic era.
- Before antibiotics the mortality rate was 80% to 100%.
- With antibiotics and early diagnosis, mortality rates have fallen to ~20%.
- Reported morbidity rates have also declined from between 50% and 70% to about 20% to 30% with advances in imaging modalities and aggressive medical care.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Can be either an acute and fulminant disease or an indolent and subacute presentation.
- Septic cases of CST commonly present with high-grade fever (picket fence pattern) and signs of sepsis.
- Headache, although not specific, is the most common presenting symptom and may precede fever and periorbital edema by several days. Elderly patients, however, may only demonstrate alteration in mental status without antecedent headache. The triad of unilateral or bilateral progressive chemosis, periorbital edema, and proptosis with headache is a classical presentation in patients with CST. These signs and symptoms are related to the anatomic structures affected within the cavernous sinus, notably cranial nerves III to VI, as well as impaired venous drainage from the orbit and eye.

Other common signs and symptoms include:

- Ptosis.
- Cranial nerve palsies (III, IV, V1, V2, VI).
  1. Ophthalmoplegia caused by involvement of cranial nerves III, IV, and VI is present in most cases. Sixth nerve palsy can occur early in some cases of septic CST, especially when originating from the sphenoid sinus owing to its anatomic proximity.
  2. Hypoesthesia or hyperesthesia of the ophthalmic and maxillary branch of the fifth nerve is common. Periorbital sensory loss and impaired corneal reflex may be noted.
- Papilledema, retinal hemorrhages, and decreased visual acuity progressing to blindness may occur from venous congestion within the retina.
- Pupil may be dilated and sluggishly reactive.
- Headache with nuchal rigidity and changes in mental status may occur if the infection spreads intracranially to the meninges and brain parenchyma.
- Infection can spread to the contralateral cavernous sinus through the intercavernous sinuses within 24 to 48 hours of initial presentation.
- Patients may also develop signs and symptoms of pituitary insufficiency.

ETIOLOGY

- CST most commonly results from contiguous spread of an infection from either the sinuses (sphenoid, ethmoid, or frontal) or the medial third of the face (areas around the eyes and nose that drain to the ophthalmic vein). Nasal furuncles are the most common facial infection to produce this complication. Less-common primary sites of infection include dental abscess, tonsils, soft palate, middle ear, or orbit (orbital cellulitis).
- CST also can result from hematogenous spread of infection to the cavernous sinus by the superior and inferior ophthalmic veins or through the lateral and sigmoid sinuses. Depending on the pressure gradients, infection can spread in a retrograde direction because the dural sinuses are valveless.
- *Staphylococcus aureus* is the most commonly identified pathogen, found in 60% to 70% of the cases.
- *Streptococcus* is the second leading cause.
- Gram-negative rods and anaerobes may also lead to CST.
- Rarely, *Aspergillus fumigatus* and mucormycosis cause CST.
- Risk factors for dural sinus thrombosis include venous hypercoagulable disorders, infections (see previous), trauma, malignancies, systemic inflammatory disorders, pregnancy, and dehydration.

DIAGNOSIS

- The diagnosis of CST is made by clinical suspicion and confirmed by appropriate imaging studies.
- Proptosis, ptosis, chemosis, and cranial nerve palsy beginning in one eye and progressing to the other eye establish the diagnosis.

DIFFERENTIAL DIAGNOSIS

- Orbital or periorbital cellulitis
- Internal carotid artery aneurysm or fistula
- Cerebrovascular disease
- Migraine headache
- Allergic blepharitis
- Thyroid ophthalmopathy
- Orbital neoplasm
- Meningitis
- Epidural and subdural infections
- Epidural and subdural hematoma
- Subarachnoid hemorrhage
- Acute angle-closure glaucoma
- Trauma

WORKUP

CST is a clinical diagnosis, with laboratory tests and imaging studies confirming the clinical impression.

LABORATORY TESTS

- Complete blood count, erythrocyte sedimentation rate, blood cultures, and sinus cultures help establish and identify an infectious primary source. Metabolic panel to look for electrolyte imbalances in cases of suspected pituitary involvement (DI/SIADH).
- Lumbar puncture (LP) helps to distinguish CST from more localized processes (e.g., sinusitis, orbital cellulitis). LP reveals inflammatory cells in 75% of cases. In half of these cases, the cerebrospinal fluid profile is typical for a parameningeal focus (high white blood cells with polymorphonuclear and/or mononuclear cells, normal glucose, normal protein, culture negative), and in one third may be similar to that of bacterial meningitis.

IMAGING STUDIES

- MRI with gadolinium, including magnetic resonance angiography and magnetic resonance venogram (Fig. 1), is more sensitive than CT scan and is the imaging study of choice to diagnose CST. Findings may include deformity of the internal carotid artery within the cavernous sinus and an obvious signal hyperintensity within thrombosed vascular sinuses.
- Noncontrast CT scan of the head and orbits may demonstrate increased density in the region of the cavernous sinus but has relatively low sensitivity. Contrast-enhanced CT scan may reveal underlying sinusitis, thickening of the superior ophthalmic vein, and irregular filling defects within the cavernous sinus; however, findings may be normal early in the disease course.

TREATMENT

NONPHARMACOLOGIC THERAPY

Recognizing the primary source of infection (i.e., facial cellulitis, middle ear, and sinus infections) and treating the primary source expeditiously is the best way to prevent CST.

ACUTE GENERAL Rx

- Appropriate therapy should take into account the primary source of infection as well as possible associated complications such as brain abscess, meningitis, or subdural empyema.
- Broad-spectrum intravenous antibiotics are used as empiric therapy until a definite pathogen is found. Treatment should include vancomycin to cover hospital or community-acquired methicillin-resistant *Staphylococcus aureus* or resistant *Streptococcus pneumoniae* plus a third- or fourth-generation cephalosporin:
  1. Vancomycin (1 g q12h with normal renal function) plus either ceftriaxone (2 g q12h) or cefepime (2 g q8 to 12h).

2. Metronidazole 500 mg IV q6h should be added if anaerobic bacterial infection is suspected (dental or sinus infection).

- Most experts recommend anticoagulation with heparin after the diagnosis is confirmed, unless surgical intervention is planned, or there is evidence of an expanding hematoma. Spontaneous intracranial hemorrhage should first be ruled out before initiating heparin therapy. Early heparinization has been suggested in patients with unilateral CST to prevent clot propagation. Coumadin therapy should be avoided in the acute phase of the illness but should ultimately be instituted to achieve an INR of 2 to 3 and continued until the infection, symptoms, and signs of CST have either resolved or significantly improved. Anticoagulation with warfarin is generally continued for a minimum of 3 to 6 mo. Retrospective case reports and case series have demonstrated a favorable outcome in terms of decreased mortality and morbidity in the anticoagulated patients.
- Steroid therapy is also controversial but may prove helpful in reducing cranial nerve dysfunction or when progression to pituitary insufficiency occurs. Corticosteroids should only be instituted after appropriate antibiotic coverage. Dexamethasone 10 mg q6h is the treatment of choice.
- Emergent surgical drainage with sphenoidotomy is indicated if the primary site of infection is believed to be the sphenoid sinus.

CHRONIC Rx

- Patients with CST are usually treated with prolonged courses (3 to 4 wk) of IV antibiotics. If there is evidence of complications such as intracranial suppuration, 6 to 8 wk of total therapy may be warranted.
- All patients should be monitored for signs of complicated infection, continued sepsis, or septic emboli while antibiotic therapy is being administered. Relapse of septic CST can occur after an initial improvement weeks after stopping antibiotic treatment.

DISPOSITION

- CST can be a life-threatening, rapidly progressive infectious disease with high morbidity and mortality rates (30%) despite antibiotic use. Morbidity and mortality rates are increased in cases of sphenoid sinus infection.
- Complications of untreated CST include extension of thrombus to other dural sinuses, carotid thrombosis with concomitant strokes, subdural empyema, brain abscess, or meningitis. Septic embolization may also occur to the lungs, resulting in acute respiratory distress syndrome, pulmonary abscess, empyema, and pneumothorax.
- Thirty percent of treated patients develop long-term sequelae, including cranial nerve palsies, blindness, pituitary insufficiency, and hemiparesis.

REFERRAL

If suspected, CST should be considered a medical emergency. Depending on source of infection, appropriate consultation should be made (i.e., ear-nose-throat, ophthalmology, and infectious disease).

PEARLS & CONSIDERATIONS

COMMENTS

CST is a medical emergency and should be suspected with progressing chemosis, proptosis, and cranial neuropathy in a patient with headaches with or without fever.

The anatomy of the cavernous sinus explains the clinical findings: The cavernous sinus lies just above and lateral to the sphenoid sinus and drains the middle portion of the face by the superior and inferior ophthalmic veins; cranial nerves III, IV, V, and VI pass alongside or through the cavernous sinus.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Cavernous Sinus Thrombosis (Patient Information)

AUTHORS: **Danyelle Evans, MD, Joseph S. Kass, MD, JD, FAAN,** and **Prashanth Krishnamohan, MBBS, MD**

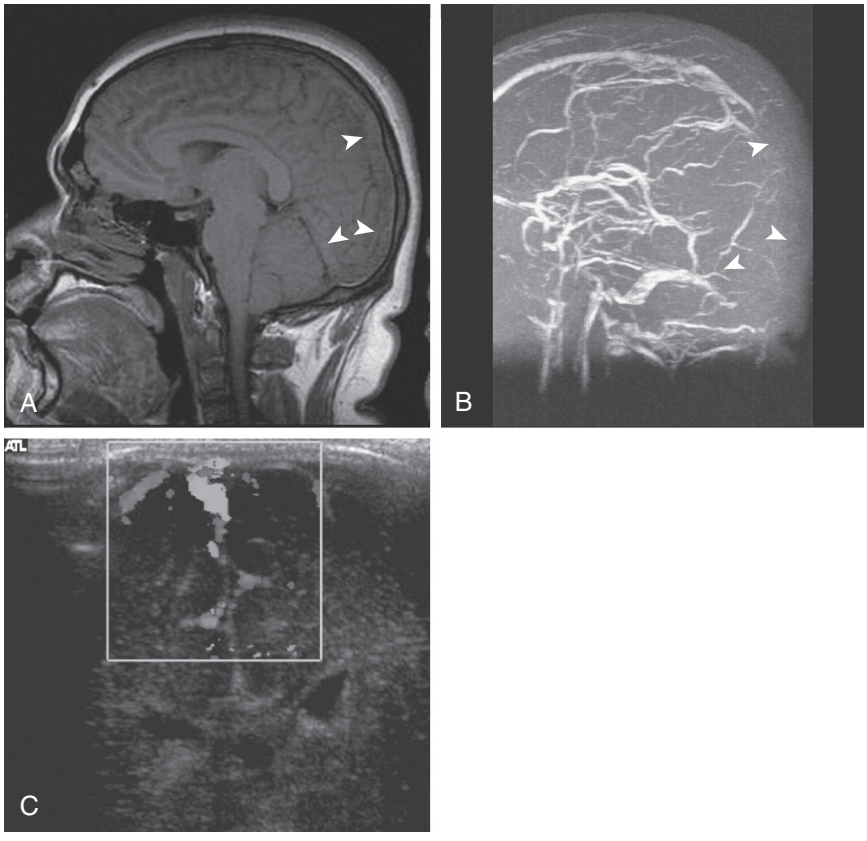

FIG. 1 Superior sagittal sinus (SSS) thrombosis on magnetic resonance venogram (MRV). Sagittal T1 magnetic resonance imaging **(A)** shows intermediate signal intensity in sagittal and straight sinuses *(arrowheads).* No flow is seen on MRV **(B)** in these vessels *(arrowheads),* which is consistent with thrombosis. Color Doppler evacuation **(C)** of the SSS in another 6-mo-old patient with suspected thrombosis demonstrated a patent SSS with normal draining cortical veins. (From Fuhrman BP, et al.: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.)

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BASIC INFORMATION

DEFINITION

Celiac disease is a chronic autoimmune disease characterized by malabsorption and diarrhea precipitated by ingestion of food products containing gluten. Gluten is a protein complex found in wheat, rye, and barley.

SYNONYMS

Gluten-sensitive enteropathy
Celiac sprue
Nontropical sprue

ICD-10CM CODE
K90.0 Celiac disease

EPIDEMIOLOGY & DEMOGRAPHICS

- The prevalence of celiac disease is 0.5% to 1% in the general population in North America and Western Europe and 5% in high-risk groups such as first-degree relatives of persons with the disease. The prevalence of celiac disease in the U.S. has increased fourfold over the past three decades, but the trend is flattening. The decline in undiagnosed celiac disease may reflect greater public and professional attention to gluten-related issues. Worldwide celiac disease affects 0.6% to 1% of the population. Celiac disease is significantly more common in persons with type 1 diabetes mellitus (DM) and is associated with greater risk of retinopathy and nephropathy in this population.
- Incidence is highest during infancy and the first 36 mo of life (after introduction of foods containing gluten), in the third decade (frequently associated with pregnancy and severe anemia during pregnancy), and in the seventh decade.
- There is a slight female predominance.
- The average age of diagnosis is in the fifth decade of life.
- The risk for celiac disease is 5% to 10% in newborn children of parents with the disease and nearly 20% in siblings.
- It is estimated that only 10% to 15% of persons with celiac disease in the U.S. have been diagnosed.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination may be entirely within normal limits.
- Weight loss, dyspepsia, short stature, and failure to thrive may be noted in children and infants.
- Weight loss, fatigue, and diarrhea are common in adults.
- Abdominal pain, nausea, and vomiting are unusual.
- Pallor as a result of iron-deficiency anemia is common.
- Atypical forms of the disease are being increasingly recognized and include osteoporosis, short stature, anemia, infertility, and neurologic problems. Manifestations of calcium deficiency, such as tetany and seizures, are rare and can be exacerbated by coexistent magnesium deficiency.
- Angular cheilitis, aphthous ulcers, atopic dermatitis, and dermatitis herpetiformis are frequently associated with celiac disease.
- Table 1 summarizes the clinical spectrum of celiac disease.
- Table 2 summarizes extraintestinal manifestations of celiac disease.
- Disorders associated with celiac disease are summarized in Box 1.

ETIOLOGY

- Celiac sprue is considered an autoimmune-type disease, with tissue transglutaminase (tTG) suggested as a major autoantigen. It results from an inappropriate T-cell–mediated immune response against ingested gluten in genetically predisposed individuals who carry either *HLA-DQ2* or *HLA-DQ8* genes. There is sensitivity to gliadin, a protein fraction of gluten found in wheat, rye, and barley. In patients with celiac disease, immune responses to gliadin fractions promote an inflammatory reaction, mainly in the upper small intestine, manifested by infiltration of the lamina propria and the epithelium with chronic inflammatory cells and villous atrophy. The susceptibility to celiac disease may also be related to other environmental factors such as bacterial microbiome and reovirus infection). Table 3 summarizes biomarkers in the diagnosis of celiac disease and monitoring compliance to gluten-free diet.
- Seroconversion to celiac autoimmunity may occur at any time.
- Timing of introduction of gluten into the infant diet is associated with the appearance of celiac disease in children at risk. Children initially exposed to gluten in the first 3 mo of life have a fivefold increased risk. Current recommendations are to delay introduction of gluten into the diet of a genetically susceptible infant until 4 to 6 mo of age while the mother continues to breastfeed.

DIAGNOSIS

Diagnostic criteria for celiac disease require at least four out of five or three out of four if the *HLA* genotype is not performed:

1. Typical symptoms of celiac disease
2. Positivity of serum celiac disease Immunoglobulin A (IgA) class autoantibodies at high titer
3. *HLA-DQ2* or *HLA-DQ8* genotypes
4. Celiac enteropathy at the small intestinal biopsy
5. Response to gluten-free diet

DIFFERENTIAL DIAGNOSIS

- Inflammatory bowel disease
- Laxative abuse
- Intestinal parasitic infestations
- Lactose intolerance
- Other: Irritable bowel syndrome, tropical sprue, chronic pancreatitis, Zollinger-Ellison syndrome, cystic fibrosis (children), lymphoma, eosinophilic gastroenteritis, short bowel syndrome, Whipple disease
- Intestinal lymphoma, tuberculosis, radiation enteritis, HIV enteropathy

LABORATORY TESTS

- IgA anti-tTG antibody by enzyme-linked immunosorbent assay (tissue transglutaminase [tTG] test) is the best screening serologic test for celiac disease. IgA antiendomysial antibodies (EMA) test is also a good screening test for celiac disease but is best used as a confirmatory test in cases of borderline positive results. In patients with IgA deficiency, the IgG deamidated gliadin peptide (DPG) test (deamidated gliadin peptides) can be used for diagnosis. Screening of close relatives is initially done with polymerase chain reaction (PCR) testing for *HLA DQ2* or *HLA DQ8.* Those that are positive should then have serum tTG IgA screening. All diagnostic serologic testing for celiac disease should be performed before a gluten-free diet is initiated. Table 4 summarizes the sensitivity, specificity, and positive and negative predictive values of serologic tests for untreated celiac disease.
- CBC, ferritin level: Iron-deficiency anemia (microcytic anemia, low ferritin level) may be present.
- Celiac disease can lead to malabsorption: Screen for vitamin B_{12} level, folate level, vitamin D level, serum calcium, albumin, magnesium; vitamin B_{12} deficiency, vitamin D deficiency, hypomagnesemia, and hypocalcemia are not uncommon in celiac disease.
- Biopsy of the small bowel, considered the gold standard, has been questioned as a reliable and conclusive test in all cases. It may be reasonable in children with significant elevations

TABLE 1 Clinical Spectrum of Celiac Disease

Symptomatic
Frank malabsorption symptoms: Chronic diarrhea, failure to thrive, weight loss
Extraintestinal manifestations: Anemia, fatigue, hypertransaminasemia, neurologic disorders, short stature, dental enamel defects, arthralgia, aphthous stomatitis
Silent
No apparent symptoms in spite of histologic evidence of villous atrophy
In most cases identified by serologic screening in at-risk groups (see Laboratory Tests)
Latent
Subjects who have a normal histology, but at some other time, before or after, have shown a gluten-dependent enteropathy
Potential
Subjects with positive celiac disease serology but without evidence of altered jejunal histology
It might or might not be symptomatic

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

TABLE 2 Extraintestinal Manifestations of Celiac Disease

Manifestation	Probable Cause(s)
Cutaneous	
Ecchymoses and petechiae	Vitamin K deficiency; rarely, thrombocytopenia
Edema	Hypoproteinemia
Dermatitis herpetiformis	Epidermal (type 3) tTG autoimmunity
Follicular hyperkeratosis and dermatitis	Vitamin A malabsorption, vitamin B complex malabsorption
Endocrinologic	
Amenorrhea, infertility, impotence	Malnutrition, hypothalamic-pituitary dysfunction, immune dysfunction
Secondary hyperparathyroidism	Calcium and/or vitamin D malabsorption with hypocalcemia
Hematologic	
Anemia	Iron, folate, vitamin B_{12}, or pyridoxine deficiency
Hemorrhage	Vitamin K deficiency; rarely, thrombocytopenia due to folate deficiency
Thrombocytosis, Howell-Jolly bodies	Hyposplenism
Hepatic	
Elevated liver biochemical test levels Autoimmune hepatitis	Lymphocytic hepatitis Autoimmunity
Muscular	
Atrophy	Malnutrition due to malabsorption
Tetany	Calcium, vitamin D, and/or magnesium malabsorption
Weakness	Generalized muscle atrophy, hypokalemia
Neurologic	
Peripheral neuropathy	Deficiencies of vitamin B_{12} and thiamine; immune-based neurologic dysfunction
Ataxia	Cerebellar and posterior column damage
Demyelinating central nervous system lesions	Immune-based neurologic dysfunction
Seizures	Unknown
Skeletal	
Osteopenia, osteomalacia, and osteoporosis	Malabsorption of calcium and vitamin D, secondary hyperparathyroidism, chronic inflammation
Osteoarthropathy	Unknown
Pathologic fractures	Osteopenia and osteoporosis

tTG, Tissue transglutaminase.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

BOX 1 Disorders Associated with Celiac Disease

Definite Association
Bird-fancier lung
Dermatitis herpetiformis
Diabetes mellitus type 1
Down syndrome
Epilepsy with cerebral calcification
Fibrosing alveolitis
Hypothyroidism or hyperthyroidism
IBD
IgA mesangial nephropathy
Idiopathic pulmonary hemosiderosis
IgA deficiency
Microscopic colitis
Recurrent pericarditis
RA
Sarcoidosis

Negative Association
Diabetes mellitus type 2

Possible Association
Addison disease
Autoimmune hemolytic anemia
Autoimmune liver diseases
Cavitary lung disease
Congenital heart disease
Cystic fibrosis
Immune thrombocytopenic purpura
Iridocyclitis or choroiditis
Macroamylasemia
Myasthenia gravis
Polymyositis
Schizophrenia
Sjögren syndrome
Systemic and cutaneous vasculitides
SLE

IBD, Inflammatory bowel disease; *IgA,* immunoglobulin A; *RA,* rheumatoid arthritis; *SLE,* systemic lupus erythematosus.
Modified from Mulder CJ, Tytgat GN: Coeliac disease and related disorders, *Neth J Med* 31:286-299, 1987. In Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

of tTG levels (>100 U) to first try a gluten-free diet and consider biopsy in those who do not improve with diet. Repeat small-bowel biopsies are no longer required to show healing when there is a clear response to a gluten-free diet.
- The HLA-DQ2 allele is identified in >90% of patients with celiac disease, and HLA-DQ8 is identified in most of the remaining patients. These genes occur in only 30% to 40% of the general population. Their greatest diagnostic value is in their negative predictive value, making them useful when negative in ruling out the disease.

IMAGING STUDIES

- Consider bone density in newly diagnosed adult patients.
- Capsule endoscopy can be used to evaluate mucosa of the small intestine, especially if future innovations will allow mucosal biopsy.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Patients should be instructed on a gluten-free diet (avoidance of wheat, rye, and barley). Safe grains (gluten-free) include rice, corn, oats, buckwheat, millet, amaranth, quinoa, sorghum, and teff (an Ethiopian cereal grain). The lowest amount of daily gluten that causes damage to the celiac intestinal mucosa is 10 to 15 mg/day. One slice of bread contains 1.6 g of gluten. Principles of initial dietary therapy for patients with celiac disease are summarized in Box 2.

GENERAL Rx

- Correct nutritional deficiencies with iron, folic acid, calcium, vitamin D, and vitamin B_{12} as needed.
- Prednisone 20 to 60 mg qd gradually tapered is useful in refractory cases.
- Lifelong gluten-free diet is necessary. A referral to a nutritionist experienced in celiac disease and gluten-free diet is recommended at initial diagnosis.

DISPOSITION

- Prognosis is good with adherence to a gluten-free diet. Rapid improvement is usually seen within a few days of treatment. Healing of the intestinal damage typically occurs within 6 to 24 mo after initiation of the diet. Lack of response to gluten-free diet occurs in 5% of patients and is due to unintentional ingestion of gluten or presence of coexisting GI disorders such as inflammatory bowel disease (IBD), lactose or other carbohydrate intolerance, and pancreatic insufficiency.
- Serial antigliadin or antiendomysial antibody tests can be used to monitor the patient's adherence to a gluten-free diet.
- Repeat small-bowel biopsy after treatment generally reveals significant improvement. It is also useful to evaluate for increased risk of small-bowel T-cell lymphoma in these patients, especially untreated patients. Some experts recommend a repeat biopsy only in selected patients who have an unsatisfactory response to a strict gluten-free diet; however, recent data (Lebwohl et al) show that the risk for lymphoproliferative malignancy (LPM) is affected by the results of follow-up intestinal biopsy performed to document mucosal healing. Increased risk for LPM in CD is associated with the follow-up biopsy results, with a higher risk among patients with persistent villous atrophy. Follow-up biopsy may effectively stratify patients with CD by risk for subsequent LPM.

TABLE 3 Biomarkers in the Diagnosis of Celiac Disease and Monitoring Compliance to Gluten-Free Diet

Biomarker	Method	Comments
Antireticulin antibodies—IgG/IgA	IFA (rat kidney)	Lack optimal sensitivity and specificity for routine diagnostic use
Total IgA	Quantitative nephelometry	Useful in ruling out IgA deficiency; specific IgG antibodies need to be tested in IgA-deficient individuals
Antigliadin antibodies—IgG/IgA	Quantitative EIA	Low sensitivity and specificity; useful in monitoring dietary compliance
Antideaminated gliadin antibodies—IgG/IgA	Quantitative EIA	Inferior performance relative to other diagnostic assays
Antiendomysial antibodies—IgG/IgA	IFA (rhesus monkey esophagus; human umbilical cord)	High sensitivity and specificity in CD; observer bias limits usefulness
Antitissue glutaminase—IgG/IgA	Quantitative EIA	Assays using purified human or recombinant human tTG are more sensitive than those using guinea pig tTG; useful in both diagnosis and monitoring dietary compliance
HLA-DQ2/HLA-DQ8	PCR-based assays	High negative predictive value; not affected by dietary gluten; found in ≈30% of general population

CD, Celiac disease; *EIA,* enzyme immunoassay; *IFA,* immunofluorescence; *IgA,* immunoglobulin A; *IgG,* immunoglobulin G; *PCR,* polymerase chain reaction; *tTG,* tissue transglutaminase.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, Philadelphia, 2017, Elsevier.

TABLE 4 Sensitivity, Specificity, and Positive and Negative Predictive Values of Serologic Tests for Untreated Celiac Disease

Serologic Test	Sensitivity* (%)	Specificity* (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Immunoglobulin A Tissue Transglutaminase				
Endomysial antibody by indirect immunofluorescence assay	85-98	97-100	98-100	80-95
Guinea pig tTG ELISA	95-98	94-95	91-95	96-98
Human tTG ELISA	95-100	97-100	80-95	100
Antigliadin Antibodies (AGAs)				
IgA	75-90	82-95	28-100	65-100
IgG	69-85	73-90	20-95	41-88

AGA, Antigliadin antibodies; *ELISA,* enzyme-linked immunosorbent assay; *IgA,* immunoglobulin A; *IgG,* immunoglobulin G; *tTG,* tissue transglutaminase.
*Wide variations in test sensitivity and specificity rates are reported among different laboratories. (Stern M: Comparative evaluation of serologic tests for celiac disease: a European initiative toward standardization, *J Pediatr Gastroenterol Nutr* 31:513-519, 2000.)
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

BOX 2 Principles of Initial Dietary Therapy for Patients with Celiac Disease

Avoid all foods containing wheat, rye, and barley gluten (pure oats usually safe).

Avoid malt unless clearly labeled as derived from corn.

Use only rice, corn, maize, buckwheat, millet, amaranth, quinoa, sorghum, potato or potato starch, soybean, tapioca, and teff, bean, and nut flours.

Wheat starch and products containing wheat starch should only be used if they contain less than 20 ppm gluten and are marked "gluten free."

Read all labels and study ingredients of processed foods.

Beware of gluten in medications, supplements, food additives, emulsifiers, or stabilizers.

Limit milk and milk products initially if there is evidence of lactose intolerance.

Avoid all beers, lagers, ales, and stouts (unless labeled gluten free).

Wine, most liqueurs, ciders, and spirits, including whiskey and brandy, are allowed.

ppm, Parts per million.
Modified from Trier JS: Celiac sprue and refractory sprue. In Feldman M, Scharschmidt BF, Sleisenger MH (eds): *Gastrointestinal and liver disease,* ed 6, Philadelphia, 1997, WB Saunders, p 1557. In Feldman M et al: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

PEARLS & CONSIDERATIONS

COMMENTS

- The presence of dermatitis herpetiformis is pathognomonic for celiac disease.
- In close relatives, repeated serum tTG IgA testing may be useful in those with positive *HLA-DQ2* or *HLA-DQ8* tests because celiac disease may not manifest until later in life, and initial negative results do not preclude the possibility of future onset of celiac disease.
- Celiac disease should be considered in patients with unexplained metabolic bone disease, osteoporosis, transaminasemia, or hypocalcemia, because gastrointestinal symptoms are absent or mild. Clinicians should also consider testing children and young adults for celiac disease if unexplained weight loss, abdominal pain or distention, or chronic diarrhea is present.
- Screening for celiac disease is recommended in first-degree relatives. It should also be considered in patients with type 1 diabetes mellitus and in those with certain autoimmune disorders such as primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, IBD, thyroid disease (hypothyroidism occurs in up to 15% of patients with celiac disease), systemic lupus erythematosus, RA, and Sjögren syndrome due to increased risk of celiac disease in these populations. Screening persons with Down syndrome or Turner syndrome has also been recommended.
- The prevalence of celiac disease in patients with dyspepsia is twice that of the general population. Screening for celiac disease should be considered in all patients with persistent dyspepsia.
- Patients with celiac disease have an overall risk of cancer that is almost twice that of the general population. The risk of adenocarcinoma of the small intestine is increased manifold compared with the risk in the general population. Celiac disease is also associated with an increased risk for non-Hodgkin lymphoma, especially of T-cell type and primarily localized in the gut. Lymphoma is 4 to 40 times more common, and death from lymphoma is 11 to 70 times more common in patients with celiac disease.
- Patients with celiac disease who have followed a gluten-free diet for prolonged periods may not experience relapse of symptoms for several months after gluten is reintroduced.
- Trials involving randomized feeding intervention in infants at high risk for celiac disease have shown that as compared to placebo, the introduction of small quantities of gluten at 16 to 24 weeks of age did not reduce the risk of celiac disease by 3 yr of age.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Celiac Disease (Patient Information)
Dermatitis Herpetiformis (Related Key Topic)
Malabsorption (Related Key Topic)

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SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Cellulitis is an infection of the deep dermis and subcutaneous tissues characterized by erythema, warmth, and tenderness of the involved area. Diagnosis is made on the basis of history and physical examination.

SYNONYMS

Erysipelas (cellulitis generally caused by group A β-hemolytic streptococci [GABHS])
SSSIs (skin and skin structure infections)
ABSSSIs (acute bacterial skin and skin structure infections)

ICD-10CM CODES

H05.011	Cellulitis of right orbit
H05.012	Cellulitis of left orbit
H05.013	Cellulitis of bilateral orbits
H05.019	Cellulitis of unspecified orbit
H60.10	Cellulitis of external ear, unspecified ear
H60.11	Cellulitis of right external ear
H60.12	Cellulitis of left external ear
H60.13	Cellulitis of external ear, bilateral
K12.2	Cellulitis and abscess of mouth
L03.011	Cellulitis of right finger
L03.012	Cellulitis of left finger
L03.019	Cellulitis of unspecified finger
L03.031	Cellulitis of right toe
L03.032	Cellulitis of left toe
L03.039	Cellulitis of unspecified toe
L03.111	Cellulitis of right axilla
L03.112	Cellulitis of left axilla
L03.113	Cellulitis of right upper limb
L03.114	Cellulitis of left upper limb
L03.115	Cellulitis of right lower limb
L03.116	Cellulitis of left lower limb
L03.119	Cellulitis of unspecified part of limb
L03.211	Cellulitis of face
L03.221	Cellulitis of neck
L03.311	Cellulitis of abdominal wall
L03.312	Cellulitis of back [any part except buttock]
L03.313	Cellulitis of chest wall
L03.314	Cellulitis of groin
L03.315	Cellulitis of perineum
L03.316	Cellulitis of umbilicus
L03.317	Cellulitis of buttock
L03.319	Cellulitis of trunk, unspecified
L03.811	Cellulitis of head [any part, except face]
L03.818	Cellulitis of other sites
L03.90	Cellulitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Occurs most frequently in diabetics, immunocompromised hosts, and patients with venous and lymphatic compromise.
- Frequently found near skin breaks (trauma, surgical wounds [surgical site infections develop in 2% to 5% of all surgical procedures], ulcerations, tinea infections). Edema, animal or human bites, subadjacent osteomyelitis, and bacteremia are potential sources of cellulitis.
- Skin and soft-tissue infections account for >14 million outpatient visits per yr and $3.7 billion in ambulatory care costs. They also are responsible for more than 650,000 admissions in the U.S./yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Variable with the causative organism:

- Erysipelas (Fig. E1): Superficial-spreading, warm, erythematous lesion distinguished by indurated, elevated margin; lymphatic involvement, vesicle formation common.
- Staphylococcal cellulitis: Area involved is erythematous, hot, and swollen; differentiated from erysipelas by nonelevated, poorly demarcated margin; local tenderness and regional adenopathy are common; up to 85% of cases occur on the legs and feet.
- *Haemophilus influenzae* cellulitis: Area involved is a blue-red/purple-red color; occurs mainly in children; generally involves the face in children and the neck or upper chest in adults.
- *Vibrio vulnificus:* Larger hemorrhagic bullae, cellulitis, lymphadenitis, myositis; often found in critically ill patients in septic shock.
- Table 1 describes anatomic variants of or predispositions to cellulitis. Typically, nonpurulent cellulitis is caused by β-hemolytic streptococci, whereas cellulitis with purulent drainage is caused by MRSA.

ETIOLOGY

- Any disruption of the skin barrier provides a portal for pathogens to enter the skin and soft tissues.
- Group A β-hemolytic streptococci (may follow a streptococcal infection of the upper respiratory tract). β-hemolytic streptococci are implicated in most cases of nontraumatic cellulitis.
- Staphylococcal cellulitis: Diabetics, athletes, men who have sex with men, people living in public housing, and incarcerated men are at greater risk for methicillin-resistant *Staphylococcus aureus* (MRSA) infection. A community-acquired MRSA strain, USA 300, is replacing nosocomial strains of MRSA in hospitals.
- IV drug use: MRSA, *Pseudomonas aeruginosa.*
- *V. vulnificus:* Higher incidence in patients with liver disease (75%) and in immunocompromised hosts. *V. vulnificus* infection is the leading cause of death related to seafood consumption in the U.S.
- *Erysipelothrix rhusiopathiae:* Common in people handling poultry, fish, or meat.
- *Aeromonas hydrophila:* Generally occurs in contaminated open wounds in fresh water.
- Fungi *(Cryptococcus neoformans):* In immunocompromised granulopenic patients.
- Gram-negative rods *(Serratia, Enterobacter, Proteus, Pseudomonas):* May be present in immunocompromised or granulopenic patients.
- Hot tub exposure: *P. aeruginosa*; fish tank exposure: *Mycobacterium marinum.*
- Bites: Human *(Eikenella corrodens),* dog *(Pasteurella multocida, C. canimorsus),* cat *(P. multocida),* rat *(Streptobacillus moniliformis).*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Necrotizing fasciitis (reddish-purple discoloration of skin, rapid increase in size, woody induration and pale appearance rather than erythema, violaceous bullae, pain out of proportion to appearance, sepsis)
- Deep vein thrombosis
- Peripheral vascular insufficiency (venous stasis dermatitis)
- Paget disease of the breast
- Thrombophlebitis
- Acute gout
- Psoriasis
- *Candida* intertrigo
- Pseudogout
- Osteomyelitis
- Insect bite
- Fixed drug eruption
- Lymphedema
- Contact dermatitis
- Olecranon bursa infection
- Herpetic whitlow, early herpes zoster (before blisters)
- Erythema migrans (Lyme disease)
- Rare: *Vaccinia* vaccination, Kawasaki disease, pyoderma gangrenosum, Sweet syndrome, carcinoma erysipeloides, anaerobic myonecrosis, erythromelalgia, eosinophilic cellulitis (Well syndrome), familial Mediterranean fever

LABORATORY TESTS

- Laboratory testing is generally not required for the evaluation of cellulitis and uncomplicated soft tissue infections in the absence of comorbidities
- CBC with differential: Leukocytosis may be present but is a non-specific finding
- Gram stain, culture (aerobic and anaerobic):
  1. Aspirated material from:
     a. Advancing edge of cellulitis
     b. Any vesicles
  2. Swab of any drainage material
  3. Punch biopsy (in selected patients)
- Blood cultures in hospitalized patients, patients with cellulitis superimposed on lymphedema, patients with buccal or periorbital cellulitis, and patients suspected of having a salt- or fresh-water source of infection. Bacteremia uncommon in cellulitis (positive blood cultures in 4% of patients)
- Anti-streptolysin O (ASLO) titer (in suspected streptococcal disease)
- The cause of cellulitis remains unidentified in most patients. Patients with recurrent lower-extremity cellulitis should be inspected for tinea pedis. If found, it should be treated.

IMAGING STUDIES

- Imaging is generally not necessary but may be helpful in suspected purulent soft tissue infections and osteomyelitis.

TABLE 1 Anatomic Variants of or Predispositions to Cellulitis

Anatomic Variant or Predisposition	Location	Likely Bacterial Cause
Periorbital cellulitis	Periorbital	*Staphylococcus aureus, Streptococcus pneumoniae,* group A streptococci
Buccal cellulitis	Cheek	*Haemophilus influenzae* type b
Cellulitis complicating body piercing	Ear, nose, umbilicus	*S. aureus,* group A streptococci
After mastectomy (with axillary node dissection)	Ipsilateral upper extremity	Non–group A β-hemolytic streptococci
After lumpectomy (with limited axillary node dissection, breast irradiation)	Ipsilateral breast	Non–group A β-hemolytic streptococci
After saphenous vein harvest for coronary artery bypass	Ipsilateral leg	Group A or non–group A β-hemolytic streptococci
After radical pelvic surgery, radiation therapy	Vulva, inguinal areas, legs	Group B and group G streptococci
After liposuction	Thigh, abdominal wall	Group A streptococci, peptostreptococci
Postoperative (very early) wound infection	Abdomen, chest, hip	Group A streptococci
Injection drug use ("skin popping")	Extremities, neck	*S. aureus,* streptococci (groups A, C, F, G)*
Perianal cellulitis	Perineum	Group A streptococcus

*Other bacteria to consider based on isolation from skin or abscesses in this setting include *Enterococcus faecalis,* viridans group streptococci, coagulase-negative staphylococci, anaerobes (including *Bacteroides* and *Clostridium* spp.), and Enterobacteriaceae.
From Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.

- CT or MRI in patients with suspected necrotizing fasciitis (deep-seated infection of the subcutaneous tissue that results in the progressive destruction of fascia and fat).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Immobilization and elevation of the involved limb. Cool sterile saline dressings to remove purulence from any open lesion. Support stockings in patients with peripheral edema.

ACUTE GENERAL Rx

Treatment should initially cover *Streptococcus* and methicillin-sensitive *S. aureus* and should be expanded for MRSA in patients with risk factors (e.g., IV drug users, residents of long-term care facilities, athletes, children, men who have sex with men, prisoners).

ERYSIPELAS:
- PO: Dicloxacillin 500 mg PO q6h or cephalexin 500 mg qid
- IV: Cefazolin 1 g q6 to 8h or nafcillin 1.0 or 1.5 g IV q4 to 6h

NOTE: Use vancomycin 1 g IV q12h in patients allergic to penicillin.

STAPHYLOCOCCAL CELLULITIS:
- PO: Dicloxacillin 250 to 500 mg qid
- IV: Nafcillin 1 to 2 g q4 to 6h
- Cephalosporins (cephalexin 500 mg qid) also provide adequate antistaphylococcal coverage, except for MRSA.
- Trimethoprim-sulfamethoxazole (160 mg/800 mg 1 PO bid) may be appropriate in outpatient mild MRSA infections. Use vancomycin 1.0 to 2.0 g IV qd or linezolid 0.6 g IV q12h in patients with moderate/severe MRSA. Daptomycin (Cubicin), a cyclic lipopeptide, can be used as an alternative to vancomycin for complicated skin and skin structure infections. Usual dose is 4 mg/kg IV given over 30 min every 24 hr. Telavancin is a new glycopeptide derivative of vancomycin effective for gram-positive skin and skin structure infections, including those caused by MRSA. Tedizolid is an oxazolidinone effective in ABSSSI as an alternative to linezolid. Ceftaroline fosamil (Teflaro) is a newer IV cephalosporin also effective against MRSA. Dalbavancin and tedizolid are two new drugs FDA-approved for skin and skin structure infections, including those caused by MRSA.

H. INFLUENZAE CELLULITIS:
- PO: Cefixime or cefuroxime
- IV: Cefuroxime or ceftriaxone

VIBRIO VULNIFICUS:
- Doxycycline 100 mg IV bid + ceftazidime 2 g IV q8h or IV ciprofloxacin 400 mg bid. Mild cases treated with oral antibiotics (doxycycline 100 mg bid + ciprofloxacin 750 mg bid).
- IV support and admission into intensive care unit (mortality rate >50% in septic shock).

E. RHUSIOPATHIAE:
- Penicillin

A. HYDROPHILA:
- Aminoglycosides
- Chloramphenicol
- Complicated skin and skin structure infections in hospitalized patients can be treated with daptomycin (Cubicin) 4 mg/kg IV q24h

PEARLS & CONSIDERATIONS

- 16.6% of acute cellulitis cases are unresponsive to initial treatment mainly due to inappropriate antibiotic selection and dosing (weight-based dosing is preferred).
- Prophylactic antibiotics (e.g., dicloxacillin 500 mg bid or erythromycin 250 mg bid) are controversial but can be considered with patients with ≥4 episodes of cellulitis despite optimized control of risk factors. Recurrent cellulitis with no identifiable cause occurs in 22% of cases despite antibiotic prophylaxis.
- In patients with uncomplicated cellulitis in the outpatient setting, adding trimethoprim-sulfamethoxazole to cephalexin for MRSA coverage is unnecessary and does not increase the likelihood of clinical cure.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Cellulitis (Patient Information)
Erysipelas (Related Key Topic)
Necrotizing Fasciitis (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Khawcharoenporn T, Tice A: Empiric outpatient therapy with trimethoprim-sulfamethoxazole, cephalexin, or clindamycin for cellulitis, *Am J Med* 123:942-950, 2010.

Moran GJ et al: Effect of cephalexin plus trimethoprim-sulfamethoxazole vs cephalexin alone on clinical cure of uncomplicated cellulitis: a randomized clinical trial, *J Am Med Assoc* 317:2088-2096, 2017.

Prokocimer P et al: Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial, *J Am Med Assoc* 309(6):559-569, 2013.

Raff AB, Kroshinsky D: Cellulitis: a review, *J Am Med Assoc* 316(3):325-337, 2016.

Talan DA et al: Trimethoprim-sulfamethoxazole versus placebo for uncomplicated skin abscess, *N Engl J Med* 374:823-832, 2016.

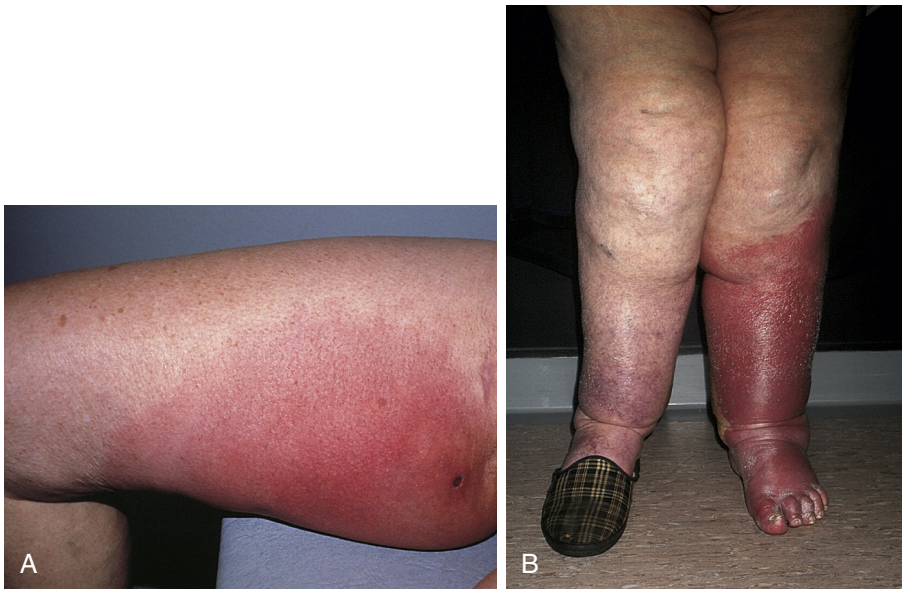

FIG. E1 Erysipelas of the leg. A, Note the open wound on the proximal thigh, which gave rise to this infection. The patient should be monitored closely for more severe skin changes (e.g., purpura, bulla, postbullous ulceration, necrosis, hypoesthesia, fluctuance), which may suggest necrotizing fasciitis or pyomyositis. **B,** Chronic lymphedema has predisposed to cellulitis in this elderly patient. (From White GM, Cox NH [eds]: *Diseases of the skin,* ed 2, St Louis, 2006, Mosby.)

BASIC INFORMATION

DEFINITION

Cerebral palsy (CP) is a group of disorders of the central nervous system characterized by aberrant control of either movement or posture, present since early in life and not the result of a progressive or degenerative disease. Table E1 provides a classification of CP and major causes.

SYNONYMS

Little disease
Congenital static encephalopathy
Congenital spastic paralysis
CP

ICD-10CM CODES

G80.0 Spastic quadriplegic cerebral palsy
G80.1 Spastic diplegic cerebral palsy
G80.2 Spastic hemiplegic cerebral palsy
G80.3 Athetoid cerebral palsy
G80.4 Ataxic cerebral palsy
G80.8 Other cerebral palsy
G80.9 Cerebral palsy, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 2 to 2.5 persons per 1000 live births
PREDOMINANT SEX: Males and females affected equally
PREDOMINANT AGE: Diagnosis typically made at 3 to 5 yr of age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Monoplegia, diplegia, quadriplegia, hemiplegia
- Often hypotonic in newborn period, followed by development of hypertonia
- Spasticity
- Athetosis
- Delay in motor milestones
- Hyperreflexia
- Seizures
- Mental retardation in many individuals

ETIOLOGY

Multifactorial, including low birth weight, congenital malformation, asphyxia, multiple gestation, intrauterine exposure to infection, neonatal stroke, hyperbilirubinemia, and maternal thyroid malfunction

DIAGNOSIS

A motor deficit is always present. The usual presenting complaint is that child is not reaching motor milestones at the appropriate age. Medical history establishes that the child is not losing function (i.e., that deficit is static and not progressive). This history, combined with a neurologic examination establishing that motor deficit is due to a cerebral abnormality, establishes the diagnosis of CP. Serial examinations may be necessary.

DIFFERENTIAL DIAGNOSIS

Other causes of neonatal hypotonia include muscular dystrophies, spinal muscular atrophy, Down syndrome, and spinal cord injuries. Causes of progressive spasticity in children include metabolic diseases involving white matter (e.g., leukodystrophy).

WORKUP

- Laboratory tests are not necessary to establish the diagnosis.
- Workup is helpful for assessment of recurrence risk, implementation of prevention programs, and medicolegal purposes.

LABORATORY TESTS

- Metabolic and genetic testing should be considered if on follow-up the child has the following: (1) evidence of deterioration or episodes of metabolic decompensation, (2) no etiology determined by neuroimaging, (3) family history of childhood neurologic disorder associated with CP, or (4) developmental malformation on neuroimaging. Hypercoagulability workup should be considered if neuroimaging is suggestive of a remote stroke.
- EEG should be obtained when a child with CP has a history suggestive of seizures.
- Children with CP should be screened for ophthalmologic and hearing impairments as well as speech and language disorders. Nutrition, growth, and swallowing function should be monitored.

IMAGING STUDIES

- Neuroimaging is recommended if the etiology has not been established previously, for example, by perinatal imaging.
- MRI, when available, is preferred to CT scanning because of higher yield in determining an etiology and timing of the insult leading to CP.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical therapy, occupational therapy, and speech therapy.
- Orthotics and casting are used to increase musculotendinous length.

ACUTE GENERAL Rx

If present, treatment of seizures

CHRONIC Rx

- Treatment of seizures, as directed by seizure type.
- Medical treatment of spasticity includes baclofen (oral and intrathecal), as well as botulinum toxin A.
- Surgical treatments of spasticity include dorsal rhizotomy, tendon lengthening, and osteotomy.

DISPOSITION

Most children with CP live at home. Those children with severely impaired mobility or other disabilities may live in chronic-care nursing facilities.

REFERRAL

If the child has difficulty with spasticity, physical medicine and rehabilitation referrals are especially helpful.

TABLE E1 Classification of Cerebral Palsy and Major Causes

Motor syndrome (Approx. % of CP)	Neuropathology/MRI	Major Causes
Spastic diplegia (35%)	Periventricular leukomalacia Periventricular cysts or scars in white matter, enlargement of ventricles, squared-off posterior ventricles	Prematurity Ischemia Infection Endocrine/metabolic (e.g., thyroid)
Spastic quadriplegia (20%)	Periventricular leukomalacia Multicystic encephalomalacia Cortical malformations	Ischemia, infection Endocrine/metabolic, genetic/developmental
Hemiplegia (25%)	Stroke: in utero or neonatal Focal infarct or cortical, subcortical damage Cortical malformations	Thrombophilic disorders Infection Genetic/developmental Periventricular hemorrhagic infarction
Extrapyramidal (athetoid, dyskinetic) (15%)	Asphyxia: symmetric scars in putamen and thalamus Kernicterus: scars in globus pallidus, hippocampus Mitochondrial: scarring of globus pallidus, caudate, putamen, brainstem No lesions: ? dopa-responsive dystonia	Asphyxia Kernicterus Mitochondrial Genetic/metabolic

CP, Cerebral palsy; *MRI,* magnetic resonance imaging. From Kliegman RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

PEARLS & CONSIDERATIONS

- In full-term infants, there is usually no history of traumatic delivery.
- Compared with delivery at 40 wks' gestation, delivery at 37 or 38 wk or at 42 wk or later was associated with an increased risk of CP.

SUGGESTED READING

Moster D et al: Cerebral palsy among term and post-term births, *JAMA* 304(9):976-982, 2010.

RELATED CONTENT

Cerebral Palsy (Patient Information)

AUTHORS: **Joseph S. Kass, MD, JD, FAAN,** and **Maitreyi Mazumdar, MD, MPH, MSc**

Cerebral Vasculitis

BASIC INFORMATION

DEFINITION

Cerebral vasculitis refers to a group of heterogeneous disorders characterized by pathologic inflammation and leukocytoclastic changes in the blood vessel walls.

SYNONYMS

Primary angiitis of the central nervous system (PACNS)
Central nervous system angiitis
Cerebral arteritis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 2.4 cases per 1,000,000 person-yr for PACNS
PEAK INCIDENCE: Fourth decade of life for PACNS
PREDOMINANT SEX: Males are affected twice as often as females by PACNS. For secondary vasculitis of the CNS, sex predominance varies by underlying autoimmune condition.
PREDOMINANT AGE: Usual age of presentation of PACNS is in the third and fourth decades of life, but it can present in age ranging from 17 to 70 yr.
GENETICS: Multifactorial
RISK FACTORS: Infections, connective tissue disorders, systemic vasculitis, and substance abuse are the prominent risk factors for secondary cerebral vasculitis. No risk factors have been clearly established for PACNS.
CLASSIFICATION:

- PACNS (see Table E1 for full diagnostic criteria): Involvement of the blood vessels in brain or spinal cord without involvement of blood vessels and organs beyond the CNS.
- Secondary CNS vasculitis: Involvement of the brain or spinal cord blood vessels by a systemic disorder such as systemic vasculitis, connective tissue disorders, infections, malignancy, or substance abuse.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presentation of cerebral vasculitis is diverse and includes the following:
  1. Nonspecific symptoms such as insidious headache, weight loss, lethargy, personality changes, delirium, and even dementia.
  2. Focal neurologic manifestations: Seen in 80% of patients during course of illness, may mimic multiple sclerosis, with a relapsing and remitting course.
  3. Stroke can occur in 40% of the patients; transient ischemic attacks have been reported in 30% to 50% of patients.
  4. Seizures occur in 25% of patients.
  5. Other common presentations include intracerebral hemorrhage (11%) and intracranial space-occupying lesions (15%).
- Secondary vasculitis often presents with strokelike symptoms. Sjögren syndrome and Behçet disease can have varied presentations that mimic multiple sclerosis, seizures, movement disorders, encephalopathy, dementia, and aseptic meningitis.

ETIOLOGY

The exact etiology of primary cerebral vasculitis is unknown. It has been associated with various infectious agents such as herpes zoster, mycoplasma, HIV, and unknown viruses. Amyloid angiopathy has been described with primary cerebral vasculitis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS (SEE TABLE E2 FOR COMPLETE DIFFERENTIAL DIAGNOSIS)

- Reversible cerebral vasoconstriction syndrome (RCVS) (see Table E3 for full diagnostic criteria)
- Intracranial artery atherosclerosis
- Cerebral emboli of multiple etiologies
- Intravascular lymphoma
- Sarcoidosis
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- Meningovascular syphilis
- Angioinvasive fungal infections
- Varicella zoster virus vasculopathy
- Tuberculosis meningitis vasculopathy

WORKUP

Brain biopsy (lesional area on MRI preferred but if not surgically feasible, then usually nondominant temporal lobe tip along with overlying leptomeninges) is the gold standard diagnostic method and is required for definitive diagnosis. Vessel histology may be granulomatous, lymphocytic, or necrotizing and will reveal vessel wall damage.

A brain MRI with and without contrast has a sensitivity approaching 100%, although it has a

TABLE E1 Diagnostic Criteria for Primary Angiitis of the CNS

1. The presence of an acquired otherwise unexplained neurologic or psychiatric deficit
2. The presence of either classic angiographic or histopathologic features of angiitis within the CNS
3. No evidence of systemic vasculitis or any disorder that could cause or mimic the angiographic or pathologic features of the disease

Hajj-Ali RA, Calabrese LH: Diagnosis and classification of central nervous system vasculitis, *J Autoimmun* 48-49:149-152, 2014.

TABLE E2 Differential Diagnosis of PACNS

Systemic vasculitides	Behçet syndrome, polyarteritis nodosa, granulomatosis with polyangiitis
Systemic inflammatory diseases	Systemic lupus erythematosus, Sjögren syndrome, Crohn disease, sarcoid granulomatosis, and angiitis
Infections	Viral (e.g., herpes zoster, HIV), bacterial (e.g., tuberculosis, syphilis, neuroborreliosis), fungal (e.g., aspergillosis, nocardiosis, *Cryptococcus,* histoplasmosis)
Conditions with cerebral angiographic abnormalities	Reversible cerebral vasoconstriction syndrome, premature intracranial atherosclerosis, fibromuscular dysplasia, moyamoya disease and syndrome, small-vessel arterial dissection, angiotropic and intervascular lymphoproliferative disorders, radiation vasculopathy
Brain diseases with MRI lesions that can mimic PACNS	Brain neoplasms (e.g., intravascular lymphoma, gliomatosis cerebri), genetic conditions (e.g., CADA-SIL, HERNS, COL4A1 mutation), posterior reversible encephalopathy syndrome, Susac syndrome, chronic hypertension ("microvascular cerebral ischemia"), demyelinating diseases (e.g., multiple sclerosis, acute disseminated encephalomyelitis, progressive multifocal leukoencephalopathy)
Miscellaneous	Hyperhomocystinemia, thrombocytic purpura, porphyria, antiphospholipid antibody syndrome, Kohlmeier-Degos
Conditions with multifocal cerebral thromboembolism	Atrial fibrillations and cholesterol atheroembolism, endocarditis, left atrial myxoma and other cardiac tumors

CADA-SIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; *EGPA,* eosinophil granulomatosis with polyangiitis; *HERNS,* hereditary endotheliopathy with retinopathy, nephropathy, and stroke; *HIV,* human immunodeficiency virus *PACNS,* primary angiitis of the central nervous system.
Hajj-Ali RA, Calabrese LH: Diagnosis and classification of central nervous system vasculitis, *J Autoimmun* 48-49:149-152, 2014.

TABLE E3 Diagnostic Criteria for RCVS

1. Severe and acute headache (often thunderclap) with or without focal deficits or seizures
2. Direct or indirect angiography documenting multifocal segmental cerebral artery vasoconstriction
3. No evidence of aneurysmal subarachnoid hemorrhage
4. Normal or near-normal CSF (protein concentrations)

CSF, Cerebrospinal fluid; *RCVS,* reversible cerebral vasoconstriction syndrome.
From Hajj-Ali RA, Calabrese LH: Diagnosis and classification of central nervous system vasculitis, *J Autoimmun* 48-49:149-152, 2014.

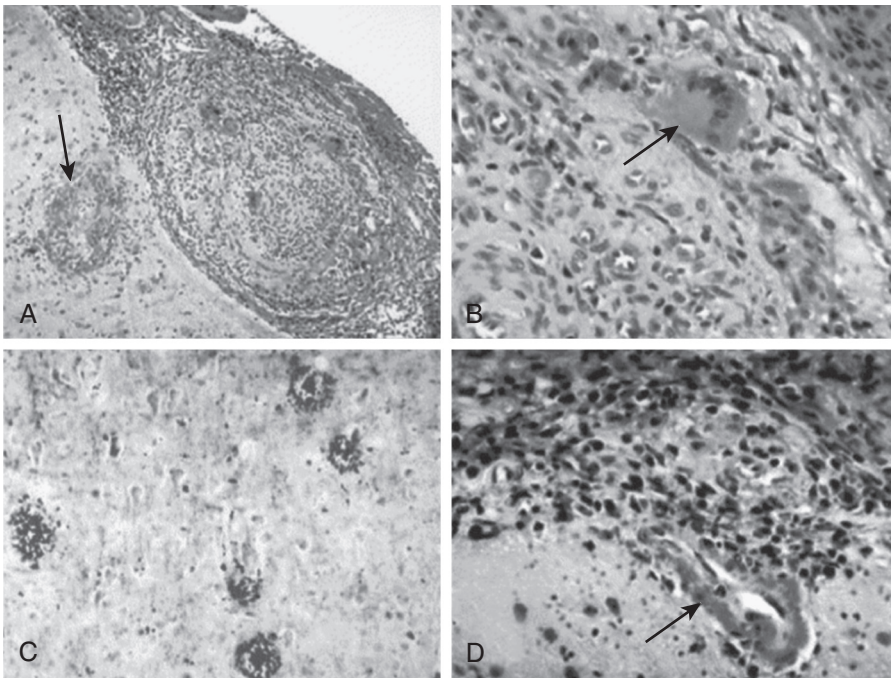

FIG. E1 **A,** Low-power hematoxylin and eosin stain (10×) demonstrates diffuse inflammation in the leptomeninges with infiltration of lymphocytes, eosinophils, and macrophages with destruction of the vessel wall *(arrow).* **B,** A multinucleated giant cell *(arrow).* **C,** Multiple neuritic plaques are seen on this silver stain. **D,** Congo red stain demonstrating the presence of amyloid within a vessel wall *(arrow).* (From Jacobs DA et al: Primary central nervous system angiitis, amyloid angiopathy and Alzheimer's pathology presenting with Balint's syndrome, *Surv Ophthalmol* 49[4]:454-459, 2004.)

very low specificity. Thus, a normal brain MRI virtually excludes the diagnosis of cerebral vasculitis. The most common lesions are ischemic strokes, occurring in 53% of cases. Strokes are often multiple and bilateral, affecting different vascular territories of variable sizes and in various stages of evolution; they can involve the cortex, subcortical areas, and leptomeninges. High-intensity T2-weighted subcortical lesions are very common but not specific. Mass lesions are seen in 5%, meningeal enhancement in 8%, and intracranial hemorrhages in 9% of cases.

Cerebral angiography, either by direct four-vessel angiography or by indirect magnetic resonance or CT angiography, may show beading: diffuse, bilateral, and alternating areas of stenosis and dilation. This finding may indicate vasculitis, but it is not specific for vasculitis. Other nonspecific angiographic findings in CNS vasculitis include tapering of the lumen of a single vessel or many vessels and fusiform arterial dilations, multifocal vascular occlusions, development of collateral circulation, or delayed contrast-medium enhancement and washout time. Furthermore, the resolution of angiography further limits its sensitivity in that it does not capture morphologic changes in small arteries and arterioles, so a cerebral vasculitis limited to these small-caliber vessels will be normal on angiography (Fig. E1).

LABORATORY TESTS

- Lumbar puncture: Cerebrospinal fluid (CSF) should show elevated protein, lymphocytic pleocytosis, and negative microbial cultures. Opening pressure may be elevated. Consider obtaining CSF cytology and flow cytometry.
- Basic laboratory testing: Should include CBC with differential, blood urea nitrogen and serum creatinine, hepatic functions and enzymes, erythrocyte sedimentation rate (ESR), RPR (for syphilis), HIV, C-reactive protein (CRP), and urinalysis with microscopy to look for signs of renal vasculitis. ESR and CRP are typically normal in PACNS.
- Specific serologic tests to evaluate for systemic autoimmune causes: ANA, rheumatoid factor, anti–double-stranded DNA, anti SS-A, anti SS-B, anti–neutrophil cytoplasmic antibodies (both c-ANCA and p-ANCA), complement 3 and 4, cryoglobulins, and testing for HIV, hepatitis B (associated with polyarteritis nodosa), and hepatitis C (associated with mixed cryoglobulinemia). Markers of systemic autoimmune diseases are typically negative in PACNS.
- Echocardiogram and cardiac telemetry should exclude cardioembolic sources such as atrial fibrillation, cardiac thrombus, and atrial myxoma.
- Consider screening for lymphoma in patients with PACNS, since both Hodgkin and non-Hodgkin lymphoma have an association with PACNS.

IMAGING STUDIES

Brain MRI with and without contrast is the neuroimaging of choice. Abnormal findings are seen in virtually 100% of the patients. Cerebral cortex and deep white and gray matter changes are commonly reported (Fig. E2). Angiography has poor sensitivity at detecting small vessel changes. Many patients, in fact, have a normal angiogram, and a vasculopathic appearance of intracerebral vessels on a four-vessel cerebral angiogram does not by itself distinguish an inflammatory vasculitis from a noninflammatory vasculopathy like RCVS (see Table E3 for RCVS diagnostic criteria and Table E4 for features distinguishing PACNS and RCVS).

Rx TREATMENT

There are no randomized controlled trials evaluating treatment of cerebral vasculitis. Treatment strategies are similar to those for systemic vasculitis.

NONPHARMACOLOGIC THERAPY

Patients with permanent deficits are provided with physical and occupational therapy.

ACUTE GENERAL Rx

Steroids: For suspected cases, empiric therapy with glucocorticoids is started after exclusion of infectious causes. Intravenous methylprednisolone 1 g daily for 3 days is preferred, followed by oral therapy for chronic therapy.

CHRONIC Rx

- Steroids: Oral prednisone is continued at high dose (1 mg/kg/day) for 4 to 6 wk and then tapered slowly over 12 mo.
- Immunosuppressive treatment: Pulse intravenous cyclophosphamide or oral cyclophosphamide should be used in addition to steroids for 3 to 6 mo to induce remission. When stable, milder and relatively safer immunosuppressants such as azathioprine, methotrexate, or mycophenolate are used for 2 to 3 yr.

DISPOSITION

Course and prognosis of the disease are variable and depend on the extent of neurologic involvement, severity of deficits, and response to treatment. Neurologic deficits may resolve acutely, slowly, or not at all. Some patients have symptomatic improvement with resolution of headache or altered mental status. Some have improvement in laboratory values, and others have improved MRI scans.

REFERRAL

- Neurologic consultation is indicated in patients with neurologic deficits of uncertain etiology, younger age, intractable headaches, or uncertain diagnosis.
- Neurosurgery consultation for brain biopsy is indicated for definitive tissue-based diagnosis.
- Interventional neuroradiology consultation is indicated for four-vessel cerebral angiogram.
- Rheumatology consultation is indicated when either a systemic vasculitis or connective tissue disease is suspected.
- Infectious diseases consultation is recommended when infection is suspected.

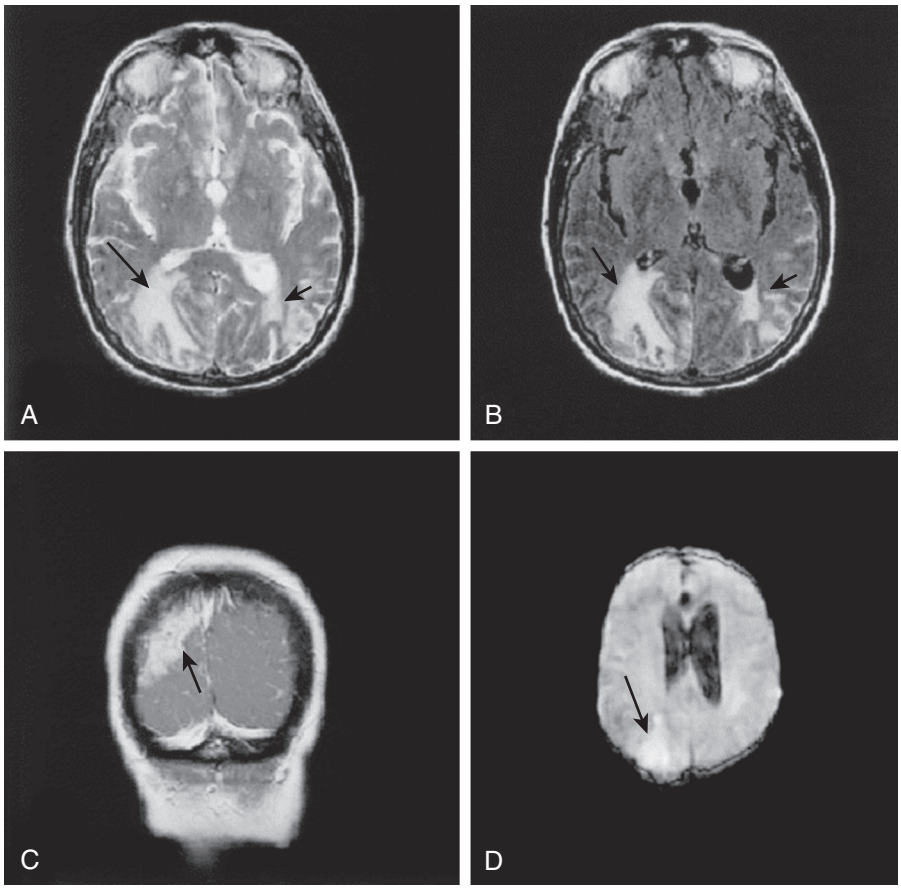

FIG. E2 A, Axial T2-weighted image shows abnormal signal in bilateral parietooccipital lobes, greater on the right than left *(arrows).* **B,** Axial fluid attenuated inversion recovery image further delineating the extent of bilateral parietooccipital lesions *(arrow).* **C,** Coronal T1-gadolinium study demonstrating nodular leptomeningeal enhancement in the lesion *(arrow).* **D,** Diffusion-weighted magnetic resonance imaging shows bright signal in the right parietooccipital region, suggesting ischemic changes *(arrow).* (From Jacobs DA et al: Primary central nervous system angiitis, amyloid angiopathy and Alzheimer's pathology presenting with Balint's syndrome. *Surv Ophthalmol* 49[4]:454-459, 2004.)

TABLE E4 Differentiating Features between PACNS and RCVS

	PACNS	RCVS
Gender, mean age at onset	Male, 50 yr	Female, 42 yr
Headache	Insidious subacute onset	Acute onset, often thunderclap
Clinical course	Chronic, relapsing	Monophasic
CSF findings	Lymphocytic pleocytosis and elevated protein	Normal
MRI of brain	Abnormal in 100% ischemic, high-intensity T2/FLAIR lesions	Normal MRI in 20% ischemia, edema, cSAH, ICH
Cerebrovascular abnormalities	Frequently irreversible	Reversible
Histological findings on brain biopsy	Vasculitic changes	No vasculitic pattern

cSAH, Convexity subarachnoid hemorrhage; *CSF,* cerebrospinal fluid; *FLAIR,* fluid-attenuated inversion recovery; *ICH,* intracranial hemorrhage; *MRI,* magnetic resonance imaging; *PACNS,* primary angiitis of the central nervous system; *RCVS,* reversible cerebral vasoconstriction syndrome.

Hajj-Ali RA, Calabrese LH: Diagnosis and classification of central nervous system vasculitis, *J Autoimmun* 48-49:149-152, 2014.

PEARLS & CONSIDERATIONS

COMMENTS

- Cerebral vasculitis is a rare disorder that is difficult to diagnose because of variable presentation.
- Early recognition of the clinical symptoms and signs is important to prevent long-term morbidity and mortality.
- Systemic, infectious, and noninflammatory vasculopathic (like RCVS) causes should be excluded.
- Patients may need chronic immunosuppressive treatment.

SUGGESTED READINGS

de Boysson H et al: Primary angiitis of the central nervous system: description of the first fifty-two adults enrolled in the French cohort of patients with primary vasculitis of the central nervous system, *Arthritis Rheumatol* 66:1315-1326, 2014.

Hajj-Ali RA, Calabrese LH: Diagnosis and classification of central nervous system vasculitis, *J Autoimmun* 149-152, 2014.

RELATED CONTENT

Vasculitis, Systemic (Related Key Topic)

AUTHORS: **Chloe Mander Nunneley, MD,** and **Joseph S. Kass, MD, JD, FAAN**

BASIC INFORMATION

DEFINITION

Tearing between the layers of the wall of an artery in the neck.

SYNONYMS

Carotid artery dissection
Vertebral artery dissection

ICD-10CM CODES
177.71 Dissection of carotid artery
177.74 Dissection of vertebral artery

EPIDEMIOLOGY & DEMOGRAPHICS

The most common cervical artery dissection (CAD) is the internal carotid; the vertebral artery is less commonly affected. The tearing of the wall can cause clot formation, leading to stroke, especially in young patients. CAD can happen intracranially (most often) or extracranially (rare but worse prognosis).

INCIDENCE: The average annual incidence rate for CAD is reported at 2.6 per 100,000 population; however, the true incidence is likely higher because many cases have self-limited clinical symptoms and remain undiagnosed.

PREVALENCE: Prevalence may reach 15% in the young adult stroke population.

PREDOMINANT SEX AND AGE: Carotid artery dissections are most commonly found in young adults. The mean age for extracranial internal carotid artery dissection is 40 yr. Intracranial dissections are more common in those aged 20 to 30 yr.

GENETICS: Marfan syndrome, type IV Ehlers-Danlos syndrome, cystic medial necrosis, and the *677TT* genotype of the 5,10-methylenetetrahydrofolate reductase gene (*MTHFR 677TT*) have been reported in association with CAD.

RISK FACTORS:

- Seasonality: 58% more patients experience a cervical artery dissection during autumn and winter for unknown causality.
- Vascular factors: Hyperhomocysteinemia is strongly associated with CAD, especially if homocysteine levels are >12 micromols/L
- Chiropractic manipulations are often listed as risk factors, with multiple case reports, although evidence is lacking
- Major cervical trauma: Hyperextension or rotation of the neck
- Although evidence is less strong, infection and migraine may also predispose to CAD, as well
- Arterial wall intrinsic factors, such as arteriopathies, may predispose to arterial dissection after trivial trauma. Angiographic evidence of fibromuscular dysplasia has been noted in 10% to 15% of patients

PHYSICAL FINDINGS & CLINICAL PRESENTATION

A young adult with nuchal rigidity, neck pain, and severe occipital headache after minor head or neck trauma is a common presentation. Focal neurologic symptoms follow as a result of ischemia and may include:

- Ipsilateral facial pain and numbness: Most common focal neurologic complaints
- Contralateral loss of pain and temperature sensation in the trunk and limbs
- Loss of taste, hiccups, vertigo, dysphagia, Horner syndrome, unilateral hearing loss, or tinnitus may also occur
- In contrast to younger patients, those over 60 rarely report mechanical triggers or pain

PATHOPHYSIOLOGY

Arterial wall tears happen either spontaneously or as a result of minor trauma. The tear allows arterial blood under pressure to leak into the wall, creating either a hematoma or a false lumen. Sometimes the tear is subintimal, whereas other times it is subadventitial. Subintimal tears usually result in stenosis of the arterial lumen, whereas subadventitial dissection tends to cause arterial dilation.

ETIOLOGY

Cervical artery dissections may be spontaneous or traumatic. The majority of cases involve minor trauma.

DIAGNOSIS

- Ultrasonography: Safe and accurate; however, it has a 31% false negative result in patients with CAD presenting with Horner syndrome
- CT angiography (Fig. E1)
- Conventional angiography
- MRA (Fig. E2) is the gold standard for diagnosis

DIFFERENTIAL DIAGNOSIS

- Cervical spine fracture
- Cluster headache
- Subarachnoid hemorrhage
- Hypoglycemia
- Stroke/transient ischemic attack (TIA)
- Migraine headache
- Other neck trauma

WORKUP

- Labs not usually required except for determination of renal status for contrast use and coagulation panel. Obtaining blood products may also be necessary in cases of planned surgical intervention (type and cross/match).
- Imaging studies such as ultrasound, conventional angiography, CT angiogram, or magnetic resonance angiography (MRA) give the ultimate diagnosis. The high false-negative rate in ultrasound limits its utility, and the high complication rate and unavailability of conventional angiography limit its widespread use.

TREATMENT

- Cervical spine immobilization is the first step in the setting of any neck trauma.
- Initial noncontrast CT of the cervical spine should be ordered to rule out fracture if suspected; if negative, follow up with CT angiography or MRA.
- Anticoagulation therapy should be performed if there is no contraindication or high risk. First one must rule out intracranial hemorrhage and other bleeding source in trauma patients. Anticoagulation with heparin followed by warfarin is generally accepted as sufficient management for prevention of thromboembolic events.
- In the case of contraindications to anticoagulation therapy, antiplatelet therapy may be used.

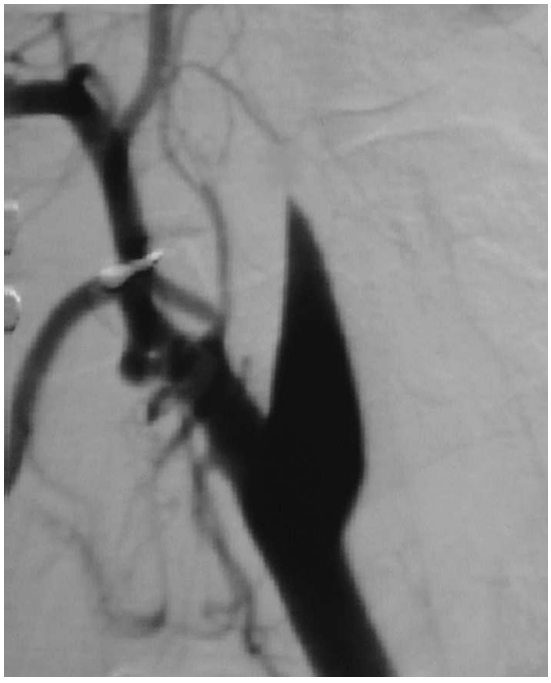

FIG. E1 Acute dissection. A digital subtraction angiogram shows sharply tapered occlusion of the internal carotid artery as a result of spontaneous dissection. (From Soto JA, Lucey BC: *Emergency radiology, the requisites*, ed 2, Philadelphia, 2017, Elsevier.)

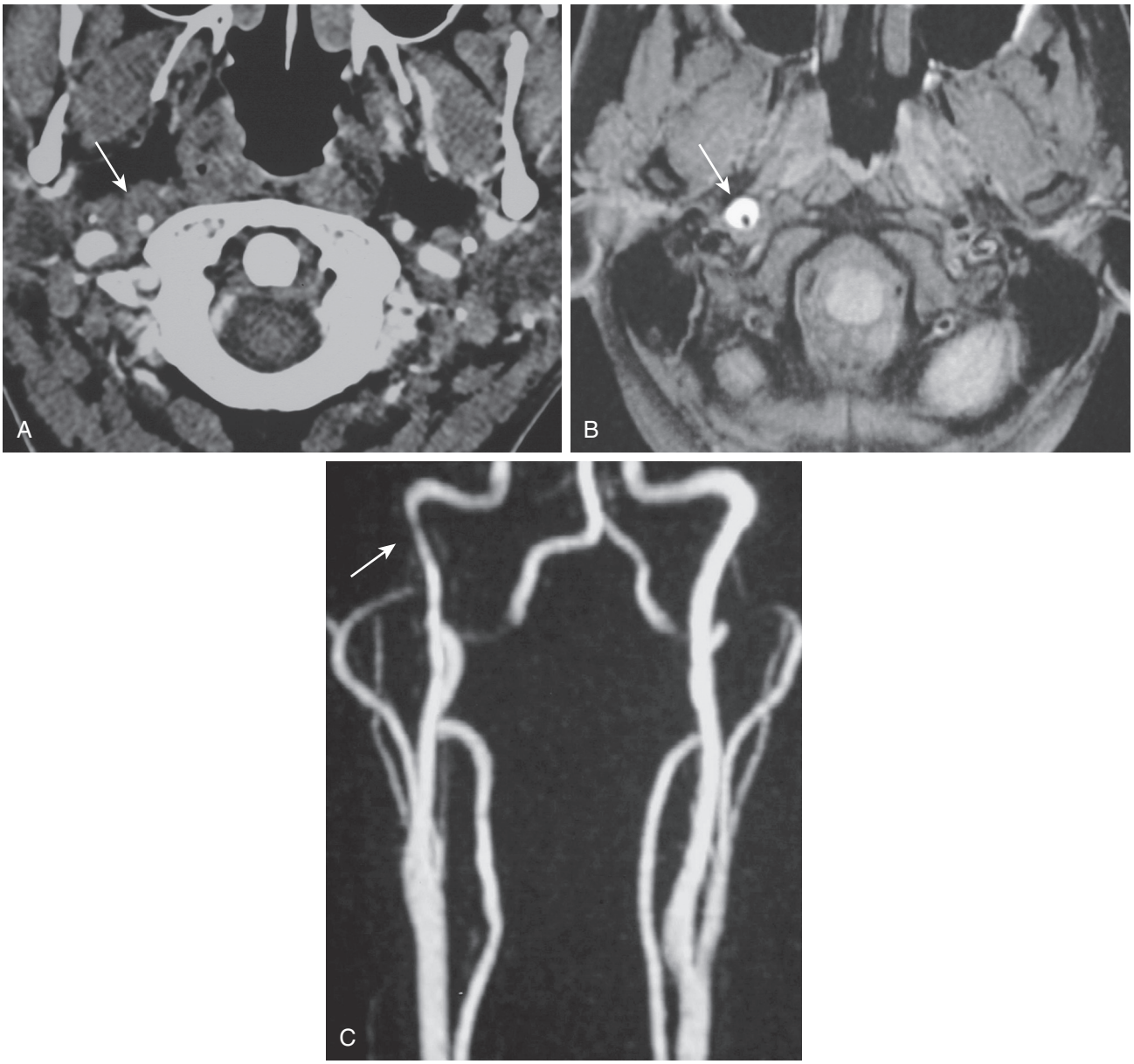

FIG. E2 Internal carotid artery dissection as seen on computed tomography (CT) and magnetic resonance (MR) angiogram. A, A CT angiogram source image shows a narrowed upper cervical right internal carotid artery lumen with an increase in the external caliber of the vessel *(arrow)*. **B,** A fat-suppressed T1-weighted image shows corresponding narrowed flow void with a hyperintense eccentric intramural hematoma *(arrow)*. **C,** A time-of-flight MR angiogram shows a narrowed segment of the right internal carotid artery *(arrow)*. (From Soto JA, Lucey BC: *Emergency radiology, the requisites*, ed 2, Philadelphia, 2017, Elsevier.)

- Do not use anticoagulation or antiplatelet therapy in a pregnant patient without an OB consultation.
- Other pharmacologic treatment modalities are currently in clinical trials.

NONPHARMACOLOGIC THERAPY

Operative endovascular management with angioplasty or stent placement is only utilized in select patients. Criteria include:

- Persistent ischemic symptoms despite adequate anticoagulation
- Contraindication to anticoagulant therapy
- An iatrogenic dissection developing during an intravascular procedure
- Significantly compromised cerebral blood flow

Surgery has limited use in CAD, although surgical consultation is recommended.

DISPOSITION

- Traumatic dissections: Admit to trauma unit with vascular service input.
- Spontaneous dissections: Admit to stroke service and potentially refer to vascular if endovascular intervention is recommended.

REFERRAL

Vascular surgery

COMPLICATIONS

- Occlusion leading to ischemic stroke
- Thrombosis and embolization leading to TIAs
- Subarachnoid hemorrhage if the dissection is intracranial
- Pseudoaneurysm formation

PEARLS & CONSIDERATIONS

In young patients with strokelike symptoms or acute onset neck pain or headache, consider cervical artery dissection.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Thomas M. Triplett, MD**

SUGGESTED READINGS

Blum CA et al: Cervical artery dissection: a review of the epidemiology, pathophysiology, treatment, and outcome, *Arch Neurosci* 2(4), 2015:e26670.

Debette S et al: Cervical-artery dissections: predisposing factors, diagnosis and outcome, *Lancet Neurol* 8(7):668-678, 2009.

Life in the Fast Lane Medical Blog: lifeinthefastlane.com/ccc/cervical-artery-dissection/

Traenka C et al: Cervical artery dissection patients ≥60 years: often painless, few mechanical triggers, *Neurology* 88:1313-1320, 2017.

BASIC INFORMATION

DEFINITION

Cervical cancer is the penetration of the basement membrane and infiltration of the stroma of the uterine cervix by malignant cells.

ICD-10CM CODES

C53.8 Malignant neoplasm of overlapping sites of cervix uteri
C53.9 Malignant neoplasm of cervix uteri, unspecified
D06.7 Carcinoma in situ of other parts of cervix
D06.9 Carcinoma in situ of cervix, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: According to the World Health Organization, cervical cancer is the fourth most common malignancy in women. It is reported that nearly 9 out of 10 women who died of cervical cancer were in an underdeveloped region of the world.
PREDOMINANCE: Higher incidence rates occur in developing countries. Among the U.S. population, Hispanics have a higher incidence than African Americans, who likewise have a higher incidence than Caucasians.
RISK FACTORS: Infection with high-risk human papillomavirus (HPV; types 16 and 18 are the most oncogenic with 31, 33, 35, 45, 52, and 58 also considered high risk). Smoking, early age of coitarche, multiple sexual partners, immunocompromised state, nonbarrier methods of contraception, and multiparity are also risk factors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Unusual vaginal bleeding, particularly postcoital (Fig.1)
- Vaginal discharge and/or odor
- Pelvic pain in early stage disease. In later stages back pain or disrupted urination or defecation may occur
- Advanced cases may present with lower-extremity edema or renal failure
- In early stages, there may be little or no obvious cervical lesion; more advanced cases may have large, bulky, friable lesions (Fig. E2) encompassing majority of vagina

ETIOLOGY

- Infection with high-risk HPV types is a necessary, although not sufficient, cause of almost all cases of cervical cancer. Persistent HPV infection leads to precancerous changes of the cervix known as cervical intraepithelial neoplasia (CIN). CIN can progress to invasive cervical cancer.
- Both squamous cell and adenocarcinoma of cervix are associated with HPV infection (Table 1).
- More than 40 HPV types can infect the cervix. Most cases are believed to be linked to presence of HPV 16, 18, 31, 35, 39, 45, 51, 52, 56, 58, 59, and 68 by interaction of E6 and E7 oncoprotein on *p53* gene product.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cervical polyp or prolapsed uterine fibroid.
- Neoplasia metastatic from a separate primary neoplasia.
- Box 1 summarizes benign mimics of cervical adenocarcinoma.
- Categories of squamous carcinoma are described in Box 2.
- Table 2 summarizes the differential diagnosis of squamous intraepithelial lesions.

WORKUP

- Thorough history and physical examination
- Pelvic examination with careful rectovaginal examination
- Table 3 summarizes the clinical evaluation of patients with newly diagnosed cervical cancer
- Compared with Pap testing, HPV testing has greater sensitivity for detection of CIN. Addition of HPV test for high-risk types to Pap test to screen women in mid-30s for cervical cancer reduces incidence of grade 2 or 3 CIN or cancer detected by subsequent screening examinations
- Colposcopy with directed biopsy and endocervical curettage
- FIGO staging is described in Table 4

LABORATORY TESTS

- Complete blood count, chemistry profile
- SCC antigen in research setting
- Carcinoembryonic antigen

IMAGING STUDIES

- Chest x-ray
- Depending on stage, may need CT scan, MRI (Fig.E3), PET/CT
- Table 3, intravenous pyelogram

TREATMENT

NONPHARMACOLOGIC THERAPY

- FIGO stage I_A: Cone biopsy or simple hysterectomy
- FIGO stage I_B or II_A: Type III radical hysterectomy and pelvic lymphadenectomy or pelvic radiation therapy. Minimally invasive radical hysterectomy is associated with shorter overall survival than open surgery among women with stage I_{A2} or I_{B2} cervical carcinoma (Melamed A et al, in Suggested Reading N Engl J Med 379:1905, 2018.)
- Advanced or bulky disease: Multimodality therapy (radiation, chemotherapy, and/or surgery); platinum use before radiation therapy

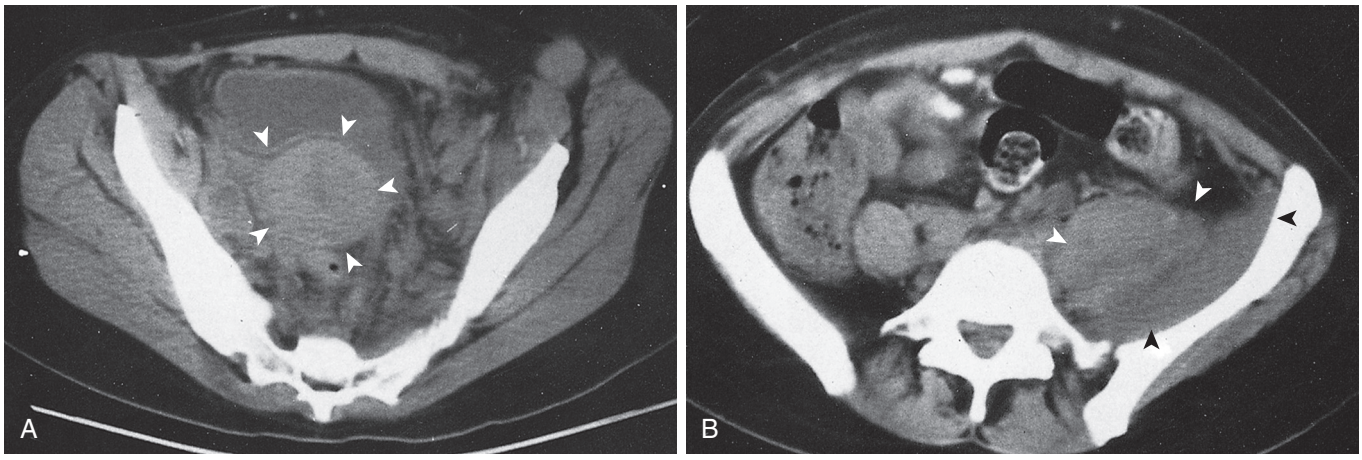

FIG. 1 Stage III_B cervical carcinoma. A 27-year-old woman presented with increased vaginal bleeding, left leg swelling, and abdominal pain. Examination revealed a large, fixed pelvic mass. Computed tomography scan evaluation **(A)** confirms the mass *(arrowheads)* and **(B)** shows extension into the left psoas and iliacus muscles *(arrowheads)*. She also had hydronephrosis. Pathologic examination showed an adenosquamous carcinoma. (From Skarin AT: *Atlas of diagnostic oncology*, ed 4, Philadelphia, 2010, Mosby.)

TABLE 1 Descriptive Categories of Low-Grade Squamous Intraepithelial Lesion and High-Grade Squamous Intraepithelial Lesion

	Descriptors	Human Papillomavirus	p16 Immunostaining
LSIL	CIN1, flat condyloma, mild dysplasia	HR (70%)	Usually diffuse
	Exophytic condyloma	LR	Negative or patchy
	Immature condyloma (papillary immature metaplasia)	LR	Negative or patchy
	Immature flat metaplastic LSIL	HR	Usually diffuse
HSIL	CIN2 or moderate dysplasia	HR (45% type 16)	Diffuse
	CIN3 or severe dysplasia/carcinoma in situ	HR (60% type 16)	Diffuse
	Keratinizing SIL	HR	Diffuse
	HSIL with immature metaplastic phenotype	HR	Diffuse
	Papillary carcinoma in situ	HR	Diffuse
	Adenosquamous carcinoma in situ	HR	Diffuse

CIN, Cervical intraepithelial lesion; *HR,* high risk; *HSIL,* high-grade squamous intraepithelial lesion; *LR,* low risk; *LSIL,* low-grade squamous intraepithelial lesion; *SIL,* squamous intraepithelial lesion.
Crum CP et al: *Diagnostic gynecologic and obstetric pathology,* ed 3, Philadelphia, 2018, Elsevier.

BOX 1 Benign Mimics of Cervical Adenocarcinoma

Deep nabothian cysts, florid deep glands
Tunnel clusters
Endocervical gland hyperplasias
  Lobular hyperplasia
  Diffuse laminar hyperplasia
Adenomyoma of the endocervical type
Endocervicosis, florid cystic endosalpingiosis
Müllerian papilloma
Microglandular hyperplasia
Mesonephric hyperplasia
Ectopic prostate
Deep tubal metaplasia

Crum CP et al: *Diagnostic gynecologic and obstetric pathology*, ed 3, Philadelphia, 2018, Elsevier.

BOX 2 Categories of Squamous Carcinoma

Squamous cell carcinoma
Large cell keratinizing (well-differentiated)
Large cell nonkeratinizing (moderately differentiated)
Small cell nonkeratinizing (poorly differentiated)
Lymphoepithelial-like carcinoma
Spindle cell (sarcomatoid) carcinoma
Verrucopapillary carcinomas
Papillary (squamotransitional) carcinoma
Verrucous carcinoma (rare)[a]
Condylomatous carcinoma[a]
Basaloid carcinomas[b]

[a]In young women, an extensive (giant) condyloma must be excluded.
[b]May be associated with adenoid basal and adenoid cystic carcinomas, as well as carcinosarcomas.
Crum CP et al: *Diagnostic gynecologic and obstetric pathology,* ed 3, Philadelphia, 2018, Elsevier.

TABLE 2 Differential Diagnosis of Squamous Intraepithelial Lesions

Category	Mimic	Distinguishing Features
LSIL	Mucosal polyp (vaginal)	Minimal acanthosis, no koilocytosis
	Reactive epithelial changes	Mild superficial karyomegaly, occasional binucleated intermediate cells
	Postmenopausal changes	Superficial cell karyomegaly, cytoplasmic halos
HSIL	Immature reactive/repair	Basal hyperchromasia, uniform nuclear spacing and nuclear contour, nucleoli
	Immature metaplasia	Uniform maturation, minimal surface hyperchromasia
	Atrophy	No mitoses, uniform chromasia, nuclear density
	Atypical atrophy	Enlarged nuclei, uncommon
	Implantation site	Uniform and wide nuclear spacing, bizarre nuclei
	Endometrial histiocytes	Small indented nuclei, granular cytoplasm, lack of polarity

HSIL, High-grade squamous intraepithelial lesion; *LSIL,* low-grade squamous intraepithelial lesion.
Crum CP et al: *Diagnostic gynecologic and obstetric pathology,* ed 3, Philadelphia, 2018, Elsevier.

ACUTE GENERAL Rx

- Table 4 summarizes treatment according to tumor stage. Fig. 4 describes a treatment algorithm for invasive cervical cancer.
- Chemotherapy is cisplatin-based. In advanced cases, cervical cancer may present with massive and acute vaginal bleeding requiring volume and blood replacement, vaginal packing or other hemostatic modalities, and/or high-dose local radiotherapy.

CHRONIC Rx

- Physical examination with Pap smear every 3 mo for 2 yr, every 6 mo for 3 to 5 yr, annually thereafter. Table 5 summarizes a proposed schedule for interval evaluation of cervical cancer after radiotherapy or surgery in asymptomatic patients
- Chest x-ray annually (optional)
- Other imaging done only as clinically indicated
- Localized pelvic recurrence may be treated and cured with pelvic exenteration

DISPOSITION

Five-yr survival varies by stage:
- Stage I: 90% to 95%
- Stage II: 40% to 80%
- Stage III: <60%
- Stage IV: <15%

Early detection by Pap smear is imperative for long-term improvements in survival. American Cancer Society guidelines for screening by cytology for the early detection of cervical neoplasia and cancer are summarized in Table 6.

REFERRAL

Gynecologic oncologist for all invasive disease

PEARLS & CONSIDERATIONS

- HPV vaccination is indicated in males and females age 9 to 26 yr for the prevention of cervical cancer caused by HPV types 6, 11, 16, and 18. HPV vaccination is over 90% effective in preventing infection and cervical cancer. There are now HPV vaccines that are effective against nine strains of high-risk HPV.
- Available evidence supports discontinuation of cervical cancer screening among women aged 65 yr or older who have had adequate screening and are not otherwise at high risk.
- Updated recommendations from the American College of Physicians on screening for cervical cancer in average-risk women are as follows.[1]
  1. Women should be screened with cervical cytology every 3 yr beginning at age 21 until age 30.

[1] Sawaya GF et al: Cervical cancer screening in average-risk women: best practice advice from the Cervical Guidelines Committee of the American College of Physicians, *Ann Intern Med* 162(12):851-859, 2015.

TABLE 3 Clinical Evaluation of Patients with Newly Diagnosed Cervical Cancer

History	Review of Systems	General Physical Examination
Risk factors (STDs, smoking, OCPs, HIV), prior abnormal Pap tests, previous dysplasia, and treatment	Abnormal vaginal bleeding or discharge, pelvic pain, flank pain, sciatica, hematuria, rectal bleeding, anorexia, weight loss, bone pain	Peripheral lymphadenopathy
Evaluation	Common procedures (FIGO)	Alternative procedures
Invasive cancer	Cervical biopsy Endocervical curettage Cervical conization	Histologic diagnosis required
Tumor size; involvement of the vagina, bladder, rectum and parametria	Pelvic examination under anesthesia	MRI of pelvis preferred over CT
Anemia	Complete blood count	—
Renal failure	Serum chemistries	—
Hematuria	Urinalysis	—
Bladder involvement	Cystoscopy with biopsy and urine cytology	CT, MRI pelvis
Rectal infiltration	Proctoscopy with biopsy	CT, MRI pelvis; barium enema
Hydronephrosis	IVP	Renal ultrasonography; CT abdomen
Pulmonary metastases	Chest radiography	CT chest; PET scan
Retroperitoneal lymphadenopathy	—	lymphangiogram, CT, MRI, PET scan

CT, Computed tomography; *FIGO,* Federation of International Gynecologists and Obstetricians; *HIV,* human immunodeficiency virus; *IVP,* intravenous pyelography; *MRI,* magnetic resonance imaging; *OCP,* oral contraceptive pill; *PET,* positron emission tomography; *STD,* sexually transmitted disease.
From Disaia PJ et al: *Clinical gynecologic oncology*, ed 9, Philadelphia, 2017, Elsevier.

TABLE 4 Federation of International Obstetrics and Gynecology Staging of Cervical Cancer

Stage	Invasion	Prognosis 5-Year Survival	Treatment
I_{A1}	Depth of invasion ≤3 mm and width ≤7 mm (includes early stromal invasion of up to 1 mm)	98%-99%	Local excision; if margins of a LLETZ/cone clear (i.e., no residual tumor or CIN) then conization is adequate, with no need for pelvic lymphadenectomy.
I_{A2}	Depth of invasion 3.1-5 mm and width ≤7 mm	95%	Simple hysterectomy and pelvic lymphadenectomy. If fertility sparing required, large cone and lymphadenectomy
I_{B1}	Tumor confined to cervix and diameter <4 cm	90%-95%	Radical hysterectomy (and lymphadenectomy)
I_{B2}	Tumor confined to cervix and diameter >4 cm	80%	Chemo–radiotherapy
II_A	Upper two-thirds of vagina	70%-90%	Chemotherapy & radiotherapy
II_B	Upper two-thirds of vagina plus parametrial disease	60%-70%	Chemo–radiotherapy
III_A	Lower third of vagina	30%-50%	Chemotherapy & radiotherapy
III_B	Pelvic sidewall and/or hydronephrosis		Chemo–radiotherapy
IV_A	Bladder, rectum	20%	Chemo–radiotherapy
IV_B	Beyond pelvis		

CIN, Cervical intraepithelial neoplasi; *LLETZ,* large loop excision of the transformation zone.
From Magowan BA: *Clinical obstetrics and gynecology,* ed 4, 2019, Elsevier.

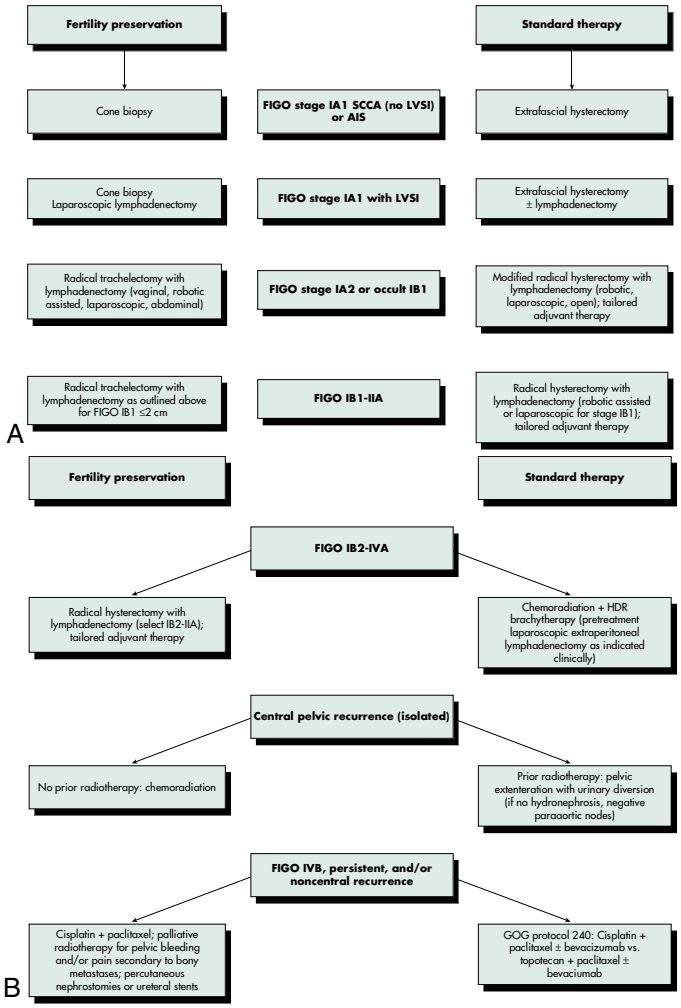

FIG. 4 A and **B,** Algorithm for therapy. *AIS,* Adenocarcinoma *in situ; FIGO,* Federation of International Gynecologists and Obstetricians; *GOG,* gynecologic oncology group; *HDR,* high-dose rate; *LVSI,* lymphovascular space invasion, *SCCA,* squamous cell carcinoma associated antigen. (From Disaia PJ et al: *Clinical gynecologic oncology*, ed 9, Philadelphia, 2017, Elsevier.)

TABLE 5 Proposed Schedule for Interval Evaluation of Cervical Cancer after Radiotherapy or Surgery (Asymptomatic Patient*)

Year	Frequency	Examination
1	3 mo	Pelvic examination, Pap smear
	6 mo	Chest radiography, CBC, BUN, creatinine
	1 yr	IVP or CT scan with contrast
2	4 mo	Pelvic examination, Pap smear
	1 yr	Chest radiography, CBC, BUN, creatinine, IVP or CT scan with contrast
3-5	6 mo	Pelvic examination, Pap smear

BUN, Blood urea nitrogen; *CBC,* complete blood count; *CT,* computed tomography; *IVP,* intravenous pyelogram; *Pap,* Papanicolaou.
*Symptomatic patients should have appropriate examination where indicated.
From Disaia PJ et al: *Clinical gynecologic oncology*, ed 9, Philadelphia, 2017, Elsevier.

TABLE 6 American Cancer Society Guidelines for Screening by Cytology for the Early Detection of Cervical Neoplasia and Cancer

- No screening is recommended regardless of sexual initiation or other risk factors before the age of 21.
- Women between the ages of 21 and 29 yr should have a Pap test every 3 yr. They should not be tested for human papillomavirus (HPV) unless such testing is needed after an abnormal Pap test result.
- Women between the ages of 30 and 65 yr should have both a Pap test and an HPV test every 5 yr. This is the preferred approach, but it is also acceptable to have a Pap test alone every 3 yr.
- Women older than 65 yr who have had regular screenings with normal results should not be screened for cervical cancer. Women who have been diagnosed with cervical precancer should continue to be screened.
- Women who have had their uterus and cervix removed in a hysterectomy and have no history of cervical cancer or precancer should not be screened.
- Women who have had the HPV vaccine should still follow the screening recommendations for their age group.
- Women who are at high risk for cervical cancer may need to be screened more often. Women who are at high risk might include those with human immunodeficiency virus (HIV) infection, organ transplantation, or exposure to the drug diethylstilbestrol (DES). They should talk with a doctor or nurse.

From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

2. After age 30, women can be screened with cytology and HPV testing every 5 yr.
3. Before age 21, women should not be screened unless HIV positive. If HIV positive, they should begin screening within 1 yr of coitarche.
4. Before age 30, women should not be screened with HPV testing.

- At age 65, screening can stop in women with three consecutive negative cytology results or two consecutive negative cytology results combined with a negative HPV test within the last 10 yr (with the most recent test within 5 yr).
- Women without a cervix should not be screened.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Cervical Cancer (Patient Information)
Cervical Dysplasia (Related Key Topic)

AUTHORS: **Allison Dillon, MD,** and **Anthony Sciscione, DO**

FIG. E2 Invasive squamous cell carcinoma. A mass is present on the external os. (From Clement PB, Young RH. *Atlas of gynecologic surgical pathology.* Philadelphia: Saunders; 2000; 103, in Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

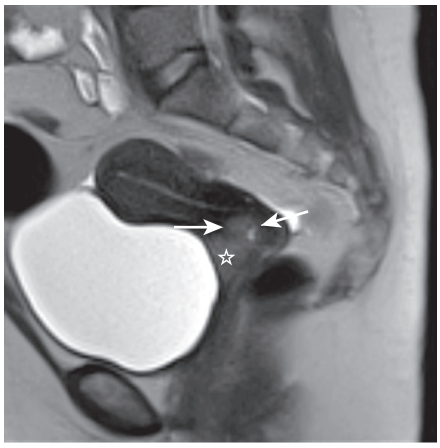

FIG. E3 Cervical carcinoma. T2-weighted sagittal image through the cervix shows an intermediate signal mass *(arrows)* disrupting the normally intense low signal ring of the cervical stroma with areas of high signal. The mass infiltrates the upper vagina *(star)*. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

SUGGESTED READINGS

Jung HS et al: Human papillomavirus: current and future RNAi therapeutic strategies for cervical cancer, *J Clin Med* 154(5):1126-1155, 2015.

Melamed A et al: Survival after minimally invasive radical hysterectomy for early-stage cervical cancer, *N Engl J Med* 379:1905-1914, 2018.

Ramirez PT et al: Minimally invasive versus abdominal radical hysterectomy for cervical cancer, *N Engl J Med* 379:1895-1904, 2018.

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Cervical Disc Syndromes (PTG)

BASIC INFORMATION

DEFINITION

Cervical disc syndromes result from disc herniation and degenerative changes in the cervical spine. The symptoms can be categorized as cervical radiculopathy (nerve root impingement) if the stenosis is most significant at the neural foramen, or as myelopathy (spinal cord impingement) if the stenosis is more central in the spinal canal. Central cord stenosis (myelopathy) can result in both upper- and lower-extremity symptoms, while foraminal narrowing typically results in radicular symptoms (Fig. E1).

SYNONYMS

Cervical myelopathy
Cervical radiculopathy
Cervical spondylopathy (degenerative vs. traumatic)

ICD-10CM CODES

M50.00	Cervical disc disorder with myelopathy, unspecified cervical region
M50.01	Cervical disc disorder with myelopathy, high cervical region
M50.02	Cervical disc disorder with myelopathy, mid-cervical region
M50.03	Cervical disc disorder with myelopathy, cervicothoracic region
M50.10	Cervical disc disorder with radiculopathy, unspecified cervical region
M50.11	Cervical disc disorder with radiculopathy, high cervical region
M50.12	Cervical disc disorder with radiculopathy, mid-cervical region
M50.13	Cervical disc disorder with radiculopathy, cervicothoracic region
M50.20	Other cervical disc displacement, unspecified cervical region
M50.21	Other cervical disc displacement, high cervical region
M50.22	Other cervical disc displacement, mid-cervical region
M50.23	Other cervical disc displacement, cervicothoracic region
M50.30	Other cervical disc degeneration, unspecified cervical region
M50.31	Other cervical disc degeneration, high cervical region
M50.32	Other cervical disc degeneration, mid-cervical region
M50.33	Other cervical disc degeneration, cervicothoracic region
M50.80	Other cervical disc disorders, unspecified cervical region
M50.81	Other cervical disc disorders, high cervical region
M50.82	Other cervical disc disorders, mid-cervical region
M50.83	Other cervical disc disorders, cervicothoracic region
M50.90	Cervical disc disorder, unspecified, unspecified cervical region
M50.91	Cervical disc disorder, unspecified, high cervical region
M50.92	Cervical disc disorder, unspecified, mid-cervical region
M50.93	Cervical disc disorder, unspecified, cervicothoracic region

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The incidence of cervical radiculopathy can be up to 107.3 and 64.5 per 100,000 men and women, respectively, in the U.S.
PREVALENCE: Up to 67% of all adults experience neck and arm pain at some point in their life.
PREDOMINANT SEX AND AGE: Males and females are affected equally between the ages of 30 and 60. Most commonly, cervical myelopathy is seen in patients >55 yr of age.
RISK FACTORS: Risk factors include aging, repetitive microtrauma to the neck, and, potentially, genetic factors, although research is ongoing.
GENETICS: No definitive genetic associations have been identified, though family history likely plays a role.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Neck pain, especially with extension, and limited neck range of motion. Spurling sign (pain on axial compression of the neck while it is extended and the head is turned to the affected side) is usually positive in the setting of foraminal stenosis.
- Referred unilateral interscapular pain.
- Numbness, tingling, or radiating pain in a dermatomal distribution may be secondary to nerve root impingement at the associated level (radicular symptoms).
- Extremity or hand weakness and clumsiness, gait disturbance and spasticity in upper and lower extremities (myelopathic symptoms), abnormal reflexes: Positive Hoffman sign, positive inverted radial reflex, and hyperactive biceps and triceps reflexes are usually seen in myelopathic patients.

ETIOLOGY

Degeneration of vertebral bodies, intervertebral disc herniations, hypertrophy of facets, uncovertebral joints, and ligamentum flavum can all lead to spinal cord and/or nerve root impingement causing cervical disc syndrome.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Muscle spasms
- Rotator cuff tendinitis/tear
- Frozen shoulder
- Carpal tunnel syndrome
- Cubital tunnel syndrome
- Radial tunnel syndrome
- Thoracic outlet syndrome
- Brachial neuritis or brachial plexopathy
- Cervical spine epidural abscess
- Malignancy (primary or metastatic) causing nerve root or spinal cord impingement

A differential diagnosis for evaluation of neck pain is described in Section II.

WORKUP

Combination of clinical diagnosis and radiologic studies (x-ray and MRI).

LABORATORY TESTS

No specific labs are required; however, CBC and inflammatory markers (erythrocyte sedimentation rate/c-reactive protein) can be obtained if infectious cause or inflammatory conditions are suspected.

IMAGING STUDIES

- Plain radiographs (Fig. E2) should be obtained first to rule out traumatic causes (fracture, subluxation, dislocation, spondylolisthesis).
  1. Usually normal in soft disc herniation or foraminal stenosis, but loss of disk height between vertebral bodies may indicate disease.
  2. With chronic degenerative disc disease, loss of disc height, anterior and posterior osteophyte formation, and encroachment on the intervertebral foramen by osteophytes may be seen.
- CT myelography or MRI (Fig. E3) is indicated in patients with neurologic symptoms that do not resolve with conservative management or when other spinal pathology is suspected.
- Electrodiagnostic studies can be used to confirm the diagnosis or rule out peripheral nerve disorders.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Rest and soft or hard cervical collar can be used to immobilize the neck for brief periods of time.
- Local modalities such as heat and ice may help.
- Physical therapy.
- Avoid extreme range-of-motion exercises in degenerative disc disease, although some find relief with traction.

ACUTE GENERAL Rx

- Nonsteroidal antiinflammatory drugs or oral steroids
- Muscle relaxants
- Analgesics as needed
- Epidural steroid injection for radicular pain

CHRONIC Rx

- If acute modalities and nonoperative therapies fail, patients can be evaluated for surgical intervention.
- Nerve ablation for chronic pain in patients who may not be safe for surgery.
- Discectomy or decompression and/or fusion for symptomatic cervical discs.

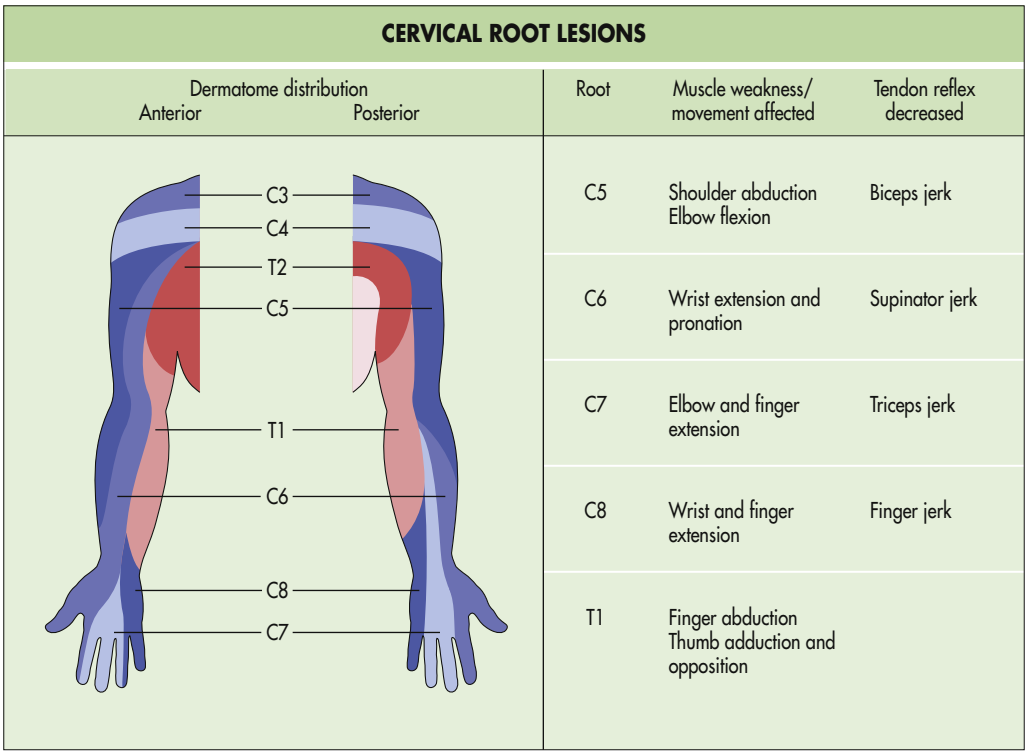

FIG. E1 Sensory and motor distribution of the cervical roots. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

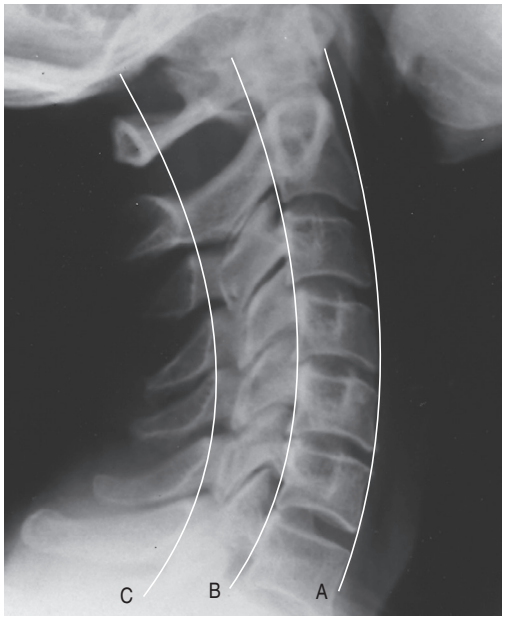

FIG. E2 Plain lateral radiograph of a normal cervical spine. Lines joining the anterior part of the vertebral body **(A)**, the posterior aspect of the vertebral body **(B)**, and the anterior border of the laminae **(C)** should describe a smooth arc. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Herbal antiinflammatory medications
- Chiropractic care
- Acupuncture
- Deep-tissue massage

DISPOSITION

- Acute radiculopathy usually improves with time.
- Myelopathy is a stepwise decline with progressive symptoms.
- Surgical intervention is normally offered to approximately 5% of the patients.

REFERRAL

Orthopedic or neurosurgical consultation for intractable pain or worsening neurologic deficit

PEARLS & CONSIDERATIONS

Myelopathy from cervical spondylosis is the most common cause of acquired spastic paralysis in the adult and is usually progressive. Decisions about surgical intervention are complicated in these patients.

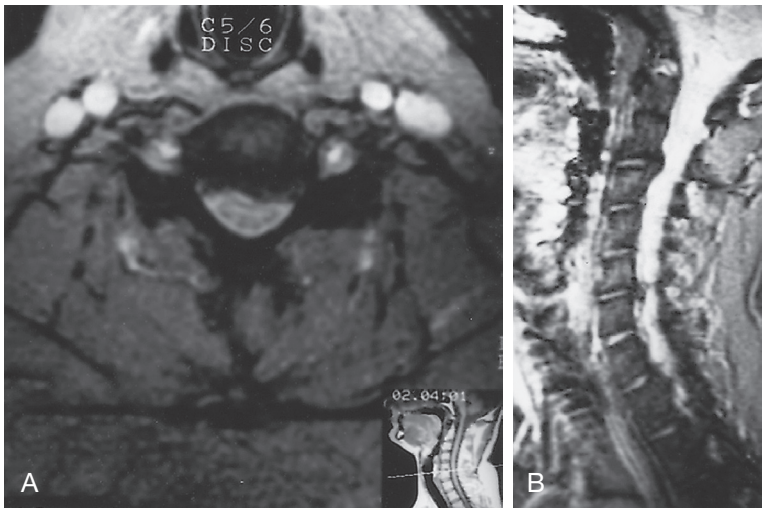

FIG. E3 Disk herniation on magnetic resonance imaging (MRI). Axial **(A)** and sagittal **(B)** MRI scans of a 47-yr-old man with neck pain, decreased left biceps jerk, and numbness over his thumb after a motor vehicle accident demonstrate a significant left posterolateral disk protrusion at C5 to C6 that is significantly compromising the exiting C6 nerve root. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

COMMENTS

- Pain relief with physical therapy is variable; any overall improvement usually parallels what would have likely occurred naturally.
- Sometimes carpal tunnel syndrome and cervical radiculopathy occur together; this is termed *double-crush syndrome,* pointing to the fact that the nerve is being compressed at two separate levels. Proximal compression may decrease the ability of the nerve to tolerate a second, more distal compression.
- Surgical intervention is indicated primarily for relief of radicular pain caused by nerve root compression or for the treatment of progressive myelopathy; it is generally not helpful when the chief complaint is neck pain alone without extremity symptoms.
- In many cases of cervical spondylosis with myelopathy, the lower extremity symptoms are much more disabling than the neck symptoms.

PREVENTION

No known prevention exists.

RELATED CONTENT

Cervical Disc Syndrome (Patient Information)

AUTHORS: **Shyam A. Patel, MD,** and **Steven F. Defroda, MD, MEng**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Cervical dysplasia refers to atypical development of immature squamous epithelium that does not penetrate the basement epithelial membrane and is caused by persistent infection with human papillomavirus (HPV). Characteristics include increased cellularity, nuclear abnormalities, and increased nuclear/cytoplasmic ratio. A progressive loss of squamous differentiation exists beginning adjacent to the basement membrane and progressing to the most advanced stage (severe dysplasia), which encompasses the complete squamous epithelial layer thickness. The revised 2001 Bethesda System terminology was used in a National Institutes of Health consensus conference, sponsored by the American Society for Colposcopy and Cervical Pathology (ASCCP) and its partner professional organizations in 2006. The conference updated therapeutic options for women based on studies such as the **A**SC-US (atypical squamous cells of undetermined significance)/**L**SIL (low-grade squamous intraepithelial lesions) **T**riage **S**tudy (ALTS) that appeared after revision of the Bethesda classification. Fig. 1 provides a comparison of grading systems for cervical squamous dysplasia.

In 2012, the American Cancer Society (ACS), ASCCP, and American Society for Clinical Pathology (ASCP) published a new set of recommendations for lifetime assessment and early diagnosis of cervical dysplasia and cancer. The recommendations attempted to reduce the number of lifetime assessments, thereby reducing the possible morbidity associated with excess testing and also optimizing the co-evaluation with Pap smear and HPV testing.

UPDATED SCREENING PROTOCOL:

- Women younger than 21 yr of age should not have cervical cancer screening unless HIV positive. If HIV positive, screening should start within 1 yr of coitarche.
- Women 21 to 29 yr of age should have testing every 3 yr with only cytology. With negative cytology or HPV-negative ASC-US, patients can repeat every 3 yr. For HPV-positive ASC-US or cytology with LG-SIL, follow-up is as per the 2006 guidelines, typically a colposcopic examination as the initial step with follow-up steps depending on the findings.
- Women between the ages of 30 and 65 yr should have co-testing every 5 yr with both Pap cytology and HPV testing. Alternatively, it is also acceptable to perform cytology alone, but then the testing interval should be every 3 yr. With negative cytology or HPV-negative ASC-US, patients can repeat with co-testing every 5 yr. For HPV-positive ASC-US or cytology with LG-SIL, follow-up is as per the 2006 guidelines, as previously documented. For patients with positive HPV but negative cytology, the patient can repeat testing 12 months later with co-testing. Patients can also specifically test for HPV 16 or HPV 16/18 genotypes and, if positive, should be referred for colposcopy. Patients with positive HPV but negative 16 and/or 18 should be retested in 12 months with co-testing.
- Women older than the age of 65 and those with a history of hysterectomy (including removal of cervix) should no longer be tested unless they had previous diagnosis of cervical intraepithelial neoplasia (CIN) 2 or more severe; these women should be tested for at least 20 yr. Women who have been vaccinated for HPV should still use age-specific recommendations for screening.

BETHESDA 2001 UPDATED CLASSIFICATION: The Bethesda 2001 System was the result of a year-long iterative process held to update the original 1991 system and to broaden participation in the consensus process, clarify reporting of abnormalities, and incorporate data that had been collected since the initial system was created.

The reporting system includes the following areas:

- *Specimen adequacy:* The system defines the specimen as either satisfactory for evaluation or unsatisfactory and then specifies the reason for inadequacy if necessary.
- *General categorization (optional):* This serves to triage the specimen into normal finding (negative for intraepithelial lesion or malignancy) or identifies it as an "epithelial abnormality." The descriptions are meant to be mutually exclusive.
- *Interpretation/result:* Makes a distinction between "interpretation" and "diagnosis" of the specimen so that the interpretation may be incorporated into the overall clinical context for the particular patient being evaluated.
- *Negative for intraepithelial lesion or malignancy:* In this screening test, no intraepithelial lesion or malignancy is identified. Non-neoplastic findings such as organisms or reactive cellular findings may be specified but are still considered to be a negative result.
- Epithelial cell abnormalities:
  1. Squamous cell:
     a. Atypical squamous cell (ASC) of undetermined significance (ASC-US) emphasizing the unusual but still possible association with underlying CIN II/III and extremely rare possibility of squamous cell carcinoma.
     b. ASC cannot exclude high-grade squamous intraepithelial lesion (HSIL) (ASC-H), suggesting a risk for CIN II/III that is intermediate between ASC-US and HSIL.
     c. LSIL suggests a transient viral infection with a greater likelihood for regression, more likely to encompass HPV infection and CIN I histologically.
     d. HSIL suggestive of a more persistent viral infection and with a greater risk for progressive disease, more likely to encompass CIN II/III and carcinoma in situ (CIS) histologically.
     e. Squamous cell carcinoma.
  2. Glandular cell:
     a. Atypical glandular cells (should specify endocervical, endometrial, or not otherwise specified).
     b. Atypical glandular cell, favor neoplasia (should specify endocervical or not otherwise specified).

Histological features	Traditional system	WHO system	British Society for Cervical Cytology	Bethesda system
Atypical squamous cells not meeting the criteria for dysplasia	Mild atypia	Mild atypia	Borderline nuclear abnormality	Atypical squamous cells (ASC)
Koilocytes plus mild atypia	HPV infection	HPV infection	HPV plus borderline change	Low-grade squamous intraepithelial lesion (SIL)
Dysplasia limited to lower third of epithelium	Mild dysplasia	CIN 1	Mild dyskaryosis (low-grade dyskaryosis)	Low-grade SIL
Dysplasia limited to lower two-thirds of epithelium	Moderate dysplasia	CIN 2	Moderate dyskaryosis (high-grade dyskaryosis)	High-grade SIL
Dysplasia extending into upper third of epithelium	Severe dysplasia	CIN 3	Severe dyskaryosis (high-grade dyskaryosis)	High-grade SIL
Dysplasia of full thickness of epithelium	Carcinoma in situ	CIN 3	Severe dyskaryosis (high-grade dyskaryosis)	High-grade SIL

FIG. 1 Comparison of grading systems. *CIN,* Cervical intraepithelial neoplasia; *HPV,* human papillomavirus; *WHO,* World Health Organization. (From Young B et al: Female reproductive system. In *Wheater's basic pathology,* Philadelphia, 2011, Elsevier, pp. 216-315.)

c. Endocervical adenocarcinoma in situ (AIS).
d. Adenocarcinoma.

3. Other: Endometrial cells in a woman ≥40 yr of age. Because menopausal status is sometimes uncertain, age was chosen to discriminate women who might, with the findings of endometrial cells on cytology, warrant further evaluation with endometrial sampling.

KEY POINTS:

- The cytologic distinctions of low grade (LSIL) and high grade (HSIL) do not necessarily equate to the histologic classifications CIN I and CIN II/III.
- The 2006 conference noted that one cytologic abnormality can have different histologic risk in different women and highlights "special populations" such as adolescent and young women, and those women who are pregnant. In young women, spontaneous HPV clearance rates are exceptionally high. The testing recommendations essentially removed the possibility of testing women younger than 21 yr of age.
- DNA testing for high-risk HPV types is incorporated into the evaluation and treatment algorithms for women with cytologic cervical abnormalities.

Histologically, a two-tiered system is developed in this guideline that distinguishes between the lower-risk CIN I and higher-risk CIN II/III diagnoses.

ICD-10CM CODES

N87.9	Dysplasia of cervix uteri, unspecified
R87.610	Atypical squamous cells of undetermined significance on cytologic smear of cervix (ASC-US)
R87.611	Atypical squamous cells cannot exclude high grade squamous intraepithelial lesion on cytologic smear of cervix (ASC-H)
R87.612	Low grade squamous intraepithelial lesion on cytologic smear of cervix (LGSIL)
R87.613	High grade squamous intraepithelial lesion on cytologic smear of cervix (HGSIL)
R87.614	Cytologic evidence of malignancy on smear of cervix
R87.615	Unsatisfactory cytologic smear of cervix
R87.618	Other abnormal cytological findings on specimens from cervix uteri
R87.619	Unspecified abnormal cytological findings in specimens from cervix uteri
Z12.4	Encounter for screening for malignant neoplasm of cervix

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT AGE:

- Dysplasia: Peak age, 26 yr (3600 cases/100,000 persons)
- CIS: Peak age, 32 yr (1100 cases/100,000 persons)
- Invasive cancer: Peak age <60 yr (800 cases/100,000 persons)

PEAK INCIDENCE:

- Age 35
- Abnormal Pap smear rate revealing dysplasia approximates 2% to 5% depending on population risk factors and false-negative rate variance
- False-negative rate approaching 40%
- Average age-adjusted incidence of severe dysplasia is 35 cases/100,000 persons
- Approximately half of the cases of new cervical cancer had never been screened, and another 10% had not been screened in more than 5 yr. Many of these women come from underserved or underresourced communities. The single biggest impact in reducing the morbidity and mortality from cervical cancer would come from appropriately addressing these health disparities.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Cervical lesions associated with dysplasia often are not visible to the naked eye; therefore, physical findings are best viewed by colposcopy of a 3% acetic acid-prepared cervix or Lugol solution
- Patients evaluated by colposcopy are identified by abnormal cervical cytology screening from Pap smear screening
- Colposcopic findings:
  1. Leukoplakia (white lesion seen by the unaided eye that may represent condyloma, dysplasia, or cancer)
  2. Acetowhite epithelium with or without associated punctation, mosaicism, abnormal vessels
  3. Abnormal transformation zone (abnormal iodine uptake, "cuffed" gland openings)
- Studies have looked at the benefit of taking random biopsies at time of colposcopy and have shown that there may be increased detection of CIN II or greater if biopsies are taken at random rather than only directed toward abnormal appearing lesions

ETIOLOGY

- Strongly associated and initiated by oncogenic HPV infection (high-risk HPV types are 16, 18, 31, 33, 35, 45, 51, 52, 56, and 58; low-risk HPV types are 6, 11, 42, 43, and 44)
- Risk factors:
  1. HPV
  2. Any heterosexual coitus
  3. Coitus during puberty (transformation-zone metaplasia peak)
  4. Diethylstilbestrol exposure
  5. Multiple sexual partners
  6. Lack of prior Pap smear screening
  7. History of STD
  8. Other genital tract neoplasia
  9. HIV
  10. Tuberculosis
  11. Substance abuse
  12. "High-risk" male partner (HPV)
  13. Low socioeconomic status
  14. Early first pregnancy
  15. Tobacco use

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Metaplasia
- Hyperkeratosis
- Condyloma
- Microinvasive carcinoma
- Glandular epithelial abnormalities
- Vulvar intraepithelial neoplasm
- Vaginal intraepithelial neoplasm
- Metastatic tumor involvement of the cervix

WORKUP

- Periodic history and physical examination (including cytologic screening) depending on age, risk factors, and history of preinvasive cervical lesions
- Consider screening for sexually transmitted disease (gonorrhea, *Chlamydia,* herpes, HIV, HPV)
- Abnormal cytology (HSIL/LSIL, initial ASC/ASC-US/ASC-H in high-risk patients, recurrent in low-risk/postmenopausal patients) and grossly evident suspicious lesions; refer for colposcopy and possible directed biopsy/endocervical curettage (ECC; examination should include cervix, vagina, vulva, and anus)
- For glandular cell abnormalities (AGCs): Refer for colposcopy and possible directed biopsy/ECC, and consider endometrial sampling
- In pregnancy: Abnormal cytology followed by colposcopy in the first trimester and at 28 to 32 wk; only high-grade lesions suspicious for carcinoma biopsied; ECC is contraindicated

LABORATORY TESTS

- Gonorrhea, chlamydia nucleic-acid amplification tests to rule out STD
- Pap cytology screening (requires appropriate sampling, preparation, cytologist interpretation, and reporting)
- Colposcopy and directed biopsy, ECC for indications (see "Workup")
- HPV DNA typing if identified abnormal cytology
- As compared with Pap testing, HPV testing has greater sensitivity for the detection of intraepithelial neoplasia

IMAGING STUDIES

- Cervicography
- Computer-enhanced Pap cytology screening (e.g., PAPNET)

MANAGEMENT

Refer to the literature for a more comprehensive approach. The following treatment paradigms in Table 1 give a general outline for care.

DISPOSITION

- Because of the large number of women in high-risk groups, the prevalence of HPV, and the high false-negative Pap smear rate, routine Pap smear screening should be strongly encouraged for all women, especially those with a history of cervical dysplasia. The

TABLE 1 Summary of Recommendations

Population	Recommended Screening Method	Management of Screen Results	Comments
<21 yr	No screening		
21-29 yr	Cytology alone every 3 yr	HPV-positive ASC-US or cytology of LSIL or more severe: Refer to ASCCP Guidelines Cytology Negative or HPV-Negative ASC-US; Rescreen with cytology in 3 yr	
30-65 yr	HPV and cytology "cotesting" every 5 yr (preferred)	HPV-positive ASC-US or cytology of LSIL or more severe: Refer to ASCCP guidelines	Screening by HPV testing alone is not recommended for most clinical settings.
		HPV positive, cytology negative: Option 1: Y 12-month follow-up with co-testing	
		Option 2: Y test for HPV16 or HPV16/18 genotypes. If HPV16 or HPV16/18 positive, refer to colposcopy. If HPV16 or HPV16/18 negative, 12-mo follow-up with cotesting	
		Co-test negative or HPV-negative ASC-US: Rescreen with cotesting in 5 yr	
	Cytology alone every 3 yr (acceptable)	HPV-positive ASC-US or cytology of LSIL or more severe: Refer to ASCCP guidelines	
		Cytology negative or HPV-negative ASC-US: Rescreen with cytology in 3 yr	
>65 yr	No screening following adequate negative prior screening		Women with a history of CIN2 or a more severe diagnosis should continue routine screening for at least 20 yr
After hysterectomy	No screening		Applies to women without a cervix and without a history of CIN2 or a more severe diagnosis in the past 20 yr or cervical cancer ever.
HPV vaccinated	Follow age-specific recommendations (same as unvaccinated women)		

ASCCP, American Society for Colposcopy and Cervical Pathology; *ASC-US,* atypical squamous cells of undetermined significance; *CIN,* cervical intraepithelial neoplasia; *HPV,* human papillomavirus; *LSIL,* low-grade squamous intraepithelial lesions.

Modified from Saslow D et al: American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer, *J Low Gen Tract Dis* 16(3):175-204, 2012.

addition of an HPV test to the Pap test reduces the incidence of CIN II or III, or cancer detected by subsequent screening.
- Success rates for treatment approach 80% to 90%.
- Detection of persistence of recurrence requires careful follow-up.
- Cervical treatment possibly results in infertility (cervical stenosis or incompetence), which requires careful consideration and discretion for use of loop electrosurgical excision procedure and cone biopsy.
- Appropriate counseling and informed consent are needed when considering any form of management of cervical dysplasia.

REFERRAL

- Patients with abnormal Pap cytology should be referred to a provider, preferably a trained obstetrician/gynecologist, who can appropriately treat the patient in an age-specific manner and also perform a colposcopy if indicated as part of the new recommendations. Given the morbidity associated with both underevaluating and treating, as well as reacting excessively to cytologic findings, a provider who is intimately familiar with ASCCP guidelines should be sought.
- If treatment is required, patient should be referred to a gynecologist or gynecologic oncologist skilled in the diagnosis and treatment of preinvasive cervical disease.

PEARLS & CONSIDERATIONS

COMMENTS

- Testing for human papillomavirus by Hybrid capture 2 DNA test will identify 91% of the small proportion of women with post-treatment residual or recurrent disease, but 30% of all women who are tested will test positive and need colposcopy.
- HPV vaccination is recommended for males and females from ages 9 to 26.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Cervical Cancer (Related Key Topic)
Cervical Dysplasia (Patient Information)
Cervical Polyps (Related Key Topic)
Pap Smear Abnormalities (Patient Information)

AUTHOR: **Ashlie Sewdass Carter, MD**

SUGGESTED READINGS

Feldman S: Making sense of the new cervical cancer screening guidelines, *N Engl J Med* 365(23):2148, 2011.

Kizer N, Peipert JF: Cervical cancer screening: primum non nocere, *Ann Intern Med* 156:896-897, 2012.

Saslow D et al: American cancer society, American society for colposcopy and lower cervical pathology, and American society for clinical pathology screening guidelines for the prevention and detection of early cervical cancer, *J Low Genit Tract Dis* 16(3):1-29, 2012.

Vesco U et al: Risk factors and other epidemiologic considerations for cervical cancer screening: a narrative review for the U.S. Preventive Services Task Force, *Ann Intern Med* 155:698-705, 2011.

BASIC INFORMATION

DEFINITION

Gradual, painless dilation of the cervix during pregnancy, leading to recurrent inability to maintain pregnancy beyond the second trimester. Cervical dilation occurs in the absence of clinical contractions and/or labor. Diagnosis is clinical.

SYNONYMS

Incompetent cervix
Shortened cervix
Preterm birth syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1 in 1000 among general obstetrical population
RISK FACTORS: Prior cervical surgery (e.g., cone biopsy, loop electrosurgical excision procedure [LEEP]), in utero diethylstilbestrol (DES) exposure, prior first- or second-trimester abortions, uterine anomalies, multiple gestations, prior spontaneous preterm births not meeting the criteria for cervical insufficiency

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Painless cervical dilation during the second trimester
- Nonspecific presentation: Backache, pelvic pressure, contractions, vaginal spotting, vaginal discharge

ETIOLOGY

Most cases are either idiopathic or iatrogenic as a result of prior cervical surgery. The cause is thought to be a loss of elastic fibers in the cervices of affected women.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Preterm labor
- Shortened cervix

WORKUP

- Prior obstetrical history, particularly with regard to previous preterm deliveries or spontaneous abortions
- Prior history of any gynecological procedures, especially those involving the cervix
- Serial digital cervical exams
- Serial transvaginal ultrasound

LABORATORY TESTS

Amniocentesis with analysis for white blood cell count, glucose, Gram stain, and culture: Abnormal results for any of these markers may indicate a subclinical infection, which increases risk for preterm birth. Abnormalities may help in selecting patients who would benefit from emergent cerclage, although this benefit should be weighed against the inherent risks of amniocentesis.

IMAGING STUDIES

Transvaginal ultrasound: Cervical shortening on ultrasound may be a diagnostic marker for cervical insufficiency.

TREATMENT

NONPHARMACOLOGIC THERAPY

Cerclage has long been the mainstay of treatment for cervical insufficiency (Fig E1 to E3). However, randomized controlled trials (RCTs) comparing the rates of preterm birth in patients receiving cervical cerclage versus those without cerclage have produced conflicting results, with many studies showing little or no improvement in preterm birth rates. A meta-analysis by Berghella et al (2005) showed that the greatest benefit of cerclage was in women with singleton pregnancies who had experienced a previous preterm birth, and cerclage was actually detrimental to women carrying multiple gestations. The most common risk associated with cerclage is cervical laceration during delivery (1% to 13%). Bed rest is often used when there is a threat of preterm birth, although its benefit is not proven and it has detrimental effects for the mother, such as venous thromboembolic events; thus it is not recommended.

ACUTE GENERAL Rx

Ultrasound-indicated cerclage should be placed in women with ultrasonographic evidence of cervical shortening (<25 mm) before 24 weeks' gestation and a history of a preterm birth before 34 weeks. Women who present with painless cervical dilation in the second trimester may be candidates for a physical-exam–indicated cerclage (rescue cerclage) after being ruled out for uterine activity and evidence of infection. Data are limited on the efficacy of placing a physical-exam–indicated cerclage. Women should be counseled about the potential risks of rescue cerclage in the setting of unclear benefit. Placement of a cervical pessary is only currently recommended in the setting of research trial protocols.

CHRONIC Rx

Prophylactic cerclage (history-indicated cerclage) has been shown by several studies and meta-analyses to be most heavily indicated in women with prior history of multiple preterm births. Women with a history of one or more

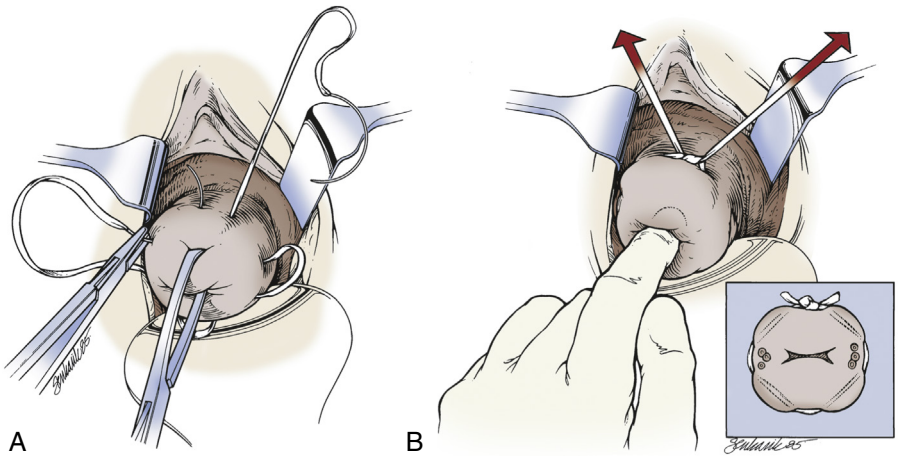

FIG. E1 Placement of sutures for McDonald cerclage. A, We use a double-headed Mersilene band with four bites in the cervix, avoiding the vessels. **B,** The suture is placed high up in the cervix, close to the cervicovaginal junction, approximately at the level of the internal os. (From Gabbe SG: *Obstetrics*, ed 6, Philadelphia, 2012, Saunders.)

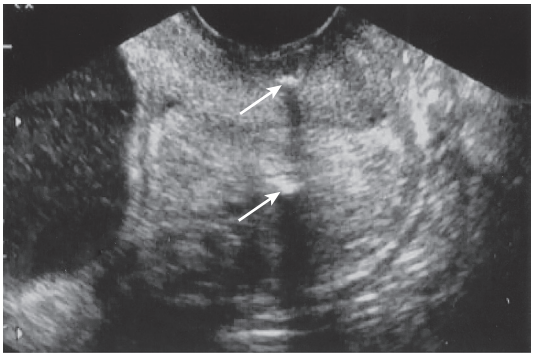

FIG. E2 Transvaginal sonogram of the cervix after cerclage placement. The internal os is closed, and there is no funneling. Echogenic spots in the cervix correspond to cerclage *(arrows).* (From Gabbe SG: *Obstetrics*, ed 6, Philadelphia, 2012, Saunders.)

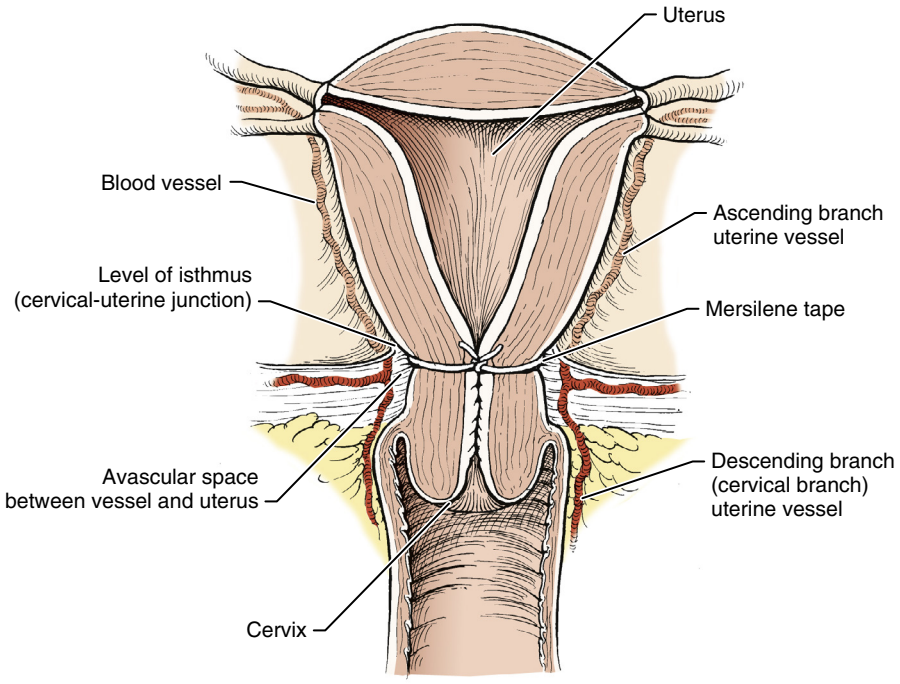

FIG. E3 Abdominal cerclage. Surgical placement of circumferential Mersilene tape around uterine isthmus and median to uterine vessels. Knot is tied anteriorly. (From Gabbe SG: *Obstetrics*, ed 6, Philadelphia, 2012, Saunders.)

second-trimester deliveries with no symptoms or signs of labor at the time of the delivery may be candidates for a prophylactic cerclage, placed at 13 to 14 weeks' gestation. Women with this history should also be offered 17-OH progesterone injections between 16 and 36 weeks.

DISPOSITION

Patients with a singleton pregnancy, prior history of preterm birth, and shortened cervix (<25 mm) on transvaginal ultrasound should be counseled regarding amniocentesis and cerclage placement.

REFERRAL

Patients at risk of preterm labor should be referred to maternal-fetal medicine.

RELATED CONTENT

Cervical Incompetence (Patient Information)
Preterm Labor (Related Key Topic)
Premature Rupture of the Membranes (Related Key Topic)

AUTHOR: **Kelly Ruhstaller, MD**

SUGGESTED READING

Cerclage for the management of cervical insufficiency: Practice bulletin No. 142. American College of Obstetricians and Gynecologists, Obstet Gyneco/ 123:372 -379, 2014.

Cervical Polyps (PTG)

BASIC INFORMATION

DEFINITION

A cervical polyp is a growth or tumor protruding from the cervix or endocervical canal. These can arise from the ectocervix or endocervix.

ICD-10CM CODES

N84.1	Polyp of cervix uteri
D26.0	Polyp uterine cervix, adenomatous

EPIDEMIOLOGY & DEMOGRAPHICS

Cervical polyps are found in approximately 4% of all gynecologic patients. They most commonly present in perimenopausal and multigravida women between the ages of 30 and 50. Ectocervical polyps are more common in postmenopausal women, whereas endocervical polyps are most common in premenopausal women. Endocervical polyps are more common overall than ectocervical polyps and are almost always benign. Malignant degeneration is extremely rare (1%).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Polyps may be single or multiple and vary in size from being extremely small (a few mm) to large (4 cm). They are soft, smooth, and reddish-purple to cherry-red in color. They bleed easily when touched. Very large polyps can cause some cervical dilation. There may be vaginal discharge and bleeding associated with cervical polyps, especially if the polyp has become infected.

ETIOLOGY

- Most unknown
- Inflammatory
- Traumatic
- Pregnancy

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Endometrial polyp
- Prolapsed myoma
- Retained products of conception
- Squamous papilloma
- Sarcoma
- Cervical malignancy

WORKUP

Polyps are most commonly asymptomatic and are usually found at the time of annual gynecologic pelvic examination. Polyps are also found in women who present for evaluation of abnormal uterine bleeding (intermenstrual or postcoital bleeding) and for profuse vaginal discharge. Polyps are generally painless. Unless a patient had a bleeding abnormality that necessitated evaluation by a physician, polyps would go undiagnosed until the next speculum examination or Pap smear was obtained.

TREATMENT

NONPHARMACOLOGIC THERAPY

Asymptomatic polyps do not require treatment. If a patient is symptomatic, simple surgical excision can be done in the office. Most commonly, a polyp is excised by grasping it at the stalk with a sponge forceps or similar device and twisting it off. The provider should be prepared for bleeding post removal, which can be controlled with silver nitrate or Monsel solution application. Polyps can also be excised by electrocautery. Sexual intercourse and tampon use are to be avoided until the patient's follow-up visit. Although cervical polyps are overwhelmingly benign, they should be sent to pathology for definitive histologic diagnosis.

ACUTE GENERAL Rx

Generally, cervical polyps do not present acutely and no medication is needed.

CHRONIC Rx

The cervix should be examined at the patient's routine office gynecologic visits before and after removal of a polyp. Patients should be screened for polyp symptoms, including abnormal vaginal discharge and bleeding at routine appointments.

DISPOSITION

Because these polyps are almost always benign, no further treatment is usually needed. Annual gynecologic examinations should be performed to check for any evidence of regrowth of the polyp.

REFERRAL

To a gynecologist for removal of polyps

PEARLS & CONSIDERATIONS

COMMENTS

A Pap smear should be obtained before removing the polyp. If an abnormal Pap smear is obtained, it is possible that the cause was the polyp. If the pathology report on the polyp reveals any histologic or cytologic abnormality, further evaluation with colposcopy, endocervical sampling, or endometrial biopsy may be necessary. If a cervical colposcopic evaluation is needed, this should also be performed.

During pregnancy the cervix is highly vascularized. If the polyps are stable and benign appearing, they should be observed during the pregnancy and removed only if they cause heavy bleeding.

RELATED CONTENT

Cervical Polyps (Patient Information)
Cervical Dysplasia (Related Key Topic)

AUTHORS: **T. Caroline Bank, MD,** and **Rachel Wright Heinle, MD, FACOG**

Cervicitis PTG

BASIC INFORMATION

DEFINITION

Cervicitis is an inflammation of the uterine cervix, primarily affecting the columnar epithelial cells of the endocervical glands. Acute cervicitis results from direct infection of the cervix secondary to a uterine or vaginal infection—most commonly chlamydia or gonorrhea—whereas chronic cervicitis is due to an exposure to a local irritant.

SYNONYMS

Endocervicitis
Ectocervicitis
Mucopurulent cervicitis

ICD-10CM CODES

N72	Inflammatory disease of cervix uteri
A54.03	Gonococcal cervicitis, unspecified
A74.89	Other chlamydial diseases
A60.03	Herpesviral cervicitis
O86.11	Cervicitis following delivery

EPIDEMIOLOGY & DEMOGRAPHICS

The published prevalence of cervicitis varies greatly, ranging from 8% to as high as 40% of women attending sexually transmitted disease (STD) clinics. Cervicitis is most common in women aged 15 to 24 but it can occur in any sexually active woman. Women who have had sex without condoms or sex with multiple partners are at increased risk of developing cervicitis as well as other STDs.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Cervicitis is usually asymptomatic or associated with mild symptoms. Patients may complain of copious purulent or mucopurulent vaginal discharge, pelvic pain, postcoital or intermenstrual bleeding, vulvovaginal irritation, or dyspareunia.

The CDC emphasizes that the two diagnostic signs of cervicitis are either mucopurulent discharge or sustained cervical bleeding with gentle trauma. On physical exam, the cervix can be erythematous and tender on palpation. The cervix may also bleed easily when obtaining cultures or a Pap smear. Yellow discharge will be seen on a Q-tip inserted into the cervix.

INFECTIOUS ETIOLOGY

- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- *Trichomonas vaginalis*
- Herpes simplex
- Human papillomavirus
- *M. genitalium*
- Bacterial vaginosis

DIAGNOSIS

The diagnosis of acute cervicitis is clinical and based upon the presence of purulent or mucopurulent cervical exudate and/or cervical friability—bleeding induced by gently touching the area with a swab.

DIFFERENTIAL DIAGNOSIS

- Carcinoma of the cervix
- Cervical erosion (from tampons or other intravaginal devices)
- Cervical metaplasia
- Cervical ectropion
- Cervical and vaginal irritation due to chemicals or hormonal imbalance

WORKUP

If cervicitis is suspected, testing for infectious causes should be performed and pelvic inflammatory disease (PID) should be excluded.

LABORATORY TESTS

- A finding of leucorrhea (>10 WBC per high-power field on microscopic examination of vaginal fluid) has been associated with chlamydial and gonococcal infection of the cervix.
- Nucleic acid amplification tests (NAAT) should be used for diagnosing *C. trachomatis* and *N. gonorrhoeae* in women with cervicitis; this testing can be performed on vaginal, cervical, or urinary samples.
- Use a wet mount to look for evidence of bacterial vaginitis (BV) and trichomonads, but because the sensitivity of microscopy to detect *T. vaginalis* is relatively low (~50%), symptomatic women with cervicitis and negative microscopy for BV and trichomonads should receive further testing with NAAT or culture if there is concern for resistant infection.
- HIV testing is recommended in all patients with supposed cervicitis.
- Although HSV-2 infection has been associated with cervicitis, the utility of specific testing (i.e., culture or serologic testing) for HSV-2 in this setting is not recommended unless there are clinical findings suggestive of herpes infection.

TREATMENT

NONPHARMACOLOGIC THERAPY

- The patient's history of hygiene habits, which may increase her risk for cervicitis, should be obtained including history of douching, tampon usage, and other potential chemical exposures to vaginal irritants.
- Uncomplicated cervicitis is typically treated as an outpatient.
- Safe sex should be recommended including monogamous relationships and the consistent use of condoms (male and female).
- Sexual partners should be offered treatment in all cases of STD infection proven by culture.

ACUTE GENERAL Rx

Because *Chlamydia* and *N. gonorrhoeae* cause 50% of cases of infectious cervicitis, if either of these infections is suspected, then treatment should be initiated without waiting for the test results. Administer ceftriaxone 250 mg IM single dose followed by azithromycin 1 g single dose or doxycycline 100 mg PO bid for 7 days. If the patient is pregnant, treat with azithromycin 1 g single dose instead of using doxycycline, which is contraindicated in pregnant or nursing mothers. If *Trichomonas* is the etiologic agent, treat with metronidazole or tinidazole 2 g single dose, which is curative in 95% of cases. An alternative treatment option is metronidazole 500 mg twice daily for 7 days. Alcohol should be avoided during the treatment course.

For herpes infection, treat with acyclovir, valacyclovir, or famciclovir.

M. genitalium might be considered for cases of clinically significant cervicitis that persist after azithromycin or doxycycline therapy in which reexposure to an infected partner or medical nonadherence is unlikely. If *M. genitalium* infection is confirmed, treatment is with moxifloxacin.

DISPOSITION

Bacterial cervicitis responds well to antibiotics. Possible complications to watch for include subsequent PID and infertility (found in 5% to 10% of patients with increasing rates with repeat episodes of PID). Repeat cervical cultures are recommended after treatment in pregnancy or if there is concern of treatment failure. Screening for reinfection is recommended within 3 months. Condoms should be recommended and sexual relations should be resumed after negative cultures for both partners.

REFERRAL

If subsequent PID develops, attempt outpatient therapy and consider hospital admission for IV antibiotics for severe or specialty cases as outlined in the CDC guidelines.

PEARLS & CONSIDERATIONS

COMMENTS

- Management of sex partners of women tested for cervicitis should be appropriate for the identified or suspected STD.
- Repeat testing 3 to 6 months after treatment is recommended for all women diagnosed with chlamydia or gonorrhea, and all sex partners in the preceding 60 days should be evaluated and treated for the STDs for which the index patient received treatment.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Cervicitis (Patient Information)
Chlamydia Genital Infections (Related Key Topic)
Gonorrhea (Related Key Topic)
Urethritis, Nongonococcal (Related Key Topic)

AUTHOR: **Helen B. Gomez, MD**

SUGGESTED READING

Workowski KA, Bolan GA: Centers for Disease Control and Prevention: sexually transmitted diseases treatment guidelines, 2015, *MMWR Recomm Rep* 64(RR-03):1-137, 2015.

Chagas Disease

BASIC INFORMATION

DEFINITION

Chagas disease is an infection caused by the protozoan parasite *Trypanosoma cruzi.* This is a vector-borne disease transmitted by reduviid bugs from multiple wild and domesticated animal reservoirs. The disease is characterized by an acute nonspecific febrile illness that may be followed, after a variable latency period, by chronic cardiac, GI, and neurologic sequelae. Globally, Chagas disease affects 8 to 11 million persons; vector-borne disease (as opposed to congenital infection) occurs only in the Americas.

SYNONYM

American trypanosomiasis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Seven cases of autochthonous transmission in California, Texas, Tennessee, and Louisiana.
- In the past two decades, six cases of laboratory-acquired infection, three cases of transfusion-associated transmission, and nine cases of imported disease reported to the CDC (none of the imported cases involved returning tourists).
- Infection has been transmitted by organ transplantation.
- Infection has been transmitted congenitally from mother to fetus over more than one generation.
- Stercorarian transmission (i.e., transmission through the feces of an infected vector) is relatively inefficient; the incidence of *T. cruzi* infection is generally estimated to be less than 1% per yr. The highest incidence is 4% per yr in the hyperendemic Bolivian Chaco (Bern C in Suggested Readings: *NJEM* 373:456-466, 2015).

PREVALENCE (IN U.S.): Based on regional seroprevalence studies in Hispanic blood donors, it is estimated that between 300,000 and 300,500 persons infected with *T. cruzi* are currently residing in the U.S. In the Americas, 8 to 10 million people are believed to be infected.

PREDOMINANT SEX: Male = female

PREDOMINANT AGE:

- In highly endemic areas, mean age of acute infection: Approximately 4 yr.
- Variable age distribution for both types of chronic disease, depending on geography.
- Mean age of onset of chronic disease: Usually between 35 and 45 yr.

PEAK INCIDENCE: Unknown

GENETICS:

- **Congenital infection:** Congenital transmission is common, with attendant high fetal mortality and morbidity in surviving infants.
- **Neonatal infection:** In rural areas, within substandard housing, transmission is likely to occur.

PHYSICAL FINDINGS & CLINICAL PRESENTATIONS

- Inflammatory lesion that develops about 1 wk after contamination of a break in the skin with infected insect feces (chagoma)
  1. Area of induration and erythema
  2. Usually accompanied by local lymphadenopathy
  3. This lesion may be easily overlooked and ignored
- Presence of Romaña sign, which consists of unilateral painless palpebral and periocular edema (Fig. E1), when conjunctiva is portal of entry. This is rare but almost pathognomonic.
- Constitutional symptoms of fever, fatigue, and anorexia, along with edema of the face and lower extremities, generalized lymphadenopathy, and mild hepatosplenomegaly after the appearance of local signs of disease
- Myocarditis in a small portion of patients, sometimes with resultant CHF, even death.
- Uncommonly, CNS disease, such as meningoencephalitis, which carries a poor prognosis
- Symptoms and signs of disease persisting for weeks to months followed by spontaneous resolution of the acute illness; patient then enters the indeterminate phase of the disease (asymptomatic with attendant subpatent parasitemia and reactive antibodies to *T. cruzi* antigens)
- Chronic disease may become manifest yrs to decades after the initial infection:
  1. Most common organ involved: Heart followed by GI tract; GI tract disease occurs most commonly in the Southern Cone of South America, due to variations in strains of *T. cruzi* resulting in different tropisms. Cardiac involvement predominates in all areas of infection. Cardiac involvement takes the form of arrhythmias or cardiomyopathy but rarely both
  2. Cardiomyopathy is bilateral but predominantly affects the right ventricle and is often accompanied by apical aneurysms and mural thrombi
  3. Arrhythmias are a consequence of involvement of the bundle of His and have been implicated as the leading cause of sudden death in adults in highly endemic areas
  4. Right-sided heart failure, thromboembolism, and rhythm disturbances associated with symptoms of dizziness and syncope are characteristic
  5. Myocardial fibrosis can serve as a nidus for ventricular tachycardia; can be excised surgically after EP mapping
     a. Patients with megaesophagus: Dysphagia, odynophagia, chronic cough, and regurgitation, frequently resulting in aspiration pneumonitis
     b. Megacolon: Abdominal pain and chronic constipation, which, when severe, may lead to obstruction and perforation
     c. CNS symptoms: Most often secondary to embolization from the heart
     d. Varying degrees of peripheral neuropathy

ETIOLOGY

- *T. cruzi:*
  1. Found only in the Americas, ranging from the southern U.S. to northern Argentina (Fig. E2)
  2. Transmitted to humans by various species of bloodsucking reduviid ("kissing") insects (Fig. E3), primarily those of the genera *Triatoma, Panstrongylus,* and *Rhodnius*
  3. Usually found in burrows and trees where infected insects transmit the parasite to natural reservoirs (e.g., opossums and armadillos)
  4. Intrusion into enzootic areas for farmland, allowing insects to take up residence in rural dwellings, thus including humans and domestic animals in the cycle of transmission
  5. Initial infection of insects by ingesting blood from animals or humans that have circulating flagellated trypanosomes (trypomastigotes)
  6. Multiplication in the insect midgut as epimastigotes, then differentiation into metacyclic trypomastigotes discharged with the feces during subsequent blood meals
  7. Transmission to the second mammalian host through contamination of mucous mem-

FIG. E1 Romaña sign in an Argentinean child with acute Chagas disease. (Courtesy Dr. Humberto Lugones, Santiago del Estero, Argentina.)

branes, conjunctivae, or wounds with insect feces containing infectious forms (Fig. E4)

- In the vertebrate host:
  1. Movement of parasites into various cell types, intracellular transformation into amastigotes, and thereafter differentiation into trypomastigotes
  2. Following rupture of the cell membrane, parasitic invasion of local tissues or hematogenous spread to distant sites, maintaining a parasitemia infective for vectors
- In addition to insect vectors, *T. cruzi* is transmitted through blood transfusions, transplacentally, and, occasionally, secondary to laboratory accidents or ingestion (including breast milk)
- Infection by the oral route causes more severe acute infection, even death
- In 2007, voluntary screening was initiated in the U.S. blood supply; it is estimated to cover 75% to 90% of the blood supply
- Platelet transfusions appear to be more infective than packed red blood cells

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Acute disease:
- Early African trypanosomiasis
- New World cutaneous and mucocutaneous leishmaniasis

Chronic disease:
- Idiopathic cardiomyopathy
- Idiopathic achalasia
- Congenital or acquired megacolon

WORKUP

Principal considerations in diagnosis:
- A history of residence where transmission is known to occur
- Recent receipt of a blood product while in an endemic area
- Occupational exposure in a laboratory
- Children of infected mothers
- Siblings/family members of infected individuals

LABORATORY TESTS

For acute diagnosis:
- Demonstration of *T. cruzi* in wet preparations of blood (Fig. E5), buffy coat, or Giemsa-stained smears.
- Xenodiagnosis, a technique involving laboratory-reared insect vectors fed on subjects with suspected infection thereafter examined for parasites, and culture of body fluids in liquid media to establish diagnosis.
  1. Hampered by the length of time required for completion
  2. Of limited use in clinical decision making with regard to drug therapy
  3. Although xenodiagnosis and broth culture are considered to be more sensitive than microscopic examination of body fluids, sensitivities may not exceed 50%
  4. This test is rarely used
- Recent advances in serologic testing include immunoblot assay, in situ indirect fluorescent antibody, PCR-based techniques, and an immunochromatographic assay (Chagas Stat Pak).
- Response to treatment in acute, reactivated, or congenital infection can be assessed by quantitative PCR. This test is now standardized and in common use.

For chronic *T. cruzi* infection:
- Traditional serologic tests, including complement fixation (CF), indirect immunofluorescence (IIF), indirect hemagglutination, and enzyme-linked immunosorbent assay (ELISA).
- Serologic tests have variable sensitivity and specificity and frequent false-positive results.
- Saliva ELISA may be useful as a screening diagnostic test in epidemiologic studies of chronic trypanosomiasis infection in endemic areas.
- Confirmation requires at least two different tests, and if discordant, three tests.

FIG. E2 Distribution of Chagas disease. Human infection is endemic in parts of Central and South America from the Andes to the Atlantic coast and as far south as the latitude of the Silver River (Río de la Plata, shown in *green*). Two major intergovernmental programs were started in 1991 to eliminate domestic vectors by a combination of spraying residual insecticides in houses, the use of insecticidal paints, and the deployment of fumigant canisters. The countries covered in the two initiatives, the second of which started in 1997, are shown. The latter program instituted universal blood screening to avoid transmission from infected blood donors. In less than a decade, remarkable progress has been made. Transmission by the major vector *Triatoma infestans* was eliminated in Uruguay by 1997 and in Chile by 1999. Major reductions in transmission have also been reported from other endemic countries but, to date, not complete control. (From Hoffman R: *Hematology, basic principles and practice*, ed 6, Philadelphia, 2013, Elsevier.)

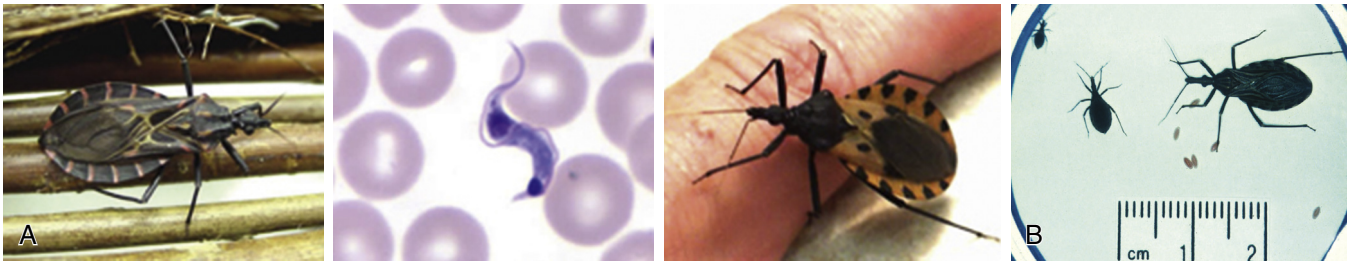

FIG. E3 Triatomine vectors of Trypanosoma cruzi. A, Triatoma infestans. **B,** Rhodnius prolixus. (**A**, Courtesy Centers for Disease Control and Prevention, Atlanta GA. **B**, From Kirchhoff LV: *Trypanosoma* species [American trypanosomiasis, Chagas' disease]: biology of trypanosomes. In (Bennett JE, Dolin R, Blaser MJ [eds]: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.)

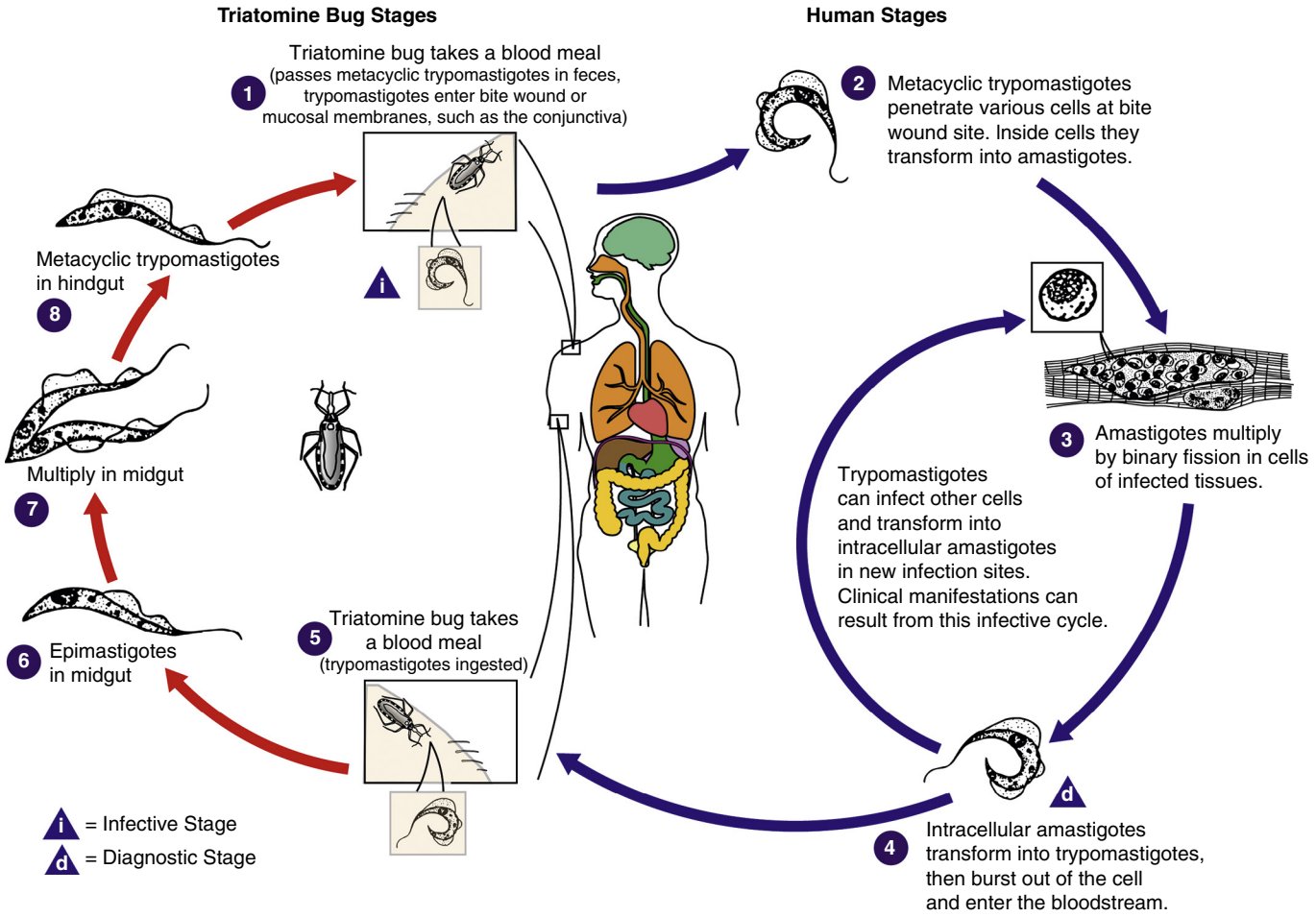

FIG. E4 Life cycle of *Trypanosoma cruzi* in its insect vectors and mammalian hosts. (Courtesy Centers for Disease Control and Prevention, Atlanta, GA.)

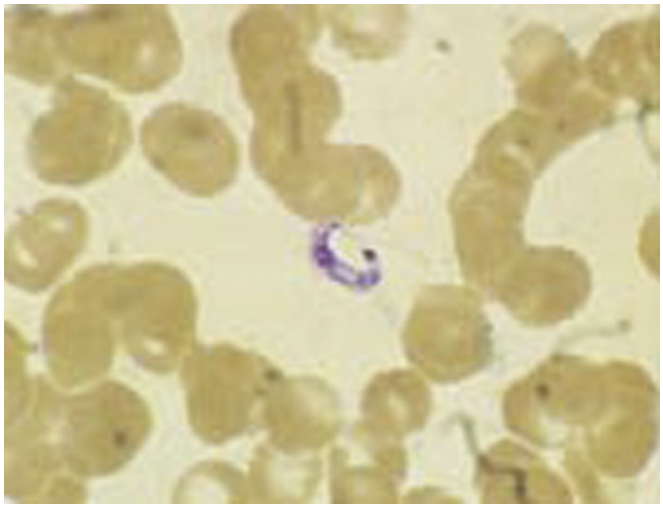

FIG. E5 *Trypanosoma cruzi* in human blood film. The causative agent occurs in blood films, characteristically as short C-shaped or S-shaped trypomastigotes with a prominent kinetoplast. It is otherwise monomorphic. (From Hoffman R et al.: *Hematology, principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Chronic chagasic heart disease: Mainly supportive including ICD, pacers, amiodarone, heart transplant.
- Megaesophagus: Symptoms usually amenable to dietary measures or pneumonic dilation of the esophagogastric junction
- Chagasic megacolon: In its early stages, responsive to a high-fiber diet, laxatives, and enemas

ACUTE GENERAL Rx

It is now recommended that all patients—acute, indeterminate, and chronic—be treated with antiparasitic therapy. Treatment for individuals older than 50 yr requires consideration of risk versus benefit because the treatment appears to be more toxic at this age. Patients with severe chronic cardiomyopathy also may not benefit. Severity of illness scores specific to Chagas disease have been developed to assess this.

A single course of benznidazole or nifurtimox is thought to offer an approximately 50% cure rate. Consultations and requests for drugs can be made to Parasitic Diseases Public Inquiries Line (770-448-7775), parasites.cdc.gov, www.cdc.gov/parasites/chagas, CDC Drug Service (404-639-3670).

Benznidazole, a nitroimidazole derivative:
- Has demonstrated similar efficacy as nifurtimox in limited trials; is usually better tolerated and is viewed by most experts as first-line treatment
- Recommended oral dosage: 5 to 7 mg/kg/day for 30 to 90 days

Nifurtimox:
- Recommended oral dosage for adults: 8 to 10 mg/kg/day given in 3 to 4 divided daily doses and continued for 90 to 120 days
- Parasitologic cure in approximately 50% of those treated; should be begun as early as possible

Neither drug can be used during pregnancy.
- Do not use in cases of severe renal or hepatic dysfunction.

Triazoles offer a new class of therapy but are so far disappointing. Case reports have had success with posaconazole. Trials have shown that posaconazole has antitrypanosomal activity in patients with chronic Chagas disease. However, significantly more patients in the posaconazole groups than in the benznidazole group had treatment failure during follow-up.

CHRONIC Rx

- Yearly cardiac evaluations and 12 lead ECG should be performed in all persons with *T. cruzi* infection regardless of treatment.
- In patients with indeterminate phase or chronic disease: Some evidence of benefit in a recent uncontrolled trial with benznidazole in patients with chagasic cardiomyopathy
- In patients exhibiting bradyarrhythmias: Pacemakers
- In individuals with congestive heart failure:
  1. Treat with standard modalities for dilated, right-sided cardiomyopathic disease
  2. Cardiac transplant is an option for end-stage cardiomyopathy; moreover, reactivation rate found to be low and amenable to therapy without subsequent infection of the allograft
  3. Myotomy or esophageal resection is reserved for patients with advanced disease
  4. Anticoagulation for patients at risk for thromboembolism
  5. Antiarrhythmic for complex arrhythmias
- In advanced chagasic megacolon associated with chronic fecal impaction, perforation, or, less commonly, volvulus: Surgical resection

DISPOSITION

Based on a few prospective studies, although most patients infected with *T. cruzi* will not develop symptomatic Chagas disease, 20% to 30% likely will.

REFERRAL

- For consultation with an infectious disease specialist for all patients
- Communication with the CDC when the disease is acutely suspected
- To a cardiologist for pacemaker implantation for patients with bradyarrhythmias and for management of CHF, complex arrhythmias
- To a surgeon for symptomatic disease with chagasic megaesophagus or megacolon

PEARLS & CONSIDERATIONS

COMMENTS

- All children of an infected mother should be screened for Chagas disease; household members should also be screened.
- In recipients of solid organ or bone marrow transplants, patients with AIDS, or those receiving chemotherapy, there may be reactivation of indeterminate phase disease.
- Mortality predictors associated with chagasic cardiomyopathy include CHF, QT-interval dispersion, left ventricular end-systolic dimension, the presence of pathologic Q waves, frequent PVCs, and isolated LAFB on ECG.
- Chagasic esophageal disease has an increased incidence of esophageal malignancy.
- The use of pyrethroid-impregnated curtains may represent an option for the reduction or elimination of Chagas disease transmission in certain endemic areas.
- Randomized trials of benznidazole for chronic Chagas cardiomyopathy have shown significant serum parasite detection but no significant reduction in clinical deterioration through 5 yr of follow-up (Morillo CA et al in Suggested Readings: *NEJM* 373:1295-1306, 2015).

AUTHOR: **Patricia Cristofaro, MD**

SUGGESTED READINGS

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Chalazion

BASIC INFORMATION

DEFINITION

Chalazia (singular, chalazion singular) are the most common inflammatory lesions of the eyelid, accounting for approximately 13% of all benign eyelid lesions. These lesions typically present as localized areas of painless swelling and feel like a rubbery nodule to palpation. Chalazia are caused by obstruction of Zeis or meibomian glands when lipid breakdown by-products incite localized inflammatory response, which then recruits white blood cells to the area. This results in a sterile, painless lesion, which grows over weeks to months. Can eventually become infected and painful if not treated.

SYNONYMS

Meibomian gland lipogranuloma
Sebaceous cyst
Meibomian cyst

ICD-10CM CODES

H00.1	Chalazion
H00.11	Right upper eyelid
H00.12	Right lower eyelid
H00.13	Right eye, unspecified eyelid
H00.14	Left upper eyelid
H00.15	Left lower eyelid
H00.16	Left eye, unspecified eyelid
H00.19	Unspecified eye, unspecified eyelid

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Common condition, exact incidence not documented
PEAK INCIDENCE: Most common in adults age 30 to 50
PREVALENCE: Unknown
PREDOMINANT SEX AND AGE: Affects males and females equally, more common in adults 30 to 50 yr old
GENETICS: Not applicable

RISK FACTORS:

- Prior chalazion, recent conjunctivitis
- Consider demodicidosis in patients with recurrent chalazia
- Consider low serum vitamin A

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Painless localized nodule on the eyelid (Fig. E1)
- Lesion will be firm and rubbery. Can see mild erythema
- Possible impaired vision
- Increased swelling for weeks/months
- Can become inflamed/painful/infected
- Can be visualized on the external eyelid or internal eyelid
- Tend to present for longer than 2 weeks compared to styes, which usually have a shorter course
- Typically, benign and self-limited lesion. If persistent or recurrent, a chalazion should be evaluated for malignancy

ETIOLOGY

Chalazia appear as small, red, rubbery nodules that are caused by local inflammation and obstruction of the sebaceous glands of the eyelids. Obstruction of the sebaceous glands results in lipid buildup and stasis. The lipid breakdown by-products incite localized inflammation, which then recruits white blood cells to the area.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Blepharitis
- Hordeolum (stye)
- Papilloma
- Xanthelasma
- Carcinoma: Sebaceous cell, basal cell, squamous cell (biopsy necessary)
- Dacryocystitis
- Molluscum contagiosum
- Leishmaniasis
- Periorbital/orbital cellulitis
- Abscess

Recurrent or persistent lesions:

- Basal cell carcinoma
- Sebaceous cell carcinoma
- Meibomian gland carcinoma

WORKUP

Diagnosis is based on symptoms, clinical presentation, and physical exam findings. Testing is largely used to rule out other diagnoses. If suspicious for cancer, biopsy is necessary as well as ophthalmologic consultation.

LABORATORY TESTS

None necessary for chalazion. Other diagnoses might indicate laboratory analysis

IMAGING STUDIES

None

TREATMENT

- Frequently resolve without intervention
- Warm compress 15 minutes 2 to 4×/day
- Massage affected area with warm soap and water
- Incision and drainage if infection persists
- Ophthalmologic consultation if persistent beyond 1 month
- Antibiotics if pain/infected
  1. Doxycycline 100 mg PO bid 10 days
  2. Minocycline 50 mg PO 10 days
  3. Metronidazole if tetracycline allergic

DISPOSITION

Excellent patient prognosis. Small chalazia can be discharged home with instructions for conservative management. Large, recurrent, or persistent lesions may require an ophthalmology referral.

REFERRAL

If not resolved in 1 month ophthalmologic consultation is warranted

PEARLS & CONSIDERATIONS

COMMENTS

Frequently chalazia are confused with stye. Chalazia are inflammatory lesions, not infectious, that usually develop slowly in the upper eyelid and tend to be painless. Styes are infected oil glands that tend to present at the lid margin with pain.

PREVENTION

No specific prevention other than normal facial washing and hygiene.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Stye (Hordeolum) (Related Key Topic)
Blepharitis (Related Key Topic)
Molluscum Contagiosum (Related Key Topic)

AUTHORS: **Curtis Lee Lowery III, MD, PhD,** and **Kito Lord, MD, MBA**

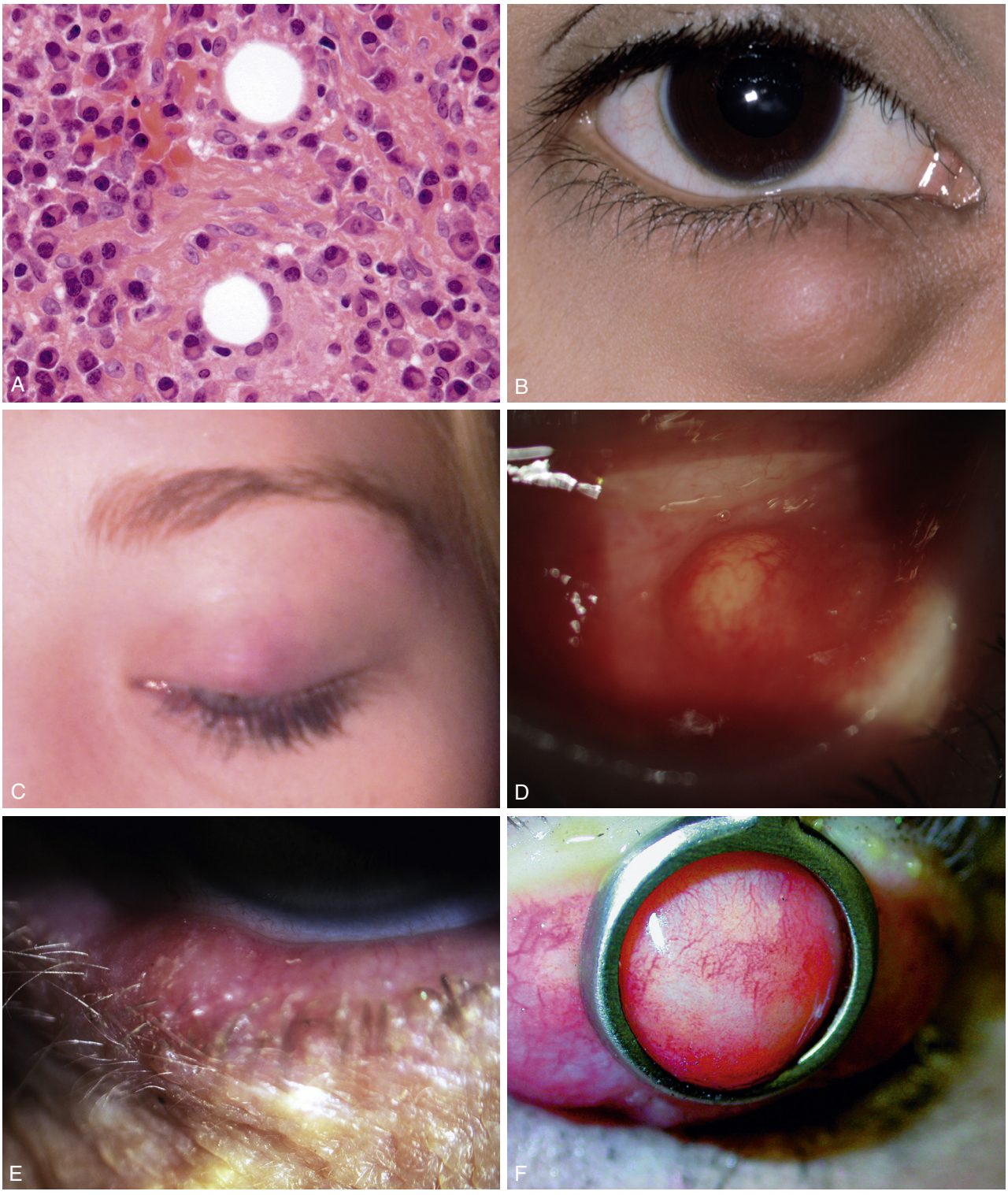

FIG. E1 Chalazion. A, Histopathology shows a lipogranuloma; the large pale cells are epithelioid cells and the well-demarcated empty space contained fat dissolved out during processing. **B,** Uninflamed chalazion. **C,** Acutely inflamed lesion. **D,** Conjunctival granuloma. **E,** Marginal chalazion. **F,** Conjunctival view of chalazion clamp in place prior to incision and curettage. (A, Courtesy of J Harry and G Misson, from Harry J, Misson G: *Clinical ophthalmic pathology: principles of diseases of the eye and associated structures,* Boston, 2001, Butterworth-Heinemann; F, from Nerad J, Carter K, Alford M: *Rapid diagnosis in ophthalmology: oculoplastic and reconstructive surgery,* St Louis, 2008, Mosby.) (From Bowling B: *Kanski's clinical ophthalmology, a systemic approach,* ed 8, Philadelphia, 2016, Elsevier.)

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BASIC INFORMATION

DEFINITION

Chancroid is a sexually transmitted disease characterized by painful genital ulceration and inflammatory inguinal adenopathy.

SYNONYMS

Soft chancre
Ulcus molle

ICD-10CM CODE
A57 Chancroid

EPIDEMIOLOGY & DEMOGRAPHICS

- Most frequent cause of genital ulcer disease worldwide.
- Endemic in the developing world.
- Exact incidence in is unknown. The prevalence of chancroid has declined in the United States and is currently rare (1 per 2 million in the developed world).
- Often due to infection with *Haemophilus ducreyi,* affecting microabrasions in skin.
- When infection occurs, it is usually associated with sporadic outbreaks and in association with trading sex for drugs or money.
- Predominantly heterosexual transmission.
- Occurs more frequently in men (male:female ratio of 5:1 to 10:1).
- There is a higher incidence in uncircumcised men and in tropical and subtropical regions.
- Incubation period is 4 to 7 days but may take up to 3 wk.
- High incidence of HIV infection associated with chancroid.
- Chancroid may facilitate the transmission of HIV.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Genital papule that evolves into soft ulcer with necrotic material at base and minimal surrounding inflammation.
- One to three extremely painful ulcers (Fig. E1) measuring 1 to 2 cm in diameter followed by tender inguinal lymphadenopathy (especially if fluctuant). The chancre is typically soft in comparison with the hard, painless chancre of syphilis.
- May present with inguinal bubo and several ulcers.
- In women: Initial lesion in the fourchette, labia minora, urethra, cervix, or anus; inflammatory pustule or papule that ruptures, leaving a shallow, nonindurated ulceration, usually 1 to 2 cm in diameter with ragged, undermined edges.
- Unilateral lymphadenopathy develops 1 wk later in 50% of patients.

ETIOLOGY

Haemophilus ducreyi, a gram-negative bacillus

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other genitoulcerative diseases such as syphilis, herpes, lymphogranuloma venereum (LGV), granuloma inguinale.
- A clinical algorithm for the initial management of genital ulcer disease is described in Section III.

WORKUP

Diagnosis based on history and physical examination is often inadequate. Must rule out syphilis and herpes simplex virus in women because of the consequences of inappropriate therapy in those who are pregnant and due to potentially similar presentation. Practitioner can base initial diagnosis and treatment recommendations on clinical impression of appearance of ulcer and most likely diagnosis for population. Definitive diagnosis is made by isolation of organism from ulcers by culture or Gram stain. Special culture media for *H. ducreyi* is not widely available commercially, and even when these media are used, sensitivity is <80%. PCR and NAAT are not cost-effective and are complex tests.

The CDC criteria for probable clinical diagnosis include all of the following:

- Single or multiple painful genital ulcers
- No evidence to support a diagnosis of syphilis (no evidence of *T. pallidum* infection by darkfield examination or ulcer exudate or by a serologic test for syphilis performed at least 7 days after onset of ulcers)
- Appearance of the ulcer and, if present, regional lymphadenopathy that are typical for chancroid
- A negative test (HSV PCR test or HSV culture) for the presence of HSV in the ulcer exudate

LABORATORY TESTS

- Darkfield microscopy, RPR, HSV cultures, *H. ducreyi* culture, HIV testing recommended
- No FDA-cleared PCR test for *H. ducreyi* is available in the U.S.

TREATMENT

NONPHARMACOLOGIC THERAPY

Fluctuant nodes should be aspirated through healthy adjacent skin to prevent formation of draining sinus. Incision and drainage of ulcer not recommended because it delays healing and may lead to persistent sinus tract. Use warm compresses to remove necrotic material.

ACUTE GENERAL Rx

- Azithromycin 1 g PO (single dose) *or*
- Ceftriaxone 250 mg IM (single dose) *or*
- Ciprofloxacin 500 mg PO bid for 3 days *or*
- Erythromycin 500 mg PO qid for 7 days

NOTE: Ciprofloxacin is contraindicated in patients who are pregnant, lactating, or <18 yr.

- HIV-infected patients may need more prolonged therapy.
- In HIV-positive patients, failures have been reported with single-dose azithromycin and ceftriaxone regimens.

DISPOSITION

- All sexual partners of the patient within 10 days of the onset of symptoms should be treated with one of the previously discussed treatment regimens (see "Acute General Rx").
- Patients should be reexamined 3 to 7 days after initiation of therapy. Ulcers should improve symptomatically within 3 days and objectively within 7 days after initiation of successful therapy.
- Lack of improvement within 7 days should raise the possibility of co-infection with another organism, a resistant strain of *H. ducreyi*, HIV positive patient, or incorrect diagnosis.

PEARLS & CONSIDERATIONS

COMMENTS

- In the U.S. HSV-1 and syphilis are the most common causes of genital ulcers followed by chancroid, LGV, and granuloma inguinale.
- The combination of a painful genital ulcer and tender suppurative inguinal adenopathy suggests the diagnosis of chancroid.

RELATED CONTENT

Chancroid (Patient Information)
Condyloma Acuminatum (Related Key Topic)
Granuloma Inguinale (Related Key Topic)
Urethritis, Gonococcal (Related Key Topic)
Lymphogranuloma Venereum (Related Key Topic)
Syphilis (Related Key Topic)

AUTHOR: **Ghamar Bitar, MD**

FIG. E1 Chancroid. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Elsevier.)

SUGGESTED READING

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BASIC INFORMATION

DEFINITION

In 1708, William Musgrave first coined the term *Charcot* to describe arthralgia associated with neuropathic joints caused by venereal disease. In 1868, Jean-Martin Charcot described Charcot with neuropathic disease caused by syphilis. Charcot arthropathy is a progressive condition following the loss of protective sensation; the hallmark features include pathologic fractures, dislocations, and gross foot and ankle deformities that can lead to ulceration, infection, and possible amputation. Charcot arthropathy is commonly associated with diabetes and diabetic peripheral neuropathy. Early recognition and diagnosis are imperative to avoid severe and irreversible foot deformities that may ultimately lead to catastrophic complications.

SYNONYMS

Neuropathic arthropathy
Charcot osteoarthropathy
Charcot neuropathic osteoarthropathy
Charcot arthropathy
Charcot foot
Charcot's joint

ICD-10CM CODES

M14.671	Charcot joint, right ankle and foot
M14.672	Charcot joint, left ankle and foot

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- The estimated prevalence of Charcot arthropathy is 0.1% to 7.5% in the general diabetic population.
- In patients with known diabetic neuropathy, the prevalence of Charcot arthropathy is approximately 35% and is not related to the type (type 1 or 2) of diabetes mellitus.
- Charcot is underdiagnosed by approximately 25%.
- Bilateral presentation is seen in 9% to 75% of patients.
- The midfoot is involved 70% of the time, followed by the forefoot and rear foot, each accounting for 15%.
- Observed in the fifth decade in diabetes mellitus type 1; observed in the sixth decade in diabetes mellitus type 2.
- Most patients with Charcot arthropathy have had diabetes mellitus for at least 10 yr.
- Unknown sex predilection and ethnic distribution.
- Risk factors include diabetic neuropathy, alcoholism, myelomeningocele, tabes dorsalis/syphilis, syringomyelia.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The natural history of Charcot arthropathy consists of four phases: Inflammation, fragmentation, coalescence, reconstruction.
- Inflammation phase: Erythema, edema, and calor. There is at least a 2° C (35.6° F) temperature difference between the involved limb and the contralateral foot. May present with mild pain or discomfort. Bounding pedal pulses. Typically, no radiologic osseous abnormalities are seen during the early acute phase. Early diagnosis is key.
- The tarso-metatarsal joints are most commonly involved, followed by the forefoot and hindfoot; a deformity in the foot may lead to unstable foot architecture.
- Fragmentation phase: As Charcot arthropathy progresses in the untreated state, osseous fragmentation and joint dislocation/subluxation occurs.
- Coalescence phase: Decreased local edema, coalescence of osseous fragments, ankylosis of joints, and new bone formation also take place during this phase.
- Reconstruction phase: Classic rigid deformity known as the "rocker bottom" foot occurs.
- Ulcerations may appear at any time during the acute and chronic stages of Charcot arthropathy.
- Distinguishing factors from Charcot arthropathy vs. diabetic peripheral neuropathy: Diabetic neuropathy is characterized by impairment of cold and warm thresholds whereas Charcot patients have preservation of warm stimuli, light touch, and peak skin blood flow at the toe.

ETIOLOGY

The most common cause of Charcot arthropathy is peripheral neuropathy associated with diabetes mellitus (Fig. E1). Less common conditions associated with Charcot arthropathy include syphilis (Fig. E2), alcoholism, spina bifida, poliomyelitis, Charcot-Marie-Tooth disease, leprosy, familial amyloid neuropathy, CNS/PNS tumors, pernicious anemia, cerebral vascular accident, lead poisoning, rheumatoid arthritis, multiple sclerosis, and trauma. Currently, three theories contribute to the etiology involved in this disease:

1. Neurotraumatic theory: Unperceived trauma or injury to an insensate foot. Osseous destruction is the result of unperceived sensory neuropathy with continued ambulation and repetitive stress. This repetitive microtrauma can lead to extensive bone destruction resulting in joint subluxation, dislocation, and pedal deformity.

FIG. E1 Diabetes mellitus and neuropathic arthritis. Note lateral displacement of metatarsals *(left)* and fragmentation and osseous debris *(right).* (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.)

2. Neurovascular theory: Autonomic neuropathy, particularly sympathetic denervation, leads to arteriovenous shunting. This increase of blood flow into the bone causes demineralization of the bone and stimulates osteoclastic activity that causes bone destruction, leading to osteopenia.
3. Inflammatory theory: During the acute inflammation phase that is seen in Charcot arthropathy, the inflammatory cytokines, tumor necrosis factor-alpha, IL-1, and IL-6 are present. The role of these inflammatory cytokines is bone resorption by promoting osteoclastic proliferation and differentiation. Receptor activator of nuclear factor-kappa B ligand (RANKL) is responsible for activating osteoclasts in Charcot arthropathy. Osteoprotegerin is the antagonist of RANKL, and thus when this pathway is disrupted, osteoclastic activity predominates. The production of calcitonin gene-related peptide, which also antagonizes RANKL expression, is reduced in peripheral and autonomic neuropathy. Nitric oxide, which suppresses osteoclastic activity, has also been found to be dramatically decreased in Charcot arthropathy. Furthermore, advanced glycation end products are associated with increased RANKL activation. Hyperglycemia is the triggering factor for production of advanced glycation end products.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Abscess
- Osteomyelitis
- Cellulitis
- Gout
- Deep vein thrombosis
- Infectious arthritis/septic joint
- Osteoarthritis
- Complex regional pain syndrome
- Peripheral vascular disease
- Trauma

WORKUP

A thorough history and physical examination is the key to recognition of Charcot arthropathy. Early diagnosis requires an astute physician to be aware of the signs associated with acute Charcot, including but not limited to edema, erythema, and calor, which play a role in the inflammatory cascade. Testing for peripheral neuropathy should be performed utilizing methods such as electromyography, nerve conduction velocity tests, nerve biopsy if warranted, biothesiometer, and Semmes-Weinstein monofilament testing.

LABORATORY TESTS

Laboratory testing can be utilized to rule in or rule out diagnoses that may present with manifestations similar to those of Charcot arthropathy.

- The following labs may be ordered if warranted: Complete blood count with differential, basic metabolic panel, vitamin B_{12}, folate, RPR, ESR, CRP, uric acid, rheumatoid panel, joint aspiration, and bone biopsy.

FIG. E2 Syphilitic Charcot knee joints showing gross destructive changes. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

IMAGING STUDIES

- Plain x-rays may or may not show evidence of early osteomyelitis. Osseous findings will depend on the stage (inflammatory, development, coalescence, remodeling) of presentation of Charcot arthropathy.
- MRI can detect subtle changes in the early stages of active Charcot arthropathy. Findings include bone marrow edema, soft tissue edema, and subchondral fractures.
- Three-phase bone scan: Results are less accurate in the setting of diminished blood flow; thus, labeled white blood cell scanning can improve specificity.
- Positron emission tomography is currently being researched for an additional imaging modality to detect Charcot arthropathy.

Rx TREATMENT

ACUTE GENERAL TREATMENT

The most instrumental aspect of medical treatment of Charcot arthropathy is offloading. Offloading is accomplished with the use of total contact cast for approximately 12 to 18 wk pending clinical and radiographic assessment.

Once the acute phase has transpired, custom-molded insoles in accommodative diabetic shoe gear, Charcot restraint orthotic walker, and customized braces, just to name a few, can be utilized.

SURGERY: There is equivocal evidence to support whether surgical intervention is recommended during the acute phase of Charcot arthropathy. The goal of surgery is to achieve a plantigrade foot that allows ambulation without skin compromise. The general surgical indications include acute fracture dislocation or infection or when there is continued recurrence of ulceration. Arthrodesis is recommended for unstable pedal construct, and Achilles tendon lengthening to reduce forefoot pressure improves the overall pedal alignment. Amputation plays a role after failed arthrodesis and/or recurrent infections.

PHARMACOLOGIC THERAPY

Studies are currently being conducted to determine the efficacy of bisphosphonates whose mechanism of action is to decrease osteoclastic resorption and symptoms in active Charcot arthropathy.

DISPOSITION

Early recognition of Charcot arthropathy and consultation to a foot and ankle surgeon is essential in preventing the devastating complications associated with this disease.

PREVENTION

Appropriate glucose control in the diabetic patient is essential for preventing the sensory deficits that lead to Charcot arthropathy.

REFERRAL

Orthopedic surgeon or podiatrist with expertise in Charcot arthropathy
Endocrinology for diabetic blood glucose control

RELATED CONTENT

Charcot Joint (Patient Information)

AUTHORS: **Michael Kutschke, MD,** and **Brad Blankenhorn, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Charcot-Marie-Tooth (CMT) disease is the eponym that refers to a phenotypic and genetically diverse group of heritable sensory and motor polyneuropathies. These neuropathies may be demyelinating or axonal. The disease is classified as CMT1 if demyelinating and autosomal dominant, CMT2 if axonal and autosomal dominant, CMTX if X-linked disease, and CMT4 if demyelinating and autosomal recessive. A letter designates the specific gene (e.g., CMT1A refers to an autosomal dominant demyelinating neuropathy secondary to PMP22 duplications).

SYNONYMS

Peroneal muscular atrophy
Hereditary motor and sensory neuropathy (HMSN)
CMT

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Estimated prevalence is 1:2500, making CMT the most common inherited peripheral neuropathy and the most common inherited neuromuscular disease.
PREDOMINANT AGE: Affected individuals, which include both men and women, commonly present in the first or second decades of life. Less commonly, infants may be severely affected, or adults may develop minor symptoms after the age of 40.

GENETICS

- More than 90 genes have been reported to be causative of CMT.
- Inheritance may be autosomal dominant, recessive, X-linked recessive, or X-linked dominant. Spontaneous mutations may also occur.
- Mutations in four genes (PMP22, GJB1, MFN2, MPZ) account for more than 90% of genetically defined cases. Of these, PMP22 (peripheral myelin protein 22) duplications on chromosome 22 are the most frequent, accounting for approximately 50% of cases.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Although there is a spectrum of disease severity, most commonly, patients present with slowly progressive weakness, starting in the feet and ascending to the legs and arms over time.
- The first manifestations may be reported as clumsiness and inability to keep up with other children in sports. Patients may experience repeated tripping and a tendency to sprain their ankles.
- Over time weakness can progress, resulting in ambulation and balance difficulties and hand weakness.
- Muscle loss in the leg results in an "inverted champagne bottle" appearance. (Fig. E1A-B.)
- Up to 70% of patients develop foot deformities, including high arches (pes cavus) and hammer toes (flexion of the toes at the interphalangeal joint, metatarsophalangeal joint dorsiflexion). (Fig. E1C-D.) Up to 8% of patients may have flat feet (pes planus).
- Patients may not complain of significant sensory symptoms, though sensory loss will be apparent on examination.
- Reflexes are often absent in the ankles and may become reduced or absent in the proximal legs and in the arms over time.
- In some cases, enlargement of peripheral nerves results in enlarged palpable nerves.

ETIOLOGY

CMT has been reported to occur with mutations in more than 90 genes, which encode proteins involved in many neuronal and Schwann cell pathways, leading to disruption in normal cell functioning or myelin production.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other inherited neuropathies
- Distal myopathies
- Acquired peripheral neuropathies

WORKUP

- CMT should be suspected in childhood-onset peripheral neuropathies, especially those with a positive family history.
- Electrophysiologic studies are used to classify the neuropathy as either demyelinating or axonal and may distinguish acquired from hereditary demyelinating neuropathies.
- Genetic testing may confirm the diagnosis and aids in prognostication and family planning.
- In patients with the classic phenotype and evidence of demyelination on nerve conduction studies, the recommended first test is PMP22 duplications.
- If negative for PMP22 duplications or for axonal neuropathies, consider next-generation sequencing panels, which include many CMT-associated genes.
- The role of whole-exome or genome sequencing is uncertain at this time.

FIG. E1 Typical appearance of lower extremities in Charcot-Marie-Tooth. **A and B,** Wasting of the muscles of the lower extremities creating "inverted champagne bottle appearance." **C and D,** Typical appearance of hammer toes and pes cavus. (From Pareyson D, Marchesi C: Diagnosis, natural history, and management of Charcot-Marie-Tooth disease, *Lancet Neurology* 8:654, 2009)

TREATMENT

CHRONIC Rx

- There are no currently approved medications to cure or slow disease progression.
- Physical and occupational therapy are used for gait and balance training, improving strength, and to prevent tendon shortening.
- Orthotic devices, such as ankle–foot orthoses, help with gait and reduce falls.
- Surgical management for foot deformities can be considered when foot deformities cannot be corrected by orthotics or for intractable pain.
- Exercise appears to be safe and may improve strength and functioning.
- Neurotoxic medications (i.e., vincristine) should be avoided when possible.
- Modafinil can be considered to treat fatigue.

DISPOSITION

- In cases of CMT1A, progression is slow and patients remain ambulatory.
- Other forms of the disease may have more rapid progression and loss of ambulation.
- Life expectancy is not reduced.

REFERRAL

- Neurology or physical medicine and rehabilitation for care coordination
- Physical and occupational therapy for stretching, gait, and balance training
- Orthotist
- Genetic counselor
- Orthopedic surgery can be considered for intractable pain or foot deformities not amenable to orthotics

PEARLS & CONSIDERATIONS

Patient information can be found at:

- CMT Association (cmtausa.org)
- Muscular Dystrophy Association (www.mda.org)
- Hereditary Neuropathy Foundation (hnf-cure.org)

RELATED CONTENT

Charcot-Marie-Tooth Disease (Patient Information)

AUTHOR: **Lydia Sharp, MD**

SUGGESTED READINGS

Bird TD: Charcot-Marie-Tooth hereditary neuropathy overview. In Pagon RA et al, [editor.]: *GeneReviews* [Internet], University of Washington, Seattle. (Initial posting September 28, 1998, revised 2019.).

Laura M et al: Prevalence and orthopedic management of foot and ankle deformities in Charcot-Marie-Tooth Disease, *Muscle & Nerve* 57:255, 2018.

Pareyson D et al: New developments in Charcot-Marie-Tooth neuropathy and related diseases, *Curr Opin Neurol* 30:471, 2017.

Saporta ASD et al: Charcot-Marie-Tooth disease subtypes and genetic testing strategies, *Ann Neurol* 69(22), 2011.

Vallat JM et al: The various Charcot-Marie-Tooth diseases, *Curr Opin Neurol* 26:473-480, 2013.

BASIC INFORMATION

DEFINITION

Chemotherapy-induced nausea and vomiting (CINV) refers to adverse emetic effects associated with the use of drugs used to treat cancer. There are five recognized subtypes:

- Acute-phase CINV: Nausea and vomiting start within minutes to hours after receiving chemotherapy.
- Delayed-phase CINV: Nausea and vomiting begin or return 24 hours or more after receiving chemotherapy.
- Breakthrough CINV: Occurring despite appropriate prophylactic treatment.
- Anticipatory CINV: Symptoms begin before receiving therapy as a conditioned response in patients who have developed significant nausea and vomiting during previous chemotherapy.
- Refractory CINV: Recurring in subsequent cycles of therapy, excluding anticipatory CINV.

SYNONYMS

Drug-induced nausea and vomiting
Chemotherapy-induced emesis
CINV

ICD-10CM CODES

R11.2	Nausea with vomiting, unspecified
R11.0	Nausea
R11.10	Vomiting, unspecified
Z51.11	Encounter for antineoplastic chemotherapy

EPIDEMIOLOGY & DEMOGRAPHICS

- The patient's risk for development of nausea and vomiting is most strongly dependent on the emetogenicity of the chemotherapy agent(s) being used (Table 1).
- Emetogenicity is classified into four categories: Highly emetic (>90%), moderately emetic (>30% to 90%), low emetic (10% to 30%), and minimally emetic (0% to 10%).
- With certain chemotherapy regimens, CINV will occur in the majority of patients. However, patients' tolerance may vary, and symptoms may occur in as low as 10% of patients.
- Symptoms may be dose dependent (the higher the dose, the greater the risk for symptoms).
- CINV is more likely to affect female and younger patients.
- Patients expecting CINV before receiving therapy (anticipatory emesis) are at greater risk of experiencing symptoms.
- Patients with a history of alcohol consumption are at lower risk.
- Patients with a history of motion sickness are at greater risk.

INCIDENCE: The highest incidence of CINV is before or during the first cycle of chemotherapy.
GENETICS: Some rapid metabolizers of certain 5-HT3 receptor antagonists and polymorphisms in the 5-HT3 receptor confer greater risk for CINV.

RISK FACTORS:

- Previous history of CINV
- History of motion sickness or vestibular dysfunction
- Higher levels of anxiety
- History of alcohol use decreases risk

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms may include anxiety and lightheadedness.
- The most common physical findings are increased pulse rate and abnormal blood pressure (elevated if the person is highly anxious, reduced if the patient is dehydrated).
- Symptoms such as diarrhea, fever, headache, and abdominal pain may suggest an alternative diagnosis; physical examination findings such as increased blood pressure, abdominal tenderness, or focal neurologic deficits may suggest symptoms caused by cancer progression or other acute illness such as infection.

PATHOPHYSIOLOGY

The pathophysiology of nausea and vomiting is illustrated in Fig. E1. CINV is likely the result of chemotherapy acting in two places: Directly in the gastrointestinal tract and in the vomiting center of the brain. In both areas, nausea and vomiting are mediated by the actions of certain neurotransmitters, with serotonin, dopamine, and neurokinin-1 being the most important.

TABLE 1 Emetogenic Potential of Commonly Used Oral Antineoplastic Agents

Risk	Frequency of Emesis (%; Without Prophylaxis)	Agent
High	>90	Altretamine
		Procarbazine
Moderate	30-90	Cyclophosphamide
		Crizotinib
		Olaparib
		Temozolomide
Low	10-30	Alectinib
		Axitinib
		Capecitabine
		Ceritinib
		Cobimetinib
		Dasatinib
		Everolimus
		Gefitinib
		Ibrutinib
		Imatinib
		Ixazomib
		Lapatinib
		Lenalidomide
		Nilotinib
		Palbociclib
		Panobinostat
		Pazopanib
		Sorafenib
		Sunitinib
		Thalidomide
		Vemurafenib
Minimal	<10	Alectinib
		Busulfan
		Chlorambucil
		Dabrafenib
		Erlotinib
		Hydroxyurea
		Idelalisib
		Melphalan
		Methotrexate
		Osimertinib
		Ruxolitinib
		6-Thioguanine
		Trametinib
		Vismodegib

Modified from Roila F et al: Guideline update for MASCC and ESMO in the prevention of chemotherapy and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference, *Ann Oncol.* 2010;21(suppl 5):v232-243.

Chemotherapy-Induced Nausea and Vomiting

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- The two main considerations are progression of cancer and infection
- Intestinal/gastric: Obstruction or partial obstruction of the digestive tract from tumor
- Neurologic: Metastases to the brain causing vomiting; metastatic infiltration of nerves affecting the digestive tract
- Infectious: Acute bacterial, viral, or parasitic infections of the digestive tract causing symptoms (can be associated with diarrhea or pain)
- Renal: Dehydration leading to acute kidney injury and failure, causing worsening of nausea and vomiting

WORKUP

No workup is indicated if patient's symptoms and onset of nausea and vomiting fit the usual presentation for CINV. If other symptoms or unexpected physical examination findings are present, then other causes need to be ruled out. A combination of blood work and imaging may be helpful.

LABORATORY TESTS

- If the onset of symptoms is not typical for CINV, then blood tests such as CBC, liver function tests, electrolytes, and kidney function tests may be indicated.
- Stool studies looking for infections from viruses, bacteria, or parasites may be ordered if diarrhea is also present.

IMAGING STUDIES

- Abdominal radiographs may be ordered to look for obstruction of the digestive tract but will not provide any information about tumor progression.
- Abdominal CT scan may provide more detailed information about local cancer progression/invasion in the proximity of the digestive tract and whether obstruction of the digestive tract is present.
- CNS imaging with CT scan or magnetic resonance imaging (MRI) of the brain may provide information about possible metastases.

TREATMENT

- A management approach to CINV is summarized in Box 1.
- Choice and duration of antiemetic use are dependent on the chemotherapy regimen used. Commonly used antiemetic agents and recommended dosing are described in Table 2.
- For chemotherapy agents with high emetogenic potential, the use of multidrug antiemetic regimens has proven to be highly effective in symptom prevention.
- The most common treatment combination includes a serotonin-receptor antagonist (ondansetron, granisetron, dolasetron, or palonosetron), a corticosteroid (methylprednisolone or dexamethasone), and a neurokinin-1 receptor antagonist (aprepitant, rolapitant, or fosaprepitant).
- A fixed-dose combination of oral palonosetron and netupitant (NK-1 receptor antagonist) is now available. Table 3 summarizes recommended antiemetic prophylaxis for patients receiving intravenous chemotherapy.
- Many other adjunct drugs are available, such as olanzapine, prochlorperazine, metoclopramide, haloperidol, and marinol; comparatively, they are less effective and have greater potential for adverse effects.
- Benzodiazepines (usually lorazepam) may help in patients with significant anxiety levels that lead to anticipatory CINV.
- Patients with uncontrolled symptoms may require hospitalization for supportive care including intravenous medications and fluids.

NONPHARMACOLOGIC THERAPY

For those patients with a significant anxiety component to their CINV, cognitive behavioral therapy may help.

DISPOSITION

Although CINV is one of the most feared complications of cancer therapy, its treatment has been revolutionized in the last 20 yr, with most patients achieving adequate symptom control.

PEARLS & CONSIDERATIONS

COMMENTS

- Aggressive symptom control in the acute phase of CINV is the key initial therapeutic approach. Prevention of the acute phase has led to much improved control of the delayed phase and has greatly decreased the incidence of anticipatory CINV.
- Prevention of symptoms is much easier to achieve than controlling or treating active symptoms.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Byung Kim, MD**

BOX 1 Management Approach: Chemotherapy-Induced Nausea and Vomiting (CINV)

Antiemetic therapy for CINV should be based on the emetic potential of the chemotherapy regimen being used and should take into account individual patient factors (e.g., sex, age, history of alcohol use, and previous emesis with chemotherapy). Excellent methods for predicting the likelihood of emesis with single chemotherapeutic agents or combination regimens have been developed.

All patients receiving chemotherapy with moderate or high emetogenic potential should receive antiemetic prophylaxis for acute (day 1) and delayed (days 2 to 5) nausea and vomiting. Patients receiving highly emetogenic regimens should receive prophylaxis on day 1 with a 5-HT_3 receptor antagonist (preferably palonosetron) plus neurokinin-1 (NK1) receptor antagonist plus dexamethasone, followed on days 2 to 4 by dexamethasone. Olanzapine should be added in patients judged to be at high risk. For moderately emetogenic regimens, treatment with a 5-HT_3 receptor antagonist (preferably palonosetron) plus dexamethasone on day 1, followed by dexamethasone on days 2 and 3, is recommended.

Patients receiving therapy with low emetic potential should receive dexamethasone (8 mg intravenously or orally); a 5-HT_3 receptor antagonist should be added with subsequent courses only if antiemetic control is inadequate. Routine prophylaxis is not necessary for patients receiving agents or regimens of minimal risk. Patients with inadequate control should have intensification of their antiemetic prophylaxis during subsequent treatment cycles.

From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

TABLE 2 Antiemetic Agents: Recommended Dosing

	Recommended Dose	
Antiemetic Agent	**Acute Emesis (Before Chemotherapy)**	**Delayed Emesis**
5-HT_3 antagonists		
Ondansetron	0.15 mg/kg or 8 mg IV; 12-16 mg PO	8 mg PO twice a day × 2-3 days
Granisetron	1 mg IV or PO; 10 mg subcutaneous (extended release)	
Dolasetron	1.8 mg/kg or 100 mg IV; 100-200 mg PO	
Palonosetron	0.25 mg IV or 0.5 mg PO	
NK1 receptor antagonists		
Aprepitant	125 mg PO	80 mg PO days 2 and 3
Fosaprepitant	150 mg IV	
Rolapitant	180 mg PO	
Combination 5-HT_3/NK1 receptor antagonist		
NEPA (palonosetron 0.5 mg/netupitant 300 mg)	1 tablet PO	
Multireceptor antagonist		
Olanzapine	10 mg PO	10 mg PO days 2-4
Corticosteroids		
Dexamethasone		
With NK1 antagonist	12 mg IV or PO	8 mg PO for 2-3 days
Without NK1 antagonist	8 mg (moderate risk) or 20 mg (high risk) IV or PO	4-8 mg PO twice a day for 2-3 days
Other agents		
Prochlorperazine		10 mg PO or IV every 3-4 hours as needed
Lorazepam	1-2 mg IV (for anticipatory nausea/vomiting)	
Dronabinol		5 mg/m^2 PO every 3-4h as needed

5-HT_3, 5-Hydroxytryptamine 3; *NK1*, neurokinin 1; *IV*, intravenous; *PO*, by mouth.
From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

TABLE 3 Summary of Recommended Antiemetic Prophylaxis for Patients Receiving Intravenous Chemotherapy

Risk of Emesis	Day 1 (Prechemotherapy)	After Day 1
High (includes cyclophosphamide and doxorubicin)	5-HT_3 receptor antagonist (palonosetron preferred) + NK1 receptor antagonist + dexamethasone + olanzapine (if patient considered high risk)	Dexamethasone days 2-4 + aprepitant days 2-3 (if used on day 1) + olanzapine days 2-4 (high-risk patients)
Moderate	5-HT_3 receptor antagonist (palonosetron preferred) + dexamethasone	Dexamethasone days 2 and 3
Low	Dexamethasone	None
Minimal	As needed	None

5-HT_3, 5-Hydroxytryptamine 3; *NK1*, neurokinin 1.
From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

SUGGESTED READINGS

Jordan K et al: Recent developments in the prevention of chemotherapy-induced nausea and vomiting (CINV): a comprehensive review, *Ann Oncol* 26(6):1081-1090, 2015.

Navari RM, Aapro M: Antiemetic prophylaxis for chemotherapy-induced nausea and vomiting, *N Engl J Med* 374:1356-1367, 2016.

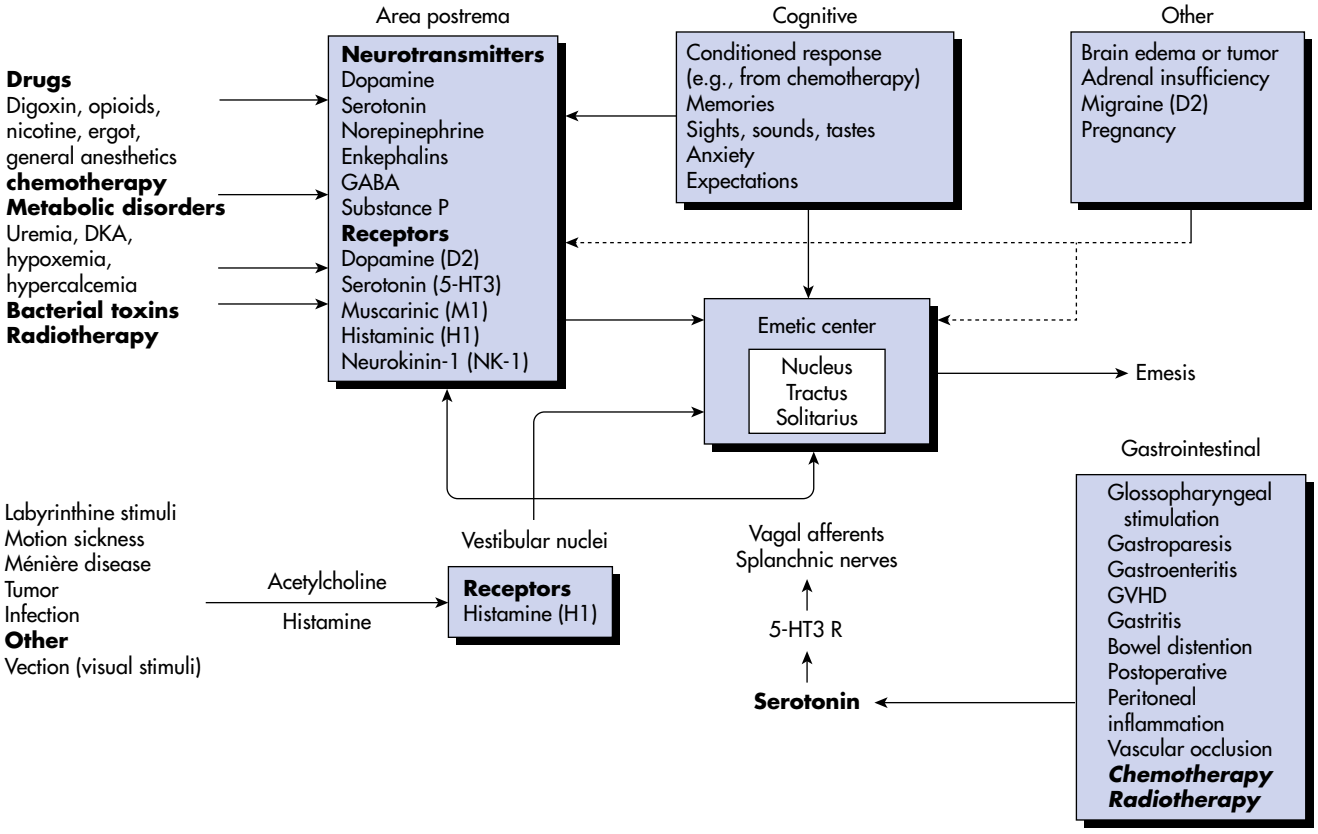

FIG. E1 Pathophysiology of nausea and vomiting. *DKA*, Diabetic ketoacidosis; *GABA*, γ-aminobutyric acid; *GVHD*, graft-versus-host-disease; *5-HT3*, serotonin; *5-HT3 R*, serotonin receptor. (From Hoffman R: *Hematology, basic principles and practice*, ed 7, 2018, Elsevier.)

Child Abuse and Neglect PTG ALG

BASIC INFORMATION

DEFINITION

Definition from the Federal Child Abuse Prevention and Treatment Act (CAPTA): Any recent act or failure to act on the part of a parent or caretaker that results in death, serious physical or emotional harm, sexual abuse or exploitation of a child; or an act or failure to act that presents an imminent risk of serious harm to a child. More specific definitions may be found in individual state criminal and Child Protective Services statutes.

- Neglect: Failure to provide for the basic needs of a child
  1. Physical neglect: Failure to provide necessary food, shelter, and supervision
  2. Medical neglect: Failure to provide necessary medical or mental health care
  3. Educational neglect: Failure to meet educational needs
  4. Emotional neglect: Failure to attend to emotional needs, exposure to domestic violence
  5. Abandonment: Child left and parents' whereabouts unknown or parents refuse to care for child
  6. Parental substance abuse: Includes prenatal exposure to mother's use of illicit drugs, manufacture of drugs (e.g., methamphetamine) in the presence of a child, selling or giving drugs to a child, use of mood-altering substance by caregivers that impairs their ability to provide care for a child
- Abuse: Act that causes harm or significant risk of harm to a child
  1. Physical abuse: Physical injury or significant risk of injury inflicted by a parent or caregiver intentionally, including in the course of excessive discipline
  2. Sexual abuse: When a child or adolescent is engaged in a sexual act, including sexual exploitation and child pornography
  3. Emotional/psychological abuse: Pattern of behavior of caretaker toward a child that impairs emotional development. This includes verbal abuse, cruelty, and threats
  4. Medical child abuse: Unnecessary, excessive, and potentially harmful medical care obtained at the instigation of a caregiver through exaggeration or falsification of symptoms

SYNONYMS

Child maltreatment syndrome
Physical abuse
Sexual abuse
Battered child syndrome
Shaken baby syndrome
Shaken impact syndrome
Abusive head trauma
Neglect

ICD-10 CM CODES

T74	Adult and child abuse, neglect or other maltreatment, confirmed
T74.02	Child neglect or abandonment, confirmed
T74.12	Child physical abuse, confirmed
T74.22	Child sexual abuse, confirmed
T74.32	Child psychological abuse, confirmed
T76.32XA	Child psychological abuse, suspected, initial encounter
T76.22XA	Child sexual abuse, suspected, initial encounter
T76.12XA	Child physical abuse, suspected, initial encounter
T74.32XA	Child emotional/psychological abuse
DSM-5	Code depends on specific diagnosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): The incidence of child maltreatment is universally underestimated due to children not disclosing abuse and neglect, the diagnosis of abuse being missed, and individuals not reporting abuse and neglect when it is identified. The following data are based on Child Protective Services (CPS) state aggregate as reported in *Child Maltreatment 2016*. These data typically include only those instances of abuse or neglect that would result in CPS involvement; therefore, physical or sexual abuse by neighbors, noncaregiving family members, teachers, and siblings may not be counted. In 2016, roughly 700,000 victims of child abuse or neglect were identified. This is a rate of 9.1 unduplicated victims per 1000 children.

- Types of abuse by percentage (note the total is greater than 100%, since children are often victims of more than one type of abuse).
  1. Neglect: 75%.
  2. Physical abuse: 18%.
  3. Sexual abuse: 8.5%.
  4. Psychological abuse: 5.6%.
  5. Medical neglect: 2.1%.
  6. Other: 6.9% (e.g., abandonment, threats of harm, congenital drug addiction).
- For 2016, an estimated 1700 child deaths were caused by abuse or neglect.
  1. Overall annual death rate resulting from abuse or neglect is estimated to be 2.25 deaths/100,000 children.
  2. 75% of these deaths were due to neglect alone or in combination with other forms of abuse; 44% were due to physical abuse, alone or in combination.
  3. 70% of these children were younger than 3 yr of age with 44% less than 1 yr old.
  4. Most fatalities were directly caused by one or both parents (78%).
  5. Of the states reporting this information, 5.7% of families had parental alcohol abuse, 15% had parental drug abuse, and 7.5% had inadequate housing.
  6. Many child abuse fatalities are underreported because of misdiagnosis or variations in state definitions and coding.
- 78% of abused children were victimized by one or both of their parents; however, most data collected by CPS involve caregivers.

PREDOMINANT SEX: There is a slight predominance of girls identified as victims. However, rates vary by age. Boys 5 and under have a higher rate of abuse, whereas girls 6 to 17 have higher rates of abuse. At all ages, boys have a higher child fatality rate than girls (2.48/100,000 for boys and 1.82/100,000 for girls).

PREDOMINANT AGE: Youngest children (0 to 3 yr old) have the highest rates of victimization, with 27% being younger than the age of 3.

GENETICS: No known genetic factors.

RISK FACTORS:

- Parent:
  1. Substance abuse
  2. Mental illness
  3. Intellectual impairment
  4. Parental history of being abused as a child
  5. Young age of parent
  6. Poor knowledge of child development leading to unrealistic expectations
- Child:
  1. Low birth weight or prematurity
  2. Chronic physical disability or illness
  3. Behavioral problems
  4. Developmental delay, intellectual disability, or expressive language disorders
  5. Unplanned, unwanted child
- Family:
  1. Social isolation
  2. Poor parent-child bonding
  3. Stress: Unemployment, chronic illness, eviction, arrest, poverty, military deployment
  4. Domestic violence
  5. Nonbiologically related adult male living in household
  6. Previous CPS involvement
- Community/society:
  1. Limited transportation
  2. Limited day care
  3. Unsafe neighborhoods
  4. Poverty

DIAGNOSIS

- Disclosures:
  1. For sexual abuse, often the only evidence is the child's disclosure.
  2. Document clearly any disclosures a child makes regarding abuse or neglect.
  3. When speaking with a young child who may have been abused or neglected, it is important to use forensically informed language and not ask direct or leading questions. The child may benefit from a referral to a Children's Advocacy Center for a forensic interview.
- Injuries:
  1. Documentation:
     a. Carefully document any injuries identified that may be the result of abuse or neglect.
     b. Photodocumentation of injuries is essential.
  2. Concerning history:
     a. The history of injury provided is incompatible with the developmental capabilities of the child.
     b. Changing history from the caregiver or a history that is different among caregivers.

c. The injury is not consistent with the mechanism provided by caregivers.
d. No history provided; especially with a nonmobile infant.
e. Delay in seeking care for a significant injury.

3. Concerning physical injuries:
   a. Patterned bruising (e.g., loop-shaped, two semicircles, rectangular, multiple parallel linear marks) (Table E1, Fig.E1).
   b. Bruising to the torso, ears, facial cheeks, jawline, upper arms and neck, especially in children under age 4 yr.
   c. Injury (bruise, burn, fracture, intracranial hemorrhage) in an infant who is not ambulatory and not cruising.
   d. Patterned burns, such as an impression of the burning object (lighter, iron, cigarette), immersion burns (Figs. E2 and E3).
   e. Certain fractures (especially in infants) are highly concerning for abuse: Metaphyseal, rib, sternum, scapula, vertebral body.
   f. Any injury that a child says is inflicted.
4. Sexual abuse:
   a. Most children who have been sexually abused will have a normal or nonspecific genital examination. A normal genital examination does not mean the child was not abused. History is the most important part of the diagnosis. Forensic interview by a trained professional is recommended, as is an examination by a health care provider experienced in sexual abuse evaluations.
   b. The identification of a sexually transmitted disease in a prepubertal child who is beyond the neonatal period is highly suspicious and, in some instances, almost diagnostic of sexual abuse. Reporting and further careful investigation are mandatory. Consult current CDC guidelines and a child sexual abuse expert for further guidance.

TABLE E1 Injury Patterns

Method of Injury/Implement	Pattern Observed
Grip/grab	Relatively round marks that correspond to fingertips and/or thumb
Closed-fist punch	Series of round bruises that correspond to knuckles of the hand
Slap	Parallel, linear bruises (usually petechial) separated by areas of central sparing
Belt/electrical cord	Loop marks or parallel lines of petechiae (the width of the belt/cord) with central sparing; may see triangular marks from the end of the belt, small circular lesions caused by the holes in the tongue of the belt, and/or a buckle pattern
Rope	Areas of bruising interspersed with areas of abrasion
Other objects/household implements	Injury in shape of object/implement (e.g., rods, switches, and wires cause linear bruising)
Human bite	Two arches forming a circular or oval shape, may cause bruising and/or abrasion
Strangulation	Petechiae of the head and/or neck, including mucous membranes; may see subconjunctival hemorrhages
Binding/ligature	Marks around the wrists, ankles, or neck; sometimes accompanied by petechiae or edema distal to the ligature mark Marks adjacent to the mouth if the child has been gagged
Excessive *hincar**	Abrasions/burns, especially to knees
Hair pulling	Traumatic alopecia; may see petechiae on underlying scalp, or swelling or tenderness of the scalp (from subgaleal hematoma)
Tattooing or intentional scarring	Abusive cases have been described, but can also be a cultural phenomenon (e.g., Maori body ornamentation)

*Punishment by kneeling on salt or other rough substance.
From Kliegman, RM: Nelson Textbook of Pediatrics, ed 21, Philadelphia, 2020, Elsevier.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis should include possible medical causes, accidental causes, and abuse.

BRUISING:
- Bleeding disorder (idiopathic thrombocytopenic purpura, hemophilia, leukemia, hemorrhagic disease of the newborn, von Willebrand disease)
- Connective tissue disorder (Ehlers-Danlos syndrome, vasculitis)
- Pigments (dermal melanocytosis)
- Dermatitis (phytophotodermatitis, nickel allergy)
- Folk treatment (coining, cupping)
- Accidental bruises

BURNS:
- Accidental burn
- Impetigo
- Folk treatment (moxibustion)
- Dermatitis (phytophotodermatitis)

INTRACRANIAL HEMORRHAGE:
- Accidental trauma
- Bleeding disorder with minor trauma
- Perinatal trauma (should resolve by 6 wk)

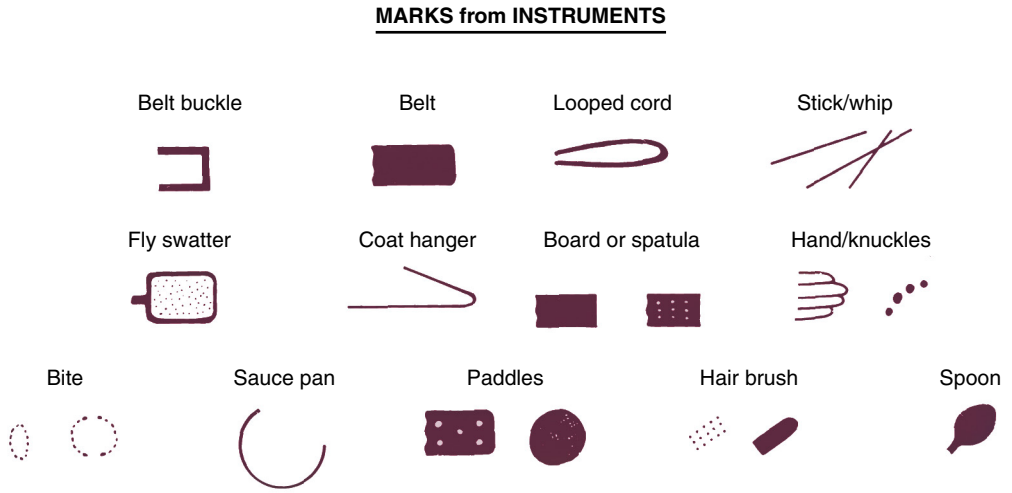

FIG. E1 A variety of instruments may be used to inflict injury on a child. Often the choice of an instrument is a matter of convenience. Marks tend to silhouette or outline the shape of the instrument. The possibility of intentional trauma should prompt a high degree of suspicion when injuries to a child are geometric, paired, mirrored, of various ages or types, or on relatively protected parts of the body. Early recognition of intentional trauma is important to provide therapy and prevent escalation to more serious injury. (From Kliegman, RM: Nelson Textbook of Pediatrics, ed 21, Philadelphia, 2020, Elsevier.)

- Arteriovenous malformation rupture
- Glutaric aciduria

FRACTURES:
- Accidental trauma
- Osteogenesis imperfecta
- Rickets
- Congenital syphilis
- Osteopenia of prematurity

SEXUAL ABUSE:
- Normal variants
- Lichen sclerosis et atrophicus
- Congenital abnormalities
- Urethral prolapse
- Hemangioma
- Nonsexually acquired infection (group A *Streptococcus, Shigella*)

WORKUP (FIG. E4)

History and physical examination:
- Careful history should be obtained and documented from all caregivers separately.
- Careful history should be obtained from the child. When children are less than 14 yr of age, history should be obtained in a forensically informed manner without asking direct or leading questions. A referral to a Children's Advocacy Center may be indicated.
- Scene investigation may be necessary and is typically conducted by law enforcement and/or CPS.
- Complete head-to-toe physical examination.
- Sexual abuse: Forensic interview and magnified examinations by trained professionals are the standard for evaluation and evidence collection. This is especially important to avoid further psychological or physical trauma to the child.

Laboratory tests to assess for bleeding disorder in the case of children with suspicious bruising. These tests may not be necessary if the abuse was witnessed or if the child has clear patterned bruising or other indicators of physical abuse:
- CBC with differential and platelets
- Prothrombin time, activated partial thromboplastin time
- Von Willebrand factor antigen and activity
- Factor VIII and IX levels
- Alanine aminotransferase, amylase, urinalysis should be considered in infants or other children with abdominal bruising to look for evidence of internal injury to the liver, pancreas, or kidneys

Laboratory tests to assess for bleeding disorder in the case of children with suspicious intracranial hemorrhage (ICH).
- CBC with differential and platelets
- Prothrombin time, activated partial thromboplastin time
- Factor VIII and IX levels
- Disseminated intravascular coagulation (DIC) panel

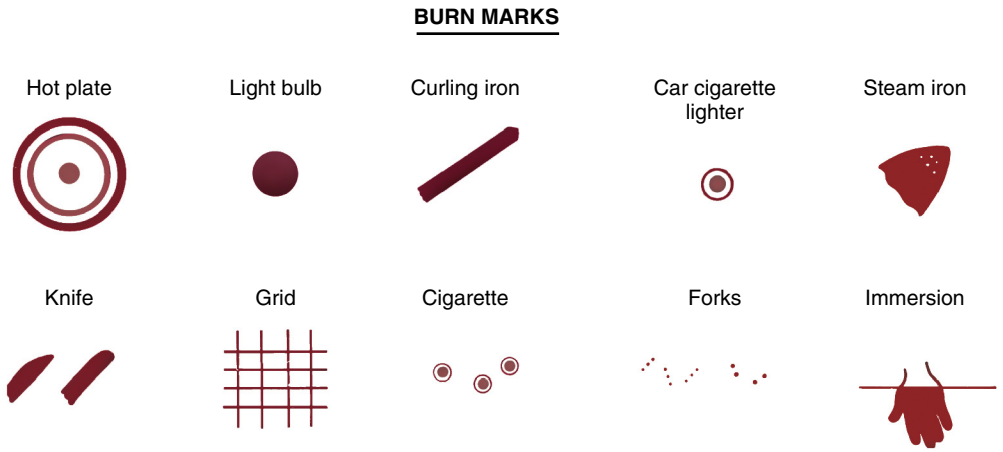

FIG. E2 Marks from heated objects cause burns in a pattern that duplicates that of the object. Familiarity with the common heated objects that are used to traumatize children facilitates recognition of possible intentional injuries. The location of the burn is important in determining its cause. Children tend to explore surfaces with the palmar surface of the hand and rarely touch a heated object repeatedly for long. (From Kliegman, RM: Nelson Textbook of Pediatrics, ed 21, Philadelphia, 2020, Elsevier.)

FIG. E3 Immersion injury patterns. **A,** Sparing of the flexoral creases. **B,** Immersion "stocking" burn. **C,** Immersion "glove" burn. **D,** Immersion buttocks burn. (From Jenny C: Child abuse and neglect: diagnosis, treatment, and evidence, Philadelphia, 2011, Saunders, p. 225, Fig 28-3 in Kliegman, RM: Nelson Textbook of Pediatrics, ed 21, Philadelphia, 2020, Elsevier.)

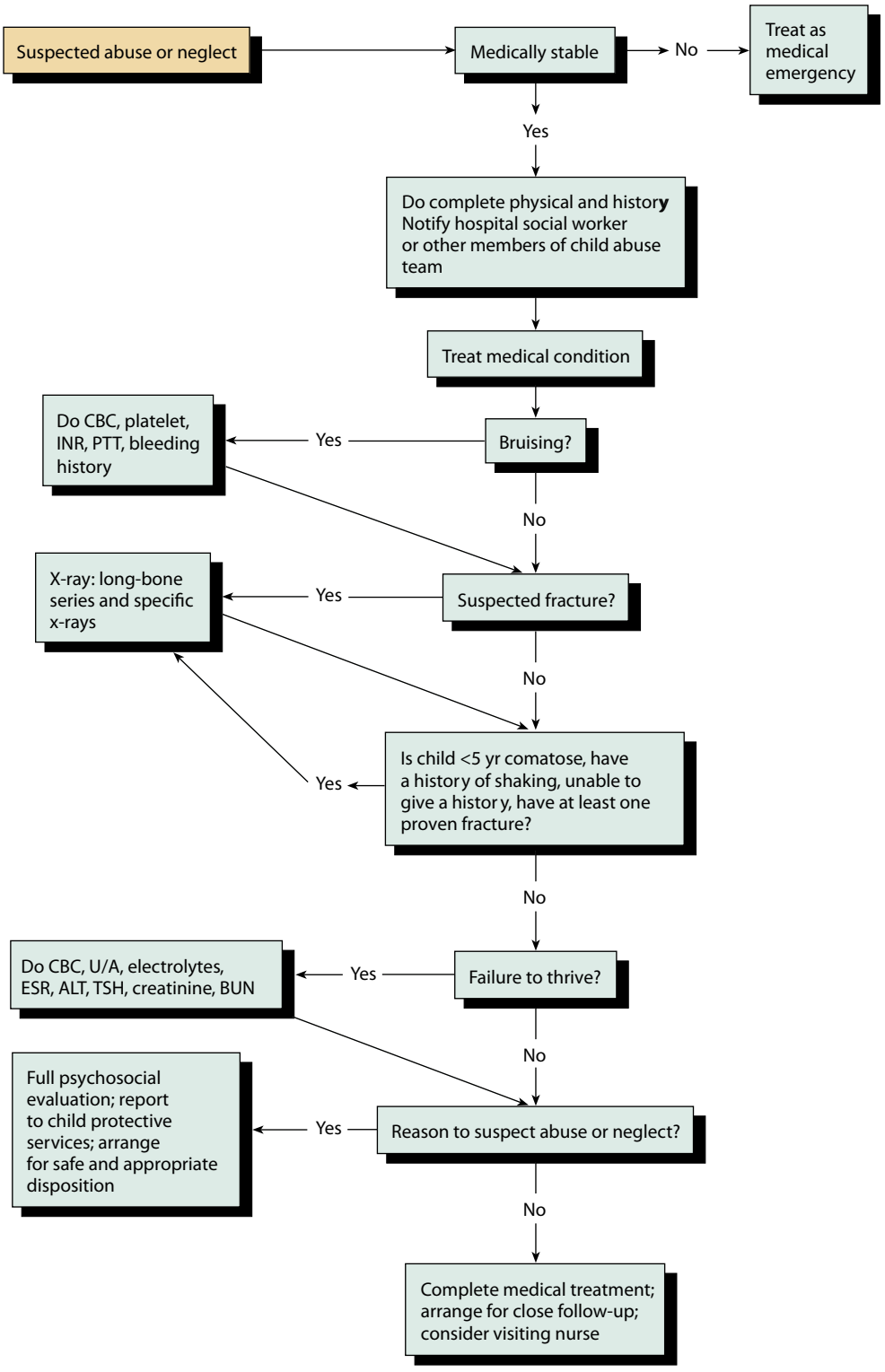

FIG. E4 Management of suspected child abuse. *ALT,* Alanine aminotransferase; *BUN,* blood urea nitrogen; *CBC,* complete blood count; *ESR,* erythrocyte sedimentation rate; *INR,* international normalized ratio; *PTT,* partial thromboplastin time; *TSH,* thyroid-stimulating hormone; *U/A,* urinalysis.

- Consultation with a child abuse expert physician should be strongly considered in children with suspicion of abusive head trauma

Laboratory tests for sexual abuse:

- If within 72 hr of acute sexual assault/abuse, a forensic evidence kit (rape kit) can be collected. Swabs are obtained from the oropharynx, areas of skin exposure (use an alternate light source or history provided to identify appropriate areas), genitalia, and rectum to send to the crime lab for DNA and other testing. Also collect samples of foreign hair, blood, saliva, or other tissue if present. Underwear and clothing can also be collected.
- Per current CDC recommendations, adolescent victims of acute assault should have appropriate specimens collected from sites of penetration or attempted penetration for *Neisseria gonorrhoeae* and *Chlamydia.* Nucleic acid amplification tests (NAATs) may be used and are preferred. In females, wet mount and culture or point-of-care (POC) testing of vaginal swab for *T. vaginalis* should also be done. If there is itching, vaginal

discharge, or malodor present, wet mount for bacterial vaginosis and *Candida* should also be done. Serum should be obtained for HIV, hepatitis B, and syphilis testing acutely. If negative, HIV and syphilis testing should be repeated 6, 12, and 24 wk after the assault.
- Child victims (i.e., prepubertal) should have specimens collected if testing for a sexually transmitted infection (STI) is clinically indicated. Gonorrhea and *Chlamydia* culture is the gold standard for diagnosis. If needed, vaginal specimens are to be collected by an experienced provider to avoid trauma to the child. Many providers now analyze specimens using urine or vaginal swabs with NAAT testing followed by culture confirmation or second NAAT if any positive results are obtained. The FDA has not approved NAAT testing for gonorrhea and *Chlamydia* of extragenital sites, so culture remains the gold standard. Testing for sexually transmitted infections (gonorrhea, *Chlamydia, T. vaginalis*, HIV, syphilis, and hepatitis) should be obtained if the child has a known STI, has symptoms of an STI, or if there is concern for sexual abuse that could result in an STI.

IMAGING STUDIES

Physical abuse:
- Radiographic skeletal survey for all children with suspicious injuries up to 2 yr. Additionally, a skeletal survey should be considered for any sibling less than 2 yr of age of a child who has been physically abused. Skeletal surveys can be done on children up to 5 yr of age when there are extenuating circumstances. A repeat skeletal survey should be done 2 wk after the initial skeletal survey. Adjunct imaging (MRI, ultrasound, bone scan) may be useful to further define suspicious lesions seen on plain films. Skeletal survey should conform to American College of Radiology Standards.
- Noncontrast head CT scan or MRI for all children <6 mo of age with concern of physical abuse. Head imaging should be considered for children 6 mo to 1 yr with concern of physical abuse. Children over 1 yr of age should have head imaging if neurological changes or per clinical judgment.
- When abusive head trauma is identified on head CT, a head MRI should be obtained.
- Abdominal CT scan if indicated by clinical examination or laboratory evaluation.
- Box E1 describes the specificity of radiologic findings for child abuse.

BOX E1 Specificity of Radiologic Findings for Child Abuse

High Specificity
Classic metaphyseal lesions
Rib fractures, especially posterior
Scapular fractures
Spinous process fractures
Sternal fractures

Moderate Specificity
Multiple fractures, especially bilateral
Fractures of different ages
Epiphyseal separations
Vertebral body fractures and sublux-ations
Digital fractures
Complex skull fractures

Common but Low Specificity
Subperiosteal new bone formation
Clavicular fractures
Long bone shaft fractures
Linear skull fractures

From Manaster BJ: *Musculoskeletal imaging—the requisites,* ed 3, Philadelphia, Mosby, 2006.

Rx TREATMENT

ACUTE GENERAL Rx

- Stabilize and treat acute medical injuries.
- Report to CPS. HIPAA allows reports for suspected child abuse without parental authorization.
- Report to law enforcement for suspected physical abuse or sexual abuse.
- Early report to CPS and/or law enforcement may allow for scene investigation.
- A safe disposition plan should be determined prior to discharge. This may involve coordination with the multidisciplinary team (physicians, law enforcement, family, and CPS). Disposition, once medically stable, is dependent on CPS. The child cannot be returned home if the environment is not safe.
- Physicians should remain available to discuss with investigators. This is often critical to determining the outcome of the case and placement of the child.
- Because follow-up of adolescent sexual assault victims can be difficult to coordinate, many experts recommend offering empiric treatment for STIs: Gonorrhea, *Chlamydia, Trichomonas,* and bacterial vaginosis. Pregnancy prophylaxis should also be offered. Hepatitis B immunization should be offered if not previously given. HIV prophylaxis is offered in certain situations depending on local epidemiology and type of assault. Consult local infectious disease experts for current recommendations. Repeat evaluation should be done in 2 wk for all victims of sexual assault, especially if they declined empiric treatment. If empiric treatment was not done, STI and pregnancy testing should be repeated at the 2-wk follow-up visit.
- Empiric treatment of child (i.e., prepubescent) who has been sexually abused is generally not recommended. This is especially important if NAATs are used for screening for STIs because confirmation is necessary for any positive results. Careful follow-up within 2 wk and treatment based on culture results are indicated. HIV prophylaxis is offered in certain circumstances according to local epidemiology and risk. Consult with a local infectious disease expert for further recommendations.

CHRONIC Rx

- Often depends on CPS and court-ordered interventions
- Treatment of parental mental illness
- Treatment of parental substance abuse, including requirements for random drug testing
- Instruction for parents in behavior management skills, including appropriate limit setting and discipline
- Anger management classes for parents
- Trauma-focused cognitive-behavioral therapy is an evidence-based practice for victims of sexual abuse and exposure to domestic violence; useful to include nonoffending parent/caregiver
- Ongoing individual and family therapy:
  1. Parent-child interactive therapy is an evidence-based practice that is used with young children with behavioral problems and parent-child relationship problems
  2. Child-parent psychotherapy is an evidence-based practice that is for young children (<5 yr) who have experienced a trauma and their caregivers
- May need long-term placement in foster care before it is safe to return home. In extreme cases of abuse, parental rights may be terminated without offering services

OUTCOMES

- Victims of chronic abuse and neglect:
  1. Have higher rates of mental illness (depression, suicide, posttraumatic stress disorder, eating disorders)
  2. Have more cognitive difficulties, often impaired academic performance
  3. Are more likely to become aggressive and have challenging behaviors
  4. Are more likely as adults to have adverse physical health outcomes (cardiovascular disease, cancer, STDs)
- Victims of abusive head trauma:
  1. One third die, one third have severe disability, one third appear normal in the short term

! PEARLS & CONSIDERATIONS

PREVENTION

- Home visitation by a specially trained nurse to high-risk families during pregnancy and infancy has shown positive outcomes (Nurse-Family Partnership).
- Anticipatory guidance at health visits to teach normal developmental expectations and appropriate discipline.
- Screening to identify at-risk or abused children.
- Targeted education in the newborn nursery for prevention of abusive head trauma has been shown to be effective.
- Substance abuse prevention and treatment.
- Identification and intervention for intimate partner violence.

RELATED CONTENT

Protecting Children from Abuse (Patient Information)

AUTHOR: **Brett Slingsby, MD**

SUGGESTED READINGS

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Anderst JD, et al: Evaluation for bleeding disorders in suspected child abuse, *Pediatrics* 131(4):e1314-e1322, 2013.

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Saperia J, et al: Guideline Development Group and Technical Team: when to suspect child maltreatment: summary of NICE guidelines, *BMJ* 339:b2689, 2009.

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Chlamydia Genital Infections

BASIC INFORMATION

DEFINITION

Genital infection with *Chlamydia trachomatis* (CT) is the most prevalent sexually transmitted disease in the U.S. Chlamydia infection can result in cervicitis, acute urethral syndrome, endometritis, pelvic inflammatory disease, ectopic pregnancy, infertility, and chronic pelvic pain in women (see "Pelvic Inflammatory Disease"). In men, CT infection may cause mucopurulent discharge, urethritis, epididymitis, and prostatitis. Newborns born via an infected birth canal are at risk for conjunctivitis and pneumonia. A majority of the men and women affected with CT are asymptomatic. Thus, screening tests play a very important role in detection of this infection to initiate treatment, impede disease sequelae, and prevent further transmissions.

ICD-10CM CODES

A56.2	Chlamydial infection of genitourinary tract, unspecified
A56	Other sexually transmitted chlamydial diseases
A56.0	Chlamydial infection of lower genitourinary tract
A56.00	Chlamydial infection of lower genitourinary tract, unspecified
A56.01	Chlamydial cystitis and urethritis
A56.02	Chlamydia vulvovaginitis
A56.09	Other chlamydial infection of lower genitourinary tract
A56.1	Chlamydial infection of pelviperitoneum and other genitourinary organs
A56.19	Other chlamydial genitourinary infection
A56.2	Chlamydial infection of genitourinary tract, unspecified
A56.3	Chlamydial infection of anus and rectum
A56.4	Chlamydial infection of pharynx
A56.8	Sexually transmitted chlamydial infection of other sites

EPIDEMIOLOGY & DEMOGRAPHICS

- *C. trachomatis* is the most commonly reported sexually transmitted disease in the U.S., with more than 1.5 million cases reported annually to the Centers for Disease Control and Prevention. However, it is thought that this number is an underestimate, since many cases of CT infection are asymptomatic and potentially can remain undiagnosed.
- Age is a strong predictor for risk of CT infection. Individuals less than 25 yr old are the largest age group affected by *C. trachomatis*. Chlamydia infections are 10 times more prevalent than gonococcal infections in young women between the ages of 18 and 26 yr.
- The prevalence of chlamydial infection varies according to race; according to a U.S. report in 2015, the rate of reported cases among African Americans was 5.9 times the rate among whites. The prevalence among sexually active non-Hispanic females of African descent 14 to 24 years of age was 13.5% as compared with 1.8% among non-Hispanic white females.[1]
- Chlamydia conjunctivitis occurs in 18% to 44% of infants, and chlamydial pneumonia occurs in 3% to 16% of infants who are delivered by mothers with untreated CT infection at the time of delivery.
- Pelvic inflammatory disease develops in 10% to 15% of women with untreated CT infections.
- Untreated CT increases a person's risk of acquiring HIV.
- In men, 15% to 55% of nongonococcal urethritis cases are caused by *C. trachomatis*.
- Table 1 summarizes clinical characteristics of common *C. trachomatis* infections.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical manifestations in symptomatic women affected with *C. trachomatis* are vaginal discharge or irregular vaginal bleeding. Purulent discharge or cervicitis may be visualized on speculum exam. Easily induced endocervical bleeding can be noted on exam and is caused by inflammation of endocervical columnar epithelium. Untreated infection can ascend the reproductive tract, causing pelvic inflammatory disease. Clinical signs of pelvic inflammatory disease are cervical, uterine, or adnexal tenderness on exam. Complications of pelvic disease are ectopic pregnancy, infertility, and chronic pelvic pain.

Most men are asymptomatic, but when they do experience symptoms, it is usually dysuria or a mucopurulent penile discharge. A complication that can arise from CT infection in men is epididymitis, which manifests as unilateral testicular pain, hydrocele, or swelling of the epididymis. An untreated CT infection can also cause prostatitis in men. Prostatitis may present as urinary dysfunction, pain with ejaculation, and pelvic pain.

Chlamydial conjunctivitis can be experienced by both men and women and is the result of conjunctiva exposed to infected genital secretions. CT infection can also cause proctitis or infection of the rectum in men and women. This usually presents with rectal pain, discharge, or bleeding. CT infection of the throat is usually asymptomatic in both men and women and not a usual cause of pharyngitis. Less frequent manifestations of CT infection may include perihepatitis (Fitz-Hugh–Curtis syndrome) or reactive arthritis (Reiter syndrome).

ETIOLOGY

- *C. trachomatis* consists of 15 serotypes
- Obligate, intracellular bacteria

[1]Wiesenfeld HC: Screening for Chlamydia trachomatis infections in women, *N Engl J Med* 376:765-773, 2017.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Differential diagnosis depends on presenting symptoms. Some of the common differentials are listed in the following:

- Candidiasis
- Conjunctivitis
- Ectopic pregnancy
- Endometriosis
- Gonorrhea
- Mycoplasma infection
- Pelvic inflammatory disease
- Trichomonas
- Urethritis
- Urinary tract infection

WORKUP

Individuals with signs and symptoms mentioned previously should be screened for CT infection. Since the majority of CT infections are asymptomatic, routine screening should be offered to individuals at risk for CT infection. Annual screening of all sexually active women less than 25 yr and women at any age at risk for sexually transmitted diseases is recommended. Risk factors include a new sexual partner, more than one sexual partner, individuals not in a mutually monogamous relationship, a previous or concurrent sexually transmitted disease, or working in the sex industry for profit. Screening interval is determined by any new risk for exposure since the last negative screening. The CDC recommends CT screening for all pregnant women under the age of 25 and for any pregnant woman over the age of 25 who is at increased risk for acquiring CT. These same pregnant women should be screened again during the third trimester.

LABORATORY TESTS

- Nucleic acid amplification tests (NAATs) are the gold standard for diagnosis because of their high sensitivity and specificity for the detection of CT infection. The FDA has approved these tests for male and female urine collection and for provider-collected endocervical, vaginal, and male urethral specimens.
- Rectal and pharyngeal collection site specimens may be taken from individuals who engage in receptive anal and oral intercourse, but these collection sites are not FDA approved.
- For best results, urine collection should be completed with a first-void urine sample.
- Self-collected vaginal swab samples for women have the same sensitivity and specificity as provider-collected samples.
- The same specimen can be used to test for chlamydia and gonorrhea.
- Sexual partners of a person testing positive for CT infection should be treated if they had sexual contact with that individual within 60 days prior to onset of symptoms or CT diagnosis.
- Microscopy should not be used for chlamydia diagnosis; however, greater than 10 white

TABLE 1 Clinical Characteristics of Common *Chlamydia trachomatis* Infections

	Infection	Symptoms and Signs	Presumptive Diagnosis	Definitive Diagnosis	Treatment
Men	Nongonococcal urethritis	Urethral discharge, dysuria	Urethral leukocytosis; no gonococci seen	Urine or urethral NAAT	Azithromycin, 1 g PO (single dose) *Or* Doxycycline, 100 mg PO bid, for 7 days
	Epididymitis	Unilateral epididymal tenderness, swelling; pain; fever, presence of NGU	Urine or urethral NAAT	Urethral leukocytosis; pyuria on urinalysis	STI likely: Ceftriaxone 250 mg IM plus doxycycline, 100 mg PO bid, for 10 days *History of insertive anal intercourse:* Ceftriaxone, 250 mg IM, plus levofloxacin, 500 mg bid for 10 days
	Proctitis (non-LGV)	Rectal pain, discharge and bleeding; history of receptive anal intercourse	≥1 PMN/OIF on rectal Gram stain; no gonococci seen	Urine or urethral NAAT; rectal culture or NAAT	Doxycycline, 100 mg PO bid, for 7 days
	LGV	Painful, tender inguinal lymphadenopathy, fever	"Groove sign"	Urine, urethral, lymph node or rectal NAAT; rectal or lymph node culture; LGV-specific testing if available	Doxycycline, 100 mg PO bid, for 21 days
	LGV proctitis	Rectal pain, discharge, and bleeding in MSM; absence of inguinal lymphadenopathy	≥1 PMN/OIF on rectal Gram stain; no gonococci seen	Urine, urethral, or rectal NAAT; rectal culture; LGV-specific testing if available	Doxycycline, 100 mg PO bid, for 21 days
	Conjunctivitis	Ocular pain, redness, discharge; simultaneous genital infection	Gram stain of conjunctival swab negative for bacterial pathogens; PMNs on smear	Rectal culture or NAAT; NAAT of conjunctivae	Azithromycin, 1 g PO (single dose) *Or* Doxycycline, 100 mg PO bid, for 7 days
Women	Cervicitis	Mucopurulent cervical discharge; ectopy, easily induced bleeding	≥20 PMN/OIF on cervical Gram stain	Urine or cervical NAAT	Azithromycin, 1 g PO (single dose) *Or* Doxycycline, 100 mg PO bid, for 7 days
	Urethritis	Dysuria, frequency; no hematuria	Pyuria on UA; negative urine Gram stain and culture	Urine, cervical, or urethral NAAT	Azithromycin, 1 g PO (single dose) *Or* Doxycycline, 100 mg PO bid for 7 days
	Pelvic inflammatory disease	Lower abdominal pain, adnexal pain, cervical motion tenderness	Evidence of mucopurulent cervicitis	Urine or cervical NAAT	Outpatient: Ceftriaxone 250 mg IM as a single dose, plus doxycycline 100 mg PO bid for 14 days, with or without metronidazole, 500 mg PO bid for 14 days
Adults	Conjunctivitis	Ocular pain, redness, discharge; simultaneous genital infection	Gram stain of conjunctival swab negative for bacterial pathogens; PMNs on smear	DFA or NAAT on conjunctival swab	Azithromycin, 1 g PO (single dose) *Or* Doxycycline, 100 mg PO bid for 7 days
Newborns	Conjunctivitis	Ocular pain, redness, discharge; simultaneous genital infection	Gram stain of conjunctival swab negative for bacterial pathogens; PMNs on smear	DFA or NAAT on conjunctival swab; vagina, rectum, pharynx also often positive	Erythromycin base 50 mg/kg/day, orally divided into four doses daily for 14 days; evaluate and treat parents as well
	Pneumonia	Staccato cough, tachypnea, hyperinflation	Diffuse interstitial infiltrate, eosinophilia	Nasopharyngeal NAATs or culture; MIF serology (IgM)	Erythromycin base 50 mg/kg/day, orally divided into four doses daily for 14 days; evaluate and treat parents as well

DFA, Direct fluorescent antibody; *IgM*, immunoglobulin M; *LGV*, lymphogranuloma venereum; *MIF,* microimmunofluorescence; *MSM,* men who have sex with men; *NAAT,* nucleic acid amplification test; *NGU*, nongonococcal urethritis; *OIF,* oil immersion field; *PMN*, polymorphonuclear neutrophil; *STI*, sexually transmitted infection; *UA*, urinalysis.

From Bennett JE, Dolin R, Blaser MJ. *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 8, Philadelphia, 2015, Saunders.

blood cells per high-power field with a mucopurulent discharge can be a presumptive diagnosis.

Rx TREATMENT

ACUTE GENERAL Rx

Nongonococcal urethritis, urethritis, cervicitis, conjunctivitis (except for lymphogranuloma venereum):

- Azithromycin 1 g PO × single dose therapy *or*
- Doxycycline 100 mg PO bid for 7 days

Infection in pregnancy:

- Azithromycin 1 gm PO single-dose therapy

Alternatives:

- Erythromycin 500 mg PO qid for 7 days *or*
- Erythromycin ethylsuccinate 800 mg PO qid for 7 days

NOTE: Azithromycin (Pregnancy Risk Category B) is generally considered safe and effective during pregnancy and with lactation. Erythromycin base (Pregnancy Risk Category B) is an acceptable alternate agent for treatment of CT infection in pregnancy. Doxycycline is contraindicated in pregnancy. Erythromycin estolate is contraindicated in pregnancy because of drug-related hepatotoxicity.

FOLLOW-UP:

- Observed single-dose therapy should be offered to individuals for whom compliance is a concern.
- To minimize disease transmission to partners, affected persons should be advised to refrain from sexual intercourse for 7 days after single-dose therapy, until completion of 7-day therapy, or until resolution of symptoms.
- To prevent reinfection, affected individuals should refrain from sexual intercourse until all of their partners have been treated.
- Test of cure to detect treatment failure is not needed.
- Re-collection by NAAT method in less than 3 weeks from treatment can yield a false-positive result due to the sensitivity of this testing method.
- Both men and women treated for chlamydia should be retested at approximately 3 months after treatment to screen for reinfection. If patients do not return to clinical settings within 3 months, rescreen the patient at the next presentation for clinical care.
- Pregnant women with *Chlamydia trachomatis* infection should have a test of cure 3 to 4 weeks after treatment and should then be retested within 3 months.

Refer partners for evaluation and treatment.

RECURRENT AND PERSISTENT URETHRITIS: Retreat noncompliant patients with the above regimens. If patient was initially compliant, recommended regimens: Metronidazole 2 g PO in single dose plus erythromycin base 500 mg PO qid for 7 days or erythromycin ethylsuccinate 800 mg PO qid for 7 days.

REFERRAL

Refer to infectious disease specialist if persistent infection or gynecologist if salpingitis is suspected.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Cervicitis (Related Key Topic)
Urethritis, Gonococcal (Related Key Topic)
Gonorrhea (Related Key Topic)
Urethritis, Nongonococcal (Related Key Topic)
Pelvic Inflammatory Disease (Related Key Topic)

AUTHOR: **Deanna Benner, MSN, APRN**

SUGGESTED READINGS

Centers for Disease Control and Prevention: 2015 Sexually transmitted diseases treatment guidelines, *MMWR Morb Mortal Wkly Rep* 54(3), 2015. www.cdc.gov/std/tg2015/default.htm.

James D et al: *High risk pregnancy: management options*, ed 4, St Louis, 2011, Elsevier, pp 521-542.

U.S. Preventive Services Task Force: Chlamydia and gonorrhea: screening. www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/chlamydia-and-gonorrhea-screening

Cholangiocarcinoma

BASIC INFORMATION

DEFINITION

Cholangiocarcinoma is a cancer that originates from the epithelial lining of bile ducts. Most commonly an adenocarcinoma, this tumor is classified based on its location within the biliary tree as intrahepatic, perihilar, or extrahepatic.

SYNONYM

Bile duct carcinoma

ICD-10CM CODES

C22.1	Intrahepatic bile duct carcinoma
C24.0	Malignant neoplasm of extrahepatic bile duct

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- The incidence rate of cholangiocarcinoma varies by region. A low rate of 1 to 2 per 100,000 occurs in the U.S., while incidence peaks at 80 per 100,000 in Thailand.
- Incidence rate of intrahepatic cholangiocarcinoma appears to be increasing.
- Higher incidence in Hispanic and Asian populations.

PREDOMINANT SEX AND AGE:

- Slightly more common in men
- Most often diagnosed between 50 and 70 yr of age
- Patients with primary sclerosing cholangitis (PSC) can present as early as 30 yr old

RISK FACTORS:

- PSC causes inflammation of the bile ducts leading to fibrosis and stricturing of the biliary tree. PSC is the most common risk factor for development of cholangiocarcinoma, with a lifetime risk of up to 15%.
- Other risk factors include infection with hepatitis B and C, liver cirrhosis, chronic hepatolithiasis, choledochal cysts, and parasitic infections of the liver.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- With early-stage cholangiocarcinoma, the patient may be completely asymptomatic, and diagnosis is made incidentally on imaging or during the workup for elevation of liver enzymes.
- Later-stage cholangiocarcinoma may present as biliary obstruction.
- The clinical presentation is also dependent on the location of the tumor. Cholangiocarcinoma involving the intrahepatic ducts tends to cause nonspecific symptoms of dull, aching right upper quadrant pain and weight loss. A tumor of the extrahepatic ducts most often causes symptoms of biliary obstruction including jaundice, pale stools, and dark urine.
- Findings on physical examination may include jaundice, pain on palpation of the right upper quadrant, hepatomegaly, and fever.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes other conditions that may cause right upper quadrant pain, fever, and symptoms of biliary obstruction or those that present with a mass on imaging.

- Primary sclerosing cholangitis
- Choledocholithiasis
- Acute cholangitis
- Liver metastases
- Pancreatic head cancer

WORKUP

Fig. E1 describes an algorithm for the diagnosis of intrahepatic cholangiocarcinoma. The approach to the diagnosis of perihilar cholangiocarcinoma is summarized in Fig. E2. The Bismuth-Corlette classification of cholangiocarcinoma based on location is illustrated in Fig E3. Staging of cholangiocarcinoma is described in Table E1.

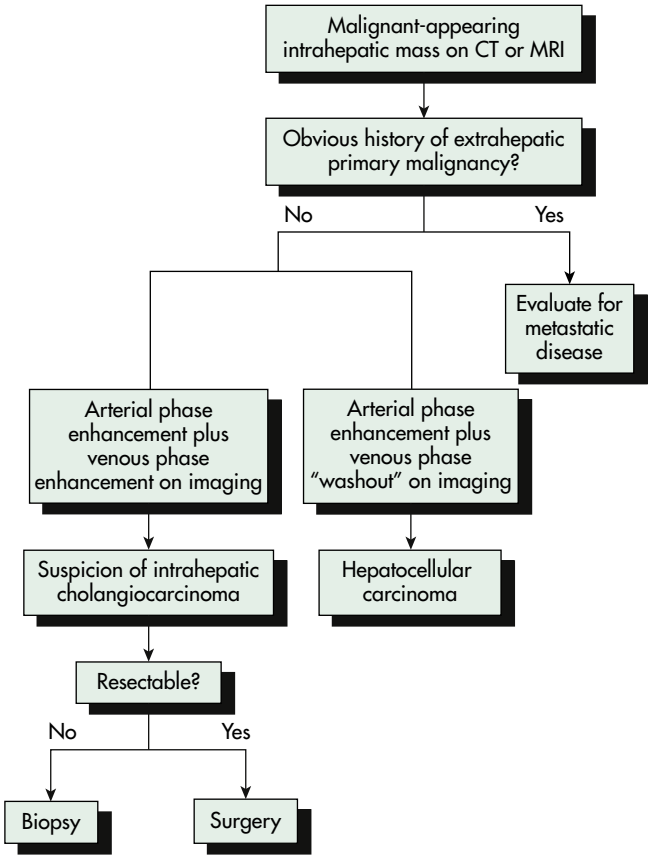

FIG. E1 Algorithm for the diagnosis of intrahepatic cholangiocarcinoma. In cases of an intrahepatic mass lesion and in the absence of known extrahepatic primary malignancy, dynamic imaging with either computed tomography *(CT)* or magnetic resonance image *(MRI)* of the liver should be performed. Contrast enhancement throughout the arterial phase with "washout" in the portal venous phase indicates a hepatocellular carcinoma. Contrast enhancement throughout the arterial and portal venous phases should raise the suspicion of an intrahepatic cholangiocarcinoma; in such cases, the resectability of the tumor should be determined. If the lesion is deemed resectable, the patient should be referred for surgical resection without biopsy. If an intrahepatic cholangiocarcinoma is deemed unresectable, a biopsy should be performed to confirm the diagnosis and guide appropriate treatment. (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.)

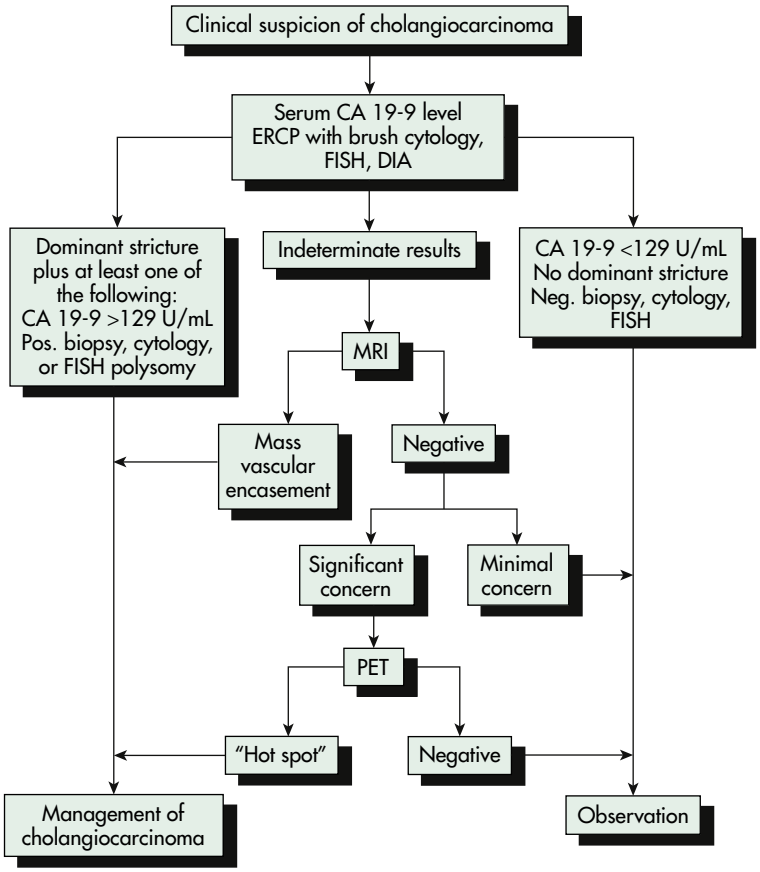

FIG. E2 Algorithm for the diagnosis of perihilar cholangiocarcinoma. In cases of clinically suspected perihilar cholangiocarcinoma, a serum CA 19-9 level, ERCP, and conventional as well as molecular cytologic analysis of endoscopically obtained biliary brushings of malignant-appearing areas should be performed. If the results of these tests are normal or negative, close follow-up of the patient is recommended. Management of cholangiocarcinoma should be prompted by identification of a dominant stricture, a serum CA 19-9 level above 129 U/ml, or a biopsy or cytology result that is positive for carcinoma or polysomy. In indeterminate cases, gadolinium-enhanced magnetic resonance image *(MRI)* of the liver is recommended. If a mass lesion or vascular encasement is identified, management of cholangiocarcinoma should be initiated. If the MRI study is negative but clinical concern about cholangiocarcinoma persists, PET can be performed. If "hot spots" are identified on PET (positive result), treatment for cholangiocarcinoma should be initiated. If the result of the PET scan is negative, close follow-up of the patient is recommended. If MRI is negative and cholangiocarcinoma is considered unlikely, the patient can be followed expectantly. *DIA,* Digital image analysis; *ERCP,* endoscopic retrograde cholangiopancreatography; *FISH,* fluorescence in situ hybridization; *neg.,* negative; *PET,* positron emission tomography; *pos.,* positive. (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.)

LABORATORY TESTS

- Liver enzymes
- INR
- Bilirubin

Blood work may reveal an "obstructive pattern" with predominant elevation of alkaline phosphatase and bilirubin.

Tumor markers:

- CEA
- CA19-9

It is important to note that these tumor markers may be elevated even in the setting of benign inflammation of the biliary tree, for example, during an episode of acute cholangitis. These markers are neither sensitive nor specific for cholangiocarcinoma, but if they are elevated at the time of diagnosis, they may be helpful in tracking response to therapy or in monitoring for disease recurrence.

IMAGING STUDIES

Abdominal ultrasound (Fig. E4):

- Initial test of choice in patients presenting with nonspecific symptoms of obstruction or elevated liver enzymes.

CT scan/magnetic resonance cholangiopancreatography (MRCP):

- Improved visualization of the biliary tree to allow for identification of the tumor, level of obstruction, and extent of disease.

Endoscopic retrograde cholangiopancreatography (ERCP) (Fig. E5):

- Can be used to obtain brushings or biopsies of the biliary tree, but diagnostic yield is poor (35% to 86%), and there is a risk of cholangitis in patients with significant obstruction of bile drainage.

Endoscopic ultrasound (EUS):

- Allows local ultrasound visualization of tumor extent and regional lymphadenopathy, as well as diagnostic fine-needle aspiration of distal biliary duct tumors and involved lymph nodes.

Rx TREATMENT

ACUTE GENERAL Rx

- The only curative treatment option for cholangiocarcinoma is surgical extirpation. Eligibility for surgical resection with curative intent is based both on the location of the tumor and the stage of disease. Box E1 summarizes criteria for unresectability of perihilar cholangiocarcinoma.
- Surgical approaches include partial liver resection, pancreaticoduodenectomy, pancreaticojejunostomy, or even liver transplantation in carefully selected patients.

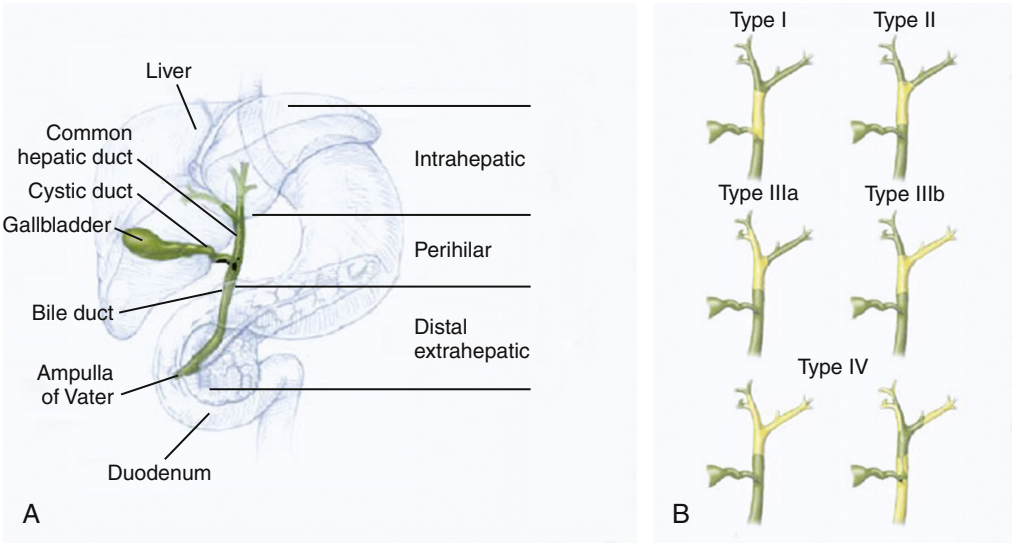

FIG. E3 Classification of cholangiocarcinoma. A, Anatomic classification of intrahepatic, perihilar, and extrahepatic cholangiocarcinoma. **B,** Bismuth-Corlette classification of hilar cholangiocarcinoma as types I to IV. Tumor is depicted in yellow and normal bile ducts in green. (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.)

TABLE E1 TNM and American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) Staging Systems for Intrahepatic Cholangiocarcinoma

TNM Stage	Criteria
T_x	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_{is}	Carcinoma in situ (intraductal tumor)
T_1	Solitary tumor without vascular invasion
T_{2a}	Solitary tumor with vascular invasion
T_{2b}	Multiple tumors, with or without vascular invasion
T_3	Tumor perforating the visceral peritoneum or involving the local extrahepatic structures by direct invasion
T_4	Tumor with periductal invasion
N_x	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastases
N_1	Regional lymph node metastases present
M_0	No distant metastases
M_1	Distant metastases

AJCC/UICC Stage	Tumor	Node	Metastasis
0	T_{is}	N_0	M_0
I	T_1	N_0	M_0
II	T_2	N_0	M_0
III	T_3	N_0	M_0
IV A	T_4	N_0	M_0
	Any T	N_1	M_0
IV B	Any T	Any N	M_1

TNM, Tumor, node, metastasis.
From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.

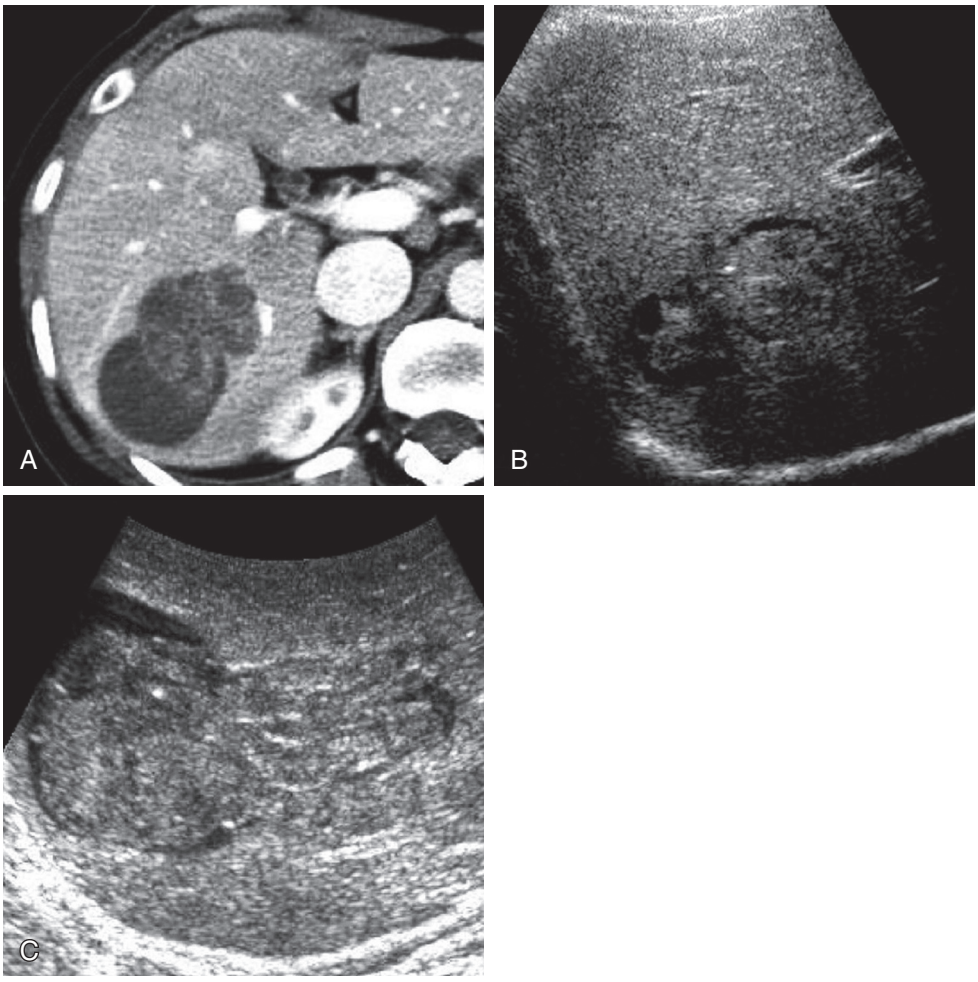

FIG. E4 Intraductal intrahepatic cholangiocarcinoma. A, Computed tomography scan, and **B,** ultrasound view, show a solid and cystic mass in the right lobe of the liver. **C,** Intraoperative sonogram demonstrates the mass to lie entirely within an extremely dilated duct. Low-grade cholangiocarcinoma was found at pathologic examination. (From Rumack CM et al: *Diagnostic ultrasound*, ed 4, Philadelphia, 2011, Mosby.)

- Adjuvant chemotherapy, gemcitabine and cisplatin, has been shown to reduce mortality in patients with both positive margins post-resection and/or involved lymph nodes.
- The use of adjuvant radiation remains an area of controversy, but there is evidence of improved survival in inoperable patients with localized disease.
- In the setting of biliary obstruction, stenting via ERCP or percutaneous drain insertion should be performed to facilitate bile flow and avoid stasis.

DISPOSITION

- Surveillance imaging for recurrence is recommended every 6 months for a total of 2 yr.
- Recurrence can occur locally or as metastatic disease, most commonly to liver, lung, or peritoneum.
- Five-yr survival rates vary between 15% and 60% based on the stage of disease. Unfortunately, even those patients with node-negative disease who undergo resection with curative intent have a high rate of disease recurrence.

REFERRAL

Referral should be made to a hepatobiliary surgeon for consideration of surgical resection and to a medical oncologist for possible adjuvant chemotherapy.

RELATED CONTENT

Primary Sclerosing Cholangitis (Related Key Topic)

AUTHORS: **Suqing Li, MD,** and **Talia Zenlea, MD**

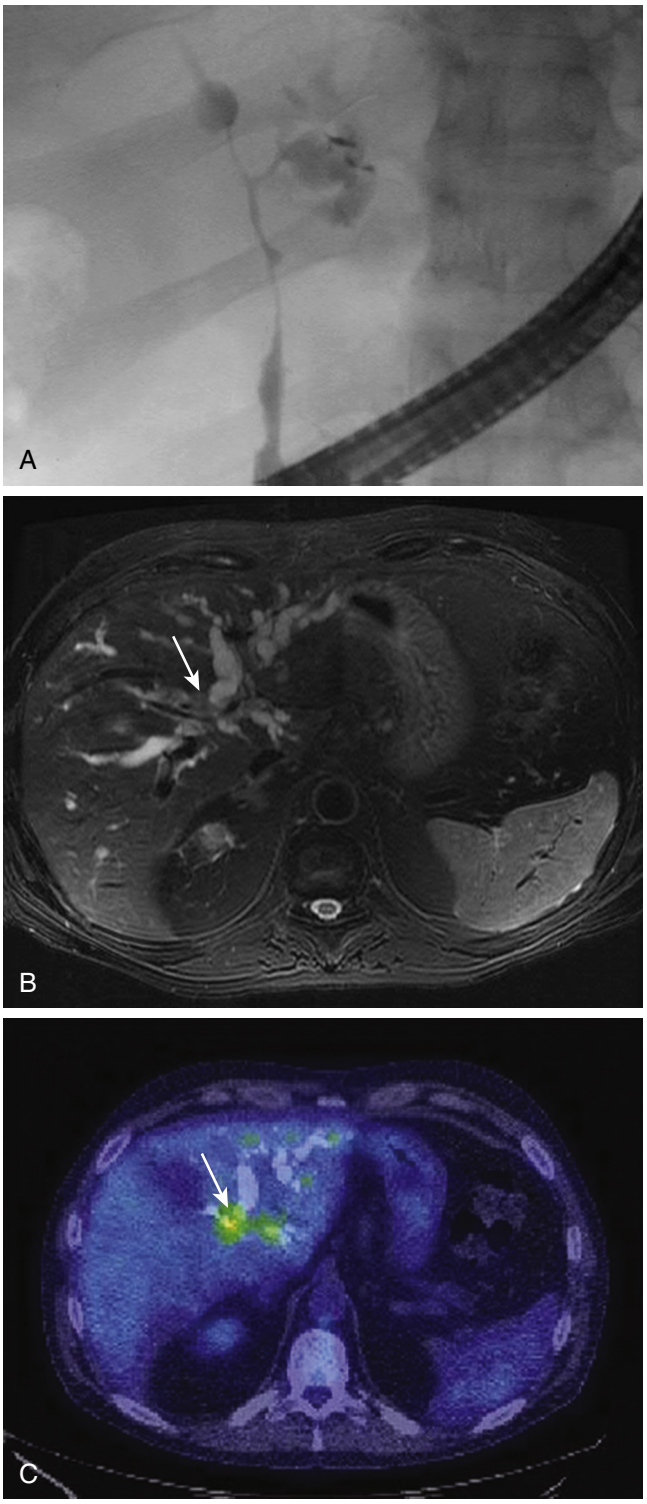

FIG. E5 Imaging of extrahepatic cholangiocarcinoma. A, Film from endoscopic retrograde cholangiography in a patient with perihilar cholangiocarcinoma demonstrating dominant strictures of the biliary tract consistent with Bismuth-Corlette type IV. **B,** Gadolinium-enhanced magnetic resonance image with ferumoxide in the same patient. The *arrow* points to the biliary tumor seen on a T2-weighted image. **C,** Positron emission tomography/computed tomography scan of the same patient. The biliary tumor is seen as an enhancing region *(arrow)*. (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.)

BOX E1 Criteria for Unresectability of Perihilar Cholangiocarcinoma

Atrophy of one liver lobe with encasement of the contralateral portal vein branch
Atrophy of one liver lobe with contralateral secondary biliary radical involvement
Bilateral portal vein branch encasement
Bilateral hepatic artery encasement
Distant lymph node metastases
Hilar cholangiocarcinoma, Bismuth-Corlette type IV
Intrahepatic or distant metastases
Primary sclerosing cholangitis
Significant comorbid conditions

From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.

SUGGESTED READINGS

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Onda S et al: EUS-guided FNA for biliary disease as first-line modality to obtain histological evidence, *Therap Adv Gastroenterol* 9:302, 2016.

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Valle JW et al: Biliary cancer: ESMO clinical practice guidelines, *Ann Oncol* 27(Suppl 5):v28-v37, 2016.

BASIC INFORMATION

DEFINITION

Cholangitis refers to an inflammation and/or infection of the hepatic and common bile ducts associated with obstruction of the common bile duct.

SYNONYMS

Biliary sepsis
Ascending cholangitis
Suppurative cholangitis

ICD-10CM CODE
K83.0 Cholangitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Complicates approximately 1% of cases of cholelithiasis
PEAK INCIDENCE: Seventh decade
PREVALENCE (IN U.S.): 2 cases/1000 hospital admissions
PREDOMINANT SEX:
- Females, for cholangitis secondary to gallstones
- Males, for cholangitis secondary to malignant obstruction and HIV infection

PREDOMINANT AGE: Seventh decade and older; unusual <50 yr of age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usually acute onset of fever, abdominal pain (RUQ), and jaundice (Charcot triad)
- All signs and symptoms in only 50% to 85% of patients
- Often, dark coloration of the urine resulting from bilirubinuria
- Complications:
  1. Bacteremia (50%) and septic shock
  2. Hepatic abscess and pancreatitis

ETIOLOGY

Obstruction of the common bile duct causing rapid proliferation of bacteria in the biliary tree
- Most common cause of common bile duct obstruction: Stones, usually migrated from the gallbladder
- Other causes: Prior biliary tract surgery with secondary stenosis, tumor (usually arising from the pancreas or biliary tree), and parasitic infections from *Ascaris lumbricoides* or *Fasciola hepatica*
- Iatrogenic after contamination of an obstructed biliary tree by endoscopic retrograde cholangiopancreatoscopy (ERCP) or percutaneous transhepatic cholangiography (PTC)
- Primary sclerosing cholangitis (PSC)
- HIV-associated sclerosing cholangitis: Associated with infection by CMV, *Cryptosporidium,* Microsporida, and *Mycobacterium avium* complex

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Biliary colic
- Acute cholecystitis
- Liver abscess
- Peptic ulcer disease (PUD)
- Pancreatitis
- Intestinal obstruction
- Right kidney stone
- Hepatitis
- Pyelonephritis

WORKUP

- Blood cultures
- CBC
- Liver function tests

LABORATORY TESTS

- Usually, elevated WBC count with a predominance of polymorphonuclear forms
- Elevated alkaline phosphatase and bilirubin in chronic obstruction
- Elevated transaminases in acute obstruction
- Positive blood cultures in 50% of cases, typically with enteric gram-negative aerobes (e.g., *Escherichia coli*, *Klebsiella pneumoniae*), enterococci, or anaerobes

IMAGING STUDIES

- Ultrasound:
  1. Allows visualization of the gallbladder and bile ducts to differentiate extrahepatic obstruction from intrahepatic cholestasis
  2. Insensitive but specific for visualization of common duct stones
- CT scan:
  1. Less accurate for gallstones
  2. More sensitive than ultrasound for visualization of the distal part of the common bile duct
  3. Also allows better definition of neoplasm
- ERCP:
  1. Confirms obstruction and its level
  2. Allows collection of specimens for culture and cytology
  3. Indicated for diagnosis if ultrasound and CT scan are inconclusive
  4. May be indicated in therapy (see "Treatment")

TREATMENT

NONPHARMACOLOGIC THERAPY

Biliary decompression:
- May be urgent in severely ill patients or those unresponsive to medical therapy within 12 to 24 hr
- May also be performed semielectively in patients who respond
- Options:
  1. ERCP with or without sphincterotomy or placement of a draining stent
  2. Percutaneous transhepatic biliary drainage for the acutely ill patient who is a poor surgical candidate
  3. Recently, endoscopic ultrasound–guided biliary drainage has been proven as an alternative to percutaneous transhepatic biliary drainage in specialized centers when ERCP fails or is not available
  4. Surgical exploration of the common bile duct

ACUTE GENERAL Rx

- Nothing by mouth
- Intravenous hydration
- Broad-spectrum antibiotics directed at gram-negative enteric organisms, anaerobes, and enterococcus such as carbapenems (meropenem: 1 g q8h or imipenem: 500 mg IV q6h if life threatening), piperacillin/tazobactam: 3.375 or 4.5 g IV q6h, or ampicillin-sulbactam, or ticarcillin-clavulanate; if infection is nosocomial, post-ERCP, or the patient is in shock, broaden antibiotic coverage
- Fig 1 illustrates a clinical algorithm for management of acute cholangitis

CHRONIC Rx

Repeated decompression may be necessary, particularly when obstruction is related to neoplasm.

DISPOSITION

Excellent prognosis if obstruction is amenable to definitive surgical therapy; otherwise relapses are common.

REFERRAL

- To biliary endoscopist if obstruction is from stones or a stent needs to be placed
- To interventional radiologist if external drainage is necessary
- To a general surgeon in all other cases
- To an infectious disease specialist if blood cultures are positive or the patient is in shock or otherwise severely ill

PEARLS & CONSIDERATIONS

- Cholangitis is a life-threatening form of intra-abdominal sepsis, though it may appear to be rather innocuous at its onset.
- Antibiotics alone will not resolve cholangitis in the presence of biliary obstruction, because high intrabiliary pressures prevent antibiotic delivery. Decompression and drainage of the biliary tract to alleviate the obstruction with antimicrobial therapy is the therapy of choice.

SUGGESTED READING

Available at ExpertConsult.com

AUTHORS: **Glenn G. Fort, MD, MPH,** and **Tanya Ali, MD**

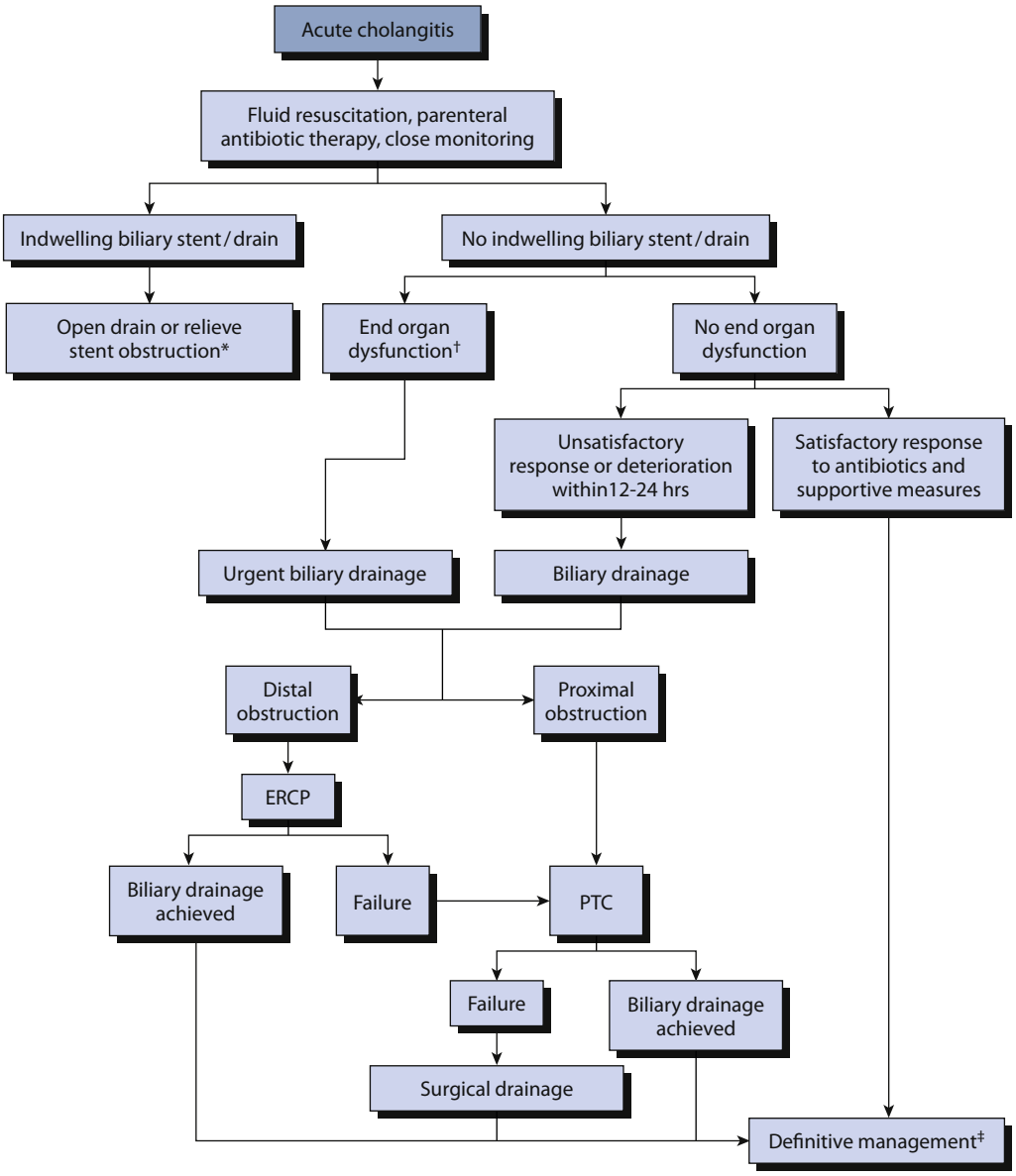

FIG. 1 Management algorithm for patients with acute cholangitis. Dotted lines represent optional progression to EUS biliary decompression; however, the priority is prompt biliary drainage, and some patients may require surgical drainage without attempted EUS biliary decompression. *ERCP*, Endoscopic retrograde cholangiopancreatography; *EUS*, endoscopic ultrasound; *PTC*, percutaneous transhepatic cholangiography. (From Cameron JL, Cameron AM: *Surgical Therapy*, ed 12, Philadelphia, 2017, Elsevier.)

SUGGESTED READING

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BASIC INFORMATION

DEFINITION

Cholecystitis is acute or chronic inflammation of the gallbladder generally caused by gallstones (>95% of cases).

SYNONYM

Gallbladder attack

ICD-10CM CODES	
K81.9	Acute cholecystitis
K80.00	Calculus of gallbladder with acute cholecystitis without obstruction
K81.9	Cholecystitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Acute cholecystitis occurs most commonly in women during the fifth and sixth decades. Approximately 120,000 cholecystectomies are performed for acute cholecystitis annually in the U.S.
- The incidence of gallstones is 0.6% in the general population and much higher in certain ethnic groups (>75% of Native Americans by age 60 yr). Most patients with gallstones are asymptomatic. Of such patients, biliary colic develops in 1% to 4% annually.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain and tenderness in the right hypochondrium or epigastrium; pain possibly radiating to the infrascapular region
- Palpation of the right upper quadrant (RUQ) eliciting marked tenderness and stoppage of inspired breath (Murphy sign)
- Guarding
- Fever (33%)
- Jaundice (25% to 50% of patients)
- Palpable gallbladder (20% of cases)
- Nausea and vomiting (>70% of patients)
- Fever and chills (>25% of patients)
- Medical history often revealing ingestion of large, fatty meals before onset of pain in the epigastrium and RUQ

ETIOLOGY

- Gallstones (>95% of cases)
- Ischemic damage to the gallbladder, critically ill patient (acalculous cholecystitis)
- Infectious agents, especially in patients with AIDS (cytomegalovirus, Cryptosporidium)
- Strictures of the bile duct
- Neoplasms, primary or metastatic
- Risk factors for cholelithiasis include age, obesity, female sex, rapid weight loss, ethnicity/race (Native American), use of contraceptives, pregnancy, diabetes mellitus, hemolysis, total parenteral nutrition, biliary parasites

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hepatic: Hepatitis, abscess, hepatic congestion, neoplasm, trauma
- Biliary: Neoplasm, stricture, sphincter of Oddi dysfunction
- Gastric: Pelvic ulcer disease, neoplasm, alcoholic gastritis, hiatal hernia, non-ulcer dyspepsia
- Pancreatic: Pancreatitis, neoplasm, stone in the pancreatic duct or ampulla
- Renal: Calculi, infection, inflammation, neoplasm, ruptured kidney
- Pulmonary: Pneumonia, pulmonary infarction, right-sided pleurisy
- Intestinal: Retrocecal appendicitis, intestinal obstruction, high fecal impaction, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD)
- Cardiac: Myocardial ischemia (particularly involving the inferior wall), pericarditis
- Cutaneous: Herpes zoster
- Trauma
- Fitz-Hugh–Curtis syndrome (perihepatitis), ruptured ectopic pregnancy
- Subphrenic abscess
- Dissecting aneurysm
- Nerve root irritation caused by osteoarthritis of the spine

WORKUP

Workup consists of detailed history and physical examination coupled with laboratory evaluation and imaging studies. No single clinical finding or laboratory test is sufficient to establish or exclude cholecystitis without further testing.

LABORATORY TESTS

- Leukocytosis (12,000 to 20,000) is present in >70% of patients.
- Elevated alkaline phosphatase, ALT, AST, bilirubin; bilirubin elevation >4 mg/dl is unusual and suggests presence of choledocholithiasis.
- Elevated amylase may be present (consider pancreatitis if serum amylase elevation exceeds 500 U).

IMAGING STUDIES

- Ultrasound of the gallbladder (Fig. E1) is the preferred initial test; it will demonstrate the presence of stones and also dilated gallbladder with thickened wall and surrounding edema in patients with acute cholecystitis.
- Nuclear imaging (HIDA scan) (Fig. E2) is useful for diagnosis of cholecystitis when sonogram is inconclusive: Sensitivity and specificity exceed 90% for acute cholecystitis. This test is only reliable when bilirubin is <5 mg/dl. A positive test result (absence of gallbladder filling within 60 min after the administration of tracer) will demonstrate obstruction of the cystic or common hepatic duct; the test will not demonstrate the presence of stones.
- CT scan of abdomen is useful in cases of suspected abscess, neoplasm, or pancreatitis.
- Plain radiograph of the abdomen generally is not useful because <25% of stones are radiopaque.

TREATMENT

NONPHARMACOLOGIC THERAPY

Provide IV hydration; withhold oral feedings.

ACUTE GENERAL Rx

- Laparoscopic (percutaneous) cholecystectomy (PC) is considered the treatment of choice for most patients. The rate of conversion to open cholecystectomy is higher when laparoscopic cholecystectomy (CCY) is performed for acute cholecystitis rather than for uncomplicated cholelithiasis; conservative management with IV fluids and antibiotics (ampicillin-sulbactam 3 g IV q6h or piperacillin-tazobactam 4.5 g IV q8h) may be justified in some high-risk patients to convert an emergency procedure into an elective one with a lower mortality rate.
- Endoscopic retrograde cholangiopancreatography with sphincterectomy and stone extraction can be performed in conjunction with laparoscopic cholecystectomy for patients with choledochal lithiasis; approximately 7% to 15% of patients with cholelithiasis also have stones in the common bile duct.

DISPOSITION

- Prognosis is good; elective laparoscopic cholecystectomy can be performed as outpatient procedure.
- Hospital stay (when necessary) varies from overnight with laparoscopic cholecystectomy to 4 to 7 days with open cholecystectomy.
- Complication rate is approximately 1% (hemorrhage and bile leak) for laparoscopic cholecystectomy and <0.5% (infection) with open cholecystectomy.

REFERRAL

Surgical referral in all patients with acute cholecystitis

PEARLS & CONSIDERATIONS

COMMENTS

- Patients should be instructed that stones may recur in bile ducts.
- Gallbladder aspiration, in which all fluid visualized by ultrasound is aspirated, represents a nonsurgical treatment when patients who are at high operative risk develop acute cholecystitis. Salvage cholecystectomy is reserved for nonresponders.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Gallbladder Attack (Cholecystitis) (Patient Information)
Cholangiocarcinoma (Related Key Topic)
Choledocholithiasis (Related Key Topic)
Cholelithiasis (Related Key Topic)
Cholangitis (Related Key Topic)
Functional Gallbladder Disorder (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

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Baron T et al: Interventional approaches to gallbladder disease, *N Engl J Med* 372:357-365, 2015.

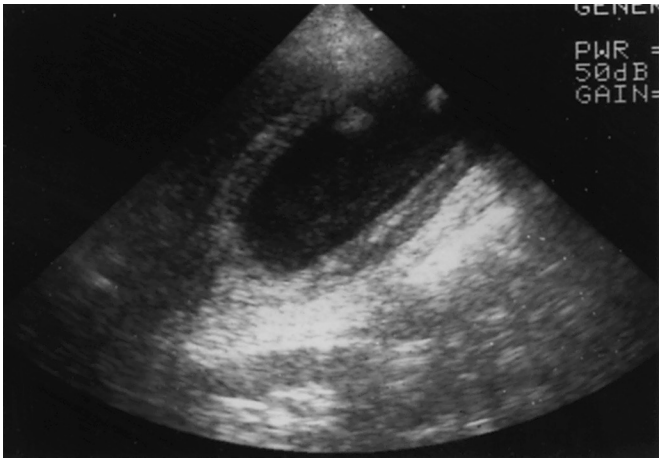

FIG. E1 Thickened gallbladder wall in acute cholecystitis. The gallbladder contains echogenic calculi. (From Grainger RG et al [eds]: *Grainger and Allison's diagnostic radiology,* ed 4, Philadelphia, 2001, Churchill Livingstone.)

FIG. E2 Acute cholecystitis. Following the intravenous administration of 200 MBq (5 mCi) of 99mTc-HIDA [technetium(99m)-hepatobiliary-iminodiacetic acid] and a stimulus of cholecystokinin (CCK), the region of the liver and gallbladder is imaged. Intrahepatic bile ducts are visualized, as is excretion through the common duct into the small bowel. The gallbladder is not seen. This patient had gallstones demonstrated by ultrasound and confirmed at surgery. The pathologic diagnosis was acute cholecystitis. (From Grainger RG et al [eds]: *Grainger and Allison's diagnostic radiology,* ed 4, Philadelphia, 2001, Churchill Livingstone.)

Choledocholithiasis

DEFINITION

Choledocholithiasis is a derivation from the Greek words of *choli* (bile), *docheion* (container), and *lithos* (stone) and refers to the presence of gallstones within the common bile duct (CBD).

SYNONYM

Common bile duct stone(s)

ICD-10CM CODE
K80.50 Calculus of bile duct

EPIDEMIOLOGY & DEMOGRAPHICS

- While the exact incidence and prevalence are unknown, an estimated 10% to 20% of patients are found to have choledocholithiasis at the time of cholecystectomy.
- Passage of gallstones into the CBD occurs in approximately 10% to 15% of those with cholelithiasis, and the incidence is known to increase with age. Approximately 95% of those with choledocholithiasis will also have cholelithiasis.
- Risk factors for gallstone formation include nonmodifiable factors such age, female sex, family history, ethnic background, and genetic predilection, while modifiable factors are centripetal obesity and metabolic syndrome, rapid weight loss, ileal Crohn disease, cirrhosis, total parenteral nutrition, and medications such as estrogen replacement therapy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Uncomplicated choledocholithiasis presents with biliary colic; it is classically described as intense and constant pain in the right upper quadrant or epigastric region, associated with nausea and vomiting.
- Occasionally patients may remain asymptomatic, but resolution of pain more often reflects passage of stone into the bowel.
- Physical examination demonstrates right upper quadrant or epigastric tenderness and occasionally jaundice.
- Courvoisier sign for a palpable gallbladder is more typically associated with malignant obstruction of the CBD, but it has been reported with choledocholithiasis.
- Other clinical findings of fever (Charcot triad), hypotension, and altered mental status (Reynolds pentad) are found only when choledocholithiasis is complicated by acute cholangitis.
- Choledocholithiasis can also be complicated by acute pancreatitis.

ETIOLOGY

- The majority of cases are due to passage of cholesterol stones from the gallbladder into the common bile duct.
- De novo formation of choledocholithiasis (primary choledocholithiasis) is uncommon but is seen among those with increased propensity for pigment stone formation due to chronic recurrent pyogenic cholangitis from trematodes, congenital biliary duct anomalies, dilated or strictured ducts or *MDR3* gene defects causing impairments in biliary phospholipid secretions, or biliary stasis such as from cystic fibrosis.
- Brown pigment stones comprise the majority of pigment stones in the bile duct, often found proximal to biliary stricture and associated with cholangitis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Biliary pain
- Acute cholecystitis
- Sphincter of Oddi dysfunction
- Functional gallbladder disorder
- Malignant obstruction
- Choledochal cyst
- Papillary stenosis
- AIDS-associated cholangiopathy

WORKUP

- The constellation of symptomatic cholelithiasis with elevated liver enzymes should prompt a transabdominal ultrasound (US) of the right upper quadrant to evaluate for a stone in the CBD, which is the most reliable predictor of choledocholithiasis.
- Elevated liver enzymes are 94% sensitive in detecting choledocholithiasis.
- Clinical predictors should be utilized to risk-stratify patients and to inform the next step in management.
- High-risk predictors of choledocholithiasis:
  1. CBD stone seen on US or cross-sectional imaging
  2. Elevated serum bilirubin (>4 mg/dl) with evidence of dilated CBD on imaging
  3. Clinical or biochemical evidence of ascending cholangitis
- Intermediate-risk predictors of choledocholithiasis include abnormal liver biochemistries, age >55 yr and/or a dilated CBD seen on imaging.
- See Fig. 1 for a proposed risk stratification model based on American Society for Gastrointestinal Endoscopy guidelines.

LABORATORY TESTS

- Elevations in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) reflect early biliary obstruction, followed by a disproportionate increase in serum bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT), which are independent predictors of a CBD stone.
- Elevation in ALP is rapid and precedes the rise in bilirubin level, the latter being proportional to the degree of obstruction.
- An isolated and transient increase in alanine transaminase or amylase reflects passage of the gallstone.
- In addition, patients with choledocholithiasis complicated by acute pancreatitis and cholangitis have elevated serum amylase or lipase (>3 times upper limit of normal) and leukocytosis, respectively.

IMAGING STUDIES

- Ultrasound of the gallbladder has a relatively poor sensitivity (22% to 55%) for stone detection but is relied on for CBD dilation, which is associated with choledocholithiasis.
- The finding of CBD dilation >6 mm in patients with an intact gallbladder or >8 mm in patients with prior cholecystectomy is indicative of biliary obstruction. Multiple small gallbladder stones (<5 mm) portend a fourfold higher risk of passage of stones into the CBD.
- Other imaging modalities such as helical CT (Fig. 2), magnetic resonance cholangiopancreatography (MRCP), CT cholangiography, and endoscopic ultrasound (EUS) have improved performance characteristics for CBD stone detection; however, their use as first-line diagnostic tools is contingent on diagnostic uncertainty, patient factors, and availability.
- Either MRCP or EUS should be used in intermediate-risk patients to confirm the diagnosis of choledocholithiasis and prompt further therapeutic management.
- High-risk patients should proceed directly to endoscopic retrograde cholangiopancreatography (ERCP) for diagnosis and treatment.

TREATMENT

ACUTE GENERAL Rx

- Presence of choledocholithiasis warrants treatment.
- The mainstay is removal of CBD stones via ERCP and papillotomy either before or at the time of laparoscopic or open cholecystectomy.
- Failure of ERCP to clear the biliary duct warrants biliary stenting for drainage as a temporary measure in the event of acute cholangitis.
- Subsequent cholecystectomy should optimally be performed within 2 wk of pre-operative ERCP to reduce the risk of recurrence.
- ERCP without subsequent cholecystectomy may be performed in select high-risk patients, but 10% of these patients will require a subsequent cholecystectomy for recurrence.

CHRONIC Rx

Patients with recurrent choledocholithiasis from cholesterol gallstones after cholecystectomy might be considered for chronic treatment with ursodeoxycholic acid to facilitate reduction of cholesterol saturation of bile.

REFERRAL

- Gastroenterology
- General surgery

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Cholangiocarcinoma (Related Key Topic)
Cholelithiasis (Related Key Topic)
Cholecystitis (Related Key Topic)

AUTHORS: **Suqing Li, MD,** and **Talia Zenlea, MD**

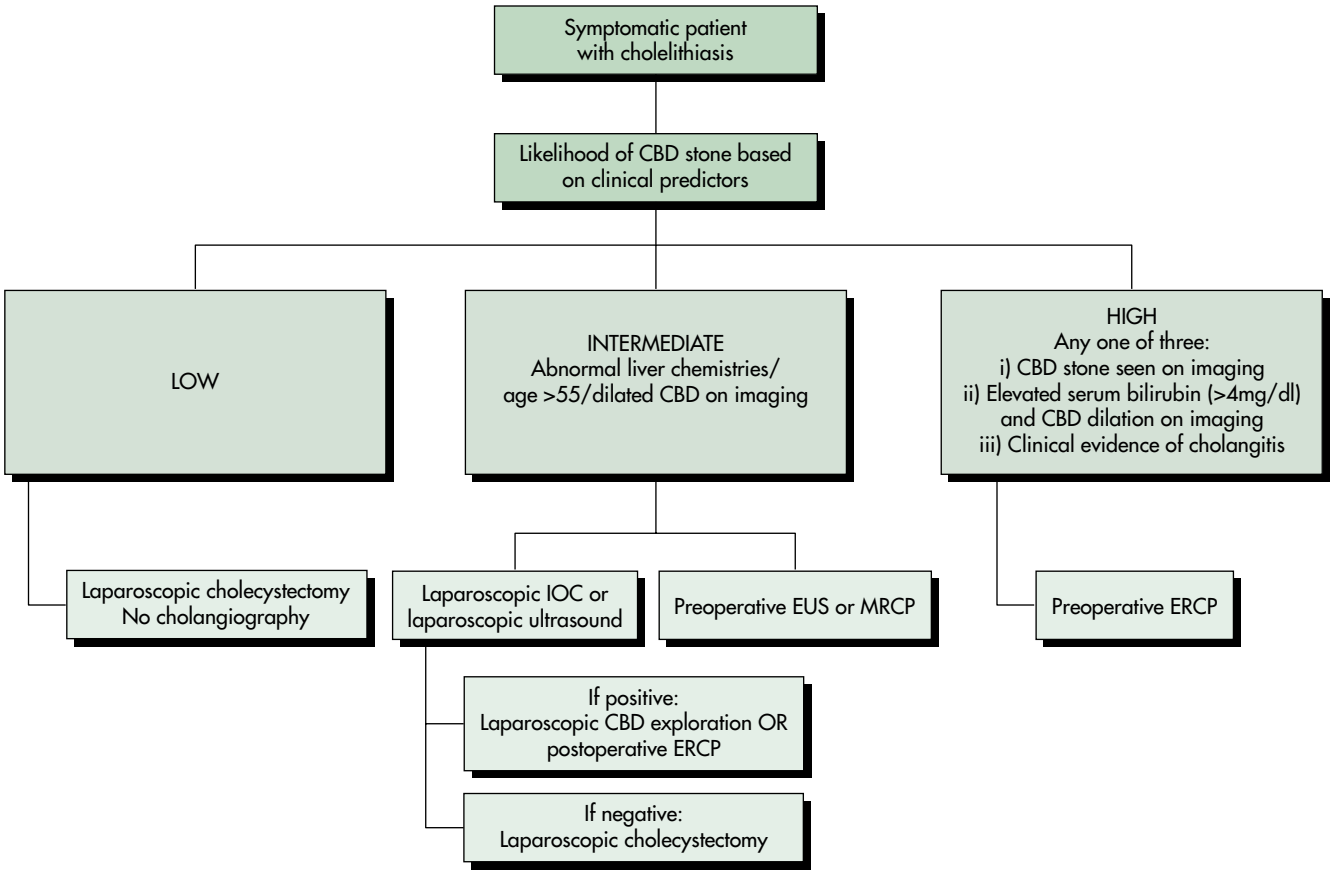

FIG. 1 Algorithm for the management of patients with symptomatic cholelithiasis. *CBD,* Common bile duct; *ERCP,* endoscopic retrograde cholangiopancreatography; *EUS,* endoscopic ultrasound; *IOC,* intraoperative cholangiogram; *MRCP,* magnetic resonance cholangiopancreatography. (Adapted from Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016; Elsevier and Buxbaum J et al: ASGE guideline on the role of endoscopy in the evaluation and management of choledocholithiasis, *Gastrointest Endosc* 89(6):1075-1105, 2019.)

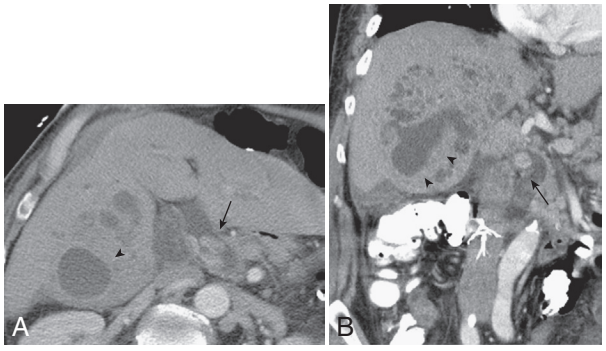

FIG. 2 A 70-year-old male with choledocholithiasis and a hepatic abscess. Axial **(A)** and coronal **(B)** portal venous phase computed tomography images demonstrate large bile duct stones *(arrows)* with a focal intrahepatic fluid collection *(arrowheads)* consistent with the patient's known pyogenic abscess. (From Soto JA, Lucey BC: *Emergency radiology: the requisites,* ed 2, Philadelphia, 2017, Elsevier.)

SUGGESTED READINGS

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Stinton LM, Shaffer EA: Epidemiology of gallbladder disease: Cholelithiasis and cancer, *Gut Liver* 6(2):172-187, 2012.

BASIC INFORMATION

DEFINITION

Cholelithiasis is the presence of stones in the gallbladder

SYNONYM

Gallstones

ICD-10CM CODES

K80.80	Other cholelithiasis without obstruction
K80.81	Other cholelithiasis with obstruction
K91.86	Retained cholelithiasis following cholecystectomy

EPIDEMIOLOGY & DEMOGRAPHICS

- Gallstone disease can be found in 12% of the U.S. population. Of these, 2% to 3% (500,000 to 600,000) are treated with cholecystectomies each yr.
- Annual medical expenditures for gallbladder surgeries in the U.S. exceed $5 billion.
- Incidence of gallbladder disease increases with age. Highest incidence is in the fifth and sixth decades. Predisposing factors for gallstones are female sex, pregnancy, age >40 yr, family history of gallstones, obesity, ileal disease, oral contraceptives, diabetes mellitus, rapid weight loss, estrogen replacement therapy.
- Patients with gallstones have a 20% chance of developing biliary colic or its complications at the end of a 20-yr period. Significant predictors of gallstone-related events are large stone (>10 mm), presence of multiple stones, and female sex.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination is entirely normal unless patient is having biliary colic; 80% of gallstones are asymptomatic.
- Typical symptoms of obstruction of the cystic duct include intermittent, severe, cramping pain affecting the right upper quadrant.
- Pain occurs mostly at night and may radiate to the back or right shoulder. It can last from a few minutes to several hours.
- Symptoms of gallstone disease and its complications are described in Table 1.

ETIOLOGY

- 75% of gallstones contain cholesterol and are usually associated with obesity, female sex, and diabetes mellitus; mixed stones are most common (80%); pure cholesterol stones account for only 10% of stones and are the result of biliary supersaturation due to cholesterol secretion into the gallbladder and accelerated cholesterol nucleation and crystallization.
- 25% of gallstones are pigment stones (bilirubin, calcium, and variable organic material) associated with hemolysis and cirrhosis. These tend to be black-pigmented stones that are refractory to medical therapy.
- 50% of mixed-type stones are radiopaque.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Peptic ulcer disease
- Gastroesophageal reflux disease
- Irritable bowel disease
- Pancreatitis
- Neoplasms
- Nonnuclear dyspepsia
- Inferior wall myocardial infarction
- Hepatic abscess

LABORATORY TESTS

Generally normal unless patient has biliary obstruction (elevated alkaline phosphatase, bilirubin).

IMAGING STUDIES

- Ultrasound of the gallbladder (Fig. E1) will detect small stones and biliary sludge (sensitivity, 95%; specificity, 90%); the presence of dilated gallbladder with thickened wall is suggestive of acute cholecystitis.
- Nuclear imaging (HIDA scan) can confirm acute cholecystitis (>90% accuracy) if gallbladder does not visualize within 4 hr of injection and the radioisotope is excreted in the common bile duct.
- Common bile duct stones can be detected noninvasively by magnetic resonance cholangiopancreatography or invasively by endoscopic retrograde cholangiopancreatography (ERCP) and intraoperative cholangiography.

TREATMENT

NONPHARMACOLOGIC THERAPY

Lifestyle changes (avoidance of diets high in polyunsaturated fats, weight loss in obese patients; however, avoid rapid weight loss)

ACUTE GENERAL Rx

- The management of gallstones is affected by the clinical presentation.
- Asymptomatic patients do not require therapeutic intervention. Proposed criteria for prophylactic cholecystectomy are described in Table 2.
- Surgical intervention is generally the ideal approach for symptomatic patients. Laparoscopic cholecystectomy is preferred over open cholecystectomy because of the shorter recovery period and lower mortality

TABLE 1 Symptoms of Gallstone Disease and Its Complications

Disease	Pathophysiology	Symptoms
Biliary colic	Transient gallstone impaction at the cystic duct or ampulla of Vater	Intermittent RUQ pain associated with nausea or vomiting. Pain in the epigastrium or radiating to the right scapular tip. Episodes last 30 min to several hours with days or months between episodes.
Acute cholecystitis	Inflammation of the gallbladder caused by obstruction of the cystic duct. May occur in the presence or absence of bacterial superinfection	Patients appear ill and cannot take deep breaths. They have constant pain that lasts 30-60 min and worsens with movement. Persistent common bile duct impaction usually promotes vomiting. Physical examination demonstrates RUQ tenderness with voluntary guarding and a positive Murphy sign (arrest of inspiration during deep palpation over the gallbladder).
Emphysematous cholecystitis	Infection with gas-producing bacteria such as *Escherichia coli*, *Clostridium perfringens*, and anaerobic streptococci	Symptoms are similar to those with acute cholecystitis. Gas may be seen on abdominal plain films or CT. Male diabetics are most commonly affected.
Chronic cholecystitis	Persistent inflammation and fibrosis of the gallbladder with poor motor and absorptive function	Patients are usually asymptomatic but may report multiple previous attacks of colic. Porcelain gallbladder develops from chronic inflammation and may progress to carcinoma.
Acalculous cholecystitis	Probably related to biliary stasis in the setting of critical illness and altered gastrointestinal motility	Seen in patients with traumatic injuries, burns, and critical illness, as well as in those receiving total parenteral nutrition. The mortality for this disorder is twice as high as that for acute calculous cholecystitis.
Gallbladder perforation	Stones erode through an inflamed and necrotic gallbladder wall. Stones may travel into the peritoneal cavity or cause adhesions between nearby structures. Bile peritonitis may develop	More than half of patients with gallbladder perforation have fever and a palpable RUQ mass. Mortality in these patients is 30%.

CT, Computed tomography; *RUQ,* right upper quadrant.
From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

rate. Between 5% and 26% of patients undergoing elective laparoscopic cholecystectomy will require conversion to an open procedure. Most common reason is the inability to clearly identify the biliary anatomy.

- Laparoscopic cholecystectomy after endoscopic sphincterectomy is recommended for patients with common bile duct stones and residual gallbladder stones. Where possible, single-stage laparoscopic treatments with removal of duct stones and cholecystectomy during the same procedure are preferable. Percutaneous cholecystectomy is an alternative for patients who are critically ill with gallbladder empyema and sepsis.
- Patients who are not appropriate candidates for surgery because of coexisting illness or patients who refuse surgery can be treated with oral bile salts: Ursodiol or chenodiol. Candidates for oral bile salts are patients with cholesterol stones (radiolucent, noncalcified stones), with a diameter of ≤15 mm and having three or fewer stones. Candidates for medical therapy must have a functioning gallbladder and must have absence of calcifications on CT scans.
- Extracorporeal shock wave lithotripsy (ESWL) is another form of medical therapy. It can be used in patients with stone diameter of ≤3 cm and having three or fewer stones.

TABLE 2 Proposed Criteria for Prophylactic Cholecystectomy

Life expectancy >20 yr
Calculi >2 cm in diameter
Calculi >3 mm and patent cystic duct
Radiopaque calculi
Gallbladder polyps >15 mm
Nonfunctioning or calcified gallbladder ("porcelain" gallbladder)
Women <60 yr
Patients in areas with high prevalence of gallbladder cancer

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

DISPOSITION

- Complicated gallstone events develop in 8% of patients with incidentally discovered gallstones after 17 yr (Shabanzadeh DM et al in Suggested Readings: *Gastroenterology* 150:156, 2016).
- After ESWL, stones recur in approximately 20% of patients after 4 yr.
- Patients with at least one gallstone <5 mm in diameter have a greater than fourfold increased risk of presenting with acute biliary pancreatitis. A policy of watchful waiting in such cases is generally warranted.
- A potential serious complication of gallstones is acute cholangitis. ERCP and endoscopic sphincterectomy followed by interval laparoscopic cholecystectomy are effective in acute cholangitis.
- Uncommon complications of gallstone disease are summarized in Table 3.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Gallstones (Patient Information)
Cholecystitis (Related Key Topic)
Choledocholithiasis (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

TABLE 3 Uncommon Complications of Gallstone Disease

Complication	Pathogenesis	Clinical Features	Diagnosis/Treatment
Emphysematous cholecystitis	Secondary infection of the gallbladder wall with gas-forming organisms (*Clostridium welchii, Escherichia coli*, and anaerobic streptococci) More common in older adult diabetic men; can occur without stones	Symptoms and signs similar to those of severe acute cholecystitis	Plain abdominal films may show gas in the gallbladder fossa US and CT are sensitive for confirming gas Treatment is with IV antibiotics, including anaerobic coverage, and early cholecystectomy High morbidity and mortality rates
Cholecystoenteric fistula	Erosion of a (usually large) stone through the gallbladder wall into the adjacent bowel, most often the duodenum, followed in frequency by the hepatic flexure, stomach, and jejunum	Symptoms and signs similar to those of acute cholecystitis, although sometimes a fistula may be clinically silent Stones >25 mm, especially in older adult women, may produce a bowel obstruction, or "gallstone ileus"; the terminal ileum is the most common site of obstruction Gastric outlet obstruction (Bouveret syndrome) may occur rarely	Plain abdominal films may show gas in the biliary tree and/or a small bowel obstruction in gallstone ileus, as well as a stone in the RLQ if the stone is calcified Contrast upper GI series may demonstrate the fistula A fistula from a solitary stone that passes may close spontaneously Cholecystectomy and bowel closure are curative Gallstone ileus requires emergency laparotomy; the diagnosis is often delayed, with a resulting mortality rate of ≈20%
Mirizzi syndrome	An impacted stone in the gallbladder neck or cystic duct, with extrinsic compression of the common hepatic duct from accompanying inflammation or fistula	Jaundice and RUQ pain	ERCP demonstrates dilated intrahepatic ducts and extrinsic compression of the common hepatic duct and possible fistula Preoperative diagnosis is important to guide surgery and minimize the risk of BD injury
Porcelain gallbladder	Intramural calcification of the gallbladder wall, usually in association with stones	No symptoms attributable to the calcified wall per se, but carcinoma of the gallbladder is a late complication in ≈20%	Plain abdominal films or CT show intramural calcification of the gallbladder wall Prophylactic cholecystectomy is indicated to prevent carcinoma

BD, bile duct; *CT,* computed tomography; *ERCP,* endoscopic retrograde cholangiopancreatography; *GI,* gastrointestinal; *IV,* intravenous; *RLQ,* right lower quadrant; *RUQ,* right upper quadrant *US,* ultrasound.
From Feldman M et al: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

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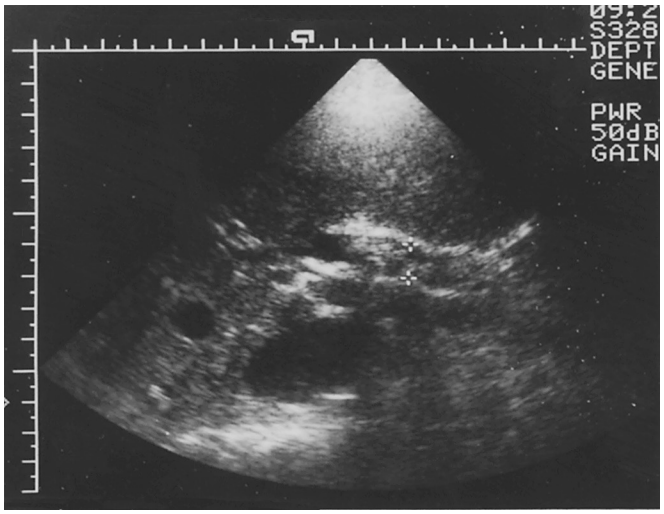

FIG. E1 Calculi in the common bile duct, casting an acoustic shadow. (From Grainger RG et al [eds]: *Grainger and Allison's diagnostic radiology,* ed 4, Philadelphia, 2001, Churchill Livingstone.)

Cholera

BASIC INFORMATION

DEFINITION

Cholera is an acute diarrheal illness caused by toxin-producing strains of *Vibrio cholerae.*

ICD-10CM CODES

A00.0 Cholera due to Vibrio cholerae 01, biovar cholerae
A00.1 Cholera due to Vibrio cholerae 01, biovar eltor
A00.9 Cholera, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Extremely rare. Less than 25 cases have been reported in the United States since 2012.
- Average 6 cases/yr.
- Cholera is endemic in 60 countries. In the world, ~2.9 million cases and 100,000 deaths occur annually.
- Currently epidemic in Yemen due to war conditions.

PREDOMINANT SEX: None

PREDOMINANT AGE: In nonendemic areas, attack rates are equal in all age groups. In epidemic areas, children older than the age of 2 yr are most commonly infected. Neonatal infection: Illness is uncommon before the age of 2 yr, likely because of passive immunity.

PEAK INCIDENCE:

- None in the U.S.
- Summer and fall in endemic areas (Africa, South and Southeast Asia) (before and after rainy season)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Infection may result in asymptomatic illness or a mild diarrhea. The classic illness is described as the abrupt onset of voluminous watery diarrhea, which may lead to severe dehydration, acidosis, shock, and death. Vomiting may occur early in the illness, but fever and abdominal pain are usually absent. The typical "rice water" stools are pale with flecks of mucus and contain no blood. Muscle cramps may be prominent and are the result of loss of fluid and electrolytes. Untreated illness results in hypovolemic shock, and death may occur in hours to days. With adequate fluid and electrolyte repletion, cholera is a self-limited illness that resolves in a few days. The use of antimicrobials can shorten the course of illness.

ETIOLOGY

The organism responsible for this illness is one of several strains of *V. cholerae.* Most infections result from the O1 serotype, the El Tor biotype. In the U.S., one outbreak occurred from the ingestion of illegally imported crab, and sporadic infection has been associated with the consumption of contaminated shellfish in Gulf Coast states. Most cases are seen in returning travelers. Transmission during epidemics is the result of the ingestion of contaminated water and, in some instances, contaminated food. Person-to-person transmission is common in epidemics.

An important outbreak of cholera followed the 2010 earthquake in Haiti, with many cases also in the Dominican Republic (which shares the island of Hispaniola with Haiti). Subsequently, cholera was detected in Cuba, Venezuela, and Florida in travelers from Hispaniola. Interestingly, the strain of cholera was related to the strains of Southeast Asia rather than South America and was possibly introduced by UN peacekeepers from Nepal.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Mild illness may mimic gastroenteritis resulting from a variety of etiologies.
- Sudden, voluminous diarrhea causing marked dehydration is uncommon in other illnesses.

WORKUP

Stool should be sent for culture and microscopy. Treatment should not be delayed while awaiting culture results.

LABORATORY TESTS

- WBC may be elevated, and hemoglobin may be increased as a result of hemoconcentration.
- Elevated blood urea nitrogen (BUN) and creatinine suggests prerenal azotemia. Hypoglycemia may occur. Stool cultures on appropriate media may grow the organism.
- Wet mount of stool under dark field or phase contrast microscopy shows organisms with characteristic darting motility.
- Dipstick tests such as Crystal VC are now available to test for O1 or O139 antigens.

TREATMENT

NONPHARMACOLOGIC THERAPY

The mainstay of therapy is adequate fluid and electrolyte replacement (Table E1). This can usually be achieved using oral rehydration solutions containing salts and glucose. Some patients may require intravenous fluid and electrolyte replacement.

ACUTE GENERAL Rx

- Antimicrobial therapy (Table E2) can decrease shedding of fluid and organisms and can shorten the course of illness:
  1. Doxycycline 300 mg PO single dose *or*
  2. Azithromycin two 500-mg tablets PO as a single dose *or*
  3. Tetracycline 500 mg PO qid × 3 days *or*
  4. Erythromycin 500 mg qid × 3 days
  5. Ciprofloxacin 1 g as a single dose
- For pregnant women: Azithromycin 1 g PO single dose.
- For children: Azithromycin 20 mg/kg PO as a single dose.
- Resistance to sulfamethoxazole and trimethoprim (SMX-TMP) is increasing in travel-associated infections, so SMX-TMP is no longer recommended.
- Zinc and vitamin A supplementation may be helpful in children.
- Susceptibility testing is often available to tailor the choice of antibiotic.

CHRONIC Rx

It is likely that asymptomatic chronic carriers exist; however, because they are difficult to identify and their role in transmission of disease appears to be rather limited, there is no recommendation for treatment of these individuals.

DISPOSITION

The mortality rate of adequately hydrated patients is less than 1%.

REFERRAL

If more than mild illness occurs

REPORTING

In the U.S., all cases of cholera must be reported to the local and state health departments. Bacterial isolates must be sent to the state health department and the CDC.

TABLE E1 Electrolyte Concentration in Cholera Stool and in Fluids Used for Rehydration and Replacement of Stool Losses

	Electrolyte Concentration (mmol/L)				
	Na^+	Cl^-	K^+	HCO_3^-	Osmolality
Cholera Stool					
Adults	130	100	20	44	300[a]
Infants and children	100	90	33	30	300[a]
Hydration Solutions					
WHO oral rehydration	75	65	20	10[b]	170[c]
Intravenous					
Dhaka	133	98	13	48	273
Lactated Ringer solution	130	109	4	28[d]	251
5:4:1[e]	129	97	11	44	281

WHO, World Health Organization.
[a]Osmolality includes unmeasured osmotically active molecules (primarily organic acids) in addition to electrolytes.
[b]As citrate.
[c]From electrolytes only; also contains 75 mmol/L of glucose.
[d]As lactate.
[e]Intravenous solution containing 5 g sodium chloride, 4 g sodium bicarbonate, and 1 g potassium chloride per liter.
(From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.)

TABLE E2 Antimicrobial Therapy of Cholera[a]

Agent	Single Dose	Multiple Dose
Azithromycin	20 mg/kg; maximal dose 1 g	
Erythromycin	Not evaluated	50 mg/kg/day erythromycin divided into 4 doses for 3 days; maximal dose 2 g/day
Doxycycline	2-4 mg/kg; maximal dose 300 mg	
Tetracycline	Not evaluated	50 mg/kg/day divided into 4 doses for 3 days; maximal dose 2 g/day
Ciprofloxacin[b]	20 mg/kg; maximal dose 1 g	30 mg/kg/day divided into 2 doses for 3 days; maximal dose 1 g/day
Trimethoprim-sulfamethoxazole	Not evaluated	10 mg trimethoprim/50 mg sulfamethoxazole/kg/day divided into 2 doses for 5 days; maximal doses 320 mg trimethoprim and 1.6 g sulfamethoxazole daily
Ampicillin	Not evaluated	50 mg/kg/day divided into 4 doses for 3 days; maximal dose 2 g/day
Furazolidone	7 mg/kg; maximal dose 300 mg[c]	5 mg/kg/day divided into 4 doses for 3 days; maximal dose 400 mg/day

Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.

[a]Antimicrobial therapy is an adjunct to fluid therapy for cholera and is not an essential component. It reduces diarrhea volume and duration, however, by approximately 50%. The choice of antimicrobial agent is determined by the susceptibility pattern of local strains of Vibrio cholerae O1 or O139. Resistance to all agents has been reported and is common in some areas.

[b]The fluoroquinolones, such as ciprofloxacin, are only approved for use in children younger than 18 yr in the United States for special indications because of concerns about arthropathy; multidose therapy has not been evaluated systematically in children, and recommendations are extrapolated from experience in adults.

[c]Single-dose therapy with these drugs has not been evaluated systematically in children, and recommendations are extrapolated from experience in adults.

PREVENTION

- A killed oral cholera vaccine (Stanchol) has been available for prevention of cholera outside the U.S. It is administered in a two-dose schedule. However, a recent trial revealed that a single dose of Stanchol was efficacious in older children (≥5 yr of age) and in adults in a setting with a high level of cholera endemicity.
- In 2016 the FDA approved Vaxchora (PaxVax, Inc., Redwood City, CA), a single-dose, oral, live-attenuated cholera vaccine, for protection against *Vibrio cholerae* serogroup 01 in adults 18 to 64 yr old traveling to endemic or epidemic areas who are at high risk of exposure. The vaccine is administered as a single dose at least 10 days before potential exposure. Cost for one dose is $200 to $250. The vaccine should not be given to patients who have taken oral or parenteral antibiotics in the previous 2 wk.

PEARLS & CONSIDERATIONS

COMMENTS

- Vaccination now recommended.
- Recent guidelines from the Advisory Committee for Immunization Practices (ACIP) were published in the May 12, 2017, Morbidity and Mortality Weekly Report (MMWR).
- Lyophilized CVD 103-HgR is now recommended for adults (ages 18 to 64) traveling to areas with endemic or epidemic cholera caused by *V. cholerae* O1.
- Brand name is Vaxchora.

SUMMARY OF FINDINGS

- This is the only vaccine licensed for use in the U.S.
- This is a LIVE, oral, single-dose vaccine.
- Efficacy against severe diarrhea is 90% at 10 days after vaccination, falling to 80% at 3 mo.
- No serious adverse events have been reported.
- The vaccine strain may be shed in the stool for 7 days or more.
- The vaccine is not routinely recommended for travelers who are not visiting areas of active cholera transmission.
- No data currently exists on the safety and effectiveness of lyophilized CVD 103-HgR vaccine in children and teens aged <18 yr or adults aged ≥65 yr and use of vaccine in immunocompromised persons and pregnant and breastfeeding women.

AUTHORS: **Patricia Cristofaro, MD,** and **Glenn G. Fort, MD, MPH**

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BASIC INFORMATION

DEFINITION

Chorea is the term used to describe brief movements that involve contiguous muscle groups. The term comes from the Greek word meaning *dance*.

SYNONYMS

Sydenham chorea
Saint Vitus dance

ICD-10CM CODES

G25.4	Drug-induced chorea
G25.5	Other chorea
I02.0	Rheumatic chorea with heart involvement
I02.9	Rheumatic chorea without heart involvement

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: No published data exist on the incidence of chorea in the U.S.
PREDOMINANT SEX AND AGE: Can affect any age and sex depending on the cause
RISK FACTORS: The most important risk factors are a family history of Huntington disease, exposure to rheumatic fever as a child, or being pregnant with a history of rheumatic fever.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Presentation depends on the underlying cause. Huntington disease (HD) (Fig. E1 and Fig. E2) typically presents with neuropsychiatric symptoms predating choreiform movements. In the case of Sydenham chorea, drug-induced chorea, or chorea gravidarum, hyperkinetic movements involving the hands and face may be noticed first. Nonrhythmic, random, brief, contiguous movement and facial grimacing can be clues to the presence of chorea. Writhing movement of the hands or feet is known as *athetosis*. An enlarged tongue and self-mutilation may accompany chorea in patients with neuroacanthocytosis. Choreiform movements tend to be suppressed during physical examination; look for suppressive techniques such as holding of the face or crossing of the legs.

Chorea involving specific body parts can be a clue to the proper differential diagnosis. For example, chorea involving the forehead muscles is seen in HD. These muscles typically are spared in tardive dyskinesia. Orobuccolingual chorea is seen in tardive dyskinesia, acquired hepatocerebral degeneration, and neuroacanthocytosis. Hemichorea/hemibalism can be seen arising in nonketotic hyperglycemia, polycythemia vera, Sydenham chorea, antiphospholid antibody syndrome, and structural lesions (such as ischemic strokes) affecting the contralateral thalamus or subthalamic nucleus, basal ganglia, or even corona radiata.

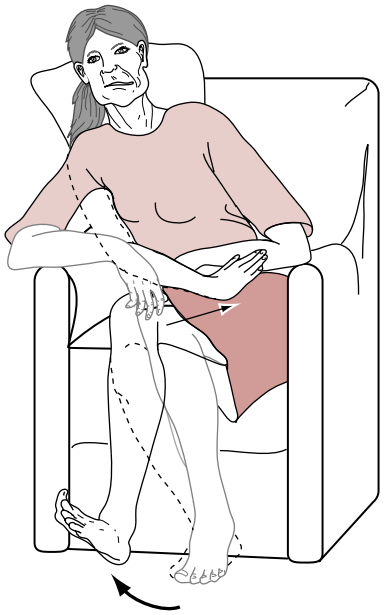

FIG. E1 As in this woman with Huntington disease, chorea consists of intermittent, random involuntary movements, such as brisk contractions in pelvic, trunk, and limb muscles. It also encompasses a mere flick of a finger or wrist, forward jutting of the leg, or shrugging of the shoulder. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.)

ETIOLOGY

- The most common genetic causes of chorea (Table E1) include benign hereditary chorea, Huntington disease, C9orf72 hexanucleotide repeat expansion (first described in families with frontotemporal dementia and ALS but then discovered to have an expanded phenotype include an HD phenocopy in those of European origin), and spinocerebellar ataxia type 17. Other genetic causes are neuroacanthocytosis, dentatorubral-pallidoluysian atrophy (DRPLA), neurodegeneration with brain iron accumulation, and Wilson disease.
- Infectious causes include rheumatic fever causing Sydenham chorea (most common cause of chorea in children), toxoplasmosis of the basal ganglia, and prion disease.
- Drug-induced causes include cocaine, amphetamine, oral contraceptives, tricyclic antidepressants, cimetidine, digoxin, verapamil, baclofen, steroids, antiepileptics, and neuroleptics. Tardive dyskinesia, most typically from dopamine-blocking agents such as neuroleptics or some antiemetics, can result in choreiform movements.
- Hemichorea may be due to antiphospholipid antibody syndrome, systemic lupus erythematosus, or hemichorea-hemiballismus syndrome due to severe nonketotic hyperglycemia, polycythemia vera, or contralateral structural lesion, such as ischemic stroke of the basal ganglia, thalamus, or subthalamic nucleus.
- Acquired causes of chorea are summarized in Table E2.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Huntington disease
- Tardive dyskinesia
- Dystonia
- Tic disorders
- Stroke
- Prion disease
- Rheumatic fever
- Conversion disorder

LABORATORY TESTS

- Complete metabolic panel, including liver function tests
- CBC with peripheral smear looking for acanthocytes
- Serum copper and ceruloplasmin levels
- Thyroid function tests
- Antistreptolysin O antibodies
- Genetic testing for Huntington disease should be done at a comprehensive center involving neurology, psychology, and genetics; complete team support is required before genetic testing is undertaken.

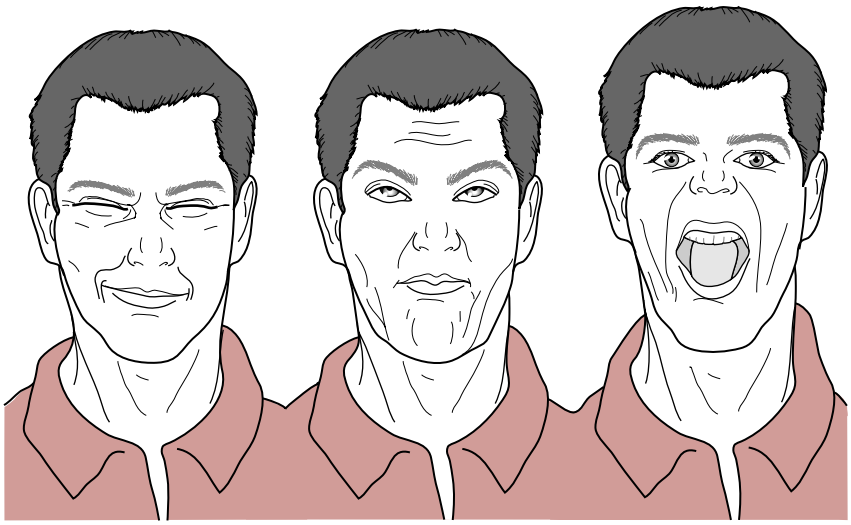

FIG. E2 Huntington disease patients characteristically make unexpected, inappropriate, and incomplete facial expressions. Without provocation, they frown, raise eyebrows, and smirk. Because the tongue frequently protrudes, this chorea occasionally mimics tardive dyskinesia. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists*, ed 8, Philadelphia, 2017, Elsevier.)

TABLE E1 Inherited Causes of Childhood-Onset Chorea

Disease Name	Inheritance	Associated Gene	Age Of Onset	Neurologic Or Psychiatric Manifestations	Systemic Symptoms
Chorea Prominent Feature					
Ataxia- telangiectasia	AR	*ATM*	18 mo-3 yr	Chorea often initial symptom; also have oculomotor apraxia, ataxia, and dystonia	Telangiectasias, increased sinopulmonary infections, increased incidence of cancer
Ataxia with oculomotor apraxia 1 and 2 (especially type 1)	AR	*APTX*	Onset later than ataxia-telangiectasia	Chorea, dystonia, oculomotor apraxia, ataxia, distal sensory axonal neuropathy	
Friedreich ataxia	AR	GAAn in *FRDA*	Over 2 yr, usually teenagers	Gait ataxia, axonal neuropathy, areflexia, extensor plantar response. Can have various movements (tremor, dystonia, chorea, myoclonus). Cases of chorea without cerebellar signs described	Cardiomyopathy, diabetes
GNAO1-related dyskinesias	AR	*GNAO1*	Infancy	Ballismus, chorea, orofacial dyskinesias; can alternatively cause Ohtahara syndrome	
Benign hereditary chorea	AD	*NKX2-1*	Prior to age 5 yr	Chorea; can have myoclonus, learning disability	Thyroid disease, lung disease
Benign hereditary chorea with or without facial "myokymia"	AD	ADCY5	Infancy to late adolescence	Chorea, choreic facial twitches (previously called myokymia); can have myoclonus or dystonia	Some reports of congestive heart failure
PDE10A-associated chorea	AD or AR	*PDE10A*	AD: Childhood AR: Infancy	Chorea, MRI striatal changes in AD form	
Paroxysmal nonkinesigenic dyskinesias	AD	*MR1*	Infancy to 10 yr	Dystonia, chorea, or a combination	
3-methylglutaconic aciduria type III (Costeff syndrome)	AR	*OPA3*	Infancy	Bilateral optic atrophy and chorea early; spasticity, ataxia, and dementia later	
Congenital cataracts, facial dysmorphism, and neuropathy	AR	*CTDP1*	Infancy or childhood	Progressive neuropathy, delayed psychomotor development, mild chorea, hypomyelination, hearing loss	Skeletal abnormalities, dysmorphic face, congenital cataracts, microcornea, hypogonadism
Dentatorubral-pallidoluysian atrophy	AD	CAGn in *atrophin-1*	Mostly adults but seen in a few children	Neurodegeneration, chorea, tics, dementia, seizures, ataxia, psychiatric symptoms	
Huntington chorea/ disease	AD	CAGn in *HTT*	Adolescence to 40s	Younger onset *without* chorea and with parkinsonism, but later, teenagers can manifest chorea, emotional disturbances similar to adult form	
Huntington disease-like-3 (HDL3)	AR	Linked to chromosome 4p15.3	Childhood	Neurodegeneration, chorea, dystonia, ataxia, dementia, seizures	
Idiopathic basal ganglia calcification (IBGC), childhood onset (bilateral striopallidodentate calcinosis)	AR or AD	*SLC20A2* or *PDGFRB*	Infancy to second decade of life	Tetraplegia, chorea, severe cognitive impairment, microcephaly, basal ganglia calcifications	Early death
Choreoacanthocytosis	AR	*VPS13A*	Mean age 20 yr but described in childhood	Psychiatric symptoms (e.g., obsessive-compulsive disorder) can precede neurologic symptoms Neurodegeneration, progressive hyperkinetic movements (limb chorea, orofacial dyskinesias, tics, dystonia), dementia, seizures, cognitive decline, sensorimotor polyneuropathy	Acanthocytosis, increased CK and/or liver transaminases
Spinocerebellar ataxia 1	AD	CAGn in *ATXN1*	Childhood	Neurodegeneration, progressive ataxia, mild cognitive impairment, dysarthria, ophthalmoplegia, optic atrophy, spasticity, dystonia or chorea	

TABLE E1 Inherited Causes of Childhood-Onset Chorea—cont'd

Disease Name	Inheritance	Associated Gene	Age Of Onset	Neurologic Or Psychiatric Manifestations	Systemic Symptoms
Spinocerebellar ataxia 17	AD	CAGn or CAAn in *TBP*	Mostly early adulthood but some teenagers reported	Neurodegeneration, psychiatric symptoms (depression, hallucinations), frontal release signs, chorea, dystonia, and parkinsonism; may have ocular movement abnormalities	
Leigh syndrome	X-linked	*PDHA1*	Infancy or childhood	Neurodegeneration, psychomotor delay, hypotonia and chorea and other hyperkinetic movements can be prominent, progresses to feeding and swallowing defects, nystagmus, ophthalmoplegia, optic atrophy, seizures Lesions in basal ganglia, cerebrum, cerebellum, spinal cord	Lactic acidemia, respiratory failure
Nonketotic hyperglycemia (glycine encephalopathy)	AR	*GLDC, GCST,* or *GCSH*	Neonates/infancy	Hypotonia, severe myoclonic epilepsy, profound cognitive impairment, restlessness	Hyperglycemia
Infantile bilateral striatal necrosis	AR	*NUP62*	Infancy	Developmental regression, intellectual disability, pendular nystagmus, optic atrophy, dysphagia, dystonia, choreoathetosis, spasticity, and severe bilateral striatal atrophy	
Chorea Sometimes Present					
Spinocerebellar ataxia 7	AD	CAGn in *ATXN7*	Childhood	Neurodegenerative mitochondrial disorder, progressive ataxia, dysarthria, dysphagia, optic atrophy, ophthalmoplegia, spasticity, dystonia or chorea may occur	Retinal degeneration
Wilson disease	AR	*ATP7B*	12 yr to early 20s	Dysarthria, drooling, pharyngeal dysmotility, clumsiness, tremor ("wing-beating"), psychiatric symptoms (decline in school, anxiety, depression, psychosis); chorea and dystonia variable	Hepatic dysfunction (asymmetric hepatomegaly, acute transient or fulminant hepatitis), Kayser-Fleischer rings of cornea
Lesch-Nyhan disease	X-linked	*HPRT*	Early childhood	Self-injurious behaviors, intellectual disability, motor disability, pyramidal signs, dystonia superimposed on hypotonia, may have chorea or ballismus, abnormal ocular motility	Hyperuricemia, nephrolithiasis, gout
Pantothenate kinase–associated neurodegeneration (PKAN), classic form	AR	*PANK2*	Prior to 6 yr old (in classic onset)	Progressive motor difficulties, personality changes, cognitive decline, dysarthria, spasticity; later onset of movements (dystonia most common, chorea or tremor may also be present); "eye of the tiger" sign on MRI of brain	Pigmentary retinal degeneration, acanthocytosis
Paroxysmal kinesigenic dyskinesia (PKD)	AD	*PRRT2*	1-20 yr	Short episodes triggered by sudden movement; dystonia is most common movement but can have chorea	
Biopterin-dependent hyperphenylalaninemia (group of disorders)	Usually AR	Multiple genetic causes	Neonate	Initially hypotonic with poor suck, decreased movements, and microcephaly; months later, oculogyric crises, swallowing difficulties, variable hypo- and hyperkinetic movements, seizures, cognitive impairment	Elevated phenylalanine level at birth Autonomic symptoms start several months later
Glutaric aciduria	AR	*GCDH*	First 6 mo	Hypotonia and jitteriness at birth; at 6-18 mo, progressive hyperkinetic movements (dystonia, choreoathetosis); may have seizures	

Continued

TABLE E1 Inherited Causes of Childhood-Onset Chorea—cont'd

Disease Name	Inheritance	Associated Gene	Age Of Onset	Neurologic Or Psychiatric Manifestations	Systemic Symptoms
Alternating hemiplegia of childhood	AR	*ATP1A-3*	Neonate to <18 mo	Transient episodes of alternating hemiplegia/hemiparesis, dystonic attacks, paroxysmal abnormal ocular movements, seizures, episodes of autonomic dysfunction; between attacks, may have ataxia, dystonia, and/or choreoathetosis; most have intellectual disability	
Succinate semialdehyde dehydrogenase deficiency	AR	*ALDH5A*	Infancy to early childhood	Intellectual disability, pronounced language dysfunction, autistic traits, hypotonia, aggression, ataxia, anxiety, hallucinations, can have choreoathetosis	

AD, Autosomal dominant; *AR*, autosomal recessive; *CK*, creatine kinase.
From Kliegman RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

TABLE E2 Acquired Causes of Chorea

Structural-Basal Ganglia Lesions

Stroke
Moyamoya disease
Vascular malformations
Hemorrhage
Choreoathetoid cerebral palsy
Postcardiac transplant (postpump chorea)
Mass lesions (CNS lymphoma, metastatic brain tumors)
Multiple sclerosis plaque
Extrapontine myelinolysis
Trauma

Parainfectious And Autoimmune Disorders

Poststreptococcal Sydenham chorea
Chorea secondary to systemic lupus erythematosus
Chorea secondary to antiphospholipid antibody syndrome
Acute disseminated encephalomyelitis
Anti-NMDA receptor encephalitis
Rasmussen encephalitis
Chorea gravidarum
Postinfectious or postvaccinal encephalitis
Paraneoplastic choreas

Infectious Disorders

HIV encephalopathy
Toxoplasmosis
Cysticercosis
Diphtheria
Bacterial endocarditis
Neurosyphilis
Scarlet fever
Viral encephalitis (mumps, measles, varicella)

Metabolic Or Toxic Disorders

Acute intermittent porphyria
Hyponatremia/hypernatremia
Hypocalcemia
Hyperthyroidism
Hypoparathyroidism
Hepatic/renal failure
Carbon monoxide poisoning
Methyl alcohol
Toluene
Manganese poisoning
Mercury poisoning
Organophosphate poisoning
Pheochromocytoma

Psychogenic Disorders

Drug-Induced Disorders

Dopamine-Blocking Agents (upon withdrawal or as a tardive syndrome)	Phenothiazines Butyrophenones Benzamides
Antiparkinsonian Drugs	L-DOPA Dopamine agonists Anticholinergics
Antiepileptic Drugs	Phenytoin Carbamazepine Valproic acid
Psychostimulants	Amphetamines Methylphenidate Cocaine
Calcium Channel Blockers	Cinnarizine Flunarizine Verapamil
Others	Lithium Baclofen Digoxin Tricyclic antidepressants Cyclosporine Steroids/oral contraceptives Theophylline Propofol

L-DOPA, Levodopa; *NMDA*, N-methyl-D-aspartate.
From Kliegman RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

IMAGING STUDIES

- MRI of the brain with and without contrast
- Echocardiogram if rheumatic fever is suspected

Rx TREATMENT

- Depending on the cause, treatment must be tailored.
- Chorea related to Huntington disease can be treated with tetrabenazine or deutetrabenazine (recently approved by the FDA). Caution must be exercised because the medication puts the patient at significant risk for depression.
- Withdrawing the offending drug can treat drug-induced chorea.
- Some conditions such as SCA3 or neuroacanthocytosis and Huntington disease have a strong neuropsychiatric component and may need to be comanaged with behavioral health specialists.

NONPHARMACOLOGIC THERAPY

- Rehabilitative services such as physical therapy, occupational therapy, and speech therapy are important for genetic forms of chorea.
- Cognitive therapy is now becoming more important in maintaining quality of life in most of these disorders.

ACUTE GENERAL Rx

- Sudden-onset chorea warrants brain imaging to evaluate for stroke.
- MRI of the brain is important for full evaluation of chorea, as it allows for the evaluation of basal ganglia structure. Huntington disease is associated with atrophy of the head of the caudate.
- Subacute onset chorea may represent autoimmune or paraneoplastic syndromes due to a host of autoantibodies including anti-NMDA, anti-Hu, and anti-CRMP-5, anti-Yo, anti-LGI1, anti-CASPR2, anti-GAD65, and anti-IgLON5.

CHRONIC Rx

- Tetrabenazine and deutetrabenazine are the only medications currently approved by the FDA to treat the chorea of Huntington disease. These medications reduce the chorea but do not halt the underlying neurodegenerative process of Huntington disease.
- Deutetrabenazine and valbenazine are the only medications currently approved by the FDA for treating tardive dyskinesia.
- A multidisciplinary approach is useful for treating Huntington disease.

COMPLEMENTARY MEDICINE

There are case reports showing some efficacy in acupuncture for the treatment of temporomandibular chorea in a patient with Sydenham chorea.

DISPOSITION

- Sydenham chorea and chorea gravidarum tend to resolve in a few weeks.
- Huntington disease is a progressive neurodegenerative disorder.
- Tardive dyskinesia due to neuroleptics may be treated medically, and offending agents should be withdrawn, but comanagement with a psychiatrist is imperative to avoid destabilization of the patient and to monitor for depression using TD-specific therapy.

REFERRAL

Refer to a neurologist.

PEARLS & CONSIDERATIONS

COMMENTS

Chorea is a symptom of an underlying disorder. Investigations are targeted to identify reversible causes.

PREVENTION

- Treat streptococcal throat infection early to prevent future complications.
- Weigh risk-benefit in using medications known to cause tardive dyskinesia.

PATIENT & FAMILY EDUCATION

For Huntington disease and other genetic forms of chorea, it is important to provide support and refer to support groups.

RELATED CONTENT

Huntington Disease (Related Key Topic)
Rheumatic Fever (Related Key Topic)

AUTHORS: **Nawaz K.A. Hack, MD,** and **Joseph S. Kass, MD, JD, FAAN**

SUGGESTED READINGS

Bansil S et al: Movement disorders after stroke in adults: a review, *Tremor Other Hyperkinet Mov* 2, 2012.

Cardoso F, Vale T: Chorea: a journey through history, *Tremor Other Hyperkinetic Mov* 28(5), 2015.

Termsarasab P: Chorea, *Continuum (Minneap Minn)* 25(4, Movement Disorders):1001-1035, 2019.

Waln O et al: An update on tardive dyskinesia: from phenomenology to treatment, *Tremor Other Hyperkinet Mov* 12(3), 2013.

Chronic Fatigue Syndrome PTG ALG

BASIC INFORMATION

DEFINITION

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and systemic exertion intolerance disease (SEID), is characterized by at least three of the following symptoms, present concurrently for at least 6 mo:

- Impaired memory or concentration (cognitive impairment)
- Sore throat
- Tender cervical or axillary lymph nodes
- Muscle pain
- Multijoint pain
- New headaches
- Unrefreshing sleep
- Postexertion malaise for longer than 24 hr
- Orthostatic intolerance

There are currently several sets of clinical criteria to define ME/CFS, yet there is no consensus regarding which set of criteria best identifies patients with this condition. In 2015, the Institute of Medicine (IOM) recommended renaming ME/CSF "systemic exertion intolerance disease (SEID)." Their definition requires that patients have: 1. Substantial reduction or impairment in the ability to engage in premorbid levels of activities persisting for >6 mo and associated with new-onset fatigue not alleviated by rest; 2. Postexertional fatigue; 3. Unrefreshing sleep; and 4. Presence of cognitive impairment and/or orthostatic intolerance.

SYNONYMS

Systemic exertion intolerance disease (SEID)
Yuppie flu
CFS
Chronic Epstein-Barr syndrome
Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
Neurasthenia

ICD-10CM CODES

R53.82 Chronic fatigue, unspecified
F45.8 Other somatoform disorders

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE IN U.S.: Prevalence rates of CFS in the U.S. range from 0.3% to 2.5%. It is estimated that 800,000 to 2.5 million Americans have CFS

PREDOMINANT AGE: Young adulthood and middle age

PREDOMINANT SEX: Females affected more often than males

ECONOMICS: The estimated annual cost of lost productivity is estimated to be between $17 billion and $24 billion annually

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- There are no physical findings specific for CFS.
- The physical examination may be useful to identify fibromyalgia and other rheumatologic conditions that may coexist with CFS.

ETIOLOGY

- The etiology of CFS is unknown. The pathophysiologic dysregulation of the thalamus, hypothalamus, and amygdala is believed by some to be a potential cause of SEID.
- Some theorize that a viral illness may trigger certain immune responses that lead to the various symptoms. Most patients often report the onset of their symptoms with a flulike illness.
- The presence of numerous psychiatric comorbidities in CFS have led some experts to question the existence of any organic etiology.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Psychosocial depression, dysthymia, anxiety-related disorders, and other psychiatric diseases
- Sleep apnea
- Infectious diseases (subacute bacterial endocarditis, Lyme disease, fungal diseases, mononucleosis, HIV, chronic hepatitis B or C, tuberculosis [TB], chronic parasitic infections)
- Autoimmune diseases: Systemic lupus erythematosus, myasthenia gravis, multiple sclerosis, thyroiditis, rheumatoid arthritis
- Endocrine abnormalities: Hypothyroidism, hypopituitarism, adrenal insufficiency, Cushing syndrome, diabetes mellitus, hyperparathyroidism, pregnancy, reactive hypoglycemia
- Occult malignant disease
- Substance abuse
- Systemic disorders: Chronic renal failure, chronic obstructive pulmonary disease, cardiovascular disease, anemia, electrolyte abnormalities, liver disease
- Other: Inadequate rest, sleep apnea, narcolepsy, fibromyalgia, sarcoidosis, medications, toxic agent exposure, Wegener granulomatosis, vitamin deficiency

LABORATORY TESTS

- No specific laboratory tests exist for diagnosing CFS. Initial laboratory tests are useful to exclude other conditions that may mimic or may be associated with CFS.
  1. Screening laboratory tests: CBC, ESR, ALT, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose, BUN, creatinine, electrolytes, TSH, and urinalysis are useful.
  2. Serologic tests for Epstein-Barr virus, *Candida albicans,* human herpesvirus 6, and other studies for immune cellular abnormalities are not useful; these tests are expensive and generally not recommended.
- Other tests may be indicated depending on the history and physical examination (e.g., ANA, RF in patients presenting with joint complaints or abnormalities on physical examination, Lyme titer in areas where Lyme disease is endemic).

IMAGING STUDIES

Generally not recommended unless history and physical examination indicate specific abnormalities (e.g., chest radiography in any patient suspected of TB or sarcoidosis)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patients should be reassured that the illness is not fatal and that most patients improve over time.
- An initially supervised exercise program to preserve and increase strength is beneficial for most patients and can improve symptoms.
- Cognitive-behavioral therapy trials have shown positive effects on fatigue levels, work, depression/anxiety, and social adjustment.

GENERAL Rx

Therapy is generally palliative. The following medications may be helpful; however, evidence is conflicting:

- Antidepressants: The choice of antidepressant varies with the desired side effects. Patients with difficulty sleeping or fibromyalgia-like symptoms may benefit from low-dose trazodone 50 mg hs. When sedation is not desirable, low-dose SSRIs (fluoxetine 20 mg qd) often help alleviate fatigue and associated symptoms.
- NSAIDs can be used to relieve muscle and joint pain and headaches.
- "Alternative" medications (herbs, multivitamins, nutritional supplements) are very popular with many CFS patients but are generally not very helpful.
- B-lymphocyte depletion using rituximab has failed to show any benefit in trials.

PEARLS & CONSIDERATIONS

COMMENTS

- In CFS the symptoms are serious enough to reduce daily activities by >50% in the absence of any other medically identifiable disorders.
- The suicide rate is nearly sevenfold higher in people with CFS.
- Moderate to complete recovery at 1 yr occurs in 22% to 60% of patients with CFS.
- Early trials using an electrical impedance assay have shown promise in identifying CFS patients.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Evaluation of Fatigue (Algorithm, Section III)
Chronic Fatigue Syndrome (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Esfandyarpour R et al: A nanoelectronics-blood-based diagnostic biomarker for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), *Proc Natl Acad Sci U S A* 116(21):10250-10257, 2019.

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Chronic Inflammatory Demyelinating Polyneuropathy

BASIC INFORMATION

DEFINITION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a chronic autoimmune neuropathy manifesting with symmetric proximal and distal weakness with associated sensory loss along with reduced or absent reflexes. By definition, the symptoms reach nadir no earlier than 8 wk after onset.

SYNONYMS

Chronic inflammatory demyelinating polyradiculoneuropathy
CIDP

ICD-10CM CODE
G61.81 Chronic inflammatory demyelinating polyneuritis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 0.5/100,000 children; 1 to 2/100,000 adults
PREDOMINANT SEX AND AGE: Slightly higher in males
RISK FACTORS: It is associated with certain systemic medical conditions (see under "Differential Diagnosis"), but the association is unclear.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symmetric weakness in both proximal and distal muscles that peaks after at least 8 wk; onset may appear acute in a minority of patients, and the disease course may be either relapsing or progressive.
- Impaired sensation with distal paresthesias, poor balance, and/or impaired proprioception.
- Reduced or absent deep tendon reflexes.
- Facial, oropharyngeal, and ocular involvement in a small minority of patients.
- Autonomic dysfunction occurs very infrequently compared with Guillain-Barré syndrome.

ETIOLOGY

Immune-mediated disorder emerging from interplay of both cell-mediated and humoral immune responses directed against incompletely characterized peripheral nerve antigens. May also be associated with antecedent illness, although no infectious etiologies have been consistently linked with disease occurrence.

DIAGNOSIS

There is no universal consensus regarding diagnostic criteria for CIDP. The three most widely used criteria are the American Academy of Neurology (AAN), Saperstein, and Inflammatory Neuropathy Cause and Treatment (INCAT) criteria. See Table E1 for a complete review of differences. Of note are the following:

- The AAN and INCAT criteria have the least stringent clinical criteria and require electrodiagnostic assessment of motor and sensory function in only one limb. The Saperstein criteria are more stringent, requiring both symmetrical proximal and distal weakness. Therefore, a patient with distal acquired demyelinating symmetric neuropathy (DADS) could fulfill AAN and INCAT criteria for CIDP.
- All require cerebrospinal fluid analysis to assess for albuminocytologic dissociation.
- All require some features of demyelination evident on nerve conduction studies, including prolonged distal latencies and F-waves, slowed conduction velocities, and at least one nerve demonstrating partial conduction block, a feature of acquired demyelination.
- INCAT criteria do not require a nerve biopsy.

DIFFERENTIAL DIAGNOSIS

- Other demyelinating neuropathies such as the following:
  1. Distal acquired demyelinating symmetric neuropathy (DADS)
  2. Multifocal motor neuropathy (MMN)
  3. Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM; Lewis-Sumner syndrome)
- Inherited neuropathies: Charcot-Marie-Tooth subtypes
- Metabolic neuropathies due to diabetes, uremia
- Paraneoplastic and neoplastic neuropathies: Lymphoma and carcinoma
- Neuropathy associated with monoclonal gammopathy:
  1. Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome
  2. Multiple myeloma
  3. Monoclonal gammopathy of undetermined significance (MGUS)
  4. Waldenström macroglobulinemia
- Neuropathy associated with infectious diseases: HIV and leprosy
- Neuropathy associated with systemic inflammatory or immune-mediated diseases:
  1. Sarcoidosis
  2. Amyloidosis
  3. Vasculitis: PAN, Behçet, Sjögren, cryoglobulinemia, lupus, Castleman disease, granulomatosis with polyangiitis (formerly Wegener granulomatosis), and eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss)
- Toxic neuropathies: ETOH, acrylamide, drugs (platinum-based agents, amiodarone, tacrolimus, perhexiline)

TABLE E1 Diagnostic Criteria

Feature	American Academy of Neurology (AAN) Criteria	Saperstein Criteria	Inflammatory Neuropathy Cause and Treatment Criteria
Clinical involvement	Motor dysfunction, sensory dysfunction of >1 limb or both	Major: Symmetric proximal and distal weakness; minor: exclusively symmetrical distal weakness or sensory loss	Progressive or relapsing motor and sensory dysfunction of >1 limb
Time course	≥2 mo	≥2 mo	≥2 mo
Reflexes	Reduced or absent	Reduced or absent	Reduced or absent
Electrodiagnostics	Any 3 of the following 4 criteria: Partial conduction block of ≥1 motor nerve, reduced velocity of ≥2 motor nerves, prolonged distal latency of ≥2 motor nerves, or prolonged F-waves of ≥2 motor nerves	2 of the 4 AAN electrodiagnostic criteria	Partial conduction block of ≥2 motor nerves and abnormal conduction velocity or distal latency or F-wave latency in 1 other nerve; or, in the absence of partial conduction block, abnormal conduction velocity, distal latency, or F-wave latency in 3 motor nerves; or electrodiagnostic abnormalities indicating demyelination in 2 nerves and histologic evidence of demyelination
CSF analysis	WBC count <10, negative CSF VDRL, and elevated protein (supportive)	Protein >45, WBC <10 (supportive)	CSF recommended but not mandatory
Biopsy findings	Evidence of demyelination and remyelination	Predominant features of demyelination; inflammation (not required)	Not mandatory (except in cases with electrodiagnostic abnormalities in only 2 motor nerves)

AAN, American Academy of Nursing; *CSF,* cerebrospinal fluid; *CSF VDRL,* neurosyphilis test; *WBC,* white blood cell.

WORKUP

Nerve conduction studies and EMG to assess for demyelinating polyneuropathy with features of acquired demyelination (temporal dispersion) and conduction block (Fig. E1)

LABORATORY TESTS

- CSF analysis to assess for albuminocytologic dissociation (i.e., elevated protein with normal cell count), along with appropriate laboratory studies to exclude associated conditions.
- Nerve biopsy specimens (rarely done now) also reveal signs of demyelination with variable degrees of inflammation and secondary axonal loss.

IMAGING STUDIES

MRI with/without gadolinium of the lumbar spine may show enlargement and enhancement of the proximal nerve root segments (Figs. E2 and E3).

Rx TREATMENT

Therapies are directed at blocking the underlying immune processes to arrest demyelination and inflammation and to prevent secondary axonal degeneration. The first-line agents for immunomodulatory therapy are intravenous immunoglobulin (IVIg), plasmapheresis, and corticosteroids. There is no difference in efficacy among these three treatment modalities. Azathioprine, mycophenolate mofetil, cyclophosphamide, rituximab, and cyclosporine may be used second-line.

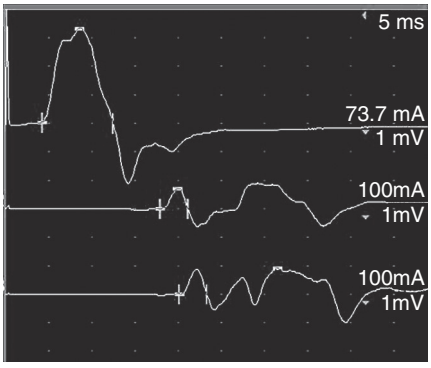

FIG. E1 Conduction block.

NONPHARMACOLOGIC THERAPY

Orthotics or braces may be useful for significant distal weakness.

ACUTE GENERAL Rx

- Prednisone 60 mg per day or 100 mg every other day
- IVIg 2 g/kg divided over 2 to 5 days
- Plasmapheresis (5 to 6 exchanges)

CHRONIC Rx

- Oral prednisone: 1 mg/kg daily starting dose, typically changed to every other day after 1 mo or when strength plateaus. Reduce by 10 mg per mo until dose reaches 20 mg every other day; then reduce by 5 mg per mo. Supplement calcium and vitamin D. Patients should receive a tuberculin skin test prior to administration as well as surveillance exams for cataracts, glaucoma, diabetes, and gastroesophageal reflux.
- Dexamethasone: PREDICT study compared dexamethasone 40 mg daily for 4 days per mo with prednisone 60 mg daily for 2 mo and then tapered over 27 wk. No difference in efficacy was found between the two groups. However, pulse steroids were associated with less weight gain, fewer cushingoid features, but more sleep and psychological disturbances.
- Pulse methylprednisolone: No standard regimen. However, 1000 mg for 3 days can be used, followed by 1000 mg per wk with the goal of reduced frequency to every 2 to 12 wk.
- IVIg: 0.4 to 1 g/kg administered every 2 to 3 wk, with adjustment based on therapeutic response. Baseline IgA level, renal function, and coagulation studies should be assessed.
- Mycophenolate mofetil: Initial dose of 500 mg every other day; increase to 2 g orally divided twice daily in 2 to 4 wk. Complete blood counts and liver panel should be assessed monthly for the first 3 mo, then every 3 mo thereafter. May cause GI upset.
- Azathioprine: Initial dose of 25 to 50 mg every other day; increase to 100 mg twice daily in 4 wk. Complete blood counts and liver panel should be assessed for first 3 mo, then every 3 mo thereafter. Idiosyncratic reaction of fever and GI upset may occur.
- Cyclophosphamide: Used for severe cases. 1000 mg/m^2 monthly for 6 mo (moderate dose) or 50 mg/kg daily for 4 days (high dose).
- Other treatments used (case reports/anecdotal evidence): Etanercept, rituximab, tacrolimus, interferon beta-1a.

FIG. E2 Contrast-enhanced magnetic resonance image shows enhancement of nerve roots.

FIG. E3 T2-weighted axial magnetic resonance image shows enlarged nerve roots.

PROGNOSIS

- Although available data on the long-term prognosis of patients are limited, most patients improve and reach stability. Relapses may occur in 50% of patients. A small minority of patients remain severely disabled, and up to 11% die from the disease.
- Patients with CIDP associated with IgM monoclonal gammopathy often respond poorly to treatment.
- Younger age, female gender, and relapsing-remitting course may portend a more favorable prognosis. Four-limb weakness at onset and prominent axonal loss on EMG may signify poor prognosis.

REFERRAL

- Neurologist, physical therapy/occupational therapy, orthotics

PEARLS & CONSIDERATIONS

- Patients are compliant with azathioprine treatment if MCV >100.
- Always place PPD prior to initiation of steroid treatment.
- Consider trimethoprim-sulfamethoxazole 3 times weekly in patients taking steroids and other immunosuppressant agents for *Pneumocystis* pneumonia prophylaxis (especially in patients with coexisting lung disease).
- Look for acquired features of demyelination on nerve conduction studies (conduction block and temporal dispersion).
- Examine CSF for albuminocytologic dissociation (high CSF protein with normal cell count).
- CIDP can present like Guillain-Barré syndrome. Sensory symptoms and proximal weakness are more common in CIDP, and symptoms continue to evolve over more than 8 wk.

PATIENT & FAMILY EDUCATION

CIDP is a chronic illness usually characterized by a relapsing-remitting course that typically responds well to treatment. Early referral to a neurologist is important, and education on steroid side effects and mitigating factors is paramount.

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BASIC INFORMATION

DEFINITION

Chronic kidney disease (CKD) is diagnosed when there is evidence for more than 3 mo of **kidney damage** (urine albumin >30 mg/g creatinine, hematuria, or parenchymal abnormalities) and/or **decreased kidney function** (glomerular filtration rate, GFR <60 ml/min per 1.73 m^2). CKD is characterized by accumulation of metabolic waste products in blood, electrolyte abnormalities, mineral and bone disorders, and anemia. The pathophysiology of CKD and its manifestations are summarized in Table 1.

SYNONYMS

CKD
Chronic renal failure
CRF
Chronic renal insufficiency
CRI

ICD-10CM CODES

N18.1	Chronic kidney disease, stage 1
N18.2	Chronic kidney disease, stage 2
N18.3	Chronic kidney disease, stage 3
N18.4	Chronic kidney disease, stage 4
N18.5	Chronic kidney disease, stage 5
N18.6	End-stage renal disease
N18.9	Chronic kidney disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Overall prevalence of CKD (Stages 1 to 5) in the U.S. adult population is about 15% based on the 2018 United States Renal Data System. The incidence of end-stage renal disease (ESRD) is 7% to 9% per yr in the U.S., primarily due to diabetes mellitus and hypertension, the leading risk factors for CKD. Annually, 3 in 10,000 persons develop ESRD, and more than 100,000 patients begin dialysis each yr.
- Total Medicare spending on CKD and ESRD patients exceeds $114 billion USD. Accompanying chronic diseases such as diabetes and heart failure compound the cost of caring for these individuals, and kidney disease has been deemed a "cost multiplier" for this reason.
- Kidney transplantation is the best option for kidney replacement therapy, but many patients are not eligible for transplantation.

TABLE 1 Pathophysiology of Chronic Kidney Disease

Manifestation	Mechanisms
Accumulation of nitrogenous waste products	Decrease in glomerular filtration rate
Acidosis	Decreased ammonia synthesis Impaired bicarbonate reabsorption Decreased net acid excretion
Sodium retention	Excessive renin production Oliguria
Sodium wasting	Solute diuresis Tubular damage
Urinary concentrating defect	Solute diuresis Tubular damage
Hyperkalemia	Decrease in glomerular filtration rate Metabolic acidosis Excessive potassium intake Hyporeninemic hypoaldosteronism
Renal osteodystrophy	Impaired renal production of 1,25-dihydroxycholecalciferol Hyperphosphatemia Hypocalcemia Secondary hyperparathyroidism
Growth retardation	Inadequate caloric intake Renal osteodystrophy Metabolic acidosis Anemia Growth hormone resistance
Anemia	Decreased erythropoietin production Iron deficiency Folate deficiency Vitamin B_{12} deficiency Decreased erythrocyte survival
Bleeding tendency	Defective platelet function
Infection	Defective granulocyte function Impaired cellular immune functions Indwelling dialysis catheters
Neurologic symptoms (fatigue, poor concentration, headache, drowsiness, memory loss, seizures, peripheral neuropathy)	Uremic factor(s) Aluminum toxicity Hypertension
Gastrointestinal symptoms (feeding intolerance, abdominal pain)	Gastroesophageal reflux Decreased gastrointestinal motility
Hypertension	Volume overload Excessive renin production
Hyperlipidemia	Decreased plasma lipoprotein lipase activity
Pericarditis, cardiomyopathy	Uremic factor(s) Hypertension Fluid overload
Glucose intolerance	Tissue insulin resistance

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Skin pallor, ecchymosis
- Sleep disorder
- Hypertension
- Edema, leg cramps, restless legs, peripheral neuropathy
- Emotional lability, depression, decreased cognitive function
- Clinical presentation varies with the degree of kidney disease and its underlying etiology. Common symptoms are generalized fatigue, nausea, anorexia, pruritus, sleep disturbances, smell and taste disturbances, hiccoughs, and seizures

ETIOLOGY

- Diabetes (43.2%), hypertension (23%), chronic glomerulonephritis (12.3%)
- Failed kidney transplant
- Polycystic kidney disease (2.9%)
- Interstitial nephritis (e.g., drug hypersensitivity, analgesic nephropathy)
- Obstructive nephropathies (e.g., nephrolithiasis, prostatic disease)
- Vascular diseases (renal artery stenosis, hypertensive nephrosclerosis)
- Autoimmune diseases

DIAGNOSIS

GFR is considered the best overall index of kidney function but is not the only measure of kidney health that should be considered. Although quantification of albuminuria has been less widely adopted in clinical practice than assessment of estimated GFR (eGFR), the evaluation of albuminuria is crucial to determining prognosis. When applying eGFR equations, one must appreciate that CKD is defined over a 3-mo interval with implications for health. (Table 2)

Therefore the serum creatinine must be repeated and trended to establish a diagnosis of CKD in individuals who also must be in a steady state of creatinine generation or production. The albuminuria is complementary to low eGFR because both independently influence prognosis.

WORKUP

- Laboratory evaluation and imaging studies can identify reversible causes of acute GFR decline (e.g., volume depletion, urinary tract obstruction, heart failure).

- Ultrasound evaluation of the kidneys often reveals small kidneys (<9 cm sagittal length) with increased echogenicity.
- Kidney biopsy is generally not considered when kidneys are small or CKD is advanced.
- Table 3 provides a summary of a practical approach to the detection and management of CKD.

LABORATORY TESTS

- Elevated blood urea nitrogen (BUN), creatinine, and low GFR are the best overall indicators of kidney function. GFR is estimated by multivariable (creatinine, age, sex, and race) prediction equations normalized to body surface area. GFR calculators are available online (www.kidney.org/kls/professionals/gfr_calculator.cfm). The Modification of Diet in Renal Disease (MDRD) equation has been in common use in clinical laboratories until recently, but has been replaced by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation that more accurately categorizes the risk of mortality and progression to ESRD.
- Urinalysis may reveal proteinuria, hematuria, or formed elements such as casts.
- Serum chemistries: Elevated BUN and creatinine, hyperkalemia, hyperuricemia, hypocalcemia, hyperphosphatemia, hyperglycemia, and decreased serum bicarbonate concentration.
- Urinary protein excretion. A urine total protein-to-creatinine ratio >1000 mg/g or albumin-to-creatinine ratio of >500 mg/g creatinine generally indicates glomerular disease.
- Special studies: Serum and urine immunoelectrophoresis (multiple myeloma), antinuclear antibody (i.e., systemic lupus erythematosus).
- Cystatin C measurement or direct glomerular filtration clearance methods may confirm CKD in situations when serum creatinine-based GFR equations are less accurate (e.g., HIV, malnutrition) or more precise measurement is desired (e.g., kidney transplant organ donation).

IMAGING STUDIES

- Ultrasound of kidneys for size measurements and to rule out cause of obstructive uropathy
- Plain radiographs of the aorta and extremities ordered for other reasons may reveal vascular and extraskeletal calcification

TABLE 2 Criteria for Definition of Chronic Kidney Disease

KD is defined as abnormalities of kidney structure or function, present for more than 3 mo, with implications for health. These may include the following:

Markers of kidney damage	Albuminuria (AER ≥30 mg/24 h; uACR ≥30 mg/g [≥3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities caused by tubular disorders Abnormalities detected through histology Structural abnormalities detected through imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2

AER, Albumin excretion rate; *GFR,* glomerular filtration rate; *uACR,* urine albumin-to-creatinine ratio.
From KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;3:1-150. In Floege J et al: *Comprehensive clinical nephrology,* ed 6, Philadelphia, 2019, Elsevier. Table 80.1

TABLE 3 Management Plan for Patients with Chronic Kidney Disease, According to Stage

Stage & GFR	Action	Clinical Testing	Treatment Considerations
1 **>90 ml/min per 1.73 m^2**	**Establish** risk or etiology of CKD **Diagnose** and treat CVD risk factors and comorbid conditions	***eGFR*:** *Every* 12 mo **UA** with microscopic evaluation **UPC** if nondiabetic**:** *Every* 12 mo **UACR** if diabetic**:** *Every* 12 mo	**Consult** nephrology if ***eGFR*** declines by ≥4 ml/min per yr **BP:** <130/80 mm Hg **Proteinuria:** UPC <0.2**;** UACR <30 mg/g with ACEI or ARB
2 **60-89 ml/min per 1.73 m^2**	**Estimate** CKD progression rate **Diagnose** and treat CVD risk factors and comorbid conditions	***eGFR*:** *Every* 6-12 mo **CBC**, reticulocyte ct, TSAT, ferritin if Hb 10-12 g/dl**:** every 12 mo **Annual** Ca/P/PTH/25(OH)D evaluations **UACR** or UPC**:** *Every* 6-12 mo	**Avoid** nephrotoxins **Treat** Hypertension **Hb:** 10-12 g/dl, TSAT >20%, and ferritin >100 ng/ml **UACR:** <30 mg/g or UPC <0.2 with ACEI or ARB
3A **45-59 ml/min per 1.73 m^2** **3B** **30-44 ml/min per 1.73 m^2**	**Estimate** CKD progression rate **Diagnose** and treat CVD risk factors and comorbid conditions **Kidney** imaging study (e.g., US or CT) **Consider** nephrology **Consultation**	**BP** monitoring**:** *Every* 3-6 mo ***eGFR*:** *Every* 6 mo, if stable every 12 mo **CBC:** Hb <10 g/dl *every* 1-3 mo until Hb 9-12 g/dl**;** then *every* 3-6 mo **TSAT** and ferritin if Hb <13 g/dl (males) or 12 g/dl (females) and after therapy **Baseline** Ca/P/PTH/Alk Phos/25(OH)D Ca/P/PTH/Alk Phos, depending on baseline and CKD progression **25(OH)D**, depending on baseline and response to treatment **UPC or UACR:** *Every* 6-12 mo	**Avoid** nephrotoxins **Treat** Hypertension **Hb:** 9-12 g/dl, TSAT >20%, ferritin >100 ng/ml with p.o. and/or *iv* iron and/or erythropoiesis stimulating agent **Ca & P:** To normal range with P-binders **25(OH)D:** ≥30 ng/ml with vitamin D2/D3 **iPTH:** 130-600 pg/ml with calcitriol or vitamin D analogs if iPTH progressively increases **NaHCO3:** 22-26 mmol/L and titrate $NaHCO_3$ therapy **UPC:** <0.2 or UACR <30 mg/g with ACEI or ARB
4 **15-29 ml/min per 1.73 m^2**	Transition of management and care to Nephrology **Initiate** decisions regarding kidney replacement therapy, vascular access, and kidney transplant **Diagnose** and treat CVD risk factors and comorbid conditions **Adjust** drug dosing for CKD stage	**BP** monitoring**:** *Every* 3 mo ***eGFR*:** *Every* 3 mo **CBC**, TSAT, ferritin**:** *Every* 3-6 mo **Baseline** Ca/P/PTH/Alk Phos/25(OH)D**;** then repeat levels *every* 6-12 mo **UPC or UACR:** *Every* 3-6 mo	**All of the above plus CKD**-specific education**:** Kidney replacement therapy modality **Immunizations:** TIV, PPV-23, and HBV **Reinforce** dietary prescription **Protect** dominant (handwriting) arm **Vascular** access surgery evaluation

ACEI, Angiotensin-converting enzyme inhibitors; *ARB*, angiotensin-receptor blockers; *BP*, blood pressure; *CKD*, chronic kidney disease; *CT*, computed tomography; *ct*, count; *CVD*, cardiovascular disease; *eGFR*, estimated glomerular filtration rate; *HBV*, hepatitis B virus; *TSAT*, transferrin saturation; *UA*, urine analysis; *UACR*, urine albumin to creatinine ratio; *UPC*, urine protein test; *US*, ultrasonography.
CKD Stage 5 (GFR <15 ml/min/1.73 m^2) patients require management by a nephrologist.
From Inker LA, Astor BC, Fox CH, et al.: *Am J Kidney Dis* 63(5);713–735, 2014.4

CLASSIFICATION

The 2012 Kidney Disease: International Global Outcomes classifies CKD with a CGA format: Cause (etiology), GFR (G1 to G5), and Albuminuria (A1 to A3) by urine albumin-to-creatinine ratio. This format now is recommended when documenting and discussing CKD. Fig. 1 depicts how CKD prognosis worsens with either increasing levels of albuminuria or declining GFR.

Rx TREATMENT

CKD usually progresses slowly. Therefore even relatively small reductions in GFR loss can delay the onset of ESRD by years. For this reason, an aggressive, multiple–risk factor intervention to slow GFR decline is warranted, except in patients with low ESRD risk. The goals of progression therapy are to reduce proteinuria as much as possible, ideally to less than 500 mg/day, which is a safe level of proteinuria for most forms of CKD, and to slow GFR decline as much as possible, ideally to about 1 ml/min/yr, which is the rate of GFR decline attributable to the nephropathy of aging. Table 4 summarizes recommended kidney protective therapies according to level of recommendation.

NONPHARMACOLOGIC THERAPY

KDIGO has recommended that protein intake should be lowered to 0.8 g/kg/day in adults with CKD and GFR below 30 ml/min/1.73 m^2, whereas high protein intake (>1.3 g/kg/day) should be avoided in adults with CKD at risk of progression. Table 5 describes nutritional recommendations in CKD.

- Referral to a dietitian for nutritional therapy for patients with GFR <50 ml/min/1.73 m^2 is recommended and is a Medicare-covered service.
- Dietary restriction of sodium (~100 mmol/day), potassium (≤60 mmol/day), and phosphorus (<800 mg/day).
- Blood pressure: Target blood pressure of ≤140/90 mm Hg if CKD (diabetic and nondiabetic) and urine albumin excretion ≤30 mg/24 hr. If CKD (diabetic and nondiabetic) and albumin excretion >30 mg/24 hr are present, consider a target blood pressure ≤130/80 mm Hg.
- Adjust medication doses for reduced GFR.
- Restrict fluid intake if significant edema or hyponatremia (serum Na <130 mmol/L) is present.
- Resistance exercise training can preserve lean body mass and improve nutritional status and muscle function in patients with moderate CKD.
- Avoid radiocontrast agents. Prophylactic volume expansion with sodium chloride or sodium bicarbonate before dye exposure is equally effective.
- Smoking cessation.
- Prompt referral to a nephrologist is helpful. Late evaluation of patients with CKD is associated with greater burden and severity of comorbid disease and complications and lesser survival. Suggested criteria for nephrology referral are described in Table 6.
- Referral for kidney transplantation in selected patients.

ACUTE GENERAL Rx

- Angiotensin–converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) reduce proteinuria and slow progression of CKD, especially in hypertensive diabetic

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g < mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73m^2) Description and range	G1	Normal or high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

FIG. 1 Risk of chronic kidney disease progression, frequency of visits, and referral to nephrology according to estimated glomerular filtration rate (eGFR) and albuminuria. The GFR and albuminuria grid depict the risk of progression, morbidity, and mortality by color, from best to worst (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of visits (number of times per yr). Green can reflect CKD with normal eGFR and albumin-to-creatinine ratio (ACR) only in the presence of other markers of kidney damage, such as imaging showing polycystic kidney disease or kidney biopsy abnormalities, with follow-up measurements annually; yellow requires caution and measurements at least once per yr; orange requires measurements twice per yr; red requires measurements 3 times per yr; and deep red 4 times per yr. These are general parameters only, based on expert opinion, and must take into account underlying comorbid conditions and disease state as well as the likelihood of impacting a change in management for any individual patient. "Refer" indicates nephrology services are recommended. *Referring clinicians may wish to discuss with their nephrology service, depending on local arrangements regarding treating or referring. *CKD,* Chronic kidney disease; *GFR,* glomerular filtration rate. (From Vassalotti JA et al: Practical approach to detection and management of chronic kidney disease for the primary care clinician. *Am J Med* 2016 Feb, Elsevier.)

patients. The combination of ACEI and ARB is not recommended due to increased risks of hyperkalemia, hypotension, and acute kidney injury. Increases of serum creatinine of up to 30% greater than baseline within 3 mo of initiating ACEI or ARB therapy may be acceptable.
- Addition of chlorthalidone to CKD patients with difficult-to-treat hypertension may reduce blood pressure and proteinuria. Successful blood pressure lowering is associated with weight loss. Loop diuretic therapy may be associated with complications of hypokalemia.
- Erythropoiesis-stimulating agents (ESAs), e.g., epoetins alfa and beta and darbepoetin alfa, are administered to reduce need for transfusions in anemic CKD patients. A target hemoglobin of 9 to 11 g/dl is reasonable to avoid premature and excessive ESA use. Higher hemoglobin values have been associated with adverse cardiovascular events. Iron sufficiency should be present, defined as transferrin saturation >20% and ferritin >100 ng/ml, before ESA therapy is initiated.
- Optimal diuretic therapy should be prescribed for edema or cardiopulmonary congestion.
- ACEIs and ARBs retard progression of CKD and lower blood pressure but may reduce GFR and renal potassium excretion.
- Treat metabolic acidosis with oral sodium bicarbonate to attain a goal serum HCO_3 level of 22 to 26 mmol/L.

TABLE 4 Recommended Kidney Protective Therapies According to Level of Recommendation

Level 1 Recommendations
- Control blood pressure (BP).
- Administer angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or renin inhibitor.
- Avoid dihydropyridine calcium channel blockers (DH-CCBs) unless needed for BP control.
- Control protein intake.

Level 2 Recommendations
- Restrict NaCl intake/diuretic therapy.
- Administer nondihydropyridine calcium channel blockers (NDH-CCB) therapy.
- Control each component of the metabolic syndrome.
- Administer aldosterone antagonist therapy.
- Administer β-blocker therapy.
- Control serum phosphorus.
- Instigate smoking cessation.
- Control hyperuricemia.
- Administer alkali therapy.
- Avoid anticoagulant-related nephropathy.
- Monitor serum creatinine in patients receiving proton pump inhibitors.
- Correct vitamin D deficiency.
- Avoid/minimize nonsteroidal antiinflammatory drug use.
- The goal for the chronic kidney disease (CKD) patient is to implement all level 1 recommendations and as many level 2 recommendations as is feasible.

From Floege J et al: *Comprehensive clinical nephrology,* ed 6, Philadelphia, 2019, Elsevier. Box 79.3.

- Statin or a combination of statin and ezetimibe is recommended in adults aged ≥50 yr with eGFRs <60 ml/min/1.73 m^2. Lipid management focuses on absolute risk for coronary events, and there are no target cholesterol levels.
- Therapy of mineral and bone disease in CKD is geared toward normalizing serum phosphorus concentration. Calcitriol and vitamin D analogs should be reserved for patients with CKD stages 4-5 and severe and progressive hyperparathyroidism.
- Dietary phosphate restriction is recommended for nearly all CKD patients. For additional management of hyperphosphatemia, phosphorus binders are recommended. Calcium-based phosphate binders, although inexpensive, should be restricted if total serum calcium is >10.2 mg/dl. Sevelamer carbonate and lanthanum carbonate are effective as phosphate binders but more expensive. Two iron-based phosphate-binding agents, sucroferric oxyhydroxide and ferric citrate, recently have been approved by the FDA.
- Uremic pruitus: Difelikefalin, a selective agonist of kappa opioid receptors has shown a significant reduction in itch intensity in Phase 3 tumors in hemodialysis patients with pruritus.
- Recommendations of the current CDC advisory committee on immunization practices call for pneumococcal vaccination of individuals >19 yr at the time of CKD diagnosis. In addition routine annual influenza vaccination for all persons aged ≥6 mo who do not have contraindications has been recommended. Those at high risk of progression of CKD with eGFR below 30 ml/min/1.73 m^2 should be immunized against hepatitis B to ensure seroconversion.
- Initiation of dialysis: Early initiation of dialysis when the GFR is 10 to 15 ml/min/1.73 m^2 does not enhance survival compared with

TABLE 5 Nutritional Recommendations in Chronic Kidney Disease.

Recommendations are for typical patients but always should be individualized on the basis of clinical, biochemical, and anthropometric indices.

Daily Intake	Predialysis CKD	Hemodialysis	Peritoneal Dialysis
Protein (g/kg ideal BW) (see KDOQI for estimation of adjusted edema-free BW)	0.6-1.0 Level depends on the view of the nephrologist. 1.0 for nephrotic syndrome.	min ≥1.1 Recommendations are in conjunction with an adequate energy intake. Requirements may be higher during illness because of multiple comorbidities or during acute periods of infection, including peritonitis.	min 1.0-1.2
Energy (kcal/kg BW)	35 (younger than 60 yr) 30-35 (older than 60 yr)	35 (younger than 60 yr) 30-35 (older than 60 yr) 30-40 kcal/kg ideal BW	35 including dialysate calories (younger than 60 yr) 30-35 including dialysate calories (older than 60 yr)
Sodium (mmol)	<100 (more if salt wasting)	<100	<100
Potassium	Reduce if hyperkalemic	Reduce if hyperkalemic	Reduce if hyperkalemic; potassium restriction is generally not required. May need to increase potassium intake if hypokalemic.
	If hyperkalemic, advice will take the form of decreasing certain foods (e.g., some fruits and vegetables) and giving information about cooking methods.		
Phosphorus	Reduce because of phosphate retention. Monitor levels. Advice will take the form of reducing certain foods (e.g., dairy, offal, some shellfish) and processed foods with high content of added phosphates, and giving information about the timing of binders with high-phosphorus meals and snacks.		

Recommendations are for typical patients but always should be individualized based on clinical, biochemical, and anthropometric indices. *BW,* Body weight; *CKD,* chronic kidney disease; *KDOQI,* Kidney Disease Outcomes Quality Initiative.

From Floege J et al: *Comprehensive clinical nephrology,* ed 6, Philadelphia, 2019, Elsevier. Table 86.6.

TABLE 6 Suggested Criteria for Referral of Patients with Chronic Kidney Disease to a Nephrologist

	NICE 2008	KDIGO 2012
Advanced CKD	Stage 4 and 5 CKD	Category G4 and G5 CKD
Proteinuria	High proteinuria: ACR ≥70 mg/mmol unless known to be caused by diabetes and appropriately treated	Consistent proteinuria: ACR ≥ 300 mg/g (≥30 mg/mmol)
Hematuria	Proteinuria (ACR ≥30 mg/mmol) together with hematuria	Urinary red cell casts, RBCs >20 per high-power field sustained; not readily explained
Progression of CKD	Rapidly declining eGFR: >5 ml/min per 1.73 m^2 in 1 yr >10 ml/min per 1.73 m^2 in 5 yr	Progression of CKD: Sustained decline in eGFR >5 ml/min per 1.73 m^2 in 1 yr Drop in GFR category with a ≥25% drop in eGFR from baseline
Uncontrolled hypertension	Hypertension that remains poorly controlled despite the use of at least four antihypertensive drugs at therapeutic doses	CKD and hypertension refractory to treatment with four or more antihypertensive agents
Hereditary kidney disease	Known or suspected rare or genetic causes of CKD	Hereditary kidney disease
Other conditions	Suspected renal artery stenosis	Recurrent or extensive nephrolithiasis Persistent abnormalities of serum potassium

ACR, Albumin-creatinine ratio; *CKD,* chronic kidney disease; *eGFR,* estimated glomerular filtration rate; *KDIGO,* Kidney Disease: Improving Global Outcomes; *NICE,* National Institute for Health and Care Excellence; *PTH,* parathyroid hormone; *RBC,* red blood cell.

From Floege J et al: *Comprehensive clinical nephrology,* ed 6, Philadelphia, 2019, Elsevier. Table 80.3) (Data from KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013; 3: pp. 1-150; and National Institute for Health and Care Excellence: *chronic kidney disease in adults: assessment and management*.

a symptom-driven strategy for initiation of dialysis at eGFR <8 to 10 ml/min/1.73 m^2.

1. Urgent indications: Uremic pericarditis, neuropathy, neuromuscular abnormalities, CHF, hyperkalemia, seizures.
2. Other indications: GFR 10 to 15 ml/min with progressive anorexia, weight loss, disordered sleep, pruritus, uncontrolled fluid gain with hypertension, and signs of heart failure.

DISPOSITION

- Prognosis is influenced by CKD stage and burden of comorbid illness. Late referral, meaning nonreferral within 6 to 12 mo before a diagnosis of ESRD is established, of patients to a nephrologist is associated with greater morbidity and mortality. Despite recommendations for early referral, nearly two thirds of CKD patients are referred late.
- *Choosing Wisely* is an initiative of the ABIM Foundation that aims to promote conversations between clinicians and patients by helping patients choose care that is supported by evidence and avoids wasteful or unnecessary medical tests, treatments, and procedures.
- Genetic susceptibility for CKD is prominent in African Americans. High-risk alleles of apolipoprotein L1 predict more rapid CKD progression independent of diabetes, race, and lipid and nonlipid factors.
- Kidney transplantation in selected patients improves survival. Whereas the 2-yr kidney graft survival rate for living related donor transplantations is >80%, the 2-yr graft survival rate for cadaveric donor transplantation is nearly 70%.

SUGGESTED READINGS

Available at ExpertConsult.com

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SUGGESTED READINGS

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Chronic Lymphocytic Leukemia PTG ALG

BASIC INFORMATION

DEFINITION

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder characterized by proliferation and accumulation of mature-appearing neoplastic B cells.

SYNONYM

CLL

ICD-10CM CODES

C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.11	Chronic lymphocytic leukemia of B-cell type in remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse

EPIDEMIOLOGY & DEMOGRAPHICS

- Most frequent form of leukemia in Western countries (20,940 new cases and 4510 deaths annually in the U.S.). Incidence rate is 5 per 100,000 person-yr, increasing to 17 cases per 100,000 at age 65. It is more common in patients with a family history of CLL or other lymphoid malignancy
- Generally occurs in older patients: Median age at diagnosis in the U.S. is 70 yr
- Male/female ratio of 2:1
- CLL accounts for 1% of all cancers and 11% of all hematologic neoplasms
- May be preceded by monoclonal B-cell lymphocytosis—a premalignant, asymptomatic condition with less than 5000 /mm^3 CLL-like cells circulating in the blood

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- At presentation most patients are asymptomatic. Many cases are diagnosed on the basis of incidentally discovered lymphocytosis.
- Symptoms include fatigue, recurrent infections (pneumonia, herpes zoster), enlarging lymph nodes.
- B symptoms (fever, weight loss, and drenching night sweats) occur in 10% of patients at presentation.
- Small diffuse lymphadenopathy and splenomegaly are typical findings on clinical examination, but they are absent in a majority of patients at diagnosis.
- A minority of CLL patients (<10%) may develop autoimmune hemolytic anemia or immune thrombocytopenia at diagnosis or during the course of the disease.
- At a rate of 1% per yr, CLL may undergo a histologic transformation into an aggressive lymphoma (Richter transformation), characterized by a rapidly growing nodal mass, elevated LDH, and constitutional symptoms.

ETIOLOGY

Remains largely unknown. Accumulation of genetic defects causing resistance to apoptosis and chronic stimulation of the B-cell receptor by autoantigens or undefined microorganisms have been implicated.

DIAGNOSIS

- The diagnosis of CLL requires presence of >5000/mm^3 clonal B cells, for >3 mo, with a characteristic immunophenotype on flow cytometry, which is essential for diagnosis.
- CLL cells are typically positive for CD5, CD19, CD23 and weakly positive for CD20, while they are negative for CD10, Cyclin D1, and CD103. In some cases, molecular studies for CLL-specific chromosomal alterations (deletion of chromosome 13q, 11q, 17p or trisomy 12) may be helpful.
- Table 1 describes the evaluation of CLL patients at diagnosis.

DIFFERENTIAL DIAGNOSIS

- Few acute infections with lymphocytosis (mononucleosis, pertussis)
- Other lymphoproliferative disorders that involve blood (can be distinguished using flow cytometry): Follicular lymphoma, mantle cell lymphoma, splenic marginal zone lymphoma, prolymphocytic leukemia, adult T-cell lymphoma/leukemia, hairy cell leukemia (Table 2)
- Acute lymphocytic leukemia can be differentiated by presence of lymphoblasts rather than mature lymphocytes
- Persistent polyclonal B-cell lymphocytosis: A rare, benign condition affecting (predominantly female) middle-aged smokers
- Differences among monoclonal B-cell lymphocytosis (MBL), CLL, and small lymphocytic leukemia (SLL) are summarized in Table 3

LABORATORY TESTS

- Complete blood count demonstrates lymphocytosis with mature lymphocytes and characteristic "smudge cells" on the peripheral smear (Fig. E1); anemia and thrombocytopenia may be present in more advanced cases.
- Bone marrow examination is **not** indicated in most cases, except when differentiation between autoimmune cytopenias and marrow infiltration by CLL is difficult.
- Hypogammaglobulinemia and elevated lactate dehydrogenase may be present at the time of diagnosis.
- Cytogenetic evaluation (using fluorescent *in-situ* hybridization, FISH) is essential for prognostic assessment and optimal treatment selection.
- Other prognostic markers include: Mutational status of the immunoglobulin heavy chain variable region (*IGHV*, unmutated gene with >98% homology indicates poor prognosis), presence of CD38 or ZAP-70 (also associated with poor prognosis). Additional mutation analysis is gaining importance for identifying patients with worse prognosis (mutations in *TP53, NOTCH1, SF3B1,* and *BIRC3* genes).

TABLE 1 Evaluation of Chronic Lymphocytic Leukemia Patients at Diagnosis

History

- B symptom and fatigue assessment
- Infectious history assessment
- Occupational assessment for chemical exposure
- Familial history of CLL and lymphoproliferative disorders
- Preventive interventions for infections and secondary cancers

Physical Examination

Laboratory assessment

- CBC with differential
- Morphology assessment of lymphocytes
- Chemistry, LFT enzymes, LDH
- Flow cytometry assessment to confirm immunophenotype of CLL
- Serum immunoglobulins
- Serum β_2M levels
- Interphase cytogenetics for del(17p13.1), del(11q22.3), del(13q14), del(6q21), and trisomy 12
- IGHV mutational analysis
- Stimulated metaphase karyotype (if available)

Selected tests under certain circumstances

- DAT, haptoglobin, reticulocyte count if anemia present
- CT scan if unexplained abdominal pain or enlargement present
- PET scan or biopsy (or both) if large nodal mass present
- BM aspirate and biopsy if cytopenias present
- Familial counseling if first-degree relative with CLL

Teaching

- Varicella zoster identification instruction
- Skin cancer identification
- Disease education (Leukemia and Lymphoma Society)

B symptoms, Fever, night sweats, weight loss; *BM,* bone marrow; β_2M, beta-2 microglobulin; *CBC,* complete blood count; *CLL,* chronic lymphocytic leukemia; *CT,* computed tomography; *DAT*, direct antiglobulin test; *IGHV,* immunoglobulin heavy chain variable region; *LDH,* lactate dehydrogenase; *LFT,* liver function test; *PET,* positron emission tomography.

From Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 2 Diseases that Can Mimic Chronic Lymphocytic Leukemia

- Follicular lymphoma
- Mantle cell lymphoma
- Marginal zone lymphoma
- Hairy cell leukemia
- Acute lymphoblastic leukemia
- T-cell prolymphocytic leukemia
- Large granular natural killer or T-cell leukemia

From Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

IMAGING STUDIES

Imaging studies (CT or PET/CT scans) are not necessary for asymptomatic patients at diagnosis. They are obtained in case of clinical concerns for bulky internal adenopathy, Richter transformation, or prior to starting chemotherapy.

Rx TREATMENT

- At present, there is no standard curative therapy for CLL, so treatment is only instituted for progressive or symptomatic disease (Table 5) with a goal of symptom relief and prolongation of life.

TABLE 3 Characteristics of Monoclonal B-Cell Lymphocytosis (MBL), Chronic Lymphocytic Leukemia (CLL), and Small Lymphocytic Leukemia (SLL)

	MBL	CLL	SLL
Clonal B cells >5 × 10^9/L	No	Yes	No
Lymph nodes >1.5cm	No	Yes/No	Yes
Enlarged spleen or liver	No	Yes/No	Yes/No
Anemia	No	Yes/No	Yes/No
Thrombocytopenia	No	Yes/No	Yes/No
Bone marrow involvement ≥30%	Yes/No	Yes	No
Molecular prognostic factors predictive of outcome	No	Yes	Yes
Higher risk of infection	Yes	Yes	Yes
Higher risk of autoimmune problems	Yes	Yes	Yes

From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

STAGING

Staging reflects the clinical burden of disease and aids assessment of prognosis and treatment decision making. The historical staging systems by Rai and Binet remain in clinical use. They use **only** physical examination and the CBC (i.e., no scans). The modified Rai system distinguishes three risk groups:

- Low risk (lymphocytosis alone, or Stage 0)
- Intermediate risk (presence of lymphadenopathy, hepatomegaly or splenomegaly, formerly Stage I/II)
- High risk (presence of anemia with hemoglobin <11 g/dl, or thrombocytopenia with platelet count <100,000/mm^3, formerly stage III/IV)

The Binet system divides CLL into three stages:

- Stage A: Involvement of <3 nodal areas (counting separately cervical, axillary, or inguinal lymph nodes, spleen, and liver)
- Stage B: Three or more areas involved
- Stage C: Presence of anemia (hemoglobin <10 g/dl) or thrombocytopenia (<100,000/mm^3), independent of the areas involved

Prognosis in CLL can be determined using the CLL-International Prognostic Index (CLL-IPI), which includes five factors: 17p/*TP53* status, *IGVH* mutational status, serum beta-2-microglobulin, Rai/Binet stage (0/A versus others), and age >65 yr. Overall 5-yr survival varies from 93% for the low-risk group to 23% for the very high-risk group (Table 4).

- "Watchful waiting" (i.e., observation without therapy) is the optimal strategy for all early-stage, asymptomatic patients outside of clinical trials because early chemotherapy provides no survival or quality-of-life benefit.
- Treatment with the Bruton tyrosine kinase (BTK) inhibitor ibrutinib or with immunochemotherapy is the standard of care for patients with symptoms related to disease, bulky adenopathy, rapidly increasing lymphocyte count, or progressive cytopenias (except for autoimmune cytopenias, which can be treated without chemotherapy).

ACUTE GENERAL Rx

- The initial chemotherapy is chosen depending on the patient's age, comorbidities, and CLL cytogenetics (Fig. 2).
- BTK inhibitor ibrutinib is the most effective first-line treatment strategy in every studied setting, demonstrating improved survival against aggressive immunochemotherapy in younger/fit patients, or against less intensive approaches in older patients. Its downsides include lack of complete remissions and need for long-term daily drug therapy. Combinations of ibrutinib with venetoclax for first-line therapy of CLL have shown impressive results in trials with almost all patients achieving a complete response without any added toxicity by combining the two drugs.[1]
- Ibrutinib is typically prescribed at the dose of 420 mg daily and is associated with diarrhea, increased risk of hypertension, atrial fibrillation (10%), and occasional bleeding (particularly with concurrent anticoagulants).
- Immunochemotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) results in complete remission in 72% of patients, with about 30% remaining in remission after 12 yr of follow-up. It may be considered for fit patients younger than 65 yr with unmutated *IGVH*, but is associated with high rates of toxicity.
- Immunochemotherapy with bendamustine and rituximab or with chlorambucil and obinutuzumab is an option for older patients, and provides at least a partial remission for most patients, with median progression-free survival of about 2 to 4 yr.
- CLL with deletion 17p or *TP53* mutation does not respond well to standard immunochemotherapy, and BTK inhibitors are the standard approach.
- Recurrent CLL is often characterized by acquired deletion or mutation of the *TP53* gene and can also be treated with a variety of salvage regimens:
  1. Ibrutinib for patients who did not receive it as first line of treatment.
  2. Venetoclax, an oral BCL2 inhibitor, in combination with rituximab or alone; Venetoclax is characterized by a high response rate (79%) and risk of tumor lysis, requiring extremely careful dosing and monitoring in the first days of therapy.
  3. Idelalisib, an oral PI3K inhibitor.
  4. Anti-CD20 monoclonal antibodies: Ofatumumab, obinutuzumab, rituximab, alone or in combination with chemotherapy: Purine analogues (fludarabine, pentostatin), alkylating agents (bendamustine, cyclophosphamide, CHOP-like combinations).
  5. Alemtuzumab (anti-CD52 monoclonal antibody).
  6. High-dose methylprednisolone.
  7. Palliative radiation therapy to bulky lymph nodes or spleen.
- Allogeneic bone marrow transplantation is occasionally used for younger patients with recurrent, refractory, or ultra-high cytogenetic risk disease, but is associated with high rates of transplant-related mortality.

CHRONIC Rx

Treatment of systemic complications:

- Tumor lysis syndrome may occur during initial or subsequent chemotherapy but is extremely unlikely without chemotherapy in CLL, even with high lymphocyte counts.
- CLL patients are at increased risk of solid tumors and should adhere to age-appropriate screening modalities; skin cancers, including melanoma, are particularly common.
- Hypogammaglobulinemia is frequent in CLL and may cause recurrent infections, particularly pneumonias. Immunoglobulin supplementation (250 mg/kg IV every 4 wk) may prevent infections but has no effect on the course of CLL.

[1] Jain N et al: Ibrutinib and venetoclax for first-line treatment of CLL, *N Engl J Med* 380(22):2095-2103, 2019.

- Patients after chemoimmunotherapy are at risk for, and often ultimately succumb to, opportunistic infections. Herpes zoster and *Pneumocystis jiroveci* prophylaxis is used during and after some chemoimmunotherapy regimens.
- Novel targeted agents are associated with specific adverse effects during prolonged therapy. Ibrutinib may cause atrial fibrillation, chronic diarrhea, and hemorrhage and must be held before surgical procedures. Idelalisib may cause severe hepatitis and pneumonitis. Venetoclax may cause tumor lysis syndrome and neutropenia.
- Autoimmune hemolytic anemia, thrombocytopenia, and (rare) neutropenia may be treated with steroids, immunoglobulin, or immune suppression without cytotoxic chemotherapy.
- CLL is a contraindication to administration of live vaccines (varicella zoster, mumps/measles/rubella, yellow fever, intranasal influenza). Patients should adhere to the recommended schedule of immunization against *Pneumococcus* and influenza.

TABLE 4 Prognosis of Patients with CLL at the Time of Diagnosis, Stratified by the CLL-International Prognostic Index.

Number of High Risk Factors	Risk Group	Percent of Patients	Median Time to First Chemotherapy	Overall Survival at 5 yr
0-1	Low	38%	5-10 yr	93%
2-3	Intermediate	34%	4-5 yr	79%
4-6	High	23%	1-3 yr	63%
7-10	Very high	5%	<1 yr	23%

Risk factors include age >65 yr (1 point), stage Rai I-IV or Binet B-C (1 point), unmutated *IGVH* (2 points), beta-2-microglobulin >3.5 mg/L (2 points), or deletion 17p/*TP53* mutation (4 points). *CLL,* Chronic lymphocytic leukemia.

TABLE 5 Modified Indications for Treatment of Chronic Lymphocytic Leukemia

- Grade 2 or greater fatigue limiting life activities
- B symptoms persisting for ≥2 wk
- Lymph nodes >10 cm or progressively enlarging lymph nodes causing symptoms
- Spleen or liver with progressive enlargement or causing symptoms
- Anemia (hemoglobin <11 g/dl) referable to CLL
- Thrombocytopenia (platelets $<100 \times 10^{12}$/L) referable to CLL or ITP poorly responsive to traditional therapy
- Severe paraneoplastic (e.g., insect hypersensitivity, vasculitis, myositis) process related to CLL not responsive to traditional therapies

B symptoms, Fever, night sweats, weight loss; *CLL,* chronic lymphocytic leukemia; *ITP,* idiopathic thrombocytopenic purpura.
From Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

DISPOSITION

Most patients die due to infectious complications of therapy for refractory disease after several lines of treatment. Histologic transformation to an aggressive lymphoma is also associated with high mortality. Palliative treatment should be offered to patients who are no longer benefiting from aggressive therapy to avoid pervasive and futile treatment with distressing complications.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Chronic Lymphocytic Leukemia (Patient Information)

AUTHOR: **Adam J. Olszewski, MD**

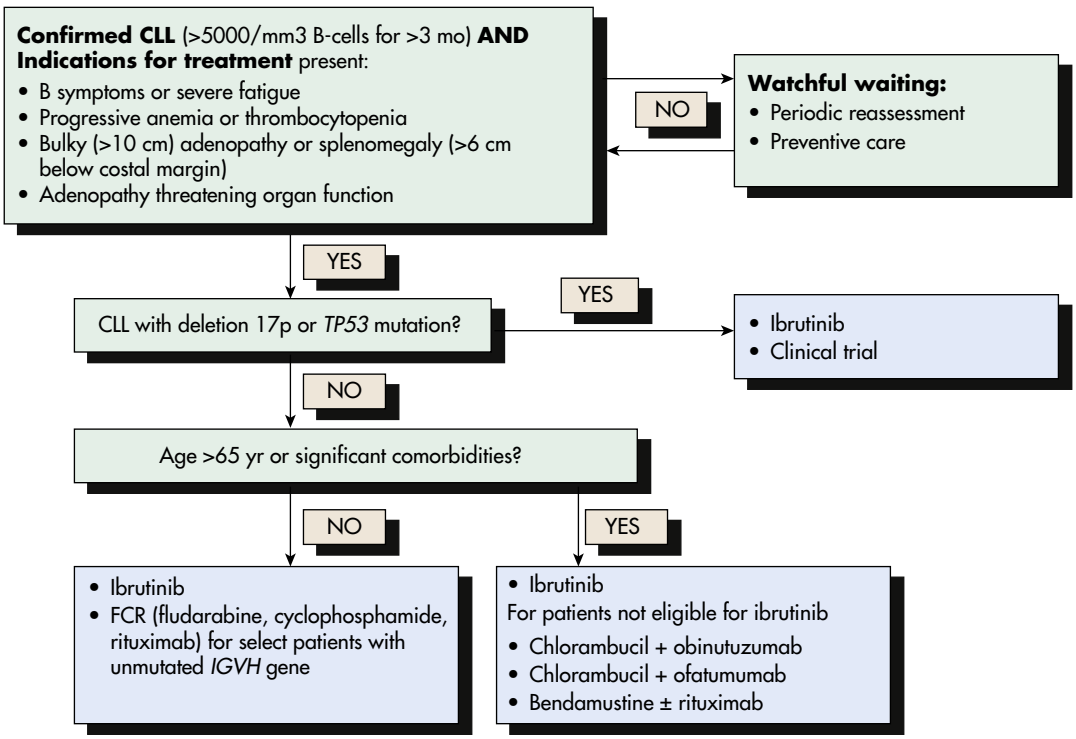

FIG. 2 Initial treatment approach in chronic lymphocytic leukemia. *CLL,* Chronic lymphocytic leukemia. (Courtesy Adam J. Olszewski, MD)

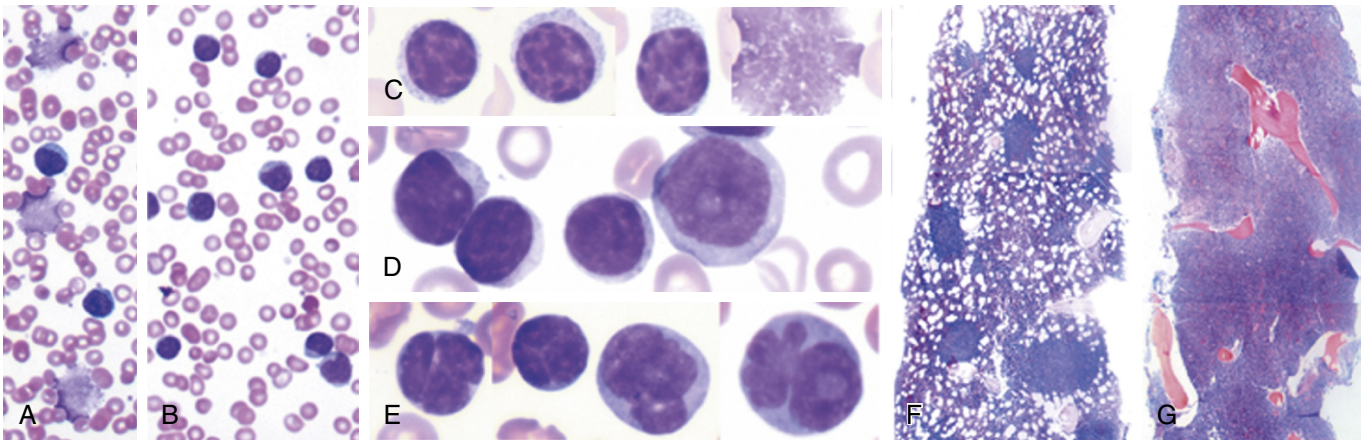

FIG. E1 Microscopic images of chronic lymphocytic leukemia. Peripheral blood smear **(A-E)** typically shows mature lymphocytes slightly larger than the red cells a with small amount of cytoplasm and smudge cells **(A)**. Bone marrow biopsy **(F, G)** shows hypercellularity with infiltration by the leukemic cells.

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BASIC INFORMATION

DEFINITION

Chronic myeloid leukemia (CML) is a malignant clonal stem disease characterized by the Philadelphia chromosome, an acquired cytogenetic abnormality arising out of the reciprocal translocation of long arms of the *ABL* and *BCR* genes on chromosomes 9 and 22. The resultant *BCR:ABL* fusion oncogene is associated with the development of abnormal myeloid proliferation and accumulation of immature granulocytes. The initial chronic phase (CP-CML) is marked by a myeloproliferative picture lasting months to years, which evolves into an advanced phase (AP-CML) characterized by poor response to therapy and worsening cytopenias; finally, this phase then evolves into a terminal blast phase (BP-CML), resulting in acute leukemia (70% myeloid and approximately 30% lymphoid subtype). The criteria for accelerated and blast phases of CML are described in Table 1.

SYNONYMS

Chronic granulocytic leukemia
Chronic myelogenous leukemia

ICD-10CM CODES

C92.10	Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission
C92.11	Chronic myeloid leukemia, BCR/ABL-positive, in remission
C92.12	Chronic myeloid leukemia, BCR/ABL-positive, in relapse

EPIDEMIOLOGY & DEMOGRAPHICS

- CML usually presents in the mid-50s range and accounts for 15% to 20% of adult leukemias.
- Incidence is 1 to 1.5 cases per 100,000 people annually.
- In 2019, nearly 8990 new cases and more than 1140 deaths are estimated to occur in the U.S.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Up to 50% patients are asymptomatic, with diagnosis based on abnormal blood counts.
- In chronic phase, symptomatic patients have fatigue, weight loss, early satiety, and left abdomen pain, and the examination can reveal splenomegaly. Occasionally, hyperleukocytosis and severe thrombocytosis may lead to hyperviscosity-related symptoms.
- Patients in accelerated phase are usually symptomatic with fevers, sweats, weight loss, abdomen pain, and progressive splenomegaly.
- Patients in blast phase in addition can have bone pain; symptoms of anemia, infectious complications, and bleeding are also present.

ETIOLOGY

The etiology of CML is unclear, although radiation exposure has been linked in its development.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Splenic lymphoma
- Primary myelofibrosis
- Chronic neutrophilic leukemia
- Essential thrombocythemia

LABORATORY TESTS

- CBC showing left-shifted myeloid cells, with the presence of precursor polymorphonuclear cells, basophils, and eosinophils; can be accompanied by thrombocytosis and anemia.
- Bone marrow biopsy demonstrates hypercellularity with granulocytic hyperplasia, increased ratio of myeloid cells to erythroid cells, and increased megakaryocytes (Fig. E1).
- Bone marrow cytogenetics demonstrated the 9:22 translocation (Philadelphia chromosome) in >95% of patients (Fig. 2).
- Leukocyte alkaline phosphatase is markedly decreased (unlike other myeloproliferative disorders).
- *BCR-ABL* fusion transcripts can be measured using quantitative RT-PCR technology using either peripheral blood or bone marrow; serial peripheral blood monitoring of transcript level is utilized at 3-mo intervals to determine molecular remission status.

RISK STRATIFICATION

- Chronic phase CML patients can be stratified into low-, intermediate-, or high-risk criteria using the Sokal or Hasford criteria; more recently, the EUTOS score has been validated as an effective tool used to stratify patients into low- or high-risk categories.
- Patients developing secondary mutations have variable response to second- or third-line therapies; the *T315I* mutation is typically associated with resistance and is treated with allogeneic stem cell transplantation (SCT).

IMAGING STUDIES

Ultrasound or CT scan of abdomen can be done.

TREATMENT

Treatment with a potential to either cure CML or prolong long-term survival should be used according to the phase of the disease.

- Chronic phase: The therapeutic approach involves the use of either a first-generation (imatinib) or second-generation (dasatinib, nilotinib, or bosutinib) oral tyrosine kinase inhibitor (TKI). Imatinib mesylate, a 2-phenylaminopyrimidine derivative, binds to the canonic adenosine triphosphate (ATP)–binding site of the Abl kinase domain. It blocks phosphorylation of tyrosine residues on substrate protein. Blocking ATP binding inactivates the Abl kinase because it cannot transfer phosphate to its substrate. Inhibiting phosphorylation prevents activation of signal transduction pathways that cause CML (Fig. E3). Imatinib inhibits several tyrosine kinases, including $p210^{BCR–ABL1}$, $p190^{BCR–ABL1}$, v-ABL1, c-ABL1, c-Kit, and platelet-derived growth factor receptor (PDGFR). The decision to select a particular TKI is based on patient comorbidities, age, and often formulary restrictions. The large majority of patients obtain hematologic and cytogenetic remissions; major molecular

TABLE 1 Definitions of the Accelerated and Blastic Phases of Chronic Myeloid Leukemia

Criteria	MD Anderson Cancer Center[a]	International Bone Marrow Transplant Registry	World Health Organization
Accelerated Phase			
Percent blasts	15-29	10-29	10-19
Percent blasts + promyelocytes	≥30	≥20	NA
Percent basophils	≥20	≥20% (basophils + eosinophils)	≥20
Platelets ($\times 10^9$/L)	<100	Unresponsive ↑, persistent ↓	<100 or >1000 unresponsive
Cytogenetics	CE	CE	CE not at diagnosis
WBCs	NA	Difficult to control, or doubling in <5 days	NA
Anemia	NA	Unresponsive	NA
Splenomegaly	NA	Increasing	NA
Other		Chloromas, myelofibrosis	Megakaryocyte proliferation, fibrosis
Blastic Phase			
30% or more blasts; or extramedullary blastic disease, except for the World Health Organization classification, which requires 20% or more			

[a]These criteria were also used in all the IFN-α and tyrosine kinase inhibitor studies.
CE, Clonal evolution; *NA,* not applicable; *WBC,* white blood cell.
From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

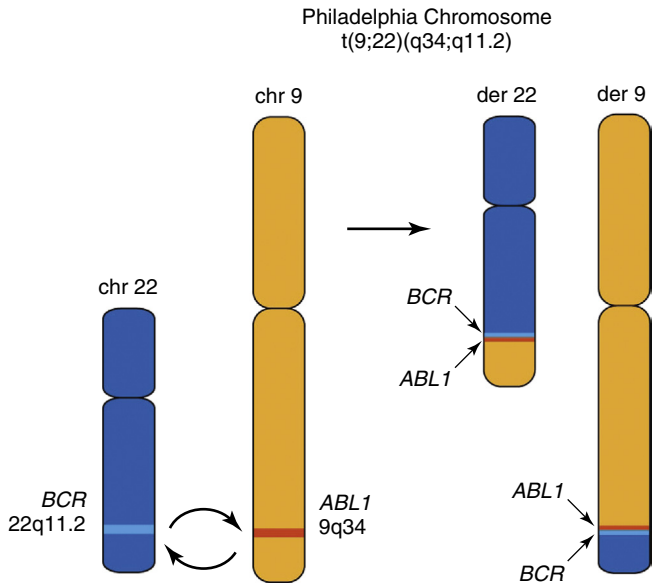


FIG. 2 The Philadelphia chromosome, der(22q), results from the reciprocal translocation of a portion of the *ABL1* gene on chromosome 9 at band q34 to the region of the *BCR* gene on chromosome 22 at band q11.2. In turn, a portion of *BCR* is translocated to chromosome 9 to the region of *ABL1*. In 5% to 10% of patients with chronic myeloid leukemia, cryptic or complex rearrangements result in a *BCR-ABL1* fusion gene, even though no Philadelphia chromosome is detected cytogenetically. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.)

TABLE 2 Approved Indications in Chronic Myeloid Leukemia

	Frontline	Salvage	Accelerated	Blastic
Imatinib	400 mg QD 340 mg/m^2 per day	400 mg QD (IFN failure)	600 mg QD (IFN failure)	600 mg QD (IFN failure)
Dasatinib	100 mg QD	100 mg QD	140 mg QD	140 mg QD
		A	A	A
Nilotinib	300 mg BID	400 mg BID	400 mg BID	—
		A	A	
Bosutinib	—	500 mg QD	500 mg QD	500 mg QD
		B	B	B
Ponatinib	—	45 mg QD	45 mg QD	45 mg QD
		B	B	B
Omacetaxine	—	1.25 mg/m^2 SC × 14 days every 28 days (induction), then × 7 days every 28 days	1.25 mg/m^2 SC × 14 days every 28 days (induction), then × 7 days every 28 days	—
		C	C	

A, Resistance or intolerance to prior therapies including imatinib; *B,* resistance or intolerance to prior tyrosine kinase inhibitors (TKIs); *BID,* twice daily; *C,* resistance or intolerance to two prior TKIs; *IFN,* interferon; *QD,* daily; *SC,* subcutaneously.
From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

remissions are observed in 25% to 60% cases. Patients who lose their initial response, develop secondary mutations, or develop intolerance to therapy can be treated with newer third-generation TKIs (bosutinib, ponatinib). Omacetaxine, a protein synthesis inhibitor, is also effective in patients who have previously received TKI therapy. The approved indications are summarized in Table 2. An algorithm of the suggested treatment approach in CML is illustrated in Fig. 4.

- Second-generation TKIs (dasatinib, nilotinib, or bosutinib) are preferred for patients with an intermediate- or high-risk Sokal or Hasford score, especially for young women whose goal is to achieve a deep and rapid molecular response and eventual drug discontinuation of TKI therapy for fertility purposes.
- During therapy for chronic phase CML, treatment efficacy is monitored by the use of serial RT-PCR to measure peripheral blood *BCR-ABL* transcripts every 3 to 6 mo.
- Accelerated phase: Patients are initially treated with second-generation TKIs but ultimately require allogeneic SCT.
- Blast phase: Patients are initially treated with conventional induction chemotherapy as per the type of evolved acute leukemia and then subsequently undergo allogeneic SCT.
- Symptomatic hyperleukocytosis is treated with leukapheresis and hydroxyurea; allopurinol should be started to prevent urate nephropathy after the rapid lysis of the leukemia cells.

DISPOSITION

- Response definition and monitoring are summarized in Table 3.
- Median survival for patients with chronic phase CML undergoing therapy with current TKIs is estimated to last 25+ yr.
- Median survivals for patients with accelerated and blast phase CML are 5 yr and 7 to 11 mo, respectively.
- Discontinuing oral TKI therapy in chronic phase CML patients who have achieved deep molecular remissions is associated with molecular relapses in up to half the cases; as such, indefinite therapy is preferred in all cases.

REFERRAL

To hematology physician

PEARLS & CONSIDERATIONS

- Chronic-phase CML patients should be risk-stratified at diagnosis to define prognosis upfront; patients achieving complete cytogenetic remission or major molecular remission by 12 mo have consistently superior long-term outcomes.
- Regular monitoring of molecular response using peripheral blood RT-PCR for BCR:ABL transcript levels is done every 3 to 6 mo for disease monitoring.
- Allogeneic stem cell transplantation is a useful modality for advanced CML patients and chronic phase CML patients who develop resistance to standard TKI therapy.

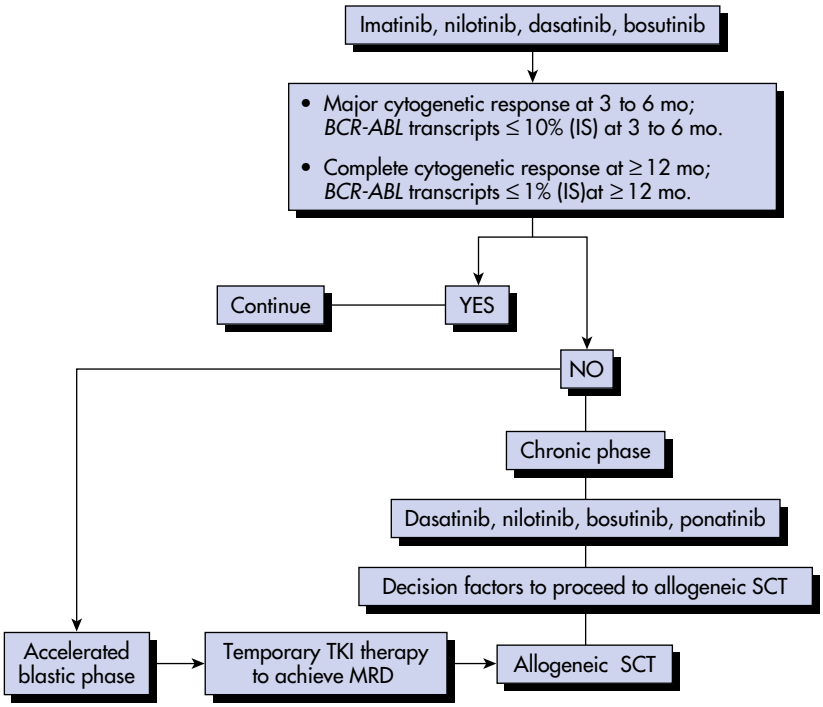
SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Chronic Myeloid Leukemia (Patient Information)

AUTHOR: **Ritesh Rathore, MD**



- Choice of salvage (TKI) depends on frontline TKI, and *BCR-ABL* mutation. If *T315I* mutation, only ponatinib is effective; if not available, use hydrea or chemotherapy, and proceed to allogeneic stem cell transplantation (SCT).

- In CML salvage the following are considered:
  - If relapse in accelerated-blastic phase, use TKIs as temporary measure to achieve minimal residual disease (MRD) and proceed to allogeneic SCT.
  - If relapse in chronic phase, choice of TKI based on mutations. Choice to continue on TKI indefinitely depends on presence of absence of clonal evolution, adverse mutations, and response to TKIs.
  - Older patients (≥65 yr) and patients with poor matching donors may decide to continue TKIs in combination with hydroxyurea or other chemotherapy to gain several years of good quality of life, rather than opt for allogeneic SCT.

FIG. 4 Algorithm of the suggested treatment approach in chronic myeloid leukemia (CML). *TKI,* Tyrosine kinase inhibitor. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

TABLE 3 Response Definition and Monitoring

Hematologic Response	Cytogenetic Response	Molecular Response
Complete: Platelet count <450 × 10^9/L; WBC count <10 × 10^9/L; differential without immature granulocytes and with less than 5% basophils; nonpalpable spleen	Complete: Ph^+ 0 Major: Ph^+ 1-35% Minor: Ph^+ 36-65% Minimal: Ph^+ 66-95% None: Ph^+ <95%	Complete: *BCR-ABL* transcripts nonquantifiable and nondetectable[a] Major: ≤0.10%

[a]Qualified by the limit of sensitivity of the polymerase chain reaction assay employed.
BCR-ABL to control gene ratio according to the proposed international scale for measuring molecular response, with a standardized "baseline," as established in the IRIS trial, taken to represent 100% on the international scale, and a 3-log reduction from the standardized baseline (major molecular response) fixed at 0.10%.
ABL, Abelson leukemia virus; *BCR,* breakpoint cluster region; *Ph^+,* Philadelphia chromosome positive; *WBC,* white blood cell.
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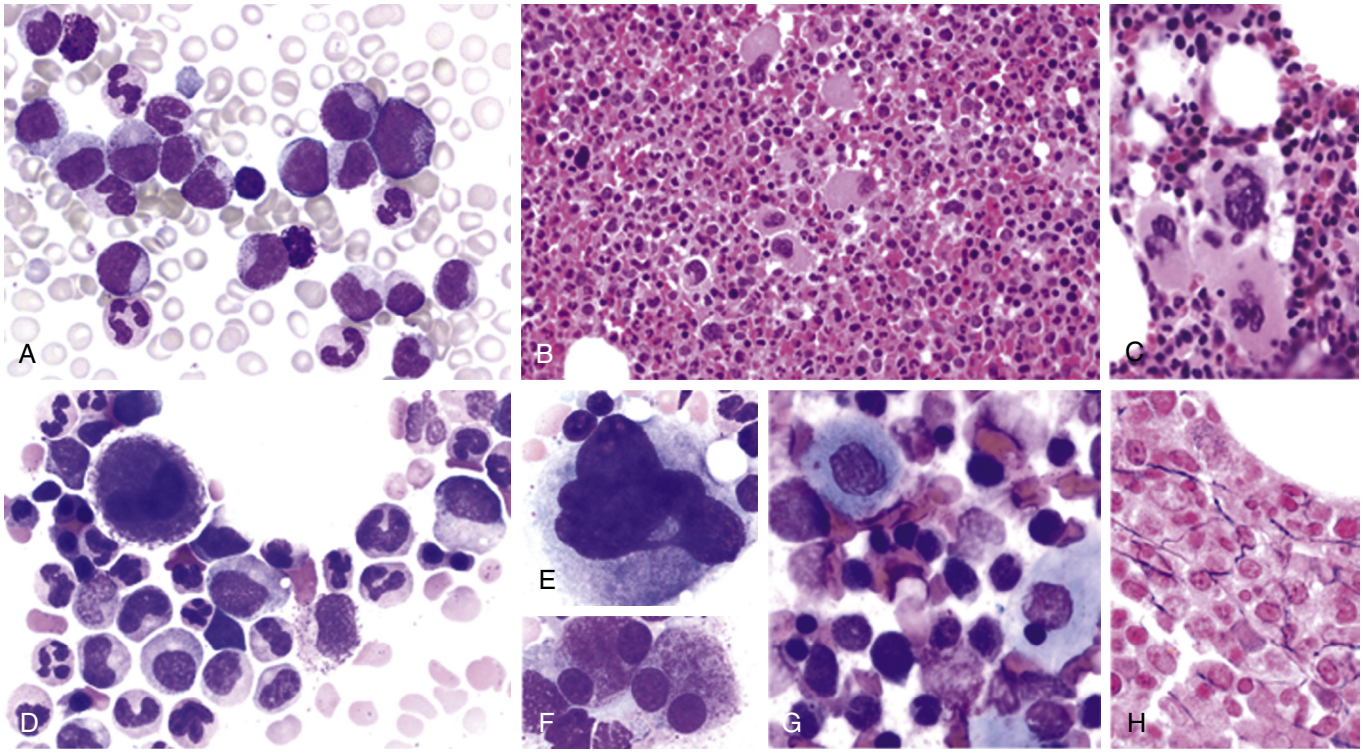

FIG. E1 Chronic myeloid leukemia, chronic phase. Peripheral smear **(A)** showing marked leukocytosis caused by a granulocytic proliferation of all stages with particularly increased myelocytes and absolute basophilia. Bone core biopsy **(B)** illustrating markedly hypercellular marrow caused by granulocytic proliferation and increased small hypolobated megakaryocytes. Compare with large megakaryocytes **(C)** from a myeloproliferative disorder other than chronic myeloid leukemia (CML). Bone marrow aspirate **(D)** showing granulocytic proliferation and small "dwarf" megakaryocyte, compared with large-size megakaryocyte **(E)** and micromegakaryocytes **(F)** typical of myelodysplastic syndrome (MDS). Pseudo-Gaucher cells **(G)** and mild fibrosis **(H)** as seen on reticulin stain. (From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Churchill Livingstone.)

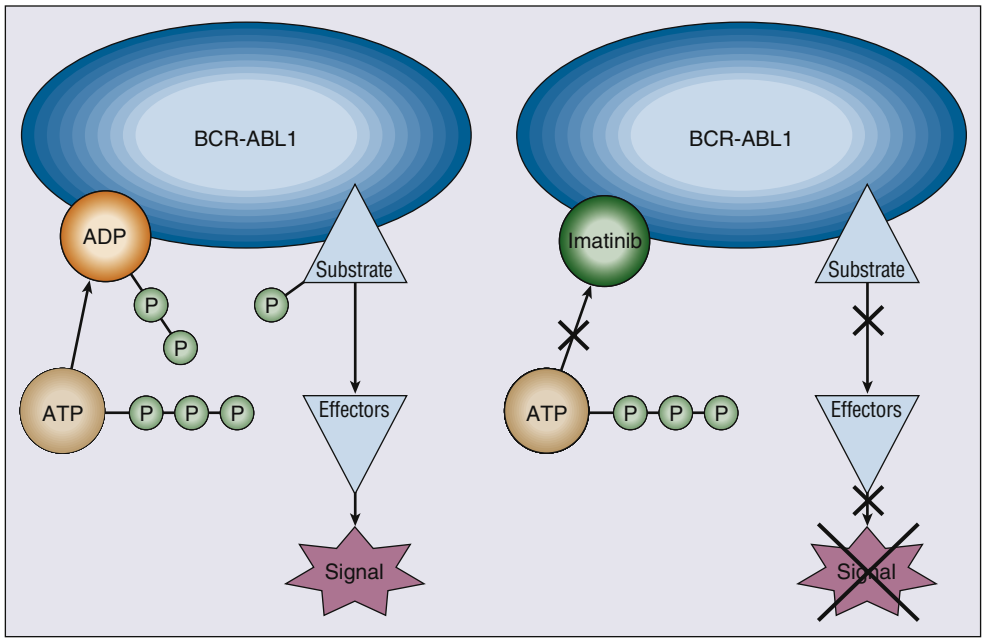

FIG. E3 The BCR-ABL1 oncoprotein has constitutive tyrosine kinase activity compared with the tightly regulated tyrosine kinase activity of the normal ABL1 product. The BCR-ABL1 kinase activates multiple substrates and binding partners, resulting in activation of downstream signaling pathways. This results in increased proliferation and reduced apoptosis of chronic myeloid leukemia (CML) cells. By binding to the ABL1 kinase domain, imatinib prevents the phosphorylation of BCR-ABL1, thus interrupting the activation of the CML pathways. *ADP,* Adenosine diphosphate; *ATP,* adenosine triphosphate. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

BASIC INFORMATION

DEFINITION

Chronic obstructive pulmonary disease (COPD) is an inflammatory respiratory disease usually caused by exposure to tobacco smoke. It is an umbrella term for various clinical entities with multiple causes resulting in airflow limitation that is not fully reversible. The pathophysiology of COPD is related to enhanced inflammatory response to noxious particles and gases, chronic airway irritation, mucus production, and pulmonary scarring and changes in pulmonary vasculature.

Acute exacerbations and comorbidities contribute to the overall severity and prognosis of the disease in individual patients.

Traditionally, COPD was described as encompassing *emphysema*, characterized by loss of lung elasticity and destruction of lung parenchyma with enlargement of air spaces, and *chronic bronchitis*, characterized by obstruction of small airways and productive cough >3 mo for more than 2 successive yrs. These terms are no longer included in the formal definition of COPD, although they are still used clinically. Although emphysema and chronic bronchitis are commonly associated with COPD, neither is required to make the diagnosis.

An overlap syndrome known as ACOS (asthma-COPD overlap syndrome), characterized by persistent airflow limitation with several features associated with asthma and several features associated with COPD, has been gaining recognition and may have treatment and mortality implications (Global Initiative for Chronic Obstructive Lung Disease [GOLD] and Global Initiative for Asthma [GINA] consensus statement).

SYNONYMS

COPD
Emphysema
Chronic bronchitis

ICD-10CM CODES

J42	Chronic bronchitis, unspecified chronic bronchitis type
J44.9	Chronic obstructive pulmonary disease, unspecified COPD type
J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection
J44.1	Chronic obstructive pulmonary disease with acute exacerbation
J43.0	Unilateral emphysema
J43.1	Panlobular emphysema
J43.2	Centrilobular emphysema
J43.8	Other emphysema
J43.9	Pulmonary emphysema, unspecified emphysema type

EPIDEMIOLOGY & DEMOGRAPHICS

- COPD affects 14% of U.S. adults aged 40 to 79 yr.
- Between 10% and 20% of COPD in the U.S. is due to occupational or other exposure to chemical vapors, irritants, and fumes; 80% to 90% is due to cigarette smoking.
- COPD is the third leading cause of death in the U.S.
- Highest incidence is in males >40 yr.
- 16 million office visits, 500,000 hospitalizations, 126,000 deaths annually, and >$18 billion in direct health care costs annually can be attributed to COPD.
- Patients with COPD living in isolated rural areas of the U.S. are at greater risk for COPD exacerbation-related mortality than those living in urban areas, independent of hospital rurality and volume.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with COPD have historically been classically subdivided in two major groups based on their phenotype:
  1. *Blue bloaters* are patients with chronic bronchitis; the name is derived from the bluish tinge of the skin (as a result of chronic hypoxemia and hypercapnia) and from the frequent presence of peripheral edema (from cor pulmonale); chronic cough with production of large amounts of sputum is characteristic.
  2. *Pink puffers* are patients with emphysema; they have a cachectic appearance but pink skin color (adequate oxygen saturation); shortness of breath is manifested by pursed-lip breathing and use of accessory muscles of respiration.
- COPD may present with combinations of the following signs and symptoms:
  1. Cyanosis, chronic cough (usually productive but may be intermittent and may be unproductive), tachypnea, tachycardia.
  2. Dyspnea (persistent, progressive), pursed-lip breathing with use of accessory muscles for respiration, decreased breath sounds, wheezing.
  3. Chronic sputum production.
  4. Chest wall abnormalities (hyperinflation, "barrel chest," protruding abdomen).
  5. Flattening of diaphragm.

TABLE 1 Systemic Manifestations and Comorbidities of COPD

Cardiovascular	Infarction Arrhythmia Congestive heart failure Aortic aneurysm
Hypercoagulability	Stroke Pulmonary embolism Deep vein thrombosis Atrophy
Systemic	Weight loss Osteoporosis Skin wrinkling Anemia Fluid retention
Lung cancer	Depression

From Mason RJ: *Murray & Nadel's textbook of respiratory medicine*, ed 5, Philadelphia, 2010, WB Saunders.

- Systemic manifestations and comorbidities of COPD are described in Table 1.
- Acute exacerbation of COPD is mainly a clinical diagnosis and generally manifests with worsening dyspnea, increase in sputum purulence, and increase in sputum volume. Respiratory symptom status, however, is not a reliable indicator of the presence of airflow obstruction. Individuals with normal spirometry values may report respiratory symptoms, whereas individuals who have severe to very severe airflow obstruction by spirometry may report no symptoms. Individuals with sedentary lifestyles may underestimate their symptoms and careful history taking is important to elicit symptoms suggestive of COPD.

ETIOLOGY

- Tobacco exposure (Fig. E1)
- Occupational exposure to pulmonary toxins (e.g., dust, noxious gases, vapors, fumes, cadmium, coal, silica); the industries with the highest exposure risk are plastics, leather, rubber, and textiles
- Atmospheric pollution
- Alpha-1-antitrypsin deficiency (rare; <1% of COPD patients)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Heart failure (HF)
- Asthma
- Tuberculosis, other respiratory infections
- Bronchiectasis
- Anemia
- Cystic fibrosis
- Neoplasm
- Pulmonary embolism
- Obliterative bronchiolitis
- Diffuse panbronchiolitis
- Sleep apnea, obstructive
- Hypothyroidism <50% predicted
- Neuromuscular disease

DIAGNOSTIC WORKUP

- Chest x-ray is seldom diagnostic but useful to visualize significant hyperinflation and to exclude alternative diagnosis (e.g., CHF, TB).
- Pulmonary function testing (spirometry). Spirometry is the reference standard for diagnosing and assessing the severity of COPD. Measurement of airflow limitation (by forced expiratory volume in 1 second [FEV_1]) is recommended to confirm diagnosis and establish prognosis.
- Oxygen saturation and arterial blood gases (useful in selected patients with FEV_1 <50% predicted, with acute exacerbation or hypoxia by pulse oximetry).
- Alpha-1-antitrypsin: All patients with COPD should be screened one time for alpha-1 antitrypsin deficiency.

LABORATORY TESTS

- CBC: Generally not helpful, may reveal leukocytosis with left shift during acute exacerbation and secondary polycythemia in COPD with significant, chronic hypoxia. Recent trials have

shown that eosinophilia in COPD patients predicts response to corticosteroids. Eosinophilia may also be found in an acute exacerbation in an asthma-COPD overlap syndrome.
- Sputum may be purulent with bacterial respiratory tract infections. Sputum staining and cultures are usually reserved for cases refractory to antibiotic therapy.
- Arterial blood gases: Normocapnia, mild to moderate hypoxemia may be present. ABGs and pulse oximetry are usually used to determine if a patient is a candidate for long-term oxygen therapy or if hypercapnia is present (ABGs).
- Spirometry pulmonary function testing (PFT) with measurement of forced vital capacity (FVC) and FEV_1. Spirometry should be obtained to diagnose airflow obstruction in clinically stable patients with respiratory symptoms. It should not be used to screen for airflow obstruction in individuals without respiratory symptoms. Spirometry reveals that the primary physiologic abnormality in COPD is an accelerated decline in FEV_1 from the normal rate in adults >30 yr of approximately 30 ml/yr to nearly 60 ml/yr. PFT results in COPD reveal abnormal diffusing capacity, increased total lung capacity and/or residual volume, and fixed reduction in FEV_1 in patients with emphysema; normal diffusing capacity and reduced FEV_1 are found in patients with chronic bronchitis. Stage and severity of COPD according to post-bronchodilator spirometry are described in Table 2. It is important to note that FEV_1 does not correlate well with individual patients' severity of dyspnea, exercise limitations, or health status. Evaluation of patients should also focus on symptom control and risk for adverse events in addition to FEV_1.
- Patients with COPD can generally be distinguished from asthmatics by their incomplete response to short-acting beta agonist (change in FEV_1 <200 ml and 12%) and absence of an abnormal bronchoconstrictor response to methacholine or other stimuli. Nearly 40% of patients with COPD will, however, respond to bronchodilators. Similarly, patients without a smoking history but with chronic asthmatic bronchitis may have airflow obstruction that is not completely reversible.

ASSESSMENT

The global initiative for chronic obstructive lung disease (GOLD) assigns patients with COPD into four groups (A, B, C, D) based on (1) the degree of airflow restriction (Table 2), (2) a patient symptom score using one of two symptom questionnaires (CAT or mMRC), or (3) the number of COPD exacerbations in 1 yr.[1]

IMAGING STUDIES

Chest x-ray:
- Hyperinflation with flattened diaphragm, tenting of the diaphragm at the rib, and increased retrosternal chest space (Fig. 2)
- Decreased vascular markings and bullae in patients with emphysema
- Thickened bronchial markings and enlarged right side of the heart in patients with chronic bronchitis
- Computed tomography: Emphysematous lung, tracheobronchomalacia

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Smoking cessation and elimination of air pollutants.
- Vaccination (pneumococcal vaccine and annual influenza vaccine).
- Supplemental oxygen, usually through a face mask/nasal cannula, to ensure oxygen saturation >90% as measured by pulse oximetry. Continuous oxygen therapy should be prescribed for patients with COPD who have arterial partial pressure of oxygen 55 mm Hg or less, or oxygen saturation 88% or less as measured by pulse oximetry. In patients with stable COPD and moderate resting desaturation (SpO2 89 to 93%) or moderate exercise-induced moderate desaturation (during the 6-minute walk test, Spo2 ≥80% for ≥5 minutes and <90% for ≥10 seconds), long-term supplemental oxygen did not improve mortality or time to first hospitalization.
- Pulmonary secretion clearance: Careful nasotracheal suction is indicated only in patients with excessive secretions and an inability to expectorate. Mechanical percussion of the chest as applied by a physical or respiratory therapist is ineffective with acute exacerbations of COPD.
- Pulmonary rehabilitation should be considered in COPD patients who remain symptomatic despite optimal medical management. Medicare will cover up to 36 sessions of pulmonary rehabilitation in COPD patients.
- Weight loss in obese patients.
- Identification of depression in patients newly diagnosed with COPD is important, as it may be associated with decreased adherence to maintenance therapy of COPD.
- Use of continuous positive airway pressure (CPAP) in patients with COPD and obstructive sleep apnea, as it improves both survival and reduces hospital admissions.

TABLE 2 Stage and Severity of COPD According to Postbronchodilator Spirometry

GOLD Stage and Severity	Definition
I: Mild	FEV_1/FVC <0.70, FEV_1 ≥80% of predicted
II: Moderate	FEV_1/FVC <0.70, 50% ≤ FEV_1 <80% of predicted
III: Severe	FEV_1/FVC <0.70, 30% ≤ FEV_1 <50% of predicted
IV: Very severe	FEV_1/FVC <0.70, FEV_1 <30% of predicted or FEV_1 <50% of predicted plus chronic respiratory failure

FEV_1, Forced expiratory volume in 1 s; *FVC,* forced vital capacity. Data from the Global Initiative for Chronic Obstructive Lung Disease, 2017 Report.

GENERAL Rx

- Pharmacologic treatment should be administered in a stepwise approach according to the severity of disease and patient's

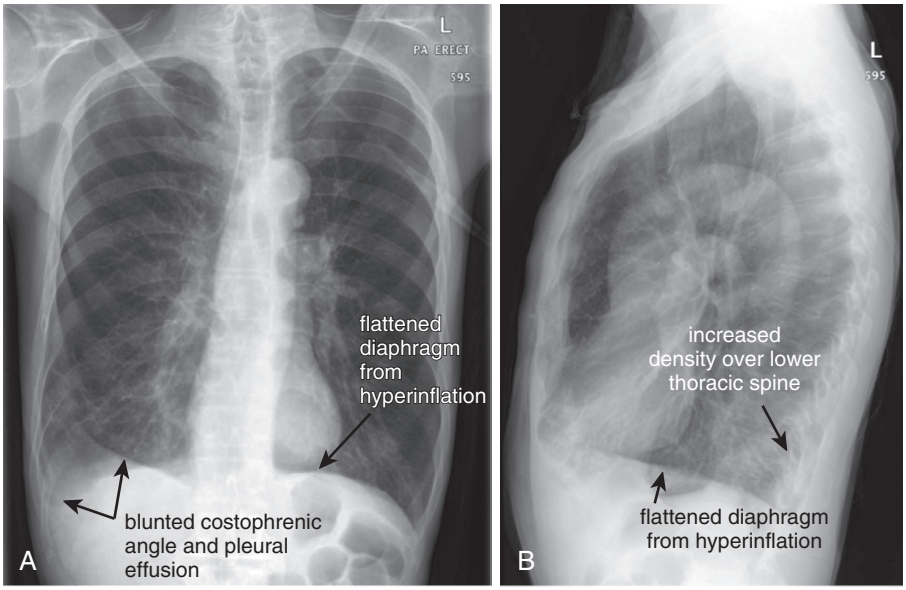

FIG. 2 Chronic obstructive pulmonary disease (COPD). A, Posterior-anterior (PA) upright chest x-ray. **B,** Lateral upright chest x-ray. This 63-yr-old man with a history of COPD presented with 2 wk of worsening cough with yellow sputum and dyspnea. His oxygen saturation was 87% in the emergency room. He has evidence of hyperinflation with flat diaphragms (particularly evident on the lateral x-ray) **(B).** The patient also has a blunted right costophrenic angle with an apparent effusion and increased densities in both the right and the left lung base **(A).** The lateral x-ray also shows increased density overlying the inferior thoracic spine, an abnormal spine sign. (From Broder JS: *Diagnostic imaging for the emergency physician*, Philadelphia, 2011, WB Saunders.)

[1] Lee H et al: Treatment of stable chronic obstructive pulmonary disease: the GOLD guidelines, *Am Fam Physician* 88(10):655-663, 2013.

tolerance for specific drugs. When using the GOLD assessment criteria, pulmonary rehabilitation is recommended for patients in groups B, C, and D. Those in group A should receive a short-acting or long-acting anticholinergic or β_2-agonist for mild intermittent symptoms. For patients in group B, long-acting anticholinergics or long-acting β_2-agonists should be added, and both if symptoms persist on one drug. Patients in group C or D are at high risk of exacerbations and should receive a long-acting anticholinergic or a combination of either an inhaled corticosteroid and a long-acting β_2-agonist or a long-acting anticholinergic and long-acting bronchodilator if symptoms persist. Patients in group D are more complicated and require individual management, multiple drugs, and consideration of roflumilast and azithromycin.

1. Bronchodilators improve symptoms, quality of life, and exercise tolerance and decrease incidence of exacerbations. Inhaled bronchodilators *should be offered* for stable COPD patients with respiratory symptoms and FEV[1] between 60% and 80% of predicted. Long-acting bronchodilators are *recommended* for stable COPD patients with respiratory symptoms and FEV_1 <60% of predicted. Recent guidelines from ACP, ACCP, ATS, and ERS recommend that clinicians prescribe monotherapy using either long-acting inhaled anticholinergics or long-acting inhaled β-agonists for symptomatic patients with COPD and FEV_1 <60% of predicted. Clinicians should base the choice of specific monotherapy on patient preference, cost, and adverse effect profile. Long-acting inhaled bronchodilators are superior to short-acting bronchodilators when taken as needed.
2. Short-acting β_2-agonists (e.g., albuterol metered-dose inhaler 1 to 2 puffs q4 to 6h prn) or short-acting anticholinergic agents (e.g., ipratropium inhaler 2 puffs qid) are acceptable in patients with mild, variable symptoms. Anticholinergics (antimuscarinic agents) are also effective and are available in combination with albuterol (e.g., Combivent). Long-acting inhaled agents (long-acting antimuscarinic agents [LAMAs]) are preferred in patients with mild to moderate or continuous symptoms. Currently available inhaled LAMAs are tiotropium (Spiriva), aclidinium (Tudorza), and glycopyrrolate (Seebri Neohaler, Yupelri). Tiotropium is an excellent long-acting bronchodilator. It is very effective for long-term, once-a-day use. It has been shown to be superior to salmeterol, an inhaled long-acting β-agonist (LABA) in patients with moderate to severe COPD and may possibly slow the rate of decline in FEV_1. Some recent trials, however, have shown higher hospitalization rates and mortality with tiotropium compared to LABAs. Indacaterol, umeclidinium, olodaterol, and vilanterol are other available LABAs for long-term maintenance treatment of bronchospasm associated with COPD. LABAs should not be used with other sympathomimetic drugs, medications that can prolong the QT interval, or beta-blockers. LABAs and LAMAs in different combinations are now available on the market. Although LAMAs and LABAs perform equally well for symptom control, LAMAs are generally preferred for symptom control.
3. Addition of inhaled steroids (fluticasone, budesonide, triamcinolone) is used to reduce exacerbations in patients with moderate to severe COPD. Inhaled steroids are reserved for patients with either ≥2 exacerbations annually or FEV_1 <50% of predicted. The role of inhaled corticosteroids (ICS) in COPD is controversial. Although some trials have demonstrated mild improvement in patients' symptoms and decreased frequency of exacerbations, most pulmonologists believe that these drugs are ineffective in most patients with COPD but should be considered for patients with moderate to severe airflow limitation who have persistent symptoms despite optimal bronchodilator therapy. ICS therapy does not affect 1-yr all-cause mortality among patients with COPD and is associated with a higher risk of pneumonia.
4. Roflumilast is a selective oral PDE4 inhibitor useful to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. It is not a bronchodilator and is not indicated for the relief of acute bronchospasm.
5. Recent guidelines from ACP (American College of Physicians), ACCP (American College of Chest Physicians), ATS (American Thoracic Society), and ERS (European Respiratory Society) suggest that clinicians may administer combination inhaled therapies for symptomatic patients with stable COPD and FEV_1 <60% predicted. They also recommend that clinicians should prescribe pulmonary rehabilitation for symptomatic patients with an FEV_1 <50% predicted and continuous oxygen therapy in patients with COPD who have resting hypoxemia (Pa_{O_2} <55 mm Hg or Sp_{O_2} <88%).
6. Chronic antibiotic therapy: Chronic antibiotic therapy, specifically macrolide such as azithromycin, should be considered in patients with frequent acute exacerbations of COPD despite optimal therapy with bronchodilators and antiinflammatory agents.
7. Systemic glucocorticoid therapy: Chronic systemic glucocorticoid therapy is generally not recommended even in severe COPD due to associated increase in mortality and morbidity.
8. Triple therapy (LAMA plus LABA plus ICS [e.g., vilanterol, umeclidinium, and fluticasone {Trelegy Ellipta}]): Indicated in patients with COPD at high risk for exacerbations. A double-blind, parallel group, RCT (TRINITY) reported that treatment with extrafine fixed triple therapy reduced rates of moderate-to-severe exacerbation and improved baseline FEV_1 at 52 wk as compared with tiotropium in patients with symptomatic COPD, FEV_1 <50%, and a history of exacerbations. Another double-blind RCT (FULFIL) reported similar benefits of single-inhaler triple therapy compared with ICS/LABA therapy in patients with advanced COPD. The greatest benefit occurs in patients with eosinophilia or concomitant asthma. Unfortunately, many patients start triple therapy without clear indications and continue it after they no longer need it.

- Acute exacerbation of COPD (increase in sputum volume and purulence, worsening dyspnea) can be treated with:
  1. Aerosolized β_2-agonists (e.g., metaproterenol nebulizer solution 5% 0.3 ml or albuterol nebulized 5% solution 2.5 to 5 mg).
  2. Anticholinergic agents, which have equivalent efficacy to inhaled beta-adrenergic agonists. Inhalant solution of ipratropium bromide 0.5 mg can be administered every 4 to 8 hr.
  3. Short courses of systemic corticosteroids have been shown to improve spirometric and clinical outcomes. Treatment failure occurs less often in patients who receive low-dose steroids than in those receiving high-dose parenteral steroids. Oral prednisone 40 mg/day for 5 to 14 days is generally effective. Courses of treatment that are extended for >14 days confer no added benefit and increase the risk of adverse events. Trials have shown that in patients with acute COPD exacerbations, systemic glucocorticoid treatment for 5 days is not inferior to treatment for 14 days.
  4. Use of noninvasive positive pressure ventilation (NIPPV) decreases the risk of endotracheal intubation and decreases intensive care unit admission rates. Contraindications to its use are uncooperative patient, decreased level of consciousness, hemodynamic instability, inadequate mask fit, and severe respiratory acidosis. Increased airway pressure can be delivered by using inspiratory positive airway pressure, continuous positive airway pressure, or bilevel positive airway pressure, which combines the other modalities. When using NIPPV, the nasal mask is usually tolerated the best; however, patients must be instructed to keep their mouths closed while breathing with the nasal apparatus. Oxygen can be delivered at 10 to 15 L/min and started in spontaneous ventilation mode with an initial expiratory positive airway pressure setting of 3 to 5 cm H_2O and an inspiratory positive airway pressure setting of up

to 10 cm H_2O. Adjustments in these settings should be made in 2-cm H_2O increments. It is important to monitor patients with frequent vital signs measurements, arterial blood gases, or pulse oximetry. Intubation and mechanical ventilation may be necessary if previous measures fail to provide improvement.

5. IV aminophylline administration is controversial and generally not recommended. When used in patients with refractory symptoms, serum levels should be closely monitored (keep level 8 to 12 mcg/ml) to minimize risks of tachyarrhythmias.

- Approximately 50% of COPD exacerbations are caused by bacterial infection. Antibiotics are indicated in suspected bacterial respiratory infection (e.g., increased purulence and volume of phlegm).
  1. *Haemophilus influenzae* and *Streptococcus pneumoniae* are frequent causes of acute bronchitis.
  2. Oral antibiotics of choice are azithromycin, levofloxacin, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, doxycycline, and cefuroxime.
  3. The two best predictors of potential benefit from antibiotics are purulent sputum and C-reactive protein (CRP) level >40 mg/L.
  4. Procalcitonin-based protocols to trigger antibiotic use are associated with significantly decreased antibiotic use without affecting clinical outcomes such hospital length of stay, treatment failure, and mortality.
- Guaifenesin may improve cough symptoms and mucus clearance; however, mucolytic medications are generally ineffective. Their benefits may be greatest in patients with more advanced disease.
- Fig. 3 illustrates the management of acute exacerbations of COPD. Guideline recommendations for hospital management of COPD exacerbations are described in Table 3. Indications for invasive mechanical ventilation are described in Box 1.
- Lung volume reduction surgery has been proposed as a palliative treatment for severe emphysema. Overall it increases the chance of improved exercise capacity but does not confer a survival advantage over medical therapy. It is most beneficial in patients with both predominantly upper-lobe emphysema and low baseline exercise capacity.
- Preliminary trials involving lung volume reduction using bronchoscopic treatment with nitinol coils have shown improved exercise capacity in patients with severe emphysema. Selection criteria for lung volume reduction surgery is described in Table 4. Box 2 summarizes indications and contraindications for lung volume reduction surgery and lung transplantation.
- Endobronchial valve (EBV) placement (Zephyr valve) via bronchoscopy to reduce lung volume with one-way valves that are allowed to leave but not enter a lung segment is now FDA approved since June 2018.
- Single-lung transplantation (Box 2) should be considered a surgical option in patients with end-stage emphysema who have an FEV_1 <25% of predicted normal value after administration of bronchodilator and additional complications such as severe hypoxemia, hypercapnia, and pulmonary hypertension.

DISPOSITION

- After the initial episode of respiratory failure, 5-yr survival is approximately 25%.
- Development of cor pulmonale or hypercapnia and persistent tachycardia are poor prognostic indicators.
- Supplemental oxygen for patients with resting hypoxemia (defined as SPO_2 <89%) improves survival. The need for oxygen at rest may be the strongest predictor of mortality in chronic respiratory failure from COPD.
- Pulmonary rehabilitation, which includes strength and endurance training and education, nutritional, and psychosocial support, improves symptoms and exercise tolerance but is underutilized.[1]

PEARLS & CONSIDERATIONS

COMMENTS

- All patients with COPD should receive pneumococcal vaccine and yearly influenza vaccine.
- Early antibiotic administration is associated with improved outcomes among patients hospitalized for acute exacerbations of COPD regardless of the risk of treatment failure.
- In assessing the severity of COPD, the FEV_1 is limited by the fact that it does not take into account the systemic manifestations of COPD. The BODE index (body mass index, degree of obstruction, dyspnea, and exercise capacity) has been proposed as a multidimensional scale to better assess the morbidity and mortality associated with COPD. It is better than the FEV_1 alone at predicting the risk of death from any cause and from respiratory causes among patients with COPD. In the BODE index, obstruction is measured by FEV_1 and dyspnea is measured by the modified Medical Research Council (MMRC) dyspnea questionnaire in a 6-minute walk test. A score of 0 on the MMRC indicates that the individual is not troubled with breathlessness except with strenuous exercise, 1 indicates shortness of breath when hurrying or walking up a slight hill, and 2 means the individual walks slower than people of the same age due to breathlessness or has to stop for breath when walking at own pace on level ground. A score of 3 means severe dyspnea because the person has to stop for breath after walking approximately 100 meters or after a few minutes on level ground, and a score of 4 indicates very severe dyspnea and is given when the individual is too breathless to leave the house or is breathless when dressing or undressing.
- Pulmonary artery enlargement as determined by a ratio of the diameter of the pulmonary artery to the diameter of the aorta [PA:A ratio] of >1 detected by CT is associated with severe exacerbations of COPD.
- The average person with COPD has one or two acute exacerbations each yr. Prophylactic use of macrolide antibiotics (azithromycin 250 mg/day) has been shown to decrease the frequency of exacerbations and improve quality of life among selected patients with COPD; however, it leads to hearing decrements in a small percentage of patients and increased prevalence of macrolide-resistant bacteria colonizing the airway and is therefore not recommended.
- Eosinophilic airway inflammation may contribute to COPD exacerbations. Patients with COPD with eosinophilic phenotype may benefit from mepolizumab, a monoclonal antibody directed against interleukin-5.
- Current and former smokers (within 15 yr) with at least a 30-pack-yr history of smoking should be assessed for lung cancer using low-dose computed tomography.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Chronic Obstructive Pulmonary Disease (Patient Information)
Emphysema (Patient Information)
Asthma-COPD Overlap Syndrome (Related Key Topic)

AUTHORS: **Aline N. Zouk, MD,** and **Samaan Rafeq, MD**

[1]Riley CM, Sciurba FC: Diagnosis and outpatient management of chronic obstructive pulmonary disease: a review, *JAMA* 321(8):786-797, 2019.

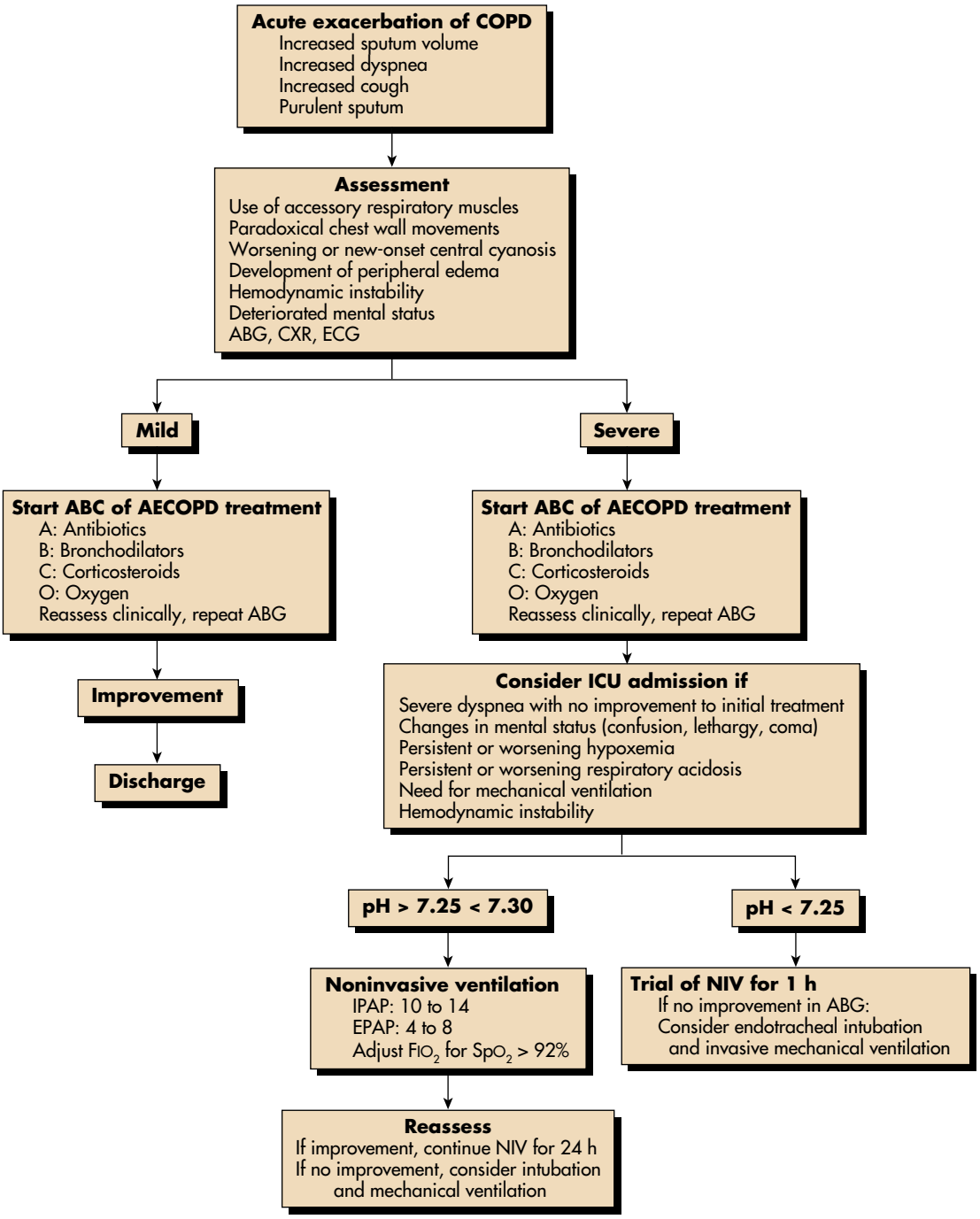

FIG. 3 Management of acute exacerbations of chronic obstructive pulmonary disease. *ABC,* Airway, breathing, circulation; *ABG,* arterial blood gas; *AECOPD,* acute exacerbations of chronic obstructive pulmonary disease; *CXR,* chest x-ray; *ECG,* electrocardiogram; *EPAP,* expiratory positive airway pressure; *FIO_2,* fraction of inspired oxygen; *ICU,* intensive care unit; *IPAP,* inspiratory positive airway pressure; *NIV,* noninvasive ventilation; *SpO_2,* oxygen saturation measured by pulse oximetry. (From Parrillo JE, Dellinger RP: *Critical care medicine: principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

TABLE 3 Guideline Recommendations for Hospital Management of COPD Exacerbations

	Global Initiative for Chronic Obstructive Lung Disease*	American Thoracic Society/ European Respiratory Society†	National Institute for Clinical Excellence‡
Date of statement	2017	2017	2010
Diagnostic testing	Chest radiograph, oximetry, ABGs, ECG. Other testing as warranted by clinical indication.	Chest radiograph, oxygen saturation, ABGs, ECG, sputum Gram stain and culture.	Chest radiograph, ABG, ECG, complete blood count, sputum smear and culture, blood cultures if febrile.
Bronchodilator therapy	Inhaled short-acting β_2-agonist is recommended. Consider ipratropium if inadequate clinical response. Methylxanthines are not recommended due to increased side effect profiles.	Inhaled short-acting β_2-agonist and/or ipratropium with spacer or nebulizer, as needed.	Administer inhaled drugs by nebulizer or handheld inhaler. Specific agents and dosing regimens not specified. Consider theophylline if inadequate response to inhaled bronchodilators.
Antibiotics	Recommended if (1) increases in dyspnea, sputum volume, and sputum purulence all are present; (2) increase in sputum purulence along with increase in either dyspnea or sputum volume; or (3) need for assisted ventilation. See original document for complex treatment algorithm.	Base choice on local bacterial resistance patterns. Consider amoxicillin/clavulanate or respiratory fluoroquinolones. If *Pseudomonas* species and/or other Enterobacteriaceae are suspected, consider combination therapy.	Administer only if history of purulent sputum. Initiate with an aminopenicillin, a macrolide, or a tetracycline, taking into account local bacterial resistance patterns. Adjust therapy according to sputum and blood cultures.
Systemic corticosteroids	Daily prednisolone 30-40 mg (or its equivalent) orally for not more than 5-7 days.	Daily prednisone 30-40 mg orally for 10-14 days. Equivalent dose intravenously if unable to tolerate oral intake. Consider inhaled corticosteroids.	Daily prednisolone 30 mg (or its equivalent) orally for 7-14 days.
Supplemental oxygen	Maintain oxygen saturation >90%. Monitor ABGs for hypercapnia and acidosis.	Maintain oxygen saturation >90%. Monitor ABGs for hypercapnia and acidosis.	Maintain oxygen saturation within the individualized target range. Monitor ABGs.
Assisted ventilation	Indications for NPPV include severe dyspnea, acidosis (pH ≤7.35) and/or hypercapnia (PCO_2 >45 mm Hg), and respiratory rate >25 breaths/min. Contraindications to NPPV include respiratory arrest, hemodynamic instability, impaired mental status, copious bronchial secretions, and extreme obesity. Intubate if contraindication to NPPV or failure of NPPV (worsening ABGs or clinical status). Consider likelihood of recovery and patient's wishes and expectations before intubation.	Consider with pH <7.35 and PCO_2 >45-60 mm Hg and respiratory rate >24 breaths/min. Institute NPPV in a controlled environment, unless there are contraindications (e.g., respiratory arrest, hemodynamic instability, impaired mental status, copious bronchial secretions, and extreme obesity). Intubate if contraindication to NPPV or failure of NPPV (worsening ABGs or clinical status).	NPPV treatment of choice for persistent hypercapnic respiratory failure. Consider functional status, body mass index, home oxygen, comorbidities, prior ICU admissions, age, and FEV_1 when assessing suitability for intubation and ventilation.

ABGs, Arterial blood gases; *ECG,* electrocardiogram; *FEV_1,* forced expiratory volume in 1 s; *ICU,* intensive care unit; *PCO2,* partial pressure of carbon dioxide; *NPPV,* noninvasive positive pressure ventilation.
*Data from https://www.goldcopd.org.
†Data from MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 23:932-946, 2004.
‡Data from https://www.nice.org.uk.

BOX 1 Indications for Invasive Mechanical Ventilation

Severe dyspnea, with use of accessory muscles and paradoxical abdominal motion
Respiratory frequency >35 breaths/min
Life-threatening hypoxemia (Pao_2 <40 mm Hg or Pao_2/Fio_2 <200 mm Hg)
Severe acidosis (pH <7.25) and hypercapnia ($Paco_2$ >60 mm Hg)
Respiratory arrest
Somnolence, impaired mental status
Cardiovascular complications (hypotension, shock, heart failure)
Other complications: Metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion
Noninvasive positive-pressure ventilation failure (or exclusion criteria)

Fio_2, Inspired oxygen fraction; $Paco_2$, partial pressure of carbon dioxide in arterial blood; *Pao_2,* partial pressure of oxygen in arterial blood.
From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, WB Saunders.

TABLE 4 Selection Criteria for Lung Volume Reduction Surgery

Inclusion Criteria	Exclusion Criteria
General	
Disability despite maximal rehabilitation	Inability to participate in rehabilitation
Cessation of tobacco use >6 mo	Continued use of tobacco
Patient´s expectation of goals reasonable	Significant comorbidity
	Previous pleurodesis or thoracotomy
	Underweight, overweight
Anatomic-Radiographic Evaluation	
Marked emphysema	Bronchiectasis
	Minimal radiographic emphysema
Heterogeneously distributed emphysema	Homogeneously distributed emphysema
Target zones of poorly perfused lung	No target zones
Areas with better preserved lung	No preserved lung tissue
Marked thoracic hyperinflation	Chest wall or thoracic cage abnormalities
Physiologic Evaluation	
Marked airflow obstruction	Minimal to moderate airflow obstruction
Marked hyperinflation	Minimal to moderate thoracic hyperinflation
Alveolar gas exchange	Markedly disordered alveolar gas exchange
DL_{co} <50% (steady state)	DL_{co} <10%
	$Paco_2$ >60 mm Hg
Cardiovascular function	Cardiovascular function
Essentially normal ejection fraction	Mean pulmonary artery pressure >35 mm Hg
	Left ventricular ejection fraction <40%
	Significant coronary artery disease

DL_{co}, Diffusing capacity of the lungs for carbon monoxide; *$Paco_2$*, partial pressure of carbon dioxide in arterial blood.
From Sellke FW et al: *Sabiston & Spencer surgery of the chest*, ed 9, Philadelphia, 2016, Elsevier.

BOX 2 Indications and Contraindications for Lung Volume Reduction Surgery and Lung Transplantation

Indications Common to Both Procedures
Emphysema with destruction and hyperinflation
Marked impairment (FEV_1 <35% predicted)
Marked restriction in activities of daily living
Failure of maximal medical treatment to correct symptoms

Contraindications to Both Procedures
Abnormal body weight (<70% or >130% of ideal)
Coexisting major medical problems increasing surgical risk
Inability or unwillingness to participate in pulmonary rehabilitation
Unwillingness to accept the risk of morbidity and mortality of surgery
Tobacco use within the past 6 mo
Recent or current diagnosis of malignant disease
Increasing age (>65 yr for transplantation, >70 yr for volume reduction)
Psychological instability, such as depression or anxiety disorder

Discriminating Conditions Favoring Lung Volume Reduction Surgery
Marked thoracic distention
Heterogeneous disease with obvious apical target areas
FEV_1 >20% predicted
Age between 60 and 70 yr

Discriminating Conditions Favoring Lung Transplantation
Diffuse disease without target areas
FEV_1 <20% predicted
Hypercapnia with $Paco_2$ >55 mm Hg
Pulmonary hypertension
Age younger than 60 yr
α_1-Antitrypsin deficiency

FEV_1, Forced expiratory volume in 1 s.
From Sellke FW et al: *Sabiston & Spencer surgery of the chest*, ed 9, Philadelphia, 2016, Elsevier.

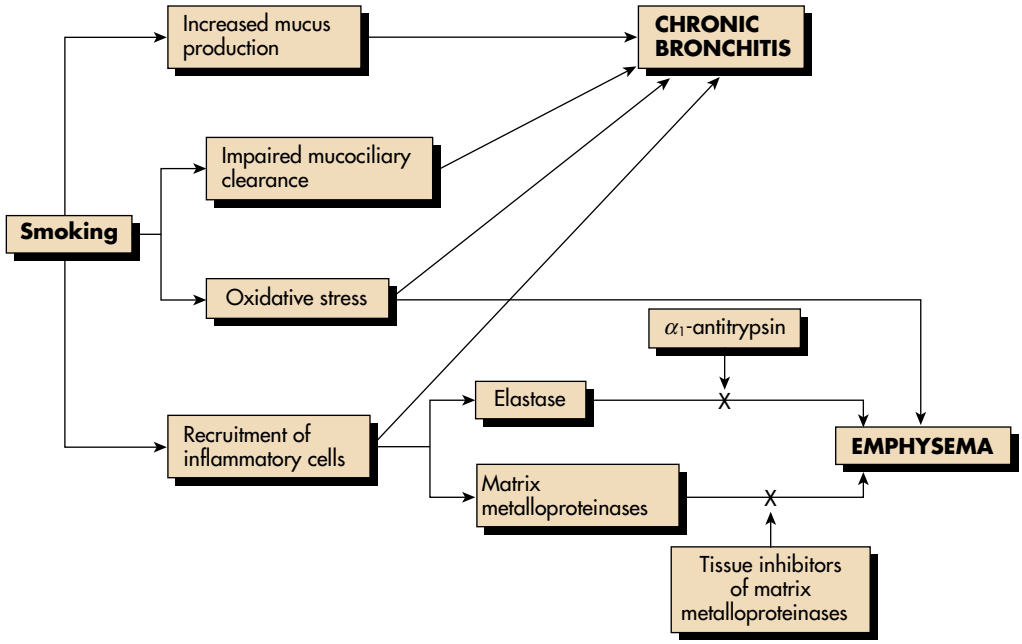

FIG. E1 Schematic diagram of the effect of smoking on airway inflammation and structural components of alveolar walls—the latter by altering the relationship between elastase and α1-antitrypsin (also called α1-protease inhibitor). (From Weinberger SE: *Principles of pulmonary medicine,* ed 7, Philadelphia, 2019, Elsevier.)

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BASIC INFORMATION

DEFINITION

Chronic pancreatitis is a recurrent or persistent inflammatory process of the pancreas characterized by chronic pain and by pancreatic exocrine and/or endocrine insufficiency. It is classified anatomically as either large-duct disease or small-duct (minimal change) disease.

ICD-10CM CODES

K86.1	Other chronic pancreatitis
K86.0	Alcohol-induced chronic pancreatitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Chronic pancreatitis occurs in approximately five to 10 per 100,000 persons in industrialized countries.
- Average age at diagnosis is 35 to 55 yr; male:female ratio is 5:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Persistent or recurrent epigastric and left upper quadrant pain that may radiate to the back
- Tenderness over the pancreas, muscle guarding
- Significant weight loss
- Bulky, foul-smelling stools, greasy in appearance
- Epigastric mass (10% of patients)
- Jaundice (5% to 10% of patients)

ETIOLOGY

- Chronic alcoholism (most common cause)
- Obstruction (ampullary stenosis, tumor, trauma [with pancreatic duct stricture], pancreas divisum, annular pancreas)
- Tobacco
- Recurrent pancreatitis
- Vascular disease/ischemia
- Hypertriglyceridemia
- Chronic kidney disease
- Hereditary pancreatitis
- Severe malnutrition
- Idiopathic
- Untreated hyperparathyroidism (hypercalcemia)
- Mutations of the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene and the TF genotype
- Other genetic mutations (Cationic trypsinogen gene, chymotrypsinogen C gene, calcium-sensing receptor gene, claudin-2 gene, serine protease inhibitor, Kazal type 1 gene)
- ***Autoimmune pancreatitis (AIP):*** (5% of chronic pancreatitis cases): Presents clinically with jaundice (63% of patients) and abdominal pain (35%). CT may reveal diffusely enlarged pancreas, enhanced peripheral rim of hypoattenuation "halo," and low-attenuation mass in head of pancreas. Laboratory values reveal elevated serum immunoglobulin (Ig) G4, elevated serum Ig or gamma-globulin level, presence of antilactoferrin antibody (ALA), anticarbonic anhydrase (ACA) II level, anti–smooth-muscle antibody (ASMA), or antinuclear antibody (ANA)
- ***Sclerosing pancreatitis:*** A form of chronic pancreatitis characterized by infrequent attacks of abdominal pain, irregular narrowing of the pancreatic duct, and swelling of the pancreatic parenchyma; patients have high levels of serum immunoglobulins (IgG4); chronic sclerosing pancreatitis is also known as *autoimmune pancreatitis*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pancreatic cancer
- Peptic ulcer disease
- Cholelithiasis with biliary obstruction
- Malabsorption from other etiologies
- Recurrent acute pancreatitis
- Renal insufficiency
- Intestinal ischemia or infarction
- Other: Crohn disease, gastroparesis, inflammatory bowel disease

WORKUP

Medical history with focus on alcohol use, laboratory tests, diagnostic imaging. Table 1 summarizes available diagnostic tests for chronic pancreatitis.

TABLE 1 Available Diagnostic Tests for Chronic Pancreatitis

Tests of Pancreatic Structure	Tests of Pancreatic Function
EUS	Direct hormonal stimulation (with pancreatic stimulation by secretin or CCK or both): Using oroduodenal tube* Using endoscopy*
MRI with MRCP, with or without secretin stimulation	Fecal elastase
CT	Serum trypsinogen (trypsin)
ERCP	Fecal chymotrypsin
Abdominal US	Fecal fat
Plain abdominal film	Blood glucose level

*See text for explanations.
Tests are listed in estimated order of decreasing sensitivity for each category.
CT, Computed tomography; *ERCP,* endoscopic retrograde cholangiopancreatography; *EUS,* endoscopic ultrasonography; *MRCP,* magnetic resonance cholangiopancreatography; *MRI,* magnetic resonance imaging.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

LABORATORY TESTS

- Serum amylase and lipase may be elevated (normal amylase levels, however, do not exclude the diagnosis).
- Hyperglycemia, glycosuria, hyperbilirubinemia, and elevated serum alkaline phosphatase may also be present.
- 72-hr fecal fat determination (rarely performed) reveals excess fecal fat. Fecal elastase test requires only 20 g of stool.
- Secretin stimulation test is the best test for diagnosing pancreatic exocrine insufficiency. Pancreatic secretory function tests are summarized in Table 2.
- Lipid panel: Significantly elevated triglycerides can cause pancreatitis.
- Serum calcium: Hyperparathyroidism is a rare cause of chronic pancreatitis.
- Elevated levels of serum IgG4 are found in sclerosing pancreatitis and AIP.
- Elevated serum Ig or gamma-globulin level, presence of ALA, ACA II level, ASMA, or ANA in AIP.

IMAGING STUDIES

- Plain abdominal radiographs may reveal pancreatic calcifications in 25% of patients (95% specific for chronic pancreatitis).
- Ultrasound of abdomen may reveal duct dilation, pseudocyst, calcification, and presence of ascites.
- Contrast-enhanced CT scan of abdomen is the initial modality of choice. It is useful to detect calcifications (Fig. E1), evaluate for ductal dilation (Fig. E2), AIP, and rule out pancreatic cancer. CT in AIP reveals narrowed main pancreatic duct and a homogenous "sausage-shaped" pancreas.
- Endoscopic retrograde cholangiopancreatography (ERCP) (Fig. E3) had been traditionally used to evaluate for the presence of dilated ducts, strictures, pseudocysts, and intraductal stones. However, for the evaluation of pancreatic parenchyma and duct system newer, less invasive modalities such as magnetic resonance cholangiopancreatography and endoscopic ultrasonography (EUS) are preferred. EUS (Fig. E4) has a sensitivity of 97% and a specificity of 60% for chronic pancreatitis and a very low complication rate. The diagnosis of chronic pancreatitis on EUS is summarized in Table E3. Fine-needle aspiration biopsy combined with EUS is the preferred modality for evaluation of cystic or mass lesions to determine malignancy.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of alcohol and tobacco
- Frequent, small-volume, low-fat meals

ACUTE GENERAL Rx

- Avoidance of narcotics if possible (simple analgesics or NSAIDs can be used). Fig. 5 describes an approach to the patient with painful chronic pancreatitis. Management of chronic pancreatitis focuses on treatment of symptoms.
- Treatment of steatorrhea with pancreatic supplements (e.g., Pancrease, Creon, pancrelipase titrated prn based on the amount of steatorrhea and patient's weight loss). Enzyme products for the treatment of chronic pancreatitis are summarized in Table 4. All non–enteric-coated enzymes should be used with acid-suppressing

TABLE 2 Pancreatic Secretory Function Tests

Test	Description	Advantages	Disadvantages	Clinical Indications
Direct				
Secretin	Measurements of volume and HCO_3– secretion into the duodenum after IV secretin	Provide the most sensitive and specific measurements of exocrine pancreatic function	Require duodenal intubation and IV administration of hormones; not widely available	Detection of mild, moderate, or severe exocrine pancreatic dysfunction
CCK	Measurements of duodenal outputs of amylase, trypsin, chymotrypsin, and/or lipase after IV CCK			
Secretin and CCK	Measurements of volume, HCO_3–, and enzymes after IV secretin and CCK			
Indirect (Requiring Duodenal Intubation)				
Lundh test meal	Measurement of duodenal trypsin concentration after oral ingestion of a test meal	Does not require IV administration of hormones	Requires duodenal intubation, a test meal, and normal anatomy, including small intestinal mucosa; not widely available	Detection of moderate or severe exocrine pancreatic dysfunction when a direct test cannot be done (e.g., due to limited availability)
Indirect (Tubeless)				
Fecal fat	Measurement of fat in the stool after ingesting meals with a known amount of fat	Provides a quantitative measurement of steatorrhea	Requires sufficient dietary fat intake and collection of stool; only detects severe pancreatic dysfunction	Detection of severe exocrine pancreatic dysfunction and steatorrhea
Fecal chymotrypsin	Measurement of chymotrypsin or elastase 1 in the stool	Do not require IVs, tubes, or administration of oral substrates	Insensitive for detecting mild or moderate dysfunction	Detection of severe exocrine pancreatic dysfunction
Fecal elastase 1				
NBT-PABA	Oral ingestion of NBT-PABA or fluorescein dilaurate with a meal, followed by measurements of PABA or fluorescein in serum or urine	Provide simple measurements for severe pancreatic dysfunction	Do not detect mild or moderate dysfunction; results may be abnormal in patients with small intestinal mucosal disease	Detection of severe exocrine pancreatic dysfunction
Fluorescein dilaurate				

CCK, Cholecystokinin; *IV,* intravenous; *NBT-PABA, N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

medications. Proton pump inhibitors and H_2 blockers reduce inactivation of the enzymes from gastric acid.
- Antioxidants (vitamin A, selenium, vitamin E) may be helpful for pain control in chronic pancreatitis.
- Percutaneous or via EUS celiac plexus blockade with corticosteroids or neurolysis with ethanol may provide temporary pain relief.
- Treatment of complications (e.g., type 1 diabetes mellitus).
- Autoimmune pancreatitis (AIP): Gluco-corticoid therapy in patients with AIP and sclerosing pancreatitis can induce clinical remission and significantly decrease serum concentrations of IgG4, immune complexes, and the IgG4 subclass of immune complexes. Starting dose of oral prednisolone is 0.6 to 1.0 mg/kg/day tapered over 3 mo. Recurrent AIP is treated with glucocorticoids and immunomodulators (azathioprine, mycophenolate, mercaptopurine) or rituximab.

CHRONIC Rx

- Surgical intervention may be necessary to eliminate biliary tract disease and improve flow of bile into the duodenum by eliminating obstruction of pancreatic duct.
- ERCP with endoscopic sphincterectomy and stone extraction is useful in selected patients.
- Transduodenal sphincteroplasty or pancreaticojejunostomy in selected patients. Surgery should also be considered in patients with intractable pain.
- Percutaneous or EUS-guided celiac plexus blockade using glucocorticoids is effective in providing short-term pain relief in nearly half of patients.

DISPOSITION

- Long-term survival is poor (50% of patients die within 10 yr from chronic pancreatitis or malignancy).
- Prognosis is best in patients with recurrent acute pancreatitis resulting from cholelithiasis, hyperparathyroidism, or stenosis of the sphincter of Oddi.

REFERRAL

Gastrointestinal referral for ERCP, surgical referral in selected patients (see "Chronic Rx")

RELATED CONTENT

Chronic Pancreatitis (Patient Information)
Malabsorption (Related Key Topic)
Pancreatitis, Acute (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

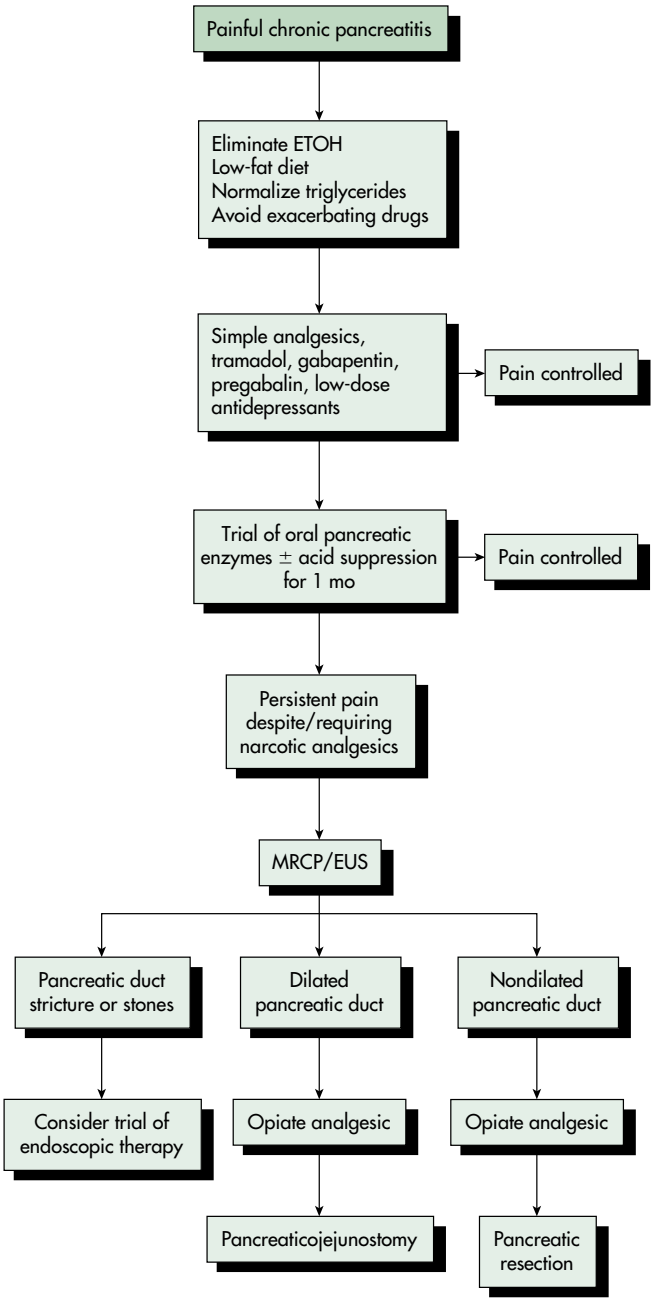

FIG. 5 Approach to the patient with painful chronic pancreatitis. *ETOH,* Alcohol; *EUS,* endoscopic ultrasound; *MRCP,* magnetic resonance cholangiopancreatography. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

TABLE 4 Enzyme Products for the Treatment of Chronic Pancreatitis

Product	Formulation	Lipase Content per Pill or Capsule (USP units)
Creon	Enteric-coated capsule	3000; 6000; 12,000; 24,000; 36,000
Zenpep	Enteric-coated capsule	3000; 5000; 10,000; 15,000; 20,000; 25,000
Pancreaze	Enteric-coated capsule	4200; 10,500; 16,800; 21,000
Ultresa	Enteric-coated capsule	13,800; 20,700; 23,000
Pertzye	Enteric-coated with bicarbonate	8000; 16,000
Viokase	Non–enteric-coated tablet*	10,440; 20,880

*Non–enteric-coated agents require cotreatment with an H2RA or PPI to avoid denaturation of the enzymes by gastric acid.
The total dose of lipase per meal should be titrated based on response but usually requires at least 60,000 and usually 90,000 USP units (30,000 international units) of lipase per meal and one half that amount with snacks. The dose should be split equally during the meal and immediately after the meal.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

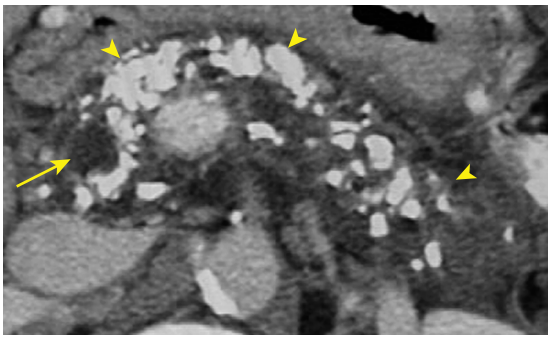

FIG. E1 Chronic pancreatitis: Calcifications. Numerous coarse calcifications are seen throughout the pancreas (*arrowheads*) in this patient with recurrent alcoholic pancreatitis. The common bile duct (*arrow*) is mildly dilated because of a benign stricture in the pancreatic head. (From Webb WR et al: *Fundamentals of body CT*, ed 4, Philadelphia, 2015, WB Saunders.)

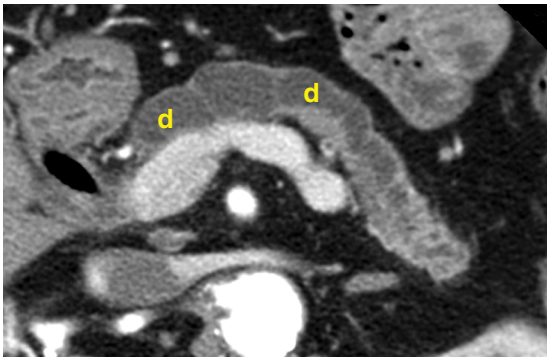

FIG. E2 Chronic pancreatitis: Dilated pancreatic duct. The pancreatic duct (*d*) shows marked beaded dilatation. The pancreatic parenchyma is severely atrophied. (From Webb WR et al: *Fundamentals of body CT*, ed 4, Philadelphia, 2015, WB Saunders.)

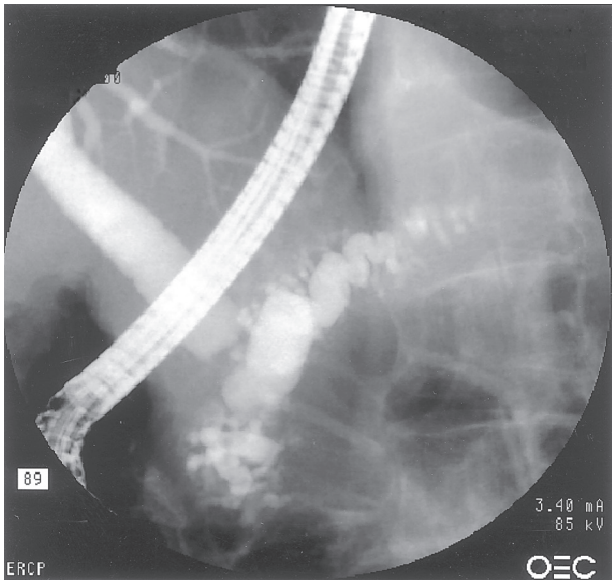

FIG. E3 Film from an endoscopic retrograde cholangiopancreatography (ERCP) showing a markedly dilated pancreatic duct with alternating strictures and dilatation. This "chain of lakes" appearance is diagnostic of chronic pancreatitis. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

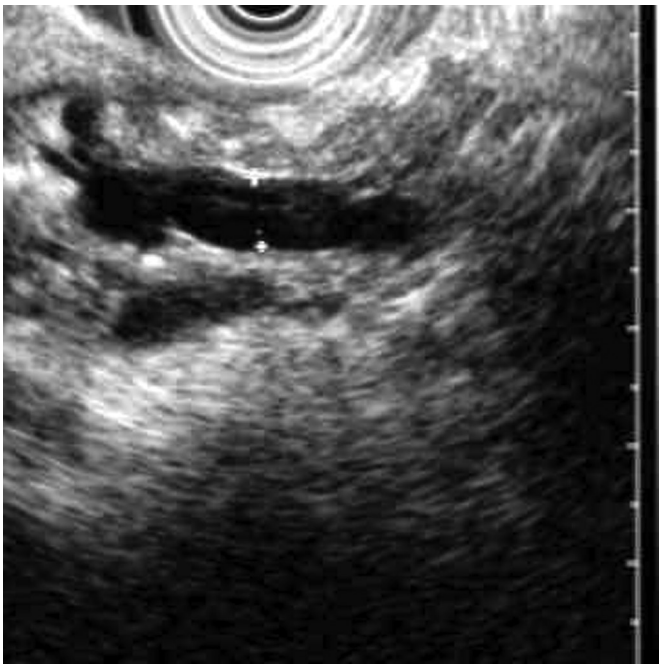

FIG. E4 Endoscopic ultrasound in a patient with chronic pancreatitis, demonstrating a dilated pancreatic duct (marks on margin of main duct). (From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.)

TABLE E3 Diagnosis of Chronic Pancreatitis on Endoscopic Ultrasound (EUS)

Standard EUS Grading System		Rosemont Criteria for EUS Diagnosis	
Parenchymal abnormalities	Hyperechoic foci Hyperechoic strands Lobularity of contour Cysts	Major features	Hyperechoic foci with shadowing (major A) Main pancreatic duct calculi (major A) Lobularity with honeycombing (major B)
Ductal abnormalities	Main duct dilatation Main duct irregularity Hyperechoic ductal walls Visible side branches Calcification	Minor features	Lobularity without honeycombing Hyperechoic foci without shadowing Stranding Cysts Irregular main pancreatic duct contour Main pancreatic duct dilatation Hyperechoic duct margin Dilated side branches
In the standard EUS grading system, each finding counts equally, and the score is the total number of findings. In the Rosemont system, the diagnostic strata are as follows:			
Most consistent with chronic pancreatitis		One major A feature and ≥3 minor features *or* One major A feature and major B feature *or* Two major A features	
Suggestive of chronic pancreatitis		One major A feature and <3 minor features *or* One major B feature and ≥3 minor features *or* ≥5 minor features	
Indeterminate for chronic pancreatitis		Three to four minor features *or* One major B feature with <3 minor features	
Normal		≤2 minor features	

From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

Chronic Rhinosinusitis

BASIC INFORMATION

DEFINITION

Chronic rhinosinusitis (CRS) is an inflammatory condition that involves the paranasal passages and linings of the nasal passages that lasts 12 wk or longer despite medical therapy. It can be divided into three categories:

- CRS without nasal polyposis
- CRS with nasal polyposis
- Allergic fungal rhinosinusitis

SYNONYMS

Chronic sinusitis
CRS

ICD-10CM CODE
J32 Chronic sinusitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: CRS occurs in children and adults but is most frequently diagnosed in young and middle-aged adults
PREVALENCE: In the U.S. it varies from 1% to 5%
PREDOMINANT SEX AND AGE: Some studies suggest women are more affected. In adults, the mean age of diagnosis was 39 yr.
GENETICS: Patients with cystic fibrosis or primary ciliary dyskinesia are more likely to develop CRS.
RISK FACTORS:

- Environmental or behavioral risk factors include:
  1. Smoking
  2. Cocaine use
  3. Chemical and air pollutants: Ozone, sulfur dioxide, nitrogen dioxide
- Host-associated risk factors: Allergic rhinitis, atopy, asthma, aspirin-exacerbated respiratory disease
- Innate immunodeficiencies: Cystic fibrosis
- Humoral immunodeficiencies: Common variable immunodeficiency, IgA or IgG subclass deficiencies, types of vasculitis (e.g., Churg-Strauss syndrome), and sarcoidosis
- Allergic fungal sinusitis
- Gastroesophageal reflux disease
- Odontogenic: Infectious agents from maxillary posterior teeth may breech into maxillary sinus

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- CRS is diagnosed clinically with a physical examination and a detailed sinonasal history. There should be at least two out of the four cardinal symptoms for at least 12 consecutive wk:
  1. Nasal obstruction: 81% to 95% of patients
  2. Nasal drainage: 51% to 83% of patients
  3. Facial pain/pressure: 70% to 85% of patients
  4. Hyposmia/anosmia: 61% to 69% of patients
- Objective evidence on physical examination using anterior rhinoscopy and nasal endoscopy includes mucopurulent drainage, edema, polyps in the middle meatus
- Radiographic evidence includes, preferably, computed tomography (CT) of sinuses.
- Features of specific subtypes:
  1. CRS without nasal polyposis: Most common type (60% to 65% of cases) with cardinal clinical symptoms
  2. CRS with nasal polyposis: Characterized with the presence of bilateral nasal polyps in the middle meatus, which are translucent masses composed of gelatinous inflammatory material, as well as cardinal clinical symptoms
  3. Allergic fungal rhinosinusitis:
     a. Type 1 hypersensitivity confirmed by history, skin test, or serology
     b. Nasal polyposis
     c. Positive fungal stain
     d. Eosinophilic mucin showing fungal hyphae without tissue invasion
     e. CT of sinuses showing high-attenuation sinus contents with bony remodeling

ETIOLOGY

- Not fully understood but multifactorial involving host genetics and immunity, as well as environmental and infectious agents that produce chronic inflammation of the upper airways.
- Various cells, including fibroblasts, epithelial cells, endothelial cells, mast cells, eosinophils, antigen-presenting cells (dendritic cells), T cells, and B cells, have been shown to coordinate the immune inflammatory network underlying CRS, by the production of mediators such as cytokines, chemokines, eicosanoids, and antibodies.
- Microbiology: Organisms that may be involved in the pathogenesis of CRX include:
  1. *Staphylococcus aureus:* This is the most common bacterium and contributes to polyp formation. Methicillin-resistant *S. aureus* is isolated in 2% to 20% of patients with CRS.
  2. Coagulase-negative staphylococci: It is not always clear whether they are pathogens or colonizers.
  3. *Pseudomonas aeruginosa:* Occurs especially in patients with cystic fibrosis. Other gram-negative rods include *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterobacter* spp., and *E. Coli.*
  4. Anaerobic bacteria include: *Peptostreptococcus*, *Fusobacterium, Prevotella* spp., *Porphyromonas* spp.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Recurrent acute rhinosinusitis: ≥4 episodes a yr but symptom-free in between
- Allergic rhinitis, nonallergic rhinitis, vasomotor rhinitis, and eosinophilic nonallergic rhinitis
- Trigeminal neuralgia
- Tension headache

WORKUP

CRS is diagnosed clinically with a physical examination and focused sinonasal history, including the CRS-associated comorbidities and a pertinent family history

LABORATORY TESTS

Testing should be done to search for chronic conditions that may affect treatment:

- Asthma
- Cystic fibrosis
- Aspirin sensitivity
- Ciliary dyskinesia
- Immunodeficiencies: IgG deficiency, IgG subclass deficiency, IgA deficiency, selective IgA deficiency
- Assessment of patient allergies and immunologic status: IgG, IgA, IgM, and IgE levels; T-cell number; and function evaluation (delayed hypersensitivity skin test and flow cytometric quantification of T cells)
- Bacterial cultures via maxillary tap (maxillary sinus aspirate [MSA]) or endoscopically directed middle meatus culture (EDMM). MSA is the gold standard, with EDMM being considered equivalent

IMAGING STUDIES

- Plain films of sinuses are no longer recommended, with noncontrast-enhanced CT being the study of choice.
- Include all of the forehead and extend to maxillary teeth, also including the ears and nasal tip.
- Maintain a maximum slice of thickness of 1 mm, and obtain scans axially with no gantry tilt.

TREATMENT

The goal of treatment is to manage symptoms and to improve or maintain quality of life. Therapies are targeted to enhancing mucociliary clearance, improving sinus drainage/outflow, eliminating local infection and inflammation, and improving access for topical medications.

NONPHARMACOLOGIC THERAPY

Nasal saline irrigation: Low-pressure, high-volume (240 ml) isotonic or hypertonic saline irrigation can reduce symptoms in 50% of patients and is better than nasal saline spray. Often used in conjunction with intranasal corticosteroid spray.

ACUTE GENERAL Rx

- Topical intranasal corticosteroids: First-generation products include beclomethasone dipropionate (QNASL), flunisolide (Nasalide, Nasarel), budesonide (Rhinocort), and triamcinolone acetonide (Nasacort). Newer agents include fluticasone propionate (Flonase), fluticasone furoate (Veramyst), mometasone furoate (Asmanex), and ciclesonide (Omnaris). Most are used once a day.
- Oral corticosteroids: Oral corticosteroids, such as prednisone, can be used in patients

with severe disease and especially in patients with nasal polyps because they will help reduce the size of polyps. Prednisone will also minimize mucosal inflammation in allergic fungal rhinosinusitis. Dose: 20 mg twice daily for 5 days, then 20 mg daily for 5 days.
- Antibiotics: Often used in conjunction with prednisone. Can be used when evidence of infection present: Facial pain, air–fluid level on sinus CT, or purulent mucous in middle meatus. Use for up to 3 to 4 wk at most. Examples include amoxicillin/clavulanic acid or moxifloxacin.

SURGERY: Endoscopic surgery is appropriate if medical therapy fails. It can provide ventilation and drainage of the paranasal sinuses and enlarge the paranasal sinuses to create better access for topical medications. In general, it does not cure the condition and patients will need continued medical therapies.

CHRONIC Rx

Use of macrolide antibiotics for prolonged periods has been tried, but studies have not shown additional benefit.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Herbal medicines, homeopathy, acupuncture, reflexology, and yoga are used but have not been studied in clinical trials.

REFERRAL

- Otolaryngologist for long-term treatments and possible surgery

PEARLS & CONSIDERATIONS

- Surfactants such as baby shampoo can be added to saline irrigations and may prevent formation of bacterial biofilm on the sinus mucosa.
- Antihistamines such as cetirizine 20 mg used daily are of unproven benefit.

PREVENTION

- Smoking cessation is recommended because it reduces the risk for sinusitis.
- Nasal irrigation can be used as prevention for exacerbations of CRS.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Kucuksezer UC et al: Chronic rhinosinusitis: pathogenesis, therapy options and more, *Expert Opin Pharmacother* 19:1805-1815, 2018.

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Chronic Traumatic Encephalopathy (CTE)

BASIC INFORMATION

DEFINITION

Chronic traumatic encephalopathy (CTE) is a neurogenerative disorder often found in athletes, veterans, and those with repeated head injuries. It presents with cognitive, psychiatric, and sometimes motor symptoms.

SYNONYMS

CTE
Traumatic encephalopathy syndrome (clinical diagnosis)
Dementia pugilistica (older term)
Punch drunk syndrome (older term)

ICD-10CM CODE
G93.49 Other encephalopathy

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE & PREVALENCE: The incidence and prevalence of CTE are currently unknown. Among 202 deceased former football players, CTE was never pathologically diagnosed in 177 players (87%). Among participants with severe CTE pathology, 89% had behavior, mood symptoms, or both, 95% had cognitive symptoms, and 85% had signs of dementia.[1]
PREDOMINANT SEX AND AGE: CTE may present early (20s to 30s) or later (50s to 60s) in adulthood. The relationship with gender is unknown.
GENETICS: Currently there are no known genetic risk factors that predispose to the development of CTE.
RISK FACTORS: Repetitive head injuries leading to concussions are the strongest risk factor for the development of CTE. Athletes, veterans, and victims of repetitive head trauma are at highest risk.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Currently, it is thought that CTE presents in two forms. The first presents early in life (later 20s to 30s), with primarily psychiatric and behavioral manifestations. These may include depression, anxiety, paranoia, impulsivity, explosivity, and aggression. Cognitive problems are more common as the disease progresses. The second form presents later in life (60s), with mainly cognitive impairments and is likely to progress to dementia. Symptoms of this variant include impairment in episodic memory, attention, and executive function. Currently it is thought that CTE progresses in four stages with increasing severity along each stage. Symptoms progress from headaches, attention problems, and depression to explosivity, aggression, dementia, and suicidality as the disease progresses.

Physical findings are not always present in CTE but may include symptoms of parkinsonism and motor dysfunction, such as gait disturbance, tremors, ataxia, and dysarthria. These have been found to be particularly more common in boxers.

Of note, the symptoms of CTE may present similarly to the behavior subtype of frontotemporal dementia (FTD), but the characteristic disinhibition found in FTD is often missing. In addition, patients with traumatic brain injury may also have some symptoms of CTE, but these will present more acutely, whereas CTE develops after multiple yr of injuries.

ETIOLOGY

CTE is believed to occur due to repetitive head injuries. Definitive diagnosis is made only through autopsy, where neurofibrillary tangles and p-tau aggregates may be found around blood vessels and in deep cortical sulci, amygdala, hippocampus, brainstem, and cerebellum depending on the stage of the disease.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Alzheimer disease
- Frontotemporal dementia
- Post-concussion syndrome
- Bipolar disorder
- Major depressive disorder

WORKUP

CTE should be suspected in those with a history of repetitive head injuries and the symptoms previously listed. The history and progression of symptoms is of most benefit in the diagnostic process. Neuropsychological testing may be helpful in delineating specific cognitive deficits.

LABORATORY TESTS

Tests including complete blood count, comprehensive metabolic panel, thyroid function tests, HIV, syphilis

IMAGING STUDIES

- MRI may aid in ruling out other causes of dementia.
- The usefulness of advanced imaging such as PET, SPECT, and DTI in CTE is still under investigation.

TREATMENT

NONPHARMACOLOGIC THERAPY

Cognitive behavioral therapy is helpful for depression and anxiety symptoms.

ACUTE GENERAL Rx

- **SSRIs,** especially sertraline and citalopram, may be effective in treating depression symptoms. Close monitoring for suicidality is recommended in all patients with CTE.
- **Methylphenidate** has been shown to help in alleviating agitation, irritability, and aggressive symptoms.
- **Pain management** to improve quality of life.

COMPLEMENTARY & ALTERNATIVE MEDICINE

None

DISPOSITION

CTE is chronic and progressive. Emphasis should be placed on improving quality of life through pain management, therapy, and symptom management.

REFERRAL

Patients may benefit from referral to neurology, psychiatry, and psychology.

PEARLS & CONSIDERATIONS

COMMENTS

CTE is a slowly developing illness. Although it should be considered in patients with repetitive head injuries, it is important to conduct a thorough work-up to rule out psychiatric illnesses and other forms of dementia that may present with similar symptoms.

PREVENTION

For athletes, wearing proper protective equipment as well as using techniques to avoid direct head impacts when playing sports is important. Furthermore, if a concussion is suspected, the player should not be allowed to resume play without further evaluation.

PATIENT & FAMILY EDUCATION

Concussion foundation—CTE resources
https://concussionfoundation.org/CTE-resources
CDC—HEADS UP: For prevention of concussions
https://www.cdc.gov/headsup/index.html

SUGGESTED READINGS
Available at ExpertConsult.com

RELATED CONTENT

Concussion (Related Key Topic)
Depression, Major (Related Key Topic)
Postconcussion Syndrome (Related Key Topic)
Suicide (Related Key Topic)

AUTHORS: **Sudad Kazzaz, MD,** and **Joseph S. Kass, MD, JD, FAAN**

[1] Mez J et al: Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football, *JAMA* 318(4):360-370, 2017.

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Stern R et al: Clinical presentation of chronic traumatic encephalopathy, *Neurology* 81:1122-1129, 2013.

BASIC INFORMATION

DEFINITION

Chronic urticaria (CU) is the occurrence of hives (edematous, pruritic pink wheals of variable size and shape) that have been present continuously or intermittently for at least 6 wk. Some patients may also experience angioedema (deep, often painful, swelling). CU can be associated with autoimmune conditions but is often idiopathic. A classification of chronic urticaria subtypes and diseases related to urticaria is summarized in Table E1. When no underlying cause is found, CU has been referred to as chronic idiopathic urticaria (CIU).

SYNONYMS

Chronic hives
CU
CIU
Chronic idiopathic urticaria
Chronic spontaneous urticaria
CSU

ICD-10CM
L50.8 Other urticaria: Chronic urticaria

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1.4% per yr.
PREVALENCE: Lifetime prevalence is 1.8%. The period prevalence in the last 12 mo is 0.6% to 0.8%. CU occurs in 0.1% to 0.3% of children.
PREDOMINANT AGE AND SEX: There is a 2:1 female to male predominance. The mean age is 40 yr.
RISK FACTORS: None.
GENETICS: Patients with demonstrable histamine-releasing autoantibodies have a very strong association with HLA-DR4 and the associated allele HLA-DQ8.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- CU lesions are edematous, pink or red wheals of variable size and shape with surrounding erythema (Fig. E1) and are usually pruritic. Individual urticarial lesions usually resolve within 24 hr, but new lesions may be developing simultaneously.
- Angioedema typically appears as brawny nonpitting edema, often without well-defined margins, and erythema, commonly affecting the lips, tongue, eyelids, and genitalia. This is often described as painful rather than pruritic.

ETIOLOGY

- CU results from cutaneous mast cells releasing histamine. It is often triggered by immunoglobulin E (IgE), components of the complement cascade, endogenous peptides, endorphins, and enkephalins.
- More than 30% of patients have autoimmune manifestations, including specific IgG antibodies against the FcεRIα subunit of the high-affinity IgE receptor or IgG antibodies against IgE itself, thyroid autoimmunity, or positive autologous serum skin test (ASST).
- Activation of the coagulation cascade, including increased levels of prothrombin fragment F112 and D-dimer, has been noted in patients with CU and may be a marker for CU severity.
- Chronic infections such as hepatitis B and C, Epstein-Barr virus (EBV), herpes simplex virus, and helminthic parasitic infections have been implicated. There is also an association with autoimmune diseases such as type 1 DM and hypothyroidism (Fig. E2).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Urticarial vasculitis
- Erythema multiforme
- Drug eruptions
- Still disease
- Insect bites

WORKUP

- Complete history and physical exam: Questioning about new drugs, travel, infection, health status, and a complete review of systems (including fever, arthralgias, abdominal pain, bone pain, weight loss, and cold/heat sensitivity) is important. Determining if an individual lesion resolves within 24 hours, whether lesions are tender or itchy, and whether lesions leave a purpuric mark is important (to screen for urticarial vasculitis).
- Fig. E3 describes an algorithm for the diagnosis and management of chronic urticaria.

LABORATORY TESTS

- In a systemic review analyzing 29 studies (6462 patients), a causative internal disease was detected in 1.6% of patients with CU, with no association between the number of tests ordered and the detection rate.
- Aside from a complete history and physical examination, a trial of antihistamine therapy without further diagnostic testing is recommended.
- In those who fail antihistamine therapy, there is consensus for a limited laboratory workup:
  1. CBC with differential, complete metabolic panel (creatinine, liver function tests), ESR, TSH

TABLE E1 Classification of Chronic Urticaria Subtypes and Diseases Related to Urticaria

Chronic urticaria subtypes	Chronic spontaneous urticaria	Spontaneous appearance of wheals, angioedema, or both ≥6 wks due to known or unknown causes
	Inducible urticaria	1. Symptomatic dermatographism* 2. Cold urticaria† 3. Delayed pressure urticaria‡ 4. Solar urticaria 5. Heat urticaria§ 6. Vibratory angioedema 7. Cholinergic urticaria 8. Aquagenic urticaria 9. Contact urticaria
Diseases related to urticaria		1. Serum sickness–like reaction; urticarial vasculitis 2. Bradykinin-mediated angioedema (e.g., hereditary angioedema) 3. Mast cell disorders (e.g., urticaria pigmentosa) 4. Exercise-induced anaphylaxis
Syndromes that present with wheals and/or angioedema		• Cryopyrin-associated periodic syndromes (CAPS) 1. Familial cold autoinflammatory syndrome (FCAS) 2. Muckle–Wells syndrome (MWS) 3. Neonatal onset multisystem inflammatory disease (NOMID) • Schnitzler syndrome • Gleich syndrome

*Also called *urticaria factitia* dermatographic urticaria.
†Also called *cold contact urticaria.*
‡Also called *pressure urticaria.*
§Also called *heat contact urticaria.*
From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.

FIG. E1 Urticarial lesions in a patient with urticarial vasculitis. These lesions may take several days to resolve. (From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

FIG. E2 Urticaria. Chronic urticaria in this teenager in association with autoimmune diseases type 1 diabetes and hypothyroidism. Treatment with antihistamines was not successful, and the patient required systemic corticosteroids and methotrexate for control. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

2. Typically also check G6PD, hepatitis B and C, HIV, and age-appropriate malignancy screening

- A skin biopsy may be performed in cases of suspected urticarial vasculitis or urticaria with atypical historical or physical findings.
- NOTE: Testing for autoantibodies to the high-affinity IgE receptor, autoantibodies to IgE, basophil histamine response assay (BHRA), or the ASST is not routinely recommended. However, in the setting of omalizumab therapy, a quick response to the medication is associated with IgG autoantibodies to IgE and a high IgE level in the serum, whereas a delayed response to the medication is associated with the presence of IgG autoantibodies to the high-affinity IgE receptor or positive BHRA and ASST testing.
- C4 testing is recommended in patients with isolated angioedema (without urticaria) to rule out C1 inhibitor deficiency.

IMAGING STUDIES

None

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Elimination of any suspected medications, herbal products, etc.

ACUTE GENERAL Rx

Oral corticosteroids are not recommended as long-term treatment because of their detrimental effects over prolonged periods. However, they may be necessary for 3 to 7 days to abort severe, acute flares.

CHRONIC Rx

FIRST-LINE TREATMENT:

- Second-generation nonsedating H1-antagonist antihistamines:
  1. Loratadine 10 mg, fexofenadine 180 mg, cetirizine 10 mg, levocetirizine 2.5 mg, or desloratadine 5 mg—started as twice daily dosing.
  2. These are the mainstay of treatment, with 50% to 95% of patients achieving satisfactory disease control with one or a combination of antihistamines only. The typical starting dose is twice daily. If no improvement after 2 wk, there is current data supporting dose-escalation to fourfold on-label dosing. Studies have shown routine (rather than episodic) use is important for efficacy.
- Sedating H1-antagonist antihistamines (diphenhydramine, hydroxyzine) are no longer recommended as first-line treatment given their potential for sedation and anticholinergic effects, as well as the availability of second-generation agents. However, these can be used as adjuncts at bedtime.

SECOND-LINE TREATMENT: For those who do not respond to monotherapy H1-antagonist, adding an additional agent with the goal of combination antihistamine therapy may be necessary:

- Addition of a second nonsedating H1 antihistamine.
- Addition of H2 blockade (ranitidine, famotidine, or cimetidine).
- Addition of doxepin 25 to 50 mg at night or twice daily (which is a potent H1/H2 blocker) may be necessary. Of note, doxepin can prolong PR interval and worsen conduction defects; an ECG before initiation may be warranted.

THIRD-LINE TREATMENT: Choice of agent depending on histologic infiltrate (e.g., neutrophilic), patient's comorbidities, and preferences. If failed the above treatments, patients are typically considered refractory CIU. International consensus groups have determined omalizumab, a monoclonal antibody against IgE, to be the most appropriate next therapeutic option.

- Omalizumab 300 mg subcutaneous injection every 4 wk. This is approved in both the U.S. and EU for the treatment of antihistamine-resistant CIU. No specific labs recommended to predict favorable response at this time. Approximately 30% to 45% are hive free by 3 mo, with response noted as early as 1 wk. Treatment failure can be determined at 16 wk. With combination maximum dose antihistamines, efficacy increased to 80% of patients being hive free. Hence antihistamines should be continued and slowly tapered. Although risk of anaphylaxis is no higher than other biologics, it is given in office with patients being given an epi-pen.
- Monthly SC injections of ligelizumab, a new anti-IgG monoclonal antibody, have shown significant efficacy in chronic urticaria.

FOURTH-LINE TREATMENT:

- Addition of leukotriene-receptor antagonist (e.g., montelukast 10 mg/day).
- Dapsone 25 to 500 mg/day (typically 100 mg/day starting dose). Must check for G6PD and monitor labs. Limited use in patients with anemia. Side effects include peripheral neuropathy, methemoglobinemia, agranulocytosis, and systemic drug hypersensitivity. Improvement is generally noted within days to wks.
- Hydroxychloroquine 200 mg twice daily (can start with dapsone or sulfasalazine because of slow onset on the order of 3 mo). Must monitor for retinal toxicity.
- Sulfasalazine 500 mg twice daily (then uptitrate to 1 g twice daily). Good option if patient is anemic and cannot tolerate dapsone.

IMMUNOSUPPRESSIVE AGENTS

- Mycophenolate mofetil 500 to 1500 mg twice daily
- Cyclosporine (3 to 5 mg/kg per day for 3 to 6 mo). Limited by nephrotoxic potential. Should not be used longer than a yr.

Phototherapy

- In a recent study, narrow band UVB (NB-UVB) was effective and safe in steroid-dependent patients with chronic refractory urticaria.

COMPLEMENTARY & ALTERNATIVE MEDICINE

A combination of ear acupuncture and conventional filiform needle acupuncture has been reported.

REFERRAL

Dermatology and/or allergy and immunology referral for patients who fail antihistamine therapy or in whom there is a concern for urticarial vasculitis.

PEARLS & CONSIDERATIONS

COMMENTS

- In atypical cases, given a patient's history or appearance, a skin biopsy for histologic evaluation can be helpful.
- Antihistamine blockade response can often be determined by the presence of dermatographism on exam (wheal produced by scratching).

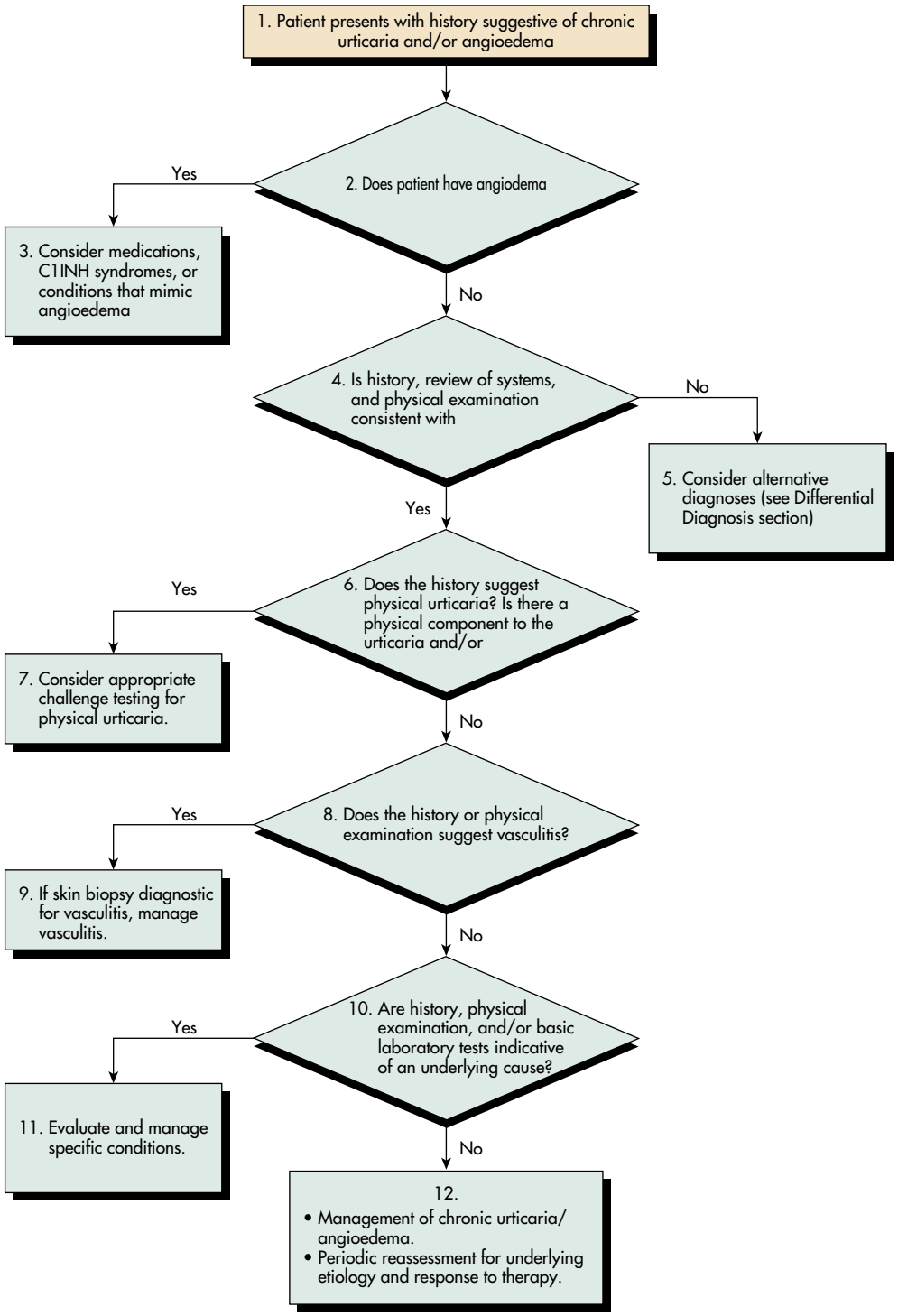

FIG. E3 Algorithm for the diagnosis and management of chronic urticaria. *C1INH,* C1-esterase inhibitor. (From Bernstein JA et al: The diagnosis and management of acute and chronic urticaria: 2014 update, *J Allergy Clin Immunol* 133:1270-1277, 2014.)

PREVENTION

- Measures that increase vasodilation such as alcoholic drinks, excessive ambient temperature, heavy clothing, hot baths or showers, and spicy food should be avoided.
- Up to 15% of CU patients experience an exacerbation of their disease after taking aspirin or other cyclooxygenase-1 (COX-1) inhibitors. Patients should be cognizant of such reactions to these medications.

PATIENT & FAMILY EDUCATION

- A cause is typically not identified.
- Patients should be aware that the course of disease is unpredictable and may last months to years. However, reassurance should be given that 50% of patients experience remission within 1 yr. In one study, the duration of disease ranged from 1 to 5 yr in 8.7% and more than 5 yr in 11.3% of patients.
- CIU is different from acute urticaria in etiology, and it is typically not a dietary cause. That said, some providers feel that pseudoallergens in foods can play a role in exacerbations but do not recommend a pseudoallergen-free diet.

RELATED TOPICS

Hives (Patient Information)
Urticaria (Related Key Topic)

AUTHOR: **Lisa Pappas-Taffer, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Cirrhosis is defined histologically as the presence of irreversible fibrosis in the liver. It can be classified as micronodular, macronodular, or mixed; however, each form may be seen in the same patient at different stages of the disease, and this classification system has little utility in determining the underlying etiology of cirrhosis. Cirrhosis manifests clinically with portal hypertension, ascites and peripheral edema, hepatic encephalopathy, and variceal bleeding.

ICD-10CM CODES

K70.30	Alcoholic cirrhosis of liver without ascites
K70.31	Alcoholic cirrhosis of liver with ascites
K71.7	Toxic liver disease with fibrosis and cirrhosis of liver
K74.3	Primary biliary cirrhosis
K74.4	Secondary biliary cirrhosis
K74.5	Biliary cirrhosis, unspecified
K74.60	Unspecified cirrhosis of liver
K74.69	Other cirrhosis of liver
P78.81	Congenital cirrhosis (of liver)

EPIDEMIOLOGY & DEMOGRAPHICS

- Cirrhosis was the fourteenth-leading cause of death in the U.S. in 2015 and the thirteenth-leading cause of death globally. In the U.S., cirrhosis-related deaths increased 3.4% annually between 2009 and 2016.
- Alcohol abuse, hepatitis C, and nonalcoholic steatohepatitis are the major causes of cirrhosis in the U.S.
- Economic burden of cirrhosis in the U.S. exceeds $2 billion in direct costs and over $10 billion in indirect costs.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

GENERAL: Fever (spontaneous bacterial peritonitis)
SKIN: Jaundice, palmar erythema, spider angiomata, ecchymosis (thrombocytopenia or coagulation factor deficiency), increased pigmentation (hemochromatosis), xanthomas (primary biliary cirrhosis), and diffuse pruritus. Cutaneous lesions often accompany cirrhosis and can be found in >40% of people with chronic alcoholism
EYES: Kayser-Fleischer rings (corneal copper deposition seen in Wilson disease; best diagnosed with slit lamp examination), scleral icterus
BREATH: Fetor hepaticus (breath has a sweet musty odor found in cirrhosis with hepatic failure)
CHEST: Possible gynecomastia in men
ABDOMEN: Tender or nontender hepatomegaly (congestive hepatomegaly), small, nodular liver (cirrhosis), palpable, nontender gallbladder (neoplastic extrahepatic biliary obstruction), palpable spleen (portal hypertension), dilated superficial periumbilical vein (caput medusae), venous hum auscultated over periumbilical veins (portal hypertension), ascites (portal hypertension, hypoalbuminemia), diffuse abdominal tenderness (spontaneous bacterial peritonitis)
RECTAL EXAMINATION: Hemorrhoids (portal hypertension), guaiac-positive stools (alcoholic gastritis, bleeding esophageal varices, peptic ulcer disease, bleeding hemorrhoids, portal gastropathy)
GENITALIA: Testicular atrophy in males (chronic liver disease, hemochromatosis)
EXTREMITIES: Pedal edema (hypoalbuminemia, anasarca), arthropathy (hemochromatosis), Dupuytren contractures
NEUROLOGIC: Asterixis (hepatic encephalopathy), choreoathetosis, dysarthria (Wilson disease)

ETIOLOGY

- Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection
- Alcoholism
- Nonalcoholic steatohepatitis
- Primary biliary cholangitis
- Secondary biliary cirrhosis, obstruction of the common bile duct (stone, stricture, pancreatitis, neoplasm, sclerosing cholangitis)
- Autoimmune hepatitis
- Drugs with chronic hepatitis (e.g., acetaminophen, isoniazid, methotrexate, methyldopa)
- Chronic hepatic congestion (e.g., CHF, constrictive pericarditis, tricuspid insufficiency, thrombosis of the hepatic vein, obstruction of the vena cava)
- Hemochromatosis
- Wilson disease
- Alpha-1-antitrypsin deficiency
- Infiltrative diseases (amyloidosis, glycogen storage diseases, nonhepatocellular malignancies)
- Nutritional: Jejunoileal bypass
- Others: Parasitic infections (schistosomiasis), idiopathic portal hypertension, congenital hepatic fibrosis, systemic mastocytosis

DIAGNOSIS

WORKUP

In addition to an assessment of liver function, the evaluation of patients with cirrhosis should also include an assessment of renal and circulatory function. Diagnostic workup is aimed primarily at identifying the most likely cause of cirrhosis. The history is extremely important:

- Alcohol abuse: Alcoholic liver disease
- History of hepatitis B or hepatitis C
- Obesity, type 2 diabetes mellitus, hyperlipidemia (nonalcoholic steatohepatitis)
- History of IBD (primary sclerosing cholangitis)
- History of pruritus, hyperlipoproteinemia, and xanthomas in a middle-aged or elderly woman (primary biliary cholangitis)
- Impotence, diabetes mellitus, hyperpigmentation, arthritis (hemochromatosis)
- Neurologic disturbances (Wilson disease, hepatolenticular degeneration)
- Family history of "liver disease" (hemochromatosis [positive family history in 25% of patients], alpha-1-antitrypsin deficiency)
- History of recurrent episodes of right upper quadrant pain (biliary tract disease)
- History of blood transfusions, IV drug abuse (hepatitis C)
- History of repetitive hepatotoxic drug exposure
- Coexistence of other diseases with immune or autoimmune features (immune thrombocytopenic purpura, myasthenia gravis, thyroiditis, autoimmune hepatitis)
- Biopsy is the gold standard to diagnosis cirrhosis and is helpful when multiple etiologies are possible that might change management (autoimmune hepatitis, small duct primary sclerosing cholangitis, antimitochondrial antibody-negative primary biliary cholangitis, and infiltrative diseases such as lymphoma, amyloidosis, and granulomatous hepatitis). However, it is generally unnecessary if the clinical picture is highly suggestive of cirrhosis and management would not change. Biopsy can be useful in actively drinking patients with cirrhosis to distinguish between decompensated cirrhosis and cirrhosis with alcoholic hepatitis

LABORATORY TESTS

- Decreased hemoglobin and hematocrit, elevated mean corpuscular volume (Fig. E1). Increased blood urea nitrogen (BUN) and creatinine (the BUN may also be "normal" or low if the patient has severely diminished liver function).
- Decreased sodium (dilutional hyponatremia), and decreased potassium (as a result of secondary aldosteronism or urinary losses). Evaluation of renal function should also include measurement of urinary sodium and urinary protein from 24-hr urine collection.
- Decreased glucose in a patient with liver disease indicates severe liver damage.
- Other laboratory abnormalities:
  1. Alcoholic hepatitis and cirrhosis: Possible mild elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), usually <500 IU; AST >ALT (ratio >2:3).
  2. Extrahepatic obstruction: Possible moderate elevations of ALT and AST to levels <500 IU.
  3. Viral, toxic, or ischemic hepatitis: Extreme elevations (>500 IU) of ALT and AST.
  4. Transaminases may be normal despite significant liver disease in patients with jejunoileal bypass operations or hemochromatosis or after methotrexate administration.
  5. Alkaline phosphatase elevation can occur with extrahepatic obstruction, primary biliary cholangitis, and primary sclerosing cholangitis.
  6. Serum lactate dehydrogenase is significantly elevated in metastatic disease of the liver; lesser elevations are seen with

hepatitis, cirrhosis, extrahepatic obstruction, and congestive hepatomegaly.
7. Serum gamma-glutamyl transpeptidase is elevated in alcoholic liver disease and may also be elevated with cholestatic disease (primary biliary cholangitis, primary sclerosing cholangitis).
8. Serum bilirubin may be elevated; urinary bilirubin can be present in hepatitis, hepatocellular jaundice, and biliary obstruction.
9. Serum albumin: Significant liver disease results in hypoalbuminemia. Malnutrition occurs in 20% to 60% of patients with cirrhosis.

- Prothrombin time/INR: Elevation in patients with liver disease indicates severe liver damage and poor prognosis. Table 1 summarizes hemostatic balance in liver disease.

1. Presence of hepatitis B surface antigen implies acute or chronic hepatitis B.
2. Presence of antimitochondrial antibody suggests primary biliary cholangitis, chronic hepatitis.
3. Elevated serum copper, decreased serum ceruloplasmin, and elevated 24-hr urine may be diagnostic of Wilson disease.
4. Protein immunoelectrophoresis may reveal decreased α-1 globulins (alpha-1-antitrypsin deficiency), increased IgA (alcoholic cirrhosis), increased IgM (primary biliary cirrhosis), increased IgG (chronic hepatitis, cryptogenic cirrhosis).
5. An elevated serum ferritin and increased iron saturation are suggestive of hemochromatosis.
6. An elevated blood ammonia suggests hepatocellular dysfunction; serial values, however, are generally not useful in monitoring patients with hepatic encephalopathy because there is poor correlation between blood ammonia level and degree of hepatic encephalopathy.
7. Serum cholesterol is elevated in cholestatic disorders.
8. Antinuclear antibodies (ANA) may be found in autoimmune hepatitis.
9. Alpha fetoprotein: Levels >1000 pg/ml are highly suggestive of hepatocellular carcinoma.
10. Hepatitis C viral testing identifies patients with chronic hepatitis C infection.
11. Elevated level of serum globulin (especially gamma-globulins) and positive ANA test may occur with autoimmune hepatitis.
12. End-stage liver disease is characterized by decreased levels of most procoagulant factors with the notable exceptions of factor VIII and von Willebrand factor, which are elevated. Table 2 summarizes hemostatic indices in liver disease.

TABLE 1 Hemostatic Balance in Liver Disease

	Promotes Thrombosis	Promotes Bleeding
Primary hemostasis	• Increased vWF • Decreased ADAMTS13	• Thrombocytopenia • Platelet dysfunction
Secondary hemostasis	• Increased factor VIII • Decreased protein C, protein S, antithrombin	• Factor deficiencies: II, V, VII, IX, XI • Vitamin K deficiency • Hypofibrinogenemia • Dysfibrinogenemia
Fibrinolysis	• Reduced plasminogen • Increased PAI-1	• Reduced α2-antiplasmin, TAFI, factor VIII • Increased t-PA

ADAMST13, A disintegrin and metalloproteinase with thrombospondin; *PAI-1,* plasminogen activator inhibitor-1; *TAFI,* thrombin activatable fibrinolysis inhibitor; *t-PA,* tissue plasminogen activator; *vWF,* von Willebrand factor.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

IMAGING STUDIES

- Ultrasonography is the procedure of choice. It can identify the size and shape of the liver (generally small and nodular in advanced cirrhosis) and can detect gallstones and dilation of bile ducts. The use of sonography on a periodic basis to screen for hepatocellular carcinoma in patients with cirrhosis should be considered.
- CT scan (Figs. 2 and 3) is useful for detecting mass lesions in liver and pancreas, assessing hepatic fat content, identifying idiopathic hemochromatosis, diagnosing Budd-Chiari syndrome early, assessing dilation of intrahepatic bile ducts, and detecting varices and splenomegaly. However, ultrasound is generally the preferred imaging modality of choice.
- MRI can be used to identify hemangiomas, hepatocellular carcinoma.
- Vibration-controlled transient elastography and magnetic resonance elastography are useful to assess advanced fibrosis. These noninvasive tests are less expensive and safer than biopsy and can be repeated over time to monitor disease progression.
- Technetium-99m sulfur colloid scanning is rarely used but can be useful for diagnosing cirrhosis (there is a shift of colloid uptake to the spleen and bone marrow), identifying hepatic adenomas (cold defect is noted), and diagnosing Budd-Chiari syndrome (there is increased uptake by the caudate lobe).
- Endoscopic retrograde cholangiopancreatography can be used for diagnosing periampullary carcinoma and common duct stones; it is also useful in diagnosing primary sclerosing cholangitis.
- Percutaneous transhepatic cholangiography is useful when evaluating patients with cholestatic jaundice and dilated intrahepatic ducts by ultrasonography; presence of intrahepatic strictures and focal dilation is suggestive of primary sclerosing cholangitis.

TABLE 2 Hemostatic Indices in Liver Disease

Laboratory Changes	PT	PTT	TCT	Fib	Clauss	Plt	Platelet Aggregation	FVII	DD	ELT
Thrombocytopenia	N	N	N	N	N	↓	N	N	N	N
Platelet dysfunction	N	N	N	N	N	N	abnormal	N	N	N
Vitamin K deficiency[a]	↑	↑	N	N	N	N	N	↓	N	N
Factor deficiency	↑	↑	N	N	N	N	N	↓	N	N
Hypofibrinogenemia	N/↑	N/↑	↑	↓	↓	N	N	N	N	N
Dysfibrinogenemia	N/↑	N/↑	↑	N	↓	N	N	N	N	N
Hyperfibrinolysis	N/↑	N/↑	N/↑	N/↓	N/↓	N	N	↓	↑	↓
DIC	N/↑	N/↑	N/↑	↓	↓	↓	N	N/↓	↑	↓

Clauss, Clauss fibrinogen; *DD,* D-dimer; *DIC,* disseminated intravascular coagulation; *ELT,* euglobulin lysis time (measure of fibrinolysis); *Fib,* fibrinogen; *FVII,* factor VII functional assay; *N,* normal; *Plt,* platelet; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *TCT,* thrombin clotting time.
[a]Differentiating between vitamin K deficiency and liver disease can be challenging with conventional laboratory tests. If available, performing a factor II assay with and without Echis venom (factor II biologic and factor II Echis) may be useful. Ecarin is derived from *Echis carinatus* snake venom and can activate prothrombin irrespective of γ-carboxylation. Factor II activity (biologic) is reduced in both vitamin K deficiency and liver disease. In contrast, the factor II Echis is reduced in liver disease but is normal in vitamin K deficiency.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid any hepatotoxins (e.g., ethanol, acetaminophen), improve nutritional status, vaccinate against hepatitis A and B if not already immune.
- Transjugular intrahepatic portosystemic shunt (TIPS) in patients with recurrent variceal hemorrhage despite optical medical therapy (Fig. 4). Early use of TIPS is associated with significant reductions in treatment failure and in mortality in patients with cirrhosis who are hospitalized for acute variceal bleeding and are at high risk for treatment failure.
- Correction of malnutrition: Daily protein intake of 1.0 to 1.5 g per kg of body weight.

ACUTE GENERAL Rx

- Nonselective beta blockers (nadolol, propranolol) in patients with cirrhosis and variceal hemorrhage, and some without hemorrhage but with high-risk bleeding features. Use with caution in patients with severe alcoholic hepatitis and decompensated cirrhosis with refractory ascites. Beta-blockers should be temporarily discontinued in patients with spontaneous bacterial peritonitis due to increased mortality and hepatorenal syndrome incidence.
- Pruritus due to liver disease may be treated with cholestyramine 4 g/day initially. Dose can be increased to 24 g/day as needed.
- Pain management: Avoid opiates (may precipitate or aggravate hepatic encephalopathy) and NSAIDs (increased risk of gastrointestinal bleeding and renal failure). Low-dose tramadol and lidocaine patches are generally well tolerated.
- Sedatives: Benzodiazepines (lorazepam or oxazepam) may be used for alcohol withdrawal but should be avoided in patients with hepatic encephalopathy. Avoid benzodiazepines with liver metabolites (diazepam, chlordiazepoxide).
- Statins: Can be safely started and continued in patients with hyperlipidemia and/or nonalcoholic fatty liver disease.
- Proton pump inhibitors: Not routinely indicated; their use in patients with cirrhosis is associated with excess risk for spontaneous bacterial peritonitis and hepatic encephalopathy; avoid indiscriminate use of PPIs in patients with cirrhosis.
- Antibiotics: Trimethoprim-sulfamethoxazole or ciprofloxacin/norfloxacin for spontaneous bacterial peritonitis prophylaxis in patients with a history of SBP, an ascites protein concentration less than 1 g/dl, or history of variceal hemorrhage.
- Liver transplantation may be indicated in otherwise healthy patients (ages <65 yr) with severe cirrhosis and lack of contraindications. Contraindications to liver transplantation are AIDS, most metastatic malignancies, active substance abuse, uncontrolled sepsis, and uncontrolled cardiac or pulmonary disease.
- Treatment of complications of portal hypertension (ascites, esophagogastric varices, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome; refer to these individual topics in Section I).
- Box 1 summarizes the management of coagulopathy in liver disease.

TREATMENT BASED ON SPECIFIC CAUSE OF CIRRHOSIS

- Remove excess body iron with phlebotomy and deferoxamine in patients with hemochromatosis.
- Remove copper deposits with D-penicillamine in patients with Wilson disease.
- Long-term ursodiol therapy will slow the progression of primary biliary cholangitis. It is, however, ineffective in primary sclerosing cholangitis.
- Glucocorticoids (prednisone 20 to 30 mg/day initially or combination therapy or prednisone and azathioprine) are useful in autoimmune hepatitis.
- Antivirals in chronic hepatitis C.

PROGNOSIS

- Prognosis varies with the etiology of the patient's cirrhosis and whether there is ongoing hepatic injury. Patients with compensated cirrhosis (no associated complications or esophageal varices without bleeding) have a good prognosis with median survival of 12 yr.
- In patients with decompensated cirrhosis, the Model for End-stage Liver Disease with sodium (MELDNa) scoring is useful to predict 3-mo mortality and so is the main method of prioritizing patients awaiting liver transplantation. It also has prognostic value following TIPS placement for patients with cirrhosis undergoing nontransplant surgeries. Mortality rate exceeds 80% in patients with hepatorenal syndrome.
- Regression of cirrhosis has been demonstrated after antiviral therapy in some patients with chronic hepatitis C. Regression is associated with decreased disease-related morbidity and improved survival.
- Cirrhosis is associated with an increased risk for hepatocellular carcinoma. However, the risk is low (1% 5-yr cumulative risk in alcoholic cirrhosis).

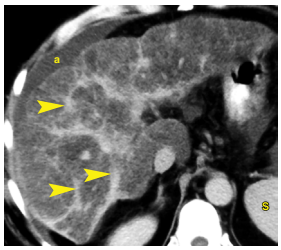

FIG. 2 Advanced cirrhosis with fatty infiltration. Delayed portal venous–phase computed tomography reveals that the liver is misshapen and nodular in contour. Parenchymal density that is significantly lower than that of the spleen *(S)* is indicative of fatty infiltration and continuing liver injury. Prominent scars and bands of fibrosis *(arrowheads)* are seen throughout the liver. Ascites *(a)* is present. (From Webb WR et al: *Fundamentals of body CT*, ed 4, Philadelphia, 2015, Saunders.)

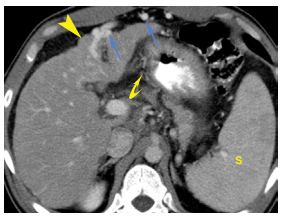

FIG. 3 Cirrhosis with portal hypertension. Postcontrast computed tomography reveals a liver that is nodular in contour *(arrowhead)* with patent enlarged paraumbilical veins (*blue arrows*) and splenomegaly *(S)*, findings indicative of portal hypertension. Mildly enlarged portosystemic collateral vessels (*curved arrow*) are also evident in the gastrohepatic ligament. (From Webb WR et al: *Fundamentals of body CT*, ed 4, Philadelphia, 2015, Saunders.)

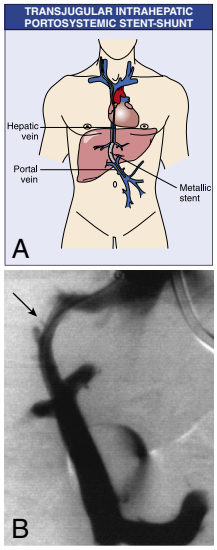

FIG. 4 Transjugular intrahepatic portosystemic stent shunt. A, An intrahepatic track has been created between the right hepatic vein and the right portal vein. **B,** The track is dilated *(arrow)* and stented, creating a shunt as demonstrated on shuntogram. (Courtesy Dr. W. K. Tso, Queen Mary Hospital, Hong Kong.)

PEARLS & CONSIDERATIONS

COMMENTS

- Thrombocytopenia and advanced Child-Pugh classes (Table 3) are associated with the presence of varices. These factors are useful to identify cirrhotic patients who benefit most from referral for endoscopic screening for varices.
- A combination of endoscopic and drug therapy reduces overall and variceal rebleeding in cirrhosis more than either therapy alone.

BOX 1 Management of coagulopathy in liver disease

- Actively bleeding patients should be adequately resuscitated. Admission to the intensive care setting may be appropriate.
- Basic coagulation tests should be ordered to identify the cause of bleeding; these include CBC, PT (INR), PTT, thrombin clotting time, fibrinogen, D-Dimer, FDP, and mixing studies. The need for more specialized tests will be dictated by the clinical situation and response to therapy.
- It is important to identify any localized source of bleeding (e.g., varices) amenable to procedural intervention to achieve hemostasis.
- A trial of 5 to 10 mg of vitamin K is reasonable in asymptomatic patients with prolonged PT and PTT but should be used with other therapies in actively bleeding patients.
- In patients with thrombocytopenia platelet transfusions can be used, targeting platelet counts greater than 50 × 109 /L.
- In patients who can tolerate volume, FP 4 to 6 units (1000–1500 ml) given over 1 to 2 hours can be used to replace coagulation factors. Coagulation parameters should be monitored to document effect and determine the timing and need for additional units.
- Dysfibrinogenemia or hypofibrinogenemia should be suspected if coagulation assays do not correct with FP or fibrinogen levels are low, respectively. Replacement can be attempted with 10 to 20 units of cryoprecipitate while following laboratory results.
- Patients who are intravascularly overloaded or who do not respond to FP should be considered for rFVIIa. Low doses of rFVIIa (25-50 μg/kg) are generally used, and repeated doses may be required because of the short rfVIIa half-life of 2 to 3 hours. rFVIIa may be most suitable as a temporizing measure to enable invasive procedures or hemostasis to be achieved by other means. Avoid use in the setting of DIC.

CBC, Complete blood count; *DIC,* disseminated intravascular coagulation; *FDP,* Fibrin degradation products; *FP,* frozen plasma; *INR,* international normalized ratio; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *rFVIIa*. recombinant factor VIIa.

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 3 Child-Pugh Staging Criteria

CHILD-PUGH SCORE			
Criteria	**1 Point**	**2 Points**	**3 Points**
Total serum bilirubin (mg/dl)	<2	2-3	>3
Serum albumin (g/dl)	>3.5	2.8-3.5	<2.8
INR	<1.70	1.71-2.20	>2.20
Ascites	No ascites	Ascites controlled	Ascites not controlled
Encephalopathy	No encephalopathy	Encephalopathy controlled	Encephalopathy not controlled
INTERPRETATION OF CHILD-PUGH SCORES			
	Points	**Life Expectancy**	**Perioperative Mortality**
Child Class A	5-6	15-20 yr	10%
Child Class B	7-9	Candidate for liver transplant	30%
Child Class C	10-15	1-3 yr	82%

INR, International normalized ratio.

- PPI use, but not H_2RA use, is associated with risk for serious infections in patients with decompensated cirrhosis.
- In patients with compensated cirrhosis and clinically significant hypertension beta-blockers reduced a composite of decompensation or death.[1]

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Cirrhosis (Patient Information)
Ascites (Related Key Topic)
Esophageal Varices (Related Key Topic)
Hepatic Encephalopathy (Related Key Topic)
Hepatopulmonary Syndrome (Related Key Topic)
Hepatorenal Syndrome (Related Key Topic)
Spontaneous Bacterial Peritonitis (Related Key Topic)
Primary Biliary Cholangitis (Related Key Topic)

AUTHOR: **David J. Lucier Jr., MD, MBA, MPH**

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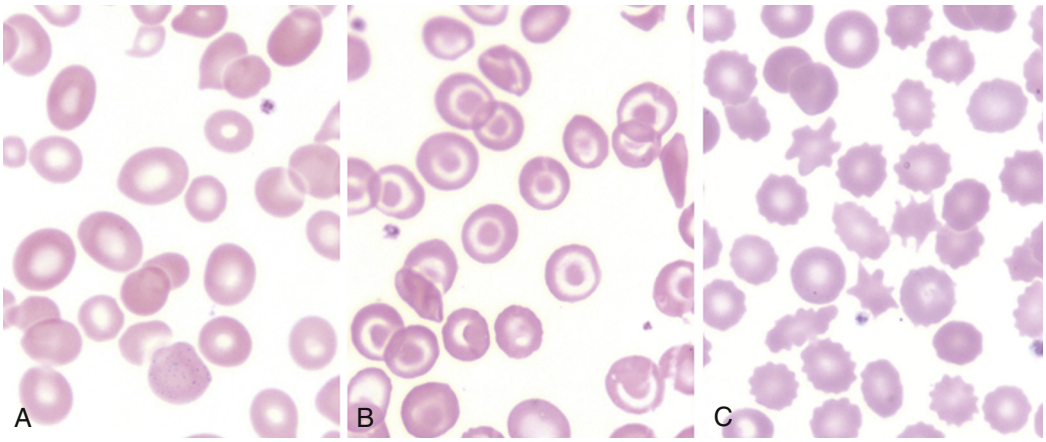

FIG. E1 Red blood cell morphology in liver disease. A, Macrocytes have a mean corpuscular volume greater than 100 fl and can be oval-shaped. Commonly associated disorders include liver disease and vitamin B_{12} and folate deficiency. **B,** Target cells are characterized by the bull's-eye appearance of the red blood cell (RBC). They are a result of an increased surface-to-volume ratio related to excess RBC membrane (e.g., liver disease) or disproportionate reduction of cytoplasmic content (e.g., hemoglobinopathies, iron deficiency). **C,** Acanthocytes, or spur cells, typically appear as contracted RBCs lacking central pallor with multiple irregular membrane projections. The morphologic appearance reflects the irreversible cytoskeletal damage that has occurred because of passage of nondeformable RBCs through the reticuloendothelial system. They are most commonly seen in severe liver disease but can also be features of rare neuroacanthocytosis syndromes or lipoprotein disorders. (From Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.)

Cirrhotic Cardiomyopathy

BASIC INFORMATION

DEFINITION

- Cirrhotic cardiomyopathy (CCM) is a clinical syndrome in cirrhotic patients characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease.
- CCM is a separate clinical entity from alcoholic cardiomyopathy.

SYNONYM

CCM

ICD-10CM CODE

I43 Cardiomyopathy in diseases classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE AND PREVALENCE:

- Prevalence between 40% to 50% in cirrhotic patients independent of liver disease etiology and 3% to 23.4% of patients undergoing orthotopic liver transplantation.
- Cardiac dysfunction is seen in 50% of patients with advanced cirrhosis.
- Heart failure is seen in 7% to 21% of patients who undergo orthotopic liver transplantation.

RISK FACTORS:

- Moderate to severe cirrhosis (Child Pugh B or C) tends to have at least one feature of CCM. There is no direct correlation between the degree of liver cirrhosis (assessed by Child Pugh or MELD score) and CCM.
- Posttransjugular intrahepatic portosystemic shunt (TIPS): Shift of splanchnic blood into the heart via the artificial shunts overloads a noncompliant left ventricle, leading to overt heart failure.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical and physical features include:

- Symptoms and signs of heart failure: Reduced exercise capacity, dyspnea on exertion, tachycardia, edema, ascites, paroxysmal nocturnal dyspnea, pulmonary congestion, increased jugular venous pressure, and an S3 or S4 gallop.
- Electrophysiological disturbances: QTc interval prolongation (>440 msec), Torsade de pointes, chronotropic incompetence.

ETIOLOGY & PATHOPHYSIOLOGY

Etiology is multifactorial in patients with liver disease. Fig. E1 illustrates proposed pathophysiology of cirrhotic cardiomyopathy.

Mechanisms of cardiac dysfunction include the following:

- Increased catecholamines in cirrhotic patients eventually leads to the downregulation of β-adrenergic receptors resulting in attenuated inotropic and chronotropic function.

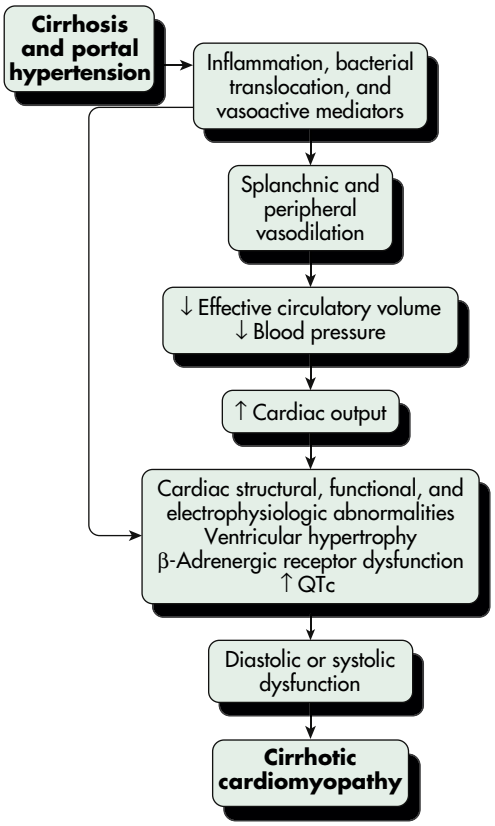

FIG. E1 Proposed pathophysiology of cirrhotic cardiomyopathy. *QTc,* Rate-corrected QT interval. (From Feldman M et al: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

- Inflammatory stimuli from nitric oxide, carbon monoxide, endocannabinoids, and cytokines, such as TNF-a, increase cardiomyocyte apoptosis.
- The decreased effective volume activates the renin–angiotensin–aldosterone system (RAAS), leading to fibrosis and stiff ventricles.
- Potassium channel defect leads to electrophysiological imbalances such as QT prolongation, chronotropic incompetence, and mechanical dyssynchrony.
- Hyperdynamic circulation: Increased volume expansion but poor volume distribution (increased splanchnic circulation, decreased central circulation) leads to relative hypovolemia, which activates the RAAS and sympathetic nervous system and leads to tachycardia and increased cardiac output.

DIAGNOSIS

The 2005 World Congress of Gastroenterology proposed the following criteria for CCM:

- Systolic dysfunction (LV EF <55%, blunted increase in cardiac output with exercise)
- Diastolic dysfunction on echocardiogram (E/A <1.0, deceleration time >200 msec, isovolumetric relaxation time >80 msec)
- Supportive criteria: Electromechanical abnormalities (prolonged QTc), heart chamber alterations (enlarged left atrium), humoral changes (increased brain natriuretic peptide [BNP], N-terminal pro-BNP [NT pro-BNP], or troponin)

DIFFERENTIAL DIAGNOSIS

- Alcoholic cardiomyopathy (ACM)
- Cardiac cirrhosis
- Iron-induced cardiac disease (hemochromatosis)
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathy
- Coronary atherosclerosis with left ventricular dysfunction

WORKUP

- BNP and NT pro-BNP: Markers of fluid overload, can correlate with the severity of cirrhosis
- Troponin I or T: Assess cardiac ischemia, increased LV mass

IMAGING STUDIES

- Electrocardiography: QTc >440 msec, ST depressions, bundle branch block
- Chest x-ray: Pulmonary congestion, left atrial and ventricular enlargement
- Echocardiogram: Resting systolic dysfunction; diastolic dysfunction (E/A <1, prolonged deceleration time [>200 msec] and prolonged isovolumetric relaxation time [>80 msec]); tissue Doppler imaging and speckle tracking echocardiography can quantitate the LV function
- MRI: Morphological evaluation of the liver and the heart (shunts, chamber quantification, tissue characterization)

DIAGNOSTIC TESTS

- Exercise testing (upright bicycle ergometry): Suppressed increase in cardiac output with exercise
- Dobutamine stress echocardiography (DSE): Lack of contractile reserve with dobutamine defined as an increase in LV EF <10% and or diastolic dysfunction. DSE has limited utility due to downregulated β-receptors)

Rx TREATMENT

There are no well-established guidelines for the management of CCM. Management should follow the same guidelines as in noncirrhotics.

NONPHARMACOLOGIC THERAPY

- Risk-factor modification: Weight loss, smoking cessation, exercise, blood pressure control
- Oxygen supplementation if signs of hypoxia
- Dietary sodium restriction (<2 g/day)
- Fluid restriction when serum sodium <120 mmol/L
- Pneumococcal and influenza vaccination

ACUTE GENERAL Rx

- Acute pulmonary edema: Head elevation ≥30 degrees, early diuretic use (furosemide, bumetanide, torsemide); nitrates are useful if concomitant hypertension or chest pain
- Cardiogenic shock: Inotropes (dobutamine, milrinone), vasopressors (norepinephrine, dopamine), and mechanical support if needed

CHRONIC Rx

Chronic management is consistent with the treatment of patients with heart failure.

- Diuretics: Furosemide and spironolactone are the mainstay for treating fluid overload in cirrhosis.
- Beta-blockers: They promote the reduction of the QT interval. Nonselective beta-blockers are known to prevent variceal bleeding. One should exercise caution because beta-blockers can reduce cardiac output.
- Liver transplantation is the cure for cirrhosis and its associated cardiomyopathy. It has been shown to restore exercise capacity within 6 to 12 months.

DISPOSITION

- Mortality rate is unclear because most patients die from repercussions of liver failure.
- Liver transplant can reverse CCM features, including systolic and diastolic dysfunction and QT prolongation.
- Patients with diastolic dysfunction have worse prognosis after liver transplantation.

REFERRAL

Follow-up with a cardiologist is recommended.

PEARLS & CONSIDERATIONS

COMMENTS

- CCM should be considered in cirrhotic patients who present with symptoms and signs of heart failure symptoms or arrhythmia.
- Diagnostic criteria are based on echocardiogram (systolic or diastolic dysfunction), stress testing, electrophysiological disturbances, and laboratory abnormalities.
- Liver transplantation is the definitive treatment for this rare clinical entity.

PREVENTION

Treatment of liver disease prior to progression to cirrhosis.

PATIENT & FAMILY EDUCATION

A multidisciplinary team involving a hepatologist and cardiologist may be useful in long-term management and patient education.

RELATED CONTENT

Cirrhosis (Related Key Topic)
Heart Failure (Related Key Topic)
Pulmonary Edema (Related Key Topic)

AUTHORS: **Maxwell Eyram Afari, MD,** and **Joe Aoun, MD**

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BASIC INFORMATION

DEFINTION

Claudication refers to reproducible pain, fatigue, discomfort, or cramping due to vascular origin in a muscle group that is consistently induced by exertion and is relieved with rest. Claudication results from inadequate blood flow to the target muscle group, which is not able to meet increased metabolic demand, resulting in a supply-and-demand mismatch due to peripheral arterial disease (PAD). Intermittent vascular claudication is more common in the lower extremities but can also affect the upper extremities.

SYNONYM

Intermittent claudication

ICD-10CM CODES

I70.211	Atherosclerosis of native arteries of extremities with intermittent claudication, right leg
I70.212	Atherosclerosis of native arteries of extremities with intermittent claudication, left leg
I70.213	Atherosclerosis of native arteries of extremities with intermittent claudication, bilateral legs
I70.219	Atherosclerosis of native arteries of extremities with intermittent claudication, unspecified extremity
I70.311	Atherosclerosis of unspecified type of bypass graft(s) of the extremities with intermittent claudication, right leg
I70.312	Atherosclerosis of unspecified type of bypass graft(s) of the extremities with intermittent claudication, left leg
I70.313	Atherosclerosis of unspecified type of bypass graft(s) of the extremities with intermittent claudication, bilateral legs
I70.319	Atherosclerosis of unspecified type of bypass graft(s) of the extremities with intermittent claudication, unspecified extremity
I70.719	Atherosclerosis of other type of bypass graft(s) of the extremities with intermittent claudication, unspecified extremity

EPIDEMIOLOGY & DEMOGRAPHICS

- Symptomatic claudication in Western countries affects 5% of patients between the ages of 55 and 74.
- Lower extremity PAD, which includes both symptomatic claudication and asymptomatic disease, is estimated to affect approximately 8.5 million Americans above age 40 and 202 million people around the world.
- At-risk patients include:
  1. All patients age 65 yr or older.
  2. Age 50 to 64 yr with risk factors for atherosclerosis, including diabetes mellitus, smoking history, hyperlipidemia, hypertension, or family history of PAD.
  3. Age <50 yr, with diabetes mellitus and one additional risk factor for atherosclerosis.
  4. Individuals with known atherosclerotic disease in another vascular bed, for example, coronary, carotid, subclavian, renal, mesenteric artery, or abdominal aortic aneurysm (AAA).
- Risk factors associated with development of PAD are similar to coronary atherosclerosis (CAD) and include increasing age, cigarette smoking (odds ratio 2.72), hypertension (odds ratio 1.55), diabetes mellitus (odds ratio 1.88), and hypercholesterolemia (odds ratio 1.19). In addition, patients with chronic kidney disease, metabolic syndrome, and elevated levels of C-reactive protein, lipoprotein(a), and homocysteine are at increased risk. Nontraditional risk factors include race/ethnicity, with African American patients being at higher risk. Hispanics also have similar to slightly higher rates of PAD compared to non-Hispanic whites.
- There is a strong correlation among PAD, CAD, carotid artery stenosis, and generalized cerebrovascular disease. Individuals with known atherosclerotic disease in one vascular bed are likely to have disease in another.
- The American College of Cardiology/American Heart Association (ACC/AHA) guidelines suggested the following distribution of clinical presentation of PAD in patients 50 yr of age or older:
  1. Asymptomatic: 20% to 50%
  2. Atypical leg pain: 40% to 50%
  3. Classic intermittent claudication: 10% to 35%
  4. Critical limb ischemia with threatened limb: 1% to 2%

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The severity of symptoms varies with degree of PAD, collateral blood supply, and exertional demands
- Classic symptoms include exertional calf pain, which limits the patient's activity and self-resolves with rest within 10 minutes. Claudication can also typically present in the buttock and hip, thigh, calf, or foot, with one or more of the following signs or symptoms, depending on the level and degree of peripheral stenosis:
  1. Diminished or absent pedal pulses
  2. Bruit over the distal aorta, iliac, or femoral arteries
  3. Pallor of the distal extremities and cool to the touch upon elevation
  4. Rubor with prolonged capillary refill upon dependent positioning
  5. Trophic changes, including hair/nail loss and muscle atrophy
  6. Nonhealing ulcers, necrotic tissue, and gangrene
  7. Weakness, numbness, or heaviness in the lower extremities
- True vascular claudication must be distinguished from "pseudoclaudication," which can be caused by severe venous obstruction or insufficiency, chronic compartment syndrome, spinal stenosis, osteoarthritis, and inflammatory muscle diseases. The characteristic features of pseudoclaudication that distinguish it from claudication are summarized in Table 1. Table 2 illustrates the differential diagnosis of intermittent claudication
- Location of pain usually corresponds to analogous anatomy:
  1. Buttock and hip: Aortic or iliac disease
  2. Thigh: Aorta, iliac, or common femoral artery
  3. Upper two thirds of calf: Superficial femoral artery
  4. Lower one third of calf: Popliteal artery
  5. Foot: Tibial or peroneal artery
- Asymptomatic PAD is typically diagnosed by screening studies (exercise ankle brachial index, lower-extremity ultrasound) or incidentally on physical exam. Patients who are at significant risk for PAD often have multiple comorbidities that can alter their presentation. In the PARTNERS program report, 47% of those with a new diagnosis of PAD had no history of leg symptoms, 47% had atypical symptoms, and only 6% had classic symptoms
- Symptoms of intermittent claudication classically start distally within a muscle group (below the stenosis) and then ascend with continued activity
- Rest pain that occurs with leg elevation and is paradoxically relieved by walking may suggest severe PAD
- Critical limb ischemia may present as tissue ulceration and gangrene, which require prompt intervention

ETIOLOGY

The primary cause of claudication is peripheral atherosclerosis, resulting in a stenosis that impedes blood flow beyond the level necessary to meet the metabolic demand of limb muscles first with activity and then ultimately at rest.

TABLE 1 Characteristic Features of Pseudoclaudication that Distinguish It from Claudication

	Claudication	Pseudoclaudication
Characteristics	Limb cramping, tightness, fatigue	Similar to claudication with numbness
Location of discomfort	Lower extremity involving buttock, hip, thigh, calf, foot	Similar to claudication
Induced by exercise	Yes	Variable
Reproducible with distance walked	Consistent	Variable
Occurs with standing	No	Yes
Actions which provide relief	Stand	Sit
Time to relief	<5 min	≥30 min

TABLE 2 Differential Diagnosis of Intermittent Claudication

	Intermittent Claudication	Venous Claudication	Neurogenic Claudication
Quality of pain	Cramping	Aching, heaviness, tightness	"Pins and needles" sensation going down the leg, weakness
Onset	Gradual, consistent	Gradual; can, however, be immediate	Can be immediate
Relieved by	Stopping walking	Activity, elevation of leg	Sitting down, stooping, flexion at the waist
Location	Muscle groups (e.g., buttocks, thigh, calf)	Entire leg, worse in calf	Poorly localized, but can affect whole leg
Legs affected	Usually one	Usually one	Often both

From Swartz MH: *Textbook of physical diagnosis,* ed 7, Philadelphia, 2014, Saunders.

Other etiologies include neuropathy, musculoskeletal or degenerative disease, compartment or entrapment syndrome, vasculitis, and embolic events.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Spinal stenosis (neurogenic or pseudoclaudication)
- Musculoskeletal disorders: Arthritis or myositis
- Degenerative osteoarthritic joint disease, predominantly of the lumbar spine and hips
- Chronic compartment or popliteal artery entrapment syndrome
- Peripheral neuropathy
- Atheromatous embolization and deep venous thrombosis
- Vasculitis: Thromboangiitis obliterans, Takayasu, or giant cell arteritis
- Symptomatic Baker cyst
- Venous claudication

WORKUP

History and physical findings suggest the diagnosis of claudication and noninvasive studies help confirm the diagnosis.

- Careful physical examinations include:
  1. Measurement of blood pressure in both arms and notation of asymmetry.
  2. Palpation and recording of carotid pulses, upstroke, amplitude, and presence of bruits.
  3. Auscultation and palpation of abdomen for bruits, aortic pulsation, and diameter.
  4. Palpation of brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial pulses. Pulse intensity should be recorded as follows: 0, absent; 1+, diminished; 2+, normal; 3+, bounding.
  5. Auscultation of femoral arteries for the presence of bruits.
  6. Extremities should be inspected for color, temperature, integrity of the skin, hair loss, and hypertrophic nails.
- Measurement of resting ankle–brachial index (ABI) should be considered first-line test in patients at risk for PAD.
- An ABI is the ratio of higher ankle systolic pressure (between the dorsalis pedis and posterior tibial arteries) of each leg to the higher systolic pressure of either arm (brachial artery).
- The severity of PAD is based on the resting ABI:
  1. Abnormal: ≤0.90
  2. Borderline: 0.91 to 0.99
  3. Normal: 1.00 to 1.40
  4. Noncompressible: >1.40
- ABI ≤0.90 has 75% sensitivity and 86% specificity in the detection of PAD.
- A low ABI has been shown to be an independent predictor of mortality.
- A high ABI (>1.4) may represent significant PAD caused by heavy calcification. In such cases, measuring a toe–brachial index (TBI) can increase the sensitivity of testing, as highly calcified arteries are incompressible and may have an elevated ABI. A toe–brachial index <0.7 is considered abnormal and diagnostic of PAD.
- Borderline resting ABI (>0.90 and ≤1.40) in patients with exertional leg symptoms should undergo exercise treadmill ABI testing to evaluate for PAD. This can help differentiate claudication from pseudoclaudication. If post-treadmill ABI is normal, alternative causes of leg pain should be considered.
- Progression of PAD is considered to have occurred if a decrease in ABI of 0.15 occurs while the patient is on treatment.
- If a patient has a history concerning for PAD but a normal ABI, and if the clinician is concerned about a potential false-negative finding, performing an exercise stress ABI can potentially demonstrate lower-extremity PAD.
- If after exercise, ABI reading decreases by more than 20% or an ankle pressure decreases by 30 mm Hg, the patient should be considered to have significant PAD.
- Segmental systolic pressures are measured at the level of the thigh, calf, ankle, metatarsal, and toes. Normally, successive segments have <20 mm Hg difference in pressures. If the gradient is >20 mm Hg, a significant stenosis is suspected in the interval vascular segment.

IMAGING STUDIES

- Duplex ultrasound can be used to assess occlusion location, length, and patency of the distal arterial system or prior grafts; it is a good choice for initial imaging and surveillance monitoring after revascularization.
- In patients with prior infra-inguinal venous bypass grafts, the long-term patency should be evaluated at regular intervals using a duplex ultrasound approximately 4 to 6 wk post procedure, 6 and 12 mo after graft placement, and then yearly.
- Magnetic resonance angiography (MRA) and CT angiography (CTA) are effective for imaging of the aorta and peripheral lower-extremity arteries above the knee. MRA has almost replaced catheter-based angiography, with 90% sensitivity and 97% specificity in identification of hemodynamically significant stenosis in the lower extremities.
- MRA and CTA are useful to define the anatomy and assist in planning percutaneous and surgical revascularization; however, the utility of each is decreased by necessity of gadolinium contrast and noniodinated contrast agents, respectively.
- Angiography (Fig. 1) remains the gold standard for diagnosing PAD, particularly below the knee.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Smoking cessation is of paramount importance. Smokers and former smokers should be asked about tobacco use status at every visit and offered pharmacotherapy, counseling, and/or referred to smoking cessation programs.
- Aggressive risk factor modification for hypertension, dyslipidemia, and diabetes mellitus, including diet, weight loss, and lifestyle counseling, is recommended (Fig. 2).
- Supervised exercise training should be performed as a first-line therapy for a minimum of 30 to 45 minutes, in sessions performed at least 3 times per wk, for a minimum of 12 wk.
- Supervised exercise training programs under direct supervision in a hospital or outpatient facility and structured exercise are recommended for all patients with PAD. This has been shown to increase maximal walking distance, pain-free walking distance, and the 6-minute walking distance. It typically requires 4 to 6 wk for patients to notice improvement.
- Structured or home-based walking exercise program may be considered as an alternative treatment modality, but it has not been shown to be as efficacious. It can be combined with group-mediated cognitive behavioral intervention that can significantly

FIG. 1 Angiogram of the distal abdominal aorta and iliac arteries demonstrates an occluded left common iliac artery with extensive collateral circulation from contralateral internal iliac artery *(left panel),* which resolved after successful stent implantation *(right panel).* (Images courtesy of Bart Domatch, MD, Radiology Department, University of Texas Southwestern Medical Center, Dallas, Texas; From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.)

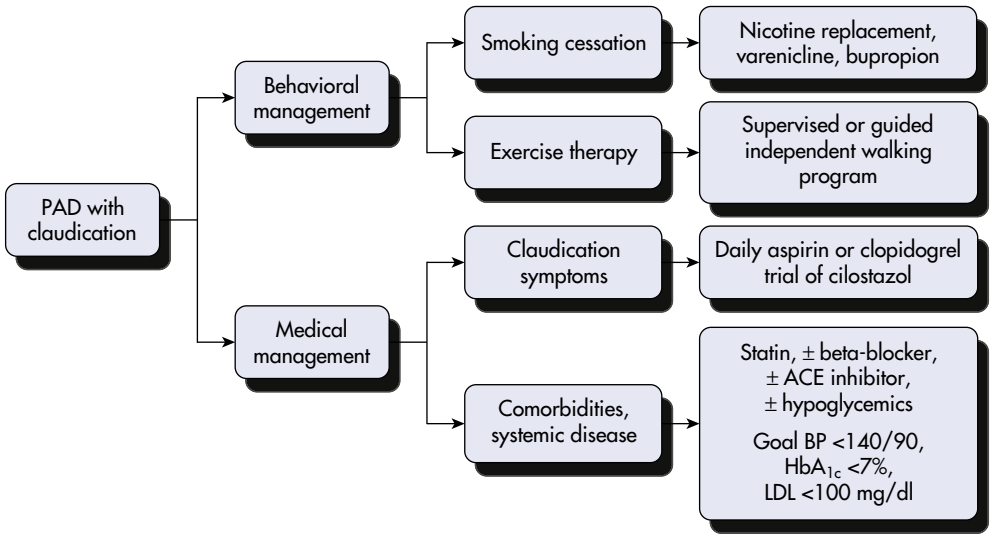

FIG. 2 Algorithm for revascularization in the management of claudication. *ACE*, Angiotensin-converting enzyme; *BP*, blood pressure; *HbA_{1c}*, hemoglobin A_{1c}; *LDL*, low-density lipoprotein; *PAD*, peripheral arterial disease. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

improve endurance and physical activity for patients unable or unwilling to participate in supervised exercise training.
- Lifestyle therapy in conjunction with exercise can be as, or more, effective than pharmacologic therapy and in some cases more effective than stent revascularization.
- Intermittent mechanical compression appears to be an effective noninvasive treatment alternative for patients with intermittent claudication.

ACUTE GENERAL Rx

Revascularization by an endovascular or surgical approach is usually reserved for patients with symptoms refractory to medical therapy or those with impending critical limb ischemia.

CHRONIC Rx

- Aspirin 75 to 325 mg daily is standard therapy.
- Thienopyridine medications such as clopidogrel 75 mg daily may be considered as an alternative to aspirin, especially for those intolerant of aspirin.
- Current data do not support combination treatment with aspirin and clopidogrel.
- Asymptomatic patients with PAD (ABI ≤0.90) without claudication symptoms may benefit from the addition of an antiplatelet agent, either ASA or clopidogrel, as there is an increased cardiovascular risk in this subgroup.
- Statin medications are indicated for all patients with PAD.
  1. LDL cholesterol level of less than 100 mg/dl is recommended.
  2. A goal LDL cholesterol level of less than 70 mg/dl is recommended for patients with PAD and high risk for coronary atherosclerotic disease.
  3. Although new lipid guidelines have been published, the guidelines did not specifically address patients with PAD; therefore, the numerical targets can be considered. In those unable to reach the targets, a reduction in LDL >50% should be approached at a minimum.
- Antihypertensive therapy with beta-adrenergic blocking drugs and/or ACE inhibitors should be administered to all hypertensive patients with PAD to reduce the risk of MI,

stroke, congestive heart failure, and cardiovascular death.
- Cilostazol 100 mg bid may be used in conjunction with aspirin or clopidogrel. It has been shown to increase walking distance by 50% to 67% in symptomatic patients.
- Among patients with intermittent claudication, a single randomized controlled trial has shown a 24-wk treatment with ramipril resulted in significant increases in pain-free and maximum treadmill walking times compared with placebo.
- Pentoxifylline is not effective for treatment of claudication. In a review of 24 studies with over 3000 participants, results remained unclear, and a randomized control trial showed no difference between pentoxifylline and placebo; thus this is not recommended as a treatment for claudication.
- In patients with type II diabetes, a secondary analysis of the BARI 2D trial showed that an insulin-sensitizing approach (metformin, glitazones) reduces the risk of developing PAD when compared to insulin-providing therapy (glipizide, insulin). These patients also have lower rates of revascularization and amputation.
- Patients who are tobacco smokers should be strongly advised to quit smoking at every visit and offered either varenicline or bupropion along with nicotine replacement therapy in the absence of any contraindications. Patients with PAD should avoid tobacco smoke exposure at work, at home, and in public places.
- Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD as there is increased morbidity with no mortality benefit. Its use to improve patency after bypass is uncertain.
- Novel agents, such as protease-activated receptor-1 (e.g., vorapaxar), added to existing antiplatelet therapy may have some benefit in decreasing acute limb-related ischemic events; however, its association with a risk of moderate to severe bleeding makes its benefits uncertain at this time.
- Fig. 3 summarizes the nonoperative management of claudication.
- Revascularization through either a percutaneous or surgical approach is indicated in patients with lifestyle-limiting claudication and inadequate response to goal-directed medical therapy. It is also indicated in those with nonhealing ulcers or gangrene and in select patients with functional disability. Before such revascularization, each patient should have:
  1. Participated in a supervised exercise training program and been given goal-directed medical therapy.
  2. Received comprehensive risk factor modification, including smoking cessation and optimal management of comorbidities.
  3. Significant disability with either the inability to perform normal work or a serious impairment of other activities important to the patient.
  4. Lower-extremity PAD lesion anatomy amenable to revascularization defined as low risk with high probability of initial and long-term success.
- Common procedures include:
  1. Aorto-iliofemoral reconstruction or bypass or infrainguinal bypass (e.g., femoropopliteal, femorotibial).
  2. Percutaneous balloon angioplasty, often with stenting, is primarily used on discrete stenotic lesions in the iliac or femoropopliteal arteries.

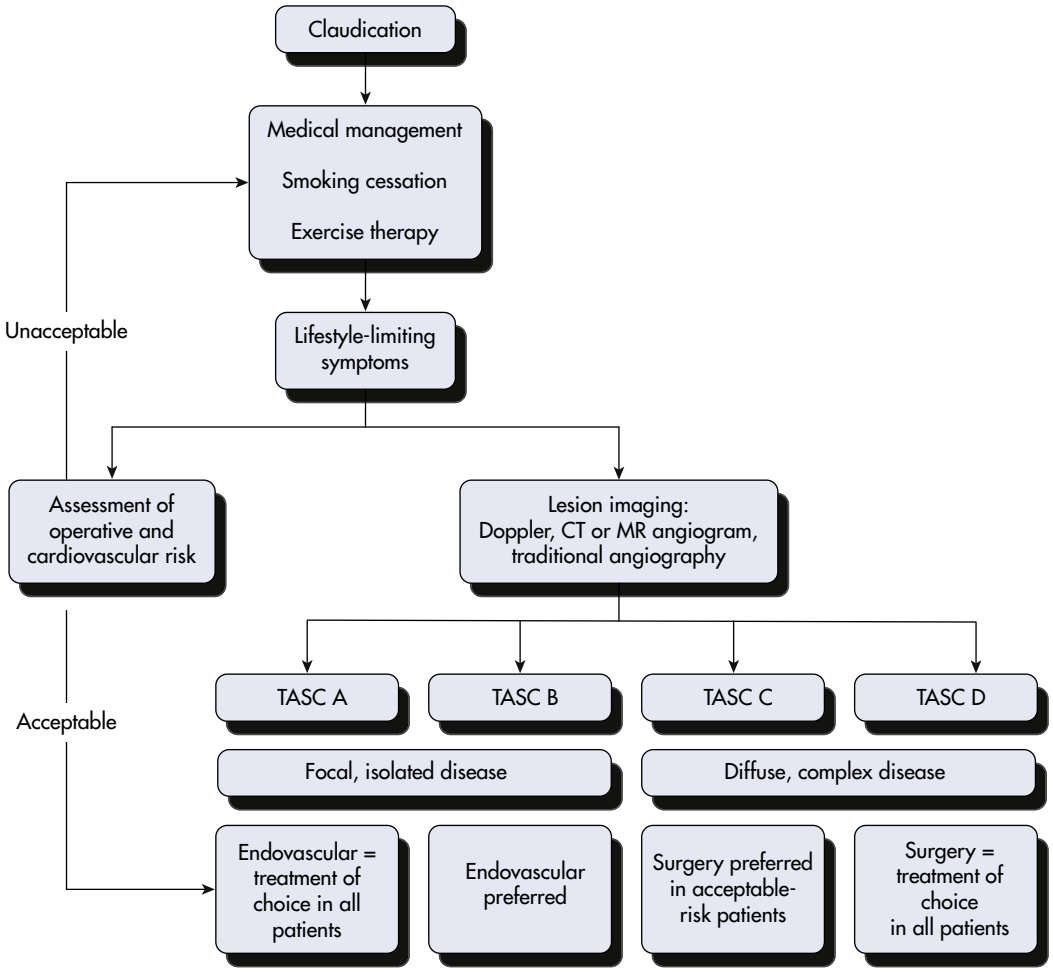

FIG. 3 Nonoperative management of claudication. *CT*, Computed tomographic; *MR*, magnetic resonance; *TASC*, TransAtlantic Inter-Society Consensus class. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

3. Endovascular intervention is recommended as the preferred revascularization technique for iliac and femoropopliteal arterial lesions.
4. Stenting is an effective primary therapy for common and external iliac artery stenosis and occlusions. However, it is not recommended in the femoral, popliteal, or tibial arteries due to a low success rate except to salvage suboptimal balloon dilation.

- Endovascular procedures should not be performed in patients with PAD solely to prevent progression to critical limb ischemia, as reported rates of amputation or progression to critical limb ischemia are <10% to 15% over 5 yr or more, and increased mortality rate associated with claudication is usually the result of cardiovascular events rather than limb-related events.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- A meta-analysis found that over 12 to 24 wk, *Ginkgo biloba* increased pain-free walking distance by 34 m compared with placebo, although the benefit is not well established according to ACC/AHA guidelines.
- Naftidrofuryl, a serotonin receptor inhibitor, available in Europe and other parts of the world, has shown some efficacy in improving claudication symptoms.
- Estrogen replacement therapy, propionyl-L-carnitine, L-arginine, oral vasodilators, prostaglandins, and chelation therapy are ineffective in the treatment of intermittent claudication.
- B-complex vitamin supplementation to lower homocysteine levels for prevention of cardiovascular events in patients with PAD is not recommended (HOPE-2 trial).
- Acupuncture has shown some improvement in symptom relief and functional capacity in small studies but mainly in neurogenic claudication or mild peripheral arterial disease.

DISPOSITION

- It is unusual for intermittent claudication to progress to ischemic leg or limb loss, especially with aggressive use of conservative treatments, risk factor modification, exercise, and smoking cessation.
- The 5-yr risk for development of ischemic ulceration in patients treated for diabetes and with ABI <0.5 was 30% compared with only 5% in patients without either characteristic.
- A screening duplex ultrasound for AAA is recommended for patients with symptomatic PAD.
- All patients with PAD should receive annual influenza vaccination based on observational studies that have demonstrated a reduced cardiovascular event rate.

REFERRAL

Consultation with physicians specializing in vascular medicine is recommended for patients with threatened limb loss, rest pain, nonhealing ulcers, functional disability from pain, and gangrene.

PEARLS & CONSIDERATIONS

- Approximately 70% of patients with peripheral vascular disease will have concomitant coronary artery disease.
- Beta-blockers may worsen claudication symptoms in some patients, although their underuse is associated with excess cardiovascular death. Patients with intermittent claudication are less likely to receive beta-blocker therapy after a myocardial infarction. Those who do not receive post-MI beta-blockers have at least a three-fold higher mortality.
- Patients with peripheral vascular disease may benefit from secondary cardiovascular prevention with clopidogrel versus aspirin more so than other high-risk patients.
- Often, PAD can be asymptomatic or with atypical symptoms, and a thorough history, physical exam, and clinical suspicion based on medical comorbidities may help guide therapy before lifestyle-limiting claudication or limb ischemia develops.

COMMENTS

- Claudication is a marker for generalized atherosclerosis. Patients have a higher risk of death from cardiovascular events than from limb loss. Patients with PAD experience diminished overall quality of life similar to patients diagnosed coronary artery or cerebrovascular disease.
- The ABI is more closely associated with exercise tolerance and severity of disease in persons with PAD rather than intermittent claudication or other leg symptoms.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Poor Circulation (Claudication) (Patient Information)
Peripheral Artery Disease (Related Key Topic)

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SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Clostridium difficile infection (CDI) is the occurrence of diarrhea and bowel inflammation associated with antibiotic use caused by *C. difficile*, an anaerobic gram-positive, spore-forming, toxin-producing bacillus transmitted through the fecal–oral route. CDI can manifest clinically in several forms ranging from fulminant diarrhea and leukocytosis associated with pseudomembranous colitis, mild to severe acute diarrhea, short-term colonization seen typically in health care facilities, and recurrent CDI within 60 days after initial treatment occurring in 20% to 30% of cases.

SYNONYMS

Antibiotic-induced colitis
Pseudomembranous colitis
CDI

ICD-10CM CODE
A04.7 Enterocolitis due to *Clostridium difficile*

EPIDEMIOLOGY & DEMOGRAPHICS

- Cephalosporins are the most frequent offending agent in CDI because of their high rates of use.
- The antibiotic with the highest incidence is clindamycin (10% incidence of CDI with its use).
- Since 1996, the incidence of CDI has more than doubled. Severity of CDI has also increased due to the emergence of an epidemic virulent strain (NAP1/BI/027). CDI is the most common infectious cause of health-care–associated diarrhea in adults. In the U.S. *C. difficile* is responsible for nearly half a million infections per year and is associated with approximately 29,000 deaths/year.
- Nosocomial CDI quadruples the cost of hospitalizations and increases annual expenditures by $4 and $6 billion in the U.S.
- Asymptomatic carriage of *C. difficile* is identified in more than 20% of patients hospitalized without diarrhea.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abdominal tenderness (generalized or lower abdominal)
- Fever
- In patients with prolonged diarrhea, poor skin turgor, dry mucous membranes, and other signs of dehydration may be present

ETIOLOGY

C. difficile colonizes the large intestines and releases two protein exotoxins (TcdA and TcdB) that cause colitis. Infection is transmitted by spores that are resistant to antibiotics, heat, and acid. The NAP1 strain is predominant among patients with *C. difficile* infection, whereas asymptomatic patients are more likely to be colonized with other strains. Risk factors for *C. difficile* (the major identifiable agent of antibiotic-induced diarrhea and colitis):

- Administration of antibiotics: Can occur with any antibiotic, but occurs most frequently with clindamycin, ampicillin, cephalosporins, and fluoroquinolone
- Prolonged hospitalization
- Advanced age
- Abdominal surgery
- Underlying disease (malignancy, renal failure, debilitated status)
- Hospitalized, tube-fed patients are at risk for *C. difficile*–associated diarrhea. Clinicians should consider testing for *C. difficile* in tube-fed patients with diarrhea unrelated to the feeding solution
- Proton pump inhibitor (PPI) and H_2 blocker therapy increases risk of CDI and recurrent CDI. Risk is 1.7-fold higher with PPIs

DIAGNOSIS

The clinical signs of CDI generally include diarrhea, fever, and abdominal cramps after use of antibiotics. Although a history of recent antibiotic use is common, it is not a requirement for diagnosis.

DIFFERENTIAL DIAGNOSIS

- Gastrointestinal bacterial infections (e.g., *Salmonella, Shigella, Campylobacter, Yersinia*)
- Enteric parasites (e.g., *Cryptosporidium, Entamoeba histolytica*)
- Inflammatory bowel disease
- Celiac sprue
- Irritable bowel syndrome
- Ischemic colitis
- Antibiotic intolerance

WORKUP

- All patients with diarrhea accompanied by current or recent antibiotic use should be tested for *C. difficile* (see later discussion). *C. difficile* stool tests are positive in 3% of outpatients and up to 29% of inpatients without signs of infection. Testing and treatment for CDI is not recommended in asymptomatic individuals.
- Sigmoidoscopy (without cleansing enema) may be necessary when the clinical and laboratory diagnosis is inconclusive and the diarrhea persists.
- In antibiotic-induced pseudomembranous colitis, the sigmoidoscopy often reveals raised white-yellow exudative plaques adherent to the colonic mucosa pseudomembranes. These are seen more commonly in severe CDI.

LABORATORY TESTS

- Stool test for *C. difficile* toxin: Enzyme-linked immunosorbent assay for *C. difficile* toxins A and B. The latter is used most widely in the clinical setting. It has a sensitivity of 85% and a specificity of 100%.
- *C. difficile* toxin can be detected by cytotoxin tissue culture assay (cytotoxin assay, gold standard for identifying *C. difficile* toxin in stool specimen). This test is difficult to perform, and results are not available for 24 to 48 hr.
- Fecal leukocytes (assessed by microscopy or lactoferrin assay) are generally present in stool samples.
- Complete blood count usually reveals leukocytosis. A sudden increase in white blood cells to >30,000/mm^3 may be indicative of fulminant colitis.
- Laboratory indicators of **severe CDI** are leukocyte count >15,000/mm^3, serum creatinine ≥1.5 times baseline level, serum albumin <2.5 g/dl.

IMAGING STUDIES

- Abdominal film (flat plate and upright) is useful in patients with abdominal pain or evidence of obstruction on physical examination.
- CT can demonstrate typical findings of colonic wall thickening, dilatation, and the so-called *accordion sign* (thickened haustral folds and trapped contrast material, ascites, or pericolonic stranding [Fig. 1]).

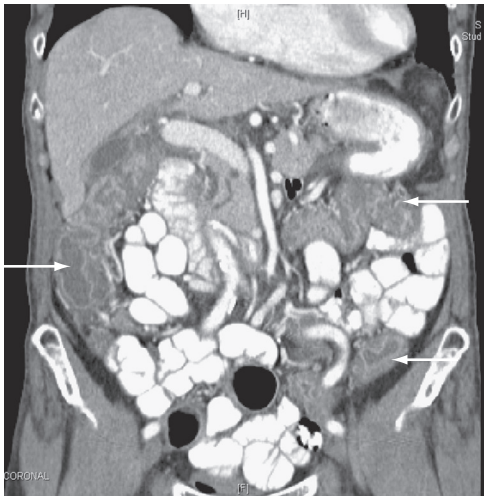

FIG. 1 Computed tomography with oral and intravenous contrast in a patient with *Clostridium difficile* colitis. Typical findings include colonic wall thickening *(arrows)*, dilation, and accordion sign (thickened haustral fold and trapped contrast material, ascites, and pericolonic stranding). (From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Discontinue offending antibiotic.
- Fluid hydration and correction of electrolyte abnormalities.
- Probiotics to restore natural defense mechanisms may be useful as adjuvant therapy; however, evidence is limited. Probiotic trials have failed to show benefit in preventing *C. difficile*–associated diarrhea.
- Fecal microbiota transplantation (FMT) is an excellent treatment modality for recurrent CDI. It replaces the altered gut flora to allow colonization resistance. Trials have shown that it is more effective than vancomycin and may become standard treatment for recurrent CDI. Recent trials have shown that donor stool administered via colonoscopy are safe and more efficacious than autologous FMT in preventing further CDI episodes.

ACUTE GENERAL Rx

- Vancomycin 125 mg PO qid for 10 days can be used as initial treatment in patients with nonsevere or severe CDI. Patients with fulminant CDI will require 500 mg qid for 10 days.
- Fidaxomicin 200 mg bid for 10 days has shown noninferiority to vancomycin and a lower rate of CDI recurrence (25% with vancomycin vs. 15% with fidaxomicin); however, its higher cost is a limiting factor. Fidaxomicin can be used for initial treatment of nonsevere or severe CDI or for recurrence of CDI if vancomycin was used for initial treatment.
- Metronidazole 500 mg PO qid for 10 days can be used in patients with mild disease if oral vancomycin or fidaxomicin are not available or contraindicated. A significant rise in clinical failure has been seen with metronidazole over the past decade, especially in patients with the BI/NAP/027 strain.
- When parenteral therapy is necessary (e.g., patient with paralytic ileus), IV metronidazole 500 mg qid can be used. It can also be supplemented with vancomycin 500 mg by nasogastric tube with intermittent clamping or retention enema.
- Fecal microbiota transplantation (FMT): When standard treatment has failed, intestinal microbiota transplantation (IMT) is an effective alternative therapy (eradication rate is 94%). It involves infusing intestinal microorganisms (in a suspension of healthy donor stool) into the intestine of a sick patient via enema, oral capsule, gastroscope/colonoscope, or nasojejunal tube to restore the microbiota. In patients with recurrent C. difficile infection, FMT by oral capsule has been shown to be noninferior to transplantation by colonoscopy for recurrence at 12 weeks. Trials comparing fresh versus frozen fecal microbiota transplantation have shown equal efficacy.
- The human monoclonal antibody bezlotoxumab has been FDA-approved for use with antibacterial drug treatment to reduce recurrence of CDI. Cost is a limiting factor.

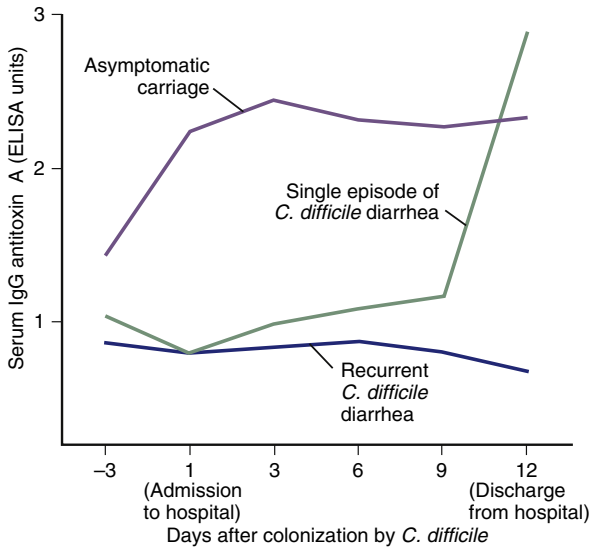

FIG. 2 Serum immunoglobulin G (IgG) antitoxin A antibody response and clinical outcome of infection with *Clostridium difficile*. Patients with nosocomial *C. difficile* diarrhea were studied prospectively, and serum IgG antitoxin A antibody concentrations were measured by enzyme-linked immunosorbent assay *(ELISA)* at regular intervals. A correlation was observed between the IgG response to toxin A and the clinical outcome of infection. Asymptomatic carriers mounted an early memory immune response to toxin A. By contrast, no significant increase was found in serum IgG antitoxin A of patients who experienced recurrent *C. difficile* diarrhea. In those who had a single episode of diarrhea, IgG antitoxin A levels generally were increased on day 12 of their first episode. Thus, a serum antibody response to toxin A during *C. difficile* infection is associated with protection against symptoms and against recurrent diarrhea. (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.)

SURGICAL MANAGEMENT

- Indications: CDI unresponsive to medical therapy, fulminant colitis
- Clinical features: Colonic distention, severe abdominal pain/tenderness, systemic inflammatory response syndrome. Diarrhea may be absent because of ileus
- Surgical approaches:
  1. Traditional (subtotal or total colectomy), high mortality (50%)
  2. Colon-sparing (loop ileostomy with intraoperative colonic lavage using warmed polyethylene glycol solution via the ileostomy and instillations of postoperative vancomycin flushes via the ileostomy); lower mortality compared to traditional approach

CHRONIC Rx

- Judicious future use of antibiotics to prevent recurrences (e.g., avoid prolonged antibiotic therapy).
- Probiotics have been shown mildly effective in reducing the risk for CDI among patients prescribed antibiotics. They should not be used in immunocompromised or severely debilitated patients.
- Alcohol-based hand gels are inadequate for eradication of spores. They are inferior to soap and water for eradication of spores.
- Gastric acid suppression with PPIs increases risk of CDI. Preferential use of H_2RA should be considered in these patients.

DISPOSITION

- Most patients recover completely with appropriate therapy. Fever resolves within 48 hr and diarrhea within 4 to 5 days. Overall mortality rate is 1% to 2.5% but exceeds 10% in untreated patients. CDI recurrence after an initial episode is 20% to 25% regardless of initial treatment with metronidazole or vancomycin. Each recurrence increases risk of repeat episodes (65% chance of recurrence after three CDI episodes). Recurrent CDI usually represents relapse rather than reinfection, no matter how long between episodes (Fig. 2). Recurrent episodes are best treated with a prolonged course of oral vancomycin tapered off over several weeks to months.
- Hospital-acquired CDI is independently associated with an increased risk of in-hospital death. All hospitalized patients with CDI should be placed in contact isolation at least until resolution of diarrhea.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Clostridium difficile Infection (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

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Cluster Headache PTG

BASIC INFORMATION

DEFINITION

The term *cluster headache* refers to attacks of severe, unilateral pain that is orbital, supraorbital, temporal, or any combination of these sites, lasting 15 to 180 minutes, and occurring from once every other day to eight times a day over a span of weeks to months. The attacks are associated with one or more ipsilateral signs and symptoms of parasympathetic activation: Conjunctival injection, lacrimation (Fig. 1), nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, or eyelid edema. Most patients are restless or agitated during an attack.

SYNONYMS

Headache, cluster
Ciliary neuralgia
Erythromelalgia of the head
Erythroprosopalgia of Bing
Horton headache

ICD-10CM CODES

G44.001	Cluster headache syndrome, unspecified, intractable
G44.009	Cluster headache syndrome, unspecified, not intractable
G44.011	Episodic cluster headache, intractable
G44.019	Episodic cluster headache, not intractable
G44.021	Chronic cluster headache, intractable
G44.029	Chronic cluster headache, not intractable

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Estimated to occur in 0.05% to 1% of the population
PREDOMINANT SEX: Occurs in males at least five times more commonly than in females
PREDOMINANT AGE: Peak age of onset between 20 and 40 yr

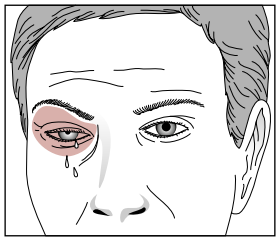

FIG. 1 This 43-year-old man with cluster headaches suffers from nightly right-sided unrelenting, severe, stabbing unilateral periorbital pain for 45 minutes to 3 hours accompanied by ipsilateral tearing and nasal discharge, along with ptosis and miosis (a partial Horner syndrome). Note that the ptosis prompts compensatory elevation of the eyebrow. (From Kaufman DM, et al.: *Kaufman's clinical neurology for psychiatrists*, ed 8, Philadelphia, 2017, Elsevier.)

GENETICS: May be inherited in up to 20% of cases, although uncertainty exists over the mode or modes of inheritance.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Many of the attacks are nocturnal and some may be provoked by alcohol ingestion.
- During attack: Conjunctival injection, lacrimation, nasal congestion, rhinorrhea, facial sweating, Horner syndrome.
- In contrast to migraine sufferers, patients are agitated and active during an attack.
- Symptoms associated with an attack remain ipsilateral during the attack but may switch sides from one attack to the next.
- Permanent partial Horner syndrome in 5% of patients; otherwise examination is normal.

ETIOLOGY

Activation of the posterior hypothalamic gray matter resulting in trigeminal activation coupled with parasympathetic activation. The pathophysiology remains controversial.

DIAGNOSIS

Per the *International Classification of Headache Disorders, 3rd edition,* the diagnosis of cluster headache requires all of the following:

- At least five attacks of severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15 to 180 minutes
- Frequency of every other day to eight per day; they may cluster seasonally or at a certain time in a patient's life
- Headache is accompanied by a sense of restlessness or agitation and/or at least one of the following (ipsilateral):
  1. Conjunctival injection and/or lacrimation
  2. Nasal congestion and/or rhinorrhea
  3. Eyelid edema
  4. Forehead and facial sweating
  5. Forehead and facial flushing
  6. Miosis and/or ptosis
  7. Sensation of fullness in the ear
  8. Restlessness or agitation

A diagnosis of episodic cluster headache requires the above criteria plus attacks that occur in bouts, also called cluster periods. These periods last 1 week to 1 yr and are separated by attack-free intervals lasting at least 1 month.

A diagnosis of chronic cluster headache requires meeting the criteria for cluster headache plus at least 1 yr of attacks without a pain-free interval of at least 1 month.

DIFFERENTIAL DIAGNOSIS

- Migraine
- Trigeminal neuralgia
- Primary stabbing headache
- Temporal arteritis
- Post-herpetic neuralgia
- Venous sinus thrombosis
- Carotid-cavernous fistula or other cavernous sinus lesions
- Other trigeminal autonomic cephalalgias
- Section II describes the differential diagnosis of headaches

WORKUP

Diagnosis is made clinically.

IMAGING STUDIES

- None, unless history or examination suggests focal neurologic deficit or headaches change in character or are of new onset.
- MRI of the brain along with vascular imaging may be necessary to exclude secondary headaches at the time of initial diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Avoidance of alcohol, histamine, nitroglycerin, and tobacco during clusters

ABORTIVE Rx

- Inhalation of 100% oxygen by face mask at a flow rate of 12 L/min or greater for 15 min aborts the attack in 60% to 80% of patients.
- Galcanezumab-gnlm is the first FDA-approved medication for episodic cluster headache in adults. First approved for migraine, this injectable medication is a humanized monoclonal antibody to calcitonin gene-related peptide (CGRP), blocking its binding to the CGRP receptor. It reduces the average number of cluster headaches per week from baseline compared to placebo.
- In approximately 75% of patients, subcutaneous or nasal triptans (e.g., sumatriptan, zolmitriptan) will result in freedom from pain within 20 minutes. Only injectable and nasal formulations achieve a response that is rapid enough to be efficacious.
- Cafergot, octreotide, intranasal lidocaine, or dihydroergotamine may abort an attack or prevent one if given just before a predictable episode. An attack typically resolves before oral analgesics can take effect, although indomethacin and other NSAIDs may be effective in prolonged attacks.

PROPHYLAXIS Rx

For patients with episodic cluster headache, prophylactic treatment should be started at the onset of the cluster period and tapered at its end. Patients with chronic cluster headache should be started on prophylactic treatment at increasing doses until good control is achieved. Preventative therapy should begin with verapamil. Alternative treatment options are also listed below.

- Verapamil: Start at 240 mg/day; increase up to 960 mg/day as tolerated. Dosing three times per day may be more effective than extended release. First-degree AV block may develop with escalating doses, so ECG should be checked.
- Topiramate: Up to 50 mg bid; can be used as add-on to verapamil.
- Lithium: 200 mg tid with frequent monitoring and adjustment to maintain therapeutic serum level of 0.4 to 1 mEq/L. Equally effective as verapamil, but with more side effects.
- Ergotamine tartrate: 3 to 4 mg/day during clusters.

- Melatonin: 10 mg per night. Evidence is weak and comes from scattered case reports.
- Prednisone: 60 mg PO daily for 1 wk followed by taper; headaches can return during taper.
- Greater and lesser occipital nerve blocks, with the use of local anesthetics including lidocaine and bupivacaine along with steroids like Depo-Medrol, dexamethasone, or triamcinolone, may be used to shorten the duration of the cluster period. Consensus guidelines from the American Headache Society have been published recently.
- There is emerging evidence for benefit of a sphenopalatine ganglion block that may be available at some centers for both treatment and prophylaxis of cluster attacks.

DISPOSITION

Headache-free periods tend to increase with increasing age.

REFERRAL

Refractory cluster headaches may require referral to a headache specialist.

PEARLS & CONSIDERATIONS

COMMENTS

- Cluster headaches are divided into episodic (attacks lasting up to 1 yr with more than 1 month pain-free periods) and chronic (>1 yr without remission). Episodic cluster headache is six times more common than the chronic form.
- Home oxygen therapy is reasonable for cluster headache sufferers.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Cluster Headaches (Patient Information)

AUTHORS: **Michael Pohlen, MD, Joseph S. Kass, MD, JD, FAAN,** and **Siddharth Kapoor, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Cocaine is an alkaloid derived from the coca plant *Erythroxylum coca,* native to South America, which contains approximately 0.5% to 1% cocaine. The drug produces physiologic and behavioral effects when administered orally, intranasally, intravenously, or by inhalation after smoking. Cocaine has potent pharmacologic effects on dopamine, norepinephrine, and serotonin neurons in the central nervous system (CNS) involving alteration and blockade of cellular membrane transport and prevention of reuptake. Cocaine's second action involves the blockage of voltage-gated sodium ion membrane channels, which is responsible for its anesthetic effect. Table 1 describes the pharmacokinetics of cocaine according to route of administration. The mechanism by which cocaine alters sympathetic tone is illustrated in Fig. 1.

SYNONYMS

Cocaine hydrochloride: Topical solution (FDA approved as a topical anesthetic)

Crack: This is produced when the hydrochloride molecule is removed by ether extraction, which frees the basic cocaine molecule or "free base." Heating does not destroy the free base; rather, it melts at 98° F and vaporizes at higher temperatures, allowing it to be smoked.

Freebase: Aqueous solution of cocaine hydrochloride converted to a more volatile base state by the addition of alkali, thereby extracting the cocaine base in a residue or precipitate.

Street names include Bernice, Blow, C, Carrie, Cecil, Charlie, Coke, Dust, Dynamite, Flake, Gin, Girl, Gold dust, Green gold, Jet, Powder, Star dust, Paradise, Pimp's drug, Snow, Stardust, White girl, Yay, Yayo

Liquid lady: Alcohol + cocaine

Speedball: Heroin + cocaine

Street measures: Git (2-200 mg), snort, line, dose, spoon (approximately 1 g)

ICD-10CM CODES

T40.5 Poisoning, cocaine
F14.20 Cocaine dependence, uncomplicated

EPIDEMIOLOGY & DEMOGRAPHICS

- The 2016 National Survey on Drug Use and Health published by the U.S. Department of Health and Human Services estimates that in 2016 1.9 million people aged 12 or older were current users of cocaine. This includes about 432,000 users of "crack" cocaine. The estimate is similar to those in most yrs between 2007 and 2015 but was lower than the estimates in 2002 to 2006.
- Table 2 summarizes characteristics of patients with cocaine-induced myocardial infarction.

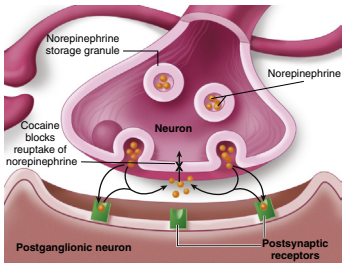

FIG. 1 Mechanism by which cocaine alters sympathetic tone. Cocaine blocks the reuptake of norepinephrine by the preganglionic neuron (X), thereby resulting in excess amounts of this neurotransmitter at postganglionic receptor sites. (From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

PHASE I:

- CNS: Euphoria, agitation, headache, vertigo, twitching, bruxism, unintentional tremor
- Nausea, vomiting, fever, hypertension, tachycardia

PHASE II:

- CNS: Lethargy, hyperreactive deep tendon reflexes, seizures (status epilepticus)
- Sympathetic overdrive: Tachycardia, hypertension, hyperthermia
- Incontinence

PHASE III:

- CNS: Flaccid paralysis, coma, fixed dilated pupils, loss of reflexes
- Pulmonary edema
- Cardiopulmonary arrest

Psychological dependence manifests with habituation, paranoia, and hallucinations (cocaine "bugs").

CNS: Cerebral ischemia and infarction, cerebral arterial spasm, cerebral vasculitis, cerebral vascular thrombosis, subarachnoid hemorrhage, intraparenchymal hemorrhage, seizures, cerebral atrophy, movement disorders, and hyperthermia

Cardiac: Acute myocardial ischemia and infarction (Fig. 2), arrhythmias (Table 3), and sudden death, dilated cardiomyopathy and myocarditis, infective endocarditis, aortic rupture, acceleration of coronary atherosclerosis

Pulmonary: Inhalation injuries (secondary to smoking crack cocaine): Cartilage and nasal septal perforation, oropharyngeal ulcers; immunologically mediated diseases: Hypersensitivity pneumonitis, bronchiolitis obliterans; pulmonary vascular lesions and hemorrhage, pulmonary infarction, pulmonary edema secondary to left ventricular failure, pneumomediastinum, and pneumothorax

Gastrointestinal: Gastroduodenal ulceration and perforation; intestinal infarction or perforation, colitis

Renal: Acute renal failure secondary to rhabdomyolysis and myoglobinuria; renal infarction; focal segmental glomerulosclerosis

Obstetric: Placental abruption, low infant weight, prematurity, microcephaly

Psychiatric: Anxiety, depression, paranoia, delirium, psychosis, suicide

Adulterants such as levamisole (an immunomodulator) and clenbuterol (a beta-adrenergic agonist) have been found mixed with cocaine. Levamisole can cause agranulocytosis, leukoencephalopathy, and cutaneous vasculitis leading to necrosis of the skin. Clenbuterol may cause tachycardia, hyperglycemia, and hypokalemia.

ETIOLOGY

Cocaine may be absorbed through different routes with varying degrees of speed:

- Nasal insufflation/snorting: 2.5 min
- Smoking: <30 sec
- Oral: 2 to 5 min
- Mucosal: <20 min
- Intravenous injection: <30 sec

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Methamphetamine ("speed") abuse

TABLE 1 Pharmacokinetics of Cocaine According to Route of Administration

Route of Administration	Onset of Action	Peak Effect	Duration of Action
Inhalation (smoking)	3-5 sec	1-3 min	5-15 min
Intravenous	10-60 sec	3-5 min	20-60 min
Intranasal or other mucosal	1-5 min	15-20 min	60-90 min

From Bonow RO et al: *Heart disease,* ed 9, Philadelphia, 2012, Saunders.

TABLE 2 Characteristics of Patients with Cocaine-Induced Myocardial Infarction

Dose of Cocaine

5-6 lines (150 mg) to as much as 2 g
Serum concentration, 0.01-1.02 mg/L

Frequency of Use

Reported in chronic, recreational, and first-time users

Route of Administration

Occurs with all routes of administration
75% of reported MIs occurred after intranasal use

Age

Mean, 34 (range, 17-71) yr
20% younger than 25 yr

Sex

80%-90% male

Timing

Often within minutes of cocaine use
Reported as late as 5-15 hr after use

From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.
MI, Myocardial infarction.

- Methylenedioxyamphetamine ("ecstasy") abuse
- Cathinone ("khat") abuse
- Lysergic acid diethylamide (LSD) abuse

WORKUP

Physical examination and laboratory evaluation

LABORATORY TESTS

- Toxicology screen (urine): Cocaine is metabolized within 2 hr by the liver to major metabolites, benzoylecgonine, and ecgonine methyl ester, which are excreted in the urine. Metabolites can be identified in urine within 5 min of IV use and up to 48 hr after oral ingestion

TABLE 3 Cardiac Dysrhythmias and Conduction Disturbances Reported with Cocaine Use

Sinus tachycardia
Sinus bradycardia
Supraventricular tachycardia
Bundle branch block
Complete heart block
Accelerated idioventricular rhythm
Ventricular tachycardia
Ventricular fibrillation
Asystole
Torsades de pointes
Brugada pattern (right bundle branch block with ST-segment elevation in leads V_1, V_2, and V_3)

From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

- Blood: CBC, electrolytes, glucose, BUN, creatinine, calcium
- Arterial blood gas analysis
- ECG
- Serum creatine kinase and troponin concentration

Rx TREATMENT

- There is no specific antidote, and at present, no drug therapy is uniquely effective in treating cocaine abuse and dependence.
- Modifying cocaine's pharmacokinetic properties by sequestering or hydrolyzing it in serum and limiting its access to its sites of action may prove helpful by using a bacterial cocaine esterase, currently investigational.
- Adulterants (such as levamisole and clenbuterol, discussed earlier), contaminants, and other drugs may be admixed with street cocaine and should be kept in mind with patients presenting with unusual manifestations.
- Amantadine may provide effective treatment for cocaine-dependent patients with severe cocaine withdrawal symptoms, as well as the other dopamine agonist, bromocriptine (1.5 mg PO tid), which may alleviate some of the symptoms of craving associated with acute cocaine withdrawal.

ACUTE GENERAL Rx

- Acute cocaine toxicity requires following advanced poisoning treatment and life support.

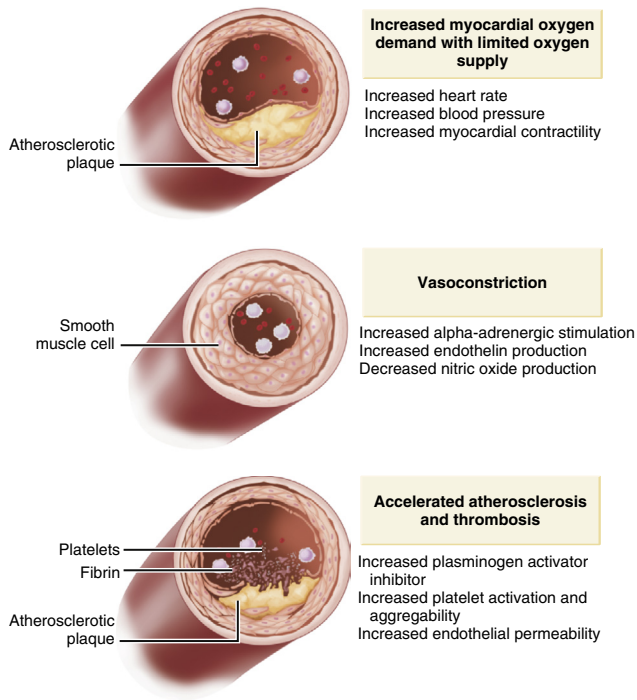

FIG. 2 Mechanisms by which cocaine may induce myocardial ischemia or infarction. Cocaine may induce myocardial ischemia or infarction by increasing the determinants of myocardial oxygen demand in the setting of limited oxygen supply (*top*), thereby causing intense coronary arterial vasoconstriction (*middle*) or inducing accelerated atherosclerosis and thrombosis (*bottom*). (From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.)

- A suspected "body packer" should have an abdominal radiograph to detect the continued presence of cocaine-containing condoms in the intestinal tract.
  - If present, gentle catharsis with charcoal and mineral oil should be performed with ICU admission and monitoring.

SPECIFIC TREATMENT

INHALATION: Wash nasal passages

AGITATION:
- Check STAT glucose
- Diazepam 15 to 20 mg PO or 2 to 10 mg IM or IV for severe agitation

HYPERTHERMIA:
- Check rectal temperature, creatine kinase, electrolytes
- Monitor with continuous rectal probe; bring temperature down to 101° F within 30 to 45 min

RHABDOMYOLYSIS:
- Vigorous hydration with urine output at least 2 ml/kg
- Mannitol or bicarbonate for rhabdomyolysis resistant to hydration

SEIZURE MANAGEMENT (STATUS EPILEPTICUS):
- Diazepam 5 to 10 mg IV over 2 to 3 min; may be repeated every 10 to 15 min
- Lorazepam 2 to 3 mg IV over 2 to 3 min; may be repeated
- Phenytoin loading dose 15 to 18 mg/kg IV at a rate not to exceed 25 to 50 mg/min under cardiac monitoring
- Phenobarbital loading dose 10 to 15 mg/kg IV at a rate of 25 mg/min; an additional 5 mg/kg may be given in 30 to 45 min if seizures are not controlled
- For refractory seizures, consider:
  1. Pancuronium 0.1 mg/kg IV
  2. Halothane general anesthesia
  3. Both require EEG monitoring to determine brain seizure activity

HYPERTENSION: Cocaine-induced hypertension usually responds to benzodiazepines. If this fails:
- Consider arterial line for continuous blood pressure monitoring.
- The use of beta-blockers may exacerbate cocaine-induced vasoconstriction and may cause paradoxical hypertension, worsening patient outcomes.
- Phentolamine (unopposed adrenergic effects) or nitroglycerin may be required.
- If diastolic pressure >120 mm Hg: Hydralazine hydrochloride 25 mg IM or IV; may repeat q1h.
- If hypertension is uncontrolled or hypertensive encephalopathy is present: Sodium nitroprusside initially at 0.5 mg/kg/min not to exceed 10 mg/kg/min.

CHEST PAIN:
- Chest radiograph, ECG, cardiac enzymes.
- Benzodiazepines (diazepam 5 mg IV or lorazepam 1 mg IV every 5 minutes) for agitation until sedation is achieved.
- Acetylsalicylic acid and nitroglycerin for ischemic pain. (Aspirin is contraindicated if dissection is suspected.)

- Percutaneous transluminal coronary angioplasty possibly better than thrombolysis for cocaine-associated myocardial infarction.
- Phentolamine will reverse cocaine-induced vasoconstriction and may be administered 5 to 10 mg every 5 to 10 min.
- Calcium channel blockers (diltiazem 20 mg IV or verapamil 2.5 to 5 mg IV) are considered safe and may be used in patients with ongoing ischemic pain.
- The use of beta-adrenergic blockers is not generally recommended for reasons highlighted earlier.
- If beta-blockers are to be used, this should be preceded by administration of phentolamine to prevent unopposed alpha-adrenergic stimulation. Many authors recommend not using beta-blockers until the cocaine has been systemically eliminated.

VENTRICULAR ARRHYTHMIAS (CONSIDERATIONS):

- The Advanced Cardiac Life Support (ACLS) protocol should be followed.
- Antiarrhythmic agents should be used with caution during the early period after cocaine exposure as a result of their proarrhythmic and proconvulsant effects.
- Termination of ventricular arrhythmias may be resistant to lidocaine and even cardioversion.
- In a cardiac arrest situation secondary to cocaine toxicity, vasopressin offers a theoretical advantage over epinephrine as it increases coronary blood flow and myocardial oxygen availability. In the 2015 ACLS update, however, vasopressin was removed from the treatment algorithm, so it may not be readily available.

DISPOSITION

Although many patients who use cocaine may not require treatment because of the short half-life of the drug, others may require specific treatment for possible cocaine-related complications. Box 1 summarizes complications associated with cocaine use.

REFERRAL

Consider psychotherapy or behavioral therapy once stable. There is some evidence that topiramate 300 mg orally daily added to cognitive behavioral therapy may be beneficial in patients with severe withdrawal symptoms.

BOX 1 Complications Associated with Cocaine Use

Cardiovascular
Myocardial ischemia, infarction
Arrhythmias
Aortic dissection, rupture
Hypertension
Atherosclerosis
Cardiomyopathy
Vasculitis

Central Nervous System
Seizures
Cerebral infarction
Transient ischemic attack
Intracranial hemorrhage (intraparenchymal, intraventricular, subarachnoid)
Cerebral vasculitis
Cognitive dysfunction

Pulmonary
Bronchospasm
Barotrauma
Noncardiogenic edema
Pulmonary hypertension

Renal
Renal infarction
Renal failure
Scleroderma renal crisis

Gastrointestinal
Mesenteric ischemia, infarction
Gastrointestinal tract perforations

Metabolic
Hyperthermia
Rhabdomyolysis
Weight loss
Multiple organ failure

Other
Deep venous thrombosis
Skin ischemia
Dystonic reactions

From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Elsevier.

PEARLS & CONSIDERATIONS

- Cocaine-induced vasoconstriction may be exacerbated by the use of selective and nonselective beta-adrenergic blocking agents.
- The use of lidocaine in treating ventricular arrhythmias may precipitate seizures and further arrhythmias.
- Clinical trials with the SSRI sertraline 200 mg/day have shown that it may help prevent relapse in individuals with some depression symptoms.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Cocaine Abuse and Dependence (Patient Information)
Drug Use Disorder (Patient Information)
Drug Use Disorder (Related Key Topic)

AUTHOR: **Sajeev Handa, MD, SFHM**

SUGGESTED READINGS

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Coccidioidomycosis PTG

BASIC INFORMATION

DEFINITION

Coccidioidomycosis is an infectious disease caused by inhaling the spores of the dimorphic fungus *Coccidioides.* There are two known species: *C. immitis* from California isolates and *C. posadasii* from other endemic areas (Texas, Arizona, New Mexico, Mexico, and Central and South America). Clinical syndromes range from subclinical pulmonary disease to pneumonia and disseminated disease mostly in immunocompromised hosts. Most cases occur in the southwest part of the U.S.

SYNONYMS

San Joaquin Valley fever
Valley fever

ICD-10CM CODES

B38.1	Chronic pulmonary coccidioidomycosis
B38.2	Pulmonary coccidioidomycosis, unspecified
B38.3	Cutaneous coccidioidomycosis
B38.4	Coccidioidomycosis meningitis
B38.9	Acute pulmonary coccidioidomycosis
B38.89	Other forms of coccidioidomycosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Estimated annual infection rate is 150,000 persons, predominantly in the southwest U.S., and appears to be rising because of increased population and construction in the area. In endemic areas, the annual risk of infection is 3%.

PREVALENCE: 28.65 cases per 1 million population in the southwest U.S. based on patients requiring hospital admission.

PREDOMINANT SEX:

- Males, between the ages of 25 and 55 yr
- Clinical disease more severe in older children and adults

PEAK INCIDENCE: Seasonal in endemic areas with the highest risk being in the dry season after a rainy season as the mold lies a few inches below desert surface in soil and can become aerosolized.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Infection is usually acquired by inhalation of aerosolized arthroconidia.
- The clinical manifestations vary widely according to the host, severity of the illness, and location of dissemination.
- Asymptomatic infections or illness consistent with a nonspecific upper respiratory tract infection in at least 60%.
- Symptoms of primary infection—cough, malaise, fever, chills, night sweats, anorexia, weakness, and arthralgias (desert rheumatism)—in remaining 40% within 3 wk of exposure.
- Erythema nodosum and erythema multiforme more common in women.
- Scattered rales and dullness on percussion.
- Spontaneous improvement within 2 wk of illness, with complete recovery usual.
- Pulmonary nodules and cavities in <10% of those patients with primary infection; half of these patients are asymptomatic.
- In a small portion of these patients: A progressive pneumonitis, often with a fatal outcome.
- Immunocompromised or diabetic patients may progress to chronic pulmonary disease.
- Over time, granulomas rupture, leading to new cavity formation and continued fibrosis, often accompanied by hemoptysis.
- Disseminated or extrapulmonary disease in approximately 0.5% of acutely infected patients.
  1. Early signs of probable dissemination: Fever, malaise, hilar adenopathy, and elevated erythrocyte sedimentation rate persisting in the setting of primary infection.
  2. Most organs are susceptible to dissemination, with the heart and GI tract generally spared.
- Musculoskeletal involvement: Bone lesions often unifocal, ribs, long bones, and vertebral lesions are common.
  1. Joint lesions predominantly unifocal, most commonly involving the ankle and knee, and often accompanying adjacent sites of osteomyelitis.
- Meningeal involvement: Headache, fever, weakness, confusion, lethargy, cranial nerve defects, seizures; meningeal signs often minimal or absent.
- Cutaneous involvement (Fig. E1): Variable lesions—pustules, papules, plaques, nodules, ulcers, abscesses, or verrucous proliferative lesions.
  1. Dissemination and fatal outcomes most common in men, pregnant women, neonates, immunocompromised hosts, and individuals of dark-skinned races, especially those of African, Filipino, Mexican, and Native American ancestry.

ETIOLOGY

- In the U.S., endemic areas coincide with the Lower Sonoran Life Zone, with semiarid climate, sparse flora, and alkaline soil in Arizona, California, New Mexico, and Texas.
- Fungus exists in the mycelial phase in soil, having barrel-shaped hyphae (arthroconidia). Arthrospores are aerosolized and deposit in the alveoli, and then fungus converts to thick-walled spherules.
- Internal spherical spores (endospores) are released through spherule rupture and mature into new spherules (parasitic cycle).
- Fungus incites a granulomatous reaction in host tissue, usually with caseation necrosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute pulmonary coccidioidomycoses:
  1. Community-acquired pneumonias caused by *Mycoplasma* and *Chlamydia* spp.
  2. Granulomatous diseases, such as *Mycobacterium tuberculosis* and sarcoidosis
  3. Other fungal diseases, such as *Blastomyces dermatitidis* and *Histoplasma capsulatum*
- Coccidioidomas: True neoplasms

WORKUP

Coccidioidomycosis is definitively diagnosed by isolation of the organism in culture. Suspected in patients with a history of residence or travel in an endemic area, especially during periods favorable to spore dispersion (e.g., dust storms and drought followed by heavy rains)

LABORATORY TESTS

- Definitive diagnosis based on demonstration of the organism by culture from body fluids or tissues. It should be noted that culture can take days to several weeks to grow.

FIG. E1 Cutaneous coccidioidomycosis. Multiple verrucous papules and plaques in a patient with cutaneous coccidioidomycosis disseminated from a primary pulmonary infection. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

1. Greatest yield with pus, sputum, synovial fluid, and soft tissue aspirations, varying with the degree of dissemination.
2. Possible positive cultures of blood, gastric aspirate, pleural effusion, peritoneal fluid, and cerebrospinal fluid (CSF) but less frequently obtained.
3. Lab personnel are at risk of infection by inhalation on opening culture plates so lab should be notified the disease is suspected, but it is not contagious from person to person.

- Serologic evaluations: Useful for diagnosing and monitoring the course of therapy. They are the preferred method for diagnosing primary coccidioidal infections.
  1. Enzyme-linked immunoassays measure immunoglobulin M (IgM) and IgG antibodies and are used as a screening test. If positive, then an immunodiffusion test is used that also measures IgM and IgG. Enzyme immunoassay tests have a high sensitivity but are less specific than the immunodiffusion test.
  2. Elevated serum complement-fixing antibody (CFA) titers ≥1:32 strongly correlated with disseminated disease, and their detection in the CSF is an especially important aid in diagnosing coccidioidal meningitis.
  3. Coccidioidal serum and urine assays are available but insensitive. They can be useful in diagnosing disease in severely immunocompromised persons (e.g., persons with AIDS) whose serologic tests are negative and in those with extensive disease.
  4. Coccidioidal antigen levels in CSF appear to be more sensitive than the antibody tests in CSF (93% vs. 85%) and much better than CSF culture.
- CBC to reveal eosinophilia, especially with erythema nodosum.
- Routine chemistries: Usually normal but may reveal hyponatremia.
- Elevated serum levels of IgE; associated with progressive disease.
- CSF cell counts and chemistry: Pleocytosis with mononuclear cell predominance associated with hypoglycorrhachia and elevated protein level.

IMAGING STUDIES

Chest radiography:

- Reveals unilateral infiltrates, hilar adenopathy, or pleural effusion in primary infection
- Shows areas of fibrosis containing usually solitary, thin-walled cavities that persist as residua of primary infection
- Possible coccidioidoma, a coinlike lesion representing a healed area of previous pneumonitis

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive care in mild symptomatic disease
- In patients with extrapulmonary manifestations involving draining skin, joint, and soft tissue infection: Local wound care to avoid possible bacterial superinfection

ACUTE GENERAL Rx

- In general, drug therapy is not required for patients with asymptomatic pulmonary disease and most patients with mild symptomatic primary infection.
- Chemotherapy is indicated under the following circumstances:
  1. Severe symptomatic primary infection.
  2. High serum CFA titers.
  3. Persistent symptoms >6 wk.
  4. Prostration.
  5. Progressive pulmonary involvement.
  6. Pregnancy.
  7. Infancy.
  8. Debilitation.
  9. Concurrent illness (e.g., diabetes, asthma, COPD, malignancy).
  10. Acquired or induced immunosuppression.
  11. Racial group with known predisposition for disseminated disease.
- Fluconazole:
  1. Most commonly, oral therapy with 400 mg/day up to 1.2 g/day appears to be the drug of choice for meningeal and deep-seated mycotic infections.
  2. In patients with AIDS, fluconazole may be considered the drug of choice for initial and maintenance therapy.
  3. All patients with coccidioidal meningitis should continue azole therapy indefinitely.
- Itraconazole:
  1. 400 to 600 mg/day achieves 90% response rate in bone, joint, soft tissue, lymphatic, and genitourinary infections.
  2. Itraconazole may be more efficacious than fluconazole in the treatment of skeletal (bone) infections but has more drug-drug interactions than fluconazole and must be taken with fatty food and an acidic beverage to increase absorption.
- Alternative regimens include posaconazole, a triazole agent that can be used as delayed release tablets or IV vs. suspension, or voriconazole: 6 mg/kg PO q 12 h × 2, then 4 mg/kg PO bid for patients weighing more than 40 kg.
- For pulmonary infections, treatment with either fluconazole or itraconazole, given for 6 to 12 wk, appears to be equal in efficacy.
- Treatment of coccidioidomycosis complicated by meningitis:
  1. Subacute or chronic meningitis presenting with headache, cranial nerve palsies, or focal neurological deficits.
  2. CSF findings include high-protein, lymphocytic pleocytosis and low glucose, and a CSF coccidioidal antigen may be more sensitive than antibody tests or CSF culture to detect meningeal involvement.
  3. Treatment can be with fluconazole: 400 to 1200 mg PO once a day; itraconazole: 400 to 800 mg PO divided two to four times daily; or voriconazole: 6 mg/kg PO/IV q12h × 24 h, then 4 mg/kg PO q12h.
  4. Alternative regimens with amphotericin B: For refractory cases can use intrathecal amphotericin B: 0.1 to 1.5 mg/dose, daily to weekly, or can use liposomal amphotericin B: 3 to 5 mg/kg IV daily.
  5. Patients who respond to azole therapy should continue for life, as relapses are common and potentially life-threatening.
- For osteomyelitis, soft tissue closed-space infections, and pulmonary fibrocavitary disease: Surgical debridement, drainage, or resection, respectively, in addition to oral azole therapy or parenteral administration of amphotericin B.

TABLE E1 Risk Factors for Poor Outcome in Young Patients with Active Coccidioidomycosis

Primary Infections
Severe, prolonged (≥6 wk), or progressive infection
Risk Factors for Extrapulmonary Dissemination
Primary or acquired cellular immune dysfunction (including patients receiving tumor necrosis factor inhibitors)
Neonates, infants, older adults
Male sex (adult)
Filipino, African, Native American, or Latin American ethnicity
Late-stage pregnancy and early postpartum period
Standardized complement fixation antibody titer >1:16 or increasing titer with persisting symptoms
Blood group B
HLA class II allele-DRB1*1301

HLA, Human leukocyte antigen.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

CHRONIC Rx

For chronically immunocompromised patients, lifelong therapy with oral azoles or amphotericin B. Azoles should be avoided in women during the first trimester of pregnancy because of their teratogenic potential.

DISPOSITION

- Prognosis for primary symptomatic infection is good.
- Immunocompromised patients are most likely to have disseminated disease and higher morbidity and mortality.
- Risk factors for poor outcome in patients with active coccidioidomycosis are described in Table E1.

REFERRAL

- To surgeon for the evaluation of chronic hemoptysis, enlarging cavitary lesions despite chemotherapy and intrapleural rupture, osteomyelitis, and other synovial or soft tissue closed-space infections
- For neurosurgical consultation in patients with meningeal disease to establish the delivery route of intrathecal drug therapy

PEARLS & CONSIDERATIONS

COMMENTS

- Although coccidioidomycosis is a great imitator, a diagnosis will become apparent if a high degree of suspicion is maintained and appropriate testing (serologic testing, cultures, and histology) is performed.
- Infected body fluids contained within a closed moist environment (e.g., sputum in a specimen cup) provide the opportunity for the fungus to revert to its hyphal form whereby spores may be made airborne on opening of the container. This is a biohazard for laboratory personnel. Another example on a hospital floor occurred when purulent drainage in a closed cast, allowed conversion of fungus to the saprophytic phase, and then was responsible for acute disease when the cast was sawed opened and the spores were unintentionally made airborne.
- Patients with a remote history of exposure, especially if immunosuppressed by medication or disease, may reactivate primary disease and suffer rapid dissemination.
- Although cardiac disease is rare, constrictive pericarditis in the setting of disseminated coccidioidomycosis has been documented and is potentially fatal.
- Organ transplant recipients may develop disease if the transplant donor has unrecognized active coccidioidomycosis at the time of death.

RELATED CONTENT

Coccidioidomycosis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Cogan syndrome is a very rare autoimmune inner ear disorder that is temporally associated with an inflammatory eye disease, usually interstitial keratitis, and is thought to be mediated by a hypersensitivity response to infectious agents associated with vasculitis.

ICD-10CM CODE
H16.3 Interstitial and deep keratitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: No population studies are available for incidence calculation. Approximately 250 cases have been described in the literature to date.
PREVALENCE: No population studies are available for prevalence analysis. The classic form of Cogan syndrome tends to affect Caucasian individuals.
PREDOMINANT SEX: No gender preference. Affects men and women equally in case reports.
PREDOMINANT AGE: Median age of onset is 22 yr, with range 5 to 63 yr. Cases reported in children and older adults.
RISK FACTORS: Cogan syndrome may have increased prevalence in patients with inflammatory bowel disease. In many case reports, infectious processes have been implicated, such as previous upper respiratory tract infections that led to cross-reactive autoantibodies. Smoking may be a trigger.
GENETICS: Unknown.

TABLE E1 Systemic Manifestations of Cogan Syndrome

Manifestations	Cases (%)
Fever	25
Fatigue	20
Arthralgia/myalgia	15
Arthritis	15
Weight loss	15
Abdominal pain	10
Gastrointestinal bleeding	10
Lymphadenopathy	10
Hepatomegaly	10
Splenomegaly	10
Central nervous system findings	5
Pleuritis	5
Rash	5
Peripheral nervous system findings	<5
Polychondritis	<5

From Hochberg MC et al: *Rheumatology,* ed 4, St Louis, 2008, Mosby.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

See Table E1 for systemic manifestations of Cogan syndrome.
Clinical hallmarks:

- Cogan syndrome is characterized by an acute, subacute, or recurrent onset of inner ear loss of function resembling Meniere disease (tinnitus, vertigo, and gradual hearing loss). The resultant hearing loss typically is sensorineural, bilateral, and progressive. This is temporally related to the onset of keratitis manifested as pain, redness, and blurry vision in the affected eye. Systemic vasculitis features are marked by large-vessel vasculitis and can occur in up to 10% of patients. Medium-vessel vasculitis resembling polyarteritis nodosa to small-vessel vasculitis manifestations are possible.
- Constitutional: Fever, headache, weight loss, malaise.
- Ocular: Redness, pain, photophobia, and blurred vision as a result of interstitial keratitis (72% to 100%). Scleritis or episcleritis (23%). The gap between involvement of audiovestibular and ocular symptoms is usually 1 to 6 months and not more than 2 yr.
- Hearing/vestibular: Hearing loss progressing to deafness, usually bilateral (100%), vertigo (90%), and tinnitus (80%). Imbalance may be associated with nausea and vomiting.
- Cardiovascular: Aortitis, aortic aneurysm, aortic insufficiency.
- Musculoskeletal: Arthralgia, arthritis, myalgia.
- Neurologic: Hemiparesis and hemiplegia.
- Gastrointestinal: Abdominal pain (13% to 16%), diarrhea, melena.
- Renal: Hematuria (7%), glomerulonephritis (3%).
- Dermatologic: Cutaneous nodules, rash.

ETIOLOGY

The exact etiology of Cogan syndrome is unknown. Evidence of an autoimmune mechanism includes binding of autoantibodies from patients with Cogan syndrome to the cochlea of mice in passive transfer studies. Autopsy specimens show nonspecific lymphocytic and plasma cell infiltration. Infection is thought to be a trigger. Some HLA loci, including HLA-B17, HLA-A9, HLA-Bw35, and HLA-Cw4, correlate with the disorder.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infectious diseases:
  1. Syphilis
  2. Tuberculosis, Lyme disease, chlamydia, leprosy, brucellosis, mumps, EBV, herpes zoster, and herpes simplex; rubeola should be considered in the differential for interstitial keratitis
- Rheumatology:
  1. ANCA-associated vasculitis: Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
  2. Takayasu arteritis
  3. Giant cell arteritis
  4. Rheumatoid arthritis with vasculitis
  5. Polyarteritis nodosa
  6. Behçet disease
  7. Sarcoidosis
- Neurology:
  1. Susac syndrome
  2. Occlusive nonvasculitis vasculopathy
- Neoplastic:
  1. Lymphoma (CNS)
- Miscellaneous:
  1. Vogt-Koyanagi-Harada syndrome
  2. Inflammatory bowel disease (Crohn disease)

LABORATORY TESTS

- Diagnosis of Cogan syndrome is usually made on clinical evidence.
- Inflammatory markers are often elevated, including the erythrocyte sedimentation rate (ESR) and C-reactive protein.
- Complete blood cell count with differential; may show leukocytosis.
- ANCA serology test to evaluate for ANCA-associated vasculitis.
- Serologic test result should be negative for syphilis.
- Anti-Hsp 70 antibodies have been suggested as possible markers of typical Cogan syndrome (also found in other forms of autoimmune sensorineural hearing loss).

IMAGING STUDIES

- Initial tone audiogram shows a hearing loss, especially at high frequencies.
- MRI with gadolinium of the brain to rule out non–inner-ear causes for acute or subacute hearing loss and vestibular dysfunction. Brain MRI can range from normal to gadolinium enhancement of the vestibular-cochlear structures.
- MRA of the aorta and its proximal branches may be used to assess for vascular inflammation that may support the diagnosis of large-vessel vasculitis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Cochlear implant

ACUTE GENERAL Rx

- Treatment guidelines are based on grade C (fair evidence from ancillary studies) recommendations. Table E2 summarizes treatment modalities for Cogan syndrome.
- Early treatment is critical for a favorable prognosis.
- Eye symptoms: Unlike audiovestibular symptoms, ocular manifestations typically respond to topical corticosteroids. Mydriatics may be considered.
- Vestibuloauditory symptoms: Divided doses of oral prednisone 1 to 2 mg/kg/day.
- Vasculitis symptoms: Divided doses of oral prednisone 1 to 2 mg/kg/day. Oral or IV cyclophosphamide should be considered for life-threatening features.

TABLE E2 Treatment of Cogan Syndrome

Disease Manifestations	Recommended Treatment
Ocular	
Interstitial keratitis	Topical ocular corticosteroids and mydriatics (atropine)
Iridocyclitis	Low-potency topical corticosteroids such as 1% prednisolone acetate (3-7 days)
Anterior uveitis	Systemic corticosteroids (only in the case of failure of topical therapy)
Suspected chlamydial infection	Treatment with a tetracycline antibiotic (doxycycline) (200 mg/day for 2-3 wk)
Posterior-segment ocular inflammation	Systemic steroids DMARDs as steroid-sparing agents
Audiovestibular	
Acute vestibular symptoms	Diuretics, antihistamines, bed rest
Chronic vestibular symptoms	Vestibular exercises
Hearing loss	
Hearing loss	Corticosteroids: Prednisolone 1 mg/kg daily (up to 60 mg) for 2 wk and then taper; duration of initial treatment, 4-6 mo Consider immunosuppressant therapy with steroid-sparing agents
Severe hearing loss unresponsive to medical treatment	Cochlear implant
Systemic Vasculitis	
Cogan syndrome with large-vessel vasculitis	Corticosteroids and cyclosporine or cyclophosphamide
Cogan syndrome with medium-vessel vasculitis	Corticosteroids and cyclophosphamide as per treatment of polyarteritis nodosa

DMARD, Disease-modifying antirheumatic drug.
From Hochberg MC et al: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

CHRONIC Rx

- Methotrexate, cyclophosphamide, or azathioprine may be considered as steroid-sparing agents.
- Treatment options such as TNF-alpha inhibitors (infliximab and etanercept), plasmapheresis, rituximab, tocilizumab, cyclosporine, and mycophenolate mofetil have been reported in the literature.

DISPOSITION

- Ocular outcomes are good.
- Hearing loss may occur in up to 50% of cases.

REFERRAL

- Ophthalmology for complete ocular examination, including slit-lamp examination.
- Rheumatology/immunology for all patients with suspected disease.
- Audiology for complete hearing assessment.
- Otolaryngology for confirmation of sensorineural hearing loss.

AUTHOR: **Bradley Schlussel, MD**

SUGGESTED READINGS

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Tayer-Shifman OE et al: Cogan's syndrome-clinical guidelines and novel therapeutic approaches, *Clin Rev Allergy Immunol* 47:65-72, 2014.

BASIC INFORMATION

DEFINITION

Colorado tick fever is an acute, self-limited febrile illness caused by infection with a Coltivirus.

ICD-10CM CODE
A93.2 Colorado tick fever

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence: Approximately 330 cases reported per yr in the U.S.
- Demographics: Children and adults of both genders.
- Geography: Rocky Mountains at elevations of 4000 to 10,000 feet. Sporadic cases have been reported from areas of California outside the range of *Dermacentor andersoni.*
- Colorado has the highest incidence Fig. E1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation: 3 to 4 days is usual but can be up to 14 days.
- First symptoms: Fever, chills, severe headache, severe myalgias, and hyperesthetic skin.
- Initial signs and symptoms:
  1. Tick bite (reported by more than 90% of parents)
  2. Fever and chills
  3. Headache
  4. Myalgias
  5. Weakness
  6. Prostration and indifference
  7. Injected conjunctivae
  8. Erythematous pharyngitis
  9. Lymphadenopathy and hepatosplenomegaly may be found in some patients
  10. Maculopapular or petechial rash 5.6%-12% of cases
- These first symptoms last for 1 wk or less, but 50% of patients have a febrile relapse 2 to 3 days after an initial remission. Weakness and fatigue may persist for several months after the acute phase(s). This chronic phase is more likely in older patients.
- In children, 5% to 10% of cases are complicated by aseptic meningitis. In adults, rare complications include pneumonia, hepatitis, myocarditis, and epididymo-orchitis. Vertically transmitted fetal infection is possible.

ETIOLOGY

- Infectious agent: Coltiviruses; seven species, including three in the U.S.
- Vector: Wood tick, *D. andersoni* (Fig. E2).
- Pathogenesis: Human transmission occurs by tick bite. Tick season spans from March to September. The virus infects marrow erythrocytic precursors, explaining the protracted disease course because viremia lasts for the life span of the infected red blood cell. Fig. E3 illustrates the ecology of Colorado tick fever virus.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rocky Mountain spotted fever
- Influenza
- Leptospirosis
- Infectious mononucleosis
- CMV infection
- Pneumonia
- Hepatitis
- Meningitis
- Endocarditis
- Scarlet fever
- Measles
- Rubella
- Typhus
- Lyme disease
- Immune thrombocytopenic purpura (ITP)
- Thrombotic thrombocytopenic purpura (TTP)
- Kawasaki disease
- Toxic shock syndrome
- Vasculitis

WORKUP

Consider Colorado tick fever in the presence of the above symptoms associated with travel to an endemic area coupled with a history of tick exposure.

LABORATORY TESTS

- Complete blood count:
  1. Leukopenia
  2. Atypical lymphocytes
  3. Moderate thrombocytopenia
- Virus identification in red blood cells by indirect immunofluorescence
- Serology with enzyme-linked immunosorbent assay, neutralization, or complement fixation

TREATMENT

- No specific therapy, although Coltiviruses are sensitive to ribavirin
- Bed rest, fluids, acetaminophen
- Avoid aspirin because of thrombocytopenia
- Prevention: Tick avoidance measures

AUTHOR: **Fred F. Ferri, MD**

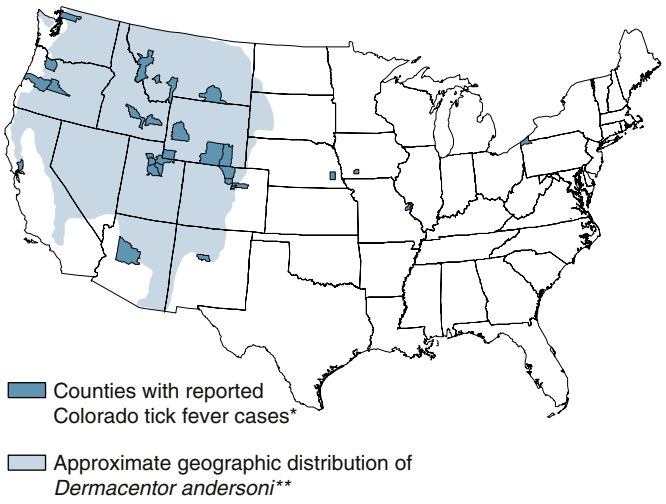

FIG. E1 Approximate geographic distribution of *Dermacentor andersoni* ticks and counties of residence for confirmed and probable Colorado tick fever virus disease cases, United States, 2002–2012. (Courtesy Centers for Disease Control and Prevention. Available at: www.cdc.gov/coloradotick-fever/statistics.html.)

FIG. E2 Adult male *(left)* and female *(right) Dermacentor andersoni* ticks. Both can transmit Colorado tick fever virus. (Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.)

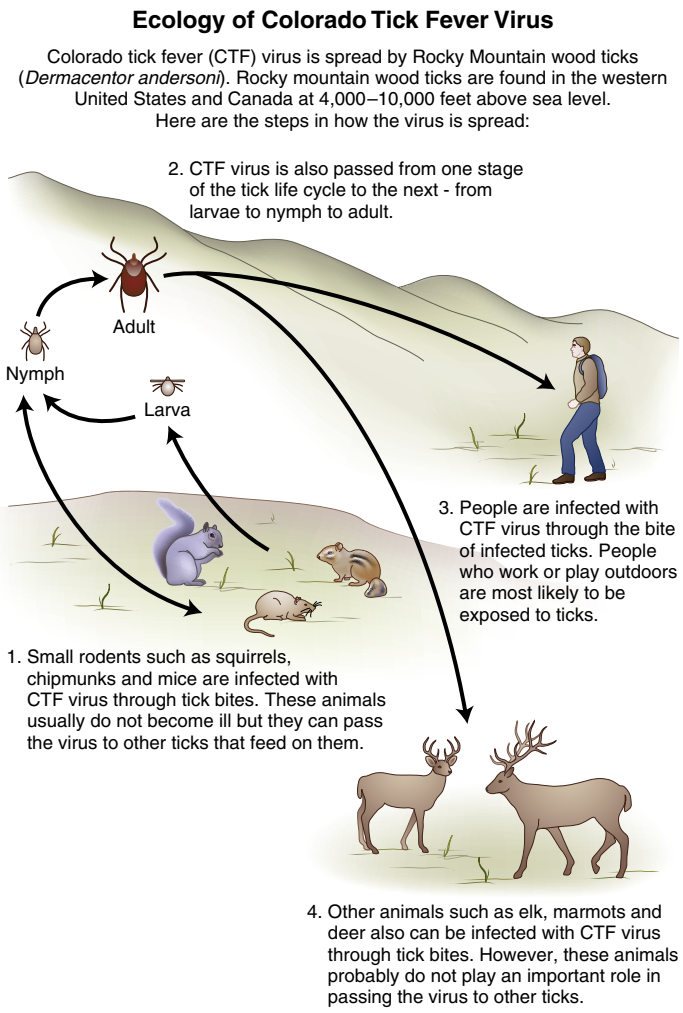

FIG. E3 Colorado tick fever virus ecology. (Courtesy Centers for Disease Control and Prevention. Available at www.cdc.gov/coloradotickfever/transmission.html.)

BASIC INFORMATION

DEFINITION

Colorectal cancer (CRC) is a neoplasm arising from the luminal surface of the large bowel; locations include descending colon (40% to 42%), rectosigmoid and rectum (30% to 33%), cecum and ascending colon (25% to 30%), and transverse colon (10% to 13%).

ICD-10CM CODES

C18	Malignant neoplasm of colon
C18.2	Malignant neoplasm of colon, ascending colon
C18.4	Malignant neoplasm of colon, transverse colon
C18.6	Malignant neoplasm of colon, descending colon
C18.7	Malignant neoplasm of colon, sigmoid colon
C19	Malignant neoplasm of rectosigmoid junction

EPIDEMIOLOGY & DEMOGRAPHICS

- Worldwide, CRC accounts for about 1.4 million new cases and 700,000 deaths annually. The highest incidence is in North America, Australasia, Europe, and South Korea
- CRC is the fourth most common cancer and the second leading cause of cancer deaths in the U.S. (145,600 new cases and 51,020 deaths for 2019). Distant metastatic disease is present in 18% to 22% of patients at time of diagnosis
- The peak incidence is in the seventh decade of life. The lifetime risk for development of CRC is 1 in 17, with 90% of cases occurring after age 50 yr
- Risk factors (Table 1):
  1. Hereditary polyposis syndromes
  2. Familial polyposis (high risk)
  3. Gardner syndrome (high risk)
  4. Turcot syndrome (high risk)
  5. Peutz-Jeghers syndrome (low to moderate risk)
  6. Inflammatory bowel disease (IBD), both ulcerative colitis and Crohn disease
  7. Family history of "cancer family syndrome"
  8. Heredofamilial breast cancer and colon carcinoma
  9. Pelvic irradiation history
  10. First-degree relatives with colorectal carcinoma
  11. Age >50 yr
  12. Dietary factors (diet high in fat or red meat, alcohol use, low vegetable intake)
  13. Hereditary nonpolyposis colon cancer (HNPCC): Autosomal dominant disorder characterized by early age of onset (mean age, 44 yr) and right-sided or proximal colon cancers, synchronous and metachronous colon cancers, mucinous and poorly differentiated colon cancers; accounts for 1% to 5% of all cases of CRC; Criteria for diagnosis of HNPCC are summarized in Table 2
  14. Previous endometrial or ovarian cancer, particularly when diagnosed at an early age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination may be completely unremarkable.
- Digital rectal examination can detect approximately 50% of rectal cancers.
- Palpable abdominal masses may indicate metastasis or complications of colorectal carcinoma (abscess, intussusception, volvulus).
- Abdominal distention and tenderness are suggestive of colonic obstruction.
- Hepatomegaly is indicative of hepatic metastasis.

ETIOLOGY

CRC can arise through either of two mutational pathways: Microsatellite instability or chromosomal instability. Germline genetic mutations are the basis of inherited colon cancer syndromes; an accumulation of somatic mutations in a cell is the basis of sporadic colon cancer. Fig. 1 illustrates the molecular carcinogenesis of colon cancer. Approximately 15% of CRC lack one or more mismatch repair enzymes (mismatch repair deficient [dMMR]-CRC).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diverticular disease
- Strictures or adhesions
- Inflammatory bowel disease (IBD)
- Infectious or inflammatory lesions
- Arteriovenous malformations
- Metastatic carcinoma
- Extrinsic masses (cysts, abscesses)

WORKUP

The clinical presentation of colorectal malignancies may consist of nonspecific symptoms (weight loss, anorexia, malaise) or of specific symptoms related to mass effect or bleeding. It is useful to divide colon cancer symptoms into those usually associated with the right- or left-sided cancers because the clinical presentation can vary with the location.

- Right side of colon:
  1. Anemia (from chronic blood loss).
  2. Abdominal pain may be present, or the patient may be completely asymptomatic.
  3. Rectal bleeding is often missed because blood is mixed with feces.
  4. Obstruction and constipation are unusual because of large lumen and more liquid stools.
- Left side of colon:
  1. Change in bowel habits (constipation, diarrhea, tenesmus, pencil-thin stools).
  2. Rectal bleeding (bright red blood coating the surface of the stool).
  3. Intestinal obstruction is frequent because of small lumen.

CLASSIFICATION (TABLE 3) AND STAGING

AJCC 8th edition classification for CRC:

A. Confined to the mucosa-submucosa (stage I)
B. Invasion of muscularis propria (stage II)
C. Local node involvement (stage III)
D. Distant metastasis (stage IV)

TNM Classification:

Stage	TNM Classification
I	T_{1-2}, N_0, M_0
II_A	T_3, N_0, M_0
II_B	T_{4a}, N_0, M_0
II_C	T_{4b}, N_0, M_0
III_A	T_{1-2}, N_1, M_0; T_1, N_{2a}, M_0
III_B	T_{3-4a}, N_1, M_0 T_{2-3}, N_{2a}, M_0 T_{1-2}, N_{2b}, M_0
III_C	T_{4a}, N_{2a}, M_0 T_{3-4a}, N_{2b}, M_0 T_{4b}, N_{1-2}, M_0
IV_A	T(any), N(any), M_{1a}
IV_B	T(any), N(any), M_{1b}
IV_C	T(any), N(any), M_{1c}

LABORATORY TESTS

- Positive fecal occult blood test (FOBT): Many primary care physicians use single digital

TABLE 1 Recognized Risk Factors for Colorectal Cancer

Family History
- Colorectal cancer (CRC)
- Inherited syndromes (e.g., familial adenomatous polyposis [FAP])
- Racial and ethnic background (e.g., African American, Ashkenazi Jews)

Personal History
- Age
- Male sex
- Previous colonic polyps or CRC
- History of inflammatory bowel disease
- Diabetes mellitus

Lifestyle
- Obesity
- High consumption of alcohol
- Diet high in red meat and fat, low in fiber

From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

TABLE 2 Criteria for Diagnosis of Hereditary Nonpolyposis Colon Cancer (HNPCC)

Amsterdam Criteria[1]

- At least three relatives have colorectal cancer, and all of the following are present:
- One is a first-degree relative (parent, sibling, or child) of the other two
- At least two successive generations are involved
- At least one relative had colorectal cancer when he or she was younger than 50
- Familial adenomatous polyposis has been excluded

Revised Bethesda Guidelines[2]

(Indicates tumors to select for microsatellite instability testing)

- Colorectal cancer in a patient younger than 50 yr
- A second synchronous or metachronous colorectal cancer or cancer associated with HNPCC
- Presence of high-level microsatellite instability histologically in a patient younger than 60 yr
- One or more first-degree relatives with either colorectal cancer or HNPCC-associated tumor diagnosed at younger than 50 yr
- Colorectal cancer in two or more first- or second-degree relatives with HNPCC-related tumors at any age

Either all of the Amsterdam criteria or one of the Bethesda criteria is used to identify an individual at risk of HNPCC

- HNPCC-associated tumors include endometrial, gastric, ovarian, pancreatic, ureter, renal pelvis, biliary tract, small bowel, and brain

[1]Vasen HF, Watson P, Mecklin JP et al: New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* 116:1453-1456, 1999.
[2]Umar A, Boland CR, Terdiman JP et al: Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 96:261-268, 2004.
From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

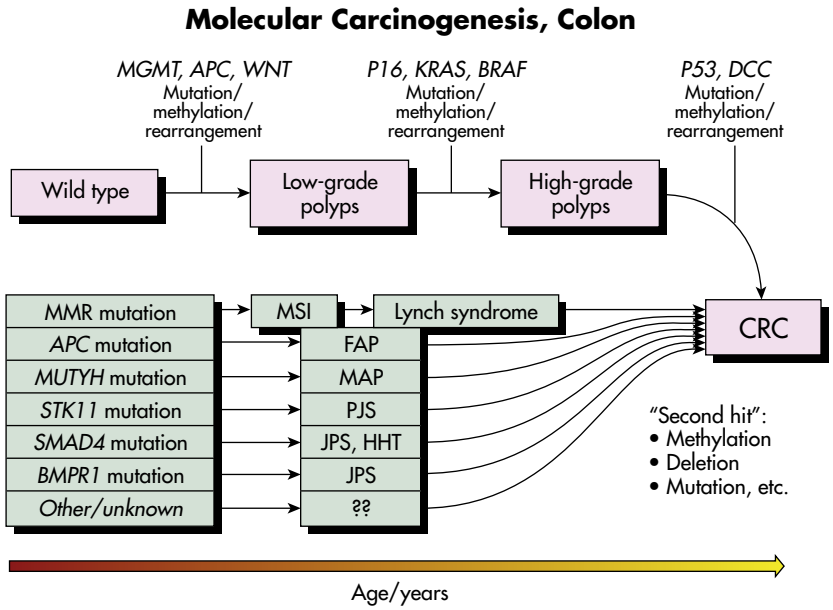

FIG. 1 Accumulation of molecular changes that precede colorectal carcinoma (CRC). Sporadic tumors are initiated by a serial accumulation of somatic mutations that may eventuate in CRC. The initiating event in these polyposes is the mutation present at birth. Second hits may include a variety of molecular changes, such as tumor suppressor gene promoter methylation, mutations, and copy number changes. Mismatch repair *(MMR)* includes *hMLH1, hMLH2, hMSH2, hPMS2,* and *EpCAMP* genes. *FAP,* Familial adenomatous polyposis; *HHT,* hereditary hemorrhagic telangiectasia; *JPS,* juvenile polyposis syndrome; *MAP, MUTYH*-associated polyposis; *MSI,* microsatellite instability; *PJS,* Peutz-Jeghers syndrome. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

FOBT as their primary screening test for CRC. Single FOBT has low specificity for detecting human hemoglobin, is a poor screening method for CRC (sensitivity, 4.9%), and is inappropriate as the only test because negative results do not decrease the odds of advanced neoplasia. The American College of Gastroenterology recommends the fecal immunochemical test (FIT), which measures intact human globin protein (as opposed to heme) in the stool and detects more advanced adenomas than FOBT.

- Fecal DNA testing is a newer screening method that detects colonic cells shed into the fecal stream that possess specific genetic or epigenetic changes. The technique has a reported sensitivity of 97% and a specificity of 90% for CRC stages I-III. In trials involving asymptomatic persons at average risk for colorectal cancer, multitarget stool DNA testing detects significantly more cancers than FIT but has more false-positive results. High cost and rate of false positives are the main obstacles inhibiting broader adoption of fecal DNA testing.
- Molecular markers including abnormal DNA from cancerous cells can be detected in stool. FIT combined with stool DNA test (FIT-DNA) has been approved by the FDA for colorectal screening. One study showed that one-time FIT-DNA had a higher sensitivity for detection of colorectal cancer than one-time FIT alone (92.3% vs. 73.8%), but specificity was lower (86.6% vs. 94.9%).[1]
- Circulating methylated SEPT9 DNA: Does not reliably detect precancerous neoplasia. Studies showing mortality benefit are lacking.
- Plasma carcinoembryonic antigen (CEA) level is not useful for screening because it can be increased in nonmalignant conditions (smoking, IBD, alcoholic liver disease). A normal CEA result does not exclude the diagnosis of CRC.

TABLE 3 World Health Organization Classification of Colorectal Carcinoma

- Adenocarcinoma
- Cribriform comedo-type adenocarcinoma
- Medullary carcinoma
- Micropapillary carcinoma
- Mucinous adenocarcinoma
- Serrated adenocarcinoma
- Signet ring cell carcinoma
- Adenosquamous carcinoma
- Spindle cell carcinoma
- Squamous cell carcinoma
- Undifferentiated carcinoma
- Neuroendocrine carcinoma (NEC):
  - Large NEC
  - Small NEC
- Mixed adenoneuroendocrine carcinoma

From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

IMAGING STUDIES

- Colonoscopy with biopsy (primary assessment tool): The American College of Physicians (ACP) recommends that patients should be offered a colonoscopy beginning at age 50, and it should be repeated every 10 yr in average-risk patients. Screening is recommended in African Americans beginning at age 45 yr. Persons with only one first-degree relative with CRC or advanced adenomas diagnosed at 60 yr or older may be screened as at average risk. The U.S. Preventive Services Task Force guidelines state that screening should not be routinely recommended in persons older than 75 yr, and it should not be recommended at

[1]Inadomi JM: Screening for colorectal neoplasia, *N Engl J Med* 376:149-156, 2017.

TABLE 4 Colorectal Cancer (CRC) Screening and Surveillance Recommendations*

Indication	Recommendations
Average risk	Beginning at age 50 yr: Colonoscopy every 10 yr; Computed tomographic colonography every 5 yr; Flexible sigmoidoscopy every 5 yr; Double-contrast barium enema every 5 yr; Stool blood testing annually or stool; DNA testing acceptable but not preferred
One or two first-degree relatives with CRC at any age or adenoma at age <60 yr	Colonoscopy every 5 yr beginning at age 40 yr, or 10 yr younger than earliest diagnosis, whichever comes first
Hereditary nonpolyposis CRC	Genetic counseling and screening† Colonoscopy every 1 to 2 yr beginning at age 25 yr and then yearly after age 40 yr‡
Familial adenomatous polyposis and variants	Genetic counseling and testing† Flexible sigmoidoscopy yearly beginning at puberty‡
Personal history of CRC	Colonoscopy within 1 yr of curative resection; repeat at 3 yr and then every 5 yr if normal
Personal history of colorectal adenoma	Colonoscopy every 3 to 5 yr after removal of all index polyps
Inflammatory bowel disease	Colonoscopy every 1 to 2 yr beginning after 8 yr of pancolitis or after 15 yr if only left-sided disease

*Recommendations proposed by the American Cancer Society and U.S. Multi-Society Task Force on Colorectal Cancer; recommendations for average-risk patients also endorsed by the American College of Radiology.
†Whenever possible, affected relatives should be tested first because of potential false-negative results.
‡Screening recommendation for individuals with positive or indeterminate tests as well as for those who refuse genetic testing.
From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

all in persons older than 85 yr. If persons between the ages of 75 and 85 yr have never undergone screening, the decision about screening should be individualized according to health status. The ACP recommends that clinicians stop screening for colorectal cancer in adults over age 75 yr or in adults with a life expectancy of <10 yr. Table 4 describes CRC screening and surveillance recommendations.

- Computed tomography colonoscopy (CTC) virtual colonoscopy (VC) uses helical (spiral) CT scanning to generate a two- or three-dimensional virtual colorectal image (Fig. E2). CTC does not require sedation, but, like optical colonoscopy, it requires some bowel preparation (either bowel cathartics or ingestion of iodinated contrast medium with meals during the 48 hr before CT) and air insufflation. It also involves substantial exposure to radiation. In addition, patients with lesions detected by VC will require traditional colonoscopy. Compared with colonoscopy, CTC sensitivity for detection of polyps >10 mm ranges from 70% to 96%, and specificity ranges from 72% to 96%. CTC has replaced double-contrast barium enema as the radiographic screening alternative when patients decline colonoscopy.
- Capsule endoscopy allows visualization of the colonic mucosa but is not recommended as a screening procedure because its sensitivity for detecting colonic lesions is low compared with colonoscopy.
- CT scanning of the abdomen (Fig. E3), pelvis, and chest assists in preoperative staging.
- PET scanning (Fig. E4) can display functional information and is accurate in the detection of CRC and its distant metastases. Colonography composed of a combined modality of PET and CT is a newer diagnostic modality that can provide whole-body tumor staging in a single session.

Rx TREATMENT

GENERAL Rx

- Surgical resection is the definitive and curative upfront treatment for stages I-III colon cancers. Selected patients (high-risk stage II, all stage III) are recommended to receive adjuvant chemotherapy. Microsatellite instability can be used alongside clinicopathologic factors in stage II and III colorectal cancer to guide therapy (Fig. 5).
- The standard chemotherapy regimen for adjuvant therapy of resected CRC is the combination of oxaliplatin with a fluoropyrimidine (5-fluorouracil or capecitabine) for a period of 3 to 6 mo. Older patients and patients with significant comorbidities have more toxicity with combination chemotherapy; treatment with single-agent fluoropyrimidine therapy only is recommended.
- Neoadjuvant chemotherapy and radiation therapy are used to downsize and downstage rectal cancers before definitive resection and improve overall survival and local disease control in stage II-III cancers.
- Adjuvant chemotherapy in stage II disease provides a modest improvement in overall survival by 3% to 4%, with current 5-yr survival rates in the 80% range. As such, current guidelines recommend consideration of adjuvant chemotherapy only in high-risk stage II patients. The magnitude of survival benefit is significantly higher in stage III patients, and combination chemotherapy is associated with 5-yr overall survival rate in the 70% range with wide variation in the subgroups. More recent data have revealed that low-risk stage III colon cancer patients may have equivalent survival with adjuvant multiagent chemotherapy of only 3 mo in duration.
- The outlook for patients with metastatic and relapsed CRC has improved dramatically in the past few yr. Median overall survival in patients with unresectable metastases is now expected in the 30-mo range with modern chemotherapeutic regimens. In patients with limited, resectable metastases in sites such as the liver, the 5-yr median overall survival is in the 50% range.
- Chemotherapy agents used in the metastatic setting include 5-fluorouracil (5-FU), capecitabine, irinotecan, oxaliplatin, and mitomycin. Chemotherapy regimens using a combination of antimetabolite (5-FU or capecitabine) in combination with either oxaliplatin or irinotecan form the backbone of systemic chemotherapy.
- Molecularly targeted therapy against the epidermal growth factor receptor (EGFR) and the angiogenesis pathway are used in combination with the chemotherapy backbone in metastatic CRC. Antiangiogenic agents include monoclonal antibodies bevacizumab, aflibercept, and ramucirumab. Cetuximab and panitumumab are EGFR receptor blockers that are active in metastatic CRC patients whose tumors do not harbor mutated RAS oncogenes.
- The liver is generally the initial and most common site of CRC metastases. Resection of liver-limited metastases followed by systemic combination chemotherapy is curative in more than 30% of selected patients. Metastasectomy of limited pulmonary metastases can also be considered in selected cases.
- Unresectable multiple liver metastases are often approached by locoregional therapeutic approaches such as transarterial chemoembolization (TACE), selective internal radiation therapy (SIRT) using yttrium-90 brachytherapy, or hepatic arterial infusional chemotherapy.
- The oral multitargeted kinase inhibitor regorafenib and the oral antimetabolite drug TAS-102 provide modest survival benefit in patients who have failed standard chemotherapy approaches.

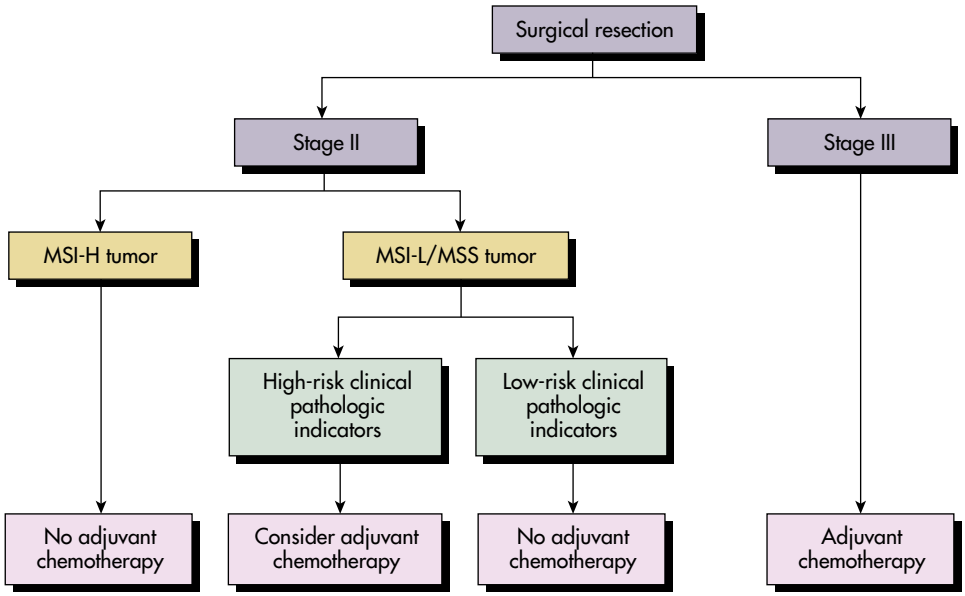

FIG. 5 Proposed algorithm for using microsatellite instability *(MSI)* alongside clinicopathologic factors in stages II and III colorectal cancer. ASCO guidelines: Inadequate samples nodes, T4 lesions, perforation, poorly differentiated histology. *MSI-H,* High-level microsatellite instability; *MSI-L/MSS,* low-level microsatellite instability/microsatellite stability. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

- Patients with tumors harboring BRAF mutations can now have improved survival with the use of combination molecularly targeted therapy consisting of encorafenib, binimetinib, and cetuximab.
- In patients with pathologically confirmed microsatellite instability in their cancers (Fig. 5), the checkpoint inhibitors (pembrolizumab, nivolumab) are effective options after failure of standard therapies and have been recently approved in this setting.
- Reviews of randomized trials in metastatic CRC have demonstrated that right-sided cancers are associated with shorter overall survival when compared with left-sided cancers.

CHRONIC Rx

Follow-up is indicated with:

- Physician visits with a focus on clinical and disease-related history, directed physical examination, coordination of follow-up, and counseling every 3 to 4 mo for the first 3 yr and then every 6 mo for 2 yr.
- Colonoscopy at end of first yr, then after 3 yr, and subsequently every 5 yr.
- Baseline CEA level, if elevated, can be used after surgery as a measure of completeness of tumor resection. It is used to monitor tumor recurrence and is obtained every 3 to 6 mo for up to 5 yr.

DISPOSITION

The 5-yr survival rate varies with the stage of the carcinoma:

TNM Stage	5-yr Survival Rate (%)
I	>90
II_{A-C}	60-85
III_{A-C}	25-65
IV	5-10

- Overall 5-yr disease-free survival rate has increased from 50% to 63% during the past two decades.
- High-frequency microsatellite instability in CRC is independently predictive of a relatively favorable outcome and reduces the likelihood of metastases.
- In patients with high-risk stage II and with stage III CRC, there is improved 5-yr survival among patients treated with adjuvant chemotherapy.
- Expression patterns of microRNA are systemically altered in colon adenocarcinomas. High miR-21 expression is associated with poor survival and poor therapeutic outcome.
- The optimal timing from surgery to initiation of adjuvant chemotherapy is 4 to 8 wk. A longer time to initiation of adjuvant chemotherapy is associated with worse survival rates.
- Regular aspirin use after the diagnosis of CRC has been reported to be associated with lower risk for CRC-specific and overall mortality, especially among individuals with tumors that overexpress cyclooxygenase-2. Regular aspirin use is associated with lower BRAF-wild type colorectal cancer but not with BRAF-mutated cancer risk. All aspirin doses starting with 75 mg daily had similar effects on CRC incidence and mortality.

REFERRAL

- Multidisciplinary referral to colorectal surgery or surgical oncology, medical oncology, radiation oncology

PEARLS & CONSIDERATIONS

COMMENTS

- Metastases of tumor cells to regional lymph nodes is the single most important prognostic factor in patients with colon cancer.
- Decreased fat intake to 30% of total energy intake, increased fiber through fruit and vegetable consumption may reduce CRC risk.
- Chemoprophylaxis with aspirin (81 mg/day) reduces the incidence of colorectal adenomas in persons at risk.
- The National Cancer Institute has published consensus guidelines for universal screening for HNPCC in patients with newly diagnosed CRC. Tumors in mutation carriers of HNPCC typically exhibit microsatellite instability, a characteristic phenotype caused by expansion or contraction of short nucleotide repeat sequences. These guidelines (Bethesda Guidelines) are useful for selective patients for microsatellite instability testing. Screening patients with newly diagnosed CRC for HNPCC is cost effective, especially if the benefits to their immediate relatives are considered.
- The use of either annual or biennial FOBT significantly reduces the incidence of CRC.
- The detection of mutations in the *APC* gene from stool samples is a promising new modality for early detection of colorectal neoplasms.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Colon Cancer (Patient Information)
Familial Adenomatous Polyposis and Gardner Syndrome (Related Key Topic)
Lynch Syndrome (Related Key Topic)
Peutz-Jeghers Syndrome and Other Polyposis Syndromes (Related Key Topic)

AUTHOR: **Ritesh Rathore, MD**

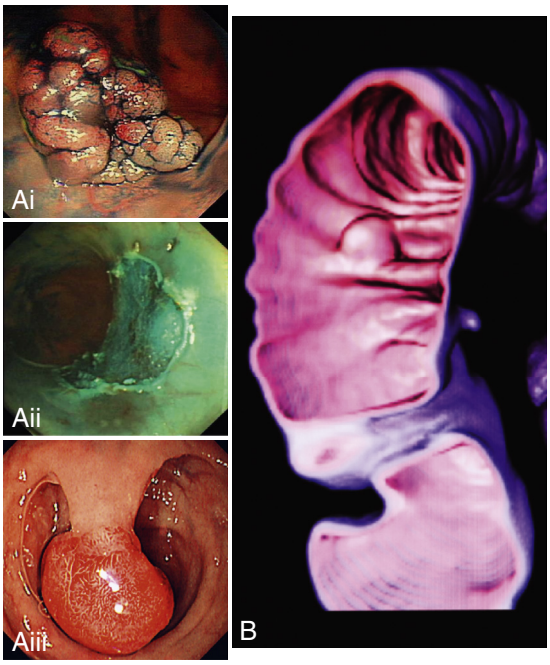

FIG. E2 Colon polyps seen at **(Ai-iii)** colonoscopy and **(B)** computed tomography (CT) colonography. **Aii,** After endoscopic resection of the polyps in **Ai.** (From Ballinger A: *Kumar & Clark's essentials of medicine*, ed 5, Edinburgh, 2012, Saunders.)

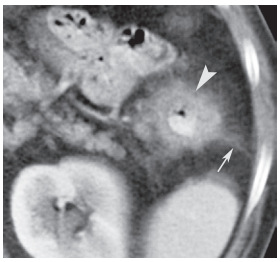

FIG. E3 Colon carcinoma: Wall thickening. A carcinoma of the descending colon near the splenic flexure causes thickening of the colon wall (*arrowhead*) and narrowing of the lumen. Stranding densities (*arrow*) extending into the pericolonic fat suggest tumor extension through the bowel wall. (From Webb WR, Brant WE, Major NM: *Fundamentals of body CT*, ed 4, Philadelphia, 2015, Saunders.)

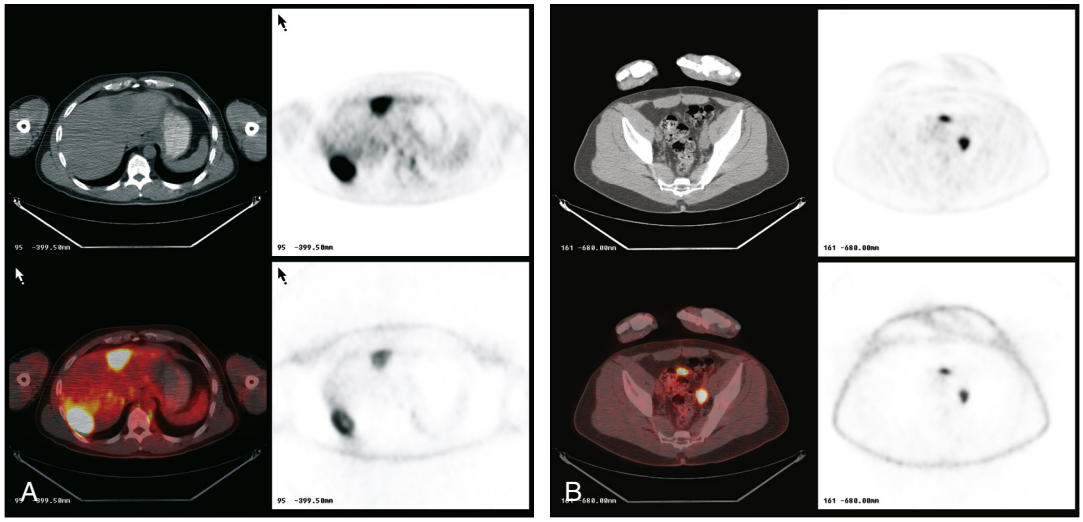

FIG. E4 Colon cancer. A, Positron emission tomography (PET) and computed tomography (CT) image display of a patient with two fluorine-18 (^{18}F)-fluorodeoxyglucose (FDG)–avid lesions in the liver. These are seen on the CT scan *(upper left)*, the attenuation-corrected PET scan *(upper right),* the non–attenuation-corrected PET scan *(lower right),* and fused images *(lower left).* **B,** PET and CT images of the pelvis, oriented as in **A,** show increased FDG uptake in a left external iliac lymph node metastasis. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

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BASIC INFORMATION

DEFINITION

Compartment syndrome is a condition caused by elevated pressure within a confined myofascial space resulting in decreased perfusion, hypoxia, and potential necrosis of the involved tissues. Acute compartment syndrome is a surgical emergency necessitating prompt diagnosis and intervention.

ICD-10CM CODES: Code x Y (Y = encounter type: (A) initial, D (subsequent), S (sequelae)

T79.A0xA	Compartment syndrome, unspecified, initial encounter
T79.A0xD	Compartment syndrome, unspecified, subsequent encounter
T79.A0xS	Compartment syndrome, unspecified, sequelae
T79.A19xY	Traumatic compartment syndrome of unspecified upper extremity
T79.A11x Y	Traumatic compartment syndrome of the right upper extremity
T79.A12x Y	Traumatic compartment syndrome of the left upper extremity
T79.A29x Y	Traumatic compartment syndrome of unspecified lower extremity
T79.A21x Y	Traumatic compartment syndrome of right lower extremity
T79.A22x Y	Traumatic compartment syndrome of left lower extremity
T79.A9x Y	Traumatic compartment syndrome of other sites
M79.A19x Y	Nontraumatic compartment syndrome of unspecified upper extremity
M79.A11x Y	Nontraumatic compartment syndrome of the right upper extremity
M79.A12x Y	Nontraumatic compartment syndrome of the left upper extremity
M79.A29x Y	Nontraumatic compartment syndrome of unspecified lower extremity
M79.A21x Y	Nontraumatic compartment syndrome of right lower extremity
M79.A22x Y	Nontraumatic compartment syndrome of left lower extremity
M79.A9x Y	Nontraumatic compartment syndrome of other sites

EPIDEMIOLOGY & DEMOGRAPHICS

- Most commonly associated with acute trauma, comprising 70% of cases. Up to 30% of cases are not associated with a fracture.
- Typically occurs in persons <35 yr of age, with approximately 10× higher incidence in males.

PATHOPHYSIOLOGY

Compartment syndrome occurs when elevated pressure within a myofascial compartment impairs blood flow and results in tissue ischemia and necrosis. As intracompartmental pressure rises, it eventually exceeds the local capillary pressure, resulting in capillary bed collapse. Venous outflow is compromised, which results in venous congestion and subsequently decreased perfusion of oxygenated blood. Hypoxia, ischemia, and cell death ensue. Tissue perfusion has been shown to decrease significantly with intracompartmental pressures between 10 and 20 mm Hg. Decreased tissue perfusion can result in reversible neurapraxia within 1 hour, followed by cell death, myonecrosis, and other irreversible changes within 4 to 6 hours.

A variety of clinical conditions are associated with the development of compartment syndrome:

- Conditions that increase the volume within a compartment: Bleeding from fracture, vascular injury, or bleeding diathesis. It is possible to develop compartment syndrome even in the setting of an open fracture.
- Conditions that lead to significant soft-tissue swelling: Reperfusion injury, crush injury, high-energy soft-tissue injury (e.g., gunshot or ballistic injury), thermal or electrical burn injuries, extravasation of intravenous fluids, injection of recreational drugs, massive fluid resuscitation, and snake bites.
- Conditions that decrease the volume of a compartment via external forces: Tight external dressings (e.g., fracture casts/splints), prolonged downtime, or external pressure seen in sedated or comatose patients who lie on an extremity for a prolonged period (e.g., drug overdose, ICU patients, and prolonged surgical procedures).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical signs and symptoms of compartment syndrome include:

- Pain out of proportion for a given injury or worsening pain despite adequate or escalating analgesia requirement (earliest sign).
- Pain with passive stretch of the muscles within the compartment. Typically, patients describe severe pain localized to the affected compartment that is exacerbated by passive stretch of the muscles within the compartment. Many trauma patients will complain of pain with any movement of the affected extremity. Therefore it may be useful for providers to attempt to distract patients while testing for pain with passive stretch.
- Tense or swollen compartment that is firm to touch or noncompressible (Fig. E1).
- Numbness, tingling, or paresthesias in the sensory distribution of the nerve(s) traversing the compartment.
- Capillary refill can be sluggish or normal.
- Palpable peripheral pulses may be present even in late stages of the disease due to collateral blood flow and reconstitution distal to the compartment of concern.
- Pediatric patients may demonstrate the three As: Agitation, Anxiety, and increasing Analgesia requirement.

DIAGNOSIS

Compartment syndrome is a clinical diagnosis based on history and examination. Acute compartment syndrome can develop quickly or evolve over time, so serial examinations are critical for patients at risk. Typically, compartment syndrome will develop within 48 hours of injury. The diagnosis may be confirmed with the use of intracompartmental pressure-measuring devices if the clinical signs of compartment syndrome are unclear, such as in the setting of unreliable, comatose, or otherwise nonresponsive patients.

DIFFERENTIAL DIAGNOSIS

- Physiologic soft-tissue edema or swelling
- Muscle strain or contusion
- Cellulitis
- Gangrene
- Peripheral vascular injury
- Necrotizing fasciitis
- Stress fracture
- Deep vein thrombosis and thrombophlebitis
- Tendinitis
- Tarsal tunnel or posterior ankle syndrome

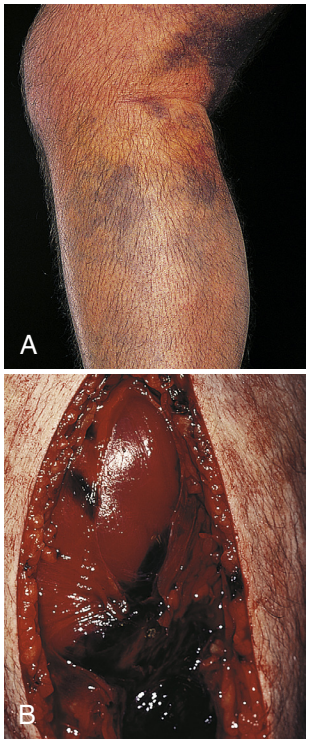

FIG. E1 A, Severe calf swelling due to anterior and posterior compartment syndromes after ischemia-reperfusion. **B,** Appearance after emergency fasciotomy. Note edematous muscle and hematoma. (Courtesy Michael J. Allen, FRCS, Leicester, UK. From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

- Popliteal artery impingement
- Claudication
- Tumor
- Venous insufficiency

LABORATORY TESTS

Laboratory values are not useful in the diagnosis of compartment syndrome but are important for other diagnoses or associated conditions.

- INR/PT and PTT to assess coagulation profile and bleeding diathesis
- CBC with differential for evaluation of infection
- Creatine phosphokinase (CK) levels, which can rise as muscle injury develops (e.g., crush injury, rhabdomyolysis)
- Metabolic panel for the assessment of electrolytes and renal function
- Urinalysis for rhabdomyolysis
- Urine and serum myoglobin levels

IMAGING STUDIES

- Radiographs of the affected extremity should be obtained to evaluate for fracture or foreign body.
- Direct intracompartmental pressure measurement can be obtained using a handheld manometer, wick or slit catheter technique, or a simple needle manometer system. Compartment syndrome is confirmed when the difference between diastolic blood pressure and compartment pressure (Δ pressure) is ≤30 mm Hg.
- Ultrasonography or Doppler ultrasonography can be used to rule out deep vein thrombosis and evaluate blood flow to the extremity. Arteriography can be used to evaluate for arterial injury and blood flow within a compartment.
- Near-infrared spectroscopy and technetium-99m methoxyisobutylisonitrile scintigraphy can also be used.

Rx TREATMENT

The goal of treatment is to reduce the intracompartmental pressure and prevent tissue ischemia and necrosis (Fig. E2).

ACUTE GENERAL Rx

- Analgesics for pain control.
- Advanced trauma life support (hypotension can worsen tissue perfusion and ischemia).
- Remove circumferential dressings, casts, and all external pressure generators.
- The affected extremity should be elevated above the level of the heart to aid in resolution of swelling.
- The standard of care is emergent fasciotomy and thorough debridement of nonviable tissue. This should be performed within 4 to 6 hours of symptom onset.
- Measurement of compartment pressure is not necessary to confirm diagnosis, and fasciotomy should not be delayed to obtain compartment pressures in the setting of high clinical suspicion.
- Associated fractures should be stabilized with internal or external fixation to reduce further soft tissue injury.

CHRONIC Rx

- Patients should return to the operating room every 48 hours to assess tissue viability and repeat debridement as needed.
- A negative pressure wound therapy system may be placed over fasciotomy wounds with delayed wound closure and skin grafting as needed.
- Local wound care should be emphasized to decrease the risk of infection.

DISPOSITION

With early diagnosis and prompt intervention, the prognosis and functional outcomes are excellent. The following are sequelae of delayed or undiagnosed compartment syndrome:

- Myonecrosis
- Permanent nerve damage and paralysis
- Muscle contracture (e.g., Volkmann contracture in the forearm)
- Gangrene
- Infection and possible sepsis
- Amputation
- Rhabdomyolysis and possible renal failure
- Cardiac arrhythmias and possible death from reperfusion injury and electrolyte abnormalities

REFERRAL

Patients with suspected compartment syndrome should be promptly referred to an orthopedic and general surgeon.

PEARLS & CONSIDERATIONS

- Compartment syndrome is a surgical emergency necessitating prompt diagnosis and intervention. It is commonly associated with fractures, most notably tibial shaft and both bone forearm fractures.
- Compartment syndrome is a clinical diagnosis, and intracompartmental pressure measurements are not required to make or confirm the diagnosis.
- Pain out of proportion to an injury, pain with passive stretch, or increasing analgesia requirement should raise concern for compartment syndrome.
- The presence of palpable peripheral pulses does not rule out compartment syndrome.
- Universal precautions and aseptic measures are necessary for patients undergoing fasciotomy due to the elevated risk of local and systemic infection following the procedure.
- Patients with fractures treated with a cast should be informed about the risks of swelling and the signs and symptoms of compartment syndrome with instructions to go to the nearest emergency department if these symptoms develop.

RELATED CONTENT

Compartment Syndrome (Patient Information)

AUTHOR: **Sebastian Orman, MD**

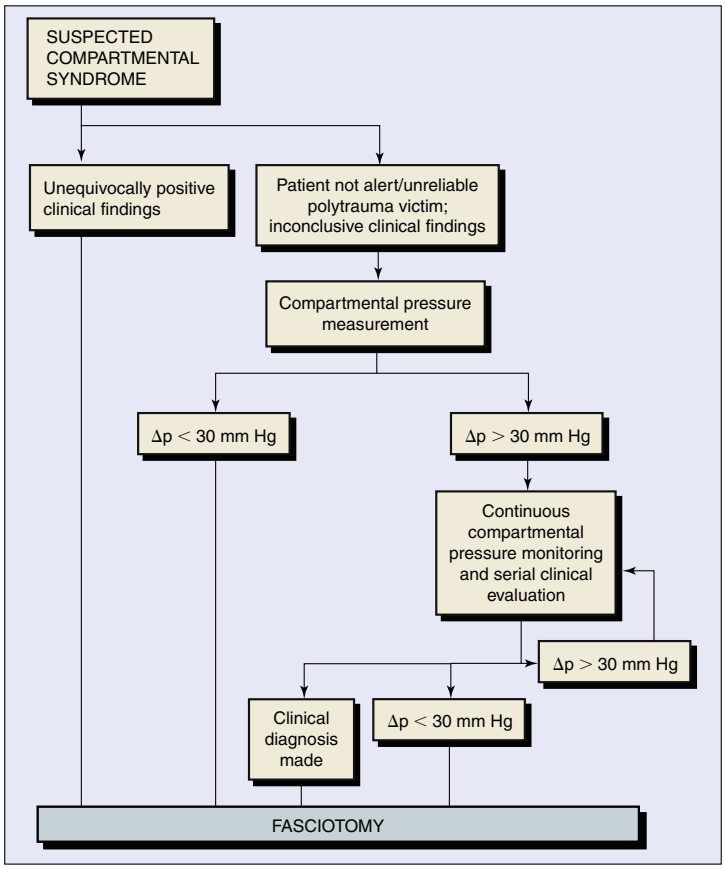

FIG. E2 Algorithm for management of a patient with suspected compartment syndrome. Δp is defined as the difference between the diastolic pressure and the measured compartment pressure in mm Hg as documented by McQueen and Court-Brown. (From Browner BD et al [eds]: *Skeletal trauma,* ed 4, Philadelphia, 2009, Saunders.)

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BASIC INFORMATION

DEFINITION

Complex regional pain syndrome (CRPS) is a pain disorder characterized by constant and intense limb pain associated with vasomotor and neurosensory abnormalities, skin changes, and demineralization of bone. CRPS has been divided into type I (about 90% of cases), in which there is usually an initiating noxious event but no distinct nerve injury, and type II, in which a definable (usually traumatic) nerve lesion exists. CRPS type I generally correlates with the syndrome formerly known as reflex sympathetic dystrophy (RSD), and CRPS type II equates with what was previously termed causalgia. The term *shoulder-hand syndrome* has been used to describe CRPS in the setting of myocardial infarction or ischemia.

SYNONYMS (BOX E1)

Reflex sympathetic dystrophy
Shoulder hand syndrome
CRPS

ICD-10CM CODES

M89.0	Algoneurodystrophy
G90.59	Complex regional pain syndrome I of other specified site
G90.511	Complex regional pain syndrome I of right upper limb
G90.512	Complex regional pain syndrome I of left upper limb
G90.513	Complex regional pain syndrome I of upper limb, bilateral
G90.519	Complex regional pain syndrome I of unspecified upper limb
G90.521	Complex regional pain syndrome I of right lower limb
G90.522	Complex regional pain syndrome I of left lower limb
G90.523	Complex regional pain syndrome I of lower limb, bilateral
G90.529	Complex regional pain syndrome I of unspecified lower limb
G90.59	Complex regional pain syndrome I of other specified site

BOX E1 Terms Used in the Definition of Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) type I (the preferred term)
Causalgia (now CRPS type II)
Reflex sympathetic dystrophy (RSD)
Sudeck atrophy
Shoulder–hand syndrome
Algodystrophy
Algoneurodystrophy
Posttraumatic dystrophy
Posttraumatic osteoporosis
Painful osteoporosis
Transient osteoporosis

From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: CRPS is rare (population prevalence less than 1 in 2000). One study in the Netherlands found an overall incidence of 26.2 per 100,000 person yr, with 3.4 times more women diagnosed than men.
PEAK INCIDENCE: Sixth decade, highest in postmenopausal women.
RISK FACTORS: Common situations in which CRPS is seen include extremity trauma, burns, stroke, and orthopedic and podiatric procedures. Fracture is the most common risk factor, and CRPS occurs more commonly in the upper extremity than in the lower. The incidence of CRPS may be increased when combined hand surgery procedures are performed. Immobilization of the limb often precedes the development of symptoms. CRPS in the setting of myocardial infarction seems to be decreasing, presumably due to early mobilization and more effective pain control.

PHYSICAL FINDINGS & CLINICAL PRESENTATION (TABLE E1)

CRPS is divided into three stages:

- Acute stage (can occur within hours of injury, usually within 4 to 6 weeks after event)
  1. Burning or aching pain occurring over the injured extremity
  2. Hyperalgesia (exaggerated response to nociceptive stimuli), allodynia
  3. Edema; motor impairment (due to pain)
  4. Dysthermia
  5. Increased hair and nail growth
- Dystrophic stage (3 to 6 months after injury)
  1. Burning pain radiating both distally and proximally from the site of injury
  2. Brawny edema (Fig. E1)
  3. Hyperhidrosis
  4. Hypothermia and cyanosis
  5. Muscle tremors and spasms
  6. Increased muscle tone and reflexes
- Atrophic stage (6 mo after injury)
  1. Spread of pain proximally
  2. Allodynia (pain response to stimuli that are not normally painful)
  3. Cold, pale, cyanotic skin
  4. Trophic skin changes with subcutaneous atrophy, brittle nails
  5. Contractures, limited movement

ETIOLOGY

The pathogenesis of CRPS remains unknown. Theories include the formation of an abnormal reflex arc in the sympathetic nervous system that is modulated by cortical centers to produce peripheral vascular disturbances. Persistent pain in the peripheral nervous system is modulated by inflammatory neuropeptides including substance P, which has been shown to be elevated in the serum of CRPS-I patients. Increased concentrations of tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, and IL-2 have been demonstrated in tissue of patients with CRPS-I. Genetic factors may play a role (one study found increased HLA-DQ1 frequency in CRPS-I patients). Typical triggering events for CRPS are summarized in Table E2.

DIAGNOSIS

Criteria proposed for the diagnosis of CRPS type I include:

- An initiating noxious event, spontaneous pain or alloying/hyperalgesia disproportionate to the inciting event.
- Evidence of edema, skin blood flow, or sweating abnormality in the region of the pain.
- Absence of other conditions that could explain the symptoms.

There is no gold-standard test to confirm diagnosis, but triple-phase bone scans, nerve conduction testing, and bilateral radiographs are often used to confirm the diagnosis and assess for other possibilities.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes nerve entrapment syndromes such as cervical radiculopathy, myofascial pain syndromes, and fibromyalgia.

TABLE E1 Clinical Features of Complex Regional Pain Syndrome

Sensory	Pain, often burning, extending beyond the area of the original injury
	Allodynia
	Hyperalgesia or hyperpathia
	Disturbed body perception
Vasomotor	Color change*
	Temperature change*
Sudomotor or edema	Edema
	Increased sweating
Motor or trophic	Weakness or inability to initiate movement
	Tremor
	Muscle spasms
	Dystonic features
	Contractures
	Skin, hair, and nail changes

*Compared with the unaffected side.
From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

WORKUP

- Bone scintigraphy (Fig. E2) shows decreased perfusion of the affected areas if done soon after the onset of symptoms. If done after 6 weeks of symptoms, bone scan may show increased uptake in the region of the peripheral joints of the involved extremity.
- Electrophysiologic testing is useful to identify nerve injury in patients with type II CRPS.
- Plain radiographs show diffuse patchy osteopenia (Fig. E3).
- Repetitive skin temperature measurements can be used as a diagnostic test.
- Autonomic testing, although not commonly done, has been proposed.
  1. Measuring resting sweat output
  2. Measuring resting skin temperature
  3. Quantitative sudomotor axon reflex test

FIG. E1 Complex regional pain syndrome affecting the lower limb, showing marked swelling and color change. (Reproduced with permission from Salford Royal NHS Foundation Trust.)

Rx TREATMENT

Treatment of CRPS is largely empiric, based mostly on anecdotal reports, extrapolation from drug trials for other painful conditions, and clinical experience. Published studies are generally of low quality and show mixed results. Therapy should be tailored to stage of disease progression and severity of symptoms. Approaches to the treatment of CRPS are summarized in Table E3.

FIG. E2 Reflex sympathetic dystrophy in a patient with a history of right wrist fracture. Three-phase bone scintigraphy shows increased tracer delivery to the right distal upper extremity diffusely *(arrow)* on flow *(top)* and blood pool *(middle)* images. Delayed images *(bottom)* reveal diffuse abnormal uptake in the wrist *(arrow)* and increased activity in a juxtaarticular distribution *(arrowheads)*. (From DeLee D, Drez D: *DeLee and Drez's orthopaedic sports medicine,* ed 2, Philadelphia, 2003, Saunders.)

TABLE E2 Typical Triggering Events for Complex Regional Pain Syndrome

Trauma	Wrist fractures
	Tibial fractures
	Soft tissue injuries
Surgery	Carpal tunnel decompression
	Arthroscopy
	Lumbar spine surgery
Central nervous system or spinal disorders	Head injury
	Hemiplegia
Visceral lesions	Myocardial infarction

From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

NONPHARMACOLOGIC THERAPY

- Physical therapy
- Patient education
- Psychosocial assessment

PHARMACOLOGIC THERAPY

Suggested regimens:

- Early CRPS, one or more of the following:
  1. NSAIDs
  2. Tricyclic antidepressant, gabapentin, pregabalin
  3. Glucocorticoids (oral prednisone 30 to 60mg daily with taper)
  4. Bisphosphonates (oral alendronate, IV pamidronate)
  5. Topical capsaicin, topical lidocaine
- Resistant course, incomplete response also can consider:
  1. Alpha-adrenergic antagonists and agonists (prazosin, phenoxybenzamine, clonidine)
  2. Ketamine infusion
  3. Use of opioids is controversial, but low doses can be considered
  4. Regional nerve blocks, sympathetic ganglion blocks, sympathectomy
  5. Spinal cord stimulation, dorsal root ganglia stimulation
  6. Referral to multidisciplinary pain center

NOTE: High-dose vitamin C may decrease the incidence of CRPS following wrist fracture, foot and ankle surgery, or trauma.

DISPOSITION

Spontaneous remission can occur after weeks to months, but many have prolonged disability.

REFERRAL

Cases in which the diagnosis is not clear or there is suboptimal response to therapy should promptly be referred to a multidisciplinary pain clinic.

PEARLS & CONSIDERATIONS

COMMENTS

- CRPS is a common clinical entity without clear definition, pathophysiologic features, or treatment.
- Early mobilization in high-risk situations is important for prevention of CRPS.
- Prompt diagnosis and aggressive physical and pharmacologic therapy may prevent progression to chronic, intractable pain.
- Trials involving intravenous immunoglobulin (IVIG) have failed to show reproducible results for pain reduction in patients with moderate to severe CRPS.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Daphne Scaramangas-Plumley, MD**

FIG. E3 Posttraumatic and surgical complex regional pain syndrome. Radiograph of the wrist demonstrates diffuse, patchy osteoporosis. This finding is usually nonspecific and positive only in chronic stages. Note associated radioulnar dislocation and vascular calcification in the radial artery. (Courtesy of Conrado Furtado A. Cavalcanti, MD, São Paulo, Brazil.)

TABLE E3 Approaches to the Treatment of Complex Regional Pain Syndrome

Prevention	Early mobilization Vitamin C
Physiotherapy	Desensitization techniques Mirror therapy Graded motor imagery Transcutaneous electrical nerve stimulation Acupuncture
Drug treatment	Possibly effective (although no large-scale studies) • Bisphosphonates • Free radical scavengers (dimethyl sulfoxide [topical] and *N*-acetylcysteine) • Ketamine (intravenous) Insufficient evidence for effectiveness • Analgesics (including paracetamol, NSAIDs, and opioids) • Anticonvulsants • Antidepressants • Baclofen (oral and intrathecal) • Botulinum toxin (intramuscular) • Calcitonin • Calcium channel blockers • Capsaicin • Corticosteroids • Lidocaine 5% plasters
Spinal cord stimulation	
Surgery (very rarely indicated)	Surgical sympathectomy Amputation

From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

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BASIC INFORMATION

DEFINITION

- Concussion is a mild traumatic brain injury manifesting with self-limited symptoms at the less severe end of the brain injury spectrum.
- The fourth International Conference on Concussion (2012) defines concussion as "a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces," characterized by the following features: (1) Caused by a direct blow to the head or blow to the body that transmits an "impulsive" force to the head; (2) results in rapid onset of short-lived neurologic impairment that resolves spontaneously; (3) variable clinical symptoms that may not include loss of consciousness; (4) symptoms that largely reflect a functional disturbance rather than structural injury (thus, no abnormalities are seen on standard structural neuroimaging studies); and (5) symptom resolution that typically follows a sequential course but may be prolonged in a small percentage of cases.

SYNONYM

Mild traumatic brain injury (mTBI)

ICD-10CM CODES	
S06.0	Concussion
S06.0X0A	Concussion without loss of consciousness, initial encounter
S06.0X0D	Concussion without loss of consciousness, subsequent encounter
S06.0X0S	Concussion without loss of consciousness, sequela
S06.0X1A	Concussion with loss of consciousness of 30 minutes or less, initial encounter
S06.0X9A	Concussion with loss of consciousness of unspecified duration, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 3.8 million sports- and recreation-related concussions occur each yr in the U.S. It is estimated that as many as 50% of concussions go unreported.

PREVALENCE: Each yr, U.S. emergency departments treat an estimated 135,000 sports- and recreation-related TBIs, including concussions, among children ages 5 to 18.

PREDOMINANT SEX AND AGE:

- Children and teens are more likely to get a concussion and take longer to recover than adults.
- Limited studies have shown that in sports that are played by both men and women, women are at more risk of sustaining a concussion. In males the incidence is highest in football, followed by hockey, and in females, soccer. Player contact is the most common cause.

RISK FACTORS:

- Participating in high-impact sports and recreational activities
- Previous history of concussion
- Athletes with a body mass index (BMI) >27 kg/m^2 and those who train <3 hr/wk
- Individuals who sustain a sports-related concussion and continue playing immediately after the injury require nearly twice as much time to recover as those who are removed immediately

PHYSICAL FINDINGS & CLINICAL PRESENTATION

See Table 1.

ETIOLOGY

- Occurs when rotational or angular acceleration forces are applied to the brain, resulting in shear strain of the underlying neural elements, including altered autonomic function and impaired control of cerebral blood flow
- May be associated with a blow to the skull; however, direct impact to the head is not required

TABLE 1 Symptoms and Signs of Concussion

Mental Status Changes
Amnesia
Confusion
Disorientation
Easily distracted
Excessive drowsiness
Feeling dinged, stunned, or foggy
Impaired level of consciousness
Inappropriate play behaviors
Poor concentration and attention
Seeing stars or flashing lights
Slow to answer questions or to follow directions
Physical or Somatic
Ataxia or loss of balance
Blurry vision
Decreased performance or playing ability
Dizziness
Double vision
Fatigue
Headache
Light-headedness
Nausea, vomiting
Poor coordination
Ringing in the ears
Seizures
Slurred, incoherent speech
Vacant stare/glassy-eyed
Vertigo
Behavior or Psychosomatic
Emotional lability
Irritability
Low frustration tolerance
Personality changes
Nervousness, anxiety
Sadness, depressed mood

From Patel DR et al: Sports concussions in adolescents, *Pediatr Clin N Am* 57:652, 2010.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Migraine
- Cervical strain
- Posttraumatic vestibular injury

WORKUP

- There is no definitive diagnostic test for concussion. Physical exam should include smooth pursuits (examiner moves finger horizontally across field of vision), saccades, gaze instability, near point of convergence, accommodation, and balance. Patients with loss of consciousness or posttraumatic convulsive seizures should be transported to the emergency department.
- Sideline assessment:
  1. No athlete with a suspected concussion should return to play that day.
  2. Neurologic assessment using a standardized tool, such as s SCAT-3 (Sports Concussion Assessment Tool), which includes the BESS (Balance Error Scoring System), Maddocks Questions, and SAC (Standardized Assessment of Concussion).
  3. Monitor for deterioration; no athlete should be left alone.
- Office assessment:
  1. History focused on current symptoms. Consider using Postconcussion Symptom Checklist.
  2. Neurologic exam
     a. Gait/balance testing. Consider the Balance Error Scoring System (BESS)
     b. Cerebellar coordination: Finger-to-nose testing (tested on SCAT-3 card)
     c. Convergence of Accommodative Sufficiency
- Neurocognitive testing:
  1. Computer-based programs, such as ImPACT, ANAM, CogSport
  2. Neuropsychiatric testing administered by a neuropsychologist
- When used in combination, symptom assessment, balance assessment, and neurocognitive testing provide a sensitivity of >90% for the identification of concussion.
- Consider the Buffalo Concussion Treadmill Test, which identifies physiologic dysfunction in concussion, rules out other diagnoses, and can quantify a safe level of activity in concussion recovery.

IMAGING STUDIES

- CT imaging is not universally indicated and should be considered on an individual basis. It is indicated in any athlete with a rapidly changing or focal neurologic exam or with a suspected intracranial bleed.
- Consider following PECARN guidelines.

TREATMENT

ACUTE GENERAL Rx

- Removal from game
- Physical rest

TABLE 2 Graduated Return to Play Protocol

Rehabilitation Stage	Functional Exercise at Each Stage of Rehabilitation	Objective of Each Stage
1. No activity	Complete physical and cognitive rest	Recovery
2. Light aerobic exercise	Walking, swimming, or stationary cycling, keeping intensity <70% maximum predicted heart rate. No resistance training	Increase heart rate
3. Sport-specific exercise	Skating drills in ice hockey, running drills in soccer. No head impact activities	Add movement
4. Noncontact training drills	Progression to more complex training drills, e.g., passing drills in football and ice hockey. May start progressive resistance training	Exercise, coordination, and cognitive load
5. Full contact practice	After medical clearance, participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6. Return to play	Normal game play	

From Putukian M: The acute symptoms of sports-related concussion: diagnosis and on-field management, *Clin Sports Med* 30(58), 2011.

1. No return to play until asymptomatic for at least 24 hours.
2. Follow the return-to-play guidelines (Table 2).
3. There is no evidence to support prolonged rest in concussed athletes longer than several weeks (see "Postconcussive Syndrome"). Prolonged inactivity after concussion has been linked to negative health effect. Light aerobic activity that avoids risk for reinjury decreases concussion symptoms, suggesting that low-level physical activity postconcussion might be beneficial.

- Cognitive rest to limit symptoms
  1. Limit screen time to less than 2 hours per day.
  2. Academic accommodations at school. Consider return to school for half-days when tolerating 2 hours of work at home.
  3. Encourage good sleep hygiene.

CHRONIC Rx

See "Postconcussive Syndrome."

DISPOSITION

- Physiologic recovery is slower than symptomatic recovery. Protocols involving a symptom-free waiting period before return to play are warranted. Table 2 summarizes the American Academy of Neurology, American Medical Society for Sports Medicine, and International Conference on Concussion recommendations on returning to play after a concussion.
- If concussion symptoms occur with activity at one level, the athlete should stop the activity, rest until symptoms resolve, and then restart his or her progression at the level that did not elicit symptoms.
- There are no evidence-based guidelines for disqualifying or retiring an athlete from sport after a concussion. Each case should be individually considered.

REFERRAL

Referral to sports-medicine physician, neuropsychology, or concussion center is indicated if there is concern about the timing of return to contact or collision sport. Referral is also indicated in patients with preexisting neurologic disorders such as migraines, depression or anxiety, and in those who have had multiple concussions.

PEARLS & CONSIDERATIONS

PREVENTION

- Pre-participation evaluations for all athletes.
- Pre-participation neurocognitive and balance testing to establish a baseline.
- There is currently no evidence to support the use of concussion prevention headbands or mouth guards.
- Spontaneous recovery from acute concussion ranges from 1 to 2 weeks in adults and up to 4 weeks in adolescents.

PATIENT & FAMILY EDUCATION

Centers for Disease Control and Prevention: www.cdc.gov/TraumaticBrainInjury/causes.html.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Concussion (Patient Information)
Postconcussion Syndrome (Related Key Topic)
Traumatic Brain Injury (Related Key Topic)

AUTHORS: **Peter J. Sell, DO,** and **Amity Rubeor, DO, CAQSM**

SUGGESTED READINGS

Centers for Disease Control and Prevention: www.cdc.gov/TraumaticBrainInjury/causes.html.

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Conduct Disorder

BASIC INFORMATION

DEFINITION

Conduct disorder (CD) is a repetitive and persistent pattern of behaviors in which either the basic rights of others are violated and/or major age-appropriate societal rules are violated. Classified under the DSM-5 category "disruptive, impulse control, and conduct disorders."

ICD-10CM CODES	
F43.24	Adjustment disorder with disturbance of conduct
F43.25	Adjustment disorder with mixed disturbance of emotions and conduct
F91.0	Conduct disorder confined to family context
F91.1	Conduct disorder, childhood-onset type
F91.2	Conduct disorder, adolescent-onset type
F91.8	Other conduct disorders
F91.9	Conduct disorder, unspecified
I45.89	Other specified conduction disorders
I45.9	Conduction disorder, unspecified
DSM-5 CODES	
312.81	Childhood onset
312.32	Adolescent onset
312.89	Unspecified onset

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1% (12 mo span, National Comorbidity Survey-Replication [NCS-R])

PREVALENCE: Approximately 2% to 10%; NCS-R: 9%. Disruptive behavior disorders are considered the most common reason for referral of children to mental health providers.

PREDOMINANT SEX: More common in males (4:1 preadolescence and 2:1 post-adolescence). It is unclear if CD females are underrepresented because diagnostic criteria were validated on male samples. Nonconfrontational aggression and promiscuity are examples of possible gender-specific criteria that, at this time, have unknown predictive validity.

PREDOMINANT AGE: Most common onset in early adolescence. Median age of onset is 11 yr.

GENETICS: Risk increased if parent or sibling with disorder.

RISK FACTORS: There are various temperamental (including lower-than-average intelligence, especially verbal), family-level (including parental rejection or neglect, early institutional living, frequent caregiver changes, large family size, parental criminality or substance use), and community-level (including peer rejection, association with delinquent peer group, exposure to violence) risk factors. A history of traumatic brain injury also confers risk for conduct disorder.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The DSM-5 lists 15 possible behavioral manifestations of CD, grouped into four categories: Aggression to people and animals, destruction of property, deceitfulness or theft, and serious violations of rules. Three of the 15 behaviors are required to have occurred in the previous 12 mo, and one behavior must have occurred in the previous 6 mo.
- Specifiers describe the age of onset and the severity of the disorder.
- New to the DSM-5 is an additional specifier addressing issues relating to intent and reaction to the behaviors, including the following options: "With limited prosocial emotions," "lack of remorse or guilt," "callous lack of empathy," "unconcerned about performance," and "shallow or deficient affect."
- CD represents a heterogeneous group with respect to presentation, etiology, severity, and course.
- Symptom severity often progresses over time with age (i.e., lying and truancy to sexual assault and robbery).
- Aggressive youth are more likely to interpret as negative or hostile the intent of neutral others and are more likely to believe that conflict can be adequately resolved via aggression.
- Poor frustration tolerance, irritability, temper outbursts, and recklessness are often associated with CD.
- Slow resting heart rate associated with reduced autonomic response to fear is the most replicated of all biologic markers for conduct problems.

ETIOLOGY

Estimated population variance in antisocial behavior accounted for by:

- Genes: 50%
- Environmental factors shared among family members: 20%
- Environmental factors unshared among family members: 20% to 30%

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Oppositional defiant disorder
- ADHD
- Mood disorder
- Adjustment disorder
- Substance use disorder, intoxication, or withdrawal
- Posttraumatic stress disorder
- Antisocial personality disorder (for those >18 yr)
- Adaptive behavior or subcultural delinquency
- Underlying neurological disorder (rare)

WORKUP

Diagnosis is made based on history, including individual and family interviews as well as collateral data from additional sources (e.g., parents, teachers, other medical providers, therapists).

LABORATORY TESTS

Consider urine toxicology for possible substance use comorbidity.

IMAGING STUDIES

None indicated; however, both structural and functional differences have been noted in certain areas of the brain in individuals with CD.

TREATMENT

Initial treatment of CD should include psychosocial and environmental interventions aimed at decreasing the frequency and severity of delinquent behaviors. If the interventions listed here are not effective or if serious concerns exist regarding safety or impairment in functioning, pharmacologic interventions targeting specific symptoms (e.g., aggression) or comorbid disorders (e.g., ADHD, anxiety disorders, or mood disorders) may help. There are currently no medications approved by the FDA for the treatment of CD.

NONPHARMACOLOGIC THERAPY

- Parent management training.
- Cognitive problem-solving skills training (including elements of social skills, conflict resolution, anger management, impulse control, and vocational training).
- Multisystemic therapy (MST).
- Social skills training.
- Individual psychotherapy.
- Family psychotherapy.
- Higher levels of care such as a hospital or acute residential setting may be required for stabilization if acute safety concerns develop in the context of CD, such as severe aggression.
- Legal involvement or out-of-home-placements may be necessary to monitor safety of both the patient and the community.

PHARMACOLOGIC THERAPY

Medication may be considered as an adjunct to behavioral treatment or in cases in which comorbidity is a factor. There is some evidence for symptom improvement with trials of several classes of psychotropic medications—including stimulants, mood stabilizers, atypical antipsychotics, antidepressants, and alpha-2 agonists—all of which seem to target aggressive symptoms in particular; medication, however, should never be used alone or as first-line treatment for CD.

DISPOSITION

- Approximately half of those with early onset of CD persist with antisocial behaviors into adulthood. There is no reliable way to predict which 50% will persist.
- Approximately half of those with early onset of CD do not develop antisocial personality disorder in adulthood. This subgroup is at higher risk for depression, anxiety, and social isolation as adults.
- Approximately 85% of those with adolescent onset of CD do not demonstrate lifetime persistent violence, convictions, and incarcerations. However, adult prognosis may often include substance use and crimes that go largely undetected.

PEARLS & CONSIDERATIONS

COMMENTS

- Treatment noncompliance is common (expect 30% treatment noncompliance rate).
- Consider community-based resources (including unique strengths of patient and family) and recruit multiple multidisciplinary team members to create the most effective possible treatment plan.

AUTHORS: **Hassan M. Minhas, MD,** and **Elizabeth A. Lowenhaupt, MD**

SUGGESTED READINGS

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Condyloma Acuminatum PTG

BASIC INFORMATION

DEFINITION

Condyloma acuminatum, also known as anogenital warts, is a sexually transmitted viral disease of the penis, vulva, vagina, cervix, perineum, and perianal area caused by the human papillomavirus (HPV). More than 100 subtypes of the HPV virus have been identified, yet 90% of genital warts are caused by HPV types 6 or 11.

SYNONYMS

Genital warts
Venereal warts
Anogenital warts

ICD-10CM CODE
A63.0 Anogenital (venereal) warts

EPIDEMIOLOGY & DEMOGRAPHICS

- The estimated prevalence rate of HPV anogenital infection in the U.S. adult population is 10% to 20% among unvaccinated individuals
- Seen mostly in young adults, with peak age of onset of 16 to 25 yr
- A sexually transmitted disease spread by skin-to-skin contact
- Highly contagious, with 75% of sexually active adults in the United States having been infected with at least one genital HPV type at some time
- Virus shed from both macroscopic and microscopic lesions
- Average incubation time is 2 mo (range, 1 to 8 mo)
- Predisposing conditions: Diabetes, pregnancy, local trauma, and immunosuppression (e.g., transplant recipients, those with HIV infection)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usually found in genital area but can be present elsewhere on the body (larynx, oropharynx, trachea, and extremities)
- Lesions usually in similar positions on both sides of perineum
- Initial lesions are pedunculated, soft papules about 2 to 3 mm in diameter, 10 to 20 mm long; may occur as single papule or in clusters
- Size of lesions varies from pinhead to large cauliflower-like masses (Fig. E1)
- Usually asymptomatic, but if infected can cause pain, odor, or bleeding
- Vulvar condyloma more common than vaginal and cervical
- Four morphologic types: Condylomatous, keratotic, papular, and flat warts
- Intra-anal warts are observed predominantly in persons who have had receptive anal intercourse

ETIOLOGY

- HPV is a group of nonenveloped, double-stranded DNA viruses belonging to the family Papillomaviridae.
- HPV DNA types 6 and 11 usually found in exophytic warts and have no malignant potential. 90% of genital warts are caused by HPV 6 and 11.
- HPV types 16 and 18 usually found in flat warts and are associated with increased risk of malignancy.
- Recurrence associated with persisting viral infection of adjacent normal skin in 25% to 50% of cases.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Molluscum contagiosum
- Seborrhea keratosis
- Fordyce spots
- Lichen planus
- Lichen nitidus
- Condylomata lata of syphilis
- Malignancy
- Abnormal anatomic variants or skin tags around labia minora and introitus
- Dysplastic warts
- Table 1 summarizes treatment options for anal warts

WORKUP

- Colposcopic examination of lower genital tract from cervix to perianal skin with 3% to 5% acetic acid
- Biopsy of vulvar lesions that lack the classic appearance of warts and that become ulcerated or do not respond to treatment
- Biopsy of flat, white, or ulcerated cervical lesions

LABORATORY TESTS

- HPV tests are available to detect oncogenic types of HPV infection and are used in the context of cervical cancer screening and management or follow-up of abnormal cervical cytology or histology
- Cervical cultures for *Neisseria gonorrhoeae* and Chlamydia
- Serologic test for syphilis
- HIV testing offered
- Wet mount or DNA testing for trichomoniasis, *Candida albicans*, and *Gardnerella vaginalis* (if patient has abnormal vaginal discharge)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cryotherapy with liquid nitrogen
- Surgical removal

ACUTE GENERAL Rx

Factors that influence selection of treatment include wart size, wart number, anatomic site of wart, wart morphology, patient preference, cost of treatment, convenience, adverse effects, and provider experience.

Keratolytic agents:

- Podophyllin (Podofilox 0.5% solution or gel)
  1. Acts by poisoning mitotic spindle and causing intense vasospasm
  2. Applied by patient directly to lesion weekly and washed off in 6 hours
  3. Used in minimal vulvar or anal disease
  4. Applied cautiously to nonkeratinized epithelial surfaces
  5. Contraindicated in pregnancy
  6. Discontinued if lesions do not disappear in 6 wk; switch to other treatment
- Sinecatechins 15% ointment (green tea flavonoid extracts)
  1. Acts by upregulating apoptosis-associated genes
  2. Applied by patient three time daily (0.5 cm strand of ointment to each wart)
  3. Should not be continued longer than 16 wk
- Trichloroacetic acid (30% to 80% solution)
  1. Acts by destruction of the warty lesions through precipitation of surface proteins
  2. Applied weekly to lesion by a trained clinician
  3. Indicated for vulvar, anal, and vaginal lesions; can be used for cervical lesions
  4. Less painful and irritating to normal tissue than podophyllin
- 5-Fluorouracil
  1. Acts by causing necrosis and sloughing of growing tissue
  2. Can be used intravaginally or for vulvar, anal, or urethral lesions
  3. Better tolerated; 3 g (two thirds of vaginal applicator) applied weekly for 12 wk
  4. Possible vaginal ulceration and erythema
  5. Patient's vagina examined after four to six applications
  6. 80% cure rate

Physical agents:

- Cryotherapy with liquid nitrogen or cryoprobe
  1. Acts by causing tissue damage by formation of ice crystals, leading to disruption of cell membranes and cell death
  2. Can be used weekly for 3 to 6 wk
  3. 62% to 79% cure rate
  4. Not suitable for large warts
- Laser therapy
  1. Done by physician with necessary expertise and equipment
  2. Painful; requires anesthesia
- Electrocautery or excision
  1. For recurrent, very large lesions
  2. Local anesthesia needed

Immunotherapy:

- Interferon A
  1. Injected intralesionally at a dose of 3 million U/m^2 three times weekly for 8 wk
  2. Side effects: Fever, chills, malaise, headache
- Imiquimod 5% cream: Immunomodulatory drug that increases the immune response to warts
  1. Applied by patient at night, 3× per wk; wash off after 6 to 10 hours
  2. Usage for 16 wk maximum
  3. Increases wart clearance after 3 mo
- 40% to 77% cure rate
- Interferon, topical: Increases wart clearance at 4 wk

TABLE 1 Treatment Options for Anal Warts

Treatment	Success Rate	Comments
Podophyllin	20%-50%	May need repeat applications
		Skin irritation can occur
		Not used in the anal canal
		Poorly absorbed by keratinized lesions (most chronic warts are keratinized)
Trichloroacetic or dichloroacetic acid	75%	Can be used in the anal canal
		Care is required to control the size of the slough
Cryotherapy	75%	Can be used in the anal canal
		Care is required to limit the size of the wound
		Fumes from the therapy can contain active HPV*
Topical 5-fluorouracil	50%-75%	Probably better used after surgical excision to decrease the frequency of recurrence
Imiquimod	75% in women 33% in men	Cannot be used in the anal canal; works better in women than in men
Surgical excision (usually combined with cautery)	60%-90%	Fumes from the cautery may contain HPV*
		May need to be done in more than one session to avoid excising or burning excessive anoderm if a thick carpet of lesions is present
Intralesional interferon-α	>70%	Injected into the base of up to 5 warts 3 times a wk for 3-8 wk
		Approved by the FDA for refractory condyloma
HspE7	Experimental	Promising treatment involving subcutaneous injections
		Fusion protein that combines immune-stimulating properties and a target antigen from HPV
External-beam radiation therapy	Variable	Reserved for giant cavitating condyloma (Buschke-Löwenstein lesions)
		Used as a last resort, usually when bleeding or tissue invasion cannot be controlled

*The risk of HPV transmission from such fumes is unknown.
FDA, Food and Drug Administration; HPV, human papillomavirus.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

DISPOSITION

- Most genital warts resolve without therapy.
- Follow-up exam every 6 to 12 mo as needed.
- Referral to a specialist experienced in the treatment of anogenital warts (e.g., dermatologist, urologist, or colorectal surgeon) is appropriate for patients who are immunosuppressed or who have treatment-refractory anogenital warts.
- Patients with large, bulky perianal or genital warts that may require extensive surgical removal should be referred to a colorectal surgeon or urologist.

PREVENTION

- Male and female condoms should be used consistently and correctly to lower the risks of acquiring and transmitting HPV. However, because HPV can infect areas not covered by a condom, condoms will not fully protect against HPV.
- New guidelines for the routine vaccination of young adolescents (females and males) ages 9 to 14 are two doses of the HPV vaccine given at a 6- to 12-mo interval, which offers the same protection as the three-dose vaccination.
- Young women from ages 15 to 26 should receive three doses of the HPV vaccine (the 9vHPV, 4vHPV, and 2vHPV are approved for females).
- Young males from ages 15 to 21 should receive three doses of the HPV vaccine. The age limit for male HPV vaccination may be extended up to age 26 (only the 4vHPV and 9vHPV vaccines are approved for males). For men who have sex with men (including young men who identify as gay and bisexual), for young transgender adults, and for young adults who are immunocompromised (secondary to HIV, chronic steroid usage, or prior history of transplant), HPV vaccination is recommended up to age 26. Three-dose HPV vaccination series are administered as IM injections over a 6-mo period, with the second and third doses given 1 to 2 and 6 mo after the first dose, respectively. The same vaccine type should be used for the entire three-dosage series.
- 4vHPV (Gardasil) vaccinates against types 6, 11, 16, and 18, which account for 66% of all cervical cancers.
- 2vHPV (Cervarix) vaccinates against types 16 and 18 (licensed for females only).
- 9vHPV (Gardasil 9) vaccine is available for preventing infection against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. It offers protection against five additional types of HPV accounting for 15% of cervical cancers not covered by Gardasil or Cervarix.
- HPV vaccines are not recommended for use in pregnant women.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Genital Warts (Patient Information)
Warts (Related Key Topic)

AUTHORS: **Helen B. Gomez, MD,** and **Rachel Wright Heinle, MD, FACOG**

SUGGESTED READING

Workowski KA, Bolan GA: Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines 2015, *MMWR Recomm Rep* 64(RR-03):1-137, 2015.

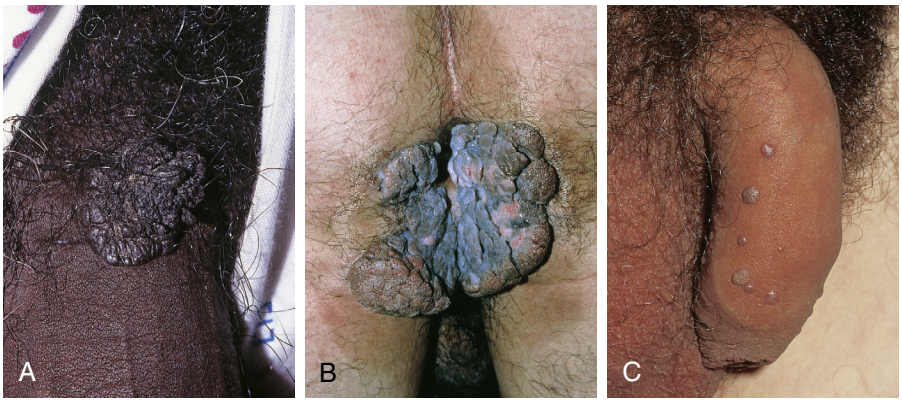

FIG. E1 Condyloma acuminatum. A, Scattered, flesh-colored or hyperpigmented, smooth or verrucous papules or erythematous macules along the shaft of the penis, scrotum, and perianal area are characteristic. The term *bowenoid papulosis* is used when the histologic picture of a lesion resembles Bowen disease. **B,** Perianal condyloma acuminatum. The viral particles causing perianal condyloma may have originated from warts elsewhere on the body and been transmitted via the patient's own hands, or they may have been contracted during anal sex. **C,** Condyloma acuminatum. Multiple lesions on the shaft of the penis. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

Congenital Adrenal Hyperplasia

BASIC INFORMATION

DEFINITION

Congenital adrenal hyperplasia (CAH) is a spectrum of disorders resulting from a deficiency or complete lack of one of the enzymes in the cortisol synthesis pathway. These autosomal recessive genetic disorders are usually characterized by cortisol deficiency and virilization, with or without salt wasting.

SYNONYMS

CAH
21-Hydroxylase deficiency (equivalent to CYP21A2 deficiency)
11β-Hydroxylase deficiency
3β-Hydroxysteroid dehydrogenase deficiency
17-Hydroxylase deficiency
Lipoid adrenal hyperplasia
Adrenal virilism
Adrenogenital syndrome
Virilizing adrenal hyperplasia

ICD-10CM CODE
E25.0 Congenital adrenogenital disorders associated with enzyme deficiency

EPIDEMIOLOGY & DEMOGRAPHICS

- About 95% of cases of CAH are caused by 21-hydroxylase deficiency, of which two-thirds are the salt-wasting form. Table E1 summarizes genotype-phenotype correlations in congenital adrenal hyperplasia owing to 21-hydroxylase deficiency.
- Autosomal recessive inheritance.
- The "classic" form presents in childhood, and the "nonclassic" form is the mild, late-onset form.
- Incidence is estimated at about 1:10,000 to 1:20,000 live births (Hispanic > American Indian > white > black > Asian).
- Most common cause of ambiguous genitalia in 46,XX females.

CLINICAL PRESENTATION

"Classic" salt-wasting form (impaired cortisol and aldosterone synthesis):
- Adrenal crisis in first weeks of life with vomiting, poor weight gain, lethargy, dehydration, hyponatremia, hyperkalemia, and elevated plasma renin.
- Females are born with ambiguous genitalia (Fig. E1) that often leads to diagnosis before adrenal crisis occurs.
- Males may have greater penile size and smaller testes than expected during childhood. Males may also develop adrenal rests, or ectopic islands of adrenal cortical tissue in the testes, in childhood and may experience infertility as adults.
- If patients survive infancy, their overall life expectancy is not compromised.
- Both males and females may exhibit rapid growth in childhood due to early epiphyseal closure, which then results in short stature in adulthood.
- Precocious puberty is common in both males and females.

"Classic" non–salt-wasting or simple virilizing form (impaired cortisol synthesis only):
- Females present with ambiguous genitalia at birth.
- The normal appearance of male genitalia in the simple virilizing form makes this a difficult diagnosis in male infants.
- Characterized by precocious puberty, short stature, and testicular adrenal rests, as in the salt-wasting form.

"Nonclassic" or mild, late-onset form (varying degrees of androgen excess):
- Usually presents in adolescence or adulthood and is not detected on newborn screening
- Often asymptomatic but can be associated with mild virilization
- PCOS-like symptoms occur in women (hirsutism, oligomenorrhea, acne, infertility, insulin resistance, and abnormal menses)
- Associated with infertility in males

ETIOLOGY

In 21-hydroxylase deficiency, the pathways for aldosterone production (from the conversion of progesterone to deoxycorticosterone) and cortisol production (from the conversion of 17-hydroxyprogesterone to 11-deoxycortisol) by the cP450 enzyme 21-hydroxylase are interrupted. The production of ACTH is thus stimulated by a negative feedback mechanism, leading to adrenal hyperplasia and mineralocorticoid deficiency as the intermediaries in aldosterone and cortisol synthesis are shunted to the androgen biosynthesis pathway. A recombination event between the active *CYP21A2* gene on chromosome 6p21.3 and the CYP21A1 pseudogene is thought to create the deficient 21-hydroxylase enzyme.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Precocious puberty
- Polycystic ovarian syndrome (PCOS)
- Androgen resistance syndromes
- Pseudohermaphroditism
- Mixed gonadal dysgenesis
- Testicular carcinoma
- Leydig cell tumors
- Adrenocortical carcinoma
- Addison disease
- Pituitary adenoma

LABORATORY TESTS

- Prenatal: Chorionic villus sampling for history; genetic testing or measurement of 17-hydroxyprogesterone if family history.
- Serum 17-hydroxyprogesterone level, which is included in the newborn screen in all states, is the first-line test for suspected CAH.
- Adrenocorticotropin (ACTH) stimulation test is the next step to confirm the diagnosis and identify type of CAH.
- Additional tests that may be useful include plasma renin activity, aldosterone level, and electrolytes.

TABLE E1 Genotype-Phenotype Correlations in Congenital Adrenal Hyperplasia Owing to 21-Hydroxylase Deficiency

Mutation Group	A	B	C
Enzymatic activity, % normal	Nil	1–2%	20–50%
CYP21 mutations (phenotype generally corresponds to the least affected allele)	Gene deletion Exon 3 del 8 bp Exon 6 cluster Q318X R356W Intron 2 splice*	I172N	P30L V281L P453S
Severity	Salt wasting	Simple virilizing	Nonclassic
Aldosterone synthesis	Low	Normal	Normal
Age at diagnosis (without newborn screening)	Infancy	Infancy (females) Childhood (males)	Childhood to adulthood, or asymptomatic
Virilization	Severe	Moderate to severe	None to mild
Incidence	1/20,000	1/50,000	1/500

*This mutation is associated with both salt wasting and simple virilizing disease.
From Kliegman, RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

IMAGING STUDIES

- Abdominal ultrasound (Fig. E2) to evaluate adrenal glands can accelerate diagnosis.
- Ultrasound to identify a uterus in cases of ambiguous genitalia.
- Ultrasound is preferred to rule out testicular adrenal rest tumors (found in classic and nonclassic forms) and should be done beginning in adolescence.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Surgical correction of ambiguous genitalia may be necessary.
- Monitoring: Serum 17-hydroxyprogesterone and androstenedione, renin, electrolytes, blood pressure, bone age and density, Tanner staging, growth velocity, weight.
- Bilateral laparoscopic adrenalectomy with lifelong glucocorticoid and mineralocorticoid replacement (controversial).
- Gene therapy (hypothetical).
- Psychological counseling.

CHRONIC Rx

- Glucocorticoids to partially suppress adrenal androgen secretion. During periods of physiologic stress, they may need to be doubled or tripled.
  1. In children, hydrocortisone is preferred because of its short half-life, which minimizes the risk of iatrogenic short stature. After patients are fully grown, long-acting glucocorticoids can be used.
  2. Adolescents and adults: Dexamethasone 0.25 to 0.75 mg PO QHS (also used to treat adrenal rests) or prednisone 5 to 7.5 mg/day in two divided doses.
- Mineralocorticoids (e.g., fludrocortisone) to normalize electrolytes and plasma renin activity.
  1. In infants, salt supplementation is also required.
- Treatment of simple virilizing form: Similar to salt-wasting form, but mineralocorticoid replacement is unnecessary.
- Treatment of nonclassic form:
  1. In adolescent and adult women: Oral contraceptives, glucocorticoids, and/or antiandrogens.
  2. In children and adult males, usually no treatment is necessary.
  3. Prenatal glucocorticoid treatment is controversial but may decrease virilization in female fetuses.

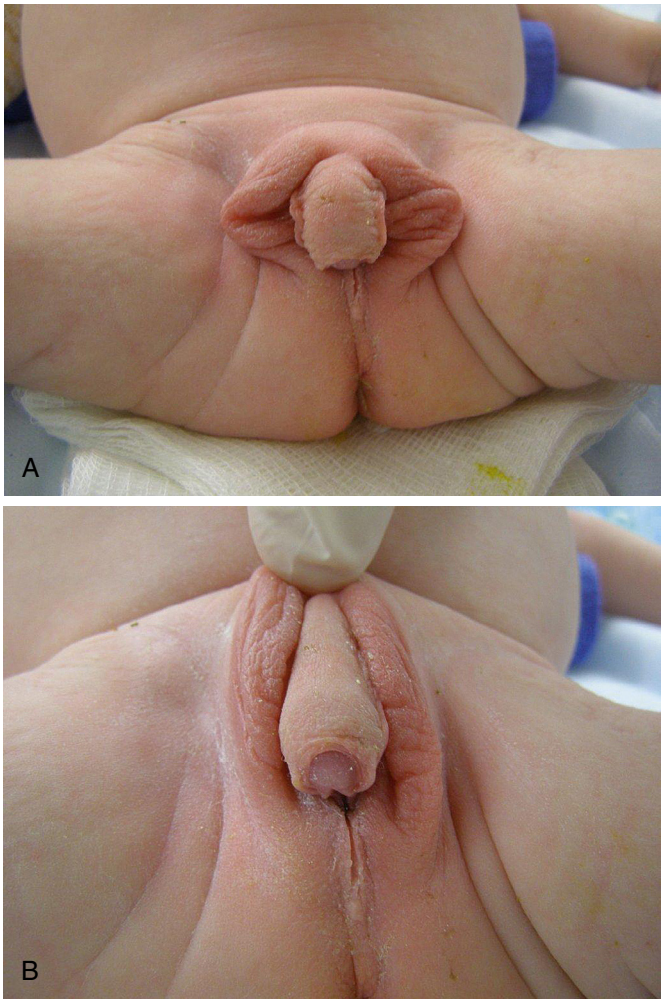

FIG. E1 Congenital adrenal hyperplasia. This newborn has ambiguous genitalia. Note the marked clitoral enlargement (resembling a penis), the rugated and partially fused labia majora **(A)**, and the common opening between the vagina and the urethra (urogenital sinus) **(B)**. (Courtesy Marleta Reynolds, MD. From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

PEARLS & CONSIDERATIONS

COMMENTS

- Consider the diagnosis of classic salt-wasting CAH in infants with failure to thrive.
- There is believed to be an increased prevalence of CAH in patients diagnosed with adrenal "incidentalomas"—adrenal gland lesions detected unexpectedly on imaging, usually by MRI or CT scanning.

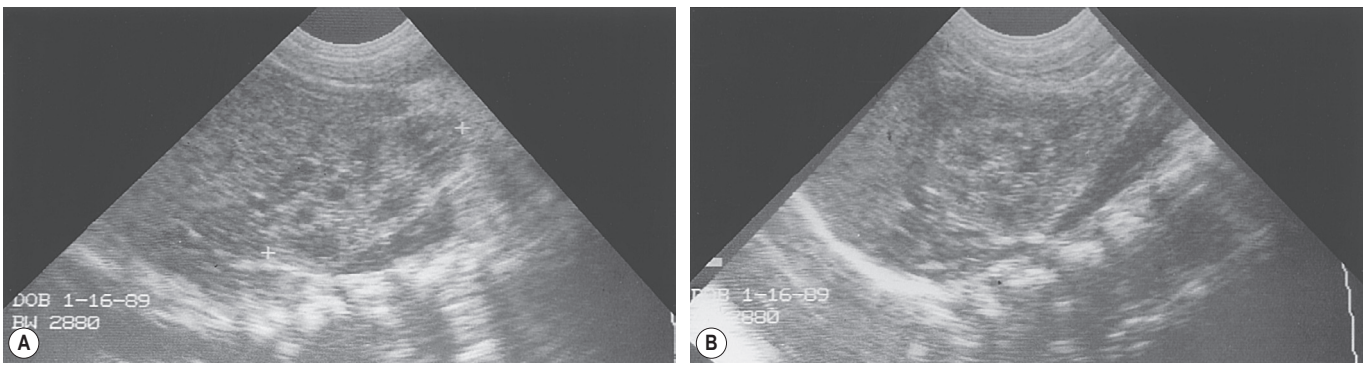

FIG. E2 Congenital adrenal hyperplasia in a patient with male pseudohermaphroditism. Sagittal US of the **(A)** right and **(B)** left adrenal glands demonstrates masslike enlargement. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, 2019, Elsevier.)

- Cushing syndrome may result from overtreatment of CAH with glucocorticoids.
- Patients with CAH may have gender dysphoria and sexual dysfunction.
- Table E2 summarizes diagnosis and treatment of CAH.

PREVENTION

- Prenatal: Early CVS sampling. Use of dexamethasone 20 to 25 mg/kg daily beginning at 5- to 8-wk gestation for female fetuses only is controversial because long-term studies are unavailable
- Neonatal screening
- Genetic counseling

AUTHOR: **Fred F. Ferri, MD**

TABLE E2 Diagnosis and Treatment of Congenital Adrenal Hyperplasia

Disorder	Affected Gene and Chromosome	Signs and Symptoms	Laboratory Findings	Therapeutic Measures
21-Hydroxylase deficiency, classic form	*CYP21* 6p21.3	Glucocorticoid deficiency	↓ Cortisol, ↑ACTH ↑↑ Baseline and ACTH-stimulated 17-hydroxy-progesterone	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
21-Hydroxylase deficiency, nonclassic form	*CYP21* 6p21.3	May be asymptomatic; precocious adrenarche, hirsutism, acne, menstrual irregularity, infertility	↑ Baseline and ACTH-stimulated 17-hydroxyprogesterone ↑ Serum androgens	Suppression with glucocorticoids
11β-Hydroxylase deficiency	*CYP11B1* 8q24.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated 11-deoxycortisol and deoxycorticosterone	Glucocorticoid (hydrocortisone) replacement
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
		Hypertension	↓ Plasma renin, hypokalemia	Suppression with glucocorticoids
3β-Hydroxysteroid dehydrogenase deficiency, classic form	*HSD3B2* 1p13.1	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated Δ5 steroids (pregnenolone, 17-hydroxy-pregnenolone, DHEA)	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females and males	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing
		Precocious adrenarche, disordered puberty	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Suppression with glucocorticoids
17α-Hydroxylase/17,20-lyase deficiency	*CYP17* 10q24.3	Cortisol deficiency (corticosterone is an adequate glucocorticoid)	↓ Cortisol, ↑ ACTH ↑ DOC, corticosterone Low 17α-hydroxylated steroids; poor response to ACTH	Glucocorticoid (hydrocortisone) administration
		Ambiguous genitalia in males	↓ Serum androgens; poor response to hCG	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Sexual infantilism	↓ Serum androgens or estrogens	Sex hormone replacement consonant with sex of rearing
		Hypertension	↓ Plasma renin; hypokalemia	Suppression with glucocorticoids

Continued

TABLE E2 Diagnosis and Treatment of Congenital Adrenal Hyperplasia—cont'd

Disorder	Affected Gene and Chromosome	Signs and Symptoms	Laboratory Findings	Therapeutic Measures
Congenital lipoid adrenal hyperplasia	*STAR* 8p11.2	Glucocorticoid deficiency	↑ ACTH Low levels of all steroid hormones, with decreased or absent response to ACTH	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↓ Aldosterone, ↑ plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in males	Decreased or absent response to hCG in males	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Poor pubertal development or premature ovarian failure in females	↑ FSH, ↑ LH, ↓ estradiol (after puberty)	Estrogen replacement
P450 oxidoreductase deficiency	*POR* 7q11.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑ Pregnenolone, ↑ progesterone	Glucocorticoid (hydrocortisone) replacement
		Ambiguous genitalia in males and females	↑ Serum androgens prenatally, ↓ androgens and estrogens at puberty	Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing
		Maternal virilization Antley-Bixler syndrome	Decreased ratio of estrogens to androgens	

↓, Decreased; ↑, increased; ↑↑, markedly increased; *ACTH*, adrenocorticotropic hormone; *DHEA*, dehydroepiandrosterone; *DOC*, 11-deoxycorticosterone; *FSH*, follicle-stimulating hormone; *hCG*, human chorionic gonadotropin; *LH*, luteinizing hormone.

From Kliegman, RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

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Pezzuti IL et al: A three-year follow-up of congenital adrenal hyperplasia newborn screening, *J Pediatr (Rio J)* 90(3):300-307, 2014.

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BASIC INFORMATION

DEFINITION

The term *conjunctivitis* refers to an inflammation of the conjunctiva resulting from a variety of causes, including allergies and bacterial, viral, and chlamydial infections.

SYNONYMS

"Red eye"
Pink eye
Acute conjunctivitis
Subacute conjunctivitis
Chronic conjunctivitis
Purulent conjunctivitis
Pseudomembranous conjunctivitis
Papillary conjunctivitis
Follicular conjunctivitis
Newborn conjunctivitis

ICD-10CM CODES

H10.9	Unspecified conjunctivitis
B30	Viral conjunctivitis
H10.0	Mucopurulent conjunctivitis
H10.1	Acute atopic conjunctivitis
H10.4	Chronic conjunctivitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 1.6% to 12% in *newborns*
PREVALENCE (IN U.S.):

- Allergic conjunctivitis (Fig. E1), the most common form of ocular allergy, is usually associated with allergic rhinitis and may be seasonal or perennial.
- Bacterial or viral conjunctivitis is often seasonal and can be extremely contagious.

PREDOMINANT AGE: Occurs at *any* age. Most cases in adults are due to viral infection. Children are more prone to develop bacterial conjunctivitis than viral forms.
PEAK INCIDENCE: More common in the spring and fall, when *viral* infections and pollens increase.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Infection and chemosis of conjunctivae with discharge. Gluing of the eyelids and no itching is more indicative of a bacterial cause (Fig. E2).
- Cornea is clear or can be involved (certain bacteria, such as *Neisseria*, can rapidly develop into corneal infection).
- Vision is often normal but can be blurred. Mucus and watering can cause fluctuating vision.
- Fig. E3 illustrates the difference between papillary and follicular conjunctivitis.

ETIOLOGY

- Bacterial: *Haemophilus influenzae, Streptococcus pneumoniae*, and *Moraxella catarrhalis* in children; *Staphylococcus* species in adults. Gram-negative infections are more common in contact lens wearers. *Gonococcal ophthalmia neonatorum* is caused by *Neisseria gonorrhoeae* acquired by exposure of the neonatal conjunctivae to infected cervicovaginal secretions during delivery
- Viral: Most common overall cause of infectious conjunctivitis
- Chlamydial
- Allergic
- Traumatic (chemical or toxin exposure)
- Chronic eyelid inflammation (blepharitis)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute glaucoma (fixed pupil with headache may indicate acute angle closure)
- Corneal lesions
- Acute iritis (with pain and photophobia, blurred vision)
- Episcleritis
- Scleritis (more severe pain, local globe tenderness, and no drainage)
- Canalicular obstruction (eye watering, inflammation near the tear punctum)
- Table 1 compares allergic diseases of the eye; histologic and laboratory manifestations of allergic ocular disease are described in Table 2

WORKUP

- History and physical examination
- Visual acuity and eye examination
- Reports of itching, pain, and visual changes

LABORATORY TESTS

Cultures are useful if not *successfully* treated with antibiotics; initial culture is usually not necessary, since normal conjunctival flora interferes with helpful culture results.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Warm compresses if infective conjunctivitis
- Cold compresses if irritative or allergic conjunctivitis
- Contact lenses should be taken out until an infection is completely resolved. Nondisposable lenses should be cleaned thoroughly as recommended by the manufacturer, and a new lens case should be used. Disposable contact lenses should be thrown away

ACUTE GENERAL Rx

- The majority of cases of bacterial conjunctivitis are self-limiting, and no treatment is necessary in uncomplicated cases.[1]

[1] Azari AA, Barney NP: Conjunctivitis, a systematic review of diagnosis and treatment, *JAMA* 310(16):1721-1729, 2013.

Antibiotic drops (e.g., levofloxacin, ofloxacin, ciprofloxacin, tobramycin, gentamicin ophthalmic solution, 1 or 2 drops q2 to 4h) are indicated for complicated bacterial conjunctivitis, in conjunctivitis caused by gonorrhea or chlamydia, and in bacterial conjunctivitis in contact lens wearers.

- Caution: Be careful with ophthalmic corticosteroid treatment and avoid unless sure of diagnosis; corticosteroids can exacerbate infections and have been associated with increased intraocular pressure and cataract formation.
- An oral antihistamine (e.g., cetirizine, loratadine, desloratadine, or fexofenadine) is effective in relieving itching.
- Mast cell stabilizers (e.g., ketotifen, olopatadine, azelastine bid) are effective for allergic conjunctivitis. Others include Elestat, Optivar, and Patanol.
- Bepotastine, alcaftadine, azelastine, epinastine, and ketotifen are H1-antihistamines and mast cell stabilizers effective for topical treatment of itching associated with allergic conjunctivitis. The topical NSAID ketorolac (0.5%, 1 drop qd) is also useful in allergic conjunctivitis. Table 3 describes topical ophthalmic medications for allergic conjunctivitis.
- Antihistamine/decongestant combinations such as pheniramine/naphazoline (Visine A), available over the counter, are more effective than either agent alone but have a short duration and can result in rebound vasodilatation with prolonged use. Others include Naphcon-A, Albalon-A, and Opcon-A.

CHRONIC Rx

- Depends on cause.
- If allergic, nonsteroidals such as ketorolac and bromfenac ophthalmic solution; mast cell stabilizers such as Patanol and Zaditor (ketotifen) are useful for improving ocular itching in patients with allergic conjunctivitis.
- If an infection, use antibiotic drops (see "Acute General Rx").
- Dry eyes need artificial tears, topical cyclosporine, or lacrimal duct plugs when indicated.
- Chronic and recurrent conjunctivitis often occurs with blepharitis. Daily warm compresses and lid scrub treatment may help relieve symptoms.

DISPOSITION

Follow carefully for the first 2 wk to ensure secondary complications do not occur. Otitis media can develop in 25% of children with *H. influenzae* conjunctivitis. Bacterial keratitis occurs in 30/1000 contact lens wearers.

REFERRAL

To ophthalmologist if symptoms are refractory to initial treatment. Indications for urgent referral are severe eye pain or headache, photophobia, decreased vision, and contact lens use.

TABLE 1 Allergic Diseases of the Eye

Disease	Clinical Parameters	Signs and Symptoms	Differential Diagnosis
Seasonal allergic conjunctivitis (SAC)	Occurs in sensitized individuals Both females and males affected Bilateral involvement Seasonal allergens Self-limiting	Ocular itching Tearing (watery discharge) Chemosis, redness Often associated with rhinitis Not sight-threatening	Infective conjunctivitis Preservative toxicity (any eye drop with preservative) Medicamentosa Dry eye Perennial allergic conjunctivitis Vernal keratoconjunctivitis (VKC) Atopic keratoconjunctivitis (AKC)
Perennial allergic conjunctivitis (PAC)	Occurs in sensitized individuals Both females and males affected Bilateral involvement Year-round allergens Self-limiting	Ocular itching Tearing (watery discharge) Chemosis, redness Often associated with rhinitis Not sight-threatening	Infective conjunctivitis Preservative toxicity Dry eye SAC/AKC/VKC
Atopic keratoconjunctivitis (AKC)	Occurs in sensitized individuals Peak incidence: 20-50 yr of age Both females and males affected Bilateral involvement Seasonal or perennial allergens Atopic dermatitis Chronic symptoms	Severe ocular itching Red, flaking periocular skin Mucoid discharge, photophobia Corneal erosions Scarring of conjunctiva Cataract (anterior subcapsular) Sight-threatening	Contact dermatitis Infective conjunctivitis Blepharitis Pemphigoid VKC/SAC/PAC/GPC
Vernal keratoconjunctivitis (VKC)	Occurs in some sensitized individuals Peak incidence: 3-20 yr of age Males predominate (in 3:1 ratio) Bilateral involvement Warm, dry climate Seasonal/perennial allergens Chronic symptoms	Severe ocular itching Severe photophobia Thick, ropy discharge Cobblestone papillae Corneal ulceration and scarring Sight-threatening	Infective conjunctivitis Blepharitis AKC/SAC/PAC/GPC
Giant papillary conjunctivitis (GPC)	Sensitization not necessary Both females and males affected Bilateral involvement Prosthetic and contact lens exposure Occurs anytime Chronic symptoms Nonseasonal occurrence	Mild ocular itching Mild mucoid discharge Giant papillae Contact lens intolerance Foreign body sensation Protein buildup on contact lens Not sight-threatening	Infective conjunctivitis Preservative toxicity SAC/PAC/AKC/VKC

From Adkinson NF et al: *Middleton's allergy principles and practice*, ed 8, Philadelphia, 2014, Saunders.

TABLE 2 Histopathologic and Laboratory Manifestations of Allergic Ocular Disease

Disease	Histopathologic Features	Laboratory Manifestations
Seasonal/perennial allergic conjunctivitis	Mast cell/eosinophil infiltration in conjunctival epithelium and substantia propria Mast cell activation Upregulation of ICAM-1 on epithelial cells	Increased in tears: Specific IgE antibody Histamine Tryptase TNF-α
Atopic keratoconjunctivitis	Increased mast cells, eosinophils in conjunctival epithelium and substantia propria Epithelial cell/goblet cell hypertrophy Increased CD4/CD8 ratio in conjunctival epithelium and substantia propria Increased collagen	Increased specific IgE antibody in tears Depressed cell-mediated immunity Increased IgE antibody and eosinophils in blood Eosinophils found in conjunctival scrapings
Vernal keratoconjunctivitis	Increased mast cells, eosinophils in conjunctival epithelium and substantia propria Eosinophil major basic protein deposition in conjunctiva $CD4^+$ clones from conjunctiva found to have helper function for local production of IgE antibody Increased collagen Increased ICAM-1 on corneal epithelium	Increased specific IgE/IgG antibody in tears Elevated histamine and tryptase in tears Reduced serum histaminase activity Increased serum levels of nerve growth factor and substance P
Giant papillary conjunctivitis	Giant papillae Conjunctival thickening Mast cells in epithelium	No increased histamine in tears Increased tryptase in tears

ICAM-1, Intercellular adhesion molecule 1; *IgE,* immunoglobulin E; *IgG,* immunoglobulin G; *TNF-α,* tumor necrosis factor-α.
From Adkinson NF et al: *Middleton's allergy principles and practice,* ed 8, Philadelphia, 2014, Saunders.

TABLE 3 Topical Ophthalmic Medications for Allergic Conjunctivitis

Drug and Trade Names	Mechanism of Action and Dosing	Cautions and Adverse Events
Azelastine hydrochloride 0.05% Optivar	Antihistamine Children ≥3 yr: 1 gtt bid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Emedastine difumarate 0.05% Emadine	Antihistamine Children ≥3 yr: 1 gtt qid	Soft contact lenses should not be worn if the eye is red. Wait at least 10 min after administration before inserting soft contact lenses.
Levocabastine hydrochloride 0.05% Livostin	Antihistamine Children ≥12 yr: 1 gtt bid-qid up to 2 wk	Not for use in patients wearing soft contact lenses during treatment.
Pheniramine maleate	Antihistamine/vasoconstrictor	Avoid prolonged use (>3-4 days) to avoid rebound symptoms. Not for use with contact lenses.
0.3% Naphazoline hydrochloride	Children >6 yr: 1-2 gtt qid	
0.025%		
Naphcon-A, Opcon-A		
Cromolyn sodium 4% Crolom, Opticrom	Mast cell stabilizer Children >4 yr: 1-2 gtt q4-6h	Can be used to treat giant papillary conjunctivitis and vernal keratitis. Not for use with contact lenses.
Lodoxamide tromethamine 0.1% Alomide	Mast cell stabilizer Children ≥2 yr: 1-2 gtt qid up to 3 mo	Can be used to treat vernal keratoconjunctivitis. Not for use in patients wearing soft contact lenses during treatment.
Nedocromil sodium 2% Alocril	Mast cell stabilizer Children ≥3 yr: 1-2 gtt bid	Avoid wearing contact lenses while exhibiting the signs and symptoms of allergic conjunctivitis.
Pemirolast potassium 0.1% Alamast	Mast cell stabilizer Children >3 yr: 1-2 gtt qid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Epinastine hydrochloride 0.05% Elestat	Antihistamine/mast cell stabilizer Children ≥3 yr: 1 gtt bid	Contact lenses should be removed before use. Wait at least 15 min after administration before inserting soft contact lenses. Not for the treatment of contact lens irritation.
Ketotifen fumarate 0.025% Zaditor	Antihistamine/mast cell stabilizer Children ≥3 yr: 1 gtt bid q8-12h	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Olopatadine hydrochloride 0.1%, 0.2%, 0.7% Patanol Pataday Pazeo	Antihistamine/mast cell stabilizer Children ≥3 yr: 1 gtt bid (8 hr apart) Children ≥2 yr: 1 gtt qd	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Alcaftadine, 0.25% Lastacaft	Antihistamine/mast cell stabilizer Children >2 yr: 1 gtt bid q8-12h	Contact lenses should be removed before application; may be inserted after 10 min. Not for the treatment of contact lens irritation.
Bepotastine besilate 1.5% Bepreve	Antihistamine/mast cell stabilizer Children >2 yr: 1 gtt bid q8-12h	Contact lenses should be removed before application, may be inserted after 10 min. Not for the treatment of contact lens irritation.
Ketorolac tromethamine 0.5% Acular	NSAID Children ≥3 yr: 1 gtt qid	Avoid with aspirin or NSAID sensitivity. Use ocular product with caution in patients with complicated ocular surgeries, corneal denervation or epithelial defects, ocular surface diseases (e.g., dry eye syndrome), repeated ocular surgeries within a short period, diabetes mellitus, or rheumatoid arthritis; these patients may be at risk for corneal adverse events that may be sight-threatening. *Do not use while wearing contact lenses.*
Fluorometholone 0.1%, 0.25% suspension (0.1%, 0.25%) and ointment (0.1%) FML, FML Forte, Flarex	Fluorinated corticosteroid Children ≥2 yr, 1 gtt into conjunctival sac of affected eye(s) bid-qid. During initial 24-48 hr, dosage may be increased to 1 gtt q4h. Ointment (~1.3 cm in length) into conjunctival sac of affected eye(s) 1-3 times daily. May be applied q4h during initial 24-48 hr of therapy.	If improvement does not occur after 2 days, patient should be reevaluated. Patient should remove soft contact lenses before administering (contains benzalkonium chloride) and delay reinsertion of lenses for ≥15 min after administration. Close monitoring for development of glaucoma and cataracts.

bid, Two times daily; *gtt,* drops; NSAID, nonsteroidal antiinflammatory drug; *q4-6h,* every 4-6 h; *qd,* every day; *qid,* four times daily.
From Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

PEARLS & CONSIDERATIONS

COMMENTS

- Red eyes are not simply conjunctivitis when the patient has significant pain or loss of sight. However, it is usually safe to treat pain-free eyes and the normal-seeing red eye with lid hygiene and topical treatment.
- Use caution with patients wearing soft contact lenses, infants, and the elderly.
- Do not use steroids indiscriminately; use only when the diagnosis is certain.
- Bacterial conjunctivitis is generally self-limiting. More than 60% of persons will improve with placebo within 2 to 5 days.

RELATED CONTENT

Conjunctivitis (Patient Information)

AUTHOR: **R. Scott Hoffman, MD**

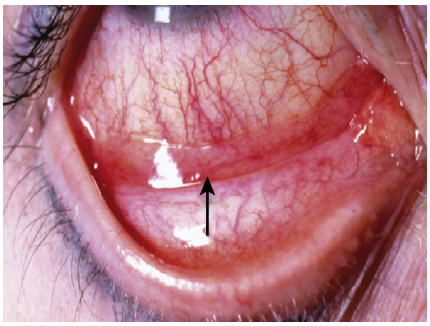

FIG. E1 Allergic conjunctivitis. *Arrow* indicates area of chemosis in the conjunctivitis. (From Adkinson NF Jr et al [eds]: *Middleton's allergy principles and practice,* ed 7, vol 2, Philadelphia, 2008, Mosby.)

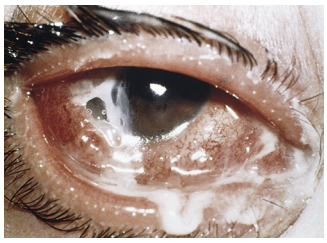

FIG. E2 Bacterial conjunctivitis. Purulent discharge and conjunctiva hyperemia suggest bacterial conjunctivitis. Viral conjunctivitis produces watery discharge, foreign body sensation, preauricular lymphadenopathy, and conjunctival follicles seen on slit lamp examination. (Reproduced with permission from the American Academy of Ophthalmology. From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

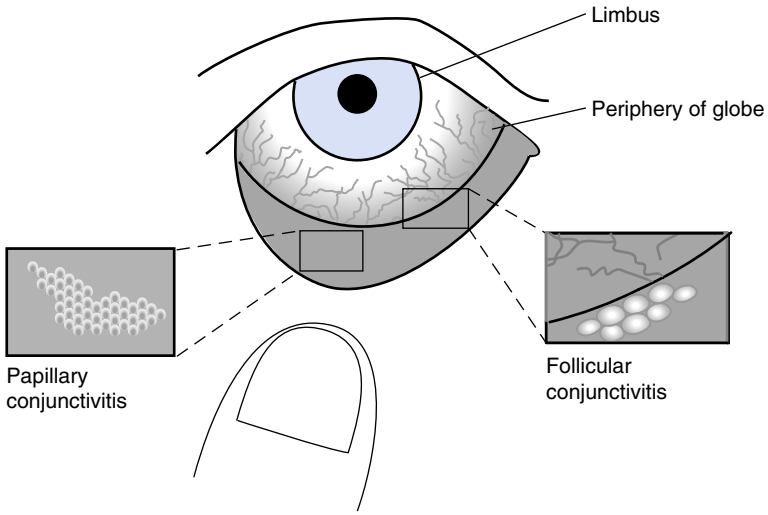

FIG. E3 Conjunctivitis: Papillary versus follicular. The erythema of conjunctivitis (*shaded dark gray*) is most intense on the inside surface of the eyelids (tarsal conjunctiva) and peripherally on the globe (near the fornices), whereas the erythema is less intense centrally near the limbus. In more severe conjunctivitis, the entire conjunctival surface (both tarsal and bulbar) is red. This pattern of erythema contrasts with iritis, which causes more intense erythema centrally around the limbus, a finding called *circumlimbal flush* or *ciliary flush*. In patients with conjunctivitis, the clinician should inspect the everted upper or lower lids, noting whether the inner membrane has its normal smooth surface or instead has small, uneven projections, which are characterized as either *papillae* or *follicles*. In this example, the clinician has used his thumb to gently evert the lower lid for inspection. Papillae *(left bottom)* are contiguous red vascular bumps; the center of each papilla contains a blood vessel. They are red on the surface and pale at the base. Papillae are often so tiny that the conjunctiva acquires a velvety appearance, and only magnification reveals their true nature. Other times, papillae may become large and produce a cobblestone appearance. Follicles *(right bottom)* are discrete 1- to 2-mm-diameter white bumps consisting of aggregates of lymphoid tissue; the center of each is avascular. They are pale on the surface and red at the base. (From McGee S: *Evidence-based physical diagnosis*, ed 4, Philadelphia, 2018, Elsevier.)

Connective Tissue Disease–Associated Vasculitis

BASIC INFORMATION

DEFINITION

Vasculitis is defined by inflammatory leukocytes and subsequent necrosis of blood vessel walls that can eventually lead to tissue ischemia. When vasculitis is associated with a connective tissue disease (CTD), it is defined as a secondary vasculitis. The connective tissue diseases that most commonly cause vasculitis include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Sjögren syndrome (SS). Vasculitis rarely occurs in the setting of other connective tissue diseases, including systemic sclerosis (SSc), relapsing polychondritis, primary antiphospholipid syndrome, inflammatory myopathies, and mixed connective tissue disease. Vasculitis is typically classified into large, medium, and small vessel vasculitis. When associated with a connective tissue disease, any type of vasculitis can occur; however, small vessel vasculitis is most common.

SYNONYMS

Connective tissue disorder–associated vasculitis
CTD

ICD-10CM CODE

M35.9 Systemic involvement of connective tissue, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Rheumatoid vasculitis: Estimated to occur in 1% to 5% of patients with RA, with no racial or ethnic predominance. Incidence is decreasing.
- Lupus-associated vasculitis: Estimates of the prevalence range from 11% to 36%.
- Sjögren-associated vasculitis: Cutaneous vasculitis occurs in approximately 10% of patients with primary Sjögren; systemic vasculitis is rare.
- Other CTD: Rare, but well described.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

GENERAL:

- Constitutional symptoms—fatigue, myalgias, weight loss, fever
- Skin manifestations—nail fold lesions (splinter hemorrhages), palpable purpura, leg ulcers, panniculitis, digital gangrene, livedo reticularis, urticaria, Janeway lesions, Osler nodes
- Neurologic manifestations—mononeuritis multiplex, distal symmetric sensorimotor neuropathy, transverse myelitis
- Ocular manifestations—episcleritis, scleritis, ulcerative keratitis
- Cardiac manifestations—arrhythmias, pericarditis, aortitis
- Gastrointestinal manifestations—pancreatitis, peritonitis, colitis
- Pulmonary manifestations—pneumonitis, alveolar hemorrhage
- Renal manifestations—glomerulonephritis

NOTE: Any organ may be involved because vasculitis can disrupt the corresponding vasculature (an example would be kidney injury due to destructive inflammation of the renal vasculature).

MOST COMMON SYNDROMES:

- Rheumatoid vasculitis:
  1. The most common clinical presentation of rheumatoid vasculitis includes skin lesions and peripheral neuropathy.
  2. Although a diagnosis of RA is needed to develop a secondary vasculitis, occasionally the vasculitic symptoms are the first manifestation of RA.
  3. Most patients with rheumatoid vasculitis have long-standing uncontrolled erosive RA, with rheumatoid nodules and high levels of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP).
  4. The diagnosis of rheumatoid vasculitis is usually confirmed by obtaining a biopsy of the clinically involved organ.
- Lupus-associated vasculitis:
  1. Skin lesions are the most common manifestation.
  2. The most common types of skin lesions are palpable purpura, petechiae, papulonodular lesions, livedo reticularis, panniculitis, and splinter hemorrhages.
- Sjögren-associated vasculitis:
  1. Vasculitis is one of the most common extraglandular manifestations of Sjögren syndrome.
  2. The most common skin lesions are palpable purpura, which most often represents a leukocytoclastic vasculitis.
  3. It can be quite difficult to tell the difference between vasculitis secondary to Sjögren disease and a concomitant primary vasculitis. Sjögren disease has been associated with several other primary vasculitides, including ANCA-associated vasculitis and polyarteritis nodosa. Should also assess for cryoglobulinemia.

ETIOLOGY

The vasculitis usually reflects the pathophysiology of the underlying connective tissue disease.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infection
- Hypercoagulable states (thrombotic thrombocytopenic purpura, hemolytic–uremic syndrome)
- Malignancy (leukemia, lymphoma)
- Primary vasculitides

WORKUP

The diagnosis usually requires multiple modalities, including a full history and physical, as well as laboratory testing, imaging, and sometimes a biopsy of skin or other involved organ. In order to have a connective tissue disease–associated vasculitis, one must meet diagnostic criteria for an underlying connective tissue disease.

LABORATORY TESTS

- Erythrocyte sedimentation rate/c-reactive protein
- CBC with diff. and platelets
- Albumin
- Complement studies
- Blood urea nitrogen and creatinine
- Urinalysis
- Antinuclear antibodies, RF, anti-CCP antibodies
- Double-stranded DNA (dsDNA) (if patient has a history suggesting SLE)
- Antineutrophil cytoplasmic antibodies (ANCA) that include ANCA-specific antibodies (anti-proteinase-3 and antimyeloperoxidase antibodies)

IMAGING AND OTHER STUDIES

- Imaging may be helpful depending on the clinical manifestations of the disease. For instance, in aortitis or renal artery vasculitis, an angiogram, computed tomography angiography, or magnetic resonance angiography may be useful.

- Biopsy of the affected site may be very useful. Skin, nerve, muscle, and kidney biopsies, depending on the affected organ system, will usually help to arrive at a final diagnosis and rule out vasculitis mimics.

Rx TREATMENT

Initial treatment is aimed at the underlying connective tissue disease. Additional immunosuppressive therapy may be needed depending on the severity of the vasculitis.

CHRONIC Rx

May need extended immunosuppressive therapy to prevent relapse

REFERRAL

Rheumatology

PEARLS & CONSIDERATIONS

COMMENTS

Patients with a history of CTD who present with new cutaneous lesions or systemic symptoms should be evaluated for vasculitis. Conversely, in patients who present with vasculitis, consideration should be given to the possibility of underlying CTD.

It is important not to confuse vasculitis with vasculopathy. The latter is a noninflammatory vascular process that is integral to the pathophysiology of some CTDs, such as SLE and SSc.

RELATED CONTENT

Rheumatoid Arthritis (Related Key Topic)
Sjögren Syndrome (Related Key Topic)
Systemic Lupus Erythematosus (Related Key Topic)
Vasculitis, Systemic (Related Key Topic)

AUTHOR: **Bradley Schlussel, MD**

SUGGESTED READINGS

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Cozzani E et al: Vasculitis associated with connective tissue diseases, *G Ital Dermatol Venereol* 150:221-232, 2015.
Makol A et al: Rheumatoid vasculitis an update, *Curr Opin in Rheum* 27(1):63-70, 2015.
Scofield R: Vasculitis in Sjögren's syndrome, *Curr Rheumatol Rep* 13(6):482-488, 2011.

BASIC INFORMATION

DEFINITION

Decreased stool frequency (fewer than three bowel movements [BM] per wk) with complaints of excessive straining, lower abdominal fullness, hard stools, feeling of incomplete evacuation, commonly associated with hardened feces or another underlying disorder.

Rome IV criteria (see "Diagnosis") are used to classify patients.

ICD-10CM CODES

K59.0	Constipation
K59.00	Unspecified
K59.01	Slow-transit constipation
K59.02	Outlet dysfunction constipation
K59.03	Drug-induced constipation
K59.04	Chronic idiopathic constipation
K59.09	Other constipation
K59.8	Other specified functional intestinal disorders
K59.9	Functional intestinal disorder, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- 12% to 19% of adults all ages
- Chronic constipation increases with age
- 33.5% of adults 60 to 101 yr of age
- Approximately 26% of men and 34% of women >65 have constipation

RISK FACTORS: More prevalent in women, nonwhites, patients with low income, patients older than 60 yr, patients who perform little physical activity, patients with low education level, or those with underlying medical condition predisposing them to constipation (e.g., Parkinson disease)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- A thorough history is paramount for evaluation. The duration of constipation, change in bowel movements, medication history, or any other concurrent medical history is important to inform your diagnosis.
- Clinical presentation varies for every patient, as their personal definition of constipation may differ from medical lexicon.
- Constipation can be accompanied by an increased frequency of liquid stools (overflow diarrhea), typically caused by stool impaction.
- Must rule out alarm features such as hematochezia, weight loss of greater than 10 lbs, a family history of colon cancer or inflammatory bowel disease, anemia, positive fecal occult blood tests, or acute onset of constipation.
- Physical examination must include a digital rectal exam.
- Rectal examination will rule out etiologies that can result in constipation. Pain on examination, asymmetric anal opening, impaired sphincter function, masses, strictures, or the presence and character of stool (soft, hard, impacted) can help determine the etiology.
- Clinical clues to an evacuation disorder are summarized in Box 1.

ETIOLOGY

- Characterized as idiopathic vs. secondary causes of constipation.
- Secondary causes include neurologic, metabolic, or endocrine disturbances; psychiatric disorders; gastrointestinal (GI) malignancies; and medication-induced constipation.
- Types of anorectal dysfunction causing rectal outlet delay in older people are summarized in Table 1.
- Medication-induced constipation is very common; frequent offenders include:
  1. Anticholinergics
  2. Iron supplements
  3. Antacids
  4. Opiates
  5. Antihypertensive medications (especially calcium channel blockers)
  6. Serotonin antagonists
  7. Ganglionic blockers

DIAGNOSIS

BASED ON ROME IV CRITERIA

- Symptoms present for at least 3 mo out of the previous 6 mo.
- Loose stools are rarely present without the use of laxatives.
- Criteria for irritable bowel syndrome (IBS) are not met.
- Presence of two or more of the following specific symptoms:
  1. Straining during more than 25% of defecations
  2. Lumpy or hard stools in more than 25% of defecations
  3. Sensation of incomplete evacuation for more than 25% of defecations
  4. Sensation of anorectal obstruction/blockage for more than 25% of defecations
  5. Manual maneuvers to facilitate more than 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
  6. Fewer than three spontaneous bowel movements per wk
- See Fig. 1 for an algorithmic approach to the diagnosis of constipation.

DIFFERENTIAL DIAGNOSIS

- First delineate between functional constipation vs. secondary causes.
- Secondary causes of constipation include medications, diabetes, hyperparathyroidism, hypothyroidism, lead poisoning, uremia, Parkinson disease, multiple sclerosis, scleroderma, lupus, and malignancy.
- Functional constipation must be differentiated from irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), appendicitis, ileus, and Ogilvie syndrome.

BOX 1 Clinical Clues to an Evacuation Disorder

History

Prolonged straining to expel stool
Assumption of unusual postures on the toilet to facilitate stool expulsion
Support of the perineum, digitation of rectum, or application of pressure to the posterior vaginal wall to facilitate rectal emptying
Inability to expel enema fluid
Constipation after subtotal colectomy for constipation

Rectal Examination (with patient in left lateral position)

Inspection

Anus "pulled" forward during attempts to simulate strain during defecation
Anal verge descends <1 cm or >4 cm (or beyond ischial tuberosities) during attempts to simulate straining at defecation.
The perineum balloons down during straining; rectal mucosa partially prolapses through anal canal.

Palpation

High anal sphincter tone at rest precludes easy entry of the examining finger (in absence of a painful perianal condition [e.g., anal fissure]).
Anal sphincter pressure during voluntary squeeze only minimally higher than anal pressure at rest.
The perineum and examining finger descend <1 cm or >4 cm during simulated straining at defecation.
The puborectalis muscle is tender to palpation through the rectal wall posteriorly, or palpation reproduces pain.
Palpable mucosal prolapse during straining.
"Defect" in anterior wall of the rectum, suggestive of rectocele.

Anorectal Manometry and Balloon Expulsion (with patient in left lateral position)

Elevated resting anal sphincter pressure
Delay in balloon expulsion test (normal values for women <50 yr: 4-75 seconds; normal values for women ≥50 yr of age: 3-15 seconds*

*Noelting J et al: Normal values for high-resolution anorectal manometry in healthy women: effects of age and significance of rectoanal gradient, *Am J Gastroenterol* 107:1530-1536, 2012.

Bharucha AE et al: American Gastroenterological Association technical review on constipation, *Gastroenterology* 2013;144(1):218-238. doi:10.1053/j.gastro.2012.10.028

From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

TABLE 1 Types of Anorectal Dysfunction Causing Rectal Outlet Delay in Older People

	Pathophysiology	Clinical Picture
Rectal dysmotility	Reduced rectal motility and contractions Increased rectal compliance Variable degree of rectal dilation Impaired rectal sensation with blunting of urge to pass stool Over time, increasing rectal distention required to reflexively trigger the defecation mechanism	Rectal hard or soft stool retention on digital examination of which patient may be unaware Chronic rectal distention leads to relaxation of the internal sphincter and fecal soiling One postulated cause is diminished parasympathetic outflow as a result of impaired sacral cord function (e.g., from ischemia or spinal stenosis); may also develop through persistent disregard or suppression of the urge to defecate as a result of dementia, depression, immobility, or painful anorectal conditions
Pelvic floor dyssynergia	Paradoxical contraction or failure to relax the pelvic floor and external anal sphincter muscles during defecation Manometric studies show paradoxical increases in anal canal pressure on straining	Severe and long-standing symptoms of rectal outlet delay Parkinson disease More common in younger women
Irritable bowel syndrome	Increased rectal tone and reduced compliance Lower pain threshold on distending the rectum during anorectal function tests	Usually constipation-predominant in older people Rome criteria symptoms: Abdominal distention or pain relieved by defecation, passage of mucus, and feeling of incomplete emptying

Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

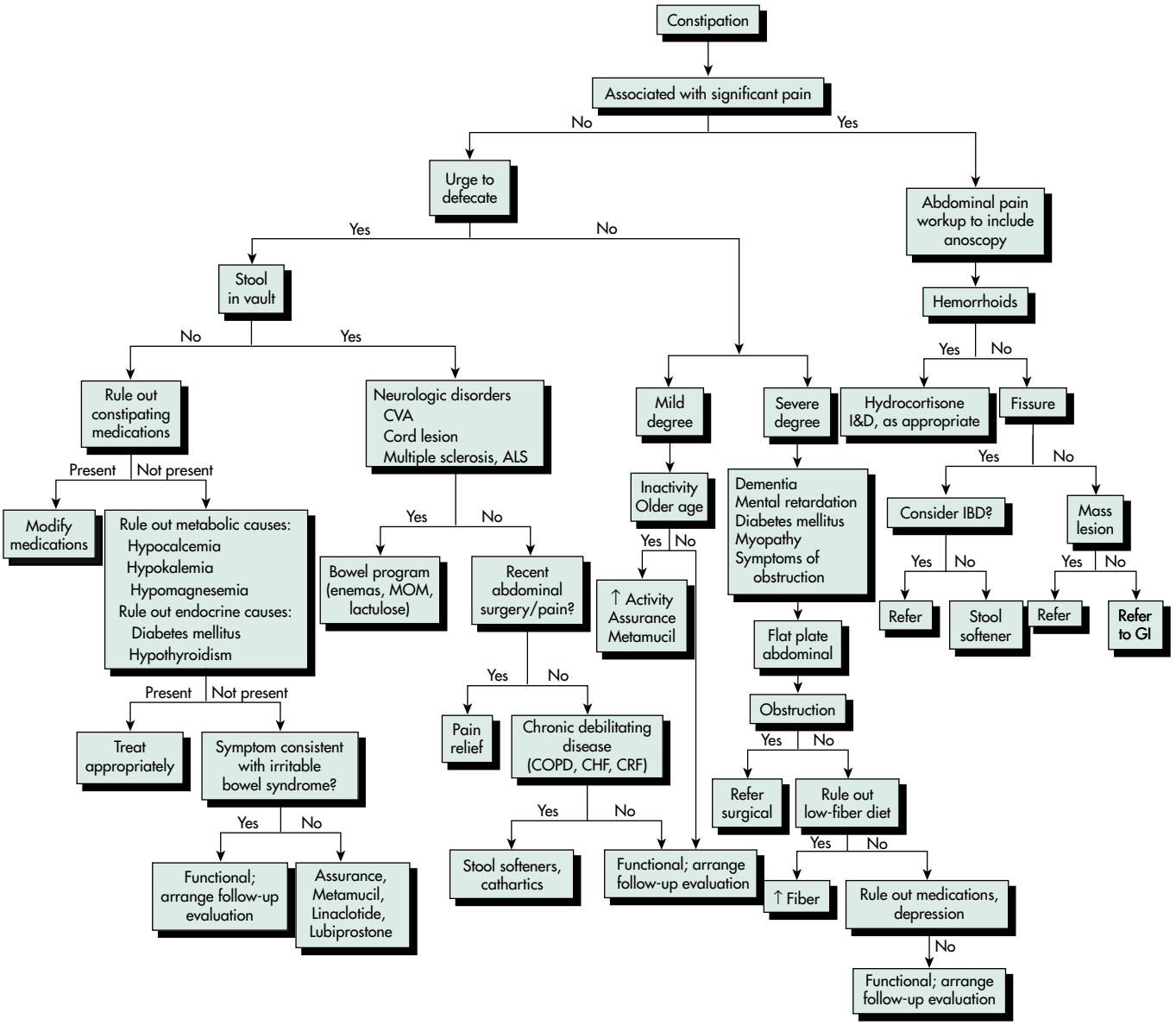

FIG. 1 Algorithmic approach to the diagnosis of constipation. *ALS,* Amyotrophic lateral sclerosis; *CHF,* congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *CRF,* chronic renal failure; *CVA,* cerebrovascular accident; *GI,* gastroenterology; *IBD,* inflammatory bowel disease; *I&D,* incision and drainage; *MOM,* milk of magnesia. (From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, WB Saunders.)

WORKUP

- A thorough history should include presence of alarm signs, dietary habits, list of medications, underlying systemic or neurological disorders, and patient's lifestyle/level of activity.
- Physical examination must include a rectal examination to evaluate for hemorrhoids, stool consistency, melena, hematochezia, rectal prolapse, abnormal rectal tone, or rectocele. The sensitivity and specificity of a digital rectal exam to diagnose dyssynergic defecation are 75% and 87%, respectively.
- Stool impaction can present as diarrhea and is diagnosed with a digital rectal exam and physical/radiologic findings consistent with increased stool burden.

LABORATORY TESTS

Routine laboratory tests are not required to diagnose constipation. However, patients with alarm signs should get a complete blood cell count, basic metabolic panel, thyroid-stimulating hormone, and fecal occult blood test.

IMAGING STUDIES

- Not required but may help rule out secondary causes.
- Plain film x-rays of the abdomen can be used to diagnose stool retention, which can possibly suggest ileus vs. obstruction vs. possible malignancy.
- If infrequent defecation is the major complaint, colon transit studies (via wireless motility capsule study) and whole-gut transit times can be useful, but they are only indicated in patients with chronic constipation that is refractory to laxatives and other conservative measures.
- Defecography is performed when the anorectum has anatomical and functional changes and is thought to contribute to constipation.
- Motility studies include anorectal manometry, colonic manometry, and balloon expulsion.

Rx TREATMENT

After a thorough history and physical examination, combined with the absence of alarm signs, it is appropriate to initiate empiric treatment, including patient education, dietary changes, and fiber therapy without further diagnostic workup. If there is no response, then laxative therapy is indicated.

See Box 2 for a general approach to the treatment of constipation.

NONPHARMACOLOGIC THERAPY

- In patients with pelvic floor dysfunction as the major cause of constipation, biofeedback is a behavioral approach that can be used to correct inappropriate contraction of the pelvic floor muscles and external anal sphincter during defecation.
- Manual disimpaction can be a necessary intervention to remove hard stool in the rectal vault; at times this must be done in the operating room (depending on the volume of impacted stool).
- In patients unresponsive to medical therapy and with favorable manometry studies, subtotal colectomy with ileorectal anastomosis may be considered.

ACUTE GENERAL Rx

- Fiber (dietary or supplemental) is the first-line treatment.
- Laxatives, including bulk-forming, osmotic, and stimulant, are the next therapy to utilize.
  1. Bulk-forming laxatives include psyllium, methylcellulose, wheat dextrin, and polycarbophil.
  2. Osmotic laxatives include polyethylene glycol, lactulose, milk of magnesia, and magnesium citrate.
  3. Stimulant laxatives include bisacodyl, senna, and sodium picosulfate.
- Suppositories and/or enemas should be used if oral therapy is ineffective.
- Many agents can be used in combination if no alarm signs are present.
- Bowel preparation in older people is summarized in Table E3.

CHRONIC Rx

- Many of the agents used in acute constipation also have a role in chronic constipation.
- Be wary of the chronic use of stimulant laxatives, as they can cause colonic epithelial dysfunction.
- Less common, but used for chronic constipation, include:
  1. Linaclotide: Guanylate cyclase-c reactor agonist. It stimulates intestinal fluid secretion and transit.
  2. Plecanatide: Guanylate cyclase-c reactor agonist. It stimulates intestinal fluid secretion and transit.
  3. Lubiprostone: Chloride channel activator that enhances chloride-rich intestinal fluid secretion.
  4. Misoprostol: Prostaglandin analog.
  5. Botulinum toxins: In patients with pelvic floor dysfunction with injection into the puborectalis muscle.
  6. Naldemedine: Opioid receptor antagonist useful for opioid-induced constipation.
  7. Prucalopride: Selective 5-HT4 receptor agonist.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Acupuncture can be recommended for chronic idiopathic constipation, but the efficacy of this treatment methodology has not been established.

DISPOSITION

- Constipation can be treated in outpatient clinic settings with dietary modifications, medications, and follow-up visits.

BOX 2 General Approach to Treatment of Constipation

For specific agents, dosages, and precautions, see Table 2.

I. Core Program for All Patients

- Adequate intake of fluid and fiber is one key to preventing constipation. Fiber is available primarily from grains and bran cereals. Flatulence, bloating, and cramps are common side effects encountered when bran fiber is introduced.
- Another source of bulk is from synthetic bulk agents (e.g., psyllium). Bulk agents require an adequate amount of fluid intake; otherwise, they may worsen constipation.
- Avoid irritant laxatives as part of a core program, because long-term use may decrease bowel motility. Encourage the patient to exercise and respond promptly to the urge to defecate.

II. Individualized Program-Specific Indications and General Comments

- *Stimulant laxatives (e.g., senna, bisacodyl):* Many believe that long-term use of these agents leads to dependency and habituation, but this is not substantiated. When used appropriately, these medications are not harmful and are very effective. Senna is probably the first-line choice among this class of laxatives.
- *Osmotic laxatives (e.g., polyethylene glycol [PEG], lactulose, milk of magnesia, magnesium citrate):* These agents are most commonly used for colonic preparation before bowel procedures. These agents are safe and well tolerated. PEG has been shown to be slightly more effective than lactulose and causes less bloating and flatus.
- *Lubricants and stool softeners:* Oral mineral oil lubricants and stool softeners are particularly helpful in patients who have acute painful perianal lesions. The softening and coating of the stool can make passage much easier and less painful, preventing constipation. Mineral oil is contraindicated in patients with swallowing problems or in those who are particularly debilitated, to prevent aspiration leading to lipid pneumonia.
- *Suppositories and enemas:* These agents may be helpful in patients who tend to have trouble expelling soft stool from the rectum. Glycerin suppositories may have a soothing effect and be helpful in patients with constipation caused by local, painful perianal lesions. Tapwater enemas are helpful when disimpaction is necessary.

From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, WB Saunders.

TABLE 2 Preparations Commonly Used in the Symptomatic Treatment of Constipation

Medication	Maximal Recommended Dose	Onset of Action	Comments
Bulk Laxatives			Indigestible fiber attracts water, which leads to larger, softer fecal mass.
Psyllium (Metamucil)	Titrate up to 20 g	12-72 hr	Natural fiber that undergoes bacterial degradation, which may contribute to bloating and flatus. Should be taken with plenty of water to avoid intestinal obstruction.
Methylcellulose (Citrucel)	Titrate up to 20 g		Semisynthetic cellulose fiber that is relatively resistant to colonic bacterial degradation.
Polycarbophil (Fibercon)	Titrate up to 20 g		Synthetic fiber of polymer of acrylic acid, resistant to bacterial degradation.
Osmotic Laxatives			Draw water into the intestines along osmotic gradient.
Magnesium or Sodium Salts			
Magnesium hydroxide (Milk of Magnesia)	30-45 ml once daily	1-6 hr	A small percentage of magnesium is absorbed. Use caution in patients. with renal insufficiency and in children.
Magnesium citrate	150-300 ml as needed	3-6 hr	
Sodium phosphate (Fleet Phospho-soda)	20-45 ml with 12 oz of water as needed		Hyperphosphatemia may result if patient has renal insufficiency. Commonly used before colonoscopy.
Poorly Absorbed Sugars			
Lactulose	15-30 ml once or twice a day	24-48 hr	Synthetic disaccharide not absorbed by the small intestine. Gas and bloating common.
Sorbitol	15-30 ml once or twice a day		Poorly absorbed by small intestine.
Polyethylene glycol and electrolytes (GoLYTELY, MiraLax)	17 g two or three times a day	12-24 hr	Organic polymers that are poorly absorbed and not metabolized by bacteria, thus may cause less bloating and cramping. Can be mixed with noncarbonated beverages.
Stimulant Laxatives			Stimulate intestinal motility or secretion.
Senna (Senokot, Ex-Lax)	8-34 mg daily	6-12 hr	Stimulates secretion and motility of small intestine and colon.
Bisacodyl (Dulcolax, Correctol)	5-10 mg daily		
Stool Softeners			Increase water penetration and soften stool.
Docusate sodium (Colace)	100 mg twice a day; some use higher doses	24-48 hr	In many studies, no better than placebo. Not recommended as first-line or solo therapy.
Mineral oil (Fleet Mineral Oil)	5-15 ml orally at night		Provides lubrication for the passage of stool. Long-term use is not recommended. Lipid pneumonia can occur in patients predisposed to aspiration.
Other Agents			
Lubiprostone (Amitiza)	24 μg once or twice per day	1 hr	A chloride channel activator. FDA-approved for treatment of chronic idiopathic constipation in adults. Adverse effects: Headache, nausea, diarrhea.
Methylnaltrexone (Relistor)	8-12 mg SQ		Used in refractory opioid-induced constipation.
Linaclotide (Linzess)	145 mcg daily 30 min prior to meals	2-6 hr	Peptide agonist of the guanylate cyclase 2C. It increases smooth muscle contractions. Useful in IBS with constipation.
Plecanatide (Trulance)	3 mg once/day	<24 hr	Peptide agonist of the guanylate cyclase 2C. It increases smooth muscle contractions. Useful in IBS with constipation.
Naldemedine (Symproic)	0.2 mg once/day	2 h	Opioid receptor antagonist.

FDA, U.S. Food and Drug Administration; *IBS,* irritable bowel syndrome; *SQ,* subcutaneously.
Modified from Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, WB Saunders.

- Occasionally, constipation must be addressed in the inpatient setting.

REFERRAL

- A referral to a gastroenterologist is not typically necessary for routine cases but is essential for refractory patients or those who may need a colonoscopy, sigmoidoscopy, or manometric studies.
- A referral to a surgeon may be required in patients with large volumes of impacted stool (requiring disimpaction under anesthesia), megacolon, megarectum, or chronic slow transit constipation that is nonresponsive to medical treatment.

PEARLS & CONSIDERATIONS

- The presence of weight loss, rectal bleeding, or anemia with constipation mandates a colonoscopy or flexible sigmoidoscopy.
- A thorough history and physical examination including digital rectal examination is important in diagnosis and cause of constipation.
- History that includes a survey of the patient's diet, medications, and psychosocial issues is key to the successful treatment of constipation.
- Key components in patient education are summarized in Table E4.

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TABLE E3 Bowel Preparation in Older People

- Older age, constipation, reported laxative use, tricyclic antidepressants, stroke, diabetes, and dementia are associated with inadequate preparation and thus takes longer to instrument the cecum.
- Even in those who take 75% to 100% of their prescribed treatment, bowel preparation is satisfactory in only 50%.

Guidance

- Give regular laxatives (e.g., Movicol two sachets daily) and enemas or suppositories for at least 1 wk before the procedure, with a longer run-up period in patients known to have constipation and in those with comorbidities such as diabetes.
- Individualize the cathartic regimen (e.g., 1 to 2 L of GoLYTELY daily over 2 to 3 days in those unable to drink 4 L, or use of alternative preparations such as sodium picosulfate).
- Identify potential nonadherence. ("Can the patient drink 4 L of GoLYTELY in 24 hours?")
- Preempt unpleasant side effects. ("Will the patient be able to reach the toilet in time to avoid fecal leakage?")
- Use oral phospho soda with caution because administration in older people increases serum phosphate, even in patients with normal creatinine clearance.
- Consider preprocedure plain abdominal x-ray for evaluation of persisting fecal loading.
- Where possible, give clear fluid diet before administration of bowel preparation.

Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

TABLE E4 Patient Education

Toilet Habits and Positioning

- Do not delay having a bowel movement when you feel the urge.
- Put aside a particular time each day (we would advise after breakfast) when you can sit on the toilet without being in a hurry.
- A relaxed attitude to bowel evacuation will help, especially if you have problems with straining or a feeling of anal blockage.
- If straining is a problem, place a footstool under your feet while sitting on the toilet because this increases the ability of your abdominal muscles to help evacuation of stool.

Abdominal Massage

- Lie on the bed with pillows under your head and shoulders.
- Bend your knees, and place a pillow underneath them for support.
- Cover your abdomen with a light sheet.
- Massage your abdomen with firm but gentle circular movements, starting at the right side and working across to the left side.
- Continue the massage for about 10 min.
- This massage should be a pleasant experience; if you feel any discomfort, then stop.

Diet

- To help prevent constipation, you should eat more of the food from list A and less of the food from list B. Food in list A tends to make the stool softer and easier to pass because it is high in fiber. Food in list B tends to make the stool harder because it binds together the contents of the bowel.
- List A: Fresh fruit, prunes and other dried fruit, whole meal bread, bran cereals and porridge, salad, cooked vegetables (with skin where possible), beans, lentils.
- List B: Milk, hard cheese, yogurt, white bread or crackers, refined cereals, cakes, pancakes, noodles, white rice, chocolate, creamed soups.
- You should increase your fiber intake gradually because sudden change in fiber content may cause temporary bloating and irregularity. It is important to eat the food that contains fiber all through the day and not just at one meal such as breakfast.
- Increase the amount of fluid that you drink gradually up to 8 to 10 glasses a day. Try to drink more water, fruit juices, and carbonated drinks.

Sphincter Strengthening

Learning to Do Your Exercises

- Sit in a comfortable position with your knees slightly apart. Now imagine that you are trying to stop yourself passing wind from the bowel. To do this, you must squeeze the muscle around the back passage. Try squeezing and lifting that muscle as tightly as you can. You should be able to feel the muscle move. Your buttocks, abdomen, and legs should not move at all. You should be aware of the skin around the back passage tightening and being pulled up and away from your chair. Really try to feel this. You are now exercising your anal sphincter muscles. (You do not need to hold your breath when you tighten the muscles!)

Practicing Your Exercises

- Tighten and pull up the anal sphincter muscles as tightly as you can. Hold tightened for at least 5 seconds and then relax for at least 10 seconds.
- Repeat this exercise at least five times. This will work on the strength of your muscles.
- Next, pull the muscles to about half of their maximum squeeze. See how long you can hold this for. Then relax for at least 10 seconds.
- Repeat at least five times. This will work on the endurance, or staying power, of your muscles.
- Pull up the muscles as quickly and tightly as you can and then relax and then pull up again. See how many times you can do this before you get tired. Try for at least 5 quick pull-ups. Try this quick pull-up exercise at least 10 times each day.
- Do all these exercises as hard as you can and at least five times a day. As the muscles get stronger, you will find that you can do more pull-ups each time without the muscle getting tired.
- It takes time for exercises to make muscle stronger. You may need to exercise regularly for several months before the muscles gain their full strength.

Instructions for Using Suppositories

- These may be inserted into your rectum (back passage) by your nurse or caregiver or yourself if you are physically able to do it.
- If necessary, go to the toilet and empty your bowels if you can.
- Wash your hands.
- Remove any foil or wrapping from the suppository.
- Either lie on your side with your lower leg straight and your upper leg bent toward your waist or squat.
- Gently but firmly insert the suppository, narrow end first, into the rectum using a finger. Push far enough (about 1 inch) so that it does not come out again.
- You may find your body wanting to push out the suppository. Close your legs and keep still for a few minutes.
- Try not to empty your bowels for at least 10 to 20 min.

Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

SUGGESTED READINGS

Bharucha AE et al: American Gastroenterological Association technical review on constipation, *Gastroenterology* 144(1):218-238, 2013, https://doi.org/10.1053/j.gastro.2012.10.028.

Bradsley A: Assessment and treatment options for patients with constipation, *Br J Nurs* 26(6):312-318, 2017.

Mitchell G: Managing constipation in primary care, *Prim Health Care* 24(5):18-22, 2015.

BASIC INFORMATION

DEFINITION

Contact dermatitis is an acute or chronic skin inflammation resulting from exposure to substances in the environment. It can be subdivided into "irritant" contact dermatitis (nonimmunologic physical and chemical alteration of the epidermis) and "allergic" contact dermatitis (delayed hypersensitivity reaction).

SYNONYMS

Irritant contact dermatitis
Allergic contact dermatitis

ICD-10CM CODES

L23	Allergic contact dermatitis
L23.0	Allergic contact dermatitis due to metals
L23.1	Allergic contact dermatitis due to adhesives
L23.2	Allergic contact dermatitis due to cosmetics
L23.3	Allergic contact dermatitis due to drugs in contact with skin
L23.4	Allergic contact dermatitis due to dyes
L23.5	Allergic contact dermatitis due to other chemical products
L25.9	Unspecified contact dermatitis, unspecified cause

EPIDEMIOLOGY & DEMOGRAPHICS

- 20% of all cases of dermatitis in children are caused by allergic contact dermatitis.
- Rhus dermatitis (poison ivy, poison oak, and poison sumac) is responsible for most cases of contact dermatitis.
- Frequent causes of irritant contact dermatitis are soaps, detergents, eye drops (Fig. E1), and organic solvents.
- Chemical irritants (e.g., cutting fluids used in machining, solvents) account for most cases of irritant contact dermatitis. Occupational skin diseases are second only to traumatic injuries as the most common types of occupational disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical presentation varies with the responsible agent and affected area of skin.

IRRITANT CONTACT DERMATITIS:

- Mild exposure may result in dryness, erythema, and fissuring of the affected area (e.g., hand involvement in irritant dermatitis caused by exposure to soap [Fig. E2], genital area involvement in irritant dermatitis caused by prolonged exposure to wet diapers).
- Eczematous inflammation may result from chronic exposure.

ALLERGIC CONTACT DERMATITIS:

- Poison ivy dermatitis can present with vesicles and blisters; linear lesions (as a result of dragging of the resins over the surface of the skin by scratching) are a classic presentation.
- The pattern of lesions is asymmetric; itching, burning, and stinging may be present.
- The involved areas are erythematous, warm to touch, swollen, and may be confused with cellulitis.

ETIOLOGY

- Irritant contact dermatitis: Cement (construction workers), rubber, ragweed, malathion (farmers), orange and lemon peels (chefs, bartenders), hair tints, shampoos (beauticians), rubber gloves (medical, surgical personnel)
- Allergic contact dermatitis: Poison ivy, poison oak, poison sumac, rubber (shoe dermatitis), nickel (jewelry), balsam of Peru (hand and face dermatitis), neomycin, formaldehyde (cosmetics)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Impetigo
- Lichen simplex chronicus
- Atopic dermatitis
- Nummular eczema, dyshidrotic eczema
- Seborrheic dermatitis
- Inverse psoriasis, palmoplantar psoriasis
- Scabies
- Tinea pedis

WORKUP

- Medical history: Gradual onset versus rapid onset, number of exposures, clinical presentation, occupational history.
- Physical examination: Contact dermatitis in the neck may be caused by necklaces, perfumes (Fig. E3), aftershave lotion. Involvement of the axillae is often secondary to deodorants, clothing. Face involvement can occur with cosmetics, airborne allergens, aftershave lotion.

LABORATORY TESTS

- Patch testing has a sensitivity and specificity of 70% to 80%. It is useful to confirm the diagnosis of contact dermatitis; it is indicated only when inflammation persists despite appropriate topical therapy and avoidance of suspected causative agent; patch testing should not be used for irritant contact dermatitis because this is a nonimmunologic-mediated inflammatory reaction.
- Dermoscopy and microscopy when suspecting scabies and mites.
- A potassium hydroxide (KOH) preparation may be useful if suspecting tinea or Candida infection.

TREATMENT

NONPHARMACOLOGIC THERAPY

Avoidance of suspected allergens (e.g., use of plain petrolatum instead of topical antibiotics for clean wounds)

ACUTE GENERAL Rx

- Removal of the irritant substance by washing the skin with plain water or mild soap within 15 min of exposure is helpful in patients with poison ivy, poison oak, or poison sumac dermatitis.
- Cold or cool water compresses for 20 to 30 min 5 to 6 times a day for the initial 72 hr are effective during the acute blistering stage.
- Topical steroids (clobetasol 0.05%, triamcinolone 0.1%) are effective for acute localized allergic contact dermatitis lesions. Lower-potency topical steroids are preferred on face, anogenital regions, and flexural surfaces to minimize risk of skin atrophy. Oral corticosteroids (e.g., prednisone 20 mg bid for 6 to 10 days) are generally reserved for severe, widespread dermatitis.

FIG. E1 Contact dermatitis of the periocular skin. The distribution in this patient is common for the area involved with the use of topically applied eye drops and ointment. (From Adkinson NF et al: *Middleton's allergy principles and practice,* ed 8, Philadelphia, 2014, Saunders.)

FIG. E2 Hand dermatitis from a cleanser. The doctor should always consider allergic contact dermatitis in a patient presenting with an eczematous eruption. The hands are a common site for both allergic and irritant contact dermatitis, because they come into contact with so many things. This patient was allergic to an ingredient in the cleanser used at work. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

FIG. E3 Perfume and medicament allergy. Multiple allergies are often found. This patient developed a reaction first to a perfume and then to a topical medication applied to soothe the initial rash. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

- IM steroids (e.g., Kenalog) are used for severe reactions and in patients requiring oral corticosteroids but unable to tolerate PO.
- Oral antihistamines (e.g., hydroxyzine 25 mg q6h) will control pruritus, especially at night; calamine lotion is also useful for pruritus; however, it can lead to excessive drying.
- Colloidal oatmeal (Aveeno) baths can also provide symptomatic relief.
- Patients with mild to moderate erythema may respond to topical steroid gels or creams.
- Patients with shoe allergy should change their socks at least once a day; use of aluminum chloride hexahydrate in a 20% solution (Drysol) qhs will also help control perspiration.
- Use hypoallergenic surgical gloves in patients with rubber and surgical glove allergy.

DISPOSITION

Allergic contact dermatitis generally resolves within 2 to 4 wk if reexposure to allergen is prevented.

REFERRAL

For patch testing in selected patients, see "Laboratory Tests."

PEARLS & CONSIDERATIONS

COMMENTS

Commercially available corticosteroid dose packs should be avoided, because they generally provide an inadequate amount of medication.

RELATED CONTENT

Contact Dermatitis (Patient Information)
Poison Ivy Dermatitis (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Bonitsis NG et al: Allergens responsible for allergic contact dermatitis among children: a systematic review and meta-analysis, *Contact Dermatitis* 64:245-257, 2011.

Hauksson I et al: Clinically relevant contact allergy to formaldehyde may be missed by testing with formaldehyde 1·0, *Br J Dermatol* 164:568-572, 2011.

Trookman NS et al: Irritation and allergy patch test analysis of topical treatments commonly used in wound care: evaluation on normal and compromised skin, *J Am Acad Dermatol* 64:S16-S22, 2011.

Usatine RP, Riojas M: Diagnosis and management of contact dermatitis, *Am Fam Physician* 82(3):249-255, 2010.

Vives R et al: Leucoderma after Chinese sofa dermatitis, *Contact Dermatitis* 64:58-62, 2011.

BASIC INFORMATION

DEFINITION

Contraception refers to the various modalities that a sexually active couple uses to prevent pregnancy. These options can be either medical or nonmedical and used by men or women or both. There are numerous options, and this chapter should not be considered to be fully comprehensive of every option. The options are as follows:

- No contraception (unprotected intercourse); failure rate 85% both typical use and perfect use
- Abstinence: Failure rate 0%
- Withdrawal: Failure rate with perfect use, 4%; with typical use, 19%
- Rhythm method (natural family planning)
  1. Failure rate with perfect use, 1% to 9%; with typical use, 20%
  2. Lactation amenorrhea method: Effective in fully breastfeeding women, especially 70 to 100 days after delivery; depends on number of feedings per day. Requires exclusive breastfeeding, amenorrhea, and <6 mo postpartum. There is a 0.5% to 2.0% failure rate in the first 6 mo after delivery
- Barriers
  1. Male condom: Failure rate with perfect use, 3%; with typical use, 12%
  2. Female condom: Failure rate with perfect use, 5.1%; with typical use, 12.4%; FDA labeling states 25% failure rate
  3. Diaphragm and cervical cap: Failure rate 5% to 9% in nulliparous women, 20% in multiparous women
  4. Spermicides (aerosols, foam, jellies, creams, tabs): Failure rate with perfect use, 3%; with typical use, 21%
- Oral contraceptives
  1. Failure rate with perfect use, <1%; with typical use, 3%
  2. Come in combinations of estrogen/progestin or as progestin only
  3. Mini pill (progesterone only pill)
     a. Failure rate with typical use, 1.1% to 13.2%
     b. With perfect use, 5 pregnancies per 1000 women
     c. Requires precise timing of daily use for effectiveness
- Hormonal implants and injectables
  1. Nexplanon (etonogestrel) single rod subdermal implant: Failure rate of 0.05%
  2. Depo-Provera: Failure rate 0.3% in first yr of use
  3. Jadelle (levonorgestrel) two rod subdermal implant, not available in the U.S.
- Emergency postcoital contraception
  1. Decreases pregnancy rate by 75% or more with women treated within 72 hrs of coitus
  2. Progestin-only method: 1.5 mg levonorgestrel single dose or 0.75 mg given 12 hrs apart (2.2% pregnancy rate)
  3. Selective progesterone receptor modulator: 30 mg Ulipristal single dose is more effective than levonorgestrel (1.4% pregnancy rate)
  4. Copper IUD: Can be inserted up to 5 days after ovulation and results in the lowest pregnancy rate (0.1%)
- Intrauterine device (IUD)
  1. Copper T (30-A): Failure rate with perfect use, 0.6%; with typical use, 0.8%
  2. Levonorgestrel (LNG-20) IUD (Mirena)
     a) 1-yr failure rate, 0.2%
     b) 5-yr cumulative failure rate, 0.7%
- Female sterilization (tubal ligation): Failure rate with perfect use, 0.2%; with typical use, 3%
- Male sterilization (vasectomy): Failure rate of 0.1% in first yr
- Vaginal ring (NuvaRing): Failure rate pearl index 0.77
- Contraceptive patch (Ortho Evra): Failure rate 0.4% to 0.7%

SYNONYMS

Birth control
Family planning

ICD-10CM CODES

Z30	Encounter for contraceptive management
Z30.0	Encounter for general counseling and advice on contraception
Z30.011	Encounter for initial prescription of contraceptive pills
Z30.012	Encounter for prescription of emergency contraception
Z30.013	Encounter for initial prescription of injectable contraceptive
Z30.014	Encounter for initial prescription of intrauterine contraceptive device
Z30.015	Encounter for initial prescription of vaginal ring hormonal contraceptive
Z30.016	Encounter for initial prescription of transdermal patch hormonal contraceptive device
Z30.017	Encounter for initial prescription of implantable subdermal contraceptive
Z30.018	Encounter for initial prescription of other contraceptives
Z30.09	Encounter for other general counseling and advice on contraception
Z30.2	Encounter for sterilization
Z30.4	Encounter for surveillance of contraceptives
Z30.430	Encounter for insertion of intrauterine contraceptive device

DIAGNOSIS

WORKUP

- To help facilitate method selection for the patient, we recommend obtaining the below information and consulting with CDC Medical Eligibility Criteria.
  1. Thorough medical history
  2. Thorough surgical history
  3. Obstetric history (was fertility desired with conception?)
  4. Gynecologic history, including:
     a. History of previous sexually transmitted diseases
     b. Previous difficulties with contraception
     c. Frequency of intercourse
  5. Family history
- Table E1 summarizes when to start using contraceptive methods.
- Examinations and tests needed before initiation of contraceptive methods described in Table 2.
- Recommendations for routine follow-up after contraceptive initiation summarized in Table E3.

LABORATORY TESTS

- Pap smear should be done as routine and is not required prior to initiation of contraception
- *Chlamydia* and *Gonorrhea* screening when appropriate
- Pregnancy test if suspected pregnancy
- Lipid profile if family history of premature vascular event

TREATMENT

NONPHARMACOLOGIC THERAPY

- Male condoms
  1. 95% latex (rubber), 5% polyurethane, or natural membrane (lamb's intestine does not block transmission of sexually transmitted infections)
  2. Proper use: Place on an erect penis and leave ½-inch empty space at the tip of the condom; use with non–oil-based lubricants
  3. Effectiveness increased when used with spermicides
  4. Main advantage: Condoms are the only method shown to reduce HIV transmission
- Female condoms
  1. Composed of polyurethane, with one end open and one end closed
  2. Proper use: Place closed end over cervix, open end hanging out of vagina to cover penis and scrotum
  3. Highly effective against HIV
- Spermicides
  1. Types: Nonoxynol, octoxynol
  2. Forms: Jellies, creams, foams, suppositories, tablets, soluble films
  3. Proper use: Put in immediately before intercourse; may be used with other barrier methods
- Diaphragm and cervical cap
  1. Must be fitted by practitioner, used with contraceptive gels, and refitted with weight gain or loss of 4.5 kg. Must also be refitted after pregnancy.
  2. Diaphragm sizes: 50 to 105 mm; cervical cap sizes 26, 28, and 30 mm.
  3. The correct fit allows the woman to remain ambulatory without feeling the device.
  4. Proper use of diaphragm: Put in immediately before intercourse and keep in for 6 hr after intercourse; must not remain in the vagina for longer than 24 hr.
  5. Proper use of cervical cap: Fit over the cervix exactly; must not remain in place for longer than 48 hr.
- Lactation amenorrhea method
  1. Requires exclusive breastfeeding, amenorrhea, and within 6 mo postpartum. If patient begins supplementing with

TABLE 2 Examinations and Tests Needed before Initiation of Contraceptive Methods

Examination or Test	Contraceptive Method and Class							
	Cu-IUD and LNG-IUD	Implant	Injectable	CHC	POP	Condom	Diaphragm or Cervical Cap	Spermicide
Examination								
Blood pressure	C	C	C	A*	C	C	C	C
Weight (BMI) (weight [kg]/height [m]^2)	—†	—†	—†	—†	—†	C	C	C
Clinical breast examination	C	C	C	C	C	C	C	C
Bimanual examination and cervical inspection	A	C	C	C	C	C	A‡	C
Laboratory Test								
Glucose	C	C	C	C	C	C	C	C
Lipids	C	C	C	C	C	C	C	C
Liver enzymes	C	C	C	C	C	C	C	C
Hemoglobin	C	C	C	C	C	C	C	C
Thrombogenic mutations	C	C	C	C	C	C	C	C
Cervical cytology (Papanicolaou test)	C	C	C	C	C	C	C	C
STD screening with laboratory tests	—¶	C	C	C	C	C	C	C
HIV screening with laboratory tests	C	C	C	C	C	C	C	C

BMI, Body mass index; *CDC*, Centers for Disease Control and Prevention; *CHC*, combined hormonal contraceptive; *Cu-IUD*, copper-containing intrauterine device; *HIV*, human immunodeficiency virus; *LNG-IUD*, levonorgestrel-releasing intrauterine device; *POP*, progestin-only pill; *STD*, sexually transmitted disease; *U.S. MEC*, U.S. Medical Eligibility Criteria for Contraceptive Use.

*In instances in which blood pressure cannot be measured by a provider, blood pressure measured in other settings can be reported by the woman to her provider.

†Weight (BMI) measurement is not needed to determine medical eligibility for any methods of contraception because all methods can be used (U.S. MEC 1) or generally can be used (U.S. MEC 2) among obese women. However, measuring weight and calculating BMI at baseline might be helpful for monitoring any changes and counseling women who might be concerned about weight change perceived to be associated with their contraceptive method.

‡A bimanual examination (not cervical inspection) is needed for diaphragm fitting.

¶Most women do not require additional STD screening at the time of IUD insertion. If a woman with risk factors for STDs has not been screened for gonorrhea and chlamydia according to CDC's *STD Treatment Guidelines* (www.cdc.gov/std/treatment), screening can be performed at the time of IUD insertion, and insertion should not be delayed. Women with current purulent cervicitis or chlamydial infection or gonococcal infection should not undergo IUD insertion (U.S. MEC 4).

From Curtis KM et al: U.S. selected practice recommendations for contraceptive use, 2016, *MMWR Recomm Rep* 65(4):1-66, 2016.

formula or has any vaginal bleeding, should counsel patient to use backup birth control as she cannot depend on this method of contraception.
2. Not a common practice in the U.S.

- Withdrawal
  1. Withdrawal of the penis from the vagina before ejaculation
  2. Depends on self-control, but there is a high typical use failure rate
- Rhythm method
  1. Symptothermal type: Mucus method and ovulation pain combined with basal body temperature
  2. Ovulation (Billings method): Takes into account mucus quality
  3. Basal body temperature method: Uses biphasic temperature chart
  4. Depends on awareness of physiology of male and female reproductive tracts
     a. Sperm viable in vagina for 2 to 7 days
     b. Ovum lifespan 24 hr
- Sterilization
  1. Male
     a. Vasectomy to interrupt vas deferens and block passage of sperm to seminal ejaculate
     b. Scalpel and nonscalpel techniques available
     c. More easily performed procedure than female sterilization and does not require general anesthesia
  2. Female
     a. Leading method of birth control in U.S. in women older than 30 yr
     b. Interrupts fallopian tubes, blocking passage of ovum proximally and sperm distally through tube
     c. Methods: Bilateral salpingectomy, tubal ligation via removal of segment of fallopian tube, fulguration, application of clips (Filshie, Hulka) or band (Falope Ring)
     d. Essure-tubal occlusion through hysteroscopic placement of micro-inserts into the fallopian tubes. Has been removed from the market

ACUTE GENERAL Rx

- Combination oral contraceptives
  1. Standard administration: Taken daily for 21 days, pill-free interval of 7 days.
  2. Alternative regimen: Extended or continuous administration of active pills.
  3. Less than 50 mcg ethinyl estradiol in most common combination oral contraceptives; progestins most commonly used in combination pills are norethindrone, levonorgestrel, norgestrel, norethindrone acetate, ethynodiol diacetate, norgestimate, or desogestrel.
  4. Triphasic combination oral contraceptives (give varying doses of progestin and estrogens throughout cycle), monophasic oral contraceptives (offer same dose of progestin and estrogen throughout cycle), Estrophasic pill (constant progesterone with variation of estrogen throughout the cycle).
  5. If pill taken with antibiotics, efficacy affected by inadequate gastrointestinal absorption in most cases; only rifampin truly reduces pill's effectiveness.
  6. Increased body weight decreases effectiveness.
  7. Table E4 describes oral contraceptive formulations available in the U.S. Guidelines for use of combination estrogen-progestin contraceptives in women 35 yr of age and older are described in Table E5.
  8. Fig. E1 describes recommended actions after late or missed combined oral contraceptives.
  9. Recommended actions after vomiting or diarrhea while using combined oral contraceptives are described in Fig. E2.
- Mini pill
  1. Progestin only; taken without a break
  2. May cause irregular bleeding because of the lack of estrogen effect on the lining of the uterus
  3. Table E6 provides a summary and recommendations for progestin-only oral contraceptive use
- Hormonal implants and injectables
  1. Nexplanon
     a. Single etonogestrel-secreting device that is inserted underneath the skin
     b. The most effective contraceptive available
     c. Approved by FDA in 2006 and effective over 3-yr period
  2. Depo-Provera
     a. Medroxyprogesterone acetate given every 3 mo in IM injection form
     b. Major side effect: Irregular bleeding

   c. Fertility return possibly delayed up to 1 yr or longer after last injection
   d. Table E7 provides a summary and recommendations for depot medroxyprogesterone acetate (DMPA) use
- Postcoital emergency contraception
  1. Done on emergency basis, usually as a result of noncompliance with birth control or failure of birth control (e.g., condom breakage) at the time of ovulation
  2. Methods:
     a. Hormonal methods:
        (1) Levonorgestrel is available either as two 0.75 mg tablets taken 12 hr apart (next choice) or as a 1.5 mg tablet taken once (Plan B, one step). It is indicated for emergency contraception to be used within 72 hr after unexpected intercourse. It can be obtained OTC by women >15 yr of age and by prescription by younger patients.
        (2) Ulipristal (ELLA) is a progesterone-receptor agonist/antagonist available by prescription only. It is a 30-mg, single-dose tablet and can be taken up to 5 days after unexpected intercourse.
        (3) Copper IUD insertion within 5 days of coitus.
- IUD
  1. Device inserted into uterus to prevent sperm and ovum from uniting in fallopian tube
  2. Types available in the U.S.:
     a. ParaGard (Copper T/30-A): A polyethylene T wrapped with a fine copper wire effective for 10 yr
     b. Mirena Levonorgestrel Intrauterine System: A T-shaped system with a chamber that contains levonorgestrel. Releases 20 mcg/day. Approved for 5 yr
     c. Skyla: Smaller and lowest dose of levonorgestrel. Releases 14 mcg/day. Approved for 3 yr
     d. Liletta: Most similar to Mirena, but less expensive. Releases 18.6 mcg/day. Recently approved for 6 yr
     e. Kyleena: Another 5-yr levonorgestrel system. Releases 19.5 mcg/day
- Vaginal ring (NuvaRing)
  1. Provides daily dose of 120 mcg of etonogestrel and 15 mcg ethinyl estradiol
  2. Stays in vagina 3 wk and is removed the fourth for a contraceptive-free interval analogous to the placebo pills in oral contraceptive pills
  3. Increased body weight decreases effectiveness
  4. Delivers lower total dose of estrogen than the combination oral contraceptive, but may have higher risk of DVT
  5. Recommended actions after delayed insertion or reinsertion with combined vaginal ring are described in Fig. E3
- Contraceptive patch
  1. Releases a progestin and estrogen (ethinyl estradiol)
  2. Each patch contains 6 mg norelgestromin and delivers an estimated continuous systemic dose of 150 mcg norelgestromin and 15 mcg of ethinyl estradiol daily
  3. Worn 3 out of 4 wk
  4. Increased body weight decreases effectiveness
  5. Concern for increased risk of thromboembolic events
  6. Ortha Evra brand discontinued; Xulane (generic) available in the U.S.
  7. Recommended actions after delayed application or detachment with combined hormonal patch are described in Fig. E4

CHRONIC Rx

- With all the previously mentioned types of birth control, patient is followed up at least yearly, or as necessary, if problems arise.
- Full history, physical examination, and Pap test (per guidelines), including cultures when needed, are performed yearly.
- Patients with medical problems are followed up approximately every 6 mo when taking hormonal therapy.

DISPOSITION

- Follow yearly or more frequently according to patient's side effects.
- Tailor birth control to patient according to different needs or side effects present at different times in life. Effective counseling also requires an understanding of a woman's preference and medical risks, benefits, side effects, and contraindications of each contraceptive method.

COMMENTS

- With hormonal contraception, if neurologic or cardiac symptoms arise, stop method immediately, evaluate, and refer to internist when appropriate.
- The effectiveness of long-acting reversible contraception (IUDs and implants) is superior to that of contraceptive pills, patch, or ring and is not altered in adolescents and young women.
- Management of women with bleeding irregularities while using contraception is described in Fig. E5.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Contraception (Patient Information)
Emergency Contraception (Related Key Topic)

AUTHORS: **Anthony Sciscione, DO,** and **Siri M. Holton, MD**

SUGGESTED READINGS

Cristobal I et al: The new LNG-releasing IUS: a new opportunity to reduce the burden of unintended pregnancy, *Eur J Obstet Gynecol Reprod Biol* 58-64, 2015.

Curtis KM, Peipert JF: Long-acting reversible contraception, *N Engl J Med* 376:461-468, 2017.

Sonalkar S, Kapp N: Intrauterine device insertion in the postpartum period: a systematic review, *Eur J Contraception Reprod Health Care* 20(1):4-18, 2015.

Spencer A et al: Helping women choose appropriate hormonal contraception: update on risks, benefits, and indications, *Am J Med* 122:497-506, 2009.

Steinbrook R: Science, politics, and over-the-counter emergency contraception, *J Am Med Assoc* 307:365, 2012.

Winner B et al: Effectiveness of long-acting reversible contraception, *N Engl J Med* 366:1998-2007, 2012.

Woodhams EJ, Gilliam M: In the clinic: contraception, *Ann Intern Med*, 2019.

TABLE E1 When to Start Using Specific Contraceptive Methods

Contraceptive Method	When to Start (if the provider is reasonably certain that the woman is not pregnant)	Additional Contraception (i.e., backup) Needed	Examinations or Tests Needed Before Initiation*
Copper-containing IUD	Anytime	Not needed	Bimanual examination and cervical inspection†
Levonorgestrel-releasing IUD	Anytime	If >7 days after menses started, use backup method or abstain for 7 days.	Bimanual examination and cervical inspection†
Implant	Anytime	If >5 days after menses started, use backup method or abstain for 7 days.	None
Injectable	Anytime	If >7 days after menses started, use backup method or abstain for 7 days.	None
Combined hormonal contraceptive	Anytime	If >5 days after menses started, use backup method or abstain for 7 days.	Blood pressure measurement
Progestin-only pill	Anytime	If >5 days after menses started, use backup method or abstain for 2 days.	None

BMI, Body mass index; *CDC*, Centers for Disease Control and Prevention; *IUD*, intrauterine device; *STD*, sexually transmitted disease; *U.S. MEC*, U.S. Medical Eligibility Criteria for Contraceptive Use.

*Weight (BMI) measurement is not needed to determine medical eligibility for any methods of contraception because all methods can be used (U.S. MEC 1) or generally can be used (U.S. MEC 2) among obese women. However, measuring weight and calculating BMI (weight [kg]/height [m]^2) at baseline might be helpful for monitoring any changes and counseling women who might be concerned about weight change perceived to be associated with their contraceptive method.

†Most women do not require additional STD screening at the time of IUD insertion. If a woman with risk factors for STDs has not been screened for gonorrhea and chlamydia according to CDC's *STD Treatment Guidelines* (www.cdc.gov/std/treatment), screening can be performed at the time of IUD insertion, and insertion should not be delayed. Women with current purulent cervicitis, chlamydial infection or gonococcal infection should not undergo IUD insertion (U.S. MEC 4).

From Curtis KM et al: U.S. selected practice recommendations for contraceptive use, 2016, *MMWR Recomm Rep* 65(4):1-66, 2016.

TABLE E3 Routine Follow-Up after Contraceptive Initiation

	Contraceptive Method				
Action	Cu-IUD or LNG-IUD	Implant	Injectable	CHC	POP
General Follow-Up					
Advise women to return at any time to discuss side effects or other problems or if they want to change the method. Advise women using IUDs, implants, or injectables when the IUD or implant needs to be removed or when a reinjection is needed. No routine follow-up visit is required.	X	X	X	X	X
Other Routine Visits					
Assess the woman's satisfaction with her current method and whether she has any concerns about method use.	X	X	X	X	X
Assess any changes in health status, including medications, that would change the method's appropriateness for safe and effective continued use based on U.S. MEC (i.e., Category 3 and 4 conditions and characteristics).	X	X	X	X	X
Consider performing an examination to check for the presence of IUD strings.	X	—	—	—	—
Consider assessing weight changes and counseling women who are concerned about weight change perceived to be associated with their contraceptive method.	X	X	X	X	X
Measure blood pressure.	—	—	—	X	—

CHC, Combined hormonal contraceptives; *Cu-IUD*, copper-containing intrauterine device; *IUD*, intrauterine device; *LNG-IUD*, levonorgestrel-releasing intrauterine device; *POP*, progestin-only pills; *U.S. MEC*, U.S. Medical Eligibility Criteria for Contraceptive Use.

TABLE E4 Oral Contraceptive Formulations Available in the U.S.

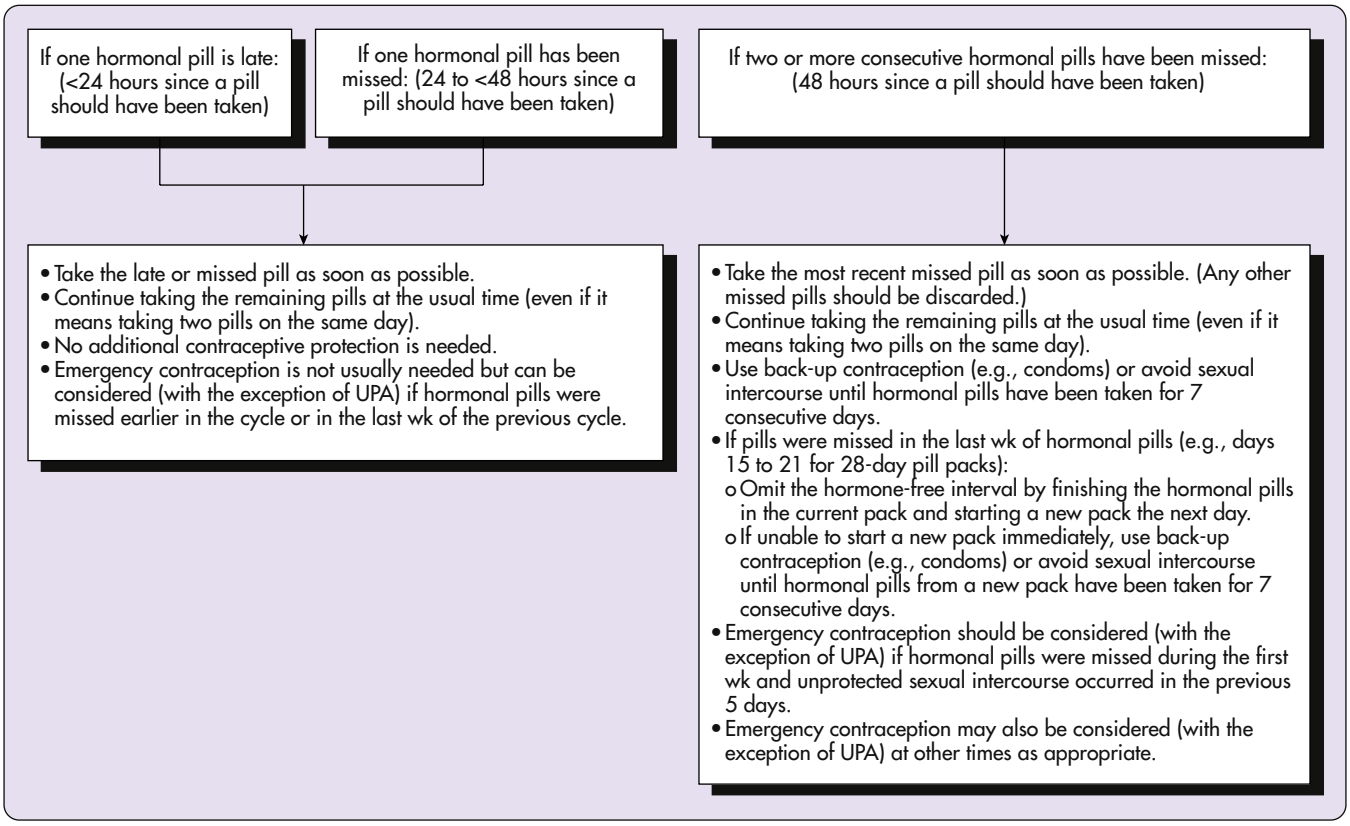
	Name	Estrogen	Progestin	Progestin Dose (mg)
EE, 50 μg monophasic	Ovcon 50*	EE	Norethindrone	1.0
	Ortho-Novum 1/50*	Mestranol	Norethindrone	1.0
	Norinyl 1 + 50*	Mestranol	Norethindrone	1.0
EE, 35 μg monophasic	Femcon Fe†	EE	Norethindrone	0.4
	Modicon*	EE	Norethindrone	0.5
	Brevicon*	EE	Norethindrone	0.5
	Ovcon 35*	EE	Norethindrone	0.4
	Ortho-Cyclen*	EE	Norgestimate	0.25
	Demulen 1/35*	EE	Ethynodiol diacetate	1.0
	Ortho-Novum 1/35*	EE	Norethindrone	1.0
	Norinyl 1 + 35*	EE	Norethindrone	1.0
EE, 35 μg biphasic	Ortho-Novum 10/11*	EE	Norethindrone	0.5/1.0
EE, 35 μg triphasic	Ortho-Novum 7/7/7*	EE	Norethindrone	0.5/0.75/1.0
	Ortho Tri-Cyclen*,‡	EE	Norgestimate	0.18/0.215/0.25
	Tri-Norinyl*	EE	Norethindrone	0.5/1.0/0.5
	Estrostep*,‡	EE (20/30/35)	Norethindrone acetate	1.0
EE, 30 μg monophasic	Loestrin 1.5/30*	EE	Norethindrone acetate	1.5
	Ortho-Cept*	EE	Desogestrel	0.15
	Desogen*	EE	Desogestrel	0.15
	Lo-Ovral*	EE	Norgestrel	0.3
	Nordette*	EE	Levonorgestrel	0.15
	Levlen*	EE	Levonorgestrel	0.15
	Yasmin*	EE	Drospirenone	3.0
EE, 30 μg triphasic	Triphasil*	EE (30/40/30)	Levonorgestrel	0.05/0.075/0.125
	Tri-Levlen*	EE (30/40/30)	Levonorgestrel	0.05/0.075/0.125
Extended cycle (84 active tablets)	Seasonale*	EE	Levonorgestrel	0.150
Extended cycle (84 estrogen/progestin tablets, 7 tablets 10 μg EE)	Seasonique	EE	Levonorgestrel	0.150
EE, 25 μg	Cyclessa*	EE	Desogestrel	0.10/0.125/0.150
	Ortho Tri-Cyclen Lo	EE	Norgestimate	0.18/0.215/0.25
EE, 20 μg monophasic	Loestrin 1/20*	EE	Norethindrone acetate	1.0
	Levlite*	EE	Levonorgestrel	0.1
	Alesse*	EE	Levonorgestrel	0.1
21 Hormonally active tablets (2 inert tablets, 5 tablets 10 μg EE)	Mircette*	EE	Desogestrel	0.15
24 Hormonally active tablets	Yaz	EE	Drosperinone	3.0
	Loestrin 24Fe	EE	Norethindrone acetate	1.0
Extended cycle (84 estrogen/progestin tablets, 7 tablets 10 μg EE)	LoSeasonique	EE	Levonorgestrel	0.1
28 Hormonally active tablets	Lybrel	EE	Levonorgestrel	0.09
Progestin-only	Micronor*		Norethindrone	0.35

*Generic versions available.
†Chewable tablets.
‡Indicated for the treatment of acne in women desiring to use oral contraception.
EE, Ethinyl estradiol.
From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders, Elsevier.

TABLE E5 World Health Organization (WHO) and American College of Obstetrics and Gynecology (ACOG) Guidelines Regarding Use of Combination Estrogen-Progestin Contraceptives (Oral Contraception, Ring, and Patch) in Women 35 Yr of Age and Older

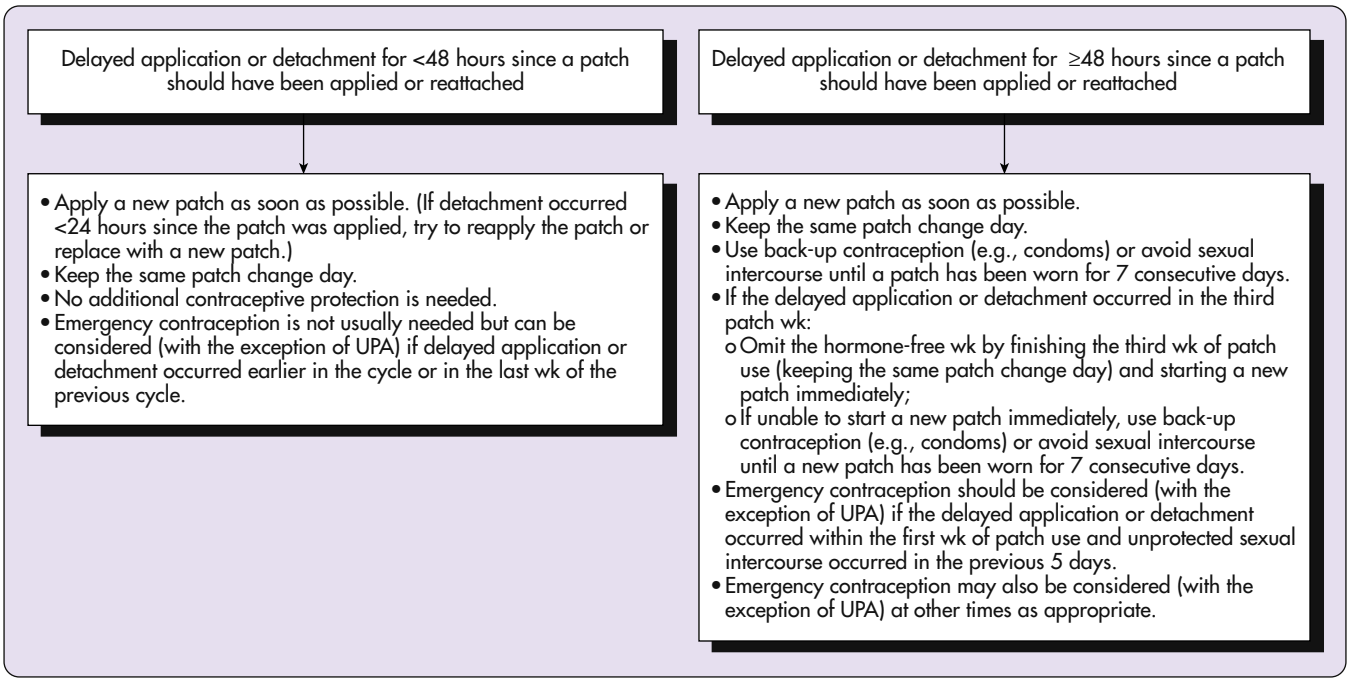
Variable	ACOG Guidelines	WHO Guidelines
Obesity	Progestin-only or intrauterine contraception* may be safer	Benefit usually outweighs risks†
Smoker	Progestin-only or intrauterine contraception* should be used	Risk unacceptable
Hypertension	Progestin-only or intrauterine contraception* should be used	Risk unacceptable
Diabetes	Progestin-only or intrauterine contraception* should be used	Risk unacceptable
Migraine	Progestin-only or intrauterine contraception* should be used	Risk unacceptable
None of the above risk factors	Healthy, nonsmoking women doing well on a combination contraceptive can continue their method until age 50-55 yr after weighing the risks and benefits.	For women ≥40 yr of age, the risk of cardiovascular disease increases with age and also may increase with use of combined hormonal contraceptives. In the absence of other adverse clinical conditions, combined hormonal contraceptives may be used until menopause.

*Generic versions available.
†Chewable tablets.
EE, Ethinyl estradiol.
From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders, Elsevier.



Abbreviation: UPA = ulipristal acetate.

FIG. E1 Recommended actions after late or missed combined oral contraceptives. (From Curtis KM et al: U.S. selected practice recommendations for contraceptive use, 2016, *MMWR Recomm Rep* 65(4):1-66, 2016.)



Abbreviation: UPA = ulipristal acetate.
*If detachment takes place but the woman is unsure when the detachment occurred, consider the patch to have been detached for ≥48 hours since a patch should have been applied or reattached.

FIG. E2 Recommended actions after delayed application or detachment* with combined hormonal patch. (From Curtis KM et al: U.S. selected practice recommendations for contraceptive use, 2016, *MMWR Recomm Rep* 65(4):1-66, 2016.)

TABLE E6 Summary and Recommendations for Progestin-Only Oral Contraceptive Use

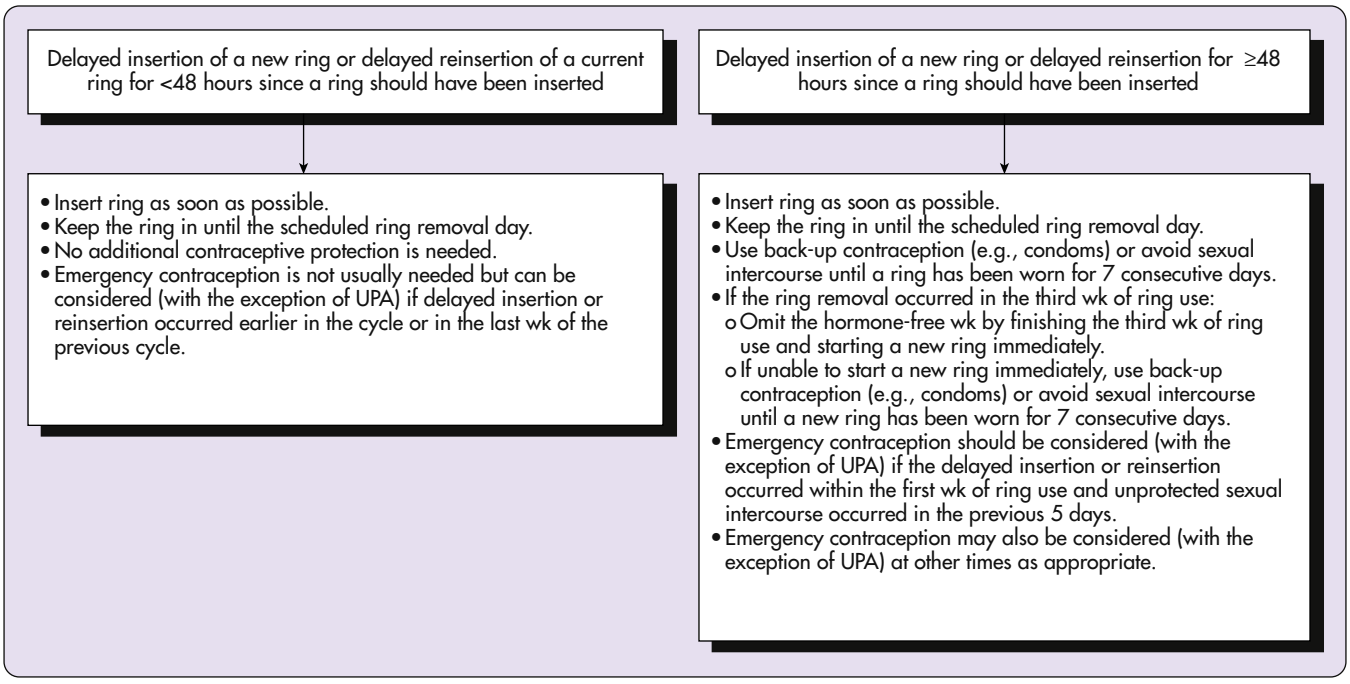
1. Progestin-only contraception is an option for women in whom an estrogen-containing contraceptive is either contraindicated or causes additional health concerns.
2. Ovulation is not consistently suppressed; the main contraceptive actions of progestin-only oral contraception are effects on cervical mucus and the endometrium.
3. The typical user failure rate with progestin-only oral contraception is estimated to be >8%. Women choosing progestin-only oral contraception are often subfertile as a result of breastfeeding or older reproductive age, so the failure rate in these populations may be lower than that in more fertile populations.
4. It is essential that the pill be taken at the same time each day to maximize contraceptive efficacy.
5. Menstrual irregularities are common in users of progestin-only oral contraception and represent the most frequent cause for contraceptive discontinuation.

From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders, Elsevier.

TABLE E7 Summary and Recommendations for Depot Medroxyprogesterone Acetate (DMPA) Use

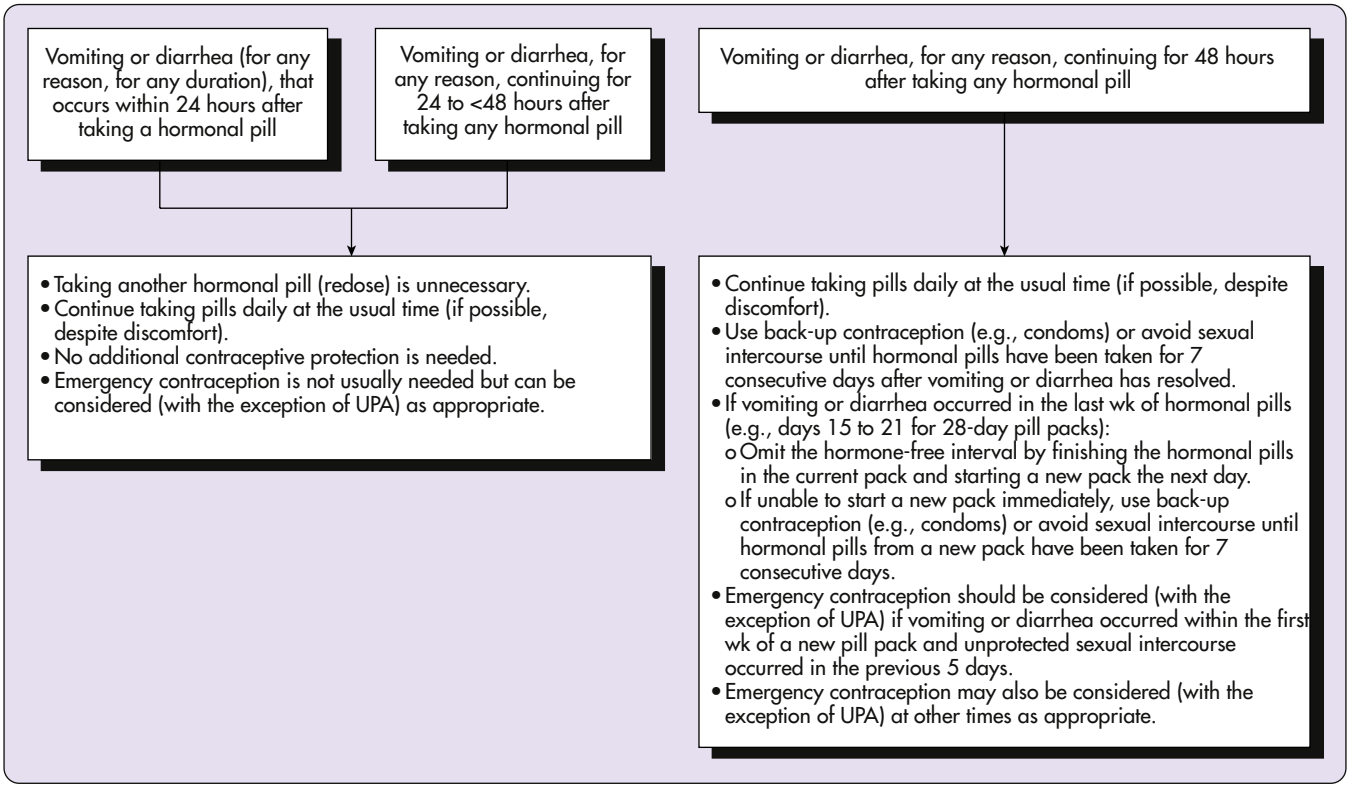
1. DMPA is an excellent method for women who desire a long-term, reversible contraceptive.
2. DMPA primarily acts by inhibiting follicular maturation and ovulation through inhibition of gonadotropin secretion. It also affects cervical mucus.
3. DMPA is available in two formulations: 150 mg/1 ml for IM injection and 104 mg/0.65 ml for SC injection.
4. The ideal time to initiate DMPA is within 5 days of the onset of menses to ensure absence of pregnancy. The dose is repeated every 3 mo, with a 2-wk grace period.
5. Although DMPA does not permanently affect endocrine function, return of fertility may be delayed.
6. Thorough, candid counseling about side effects is important. Women who are well informed when they choose this method of contraception are much more likely to become highly satisfied users with high continuation rates.
7. Menstrual changes occur in all women using DMPA and are the most frequent cause for discontinuation.
8. Because DMPA induces amenorrhea, it can be used for managing a variety of gynecologic and nongynecologic disorders such as menorrhagia, dysmenorrhea, and iron-deficiency anemia.
9. There is no high-quality evidence that use of DMPA increases the risk of developing cancer, cardiovascular disease, or sexually transmitted infection. DMPA use significantly reduces the risk of developing endometrial cancer.
10. There is an association between current DMPA use and decreased bone mineral density; losses in bone mineral density are temporary, reverse after discontinuation of DMPA, and have not been linked to postmenopausal osteoporosis or fractures.

IM, Intramuscular; SC, subcutaneous.
From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders, Elsevier.



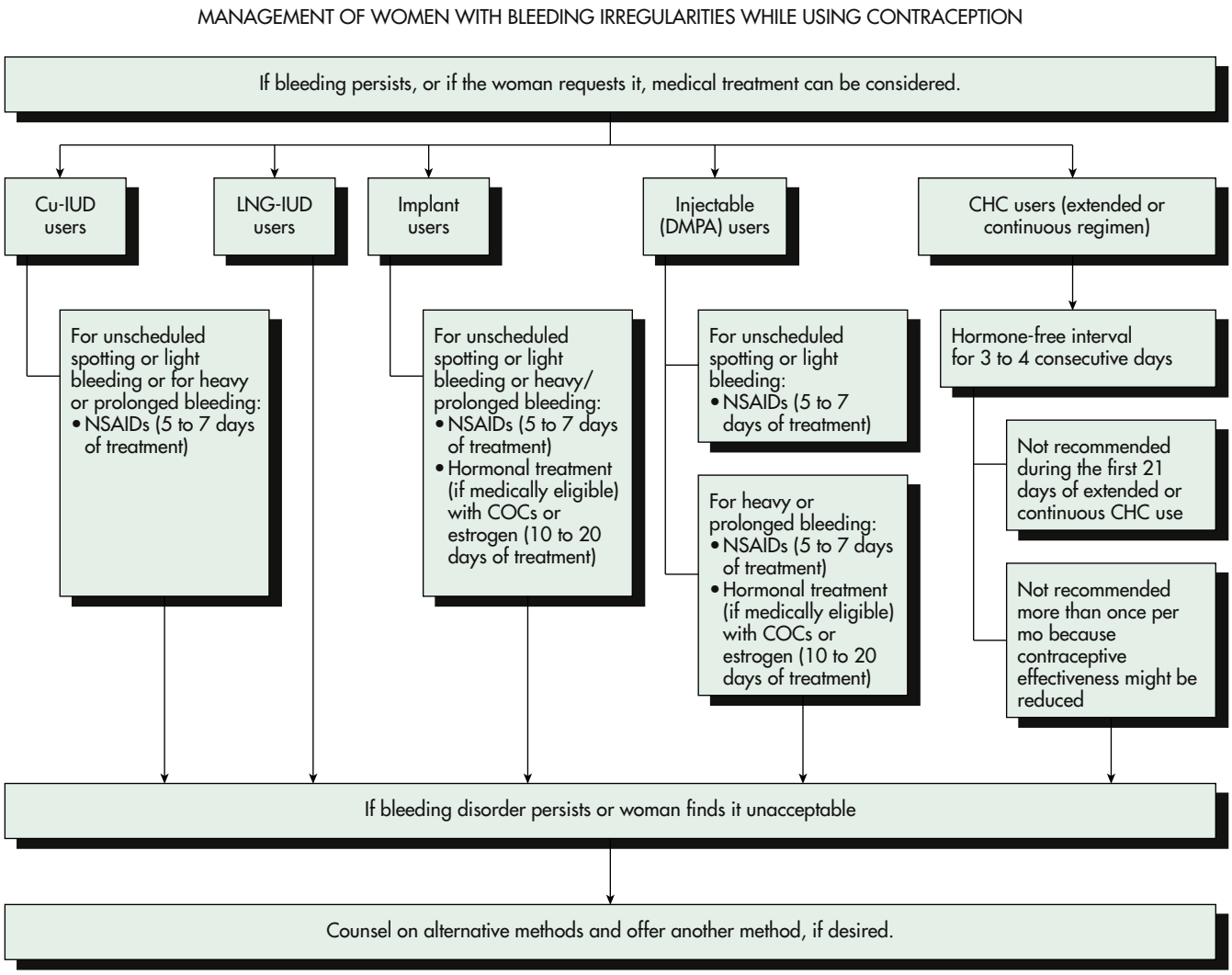
Abbreviation: UPA = ulipristal acetate.
*If removal takes place but the woman is unsure of how long the ring has been removed, consider the ring to have been removed for ≥48 hours since a ring should have been inserted or reinserted.

FIG. E3 Recommended actions after delayed insertion or reinsertion* with combined vaginal ring. (From Curtis KM et al: U.S. selected practice recommendations for contraceptive use, 2016, *MMWR Recomm Rep* 65(4):1-66, 2016.)



Abbreviation: UPA = ulipristal acetate.

FIG. E4 Recommended actions after vomiting or diarrhea while using combined oral contraceptives. (From Curtis KM et al: U.S. selected practice recommendations for contraceptive use, 2016, *MMWR Recomm Rep* 65(4):1-66, 2016.)



Abbreviations: CHC = combined hormonal contraceptive; COC = combined oral contraceptive; Cu-IUD = copper-containing intrauterine device; DMPA = depot medroxyprogesterone acetate; LNG-IUD = levonorgestrel-releasing intrauterine device; NSAIDs = nonsteroidal antiinflammatory drugs.
*If clinically warranted, evaluate for underlying condition. Treat the condition or refer for care. Heavy or prolonged bleeding, either unscheduled or menstrual, is uncommon among LNG-IUD users and implant users.

FIG. E5 Management of women with bleeding irregularities while using contraception. (From Curtis KM et al: U.S. selected practice recommendations for contraceptive use, 2016, *MMWR Recomm Rep* 65(4):1-66, 2016.)

BASIC INFORMATION

DEFINITION

An increase of serum creatinine of >0.5 mg/dl or >25% from baseline that occurs within 48 hours after iodinated contrast media administration (Table E1).

SYNONYMS

Contrast-induced nephropathy (CIN)
Contrast nephropathy
Radiocontrast-induced nephropathy (RCIN)
Contrast-induced acute kidney injury (CA-AKI)

ICD-10CM CODE

N14.1 Nephropathy induced by other drugs, medicaments, and biological substances

EPIDEMIOLOGY & DEMOGRAPHICS

NOMENCLATURE: The term contrast-induced acute kidney injury (CI-AKI), formerly called contrast-induced nephropathy (CIN), implies that contrast medium is the sole etiologic factor of AKI during circumstances of contrast administration. However, frequently, multiple potential etiologic factors are present. The term CI-AKI should only be used when contrast medium administration is the sole putative risk factor for development of AKI. Thus, the term, contrast-associated AKI (CA-AKI) is more appropriate in the majority of cases of AKI that transpire in the context of contrast media administration. Therefore, CI-AKI is a subset of CA-AKI, which encompasses any AKI occurring with 48 hours of contrast media administration.

Low osmolar contrast media (LOCM) are hyperosmolar (~600 mOsm/kg H_2O) relative to isosmolar contrast media (IOCM; ~290 mOsm/kg) and serum (~285 to 295 mOsm/kg). The dimeric structure of IOCM renders them more viscous than LOCM. The majority of contemporary iodinated contrast media are categorized as LOCM. High osmolar iodinated contrast media (HOCM) have higher osmolalities than LOCM and IOCM. HOCM have been replaced by LOCM and IOCM for intravenous administration in modern clinical practice.

INCIDENCE: The overall incidence of CA-AKI has been reported to be approximately 7%, and 11% of acquired AKI cases during hospitalization have been attributed to CA-AKI. However, recent retrospective studies using statistical techniques to minimize confounding factors suggest that CA-AKI incidence has been greatly overestimated. The following opinions and recommendations apply to intravenous (IV), e.g., contrast-enhanced CT, versus intraarterial (e.g., coronary artery angiography) contrast media administration. The latter has unique considerations that do not apply to IV contrast media administration (e.g., requirement for arterial access, atheroembolic complications, and population-specific AKI risk factors).

PEAK INCIDENCE: Incidence rates of CA-AKI vary widely in the literature—a result of discrepancies in type and dose of contrast media used, reason for the imaging study, and definitions of CA-AKI. In one risk prediction model of CA-AKI, 24% of patients in the highest-risk decile undergoing percutaneous coronary intervention (PCI) developed CA-AKI. In another large, retrospective study using propensity-matched controls, no increased risk of acute kidney injury was seen in patients receiving CT with IV contrast compared with those not receiving CT.

SEX AND AGE: Current controversies surrounding the true incidence of CA-AKI call into question the relationship of age to CA-AKI risk. Incidence of CA-AKI appears to increase with age, but age may in fact be simply a risk factor for other causes of AKI that occur in patients receiving contrast media, in particular, declining glomerular filtration rate (GFR). There is no sex predilection for CA-AKI.

RISK FACTORS: Patient-related factors include chronic kidney disease (CKD) with estimated GFR <30 ml/min per 1.73 m^2 (CKD stage 4 or greater), age >75 yr, diabetes mellitus when CKD is present, albuminuria, nonnormovolemic states such as heart failure and volume depletion, and hemodynamic instability. Non–patient-related factors include contrast osmolality, exposure to ionic contrast (rarely used), total contrast dose, sequential contrast doses, concomitant exposure to nephrotoxic agents, and requirement for an intraaortic balloon pump. Although initially thought to enhance risk for CA-AKI, it is unclear if intraarterial contrast administration (e.g., cardiac catheterization) is riskier than IV contrast (e.g., CT). Inpatients have a higher risk of developing CA-AKI than outpatients (Box E1).

TABLE E1 Classification of Iodinated Contrast Media

Chemical Property	Relative Osmolality	Contrast Agent	Osmolality (mOsm/kg H2O)
Ionic	High osmolality	Diatrizoate	1500-1860
		Ioxithalamate	
		Ioxithalamate	
Ionic	Low osmolality	Ioxaglate	600
Nonionic	Low osmolality	Iobitridol	521-695
		Iohexol	
		Iomeprol	
		Iopamidol	
		Iopromide	
		Ioversol	
Nonionic	Isoosmolal	Ioxaglate	270-320
		Iotrolan	
		Iodixanol	

Adapted from Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, WB Saunders.

BOX E1 Recommendations to Reduce the Risk of Contrast-Induced Nephropathy

1. Identify patients at risk for CA-AKI.
2. Assess the risk-to-benefit ratio of the proposed contrast medium-requiring intervention. Consider alternatives to procedures or imaging that requires iodinated contrast. Do not withhold IV contrast in emergent situations where administration of contrast is necessary for optimal patient care, i.e., risk-to-benefit ratio is justifiable.
3. Assess kidney function by estimated glomerular filtration rate (eGFR) or calculated creatinine clearance before contrast, especially in patients at risk for CA-AKI.
4. Modify correctable risk factors and withhold medications that may increase risk of nephrotoxicity, i.e., withhold nonsteroidal antiinflammatory agents.
5. Use the lowest dose of appropriate contrast medium.
6. In high-risk patients, correct hypovolemia. Stop diuretics and consider IV fluid if no contraindication exists. Heart failure patients should not have diuretics withheld or stopped, unless overdiuresed and volume depleted.
7. Intravenous, isotonic fluid expansion with either 0.9% saline or isotonic sodium bicarbonate solution (150 mM). The optimal fluid type and quantity have not been definitively determined. Volume expansion generally begins 1 hour precontrast administration and continues for 3 to 12 hours postcontrast delivery. Typical regimens are fixed volumes (e.g., 500 ml before and after) or weight-based (1–3 ml/kg/hr). Longer regimens (~12 hours) have been shown to lower the risk of CA-AKI compared to shorter regimens. The patient should be monitored for signs and symptoms of hypervolemia or pulmonary edema.
8. *N*-acetylcysteine prophylaxis is not recommended.
9. Prophylactic hemodialysis or hemofiltration is not recommended.

IV, Intravenous.
Adapted from Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, WB Saunders.

Contrast-Associated Acute Kidney Injury (CA-AKI) ALG

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Elevation in serum creatinine generally occurs 24 to 48 hours after administration of contrast. Typically, there are no accompanying symptoms or exam findings. Acute kidney injury usually resolves within 10 days of radiocontrast exposure. Less than 1% of patients with CA-AKI will require dialysis, typically patients with a history of advanced kidney disease.

ETIOLOGY

- Nephrotoxicity occurs due to renal medullary ischemia, a result of vasoconstrictive effects of the contrast medium on the large and small renal arteries.
- Contrast also exerts a direct cytotoxic effect on the vascular endothelium and renal tubular cells, leading to cell injury and death due to generation of damaging reactive oxygen species.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Acute tubular injury (ATI), atheroembolic renal disease (i.e., postcardiac catheterization), acute interstitial nephritis, prerenal azotemia

WORKUP

- Diagnosis is dependent primarily on history and laboratory values. A search for clinical findings more suggestive of other etiologies of AKI should be conducted (e.g., livedo reticularis or dusky lower-extremity digits in the presence of atheroembolic disease, evidence of systemic infection accompanied by hypotension in the case of sepsis-mediated ATI).
- Urinalysis often reveals a fractional excretion of sodium (FE_{Na}) of <1% despite ATI. A high urine specific gravity may reflect the filtration of hyperosmolar contrast medium. Markers of renal tubular damage including muddy brown granular casts or renal epithelial cells may be seen on urinalysis.
- A kidney biopsy is not recommended for diagnostic confirmation, since biopsy findings are nonspecific for acute tubular injury. If the course of AKI is atypical, a biopsy may be useful to examine for atheroembolic disease or acute interstitial nephritis.

LABORATORY TESTS

- Serum creatinine, urinalysis, and urine microscopy
- Urine and serum sodium and creatinine concentrations for determination of FE_{Na}

IMAGING STUDIES

No radiologic tests aid in the diagnosis of CA-AKI. A renal ultrasound should be obtained if postrenal obstruction is in the differential diagnosis.

Rx TREATMENT

Treatment for CA-AKI is supportive. An algorithm for the prevention and management of CI-AKI is illustrated in Fig. E1. Prevention has been the focus of research efforts.

Recommended strategies for CA-AKI prophylaxis:

- Avoidance of studies and procedures using IV contrast, if not emergent. Consider an alternative imaging modality, if available, for patients at high risk for development of CIN.
- Use low-osmolar nonionic contrast media.
- Minimize contrast volume (dose).
- Volume expansion with IV isotonic fluid. Normal saline (0.9% saline) and sodium bicarbonate solutions are both effective in reducing the risk of CA-AKI.

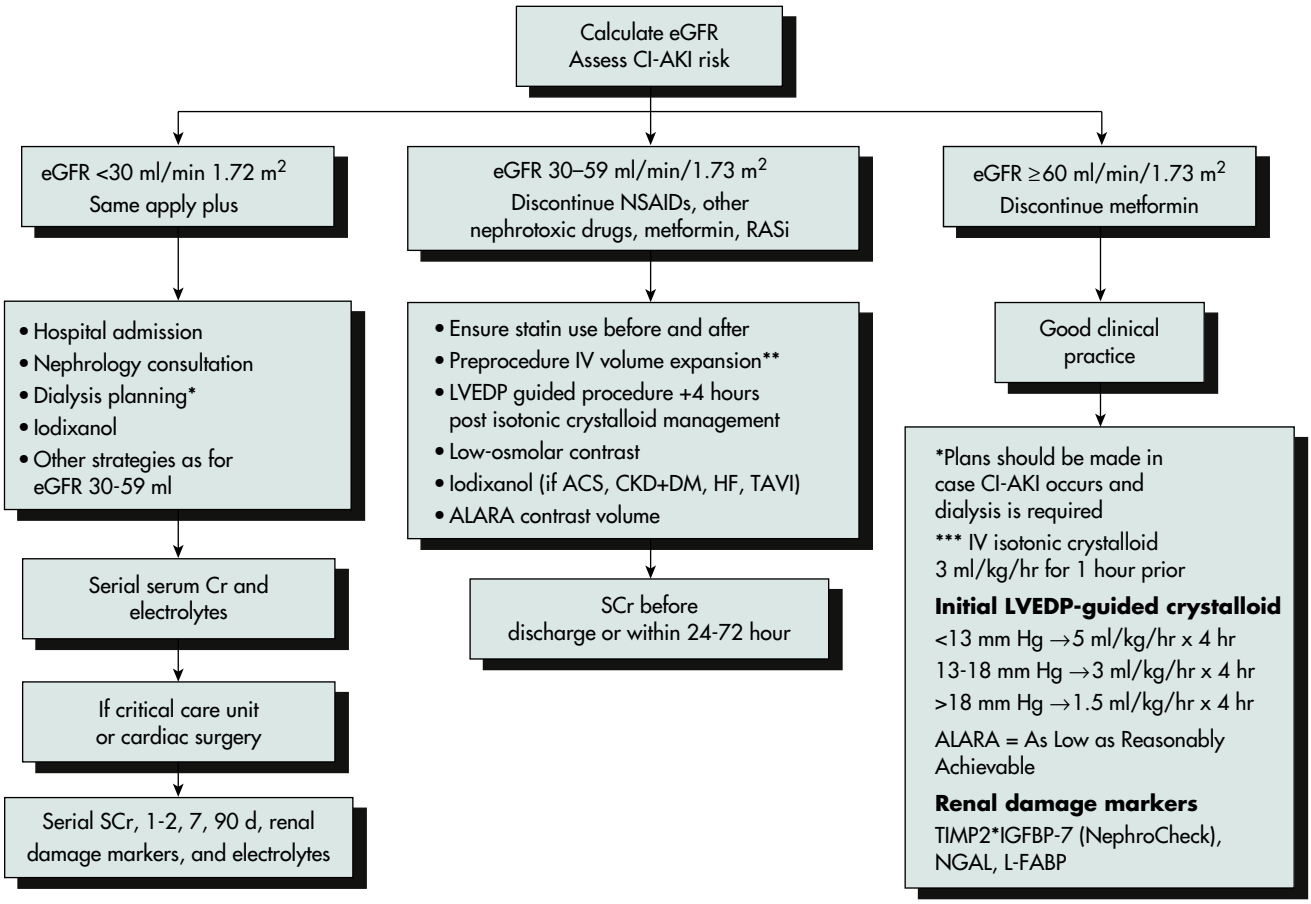


FIG. E1 Algorithm for the prevention and management of contrast-induced acute kidney injury. *ACS,* Acute coronary syndromes; *ALARA,* as low as reasonably achievable; *CI-AKI,* contrast-induced acute kidney injury; *CKD,* chronic kidney disease; *DM,* diabetes mellitus; *eGFR,* estimated glomerular filtration rate; *HF,* heart failure; *IV,* intravenous; *L-FABP,* L-type fatty-acid binding protein; *LVEDP,* left ventricular end-diastolic pressure; *NGAL,* neutrophil-associated lipocalin; *NSAIDs,* nonsteroidal antiinflammatory drugs; *RASi,* renin angiotensin system inhibitors; *SCr,* serum creatinine; *TAVI,* transcatheter aortic valve insertion; *TIMP2*IGFBP-7,* tissue inhibitor of metalloproteinase-2 concentration multiplied by insulin-like growth factor binding protein-7 concentration. (Ronco C et al: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.)

Preventive measures for CA-AKI that have *not* shown significant benefit include:

- Oral hydration solutions
- Prophylactic hemodialysis or hemofiltration
- Diuresis from diuretic medications or by osmotic diuretics (e.g., mannitol)
- Vasodilators (e.g., fenoldopam, nifedipine, theophylline)
- Ascorbic acid
- *N*-acetylcysteine

GENERAL PROPHYLAXIS: INTRAVENOUS HYDRATION

- Outpatients with glomerular filtration rate (GFR) <60 ml/min: Withhold medications that reduce GFR, e.g., nonsteroidal antiinflammatory drugs and, possibly, diuretics. An outpatient hydration protocol with either 0.9% saline or sodium bicarbonate may be considered, particularly with eGFRs <45 ml/min per 1.73 m^2. Outpatient hydration protocols have not been rigorously evaluated. Sodium bicarbonate infused at 3 ml/kg per hr for 1 hour preprocedure and 1.5 mg/kg per hour 4 to 6 hours intra- and postprocedure can be performed in the outpatient setting.
- Inpatients with eGFRs <60 ml/min per 1.73 m^2: IV 0.9% saline or D_5W with 150 mM sodium bicarbonate at 1 ml/kg per hr for 6 to 12 hours preprocedure, during the procedure, and 6 to 12 hours postprocedure. With contraindications to IV fluid administration (e.g., congestive heart failure with pulmonary edema), consider postponement of studies involving contrast media, if not emergently indicated. If the procedure is unavoidable, fluid management should be tailored to the individual patient.

DISPOSITION

CA-AKI is usually self-limited. Patients with severe renal functional impairment may require hospitalization for supportive care and potential dialysis.

REFERRAL

- Patients at high risk for CA-AKI or who develop significant CA-AKI should be referred to nephrology.

PEARLS & CONSIDERATIONS

- Although there has been agreement that iodinated contrast dye has nephrotoxic effects, the true incidence of CA-AKI has been reconsidered due to the findings of several recent studies showing that IV contrast administration does not increase the risk of AKI in patients with other reasons for development of AKI. There is concern that potentially beneficial diagnostic contrast media-imaging studies or procedures are being withheld due to fears of developing CA-AKI.
- A diagnosis of CA-AKI can be considered in patients who develop AKI 24 to 72 hours after contrast exposure. Urine sediment may be bland or show signs of tubular injury. The FE_{Na} may be <1% due to altered renal hemodynamics.
- Administration of isotonic IV fluids is appropriate for CKD patients with eGFRs <30 ml/min per 1.73 m^2 or who are otherwise at high risk for CA-AKI.
- Nonsteroidal antiinflammatory drugs and other potential nephrotoxic drugs should be avoided in patients receiving IV contrast media. Metformin does not predispose to CA-AKI, but should be discontinued if AKI occurs. There is no evidence-based guidance regarding continuation or withdrawal of ACEIs or ARBs before contrast administration. Clinical judgment is warranted.
- Diabetic patients should have metformin held before receiving IV contrast due to an increased risk of metformin-related lactic acidosis in the setting of CA-AKI.

RELATED CONTENT

Acute Kidney Injury (Related Key Topic)

AUTHORS: **Jerry Yee, MD,** and **Mark Perazella, MD**

SUGGESTED READINGS

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Windpessl M, Kronbichler A: Pro: contrast-induced nephropathy—should we try to avoid contrast media in patients with chronic kidney disease? *Nephrol Dial Transplant* 33:1317-1319, 2018.

Conversion Disorder (Functional Neurologic Symptom Disorder) PTG ALG

BASIC INFORMATION

DEFINITION

Conversion disorder (functional neurologic symptom disorder) presents with symptoms that affect voluntary motor or sensory function or that cause a transient loss of consciousness. Symptoms might include paralysis, blindness, numbness, or the inability to speak. Symptoms can be sporadic, sustained, acute, or chronic. The symptoms, after medical assessment, cannot be explained by a medical condition, direct effects of a substance, or a culturally sanctioned behavior or experience.

Diagnostic features provide evidence of internal inconsistency or incongruity with recognized features of neurological or medical disorders. The symptoms cause clinically significant distress and/or impairment in social, occupational, and other important areas of functioning and warrant medical evaluation. Oftentimes, there is a relevant psychological stressor present, although this is not required to establish the diagnosis. Functional symptoms are not voluntarily produced and are presumed to be unconsciously elaborated.

There is no well-validated physiologic model for conversion disorder, but advances in neuroscience and neuroimaging may reveal new etiologies. A patient found to have conversion disorder should be periodically reevaluated for any medical etiology that has been slow to present or that may be newly diagnosable with advances in medical knowledge and technology.

SYNONYMS

Psychogenic nonepileptic seizure
Psychogenic movement disorder
Hysterical neurosis (historical)
Functional neurologic symptom disorder

ICD-10CM CODES

F44.4	Conversion disorder with motor symptom or deficit
F44.5	Conversion disorder with seizures or convulsions
F44.6	Conversion disorder with sensory symptom or deficit
F44.7	Conversion disorder with mixed symptom presentation
F44.89	Other dissociative and conversion disorders
F44.9	Dissociative and conversion disorder, unspecified

DSM-5 CODE

300.11 Conversion disorder

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence ~5 to 10/100,000 in general population and 20 to 100/100,000 in hospital inpatients
- All ages, including early childhood, but rare in children younger than 10 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presents with one or more motor symptoms (e.g., paralysis, aphonia, difficulty swallowing), sensory symptoms (loss of sensation, double vision, blindness, deafness), or a nonepileptic seizure, or a combination of these symptoms.
- Physical exam findings that are not consistent with anatomical pathways or physiologic mechanisms, such as Hoover sign (weakness of hip extension returns to normal strength with contralateral hip flexion against resistance), weakness of plantar flexion on the exam table in an individual able to walk on tiptoes, positive tremor entrainment test, normal EEG or closed eyes with resistance to opening during nonepileptic seizure, or tubular vision. Features that suggest nonepileptic (conversion) seizures are summarized in Table E1.
- The symptoms or signs persist whether the patient is observed or unobserved, though are typically worse when the patient is attentive to them.
- May occur in the context of documented medical illness (e.g., a patient with epileptic seizure may also have psychogenic seizure).
- May have comorbid axis I or axis II disorders, commonly depression; generalized anxiety; posttraumatic stress disorder (PTSD); or borderline, histrionic, or narcissistic personality disorder.

ETIOLOGY

- Complex interplay of neurologic and psychological factors is not well understood.
- The classic psychodynamic hypothesis is that the conversion symptom is preceded by psychological conflict or stressor and functions to express and manage the psychological distress—that is, "convert" the distress into a neurologic symptom.
- A neurobiologic hypothesis suggests an abnormality in neural networks, possibly triggered by emotional stress. Brain imaging studies suggest alterations in processing of sensory and motor signals.
- Associated with psychiatric comorbidities, most commonly depression, anxiety, PTSD, and personality disorders (most commonly histrionic, borderline, or narcissistic).
- Associated with trauma, interpersonal conflicts, and other life stressors.
- Associated with childhood sexual abuse in many, but not all, studies.
- Associated with preexisting neurologic illness.
- Associated with physical injury that may occur immediately before onset.
- May occur after general anesthesia.
- Family history of medical or psychiatric illness is common.

DIAGNOSIS

Diagnosis is specific to symptom type:

- Psychogenic nonepileptic seizure
- Weakness or paralysis
- Abnormal movement (tremor, dystonic movement, myoclonus, gait disorder)
- Swallowing symptom ("globus hystericus")
- Speech symptom (e.g., dysphonia, slurred speech)
- Anesthesia or sensory loss
- Special sensory symptom (e.g., visual, olfactory, auditory)
- Mixed symptoms

DIFFERENTIAL DIAGNOSIS

Broad differential diagnosis depending on presenting signs and symptoms, including movement disorders, seizure, stroke, spinal disorders, malignancy, vasculitis, infectious disease, autoimmune disorders, vitamin B_{12} deficiency, migraine, dystonia, limbic encephalopathy, stiff

TABLE E1 Features that Suggest Nonepileptic (Conversion) Seizures

Historical Features
History of sexual abuse
History of other unexplained neurologic symptoms occurring during stress
Seizures despite multiple adequate trials of anticonvulsants at therapeutic levels
Features of Event
Events occur with suggestion/provocation
Gradual onset and offset of symptoms
Responsiveness during event
Weeping, speaking, or yelling during the event
Asymmetric clonic activity
Head bobbing or pelvic thrusting
Rapid kicking or thrashing
Prolonged duration of symptoms (>3 minutes)
No EEG abnormalities during the event
Postevent Features
Lucid during immediate postictal period
Able to recall event
Lack of incontinence, tongue biting, or physical injury despite numerous events
Postictal prolactin is normal
Neuropsychological testing suggestive of conversion symptoms

Stern TA et al: *Massachusetts General Hospital handbook of general hospital psychiatry,* ed 7, Philadelphia, 2018, Elsevier.

person syndrome, somatic symptom disorder, factitious disorder, and malingering.

LABORATORY TESTS

Laboratory tests or procedures needed to rule out other medical conditions (e.g., EEG for seizures, EMG for lower motor neuron paralysis, optokinetic drum test in blindness).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Education about illness including explanation and diagnosis. A multidisciplinary treatment team including a neurologist and psychiatrist can be helpful for some patients.
- Medical providers who fail to explain the diagnosis, misattribute the symptoms, and/or continue to pursue medical investigations and procedures can contribute to the patient's belief that there is an irreversible medical cause and thereby risk perpetuating the symptoms. Guidelines for presenting a diagnosis of nonepileptic seizures and developing a treatment plan are summarized in Table E2.
- Cognitive behavioral therapy is often the treatment of choice, although evidence is mixed.
- A long tradition of psychodynamic therapy exists but has not been validated by controlled trials.
- Treatment success has been associated with a caring, long-term relationship between patient and physician.
- Physical and occupational therapy can help reestablish normal function and is important for maintaining strength and function in extended cases of paralysis.
- Studies have shown no additional benefit to hypnosis, although case records describe successful treatment with hypnosis.
- Family therapy and group therapy.
- Physical therapy approaches.

GENERAL Rx

- Antidepressants may be helpful for underlying mood or anxiety disorders.
- Sedation and abreaction: One study showed that sedation with propofol improved symptoms. Abreaction functions as a pharmacologically induced hypnosis in which a lightly sedated patient is interviewed. Amobarbital was used for this purpose in the past. Abreaction is rarely used today.
- Inpatient psychiatric treatment or physical rehabilitation may be required depending on acuity, comorbidities, and functional impairment.

DISPOSITION

Long-term follow-up is essential for recurrent conversion symptoms and underlying mood disorders.

PEARLS & CONSIDERATIONS

COMMENTS

Good prognostic factors: Sudden onset, presence of psychological stressors at onset, short duration between diagnosis and treatment, high level of intelligence, and absence of other psychiatric or medical disorders. Poor prognostic factors: Severe disability, long duration of symptoms, age >40 yr at onset, and convulsions or paralysis as presenting symptoms.

- Studies show an association between sexual trauma and conversion symptoms, although evidence does not support causality due to confounding and methodologic factors.
- Although not well demonstrated, some argue that conversion and somatic symptoms are more prevalent in cultures without an articulated concept of affective disorder or in which mental illness is highly stigmatized.
- A strong therapeutic alliance and education about illness are essential treatment components.

RELATED CONTENT

Conversion Disorder (Patient Information)

AUTHOR: **Christina D. Scully, MD**

TABLE E2 Guidelines for Presenting a Diagnosis of Nonepileptic Seizures and Developing a Treatment Plan

Presentation of the Diagnosis	Treatment Plan
1. Frame the diagnosis in a positive way: Symptoms are not due to abnormal electrical activity, and risks of anticonvulsants need not be undertaken.	1. The treatment plan should include as much psychiatric care as the patient will allow. Weekly psychotherapy to assess unconscious motivation, to allow psychoeducation, and to provide support is ideal.
2. Explain that symptoms are likely due to a problem with the *function* of the nervous system, rather than electrical or structural abnormalities.	2. Psychotropic medications should be used to treat comorbid psychiatric symptoms (e.g., associated with major depression).
3. Explain that these symptoms are common and are likely to improve gradually over time. Give specific suggestions regarding how they will improve (e.g., episodes will become less prolonged, then become less frequent, then have fewer symptoms during each episode, and so forth).	3. Regular follow-up from other caregivers is a key component of the treatment plan. Appointments should be scheduled at regular intervals, whether or not the patient is symptomatic, and patients should receive positive reinforcement (and not a decrease in frequency of follow-up) when symptoms subside.
4. Acknowledge the disability that such symptoms have caused and the importance of developing a treatment plan that will improve the function of the nervous system and reduce disability.	4. Physical examinations should be done regularly, but diagnostic studies should be avoided unless clearly indicated.
5. Introduce the idea that anxiety, stress, and mood significantly affect the frequency and severity of these events and that reduction of these symptoms is crucial in the patient's treatment.	5. Despite the diagnosis of nonepileptic seizures, all caregivers should remain vigilant for the possibility that an organic diagnosis has been missed or that nonepileptic seizures and epilepsy are both present.
6. Describe a treatment plan that includes integrated, consistent treatment from providers in psychiatry, neurology, and primary care.	

Stern TA et al: *Massachusetts General Hospital handbook of general hospital psychiatry,* ed 7, Philadelphia, 2018, Elsevier.

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Cor Pulmonale

BASIC INFORMATION

DEFINITION

Cor pulmonale is an alteration in the structure and function of the right ventricle (RV) from pulmonary hypertension (PH) caused by diseases of the upper or lower airways, lungs, or pulmonary vasculature. It is the end result of disorders of pulmonary circulation due to chronic lung disease. Acute cor pulmonale is a disorder in which the RV is dilated and the muscular wall is stretched thin because of acute increase in RV afterload, which usually is a result of acute pulmonary embolism (PE) or acute respiratory distress syndrome (ARDS). This may present with often life-threatening obstructive shock or death, but if the patient survives the initial event, he or she can experience PH, right ventricular hypertrophy, and subsequent right heart failure. Chronic cor pulmonale is a disorder where RV is dilated and hypertrophied because of PH caused by long-standing upper and lower airway disease and not because of left-sided heart disease.

Right-sided heart failure resulting from primary disease of the left heart and congenital heart disease are not considered in this disorder.

SYNONYMS

Acute cor pulmonale
Chronic cor pulmonale

ICD-10CM CODES

I26.0	Pulmonary embolism with acute cor pulmonale
I27.81	Cor pulmonale (chronic)
I26.01	Septic pulmonary embolism with acute cor pulmonale
I26.02	Saddle embolus of pulmonary artery with acute cor pulmonale
I26.09	Other pulmonary embolism with acute cor pulmonale
I26.90	Septic pulmonary embolism without acute cor pulmonale
I26.92	Saddle embolus of pulmonary artery without acute cor pulmonale
I26.99	Other pulmonary embolism without acute cor pulmonale

ETIOLOGY

Acute cor pulmonale is mainly caused by a massive PE and ARDS.

Chronic cor pulmonale is the end result of diverse group of diseases that affect the pulmonary microcirculation in one way or another. Survivors of acute cor pulmonale may also experience chronic disease over the long term. The pathophysiology of cor pulmonae is outlined in Fig. E1.

Common conditions that lead to cor pulmonale:

- Chronic obstructive pulmonary disease (leading cause)
- Interstitial lung disease (ILD)
- Chronic thromboembolic disease
- Sleep disordered breathing
- Chronic mountain sickness
- Connective tissue disease, such as scleroderma
- Miscellaneous: Schistosomiasis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

No symptoms are specific for cor pulmonale. Typically, the symptoms depend on the underlying disease process. The symptoms are most often a result of right ventricular failure:

- Dyspnea, fatigue, chest pain, or syncope with exertion (from PH, RV ischemia, and impaired cardiac output)
- Right upper quadrant abdominal pain and anorexia (from passive hepatic congestion)
- Hoarseness (caused by compression of the left recurrent laryngeal nerve by dilation of the main pulmonary artery; known as *Ortner syndrome*)
- Signs of right ventricular failure: Jugular venous distention, peripheral edema, hepatic congestion, ascites, and a right ventricular third heart sound
- Signs of associated tricuspid regurgitation: Holosystolic murmur heard best along the left parasternal border (augments during inspiration), prominent V-wave on jugular venous pulse, and pulsatile hepatomegaly (in severe tricuspid regurgitation)
- PH will increase the intensity of the pulmonic component of S2, which may be narrowly split
- Rarely, cough and hemoptysis

DIAGNOSIS

WORKUP

Search for an underlying pulmonary process resulting in PH:

- Left ventricular dysfunction should be excluded in the initial assessment with an echocardiogram.
- Echocardiography is essential and defines acute cor pulmonale as the presence of RV dilation, along with a paradoxical interventricular septal motion at end systole, suggesting both RV systolic and diastolic overload.
- Prevalence of cor pulmonale cases attributable to chronic obstructive pulmonary disease (COPD) ranges from 25% to 90%. Workup should include complete pulmonary function tests (PFTs) and chest CT.
- ILD (idiopathic pulmonary fibrosis, connective tissue disease, Pneumoconioses) accounts for 30% to 90% of cases of cor pulmonale.
- In the majority of cases of COPD and ILD, the PH is usually mild to moderate and rarely severe.
- Consideration of obstructive sleep apnea (OSA), chronic thromboembolic disease, pulmonary arterial hypertension, and musculoskeletal disease should be given in the absence of parenchymal lung disease.
- A multiple gated acquisition right ventricular ejection fraction (MUGA RVEF) <45% is considered abnormal. However, MUGA scan is largely being replaced by cardiac MRI (CMR), which is the gold standard for RV function and size.

LABORATORY TESTS

- Complete blood count may show erythrocytosis from chronic hypoxia.
- Arterial blood gas levels confirm hypoxemia and acidosis or hypercapnia.
- B-type natriuretic peptide (BNP) may be elevated from RV dilation and/or hypoxia.
- Connective tissue disorder workup to exclude scleroderma, lupus, rheumatoid arthritis.
- Stool ova and parasites in suspected cases of schistosomiasis.
- HIV testing.

IMAGING STUDIES

- Chest radiograph may show underlying pulmonary disease and evidence of PH (e.g., enlargement of the pulmonary arteries or right atrium and right ventricular dilation or "pruning" of the peripheral vasculature) (Fig. E2).
- ECG (Fig. 3) may reveal right ventricular hypertrophy with R/S ratio >1 in leads V_1 and R/S ratio <1 in leads V_5, V_6, right atrial enlargement

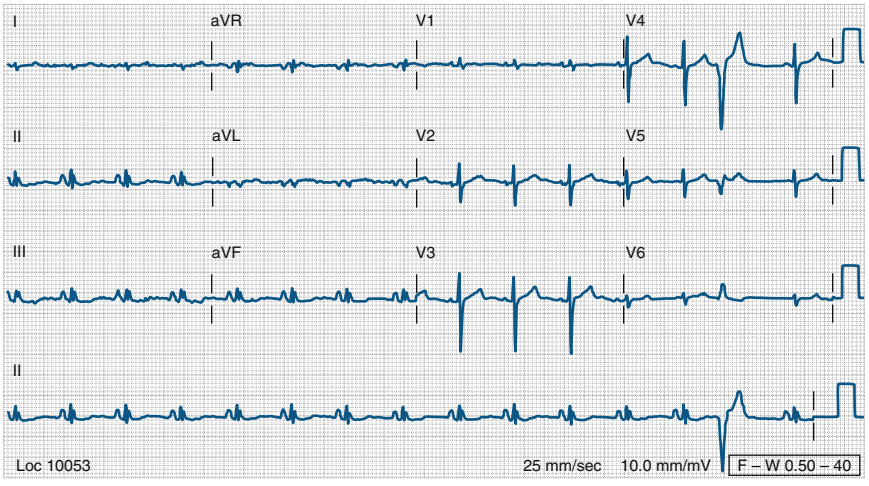

FIG. 3 An electrocardiogram in a patient with chronic cor pulmonale reveals prominent "P pulmonale" and other characteristic features (see text). *aVF*, Augmented vector foot; *aVL*, augmented vector left; *aVR*, augmented vector right. (From Mason RJ: *Murray & Nadel's textbook of respiratory medicine*, ed 5, Philadelphia, 2010, Saunders.)

TABLE 1 Therapeutic Strategies for Cor Pulmonale

Diet and Lifestyle
Smoking cessation
Weight loss
Sodium restriction
Judicious exercise training
Structured rehabilitation and breathing training programs
Avoidance of overexertion
Avoidance of pregnancy
Avoidance of high altitudes
Interventions
Treatment of underlying condition
• COPD (bronchodilators, corticosteroids, antibiotics, oxygen)
• ILD (immunosuppression, oxygen, interferon gamma [investigational])
• Sleep-disordered breathing and alveolar hypoventilation disorders (CPAP, BiPAP, surgery)
• Chronic exposure to high altitudes (return to sea level)
• Chronic thromboembolic disease (anticoagulation, inferior vena cava filters, thromboendarterectomy)
Supplemental oxygen
Pulmonary vasodilators
Anticoagulation
Diuretics
Digitalis glycosides (chronic therapy)
Nonglycoside inotropes (low-dose dobutamine or milrinone in acute severe right heart decompensation with hypoperfusion)
Lung volume reduction surgery
Lung transplantation
Heart-lung transplantation (PAH secondary to complex congenital heart disease)
Percutaneous blade-balloon atrial septostomy (investigational)
• Severe right-sided heart failure
• Recurrent syncope

BiPAP, Bilevel positive airway pressure; *COPD*, chronic obstructive pulmonary disease; *CPAP*, continuous positive airway pressure; *ILD*, interstitial lung disease; *PAH*, pulmonary arterial hypertension.
From Mason RJ: *Murray & Nadel's textbook of respiratory medicine*, ed 5, Philadelphia, 2010, Saunders.

(P-pulmonale), right-axis deviation, or the triad of $S_1Q_3T_3$ indicative of RV strain.
- Echocardiogram to detect right ventricular enlargement and/or hypertrophy and estimate systolic pulmonary artery pressure. In acute cor pulmonale, McConnell sign may be seen, which is a relative hyperkinesis of the RV apex relative to mid-free wall. It is caused by an abrupt increase in RV afterload resulting in regional wall stress.
- PFTs, including spirometry, lung volumes, and diffusion capacity, should be performed in all patients to evaluate for restrictive, obstructive, or combined restrictive-obstructive lung disease. Severe reductions in diffusing capacity that are out of proportion to the parenchymal lung disease can be seen.
- Perfusion scintigraphy (VQ scan) to rule out chronic thromboembolic pulmonary hypertension (CTEPH).
- Cardiac MRI can accurately measure right ventricular dimensions and function.
- Right-sided heart catheterization measures pulmonary artery pressures and pulmonary vascular resistance. It can also determine response to vasodilators. Importantly, right heart catheterization allows assessment of pulmonary capillary wedge pressure, allowing right heart failure from pulmonary venous hypertension due to left heart disease to be ruled out.
- High-resolution computed tomography (HRCT) of the chest is useful in the diagnosis of various pulmonary parenchymal diseases and also for the presence of PH. A main pulmonary artery diameter >29 mm has shown to diagnose the presence of PH with 89% sensitivity and 83% specificity.
- Additional tests: Several additional tests may be undertaken if the underlying cause of cor pulmonale is not exactly clear or to exclude other etiologies. These tests include:
  1. Overnight oximetry for nocturnal hypoxemia
  2. Polysomnography for OSA
  3. CT angiography to detect pulmonary thromboembolism
  4. Six-minute walk test to determine the WHO functional class
  5. Connective tissue disease screening

Rx TREATMENT

The treatment of cor pulmonale is directed toward the underlying etiology while also reversing hypoxemia, improving right ventricular contractility, decreasing pulmonary artery vascular resistance, and improving PH. Table 1 summarizes therapeutic strategies for cor pulmonale.

NONPHARMACOLOGIC THERAPY

- Supplemental oxygen to correct hypoxemia is an important management step in the treatment of cor pulmonale related to hypoxemia. Goal O_2 sat of more than 90% is recommended. Oxygen is the only modality that has demonstrated mortality benefit in patients with group 3 PH.
- Continuous positive airway pressure is used in patients with OSA.
- Sodium and fluid restriction in setting of edema from RV failure.
- Low-level aerobic exercise, avoiding heavy physical exercise or isometric exercises that may cause syncope.

ACUTE GENERAL Rx

- PE is the most common cause of acute cor pulmonale (see "Pulmonary Embolism"). The treatment is anticoagulation, hemodynamic support, and consideration of thrombolytics. Thrombolytics have been reserved for patients with large PE resulting in hemodynamic instability. Catheter-based thrombectomy or surgical embolectomy are potential salvage therapies in patients who cannot receive anticoagulation or thrombolysis, or whose condition continues to deteriorate despite thrombolytics and anticoagulation.
- Acute cor pulmonale may also be seen in cases of ARDS, related to hypercapnia/acidosis, hypoxic pulmonary vasoconstriction, and the effects of mechanical ventilation. The treatment is supportive care for ARDS with low tidal volume ventilation. Extracorporeal membrane oxygen support (ECMO) while awaiting lung recovery from ARDS may also be helpful in maintaining blood oxygenation. Venoarterial ECMO can provide hemodynamic support as well as blood oxygenation.
- In patients with preexisting cor pulmonale, acute pulmonary illnesses or hypoxia can increase PH and worsen right ventricular function. The underlying exacerbating conditions should be treated.
- Careful attention to fluid balance is important in the management of acute decompensated right heart failure. Both overhydration and overdiuresis should be avoided, with careful monitoring of intake and output, electrolytes and creatinine, and hemodynamics.
- Intravenous inotropes may be employed to support right heart contractility in decompensated right heart failure. Dobutamine, milrinone, or epinephrine all have been used in clinical studies with variable success.
- In acutely decompensated right heart failure due to pulmonary arterial hypertension, IV prostanoid medications are the treatment of choice to acutely decrease pulmonary vascular resistance. Oral pulmonary vasodilators may also be added to the IV prostanoids, but should not be initiated as monotherapy in patients with advanced right heart failure from pulmonary arterial hypertension (PAH).

CHRONIC Rx

- Primary treatment of cor pulmonale is treating the underlying cause of hypoxemia. Treatment of primary associated conditions, such as COPD, ILD, and OSA, is indicated in all patients. The long-term use of oxygen therapy results in decreased clinical right

heart failure and improved pulmonary hemodynamics in hypoxic patients.

- Indications for oxygen in chronic obstructive pulmonary disease (COPD) patients include the following:
  1. Resting PaO_2 ≤55 mm Hg on arterial blood gas
  2. Resting PaO 56 to 59 mm Hg if clinical presence of right heart failure with dependent edema, P pulmonale on ECG
  3. Desaturation to SpO_2 ≤88% on oximetry with activity or at night
     a. Right ventricular volume overload should be treated with loop diuretics (e.g., furosemide) and potassium-sparing diuretics such as spironolactone.
- Continuous oxygen therapy has a greater mortality benefit over nocturnal oxygen therapy alone.
- Diuretics should be used for fluid management in cases of fluid overload.
- Anticoagulation with warfarin has been shown to have some benefit in patients with idiopathic pulmonary arterial hypertension and CETPH, provided that there are no obvious contraindications to long-term anticoagulation. Experience with use of new oral anticoagulants (NOACs) for these conditions is still limited, and hence warfarin remains the drug of choice for anticoagulation.
- Digoxin, though controversial, may be employed as an oral inotropic agent to improve right heart contractility and control atrial arrhythmias.
- Selective oral or parenteral pulmonary vasodilators such as oral calcium channel blockers (CCBs), prostanoids, phosphodiesterase inhibitors, and endothelin receptor blockers may be used after a right heart catheterization that establishes PH.
- If vasoreactivity is established, CCBs may be used to lower pulmonary vascular resistance. However, if there is no vasoreactivity, prostanoids such as epoprostenol or treprostinil, phosphodiesterase type 5 inhibitors such as sildenafil, or endothelin receptor blockers such as bosentan and ambrisentan may be tried. However, such agents have been shown to be beneficial in the treatment of idiopathic PAH, PAH related to connective tissue disease, and PAH caused by congenital heart disease. These drugs are effective in patients whose parenchymal destruction is mild or mild to moderate and cor pulmonale is clearly linked to changes in the pulmonary artery itself. However, in patients with severe parenchymal damage, these medications need special caution because they may cause ventilation-perfusion mismatch. The soluble guanylate cyclase stimulator riociguat has been shown to improve exercise capacity and WHO functional class in CTEPH and idiopathic PH. It can be used as monotherapy or in combination with endothelin receptor antagonists or prostanoids. In small observational studies, long-term treatment with riociguat has been shown to reduce RV size and improve RV function.
- Pulmonary endarterectomy may be curative in the special case of cor pulmonale due to chronic thromboembolic PH in proximal pulmonary arteries. Before proceeding with surgery, a trial of 3 mo of anticoagulation is required.
- Atrial septostomy is a salvage option for patients with ongoing decompensated right heart failure from PAH despite pulmonary vasodilators. Such patients should undergo rapid assessment for possible transplantation.
- Lung transplantation or heart-lung transplantation should be considered in the setting of cor pulmonale from lung diseases or from pulmonary vascular disease.
- All patients should be encouraged to quit smoking and should be vaccinated against influenza and with two doses of pneumococcal vaccine.

DISPOSITION

Patients with cor pulmonale should have regular assessment of their functional class (e.g., New York Heart Association or World Health Organization [NYHA or WHO] functional class); worse functional class indicates a poorer prognosis. Other poor prognostic features include high right atrial pressure, impaired cardiac output, elevated BNP levels, low systemic blood pressure, and poor exercise tolerance as demonstrated by a 6-minute walk test.

REFERRAL

Patients with pulmonary disease who have progressed to cor pulmonale should be followed up by a pulmonologist and a tertiary care center that specializes in treatment of advanced PH.

PEARLS & CONSIDERATIONS

- Identification and treatment of the underlying cause of cor pulmonale is key.
- Prognosis and treatment are related to the underlying cause, whereas the presence of cor pulmonale is merely a marker of the underlying disease severity.
- Right heart catheterization is the gold standard to establish diagnosis and to determine treatment, including response to calcium channel blockers, prostanoids, and endothelin receptor blockers.

COMMENTS

There is increasing interest in selective pulmonary vasodilators to improve right ventricular heart function in patients with cor pulmonale outside of the setting of idiopathic PAH, PAH related to connective tissue disease, and PAH related to congenital heart disease. However, more data on the safety and efficacy of these agents, especially in the setting of hypoxemic lung disease, is needed.

The importance of maintaining or improving right heart function, rather than solely lowering pulmonary pressures, is becoming increasingly apparent in the therapeutic management of patients with PH and right heart failure.

Long-term survival is related to improved pulmonary artery hemodynamics (lower mean PAP). Improved pulmonary hemodynamics are apparent within the first 6 mo of oxygen therapy. Continuous oxygen therapy improves pulmonary hemodynamics with more than 19 hr/day therapy.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pulmonary Embolism (Related Key Topic)
Pulmonary Hypertension (Related Key Topic)
Chronic Obstructive Pulmonary Disease (Related Key Topic)

AUTHOR: **Shruti Hegde, MD,** and **Wajih A. Syed, MD**

SUGGESTED READINGS

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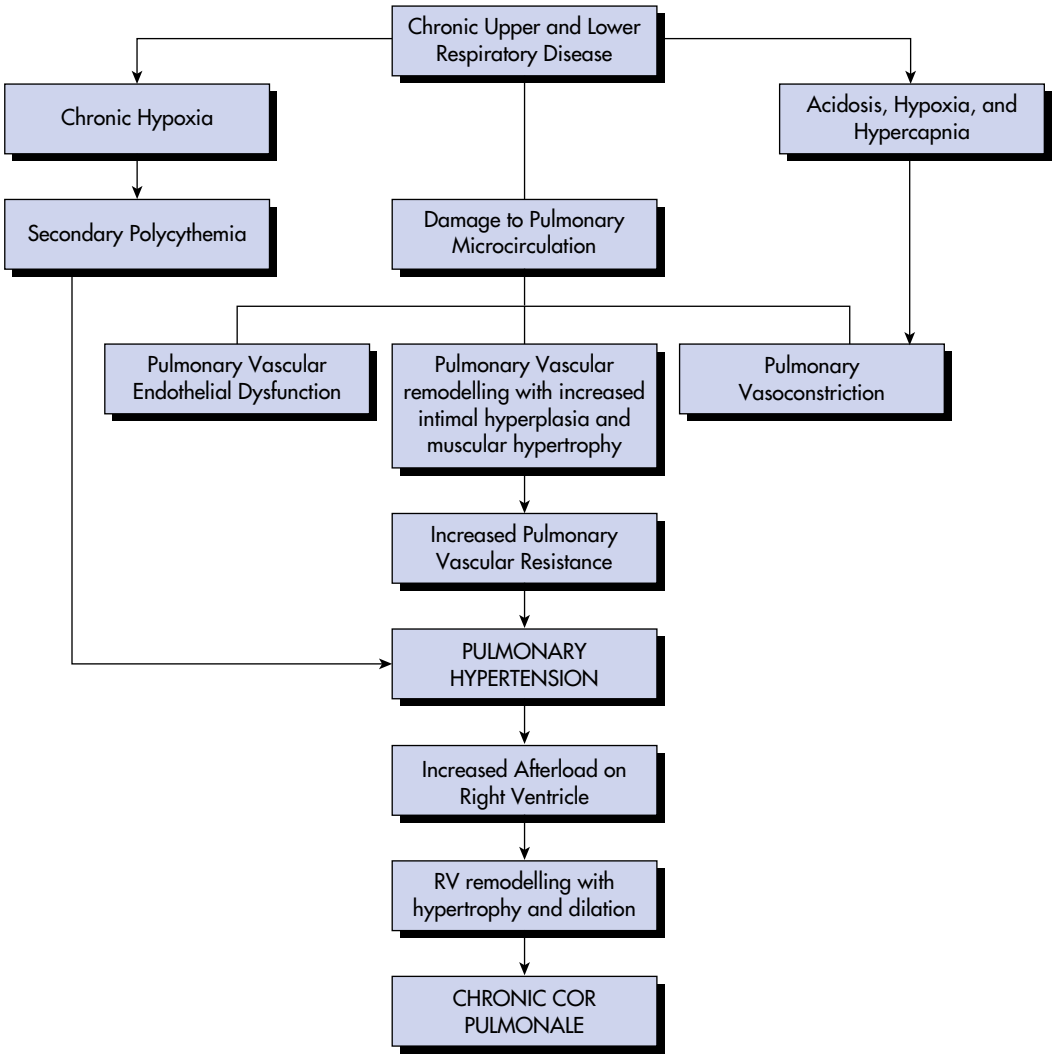

FIG. E1 Pathophysiology of cor pulmonale.

FIG. E2 Chest radiography in a patient with severe intrinsic pulmonary vascular disease demonstrating enlargement of the main pulmonary artery, right ventricle, and right atrium. (From Crawford MH, et al. [eds]: *Cardiology*, ed 2, St Louis, 2004, Mosby.)

BASIC INFORMATION

DEFINITION

A corneal abrasion is a loss of surface epithelial tissue of the cornea caused by trauma.

SYNONYMS

Corneal erosion (term for recurrent epithelial defect from previous abrasion)
Corneal contusion
Corneal epithelial defect
Corneal ulcer (term suggests infiltrative infection of an epithelial defect)

ICD-10CM CODES	
S05.00XA	Injury of conjunctiva and corneal abrasion without foreign body, unspecified eye, initial encounter
S05.01XA	Injury of conjunctiva and corneal abrasion without foreign body, right eye, initial encounter
S05.02XA	Injury of conjunctiva and corneal abrasion without foreign body, left eye, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): A universal problem. Corneal abrasions comprise 8% of all eye presentations in primary care
PEAK INCIDENCE: Childhood through active adulthood and older and debilitated patients
PREDOMINANT AGE: Any age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Haziness of the cornea
- Disruption of the corneal surface
- Redness and injection of the conjunctiva, often around the edge of the cornea, limbus
- Pain
- Light sensitivity
- Tearing
- Gritty or foreign-body feeling
- Pain on opening or closing eyes

ETIOLOGY

- Trauma (direct mechanical event)
- Foreign body (on cornea or upper tarsal conjunctiva, found with lid eversion)
- Contact lenses
- Chemical or flash ultraviolet burns

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute-angle closure glaucoma (pupil may be fixed, supraorbital headache)
- Herpes ulcers and other corneal ulcers (infections may appear white and hazy)
- Foreign body in the cornea (be certain it is not a keratitis)
- Infectious keratitis (be cautious in contact lens wearers; bacterial infections are common, and symptoms are similar)
- Autoimmune corneal ulceration (RA, SLE): Peripheral ulceration

WORKUP

- Fluorescein staining, slit lamp evaluation. After fluorescein staining of the cornea, an abrasion will appear yellow under normal light and green in cobalt blue light (Fig. E1).
- Assessment of visual acuity. Vision loss requires referral.
- Intraocular pressure.
- Rule out corneal laceration (flattened anterior chamber with perforation; refer urgently).
- Rule out other eye pathology. Inspect anterior chamber for blood (hyphema) or pus (hypopyon). If present, refer immediately to ophthalmologist.
- Examine for foreign bodies and remove them if present. (Evert upper eyelid to locate foreign body on the palpebral conjunctiva.)
- Confirm red reflex to rule out significant globe injury.
- Significant blunt or sharp trauma to the cornea or globe should be referred for evaluation.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Bandage contact lens can help speed healing for large epithelial abrasions.
- Warm compresses.
- Pressure dressing (patching) is controversial. Although eye patching traditionally has been recommended in the treatment of corneal abrasions, several studies show that patching does not help and should be avoided since it may hinder healing.
- Removal of any foreign particles if present.

ACUTE GENERAL Rx

- Topical antibiotics such as 10% sulfacetamide or ofloxacin 0.3% solution two drops qid are commonly prescribed to prevent bacterial superinfection, but evidence for their use is lacking and should generally be avoided. Ointment forms are also often used (e.g., erythromycin, bacitracin ophthalmic qid) to also improve corneal surface lubrication. Antipseudomonal topical antibiotics are,

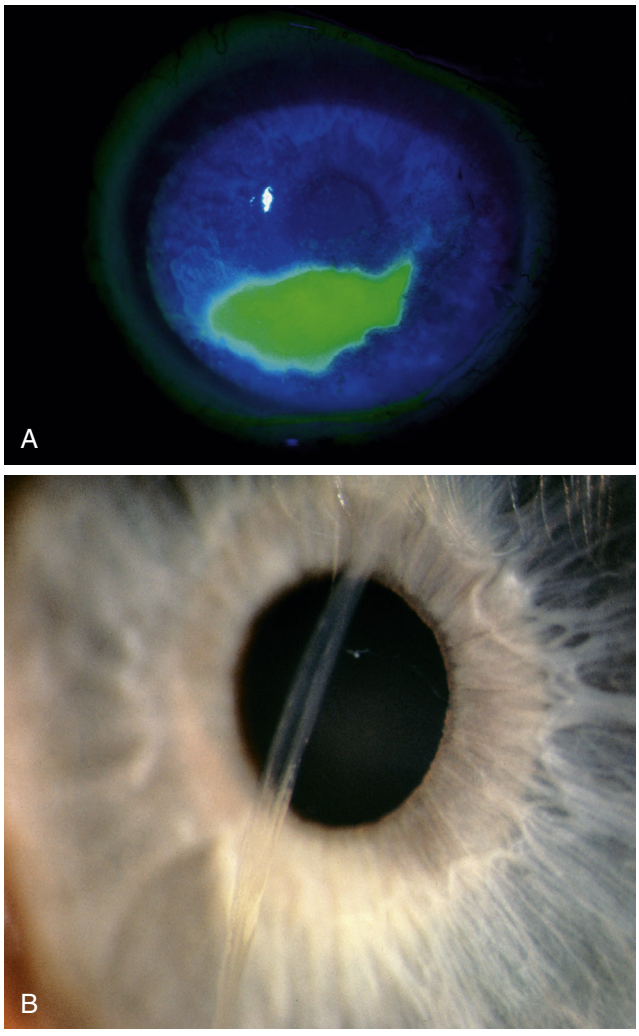

FIG. E1 Corneal complications of blunt trauma. A, Large corneal abrasion stained with fluorescein. **B,** Tears in Descemet membrane. (Courtesy C. Barry [Fig. **A**] and R. Curtis [Fig. **B**]. In Bowling B: *Kanski's clinical ophthalmology, a systematic approach,* ed 8, Philadelphia, 2016, Elsevier.)

however, recommended for contact lens–related abrasions.
- Pressure patching of eye with eyelid closed is no longer recommended because it can result in decreased oxygen delivery, increased moisture, and a higher chance of infection.
- Cycloplegics such as 5% homatropine are often prescribed to relieve ciliary muscle spasm; however, their benefit has been questioned, and they are no longer routinely recommended.
- Topical nonsteroidal antiinflammatory drugs (NSAIDs) (e.g., diclofenac 0.1% or ketorolac 0.5%) one drop qid may be used for pain relief.
- Topical anesthetic drops immediately improve comfort for purposes of examination, but repeated use can lead to severe problems, delayed or arrested healing, infections, perforations, and loss of the eye.
- Oral NSAIDs may be used for severe pain.

DISPOSITION

Follow-up in 24 hr, then every 3 days until abrasion has cleared and vision has returned to normal. Less frequent follow-up is appropriate for abrasions ≤4 mm or for uncomplicated abrasions.

REFERRAL

To ophthalmologist if patient has no relief within 24 hr or for patients with deep eye injuries, foreign bodies that cannot be removed, or suspected recurrent corneal erosion or infections.

PEARLS & CONSIDERATIONS

COMMENTS

- Never give the patient topical anesthetic to use at home because these can cause decompensation of the cornea, severe delay of epithelial healing, and permanent damage.
- Corticosteroid drops (e.g., dexamethasone, prednisolone) should be avoided, since they can delay healing and exacerbate some corneal infections (herpes viral keratitis, pseudomonas, and fungal ulcers).
- Most corneal abrasions heal in 24 to 48 hr and rarely progress to corneal erosion or infection.
- Improvement in pain is a good indication of corneal epithelial healing. Severe worsening of pain could indicate corneal bacterial infection (keratitis) and should be evaluated urgently.

RELATED CONTENT

Corneal Foreign Body or Abrasion (Patient Information)

AUTHOR: **R. Scott Hoffman, MD**

SUGGESTED READING

Wipperman JL, Dorsch JN: Evaluation and management of corneal abrasions, *Am Fam Physician* 87(2):114-120, 2013.

BASIC INFORMATION

DEFINITION

Corneal ulceration refers to the disruption of the corneal surface and/or deeper layers caused by trauma, contact lenses, infection, degeneration, or other means. Rather than simple epithelial abrasion, ulceration implies inflammation, such as with infection of the deeper corneal stroma.

SYNONYMS

Infectious keratitis with ulceration
Bacterial keratitis with ulceration
Viral keratitis with ulceration
Fungal keratitis with ulceration

ICD-10CM CODES	
H16.009	Unspecified corneal ulcer, unspecified eye
E50.3	Vitamin A deficiency with corneal ulceration and xerosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Four to six cases per month seen by an average general ophthalmologist
PREVALENCE (IN U.S.): Common
PREDOMINANT SEX: Either
PREDOMINANT AGE: All ages

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Localized, well-demarcated, infiltrative lesion with corresponding focal ulcer or oval, yellow-white stromal suppuration with thick mucopurulent exudate and edema. Usually red, angry-looking eye with infiltration in surrounding area of cornea.
- Eye possibly painful, with conjunctival edema and infection (pain is a helpful indicator of progression or improvement in infectious keratitis).
- Active keratitis is usually extremely painful, with photophobia and ciliary injection.
- Sterile neurotrophic ulcers with tissue breakdown and no pain.
- Fig. E1 illustrates various deep corneal lesions.

ETIOLOGY

- Complication of contact lens wear, trauma, or diseases such as herpes simplex keratitis or keratoconjunctivitis sicca. Often associated with collagen vascular disease and severe exophthalmos and thyroid disease.
- Viral causes often contagious.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- *Pseudomonas* and pneumococcus and other bacterial infection: Virulent
- *Moraxella, Staphylococcus,* α-*Streptococcus* infection: Less virulent
- Herpes simplex infection or disease caused by other viruses
- Contact lens ulcers differ
- Autoimmune keratitis (e.g., peripheral ulceration with rheumatoid arthritis, systemic lupus erythematosus [RA, SLE])
- Acute angle closure glaucoma

WORKUP

- Fluorescein staining, slit lamp
- Appearance often typical
- Differentiate carefully with contact lens wearers
- Note previous eye surgery or laser vision correction

LABORATORY TESTS

Microscopic examination and culture of scrapings are indicated for vision-threatening keratitis (lesions are large or central location in the cornea) or atypical presentations, such as keratitis not responding to treatments as expected.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Warm compresses for blepharitis, eyelid hygiene
- Bandage contact lenses
- Stop contact lens wearing

ACUTE GENERAL Rx

- An ophthalmic emergency; refer to ophthalmologist same day.
- Intense antibiotic and antiviral therapy may be needed for infectious keratitis.
- Topical antibiotics (often broad-coverage, new-generation fluoroquinolones).
- Nonsteroidal antiinflammatory drugs and cycloplegic may help with comfort.
- Bacterial infection: Subconjunctival cefazolin or gentamicin (e.g., topical Zymar, Vigamox).
- Fungal infection (rare): Hospitalization and topical application of antifungal agents.
- Herpes: Viral keratitis can have similar symptoms; should avoid steroid drops unless diagnosis is near certain and showing improvement because viral keratitis can worsen with steroids.
- Acanthamoeba keratitis may be suspected, particularly in contact lens wearers with severe pain who are unresponsive to other treatments.

DISPOSITION

Ideally treated by an ophthalmologist if the patient does not rapidly respond to antibiotics (within 24 hr). Improvement in pain is often a good indication of improvement in the infection.

Corneal ulcer may be managed every 1 to 2 days until epithelium has healed over and improvement is apparent.

PEARLS & CONSIDERATIONS

- Always stop contact lens wearing.
- Always refer ulcers to ophthalmologist.
- Never treat with topical anesthetics or steroids.

COMMENTS

Do not use topical steroids because herpes, fungal, or other ulcers may be aggravated, leading to perforation of the cornea. Antibiotics may delay response and result in overgrowth of nonbacterial (fungal and amoebic) pathogens.

AUTHOR: **R. Scott Hoffman, MD**

FIG. E1 Deep corneal lesions. A, Infiltration; **B,** ulceration; **C,** lipid deposition with vascularization; **D,** folds in Descemet membrane; **E,** descemetocele; and **F,** traumatic breaks in Descemet membrane. (Courtesy C. Barry **[C, D]** and R. Curtis **[F].** In Bowling B: *Kanski's clinical ophthalmology, a systematic approach*, ed 8, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Coronary artery disease (CAD) is a clinical syndrome that suggests limitation of coronary blood flow to the myocardium as a result of atherosclerotic lesions. Atherosclerosis can be defined as the narrowing of the artery due to plaque formation in the setting of lipid accumulation inside the arterial walls. It is silent in the early stages and characterized by exertional symptoms in later stages as described in the following.

This topic addresses only stable CAD. Acute coronary syndromes (ACS), angina pectoris, and myocardial infarction are addressed as separate topics elsewhere.

SYNONYMS

Atherosclerotic heart disease
CAD
Chronic stable angina
Stable ischemic heart disease
Coronary arteriosclerosis

ICD-10CM CODES

I25.0	Atherosclerotic cardiovascular disease
I25.1	Atherosclerotic heart disease
I25.10	Atherosclerotic heart disease of native coronary artery without angina pectoris
I25.110	Atherosclerotic heart disease of native coronary artery with unstable angina pectoris
I25.111	Atherosclerotic heart disease of native coronary artery with angina pectoris with documented spasm
I25.118	Atherosclerotic heart disease of native coronary artery with other forms of angina pectoris
I25.119	Atherosclerotic heart disease of native coronary artery with unspecified angina pectoris

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: For persons who are 40 yr old, the lifetime risk of developing CAD is 49% in men and 32% in women. The risk increases with age in both men and women; however, the incidence in women lags behind that seen in men by approximately 10 yr.

The incidence in premenopausal women is relatively low, while the incidence increases significantly in postmenopausal women.

The initial presentation in men is more likely to be that of a myocardial infarction, whereas women often present initially with angina.

PREVALENCE: The 2017 Heart Disease and Stroke Statistics update from the American Heart Association estimated that 16.5 million Americans ≥20 yr of age have CAD. There is a slight male predominance at 55%, with incidence increasing with age. CAD prevalence is 7.9% for men and 5.1% for women.

RISK FACTORS: The most prevalent risk factors include age, male sex, hypertension, hyperlipidemia, diabetes mellitus, obesity, tobacco use, family history, and peripheral vascular disease. Coronary plaque, especially noncalcified plaque, is more prevalent and extensive in HIV-infected men, independent of CAD risk factors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Left anterior chest discomfort often described as squeezing, heavy pressure, and burning. Associated symptoms include fatigue, dyspnea, weakness, lightheadedness, nausea, diaphoresis, altered mental status, and syncope.
- Angina typically lasts 3 to 5 min but usually does not last more than 30 min.
- Women and diabetics may not present with classic symptoms, but may manifest more frequently with dyspnea or GI complaints.
- Discomfort is elicited by physical exertion, emotional stress, cold exposure, consumption of a large meal, and smoking.
- Early coronary disease is asymptomatic.
- Stigmata of atherosclerosis may include xanthelasma, tendon xanthomata, and evidence of peripheral vascular disease such as claudication and diminished peripheral pulses.

ETIOLOGY

The development of atherosclerosis occurs over many yr. The order of events has been well studied. Multiple factors contribute to the pathogenesis, including endothelial dysfunction, dyslipidemia, inflammatory conditions, and smoking. Under such conditions, cholesterol molecules, primarily low-density lipoprotein (LDL), adhere to the intima of the vessel walls and are taken into the intimal layers. LDL is then oxidized, causing cytokine release, which initiates adhesion molecule expression on endothelial layers. Monocytes are then recruited and pass across the endothelium, where they digest the LDL and become "foam cells." Smooth muscle cells then migrate from the media to the intima. This causes further smooth cell proliferation and fibrosis to occur. In later stages, calcification of the matrix also develops. This causes a relatively acellular fibrous capsule to surround a lipid-rich core. This "plaque" then causes narrowing of the vessel lumen, ultimately leading to symptoms related to ischemia.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS OF ACUTE CHEST PAIN

- Cardiovascular causes
  1. Acute coronary syndrome
  2. Aortic dissection
  3. Pericarditis
  4. Coronary arterial vasospasm
- Pulmonary causes
  1. Pulmonary embolism
  2. Pneumonia
  3. Pleuritis
  4. Pneumothorax
- Gastrointestinal causes
  1. Esophageal spasm
  2. Esophagitis
  3. GERD
- Chest wall causes
  1. Rib fracture
  2. Sternoclavicular arthritis
  3. Herpes zoster
  4. Costochondritis
- Psychiatric causes
  1. Anxiety disorders

WORKUP

See Fig. 1. ACCF/HFA guidelines for stress testing and advanced imaging are summarized in Tables 1 to 3.

LABORATORY TESTS

- Focused metabolic studies to rule out noncardiac causes (BMP, liver function tests).
- Complete blood count can help rule out anemia-related chest discomfort.
- Fasting cholesterol panel is important in assessment of lipid-related risk factors.
- Hemoglobin A1c is important to follow glycemic control.
- High-sensitivity C-reactive protein.

IMAGING STUDIES

- Electrocardiography (ECG) is important for assessing for prior cardiac injury or ischemia.
- Exercise treadmill test (ETT) is the gold standard to assess physiologic cardiac stress response if the patient is able to exercise and has a normal baseline ECG.
- Stress tests combined with imaging is the next best option if ETT cannot be performed due to physical limitation or if baseline ECG is abnormal.
- Echocardiogram to assess left ventricular ejection fraction (LVEF) and the presence of wall motion abnormalities.
- Although not used in the acute setting, a coronary artery calcium (CAC) score can be used to improve CVD risk classification. The CAC is estimated from noncontrast CT (Fig. E2) images. Normal coronary arteries do not have plaques or calcium, and the normal score is 0. A CAC score of 300 or higher, or 75th percentile or higher for age, sex, and ethnicity is considered a high risk. According to the recent ACC/AHA guidelines, CAC is most appropriate among adults with an estimated 10-yr ASCVD risk <7.5% in whom questions remain about whether statin therapy is indicated. A CAC score >75th percentile for age, sex, and ethnicity is considered high risk and would justify revising a patient's risk upward.
- Those with high-risk features (Box 1) should undergo coronary angiography to assess coronary anatomy for revascularization.
- Cardiac computed tomography angiography is an emerging imaging modality that can be considered as an alternative to stress testing.

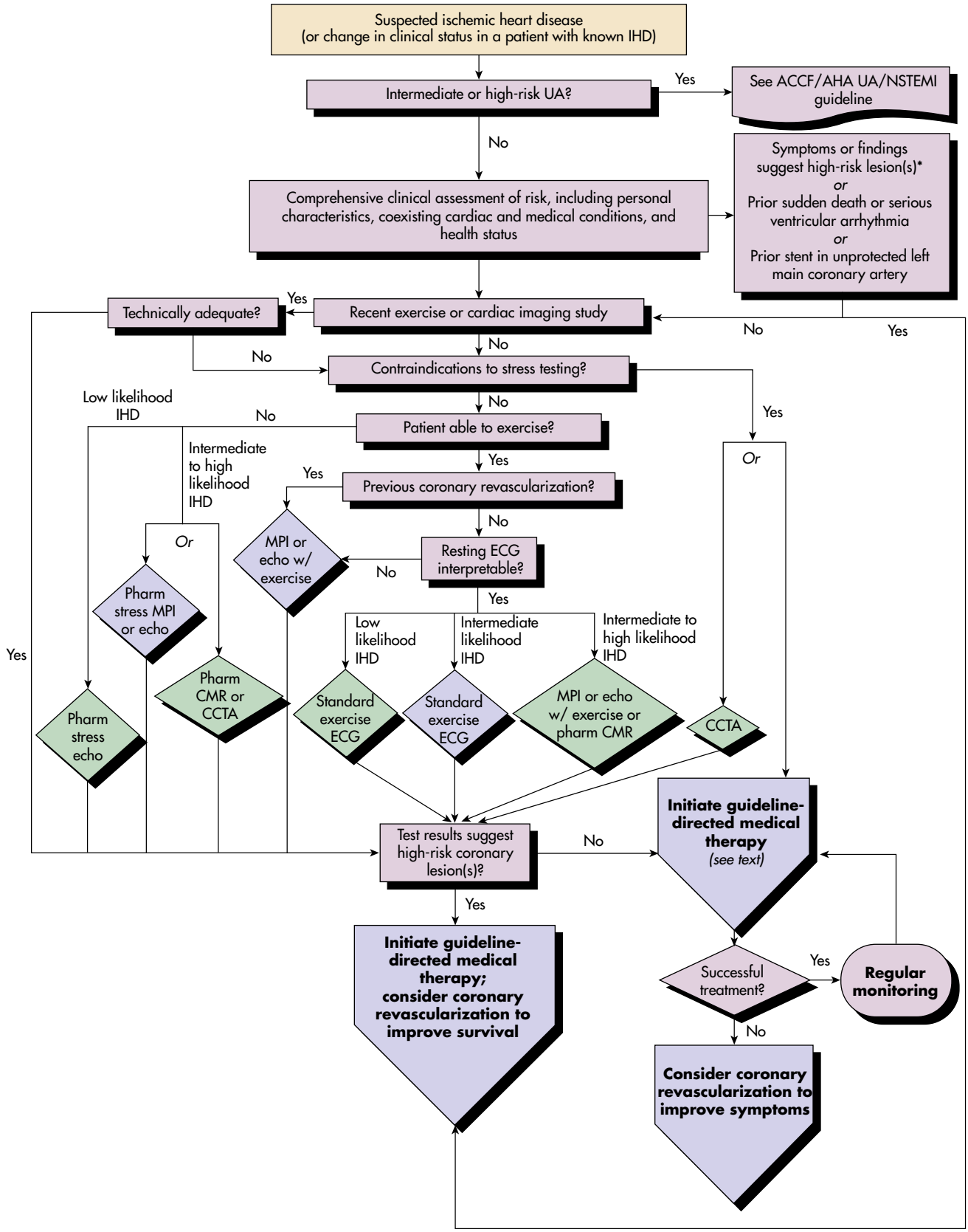

FIG. 1 Diagnosis of patients with suspected ischemic heart disease.

*CCTA is reasonable only for patients with intermediate probability of IHD. *ACCF/AHA,* American College of Cardiology Foundation/American Heart Association; *CCTA,* Computed coronary tomography angiography; *CMR,* cardiac magnetic resonance; *ECG,* electrocardiogram; *Echo,* echocardiography; *IHD,* ischemic heart disease; *MPI,* myocardial perfusion imaging; *Pharm,* pharmacologic; *UA,* unstable angina; *UA/NSTEMI,* unstable angina/non–ST-elevation myocardial infarction. (From 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, *J Am Coll Cardiol* 60:e44-e164, 2012.)

TABLE 1 ACCF/AHA Guidelines for Stress Testing and Advanced Imaging for Initial Diagnosis in Patients with Suspected Stable Ischemic Heart Disease Who Require Noninvasive Testing

	Exercise Status		ECG Interpretable		Pretest Probability of Ischemic Heart Disease				
Test	**Able**	**Unable**	**Yes**	**No**	**Low**	**Intermediate**	**High**	**Recommendation**	**Level of Evidence**
Patients Able to Exercise									
Exercise ECG	X		X			X		I	A
Exercise ECG with MPI or Echo	X			X		X	X	I	B
Exercise ECG	X		X		X			IIa	C
Exercise ECG with MPI or Echo	X		X			X	X	IIa	B
Pharmacologic stress CMR	X			X		X	X	IIa	B
CCTA	X		Either			X		IIb	B
Exercise Echo	X		X			X		IIb	C
Pharmacologic stress with nuclear MPI, Echo, or CMR	X		X			Any		III	C
Exercise stress with MPI	X		X		X			III	C
Patients Unable to Exercise									
Pharmacologic stress with nuclear MPI or Echo		X	Either			X	X	I	B
Pharmacologic stress Echo		X	Either		X			IIa	C
CCTA		X	Either		X	X		IIa	B
Pharmacologic stress CMR		X	Either			X	X	IIa	B
Exercise ECG		X		X		Any		III	C
Other Reasons for Cardiac Computed Tomography Angiography									
Continued symptoms after normal test results Inconclusive stress test results Unable to undergo stress test	Either		Either			X		IIa	C
CAC	Either		Either		X			IIb	C

ACCF/AHA, American College of Cardiology Foundation/American Heart Association; *CAC,* coronary artery calcium (imaging); *CCTA,* coronary computed tomography angiography; *CMR,* cardiac magnetic resonance; *ECG,* electrocardiography; *Echo,* echocardiography; *MPI,* myocardial perfusion imaging.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 2 ACCF/AHA Guidelines for Stress Testing and Advanced Imaging for Patients with Known Stable Ischemic Heart Disease Who Require Noninvasive Testing for Risk Assessment

	Exercise Status		ECG Interpretable				
Test	**Able**	**Unable**	**Yes**	**No**	**Additional Considerations**	**Recommendation**	**Level of Evidence**
Patients Able to Exercise							
Exercise ECG	X		X			I	B
Exercise ECG with MPI or Echo	X			X	Abnormalities other than LBBB or ventricular pacing	I	B
Exercise ECG with MPI or Echo	X		X			IIa	B
Pharmacologic stress CMR	X			X		IIa	B
CCTA	X			X		IIb	B
Pharmacologic stress imaging or CCTA	X		X			III	C
Patients Unable to Exercise							
Pharmacologic stress with nuclear MPI or Echo		X	Either			I	B
Pharmacologic stress CMR		X	Either			IIa	B
CCTA		X	Either		Without previous stress test	IIa	C
Regardless of Ability to Exercise							
Pharmacologic stress with nuclear MPI or Echo	Either			X	LBBB present	I	B
Exercise or pharmacologic stress with nuclear MPI, Echo, or CMR	Either		Either		Known coronary stenosis being considered for revascularization	I	B
CCTA	Either		Either		Indeterminate result of functional testing	IIa	C
	Either		Either		Unable to undergo stress imaging	IIb	C
	Either		Either		Alternative to invasive coronary angiography when functional testing indicates moderate to high risk	IIb	C
Multiple stress tests or cardiac imaging at the same time	Either		Either			III	

ACCF/AHA, American College of Cardiology Foundation/American Heart Association; *CCTA,* coronary computed tomography angiography; *CMR,* cardiac magnetic resonance; *ECG,* electrocardiography; *Echo,* echocardiography; *LBBB,* left bundle branch block; *MPI,* myocardial perfusion imaging.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 3 ACCF/AHA Guidelines for Coronary Angiography to Assess Risk in Patients with Known or Suspected Stable Ischemic Heart Disease

Class	Indication	Level of Evidence
I (indicated)	1. Patients with SIHD who have survived sudden cardiac death or potentially life-threatening ventricular arrhythmia should undergo coronary angiography to assess cardiac risk.	B
	2. Patients with SIHD in whom symptoms and signs of heart failure develop should be evaluated to determine whether coronary angiography should be performed for risk assessment.	B
	3. Coronary arteriography is recommended for patients with SIHD whose clinical characteristics and results of noninvasive testing indicate a high likelihood of severe IHD and when the benefits are deemed to exceed risk.	C
IIa (good supportive evidence)	1. Coronary angiography is reasonable to further assess risk in patients with SIHD who have depressed LV function (EF <50%) and moderate-risk criteria on noninvasive testing with demonstrable ischemia.	C
	2. Coronary angiography is reasonable to further assess risk in patients with SIHD and inconclusive prognostic information after noninvasive testing or in patients for whom noninvasive testing is contraindicated or inadequate.	C
	3. Coronary angiography for risk assessment is reasonable for patients with SIHD who have unsatisfactory quality of life because of angina, have preserved LV function (EF >50%), and have intermediate-risk criteria on noninvasive testing.	C
III (no benefit)	1. Coronary angiography for risk assessment is not recommended in patients with SIHD who elect not to undergo revascularization or who are not candidates for revascularization because of comorbid conditions or individual preferences.	B
	2. Coronary angiography is not recommended to further assess risk in patients with SIHD who have preserved LV function (EF >50%) and low-risk criteria on noninvasive testing.	B
	3. Coronary angiography is not recommended to assess risk in patients who are at low risk according to clinical criteria and who have not undergone noninvasive risk testing.	C
	4. Coronary angiography is not recommended to assess risk in asymptomatic patients with no evidence of ischemia on noninvasive testing.	C

ACCF/AHA, American College of Cardiology Foundation/American Heart Association; *EF,* ejection fraction; *LV,* left ventricle; *SIHD,* stable ischemic heart disease.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

BOX 1 Noninvasive Risk Stratification

High risk (>3% annual mortality rate)
1. Severe resting left ventricular dysfunction (LVEF <35%).
2. High-risk treadmill score (≤–11).
3. Severe exercise left ventricular dysfunction (exercise LVEF <35%).
4. Stress-induced large perfusion defect (particularly if anterior).
5. Stress-induced multiple perfusion defects of moderate size.
6. Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201).
7. Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (thallium-201).
8. Echocardiographic wall motion abnormality (involving >2 segments) developing at low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 beats/min).
9. Stress echocardiographic evidence of extensive ischemia.

Intermediate risk (1% to 3% annual mortality rate)
1. Mild/moderate resting left ventricular dysfunction (LVEF 35% to 49%).
2. Intermediate-risk treadmill score (score between –11 and <5).
3. Stress-induced moderate perfusion defect without LV dilation or increased lung intake (thallium-201).
4. Limited stress echocardiographic ischemia with a wall motion abnormality only at doses of dobutamine involving ≤2 segments.

Low risk (<1% annual mortality rate)
1. Low-risk treadmill score (≥5).
2. Normal or small myocardial perfusion defect at rest or with stress.
3. Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress.

LV, Left ventricle; *LVEF,* left ventricular ejection fraction.

- Coronary angiography is useful for both diagnostic and therapeutic interventions if there is evidence of significant ischemia by noninvasive assessment or progressive symptoms despite optimal medical therapy (as in the following).

Rx TREATMENT

- See Fig. 3. Table 4 summarizes ACCF/AHA guidelines for risk factor modification. Note that hypertension and cholesterol management guidelines have been revised since release of these CAD guidelines, and these are summarized in the "Hypertension" and "Hypercholesterolemia" chapters in this text.
- Successful treatment of CAD entails minimizing the likelihood of major adverse cardiac events (MACE), which include death, myocardial infarction, need for emergent coronary artery bypass grafting, or target lesion revascularization, while maximizing health and function.

NONPHARMACOLOGIC THERAPY

LIFESTYLE MODIFICATION:
- ≥150 min/wk of moderate-intensity activity or ≥75 min/wk of vigorous-intensity activity or a combination thereof (for adults) as 1 of the 7 components of ideal cardiovascular health.
- Mediterranean diet with a focus on vegetables, fruit, fish, whole grains, and olive oil has proven to reduce cardiovascular events to a degree greater than low-fat diets and equal to or greater than the benefit observed in statin trials.
- Smoking cessation.
- Weight reduction can reduce various risk factors with improved lipid and glycemic control.

THERAPEUTIC INTERVENTIONS: Coronary angiography with PCI or CABG for patients on optimal medical therapy with persistent symptoms.

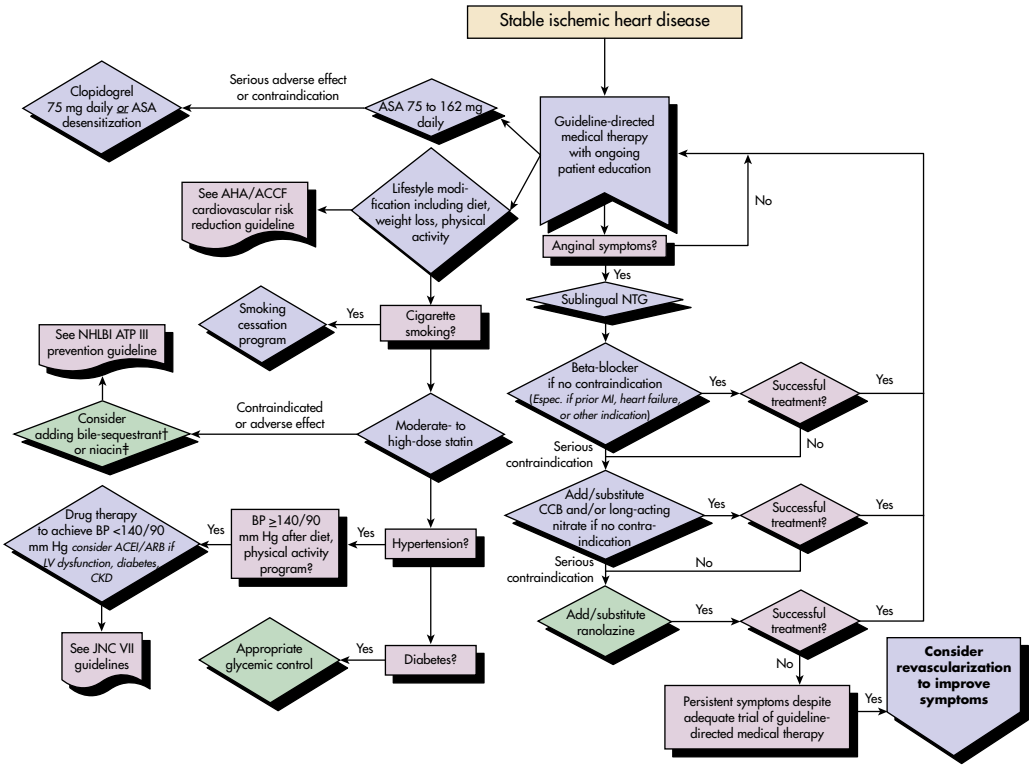

FIG. 3 Algorithm for guideline-directed medical therapy for patients with SIHD.*

*The algorithms do not represent a comprehensive list of recommendations (see text for all recommendations). †The use of bile acid sequestrant is relatively contraindicated when triglycerides are ≥200 mg/dl and is contraindicated when triglycerides are ≥500 mg/dl. ‡Dietary supplement niacin must not be used as a substitute for prescription niacin. *ACCF,* American College of Cardiology Foundation; *ACEI,* angiotensin-converting enzyme inhibitor; *AHA,* American Heart Association; *ARB,* angiotensin-receptor blocker; *ASA,* aspirin; *ATP III,* Adult Treatment Panel 3; *BP,* blood pressure; *CCB,* calcium channel blocker; *CKD,* chronic kidney disease; *JNC VII,* Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; *LV,* left ventricular; *MI,* myocardial infarction; *NHLBI,* National Heart, Lung, and Blood Institute; *NTG,* nitroglycerin; *SIHD,* stable ischemic heart disease. (From 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, *J Am Coll Cardiol* 60:e44-e164, 2012.)

ACUTE GENERAL Rx FOR STABLE ANGINA

- Rest.
- Sublingual nitroglycerin if rest does not provide adequate relief.

CHRONIC Rx

- Antianginal therapy:
  1. Nitrates (isosorbide mononitrate and isosorbide dinitrate). These medications treat ischemia by venodilation to decrease preload, dilate epicardial coronary arteries, and recruit coronary collaterals. Furthermore, they attenuate platelet aggregation. Although they do not influence survival or decrease cardiovascular death in patients with chronic CAD, they do lower the rate of angina frequency and increase time to ischemic ECG findings on treadmill testing.
  2. Beta-adrenergic antagonists (metoprolol, atenolol, carvedilol, or any other beta-blockers with the exception of those with intrinsic sympathomimetic activity). These medications work to relieve angina by decreasing myocardial oxygen demand by reducing heart rate, blood pressure, and contractility. Drugs should be titrated to a heart rate of 50 to 60 beats/min at rest and ≤100 beats/min with exercise.
  3. Calcium channel blockers (CCBs; amlodipine or verapamil). The antianginal efficacy of CCBs is comparable to beta-blockers; however, the efficacy of monotherapy for reducing MI or cardiac death has not been demonstrated.
  4. Ranolazine. This is a selective inhibitor of late sodium influx into myocytes, which leads to decreased myocardial contractility. It can be used in combination with beta-blockers and significantly reduces frequency of angina and increases exercise duration and time to onset of angina (CARISA trial). Although it rarely may cause QT prolongation, it has not been linked to any clinically important arrhythmias.
  5. May benefit from combination therapy of the above.
- Antiplatelet therapy:
  1. Aspirin therapy (81 to 162 mg/day).
  2. Clopidogrel for those intolerant to aspirin therapy.
  3. Combination of aspirin and clopidogrel does not reduce cardiovascular events in stable CAD (CHARISMA trial).
  4. Newer antiplatelet drugs such as Prasugrel and Ticagrelor have been studied and are recommended in ACS.
- Statins:
  1. HMG-CoA reductase inhibitors (statins) (atorvastatin, rosuvastatin) with high-intensity therapy for a target LDL reduction of >50% if safely achieved in high-risk patients; if not a candidate for high-intensity therapy, patient should receive at least moderate-intensity statin therapy that lowers LDL by 30% to 50%. The initiation of

TABLE 4 ACCF/AHA Guidelines for Risk Factor Modification

Class	Indication	Level of Evidence
Lipid Management		
I (indicated)	1. Lifestyle modifications, including daily physical activity and weight management, are strongly recommended for all patients with SIHD.	B
	2. Dietary therapy for all patients should include reduced intake of saturated fats (to <7% of total calories), trans fatty acids (to <1% of total calories), and cholesterol (to <200 mg/day).	B
	3. In addition to therapeutic lifestyle changes, a moderate or high dose of a statin should be prescribed in the absence of contraindications or documented adverse effects.	A
IIa (good supportive evidence)	For patients who do not tolerate statins, LDL cholesterol–lowering therapy with bile acid sequestrants, niacin, or both is reasonable.	B
Blood Pressure Management		
I (indicated)	1. All patients should be counseled about the need for lifestyle modification: Weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products.	B
	2. In patients with SIHD and a BP of 140/90 mm Hg or higher, antihypertensive drug therapy should be instituted in addition to or after a trial of lifestyle modifications.	A
	3. The specific medications used for the treatment of high BP should be based on specific patient characteristics and may include ACE inhibitors and/or beta-blocking agents, as well as the addition of other drugs such as thiazide diuretics or calcium channel blocking agents if needed to achieve a goal BP of less than 140/90 mm Hg.	B
Diabetes Management		
IIa (good supportive evidence)	1. For selected individual patients, such as those with a short duration of diabetes mellitus and a long life expectancy, a goal hemoglobin A1c (HbA1c) of 7% or less is reasonable.	B
	2. A goal HbA1c between 7% and 9% is reasonable for certain patients according to age, history of hypoglycemia, presence of microvascular or macrovascular complications, or presence of coexisting medical conditions.	C
IIb (weak supportive evidence)	Initiation of pharmacotherapy interventions to achieve a target HbA1c might be reasonable.	A
III (not indicated)	Therapy with rosiglitazone should not be initiated in patients with SIHD.	C
Physical Activity		
I (indicated)	1. For all patients, clinicians should encourage 30 to 60 min of moderate-intensity aerobic activity at least 5 days and preferably 7 days per wk, supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, household work) to improve cardiorespiratory fitness and move patients out of the least-fit, least-active, high-risk cohort (bottom 20%).	B
	2. For all patients, risk assessment with a physical activity history and/or an exercise test is recommended to guide prognosis and prescription.	B
	3. Medically supervised programs (cardiac rehabilitation) and physician-directed, home-based programs are recommended for at-risk patients at first diagnosis.	A
IIa (good supportive evidence)	It is reasonable for clinicians to recommend complementary resistance training at least 2 days per wk.	C
Weight Management		
I (indicated)	1. BMI and/or waist circumference should be assessed at every visit, and clinicians should consistently encourage weight maintenance or reduction through an appropriate balance of lifestyle physical activity, structured exercise, caloric intake, and formal behavioral programs when indicated to maintain or achieve a BMI of between 18.5 and 24.9 kg/m^2 and a waist circumference of less than 102 cm (40 inches) in men and less than 88 cm (35 inches) in women (less for certain racial groups)	B
	2. The initial goal of weight loss therapy should be to reduce body weight by approximately 5% to 10% from baseline. With success, further weight loss can be attempted if indicated.	C
Smoking Cessation		
I (indicated)	Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home should be encouraged for all patients with SIHD. Follow-up, referral to special programs, and pharmacotherapy are recommended, as is a stepwise strategy for smoking cessation (Ask, Advise, Assess, Assist, Arrange, Avoid).	B
Management of Psychological Factors		
IIa (good supportive evidence)	It is reasonable to consider screening patients with SIHD for depression and to refer or treat when indicated.	B
IIb (weak supportive evidence)	Treatment of depression has not been shown to improve cardiovascular disease outcomes but might be reasonable for its other clinical benefits.	C
Alcohol Consumption		
IIb (weak supportive evidence)	In patients with SIHD who drink alcohol, it might be reasonable for nonpregnant women to have 1 drink (4 oz of wine, 12 oz of beer, or 1 oz of spirits) a day and for men to have 1 or 2 drinks a day unless alcohol is contraindicated (such as in patients with a history of alcohol abuse or dependence or those with liver disease).	C
Exposure to Air Pollution		
IIa (good supportive evidence)	It is reasonable for patients with SIHD to avoid exposure to increased air pollution to reduce their risk for cardiovascular events.	C

ACE, Angiotensin-converting enzyme; *ACCF/AHA,* American College of Cardiology Foundation/American Heart Association; *BMI,* body mass index; *BP,* blood pressure; *LDL,* low-density lipoprotein; *SIHD,* stable ischemic heart disease.

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

a statin can be determined by the ASCVD 10-yr risk calculator. Statins are recommended for primary prevention in patients with LDL >190, patients with type 2 diabetes mellitus (moderate intensity for ASCVD score <7.5% and high intensity for ASCVD risk score >7.5%), and patients with an elevated ASCVD risk score of >7.5%.

- PCSK9 inhibitors:
  1. This is a novel class of monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9. They cause dramatic reductions in LDL cholesterol and have been shown to reduce cardiovascular events. They are generally reserved for patients with familial hypercholesterolemia and patients with established vascular disease with LDL above goal despite maximal tolerated dose of statin. No overall mortality benefit has been demonstrated in studies to date.
- ACE-inhibitors (captopril, enalapril, lisinopril) are a class I recommendation for patients with chronic CAD with LV dysfunction LVEF <40% or diabetes and a class II recommendation for CAD patients without these features.

CORONARY ARTERY REVASCULARIZATION

- Patients with symptoms refractory to optimal medical therapy (OMT) as above or those with high clinical, stress testing, or an angiographic risk profile and suitable coronary anatomy may benefit from revascularization with either PCI (percutaneous coronary intervention) or CABG (coronary artery bypass graft) surgery. ACCF/AHA guidelines for

TABLE 5 ACCF/AHA Guidelines for Revascularization to Improve Survival Versus Medical Therapy in Patients with Stable Ischemic Heart Disease

Anatomic Setting	Class	Recommendation	Level of Evidence
Unprotected Left Main or Complex Coronary Artery Disease			
CABG and PCI	I	Heart team approach	C
CABG and PCI	IIa	Calculation of STS and SYNTAX Scores	B
Unprotected Left Main			
CABG	I		B
PCI	IIa	For SIHD when both of the following are present: 1. Anatomic conditions associated with a low risk for PCI procedural complications and a high likelihood of a good long-term outcome 2. Clinical characteristics that predict a significantly increased risk for adverse surgical outcomes	B
	IIb	For SIHD when both of the following are present: 1. Anatomic conditions associated with a low to intermediate risk for PCI procedural complications and an intermediate to high likelihood of a good long-term outcome 2. Clinical characteristics that predict increased risk for adverse surgical outcomes (e.g. STS-predicted operative mortality >2%)	B
	III	For SIHD in patients (versus performing CABG) with unfavorable anatomy for PCI and who are good candidates for CABG	B
Three-Vessel Coronary Artery Disease with or without Proximal Left Anterior Descending Coronary Artery Disease			
CABG	I		B
	IIa	It is reasonable to choose CABG over PCI in patients with complex 3-vessel CAD (e.g., SYNTAX score ≥22) who are good candidates for CABG	B
PCI	IIb		B
Two-Vessel Coronary Artery Disease with Proximal Left Anterior Descending Coronary Artery Disease			
CABG	I		B
PCI	IIb		B
Two-Vessel Coronary Artery Disease without Proximal Left Anterior Descending Coronary Artery Disease			
CABG	IIa	With extensive ischemia	B
	IIb	Without extensive ischemia	C
PCI	IIb		B
One-Vessel Proximal Left Anterior Descending Coronary Artery Disease			
CABG	IIa	With LIMA	B
PCI	IIb		B
One-Vessel Coronary Artery Disease without Proximal Left Anterior Descending Coronary Artery Disease			
CABG	III	Harm	B
PCI	III	Harm	B
Left Ventricular Dysfunction			
CABG	IIa	EF of 35% to 50%	B
CABG	IIb	EF <35% without significant left main disease	B
PCI	N/A	Insufficient data	
Survivors of Sudden Cardiac Death with Presumed Ischemia-Mediated Ventricular Tachycardia			
CABG	I		B
PCI	I		C
No Anatomic or Physiologic Criteria for Revascularization			
CABG	III	Harm	B
PCI	III	Harm	B

ACCF/AHA, American College of Cardiology Foundation/American Heart Association; *CABG,* coronary artery bypass graft; *CAD,* coronary artery disease; *EF,* ejection fraction; *LIMA,* left internal mammary artery; *N/A,* not applicable; *PCI,* percutaneous coronary intervention; *SIHD,* stable ischemic heart disease; *STS,* Society of Thoracic Surgery; *SYNTAX,* synergy between PCI with taxus and cardiac surgery.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 6 ACCF/AHA Guidelines for Revascularization to Improve Symptoms in Patients with Significant Anatomic (>50% Left Main or >70% Non–Left Main Coronary Artery Disease) or Physiologic (Fractional Flow Reserve <0.80) Coronary Artery Stenoses

Clinical Setting	Recommendation		Level of Evidence
≥1 significant stenosis amenable to revascularization and unacceptable angina despite GDMT	I	CABG or PCI	A
≥1 significant stenoses and unacceptable angina in whom GDMT cannot be implemented because of medication contraindications, adverse effects, or patient preferences	IIa	CABG or PCI	C
Previous CABG with ≥1 significant stenosis associated with ischemia and unacceptable angina despite GDMT	IIa	PCI	C
	IIb	CABG	C
Complex 3-vessel CAD (e.g., SYNTAX score ≥22) with or without involvement of the proximal LAD artery and a good candidate for CABG	IIa	CABG preferred over PCI	B
Viable ischemic myocardium that is perfused by coronary arteries that are not amenable to grafting	IIb	TMR as an adjunct to CABG	B
No anatomic or physiologic criteria for revascularization	III	CABG or PCI	C

ACCF/AHA, American College of Cardiology Foundation/American Heart Association; *CABG,* coronary artery bypass graft; *GDMT,* guideline-directed medical therapy; *LAD,* left anterior descending; *PCI,* percutaneous coronary intervention; *SYNTAX,* synergy between PCI with taxus and cardiac surgery; *TMR,* transmyocardial revascularization.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

revascularization are summarized in Tables 5 and 6.

- ACC/AHA class I indications for bypass surgery in chronic CAD patients include the following:
  1. High grade (>50%) left main CAD
  2. Left main CAD-equivalent anatomy including >70% luminal stenosis in the left anterior descending artery and left circumflex arteries
  3. Three-vessel disease with LVEF <50%
  4. Single- or two-vessel CAD with a large area of viable myocardium at risk
  5. Severe angina despite medical therapy if CABG can be performed with acceptable risk
- Percutaneous coronary intervention (PCI) has not been shown to reduce long-term rates of MI and death in patients with stable chronic CAD and therefore has no class I indications in this group. PCI is suitable in patients with suitable anatomy with refractory or lifestyle-limiting angina who have failed optimal medical therapy (OMT). Recent trials such as the COURAGE Trial have demonstrated no significant difference between OMT and PCI in overall survival, MI, and ACS over 5 yr in patients with chronic stable CAD.
- The SYNTAX trial, which used a numerical score based on qualitative plaque features on angiography, showed that surgical revascularization was associated with a lesser risk of stroke and major cardiac events if the SYNTAX score was high (>33).
- Trials continue to support CABG as superior to PCI in diabetic patients with multivessel CAD and should remain the revascularization strategy of choice in this patient population.

DISPOSITION

CAD is a common chronic condition with which many patients can live for years with good symptom control on optimal medical therapy.

REFERRAL

Cardiovascular disease specialist

PEARLS & CONSIDERATIONS

COMMENTS

- The transition from stable CAD to unstable angina must be carefully monitored. Symptoms of concern include more frequent episodes of chest pain, exertional dyspnea, chest pain that is less responsive to nitroglycerin, or first episode of chest pain. Regarding unstable angina, please refer to section on acute coronary syndromes.
- ACC/AHA guidelines for follow-up noninvasive testing are summarized in Tables 7 and 8.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Coronary Artery Disease (Patient Information)
Acute Coronary Syndrome (Related Key Topic)
Angina Pectoris (Related Key Topic)
Hypercholesterolemia (Related Key Topic)
Hyperlipoproteinemia, Primary (Related Key Topic)
Myocardial Infarction (Related Key Topic)

AUTHOR: **Nathan Riddell, MD**

TABLE 7 ACC/AHA Guidelines for Follow-Up Noninvasive Testing in Patients with Known Stable Ischemic Heart Disease: New, Recurrent, or Worsening Symptoms (Not Consistent with Unstable Angina)

	Exercise Status		ECG Interpretable				
Test	**Able**	**Unable**	**Yes**	**No**	**Additional Considerations**	**Recommendation**	**Level of Evidence**
Patients Able to Exercise							
Exercise ECG	X		X			I	B
Exercise ECG with MPI or Echo	X			X		I	B
Exercise ECG with MPI or Echo	X		Either		Previous requirement for imaging or known to be at high risk for multivessel CAD	IIa	B
Pharmacologic stress MPI, Echo, or CMR	X		X			III	C
Patients Unable to Exercise							
Pharmacologic stress with nuclear MPI or Echo		X	Either			I	B
Pharmacologic stress CMR		X	Either			IIa	B
Exercise ECG		X		X		III	C
Regardless of Ability to Exercise							
CCTA	Either		Either		To assess patency of coronary stent or bypass graft ≥3 mm in diameter	IIb	C
	Either		Either		In absence of known moderate or severe calcification and to assess coronary stent <3 mm in diameter	IIb	C
	Either		Either		Known moderate or severe calcification or assessment of stent <3 mm in diameter	III	C

ACC/AHA, American College of Cardiology/American Heart Association; *CAD,* coronary artery disease; *CCTA,* cardiac computed tomography angiography; *CMR,* cardiac magnetic resonance; *ECG,* electrocardiography; *Echo,* echocardiography; *MPI,* myocardial perfusion imaging.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 8 ACC/AHA Guidelines for Follow-Up Noninvasive Testing in Patients with Known Stable Ischemic Heart Disease: Asymptomatic or Stable Symptoms

	Exercise Status		ECG Interpretable					
Test	**Able**	**Unable**	**Yes**	**No**	**Pretest Probability of Ischemia**	**Additional Considerations**	**Recommendation**	**Level of Evidence**
Exercise or pharmacologic stress with MPI, Echo, or CMR at ≥2-yr intervals		X		X	Previous evidence of silent ischemia or at high risk for recurrent event	Unable to exercise, uninterpretable ECG, or incomplete revascularization	IIa	C
Exercise ECG at ≥1-yr intervals	X		X		Previous silent ischemia or at high risk for recurrent event		IIb	C
Exercise ECG	X		X		No previous silent ischemia and not at high risk for recurrent events		IIb	C
Exercise or pharmacologic stress imaging or CCTA	Either		Either			<5-yr intervals after CABG or <2 yr intervals after PCI	III	C

ACC/AHA, American College of Cardiology/American Heart Association; *CABG,* coronary artery bypass graft; *CCTA,* cardiac computed tomography angiography; *CMR,* cardiac magnetic resonance; *ECG,* electrocardiography; *Echo,* echocardiography; *MPI,* myocardial perfusion imaging; *MPI,* myocardial perfusion imaging; *PCI,* percutaneous coronary intervention.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

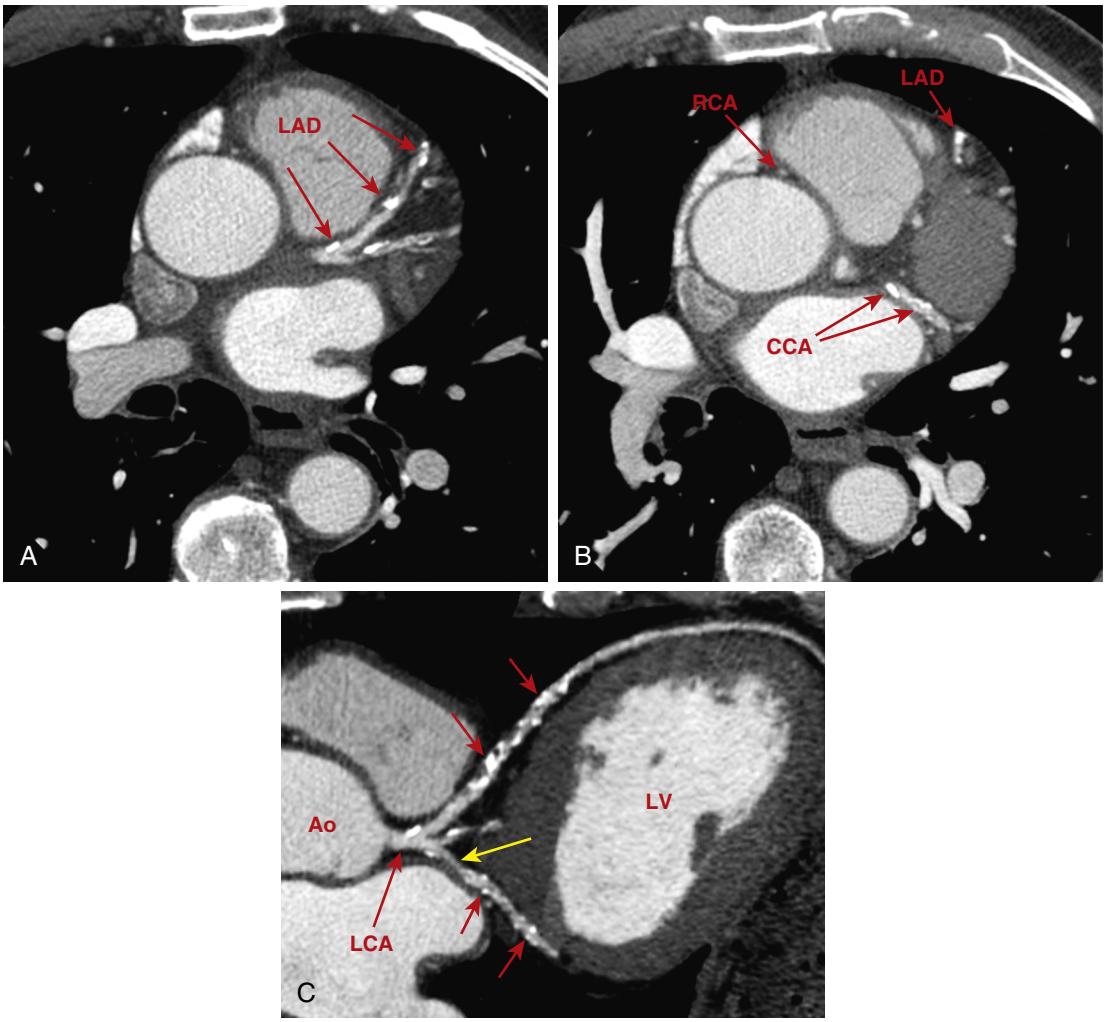

FIG. E2 Coronary artery calcification and computed tomography angiography. A, Electrocardiogram-gated contrast-enhanced computed tomography shows calcification of the left anterior descending *(LAD)* coronary artery and a branch. **B,** At a lower level, calcification (*arrows*) of the LAD artery and circumflex coronary artery *(CCA)* is visible. The right coronary artery *(RCA)* is noncalcified. **C,** A curved reconstruction showing the left coronary artery *(LCA)* and the LAD artery and CCA along their axes. Multiple calcifications are visible (*red arrows*). A noncalcified stenosis of the CCA (*yellow arrow*) is also shown. *Ao,* Aorta; *LV,* left ventricle. (From Webb WR et al: *Fundamentals of body CT*, ed 4, Philadelphia, 2015, WB Saunders.)

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Costochondritis (PTG)

BASIC INFORMATION

DEFINITION

Clinical condition characterized by pain and tenderness at costochondral or chondrosternal joints of the anterior chest wall without obvious swelling or induration.

SYNONYMS

Anterior chest wall syndrome
Chest wall pain syndrome
Costosternal syndrome
Parasternal chondrodynia

ICD-10CM CODE
M94.0 Chondrocostal junction syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Comprises approximately 28% of undifferentiated noncardiac chest pain patients
PREDOMINANT SEX: Women
PREDOMINANT AGE: >40 yr of age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

SYMPTOMS:

- Anterior chest wall pain, usually described as sharp, aching, or pressure-like. Pain is usually aggravated by coughing, sneezing, deep inspiration, or any chest wall movement.
- Pain is usually self-limited.
- May radiate to arms and shoulders mimicking cardiac chest pain.

SIGNS:

- Reproducible tenderness of costochondral (mostly second through fifth) or chondrosternal junction without localized swelling or induration is generally considered diagnostic for a chest wall syndrome.
- Various maneuvers can be utilized to reproduce chest wall pain, such as the "crowing rooster maneuver" (examiner stands behind the patient and exerts traction on the upper arms by pulling them backward and slightly superiorly) and horizontal arm flexion (the arm is flexed across the anterior chest while steady traction is applied in a horizontal direction).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cardiac pain: Ischemic chest pain, acute pericarditis, aortic dissection
- Gastrointestinal: Gastroesophageal reflux disease
- Pulmonary: Pulmonary embolism, pneumonia, pneumothorax, pleurisy, malignancy
- Musculoskeletal (Table E1): Tietze syndrome, cervical or thoracic spine disease, arthritides
- Involvement of ribs by trauma, infections (*Candida albicans*), or neoplasms (breast cancer, prostate cancer, sarcoma, plasma cell cytoma, non-Hodgkin lymphoma)
- Miscellaneous: Fibromyalgia, panic attack

WORKUP

- A diagnosis of exclusion for chest pain after ruling out more serious conditions, including cardiac chest pain. Keys to diagnosis are a detailed history, a meticulous physical examination, and a few rationally selected diagnostic studies, including electrocardiogram and chest x-ray to rule out cardiopulmonary causes. Usefulness of nuclear scanning with technetium-99m scintigraphy, gallium, or bone scanning to assist diagnosis of costochondritis is not clear.

TREATMENT

ACUTE GENERAL Rx

- Often self-limiting, so reassurance is important.
- Symptomatic treatment includes local application of heat, minimizing activities that aggravate symptoms, stretching exercises for chest wall muscles, and nonsteroidal anti-inflammatory drugs or acetaminophen.
- Refractory cases can be treated with local injections of combined lidocaine and corticosteroid (may be a useful diagnostic and therapeutic tool). Dry needling by a trained physical therapist may be helpful.
- Recurrent costochondritis may respond to sulfasalazine; however, there is minimal evidence and no clinical trials of pharmacologic therapy for costochondritis.

PEARLS & CONSIDERATIONS

Presence of costochondritis in a patient with chest pain does not exclude more serious problems including cardiac pain. Further testing is required as clinically indicated.

RELATED CONTENT

Costochondritis (Patient Information)

AUTHOR: **Asha Shrestha, MD**

TABLE E1 Musculoskeletal Chest Pain

Disorder	Clinical Features	Comments
Tietze syndrome	Painful swelling of usually second or third costochondral junctions.	Less common than costochondritis; commonly affects young people of either sex. Exact cause is unknown, but a traumatic pathogenesis has been associated. The disease course is mostly self-limited. Non-Hodgkin lymphoma of medial clavicular head has been reported to mimic Tietze syndrome.
Slipping rib syndrome	Pain at the lower costal cartilages, associated with increased mobility of the anterior end of costal cartilage. Most commonly affects 10th rib and occasionally affects 8th and 9th ribs.	Maneuver such as hooking the fingers under the anterior costal margin and pulling the rib cage anteriorly may produce a palpable click of the cartilages slipping over one another.
Cervical, thoracic disc disease	Referred regional pain from affected areas. Often aggravated by spine motion and may be accompanied by radicular pain into arm if cervical origin or along intercostal nerve if thoracic origin. Symptoms are reproduced by Spurling maneuver (steady pressure to head causing increased axial loading on the nerve root).	May mimic chest disease if spinal complaints are minimal and referred or radicular symptoms predominate.
Sternoclavicular or manubriosternal joint involvement in osteoarthritis, inflammatory conditions (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, relapsing polychondritis), and infection	Dull, aching local pain with tenderness. Occasional bony joint enlargement with soft tissue swelling.	Crepitus may rarely be present.

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Craniopharyngioma PTG ALG

BASIC INFORMATION

DEFINITION

Craniopharyngiomas are tumors arising from squamous cell remnants of Rathke pouch, located in the infundibulum or upper anterior hypophysis.

SYNONYM

Subset of nonadenomatous pituitary tumors

ICD-10CM CODE

D44.3 Neoplasm of uncertain behavior of pituitary gland

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Occurs at all ages; peak during the first two decades of life, with a second small peak occurring in the sixth decade

PREDOMINANT SEX:

- Both sexes are usually equally affected.
- Craniopharyngiomas are the most common nonglial tumors in children and account for 3% to 5% of all pediatric brain tumors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The typical onset is insidious and a 1- to 2-yr history of slowly progressive symptoms is common.
- Presenting symptoms are usually related to the effects of a sella turcica mass. Approximately 75% of patients report headache and have visual disturbances.
- The usual visual defect is bitemporal hemianopsia. Optic nerve involvement with decreased visual acuity and scotomas and homonymous hemianopsia from optic tract involvement may also occur.
- Other symptoms include mental changes, nausea, vomiting, somnolence, or symptoms of pituitary failure. In adults, sexual dysfunction is the most common endocrine complaint, with impotence in men and primary or secondary amenorrhea in women. Diabetes insipidus is found in 25% of cases. In children, craniopharyngiomas may present with dwarfism.
- More than 70% of children at the time of diagnosis present with growth hormone deficiency, obstructive hydrocephalus, short-term memory deficits, and psychomotor slowing.

ETIOLOGY

Craniopharyngiomas are believed to arise from nests of squamous epithelial cells that are commonly found in the suprasellar area surrounding the pars tuberalis of the adult pituitary.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pituitary adenoma
- Empty sella syndrome
- Pituitary failure of any cause
- Primary brain tumors (e.g., meningiomas, astrocytomas)
- Metastatic brain tumors
- Other brain tumors
- Cerebral aneurysm

LABORATORY TESTS

- Hypothyroidism (low FT_4, FT_3 with high thyroid-stimulating hormone).
- Hypercortisolism (low cortisol) with low adrenocorticotropic hormone.
- Low sex hormones (testosterone, estriol) with low follicle-stimulating hormone and luteinizing hormone.
- Diabetes insipidus (hypernatremia, low urine osmolarity, high plasma osmolarity).
- Prolactin may be normal or slightly elevated.
- Pituitary stimulation tests may be required in some cases.

IMAGING STUDIES

- MRI (Fig. E1) or head CT if MRI is contraindicated. MRI features include a multicystic and solid enhancing suprasellar mass. Hydrocephalus may also be present if the mass is large. CT usually reveals intratumoral calcifications.
- Visual field testing for bitemporal hemianopsia.
- Skull film may show:
  1. Enlarged or eroded sella turcica (50%).
  2. Suprasellar calcification (50%).

TREATMENT

GENERAL Rx

- Traditionally, surgery has been the main treatment for craniopharyngioma. However, radiation treatment instead of surgery may be an option in selected cases.
- Surgical resection (curative or palliative):
  1. Transsphenoidal surgery for small intrasellar tumors.
  2. Subfrontal craniotomy for most patients.
- Overall prognosis is good with 80% to 90% chance of permanent cure.
- Postoperative radiation.
- Intralesional ^{32}P irradiation or bleomycin for unresectable tumors. Long-term complications of radiation include secondary malignancies, optic neuropathy, and vascular injury.

PROGNOSIS

- Overall prognosis is good with 80% to 90% chance of permanent cure.
- Operative mortality rate: 3% to 16% (higher with large tumors).
- Postoperative recurrence rate: <20% of cases after total resection and 60% of cases after subtotal resection. Most recurrences occur within the first 2 yr after surgery.
- 5-yr and 10-yr survival: 88% and 76%, respectively, with surgery and radiation.
- The most important factors that correlate with prognosis are the extent of resection and postoperative radiation.
- Long-term posttreatment hormonal, visual, and neurologic problems occur in a significant percentage of patients.

RELATED CONTENT

Craniopharyngioma (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

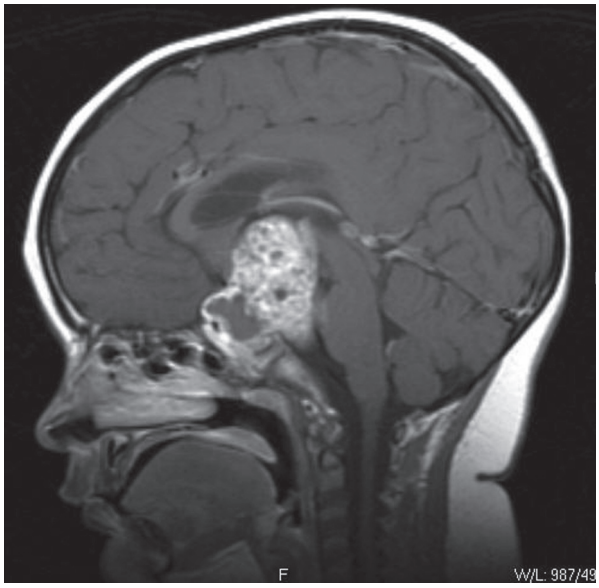

FIG. E1 Craniopharyngioma. Magnetic resonance imaging (MRI)—Note the heterogeneous nature (solid > cystic) of this craniopharyngioma on MRI with significant suprasellar extension. Despite its location, potentially obstructing the foramen of Monro, there was no hydrocephalus. (Swaiman KF et al: *Swaiman's pediatric neurology, principles and practice,* ed 6, Philadelphia, 2017, Elsevier.)

BASIC INFORMATION

DEFINITION

Creutzfeldt-Jakob disease (CJD) is a progressive, fatal, dementing neurologic illness caused by an infectious protein agent known as a *prion.*

SYNONYMS

Transmissible spongiform encephalopathy
Prion disease
CJD

OTHER PRION DISEASES

Fatal familial insomnia
Gerstmann-Sträussler-Scheinker syndrome (GSS)
Bovine spongiform encephalopathy ("mad cow" disease)
Kuru

ICD-10CM CODE
A81.00 Creutzfeldt-Jakob disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence of 1 per 1 million population per yr.
- Peak age 60 yr (range, 16 to 82 yr); whereas sporadic cases are seen in an older population, the variant subtype is commonly seen in younger patients.
- Most common cause of rapidly progressive dementia, with a disease duration of less than 1 yr until death.
- 5% to 10% familial; remaining cases are sporadic; iatrogenic cases (corneal or liver transplants, dura mater allograft, human pituitary extract, blood or blood product transfusion, reused medical equipment such as electroencephalogram [EEG] depth electrodes) are very rare—about 1%; variant CJD is caused by ingestion of meat from cows with prion disease and is more commonly seen in Great Britain, but cases from Canada, France, Saudi Arabia, and the U.S. have also been reported.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Cognitive deficits: Patients present with cognitive deficits (dementing illness—memory loss, behavioral abnormalities, higher cortical function impairment), usually a subacute rapid progressive encephalopathy or dementia. Prodromal symptoms such as fatigue, depression, weight loss, and disorders of sleep and appetite may be seen in about one third of patients. Early stages are characterized by confusion with hallucinations, delusions, and agitation.
- More than 80% will have myoclonus—generalized and exaggerated by startle.
- Pyramidal tract signs (weakness), cerebellar signs (clumsiness), and extrapyramidal signs (parkinsonian features) are seen in more than 50% of the cases.
- Less common features include cortical visual abnormalities, abnormal eye movements, vestibular dysfunction, sensory disturbances, autonomic dysfunction, lower motor neuron signs, and seizures.

ETIOLOGY

Small proteinaceous infectious particle (prion): Noninfectious prion protein (PrP) is a cellular protein found on the surfaces of neurons. Normal function is not known. This normal protein is converted to a protease-resistant infectious agent by the infectious prion protein.

- Normal prion protein *(PRNP)* gene is found on human chromosome 20.
- Methionine and valine distribution on codon 129 of the PRNP determines the six clinical phenotypes of CJD.

DIAGNOSIS

- Definite CJD: Neuropathologically confirmed spongiform encephalopathy in a case of progressive dementia
- Probable CJD: History of rapidly progressive dementia (<2 yr) with typical EEG and with at least two of the following clinical features: myoclonus, visual or cerebellar dysfunction, pyramidal or extrapyramidal features, akinetic mutism
- Possible CJD: Same as probable CJD without EEG findings

DIFFERENTIAL DIAGNOSIS

- Other progressive dementias (Alzheimer disease, frontotemporal dementia, Lewy body dementia, and vascular dementia)
- Infectious (viral, HIV, fungal, TB, Whipple disease)
- Inflammatory or autoimmune (CNS vasculitis, autoimmune encephalitis, Hashimoto encephalopathy, subacute sclerosing panencephalitis [SSPE])
- Metabolic (vitamin deficiency, endocrine)
- Cancers (CNS lymphoma, gliomatosis cerebri, paraneoplastic encephalitis)
- Other conditions, toxic (heavy metal poisoning)

A clinical algorithm for the evaluation of dementia is described in Section III, "Dementia."

WORKUP

- Evaluate for treatable causes of dementia (see section on "Alzheimer Disease").
- Brain biopsy is gold standard for diagnosis but may not be performed because there is no treatment or cure, and there is the potential risk of iatrogenic spread.
- Lumbar puncture with spinal fluid analysis for presence of 14-3-3 protein or human prion protein (PrP^{Sc}).
- Recent guidelines issued by the American Academy of Neurology states that clinicians should order assays for 14-3-3 in patients with rapidly progressive dementia, strong suspicion of sporadic CJD, and an uncertain diagnosis (pretest probability of 20% to 90%). The test has a high false-positive and false-negative rate because of its presence in other chronic noninflammatory dementing diseases.

LABORATORY TESTS

- Presence of periodic sharp wave complexes on EEG in cases of rapidly progressive dementia has a sensitivity of 67% and a specificity of 86%.
- In cases of probable or possible CJD, presence of the 14-3-3 protein in CSF has a 95% positive predictive value with its absence having a 92% negative predictive value. Test for presence of human prion protein (PrP^{Sc}) in CSF has been reported to be 83% sensitive and 100% specific. Repeated testing for 14-3-3 protein increases the probability of a positive result. Enolase and neopterin in CSF are the other nonspecific markers that may have adjunct diagnostic value.
- Recent reports indicate that testing of nasal brushings using RT-QuIC, an ultrasensitive, multiwall plate–based fluorescence assay involving PrP^{CJD}–seeded polymerization of recombinant PrP into amyloid fibrils, is accurate in diagnosing CJD.
- PRP^{Sc} can also be detected in urine samples obtained from patients with variant CJD.
- The National Prion Disease Pathology Surveillance Center at Case Western Reserve University performs specific diagnostic tests free of charge and acts as a reporting center to the CDC.

IMAGING STUDIES

MRI scan is one of the most sensitive diagnostic tools for CJD. It can show areas of restricted diffusion in the basal ganglia and/or cerebral cortex. MRI diffusion-weighted imaging has a sensitivity of 92.3% and a specificity of 93.8% in cases of rapidly progressive dementia. T2-weighted imaging may also show subtle hyperintensities in the lenticular nuclei in about 82% of cases.

TREATMENT

NONPHARMACOLOGIC THERAPY

Full-time caregiver or nursing home: Social work can be helpful with end-of-life discussions, family counseling, and optimizing appropriate home services. Proper disposal of medical equipment and avoidance of organ transplants from these patients prevent transmission of the disease.

ACUTE GENERAL Rx

No known therapy

CHRONIC Rx

No known therapy

DISPOSITION

The disease is fatal. Mean duration of illness is 8 mo (range, 1 to 130 mo). One in 7 survives to 1 yr, and 1 in 30 survives to 2 yr. Better survival found in younger age at onset of disease and female gender. Increased survival may be falsely reported due to coexisting dementias such as Alzheimer disease with earlier onset of dementia than CJD.

REFERRAL

- Neurology for evaluation of any rapidly progressive dementia
- Social work

PEARLS & CONSIDERATIONS

COMMENTS

- A diagnosis of CJD should be considered in patients with rapid progression of dementia from unknown causes.
- Exposure to human or animal nervous tissues increases the odds of CJD in patients presenting with progressive dementia.
- Related diseases in human beings: Kuru, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, new-variant CJD.
- Related diseases in animals: Scrapie, bovine spongiform encephalopathy (mad cow disease).

SUGGESTED READINGS

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Crohn Disease PTG

BASIC INFORMATION

DEFINITION

Crohn disease (CD) is an inflammatory disease of the bowel of unknown etiology, most commonly involving the terminal ileum and manifesting primarily with diarrhea, abdominal pain, fatigue, and weight loss.

SYNONYMS

CD
Regional enteritis
Inflammatory bowel disease (IBD)

ICD-10CM CODES

K50.00	Crohn disease of small intestine without complications
K50.011	Crohn disease of small intestine with rectal bleeding
K50.012	Crohn disease of small intestine with intestinal obstruction
K50.013	Crohn disease of small intestine with fistula
K50.014	Crohn disease of small intestine with abscess
K50.018	Crohn disease of small intestine with other complication
K50.019	Crohn disease of small intestine with unspecified complications
K50.10	Crohn disease of large intestine without complications
K50.111	Crohn disease of large intestine with rectal bleeding
K50.112	Crohn disease of large intestine with intestinal obstruction
K50.113	Crohn disease of large intestine with fistula
K50.114	Crohn disease of large intestine with abscess
K50.118	Crohn disease of large intestine with other complication
K50.119	Crohn disease of large intestine with unspecified complications
K50.80	Crohn disease of both small and large intestine without complications
K50.811	Crohn disease of both small and large intestine with rectal bleeding
K50.812	Crohn disease of both small and large intestine with intestinal obstruction
K50.813	Crohn disease of both small and large intestine with fistula
K50.814	Crohn disease of both small and large intestine with abscess
K50.818	Crohn disease of both small and large intestine with other complication
K50.819	Crohn disease of both small and large intestine with unspecified complications
K50.90	Crohn disease, unspecified, without complications
K50.911	Crohn disease, unspecified, with rectal bleeding
K50.912	Crohn disease, unspecified, with intestinal obstruction
K50.913	Crohn disease, unspecified, with fistula
K50.914	Crohn disease, unspecified, with abscess
K50.918	Crohn disease, unspecified, with other complication
K50.919	Crohn disease, unspecified, with unspecified complications

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- Annual incidence ranges from 3 to 20 cases per 100,000.
- Median age of onset is 30 yr.
- Crohn disease has 2 peaks, the first between age 20 and 30 yr and the second a smaller peak around 50 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical exam findings vary depending on disease location and severity
- Abdominal tenderness, mass, or distention
- Chronic or nocturnal diarrhea
- Weight loss, fever, night sweats
- Hyperactive bowel sounds in patients with partial obstruction, bloody diarrhea
- Delayed growth and failure of normal development in children
- Perianal and rectal abscesses, multiple sinuses and scarring (Fig. E1), mouth ulcers, cobblestone appearance of oral mucosa (Fig. E2), and atrophic glossitis
- Extraintestinal manifestations (Table E1): Joint swelling and tenderness, hepatosplenomegaly, erythema nodosum, clubbing, tenderness to palpation of the sacroiliac joints
- Symptoms may be intermittent, with varying periods of remission
- Overall 45% to 50% of patients have ileocolonic inflammation, 30% have isolated small bowel disease, 20% have isolated colonic disease, and 5% have isolated upper GI or perianal manifestations

ETIOLOGY

Unknown. Pathophysiologically, Crohn disease involves an immune system dysfunction.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ulcerative colitis (see Table 2)
- Infectious diseases (tuberculosis, *Yersinia, Salmonella, Shigella, Campylobacter*)
- Parasitic infections (amebic infection)
- Pseudomembranous colitis
- Ischemic colitis in elderly patients
- Lymphoma
- Colon carcinoma
- Diverticulitis
- Radiation enteritis
- Collagenous colitis
- Fungal infections (*Histoplasma, Actinomyces*)
- Anorectal and colon diseases, formerly referred to as gay bowel syndrome
- Carcinoid tumors
- Celiac sprue
- Mesenteric adenitis

LABORATORY TESTS

- Decreased hemoglobin and hematocrit from chronic blood loss, effect of inflammation on bone marrow, and malabsorption of vitamin B_{12}
- Hypokalemia, hypomagnesemia, hypocalcemia, and low albumin in patients with chronic diarrhea
- Vitamin B_{12} and folate deficiency
- Elevated erythrocyte sedimentation rate and CRP
- Positive anti–*Saccharomyces cerevisiae* antibodies
- Elevated INR (due to vitamin K malabsorption)
- Fecal calprotectin has been reported as useful in screening of patients with suspected IBD. Based on a pretest probability of 32% in adults, an abnormal calprotectin test result increases the posttest probability to 91%, and a normal result reduces the probability of IBD to 3%. False elevations may occur with other gastrointestinal diseases such as bacterial, viral, and protozoal causes of infective diarrhea

TABLE 2 Differentiating Features

	Ulcerative Colitis	Crohn Disease
Site of involvement	Only involves colon Rectum almost always involved	Any area of the gastrointestinal tract Rectum usually spared
Pattern of involvement	Continuous	Skip lesions
Diarrhea	Bloody	Usually nonbloody
Severe abdominal pain	Rare	Frequent
Perianal disease	No	In 30% of patients
Fistula	No	Yes
Endoscopic findings	Erythematous and friable Superficial ulceration	Aphthoid and deep ulcers Cobblestoning
Radiologic findings	Tubular appearance resulting from loss of haustral folds	String sign of terminal ileum RLQ mass, fistulas, abscesses
Histologic features	Mucosa only Crypt abscesses	Transmural crypt abscesses, granulomas (about 30%)
Smoking	Protective	Worsens course
Serology	p-ANCA more common	ASCA more common

ASCA, Anti–*Saccharomyces cerevisiae* antibodies; *p-ANCA,* perinuclear antineutrophil cytoplasmic antibody; *RLQ,* right lower quadrant.
From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

ENDOSCOPIC EVALUATION

Endoscopic features of Crohn disease include asymmetric and discontinued disease, deep longitudinal fissures, cobblestone appearance, and presence of strictures (Fig. E3). Crypt distortion and inflammation are also present. Granulomas may be present.

IMAGING STUDIES

- CT of abdomen may show thickening of the terminal ileum and is helpful in identifying abscesses, fistulas (Fig. E4), and other complications.
- Magnetic resonance enterography (MRe) is superior to other imaging modalities in its ability to distinguish active from chronic fibrotic disease. It is, however, more expensive.
- In 10% to 15% of patients with IBD, a clear distinction between ulcerative colitis and Crohn disease cannot be made. In general, Crohn disease can be distinguished from ulcerative colitis by the presence of transmural involvement and the frequent presence of noncaseating granulomas and lymphoid aggregates on biopsy.

Rx TREATMENT

The medical management of Crohn disease is based on disease activity. According to Hanauer and Sanborn, disease activity can be defined as follows:

- Mild to moderate disease: The patient is ambulatory and able to take oral alimentation. There is no dehydration, high fever, abdominal tenderness, painful mass, obstruction, or weight loss of >10%.
- Moderate to severe disease: Either the patient has not responded to treatment for mild to moderate disease or has more pronounced symptoms, including fever, significant weight loss, abdominal pain or tenderness, intermittent nausea and vomiting, or significant anemia.
- Severe fulminant disease: Either the patient has persistent symptoms despite outpatient steroid therapy or has high fever, persistent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess.
- Remission: The patient is asymptomatic or without inflammatory sequelae, including patients responding to acute medical intervention.

NONPHARMACOLOGIC THERAPY

- Nutritional supplementation is needed in patients with advanced disease. Total parenteral nutrition may be necessary in selected patients.
- Low-residue diet is necessary when obstructive symptoms are present.
- If diarrhea is prominent, increased dietary fiber and decreased fat in the diet are sometimes helpful.
- Psychotherapy is useful for situational adjustment crises. A trusting and mutually understanding relationship and referral to self-help groups are very important because of the chronicity of the disease and the relatively young age of the patients.
- Avoid oral feedings during acute exacerbation to decrease colonic activity: A low-roughage diet may be helpful in early relapse.

ACUTE GENERAL Rx

- Corticosteroids are used to induce remission. They have been the mainstay for treating moderate to severe active Crohn disease. Prednisone 40 to 60 mg/day is useful for acute exacerbation. Steroids are usually tapered over approximately 2 to 3 mo. Some patients require a low dose for a prolonged period of maintenance.
- Steroid analogues are locally active corticosteroids that target specific areas of inflammation in the gastrointestinal tract. Budesonide is available as a controlled-release formulation and is approved for mild to moderate active Crohn disease involving the ileum and/or ascending colon. The adult dose is 9 mg qd for a maximum of 8 wk.
- Patients responding to glucocorticoids are transitioned to immunomodulators as their glucocorticoid is tapered.
- Immunosuppressants such as azathioprine or mercaptopurine are used for maintenance of remission. Methotrexate is an alternative agent.
- Metronidazole 500 mg qid may be useful for colonic fistulas and treatment of mild to moderate active Crohn disease. Ciprofloxacin 1 g qd has also been found to be effective in decreasing disease activity.
- TNF inhibitors are agents useful to induce remission and maintain remission in patients with moderate to severe Crohn disease. Infliximab, a chimeric monoclonal antibody targeting tumor necrosis factor-α, is effective in the treatment of enterocutaneous fistulas. This medication can induce clinical improvement in 80% of patients with Crohn disease refractory to other agents. It can be used in combination with other medications such as azathioprine in patients with severe Crohn disease. A PPD test should be done before using this medication. Adalimumab and certolizumab are other TNF inhibitors also effective in inducing remissions and may be useful in adult patients with Crohn disease who cannot tolerate infliximab or have symptoms despite receiving infliximab therapy. Efficacy is better when an anti-TNF is used together with an immunomodulator.
- Natalizumab, a selective adhesion-molecule inhibitor, has been reported to be effective in increasing the rate of remission and response in patients with active Crohn disease. It is effective for patients in whom anti-TNF therapy has been unsuccessful. Prior to using natalizumab, serologic testing should be done for JC virus, which causes multifocal leukoencephalopathy (PML), and if the patient is seronegative, the risk of PML from natalizumab is low. Vedolizumab is another IV integrin receptor antagonist recently FDA approved for moderate to severe Crohn disease patients who have not responded to or cannot tolerate standard treatment. Vedolizumab use is not associated with high risk of PML. Ustekinumab, a monoclonal antibody to the P_40 subunit of interleukin-12 and interleukin-23, has shown efficacy for induction and maintenance therapy for Crohn disease. It has been FDA-approved for moderate to severely active Crohn disease unresponsive to immunomodulators or corticosteroids or a tumor necrosis factor inhibitor.
- Hydrocortisone enema bid or tid is useful for proctitis.
- Most patients who have anemia associated with Crohn disease respond to iron supplementation. Erythropoietin is useful in patients with anemia refractory to treatment with iron and vitamins.

CHRONIC Rx

- Monitor disease activity with symptom review and laboratory evaluation (complete blood count and sedimentation rate).
- Liver tests and vitamin B_{12} levels monitored on a yearly basis.

DISPOSITION

There is no cure for CD, and most patients require at least one surgical resection. One tenth of patients have prolonged remission, three quarters have a chronic intermittent disease course, and one eighth have an unremitting course. Patients with IBD are at increased risk of colon cancer.

REFERRAL

Surgical referral is needed for complications such as abscess formation, obstruction, fistulas, toxic megacolon, refractory disease, or severe hemorrhage. Approximately 40% to 50% of patients will require some type of bowel surgery within the first 5 yr of Crohn disease. A conservative surgical approach is necessary because surgery is not curative. Multiple surgeries may also result in short bowel syndrome.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Crohn Disease (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Colombel JF et al: Infliximab, azathioprine, or combination therapy for Crohn's disease, *N Engl J Med* 362:1383-1395, 2010.

Feagan BG et al: Ustekinumab as induction and maintenance therapy for Crohn's disease, *N Engl J Med* 375:1946-1960, 2016.

Feuerstein JD, Cheifetz AS: Crohn disease: epidemiology, diagnosis, and management, *Mayo Clin Proc* 92(7):1088-1107, 2017.

Meyer A et al: Effectiveness and safety of reference infliximab and biosimilar in Crohn disease: a French equivalence study, *Ann Intern Med* 170:99-107, 2019.

Van Rheenen PF et al: Fecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis, *BMJ* 341:c3369, 2010.

FIG. E1 Crohn disease affecting the skin of the buttocks, with multiple sinuses and scarring. This patient had a lesion of pyoderma gangrenosum when first seen and developed inflammatory plaques with the appearance of Sweet disease on the trunk (with the novel feature of a Koebner reaction into recent scars). (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

FIG. E2 Crohn disease of the oral mucosa. In this fairly quiescent example, there is a granular cobblestoned appearance. Some patients have more aggressive fissured and ulcerated plaque lesions. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

TABLE E1 Extraintestinal Manifestations of Inflammatory Bowel Disease

Feature or Disease	Crohn	Ulcerative Colitis
Peripheral arthritis	~15%	~10%
Axial or sacroiliac arthritis	~15%-20%	~10%-15%
Septic arthritis	Rare	Not reported
Skin		
Erythema nodosum	Up to 15%	<15%
Erythema multiforme	Rare	?
Pyoderma gangrenosum	0.5%-2%	0.3%-0.4% in severe disease
Aphthous ulcers	Rare	1%-8%
Nephrolithiasis (oxalate)	<15%	?
Amyloidosis	Very rare	Not reported
Liver disease	3%-5%	7%
Uveitis	13%	4%
Vasculitis	Takayasu	<5%
Clubbing of fingers	Yes	1%-5%
Increased prevalence of asthma	Yes	Yes
Increased prevalence of multiple sclerosis	No	Yes

From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.

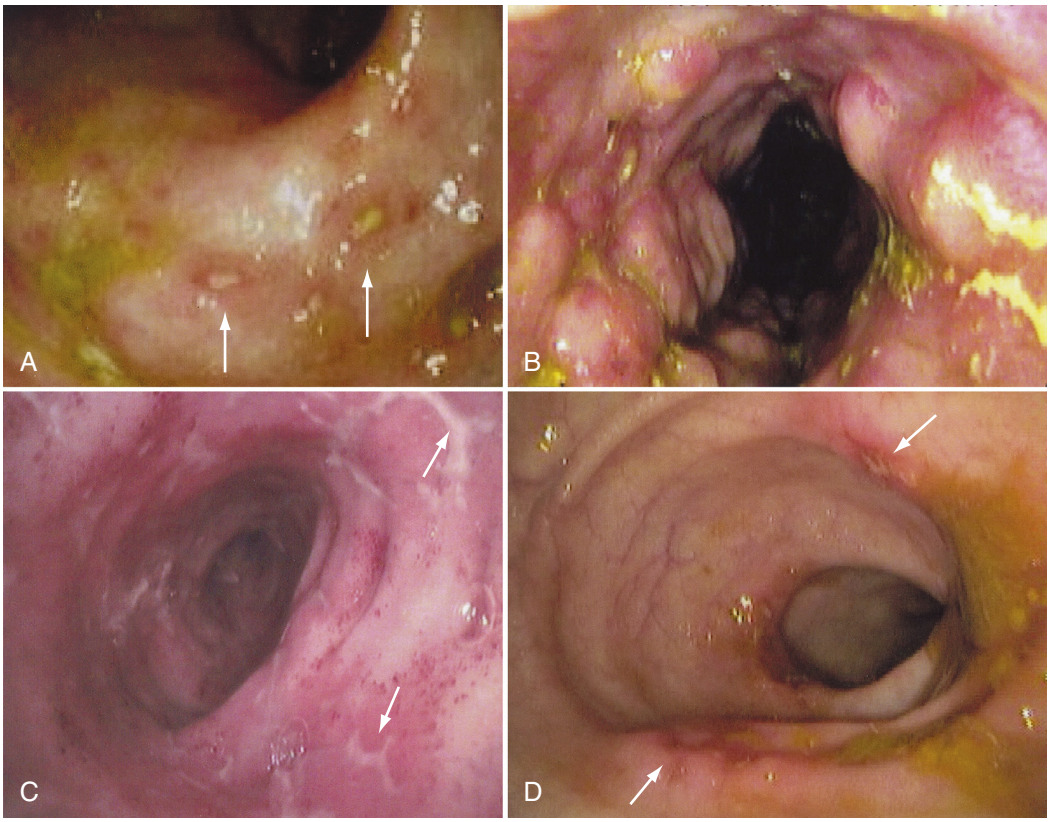

FIG. E3 Endoscopic appearance of Crohn disease. A wide variety of findings may be visualized on endoscopy, in part depending on the duration and severity of the inflammation. **A,** Typical aphthous ulcers *(arrows)* consisting of a central white depression surrounded by a slightly elevated, erythematous rim only a few millimeters in diameter. **B,** Findings more typical of advanced disease, with erythema, edema, and a cobblestone appearance. **C,** Stellate ulcers *(arrows)* in the terminal ileum. **D,** Discrete ulcers *(arrows)* with normal intervening mucosa typical of the patchy inflammation seen in Crohn disease. (From Feldman M et al: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

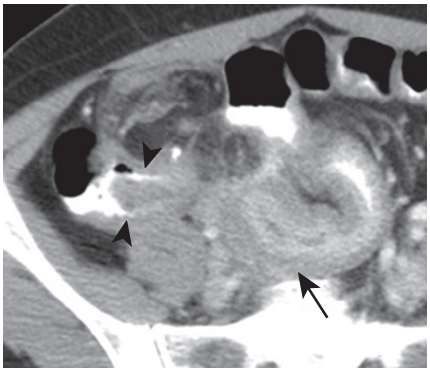

FIG. E4 Crohn disease: Fistulas. The ileum *(arrow)* in the right lower quadrant exhibits marked wall thickening and matting of bowel loops caused by inflammation of the mesentery. A double-tract bowel lumen *(arrowheads)* is seen, indicating the formation of an ileo–ileal fistula. (From Webb WR, Brant WE, Major NM: *Fundamentals of body CT,* ed 4, Philadelphia, 2015, Saunders.)

BASIC INFORMATION

DEFINITION

Acute laryngotracheobronchitis is a viral infection of the upper and lower respiratory tract leading to erythema and edema of the tracheal walls and narrowing of the subglottic region. Laryngotracheitis, which is limited to larynx and trachea, is also known as croup.

SYNONYM

Laryngotracheobronchitis

ICD-10CM CODE
J05.0 Acute obstructive laryngitis [croup]

EPIDEMIOLOGY & DEMOGRAPHICS

- Croup is primarily a disease of children occurring between the ages of 1 and 6 yr.
- The peak incidence of croup is between 6 and 36 mo.
- Most cases occur in the fall and represent parainfluenza type 1 viral infection.
- Winter outbreaks usually represent infection by influenza A and B viruses. Fig. E1 illustrates the seasonal occurrence of croup cases in relation to the epidemiologic activity of the respiratory viruses associated with croup.
- Croup accounts for 10% to 15% of lower respiratory tract infections in young children.
- Boys are affected more often than girls at a ratio of 1.4:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Most children with croup present with symptoms of an upper respiratory infection for several days (Fig. E2):

- Rhinorrhea
- Cough
- Low-grade fever
- Barking cough that usually occurs at night and awakens the child
- Sore throat
- Stridor
- Apprehension
- Use of accessory muscles of respiration
- Tachypnea
- Tachycardia
- Wheezing

ETIOLOGY

- Parainfluenza viruses (types 1, 2, and 3) are the most common causes of croup in the United States.
- Type 1 is the most common cause of fall and winter outbreaks, with type 2 causing milder disease outbreaks. Parainfluenza type 3, although sporadic, can be more severe than other types.
- Respiratory syncytial virus (RSV) and adenovirus are common causes of croup as well.
- Human coronavirus NL63, rhinoviruses, enteroviruses such as Coxsackie and echovirus.
- Influenza A and B, although not common causes of croup, do lead to more severe cases of the disease.
- *Mycoplasma pneumoniae* (rare).

DIAGNOSIS

The diagnosis of croup is usually based on the characteristic clinical presentation of a young child between the ages of 1 and 6 yr waking up with a barking cough ("seal's bark") and stridor.

DIFFERENTIAL DIAGNOSIS

- Spasmodic croup
- Epiglottitis
- Bacterial tracheitis
- Angioneurotic edema
- Diphtheria
- Peritonsillar abscess
- Retropharyngeal abscess
- Smoke inhalation
- Foreign body

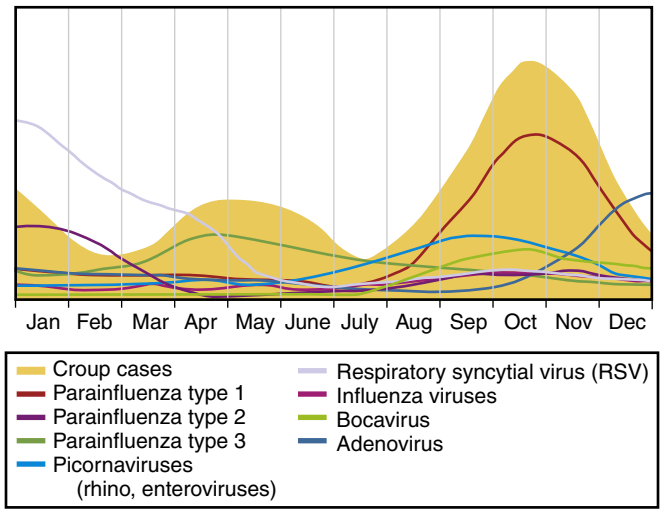

FIG. E1 The seasonal occurrence of croup cases is shown in relation to the epidemiologic activity of the respiratory viruses associated with croup. The major seasons of croup cases in temperate climates occur from fall to winter every other year, when outbreaks of parainfluenza type 1 virus occur, and from spring to summer, when parainfluenza type 3 is prominent. Influenza and respiratory syncytial virus are epidemic during winter to spring but contribute small proportions of cases. The picornaviruses, adenovirus, coronaviruses, and bocavirus are present through many months of the year. (From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.)

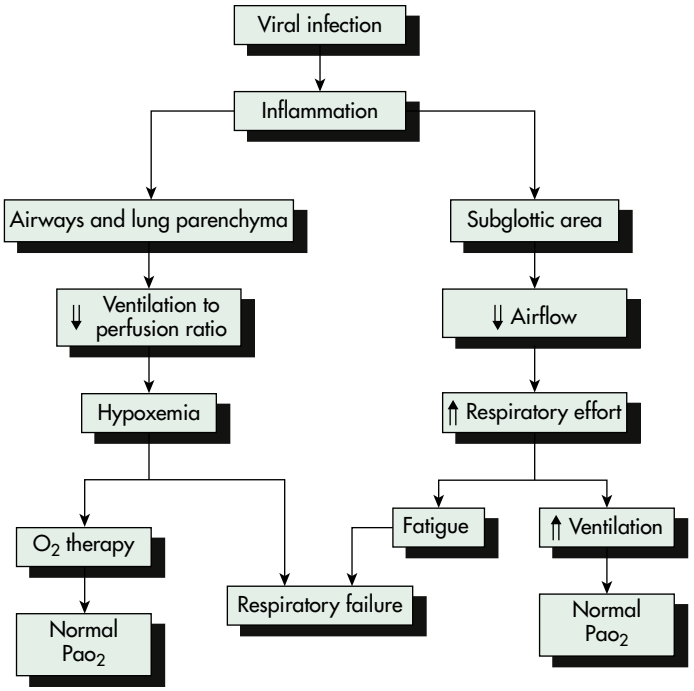

FIG. E2 Physiologic abnormalities in croup. O_2, Oxygen; Pao_2, partial pressure of oxygen in arterial blood. (From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.)

TABLE E1 Characteristics of Laryngotracheobronchitis, Bacterial Tracheitis, and Epiglottitis

	Laryngotracheobronchitis	Bacterial Tracheitis	Epiglottitis
Age	3 mo to 3 yr	6 mo to 12 yr	12 yr (average)
Onset	Gradual	Intermediate	<24 hr
Fever	Usually low	Usually high	High
Cough	Characteristic "barking"	Characteristic "barking"	None
Sore throat	None	Usually absent	Often severe
Drooling	No	No	Usually
Posture	Any position	Any position	Sitting forward, mouth open, drooling
Voice	Normal	Normal or hoarse	Muffled
Appearance	Nontoxic	Toxic	Toxic
Seasonal distribution	Usually winter, epidemic	Throughout the year	Throughout the year

From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

WORKUP

- The workup of a child with croup is to differentiate viral laryngotracheobronchitis from noninfectious causes of stridor, bacterial tracheitis, and epiglottitis caused by *H. influenzae* (Table E1).
- The clinical presentation and plain films of the soft tissues of the neck assist in differentiating viral from nonviral and noninfectious causes.

LABORATORY TESTS

- Laboratory tests are not often used to make the diagnosis of viral tracheobronchitis.
- CBC, viral antibody serology panels, and tissue cultures can be ordered and may detect the infecting agent in up to 65% of cases.
- Pulse oximetry and arterial blood gas (ABG) determination for patients with tachypnea and respiratory distress.

IMAGING STUDIES

- Plain (anteroposterior and lateral) films of the soft tissues of the neck (Fig. E3) may show the classic radiographic finding of subglottic stenosis or "steeple" sign.
- CT scan of the soft tissues of the neck may be performed in cases in which the differentiation between croup, epiglottitis, and noninfectious causes is more difficult.
- Direct visualization via laryngoscopy may be useful in some situations under a controlled setting.

Rx TREATMENT

Treatment of croup focuses on airway management. Table E2 summarizes the evaluation and management of children with croup.

NONPHARMACOLOGIC THERAPY

- Humidified oxygen or humidified air
- Cool mist
- Hot steam

ACUTE GENERAL Rx

- 0.25 to 0.75 ml of 2.25% racemic epinephrine every 20 min is used in children with severe respiratory symptoms, rest stridor, and impending intubation.
- Corticosteroids (e.g., dexamethasone 0.6 mg/kg IV or PO, prednisone 2 mg/kg/day) have been shown to be effective.
- Budesonide, a nebulized corticosteroid given at 4 mg, has been shown to improve symptoms in patients with moderate to severe croup.

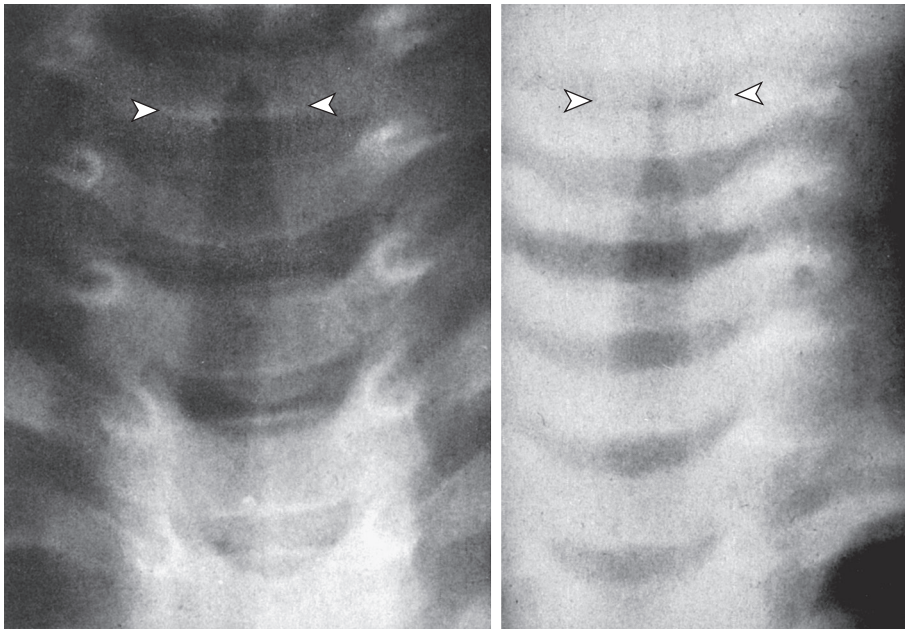

FIG. E3 Laryngotracheobronchitis. Anteroposterior radiograph of the neck. *Left,* A normal tracheal air column (between the *arrows*). *Right,* Trachea narrowed *(arrows)* by laryngotracheobronchitis. (From Fuhrman BP et al: *Pediatric critical care,* Philadelphia, ed 4, 2011, Saunders.)

DISPOSITION

- Croup is usually benign and self-limited, resolving within 3 to 4 days.
- Complications include:
  1. Airway obstruction
  2. Otitis media
  3. Pneumonia
  4. Dehydration

REFERRAL

If intubation is needed (rarely), an emergency consultation with otolaryngology (ENT) and/or anesthesiology is recommended.

PEARLS & CONSIDERATIONS

COMMENTS

- Most patients with croup can be managed at home (e.g., patients without stridor and in no respiratory distress).
- Hospitalization and observation are required for children with moderate to severe croup (e.g., rest stridor, respiratory distress refractory to the previously mentioned acute treatments). A family history of croup is a risk factor for croup and recurrent croup.
- Heliox: Helium-oxygen therapy has shown benefit in acute RSV infections and bronchiolitis, but in general there is little evidence to support its use in croup.

SUGGESTED READINGS

Choi J, Lee GL: Common pediatric respiratory emergencies, *Emerg Med Clin North Am* 30(2):529-563, 2012.

Johnson DW: Croup, *BMJ Clin Evid* pii: 0321, 2014.

Zoorob R et al: Croup: an overview, *Am Fam Physician* 83:1067-1073, 2011.

RELATED CONTENT

Croup (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

TABLE E2 Evaluation and Management of Children with Croup

	Croup Severity		
	Mild (≤2)	**Moderate (3-7)**	**Severe (≥8)**
	Barking cough, hoarseness; no stridor, no or minimal chest wall retractions *at rest*	Stridor and chest wall retractions *at rest; no agitation*	Stridor, sternal contractions *at rest, accompanied by agitation or fatigue*
Therapy			
Decongestants, cough suppressants, antibiotics	Not recommended	Not recommended	Not recommended
Humidification	Not proven beneficial	Not effective	Not effective
Corticosteroids	Dexamethasone (0.6 mg/kg, 1 dose PO)	Dexamethasone (0.6 mg/kg, one dose PO or IM)	Dexamethasone (0.6 mg/kg, one dose PO or IM)
Nebulized epinephrine	Not recommended	Not recommended	Nebulized racemic epinephrine (2.25%, 0.5 ml in 2.5 ml of saline or L-epinephrine [1:1000 dilution in 5 ml of saline])
Disposition	Discharge home	Discharge to home if no stridor and no retractions at rest. If no improvement in 4 hr, consider hospitalization	Observe for 2 hr. *Good response:* No recurrence, no stridor, no retractions at rest. Discharge to home. *Poor response:* Stridor, retractions at rest after two epinephrine doses. Hospitalize.

IM, Intramuscular; *PO,* by mouth.
From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.

Cryoglobulinemia

BASIC INFORMATION

DEFINITION

Cryoglobulins are serum immunoglobulins that precipitate when cooled and redissolve when heated. A classification of cryoglobulins is described in Table 1 and Fig. 1. Cryoglobulinemia is a clinical syndrome that results from systemic inflammation caused by cryoglobulin-containing immune complexes. Mixed cryoglobulinemia is a vasculitis of small and medium-sized arteries and veins due to the deposition of complexes of antigen, cryoglobulin, and complement in the vessel walls. Classification criteria for cryoglobulinemic vasculitis is summarized in Table 2.

SYNONYMS

Cryoglobulinemic vasculitis
Cryoproteinemia
Mixed cryoglobulinemia
Essential cryoglobulinemia

ICD-10CM CODES

D89.1 Cryoglobulinemia

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- Prevalence of mixed cryoglobulinemia is approximately 1:100,000 and accounts for 85% to 90% of cryoglobulinemic vasculitis cases.
- Approximately 19% to 50% of patients with HCV are found to have mixed cryoglobulinemia; only 5% to 10% develop vasculitis.
- Three types: I (monoclonal), II (IgM monoclonal and IgG polyclonal), and III (polyclonal).

PREDOMINANT SEX AND AGE: Female-to-male ratio of 3:1

PREDOMINANT AGE: Mean age reported is 42 to 52 yr.

RISK FACTORS:

- HCV infection
- Connective tissue disorders
- Lymphoproliferative disorders

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- *Meltzer triad* of purpura, arthralgias/myalgia, and weakness is seen in one third of patients.
- Palpable purpura occurs in approximately 90% of patients.
- Other symptoms include dyspnea, cough, numbness, abdominal pain, acrocyanosis, Raynaud phenomenon, ischemic ulcers, hypertension, hepatomegaly, livedo reticularis, and in severe cases, distal necrosis, retiform purpura of lower extremities (Fig.E2), and ulcerations of lower limbs.

ETIOLOGY

- Intravascular deposition of cryoglobulins leading to ischemic insults in territory supplied by vasa nervorum
- Necrotizing vasculitis caused by cryoglobulin precipitation in cooler areas (distal extremities) and kidneys (increased concentration due to ultrafiltration)

TABLE 1 Classification of Cryoglobulins

Type	Composition	Associated Disease
I	Monoclonal IgG, IgA, or IgM	Multiple myeloma (IgG, IgM) Chronic lymphocytic leukemia Waldenstrom macroglobulinemia Idiopathic monoclonal gammopathy Lymphoproliferative disorders
II	Polyclonal IgG and monoclonal IgM (with rheumatoid factor activity)	Hepatitis C, hepatitis B, HIV Neoplasms: Chronic lymphocytic leukemia, diffuse lymphoma, B lymphocytic neoplasia
III	Polyclonal IgG and polyclonal IgM	Infections: Viral (hepatitis B and C, Epstein-Barr virus, cytomegalovirus), bacterial (endocarditis, leprosy, poststreptococcal glomerulonephritis), parasitic (schistosomiasis, toxoplasmosis, malaria) Autoimmune disorders: Systemic lupus erythematosus, rheumatoid arthritis Lymphoproliferative disorders Chronic liver disease

IgG, Immunoglobulin G; *IgA,* immunoglobulin A; *IgM,* immunoglobulin M.
From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

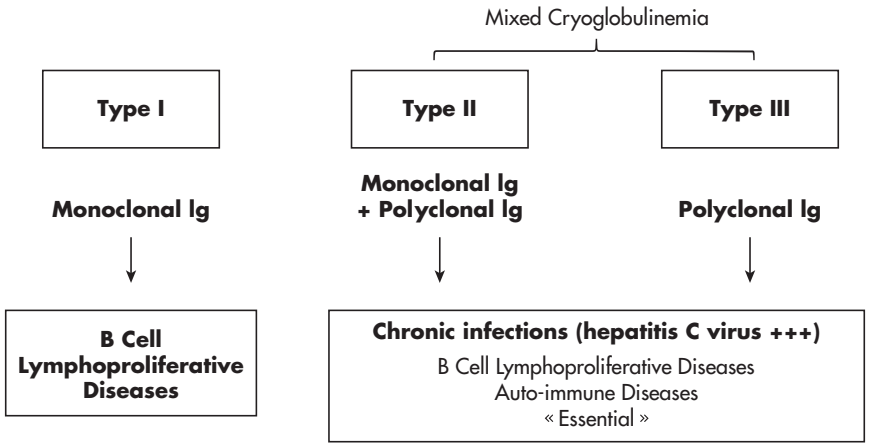

FIG. 1 Cryoglobulin immunotyping and related underlying diseases. *Ig,* Immunoglobulin. (From Cacoub P et al: Cryoglobulinemia vasculitis. *Am J Med* 128[9]:950–955.)

TABLE 2 Classification Criteria for Cryoglobulinemic Vasculitis

Satisfied if at least two of the three items (questionnaire, clinical, laboratory) are positive. The patient must be positive for serum cryoglobulins in at least two determinations at ≥12-wk intervals.

1. Questionnaire item: At least two of the following

- Do you remember one or more episodes of small red spots on your skin, particularly involving the lower limbs?
- Have you ever had red spots on your lower extremities that leave a brownish color after their disappearance?
- Has a doctor ever told you that you have viral hepatitis?

2. Clinical item: At least three of the following four (present or past)

Constitutional symptoms	Fatigue Low-grade fever (37-37.9 °C, >10 days, no cause) Fever (>38 °C, no cause) Fibromyalgia
Articular involvement	Arthralgias Arthritis
Vascular involvement	Purpura Skin ulcers Necrotizing vasculitis Hyperviscosity syndrome Raynaud phenomenon
Neurologic involvement	Peripheral neuropathy Cranial nerve involvement Vasculitic CNS involvement

3. Laboratory item: At least two of the following three (present)

- Reduced serum C4
- Positive serum RF
- Positive serum M component

CNS, Central nervous system; *RF,* rheumatoid factor.
From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

- Infections: HCV, mycosis fungoides, HBV, HIV, Epstein-Barr virus, cytomegalovirus, *Treponema pallidum,* Mycobacterium leprae, and in post-streptococcal glomerulonephritis
- Lymphoproliferative disorders: Chronic lymphocytic leukemia, Waldenström macroglobulinemia, multiple myeloma
- Connective tissue disorders: Sjögren syndrome, rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma, vasculitis
- Renal diseases including proliferative glomerulonephritis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Antiphospholipid syndrome
- SLE
- Churg-Strauss syndrome
- Cirrhosis
- Glomerulonephritis
- Goodpasture syndrome
- Hemolytic uremic syndrome
- Hepatitis
- Lymphoma
- Sarcoidosis
- Waldenström hypergammaglobulinemia

WORKUP

History and physical examination; laboratory tests; imaging tests depending on patients' presentation.

LABORATORY TESTS

- Serum cryoglobulins, rheumatoid factor, serum complement, hepatitis C titer, urinalysis, CBC, ALT, AST, BUN, creatinine.
- Sample collection for cryoglobulins is essential. Sample tubes should be prewarmed and kept at 37 °C through transport and processing.
- Electromyogram/nerve conduction studies may demonstrate axonal changes and distal muscle denervation.
- Sural nerve and skin biopsy.

IMAGING STUDIES

Chest x-ray for pulmonary involvement, CT scan to evaluate for malignancy, and angiography for vasculitis

TREATMENT

- Management of type I cryoglobulinemia is directed at treating the underlying disorder.

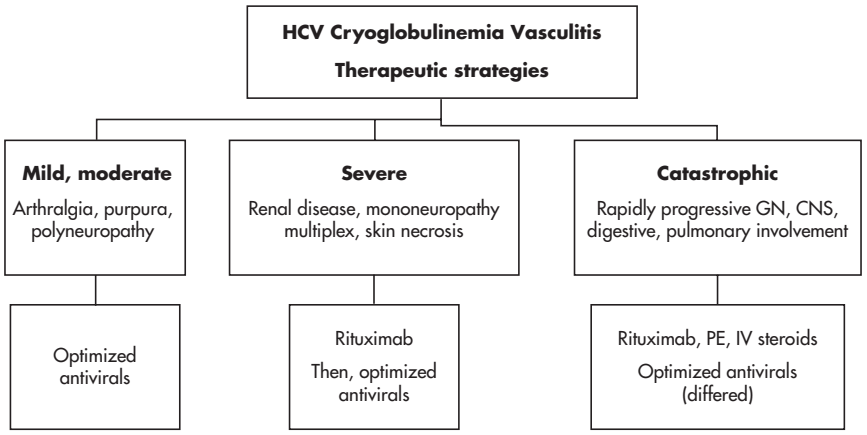

FIG. 3 Treatment of HCV-related mixed cryoglobulinemia vasculitis according to the presentation. *CNS,* Central nervous system; *GN,* glomerulonephritis; *HCV,* hepatitis C virus; *IV,* intravenous; *PE,* pulmonary embolism. (From Cacoub P et al: Cryoglobulinemia vasculitis, *Am J Med* 128[9]:950–955.)

- For noninfectious mixed cryoglobulinemia, treatment is based on disease severity. Low-dose corticosteroids, NSAIDs, and colchicine should be given for mild symptoms. Rituximab, high-dose corticosteroids, cyclophosphamide, and/or plasmapheresis should be given for severe disease.
- In patients with HCV, mild symptoms can be managed by treatment with direct-acting antivirals (DAA). Therapy is aimed at eradicating the HCV infection, suppressing B-cell clonal expansion and cryoglobulin production, and ameliorating symptoms.
- For severe disease in HCV-infected patients, initial immunosuppression with rituximab is warranted, followed by initiation of antiviral therapy.
- Fig. 3 illustrates the treatment of HCV-related mixed cryoglobulinemia vasculitis according to presentation.
- Sustained virologic response due to DAA does not always fully eradicate cryoglobulinemia but can help mitigate its manifestations.

NONPHARMACOLOGIC THERAPY

Avoidance of cold exposure, diabetic food care guidelines

ACUTE GENERAL Rx

NSAIDs in those with general fatigue and arthralgia; see "Treatment" for further management.

DISPOSITION

Overall prognosis is worse with concomitant renal disease. Mean survival rate is ~50% at 10 yr.

REFERRAL

Consider referring to the following:

- Nephrologist if there is renal involvement
- Hematologist in patients with lymphoproliferative disorders
- Gastroenterologist/hepatologist in patients with hepatitis
- Rheumatologist in patients with connective tissue disease cases
- Clinical immunologist in severe cases

PEARLS & CONSIDERATIONS

COMMENTS

Always look for underlying cause of cryoglobulinemia.

PREVENTION

Avoidance of cold exposure, avoidance of late complications.

PATIENT & FAMILY EDUCATION

Inform patients about early signs/symptoms of cryoglobulinemia so that treatment can be rendered before the development of complications.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Rebecca Soinski, MD**

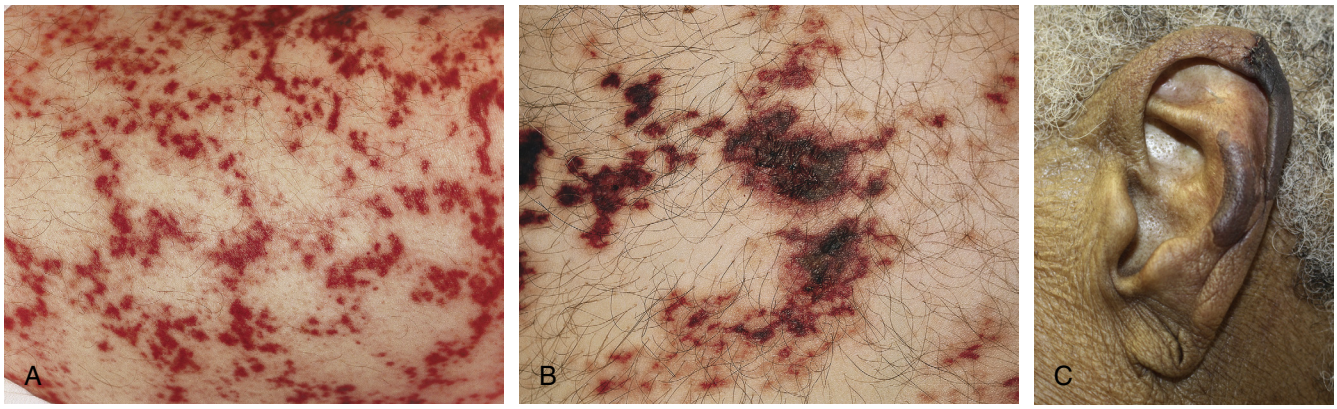

FIG. E2 Type I cryoglobulinemia in two patients with multiple myeloma (IgG type). A, Retiform purpura of the lower extremity. **B**, Areas of necrosis within the areas of retiform purpura. **C**, Purpuric lesions of the antihelix and helix of the ear. (**A, B**, Courtesy, Jean L. Bolognia, MD; **C**, Courtesy, Jonathan Leventhal, MD, In Bolognia J: *Dermatology*, ed 4, Philadelphia, 2018, Elsevier.)

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Cryptococcosis PTG

BASIC INFORMATION

DEFINITION

Cryptococcosis is an infection caused by the encapsulated yeast *Cryptococcus* spp.

SYNONYMS

C. neoformans infection
C. gattii infection
C. albidus infection
C. laurentii infection

ICD-10CM CODES

B45.09	Pulmonary cryptococcosis
B45.1	Cerebral cryptococcosis
B45.2	Cutaneous cryptococcosis
B45.3	Osseous cryptococcosis
B45.7	Disseminated cryptococcosis
B45.9	Cryptococcosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- 0.8 cases per million persons/yr; *C. neoformans* is an important opportunistic infection in patients with deficits in cell-mediated immunity.
- 2 to 7 per 1000 persons living with AIDS/yr.

PEAK INCIDENCE: 20 to 40 yr (parallel to HIV/AIDS epidemic)
PREDOMINANT SEX: Equal sex distribution when adjusted for HIV status
PREDOMINANT AGE: Less than 2 yr of age; 20 to 40 yr of age
NEONATAL INFECTION: Very uncommon

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- More than 90% present with meningitis (generally subacute); almost all have fever and headache
- Meningismus, photophobia, mental status changes are seen in approximately 25%
- Increased intracranial pressure may be present
- Most common infections outside the CNS:
  1. In the lungs (fever, cough, dyspnea, and typically with lobar consolidation)
  2. In the skin (cellulitis, papular eruption)
  3. In the lymph nodes (lymphadenitis)
  4. Potential involvement of virtually any organ (e.g., prostate and bone)

ETIOLOGY

- There are four *Cryptococcus spp.* that cause disease in humans, although most laboratories are not able to differentiate between species. *C. neoformans* (Table E1) is the cause of a majority of global disease burden, primarily in immunocompromised patients. *C. gattii* infections are much less common and occur more often in normal hosts, with recent outbreaks in the Pacific Northwest. *C. albidus* and *C. laurentii* are even rarer causes of disease.
- Infection originates by inhalation into the respiratory tract followed by dissemination to the CNS in most cases, usually without recognizable lung involvement.
- Almost always in the setting of AIDS (most with CD4 counts <100) or other disorders of cellular immune function, such as organ transplantation.
- Neutropenia alone poses a much lower risk of significant cryptococcal infection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Subacute meningitis (caused by *Listeria monocytogenes,* Mycobacterium tuberculosis, *Histoplasma capsulatum,* viruses)
- Intracranial mass lesion (neoplasms, toxoplasmosis, TB)
- Pulmonary involvement confused with *Pneumocystis jiroveci* pneumonia when diffuse or confused with TB or bacterial pneumonia when focal or involving the pleura
- Skin lesions can take many forms and may be confused with bacterial cellulitis or molluscum contagiosum

WORKUP

- Lumbar puncture to exclude cryptococcal meningitis, with measurement of opening pressure because CSF opening pressure is elevated in 60% to 80% of HIV patients and may require drainage. In cryptococcal meningitis, CSF reveals lymphocytic pleocytosis (although a paucity of WBCs may be found in CSF of HIV patients)
- CT scan of the head when focal lesion or increased intracranial pressure is suspected
- Biopsy of enlarged lymph nodes and skin lesions if feasible

LABORATORY TESTS

- Culture and India ink stain (60% to 80% sensitive in culture-proven cases [Fig. E1]); examination of the CSF in all cases when CNS involvement is suspected
- Blood and serum cryptococcal antigen assay (>90% sensitivity and specificity in immunocompromised patients; lower sensitivity in immunocompetent patients)
- Culture and histologic examination of biopsy material
- HIV antibody testing

IMAGING STUDIES

- CT scan or MRI of the head if focal neurologic involvement or cryptococcoma is suspected
- Chest x-ray examination to exclude pulmonary involvement

TREATMENT

ACUTE GENERAL Rx

- Treatment of cryptococcosis consists of three stages: Induction, consolidation, and maintenance. Induction therapy for CNS disease (meningitis) was historically initiated with IV amphotericin B deoxycholate (0.7 to 1.0 mg/kg/day) with flucytosine 100 mg/kg/day PO in four divided doses; however, there is growing clinical evidence for liposomal amphotericin B (3 to 6 mg/kg/day) plus flucytosine, especially in HIV-infected patients and in those with renal dysfunction. Induction therapy is generally recommended for 2 to 4 wk and until repeat CSF cultures are negative; it is then recommended to transition to consolidation therapy with fluconazole 400 mg PO q24h for 8 wk, followed by ongoing fluconazole 200 mg PO q24h maintenance therapy (up to 2 yr) to reduce relapse rate. Maintenance therapy is indicated in patients with AIDS until these patients have been receiving antifungal therapy for at least 1 yr and they have responded to antiretroviral therapy (CD4 cell count ≥100/microliter for ≥3 mo). In patients without HIV, the duration of maintenance therapy is generally 6 to 12 mo. Lifelong antifungal therapy is needed in organ transplant patients.
- Alternative: IV fluconazole combined with flucytosine for initial therapy in patients unable to tolerate amphotericin B.
- If symptomatic increased intracranial pressure, consider multiple therapeutic lumbar taps or intraventricular shunt.
- Data support increased mortality with early initiation of antiretroviral therapy in the setting of cryptococcal meningitis due to immune reconstitution syndrome; therefore it is generally recommended to wait 2 to 10 wk after starting cryptococcal therapy prior to starting antiretroviral therapy.
- CSF removal with daily lumbar puncture or insertion of a shunt is beneficial in patients with elevated intracranial pressure.

CHRONIC Rx

- Fluconazole (200 to 400 mg PO qd) is highly effective in preventing a relapse in HIV-infected patients; development of resistance may occur. Itraconazole is an alternative agent, along with growing evidence for voriconazole and posaconazole use.

DISPOSITION

Without maintenance therapy, relapse rate is >50% among AIDS patients.

REFERRAL

- For consultation with infectious diseases specialist in all cases
- For neurologic consultation if level of consciousness is depressed or focal lesion is present

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Cryptococcosis (Patient Information)

AUTHORS: **Philip A. Chan, MD, MS,** and **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Boulware D et al: Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis, *N Engl J Med* 370:2487-2498, 2014.

Maziarz EK, Perfect JR: Cryptococcosis, *Infect Dis Clin North Am* 30:179-206, 2016.

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents: Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.

Perfect JR et al: Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America, *Clin Infect Dis* 50:291-322, 2010.

TABLE E1 Summary of Characteristics of *Cryptococcus gattii* and *Cryptococcus neoformans*

	Cryptococcus gattii	***Cryptococcus neoformans***
Microbiology	Serotypes B and C Molecular type VGI associated with Australia and VGIIa with outbreak in Pacific Northwest Bluish discoloration on CGB media Distinction can also be made by MALDI-MS	Serotypes A and D Molecular type VNI most common cause of *C. neoformans* diseases
Ecology	Eucalyptus and other trees	Bird droppings and trees
Epidemiology	Immunocompetent > immunocompromised Endemic in certain tropical/subtropical regions Outbreak in Pacific Northwest	Immunocompromised (especially AIDS and T-cell defects) > immunocompetent High incidence in sub-Saharan Africa and Southeast Asia Decreased incidence in regions where HAART is available
Clinical manifestations	Primary pulmonary infection and CNS cryptococcomas with associated complications	Meningoencephalitis and disseminated disease a common presentation, especially among AIDS patients

AIDS, Acquired immunodeficiency syndrome; *CGB,* l-canavanine, glycine, and bromothymol blue; *CNS,* central nervous system; *HAART,* highly active antiretroviral therapy; *MALDI-MS,* matrix-assisted laser desorption/ionization time of flight.

From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.

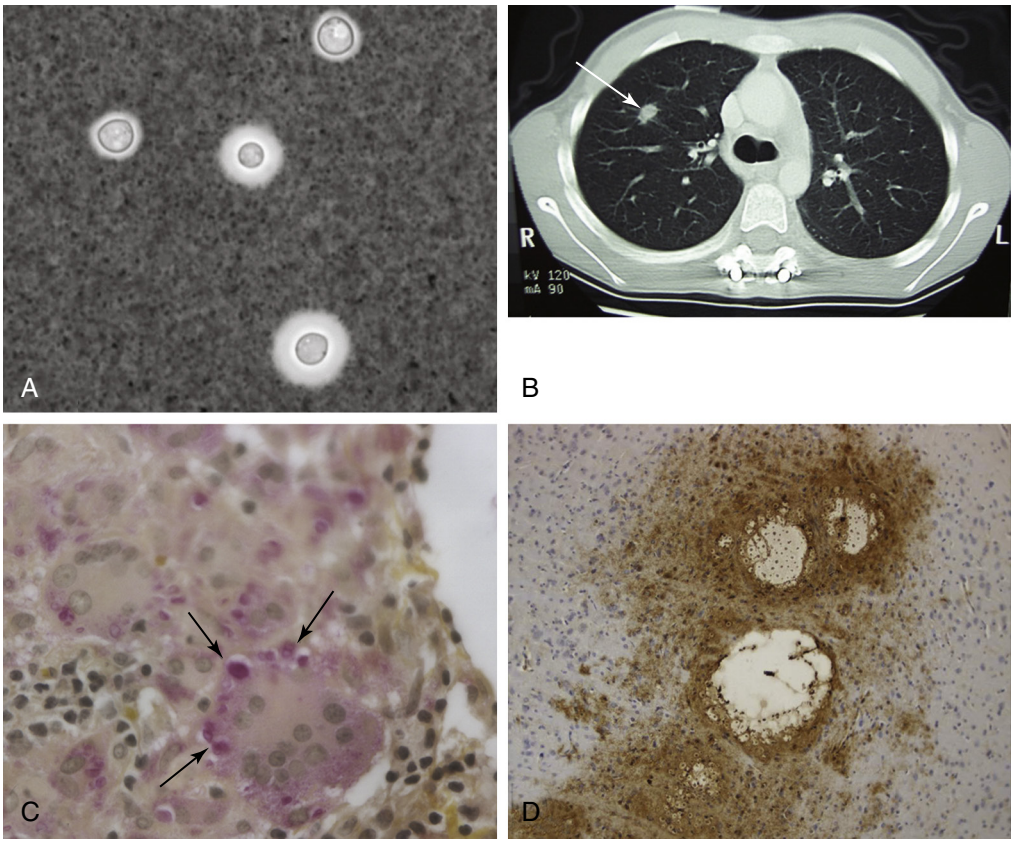

FIG. E1 A, India ink staining of cerebrospinal fluid demonstrates *Cryptococcus neoformans* and capsule, which excludes the stain and results in a halo around the organism. **B,** Computed tomography scan of a child with rhabdomyosarcoma reveals nodule *(white arrow)* secondary to *C. neoformans*. **C,** Mucicarmine staining of a lung from a rat with experimentally induced pulmonary cryptococcosis shows granulomas containing *C. neoformans (black arrows).* **D,** Immunostaining for cryptococcal polysaccharide reveals extensive shedding of polysaccharide within the brain parenchyma and around cryptococcomas of a rat with experimentally induced cryptococcal meningoencephalitis. (From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Cryptogenic organizing pneumonia (COP) is a type of idiopathic interstitial pneumonia, which has a histologic pattern of organizing pneumonia combined with characteristic clinical and radiographic features. The histologic pattern of organizing pneumonia consists of intraluminal organizing fibrosis in distal airways with intraalveolar buds of granulation tissue composed of connective tissue, fibroblasts, and myofibroblasts. Foci of organizing pneumonia tend to have a patchy distribution and uniform appearance with relative preservation of underlying lung architecture. Cryptogenic organizing pneumonia has no known underlying cause. Secondary causes associated with a histologic pattern of organizing pneumonia must be clinically excluded.

SYNONYMS

Bronchiolitis obliterans organizing pneumonia (BOOP)
COP

ICD-10CM CODE
J84.116 Cryptogenic organizing pneumonia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Estimated incidence is six to seven cases per 100,000 per yr
PEAK INCIDENCE: Typically, age of onset is 50 to 60 yr old
PREVALENCE: Unknown
PREDOMINANT SEX AND AGE: No sex predominance
GENETICS: Unknown
RISK FACTORS: Unknown

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The clinical presentation ranges from an acute onset of flulike symptoms to a subacute illness with cough and dyspnea. Common presenting symptoms are fevers, dyspnea, nonproductive cough, malaise, and weight loss. Symptoms are typically present for less than 3 months in the majority of cases. A lack of response to antibiotics for the treatment of community-acquired pneumonia may raise suspicion for cryptogenic organizing pneumonia. Lung examination may be remarkable for inspiratory crackles or may be normal.

ETIOLOGY

The etiology of cryptogenic organizing pneumonia is unknown. The pathogenesis may begin with alveolar epithelial injury of an unknown cause.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Community-acquired pneumonia, chronic eosinophilic pneumonia, and hypersensitivity pneumonitis can have similar clinical presentations and radiographic features. The differential diagnosis also includes other types of idiopathic interstitial pneumonias and secondary causes of organizing pneumonia, which need to be excluded (Table E1).

WORKUP

Chest imaging is commonly performed (see "Imaging Studies"). Pulmonary function testing may show a mild to moderate restrictive pattern with a reduced diffusion capacity. Bronchoscopy with bronchoalveolar lavage (BAL) is performed to evaluate for other disease processes, such as active infection, eosinophilic pneumonia, hypersensitivity pneumonitis, and malignancy. Transbronchial biopsies may be unreliable for detecting organizing pneumonia due to the patchy distribution of the disease. Additionally, when foci of organizing pneumonia are detected (Fig. E1), the relatively small tissue specimens may not be sufficient to exclude other coexisting histopathologic processes. A surgical lung biopsy may be needed to make a definitive diagnosis, especially if clinical and radiographic features are not typical. After a histologic diagnosis of organizing pneumonia is made, additional evaluation for secondary causes is necessary. This may include serologic testing for connective tissue diseases and human immunodeficiency virus, in addition to infectious and hematologic evaluation (Table E1).

LABORATORY TESTS

Leukocytosis without peripheral eosinophilia and elevated inflammatory markers, including elevated erythrocyte sedimentation rate and C-reactive protein, are frequently present. BAL cell counts are remarkable for a mixed pattern, typically with increased lymphocytes (20% to 40%), neutrophils (approximately 10%), and eosinophils (approximately 5%). CD4/CD8 ratio is also decreased in the majority of cases. However, these laboratory tests are all nonspecific.

TABLE E1 Secondary Causes of Organizing Pneumonia

Drug toxicity
Connective tissue disease
Solid and hematologic malignancies
Infection
Radiation injury
Immunodeficiency syndromes including post-organ transplantation

IMAGING STUDIES

Chest radiograph (Fig. E2) and chest computed tomography (CT) scan will typically show unilateral or bilateral peripheral airspace consolidations that may be migratory. On chest CT scan, consolidations are often subpleural or peribronchial in location. Additionally, a perilobular pattern (airspace consolidation at the periphery of a secondary pulmonary lobule) can be present in over half of cases. Ground-glass opacities, nodular or mass-like opacities, and small ill-defined nodules are common (Fig. E3). The reverse halo sign (central ground-glass opacity surrounded by airspace consolidation) is infrequently seen.

TREATMENT

ACUTE GENERAL Rx

For patients with persistent or progressive symptoms, prednisone is initiated at a dose of 0.75 to 1 mg/kg PO daily. Most cases have a rapid improvement with initiation of prednisone.

CHRONIC Rx

Prednisone is weaned over months. Relapse is common but rarely associated with poor outcomes. Prolonged prednisone therapy can be considered for relapsing cases after weighing risks and benefits. Other immunosuppressors, such as cyclophosphamide or azathioprine, can be considered as adjunctive or steroid-sparing therapies. Up to 75% of treated patients continue to have residual CT scan abnormalities.

PEARLS & CONSIDERATIONS

- Chest imaging with peripheral airspace consolidations combined with a clinical presentation of an acute, flulike illness or subacute dyspnea and cough that does not respond to antibiotics should raise suspicion for cryptogenic organizing pneumonia.

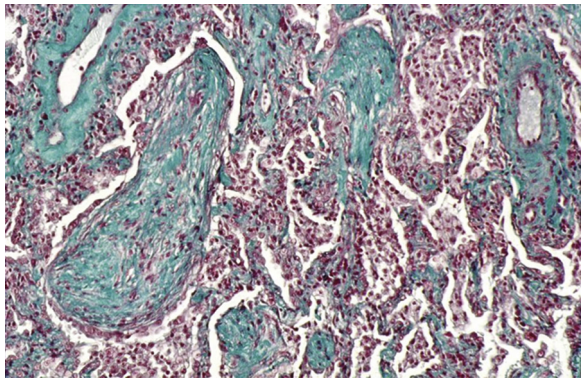

FIG. E1 Photomicrograph indicates organizing pneumonia. Immature connective tissue and proliferating fibroblasts appearing light blue (pentachrome stain) are present in alveolar ducts and alveolar spaces, and there is an interstitial infiltrate consisting of mononuclear cells. (Original magnification ×40.) (From Mason RJ et al: *Murray & Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, Saunders.)

FIG. E2 Chest radiograph demonstrating patchy alveolar opacities in a patient with cryptogenic organizing pneumonia. Enlarged cardiac silhouette is due to an unrelated cardiomyopathy. (From Weinberger SE: *Principles of Pulmonary Medicine,* ed 7, Philadelphia, 2019, Elsevier.)

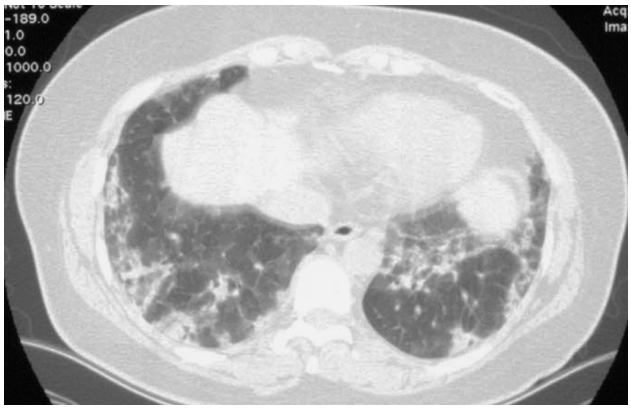

FIG. E3 High-resolution computed tomography image from a patient with cryptogenic organizing pneumonia shows patchy areas of consolidation and diffuse ground-glass opacities (gray-appearing areas). (From Mason RJ et al: *Murray & Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, Saunders.)

- Cryptogenic organizing pneumonia has no known underlying cause. Secondary causes associated with a histologic pattern of organizing pneumonia must be clinically excluded.
- When cryptogenic organizing pneumonia is suspected, bronchoscopy with bronchoalveolar lavage can evaluate for disease mimics, including infection, eosinophilic pneumonia, hypersensitivity pneumonitis, and malignancy. However, tissue biopsies are needed to make a definitive diagnosis, which may require a surgical lung biopsy.

RELATED CONTENT

Interstitial Lung Disease (Related Key Topic)

AUTHOR: **Samaan Rafeq, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Cryptorchidism is the incomplete or improper descent of the testis (testes) into the scrotum during fetal development. Testes that can be manually manipulated into the scrotum and that remain there without traction until cremasteric reflexes are induced are called *retractile.* Testes previously located but no longer palpable in the scrotum are called *ascended testes.*

SYNONYM

Undescended testis

ICD-10CM CODES

Q53.9	Undescended testicle, unspecified
Q53.10	Unspecified undescended testicle, unilateral
Q53.20	Undescended testicle, unspecified, bilateral

EPIDEMIOLOGY & DEMOGRAPHICS

- Cryptorchidism is the most common genitourinary disorder of male children.
- Occurs in approximately 30% of premature and 5% of term male infants. In 10%, it can be bilateral.
- Spontaneous descent occurs in 35% to 43% of newborn boys with congenital cryptorchidism, usually before 3 mo of age.
- Increased rates with premature birth, low birth weight, twins, cerebral palsy, and family history of cryptorchidism.
- With retractile testes, there is a reported 2% to 45% risk of subsequent ascent leading to an undescended testis, with histopathology in these testes comparable to congenital undescended testis.
- Prevalence of acquired cryptorchidism is 1% to 7%; peaks around 8 yr of age.

CLINICAL PRESENTATION

- Typically asymptomatic and is noted incidentally on screening examination. Undescended testes are at risk for testicular torsion and inguinal hernia.
- The testis may be nonpalpable or palpable in a location along the path of normal descent, or less commonly ectopic and located in the perineum, femoral canal, superficial inguinal pouch, suprapubic area, or contralateral hemiscrotum. Fig. E1 illustrates various positions of the ectopic testis. The majority are located in the inguinal canal.
- Associated with infertility and a threefold increased risk of testicular cancer. Risk of infertility is the greatest for a child with bilateral intraabdominal testes and longer duration of cryptorchidism.

ETIOLOGY

Normal testicular descent is a complex interplay among mechanical (gubernaculums, vas deferens and testicular vessel length, cremasteric muscles, and abdominal pressure), hormonal (gonadotropin, testosterone, dihydrotestosterone, and müllerian inhibiting substance), and neural (ilioinguinal and genitofemoral nerves) factors.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Retractile testis
- Ascended testis
- Atrophic testis
- Vanished testis

WORKUP

- Physical examination:
  1. Examine patient in supine, sitting, and standing positions in a warm room with warm hands, and with adequate cremasteric relaxation to differentiate true cryptorchidism from retractile testes.
  2. Often associated with an indirect inguinal hernia as the tunica vaginalis fails to close above the testis.
  3. An enlarged contralateral testis (16.1 mm or greater in length for patients 6 to 18 mo old; 19 to 20 mm for those 11 to 30 mo old) in the presence of a nonpalpable undescended testis is suggestive of but not definitive for testicular atrophy/absence.

If there are bilateral nonpalpable undescended testes, first rule out congenital adrenal hyperplasia (CAH). If no CAH, then rule out disorders of sexual development (DSD). Müllerian inhibiting substance (MIS or antimüllerian hormone) should be measured and consider additional hormonal testing to evaluate for anorchia (inhibin B, FSH, LH, and testosterone) (evidence grade C).

IMAGING STUDIES

Scrotal/inguinal ultrasound (Fig. E2) and other imaging is not routinely needed because such studies rarely assist in decision making (evidence grade B).

TREATMENT

- Repeat examination at 3 mo of age because many testes will descend spontaneously. Spontaneous descent is rare after 3 mo of age.
- Treatment is primarily surgical and rarely hormonal. Fig. E3 illustrates an algorithm for the management of the undescended testis.
- Referral to an appropriate specialist if spontaneous descent does not occur by 6 mo of age. Earlier orchiopexy may improve testicular function and decrease the risk of testicular cancer. Orchiopexy allows testicular self-examination and detection of testicular cancer if it occurs (evidence grade B).

HORMONAL Rx

- Hormonal therapy (hCG) is not recommended in the American Urological Association Guidelines for the treatment of cryptorchidism.

SURGICAL Rx

- For the palpable undescended testis, orchiopexy (Fig. E4), the surgical placement of an undescended testis into the scrotum, is the standard approach, performed between 6 mo and 1 yr of age in a healthy child. This may be performed through a combined inguinal and scrotal incision or a single scrotal incision, depending on the location of the testis and surgeon preference.
- With a nonpalpable undescended testis, laparoscopy/abdominal exploration is recommended
  1. to identify the presence or absence of a testis,
  2. to identify the location of the testis if present, and
  3. to determine the length of the testicular vessels (evidence grade B) and is the best method of surgical intervention (primary orchiopexy, Fowler-Stephen orchiopexy; one- or two-stage).
- Some surgeons prefer an initial inguinal approach and, if the testis is not identified, then proceed with transinguinal laparoscopy.

DISPOSITION

- Earlier orchiopexy may decrease the risk of malignancy and infertility.
- Lifelong testicular examinations after puberty.

REFERRAL

Early referral (ideally by 6 mo of age) to a pediatric urologist or pediatric surgeon

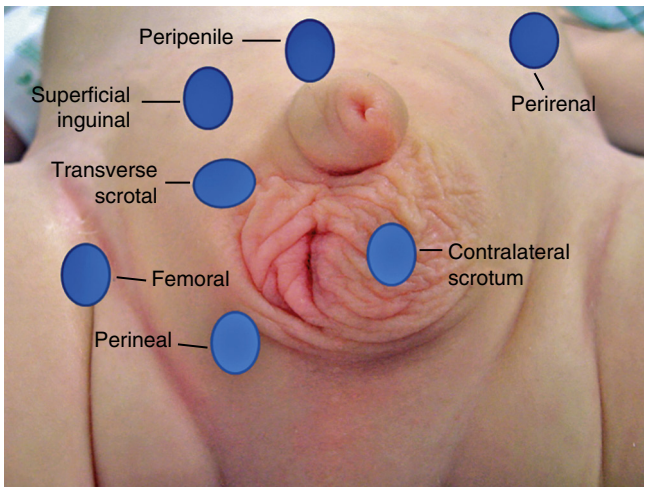

FIG. E1 Positions of the ectopic testis. The ectopic testis can be identified in various positions, as shown. The most common location is the superficial inguinal pouch. (From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.)

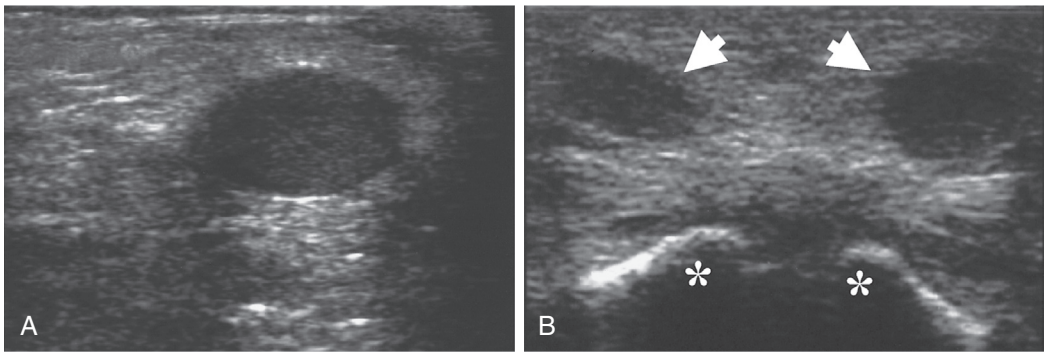

FIG. E2 A, Ultrasound (US) of an undescended infantile testis. The testis lies within the inguinal canal surrounded by suprapubic fat. **B,** Transverse US view of bilateral undescended testes. The testes *(arrows)* are demonstrated at the level of the superior pubic rami *(asterisks).* (From Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.)

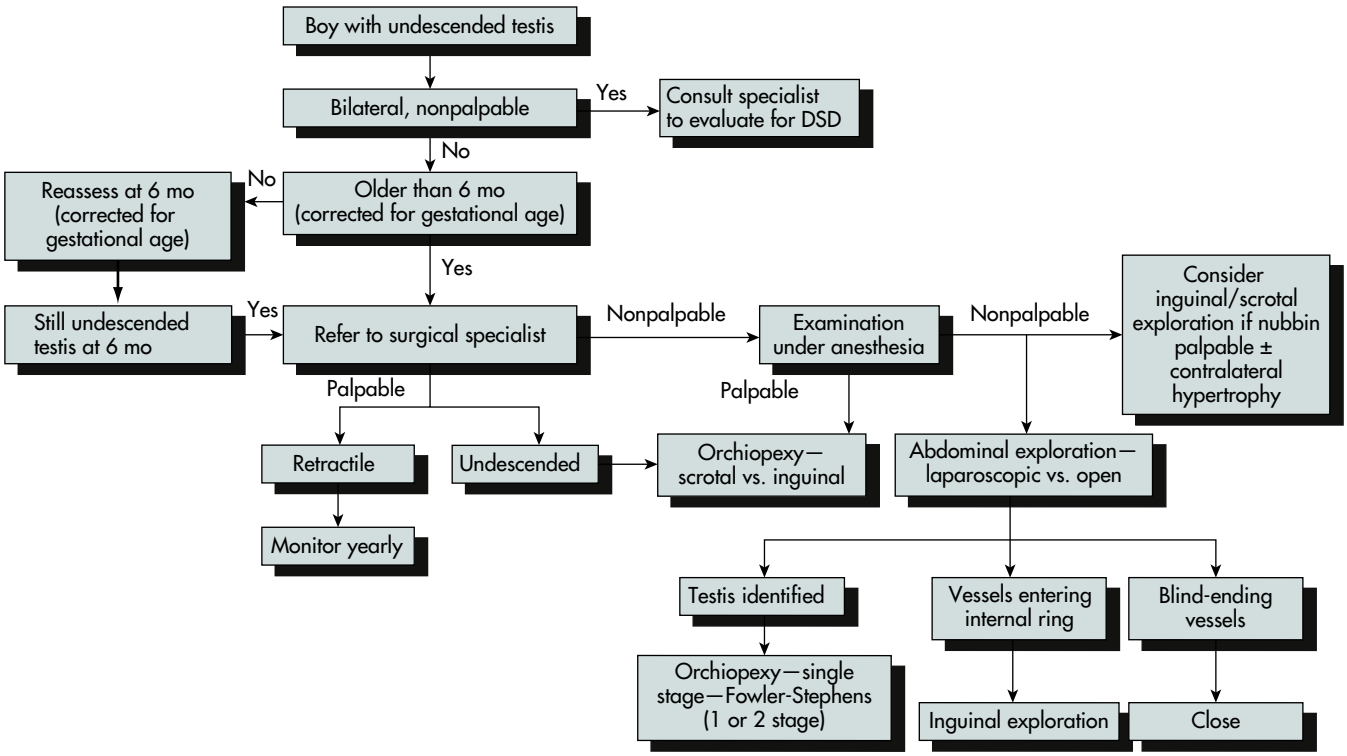

FIG. E3 Algorithm for the management of the undescended testis. The American Urological Association guideline algorithm for the diagnosis and treatment of palpable and nonpalpable testes in patients confirmed to have undescended testis by an experienced examiner. *DSD,* Disorder of sexual differentiation. (From Kolon TF et al: Evaluation and treatment of cryptorchidism: AUA guideline, 2014. Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.)

PEARLS & CONSIDERATIONS

Regular testicular examinations should be performed in infants and children, particularly those with retractile testes, because ascent of scrotal testis can occur.

RELATED CONTENT

Undescended Testicle (Patient Information)

AUTHOR: **Pamela Ellsworth, MD**

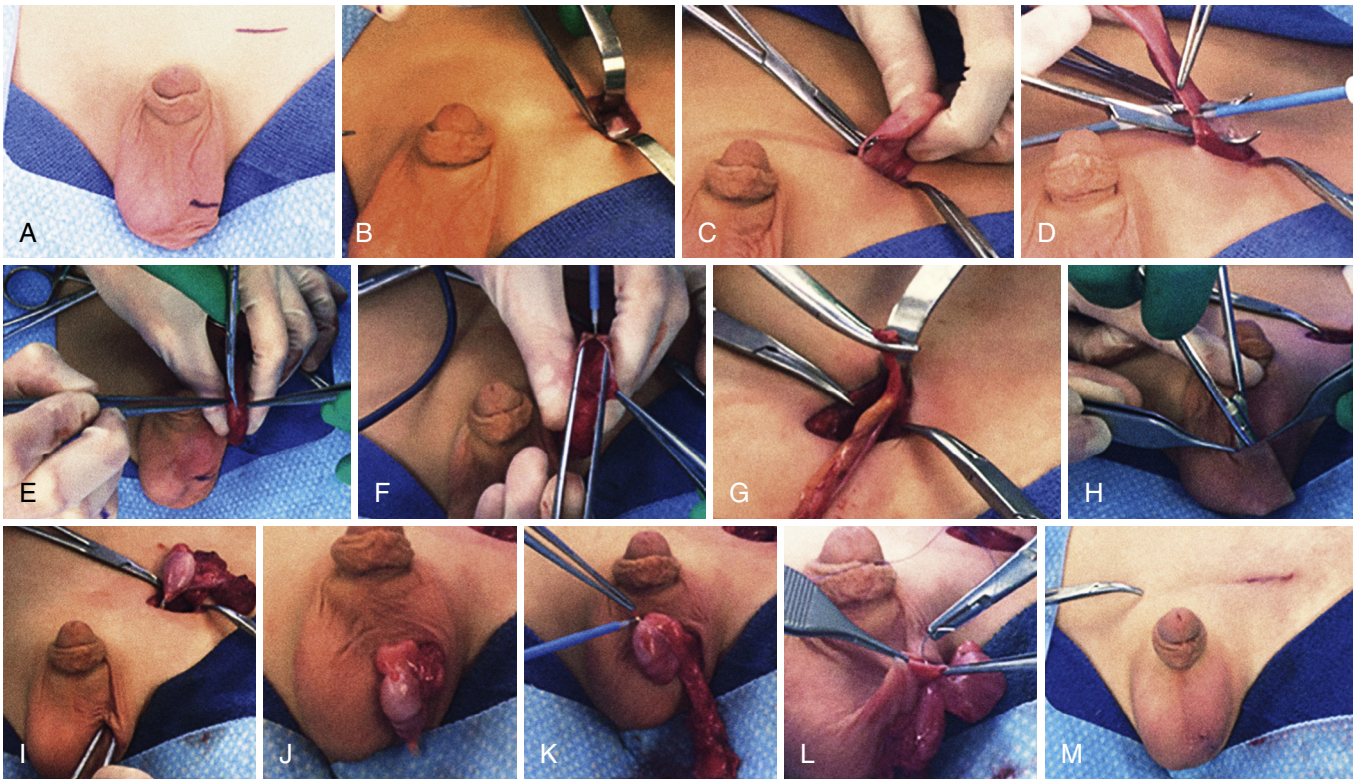

FIG. E4 Inguinal orchiopexy. A, An incision is made at or below the inguinal crease superolateral to the pubic tubercle. **B,** The external oblique fascia is incised to expose the canal. **C,** The gubernaculum is transected distal to the sac. **D,** The internal spermatic fascia is incised. **E,** The tunica vaginalis is opened over the testis, and **(F)** the incision is extended proximally along the length of the cord. **G,** The sac is mobilized to the level of the internal inguinal ring and suture-ligated. **H,** A transverse scrotal incision is made and a subdartos pouch created. **I,** A large clamp or a finger can be used to create a tunnel just anterior to the pubis. **J,** The testis is passed into the scrotum. **K,** Existing appendages are excised. **L,** The testis is secured within the pouch. **M,** Closure is completed with absorbable sutures. (From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.)

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BASIC INFORMATION

DEFINITION

The intracellular protozoan parasite *Cryptosporidium parvum* is associated with gastrointestinal disease and diarrhea, especially in patients with AIDS or other immunocompromised hosts. It is also associated with sporadic infections and waterborne outbreaks in immunocompetent hosts. Cryptosporidiosis is a notifiable disease in the U.S.

Other species, including *C. hominis, C. felis, C. muris,* and *C. meleagridis,* are now described to be pathogens as well.

SYNONYM

Cryptosporidiosis

ICD-10CM CODE
A07.2 Cryptosporidiosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Approximately 2% in industrial countries, 5% to 10% in developing countries.
- Immunocompromised patients, especially those with HIV/AIDS, are particularly susceptible to infection. 10% to 20% of HIV patients in the United States may excrete cyst.
- Cryptosporidiosis is a leading cause of all waterborne outbreaks in the U.S. An estimated 748,000 cryptosporidiosis cases occur annually, although fewer than 2% are reported. In 2011, more than 9000 cases of cryptosporidiosis were reported in the country. The highest overall reporting rates were observed in the Midwest.[1]

PREVALENCE: Worldwide, especially third-world countries; associated with poor hygiene as a waterborne pathogen.

PREDOMINANT SEX: Male = female

TRANSMISSION:

- Person-to-person (day care, family members)
- Animal-to-person (pets, farm animals). Fig. E1 describes the life cycle of *Cryptosporidium*
- Environmental (water-associated outbreaks, including travel associated with swimming in or drinking contaminated water or eating contaminated food)
- May be significant pathogen causing diarrhea in patients with AIDS

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Spectrum of illness ranging from asymptomatic to severe enteritis (Table E1). Typical cases in immunocompetent hosts result in self-limited diarrhea, whereas immunocompromised hosts are characterized by profuse, watery, nonbloody diarrhea that may lead to dehydration and weight loss
- Usually limited to the gastrointestinal tract; however, in individuals with AIDS, the disease may be fulminant and life-threatening (CD4 counts <50)
- Diarrhea, severe abdominal pain (2 to 28 days)
- Impaired digestion, dehydration
- Fever, malaise, fatigue, nausea, vomiting
- Pneumonia if aspirated

ETIOLOGY

C. hominis, C. parvum, C. felis, C. muris, C. meleagridis

DIAGNOSIS

Clinical presentation of acute gastrointestinal illness, especially associated with HIV/AIDS or with travel and waterborne outbreaks.

DIFFERENTIAL DIAGNOSIS

- *Campylobacter*
- *Clostridium difficile*
- *Entamoeba histolytica*
- *Giardia lamblia*
- *Salmonella*
- *Shigella*
- Microsporidia
- Cytomegalovirus
- *Mycobacterium avium*
- Disease may cause cholecystitis, reactive arthritis, hepatitis, urethritis, pancreatitis, or pneumonia in immunocompromised or HIV-infected patients.

WORKUP

(Table E2)

- Stool evaluation looking for characteristic oocyst by modified acid-fast stain (Fig. E2)
- Direct immunofluorescence using monoclonal antibodies is the gold standard for stool exams
- Rapid antigen detection
- PCR
- HIV antibody testing

TREATMENT

- Handwashing and appropriate decontamination of drinking and recreational water sources.
- May be self-limited in normal host, lasting days to weeks. Antidiarrheal agents Pepto-Bismol, Kaopectate, or loperamide may give symptomatic relief.
- Pharmacologic treatment with antibiotics has been largely unsatisfactory in patients with AIDS. Antiviral therapy is the treatment of choice to restore the immune system. Consider prolonged therapy while awaiting CD4 count recovery and combination therapy in those who fail initial course.
- Oocyst excretion reduction has been shown with nitazoxanide 500 mg PO bid for 3 days in immunocompetent patients. If treatment fails, consider paromomycin, metronidazole, azithromycin, or trimethoprim/sulfamethoxazole. However, these medications have not been approved for treatment of *Cryptosporidium.*
- Nitazoxanide elixir has been approved for the treatment of cryptosporidiosis in children ages 1 to 11 yr.
- Biliary cryptosporidiosis can be treated with antiretroviral therapy in the HIV setting.

DISPOSITION

- A self-limited disease in immunocompetent patients with complete recovery over 2 to 3 weeks.
- In patients with AIDS, chronic infection often clears with initiation and maintenance of antiretroviral therapy.
- Chronic arthralgia, headache, malaise, and weakness may persist after infection, even in immunologically normal people.
- If severe and prolonged disease (>30 days), testing for HIV and other immunocompromised states is appropriate, along with a referral to an infectious diseases specialist or gastroenterologist.

REFERRAL

- To an infectious diseases specialist if symptoms persist and/or HIV infection is found
- To a gastroenterologist if chronic malabsorption, or biliary or pancreatic complications occur

PEARLS & CONSIDERATIONS

- Chronic cryptosporidiosis (>30 days of diarrhea from *Cryptosporidium* spp. infection) in a patient with HIV is an AIDS-qualifying opportunistic infection.
- *Cryptosporidium hominis* has a limited host range (humans), whereas *Cryptosporidium parvum* has a wide host range including humans, horses, cattle, other domesticated animals, and wild animals; both species present similarly in humans.

SUGGESTED READING

Available at ExpertConsult.com

AUTHORS: **Tara C. Bouton, MD, MPH, TM, Philip A. Chan, MD, MS,** and **Glenn G. Fort, MD, MPH**

[1] Cryptosporidiosis surveillance, United States, 2011-2012. MMWR 64 3 (2015).

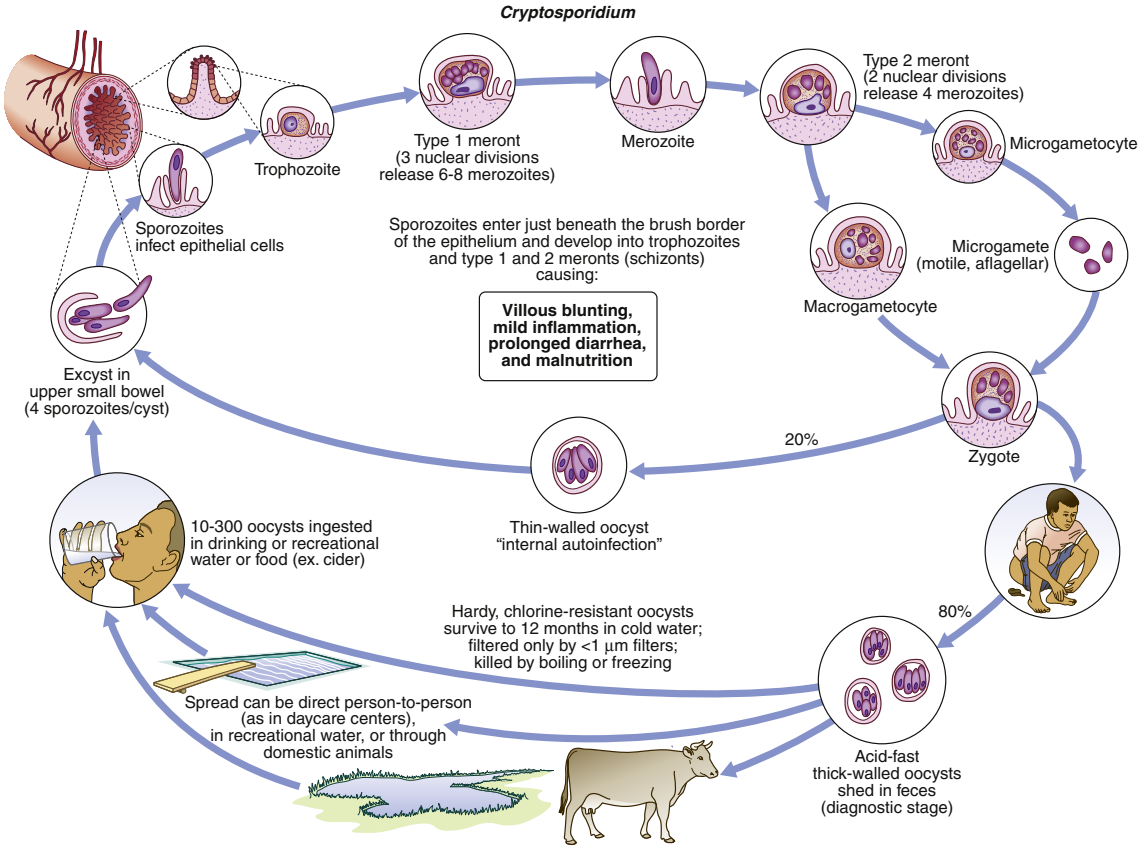

FIG. E1 Life cycle of *Cryptosporidium.* Oocysts are excreted in the feces. After ingestion, the sporozoites are released from the oocysts and attach to and invade intestinal epithelial cells. The cells engulf the parasites into a parasitophorous vacuole, where they enlarge to form the trophozoites; undergo asexual multiplication, forming type 1 meronts; and release the motile merozoites. The type II meronts differentiate into microgamonts and macrogamonts. The microgametes fertilize the macrogametes to form the zygote. The zygotes develop into the oocysts. Two different types of oocysts are produced: the thick-walled, which is commonly excreted from the host, and the thin-walled, which is primarily involved in autoinfection. Oocysts are infective upon excretion, thus permitting direct and immediate fecal-oral transmission. (From Lima AM et al: Cryptosporidiosis. In Guerrant RL et al [eds]: *Tropical infectious diseases,* ed 3, Philadelphia, 2011, Saunders; Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2005, Saunders.)

TABLE E1 Clinical Manifestation of Cryptosporidiosis

Host	Clinical Manifestations	Comments
Normal host	Acute watery diarrhea	Relapses common Persistent diarrhea common
Children in developing countries	Acute watery diarrhea	Diarrhea more severe in children with malnutrition
	Persistent diarrhea	Persistent diarrhea affecting nutritional status, growth, and intellectual function
Immunocompromised host	Acute watery diarrhea	Transient, self-limited, similar to disease in normal host
	Relapsing diarrhea	Very common
	Persistent or chronic diarrhea	Usually found in patients with low CD4 count or malnutrition
	Cholera-like illness	Voluminous watery diarrhea, only with very low CD4 count
	Extraintestinal involvement	Respiratory tract, biliary tract, and pancreas

From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.

TABLE E2 Diagnosis of *Cryptosporidium* Infection

Test Type	Method	Comments
Microscopic examination of stools	Modified acid-fast stain of stools	Inexpensive and widely available diagnostic test
	Fluorescent stains (auramine O, auramine-rhodamine)	Faster than other acid-fast stains and may improve sensitivity
	Immunofluorescent assays	More sensitive than acid-fast staining but also more expensive
Antigen-detection assays	Enzyme immunoassay and immunochromatographic tests: Direct and indirect immunofluorescence assay	Good sensitivity (66%-100%) and excellent specificity (93%-100%), but occasional lots associated with false-positive test results
Molecular methods	Polymerase chain reaction	Increased sensitivity in contrast to microscopic or antigen-detection studies

From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

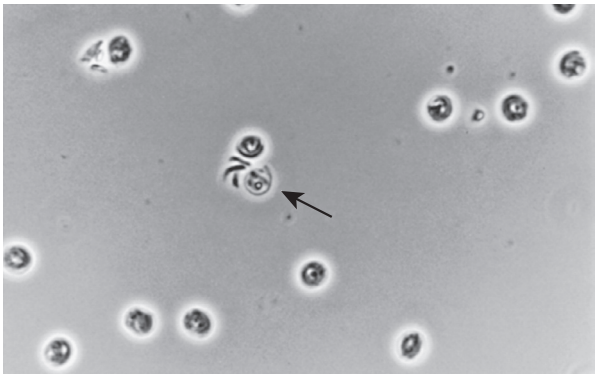

FIG. E2 Human stool-derived *Cryptosporidium* oocysts. Excysting oocyst *(arrow)* is releasing three of its four sporozoites. (Phase-control microscopy ×630.) (From Gorbach SL: *Infectious diseases,* ed 2, Philadelphia, 1998, Saunders.)

SUGGESTED READING

Centers for Disease Control and Prevention: Cryptosporidiosis outbreak at a summer camp, North Carolina, 2009, *MMWR Morb Mortal Wkly Rep* 60:918-922, 2011.

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.

BASIC INFORMATION

DEFINITION

Cubital tunnel syndrome is a compressive or entrapment neuropathy of the ulnar nerve as it traverses the cubital tunnel at the elbow, causing weakness, pain, and sensory disturbances in the hand (Fig. E1). If left untreated, cubital tunnel syndrome may lead to permanent disability in the affected hand. The cubital tunnel lies between the medial epicondyle of the humerus and the olecranon process of the ulna. The roof of the cubital tunnel is formed by a fascial band (Osborne ligament) between the two heads of the flexor carpi ulnaris. The floor consists of the medial collateral ligament and olecranon.

ICD-10CM CODE

G56.20 Lesion of ulnar nerve, unspecified upper limb

EPIDEMIOLOGY & DEMOGRAPHICS

Cubital tunnel syndrome is the second most commonly diagnosed compressive neuropathy of the upper extremity after carpal tunnel syndrome, and it is the most common ulnar nerve neuropathy. Its incidence is 24.7 cases per 100,000 persons per yr. Men are more frequently affected than women at a 2:1 ratio.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients often complain of numbness and paresthesia along the distribution of the ulnar nerve (little finger and medial half of ring finger); pain rarely occurs in the hand.
- Pain is typically localized to the cubital area, but symptoms can affect the medial epicondyle and forearm.
- Complaints of hand grip problems (weakness) or hand clumsiness are common.
- If the condition is left untreated, patients may present with atrophy of the first dorsal interosseus or hypothenar eminence atrophy, or with an ulnar claw hand deformity.

The following provocative maneuvers and physical signs are helpful in identifying ulnar neuropathy when interpreted in the proper clinical context.

- Positive Tinel sign (at elbow over the ulnar groove—highest negative predictive value
- Positive elbow flexion test (flexion of elbow with wrist extended for 30 seconds reproduces symptoms)
- Pressure provocation test (direct pressure over cubital tunnel for 60 seconds elicits symptoms)
- "Scratch collapse" test (positive if temporary loss of external rotation resistance occurs after examiner scratches over the compressed ulnar nerve)
- Signs of old trauma or elbow instability (valgus stress)
- Ulnar nerve may sublux over medial epicondyle with elbow motion
- Weakness or atrophy of intrinsic musculature of hand in longstanding cases
- Altered 2-point discrimination
- Duchenne sign, also known as intrinsic minus or claw hand; caused by paralysis of lumbrical and interosseous muscles (clawing is usually worse in ring and small fingers)
- Masse sign—hand appears flattened due to hypothenar muscle paralysis
- Wartenberg sign—caused by weakness of interossei: Weak adduction of small finger
- Froment sign—compensation by thumb flexor (flexor pollicis longus, median-nerve innervated) for diminished thumb pinch strength (paralysis of adductor pollicis, which is innervated by ulnar nerve)

ETIOLOGY

Cubital tunnel syndrome can be idiopathic or caused by some predisposing factors:

- Blunt trauma, fractures
- Metabolic derangements (e.g., diabetes)
- Compression during general anesthesia
- Hemophilia (leading to hematomas)
- Cigarette smoking
- Chronic pressure over ulnar groove from occupational stress, unusual elbow positioning
- Cubitus valgus deformity secondary to old trauma (childhood supracondylar fracture)
- Subluxation of ulnar nerve
- Repeated stretching during throwing motion
- Elbow synovitis, osteophytes
- Local muscular hypertrophy
- Increased cubital tunnel pressure, particularly in elbow flexion
- Anconeus epitrochlearis (an accessory anconeus muscle at the medial elbow)

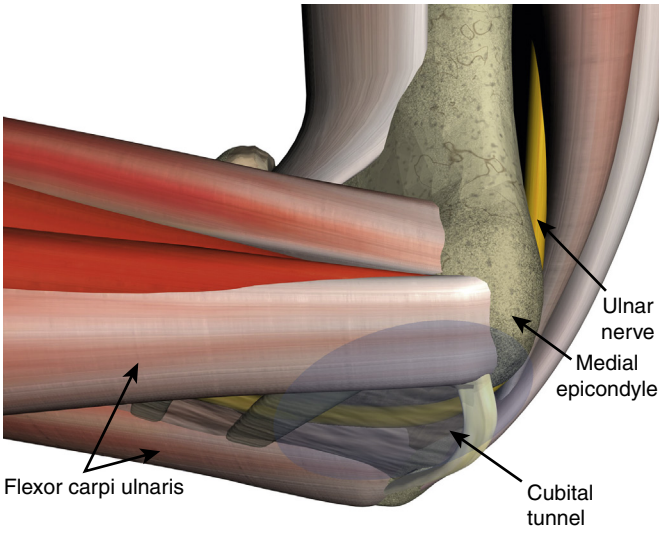

FIG. E1 Cubital tunnel. (Original art by Dr. DaSilva)

DIAGNOSIS

In most patients, a thorough history and physical examination are sufficient to make the diagnosis. Laboratory, electrophysiologic, and imaging studies can help support the diagnosis.

DIFFERENTIAL DIAGNOSIS

- Medial epicondylitis
- Carpal tunnel syndrome
- Cervical disc disease (radiculopathy)
- Thoracic outlet syndrome
- Ulnar nerve compression at wrist (Guyon canal)
- Guillain-Barré syndrome
- Amyotrophic lateral sclerosis
- Pancoast tumor

WORKUP

LABORATORY STUDIES: Specific laboratory studies can help rule out alternate diagnoses and confirm predisposing conditions:

- Complete blood count
- Folate and vitamin B_{12} levels
- Urinalysis
- Thyroid function tests
- Renal function tests
- Fasting blood glucose
- Hemoglobin A1C
- Inflammatory markers (erythrocyte sedimentation rate, C-reactive protein [ESR, CRP]), antinuclear antibodies (ANA)
- HIV, hepatitis, and Lyme serology

IMAGING STUDIES

- Radiographs of the elbow should be obtained in all patients.
- Radiographs of the neck and chest may be done to rule out suspected conditions such as cervical disc disease or Pancoast tumor.
- High-resolution ultrasound can be a valuable adjunct to the diagnosis and may identify the structural etiology of nerve compression. Because of the real-time nature of ultrasound evaluation, dynamic testing can be performed and ulnar nerve subluxation may be observed during elbow flexion and extension motions.
- Trials of diagnostic ultrasound have shown a strong correlation between greater ulnar nerve cross-sectional area at the elbow and presence of cubital tunnel syndrome diagnosed by electrodiagnostic criteria.

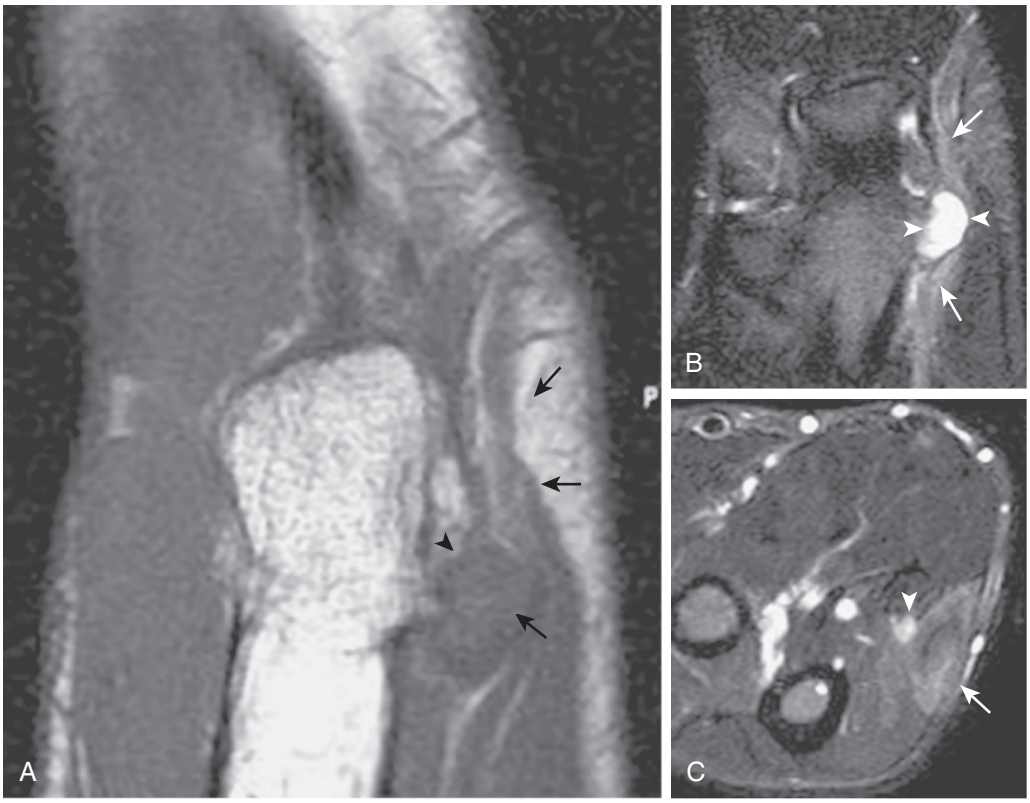

FIG. E2 Cubital tunnel syndrome. Coronal T1-weighted **(A)** and coronal short tau inversion recovery **(B)**. Magnetic resonance (MR) images show a ganglion cyst *(arrowheads)* within the cubital tunnel, producing compression and displacement of the ulnar nerve *(arrows)*. **(C),** Axial T2-weighted MR image distal to the elbow joint demonstrates an enlarged and hyperintense ulnar nerve *(arrowhead)* and early denervation with edema of the flexor carpi ulnaris muscle *(arrow)*. (From Pope TL et al: *Musculoskeletal imaging*, ed 2, Philadelphia, 2014, Saunders.)

- MRI (Fig. E2) may be useful in patients in whom history, physical examination, and electrophysiologic studies fail to support the diagnosis.

ELECTRODIAGNOSTIC STUDIES

Nerve conduction tests and electromyography are useful to confirm the clinical diagnosis and can help localize the site of compression.

Rx TREATMENT

- Nonsurgical options:
  1. Activity modification; avoiding prolonged/repetitive flexion of elbow
  2. Anterior shell splint limiting flexion to 45 degrees to be worn at night
  3. Elbow pads to relieve pressure; physical and occupational therapy
  4. Pain control and alleviation of sensory symptoms using NSAIDs, tricyclic antidepressants, or anticonvulsants
- If nonsurgical options fail to control symptoms or if the patient has significant muscle weakness or atrophy, then surgical options are available:
  1. Endoscopic cubital tunnel release
  2. Ulnar nerve decompression in situ
  3. Anterior transposition of the ulnar nerve
- Common causes for failed surgical management include:
  1. Technical factors such as incomplete decompression or creation of a new area of compression
  2. Incorrect diagnosis or a concomitant double crush lesion such as thoracic outlet syndrome, cervical radiculopathy, or Guyon canal syndrome
  3. Biologic causes such as severe preoperative nerve damage or perineural scarring

DISPOSITION

- There is a tendency toward spontaneous recovery with mild or moderate or intermittent symptoms if provocative causes are avoided.
- If muscle atrophy has developed, recovery of strength may be incomplete despite treatment, suggesting the importance of prompt diagnosis and appropriate treatment.

REFERRAL

Surgical referral is needed in cases of failed nonsurgical management. Patients with constant symptoms or muscle atrophy usually require surgical treatment.

PEARLS & CONSIDERATIONS

- A thorough history and physical examination and knowledge of the sensory and motor innervation of the upper extremity are usually sufficient to make the diagnosis.
- Patients with mild, intermittent symptoms can have spontaneous recovery if provocative causes are avoided.
- Nonsurgical management should be attempted, but if symptoms are persistent or if significant hand muscle weakness or atrophy is present, then surgery may be indicated.
- In patients with advanced findings, electromyogram/nerve conduction studies can help predict nerve and muscle function recovery after surgery.
- Surgical decompression has been shown to be successful in most cases. More recently, endoscopic decompression techniques have been described.

RELATED CONTENT

Cubital Tunnel Syndrome (Patient Information)

AUTHORS: **Manuel F. DaSilva, MD, Edward J. Testa, MD,** and **Nicholas J. Lemme, MD**

SUGGESTED READINGS

Andrews K et al: Cubital tunnel syndrome: anatomy, clinical presentation, and management, *J Orthop* 15(3):832-836, 2018.

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Frost P et al: Lifestyle risk factors for ulnar neuropathy and ulnar neuropathy-like symptoms, *Muscle Nerve* 48(4):507-515, 2013.

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Staples R et al: Comparative morbidity of cubital tunnel surgeries: a prospective cohort study, *J Hand Surg Am* 43(3):207-213, 2018.

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Cushing Disease and Syndrome ALG PTG

BASIC INFORMATION

DEFINITION

- Cushing syndrome is the occurrence of clinical abnormalities associated with glucocorticoid excess as a result of exaggerated adrenal cortisol production or long-term glucocorticoid therapy.
- Cushing disease is Cushing syndrome caused by pituitary adrenocorticotropic hormone (ACTH) excess.

ICD-10CM CODES

E24 Cushing syndrome
E24.2 Drug-induced Cushing syndrome
E24.3 Ectopic ACTH syndrome
E24.8 Other Cushing syndrome
E24.9 Cushing's syndrome, unspecified
E24.9 Pituitary-dependent Cushing disease

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hypertension
- Central obesity with rounding of the facies (moon facies); thin extremities. Fig. 1 illustrates the distribution of adipose tissue in Cushing syndrome
- Hirsutism, menstrual irregularities, hypogonadism
- Skin fragility, ecchymoses, red-purple abdominal striae (Fig. E2), acne, poor wound healing, hair loss, facial plethora, hyperpigmentation (with ACTH excess). The frequency of individual findings in Cushing syndrome is summarized in Table 1
- Psychosis, emotional lability, paranoia
- Muscle wasting with proximal myopathy

NOTE: The previous characteristics are not commonly present in Cushing syndrome caused by ectopic ACTH production. Many of these tumors secrete a biologically inactive ACTH that does not activate adrenal steroid synthesis. These patients may have only weight loss and weakness.

ETIOLOGY

- Iatrogenic from long-term glucocorticoid therapy (common).

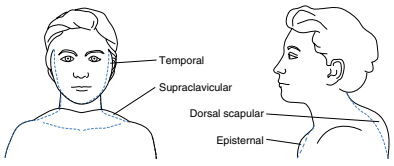

FIG. 1 Distribution of adipose tissue in Cushing syndrome. Rounding of the cheeks and prominent bitemporal fat produce the characteristic moon facies. Fat also may accumulate bilaterally above the clavicles (supraclavicular collar), in front of the sternum (episternal area, or dewlap), and over the back of the neck (dorsal cervical fat pad, or buffalo hump). In these drawings, the dotted line depicts normal contours of patients without Cushing syndrome. (From McGee S: *Evidence-based physical diagnosis,* ed 4, Philadelphia, 2018, Elsevier.)

- Pituitary ACTH excess (Cushing disease; 60%).
- Adrenal neoplasms (30%).
- Ectopic ACTH production (neoplasms of lung, pancreas, kidney, thyroid, thymus; 10%).
- Table E2 summarizes the incidence of tumors associated with the ectopic adrenocorticotropic hormone syndrome.
- A classification of causes of Cushing syndrome is described in Table E3.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Alcoholic pseudo-Cushing syndrome (endogenous cortisol overproduction)
- Obesity associated with diabetes mellitus
- Adrenogenital syndrome

WORKUP

- Initial tests include the overnight low-dose dexamethasone suppression test (LDST), 24-hour urine free cortisol (UFC), and late-night (LN) salivary cortisol. The LN and UFC tend to be more convenient.
- Late-night salivary cortisol: A single midnight serum cortisol level (normal diurnal variation leads to a nadir around midnight) >7.5 mcg/dl has been reported as 96% sensitive and 100% specific for the diagnosis of Cushing syndrome. This test assesses the normal diurnal rhythm of cortisol (lost in Cushing syndrome) and is not useful in patients who have inconsistent sleep patterns or do shift work. It can also be affected by tobacco use and use of topical corticosteroids.
- In patients with a clinical diagnosis of Cushing syndrome, the classic initial screening test is the overnight dexamethasone suppression test:
  1. Dexamethasone 1 mg PO given at 11 PM.
  2. Plasma cortisol level measured 9 hr later (8 AM).
  3. Plasma cortisol level <5 mcg/100 ml excludes Cushing syndrome.
- Serial measurements (two or three consecutive measurements) of 24-hr urinary free cortisol and creatinine (to ensure adequacy of collection) are undertaken if overnight dexamethasone test is suggestive of Cushing syndrome. Persistent elevated cortisol excretion (>300 mcg/24 hr) indicates Cushing syndrome.
- The low-dose (2 mg) dexamethasone suppression test is useful to exclude pseudo-Cushing syndrome if the previous results are equivocal. Corticotropic-releasing hormone (CRH) stimulation after low-dose dexamethasone administration (dexamethasone-CRH test) is also used to distinguish patients with suspected Cushing syndrome from those who have mildly elevated urinary free cortisol level and equivocal findings.
- The high-dose (8 mg) dexamethasone test and measurement of ACTH by radioimmunoassay are useful to determine the etiology of Cushing syndrome.
  1. ACTH undetectable or decreased and lack of suppression indicate adrenal cause of Cushing syndrome.
  2. ACTH normal or increased and lack of suppression indicate ectopic ACTH production.
  3. ACTH normal or increased and partial suppression suggest pituitary excess (Cushing disease).
- Bilateral inferior petrosal sinus sampling (BIPSS) can be used to distinguish pituitary Cushing disease from the ectopic ACTH syndrome.

TABLE 1 Cushing Syndrome—Frequency of Individual Findings

Physical Finding†	Frequency (%)‡
Vital Signs	
Hypertension	64-88
Body Habitus	
Moon facies	67-92
Central obesity	44-97
Buffalo hump	34-75
Skin Findings	
Thin skin	27
Plethora	28-94
Hirsutism, women	48-81
Ecchymoses	23-75
Red or purple striae	46-68
Acne	21-52
Extremity Findings	
Proximal muscle weakness	39-68
Edema	15-66
Other	
Significant depression	12-40

†*Diagnostic standard*: For Cushing syndrome, elevated daily cortisol or corticosteroid metabolites, or both, with loss of circadian rhythm and with abnormal dexamethasone suppression tests.
‡Results are overall mean frequency or, if statistically heterogeneous, the range of values.
From McGee S: *Evidence-based physical diagnosis,* ed 4, Philadelphia, 2018, Elsevier.

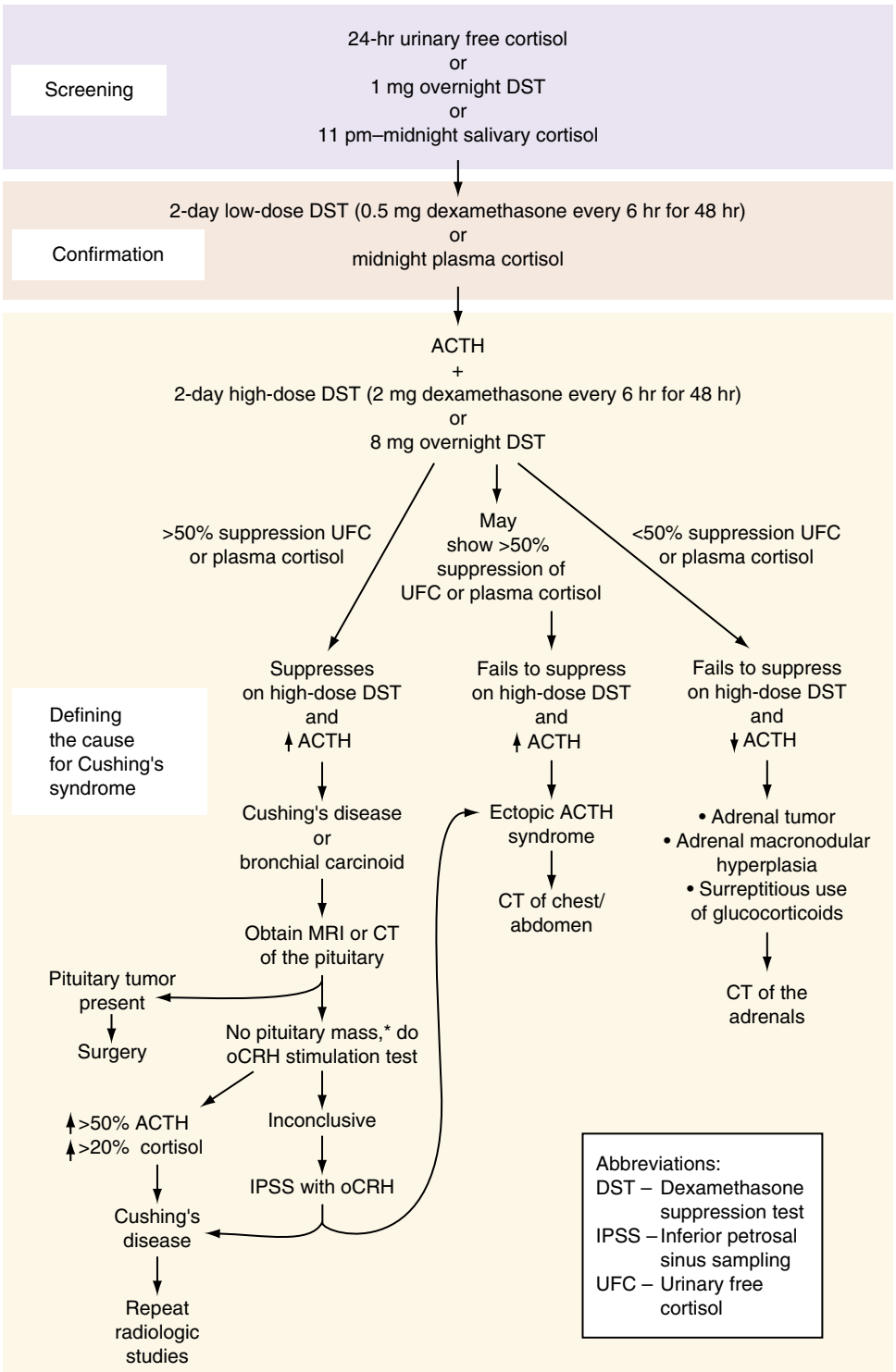

FIG. 3 Algorithm for the evaluation of Cushing syndrome. All screening tests must be followed by a confirmatory test. If there is no pituitary mass, obtain a chest radiograph and chest CT to rule out bronchial carcinoid before proceeding to IPSS. *ACTH,* Adrenocorticotropin; *CT,* computed tomography; *oCRH,* ovine corticotropin-releasing hormone; *MRI,* magnetic resonance imaging. (From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, Philadelphia, 2017, Elsevier.)

LABORATORY TESTS

- Hypokalemia, hypochloremia, metabolic alkalosis, hyperglycemia, hypercholesterolemia.
- Increased 24-hr urinary free cortisol (>100 mcg/24 hr).
- Table 4 describes the differential diagnosis of hormonal values seen in Cushing syndrome.
- Fig. 3 describes an algorithm for the evaluation of Cushing syndrome.

IMAGING STUDIES

- CT scan or MRI of adrenal glands in suspected adrenal Cushing syndrome (Fig. E4).
- MRI of pituitary gland with gadolinium is the preferred procedure for localizing a pituitary edema in suspected pituitary Cushing syndrome.
- Additional imaging studies to localize neoplasms of the lung, pancreas, kidney, thyroid, or thymus in patients with ectopic ACTH production.

Rx TREATMENT

GENERAL Rx

The definitive treatment of Cushing syndrome is surgical removal of the tumor causing excessive production of cortisol:

- Pituitary adenoma: Transsphenoidal microadenomectomy is the therapy of choice in adults. Pituitary irradiation is reserved for patients not cured by transsphenoidal surgery. In children, pituitary irradiation may be considered as initial therapy because 85% of children are cured by radiation. Stereotactic radiotherapy (photon knife or gamma knife) is effective and exposes the surrounding neuronal tissues to less irradiation than does conventional radiotherapy. Total bilateral adrenalectomy is reserved for patients not cured by transsphenoidal surgery or pituitary irradiation

TABLE 4 Differential Diagnosis of Hormonal Values Seen in Cushing Syndrome

Cause	Plasma ACTH	Plasma Cortisol (PM)	High-Dose or Overnight Dexamethasone Suppression
Pituitary-dependent	N—slightly ↑	↑	Yes
Adrenal disease	↓—undetectable	↑	No
Ectopic Cushing*	↑↑↑	↑↑	Usually no
Pseudo-Cushing	N—slightly ↑	N–↑	Usually yes

ACTH, Adrenocorticotropin; *N,* normal.
*ACTH levels may overlap with values seen in pituitary-dependent disease.
From McPherson RA, Pincus MR (eds): *Henry's clinical diagnosis and management by laboratory methods,* ed 23, St Louis, 2017, Elsevier.

- Adrenal neoplasm:
  1. Surgical resection of the affected adrenal
  2. Glucocorticoid replacement for approximately 9 to 12 mo after the surgery to allow time for the contralateral adrenal gland to recover from its prolonged suppression
  3. In nonsurgical candidates, suppression of adrenal steroid production can be accomplished with ketoconazole. Mifepristone, an antiprogestin, can also be used for control of hyperglycemia secondary to hypercortisolism in adults with endogenous Cushing syndrome. It should be avoided in women who are or who could become pregnant
- Bilateral micronodular or macronodular adrenal hyperplasia: Bilateral total adrenalectomy
- Ectopic ACTH:
  1. Surgical resection of the ACTH-secreting neoplasm
  2. Control of cortisol excess with metyrapone, aminoglutethimide, mifepristone, or ketoconazole
  3. Control of the mineralocorticoid effects of cortisol and 11-deoxycorticosteroid with spironolactone
  4. Bilateral adrenalectomy: A rational approach to patients with indolent, unresectable tumors

DISPOSITION

Prognosis is favorable in patients with surgically amenable disease.

PEARLS & CONSIDERATIONS

COMMENTS

Screening for multiple endocrine neoplasia type I should be considered in patients with Cushing disease.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Cushing Syndrome (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READING

Loriaux DL: Diagnosis and differential diagnosis of Cushing's syndrome, *N Engl J Med* 376:1451-1459, 2017.

FIG. E2 Clinical features of Cushing syndrome. A, Centripetal and some generalized obesity and dorsal kyphosis in a 30-year-old woman with Cushing disease. **B,** Same patient as in **A** showing moon facies, plethora, hirsutism, and enlarged supraclavicular fat pads. **C,** Facial rounding, hirsutism, and acne in a 14-year-old girl with Cushing disease. **D,** Central and generalized obesity and moon facies in a 14-year-old boy with Cushing disease. **E** and **F,** Typical centripetal obesity with livid abdominal striae seen in a 41-year-old woman **(E)** and a 40-year-old man **(F)** with Cushing syndrome. **G,** Striae in a 24-year-old patient with congenital adrenal hyperplasia treated with excessive doses of dexamethasone as replacement therapy. **H,** Typical bruising and thin skin of a patient with Cushing syndrome. In this case, the bruising occurred without obvious injury. (From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

TABLE E2 Tumors Associated with the Ectopic Adrenocorticotropic Hormone Syndrome

Tumor Type	Approximate Incidence (%)
Small-cell lung carcinoma	50
Non–small-cell lung carcinoma	5
Pancreatic tumors (including carcinoids)	10
Thymic tumors (including carcinoids)	5
Lung carcinoids	10
Other carcinoids	2
Medullary carcinoma of thyroid	5
Pheochromocytoma and related tumors	3
Rare carcinomas of prostate, breast, ovary, gallbladder, colon	10

From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

TABLE E3 Classification of Causes of Cushing Syndrome

ACTH-Dependent Causes
Cushing disease (pituitary-dependent)
Ectopic ACTH syndrome
Ectopic CRH syndrome
Macronodular adrenal hyperplasia
Iatrogenic (treatment with 1-24 ACTH)
ACTH-Independent Causes
Adrenal adenoma and carcinoma
Primary pigmented nodular adrenal hyperplasia and Carney syndrome
McCune-Albright syndrome
Aberrant receptor expression (gastric inhibitory polypeptide, interleukin-1β)
Iatrogenic (e.g., pharmacologic doses of prednisolone, dexamethasone)
Pseudo-Cushing Syndromes
Alcoholism
Depression
Obesity

ACTH, Adrenocorticotropic hormone; *CRH,* corticotropin-releasing hormone.
From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

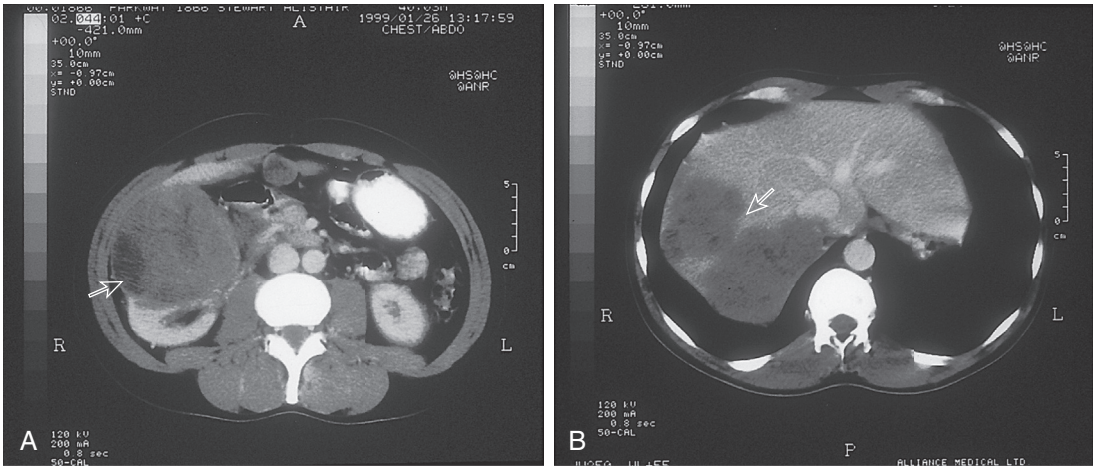

FIG. E4 Computed tomography scan of a patient with rapidly progressing Cushing syndrome caused by an adrenal carcinoma. An irregular right adrenal mass is shown **(A),** and a large liver metastasis is evident **(B).** (From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DESCRIPTION

Cutaneous larva migrans (CLM) is a syndrome defined clinically and parasitologically by subcutaneous larval migration of nematodes. Creeping eruption is the cardinal manifestation. It includes neither diseases in which creeping eruption is due to nonlarval forms of parasites nor diseases without creeping eruptions from subcutaneous migration of larval parasites. Because animal hookworms are the most common cause, some people use the term "hookworm-related cutaneous larva migrans" (HrCLM) instead. Table E1 describes other clinical syndromes associated with unusual helminth infections in humans.

SYNONYMS

CLM
Creeping eruption
Plumber's itch
Creeping verminous dermatitis
Sand worm eruption
Duck hunter's itch
Hookworm-related cutaneous larva migrans HrCLM

ICD-10CM CODES

B76.8	Other hookworm diseases
B76.9	Hookworm disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALANCE: Commonly seen in tropical and subtropical countries. In the U.S., it is most prevalent in southeastern states. Florida has the most cases among these states.
PREDOMINANT AGE: More often seen in children than adults.
GENETICS: Has no racial or sexual predilection.
PEAK INCIDENCE: Peak incidence is seen during rainy season.

- Second to pinworm among helminth infection in developed countries.
- Most common tropically acquired dermatosis.
- Most common imported ectoparasites in travelers returning to the U.S. after a holiday.

RISK FACTORS

Hobbies and occupations that involve contact with warm, moist, sandy soil:

- Tropical or subtropical climate travels
- Barefoot beach goers or sunbathers
- Children playing in sandboxes
- Carpenters, electricians, plumbers, farmers, gardeners, pest exterminators

ETIOLOGY

- Animal hookworms
- *Ancylostoma braziliense* (commonest cause)
- *Ancylostoma caninum*
- *Uncinaria stenocephala*
- *Bunostomum phlebotomum*
- *Pelodera strongyloides*
- *Gnathostoma* species
- *Strongyloides stercoralis*
- *Spirulina* species

PATHOGENESIS

The infection is usually acquired via skin contact with the soil or sand contaminated with feces of infected dogs or cats. The filariform larva is the infective form. It penetrates the skin and migrates within the epidermis by releasing protease and hyaluronidase. The inflammatory reaction along the cutaneous tract of their migration results in creeping eruptions. The larvae are believed to lack the collagenase enzymes required to penetrate the basement membrane to invade the dermis. In contrast to cats and dogs, humans are incidental host. Thus, the larvae are unable to complete their natural cycles in humans. The larvae die without treatment and are resorbed within weeks to months of invasion. This explains why CLM is a self-limiting disease and rarely has systemic features.

CLINICAL FEATURES

- Often associated with a history of sunbathing, walking barefoot on a beach, or similar activity in a tropical location.
- Incubation period is around 1 to 6 days.
- Intense pruritus at the site of invasion within hours of invasion.
- Many patients report a stinging sensation, which they may misinterpret as a puncture or insect bite.
- Erythematous papules develop at the larval penetration site. Feet, buttocks, and thighs are most commonly affected anatomical locations.
- The most frequent and cardinal finding of HrCLM is *creeping dermatitis*, which takes a few days to develop. It is defined as an erythematous, slightly elevated, linear, or serpiginous track that is 3 mm in width and may be up to 15 to 20 cm in length. The mean number of lesions per person varies from one to three. The creeping track associated with the larva migration may extend a few millimeters to few centimeters daily (Fig. E1). These eruptions last 2 to 8 wk without treatment.

TABLE E1 Clinical Syndromes Associated with Unusual Helminth Infections in Humans

Clinical Syndrome	Parasite	Usual Host
Visceral larva migrans	*Toxocara canis*	Canines
	Toxocara cati	Felines
	Baylisascaris procyonis	Raccoons
Eosinophilic gastroenteritis	*Anisakis* spp.	Sea mammals
	Phocanema spp.	Sea mammals
	Ancylostoma caninum	Canines
Cutaneous larva migrans	*Ancylostoma braziliense*	Canines, felines
	Ancylostoma caninum	Canines, felines
	Uncinaria stenocephala	Canines, felines
Eosinophilic meningitis	*Angiostrongylus cantonensis*	Rats
	Gnathostoma spinigerum	Felines, other mammals
Pulmonary or cutaneous nodules	*Dirofilaria* spp.	Canines, other mammals
Abdominal angiostrongyliasis	*Angiostrongylus costaricensis*	Cotton rats
Capillariasis	*Capillaria philippinensis*	Birds
Diarrhea	*Nanophyetus salmincola*	Mammals, birds
Swimmer's itch	*Trichobilharzia* spp.	Birds

FIG. E1 Cutaneous larva migrans characterized by a serpiginous erythematous migratory lesion caused by an infection with dog hookworm. (Courtesy Dr. Timothy Berger, San Francisco. In Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

- Edema and vesicobullous lesions along the course of the larva.
- Rare presentation is hookworm folliculitis. It is characterized by numerous (20 to 100) follicular, erythematous, and pruritic papules and pustules, located mainly in the buttocks. Generally numerous short tracks are seen arising from these follicular lesions.
- In case of rare pulmonary involvement, dry cough and wheezing develop 1 wk after the dermal invasion.

Dx DIAGNOSIS

Diagnosis is made on clinical grounds and history of potential exposure. Clinical characteristics of the creeping trails (length, width, speed of migration, location, duration) help differentiate HrCLM from other causes of creeping dermatitis.

- Blood tests are not necessary for diagnosis. Theoretically, blood test could detect eosinophilia and elevated IgE level.
- Biopsy specimens usually show an eosinophilic inflammatory infiltrate but not the migratory parasite. For this reason, biopsy is not indicated to establish the diagnosis. Nonetheless, in case of hookworm folliculitis, skin biopsy specimens may reveal nematode larvae in the follicular canal.
- Stool studies and serology are not helpful.
- Radiography of the chest is indicated when migratory pulmonary infiltrates are suspected.
- A new technology, optical coherence tomography, has been found to identify the larvae in the epidermis, allowing direct removal.

DIFFERENTIAL DIAGNOSIS

- Superficial thrombophlebitis
- Mondor disease
- Lichen striatus
- Phytophotodermatitis
- Herpes zoster
- Migratory myiasis
- Scabies
- Loiasis
- Dracunculiasis
- Cercarial dermatitis
- Onchocerciasis
- Dirofilariasis
- Contact dermatitis
- Creeping hair
- Jelly fish stings
- Fascioliasis
- Bacterial folliculitis
- Tinea pedis/corporis
- Impetigo
- Erythema chronicum migrans of Lyme disease
- Ground itch
- Toxocariasis

Rx TREATMENT

- Oral albendazole and ivermectin are the first-line drug treatments.
- Oral administration is preferred in the presence of extensive lesions or when topical application fails.
- Topical application should cover the tracks and area covering up to 2 cm from the leading edge.
- Albendazole should be given (400 mg orally per day for 3 to 5 days).
- At times, when oral drugs are contraindicated, topical 10% albendazole creams are applied twice a day for a period of 10 days.
- Ivermectin should be given (200 mcg/kg given as a single dose).
- Thiabendazole should be given (25 to 50 mg/kg divided into twice-daily doses for 2 days).
- Because of its higher side effect profile when given orally, it is more often applied topically (10% to 15% cream or aqueous suspension of 500 mg/5 ml) four times a day for 5 to 10 days.
- Mebendazole should be given (100 mg orally twice for 3 days).
- Cryotherapy with liquid nitrogen is obsolete. It is ineffective as the larva is usually located 1 to 2 cm beyond the visible end of the trail, and the larva is capable of withstanding temperature as low as –21° C (–5º F) for more than 5 minutes. Moreover, this procedure is painful and can lead to chronic ulcerations.
- Specific antihelmintic therapy for pulmonary involvement is generally not required because the illness is usually mild and self-limiting.
- In the case of hookworm folliculitis, treatment is more difficult than the traditional form and necessitates repeated courses of oral antihelmintic agents.
- Antihistamines and topical steroids relieve intense pruritus.
- Antibiotics are indicated for bacterial superinfection.
- Generally, there should be no attempt to extract the worm.

COMPLICATIONS

- Secondary bacterial infection
- Erythema multiforme
- Migratory eosinophilic pneumonitis (Loeffler syndrome)
- Eosinophilic enteritis

PROGNOSIS

Self-limiting benign disease. Even without treatment, most cases resolve within 4 to 8 wk.

PREVENTION

- Prohibit pets such as dogs and cats walking on the beaches in tropical areas.
- Avoid allowing pets in sandboxes.
- Deworm household pets.
- Clean up pet droppings.
- Wear protective footwear while walking on the beach.
- Avoid tropical beaches frequented by dogs and cats.
- When lying on tropical beaches potentially frequented by dogs and cats, areas of sand washed by the tide are preferable to dry sand, and mattresses are preferable to towels.
- Towels and clothes should not touch the ground when hung up for drying.

AUTHOR: **Hemant K. Satpathy, MD**

BASIC INFORMATION

DEFINITION

Blue or purple skin discoloration due to increased circulating levels of deoxygenated blood

SYNONYMS

Methemoglobinemia
Sulfhemoglobinemia
Acrocyanosis
Pseudocyanosis

ICD-10CM CODES

R23.0	Cyanosis
P28.2	Cyanotic attacks of the newborn
I73.8	Acrocyanosis
I73.89	Other specified peripheral vascular diseases

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown
PEAK INCIDENCE: Unknown
PREVALENCE: Unknown
PREDOMINANT SEX AND AGE: Unknown
GENETICS: None
RISK FACTORS: Congenital heart disease, high altitude, hypercoagulable state, cardiopulmonary disease, cirrhosis, exposure to aniline dyes, lidocaine use

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History: Onset; time of day of symptoms; prior episodes of cyanosis; recent medication use; associated symptoms, including fever or cough; past medical history (PMHx) of congenital heart disease, cardiopulmonary disease, neurologic condition that results in decreased respiratory effort including seizures, breath-holding spells; family history of congenital heart disease
- Physical examination: Bluish discoloration of perioral skin, conjunctivae, and oral mucosa suggests central cyanosis; peripheral cyanosis will result in discoloration of extremities and nail beds; trauma to chest wall or upper airway may cause central cyanosis due to lung injury or obstruction; tachypnea and retractions are seen in patients with respiratory causes of cyanosis, as well as abnormal lung examination findings (wheezes, crackles); tachycardia frequently accompanies cyanosis in children; bradycardia in the setting of cyanosis can indicate pending circulatory collapse

ETIOLOGY

Various causes are responsible for this clinical finding (see "Differential Diagnosis"). Investigation for the underlying cause is critical to determining appropriate treatment.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Cyanosis should be separated into central or peripheral causes to guide the differential diagnosis.

Central cyanosis

- Decreased arterial O_2 saturation
  1. Decreased atmospheric pressure—high altitude
  2. Impaired pulmonary function—hypoventilation, V/Q mismatch, impaired O2 diffusion
- Anatomic shunts—fistulae (cerebral, pulmonary, hepatic, peripheral), cyanotic congenital heart disease
- Hemoglobin with low O_2 affinity
- Hemoglobin abnormalities—methemoglobinemia (hereditary), sulfhemoglobinemia (acquired), carboxyhemoglobinemia (not true cyanosis)

Peripheral cyanosis

- Low cardiac output states (cardiogenic shock, hypovolemia with or without bleeding, sepsis)
- Environmental exposures: Air, water
- Arterial occlusion: Thrombosis, embolism, vasospasm (Raynaud), peripheral vascular disease
- Venous obstruction
- Redistribution of blood flow from extremities
- Cyanide-related nitroprusside toxicity (initially, skin may be "cherry red" due to increased venous hemoglobin levels, progressing to cyanosis that accompanies shock)

WORKUP

- Fig. E1 outlines the approach to a patient with central cyanosis. The evaluation of peripheral cyanosis is summarized in Fig. E2.
- Examine patient's circulation/airway/breathing (CAB) and arterial blood gas (ABG), administer supplemental O_2; if concern for shock or patient otherwise unstable, obtain emergency medical services immediately for management of airway and breathing as needed, as well as for additional evaluation of shock (hypovolemic, septic, cardiogenic).
- If improvement with O_2, obtain chest x-ray to evaluate cardiac silhouette:
  1. Normal cardiac silhouette suggests decreased pulmonary function from infiltrates, effusion, edema, pulmonary embolism (PE), or arteriovenous fistulae.
  2. Enlarged cardiac silhouette may suggest cardiogenic shock; obtain electrocardiogram or echocardiogram to further evaluate.
  3. If no improvement with supplemental O_2 (PaO_2 <100 or SaO_2 <70), obtain chest x-ray and methemoglobin, carbon monoxide, and cyanide levels.
  4. If respiratory distress, evaluate for pneumothorax, upper airway obstruction, or bronchospasm.
  5. If no respiratory distress, evaluate for chronic methemoglobinemia, sulfhemoglobinemia, G6PD deficiency, or cyanotic heart disease.

LABORATORY TESTS

- Deoxygenated hemoglobin in the capillary blood is elevated to ≥5 g/dl
- Complete blood count to evaluate for erythrocytosis, polycythemia, or anemia
- D-dimer if pulmonary embolism is suspected
- Peripheral smear to look for red blood cell count morphology and fragments
- Thiocyanate levels if suspected nitroprusside toxicity

IMAGING STUDIES

- Chest x-ray to evaluate for new pulmonary infiltrates, effusions, edema, or consolidations
- ECG for those with abnormal cardiac examination findings
- Echocardiography for infants and children with suspected congenital heart disease
- Compression ultrasonography of lower extremity or chest computed tomography angiography if deep venous thrombosis or PE suspected as cause for cyanosis

TREATMENT

NONPHARMACOLOGIC THERAPY

Decontamination with soap and water after discontinuing offending agent

ACUTE GENERAL Rx

- Administer high-flow oxygen first and monitor response in all patients
- Methylene blue (1 to 2 mg/kg IV over 5 minutes) if patients have symptomatic hypoxia or methemoglobin level >30% in methemoglobinemia
- Phlebotomy and crystalloid fluid expansion to achieve hematocrit <45% if polycythemia
- Elevate head of bed and oxygen for superior vena cava syndrome; radiation/chemotherapy/vascular stenting if caused by malignancy
- Intravenous fluid resuscitation if hypovolemia is present
- Cyanotic patients with altered mental status often have decreased oxygen saturation due to disordered breathing or neuromuscular weakness causing respiratory depression. Such patients typically cannot maintain their airway and will require advanced airway support unless their underlying cause of coma can be treated rapidly (dextrose for hypoglycemia, naloxone for opiod overdose, benzodiazepine for seizures). Transient central cyanosis is a common feature of breath-holding spells and seizures
- Provide guideline-directed medical therapy for congestive heart failure, arrhythmias, or poor cardiac output
- Supportive care and antidotes if toxin-mediated cyanosis is present

DISPOSITION

- Admit patients with first episode or unexplained cyanosis
- Discharge patients with peripheral cyanosis from vasoconstriction, methemoglobin <15%, and primary pulmonary disease

REFERRAL

- Pediatric cardiology if children have first episode of congestive heart failure or newly diagnosed congenital heart disease as suggested by abnormal ECG and/or chest radiograph findings

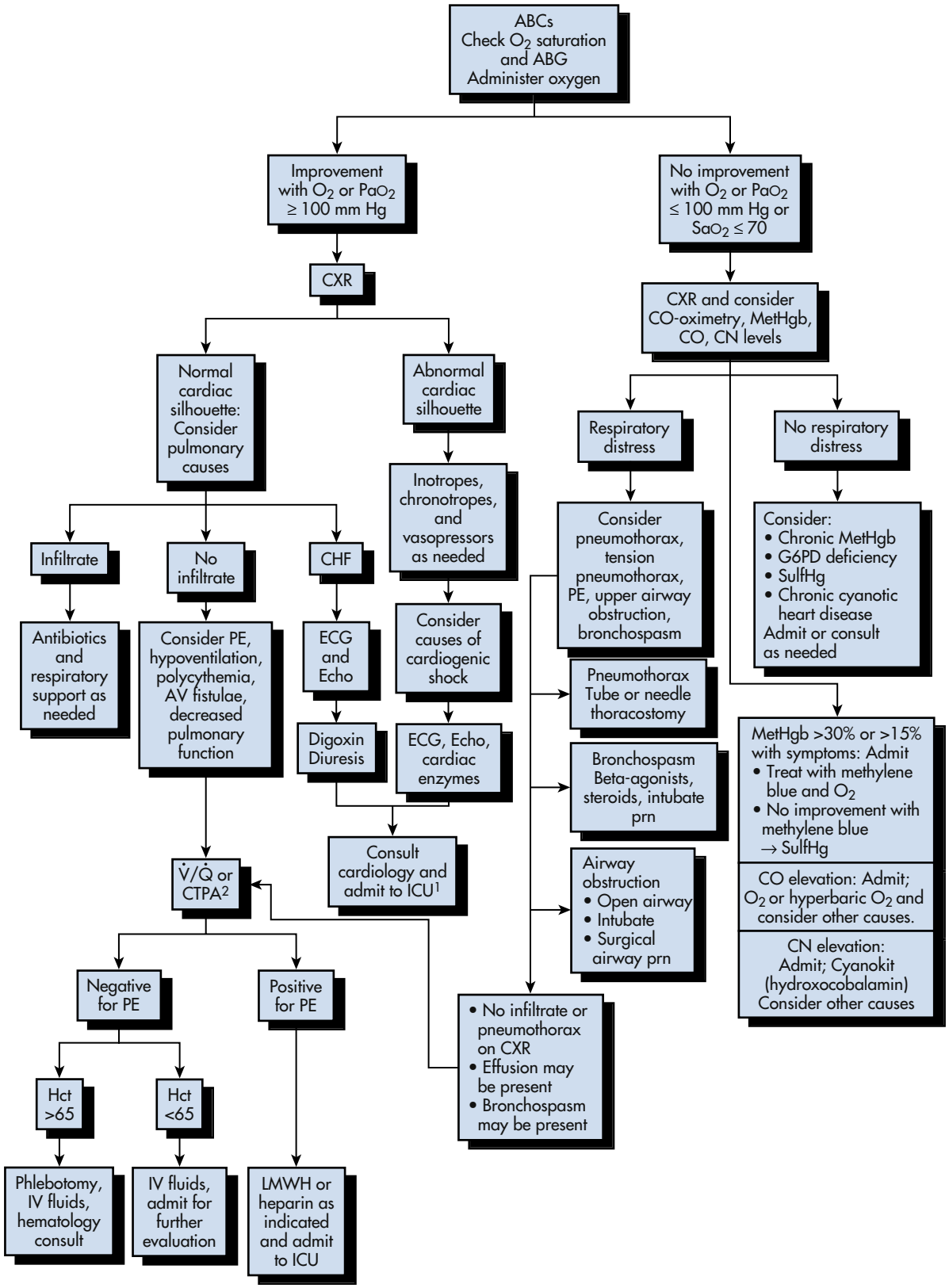

FIG. E1 Approach to central cyanosis. *ABCs*, Airway, breathing, circulation; *ABG*, arterial blood gas; *CHF*, congestive heart failure; *CN*, cranial nerve; *CO*, carbon monoxide; *CTPA*, computed tomography pulmonary angiogram; *CXR*, chest x-ray; *Echo*, echocardiogram; *ECG*, electrocardiogram; *Hct*, hematocrit; *ICU*, intensive care unit; *IV*, intravenous; *LMWH*, low-molecular-weight heparin; *MetHgb*, methemoglobin; *PE*, pulmonary embolism; *prn*, as needed; *V/Q*, ventilation/perfusion. (From Walls RM, Hockberger RS, Gausche-Hill M: *Rosen's emergency medicine: concepts and clinical practice,* ed 9, Philadelphia, 2018, Elsevier.)

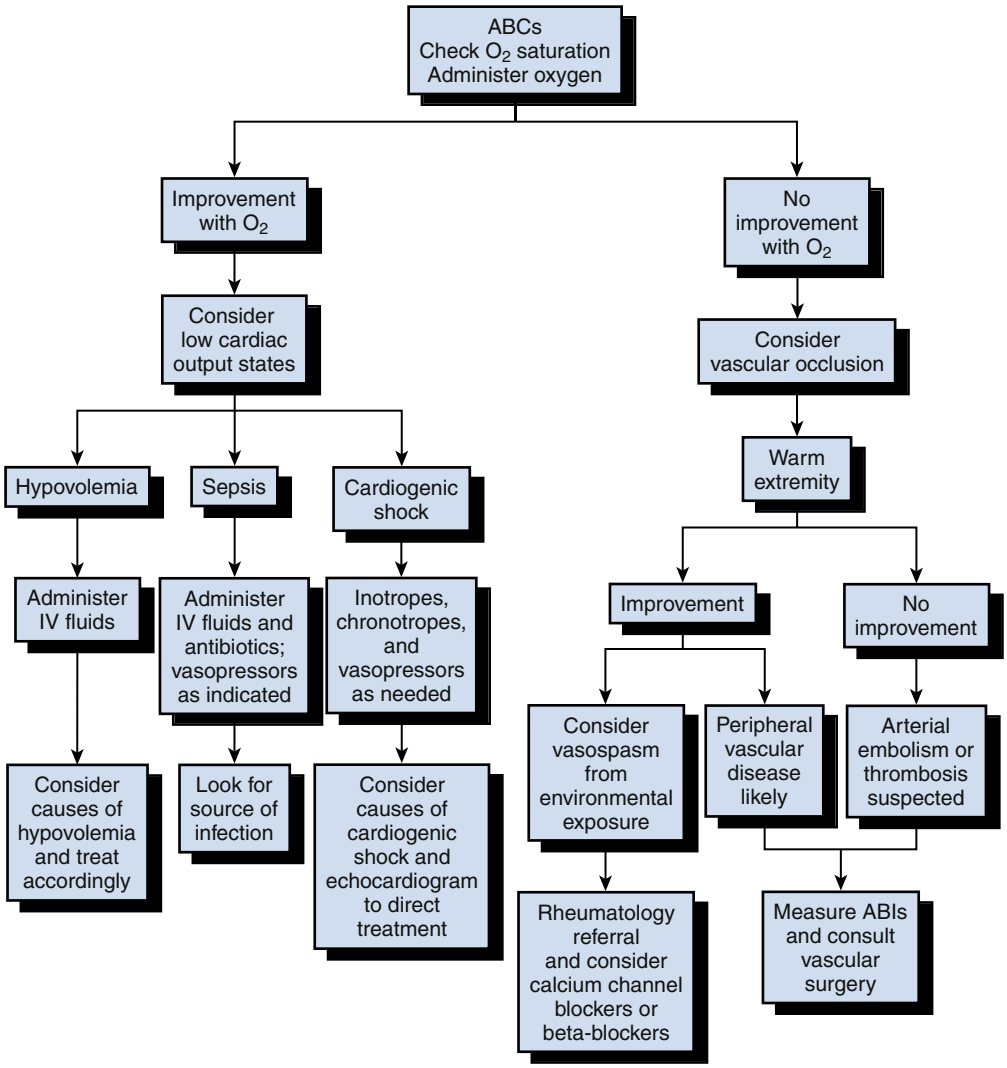

FIG. E2 Approach to peripheral cyanosis. *ABCs*, Airway, breathing, circulation; *ABI*, ankle-brachial index; *IV*, intravenous. (From Walls RM, Hockberger RS, Gausche-Hill M: *Rosen's emergency medicine: concepts and clinical practice,* ed 9, Philadelphia, 2018, Elsevier.)

- Congenital vascular surgery evaluation if acute arterial occlusion is suspected or confirmed
- Suspected intensive care unit and/or cardiology assessment if cyanosis is due to acute cardiovascular or pulmonary collapse from shock
- Consider rheumatology for Raynaud phenomenon to assess for systemic autoimmune disorder

PEARLS & CONSIDERATIONS

- In all patients with cyanosis, evaluate CAB, O_2 saturation, and ABG; provide supplemental O_2 to all patients with cyanosis.
- An increase in PaO_2 >100 or resolving cyanosis suggests oxygen diffusion defect.
- All patients with new-onset or unexplained cyanosis require hospitalization.
- Methylene blue in patients with methemoglobinemia if levels >30% or symptomatic hypoxia.
- Failure of methemoglobinemia to improve with methylene blue indicates sulfhemoglobinemia.
- In infants with or who have a clinical suspicion for a ductal-dependent congenital heart defect, prostaglandin E1 (alprostadil) should be administered until a definitive diagnosis or treatment is established.

PREVENTION

- Avoid offending agents.
- Avoid excessive exposure to cold air or water.

PATIENT & FAMILY EDUCATION

- Avoid excessive exposure to cold air or water if diagnosed with Raynaud phenomenon.
- Return to the emergency department if cyanosis is accompanied by dyspnea, altered mentation, or chest pain.

AUTHOR: **Juan Guerra, DO**

Cyclic Vomiting Syndrome

BASIC INFORMATION

DEFINITION

Cyclic vomiting syndrome (CVS), an idiopathic disorder primarily seen in children, is characterized by recurrent, stereotypical episodes of vomiting with varying asymptomatic periods.

SYNONYM

CVS

ICD-10CM CODES
G43.A0 Cyclical vomiting, not intractable
G43.A1 Cyclical vomiting, intractable

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE & PREVALENCE:

- Cross-sectional study of school-age children in Aberdeen, Scotland, estimated that 1.6% fulfilled diagnostic criteria.
- Average age of time of diagnosis: 9.6 yr.
- Average age of onset of symptoms: 5.3 yr.
- This study showed gender ratio was equivalent, although isolated reports say it may be more common in girls.
- In adults, no population studies exist to extrapolate prevalence. In one study with 17 patients followed over a 10-yr interval, it was found that average age of onset was 35 yr, but diagnosis was 41 yr. Gender distribution was again found to be equal.

GENETICS: Mutations in mitochondrial DNA (mtDNA) have been associated with cyclical vomiting syndrome and neuromuscular disease in pediatric patients. These mutations were also more commonly associated with migraines, irritable bowel syndrome, and hypothyroidism. Evidence shows that the mtDNA mutations seen in pediatric patients have a maternal inheritance pattern.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- There is a stereotypical pattern to the vomiting episodes. They normally begin in the early morning hours and may involve a prodrome that includes pallor, nausea, abdominal pain, or lethargy.
- High rates of emeses per hour with the peak in the first hour with a decline in the next 4 to 8 hr. These episodes normally last up to 24 hr.
- Many patients may have neurologic symptoms, including headache, photophobia, or vertigo, which supports the genetic relation between CVS and migraines.

ETIOLOGY

- mtDNA mutations that were also associated with migraines in pediatric patients with two mtDNA polymorphisms in particular, 16519T and 3010A, that are expressed in high frequency in subjects with CVS. In adults, CVS is not associated with these polymorphisms.
- Sympathetic hyperresponsiveness and autonomic dysregulation may contribute to the pathogenesis of CVS. Elevated corticotropin, cortisol, vasopressin, and catecholamines have been described in patients with vomiting, lethargy, and hypertension. Studies in animals suggest that corticotropin-releasing factor induces gastric stasis, leading to emesis. Stress responses, which are mediated by the hypothalamic-pituitary-adrenal axis, can therefore potentially induce episodes of vomiting. Triggers of stress responses can be infectious, psychological, or physical.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute porphyria
- Abdominal migraines
- Diabetic ketoacidosis
- *Helicobacter pylori* infection
- Cannabis hyperemesis syndrome
- Jamaican vomiting sickness
- Munchausen syndrome by proxy
- Mechanical obstruction
- Gastrointestinal malignancies
- Intestinal malrotation

WORKUP

- CVS is a clinical diagnosis because there are no biochemical markers or imaging that exist to make the diagnosis. The North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) has set forth criteria (all criteria must be met). Box E1 summarizes criteria. In adults, Rome IV criteria should be met to make diagnosis. Box E2 summarizes Rome IV criteria. Supportive criteria in addition to either set of guidelines include a personal or family history of migraine headaches. Rome IV also divides patients with prolonged excessive cannabis use from CVS into cannabinoid hyperemesis syndrome (CHS). It also differentiates chronic nausea vomiting syndrome from CVS by distinct temporal characteristics of weekly acute episodes.
- All patients with suspected CVS should be questioned about cannabis use to rule out cannabis hyperemesis syndrome.

SUPPORTIVE CRITERION

History or family history of migraine headaches

LABORATORY TESTS

In the evaluation for possible GI disease as an etiology of vomiting, screening blood work should be performed. CBC, basic metabolic panel (BMP), liver function tests, pancreatic amylase and lipase, and erythrocyte sedimentation rate (ESR) should be done. Screening for endocrine and metabolic disorders is also warranted and can include lactic acid, ammonia, amino acids, adrenocorticotropic hormone (ACTH), and antidiuretic hormone (ADH) as well as urinary ketones, organic acids, porphobilinogen, and aminolevulinic acid. Drug screening should also be considered if CHS is a possibility.

IMAGING STUDIES

An upper GI series with small bowel follow-through, CT/MRI of the head, and endoscopy should be performed in between episodes. In adults, a CT of the abdomen and pelvis should be done in addition to the mentioned testing to exclude malignancy. Additional testing may include antroduodenal manometry to assess for neuropathy or myopathy, esophageal pH testing to rule out vomiting as an atypical presentation of GERD, and CT of head to rule out space-occupying lesions.

TREATMENT

- Treatment of CVS includes avoidance of certain triggers that precipitate attacks as well as pharmacologic therapy divided into prophylactic, abortive, and supportive treatment.
- Patients with regular use of cannabis should be asked to abstain for a short period and if symptoms resolve or improve then cannabis hyperemesis syndrome is likely.

NONPHARMACOLOGIC THERAPY

- Avoidance of dietary triggers such as chocolate, cheese, or monosodium glutamate (MSG) may prevent episodes.
- Stress management techniques for psychosocial stressors may decrease the frequency of episodes exacerbated by stress.

ACUTE GENERAL Rx

Treatment can be considered as prophylactic, abortive, or supportive.

- Prophylactic therapy is reserved for patients who have more than one attack per month or with attacks that are severe enough to cause hospitalization. A trial of prophylactic antimigraine medications is recommended even in the absence of personal or family history of migraine headaches. Prophylactic therapy includes cyproheptadine, amitriptyline, propranolol, erythromycin, and topiramate. Some specialists recommend starting amitriptyline at 0.5 mg/kg per day in children older than 5 yr. It often is increased to 1 mg/

Box E1 North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) Criteria for Cyclic Vomiting Syndrome

- At least five episodes over any interval or a minimum of three attacks over a 6-mo period
- Episodic attacks of intense nausea and vomiting lasting from 1 hour to 10 days and occurring at least 1 wk apart
- Stereotypical in the individual patient
- Vomiting during attacks occurs at least four times per hour for at least 1 hour
- A return to baseline health between episodes

Box E2 Rome IV Diagnostic Criteria for Cyclic Vomiting Syndrome

Must include all of the following:
- Stereotypical episodes of vomiting regarding onset (acute) and duration (<1 wk)
- At least two acute-onset episodes in the past 6 mo, each occurring at least 1 wk apart and persisting less than 1 wk
- Absence of nausea and vomiting between episodes but other, milder symptoms can occur between cycles

kg per day, with effects typically taking a few months to become evident.
- There is emerging evidence that carnitine and coenzyme Q10 along with strict dietary protocol can reduce episodes.
- Abortive therapy is used during episodes. Agents that are used in migraine attacks such as triptans have also been found to be effective in aborting episodes in CVS. If abortive therapy fails, antiemetic therapy with ondansetron can be used as supportive therapy. If attack is severe, ondansetron may be used in conjunction with a benzodiazepine or diphenhydramine.

DISPOSITION

If episode is severe, the patient may need hospital admission. Treatment includes IV fluids, antiemetics, and analgesics. Otherwise, this can be managed on an outpatient basis.

REFERRAL

Referral should be made to a gastroenterologist for thorough investigation of vomiting until definitive diagnosis of CVS can be established. If certain neurologic findings or laboratory study results suggest a metabolic disorder, early referral to a metabolic specialist or neurologist should be considered.

PEARLS & CONSIDERATIONS

COMMENTS

CVS is a clinical diagnosis that is seen in pediatric and adult populations. Laboratory testing and appropriate imaging should be done to rule out other differential diagnoses. A thorough history including family history, onset and duration of episodes, alarming symptoms, and so on as well as a complete physical examination will allow clinician to narrow differential diagnoses.

PREVENTION

There is emerging evidence of carnitine and coenzyme Q10 in a certain subtype of patients to prevent frequent attacks. Prophylactic therapy includes pharmacologic agents stated earlier. Avoidance of stress and dietary triggers are also warranted if this can be identified as causative etiology.

PATIENT & FAMILY EDUCATION

Families are encouraged to view https://.cvsaonline.org for more information and education about the disease.

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Cyclic Vomiting Syndrome Association: Available at http://cvsaonline.org.

Li BU et al: North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome, *J Pediatr Gastroenterol Nutr* 47:379-393, 2008.

Rome III Criteria: Available at http://theromefoundation.org.

Cystic Fibrosis PTG ALG

BASIC INFORMATION

DEFINITION

Cystic fibrosis (CF) is an autosomal recessive disorder characterized by dysfunction of chloride channels of exocrine glands.

ICD-10CM CODES

- E84.0 Cystic fibrosis with pulmonary manifestations
- E84.11 Meconium ileus in cystic fibrosis
- E84.19 Cystic fibrosis with other intestinal manifestations
- E84.8 Cystic fibrosis with other manifestations
- E84.9 Cystic fibrosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- CF is the most common fatal hereditary disorder among Caucasians of Northern European descent in the U.S. (one case per approximately 3000) and the second most common life-shortening childhood-onset inherited disorder in the U.S., behind sickle cell disease.
- Worldwide it affects 80,000 children and adults.
- Median age at diagnosis is 5.3 mo. Median survival is now greater than 40 yr due to advancements in treatment.
- Carrier screening is associated with a decrease in incidence of CF.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Meconium ileus
- Failure to thrive in children
- Increased anterior/posterior chest diameter
- Basilar crackles and hyperresonance to percussion
- Digital clubbing
- Chronic cough
- Abdominal distention
- Greasy, foul-smelling feces
- Clinical manifestations of CF are summarized in Box E1
- The frequency of selected GI manifestations in CF is summarized in Table E1
- See Box E1

ETIOLOGY

CF is an autosomal-recessive disease caused by mutations to the gene encoding for the CFTR protein on chromosome 7; over gene mutations organized into six classes (Table E2) have been associated with CF. About half of patients in the U.S. with CF are homozygous for the Phe508del mutation in *CFTR*, and more than 90% have at least one Phe508del allele. These mutations result in abnormalities in chloride transport and thus water flux across the surface of epithelial cells (Fig. E1); the resulting abnormally viscous secretions cause obstruction of glands and ducts in various organs and subsequent damage to exocrine tissue (recurrent pneumonia, atelectasis, bronchiectasis, diabetes mellitus, biliary cirrhosis, cholelithiasis, intestinal obstruction, increased risk of gastrointestinal malignancies).

BOX E1 Clinical Manifestations of CF

Upper Respiratory
Sinusitis
Mucous membrane hypertrophy, nasal polyposis

Lower Respiratory
Atelectasis
Emphysema
Infections
Bronchitis, bronchopneumonia, bronchiectasis, lung abscess
Respiratory failure, right-sided heart failure

GI
Bile salt deficiency
Pancreatic insufficiency
GERD
PUD
Meconium ileus
Volvulus
Peritonitis
Ileal atresia
Distal intestinal obstruction syndrome
Fecal masses
Intussusception
Rectal prolapse

Pancreatic
Pancreatitis
Nutritional failure
Diabetes mellitus
Calcification
Maldigestion with steatorrhea and azotorrhea
Vitamin deficiencies

Hepatobiliary
Mucus hypersecretion
Gallstones, atrophic gallbladder
Focal biliary cirrhosis
Portal hypertension ± esophageal varices
Hypersplenism

Reproductive
Females: Increased viscosity of vaginal mucus, decreased fertility
Males: Sterility; absent ductus deferens, epididymis, and seminal vesicles

Skeletal
Retardation of bone age
Demineralization
Hypertrophic pulmonary osteoarthropathy

Ophthalmologic
Venous engorgement
Retinal hemorrhage

Other
Salt depletion through excessive loss of salt through skin
Heat stroke
Hypertrophy of apocrine glands

GERD, Gastroesophageal reflux disease; *GI,* gastrointestinal; *PUD,* peptic ulcer disease.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE E1 Frequency of Selected GI Manifestations in CF*

Organ	Manifestation	Frequency in All Patients (%)	Frequency in Adults (%)
Pancreas	Total achylia	85-90	85-90*
	Abnormal glucose tolerance	20-30	20-30
	Partial or normal function	10-15	10-15
	Pancreatitis	1-2 (all CF) 22 (PS-CF)	2-3
	Diabetes mellitus	4-7	4-7
Intestine	Meconium ileus	10-25	
	Rectal prolapse	1-2	
	Distal intestinal obstruction syndrome	3	18
	Intussusception	1	1-2
Liver	Fatty liver	7	20-60
	Focal biliary cirrhosis	2-3	11-70
	Portal hypertension	2-3	28
Biliary tract	Gallbladder abnormal, nonfunctional, or small	25	5-20
	Gallstones	8	10-25
	Bile duct strictures	1-20	1-20
Esophagus	GERD	Unknown	80

CF, Cystic fibrosis; *GERD,* gastroesophageal reflux disease; *PS-CF,* CF with pancreatic sufficiency.
*Frequency may depend on the genotype.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Immunodeficiency states
- Celiac disease
- Asthma
- Recurrent pneumonia
- Primary ciliary dyskinesia

WORKUP

A diagnosis of CF requires proof of both CFTR dysfunction (i.e., elevated sweat chloride ≥60 mmol/L measured twice, two disease-causing mutations

TABLE E2 Classes of Cystic Fibrosis Transmembrane Conductance Regulator Mutations

Class	Effect on CFTR	Functional CFTR	Presence of CFTR on Cell Membrane
I	Defective protein production due to premature termination of CFTR messenger RNA	No	No
II	Impaired protein processing due to misfolding (e.g., ΔF508 deletion)	No	No, CFTR is degraded in the cytoplasm
III	Defective regulation with reduced channel opening time (e.g., G551D mutation)	No	Yes
IV	Impaired function causing reduced chloride transport	Yes, but reduced in function	Yes
V	Reduced synthesis of normally functioning CFTR	Yes, but reduced in number	Reduced in number
VI	Impaired membrane insertion or stability	Yes, but reduced in number	Reduced in number

CFTR, Cystic fibrosis transmembrane conductance regulator; *RNA,* ribonucleic acid.
From Weinberger SE: *Principles of pulmonary medicine*, ed 7, Philadelphia, 2019, Elsevier.

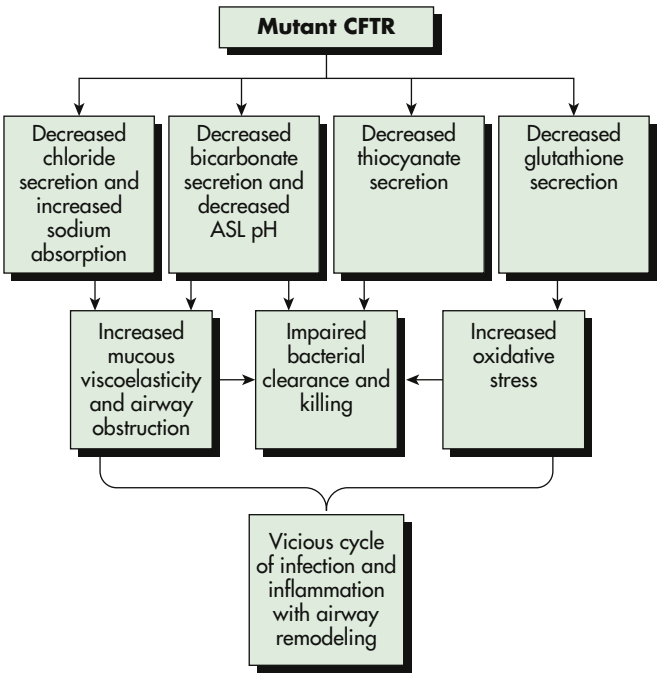

FIG. E1 Schema of mutant cystic fibrosis transmembrane conductance regulator (CFTR) mechanisms of chronic airway disease. CFTR conducts several anions including chloride, bicarbonate, thiocyanate, and glutathione. The loss of CFTR function impacts critical airway epithelial functions: (1) It increases the risk for dehydration of airway surface liquid (ASL) with loss of chloride efflux and associated increased sodium channel activity. (2) The loss of secreted bicarbonate and/or acidic pH of the ASL increases mucous viscoelasticity, resulting in failure of mucociliary transport. (3) Acidic pH in the ASL impairs normal innate immune clearance of bacteria. (4) Loss of thiocyanate impairs lactoperoxidase bacterial killing. (5) Loss of glutathione secretion depletes the antioxidant capacity of the airway, resulting in increased inflammation, increased mucous secretion, and increased mucous viscoelasticity. These factors lead to a vicious cycle of infection and inflammation that is progressive. *ASL,* Airway surface liquid; *CFTR,* cystic fibrosis transmembrane conductance regulator. (From Kliegman, RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.)

in CFTR from each parental allele, or abnormal nasal potential difference) and one or more phenotypic features consistent with CF (e.g., chronic suppurative obstructive lung disease, pancreatic insufficiency). Table E3 describes diagnostic criteria for CF. Conditions suggesting the diagnosis of CF in adults and recommended diagnostic studies are described in Table E4.

LABORATORY TESTS

- Pilocarpine iontophoresis (sweat chloride test): Diagnostic of CF in children if sweat chloride is >60 mmol/L (>80 mmol/L in adults) on two separate tests on consecutive days. Repeat testing may be necessary because not all infants have sufficient quantities of sweat for reliable testing. Indications for sweat test and conditions with associated high electrolyte levels are summarized in Table E5. Table E6 describes conditions associated with false-positive and false-negative sweat test results.
- DNA testing may be useful for confirming the diagnosis and providing genetic information for family members.
- Sputum culture and sensitivity and Gram stain (frequent bacterial infections with *Staphylococcus aureus* [both MSSA and MRSA], *Pseudomonas aeruginosa* [most common virulent respiratory pathogen], *Stenotrophomonas maltophilia,* and *Burkholderia cepacia*).
- Bronchoalveolar lavage (BAL) may be used to aid in the early diagnosis of pulmonary infection in nonexpectorating patients; however, evidence for its clinical benefit is lacking. Trials have shown that among infants diagnosed with CF, BAL-directed therapy did not result in a lower prevalence of *P. aeruginosa* infection or lower total CF-CT score when compared with standard therapy at age 5 yr.
- Low albumin level, increased 72-hr fecal fat excretion.
- Pulse oximetry or arterial blood gases: Hypoxemia.
- Pulmonary function studies: Decreased total lung capacity, forced vital capacity, pulmonary diffusing capacity.

IMAGING STUDIES

- Chest x-ray (Fig. E2): May reveal focal atelectasis, peribronchial cuffing, bronchiectasis, increased interstitial markings, hyperinflation
- High-resolution chest CT scan (Fig. E3): Bronchial wall thickening, cystic lesions, ring shadows (bronchiectasis)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Mucus clearance (i.e., using postural drainage techniques, chest percussion, pneumatic vest, acapella)
- Encouragement of regular exercise and proper nutrition (daily caloric intake of 120%-200% of healthy population)
- Psychosocial evaluation and counseling of patient and family members

ACUTE GENERAL Rx

- Primary goal of CF treatment in regard to pulmonary disease is to maintain lung function as near to normal as possible by controlling respiratory infections and clearing airways of mucus.
- Antibiotic therapy is based on the results of sputum Gram stain and culture and sensitivity. *S. aureus* infections are treated with either cefazolin 1.5 g q6h or nafcillin 2 g 4-6h. MRSA should be treated with vancomycin 45-60 mg/kg/day in 3 divided doses

TABLE E3 Diagnostic Criteria for Cystic Fibrosis (CF)

Presence of typical clinical features (respiratory, gastrointestinal, or genitourinary)

or

A history of CF in a sibling

or

A positive newborn screening test

plus

Laboratory evidence for CFTR (CF transmembrane regulator) dysfunction:

Two elevated sweat chloride concentrations obtained on separate days

or

Identification of two CF mutations

or

An abnormal nasal potential difference measurement

CFTR, Cystic fibrosis transmembrane conductance regulator.
From Kliegman, RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

TABLE E4 Approach to Diagnosis of Cystic Fibrosis in Adult Patients

Conditions Suggesting the Diagnosis of Cystic Fibrosis in Adults	Recommended Diagnostic Studies
Recurrent pancreatitis	Sweat electrolyte determination
Male infertility	Extended CFTR mutation analysis
Chronic sinusitis	Nasal potential difference
Nasal polyposis	High-resolution CT scan to identify bronchiectasis
Nontuberculous mycobacterial infection	CT scan of sinuses for polyposis
Allergic bronchopulmonary mycosis	Sputum induction or bronchoalveolar lavage to identify bacterial and fungal pathogens
Bronchiectasis	

CFTR, Cystic fibrosis transmembrane conductance regulator; *CT,* computed tomography.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

TABLE E5 Sweat Test (Quantitative Pilocarpine Iontophoresis): Indications and Conditions with High Electrolyte Levels

Indications	Conditions with High Sweat Electrolyte Levels
Siblings with CF	CF
Chronic pulmonary symptoms	Ectodermal dysplasia
Persistent cough	Glycogen storage disease, type 1
Recurrent respiratory infection	Adrenal insufficiency
Bronchitis	Familial hypoparathyroidism
Bronchiectasis	Fucosidosis
Lobar atelectasis	Pitressin-resistant diabetes insipidus
Failure to thrive (stunting of growth)	Mucopolysaccharidosis
Rectal prolapse	Familial cholestasis syndrome
Nasal polyposis	Environmental deprivation syndrome
Intestinal obstruction of newborn	Acute respiratory disorders (croup, epiglottitis, viral pneumonia)
Meconium ileus	Chronic respiratory disorders (bronchopulmonary dysplasia)
Jaundice in early infancy	α_1-Antitrypsin deficiency
Cirrhosis in childhood or adolescence	
Portal hypertension	
Adult males with aspermia or azoospermia	
Heat stroke	
Hypoproteinemia	
Hypoprothrombinemia	

CF, Cystic fibrosis.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE E6 Conditions Associated with False-Positive and False-Negative Sweat Test Results

With False-Positive Results	With False-Negative Results
Eczema (atopic dermatitis)	Dilution
Ectodermal dysplasia	Malnutrition
Malnutrition/failure to thrive/deprivation	Edema
Anorexia nervosa	Insufficient sweat quantity
Congenital adrenal hyperplasia	Hyponatremia
Adrenal insufficiency	Cystic fibrosis transmembrane conductance regulator mutations with preserved sweat duct function
Glucose-6-phosphatase deficiency	
Mauriac syndrome	
Fucosidosis	
Familial hypoparathyroidism	
Hypothyroidism	
Nephrogenic diabetes insipidus	
Pseudohypoaldosteronism	
Klinefelter syndrome	
Familial cholestasis syndrome	
Autonomic dysfunction	
Prostaglandin E infusions	
Munchausen syndrome by proxy	

From Kliegman, RM: *Nelson Textbook of Pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

or with linezolid 600 mg q12h. *P. aeruginosa* infections can be treated with piperacillin-tazobactam 4.5 g q6h plus ciprofloxacin 750 mg PO q12h. Treatment of CF exacerbations should be aimed at least at mucoid *P. aeruginosa* and *S. aureus* (i.e., piperacillin-tazobactam and ciprofloxacin). A recent study using azithromycin maintenance in children with CF for 6 mo found less use of additional antibiotics and improvement in some aspects of pulmonary function. Additional studies will be necessary to determine if azithromycin should be used as a primary therapy or rescue treatment. Inhaled antibiotics (aztreonam or tobramycin) can also be used and can achieve high airway concentration with lower systemic side effects. Intermittent administration of inhaled tobramycin has been reported to be beneficial in CF.

- Bronchodilators for patients with airflow obstruction.
- Long-term pancreatic enzyme replacement.
- Alternate-day prednisone (2 mg/kg) possibly beneficial in children with CF (decreased hospitalization rate, improved pulmonary function). Glucocorticoids are used in selected patients during an exacerbation that has characteristics of an acute asthmatic episode (e.g., chest tightness, wheezing, acute symptomatic response to inhaled beta-adrenergic agonists). Routine use of corticosteroids not recommended in adults. Boys with CF who have received alternate-day treatment with prednisone have shown persistent growth impairment after treatment is discontinued.
- Proper nutrition and vitamin supplementation (including fat-soluble vitamins A, D, E, and K).
- The mucolytic recombinant human deoxyribonuclease (DNase [dornase alfa]) 2.5 mg qd or bid given by aerosol for patients ≥6 yr of age with viscid sputum. It lowers the viscosity of sputum. It is useful to improve mucociliary clearance by liquefying difficult-to-clear pulmonary secretions. It is, however, very expensive. It is most beneficial in patients with forced vital capacity values >40% of predicted. Its cost can be decreased by using alternate-day rhDNase therapy.
- Newer treatment modalities act by improving production, intracellular processing, and/or function of the defective CFTR protein. Ivacaftor (a CFTR potentiator) is FDA approved for oral treatment of CF in patients 2 yr and older with the G551D mutation (5% of patients with CF). It can decrease the frequency of pulmonary exacerbations and improve lung function. Cost is a significant limiting factor. A new combination drug, tezacaftor-ivacaftor, has been reported to work as well or better than ivacaftor for most of the same mutations as were approved for ivacaftor. Tezacaftor-ivacaftor is approved only for patients aged 12 yr and above. Another combination treatment, lumacaftor-ivacaftor, has been FDA-approved for patients aged 12 yr and above who are homozygous for the F508del mutation in the *CFTR* gene. Most recommendations call for

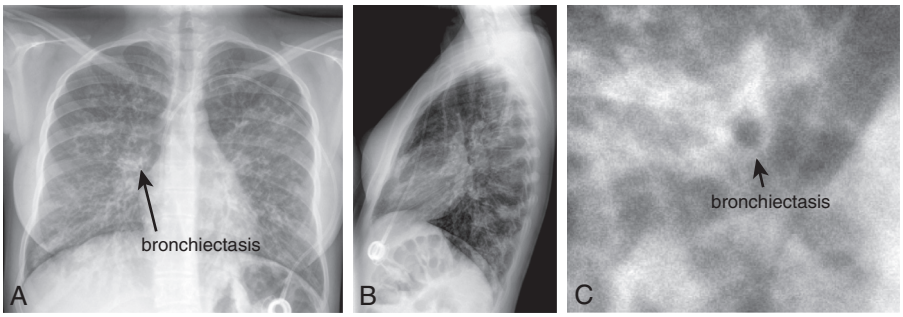

FIG. E2 Cystic fibrosis. Cystic fibrosis is aptly named. Chest x-ray findings include increased interstitial density of fibrosis and cystic changes of lung parenchyma similar to chronic obstructive pulmonary disease. Bronchiectasis (dilation of bronchi, potentially eroding into bronchial arteries and presenting with hemoptysis) may be visible on chest x-ray as large and thickened bronchioles, particularly when viewed in short axis (when bronchioles are oriented perpendicular to the frontal plane). This 15-yr-old with cystic fibrosis presented with cough and dyspnea. Does she have pneumonia? Comparison with prior x-rays showed no changes. **A,** Posterior-anterior chest x-ray. **B,** Lateral chest x-ray. **C,** Close-up of **A** showing bronchiectasis. (From Broder JS: *Diagnostic imaging for the emergency physician*, Philadelphia, 2011, Saunders.)

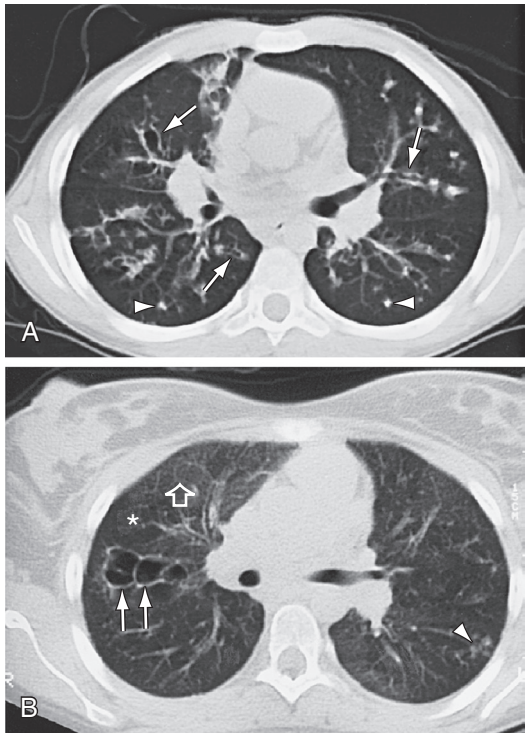

FIG. E3 CT scans of the chest in cystic fibrosis. A, A 12-yr-old boy with moderate lung disease. Airway and parenchymal changes are present throughout both lungs. Multiple areas of bronchiectasis *(arrows)* and mucous plugging *(arrowheads)* can be seen. **B,** A 19-yr-old girl has mostly normal lung with one area of saccular bronchiectasis in the right upper lobe *(arrows)* and a focal area of peripheral mucous plugging in the right lower lobe *(arrowhead).* Lung density is heterogenous, with areas of normal lung *(open arrow)* and areas of low attenuation reflecting segmental and subsegmental air trapping *(asterisk).* (From Kliegman, RM: Nelson *textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.)

the use of tezacaftor-ivacaftor for residual function mutations and F508del homozygotes mutations >12 yr of age. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the *CFTR* gene. Recent phase 3 trials involving the next-generation cystic fibrosis transmembrane conductance regulator (CFTR) corrector VX-659 in triple combination with tezacaftor and ivacaftor resulted in significant improvements for patients with Phe508del-MF or Phe508del-Phe508del genotypes. Based on these results, VX-659 triple combination regimens have the potential to treat the underlying cause of disease in ~90% of patients with CF.

- Limitations of use: Efficacy and safety have not been established in patients with CF other than those homozygous for the F508del mutation.
- Treatment of impaired glucose tolerance and diabetes mellitus.

CHRONIC Rx

- Pneumococcal and influenza vaccination.
- Chronic treatment with oral antibiotics to control infection is not recommended with two exceptions (see below).
- Azithromycin is recommended for many patients due to its benefits from antiinflammatory and/or antibacterial properties. Should be started on patients ≥6 yr of age with persistent *P. aeruginosa* in airway cultures for inhibition of neutrophil migration and elastase production.
- Chronic treatment with nebulized antibiotics (aztreonam or tobramycin) can be used daily for *P. aeruginosa* colonization.

DISPOSITION

- Bronchiectasis develops early in the course of cystic fibrosis, being detectable in infants as young as 10 wk of age, and is persistent and progressive. Recent data[1] reveal that neutrophil elastase activity in BAL fluid in early life is associated with early bronchiectasis in children with cystic fibrosis.
- More than 50% of children with CF live beyond age 20 yr. During the past 2 decades, survival among patients with late-stage CF has lengthened substantially. Survival has improved at the rate of 1.8% annually during the past decade. This is believed due to increased use of NBH DNase.
- Lung transplantation is the only definitive treatment; 3-yr survival after transplantation exceeds 50%.
- Obstructive azoospermia is present in >98% of postpubertal males.
- The SERPINA Z allele is a risk factor for liver disease in CF. Patients who carry the Z allele are at a greater risk of developing severe liver disease with portal hypertension.

REFERRAL

- Lung transplantation is advised in selected patients. Indications for lung transplantation include FEV_1 <30% of predicted, rapidly progressive respiratory deterioration, increasing number of hospital admissions, massive hemoptysis, recurrent pneumothorax, arterial partial pressure of oxygen <55 mm Hg, arterial partial pressure of carbon dioxide >50 mm Hg, multidrug-resistant organisms (although most centers will deny transplant to patients with *Burkholderia* colonization), and wasting. Young female patients should be referred earlier because of overall poorer prognosis. Selected patients must undergo double lung transplant.
- For screening of family members with DNA analysis.

[1]Sly PD et al: Risk factors for bronchiectasis in children with cystic fibrosis, *N Engl J Med* 368:1963-1970, 2013.

PEARLS & CONSIDERATIONS

COMMENTS

- Clinicians should think of CF in any patient with bronchiectasis plus any of the following: Male infertility, recurrent idiopathic pancreatitis, recurrent nasal polyposis.
- Genetic testing for CF should be offered to adults with a positive family history of CF, couples currently planning a pregnancy, and couples seeking prenatal care.
- Inhalation of hypertonic saline (5 ml of 7% sodium chloride qid) has been reported to produce a sustained acceleration of mucus clearance and improved lung function.
- The prevalence of MRSA in the respiratory tract of individuals with CF has increased dramatically over the past decade and is associated with worse survival.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Cystic Fibrosis (Patient Information)
Bronchiectasis (Related Key Topic)

AUTHORS: **Harinder P. Singh, MD,** and **Samaan Rafeq, MD**

SUGGESTED READINGS

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Wainwright CE et al: Effect of bronchoalveolar lavage-directed therapy on Pseudomonas aeruginosa infection and structural lung injury in children with cystic fibrosis, *JAMA* 306(2):163-171, 2011.

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BASIC INFORMATION

DEFINITION

Cysticercosis is an infection caused by the tissue deposition of larval forms of the pork tapeworm *Taenia solium. T. solium* cysts, or cysticerci, may accumulate in any human tissue, including the eyes, spinal cord, skin, muscle, heart, and brain. Central nervous system (CNS) involvement is common and is known as neurocysticercosis. Humans most commonly acquire cysticercosis via fecal-oral transmission from human tapeworm carriers or via ingestion of larval cysts in infected pork or tapeworm eggs in contaminated water or soil. Larvae in the gastrointestinal tract migrate hematogenously to tissues, where they encyst, forming cysticerci.

SYNONYMS

Cysticerciasis
Taeniasis
Pork tapeworm

ICD-10CM CODES	
B69	Cysticercosis
B69.0	Cysticercosis of central nervous system
B69.1	Cysticercosis of eye
B69.81	Myositis in cysticercosis
B69.89	Cysticercosis of other sites
B69.9	Cysticercosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- *T. solium* infection is worldwide in distribution. Tapeworm infection and cysticercosis are endemic in developing countries where pigs are raised as a food source, including developing countries of Central America, South America, and parts of Africa and Asia.
- Serologic studies from endemic areas of Latin America and Africa have demonstrated seroprevalence rates of 4% to 24% in native populations.
- Neurocysticercosis is most common in the United States in areas with large immigrant populations from countries where the disease is endemic.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- After ingestion of *T. solium* eggs or cysts, humans may remain asymptomatic for years.
- Cysticerci in muscles and skin may form subcutaneous nodules without erythema, warmth, or tenderness, mimicking lipomas or subcutaneous cysts.
- Neurocysticercosis, the presence of cysts within the brain parenchyma, is usually asymptomatic. Symptoms develop due to the inflammatory response to degeneration of cysts, which can result in focal encephalitis, vasculitis, chronic meningitis, and cranial nerve palsies.
- Seizures are the most common manifestation of neurocysticercosis, occurring in 70% to 90% of symptomatic cases. Headache and focal neurologic deficits can also occur.
- Up to 40% of patients with epilepsy in endemic areas have neurocysticercosis.
- In 10% to 20% of cases of neurocysticercosis, cysts lodge within the ventricular system and result in obstructive hydrocephalus, causing acute intracranial hypertension. Symptoms are caused by the presence of the parasite itself, ependymal inflammation, and/or fibrosis, each of which blocks the circulation of cerebrospinal fluid (CSF). Death may occur from progressive hydrocephalus, cerebral edema, or intractable seizures.
- Ocular cysticercosis occurs in less than 5% of infections and is generally asymptomatic. Inflammation in response to degenerating cysticerci may result in chorioretinitis, vasculitis, or retinal detachment, threatening vision.
- Cysticercosis cellulosae cutis presents with multiple firm, nontender subcutaneous nodules mimicking lipomas or epidermoid cysts.

ETIOLOGY

- *T. solium* has a complex two-host life cycle.
- Humans are the only definitive host and harbor the adult worm in the intestine (taeniasis). However, both humans and pigs can serve as intermediate hosts and harbor the larvae or cysticerci.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Epilepsy of unknown etiology
- Migraine
- CNS vasculitis
- Primary neoplasia of CNS
- Chronic CNS infections, including toxoplasmosis, coccidioidomycosis, tuberculosis, and cryptococcosis
- Brain abscess
- CNS involvement with sarcoidosis or systemic lupus erythematosus

WORKUP

Comprehensive clinical history: Obtain information on current and previous travel and residence, including geographic area, sanitary conditions, and consumption of undercooked pork.

LABORATORY TESTS

- Serum antibody detection by enzyme-linked immunoelectrotransfer blot (EITB) assay has a sensitivity of 98% and a specificity of 100% in patients with more than one cyst but has less predictive value in patients with a single cyst, in which up to 38% can be falsely negative. The same assay can be performed in CSF, with lower sensitivity. Antibodies detected by EITB can persist for years after successful therapy, limiting the usefulness of this assay in following patients after treatment. In endemic regions, a negative test result is useful in ruling out disease but a positive result is a marker of exposure, not necessarily symptomatic infection.
- Circulating *T. solium* antigens (B158/B60 monoclonal antibody-based sandwich ELISA, Ag-ELISA) can be detected in serum and CSF, providing a marker of viable organisms, even when CNS lesions are calcified and presumed to be inactive. This method may be particularly useful in monitoring patients after therapy. Antigen levels usually fall within 3 mo of successful treatment.
- Polymerase chain reaction (PCR) detection of *T. solium* DNA has been developed, with a reported sensitivity of 96.7%, but it is not widely available.
- Definitive diagnosis is based on the histopathologic demonstration of cysticerci in the tissue involved. Fine-needle aspiration cytology may be useful in diagnosing infection.
- Peripheral eosinophilia is usually absent.
- Stool examination for ova and proglottids of *T. solium* is insensitive and not specific for the diagnosis of cysticercosis.
- CSF examination in neurocysticercosis is usually unremarkable, but may demonstrate pleocytosis, with lymphocytic or eosinophilic predominance, low glucose, and elevated protein.

IMAGING STUDIES

- Plain radiographs of the extremities may reveal calcified cysts in patients with soft tissue or muscle involvement.
- High-resolution ultrasound may be useful in detecting subcutaneous cysts containing scoleces.
- For diagnosis of neurocysticercosis, CT and MRI are most commonly used.
- Brain CT (Fig. E1) has a sensitivity and specificity of 95% and can identify living cysticerci, which appear as hypodense lesions, as well as degenerating cysts, which appear as isodense or hyperdense lesions with surrounding edema. CT is the best method for detecting calcification associated with prior infection, which suggests inactivity.
- Brain MRI is the most accurate technique to assess the extent of infection, location, and evolutionary stage of the parasites. MRI provides detailed images of living and degenerating cysts, perilesional edema, as well as small cysts or those located in the ventricles, brainstem, and cerebellum. However, MRI has a low sensitivity for detecting calcified lesions, which are the most common neuroimaging finding in endemic populations.

TREATMENT

ACUTE GENERAL Rx

Asymptomatic cysticercosis:

- There is no evidence that administering antiparasitic therapy is beneficial.

Symptomatic neurocysticercosis:

- The goals of treatment are to control seizures and mass effect from cysticercal lesions, control intracranial hypertension, and reduce the size of active cysts.
- Treatment decisions in neurocysticercosis should be individualized. Initial measures should focus on the symptomatic management, considering antiparasitic therapy when appropriate.

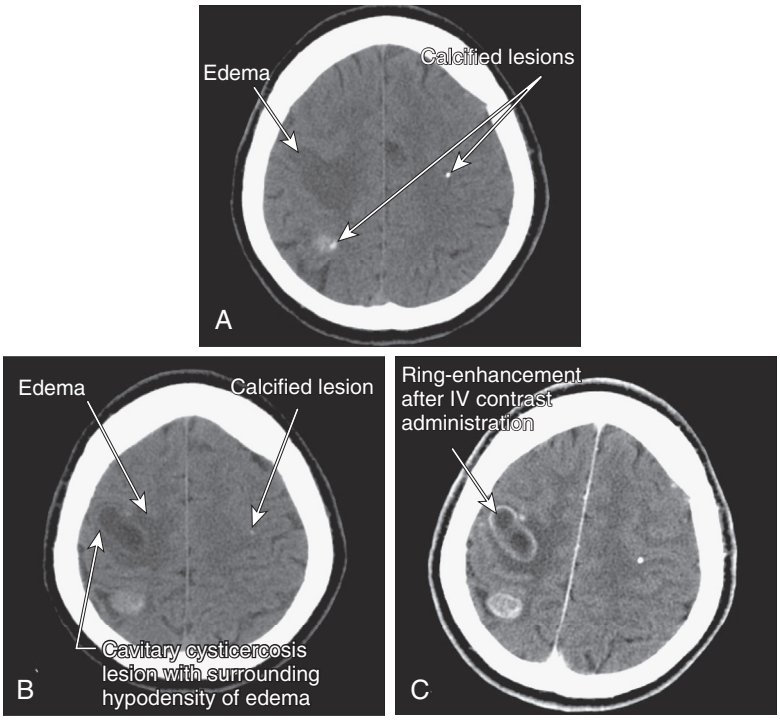

FIG. E1 Neurocysticercosis. This 40-yr-old Bolivian man presented with left-hand weakness. **A, B,** Noncontrast head computed tomography (CT) scan, brain windows. **C,** CT scan with contrast moments later; compare this with **(B)**. A slice through the same level of the brain before contrast administration. Hypodense lesions are present, with surrounding hypodensity *(dark gray)* representing edema. Scattered calcifications also are seen, a common feature of old neurocysticercosis lesions. Administration of intravenous contrast leads to ring enhancement, a feature of many infectious and inflammatory conditions, including neurocysticercosis, brain abscess, and toxoplasmosis. (From Broder JS: *Diagnostic imaging for the emergency physician*, Philadelphia, 2011, Saunders.)

- Patients with active lesions, with evidence of surrounding edema and/or inflammation, generally warrant treatment with antiparasitics, corticosteroids, and anticonvulsants.
  1 Patients who have seizures or are considered at risk for recurrent seizures based on imaging should be treated with anticonvulsants.
  2 Corticosteroids may decrease inflammation and edema and should be given whenever antiparasitic therapy is given.
  3 Antiparasitic therapy is indicated in the treatment of symptomatic patients with multiple viable brain parenchymal cysticerci. Despite treatment, only 30% to 50% of lesions resolve within 6 mo.
  4 Calcified cysticerci are generally inactive and do not warrant antiparasitic treatment.
  5 Antiparasitic therapy is often unnecessary in patients with single cysts, which are usually self-limited and resolve spontaneously within 6 mo.

Antiparasitic therapy:

- Patients with one or two viable parenchymal or subarachnoid cysts should be treated with albendazole 15 mg/kg/day PO divided twice daily for 10 to 14 days.
- Patients with three or more viable cysticerci should receive combination therapy with praziquantel (50 mg/kg per day) and albendazole (15 mg/kg per day) for 14 days.
- Praziquantel, while active against *Taenia solium,* is no longer preferred treatment for cysticercosis.
- Patients should receive prednisolone (2 mg/kg/day) or dexamethasone (0.15 mg/kg/day) orally before initiation of antiparasitic therapy.
- Antiparasitics should be used cautiously in patients with massive cysticercal infection of the brain parenchyma (≥50 cysts) or cysticercal encephalitis. These patients should be managed initially with corticosteroids, and perhaps mannitol, to control intracranial hypertension. Once the inflammation and edema have resolved by MRI, antiparasitics can be administered.

Surgical therapy:

- Surgery may be indicated in patients with obstructive hydrocephalus or giant cysts with associated intracranial hypertension.
- Minimally invasive neurosurgery (neuroendoscopy) for cyst removal and ventricular shunt formation has greatly improved the management of intraventricular neurocysticercosis.
- Extraparenchymal neurocysticercosis, including ocular, subarachnoid, and intraventricular disease, carries a poor prognosis and requires a more aggressive approach. When feasible, complete surgical excision of lesions remains the definitive therapy.

CHRONIC Rx

- Prolonged antiparasitic therapy does not improve outcomes in neurocysticercosis and may delay calcification of lesions. Antiepileptic medications should be continued for 2 yr or 6 to 12 mo after CT/MRI resolution of viable cysts, before tapering. In some cases, antiepileptic therapy needs to be continued indefinitely.
- Rare patients with neurocysticercosis develop chronic or recurrent perilesional inflammation, requiring long-term, high-dose steroid therapy. Methotrexate has been reported to be of use as a steroid-sparing agent in this setting.

DISPOSITION

- In seizure-free, stable neurocysticercosis, outpatient management is appropriate.
- Patients with seizures should be restricted from driving.

REFERRAL

- Infectious diseases consultation
- Neurology consultation in patients with seizures
- Neurosurgical consultation if extraparenchymal neurocysticercosis or obstructive hydrocephalus is present

PREVENTION

- Eradication of taeniasis/cysticercosis is possible with implementation of meat inspection, improvement of pig husbandry, and improvement of socioeconomic conditions in endemic areas.
- A porcine vaccine against *T. solium* has been developed and successfully implemented in Peru, Mexico, and Australia.
- There is currently no human vaccine to prevent tapeworm infection or cysticercosis.

PATIENT & FAMILY EDUCATION

- Pork should be inspected for the presence of cysticerci, which are visible in raw meat.
- Pork must be well cooked.
- Proper disposal of human excreta and handwashing are of utmost importance to break the transmission cycle in households.

RELATED CONTENT

Cysticercosis (Patient Information)

AUTHOR: **Staci A. Fischer, MD**

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Cytomegalovirus Infection

BASIC INFORMATION

DEFINITION

Infection with cytomegalovirus (CMV), a herpes virus, is common in the general population, with multiple mechanisms for transmission, often during childhood and adolescence. CMV is associated with pregnancy and can be a congenital disease. CMV is also associated with immunocompromised states and may be life-threatening.

SYNONYMS

CMV
Heterophil-negative mononucleosis
Cytomegalic inclusion disease virus

ICD-10CM CODES

B25.9	Cytomegaloviral disease, unspecified
P35.1	Congenital cytomegalovirus infection
Z20.820	Contact with and (suspected) exposure to varicella

EPIDEMIOLOGY & DEMOGRAPHICS

- Seroprevalence is widespread: 60% to 90% antibody positivity in adults.
- Increased infection develops perinatally, in day care exposure, and then during reproductive age, related to sexual activity.

ROUTES OF TRANSMISSION

- Blood transfusions
- Sexually transmitted diseases (STDs) via uterus, cervix, and semen
- Perinatally via breast milk
- Transplant of organs—bone marrow, kidneys, liver, heart, or lung
- Saliva

PHYSICAL FINDINGS & CLINICAL PRESENTATION

CHILDREN: Congenital—25% of infected children with symptoms if congenital:
- Petechial rash
- Jaundice and/or hepatosplenomegaly
- Lethargy
- Respiratory distress
- CNS involvement, seizures

Postnatal acquisition:
- CMV mononucleosis
- Pharyngitis, croup, bronchitis, pneumonia

HEALTHY ADULTS: Common:
- May be asymptomatic
- CMV mononucleosis similar to EBV mononucleosis
- Fever—lasting 9 to 30 days—mean of 19 days

Less common:
- Exudative pharyngitis
- Lymphadenopathy, hepatitis, splenomegaly
- Interstitial pneumonia (rare)
- Nonspecific rash
- Thrombocytopenia/hemolytic anemia

Rare:
- Guillain-Barré syndrome
- Meningoencephalitis
- Myocarditis

IMMUNOSUPPRESSED PATIENTS:
- Febrile mononucleosis
- GI ulcerations, hepatitis, pneumonitis, retinitis, encephalopathy, meningoencephalopathy
- HIV associated—dementia, demyelination, retinitis, acalculous cholecystitis, adrenalitis, diarrhea, enterocolitis, esophagitis
- Diabetes associated with pancreatitis
- Adrenalitis associated with HIV

ETIOLOGY

- Human herpesvirus (HHV)-5
- CMV infection can remain latent and reactivate with immunosuppression

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Congenital:
- Acute viral, bacterial, parasitic infections including other congenitally transmitted agents (toxoplasmosis, rubella, syphilis, pertussis, croup, bronchitis)

Acquired:
- EBV mononucleosis
- Viral hepatitis—A, B, C
- Cryptosporidiosis
- Toxoplasmosis
- *Mycobacterium avium* infections
- Human herpesvirus 6
- Acute HIV infection

WORKUP

- Laboratory confirmation combined with clinical findings often with leukopenia, thrombocytopenia, lymphocytosis. Diagnostic modalities include serologic assays, PCR, detection of CMV PP25 antigen in leukocytes, isolation of virus from body fluids and urine, and cytopathic demonstration of "owl eye" intracellular inclusions.
- Serology:
  1. Detection of CMV-IgM antibodies suggests recent infection. CMV-IgG antibodies usually appear 2 to 3 wk after infection.
  2. Molecular assays (PCR viral loads): On plasma.
  3. CMV antigenemia assays: Detects antibodies to the pp65 protein of the virus in peripheral blood leukocytes. These tests and the PCR tests are used in immunocompromised, AIDS, and transplant patients.
- Cultures: Using human fibroblast cultures of blood, CSF, urine, BAL, and biopsy specimens but can take 1 to 6 wk.
- Funduscopic—necrotic patches with white granular component of retina.
- Biopsy—"owl eye" inclusion bodies on tissue sample.
- HIV.

IMAGING STUDIES

- Chest radiograph—if pneumonitis suspected, consider bronchoscopy
- Endoscopy—if GI involvement
- CT scan/MRI—if CNS involvement

TREATMENT

NONPHARMACOLOGIC THERAPY

- Strict hand washing and standard precautions limit CMV transmission in health care facilities.
- Antiretroviral therapy (ART) in patients with CD4 count $<50/mm^3$ for the goal of CD4 $>100/mm^3$ for a 3- to 6-mo period.

ACUTE GENERAL Rx

Antiviral therapy with intravenous ganciclovir or oral valganciclovir is appropriate in immunocompromised patients. It can also be used in immunocompetent patients with severe disease.

For compromised hosts with CMV retinitis or pneumonitis:
- Ganciclovir 5 mg/kg q12h IV × 14 to 21 days, then valganciclovir: 900 mg PO q24h or alternative regimen
- Ganciclovir intraocular implant plus valganciclovir 900 mg PO q24h or alternative regimen
- Foscarnet 90 mg/kg q12h × 14 to 21 days, then 90 mg to 120 mg/kg IV q24h or alternative regimen
- Cidofovir 5 mg/kg IV q day × 14 days, then 5 mg/kg IV q 2 wk
- Fomivirsen-salvage therapy for CMV retinitis 300 μg injected into vitreous

DISPOSITION

- CMV infection in patients who are immunocompromised (especially those with AIDS, bone marrow and solid organ transplant recipients, and disorders of cell-mediated immune function) will need expert, long-term follow-up by an infectious disease specialist or immunologist familiar with the care of such patients.
- CMV mononucleosis, hepatitis, pharyngitis, etc. in immunologically normal hosts are usually self-limiting infections requiring no special follow-up plans.

REFERRAL

- To an ophthalmologist if CMV retinitis is present
- To an infectious disease specialist or AIDS specialist for patients who are HIV-positive with CMV disease
- To a cellular immunologist or transplant specialist in the case of CMV infection in a transplant recipient
- To a pediatric infectious disease specialist for congenital CMV infection

PEARLS & CONSIDERATIONS

CMV is ubiquitous in the environment and is asymptomatically shed by latently infected persons with CMV infection, making it difficult to protect patients who are immunocompromised from acquiring this infection.

AUTHOR: **Glenn G. Fort, MD, MPH**

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BASIC INFORMATION

DEFINITION

Venous thromboembolism is any thromboembolic event occurring within the venous system. Deep vein thrombosis (DVT) is the development of thrombi in the deep veins of the extremities or pelvis.

SYNONYMS

DVT
Venous thromboembolism (VTE) (VTE includes DVT and pulmonary embolism [PE])
Deep venous thrombosis
VTE

ICD-10CM CODES

I82.401	Acute embolism and thrombosis of unspecified deep veins of right lower extremity
I82.402	Acute embolism and thrombosis of unspecified deep veins of left lower extremity
I82.403	Acute embolism and thrombosis of unspecified deep veins of lower extremity, bilateral
I82.621	Acute embolism and thrombosis of deep veins of right upper extremity
I82.622	Acute embolism and thrombosis of deep veins of left upper extremity
I82.623	Acute embolism and thrombosis of deep veins of upper extremity, bilateral

EPIDEMIOLOGY & DEMOGRAPHICS

- Annual incidence of VTE is 0.1% to 0.27%, affecting up to 5% of the population during their lifetimes.
- The risk of recurrent thromboembolism is higher among men than women.
- In the U.S., there are approximately 900,000 DVT events annually. About 5% to 15% of persons with untreated DVT die from pulmonary embolism.
- Venous thromboembolism occurs in nearly 2 cases per 1000 pregnancies and is a leading cause of maternal mortality and morbidity.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain and swelling of the affected extremity
- In lower extremity DVT: Leg pain on dorsiflexion of the foot (***Homan* sign**)
- Physical examination may be unremarkable in early DVT

ETIOLOGY

The etiology is often multifactorial (prolonged stasis, coagulation abnormalities, vessel wall trauma (Fig. 1). The following are risk factors for DVT:

- Prolonged immobilization (>3 days)
- Postoperative state
- Trauma to pelvis and lower extremities for lower extremity DVT; central line placement for upper extremity DVT
- Birth control pills, high-dose estrogen therapy; conjugated equine estrogen but not esterified estrogen is associated with increased risk of DVT; estrogen plus progestin is associated with doubling the risk of venous thrombosis. The use of bevacizumab is also significantly associated with an increased risk of developing DVT in cancer patients receiving this drug
- Visceral cancer (lung, pancreas, alimentary tract, genitourinary tract)
- Occult cancer is detected in 1 in 20 patients within a year of receiving a diagnosis of unprovoked VTE
- Age >60 yr
- History of thromboembolic disease
- Hematologic disorders (e.g., factor V Leiden mutation [FVL], antithrombin III deficiency, protein C deficiency, protein S deficiency, heparin cofactor II deficiency, sticky platelet syndrome, G20210A prothrombin mutation, lupus anticoagulant, dysfibrinogenemias, anticardiolipin antibody, hyperhomocysteinemia, concurrent homocystinuria, high levels of factors VIII, XI, and single nucleotide polymorphisms [SNPs] such as CYP4V2). A classification of hypercoagulable states is described in Table 1
- Pregnancy and early puerperium
- Obesity (BMI >30)
- Congestive heart failure
- Surgery, fracture, or injury involving lower leg or pelvis
- Plaster cast immobilization
- Surgery requiring >30 min of anesthesia
- Gynecologic surgery (particularly gynecologic cancer surgery)
- Recent travel (within 2 wk, lasting ≥2 hr). Every 2 hr spent traveling increases VTE risk by 18%
- Smoking and abdominal obesity
- Central venous catheter or pacemaker insertion
- Superficial vein thrombosis (10% risk of DVT within 3 mo), varicose veins
- Collagen vascular disease
- Nephrotic syndrome
- Myeloproliferative disorders
- Testosterone therapy
- Long-term exposure to particulate air pollution is also associated with altered coagulation function and DVT risk
- Varicose veins

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Postphlebitic syndrome
- Superficial thrombophlebitis
- Ruptured Baker cyst
- Cellulitis, lymphangitis, Achilles tendinitis
- Hematoma
- Muscle or soft tissue injury, stress fracture
- Varicose veins, lymphedema
- Arterial insufficiency
- Abscess
- Claudication
- Venous stasis

WORKUP

- The clinical diagnosis of DVT is inaccurate. Pain, tenderness, swelling, or color changes are not specific for DVT.
- Clinical prediction rules can be used to establish pretest probability of DVT. The Wells prediction rules for DVT and for pulmonary embolism are described in Table 2. These rules perform better in younger patients without a history of DVT and in those without comorbidities. In younger patients without

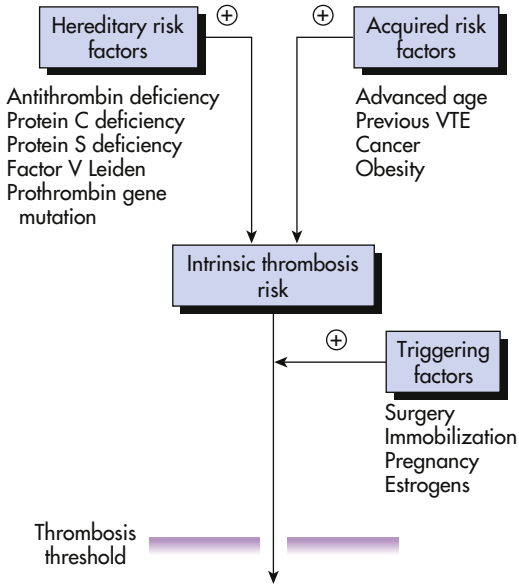

FIG. 1 Thrombosis threshold. Hereditary and acquired risk factors combine to create an intrinsic risk for thrombosis in each individual. This risk is increased by extrinsic triggering factors. If the intrinsic and extrinsic forces exceed a critical threshold at which thrombin generation overwhelms protective mechanisms, thrombosis occurs. *VTE,* Venous thromboembolism. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

TABLE 1 Classification of Hypercoagulable States

Hereditary	Mixed	Acquired
Loss of Function		
Antithrombin deficiency	Hyperhomocysteinemia	Advanced age
Protein C deficiency		Previous venous thromboembolism
Protein S deficiency		Surgery
Gain of Function		Immobilization
Factor V Leiden		Obesity
Prothrombin gene mutation		Cancer
Elevated factor VIII, IX, or XI levels		Pregnancy, puerperium
		Drug-induced: L-asparaginase, hormonal therapy

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 2 Wells Scoring Scheme for Pre-Test Probability of Deep Vein Thrombosis*

Clinical Feature	Points
Risk Factors	
Active cancer	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery, within 4 wk	1
Signs	
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Asymmetric calf swelling (>3 cm difference, 10 cm below tibial tuberosity)	1
Asymmetric pitting edema	1
Collateral superficial veins (nonvaricose)	1
Alternative Diagnosis	
Alternative diagnosis as likely or more likely than deep venous thrombosis	–2

*Interpretation of score: High probability if 3 points or more, moderate probability if 1 or 2 points, and low probability if 0 points or less.

From Wells PS, et al.: Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet* 350:1795–1798, 1997. In McGee S: *Evidence-based physical diagnosis*, ed 4, Philadelphia, 2018, Elsevier.

associated comorbidities and a low pretest probability using Wells criteria and a negative high-sensitivity D-dimer test, the diagnosis of DVT can be reasonably excluded.

- Compression ultrasonography (CUS; Fig. E2) is preferred as the initial study to diagnose DVT in patients with intermediate to high pretest probability. An initial negative test limited to the proximal leg should be repeated after 5 days (if the clinical suspicion of DVT persists) to exclude DVT that is propagating proximally from the calf. Comprehensive ultrasonography (whole-leg CUS) is a more extensive test that examines the deep veins from the inguinal ligament to the level of the malleolus. Literature reports indicate that it may be safe to withhold anticoagulation after negative results on comprehensive duplex ultrasonography in nonpregnant patients with a suspected first episode of symptomatic DVT of the leg.

LABORATORY TESTS

- Laboratory tests are not specific for DVT.
- Baseline prothrombin time (INR), partial thromboplastin time, and platelet count should be obtained on all patients.
- D-dimer testing is sensitive but not specific for DVT. A negative result (D-dimer <0.5 mcg/ml) can exclude the diagnosis in a patient with low probability of DVT, but a positive result (≥0.5 mcg/ml) mandates additional testing with venous ultrasonography.
- Laboratory evaluation of young patients with DVT, patients with recurrent thrombosis without obvious causes, and those with a family history of thrombosis should include protein S (both total and free PS), protein C, fibrinogen, antithrombin III level, lupus anticoagulant, anticardiolipin antibodies, anti-b2 glycoprotein1, factor V Leiden, factor VIII, factor IX, and fasting plasma homocysteine levels. It is important to remember that the lupus anticoagulant assay and antithrombin, protein C, protein S, and dysfibrinogenemia testing cannot be properly interpreted if a patient is already on warfarin, whereas anticardiolipin antibody test, prothrombin G20210A factor VII:C, factor V Leiden, and PT polymorphism can be performed when a patient is on warfarin.

IMAGING STUDIES

- Compression ultrasonography (CUS) is generally preferred as the initial study because it is noninvasive and can be repeated serially (useful to monitor suspected acute DVT); it offers good sensitivity for detecting proximal vein thrombosis (in the popliteal or femoral vein). Its disadvantages are poor visualization of deep iliac and pelvic veins and poor sensitivity in isolated or nonocclusive calf vein thrombi. Whole-leg compression ultrasound can generally exclude proximal and distal DVT in a single evaluation. Withholding anticoagulation following a single negative whole-leg CUS is associated with a relatively low risk of venous thromboembolism (3.5% of inpatients will develop DVT) during a 3-mo follow-up.
- Contrast venography is the gold standard for evaluation of DVT of the lower extremity. It is, however, invasive and painful and rarely used in clinical practice. Additional disadvantages are the increased risk of phlebitis, new thrombosis, renal failure, and hypersensitivity reaction to contrast media; it also gives poor visualization of the deep femoral vein in the thigh and the internal iliac vein and its tributaries.
- Magnetic resonance direct thrombus imaging (MRDTI) is an accurate noninvasive test for diagnosis of DVT. It is particularly useful in suspected DVT patients with leg casts, which prevent CUS, and in pregnant patients with positive D-dimer and negative CUS. Current limitations are its cost and lack of widespread availability.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Gradual resumption of normal activity. Immobility promotes stasis and propagation of DVT. Patients should get up and walk as tolerated. The theoretical risk that ambulation may dislodge thrombi in the legs, precipitating PE, is unfounded.
- Patient education on anticoagulant therapy and associated risks.

ACUTE GENERAL Rx

- Direct oral anticoagulants (DOACs) apixaban or rivaroxaban are prepared as monotherapy for initial treatment of DVT. These new anticoagulants (Table 3) are noninferior to warfarin, do not require periodic lab monitoring, and have a relatively low bleeding risk. They are preferred agents for extended treatment of venous thromboembolism if cost is not a significant issue.

TABLE 3 Comparison of Dabigatran, Rivaroxaban, Apixaban, and Edoxaban

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin (IIa)	Factor Xa	Factor Xa	Factor Xa
Active drug	No	Yes	Yes	Yes
Onset time (hr)	0.5-2	2-4	3-4	1-3
Half-life (hr)	12-17	5-13	~12	9-11
Renal excretion (%)	80	33	27	50

Hoffman R, et al.: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2017, Elsevier.

BOX 1 Contraindications to Outpatient Treatment of Venous Thromboembolism[a]

- Active or high risk of bleeding
- Recent surgery (within 7 days)
- Cardiopulmonary instability
- Severe symptomatic venous obstruction
- High risk of pulmonary embolism
- Thrombocytopenia (platelets <50,000/μL)
- Other medical or surgical condition requiring inpatient management
- Medical noncompliance
- Geographic or telephone inaccessibility
- Poor hepatic function (international normalized ratio ≥1.5)
- Unstable renal function (e.g., rising serum creatinine)
- Poor home health care support environment

[a]Not an all-inclusive list.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

- When apixaban or rivaroxaban are not available or contraindicated, initial treatment of DVT requires therapeutic doses of heparin (low-molecular-weight heparin [LMWH] or unfractionated). LMWH is preferred due to ease of administration, less hemorrhage, and significantly fewer deaths. Unfractionated heparin is preferred in patients with renal insufficiency because LMWH is predominantly excreted in the urine.
- LMWH is generally administered for 5 to 7 days. Recommended dose of enoxaparin is 1 mg/kg q12h SC. Once-daily fondaparinux, a synthetic analogue of heparin, is also as effective and safe as twice-daily enoxaparin in the initial treatment of patients with symptomatic DVT. Once systemic anticoagulation is initiated, vitamin K antagonist warfarin is initiated. Warfarin is titrated to maintain an INR between 2 and 3. After ≥5 days, heparin is stopped and warfarin is continued as monotherapy. Long-term LMWH may be preferable to warfarin in patients with cancer or those whose INR is difficult to control.
- Outpatient treatment of DVT is appropriate for patients without thrombophilic conditions or substantial comorbidity. Exclusions from outpatient treatment of DVT (Box 1)include patients with potential high complication risk (e.g., active or high risk of bleeding, hemoglobin <7, platelet count <50,000, guaiac-positive stool, recent cerebrovascular accident or noncutaneous surgery, noncompliance).
- Compression stockings are effective in reducing the incidence of postthrombotic syndrome and should be used starting within 1 mo of proximal DVT and continued for at least 1 yr after diagnosis.
- Insertion of an inferior vena cava filter to prevent pulmonary embolism is recommended in patients with contraindications to anticoagulation (e.g., hemorrhagic stroke, active internal bleeding, pregnancy), HIT in a patient with an active VTE/PE, recurrent PE despite adequate anticoagulant therapy, emergent surgery in patient with DVT, presence of free-floating iliofemoral thrombus, lower IVC thrombosis (incipient embolization), and chronic pulmonary (thromboembolic) hypertension with limited pulmonary reserve. Table 4 summarizes indications for IVC filter placement.
- Thrombolytic therapy (streptokinase) can be used in rare cases (unless contraindicated) in patients with extensive iliofemoral venous thrombosis and a low risk of bleeding. There are concerns about hemorrhagic complications related to the large doses of thrombolytics required in systemic thrombolysis for DVT (2% to 10% risk of major hemorrhagic complications).
- Other treatment modalities for DVT include surgical thrombectomy and catheter-directed thrombolysis (CDT). Thromboreduction by surgical thrombectomy is effective but invasive and expensive. CDT is also invasive, carries a bleeding risk, and will generally require ICU admission.

CHRONIC Rx

- The optimal duration of anticoagulant therapy varies with the cause of DVT and the patient's risk factors. The risk of recurrence is low if VTE is provoked by surgery, intermediate if provoked by a nonsurgical risk factor, and high if unprovoked. These risks should determine whether patients with VTE should undergo short-term vs. indefinite treatment.
- Therapy for 3 mo is generally satisfactory in patients with reversible risk factors (low-risk group). A high D-dimer level measured after 3 mo of anticoagulation in patients with unprovoked DVT should favor a longer duration of therapy. The American College of Chest Physicians Guidelines suggests that patients with first unprovoked VTE receive indefinite anticoagulation unless their bleeding risk is high.
- The risk of recurrence in patients with a first unprovoked VTE who have negative D-dimer results is not low enough to justify stopping anticoagulant therapy in men but may be low enough in some cases to justify stopping therapy in women who were taking estrogen at the time of initial VTE.[1]
- Anticoagulation for 6 mo is recommended for patients with idiopathic venous thrombosis or medical risk factors for DVT (intermediate-risk group). About 20% of patients with unprovoked venous thromboembolism have a recurrence within 2 yr after the withdrawal of oral anticoagulant therapy. Use of daily low-dose aspirin after discontinuation of anticoagulant treatment may provide a modest reduction in DVT risk.
- Indefinite anticoagulation is necessary in patients with DVT associated with active cancer; long-term anticoagulation is also indicated in patients with inherited thrombophilia (e.g., deficiency of antithrombin III, protein C or S antibody), high factor VIII levels, antiphospholipid antibody, and those with recurrent episodes of idiopathic DVT (high-risk group). Long-term anticoagulation should also be considered in the presence of comorbidities such as paroxysmal nocturnal hemoglobinuria (PNH), SLE (especially with nephrotic syndrome), some myeloproliferative disorders, IBD, and Cushing syndrome.
- Measurement of D-dimer after withdrawal of oral anticoagulation may be useful to estimate the risk of recurrence in selected patients. In patients with a first unprovoked DVT, positive D-dimer test results after cessation of anticoagulation predict recurrence, regardless of test timing or patient's age. Patients with a first spontaneous DVT and a D-dimer level <250 mg/ml after withdrawal of oral anticoagulation have a low risk of DVT recurrence. Risk is lower in women than in men. In patients who have completed at least 3 mo of anticoagulation for a first episode of unprovoked DVT and after approximately 2 yr of follow-up, a negative D-dimer result is associated with a 3.5% annual risk of recurrent disease, whereas a positive D-dimer result is associated with an 8.9% annual

[1]Kearon C, et al.: D-Dimer testing to select patients with a first unprovoked venous thromboembolism who can stop anticoagulant therapy: a cohort study. *Ann Intern Med* 162:27–34, 2015.

risk for recurrence. Hence, elevated D-dimer levels would be an indication for prolonged therapy (for 1 or 2 more yr at a minimum).
- The presence of residual thrombosis on ultrasonography when anticoagulant therapy is discontinued is also associated with an increased risk for subsequent recurrent DVT; a recent trial showed that tailoring the duration of anticoagulation on the basis of the persistence of residual thrombi on ultrasonography may reduce the rate of recurrent DVT. Additional trials are needed before this approach can be adapted for all patients.
- Patients with DVT and pulmonary embolism are at high risk of recurrence whenever anticoagulation is discontinued; therefore, many experts recommend prolonged anticoagulation in this population group, especially if other risk factors for recurrence are present.

PEARLS & CONSIDERATIONS

COMMENTS

- The prevalence of occult cancer is low among patients with a first unprovoked venous embolism. Routine screening with CT of the abdomen and pelvis does not provide a clinically significant benefit.[2]
- When using heparin, there is a risk of heparin-induced thrombocytopenia (HIT) (with unfractionated more so than with LMWH). Platelet count should be obtained initially and repeated every 3 days while on heparin.
- Therapeutic options for cancer-associated venous thromboembolism are summarized in Box 2.
- ***ISOLATED DEEP VEIN THROMBOSIS OF THE CALF:*** The American College of Chest Physicians Guidelines suggest (1) anticoagulation in patients with severe symptoms or risk factors for proximal extension, and (2) repeat sonogram in 2 wk in lower risk patients and anticoagulation only in those patients whose DVTs extend proximally.
- ***PROPHYLAXIS OF DVT:*** Recommended in all patients at risk (e.g., low-molecular-weight heparin [enoxaparin 30 mg SC bid or fondaparinux 2.5 mg SC daily] after major trauma, postsurgery of hip and knee; enoxaparin 40 mg SC qd post–abdominal surgery in patients with moderate to high DVT risk; gradient elastic stockings alone or in combination with intermittent pneumatic compression [IPC] boots following neurosurgery). Graduated compression stockings (GCSs) are effective for preventing air-travel-related DVT and in reducing the risk of DVT in patients hospitalized for conditions other than stroke. The type of GCSs is also important because proximal DVT occurs more often in patients with stroke who wear below-knee stockings than in those who wear high-length stockings. The new oral anticoagulants (rivaroxaban, apixaban, etc.) are effective for thromboprophylaxis after THR and TKR. However, their clinical benefits over LMWH are marginal. Betrixaban is the first FDA-approved once-daily oral direct factor Xa inhibitor for prophylaxis of VTE in adults hospitalized for an acute medical illness with risk factors for VTE and moderately or severely restricted mobility. Apixaban appears to be as effective as LMWH for thromboprophylaxis in cancer patients but poses similar risk of bleeding and should be used with caution in patients with GI malignancies, thrombocytopenia, or renal impairment. Common regimens for venous thromboembolism prevention are summarized in Table 5. Box 3 describes traditional absolute and relative contraindications to pharmacologic

[2]Carrier M, et al.: Screening for occult cancer in unprovoked venous thromboembolism, *N Engl J Med* 373:697–704, 2015.

TABLE 4 Indications for Inferior Vena Cava Filter Placement

	Indications for IVC Filter Placement	Examples
1.	DVT and contraindication to anticoagulation (A)	Hemorrhage while on anticoagulation
2.	DVT and failure of anticoagulation (A)	Recurrent DVT or PE despite anticoagulation, inability to achieve or maintain adequate anticoagulation
3.	DVT and low cardiopulmonary reserve or high mortality risk from possible PE (R)	Severe pulmonary hypertension, right heart failure, known large right-to-left shunt
4.	Populations with very high risk for PE (R)	Some postbariatric, orthopedic, or neurosurgical patients or multitrauma patients. Patients with expected prolonged immobilization
5.	High risk for life-threatening PE (R)	Large, unstable (free-floating) IVC clot
6.	DVT and high fall risk (R)	
7.	Prophylaxis during catheter-directed thrombolysis of DVT (R)	

There are two absolute indications for IVC filter placement: First, if the patient is at risk for PE (i.e., DVT) but for whatever reason he/she is not a candidate for systemic anticoagulation (i.e., hemorrhage); and second, if the patient developed a PE, new DVT, or an extension of DVT while on proper anticoagulation. There are a number of relative indications for filter placement. They are presented in rows 3 through 7. In every case the decision to place a filter compels careful consideration of the risks and benefits and may require multidisciplinary input.

(A), Absolute; *DVT,* deep vein thrombosis; *IVC*, inferior vena cava; *PE*, pulmonary embolism; *(R),* relative.

From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.

BOX 2 Therapeutic Options for Cancer-Associated Venous Thromboembolism (VTE)

Acute VTE Treatment Options
- Unfractionated heparin: 80 units/kg intravenous bolus followed by 18 units/kg/hr infusion adjusted to aPTT ratio
- Dalteparin, 200 units/kg subcutaneously every 24 hr
- Enoxaparin, 1 mg/kg subcutaneously every 12 hr
- Tinzaparin, 175 units/kg subcutaneously every 24 hr
- Fondaparinux, 5-10 mg subcutaneously every 24 hr (5 mg for weight <50 kg, 7.5 mg for weight 50-100 kg, and 10 mg for weight >100 kg)
- Initial rivaroxaban dose 15 mg twice daily; switch to 20 mg once daily after 3 wk
- Dabigatran 150 mg bid after 5 days of parenteral agent
- Apixaban 10 mg bid × 7 days followed by 5 mg bid[a]
- Edoxaban 60 mg once daily after 5 days of parenteral agent
- Vena caval filter

Chronic VTE Treatment Options
- Dalteparin, 200 units/kg subcutaneously every 24 hr for 1 mo then 150 units/kg subcutaneously every 24 hr
- Enoxaparin, 1 mg/kg every 12 hr or 1.5 mg/kg subcutaneously every 24 hr
- Tinzaparin, 175 units/kg subcutaneously every 24 hr
- Vitamin K antagonists (e.g., warfarin) adjusted for an INR of 2-3
- Rivaroxaban 20 mg once daily; consider 10 mg once daily if appropriate
- Dabigatran 150 bid after 5 days of parenteral agent
- Apixaban 10 mg bid initial × 7 days followed by 5 mg bid[a]
- Edoxaban 60 mg once daily after 5 days of parenteral agent
- Vena cava filter

Rivaroxaban should be used with caution in patients with cancer, given the limited information on this medication in patients with cancer.

[a]No data currently available for use in the cancer population.

aPTT, Activated partial thromboplastin time; *bid,* twice daily; *INR,* international normalized ratio.

From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

and mechanical venous thromboembolism prophylaxis.

- ***RECURRENT THROMBOEMBOLISM:*** The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism is similar to that of noncarriers of factor V Leiden; therefore, heterozygous patients should receive secondary thromboprophylaxis for a similar length of time as patients without factor V Leiden. Management of recurrent venous thromboembolism in patients with cancer is summarized in Table 6.
- ***POSTTHROMBOTIC SYNDROME:*** Approximately 20% to 50% of patients with DVT develop postthrombotic syndrome characterized by leg edema, pain, venous ectasia, skin induration, and ulceration. Patients with extensive DVT and those with more severe postthrombotic manifestations 1 mo after DVT have poorer long-term outcomes. Recent trials have shown that compression stockings after DVT do not prevent postthrombotic syndrome.
- Exercise following DVT is reasonable because it improves flexibility of the affected leg and does not increase symptoms in patients with postthrombotic syndrome.
- ***UPPER EXTREMITY DVT:*** It is less common than lower extremity DVT and is seen more frequently in patients requiring central venous catheters or wires. It confers risk for mortality, recurrent thromboembolic events, and postthrombotic syndrome similar to that of lower extremity DVT. It is classified as primary upper extremity DVT ***(Paget-Schroetter syndrome)***, defined as a thrombus in the axillary and subclavian veins in absence of identifiable thrombosis risk factors. It accounts for 20% of upper extremity DVT cases and may be due to an underlying anatomic abnormality at the thoracic outlet in combination with local hypercoagulability due to venous stretching or perivascular fibrosis from recurrent venous compression. Secondary upper extremity DVT is defined as any DVT related to a predisposing factor (e.g., insertion of central venous catheter, wires, or other devices, malignancy). In patients with secondary upper extremity DVT removal of the catheter is not routinely recommended but is warranted if there is a catheter malfunction or infection, if anticoagulation therapy is contraindicated or has failed, or if the catheter is no longer needed. Anticoagulation therapy in upper extremity DVT consists of use of vitamin K antagonists, except in patients with cancer, for whom LMWH is preferred. Optimal duration of anticoagulation treatment in upper extremity DVT is 3 to 6 mo (including in those in whom a central catheter has been removed).
- ***DVT THERAPY IN PREGNANCY:*** Vitamin K antagonists such as warfarin are

TABLE 5 Common Regimens for Venous Thromboembolism Prevention

Condition	Prophylaxis
Hospitalization with medical illness	Unfractionated heparin 5000 units SC bid or tid *or* Enoxaparin 40 mg SC qd *or* Dalteparin 2500 units or 5000 units SC qd *or* Fondaparinux 2.5 mg SC qd with normal renal function (in patients with a heparin allergy such as heparin-induced thrombocytopenia) *or* Graduated compression stockings or intermittent pneumatic compression for patients with contraindications to anticoagulation Consider combination pharmacologic and mechanical prophylaxis for high-risk patients
General surgery	Unfractionated heparin 5000 units SC bid or tid *or* Enoxaparin 40 mg SC qd *or* Dalteparin 2500 or 5000 units SC qd
Major orthopedic surgery	Warfarin (target INR 2 to 3) *or* Enoxaparin 30 mg SC bid *or* Enoxaparin 40 mg SC qd *or* Dalteparin 2500 or 5000 units SC qd *or* Fondaparinux 2.5 mg SC qd *or* Rivaroxaban 10 mg qd *or* Aspirin 81 mg qd *or* Dabigatran 220 mg qd *or* Apixaban 2.5 mg twice daily *or* Intermittent pneumatic compression (with or without pharmacologic prophylaxis)

bid, Twice daily; *INR,* international normalized ratio; qd, every day; *SC*, subcutaneous; *tid,* three times a day.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

BOX 3 Traditional Absolute and Relative Contraindications to Pharmacologic and Mechanical Venous Thromboembolism Prophylaxis[a]

Contraindications to Pharmacologic Prophylaxis
- Active, recent, or high risk of clinically significant bleeding
- Thrombocytopenia (platelet count <50,000/μL)
- Systemic coagulopathy (e.g., disseminated intravascular coagulation, international normalized ratio >1.4, or activated partial thromboplastin time ratio >1.2, excluding lupus inhibitors)
- Known congenital bleeding disorders (e.g., hemophilia A or B and von Willebrand disease)
- Known functional acquired or congenital platelet disorder (e.g., Bernard-Soulier syndrome and uremic platelet dysfunction)
- Heparin-induced thrombocytopenia (for unfractionated or low-molecular-weight heparin)

Contraindications to Mechanical Prophylaxis
- Acute or recent deep venous thrombosis (within 3 mo)
- Arterial insufficiency in target limb
- Open lower extremity wound

[a]List not inclusive.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE 6 Management of Recurrent Venous Thromboembolism in Patients with Cancer

Causes	Management
Extrinsic vascular compression (causes sluggish flow)	Relieve vascular compression due to tumor, nodal masses, or anatomic abnormalities (i.e., May-Thurner syndrome/iliac vein compression, thoracic outlet syndrome) with surgical decompression, vascular stents, or other
Intrinsic vascular obstruction	Remove central venous catheter or devices responsible for sluggish flow
Trousseau syndrome	Switch to LMWH
Heparin-induced thrombocytopenia	Discontinue unfractionated or LMWH and start a direct thrombin inhibitor (preferred) or fondaparinux
Therapeutic resistance	If the patient is taking warfarin, switch to LMWH If the patient is taking LMWH, check to ensure the correct full weight-based dose is being used, switch to twice-daily dosing (if administration is once daily), consider checking LMWH (anti-Xa) level, initiate an empiric 25% dose increase, or switch to fondaparinux

LMWH, Low-molecular-weight heparin.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

contraindicated in pregnancy. Low-molecular-weight heparins are safe and effective. Typical agents used in pregnancy include dalteparin (200 IU per kilogram of body weight daily or 100 IU per kilogram twice daily) or enoxaparin (1.5 mg per kilogram daily or 1 mg per kilogram twice daily).

- ***REVERSAL OF ANTICOAGULATION:*** Vitamin K (1 mg PO or 2 mg IV) can be used to reverse elevated INR (3 to 6) from warfarin when elective or urgent procedures are needed. The administration of vitamin K can take more than 24 hr to fully restore vitamin K dependent coagulation factors II, VII, IX, and X. The American College of Chest Physicians recommends the following guidelines for managing elevated INRs or bleeding in patients receiving vitamin A antagonist therapy:
  1. INR between 4.5 and 10 and no significant bleeding: Omit dose and monitor the next day, routine use of vitamin K is not recommended.
  2. INR >10 and no significant bleeding: Hold vitamin K antagonist, give 5 to 10 mg orally of vitamin K. Monitor the next day and use additional vitamin K if necessary. Resume therapy at lower dose when INR therapeutic.
  3. Serious bleeding at any elevation of INR: Hold vitamin K antagonist and supplement with prothrombin complex concentrates (PCC). Give vitamin K (10 mg by slow IV infusion over 30 min to reduce the risk of anaphylaxis). Vitamin K1 can be repeated every 12 hr. PCC composition in the U.S. (3-factor PCC) includes clotting factors II, IX, and X but minimal amounts of factor VII (unlike PCC products available outside of the U.S. [4-factor PCC], which have a significant amount of factor VII). In order to replace the low factor VII, some clinicians in the U.S. will also give fresh frozen plasma (FFP) in addition to vitamin K and PCC in patients with life-threatening warfarin-related bleeding.
- ***SPECIFIC REVERSAL AGENTS FOR NON–VITAMIN K ANTAGONIST ANTICOAGULANTS*** (**Table 7**):
  1. Idarucizumab, an antibody fragment given at a dose of 5 g IV, has been shown to completely reverse the anticoagulant effect of dabigatran within minutes.
  2. The anticoagulant activity of factor Xa inhibitors apixaban, rivaroxaban, and edoxaban can be rapidly reversed with IV administration of andexanet alfa.
  3. These reversal agents are very expensive (over $20,000 for each use).

TABLE 7 Reversal Agents for Direct Oral Anticoagulants

Feature	Idarucizumab	Andexanet Alfa	Ciraparantag
Structure	Humanized antibody fragment	Recombinant human factor Xa variant	Synthetic, small cationic molecule
Mass (Da)	47,776	39,000	573
Mechanism of action	Binds dabigatran with high affinity	Competes with factors Xa (and IIa) for binding	Binds via hydrogen bonding
Target	Dabigatran	Rivaroxaban, apixaban, edoxaban and heparins	Dabigatran, rivaroxaban, apixaban, edoxaban and heparins
Administration	Intravenous bolus	Intravenous bolus followed by a 2-hour infusion	Intravenous bolus
Measurement of reversal	Activated partial thromboplastin time, diluted thrombin time, or ecarin clotting time or chromogenic assay	Calibrated anti-factor Xa assays	Whole-blood clotting time
Elimination	Renal (catabolism)	Not reported	Not reported
Cost	$3500 per dose in the U.S.	Unknown; likely to be at least as much as idarucizumab	Likely to be low

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Deep Vein Thrombosis (DVT) (Patient Information)
Antiphospholipid Antibody Syndrome (Related Key Topic)
Hypercoagulable State (Related Key Topic)
Postthrombotic Syndrome (Related Key Topic)
Pulmonary Embolism (Related Key Topic)
Upper Extremity Deep Vein Thrombosis (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

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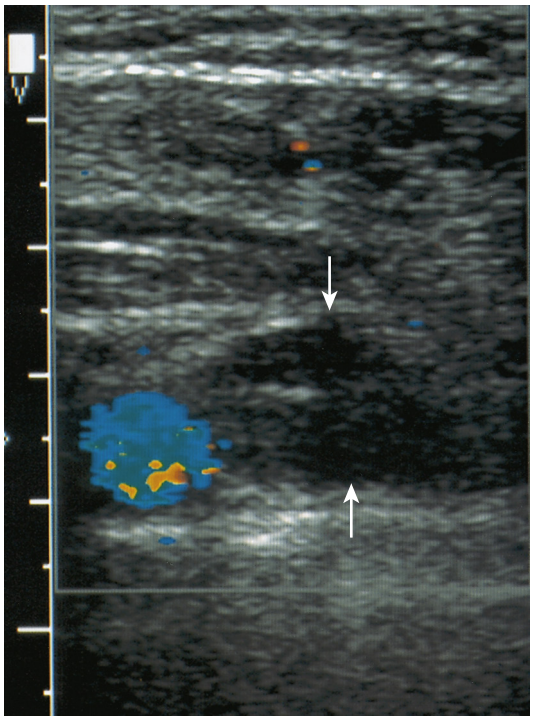

FIG. E2 Doppler ultrasound appearance of deep vein thrombosis. The superficial femoral vein is filled with echogenic material representing thrombus, and no flow can be identified in the vein on Doppler evaluation. Flow can be identified in the adjacent artery on color Doppler evaluation *(arrows).* (From Crawford MH, et al.: [eds]: *Cardiology,* ed 2, St Louis, 2004, Mosby.)

BASIC INFORMATION

DEFINITION

Delayed puberty is clinically defined as the absence of or incomplete development of secondary sexual characteristics by an age at which 95% of the population begins to mature sexually. For girls, a delay is defined as an absence of breast development by age 13 or primary amenorrhea by age 16. For boys, a delay is classified as an absence of testicular enlargement by age 14.

SYNONYM

Pubertal delay

ICD-10CM CODE
E30.0 Delayed puberty

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: The actual prevalence and incidence for children presenting with delayed puberty is unknown. Delayed puberty is more common in boys.

GENETICS: Constitutional pubertal delay (CPD) often runs in families. Although specific gene mutations have yet to be identified, studies have shown that 50% to 75% of patients with CPD have at least one parent who experienced a delay in puberty. The inheritance pattern for CPD is thought to be autosomal dominant.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Girls with pubertal delay have an absence of breast development by age 13, absence of menarche by age 16, or absence of menarche within 3 yr of thelarche. Boys with pubertal delay show no evidence of testicular enlargement, further defined as testes <2.5 cm, by age 14. Absence of pubic and/or axillary hair is common, as is lack of growth spurt.
- Patients with a constitutional delay in puberty are short in stature with a normal growth rate and otherwise good health.
- Boys often fall below the 10th percentile on a height chart with normal rate of growth between 4 and 6 cm per yr.

ETIOLOGY

Causes for pubertal delay (Fig. E1) can be separated into four categories (from most to least common):

1. Constitutional delay, which is a temporary delay in puberty that is seen mostly in boys and is genetic. Patients are typically short in stature with normal growth rate and appropriate skeletal age.
2. Functional hypogonadotropic hypogonadism secondary to malnutrition or chronic disease. Celiac sprue, inflammatory bowel disease (IBD), hypothyroidism, diabetes mellitus, cystic fibrosis, and eating disorders such as anorexia nervosa are examples of illnesses that may cause a temporary, reversible delay in puberty. Clinical suspicion is warranted when underweight children present with pubertal delay.
3. Hypergonadotropic hypogonadism caused by primary gonadal failure. Congenital disorders such as cryptorchidism; chromosomal disorders such as gonadal dysgenesis, Klinefelter syndrome, and Turner syndrome; and acquired causes secondary to chemotherapy, pelvic radiation, and gonadal surgery are organic dysfunctions that result in gonadal failure despite adequate hypothalamic-pituitary function. In this group of disorders, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are elevated yet cannot stimulate ovaries and testicles to produce estrogen and testosterone, respectively, leading to hypogonadism and absence of secondary sex characteristics.
4. Permanent hypogonadotropic hypogonadism secondary to genetic or acquired defects along the hypothalamic-pituitary-gonadal (HPG) axis. Kallmann syndrome is a genetic mutation in *KAL1* on the X chromosome and is responsible for the migration of gonadotropin-releasing hormone and olfactory neurons into the hypothalamus. Children with Kallmann syndrome typically present with pubertal delay and anosmia. Other mutations such as *FGFR1* and *DAX1* have been linked to congenital gonadotropin deficiencies and pubertal delay. Acquired defects such as hemochromatosis, sickle cell anemia, and pituitary tumors can cause delayed puberty and other hypothalamic syndromes, including Prader-Willi. Table E1 provides a classification of puberty and sexual infantilism.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Normal or low serum LH and FSH

- Constitutional pubertal delay
- Functional hypogonadotropic hypogonadism:
  1. Malnutrition or eating disorder
  2. Strenuous exercise
  3. Chronic illness (e.g., hypothyroidism, celiac disease, IBD, cystic fibrosis)
- Hypopituitarism:
  1. Panhypopituitarism
  2. Isolated gonadotropin deficiency
  3. Kallmann syndrome (associated with anosmia)
  4. Prader-Willi syndrome
- Hyperprolactinemia:
  1. Pituitary adenoma
  2. Drug-associated (e.g., cannabis, cocaine)

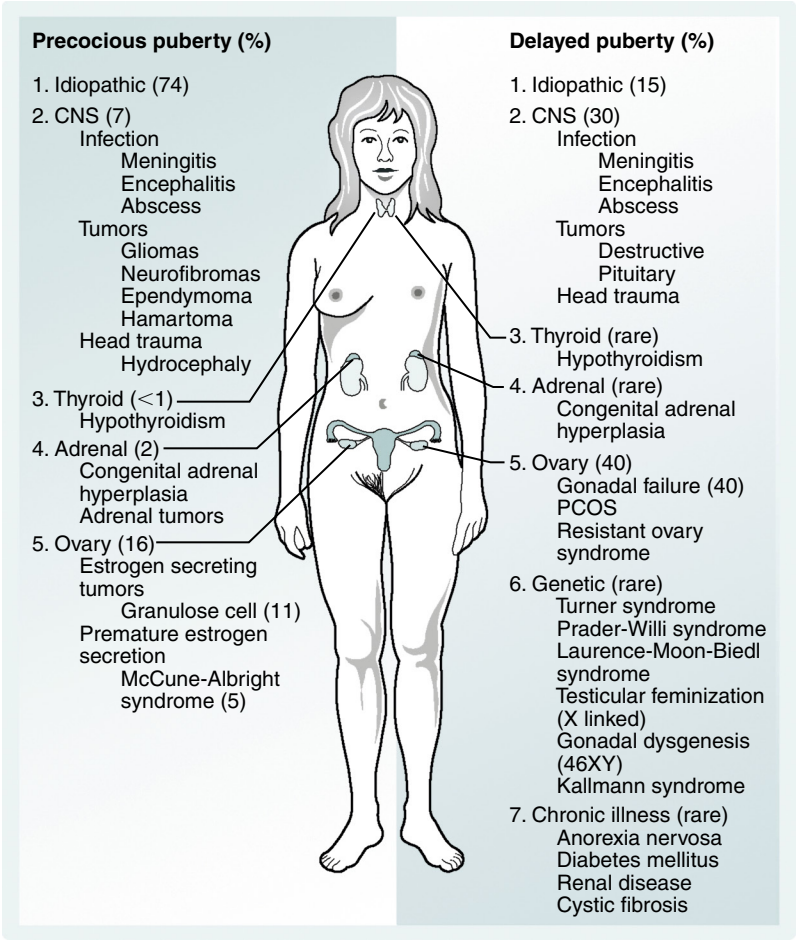

FIG. E1 Causes of precocious puberty and delayed puberty. CNS, Central nervous system; PCOS, polycystic ovarian syndrome. (From Pariseai M: Gynaecological endocrinology. In Pariseai M et al [eds]: *Obstetrics and gynaecology,* St Louis, 2008, Mosby.)

TABLE E1 Differential Diagnostic Features of Delayed Puberty and Sexual Infantilism

Condition	Stature	Plasma Gonadotropins	GnRH Test LH Response	Plasma Gonadal Steroids	Plasma DHEAS	Karyotype	Olfaction
Constitutional delay in growth and adolescence	Short for chron. age, usually appropriate for bone age	Prepubertal, later pubertal	Prepubertal, later pubertal	Low, later normal	Low for chron. age, appropriate for bone age	Normal	Normal
Hypogonadotropic Hypogonadism							
Isolated gonadotropin deficiency	Normal, absent pubertal growth spurt	Low	Prepubertal or no response	Low	Appropriate for chron. age	Normal	Normal
Kallmann syndrome	Normal, absent	Low	Prepubertal or no response	Low	Appropriate for chron. age	Normal	Anosmia; pubertal growth spurt or hyposmia
Idiopathic multiple pituitary hormone deficiencies	Short stature and poor growth since early childhood	Low	Prepubertal or no response	Low	Usually low	Normal	Normal
Hypothalamic-pituitary tumors	Late-onset decrease in growth velocity	Low	Prepubertal or no response	Low	Normal or low for chron. age	Normal	Normal
Primary Gonadal Failure							
Syndrome of gonadal dysgenesis (Turner syndrome) and variants	Short stature since childhood	High	Hyperresponse for age	Low	Normal for chron. age	45,X or variant	Normal
Klinefelter syndrome and variants	Normal to tall	High	Hyperresponse at puberty	Low or normal	Normal for chron. age	47,XXY or variant	Normal
Familial XX or XY gonadal dysgenesis	Normal for age	High	Hyperresponse	Low	Normal for chron. age	46,XX or 46,XY	Normal

chron., Chronologic; *DHEAS*, dehydroepiandrosterone sulfate; *GnRH*, gonadotropin-releasing hormone; *LH*, luteinizing hormone.
From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.

3. Increased serum gonadotropins
- Hypergonadotropic hypogonadism:
  1. Turner syndrome (gonadal dysgenesis)
  2. Klinefelter syndrome
  3. Gonadal dysgenesis
  4. Noonan syndrome
  5. Bilateral gonadal failure:
     a. Primary testicular failure
     b. Anorchia
     c. Premature ovarian failure
     d. Resistant ovary syndrome
     e. Radiation, chemotherapy
     f. Trauma
     g. Infections (e.g., mumps, orchitis)

Other conditions
- Androgen sensitivity syndrome
- Steroidogenic enzyme defects

WORKUP

- Given the extensive differential diagnosis for pubertal delay, a systematic and focused approach is necessary. Table E2 describes a classification of delayed puberty and sexual infantilism. A careful history, including family and social history, can identify eating, exercise habits, chronic illnesses, weight loss, poor weight gain, changes in bowel habits, and parental history of pubertal delay. Figs. E2 and E3 describe an algorithm for the evaluation of delayed puberty in males and females.
- Growth measurement should include height and weight, a growth chart to assess rate of growth, and calculation of the sex-adjusted midparental height that represents the statistically probable adult height for the child.
  1. For boys, add 2.5 inches (6.5 cm) from the mean of the parents' heights. For girls, subtract 2.5 inches (6.5 cm) from the mean of the parents' heights.
  2. Physical exam can reveal signs of sexual maturation, stigmata of congenital syndromes, and nutritional deficiencies. It is important to include a neurologic (visual fields, ophthalmologic), thyroid, respiratory, cardiovascular, and abdominal examination, in addition to evaluation of the Tanner stages of sexual characteristics.

LABORATORY TESTS

- Serum LH, FSH, testosterone, and estradiol can help distinguish disorders of congenital or acquired gonadal failure from other causes. By the age of 10 to 12 yr gonadal failure produces elevated levels of serum LH and FSH. If levels are low or normal, constitutional delay is the most common diagnosis.
- Chromosomal analysis is indicated if there is a suspicion of gonadal dysgenesis or Klinefelter syndrome.
- Screening studies include complete blood count, erythrocyte sedimentation rate, prolactin, thyroid-stimulating hormone, and free thyroxine level.
- Endocrinologist may incorporate further studies such as IGF-1 to screen for growth hormone disorders and GnRH stimulation testing.

IMAGING STUDIES

Bone age skeletal radiograph of the left hand and wrist determines skeletal age, which is delayed in constitutional delay and GnRH deficiency. MRI of the head should be considered if there is high clinical suspicion for tumors of pituitary or hypothalamic origin. Pelvic ultrasound can be helpful in detecting intraabdominal testes and evaluating müllerian anatomy.

Rx TREATMENT

- Treat underlying cause.
- Constitutional delay can be managed with reassurance that the delay will have no effect on the final adult height or overall

TABLE E2 Classification of Delayed Puberty and Sexual Infantilism

Idiopathic (Constitutional) Delay in Growth and Puberty (Delayed Activation of Hypothalamic LRF Pulse Generator)

Hypogonadotropic Hypogonadism: Sexual Infantilism Related to Gonadotropin Deficiency

CNS Disorders

Tumors

- Craniopharyngiomas
- Germinomas
- Other germ cell tumors
- Hypothalamic and optic gliomas
- Astrocytomas
- Pituitary tumors (including MEN-1, prolactinoma)

Other Causes

- Langerhans histiocytosis
- Postinfectious lesions of the CNS
- Vascular abnormalities of the CNS
- Radiation therapy
- Congenital malformations especially associated with craniofacial anomalies
- Head trauma
- Lymphocytic hypophysitis

Isolated Gonadotropin Deficiency

- Kallmann syndrome
- With hyposmia or anosmia
- Without anosmia
- LHRH receptor mutation
- Congenital adrenal hypoplasia (*DAX1* mutation)
- Isolated LH deficiency
- Isolated FSH deficiency
- Prohormone convertase 1 deficiency (PCI)

Idiopathic and Genetic Forms of Multiple Pituitary Hormone Deficiencies Including Prop1 Mutation

Miscellaneous Disorders

- Prader-Willi syndrome
- Laurence-Moon and Bardet-Biedl syndromes
- Functional gonadotropin deficiency
- Chronic systemic disease and malnutrition:
  1. Sickle cell disease
  2. Cystic fibrosis
  3. Acquired immunodeficiency syndrome (AIDS)
  4. Chronic gastroenteric disease
  5. Chronic renal disease
- Malnutrition
- Anorexia nervosa
- Bulimia
- Psychogenic amenorrhea
- Impaired puberty and delayed menarche in female athletes and ballet dancers (exercise amenorrhea)
- Hypothyroidism
- Diabetes mellitus
- Cushing disease
- Hyperprolactinemia
- Marijuana use
- Gaucher disease

Hypergonadotropic Hypogonadism

Males

- The syndrome of seminiferous tubular dysgenesis and its variants (Klinefelter syndrome)
- Other forms of primary testicular failure:
  1. Chemotherapy
  2. Radiation therapy
  3. Testicular steroid biosynthetic defects
  4. Sertoli-only syndrome
  5. LH receptor mutation
  6. Anorchia and cryptorchidism
- Trauma/surgery

Females

- The syndrome of gonadal dysgenesis (Turner syndrome) and its variants
- XX and XY gonadal dysgenesis
- Familial and sporadic XX gonadal dysgenesis and its variants
- Familial and sporadic XY gonadal dysgenesis and its variants
- Aromatase deficiency
- Other forms of primary ovarian failure
- Premature menopause
- Radiation therapy
- Chemotherapy
- Autoimmune oophoritis
- Galactosemia
- Glycoprotein syndrome type 1
- Resistant ovary
- FSH receptor mutation
- LH/hCG resistance
- Polycystic ovarian disease
- Trauma/surgery
- Noonan or pseudo-Turner syndrome
- Ovarian steroid biosynthetic defects

CNS, Central nervous system; *FSH,* follicle-stimulating hormone; *hCG,* human chorionic gonadotropin; *LHRH,* luteinizing hormone–releasing hormone; *LRF,* luteinizing hormone–releasing factor; *MEN,* multiple endocrine neoplasia.

From Styne DM, Grumbach MM: Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM [eds]: *Williams textbook of endocrinology,* ed 13, Philadelphia, 2016, Elsevier, Table 25.15, p. 1129; and Kliegman RM: *Nelson Textbook of Pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

development. Short-term hormonal therapy can be used to hasten puberty if the delay is causing severe psychosocial difficulties. Oxandrolone orally can be given daily or IM depot testosterone q6wk for 3 to 6 mo for boys to improve velocity of growth. Girls can receive oral estradiol once daily for 3 to 6 mo.

- Malnutrition and chronic disease can best be treated by correcting the underlying etiology. A short (3 to 6 mo) treatment course, as described above, may be indicated for children with psychosocial difficulties.
- Permanent causes of pubertal delay can be treated by inducing puberty with testosterone for boys and estrogen plus progesterone for girls.
- Patients with Turner syndrome will need adjunct growth hormone with or without oxandrolone.
- Gonadotropin deficiency or hypogonadism may require lifelong sex steroid replacement.
- Psychosocial evaluation, support, and treatment as needed.
- Table E3 summarizes the management and treatment of delayed puberty.

REFERRAL

Pediatric endocrinology

PEARLS & CONSIDERATIONS

COMMENTS

- Constitutional delay is the most common cause of pubertal delay and is often associated with a positive family history in parents and/or siblings, but it is a diagnosis of exclusion, so other causes, such as Turner syndrome and systemic disorders, need to be ruled out first.
- Bone age demonstrates more clearly than chronologic age how far an individual has progressed toward maturity and predicts the potential for further growth.
- No studies reliably differentiate constitutional delay from gonadotropin deficiency.

PATIENT & FAMILY EDUCATION

- The Magic Foundation, a support group for patients and their families (https://www.magicfoundation.org)
- The American Academy of Family Physicians (https://www.aafp.org)
- American Academy of Pediatrics (http://www.aap.org)
- Pediatric Endocrine Society (https://lwpes.org)
- Nemours Foundation (https://kidshealth.org/en/teens/puberty.html)

RELATED CONTENT

Delayed Puberty (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

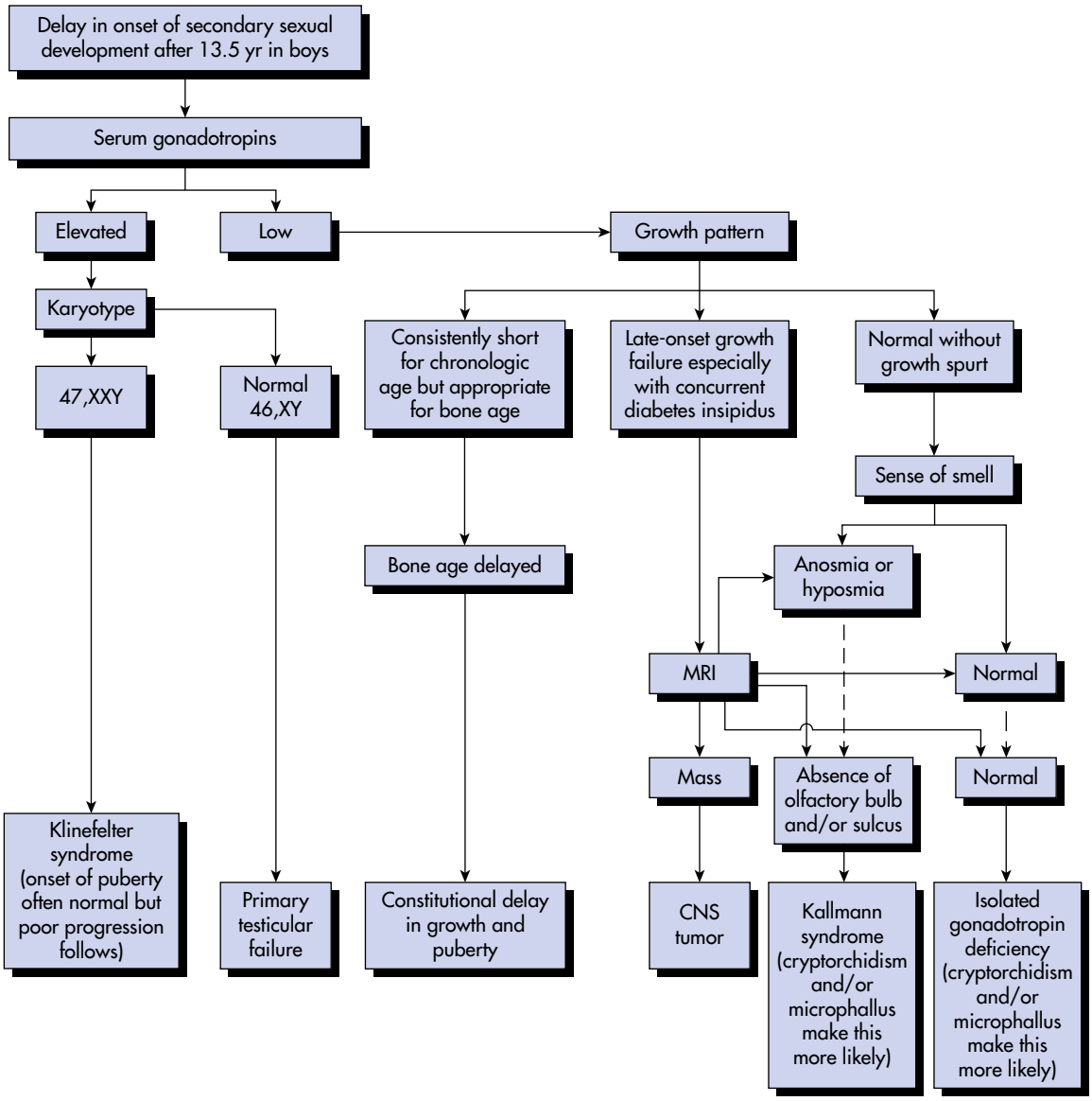

FIG. E2 Diagnostic algorithm for the evaluation of delayed puberty in males. *CNS*, Central nervous system; *MRI*, magnetic resonance imaging. (From Styne DM, Grumbach MM: Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM [eds]: *Williams textbook of endocrinology*, ed 13, Philadelphia, 2016, Elsevier, Fig. 25.48; and Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.)

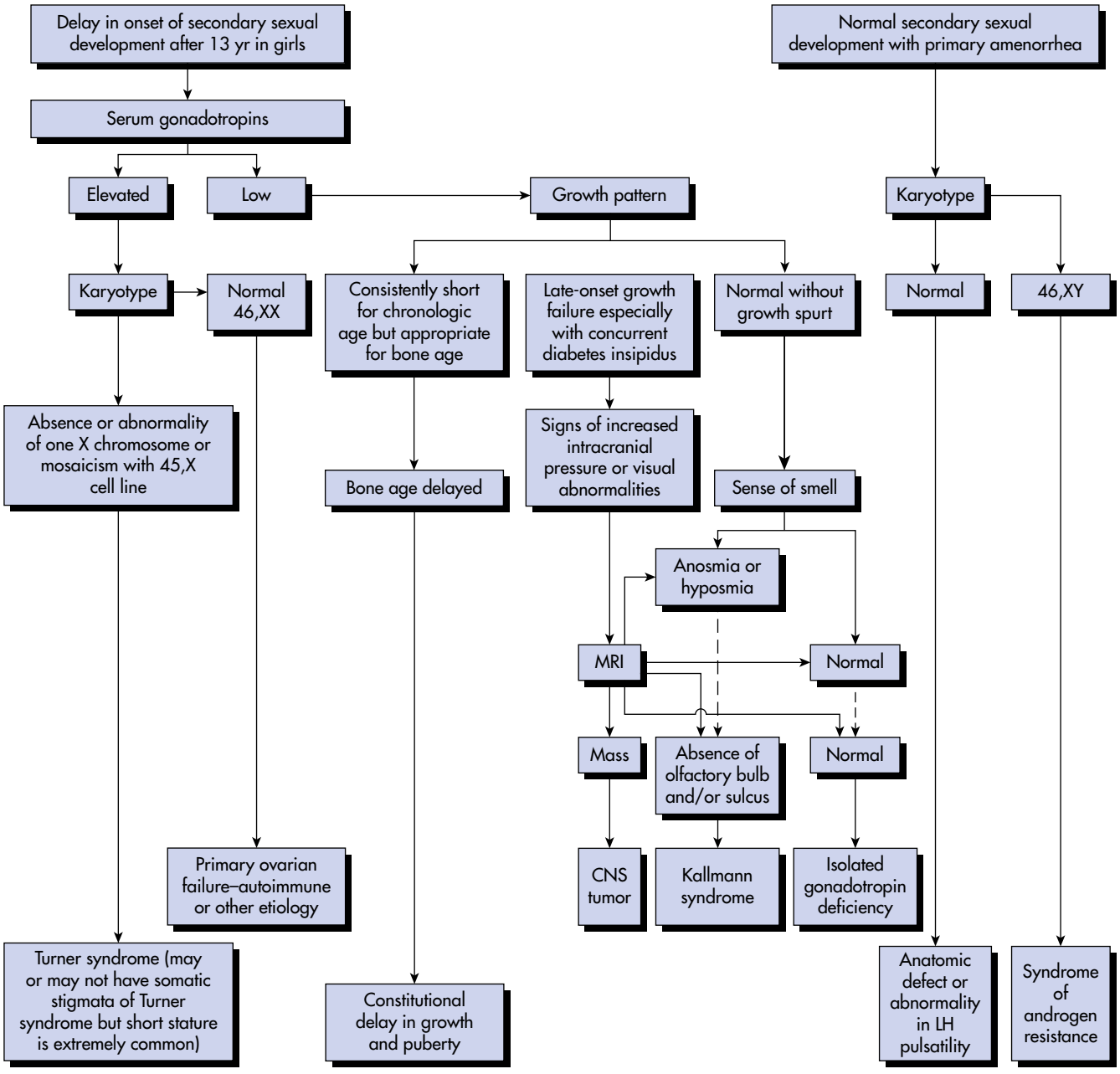

FIG. E3 Diagnostic algorithm for the evaluation of delayed puberty in females. *CNS*, Central nervous system; *LH,* luteinizing hormone; *MRI*, magnetic resonance imaging. (From Styne DM, Grumbach MM: Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM [eds]: *Williams textbook of endocrinology*, ed 13, Philadelphia, 2016, Elsevier, Fig. 25.49, p. 1157; and Kliegman, RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.)

TABLE E3 Management and Treatment of Delayed Puberty

Objective

- Determine site and etiology of abnormality
- Induce and maintain secondary sexual characteristics
- Induce pubertal growth spurt
- Prevent the potential short-term and long-term psychological, personality, and social handicaps of delayed puberty
- Ensure normal libido and potency
- Attain fertility

Therapy

Concerned but Not Anxious or Socially Handicapped Adolescent

- Reassurance and follow-up (tincture of time)
- Repeat evaluation (including serum testosterone or estradiol) in 6 mo

Psychosocial Handicaps, Anxiety, Highly Concerned

Therapy for 4 mo

- *Boys:* Testosterone enanthate 100 mg IM q4wk at 14-14.5 yr of age, or overnight transdermal testosterone patch
- *Girls:* Ethinyl estradiol 5-10 mg/day PO or conjugated estrogens 0.3 mg/day PO or overnight ethinyl estradiol patch at 13 yr of age
- No therapy for 4-6 mo; reevaluate status including serum testosterone or estradiol; if indicated, repeat treatment regimen

IM, Intramuscular; *PO,* by mouth.
From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.

SUGGESTED READINGS

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Lazar L, Phillip M: Pubertal disorders and bone maturation, *Endocrinol Metab Clin North Am* 41(4):805-825, 2012.

Mauras N: Strategies for maximizing growth in puberty in children with short stature, *Pediatr Clin North Am* 58(5):1167-1179, 2011.

Palmert MR, Dunkel L: Delayed puberty, *N Engl J Med* 166:443-453, 2012.

BASIC INFORMATION

DEFINITION

The American Psychiatric Association's *Diagnostic and Statistical Manual*, 5th edition, (DSM-5) defines delirium as:

- Disturbance of consciousness with reduced ability to focus, sustain, or shift attention.
- The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of a day.
- An additional disturbance in cognition (e.g., memory deficit, disorganization, language, visuospatial ability, or perception).
- A change in cognition or development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
- There is evidence from history, physical exam, or lab findings that the disturbance is caused by medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

SYNONYMS

Acute confusional state
Toxic or metabolic encephalopathy

THEORIES REGARDING PATHOPHYSIOLOGY

- Neuroinflammation, with increased permeability of the blood-brain barrier
- Acetylcholine deficiency
- Other neurotransmitter imbalances, including excesses of norepinephrine, serotonin, and, most important, dopamine

CLASSIFICATION

Hyperactive, hypoactive, and mixed subtype

ICD-10CM CODES

F05	Delirium, not induced by alcohol and other psychoactive substances
F05.9	Delirium, unspecified
F06.0	Organic hallucinosis
F05.8	Other delirium
F05.0	Delirium not superimposed on dementia
F05.1	Delirium superimposed on dementia

EPIDEMIOLOGY & DEMOGRAPHICS

Nearly 30% of older patients experience delirium at some time during the hospital course. In old surgical patients, the risk varies from 10% to 50%. Hypoactive is more common. Delirium is the most common mental disorder in patients with medical illness. Any age, race, or gender can be affected. Pediatric delirium is often missed but remains important because delirium is associated with longer hospital stays, decreased cognitive performance, and increased mortality. Risk factors include extremes of age, severe pain, illicit substance use, surgery, dementia, and kidney or liver failure (Table 1).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- One of the earliest symptoms is change in level of awareness and ability to focus, sustain, or shift attention. Symptoms may differ both among patients and within one patient. Family members or caregivers report that the patient "isn't acting quite right." Symptoms may include poor attention, sleepiness, agitation, or psychosis.
- Acuteness of presentation helps in differentiating delirium with dementia. Change in cognition, perceptual problems (such as visual, auditory, or somatosensory hallucination usually with lack of insight), memory loss, disorientation, difficulty with speech and language. It is important to ascertain from family member or caregivers the patient's level of functioning before onset of delirium.
- Elderly patients with delirium often do not look sick, but patients with delirium are sick by definition.
- Hyperactive delirium represents only 25% of cases, with the others having hypoactive (quiet) delirium.
- There is often a prodrome phase that later blends into hypoactive delirium or erupts into an agitated confusional state.
- Physical examination should be performed, focusing on signs of infection, dehydration, or chronic disease that may be exacerbated. Vital signs are key. Consider using the Mini-Mental Status Exam or the Montreal Cognitive Assessment.
- Fig. 1 describes an algorithm for evaluation of mental status changes in an older patient.
- Table 2 summarizes delirium assessment tools.

ETIOLOGY

Can be multifactorial; often falls into one of the following categories:

- Drugs: Benzodiazepines are the worst offenders, but other drugs such as narcotics, anticholinergics, beta-blockers, steroids, nonsteroidal antiinflammatory drugs, digoxin, cimetidine can cause delirium; also, withdrawal states such as alcohol withdrawal or benzodiazepine withdrawal can cause delirium
- Infection or inflammation
- Metabolic: Kidney or liver failure, thyroid, adrenal, or glucose dysregulation, anemia, vitamin deficiency such as Wernicke encephalopathy or vitamin B_{12} deficiency, inborn metabolic errors such as porphyrias or Wilson disease
- Stress: Surgery, sleep problems, pain, fever, hypoxia, anesthesia, environmental changes, fecal or urinary retention, burns
- Fluids, electrolytes, nutrition (FEN): Dysregulation of calcium, magnesium, potassium, or sodium; dehydration; volume overload; altered pH
- Brain disorder: CNS infection, head injury, hypertensive encephalopathy

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary psychiatric illness
- Focal syndromes
- Dementia
- Sundowning
- Nonconvulsive status epilepticus

Remember, delirium may coexist with any of the above. Table 3 summarizes the differential diagnosis of delirium. Table 4 describes clinical factors that help differentiate delirium and dementia from psychiatric disease.

LABORATORY TESTS

- Complete blood count, electrolytes, liver function tests, ammonia, drug levels (digoxin, lithium)
- Toxicology screen, urinalysis, urine culture
- Thyroid function tests, vitamin B_{12}, and folate levels
- Rapid plasma reagin for syphilis, blood, urine, and spinal fluid culture
- Arterial blood gas
- Lumbar puncture is mandatory when cause of delirium is not obvious

IMAGING STUDIES

- Consider head CT (to look for bleed, trauma, tumor, atrophy, dementia, stroke)
- Chest radiograph (to look for tumor, infection)

TABLE 1 Mnemonic for Risk Factors for Delirium and Agitation

I Watch Death	Delirium
Infection	**D**rugs
Withdrawal	**E**lectrolyte and physiologic abnormalities
Acute metabolic	**L**ack of drugs (withdrawal)
Trauma/pain	**I**nfection
Central nervous system pathology	**R**educed sensory input (blindness, deafness)
Hypoxia	**I**ntracranial problems (CVA, meningitis, seizure)
Deficiencies (vitamin B_{12}, thiamine)	**U**rinary retention and fecal impaction
Endocrinopathies (thyroid, adrenal)	**M**yocardial problems (MI, arrhythmia, CHF)
Acute vascular (hypertension, shock)	
Toxins/drugs	
Heavy metals	

CHF, Congestive heart failure; *CVA,* cerebrovascular accident; *MI,* myocardial infarction.
From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

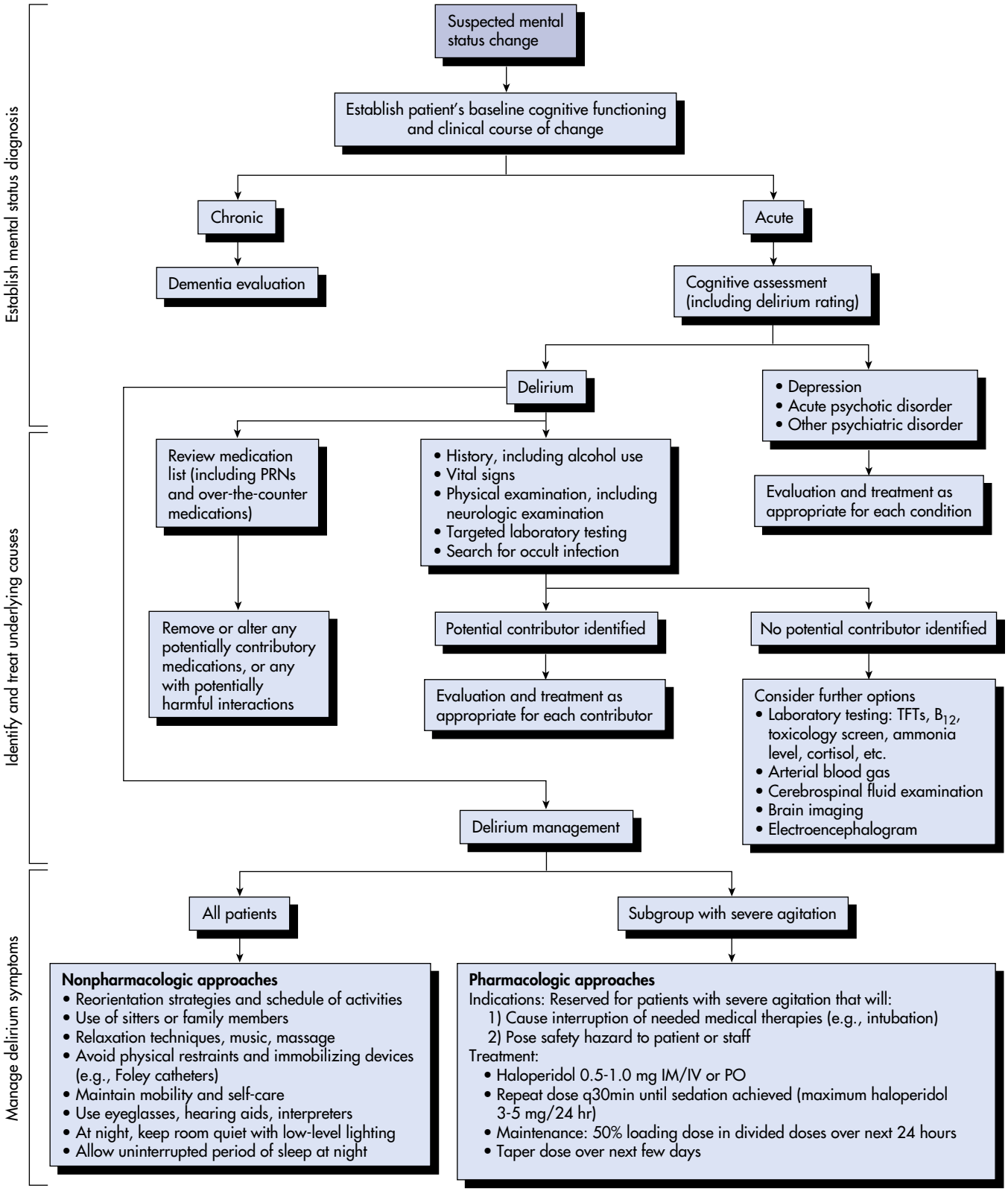

FIG. 1 Algorithm for evaluation of suspected mental status change in an older patient. *IM,* Intramuscular; *NG,* nasogastric; *PO,* by mouth; *PRN,* as needed; *TFTs,* thyroid function tests. (Modified from Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

TABLE 2 Delirium Assessment Tools

Tool	Structure	Notes
Confusion Assessment Method (CAM)	Full scale of 11 items Abbreviated algorithm targeting four cardinal symptoms	Intended for use by nonpsychiatric clinicians
Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)	Algorithm targeting four cardinal symptoms	Designed for use by nursing staff in the ICU
Intensive Care Delirium Screening Checklist (ICDSC)	8-item screening checklist	Bedside screening tool for use by nonpsychiatric physicians or nurses in the ICU
Delirium Rating Scale (DRS)	Full scale of 10 items Abbreviated 7- or 8-item subscales for repeated administration	Provides data for confirmation of diagnosis and measurement of severity
Delirium Rating Scale—Revised–98 (DRS-R-98)	16-item scale that can be divided into a 3-item diagnostic subscale and a 13-item severity subscale	Revision of DRS is better suited to repeat administration
Memorial Delirium Assessment Scale (MDAS)	10-item severity rating scale	Grades severity of delirium once diagnosis has been made
Neecham Confusion Scale	10-item rating scale	Designed for use by nursing staff and primarily validated for use in elderly populations in acute medical or nursing home setting

ICU, Intensive care unit.
Stern TA et al: *Massachusetts General Hospital handbook of general hospital psychiatry,* ed 7, Philadelphia, 2017, Elsevier.

ELECTROENCEPHALOGRAM

To exclude seizure, confirm diagnosis of metabolic encephalopathy

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- The most important consideration is to keep the patient safe by using a variety of methods, including frequent reorientation.
- A quiet, restful, simplified environment with cues to time and location such as clock or calendar is helpful, as well as consistent staff providing both personal and medical care. If possible, encourage familiar family members and friends to keep the patient company.
- Early mobilization and minimized use of physical restraints (use of physical restraints if necessary to ensure safety).
- Visual and hearing aids for patients with these impairments.

ACUTE GENERAL Rx

- Reverse any treatable cause, such as volume repletion for patients with dehydration, antibiotics for urinary tract infection.
- Antipsychotic agents should not be used routinely for preventing or treating delirium. Pharmacologic treatment with antipsychotic agents should be initiated only when symptoms are severe, dangerous, or cause significant distress to the patient. In general these agents are similarly effective and the choice among them is usually made on the basis of side effects. Haloperidol is the least sedating but has a high risk of extrapyramidal side effects; quetiapine has the fewest side effects but is highly sedating.
- Haloperidol can be used with caution to control agitation, with doses ranging from 0.25 to 2 mg IM/IV twice daily, repeating the dose every 20 to 30 min until patient has calmed and using lower doses for the elderly.
- Most antipsychotics can prolong the QT interval and increase the risk of torsades de

TABLE 3 Differential Diagnosis of Delirium

General Cause	Specific Cause
Vascular	Hypertensive encephalopathy Cerebral arteriosclerosis Intracranial hemorrhage or thrombosis Emboli from atrial fibrillation, patent foramen ovale, or endocarditic valve Circulatory collapse (shock) Systemic lupus erythematosus Polyarteritis nodosa Thrombotic thrombocytopenic purpura Hyperviscosity syndrome Sarcoid Posterior reversible encephalopathy syndrome (PRES) Cerebral aneurysm
Infectious	Encephalitis Bacterial or viral meningitis, fungal meningitis (*cryptococcal*, *coccidioidal*, *histoplasma*) Sepsis General paresis Brain, epidural, or subdural abscess Malaria Human immunodeficiency virus Lyme disease Typhoid fever Parasitic (*toxoplasma*, *trichinosis*, *cysticercosis*, *echinococcosis*) Behçet syndrome Mumps
Neoplastic	Space-occupying lesions, such as gliomas, meningiomas, abscesses Paraneoplastic syndromes Carcinomatous meningitis
Degenerative	Dementias Huntington disease Creutzfeldt–Jakob disease Wilson disease
Intoxication	Chronic intoxication or withdrawal effect of drugs, including sedative-hypnotics, opiates, tranquilizers, anticholinergics, dissociative anesthetics, anticonvulsants
Neurophysiologic	Epilepsy Postictal states Complex partial status epilepticus
Traumatic	Intracranial bleeds Postoperative trauma Heat stroke Fat emboli syndrome

Continued

TABLE 3 Differential Diagnosis of Delirium—cont'd

General Cause	Specific Cause
Intraventricular	Normal-pressure hydrocephalus
Vitamin deficiency	Thiamine (Wernicke–Korsakoff syndrome) Niacin (pellagra) B_{12} (pernicious anemia)
Endocrine/metabolic	Diabetic coma and shock Uremia Myxedema Hyperthyroidism Parathyroid dysfunction Hypoglycemia Hepatic or renal failure Porphyria Severe electrolyte or acid/base disturbances Cushing or Addison syndrome Sleep apnea Carcinoid Whipple disease
Autoimmune	Autoimmune encephalitides Steroid-responsive encephalopathy associated with thyroiditis (SREAT)/ Hashimoto encephalopathy Systemic lupus erythematosus Multiple sclerosis
Poisoning	Heavy metals (lead, manganese, mercury) Carbon monoxide Anticholinergics Other toxins
Anoxia	Hypoxia and anoxia secondary to pulmonary or cardiac failure, anesthesia, anemia
Psychiatric	Depressive pseudodementia, catatonia, Bell mania

Stern TA et al: *Massachusetts General Hospital handbook of general hospital psychiatry, ed 7, Philadelphia*, 2017, Elsevier.

pointes. The effect is greatest with IV haloperidol and least with aripiprazole. Aripiprazole is available in tablets, solution, and injection. Starting dose is 1 mg twice a day.

- Risperidone 0.5 mg twice daily (off-label use, non-FDA approved) can also be used with caution with a slow increase to desired dose, not to exceed 1.0 to 2.0 mg.
- Avoid benzodiazepines and meperidine. Drug toxicity accounts for approximately 30% cases of delirium.

CHRONIC Rx

Delirium is not a chronic condition; if assessing a more long-term mental status change, consider other diagnoses.

DISPOSITION

Requires frequent monitoring often necessitating hospital level of care to ensure safety and assess etiology.

REFERRAL

Consider neurologic or psychiatric consultation if not improved in several days or in complicated cases.

PEARLS & CONSIDERATIONS

COMMENTS

Although benzodiazepines are frequently used in hospitalized patients for sedation and are the mainstay of therapy for alcohol withdrawal, they must be used with caution in the elderly because they can have a paradoxical effect on agitation.

PREVENTION (TABLE 5)

- Avoid polypharmacy as much as possible.
- Optimize chronic medical conditions.
- Provide frequent reorientation and a soothing environment for high-risk patients (e.g., lights on during the day, off at night; open curtains during the day so patient can see the weather).
- In patients over 70 without dementia, regular exercise has been associated with lower risk for developing delirium, and early return to physical activity can improve outcomes in ill patients.

PATIENT & FAMILY EDUCATION

Inform about the above preventive techniques, especially polypharmacy risks.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Delirium Tremens (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

TABLE 4 Clinical Factors That Help Differentiate Delirium and Dementia from Psychiatric Disease

Characteristic	Delirium	Dementia	Psychiatric Illness
Symptoms			
Age at onset	<12 or >40 yr	Usually elderly, >50 yr	13-40 yr
Onset	Acute	Gradual or insidious	Gradual
Symptom course	Rapid, fluctuating	Stable and progressive	Stable
Duration	Days to weeks	Months to years	Months to years
Reversibility	Usually	Rarely	Rarely
History			
Past medical history	Substance abuse, medical illness	Comorbid conditions of aging	Previous psychiatric history
Family history	Unusual	History of dementia	History of psychiatric illness
Physical Examination			
Vital signs	Usually abnormal	Usually normal	Usually normal
Involuntary activity	May have tremors, asterixis, etc.	None unless coexistent disease	None
Mental Status			
Affect	Emotional lability	Flat affect with advanced disease	Flat affect
Orientation	Usually impaired	Impaired with advanced disease	Rarely impaired
Attention	Impaired	Slow to focus	Disorganized
Hallucinations	Primarily visual	Rare	Primarily auditory
Speech	Slow, incoherent, dysarthric	Usually coherent	Usually coherent
Consciousness	Decreased to impaired	Normal (clear)	Alert
Intellectual function	Usually impaired	Impaired	Intact

From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

TABLE 5 Priorities (Consensus, Evidence-Based, and Speculative) for the Prevention, Management, and Advancement of the Treatment of Delirium

Community-Based Prevention	Hospital-Based Prevention	Hospital-Based Management	Postdischarge Management	Clinical Research Opportunities
Hospital avoidance strategies	Implementation of basic standards (e.g., screening for delirium) Minimization of iatrogenesis*	Implementation of basic standards (e.g., review of medications)*	Responsive, proportionate, and holistic follow-up*	Pragmatic research into optimizing care delivery
Identification and management of frailty	Multicomponent interventions to address frailty† Reorientation† Nutrition† Multidisciplinary care* Physiologic correction† Sensory optimization† Minimization of ward transfers* Avoidance of polypharmacy†	Multicomponent interventions to address frailty* Reorientation* Nutrition* Multidisciplinary care* Physiologic correction* Sensory optimization* Minimization of ward transfers* Reduction of drug burden*	Identification and management of frailty Reduction and cessation of antipsychotics	The interaction between frailty, interventions to ameliorate frailty, and delirium Transference from basic science models to trials of newer therapies Validation of delirium models using advanced imaging
Pleiotropic interventions (e.g., exercise/ nutrition)	Monitor and promote early mobilization†	Monitor and promote early mobilization*	Review of the primary triggers for delirium and other state variables (e.g., mobility)	Delirium, mobility, and response to physical therapy
Early diagnosis and management of dementia	Screening for dementia*	Screening for delirium resolution and residual cognitive impairment	Screening for subsyndromal delirium or dementia*	The interaction between dementia, including non-Alzheimer dementia, and delirium
Education of nursing home facilities and staff	Education of nursing and medical staff*	Education of medical and nursing staff*	Caregiver support and education	The role of education of non-medical staff, families,‡ and general public using multimedia solutions
Integrated geriatric care for planned major surgery	Targeted drug treatments (e.g., melatonin for sleep disturbance)† Family-based screening/ reorientation†	Delirium units Supported early discharge Family-based screening/ reorientation* Management in the nursing home with CGA capability	Adaptive and versatile methods of follow-up such as telemedicine	The role of novel and targeted interventions and models of care supported by assistive technologies
Public health awareness	Audit of care and cycle of care improvement*	Audit of care and cycle of care improvement*	Public health awareness/NGO engagement	Development of key indicators in the management of delirium

CGA, Comprehensive geriatric assessment; *NGO*, nongovernmental organization.
*Consensus role.
†Evidence-based role.
‡Speculative role.
Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology*, ed 8, 2017, Elsevier.

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Delirium Tremens PTG

BASIC INFORMATION

DEFINITION

Delirium tremens, also known as withdrawal delirium, is overactivity of the central nervous system after cessation of alcohol intake. The time interval is variable; it usually occurs within 1 wk after reduction or cessation of heavy alcohol intake and persists for 1 to 3 days.

SYNONYMS

Withdrawal delirium
Alcohol withdrawal syndrome
DTs
Alcoholic delirium

ICD-10CM CODE

F10.231 Alcohol dependence with withdrawal delirium

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Up to 500,000 cases annually, 3% to 5% of patients who are hospitalized for alcohol withdrawal meet the criteria for withdrawal delirium
PEAK INCIDENCE: 30 yr and older
PREDOMINANT SEX: Male
PEAK AGE: Teenage yrs and older
GENETICS: More common with patients who have relatives who are alcoholics

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Ethanol withdrawal symptoms usually begin within 8 hours after blood alcohol levels decrease, peak at about 72 hours, and are markedly reduced by days 5 to 7 of abstinence
- Initially: Anxiety, insomnia, tremulousness
- Early: Tachycardia, sweating, anorexia, agitation, headache, gastrointestinal distress
- Late: Seizures, visual hallucinations, delirium

ETIOLOGY

Alcoholism

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Coexisting illness
- Trauma
- Drug use

WORKUP

- Frequent rating of symptoms (hallucinations, tremor, sweating, agitation, orientation)
- The Clinical Institute Withdrawal Assessment-Alcohol (CIWA-A) scale can be used to measure the severity of alcohol withdrawal. It consists of the 10 following items:
  1. Nausea
  2. Tremor
  3. Autonomic hyperactivity
  4. Anxiety
  5. Agitation
  6. Tactile disturbances
  7. Visual disturbances
  8. Auditory disturbances
  9. Headache
  10. Disorientation

  The maximum score is 67. Scores <8 indicate mild symptoms; scores 8-15 indicate moderate withdrawal symptoms; and scores >15 indicate severe withdrawal symptoms.

LABORATORY TESTS

- Electrolytes (including magnesium, phosphate)
- Close monitoring of glucose levels
- Drug screen (blood and urine)

IMAGING STUDIES

CT scan of head if there is a history of head trauma.

TREATMENT

NONPHARMACOLOGIC THERAPY

Refer to drug rehabilitation program after patient recovers.

ACUTE GENERAL RX:

- Admission to a detoxification unit where patient can be observed closely.
- Vital signs q30min initially (neurologic signs, if necessary).
- Use of lateral decubitus or prone position if restraints are necessary.
- Nothing by mouth: Nasogastric tube for abdominal distention may be necessary but should not be routinely used.
- Vigorous hydration (4-6 L/day): IV with glucose (Na^+, K^+, PO_4^{-3}, and Mg^{2+} replacement). May be necessary in some patients but commonly there is little support for routine administration of magnesium. Use vigorous hydration with caution in patients with CHF.
- Vitamins: Thiamine 500 mg infused IV over the course of 30 minutes daily for 3 days. The initial dose of thiamine should precede the administration of IV dextrose; multivitamins (may be added to the hydrating solution).
- Sedation (sedation can be achieved using fixed-dose regimen or individualized benzodiazepine administration [see CIWA-Ar score] in "Alcohol Abuse" Chapter):
  1. Initially: Lorazepam 8 mg IM/IV every 15 minutes as needed, after the patient has received 16 mg. If delirium is still severe, administer an 8 mg bolus IV, then administer 10 to 30 mg/hr.[1]
  2. Maintenance (individualized dosage): Chlordiazepoxide, 50 to 100 mg PO q4 to 6h, lorazepam 2 mg PO q4h, or diazepam 5 to 10 mg PO tid; withhold doses or decrease subsequent doses if signs of oversedation are apparent.
  3. Midazolam is also effective for managing DTs. Its rapid onset (sedation within 2 to 4 min of IV injection) and short duration of action (approximately 30 min) make it an ideal agent for titration in continuous infusion.
- In addition to benzodiazepines, administer medications such as the antipsychotic agent haloperidol for uncontrolled agitation or hallucinations (0.5-5 mg IV/IM every 30-60 minutes as needed for severe agitation or hallucinations, not to exceed 20 mg).
- Treatment of seizures: Diazepam 2.5 mg/min IV until seizure is controlled (check for respiratory depression or hypotension) may be beneficial for prolonged seizure activity; IV lorazepam 1 to 2 mg q2h can be used in place of diazepam. In general, withdrawal seizures are self-limited and treatment is not required; the use of phenytoin or other anticonvulsants for short-term treatment of alcohol withdrawal seizures is not recommended.
- Diagnosis and treatment of concomitant medical, surgical, or psychiatric conditions.

CHRONIC Rx

Alcoholics Anonymous has the best record in breaking addiction, but the results are still disappointing.

DISPOSITION

Refer to drug rehabilitation program

REFERRAL

If cardiac arrhythmias are prominent or respiratory distress develops.

PEARLS & CONSIDERATIONS

COMMENTS

- This is a potentially lethal disease if not carefully treated. Mortality rate is 15% in untreated patients, and approximately 1% to 6% of hospitalized patients who have withdrawal delirium die.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Delirium Tremens (Patient Information)
Alcohol Abuse (Related Key Topic)
Delirium (Related Key Topic)
Wernicke Syndrome (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

[1]Schuckit MA: Recognition and management of withdrawal delirium (delirium tremens). *N Engl J Med* 371:2109-2113, 2014.

SUGGESTED READING

Schuckit MA: Recognition and management of withdrawal delirium (delirium tremens), *N Engl J Med* 371:1786-2113, 2014.

Delusional Parasitosis

BASIC INFORMATION

DEFINITION

A fixed belief characterized by a person's preoccupation that his or her skin is infested by insects, worms, or other living organisms.

SYNONYMS

Morgellons disease
Ekbom syndrome

ICD-10CM CODE
F22 Delusional disorders
DSM-5 CODE
297.1 Delusional disorder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown
PEAK INCIDENCE: Occurs more often later in life
PREVALENCE: The disorder is rare. It has a prevalence estimated at 80 cases per million and appears to have a bimodal distribution peaking around ages 20 to 30 and again over 50.
PREDOMINANT SEX AND AGE: For patients less than age 50, the male/female ratio is 1:1; for patients older than 50, females predominate by a ratio of 3:1.
GENETICS: Unknown
RISK FACTORS: From 5% to 15% of individuals close to patients with delusional parasitosis will be at risk for developing shared psychotic disorder (folie a deux).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients complain of living organisms infesting their skin, sometimes including mucosal tissues.
- Patients have often been to specialists, including dermatologists, allergists, and infectious disease specialists.
- Patients may bring in samples of skin or hair, stating that they have looked at tissue under a microscope and have seen organisms. These samples are often brought in a matchbox ("matchbox sign") or wrapped in plastic wrap ("Saran sign"). This is generally called the "specimen sign."
- Skin may show areas of excoriation.

ETIOLOGY

Unknown: Thought to be mediated through dopaminergic pathways in the brain given the known etiology of other psychotic disorders and the ability of cocaine use to create symptoms of formication (see the following).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary psychiatric disorders include formication, in which patients experience crawling and biting sensations on their skin, although they are not delusional about the cause.
- Substance abuse should be considered. Case reports exist of cocaine and amphetamine use leading to these delusions.
- Delusional symptoms as the result of a primary mood disorder, such as major depression, should be considered.
- Delusional symptoms as the result of a primary psychotic disorder should be ruled out.
- Neuropsychiatric conditions: B_{12} deficiency, dementia, diabetic neuropathy, cardiovascular disease, multiple sclerosis, hyperthyroidism, and brain lesions can all cause similar delusions.
- Other medical causes that deserve workup include severe anemia, organophosphate poisoning, primary skin lesions, systemic diseases that may present with skin lesions, and disorders of infestation. There are case reports of delusional parasitosis being precipitated by herpes zoster.
- Dopaminergic agents, such as those that treat Parkinson disease, have also been shown to cause these symptoms.

WORKUP

- Skin biopsy may exclude dermatitis herpetiformis (although many patients have already been to their primary care doctor and dermatologist and have had a skin biopsy done, likely many times).
- Mineral oil preparation may exclude scabies, and a microscopic examination may exclude louse infestation.
- Thorough history is likely to yield the very fixed nature of the belief and an unwillingness to come to terms with the lack of findings on the exam.

LABORATORY TESTS

- Pruritus workup: Iron studies, LFTs, CBC, UA, TSH, chem 7, folate, B_{12}
- Lumbar puncture (especially when multiple sclerosis is highly suspected)
- CRP (especially when an inflammatory/infectious etiology is suspected)
- Urine toxicology screen to evaluate substance use

IMAGING STUDIES

- Head CT, without contrast
- MRI
- There has been evidence of environmental filaments being placed under the skin

TREATMENT

- Antipsychotics have been shown to lead to full to partial remission in approximately 65% to 75% of those treated with antipsychotics.
- Classically, pimozide (Orap) was the treatment of choice, although it has been associated with QTc prolongation.
- Multiple studies describe the use of second-generation antipsychotics and they have all shown some efficacy in small studies, but these have been shown to cause weight gain and metabolic syndrome.
- Numerous antipsychotics have a black box warning about the risk of sudden death in the elderly and must be administered carefully for patients who have issues with QTc.
- Given all of these issues, a careful risk-benefit analysis is needed, including the assistance of family members of elderly patients.

NONPHARMACOLOGIC THERAPY

- Given the fixed nature of the belief, patients often refuse referral to a mental health specialist.
- A treatment (e.g., Permethrin) should not be recommended "just in case" because it may reinforce the patient belief.
- Repeat visits with medical providers may be helpful to provide assurance and prevent harm from further workup.

ACUTE GENERAL Rx

Antipsychotics (Table E1)

TABLE E1 Antipsychotics

Antipsychotic Drug	Dosage
Haloperidol	0.5-10 mg PO bid
Pimozide	2-12 mg PO qAM
Perphenazine	4-16 mg PO tid
Olanzapine	2.5-10 mg PO bid
Aripiprazole	2.5-20 mg PO qAM
Quetiapine	12.5-200 mg PO bid
Ziprasidone	20-80 mg PO bid
Risperidone	0.5-3 mg PO bid

COMPLEMENTARY & ALTERNATIVE MEDICINE

There is no evidence on the use of complementary or alternative medicine for this disorder.

REFERRAL

Referral to an outpatient psychiatrist may be helpful, but patients are often resistant.

PREVENTION

No preventive measures have been identified.

PATIENT & FAMILY EDUCATION

Psychoeducation may be helpful for the patient and family, although resistance from the patient can be expected.

RELATED CONTENT

Alcohol Abuse (Related Key Topic)
Cocaine Overdose (Related Key Topic)
Delirium (Related Key Topic)
Schizophrenia (Related Key Topic)

AUTHOR: **Anthony Gallo, MD**

SUGGESTED READING

Locala JA: Ch 62. Dermatology. In Fogel BS, Greenberg DB, editors: *Psychiatric care of the medical patient*, Oxford, 2015, pp 1279-1292.
Lopez O et al: Delusional parasitosis as a treatment complication of Parkinson disease, *Psychosomatics* 56(6):696-699, 2015.

BASIC INFORMATION

DEFINITION

Dementia with Lewy bodies (DLB) is a neurodegenerative dementia occurring concurrently with or within 1 yr (either before or after) of the onset of parkinsonism. DLB also has other core features including fluctuations in attention and alertness and recurrent vivid visual hallucinations. Diagnostic criteria for dementia syndrome associated with Lewy body pathology are described in Box 1. Patients generally respond to cholinesterase inhibitors, are very sensitive to the adverse effects of neuroleptics, and compared with Parkinson disease patients, are relatively unresponsive to L-dopa.

SYNONYMS

DLB
Lewy body dementia
Diffuse Lewy body disease
Lewy body type senile dementia
Cortical Lewy body disease

ICD-10CM CODE
G31.83 Dementia with Lewy bodies

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Accounts for 10% to 15% of all dementias. DLB is the second most common neurodegenerative cause of dementia after Alzheimer disease.
PEAK INCIDENCE: Affects individuals in their sixth decade or older
PREVALENCE: Estimated 0.7% of individuals older than age 65
PREDOMINANT SEX AND AGE:
- Sex: Male predominance
- Mean age of onset: 75 yr. On average, 10 yr greater for dementia with Lewy bodies (DLB) than Parkinson disease (PD).

GENETICS:
- Most cases are sporadic with a discordance among monozygotic twins, suggesting that either environmental or other epigenetic factors may play a major role in the incidence of DLB.
- Copy number variation of the alpha-synuclein gene (*SNCA*) has been reported in families with DLB. Rare autosomal dominant variants in *LRRK2* have also been reported. These genes are associated with Parkinson disease and Parkinson disease dementia in addition to DLB, suggesting a common molecular etiology with a spectrum of clinical phenotypes.
- The *APOE* ε4 allele has a higher prevalence in DLB than in control individuals, suggesting heightened disease risk conferred by the allele. Conversely, the *APOE* ε2 allele is enriched in control individuals, suggesting a neuroprotective role, or at least the lack of a deleterious effect, for the allele.
- Other factors include glucocerebrosidase genetic mutations, high prevalence of Lewy bodies with presenilin-1 mutations, and polymorphisms of the coding region for the synuclein genes.

RISK FACTORS:
- Male sex
- Advanced age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Importance of recognizing DLB relates to its pharmacologic management, including responsiveness to cholinesterase inhibitors, sensitivity to the adverse effects of neuroleptics, and relative unresponsiveness to L-dopa.
- Onset of dementia is insidious, with core features of fluctuations in cognition, attention, and alertness; recurrent vivid visual hallucinations; and extrapyramidal motor symptoms, along with other features either suggestive or supportive of the clinical diagnosis.
- Syncopal events or unexplained episodes of severe alteration in mentation.
- Repeated falls.
- Detailed neuropsychological assessment demonstrates a characteristic profile of impairments in visuoperceptual, attentional, and executive functions, with relative sparing of episodic memory (in contradistinction to Alzheimer diseases, in which impairment in episodic memory is a hallmark), reflecting a combination of cortical and subcortical damage.

ETIOLOGY

- *SNCA* encodes for a protein normally found at the synapse with a role in vesicle production. In its insoluble form, SNCA aggregates into Lewy bodies found at the cortical and subcortical levels.
- Lewy bodies (Fig. E1) are round, eosinophilic, intracytoplasmic inclusions in the nuclei of neurons.
- Cortical Lewy bodies are found in deep cortical layers of the anterior frontal and temporal lobes, the cingulate gyrus, and insula.
- As in Parkinson disease, Lewy bodies aggregate in the following structures: substantia nigra, locus ceruleus, raphe nuclei, nucleus basalis of Meynert, and brainstem nuclei.
- Fig. 2 shows the relationships among the subtypes of dementia.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diagnosis of DLB when dementia occurs before or concurrently with extrapyramidal features—arbitrarily set as the "1-yr rule" vs. Parkinson disease with dementia, which occurs in the setting of well-established Parkinson disease.
- Dementia: Alzheimer disease (AD), vascular dementia, frontotemporal dementia. However, some patients have pathological overlap of AD and DLB or DLB and vascular dementia.
- Parkinsonian features: Parkinson disease dementia, progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and multisystem atrophy (MSA).
- Rapidly progressive form: Creutzfeldt-Jakob disease (CJD). Lack of cerebellar signs and lack of typical MRI may help distinguish DLB from classic CJD (but not variant form of CJD).
- Psychiatric features: Late-onset psychosis or depression with psychotic features.
- Hallucinations with fluctuations in consciousness: Temporal lobe epilepsy (TLE) or delirium due to metabolic or autoimmune derangement.

WORKUP

- MRI of the brain to evaluate for structural causes of dementia and exclude MRI features of vascular dementia or CJD
- Lumbar puncture to rule out underlying chronic infections, especially if there are atypical features
- Electroencephalogram (EEG) if there is concern about TLE. However, both DLB and TLE may show nonspecific slowing or periodic complexes.

LABORATORY TESTS

Rule out other potential reversible causes for dementia including: Complete blood count, complete metabolic panel, thyroid stimulating hormone, and B12. Consider RPR and HIV testing as well.

IMAGING STUDIES

- MRI typically shows a relative preservation of the hippocampi and medial temporal lobe volumes (in contrast to AD) but generalized atrophy and white matter changes.

BOX 1 Diagnostic Criteria for the Dementia Syndrome Associated with Lewy Body Pathology

The cognitive disturbance is of insidious onset and is progressive, based on evidence from the history or serial cognitive examination
The presence of at least two of the following:
- Parkinsonism (rigidity, resting tremor, bradykinesia, postural instability, parkinsonian gait disorder)
- Prominent, fully formed visual hallucinations
- Substantial fluctuations in alertness or cognition
- Rapid eye movement sleep behavior disorder
- Severe worsening of parkinsonism by antipsychotic drugs
- The disturbance is not better accounted for by a systemic disease or another brain disease

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

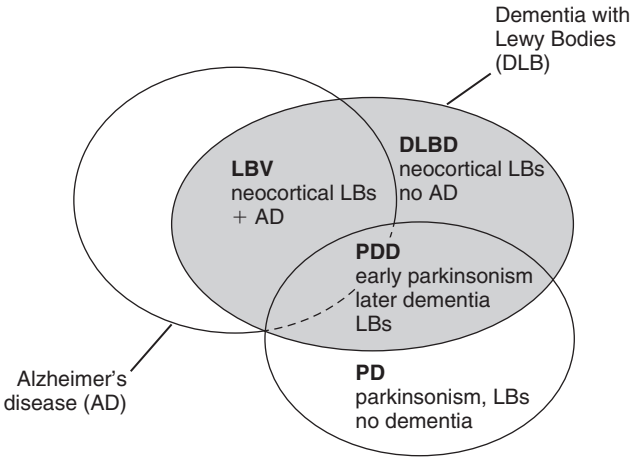

FIG. 2 Relationships among Alzheimer disease (AD), the three subtypes of dementia with Lewy bodies (DLB), and Parkinson disease (PD). Parkinsonism refers to the clinical symptoms of PD (hypokinesia, tremor, and muscular rigidity). *DLBD,* Diffuse Lewy body disease; *LBs,* Lewy bodies; *LBV,* Lewy body variant of Alzheimer disease; *PD,* Parkinson disease; *PDD,* Parkinson disease dementia. (From Lewis KA, et al.: Abnormal neurites containing C-terminally truncated α-synuclein are present in Alzheimer's disease without conventional Lewy body pathology, *Am J Pathol* 177(6):3037–3050, 2010.)

- Functional imaging including single photon emission computed tomography (SPECT) may demonstrate hypoperfusion of the occipital region (specific finding but not sensitive).

Rx TREATMENT

Patient and caregiver education about benefits, side effects, and limitations of treatment is very important. Caregivers may be encouraged to avoid neuroleptics unless the psychotic features either trouble or endanger the patient. If neuroleptics must be used, typical neuroleptics must be avoided.

NONPHARMACOLOGIC THERAPY

- Social interaction and environmental novelty may improve cognitive dysfunction and psychiatric features often exacerbated by low levels of arousal and attention
- Behavioral methods, such as avoiding previously exposed environmental triggers known to cause anxiety, agitation, or aggression
- Physical therapy, mobility aids, and daily exercise

ACUTE GENERAL Rx

Atypical neuroleptic for disabling, persistent, bothersome (to the patient) psychotic features despite initiation of a cholinesterase inhibitor. A very low dose of an atypical antipsychotic (quetiapine 12.5 mg daily) may be started after patient/caregiver education regarding the sensitivity to neuroleptics. However, all neuroleptics do carry a boxed warning from the FDA about the increased mortality risk associated with neuroleptic use in patients with dementia. Patients and/or caregivers should be informed of this risk and allowed to balance the risk against the perceived benefit.

CHRONIC Rx

- Cholinesterase inhibitors for cognitive and behavioral symptoms. Rivastigmine (6 to 12 mg per day orally or 9.5 mg per day by transdermal patch) has shown in randomized controlled trial (RCT) to significantly reduce anxiety, delusions, and hallucinations, as well as significantly improved performance on neuropsychological testing.
- Parkinson disease medications for disabling parkinsonian features. Carbidopa/levodopa is reported to be more effective with fewer side effects than dopamine agonists. Begin at a low dose—25/100 mg three times a day—and slowly titrate over several weeks as tolerated and according to response.
- Selective serotonin reuptake inhibitors are commonly used for depression.
- If rapid eye movement (REM) sleep disorder remains disabling (or patient has not responded to an atypical antipsychotic initiated for psychosis), a trial of low-dose clonazepam (0.25 to 0.5 mg) or melatonin (3 mg) at bedtime remains an option.
- Orthostatic hypotension may be aided by nonpharmacologic therapy such as supportive stockings or pharmacologically by midodrine, fludrocortisone, or droxidopa.
- Memantine demonstrated an improvement in clinical global measure and remains well tolerated but may worsen hallucinations or delusions.
- Avoid anticholinergics (including tricyclic antidepressants) and benzodiazepines, as they can trigger delirium and worsen symptoms.

DISPOSITION

- Survival resembles the progression of AD, but a minority of cases may have a rapid disease course.
- Progression in cognitive decline, similar to AD, by approximately 10% per yr on cognitive testing.

REFERRAL

DLB requires a multidisciplinary approach including the general practitioner, neurologist, neuropsychologist, and/or neuropsychiatrist.

PEARLS & CONSIDERATIONS

COMMENTS

- Clinical presentation helps differentiate DLB from AD. AD presents with early signs of anterograde episodic memory loss without the benefit of cues on neuropsychological testing due to cortical atrophy at the medial temporal lobe region.
- Vascular dementia may also present with evidence of frontal-subcortical features but typically without the core features listed in the criteria above.
- Bed partners may report that individuals with DLB "act out their dreams," sometimes violently, leading to sleeping in separate beds. This history may indicate REM sleep behavior disorder. A history of REM sleep behavior may precede the diagnosis by many yr. However, REM sleep behavior does not necessarily lead to DLB.

PATIENT & FAMILY EDUCATION

- Visual hallucinations (VH) typically consist of innocuous, well-formed, detailed images of animate figures. These are classically labeled Lilliputian, as the hallucinatory images are often relatively small. Unless VH lead to a potential threat to self or others, avoid antipsychotics due to the sensitivity of neuroleptics. Family/friends are often more alarmed by the VH than the patient with DLB.
- Apathy is a common clinical feature of DLB and mimics changes in mood, including depression or excessive daytime somnolence. These features are often noticed by family/friends.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Angad Jolly, PhD,** and **Joseph S. Kass, MD, JD, FAAN**

SUGGESTED READINGS

Morra LF, Davovich PJ et al: Clinical presentation and differential diagnosis of dementia with Lewy bodies: a review, *Int J Geriatr Psychiatry* 29(6):569-576, 2014.

Walker Z et al: Lewy body dementias, *Lancet* 386:1683-1697, 2015.

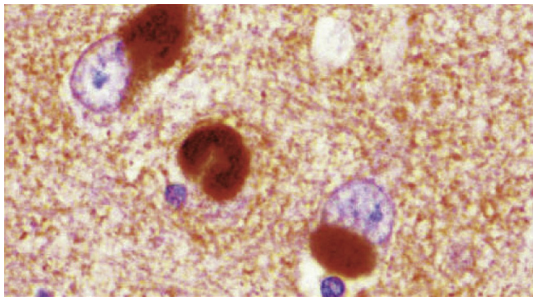

FIG. E1 Cortical Lewy bodies present in cerebral cortex, as opposed to Parkinson disease without dementia, in which Lewy bodies are found in the substantia nigra. Immunostain for alpha synuclein is characteristic for Lewy body immunohistological profile. (From MacDonald AB: Spirochetal cyst forms in neurodegenerative disorders, hiding in plain sight, *Med Hypotheses* 67(4):819–832, 2006.)

Dengue Fever

BASIC INFORMATION

DEFINITION

Dengue fever (DF) is an infectious disease endemic in most tropical and subtropical countries. It is the most widespread arboviral illness worldwide. The causative agent is the dengue virus, a single positive-stranded RNA virus of the Flaviviridae family, which has four distinct but closely related serotypes (DEN-1, DEN-2, DEN-3, DEN-4). Dengue virus is transmitted by the *Aedes* mosquito. The primary vector is *Aedes aegypti*; the secondary vector is *Aedes albopictus*. Box E1 describes the World Health Organization case classification of dengue.

SYNONYMS

Classic dengue fever
Dengue
Dengue hemorrhagic fever
Dengue shock syndrome
DF

ICD-10CM CODES

A90 Dengue fever [classical dengue]
A91 Dengue hemorrhagic fever

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE AND PREVALENCE: The incidence of dengue is underestimated. Recent estimates indicate 390 million dengue infections per yr, of which 96 million manifest clinically. Attack rates during epidemics range from 1 to 10/1000 per yr and as high as 292/1000 among children in hyperendemic countries. There has been a thirtyfold increased incidence over the past 30 yr. During 2010 to 2017, a total of 5387 dengue cases were reported from U.S. states; 93% were travel-associated. Locally acquired cases were reported from Hawaii (<50 cases), Florida (103), Texas (24), and New York (one). Dengue is endemic in more than 100 countries in the regions of Africa, Asia, and West Pacific. Outbreaks have also occurred in Europe.

Dengue shows cyclical variation with large outbreaks every 3 to 5 yr. DF is confirmed in up to 8% of febrile travelers returning from the tropics.

RISK FACTORS: Travel to endemic regions. Few locally acquired U.S. cases have been documented in Texas, Hawaii, and Florida. The majority of indigenous cases presented as uncomplicated fever, and a minor percentage developed dengue hemorrhage fever (DHF) or dengue shock syndrome (DSS). Local transmission has also been reported in recent yrs in Europe (Southern France, Croatia, and Portugal).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical presentation ranges from asymptomatic infection to shock syndrome.
- Symptomatic DF infection can be classified into three categories:
  1. Undifferentiated fever.
  2. Classic DF: Characterized by acute febrile illness accompanied by symptoms such as headache, retroorbital pain, fatigue, mild respiratory and gastrointestinal symptoms, and myalgias or arthralgias ("break bone fever"); DF usually follows an incubation period of 3 to 14 days and fever typically lasts 5 to 7 days; physical findings may include a maculopapular rash (Fig. E1), lymphadenopathy, pharyngeal erythema, and injected conjunctivae; some patients may experience development of hemorrhagic manifestations with petechiae, purpura (Fig. E2), and rarely, epistaxis, gum bleeding, and gastrointestinal bleeding; during pregnancy, DF has been associated with increased risk for premature labor and birth, uterine hemorrhage, intrautero death, neonatal death, and maternofetal transmission.
  3. DHF/DSS: Occurs in fewer than 3% of infected individuals; early course is similar to presentation of classic dengue, but 4 to 7 days after onset of illness, plasma leakage with hemorrhagic manifestations develops, resulting in hypoproteinemia, peripheral edema, ascites, and pleural and cardiac effusions, and is suggested by a hematocrit increase of 20% during course of illness; thrombocytopenia is also a hallmark, with resultant clinical manifestations such as petechiae, ecchymosis, mucosal hemorrhage, and GI bleeding; may progress to DSS with circulatory collapse, manifested by rapid/weak pulse, profound hypotension, and pulse pressure of <20 mm Hg; warning signs for DHF/DSS include mucosal bleed, abdominal pain, persistent vomiting, abrupt defervescence, change in mental status, and respiratory distress.

ETIOLOGY

After a bite by infected mosquito, the virus replicates in regional lymph nodes and then spreads by blood and the lymphatic system to other tissues. The incubation period is typically 4 to 7 days (range, 3 to 14 days). The most important risk factors for development of severe disease (DHF/DSS) are young age, female sex, prior infection, and viral genotype. The majority of DHF/DSS cases occur during secondary heterologous (different from first exposure) infection or during primary infection in infants born to dengue-immune mothers. In such cases, nonneutralizing cross-reactive antibodies facilitate viral entry into cells, generating higher viral burdens and stronger inflammatory responses. Additionally, T-memory cells from a previous infection are preferentially expanded because of a lower threshold of activation compared with naïve T cells of higher affinity to the current serotype. This results in suboptimal clearance of the virus and quicker, more robust cytokine production, leading to increased vascular permeability and plasma leakage. "Asian" genotypes DEN-2 and DEN-3 are associated with severe disease.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Influenza
- Measles
- Rubella
- Epstein-Barr virus
- West Nile virus
- HIV conversion
- Malaria
- Zika virus
- Typhoid
- Leptospirosis
- Chikungunya
- Rickettsial diseases
- Early severe acute respiratory syndrome
- Other viral hemorrhagic fevers

DHF is defined by the following World Health Organization (WHO) criteria:

- Fever lasting 2 to 7 days
- Hemorrhagic tendency (spontaneous bleeding or positive tourniquet test)
- Thrombocytopenia
- Evidence of plasma leakage

WORKUP

- Suspicion for DF based on travel, exposure history, and clinical presentation
- Tourniquet test can be performed to look for hemorrhagic manifestations; inflate blood pressure cuff midway between systolic and diastolic blood pressure for 5 min; the test result is positive when more than 20 petechial hemorrhages per square inch are counted on the forearm

BOX E1 World Health Organization Case Classification of Dengue, 2009

Dengue
Acute febrile illness, live in or travel to endemic region, with two or more of the following:
Headache or retroorbital pain
Nausea or vomiting
Rash
Aches and pains
Tourniquet test positive
Leukopenia
Any warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increase in hematocrit, falling platelet count with laboratory confirmation)

Severe Dengue including Dengue Shock Syndrome
Severe capillary permeability and plasma leakage leading to dengue shock syndrome
Fluid accumulation and respiratory distress
Severe bleeding
Severe organ involvement (liver, central nervous system, heart, kidneys, and others)

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.

LABORATORY TESTS

- CBC, liver function tests, chemistries.
- Additional laboratory tests based on differential diagnoses (e.g., malaria smears, monospot/Epstein-Barr virus titers, HIV testing).
- With compatible exposure history and symptom profile, positive anti–dengue IgM suggests recent infection, and positive anti–dengue IgG may indicate past infection.
- Confirm diagnosis with a fourfold increase of IgG and IgM between acute (<6 days after illness onset) and convalescence titers; IgM capture enzyme-linked immunosorbent assay (ELISA) commonly used, but the test result is negative early in the course of disease.
- Identification of DENV from serum by reverse transcriptase polymerase chain reaction (distributed by CDC to departments of health laboratories). Nucleic acid amplification tests (NAATs) are the preferred method of diagnosis.
- Dengue fever and Zika are closely related mosquito-borne flaviviruses with similar transmission cycles, distribution throughout the tropics and subtropics, and disease manifestations. Figs. E3 and E4 illustrate dengue and Zika virus testing recommendations for nonpregnant persons with a clinically compatible illness and risk for infection with both viruses.

IMAGING STUDIES

As dictated by clinical course

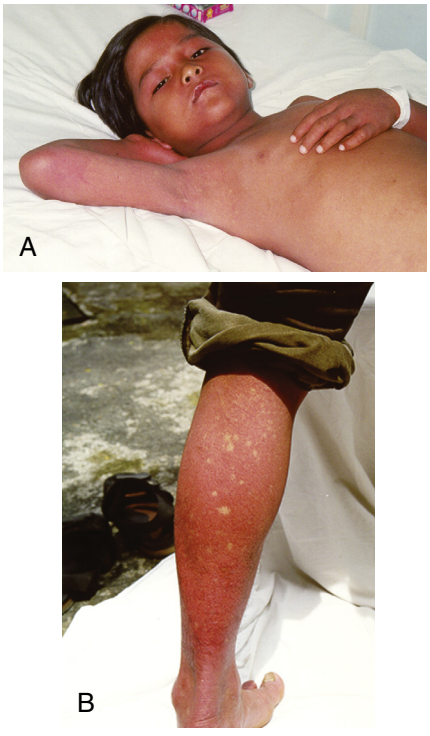

FIG. E1 Characteristic skin manifestations in convalescent dengue. A, Early convalescent macular diffuse rash occurring in the first week after recovery. **B,** Typical convalescent rash with "islands of white in a sea of red." (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.)

Rx TREATMENT

No specific pharmacologic treatment for dengue

NONPHARMACOLOGIC THERAPY

- Treatment is based on supportive measures.
- Mortality rate from DHS/DSS is improved by early and correct fluid replacement.

ACUTE GENERAL Rx

- Therapy is supportive.
- Monitor platelet count and hematocrit at least daily.
- Patients with platelet counts <100,000 have increased risk for DHF and should be monitored as inpatients.
- Hematocrit increase of 20% suggests substantial plasma loss for which patients should be admitted for intensive care and IV fluid replacement.
- Fever should be managed with acetaminophen; aspirin and NSAIDs should be avoided because of their anticoagulant properties.

DISPOSITION

- Classic dengue is usually self-limiting and rarely fatal.
- Of an estimated 500,000 cases of DHF/DSS admitted early, the mortality rate is approximately 2.5%.
- Mortality rate for DHF/DSS is as high as 20% without proper treatment but decreases to <1% with prompt recognition and appropriate treatment.

REFERRAL

- Infectious disease consultation for suspicion of DF
- Referral or transfer to center experienced with DHF/DSS if available

PEARLS & CONSIDERATIONS

COMMENTS

- Health care providers should consider dengue infection in any traveler returning from endemic areas who presents with fever.
- Given the incubation period, dengue infection can be ruled out if onset of symptoms begins 2 wk after individual leaves endemic area.
- Asymptomatic dengue infections are common; however, immunity that results from primary infection increases the risk for DHF/DSS during subsequent infections.
- Serologic testing is complicated by cross-reactions with flaviviruses (including vaccines for yellow fever and Japanese encephalitis).
- Contact the Dengue Branch at the CDC for additional information and testing (www.cdc.gov/dengue).

PREVENTION

- There is no approved vaccine against dengue in the U.S. A live attenuated tetravalent vaccine (CYD-TDV) is available outside the U.S. and recommended for use only in persons previously infected by dengue virus.[1]
- A recent phase 3 trial of a tetravalent dengue vaccine candidate (TAK-003) found it efficacious against symptomatic dengue in countries in which the disease is endemic.[2]
- For travelers, the most effective preventive measure is avoidance of mosquito bites by using protective clothing and insect repellents containing DEET.
- *Aedes* mosquitoes primarily bite during the day and typically live in urban areas.

AUTHOR: **Glenn G. Fort, MD, MPH**

[1]Villar L et al: Efficacy of a tetravalent dengue vaccine in children in Latin America, *N Engl J Med* 372:113-123, 2015.
[2]Biswal S et al: Efficacy of a tetravalent dengue vaccine in healthy children and adolescents, *N Engl J Med* 381(21):2009-2019, 2019.

FIG. E2 Acute skin manifestations of dengue. A, Characteristic minor bleeding near injection sites. **B,** Rash in established dengue shock syndrome. **C,** Severe bleeding after intravenous (IV) injection. Staff should press after IV injections for 5 min to ensure that bleeding stops. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.)

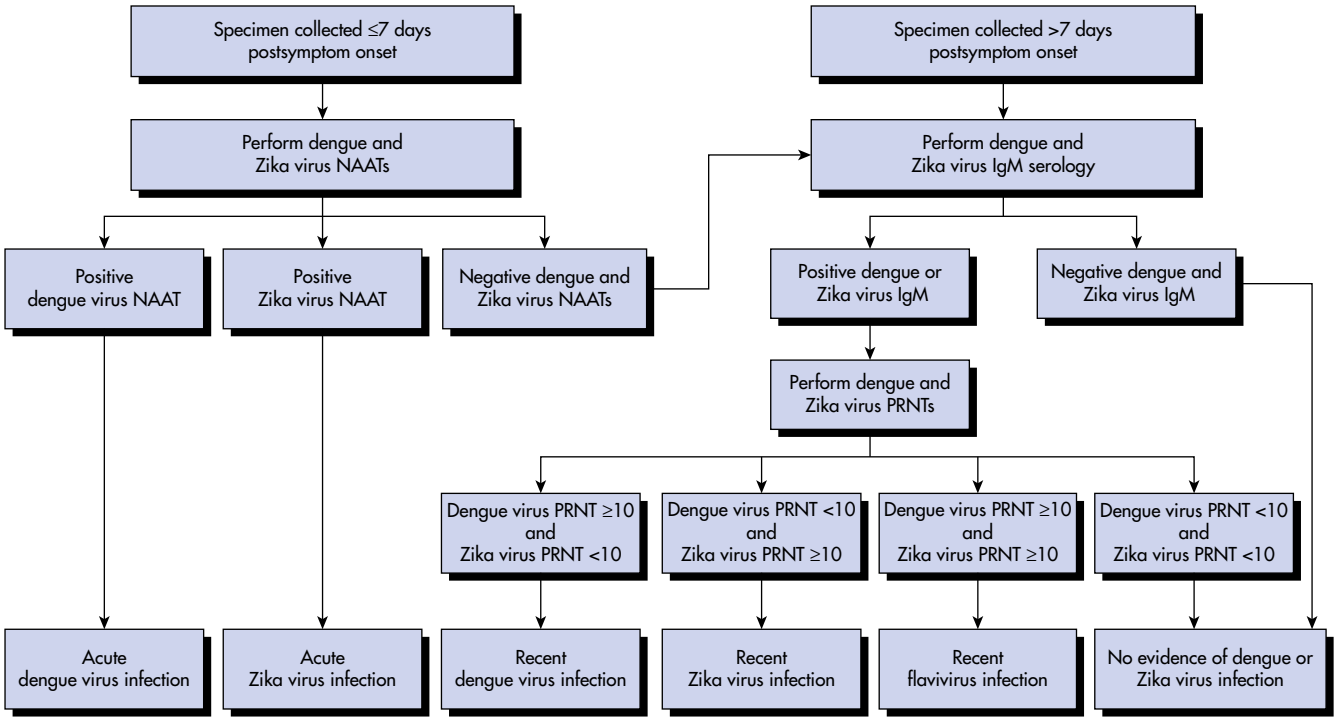

FIG. E3 Dengue and Zika virus testing recommendations for nonpregnant persons with a clinically compatible illness and risk for infection with both viruses. Specimen and test selection: Dengue and Zika virus NAATs, IgM antibody testing, and PRNTs should be performed on serum. Some NAATs also can be performed on plasma, whole blood, cerebrospinal fluid, or urine, and some antibody tests can be performed on plasma, whole blood, or cerebrospinal fluid. Laboratories may choose to perform dengue and Zika virus NAATs and IgM antibody testing simultaneously rather than sequentially, or to perform dengue virus nonstructural protein-1 testing instead of dengue virus NAAT. Indications to repeat assay(s): If the patient's illness has epidemiologic or clinical significance (e.g., first case of local transmission in area, new transmission mode, or unusual clinical syndrome), repeat a positive NAAT on newly extracted RNA from the same specimen. For indeterminate IgM antibody test results, repeat IgM antibody testing or perform PRNT on the same specimen. In areas where PRNTs are not performed, report the indeterminate results and request a second serum specimen for IgM antibody testing. Interpretation of results: Dengue and Zika virus IgM antibodies can be detected in serum for mos after infection. The specific timing of infection cannot be determined. Data on the epidemiology of viruses known to be circulating at the location of exposure and clinical findings should be considered when interpreting the results of serologic diagnostic testing. *IgM,* Immunoglobulin M; *NAAT,* nucleic acid amplification test; *PRNT,* plaque reduction neutralization test. (From Sharp TM et al: Dengue and Zika virus diagnostic testing for patients with a clinically compatible illness and risk for infection with both viruses, *MMWR Recomm Rep* 68[RR-1]:1-10, 2019.)

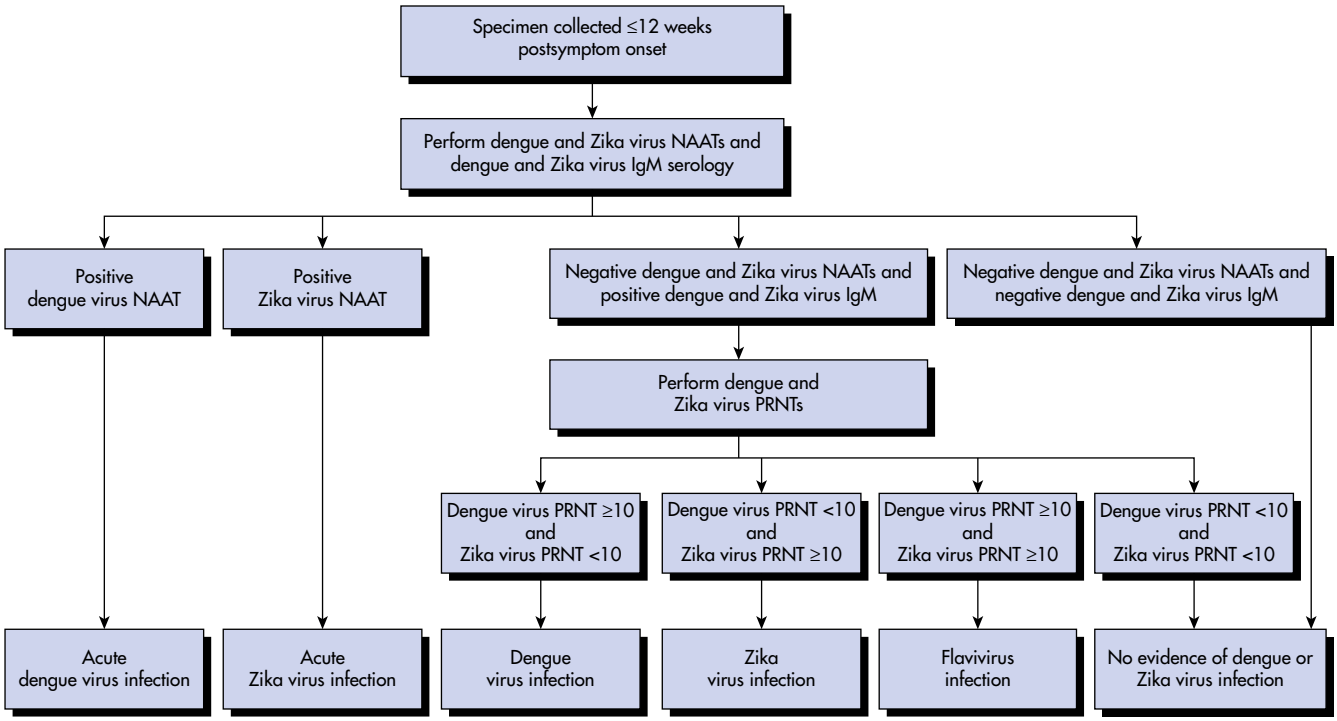

FIG. E4 Dengue and Zika virus testing recommendations for pregnant persons with a clinically compatible illness and risk for infection with both viruses. Specimen and test selection: Dengue and Zika virus NAATs, IgM antibody testing, and PRNTs should be performed on serum. Some NAATs also can be performed on plasma, whole blood, cerebrospinal fluid, or urine, and some antibody tests can be performed on plasma, whole blood, or cerebrospinal fluid. Dengue virus NAAT does not need to be performed on specimens collected >7 days after illness onset. Some laboratories may choose to perform dengue virus nonstructural protein-1 testing instead of dengue virus NAAT. Indications to repeat assay(s): If Zika virus NAAT is positive on a single specimen but IgM antibody tests are negative, repeat NAAT on newly extracted RNA from the same specimen. For indeterminate IgM antibody test results, repeat IgM antibody testing or perform PRNT on the same specimen. In areas where PRNTs are not performed, report the indeterminate results and request a second serum specimen for IgM antibody testing. Interpretation of results: Dengue and Zika virus IgM antibodies can be detected in serum for months after infection. The specific timing of infection cannot be determined. Data on the epidemiology of viruses known to be circulating at the location of exposure and clinical findings should be considered when interpreting the results of serologic diagnostic testing. *IgM,* Immunoglobulin M; *NAAT,* nucleic acid amplification test; *PRNT,* plaque reduction neutralization test. (From Sharp TM et al: Dengue and Zika virus diagnostic testing for patients with a clinically compatible illness and risk for infection with both viruses, *MMWR Recomm Rep* 68[RR-1]:1-10, 2019.)

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Dependent Personality Disorder

BASIC INFORMATION

DEFINITION

Dependent personality disorder (DPD) is characterized by a pervasive and excessive need to be taken care of that leads to submissive and clinging behavior and fears of separation. DPD begins by early adulthood and causes significant distress or impairment in multiple domains of functioning. Individuals must meet five or more of the following criteria, each of which should be enduring and pervasive across contexts:

1. Difficulty making routine decisions without an excessive amount of advice and reassurance from others
2. Need others to assume responsibility for most major areas of their lives
3. Difficulty expressing disagreement with others because of fear of loss of support or approval
4. Difficulty initiating or completing projects on own because of a lack of self-confidence in abilities rather than lack of motivation or energy
5. Excessive attempts to obtain nurturance and support from others
6. Feeling uncomfortable or helpless when alone because of exaggerated fears of being unable to care for self
7. Urgently seeking another relationship when a close relationship ends
8. Unrealistically preoccupied with being left to take care of self

SYNONYMS

None

ICD-10CM CODE	
F60.7	Dependent personality disorder
DSM-5 CODE	
301.6	Dependent personality disorder

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 0.5% in general population. Dependent traits, as opposed to the disorder itself, are among the most frequently reported in outpatient mental health clinics.

PREDOMINANT SEX: Female (2:1) in clinical settings. There is concern about under-diagnosis in men.

CLINICAL PRESENTATION

- Early onset and chronic course. Impairment may be apparent only on close inspection.
- On interview, will defer excessively to partner or parent.
- Indecision in routine decisions.
- Depend on a parent or spouse to decide where they should live, work, and recreate and who they should befriend.
- Need for others to function for them goes beyond age-appropriate and situation-appropriate requests for assistance.
- Will agree with objectionable opinions, submit to unreasonable requests, and not express appropriate anger or disappointment for fear of alienating the person without whom they believe they cannot function.
- Convinced that they are not capable of independent function and present themselves as inept.
- Often do not develop independent living skills, perpetuating their dependency.
- Social relations tend to be limited to the few people on whom the person depends.

ETIOLOGY

Chronic physical illness or separation anxiety disorder may predispose for DPD.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Dependency and personality changes arising as a consequence of another psychiatric disorder.
- Dependency arising as a consequence of a general medical condition.
- Most common comorbid psychiatric conditions are social anxiety disorder, panic disorder, agoraphobia, obsessive-compulsive disorder, major depressive disorder, and other personality disorders.
- Most common comorbid personality disorders are histrionic, avoidant, and borderline. Each of these disorders is characterized by dependent features. DPD is distinguished by its predominantly submissive, reactive, and clinging behavior.

WORKUP

- History: Collateral information is essential to establishing the presence of longstanding interpersonal pattern in multiple domains of the patient's life
- Physical examination
- Mental status examination

LABORATORY TESTS

Tests necessary to rule out medical causes of personality changes

IMAGING STUDIES

Tests necessary to rule out medical causes of personality changes

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral psychotherapy to diminish and better contain anxiety and to help patients develop sense of self as competent and learn requisite assertiveness skills.
- Psychodynamic psychotherapy to help develop improved self-concept and interpersonal functioning.
- Guidelines for general management of the patient with DPD:
  1. General strategy is to provide reassurance and allay fear of abandonment.
  2. Schedule frequent visits that occur regularly, regardless of how ill the patient feels (i.e., noncontingent care).
  3. Establish firm and realistic limits to availability as early as possible in treatment.
  4. Enlist other members of health care team for support.
  5. Encourage patient to develop additional "outside" support systems.

ACUTE GENERAL Rx

Benzodiazepines are used to control highly anxious states, although caution is warranted with regard to habituation and abuse potential in those with a dependent personality.

CHRONIC Rx

Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) for comorbid depression, social phobia, agoraphobia, and other anxiety disorders

COMPLEMENTARY & ALTERNATIVE MEDICINE

No evidence of efficacy in DPD

DISPOSITION

- Chronic course; severity is variable.
- At increased risk for major depression, social phobia, agoraphobia, and other anxiety disorders.
- Patients with DPD are at risk of victimization by partners. They are also at risk of suicidal or violent behavior if their relationships are threatened.

REFERRAL

- If pharmacotherapy or psychotherapy is indicated
- If patient's functioning is impaired

PEARLS & CONSIDERATIONS

COMMENTS

- Patients with DPD fear that a medical illness will lead to abandonment by others.
- This fear of simultaneous helplessness and abandonment intensifies neediness and may lead to dramatic demands for urgent medical attention.
- When physicians do not respond as wanted, angry outbursts may ensue.
- Medical care can also become a means by which dependency needs are met. As a result, some of these patients may unconsciously or consciously exaggerate their other illnesses (e.g., have primary gain from being sick). They may become high utilizers of health care.
- Physicians often react to the extreme neediness with avoidance or over-engagement, leading to burnout.

AUTHORS: **Timothy R. Kreider, MD, PhD,** and **John Q. Young, MD, MPP, PhD**

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BASIC INFORMATION

DEFINITION

Major depression is an episodic, frequently recurring syndrome. The diagnosis requires that five of nine criteria be present for 2 wk. One of these nine criteria must be either a persistent depressed mood or pervasive anhedonia (loss of interest or pleasure in all, or almost all, usual interests or activities). Other symptoms include sleep disturbance (insomnia or hypersomnia), appetite loss/gain or weight loss/gain, fatigue, psychomotor retardation or agitation, difficulty concentrating or indecisiveness, feelings of guilt or worthlessness, and recurrent thoughts of death or suicidal ideation.

SYNONYMS

Unipolar affective disorder
Clinical depression
Melancholia
Manic-depressive illness, depressed type
Depressive episode

Codes depend on whether the episode is single or recurrent, and also on clinical severity.

ICD-10CM CODES

F32.9	Depressive episode, unspecified
F33.0	Recurrent depressive episode, current episode mild
F33.1	Recurrent depressive disorder, current episode moderate
F33.2	Recurrent depressive disorder, current episode severe without psychotic symptoms
F33.3	Recurrent depressive disorder, current episode severe with psychotic symptoms
F33.4	Recurrent depressive disorder, currently in remission
F33.9	Recurrent depressive disorder, unspecified

DSM-5 CODES

296.21	Single episode
296.22	Single episode, moderate
296.23	Single episode, severe
296.24	Single episode, with psychotic features
296.31	Recurrent, mild
296.32	Recurrent, moderate
296.33	Recurrent severe
296.34	Recurrent, with psychotic features

EPIDEMIOLOGY & DEMOGRAPHICS

LIFETIME RISK (IN U.S.): 10% of men, 20% of women

PREVALENCE (IN U.S.): Point prevalence in a community sample is 3% of men, 4.5% to 9.3% of women, and 1% of children. Prevalence of 20% to 40% in patients with comorbid medical conditions.

PREDOMINANT SEX: Female/male ratio 2:1

PREDOMINANT AGE: 25 to 44 yr; 5% of adolescents

PEAK INCIDENCE: 30 to 40 yr; 13% of postpartum women

GENETICS:

- Clear evidence of familial predominance.
- Prevalence is 2 to 3 times greater among first-degree relatives.
- Concordance among monozygotic twins approximately 50%.
- Several studies have documented associations between various genes and increased risk for major depressive disorder (MDD), but there remains no established pattern of inheritance.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical evaluation facilitated by organizing the major symptoms into four hallmarks: (1) Depressed mood, (2) anhedonia, (3) physical symptoms (sleep disturbance, appetite problem, fatigue, psychomotor changes), and (4) psychological symptoms (difficulty concentrating or indecisiveness, guilt or worthlessness, and suicidal ideation).
- A stressful life event, typically a serious loss, may trigger a depressive episode. DSM-5 recommends that clinical judgment be used to determine if depression in the context of a loss should be diagnosed as a major depressive episode.
- Patients often present with somatic complaints such as pain, fatigue, insomnia, dizziness, headache, or gastrointestinal problems. Somatic complaints may be reported more frequently among certain ethnic groups than depressed mood, increasing risk for underdetection in these groups.
- Comorbid psychiatric disorders are often present. Anxiety disorders are the most common comorbid conditions.
- May be associated with mood-congruent delusional thinking (paranoid and melancholic themes).
- May be associated with active or passive suicidal ideation.
- Serious misconduct may appear in adolescents.
- May be underdiagnosed in elderly patients, with signs and symptoms attributed to normal aging.
- May be underdiagnosed in medically ill patients, with signs and symptoms attributed to medical illness or considered appropriate reaction to medical condition.

ETIOLOGY

- A heterogeneous group of disorders probably arising from various etiologies.
- Genetic and environmental experiences, and their interaction, each contribute.
- Significant psychosocial stressors, including loss and history of childhood abuse or adversity, often trigger depression, particularly for first episodes.
- Numerous biologic correlates have been identified, though none is considered causative or diagnostic. Genes that influence the production and reuptake of serotonin, norepinephrine, dopamine, and glutamate, as well as nerve cell growth in brain regions underlying memory and emotional processing, are of greatest interest. Abnormalities in brain regions underlying executive functioning, emotion regulation, and reward processing, as well as irregularities in functional connectivity have been identified. Irregularities in cortisol responding and inflammation also may play a role.
- Cognitive risk factors include a pessimistic style of explaining negative events, a tendency to ruminate, and biases in processing emotional information and events.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Anxiety disorders (e.g., social phobia, posttraumatic stress disorder [PTSD], obsessive compulsive disorder), substance abuse, and personality disorders often present with depressive symptoms.
- Important to determine if a depressive episode is part of major depression or part of bipolar disorder.
- Important to distinguish from adjustment disorder. Depression in the context of a stressful life event is diagnosed as major depressive disorder if the symptom criteria are met and adjustment disorder if the symptom criteria are not met. There is no evidence that medication is effective for adjustment disorder.
- Approximately 10% to 15% of depression caused by general medical illnesses, such as Alzheimer disease, Parkinson disease, stroke, end-stage renal failure, cardiac disease, HIV infection, and cancer.
- Some medical conditions present as depression (e.g., hypothyroidism, hyperthyroidism, pancreatic cancer, or neurosyphilis).
- Premenstrual dysphoric disorder.
- In elderly, depression often coexists with dementia.

WORKUP

- Careful medical history is required.
- Physical examination reveals no specific diagnostic signs of depression.
- Mental status examination.
- Self-report scales can assist in screening.
- Commonly used validated screening tools include the 15-item Geriatric Depression Scale in the elderly and the Patient Health Questionnaire (PHQ)-2 and PHQ-9. The PHQ-2 has a 97% sensitivity and 67% specificity in adults. If it is positive for depression, the PHQ-9 should be administered. The PHQ-9 has a 61% sensitivity and 94% specificity for depression in adults.

LABORATORY TESTS

- Research is underway to identify biomarkers that may be useful in diagnosis, but as of yet no laboratory studies are diagnostic.
- The following can assist in ruling out other confounding issues:
  1. Routine blood chemistry evaluation
  2. CBC with differential
  3. Thyroid function studies
  4. Vitamin B_{12} levels

IMAGING STUDIES

With unusual presentations (e.g., associated with new-onset severe headache, focal neurologic signs, a cognitive or sensory disturbance), the following may be performed:

- Electroencephalogram (EEG) (diffuse slowing indicates metabolic encephalopathy)
- Anatomic brain imaging (CT scan or MRI)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Good evidence that cognitive-behavioral therapy is as effective as antidepressant medication in achieving significant reduction or remission (Table 1).
- Problem solving and interpersonal psychotherapies are comparably efficacious.
- "New wave" cognitive-behavioral therapies (e.g., acceptance and commitment therapy, mindfulness-based cognitive-behavioral therapy [CBT]) have demonstrated efficacy in numerous studies. It is unclear as of yet whether new-wave versus traditional behavioral therapies differ in mechanisms of action. Individuals not responding adequately to traditional behavioral therapies may benefit.
- Growing evidence indicates that Internet-based CBT and brief therapy interventions integrated into primary care to expand access to therapy are efficacious, with some studies finding comparable efficacy to standard length interventions, but further research is needed.
- By 12 wk or earlier, psychotherapy and medication approaches are equally effective.
- Augmentation of standard depression treatment with CBT to address insomnia (CBT-I) was found to significantly improve response rates.
- Official treatment guidelines recommend that medication be used as the first-line treatment for patients with severe depression, although some studies have found equal efficacy of medication and psychotherapy in the treatment of severe depression.
- Evidence, although mixed, indicates that combined psychotherapy and medication may be more effective than either treatment alone. Various types of evidence-based psychotherapy or augmentation with psychotherapy, including CBT and mindfulness-based behavioral therapy, appear to reduce the risk for future recurrences compared to medication alone in some but not all studies, particularly when medication is discontinued after symptomatic remission.
- Factors, including history of childhood maltreatment, presence of precipitant stressful life events, family psychiatric history, the presence of anhedonia, and depression severity, may affect treatment response and risk of recurrence. Numerous genetic and neurobiologic variables that predict treatment response have been identified, particularly in combination with one another or with clinical characteristics. However, as of yet there are no universally accepted markers that can aid clinicians in matching individuals to particular medications or interventions.

ACUTE GENERAL Rx

- Concurrent medical or psychiatric illnesses, history of prior response, cost, patient preference, and side effects should be considered when selecting initial treatment.
- Antidepressants are helpful in approximately 60% to 70% of cases, though sustained remission rates are lower.
- Selective serotonin reuptake inhibitors (SSRIs) generally are first line. According to the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) trial, approximately 30% achieve remission with the first prescribed medication after 3 mo of treatment. Another 25% to 30% respond to treatment but do not achieve remission. Treatment-refractory patients should be switched to another SSRI or to another class of medication, offered adjunctive medication such as bupropion, or referred for evidence-based counseling. Approximately 25% more patients will achieve remission with this secondary intervention.
- Response to antidepressants for many patients is seen as early as 2 wk, and among patients showing little to no response, the odds of later response decrease the longer patients remain unimproved. Conversely, rapid response to treatment predicted improved outcomes in multiple studies.
- To date no benefit of combining antidepressants as first-line treatment. Also no clear advantage has been identified for switching medications within vs. across different classes, or to switching vs. augmentation. The Veterans Affairs (VA) Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) trial found that switching to the antipsychotic aripiprazole resulted in statistically significant, though modest, improvement in remission rates compared with switching or augmenting with an antidepressant, although greater side effects resulted. More research is needed.
- Therapy should be continued for 4 to 9 mo after the full remission of symptoms.
- Electroconvulsive therapy is the most effective means available for the treatment of severe, refractory depression. Transcranial magnetic stimulation has also shown evidence of efficacy though the magnitude of effects is more variable. To date electroconvulsive therapy has shown superior efficacy; research is under way to investigate mechanisms to increase the efficacy of transcranial magnetic stimulation (TMS).
- Antipsychotic medication should be added for psychotic depression. Antipsychotic medication has also been shown to be helpful in augmenting antidepressants for nonpsychotic depression, and it may be beneficial for individuals with mixed features, although more research is needed.
- Ketamine IV has been found to be rapidly effective in treatment-resistant and suicidal depression. Recently intranasal esketamine (Spravato) has been approved for use in treatment-resistant depression. Further research is needed to determine whether positive effects are maintained, because effectiveness appears to fade without repeated use.

CHRONIC Rx

Long-term treatment, in some cases lifelong, is recommended for multiple depressive episodes, an episode duration longer than 2 yr, a severe episode or significant suicidality, or a strong family history of severe depression or bipolar disorder.

DISPOSITION

- Major depression is often a relapsing and remitting illness.
- Physical symptoms may predict a favorable response to biologic intervention in some but not all studies.
- Additional episodes experienced by >50% after one episode, with each additional episode linked to increased risk for subsequent episodes.
- Without treatment, episodes last an average of 6 to 12 mo; risk of recurrence higher without treatment.
- For many depressed individuals, subthreshold residual symptoms are present between episodes and define the majority of an individual's course of depression. Such symptoms may lead to impairment and warrant prolonged treatment.
- Anxious distress, as defined by the DSM-5 specifier, was found in one recent study to predict greater clinical severity and functional impairment, above and beyond comorbid anxiety disorder diagnoses.

TABLE 1 Treatments of Depression

Name of Psychotherapy	Approach
Cognitive psychotherapy	Identify and correct negativistic patterns of thinking.
Interpersonal psychotherapy	Identify and work through role transitions or interpersonal losses, conflicts, or deficits.
Problem-solving therapy	Identify and prioritize situational problems; plan and implement strategies to deal with top-priority problems.
Psychodynamic psychotherapy	Use therapeutic relationship to maximize use of the healthiest defense mechanisms and coping strategies.

From Goldman L et al: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

REFERRAL

- If treatment refractory
- If patient suicidal or psychotic
- For suspected bipolar depression

PEARLS & CONSIDERATIONS

COMMENTS

- All threats of suicide should be taken very seriously. Clinicians can use the mnemonic SAL: Is the method specific? Is it available? Is it lethal?
- Rule out bipolar affective disorder before initiating antidepressant medication. Screening scales for bipolar disorder can be helpful in primary care settings to identify patients at increased risk for bipolar disorder, although unclear benefit in mental health settings.
- Many patients and families reluctant to acknowledge depression because of stigma.
- A two-question screener is as effective as longer instruments. A positive answer to either question warrants a full assessment.
  1. Over the past 2 weeks, have you ever felt down, depressed, or hopeless?
  2. Over the past 2 weeks, have you felt little interest or pleasure in doing things?
- Depression screening programs without treatment programs are unlikely to improve depression outcomes.
- Strict monitoring of patients who initiate antidepressant therapy is necessary both for safety and to ensure optimal treatment. Use of self-report scales to measure symptom severity is helpful in monitoring outcome and may result in improved outcomes.
- St. John's wort *(Hypericum perforatum)* is sold as a dietary supplement in the United States and is used for depression in the community. It is not consistently effective and should not be used in combination with antidepressants given the possibility of severe serotonin-related side effects.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Depression (Patient Information)
Bipolar Disorder (Related Key Topic)

AUTHORS: **Mark Zimmerman, MD,** and **Catherine D'Avanzato, PhD**

SUGGESTED READING

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De Quervain Tenosynovitis PTG

BASIC INFORMATION

DEFINITION

De Quervain tenosynovitis is a tenosynovitis of the wrist's first dorsal extensor compartment, containing the abductor pollicis longus (APL) and extensor pollicis brevis (EPB) tendons.

SYNONYMS

Stenosing tenosynovitis of the radial styloid process
Stenosing tenovaginitis of the first dorsal compartment
Radial styloid tenosynovitis
Tenosynovitis of radial styloid
De Quervain disease
De Quervain stenosing tenosynovitis
De Quervain tendinitis
Washerwoman sprain/strain
Tendinosis
Styloid tenovaginitis

ICD-10CM CODES

M65.4	Radial styloid tenosynovitis [de Quervain]
M65.9	Synovitis and tenosynovitis, unspecified
M65.849	Other synovitis and tenosynovitis, unspecified hand

EPIDEMIOLOGY & DEMOGRAPHICS

- More common in women than in men (10:1)
- Usually occurs between the ages of 30 and 50
- May be associated with systemic inflammatory diseases (rheumatoid arthritis)
- Often seen in new mothers or day care providers due to holding the babies with an extended and abducted thumb
- Seen more frequently in certain occupations involving repetitive wrist motion

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain over the styloid process of the radius with grasping and resisted thumb abduction
- Tenderness with palpation over the radial styloid and first dorsal extensor compartment
- Pain may radiate up to the volar aspect of the wrist or to the thumb
- Swelling on the radial styloid
- Positive Finkelstein test (Fig. E1)
- Crepitance
- Rarely, numbness of dorsum of thumb
- Absence of local heat on examination

ETIOLOGY

- Repetitive use or overuse of the hand and thumb involving pinching with the thumb while moving wrist in radial and ulnar directions (e.g., typing, writing, nailing, golfing, fly-fishing)
- Acute trauma to the first dorsal extensor compartment
- Anatomic abnormality or variation
- Increased volume states or hormonal causes, such as occurring during pregnancy

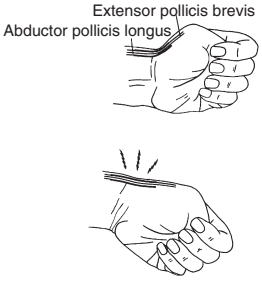

FIG. E1 Finkelstein test is positive in de Quervain stenosing synovitis. Ulnar flexion of the wrist produces pain over the dorsal compartment containing the extensor pollicis brevis and abductor pollicis longus.

DIAGNOSIS

- The diagnosis of de Quervain tenosynovitis is based on the clinical triad of:
  1. Tenderness over the radial styloid
  2. Pain over the first dorsal extensor compartment on resisted thumb abduction or extension
  3. Pain on ulnar movement of the wrist with the thumb adducted and flexed (Finkelstein test; see Fig. E1)
- Consideration can be given to injecting 1.5 ml of 1% Xylocaine into the tenosynovial sac, and if all three physical signs resolve, the diagnosis is confirmed, allowing for differentiation from carpometacarpal (CMC) osteoarthritis (OA)
- Finkelstein maneuver can also be present in first CMC joint OA

DIFFERENTIAL DIAGNOSIS

- Carpal tunnel syndrome
- Radiocarpal arthritis, thumb carpometacarpal arthritis
- Gout
- Infiltrative tenosynovitis
- Compression neuropathy (e.g., superficial branch of the radial nerve "bracelet syndrome")
- Ganglion cysts
- Infection (e.g., tuberculosis, bacterial)
- Radial styloid fracture

IMAGING STUDIES

- Imaging of the wrist and thumb is not necessary unless fracture or arthritis is suspected.
- Radiographs (three views) of the wrist should be obtained if fracture is suspected.
- Magnetic resonance imaging is helpful in selected cases. Tenosynovitis is seen as fluid signal on T2-weighted sequences within the tendon sheath as well as surrounding soft tissue edema with loss of adjacent fat planes (Fig. E2). Tendinosis represents a more advanced overuse injury manifested as an

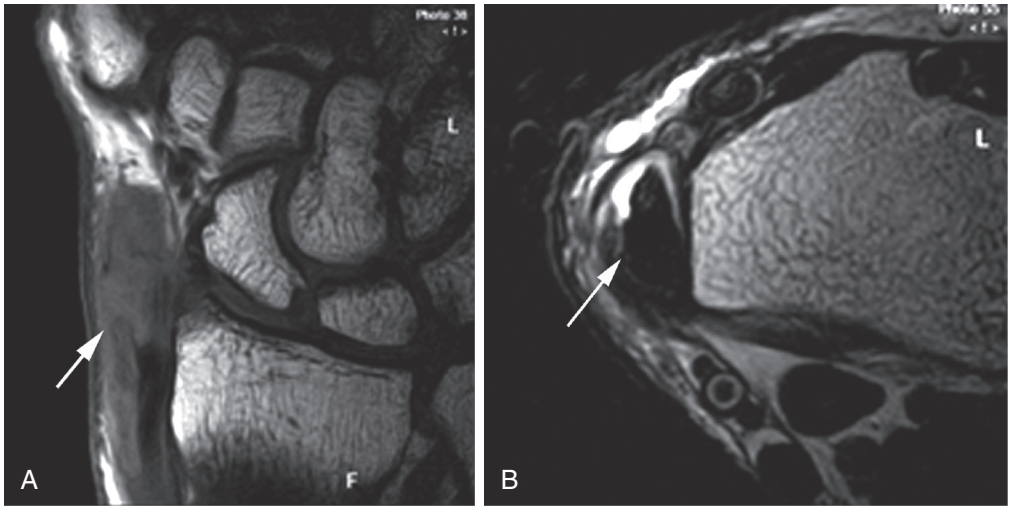

FIG. E2 De Quervain tenosynovitis. Coronal **(A)** and axial **(B)** T1-weighted MR images demonstrate thickening and synovial enlarged sheath of the first extensor compartment tendons *(arrows)*. (From Pope TL, et al.: *Musculoskeletal imaging*, ed 2, Philadelphia, 2015, Elsevier.)

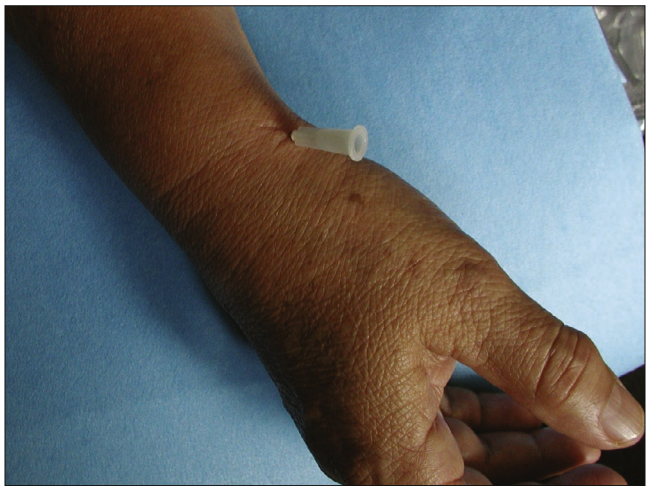

FIG. E3 Injection for right de Quervain tenosynovitis. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

enlarged tendon with internal increased signal intensity. Increased signal intensity within the tendon substance as an isolated sign is unreliable for de Quervain disease. Stenosing tenosynovitis appears as an intermediate–signal-intensity ring surrounding the tendons in both T1- and T2-weighted images.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoiding repetitive movements of hand or thumb
- Thumb spica splint
- Icing (4 to 6 times a day for 15 min)
- Physiotherapy

ACUTE GENERAL Rx

- Corticosteroid injection using 20 to 40 mg triamcinolone acetonide and 1% Xylocaine (Fig. E3) is often diagnostic and therapeutic
- Oral NSAIDs (ibuprofen 800 mg tid or naproxen 500 mg bid)
- Topical NSAIDs (Voltaren gel)

CHRONIC Rx

- Once signs of active inflammation have resolved after 3 to 4 wk, gentle stretching exercises involving abductor and extensor tendons usually help recovery.
- Maximum trial of three corticosteroid injections at minimum 3-mo intervals (one every 3 mo or more).
- Surgical intervention is generally reserved for those patients not responding to above treatments.
- Surgery includes first dorsal extensor compartment and subcompartment releases with or without tenosynovectomy.

DISPOSITION

- ~82% of patients have initial relief of symptoms with corticosteroid injection.
- ~52% of patients remain symptom-free at 12 mo after corticosteroid injection.
- ~73% of patients report successful results after two corticosteroid injections.
- Rarely, steroid injection can lead to infection, skin hypopigmentation, fat atrophy, and tendon rupture.
- Diabetics may experience mild temporary hyperglycemia after corticosteroid injection.
- Accidental injection of the corticosteroid in the subcutaneous tissue instead of the sheath of the extensor compartment should be avoided to prevent fat and dermal atrophy.
- If left untreated, can lead to fibrosis and decrease in mobility (stenosing tenosynovitis).
- Surgical resolution of symptoms achieved in 90% of referred cases.
- Complications of surgery include:
  1. Superficial branch of the radial nerve injury
  2. Paresthesia (10%)
  3. Neuroma formation
  4. Hypertrophic or painful scar
  5. Chronic regional pain syndrome
- Recovery rates with early treatment are at least 80% after 6 wk but <40% after 4 yr.

PEARLS & CONSIDERATIONS

- Steroid injection is generally recommended after failure of 2 to 6 wk of conservative treatment.
- Pain relief usually noted within 48 hours, with patient becoming asymptomatic 1 to 2 wk after corticosteroid injection.
- If no improvement 6 wk after second corticosteroid injection, consider referral to an orthopedic hand surgeon.
- Condition can recur if triggering activity continues.

RELATED CONTENT

De Quervain Tenosynovitis (Patient Information)

AUTHOR: **Daphne Scaramangas-Plumley, MD**

SUGGESTED READINGS

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Pope TL, Bloem HL et al: *Musculoskeletal imaging*, ed 2, Elsevier, 2015.

Dermatitis Herpetiformis ALG

BASIC INFORMATION

DEFINITION

Dermatitis herpetiformis (DH) is an autoimmune blistering disease that is considered to be a cutaneous manifestation of celiac disease (CD). It is associated with gluten-sensitive enteropathy in nearly all cases, although only 20% of patients have gastrointestinal symptoms. 15% to 25% of patients with CD will have DH.

SYNONYMS

DH
Duhring disease

ICD-10CM CODE
L13.0 Dermatitis herpetiformis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.): 11 cases per 100,000 persons per yr; prevalence for CD is one in 133 adults
PREDOMINANT SEX: Male predominance (2:1); however, female predominance in children
PREDOMINANT AGE: Fourth decade of life, but can occur at any age
PREDOMINANT RACE: Most common in Caucasians of Northern European ancestry
GENETICS: Both CD and DH have a strong genetic component. 10% to 15% of patients with DH have a first-degree relative with either DH or CD. Specific HLA genes (involved in processing gliadin antigen in genetically susceptible individuals) have also been shown to predispose to developing DH (HLA-DQ2 in 90%, DQ8 in the remaining 10%). However, less than 50% of genetic predisposition is attributed to HLA genes.

PHYSICAL FINDINGS & CLINICIAL PRESENTATION

- Classically, the lesions of DH are small, grouped, "herpetiform" vesicles that are distributed symmetrically on extensor surfaces (elbows, knees [Fig. E1], scalp, back, and buttocks). However, due to intense pruritus and scratching, pinpoint erosions and excoriations in the above distribution are often the most prominent findings on examination, with intact vesicles rarely seen.
- Spontaneous improvement with cyclic exacerbations is common.
- Celiac-type enamel defects to permanent teeth, oral vesicles, or palmoplantar purpura have been reported as potential associated findings.

PATHOGENESIS

CD and DH are both autoimmune-mediated by immunoglobulin A (IgA) class autoantibodies. Dietary gluten is central to the pathogenesis in both. In genetically predisposed individuals, it is hypothesized that the gluten by-product, gliadin, complexes with tissue transglutaminase (tTG) in the gut, binding as an antigen to HLA-DQ2 on T cells, creating an immune response that results in anti-tTG IgA antibodies (i.e., antiendomysial antibodies) in the blood. tTG cross-reacts with epidermal TG (eTG). The blood of CD patients with and without skin disease is found to have both skin and gut anti-TG IgA antibodies. Yet, it is thought that the high-affinity IgA against eTG form complexes that are responsible for DH. The deposition of IgA-eTG complexes in the papillary dermis triggers an immunologic cascade resulting in neutrophil recruitment and complement activation.

DIAGNOSIS

Physical examination and routine histopathology are often suggestive of DH; however, direct immunofluorescence (DIF) of a perilesional skin biopsy has pathognomonic findings and is the gold standard for diagnosis. Fig. 2 describes an approach to the patient with suspected dermatitis herpetiformis.

DIFFERENTIAL DIAGNOSIS

- Clinically and histologically, the differential diagnosis includes:
  1. Linear IgA dermatosis
  2. Bullous pemphigoid
  3. Bullous lupus

  These diagnoses can be differentiated by DIF on perilesional skin biopsy.
- Other clinical diagnoses to consider:
  1. Scabies (check for interdigital burrows and involvement of genitalia)
  2. Arthropod bite (papular urticaria over exposed areas)
  3. Eczematous dermatitis (ill-defined, weeping erythematous plaques)
  4. Herpes simplex or zoster infection (painful, not symmetric)
  5. Generalized pruritus (no blister history)

WORKUP AND LABORATORY TESTS

- Evaluation for gastrointestinal symptoms, family history of DH or CD, and pruritus should be sought in patients with suspected DH.
- **Lesional skin biopsy:** Will demonstrate a neutrophil-rich subepidermal bulla and rule out many conditions.
- **DIF of normal-appearing perilesional skin biopsy:** Will demonstrate pathognomonic IgA deposits localized to the dermal papillae and dermal-epidermal junction in a granular pattern.
- Serology (enzyme-linked immunosorbent assay [ELISA]) for IgA tissue transglutaminase, ELISA for IgA epidermal transglutaminase, if available, and indirect immunofluorescence for IgA endomysial antibodies (total IgA) can be used to aid in the diagnosis of DH in cases where the DIF is negative or equivocal, or for monitoring disease activity response to treatment. Although these circulating antibodies in the blood exist, there is a high false-positive rate for antitissue TG and for antiendomysial antibodies (one third of DH patients are negative for antiendomysial antibodies), and their absence does not exclude the diagnosis. Also, IgA-deficient DH patients may also have negative serologic results. Those with the presence of circulating antibodies will have a reduction in levels in response to treatment adherence.

TREATMENT

A gluten-free diet (GFD) and dapsone are considered first-line therapy and are often started in conjunction.

- GFD improves symptoms of both GI and skin disease, with GI responding quicker (skin responds after 2 mo). A retrospective study showed remission (2 yr without symptoms) in 12%.
- Dapsone results in improvement of skin manifestations within days but does not treat GI manifestations. Dapsone is typically tapered over time, while lifelong gluten avoidance is often necessary.
- One study demonstrated GFD alone was comparable to GFD plus dapsone in the treatment of DH; hence GFD is an essential component in the treatment of DH.

NONPHARMACOLOGIC THERAPY

- First line: GFD:
  1. Avoid barley, rye, wheat (can consume rice, corn, and oats).
  2. Consultation with a dietitian is recommended.
  3. Most patients need to follow diet indefinitely; however, cases of spontaneous remission have been reported.
- Second line: Elemental diet (controversial):
  1. Can consider elemental diet (avoidance of whole proteins) in those patients who do not adequately respond to a strict GFD; however, data are limited.

ACUTE GENERAL Rx

- First line: Dapsone:
  1. Initial dose 25 to 50 mg PO daily with gradual increase to an average maintenance dose of 0.5 to 1 mg/kg daily (often maintenance dose of 100 mg daily).
  2. Clinical monitoring weekly is recommended to optimize dose (optimal dose is when 1 to 2 new lesions/wk).
  3. Caution: Dapsone may produce hemolysis (especially if G6PD deficiency), agranulocytosis, methemoglobinemia, systemic drug hypersensitivity reaction (DRESS), and a peripheral neuropathy.
  4. Baseline labs: CBC, LFTs, G6PD levels. After the initiation of therapy, monitor CBC every wk ×1 mo, then every other wk ×2 mo, monthly ×3 mo, then every 3 to 4 mo. Monitor LFTs every 3 to 4 mo.
- Second-line alternatives:
  1. Sulfapyridine (500 to 1500 mg/day, compounded medication) or sulfasalazine (500 to 1000 mg bid) may be substituted in cases of dapsone intolerance or in the rare case that neuropathy develops.
  2. Case reports of efficacy using topical dapsone 5% twice daily in patients who do not tolerate oral dapsone; also report-

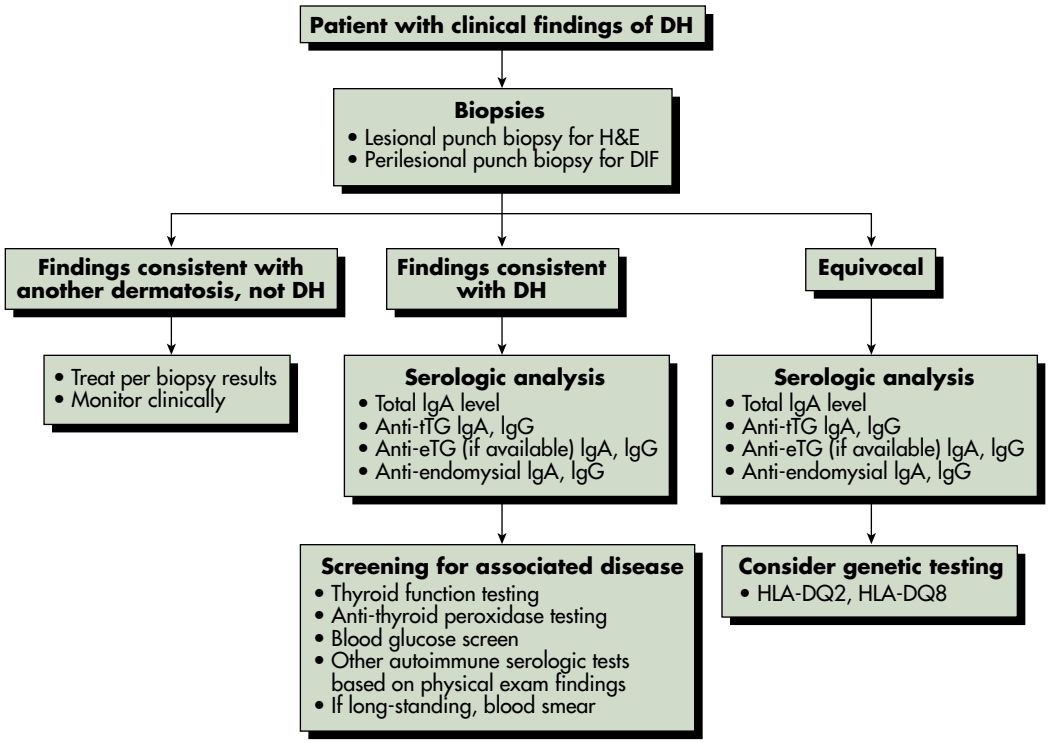

FIG. 2 Approach to the patient with suspected dermatitis herpetiformis. *DH,* Dermatitis herpetiformis; *DIF,* direct immunofluorescence; *eTG,* epidermal transglutaminase; *H&E,* hematoxylin and eosin; *HLA-DQ2,* histocompatibility locus antigen haplotype DQ2; *HLA-DQ8,* histocompatibility locus antigen haplotype DQ8; *Ig,* immunoglobulin; *tIG,* tetanus immune globulin. (From Bolotin D, Petronic-Rosic V: Dermatitis herpetiformis: part II. Diagnosis, management, and prognosis, *J Am Acad Dermatol* 64:1027-1033, 2011.)

ed to be efficacious as an adjuvant to oral dapsone.
3. Uncontrolled studies and case reports have suggested efficacy with tetracyclines, nicotinamide, cyclosporine, colchicine, and heparin.

- Symptomatic relief for pruritus:
1. Potent and superpotent topical corticosteroids (atrophy with prolonged use, limit to 14 days per mo), nonsedating antihistamines twice daily, sedating antihistamines at bedtime, mentholated lotion

CHRONIC Rx

- As DH is considered to represent the cutaneous manifestations of CD, lifelong avoidance of gluten is typically recommended. Information about educational resources, such as national and local support groups, should be provided (www.celiac.org).
- Patients with DH and CD have an increased risk of developing Hashimoto thyroiditis (50% with thyroid disease), non-Hodgkin lymphoma, and GI lymphomas. An increased incidence of other autoimmune disorders (type 1 diabetes mellitus, pernicious anemia, Addison disease, vitiligo, systemic lupus erythematosus, rheumatoid arthritis, and Sjögren syndrome) and osteoporosis have also been reported.
1. Screening for thyroid disease (TSH, antithyroid peroxidase antibody titers) is typically recommended.
2. Screening for autoimmune connective tissue diseases should be considered if there are suspicious signs or symptoms.
3. Routine screening for GI lymphomas is controversial.

REFERRAL

- Dermatologist for skin biopsy and management of cutaneous disease
- Gastroenterologist for evaluation of CD
- Nutritionist to educate patients about gluten-free diet
- National support groups (www.celiac.org) and local support groups

PEARLS & CONSIDERATIONS

- Classic areas involved are those that are exposed if in a "fetal position."
- Lesions may be worsened by iodides and certain NSAIDs; systemic steroids ineffective.
- Location of biopsies is IMPORTANT: False-negative DIF can result if biopsies are taken from lesional skin (should be taken from normal-appearing skin adjacent to lesion) as diagnostic IgA deposits are usually destroyed by the blistering process.
- GFD results in reduced IgA in skin on DIF (with eventual disappearance) and reduced antiendomysial antibodies in the blood. Hence, serologies (e.g., antiendomysial antibodies) can be used to monitor degree of compliance to dietary gluten restriction.
- Some studies have suggested a possible protective effect of GFD against intestinal lymphoma. First-degree relatives do not appear to be at increased risk for GI or systemic lymphomas in the absence of DH or CD.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Celiac Disease (Related Key Topic)

AUTHOR: **Lisa K. Pappas-Taffer, MD**

FIG. E1 Dermatitis herpetiformis. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Elsevier.)

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Burbidge T, Haber RM: Topical dapsone 5% gel as an effective therapy in dermatitis herpetiformis, *J Cutan Med Surg* 20:600-601, 2016.

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Salmi TT: Dermatitis herpetiformis, *Clin Exp Dermatol* 44(7):728-731, 2019.

Diabetes Insipidus (ALG) (PTG)

BASIC INFORMATION

DEFINITION

Diabetes insipidus (DI) is a disorder involving insufficient production and secretion of arginine vasopressin (AVP), also known as antidiuretic hormone (ADH). Decreased sensitivity to AVP also results in polyuria of hypotonic urine. The former condition is known as central DI (CDI), and the latter is referred to as nephrogenic DI (NDI). The main presentation of DI is hypernatremia from the loss of large amounts of hypotonic urine.

ICD-10CM CODE
E23.2 Diabetes insipidus

EPIDEMIOLOGY & DEMOGRAPHICS

GENETICS: The annual incidence of DI is 3 in 100,000. CDI usually manifests between the ages of 10 and 20 yr, with no sex predilection. NDI can begin at any age. During childhood, the most common cause is attributed to a vasopressin receptor-2 mutation, which is an X-linked mutation in the AVP receptor-2 gene. Less common hereditary forms of nephrogenic DI involve mutations in the aquaporin-2 water channel gene that affect the AVP-sensitive water channel and that may be autosomal dominant or recessive. The most common cause of CDI is idiopathic and likely related to autoimmune disorders.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The physical findings and clinical manifestations are generally not evident until AVP secretion capacity is <20% of normal.

- Unexplained nocturia (often the first manifestation of DI)
- Polyuria
- Polydipsia
- Neurologic manifestations (seizures, headaches, visual field defects)
- Symptoms of dehydration

ETIOLOGY

Central DI

- Idiopathic: Most common cause of CDI (destruction of AVP-secreting cells) likely due to an autoimmune mechanism.
- Hereditary (familial neurohypophyseal): Multiple genetic causes have been identified. An autosomal dominant form affects neurophysin II, a carrier protein for vasopressin. Wolfram syndrome involves an autosomal recessive form of DI that may be accompanied by childhood-onset diabetes mellitus, optic atrophy, and deafness (DIDMOAD).
- Malignancy: Neoplasms of the brain or pituitary fossa. They may be primary, as with craniopharyngiomas, or secondary to metastatic diseases, such as leukemia, lymphoma, breast cancer, or lung cancer.
- Hypoxic encephalopathy.
- Infiltrative disease: Histiocytosis, sarcoidosis, granulomatosis with polyangiitis, or tuberculosis.
- Other: Intraventricular hemorrhage, aneurysms, meningitis, postencephalitis complication, multiple sclerosis, Guillain-Barré syndrome, IgG4-related disease, and lymphocytic hypophysitis.

Nephrogenic diabetes insipidus:

- Familial: X-linked (~90%), autosomal dominant and recessive (<10%)
- Toxic (drugs): Lithium via downregulation of aquaporin-2 water channel production. Other medications: Aminoglycosides, antivirals (foscarnet, didanosine), amphotericin B, demeclocycline, ifosfamide, and methoxyflurane
- Metabolic: Hypercalcemia and hypokalemia. Both conditions are reversible after correction of the respective metabolic abnormality
- Renal disorders: Medullary interstitial diseases resulting in hypoxia (e.g., sickle cell disease) and infiltration (e.g., sarcoidosis) lead to loss of the corticomedullary concentration gradient with inability to produce an appropriately concentrated urine
- Other: Urinary tract infection, Sjögren syndrome, pyelonephritis, nephronophthisis, polycystic disease, postobstructive, and low-protein diets (protein malnutrition), which prevents development of a maximal corticomedullary concentration gradient, with inability to produce an appropriately concentrated urine

Gestational DI due to a circulating vasopressinase.

- A third-trimester or early postpartum disorder of accelerated vasopressin degradation from elevated placental production and circulation of a cysteine aminopeptidase. Placental abruption or retained necrotic placenta may produce postpartum DI following release of large amounts of vasopressinase into the bloodstream. This disorder may occur after extensive tissue injury (e.g., large abscesses). Gestational DI demonstrates a salutary response to the administration of the synthetic AVP analogue, 1-desamino-8-D-arginine vasopressin (dDAVP), resistant to placental enzyme degradation.

TABLE E1 Differential Diagnosis of Nephrogenic Diabetes Insipidus

Hereditary causes	Aquaporin-2 mutations
	Arginine vasopressin receptor mutations
Drug-related causes	
V_2 -receptor antagonists	Lithium
	Demeclocycline
Antibiotic agents	Ofloxacin
	Rifampin
	Netilmicin
	Antifungal agent amphotericin B
Antiviral agents	
	Cidofovir
	Foscarnet
	Indinavir
	Tenofovir
Antineoplastic agents	
	Cyclophosphamide
	Ifosfamide
	Methotrexate
Other drugs	
	Radiocontrast agents
	Colchicine
	Ethanol
	Orlistat
Metabolic	Hypokalemia
Other conditions	Hypercalcemia
	Sjögren syndrome
	Sickle cell disease
	Release of urinary tract obstruction
	Amyloidosis
	Pregnancy

From Ronco C et al: *Critical care nephrology*, ed 3, Philadelphia, 2019, Elsevier.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diabetes mellitus, nephropathies
- Primary polydipsia, medications (e.g., chlorpromazine)
- Osmotic diuresis, including glucose, mannitol, anticholinergics
- Primary polydipsia and electrolyte disturbances

WORKUP

- The diagnostic workup is aimed at demonstrating polyuria due to an inability to appropriately concentrate urine and determine whether the polyuria results from decreased vasopressin availability or insensitivity to its action. This may be carried out by a water restriction test (Table E2) when the plasma sodium is <145 mmol/L or plasma osmolality is <295 mOsm/kg of water (Table E3):
  1. The diagnostic workup is aimed at demonstrating that polyuria is caused by an inability to concentrate urine and determining whether the problem results from reduced circulating vasopressin or insensitivity to this hormone. A water restriction test may be conducted if the plasma sodium is <145 mmol/L and plasma osmolality is <295 mOsm/kg of water (Table E3).
  2. After baseline measurement of body weight, vasopressin, plasma sodium, and urine and plasma osmolalities, the patient is deprived of fluids under medical supervision.
  3. Plasma and urine osmolalities are monitored every 2 hr.
  4. Test is generally terminated when plasma osmolality is >295 mOsm/kg of water or body weight decreases by >3.5% of baseline body weight.
  5. DI is confirmed if plasma osmolality is >295 mOsm/kg of water and urine osmolality is <500 mOsm/kg of water.

TABLE E2 Fluid Deprivation Test for the Diagnosis of Diabetes Insipidus

Procedure

1. Initiation of the deprivation period depends on the severity of the DI; in routine cases, the patient is made NPO after dinner. In patients with more severe polyuria and polydipsia, this interval may be not be tolerable. If this is the case, water deprivation should proceed in the early morning (e.g., 6:00 AM).
2. Obtain plasma and urine osmolalities, plasma electrolytes, and plasma AVP levels at the start of the test.
3. Measure urine volume and osmolality hourly or with each voided urine.
4. Stop the test when body weight decreases by ≥3%, orthostatic blood pressure changes appear, the urine osmolality plateaus (i.e., <10% change over two or three consecutive measurements), or the plasma sodium concentration increases to >145 mmol/L.
5. Obtain plasma and urine osmolalities, plasma electrolytes, and plasma AVP levels at the end of the test, when the plasma osmolality is elevated, preferably >300 mOsm/kg of water.
6. If plasma Na^+ <146 mmol/L or plasma osmolality <300 mOsm/kg of water when the test is stopped, then consider a short infusion of hypertonic saline (3% NaCl at a rate of 0.1 ml/kg/min for 1 to 2 hours) to reach these end points.
7. If hypertonic saline infusion is not required to achieve hyperosmolality, administer AVP (5 U) or desmopressin (dDAVP; 1 μg) subcutaneously and continue following urine osmolality and volume for an additional 2 hours.

Interpretation

1. An unequivocal urine concentration after AVP or dDAVP (>50% increase) indicates central diabetes insipidus (CDI); an unequivocal absence of urine concentration (<10%) strongly suggests nephrogenic DI (NDI) or primary polydipsia (PP).
2. Differentiating between NDI and PP, as well as cases in which the increase in urine osmolality after AVP or dDAVP administration is more equivocal (e.g., 10%-50%), is best done using the relation between plasma AVP levels and plasma osmolality obtained at the end of the dehydration period and/or hypertonic saline infusion and the relation between plasma AVP levels and urine osmolality determined under basal conditions.

From Skorecki K et al: *Brenner & Rector's the kidney*, ed 10, Philadelphia, 2016, Elsevier.

TABLE E3 Water Deprivation Test

Diagnosis	U_{Osm} with Water Deprivation (mOsm/kg of Water)	Plasma AVP after Dehydration	Increase in U_{Osm} with Exogenous AVP
Normal	>800	>2 pg/ml	Little or none
Complete central diabetes insipidus	<300	Undetectable	Substantial
Partial central diabetes insipidus	300-800	<1.5 pg/ml	>10% of U_{Osm} after water deprivation
Nephrogenic diabetes insipidus	<300-500	>5 pg/ml	Little or none
Primary polydipsia	>500	<5 pg/ml	Little or none

AVP, Arginine vasopressin.
Adapted from Lanese D, Teitelbaum I: Hypernatremia. In Jacobson HR et al [eds]: *The principles and practice of nephrology*, Philadelphia, 1998, Mosby.

6. To distinguish NDI from CDI, the change in urine osmolality is measured after a vasopressin dose of 5 units. A significant increase (>50%) in urine osmolality after administration of vasopressin is consistent with the diagnosis of CDI.
7. Copeptin is a surrogate of ADH and is cleaved from the C-terminal segment of the arginine vasopressin prohormone. A recent study in 2018 evaluated direct measurement of hypertonic saline-stimulated plasma copeptin and was found to be more accurate than the indirect water deprivation test.
8. A diagnostic algorithm for diabetes insipidus is displayed in Fig. E1.

LABORATORY TESTS

- Decreased urinary specific gravity (≤1.005).
- Baseline plasma osmolality >295 mOsm/kg of water suggests CDI. Levels <270 mOsm/kg of water favor compulsive water drinking.
- Hypernatremia, increased plasma osmolality, hypercalcemia, and hypokalemia from water-induced potassium losses.

IMAGING STUDIES

Pituitary MRI if CDI is confirmed

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient education regarding control of fluid balance, low-solute diet, and prevention of dehydration with adequate fluid intake or intravenous D_5W solution
- Daily weight

ACUTE GENERAL Rx

Therapy varies with degree and type of DI (Table E4). Initial therapy is directed toward alleviating nocturia with bedtime desmopressin followed by partial control of diuresis. Care must be given to avoid an abrupt onset of hyponatremia with potential cerebral edema by careful dDAVP titration.

- Central diabetes insipidus:
  1. Desmopressin (dDAVP): Intranasal route is preferred due to better bioavailability. First dose is 5 to 10 mcg intranasally or 0.1 to 0.2 mg by mouth at bedtime. Daytime dosing is dictated by the response to the evening dose. Typical maintenance doses are 10 to 20 mcg intranasally once or twice daily. The oral form has poor absorption from the gut with approximately 5% absorbed, with relative potency of just 5% to 10% of the intranasal formulation. A 0.1 mg tablet is equivalent to 2.5 to 5 mcg of the nasal spray. A sublingual form is available in 60, 120, and 240 mcg with improved bioavailability of approximately 60%. If intranasal or oral desmopressin cannot be administered, an injectable subcutaneous form can be given with typical doses of 1 mcg administered every 12 hours.
  2. Chlorpropamide enhances the effects of AVP or desmopressin. The efficacy of this agent is limited by the risk of inducing hypoglycemia.
  3. In mild cases of central DI, polyuria may be controlled with hydrochlorothiazide at daily doses of 25 to 50 mg.
  4. Carbamazepine at doses of 100 to 300 mg twice daily enhances tubular responsiveness to AVP, but is a rarely employed treatment.
  5. Clofibrate administered at 500 mg every 6 hours can lower urine output by enhancing AVP release.
  6. NSAIDs inhibit the synthesis of prostaglandins and antagonize AVP. Potential nephrotoxic effects of NSAIDs must be balanced against efficacy of this adjunctive therapy.
- Nephrogenic diabetes insipidus:
  1. Remove the underlying cause. In the case of prolonged lithium therapy, NDI may be permanent despite withdrawal of the offending agent.
  2. Amiloride can antagonize lithium-induced NDI.
  3. A low-sodium diet and thiazide diuretic represent additive therapies for NDI.

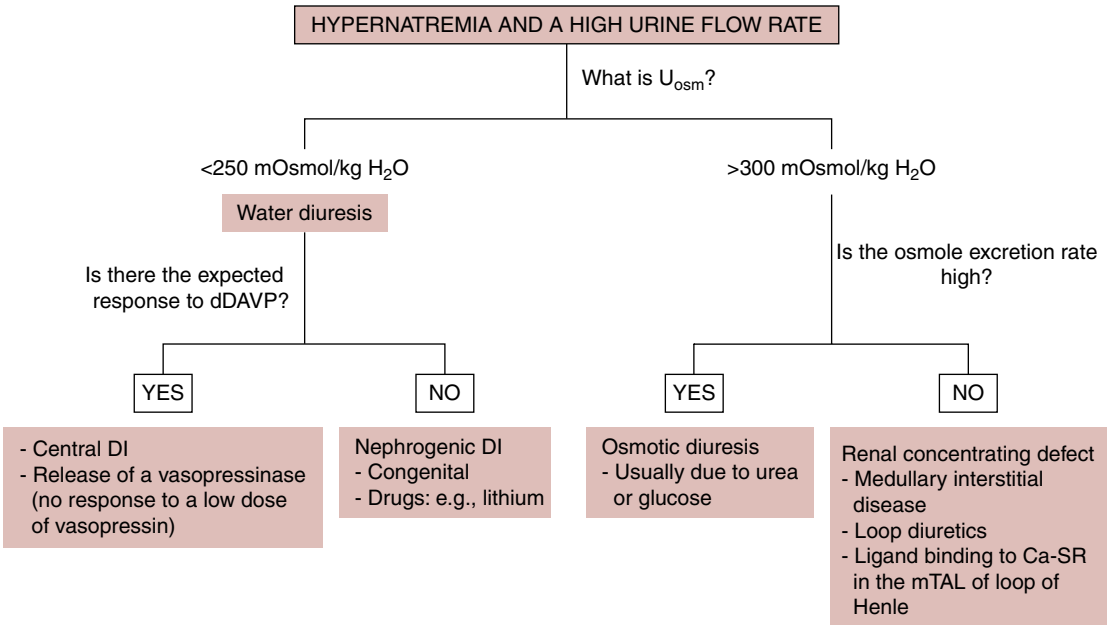

FIG. E1 Diagnostic flowchart for diabetes insipidus. The first step is to determine whether the water loss is caused by a water diuresis or an osmotic diuresis, or whether there is a renal concentrating defect. The principal tools are assessment of the U_{0sm} and calculation of the osmole excretion rate. In a patient with central diabetes insipidus (DI) or a water diuresis caused by the release of a vasopressinase, U_{0sm} should rise to a value that is higher than the P_{0sm} in response to the administration of desamino-D-arginine vasopressin (dDAVP). If not, nephrogenic DI is the basis of the water diuresis. A value of the U_{0sm} that is higher than 300 mOsm/kg of water suggests that the basis of hypernatremia is an osmotic diuresis if the osmole excretion rate is appreciably higher than 1000 mOsm/day or a renal concentrating defect if the osmole excretion rate is not high. Examples of ligand binding to the calcium sensing receptor (Ca-SR) in the medullary thick ascending limb (mTAL) of the loop of Henle include calcium ions in a patient with hypercalcemia and cationic drugs (e.g., gentamicin, cisplatin). (From Kamel et al: *Fluid, electrolyte, and acid-base physiology: a problem-based approach*, ed 5, Philadelphia, 2017, Elsevier, p 325.)

TABLE E4 Treatments for Diabetes Insipidus

Type of Diabetes Insipidus	Drug	Dose
Complete central	dDAVP	10-20 g intranasally every 12-24 hr
Partial central	Aqueous vasopressin	5-10 U subcutaneously every 4-6 hr
	Chlorpropamide	250-500 mg/day
	Clofibrate	500 mg 3-4× daily
	Carbamazepine	400-600 mg/day
Nephrogenic	Thiazide diuretics	5 mg/day
	NSAIDs	
	Amiloride (for lithium-related disease)	
Gestational	dDAVP	As for complete central

dDAVP, Desmopressin; *NSAIDs,* nonsteroidal anti-inflammatory drugs.
Adapted from Lanese D, Teitelbaum I: Hypernatremia. In Jacobson HR et al [eds]: *The principles and practice of nephrology*, Philadelphia, 1998, Mosby.

CHRONIC Rx

Patients should be aware of the danger of dehydration and need for liberal water intake.

REFERRAL

Endocrinology consultation for diagnostic testing

PEARLS & CONSIDERATIONS

COMMENTS

- Suspect DI when urine osmolality is lower than plasma osmolality in the setting of hypernatremia.
- Patients should be instructed to wear a medical identification tag or bracelet identifying their medical illness.
- In CDI, dDAVP represents the standard-of-care and is safe with prolonged use.
- The treatment of NDI is more complicated than CDI. Consultation with a specialist is always recommended in this setting.

PATIENT & FAMILY EDUCATION

- Materials regarding nephrogenic diabetes insipidus can be obtained from the Nephrogenic Diabetes Insipidus foundation at http://www.ndif.org.
- Material regarding central diabetes insipidus can be obtained at https://rarediseases.org/rare-diseases/central-diabetes-insipidus/.

RELATED CONTENT

Hypernatremia (Related Key Topic)
Diabetes Insipidus (Patient Information)

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SUGGESTED READING

Fenske W et al: A copeptin-based approach in the diagnosis of diabetes insipidus, *N Engl J Med* 379:428-439, 2018.

Kamel S, Halperin M: *Fluid, electrolyte, and acid base physiology: a problem based approach*, Philadelphia, 2016, Elsevier, P 325.

Qureshi S et al: Diabetes insipidus: celebrating a century of vasopressin therapy, *Endocrinology* 155(12):4605-4621, 2014.

Saborio P, Tipton GA, Chan JC: Diabetes insipidus, *Pediatr Rev* 21(4):122-129, 2000.

Sands JM, Bichet DG: Nephrogenic diabetes insipidus, *Ann Intern Med* 144:186, 2006.

BASIC INFORMATION

DEFINITION

- Diabetes mellitus (DM) refers to a syndrome of hyperglycemia resulting from many different causes (see "Etiology"). It is broadly classified into type 1 (T1DM) and type 2 DM (T2DM). The terms *insulin-dependent* and *non–insulin-dependent* diabetes are obsolete because when a person with type 2 diabetes needs insulin, he or she remains labeled as type 2 and is not reclassified as type 1. Immune-mediated type 1 DM (type 1A) represents 5% to 10% of newly diagnosed diabetics. Table 1 provides a general comparison of the two types of DM. One difference is that type 1 has usually complete or near-total knockout of insulin reserves mediated solely by immunogenic responses from carriers of certain genotypes, whereas type 2 is of polygenetic origin and may have patients who may start with hyperinsulinemia but have insulin resistance and through environmental factors such as diet and sedentary lifestyle leads to an imbalance between glucagon and insulin levels, resulting in combination of causes toward hyperglycemia.
- Some type 1 diabetics also may exhibit high levels of glucagon and not all type 1 diabetics have complete islet cell destruction.
- The classification of diabetes also includes:
  1. **LADA**: Latent autoimmune diabetes of adult onset (sometimes called type 1.5 DM). These individuals are typically not insulin dependent initially and are often misclassified as having type 2 DM.
  2. **MODY**: Maturity onset diabetes of youth. These have various genetic expressions and can be classified into various subtypes:
     a. MODY 1, 2, 3, 4, and 5 (with 3 being most prevalent: 70% incidence with HNF-1-alpha [12q24] genetic expression)
     b. MODY 7 and 8 (rare)
  3. Ketosis-prone diabetes: Relapsing/remitting beta cell function with slow deterioration over time. It presents with ketoacidosis requiring insulin, then regains beta cell function and patient is able to discontinue insulin. This form is most common under age 40, in those of African or Afro-Caribbean origin, and in obese or overweight patients.
  4. Secondary diabetes:
     a. Pancreatic disease or resection (e.g., cystic fibrosis)
     b. Chronic excessive corticosteroid exposure or Cushing syndrome
     c. Glucagonoma
     d. Acromegaly
     e. Other rare genetic disorders (e.g., mitochondrial diabetes MELAS syndrome)
  5. Rare autoimmune (e.g., type A and B insulin resistance syndrome)
- Diabetes mellitus can be diagnosed by the following tests:
  1. A hemoglobin A_{1c} (HbA_{1c}) value ≥6.5% is considered diagnostic for diabetes. This test is preferred because of ease of administration and reliability.
  2. A fasting plasma glucose (FPG) ≥126 mg/dl, which should be confirmed with repeat testing on a different day. Fasting is defined as no caloric intake for at least 8 hr.
  3. An oral glucose tolerance test (OGTT) with a plasma glucose ≥200 mg/dl 2 hr after a 75 g (100 g for pregnant women) glucose load.
  4. Symptoms of hyperglycemia and a casual (random) plasma glucose ≥200 mg/dl are also indicative of DM. Classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss. At the time of diagnosis as a diabetic, B-cell function is at 25% to 30%.
- Individuals with glucose levels higher than normal but not high enough to meet the criteria for diagnosis of DM are considered to have "prediabetes," the diagnosis of which is made as follows:
  1. A fasting plasma glucose 100 to 125 mg/dl; this is referred to as ***impaired fasting glucose.***
  2. After OGTT, a 2-hr plasma glucose of 140 to 199; this is referred to as ***impaired glucose tolerance.*** Patients with impaired glucose tolerance or prediabetes have B-cell function at 50% of normal.
  3. A hemoglobin A_{1c} value of 5.7% to 6.4%.
- Table 2 describes diagnostic categories for DM and at-risk states.

SYNONYMS

IDDM (insulin-dependent diabetes mellitus)
NIDDM (non–insulin-dependent diabetes mellitus)
Type 1 diabetes mellitus (insulin-dependent diabetes mellitus)
Type 2 diabetes mellitus (non–insulin-dependent diabetes mellitus)
LADA (latent autoimmune diabetes of adult)
MODY (mature onset diabetes of youth)

ICD-10CM CODES

E11.5	Type 2 diabetes mellitus with peripheral circulatory complications
E11.7	Type 2 diabetes mellitus with multiple complications
E11.8	Type 2 diabetes mellitus with unspecified complications
E11.9	Type 2 diabetes mellitus without complications
E10.69	Type 1 diabetes mellitus with other specified complication
E10.8	Type 1 diabetes mellitus with unspecified complications
E10.9	Type 1 diabetes mellitus without complications
E11.69	Type 2 diabetes mellitus with other specified complication
E11.8	Type 2 diabetes mellitus with unspecified complications
E11.9	Type 2 diabetes mellitus without complications

TABLE 1 General Comparison of the Two Types of Diabetes Mellitus

	Type 1	Type 2
Previous terminology	Insulin-dependent diabetes mellitus (IDDM), type I, juvenile-onset diabetes	Non–insulin-dependent diabetes mellitus, type II, adult-onset diabetes
Age of onset	Usually <30 yr, particularly childhood and adolescence, but any age	Usually >40 yr, but any age
Genetic predisposition	Moderate; environmental factors required for expression; 35%-50% concordance in monozygotic twins; several candidate genes proposed	Strong; 60%-90% concordance in monozygotic twins; many candidate genes proposed; some genes identified in maturity-onset diabetes of the young
Human leukocyte antigen associations	Linkage to DQA and DQB, influenced by DRB (3 and 4) (DR2 protective)	None known
Other associations	Autoimmune; Graves disease, Hashimoto thyroiditis, vitiligo, Addison disease, pernicious anemia	Heterogeneous group, ongoing subclassification based on identification of specific pathogenic processes and genetic defects
Precipitating and risk factors	Largely unknown; microbial, chemical, dietary, other	Age, obesity (central), sedentary lifestyle, previous gestational diabetes
Findings at diagnosis	85%-90% of patients have one and usually more autoantibodies to ICA512/IA-2/IA-2b, GAD_{65}, insulin (IAA)	Possibly complications (microvascular and macrovascular) caused by significant preceding asymptomatic period
Endogenous insulin levels	Low or absent	Usually present (relative deficiency), early hyperinsulinemia
Insulin resistance	Only with hyperglycemia	Mostly present
Prolonged fast	Hyperglycemia, ketoacidosis	Euglycemia
Stress, withdrawal of insulin	Ketoacidosis	Nonketotic hyperglycemia, occasionally ketoacidosis

GAD, Glutamic acid decarboxylase; *IA-2/IA-2b,* tyrosine phosphatases; *IAA,* insulin autoantibodies; *ICA,* islet cell antibody; *ICA512,* islet cell autoantigen 512 (fragment of IA-2).
From Andreoli TE (ed): *Cecil essentials of medicine,* ed 6, Philadelphia, 2005, WB Saunders.

TABLE 2 Diagnostic Categories*: Diabetes Mellitus and At-Risk States

Fasting Plasma Glucose Level	2-Hour (75-g) OGTT Result		
	<140 mg/dl	**140-199 mg/dl**	**≥200 mg/dl**
<100 mg/dl	Normal	IGT†	DM
100-125 mg/dl	IFG†	IGT† *and* IFG†	DM
≥126 mg/dl	DM	DM	DM
HbA_{1C} Level	**<5.7%**	**5.7-6.4%**	**≥6.5%**
	Normal	High-risk†	DM

*These diagnostic categories are based on the combined fasting plasma glucose level and a 2-hour, 75-g oral glucose tolerance test (OGTT) result. Note that a confirmed random plasma glucose level of 200 mg/dl or higher in the appropriate clinical setting is diagnostic of diabetes and precludes the need for further testing.
†May be referred to as prediabetes.
DM, Diabetes mellitus; *IFG,* impaired fasting glucose; *IGT,* impaired glucose tolerance; *OGTT*, oral glucose tolerance test.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.

EPIDEMIOLOGY & DEMOGRAPHICS

- DM affects 9% to 10% of the U.S. population. Prevalence rates vary considerably by race/ethnicity. T1DM accounts for approximately 5% of diagnosed diabetes cases and is defined by the presence of one or more autoimmune markers. While incidence of diabetes in adolescents is mostly type 1, the rate of type 2 being diagnosed in adolescents has increased by 1.5 times in certain given areas. This seems to correlate with the epidemic of pediatric obesity.
- Incidence rate increases with age, varying from 2% in persons age 20 to 44 yr to 18% in persons 65 to 74 yr. T2DM can have a long presymptomatic phase, leading to a 4- to 7-yr delay in diagnosis. In the U.S. 1.2 million new cases of diabetes are diagnosed each yr, and 86 million have prediabetes. Currently, 30 million Americans have diabetes; with this current trend, it is predicted that by 2050 1 out of 3 Americans will be diabetic.
- Diabetes accounts for 8% of all legal blindness in the U.S. and is the leading cause of end-stage renal disease (ESRD). Approximately 40% of patients in a given dialysis center are diabetic.
- Patients with diabetes are 2 to 4 times more likely than nondiabetic patients to experience development of cardiovascular disease (CVD).

PHYSICAL FINDINGS & CLINCIAL PRESENTATION

- Physical examination varies with the presence of complications and may be normal in early stages.
- Diabetic retinopathy:
  1. Nonproliferative (background diabetic retinopathy):
     a. Initially: Microaneurysms, capillary dilation, waxy or hard exudates, dot and flame hemorrhages, arteriovenous shunts
     b. Advanced stage: Microinfarcts with cotton wool exudates, macular edema
  2. Proliferative retinopathy: Characterized by formation of new vessels, vitreous hemorrhages, fibrous scarring, and retinal detachment
- Cataracts and glaucoma occur with increased frequency in patients with diabetes.
- Diabetic macular edema: Swelling of the macula leading to loss of sharp vision in this part of the eye. People with this disorder usually already have retinopathy but may present separately as well.
- Diabetic neuropathy:
  1. Distal sensorimotor polyneuropathy:
     a. Symptoms include paresthesia, hyperesthesia, or burning pain involving bilateral distal extremities in a "stocking glove" distribution. This can progress to motor weakness and ataxia.
     b. Physical examination may reveal decreased pinprick sensation, decreased sensation to light touch, decreased vibration sense, and loss of proprioception. Motor disturbances such as decreased deep tendon reflexes and atrophy of interosseous muscles can also be seen.
  2. Autonomic neuropathy:
     a. GI disturbances: Esophageal motility abnormalities, gastroparesis, diarrhea (usually nocturnal):
        (1) Increased gastric emptying seen in type 2
        (2) Decreased gastric emptying seen in type 1
     b. Genitourinary (GU) disturbances: Neurogenic bladder (hesitancy, weak stream, and dribbling), impotence
     c. Cardiovascular (CV) disturbances: Orthostatic hypotension, tachycardia, decreased heart rate variability (HRV). Decreased heart rate variability is associated with increased cardiac mortality, independent of ejection fraction.
  3. Polyradiculopathy: Painful weakness and atrophy in the distribution of ≥1 contiguous nerve root.
  4. Mononeuropathy involving cranial nerves III, IV, or VI or peripheral nerves can also occur.
- Diabetic nephropathy: Pedal edema, pallor, weakness, uremic appearance
- Nephrotic syndrome: Proteinuria, hypertriglyceridemia, edema
- Nephritis: Progressive degeneration of nephrons focal glomerulosclerosis

Type IV renal tubular acidosis, hyperkalemic nephropathy, interstitial nephritis, causing hyporeninemic hypoaldosteronism. It is important to keep in mind that NSAIDs, ACE inhibitors, trimethoprim, and heparin can all reduce aldosterone and can cause or exacerbate the condition. 50% of patients on dialysis have diabetes as primary diagnosis; whereas glycemia is important to prevent nephropathy, the most significant contributing factor is hypertension.

- Foot ulcers: Occur in 15% of individuals with diabetes (annual incidence rate 2%) and are the leading causes of hospitalization; they are usually secondary to a combination of factors, including peripheral vascular insufficiency, repeated trauma (unrecognized because of sensory loss), and superimposed infection.
  1. Patient symptoms are usually less than would be expected from clinical findings, due to loss of sensation related to peripheral neuropathy.
  2. Comprehensive foot exams include visual inspection, assessment of pedal pulses, and assessment of protective sensation using a 10-g monofilament to test sensation.
  3. Prevention of foot ulcers in an individual with diabetes includes strict glucose control, patient education, prescription footwear, intensive podiatric care, and evaluation for surgical interventions.
  4. Foot examination should be done annually on all diabetics.
- Neuropathic arthropathy (Charcot joints): Bone or joint deformities from repeated trauma (secondary to peripheral neuropathy; Fig. E1).
- Necrobiosis lipoidica diabeticorum: Plaque-like reddened areas with a central area that fades to white-yellow, found on the anterior surfaces of the legs (Fig. E2); in these areas, the skin becomes very thin and can ulcerate easily.
- Other diabetic skin manifestations with diabetes include:
  1. Scleredema diabeticorum: Thickening of skin and epidermis giving skin a "leather-like texture"; typically affects type 2, mainly on upper back and neck.
  2. Dermatitis herpetiformis: Diffuse petechial rash associated with gluten insensitivity.
  3. Vitiligo: Associated with type 1 and type 2, and affects skin coloration due to autoimmune reaction to pigmentation (at times may be associated with adrenal insufficiency, especially in type 1 patients). Patients should use SPF 30 sunscreen to prevent sunburn.
  4. Acanthosis nigricans: Darkening of skin folds in neck and axilla, at times raised and velvety, thought to be associated with insulin resistance; other conditions such as Cushing and acromegaly can have this as well.
  5. Diabetic dermopathy: Appears as shiny round or oval lesions on thin skin of the lower extremity, also known as "shin

spots"; these are usually not painful and do not require treatment.
6. Eruptive xanthomatosis: Associated with uncontrolled blood sugars and extremely high triglycerides. There is a high risk for pancreatitis in patients with this finding; treatment is aimed at lowering blood sugars with insulin and fibrates.
7. Digital sclerosis: Skin on toes fingers and hands become waxy, thick, and tight, with joint stiffness; treatment is aimed at lowering blood sugars and encouraging use of lotions and moisturizers.
8. Bullosis diabeticorum: Rare disorder manifesting with blisters on hands, forearms, toes, and feet, usually painless. Lesions generally heal on their own.
9. Box 1 summarizes cutaneous associations with diabetes mellitus.

ETIOLOGY

IDIOPATHIC DIABETES: Type 1 DM: Results from autoimmune beta-cell destruction, usually leading to absolute insulin deficiency.
- Hereditary factors:
  1. Islet cell antibodies (found in 90% of patients within the first yr of diagnosis)
  2. Higher incidence of human leukocyte antigen (HLA) types DR3, DR4
  3. 50% concordance rate in identical twins
- Environmental factors: Viral infection (possibly coxsackievirus, mumps virus)

Type 2 DM: Results from insulin resistance and a progressive defect in insulin secretion.
- Hereditary factors: 90% concordance rate in identical twins
- Environmental factors: Obesity, sedentary lifestyle, high carbohydrate content in food

DIABETES SECONDARY TO OTHER FACTORS:
- Hormonal excess: Cushing syndrome, acromegaly, glucagonoma, pheochromocytoma
- Drugs: Glucocorticoids, diuretics, oral contraceptives
- Insulin receptor unavailability (with or without circulating antibodies)
- Pancreatic disease: Pancreatitis, pancreatectomy, hemochromatosis, cystic fibrosis
- Genetic syndromes: Maturity onset diabetes of the young (MODY, monogenetic diabetes accounting for 2% to 5% of diabetes), familial hyperlipidemias, myotonic dystrophy, lipoatrophy
- Gestational diabetes (GDM): Diabetes diagnosed during pregnancy that is due to pregnancy-related insulin resistance

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diabetes insipidus
- Stress hyperglycemia
- Diabetes secondary to hormonal excess, drugs, pancreatic disease

LABORATORY TESTS

- Diagnosis of DM is made on the basis of the following tests:
  1. Fasting glucose ≥126 mg/dl on two occasions.
  2. Non-FPG ≥200 mg/dl and symptoms of DM.
  3. OGTT (75 g glucose load for nonpregnant individuals) with 2-hr value >200 mg/dl.
  4. Glycosylated hemoglobin (HbA_{1c}) ≥6.5%. HbA_{1c} level reflects average glycemia over previous 3 mo or longer. In known diabetics, this test should be performed at least twice yearly in stable patients and more frequently when therapy changes or patients are not meeting glycemic goals. HbA_{1c} alone does not provide a measure of glycemic variability or hypoglycemia and is affected by the presence of hemoglobin variants, hemolysis, or blood loss.
- Measurement of autoantibodies glutamic acid decarboxylase (GAD65) and tyrosine phosphatase IA-2 are useful in suspected immune mediated type 1 DM (strong association).
- Screening for prediabetes and diabetes in asymptomatic patients (see Table 3):
  1. Should be considered in adults of any age who are overweight (body mass index [BMI] >25 kg/m^2) or obese (BMI >30) and who have one or more additional risk factors for diabetes.
  2. In those who are without these risk factors, testing should begin at age 45 yr.

BOX 1 Some Cutaneous Associations with Diabetes Mellitus

Established or Probable Association
- Necrobiosis lipoidica (NL) diabeticorum
- Diabetic dermopathy
- Diabetic bullae
- Acanthosis nigricans
- Acrochordons (skin tags)
- Scleredema diabeticorum
- Limited joint mobility and waxy skin syndrome
- Partial lipodystrophy
- Malignant otitis externa
- Neuropathic leg ulcers
- Perforating disorders
- Eruptive xanthomas
- Hemochromatosis
- Carotenemia
- Pruritus
- Xerosis and anhidrosis
- Yellow nails, koilonychia
- Increased susceptibility to infections:
  - *Candida albicans*
  - *Staphylococcus aureus*
  - Group A β-hemolytic streptococcus
  - *Pseudomonas aeruginosa*
  - Dermatophytes (tinea pedis, onychomycosis)
  - *Corynebacterium minutissimum* (erythrasma)

Possible Association
- Disseminated granuloma annulare
- Vitiligo

From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.

TABLE 3 Criteria for Diabetes Screening in Asymptomatic Individuals

1. Testing should be considered in all adults who are overweight (BMI >25 kg/m^2*) and have additional risk factors:
   1. Physical inactivity
   2. A first-degree relative with diabetes
   3. High-risk ethnic population (e.g., African American, Hispanic American, Native American, Asian American, Pacific Islander)
   4. Delivered a baby weighing more than 9 lb or diagnosed with gestational diabetes mellitus
   5. Systemic hypertension (blood pressure >140/90 mm Hg or on antihypertensive therapy)
   6. High-density lipoprotein cholesterol level <35 mg/dl or triglyceride level >250 mg/dl
   7. Polycystic ovary syndrome
   8. Hemoglobin A_{1c} ≥5.7%, impaired glucose tolerance or impaired fasting glucose on prior testing
   9. Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   10. History of cardiovascular disease
2. If none of the above criteria are present, screening for diabetes should begin at age 45 yr.
3. If the results are normal, screening should be repeated at least every 3 yr. Depending on initial results and risk status, more frequent testing may need to be considered.

*In some ethnic groups, such as Asians, at-risk body mass index (BMI) may be lower.

Modified from American Diabetes Association: Diagnosis and classification of diabetes mellitus, *Diabetes Care* 33(Suppl 1):S14, 2010; and from Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.

3. If screen is normal, repeat testing should be carried out at least at 3-yr intervals.
4. ADA recommends screening all Asian Americans with BMI 23 or higher every 2 yr.

- Detection and diagnosis of gestational diabetes mellitus (GDM):
  1. Screen for GDM using risk factor analysis and use of an OGTT. Pregnant women who are not known to have diabetes should be screened for gestational diabetes at 24 to 28 wks' gestation with a "1-step" strategy with 75 g oral glucose tolerance test or a "2-step" approach with a 50-g (nonfasting) screen followed by a 100-g oral glucose tolerance test for those who screen positive. A diagnosis of GDM is made if any of the following levels of plasma glucose are exceeded: ≥92 mg/dl (5.1 mmol/L) when fasting, ≥80 mg/dl (10 mmol/L) at 1 hour, or ≥153 mg/dl (8.5 mmol/L) at 2 h.
  2. Women with GDM should be screened for diabetes 6 to 12 wk postpartum and should be followed with subsequent screening for the development of diabetes or prediabetes at least every 3 yr. A woman who had GDM during pregnancy has 50% risk of developing diabetes later in life; this is dependent on ethnicity (e.g., Pima Indians, Hispanic, African American).
- Screening for diabetic nephropathy:
  1. Screening should be done at diagnosis and then yearly for type 2 diabetes and 5 yr after diagnosis then yearly in type 1 diabetes. 18% of type 1 DM may have early kidney changes, and future guidelines may change screening to 1 yr after diagnosis if poorly controlled then annually for both type 1 and type 2.
  2. Screening can be performed using an albumin:creatinine ratio (microalbumin) in a random spot urine collection or by measurement of a 24-hr urine collection for albumin and creatinine clearance. The urine albumin to creatinine ratio (ACR) is independently associated with mortality at all levels of estimated glomerular filtration rate (eGFR) in older adults with diabetes.
  3. The diagnosis of microalbuminuria (ACR 30-299 mg/24 hr) should be based on 2 to 3 elevated levels within a 3- to 6-mo period because there is a marked variability in day-to-day albumin excretion. Patients with overt macroalbuminuria (>300 mg albumin/24 hr or albumin:creatinine ratio >300) should be followed by urine protein:creatinine ratio.
- A fasting serum lipid panel, serum creatinine, and electrolytes should be obtained yearly on all adult patients with diabetes.
- Self-monitoring of blood glucose (SMBG) is crucial for assessing the effectiveness of the management plan. The frequency and timing of SMBG varies with the needs and goals of each patient. In most patients with type 1 DM and pregnant women taking insulin, SMBG is recommended at least 3 times/day. In patients with type 2 DM not on insulin, recommendations are unclear for SMBG, but testing once or twice/day is acceptable in most patients. Glycemic control is best evaluated when SMBG is combined with HbA_{1c} testing.
- Continuous glucose monitoring (CGM) is now starting to play a more prominent role in reducing the number of fingersticks. Dexcom CGM has been approved by FDA for use by patients to adjust insulin based on CGM readings.
- The use of insulin pump and CGM readings and computer software can adjust insulin automatically (known as the "artificial pancreas").
- CGM can also be used in patients with type 2 on multiple daily injections.
- Limitations of CGM are that it cannot predict accuracy of blood glucose when <70 mg/dl.
- Screening for thyroid dysfunction (TSH level), vitamin B_{12} deficiency, and celiac disease should be considered in type 1 diabetes due to the increased frequency of other autoimmune diseases in these individuals.
- Consider screening for autoimmune polyendocrine syndromes (APS-2):
  1. APS-2: Most commonly known as Schmidt syndrome, heterogeneous not linked to one gene (HDLA-DQ2, HDLA-DQ8, AND HLA-DR4). Patients can have IDDM, hyperthyroidism, other autoimmune conditions, B_{12} deficiency, and myasthenia.

Rx TREATMENT

- Type 1 diabetes requires immediate initiation of insulin therapy.
- In type 1 diabetes, intensive glycemic control (HbA_{1c} <7) has been shown in randomized controlled trials (RCT) to reduce the risk of microvascular (neuropathy, retinopathy, nephropathy) and macrovascular (cardiovascular events) complications.
- Type 2 DM: The ADA and European Association for the Study of Diabetes recommend lifestyle intervention (diet and exercise) and metformin initiation (unless contraindications exist such as serum creatinine levels ≥1.5 mg/dl in males or ≥1.4 mg/dl in females or patients ≥30 yr of age with reduced renal function as measured by creatinine clearance) at the time of diagnosis of type 2 diabetes. Therapy should then be augmented with additional agents (including early initiation of insulin therapy) to achieve adequate glycemic control.
- In type 2 diabetes, intensive glycemic control (HbA_{1c} <7) has been shown in RCT to reduce the risk of microvascular complications. While intensive glucose control reduced the risk of some CVD outcomes (such as nonfatal MI), it did not reduce the risk of cardiovascular death or all-cause mortality and increased the risk of severe hypoglycemia.
- Table 4 summarizes American College of Cardiology/American Heart Association (ACC/AHA) recommendations for primary prevention of CVD in patients with diabetes. Recommendations for secondary prevention of CVD are described in Table 5.
- It is important to remember that tight glycemic control may burden patients with complex treatment programs, hypoglycemia, weight gain, and costs. Clinicians should individualize HbA_{1c} targets so that they are reasonable and reflect patients' personal and clinical contexts and their informed values and preferences. A target HbA_{1c} <7 is reasonable for motivated new diabetic patients with long life expectancies, whereas less stringent controls (HbA_{1c} 7.5 or higher) may be reasonable in elderly patients with limited life expectancy and elevated risk of hypoglycemia. The American Geriatrics Society recommends a general goal for glycated hemoglobin in older adults of 7.5% to 8.0%. Higher HbA_{1c} targets (8% to 9%) are appropriate for older adults with multiple comorbidities, poor health, and limited life expectancy.[1]

NONPHARMACOLOGIC THERAPY

- Diet: The ADA does not recommend a special diet. However, newly diagnosed diabetics who are overweight or obese should be counseled to lose at least 5% of their body weight. Medical association therapy with a registered dietitian is recommended.
  1. Calories:
     a. The patient with diabetes can be started on 15 calories/lb of ideal body weight; this number can be increased to 20 calories/lb for an active person and 25 calories/lb if the patient does heavy physical labor.
     b. The calories should be distributed as 45% to 65% carbohydrates, <30% fat, with saturated fat limited to <7% of total calories, and 10% to 30% protein. Daily cholesterol intake should not exceed 300 mg.
     c. The emphasis should be on complex carbohydrates rather than simple and refined starches, and on polyunsaturated instead of saturated fats in a ratio of 2:1.
     d. The glycemic index compares the increase in blood sugar after the ingestion of simple sugars and complex carbohydrates with the increase that occurs after the absorption of glucose; equal amounts of starches do not give the same increase in plasma glucose (pasta equal in calories to a baked potato causes less of an increase than the potato); thus, it is helpful to know the glycemic index of a particular food product.
  2. Fiber: Insoluble fiber (bran, celery) and soluble globular fiber (pectin in fruit)

[1]Huang ES, Davis AM: Glycemic control in older adults with diabetes mellitus, *JAMA* 314:1509-1510, 2015.

TABLE 4 American College of Cardiology Foundation/American Heart Association Recommendations for Primary Prevention of Cardiovascular Disease in People with Diabetes

Lifestyle Management

Weight

Structured programs that emphasize lifestyle changes such as reduced fat (<30%-35% of daily energy) and total energy intake and increased regular physical activity, along with regular participant contact, can produce long-term weight loss on the order of 5% to 7% of starting weight, with improvement in BP.

For persons with elevated plasma triglycerides and reduced HDL-C, improved glycemic control, moderate weight loss (5%-7% of starting weight), dietary saturated fat restriction, increased physical activity, and modest replacement of dietary carbohydrate (5%-7%) by either monounsaturated or polyunsaturated fats may be beneficial.

Medical Nutrition Therapy

To achieve reductions in LDL-C:

Saturated fats should be less than 7% of energy intake.

Dietary cholesterol intake should be less than 200 mg/day. Intake of *trans* unsaturated fatty acids should be less than 1% of energy intake.

Total energy intake should be adjusted to achieve body weight goals.

Total dietary fat intake should be moderated (<30%-35% of total calories) and should consist mainly of monounsaturated or polyunsaturated fat.

Ample intake of dietary fiber (≥14 g/1000 calories consumed) may be of benefit.

If individuals choose to drink alcohol, daily intake should be limited to one drink for adult women and two drinks for adult men. One drink is defined as 12 ounces (oz) of beer, 4 oz of wine, or 1.5 oz of distilled spirits. Alcohol ingestion increases caloric intake and should be minimized when weight loss is the goal.

Individuals with elevated plasma triglyceride levels should limit intake of alcohol because it may exacerbate hypertriglyceridemia.

In both normotensive and hypertensive persons, a reduction in sodium intake may lower BP. The goal should be to reduce sodium intake to 1200-2300 mg/day (50-100 mmol/day), equivalent to 3000-6000 mg/day sodium chloride.

Physical Activity

To improve glycemic control, assist with weight loss or maintenance, and reduce risk for CVD, at least 150 min of moderate-intensity aerobic physical activity or at least 90 min of vigorous aerobic exercise per wk is recommended. The physical activity should be distributed over at least 3 days per wk, with no more than 2 consecutive days without physical activity.

For long-term maintenance of major weight loss, a larger amount of exercise (7 hours of moderate or vigorous aerobic physical activity per wk) may be helpful.

Blood Pressure

BP should be measured at every routine diabetes visit. Patients found to have SBP ≥130 mm Hg or DBP ≥80 mm Hg should have BP confirmed on a separate day.

Patients with diabetes should be treated to achieve SBP at least <140 mm Hg and DBP <90 mm Hg, and for patients who can tolerate without adverse symptoms, targets can be as low as SBP <130 mm Hg and DBP <80-85 mm Hg. Patients with SBP of 130-139 mm Hg or DBP of 80-89 mm Hg should initiate lifestyle modification alone (weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products) for a maximum of 3 mo. If, after these efforts, targets are not achieved, treatment with pharmacologic agents should be initiated.

Patients with hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg) should receive drug therapy in addition to lifestyle and behavioral therapy.

All patients with diabetes and hypertension should be treated with a regimen that includes either an ACE inhibitor, or if intolerant to an ACE inhibitor, an ARB. If one class is not tolerated, the other should be substituted. Other drug classes demonstrated to reduce CVD events in patients with diabetes—dihydropyridine calcium channel blockers, thiazide diuretics (chlorthalidone and indapamide), and beta-blockers—should be added, in listed order of preference, as needed to achieve BP targets.

If ACE inhibitors, ARBs, or diuretics are used, kidney function and serum potassium levels should be monitored within the first 3 mo. If BP is stable, follow-up could occur every 6 mo thereafter.

Multidrug therapy generally is required to achieve BP targets.

In elderly hypertensive patients, BP should be lowered gradually to avoid complications.

Orthostatic measurement of BP should be performed in people with diabetes and hypertension when clinically indicated.

Patients not achieving target BP despite multidrug therapy should be referred to a physician specializing in the care of patients with hypertension.

Lipids

In adult patients with diabetes, lipid levels should be measured at least annually and more often if needed to achieve goals. In adults with diabetes who are younger than 40 with low-risk lipid values (LDL-C <100 mg/dl, HDL-C >50 mg/dl, triglycerides <150 mg/dl), lipid assessments may be repeated every 2 yr.

Lifestyle modification deserves primary emphasis in all individuals with diabetes. Patients should focus on the reduction of saturated fat and cholesterol intake, weight loss (if indicated), and increases in dietary fiber and physical activity. These lifestyle changes have been shown to improve the lipid profile in patients with diabetes. In persons with diabetes who are older than 40 yr, without overt CVD, statin therapy should be considered for primary prevention with recommendation to use at least moderate-dose and ideally intense-dose statins, independent of baseline LDL-C levels. On maximally tolerated statin, the goal is an LDL-C level <100 mg/dl (2.6 mmol/L), and ideally <70 mg/dl (1.8 mmol/L) for those at highest CVD risk. If LDL-lowering drugs are used, a reduction of at least 50% in LDL-C levels should be obtained.

If baseline LDL-C is <100 mg/dl, statin therapy should be initiated based on risk factor assessment and clinical judgment. Major risk factors in this category include age, sex, race/ethnicity, cigarette smoking, hypertension (BP >140/90 mm Hg or use of antihypertensive medication), high total cholesterol and low HDL-C (<40 mg/dl), and family history of premature CHD (CHD in male first-degree relatives ≤55 yr of age; CHD in female first-degree relatives ≤65 yr of age).

In people with diabetes who are younger than 40, without overt CVD, but who are estimated to be at increased risk for CVD either by clinical judgment or by risk calculator, at least moderate-intensity statin therapy is recommended, with an LDL-C goal of <100 mg/dl.

Combination therapy with LDL-lowering drugs (e.g., statins, ezetimibe, PCSK9 inhibitors) and fibrates or niacin may be necessary to achieve lipid targets, but to date, only the addition of ezetimibe to statin therapy has proven incremental CV outcomes benefit.

Beyond the consensus of therapeutic lifestyle intervention, the ADA and AHA guidelines have evolved significantly over recent years, no longer recommending pharmacologic treatment of low HDL-C or high triglyceride levels, except for those with extremely high fasting triglyceride levels, to consider fish oil or a fibrate to mitigate pancreatitis risk.

Tobacco

All patients with diabetes should be asked about tobacco use status at every visit.

Every tobacco user should be advised to quit.

The tobacco user's willingness to quit should be assessed.

The patient can be assisted by counseling and by developing a plan to quit.

Follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and bupropion) should be incorporated as needed.

TABLE 4 American College of Cardiology Foundation/American Heart Association Recommendations for Primary Prevention of Cardiovascular Disease in People with Diabetes—cont'd

Antiplatelet Agents

The ADA and AHA recommend aspirin therapy (75-162 mg/day) for primary prevention in patients with diabetes at increased CV risk (e.g., estimated 10-yr risk >10%), including most age ≥50 yr who have additional risk factors (e.g., family history of CVD, hypertension, smoking, dyslipidemia, albuminuria). In contrast, the ESC/EASD guidelines discourage aspirin for primary prevention in patients with diabetes, except for those estimated to be at the very highest CV risk, in whom such use may be considered.

People with aspirin allergy, bleeding tendency, existing anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease are poor candidates for aspirin, especially for primary prevention. Other antiplatelet agents may be a reasonable alternative for patients with high risk.

Glycemic Control

The HbA_{1c} goal for most patients with diabetes in general is less than 7% in the absence of CVD, with higher targets such as 8% (or higher) endorsed for patients with moderate to severe CVD or other serious comorbidities.

Type 1 Diabetes Mellitus

At present, all of the recommendations listed above for patients with type 2 DM appear to be appropriate for those with type 1 DM as well.

ACE, Angiotensin-converting enzyme; *ADA,* American Diabetes Association; *AHA,* American Heart Association; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CHD,* coronary heart disease; *CV,* cardiovascular; *CVD,* cardiovascular disease; *DBP,* diastolic blood pressure; *DM,* diabetes mellitus; *EASD,* European Association for the Study of Diabetes; *ESC,* European Society of Cardiology; *HbA_{1c},* glycosylated hemoglobin; *HDL-C,* high-density lipoprotein cholesterol; *LDL-C,* low-density lipoprotein cholesterol; *SBP,* systolic blood pressure.

Data are from Fox CS et al: Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association, *Circulation* 132:691-718, 2015; Ryden L et al: ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. The Task Force on Diabetes, Pre-diabetes, and Cardiovascular Diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD), *Eur Heart J* 34:3035-3087, 2013; ADA Standards of Medical Care in Diabetes—2016: abridged for primary care providers, *Diabetes Care* 34:3-21, 2016; Inzucchi SE et al: Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach—update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes, *Diabetes Care* 38:140-149, 2013; and Stone NJ et al: 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *Circulation* 129(Suppl 2):S1-S45, 2014; in Zipes DP: *Braunwald's heart disease: a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 5 American College of Cardiology Foundation/American Heart Association Recommendations for Secondary Prevention of Cardiovascular Disease Specific to Patients with Diabetes

Class	Indication	Level of Evidence
I	Care for diabetes should be coordinated with the patient's primary care physician and/or endocrinologist.	C
	Lifestyle modifications including daily physical activity, weight management, blood pressure control, and LDL cholesterol management are recommended for all patients with diabetes.	B
	ACE inhibitors (or ARBs for those with ACE inhibitor intolerance) should be started and continued indefinitely in patients with diabetes, unless contraindicated.	A
	Use of aldosterone blockade in post-MI patients without significant kidney dysfunction or hyperkalemia is recommended in patients who are already receiving therapeutic doses of an ACE inhibitor and beta-blocker, who have a left ventricular ejection fraction ≤40% and diabetes.	A
IIa	Metformin is an effective first-line pharmacotherapy and can be useful if not contraindicated.	A
	Individualizing the intensity of blood glucose–lowering interventions based on the individual patient's risk for hypoglycemia during treatment is reasonable.	C
IIb	Initiation of pharmacotherapy interventions to achieve target HbA_{1c} may be reasonable.	A
	A target HbA_{1c} of ≤7% may be considered, whereas the ADA/EASD endorse a target ≥8% for those with moderate to severe CVD.	C
	Less stringent HbA_{1c} goals may be considered for other patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular complications, or extensive comorbidity, or those in whom the goal is difficult to attain despite intensive therapeutic interventions.	C

ACE, Angiotensin-converting enzyme; *ADA,* American Diabetes Association; *ARB,* angiotensin receptor blocker; *CVD,* cardiovascular disease; *EASD,* European Association for the Study of Diabetes; *HbA_{1c},* glycosylated hemoglobin; *LDL,* low-density lipoprotein; *MI,* myocardial infarction.

Data are from Fox CS et al: Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association, *Circulation* 132:691-718, 2015; Ryden L et al: ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. The Task Force on Diabetes, Pre-diabetes, and Cardiovascular Diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD), *Eur Heart J* 34:3035-3087, 2013; ADA Standards of Medical Care in Diabetes—2016: abridged for primary care providers, *Diabetes Care* 34:3-21, 2016; Inzucchi SE et al: Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach—update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 38:140-149, 2015; and Stone NJ et al: 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *Circulation* 129(Suppl 2):S1-S45, 2014; in Zipes DP: *Braunwald's heart disease: a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

delay glucose absorption and attenuate the postprandial serum glucose peak.
   a. They also appear to reduce the increased triglyceride level often present in patients with uncontrolled diabetes. A diet high in fiber should be emphasized (20 to 35 g/day of soluble and insoluble fiber).
   b. Diet programs: In 2015, a meta-analysis review of all research revealed that weight loss was equal no matter which diet program patients were involved in.
   c. However, the only data to show evidence-based prevention of diabetes in prediabetics was the "Mediterranean diet."
   d. The Mediterranean diet also showed a significant decrease in the percentage of established diabetics from needing insulin in the future and significant benefit in reducing cardiovascular events.
3. Other principles:
   a. Modest sodium restriction to 2400 to 3000 mg/day. If hypertension is present, restrict to <2400 mg/day; if nephropathy and hypertension are present, restrict to <2000 mg/day.
   b. Moderation of alcohol intake recommended (≤2 drinks/day in men, ≤1 drink/day in women).
   c. Nonnutritive artificial sweeteners are acceptable in moderate amounts.
      (1) However, it has been shown that artificial sweeteners may actually increase insulin resistance by affecting the action of insulin at receptor level.

- Exercise: Increases the cellular glucose uptake by increasing the number of

insulin receptors. The following points must be considered:

1. Exercise program must be individualized and built up slowly. Consider beginning with 15 min of low-impact aerobic exercise 3 times per wk and increasing the frequency and duration to 30 to 45 min of moderate aerobic activity (50% to 70% of maximum age predicted heart rate) to 3 to 5 days/wk.
   a. In the absence of contraindications, resistance training three times per wk should be encouraged.
2. Insulin is more rapidly absorbed when injected into a limb that is then exercised, and this can result in hypoglycemia.
3. Physical activity can result in hypoglycemia if medication dose or carbohydrate consumption is not modified. Ingestion of additional carbohydrates is recommended if pre-exercise glucose levels are <100 mg/dl.
4. Diabetes prevention program: Low-fat diet with exercise reduced diabetes by 58%. This encompassed diet of 1200 to 1800 kcal/day <30% from fat, exercise unsupervised and supervised, akin to brisk walking >150 min/wk of moderately intensity physical activity.

- Weight loss: To ideal body weight if the patient is overweight. Recent trials have shown that although weight loss has many positive health benefits for people with type 2 DM, such as slower decline in mobility, it does not reduce the number of cardiovascular events.
- Screening for nephropathy, neuropathy, and retinopathy: Annual serum creatinine and urine albumin excretion; initial comprehensive eye examination and at least annually thereafter.
- Diabetes self-management education: Could also address psychosocial issues.
- Self-monitoring of blood glucose should occur three to four times per day for patients using multiple insulin injections or on insulin pump therapy.
- Perform HbA_{1c} at least two times a yr in patients who are meeting treatment goals and who have stable glycemic control.
  1. HbA_{1c} quarterly in patients whose therapy has changed or who are not meeting glycemic goals.
  2. The HbA_{1c} goal for nonpregnant adults in general is <7%.
  3. In the elderly, those with comorbidities, or those at risk for complications from hypoglycemia, a more moderate glycemic target (HbA_{1c} 7-8) may be appropriate.
  4. In elderly patients (>80 yr of age) with average life expectancy of 5 yr, a target HbA_{1c} <8.0 is reasonable. In patients >80 yr with comorbidities and life expectancy of 3 yr, a target HbA_{1c} of <9.0 may be appropriate.

GENERAL Rx

- Type 1 DM: Lifelong insulin therapy is required for persons with type 1 DM. It should consist of basal coverage, prandial coverage, and supplemental insulin for correction of hyperglycemia. Initial total insulin dosing ranges from 0.4 to 1.0 U/kg/day, 50% of which is basal insulin and 50% prandial insulin.
- Type 2 DM: When the previous measures fail to normalize the serum glucose, oral hypoglycemic agents should be added to the regimen in T2DM. Treatment options in patient with type 2 diabetes should be tailored to try to target core diabetic defects and apply therapies that lower HbA_{1c} in a weight-neutral or weight-lowering fashion if possible; of course, cost of therapies needs to be considered as well.
- **Metformin:** The primary mechanism of metformin is to decrease hepatic glucose production and improve insulin sensitivity. Because metformin does not produce hypoglycemia when used as a monotherapy, it is preferred initially for most patients. Metformin reduces mean HbA_{1c} level by 1.1%. It is contraindicated in patients with severe renal insufficiency with an estimated glomerular filtrate rate <30 ml/min, serum creatinine level of 1.5 per dl or greater in men or 1.4 per dl or greater in women, heart failure, or other clinical states of hypoperfusion, and in patients with significant liver disease. Starting metformin in patients with GFR between 30 and 45 ml/min is also not recommended. Renal dosing of metformin is preferred, based on GFR levels rather than creatinine levels. When metformin alone does not achieve the desired A_{1C} goal, the choice of a second drug is dictated by the comorbidities or cost. For example, an SLGT2 inhibitor is preferred in patients with heart failure or cardiovascular disease.
  1. When the HbA_{1c} level is 9% or greater, initial dual-regimen combination therapy should be considered. It is important to consider that some drug classes provide benefit in cardiovascular and renal outcomes that may be independent of glucose control. Clinicians should consider adding either a GLP-1 agonist or an SGLT-2 inhibitor to metformin to improve glycemic control when a dual regimen is considered.
- **GLP-1 agonists:** Exenatide, dulaglutide, semaglutide, lixisenatide, and liraglutide are glucagon-like peptide-1 (GLP-1) agonists. These injectable agents are incretin mimetics that stimulate release of insulin from pancreatic beta cells and can be used as adjunctive therapy for patients with T2DM. GLP-1 agonists are not indicated in T1DM and are contraindicated in patients with severe renal impairment. Advantages are weight loss, no hypoglycemia when used as monotherapy and reduced incidence of cardiovascular events and nephropathy. Side effects include injection site reactions, GI side effects (nausea, diarrhea, vomiting), increased risk of pancreatitis and thyroid C-cell carcinoma. Cost is a barrier to their use.
- **Sodium-glucose co-transporter 2 ($SGLT_2$) inhibitors** (e.g., canagliflozin, dapagliflozin, empagliflozin) are useful for oral treatment of type 2 DM. By inhibiting $SGLT_2$, these medications decrease glucose reabsorption, increase urinary glucose excretion, and lower blood glucose levels (decrease HbA_{1c} by 0.7%). Empagliflozin has been shown to slow progression of renal disease in type 2 diabetics with CVD. Potential advantages include weight loss (up to 3.5% of BMI) and mild lowering of blood pressure (2 to 4 mm Hg). Side effects include increased risk of genital mycotic infections, UTIs, and volume depletion. Renal function should be evaluated before starting $SGLT_2$ inhibitors and periodically thereafter. Temporary discontinuation of these meds is recommended in cases of reduced oral intake or fluid loss. Higher cost and limited drug formulary availability are limiting factors.
- **DPP-4 inhibitors:** Sitagliptin, saxagliptin, vildagliptin, alogliptin, and linagliptin inhibit the enzyme DPP-4, responsible for inactivation and degradation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These drugs, known as "DPP-4 inhibitors" or "gliptins," raise blood incretin levels, thereby inhibiting glucagon release and lowering blood glucose levels. When used with metformin, they do not cause hypoglycemia. They have modest efficacy (hemoglobin A_{1C} reductions of 0.5% to 1%, neutral effect on weight). Linagliptin does not require a dosage adjustment in renal insufficiency. Cost is a major barrier to their use. Sitagliptin can be used in any degree of kidney disease but needs to be dosed based on GFR and creatinine levels.
- **Sulfonylureas:** Sulfonylureas increase insulin secretion and work best when given before meals. All sulfonylureas are contraindicated in patients who are allergic to sulfa. Use of sulfonylureas confers a greater risk of hypoglycemia than the other agents. These agents are now being considered to be used as last or later resort or when cost is of major concern for the patient and when other therapies cannot be incorporated or are contraindicated.
- **Acarbose and miglitol:** These agonists inhibit pancreatic amylase and small intestinal glucosidases, thereby delaying carbohydrate absorption in the gut and reducing associated postprandial hyperglycemia. The major side effects are flatulence, diarrhea, and abdominal cramps.
- **The meglitinides nateglinide and repaglinide and the bile acid sequestrant colesevelam** can also be used to lower glucose levels but are expensive and generally poorly tolerated.
- **Pramlintide** is a synthetic analog of human amylin, which is synthesized by pancreatic

TABLE 6 Onset, Peak, and Duration of Action of Currently Available Insulin Preparations

Insulin Preparation	Onset of Action	Peak Action	Duration of Action
Lispro	5-15 min	1-2 h	4-6 h
Aspart	5-15 min	1-2 h	4-6 h
Glulisine	5-15 min	1-2 h	4-6 h
Regular	30-60 min	2-3 h	6-10 h
NPH	2-4 h	4-10 h	12-18 h
Detemir	2 h	Relatively peakless	12-24 h
Glargine	2 h	Relatively peakless	20-24 h
Degludec	2 h	Relatively peakless	33-42 h

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beta cells and cosecreted with insulin in response to food intake. It suppresses glucagon secretion and slows stomach emptying and can be used as an adjunctive treatment for patients with T1DM or T2DM who inject insulin at mealtime. Nausea is its major side effect. This therapy has been largely replaced with use of GLP-1 analogs.

- **Thiazolidinediones (pioglitazone and rosiglitazone)** increase insulin sensitivity and have been used in the therapy of type 2 diabetes. Serum transaminase levels should be obtained before starting therapy and monitored periodically. Thiazolidinediones, in general, result in moderate weight gain and increase the risk for heart failure and osteoporosis/fractures. Rosiglitazone has an FDA black box warning for heart failure exacerbations and myocardial ischemia. Pioglitazone and rosiglitazone cause increased incidence of bladder cancer. Use thiazolidinediones with caution with calcium channel blockers, especially amlodipine (can cause fluid retention and edema).
- Combination therapy of various hypoglycemic agents is commonly used when dual therapy results in inadequate glycemic control.
  1. **Insulin** is indicated for the treatment of all T1DM and for T2DM patients whose condition cannot be adequately controlled with diet and oral agents. The American College of Endocrinology and the American Association of Clinical Endocrinologists recommend initiation of insulin therapy in patients with type 2 diabetes and an initial HbA_{1c} level >9%, or if the diabetes is uncontrolled despite optimal oral glycemic therapy. Insulin therapy may be initiated as augmentation, starting at 0.1 to 0.2 unit/kg of body weight, or as replacement, starting at 0.6 to 1.0 unit/kg. Table 6 summarizes onset, peak, and duration of action of currently available insulin preparations. The risks of insulin therapy include weight gain, hypoglycemia, and in rare cases, allergic or cutaneous reactions.
  2. Replacement insulin therapy should mimic normal release patterns.
     a. Approximately 50% to 60% of daily insulin can be given as a long-acting insulin (NPH, Ultralente, glargine, detemir) injected once or twice daily.
     b. The remaining 40% to 50% can be short-acting (regular) or rapid-acting (lispro, aspart, glulisine) to cover mealtime carbohydrates and correct increased current glucose levels.
     c. NPH and older basal insulins can be mixed with rapid-acting insulins like Humalog and regular; all newer basal insulins cannot be mixed in one syringe.
     d. Basal-bolus regimens are now preferred on injection of long-acting basal at bedtime or in AM to target fasting glycemia between 80 and 130, and rapid-acting mealtime insulins to target lower postprandial blood glucose <140 mg/dl.
     e. New combinations of basal insulins with GLP-1 analogs are now available:
        (1) Soliqua: Combines glargine insulin and lixisenatide in one pen. Patients taking <30 units start at 15 units and patient taking >30 units start at 30 units and are titrated every 3 to 4 days until fasting blood glucose levels are between 80 and 130 mg/dl. One should not exceed 60 units of glargine insulin.
        (2) Xultophy 100/3.6 is degludec insulin and liraglutide combination in one pen. Dosing is based on Tresiba dose. Patients start at 16 units and increase by 2 units every 5 to 7 days to target fasting glycemia between 80 and 130 mg/dl, and dose cannot exceed 50 units. The use of this combination may eliminate or reduce prandial insulin needs and limits weight gain caused by insulin.
- Continuous subcutaneous insulin infusion (CSII, or insulin pump) provides comparable or slightly better control than multiple daily injections. It should be considered for diabetes presenting in childhood or adolescence and during pregnancy. The guidelines for insulin pump therapy from the American Association of Diabetes Educators include "frequent and unpredictable fluctuations in blood glucose" and "patient perceptions that diabetes management impedes the pursuit of personal or professional goals." Use of insulin pumps are today coupled with CGM monitoring and with software in which the computer is making the automatic adjustments to glucose levels, constituting what is referred to as an "artificial pancreas." This allows for fewer fluctuations of glycemia.
- Antiplatelet therapy: Low-dose aspirin (ASA; 81 mg/day) has been proven to lower the risk of subsequent myocardial infarction, stroke, or vascular death in secondary prevention studies. The ADA recommends low-dose aspirin for primary prevention in diabetic patients with one additional cardiovascular risk factor, including age older than 50 yr, cigarette smoking, hypertension, obesity, albuminuria, hyperlipidemia, and family history of coronary artery disease. Clopidogrel can be used in patients with atherosclerotic cardiovascular disease (ASCVD) and a documented aspirin allergy. The ADA does not recommend aspirin therapy in diabetics younger than 50 yr of age at low risk for coronary artery disease.
- Lipid management: Measure fasting lipid profile at least annually in adults.
  1. All patients with diabetes with one or more additional risk factors for CVD should be on statin therapy together with lifestyle modification regardless of baseline lipid levels.
  2. Diabetic patients aged 40 to 75 with LDL cholesterol of 70 to 189 mg/dl and without clinical ASCVD should receive at least moderate-intensity statin therapy and consider high-intensity statin therapy if 10-yr ASCVD risk is ≥7.5%.
  3. Ezetimibe can be added to moderate-intensity statin therapy in those who cannot tolerate high-intensity statin therapy.
  4. Combination therapy with statin and fenofibrate is not recommended but may be considered in those with triglyceride levels equal or greater than 204 mg/dl. If triglycerides are not at goal with combination of statin and fibrate, then prescription fish oil is advised if triglyceride levels still exceed 300 mg/dl.
  5. PCK-9 inhibitors may be considered in diabetics with CAD risk when statins are insufficient and in those who cannot tolerate statins, have had cardiovascular events, and cannot achieve A_{1c} to target goal.
- Hypertension: Antihypertensive therapy is recommended to keep systolic blood pressure (BP) <140 and diastolic BP <90 mm Hg. Use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) to decrease albuminuria and for prevention of progression of kidney disease should be considered regardless of presence of hypertension. Combination

BOX 2 Sick Day Management Protocol for Diabetic Patients

Examples of "Sick Day" Scenarios
- Feeling sick or presence of fever for 2 days or longer without getting better
- Vomiting or diarrhea for more than 6 h

Management

General Measures
- Check blood sugar levels at least every 4 h, but when values are changing quickly, check more often.
- Check urine or blood ketones.
- Modify usual insulin regimen according to a plan developed by the diabetes physician or team.
- Maintain adequate food and fluid intake. If your appetite is poor, aim for consumption of 50 g of carbohydrate every 3-4 h. If you are nauseous, high-carbohydrate liquids, such as regular (not diet) soft drinks or juice, or frozen juice bars, sherbet, pudding, creamed soups, or fruit-flavored yogurt usually are tolerated. Broth also is a good alternative.

Taking Medications When You Are Sick
- If you are eating: Continue taking your pills for diabetes or your insulin. Your blood sugar may continue to rise because of your illness.
- If you are nauseous or vomiting or otherwise cannot take your medicines:
  - Continue to take your long-acting insulin (Lantus, Levemir, NPH).
  - Call your doctor and discuss whether you need to adjust your short- or rapid-acting insulin dose (regular, lispro [Humalog], aspart [Novolog], glulisine [Apidra]) or your other diabetes medicines.

Examples of When to Call Physician or Diabetes Team
- If glucose levels are higher than 240 mg/dl despite taking extra insulin according to a sick day plan
- If you take diabetes pills and blood sugar is still above 240 mg/dl before meals and remains there for more than 24 h
- If symptoms/signs develop that might signal diabetic ketoacidosis or dehydration, such as dizziness, trouble breathing, fruity breath, or dry and cracked lips or tongue

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therapy with an ACE inhibitor and an ARB should be avoided due to increased risk of adverse effects among patients with diabetic nephropathy. In older adults a treatment goal of <130/70 mm Hg is not recommended due to higher mortality and morbidity.
- Bariatric surgery should be considered in adults with BMI >35 kg/m2 and type 2 diabetes, especially if the diabetes is difficult to control with lifestyle and pharmacologic therapy. Five-yr outcome data showed that, among patients with type 2 DM and a BMR of 27 to 43, bariatric surgery plus intensive medical therapy was more effective than intensive medical therapy alone in decreasing, or in some cases resolving, hyperglycemia.[2]
- Treat hypoglycemia in a conscious person with glucose tab or gel 15 to 20 g, and intramuscular injection of glucagon if unconscious. Patient and family members should be instructed on the administration of glucagon for individuals at significant risk for severe hypoglycemia. A sick day management protocol for diabetic patients is described in Box 2.

DISPOSITION

- Diabetic retinopathy occurs in nearly 15% of patients with diabetes after 15 yr of diagnosis and increases 1%/yr after diagnosis. Glycemic, lipid, and blood pressure controls are essential to reduce the risk and progression of diabetic retinopathy. An annual comprehensive eye exam by an ophthalmologist or optometrist should begin at the time of diagnosis for those with T2DM and after 5 yr in those with T1DM. Retinal laser photocoagulation and vitrectomy are effective treatment modalities. Prevention is best accomplished by strict glucose and BP control. Early blockade of the renin-angiotensin system has been shown to slow progression of retinopathy in patients with type 1 diabetes.
- The frequency of neuropathy in patients with type 2 diabetes approaches 70% to 80%. It can be subdivided into sensorimotor neuropathy and autonomic neuropathy. Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, is effective and FDA approved for relief of diabetic peripheral neuropathy. Pregabalin and gabapentin (900 to 3600 mg/day) are also effective for the symptomatic treatment of peripheral neuropathic pain. Topical capsaicin, 5% lidocaine transdermal patches, amitriptyline, and carbamazepine are also modestly effective. Use of high-dose vitamin combination of B_{12}, B_6 with alpha lipoic acid may help with nerve preservation and worsening of neuropathy, but will have no immediate effect on pain.
- Diabetic gastroparesis is most often seen in patients who have had diabetes for at least 10 yr and typically have retinopathy, neuropathy, and nephropathy. Major manifestations are postprandial fullness, nausea, vomiting, and bloating. Pharmacologic therapy involves prokinetic agents (metoclopramide). Endoscopic injection of botulinum toxin into the pylorus and gastric electrical stimulation (using f electrodes placed laparoscopically in the muscle wall of the stomach antrum and connected to a neurostimulator) represent newer approaches to nonpharmacologic therapy.
- Nephropathy: The first sign of renal involvement in patients with DM is most often microalbuminuria, which is classified as incipient nephropathy. Before the current period of intensive glycemic control and blood pressure with ACE inhibitors and angiotensin receptor blockade, it was suggested that 25% to 45% of diabetic patients would develop clinically evident renal disease (proteinuria) and 4% to 17% would progress to end-stage renal disease. In the current era of intensive glycemic and blood pressure control and ACE/ARB use, clinically evident diabetic nephropathy has declined to 9% and end-stage renal disease 2% to 7%. Use of ACE inhibitor or ARB is not recommended in diabetics with normal blood pressure, no microalbuminuria (urine albumin to creatinine ratio less than 30 mg/g creatinine) and normal renal function (eGFR >60 ml/min/1.73 m^2).
- Infections are generally more common in patients with diabetes because of multiple factors, such as impaired leukocyte function, decreased tissue perfusion secondary to vascular disease, repeated trauma because of loss of sensation, and urinary retention secondary to neuropathy.
- Prevention/delay of type 2 diabetes: Patients with prediabetes should achieve weight loss of 5% to 10% of body weight and increase physical activity to at least 150 min/wk of moderate activity such as walking. Metformin therapy may be considered in those at high risk, especially if they have hyperglycemia (HbA_{1c} ≥6) despite lifestyle interventions.
- The Mediterranean diet has been shown to prevent type 2 diabetes in patients with prediabetes and can delay the need of insulin use in type 2 diabetes in up to 50% of patients.
- Use of metformin in prediabetics can prevent onset of diabetes in up to 30% of patients, independent of diet.

REFERRAL

- Patients with diabetes should be advised to have annual ophthalmologic examinations. In T1DM, ophthalmologic visits should usually begin 5 yr after diagnosis, whereas T2DM patients should be seen from disease onset.
- Podiatric care can significantly reduce the rate of foot infections and amputations in patients with DM. Noninfected neuropathic foot ulcers require debridement and reduction of pressure.

[2]Schauer PR et al: Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes, *N Engl J Med* 376(7):641-651, 2017.

- Nephrology consultation in all cases of proteinuria, hyperkalemia, uncontrolled BP, and when GFR has decreased to <30 ml/min/1.73 m^2.

PEARLS & CONSIDERATIONS

COMMENTS

- Because normalization of serum glucose level is the ultimate goal, every patient with diabetes should measure his or her blood glucose with commercially available glucometers unless contraindicated by senility or blindness.
- Continuous glucose monitoring is now commercially available for all types of diabetics on multiple daily injections of insulin. In the near future there will be weekly disposable sensors that can replace fingersticks. The advantage of CGM is that it not only gives a patient a value, but it shows a rate of change at that moment and predicts impending hyperglycemia or hypoglycemia, allowing a patient to react appropriately.
- Underinsured children and those with psychiatric illness are at greater risk for acute complications in T1DM and require frequent monitoring and aggressive risk management with diet, exercise, and periodic laboratory evaluation.
- Significant sustained weight loss using bariatric surgery has been reported as effective in achieving remission of type 2 diabetes in morbidly obese patients. Bariatric surgery may be considered for adults with BMI >35 kg/m2 and T2DM, especially if diabetes or associated comorbidities are difficult to control with lifestyle and pharmacologic therapy.
- Cigarette smoking predicts incident type 2 diabetes. For a smoker at risk for diabetes, smoking cessation should be coupled with strategies for diabetes prevention and early detection.
- Glycemic control in hospitalized patients: The American College of Physicians (ACP) recommends against using intensive insulin therapy to strictly control blood glucose in nonsurgical intensive care unit (SICU)/medical intensive care unit (MICU) in patients with or without DM. The ACP recommends a target blood glucose level of 130 to 180 mg/dl if insulin therapy is used.
- Studies have shown that tight glycemic control in SICU patients can reduce infection rates and ICU stay. This was not seen in MICU patients. However, there is evidence showing that patients using continuous IV insulin infusions to keep tight glycemic control after open heart surgery reduces sternal wound infection rates.
- Now many institutions are incorporating automated log adjustment, such as Glucommander, which reduces workload of staff in maintaining smooth glycemic control.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Diabetes Mellitus Type 1 (Patient Information)
Diabetes Mellitus Type 2 (Patient Information)
Diabetic Foot (Related Key Topic)
Diabetic Gastroparesis (Related Key Topic)
Diabetic Ketoacidosis (Related Key Topic)
Diabetic Polyneuropathy (Related Key Topic)
Diabetic Retinopathy (Related Key Topic)
Gestational Diabetes Mellitus (Related Key Topic)
Hyperglycemic Hyperosmolar Syndrome (Related Key Topic)

AUTHOR: **David J. Domenichini, MD,** and **Fred F. Ferri, MD**

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FIG. E1 Diabetic neuropathy of the hindfoot. Destruction of the joint with collapse and fragmentation. (From Hochberg MC et al [eds]: *Rheumatology,* ed 3, St Louis, 2003, Mosby.)

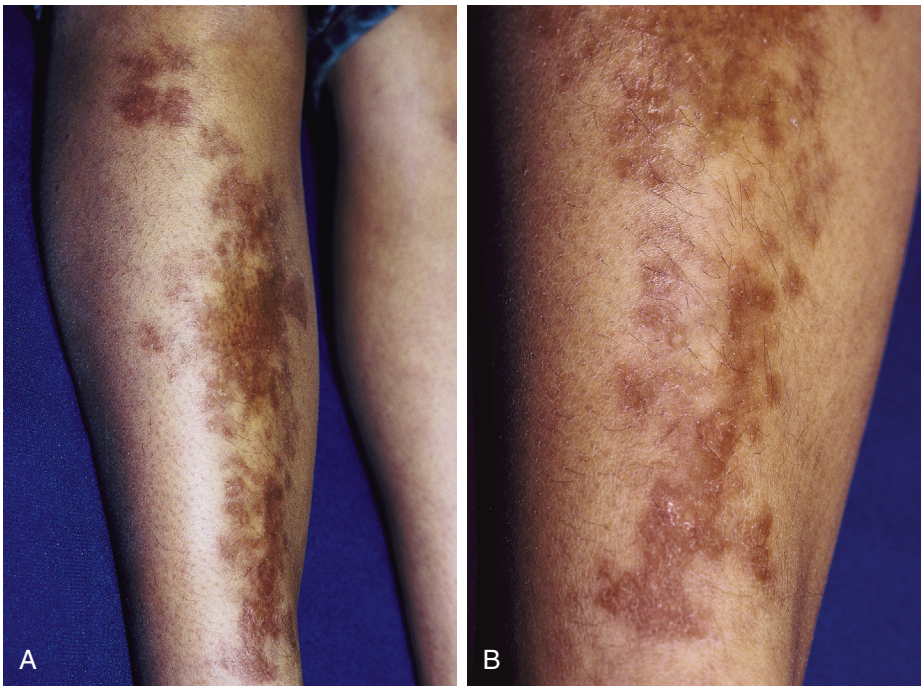

FIG. E2 Necrobiosis lipoidica diabeticorum. Waxy, yellow-brown plaques **(A)** were present in this young girl with diabetes mellitus, with subtle atrophy present on closer inspection **(B)**. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* Philadelphia, ed 5, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Diabetic foot infections (DFIs) are a common and potentially serious problem in persons with diabetes. They usually arise from either a skin ulceration that occurs secondarily to peripheral neuropathy or in a wound caused by some form of trauma. The infection usually involves one or more bacteria and can spread to contiguous tissues including bone, causing an osteomyelitis.

SYNONYMS

Diabetic foot ulcer
Diabetic foot infection
DFI

ICD-10CM CODES

E10.5	Diabetes mellitus with peripheral circulatory complications
E10.6D	Diabetes mellitus with other specific complications
E11.621	Type 2 diabetes mellitus with foot ulcer

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: DFIs are the most common cause of hospitalizations for diabetic patients. They account for 20% of all hospital admissions. Nearly one in six patients will die within 1 yr of their infection.

PEAK INCIDENCE: More common in Hispanics, African Americans, and Native Americans due to increased rates of diabetes in those populations

PREVALENCE: 25 million people in the U.S. have diabetes, of which 19% to 34% will develop a foot ulcer in their lifetime and more than 50% of these will become infected.

PREDOMINANT SEX AND AGE: Females greater than males

RISK FACTORS:

- Diabetes greater than 10 yr
- Poor glucose control
- Peripheral neuropathy: Altered protective sensation and altered pain response
- Diabetic angiopathy: Atherosclerotic obstruction of larger vessels leading to peripheral vascular disease
- Evidence of increased local pressure: Callus or erythema

PHYSICAL FINDINGS & CLINCIAL PRESENTATION

- Based on guidelines by Infectious Diseases Society of America, infection is present if obvious purulent drainage and/or the presence of two or more signs of inflammation:
  1. Erythema
  2. Pain
  3. Tenderness
  4. Warmth
  5. Induration
- Systemic signs of infection include:
  1. Anorexia, nausea/vomiting
  2. Fever, chills, night sweats
  3. Change in mental status and recent worsening of glycemic control

An earlier and commonly used classification system was originally proposed by Wagner.

An update to the Wagner system was introduced at the University of Texas (UT), San Antonio, U.S. While similar to Wagner in its first three categories, this later system eliminated grades 4 and 5 and added stages A-D for each of the grades. The UT system was the first diabetic foot ulcer classification to be validated.

University of Texas system Grade:

- Grade 0: Pre- or postulcerative (Stages A to D)
- Grade 1: Full-thickness ulcer not involving tendon, capsule, or bone (Stages A to D)
- Grade 2: Tendon or capsular involvement without bone palpable (Stages A to D)
- Grade 3: Probes to bone (Stages A to D)

Stage:

1. A: Noninfected
2. B: Infected
3. C: Ischemic
4. D: Infected and ischemic

ETIOLOGY

- Most diabetic foot infections are polymicrobial (can involve 5 to 7 different bacteria) and depend on the extent of involvement.
- Superficial infections are likely due to gram-positive skin bacteria:
  1. *Staphylococcus aureus*, includes methicillin-resistant *S. aureus* (MRSA)
  2. *Streptococcus agalactiae* (group B streptococcus) and *Streptococcus pyogenes* (group A streptococcus)
  3. Coagulase-negative *Staphylococcus*
- Infections that are deep, chronically infected, or previously treated are likely to be polymicrobial:
  1. Include above bacteria plus enterococci, gram-negative rods including *Pseudomonas aeruginosa* and anaerobes
  2. With gangrene can expect more anaerobic bacteria such as *Clostridia* and *Bacteroides* species
  3. Patients with multiple admissions can have more resistant bacteria such as ESBL-type resistant gram-negative rod bacteria, MRSA, and *Acinetobacter*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other inflammatory conditions that can mimic diabetic foot infections include:

- Crystal-associated arthritis such as gout
- Trauma
- Acute Charcot arthropathy from long-standing diabetes
- Venous stasis ulcers
- Deep vein thrombosis

WORKUP

Evaluation of a patient with a DFI involves determining the extent and severity of the infection, identifying the underlying factors that predispose to the infection, and determining the microbiologic etiology.

PHYSICAL EXAMINATION

- Vital signs: Fever, chills, hypotension, tachycardia can be present.
- Detailed wound description: Length, width, and depth of wound, consistency of drainage, character of wound base: Granular fibrous necrotic.
- Determination of osteomyelitis: Highly likely if bone visible. A positive probe test to bone has a sensitivity of 66% and specificity of 85% in diagnosing bone infection.
- Necrotizing infections may present with cutaneous bullae, soft tissue gas, foul odor, and skin discoloration (Fig. E1).
- Severe infections may present with gangrene, tissue necrosis, and evidence of tissue ischemia (Fig. E2), all of which may be limb threatening.

LABORATORY TESTS

Important to obtain at baseline and to assess response to therapy:

- Fewer than 50% of patients have an elevated WBC.
- Determine BUN/Cr, acidosis, hemoglobin A_{1C}, and blood sugar.
- Acute phase reactants: Sed rate and CRP are markers for inflammation.
  1. Sed rate >70 increases probability of bone infection.
- Serum prealbumin and albumin are markers for nutritional status and ability to heal.
- An ulcer size larger than 2 cm^2 is indicative of osteomyelitis.
- Gram stains and cultures: Superficial cultures should not be obtained as they may contain colonizing bacteria; instead deep tissue cultures (aerobic and anaerobic) should be obtained.

IMAGING STUDIES

- Plain film x-ray evaluates bones and soft issues and can detect presence of tissue gas, which would represent an emergent situation (Fig. 3).
- Osteomyelitis appears as radiolucencies, periosteal reaction, and destructive changes. Plain films are 67% specific and 60% sensitive for osteomyelitis.
- Bone scan: Indium-111 or technetium-99 can distinguish acute and chronic infections.
- CT and MRI: MRI is the most sensitive and specific test to detect osteomyelitis and abscess formation.

OTHER DIAGNOSTIC TESTS

- Annual noninvasive vascular studies: Ankle brachial index (ABI): <0.90 or >1.30 indicates peripheral arterial disease
- Transcutaneous oxygen (TcPO2) tension measurements: Predictive of wound healing failure at levels below 25 mm Hg

TREATMENT

Empiric antibiotic regimen should be started based on likely pathogens suspected and severity of disease. Wound management and debridement including surgical consultation are important as well.

FIG. 3 X-ray. Significant soft tissue swelling in midfoot with numerous gas bubbles seen in the soft tissues.

NONPHARMACOLOGIC THERAPY

- Good nutrition will promote wound healing.
- Glycemic control will promote healing.
- Fluid and electrolyte balance will improve healing.

ACUTE GENERAL TREATMENT

WOUND MANAGEMENT:

- Debridement of callus and necrotic tissues by wound care specialist or surgeon and at times may require multiple debridements.
- Wound dressing: To absorb exudates and promote healing. Many products are available but none has been proven superior and include:
  1. Enzymes
  2. Gels
  3. Hydrocolloids
  4. Antiseptics containing iodine or silver salts
  5. Honey
- Relieve pressure on the foot: Casts or special shoes.
- Amputation or revascularization procedures such as angioplasty or bypass grafting may be necessary.

ANTIBIOTIC MANAGEMENT:

- Prior to receiving culture results an empiric antibiotic regimen should be started as soon as possible to cover skin bacteria, gram-negative rods, and anaerobes. Options for intravenous therapy include:
  1. Piperacillin-tazobactam: 3.375 g IV q6h with normal kidney function. Will cover gram-negative rods including *Pseudomonas aeruginosa*, streptococci, anaerobes, and *Staphylococcus aureus.* Adjust dose based on CrCl.
  2. Meropenem: 1 g IV q8h with normal kidney function has comparable coverage as piperacillin-tazobactam. Similar agents include imipenem and doripenem.
  3. Third-generation cephalosporin such as cefepime, 2 g IV q8h, or ceftriaxone, 2 g IV qd, have excellent gram-negative coverage, and for anaerobic coverage add metronidazole, 500 mg IV q8h, or clindamycin 900 mg IV q8h. Cefepime will cover *Pseudomonas aeruginosa* but ceftriaxone will not.
  4. For penicillin-allergic patients a combination of ciprofloxacin, 400 mg IV q12h, plus metronidazole or clindamycin is an option. Aztreonam is another option for gram-negative rod coverage, 2 g IV q8h.
  5. If MRSA is suspected, need to add IV vancomycin, 15-20 mg/kg IV q8-12h, depending on age and CrCL and follow trough levels to keep above 15. Other options include daptomycin, 4 mg/kg IV qd, which does not have to be adjusted for CrCL, or linezolid, 400-600 mg IV q12h.
  6. If VRE is suspected, options include tigecycline, 100-mg IV load dose, then 50 mg IV q12h, which also covers MRSA and gram-negative rods but not *Pseudomonas aeruginosa,* or can use daptomycin or linezolid.
  7. If ESBL gram-negative bacteria are suspected, then options include meropenem or ertapenem, 1 g IV qd, or tigecycline.
  8. Once culture results are known can tailor antibiotics to more specific agent.
- Oral antibiotics used for milder infections include amoxicillin-clavulanate, 875 mg PO q12h, which will cover gram-negative rods, streptococci, and anaerobes, or ciprofloxacin plus metronidazole or clindamycin. Bactrim will cover MRSA and MSSA and some gram-negative rods.

The expert panel on diabetic foot infection (DFI) of the International Working Group on the Diabetic Foot conducted a systematic review. Results of comparisons of different antibiotic regimens generally demonstrated that newly introduced antibiotic regimens appeared to be as effective as conventional therapy.

CHRONIC TREATMENT

- Length of therapy: Highly variable depending on the severity of the infection. In general, 2 to 4 wk of antibiotics is sufficient. If bone infection suspected or documented, may need 4 to 8 wk of antibiotics, preferably intravenous via a peripherally inserted central line (PICC line).
- Surgical debridement may also be necessary for several wk.

COMPLEMENTARY MEDICINE

- Hyperbaric oxygen (HBO): Used as an adjunct to antibiotics, debridement, and revascularization in the therapy of chronic, nonhealing wounds associated with diabetes. Evidence of effectiveness is conflicting, and recent trials have failed to show improvement in clinical outcomes.[1] HBO acts by:
  1. Inducing vasoconstriction and reducing vasogenic edema
  2. Facilitating fibroblast activity, angiogenesis, and wound healing
  3. Killing anaerobic bacteria and augmenting neutrophil bactericidal activity
- Negative pressure wound therapy (wound vac): Controlled, subatmospheric pressure applied to an open wound can accelerate healing and closure.
  1. An open cell foam insert is cut to fit the open wound and then secured under a clear, vapor-permeable, plastic dressing.
  2. Tubing extends from the sponge to a disposable collection canister.
  3. A portable pump applies 125 mm Hg of controlled suction to the system. The subatmospheric pressure (suction) is equally distributed across the open wound and evacuates stagnant fluid from the wound.

DISPOSITION

- Following up on sed rates, CRP, BUN/CR, and levels of vancomycin if that antibiotic used.
- Surgical or wound center care follow-up.
- HBO usually involves multiple sessions over several wks.
- Wound vac is applied for wks and requires periodic nursing follow-up.
- The risk of death at 5 yr for a patient with a diabetic foot ulcer is 2 to 5 times as high as the risk for a patient with diabetes without a foot ulcer.

REFERRAL

- Infectious disease consultant for antibiotic management
- Surgeon or wound care center for surgical treatments
- Endocrinologist for good diabetes care
- Vascular surgeon for angioplasty or bypass procedures

PEARLS & CONSIDERATIONS

- In a meta-analysis of randomized controlled trials on the outcome of DFIs, there was a 22.7% treatment failure rate.
- Patients should be advised to seek prompt medical attention as these infections can progress rapidly to gangrene.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Glenn G. Fort, MD, MPH**

[1] Santema KTB et al: Hyperbaric oxygen therapy in the treatment of ischemic lower-extremity ulcers in patients with diabetes: results of the Damocles multicenter randomized clinical trial, *Diabetes Care* 41:112, 2018.

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FIG. E1 Foot. Severe diabetic foot infection with significant tissue swelling and necrosis.

FIG. E2 Diabetic foot complication. Oblique radiograph of the foot shows extensive vascular calcification. There is gas in the soft tissues of the great toe; this more commonly occurs because of air forced in through an open ulcer than a gas-forming organism infection. The loss of soft tissue around the great toe indicates ischemic mummification of the toe. (From Adam A, Dixon AK, Gillard JH, Schaefer-Prokop CM: Grainger and Allison's diagnostic radiology, ed 6, Philadelphia, 2015, Elsevier, in Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.)

Diabetic Gastroparesis

BASIC INFORMATION

DEFINITION

Gastroparesis is a syndrome characterized by delayed gastric emptying in the absence of a mechanical obstruction of the stomach. It is associated with the cardinal symptoms of nausea, vomiting, early satiety, belching, bloating, and/or upper abdominal pain. It is commonly associated with longstanding, poorly controlled diabetes.

SYNONYMS

Gastroparesis diabeticorum
Gastrointestinal autonomic neuropathy
Delayed gastric emptying

ICD-10CM CODE
K31.84 Diabetic gastroparesis

EPIDEMIOLOGY & DEMOGRAPHICS

- Age-adjusted incidence of gastroparesis is 2.4 per 100,000 person-yr for men and 9.8 per 100,000 person-yr for women. The age-adjusted prevalence of definite gastroparesis is 9.6 per 100,000 persons for men and 38 per 100,000 persons for women
- Gastroparesis is seen more commonly in women, and there is no known genetic predisposition to the disease
- There are certain risk factors for development of gastroparesis, and diabetes is the most frequently recognized systemic disease. However, the most common form is idiopathic, where no detectable primary underlying abnormality is found. The idiopathic form accounts for approximately 50% of the patients with delayed gastric emptying
- Other risk factors include:
  1. Postviral, especially Rotavirus and Norwalk virus
  2. Medications including narcotics, calcium channel blockers, and tricyclic antidepressants
  3. Postsurgical
  4. Neurologic illnesses, such as multiple sclerosis, brain stem stroke, or tumor, etc.
  5. Autoimmune gastrointestinal dysmotility
  6. Others such as mesenteric ischemia, scleroderma

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with gastroparesis present with nausea, vomiting (vomitus may contain food ingested a few hours earlier), abdominal pain, early satiety, postprandial fullness, bloating, and in severe cases, weight loss. Although abdominal pain is a frequent symptom in patients with gastroparesis, it is rarely the predominant symptom.
- Interestingly, in patients with diabetes as the cause for gastroparesis, severe retching and vomiting are more commonly reported.
- Symptoms of gastroparesis are more pronounced in patients with type 1 diabetes, as compared with patients with type 2 diabetes.
- Physical examination findings may include epigastric distention or tenderness, but not guarding or rigidity. A succussion splash may be heard on auscultation by gently rocking the patient.

ETIOLOGY

- Diabetic gastroparesis is thought to result from impairment of neural control of gastric function. Various mechanisms of nerve injury include inflammatory changes to the autonomic ganglia or dropout of myelinated fibers involving the vagus nerve.
- Acute hyperglycemia has been found to have effects on the gastric sensory and motor functions by causing altered gastric electrical activity. It can also result in relaxation of the proximal stomach and decreased pressure in the antrum and pylorus. All of these processes can contribute to the retardation of gastric emptying.
- Achieving euglycemia can correct the gastric emptying delay.
- The effect of chronic hyperglycemia on the stomach is less clear, but there is some evidence that gastric emptying of meals is slower in patients with high glycated hemoglobin levels.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gastric outlet obstruction
- Cyclic vomiting syndrome
- Chronic use of cannabinoids
- Functional dyspepsia
- Irritable bowel syndrome
- Rumination syndrome
- Eating disorders such as anorexia nervosa and bulimia

WORKUP

- Thorough history and physical examination.
  1. An associated history of poorly controlled blood sugars may be present.
  2. A history of retinopathy, nephropathy, and neuropathy may be present in association with diabetes.
- All medications that can delay gastric emptying should be stopped before formal workup.

LABORATORY TESTS

No specific labs are needed to confirm the diagnosis, but the following can help to arrive at diagnosis:

- Hemoglobin A_{1c} (HbA_{1c})
- TSH
- Total protein/albumin
- Hemoglobin
- Vitamin B_{12}
- Antinuclear antibody titers

IMAGING STUDIES

- Initial imaging should be done to rule out a mass causing mechanical obstruction.
  1. Upper GI endoscopy is first line.
  2. Computed tomography (CT) enterography vs. magnetic resonance (MR) enterography may also be done to rule out mechanical obstruction from a small-bowel mass.
  3. Barium follow-through if CT or MR enterography unavailable.
- Food retained after overnight fasting may be suggestive of gastroparesis.
- After a mechanical obstruction has been ruled out, scintigraphic gastric emptying should be done as a confirmatory test.
  1. It is the simplest and most cost-effective test.
  2. Documenting the presence of delayed gastric emptying and assessing its severity is best done by measuring the delay in gastric emptying of solids.
  3. Patient is asked to ingest a standard, low-fat meal.
  4. Abnormal gastric emptying is defined as >10% gastric retention of solid food at 4 h and/or >60% at 2 h.
- ^{13}C breath test can also be used to measure gastric emptying.
  1. Not as sensitive as the scintigraphy method
- An alternative testing modality, called the *wireless motility capsule,* is as sensitive and specific as scintigraphy, but it is rather expensive and has not been shown to offer any added clinical information that scintigraphy has already provided.
  1. It is an ingestible, wireless capsule that measures pH, pressure, and temperature as it traverses the GI tract. Gastric emptying of the capsule occurs with phase III of the migrating motor complex, signifying completion of the postprandial phase.

TREATMENT

- Diabetic gastroparesis is not progressive, and treatment is mainly directed toward alleviating patient symptoms. Exacerbating factors must be corrected as well.
- Patients can have a calorie-deficient diet, along with deficiencies in minerals and vitamins.

NONPHARMACOLOGIC THERAPY

- Nonpharmacologic therapy includes provision of nutritional support along with dietary modifications.
  1. Oral nutrition is preferred in mild disease. Diet should include small meals that are low in fiber (low-residue) and fat.
  2. Avoidance of carbonated beverages is recommended because these can lead to symptoms of bloating.
  3. Alcohol and tobacco smoking should also be stopped because these also delay gastric emptying.
  4. For patients with severe disease, a feeding jejunostomy tube may be considered. A successful trial of a nasojejunal feeding tube should precede placement.
  5. Optimize glucose and electrolyte levels.

ACUTE GENERAL Rx

- Prokinetic agents can be used to improve gastric motility.

1. Metoclopramide and erythromycin are both available in intravenous and liquid form, which makes medication administration, tolerance, and efficacy more acceptable if patient symptoms are severe.

- Antiemetic agents may also be needed for symptom relief in the acute setting.
  1. Phenothiazines, such as promethazine.
  2. 5-HT3 antagonists, such as ondansetron.
  3. Neurokinin receptor antagonist, such as aprepitant.
- Intravenous fluid resuscitation may be required if signs or symptoms of dehydration are present due to persistent nausea and vomiting.
- Correct hyperglycemia even in the acute setting, because delayed gastric emptying can be quickly corrected in the immediate setting.
- Discontinue medications that may delay gastric emptying.
  1. Pain medications.
     a. Avoid opioids.
     b. Tramadol may be used; however, one study showed that although gastric emptying was improved, colonic transit time was delayed.
  2. Incretin-based therapies and glucagon-like peptide 1 (GLP-1) analogues have been shown to retard gastric emptying.

CHRONIC Rx

- Metoclopramide should not be used for more than 12 wk unless the benefits outweigh the risks. Side effects include restlessness, anxiety, QT prolongation, and extrapyramidal effects such as dystonia and tardive dyskinesia.
- Erythromycin use is limited to 4 wk because longer use leads to tachyphylaxis. Similar effect is seen with the higher dose (250 mg) vs. a lower dose (40 mg).
- Pain management may need to be addressed for patients receiving chronic opioids.
  1. Low-dose tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and pregabalin can be used as alternatives for long-term pain control.
- Endoscopic intrapyloric injection of botulinum toxin may be considered.
  1. Not shown to improve symptoms associated with diabetic gastroparesis but does have a modest effect on improving gastric emptying.
  2. Not approved as a mainstay treatment modality.
- Gastric electrical stimulation via a gastric electrical neurostimulator can be offered to patients with diabetic gastroparesis.
  1. Shown to improve symptom severity and gastric emptying.
  2. Approved as a humanitarian exemption device for patients with refractory symptoms.
- Surgical intervention.
  1. Venting gastrostomy, gastrojejunostomy, pyloroplasty, and gastrectomy are available.
  2. Rarely employed and is reserved for patients with severe, debilitating disease.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Dietary modifications as described earlier
- Acupuncture
- Autonomic retraining

PEARLS & CONSIDERATIONS

COMMENTS

- Gastroparesis can be one of the consequences of chronic, poorly controlled diabetes.
- Symptoms of nausea, vomiting, bloating, early satiety, and abdominal pain in a patient with chronic, poorly controlled diabetes should prompt the possibility of gastroparesis.
- The diagnostic study of choice is gastric scintigraphy, performed by the nuclear medicine department.
- Discontinue all medications that can slow gastric emptying, especially opioids.
- Improve blood sugar control and avoid hyperglycemia.
- Antiemetics with prokinetic properties, such as metoclopramide, are most helpful in relieving nausea and vomiting, in both the acute and chronic presentations.
- Refer to gastroenterology for consideration of botulinum toxin injection or gastric neurostimulator placement if patients have poorly controlled and refractory disease.

PREVENTION

Focus on improved glycemic control in the long term.

PATIENT & FAMILY EDUCATION

- Gastroparesis Patient Association for Cures and Treatments (G-PACT)
- Association of Gastrointestinal Motility Disorders, Inc. (AGMD)

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Diabetes Mellitus (Key Related Topic)
Diabetic Polyneuropathy (Key Related Topic)

AUTHOR: **Hussain R. Khawaja, MD**

SUGGESTED READINGS

Camilleri M et al: Clinical guideline: management of gastroparesis, *Am J Gastroenterol* 2013.

Camilleri M: Clinical practice: diabetic gastroparesis, *N Engl J Med* 2007.

Johns Hopkins Medicine: Gastroparesis, www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/esophagus_stomach/gastroparesis.pdf.

Diabetic Ketoacidosis

BASIC INFORMATION

DEFINITION

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus (DM). It results from an absolute or relative insulin deficiency that results in insulin resistance when paired with counterregulatory hormone and free fatty acid excess. DKA is characterized by the presence of an anion gap metabolic acidosis, ketonemia, and hyperglycemia.

ICD-10CM CODES

E10.10	Type 2 diabetes mellitus with other specified complication
E10.11	Diabetic ketoacidosis with coma associated with type 1 diabetes mellitus
E08.10	Diabetes mellitus due to underlying condition with ketoacidosis without coma
E08.11	Diabetes mellitus due to underlying condition with ketoacidosis with coma
E13.10	Diabetic ketoacidosis
E13.11	Diabetic ketoacidosis with coma

EPIDEMIOLOGY & DEMOGRAPHICS

DKA is the most common hyperglycemic emergency among patients with type 1 (T1D) and type 2 diabetes (T2D). The reported number of DKA hospitalizations in the United States is >140,000/yr. DKA most commonly occurs in T1D, with one-third in T2D. Those with ketosis-prone T2D are especially vulnerable. Overall, DKA prevalence has increased, yet mortality has decreased to <5%, significantly less than from hyperglycemic hyperosmolar syndrome (HHS). Mortality from DKA in children and adolescents is most commonly due to cerebral edema, whereas in adults it is usually related to the precipitating illness (i.e., sepsis, cardiac or CNS ischemia, pneumonia).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Polyuria, polydipsia, weight loss, weakness
- Signs of dehydration (tachycardia, hypotension, dry mucous membranes, sunken eyes, poor skin turgor)
- Nausea, vomiting, abdominal tenderness, ileus
- Mental obtundation (can range from full alertness to coma)
- Tachypnea with air hunger (Kussmaul respirations)
- Fruity breath (caused by acetone)
- Evidence of precipitating factors (i.e., ischemia or infection)

ETIOLOGY

Hyperglycemia occurs from relative insulinopenia for the degree of transient insulin resistance plus increased hepatic gluconeogenesis and glycogenolysis. The resulting lipolysis and fatty oxidation produce ketonemia and metabolic acidosis.

DKA can be precipitated by various conditions:

- Infection
- Insulin deficiency (undiagnosed diabetes, medication nonadherence/inadequacy, insulin pump malfunction/disconnect, diabulimia)
- Inflammatory conditions (i.e., acute pancreatitis)
- Ischemia/infarction (i.e., myocardial infarction, stroke, bowel ischemia)
- Severe extracellular fluid volume depletion
- Drugs (i.e., steroids, thiazides, atypical antipsychotics, SGLT2 inhibitors, alcohol, sympathomimetics including cocaine, cancer immunotherapy [such as anti-programmed death 1 {PD-1} antibody treatment])

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hyperosmolar nonketotic state
- Alcoholic/starvation ketoacidosis
- Lactic acidosis
- Acute kidney injury/chronic kidney disease
- Metabolic acidosis caused by exogenous poisons, e.g., methanol, ethylene glycol, paraldehyde
- Salicylate poisoning
- Hypovolemic or septic shock

WORKUP

After initial history is obtained, perform physical examination, including evaluation of airway, breathing, circulation, mental status, volume status, and signs suggestive of precipitating event(s).

LABORATORY TESTS

- Serum glucose level: Generally >250 mg/dl. However, "euglycemic DKA" can occur in 10% of the DKA population (i.e., exogenous insulin injection en route to hospital, administration of an SGLT2-inhibitor, food restriction).
- Arterial blood gas (demonstrating metabolic acidosis): Arterial pH <7.30.
- Serum beta hydroxybutyrate and urine ketones: Positive (beta hydroxybutyrate >3 mmol/L, ≥2+ urine ketones).
- Serum electrolytes:
  1. Serum bicarbonate concentration: <15 mmol/L (mild DKA may reduce levels to <18 mmol/L).
  2. Serum potassium concentration: Levels may initially measure as normal or high from extracellular shift with insulin deficiency and hyperosmolality. However, overall total body potassium depletion occurs from urinary losses and vomiting.
  3. Serum sodium concentration: May be low, normal, or high. Hyperglycemia increases plasma osmolality, which attracts intracellular water to the extracellular compartment and decreases the sodium level. Correct the serum sodium concentration: Add 1.6 mmol/L to the measured serum sodium level for every 100 mg/dl increase of serum glucose >100 mg/dl and <400 mg/dl, and then increase the sodium level by 4 mmol/L for each glucose increment of 100 mg/dl above 400 mg/dl.
  4. Serum calcium, magnesium, and phosphorus: May be significantly low and may decrease further with DKA treatment.
  5. Anion gap (AG): Na – (Cl + HCO_3). AG is increased (>10 mmol/L) from elevated ketones.
  6. Blood urea nitrogen (BUN) and creatinine: Generally reveals acute kidney injury.
- Hemoglobin A1c if not performed within the preceding 3 mo.
- Complete blood count with differential: May indicate underlying infection (leukocytosis >25,000/mm^3), inflammatory condition, or hemoconcentration. A leukocytosis of 10,000 to 15,000/mm^3 is expected from the stress of illness alone.
- Urinalysis, urine/blood cultures: As indicated based on exam findings.
- Pregnancy test: Perform in all female patients of reproductive age. DKA in pregnancy bodes significant fetal morbidity and mortality.
- Lipase/liver enzymes: Obtain if abdominal pain present. Elevated lipase can occur without underlying pancreatitis.

IMAGING STUDIES

ECG, chest x-ray, and other imaging studies as indicated to evaluate the precipitating cause(s).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Monitor mental status, vital signs, and urine output hourly until improved.
- Monitor serum glucose hourly and serum electrolytes, BUN, and creatinine every 2 to 4 hours until DKA resolves.

ACUTE GENERAL Rx (FIG. 1)

FLUID REPLACEMENT: Fluid therapy is initiated to expand volume and restore renal perfusion for a typical total body water deficit of 8 to 10 L. In the absence of cardiac compromise or severe kidney impairment, infuse 0.9% normal saline (NS) at an initial rate of 1 to 1.5 L/hr (alternatively, use 15 to 20 ml/kg per hour) for the first 1 to 2 hours. The subsequent fluid choice depends on patient hemodynamics, electrolytes, and urinary output. If corrected serum sodium is normal or high, infuse 0.45% NS at 250 to 500 ml/hr. If corrected serum sodium is low, continue 0.9% NS at a similar rate. Once serum glucose decreases to 200 mg/dl, add 5% dextrose to the IV fluid. The recommended sodium decline is 0.5 mmol/L per hour and should not surpass 10 to 12 mmol/L per day. Hyperglycemia (>250 mg/dl) resolves sooner than ketoacidosis (6 versus 12 hours, respectively).

INSULIN ADMINISTRATION: Administer initial bolus of IV regular insulin 0.1 units/kg followed by 0.1 units/kg per hour infusion or a continuous infusion of 0.14 units/kg per hour without initial bolus. If the serum glucose declines to <50 to 75 mg/dl in the first hour, increase insulin infusion rate hourly until a steady glucose decline is seen. After the serum glucose reaches 200 mg/dl and until DKA resolves, maintain the serum glucose concentration between 150 and

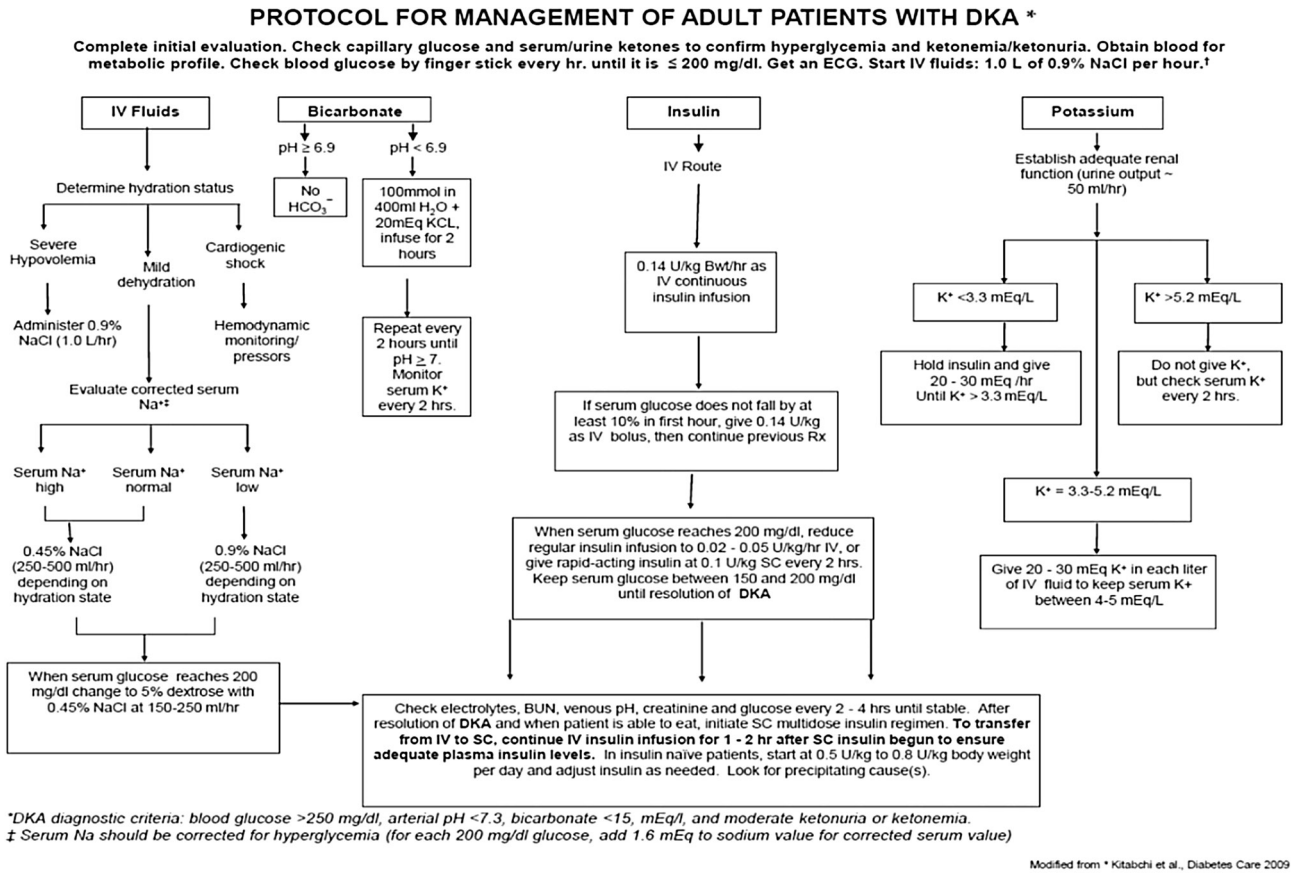

FIG. 1 Management of diabetic ketoacidosis. (From Nyenwe EA et al: The evolution of diabetic ketoacidosis: an update of its etiology, pathogenesis, and management, *Metabolism* 65(4):507-521, 2016.)

200 mg/dl by decreasing the insulin infusion to 0.02 to 0.05 units/kg per hour or deliver subcutaneous rapid-acting insulin at 0.1 units/kg every 2 hours.

POTASSIUM REPLACEMENT: Insulin therapy shifts potassium intracellularly, frequently causing hypokalemia. If the serum potassium concentration at presentation is between 3.3 and 5.2 mmol/L, infuse 20 to 30 mmol of potassium chloride (KCl) with each liter of IV fluid to maintain serum potassium at 4 to 5 mmol/L. If serum potassium is <3.3 mmol/L, withhold insulin until the serum potassium level is >3.3 mmol/L, and replace potassium by administering KCl infusion at 20 to 30 mmol/hr. If the serum potassium level at presentation is >5.2 mmol/L, monitor the level every 2 hours without replacement.

BICARBONATE REPLACEMENT: The administration of bicarbonate in DKA is generally not recommended. Bicarbonate does not improve time to resolution of acidosis or discharge, although adverse effects are associated with severe metabolic acidosis (decreased cardiac contractility, cerebral vasodilation). In adult patients with pH <6.9, administer 100 mmol (2 ampules) of sodium bicarbonate in 800 ml of sterile water (isotonic solution) with 20 mmol KCl at 200 ml/hr for 2 hours until venous pH is >7.0. If pH is still <7 after infusion, repeat infusion every 2 hours until pH is >7.

PHOSPHATE REPLACEMENT: Phosphate replacement is not routinely recommended, although phosphorus concentrations decrease with insulin administration. In patients with cardiac dysfunction, respiratory depression, or anemia and serum phosphorus <1 mg/dl, add 20 to 30 mmol/L of potassium phosphate to IV fluids to prevent diaphragmatic muscle weakness.

TRANSITION TO SUBCUTANEOUS INSULIN: Resolution of DKA occurs when blood glucose is <200 mg/dl and two of the following occur: Venous pH >7.3, serum bicarbonate >15 mmol/L, anion gap ≤12 mmol/L. At this point, patients can transition to subcutaneous insulin but may remain on IV insulin if NPO. Subcutaneous intermediate- or long-acting insulin should be overlapped with IV insulin by 2 to 4 hours to maintain adequate insulin levels and prevent rebound hyperglycemia. In patients with a known history of controlled diabetes, their home insulin regimens may be resumed. In patients with known poorly controlled diabetes, the subcutaneous insulin dose can be determined based on stable insulin drip requirements. Insulin-naïve patients may be started on basal-bolus insulin therapy by calculation of total daily dose of 0.5 to 0.8 units/kg (split as half-basal and half-bolus; administer one third of total bolus for each meal) or by stable insulin drip requirements. Further subcutaneous insulin dose titration is based on blood glucose results. Resolution of glucotoxicity and the inciting condition(s) will decrease insulin requirements.

DISPOSITION: In general, patients with DKA should be admitted to an intensive care unit with an insulin infusion. Alert patients who are able to ingest fluids orally and have mild DKA (plasma glucose >250 mg/dl, arterial pH 7.25 to 7.3, bicarbonate 15 to 18 mmol/L with anion gap >10 mmol/L, and alert mental status) may be treated with rapid-acting insulin analogues under observation and discharged. Timely follow-up with primary care or endocrinology is important, preferably with an appointment made before discharge.

PEARLS & CONSIDERATIONS

COMMENTS

- DKA is the initial presentation of diabetes in 15% to 20% of adults and 30% to 40% of children. This underscores the importance of educating patients, families, and school administrators regarding early symptoms of diabetes with the aim of earlier diagnosis.
- DKA in end-stage renal disease (ESRD) patients is relatively uncommon secondary to decreased insulin clearance. In fact, low GFR increases the risk for hypoglycemia. However, when ESRD patients develop DKA, special management considerations are needed. These patients are usually anuric and do not produce an osmotic diuresis, negating the need for aggressive volume repletion. Vigorous volume resuscitation may lead an

ESRD patient to volume overload, pulmonary edema, and respiratory distress. Anuric ESRD patients do not have urinary potassium loss, thus making potassium replacement unnecessary. Similarly, phosphorus supplementation is not required. In fact, in severe acidosis, transcellular potassium shifts for hydrogen may produce hyperkalemia, prompting some providers to request immediate dialysis. Insulin therapy alone for hyperglycemia may also correct hyperkalemia without the need for dialysis. During DKA in ESRD patients, dialysis is generally only recommended if there are hyperkalemia-induced electrocardiographic manifestations. A precipitous drop in serum glucose from an insulin infusion and hemodialysis may result in rapid tonicity shifts, predisposing to cerebral edema. Thus, hemodialysis is typically delayed until the serum glucose is corrected. Due to increased risk for hypoglycemia, ESRD patients require careful and preemptive insulin reduction from the hospital DKA protocol.

- Address affordability of insulin before discharge. Consider use of NPH and regular insulin for as little as $25 per vial.
- Proper instructions for insulin storage, dosing, timing of mealtime insulin before meals, preparation of insulin before injection (i.e., resuspend NPH), and use of syringe/vial or pen are essential.

PREVENTION

Many cases of DKA can be prevented by effective patient education and communication. Education of patients regarding sick day management includes early communication with the health care provider, continuing insulin during illness, checking ketones, and continuing an easily digestible liquid diet that contains carbohydrates.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Diabetes Mellitus (Related Key Topic)
Hyperglycemic Hyperosmolar Syndrome (Related Key Topic)

AUTHORS: **Stanley Linder, DO,** and **Jessica E. Shill, MD**

SUGGESTED READING

Fayfman M et al: Management of hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state, *Med Clin North Am* 101(3):587-606, 2017.

Kitabchi AE et al: Hyperglycemic crises in adult patients with diabetes, *Diabetes Care* 32:1335-1343, 2009.

Sharayah AM et al: Gastroparesis in a patient with diabetic ketoacidosis, *Clev Clin J Med* 86:238-239, 2019.

Verbalis JG et al: Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations, *Am J Med* 126(Suppl):S1-S42, 2013.

BASIC INFORMATION

DEFINITION

Diabetic nephropathy (DN) is chronic kidney disease defined by structural and functional changes that develop as a result of microvascular complications associated with long-standing or poorly controlled diabetes mellitus (DM). The clinical presentation includes proteinuria, hypertension (HTN) and progressive reduction in renal function. This is seen histologically as glomerular basement membrane thickening, mesangial matrix expansion, foot process effacement, arteriolar hyalinosis, microaneurysms, nodular glomerulosclerosis (Kimmelstiel-Wilson nodules) and tubulointerstitial fibrosis.

SYNONYMS

Diabetic kidney disease
DN

ICD-10CM CODES

E10.21	Type 1 diabetes mellitus with diabetic nephropathy
E11.21	Type 2 diabetes mellitus with diabetic nephropathy

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Diabetes is present in 10% of the U.S. population. DN occurs in approximately 40% of patients who have diabetes for more than 10 yr.

PREVALENCE: DN develops in approximately 30% of patients with type 1 diabetes mellitus (T1DM) and 40% of patients with type 2 diabetes mellitus (T2DM) and is the leading cause of chronic kidney disease (CKD) and end stage renal disease (ESRD) worldwide. Among U.S. ESRD patients, 50% have DN as the primary cause for ESRD.

PREDOMINANT SEX AND AGE: Male patients and older age

GENETICS: Polygenetic. Patients with first-degree relative with DN are at increase risk.

RISK FACTORS:

- Male
- Older age
- Race: People of African descent, American Indian, Hispanic, Asian/Pacific Islander
- Family history of diabetic nephropathy
- Hyperglycemia
- Hypertension
- Obesity
- Diabetic retinopathy (DR)
- Smoking
- Hyperlipidemia

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Peripheral edema
- Foamy urine
- Weight gain or weight loss
- Hypertension
- Diabetic retinopathy
- Microalbuminuria/Proteinuria
- Decline in glomerular filtration rate (GFR)

ETIOLOGY

- DN develops as a result of microvascular complications associated with long-standing DM.
- DN is characterized by histologic changes (Fig. E1) including glomerular basement membrane thickening, mesangial matrix expansion, foot process effacement, arteriolar hyalinosis, microaneurysms, nodular glomerulosclerosis (Kimmelstiel-Wilson nodules) and tubulointerstitial fibrosis. These changes lead to urine albumin/protein excretion and decreased GFR.
- The pathophysiology leading to DN (Fig. 2) includes the generation of advance glycation end products, elaboration of growth factors, hemodynamic changes, and hormonal changes resulting in the release of reactive oxygen species and inflammatory mediators such as TNF-A, IL-1, and IL-6. These changes lead to glomerular hyperfiltration, glomerular hypertension, renal hypertrophy, and altered glomerular composition, which manifest as albuminuria, HTN, and progressive decline in renal function.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hypertensive nephrosclerosis
- Focal segmental glomerulosclerosis
- Amyloidosis and light chain deposition disease
- IgA nephropathy
- Membranous nephropathy

WORKUP

- Workup should include thorough history and physical with focus on duration of DM, degree of hyperglycemia, and presence of complications (including DR) as well as appropriate laboratory testing (Fig. 3).

LABORATORY TESTS

- Urine albumin:creatinine ratio
  1. Microalbuminuria is defined as 30 to 299 mg/g and macroalbuminuria is defined as >300 mg/g
  2. Screening should be performed annually in patients with T1DM with >5-yr duration and annually for T2DM from its onset
  3. Confirm microalbuminuria with 2 to 3 elevated levels within a 3 to 6 mo period
  4. Early morning urine sample is recommended for identification of albuminuria. Prolonged standing, heavy exercise, UTI, and acute illness can cause transient albuminuria
  5. In T1DM microalbuminuria occurs 5 to 10 yr from onset
  6. In T2DM up to 25% of patients with DN may have little or no proteinuria
- GFR <60 ml/min/1.73 m^2
- Other tests
  1. Electrolytes
  2. Lipid profile

IMAGING STUDIES

- Renal ultrasound may help identify disease since kidney volume increases by an average of 15% with the onset of diabetes mellitus.
- Renal biopsy is confirmatory but is only reserved for patients with atypical features. Atypical features include rapid decline in GFR, overt proteinuria without prior microalbuminuria, active urine sediment, or features to suggest other systemic disease. In T2DM, DN can be present from the onset whereas in T1DM it typically develops after 5 yr. In general, patients with albuminuria, presence of DR, and lack of atypical features do not need renal biopsy (Fig. 4).

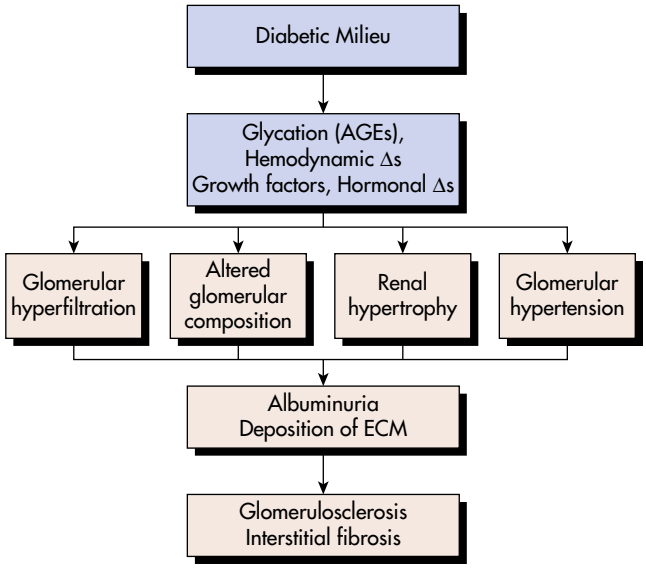

FIG. 2 Pathophysiology. *AGEs,* Advanced glycation end products; *ECM,* extracellular matrix. (From Umanath K et al: Update on diabetic nephropathy, *Am J Kidney Dis* 71:884, 2018.)

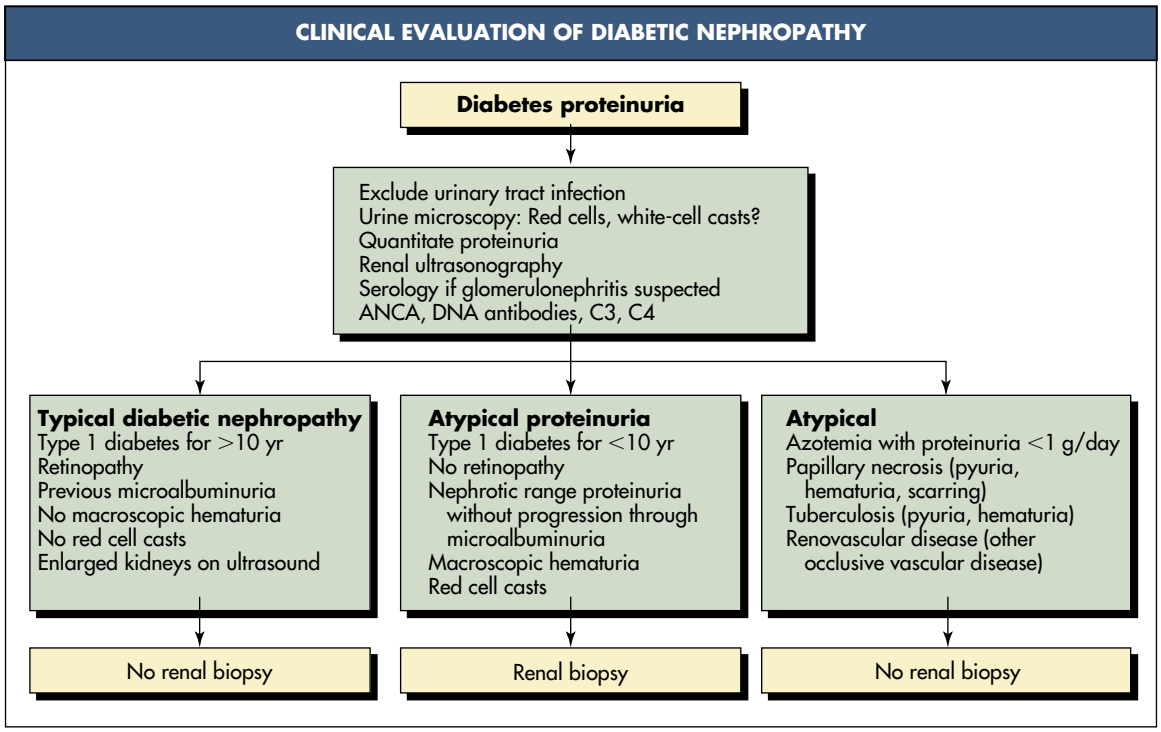

FIG. 3 Clinical evaluation of diabetic renal disease. *ANCA,* Anti-neutrophil cytoplasmic antibody. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, WB Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Smoking cessation
- Weight loss
- Dietary modifications—low carb, low fat, low potassium

ACUTE GENERAL Rx

- Early identification and an aggressive multiprong approach toward treatment of DN is of key importance to slow its progression (Table 1).
- Glycemic control with a goal A1C <7% is recommended as per KDOQI guidelines, with modification for patients at risk for hypoglycemia. Glycemic control delays microvascular complications and progression of DN.
- The ideal blood pressure goal is debatable. The current Kidney Disease Outcomes Quality Initiative (KDOQI) guideline recommends a goal BP <130/80; however, the Eighth Joint National Committee (JNC 8) guidelines recommend a goal BP <140/90.
- Use of renin-angiotensin-aldosterone system (RAAS) blockers should be the cornerstone of HTN management. ARB and ACE-I have been shown to reduce proteinuria, lower blood pressure, and slow the progression of DN. Combination therapy of ARB and ACE-I is not recommended due to risk of hyperkalemia and acute kidney injury.
- Lipid lowering therapy with an aim at cardiovascular risk reduction is recommended.

CHRONIC Rx

- Identify CKD anemia. Patients with DN are twice as likely to develop anemia compared to nondiabetic CKD and may need treatment with erythropoietin stimulating agents.
- Identify CKD bone-mineral metabolism disorder, especially adynamic bone disease, which develops more often with DN.
- Patients with DN should have timely referral for renal transplant and access evaluation as they progress to ESRD.
- Type IV renal tubular acidosis causing hyporeninemic hypoaldosteronism and hyperkalemia is common in DN, especially with the use of RAAS blockers and may require treatment with low potassium diet, diuretics, and/or potassium binders.

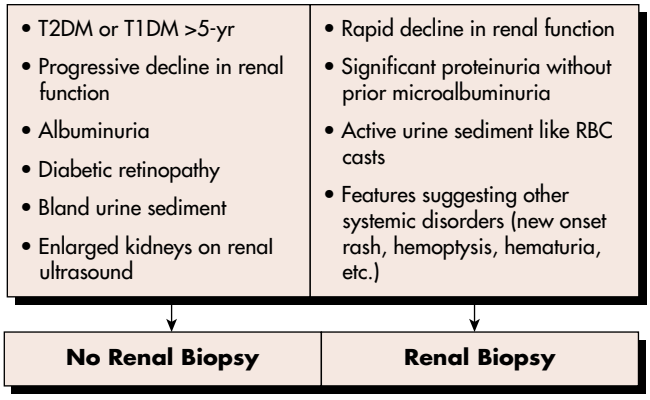

FIG. 4 Role of renal biopsy.

TABLE 1 Multiprong Approach Toward Diabetic Nephropathy

Glycemic control	Goal HbA_{1C} <7%
HTN control	Goal BP <130/80 mm Hg
RAAS blockers	ACE-I or ARB
Cardiovascular risk reduction	Smoking cessation and lipid management

ARB, Angiotensin receptor blocker; *ACE-I,* angiotensin-converting enzyme inhibitor; *BP,* blood pressure; *HbA_{1C},* glycosylated hemoglobin; *HTN,* hypertension; *RAAS,* renin-angiotensin-aldosterone system.

DISPOSITION

- Patients with DN with severe albuminuria and decreased GFR have poor prognosis and are at higher risk of cardiovascular events and deaths.
- The 5-yr survival rate of patients with diabetes and ESRD is approximately 30%.

REFERRAL

- Nephrology for CKD management
- Endocrinology for glycemic control
- Podiatry for foot care in the setting of neuropathy/peripheral vascular disease
- Ophthalmology for retinopathy management
- Dietician for specific dietary counseling

PEARLS & CONSIDERATIONS

- DN is the leading cause of CKD and ESRD worldwide. Early identification and an aggressive multiprong approach toward treatment of DN are key to slow its progression. Timely referral for renal transplant and access evaluation as they progress to ESRD are essential.
- DN is characterized by specific histologic findings; however, the diagnosis usually is made without renal biopsy due to the presence of clinic indicators including long duration of disease (usually >10 yr) and presence of other complications of the disease (albuminuria, retinopathy).
- RAAS blockage is a vital component of DN treatment. After initiation of RAAS blockage, chemistry panel should be periodically monitored to identify hyperkalemia or AKI.
- Insulin and many oral diabetic mediations are metabolized and cleared by kidneys and need dose adjustment with decline in renal function. Metformin is contraindicated with GFR <30 ml/min/1.73 m^2 and should be limited to <1000 mg/day in patients with GFR <45 ml/min/1.73 m^2 due to its association with lactic acidosis.
- Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown in recent trials to improve renal outcomes in patients with T2DM.
- Patients with DN are at risk for AKI and should be counselled to avoid nephrotoxins such as nonsteroidal antiinflammatory drugs (NSAIDs).

PREVENTION

Treatment of risk factors including blood pressure, blood sugars, and obesity.

PATIENT & FAMILY EDUCATION

Diabetes and Chronic Kidney disease by National Kidney Foundation https://www.kidney.org/sites/default/files/docs/diabckd_stg5.pdf

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Diabetes Mellitus (Related Key Topic)

AUTHORS: **Jyothsna I. Herek, MD,** and **Yuvraj Sharma, MD**

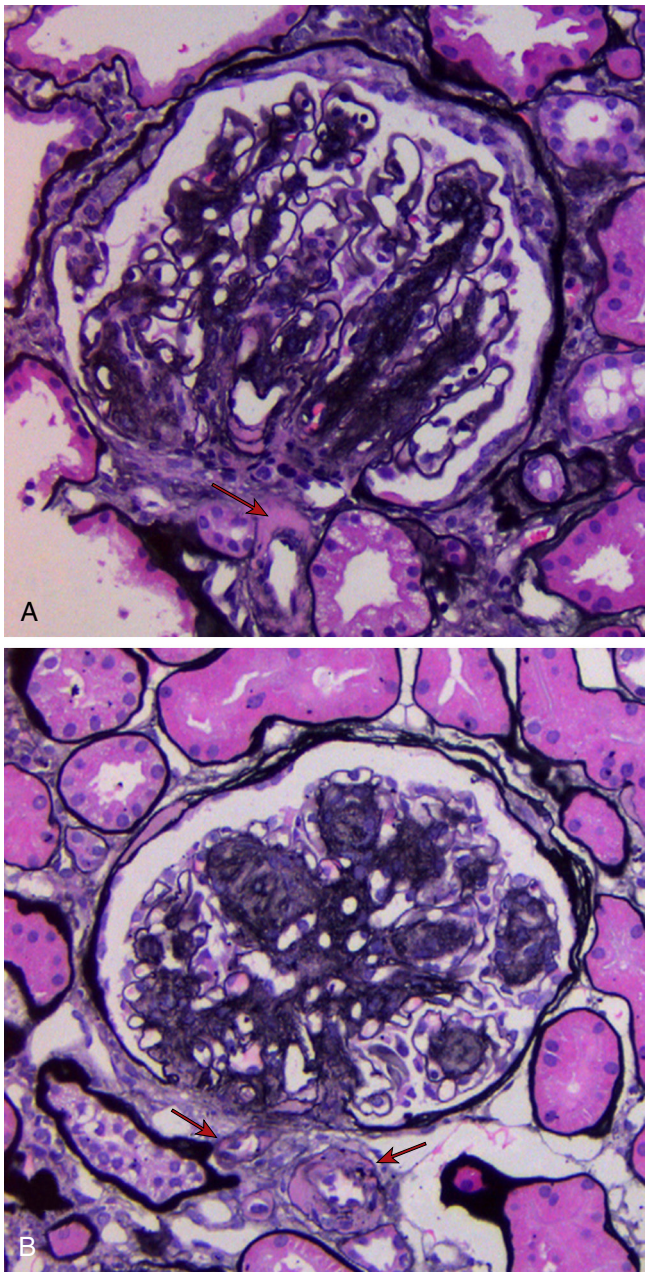

FIG. E1 Histologic changes. A, Diabetic nephropathy with diffuse mesangial expansion and arteriolar hyalinosis (*red arrow*). **B,** Diabetic nephropathy with nodular mesangial expansion (Kimmelstiel-Wilson nodules) and concomitant hyalinosis of afferent and efferent arterioles (*red arrows*; Jones silver stain). (From Najafian B et al: AJKD Atlas of renal pathology: diabetic nephropathy, *Am J Kidney Dis* 66:e37, 2015.)

SUGGESTED READINGS

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Doshi SM et al: Diagnosis and management of type 2 diabetic kidney disease, *Clin J AM Soc Nephrol* 12:1366-1373, 2017.

Najafian B et al: AJKD atlas of renal pathology: diabetic nephropathy, *AJKD* 66: e37, 2

Rao V et al: Diabetic nephropathy: an update on the pathogenesis and drug development, Diab & Metab Syndrome, *Clin Res and Rev* 13:754-762, 2018.

Umanath K et al: Update on diabetic nephropathy: core curriculum 2018, *AJKD* 6:884-895, 2018.

Diabetic Polyneuropathy ALG

BASIC INFORMATION

DEFINITION

Diabetic polyneuropathy is a distal symmetric polyneuropathy (DSPN) characterized by numbness, tingling, pain, or weakness that affects the nerves in a stocking-and-glove pattern, beginning in the distal extremities. DSPN leads to substantial pain, morbidity, and impaired quality of life. A number of different classification schemes exist for diabetic neuropathy; a common one is outlined in Box 1.

SYNONYMS

Distal symmetric polyneuropathy (DSPN)
Diabetic peripheral neuropathy

ICD-10CM CODES

E11.40	Type 2 diabetes mellitus with neurological complications
E11.40	Type 2 diabetes mellitus with diabetic neuropathy, unspecified
E11.41	Type 2 diabetes mellitus with diabetic mononeuropathy
E11.42	Type 2 diabetes mellitus with diabetic polyneuropathy
E11.43	Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy
E11.44	Type 2 diabetes mellitus with diabetic amyotrophy
E11.49	Type 2 diabetes mellitus with other diabetic neurological complication

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: The prevalence of diabetic polyneuropathy varies from 10% to 100% in patients with diabetes mellitus in population-based studies. It is the most common form of peripheral neuropathy in the Western world.
RISK FACTORS: Patients with poor glycemic control, diabetic nephropathy, or retinopathy are at increased risk.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients most commonly experience numbness and tingling, but they may also experience either feelings of tightness or a sensation of heat or cold.
- Pain is common, is often worst at night, and can be burning, aching, shooting, or lancinating in nature.
- Sensory symptoms begin in the feet and may slowly ascend over months to years. Symptoms in the hands do not generally occur until symptoms in the lower extremities have reached the level of the knees. In more severe cases, the symptoms can spread to the trunk and head.
- Neurologic examination reveals early loss of small-fiber modalities resulting in decreased pinprick and temperature sensation and later involvement of large-fiber modalities leading to a reduction in vibratory and proprioceptive sensation. Ankle reflexes are usually reduced or absent, and more proximal reflexes may also become involved as the neuropathy progresses. Strength is usually normal, but there can be some motor involvement leading to mild weakness and atrophy, which is usually limited to intrinsic foot muscles and ankle dorsiflexors.

BOX 1 Clinical Classification of Diabetic Neuropathies

Symmetric
- Diabetic polyneuropathy
- Diabetic autonomic neuropathy
- Painful diabetic neuropathy

Asymmetric
- Diabetic radiculoplexopathy
- Diabetic thoracic radiculoneuropathy
- Mononeuropathies
- Carpal tunnel syndrome
- Ulnar neuropathy at the elbow
- Peroneal neuropathy at fibular head
- Cranial neuropathies

From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

ETIOLOGY

The precise etiology is unknown but most likely involves a complex interaction of metabolic derangements and microvascular insults occurring in the setting of diabetes.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Although diabetes is the leading cause of peripheral neuropathy in developed countries, there are numerous other causes requiring further investigation(s).

WORKUP

- A thorough history and neurologic examination are essential to confirm features consistent with a diabetic polyneuropathy and exclude other features suggesting alternative diagnoses.
- For some patients, neuropathy may be the presenting feature of previously undiagnosed diabetes.
- Electrodiagnostic evaluation to include nerve conduction studies and electromyography can be helpful in confirming the presence, extent, and severity of a neuropathy.
- Patients with DSPN typically have a reduction of amplitudes and slowing of conduction velocities involving sensory and possibly motor nerves in a length-dependent and symmetric fashion.
- Electromyographic examination of distal muscles may reveal fibrillation potentials, positive sharp waves, and large motor unit action potentials, all suggestive of denervation and reinnervation.
- Electrodiagnostic testing may be negative if the neuropathy is limited to small fiber involvement.
- Neither skin biopsy nor nerve biopsy is necessary in the vast majority of cases.
- Fig. 1 describes a diagnosis and treatment algorithm of diabetic autonomic neuropathy.

LABORATORY TESTS

- Fasting blood sugar, hemoglobin A1c, and 2-hour oral glucose tolerance tests should all be considered in patients with peripheral neuropathy without a known history of diabetes.
- A focused laboratory evaluation for other common or potentially treatable causes of neuropathy is also indicated: Complete blood cell count, comprehensive metabolic panel to include electrolytes and liver function tests, vitamin B_{12} and folate levels, thyroid function tests, serum protein electrophoresis with immunofixation.
- Additional laboratory tests can be considered, based on either history or exam findings suggesting other underlying diagnoses, such as antinuclear antibodies, extractable nuclear antigens, ANCAs, rheumatoid factor, HIV, hepatitis B and C, and cryoglobulins.

IMAGING STUDIES

Imaging is not necessary unless there is concern for an alternate or coexisting process based on the history and examination.

TREATMENT

CHRONIC Rx

- Table 1 summarizes clinical features, diagnosis, and treatment of diabetic autonomic neuropathy.
- Glycemic control: The primary treatment for diabetic polyneuropathy is effective glycemic control, as this may either improve or at least slow progression of the neuropathy.
- Symptomatic management: Another aspect of treatment is the symptomatic management of pain and paresthesias. The American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation have together developed an evidence-based guideline for the treatment of painful diabetic neuropathy. Pregabalin, an anticonvulsant, is the only agent in the guideline that has been established as effective for painful diabetic neuropathy. Other probably effective agents are listed in the following:
  1. Topical agents: Lidocaine 5% patch can be applied to painful areas for 12 hours a day, capsaicin 0.075% applied qid.
  2. Anticonvulsants: Gabapentin (100 to 1200 mg tid), pregabalin (50 to 100 mg tid), carbamazepine (100 mg bid).
  3. Antidepressants: Amitriptyline (10 to 100 mg qhs), nortriptyline (25 to 150 mg qhs), duloxetine (60 to 120 mg daily).
  4. Tramadol (50 mg qid as needed) can be a useful adjunctive analgesic.
- Fig. 2 describes a treatment algorithm for neuropathic pain after exclusion of nondiabetic etiologies and stabilization of glycemic control.

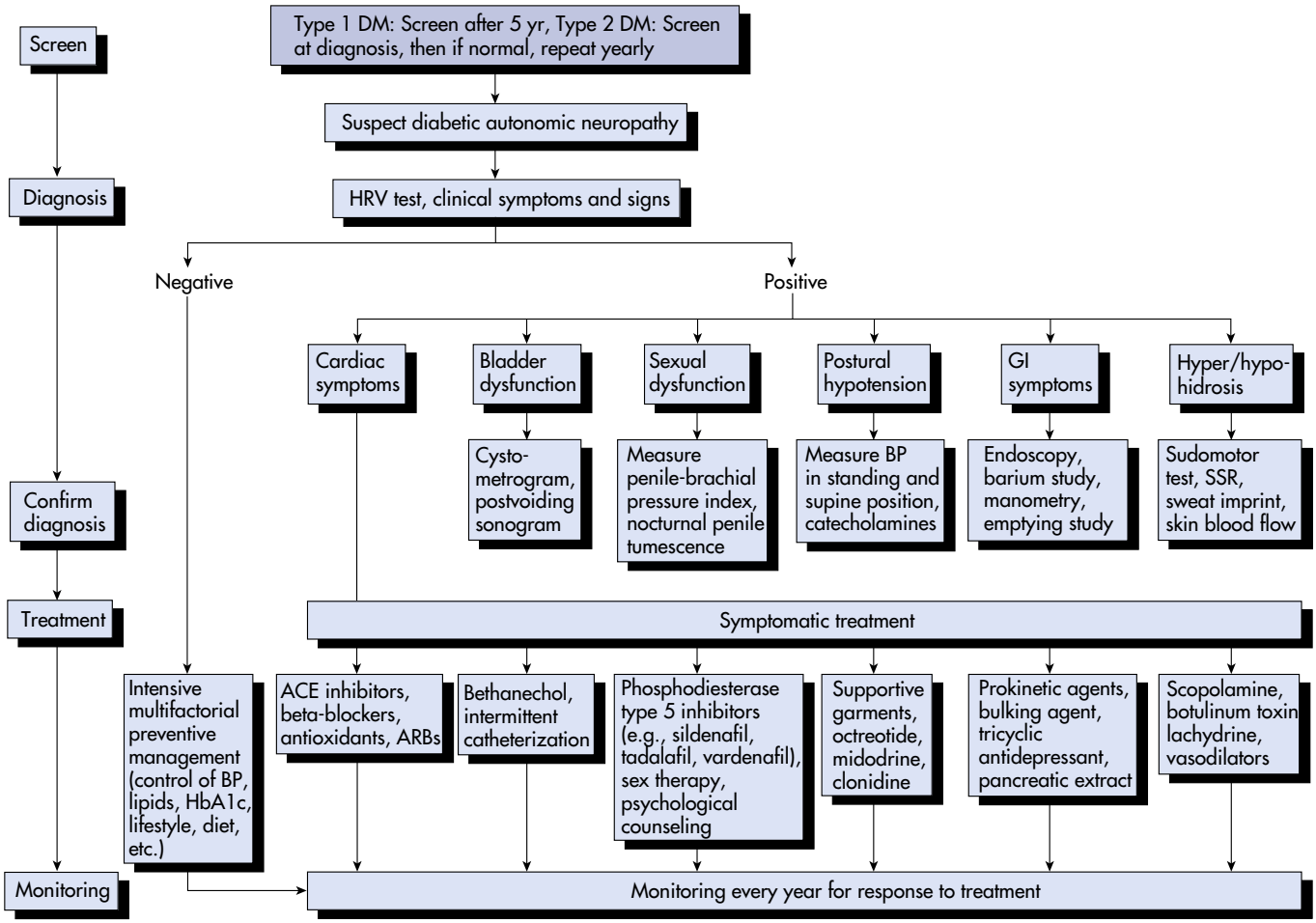

FIG. 1 Diagnosis and treatment algorithm of diabetic autonomic neuropathy. *ACE*, Angiotensin-converting enzyme; *ARBs*, angiotensin receptor blockers; *BP*, blood pressure; *DM*, diabetes mellitus; *GI*, gastrointestinal; *HbA1c*, glycohemoglobin; *HRV*, heart rate variability; *SSR*, sympathetic skin response. (Modified from Larsen PR et al [eds]: *Williams textbook of endocrinology*, ed 11, Philadelphia, 2008, WB Saunders.)

DISPOSITION

The distal sensory loss of diabetic polyneuropathy places patients at increased risk of trauma to the extremities, with the potential for ulceration and infection that could ultimately require amputation if not attended to in a timely fashion.

REFERRAL

- A neurologist can assist in the diagnosis and management of diabetic polyneuropathy.
- Patients with diabetic polyneuropathy should also be evaluated at least annually by a podiatrist and ophthalmologist.
- Progression of diabetic polyneuropathy can be minimized by paying close attention to strict glycemic control as well as other risk factors such as hypertension and obesity.

PEARLS & CONSIDERATIONS

COMMENTS

- For many patients, either DSPN or another form of diabetic neuropathy may be the initial presentation of previously undiagnosed diabetes.
- In addition to regular visits with podiatry, patients with diabetic polyneuropathy should be educated on aggressive foot hygiene and the importance of examining their own feet.

PATIENT & FAMILY EDUCATION

The following websites are recommended:

- http://patienteducationcenter.org/articles/diabetic-neuropathies/
- www.mayoclinic.com/health/diabetic-neuropathy/DS01045

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Divya Singhal, MD**

TABLE 1 Clinical Features, Diagnosis, and Treatment of Diabetic Autonomic Neuropathy

Symptoms	Tests	Treatments
Cardiac		
Resting tachycardia, exercise intolerance	HRV, MUGA thallium scan, MIBG scan	Graded supervised exercise, ACE inhibitors, β-blockers
Postural hypotension, dizziness, weakness, fatigue, syncope	HRV, supine and standing BP, catecholamines	Mechanical measures, clonidine, midodrine, octreotide, erythropoietin
Gastrointestinal		
Gastroparesis, erratic glucose control	Gastric emptying study, barium study	Frequent small meals, prokinetic agents (metoclopramide, domperidone, erythromycin)
Abdominal pain, early satiety, nausea, vomiting, bloating, belching	Endoscopy, manometry, electrogastrogram	Antibiotics, antiemetics, bulking agents, tricyclic antidepressants, pyloric botulinum toxin, gastric pacing
Constipation	Endoscopy	High-fiber diet, bulking agents, osmotic laxatives, lubricating agents
Diarrhea (often nocturnal alternating with constipation)		Soluble fiber, gluten and lactose restriction, anticholinergic agents, cholestyramine, antibiotics, somatostatin, pancreatic enzyme supplements
Sexual Dysfunction		
Erectile dysfunction	H&P, HRV, penile-brachial pressure index, nocturnal penile tumescence	Sex therapy, psychological counseling, phosphodiesterase inhibitors, PGE_1 injections, devices or prostheses
Vaginal dryness		Vaginal lubricants
Bladder Dysfunction		
Frequency, urgency, nocturia, urinary retention, incontinence	Cystometrogram, postvoid sonography	Bethanechol, intermittent catheterization
Sudomotor Dysfunction		
Anhidrosis, heat intolerance, dry skin, hyperhidrosis	Quantitative sudomotor axon reflex, sweat test, skin blood flow	Emollients and skin lubricants, scopolamine, glycopyrrolate, botulinum toxin, vasodilators
Pupillomotor and Visceral Dysfunction		
Blurred vision, impaired adaptation to ambient light, Argyll-Robertson pupil	Pupillometry, HRV	Care with driving at night
Impaired visceral sensation: Silent MI, hypoglycemia unawareness		Recognition of unusual presentation of MI, control of risk factors, control of plasma glucose levels

ACE, Acetylcholinesterase; *BP*, blood pressure; *H&P*, history and physical examination; *HRV*, heart rate variability; *MI*, myocardial infarction; *MIBG*, metaiodobenzylguanidine; *MUGA*, multigated angiography; *PGE_1*, prostaglandin E_1.
From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, WB Saunders.

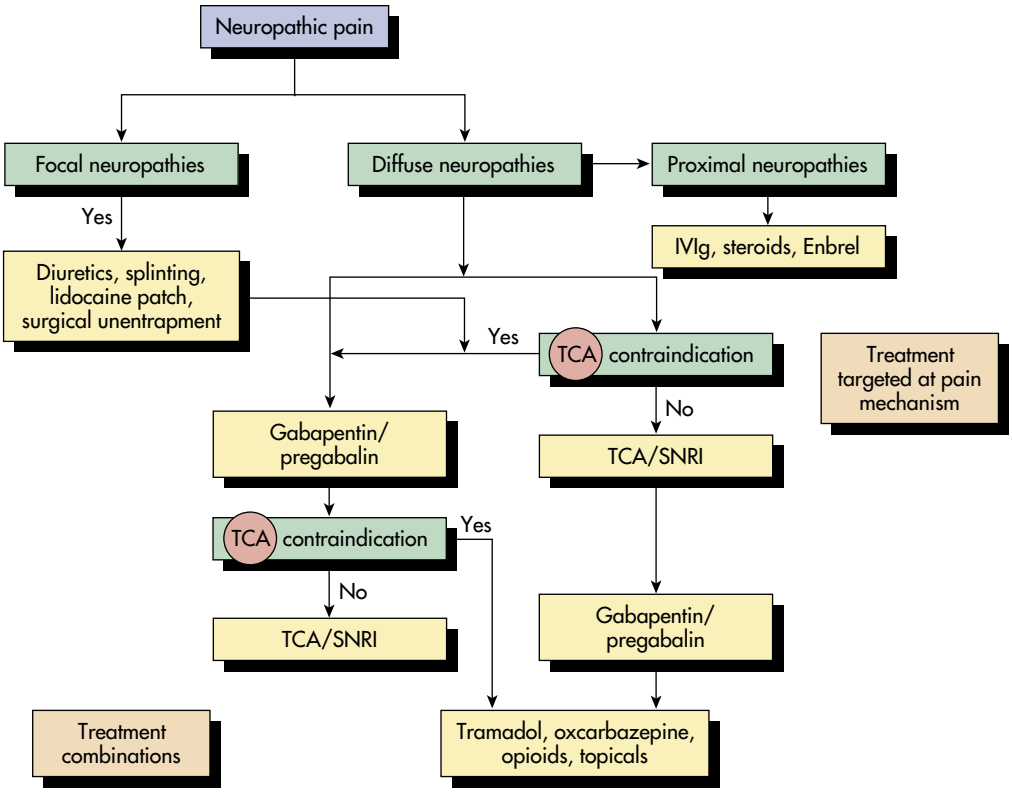

FIG. 2 Treatment algorithm for neuropathic pain after exclusion of nondiabetic etiologies and stabilization of glycemic control. *IVIg*, Intravenous immune globulin; *SNRI*, serotonin-norepinephrine reuptake inhibitors; *TCA*, tricyclic antidepressants. (From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, WB Saunders.)

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Diabetic retinopathy (Fig. 1) is a microvascular abnormality of the retina resulting in microaneurysms (Fig. E2), retinal hemorrhages, lipid exudates (Fig. E3), macular edema, and neovascular vessel growth (Fig. E4) and can ultimately end in blindness. Diabetic retinopathy can be classified into two stages: Nonproliferative (mild, moderate, and severe) and proliferative.

SYNONYMS

Nonproliferative diabetic retinopathy (NPDR)
Proliferative diabetic retinopathy (PDR)
Diabetic macular edema (DME)

ICD-10CM CODES

E08.311	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy with macular edema
E08.319	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy without macular edema
E08.321	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy with macular edema
E08.329	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy without macular edema
E08.331	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy with macular edema
E08.339	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy without macular edema
E08.341	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy with macular edema
E08.349	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy without macular edema
E08.351	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema
E08.359	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy without macular edema

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- After 20 yr of diabetes mellitus, nearly 99% of patients with type 1 and 60% with type 2 disease demonstrate some degree of diabetic retinopathy.
- A leading preventable cause of blindness in the U.S. between the ages of 20 and 74 yr.
- There are approximately 8000 new cases of diabetic retinopathy–induced blindness each yr in the U.S.

PREVALENCE (IN U.S.):

- Prevalence of retinopathy increases with duration of diabetes. Found in 18% of people diagnosed with diabetes for 3- to 4-yr duration and in up to 80% of diabetics with a diagnosis of ≥15 yr.
- In the U.S., the prevalence of diabetic macular edema (the most common cause of vision impairment) is 4%, or approximately 750,000 people.
- CDC data reveal that 4 million Americans were visually impaired due to diabetic retinopathy in 2011.
- The number of Americans with diabetic retinopathy is expected to nearly double, from 7.7 million to 14.6 million between 2010 and 2050. Expected to triple in the Hispanic population.

PREDOMINANT SEX: Males and females affected equally

PREDOMINANT AGE: ≥30 yr

GENETICS:

- The development of diabetes involves the interaction of genetic and nongenetic factors.
- Type 1 has an autoimmune basis, resulting in destruction of beta islet cells and has strong HLA associations.
- Type 2 has genetic predisposition, but the specific genes are not yet well characterized.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Microaneurysms
- Hemorrhages
- Cotton-wool spots
- Lipid exudates
- Macular edema
- Neovascularization
- Retinal detachment (in advanced cases)
- Vitreous hemorrhage
- In early cases, patient may not report a visual disturbance

ETIOLOGY

Prolonged hyperglycemia results in basement membrane thickening in retinal capillaries with subsequent loss of pericytes and endothelial

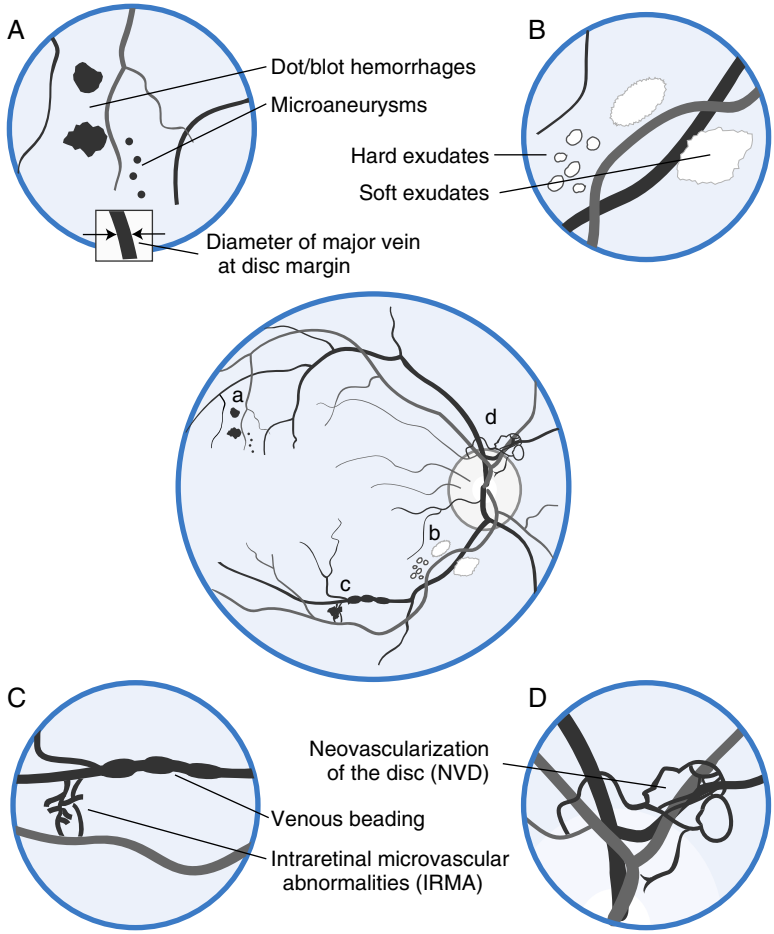

FIG. 1 Types of diabetic retinopathy. The center figure depicting the fundus of a patient with diabetic retinopathy is surrounded by four enlarged views, each labeled with a letter (a to d) corresponding to specific locations on the center figure. **A,** Microaneurysms and dot and blot hemorrhages. The diameter of microaneurysms is less than the width of a major vein at the disc margin (reproduced in square inset). **B,** Hard and soft exudates. **C,** Venous beading and intraretinal microvascular abnormalities (IRMA). **D,** Neovascularization, which may be located within one disc diameter of the optic disc (NVD) or elsewhere (NVE). Although both IRMA and neovascularization represent the formation of new blood vessels, IRMA are confined to the layers of the retina, whereas neovascularization is on the inner surface of the retina or vitreous. (From McGee S: *Evidence-based physical diagnosis*, ed 4, Philadelphia, 2018, Elsevier.)

decompensation resulting in breakdown of the blood–retina barrier and capillary occlusion, ischemia, and serum leakage. This leads to the clinical findings of dot hemorrhages, microaneurysms, lipid exudate, and edema. Upregulation of vascular endothelial growth factor (VEGF) and other cytokines contributes to vascular incompetence and promotes growth of neovascular tissue.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Branch or central retinal vein occlusion
- Hypertensive retinopathy
- Ocular ischemic syndrome (carotid occlusion)
- Radiation retinopathy
- Retinal macroaneurysm
- Sickle cell retinopathy
- Valsalva retinopathy
- Lupus
- Retinal vasculitis
- Terson syndrome

WORKUP

- Fundus photography
- Optical coherence tomography
- Optical coherence angiography
- Fluorescein angiogram
- Laboratory workup if indicated based on DDx

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Tight glycemic control remains the cornerstone in the primary prevention of diabetic retinopathy, particularly in type 1 as seen in the Diabetes Control and Complications Trial (DCCT) and less so in type 2 as seen in the United Kingdom Prospective Diabetes Study (UKPDS) and more recently in the Action to Control Cardiovascular Risk in Diabetes Trial (ACCORD). ADA guidelines recommend A1c <7.0.
- Intensive lowering of blood pressure was shown in UKPDS but not ACCORD to reduce progression of diabetic retinopathy. ADA guidelines recommend BP target of <140/90 mm Hg.
- Lipid lowering results in reduction of retinopathy progression (ACCORD Trial).
- Laser treatment (photocoagulation) for proliferative disease or noncenter involving macular edema.
- Table 1 summarizes classification and management of diabetic retinopathy.

ACUTE GENERAL Rx

- Intravitreal pharmacotherapy with anti-VEGF agents (e.g., bevacizumab, ranibizumab, aflibercept) and/or corticosteroids is the standard of care for patients with center-involved diabetic macular edema.
- Laser therapy: Panretinal laser photocoagulation reduces the risk of severe visual loss in patients with proliferative retinopathy.
- Focal laser reduces risk of moderate visual loss by 50% in patients with clinically significant macular edema.

TABLE 1 Abbreviated Early Treatment Diabetic Retinopathy Study (ETDRS) Classification of Diabetic Retinopathy

Category/Description	Management
Nonproliferative diabetic retinopathy (NPDR)	
No DR	Review in 12 mo
Very mild NPDR Microaneurysms only	Review most patients in 12 mo
Mild NPDR Any or all of: Microaneurysms, retinal hemorrhages, exudates, cotton wool spots, up to the level of moderate NPDR. No intraretinal microvascular anomalies (IRMA) or significant beading	Review range 6-12 mo, depending on severity of signs, stability, systemic factors, and patient's personal circumstances
Moderate NPDR • Severe retinal hemorrhages (more than ETDRS standard photograph 2A: About 20 medium to large per quadrant) in 1-3 quadrants or mild IRMA • Significant venous beading can be present in no more than 1 quadrant • Cotton wool spots commonly present	Review in approximately 6 mo Proliferative diabetic retinopathy (PDR) in up to 26%, high-risk PDR in up to 8% within a yr
Severe NPDR The 4–2–1 rule; one or more of: • Severe hemorrhages in all 4 quadrants • Significant venous beading in 2 or more quadrants • Moderate IRMA in 1 or more quadrants	Review in 4 mo PDR in up to 50%, high-risk PDR in up to 15% within a yr
Very severe NPDR Two or more of the criteria for severe NPDR	Review in 2-3 mo High-risk PDR in up to 45% within a yr
Proliferative diabetic retinopathy (PDR)	
Mild–moderate PDR New vessels on the disc (NVD) or new vessels elsewhere (NVE), but extent insufficient to meet the high-risk criteria	Treatment considered according to severity of signs, stability, systemic factors, and patient's personal circumstances such as reliability of attendance for review. If not treated, review in up to 2 mo
High-risk PDR • New vessels on the disc (NVD) greater than ETDRS standard photograph 10A (about ⅓ disc area) • Any NVD with vitreous hemorrhage • NVE greater than ½ disc area with vitreous hemorrhage	Treatment advised (see text) Should be performed immediately when possible, and certainly same day if symptomatic presentation with good retinal view

DR, Diabetic retinopathy.
From Bowling B: *Kanski's clinical ophthalmology, a systematic approach,* ed 8, Philadelphia, 2016, Elsevier.

- Vitrectomy for traction retinal detachment or vitreous hemorrhage.

CHRONIC Rx

- Monthly anti-VEGF injections until macular edema has resolved with surveillance at regular intervals for additional treatment
- Both ranibizumab (Lucentis) and aflibercept (Eylea) have been FDA-approved for treatment of diabetic retinopathy in patients with macular edema
- Repeated laser treatments may be necessary
- Diet and exercise; good medical control of disease, blood pressure, and cholesterol

DISPOSITION

- Retinal examination should be performed on all routine medical visits. Referral if abnormality seen.
- Routine annual eye examination in all patients with diabetes.
- Prognosis is improved with early diagnosis and treatment.

REFERRAL

Refer to ophthalmologist immediately on finding retinal abnormality to institute early treatment.

! PEARLS & CONSIDERATIONS

COMMENTS

- Early treatment of severe nonproliferative and proliferative retinopathy may minimize complications and visual loss.
- Tight blood sugar control in type 1 patients significantly reduces the probability of developing new-onset retinopathy as well as progression of existing retinopathy.
- Retinopathy is an independent risk marker for cardiovascular disease in patients with type 2 DM.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Diabetic Retinopathy (Patient Information)
Diabetes Mellitus (Related Key Topic)

AUTHOR: **Robert H. Janigian Jr., MD**

SUGGESTED READINGS

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Writing Committee for the Diabetic Retinopathy Clinical Research Network: Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy, a randomized clinical trial, *JAMA* 314(20):2137-2146, 2015.

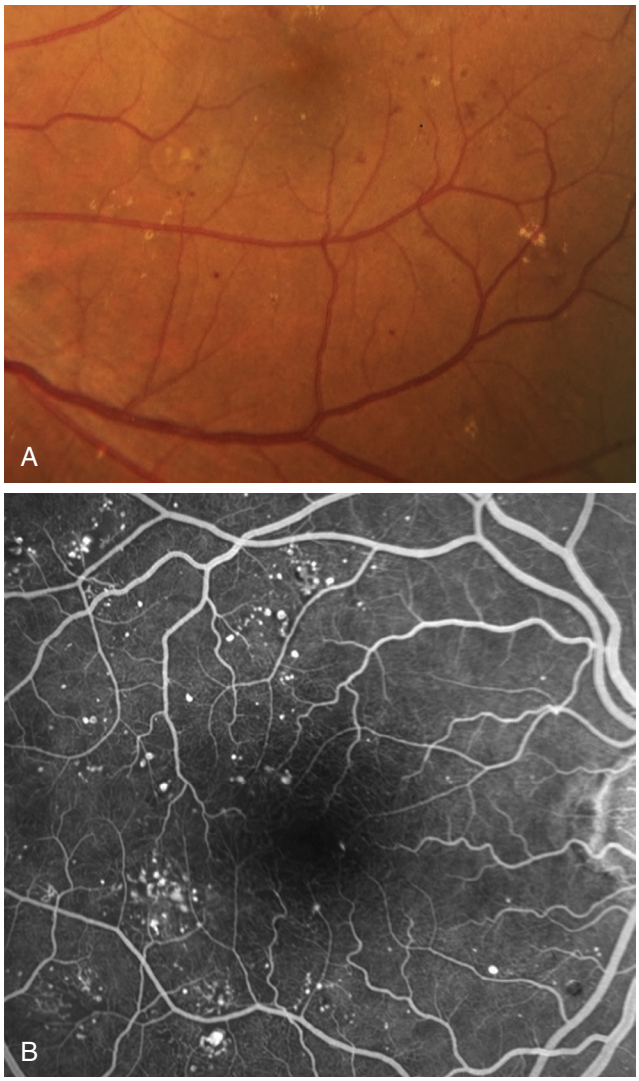

FIG. E2 Microaneurysms. A, Microaneurysms and dot/blot hemorrhages at the posterior pole. **B,** Fluorescein angiogram (FA) shows scattered hyperfluorescent spots in the posterior fundus. (From Bowling B: *Kanski's clinical ophthalmology, a systematic approach,* ed 8, Philadelphia, 2016, Elsevier.)

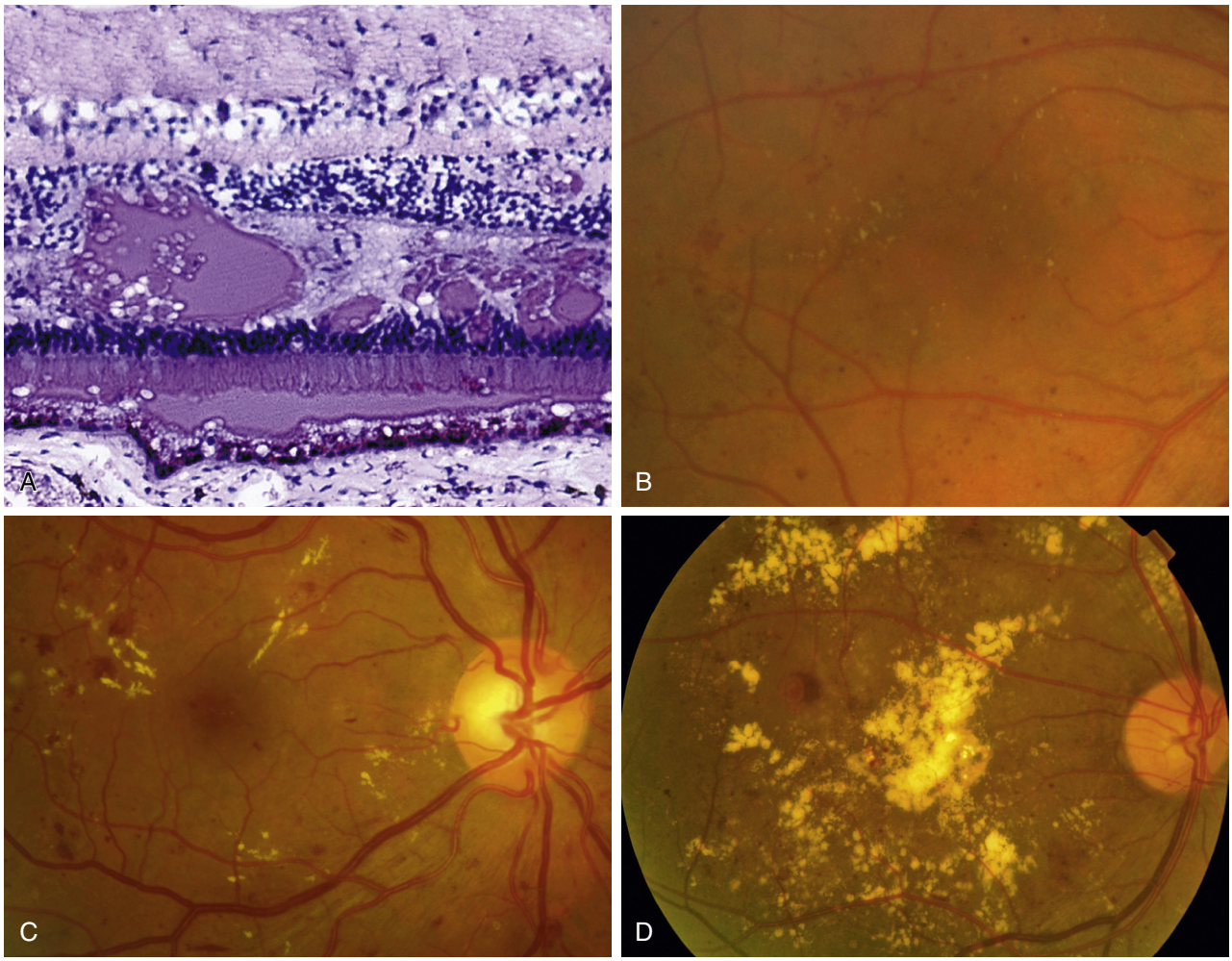

FIG. E3 Exudates. A, Histology shows irregular eosinophilic deposits mainly in the outer plexiform layer. **B,** Small exudates and microaneurysms. **C,** More extensive exudates, some associated with microaneurysms. **D,** Exudates involving the fovea, including central crystalline cholesterol deposition—focal laser has recently been applied superotemporal to the fovea. (Courtesy J Harry [**A**]; S Chen [**C** and **D**]. In Bowling B: *Kanski's clinical ophthalmology, a systematic approach*, ed 8, Philadelphia, 2016, Elsevier.)

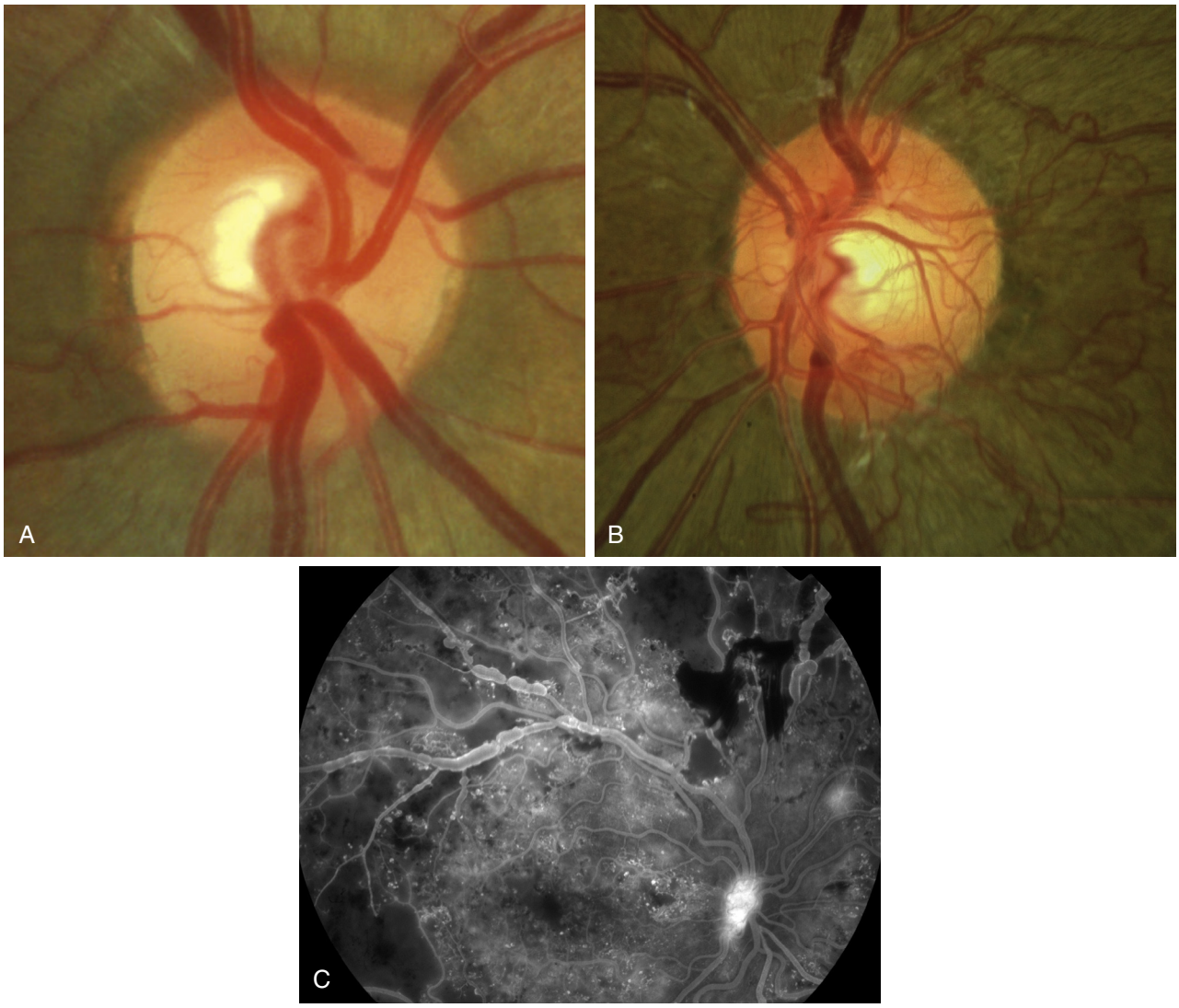

FIG. E4 Disc new vessels. A, Mild. **B**, Severe. **C,** Fluorescein angiogram (FA) shows leaking disc vessels, with extensive peripheral capillary dropout and a small focus of leaking vessels elsewhere. (Courtesy S Chen [**B**]. In Bowling B: *Kanski's clinical ophthalmology, a systematic approach*, ed 8, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Persistent diarrhea is generally defined as an increase in stool frequency (>3 per day) or loose stool consistency for ≥4 wk. Some clinicians define persistent diarrhea as diarrhea lasting ≥14 days.

SYNONYM

Chronic diarrhea

ICD-10CM CODES	
R19.7	Diarrhea, unspecified
K52.9	Noninfective gastroenteritis and colitis, unspecified
K58.0	Irritable bowel syndrome with diarrhea
K59.1	Functional diarrhea
K90.9	Intestinal malabsorption, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- Chronic diarrhea affects approximately 3% to 5% of the U.S. population.
- According to the World Health Organization, the prevalence of chronic diarrhea in children worldwide ranges from 3% to 20%.

PREDOMINANT SEX & AGE: Dependent on etiology:

- Irritable bowel syndrome (IBS) has a female/male ratio of 2:1, with peak prevalence from 20 to 39 yr of age.
- Celiac disease has a slight female predominance, and incidence is highest during infancy, in the third decade, and in the seventh decade.
- Crohn disease has bimodal incidence with peaks in the third and fifth decades.
- Ulcerative colitis has bimodal incidence first between ages 15 and 40 yr and then between ages 50 and 80 yr.
- Lactose intolerance incidence generally increases with age.
- Microscopic colitis is most common in middle-aged women.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

History:

- Specific symptoms: Loose stools, frequent stools, or urgency
- Fecal incontinence: Present or absent
- Duration
- Onset: Congenital, abrupt (infectious, idiopathic secretory diarrhea), or gradual
- Stool characteristics: Watery, bloody, fatty, malodorous
- Stool volume (watery, voluminous stool suggests disorder of small bowel or proximal colon. Frequent small stools suggest a disorder of left colon or rectum.)
- Abdominal pain: Location, relation to meals or bowel movements (inflammatory bowel disease [IBD], IBS, ischemia)
- Weight loss or fever (malabsorption, malignancy, IBD)
- Medical history: Immunologic, endocrine, neoplastic, human immunodeficiency virus (HIV), diabetes, surgery, radiation
- Surgical history: Any prior GI surgeries
- Travel history: Countries with bacterial and parasitic infectious sources
- Medications: All medications and supplements, especially focusing on new medications, drugs containing magnesium, any antibiotics in the past 6 to 8 wk; Box 1 summarizes medications and toxins associated with diarrhea
- Dietary history: Recent changes, "sugar-free" foods, fiber intake, raw seafood or shellfish, raw milk, impure drinking water, alcohol, associated of symptoms with specific food ingestion
- Family history: Absorptive defects (lactose intolerance), IBD, celiac disease, IBS, cancer
- Social history: Risk factors for HIV, receptive anal intercourse (infection or proctitis)
- Aggravating and alleviating factors: Relation to meals, diet, stress
- Excessive flatus, bloating (carbohydrate malabsorption)
- Nocturnal diarrhea (suggests secretory diarrhea)
- Symptoms suggesting IBS: Abdominal pain associated with altered bowel habits and improvement with defecation; often also associated with stress and depression with onset and severity of diarrhea

Physical:

- General: Fluid balance, nutrition (dehydration, malnutrition)
- Skin: Flushing (carcinoid syndrome), dermatitis herpetiformis (celiac disease)
- Mouth: Ulcers (Crohn disease)
- Neck: Thyroid mass or nodule (hyperthyroidism, multiple endocrine neoplasia), lymphadenopathy (malignancy or chronic infection)
- Abdomen
  1. Hepatomegaly (endocrine tumor, amyloidosis)
  2. Scars (surgical causes of diarrhea)
  3. Tenderness (inflammation)
  4. Mass, ascites, tenderness (multiple)
- Rectal:
  1. Sphincter weakness (fecal incontinence), anal fistula, fecal impaction

ETIOLOGY

Cause-specific etiology: Secretory, osmotic, steatorrheal, inflammatory, dysmotile, factitial, iatrogenic

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

(See Box E2)

- Steatorrheal (fatty) diarrhea
  1. Malabsorption syndromes
     a. Mesenteric ischemia
     b. Mucosal diseases (e.g., celiac disease, Whipple disease)
     c. Small intestinal bacterial overgrowth (SIBO)
     d. Drug-induced enteropathy
  2. Maldigestion
     a. Inadequate luminal bile acid
     b. Pancreatic exocrine insufficiency
     c. Liver disease
     d. Bariatric surgery
- Inflammatory diarrhea (Table 1)
  1. Diverticulitis
  2. IBD (Crohn disease, ulcerative colitis, microscopic colitis)
  3. Infectious diseases
     a. Bacterial (e.g., tuberculosis, yersiniosis)
     b. Parasitic (e.g., amebiasis, strongyloidiasis)
     c. Pseudomembranous colitis (*C. difficile*)
     d. Ulcerating viral (e.g., cytomegalovirus, herpes simplex virus)
  4. Ischemic colitis
  5. Neoplasia (colon cancer, lymphoma)
  6. Radiation colitis
- Watery diarrhea (Table 2)
  1. Osmotic diarrhea
     a. Carbohydrate malabsorption (e.g., lactose intolerance)
     b. Osmotic laxatives (e.g., magnesium, phosphate, sulfate, sorbitol)
     c. Gluten and FODMAP intolerance

BOX 1 Medications and Toxins Associated with Diarrhea

Acid-reducing agents (e.g., H_2RAs, PPIs)
Antacids (e.g., those that contain magnesium)
Antiarrhythmics (e.g., quinidine)
Antibiotics (most)
Anti-inflammatory agents (e.g., 5-aminosalicylates, gold salts, NSAIDs)
Antihypertensives (e.g., β-adrenergic receptor blocking drugs)
Antineoplastic agents (many)
Antiretroviral agents
Colchicine
Heavy metals
Herbal products
Prostaglandin analogs (e.g., misoprostol)
Theophylline
Vitamin and mineral supplements

H_2RA, Histamine-2 receptor agonist; *NSAID,* nonsteroidal anti-inflammatory drug; *PPI,* proton pump inhibitor.

From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE 1 Clinical Findings that Suggest the Causative Organisms for Some Inflammatory Diarrheas

Finding	Causative Organisms
Hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura	Shiga toxin-producing *Escherichia coli*; most common with *Shigella dysenteriae* among *Shigella* spp., but *S. dysenteriae* is not found in the U.S.
Reactive arthritis*	*Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Yersinia* spp.
Bone-marrow suppression	*Salmonella* serovars Typhi and Paratyphi
Guillain-Barré syndrome	*Campylobacter jejuni*
Toxic megacolon	*Shigella* spp., *Clostridium difficile, Salmonella* (rarely)
Aortitis/endovascular infection	Nontyphoidal *Salmonellae*
Intestinal hemorrhage/perforation	*Salmonella* serovars Typhi and Paratyphi, TB enteritis
Right lower quadrant tenderness	*Yersinia* spp.
Cellulitis	*Vibrio vulnificus* and *alginolyticus* (see text)
Postinfection IBS	All, including viral gastroenteritis; viruses typically yield less severe postinfection IBS
Small-bowel lymphoproliferative disease	*Campylobacter jejuni*

*Can occur with any enteric pathogen.
IBS, Inflammatory bowel syndrome.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

2. Secretory diarrhea
   a. Bacterial toxins
   b. Congenital syndromes (e.g., congenital chloridorrhea)
   c. Disordered motility
      (1) Diabetic neuropathy
      (2) IBS
      (3) Postsympathectomy
      (4) Postvagotomy
      (5) Diabetic neuropathy
   d. Endocrinopathies
      (1) Addison disease
      (2) Carcinoid syndrome
      (3) Gastrinoma
      (4) Hyperthyroidism
      (5) Mastocytosis
      (6) Medullary carcinoma of the thyroid
      (7) Pheochromocytoma
      (8) Somatostatinoma
      (9) VIPoma
   e. Idiopathic secretory diarrhea
   f. Ileal bile acid malabsorption
   g. IBD (Crohn disease, ulcerative colitis, microscopic colitis [collagenous])
   h. Laxative abuse
   i. Medications and toxins
   j. Lymphocytic colitis
   k. Neoplasia (colon carcinoma, lymphoma, villous adenoma in rectum)
   l. Vasculitis
3. Factitial causes
   a. Munchausen
   b. Eating disorders
4. Iatrogenic causes
   a. Cholecystectomy
   b. Ileal resection
   c. Bariatric surgery

WORKUP

- Due to the many potential causes of chronic diarrhea, it is impractical to use the same diagnostic tests on every patient.
- Good history and physical examination should be obtained (as mentioned previously), and the workup should be tailored accordingly.
- First determine the type of diarrhea (watery, fatty, or inflammatory) based on the history and physical examination. Further tests may then be obtained to differentiate the diseases in that subtype of diarrhea.
- Basic laboratory testing may include complete blood count (CBC) (anemia, leukocytosis), electrolyte tests, liver function tests, albumin, erythrocyte sedimentation rate, C-reactive protein, and thyroid stimulating hormone.
- Initial stool studies may include fecal leukocyte and fecal occult blood testing.
- Further lab testing as indicated by clinical suspicion:
  1. IBD: Fecal calprotectin
  2. Diarrhea after hospitalization or recent antibiotics: *Clostridium difficile* stool toxin
  3. Suspected laxative abuse: Stool laxative screen
  4. Malabsorption: Fecal fat, Sudan stain
  5. Celiac panel (tissue transglutaminase immunoglobulin A), especially in patients with iron deficiency anemia on CBC
  6. Watery diarrhea
     a. Fecal osmotic gap: 290 – 2([Na^+] – [K^+])
        (1) Gap >125 mOsm/kg suggests osmotic diarrhea.
        (2) Gap <50 mOsm/kg suggests secretory diarrhea.
     b. Fecal pH
        (1) pH <5.3 suggests carbohydrate malabsorption (lactose intolerance).

Rx TREATMENT

In most cases, an underlying etiology should be discovered and treated accordingly. However, nonspecific treatment may be used in several situations:

- Volume depletion that requires treatment (or hospitalization) during evaluation.
- Specific treatment for a condition fails to adequately treat diarrhea.
- No specific treatment is available.

NONPHARMACOLOGIC THERAPY

- If etiology can be managed with diet modification (e.g., lactose intolerance or celiac disease), offending substance should be eliminated from diet.
- Reasonable to have trial of reduced dietary lactose and caffeine and monitor for improvement.
- Fiber supplementation (psyllium) can thicken stool consistency; however, it may increase stool output.
- Patients with stool output greater than 1000 g per day often receive IV hydration, but as an alternative, most could be managed with oral rehydration solution (ORS).
- Other therapies would be determined by the specific etiology of persistent diarrhea.

CHRONIC Rx

- General principles:
  1. Opiates are the most effective nonspecific antidiarrheal drugs. In general, they should not be used in severe diarrhea due to acute infections, massive intestinal resection, or secretion of endogenous secretagogues.
  2. Less potent opiate agents (loperamide) should be attempted first, but treatment should be escalated to more potent agents if low-potency opiates fail.
  3. Avoid high-potency agents when concerns of narcotic abuse and/or dependence exist.
  4. When prescribed, opiates should be used on a scheduled basis rather than as needed.
- Low-potency opiate antidiarrheals
  1. Diphenoxylate with atropine (Lomotil) 2.5 to 5 mg 4× daily
  2. Loperamide (Imodium) 2 to 4 mg 4× daily
- More potent opiate antidiarrheals (avoid in alcoholics or history of drug abuse)
  1. Codeine 15 to 60 mg 4× daily
  2. Morphine 2 to 20 mg 4× daily
  3. Tincture of opium 2 to 20 drops 4× daily
- Alpha-2 agonist
  1. Clonidine 0.1 to 0.3 mg 3× daily.
  2. Utility limited by hypotensive effect. Opiate agents should be attempted first.
- Intraluminal agents
  1. Used to bind toxins and change stool consistency
  2. Usually ineffective as monotherapy in managing chronic diarrhea
  3. Fibers: Psyllium, calcium polycarbophil, methylcellulose
  4. Bismuth: Pepto-Bismol
  5. Clays: Attapulgite, kaolin
  6. Bile acid–binding resins: Cholestyramine, colestipol
- Newer agent
  1. Racecadotril, an antisecretory enkephalinase inhibitor
  2. Not yet available in the U.S.

TABLE 2 Secretory versus Osmotic Diarrhea

Type of Diarrhea	Causes	Examples
Secretory	Exogenous secretagogues	Enterotoxins (e.g., cholera)
	Endogenous secretagogues	Neuroendocrine tumors (e.g., carcinoid syndrome)
	Absence of ion transporter	Congenital chloridorrhea
	Loss of intestinal surface area	Intestinal resection, diffuse intestinal mucosal disease
	Intestinal ischemia	Diffuse mesenteric atherosclerosis
	Rapid intestinal transit	Intestinal hurry following vagotomy
Osmotic	Ingestion of poorly absorbed agent	Magnesium ingestion
	Reduced nutrient transport	Lactase deficiency

From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

COMPLEMENTARY & ALTERNATIVE MEDICINE

There is growing evidence that shows some benefit of probiotics in the treatment of infectious diarrhea, IBS, *Clostridium difficile* disease, and antibiotic-associated diarrhea.

DISPOSITION

Etiology dependent

REFERRAL

Gastroenterology referral is warranted depending on severity of symptoms, need for endoscopic procedures, and/or need for long-term disease management.

PEARLS & CONSIDERATIONS

COMMENTS

- A good history is crucial in the evaluation of chronic diarrhea. An attempt should be made to classify diarrhea as watery, fatty, or inflammatory.
- Fecal incontinence is often described by patients as diarrhea, and many patients are reluctant to volunteer more information on this subject unless specifically asked.
- IBS is one of the most common causes of chronic diarrhea and requires minimal laboratory studies. Patients should be screened appropriately.
- An underlying etiology of chronic diarrhea should be determined and treated accordingly.

PATIENT & FAMILY EDUCATION

- Disease-specific education

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Amebiasis (Related Key Topic)
Celiac Disease (Related Key Topic)
Colorectal Cancer (Related Key Topic)
Crohn Disease (Related Key Topic)
Gastroenteritis (Related Key Topic)
Giardiasis (Related Key Topic)
Hyperthyroidism (Related Key Topic)
Incontinence, Bowel, Elderly Patient (Related Key Topic)
Irritable Bowel Syndrome (Related Key Topic)
Lactose Intolerance (Related Key Topic)
Malabsorption (Related Key Topic)
Chronic Pancreatitis (Related Key Topic)
Paraneoplastic Syndromes (Related Key Topic)
Small Bowel Intestinal Bacterial Overgrowth (Related Key Topic)
Traveler's Diarrhea (Related Key Topic)
Tropical Sprue (Related Key Topic)
Ulcerative Colitis (Related Key Topic)
Whipple Disease (Related Key Topic)

AUTHOR: **Juan Guerra, DO**

SUGGESTED READINGS

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Juckett G, Rupal T: Evaluation of chronic diarrhea, *Am Fam Physician* 84(10):1119-1126, 2011.

Ritchie ML, Romanuk TN: A meta-analysis of probiotic efficacy for gastrointestinal diseases, *PLoS One* 7:e34938, 2012.

Schiller L, Sellin J: Diarrhea. In ed 10, Sleisenger MH, Feldman M, Friedman LS, Brandt LJ, editors: *Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology, diagnosis, management, ed 10,* Philadelphia, PA, 2016, Saunders/Elsevier, pp 221-224.

van Rheenen PF, Van de Vijver E, Fidler V: Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis, *BMJ* 341:c3369, 2010.

BOX E2 Differential Diagnosis of Diarrhea

Acute Diarrhea
- Infection
  - Bacteria
  - Parasites
  - Protozoa
  - Viruses
- Food allergies
- Food poisoning
- Medications
- Initial presentation of chronic diarrhea

Chronic Diarrhea
- Fatty diarrhea
- Malabsorption syndromes
  - Mesenteric ischemia
  - Mucosal diseases (e.g., celiac disease, Whipple disease)
  - Short bowel syndrome
  - SIBO
- Maldigestion
  - Inadequate luminal bile acid concentration
  - Pancreatic exocrine insufficiency

Inflammatory Diarrhea
- Diverticulitis
- Infectious diseases
  - Invasive bacterial infections (e.g., tuberculosis, yersiniosis)
  - Invasive parasitic infections (e.g., amebiasis, strongyloidiasis)
  - Pseudomembranous colitis (*Clostridium difficile* infection)
  - Ulcerating viral infections (e.g., cytomegalovirus, HSV)
- Inflammatory bowel diseases
  - Crohn disease
  - UC
  - Ulcerative jejunoileitis
- Ischemic colitis
- Neoplasia
  - Colon cancer
  - Lymphoma
- Radiation colitis

Watery Diarrhea
- Osmotic diarrhea
  - Carbohydrate malabsorption
  - Osmotic laxatives (e.g., Mg^{2+}, PO_4^{3-}, SO_4^{2-})
- Secretory diarrhea
  - Bacterial toxins
  - Congenital syndromes (e.g., congenital chloridorrhea)
  - Disordered motility, regulation
    - Diabetic autonomic neuropathy
    - IBS
    - Postsympathectomy diarrhea
    - Postvagotomy diarrhea
  - Diverticulitis
  - Endocrinopathies
    - Addison disease
    - Carcinoid syndrome
    - Gastrinoma
    - Hyperthyroidism
    - Mastocytosis
    - Medullary carcinoma of the thyroid
    - Pheochromocytoma
    - Somatostatinoma
    - VIPoma
  - Idiopathic secretory diarrhea
    - Epidemic secretory (Brainerd) diarrhea
    - Sporadic idiopathic secretory diarrhea
  - Ileal bile acid malabsorption
  - IBD
    - Crohn disease
    - Microscopic colitis
    - Collagenous colitis
    - Lymphocytic colitis
    - UC
  - Laxative abuse (stimulant laxatives)
  - Medications and toxins (see Box 1)
  - Neoplasia
    - Colon carcinoma
    - Lymphoma
    - Villous adenoma in rectum
  - Vasculitis

HSV, Herpes simplex virus; *IBD,* inflammatory bowel disease; *IBS,* inflammatory bowel syndrome; *SIBO,* small bacterial overgrowth; *UC,* ulcerative colitis.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

Diffuse Idiopathic Skeletal Hyperostosis

BASIC INFORMATION

DEFINITION

Diffuse idiopathic skeletal hyperostosis (DISH) is a systemic disorder primarily involving the axial skeleton. DISH is characterized by widespread bone proliferation as well as calcification and ossification of soft tissues, including ligaments and their sites of insertion. DISH is known to be associated with certain metabolic abnormalities.

SYNONYMS

Ankylosing hyperostosis
Forestier disease
DISH

ICD-10CM CODES

M48.10	Ankylosing hyperostosis, site unspecified
M48.11	Ankylosing hyperostosis, occipito-atlanto-axial region
M48.12	Ankylosing hyperostosis, cervical region
M48.13	Ankylosing hyperostosis, cervico-thoracic region
M48.14	Ankylosing hyperostosis, thoracic region
M48.15	Ankylosing hyperostosis, thoraco-lumbar region
M48.16	Ankylosing hyperostosis, lumbar region
M48.17	Ankylosing hyperostosis, lumbosacral region
M48.18	Ankylosing hyperostosis, sacral and sacrococcygeal region
M48.19	Ankylosing hyperostosis, multiple sites in spine

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: The prevalence of DISH varies in different populations. Factors such as age, ethnicity, geography, and clinical setting affect the prevalence of the disease. Studies have shown DISH is more common in developed nations, although this may be secondary to more frequent use of radiologic imaging in these countries. Higher prevalence rates are seen in men, 10% to 25% versus 5% to 15% in women over the age of 50 yr. Rates increase with age, with prevalence reported as high as 35% in men and 26% in women over the age of 70 yr.

PREDOMINANT SEX AND AGE:

- Male predominance with a ratio of 2:1
- Mostly seen in elderly patients, usually after the age of 50 yr

GENETICS: Association with *COL6A1* gene in some populations, causing ossification of the posterior longitudinal ligament, a condition related to DISH. Matrix Gla protein and Dickkopf-1 (inhibitors of bone formation) may be deficient in DISH patients, leading to hyperostosis.

RISK FACTORS:

- Obesity
- Type II diabetes mellitus
- Dyslipidemia
- Hypertension
- Hyperinsulinemia
- Elevated growth hormone and insulin-like growth factor (IGF-1) levels
- Chronic vitamin A toxicity/retinoid use

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients with DISH are usually asymptomatic or experience increased stiffness in the spine or peripheral joints. In the spine, osteophytes can obstruct or impinge on other structures or tissues, causing dysphagia (DISH affecting the cervical spine), myelopathy, quadriplegia, spinal stenosis, and ossification of posterior longitudinal ligament. Spinal ligament calcification and ossification leads to decreased range of motion and a stooped posture as well as an increasing risk for fractures. Peripheral enthesopathies are usually asymptomatic, but mechanical stresses can injure the entheses and cause pain. In patients with DISH, pronounced hypertrophic changes can be seen affecting certain peripheral joints that are not typically associated with OA, such as the metacarpophalangeal joints, elbows, shoulders, and ankles. Thoracic spinal involvement is common in DISH and not usually seen in OA. Patients with DISH are at increased risk for heterotopic ossification after orthopedic surgery (i.e., hip arthroplasty).

ETIOLOGY

Etiology of DISH is unknown and the cause of excess bone formation is unclear. Chondrocytes located in entheseal areas become activated and cause changes in the adjacent matrix leading to ossification (Fig. E1). Local vascular infiltration also promotes ossification.

DIAGNOSIS

Diagnosis of DISH is made by radiographic imaging. Bone formation is typically seen in the thoracic spine, and less frequently in the cervical and lumbar spines. Coarse osteophytes that seem to "flow" between adjacent vertebrae are seen on the right side of the thoracic spine (Fig. E2), thought to be subsequent to the pressure effect of the left-sided aorta. Ossification occurs within the overlying anterior longitudinal ligament (Fig. E3), preserving the original bone cortex. The intervertebral disc height is preserved in the involved segments. Peripheral bone formation is seen in entheseal areas, especially around the heels (Achilles tendon and plantar fascia), knees (peripatellar ligaments), and elbows (olecranon). Peripheral new bone formation can be seen as well, with increased distal finger tuft thickening, increased sesamoid bone size, and increased cortical bone thickness. There is no evidence of apophyseal joint ankylosis or sacroiliac involvement.

Resnick and Niwayama criteria: Most frequently used and is based on radiographic findings in the spine:

- Findings of new bone formation/osteophytes bridging four adjoining vertebral bodies or ossification of the anterolateral longitudinal ligament
- Preserved intervertebral disc height
- Absence of degenerative disc disease, sacroiliac joint, or facet joint involvement or changes

Others have proposed different criteria for diagnosis, which include the presence of peripheral enthesopathy. New diagnostic criteria

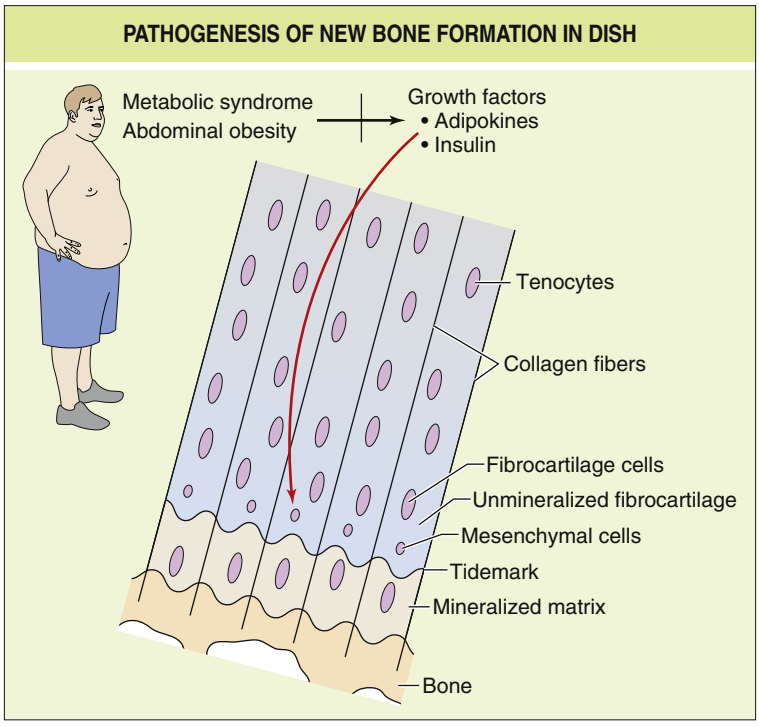

FIG. E1 Diagram of the enthesis showing cellular components that respond to growth factor stimulation, resulting in new bone formation that characterizes diffuse idiopathic skeletal hyperostosis (DISH). (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

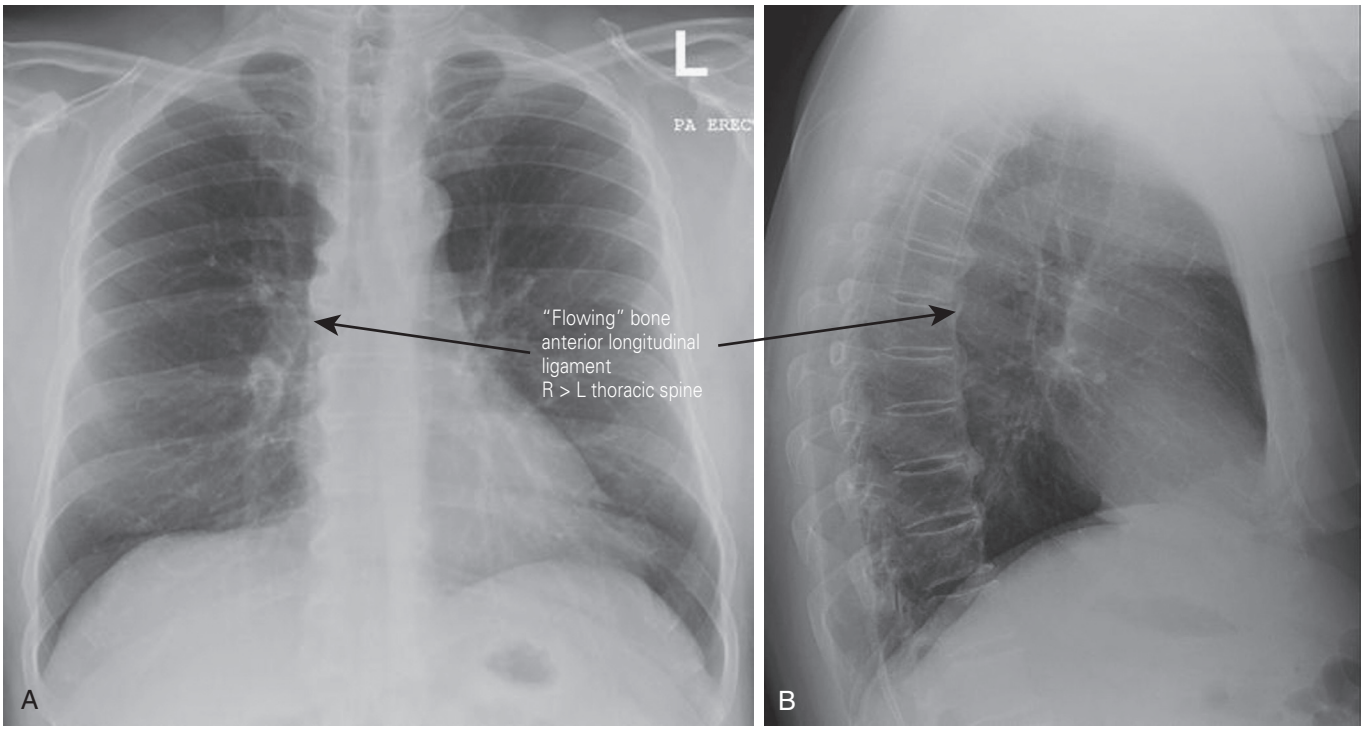

FIG. E2 Typical radiographic findings in the thoracic spine on routine chest radiographs (posteroanterior **[A]** and lateral **[B]**), with "flowing" new bone formation linking four contiguous vertebrae, predominantly right-sided, in absence of intervertebral disk change. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

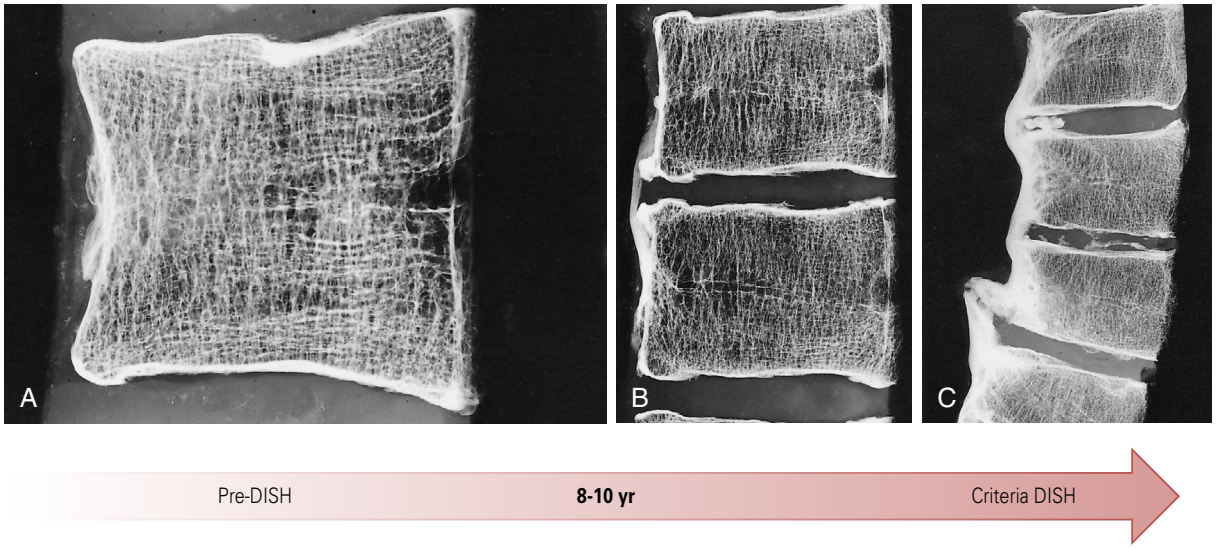

FIG. E3 Progressive spinal entheseal changes in diffuse idiopathic skeletal hyperostosis (DISH). (A) The earliest change is seen, with ossification at the site of attachment of the anterior longitudinal ligament to the middle of the vertebral body, well away from the annulus. Note the separation of the ossification from the intact cortex, except at the site of attachment. **(B)** Moderately advanced changes, with ossification bridging the disk space but still firmly attached to cortex at the middle of the vertebral body. **(C)** Advanced changes, typical of established DISH, with smooth attachment of the new bone to the original cortex. The ossified ligament is much thickened and interrupted at the lower level. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

are needed to help recognize milder forms of the disease, those affecting other parts of the spine, and those that manifest initially with peripheral enthesopathy.

DIFFERENTIAL DIAGNOSIS

- Ankylosing spondylitis (Table E1 describes selected differences)
- Degenerative disc disease—spondylosis deformans
- Acromegaly
- Ossification of the posterior longitudinal ligament

WORKUP

Diagnosis of DISH is made with radiologic imaging. Patients with the above risk factors (increased weight, BMI, waist circumference, and systolic blood pressure) are at risk for cardiovascular disease and evaluation for this also should be pursued.

LABORATORY TESTS

- Routine biochemical tests and erythrocyte sedimentation rate (ESR) are normal
- Laboratory testing should include evaluation for metabolic syndrome, i.e., fasting glucose or HgbA1c, cholesterol panel, etc.
- Uric acid

TABLE E1 Selected Differences between Diffuse Idiopathic Skeletal Hyperostosis and Axial Spondyloarthropathy

Disorder	Diffuse Idiopathic Skeletal Hyperostosis	Axial Spondyloarthropathy
Age at presentation	Usually older than 50 yr	Usually younger than 40 yr
Associated metabolic disorder	Usually present	Not necessarily present
HLA B27	No association	Strong association
Spinal new bone	Usually exuberant, with preservation of bony cortex; there may be a gap between new bone in anterior longitudinal ligament and vertebra	Usually narrow, vertically aligned new bone that is confluent with the underlying vertebra
Sacroiliac joints	Plain radiographs may show anterior osteophytosis, causing "bland fusion" without erosion or sclerosis. CT scan may show sacroiliac anterior joint-line fusion, without erosion or sclerosis. Bone scan and MRI are normal	Plain radiographs show variable joint irregularity caused by erosions, bridging new bone, and joint line sclerosis. CT scan shows variable sacroiliac joint irregularity, erosion, fusion, or sclerosis. In active inflammatory regions, bone scan shows increased uptake, and MRI shows bone marrow edema and synovitis
Entheseal regions	Usually large, well-corticated enthesophyte; sometimes radiologic gap at the entheseal attachment	Entheseal new bone usually smaller with less well-defined margins and irregular, fluffy new bone at distal entheseal area

CT, Computed tomography; *HLA,* human leukocyte antigen; *MRI,* magnetic resonance imaging.
From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

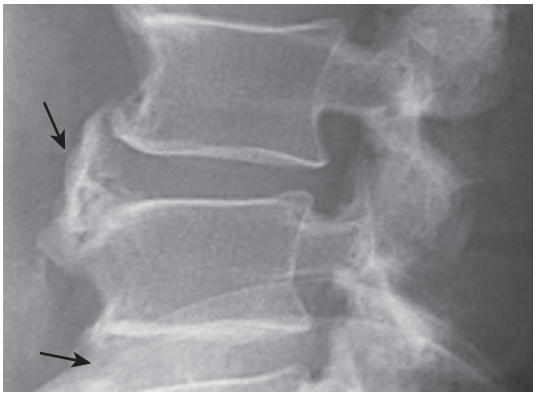

FIG. E4 Diffuse idiopathic skeletal hyperostosis (DISH): Lumbar spine. This lateral radiograph of the lumbar spine shows early changes of DISH. Calcifications of the anterior longitudinal spinal ligament *(arrows)* are evident and will eventually evolve into flowing osteophytes extending across multiple spinal levels. (From Firestein GS: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.)

IMAGING STUDIES

- Posteroanterior and lateral (Fig. E4) x-ray views of the spine
- Computed tomography (CT) or magnetic resonance imaging (MRI) of the spine (Fig. E5) (not routinely needed unless evaluating for other possible conditions such as spinal stenosis)
- Plain radiographs of symptomatic peripheral joints

Rx TREATMENT

There is no specific treatment available for DISH, and it is largely symptomatic. Management issues are summarized in Table E2.

- Weight management
- Treatment and control of components of metabolic syndrome
- Treat cardiovascular risk factors

NONPHARMACOLOGIC THERAPY

- Physical therapy, light exercise
- Heat
- For peripheral enthesopathy pain, local soft applications such as insoles for plantar spurs or orthotics can be used as well as protective bandages at other sites
- Surgical intervention rarely necessary, unless complications such as dysphagia from cervical osteophytes or spinal stenosis occurs

ACUTE GENERAL Rx

- Analgesics and nonsteroidal anti-inflammatory medications (NSAIDs)
- Local corticosteroid injections

CHRONIC Rx

- Pain management as above
- Prevention of heterotopic ossification after orthopedic surgical procedures: NSAIDs, anti-vitamin K, and irradiation

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Ankylosing Spondylitis (Related Key Topic)
Osteoarthritis (Related Key Topic)

AUTHOR: **Joanne Szczygiel Cunha, MD**

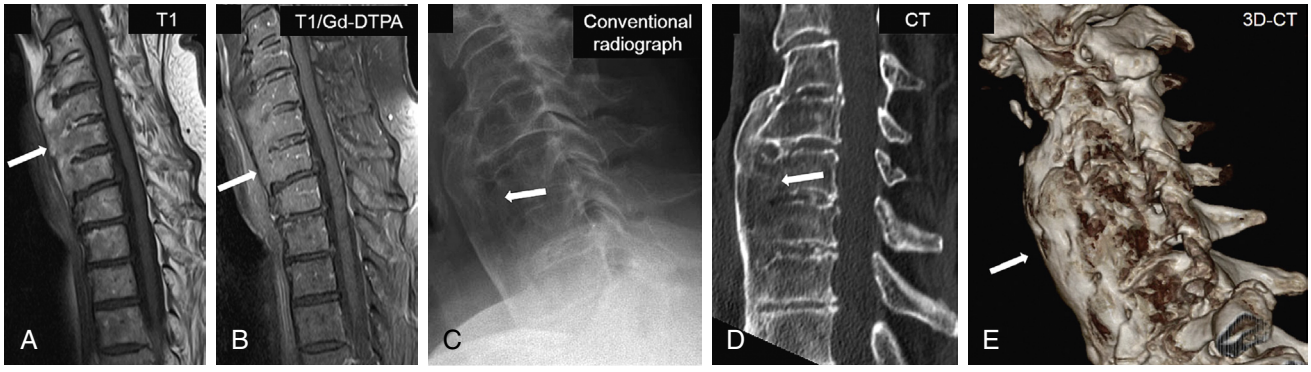

FIG. E5 Diffuse idiopathic skeletal hyperostosis (DISH) in the cervical spine, characterized by bulky osteophytes *(arrow),* which exceed the length of the anterior longitudinal ligament. (A) T1-weighted image. **(B)** T1/gadolinium diethylenetriamine–pentaacetic acid (T1/Gd-DTPA) image. **(C)** Conventional radiograph. **(D)** Computed tomography (CT) image. **(E)** Three-dimensional computed tomography (3D-CT) image. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

TABLE E2 Management Issues in Diffuse Idiopathic Skeletal Hyperostosis

Issue	Management
Spinal and Peripheral Enthesopathy	
Asymptomatic (usual)	Encourage exercise and ideal body weight; assess cardiovascular risk factors
Symptomatic	As above plus physical therapy, local corticosteroid injection therapy, and analgesic and anti-inflammatory agents
Complications	
Facet arthritis	Physical therapy, corticosteroid injection
Spinal stenosis	Exercise, corticosteroid injection, surgery
Dysphagia	Conservative (e.g., smaller meal servings), surgery
Osteoarthritis	Standard approaches
Associated Metabolic Syndrome	
Hypertension, diabetes, dyslipidemia, gout, obesity	Treat vigorously

From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

SUGGESTED READING

Hiyama A et al: Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) assessed with whole-spine computed tomography in 1479 subjects, *BMC Musculoskelet Disord* 19(1):178, 2018.

Katzman WB et al: Diffuse idiopathic skeletal hyperostosis (DISH) and impaired physical function: the Rancho Bernardo Study, *J Am Geriatr Soc* 65(7):1476-1481, 2017.

Mader R, Verlaan J, Buskila D: Diffuse idiopathic skeletal hyperostosis: clinical features and pathogenic mechanisms, *Nat Rev Rheumatol* 9:741-750, 2013.

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Digoxin Overdose

BASIC INFORMATION

DEFINITION

Digoxin, a cardiac glycoside, is used for the treatment of symptomatic heart failure with reduced ejection fraction and ventricular rate control in atrial fibrillation.

Chronic digoxin therapy or acute overdose can cause toxicity. Toxicity can occur even when serum levels are within the therapeutic range.

SYNONYMS

Digitalis overdose
Cardiac glycoside toxicity

ICD-10CM CODE

T46.0X1A Poisoning by cardiac-stimulant glycosides and drugs of similar action, accidental (unintentional), initial encounter

PHARMACOKINETICS

Steady-state levels (not peak levels) correlate with toxicity; digoxin reaches steady state in 5 to 7 days.
BIOAVAILABILITY: Approximately 80% tablets; 100% capsules or IV
VOLUME OF DISTRIBUTION: 5 to 7 L/kg, highly tissue bound
HALF-LIFE: 36 to 48 hr
EXCRETION: Predominantly renal
THERAPEUTIC LEVEL: 0.5 to 2 ng/ml (0.5 to 0.9 ng/ml suggested in heart failure and <1.2 for atrial fibrillation); check level 1 wk after starting therapy or changing dose. Sample should be drawn at least 6 hr after last dose.

EPIDEMIOLOGY & DEMOGRAPHICS

- Digoxin toxicity remains relatively common despite decline in digoxin use, likely because of its narrow therapeutic range. Occurs in up to 5% of individuals on therapy.
- Factors that potentiate toxicity (may increase level or modify cardiac sensitivity): Advanced age, female gender, renal insufficiency, cardiac or pulmonary disease, hypokalemia, hyperkalemia, hypomagnesemia, hypercalcemia, hypernatremia, acid-base disturbance, hypoxia, hypothyroidism, volume depletion, and drugs that affect elimination (ACE inhibitors, amiodarone, carvedilol, clarithromycin, cyclosporine, diltiazem, erythromycin, itraconazole, ketoconazole, NSAIDs, rifampin, spironolactone, tetracyclines, quinidine, verapamil, and herbal supplements), coingestion of cardiotoxic drugs (beta-blockers, calcium channel blockers, tricyclic antidepressants).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Cardiac, gastrointestinal, and central nervous systems are affected. Fatigue, malaise, and weakness are common symptoms. Presentation may differ in acute vs. chronic toxicity. Acute toxicity may be asymptomatic for several hours. Chronic toxicity is more difficult to recognize because of the nonspecific presentation; visual disturbance and mental status changes may be most prominent.

CARDIAC: Initial presentation often due to proarrhythmic effects; can present with almost any dysrhythmia or conduction block except rapidly conducted atrial arrhythmias. Premature ventricular complexes and bradycardia are common. Patients with healthy hearts usually present with bradyarrhythmias and AV block, and those with underlying heart disease often present with ventricular arrhythmias.
GASTROINTESTINAL: Anorexia, nausea, vomiting, diarrhea, abdominal pain
CENTRAL NERVOUS SYSTEM:

- Headache, dizziness, visual disturbance (flashing lights, halos, blurred vision, scotomas, change in color perception), lethargy, confusion, hallucinations, delirium, syncope.
- Hyperkalemia is usually seen in acute poisoning; hypokalemia is more common in chronic toxicity.

ETIOLOGY

Digoxin affects cardiac cells, the autonomic nervous system, and vascular smooth muscle. Digoxin reversibly inhibits the sodium-potassium ATPase pump (Na^+, K^+-ATPase) in myocardial cells, increasing extracellular K^+ and intracellular Na^+. This reduces the activity of the Na-Ca exchanger, leading to intracellular accumulation of calcium. This increases myocardial contractility and cardiac output, the positive inotropic effect associated with digoxin therapy. Cardiac glycosides also decrease the heart rate (effect on SA node) and slow conduction through the AV node by increasing vagal tone. Digoxin also has other neurohormonal and hemodynamic effects that are not completely understood. In toxicity, enhanced automaticity and excitability of cardiac tissue and depressed conduction facilitate extrasystoles and arrhythmias.

DIAGNOSIS

Digoxin toxicity is a clinical diagnosis; patients can have toxicity even when the digoxin level is within therapeutic range.

DIFFERENTIAL DIAGNOSIS

Toxicity due to other cardiac glycosides:

- Digitoxin
- Deslanoside
- Lanatoside C
- Ouabain

Side effects from other medications:

- Beta-blockers
- Calcium channel blockers
- Clonidine
- Cyclic antidepressants
- Encainide and flecainide
- Procainamide
- Propoxyphene
- Quinidine

Ingestion of plants producing digitalis-like glycosides:

- Foxglove
- Oleander
- Lily of the valley

Cardiac conduction abnormalities:

- Sick sinus syndrome
- AV node dysfunction

Electrolyte abnormalities:

- Hyperkalemia

WORKUP

- History: Change in medical condition, medication changes, herbal supplements, deliberate overdose. In acute toxicity, determine the amount and time of ingestion and possible coingestions.
- Physical examination.

LABORATORY TESTS

- Chronic toxicity—check stat digoxin level.
- Acute toxicity—check stat digoxin level and recheck 6 hr after ingestion (initial high levels may not be toxic, as tissue redistribution will occur).
- Potassium, BUN, creatinine, magnesium, calcium, glucose.
- Serial ECG (Figs. E1, E2, and E3).
- Almost any arrhythmia can occur, but simultaneous increased automaticity of cardiac tissue and conduction delay in the AV node should raise suspicion. Findings suggestive of toxicity include the following:
  1. Frequent premature ventricular complexes, bigeminy (Fig. E4)
  2. Bradyarrhythmias
  3. AV block
  4. Atrial tachycardia with AV block
  5. Junctional rhythms
  6. Ventricular arrhythmias: Ventricular tachycardia, ventricular fibrillation, bidirectional ventricular tachycardia (alternating QRS axis)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Ensure adequate airway, IV access
- Continuous cardiac monitor, pulse oximetry

ACUTE GENERAL Rx

DECREASE TOXICITY:

- Acute poisoning: Single dose of activated charcoal if within 2 hr of ingestion.
- Treat hypokalemia and hypomagnesemia; both potentiate toxicity.
- Most life-threatening complications of digoxin toxicity are treated with digoxin-specific antibody fragments (Fab).
- Digoxin-specific Fab fragments (DigiFab):
  1. Specific antibodies that bind to digoxin and to a lesser extent other cardiac glycosides. By binding to free digoxin, the plasma digoxin level decreases, facilitating dissociation of digoxin from the Na^+, K^+-ATPase.
  2. Initial response usually seen within 30 min, and complete reversal usually occurs within 4 hr.
  3. Indications: Hyperkalemia (>5.0 mEq/L), hemodynamic instability, severe arrhythmias, massive overdose (acute ingestion of ≥10 mg digoxin; acute ingestion resulting in steady-state serum level ≥10 ng/ml; chronic toxicity with level >6 ng/ml), coingestion of cardiotoxic drugs or plants containing cardiac glycosides.
  4. Dosing: 1 vial of Fab fragments binds 0.5 mg of digoxin. Round up when calculating number of vials to administer.

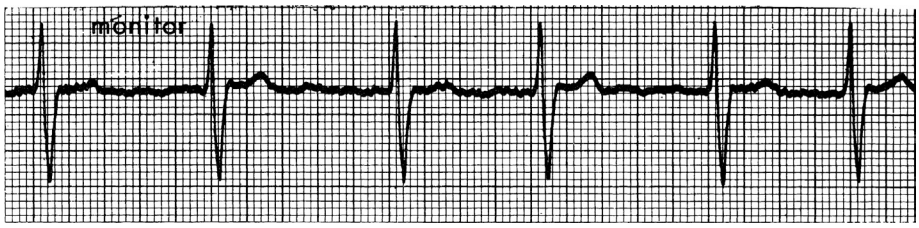

FIG. E1 Ventricular bigeminy caused by digoxin toxicity. Ventricular ectopy is one of the most common signs of digoxin toxicity. The underlying rhythm here is atrial fibrillation. (From Goldberger AL [ed]: *Clinical electrocardiography,* ed 5, St Louis, 1994, Mosby.)

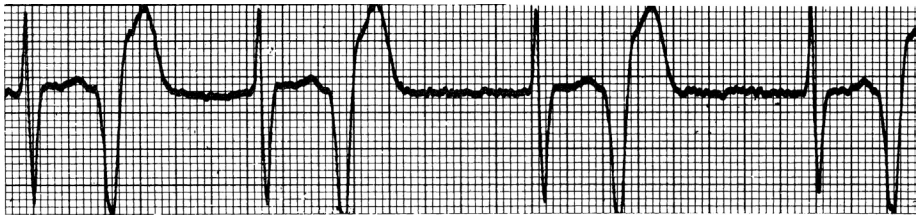

FIG. E2 Ventricular bigeminy caused by digoxin toxicity. In this figure, each normal QRS is followed by a ventricular premature beat. (From Goldberger AL [ed]: *Clinical electrocardiography,* ed 5, St Louis, 1994, Mosby.)

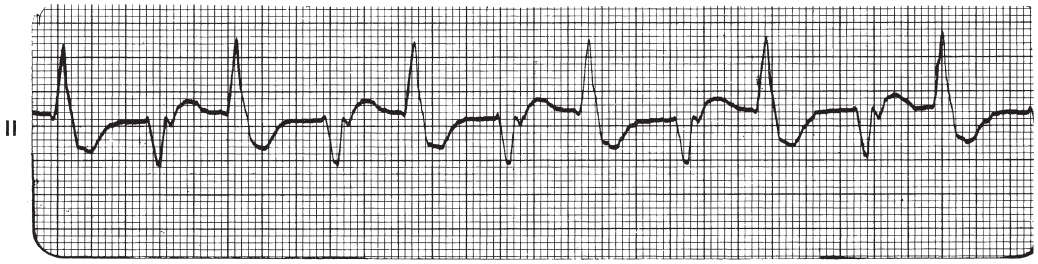

FIG. E3 This digoxin-toxic arrhythmia is a special type of ventricular tachycardia (bidirectional tachycardia) with QRS complexes that alternate in direction from beat to beat. No P waves are present. (From Goldberger AL [ed]: *Clinical electrocardiography,* ed 5, St Louis, 1994, Mosby.)

a. Acute ingestion of known amount: Number of vials = (ingested digoxin [mg] × B)/0.5; B = bioavailability for tablets (0.8) and capsules or IV (1.0)
b. Steady-state level known: Number of vials = (serum digoxin level [ng/ml]) × weight [kg]/100
c. If neither the amount ingested nor steady-state serum level is known, treat empirically:
   (1) Acute intoxication: 10 vials and repeat in 30 min if inadequate response
   (2) Chronic toxicity: 6 vials

NOTE: Underdosing of Fab fragments may result in rebound toxicity as free digoxin is released from tissue stores. In chronic toxicity without life-threatening symptoms, consider giving half the calculated dose initially to decrease the risk of exacerbating underlying heart disease.

- After use of Fab fragments, the free digoxin level decreases, but the measured digoxin level may increase because most assays measure free and bound digoxin levels. Serum levels are unreliable for days. Can measure free digoxin level if needed.
- Renal elimination: Half-life of inactive complex is 15 to 20 hr. Elimination of complex is prolonged in renal failure. May get recurrence of toxicity days later in patients with renal failure (complexes may dissociate before excretion), so require monitoring for >72 hr.
- Class C for pregnancy.
- Adverse effects of treatment:
  1. May undo desirable action of digoxin and exacerbate heart failure or increase ventricular response in previously controlled atrial fibrillation.
  2. Hypotension.
  3. Hypokalemia (as toxicity is corrected, potassium moves back into the cell and hypokalemia can develop); monitor potassium level hourly for 6 hours and then at least daily.
  4. Allergic reactions (higher if history of prior use): Serum sickness.

Hemodialysis, hemoperfusion, plasma exchange: Ineffective and not recommended for removal of digoxin or Fab-digoxin complex.

Digoxin toxicity not requiring Fab fragments: Hospitalize with cardiac monitoring. Monitor potassium and digoxin concentrations; serial ECGs.

COMPLICATIONS: These recommendations are temporizing measures until digoxin-specific Fab fragments can be given.

- Hyperkalemia: Due to redistribution; treatment to lower K^+ not recommended unless life threatening because hypokalemia may occur once toxicity is corrected with Fab fragments
- Hypotension: IV fluids
- Severe bradycardia and heart block:
  1. Atropine
  2. Cardiac pacing: Use with caution; may precipitate life-threatening ventricular arrhythmias
- Tachyarrhythmias:
  1. Lidocaine or phenytoin: Decrease ventricular automaticity without slowing AV node conduction.
  2. Avoid amiodarone, procainamide, beta-blockers, calcium channel blockers because they may increase ventricular arrhythmias/AV node block.
  3. Elective electrocardioversion is relatively contraindicated because it may precipitate ventricular fibrillation.

DISPOSITION

- Patients require inpatient continuous cardiac monitoring on medical or intensive care units depending on severity of toxicity.
- Prognosis is good with prompt treatment.
- Chronic poisoning is associated with higher mortality rate than acute poisoning.

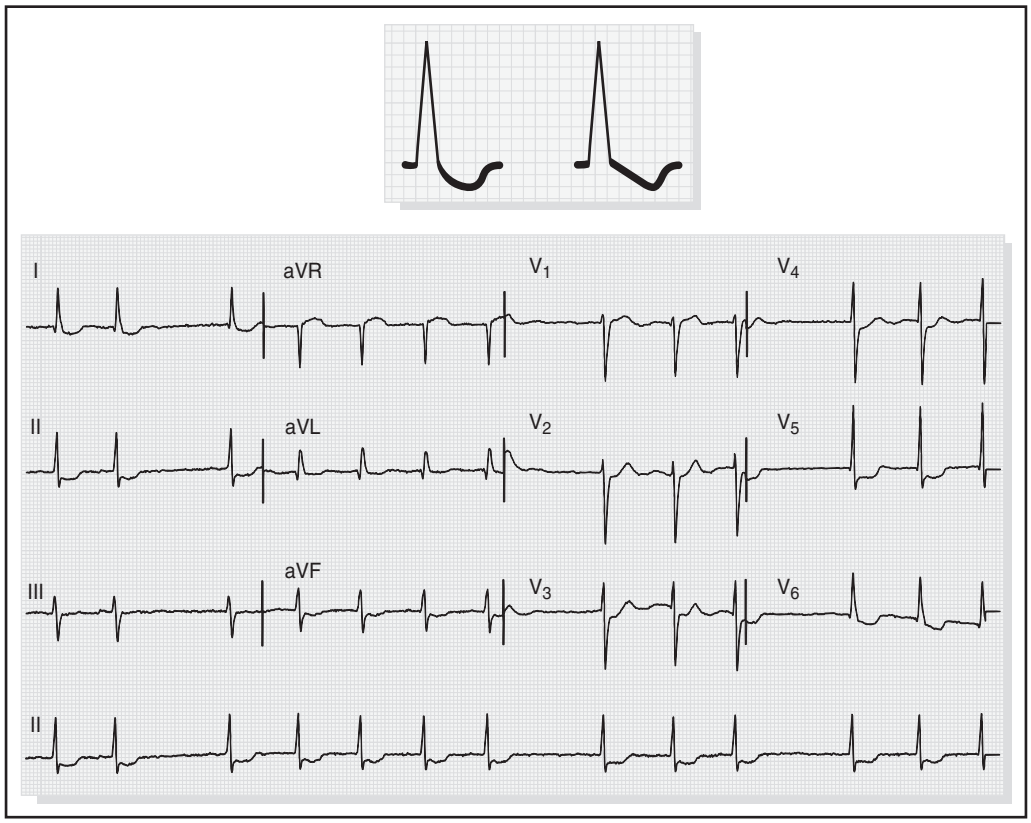

FIG. E4 *Top panel*, Digitalis effect. Digitalis glycosides characteristically produce shortening of the QT interval with a scooped or downsloping ST-T complex. *Bottom panels*, Digitalis effect in combination with digitalis toxicity. The underlying rhythm is atrial fibrillation. A group beating pattern of QRS complexes with shortening of the R-R intervals is consistent with nonparoxysmal junctional tachycardia with exit (AV Wenckebach) block. ST-segment depression and scooping (lead V_6) are consistent with the digitalis effect, although ischemia or left ventricular hypertrophy (LVH) cannot be excluded. Findings are strongly suggestive of digitalis excess; the serum digoxin level was higher than 3 ng/ml. The digitalis effect does not necessarily imply digitalis toxicity, however. *aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right. (Top panel from Goldberger A: *Clinical electrocardiography*, ed 6, St. Louis, 1999, Mosby; From Bonow RO et al: *Braunwald's heart disease,* ed 9, Philadelphia, 2012, WB Saunders.)

REFERRAL

American Association of Poison Control Centers: 800-222-1222

PEARLS & CONSIDERATIONS

- High index of suspicion is necessary; the signs and symptoms of toxicity often are similar to those of the underlying disease.
- To minimize toxicity, digoxin levels should be checked if the patient's condition changes (e.g., weight loss, worsening renal function) or an interacting drug is started or stopped.
- Hyperkalemia in acute toxicity is suggestive of significant poisoning (reflects amount of Na^+, K^+-ATPase poisoning) and is associated with increased mortality.
- Falsely elevated digoxin levels may be seen in pregnant women, renal failure, liver disease, and heart failure due to the presence of an endogenous digoxin-like substance.
- Severe toxicity from ingestion of nondigoxin cardiac glycosides (e.g., plants) may present with low digoxin levels because of low cross-reactivity between these substances and the digoxin assay. Empiric dosing of Fab fragments should be used to treat these poisonings.

AUTHOR: **Sudeep K. Aulakh, MD**

SUGGESTED READINGS

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Mowry JB et al: Extracorporeal treatment for digoxin poisoning: systematic review and recommendations from the EXTRIP workgroup, *Clin Toxicol (Phila)* 54(2):103, 2016.

BASIC INFORMATION

DEFINITION

Diphtheria is an infection of the mucous membranes or skin caused by *Corynebacterium diphtheriae.*

Rarely, a similar disease can be caused by other *Corynebacterium* species, which may elaborate a toxin similar to toxigenic *C. diphtheriae.*

C. ulcerans, a zoonotic bacteria, has been most consistently implicated.

At least four biotypes of *C. diphtheriae* exist, including gravis, intermedius, mitis, and belfanti. Mitis strains usually cause less severe disease with less toxin production.

SYNONYMS

Pharyngeal diphtheria
Wound diphtheria
Diphtheric cardiomyopathy
Diphtheric polyneuropathy

ICD-10CM CODE
A36.9 Diphtheria, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Since 1980, the incidence in the U.S. has been about 0.001 cases per 100,000 population because of widespread vaccination.
PREDOMINANT AGE: Adult yr (in the U.S.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

RESPIRATORY DIPHTHERIA:

- Commonly presenting as pharyngitis, but any part of the respiratory tract may be involved, including the nasopharynx, larynx, trachea, or bronchi
- Areas of gray or white exudate coalescing to form a "pseudomembrane" that bleeds when removed (Fig. E1)
- Possible fever and dysphagia
- Complications: Respiratory tract obstruction and pneumonia
- Systemic effects of the toxin: Myocarditis and polyneuritis (frequently involving a bulbar distribution), less often nephritis
- Occurs mostly in nonimmune individuals; usually milder and less likely to be complicated in those adequately immunized

CUTANEOUS DIPHTHERIA:

- Usually complicates existing skin lesion (i.e., impetigo or scabies)
- Resembles the underlying condition or presents as a nonhealing ulcer with a grayish membrane

ETIOLOGY

- Caused by *C. diphtheriae,* an aerobic, gram-positive rod
- Transmitted by close contact through droplets of nasopharyngeal secretions
- Symptomatic disease of the respiratory system caused by toxin-producing strains (tox^+)
- Systemic effects of toxin: Ranging from nausea and vomiting to polyneuropathy, nephritis, myocarditis, and vascular collapse
- Presence of strains not producing toxin (tox^+) in the respiratory tract of asymptomatic carriers and in skin lesions of cutaneous diphtheria
- Humans are the only known reservoir for *C. diphtheriae*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Streptococcal pharyngitis
- Viral pharyngitis
- Mononucleosis

WORKUP

- Presence of a pseudomembrane in the oropharynx suggestive of diagnosis (not always present)
- Gram stains of secretions to show club-shaped organisms, which appear as "Chinese letters"
- Nasolaryngoscopy to identify lesions in the nares, nasopharynx, larynx, or tracheobronchial tree

LABORATORY TESTS

- Cultures of mucosal lesions or of nasal discharge:
  1. Positive culture for *C. diphtheriae* confirms the diagnosis.
  2. Laboratory is notified of the suspected diagnosis so that appropriate culture medium (Tinsdale agar) is used.
- Testing of all isolated organisms for toxin production. The CDC Pertussis and Diphtheria Lab offers culture, toxin testing, PCR, and serology; phone: 404-639-1231.

Repeat cultures should be obtained 2 wk after completing therapy to ensure eradication of the bacteria.

IMAGING STUDIES

Chest x-ray to rule out pneumonia

TREATMENT

NONPHARMACOLOGIC THERAPY

- Intubation or tracheostomy if signs of respiratory distress occur
- Cardiac monitoring with serial ECGs, troponin measurements
- Nasogastric or parenteral nutrition in those with bulbar signs
- ICU monitoring for patients with signs of systemic toxicity
- Cardiac pacing in patients with heart block
- Respiratory isolation

ACUTE GENERAL Rx

- Administration of diphtheria antitoxin after a clinical diagnosis is made. Do not wait for laboratory confirmation of toxin production; give ASAP, as the effect of toxin is irreversible once it enters the host's cells.
- If test results for hypersensitivity to horse serum are negative: 20,000 to 40,000 units for pharyngeal/laryngeal disease present less than 48 hr, 40,000 to 60,000 units for nasopharyngeal disease, and 80,000 to 120,000 units for longer than 3 days of illness or diffuse neck swelling ("bull-neck") (available via the CDC).
- IV infusion of antitoxin over 60 min.
- Serum sickness in 10% of treated individuals; those with hypersensitivity to horse serum should be desensitized before administration of antitoxin.
- Antibiotics to eradicate the organism in carriers or patients.
- For respiratory diphtheria:
  1. Erythromycin 500 mg qid PO or IV (clarithromycin and azithromycin are acceptable alternatives) or IV penicillin G 25,000 to 50,000 units/kg to a maximum of 1.2 million units bid for 14 days. The course may be completed orally when able.
  2. Carriers or patients with cutaneous disease: Erythromycin 500 mg PO qid or IM penicillin.
  3. Patients should be given diphtheria toxoid vaccine during convalescence because disease neither interferes with nor confers immunity.
- Patients should be appropriately isolated: Droplet precautions for respiratory cases, contact for cutaneous cases.
- Contacts should be screened for prophylactic antibiotics.

CHRONIC Rx

Antibiotics to limit toxin production and eradicate carrier state, thereby preventing transmission

DISPOSITION

- Complete recovery with adequate supportive measures and antitoxin
- Cardiomyopathy is due to toxin and has a mortality rate of ~20% even with supportive care
- Neuropathy may not completely resolve

REFERRAL

- Hospitalization and referral to an infectious disease specialist for all suspected patients
- To an otolaryngologist for evaluation in cases of respiratory diphtheria
- All cases reported to the public health authorities

PEARLS & CONSIDERATIONS

COMMENTS

- Most cases are imported by travelers in epidemic areas, so recent epidemics in Eastern Europe are a cause for concern. A widespread epidemic of diphtheria began in 1990 in the former Soviet Union.
- Vaccination with diphtheria toxoid (attenuated toxin) is safe and effective in the form of DPT or Td; Td boosters should be given to adults every 10 yr. A new formulation of Tdap vaccine with reduced amounts of diphtheria toxoid and acellular pertussis antigens is available; it is well tolerated in clinical trials and provides excellent protection in adolescents and adults.
- According to serologic studies, 20% to 60% of U.S. adults >20 yr of age are susceptible to diphtheria.

AUTHOR: **Patricia Cristofaro, MD**

FIG. E1 Pharynx of a 39-yr-old woman with bacteriologically confirmed diphtheria. Photograph taken 4 days after the onset of fever, malaise, and sore throat. Hemorrhage caused by removal of the membrane by swabbing appears as a *dark area* on the left. (Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.)

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ACIP Childhood/Adolescent Immunization Work Group: Recommended immunization schedule for persons aged 0 thru 18 yrs–US 2013, *MMWR Surveill Summ* 62(Suppl 1):2, 2013.

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BASIC INFORMATION

DEFINITION

Diplopia is the perception of two images of a single object that may be displaced horizontally, vertically, or obliquely. Diplopia may be monocular or binocular. Monocular diplopia is double vision in one eye and persists when the unaffected eye is covered. It is an ophthalmologic problem that results from abnormal light transmission to the retina. Binocular diplopia results from ocular misalignment and resolves when either eye is covered. There are multiple possible causes that can be localized along the visual pathway, from the eye to the brainstem.

SYNONYM

Double vision

ICD-10CM CODE
H53.2 Diplopia

EPIDEMIOLOGY & DEMOGRAPHICS

- Diplopia represents 1.4% of ophthalmologic emergencies.
- The majority of cases are binocular.

GENETICS: Some diseases have a genetic basis, such as Marfan syndrome (dislocation of lens), or to a lesser degree, autoimmune conditions (myasthenia gravis [MG], Graves) that have a possible genetic link.

RISK FACTORS: Risk factors for diplopia include risk factors for vasculopathies (e.g., hypertension, diabetes mellitus, smoking, cerebrovascular accident) or trauma.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Monocular diplopia persists when the unaffected eye is covered and, unless caused by a retinal defect, resolves when a pinhole is used.
- Restrictive, mechanical orbitopathy: Typically gradual in onset, with a sensation of mass effect/discomfort/pain in a single eye unless caused by thyroid disease, which may be unilateral or bilateral. It may be the result of rectus muscle entrapment secondary to orbital blowout fracture, or may be accompanied by fever if infectious in etiology. Diplopia that is worse in the morning may be attributed to Graves myopathy with proptosis, periorbital swelling, edema, palpebral swelling, conjunctival or scleral injection, and abrupt restriction of eye movement away from the affected muscle.
- Cranial nerve (CN; III, IV, or VI) palsy: May occur as an isolated nerve palsy as a result of microvascular ischemia, or in combination in the case of cavernous sinus or posterior orbit pathologies.
  1. CN III (oculomotor) palsy: Vertical and horizonal diplopia. Complete CN III palsy will have ptosis; large unreactive pupil; and paralysis of adduction, elevation, and depression so eye rests in position of abduction, depression, and intorsion.
  2. CN IV (trochlear) palsy: Vertical and/or torsional diplopia that worsens looking down and toward the nose; difficulty descending stairs, reading, or watching television in bed.
  3. CN VI (abducens) palsy: Horizontal diplopia that worsens on lateral gaze toward the affected side.
- Neuroaxial process: Diplopia may occur in isolation or may be accompanied by multiple neurological signs and symptoms; vertical diplopia without vertical skew deviation suggests a brainstem lesion.
- Neuromuscular disorder: Muscle atrophy/weakness, weakness on forced eyelid closure, normal reflexes, and no sensory deficits.

ETIOLOGY

- The etiology of diplopia differs between monocular and binocular diplopia. Monocular diplopia is caused by primary ophthalmologic structural problems in the transmission of light to the retina and generally should be referred to an ophthalmologist. Binocular diplopia, when not caused by trauma, is most often a vascular lesion (small-vessel vasculopathy or aneurysmal disease) or occasionally due to endocrinopathy, neuromuscular, neoplastic, or autoimmune sources.
- Table E1 summarizes important causes of diplopia.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Psychogenic (functional deficit)
- Monocular diplopia:
  1. Dry eyes
  2. Corneal irregularity
  3. Astigmatism
  4. Cataract
  5. Lens dislocation
  6. Retinal wrinkles involving the macula
- Binocular diplopia:
  1. Restrictive, mechanical orbitopathy
     a. Abscess
     b. Trauma
     c. Entrapment
     d. Orbital myositis (may be associated with Wegener granulomatosis, giant cell arteritis, systemic lupus erythematosus, dermatomyositis, sarcoidosis, rheumatoid arthritis, Graves disease, or orbital pseudotumor)
     e. Craniofacial mass
  2. Cranial nerve (III, IV, or VI) palsy
     a. Isolated mononeuropathy of a single nerve
        (1) Demyelination (e.g., multiple sclerosis)
        (2) Hypertensive or diabetic vasculopathy
        (3) Nerve compression (e.g., aneurysm, tumor)
     b. Unilateral palsy of multiple oculomotor nerves
        (1) Infection, mass, or vasculitis affecting cavernous sinus or posterior orbit
  3. Neuroaxial process involving the brainstem
     a. Multiple sclerosis may manifest as a focal brainstem lesion.
     b. A more diffuse but localized brainstem lesion may result from brainstem tumor, brainstem lacunar stroke, basilar artery thrombosis, vertebral artery dissection, ophthalmoplegic migraine, infection, autoimmune disorder (e.g., Miller-Fischer or Guillain-Barré syndrome), Wernicke encephalopathy, meningoencephalitis, or botulism.
- Neuromuscular disorder
  1. Myasthenia gravis
  2. Lambert-Eaton syndrome

WORKUP

- Full neurologic examination with careful attention to the cranial nerves.
- Monocular diplopia: Slit-lamp, funduscopic examination, and ophthalmology referral.
- Diagnostic testing should be guided by clinical judgment as applied to the differential diagnosis. Imaging is the mainstay of the workup and is indicated in most cases of undifferentiated binocular diplopia. Laboratory studies are rarely helpful.
- Fig. E1 describes an algorithm for the diagnostic approach to diplopia.

LABORATORY TESTS

- Thyroid panel may be useful in cases of suspected thyroid disease.
- Lumbar puncture for meningitis or Miller-Fischer syndrome.

IMAGING STUDIES

- Magnetic resonance imaging (MRI) of the orbits with gadolinium is the test of choice in patients with suspected restrictive, mechanical orbitopathy; cavernous sinus; or posterior orbit pathology. Computed tomography (CT) of the head with contrast is a second-line option.
- For an isolated mononeuropathy, MRI of the brain and orbits with gadolinium is preferred. CT angiography (CTA) or magnetic resonance angiography (MRA) should be obtained in cases of suspected aneurysm. MRA should be used with caution when aneurysm is highly suspected because the sensitivity of MRA decreases with aneurysm size less than 5 mm.
- MRI with and without gadolinium is recommended for detection of brainstem lesions. The addition of a diffusion-weighted imaging protocol may be useful when ischemia is suspected.

TREATMENT

- The treatment of diplopia is directed at the underlying disorder
- Signs of basilar meningoencephalitis: Empiric antibiotics pending CT, lumbar puncture, and confirmation of infection
- Signs of Wernicke encephalopathy: Give thiamine
- Signs of stroke: IV fluid bolus and emergent evaluation for reperfusion therapy

TABLE E1 Important Causes of Diplopia

Diplopia-Causing Entity	Mechanism and Mortality	Distinguishing Features
Tier 1—Critical		
Basilar artery thrombosis	Acute thrombosis of the basilar artery with brainstem ischemia; untreated, mortality 70%-90%	Vertigo, dysarthria, other cranial nerve involvement; risk factors for stroke
Botulism	Toxin inhibits release of acetylcholine (ACh) at cholinergic synapses and presynaptic myoneural junctions; untreated, mortality 60%	Dysarthria, dysphagia, autonomic dysreflexia, pupillary dysfunction
Basilar meningitis	Infection; untreated, mortality close to 100% if bacterial (25%-40% if treated)	Headache, meningismus, fever
Aneurysm	Enlarging aneurysm directly compresses cranial nerve; untreated, rupture risk is 1% per yr; mortality 26%-50% per rupture	CN III palsy with pupillary involvement
Tier 2—Emergent		
Vertebral dissection	Dissection causes vertebrobasilar ischemia; acute untreated, mortality 28% (2%-5% if neurologically asymptomatic)	Neck pain, vertigo; risk factors for vertebral dissection
Myasthenia gravis	Autoantibodies develop against ACh nicotinic postsynaptic receptors; untreated, crisis mortality 42% (5% if treated)	Fluctuating muscle weakness, ptosis, and diplopia worsen with activity and improve with rest
Wernicke encephalopathy	Thiamine-dependent metabolic failure and tissue injury; untreated, mortality 20%	Nystagmus, ataxia, altered mental status, and ophthalmoplegia; risk factors and nutritional deficiency
Orbital apex syndrome, cavernous sinus process	Inflammation or infection in the orbital apex or cavernous sinus directly affects oculomotor cranial nerves; acute mortality low unless infectious and complicated by meningitis	A combination of palsies of CN III, IV, or VI, with retroorbital pain, conjunctival injection, and possible periorbital or facial numbness
Tier 3—Urgent		
Brainstem tumor	Tumor involvement at the supranuclear level; acute mortality low (long-term mortality variable)	Skew deviation vertical diplopia, internuclear ophthalmoplegia
Miller-Fisher syndrome	Autoantibodies develop to a cranial nerve ganglioside, GQ1b; acute mortality low if fully differentiated from GBS; mortality 2%-12% if GBS	Ophthalmoplegia, ataxia, areflexia
Multiple sclerosis	Demyelinating lesions; acute mortality low	Internuclear ophthalmoplegia
Thyroid myopathy (Graves disease)	Autoimmune myopathy; acute mortality low with regard to ocular complaints	Proptosis, restriction of elevation and abduction of the eye, signs of Graves disease
Ophthalmoplegic migraine	Inflammatory cranial neuropathy; low mortality—self-limited disease	Ipsilateral headache, CN (usually III) palsy
Ischemic neuropathy	Microvascular ischemia; mortality low—self-limited disease	Isolated CN palsy (pupil-sparing if CN III)
Orbital myositis, pseudotumor	Autoimmune or idiopathic myositis; acute mortality low with regard to ocular complaints	Eye pain, restriction of movement, periorbital edema; exophthalmos and chemosis when more severe
Orbital apex mass	A tumor, infiltration, or mass effect in the orbital apex or cavernous sinus directly compresses oculomotor cranial nerves; acute mortality low	A combination of palsies of CN III, IV, or VI, and possible periorbital or facial numbness, with retroorbital pain, proptosis, signs of venous congestion

CN, Cranial nerve; *GBS*, Guillain-Barré syndrome.
From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.

DISPOSITION

Most patients will require hospital admission for further evaluation and treatment. However, a CN III or CN IV palsy from microvascular ischemia typically self-resolves over a few days; these patients can usually be followed on an outpatient basis for spontaneous resolution.

PEARLS & CONSIDERATIONS

- All patients with diplopia merit a thorough neurologic examination.
- Consider potential critical and emergent causes, including infection, stroke, and Wernicke encephalopathy.
- Treat the underlying problem.
- Most patients merit hospital admission.

PREVENTION

No specific prevention has been published, although it stands to reason that preventing the antecedent vascular insults by managing hypertension and diabetes, as well as avoiding tobacco use and trauma, should have an impact on the disease prevalence.

PATIENT & FAMILY EDUCATION

Patients should be counseled to avoid driving or performing tasks that could be considered dangerous with impaired vision until symptoms resolve.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Botulism (Related Key Topic)
Giant Cell Arteritis (Related Key Topic)
Granulomatosis With Polyangiitis (Related Key Topic)
Graves Disease (Related Key Topic)
Guillain-Barré Syndrome (Related Key Topic)
Inflammatory Myopathies (Related Key Topic)
Multiple Sclerosis (Related Key Topic)
Myasthenia Gravis (Related Key Topic)
Rheumatoid Arthritis (Related Key Topic)
Sarcoidosis (Related Key Topic)
Systemic Lupus Erythematosus (Related Key Topic)
Wernicke Syndrome (Related Key Topic)

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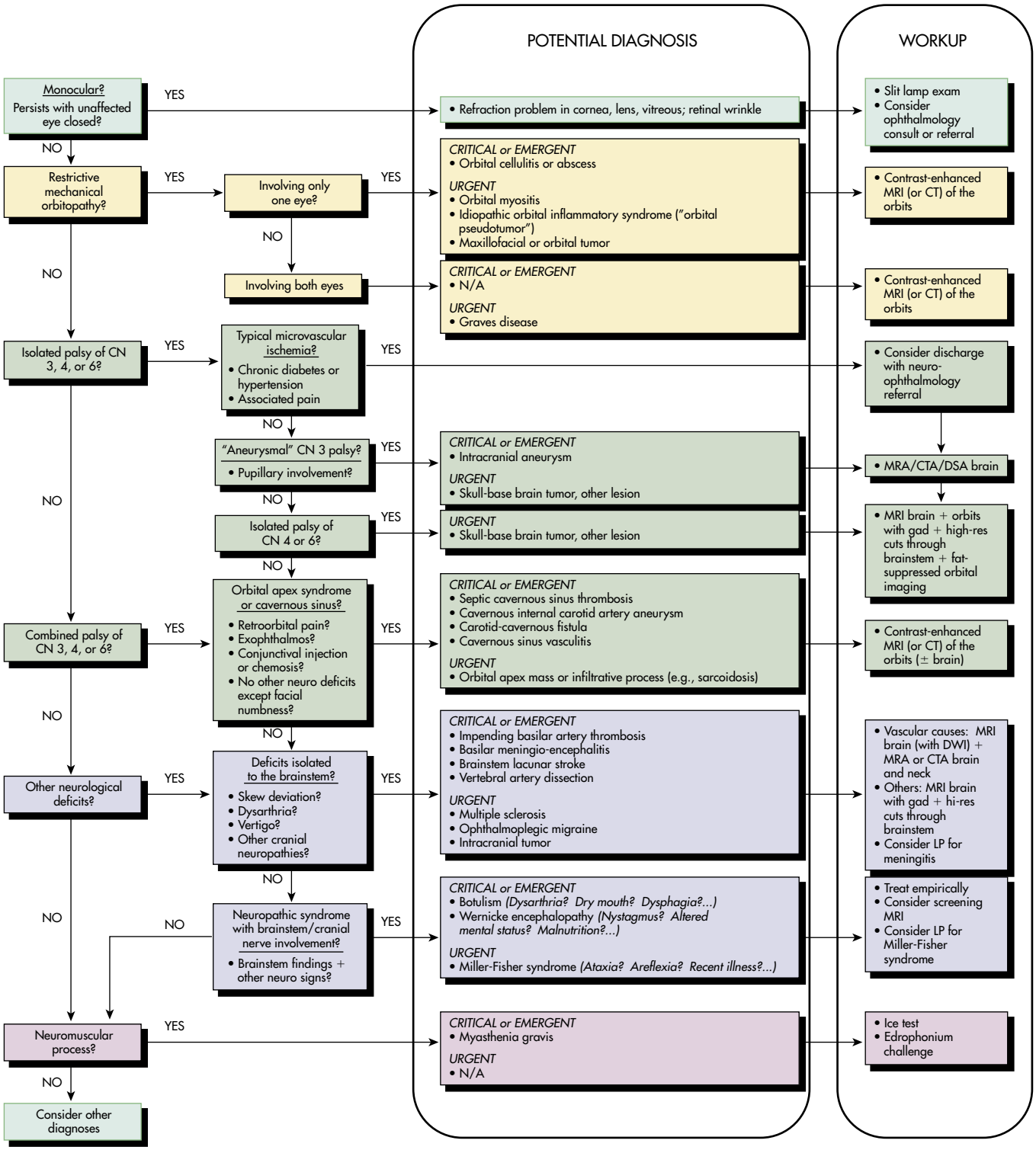

FIG. E1 Algorithm for the diagnostic approach to diplopia in the emergency department—a guideline. *CN,* Cranial nerve; *CT,* computed tomography; *CTA,* CT angiogram; *DSA,* digital subtraction angiography (conventional angiography); *DWI,* diffusion-weighted imaging; *gad,* gadolinium; *hi-res,* high-resolution; *LP,* lumbar puncture; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging. (From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.)

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Discoid lupus erythematosus (DLE) is a chronic inflammatory autoimmune cutaneous disorder that can lead to significant disfiguration and scarring. It can be associated with or occur independently of systemic lupus erythematosus (SLE).

SYNONYM

Discoid lupus

ICD-10CM CODES

L93.0 Discoid lupus erythematosus
L93.2 Other local lupus erythematosus

EPIDEMIOLOGY & DEMOGRAPHICS

- Slightly more common in African Americans than in Asians or whites.
- DLE is two to three times more likely in women than in men.
- DLE most commonly occurs on the face, scalp, and ears, but can also appear on mucosal surfaces such as the conjunctiva, nasal mucosa, and lips.
- DLE is the most common chronic cutaneous manifestation of SLE, occurring in nearly 20% of SLE patients.
- Approximately 5% to 10% of patients presenting with DLE will develop SLE; those with widespread, numerous lesions are more likely to progress.
- Highest prevalence of SLE occurs in persons ages 40 to 60, with SLE onset most often occurring in patients in their 20s and 30s.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

General:

- Early lesions: Single or multiple erythematous or violaceous, discrete papules or plaques with scale (Figs. E1 and E2), often extending into dilated hair follicles (follicular plugging). Intense inflammatory nature results in an indurated feel on palpation (Fig. E3).
- Older lesions: Peripheral hyperpigmentation with scarring, central hypopigmentation, atrophy (Fig. E4), and telangiectasia.
- Table E1 summarizes features of drug-induced lupus erythematosus.

Anatomic distribution:

- Commonly involves the scalp, face, ears (conchal bowls), and extensor surface of the arms (photodistributed pattern).
- Mucosal and nail involvement is also possible.

Lesion configuration:

- Irregularly grouped, confluent and disfiguring plaques

Lesion morphology:

- Erythematous plaque with scale
- Rarely, hypertrophic plaques with thick scale
- Follicular plugging
- Atrophy
- Irreversible, scarring alopecia (34%)
- May be associated with other clinical findings of SLE (e.g., oral ulcers, arthritis, pleuritis, pericarditis)

FIG. E1 Discoid lupus erythematosus (DLE). This young girl showed well-circumscribed, elevated, indurated, red to purplish annular plaques of DLE. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E2 Discoid lupus erythematosus (DLE). The ear is often involved with DLE. Note the well-defined plaques of purplish erythema, focal overlying scaling, and postinflammatory hyperpigmentation and depigmentation. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E3 Classic discoid lupus erythematosus of the face. Note central scarring and erythematous hyperkeratotic borders. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

ETIOLOGY

Unknown, but thought to be an autoimmune-mediated disorder and due to interaction between environmental and genetic factors

Dx DIAGNOSIS

Clinical findings and skin biopsy are used to establish the diagnosis of DLE.

DIFFERENTIAL DIAGNOSIS

- Table E2 compares various cutaneous connective tissue diseases
- Burn scar
- Dermatophyte infection
- Granuloma annulare
- Granuloma faciale
- Lichen planus
- Lichen planopilaris
- Psoriasis
- Radiation dermatitis
- Rosacea
- Sarcoidosis
- Scarring alopecia
- Subacute cutaneous lupus erythematosus
- Syphilis
- Vitiligo

LABORATORY TESTS

- Complete blood count is usually normal in isolated DLE.
- Blood urea nitrogen and creatinine are normal in isolated DLE.
- Erythrocyte sedimentation rate is elevated in active disease.
- Urinalysis may show proteinuria.
- Antinuclear antibody is positive in 20% of patients with isolated DLE.
- Anti-Ro (SS-A) and anti-La (SS-B) autoantibodies are present in 1% to 3% of patients.
- Histology of skin biopsy is diagnostic and reveals hyperkeratosis with follicular plugging; interface dermatitis with Civatte bodies; melanophages at dermal-epidermal junction; a thickened basement membrane; and a perivascular, interstitial, and perifollicular lymphocytic infiltrate.

FIG. E4 Discoid lupus erythematosus. Dyspigmentation and atrophy of the hard palate. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Avoid sun exposure by using protective clothing and a broad-spectrum sunscreen of SPF >30 that blocks UVB and UVA light (e.g., avobenzone with octocrylene, titanium dioxide, zinc oxide). Avoid exposure to sunlight during peak hours. Use sun-protective clothing.

ACUTE GENERAL Rx

- Topical steroids: Intermediate- to high-potency steroids are needed; use caution when applying to the face
- Intralesional triamcinolone acetonide (3 to 10 mg/cc)
- Topical calcineurin inhibitors: Pimecrolimus 1% cream and tacrolimus 0.1% ointment
- Systemic antimalarials: Hydroxychloroquine sulfate 200 mg PO bid alone or in combination with quinacrine 100 mg PO daily
- Avoid use of systemic glucocorticoids in patients with isolated DLE because of risks of side effects

CHRONIC Rx

- Antimalarials remain the cornerstone of treatment: Hydroxychloroquine 6 mg/kg of ideal body weight per day or chloroquine 4 mg/kg of ideal body weight per day. Combination therapy with quinacrine can also be used.
- Second-line agents are methotrexate, acitretin, isotretinoin, and dapsone. Labs should be followed regularly on these medications.

TABLE E1 Features of Drug-Induced Lupus Erythematosus

	Skin Features	Noncutaneous Signs	Laboratory Findings	Most Common Pediatric Trigger(s)
Drug-induced SLE	Photosensitivity, purpura, erythema nodosum, urticaria and urticarial vasculitis, necrotizing vasculitis Usually absent: Malar or discoid rash (except TNF inhibitors), mucosal ulcers, alopecia, Raynaud phenomenon	Fever, arthralgias, myalgias, pericarditis, pleuritic, sometimes hepatitis Usually absent: CNS, renal, pulmonary involvement Hepatic changes from minocycline	ANA, antihistone antibodies, elevated ESR May be mild cytopenia	Minocycline, occasionally TNF-α inhibitors
Drug-induced SCLE	Annular polycyclic lesions and/or papulosquamous lesions, including on legs Less commonly, erythema multiforme-like or vesiculobullous lesions, necrotizing vasculitis	Usually no arthritis, serositis, or major organ involvement	ANA, anti-Ro, anti-La	Terbinafine, griseofulvin NSAIDs (piroxicam, naproxen)
Drug-induced CCLE	Discoid lesions in photosensitive distribution	Usually no other signs	ANA	TNF-α inhibitors

ANA, Antinuclear antibody; *CCLE,* chronic cutaneous lupus erythematosus/discoid lupus; *CNS,* central nervous system; *ESR,* erythrocyte sedimentation rate; *NSAID,* nonsteroidal antiinflammatory drug; *SCLE,* subacute cutaneous lupus erythematosus; *SLE,* systemic lupus erythematosus; *TNF,* tumor necrosis factor.
From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.

TABLE E2 Autoimmune Cutaneous Connective Tissue Diseases

Autoimmune Disease	Indirect Immunofluorescence Pattern of Antinuclear Antibody Staining in Serum*	Nuclear Antigens to Which Autoantibodies Are Directed	Direct Immunofluorescence of Tissue
Lupus Erythematosus			
Systemic LE	Peripheral (rim), homogeneous, nucleolar, speckled	nDNA or double-stranded DNA, single-stranded DNA, histones, nucleolar RNA, various ribonucleoproteins, cardiolipin, Sm (Smith), U1-snRNP, HMG-17	Two or more granular immunoglobulin and complement deposits at BMZ, IgG, IgM, and/or IgA with C3 in involved and uninvolved skin (lupus band); lichenoid changes with numerous cytoids and shaggy fibrinogen staining of BMZ also found
Discoid LE	Usually no circulating antibodies	Usually none detected	Two or more granular immunoglobulin and complement deposits at BMZ, IgG, IgM, and/or IgA with C3 in involved skin; lichenoid changes with numerous cytoids and shaggy fibrinogen staining of BMZ also found
Subacute cutaneous LE	Fine speckled or speckled, may be negative	SS-A/Ro, SS-B/La	Particulate intercellular staining with or without granular immune deposits at BMZ or lichenoid changes
Neonatal LE	Fine speckled or speckled, may be negative	SS-A/Ro, SS-B/La	Granular IgG (transplacental) at BMZ
Drug-induced LE	Peripheral, homogeneous	Histones	Granular immune deposits at the BMZ
Scleroderma			
Cutaneous scleroderma (localized and generalized morphea)	Peripheral	SCL-70, SS-A/Ro, SS-B/La	No characteristic changes; vascular staining may be observed
Limited disease (acrosclerosis, CREST)	Centromere	Centromere, SCL-70, U1-snRNP, HMG-17	No characteristic changes; vascular staining may be observed
Diffuse disease (systemic sclerosis)	Nucleolar, speckled	SCL-70, U1- and U3-snRNP, RNA pol I, II, and III	No characteristic changes; vascular staining may be observed
Dermatomyositis, polymyositis	Speckled, nucleolar	Jo-1, PM-Scl, Mi-2, U1-snRNP, SS-A/Ro	No characteristic changes; lichenoid features and vascular staining may be observed
Sjögren syndrome	Fine speckled, nucleolar	SS-A/Ro, SS-B/La, histones, U1-snRNP	No characteristic changes; vascular staining may be observed
Mixed connective tissue disease	Speckled	U1-snRNP, PM-Scl	No characteristic changes; granular immune deposits at the BMZ lichenoid features and vascular staining may be observed
Overlap and undifferentiated connective tissue disease	Any single or combination pattern	Any one or multiple	
PM-Scl	May show granular immune complex deposition at BMZ (lupus band), vascular staining, or lichenoid changes		

BMZ, Basement membrane zone; *CREST,* calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia; *DNA,* deoxyribonucleic acid; *Ig,* immunoglobulin; *LE*, lupus erythematosus; *nDNA,* nuclear DNA; *RNA,* ribonucleic acid.
From Adkinson NF et al: *Middleton's allergy principles and practice*, ed 8, Philadelphia, 2014, WB Saunders.

- Third-line agents are azathioprine, thalidomide, mycophenolate mofetil, sulfasalazine, and oral gold.
- Oral corticosteroids can be considered in resistant cases with associated symptoms refractory to other measures.

DISPOSITION

If untreated, DLE can lead to significant and permanent atrophy and scarring of the skin.

REFERRAL

Dermatology, rheumatology, nephrology, internal medicine, ophthalmology

PEARLS & CONSIDERATIONS

- Discoid rash is one of 11 diagnostic criteria for SLE.
- Rarely, patients with DLE may develop cutaneous squamous cell carcinoma in areas of disease.
- It is unusual to see DLE involving areas below the neck if there is no disease above the neck. Biopsy for definitive diagnosis in these cases.
- Localized DLE is associated with SLE in 5% to 10%.
- Generalized DLE is associated with SLE in 15% to 28%.

RELATED CONTENT

Discoid Lupus Erythematosus (Patient Information)
Systemic Lupus Erythematosus (Related Key Topic)

AUTHOR: **Kachiu C. Lee, MD, MPH**

SUGGESTED READINGS

Chang AY et al: Response to antimalarial agents in cutaneous lupus erythematosus: a prospective analysis, *Arch Dermatol* 147(11):1261, 2011.

Garza-Mayers AC et al: Review of treatment for discoid lupus erythematosus, *Dermatol Ther* 29(4):274-283, 2016.

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Disseminated Intravascular Coagulation

BASIC INFORMATION

DEFINITION

Disseminated intravascular coagulation (DIC) is an acquired thromboembolic disorder characterized by generalized activation of the clotting pathways, which results in the intravascular formation of fibrin and ultimately thrombotic occlusion of small and midsize vessels, followed by end-organ damage.

SYNONYMS

Consumptive coagulopathy
DIC
Defibrination syndrome

ICD-10CM CODE
D65 Disseminated intravascular coagulation [defibrination syndrome]

EPIDEMIOLOGY & DEMOGRAPHICS

About 1% of hospitalized patients may have evidence of DIC. There is no predilection for age or gender. More than 50% of cases are associated with gram-negative sepsis or other septicemic infections, and up to 35% of patients with severe sepsis have DIC.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

DIC occurs in both acute and chronic forms and can present with bleeding, thrombosis, or laboratory evidence of clotting cascade activation and fibrinolysis without evident clinical sequelae. Acute DIC is more common and predominantly manifests as bleeding complications. The risk of bleeding increases with worsening thrombocytopenia and is fivefold higher when platelet count is below $<50 \times 10^9$/liter. Sudden exposure to procoagulants may extensively activate a coagulation cascade and platelet consumption, resulting in thrombosis. In contrast, chronic DIC more frequently causes thrombotic complications. The diagnosis of chronic DIC can be challenging, as the PT and PTT are frequently normal. Multiple pathways are involved simultaneously in DIC to create the clinical presentation. These include: (1) thrombin generation due to release of tissue factor, (2) suppression of physiologic anticoagulant (e.g., protein C or antithrombin insufficiency), (3) impaired fibrinolysis characterized by increased level of plasminogen activator inhibitor type 1 (PAI-1), and (4) activation of inflammatory pathways.

With DIC, multiple organs may be involved, and clinical presentations may vary. They can include:

- Central nervous system: Altered mental status, transient neurological deficits
- Cardiovascular: Hypotension, tachycardia
- Respiratory: Hypoxia, dyspnea, localized rales, and acute respiratory syndrome
- Gastrointestinal: Intestinal bleeding, bowel infarction
- Genitourinary: Oliguria, anuria, uremia, acidosis, metrorrhagia
- Skin: Wound site bleeding, epistaxis, gingival bleeding, hemorrhagic bullae, petechiae, ecchymosis, purpura

ETIOLOGY

DIC results from the aberrant and generalized activation of the clotting system, resulting in simultaneous formulation of coagulation and fibrinolysis. Clotting factors are consumed at a rate in excess of the capacity of the liver to synthesize them, and platelets are consumed in excess of the capacity of the bone marrow megakaryocytes to release them. It frequently occurs in the setting of severe infection; common triggers are listed below:

- Infections (e.g., gram-negative sepsis, Rocky Mountain spotted fever, malaria, viral or fungal infection)
- Obstetric complications (e.g., fetal demise, amniotic fluid embolism, toxemia, abruptio placentae, septic abortion, eclampsia, placenta previa, uterine atony)
- Tissue trauma (e.g., burns, hypothermia rewarming)
- Malignancy (e.g., adenocarcinomas [gastrointestinal, prostate, lung, breast], lymphoproliferative/myeloproliferative; DIC is a hallmark of acute promyelocytic leukemia and a main cause of mortality.)
- Quinine, cocaine-induced rhabdomyolysis
- Liver failure
- Acute pancreatitis
- Transfusion reactions
- Respiratory distress syndrome
- Toxins (snake bites, amphetamine overdose)
- Other: Systemic lupus erythematosus (SLE), vasculitis, aneurysms, polyarteritis, hemangiomas with thrombocytopenia, and consumptive coagulopathy (Kasabach-Merritt syndrome)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hepatic necrosis: Normal or elevated factor VIII concentrations
- Vitamin K deficiency: Normal platelet count
- Hemolytic uremic syndrome: Coagulation assays are usually normal
- Thrombotic thrombocytopenic purpura: Low ADAMTS13 activity
- Renal failure, SLE, sickle cell crisis, dysfibrinogenemias
- HELLP syndrome (**h**emolysis, **e**levated **l**iver function tests, and **l**ow **p**latelets)

WORKUP

The diagnostic workup includes laboratory testing to characterize the coagulopathy and its severity and exclude conditions noted in the differential diagnosis (Tables 1 and 2, Box 1). Additional workup is guided by the clinical scenario and may include distinguishing DIC progression (acute vs. chronic), chief manifestations (thrombotic or hemorrhagic), and extent (localized or systemic).

LABORATORY TESTS

- Peripheral blood smear generally shows red blood cell fragments (schistocytes) and low platelet counts.
- Coagulation testing: Diagnostic characteristics of DIC are decreased fibrinogen level; thrombocytopenia; and increased prothrombin time (PT), partial thromboplastin time (PTT), thrombin time (TT), fibrin split products, and D-dimer.
- Coagulopathy secondary to DIC must be differentiated from other coagulopathies that result from underproduction of clotting

TABLE 1 Differential Diagnosis of Thrombocytopenia in Suspected Disseminated Intravascular Coagulation

Differential Diagnosis	Additional Diagnostic Clues
DIC	Prolonged aPTT and PT, increased FDP, low levels of antithrombin or protein C
Sepsis without DIC	Positive (blood) cultures, positive sepsis criteria, hemophagocytosis in bone marrow
Massive blood loss	Major bleeding, low hemoglobin, prolonged aPTT and PT
Thrombotic microangiopathy	Schistocytes evident on blood smear, Coombs-negative hemolysis, fever, neurologic symptoms, renal insufficiency, coagulation tests usually normal, ADAMTS13 levels decreased
Heparin-induced thrombocytopenia	Use of heparin, venous or arterial thrombosis, positive HIT test (usually immunoassay for heparin-platelet factor 4 antibodies), increase in platelet count after cessation of heparin; coagulation tests usually normal
Immune thrombocytopenia	Antiplatelet antibodies, normal or increased number of megakaryocytes in bone marrow aspirate, normal levels of TPO (TPO levels are usually normal or slightly increased in ITP); coagulation tests usually normal
Drug-induced thrombocytopenia	Decreased number of megakaryocytes in bone marrow aspirate or detection of drug-induced antiplatelet antibodies, increase in platelet count after cessation of drug; coagulation tests usually normal

ADAMTS13, A disintegrin and metalloproteinase with thrombospondin 13; *aPTT,* activated partial thromboplastin time; *DIC,* disseminated intravascular coagulation; *FDP,* fibrin degradation products; *HIT,* heparin-induced thrombocytopenia; *PT,* prothrombin time; *ITP,* immune thrombocytopenia; *TPO,* thrombopoietin.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 2 Differential Diagnosis of Prolonged aPTT and/or PT in Suspected Disseminated Intravascular Coagulation

Test Result	Cause
PT prolonged, aPTT normal	Factor VII deficiency Mild vitamin K deficiency Mild liver insufficiency Low doses of vitamin K antagonists
PT normal, aPTT prolonged	Factor VIII, IX, or XI deficiency Unfractionated heparin Inhibitory antibody and/or antiphospholipid antibody Factor XII or prekallikrein deficiency
Both PT and aPTT prolonged	Factor X, V, II, or fibrinogen deficiency Severe vitamin K deficiency Vitamin K antagonists Global clotting factor deficiency • Decreased synthesis: Liver failure • Increased loss: Massive bleeding, DIC

aPTT, Activated partial thromboplastin time; *PT,* prothrombin time.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

BOX 1 Diagnostic Algorithm for the Diagnosis of Overt Disseminated Intravascular Coagulation[a]

- Presence of an underlying disorder known to be associated with disseminated intravascular coagulation (DIC) (Table 2) (no = 0, yes = 2)
- Score global coagulation test results
  1. Platelet count (>100 = score 0; <100 = score 1; <50 = score 2)
  2. Level of fibrin markers (e.g., D-dimer, fibrin degradation products) (no increase = score 0; moderate increase = score 2; strong increase = score 3)[b]
  3. Prolonged prothrombin time (<3 s = score 0; >3 s but <6 s = score 1; >6 s = score 2)
  4. Fibrinogen level (>1.0 g/L = score 0; <1.0 g/L = score 1)

Calculate score

If ≥5: Compatible with overt DIC; repeat scoring daily if <5: Suggestive (not affirmative) for nonovert DIC; repeat next 1–2 days.

[a]According to the Scientific Standardization Committee of the International Society of Thrombosis and Haemostasis.
[b]Strong increase, greater than 5× upper limit of normal; moderate increase, greater than upper limit of normal but less than 5× upper limit of normal.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

factors, including liver disease or vitamin K deficiency.

1. Vitamin K deficiency manifests with prolonged PT but normal PTT, TT, platelet, and fibrinogen levels; PTT may be elevated in severe cases.
2. Patients with liver disease have abnormal PT and PTT; TT and fibrinogen are usually normal unless severe disease is present; platelets are usually normal unless splenomegaly is present.
3. Factor VIII is not synthesized exclusively by the liver. It can differentiate between DIC, where it is low, and coagulopathy of liver disease, where it is normal.

IMAGING STUDIES

Imaging studies are generally not useful. Imaging may be helpful for identifying sequelae of DIC, including chest radiographs to exclude infectious processes in patients with pulmonary symptoms such as dyspnea, cough, or hemoptysis.

Rx TREATMENT

ACUTE GENERAL Rx

- Correcting and eliminating the underlying cause is often sufficient to halt DIC (e.g., antimicrobial therapy for infection, removal of necrotic bowel, evacuation of uterus in obstetric emergencies).
- Patients with bleeding should be given replacement therapy with fresh frozen plasma (FFP) and platelets:
  1. FFP 10 to 15 ml/kg can be given with a goal of normalizing international normalized ratio.
  2. Platelet transfusions are given when platelet count is <10,000 (or higher if major bleeding is present).
  3. Cryoprecipitate 1 U/5 kg is given for low fibrinogen. It also can be given for prevention of bleeding in patients with fibrinogen level <100 mg/dl.
  4. Patients with extensive thrombosis (e.g., in acute promyelocytic leukemia, purpura fulminans, acral ischemia) require anticoagulation, despite thrombocytopenia and abnormal coagulation parameters. Heparin therapy using unfractionated heparin at lower doses than those used in venous thrombosis may be useful with a view to increase neutralization of thrombin. Low-molecular-weight heparin also may be used in this scenario.
- The mainstays of supportive treatment of DIC are summarized in Box E2.

DISPOSITION

Mortality rate in severe DIC exceeds 75%. The high mortality rate is often due to the severity of the underlying trigger and complications including acute renal failure, intracerebral bleeding, shock, or cardiac tamponade.

REFERRAL

Hematology consultation is recommended in all cases of severe DIC and DIC with hemorrhagic or thrombotic complications.

PEARLS & CONSIDERATIONS

COMMENTS

The treatment of chronic DIC is controversial. Low-dose SC heparin and/or combination antiplatelet agents such as aspirin and dipyridamole may be useful.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Disseminated Intravascular Coagulation (Patient Information)

AUTHORS: **Andrew Gillis-Smith, MD,** and **Patan Gultawatvichai, MD**

SUGGESTED READINGS

Levi M, Scully M: How I treat disseminated intravascular coagulation, *Blood* 131:845-854, 2018.

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BOX E2 Mainstays of Supportive Treatment of Disseminated Intravascular Coagulation

Modality	Details	Expectations/Rationale
Treating the underlying disorder	Dependent on the primary diagnosis	Inhibit or block the complicating pathologic mechanism of disseminated intravascular coagulation (DIC) in parallel with the response (if any) of the disorder
Antithrombotic agents	Prophylactic heparin to prevent venous thromboembolic complications	Risk of thromboembolism is increased in critically ill patients, trauma patients, or patients with cancer
	(Low-dose) therapeutic heparin in case of confirmed thromboembolism or if clinical picture is dominated by (micro) vascular thrombosis and associated organ failure	Prevent fibrin formation; tip the balance within the microcirculation toward anticoagulant mechanisms and physiologic fibrinolysis; allow reperfusion of the skin, kidneys, and brain
Transfusion	Infuse platelets, plasma, and fibrinogen (cryoprecipitate) if there is overt bleeding or a high risk of bleeding	Bleeding should diminish and stop over the course of hours Platelet count, coagulation tests, and fibrinogen should return toward normal
Anticoagulant factor concentrates	Recombinant human activated protein C may be effective in sepsis and DIC (24 μg/kg per hour for 4 days); currently withdrawn from the market	Restore anticoagulation in microvascular environment and may have antiinflammatory activity Latest trials were negative.
Fibrinolytic inhibitors	Tranexamic acid (e.g., 500–1000 mg q8–12 h or ε-aminocaproic acid 1000–2000 mg q8–12 h)	May be useful if there is (hyper)fibrinolysis Bleeding ceases, but there is a risk of microvascular thrombosis and renal failure

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

BASIC INFORMATION

DEFINITION

Dissociative disorders (DDs) feature a disturbance in identity, memory, perception, and consciousness and include dissociative identity disorder (DID), dissociative amnesia (DA), dissociative fugue (DF), and depersonalization/derealization disorder (DPD).

SYNONYMS

DD
DID
DA
DF
DPD

ICD-10CM CODES

F44.81	Dissociative identity disorder
F44.0	Dissociative amnesia
F44.1	Dissociative amnesia with dissociative fugue
F48.1	Depersonalization/derealization disorder
F44.89	Other specified dissociative disorder
300.14	Dissociative identity disorder
300.12	Dissociative amnesia
300.13	Dissociative amnesia with dissociative fugue
300.6	Depersonalization/derealization disorder
300.15	Other specified dissociative disorder
300.15	Dissociative disorder, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Limited research documents the incidence of DDs, and estimates vary based on the assessment utilized and the sample studied.
PEAK INCIDENCE: Age of peak incidence varies by the type of DD.
PREVALENCE: The prevalence of DDs using various screening instruments is estimated to be 10%, with higher rates evidenced in studies of individuals seeking psychiatric care. The estimated prevalence of dissociative experiences in the general population is much higher.
PREDOMINANT SEX AND AGE: Females are diagnosed with DDs more frequently than males. Diagnoses may be made among individuals of all ages; however, the age of onset is thought to vary by subtype. Specifically, DID is thought to begin in childhood during the course of severe or prolonged trauma, whereas other DDs are thought to begin within the immediate context of stressful events at any age.
GENETICS: There is some evidence that biologic differences may play a role the likelihood of dissociation following the experience of trauma.
RISK FACTORS: DDs have been linked to experiencing chronic stress, especially during adolescence, as well as experiencing or witnessing acute traumatic events. A greater frequency of severe childhood sexual abuse is a significant specific predictor of dissociative disorders.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- **Dissociative amnesia (DA)**: Loss of autobiographic memory for previous experiences or before a certain point in time. Types of DA include:
  1. Localized amnesia: Inability to recall a specific (traumatic) period of time.
  2. Selective amnesia: Inability to recall parts, but not all, of a specific period of time.
  3. Systematized amnesia: Inability to recall categorical autobiographical memories, but not memory loss in chronologic order such as with localized amnesia.
  4. Continuous amnesia: Anterograde loss of memory, or inability to remember successive events as they occurred.
  5. Generalized (global) amnesia: Inability to recall one's whole life, including personal details.
  6. Thematic amnesia (as seen in DID and dissociative disorders not otherwise specified [DDNOS]): As identity states change, ability to recall specific periods of time is altered.
- **Dissociative fugue (DF):** DF carries the same characteristics as DA, with the distinguishing feature of sudden and unplanned purposeful travel away from one's home.
- **Dissociative identity disorder (DID):** Formerly referred to as *multiple personality disorder* (MPD), patients appear to possess two (or more) distinct identities or personality states, associated with the patient's consciousness, perception, thoughts, and actions.
- **Depersonalization disorder (DPD):** Also known as *derealization disorder,* DPD is a state in which patients believe that they have been altered in some way or that they are no longer real. Features include persistent and recurring experiences of feeling detached from one's own body and mental processes (i.e., one observing oneself as an outsider). Reality testing remains intact.
- **Dissociative disorders not otherwise specified (DDNOS):** Some dissociative symptoms of varying degrees but not meeting criteria for a distinct diagnosis.

ETIOLOGY

DDs are thought to develop after experiencing severe emotional or physical trauma. There is limited understanding of the neurobiologic underpinnings of DDs. However, research indicates that individuals with DPD report blunted reactions to arousing stimuli, suggesting that DDs may be caused by problems in connections between sensory systems (i.e., eyesight, hearing) and the limbic system. Other studies indicate variations in serotonin, endogenous opioid, and glutamate systems among individuals with DPD. Other studies document decreased blood flow in the right frontotemporal cortex of individuals with DA. Alterations in brain regions associated with emotion processing and memory, attention and interoceptive awareness, filtering of sensory input, self-referential processes, cognitive control, and arousal modulations have been linked to dissociative disorders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- DDs should be distinguished from acute substance intoxication, withdrawal, or substance-induced persisting amnestic disorder.
- Symptoms due to the physiologic consequences of a medical condition should be diagnosed as a mental disorder NOS due to a general medical condition.
- DA should be distinguished from amnestic disorder due to a brain injury, transient global amnesia, seizure disorders, delirium, dementia, age-related cognitive decline, and nonpathologic forms of amnesia (i.e., amnesia for sleep, memory loss).
- DA and DPD should not be diagnosed separately if symptoms occur only during the course of DF.
- DPD should not be diagnosed when symptoms occur only during a panic attack or in the context of panic disorder, specific phobia, or posttraumatic or acute stress disorders.
- If fugue symptoms occur only in the context of DID, DF should not be diagnosed separately.
- DID diagnoses take precedence over diagnosis of other DDs (i.e., DA, DF, DPD).
- Purposeful travel that occurs during a manic episode should be distinguished from a DF.
- Differential diagnosis should also consider schizophrenia and other psychotic disorders, bipolar disorder with rapid cycling, anxiety disorders, somatization disorders, and personality disorders.
- Amnesia for trauma may also occur in posttraumatic stress disorder and acute stress disorder.
- Clinicians may also consider malingered amnesia and malingered fugue states.

WORKUP

Diagnosis is made based on structured clinical interviews such as Dissociative Disorders Interview Schedule (DDIS) or the Structured Clinical Interview for Dissociative Disorders (SCID-D). The Dissociative Experiences Scale (DES) is a self-questionnaire diagnostically useful in DDs. Diagnosis also includes a review of personal history and symptoms as well as ruling out any physical injury (i.e., head trauma).

TREATMENT

There are currently no FDA-approved drugs for the treatment of DDs. Clinicians may consider FDA-approved medications (i.e., antianxiety medications, antidepressants, or antipsychotics) to treat co-occurring mood and anxiety symptoms associated with DDs.

NONPHARMACOLOGIC THERAPY

Psychotherapy for DDs generally proceeds in three phases. Phase 1 focuses on stabiliza-

tion and symptom control, education about treatment, affect and impulse regulation skill building, increasing awareness of dissociated self-states, and establishment of a therapeutic alliance. Phase 2 focuses on processing of traumatic memories, resolution of trauma-related cognitive distortions, and the development of a narrative of traumatic experiences. Phase 3 involves a resolution of dissociated self-state and a focus on current and future life issues.

- Treatment may be enhanced when therapists include continuous and frequent assessments of the therapeutic alliance and consider methods for enhancing it.
- Experts treating dissociative disorders advise only occasionally processing traumatic material. During the trauma-processing stage, experts frequently stabilize safety and augment trauma processing by using containment and grounding modalities.

ACUTE GENERAL Rx

Given the association between DDs and trauma, best practices suggest that a critical component of early treatment is the provision of a safe therapeutic environment. Identification of triggers associated with the onset of dissociation is useful. Controversy exists regarding the use of hypnosis for the purpose of recovering memories.

CHRONIC Rx

All stages of treatment may include psychoeducation, skill-building, alliance building, processing of reactions to therapy, emotion regulation, management of relationships, and stabilization. Grounding techniques, containment (i.e., imagery aimed at decreasing the intrusiveness of a memory), skill building (i.e., relaxation training and self-affirmation), and cognitive behavioral interventions (i.e., addressing irrational beliefs) are also used.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Research is lacking on complementary and alternative medicine for DDs.

DISPOSITION

Treatment should be delivered in the least restrictive environment possible to ensure patient safety. Patients who have comorbid psychiatric or medical diagnoses; who are experiencing suicidal or homicidal ideation, plans, or intention; or who are severely ill may require partial or inpatient hospitalization for the purpose of stabilization.

REFERRAL

Patients are treated by a mental health clinician.

PEARLS & CONSIDERATIONS

COMMENTS

- Diagnosis remains particularly challenging, as the features that present with this group of disorders (i.e., derealization, dissociation) are seen in many other psychiatric disorders (e.g., panic disorder, posttraumatic stress disorder [PTSD]). Incidence of dissociative symptoms following severe trauma is high. However, for most individuals, dissociative symptoms subside on their own within a few weeks following a traumatic event.
- Treatment approach may vary by the specific type of DD. Rigorous empirical studies assessing the treatment of specific DDs are lacking. For example, no randomized treatment studies have investigated the effectiveness of hypnosis in treating acute DA. Additionally, for chronic DA, pharmacologic facilitated intervention for the retrieval of memories (i.e., utilization of sodium pentobarbital or administration of intravenous lorazepam) is not well researched.

PREVENTION

Data are lacking on the prevention of DDs, but the prevention of child maltreatment may be useful in this regard.

PATIENT & FAMILY EDUCATION

International Society for the Study of Trauma and Dissociation (www.isst-d.org)

RELATED TOPICS

Acute Stress Disorder (Related Key Topic)
Posttraumatic Stress Disorder (Related Key Topic)

AUTHORS: **Lindsay M. Orchowski, PhD,** and **Lauren Grocott, BA**

SUGGESTED READINGS

International Society for the Study of Trauma and Dissociation: Guidelines for treating dissociative identity disorder in adults, third revision, *J Trauma Dissociation* 12:115-187, 2011.

Myrick AC et al: Six-year follow-up of the treatment of patients with dissociative disorders study, *Eur J Psychotraumatol* 8:1-7, 2017.

Myrick AC et al: Treatment of complex dissociative disorders: a comparison of interventions reported by community therapists versus those recommended by experts, *J Trauma Dissoc* 16:51-67, 2015.

Van der Hart O et al: The treatment of traumatic memories in patients with complex dissociative disorders, *Eur J Trauma Dissoc* 1:25-35, 2017.

Diverticular Disease (Diverticulosis, Diverticulitis, Diverticular Hemorrhage) ALG PTG

BASIC INFORMATION

DEFINITION

- Colonic diverticula are herniations of mucosa and submucosa (Figs. 1 and 2) through the muscularis. They are generally found along the colon's mesenteric border at the site where the vasa recta penetrates the muscle wall (anatomic weak point).
- *Diverticulosis* is the asymptomatic presence of multiple colonic diverticula.
- *Diverticulitis* is an inflammatory process or localized perforation of diverticulum.

ICD-10CM CODES

K57.30	Diverticulosis of large intestine without perforation or abscess without bleeding
K57.32	Diverticulitis of large intestine without perforation or abscess without bleeding
K57.31	Diverticulosis of large intestine without perforation or abscess with bleeding

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence of diverticulosis in the general population is 35% to 50%. Prevalence of diverticulosis increases with ages (<10% under age 40 to over 50% in those >85).
- Diverticulosis is more common in Western countries, affecting >30% of people >40 yr and >50% of people >70 yr.
- Approximately 20% of patients with diverticula have an episode of diverticulitis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination in patients with diverticulosis is generally normal.
- Painful diverticular disease can present with left lower quadrant (LLQ) pain, often relieved by defecation; location of pain may be anywhere in the lower abdomen because of the redundancy of the sigmoid colon.
- Diverticulitis can cause muscle spasm, guarding, and rebound tenderness predominantly affecting the LLQ. Factors associated with diverticulitis are pain localized to left lower quadrant and exacerbated by movement, left-lower-quadrant tenderness on examination, fever 38.5°C or higher, absence of vomiting, age >50 yr, and history of one or more episodes of diverticulitis.

ETIOLOGY

- Diverticular disease is believed to be secondary to low intake of dietary fiber.
- Recent studies indicate a pathogenetic role for inflammation in diverticulitis that may be similar to that of IBS, IBD, or both, based on common histologic findings such as granulomas, infiltrating lymphocytes, TNF, histamine, and matrix metalloproteinases.[1]

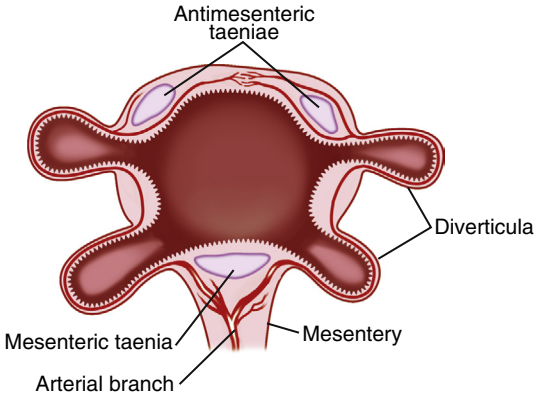


FIG. 1 Diagram showing colonic diverticula and their relationship to the taeniae coli. (From Feldman M et al [eds.]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.)

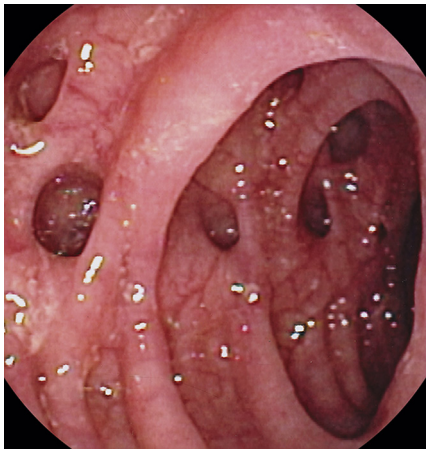


FIG. 2 Colonoscopic view of sigmoid diverticulosis. (From Feldman M et al [eds.]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- IBS
- IBD
- Colorectal cancer
- Endometriosis
- Ischemic colitis
- Bowel obstruction/volvulus
- Urinary tract disorders (urolithiasis, hydronephrosis)
- Infections (pseudomembranous colitis, appendicitis, pyelonephritis, PID)
- Lactose intolerance
- Celiac disease
- Epiploic appendagitis
- Gynecologic disorders (ectopic pregnancy, menstrual irregularities, dyspareunia, endometriosis)
- Cholecystitis, biliary disease

LABORATORY TESTS

- WBC count in diverticulitis reveals leukocytosis with left shift.
- Microcytic anemia can be present in patients with chronic bleeding from diverticular disease. MCV may be elevated in acute bleeding secondary to reticulocytosis.
- Urinalysis is useful to exclude urinary causes of pain.
- Pregnancy test is indicated in women of child-bearing age.
- Electrolytes and liver enzymes are useful in ruling out biliary causes of pain.
- CRP levels of 50 mg/L or greater is common in acute diverticulitis.

PROCEDURES: Colonoscopy should be avoided during acute diverticulitis due to the risk of perforation. It can generally be performed after 6 wk to rule out the presence of cancer and IBD.

IMAGING STUDIES

- If clinical features are highly suggestive of diverticulitis, imaging studies are generally not necessary.
- A CT scan of the abdomen (Fig. E3) with IV and luminal contrast is the preferred radiologic examination to diagnose acute diverticulitis. It can also diagnose diverticulosis.

[1]Morris AM et al: Sigmoid diverticulitis: a systematic review, *JAMA* 311(3):287-297, 2014.

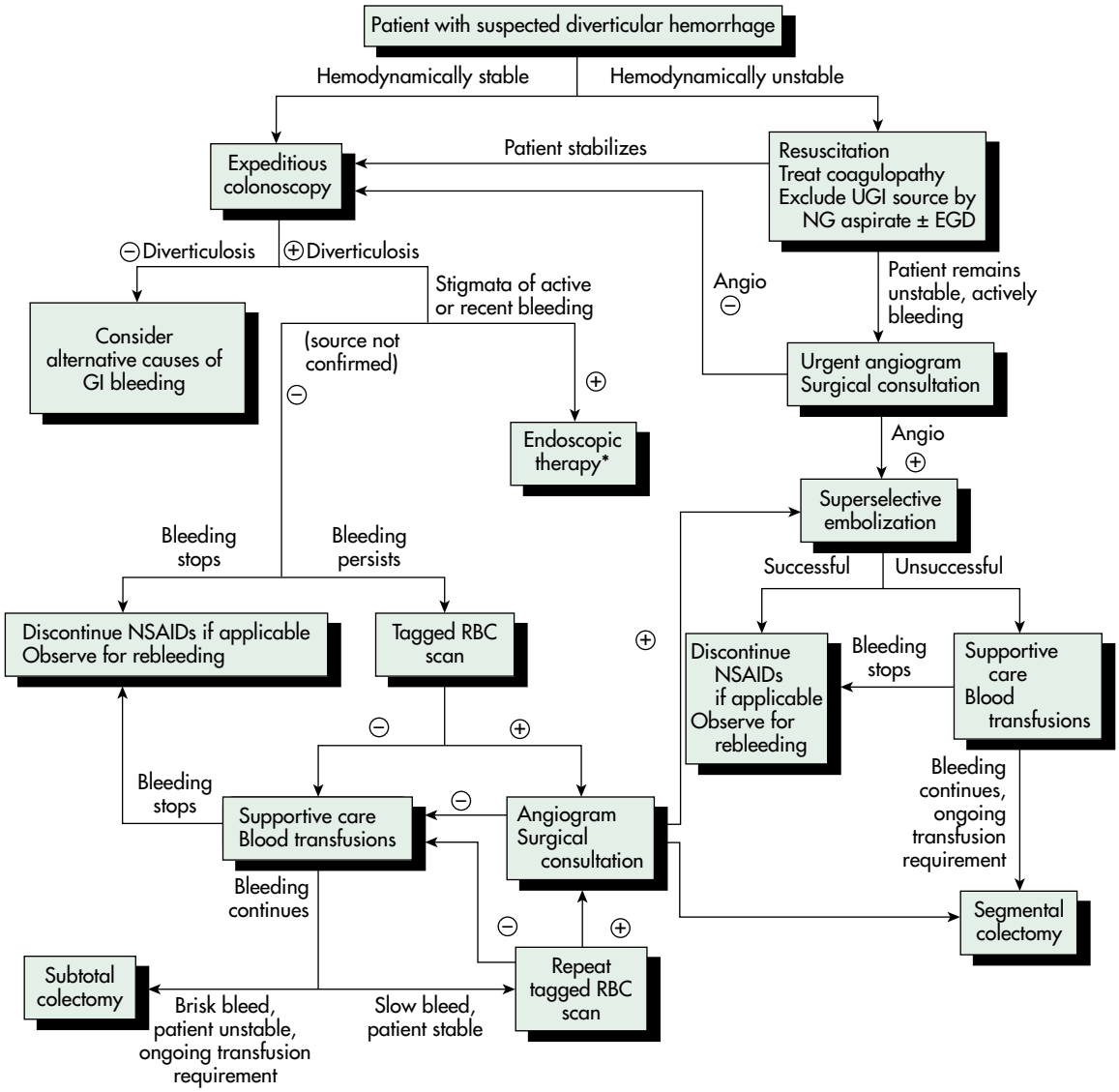


FIG. 4 Algorithm for the management of patients with suspected diverticular hemorrhage. *Angio*, Angiogram; *EGD*, esophagogastroduodenoscopy; *NG*, nasogastric; *NSAID*, nonsteroidal antiinflammatory drug; *RBC*, red blood cell; *UGI*, upper GI. *Endoscopic therapy may consist of epinephrine injection alone or in combination with other therapies, such as heater probe coagulation, bipolar coagulation, endoclips, fibrin sealant, and band ligation. (From Feldman M et al [eds.]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.)

It has a sensitivity of 93% to 97% and a specificity approaching 100% for diverticulitis. Typical findings are thickening of the bowel wall, fistulas, or abscess formation. CT may also reveal other disease processes (e.g., appendicitis, tubo ovarian abscess, Crohn disease) accounting for lower abdominal pain. In the Hinchey classification scheme based on CT results, stages 0 and Ia indicate uncomplicated diverticulitis, whereas stages Ib (pericolic or mesenteric abscess in proximity to the primary inflammatory process), II (intraabdominal abscess distant from primary inflammatory process or pelvic/retroperitoneal abscess), III (generalized purulent peritonitis), and IV (generalized fecal peritonitis) indicate complicated diverticulitis.

Ultrasonography and MRI can also be used. Abdominal ultrasonography has a 90% sensitivity and specificity for acute diverticulitis. MRI is also highly sensitive and specific for acute diverticulitis.

- Evaluation of suspected diverticular bleeding (Fig. 4):
  1. Arteriography if the bleeding is faster than 1 ml/min (advantage: The possible infusion of vasopressin directly into the arteries supplying the bleeding, as well as selective arterial embolization; disadvantages: Its cost and invasive nature)
  2. Technetium-99m sulfa colloid
  3. Technetium-99m labeled RBC (can detect bleeding rates as low as 0.12 to 5 ml/min)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Increase in dietary fiber intake and regular exercise to improve bowel function. However, recent studies have challenged the common view that fiber intake protects against diverticulosis.
- Oral diet of clear liquids is recommended until pain resolves in cases of mild uncomplicated diverticulitis.
- NPO and IV hydration in severe diverticulitis; NG suction if ileus or small bowel obstruction is present.
- Emergent surgery is required for perforation, peritonitis, or uncontrolled sepsis.

ACUTE GENERAL Rx

TREATMENT OF DIVERTICULITIS:

- Mild uncomplicated diverticulitis (75% of cases of diverticulitis): Broad-spectrum PO antibiotics (e.g., ciprofloxacin 750 mg bid or levofloxacin 750 mg bid or trimethoprim/sulfamethoxazole DS bid to cover aerobic component of colonic flora *and* metronidazole 500 mg q6h for anaerobes) and liquid diet for 7 to 10 days are commonly prescribed. Single-agent therapy with amoxicillin-clavulanic acid 875 mg/125 mg PO every 12 hours or moxifloxacin 400 mg PO every hour is also effective. Trials have shown no benefit of IV versus oral antibiotics and similar outcomes when using a 4-day course instead of a 7-day course of antibiotics. Other randomized trials and cohort studies have shown that antibiotics are not as beneficial or necessary as previously thought in cases of mild diverticulitis. Other modalities such as 5-aminosalicylate products and probiotics remain controversial and of unclear benefit.
- Mild to moderate complicated diverticulitis, in-patient treatment: Single-agent therapy with ertapenem 1 mg IV every 24 hours, ticarcillin-clavulanic acid 200 to 300 mg/kg per day divided doses every 6 hours, or moxifloxacin 400 mg IV every 24 hours for 4 to 7 days. Combination therapy of cefazolin (1 to 2 mg every 8 hours) or levofloxacin (750 mg every 24 hours) plus metronidazole (500 mg every 8 hours) is also effective.
- Severe complicated diverticulitis: NPO and aggressive IV antibiotic therapy
  1. Imipenem-cilastin 500 mg IV q6h *or*
  2. Piperacillin-tazobactam 4.5 g IV q8h *or*
  3. Meropenem 1 g IV q8h *or*
  4. Doripenem 500 mg IV q8h
  5. Cefepime 2 g IV q8h or ciprofloxacin 400 mg IV q12h each in combination with metronidazole 500 mg IV q8h
- Surgical treatment (laparoscopic preferred over open colectomy) consisting of resection of involved areas and reanastomosis (if feasible); otherwise, a diverting colostomy with reanastomosis is performed when infection has been controlled. The need for surgery as well as its optimal timing is unclear, and surgery is no longer considered necessary after a couple of episodes of diverticulitis. Surgery may be considered in patients with:
  1. Repeated episodes of diverticulitis
  2. Poor response to appropriate medical therapy (failure of conservative management)
  3. Abscess or fistula formation
  4. Obstruction
  5. Peritonitis: Colonic resection with a Hartmann pouch is the procedure of choice in critically ill patients with generalized peritonitis
  6. Immunocompromised patients, first episode in young patient (<40 yr old)
  7. Inability to exclude carcinoma (10% to 20% of patients diagnosed with diverticulosis on clinical grounds are subsequently found to have carcinoma of the colon)

DIVERTICULAR HEMORRHAGE:

- Bleeding is painless and stops spontaneously in the majority of patients (60%); it is usually caused by erosion of a blood vessel by a fecalith present within the diverticular sac.
- Medical therapy consists of blood replacement and correction of volume and any clotting abnormalities.
- Colonoscopic treatment with epinephrine injections, bipolar coagulation, or both may prevent recurrent bleeding and decrease the need for surgery. Endoclips (Fig. E5) can also be used to stop the bleeding.
- Surgical resection is necessary if bleeding does not stop spontaneously after administration of 4 to 5 U of PRBCs or recurs with severity within a few days; if attempts at localization are unsuccessful, total abdominal colectomy with ileoproctostomy may be indicated (high incidence of rebleeding if segmental resection is performed without adequate localization).

DISPOSITION

- The risk of recurrence among patients with uncomplicated diverticulitis is 32% to 36%. Most patients with diverticulitis respond well to antibiotic management and bowel rest. Up to 30% of patients with diverticulitis will eventually require surgical management.
- Diverticular bleeding can recur in 15% to 20% of patients within 5 yr.

REFERRAL

- GI referral for colonoscopy 4 to 6 wk after resolution of symptoms. In patients who have complications from diverticulitis, colonoscopy is generally not necessary after radiologically proven uncomplicated diverticulitis.
- Surgical referral when considering resection.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Diverticular Disease (Patient Information)
Diverticulitis (Patient Information)
Diverticulosis (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

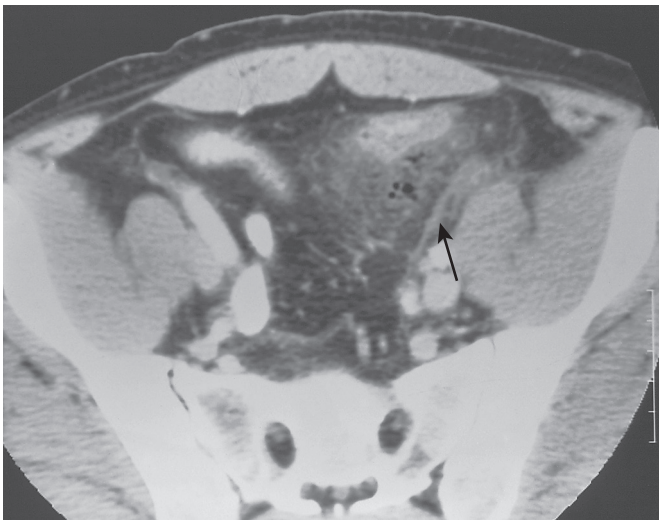


FIG. E3 Sigmoid diverticulitis. Enhanced CT shows haziness associated with extraluminal air in the sigmoid mesocolon due to perforated diverticulitis, also manifested as a thickened sigmoid wall. Thickening at the root of the sigmoid mesocolon is also present *(arrow)*. (From Grainger RG et al [eds.]: *Grainger and Allison's diagnostic radiology,* ed 4, Philadelphia, 2001, Churchill Livingstone.)

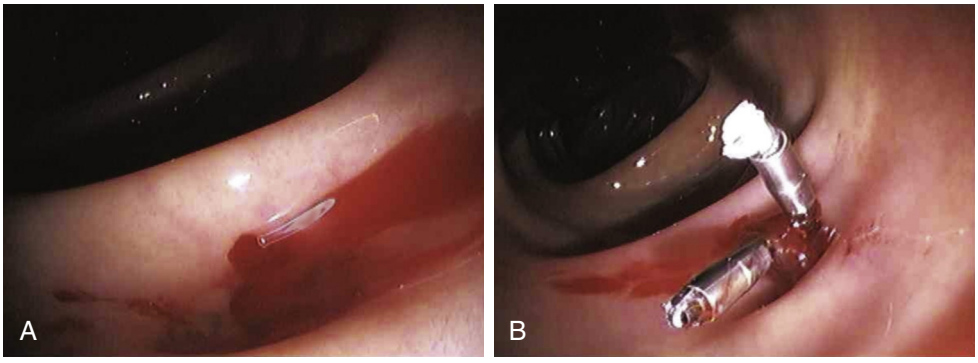


FIG. E5 Colonoscopy in a patient with lower intestinal bleeding from a diverticulum in whom a site of active bleeding was identified **(A)** and treated successfully with placement of two endoclips **(B)**. (Courtesy Janak Shah, MD. San Francisco, CA.) (From Feldman M et al [eds.]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.)

SUGGESTED READINGS

Feuerstein JD, Falchuk KR: Diverticulosis and diverticulitis, *Mayo Clin Proc* 91(8):1094-1104, 2016.

Perry AF et al: A high-fiber diet does not protect against asymptomatic diverticulosis, *Gastroenterology* 142(266), 2012.

Swanson SM, Strate LL: In the clinic: acute colonic diverticulitis, *Ann Intern Med*, 2018.

Wilkins T et al: Diagnosis and management of acute diverticulitis, *Am Fam Physician* 87(9):612-620, 2013.

Young-Fadok TM et al: Diverticulitis, *N Engl J Med* 379:1635-1642, 2018.

BASIC INFORMATION

DEFINITION

Down syndrome is a disorder characterized by mental retardation and multiple organ defects and is caused by a chromosomal abnormality (trisomy 21).

SYNONYMS

Trisomy 21
Mongolism

ICD-10CM CODE
Q90.9 Down syndrome, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 1 in 733 births
PEAK INCIDENCE: Newborn
PREVALENCE (IN U.S.): 300,000 persons
PREDOMINANT SEX: Male:female ratio of 1.3:1.0
PREDOMINANT AGE: Newborn to early adulthood
GENETICS: Nondisjunction causing trisomy 21

PHYSICAL FINDINGS & CLINICAL PRESENTATION

(Fig. E1)
- Microcephaly
- Flattening of occiput and face
- Upward slant to eyes with epicanthal folds
- Brushfield spots on iris
- Broad, stocky neck
- Small feet, hands, digits
- Single palmar crease

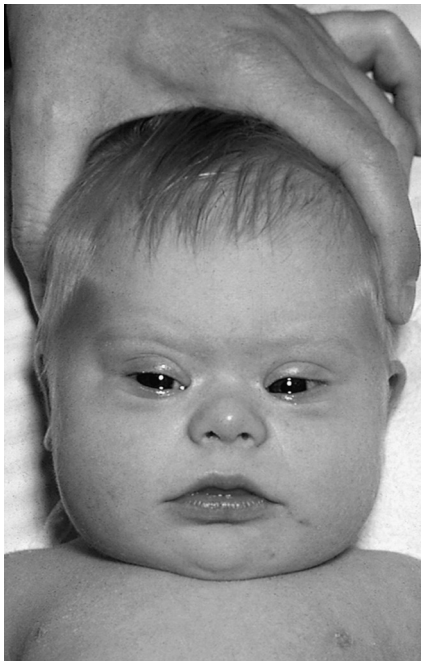


FIG. E1 Individual with Down syndrome. Note depressed nasal bridge, epicanthal folds, mongoloid slant of eyes, low-set ears, and large tongue. (From Zitelli BJ, Davis HW: *Atlas of pediatric physical diagnosis,* ed 3, St Louis, 1997, Mosby.)

- Hypotonia
- Short stature
- Clinical features of Down syndrome in the neonatal period are summarized in Table E1
- Associated with congenital heart disease, malformations of the GI tract, cataracts, hypothyroidism, hip dysplasia, obstructive sleep apnea, infantile spasms, Moyamoya disease, and myeloproliferative disorders
- About half of children with Down syndrome are born with congenital heart disease, with the most common lesions being atrial septal defect and ventricular septal defect
- Persistent primary congenital hypothyroidism is found in 1 in 141 newborns with Down syndrome compared with 1 in 4000 in the general population
- Ophthalmologic disorders increase in frequency with age; >80% of children ages 5 to 12 yr have disorders that need monitoring or intervention, such as refractive errors, strabismus, or cataracts
- Renal and urinary tract abnormalities
- Table E2 summarizes additional features of Down syndrome that can develop or become symptomatic with time

ETIOLOGY

Nondisjunction of chromosome 21

DIAGNOSIS

- The American College of Obstetrics and Gynecology recommends offering fetal chromosomal screening to all pregnant women regardless of age because of improvements in noninvasive screening methods. Cell-free DNA (CF DNA) testing for trisomy 21 has a higher sensitivity, a lower false positive rate, and a higher positive predictive value than standard screening with the measurement of nuchal translucency and biochemical analysis.[1]
- Combined use of serum screening and fetal ultrasound testing for thickened nuchal fold has 85% detection rate with 5% false-positive results. Second-trimester serum screening in combination with maternal age is improved with use of multiple serum markers.
- Prenatal cytogenic diagnosis by amniocentesis or chorionic villus sampling.
- Postnatal chromosomal karyotype.

DIFFERENTIAL DIAGNOSIS

- Congenital hypothyroidism
- Other chromosomal abnormalities

WORKUP

Postnatal chromosomal karyotype (Fig. E2)

TREATMENT

- Thyroid screen at birth, at age 6 mo, and yearly thereafter
- Echocardiogram in all newborns and cardiac assessment of adolescents for development of mitral valve prolapse
- Treatment consists of vigilant monitoring for comorbid states, such as obesity, hypothyroidism, leukemia, hearing loss, and valvular heart disease
- Prevention of obesity with low-calorie, high-fiber diet
- Auditory brain stem responses in all newborns and aggressive testing for hearing loss in children with chronic otitis media
- Ophthalmologic assessment by age 6 mo for congenital cataracts and annual examinations for monitoring of refractive errors and strabismus
- Regular dental care
- Pelvic examination of women who are sexually active or who have menstrual problems
- Dermatologic issues such as folliculitis can become problematic in adolescents and require topical antibiotics and careful attention to hygiene

DISPOSITION

Most children with Down syndrome live at home. As these individuals reach adulthood, those with higher functioning sometimes live in supervised settings away from their families.

REFERRAL

Down syndrome clinics use a preventive checklist to anticipate many clinical challenges.

PEARLS & CONSIDERATIONS

COMMENTS

- Screening for atlantoaxial subluxation is controversial.
- Most patients experience neuropathologic changes typical of Alzheimer disease. Presenting symptoms include seizures, focal neurologic signs, and apathy. If Alzheimer disease is suspected, screen for treatable diseases such as depression or hypothyroidism.
- This syndrome accounts for approximately one third of moderate to severe cases of mental retardation.
- Individuals with Down syndrome have a wide range of function, but all have a decrease in intelligence quotient (IQ) in the first decade of life.
- Deficiency of language production relative to other areas of development often causes substantial impairment.
- Although increased maternal age is a risk factor, most children with Down syndrome are born to women younger than age 35 yr.

RELATED CONTENT

Down Syndrome (Trisomy, Mongolism) (Patient Information)

AUTHORS: **Joseph S. Kass, MD, JD, FAAN,** and **Maitreyi Mazumdar, MD, MPH, MSc**

[1] Norton ME et al: Cell-free DNA analysis for noninvasive examination of trisomy, *N Engl J Med* 37:1589-1599, 2015.

TABLE E1 Clinical Features of Down Syndrome in the Neonatal Period

Central Nervous System
- Hypotonia*
- Developmental delay
- Poor Moro reflex*

Craniofacial
- Brachycephaly with flat occiput
- Flat face*
- Upward slanted palpebral fissures*
- Epicanthal folds
- Speckled irises (Brushfield spots)
- Three fontanels
- Delayed fontanel closure
- Frontal sinus and midfacial hypoplasia
- Mild microcephaly
- Short, hard palate
- Small nose, flat nasal bridge
- Protruding tongue, open mouth
- Small dysplastic ears*

Cardiovascular
- Endocardial Cushing defects
- Ventricular septal defect
- Atrial septal defect
- Patent ductus arteriosus
- Aberrant subclavian artery
- Pulmonary hypertension

Musculoskeletal
- Joint hyperflexibility*
- Short neck, redundant skin*
- Short metacarpals and phalanges
- Short 5th digit with clinodactyly*
- Single transverse palmar creases*
- Wide gap between 1st and 2nd toes
- Pelvic dysplasia*
- Short sternum
- Two sternal manubrium ossification centers

Gastrointestinal
- Duodenal atresia
- Annular pancreas
- Tracheoesophageal fistula
- Hirschsprung disease
- Imperforate anus
- Neonatal cholestasis

Cutaneous
- Cutis marmorata

*Hall's criteria to aid in diagnosis.

From Kliegman RM: *Nelson's textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

TABLE E2 Additional Features of Down Syndrome That Can Develop or Become Symptomatic with Time

Neuropsychiatric
- Developmental delay
- Seizures
- Autism spectrum disorders
- Behavioral disorders (disruptive)
- Depression
- Alzheimer disease

Sensory
- Congenital or acquired hearing loss
- Serous otitis media
- Refractive errors (myopia)
- Congenital or acquired cataracts
- Nystagmus
- Strabismus
- Glaucoma
- Blocked tear ducts

Cardiopulmonary
- Acquired mitral, tricuspid, or aortic valve regurgitation
- Endocarditis
- Obstructive sleep apnea

Musculoskeletal
- Atlantoaxial instability
- Hip dysplasia
- Slipped capital femoral epiphyses
- Avascular hip necrosis
- Recurrent joint dislocations (shoulder, knee, elbow, thumb)

Endocrine
- Congenital or acquired hypothyroidism
- Diabetes mellitus
- Infertility
- Obesity
- Hyperthyroidism

Hematologic
- Transient myeloproliferative syndrome
- Acute lymphocytic leukemia
- Acute myelogenous leukemia

Gastrointestinal
- Celiac disease
- Delayed tooth eruption
- Respiratory
- Obstructed sleep apnea
- Frequent infections (sinusitis, nasopharyngitis, pneumonia)

Cutaneous
- Hyperkeratosis
- Seborrhea
- Xerosis
- Perigenital folliculitis

From Kliegman RM: *Nelson's textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

SUGGESTED READINGS

Allred SK et al: Second trimester serum tests for Down's syndrome screening, *Cochrane Database Syst Rev* 6:CD009925, 2012.

Norton ME et al: Cell-free DNA analysis for noninvasive examination of trisomy, *N Engl J Med* 372:1588-1599, 2015.

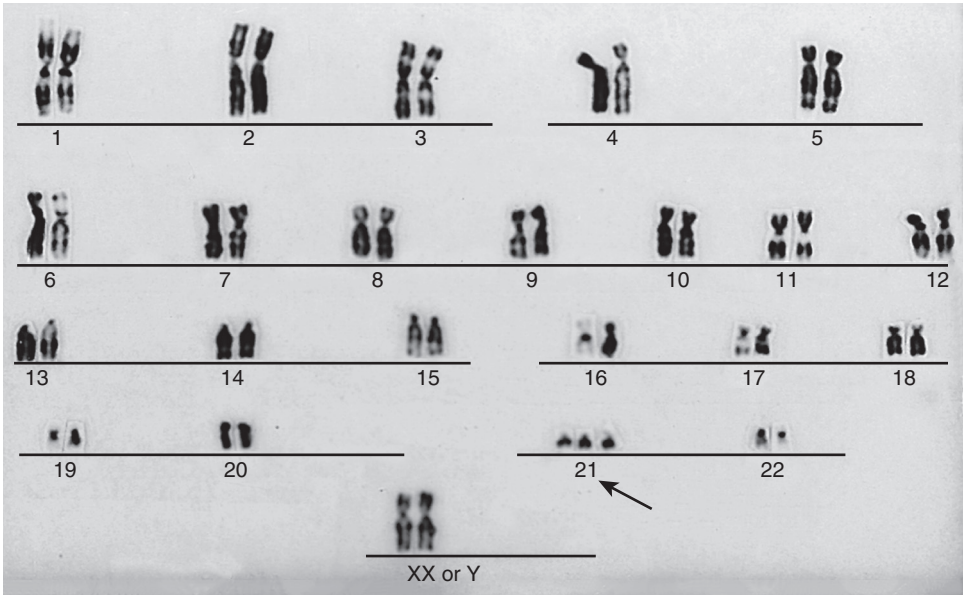


FIG. E2 Chromosomal karyotype showing trisomy (*arrow*).

BASIC INFORMATION

- Drowning aftereffects should be classified as death, morbidity, and absence of morbidity.
- The previously used terms *wet, dry, active, passive, silent,* and *secondary drowning* should no longer be used when considering statistical analysis; however, they remain in common use.

DEFINITION

Drowning is the process of experiencing respiratory impairment from submersion/immersion in liquid.

SYNONYMS

Suffocation
Asphyxiation

ICD-10CM CODES

W65	Accidental nontransport drowning and submersion
W67	Accidental drowning and submersion while in swimming pool
W69	Accidental drowning and submersion while in natural water
W74	Unspecified cause of accidental drowning and submersion

EPIDEMIOLOGY & DEMOGRAPHICS

- The fifth-leading cause of unintentional-injury death in the U.S.; 10 people die each day from drowning. Worldwide drowning accounts for more than 370,000 deaths/yr.
- Drowning is the most common injury-related cause of death in children 1 to 4 yr of age.
- Nearly 6000 persons are treated in U.S. emergency departments each yr for submersion or drowning injuries, with 50% of these patients requiring hospital admission.
- Between 2000 and 2007, the rate of fatal accidental drowning for African Americans was 130% that of whites; for Native Americans and Alaskan Natives, this rate was 170% that of whites.

INCIDENCE:

- From 2005 to 2014, an average of 3536 fatal unintentional drownings (nonboating related) occurred annually in the U.S. In California, Arizona, and Florida, drowning is the number one cause of injury-related death.
- Internationally the incidence is likely underestimated due to lack of reporting.

PEAK INCIDENCE:

- Ages 14 yr of age or younger account for 25%. High-risk groups are in the toddler age group and in young males. Fifteen percent of children admitted for drowning die in the hospital.
- Highest occurrence on weekends (~40%) in the summertime months (May through August), and more commonly in the rural southern and western U.S. (62%).

PREDOMINANT SEX & AGE:

- Males are 400% more likely to suffer a drowning due to increased risk-taking behavior.
- Age distribution is bimodal with the very young and elderly showing higher rates of submersion injury.

RISK FACTORS:

- Alcohol abuse
- Male
- Youth, elderly
- Seizure disorder
- Mental illness
- Cardiac disease
- Neuromuscular disorder, musculoskeletal disorder
- Frigid liquid temperature

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presentation varies; it most commonly is an unobserved individual found unconscious.
- Swimmers can suffer blackouts from hypocapnia when hyperventilating, and ascending divers may experience shallow water blackouts.
- A drowning classification system is used to classify victims at the rescue scene based on the following clinical parameters: Pulse, respirations, pulmonary auscultation, and blood pressure.

ETIOLOGY

- The primary factor is hypoxemia with subsequent multiorgan damage.
- The initiation of breath holding is complicated by laryngospasm if liquid is detected in the posterior pharynx/larynx, which impedes immediate inhalation. Once serum oxygen levels decrease, involuntary larynx relaxation occurs, and the victim aspirates liquid.
- If hypoxemia ensues and progresses to acidosis, myocardial ischemia and CNS ischemia are the predominant threats.
- A minority of drownings are considered "dry," with laryngospasm persisting until death.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Suicide
- Homicide
- Abuse
- Cranial/cervical trauma
- Seizure
- Cardiac arrhythmia
- Hypoglycemia

WORKUP

- Initiation of basic life support/advanced cardiac life support (BLS/ACLS)
- Cardiopulmonary monitoring
- Pulse oximetry
- ECG
- Assess for trauma
- Glasgow Coma Scale assessment

LABORATORY TESTS

- ABG
- Chemistry panel 7
- Toxicology screen
- Troponin
- Liver function tests
- Lactate
- Urinalysis

IMAGING STUDIES

- CXR for evaluation of pulmonary edema, aspiration, endotracheal tube placement, foreign body (Fig. E1)
- CT cervical/head for assessment of trauma and/or intracranial pathology

TREATMENT

- The foundation is management of basic cardiopulmonary functions of oxygenation, ventilation, respiration, and cardiac output (Table E1) as well as thermoregulation.
- An algorithm for drowning-severity classification and flow-chart strategy decision based on evaluation is described in Fig. E2.

NONPHARMACOLOGIC THERAPY

- Supplemental oxygen.
- CPAP or intubation with mechanical ventilation for respiratory failure.
- Permissive therapeutic hypothermia may benefit comatose patients.
- Extracorporeal membrane oxygenation is beneficial under specific circumstances.
- Bronchoscopy to remove foreign aspirated bodies.
- Treat secondary causes such as seizure, trauma, hypoglycemia.
- Table E2 summarizes which patients need further medical help after rescue from the water.

DISPOSITION

- Mental and cardiopulmonary status are core measures. Table E3 summarizes clinical prognostic scores for the immediate period after successful CPR based on the Glasgow coma score.
- ABG normalization.
- Correction of potential secondary etiologies.

REFERRAL

Once the patient is stabilized, transfer to a tertiary care facility is ideal with comatose patients or those requiring a specialist.

PEARLS & CONSIDERATIONS

- Early resuscitation is key.
- All guardians should have BLS training.

PREVENTION

Unattended access to bodies of water and poor rescue/safety training are key. Table E4 summarizes an approach to prevention strategies for drowning.

PATIENT & FAMILY EDUCATION

All guardians should have BLS training.

AUTHOR: **Kevin V. Plumley, MD, MPH**

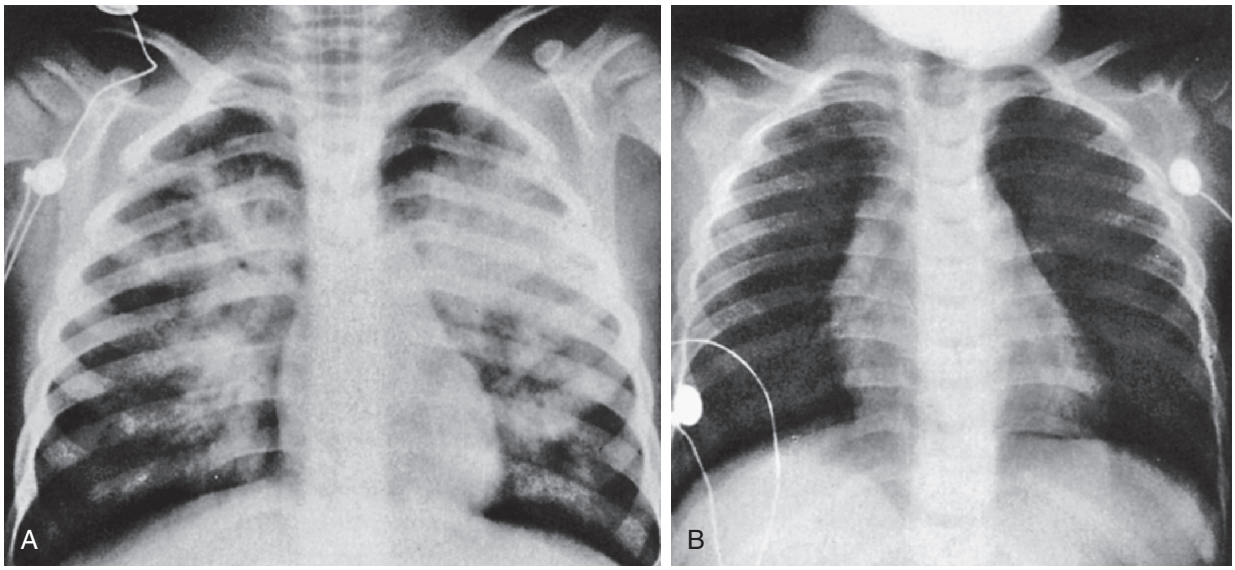
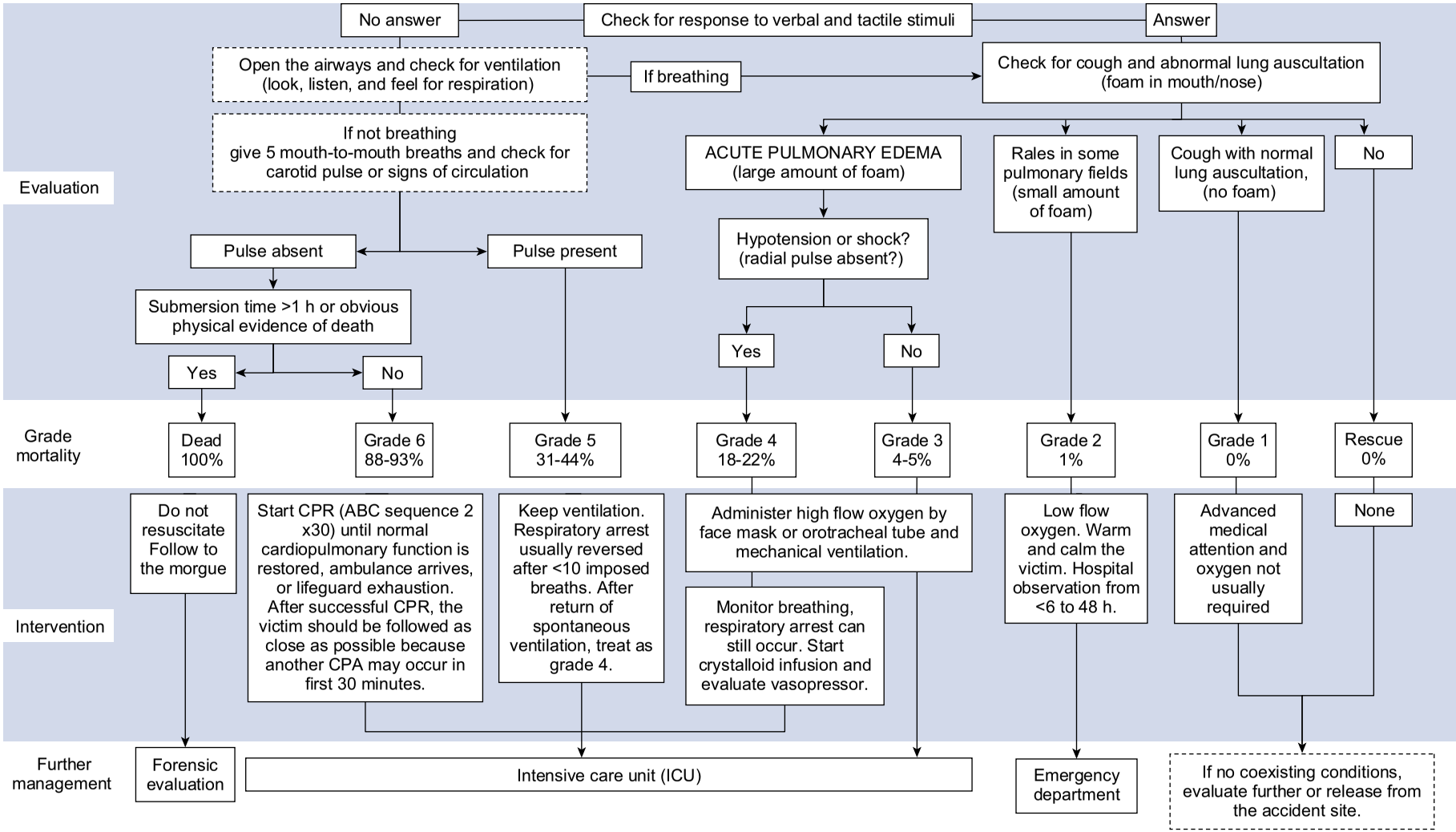


FIG. E1 Drowning with and without aspiration. Radiographs show a patient with severe pulmonary edema **(A)** and another without significant fluid aspiration **(B)**. (From Fuhrman BP, Zimmerman JJ: *Pediatric critical care*, ed 4, Philadelphia, 2011, Mosby.)

TABLE E1 Drowning: When to Initiate CPR and When to Discontinue

Question	Recommendations
In whom to begin?	Give ventilatory support for respiratory distress/arrest to avoid cardiac arrest. Start CPR in all submersions <60 min who do not present with obvious physical evidence of death.
When to discontinue?	Basic life support should continue unless signs of life reappear, rescuers are exhausted, or advanced life support can take over. Advanced life support should be ongoing until patient has been rewarmed (if hypothermic) and asystole persists for more than 20 min.

From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.



Abbreviations: CPR (cardiopulmonary resuscitation); CPA (cardiopulmonary arrest); recovery position (lateral decubitus position). Lay classification of severity terminology in bracket.

FIG. E2 Drowning severity classification and flow-chart strategy decision based on evaluation of 87,339 rescues. (From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.)

TABLE E2 Who Needs Further Medical Help after Rescue from the Water

(a) A patient who has experienced or required any of the following should be sent to a hospital:
   1. Loss of consciousness, even for a brief period
   2. Rescue breathing
   3. Cardiopulmonary resuscitation
   4. A serious condition such as heart attack, spinal injury, other injury, asthma, epilepsy, intoxication, or delirium

(b) The following persons may be considered for release from care at the scene if—after 10 to 15 min of careful observation while being warmed with blankets or other coverings as required—the patient meets *all* of the following criteria:
   1. No cough
   2. Normal rate of breathing
   3. Normal circulation as measured by pulse in strength, rate, and blood pressure (if available)
   4. Normal color and skin perfusion
   5. No shivering
   6. Is fully conscious, awake, and alert

   In such cases, it is unwise for the patient to drive a vehicle, and the patient should be so advised. If any of these conditions does not apply or if the lifesaver has any doubt, the patient should be advised to seek early medical attention

(c) There is always a risk of delayed lung complications. All immersion victims should therefore be warned that if they later develop cough, breathlessness, fever, or any other concerning respiratory symptoms, they should seek medical advice immediately. It is preferable that these persons not return to a home environment where they are alone for the next 24 hours

From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.

TABLE E3 Clinical Prognostic Score for the Immediate Period after Successful CPR Based on Glasgow Coma Score

Neurologic Prognostic Score after Successful CPR upon Drowning	
A: First hr	**B: After 5-8 hr**
Alert, 10	Alert, 9.5
Confused, 9	Confused, 8
Torpor, 7	Torpor, 6
Coma with normal brain stem functions, 5	Coma with normal brain stem functions, 3
Coma with abnormal brain stem functions, 2	Coma with abnormal brain stem functions, 1
A + B	
Recovery without Sequelae	
Excellent, ≥13	≥95%
Very good, 10-12	75%-85%
Good, 8	40%-60%
Regular, 5	10%-30%
Poor, 3	≤5%

CPR, Cardiopulmonary resuscitation.

From Orlowski JP, Szpilman D: Drowning—Rescue, resuscitation, and reanimation. In *Pediatric critical care: A new millennium*, Vol. 48, 2001, W. B. Saunders Company, Pediatric Clinics of North America, pp 627–646.

From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.

TABLE E4 Approach to Prevention Strategies for Drowning

	Home	Recreation	Neighborhood
Water hazards	Swimming pools Ponds Bathtubs Large buckets	Playing in water: Swimming, wading Playing near water Being on water: Boating	Irrigation ditches Watering holes Water drainage
Common risks	Lapse in supervision Unexpected toddler exposure Delayed discovery of child Reliance on water wings or pool toys Reliance on sibling or bath seat for bathing supervision	Lapse in supervision Change in weather Unfamiliarity with or change(s) in water conditions: Steep drop-off Current/tide Low temperature Alcohol use Peer pressure	Lapse in supervision, particularly when caregiver is socializing Risky behavior when with peers
Prevention strategies	Recognize hazards and risks. Provide constant adult supervision around water. Install 4-sided, isolation fencing around pools. Install rescue equipment and phone at poolside. Learn swimming and water survival skills. Avoid bath; instead shower, if a child/teen with seizure disorder. Learn first aid and CPR.	Provide constant adult supervision. Swim in lifeguarded areas. Know when and how to wear U.S. Coast Guard–approved PFDs. Avoid alcohol and other drugs. Learn swimming and water survival skills. Teach children about water safety. Be aware of current weather and water conditions. Learn first aid and CPR.	Identify hazardous bodies of water. Prevent access to water with the use of barriers. Provide fenced-in "safe area" for water recreation. Provide lifeguarded swim sites. Provide access to low-cost swim/water survival lessons.

CPR, Cardiopulmonary resuscitation; *PFDs*, personal flotation devices.
From Kliegman, RM: *Nelson Textbook of Pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

SUGGESTED READINGS

Centers for Disease Control and Prevention: National Center for Injury Prevention and Control: Web-based injury statistics query and reporting system (WISQARS). Available at www.cdc.gov/injury/wisqars.

Mott TF, Latimer KM: Prevention and treatment of drowning, *Am Fam Physician* 93(7):576-582, 2016.

Szpilman D et al: Drowning, *N Engl J Med* 366(22):2010-2102, 2012.

Drug-Induced Liver Injury

BASIC INFORMATION

DEFINITION

Drug-induced liver injury (DILI) is defined as any injury to the liver by any medication such as a prescription medication, an over-the-counter medication, or an herbal/dietary supplement. It can present as asymptomatic liver test elevations or as acute liver failure.

SYNONYMS

Toxic liver disease
DILI

ICD-10CM CODES

K71.0	Toxic liver disease with cholestasis
K71.1	Toxic liver disease with hepatic necrosis
K71.10	Toxic liver disease with hepatic necrosis without coma
K71.11	Toxic liver disease with hepatic necrosis with coma
K71.2	Toxic liver disease with acute hepatitis
K71.3	Toxic liver disease with chronic persistent hepatitis
K71.4	Toxic liver disease with chronic lobular hepatitis
K71.5	Toxic liver disease with chronic active hepatitis
K71.50	Toxic liver disease with chronic active hepatitis without ascites
K71.51	Toxic liver disease with chronic active hepatitis with ascites
K71.6	Toxic liver disease with hepatitis, not elsewhere classified
K71.7	Toxic liver disease with hepatitis with fibrosis and cirrhosis of the liver
K71.8	Toxic liver disease with hepatitis, not elsewhere classified
K71.8	Toxic liver disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Estimated annual incidence between 10 and 15 per 10,000 to 100,000 has been reported.

PEAK INCIDENCE: N/A
PREVALENCE: N/A
PREDOMINANT SEX AND AGE: Incidence increases with age and is more common in females.
RISK FACTORS:

- Predisposing factors: Female gender, race, and older age.
- Acquired risk factors: Chronic alcohol use, extrahepatic disease (i.e., hyperthyroidism, HIV, etc.).
- A patient's nutritional status can influence their ability to metabolize medications.

GENETICS: Genetic polymorphisms can lead to altered expressions of various liver cytochrome p450 enzymes. Table E1 summarizes factors influencing the risk of liver diseases caused by drugs.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The physical findings and presentation depend on the classification of hepatic injury incited by the drug.
- These are usually divided into hepatocellular, cholestatic, or a mixed picture of hepatocellular and cholestatic injury. Table E2 describes a clinicopathologic classification of drug-induced liver disease.
- Some patients are asymptomatic, and DILI is detected only because of abnormal labs.
- Symptomatic patients present with fever, nausea, vomiting, malaise, anorexia, right upper quadrant pain, jaundice, acholic stools, or dark urine.
- Patients may also present with pruritus and hepatomegaly on physical examination.
- Patients may have muscular symptoms such as myalgia, stiffness, weakness, and elevated creatinine kinase level.

ETIOLOGY

- Drug-induced liver injury can result due to toxicity of over-the-counter drugs, prescription medications, anesthetics (Table E3), or herbal remedies/supplements (Table E4). The clinicopathologic spectrum of chemical hepatotoxins is summarized in Box E1.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hepatitis (Tables E5 and E6): Viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease, autoimmune hepatitis, and Wilson disease
- Cholestasis: Biliary obstruction, primary biliary cirrhosis, primary sclerosing cholangitis, and intrahepatic cholestasis of pregnancy
- Steatosis: Nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and acute fatty liver of pregnancy
- Granulomatous hepatitis (Table E7): Sarcoidosis, infection, and primary biliary cirrhosis
- Peliosis hepatitis: Infections, hematologic disorders, and organ transplantation

WORKUP

- A thorough history and blood tests to evaluate other possible causes of hepatic injury help make the diagnosis
- Liver function tests
- Hepatitis A, B, and C serologies, antinuclear antibody, anti-smooth muscle antibody, anti-liver kidney microsomal antibody, alpha 1 antitrypsin, ceruloplasmin, fasting glucose, triglycerides, and hemoglobin A1c

LABORATORY TESTS

- Hepatocellular findings:
  1. Abnormal elevations in serum aminotransferases when compared to alkaline phosphatase (ALP)
  2. Alanine aminotransferase (ALT)/ALP ratio greater than 5
- Cholestatic findings:
  1. Abnormal elevations in the alkaline phosphatase compared to the serum aminotransferases
  2. ALP >2 times the upper limit of normal and/or ALT to ALP ratio <2
- Mixed hepatocellular/cholestatic findings:
  1. ALT/ALP ratio >2 but <5
- In either of these types of DILI, the serum bilirubin may or may not be elevated.

TABLE E1 Factors Influencing the Risk of Liver Diseases Caused by Drugs

Factor	Examples of Drugs Affected	Influence
Genetic factors	Halothane, phenytoin, sulfonamides	Multiple cases in families
	Amoxicillin-clavulanic acid, flucloxacillin, abacavir	Strong HLA association
	Valproic acid	Familial cases; association with mitochondrial enzyme deficiencies
Age	Isoniazid, nitrofurantoin, halothane, troglitazone	Age >60 yr; increased frequency, increased severity
	Valproic acid, salicylates	More common in children
Gender	Halothane, minocycline, nitrofurantoin	More common in women, especially in cases with chronic hepatitis
	Amoxicillin-clavulanic acid, azathioprine	More common in men
Dose	Acetaminophen, aspirin, some herbal medicines	Blood levels are directly related to the risk of hepatotoxicity
	Tetracycline, tacrine, oxypenicillins	Idiosyncratic reactions, with partial relationship to dose
	Methotrexate, vitamin A	Total dose, dosing frequency, and duration of exposure are related to the risk of hepatic fibrosis
Other drugs	Acetaminophen	Isoniazid, zidovudine, and phenytoin lower the dose threshold and increase the severity of hepatotoxicity

Continued

TABLE E1 Factors Influencing the Risk of Liver Diseases Caused by Drugs—cont'd

Factor	Examples of Drugs Affected	Influence
	Valproic acid	Other antiepileptic drugs increase the risk of hepatotoxicity
	Anticancer drugs	Interactive vascular toxicity
History of other drug reactions	Isoflurane, halothane, enflurane Erythromycins Diclofenac, ibuprofen, tiaprofenic acid Sulfonamides, COX-2 inhibitors	Instances of cross-sensitivity have been reported among members of each drug class but are rare
Excessive alcohol use	Acetaminophen	Lowered dose threshold, poorer outcome
	Isoniazid, methotrexate	Increased risk of liver injury, hepatic fibrosis
Nutritional Status:		
Obesity	Halothane, troglitazone, tamoxifen, methotrexate	Increased risk of liver injury, hepatic fibrosis
Fasting	Acetaminophen	Increased risk of hepatotoxicity
Preexisting liver disease	Hycanthone, pemoline	Increased risk of liver injury
	Antituberculosis drugs, ibuprofen	Increased risk of liver injury with chronic hepatitis B and C
Other Diseases/Conditions:		
Diabetes mellitus	Methotrexate	Increased risk of hepatic fibrosis
HIV/AIDS	Sulfonamides	Increased risk of hypersensitivity
Renal failure	Tetracycline, methotrexate	Increased risk of liver injury, hepatic fibrosis
Organ transplantation	Azathioprine, thioguanine, busulfan	Increased risk of vascular toxicity

AIDS, Acquired immunodeficiency syndrome; *COX-2,* cyclooxygenase-2; *HIV,* human immunodeficiency virus; *HLA,* human leukocyte antigen.
From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE E2 Clinicopathologic Classification of Drug-Induced Liver Disease

Category	Description	Implicated Drugs: Examples
Hepatic adaptation	No symptoms; raised serum GGTP and AP levels (occasionally raised ALT)	Phenytoin, warfarin, heparins
	Hyperbilirubinemia	Rifampin, HIV protease inhibitors
Dose-dependent hepatotoxicity	Symptoms of hepatitis; zonal, bridging, and massive necrosis; serum ALT level >5-fold increased, often >2000 U/L	Acetaminophen, nicotinic acid, amodiaquine, hycanthone
Other cytopathic toxicity, acute steatosis	Microvesicular steatosis, diffuse or zonal; partially dose dependent, severe liver injury, features of mitochondrial toxicity (lactic acidosis)	Valproic acid, didanosine, HAART agents, fialuridine, L-asparaginase, some herbal medicines
Acute hepatitis	Symptoms of hepatitis, focal, bridging, and massive necrosis; serum ALT level >5-fold increased; extrahepatic features of drug allergy in some cases	Isoniazid, dantrolene, nitrofurantoin, halothane, sulfonamides, phenytoin, disulfiram, acebutolol, etretinate, ketoconazole, terbinafine, troglitazone
Chronic hepatitis	Duration >3 mo; interface hepatitis, bridging necrosis, fibrosis, cirrhosis; clinical and laboratory features of chronic liver disease; autoantibodies with some types of reaction	Nitrofurantoin, etretinate, diclofenac, minocycline, nefazodone
Granulomatous hepatitis	Hepatic granulomas with varying hepatitis and cholestasis; raised serum ALT, AP, GGTP levels	Allopurinol, carbamazepine, hydralazine, quinidine, quinine
Cholestasis without hepatitis	Cholestasis, no inflammation; serum AP levels > twice normal	Oral contraceptives, androgens
Cholestatic hepatitis	Cholestasis with inflammation; symptoms of hepatitis; raised -serum ALT and AP levels	Chlorpromazine, tricyclic antidepressants, erythromycins, amoxicillin–clavulanic acid, cyproterone acetate
Cholestasis with bile duct injury	Bile duct lesions and cholestatic hepatitis; clinical features of cholangitis	Chlorpromazine, flucloxacillin, dextropropoxyphene
Chronic cholestasis	Duration >3 mo	
Vanishing bile duct syndrome (VBDS)	Paucity of small bile ducts; resembles PBC but AMA negative	Chlorpromazine, flucloxacillin, trimethoprim/sulfamethoxazole
Sclerosing cholangitis	Strictures of large bile ducts	Intraarterial floxuridine, intralesional scolicidals
Steatohepatitis	Steatosis, focal necrosis, Mallory hyaline, pericellular fibrosis, cirrhosis; chronic liver disease, portal hypertension	Perhexiline, amiodarone, tamoxifen
Fibrosis and cirrhosis	Fibrosis, nodular regeneration (other features [e.g., interface hepatitis, steatohepatitis, paucity of bile ducts, cholestasis] depend on etiology)	Methotrexate, cyproterone acetate; also see VBDS, chronic hepatitis, steatohepatitis
Vascular disorders	Sinusoidal obstruction syndrome, nodular regenerative hyperplasia, others	Many
Tumors	Hepatocellular carcinoma, adenoma, angiosarcoma, others	Many

ALT, Alanine aminotransferase; *AMA,* antimitochondrial antibody; *AP,* alkaline phosphatase; *GGTP*, gamma-glutamyl transpeptidase; *HAART*, highly active antiretroviral therapy; *HIV,* human immunodeficiency virus; *PBC,* primary biliary cirrhosis.
From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE E3 Comparative Features of Causes of Acute Postoperative Liver Injury

Feature	Haloalkane Anesthetic Toxicity	Ischemic Hepatitis	Postoperative Cholestasis
Incidence	Rare	Not uncommon	Common
Latency	2-15 days	Within 24 hours	A few days
Fever, rash, eosinophilia	Present	Absent	Absent
Serum ALT/AST (×ULN)	25-200×	Can exceed 200× (AST≫ALT)	Minimal or normal
Jaundice	Common	Rare	Common (direct hyperbilirubinemia)
Histology	Zone 3 necrosis	Coagulative necrosis, sinusoidal congestion	Bile plugs, cholestasis
Mortality	High	Varies with diagnosis	Not from liver disease
Recovery time	Up to 12 wk	10-12 days with supportive care	Variable, may be prolonged
Risk Factors			
Age	Adults, age >40 yr	Any	Any
Gender	F > M 2:1	F = M	F = M
Body weight	Obese	Any	Any
Hypotension	May or may not be present	Documented in 50%	Absent

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase; *F*, Female; *M*, male; *ULN*, upper limit of normal.
From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE E4 Hepatotoxic Herbal Remedies, Dietary Supplements, and Weight Loss Products

Remedy	Popular Uses	Source	Hepatotoxic Component	Type of Liver Injury
Ayurvedic herbal medicine	Multiple	Multiple	Uncertain (may contain heavy metal contaminants)	Hepatitis
Barakol	Anxiolytic	*Cassia siamea*	Uncertain	Reversible hepatitis or cholestasis
Black cohosh	Menopausal symptoms	*Cimicifuga racemosa*	Uncertain	Hepatitis (causality uncertain)
"Bush tea"	Fever	*Senecio, Heliotropium, Crotalaria* spp.	Pyrrolizidine alkaloids	SOS
Cascara	Laxative	*Cascara sagrada*	Anthracene glycoside	Cholestatic hepatitis
Chaparral leaf (greasewood, creosote bush)	"Liver tonic," burn salve, weight loss	*Larrea tridentate*	Nordihydroguaiaretic acid	Acute and chronic hepatitis, FHF
Chaso/onshido	Weight loss	—	*N*-nitro-fenfluramine	Acute hepatitis, FHF
Chinese medicines (traditional)				
Jin bu huan	Sleep aid, analgesic	*Lycopodium serratum*	Levo-tetrahydropalmatine	Acute or chronic hepatitis or cholestasis, steatosis
Ma huang	Weight loss	*Ephedra* spp.	Ephedrine	Severe hepatitis, FHF
Shou-wu-pian	Anti-aging, neuroprotection, laxative	*Polygonum multiflorum* Thumb (fleeceflower root)	Anthraquinone	Acute hepatitis or cholestasis
Sho-saido-to	Multiple	*Scutellaria* root	Diterpenoids	Hepatocellular necrosis, cholestasis, steatosis, granulomas
Comfrey	Herbal tea	*Symphytum* spp.	Pyrrolizidine alkaloid	Acute SOS, cirrhosis
Germander	Weight loss, fever	*Teucrium chamaedrys, T. capitatum, T. polium*	Diterpenoids, epoxides	Acute and chronic hepatitis, FHF, autoimmune injury
Greater celandine	Gallstones, IBS	*Chelidonium majus*	Isoquinoline alkaloids	Cholestatic hepatitis, fibrosis
Green tea leaf extract	Multiple	*Camellia sinensis*	Catechins	Hepatitis (causality questioned)
Herbalife	Nutritional supplement, weight loss	—	Various; ephedra	Severe hepatitis, FHF
Hydroxycut	Weight loss	*Camellia sinensis*, among other constituents	Uncertain	Acute hepatitis, FHF
Impila	Multiple	*Callilepis laureola*	Potassium atractylate	Hepatic necrosis
Kava	Anxiolytic	*Piper methysticum*	Kava lactone, pipermethystine	Acute hepatitis, cholestasis, FHF
Kombucha	Weight loss	Lichen alkaloid	Usnic acid	Acute hepatitis
Limbrel (Flavocoxid)	Osteoarthritis	Plant bioflavonoids	Baicalin, epicatechin	Acute mixed hepatocellular-cholestatic injury
LipoKinetix	Weight loss	Lichen alkaloid	Usnic acid	Acute hepatitis, jaundice, FHF

Continued

TABLE E4 Hepatotoxic Herbal Remedies, Dietary Supplements, and Weight Loss Products—cont'd

Remedy	Popular Uses	Source	Hepatotoxic Component	Type of Liver Injury
Mistletoe	Asthma, infertility	*Viscus album*	Uncertain	Hepatitis (in combination with skullcap)
Oil of cloves	Dental pain	Various foods, oils	Eugenol	Zonal necrosis
Pennyroyal (squaw mint oil)	Abortifacient	*Hedeoma pulegioides, Mentha pulegium*	Pulegone, monoterpenes	Severe hepatocellular necrosis
Prostata	Prostatism	Multiple	Uncertain	Chronic cholestasis
Sassafras	Herbal tea	*Sassafras albidum*	Safrole	HCC (in animals)
Senna	Laxative	*Cassia angustifolia*	Sennoside alkaloids; anthrone	Acute hepatitis
Skullcap	Anxiolytic	*Scutellaria*	Diterpenoids	Hepatitis
Valerian	Sedative	*Valeriana officinalis*	Uncertain	Elevated liver enzymes

FHF, Fulminant hepatic failure; *HCC,* hepatocellular carcinoma; *IBS*, irritable bowel syndrome; *SOS,* sinusoidal obstruction syndrome.
From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

BOX E1 Clinicopathologic Spectrum of Chemical Hepatotoxins

Acute Injury
Necrosis
Carbon tetrachloride and other haloalkanes
Cocaine, "ecstasy," phencyclidine
Haloaromatics, nitroaromatics, nitroaliphatics
Hydrochlorofluorocarbons
Phosphorus, iron, copper salts, inorganic arsenic

Microvesicular Steatosis
Boric acid
Chlordecone
Cocaine
Dimethylformamide
Hydrazine
Hypoglycin
Thallium
Toluene, xylene

Cholestasis
Alpha-naphthylisocyanate
Aniline—rapeseed oil
Dinitrophenol
Methylenedianiline
Paraquat

Subacute Injury
Necrosis
Trinitrotoluene

Sinusoidal Obstruction Syndrome
Pyrrolizidine alkaloids, arsenic, thorium dioxide

Toxic Cirrhosis
Hexachlorobenzene, polychlorinated biphenyls
Tetrachloroethane

Peliosis Hepatis
Dioxin

Chronic Injury
Cirrhosis
Chlor aliphatics, trinitrotoluene, arsenic, pyrrolizidine alkaloids

Hepatoportal Sclerosis
Arsenic, vinyl chloride

Neoplasia
Hepatocellular Carcinoma
Arsenic, aflatoxins, thorium dioxide

Angiosarcoma
Vinyl chloride, thorium dioxide, arsenic

Hemangioendothelioma
Arsenic

From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

TABLE E5 Drug-Induced Chronic Hepatitis: Causative Agents, Risk Factors, Clinicopathologic Features, and Outcomes

Causative Agent*	Risk Factors	Clinicopathologic Features	Outcomes
Nitrofurantoin	Age >40 yr; 90% of cases in women; continued ingestion after onset	Clinical features of chronic hepatitis, liver failure; some cases with features of cholestasis; 20% with pneumonitis; hyperglobulinemia usual, ANA, SMA	Mortality rate 10%
Methyldopa	Age >50 yr; 80% of cases in women; repeated courses, continued ingestion in sensitized patient	Jaundice, diarrhea, liver failure; hyperglobulinemia, ANA, SMA positive; protracted course	High mortality rate
Diclofenac	Age >65 yr; most cases in women	Clinical features of chronic hepatitis, liver failure; hyperglobulinemia, ANAs, SMA	Response to glucocorticoids in a few cases
Minocycline	Young women; prolonged use of drug	Often part of drug-induced systemic lupus erythematosus syndrome (arthritis, rash, rarely nephritis); hyperglobulinemia, ANAs	Cases may be severe, with a fatal outcome or need for liver transplantation; glucocorticoid treatment may be indicated
Isoniazid	Age >50 yr; continued drug ingestion after onset; duration of therapy	Severe and fatal cases with cirrhosis; no immune phenomena	High mortality rate or need for liver transplantation
Dantrolene	Age >30 yr; dose, duration of therapy	Jaundice, liver failure; no immune phenomena	High mortality rate
Etretinate	Age >50 yr; two-thirds in women	Jaundice, weight loss, liver failure; deterioration after stopping drug	Response to glucocorticoids in two reported cases
Acetaminophen	Regular intake at moderate doses (2-6 g/day); alcohol, fasting, other drugs	No features of chronic liver disease, no autoimmune phenomena; these are cases of chronic toxicity	Rapid normalization of liver biochemical test levels after the drug is stopped

*Several other agents, including sulfonamides, aspirin, halothane, cimetidine, methotrexate, trazodone, fluoxetine, fenofibrate, and germander, have been mentioned as associated with chronic hepatitis, but evidence of causation is not robust. In the past, causes included oxyphenisatin and tienilic acid, which are no longer available.
ANA, Antinuclear antibody; *SMA*, smooth muscle antibody.
From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE E6 Drug-Induced Acute Hepatitis: Immunoallergic Reaction vs. Metabolic Idiosyncrasy

Characteristic	Immunoallergic Reaction	Metabolic Idiosyncrasy
Frequency	<1 case per 10,000 persons exposed	1-50 cases per 10,000 persons exposed
Gender predilection	Women, often ≥2:1	Variable, slightly more common in women
Latent period to onset of hepatitis	Fairly constant, 2-10 wk	More variable, 2-24 wk, occasionally >1 yr
Relationship to the dose	None	Usually none, but drugs with daily doses >50 mg/day are overrepresented in cases of DILI
Interactions with other agents	None	Alcohol; occasionally other drugs (e.g., isoniazid with rifampin)
Course after stopping the drug	Prompt improvement (rare exceptions [e.g., minocycline])	Variable; occasionally slow improvement or deterioration (e.g., troglitazone)
Positive rechallenge	Always; often fever within 3 days	Usual (in two thirds of cases), abnormal liver biochemical test levels in 2-21 days
Fever	Usual; often initial symptom, part of prodrome	Infrequent, less prominent
Extrahepatic features (rash, lymphadenopathy)	Common	Rare
Eosinophilia		
Blood	33%-67% of cases	<10% of cases
Tissue	Usual, pronounced	Common but mild
Autoantibodies	Often present	Rarely present
Examples	Nitrofurantoin, phenytoin, methyldopa, sulfonamides, etretinate, minocycline	Isoniazid, pyrazinamide, ketoconazole, dantrolene, troglitazone

DILI, Drug-induced liver injury.
From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE E7 Drug-Induced Granulomatous Hepatitis: Major Causative Agents, Frequency, Risk Factors, Clinicopathologic Features, and Outcomes

Causative Agent*	Frequency	Risk Factors	Clinicopathologic Features	Outcomes
Carbamazepine	16:100,000 treatment-yr	Age >40 yr, no gender predilection	Two thirds of cases show granulomatous hepatitis; the remainder show acute hepatitis, cholangitis; no features of drug allergy	No reported fatality, rapid recovery
Phenylbutazone	1:5000 exposed	No age or gender predilection	Severe acute hepatitis, cholestasis, and bile duct injury are also reported; features of drug allergy are common; occasionally vasculitis	Mortality rate 25%, particularly in cases with hepatocellular necrosis
Allopurinol	Rare (<40 cases)	Older men, black race, renal failure, use of thiazides	Acute hepatitis, cholestatic hepatitis, bile duct injury are also frequent; rash (exfoliative dermatitis), nephritis, vasculitis are usual	Mortality rate 15%, especially with vasculitis
Hydralazine	Rare	Older patients, possibly slow acetylators	Other types of reaction are also common: Acute hepatitis, cholestatic hepatitis, cholangitis; features of drug allergy are uncommon; vasculitis is not described	Reactions severe, but no mortality reported
Quinine	Rare	No recognized risk factors	Acute hepatitis occurs in two thirds of cases; rash, interstitial pneumonitis, positive Coombs test, thrombocytopenia	Good prognosis

*Other drugs that have been reliably reported to cause granulomatous hepatitis include quinidine, phenytoin (usually with vasculitis), sulfonamides (usually with vasculitis), nitrofurantoin, aspirin, papaverine, procainamide, sulfasalazine, mesalamine, and glyburide. Single-case reports have implicated many other agents, as referred to briefly in the text.
From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

IMAGING STUDIES

- Imaging studies such as right upper quadrant ultrasound or magnetic resonance cholangiopancreatography (MRCP) to rule out biliary obstruction may be needed if there is evidence of cholestasis.
- Typically there is no need to do a liver biopsy unless the diagnosis is uncertain.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Avoiding certain drugs and herbal supplements with underlying liver disease is very important.

ACUTE GENERAL Rx

- The mainstay of treatment is to avoid the offending agent.
- N-acetylcysteine is used for acetaminophen toxicity.
- L-carnitine is used for valproic acid toxicity.
- Glucocorticoids do not have proven benefit but are sometimes given for hypersensitivity reactions of the liver in which there is progressive cholestasis or in which biopsy reveals features similar to that of autoimmune hepatitis.
- For patients who present with pruritus in the setting of cholestatic liver disease, a bile acid sequestrant can be given.

CHRONIC Rx

There is insufficient evidence to support the use of any medication, vitamin, or nutritional supplement for long-term treatment of DILI.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- There are some studies on complementary and alternative medicine to help with prevention of drug-induced liver disease with certain medications.
- Alternative medicine such as herbal supplements can have adverse effects on the liver if they have not been well-tested for use in the general population. Table E4 summarizes hepatotoxic herbal remedies, dietary supplements, and weight loss products.

DISPOSITION

- Hy rule, which is known as a combination of high aminotransferases and jaundice, has been associated with mortality rate of 10% to 50% for various drugs.
- The mortality rate in hepatocellular injury depends on the drug involved.

REFERRAL

Referral to a hepatologist may be needed if the patient develops signs of acute liver failure or chronic liver disease.

PEARLS & CONSIDERATIONS

COMMENTS

- Liver injury can occur due to many different drugs. The NIH has a searchable database of drugs that cause drug-induced liver injury.
- Taking a thorough history and ruling out other causes of liver injury is important.
- Withdrawal of the offending agent is the first and best form of management of the patient.
- Liver enzyme tests need to be carefully monitored with DILI.

PREVENTION

Educating patients about potential hepatotoxic medications and possible drug-to-drug interactions can prevent DILI.

PATIENT & FAMILY EDUCATION

http://livertox.nih.gov/

RELATED CONTENT

Acute Liver Failure (Related Key Topic)
Acetaminophen Poisoning (Related Key Topic)

AUTHORS: **Vicky H. Bhagat, MD, MPH,** and **Mariam Fayek, MD**

SUGGESTED READINGS

Leise MD, Poterucha JJ, Talwalkar JA: Drug induced liver injury, *Mayo Clin Proc* 89(1):95-106, 2014.
O'Donnell JT, Marks DH, Danese P, O'Donnell JJ: Drug-induced liver disease: primer for the primary care physician, *Disease-a-Month* 60(2):55-104, 2014.

Drug-Induced Parenchymal Lung Disease (DILD)

BASIC INFORMATION

DEFINITION

Damage to lung parenchyma caused by toxic effects of drugs. It is a diagnosis of exclusion.

SYNONYMS

Drug-induced interstitial lung disease
Drug-induced lung toxicity
DILD
Interstitial lung disease, drug-induced
Parenchymal lung disease, drug-induced

ICD-10CM CODE
J70.2 Acute drug induced interstitial lung disorders

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Global incidence is not known but likely accounts for 2.5% to 3% of interstitial lung disease (ILD) cases. More than 350 medications are known to cause pulmonary toxicity, including ILD. In the U.S., up to 10% of patients who receive chemotherapeutic agents develop lung toxicity.
PREVALENCE: Not reported
PREDOMINANT AGE AND SEX: Extreme ends of ages are prone to develop severe drug-induced side effects. Some studies have shown severe side effects in individuals >40 yr of age. Gender is not an independent risk factor.
GENETICS: Limited studies have shown that there may be a racial difference in the incidence of DILD.
RISK FACTORS: Age, sex, ethnicity, drug dose, oxygen, drug interaction, radiation, presence of underlying lung disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presentation is similar to other parenchymal lung diseases including shortness of breath, dry cough, fever, general malaise, and fatigue.
- No pathognomonic clinical, laboratory, physical, radiographic, or histologic findings. DILD is considered a diagnosis of exclusion.
- Lung examination findings are nonspecific and include dry crackles, Velcro rales, and inspiratory squeaks. In advanced stages, clubbing can be seen.

ETIOLOGY

- Mechanism varies by offending drug and is not fully understood in some cases. Both direct cytotoxic effects and immune mechanisms of action may be involved independently or in combination. Table E1 summarizes the histiologic pattern of drug-induced lung disease.
- Two possible routes of exposure have been identified: Inhalation vs. vasculature system.
- Initial exposure leading to acute toxicity may progress to chronic inflammation and fibrotic changes, which interfere with gas exchange.
- Amiodarone is a well-known cause of DILD and is usually associated with DILD at higher doses of administration (≥400 mg daily) in 5% to 15% of patients. The mechanism of lung damage is unknown. Chronic interstitial pneumonitis is the most common manifestation of amiodarone pulmonary toxicity, but there are reports of confluent lesions occurring as a result of amiodarone pneumonitis. Many of these lesions are bronchiolitis obliterans. CT scan of the lung (Fig. E1) can further define these lesions.
- Lung toxicity can occur after weeks to months of both low- and high-dose methotrexate administration. Hypersensitivity pneumonitis is its most common manifestation of lung toxicity. The mechanism by which it occurs is unknown.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute respiratory distress syndrome
- Alveolar proteinosis
- Congestive heart failure
- Diffuse lung diseases
- Hypersensitivity pneumonitis
- Lung malignancy
- Pulmonary infections
- Pulmonary vasculitis syndromes
- Radiation pneumonitis
- Respiratory failure secondary to hypoxia
- Occupational lung diseases:
  1. Asbestosis
  2. Berylliosis
  3. Chemical worker's lung
  4. Coal worker's pneumoconiosis
  5. Farmer's lung
  6. Silicosis
  7. Nitrous dioxide toxicity (i.e., silo filler's disease)
  8. Tobacco worker's lung

WORKUP

- DILD is suspected after exclusion of other etiologies in patients with recent exposure to offending drug.
- Tables E2 and E3 list medications associated with pulmonary toxicities.
- Fig. E2 illustrates various radiographic presentations of DILD.

LABORATORY TESTS

- CBC may show increased eosinophils.
- Arterial blood gas (ABG) may show hypoxemia.

IMAGING STUDIES

- Chest x-ray (Fig. E3)
- CT scan (Fig. E4)
- Other studies include pulmonary function tests (PTFs), flexible bronchoscopy with bronchoalveolar lavage (BAL), open lung biopsy

TABLE E1 Histological Pattern of Drug-Induced Lung Disease

Diffuse Alveolar Damage	Diffuse Alveolar Hemorrhage	Interstitial Pneumonia	Organizing Pneumonia	Eosinophilic Pneumonia
Amiodarone	Anticoagulants Amphotericin B	Amiodarone	Amiodarone Bleomycin Cyclophosphamide	Nitrofurantoin Nonsteroidal antiinflammatory drugs Paraaminosalicylic acid Penicillamine Sulfasalazine
Bleomycin	Cyclophosphamide	Carmustine	Gold salts	
Cyclophosphamide Methotrexate	Cytosine arabinoside (ara-c)	Chlorambucil Cyclophosphamide	Penicillamine	
		Methotrexate Nitrofurantoin	Methotrexate	
	Penicillamine		Nitrofurantoin	
Mitomycin Melphalan Gold salts			Sulfasalazine	

From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.

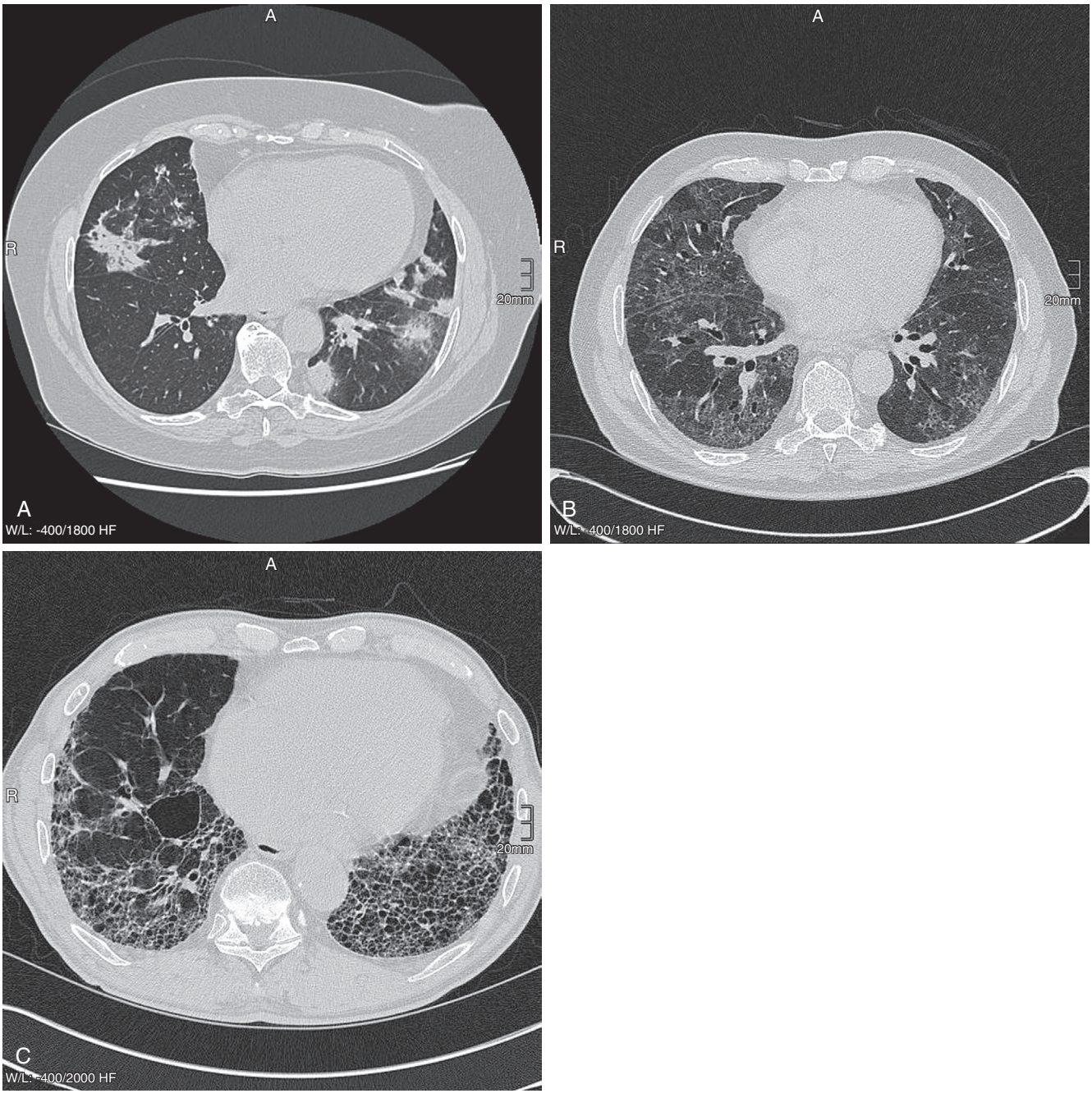


FIG. E1 Radiologic examples of drug-induced parenchymal lung disease (DILD). A, Cryptogenic organizing pneumonia. **B,** Nonspecific interstitial pneumonia. **C,** Usual interstitial pneumonia. (From Schwaiblmair MM et al: Drug induced interstitial lung disease, *Open Respir Med J* 6:63-74, 2012.)

Rx TREATMENT

There is no specific recognized treatment of DILD other than removal of offending agent.

NONPHARMACOLOGIC THERAPY

Removal of offending agent. Supportive measures including smoking cessation, control of underlying lung disease, and prompt treatment of concomitant respiratory infection.

ACUTE GENERAL Rx

Glucocorticoids have been used with rapid improvement in gas exchange and reversal in radiographic abnormalities.

CHRONIC Rx

None

COMPLEMENTARY & ALTERNATIVE MEDICINE

Lung transplantation in cases of severe irreversible fibrosis

DISPOSITION

Most patients can be treated in the community setting. Transfer to a tertiary center is indicated when diagnosis is unclear.

REFERRAL

For workup and diagnosis, early involvement of a pulmonary specialist is advised.

TABLE E2 Drugs Associated with the Development of Interstitial Lung Disease

Antimicrobial Agents
- Aspirin
- Etanercept
- Gold
- Infliximab
- Methotrexate
- Nonsteroidal antiinflammatory drugs
- Penicillamine

Antiinflammatory Agents
- Amphotericin B
- Isoniazid
- Nitrofurantoin
- Sulfasalazine

Biological Agents
- Adalimumab
- Alemtuzumab
- Bevacizumab
- Cetuximab
- Rituximab
- Trastuzumab
- Tumor necrosis factor (TNF)-α blockers

Cardiovascular Agents
- ACE inhibitors
- Amiodarone
- Anticoagulants
- β-Blockers
- Flecainide
- Hydrochlorothiazide
- Procainamide
- Statins
- Tocainide

Chemotherapeutic Agents
- Azathioprine
- BCNU
- Bleomycin
- Bortezomib
- Busulfan
- Carmustine
- Chlorambucil
- Colony-stimulating factors
- Cyclophosphamide
- Cytarabine
- Deferoxamine
- Docetaxel
- Doxorubicin
- Erlotinib
- Etoposide
- Fludarabine
- Flutamide
- Gefitinib
- Gemcitabine
- Hydroxyurea
- Imatinib
- Interferons
- Lomustine
- Melphalan
- Methotrexate
- Methyl-CCNU
- Mitomycin-C
- Nitrosoureas
- Paclitaxel
- Procarbazine
- Thalidomide
- Vinblastine
- Zinostatin

Miscellaneous
- Bromocriptine
- Carbamazepine
- Cabergoline
- Methysergide
- Penicillamine
- Phenytoin
- Sirolimus
- Talc

ACE, Angiotensin-converting enzyme; *BCNU,* bischloroethyl nitrosourea (carmustine); *CCNU,* chloroethyl cyclohexyl nitrosourea (lomustine).
From Schwaiblmair M et al: Drug induced interstitial lung disease, *Open Respir Med J* 6:63-74, 2012.

PEARLS & CONSIDERATIONS

COMMENTS

- DILD can manifest as noncardiogenic pulmonary edema (NCPE)/capillary leak syndrome, hypersensitivity reaction, cryptogenic pulmonary edema, or interstitial pneumonitis. Almost all histopathologic subtypes of ILD may be observed.
- PFT findings are usually consistent with restrictive lung disease, demonstrating reduced total lung capacity (TLC) as well as reduced diffusion capacity of the lung (DLCO).
- BAL findings are nonspecific but may be helpful in the right context. Low CD4+ to CD8+ ratio suggests DILD. Elevated eosinophils (>40%) can be seen in patients with DILD.

PREVENTION

- When prescribing drugs known to cause DILD, close observation is in order.
- Avoidance of unnecessary drug administration.

RELATED CONTENT

Acute Respiratory Distress Syndrome (ARDS) (Related Key Content)
Interstitial Lung Disease (Related Key Content)

AUTHORS: **Javeryah Safi, MD,** and **Samaan Rafeq, MD**

TABLE E3 Pharmacologic Action of Selected Chemotherapeutic Agents with Associated Pulmonary Toxicities

Antibiotic-Derived Agents
- Bleomycin
- Mitomycin C

Alkylating Agents
- Busulfan
- Cyclophosphamide
- Chlorambucil
- Melphalan

Antimetabolites
- Methotrexate
- 6-Mercaptopurine
- Azathioprine
- Cytosine arabinoside
- Gemcitabine
- Fludarabine

Nitrosoureas
- Bischloroethyl nitrosourea (BCNU)
- Chloroethyl cyclohexyl nitrosourea (CCNU)
- Methyl-CCNU

Podophyllotoxins
- Etoposide
- Paclitaxel
- Docetaxel

Novel Antitumor Agents
- All-*trans* retinoic acid (ATRA)
- Gefitinib
- Imatinib mesylate
- Irinotecan

Immune Modulatory Agents Used in Malignancy
- Interferons
- Interleukin-2
- Tumor necrosis factor α
- Nivolumab
- Pembrolizumab

Other Miscellaneous Chemotherapy Agents
- Procarbazine
- Zinostatin
- Vinblastine

From Mason RJ et al: *Murray & Nadel's textbook of respiratory medicine*, ed 5, Philadelphia, 2010, WB Saunders.

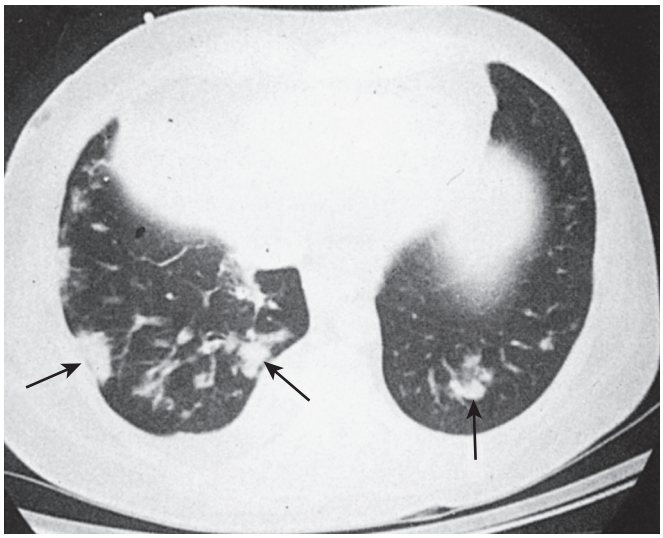


FIG. E2 A computed tomography scan of bleomycin pneumonitis showing a nodular pattern (*arrows*). The histologic features of this form of bleomycin-induced lung injury are typical of bronchiolitis obliterans with organizing pneumonitis. (From Mason RJ et al: *Murray & Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, WB Saunders.)

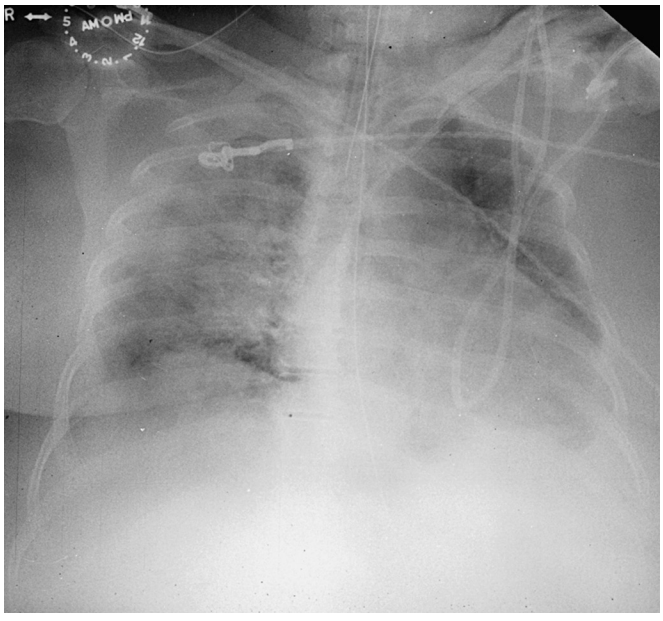


FIG. E3 A chest radiograph of a 44-yr-old woman showing acute noncardiogenic pulmonary edema that resulted from cytosine arabinoside–induced pulmonary disease. Histologic examination typically demonstrates intense intra-alveolar proteinaceous material forming hyaline membranes but little other reaction. (From Mason RJ et al: *Murray & Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, WB Saunders.)

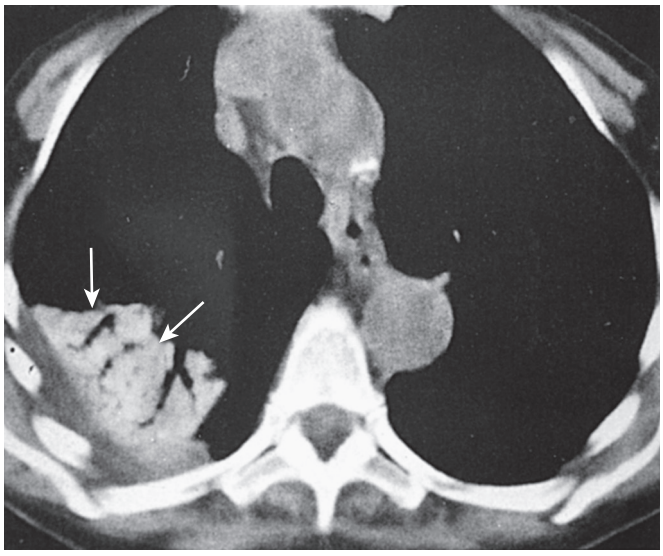


FIG. E4 A chest computed tomography (CT) scan showing confluent pulmonary masses (*arrows*) from amiodarone pneumonitis. Note that the masses are appreciably denser than the surrounding soft tissue in the chest wall in this CT scan obtained without contrast. (From Mason RJ et al: *Murray & Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, WB Saunders.)

SUGGESTED READING

Schwaiblmair: Drug induced interstitial lung disease, *Open Respir Med J* 6:63-74, 2012.

BASIC INFORMATION

DEFINITION

Drug use disorder is a recurring pattern of harmful use of a substance despite adverse consequences to work, school, relationships, the legal system, or physical health. This may occur concurrently with or independently from *substance dependence,* in which the impairment or distress is more pervasive and often (though not necessarily) includes physical dependence and withdrawal symptoms (Table 1).

SYNONYMS

Substance use disorder
Substance abuse
Addiction

ICD-10CM CODES

F19.129	Other psychoactive substance abuse, unspecified
F10-F19	Defined by specific substance
Z71.51	Drug abuse counseling and surveillance of drug abuser

The new term *substance use disorder* in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) combines the categories of substance abuse and substance dependence into a single disorder measured on a continuum from mild to severe.

DSM-5 CODE

Depends on specific drug of abuse

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Alcohol or drug dependence: 5% to 10% of population.

PREVALENCE (IN U.S.): Approximately 15% of patients in primary care practice have an at-risk pattern of drug and/or alcohol use; lifetime prevalence of any alcohol use disorder: 30%; prescription drug misuse is on the rise with 5% past-yr prevalence. Almost 9% of the U.S. population greater than age 12 has used an illicit drug in the past month (2011 National Survey on Drug Use and Health).

PREDOMINANT SEX: Males > females

PREDOMINANT AGE:

- Problematic use of substances may begin in early life (8 to 10 yr).
- Mean age of onset of problem drinking is approximately 25 yr for men and 30 yr for women.

PEAK INCIDENCE: For most substances: Age 15 to 30 yr

DURATION OF CONDITION:

- Men: Average >20 yr of heavy drinking
- Women: Average 15 yr of heavy drinking
- In general, substance use disorders are chronic and relapsing and often progressive

GENETICS: There is evidence of nonspecific genetic factors. Addiction may result in part from underlying, inherited abnormalities in brain structure that impair behavior control and encourage impulsive behavior.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Polysubstance use and comorbidity with psychiatric disorders are common.
- History often reveals recurring behavioral problems, such as relationship, work, or legal problems; violence and traumatic injuries; and anxiety, depression, insomnia, and cognitive and memory dysfunction.
- Repeated requests for early refills of controlled substances and obtaining prescriptions from multiple providers should raise concern for prescription drug use disorder (Table 2).
- Physical findings may include injection marks (Fig. E1), nasal lesions or recurrent epistaxis, poor dentition, scars or bruises from falls or trauma, and poor nutritional status; signs/symptoms of intoxication or withdrawal are highly suggestive of substance use disorder.

ETIOLOGY

Several models of addiction have been proposed:

- Disease model: Addiction is a mental illness, which occurs as a result of the impairment of healthy neurochemical or behavioral processes.
- Genetic model: Genetic predisposition is often a factor in dependency and certain addictive behaviors.
- Social model: Person–environment interactions (i.e., socialization, imitation of observable behavior, and the influence of modeling) shape addictive behavior.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Psychiatric disorders such as depression, mania, psychosis, and anxiety disorders may coexist or occur as a consequence of substance use.
- Rule out seizure disorder and underlying illness.

WORKUP

- A thorough history is crucial for diagnosis.
- The physician's history-taking style and techniques strongly affect patient's willingness to report use and participate in future treatment activities.
- A structured, nonjudgmental approach is generally preferable:
  1. Ask about quantity and frequency of alcohol or drug use. For example, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) declares that *problem drinking* is defined as more than two drinks per day for men and more than one drink per day for women or anyone older than 65 yr.
  2. Use a short screening instrument such as the CAGE questionnaire ("1. Have you ever felt you need to **C**ut down on your alcohol or drug use? 2. Have people **A**nnoyed you by criticizing your alcohol or drug use? 3. Have you ever felt **G**uilty about alcohol or drug use? 4. Have you ever felt you need to drink first thing in the morning [**E**ye opener] to stop shakiness?").
- Problematic behavior during intoxication or withdrawal is diagnostic.

TABLE 1 Key Features of Substance Abuse

1. The substance is often taken in larger amounts over a longer period than intended
2. Unsuccessful efforts to cut down
3. A great deal of time spent obtaining the substance or recovering from its effects
4. Craving
5. Social, occupational, or recreational
6. Recurrent despite hazards
7. Tolerance or withdrawal

Reprinted from Goldman L, Bennett JC (eds): *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.

TABLE 2 "Red Flags" for Abuse Behavior and Opioid Addiction

Potential Abuse/Addiction Behaviors*

1. Patient displays an overwhelming focus on opioid issues during clinic visits that occupies a significant proportion of the clinic visit and impedes progress with other pain issues or medical problems.
2. Patient has a pattern of early refills (three or more) or escalating drug use in the absence of acute change or progression of his or her medical condition.
3. Patient generates multiple telephone calls or unscheduled visits to request more opioids, early refills, or problems associated with the opioid prescription that often creates a disturbance of the clinic staff.
4. There is a pattern of prescription problems with reports of medications lost, spilled, or stolen.
5. Patient has supplemental sources of opioids from multiple providers, emergency departments, or illegal sources.

Additional "Red Flag" Abuse Behavior

1. Selling prescribed medications
2. Prescription forgery
3. Stealing another patient's medications
4. Injecting or snorting oral medication
5. Concurrent use of illicit drug(s)
6. Appearing intoxicated or oversedated
7. Insisting on obtaining a specific opioid medication

*Adapted from Chabal criteria for opioid abuse.
From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

- Because self-report of substance use and its consequences can be unreliable, obtaining corroborating information, such as from family members, past detoxifications, or drug rehabilitations, is often helpful.
- Adolescent drug use disorder detection and treatment is extremely challenging. Stages of adolescent substance use are described in Table E3. An assessment for evaluating the seriousness of adolescent drug use disorder is described in Table E4.

LABORATORY TESTS

- Blood alcohol content (BAC) measured on the breath is practical to define intoxication and provides a rough measure of impairment. In general, two standard drinks may cause BAC 0.08% or higher, which is considered legally impaired.
- Obtain toxicology screen in urine or blood samples.
- Biologic markers such as elevated mean corpuscular volume (MCV), γ-glutamyltransferase (GGT), liver function tests (AST and ALT; AST:ALT ratio of 2:1 or greater is suggestive of alcoholic liver disease), and carbohydrate deficient transferrin (CDT) may also be used to diagnose and monitor.

IMAGING STUDIES

Not helpful in routine diagnosis and management of substance abuse, but possibly useful in the management of sequelae of substance abuse (e.g., brain imaging to evaluate the alcohol abuse–associated increased risk of subdural hematomas or increased evidence of cerebral atrophy).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- First assess readiness for change; if precontemplative or contemplative, counsel about risks of use and benefits of abstinence; a motivational interviewing approach has been shown to be effective.
- Nonpharmacologic strategies have the greatest documented efficacy: Advice, feedback, goal setting, problem solving, and additional contacts for further assistance.
- Opiate contracts, prohibiting a patient from getting early refills or obtaining opiates from multiple prescribers, should be considered for all patients with chronic pain receiving opioid painkillers, especially for patients with a history of substance abuse or medication abuse.
- Relapse prevention facilitated by avoidance of trigger stimuli or by uncoupling trigger stimuli from substance ingestion.
- Self-help and 12-step support groups such as Alcoholics Anonymous and Narcotics Anonymous are helpful in achieving and maintaining sobriety.
- Residential or inpatient treatment programs should be a consideration for any individual with continued or escalating use despite outpatient treatment.

ACUTE GENERAL Rx

- Detoxification is an important first step. Seizure risk is greatest within the first 48 hours of alcohol abstinence. Detoxification goals are to facilitate withdrawal and initiate abstinence safely, prevent withdrawal seizures and reduce symptoms, and refer the patient to ongoing treatment.
- Benzodiazepines are effective in acute alcohol withdrawal for the management of symptoms as well as the prevention of seizures. One strategy is to give the patient a loading dose of a long-acting benzodiazepine (e.g., 20 mg of diazepam) and then continue the benzodiazepine as scheduled while tapering down the dose gradually. An example would be chlordiazepoxide 25 to 50 mg every 6 hours on day 1, 25 to 50 mg every 8 hours on day 2, 25 to 50 mg every 12 hours on day 3, and 25 to 50 mg at hour of sleep on day 4 and day 5 and then discontinue. An alternative "symptom-driven" strategy is to follow the patient closely with serial assessments, such as the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) scale, and to dose with 1 to 2 mg of lorazepam as needed to treat specified withdrawal symptoms.
- The prophylactic administration of thiamine and folic acid (first intravenously or intramuscularly followed by supplemental oral doses) in alcohol withdrawal is recommended before starting any carbohydrate-containing fluids or food to prevent Wernicke-Korsakoff syndrome (alcoholic encephalopathy and psychosis). Magnesium appears to be effective in the treatment of alcohol withdrawal–related cardiac arrhythmias, but not other symptoms of alcohol withdrawal.
- Beta-blockers and clonidine generally should be avoided in alcohol withdrawal; they may mask markers of the severity of the withdrawal (blood pressure and pulse rate).
- Unlike withdrawal from alcohol or benzodiazepines, opioid withdrawal is not life threatening.
- Clonidine alleviates the discomfort of opiate withdrawal. Clonidine tablets, 0.1 mg q4-6h as needed, can be used while monitoring patient's blood pressure. Clonidine transdermal patch, 0.1 mg/24 hr, can be used to treat autonomic hyperactivity symptoms; however, it has a very slow onset and may take 2 to 3 days to achieve therapeutic levels. Antidiarrheals, ibuprofen, and dicyclomine can be used as adjuncts to treat opiate withdrawal symptoms.
- Methadone taper is an effective approach for detoxification in opioid dependence.
- Buprenorphine is a partial μ-opioid receptor agonist that may be used for detoxification and maintenance in treatment of opioid dependence (see dosing in next section).

LONG-TERM Rx

- Naltrexone helps reduce craving for alcohol. Naltrexone 50 mg once daily for 12 wk can be a useful adjunct to substance abuse counseling or rehabilitation programs. Randomized treatment studies are equivocal for long-term outcomes. Naltrexone reduces relapse and the intensity or frequency of any drinking that does occur. It can be hepatotoxic and is contraindicated in opiate users. Intramuscular naltrexone (380 mg monthly) may be considered if adherence is an issue.
- Acamprosate also helps reduce craving for alcohol. Acamprosate 666 mg three times daily may be an effective adjunct to counseling. A recent meta-analysis showed overall benefit with increase in the number of abstinent days.
- Disulfiram provokes acetaldehyde accumulation after alcohol ingestion, producing a toxic state manifested by nausea, headache, flushing, and respiratory distress. Studies have shown limited efficacy mostly due to noncompliance.
- Topiramate may be an alternative treatment for alcoholism. In a 12-wk randomized trial topiramate up to 300 mg daily significantly reduced the number of heavy drinking days.
- Methadone maintenance for opiate addiction is effective and involves once-daily dosing of methadone in a controlled setting via methadone clinics.
- Buprenorphine is as effective as low-dose methadone and may be prescribed by physicians who have completed approved training. For induction, initiate 12 to 24 hr after short-acting opioid use and 24 to 48 hr after long-acting opioid use. Use buprenorphine/naloxone (Suboxone) tablets in most patients, since buprenorphine-only tablets have risk of abuse. Maximum first-day dosage is 4 to 8 mg of buprenorphine. Titrate buprenorphine dose up to 12 mg on day 2 for signs of withdrawal. Then adjust dosage in frequent outpatient visits (weekly) to minimum needed for maintenance (up to 32 mg daily).
- Naltrexone (oral or injectable) may also be used for maintenance in opioid dependence treatment, though evidence of effectiveness is limited.
- Always combine pharmacotherapy with counseling. There is good evidence that this combination improves outcome.
- Treatment of comorbid psychiatric disorders improves outcomes.
- Intervention may be used to break through **denial** of a person with a serious addictive disorder to help the person acknowledge that he or she suffers from a disorder and agree to treatment.

STIMULANT ABUSE: COCAINE AND METHAMPHETAMINE

COCAINE: Health effects of cocaine use include:

- Constricted blood vessels
- Dilated pupils
- Nausea
- Raised body temperature and blood pressure
- Fast or irregular heartbeat
- Tremors and muscle twitches
- Restlessness

Long-term effects of cocaine use include vulnerability to HIV and hepatitis C infections; malnourishment because cocaine decreases appetite; and movement disorders, including Parkinson disease, irritability and restlessness from cocaine

binges, and severe paranoia and perceptual changes such as auditory hallucinations. Cocaine abuse can cause cardiomyopathy, myocardial infarction and arrhythmias, and cerebrovascular accidents and lower the threshold for seizures.

During cocaine withdrawal patients can experience:

- Depression
- Agitation
- Intense cravings
- Need for higher doses
- Apathy
- Exhaustion
- Long periods of sleep

Behavioral therapy may be used to treat cocaine addiction. Examples include:

- Cognitive-behavioral therapy (CBT)
- Contingency management or motivational incentives—providing rewards to patients who remain substance free
- Therapeutic communities
- Community-based recovery groups, such as 12-step programs

Most pharmacotherapies have been ineffective for treating cocaine use disorder. Bupropion, psychostimulants, and topiramate may improve abstinence. While no government-approved medicines are currently available to treat cocaine addiction, researchers are testing some treatments that have been used to treat other disorders, including:

- Disulfiram (used to treat alcoholism)
- Modafinil (used to treat *narcolepsy*—a disorder characterized by uncontrollable episodes of deep sleep)
- Lorcaserin (used to treat obesity)
- Buprenorphine (used to treat opioid addiction)

Observational studies suggest that cannabidiol may reduce problems related with crack-cocaine addiction, such as withdrawal symptoms, craving, impulsivity, and paranoia.

METHAMPHETAMINE: Even small amounts of methamphetamine can result in many of the same health effects as those of other stimulants, such as cocaine or amphetamines. These include:

- Increased wakefulness and physical activity
- Decreased appetite
- Faster breathing
- Rapid and/or irregular heartbeat
- Increased blood pressure and body temperature

Injecting methamphetamine increases risk of contracting HIV and hepatitis B and C. Methamphetamine use can also alter judgment and decision making leading to risky behaviors, such as unprotected sex, which also increases risk for infection. Methamphetamine may worsen the progression of HIV/AIDS and its consequences. Long-term methamphetamine use has many other negative consequences, including:

- Extreme weight loss
- Addiction
- Severe dental problems ("meth mouth")
- Intense itching, leading to skin sores from scratching
- Anxiety
- Changes in brain structure and function
- Confusion
- Memory loss
- Sleeping problems
- Violent behavior
- Delusions
- Hallucinations

There are no approved medications for methamphetamine treatment, although medications are used for symptoms such as psychotic symptoms. Behavior therapies such as CBT and contingency management or motivational incentives as noted above for cocaine treatment are also used for methamphetamine treatment.

DISPOSITION

- Substance abuse is a chronic relapsing illness, so relapses are best approached as part of the course of the illness, as opposed to treatment failure.
- The goal of treatment is always abstinence, but success of treatment is measured by return of function, increasing duration between relapses, and prevention of sequelae of use.

REFERRAL

Physicians should refer patients who do not make progress on changing substance use patterns to addiction specialists and/or specialized substance abuse programs. Patients with comorbid psychiatric illness should be referred for mental health care.

PEARLS & CONSIDERATIONS

- The opioid crisis, which has led to an epidemic of overdose deaths in the U.S., was partially fueled by the use of oral narcotics in the treatment of chronic pain and this has prompted a revision of chronic pain management with strict guidelines for the use of opiate medications for this condition.
- Fentanyl involvement in opioid overdose deaths rose from 14.3% in 2010 to 46% in 2016 (National Vital Statistics System data). Fentanyl is now involved in more deaths than prescription opioids (40% in 2016) or heroin (36.6% in 2016). In many deaths, more than one drug is involved, and combining fentanyl with heroin may enhance its lethality.
- Acute withdrawal from alcohol can become life threatening.
- Withdrawal from opioids can resemble a severe case of the flu.
- A brief intervention (providing information and advising the patient to reduce consumption of alcohol) by the primary care doctor has been demonstrated in randomized trials to reduce drinking in at-risk patients.
- Treatment rates for alcohol use disorders remain low despite available effective treatments.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Drug Use Disorder (Patient Information)
Alcohol Use Disorder (Related Key Topic)
Opioid Use Disorder (Related Key Topic)

AUTHOR: **Tahir Tellioglu, MD**

SUGGESTED READINGS

www.drugabuse.gov/publications/finder/t/160/drugfacts.
www.drugabuse.gov/publications/infofacts/.
Commonly Abused Drug Charts, www.drugabuse.gov/drugs-abuse/commonly-abused-drugs-charts.
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FIG. E1 Tracks secondary to intravenous heroin abuse. (Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.)

TABLE E3 Stages of Adolescent Substance Abuse

Stage	Description
1	Potential for abuse Decreased impulse control Need for immediate gratification Available drugs, alcohol, inhalants Need for peer acceptance
2	Experimentation: Learning the euphoria Use of inhalants, tobacco, marijuana, and alcohol with friends Few, if any, consequences Use may increase to weekends regularly Little change in behavior
3	Regular use: Seeking the euphoria Use of other drugs, e.g., stimulants, LSD, sedatives Behavioral changes and some consequences Increased frequency of use; use alone Buying or stealing drugs
4	Regular use: Preoccupation with the "high" Daily use of drugs Loss of control Multiple consequences and risk-taking Estrangement from family and "straight" friends
5	Burnout: Use of drugs to feel normal Polysubstance use/cross-addiction Guilt, withdrawal, shame, remorse, depression Physical and mental deterioration Increased risk-taking, self-destructive, suicidal

LSD, Lysergic acid diethylamide.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

TABLE E4 Assessing the Seriousness of Adolescent Drug Use Disorder

Variable	0	+1	+2
Age (yr)	>15	<15	
Sex	Male	Female	
Family history of drug use disorder		Yes	
Setting of drug use	In group		Alone
Affect before drug use	Happy	Always poor	Sad
School performance	Good, improving		Recently poor
Use before driving	None		Yes
History of accidents	None		Yes
Time of week	Weekend	Weekdays	
Time of day		After school	Before or during school
Type of drug	Marijuana, beer, wine	Hallucinogens, amphetamines	Whiskey, opiates, cocaine, barbiturates

Total score: 0-3, less worrisome; 3-8, serious; 8-18, very serious.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

BASIC INFORMATION

DEFINITION

Dumping syndrome refers to a constellation of postprandial symptoms resulting from rapid delivery of hypertonic stomach contents into the small bowel that is most often caused by gastric surgery, such as procedures for peptic ulcer disease and gastric bypass.

SYNONYMS

Postgastrectomy syndrome
Rapid gastric emptying
Postprandial hyperinsulinemic hypoglycemia (PHH; late dumping syndrome)
Post-gastric bypass hypoglycemia (PGBH; late dumping syndrome)

ICD-10CM CODE
K91.1 Postgastric surgery syndromes

EPIDEMIOLOGY & DEMOGRAPHICS

Twenty percent to 50% of postgastric surgery patients are estimated to suffer from dumping-related symptoms. Ten percent to 20% with more pronounced symptoms, 1% to 5% with severe symptoms (these data were reported from studies in the 1980s)

- Vagotomy and pyloroplasty (8.5% to 20%)
- Vagotomy and antrectomy (4% to 27%)
- Subtotal gastrectomy (10% to 40%)
- Parietal cell vagotomy (3% to 5%)
- Gastric bypass surgeries (≤50%)
- Males and females are affected equally

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Early dumping syndrome: Symptoms start within 1 hr after eating food:
  1. No symptoms in fasting state
  2. Early satiety, nausea, vomiting, and belching
  3. Epigastric fullness, cramping, and diarrhea
  4. Dizziness, flushing, diaphoresis, and syncope
  5. Palpitations and tachycardia
- Late dumping syndrome: Symptoms occurring 1 to 3 hr after eating:
  1. Dizziness, diaphoresis
  2. Irritability, fatigue
  3. Difficulty in concentration
  4. Tremulousness, anxiety, palpitations
  5. Confusion, seizure, coma

ETIOLOGY

Dumping syndrome occurs almost exclusively in patients who have had gastric surgery. However, nonsurgical etiologies do exist.

- Systemic symptoms in early dumping syndrome are thought to be partially due to hypovolemia caused by rapid shifts of fluid from the intravascular space into the lumen of the bowel as well as increased release of GI hormones that disrupt motility and hemodynamic status.
- Increase in vasoactive substances related to rapid gastric emptying is thought to play a role in dumping syndrome.
- Late dumping symptoms are thought to be due to reactive hypoglycemia and release of counter-regulatory hormones, especially norepinephrine.

DIAGNOSIS

A detailed clinical history and evidence of prior gastric surgery are necessary for the diagnosis.

DIFFERENTIAL DIAGNOSIS

- Gastroparesis
- Pancreatic insufficiency
- Inflammatory bowel disease
- Afferent loop syndromes
- Bile acid reflux after surgery
- Bowel obstruction
- Gastroenteric fistula

WORKUP

Diagnosis is typically made on clinical grounds. In certain clinical settings in which patients exhibit symptoms with no prior history of gastric surgery, oral glucose challenge and imaging studies may be pursued and aid in establishing the diagnosis.

LABORATORY TESTS

Oral glucose challenge test:

- After overnight fasting, oral intake of 50 g of glucose is followed by serial measurements of heart rate, serum glucose, and hydrogen breath test every 15 to 30 min for 3 to 6 hr. A 30-min hematocrit can also be taken.
- An increase in the heart rate >12 beats/min and a rise in hydrogen breath excretion have a sensitivity of 94% and specificity >92%. An increase of >3% in the 30-min hematocrit is also suggestive of a positive test. A nadir blood glucose <3.3 mmol/L (<59 mg/dl) was present in 75% of late dumpers.

IMAGING STUDIES

- Upper GI series properly defines anatomy.
- Scintigraphic imaging documents rapid gastric emptying and may be useful in patients with dumping syndrome and no history of gastric surgery.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Diet modification is first-line treatment in Dumping syndrome:
  1. Divide caloric intake over six small meals.
  2. Limit fluid intake with meals (try to avoid fluids 30 min before meals and following meals).
  3. Decrease carbohydrate intake and avoid simple sugars.
  4. Increase protein and fat intake.
  5. Increase or supplement dietary fibers.
  6. Avoid milk and milk products.
  7. Avoid alcohol.
- Lying down for 30 minutes after a meal to slow gastric emptying and diminish symptoms of hypovolemia may be helpful.

ACUTE GENERAL Rx

- Acarbose 50 mg PO daily can be tried if dietary modification does not help.
- Octreotide 25 to 50 mg SC 30 min before meals is effective in relieving symptoms of dumping syndrome. (In 2009 a small study of 30 patients showed that when given monthly long-acting octreotide, patients reported relief of symptoms and preferred this to subcutaneous octreotide tid.)
- Pectin and guar have been used to increase viscosity of intraluminal contents and relieve symptoms from rapid emptying and absorption.
- Diazoxide 50 mg PO twice daily can be used to inhibit insulin secretion and can be used to treat late dumping hypoglycemia when acarbose/diet modifications are inadequate.

CHRONIC Rx

- Surgery is considered in patients with severe symptoms refractory to the above-mentioned dietary and acute general treatment.
- Surgical procedures include reconstruction of the pylorus, converting Billroth II to a Billroth I anastomosis, Roux-en-Y reconstruction, enteral tube feedings, and reversal of gastric bypass.
- In severe cases, can consider depot long-acting-release octreotide, given as 10 mg intramuscularly every 4 wk for symptom relief.

DISPOSITION

- Dumping syndrome improves with time. Approximately 1% to 2% of patients will continue to have significant symptoms several months after surgery.
- Early dumping syndrome is typically self-limiting and resolves within 7 to 12 wk.
- Dietary modification effectively treats the majority of patients.

REFERRAL

- A GI specialist consult is recommended in patients suspected of having dumping syndrome.
- If medical management is unsuccessful, a general surgical consultation is warranted.

PEARLS & CONSIDERATIONS

COMMENTS

- The majority of patients usually manifest with early dumping symptoms or a combination of early and late symptoms. Few have late dumping symptoms alone.
- Octreotide has an inhibitory effect on the release of insulin and other vasoactive substances released by the gut. It also works by decreasing gastric emptying.
- A notable nonsurgical association with dumping syndrome is diabetes mellitus, and idiopathic cases have been reported.
- Malnutrition is a primary concern for patients with dumping syndrome. Patients may modify their eating habits as a result of dumping syndrome.

AUTHORS: **Samantha Ni, MD,** and **Mark F. Brady, MD, MPH, MMSc**

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BASIC INFORMATION

DEFINITION

Dupuytren contracture is a disease of the palmar fascia characterized by nodular fibroblastic proliferation that progresses into bands of fibrous tissues. These bands eventually result in contractures of the palmar fascia. As the fibrous bands thicken, they also shorten, leading to permanent flexion deformities of the finger joints. The ring finger tends to be the most commonly affected digit. Dupuytren diathesis is a more aggressive presentation of the disease.

SYNONYMS

Palmar fibroma
Palmar fibromatosis

ICD-10CM CODE

M72.0 Palmar fascial fibromatosis [Dupuytren]

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Varies by ethnicity but estimated at 3 per 10,000 men in the U.S.

PREVALENCE: Varies depending on ethnicity and age. In the U.S., the overall prevalence is estimated to be about 7% but can be as high as 30% in males over age 65.

PREVALENT SEX: Male:female ratio of 5.9:1. Approaches a 1:1 ratio after age 80

PREVALENT AGE: Increases significantly after age 40

GENETICS: No specific gene has been identified that is responsible for Dupuytren contracture, although abnormalities in the Wnt signaling pathway have been implicated. However, many studies have shown inheritance to be polygenetic with variable penetrance.

RISK FACTORS: Age older than 40 yr, male sex, northern European descent, positive family history, diabetes mellitus, alcoholism, smoking, HIV infection, hyperlipidemia, and exposure to vibration

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usually asymptomatic, but the flexed fingers can interfere with use of the affected hand (Fig. E1).
- Isolated, painless palmar nodules that eventually harden and progress into a cord that extends into the finger. As the cord enlarges, it also contracts, creating the flexion deformity usually seen at the metacarpophalangeal (MCP) or proximal interphalangeal (PIP) joints.
- Skin pitting.
- Process usually begins on the ulnar side of the hand, often starting at the ring finger, but other fingers can also become involved over time.
- Tabletop test of Hueston: Place hand and fingers prone on a table. Test is positive if hand will not go flat (Fig. E2). Surgery is generally not indicated if test is negative.
- A staging classification for Dupuytren contracture is described in Table E1.

ETIOLOGY

The cause of Dupuytren contracture is unknown; however, there seems to be some genetic predisposition to this disorder. There is evidence that a T-cell–mediated autoimmune response may cause proliferation of myofibroblasts, the cells typically implicated in development of the nodules. Male sex, environmental exposures (e.g., smoking, vibrational devices), and certain diseases (e.g., HIV, DM) also seem to play a role in acquiring this disorder.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Trigger finger
- Soft tissue tumor
- Camptodactyly
- Volkmann contracture
- Traumatic scars
- Tendon cyst
- Fracture malunion

IMAGING STUDIES

Imaging studies are not necessary to establish the diagnosis of Dupuytren contracture. Plain film radiographs and advanced imaging (CT scan or MRI) may be helpful if considering other differential diagnoses.

TREATMENT

- Mild disease: Avoidance of repetitive hand trauma; measures include the use of padded gloves and the use of pipe insulation or cushion tape to build up handles. Physical therapy and stretching exercises can be tried; however, strong evidence does not exist to support routine use.

FIG. E1 Dupuytren contracture. A flexion deformity of the finger is present, with nodular thickening of the fascia to the ring finger.

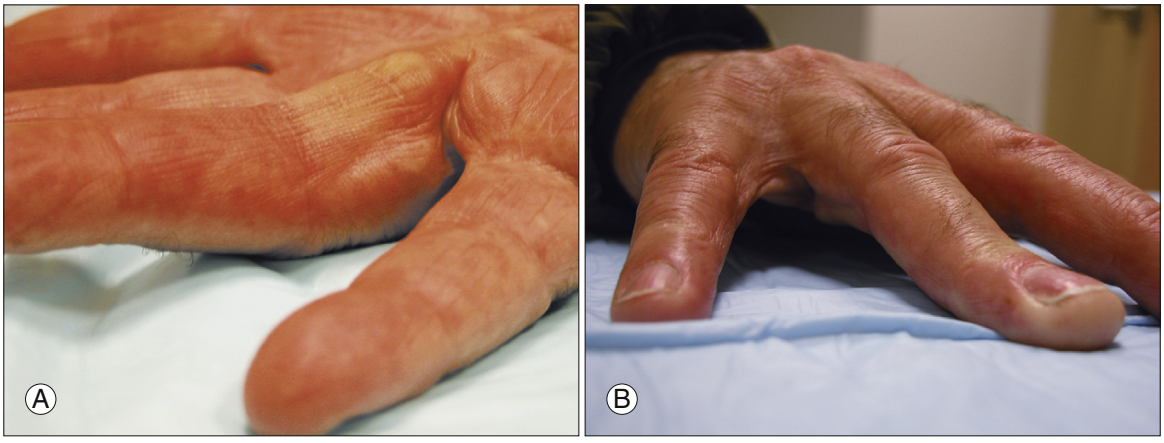

FIG. E2 Dupuytren contracture of the ring finger. A, Pitting of the skin and a longitudinal cord causing flexion of the metacarpophalangeal (MCP) joint can be seen. **B,** A contracture and flexion deformity at the MCP joint keep this patient from flattening his hand against a flat surface. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

TABLE E1 Staging Classification for Dupuytren Contracture

Stage	Description	Management
1	Early palmar disease with no contracture	Leave alone
2	One finger involved, with only metacarpophalangeal joint contracture	Surgery
3	One finger—metacarpophalangeal joint 1 proximal interphalangeal joint	Surgery difficult
4	More than one finger involved	Surgery prolonged and only partly successful
5	Finger-in-palm deformity	Consider amputation

From Parvizi J: *High-yield orthopedics,* Philadelphia, 2010, Saunders.

- Moderate disease: Intralesional corticosteroid injection can be effective in softening and flattening nodules without significant joint contracture, especially if there is tenderness associated with a palmar nodule. Percutaneous needle aponeurotomy has also shown good results, especially if the majority of the contracture is at the MCP joint rather than at the PIP joint. However, more than 85% of contractures recur after undergoing needle aponeurotomy. Enzymatic fasciotomy by *Clostridium histolyticum* collagenase injection for early and less severe cases (less than 50 degrees contracture) has shown good efficacy. Collagenase *C. histolyticum* (Xiaflex) is the first FDA-approved, nonsurgical treatment option for adult Dupuytren contracture patients with a palpable cord and has been shown to reduce the nodule size and hardness. A prospective study with collagenase injections performed in Sweden showed maintained clinical improvement in 72% of patients at 2 yr, including complete contracture correction of MCP joints in more than 80% of patients but less than 50% of PIP contractures. This overall clinical improvement was maintained in about 64% of patients at the 3-yr time point. Collagenase injections continue to be an excellent, safe option for patients with moderate disease.
- Severe disease: Surgery is usually performed when the metacarpophalangeal joint contracture exceeds 30 degrees, the proximal interphalangeal joint exceeds 20 degrees of contracture, or the tabletop test of Hueston is positive. Another indication for surgery is neurovascular damage of the finger.
- Complications: Flexor tendon rupture is a rare but serious complication, which can result from collagenase injection. Surgery that involves excision of the pathologic cords and nodules may directly injure or cause stretch neuropraxia to the neurovascular bundle.

REFERRAL

Evaluation by a hand surgeon is warranted if joint contracture begins to develop or for excision of a nodule that is painful (at any stage).

PEARLS & CONSIDERATIONS

COMMENTS

- Approximately 5% of patients develop a similar condition elsewhere, such as Peyronie disease or Ledderhose disease (involvement of the plantar fascia).
- Tender knuckle pads *(Garrod knuckle pad)* over the dorsal aspect of the PIP joints may also be present.
- Individuals with these additional findings are considered to have Dupuytren diathesis, and their disease is generally more severe and recurrent.

RELATED CONTENT

Dupuytren Contracture (Patient Information)

AUTHORS: **Kalpit N. Shah, MD,** and **Ryan M. O'Donnell, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Dysmenorrhea is painful menstrual cramps of uterine origin. Prevalence is estimated to vary between 45% and 95%. Dysmenorrhea is the most common gynecologic condition in women, regardless of age and nationality.

Types of Dysmenorrhea:

- Primary dysmenorrhea is menstrual pain without organic disease.
- Secondary dysmenorrhea is menstrual pain associated with an identifiable disease.

SYNONYMS

Menstrual cramps
Painful periods

ICD-10CM CODES

N94.3 Primary dysmenorrhea
N94.5 Secondary dysmenorrhea
N94.6 Dysmenorrhea, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Approximately 50% of menstruating women are affected by dysmenorrhea, with approximately 10% of them having severe dysmenorrhea with incapacitation for 1 to 3 days/mo.
- Dysmenorrhea is most common in the age group from 20 to 24 yr.
- Primary dysmenorrhea may appear 6 to 12 mo after ovulatory menstrual cycles begin.
- Secondary dysmenorrhea may occur at any time after menarche, but it may arise in a woman's 30s to 40s due to a causative underlying condition. The woman may also complain of dyspareunia, menorrhagia, intermenstrual bleeding, or postcoital bleeding.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Sharp, crampy, midline, lower abdominal pain without a lower quadrant or adnexal component but possible radiation to the lower back and upper thighs
- Unremarkable pelvic examination in nonmenstruating patient
- Accompanying symptoms: Nausea, vomiting, headaches, anxiety, fatigue, diarrhea, fainting, and abdominal bloating
- Cramps usually lasting <24 hr and seldom lasting >2 to 3 days
- Secondary dysmenorrhea: Dyspareunia is a common complaint, and bimanual pelvic-abdominal examination may demonstrate uterine or adnexal tenderness, fixed uterine retroflexion, uterosacral nodularity, a pelvic mass, or an enlarged, irregular uterus

ETIOLOGY

Prostaglandin $F_2\alpha$ is the agent responsible for dysmenorrhea. It stimulates uterine contractions and cervical stenosis (narrowing) and increases vasopressin release. Behavior and psychological factors have also been implicated in the etiology of primary dysmenorrhea. Primary dysmenorrhea only occurs in ovulatory cycles. Secondary dysmenorrhea is usually caused by endometriosis, adenomyosis, leiomyomas, and, less commonly, intrauterine device (IUD) use, or congenital or acquired outflow tract obstruction, including cervical stenosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS: SECONDARY DYSMENORRHEA

- Adenomyosis
- Adhesions
- Cervical structures or stenosis
- Congenital malformation of Müllerian system
- Ectopic pregnancy
- Endometriosis
- Imperforate hymen
- IUD use
- Leiomyomas
- Ovarian cysts
- Pelvic congestion syndrome
- Pelvic inflammatory disease
- Polyps
- Transverse vaginal septum
- Table 1 summarizes the differential diagnosis of dysmenorrhea in adolescents

WORKUP AND EVALUATION

- Primary dysmenorrhea: Characteristic history, physical examination and ultrasound normal with the absence of an identifiable cause of pelvic pain
- Secondary dysmenorrhea: Physical examination and ultrasound may reveal vaginal/uterine abnormalities, fibroids, adenomyosis, polyps, endometriomas

LABORATORY TESTS

- No specific tests diagnostic for dysmenorrhea
- Elevated white blood cell count in the presence of infection
- Human chorionic gonadotropin to rule out ectopic pregnancy

IMAGING STUDIES

- Ultrasound scan of the pelvis to evaluate the presence of leiomyomas, adenomyosis, ovarian cysts
- Saline ultrasonography to assess the uterine cavity to rule out endometrial polyps or submucosal or intraluminal leiomyomas

TREATMENT

NONPHARMACOLOGIC THERAPY

- Applying heat to the lower abdomen with hot compresses, heating pads, or hot water bottles seems to offer some relief.
- Offer reassurance that this is a treatable condition.

ACUTE GENERAL Rx

- Treatment of dysmenorrhea is summarized in Table 2

TABLE 1 Differential Diagnosis of Dysmenorrhea in Adolescents

	PRESENTATION	DIAGNOSIS
Primary	Crampy pelvic pain may be accompanied by aching/heaviness in lower back and upper thighs, nausea, emesis, diarrhea, headache, mastalgia, fatigue, and dizziness; symptoms begin at or shortly before onset of menstrual flow and last 1-3 days.	Normal physical exam; internal exam only for sexually active adolescents. Ultrasound can be reserved for those patients with atypical presentations (e.g., onset at menarche) or those whose pain does not respond to NSAIDs and hormonal therapy.
Endometriosis and adenomyosis*	**Increasingly severe dysmenorrhea despite adequate therapy;** pain exacerbated during menses can occur acyclically as well.	Increased risk in patients with obstructive anomalies and possibly bleeding disorders; however, most teenagers with endometriosis have normal anatomy and bleeding indices; diagnosis is made visually during surgery. *Found in up to 69% of adolescents who underwent laparoscopy for persistent pelvic pain.*
Müllerian anomalies with partial outflow obstruction	**Pain begins at or shortly after menarche** and occurs with bleeding; presence of **known renal tract anomaly** (often coexists with Müllerian anomaly).	Pelvic ultrasound will demonstrate uterine anomalies (e.g., rudimentary uterine horn); MRI may be required to identify some lesions (e.g., obstructed hemivagina). *Found in 8% of adolescents who underwent laparoscopy for persistent pelvic pain.*
Pelvic inflammatory disease	Abrupt onset of dysmenorrhea more severe than baseline in a sexually active adolescent; presentation can range from mild discomfort to acute abdomen.	Clinical diagnosis made by findings of uterine or adnexal tenderness on bimanual pelvic examination; supporting features include dysuria, dyspareunia, **vaginal discharge,** fever, and increased white blood cell count.
Pregnancy complication	Coincident pain and bleeding may be misdiagnosed as dysmenorrhea.	Urine test positive for human chorionic gonadotropin.

Bold entries indicate "red flags" for diagnosis.
*Adenomyosis is the presence of endometrial tissue within the uterine myometrium.
From Kliegman, RM: *Nelson Textbook of Pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

TABLE 2 Treatment for Dysmenorrhea

	MEDICATION	REGIMEN	COMMENTS
NSAIDs for up to 5 days	Ibuprofen, 200 mg	2 tablets PO q 4-6 hr	Over-the-counter
	Naproxen sodium, 275 mg	550 mg loading dose, then 275 mg PO q 6 hr	Patients may prefer the equivalent 550 mg PO q 12 hr dosing regimen
	Celecoxib (cyclooxygenase [COX]-2 inhibitor)*	400 mg, then 200 mg PO q 12 hr prn pain	Can be used for patients with von Willebrand disease
Hormonal contraception	Combined oral contraceptive pills or vaginal ring	Continuous hormone regimens (vs standard 21 hormone days followed by 7 placebo days) may offer better relief but may increase the risk of unexpected intermenstrual bleeding	The data favoring rings and pills over the combined hormone patch for this indication are sparse; treatment can be based on patient preference.
	Progestin-only methods	DMPA 150 mg IM or 104 mg SC q 3 mo; levonorgestrel intrauterine device for up to 5 yr; etonogestrel implant for up to 3 yr	DMPA has potential side effects of weight gain and interference with expected bone density increase during adolescence, as well as a higher discontinuation rate than LARC methods.
Gonadotropin-releasing hormone agonist	Depot leuprolide	11.25 mg IM q 3 mo	Consider for patients with presumed endometriosis not responsive to hormonal methods; add-back hormones are recommended to prevent bone loss.

*This medication may cause serious cardiovascular and gastrointestinal events. Use with caution in patients with impaired renal or liver function, heart failure, or a history of GI bleeding or ulcer. Full prescribing information can be found at: www.accessdata.fda.gov/drugsatfda_docs/label/2011/020998s033,021156s003lbl.pdf.

DMPA, Depot medroxyprogesterone acetate; *IM,* intramuscular; *LARC*, long-acting reversible contraceptive; *NSAIDs*, nonsteroidal antiinflammatory drugs; *PO,* by mouth; *SC,* subcutaneous.

From Kliegman, RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

- Nonsteroidal antiinflammatory drugs such as ibuprofen 400 to 600 mg q4 to 6h or naproxen sodium 500 mg q12h
- Oral contraceptives cyclically or continuously (taking only active pills), primarily in women with primary dysmenorrhea
- The levonorgestrel-containing IUD is increasingly being used to ameliorate symptoms of dysmenorrhea. Pain improvement has been shown in many cases to be even better than oral contraceptive pills
- Magnesium supplements (research ongoing)
- Thiamine supplements (research ongoing)
- Fish oil supplements (research ongoing)
- Secondary dysmenorrhea: Treatment directed to the specific underlying condition

CHRONIC Rx

Acupuncture and transcutaneous electrical nerve stimulation may be tried. However, there is not enough evidence to support the use of yoga, acupuncture, or massage. In cases in which medical therapy has not worked, laparoscopy or other surgical treatments should be considered depending on the secondary cause of the dysmenorrhea. A directed physical examination looking for gynecologic masses or nodularity should be performed. Nontraditional approaches such as acupuncture have been tried with relief in some patients. The levonorgestrel IUD has been shown to effectively reduce pain in women with primary dysmenorrhea.

DISPOSITION

The majority of patients are satisfactorily treated with good outcomes. Possible chronic complications with primary dysmenorrhea that has not been adequately treated can lead to anxiety and depression. With certain causes of secondary dysmenorrhea, infertility can become a problem.

REFERRAL

If a secondary cause of dysmenorrhea is revealed, refer to the appropriate specialist for further medical or surgical treatment (e.g., gynecologist, urogynecologist, reproductive endocrinologist, pain management center).

RELATED CONTENT

Dysmenorrhea (Patient Information)
Dyspareunia (Related Key Topic)
Endometriosis (Related Key Topic)
Premenstrual Dysphoric Disorder (Related Key Topic)
Premenstrual Syndrome (Related Key Topic)

AUTHOR: **Barbara McGuirk, MD**

BASIC INFORMATION

DEFINITION

Persistent and/or recurrent pain associated with sexual activity that causes marked distress or interpersonal conflict.

SYNONYM

Painful intercourse

ICD-10CM CODES

N94.1 Dyspareunia
F52.6 Dyspareunia not due to a substance or known physiological condition

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.): Affects 10% to 20% of women
PREDOMINANT SEX: Female
AT-RISK POPULATION: No consistent findings regarding:

- Age
- Parity
- Educational status
- Race
- Income
- Marital status
- However, postmenopausal status is significant: More than 50% of postmenopausal women note that sex can be painful

RISK FACTORS: Dyspareunia can lower:

- Frequency of intercourse
- Levels of desire and arousal
- Orgasmic response
- Physical and emotional satisfaction
- General happiness
- Relationship quality

HISTORICAL FACTORS—ASSESSMENT:

- Pain parameters:
  1. Character (dryness, tightness, pain, burning, soreness)
  2. Location (introital, middle, deep vaginal canal)
  3. Onset
  4. Duration
  5. Timing (e.g., during sex or anticipation before sex)
  6. Chronicity (worsening over the yr)
  7. Cyclicity (related to menstrual cycle, other recurrent life events)
  8. Recurrence (one particular partner, positional, more/less frequent)
- Gynecologic history
  1. History of sexually transmitted disease
  2. History of herpes simplex virus (HSV) or human papillomavirus (HPV)
  3. Other sexual dysfunctions
  4. Prior abdominal or gynecologic surgery
  5. Prior pelvic or abdominal radiation
  6. History of endometriosis, adenomyosis, leiomyomata, pelvic mass/ovarian cyst
  7. History of genital or uterine prolapse
  8. History of gynecologic infection
  9. History of pelvic pain
  10. History of menopausal symptoms/genitourinary syndrome of menopause—most common cause of dyspareunia in women over 50 yr old
  11. Diminished lubrication
  12. Sexual misinformation
  13. History of abuse, trauma
  14. Primary vs. secondary dyspareunia (Secondary dyspareunia—prior history of pain-free coitus)
- Obstetric history:
  1. Lacerations
  2. Episiotomy
  3. Operative vaginal birth
  4. Prolonged labor
  5. Difficult vaginal birth
- General medical causes:
  1. History of chronic diseases
  2. Gastrointestinal or genitourinary symptoms
  3. Medications
  4. History of psychological disorders
  5. History of dermatologic condition
  6. Religious beliefs
  7. Generalized anxiety
  8. Stress
  9. Relationship issues

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Visual inspection of lower genital tract:
  1. Discoloration—consider hypopigmented lichen sclerosis
  2. Ulcerations
  3. Discharge
  4. Prolapse
  5. Dysplastic changes
  6. Infestations
  7. Dry/pale/thin vaginal walls
- Physical examination:
  1. Sensitivity to light touch—single or multiple points
  2. Tenderness to palpation—single or multiple points
  3. Genital prolapse:
     a. Uterus
     b. Bladder
     c. Cervix
     d. Vagina
     e. Adnexa
     f. Rectum
     g. Bowel
  4. Longitudinal or transverse vaginal septum
  5. Levator muscle tone
  6. Evidence of previous surgery
  7. Vaginal length, depth, caliber constrictions: Assess for shortened, narrowed and/or absent vagina
  8. Less rugated, friable vaginal walls
  9. Vaginismus—vaginal muscle tightening

ETIOLOGY

- Pathology or alteration of genital-associated tissue
- Psychosocial factors
- Marital or relationship discord
- History of sexual or generalized physical/emotional abuse
- Menopause/aging
- Medication side effect
- Infection

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Congenital deformities (septa/agenesis)
- Imperforate hymen
- Menopausal changes
- Atrophic/aging tissue
- Impaired lubrication
- Aromatase inhibitor usage/low estrogen levels
- Psychogenic
- Vaginismus
- Inadequate foreplay
- Virginity/hymenal factors
- Endometriosis/adenomyosis
- Levator ani myalgia
- Chronic pelvic pain
- Previous surgery (anterior/posterior colporrhaphy, perineorrhaphy, pelvic floor reconstruction, hysterectomy, episiotomy repair, labiaplasty, vaginoplasty):
  1. Alteration in vaginal length, depth, caliber, architecture, shape, elasticity
  2. Adhesions
- Infectious:
  1. HPV
  2. HSV
  3. Candidiasis
  4. *Tinea cruris*
  5. Acute or chronic salpingitis or endometritis
  6. Sexually transmitted infections
- Pelvic carcinoma
- Previous radiation
- Adnexal attachment or tubal prolapse
- Pelvic tumor/leiomyoma/ovarian cyst or torsion
- Uterine prolapse, malposition, enlargement, or retroversion
- Genital prolapse
- Cystourethrocele, rectocele, enterocele
- Urethral or bladder pathology (e.g., interstitial cystitis)
- Pelvic congestion (controversial)
- Vulvar vestibulitis
- Postcoital cystitis
- Broad ligament pathology
- Neuroma at the site of previous episiotomy
- Previous sexual/physical/emotional abuse
- Marital/relationship discord
- Vulvodynia
- Lichen sclerosus
- Contact or allergic dermatitis
- Vitamin A, B, or C deficiency
- Equestrian dyspareunia
- Pudendal neuralgia
- Myofascial pain syndrome
- Rectal/colon pathology
- Structural abnormalities or alterations:
  1. Muscle
  2. Bone
  3. Ligament
  4. Nerve
  5. Adjacent tissues/structures

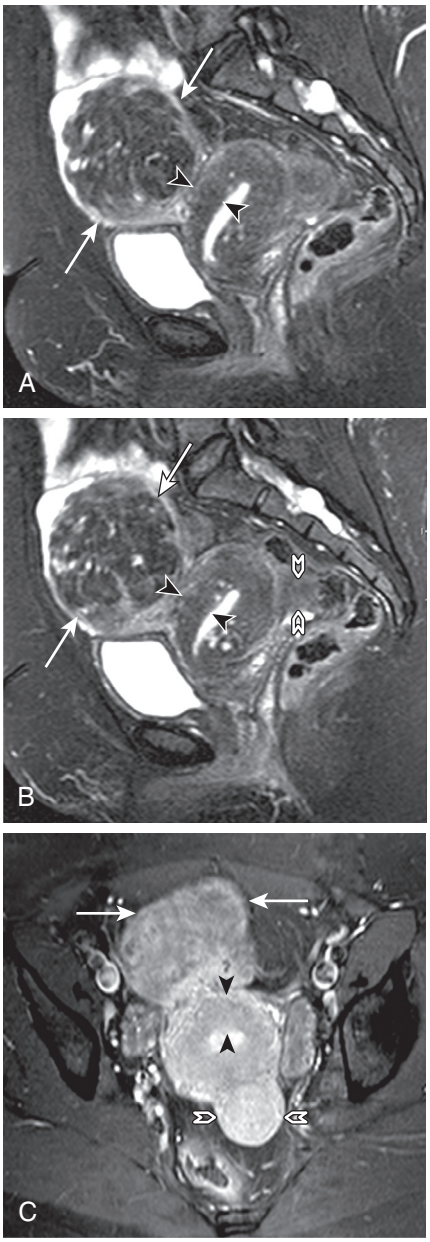

FIG. E1 Adenomyosis and leiomyomata in a 41-yr-old woman with pelvic pain, irregular menses, menorrhagia, and dyspareunia. A and **B,** Sagittal T2-weighted fat-suppressed images show a large anterior subserosal fibroid with mixed but predominantly low signal *(arrows)* and a smaller posterior subserosal fibroid with low to intermediate signal *(chevrons).* There is also widening of the junctional zone *(black arrowheads)* with areas of increased T2 signal, indicative of adenomyosis. **C,** Axial three-dimensional gradient echo postcontrast image with fat suppression shows enhancement of the leiomyomata *(white arrowheads* and *chevrons)* and the thickened junctional zone *(black arrowheads).* (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

WORKUP

- History and physical examination are key and most likely all that is needed
- If needed (unlikely, however):
  1. Colposcopy
  2. Cystoscopy
  3. Ultrasonography
  4. MRI
  5. Consider laparoscopy for unexplained deep dyspareunia

LABORATORY TESTS

- Wet mount:
  1. Trichomoniasis
  2. Candidiasis
  3. Bacterial vaginosis
- Cultures:
  1. Cervical
     a. Gonorrhea
     b. *Chlamydia*
  2. Vaginal
  3. Lesions
  4. Urine
- Vulva, vaginal, or cervical biopsy
- Pap smear
- HSV antibodies
- Gonadotropin levels

IMAGING STUDIES

Pelvic or abdominal ultrasonography. Transvaginal ultrasonography provides for greater resolution of the uterus and adnexa (tubes/ovaries) due to proximity to pelvic organs. Consider an MRI when the diagnosis is unclear with other diagnostic modalities (Fig. E1).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient education
- Discontinue exacerbating activity, irritants, medications
- Lubrication with coitus
- Coital position changes
- Avoid deep thrusting
- Warm or cool soaks
- Reassurance to patient of nonmalignant/other worrisome conditions
- Emphasize that this is a normal aging and postmenopausal finding
- Psychosocial interventions:
  1. Systemic desensitization techniques
  2. Behavior modification
  3. General counseling
  4. Marital/relationship counseling
- Vaginal dilators
- Vaginal muscle exercises and relaxation techniques
- Excision of pathologic tissue
- Surgical correction of altered, reduced, or deformed tissues

ACUTE GENERAL Rx

- Topical lidocaine, nonhormonal moisturizers and lubricants
- Corticosteroids—e.g., for lichen sclerosus
- Antiinfective agents if vaginitis/cervicitis/adnexal abscess is found
- Trigger point injections
- Massage or physical therapy
- Acupuncture
- Transcutaneous electrical nerve stimulation
- Stress reduction techniques
- Safe sexual practices
- Menopausal hormone (estrogen) therapy: To address vulvovaginal atrophy (VVA)/genitourinary syndrome of menopause (GSM)
  1. Local/intravaginal (pill/ring/cream/gel)
  2. Systemic (pill/patch/gel/spray/cream/injection)
- Ospemifene (Osphena), an oral estrogen agonist/antagonist for treatment of moderate to severe dyspareunia in postmenopausal women with suspected vaginal atrophy. Dosage is a 60 mg tablet daily
- Prasterone (Intrarosa), which does not contain estrogen but converts the precursor, DHEA, intravaginally to estrogen and androgen, is used for the treatment of moderate to severe dyspareunia in postmenopausal women with suspected vaginal, vulvar, introital, and/or urogenital atrophy. Dosage is a daily intravaginal pellet insertion
- Imvexxy (Estradiol) is a bio-identical estradiol vaginal insert used to treat moderate to severe dyspareunia in postmenopausal women. The dosage is a daily placement of the vaginal insert for the first two wk, followed by twice weekly application
- Antiviral agents
- Intralesional interferon
- Mild analgesics
- Antidepressants

CHRONIC Rx

All the previous plus:

- Set supportive visits as needed
- Oral contraceptives
- Regular sexual activity
- Balanced diet
- Vitamin supplementation
- Proper hygiene

DISPOSITION

Most patients will have a reduction and/or resolution of their symptoms by using the appropriate therapeutic approaches.

REFERRAL

As with other pain conditions, a multidisciplinary approach using the expertise of psychologists, dermatologists, gynecologic surgeons, infectious disease specialists, urologists, and others may be helpful.

! PEARLS & CONSIDERATIONS

- Dyspareunia is a symptom complex resulting from a multitude of etiologies, some of which act simultaneously.
- Uncovering the etiology of dyspareunia is predominantly based on a comprehensive history and physical examination.
- Ask about dyspareunia as part of your routine patient assessment. Don't wait for the patient to initiate the conversation.
- Sorting the differential diagnosis into superficial, intermediate, and deep dyspareunia categories is immensely helpful.

- As with the physical evaluation of any painful condition, attempt—by precise touching (moistened cotton swab), palpation, or applied pressure—to reproduce the patient's chief complaint.
- Performing a one-finger pelvic examination without concurrent abdominal palpation allows a more precise assessment as to the source of genital pain.
- Individualize therapy.
- Initiate and maintain an honest dialogue and compassionate demeanor with the patient and her partner.
- Be open minded, approachable, nonjudgmental, and diligent in your search for a solution to help these often silently suffering patients.

PATIENT & FAMILY EDUCATION

www.menopause.org

SUGGESTED READING

Seehusen DA et al: Dyspareunia in women, *Am Fam Physician* 90(7):465-470, 2014.

RELATED CONTENT

Painful Intercourse (Patient Information)
Dysmenorrhea (Related Key Topic)
Endometriosis (Related Key Topic)
Menopause (Related Key Topic)
Sexual Dysfunction in Women (Related Key Topic)
Vaginitis, Estrogen-Deficient (Related Key Topic)

AUTHORS: **David I. Kurss, MD, FACOG, NCMP,** and **Anthony Sciscione, DO**

Dyspepsia, Nonulcerative

BASIC INFORMATION

DEFINITION

Dyspepsia is a constellation of symptoms referable to the gastroduodenal region of the upper GI tract. *Nonulcerative dyspepsia* is a term used to describe signs and symptoms of persistent or recurrent dyspepsia that have no identifiable organic cause.

SYNONYMS

Nonulcer dyspepsia
Functional dyspepsia
Idiopathic dyspepsia

ICD-10CM CODE
K30 Functional dyspepsia

EPIDEMIOLOGY & DEMOGRAPHICS

Up to 25% of the general population will experience dyspepsia each yr. Of these, 75% will have no evident causative agent.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Typical clinical presentation is dyspepsia without findings on physical examination to explain the symptoms.

ETIOLOGY

The etiology and pathophysiology are still unclear. Box 1 summarizes causes of dyspepsia. Research is focused on abnormalities of gastric motor function and visceral hypersensitivity, as well as:

- *Helicobacter pylori* infection
- Psychosocial factors—associated with anxiety and depression

RISK FACTORS

Risk factors include the following:

- Genetic predisposition: Homozygous *GNB3* gene
- Dietary habits such as caffeine, alcohol, or smoking
- Medications such as NSAIDs, calcium channel blockers, methylxanthines, alendronate, orlistat, acarbose, and potassium supplements
- Psychological disorders such as anxiety, depression, somatization, or personal history of childhood sexual or physical abuse

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Nonulcerative dyspepsia is diagnosed when all other organic causes have been excluded, including:

- Peptic ulcer disease (PUD)
- Gastroesophageal reflux
- Gastric/esophageal/other abdominal cancers
- Biliary tract disease
- Gastroparesis, including diabetic gastroparesis
- Pancreatitis
- Medications (i.e., NSAIDs, erythromycin)
- Metabolic disturbances (i.e., hypercalcemia, heavy metals, or hyperkalemia)
- Ischemic bowel disease
- Systemic disorders (i.e., eosinophilic gastritis, Crohn disease, sarcoidosis, celiac disease, thyroid disorders)

DIAGNOSIS

The Rome IV criteria lists the following factors, which must be present at least 3 mo and first noticed within 6 mo of diagnosis:

- At least one of the following:
  1. Postprandial fullness, *or*
  2. Early satiety, *or*
  3. Epigastric pain, *or*
  4. Epigastric burning
  5. *And* no evidence of structural disease likely to explain the symptoms

WORKUP

The American Gastroenterological Association, as well as the Maastricht III and the IV European consensus, suggest the following:

- The pattern of symptoms overlaps considerably for all types of dyspepsia; therefore, the history and physical should focus on finding specific symptoms that help exclude other causes of dyspepsia.
- Endoscopy should be performed only in patients >55 yr old and in younger patients with alarming symptoms (e.g., weight loss, progressive dysphagia, recurrent vomiting, evidence of gastrointestinal bleeding, or family history of cancer) presenting with new-onset dyspepsia. Findings consistent with diagnosis of nonulcerative dyspepsia are not conclusive, no presence of *H. pylori*, no signs of gastroesophageal reflux disease, no mucosal inflammation. NOTE: Patients <55 yr old and without any alarming symptoms can be treated without endoscopy.

LABORATORY TESTS

H. pylori: Laboratory methods include serologic tests,[1] monoclonal stool antigen, or urea breath test.

[1]Serologic testing for *H. pylori* has a low predictive value because colonization is lifelong; it can therefore determine prevalence better than incidence.

BOX 1 Causes of Dyspepsia

Luminal GI Tract
Functional dyspepsia
Chronic gastric volvulus
Chronic gastric or intestinal (mesenteric) ischemia
Food intolerance
Gastric or esophageal neoplasm
Gastric infections (cytomegalovirus, fungus, tuberculosis, syphilis)
Gastroparesis (diabetes mellitus, postvagotomy, scleroderma, chronic intestinal pseudo-obstruction, postviral, idiopathic)
GERD
Infiltrative gastric disorders (Ménétrier disease, Crohn disease, eosinophilic gastroenteritis, sarcoidosis, amyloidosis)
IBS
Parasites (*Giardia lamblia, Strongyloides stercoralis*)
PUD

Systemic Conditions
Adrenal insufficiency
Diabetes mellitus
Heart failure, myocardial ischemia
Intraabdominal malignancy
Pregnancy
Renal insufficiency
Thyroid disease, hyperparathyroidism

Medications
Acarbose
Aspirin and other NSAIDs (including COX-2 selective agents)
Colchicine
Digitalis preparations
Estrogens
Ethanol
Gemfibrozil
Glucocorticoids
Iron
Levodopa
Narcotics
Niacin
Nitrates
Orlistat
Potassium chloride
Quinidine
Sildenafil
Theophylline

Pancreaticobiliary Disorders
Biliary pain: cholelithiasis, choledocholithiasis, sphincter of Oddi dysfunction
Chronic pancreatitis
Pancreatic neoplasms

COX-2, Cyclooxygenase-2; *GERD,* gastroesophageal reflux disease; *IBS,* irritable bowel syndrome; *NSAID,* nonsteroidal antiinflammatory drug; *PUD,* peptic ulcer disease.
From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

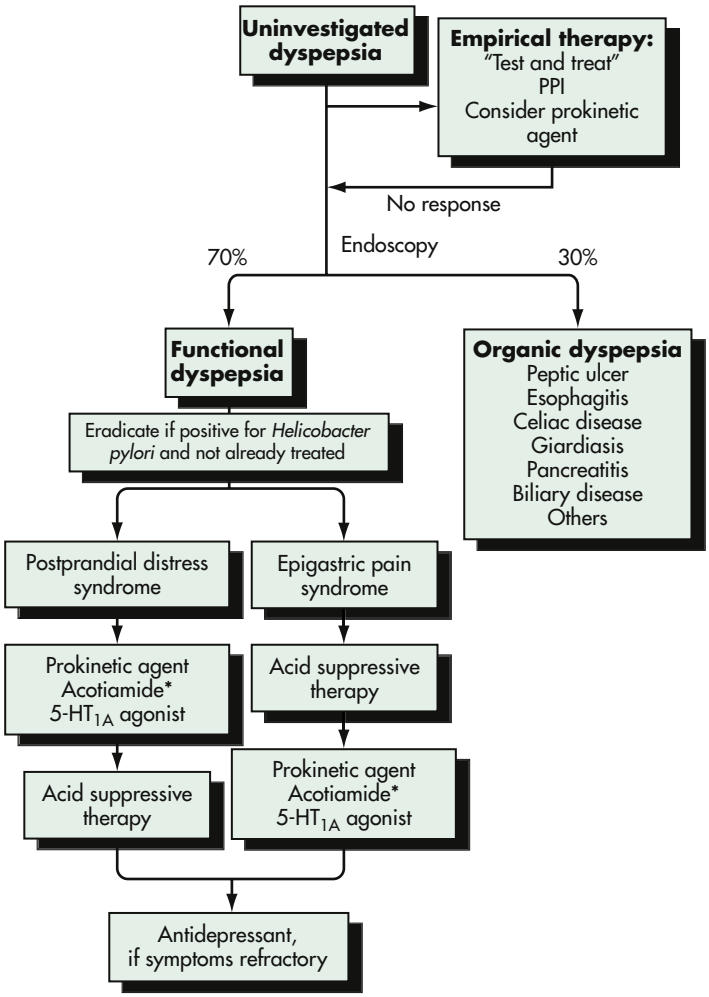

FIG. 1 An algorithm for management of patients with dyspepsia. Patients younger than age 45 to 55 yr who do not have alarm features may be treated empirically, whereas all others should be evaluated initially by endoscopy. *5-HT,* 5-hydroxytryptamine; *PPI,* proton pump inhibitor. *Not available in the U.S. (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

Rx TREATMENT

ACUTE GENERAL Rx

PHARMACOLOGIC THERAPY: Primary treatment is usually initiated with proton pump inhibitors (PPIs), which can be started without performing endoscopy, especially if the patient comes from a population with low prevalence of *H. pylori* infection. If symptoms persist, a trial of antidepressants can be started. An algorithm for the management of patients with dyspepsia is described in Fig. 1.

Treatment of accompanying symptoms includes:

Predominant Symptom	Possible Etiology	Medication Recommended
Nausea	Motility dysfunction	Prokinetic agent
Bloating	Motility dysfunction	Simethicone and/or prokinetic agent
Pain	Mucosal disease or *H. pylori* infection	Antibiotic trial
Somatic complaints	Psychosocial	Psychotropic medication trial

Medication categories:

- Antacids (i.e., aluminum hydroxide, calcium carbonate)
- Gas-reducing agents, such as those containing simethicone
- H_2-receptor antagonists (i.e., cimetidine)
- PPIs (i.e., omeprazole)
- Prokinetic agents (i.e., metoclopramide, domperidone)
- Antidepressants (i.e., selective serotonin receptor inhibitors, tricyclics)
- *H. pylori* therapy/antibiotic therapy (various antibiotic regimens, usually 1 PPI) if *H. pylori* present

CHRONIC Rx

Controversy currently exists around the long-term use of PPIs. Due to the high association with psychological factors, patients with functional dyspepsia should undergo psychological intervention, even if there is good response to pharmacotherapeutic approaches.

COMPLEMENTARY & ALTERNATIVE THERAPIES

Peppermint and caraway oil may be helpful, as well as acupuncture; however, no definitive trials have been performed.

REFERRAL

- Referral to gastroenterology if patient has alarming symptoms (such as GI bleeding, dysphagia, odynophagia, unexplained anemia, change in appetite, and weight loss) or when endoscopy is indicated—although controversy exists about the workup of younger patients
- Referral to cardiology if cardiac etiology suspected

PEARLS & CONSIDERATIONS

PREVENTION

Avoid excessive amounts of caffeine, alcohol, smoking, or long-term use of steroids and NSAIDs.

PATIENT & FAMILY EDUCATION

http://www.mayoclinic.com/health/stomach-pain/DS00524

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Approach to the patient with dyspepsia (Algorithm, Section III)

AUTHORS: **Alvaro M. Rivera, MD,** and **Nadine Mbuyi, MD**

SUGGESTED READINGS

Lloyd RA, McClellan DA: Update on the evaluation and management of functional dyspepsia, *Am Fam Physician* 83(5):547-552, 2011.

Malfertheiner P et al: for the European Helicobacter Study Group: Management of Helicobacter pylori infection—the Maastricht IV/Florence Consensus Report, *Gut* 61(5):646-664, 2012.

Rome III: Criteria. Available at http://www.romecriteria.org/assets/pdf/19_RomeIII_apA_885-898.pdf. and http://www.romecriteria.org/criteria/.

Talley NJ, Ford AC: Functional dyspepsia, *N Engl J Med* 373:1853-1863, 2015.

BASIC INFORMATION

DEFINITION

The term "dysphagia" is derived from the Greek words *dys* (with difficulty) and *phagia* (to eat). It is characterized by abnormal transfer of food from mouth to the stomach, which may involve the oral, pharyngeal, or esophageal stages of swallowing.

ICD-10CM CODES

D50.1	Sideropenic dysphagia
I69.091	Dysphagia following nontraumatic subarachnoid hemorrhage
I69.191	Dysphagia following nontraumatic intracerebral hemorrhage
I69.291	Dysphagia following other nontraumatic intracranial hemorrhage
I69.391	Dysphagia following cerebral infarction
I69.891	Dysphagia following other cerebrovascular disease
I69.991	Dysphagia following unspecified cerebrovascular disease
R13.10	Dysphagia, unspecified
R13.11	Dysphagia, oral phase
R13.12	Dysphagia, oropharyngeal phase
R13.13	Dysphagia, pharyngeal phase
R13.14	Dysphagia, pharyngoesophageal phase
R13.19	Other dysphagia

EPIDEMIOLOGY & DEMOGRAPHICS

- This is seen in 10% of individuals above the age of 50 yr. Its prevalence increases with advancing age.
- Nearly 12% of hospitalized patients have symptoms of dysphagia.
- Up to 30% to 60% of nursing home patients have some form of dysphagia.
- Special populations, including patients with head injury, stroke, or Parkinson disease, have 30% to 50% prevalence of oropharyngeal dysphagia.

ETIOLOGY

- Oropharyngeal:
  1. Neuromuscular causes:
     a. Stroke
     b. Parkinson disease
     c. Multiple sclerosis
     d. Myasthenia gravis
     e. Amyotrophic lateral sclerosis
     f. CNS tumors
     g. Muscular dystrophy
     h. Thyroid dysfunction
     i. Polymyositis and dermatomyositis
     j. Sarcoidosis
     k. Cerebral palsy
     l. Head trauma
     m. Metabolic encephalopathy
     n. Dementia
     o. Bell palsy
  2. Structural causes:
     a. Oropharyngeal tumors
     b. Zenker diverticulum
     c. Infection of pharynx or neck (mucositis from *Candida,* herpes, and CMV)
     d. Thyromegaly
     e. Prior surgery or radiotherapy
     f. Osteophytes and other spinal disorders
     g. Proximal esophageal webs
     h. Congenital anomalies (e.g., cleft palate)
     i. Poor dentition
- Esophageal:
  1. Neuromuscular disorders:
     a. Achalasia
     b. Diffuse esophageal spasm
     c. Nutcracker esophagus
     d. Hypertensive lower esophageal sphincter
     e. Ineffective esophageal motility
     f. Scleroderma
     g. Reflex-associated dysmotility
  2. Structural disorder:
     a. Peptic stricture
     b. Esophageal rings and webs
     c. Diverticuli
     d. Carcinoma and benign tumors
     e. Foreign bodies
     f. Vascular compression
     g. Mediastinal masses
     h. Spinal osteophytes
     i. Mucosal injury (from pills, infection, gastroesophageal reflux disease [GERD], etc.)

PATHOGENESIS

The inability to swallow is caused either by a problem in strength or coordination of the muscles required to move material from the mouth to stomach or by a fixed obstruction somewhere between the mouth and the stomach.

CLINICAL FEATURES

Oropharyngeal dysphagia (transfer dysphagia):

- The patient is unable to transfer the food bolus from the mouth to the upper esophagus. Problem arises within 2 seconds of initiating the voluntary phase of swallowing.
- Typical symptoms include drooling, spillage of food, postnasal regurgitation, difficulty in initiation of swallowing, sialorrhea, sensation of food stuck in the neck, coughing or choking during swallowing, the need to swallow repeatedly to clear food or fluid from the pharynx, dysphonia, nasal speech, hoarseness of voice, and dysarthria.
- A thorough physical examination including that of the nervous system, oral cavity, and the head/neck is very important in patients with oropharyngeal dysphagia.

Esophageal dysphagia:

- Problem usually arises several seconds after swallowing.
- Patients often complain of food being stuck in lower substernal area.
- Dysphagia to solids suggests mechanical obstruction whereas dysphagia with liquids or combination of solids and liquids favors a motility disorder.
- Neuromuscular causes result in dysphagia to both solids and liquids. Particularly, patients with achalasia tend to drink a lot of fluids while eating or apply maneuvers such as straightening the back, raising their arms over their heads, or standing to increase intraesophageal pressure to facilitate the emptying of food into the stomach.
- Oftentimes, ingestion of very cold or very hot foods precipitates the dysphagia associated with neuromuscular disorder.
- Delayed regurgitation of food, heartburn, and chest pain are usually present.
- Weight loss is usually associated with malignancy or achalasia.
- Symptoms are intermittent in patients with esophageal dysphagia from benign causes of structural obstruction or diffuse esophageal spasm. However, it is progressive in patients with peptic stricture, esophageal carcinoma, scleroderma, and achalasia.
- In patients with structural obstruction, when the luminal diameter is more than 18 to 20 mm, they are rarely symptomatic, whereas those with a diameter of less than 13 mm are nearly always symptomatic.
- These patients with esophageal dysphagia usually do not have any characteristic physical findings.

DIAGNOSIS

Laboratory Evaluation:

- CBC
- Thyroid studies
- Nutritional assessment by checking serum protein and albumin levels
- Other studies based on specific clinical conditions

Special studies:

- Oropharyngeal dysphagia
  1. Videofluoroscopy is the first test often ordered in evaluation of patients with oropharyngeal dysphagia.
  2. Double contrast modified barium swallow study (Fig. E1).
  3. Fiberoptic flexible nasopharyngeal laryngoscopy is mandatory in all cases when a structural lesion, particularly malignancy, is suspected.
  4. Pharyngeal and upper esophageal manometry (Fig. E2) is occasionally of value to predict which patients will have a favorable outcome from cricopharyngeal myotomy or dilation.
  5. Radiography of head and neck when indicated.
- Esophageal dysphagia
  1. Barium esophagography should precede upper endoscopies to identify patients at risk from potential perforation with an endoscopy and to help plan fluoroscopically guided dilation. It is often the first step in evaluating patients with dysphagia, especially if an obstructive lesion is suspected
  2. EGD
  3. Esophageal manometry is indicated if no abnormality is identified by barium study or EGD
  4. Esophageal pH monitoring in patients with suspected reflux disease
  5. Endoscopic ultrasonography
  6. Radiograph, CT, and MRI of chest

DIFFERENTIAL DIAGNOSIS (FIG. 3)

- Globus pharyngeus
- Odynophagia
- Phagophobia
- GERD

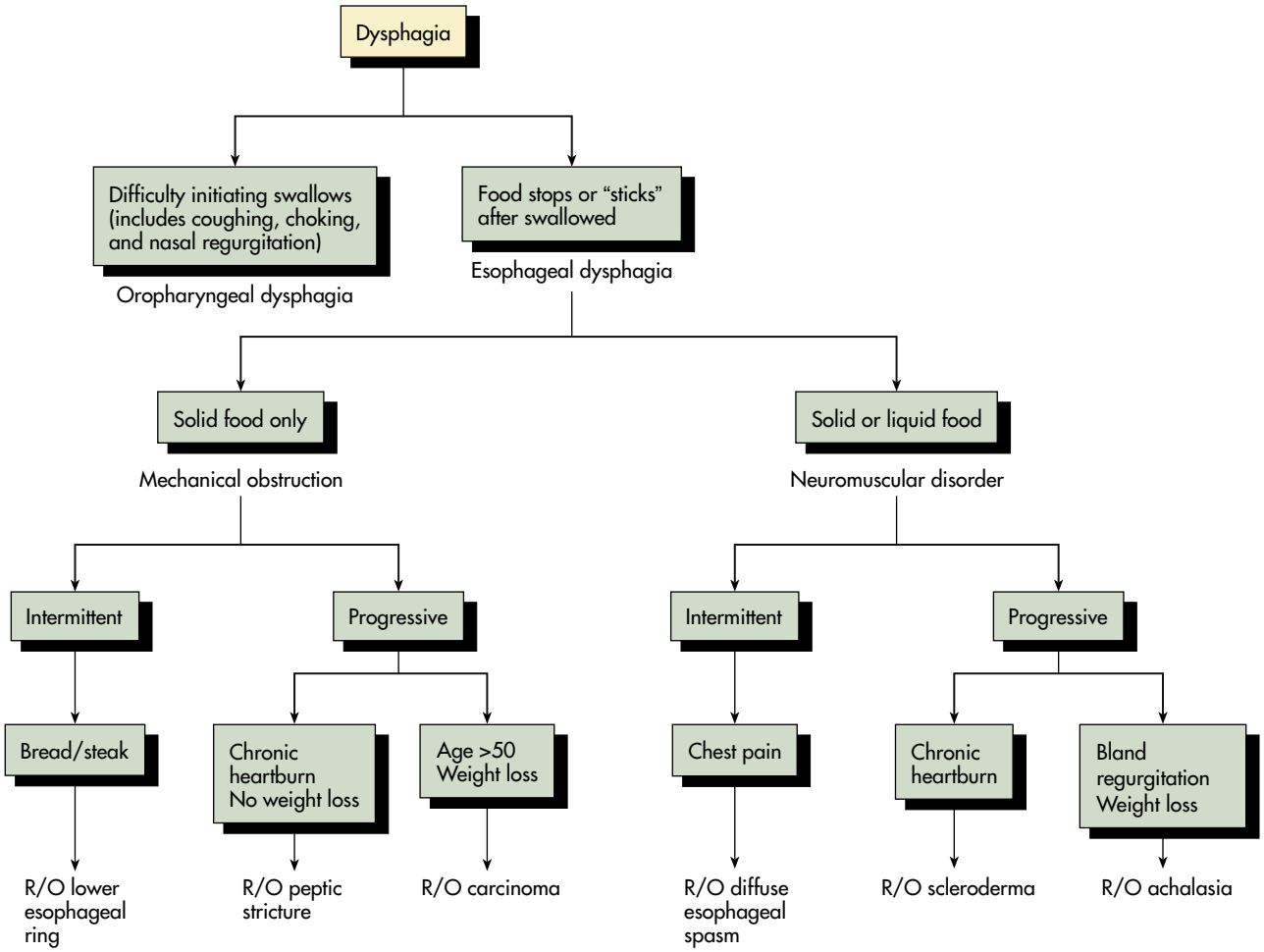

FIG. 3 Differential diagnosis of dysphagia. *R/O,* Rule out. (Modified from Andreoli TE [ed]: *Cecil essentials of medicine,* ed 7, Philadelphia, 2008, Saunders.)

Rx TREATMENT

- Treatment should be approached with the help of specialists of multiple disciplines (ENT, head and neck surgeon, radiologist, speech pathologist, physical therapist, dietitian, gastroenterologist, physical medicine and rehabilitation specialist, dentist, neurologist, etc.).
- Goal of therapy is airway protection and maintenance of nutrition.
- Alteration of food consistency, volume, and delivery rate plays a major role.
- The goal of direct therapy is to change swallowing physiology with medical treatment of primary disease, maxillofacial prosthesis, and cricopharyngeal myotomy.
- Indirect therapies include exercise programs for tongue coordination and chewing under the guidance of a speech therapist.
- Maintenance of oral feeding often requires compensatory techniques such as chin-tuck position, rotation of head to the affected side, tilting of head to the strong side, and lying on one's back or on one's side during swallowing.
- Some of the voluntary maneuvers applied include supraglottic swallow, effortful swallow, Mendelson maneuver, Shaker exercise, and the Heimlich maneuver.
- Placement of nasogastric tube, jejunostomy tube, or percutaneous endoscopic gastrotomy (PEG) tube is considered for enteral feeding when other measures fail and the patient remains at significant risk for aspiration or nutrition becomes compromised.
- Treatment of associated GERD should not be forgotten.
- Surgery for chronic aspiration may involve tracheostomy, medialization, laryngeal suspension, laryngeal closure, and/or laryngotracheal separation-diversion.
- Other measures include esophageal dilation removal of foreign body, esophageal resection, chemotherapy, radiotherapy, endoscopic ablation of tumor, photodynamic therapy, esophageal prosthesis/stents, diverticulectomy, intrasphincteric injection of botulinum toxin, surgical myotomy, and others. Smooth muscle relaxants such as nitrates and calcium channel blockers have been used to effectively treat patients with diffuse esophageal spasm and nutcracker esophagus.
- Several scales have been suggested to determine patients' functional outcome. One of them is the "Swallowing Rating Scale."

COMPLICATIONS

- Dehydration
- Malnutrition
- Aspiration pneumonia
- Airway obstruction
- Death resulting from pulmonary complications

PROGNOSIS

- Depends on the etiology.
- Nursing home patients with oropharyngeal dysphagia and a history of aspiration have an approximately 45% mortality rate over 1 yr.
- All patients, especially the elderly, should take their medications with a full glass of water while in upright position well before bedtime.
- Dysphagia should be considered an alarm symptom, indicating the need for immediate evaluation.

PATIENT EDUCATION

Elderly patients with dysphagia should not attribute their symptoms to aging.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Achalasia (Related Key Topic)
Dyspepsia, Nonulcerative (Related Key Topic)
Esophageal Tumors (Related Key Topic)
Gastroesophageal Reflux Disease (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READING

Brodsky MB et al: Screening accuracy for aspiration using bedside water swallow tests: a systematic review and meta-analysis, *Chest* 150(1):148-163, 2016.

FIG. E1 Barium swallow demonstrating a benign peptic stricture in a patient with gastroesophageal reflux disease and dysphagia. (From Talley NJ, Martin C: *Clinical gastroenterology: a practical problem-based approach,* ed 2, Sydney, 2006, Churchill Livingstone.)

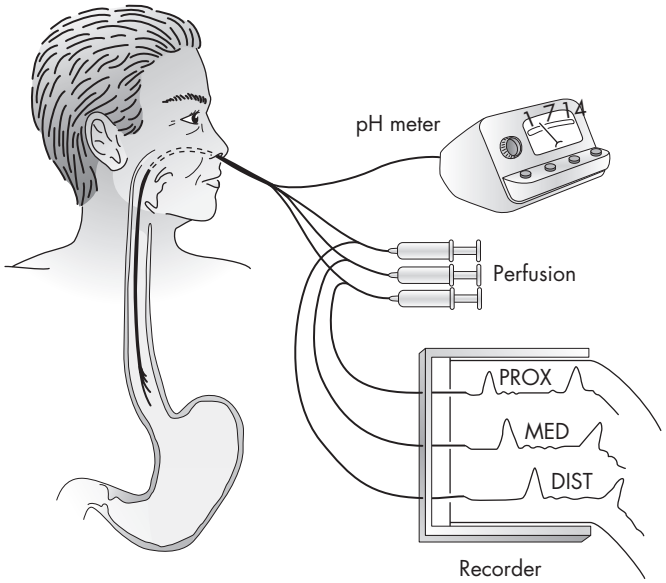

FIG. E2 Combined manometric-pH recording system used in the evaluation of esophageal function. The triple-lumen perfused recording catheter measures intraluminal pressures from three levels in the esophagus. Measurements are made in terms of centimeters from the nostrils to the proximal opening of the recording catheter *(PROX).* The medial catheter *(MED)* records pressures 5 cm distal to the proximal opening and the distal catheter *(DIST)* 5 cm below this. The intraesophageal pH electrode is used to document gastroesophageal reflux. (From Townsend CM et al: *Sabiston textbook of surgery,* ed 17, Philadelphia, 2004, Saunders.)

BASIC INFORMATION

DEFINITION

Dystonia refers to a group of disorders characterized by involuntary muscle contractions (sustained or spasmodic) that lead to abnormal body movements or postures. Dystonia can be generalized or focal, of early (<20 yr) or late onset, and primary or secondary.

SYNONYMS

Blepharospasm
Oromandibular (orofacial) dystonia
Spasmodic (limb or axial) dystonia
Torticollis
Writer's cramp

ICD-10CM CODES

G24	Dystonia
G24.1	Idiopathic familial dystonia
G24.0	Drug induced dystonia
G24.3	Spasmodic torticollis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Estimated at 1 in 3000 persons.
PREDOMINANT SEX: Cervical dystonia has a 3:2 female preponderance.
PREDOMINANT AGE:

- Onset of focal cervical dystonia is usually in the fifth decade.
- Hereditary forms may have an onset in childhood or adulthood and tend to be more severe.

GENETICS: Autosomal-dominant, autosomal-recessive, and X-linked forms of dystonia have been identified. Metabolic conditions in which dystonia is a feature can be inherited or, more frequently, caused by sporadic mutations.

CLINICAL PRESENTATION

Focal dystonias produce abnormal sustained muscle contractions in a single region of the body. Most frequently encountered examples include:

- Neck (***torticollis***): Most commonly affected site with a tendency for the head to turn to one side. Jerky or tremulous movements of the head might occur, which can resemble essential tremor. Patients find that lightly touching the face can reduce the dystonia; this is known as a "sensory trick" or "*geste antagoniste.*"
- Eyelids (***blepharospasm***): Involuntary closure of the eyelids that leads to excessive eye blinking (Fig. E1), sometimes with persistent eye closure (Fig. E2) and functional blindness. Stress and bright sunlight can be triggers for patients prone to this condition.
- Mouth (***oromandibular dystonia***): Involuntary contraction of muscles of the mouth, tongue, or face, resulting in difficulty speaking or swallowing.
- Hand (***writer's cramp***) (Fig. E3). The act of writing is the trigger for this form of focal dystonia. Task-specific dystonias can also occur with other activities, such as playing a musical instrument.
- Spasmodic dysphonia: A dystonia of the vocal cords that results in a strained-sounding voice.
- Isolated foot dystonia: Very rare and may suggest an underlying parkinsonian disorder or brain structural abnormality.

Generalized dystonia affects multiple areas of the body and can lead to marked joint deformities.

ETIOLOGY

- Exact pathophysiology of primary dystonia is unknown but believed to involve abnormalities of basal ganglia. Specifically, reduced and abnormal patterns of neuronal activity in the basal ganglia result in disinhibition of the motor thalamus and cortex, leading to abnormal movement.
- Numerous genetic forms of dystonia exist, some in the context of underlying metabolic disorders. Genetic testing is available but is usually reserved for individuals with a family history of dystonia.
- Secondary dystonia results from central nervous system (CNS) disease of the basal ganglia (stroke, demyelination, hypoxia,

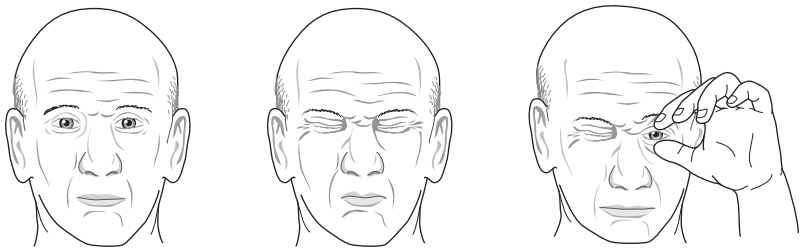

FIG. E1 This man with blepharospasm has repeated, unprovoked closure of both eyelids lasting about 5 seconds at a time due to involuntary contractions of his orbicularis oculi muscles. Because the spasms block his vision, he often resorts to prying open his eyelids. In contrast to eyelid closure as a tic, the closures in blepharospasm are longer, more forceful, and not preceded by an urge to close the eyes. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists*, ed 8, Philadelphia, 2017, Elsevier.)

FIG. E3 Focal dystonia of the distal right arm. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.)

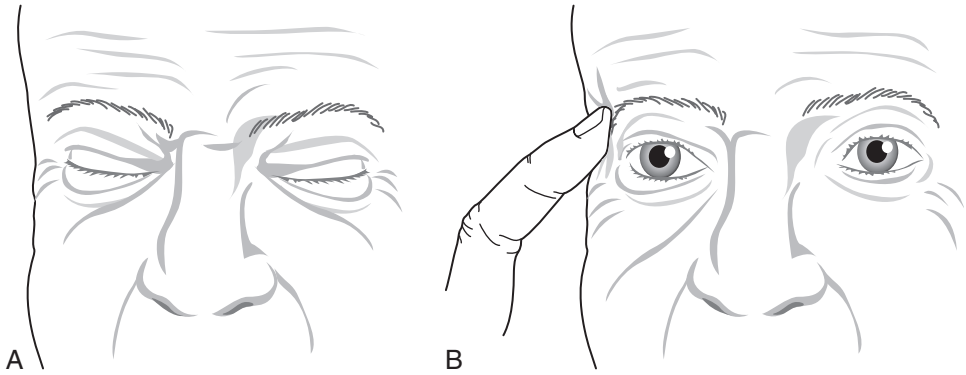

FIG. E2 A, During periods of blepharospasm, this man cannot open his eyelids. He attempts, perhaps unconsciously, to open them by contracting his frontalis muscle. **B**, He has instinctively learned that the sensory trick of lightly touching one eyebrow (a *geste antagoniste*) suppresses the spasms briefly. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists*, ed 8, Philadelphia, 2017, Elsevier.)

trauma), Huntington disease, Wilson disease, Parkinson syndromes, and lysosomal storage diseases.
- Acute dystonia can occur with drugs that block dopamine receptors, such as phenothiazines or butyrophenones.
- Tardive dyskinesia and tardive dystonia can result from long-term treatment with antiemetics (e.g., phenothiazines), antipsychotics (e.g., haloperidol), levodopa, anticonvulsants, or ergots.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Drug effects
- Parkinson disease
- Progressive supranuclear palsy
- Wilson disease
- Huntington disease
- Table E1 describes selected causes of primary and secondary dystonia in childhood

WORKUP

History (family history, birth history, trauma, medication use, age of onset, and temporal pat-

TABLE E1 Selected Causes of Primary and Secondary Dystonia in Childhood

Diagnosis	Additional Clinical Features
Aicardi-Goutieres syndrome	Encephalopathy, developmental regression Acquired microcephaly Sterile pyrexias Lesions on the digits, ears (chilblain) Epilepsy CT: Calcification of the basal ganglia
Alternating hemiplegia of childhood	Episodic hemiplegia/quadriplegia Abnormal ocular movements Autonomic symptoms Epilepsy Global developmental impairment Environmental triggers for spells
Aromatic amino acid decarboxylase deficiency (AADC)	Developmental delay Oculogyric crises Autonomic dysfunction Hypotonia
ARX gene mutation (X-linked)	Male Cognitive impairment Infantile spasms, epilepsy Brain malformation
Benign paroxysmal torticollis of infancy	Episodic Cervical dystonia only Family history of migraine
Complex regional pain syndrome	Lower limb involvement Prominent pain
Dopa-responsive dystonia (DRD)	Diurnal variation
Drug-induced dystonia	
Dystonia-deafness optic neuropathy syndrome	Sensorineural hearing loss in early childhood Psychosis Optic atrophy in adolescence
DYT1 dystonia	Lower limb onset followed by generalization
Glutaric aciduria type 1	Macrocephaly Encephalopathic crises MRI: Striatal necrosis
GM1 gangliosidosis type 3	Short stature, skeletal dysplasia Orofacial dystonia Speech/swallowing disturbance Parkinsonism MRI: Putaminal hyperintensity
Huntington disease (HD)	Parkinsonism Epilepsy Family history of HD
Kernicterus	Jaundice in infancy Hearing loss Impaired upgaze Enamel dysplasia MRI: Hyperintense lesions in the globus pallidus
Leigh syndrome	Motor delays, weakness, hypotonia Ataxia, tremor Elevated lactate MRI: Bilateral symmetric hyperintense lesions in the basal ganglia or thalamus
Lesch-Nyhan syndrome (X-linked)	Male Self-injurious behavior Hypotonia Oromandibular dystonia, inspiratory stridor Oculomotor apraxia Cognitive impairment Elevated uric acid
Myoclonus dystonia	Myoclonus Head, upper limb involvement
Neuroacanthocytosis	Oromandibular and lingual dystonia
Neurodegeneration with brain iron accumulation	Cognitive impairment Retinal pigmentary degeneration, optic atrophy
Niemann-Pick type C	Hepatosplenomegaly Hypotonia Supranuclear gaze palsy Ataxia, dysarthria Epilepsy Psychiatric symptoms
Rapid onset dystonia parkinsonism (DYT12)	Acute onset Distribution face>arm>leg Prominent bulbar signs
Rett syndrome	Female Developmental regression following a period of normal development Stereotypic hand movements Acquired microcephaly Epilepsy
Spinocerebellar ataxia 17 (SCA17)	Ataxia Dementia, psychiatric symptoms Parkinsonism
Tics	Stereotyped movements Premonitory urge, suppressible
Tyrosine hydroxylase deficiency	Infantile encephalopathy, hypotonia Oculogyric crises, ptosis Autonomic symptoms Less diurnal fluctuation than DRD

CT, Computed tomography; *MRI*, magnetic resonance imaging.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

tern), physical examination to determine associated features (weakness, myoclonus, tremor) and to determine pattern of dystonia—focal (single body region), segmental (two or more body contiguous body regions), multifocal (two or more noncontiguous body regions), generalized (involving the trunk and at least two other sites), or hemidystonia (involving more regions but restricted to one body side).

LABORATORY TESTS

- Usually not helpful for diagnosis
- Serum ceruloplasmin if Wilson disease is suspected
- Genetic testing (*DYT* gene mutations, inborn errors of metabolism, or mitochondrial disease) if indicated, based on family history
- Comprehensive toxicology screen indicated if causative drugs suspected (dopamine-blocking agents) and history unavailable

IMAGING STUDIES

- Primary dystonias are generally not associated with structural CNS abnormalities. CT scan or MRI of brain if a CNS lesion is suspected as a cause of secondary dystonia.
- Electrophysiologic testing can provide diagnostic support for the diagnosis, but dystonia is a clinical diagnosis.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Heat, massage, physical therapy to relieve pain.
- Splints to prevent contractures.
- "Sensory trick" (*geste antagoniste*) involves lightly touching the affected body part; this can relieve the discomfort of dystonia.

ACUTE GENERAL Rx

- For acute dystonic reactions to phenothiazines/butyrophenones, use diphenhydramine 50 mg IV or benztropine 2 mg IV.
- For patients presenting with subacute or chronic dystonia, a trial of L-dopa can be useful in distinguishing dopa-responsive dystonia from other causes.

CHRONIC Rx

- For treatment of drug-induced dystonia, slowly withdraw offending agents (antiemetics, antipsychotics most commonly).
- For generalized dystonia, a trial of carbidopa/levodopa may be beneficial and diagnostic of dopa-responsive dystonia.
- Trihexyphenidyl and tetrabenazine are the mainstays of medical treatment for generalized dystonias not responsive to dopa.
- Diazepam, clonazepam, or baclofen may be helpful as adjunctive agents.
- Injections of botulinum toxin into the affected muscles are the standard treatment for focal or multifocal dystonias but cannot be used for generalized dystonia. The mechanism of action involves blockage of the neuromuscular junction acetylcholine transmission.
- Surgical procedures, most commonly deep brain stimulation of the internal globus pallidus, may be helpful for severe, refractory cases.
- Intrathecal baclofen can be useful for spastic or truncal dystonia.

DISPOSITION

Spontaneous remission of focal cervical dystonia can occur, but dystonia is generally progressive, and pharmacologic therapy is often ineffective.

REFERRAL

- Neurology (movement disorders) and/or neurosurgery for severe or refractory cases.
- Physical therapy for maintaining flexibility.

PEARLS & CONSIDERATIONS

COMMENTS

- Avoid triggers/exacerbating factors.
- Early physical therapy and splinting to prevent contractures.
- Consider botulinum toxin injections early in the course.
- Consider deep brain stimulation surgery for severe or refractory dystonia and for focal dystonias.

RELATED CONTENT

Blepharospasm (Related Key Topic)
Torticollis (Related Key Topic)

AUTHOR: **Julie L. Roth, MD**

SUGGESTED READING

Albanese A et al: Phenomenology and classification of dystonia: a consensus update, *Mov Disord* 28:863, 2013.

Fox MD, Alterman RL: Brain stimulation for torsion dystonia, *JAMA Neurol* 72(6):713, 2015.

Simpson DM et al: Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the guideline development subcommittee of the American Academy of Neurology, *Neurology* 86(19):1818, 2016. Epub 2016 Apr 18.

BASIC INFORMATION

DEFINITION

An early repolarization pattern (ERP) in a QRS complex with a duration <120 ms, a peak J point elevation of ≥0.1 mV in two or more contiguous leads **excluding** leads V_1-V_3, with a notch or slur noted in the end of the QRS complex at the downslope of a prominent R wave (Fig. E1). This notch must be above the baseline T-P segment (Fig. E2). Previously thought to be benign, the pattern has been noted in higher prevalence in patients with idiopathic ventricular fibrillation (VF). Recently it has been cited as a predictor of symptoms in the setting of long QT syndrome, as well as a predictor of arrhythmic events in patients with structural heart disease.

SYNONYMS

Early repolarization syndrome—sudden cardiac arrest in a patient with ERP
J point elevation
Persistent juvenile pattern

ICD-10CM CODES

R94.310	Abnormalities ECG—Abnormalities of ST segment
R00.9	Unspecified abnormalities of heart beat
I49.9	Cardiac arrhythmia unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The clinical entity "early repolarization pattern" is commonly asymptomatic; therefore, the true incidence of the pattern is difficult to definitively establish. In one comparison of patients with idiopathic ventricular fibrillation (VF) vs. young athletes vs. age-matched controls, the presence of ERP, defined as J point elevation >1.0 mm, in idiopathic VF patients was 31.1% in any lead, 17.8% in inferior leads, 11.1% in leads I and aVL, and 6.7% in leads V_4 to V_6. For comparison, the incidence in age-matched controls was 8.9% in any lead, 6.5% in inferior leads, 0% in leads I and aVL, and 4.9% in leads V_4 to V_6.

PREDOMINANT SEX: J point elevation >1 mm was documented significantly higher in males vs. females.

GENETICS: The mode of transmission and the genetic basis of the syndrome are unclear. An autosomal dominant pattern of inheritance of the *KCNJ8* gene, which has been associated with sporadic cases, has been shown. The prognostic value of the inheritance pattern is not known.

RISK FACTORS: Male sex, younger age, lower systolic blood pressure, higher Sokolow-Lyon index, and lower Cornell voltage have been shown to be associated with the presence of the early repolarization pattern. The early repolarization pattern carries an increased risk for future arrhythmic death. This is considered to be higher in the setting of a downsloping ST segment.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The physical exam will not show any findings specific for early repolarization. Rather, the clinical presentation is well documented in patients resuscitated from cardiac arrest. This is particularly shown in a pattern in which the early repolarization is seen in the inferior and/or the lateral leads but not in the precordial leads. The pattern has been shown to have an intermittent pattern of expression.

ETIOLOGY

J point elevation is considered to be the electrocardiographic representation of a voltage gradient between different layers from the epicardium to the endocardium. The epicardium has a relatively higher density of transient outward potassium current (I_{TO}), when compared to the endocardium, resulting in a prominent notch in phase I of the action potential. The Brugada syndrome is considered an extreme version of this phenomenon, where a loss of function mutation in the *SCN5A* gene results in loss of phase II in the action potential, causing marked J point and ST segment elevation, allowing for polymorphic ventricular tachycardia.

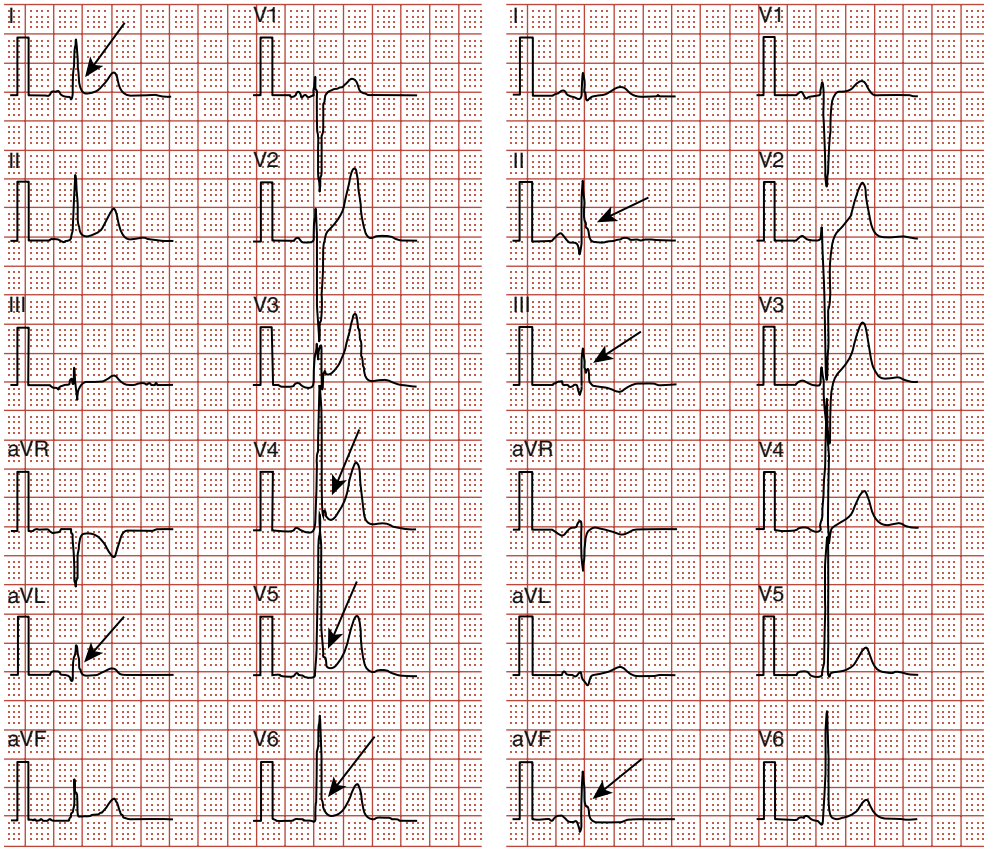

FIG. E1 A, Notching in lead V_4 progressing to slurring in V_6, I, aVL. **B,** Notching in lead III, aVF and slurring in lead II. aVF, Augmented vector foot; aVL, augmented vector left; aVR, augmented vector right. (From Macfarlane PW et al: The early repolarization pattern: a consensus pattern, *J Am Coll Cardiol* 66:470-477, 2015.)

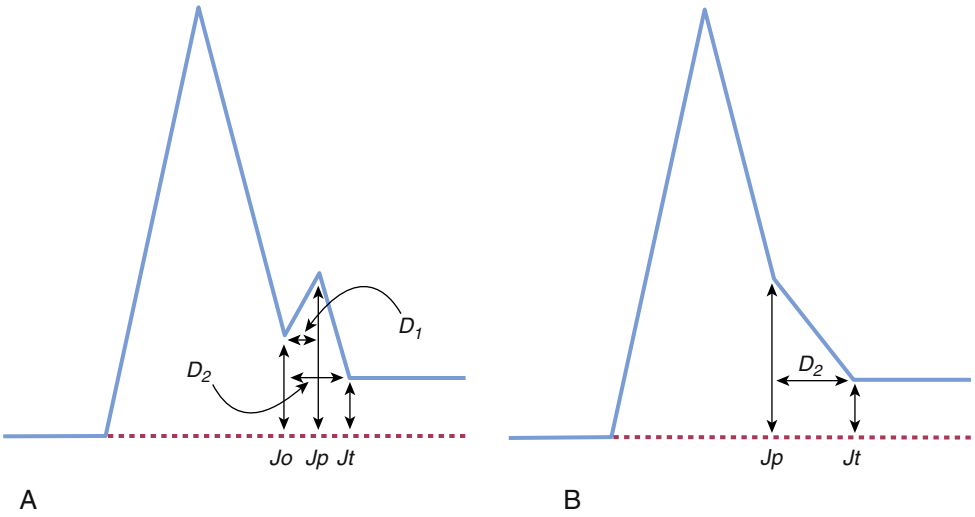

FIG. E2 A, Illustration of the amplitudes J onset (Jo), J peak (Jp), and J termination (Jt) as well as durations D1 and D2 in relation to an end QRS notch, as defined previously. **B,** Illustration of Jp and Jt as well as D2 in relation to an end QRS slur. (From Macfarlane PW et al: The early repolarization pattern: a consensus pattern, *J Am Coll Cardiol* 66:470-477, 2015.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Benign vs. malignant early repolarization
- Brugada syndrome
- Persistent juvenile pattern

WORKUP

- Primarily guided by the clinical scenario. In a patient where the early repolarization pattern is an incidental finding (Figs. E3 and E4), detailed family history for sudden cardiac death is indicated
- However, should the pattern be identified in the setting of a cardiac arrest, then the workup would be directed to identification of potentially reversible causes
  1. Basic metabolic panel
  2. Echocardiogram
  3. Ischemic evaluation—noninvasive stress testing vs. left heart catheterization
  4. Electrophysiology testing
  5. ICD implant for secondary prevention of sudden cardiac death if no reversible cause is identified

LABORATORY TEST

- BMP
- Thyroid function studies

IMAGING STUDIES

Echocardiogram

TREATMENT

No treatment is indicated in the case of the early repolarization pattern. In the setting of early repolarization syndrome with sudden cardiac death, the treatment would be that of sudden cardiac death as detailed under "Workup."

REFERRALS

Cardiology referral should be obtained, particularly in the setting of syncope, nonsustained ventricular tachycardia, or cardiac arrest.

PEARLS & CONSIDERATIONS

COMMENTS

The early repolarization pattern has previously been considered a benign pattern; however, the body of evidence suggests it to be a risk factor for sudden cardiac death. Therefore, all patients with early repolarization, particularly with risk factors or an isolated pattern in the inferior leads, merit a detailed evaluation.

PREVENTION

None

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Brugada Syndrome (Related Key Topic)
Long QT Syndrome (Related Key Topic)
Ventricular Fibrillation (Related Key Topic)
Ventricular Tachycardia (Related Key Topic)

AUTHOR: **Aleem I. Mughal, MD**

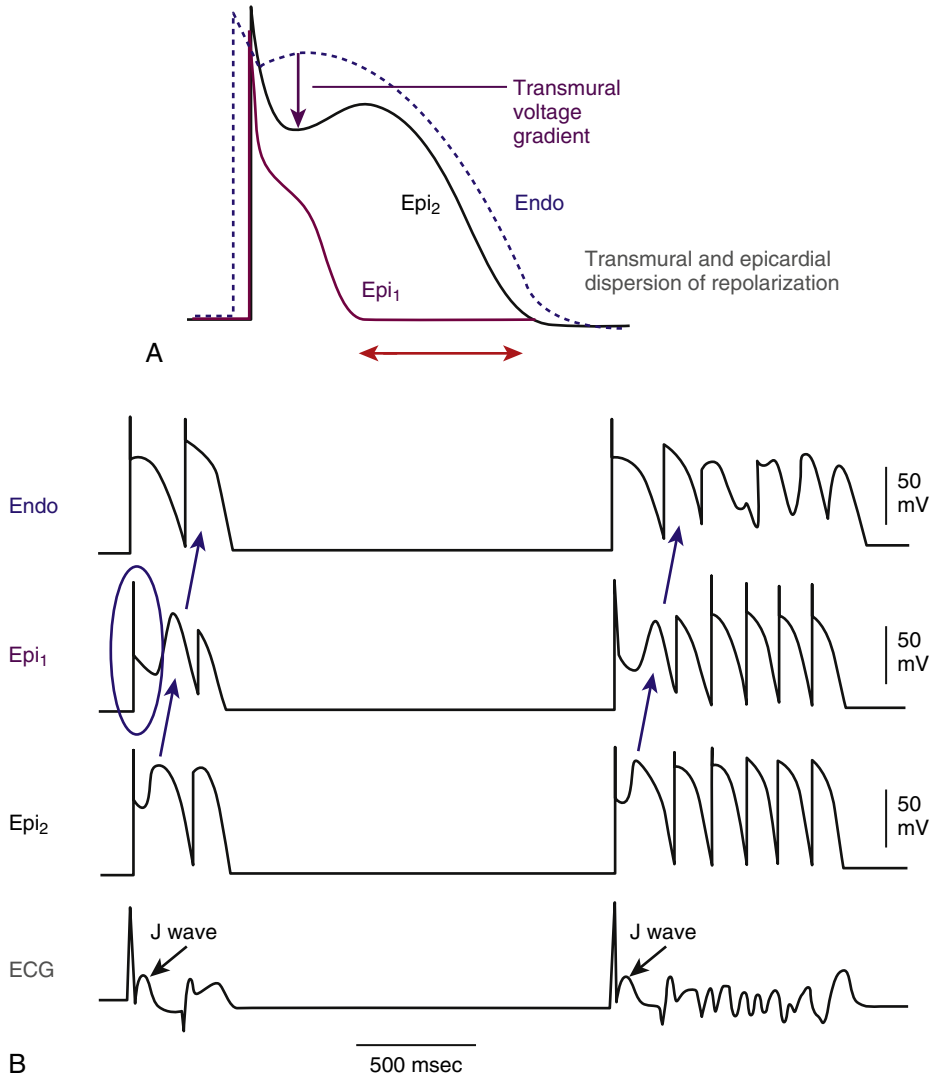

FIG. E3 Potential mechanism for arrhythmogenesis in the Brugada and early repolarization syndromes. A, With enhanced repolarization in regions with prominent transient outward current (I_{to}), all-or-none repolarization can occur, creating a substrate for arrhythmias. **B,** Simultaneous action potentials from two epicardial sites (Epi_1 and Epi_2) and one endocardial site (Endo), and surface ECG. A loss of the action potential dome in Epi_1, but not in Epi_2, leads to apparent propagation of the dome from Epi_2 to Epi_1, inducing reentry. (From Issa ZF, Miller JM: *Clinical arrhythmology and electrophysiology: a companion to Braunwald's heart disease*, ed 2, Philadelphia, 2012, Saunders.)

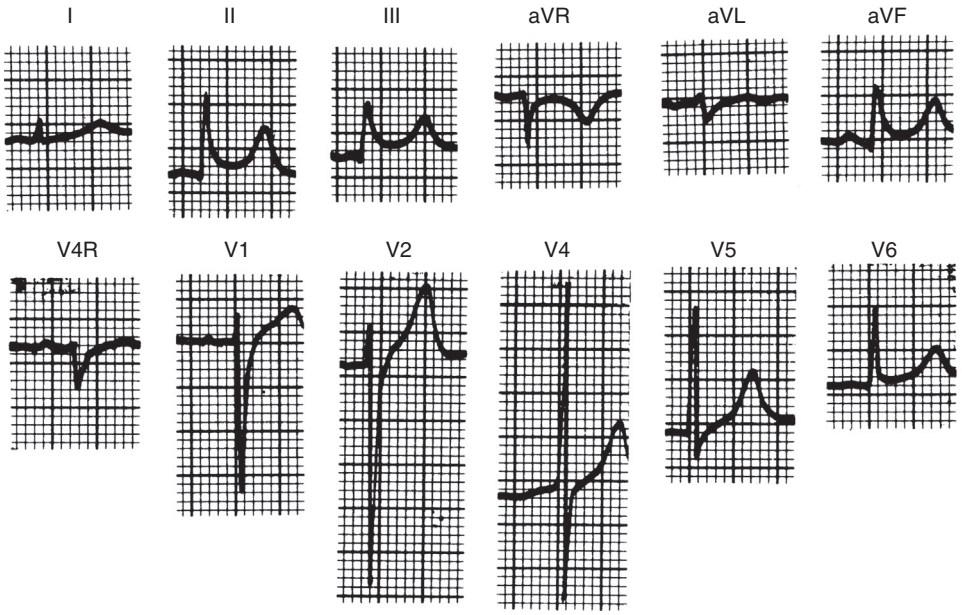

FIG. E4 Tracing from a healthy 16-yr-old boy that exhibits early repolarization and J-depression. The ST segment is shifted toward the direction of the T wave and is most marked in II, III, and aVF. J-depression is seen in most of the precordial leads. aVF, Augmented vector foot; aVL, augmented vector left; aVR, augmented vector right. (From Park MK: *Park's pediatric cardiology for practitioners*, ed 6, Philadelphia, 2014, Saunders.)

SUGGESTED READINGS

Abe A et al: Circadian variation of late potentials in idiopathic ventricular fibrillation associated with J waves: insights into alternative pathophysiology and risk stratification, *Heart Rhythm* 7:675, 2010.

Derval N et al: Prevalence and characteristics of early repolarization in the CASPER registry: cardiac arrest survivors with preserved ejection fraction registry, *J Am Coll Cardiol* 58:722, 2011.

Gourraud JB et al: Identification of large families in early repolarization syndrome, *J Am Coll Cardiol* 61:164, 2013.

Macfarlane PW et al: The early repolarization pattern: a consensus pattern, *J Am Coll Cardiol* 66:470-477, 2015.

Noseworthy PA et al: The early repolarization pattern in the general population: clinical correlates and heritability, *J Am Coll Cardiol* 57:2284, 2011.

BASIC INFORMATION

DEFINITION

Echinococcosis is a chronic infection caused by the larval stage of several animal cestodes (tapeworms) of the genus *Echinococcus* after ingestion of parasite eggs.

SYNONYMS

Hydatid disease, hydatidosis, cystic echinococcosis (CE)
Alveolar echinococcosis (AE)
Polycystic echinococcosis

ICD-10CM CODES	
B67.8	Echinococcosis, unspecified, of liver
B67.90	Echinococcosis, unspecified
B67.99	Other echinococcosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Seen primarily in foreign-born patients, but local transmission of CE can occur in southwestern U.S., California, and Alaska. Found in areas where humans live in close proximity to dogs and livestock slaughtering. AE is found where humans have contact with wild foxes or coyotes, predominantly in the north central region of the U.S.
PEAK INCIDENCE: Presumed to be acquired in childhood or early adulthood in most cases, although prevalence increases with age.
PREVALENCE (IN U.S.): Prevalence in the U.S. is unknown.
PREDOMINANT SEX: Globally, women are more often affected by cystic echinococcosis than men. This higher prevalence in women is felt to be related to domestic activities that bring them in closer contact with dogs.
PREDOMINANT AGE: 0 to 50 yr of age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- There are two predominant forms: Cystic echinococcosis (hydatidosis), caused primarily by *E. granulosus* and to a lesser extent other species, and alveolar echinococcosis, caused by *E. multilocularis.* Rarely, polycystic/unicystic echinococcus occurs in humans caused by *E. vogeli* and *E. oligarthrus.*
- Uncomplicated cystic echinococcosis is generally asymptomatic but may cause mass effect with signs of an enlarging mass lesion in a visceral site such as the liver, lungs, kidneys, bone, or CNS.
- Occasional cyst rupture may cause allergic manifestations such as urticaria, angioedema, or anaphylaxis that bring the patient to medical attention. Additionally, in the case of rupture, secondary bacterial infection may occur, or fistulas may develop (e.g., cystobiliary).
- Incidental discovery of cysts by abdominal or thoracic imaging studies performed for other reasons.
- Alveolar echinococcosis may mimic cirrhosis or liver cancer with upper abdominal discomfort, weight loss, and weakness. Rarely, it can spread to other tissues, including the brain.

ETIOLOGY

- There are several recognized species of *Echinococcus,* of which at least seven cause human disease: *E. granulosus sensu stricto, E. equinus, E. ortleppi, E. canadensis, E. multilocularis, E. oligarthrus,* and *E. vogeli.*
  1. Predominantly *E. granulosus* is the cause of cystic echinococcosis.
  2. *E. multilocularis* is the cause of alveolar echinococcosis.
- The disease is transmitted to humans by infected canines (domestic or wild dogs, wolves, foxes), which are the definitive hosts, and is seen most commonly in livestock-producing areas of the Middle East, Africa, Australia, New Zealand, Europe, and the Americas, including the southwestern U.S., whereby sheep, goats, camels, or cattle serve as intermediate hosts to humans. Humans are incidental hosts and do not play a role in the transmission cycle.
- The adult tapeworm resides in the small intestine of the canine definitive hosts. Eggs are then shed in the feces of infected canines; human infection occurs by ingestion of viable eggs in contaminated food from intermediate hosts or direct fecal-oral transmission.
- After ingestion of the eggs by intermediate hosts or humans, eggs hatch and release oncospheres, which migrate through intestinal mucosa to definitive organs and develop into enlarging fluid-filled cysts known as hydatid cysts (metacestode) (Fig. E1). The cyst is acellular and is surrounded by fibroblasts and lymphocytic infiltrate (Fig. E2).
- It is common in many areas of the world, especially the Middle East.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cystic neoplasms (see Table E1)
- Abscess (amebic or bacterial)
- Congenital polycystic disease

WORKUP

- Antibody assay (with limitations in sensitivity and specificity).
- Imaging study (CT scan [Fig. E3], ultrasonography).
- Classification (Fig. E4): Table E2 describes the World Health Organization Informal Working Group on Echinococcosis classification of hepatic echinococcal cysts.

FIG. E1 Hydatid cysts removed surgically. (From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.)

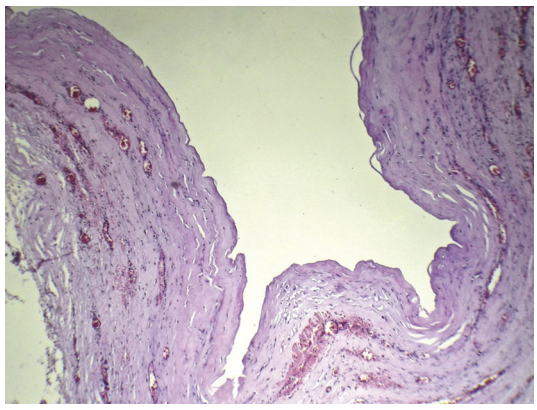

FIG. E2 Echinococcosis. The cyst is acellular and is surrounded by fibroblasts and lymphocytic infiltrate. (From Prieto-Granada CN et al: Skin infections. In Kradin RL [ed], *Diagnostic pathology of infectious disease*, Philadelphia, 2010, Elsevier, pp 519–616.)

TABLE E1 Hepatic Cyst Disease: Differential Features on Imaging Studies

Characteristics	Hydatid Cyst	Congenital Cyst	Cystadenoma
Configuration	Cyst within cyst	Single or multiple ± septations	Single ± septations
Wall character	Thick, uniform ± calcification	Thin, uniform	Mural nodules
Cyst contents	Daughter cysts hydatid sand	Low density	Low density

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

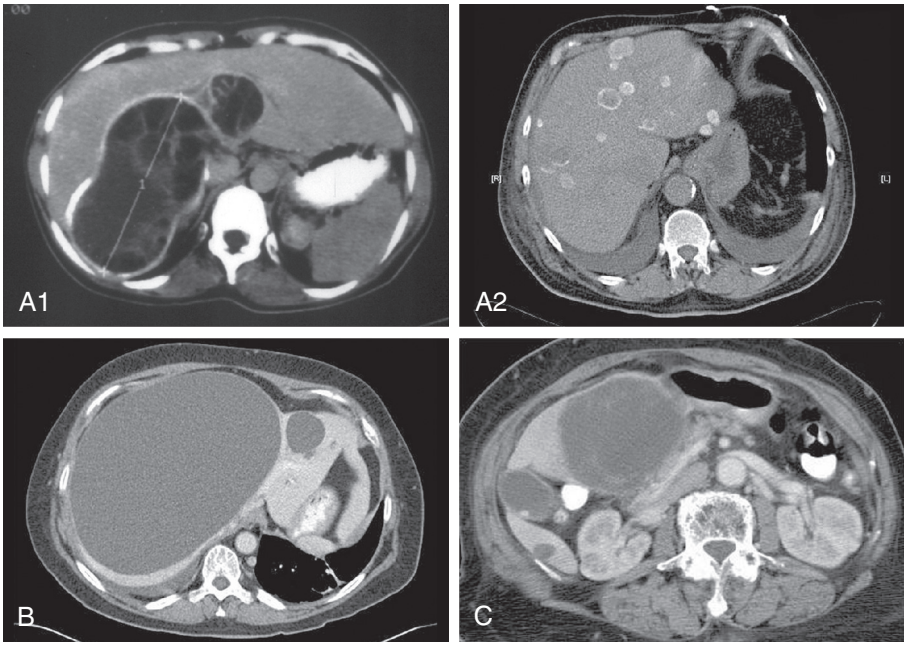

FIG. E3 A comparison of computed tomography scans. A, Hepatic echinococcal cysts. **B,** Congenital cyst. **C,** Cystadenoma. For echinococcal cyst. **A1** demonstrates a single cyst with calcification and daughter cyst caused by *E. granulosa*. **A2** shows multiple small cysts characteristic of *E. multilocularis* infection. (Courtesy of Barbara M. Kadell, MD, Professor of Radiology, David Geffen School of Medicine at University of California, Los Angeles. From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

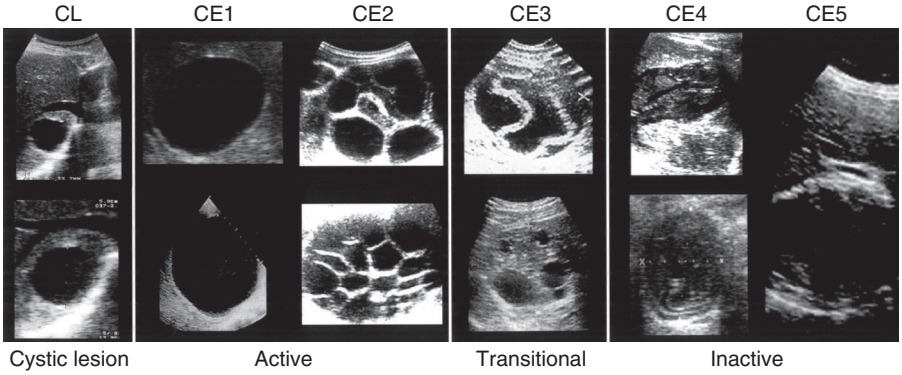

FIG. E4 World Health Organization (WHO) Informal Working Group on Echinococcosis standardized ultrasound classification of cystic echinococcosis. *CL* lesions are cystic lesions lacking a distinct wall and may have other diagnoses. *CE1* lesions are cystic lesions with a visible wall that may demonstrate protoscoleces ("hydatid sand"). *CE2* lesions include internal septation. *CE3* lesions may be detached from the wall or have daughter cysts with internal thickening. *CE4* lesions are heterogeneous lesions with degeneration. *CE5* lesions show thick calcification. (From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.)

- Histologic examination of cyst or contents obtained by aspiration or resection (if possible) to confirm diagnosis, although this is rarely indicated.

LABORATORY TESTS

Antibody assays (ELISA or Western blot) available through CDC: 80% to 100% sensitive and 88% to 96% specific for liver cysts, but less accurate for cysts in other sites, such as lung. A PCR assay is now available for problematic cases. Eosinophilia is not consistently seen and thus is not a reliable indicator.

IMAGING STUDIES

Ultrasonography, CT, and MRI:

- All are extremely sensitive for the detection of cysts, especially in the liver.
- All lack specificity and are inadequate to establish the diagnosis of echinococcosis with certainty.

Rx TREATMENT

ACUTE GENERAL Rx

- There are four treatment modalities: Percutaneous intervention, surgery, chemotherapy, and observation. Expert consultation is recommended, and treatment decisions are based on size and appearance of the cysts (Fig. E4).
- Albendazole 400 mg PO bid followed by percutaneous aspiration-injection-reaspiration (PAIR) for uncomplicated larval cysts. It consists of puncture (P) and needle aspirate (A) of cyst content followed by inspiration (I) of hypertonic saline (15% to 30%) or absolute alcohol, waiting 20 to 30 minutes, then re-aspirating (R) with final irrigation. Albendazole is continued for 28 days. Cure rate is 96%.
- Surgical resection: Cure rate 90%.
- Treatment course depends on presentation and clinical response, with chemotherapy alone often given continuously for months to years. Alternatives to albendazole include mebendazole and praziquantel alone or in combination with mebendazole.

DISPOSITION

- Long-term follow-up is necessary following surgical or medical therapy because of the potential for late relapse.
- Antibody assays and imaging studies are repeated every 6 to 12 mo for several yr following successful surgical or medical therapy.

REFERRAL

All patients should be referred for expert consultation.

TABLE E2 WHO-IWGE Classification of Hepatic Echinococcal Cysts

Type of Cyst	Status	Ultrasound Features	Remarks
CL	Active	Signs not pathognomonic, unilocular, no cyst wall	Usually early stage, not fertile; differential diagnosis necessary
CE 1	Active	Cyst wall, hydatid sand	Usually fertile
CE 2	Active	Multivesicular, cyst wall, rosettelike	Usually fertile
CE 3	Transitional	Detached laminated membrane, "water lily" sign, less round, decreased intracystic pressure	Starting to degenerate, may produce daughter cyst
CE 4	Inactive	Heterogeneous hypoechogenic or hyperechogenic degenerative contents; no daughter cyst	Usually no living protoscoleces; differential diagnosis necessary
CE 5	Inactive	Thick, calcified wall, calcification partial to complete; not pathognomonic but highly suggestive of diagnosis	Usually no living protoscoleces

CE, Cystic echinococcosis; *CL*, cystic lesion; *WHO-IWGE,* World Health Organization Informal Working Group on Echinococcosis.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

PEARLS & CONSIDERATIONS

COMMENTS

Cyst resection, if indicated, should be performed by surgeons experienced with this procedure.

RELATED CONTENT

Echinococcosis (Patient Information)

AUTHORS: **Tara C. Bouton, MD, MPH, TM, Philip A. Chan, MD, MS,** and **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Agudelo Higuita NI et al: Cystic echinococcosis, *J Clin Microbiol* 54:518-523, 2016.

McManus DP et al: Diagnosis, treatment and management of echinococcosis, *BMJ* 344:e3866, 2012.

BASIC INFORMATION

DEFINITION

Eclampsia is the occurrence of seizures or coma in a woman with signs or symptoms of preeclampsia, occurring at >20 wk of gestation or <48 hr postpartum. Atypical eclampsia occurs at <20 wk of gestation or as much as 23 days postpartum.

SYNONYMS

Toxemia
Seizures of pregnancy

ICD-10CM CODES

O15.00	Eclampsia in pregnancy, unspecified trimester
O15.02	Eclampsia in pregnancy, second trimester
O15.03	Eclampsia in pregnancy, third trimester
O15.1	Eclampsia in labor
O15.2	Eclampsia in the puerperium
O15.9	Eclampsia, unspecified as to time period

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: One case per 1500 to 3000 pregnancies; 2% to 4% of those with preeclampsia; one large Australian series found 8.6 cases per 10,000 live births.
GENETICS: Increased incidence with a first-degree relative (sister or mother) having had eclampsia.
RISK FACTORS: Multifetal gestation (3.6% in twin gestation), molar pregnancy, nonimmune hydrops fetalis, uncontrolled hypertension, preexisting hypertension, renal disease, systemic lupus, and existing heart disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Seizure often begins as facial twitching, then spreads to generalized tonic-clonic state, with cessation of respiration followed by a postictal period of amnesia, agitation, and confusion.
- The most common symptoms preceding eclampsia are headache (80%), visual disturbance (45%), and epigastric pain (20%). Seventeen percent are completely asymptomatic prior to seizure.
- Forty percent have severe hypertension, 40% have mild to moderate hypertension, and 20% are normotensive.
- Generalized edema with rapid weight gain (>2 lb/wk) may precede eclampsia.

ETIOLOGY

Common pathway relates to abnormalities in autoregulation of cerebral blood flow. This may involve transient vasospasm, ischemia, cerebral hemorrhage, and edema occurring by a mechanism involving hypertensive encephalopathy, decreased colloid osmotic pressure, and prostaglandin imbalance.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Preexisting seizure disorder
- Metabolic abnormalities (hypoglycemia, hyponatremia, hypocalcemia)
- Substance abuse
- Head trauma, infection (meningitis, encephalitis)
- Intracerebral bleeding or thrombosis
- Amniotic fluid embolism
- Space-occupying brain lesions or neoplasms
- Pseudoseizure
- Hypertensive encephalopathy
- Venous or arterial thrombosis, arterial embolism
- Posterior reversible encephalopathy syndrome (often seen in eclampsia)
- Vasculitis, angiopathy
- Thrombotic thrombocytopenic purpura

WORKUP

- Rule out other causes of seizures during pregnancy.
- Atypical presentations such as prolonged postictal state; status epilepticus; gestational age <20 wk or >48 hr postpartum; or signs of meningitis, substance abuse, or severe uncontrolled hypertension should prompt a search for other seizure etiologies.

LABORATORY TESTS

- Proteinuria: Severe (49%), mild to moderate (29%), absent (22%)
- HCT: Elevated as a result of hemoconcentration
- Platelet count: Decreased; LFTs elevated in HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count)
- BUN and creatinine: Elevated with renal involvement
- Serum electrolytes, glucose, calcium, toxicology profile: Rule out other causes of seizures
- ABG: Maternal acidemia and hypoxia

IMAGING STUDIES

- CT scan or MRI indicated in atypical presentation, suspected intracerebral bleeding, or focal neurologic deficit.
- Over 90% of patients will have findings consistent with posterior reversible encephalopathy syndrome on MRI.
- There are other abnormal findings, including cerebral edema, hemorrhage, and infarction, in 50% of patients.

TREATMENT

ACUTE GENERAL Rx

- Maintain airway, adequate oxygenation, and IV access.
- Fetal resuscitation involving maternal oxygenation, left lateral positioning, and continuous fetal heart rate monitoring is needed.
- Magnesium sulfate is the drug of choice. Give magnesium sulfate 6 g IV load over 20 min, then 2 g/hr maintenance, for treatment and recurrent seizure prophylaxis. Adjust maintenance dose for renal insufficiency. If there is no IV access, may give 10 g IM (5 g to each buttock). If repeated convulsions, may give an additional 2 g IV over 3 to 5 min. Approximately 10% to 15% of patients will have a second seizure after initial loading dose. Clinical signs of progressive Mg^{2+} toxicity, such as loss of reflexes, should also be followed. If magnesium toxicity is suspected, check magnesium level (therapeutic range 4 to 7 mEq/L). If serum level >9.6 mg/dl, stop infusion. Respiratory and cardiac arrest occur at extremely high magnesium levels. Antidote for toxicity is calcium gluconate 10 ml of 10% solution. Phenytoin has been used as an alternative in patients in whom magnesium sulfate is contraindicated (e.g., heart block, myasthenia gravis).
- Give sodium amobarbital 250 mg IV over 3 min for persistent seizures not responsive to magnesium sulfate.
- Treat BP >160 mm Hg systolic or BP >110 mm Hg diastolic with either hydralazine 5 to 10 mg IV, then 10 mg, then 10 mg every 20 minutes to a maximum of 20 mg; or labetalol hydrochloride 20, 40, 80 mg IV, escalating the dose every 10 minutes to maximum total dose of 300 mg; or nifedipine 10 - 20 mg orally every 20 minutes can be used for acute blood pressure control, if no IV access, to a total dose of 180 mg/day. If maximum dose of one medication is reached, add an additional medication to reach goal of BP 140 to 150/90 to 100 mm Hg.
- Evaluate patient for delivery.

CHRONIC Rx

- The first priority is stabilization of the mother in terms of adequate oxygenation, hemodynamics, and laboratory abnormalities, such as associated coagulopathies.
- Cervical status and gestational age should be assessed. If unfavorable cervix and <30 wk of gestation, consider C-section; otherwise consider induction.
- Give antenatal corticosteroids if 24 to 34 wks' gestation. Consider antenatal corticosteroids if 34 to 36-6/7 wks' gestation or 23-0/7 to 24 wks' gestation.
- Controlled epidural is the anesthesia of choice for labor or C-section.
- Avoid general anesthesia in uncontrolled hypertension to minimize risk of catastrophic cerebral events.
- Continue magnesium sulfate through delivery process and for 24 hr postpartum or for at least 24 hr after the last convulsion.

DISPOSITION

- The maternal mortality rate for eclampsia averages 5% to 6%. Morbidity rate is 25%, including placental abruption (10%), disseminated intravascular coagulation, maternal apnea with fetal asphyxia, aspiration pneumonia, pulmonary edema (4%), renal failure, cardiopulmonary arrest, and coma.
- There is an increased risk of fetal death, neonatal death, preterm birth, and small-for-gestational-age birth.
- In patients with eclampsia, the risk of recurrence of eclampsia in a subsequent pregnancy is

about 2% and the risk of preeclampsia is about 25%. The use of daily low-dose aspirin starting at 12 to 16 (28) wk may decrease that risk.

REFERRAL

Because of the potential for serious permanent maternal and fetal sequelae, all cases should be managed by a team approach of obstetrician, maternal and fetal medicine, neonatologist, and intensivist.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Eclampsia (Patient Information)
HELLP Syndrome (Related Key Topic)
Preeclampsia (Related Key Topic)

AUTHOR: **Philip A. Shlossman, MD**

SUGGESTED READINGS

American College of Obstetricians and Gynecologists: *Hypertension in pregnancy*, Washington, DC, 2013, American College of Obstetrics and Gynecologists.

American College of Obstetricians and Gynecologists: Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period: committee opinion no. 692 *Obstet Gynecol* 129:e90-e95, 2017.

Cooray SD et al: Characterization of symptoms immediately preceding eclampsia, *Obstet Gynecol* 118:995-999, 2011.

Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin No. 202. American College of Obstetricians and Gynecologists, *Obstet Gynecol* 133:e1-25, 2019.

Liu S et al: Incidence, risk factors, and associated complications of eclampsia, *Obstet Gynecol* 118(5):987, 2011.

Mayama M et al: Incidence of posterior reversible encephalopathy syndrome in eclamptic and patients with preeclampsia with neurologic symptoms, *Am J Obstet Gynecol 215* 239:e1-e5, 2016.

BASIC INFORMATION

DEFINITION

An ectopic pregnancy (EP) occurs when a fertilized ovum implants outside the endometrial cavity.

SYNONYMS

Tubal pregnancy (97%) Interstitial (cornual) pregnancy (1% to 2%)
Ovarian pregnancy (1% to 3%)
Abdominal pregnancy (0.03% to 1%)
Cervical pregnancy (0.5%)
Cesarean scar pregnancy (6% of women with prior cesarean)

ICD-10CM CODES	
O00.0	Abdominal pregnancy
O00.1	Tubal ectopic pregnancy
O00.2	Ovarian ectopic pregnancy
O00.8	Other ectopic pregnancy
O00.9	Ectopic pregnancy, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- 1.5% to 2% of pregnancies
- 2.7% of maternal deaths

PREVALENCE (IN U.S.): Accounts for up to 18% of women presenting to the emergency room with vaginal bleeding or abdominal pain. Currently over 100,000 reported cases/yr.

RISK FACTORS: Previous EP, previous pelvic infection (pelvic inflammatory disease, tuboovarian abscess, salpingitis), previous tubal ligation, previous tuboplasty, previous cesarean section, intrauterine device use, assisted reproductive techniques, infertility, cigarette use, age >35 yr, multiple lifetime sexual partners, DES exposure in utero

PHYSICAL FINDINGS & CLINICAL PRESENTATION:

- Abdominal tenderness: 95%
- Adnexal tenderness: 87% to 99%
- Peritoneal signs: 71% to 76%
- Amenorrhea or abnormal vaginal bleeding: 75%
- Adnexal mass: 33% to 53%
- Enlarged uterus: 6% to 30%
- Shock: 2% to 17%
- Shoulder pain: 10%
- Tissue passage: 6% to 7%

ETIOLOGY

- Anatomic obstruction to zygote passage
- Abnormalities in tubal motility
- Transperitoneal migration of the zygote

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Corpus luteum cyst
- Rupture or torsion of ovarian cyst
- Threatened or incomplete abortion
- Pelvic inflammatory disease
- Appendicitis
- Gastroenteritis
- Dysfunctional uterine bleeding
- Degenerating uterine fibroids
- Endometriosis

WORKUP

- The classic presentation of EP includes the triad of abnormal vaginal bleeding, pelvic pain, and an adnexal mass. Fig. 1 describes a diagnostic approach to suspected EP. Fig. 2 *(top)* describes potential sites of ectopic implantations. Consider in all women with abdominopelvic pain and a positive pregnancy test.
- Transvaginal ultrasound (Fig. 2 [bottom]).
- Quantitative serum human chorionic gonadotropin level.
- Type and screen if presents with vaginal bleeding; give Rhogam if Rh-negative status on initial presentation of vaginal bleeding with positive pregnancy test.
- Laparoscopy in equivocal situations and possibly for treatment.

LABORATORY TESTS

- Quantitative human chorionic gonadotropin (qhCG): Check on initial presentation. qhCG allows one to interpret initial ultrasound. If qhCG >6000 mIU/ml, should see intrauterine pregnancy (IUP) on abdominal scan; qhCG >1500 mIU/ml for transvaginal scan. The ability to visualize an early pregnancy is dependent on the gestational age and expertise of the ultrasonographer; therefore, some may use up to qhCG >3500 mIU/ml as the discriminatory threshold for transvaginal ultrasonography.
- Approximately 25% to 50% of women with an EP present with a pregnancy of unknown location, meaning that the initial ultrasound does not show a pregnancy in the uterus or the fallopian tube. Therefore, serial measurement of qhCG, typically obtained every 2 days, can help distinguish between an IUP, resolving miscarriage, or EP.
- The expected rate of qhCG increase varies by the initial starting hCG. For an initial hCG level <1500 mIU/ml, the expected rate of increase is 49%, compared to 40% for an initial hCG level between 1500 and 3000 mIU/ml, and a 33% increase for an initial hCG >3000 mIU/ml.
- Dropping hematocrit may be associated with tubal rupture or possible abnormal intrauterine pregnancy.

IMAGING STUDIES

- Ultrasound: Presence of an intrauterine yolk sac makes EP extremely unlikely. However, if the patient used assisted reproductive technologies, a heterotopic pregnancy (an EP with concurrent IUP) is a possibility. A repeat ultrasonographic examination within 7 days after presentation may identify the location of a pregnancy that was not identified on initial ultrasonographic examination.
- Findings on ultrasound in EP include:
  1. Empty uterus (i.e., no yolk sac or fetal pole; a pseudosac in uterus may appear similar to a gestational sac)
  2. Adnexal mass (typically separate from adjacent ovary, commonly seen with "ring of fire" appearance)
  3. Enlarged hysterotomy scar, may bulge beyond contour of the uterus
  4. Fluid in cul-de-sac
  5. Yolk sac and/or fetal pole in tube
  6. Fetal cardiac activity in adnexa

TREATMENT

NONPHARMACOLOGIC THERAPY

Surgery performed via laparoscopy is preferred; however, laparotomy is appropriate if patient is very unstable or if visualization of the pelvis is poor at the time of laparoscopy.

- Salpingostomy, or resecting EP with conservation of tube, has the potential benefit of higher rates of subsequent IUP; however, recent randomized controlled trials suggest there is no difference in fecundity rate between salpingostomy and salpingectomy. The procedure requires postoperative serial monitoring of qhCG.
- Salpingectomy, or removal of affected fallopian tube, is considered the standard surgical procedure and is preferred in the following circumstances:
  1. Ruptured tube
  2. Future fertility not desired
  3. Recurrent EP in the same tube
  4. Uncontrolled hemorrhage
- Direct injection of chemotherapy into the EP by laparoscopy, transvaginal ultrasound, or hysteroscopy. Direct injection of methotrexate, and possibly KCl if there is active cardiac activity, may be performed when the pregnancy is in a location where there is high morbidity, such as the cervix, cesarean section scar, or cornu.
- Cervical and cesarean scar pregnancies may be managed with a combination of methotrexate administration, laparoscopic and/or hysteroscopic techniques, uterine artery embolization, laparotomy, and possible hysterectomy.

ACUTE GENERAL Rx

- Medical management with methotrexate, a folic acid antagonist, is a safe alternative if the patient is stable. Check the methotrexate safety labs prior to administration (CBC, creatinine, LFTs).
- Contraindications:
  1. Hemodynamically unstable; ruptured EP
  2. Patient unable to comply with follow-up
  3. Medical contraindication to methotrexate including the following: Hepatic or renal disease, thrombocytopenia, leukopenia, or significant anemia
  4. Breastfeeding, preexisting blood dyscrasias, known sensitivity to methotrexate, active pulmonary disease, chronic liver disease, alcoholism, laboratory evidence of immunodeficiency, renal disease, and peptic ulcer disease
  5. Intrauterine gestation

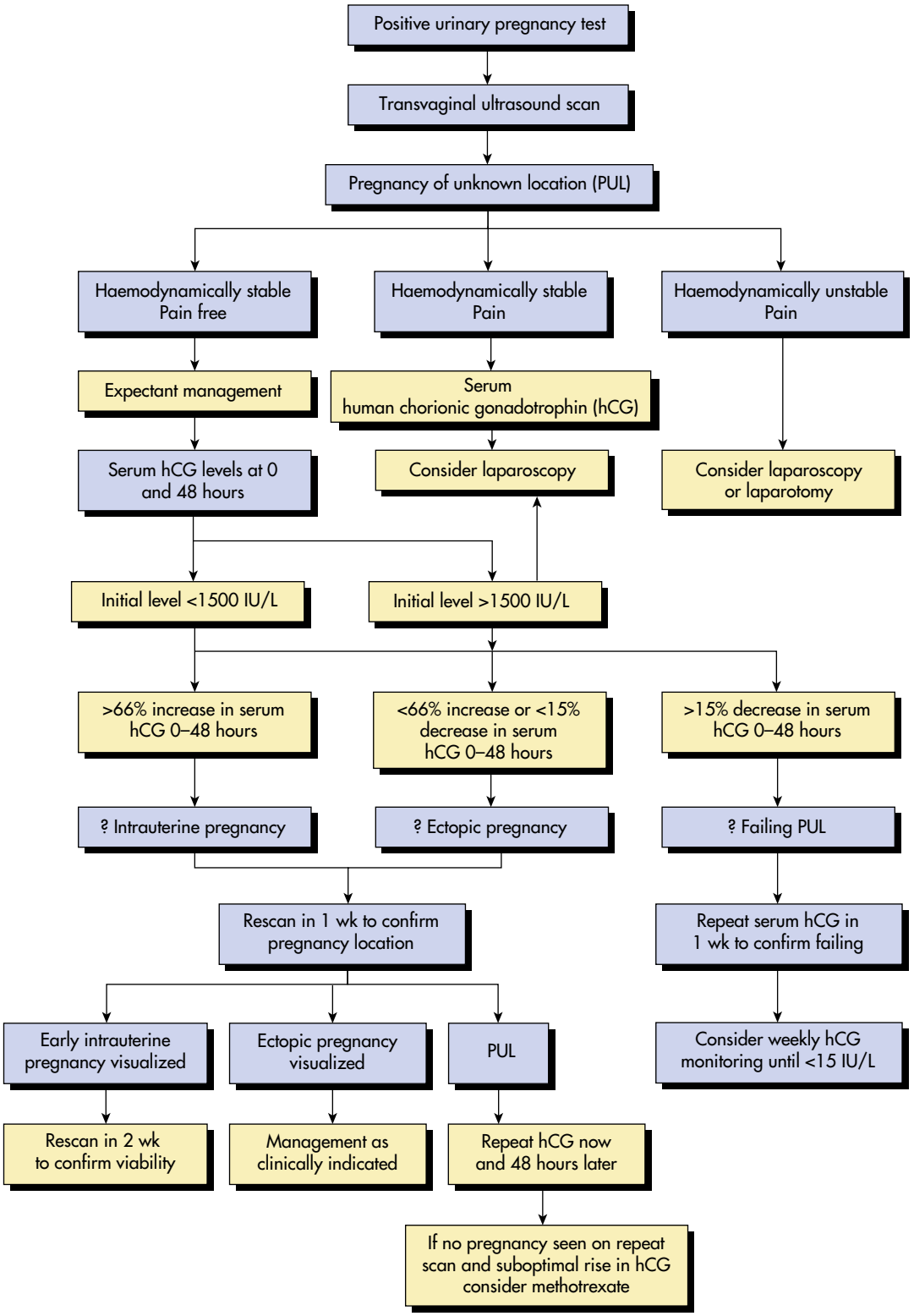

FIG. 1 Algorithm for managing suspected ectopic pregnancy. *hCG,* Human chorionic gonadotrophin; *PUL,* pregnancy of unknown location. (From Magowan BA: *Clinical obstetrics & gynecology,* ed 4, 2019, Elsevier.)

- Relative contraindications:
  1. EP >3.5 cm mass
  2. qhCG >5000 mIU/ml (more likely to require multidose regimen)
  3. Presence of cardiac activity in the fetus
- Most common regimen is methotrexate 50 mg/m^2 of body surface area and is administered on day 1. May require second dose or surgical intervention if qhCG increases or plateaus (<15% drop) when comparing values from day 4 and 7.
- Success rate of single-dose protocol approximately 88.1%. Rupture during methotrexate treatment ranges from 7% to 14%.
- Other methotrexate regimens include multidose protocol ± leucovorin rescue.
- Methotrexate side effects include nausea, vomiting, stomatitis, diarrhea, elevated LFTs, abdominal pain, and nephrotoxicity.

CHRONIC Rx

Persistent EP results from residual trophoblastic tissue or secondary implantation after conservative surgery. There is a 5% incidence of persistent EP with conservative treatment.

DISPOSITION

If diagnosed and treated early (before rupture), prognosis is excellent for good recovery. Monitor qhCG weekly until negative. Use reliable contraception until qhCG is negative. With subsequent pregnancies, follow qhCG and perform early ultrasound to confirm IUP. There is a 10% recurrence rate for EP.

REFERRAL

Should obtain gynecologic consultation if EP is suspected.

PEARLS & CONSIDERATIONS

Any patient who presents with vaginal bleeding, abdominal pain, or both with a positive pregnancy test and no prior documented IUP needs to be assessed for ectopic pregnancy.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Ectopic Pregnancy (Patient Information)
Spontaneous Abortion (Related Key Topic)
Vaginal Bleeding During Pregnancy (Related Key Topic)

AUTHORS: **Terri Q. Huynh, MD, MSCR,** and **Nima R. Patel, MD, MS**

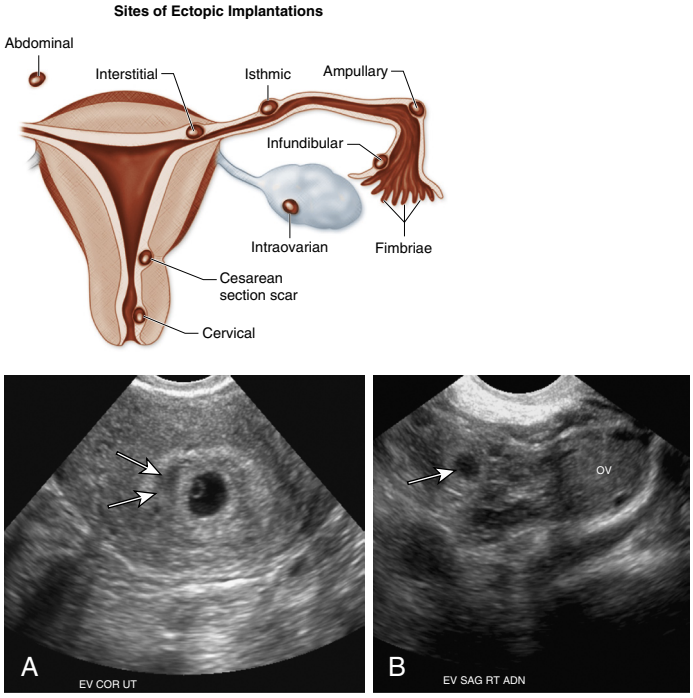

FIG. 2 ***Top*****, Schematic drawing depicting implantation sites of ectopic pregnancies. A** and **B,** Heterotopic pregnancy. This pregnant patient presented with vaginal bleeding at 5 to 6 wk of gestational age. **A,** Transverse transvaginal ultrasound (TVUS) image of the uterus reveals an intrauterine gestational sac containing a yolk sac. Note small subchorionic hemorrhage (*arrows*), most likely accounting for the vaginal bleeding. **B,** Sagittal TVUS image of the right adnexa reveals an echogenic tubal ring (*arrow*) clearly separate from the right ovary (*OV*), which was surgically confirmed to be an ectopic pregnancy. (From Fielding JR et al: *Gynecologic imaging*, Philadelphia, 2011, Saunders.)

SUGGESTED READINGS

Barnhart KT, Franasiak JM: ACOG Practice Bulletin Number 193: tubal ectopic pregnancy, *Obstetrics & Gynecology* 131(3):e91-e103, 2018.

Ehlers-Danlos Syndrome (PTG)

BASIC INFORMATION

DEFINITION

Ehlers-Danlos syndrome (EDS) is a clinically and genetically heterogeneous group of connective tissue disorders (HCTDs) characterized by joint hypermobility, skin hyperextensibility, and tissue fragility.

SYNONYM

EDS

ICD-10CM CODE
Q79.6 Ehlers-Danlos syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- The prevalence of EDS is estimated to be approximately 1 in 5000 births, although it is somewhat higher in African Americans.
- The 2017 International Classification of Ehlers-Danlos Syndromes recognizes 13 subtypes (Table E1).
- In view of the vast genetic heterogeneity and phenotypic variability of the EDS subtypes and clinical overlap between many of the subtypes, but with other HCTDs, the definite diagnosis relies for all subtypes, except hEDS, on molecular confirmation with identification of causative variants(s) in the respective gene.
- For most of the subtypes, mutations have been identified in collagen-encoding genes, or in genes encoding collagen-modifying enzymes.
- Classical EDS (cEDS) and hypermobile EDS (hEDS) are most prevalent. cEDS accounts for approximately 80% of reported cases.
- Diagnosis of hEDS remains a clinical one.
- Vascular EDS (vEDS) is the most dangerous because it is associated with spontaneous rupture of medium and large arteries and hollow organs, especially the large intestine and uterus.
  1. Vascular events occur in 4% of patients with vEDS.
  2. They typically occur between the third and fifth decades of life.
  3. Most vascular complications consist of arterial dissections.
- Inheritance pattern is either autosomal dominant (AD) or autosomal recessive (AR).
- The 2017 classification of Ehlers-Danlos syndrome is summarized in Table E1.
- Diagnostic criteria for the various subtypes of EDS may require fulfilling components of either major and/or minor criterion with minimal criteria suggestive for each EDS subtypes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- cEDS: Patients have moderate to severe skin hyperelasticity (Fig. E1); easy scarring and bruising ("cigarette-paper scars"); smooth, velvety "doughy" skin, "piezogenic papules" (fat herniations through the fascia on sides of feet), molluscoid pseudotumors (bluish-gray to violaceous, spongy 1 to 2 cm nodules over easily traumatized bony areas such as the shin, forearms, and Achilles tendon, which represents herniation of subcutaneous fat through atrophic dermal scars), and subcutaneous spheroids (small, firm, hard calcified, subcutaneous nodules due to fat necrosis); hyperextensibility ("Gorlin sign": Ability to touch tip of tongue to nose [Fig. E2]); and joint hypermobility (Fig. E3) and dislocation (Fig. E4). Patients have complications such as hernias, pelvic organ prolapse, premature osteoarthritis, and cervical insufficiency.
- hEDS: Most frequent form, large- and small-joint and spine hypermobility, causes recurrent joint dislocations, often leaving a patient unable to walk.
  1. Chronic limb or joint pain is a prominent feature and may resemble fibromyalgia.
  2. Patients develop scoliosis and premature osteoarthritis.
  3. Skin involvement is less prominent
     a. Skin is sometimes soft and smooth with mild hyperextensibility. Piezogenic papules may be seen. Keratosis pilaris/hyperkeratosis of the extensor surfaces and striae can occur.
  4. Other features include delayed gastric emptying and irritable bowel syndrome.
  5. Autonomic dysfunction, including postural orthostatic tachycardia syndrome (POTS), can occur.
  6. Sleep apnea and headaches are reported in one-third of patients (migraines; tension-type headaches, including "brain fog" and headaches form cerebrospinal fluid leakage; Chiari malformation; and cervicogenic), and poor proprioception, swelling, and varicosities of legs. Resistance to local anesthetic drugs and opioids has been reported.
  7. Mild aortic root dilatation and mitral valve prolapse can be seen.
- Vascular EDS (vEDS): vEDS is a potentially life-threatening condition with increased risk of spontaneous vascular or visceral rupture and the absence of large-joint hyperextensibility.
  1. Cardinal features include distinctive facial features (pinched nose, thin lips, tight skin, hollow cheeks, lobeless ears); acrogeria; thin translucent skin; excessive bruising; and, most important, rupture of vessels and viscera, including the arterial, intestinal, and uterine walls.
  2. Vessels most prone to rupture are the abdominal aorta and its branches, great vessels of aortic arch, and large arteries of limbs.
     a. Preexisting aneurysms are rarely detected before rupture, as they are typically pseudoaneurysms.
     b. Spontaneous rupture of internal organs occurs in the sigmoid colon, spleen, liver, and uterus.
  3. Facial features are often not prominent in children, and vascular EDS is usually not diagnosed until adulthood.
  4. Vascular rupture, GI perforation, or other organ rupture are presenting signs in 70% of adults with vascular EDS; presentation is often dramatic and unexpected. The average age for first major arterial or GI complication is 23 yr.
  5. Maternal mortality during pregnancy is about 12%; delivery is often uneventful.
- Kyphoscoliotic EDS (kEDS): Rare; characterized by marked muscular hypotonia, osteopenia, joint hypermobility, club foot deformity, progressive scoliosis, ocular fragility and possible globe rupture, mitral valve prolapse, and aortic dilation. Progressive kyphoscoliosis can result in respiratory complications requiring surgery. The skin is hyperextensible and typically velvety, pale, and translucent, with poor wound healing.
- Arthrochalasia EDS (aEDS): Prominent joint hypermobility with subluxations, congenital bilateral hip dislocation, extremity contractures, thoracolumbar scoliosis (short stature), skin hyperextensibility, and tissue fragility.
- Dermatosparaxis EDS (dEDS): Characterized by severe skin fragility with decreased elasticity, sagging redundant skin, and large hernias. Blue sclerae, typical facial feature, and severe bruising are present.
- Spondylodysplastic EDS (spEDS): Characterized by short stature; blue sclera; delayed tooth eruption and hypodontia; joint laxity with particular skeletal pattern (platyspondyly, osteopenia, widened metaphyses, flattened epiphyses, small ilia, short broad femoral neck, and short metacarpals and phalanges); velvety, hyperextensible, thin skin with prominent veins; and delayed wound healing with atrophic scars.
- Musculocontractural EDS (mcEDS): Characterized by craniofacial features (broad forehead, small mouth, and micrognathia in infancy, protruding jaw in adolescence, low set prominent rotated ears, blue sclerae, short nose, thin upper lip, and long philtrum), thumb and finger contractures, club feet, severe kyphoscoliosis, hypotonia, hyperextensible thin skin with easy bruising, atrophic scars, joint laxity, and organ fragility.

ETIOLOGY

- The underlying genetic and pathogenic mechanisms of EDS subtypes are outlined in Table E2.
- Defects of collagen-encoding genes, or in genes encoding collagen-modifying enzymes expressed in multiple tissues (skin, tendons, blood vessels, and viscera) underlie all forms of EDS.
- cEDS is associated with defects in type V collagen, corresponding to mutations of *COL5A1* and *COL5A2* genes, rarely defects in type I collagen, corresponding to mutations in *COL1A1*.
- Vascular EDS (vEDS) involves a deficiency in type III collagen, and several genetic studies suggest that heterozygous mutations in the *COL3A1* gene lead to this deficiency. There are rare exception(s) of specific heterozygous arginine-to-cysteine substitution in *COL1A1* that are also associated with vascular fragility mimicking *COL3A1-vEDS.*
- Arthrochalasia EDS (aEDS) results from a defect in type I collagen, caused by mutations in the *COL1A1* and *COL1A2* genes.
- Genetic testing for hEDS is not available. Diagnosis is made on clinical basis.

TABLE E1 Clinical Classification of the Ehlers-Danlos Syndromes Inheritance Patterns and Genetic Basis

Clinical EDS Subtypes	Abbreviation*	Inheritance Pattern	Genetic Basis	Protein	Diagnostic Criteria
Classical EDS	cEDS (classical EDS types I and II)	AD	Major: *COL5A1*, *COL5A2* Rare: *COL1A1*	Type V collagen Type I collagen	• Major criteria: Skin hyperextensibility and atrophic scarring Generalized joint hypermobility (GJH) • Minor criteria: Easy bruising Soft, doughy skin Skin fragility Molluscoid pseudotumors Subcutaneous spheroids Hernia Epicanthal folds Complications of joint hypermobility (e.g., sprains, luxation/subluxation, pain, flexible flatfoot) Family history of a first-degree relative who meets clinical criteria • Minimal criteria suggestive for cEDS: - Major criteria: Skin hyperextensibility and atrophic scarring Plus - Either major criterion: GJH - And/or: At least three minor criteria Confirmatory molecular testing
Classical-like EDS	clEDS (tenascin X deficiency)	AR	*TNXB*	Tenascin XB	• Major criteria: Skin hyperextensibility, with velvety skin texture and absence of atrophic scarring GJH (most common shoulder and ankle) Easily bruised skin/spontaneous ecchymoses • Minor criteria: Foot deformities: Broad/plump forefoot Brachydactyly, with excessive skin; pes planus; hallus valgus, piezogenic papules Edema of the legs in the absence of cardiac failure Mild proximal and distal muscle weakness Axonal polyneuropathy Atrophy of muscles in hands and feet Acrogenic hands, mallet finger(s) Clinodactyly, brachydactyly Vaginal/uterine/rectal prolapse • Minimal criteria suggestive for clEDS: All three major criteria AND a family history compatible with AR transmission Confirmatory molecular testing
Cardiac-valvular	cvEDS	AR	*COL1A2*	Type I collagen	• Major criteria: Severe progressive cardiac-valvular problems (aortic valve, mitral valve) Skin involvement: Skin hyperextensibility, atrophic scars, thin skin, easy bruising Joint hypermobility (generalized or restricted to small joints) • Minor criteria: Inguinal hernia Pectus excavatum Joint dislocation Foot deformities: Pes planus, pes planovalgus, hallus valgus • Minimal criteria for cvEDS: - Major criterion: Severe progressive cardiac-valvular - AND family history compatible with AR inheritance Plus - Either: One or more major criterion - And/or: At least two minor criteria Confirmatory molecular testing

Continued

TABLE E1 Clinical Classification of the Ehlers-Danlos Syndromes Inheritance Patterns and Genetic Basis—cont'd

Clinical EDS Subtypes	Abbreviation*	Inheritance Pattern	Genetic Basis	Protein	Diagnostic Criteria
Vascular EDS	vEDS (EDS type IV)	AD	Major: *COL3A1* Rare: *COL1A1*	Type III collagen Type I collagen	• Major criteria: Family history of vEDS with *COL3A1* mutation Arterial rupture at young age Spontaneous sigmoid colon perforation in the absence of diverticular disease or other bowel pathology Uterine rupture during third trimester in the absence of previous C-section and/or severe peripartum perineum tears Carotid-cavernous sinus fistula (CCSF) in the absence of trauma • Minor criteria: Bruising Thin, translucent skin with increased venous visibility Characteristic facial appearance Spontaneous pneumothorax Acrogeria Talipes equinovarus (club foot) Congenital hip dislocation Hypermobility of small joints Keratoconus Gingival recession and gingival fragility Early-onset varicosities (age <30 yr and nulliparous female) • Minimal criteria for vEDS: Family history of vEDS, arterial rupture or dissection in individuals less than 40 yr of age, unexplained sigmoid colon rupture, or spontaneous pneumothorax in the presence of other vEDS features Confirmatory molecular testing
Hypermobile EDS	hEDS (EDS type III)	AD	Unknown	Unknown	Diagnosis of hEDS remains a clinical one. The clinical diagnosis of hEDS needs the simultaneous presence of criterion 1 AND 2 AND 3 as outline in text.
Arthrochalasia EDS	aEDS (EDS type VIIA and B)	AD	*COL1A1*, *COL2A1*	Type I collagen	• Major criteria: Congenital bilateral hip dislocation Severe GJH, with multiple dislocations/subluxations Skin hyperextensibility • Minor criteria: Muscle hypotonia Kyphoscoliosis Mild radiographic osteopenia Tissue fragility, atrophic scars Easily bruised skin • Minimal criteria for aEDS: - Major criteria: Congenital hip dislocation Plus - Either major criterion: Skin hyperextensibilitylistb - Or major criterion: Severe GJH with multiple dislocations/subluxations and at least two other minor criteria Confirmatory molecular testing
Dermatosparaxis EDS	dEDS (EDS type VIIC)*	AR	*ADAMTS2*	*ADAMTS2*	• Major criteria: Extreme skin fragility with congenital or postnatal skin tears Craniofacial features evident at birth or early infancy Redundant, almost lax skin, with excessive skin folds at the wrist and ankles Palmar wrinkling Severe bruisability with a risk of subcutaneous hematoma and hemorrhage Umbilical hernia Postnatal growth retardation Short limbs, hands, and feet Perinatal complications due to connective tissue fragility

TABLE E1 Clinical Classification of the Ehlers-Danlos Syndromes Inheritance Patterns and Genetic Basis—cont'd

Clinical EDS Subtypes	Abbreviation*	Inheritance Pattern	Genetic Basis	Protein	Diagnostic Criteria
					• Minor criteria: Soft and doughy skin texture Skin hyperextensibility Atrophic scar GJH Visceral fragility (bladder rupture, diaphragmatic rupture, rectal prolapse) Osteopenia Hirsutism Refractive errors (myopia, stigmatism) Strabismus • Minimal criteria for dEDS: Major criteria: Extensive skin fragility AND major criteria: Craniofacial features Plus Either: One other major criterion And/or: Three minor criteria Confirmatory molecular testing
Kyphoscoliotic EDS	kEDS (EDS type VI)	AR	*PLOD1* *FKBP14*	*LH1* *FKBP22*	• Major criteria: Congenital muscle hypotonia Congenital or early onset kyphoscoliosis GJH with dislocation/subluxations (shoulder, hips, and knees) • Minor criteria: Skin hyperextensibility Easily bruised skin Ruptures/aneurysm of medium-sized artery Osteoporosis/osteopenia Blue sclerae Hernia (umbilical or inguinal) Pectus deformity Marfanoid habitus Talipes equinovarus Refractive errors (myopia, hypermetropia) • Gene-specific minor criteria: 1. *PLOD1* - Skin fragility - Scleral and ocular fragility/rupture - Microcornea - Facial dysmorphology 2. *FKBP14* - Congenital hearing impairment (sensorineural, conductive, or mixed) - Follicular hyperkeratosis - Muscle atrophy - Bladder diverticula • Minimal criteria for kEDS: - Major criteria: Congenital muscle atonia - AND major criterion: Congenital early-onset kyphoscoliosis Plus - Either major criterion: *GJH* - And/or three minor criteria (either general or gene specific criteria) Confirmatory molecular testing
Brittle cornea syndrome	BCS	AR	*ZNF469* *PRDM5*	*ZNF469* *PRDM5*	• Major criteria: Thin cornea with or without rupture (corneal thickness <400 μm) Early onset progressive keratoconus Early onset progressive keratoglobus Blue sclerae • Minor criteria: Enucleation or corneal scarring as a result of previous rupture Progressive or corneal stromal depth, especially in central cornea High myopia, with normal or increase axial length Retinal detachment

Continued

TABLE E1 Clinical Classification of the Ehlers-Danlos Syndromes Inheritance Patterns and Genetic Basis—cont'd

Clinical EDS Subtypes	Abbreviation*	Inheritance Pattern	Genetic Basis	Protein	Diagnostic Criteria
					Deafness, often with mixed conductive and sensorineural components, progressive, higher frequencies often more severely affected ("slopping" pure tone audiograms) Hypercompliant tympanic membranes Development of dysplasia of the hip Hypotonia in infancy, usually mild if present Scoliosis Arachnodactyly Hypermobility of distal joints Pes planus, hallus valgus Mild contractures of fingers (especially 5th) Soft, velvety skin, translucent Minimal criteria for BCS: - Major criteria: Thin cornea, with or without rupture (central corneal thickness often <100 micrometer) Plus - Either: At least one other major criterion - And/or three minor criteria Confirmatory molecular testing
Spondylodysplastic EDS	spEDS	AR	*B4GALT7* *B3GALT6* *SLC39A13*	β4GalT7 β3GalT6 ZIP13	• Major criteria: Short stature (progressive in childhood) Muscle hypotonia (severe congenital to late onset) Bowing of limbs • Minor criteria: Skin hyperextensibility, soft doughy skin, thin translucent skin Pes planus Delayed motor development Osteopenia Delayed congenital development • Gene-specific minor criteria: 1. *PB4GAL7* - Radioulnar synostosis - Bilateral elbow contractures or limited elbow movements - *GJH* - Single transverse palmar crease - Characteristic craniofacial features - Characteristic radiographic findings - Severe hypermetropia - Clouded cornea 2. *B3GALT6* - Kyphoscoliosis (congenital or early onset, progressive) - Joint hypermobility, generalized or restricted to distal joints, with joints dislocation - Joint contractures (congenital or progressive; especially hands) - Peculiar fingers (slender, tapered, arachnodactyly, spatulate, with broad distal phalanges) - Talipes equinovarus - Characteristic craniofacial features - Tooth discoloration, dysplastic teeth - Characteristic radiographic findings - Osteoporosis with multiple spontaneous fractures Ascending aortic aneurysms Lung hypoplasia, restrictive lung disease 3. *SLC39A13* - Protuberant eyes with bluish sclerae - Hands with wrinkled palms - Atrophy of the thenar muscles, and tapering fingers - Hypermobility of the distal fingers - Characteristic radiologic findings • Minimal criteria for spEDS: - Major criteria: Short stature - AND major criterion: Muscle hypotonia Plus - Characteristic radiographic abnormalities and at least three other minor criteria (general or type specific) Confirmatory molecular testing

TABLE E1 Clinical Classification of the Ehlers-Danlos Syndromes Inheritance Patterns and Genetic Basis—cont'd

Clinical EDS Subtypes	Abbreviation*	Inheritance Pattern	Genetic Basis	Protein	Diagnostic Criteria
Musculocontractural EDS	mcEDS	AR	*CHST14* *DSE*	*D4ST1* *DSE*	• Major criteria: Congenital multiple contractures, characteristically adduction-flexion contractures and/or talipes and/or talipes equinovarus (clubfoot) Characteristic craniofacial features, which are evident at birth and in early infancy Characteristic cutaneous features including skin hyperextensibility, easy bruisability, skin fragility with atrophic scars, increased palmar wrinkling • Minor criteria: Recurrent/chronic dislocations Pectus deformities (flat, excavated) Spinal deformities (scoliosis, kyphoscoliosis) Peculiar fingers (tapering, slender, cylindrical) Progressive talipes deformities (valgus, planus, cavum) Large subcutaneous hematoma Chronic constipation Colonic diverticula Pneumothorax/pneumohemothorax Nephrolithiasis/cystolithiasis Hydronephrosis Cryptorchidism in males Strabismus Refractive errors (myopia, astigmatism) Glaucoma/elevated intraocular pressure • Minimal criteria for mcEDS: At birth or in early childhood: Major criterion: Congenital multiple contractures In adolescence and in adulthood: Major criteria: Congenital multiple contractures AND characteristic cutaneous features Confirmatory molecular testing
Myopathic EDS	mEDS	AD or AR	*COL12A1*	Type XII collagen	• Major criteria: Congenital muscle hypotonia, and/or muscle atrophy, that improves with age Proximal joint contractures (knee, hip, and elbows) • Minor criteria: Soft doughy skin Atrophic scarring Motor developmental delay Myopathy on muscle biopsy • Minimal criteria for mEDS: Major criteria: Congenital muscle hypotonia that improves with age PLUS Either: One other major criterion And/or: Three minor criteria Confirmatory molecular testing
Periodontal	pEDS	AD	*CIR* *C1S*	Cir C1s	• Major criteria: Severe and intractable periodontitis of early onset (childhood or adolescence) Lack of attached gingiva Pretibial plaques Family history of a first-degree relative who meets clinical criteria • Minor criteria: Easy bruising Joint hypermobility, mostly distal joints Skin hyperextensibility and fragility, abnormal scarring (wide and atrophic) Increased rate of infections Hernias Marfanoid facial features Acrogeria Prominent vasculature • Minimal criteria for pEDS: Major criterion: Severe and intractable periodontitis of early onset (childhood or adolescence) OR major criterion: Lack of attached gingiva Confirmatory molecular testing

*Original Villefranche classification.
AD, Autosomal dominant; *AR,* autosomal recessive; *EDS,* Ehlers-Danlos syndrome.
Modified from Malfait F et al: The 2017 International Classification of the Ehlers-Danlos syndromes, *Am J Med Genet Part C Semin Med Genet* 175(1):8-12, 2017.

FIG. E1 Ehlers-Danlos syndrome. Skin hyperextensibility on the arm. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

Dx DIAGNOSIS

- The diagnosis of hEDS remains clinical as there is no reliable or appreciable genetic test. The syndromic presentation may vary with age and gender
- There is also a clinical spectrum ranging from asymptomatic joint hypermobility through nonsyndromic hypermobility with secondary manifestations to hEDS
- The clinical diagnosis of hEDS needs the simultaneous presence of three criteria, all of which must be present

  Criterion 1: Generalized joint hypermobility (small and large joints)

  Criterion 2: Two or more features of A, B, or C

  Feature A: Five or more of the following:
  1. Unusual velvety skin
  2. Mild skin hyperextensibility
  3. Unexplained striae (without weight gain or loss)
  4. Bilateral piezogenic heel papules
  5. Recurrent or multiple abdominal hernias(s) (e.g., umbilical, inguinal, crural)
  6. Atrophic scarring (not as severe as seen in cEDS or vEDS)
  7. Pelvic floor, rectal, and/or uterine prolapse in children, men, or nulliparous women without a history of morbid obesity or etiology
  8. Dental crowding and high or narrow palate
  9. Arachnodactyly, as defined as one or more of the following: (i) Positive wrist sign (Steinberg sign) on both sides; (ii) positive thumb sign (Walker sign) on both sides
  10. Arm span-to-height ≥1.05
  11. Mitral valve prolapse (MVP) mild or greater based on echocardiogram
  12. Aortic root dilatation with Z-score >+2 standard deviation above the mean

  Feature B: Positive family history in first-degree relatives diagnosed with these criteria

  Feature C: Musculoskeletal complications (must have at least one):
  1. Daily musculoskeletal pain in two or more extremities (at least 3 mo)
  2. Chronic, widespread pain for 3 mo or more
  3. Recurrent joint dislocations or atraumatic joint instability

  Criterion 3: No evidence of skin fragility or other connective tissue disorder
- Caveats
  1. Joint hypermobility is more common in females and young children, and as patient gets older, joint hypermobility decreases with development of early onset osteoarthritis followed by surgical intervention
  2. Diagnostic testing-genetic testing is not available
- Differential diagnosis for hEDS
  1. Neuromuscular disorders
  2. Other EDS subtypes
  3. Other HCTD
     a. Marfan syndrome
     b. Autosomal dominant cutis laxa
     c. Larsen syndrome
     d. Stickler syndrome
     e. Loeys-Dietz syndrome
     f. Osteogenesis imperfecta
     g. Arterial tortuosity syndrome

WORKUP

Diagnosis is based on clinical criteria and genetic testing.

LABORATORY TESTS

- Genetic testing for known molecular defects recommended to confirm the diagnosis, but genetic testing is not available for hEDS.
- Plain radiographs may reveal calcified nodules along the shin or forearms corresponding to the subcutaneous spheroids.
- Echocardiography can identify valvular abnormalities and aortic dilation.

Rx TREATMENT

- All patients should receive genetic counseling about the mode of inheritance of their EDS.
- Management of most skin and joint problems should be conservative and preventative.
  1. Physical therapy to strengthen muscles can be helpful.
  2. Acetaminophen for pain control. NSAIDs can be used but may exacerbate easy bruising.
  3. Joint hypermobility and pain in EDS usually does not require surgical intervention.
     a. Surgical repair and tightening of joint ligaments can be performed, but ligaments frequently will not hold sutures.
     b. Surgical intervention should be considered on an individual basis.
- Annual ophthalmologic examinations should be performed in all patients with EDS to detect early retinal or scleral fragility, myopia, and glaucoma.
- For patients with vascular EDS:
  1. Special surgical care is required because of increased tissue friability.
  2. Patients should be advised to avoid contact sports.
  3. Elevated blood pressure should be aggressively treated with beta-blockers, given the risk of arterial dissection.
  4. A β_1-selective agent with partial β_2-agonist activity, celiprolol, has been shown to decrease the incidence of arterial rupture or dissection in a small study.
  5. In the case of bleeding, desmopressin should be considered as it stimulates release of endothelial von Willebrand factor and of aminocaproic acid to counteract fibrinolysis.

DISPOSITION

Prognosis varies according to the subtypes of EDS. For vEDS:

- 25% will have a complication by age 25 yr; >80% will have a complication by age 40 yr.
- Most vascular complications consist of arterial dissections.
- Vascular events typically occur between the third and fifth decades of life.
- Median age of survival is 48 yr. Most deaths are related to arterial rupture.

REFERRAL

- Geneticist for genetic testing, if applicable, and genetic counseling
- Cardiology for ongoing monitoring and treatment of valvular abnormalities and aortic dilation
- Ophthalmology for annual examination to detect retinal or scleral fragility, myopia, and glaucoma
- Physical therapy for strengthening of core and extremity muscles and joint stability
- Orthopedic surgeon, general surgeon, or obstetrician/gynecologist as needed

FIG. E2 Ehlers-Danlos syndrome (EDS). Gorlin sign is five times more common in EDS patients than in normal individuals. Note the scars on the forehead. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

FIG. E3 Joint hyperextensibility in classical Ehlers-Danlos syndrome. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

FIG. E4 Ehlers-Danlos syndrome. Hyperextensible joints may result in double-jointed fingers, as seen in this girl. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

PEARLS & CONSIDERATIONS

- Women with vascular EDS should be counseled about the risk of uterine, intestinal, and arterial rupture.
- Pregnancy is associated with up to a 25% mortality rate; however, successful childbirth is possible.
- There is a 50% chance that the child will be affected.
- Family members of patients with different EDS subtypes should be recommended for evaluation for EDS and genetic testing and counseling.

RELATED CONTENT

Ehlers-Danlos Syndrome (Patient Information)

AUTHOR: **Anthony M. Reginato, PhD, MD**

TABLE E2 Regrouping of Ehlers-Danlos Syndrome According to Underlying Genetic and Pathogenic Mechanisms

Former Nomenclature and Other Names	Villefranche Nomenclature	New Nomenclature	OMIM Condition	Locus	Gene	OMIM Gene	Protein	IP
Group A: Defects in Collagen Primary Structure and Collagen Processing								
Gravis/EDS I	Classical type	Classical EDS (cEDS)	130000	9q34.3	*COL5A1*	120215	Type V collagen	AD
Mitis/EDS II			130010	2q32.2	*COL5A2*	120190	Type I collagen	
				17q21.33	*COL1A1*	120150	p.(Arg312Cys)	
Arterial-ecchymotic EDS	Vascular type	Vascular EDS (vEDS)	130050	2q32.2	*COL3A1*	120180	Type III collagen	AD
EDS IV				17q21.33	*COL1A1*	120150	Type I collagen p.(Arg312Cys) p.(Arg574Cys) p.Arg1093Cys)	
Arthrochalasis multiplex congenita	Arthrochalasia type	Arthrochalasia EDS (aEDS)	130060	17q21.33	*COL1A1*	120150	Type I collagen	AD
			130060	7q21.3	*COL1A2*	120160		
EDS VIIA								
EDS VIIB								
Human dermatosparaxis EDS VIIC	Dermatosparaxis type	Dermatosparaxis EDS (dEDS)	225410	5q35.3	*ADAMTS2*	604539	ADAMTS-2	AR
Cardiac-valvular EDS	/	Cardiac-valvular EDS (cvEDS)	225320	7q21.3	*COL1A2*	120160	Type I collagen Total absence of pro α2(I) collagen chains	AR
Group B: Defects in Collagen Folding and Collagen Cross-Linking								
Ocular-scoliotic EDS	Kyphoscoliosis type	Kyphoscoliotic EDS (kEDS-*PLOD1*)	225400	1p36.22	*PLOD1*	153454	Lysyl hydroxylase 1	AR
EDS VI								
EDS VIA								
/	/	Kyphoscoliotic EDS (kEDS-*FKBP14*)	614557	7p14.3	*FKBP14*	614505	FKBP22	AR
Group C: Defects in Structure and Function of Myomatrix, the Interface between Muscle and ECM								
		Classical-like EDS (clEDS)	606408	6p21.33-p21.32	*TNXB*	600985	Tenascin XB	AR
/	/	Myopathic EDS (mEDS)	616471	6q13-q14	*COL12A1*	120320	Collagen XII	AD/AR
Group D: Defects in Glycosaminoglycan Biosynthesis								
EDS progeroid	EDS progeroid type	Spondylodysplastic EDS (spEDS-*B4GALT7*)	130070	5q35.3	*B4GALT7*	604327	Galactosyltransferase I β4GalT7	AR
	EDS progeroid type 1							
EDS progeroid type 2	β3GalT6-deficient EDS	Spondylodysplastic EDS (spEDS-*B3GALT6*)	615349	1p36.33	*B3GALT6*	615291	Galactosyltransferase II β3GalT6	AR
β3GalT6-deficient EDS								
Adducted thumb clubfoot syndrome		Musculocontractural EDS (mcEDS-*CHST14*)	601776	15q15.1	*CHST14*	608429	Dermatan-4 sulfotransferase-1	AR
EDS Kosho type		Musculocontractural EDS (mcEDS-*DSE*)	615539	6q22.1	*DSE*	605942	Dermatan sulfate epimerase-1	AR

EDS musculocontractural type								
D4ST1-deficient EDS								
Group E: Defects in Complement Pathway								
EDSVIII	EDS periodontitis	Periodontal EDS (pEDS)	130080	12p13.31	*C1R*	613785	C1r	AD
					C1S	120580	C1s	
Group F: Disorders of Intracellular Processes[a]								
Spondylocheirodysplastic EDS		Spondylodysplastic EDS (spEDS-*SLC39A13)*	612350	11p11.2	*SLC39A13*	608735	ZIP13	AR
Brittle cornea syndrome		Brittle cornea syndrome (BCS)	229200	16q24	*ZNF469*	612078	ZNF469	AR
			614170	4q27	*PRDM5*	614161	PRDM5	AR
Unresolved Forms of EDS								
Hypermobile EDS III	Hypermobility type	Hypermobile EDS (hEDS)	130020	?	?		?	AD
Conditions Not Included in EDS Spectrum Anymore								
Occipital horn syndrome	/	/	304150	Xq21.1	*ATP7A*	300011	ATP7A	X-L
Fibronectin-deficient (EDS X)	/	/						AD
Familial articular hypermobility (EDS XI)	/	/						AD
X-linked EDS with muscle hematoma (EDSV)	/	/						X-L
Filamin A related EDS with periventricular nodular heterotopia	/	/	300049	Xq28	*FLNA*	300017	Filamin A	X-L

[a]For EDS subtypes implemented in this category, the underlying pathophysiological mechanism is not readily understood, and classification within this subgroup is provisionary, until further functional information becomes available.
AD, Autosomal dominant; *AR,* autosomal recessive; *EDS,* Ehlers-Danlos syndrome; *IP,* inheritance pattern; *X-L,* X-linked recessive.
From Malfait F et al: The 2017 international classification of the Ehlers-Danlos syndromes, *Am J Med Genet Part C Semin Med Genet* 175(1):8-26, 2017 (Table II).

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Ehrlichiosis and Anaplasmosis PTG

BASIC INFORMATION

DEFINITION

Human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA) are tick-borne rickettsial diseases. Ehrlichiosis is the generic name for infections caused by both *Ehrlichia* and *Anaplasma* genera. Table 1 describes the agent, vector, and geographic prevalence of these diseases.

SYNONYMS

Human granulocytic ehrlichiosis (HGE)
Ehrlichiosis
Human monocytic ehrlichiosis (HME)
Human monocytotropic ehrlichiosis
Human granulocytic anaplasmosis (HGA)
Human granulocytotropic ehrlichiosis
Anaplasmosis
Human granulocytropic anaplasmosis
HGE
HGA
HME

ICD-10CM CODES

A77.40 Ehrlichiosis, unspecified
A77.41 Ehrlichiosis chaffeensis [*E. chaffeensis*]
A77.49 Other ehrlichiosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Highest overall incidence in Rhode Island (36.5 per 1 million), New York, New Jersey, Connecticut, Wisconsin, Minnesota, and northern California; >3000 cases identified in the United States since 2006.
PREDOMINANT SEX: Males outnumber females by 2 to 1.
PREDOMINANT AGE: Most severe disease 50 to 70 yr
PEAK INCIDENCE: Occurs throughout the yr, with peak incidence between May and July and again in September

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms of ehrlichiosis typically appear after a median of 9 days (range 5 to 14 days)
- Most common initial symptoms
  1. Fever (96%)
  2. Chills, rigor
  3. Headache (72%)
  4. Myalgia
- Subsequent symptoms
  1. Anorexia, nausea
  2. Arthralgia
  3. Cough
  4. Confusion (meningoencephalitis in 20% of patients with HME)
  5. Abdominal pain
  6. Rash (erythematous to pustular) <30% in HME, uncommon in HGA
- Complications
  1. Hepatitis
  2. Interstitial pneumonitis; acute respiratory distress syndrome
  3. Renal and respiratory failure
  4. Demyelinating polyneuropathy
  5. Toxic shock–like syndrome
  6. Life-threatening opportunistic infections, usually HGA

ETIOLOGY

- The causative agents are *Ehrlichia chaffeensis* for human monocytic ehrlichiosis (HME) and *Anaplasma phagocytophilum* for human granulocytic anaplasmosis (HGA) and *Ehrlichia ewingii* for human granulocytic ehrlichiosis (HGE)
- Vector
  1. Almost certainly tick-borne, recently confirmed to be rarely transmitted by infected blood (including nosocomial infection). Perinatal and transplant transmission have been documented.
  2. Transmitted by *Ixodes scapularis* in the northeastern states and *Amblyomma americanum* in the south central, southeastern, and mid-Atlantic states. Fig. 1 illustrates the life cycles of human monocytic ehrlichiosis (HME, with *Ehrlichia chaffeensis*) and human granulocytic ehrlichiosis (anaplasmosis).
  3. Tick exposure reported in >90% of patients, with ~60% reporting tick bite.
- Mammalian host: Deer, horses, dogs, white-footed mice, cattle, sheep, goats, bison
- Host inflammatory and immune responses define final spectrum of disease beyond granulocytes, including hepatitis, interstitial pneumonitis, and nephritis with mild azotemia
- Between 6% and 21% of patients with HGA also have serologic evidence of other *Ixodes* spp. tick-borne diseases: Lyme disease or babesiosis
- Recovery is usual outcome; fatality rate of HGE is about 1%
- ICU care required: 7%

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rocky Mountain spotted fever, Colorado tick fever, Q fever, relapsing fever
- Babesiosis
- Leptospirosis
- Lyme disease
- Tularemia
- Typhoid fever, paratyphoid fever
- Brucellosis
- Viral hepatitis
- Meningococcemia
- Infectious mononucleosis
- Hematologic malignancy
- TTP (thrombotic thrombocytopenic purpura)
- Table 2 describes clinical clues suggesting a diagnosis of a tick-borne illness manifesting as a nonspecific febrile illness

WORKUP

- Acute blood samples for Giemsa-stained smears
- CBC (leukopenia, thrombocytopenia), liver function (elevated), blood urea nitrogen (BUN)/creatinine
- Acute serum samples for serology: Antibodies are seldom detected at time of acute infection (they usually appear 2 to 4 wk following clinical illness)
- Chest radiograph examination
- Bone marrow rarely needed

LABORATORY TESTS

- Polymerase chain reaction (PCR) to facilitate early diagnosis: Detection of *Ehrlichia/Anaplasma* DNA in blood or cerebrospinal fluid (CSF) by PCR (Table E3)
- Giemsa-stained smear demonstrating morulae of the organism within granulocytes or monocytes (sensitivity 20% to 75%) (Fig. E2)
- CBC: Progressive leukopenia and thrombocytopenia with nadir near day 7
- C-reactive protein concentration is generally elevated
- Liver function tests (LFTs): Increase in hepatic transaminases, lactate dehydrogenase, and alkaline phosphatase
- Elevated plasma creatinine concentration may be seen
- Serologic titer (IFA) >80 or fourfold increase in titer to antigen

IMAGING STUDIES

- Chest radiograph examination to show interstitial pneumonitis (unusual)
- MRI of the brain in cases of encephalitis

TREATMENT

ACUTE GENERAL Rx

- Immediate therapy to limit extent of acute illness and complication
- Doxycycline: 100 mg twice a day for 7 to 14 days is therapy of choice for adults and children >8 yr (4 mg/kg/day in 2 divided doses)
- Doxycycline is now recommended as well for children aged <8 yr (Redbook 2018)
- Rifampin: 300 mg twice a day for 7 to 10 days can be used in pregnancy and for children <8 yr at 10 mg/kg twice per day
- Most patients defervesce within 24 to 48 hr given appropriate treatment.

PROGNOSIS

Poor prognostic indicators include:
- Advanced age or immunosuppression
- Concomitant chronic illness (such as diabetes mellitus, collagen-vascular disease)
- Lack of diagnosis recognition
- Delayed onset of specific antibiotic therapy
- Concomitant HIV or organ transplant status

DISPOSITION

Repeat CBC every 2 to 4 wk until normal.

REFERRAL

For consultation with infectious diseases specialist in suspected cases

PEARLS & CONSIDERATIONS

- A new pathogenic *Ehrlichia* species, closely related to *E. muris,* has been identified in Minnesota and Wisconsin. Organism-specific PCR and serologic testing can be used for identification.
- Duration of time tick must be attached to produce illness as few as 4 hr.

- Delay in antibiotic treatment results in poorer outcome. Antibiotic treatment should be initiated as soon as infection is suspected.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Anaplasmosis (Patient Information)

AUTHOR: **Patricia Cristofaro, MD**

TABLE 1 Human Ehrlichioses and Anaplasmosis

	Human Monocytotropic Ehrlichiosis	Human Granulocytotropic Ehrlichiosis	Human Granulocytotropic Anaplasmosis
Former disease nomenclature	Human monocytic ehrlichiosis	Human granulocytic ehrlichiosis	Human granulocytic ehrlichiosis
Causative agent(s)	*Ehrlichia chaffeensis*	*Ehrlichia ewingii, Ehrlichia cani*—one asymptomatic human case reported in Venezuela	*Anaplasma phagocytophilum*
Leukocyte targets	Monocytic cell phagosomes	Neutrophil phagosomes	Granulocyte-neutrophil phagosomes
Tick vectors	*Amblyomma americanum* (lone star ticks)	*Amblyomma americanum* (lone star ticks), *Dermacentor variabilis* (American dog ticks)	*Ixodes persulcatus* complex (American deer ticks)—*I. scapularis, I. ricinus, I. pacificus*
Animal reservoirs	White-tailed deer, coyotes, dogs	White-tailed deer, dogs	Rodents, deer, ruminants, horses
U.S. regional distribution	Southeastern and south central United States	South central United States	Northeastern United States, upper Midwest, northern California
U.S. regional prevalence	2-5 cases/100,000	≤10% of presumed HME cases have *E. ewingii* infections in south central United States	50-60 cases/100,000; high seroprevalence rates in children (>20%) who have had subclinical infections
Seasonal occurrences	April-September, peaking in July	Spring-fall	May-July
Incubation periods (wk)	1-4	1-4	1-4
Modes of transmission	Tick bite, blood product transfusion	Tick bite, blood product transfusion	Tick bite, blood product transfusion, nosocomial
Frequently presenting clinical manifestations	Fever, malaise, headache, myalgias, rash in <40%	Same initial manifestations, but much milder, except in immunocompromised individuals	Fever, malaise, headache, myalgias; rarely rash
Laboratory abnormalities	Leukopenia, thrombocytopenia, transaminitis	Leukopenia, thrombocytopenia, transaminitis	More pronounced and prolonged leukopenia, thrombocytopenia, transaminitis
Potential complications, especially in immunocompromised individuals	Meningoencephalitis, acute renal and respiratory failure, hepatitis, myocarditis	Milder and less likely, except in patients immunocompromised by HIV/AIDS, organ transplantation, prolonged corticosteroid therapy	May be significant in immunocompromised patients with high fevers, seizures, confusion, hemorrhagic diathesis, rhabdomyolysis, shock, acute tubular necrosis, adult respiratory distress syndrome; some specific CNS complications may include eighth nerve palsy, brachial plexopathy, demyelinating polyneuropathy
Case-fatality rate (CFR)	3%, higher in immunocompromised individuals	No deaths reported	0.5%, higher CFR in immunocompromised individuals
Recommended confirmatory diagnostic tests	Wright-stained peripheral blood smears with characteristic intracytoplasmic morulae in monocytes, DNA detection by PCR assay, culture	Wright-stained peripheral blood smears with characteristic intracytoplasmic morulae in neutrophils, DNA detection by PCR	Wright-stained peripheral blood smears with characteristic intracytoplasmic aggregates in neutrophils, DNA detection by PCR assay, increased immunofluorescent antibodies in initial and paired serum samples
Current antibiotic resistance	Fluoroquinolones	Fluoroquinolones	Fluoroquinolones
Currently recommended antibiotic therapy, adults	Doxycycline, 100 mg PO bid, or tetracycline, 250-500 mg PO qid, for minimum of 3 days after defervescence to maximum of 14-21 days	Doxycycline, 100 mg PO bid, or tetracycline, 250-500 mg PO qid, for minimum of 3 days after defervescence to maximum of 14-21 days	Doxycycline, 100 mg PO bid, or tetracycline, 250-500 mg PO qid for minimum of 3 days after defervescence to maximum of 14-21 days
Currently recommended antibiotic therapy, children	Doxycycline, 4.4 mg/kg PO bid, or tetracycline, 25-50 mg/kg PO qid, for minimum of 3 days after defervescence to maximum of 14-21 days	Doxycycline, 4.4 mg/kg PO bid, or tetracycline, 25-50 mg/kg PO qid, for minimum of 3 days after defervescence to maximum of 14-21 days	Doxycycline, 4.4 mg/kg PO bid, or tetracycline, 25-50 mg/kg PO qid, for minimum of 3 days after defervescence to maximum of 14-21 days

bid, Twice daily; *CNS,* central nervous system; *DNA,* deoxyribonucleic acid; *HME,* human monocytotropic ehrlichiosis; *HIV/AIDS,* human immunodeficiency virus infection/acquired immunodeficiency syndrome; *PCR,* polymerase chain reaction; *PO,* by mouth; *qid,* four times a day.

From Bennett JE, et al.: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 8, Philadelphia, 2015, Saunders.

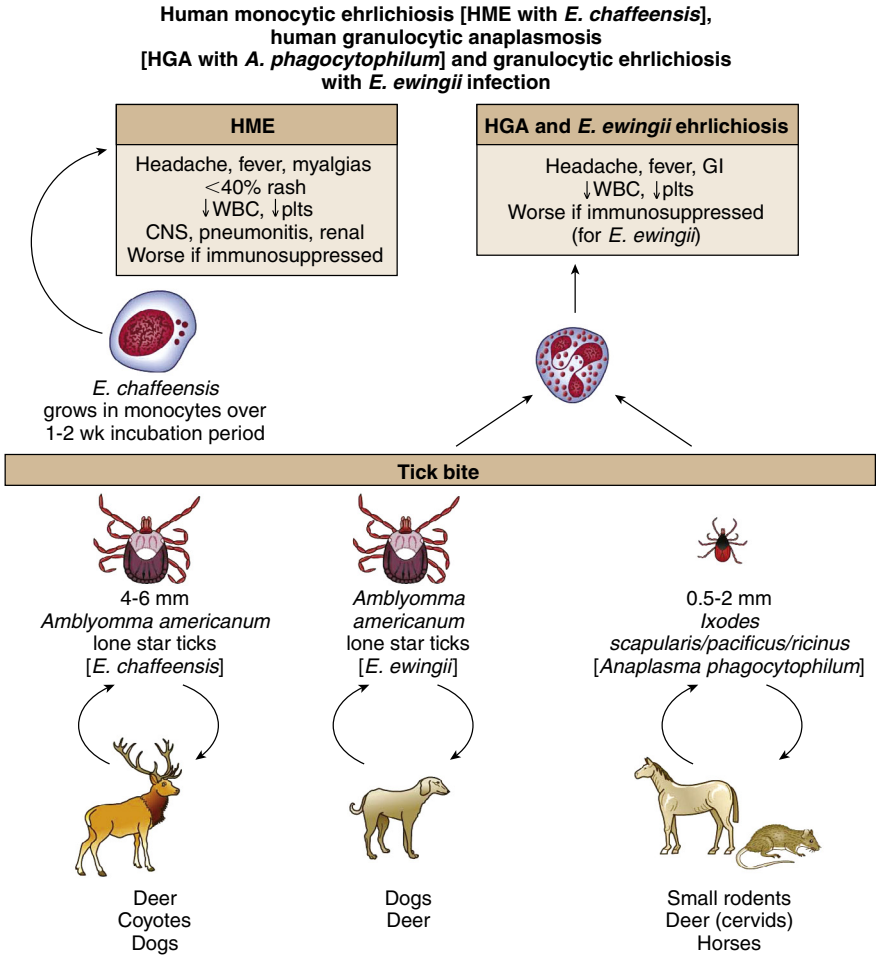

FIG. 1 Life cycles of human monocytic ehrlichiosis (*HME*, with *Ehrlichia chaffeensis*) and human granulocytic ehrlichiosis (anaplasmosis, *HGA* with *Anaplasma phagocytophilum*) or infection with *E. ewingii*. *CNS*, Central nervous system; *GI*, gastrointestinal; *WBC*, white blood cell count. (From Dumler JS: Ehrlichiosis and anaplasmosis. In Guerrant RL, Walker DH, Weller PF (eds): *Tropical infectious diseases: principles, pathogens and practice*, 3rd ed, Philadelphia, 2011, Elsevier, pp. 339-343.)

TABLE 2 Clinical Clues (History, Physical Examination, or Laboratory) Suggesting the Diagnosis of a Tick-Borne Illness Manifesting as a Nonspecific Febrile Illness*

Disease	Clues
Anaplasmosis	Faint rash possible Low white blood cell or platelet count Elevated hepatic transaminases
Babesiosis	Findings of hemolysis History of splenectomy Presence of faint rash, hepatomegaly, or splenomegaly
Lyme disease	Careful skin examination for any rash consistent with erythema migrans Bradycardia from heart block Associated seventh nerve palsy or lymphocytic meningitis
Colorado tick fever	Saddle-back fever curve
Rocky Mountain spotted fever	Maculopapular or petechial rash Normal white blood cell count or low platelet count Hyponatremia Peripheral edema
Relapsing fever	Recurring episodes of fever with afebrile intervals
Tularemia	Acrally located ulcer Regional lymphadenopathy Possible associated pneumonia

*Apart from an epidemiologic context suggesting a tick-borne disease.

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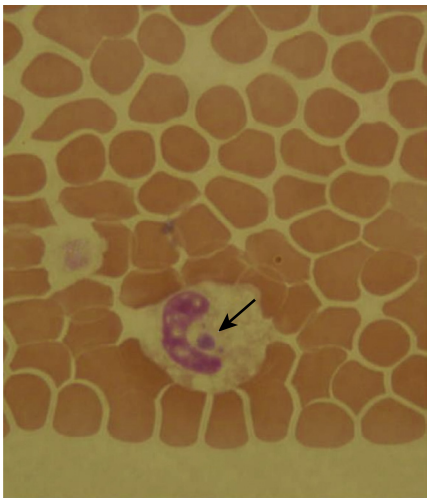

FIG. E2 White blood cells infected with the agent of human granulocytic ehrlichiosis (*Anaplasma phagocytophilum*). (Courtesy of Dr. Daniel Caplivski, Division of Infectious Diseases, Mount Sinai School of Medicine.)

TABLE E3 Diagnostic Tests for Human Monocytic Ehrlichiosis with the Corresponding Sensitivities and Specificities in Relation to Disease Course

Diagnostic Test	Time Course	Sensitivity (%)	Specificity (%)
Peripheral smear showing morulae	Early (first wk)	3-2	>90
Polymerase chain reaction (PCR)	Early (first wk)	55-87	99
Serology with immunofluorescence assay (IFA)	Late (after 7-14 days) and requires documented fourfold rise in 2-3 wk	94-100	99

From Hilal T, Snapp WK: The perils of country life: human monocytic ehrlichiosis, *Am J Med* 128(8), 2015.

BASIC INFORMATION

DEFINITION

Disorders of ejaculation and orgasm include premature ejaculation, delayed ejaculation, anejaculation, retrograde ejaculation, painful ejaculation, hematospermia, and anorgasmia. Premature ejaculation refers to ejaculation that occurs sooner than desired, while delayed ejaculation refers to ejaculation that occurs after prolonged sexual stimulation. Anejaculation is the absence of semen propulsion from the urethra, with or without orgasm. Retrograde ejaculation is the backward flow of semen into the bladder. Hematospermia is the appearance of blood in the ejaculate. Anorgasmia is the inability to achieve orgasm despite sexual stimulation.

SYNONYMS

Ejaculatory dysfunction
Anejaculation
Anorgasmia
Aspermia
Dry orgasm
Dry ejaculate
Failure of emission

ICD-10CM CODES

R36.1	Hematospermia; Bloody ejaculation
F52.4	Premature ejaculation
F52.32	Male orgasmic disorder; Inhibited male orgasm; Anorgasmia
N53.11	Delayed ejaculation; Retarded ejaculation
N53.12	Painful ejaculation
N53.13	Anejaculatory orgasm; Anejaculation
N53.14	Retrograde ejaculation
N53.19	Other ejaculatory dysfunction

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Not well understood, due to variability in definitions and reporting.

PEAK INCIDENCE: Not well understood. Ejaculatory and orgasmic disorders may be primary (lifelong) if the condition has always been present, or secondary (acquired) if the condition developed after a period of normal function.

PREVALENCE: Premature ejaculation is the most prevalent male sexual complaint, affecting up to 30% of men. Delayed ejaculation is the least commonly reported, least studied, and least understood of the male sexual dysfunctions, with a prevalence rate of 1% to 5% according to some studies.

PREDOMINANT SEX AND AGE: These disorders have been reported among men aged 18 to 70 yr.

GENETICS: No known genetic predisposition.

RISK FACTORS: Men with ejaculatory dysfunction of any type usually indicate higher levels of relationship stress, sexual dissatisfaction, anxiety about sexual performance, and general health issues, compared to sexually functional men.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Premature ejaculation: Ejaculation occurs sooner than desired, often within 1 minute of penetration. Physical examination is normal. Up to 30% of patients may report concomitant erectile dysfunction.
- Delayed ejaculation: Ejaculation requires prolonged sexual stimulation, often 25 minutes or longer. Physical examination is normal.
- Anejaculation: No ejaculate (neither antegrade nor retrograde) is produced during orgasm, or the patient may not be able to achieve orgasm. Physical findings may reveal nervous system dysfunction (e.g., spinal cord injury); may present with infertility.
- Retrograde ejaculation: Little or no ejaculate is expelled out of the urethra at orgasm. Patients may report cloudy postcoital urine. Physical examination is usually normal; may present with infertility.
- Painful ejaculation: Urethral, perineal, scrotal, or testicular pain during or shortly after ejaculation. Physical examination is often normal but may demonstrate tenderness with palpation of external genitalia, or with digital rectal examination.
- Hematospermia: Reddish-brown ejaculate, usually painless. Physical findings are usually unremarkable; not associated with malignancy.
- Anorgasmia: The inability to achieve orgasm, despite adequate stimulation. Patients will not experience perineal contractions nor the pleasurable sensation associated with normal orgasm. Physical findings are usually unremarkable.

ETIOLOGY

- Premature and delayed ejaculation represent opposite ends of the spectrum of ejaculatory disorders. The underlying etiology is complex and multifactorial, and includes organic and psychogenic contributions. Box E1 summarizes the recommended and optional questions to establish the diagnosis of delayed ejaculation and to direct treatment.
- Anejaculation may result from pelvic surgery, trauma, or radiation; from neurologic sequalae of Parkinson disease, multiple sclerosis, spinal cord injury, or diabetes mellitus; from bilateral ejaculatory duct obstruction; or from psychological stress and anxiety.
- Retrograde ejaculation is most commonly caused by the use of medications (e.g., alpha-blockers) or surgical procedures (e.g., transurethral resection of prostate) that relax or disrupt the bladder neck. It can also result from retroperitoneal surgery, diabetes mellitus, and the previously mentioned neurologic diseases. Box 2 summarizes the causes of retrograde ejaculation, delayed ejaculation, anejaculation, and anorgasmia.
- Causes of painful ejaculation may be infectious (e.g., epididymo-orchitis, urethritis, prostatitis), obstructive (e.g., vasectomy, prostatectomy, hernia repair), nervous/musculoskeletal, or psychological. Temporary painful ejaculation is common after radical prostatectomy but usually resolves over time.
- Hematospermia is usually idiopathic, but may be secondary to prolonged abstinence, or due to infection or inflammation of the genitourinary tract.
- Anorgasmia may be caused by spinal cord injury, hormonal dysfunction, psychological factors, dysfunctional sexual techniques, or medications, particularly serotonin reuptake inhibitors.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Erectile dysfunction
- Hypogonadism
- Ejaculatory duct obstruction
- Urethral stricture disease
- Urethritis or sexually transmitted infection

LABORATORY TESTS

- For a low-volume ejaculate, post-ejaculate urine may be evaluated for the presence of spermatozoa to differentiate between failure of emission and retrograde ejaculation.
- Hematuria, in the setting of hematospermia or painful ejaculation, may signal an underlying inflammatory disorder or a malignancy and should prompt a complete evaluation.
- A fasting blood glucose or hemoglobin A1c test may be considered if diabetes is suspected as a cause of lack of emission or retrograde ejaculation.
- Urinalysis, urine culture, and screening for sexually transmitted diseases, when indicated, can rule out an infectious etiology of painful ejaculation.

IMAGING STUDIES

Transrectal ultrasonography or pelvic MRI can detect an ejaculatory duct obstruction or absence of the seminal vesicles. While not routinely used in the evaluation of ejaculatory and orgasmic disorders, they may be useful with persistently painful ejaculation

TREATMENT

NONPHARMACOLOGIC THERAPY

- Premature ejaculation can improve with psychotherapy and behavioral interventions (e.g., "coronal squeeze" or "start-and-stop" technique) and effective partner communication. These approaches may be more effective when combined with pharmacologic therapy.
- Retrograde ejaculation and anejaculation do not require treatment unless fertility is desired.
- In the setting of retrograde ejaculation, viable sperm can be recovered from the post-ejaculate urine and used for intrauterine insemination or in vitro fertilization.
- Idiopathic hematospermia may be followed expectantly and is usually self-limited to 10 or 15 ejaculations.

BOX 2 Causes of Retrograde Ejaculation, Delayed Ejaculation, Anejaculation, and Anorgasmia

Aging Male
Degeneration of penile afferent nerves

Psychogenic
Inhibited ejaculation

Congenital
Müllerian duct cyst
Wolffian duct abnormality
Prune belly syndrome

Anatomic Causes
Transurethral resection of prostate
Bladder neck incision

Neurogenic Causes
Diabetic autonomic neuropathy
Multiple sclerosis
Spinal cord injury
Radical prostatectomy
Retroperitoneal lymph node dissection
Proctocolectomy
Bilateral sympathectomy
Abdominal aortic aneurysmectomy
Para-aortic lymphadenectomy

Infectious
Urethritis
Genitourinary tuberculosis
Schistosomiasis

Endocrine
Hypogonadism
Hypothyroidism

Medication
α-Methyldopa
Alpha blockers
Thiazide diuretics
Tricyclic and SSRI antidepressants
Phenothiazine
Alcohol abuse

SSRI, Selective serotonin reuptake inhibitor.
From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

- Delayed ejaculation or anorgasmia caused by serotonin reuptake inhibitors usually improves with withdrawal of the medication. Sexual therapy and counseling can improve these conditions if they are caused by dysfunctional sexual techniques or psychological issues. Vibratory or electrical stimulation of emission is helpful in selected cases.
- Painful ejaculation that is myofascial rather than infectious in origin may benefit from pelvic floor physical therapy.
- Fig. E1 illustrates an algorithm for the management of delayed ejaculation, anejaculation, and anorgasmia. Drug therapy for delayed ejaculation and anejaculation is summarized in Table E1.

ACUTE GENERAL Rx

- Premature ejaculation: Selective serotonin reuptake inhibitors (SSRI) (e.g., sertraline, fluoxetine) and the tricyclic antidepressant clomipramine can successfully delay ejaculation when taken daily. Dapoxetine, a short-acting SSRI, may be used as an "on-demand" treatment for premature ejaculation (not available in the U.S.). Topical anesthetics such as lidocaine cream and topical sprays have been used with variable success. A meter-dosed lidocaine-prilocaine spray gained approval for use in Europe in 2017. The use of phosphodiesterase inhibitors (PDE5i) (e.g., sildenafil, vardenafil, tadalafil) with SSRIs may be beneficial in men with concomitant erectile dysfunction and premature ejaculation. Table E2 summarizes drug therapy for premature ejaculation.
- Retrograde ejaculation: Pharmacologic therapy is only effective in patients without an anatomic disturbance of the bladder neck. Sympathomimetic medications (phenylpropanolamine, ephedrine, pseudoephedrine) and imipramine may be useful in converting retrograde ejaculation to antegrade ejaculation.
- Antimicrobial treatment for infections, NSAIDs, and muscle relaxants may help decrease discomfort associated with painful ejaculation.
- The use of the pharmacologic therapies listed above for the treatment of various disorders of ejaculation is strictly off label in the U.S. and does not carry FDA approval.
- Fig. E2 illustrates an algorithm for the office management of premature ejaculation.

CHRONIC Rx

Rarely, painful ejaculation due to long-standing obstructive causes may show improvement with surgical intervention (e.g., vasectomy reversal). The pharmacologic therapies listed above can also be used for the chronic treatment of disorders of ejaculation and orgasm.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- A variety of nutritional supplements and herbs have been used for the treatment of erectile dysfunction, but their benefit for the specific treatment of ejaculation and orgasm disorders is unknown.
- Acupuncture and traditional Chinese medicine may be helpful in treating underlying hormonal imbalances.
- Yoga and meditation can reduce the effects of stress and relieve anxiety about sexual dysfunction.
- Therapeutic massage can decrease stress.

DISPOSITION

Prognosis varies with etiology. Ejaculatory dysfunction attributable to sexual techniques, psychological issues, or pelvic floor musculature can improve with psychotherapy or physiotherapy. Pharmacologic treatment may be helpful in treating premature, retrograde, or painful ejaculation.

REFERRAL

All fertility issues and suspected anatomic problems should be referred to a urologist. Professional psychotherapy should be considered for appropriate patients.

PEARLS AND CONSIDERATIONS

COMMENTS

Ejaculatory and orgasmic disorders are common male sexual dysfunctions and include premature ejaculation, delayed ejaculation, anejaculation, retrograde ejaculation, painful ejaculation, hematospermia, and anorgasmia. Physical exam is usually normal.

PREVENTION

Preventing sexually transmitted infections and treating other inflammatory disorders of the genitourinary tract may be of some benefit in reducing the incidence of these sexual disorders.

PATIENT & FAMILY EDUCATION

These sexual disorders can exert a significant psychological burden on affected men and their partners. A combination of pharmacologic and nonpharmacologic therapies, including a urologic and psychologic evaluation, when indicated, may be helpful in the treatment of these complaints.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Erectile Dysfunction (Patient Information)
Premature Ejaculation (Patient Information)
Erectile Dysfunction (Related Key Topic)

AUTHORS: **David Guo, MD,** and **Mark Sigman, MD**

SUGGESTED READINGS

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Althof SE, McMahon CG: Contemporary management of disorders of male orgasm and ejaculation, *Urology* 93(9-21), 2016.

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Jenkins LC, Mulhall JP: Delayed orgasm and anorgasmia, *Fertil Steril* 104(5):1082-1088, 2015.

Porst H, Burri A: Fortacin spray for the treatment of premature ejaculation, *Urologia* 84(2 Suppl):1-10, 2017, https://doi.org/10.5301/uj.5000275.

BOX E1 Recommended and Optional Questions to Establish the Diagnosis of Delayed Ejaculation (DE) and Direct Treatment

Recommended Questions for Diagnosis of DE

For Diagnosis

What proportion of the time can you ejaculate during sexual intercourse?
During intercourse, how long after penetration does it take for you to ejaculate?
When you cannot ejaculate during sexual intercourse, how often do you feel that you are close to ejaculation?
If you cannot ejaculate, why do you stop intercourse?
Do you ever feel that you have ejaculated, but fail to release semen?
Do you feel bothered, annoyed, and/or frustrated by your DE?
How often can you ejaculate during masturbation by yourself or with your partner?

Optional Questions

Differentiate Lifelong and Acquired DE

When did you first experience DE?
Have you experienced DE since your first sexual experience on every/almost every attempt and with every partner?

Assess Erectile Function

Is your erection hard enough for penetration?
Do you have difficulty in maintaining your erection during intercourse?
During masturbation, are you able to achieve an erection that is hard enough for penetration?
Do you wake up at night or in the morning with an erection that is hard enough for penetration?

Assess Relationship Impact

How upset is your partner with your DE?
Do you or your partner avoid sexual intercourse?
Is your DE affecting your overall relationship?

Previous Treatment

Have you received any medial or psychological treatment for your DE?

Impact on Quality of Life

Do you feel anxious, depressed, or embarrassed because of your DE?

From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

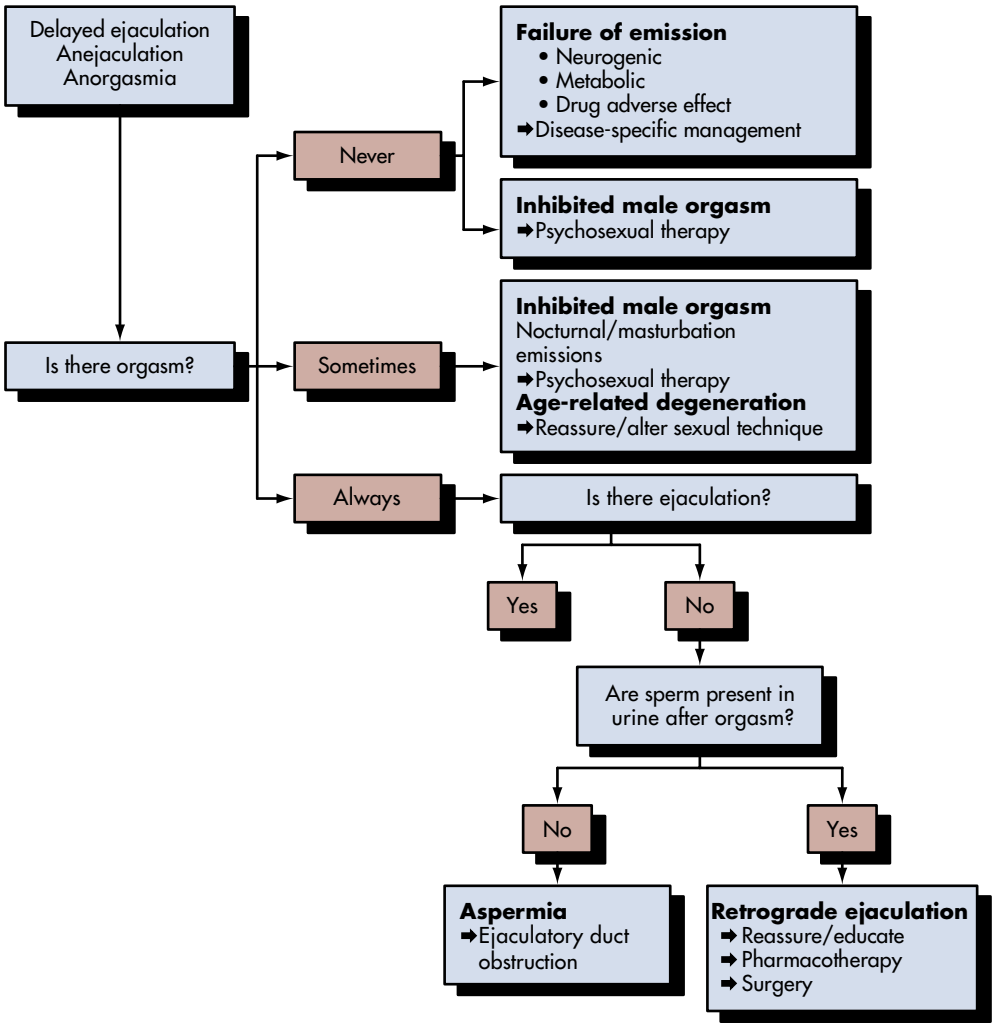

FIG. E1 Algorithm for the office management of premature ejaculation (PE). (From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.)

TABLE E1 Drug Therapy for Delayed Ejaculation and Anejaculation

	Dosage	
Drug	**As Needed**	**Daily**
Cabergoline	—	0.5-2 mg every 3 days
Amantadine	100-400 mg (for 2 days before coitus)	100-200 mg twice daily
Pseudoephedrine	60-120 mg (1-2 hr before coitus)	—
Reboxetine	—	4-8 mg
Oxytocin	24 IU intranasal during coitus	—
Bupropion	—	150 mg/day or twice daily
Buspirone	—	5-15 mg twice daily
Cyproheptadine	4-12 mg (3-4 hr before coitus)	—

From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

TABLE E2 Drug Therapy for Premature Ejaculation (PE)

Drug	Dose	Dosing Instructions	Indication	Comments	Level of Evidence
Dapoxetine	30-60 mg	On demand, 1-3 hr before intercourse	Lifelong PE Acquired PE	Approved in >50 countries	High
Paroxetine	10-40 mg	Once daily or 4-5 hours prior to sexual activity	Lifelong PE Acquired PE		High
Sertraline	50-200 mg	Once daily or 4-5 hours prior to sexual activity	Lifelong PE Acquired PE		High
Fluoxetine	20-40 mg	Once daily or 4-5 hours prior to sexual activity	Lifelong PE Acquired PE		High
Citalopram	20-40 mg	Once daily	Lifelong PE Acquired PE		High
Clomipramine	12.5-50 mg	Once daily	Lifelong PE Acquired PE		High
	12.5-50 mg	On demand, 3-4 hr before intercourse	Lifelong PE Acquired PE		High
Tramadol	25-50 mg	On demand, 3-4 hr before intercourse	Lifelong PE Acquired PE	Potential risk for opiate addiction	Low
Topical lignocaine/prilocaine	Patient titrated	On demand, 20-30 min before intercourse	Lifelong PE Acquired PE		High
Alprostadil	5-20 μg	Patient administered intracavernous injection 5 min before intercourse	Lifelong PE Acquired PE	Risk for priapism and corporal fibrosis	Very low
PDE5 inhibitors	Sildenafil 25-100 mg Tadalafil 10-20 mg Vardenafil 10-20 mg	On demand, 30-50 min before intercourse	Lifelong and acquired PE in men with normal erectile function		Very low
			Lifelong and acquired PE in men with ED	? Improved efficacy if combined with SSRI	Moderate

ED, Erectile dysfunction; *PDE5*, phosphodiesterase type 5; *SSRI*, selective serotonin reuptake inhibitor.
From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

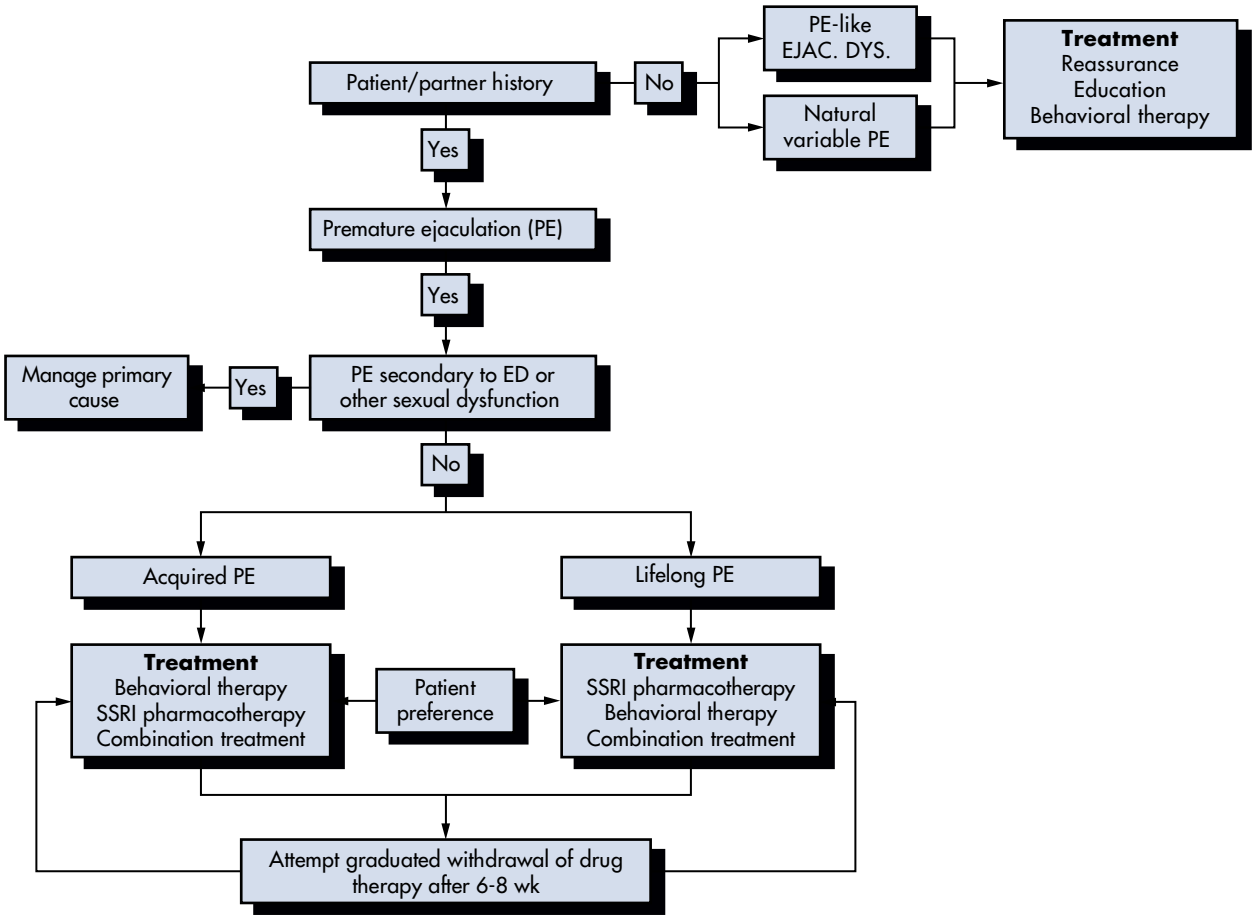

FIG. E2 Algorithm for the office management of premature ejaculation (PE). *ED*, Erectile dysfunction; *EJAC DYS*, ejaculation dysfunction; *SSRI*, selective serotonin reuptake inhibitor. (From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Elder abuse consists of actions that cause harm committed by someone in a trust relationship whether in the community or institutional setting.

- Physical abuse: Inflicting physical pain or injury
- Sexual abuse: Inflicting nonconsensual sexual activity
- Psychological abuse: Inflicting mental anguish, including intimidation, humiliation, or threats
- Financial abuse: Improper use of resources, property, or assets without the person's consent
- Neglect: Abandonment, failure to fulfill a care-taking obligation, including provision of food, safe shelter, physical health and mental health care, or basic custodial care
- Box E1 summarizes definitions of types of abuse, with examples of behavior and effects

SYNONYMS

Battered elder syndrome
Elder mistreatment
Domestic violence in the elderly
Diogenes syndrome
Intimate partner violence (IPV)

Adult abuse, neglect, and maltreatment cover a range of diagnostic codes depending on whether the issue is confirmed or suspected and whether the problem is neglect, physical, psychological, or sexual. The DSM-5 includes these codes under other conditions that may be a focus of clinical attention.

Core Codes:

ICD-10CM CODES

T74 and T76	Abuse, neglect, and other maltreatment
T74.0 and T76.0	Neglect or abandonment
T74.1 and T76.1	Physical abuse
T74.2 and T76.2	Sexual abuse
T74.3 and T76.3	Psychological abuse
T74.9 and T76.9	Unspecified adult maltreatment

DSM-5 CODES

Depends on specific diagnosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: As many as 5,000,000 elders are abused annually in the U.S.

PEAK INCIDENCE: >75 yr; more recent studies now suggest <75 yr

PREVALENCE:

- About 10% of those 60 yr or older have been abused.
- Emotional followed by financial abuse are the most common forms.
- 12-mo U.S. prevalence rates: Emotional abuse 9.0% and 4.6%; physical abuse 0.2% and 1.6%; sexual abuse 0.6%; neglect 0.5%; and financial abuse 3.5% and 5.2%.
- Family members reported 21% of nursing home residents were neglected on one or more occasion in the past 12 mo, and over 24% had been subjected to physical abuse during their entire stay.
- Among caregivers of patients with dementia in the U.K., one half reported behaving abusively at least some of the time, and one third reported "important" levels of abuse. Verbal abuse was common and physical abuse was rare.
- Elder abuse is associated with increased risk of mortality, with the highest for caregiver neglect, functional impairment, and greater emotional distress, including depression, anxiety, and posttraumatic stress.
- Adult intimate partner violence perpetrators are significantly more likely to have witnessed intimate partner violence as a child than non perpetrators.
- Older women are more likely than older men to be victims of abuse.

RISK FACTORS (VICTIM):

- Impaired cognition
- Behavioral problems
- Psychiatric illness or psychological problems
- Mental or physical dependence
- Poor physical health or frailty
- Trauma or past abuse
- Shared living situation and premorbid relationship with abuser
- Social isolation and poor social support
- Low household income

RISK FACTORS (PERPETRATOR):

- Relationship conflict with the victim
- Substance abuse, mental illness, particularly depression
- Caregiver burden or stress, being an involuntary caregiver, overwhelmed or resentful

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical abuse with multiple injuries at various stages with implausible descriptions of their origins
- Fear, hypervigilance, or withdrawal
- Evidence of poor nutrition, dehydration, poor hygiene, multiple or neglected pressure ulcers, genital or anal pain, neglected medical conditions, or evidence of restraint use (bruises around wrists or ankles)
- Toxicologic evidence of unprescribed medications
- Poor adherence, frequent no-shows, or little contact with health care system
- Caregiver not allowing interviewing the patient alone

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Dementia
- Depression, substance misuse, posttraumatic stress disorder (PTSD), or other psychiatric disorder

BOX E1 Definitions of Types of Abuse, with Examples of Behavior and Effects

- **Physical abuse:** Nonaccidental infliction of physical force that results in bodily injury, pain, or impairment
  - *Examples of behavior:* Hitting, slapping, pushing, burning, physical restraint
  - *Examples of effects:* Bruises, fractures, burns, broken teeth, sprains, cuts, hair loss, bleeding from scalp, fear, anxiety, depression
- **Psychological abuse:** The persistent use of threats, humiliation, bullying, swearing and other verbal conduct, and/or of any other form of mental cruelty that results in mental or physical distress
  - *Examples of behavior:* Treating an older person as a child, blaming, swearing, intimidating, name-calling, threatening violence, isolating older person
  - *Examples of effects:* Fear, depression, confusion, loss of sleep, loss of appetite
- **Financial abuse:** Unauthorized and improper use of funds, property, or any resources of an older person
  - *Examples of behavior:* Misappropriating money, valuables, or property; forcing changes to will; denying access to personal funds
  - *Examples of effects:* Loss of money, etc., inability to pay bills, deterioration in health or standard of living, lack of amenities, unusual activity in bank accounts, signatures on documents uncertain, lack of solid arrangements for financial management, eviction or house sale notices
- **Sexual abuse:** Direct or indirect involvement in sexual activity without consent
  - *Examples of behavior*:
    - *Noncontact:* Looking, photography, indecent exposure, harassment, serious teasing or innuendo, pornography
    - *Contact:* Touching breast, genitals, anus, mouth; masturbation of either or both persons; penetration or attempted penetration of vagina, anus, mouth, with or by penis, fingers, other objects
  - *Examples of effects*: Difficulty in walking or sitting, bruises, bleeding, venereal disease, psychological trauma
- **Neglect:** Repeated deprivation of assistance needed by the older person for important activities of daily living
  - *Examples of behavior:* Failure to provide food, shelter, clothing, medical care, hygiene, personal care; inappropriate use of medication or overmedication
  - *Examples of effects:* Malnutrition, pressure ulcers, oversedation, untreated medical problems, depression, confusion

From Fillet HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

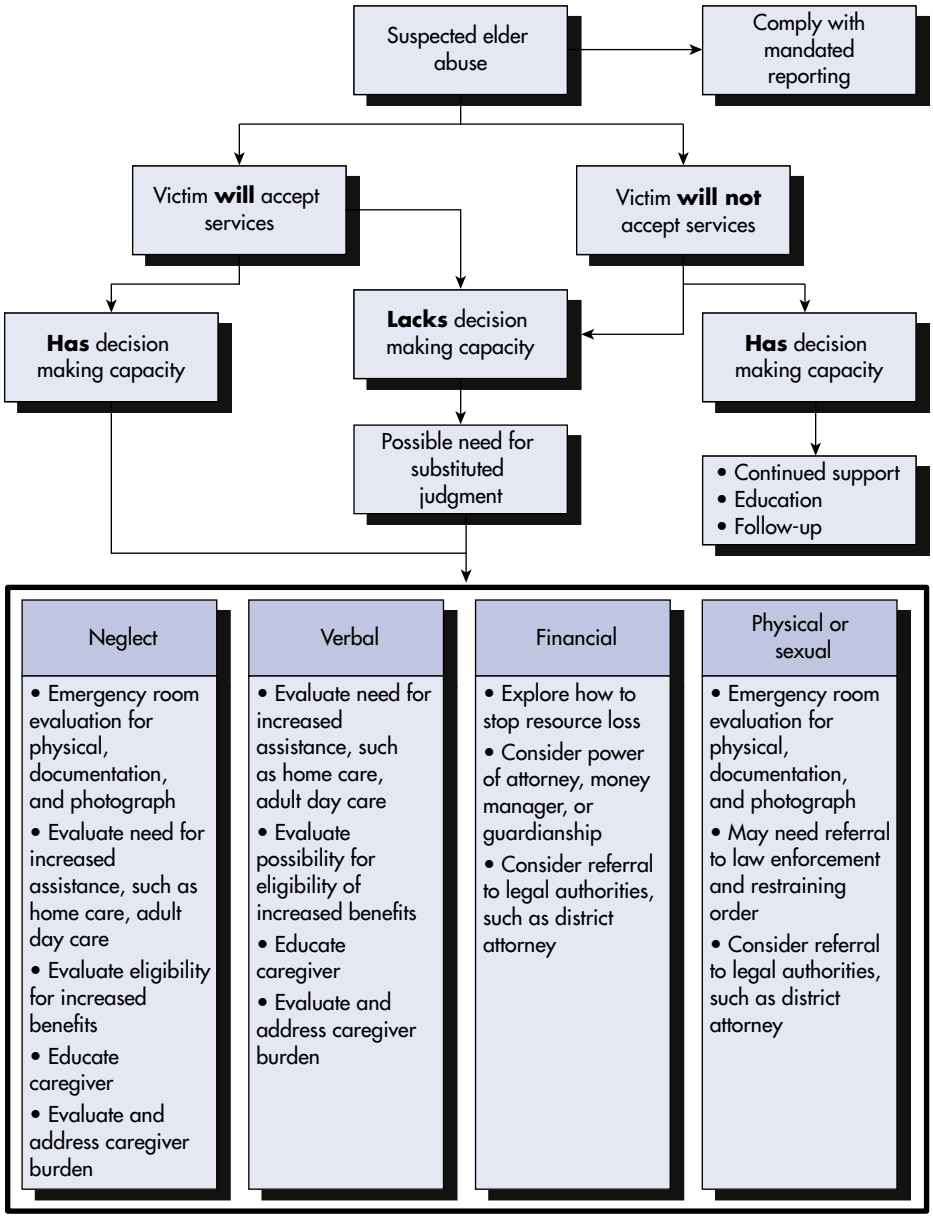

FIG. E1 Management of elder abuse. (Adapted from Kohn R, Warner J, Murphy E, Verhoek-Oftedahl W: Elder abuse. In Holzer JC, Kohn R, Recupero PR, Ellison JM [eds]: *Textbook of geriatric forensic psychiatry*, New York, 2018, Oxford University Press.)

- Malnutrition from intrinsic causes
- Nonadherence to medical treatment
- Relationship distress
- Falling

WORKUP

- Ask direct specific questions such as:
  1. "Has anyone close to you called you names or put you down recently?"
  2. "Are you afraid of anyone who lives with you or cares for you?"
  3. "Has anyone at home ever hurt you?"
  4. "Has anyone touched you without your consent?"
  5. "Has anyone forced you to do things you didn't want to do?"
  6. "Has anyone taken things or money that belong to you without your OK?"
  7. "Have you signed any documents that you don't understand?"
  8. "Are you often alone?"
  9. "When you need help has anyone ever failed to help you take care of yourself?"
  10. If appropriate, ask, "Have you been abused?"
- Interview patient and alleged perpetrator separately.
- Pelvic examination if sexual abuse suspected.
- Take photographs of physical injuries as legal evidence.

LABORATORY TESTS & IMAGING STUDIES

- Screen for dehydration, malnutrition, and rhabdomyolysis.
- Toxicology screens and therapeutic drug monitoring are sometimes helpful.
- Other tests and radiology according to presentation.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Separate patient and abuser.
- Patient and caregiver may benefit from psychiatric evaluation and treatment for substance abuse, mental illness, or cognitive impairment.
- If appropriate, assess the patient's capacity.
- Fig. E1 describes a management algorithm for elder abuse.

ACUTE GENERAL Rx

- As indicated for injury or pain relief
- As indicated for mental disorders, dementia, or delirium

DISPOSITION

If the patient's level of disability does not allow independent living, institutionalization may be required. Guidelines vary at the state and county levels regarding guardianship and conservatorship requirements.

REFERRAL

- For outpatients, report to local adult protective services agency. Reporting is mandatory in most states.
- Resident-to-resident elder mistreatment (R-REM) in nursing homes is highly prevalent. For nursing home patients, report to regional long-term care ombudsman. Reporting is mandatory under federal law.
- Mental health services may be needed.

PEARLS & CONSIDERATIONS

COMMENTS

Care should be taken in interacting with the alleged abuser so that access to the victim is not lost.

PREVENTION

- Offer social services (e.g., respite care or homecare) for stressed caregivers.
- Make financial arrangements and arrange durable power of attorney for health care and finances while patient is still cognitively intact.

PATIENT & FAMILY EDUCATION

In the U.S., the elder care help line is 1-800-677-1116.
National Center on Elder Abuse: www.ncea.aoa.gov
National Domestic Violence Hotline: 800-799-7233 or 800-799-SAFE
TTY: 800-787-3224
CDC: Violence Prevention
www.cdc.gov/violenceprevention/intimatepartnerviolence

RELATED CONTENT

Elder Abuse (Patient Information)

AUTHOR: **Robert Kohn, MD**

SUGGESTED READINGS

Burnes D et al: Prevalence of financial fraud and scams among older adults in the United States: a systematic review and meta-analysis, *Am J Public Health* 107:e13-e21, 2017.
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Gibbs LM, Mosqueda L: Medical implications of elder abuse and neglect, *Clin Geriatr Med* 30:671-902, 2014.
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Miller E, McCaw B: Intimate partner violence, *N Engl J Med* 380(9):850-857, 2019.
Pillemer K et al: Elder abuse: global situation, risk factors, and prevention strategies, *Gerontologist* 56(Suppl 2):S194-S205, 2016.

Electrical and Lightning Injury PTG

BASIC INFORMATION

DEFINITION

Injuries or wounds that occur as a result of contact with an electrical current or lightning.

ICD-10CM CODES	
W87	Exposure to unspecified electric current
W86	Exposure to other specified electric current
W85	Exposure to electric transmission lines
X33	Victim of lightning
T75.4XXA	Electrocution, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

- Causes approximately 1000 deaths annually, with two thirds occurring in persons between ages 15 and 40 yr.
- Most electrical injuries in children occur at home (e.g., oral burns from electrical appliances).
- Most electrical injuries in adults are occupationally related. They rank fifth as a cause of occupational death.
- Account for 4% to 6.5% of all admissions to burn units.
- Lightning strikes kill on average 100 people annually.
  1. Eight of every 10 lightning strike victims are male; 75% of lightning deaths in the U.S. occur in the South and Midwest.
  2. 25% of lightning deaths are work related.
- Electronic weapons (stun gun and Taser) are capable of causing fatal cardiac arrhythmias.
- Table E1 compares lightning injuries with high-voltage electrical injuries.

TABLE E1 Lightning Injuries Compared with High-Voltage Electrical Injuries

Factor	Lightning	High Voltage
Energy level	30 million volts, 50,000 Å	Usually much lower*
Time of exposure	Brief, instantaneous	Seconds
Pathway	Flashover, orifice	Deep, internal
Burns	Superficial, minor	Deep, major injury
Renal	Rare myoglobinuria or hemoglobinuria	Myoglobinuric renal failure common
Fasciotomy	Rarely if ever necessary	Common, early, and extensive
Blunt injury	Explosive thunder effect	Falls, being thrown

*Range is 500 V up to millions of volts in transmission lines.
From Auerbach P: *Wilderness medicine, expert consult.* Premium Edition—Enhanced Online Features and Print, Philadelphia, 2012, Saunders.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Cognitive changes: Depending on the extent of injury, the patient may be unconscious, seizing, or confused and unable to present a history
- Extensive skin burns (>10% of the body surface):
  1. Located over the entry and exit sites (Fig. E1)
  2. Most common entry sites are the hands (Fig. E2) and skull
  3. Most common exit sites are the heels
  4. "Kissing burns" over the flexor creases
  5. Oral burns are common in children; bleeding from the labial artery may present 7 to 10 days after the injury
  6. Charring at the contact site (Figs. E3 and E4)
- Asystole or ventricular fibrillation may be the initial cardiac rhythm
- Bone fractures and periosteal burns
- Compartment syndrome from severe muscle tissue damage
- Headaches, memory disturbances
- Weakness and paresthesias
- Otologic injury, conductive hearing loss from tympanic membrane rupture or ossicular disruption
- Rhabdomyolysis and myoglobin-induced acute tubular necrosis
- Vascular injury from coagulation of small vessels or compartment syndrome

FIG. E1 The arborescent current markings on the face, neck, and anterior trunk of this young patient, which are characteristic of lightning injury, healed without the need for grafting. Note the focal lesions on the right arm, indicating the spread of the current that produced the marks on the right anterolateral aspect of the chest wall. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

- Box E1 summarizes the immediate and delayed effects of lightning injuries
- Tables E2 and E3 describe examples of acute and late direct electrical injury organ tissue dysfunction
- Table E4 compares lightning, high-voltage, and low-voltage electrical injury

ETIOLOGY

- Electricity causes tissue injury by converting electrical energy into heat or by blunt trauma from being thrown from the electrical source or from continuous muscle contraction (tetany).
- The effects of electricity are determined by seven factors: (1) type of current, (2) amount of current, (3) pathway of current, (4) duration, (5) area of contact, (6) resistance of the body, and (7) voltage.
- Tissue damage is greater with higher voltage and longer duration of contact.
- Direct current (DC) contact causes a single muscle contraction, throwing the patient away from the source. Alternating current (AC) contact precipitates a tetanic contraction, not allowing the patient to withdraw from the source and prolonging the duration of contact. AC contact is more ominous than DC contact.
- Electrical injuries are arbitrarily divided into high-voltage (>1000 volts) and low-voltage (<1000 volts) burns. Low-voltage burns involve almost exclusively either the hands or oral cavity. High-voltage injuries have a wide variety of systemic manifestations.
- The entry and exit path of the electrical current determines which tissues are affected.
- Box E2 describes the mechanisms of lightning injury.

DIAGNOSIS

WORKUP

Physical examination may not reveal the extent of damage that has occurred. Detailed testing to determine the extent of internal organ damage is indicated. In lightning injuries, male victims may have scrotal (on the undersurface of the scrotum) and penile burns, which may often be overlooked. Hemorrhage behind the eardrum with or without perforation is not uncommon. An otoscopic examination is indicated in all lightning-strike victims.

LABORATORY TESTS

- Complete blood count
- Blood chemistry profile including electrolytes
- Blood urea nitrogen and creatinine
- Arterial blood gas analysis
- Myoglobin
- Creatinine kinase with isoenzyme fractionation
- Urinalysis, including screening for myoglobinuria
- Liver function tests
- Type and cross-match
- ECG

FIG. E2 A, A farmer working in the field came in direct contact with a low-hanging wire (7000 V). **B,** An electrician grabbed a cable (270 V, alternating current) overhead to avoid falling into a ditch. **C** and **D,** A lineman touched a power line (7620 V, alternating current). (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

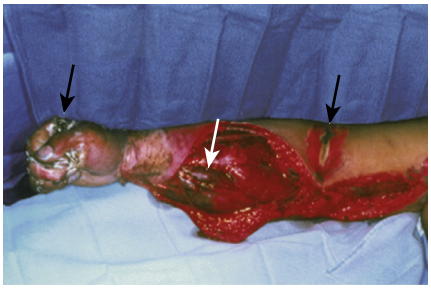

FIG. E3 Charring at the contact site in the first web space and at the site of arcing in the antecubital space *(black arrows)* of a victim of electric injury. The fixed flexion deformity of the thumb and other digits is characteristic of severe high-voltage injury to the hand and forearm. The severity of the injury is indicated by the marked edema of the forearm muscles, bulging above the cut edges of the fasciotomy incision, and the patchy dark discoloration of the muscles of the arm and the forearm, particularly the deeper muscle exposed in the central portion of the forearm incision *(white arrow).* (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

FIG. E4 High-voltage electrical injury. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

IMAGING STUDIES

- Radiographs: Any suspicious area for bone fractures
- CT scan of the head and cervical spine in patients with suspected head injury, coma, or neurologic deficit

BOX E1 Lightning Injuries

Immediate
- Cardiac arrest and cardiac injuries
- Pulmonary injuries
- Neurologic signs
- Seizures
- Deafness
- Confusion, amnesia
- Blindness
- Dizziness
- Contusion from shock wave
- Chest pain, muscle aches
- Tympanic membrane rupture
- Headache, nausea, postconcussion syndrome

Delayed
- Neurologic symptoms and signs
- Neuropsychological changes
- Memory deficits
- Attention deficit
- Coding and retrieval problems
- Distractibility
- Personality changes
- Irritability
- Chronic pain
- Seizures

From Auerbach P: *Wilderness medicine, expert consult.* Premium Edition—Enhanced Online Features and Print, Philadelphia, 2012, Saunders.

TABLE E2 Examples of Acute, Direct Electrical Injury Organ Tissue Dysfunction

Tissue	Acute Effects
Heart	Asystole, arrhythmia, cardiac tissue necrosis (myocardium, nodal tissue, conduction pathways, coronary arteries)
Central nervous system	Brainstem dysfunction, central apnea, loss of consciousness, seizure, confusion, amnesia, cranial nerve deficits, spine fracture, paralysis or keraunoparalysis, spinal cord transection, visual and hearing disturbances, tympanic membrane rupture
Muscle	Tetany: Rhabdomyolysis, lactic acidosis, bone stress fracture, "locking-on" phenomenon

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

TABLE E3 Examples of Late Electrical Injury Organ Tissue Dysfunction

Tissue	Late Effects
Heart	Patchy cardiac tissue necrosis (myocardium, nodal tissue, conduction pathways, coronary arteries), late arrhythmias are rare
Central nervous system	Cognitive deficits, spinal cord and peripheral nerve dysfunction, cataracts
Muscle	Weakness, arthropathy, nonspecific myopathy and fibrosis, limitation of joint function
Vascular	Venous thrombosis, arterial rupture

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

TABLE E4 Comparison of Lightning, High-Voltage, and Low-Voltage Electrical Injury

	Lightning	High Voltage	Low Voltage
Voltage (V)	$>100 \times 10^6$	>1000	<1000
Current (A)	>200,000	Variable	240
Duration	Instantaneous	Brief	Prolonged
Type of current	Mostly DC	DC or AC	Mostly AC
Cardiac effect	Arrest: Asystole	Arrest: Ventricular fibrillation	Arrest: Ventricular fibrillation
Respiratory effect	Respiratory arrest: Direct CNS injury	Respiratory arrest: Indirect trauma or tetanic contractions of respiratory muscles	Respiratory arrest: Tetanic contractions of respiratory muscles
Muscle effect	Single	Contraction:DC—single AC—tetanic	Contraction: Tetanic
CNS effect	Early and delayed brain injury, coma, seizures, blindness, deafness, aphasia, cerebral vein thrombosis, late spinal cord deficits, cataracts	Early and delayed brain injury, coma, seizures, blindness, deafness, aphasia, cerebral vein thrombosis, late spinal cord deficits, cataracts	Paresthesias, transient neuropathy
Burns	Rare: Superficial ("flashover" diverts current around the body)	Common: Superficial (less) and deep (most)	Usually superficial, can be full thickness
Rhabdomyolysis	Uncommon	Very common	Common
Blunt injury	Blast effect, shock wave	Muscle contraction, fall	Fall (uncommon)
Mortality (early)	Very high (about 30%)	Moderate (about 5%-15%)	Low

AC, Alternating current; *CNS,* central nervous system; *DC,* direct current.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

BOX E2 Mechanisms of Lightning Injury

Electrothermal Effects
- Direct strike
- Contact potential
- Side flash, sometimes called "splash" (1 to 3 may include surface arcs over the body surface)
- Step voltage (also termed "Earth potential rise" or "ground current"):
  1. Transmitted through the ground
  2. Surface arcing
- Upward streamer current (also called "fifth mechanism")

Blunt Force Trauma Effects
- Barotrauma
- Concussive injury
- Musculoskeletal injury from muscle contraction, falls

From Auerbach P: *Wilderness medicine, expert consult.* Premium Edition—Enhanced Online Features and Print, Philadelphia, 2012, Saunders, Elsevier.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- At the scene: Ensure the electrical power source of injury is turned off before approaching patients
- Basic and advanced cardiac life support with cervical spine precautions. Prolonged cardiopulmonary resuscitation should be undertaken regardless of the initial cardiac rhythm
- Cardiac monitoring
- Oxygen
- Tetanus prophylaxis

ACUTE GENERAL Rx

- IV fluids to maintain urine output of 50 to 100 ml/hr (IV hydration should be reassessed with central nervous system expert in patients at risk of developing cerebral edema).
- Alkalinization of the urine (sodium bicarbonate 50 mEq in 1 L of normal saline) in patients with or at risk of myoglobinuria.
- Furosemide 20 to 40 mg PO or IV and/or mannitol 12.5 g/kg/hr may be used to force diuresis.
- Seizures are treated in the standard fashion.
- Treat burns with sulfadiazine silver dressings.
- Table E5 summarizes critical care management of the electrical injury patient in the first hour.

CHRONIC Rx

- Hospitalization is indicated in patients with high-voltage injuries, extensive burns, central nervous system symptoms, myonecrosis (creatine kinase level more than twice normal, high serum myoglobin levels, or myoglobinuria), new cardiac arrhythmia or ECG changes, or any internal organ damage.
- Ophthalmology consultation at the follow-up to screen for cataract formation (occurs

TABLE E5 Critical Care Management of the Electrical Injury Patient (First Hour)

Concern	Action	Goal
Airway (PRIORITY) Assess for: • Airway patency • Altered mental status • Facial injuries • Airway obstruction • Aspiration	1. Manual airway support as needed (e.g., clear airway, bag valve mask) 2. Intubate *early*; diffuse edema and multisystem organ dysfunction may progress quickly (surgical airway may be necessary) 3. Clinically confirm placement with examination and end-tidal CO_2 monitor (radiologic confirmation of ETT placement ASAP); well-secure ETT in place 4. Immediate C/T/L/S spine immobilization 5. Initiate pulse oximetry	• Secure airway
Breathing Assess for: • Spontaneous effort • Pneumothorax • Hemothorax • Chest wall compromise (musculoskeletal or burn) • Smoke inhalation (if associated material ignition)	1. Treat pneumothorax immediately 2. Initiate mechanical ventilation if needed 3. Correct hypoxia with supplemental O_2 (start with 100% FiO_2) 4. Check ABG 5. CXR (confirm tube placement, identify injury) 6. Consider early bronchoscopy to assess for inhalation injury if flame exposure is involved 7. Early escharotomy if needed	• *Avoid* hypoxia • SaO_2 >92% • pCO_2 35-45 mm Hg • Plateau pressure <30 mm Hg
Circulation Assess for: • Shock • Distended neck veins • Cardiac tamponade • Cardiac arrhythmia • Cardiac dysfunction • Hemorrhage • Peripheral pulses	1. BLS/ACLS/ATLS algorithms 2. Treat cardiac tamponade immediately 3. Establish adequate IV access; edema and multisystem organ dysfunction will progress quickly 4. Infuse isotonic IV fluids toward target goals 5. Continuous ECG and blood pressure monitoring 6. Place urinary catheter 7. FAST +/– focused CT to assess for hemorrhage 8. Consider central venous access for resuscitation monitoring 9. Early fasciotomy 10. Complete blood count, type and cross, cardiac enzymes, lactate	• MAP ≥60-65 mm Hg • UO ≥0.5 cc/kg/hr (if suspect rhabdomyolysis: UO >1.0 cc/kg/hr) • SvO_2 60-65 mm Hg • Lactic acid <2.0 • Closely monitor for development of pulmonary edema
Disability Assess for: • Acute brain injury • Acute spine injury • Musculoskeletal deformity	1. Assess consciousness, pupillary size and response, lateralizing signs, level of spinal cord injury 2. Assess using Glasgow Coma Score 3. Assess spine pain and gross function 4. Full neurologic examination when possible 5. Head and spine CT as needed	
Exposure Assess for: • Core temperature • Cutaneous injury	1. Warm IV fluids 2. Warm room 3. Insulating covers (if needed) 4. Burn wound area assessment 5. Cover burn sites with dry, clean linen (pending definitive burn care) 6. Splint unstable fracture sites to avoid neurovascular compromise 7. Serial, focused neurovascular checks	• *Avoid* hypothermia • Core temperature 98.6° F (37° C)
Comprehensive evaluation Assess for: • Efficacy of current treatment • Additional or missed injuries	1. Secondary and tertiary surveys per ACS trauma protocol 2. Pertinent additional studies and laboratory tests such as UA, CK-MB, troponin, ECG 3. Focused radiologic studies 4. Consider transfer to burn center	

ABG, Arterial blood gas; *ACLS,* advanced cardiovascular life support; *ACS,* American College of Surgeons; *ASAP,* as soon as possible; *ATLS,* advanced trauma life support; *BLS,* basic life support; *CK-MB,* creatine kinase-MB; *CO_2,* carbon dioxide; *CT,* computed tomography; *C/T/L/S,* cervical, thoracic, lumbar, sacral; *CXR,* chest x-ray; *ECG,* electrocardiogram; *ETT,* endotracheal tube; *FAST,* focused assessment with sonography for trauma; *FiO_2,* fraction of inspired oxygen; *IV,* intravenous; *MAP,* mean arterial pressure; *O_2,* oxygen; *pCO_2,* partial pressure of carbon dioxide; *SaO_2,* saturated oxygen; *SvO_2,* mixed venous oxygen saturation; *UA,* urinalysis; *UO,* urine output.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

within 1 to 24 mo of a high-voltage electrical injury in 5% to 20% of patients).

DISPOSITION

- Patients with severe burns should be transferred to the regional burn center.
- Complications of electrical injuries include:
  1. Infection
  2. Renal failure from rhabdomyolysis
  3. Seizure disorder
  4. Fasciotomies
  5. Amputation
- Delayed neurologic damage may present as ascending paralysis, amyotrophic lateral sclerosis, or transverse myelitis weeks to yrs after the injury.
- Vascular damage may also present in a delayed fashion.

REFERRAL

- Referrals to general surgery, burn surgery, trauma surgery, orthopedic surgery, and/or critical care specialists as appropriate in any patient that meets hospitalization criteria. Ophthalmology and ear-nose-throat specialist referral may be indicated.
- Plastic surgery is recommended in children with oral burns.

PEARLS & CONSIDERATIONS

COMMENTS

- The size of external skin burns can often underestimate the degree of internal injury.
- Lightning Strike and Electric Shock Survivors International is a support group that serves people from around the world who have sustained an electric injury (www.lightning-strike.org).
- Home safety education provided one-to-one in a clinical setting or at home, especially with the provision of safety equipment, is effective in increasing the range of safety practices.
- Box E3 describes myths regarding electrical and lightning injury commonly cited as facts in litigation.

INVESTIGATIONS

- If computed tomography (CT) and magnetic resonance imaging (MRI) scans are normal, there are no injuries.

- Negative investigations (e.g., nerve conduction study, electroencephalogram, CT, MRI) mean a victim has not sustained an electric shock.
- Neuropsychological testing is objective and easily interpreted.
- Burns of electrical origin can be distinguished on histologic examination.

REMOTE SYMPTOMS

- Remote symptoms do not exist.
- Remote symptoms are proportional to the size of the shock.
- Symptoms of the shock that are not present immediately after the shock are not related to it.
- A person getting remote symptoms was psychologically vulnerable all the time.

MISCELLANEOUS

- Litigation increases the potency of the claimed symptoms. Corollary: Resolving litigation terminates symptoms.
- Medical specialists understand electricity or lightning.
- Electrical experts can predict lightning or electrical injury.
- A diagnosis of depression, posttraumatic stress disorder, adjustment disorder, and so on negate an electrical injury causation.
- Residual current devices (RCDs) eliminate the possibility of all shocks. Corollary: A shock occurring when an RCD breaks the circuit cannot be severe.

RELATED CONTENT

Electrical Injury (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

BOX E3 Myths Commonly Cited as Facts in Litigation

These apply to electrical injury as well as lightning injury.

Behavior of Current in the Body

- Current seeks earth.
- Current seeks the path of lowest resistance.
- Nerve tissue is a good conductor, or alternatively, current is preferentially conducted by nerve tissue.
- When a person touches a source of potential, current flows through the skin to other parts of the skin in contact with the same conductor (i.e., current passage is local only).

The Severity of Electric Shock

Myth: If the following are absent, the shock cannot be severe and no deleterious effect can result:

- Being thrown (i.e., if a person is not thrown, the shock is not severe).
- Burns (i.e., if burns are not present, the shock is not severe).
- If the only surface change is a blister, the shock was not severe.
- Entry and exit wounds:
  1. Must be present.
  2. Demonstrate the current path.
  3. If not present, indicate no shock occurred.
- Fuses being blown (i.e., if a fuse does not blow, the shock is not severe enough to harm a victim).
- Low voltage cannot harm.
- Electroconvulsive therapy does not give long-term post–electric-shock symptoms (also false), so any other electric shock cannot be harmful.

From Auerbach P: *Wilderness medicine, expert consult.* Premium Edition—Enhanced Online Features and Print, Philadelphia, 2012, Saunders, Elsevier.

BASIC INFORMATION

DEFINITION

Emergency contraception (EC) can prevent pregnancy soon after unprotected intercourse, sexual assault, or failure or improper use of a birth control method. EC reduces the risk of pregnancy when used up to 120 hours (5 days) after unprotected sex but is more effective if used earlier.

MECHANISM: The primary mechanism of all EC pills is inhibition or delay of ovulation or follicular development. Emergency insertion of the copper IUD prevents fertilization by affecting sperm motility and viability.

EFFECTIVENESS: The copper IUD prevents 99% of expected pregnancies and should be considered the first-line option for all women of childbearing age. Oral ulipristal acetate and levonorgestrel prevent the majority of pregnancies after unprotected intercourse. Ulipristal acetate is more effective than levonorgestrel, particularly in overweight and obese patients.

SYNONYMS

Morning-after pill, postcoital contraception
EC

ICD-10CM CODES

Z30.012	Encounter for prescription of emergency contraception
Z30.09	Encounter for other general counseling and advice on contraception

EPIDEMIOLOGY & DEMOGRAPHICS

Approximately 49% of all pregnancies and more than 82% of teen pregnancies in the U.S. are unintended. An estimated 1.7 million unintended pregnancies could be prevented annually if EC use were widespread.

DIAGNOSIS

LABORATORY TESTS

- If there is doubt about whether a patient is already pregnant from intercourse that occurred more than 2 wk previously, a pregnancy test may be helpful. However, there is no need for a pregnancy test before administering EC pills. Delays in administration of the medication will reduce its efficacy. The medication in EC pills will not harm an established pregnancy.
- A pregnancy test should be performed before insertion of a copper IUD.

TREATMENT

ACUTE GENERAL Rx

- Administer EC as soon as possible after unprotected intercourse. All forms of EC reduce the risk of pregnancy when used up to 5 days after unprotected intercourse but are more effective if used earlier. EC pills function by delaying ovulation, thus it is important to counsel patients to abstain or use a barrier method for 2 wk following EC use in order to avoid a later-cycle pregnancy.
- Copper IUD for EC:
  1. Emergency insertion of the copper IUD is the most effective option for EC.
  2. Ideal for women who desire effective long-term contraception and have no contraindications to IUD insertion.
  3. A pregnancy test should be performed before IUD insertion.
  4. Requires insertion by a clinician.
  5. Some women may experience changes in bleeding patterns that are bothersome.
- Emergency contraceptive pills (see Table E1):
  1. Ulipristal acetate (Ella).
     a. Single dose 30 mg ulipristal acetate, a progesterone-receptor modulator.
     b. More effective than levonorgestrel EC. Most effect hormonal option to EC. Prescription is required.
  2. Levonorgestrel (Next Choice, Plan B One-Step):
     a. Total dose 1.5 mg levonorgestrel.
     b. A single dose is equally effective and causes no more side effects than two divided doses.
     c. Less effective in overweight and obese women (BMI >25).
     d. Available over the counter without a prescription for all ages. Providing a prescription may decrease the cost of the medication, especially for Medicaid recipients.
  3. Combined estrogen/progestin contraceptive pills:
     a. Least effective method with highest incidence of side effects.
     b. Two doses, 12 hours apart, of 100 to 120 mcg ethinyl estradiol and 0.5 to 0.6 mg of levonorgestrel (or 1.0 to 1.2 mg of norgestrel) per dose.
     c. Prescription is required, but if patient uses combined oral contraceptives, she may have the product on hand.
     d. The Emergency Contraception website provides instructions for using available combined oral contraceptive pills for EC. (See http://ec.princeton.edu/questions/dose.html#dose.)
- Side effects:
  1. Nausea: Combined estrogen-progestin EC will cause nausea in 50% of women and vomiting in 20%. Side effects resolve within 1 to 2 days. Antiemetics such as meclizine 25 mg orally are recommended 1 hour before taking combined estrogen-progestin EC. It can be used on an as-needed basis with the other EC methods.
  2. Irregular bleeding: Many patients may experience irregular bleeding from 1 wk to 1 mo after EC. Irregular bleeding is typically self-limited.
  3. Other side effects include, but are not limited to, headache, fatigue, cramping, and breast tenderness.
- Contraindications:
  1. Few contraindications to EC exist other than hypersensitivity to the product. EC pills will not affect an established pregnancy.
  2. There are no other evidence-based medical contraindications to the use of EC pills. The benefits of EC in preventing pregnancy generally outweigh the theoretical risks for women with contraindications to long-term use of combined hormonal contraception, such as thromboembolic disease, smoking after age 35 yr, heart disease, or liver disease. Non–estrogen-containing EC is preferable for all women because of better efficacy but particularly for those with any of these conditions or who are breastfeeding.

CHRONIC Rx

Because EC pills are less effective than other forms of contraception, they are not recommended as an ongoing method of contraception. The copper IUD is highly effective for EC and can be kept in place to prevent pregnancy for up to 12 yr.

DISPOSITION

After using EC, most women will have their menses within 1 to 2 wk of the expected date. If a woman's next expected menses are delayed by more than 3 wk, a pregnancy test should be performed.

PEARLS & CONSIDERATIONS

COMMENTS

- The copper IUD is the most effective form of EC and is the only method that provides users with long-term contraception.
- All forms of EC pills reduce the risk of pregnancy up to 5 days after unprotected intercourse, with ulipristal acetate being the most

TABLE E1 Emergency Contraceptive Pills Available in the United States

Emergency Contraception Pills		
Brand	**Dose**	**Dose**
Ella	1 pill	30 mg ulipristal acetate
Plan B One-Step	1 pill	1.5 mg levonorgestrel
Next Choice One Dose	1 pill	1.5 mg levonorgestrel
My Way	1 pill	1.5 mg levonorgestrel
Levonorgestrel 0.75 mg	2 pills	1.5 mg levonorgestrel

effective pill. Delayed ovulation can result in a later-cycle pregnancy, so patients should use a barrier method for 2 wk following EC pill use.
- The copper IUD is highly effective regardless of BMI. EC pills are less effective in overweight and obese women, but the weight at which they lose efficacy is unclear and may vary between women. Therefore, regardless of BMI, all EC methods should be offered to all women with appropriate counseling that some forms may be less effective with higher BMI. Ulipristal acetate is more effective than levonorgestrel, particularly in overweight and obese women.
- A pregnancy test is not necessary before administering EC pills because the medications will not harm an existing pregnancy.
- Advanced prescription of EC pills at routine visits may increase timely use of EC and does not decrease the use of more reliable means of contraception. Health care providers who speak with the pharmacist directly are more likely to ensure timely distribution of EC pills to their patients.
- Levonorgestrel EC is available in the U.S. without a prescription or proof of age.

PREVENTION

- Women should be counseled about contraceptive options and the availability of EC before it is needed.
- Patients should begin an effective method of birth control immediately after using EC. Hormonal contraceptives can be started the day after EC is administered. Abstinence or a barrier method should be used for 2 wk.
- EC should be offered to all women after sexual assault.

PATIENT & FAMILY EDUCATION

EC website: http://ec.princeton.edu/index.html

RELATED CONTENT

Contraception (Related Key Topic)

AUTHORS: **Emelia Argyropoulos Bachman, MD, Jennifer Buckley, MD,** and **Melissa Nothnagle, MD, MSc**

SUGGESTED READING

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Brache V et al: Ulipristal acetate prevents ovulation more effectively than levonorgestrel: analysis of pooled data from three randomized trials of emergency contraception regimens, *Contraception* 88(5):611-618, 2013.

Cheng L et al: Interventions for emergency contraception, *Cochrane Database Syst Rev* 8:CD001324, 2012.

Raymond EG et al: Clinical practice. Emergency contraception, *N Engl J Med* 372:1342-1348, 2015.

BASIC INFORMATION

DEFINITION

An accumulation of pus in the pleural space, most often caused by bacterial infection.

SYNONYMS

Infected pleuritis
Infected pleural effusion
Purulent pleural effusion

ICD-10CM CODES
J86 Pyothorax
A16.5 Empyema due to tuberculosis

EPIDEMIOLOGY & DEMOGRAPHICS

- Empyema is most commonly a complication of bacterial pneumonia, especially in association with pneumococcal or anaerobic infection (40% to 60% of cases of empyema)
- Occurs as a complication of thoracic surgery (<20% of cases)
- Penetrating chest trauma (4% to 10% of cases)
- Bronchopleural fistulae resulting from malignancy or lung biopsy

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- May be abrupt or chronic and insidious depending on the etiologic agent and host factors.
- Typically presents as progressive pleuritic chest pain, persistent fever, and other sustained signs and symptoms of infection.
- In anaerobic empyema, particularly that caused by the actinomycetes, the clinical picture is dominated by systemic symptoms and signs: Weight loss, malaise, and low-grade fever.
- A slowly enlarging chest wall mass.
- As a complication of thoracic trauma or surgery, empyema typically results from contamination of blood within the pleural space several days following the event.
- The physical findings of empyema are those of pleural effusion. Decreased breath sounds and dullness to percussion over the involved part of the thorax is typical. Systemic signs include fever, tachycardia, leukocytosis, and warmth and erythema over the involved area.

ETIOLOGY

Infection of the lung parenchyma spreading to pleural space caused by

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Staphylococcus aureus*
- *Legionella* species
- *Mycobacterium tuberculosis*
- *Actinomyces* spp.
- A variety of oral anaerobic bacteria have been cultured in 36% to 37% of empyemas: *Bacteroides fragilis, Prevotella* species, *Fusobacterium nucleatum,* and *Peptostreptococcus* are the most common

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Uninfected parapneumonic effusion
- Lung abscess (see Fig. 1)
- Congestive heart failure
- Malignancy involving the pleura
- Tuberculous pleurisy
- Collagen vascular disease (particularly rheumatoid lung and systemic lupus erythematosus)

LABORATORY TESTS

- Complete blood count; arterial blood gas.
- Blood cultures; pleural fluid cultures.
- Pleural fluid cultures identify pathogens in only 60% of cases.
- Pleural fluid analysis in empyema has the characteristics of an exudate with a ratio of pleural fluid to serum protein >0.5 or pleural fluid to serum LDH >0.6. Characteristically, empyema fluid is grossly purulent with visible organisms on Gram stain with glucose <50 mg/dl and pH <7. These findings justify immediate drainage by chest tube or surgery because of the high risk of loculation and progressive systemic infection.

IMAGING STUDIES

- Chest x-ray (Fig. E2*A*)
- Lateral decubitus view to establish the presence of free fluid in the pleural space
- Computed tomography (Fig. E2*B*) to establish the presence of fluid loculation, underlying mass lesions, and other intrathoracic pathology

TREATMENT

NONPHARMACOLOGIC THERAPY

Prompt drainage by thoracostomy (chest tube) or open thoracotomy. Video-assisted thoracoscopic surgery (VATS) has greatly improved surgical management of empyemas.

ACUTE GENERAL Rx

- Maintenance of drainage until infection controlled.
- Antibiotics directed at suspected or proven bacterial or fungal pathogens. Initial regimens include cefotaxime or ceftriaxone for suspected *S. pneumoniae* or group A *Streptococcus,* nafcillin or oxacillin for suspected methicillin-sensitive *S. aureus,* vancomycin or linezolid for suspected MRSA, ceftriaxone for suspected *H. influenzae,* and clindamycin plus ceftriaxone when suspecting anaerobes. Other agents with excellent anaerobic coverage include carbapenem antibiotics such as meropenem and ertapenem and piperacillin/tazobactam. These agents also have excellent gram-negative coverage.
- Thoracoscopy or instillation of thrombolytic agents (streptokinase or urokinase) may be considered in refractory, loculated empyema.

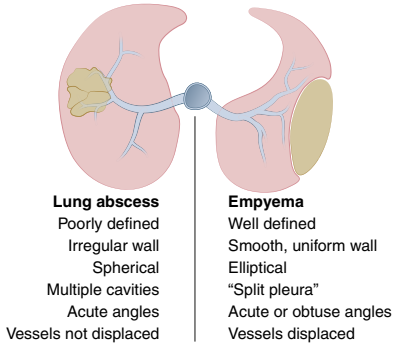

FIG. 1 Empyema versus lung abscess. (From Webb WR, Brant WE, Major NM: *Fundamentals of body CT*, ed 4, Philadelphia, 2015, Saunders.)

CHRONIC Rx

- If thorough drainage cannot be accomplished, open thoracotomy with pleural decortication may be required.
- Lung function should be monitored following completion of therapy.

DISPOSITION

Hospitalization with supplemental oxygen with ventilatory support if necessary

REFERRAL

Consultation by infectious diseases, pulmonary, or thoracic surgery specialists as needed

PEARLS & CONSIDERATIONS

COMMENTS

- Empyema caused by actinomycetes may present with erosion through the chest wall and formation of a fistulous tract.
- Nosocomial infection caused by relatively resistant bacterial or fungal pathogens may result in empyema in patients with indwelling thoracostomy tubes.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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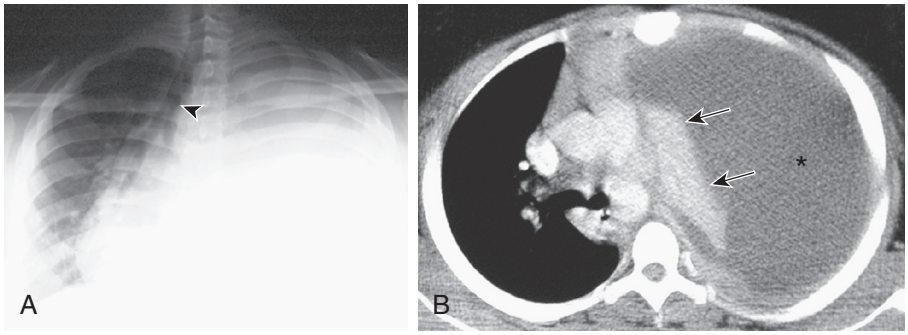

FIG. E2 Empyema and pneumonia in a teenager. A, Chest radiograph shows opacification of the left thorax. Note shift of mediastinum and trachea *(arrowhead)* to right. **B,** Thoracic computed tomography scan shows massive left pleural effusion *(asterisk).* Note the compression and atelectasis of the left lung *(arrows)* and shift of the mediastinum to the right. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

Encephalitis, Acute Viral ALG PTG

BASIC INFORMATION

DEFINITION

Acute viral encephalitis is an acute febrile syndrome with evidence of meningeal involvement and of derangement of the function of the cerebrum, cerebellum, or brain stem.

SYNONYMS

Arboviral encephalitis
Brain stem encephalitis
Acute necrotizing encephalitis
Rasmussen encephalitis
Encephalitis lethargica

ICD-10CM CODES

A86	Unspecified viral encephalitis
A83.0	Japanese encephalitis
A83.1	Western equine encephalitis
A83.2	Eastern equine encephalitis
A83.3	St Louis encephalitis
A83.4	Australian encephalitis
A83.5	California encephalitis
A83.8	Other mosquito-borne viral encephalitis
A83.9	Mosquito-borne viral encephalitis, unspecified
A84.8	Other tick-borne viral encephalitis
A84.9	Tick-borne viral encephalitis, unspecified
A85.0	Enteroviral encephalitis
A85.1	Adenoviral encephalitis
A85.2	Arthropod-borne viral encephalitis, unspecified
A85.8	Other specified viral encephalitis
A92.31	West Nile virus infection with encephalitis
B00.4	Herpesviral encephalitis
B01.11	Varicella encephalitis and encephalomyelitis
B02.0	Zoster encephalitis
B05.0	Measles complicated by encephalitis
B06.01	Rubella encephalitis
B10.01	Human herpesvirus 6 encephalitis
B10.09	Other human herpesvirus encephalitis
B26.2	Mumps encephalitis
B94.1	Sequelae of viral encephalitis
G04.00	Acute disseminated encephalitis and encephalomyelitis, unspecified
G04.81	Other encephalitis and encephalomyelitis
G04.90	Encephalitis and encephalomyelitis, unspecified
G05.3	Encephalitis and encephalomyelitis in diseases classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): About 20,000 cases/yr are reported to the CDC. In 2016, there were 2149 cases of West Nile virus with 106 deaths. Each yr in the U.S. approximately seven patients are hospitalized for encephalitis per 100,000 population.

PEAK INCIDENCE: Any age, but children and older adults are more likely to have significant morbidity

PREVALENCE (IN U.S.):

- Arbovirus infections are transmitted by mosquitoes and thus cause infection when mosquitoes are active, especially summer and fall. Herpes simplex infections can occur at any time.
- Geography also plays a role (Fig. 1): Whereas Eastern equine encephalitis is more likely on the East Coast of U.S., West Nile virus has spread to 48 states. Powassan virus is more common in northern New England and Canada. La Crosse virus is more common in the upper Midwestern and mid-Atlantic and southeastern states.

PREDOMINANT SEX: Male = female

PREDOMINANT AGE: Any age

GENETICS: No specific genetic or congenital predisposition

ETIOLOGY

- Can be caused by a host of viruses (Table E1), with herpes simplex the most common virus identified.
- Arboviruses transmitted by mosquitoes include Eastern equine encephalitis, Western equine encephalitis, St. Louis encephalitis, Venezuelan equine encephalitis, California virus encephalitis, Japanese B encephalitis, La Crosse encephalitis, Murray Valley and West Nile encephalitis. Tick-borne diseases include Russian spring-summer encephalitis, Powassan encephalitis, and other lesser known agents.
- Also implicated: Rabies-causing agents, CMV, Epstein-Barr, varicella-zoster, echo virus, mumps, adenovirus, coxsackie, rubeola, and herpes viruses.
- Meningoencephalitis: Acute retroviral infection from HIV.
- In the U.S., the most commonly identified etiologies are herpes simplex virus, West Nile virus, and the enteroviruses.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Initially, fever and evidence of meningeal irritation
- Headache and stiff neck
- Later, development of signs of cortical dysfunction: Lethargy, coma, stupor, weakness, seizures, facial weakness, as well as brainstem findings
- Cerebellar findings: Ataxia, nystagmus, hypotonia, myoclonus, cranial nerve palsies, and abnormal tendon reflexes
- Patients with rabies: Hydrophobia, anxiety, facial numbness, psychosis, coma, or dysarthria
- Rarely, movement disorders, such as chorea, hemiballismus, or dystonia
- Recall of a prodromal viral-like illness (this finding is not at all uniform)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bacterial infections: Brain abscess, toxic encephalopathies, TB
- Protozoal infections
- Behçet syndrome
- Lupus encephalitis
- Sjögren syndrome
- Multiple sclerosis
- Syphilis
- Cryptococcus
- Toxoplasmosis
- Brucellosis
- Leukemic or lymphomatous meningitis
- Other metastatic tumors
- Lyme disease
- Cat-scratch disease
- Vogt-Koyanagi-Harada syndrome
- Mollaret meningitis

WORKUP (BOX 1)

- Lumbar puncture to reveal pleocytosis, usually lymphocytic, although neutrophils may be seen early on
- Usually, elevated CSF protein
- Normal or low CSF glucose
- In herpes simplex encephalitis: RBCs and xanthochromia
- Selected tests on CSF fluid in viral encephalitis are described in Table 2
- EEG changes showing periodic high-voltage sharp waves in the temporal regions and slow wave complexes suggestive of herpes encephalitis (Fig. E2)
- CT scan and MRI (Fig. 3) to reveal edema and hemorrhage in the frontal and temporal lobes
- Temporal lobe involvement suggests herpes simplex encephalitis (Fig. E4)
- Basal ganglia and thalami are areas involved as generally seen in Eastern equine encephalitis
- With West Nile infection, MRI changes have shown changes in basal ganglia, thalami, mesial temporal structures, brain stem, and cerebellum
- Arboviral infections suspected during outbreaks in specific areas
- Rising titers of neutralizing antibodies from the acute to the convalescent stage demonstrated but often not helpful in the acutely ill patient
- Polymerase chain reaction (PCR) that amplifies DNA from the CSF for herpes simplex encephalitis
- Rarely, brain biopsy to assist in the diagnosis; viral culture of cerebral tissue obtained if biopsy done
- Classic herpetic skin lesions suggestive of herpes encephalitis
- In diagnosing arboviral encephalitis:
  1. Presence of antiviral IgM within the first few days of symptomatic disease; detected and quantified by ELISA
  2 Unusual to recover an arbovirus from the blood or CSF

LABORATORY TESTS

- Aside from the lumbar puncture, most other laboratory studies are nonspecific.
- Skin lesions and urine may be cultured for herpes simplex and CMV.

TREATMENT

ACUTE GENERAL Rx

- Supportive care, frequent evaluation, and neurologic examination

FIG. 1 Map showing the worldwide geographic distribution of encephalitis caused by arthropod-borne viruses (the "arboviruses"). (Swaiman KF et al: *Swaiman's pediatric neurology, principles and practi*ce, ed 6, Philadelphia, 2017, Elsevier.)

BOX 1 Diagnostic Algorithm

All Cases

CSF
- WBC count with differential, RBC count, protein, glucose
- Gram stain and bacterial culture
- Herpes simplex virus–1/2 PCR (if test available, consider HSV CSF IgG and IgM in addition)
- VZV PCR (sensitivity may be low; if test available, consider VZV CSF IgG and IgM in addition)
- Enterovirus PCR

Blood/Serum
- Routine blood culture
- Epstein-Barr virus (EBV) antibodies (if positive for acute infection, check CSF EBV PCR)
- Hold acute serum and collect convalescent serum 10-14 days later for paired antibody testing

Respiratory, Stool
- Enterovirus PCR (respiratory, stool)
- Enterovirus (stool)

Conditional

Host Factors
- Neonate: Herpes simplex virus–2 PCR (CSF), swabs of skin vesicles, mouth, nasopharynx, conjunctivae, and rectum (viral culture)
- ≤3 yr: Parechovirus PCR (CSF and respiratory)
- Immunocompromised: Cytomegalovirus, human herpesvirus–6/7, JC virus, human immunodeficiency virus PCR (CSF)

Season and Exposure
- Summer/fall: West Nile virus (WNV) IgM (CSF, serum), WNV IgG (paired serum), and other appropriate arboviruses as geographically relevant
- Cat (particularly if with seizures and paucicellular CSF): *Bartonella* antibody (serum)
- Animal bite exposure: Rabies test[a]
- Rodent exposure: LCM antibody (serum)
- Tick and/or camping exposure: *Rickettsia* spp., antibody (serum), *Anaplasma* phagocytophila antibody (serum)
- Swimming or diving in brackish water: *Naegleria fowleri* (wet mount)[a]
- If history of sexual activity: Herpes simplex virus–2 (CSF PCR)

Signs and Symptoms
- Psychotic component or movement disorder: Anti-NMDAR antibody (CSF and serum), and abdominal ultrasound evaluation for teratoma
- Vesicular rash: Varicella zoster virus PCR (CSF)
- Rapid decompensation (especially with bite history or foreign travel): Rabies test[a]
- Respiratory (during influenza season): Influenza PCR (respiratory)
- Diarrhea and seizure (especially young child): Rotavirus (check stool for antigen), if positive then rotavirus PCR (CSF)

Laboratory Features
- CSF protein >100 mg/dl or CSF glucose less than two-thirds peripheral glucose and/or lymphocytic pleocytosis:
  1. Mycobacterial tuberculosis: Culture (CSF, respiratory), place PPD, and check IGRA, chest radiograph, fungal culture (CSF)
  2. Fungal (specific types depend on geographic residence and/or travel to endemic areas): Culture CSF *and* check antibody and antigen
  3. *Balamuthia mandrillaris:* Contact health department/CDC for assistance with testing
- CSF eosinophilia: *Baylisascaris procyonis* antibody

Travel
- Consider consultation with public health department concerning specific diseases such as arboviruses, rabies, and other diseases

CDC, Centers for Disease Control and Prevention; *CSF,* cerebrospinal fluid; *HSV,* herpes simplex virus; *Ig,* immunoglobulin; *IGRA,* interferon gamma release assay; *LCM,* lymphocytic choriomeningitis; *NMDAR, N*-methyl-D-aspartate receptor; *PCR,* polymerase chain reaction; *PPD,* purified protein derivative; *RBC,* red blood cell; *VZV,* varicella zoster virus.

[a]Contact health department for assistance with testing.

Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

TABLE 2 Selected Tests for Viral Encephalitis

Organism/Syndrome	Test	Comment
West Nile Virus		
West Nile encephalitis	IgM in CSF	Diagnostic of CNS invasive disease or acute flaccid paralysis
Herpes Simplex Virus Type 1		
Herpes simplex encephalitis	PCR in CSF	Sensitive and specific in the acute phase
	CSF–serum antibody ratio	Useful 2 wk to 3 mo after onset
Herpes Simplex Virus Type 2		
Neonatal encephalitis	PCR in CSF	Confirmatory, high sensitivity
Relapsing meningitis	PCR in CSF	Sensitive and specific in first 3 days of illness
Varicella-Zoster Virus		
Meningoencephalitis	PCR in CSF	Confirmatory when used with clinical and spinal fluid findings; sensitivity unclear
Epstein-Barr Virus		
EBV encephalitis	PCR in CSF	Suggests CNS invasion by virus
JC virus		
Progressive multifocal leukoencephalopathy	PCR in CSF	Diagnostic but incompletely (70%) sensitive
Cytomegalovirus		
CMV ventriculitis	PCR in CSF	Sensitive and specific

CMV, Cytomegalovirus; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *EBV,* Epstein-Barr virus; *IgM,* immunoglobulin M; *PCR,* polymerase chain reaction.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2011, Saunders.

FIG. 3 Gadolinium-enhanced, T1-weighted brain magnetic resonance imaging in a teenager with herpes simplex virus encephalitis. The scan shows gadolinium enhancement in the right insular cortex *(arrows).* (From Swaiman KF et al: *Swaiman's pediatric neurology, principles and practice,* ed 6, Philadelphia, 2017, Elsevier.)

- Ventilatory assistance for patients who are moribund or at risk for aspiration
- Avoidance of infusion of hypotonic fluids to minimize the risk of hyponatremia
- For patients who develop seizures: Anticonvulsant therapy and follow-up in a critical care setting
- For comatose patients:
  1. Aggressive care to avoid decubitus ulcers, contractures, and DVT
  2. Close attention to weights, input/output, and serum electrolytes
- Acyclovir 30 mg/kg/day IV total dose divided in q8 hour intervals for 14 days for herpes simplex encephalitis
- Short courses of corticosteroids to control brain edema and prevent herniation
- In patients with suspected rabies:
  1. Human rabies immune globulin (HRIG) should be given at a dose of 20 U/kg
  2. Active immunization may be stimulated by rabies vaccine, which is grown on a human diploid cell line (HDCV) and has reduced the number of doses needed to five
  3. If suspect animal is a dog or cat and can be found, observe closely for 10 days to detect rabid behavior; any significant illness in the animal should promptly initiate humane sacrifice of the animal with the brain submitted to local or state health departments for pathology and immunologic testing for rabies. Any wild animal suspected of rabies should be humanely sacrificed, if possible, and submitted for rabies testing immediately
  4. If signs are seen, animal should be euthanized and its brain examined for signs of rabies
- No specific pharmacologic therapy for most other viral pathogens

CHRONIC Rx

Some patients may develop permanent neurologic sequelae; these patients will benefit from intensive rehabilitation programs, including physical, occupational, and speech therapy.

DISPOSITION

- Patients with suspected encephalitis of any cause should generally be admitted for initial diagnostic workup and specific treatment (if available).
- Long-term management of patients with significant neurologic sequelae from encephalitis (e.g., memory defects, depression, difficulty with organization of thoughts, movement disorders) may benefit from rehabilitation services, home care, or nursing home placement.

REFERRAL

- To a neurologist for initial workup and management
- To an infectious disease specialist for diagnostic and therapeutic plan
- To a rehabilitation service for long-term evaluation and convalescent services

PEARLS & CONSIDERATIONS

- West Nile virus encephalitis occurs primarily in elderly patients >65 yr of age.
- Rabies may occur months after contact with the rabid animal, and the exposure (especially bat rabies) may have been seemingly insignificant and even inapparent.
- Experimental therapies are worthy of consideration for some forms of viral encephalitis (e.g., immune plasma, ribavirin, interferons), and expert consultation should be obtained early on for possible treatment interventions with promising experimental therapies.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Herpes Encephalitis (Patient Information)
Rabies (Related Key Topic)
West Nile Virus Infection (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

TABLE E1 Encephalitis (with a Focus on Immunocompetent Patients and Pathogens in the United States)

Etiology	Association with Encephalitis	Epidemiology	Clinical and Laboratory Hallmarks	Recommended Tests and "Pitfalls"
Viruses				
Adenovirus	Mostly anecdotal data; unclear neurotropic potential	Sporadic; children and immunocompromised persons at greatest risk	Respiratory symptoms common	Viral culture or PCR from respiratory site, CSF, or brain tissue
Eastern equine encephalitis virus	Proven neurotropic potential, but uncommon	Atlantic and Gulf U.S. states	Subclinical to fulminant; 50%-70% mortality	Serology
Enteroviruses (include coxsackieviruses and enterovirus 71)	Most common cause of encephalitis in pediatric population	Highest incidence in late summer and early fall but can occur year round; large outbreaks of enterovirus 71 infection in Asia have occurred.	Aseptic meningitis most common but also encephalitis; hand, foot, and mouth rash may be present; enterovirus 71 can cause rhombencephalitis	CSF PCR single best test but not always sensitive; to increase sensitivity of detection add serum/plasma, throat PCR, or culture.
Epstein-Barr virus	Relatively common	During acute infection	Infectious mononucleosis during acute infection, cerebellar ataxia, sensory distortion ("Alice-in-Wonderland" syndrome)	Serology and CSF PCR. Beware of PCR false-positive results (detection of low levels may represent latent infection) and false-negative results (not all cases are CSF positive).
Hendra virus	Less common	Endemic in Australia; associated with equine exposure	Nonspecific	Contact local health department or Special Pathogens Branch at CDC.
Hepatitis C	Mostly anecdotal data; unclear neurotropic potential; neurologic symptoms may be related to vasculitis	Hepatitis C–seropositive patients		CSF PCR
Herpes B virus	Proven neurotropic potential; rare	Transmitted by bite of Old World macaque	Vesicular eruption at site of bite followed by neurologic symptoms, including transverse myelitis	Culture and PCR of vesicles, CSF; contact CDC or Dr. Julia Hilliard.
Herpes simplex virus (HSV) types 1 and 2	Relatively common	HSV type 1 accounts for 5%-10% of encephalitis; typically a reactivation disease, HSV type 2 occurs in neonates.	Temporal lobe seizures (apraxia, lip smacking), olfactory hallucinations, behavioral abnormalities, but children often have extratemporal lesions as well	CSF PCR single best test, but false-negative results can occur; if HSE strongly suspected, repeat lumbar puncture within 3-7 days and recheck HSV PCR and intrathecal antibodies.
Human herpesvirus–6	Unknown, especially owing to difficult interpretation of CSF PCR false-positive results	Young children (≤2 yr) or immunocompromised patients, particularly bone-marrow-transplant recipients	May be associated with "roseola rash"	CSF PCR. Beware of false-positive findings due to chromosomal integration and latent infections.
Human metapneumovirus	Anecdotal evidence only	Newly described; almost exclusively in children	Often with associated respiratory symptoms	Respiratory tract PCR (most CSF PCR negative)
Human parechoviruses	Proven neurotropic potential but frequency unknown	Children <3 yr	In young infants periventricular white matter changes resemble hypoxic ischemic encephalopathy.	Parechovirus PCR (enterovirus PCR will not detect)
Influenza virus	Unclear neurotropic potential; good data to support flu-associated encephalopathy but unclear if encephalitis and unclear mechanism	Neurologic complications occur; sporadically reported during influenza seasons; higher numbers reported in Japan and Southeast Asia	Upper respiratory tract symptoms; CSF often acellular in 10% with bilateral thalamic necrosis	Respiratory tract culture, PCR, or rapid antigen; CSF and brain PCR infrequently positive
Japanese encephalitis virus	Relatively common (but only in endemic areas)	Mosquito-borne; most common worldwide cause of encephalitis; endemic throughout Asia; vaccine preventable	Seizures, parkinsonian features, acute flaccid paralysis variably seen. MRI classically shows thalamic and basal ganglia involvement.	CSF and serum antibodies
La Crosse virus	Relatively common	Mosquito-borne; endemic in U.S. East and Midwest; highest incidence in school-aged children	Varies from subclinical illness to seizures and coma	CSF and serum antibodies
Lymphocytic choriomeningitis virus	Rare	Highest incidence in fall and winter; rodent exposure	One of few viral causes of hypoglycorrhachia	Serology

Continued

TABLE E1 Encephalitis (with a Focus on Immunocompetent Patients and Pathogens in the United States)—cont'd

Etiology	Association with Encephalitis	Epidemiology	Clinical and Laboratory Hallmarks	Recommended Tests and "Pitfalls"
Measles virus	Less common in countries where vaccine is routinely used	Vaccine preventable; measles inclusion body encephalitis onset 1-6 mo after infection; SSPE can manifest >5 yr after infection.	Measles encephalitis nonspecific. SSPE has a subacute onset with progressive dementia, myoclonus, seizures, and, ultimately, death. EEG changes are often diagnostic.	Acute form: Measles IgM SSPE: Measles IgG in CSF and serum
Mumps virus	Less common	Vaccine preventable; used to be leading cause of encephalitis-meningitis, now rarely seen	Parotitis, orchitis, hearing loss; one of few viral causes of hypoglycorrhachia	Serology, throat swab PCR, CSF culture, or PCR
Murray Valley encephalitis virus	Less common	Highest incidence in Aboriginal children in Australia and New Guinea	Nonspecific presentation; case fatality 15%-30%	Serology (may cross react with other flaviviruses)
Nipah virus	Less common	Epidemics in Southeast Asia; contact with pigs	Myoclonus, dystonia, pneumonitis	Serology (Special Pathogens Branch, CDC)
Parainfluenza 1-4	Unknown neurotropic potential; anecdotal evidence	Worldwide	Associated with respiratory symptoms	Respiratory DFA or PCR; CSF PCR rarely positive
Parvovirus B19	Anecdotal evidence only	Sporadic cases	Variably associated with rash	IgM antibody, CSF PCR
Powassan virus	Less common	Tick-borne; endemic to New England, Canada	Nonspecific	Serology
Rabies virus	Uncommon in developed countries; relatively common in Africa, Asia, South America	Vaccine preventable; most common vector is bat (bites often unrecognized); dogs important source in developing countries; worldwide distribution	Paresthesia at site of bite Furious form: Hydrophobia, agitation, delirium, autonomic instability, coma Paralytic form: Ascending paralysis in 30% Two forms sometimes overlap	Multiple tests and assays needed for antemortem testing: Antibodies (serum, CSF), PCR of saliva or CSF, IFA of nuchal biopsy, or CNS tissue. Coordinate testing with health department.
Rotavirus	Correlation with seizures in young child but unclear association with encephalitis	Typically children; winter; vaccine preventable	Usually with diarrhea	Stool antigen, CSF PCR (CDC)
Rubella virus	Less common in countries where vaccine is routinely used	Vaccine preventable	Neurologic findings typically occur at same time as rash and fever	Serology, CSF antibodies
St. Louis encephalitis virus	Relatively common	Mosquito-borne; endemic to western U.S.; occasional outbreaks in central/eastern U.S.; highest incidence in adults >50 yr	Tremors, seizures, paresis, urinary symptoms, SIADH variably present	Serology (cross reacts with other flaviviruses)
Tick-borne encephalitis virus	Relatively common in affected geographic areas	Vaccine-preventable; transmitted via tick or ingestion of unpasteurized milk; endemic to Asia, Europe, and areas of former Soviet Union	Weakness ranging from mild paresis to acute flaccid paralysis	Serology
Vaccinia	Less common	Primarily associated with vaccination	Vaccinia rash (localized or disseminated)	CSF antibodies, serum IgM (natural infection)
Venezuelan equine encephalitis virus	Less common	Central and South America; sometimes in U.S. border states (Texas, Arizona)	Myalgias, pharyngitis, upper respiratory tract infection variably present	Serology, viral cultures (blood, oropharynx), CSF antibody
Varicella zoster virus	Relatively common	Acute infection (chickenpox) or reactivation (shingles)	Vesicular rash (disseminated or dermatome), cerebellar ataxia, large vessel vasculitis	DFA or PCR of skin lesions, CSF PCR, serum IgM (acute infection)
Western equine encephalitis virus	Less common	Onset in summer and early fall; western U.S. and Canada, Central and South America	Nonspecific	Serology
West Nile virus	Relatively common	Mosquito-borne; emerging cause of epidemic encephalitis in U.S., Europe; endemic in Middle East; highest incidence in adults >50 yr; documented transmission through organ and blood	Weakness and acute flaccid paralysis, tremors, myoclonus, parkinsonian features; MRI shows basal ganglia and thalamic lesions.	CSF IgM, serum IgM/IgG, paired serology (cross reactivity with West Nile virus and SLE)

TABLE E1 Encephalitis (with a Focus on Immunocompetent Patients and Pathogens in the United States)—cont'd

Etiology	Association with Encephalitis	Epidemiology	Clinical and Laboratory Hallmarks	Recommended Tests and "Pitfalls"
Bacteria				
Bartonella henselae and other *Bartonella* spp.	Relatively common	Often occurs after scratch or bite from kitten	Encephalopathy with seizures (often status epilepticus); peripheral lymphadenopathy; CSF is usually paucicellular.	Serology (acute usually diagnostic), PCR of lymph node; CSF PCR rarely positive
Borrelia burgdorferi	Less common	Tick-borne infection; in U.S. and mostly in New England and eastern Mid-Atlantic states	Facial nerve palsy (often bilateral), meningitis, radiculitis; may be associated with or follow erythema migrans rash.	Serology (serial EIA and Western blot), CSF antibody index, CSF PCR
Chlamydia spp.	Anecdotal evidence only	Associated with *C. psittaci* and *Chlamydophila pneumoniae*	Often with associated respiratory symptoms	NP swab, respiratory, or CSF PCR
Coxiella burnetti	Less common	Animal exposures, particularly placenta and amniotic fluid	Flulike symptoms	Serology
Ehrlichia/Anaplasma	Relatively common	Tick-borne bacteria causing human monocytic and human granulocytic ehrlichiosis (HME, HGE), respectively; HME endemic to southern and central U.S.; HGE endemic to northeastern U.S. and Midwest	Acute onset of fever and HA; rash seen in <30% of cases; leukopenia, thrombocytopenia, and elevated LFTs frequent manifestations	Morulae in white blood cells, PCR of whole blood, serology (seroconversion may occur several weeks after symptoms)
Mycoplasma pneumoniae	One of most frequently identified agents in case series but mostly anecdotal evidence	Worldwide distribution	Respiratory symptoms variably present, but pneumonia rare; often with white matter involvement consistent with ADEM	PCR of NP swab or respiratory culture, serum IgM; CSF PCR rarely positive
Mycobacterium tuberculosis	Relatively common	Most common in developing countries; disease of very young and very old or immunocompromised	Subacute basilar meningitis, lacunar infarcts, hydrocephalus; CSF often with low glucose, high protein levels; pulmonary findings often associated	CSF AFB smear, culture, PCR, respiratory cultures highly suggestive
Rickettsia rickettsii	Relatively common in affected geographic areas	Tick-borne infection in North America; highest incidence in southeast and south central U.S.	Acute onset of fever and headache; petechial rash in 85% of cases beginning 3 days after onset of symptoms	Serology (seroconversion may occur several weeks after symptoms), PCR or IHC on skin biopsy of rash
Treponema pallidum	Rare (especially in pediatrics)	Sexually transmitted disease; meningoencephalitis in early disseminated disease; progressive dementia in late disease	Protean manifestations, including temporal lobe focality (mimics HSV), general paresis, psychosis, dementia	CSF VDRL (sensitive but not specific), serum RPR with confirmatory FTA-ABS
Tropheryma whippelii	Rare (especially in pediatrics)		Progressive subacute encephalopathy, oculomasticatory myorhythmia pathognomonic; variable enteropathy, uveitis	CSF PCR, PAS-positive cells in CSF, small bowel biopsy
Protozoa				
Acanthamoeba spp.	Less common; more common in immunocompromised	Worldwide, inhalation of windblown soil	Subacute progressive	Contact CDC/Parasitology
Balamuthia mandrillaris	Less common	Worldwide (but most case reports in U.S. and South America), inhalation of windblown soil	Subacute progressive disease characterized by space-enhancing lesions, often with cranial nerve palsies and hydrocephalus (similar to tuberculosis)	Serology (research laboratories), brain histopathology, CDC laboratories Contact CDC/Parasitology for testing
Naegleria fowleri	Less common	Summer; swimming or diving in brackish water or poorly chlorinated pools	Anosmia, progressive obtundation; CSF resembles bacterial meningitis, but sterile	Mobile trophozoites on wet mount of warm CSF, brain histopathology
Toxoplasma gondii	Rare in normal hosts	Worldwide; cats definitive hosts but humans often infected via consumption of undercooked meats, unwashed produce		
Helminths				
Angiostrongylus cantonensis	Most common cause of eosinophilic meningitis worldwide; rare in U.S.	In the U.S. in Louisiana and Hawaii; South Pacific, Asia, Australia, and Caribbean	Meningitis or encephalitis; eosinophils in CSF; also associated with eosinophilic pneumonitis	Identification of worm in tissues

Continued

TABLE E1 Encephalitis (with a Focus on Immunocompetent Patients and Pathogens in the United States)—cont'd

Etiology	Association with Encephalitis	Epidemiology	Clinical and Laboratory Hallmarks	Recommended Tests and "Pitfalls"
Baylisascaris procyonis	Less common	North America, Europe, and Asia; pica, particularly near raccoon latrines	Obtundation, coma; significant CSF and peripheral eosinophilia	CSF and serum antibodies; contact CDC/Parasitology for testing
Gnasthostoma spinigerum	Relatively common in affected geographic areas	Southeast Asia, some areas of South/Central America; undercooked freshwater fish, chicken, or pork; also reported with reports of ingestion of frogs/snakes	Eosinophilic myeloencephalitis; can cause intermittent symptoms for 10-15 yr because larvae are long-lived	Identification of worm in tissues
Fungi				
Coccidioides spp.	Relatively common	Southwest U.S., northern Mexico, areas of Central and South America	Neurologic manifestations are result of disseminated disease; more often meningitis than encephalitis; CSF eosinophils sometimes seen	CSF fungal culture (but need to alert lab); CSF and serum antigen and antibody. EDTA-heat–treated antigen increases sensitivity of CSF and serum.
Histoplasma capsulatum	Relatively common	Eastern and central U.S., especially Mississippi, Ohio, and Missouri River valleys; grows on mold, bird, and bat droppings; especially found in caves, barns, or excavation areas	Neurologic manifestations are result of disseminated disease.	CSF fungal culture; CSF and serum antigen and antibody. EDTA-heat–treated antigen increases sensitivity of CSF and serum. Urine antigen
Blastomyces dermatitidis	Relatively common	Southeast, central, and midwestern U.S.; also in Canada, Africa, and India	Neurologic manifestations are result of disseminated disease.	CSF fungal culture; CSF and serum antigen and antibody. EDTA-heat–treated antigen increases sensitivity of CSF and serum.

ADEM, Acute demyelinating encephalomyelitis; *AFB,* acid-fast bacilli; *CDC,* Centers for Disease Control and Prevention; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *DFA,* direct fluorescent antibody test; *EDTA,* ethylenediaminetetraacetic acid; *EEG,* electroencephalogram; *EIA,* enzyme immunoassay; *FTA-ABS,* fluorescent treponemal antibody absorption test; *HA,* hemagglutination assay; *HSV,* herpes simplex virus; *IFA,* indirect fluorescent antibody test; *Ig,* immunoglobulin; *IHC,* immunohistochemistry; *LFTs,* liver function tests; *MRI,* magnetic resonance imaging; *NP,* nasopharyngeal; *PAS,* periodic acid–Schiff; *PCR,* polymerase chain reaction; *RPR,* rapid plasma reagin; *SIADH,* syndrome of inappropriate secretion of antidiuretic hormone; *SLE,* systemic lupus erythematosus; *SSPE,* subacute sclerosing panencephalitis; *VDRL,* Venereal Disease Research Laboratory.

Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

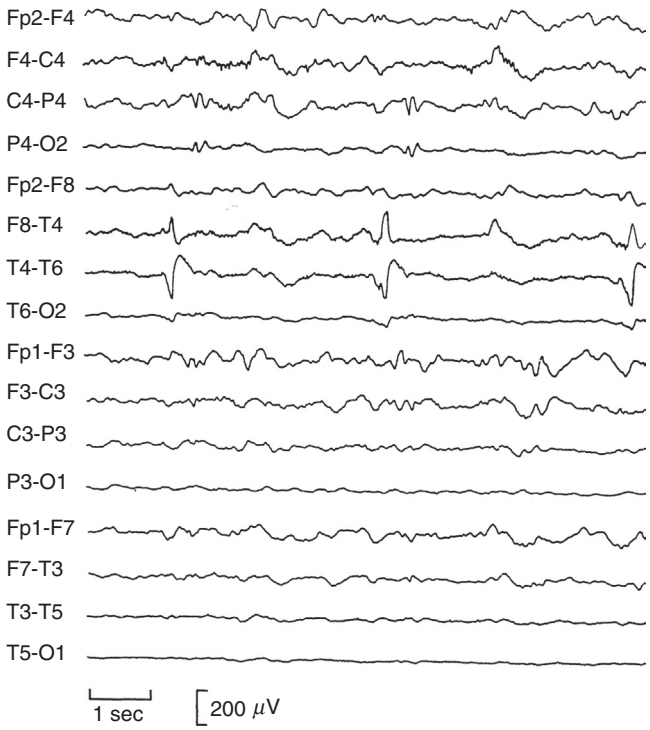

FIG. E2 Repetitive complexes occurring in the right temporal region of a child with herpes simplex encephalitis. (From Goetz CG, Pappert EJ: *Textbook of clinical neurology*, Philadelphia, 1999, Saunders.)

FIG. E4 An axial projection of a magnetic resonance image of a young man with acute herpes simplex encephalitis shows hyperintensity in inferior gyri of the right temporal lobe (*circled*). As in this case, herpes simplex infection typically causes hemorrhagic inflammation in the inferior surface of the temporal and frontal lobes. Permanent temporal lobe damage, which is often bilateral, subjects survivors to memory impairment (amnesia), partial complex seizures, and the Klüver–Bucy syndrome. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists*, ed 8, Philadelphia, 2017, Elsevier.)

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Encephalopathy is a clinical syndrome of global cognitive impairment characterized by impaired arousal, inattention, and disorientation.

SYNONYMS

Acute confusional state
Altered mental status

ICD-10CM CODES

G93.40	Encephalopathy, unspecified
G93.41	Metabolic encephalopathy
G93.49	Other encephalopathy
G92	Toxic encephalopathy
E51.2	Wernicke encephalopathy
G04.30	Acute necrotizing hemorrhagic encephalopathy, unspecified
G04.31	Postinfectious acute necrotizing hemorrhagic encephalopathy
G04.32	Postimmunization acute necrotizing hemorrhagic encephalopathy
G04.39	Other acute necrotizing hemorrhagic encephalopathy
G93.49	Other encephalopathy
I67.4	Hypertensive encephalopathy
I67.83	Posterior reversible encephalopathy syndrome
J10.81	Influenza due to other identified influenza virus with encephalopathy
J11.81	Influenza due to unidentified influenza virus with encephalopathy
P91.60	Hypoxic ischemic encephalopathy [HIE], unspecified
P91.61	Mild hypoxic ischemic encephalopathy [HIE]
P91.62	Moderate hypoxic ischemic encephalopathy [HIE]
P91.63	Severe hypoxic ischemic encephalopathy [HIE]

EPIDEMIOLOGY & DEMOGRAPHICS

POINT PREVALENCE: 1.1% of adults in the general population >55 yr, 10% to 40% of hospitalized elderly, and 60% of nursing home patients >75 yr; 100,000 to 200,000 cases annually with anoxic encephalopathy

RISK FACTORS: Advanced age; cancer; AIDS; terminal illness; bone marrow transplant; postoperative state; poor nutritional status; acute or chronic cardiac, pulmonary, renal, or hepatic dysfunction; history of previous insult to the brain; epilepsy; drug abuse; alcoholism; overtreatment and undertreatment of pain; use of anticholinergics, benzodiazepines, narcotics, barbiturates, and neuroleptics

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Common to all encephalopathies is a fluctuating level of arousal, poor attention, and disorientation. Table 1 summarizes stages of encephalopathy in chronic liver disease.
- Some patients may appear agitated and others lethargic.
- Delusions (fixed false beliefs) and hallucinations are common.
- Asterixis (negative myoclonus) is common.
- Other physical findings, such as fever, ascites, jaundice, or tachycardia, may vary depending on the underlying cause of encephalopathy.
- Because toxins and metabolic disturbances are common causes of encephalopathy, the history should focus on exposure to toxins, especially medications, and symptoms suggesting a concurrent illness such as a urinary tract infection, pneumonia, sepsis, meningitis, or encephalitis. Clinical events precipitating hepatic encephalopathy in patients with cirrhosis are summarized in Box 1.

ETIOLOGY

The final common pathway of all causes of encephalopathy is widespread neuronal dysfunction from either a structural or functional cause. Many conditions are reversible and carry a good prognosis if treated in a timely manner.

- Organ failure (e.g., hepatic encephalopathy [Fig. 1], hypoxia, hypercapnia, uremia)
- Infection: Systemic (e.g., urinary tract, pneumonia, sepsis) or involving the central nervous system (e.g., meningitis, encephalitis)
- Toxin ingestion or withdrawal: Special consideration should be paid to alcohol, benzodiazepines, anticholinergics, neuroleptics, antibiotics (such as fluoroquinolones), and recreational drugs
- Metabolic disturbance: Hyperosmolar states, hypernatremia, hyponatremia, hyperglycemia, hypoglycemia, hypercalcemia, hypophosphatemia, acidosis, alkalosis, inborn errors of metabolism
- Endocrinopathy: Hyperthyroidism, hypothyroidism, Cushing syndrome, adrenal insufficiency, pituitary failure
- Neoplasm: Tumors of the central nervous system, primary or metastatic; effects of distant tumors (e.g., paraneoplastic limbic encephalitis)
- Nutritional deficiency, mostly in alcoholics and chronically ill patients, such as vitamin B_1 deficiency (Wernicke encephalopathy)
- Seizures: Postictal state, nonconvulsive status epilepticus, complex partial seizures, absence seizures
- Trauma: Concussion, contusion, subdural hematoma, epidural hematoma, diffuse axonal injury
- Vascular: Ischemic and hemorrhagic strokes, vasculitis, venous thrombosis
- Post-anoxic encephalopathy
- Psychiatric disease: Acute psychosis, depression with psychiatric features
- Acute demyelinating disease: Acute disseminating encephalomyelitis, tumefactive multiple sclerosis
- Other autoimmune diseases: Autoimmune encephalitis (e.g., anti-NMDA receptor encephalitis), lupus cerebritis, cerebral vasculitis (primary angiitis of the central nervous system or a secondary cerebral vasculitis)
- Other: Posterior reversible encephalopathy syndrome (PRES), hypertensive encephalopathy, postoperative status, sleep deprivation

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Differential diagnosis for encephalopathy is broad. It is typically helpful to distinguish toxic/metabolic causes from primary neurologic causes.

TABLE 1 Stages of Encephalopathy in Chronic Liver Disease (West Haven Criteria)

Stage	Clinical Signs
Stage I	Mental slowness, euphoria or anxiety, shortened attention span, impaired calculating ability
Stage II	Lethargy or apathy, inappropriate behavior, personality change, more obvious problems with calculations
Stage III	Lethargic, somnolent, marked confusion and disorientation, but responds to verbal stimuli
Stage IV	Coma, patient may or may not respond to noxious stimuli

Patients with chronic liver disease rarely, if ever, demonstrate cerebral edema, regardless of the stage of encephalopathy.
From Vincent JL, Abraham E, Moore FA et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.

BOX 1 Clinical Events Precipitating Hepatic Encephalopathy in Patients with Cirrhosis

Gastrointestinal hemorrhage
Infection (including spontaneous bacterial peritonitis)
Sepsis
Dehydration
Imbalance of electrolytes or acid-base
Renal failure
Drugs, toxins, medications (especially sedative-hypnotics or narcotics)
Illicit substances
Alcohol
Dietary indiscretion (excessive protein intake)

From Vincent JL, Abraham E, Moore FA et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.

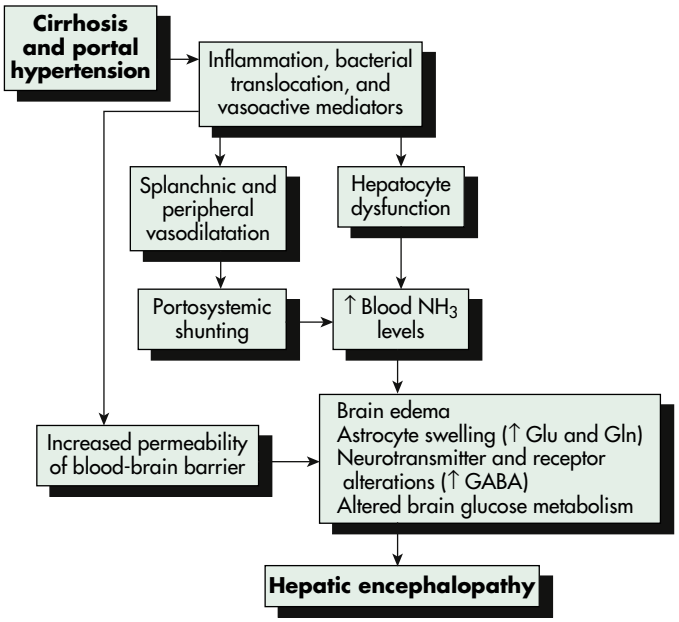

FIG. 1 Proposed pathophysiology of hepatic encephalopathy. *GABA*, Gamma-aminobutyric acid; *Gln*, glutamine; *Glu*, glutamate; *NH_3*, ammonia. (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.)

- Dementia: Distinguished from encephalopathy by a history of slowly progressive cognitive decline over time (fluctuating cognitive function is rare except in Dementia with Lewy Bodies)
- Hypersomnia
- Aphasia: Distinguished from encephalopathy by virtue of its representing a specific disorder of language rather than a global disturbance of cognitive function
- Depression
- Psychosis: Some overlap with encephalopathy because delusions and hallucinations may be common to both
- Mania
- Vegetative state from cerebral injury; these patients appear awake (eyes are open) but there is no content to their consciousness
- Akinetic mutism: These patients do not talk and do not move; there is little fluctuation in their state, and there is no asterixis or other focal deficit
- Locked-in syndrome: May be distinguished from encephalopathy by the presence of fixed neurologic deficits (e.g., paralysis of all four limbs); however, the patient is aware of his or her environment

WORKUP

The best tool in the evaluation of encephalopathy is a good history and physical exam, which will help tailor the remainder of the diagnostic workup. Interview family members and other providers to identify preceding events, medication changes, and medical history. Evaluate focal deficits.

LABORATORY TESTS

- Comprehensive metabolic panel, amylase, lipase, ammonia, TSH, B_{12}
- Complete blood count with differential
- Drug screen and alcohol level (must order ethylene glycol separately if suspected)
- Lumbar puncture if meningitis, encephalitis, autoimmune process, or subarachnoid hemorrhage with negative imaging is suspected
- HIV, RPR
- Urinalysis and microscopy, urine culture, blood cultures
- Arterial blood gases

IMAGING STUDIES

The following imaging and diagnostic studies may be indicated depending on history and physical examination:

- Chest radiograph to rule out pneumonia
- Head CT to rule out intracranial hemorrhage, hydrocephalus, tumors
- Brain MRI with and without contrast and with diffusion-weighted images for suspected encephalitis, tumors, acute strokes, or acute autoimmune processes
- Magnetic resonance angiography/venography for strokes, arterial dissection, venous thrombosis
- Conventional angiography for CNS vasculitis and aneurysms
- EEG: Evaluate for subclinical status epilepticus

Rx TREATMENT

The encephalopathy itself is a symptom of these underlying problems. In general, it is best to avoid treating the symptom of encephalopathy with antipsychotics or sedatives. The best approach is to treat the underlying toxic or metabolic disturbance.

- Thiamine supplementation.
- Glucose for hypoglycemia.
- Antibiotics in cases of infections (choose an agent with good CNS penetration in cases of primary CNS infections; to prevent exacerbation of underlying problem, ensure also that the agent is not associated with causing encephalopathy, if possible).
- Insulin in hyperglycemic conditions (e.g., diabetic ketoacidosis, hyperosmolar nonketosis, and sepsis).
- Correct electrolyte disturbances properly.
- Treat organ failure and its sequelae; for example, implement appropriate therapy for hyperammonemia and uremia.
- Ensure hemodynamic stability (blood pressure and heart rate).
- Eliminate medications that can cause or exacerbate encephalopathy: Anticholinergic drugs, benzodiazepines and other sedative-hypnotics, neuroleptics, and narcotics.
- Consider acute intoxication with, or withdrawal from, drugs or alcohol and treat withdrawal appropriately.
- Consider serotonin syndrome and neuroleptic malignant syndrome in the appropriate clinical setting.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Delirium (Related Key Topic)
Encephalitis, Acute Viral (Related Key Topic)
Hepatic Encephalopathy (Related Key Topic)

AUTHORS: **Chloe Mander Nunneley, MD, Joseph S. Kass, MD, JD, FAAN,** and **Joshua Chalkely, DO, MS**

SUGGESTED READINGS

Agrawal A et al: Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open-label, randomized controlled trial of lactulose, probiotics, and no therapy, *Am J Gastroenterol* 107:1043, 2012.

Bass N et al: Rifaximin treatment in hepatic encephalopathy, *N Engl J Med* 362:1071-1081, 2010.

Riordan SM, Williams R: Gut flora and hepatic encephalopathy in patients with cirrhosis, *N Engl J Med* 362:1140-1141, 2010.

BASIC INFORMATION

DEFINITION/DIAGNOSTIC CRITERIA (DSM-5; ROME IV)

- Reverted passage of feces into inappropriate places (e.g., clothing, floor), whether involuntary or intentional
- At least one such event occurs each month for at least 3 mo
- The behavior is not attributable to the physiologic effects of a substance (e.g., laxatives) or another medical condition except through a mechanism involving constipation

In May 2016, Rome Foundation published the revised criteria for anorectal disorders. Encopresis is no longer named as a subclassification of functional anorectal disorders. Fecal incontinence (FI) and nonretentive fecal incontinence (NFI) are now the terms used. FI is defined as recurrent uncontrolled passage of fecal material in an individual with a developmental age of at least 4 yr for at least 3 mo. Diagnostic criteria for NFI include at least a 1-mo history of the following symptoms in a child with a developmental age older than 4 yr:

1. Defecation into places inappropriate to the sociocultural context;
2. No evidence of fecal retention;
3. After appropriate medical evaluation, the fecal incontinence cannot be explained by another medical condition.

SYNONYMS

Stool/fecal incontinence; soiling

ICD-10CM CODES

R15.9	Fecal incontinence
F98.1	Encopresis not due to a substance or known physiological condition; fecal incontinence (non-retentive) not due to an organic medical etiology

DSM-5 CODE

307.7	Encopresis with or without constipation and overflow incontinence

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Preschool age (though also occurs during school age and adolescence)
PREVALENCE (IN U.S.): 1.5% to 7.5% of children 4 to 12 yr old
PREDOMINANT SEX: More often in males (estimates range from 1.9:1 to 9:1)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most children are toilet-trained for stool by age 4. Constipation and withholding of stool are significant factors in 80% to 90% of cases ("retentive encopresis" or FI). In 10% to 20%, constipation is not a factor (NFI).
- When constipation is longstanding, soft or liquid stool may flow around the retained feces, resulting in overflow incontinence. This may occur several times per day and may mistakenly be construed as diarrhea.
- Children may report a lack of awareness of stool passage when longstanding constipation/impaction has resulted in loss of rectal tone and sensation. Furthermore, some children habituate to the odor.
- In NFI, physical examination is normal. Abdominal radiograph does not reveal fecal loading.

ETIOLOGY

- Approximately 96% of children have bowel movements between three times daily to once every other day. When bowel movements are less frequent, stool becomes drier and harder and much more uncomfortable or painful to pass. Children may avoid the discomfort or pain by avoiding elimination, resulting in worsening constipation and overflow incontinence.
- Constipation may begin gradually as a result of a decrease in elimination frequency, or more acutely after an illness or changes in diet.
- Toilet training practices that increase anxiety may also play a role in stool retention, the development of constipation, and eventual encopresis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hirschsprung disease
- Endocrine disease (hypothyroidism)
- Cerebral palsy
- Myelomeningocele
- Pseudoobstruction
- Anorectal lesions (rectal stenosis)
- Malformations
- Trauma
- Rectal prolapse
- Celiac disease
- Hypothyroidism
- Medications

WORKUP

- History: Frequency of elimination, character of the stool, associated pain, and presence of enuresis (with which it is frequently associated).
- Evaluate for other developmental or psychiatric problems.
- Common physical findings in retentive encopresis: Abdominal fecal mass, stool impacted rectum, loose anal sphincter, fecal material in the perianal area, anal tags or fissures.
- Perform a complete neurologic examination to exclude sensory-neural or spinal cord abnormalities.

LABORATORY TESTS

- Consider thyroid function tests, celiac screening tests, electrolytes, calcium, urinalysis, and urine culture.
- If concerned about the possibility of Hirschsprung disease, obtain rectal biopsy or anorectal manometry.

IMAGING STUDIES

Abdominal radiograph to determine presence of fecal impaction; MRI of spine to assess for neural tube defects or tethered cord

TREATMENT

ACUTE GENERAL Rx

- Disimpaction is a necessary first step, by oral or rectal route (or combination).
- For oral disimpaction, polyethylene glycol, magnesium citrate, or high doses of mineral oil are effective (avoid use of mineral oil in patients at risk for aspiration).
- Adding stimulant laxatives such as senna or bisacodyl can make oral disimpaction more effective.
- For rectal disimpaction, phosphate, saline, or mineral oil enemas are effective.
- When medical workup determines that constipation is not present (nonretentive encopresis/NFI), consider implementing toilet-training routines or referral to behavioral health provider.

CHRONIC Rx

- Prevent recurrence of constipation with oral stool softeners (e.g., polyethylene glycol or lactulose) or stool lubricants (mineral oil).
- In immediate post disimpaction period (1 mo after acute treatment), stimulant laxatives may be needed because bowel tone remains low; taper use as quickly as possible to avoid dependence.
- Family documentation of stool passage, including location and amount, on a chart or calendar helps inform medication changes and best times for toilet sitting.
- Praise and other small incentives for positive toileting routines and taking medication can help to maintain good bowel habits. Balanced diet and increased fiber intake/supplementation may also help.
- Formal behavioral treatment (education, reinforcement of treatment adherence and exercises to improve anal sphincter control) increases treatment success. Biofeedback to improve sphincter function is advocated by some, with 1-yr results comparable to behavioral treatment. Adjunctive Internet-based interventions that incorporate behavioral therapy and medical management are also beginning to show promise.

DISPOSITION

Encopresis may be self-limited or relatively brief in duration; may require prolonged maintenance therapy. Relapses are common.

REFERRAL

Behavioral family therapy should be considered for patients who do not respond to medical treatment within a few months or who have significant contributing psychiatric or family factors.

PEARLS & CONSIDERATIONS

- It is crucial to educate parents and children about constipation and encopresis and to defuse negative interactions.
- Emphasize that this can require prolonged maintenance therapy and that relapses are common.

SUGGESTED READINGS

Hyams JS et al: Childhood functional gastrointestinal disorders: child/adolescent, *Gastroenterology* 150:1456-1468, 2016.

Tabbers MM et al: Evaluation and treatment of functional constipation in infants and children: evidence based recommendations from ESPGHAN and NASPGHAN, *J Pediatr Gastroenterol Nutr* 58(2):258-274, 2014.

RELATED CONTENT

Encopresis (Patient Information)

AUTHORS: **Carolina S. Cerezo, MD, FAAP,** and **Wendy A. Plante, PhD**

BASIC INFORMATION

DEFINITION

Infective endocarditis is an infection of the endocardial surface of the heart or mural endocardium. Box 1 describes the modified Duke criteria for the diagnosis of infective endocarditis.

ACUTE ENDOCARDITIS: Usually caused by *Staphylococcus aureus, Streptococcus pyogenes, S. pneumoniae,* and *Neisseria* organisms; classic clinical presentation of high fever, positive blood cultures, vascular and immunologic phenomenon

SUBACUTE ENDOCARDITIS: Usually caused by viridans streptococci in the presence of valvular pathology; less toxic, often indolent presentation with lower fevers, night sweats, fatigue

ENDOCARDITIS IN INJECTION DRUG USERS: Often involving *S. aureus* or *Pseudomonas aeruginosa* with variation that may be geographically influenced; tricuspid or multiple valvular involvement; high mortality rate of 50% to 60%

PROSTHETIC VALVE ENDOCARDITIS (EARLY): Usually caused by *S. aureus* (leading cause of PVE) within 2 mo of valve replacement; other organisms include *S. epidermidis,* gram-negative bacilli, diphtheroids, *Candida* organisms

PROSTHETIC VALVE ENDOCARDITIS (LATE): Typically develops >60 days after valvular replacement; involved organisms similar to early prosthetic valve endocarditis, including viridans streptococci, enterococci, and group D streptococci

NOSOCOMIAL ENDOCARDITIS: Secondary to intravenous catheters, TPN lines, pacemakers; coagulase-negative staphylococci, *S. aureus,* and streptococci most common

Non-HACEK gram-negative bacillus endocarditis is not primarily a disease of injection drug users. More than half of all cases are associated with health care contact

SYNONYMS

Bacterial endocarditis
Subacute bacterial endocarditis (SBE)
Endocarditis

ICD-10CM CODES

I33.0 Acute and subacute infective endocarditis
I33.9 Acute endocarditis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Yearly incidence is 15 cases/100,000 persons and is increasing due to medical interventions in the elderly and an increase in implanted cardiac devices.

PEAK INCIDENCE: Females: Often <35 yr old; males: 45 to 65 yr old

NOSOCOMIAL ENDOCARDITIS: 14% to 28% of cases

PREVALENCE (IN U.S.): 0.3 to 3 cases/1000 hospital admissions. 40,000 to 50,000 new cases a yr in the U.S.

BOX 1 Modified Duke Criteria for the Diagnosis of Infective Endocarditis*

Major Criteria

- Positive blood cultures for infective endocarditis.
- Typical microorganism for infective endocarditis from two separate blood cultures in the absence of a primary focus: *Streptococcus viridans, Streptococcus bovis*
- HACEK group: *Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae*
- Community-acquired *Staphylococcus aureus* or enterococci
- Persistently positive blood cultures, defined as recovery of a microorganism consistent with infective endocarditis from blood cultures drawn more than 12 hr apart or all of three or the majority of four or more separate blood cultures, with first and last drawn at least 1 hr apart
- Single positive blood culture for *Coxiella burnetii* or antiphase IgG antibody titer >1:800
- Evidence for endocardial involvement
- TTE (TEE in prosthetic valve) showing oscillating intracardiac mass on a valve or supporting structures, in the path of regurgitant jet or on implanted material, in the absence of an alternative anatomic explanation, *or*
- Abscess, *or*
- New partial dehiscence of prosthetic valve.

Minor Criteria

- Predisposition (e.g., prosthetic valve, intravenous drug use).
- Fever: 38° C (100.4° F).
- Vascular phenomena.
- Immunologic phenomena.
- Microbiologic evidence: Positive blood culture but not meeting major criteria.

Ig, Immunoglobulin; *TEE,* transesophageal echocardiogram; *TTE,* transthoracic echocardiogram.
*Adapted from Li JS et al: Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis, *Clin Infect Dis* 30:633-638, 2000.
From Ballinger A: *Kumar & Clark's essentials of clinical medicine,* ed 6, Edinburgh, 2012, WB Saunders.

PREDOMINANT SEX: Male < female
PREDOMINANT AGE: 45 to 65 yr

ENDOCARDITIS TRENDS

From 1998 through 2013 the population of patients with prosthetic valve endocarditis increased from 2% to 13.8%, as did cardiac device-related endocarditis, from 1.3% to 4.1%, whereas native valve endocarditis decreased from 74.5% to 68.4%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical manifestations of infective endocarditis are described in Table 1 and Table 2.
- Fever may be variable in presentation; may be high, hectic, or absent.
- Fever, chills, fatigue, and rigors occur in 25% to 80% of patients.
- Heart murmur may be absent in right-sided endocarditis.
- Embolic phenomenon with peripheral manifestations is found in 50% of patients.
- Skin manifestations include petechiae, Osler nodes (Fig. E1), splinter hemorrhages, Janeway lesions (Fig. E2).
- Splenomegaly is more common with subacute course.

ETIOLOGY

Staphylococcal infection is now the leading cause of native or prosthetic valve infection. Variation in incidence may occur that is influenced by the patient's risk for developing infection. Table 3 summarizes the microbiology of infective endocarditis. Risk factors include hemodialysis (8%), IV drug use (10%), mitral regurgitation (43%), aortic regurgitation (26%), and rheumatic heart disease (3.3%).

TABLE 1 Symptoms in Infective Endocarditis

Symptom	Patients Affected (%)
Fever	80-95
Chills	40-70
Weakness	40-50
Malaise	20-40
Sweats	20-40
Anorexia	20-40
Headache	20-40
Dyspnea	20-40
Cough	20-30
Weight loss	20-30
Myalgia/arthralgia	10-30
Stroke	10-20
Confusion/delirium	10-20
Nausea/vomiting	10-20
Edema	5-15
Chest pain	5-15
Abdominal pain	5-15
Hemoptysis	5-10
Back pain	5-10

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.

ACUTE ENDOCARDITIS:

- *Staphylococcus aureus* (MSSA and MRSA)
- *Staphylococcus lugdunensis*
- *Streptococcus pneumoniae*
- Streptococcal species and groups A through G
- *Haemophilus influenzae*

SUBACUTE ENDOCARDITIS:

- *Viridans streptococci* (alpha-hemolytic) including nutritionally variant species:

TABLE 2 Physical Findings in Infective Endocarditis

Finding	Patients Affected (%)
Fever	80-90
Heart murmur	75-85
New murmur	10-50
Changing murmur	5-20
Central neurologic abnormality	20-40
Splenomegaly	10-40
Petechiae/conjunctival hemorrhage	10-40
Splinter hemorrhages	5-15
Janeway lesions	5-10
Osler nodes	3-10
Retinal lesion or Roth spot	2-10

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.

1. *Abiotrophia* spp *and Granulicatella* spp;
- *S. bovis* (now called S. *gallollyticus*)
- Enterococci
- *S. aureus*

ENDOCARDITIS IN INJECTION DRUG USERS:
- *S. aureus*
- *P. aeruginosa*
- *Candida* spp.
- Enterococci

PROSTHETIC VALVE ENDOCARDITIS (EARLY):
- *S. epidermidis*
- *S. aureus*
- Gram-negative bacilli
- Group D streptococci

PROSTHETIC VALVE ENDOCARDITIS (LATE):
- *S. epidermidis*
- *Viridans streptococci*
- *S. aureus*
- Enterococci and group D streptococci

NOSOCOMIAL ENDOCARDITIS:
- Coagulase-negative staphylococci
- *S. aureus*
- Streptococci: Viridans, group B, enterococcus

HACEK ORGANISMS:
- Fastidious gram-negative bacilli
- ***H.*** *parainfluenzae*
- ***H.*** *aphrophilus*
- ***A.*** *actinomycetemcomitans*
- ***C****ardiobacterium hominis*
- ***E****ikenella corrodens*
- ***K****ingella kingae*

Other unusual pathogens:
- Q fever: *Coxiella burnetii*
- *Bartonella henselae* (etiologic agent of cat scratch disease)
- *Tropheryma whippelii* (Whipple disease)

RISK FACTORS
- Poor dental hygiene
- Long-term hemodialysis
- Diabetes mellitus
- HIV infection
- Mitral valve prolapse

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS
- Brain abscess
- FUO
- Pericarditis
- Meningitis
- Rheumatic fever
- Osteomyelitis
- Salmonella
- TB
- Bacteremia
- Pericarditis
- Glomerulonephritis

WORKUP
Physical examination to evaluate for the previous physical findings followed by laboratory testing (see "Laboratory Tests"). Fig. 3 describes a diagnostic evaluation of suspected endocarditis. The modified Duke criteria for diagnosis of endocarditis defines "major criteria" as persistently positive blood cultures of organisms typical of endocarditis or endocardial involvement (new valvular regurgitation or positive echocardiogram). "Minor criteria" are defined as presence of predisposing condition or injection drug use, fever, embolic vascular pneumonia (e.g., glomerulonephritis, rheumatoid factor), or positive blood cultures not meeting major criteria. Definite endocarditis is two major criteria or one major criteria and three minor criteria or five minor criteria or presence of organisms by culture or histologic examination of a vegetation.

LABORATORY TESTS
- Blood cultures: Three sets in first 24 hr. Table 4 describes causes of culture-negative endocarditis.
- More culturing if patient has received prior antibiotic
- CBC (anemia possibly present, subacute)
- WBC (leukocytosis is higher in acute endocarditis)
- ESR and C-reactive protein (elevated)
- Positive rheumatoid factor (subacute endocarditis)
- Proteinuria, hematuria, RBC casts
- Serologies or PCR for more unusual pathogens (*B. henselae, C. burnetii, etc.*)

IMAGING STUDIES
- Echocardiogram: Two-dimensional. Transthoracic echocardiography (TTE) (Fig. E4) is noninvasive and more easily available but has less-than-optimal sensitivity (50% to 80%) for endocarditis.
- Transesophageal echocardiography (TEE): More sensitive in detecting vegetations and preferred diagnostic modality. It is especially helpful with prosthetic valves or in detecting perivalvular disease (Fig. E5). Echocardiographic features that suggest potential need for surgical intervention are summarized in Table 5.
- Electrocardiogram: Look for cardiac conduction abnormalities, injury pattern, or evidence of pericarditis—any such new findings are suggestive of myocardial abscess.

Rx TREATMENT

Initial IV antibiotic therapy (before culture results) is aimed at the most likely organism. The American Heart Association has developed guidelines based on the most frequently encountered bacteria. Tables 6 through 10 summarize treatment recommendations.

- **Native valve endocarditis** caused by penicillin-susceptible *S. viridians, S. gallolyticus* (previously called *S. bovis*), and other streptococci (MIC of penicillin ≤0.12 mcg/ml): Pen G 12 to 18 million U IV q24h continuous or divided q4h for 4 wk **or** ceftriaxone 2 g IV or IM q day for 4 wk for penicillin-allergic patients. Vancomycin at 30 mg/kg per 24 hr in two equally divided doses assuming normal kidney function, for 4 wk.
- **Native valve endocarditis** caused by strains of viridians streptococci and *S. gallolyticus (S. bovis)* relatively resistant to penicillin (MIC >0.12 mcg/ml): Pen G: 24 million units per 24 hr IV either continuously or in 4 or 6 equally divided doses for 4 wk **or** ceftriaxone 2 g per 24 hr IV or IM for 4 wk **plus** gentamicin 3 mg/kg per 24 hr IV or IM in one dose or in 2 to 3 equally divided doses for 2 wk or monotherapy with vancomycin 30 mg/kg per 24 hr IV in 2 equally divided doses for 4 wk not to exceed 2 g per 24 hr unless concentrations in serum too low.
- **Native valve endocarditis** due to *Staphylococcus:*
  1. **MSSA:** Nafcillin (or oxacillin) 12 per 24 hr IV in 4 or 6 equally divided doses for 6 wk **plus** optional addition of gentamicin 3 mg/kg per 24 hr IV or IM in 2 or 3 equally divided doses for 3 to 5 days **or** cefazolin 6 g per 24 hr IV in 3 equally divided doses for 6 wk, **plus** optional addition of gentamicin 3 mg/kg per 24 hr IV or IM in 2 or 3 equally divided doses for 3 to 5 days. A newer antibiotic daptomycin has an indication for right-sided endocarditis with MSSA at 6 mg/kg IV q24h.
  2. **MRSA:** Vancomycin 30 mg/kg per 24 hr in 2 equally divided doses for 6 wk; not to exceed 2 g per 24 hr unless concentrations in serum are low.
- For culture-negative native valve endocarditis one of the following regimens is suggested: Ampicillin-sulbactam: 12 g per 24 hr IV in 4 equally divided doses for 4 to 6 wk **plus** gentamicin 3 mg/kg per 24 hr IV or IM in 3 equally divided doses for 4 to 6 wk **or** vancomycin 30 mg/kg per 24 hr IV in 2 equally divided doses for 4 to 6 wk; not to exceed 2 g per 24 hr unless concentrations in serum low **plus** gentamicin 3 mg/kg per 24 hr IV or IM in 3 equally divided doses for 4 to 6 wk **plus** ciprofloxacin 1000 mg per 24 hr orally or 800 mg per 24 hr IV in 2 equally divided doses for 4 to 6 wk.
- For treatment of native valve endocarditis due to HACEK organisms: Ceftriaxone 2 g per 24

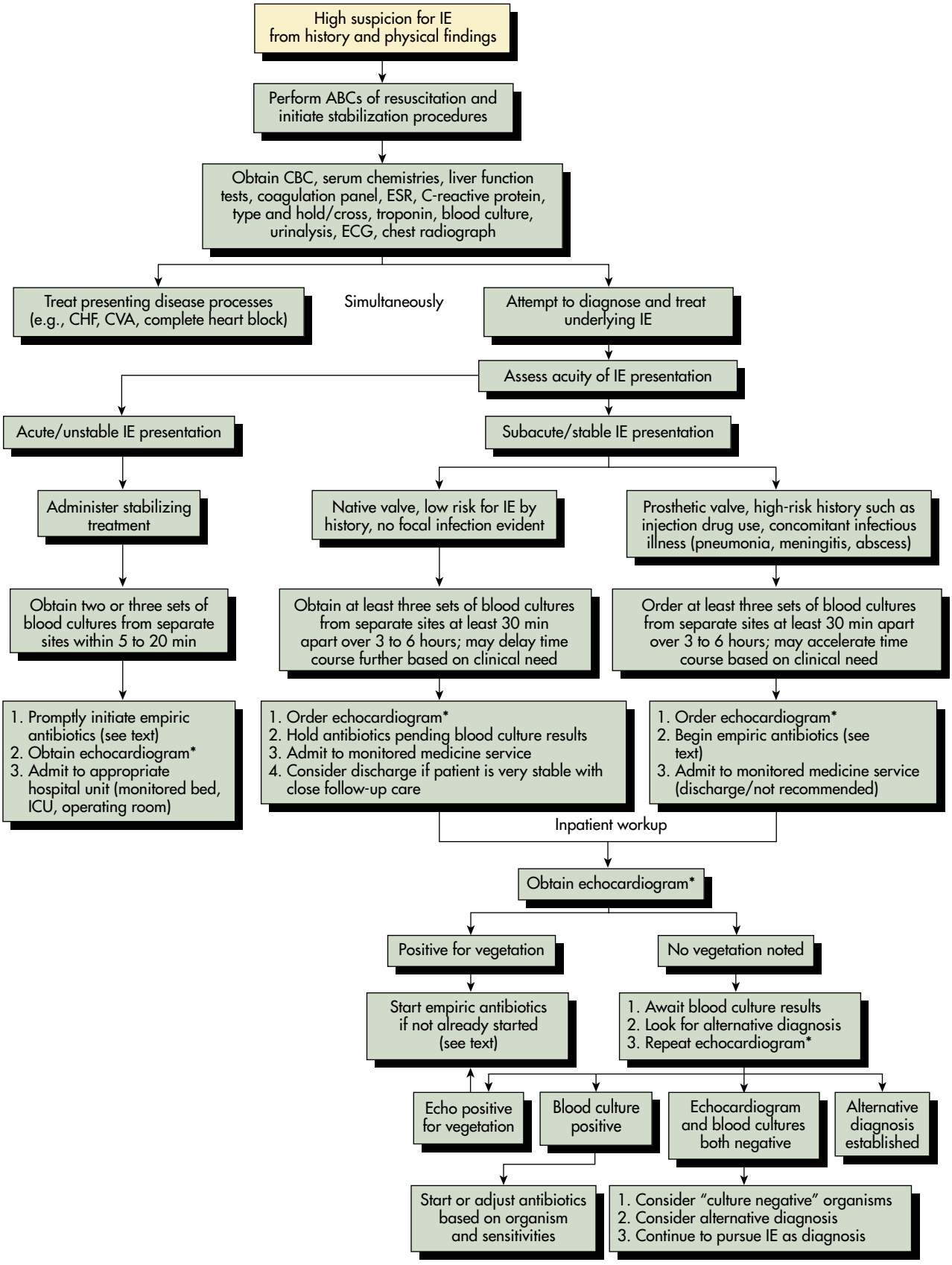

FIG. 3 Diagnostic algorithm for the emergency department management of patients in whom infective endocarditis *(IE)* is suspected. *Echocardiography can be performed via either the transthoracic *(TTE)* or transesophageal *(TEE)* technique. TEE is more invasive but is more sensitive for detecting vegetations and complications of IE, such as perivalvular abscesses; it is recommended for prosthetic valves; for situations in which optimal visualization by TTE will be difficult, such as emphysema and morbid obesity; for high suspicion of IE but normal TTE findings; and for high suspicion of a complication of IE, such as perivalvular abscess. Normal findings with either technique do not exclude IE if clinical suspicion is high. Echocardiograms can be repeated in an attempt to identify problems such as vegetations and abscesses that may not be noted initially. *ABCs,* Airway, breathing, and circulation; *CBC,* complete blood count; *CHF,* congestive heart failure; *CVA,* cerebrovascular accident; *ECG,* electrocardiogram; *ESR,* erythrocyte sedimentation rate; *ICU,* intensive care unit. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

TABLE 3 Microbiology of Infective Endocarditis (IE)

	Native Valve				Prosthetic Valve	
	Health Care-Associated IE (%)					
ORGANISM	Community-Acquired IE (%) (*n* = 1201)	Nosocomial (*n* = 370)	Nonnosocomial (*n* = 254)	Intravenous Drug Users with IE (%) (*n* = 237)	Early IE (%) (*n* = 140)	Late IE (%) (*n* = 390)
Staphylococcus aureus	21	45	42	68	34	19
Coagulase-negative staphylococci	6	12	15	3	28	20
Enterococcus species	10	14	16	5	10	13
Viridans group streptococci	26	10	6	10	1	11
*Streptococcus gallolyticus**	10	3	3	1	1	7
HACEK	3	0	0	0	0	2
Fungi	0	2	2	1	6	3
Other	13	7	10	7	6	15
Negative blood culture	11	7	6	5	14	10

*Formerly *Streptococcus bovis.*
HACEK, Haemophilus spp., *Aggregatibacter* spp., *Cardiobacterium hominis, Eikenella corrodens, and Kingella* spp.
From Zipes DP: *Braunwald's Heart Disease, A textbook of Cardiovascular Medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 4 Causes of Culture-Negative Endocarditis

Organism	Epidemiology and Exposures	Diagnostic Approaches
Aspergillus and other noncandidal fungi	Prosthetic valve	Lysis-centrifugation technique; also culture and histopathologic examination of any emboli
Bartonella spp.	*B. henselae:* Exposure to cats or cat fleas *B. quintana:* Louse infestation; homelessness, alcohol abuse	Most common cause of culture-negative IE in U.S.; serologic testing (may cross-react with *Chlamydia* spp.); PCR assay of valve or emboli is best test; lysis-centrifugation technique may be useful
Brucella spp.	Ingestion of unpasteurized milk or dairy products; livestock contact	Blood cultures ultimately become positive in 80% of cases with extended incubation time of 4-6 wk; lysis-centrifugation technique may expedite growth; serologic tests are available
Chlamydia psittaci	Bird exposure	Serologic tests available but exhibit cross-reactivity with *Bartonella;* monoclonal antibody direct stains on tissue may be useful; PCR assay now available
Coxiella burnetii (Q fever)	Global distribution; exposure to unpasteurized milk or agricultural areas	Serologic tests (high titers of antibody to both phase 1 and phase 2 antigens); also PCR assay on blood or valve tissue
HACEK spp.	Periodontal disease or preceding dental work	Although traditionally a cause of culture-negative IE, HACEK species are now routinely isolated from most liquid broth continuous monitoring blood culture systems without prolonged incubation times
Legionella spp.	Contaminated water distribution systems; prosthetic valves	Serology available; periodic subcultures onto buffered charcoal yeast extract medium; lysis-centrifugation technique; PCR assay available
Nutritionally variant streptococci	Slow and indolent course	Supplemented culture media or growth as satellite colonies around *Staphylococcus aureus* streak; antimicrobial susceptibility testing often requires processing specialized microbiology laboratory
Tropheryma whipplei (Whipple disease)	Typical signs and symptoms include diarrhea, weight loss, arthralgias, abdominal pain, lymphadenopathy, central nervous system involvement; IE may be present without systemic symptoms	Histologic examination of valve with periodic acid–Schiff stain; valve cultures may be done using fibroblast cell lines; PCR assay on vegetation material

HACEK, Haemophilus spp., *Aggregatibacter* spp., *Cardiobacterium hominis, Eikenella corrodens*, and *Kingella* spp.; *IE*, infective endocarditis; *PCR*, polymerase chain reaction.
From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 8, Philadelphia, 2015, WB Saunders.

hr IV or IM in 1 dose for 4 wk **or** ampicillin-sulbactam 12 g per 24 hr IV in 4 equally divided doses for 4 wk **or** ciprofloxacin 1000 mg per 24 hr orally or 800 mg per 24 hr IV in 2 equally divided doses for 4 wk.

- **Patients with prosthetic valves** endocarditis:
- Methicillin-susceptible strains: Nafcillin or oxacillin 12 g per 24 hr IV in 6 equally divided doses for at least 6 wk **plus** rifampin 900 mg per 24 hr IV or orally in 3 equally divided doses for at least 6 wk **plus** gentamicin 3 mg/kg IV or IM in 2 or 3 equally divided doses for 2 wk.
- Methicillin-resistant strains: Vancomycin 30 mg/kg per 24 hr in two equally divided doses for at least 6 wk **plus** rifampin 900 mg per 24 hr IV or orally in three equally divided doses for at least 6 wk **plus** gentamicin 3 mg/kg per 24 hr IV or IM in two or three equally divided doses for 2 wk.

Antibiotic therapy after identification of the organism should be guided by susceptibility testing, preferably by formal testing by MIC (minimum inhibitory concentration).

TABLE 5 Echocardiographic Features That Suggest Potential Need for Surgical Intervention

Vegetation

Persistent vegetation after systemic embolization
Anterior mitral valve leaflet vegetation, particularly if it is highly mobile with size >10 mm*
One or more embolic events during the first 2 wk of antimicrobial therapy*
Increase in vegetation size despite appropriate antimicrobial therapy*†

Valvular Dysfunction

Acute aortic or mitral insufficiency with signs of ventricular failure†
Heart failure unresponsive to medical therapy†
Valve perforation or rupture†

Perivalvular Extension

Valvular dehiscence, rupture, or fistula†
New heart block†‡
Large abscess or extension of abscess despite appropriate antimicrobial therapy†

*Surgery may be required because of risk of embolization.
†Surgery may be required because of heart failure or failure of medical therapy.
‡Echocardiography should not be the primary modality used to detect or monitor heart block.
From Zipes DP: *Braunwald's Heart Disease, A textbook of Cardiovascular Medicine*, ed 11, Philadelphia, 2019, Elsevier.

TABLE 6 Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *Streptococcus gallolyticus*

Regimen	Dosage* and Route	Duration (wk)	Class	LOE	Comments
Aqueous crystalline penicillin G sodium	12-18 million U/24 hr IV either continuously or in four or six equally divided doses	4	IIa	B	Preferred in most patients >65 years of age or patients with impairment of 8th cranial nerve function or renal function
or					
Ceftriaxone sodium	2 g/24 hr IV/IM in one dose	4	IIa	B	
Aqueous crystalline penicillin G sodium	12-18 million U/24 hr IV either continuously or in six equally divided doses	2	IIa	B	2-wk regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 ml/min, impaired 8th cranial nerve function, or *Abiotrophia, Granulicatella*, or *Gemella* spp. infection; gentamicin dosage should be adjusted to achieve peak serum concentration of 3-4 μg/ml and trough serum concentration of <1 μg/ml when three divided doses are used; there are no optimal drug concentrations for single daily dosing‡
or					
Ceftriaxone sodium	2 g/24 hr IV/IM in one dose	2	IIa	B	
plus					
Gentamicin sulfate†	3 mg/kg/24 hr IV/IM in one dose	2			
Vancomycin hydrochloride§	30 mg/kg/24 hr IV in two equally divided doses, not to exceed 2 g/24 hr unless concentrations in serum are inappropriately low	4	IIa	B	Vancomycin recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to a trough concentration range of 10-15 μg/ml

MIC ≤0.12 μg/ml.
IM, Intramuscular; *IV,* intravenous; *LOE*, level of evidence; *MIC,* minimum inhibitory concentration.
*Dosages recommended are for patients with normal renal function.
†Other potentially nephrotoxic drugs (e.g., nonsteroidal antiinflammatory drugs) should be used with caution in patients receiving gentamicin therapy.
‡Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of IE are available.
§Vancomycin dosages should be infused over at least 1 hr to reduce the risk of histamine-release "red man" syndrome.
From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

TABLE 7 Therapy of Native Valve Endocarditis Caused by Strains of Viridans Group Streptococci and *Streptococcus gallolyticus* Relatively Resistant to Penicillin

Regimen	Dosage* and Route	Duration (wk)	Class	LOE	Comments
Aqueous crystalline penicillin G sodium	24 million U/24 hr IV either continuously or in four to six equally divided doses	4	IIa	B	Patients with endocarditis caused by penicillin-resistant (MIC ≥0.5 μg/ml) strains should be treated with regimen recommended for enterococcal
or					
Ceftriaxone sodium	2 g/24 hr IV/IM in one dose	4	IIa	B	
plus					
Gentamicin sulfate†	3 mg/kg/24 hr IV/IM in one dose	2			
Vancomycin hydrochloride§	30 mg/kg/24 hr IV in two equally divided doses, not to exceed 2 g/24 hr, unless serum concentrations are inappropriately low	4	IIb	C	Vancomycin‡ therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy

Minimum inhibitory concentration (MIC) >0.12 μg/ml to <0.5 μg/ml.
IM, Intramuscular; *IV,* intravenous; *LOE*, level of evidence.
*Dosages recommended are for patients with normal renal function.
†See Table 6 for appropriate dosage of gentamicin.
‡See Table 6 for appropriate dosage of vancomycin.
From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

TABLE 8 Therapy for Endocarditis of Prosthetic Valves or Other Prosthetic Material Caused by Viridans Group Streptococci and *Streptococcus gallolyticus*

Regimen	Dosage* and Route	Duration (wk)	Class	LOE	Comments
Penicillin-Susceptible Strain (MIC ≤0.12 μg/ml)					
Aqueous crystalline penicillin G sodium	24 million U/24 hr IV either continuously or in four to six equally divided doses	6	IIa	B	Penicillin or ceftriaxone together with gentamicin has not demonstrated cure rates superior to those for monotherapy with penicillin or ceftriaxone for patients with highly susceptible strain; gentamicin should not be administered to patients with creatinine clearance of <30 ml/min.
or					
Ceftriaxone	2 g/24 hr IV/IM in one dose	6	IIa	B	
with or without					
Gentamicin sulfate†	3 mg/kg/24 hr IV/IM in one dose	2			
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in two equally divided doses	6	IIa	B	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone.
Penicillin–Relatively or Fully Resistant Strain (MIC >0.12 μg/ml)					
Aqueous crystalline penicillin sodium	24 million U/24 hr IV either continuously or in four to six equally divided doses	6	IIa	B	
or					
Ceftriaxone	2 g/24 hr IV/IM in one dose	6	IIa	B	
plus					
Gentamicin sulfate	3 mg/kg/24 hr IV/IM in one dose	6			
Vancomycin hydrochloride	30 mg/kg/24 hr IV in two equally divided doses	6	IIb	C	Vancomycin therapy is recommended only for patients unable to tolerate penicillin or ceftriaxone.

IM, Intramuscular; *IV,* intravenous; *LOE,* level of evidence; *MIC,* minimum inhibitory concentration.
*Dosages recommended are for patients with normal renal function.
†See Table 6 for appropriate dosage of gentamicin.
‡See text and Table 6 for appropriate dosage of vancomycin.
From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

TABLE 9 Therapy for Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

Regimen	Dosage* and Route	Duration (wk)	Class	LOE	Comments
Oxacillin-Susceptible Strains					
Nafcillin or oxacillin†	12 g/24 hr IV in four to six equally divided doses	6	IIa	B	For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk (see text)
For penicillin-allergic (nonanaphylactoid type) patients:					Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin
Cefazolin	6 g/24 hr IV in three equally divided doses	6	IIa	B	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases‡
Oxacillin-Resistant Strains					
Vancomycin‡	30 mg/kg/24 hr IV in two equally divided doses	6	IIa	B	Adjust vancomycin dosage to a trough serum concentration of 10-15 μg/ml (see text for vancomycin alternatives)

IE, Infective endocarditis; *IV,* intravenous; *LOE,* Level of evidence.
*Dosages recommended are for patients with normal renal function.
†Penicillin G 24 million U/24 hr IV in four to six equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin-susceptible (MIC ≤0.1 μg/ml) and does not produce beta-lactamase.
‡For specific dosing adjustment and issues concerning vancomycin, see Table 6 footnotes.
From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

DISPOSITION

- The patient may need outpatient IV antibiotic therapy, and arrangements need to be made to ensure safe vascular access and continuity of care with outpatient IV therapy team.
- Long-term follow-up is essential after therapy has ended; relapse of endocarditis may occur.
- Prophylaxis with antibiotics will be needed before dental procedures as a previous episode of endocarditis increases the risk of recurrent endocarditis associated with transient bacteremia from dental procedures.

REFERRAL

- To an infectious disease specialist.
- To a cardiologist or a cardiac surgeon if evidence of heart failure, refractory infection, myocardial abscess, valve disruption, or major embolic events occur.
- The timing and indications for surgical intervention to prevent systemic embolism in infective endocarditis remain controversial. Trials have shown that early surgery in patients with infective endocarditis and large vegetations significantly reduced death and embolic events by decreasing the risk of systemic embolism.

TABLE 10 Therapy for Endocarditis of Prosthetic Valves or Other Prosthetic Material Caused by Staphylococci

Regimen	Dosage* and Route	Duration (wk)	Class	LOE	Comments
Oxacillin-Susceptible Strains					
Nafcillin or oxacillin	12 g/24 hr IV in six equally divided doses	≥6	IIa	B	Penicillin G 24 million U/24 hr IV in four to six equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (MIC ≤ 0.1 μg/ml) and does not produce beta-lactamase; vancomycin should be used in patients with immediate-type hypersensitivity reactions to beta-lactam antibiotics (see Table 6 for dosing guidelines); cefazolin may be substituted for nafcillin or oxacillin in patients with nonimmediate hypersensitivity reactions to penicillins
Plus					
Rifampin	900 mg/24 hr IV/PO in three equally divided doses	≥6			
Plus					
Gentamicin†	3 mg/kg/24 hr IV/IM in two or three equally divided doses	2			
Oxacillin-Resistant Strains					
Vancomycin	30 mg/kg/24 hr in two equally divided doses	≥6	IIa	B	Adjust vancomycin to achieve a trough serum concentration of 10-15 μg/ml (see text for gentamicin alternatives)
plus					
Rifampin	900 mg/24 hr IV/PO in three equally divided doses	≥6			
plus					
Gentamicin	3 mg/kg/24 hr IV/IM in two or three equally divided doses	2			

IM, Intramuscular; *IV,* intravenous; *LOE,* level of evidence; *MIC,* minimum inhibitory concentration; *PO,* oral.
*Dosages recommended are for patients with normal renal function.
†Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing.
From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

PEARLS & CONSIDERATIONS

- Serologies and/or PCR exist for more unusual zoonotic causes of endocarditis such as *Bartonella henselae* (cat exposure), *Coxiella burnetii* (farm animals), *Brucella* spp (unpasteurized milk or cheese), and *Tropheryma whipllei* (soil and farm animals).
- 1-yr mortality has not improved and remains at 30%.

COMMENTS

- For endocarditis prophylaxis refer to Section V.
- In regards to antibiotic prophylaxis before dental procedures in patients with orthopedic implants, the 2013 guidelines from the American Academy of Orthopedic Surgeons (AAOS) and the American Dental Association (ADA) advises clinicians to consider discontinuing the practice of routinely prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants undergoing dental procedures.
- *Streptococcus viridians* are a large group of commensal bacteria that are either alpha hemolytic on blood agar plates or nonhemolytic. Common members of this family include *S. mutans*, *S. anginosus*, *S. mitis*, *S. sanguis*, *S. oralis,* and *S. salivarius.* These tend to be oral/dental flora and most highly penicillin susceptible.
- Recent European trials have shown that in patients with endocarditis in the left side of the heart who were in stable condition, changing to oral antibiotic treatment was noninferior to continued intravenous antibiotic treatment.[1] Additional trials will be necessary before changing current parenteral antibiotic guidelines to include oral antibiotic regimens.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Endocarditis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

[1]Iverson K et al: Partial oral versus intravenous antiobiotic treatment of endocarditis, *N Engl J Med* 380:415-424, 2019.

SUGGESTED READINGS

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Wang A et al: Management considerations in infective endocarditis: a review, *JAMA* 320:72-83, 2018.

FIG. E1 Osler nodes. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

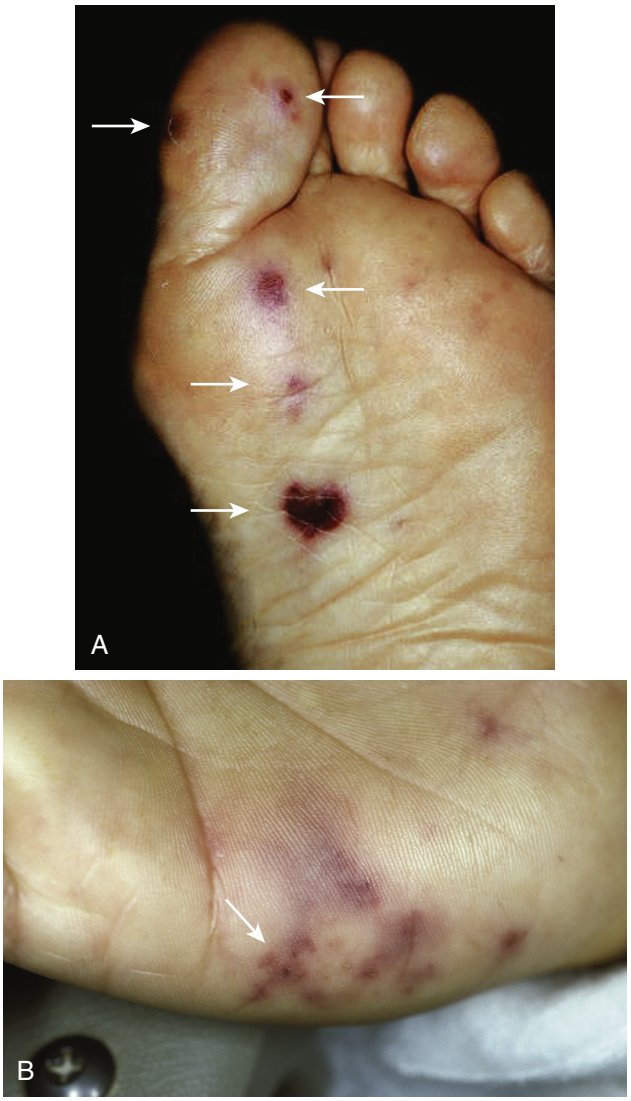

FIG. E2 Janeway lesions. These nontender, often hemorrhagic lesions *(arrows)* are most commonly associated with *Staphylococcus aureus* endocarditis. They result from septic microembolization. The lesions are usually macular to slightly nodular and involve the soles **(A)** and the thenar and hypothenar eminences of the palms **(B).** (From Mandell GL et al [eds]: *Principles and practice of infectious diseases,* ed 6, Philadelphia, 2005, Churchill Livingstone; **B,** courtesy Marc E. Grossman, MD, FACP.)

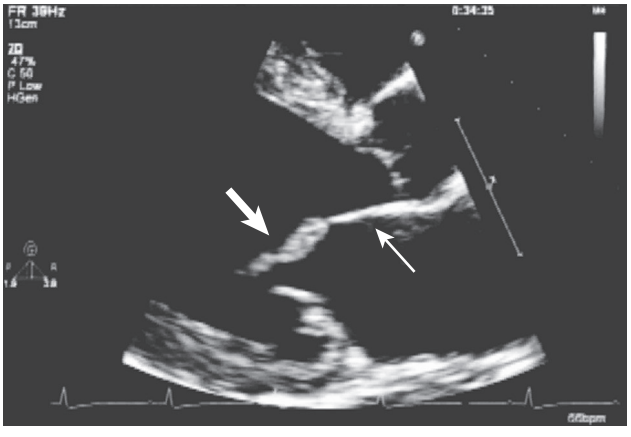

FIG. E4 Valvular vegetations. This parasternal long view on a transthoracic echocardiogram shows a large vegetation *(thick arrow)* on the mitral valve *(thin arrow).* The *thick arrow* is in the left ventricle and the *thin arrow* is in the left atrium. (Courtesy Mark Goldberger, MD.)

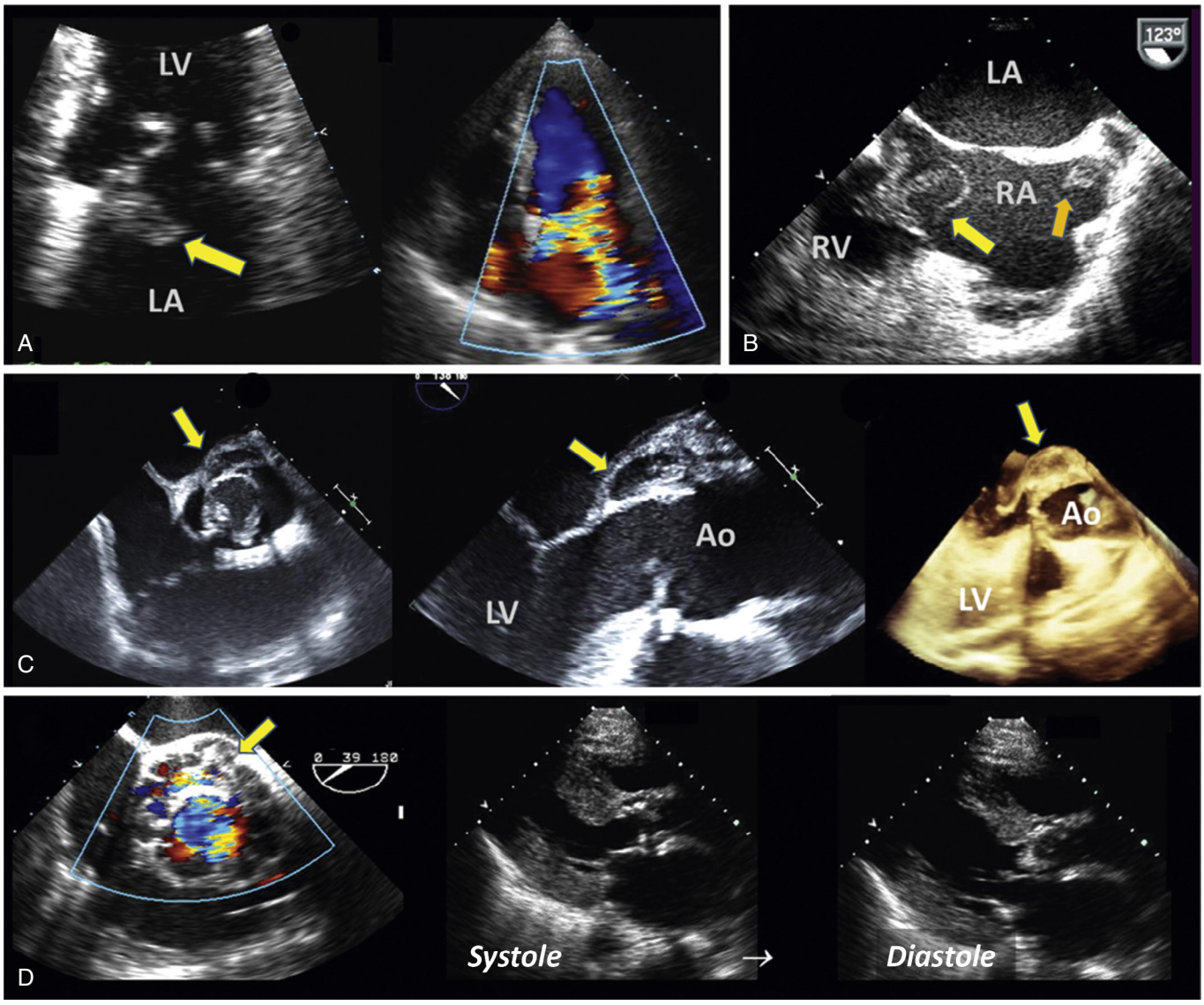

FIG. E5 Echocardiography in endocarditis. A, Vegetation (*arrow*) on the left atrial aspect of a rheumatic mitral valve (*left panel*) with color Doppler demonstration of a second noncentral jet of MR at the base of the leaflet and vegetation indicative of leaflet perforation (*right panel*). **B,** Vegetation (*arrow*) on the right atrial aspect of the tricuspid valve on a TEE long-axis view. An additional vegetation (*arrow*) in the SVC associated with a previous indwelling catheter is noted, and the eustachian valve also was infected in this patient with a history of intravenous drug abuse. **C,** Perivalvular abscess (*arrow*) as indicated by the crescentic echolucent area with thickening from the 11 to the 1 o'clock position on short-axis (*left panel*) and long-axis (*middle panel*) TEE views anterior to the annulus of a bicuspid aortic valve (open in systole); also visualized on the 3D TEE view (*right panel*). **D,** Ringlike abscess around the annulus of a bioprosthetic aortic valve as seen on a short-axis TEE view (*left panel*). This causes dehiscence of the valve, as seen on long-axis TEE views (*middle* and *right panels*) in which it rocks forward in systole and prolapses into the LVOT in diastole. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *LVOT,* left ventricular outflow tract; *MR,* mitral regurgitation; *RA,* right atrium; *RV,* right ventricle; *TEE,* transesophageal echocardiography. (From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015. Elsevier.)

Endometrial Cancer ALG PTG

BASIC INFORMATION

DEFINITION

Endometrial carcinoma (EC) is the malignant transformation of endometrial glands with stromal invasion. The changes are typified by irregular nuclear membranes, nuclear atypia, mitotic activity, loss of glandular pattern, loss of intervening stroma, and irregular cell size. The two main histologic subcategories of EC (Table 1), low-grade endometrioid (type 1) and high-grade endometrioid and nonendometrioid EC (type 2), show unique molecular aberrations and differing clinical behaviors.

SYNONYMS

Uterine cancer (some forms)
Carcinoma of the endometrium
EC

ICD-10CM CODES

C54.1 Malignant neoplasm of endometrium
C54.9 Malignant neoplasm of corpus uteri, unspecified
C55 Malignant neoplasm of uterus, part unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: In 2015, 53,911 new cases of uterine cancer were diagnosed. This corresponds to an incidence of 27 cases per 100,000 women. Incidence was greater among white and black women compared with American Indian/Alaska Native, Hispanic, and Asian Pacific Islander women. It is the most common gynecologic malignancy in the U.S. A woman's lifetime risk for development of endometrial cancer is between 2% and 3%.

PREDOMINANCE: Median age at diagnosis: 62 yr; only 5% occur in women <40 yr; 5-yr survival >80%

RISK FACTORS: Obesity, diabetes, nulliparity, early menarche and late menopause, unopposed estrogen therapy, tamoxifen use, oligoovulation with chronic unopposed estrogen exposure such as with polycystic ovary syndrome (PCOS), endometrial atypical hyperplasia, endometrial polyps (malignancy is found in 3.6% of endometrial polyps), family history. Other risk factors include a personal history of ovarian, breast, or colonic cancer, as well as certain genetic syndromes, such as Lynch syndrome and Cowden syndrome. The relative risk for endometrial cancer is summarized in Table 2.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abnormal uterine bleeding or postmenopausal bleeding in 90%
- Pyometra or hematometra
- Abnormal Pap smear: Endometrial cells, atypical glandular cells, or adenocarcinoma
- Incidental finding at hysterectomy

ETIOLOGY

Endogenous or exogenous chronic unopposed estrogen stimulation of the endometrium

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Endometrial atypical hyperplasia
- Other genital tract malignancy
- Uterine polyps
- Atrophic vaginitis
- Granulosa cell tumor
- Fibroid uterus
- Adenomyosis

WORKUP

- Complete history and physical examination
- Endometrial biopsy or dilation and curettage (Table 3)
- Assessment of operative risk
- Staging (Tables 4, 5, and 6)

TABLE 1 Pathogenetic Subsets of Endometrial Carcinoma

Parameter	Type I	Type II
Age	50s-60s	60s-70s
Obesity	Common	Uncommon
Estrogenic stimuli	Common	Uncommon
Endometrium	Anovulatory	Atrophic
Precursor	Endometrial intraepithelial neoplasia	Presumed EmGD
Transition	Slow	Unknown
Type	Endometrioid	Papillary serous or mixed
Molecular genetics	MSI, *PTEN* mutation; loss of PAX2	p53 mutation, 1p deletions; loss of PAX2
Familial	Hereditary nonpolyposis colonic cancer syndrome	
Spread	Lymph nodes	Peritoneum
Concurrent ovarian	Common	Uncommon
Prognosis	Good	Poor

EmGD, Endometrial glandular dysplasia; *MSI,* microsatellite instability.
From Crum CP et al: *Diagnostic gynecologic and obstetric pathology,* ed 3, Philadelphia, 2018, Elsevier.

TABLE 2 Risk Factors for Endometrial Cancer

Factor	Relative Risk
Overweight (lb):	
• 20-50	3.0
• 50+	10.0
Nulliparous:	
• vs. one child	2.0
• vs. five children	5.0
Late menopause (>52 vs. 49 yr)	2.4
Diabetes mellitus	2.7
Unopposed estrogen therapy	6.0
Tamoxifen therapy	2.0
Sequential oral contraceptives	7.0
Combination oral contraceptives	0.5
Cowden syndrome (*PTEN* mutation)	Three- to fivefold increased risk
Hereditary nonpolyposis colonic cancer syndrome	40%-60% lifetime risk
Family member with endometrial cancer	3.4

From Crum CP et al: *Diagnostic gynecologic and obstetric pathology,* ed 3, Philadelphia, 2018, Elsevier.

TABLE 3 Differential Diagnosis of Endometrial Carcinoma (Curettings)

Parameter	Mimicking	Differential Diagnosis
Gland architecture	Cancer	Telescoping artifact; stromal collapse breakdown; sectioning artifacts
	Benign	Microglandular mucinous carcinoma; surface endometrioid carcinoma
Nuclear atypia	Cancer	Surface or glandular repair; Arias-Stella changes (hormonal therapy); radiation effect
Papillary changes	Cancer	Exfoliation artifact; stromal breakdown with papillary changes; papillary syncytial changes
	Benign	Papillary mucinous carcinoma

From Crum CP et al: *Diagnostic gynecologic and obstetric pathology,* ed 3, Philadelphia, 2018, Elsevier.

TABLE 4 National Comprehensive Cancer Network Treatment Guidelines for Endometrial Carcinoma after Comprehensive Surgical Staging

Stage I_A	
Grade 1 without ARF	Observe
Grade 1 with ARF	Observe or VBT
Grade 2 or 3 without ARF	Observe or VBT
Grade 2 or 3 with ARF	Observe or VBT and/or pelvic RT
Stage I_B	
Grade 1 without ARF	Observe
Grade 1 with ARF	Observe or VBT
Grade 2 without ARF	Observe or VBT
Grade 2 with ARF	Observe or VBT and/or pelvic RT
Grade 3 without ARF	Observe or VBT and/or pelvic RT
Grade 3 with ARF	Observe or VBT and/or pelvic RT ± chemotherapy
Stage II	
Grade 1	VBT and/or pelvic RT
Grade 2	Pelvic RT and VBT
Grade 3	Pelvic RT and VBT ± chemotherapy
Stage III_A	Chemotherapy ± pelvic RT or tumor-directed RT ± chemotherapy or pelvic RT ± VBT
Stage III_B-III_C	Chemotherapy and/or tumor-directed RT
Stage IV_A-IV_B	Chemotherapy ± RT

ARF, Adverse risk factors (age, positive lymphovascular space invasion, tumor size, lower uterine or cervical involvement); *RT,* radiation therapy; *VBT,* vaginal brachytherapy.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE 5 Revised FIGO Staging for Endometrial Cancer (Adopted 2009)

Stages*	Characteristic
I	Tumor confined to the corpus uteri
I_A	No or less than half myometrial invasion
I_B	Invasion equal to or more than half of the myometrium
II	Tumor invades cervical stroma but does not extend beyond the uterus†
III	Local or regional spread of the tumor
III_A	Tumor invades serosa of the corpus uteri or the adnexa‡
III_B	Vaginal or parametrial involvement‡
III_C	Metastases to pelvic or paraaortic lymph nodes‡
III_{C1}	Positive pelvic nodes
III_{C2}	Positive paraaortic lymph nodes with or without positive pelvic lymph nodes
IV	Tumor invades bladder or bowel mucosa, or distant metastasis
IV_A*	Tumor invasion of bladder or bowel mucosa
IV_B	Distant metastases, including intraabdominal or inguinal lymph nodes

*G1, G2, or G3.
†Endocervical glandular involvement should be considered only as stage I and no longer as stage II.
‡Positive cytology has to be reported separately without changing the stage.
FIGO, Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics).
From Lobo RA et al: *Comprehensive gynecology,* ed 7, Philadelphia, 2017, Elsevier.

- Fig. 1 is a diagnostic algorithm for diagnosing endometrial carcinoma for women with abnormal uterine bleeding

LABORATORY TESTS

- Complete blood count
- Prothrombin time and partial thromboplastin time if bleeding is heavy
- Chemistry profile including liver function tests
- Consider CA-125 level

IMAGING STUDIES

- Chest x-ray
- CT scan if concern for metastatic disease, and/or pelvic ultrasound (Fig. E2)
- Transvaginal ultrasound (Fig. E3) in postmenopausal women with vaginal bleeding

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Surgery is the mainstay of treatment, with or without adjuvant radiation and/or chemotherapy, depending on tumor histology, stage, and grade. Laparoscopic surgery for early-stage EC is as safe and effective as laparotomy. Robotic laparoscopy procedures have increased significantly in recent yrs for this indication.
- Surgery generally consists of pelvic washings, total hysterectomy and bilateral salpingo-oophorectomy, selective pelvic and periaortic lymphadenectomy, and omental biopsy depending on stage, grade, and histology.
- Brachytherapy and/or teletherapy are added in an advanced stage.
- Chemotherapy (carboplatin, paclitaxel) may be used for patients with high-risk endometrial cancer. Hormonal therapy (progestins alone or in combination with tamoxifen, selective estrogen-receptor modulators, aromatase inhibitors, synthetic steroid derivatives, and gonadotropin-releasing hormone analogues) may also be considered in cases where palliation, rather than cure, is the main intent of treatment, or in patients with multiple coexisting medical conditions who may not be surgical candidates.
- Hormonal therapy, commonly a levonorgestrel intrauterine device, is an option for some young women with early-stage, low-grade EC who wish to preserve fertility. This choice should be discussed with a gynecologic oncologist.

ACUTE GENERAL Rx

- A thorough workup should be completed before any therapy for EC.
- Surgery hysterectomy with bilateral salpingo-oophorectomy is the treatment of choice.

CHRONIC Rx

- Physical and pelvic examination every 3 mo for 2 yr, then every 6 mo for 2 yr, and annually thereafter with imaging as clinically indicated
- Hormone replacement (combination) a consideration in low-risk patients (stage I or early stage II)

DISPOSITION

- Survival is generally defined by the stage of the disease and histology.
- The majority of cases present early, and the 5-yr survival is generally good (Fig. E4).
- Some histologic types (clear cell, papillary serous) have worse survival rates, as they tend to be more aggressive with higher rates of metastatic disease at the time of diagnosis.

PEARLS & CONSIDERATIONS

Any woman with postmenopausal bleeding or abnormal uterine bleeding with risk factors for endometrial cancer needs evaluation by a gynecologist and either endometrial biopsy and/or pelvic ultrasound. When endometrial cancer is diagnosed, the patient should be cared for by a gynecologic oncologist and undergo surgical staging in a minimally invasive procedure when possible.

SUGGESTED READINGS

Available at ExpertConsult.com

TABLE 6 Carcinoma of the Corpus Uteri: Patients Treated in 1990-1992: Survival by 1988 FIGO Surgical Stage, *N* = 5562

Stage	5-Yr Survival Rate
I_A	90.9%
I_B	88.2%
I_C	81.0%
II	71.6%
III	51.4%
IV	8.9%

FIGO, Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics).
From Lobo RA et al: *Comprehensive gynecology*, ed 7, Philadelphia, 2017, Elsevier.

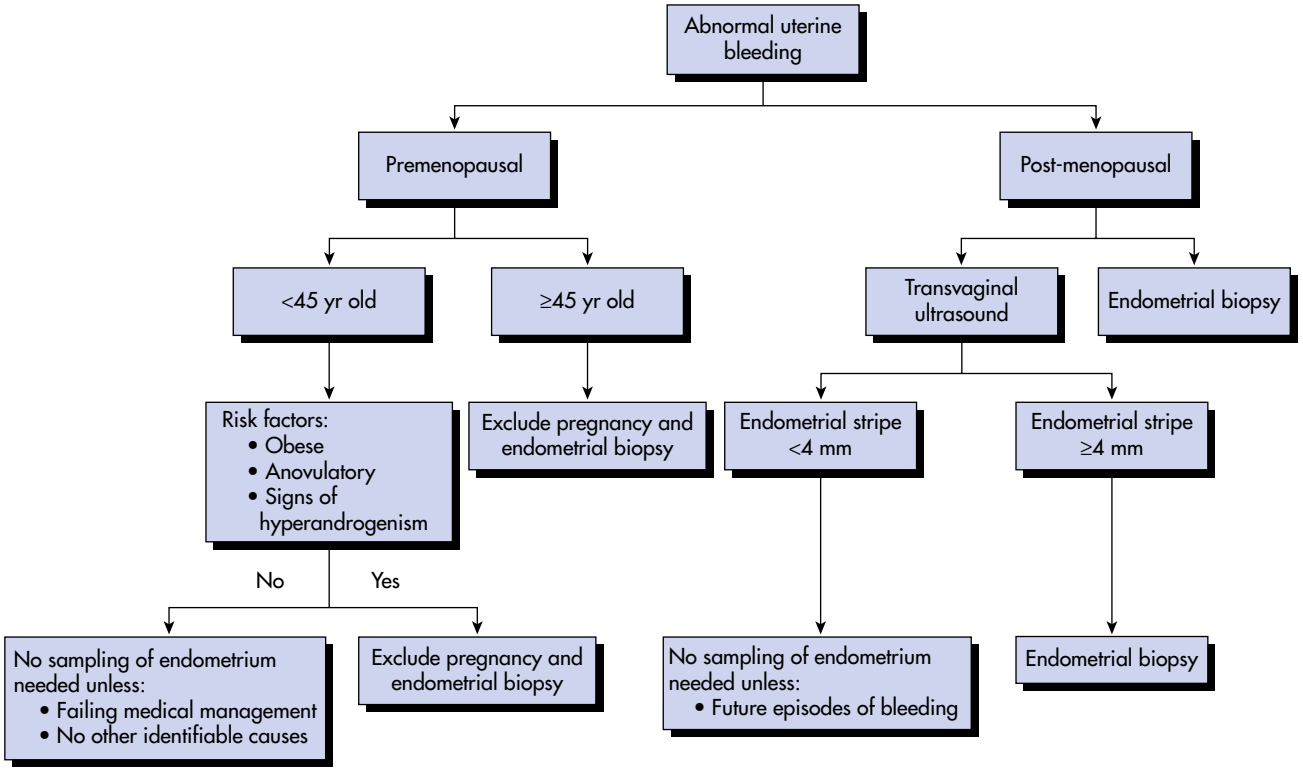

FIG. 1 Diagnostic algorithm to diagnose endometrial carcinoma for women with abnormal uterine bleeding. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

RELATED CONTENT

Endometrial Cancer (Patient Information)
Abnormal Uterine Bleeding (Related Key Topic)
Uterine Malignancy (Related Key Topic)

AUTHORS: **Helen Toma, MD, MSPH,** and **Anthony Sciscione, DO**

SUGGESTED READINGS

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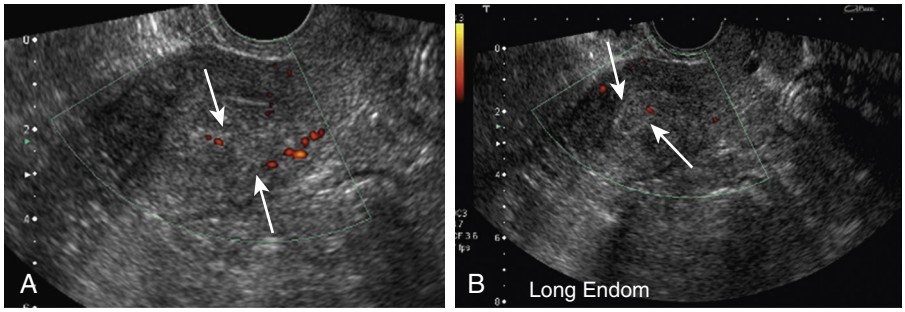


FIG. E2 A 48-yr-old woman with endometrial carcinoma. A, Endovaginal ultrasound (US) showing thickened, heterogeneous, cystic, and vascular hyperechoic tissue filling the endometrial cavity *(arrows).* **B,** Second sagittal US image showing the same *(arrows).* (From Fielding JR et al: *Gynecologic imaging*, Philadelphia, 2011, WB Saunders.)

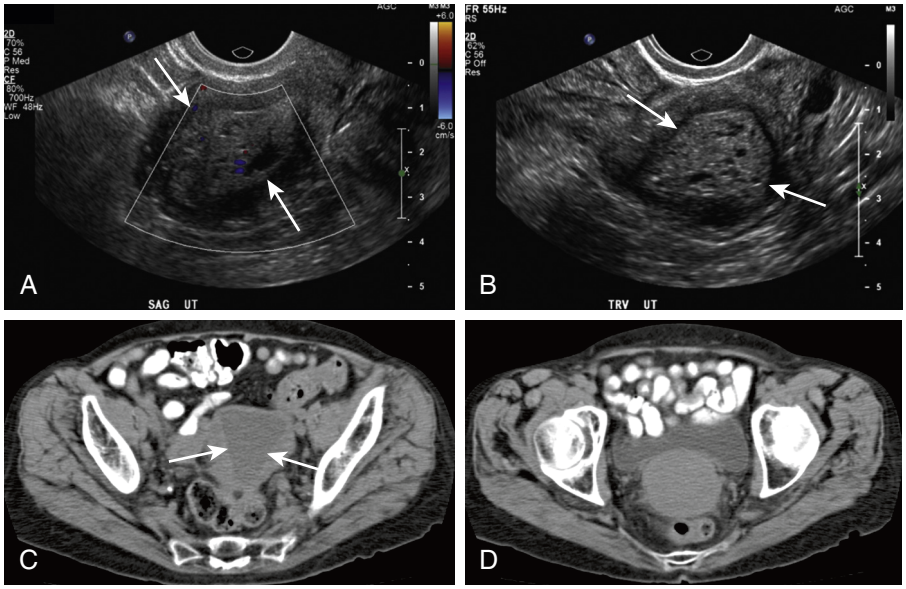
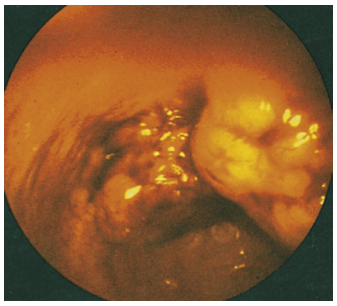


FIG. E3 A 56-yr-old woman with endometrial carcinoma. A, Sagittal ultrasound (US) image showing thickened cystic echogenic soft tissue filling the endometrial cavity *(arrows).* **B,** Axial US image showing thickened cystic echogenic soft tissue filling the endometrial cavity *(arrows).* **C,** Non–contrast-enhanced axial computed tomographic (CT) image showing low-attenuation tissue filling the endometrial canal *(arrows)* in a postmenopausal patient. Note fundal thinning. **D,** Non–contrast-enhanced axial CT image showing cervical soft tissue fullness. (From Fielding JR et al: *Gynecologic imaging*, Philadelphia, 2011, WB Saunders.)



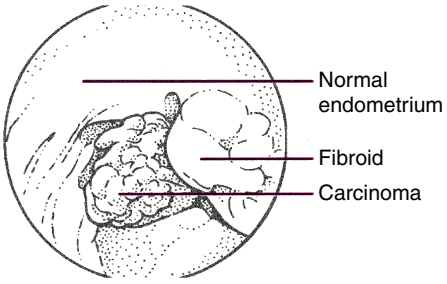


FIG. E4 Stage I endometrial carcinoma. A small carcinoma can be seen adjacent to a uterine fibroid in this hysteroscopy photograph. Occasionally, a tumor this small may be missed on curettage. (From Skarin AT: *Atlas of diagnostic oncology*, ed 4, St Louis, 2010, Mosby.)

BASIC INFORMATION

DEFINITION

Endometriosis is defined as the presence of functioning endometrial glands and stroma outside the uterine cavity. It is a chronic, estrogen-dependent condition that causes dysmenorrhea and pelvic pain.

ICD-10CM CODES

N80.0	Endometriosis of uterus
N80.1	Endometriosis of ovary
N80.2	Endometriosis of fallopian tube
N80.3	Endometriosis of pelvic peritoneum
N80.4	Endometriosis of rectovaginal septum and vagina
N80.5	Endometriosis of intestine
N80.6	Endometriosis in cutaneous scar
N80.8	Other endometriosis
N80.9	Endometriosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- Endometriosis affects 10% of reproductive-aged women.
- Women with dysmenorrhea: 40% to 60%.
- Subfertile women: 28% to 50%.
- Incidence peaks at approximately 40 yr.

MOST COMMON AGE AT DIAGNOSIS: 25 to 29 yr.

GENETICS:

- Familial association: If first-degree relative is affected, the patient has a seven- to tenfold increased risk of having the disease.
- Polygenic-multifactorial inheritance pattern.
- 6.9% occurrence rate in first-degree female relatives.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Classic triad is dysmenorrhea, dyspareunia, and infertility.
- Presence of pelvic pain does not correlate with the total area of endometriosis (stage of disease), type of lesion, or volume of disease but is correlated with the depth of infiltration.
- Other symptoms include abnormal bleeding (premenstrual spotting, menorrhagia), cyclic abdominal pain, intermittent constipation/diarrhea, dyschezia, dysuria, hematuria, and urinary frequency.
- Rare manifestations: Catamenial hemothorax, bloody pleural effusion, massive ascites occurring during menses.
- Most severe discomfort is associated with lesions >1 cm in depth.
- Bimanual examination may reveal tender uterosacral ligaments, cul-de-sac nodularity, induration of the rectovaginal septum, fixed retroversion of the uterus, adnexal mass, and generalized or localized tenderness.

ETIOLOGY

- Reflux and direct implantation theory: Retrograde menstruation with implantation of viable endometrial cells to surrounding pelvic structures (Sampson theory)
- Coelomic metaplasia theory: Transformation of multipotential cells of the coelomic epithelium into endometrium-like cells
- Vascular dissemination theory: Transport of endometrial cells to distant sites by the uterine vascular and lymphatic systems
- Autoimmune disease theory: Disorder of immune surveillance allows growth of endometrial implants

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ectopic pregnancy
- Acute appendicitis
- Chronic appendicitis
- Pelvic inflammatory disease (PID)
- Pelvic adhesions
- Hemorrhagic cyst
- Hernia
- Irritable bowel syndrome
- Uterine leiomyomata
- Adenomyosis
- Nerve entrapment syndrome
- Interstitial cystitis

WORKUP

- Thorough history and physical examination including ultrasound.
- Definitive diagnosis of endometriosis can be made only by histologic confirmation during surgery (gold standard).
- Fig. 1 illustrates a diagnostic and management algorithm for endometriosis.

SURGICAL STAGING

- American Society for Reproductive Medicine classification system for endometriosis (ASRM revised 1996) is the most widely accepted staging system.
- Value: Uniform recording of operative findings.
- Limitations
  1. Not a good predictor of successful pregnancy after treatment.
  2. Does not correlate well with the symptoms of pain, dyspareunia, or infertility.

Stage I	Minimal
Stage II	Mild
Stage III	Moderate
Stage IV	Severe

LABORATORY TESTS

Cancer antigen 125 (CA125): Limited overall value in the diagnosis of endometriosis

- Also elevated in ovarian epithelial neoplasm, myomas, adenomyosis, acute PID, ovarian cysts, pancreatitis, chronic liver disease, menstruation, and pregnancy.
- CA125 value >35 U/ml: Positive predictive value of 0.58 and a negative predictive value of 0.96 for the presence of endometriosis.

IMAGING STUDIES

- Ultrasound: For evaluating adnexal mass; ultrasound characteristics may suggest endometriomas versus other benign or malignant ovarian conditions but persistent solid or cystic-solid ovarian masses require definitive tissue diagnosis with laparoscopy.
- MRI:
  1. Highly accurate in detecting endometriomas.
  2. Limited sensitivity in detecting diffuse pelvic endometriosis, especially if sessile lesions.
- CT scan may show adnexal masses of varying density (Fig. 2).

TREATMENT

NONPHARMACOLOGIC THERAPY

Expectant management (observation for 5 to 12 mo) for stage I or stage II endometriosis-associated infertility. Evaluation should take place if the couple meets the diagnostic criteria for infertility.

ACUTE GENERAL Rx

Nonsteroidal antiinflammatory drugs for symptomatic relief of dysmenorrhea.

CHRONIC Rx

PHARMACOLOGIC MANAGEMENT:

Estrogen-progesterone:

- State of "pseudopregnancy" created by continuous (discarding pill pack when placebo pills remaining and starting active pills from new pill pack) use of combination oral contraceptives for minimum of 6 mo and continuing indefinitely.

Progestins:

- Medroxyprogesterone acetate 10 to 30 mg orally qd and occasionally up to 100 mg orally qd.
- Alternatively, 100 mg IM q2wk for four doses, followed by 200 mg IM monthly for 4 mo.
- Comparison with danazol: Progestins cost less, have a more tolerable side-effect profile, and have comparable efficacy with regard to pain relief and so are often the first-line drug. Very little justification for the use of danazol.

Gonadotropin-releasing hormone (GnRH) agonists:

- Induces medical menopause.
- Use usually limited to 6 to 12 mo due to hypoestrogenic effects such as osteopenia or osteoporosis but can be given longer in certain circumstances, particularly when paired with estrogen add-back therapy. Referral to specialist strongly advised.
- Elagolix is an oral GnRH antagonist that provides partial to nearly full estrogen suppression. Dosage is 150 mg once daily or 200 mg twice daily. It is effective in improving dysmenorrhea and nonmenstrual pain, but is associated with hypoestrogenic side effects (hot flashes, hyperlipidemia, decreased bone density).
- Leuprolide acetate depot 3.75 mg IM monthly or 11.25 mg IM q3mo or nafarelin 400 mcg nasal puffs bid or goserelin 3.6 mg SC monthly.
- Add-back therapy for protection against vasomotor symptoms and bone loss: Norethindrone acetate 5 mg PO qd alone

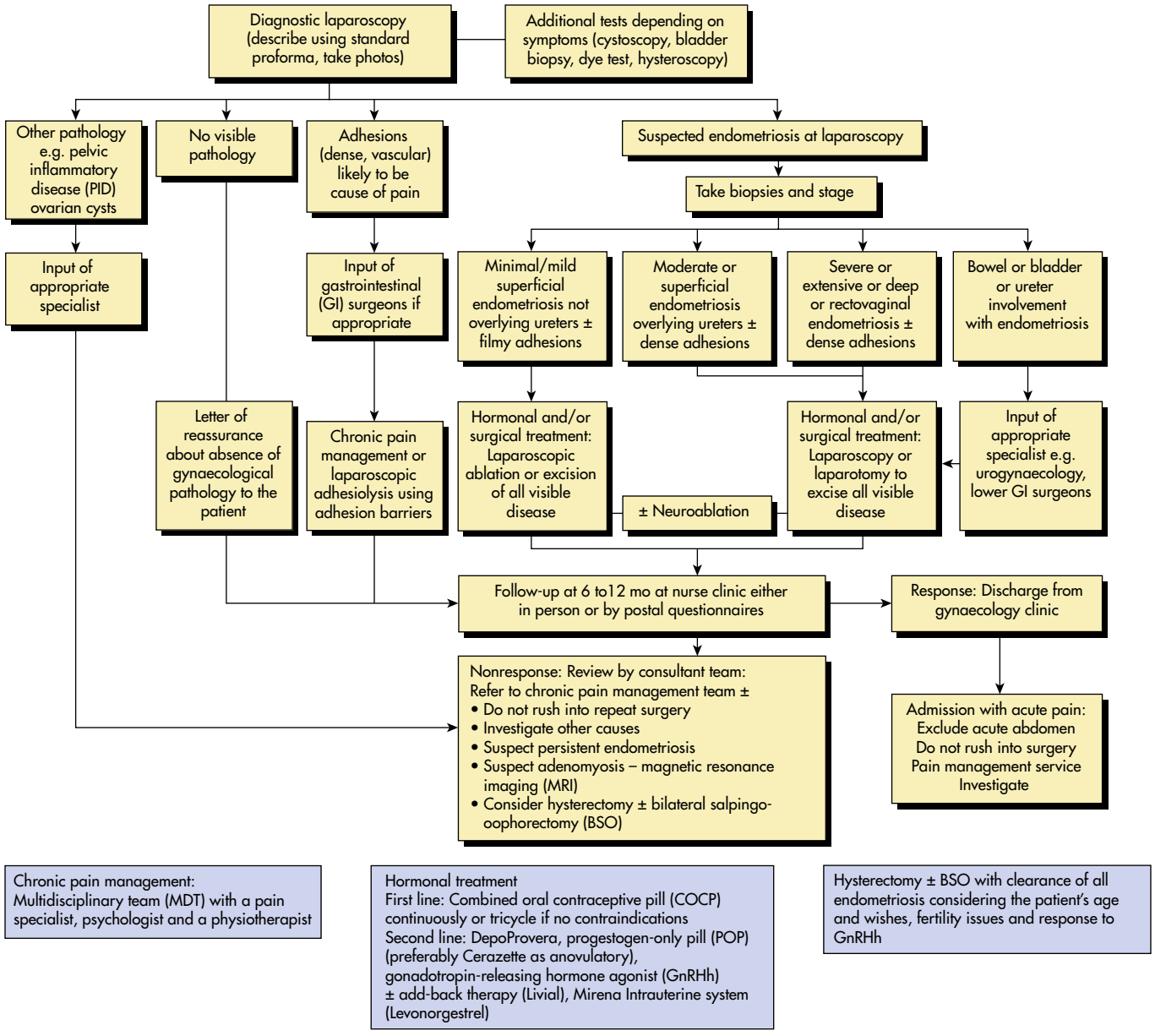


FIG. 1 An example of a management pathway for patients with endometriosis after laparoscopy.
(From Magowan BA: *Clinical obstetrics & gynecology,* ed 4, 2019, Elsevier.)

FIG. 2 Computed tomographic scan demonstrates adnexal masses of varying density, subsequently proven to be endometriomas. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, WB Saunders.)

or in combination with conjugated estrogen 0.625 mg orally qd.
- Add-back therapy allows gonadotropin-releasing hormone (GnRH) agonist use to be extended to 1 yr based on limited studies available.

Alternative therapies for inhibition of estrogen action currently under investigation are:
- Aromatase inhibitors: Anastrozole, letrozole
- SERM: Raloxifene
- Agents enhancing cell-mediated immunity are cytokines (interleukin-12 and interferon-α2b)
- Immunomodulators (loxoribine, levamisole)
- Antiinflammatory: Pentoxifylline

SURGICAL MANAGEMENT:

Conservative:
- Directed at enhancing fertility or treating pain unresponsive to first-line medical treatment.
- Usually accomplished through laparoscopy.
- Removal or destruction of endometriotic implants by excision, electrocautery, or laser.
- Cystectomy for endometrioma; must remove cyst wall to be effective long-term.
- Laparoscopic uterosacral nerve ablation (LUNA) for midline pain such as dysmenorrhea or dyspareunia (evidence does not support its use).
- Unless pregnancy is desired, patient is usually started on GnRH agonist therapy or continuous OCP immediately after surgery.
- For those desiring pregnancy, surgery alone results in significant increase in fertility.

Definitive:
- Directed at relieving endometriosis-associated pain.
- Total abdominal hysterectomy with bilateral salpingo-oophorectomy and complete excision or ablation of endometriosis.
- Thorough abdominal exploration to ensure removal of all disease.
- Must be prepared to manage possible gastrointestinal and urinary tract endometriosis.
- 90% effective in pain relief; patient must be counseled that pain relief is not guaranteed.
- Estrogen replacement therapy (ERT) to be considered in all women undergoing definitive surgical management; after ERT, recurrence rate is 0% to 5% in women with endometriosis confined to the pelvis but 18% in women with bowel involvement.
- Concern for malignant degeneration exists in implants if unopposed estrogen is used after definitive surgical therapy.

MANAGEMENT OF ENDOMETRIOSIS-ASSOCIATED INFERTILITY:

Conservative surgery:
- Yields significantly higher pregnancy rate than does expectant management, in part because of correction of mechanical factors such as adhesions.

Assisted reproductive technologies:
- Can be used to circumvent unknown mechanism of endometriosis-associated infertility.
- Superovulation with clomiphene citrate or human menopausal gonadotropins; clomiphene citrate results in threefold pregnancy rate over expectant management.
- Further improvement with intrauterine insemination combined with superovulation.
- In vitro fertilization if above procedures are unsuccessful.

DISPOSITION

Tends to recur unless definitive surgery is performed, and should be considered a chronic condition.

REFERRAL

To a reproductive endocrinologist for advanced surgical management or infertility management

PEARLS & CONSIDERATIONS

COMMENTS

Patient information can be obtained through the following organizations: Endometriosis Association, 8585 North 76th Place, Milwaukee, WI 53223, 414-355-2200 or 800-992-ENDO; Women's Reproductive Health Network, P.O. Box 30167, Portland, OR 97230-9067 or 503-667-7757.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Endometriosis (Patient Information)
Dysmenorrhea (Related Key Topic)
Dyspareunia (Related Key Topic)

AUTHOR: **Barbara McGuirk, MD**

SUGGESTED READINGS

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ACOG: Updated guideline on diagnosis and treatment of endometriosis, *Obstet Gynecol,* July 2010. Available at http://journals.lww.com/greenjournal/citation/2010/07000/practice_bulletin_no__114__management_of.41.aspx.
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Schrager S et al: Evaluation and treatment of endometriosis, *Am Fam Physician* 87(2):107-113, 2013.
Taylor HS et al: Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist, *N Engl J Med* 377:28-40, 2017.

Endometritis

BASIC INFORMATION

DEFINITION

Endometritis is defined as inflammation of the endometrium and can occur postpartum or postabortal. Endometritis can also be unrelated to pregnancy (in an acute or chronic state); however, this chapter is primarily in reference to postpartum endometritis.

SYNONYMS

Endomyometritis
Endoparametritis
Metritis with pelvic cellulitis

ICD-10CM CODES

O85	Puerperal sepsis
O86	Other puerperal infections
O86.11	Cervicitis following delivery
O86.12	Endometritis following delivery
O86.13	Vaginitis following delivery
O86.19	Other infection of genital tract following delivery
O86.89	Other specified puerperal infections
N71.0	Acute inflammatory disease of uterus
N71.1	Chronic inflammatory disease of uterus

EPIDEMIOLOGY & DEMOGRAPHICS

- Overall rate of postpartum uterine infection: Estimated between 1% and 6%, as high as 13% when associated with chorioamnionitis
- Most common genital tract infection after delivery
- Usually presents early in postpartum period; more commonly seen after cesarean section or operative vaginal delivery than spontaneous vaginal delivery
- Additional risk factors include preterm delivery, prolonged labor, prolonged rupture of membranes, chorioamnionitis, multiple cervical examinations, and internal maternal or fetal monitoring

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Postpartum oral temperature >38° C (after first 24 hours)
- Symptoms of abdominal pain, fevers, chills, purulent or foul-smelling lochia, heavier vaginal bleeding
- On physical exam, tachycardia, localized uterine or parametrial tenderness, purulent or malodorous lochia; physical examination revealing uterine or parametrial tenderness

ETIOLOGY

Endometritis is usually polymicrobial including aerobic and anaerobic organisms: Group A or B streptococci, *Staphylococcus aureus* and *Bacteroides* species, *Neisseria gonorrhoeae, Chlamydia trachomatis,* enterococci, *Gardnerella vaginalis, Escherichia coli,* and *Mycoplasma.* Table E1 summarizes categories of endometritis and common pathogens.

TABLE E1 Endometritis

Category	Pathogen
Purpura sepsis	Staphylococcus, clostridia
Chronic (or acute and chronic) plasmacytic endometritis (CPE)	Chlamydia, gonorrhea, enteric organisms
Granulomatous endometritis	Tuberculosis, herpes simplex virus (HSV) infection, cytomegalovirus (CMV) infection, idiopathic
Xanthogranulomatous endometritis	Unknown
Lymphocytic endometritis	
Reactive endometritis	
Endometrial polyp	
Submucosal leiomyoma	
Intrauterine device (IUD)	
Ablation related	

From Crum CP et al: *Diagnostic gynecologic and obstetric pathology,* ed 3, Philadelphia, 2018, Elsevier.

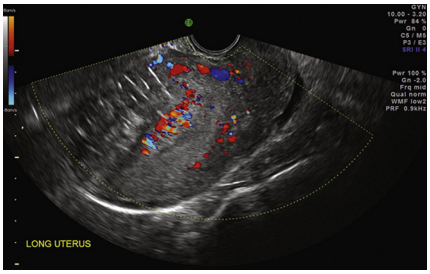

FIG. E1 Endometritis. Patient with uterine tenderness and fever 7 days after classic cesarean section for premature rupture of membranes, chorioamnionitis, and fundic presentation at 27 wks' gestational age. Sagittal transvaginal ultrasonography shows increased vascularity within the endometrium, which can be seen with endometritis. Linear echogenic foci within the anterior myometrium likely represent air and suture material in the vertical uterine incision. Patient's symptoms resolved with antibiotics. (From Fielding JR et al: *Gynecologic imaging*, Philadelphia, 2011, Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Chorioamnionitis (intrapartum intra-amniotic infection)
- Pelvic inflammatory disease
- Sepsis
- Urinary tract infection or pyelonephritis
- Wound infection or abscess
- Septic pelvic thrombophlebitis

WORKUP

Laboratory Tests:

- Complete blood count with differential
- If concerned for systemic infection, consider blood cultures or urine cultures
- Consider lactate if concerned for sepsis

IMAGING STUDIES

- Ultrasound (Fig. E1) may be useful if retained products are considered a possible source of infection.
- Consider CT imaging if concern for intraabdominal abscess.

Postpartum endometritis is overall a clinical diagnosis and based on documented fever (>38.0° C), with leukocytosis (WBC >15,000), abdominal pain, uterine tenderness, and purulent, malodorous vaginal discharge, with no other clear source of infection

TREATMENT

ACUTE GENERAL Rx

IV regimens:

- Clindamycin and gentamicin +/- ampicillin (considered "gold standard")
- Clindamycin and aztreonam
- Extended-spectrum penicillins: Piperacillin-tazobactam, ampicillin-sulbactam, ticarcillin-clavulanate
- Cephalosporins: Cefoxitin, cefotetan, cefotaxime
- Metronidazole, ampicillin, and gentamicin
- Carbapenems: Imipenem-cilastatin, meropenem, ertapenem
- Vancomycin: Consider adding to above regimens

Regimen should be continued for at least 24 to 48 hr after substantial clinical improvement. If response is not adequate (Table E2), broaden your differential and consider other sources of infection.

DISPOSITION

With appropriate antibiotic therapy, 95% to 98% cure rate. Patient can be discharged once 24 hours afebrile, and oral antibiotics are not typically indicated or recommended.

REFERRAL

For patients who do not respond within 48 to 72 hr of appropriate antibiotic therapy, obtain an infectious disease consultation or gynecologic consultation.

AUTHORS: **Siri M. Holton, MD,** and **Rachel Wright Heinle, MD, FACOG**

TABLE E2 Identified Causes of Poor Response to Antibiotic Therapy in Patients with Endometritis

Cause	Approximate Prevalence (%)
Infected mass, including abscess, hematoma, septic pelvic thrombophlebitis, pelvic cellulitis, retained placenta	40-50
Resistant organisms, commonly enterococci, in a patient receiving clindamycin-aminoglycoside or a cephalosporin	20
Additional cause, including catheter phlebitis, inadequate dose of antibiotics	10
No cause evident but response to empirical change in antibiotic therapy	20-30

From Gorbach SL: *Infectious diseases,* ed 2, Philadelphia, 1998, Saunders.

End-Stage Kidney Disease

BASIC INFORMATION

DEFINITION

End-stage kidney disease (ESKD) refers to chronic kidney disease (CKD) that is treated with renal replacement therapy (RRT), i.e., dialytic therapy or kidney transplantation.

SYNONYMS

End-stage renal disease
ESKD
Dialysis dependency
Renal replacement therapy
Chronic irreversible renal failure

ICD-10CM CODES

N18.6	End-stage renal disease
Z99.2	Dependence on renal dialysis
Z94.0	Kidney transplant status

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: According to the U.S. Renal Data System (USRDS), there were 124,675 incident cases of ESKD in the U.S. in 2016.

- 87.3% of incident individuals began RRT with hemodialysis (HD)
- 9.7% of incident individuals began RRT peritoneal dialysis (PD)
- 2.8% of incident individuals began RRT with a preemptive kidney transplant
- There has been an increase in incident PD cases more recently
- There is a significant cost difference among modalities, with average Medicare spending for HD at $90,971 per patient-yr versus PD at $76,177 per patient-yr

The incidence of ESKD differs among countries; the highest incidences are noted in Taiwan, the U.S., and the Jalisco region of Mexico.

PREVALENCE: According to the USRDS, there were 726,331 prevalent cases of ESKD in 2016. The number of prevalent cases has increased by approximately 20,000/yr.

- 63.1% of all prevalent ESKD patients in the U.S. were treated by HD.
- 7.0% of all prevalent ESKD patients were treated by PD.
- 29.6% of all prevalent ESKD patients had a functioning kidney transplant.

ESKD prevalence varies greatly by country, with Hong Kong, the Jalisco region of Mexico, and Guatemala having >50% PD utilization. Home HD use is highest in New Zealand and Australia.

PREDOMINANT SEX AND AGE: The incidence and prevalence of ESKD increases with age, but individuals can experience ESKD at any age. Older patients are more likely to be dialyzed with HD than PD. Males constitute 59% of prevalent ESKD patients.

GENETICS: Genome-wide association studies (GWAS) have shown several genes that are associated with the development of CKD and progression to ESKD. The *APOL1* gene is most strongly implicated. Single-nucleotide polymorphisms of the following genes are associated with greater risk for the development of ESKD: *UMOD, PRKAG2, ANXA9, DAB2,* and *SHROOM3.*

RISK FACTORS: Risk factors for the development of ESKD include proteinuria, higher body mass index, diabetes mellitus, high blood pressure, higher serum creatinine, male gender, lower educational status, and African American descent.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical presentations of uremia are myriad. Signs and symptoms may include hypertension, edema, uremic frost, asterixis, ankle clonus, altered mentation, pallor, and pericardial friction rub. Classic uremic symptoms include anorexia, dysgeusia, aversion to meat, nausea or vomiting, hiccups, pruritus, weight loss, reversal of sleep cycles, and loss of energy.

ETIOLOGY

The most common causes of ESKD in the U.S. are, in order of frequency, diabetes, hypertension, glomerulonephritis, and cystic diseases.

DIAGNOSIS

WORKUP

The diagnosis of ESKD is made in the setting of CKD, manifested by an elevated creatinine concentration and decrease of the glomerular filtration rate, typically <10 ml/min/1.73 m^2. Dialysis is initiated when uremia, volume overload refractory to diuretic therapy, or electrolyte abnormalities refractory to medical therapy is present. The workup of CKD is discussed elsewhere (see "Chronic Kidney Disease"). The ongoing workup of the consequences of ESKD include measures of anemia, iron metabolism, metabolic acidosis, and mineral and bone disease.

LABORATORY TESTS

Laboratory tests that warrant monitoring in ESKD include electrolytes, blood urea nitrogen, creatinine, glucose, calcium, phosphorus, intact parathyroid hormone, 25-hydroxyvitamin D, hemoglobin, ferritin, and transferrin saturation.

TREATMENT

- A patient with HD will require vascular access for dialysis, which may be a catheter, graft, or fistula (Table 1).
  1. A tunneled dialysis catheter is usually subcutaneously tunneled into the right internal jugular vein.
  2. An arteriovenous graft or fistula should be palpated regularly to ensure flow, which is noted by the presence of bruit and thrill. If the thrill is absent, this may indicate access thrombosis that is promptly addressed by percutaneous or surgical intervention.
  3. The most common arteriovenous fistulas are radiocephalic, brachiocephalic, and brachiobasilic. It is important in patients with CKD and ESKD to preserve veins in nondominant upper extremities by avoiding unnecessary venipunctures and intravenous lines, including central venous catheters and peripherally inserted central catheters.
- Patients who require dialysis have two primary options for RRT: HD and PD.
  1. In HD, the bloodstream is cannulated and diverted through a hemodialyzer that filters the plasma phase of blood running countercurrent to a dialysate.
     a. Dialysis kinetics are based primarily on diffusion down a concentration gradient, and the dialysate composition is produced such that solutes that are to be removed from the body (e.g., potassium) are in low concentration and solutes that are delivered during dialysis (e.g., bicarbonate) are at greater concentrations (Table 2).
     b. Dialysis is effective only for the clearance of non–protein-bound molecules.
     c. Blood flow rate varies from 300 to 400 ml/min. Dialysate flow rate ranges from 500 to 800 ml/min.
     d. Small solutes such as potassium will equilibrate quickly, whereas larger solutes such as beta 2-microglobulin take longer to equilibrate.
     e. Convective clearance also occurs because of solute drag, which accom-

TABLE 1 Hemodialysis Vascular Access

Vascular Access	Description	Benefits	Drawbacks
Tunneled catheter	Tunneled under skin to reduce communication from skin flora with blood	Immediate use	High infection risk High thrombosis risk
Arteriovenous graft	Tube made of biocompatible material attached end to side to artery and vein	Ready to use when swelling resolves (~2 wk) Able to use in most patients	High stenosis/thrombosis rate Moderate infectious risk
Arteriovenous fistula	Vein cross-cut attached end to side to artery High-pressure flow dilates and thickens vein	Lowest infectious risk Longest lasting with least thromboses	Maturation time Primary patency

TABLE 2 Composition of Typical Hemodialysis and Peritoneal Dialysis Solutions

Component	Concentration in Hemodialysis Solutions	Concentration in Peritoneal Dialysis Solutions
Sodium	135-145 mEq/L	132 mEq/L
Potassium	1-3 mEq/L	0 mEq/L
Calcium	2.5-3.5 mEq/L	2.5-3.5 mEq/L
Chloride	95-110 mEq/L	95-105 mEq/L
Magnesium	0.5-1 mEq/L	0.5 mEq/L
Bicarbonate	32-40 mEq/L	
Lactate		35-40 mEq/L
Acetate	2.5-5 mEq/L	
Glucose	200 mg/dl	1500-4250 mg/dl

panies ultrafiltration, the method of fluid removal.

2. In PD, the blood flow originates from the richly vascular parietal and visceral peritoneum, and the semipermeable membrane is the peritoneal membrane.
   a. A tunnelled catheter is placed to be able to infuse and drain dialysate directly into the peritoneum, and solute transfer occurs via convection or diffusion across concentration gradients.
   b. PD can be performed manually throughout the day or overnight via an automated cycler device.
   c. Peritoneal dialysate is dextrose based and hypertonic. The hypertonicity produces ultrafiltration, and the concentration of dextrose is used to create a hypertonic dialysate that ultrafilters plasma fluid across the peritoneal membrane.

- In patients who are indicated for RRT, withholding dialysis is not without risk.
  1. Patient with hyperkalemia are at risk for sudden cardiac death from hyperkalemia, and patients with metabolic acidosis are at risk for cardiovascular compromise, bone demineralization, and other electrolyte and mineral disturbances.
  2. Patients with untreated uremia are at risk for confusion, altered mentation, and coma.
  3. Uremia may cause platelet dysfunction and increased risk for bleeding.
  4. Patients with late-stage CKD are typically hypertensive. If hypertension is untreated, the risks for accelerated heart disease and/or stroke increase.
- In addition to the provision of dialysis, the management of the patient with ESKD also involves close attention to other related conditions, including anemia, mineral and bone disease, and cardiovascular disease.
  1. Patients receiving dialysis experience anemia for several reasons, including erythropoietin deficiency, gastrointestinal bleeding, functional and absolute iron deficiency, increased red blood cell fragility, and blood loss from HD.
     a. Management of anemia in CKD depends on the primary causative factor.
     b. Iron utilization is estimated using ferritin (>100 ng/ml) and transferrin saturation (>20%). Patients who do not meet these parameters are managed with intravenous iron or a trial of oral iron. Intravenous iron may be administered without a trial of oral iron. In patients who are iron repleted, erythropoiesis-stimulating agents are used to increase hemoglobin. Large randomized controlled trials demonstrate an association between increased cancer death and stroke with attainment of hemoglobin levels >11g/dl. The target hemoglobin range for a dialysis patient is 9 to 11 g/dl.
- Patients with ESKD are at risk for several different metabolic bone diseases.
  1. Secondary hyperparathyroidism of renal origin, which is aggravated by metabolic acidosis. The intact PTH level is characteristically elevated in these individuals (>600 pg/ml).
  2. Adynamic bone disease, which occurs more frequently in individuals with diabetes. Typically, the intact PTH level is low (<150 pg/ml) in these patients who typically have diabetes.
  3. Mixed uremic osteodystrophy, which has characteristics of hyperdynamic and adynamic bone remodeling.
  4. Osteopenia.
  5. The gold standard diagnosis for establishing a histologic diagnosis is via bone biopsy. Bone lesion parameters are reported as turnover, mineralization, and volume.
  6. Patients who do not undergo bone biopsy are managed by serologic markers, calcium, phosphate, and intact parathyroid hormone.
  7. PD has a higher risk for adynamic bone disease, whereas patients receiving HD are at greatest risk for osteitis fibrosis cystica and mixed lesions.
- Patients with ESKD are considered to have a coronary heart disease equivalent and are at increased risk for mortality from cardiovascular causes. However, data are lacking regarding the efficacy of cardiovascular risk modification.
  1. Studies of statin therapy in patients with ESKD have not shown a reduction in cardiovascular mortality.
  2. Levels of cardiac biomarkers such as troponin-I and N-terminal pro-B-type natriuretic peptide (NT-proBNP) can be chronically elevated in patients with ESKD. Interpretation of these biomarkers must be considered in the context of clinical findings.
  3. Hemoglobin A1c levels are not equivalent to comparable levels in non-CKD patients. The levels of patients with ESKD should be considered greater by ~0.3% than reported.
- Because multiple medications are renally excreted or nephrotoxic, careful attention must be paid to dosing and choice of medications. Commonly used medications that should be used with caution in patients with ESKD include low-molecular-weight heparin, morphine, oxycodone, gabapentin, pregabalin, digoxin, bisphosphonates, metformin, and electrolyte-containing solutions, including milk of magnesium, magnesium citrate, aluminum hydroxide, and magnesium hydroxide.

DISPOSITION

Morbidity and mortality remain exceptionally high for patients who require RRT.

- Dialysis patients in 2016 had a mortality rate of 164 deaths per 1,000 patient-yr.
- This rate has been improving, with net reductions in mortality from 2001 to 2016 of 28% for HD patients and 43% for PD patients.
- HD patients have greater earlier mortality, and PD patients have greater delayed mortality.
- 5-yr survival probability rates are 42% for HD patients and 52.1% for PD patients. It is likely that this discrepancy is related to patient selection factors, not inherent differences within modalities.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Chronic Kidney Disease (Related Key Topic)

AUTHOR: **Ankur Shah, MD**

SUGGESTED READINGS

Chan CT et al: Dialysis initiation, modality choice, access, and prescription: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference, *Kidney Int* 96(1):37-47, 2019.

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Enteropathic Arthritis

BASIC INFORMATION

DEFINITION

Enteropathic arthritis (EA) is an inflammatory joint disease associated with inflammatory bowel diseases (IBD) such as Crohn disease (CD), ulcerative colitis (UC), and microscopic colitis. Less frequently, EA is associated with other gastrointestinal disorders, including Whipple disease, celiac disease, and bowel-associated dermatitis-arthritis syndrome related to bypass surgery or intestinal disease. EA is included in the family of spondyloarthropathies (SpA), which have features of peripheral inflammatory arthritis, axial spondylitis and sacroiliitis, enthesitis, dactylitis, uveitis, and rashes. Arthritis is the most common extraintestinal manifestation of IBD.

SYNONYMS

IBD-related spondyloarthropathy
Enteroarthritis
Arthritis associated with gastrointestinal disease

ICD 10-CM CODE(S)

M07.60	Enteropathic arthropathies, unspecified sites
M07.68	Enteropathic arthropathies, vertebra
M07.69	Enteropathic arthropathies, multiple sites
M07.611	Enteropathic arthropathies, right shoulder
M07.612	Enteropathic arthropathies, left shoulder
M07.619	Enteropathic arthropathies, unspecified shoulder
M07.621	Enteropathic arthropathies, right elbow
M07.622	Enteropathic arthropathies, left elbow
M07.629	Enteropathic arthropathies, unspecified elbow
M07.631	Enteropathic arthropathies, right wrist
M07.632	Enteropathic arthropathies, left wrist
M07.639	Enteropathic arthropathies, unspecified wrist
M07.641	Enteropathic arthropathies, right hand
M07.642	Enteropathic arthropathies, left hand
M07.649	Enteropathic arthropathies, unspecified hand
M07.651	Enteropathic arthropathies, right hip
M07.652	Enteropathic arthropathies, left hip
M07.659	Enteropathic arthropathies, unspecified hip
M07.661	Enteropathic arthropathies, right knee
M07.662	Enteropathic arthropathies, left knee
M07.669	Enteropathic arthropathies, unspecified knee
M07.671	Enteropathic arthropathies, right ankle and foot
M07.672	Enteropathic arthropathies, left ankle and foot
M07.679	Enteropathic arthropathies, unspecified ankle and foot
M07.68	Enteropathic arthropathies, vertebrae
M07.69	Enteropathic arthropathies, multiple sites

EPIDEMIOLOGY & DEMOGRAPHICS

Peripheral arthritis occurs in 5% to 15% of patients with IBD in most studies and is slightly more common in CD than in UC. Spinal involvement occurs in 10% to 20% of cases and may be the only articular manifestation or be accompanied by peripheral arthritis.

PREDOMINANT SEX AND AGE: Males and females equally affected. Inflammatory back pain usually presents before the age of 45 yr. Onset of peripheral arthritis is usually between 25 and 45 yr of age.

RISK FACTORS:

- Active large bowel disease
- Family history of IBD
- Cigarette smoking
- Genetics
- Complicating intestinal manifestations such as abscesses and perianal disease

GENETICS: The presence of *HLA-B27* is the strongest association with SpA. Recent genome-wide association studies demonstrated a genetic overlap between IBD and SpA, implicating *NOD2 (CARD15)* and interleukin 23 receptor *(IL23R)* as susceptibility genes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Two types of joint involvement in IBD: Peripheral and/or axial. Peripheral: Affects peripheral joints, predominantly lower limb joints. Axial: Affects the spine in the form of sacroiliitis with or without spondylitis; can be similar to ankylosing spondylitis or other idiopathic SpA (e.g., psoriatic arthritis, reactive arthritis, undifferentiated SpA).
- Axial involvement is found more commonly in CD than in UC. Axial disease is independent of IBD activity. Can have asymptomatic sacroiliitis.
- Peripheral arthritis is the most frequent extra intestinal finding in both CD and UC. Peripheral and spinal disease equally affects both sexes (Table 1).
- Type 1 peripheral arthropathy (pauciarticular, fewer than five joints): Usually acute and self-limited asymmetric inflammatory arthritis; commonly affects large joints of legs such as the knee; occurs early in the course of IBD and commonly parallels the disease activity or flares of IBD, generally self-limiting.
- Type 2 peripheral arthropathy (polyarticular, five or more joints): Affects mainly the metacarpophalangeal, proximal interphalangeal, knee and ankle joints; bilateral and symmetric; may be migratory, nonerosive. Symptoms may take a more chronic course, independent of IBD activity.
- Main complaints are inflammatory back pain, buttock pain, joint pain, and swelling (with prolonged morning stiffness and fatigue); symptoms worse with rest or inactivity and improve with exercise.
- Examination reveals evidence of synovitis, progressive limitation of spinal mobility.
- Periarticular and other extraintestinal manifestations include enthesitis (inflammation of tendon insertion sites into bone such as Achilles or plantar fascia), dactylitis (flexor tenosynovitis of a finger or toe causing sausage like swelling of digit), uveitis, and psoriasis.
- Uveitis in IBD is more often bilateral and more prone to chronicity.
- Erythema nodosum, pyoderma gangrenosum can be associated with skin lesions in IBD.

ETIOLOGY

In genetically predisposed individuals with intestinal disease, the co-occurrence of joint inflammation provides important support to the theory that dysbiosis in the gut microbiome can link colitis to the development of EA.

TABLE 1 Enteropathic Arthritis

Feature	Peripheral Arthritis	Sacroiliitis, Spondylitis
Crohn Disease		
Frequency in CD	10%-20%	2%-7%
HLA-B27 associated	No	Yes
Pattern	Transient, symmetrical	Chronic
Course	Related to activity of CD	Unrelated to activity of CD
Effect of surgery	Remission of arthritis uncommon	No effect
Effect of anti-TNF therapy	Effective	Effective
Ulcerative Colitis		
Frequency in UC	5%-10%	2%-7%
HLA-B27 associated	No	Yes
Pattern	Transient	Chronic
Course	More common in pancolitis than proctitis; related to activity of UC	Unrelated
Effect of surgery	Remission of arthritis	No effect

CD, Crohn disease; *HLA,* human leukocyte antigen; *TNF,* tumor necrosis factor; *UC,* ulcerative colitis.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hypertrophic osteoarthropathy
- Osteonecrosis (avascular necrosis)
- Septic arthritis
- Other idiopathic seronegative spondyloarthropathies (e.g., reactive arthritis, psoriatic arthritis, ankylosing spondylitis)
- Behçet syndrome
- Rheumatoid arthritis

WORKUP

Diagnosis mainly relies on clinical features and imaging data. There is no gold standard for diagnosis.

LABORATORY TESTS

- Laboratory testing: Markers of inflammation such as sedimentation rate and C-reactive protein (CRP) may reflect underlying disease activity of bowel disease and thus may not be useful to track for EA activity. CBC can reveal leukocytosis, anemia, thrombocytosis suggestive of inflammatory response.
- Synovial fluid is nonspecific; shows mild to marked inflammation: WBC 1500 to 50,000/mm^3.
- Serologic tests for rheumatoid arthritis are negative (rheumatoid factor, cyclic-citrullinated peptide antibodies), and lupus-related antinuclear antibodies are absent.
- Tests for other intestinal diseases based on clinical suspicion: Whipple diagnosis is based on histology with Periodic acid–Schiff (PAS)-positive cells, serology for *T. whipplei*, and culture; celiac disease immunoglobulin A (IgA) antitissue transglutaminase and anti-endomysial antibodies along with diagnostic villous atrophy on small bowel biopsy; microscopic colitis diagnosed only through histology from colonoscopy showing collagenous colitis or lymphocytic colitis.
- Calprotectin measured in the serum or in the stools has been used to identify subclinical bowel inflammation in patients with SpA. Individuals who had both CRP and calprotectin elevated had an increased frequency of bowel inflammation compared to patients who had low levels of these proteins.

IMAGING STUDIES

- Plain x-ray of the spine and pelvis may appear normal in early disease but with progression may show evidence of sacroiliitis, spondylitis, ankyloses.
- X-ray of peripheral joints may show soft tissue swelling, periostitis, or joint effusion.
- MRI may be used to assess early changes of spondyloarthritis when plain x-rays are negative. MRI is the most sensitive method of detecting sacroiliitis in IBD patients.
- Musculoskeletal ultrasonography is a noninvasive, safe, and easily reproducible means of detecting early pathologic changes in SpA patients. It can identify characteristic features of enthesitis, bone erosions, synovitis, bursitis, and tenosynovitis.

Rx TREATMENT

- Effective treatment of underlying IBD is helpful in controlling the peripheral arthritis. The goal of treatment of EA is reducing inflammation to relieve suffering and prevent joint deformity and disability.
- When IBD and SpA coexist, treatment strategy should also address extraintestinal and extraarticular features such as enthesitis, dactylitis, uveitis, and psoriasis, with need for tailored consideration of certain limited biologic options.
- Avoidance of NSAIDs due to controversial increased risk of exacerbation of intestinal disease.

NONPHARMACOLOGIC THERAPY

Rest, physical therapy, and exercise such as swimming

ACUTE GENERAL Rx

- There has been concern that NSAIDs exacerbate IBD and that NSAID-related adverse events such as ulcers and GI bleeding may mimic IBD flares. COX-2 inhibitors may be preferred to traditional NSAIDs, but similar concerns and cautions apply.
- Intraarticular steroid injections may help treat joint synovitis.
- Systemic steroids can help reduce polyarticular joint and IBD activity but should be used at the lowest effective dose and ideally for only short courses.

CHRONIC Rx

- Immunomodulatory agents such as sulfasalazine, azathioprine, 6-mercaptopurine, methotrexate, and cyclosporine can be used to treat active IBD, peripheral arthritis, and associated skin conditions. Peripheral joint disease responds better to these agents than axial disease. Tumor necrosis factor (TNF) inhibitors, particularly infliximab, adalimumab, and certolizumab, are useful to treat both arthritis (axial or peripheral) and severe, refractory IBD. Golimumab is also in use for refractory IBD and is used for arthritis. Etanercept is not effective to control IBD.
- The axial disease associated with IBD is treated similar to other SpA. Medications approved for other SpAs, such as ustekinumab (anti-IL12/23), secukinumab (anti-IL17A), ixekizumab (anti-IL17), and Janus kinase (JAK) inhibitors, may be effective therapies for EA, although their effectiveness for IBD is not clear. Anti-IL17 is usually avoided with IBD, given possible worsening of IBD.
- The choice of biologic requires the consideration of extraarticular and extraintestinal features such as skin disease or uveitis. The latter can be treated with infliximab or adalimumab, both of which also treat the IBD.
- For highly active IBD, particularly UC, colectomy has been found to ameliorate peripheral joint inflammatory disease but does not influence axial involvement.
- Interdisciplinary approach and active cooperation between rheumatologist and gastroenterologist through combined clinics, for example, are essential.

REFERRAL

Rheumatology and gastroenterology

PEARLS & CONSIDERATIONS

- When a single joint is affected, consider joint aspiration to rule out septic arthritis. Signs of infection may be atypical in those receiving anti-inflammatory or immunosuppressive medications.
- Other extraintestinal manifestations of enteropathic arthritis include skin and mucous membrane involvement, anterior uveitis, Hashimoto thyroiditis, genitourinary involvement (nephrolithiasis), aortic insufficiency, and cardiac conduction abnormalities. These are often seen in patients with prolonged disease activity and positive *HLA-B27*.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED TOPICS

Ankylosing Spondylitis (Related Key Topic)
Crohn Disease (Related Key Topic)
Psoriatic Arthritis (Related Key Topic)
Ulcerative Colitis (Related Key Topic)

AUTHORS: **Candice Reyes, MD, RhMSUS,** and **Amani A. Elghafri, MD, MSC, Med Ed**

SUGGESTED READINGS

Atzeni F et al: Rheumatic manifestations in inflammatory bowel disease, *Autoimmun Rev* 13(1):20-23, 2014.

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BASIC INFORMATION

DEFINITION

Enuresis refers to the voiding of urine into clothes or in bed that is either voluntary or involuntary in individuals who are expected to be continent (>5 yr of age). The diagnosis is made if voiding occurs at least twice a wk for 3 mo. Primary enuresis refers to enuresis without a period of continence, whereas secondary enuresis occurs after a 6-mo period of normal bladder control.

SYNONYMS

Urinary incontinence
Bedwetting
Nocturia

ICD-10CM CODES

N39.44	Nocturnal enuresis
F98.0	Enuresis not due to a substance or known physiological condition

DSM-5 CODES

307.6

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Ages 5 to 10 yr. 5 to 7 million children in the U.S. have enuresis.

PREVALENCE (IN U.S.):

- Age 5 yr: 7% of males and 3% of females
- Age 10 yr: 3% of males and 2% of females
- Ages 15 and older: 1% of males and females

PREDOMINANT SEX: Twice as many males as females at all ages

PREDOMINANT AGE: Highest prevalence at age 5 with a steady decrease thereafter at a rate of approximately 12% to 15% per yr

GENETICS:

- Approximately 75% of children with enuresis have a first-degree relative with enuresis.
- Almost twice as common in monozygotic than dizygotic twins.

RISK FACTORS:

- Developmental delays
- Behavior problems and attention deficit hyperactivity disorder (ADHD)
- Younger age
- Male
- Positive family history

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Three enuresis subtypes are defined in DSM-5:

1. Nocturnal only (also known as monosymptomatic enuresis): Occurs in each sleep stage in proportion to the time spent in the particular stage. May occur during transition from deep sleep to rapid eye movement (REM) and is without other lower urinary tract symptoms.
2. Diurnal only (also referred to as nonmonosymptomatic or urinary incontinence): More frequent in girls and rarely after age 9 yr; voiding occurs in early afternoon on school days. Within this subtype, individuals have "urge incontinence" with sudden symptoms of urgency and detrusor instability or "voiding postponement" where individuals ignore urges until the point of incontinence.
3. Combined nocturnal and diurnal.

ETIOLOGY

- Enuresis often correlates with other maturational delays, particularly language, motor skills, and social development.
- May be related to toilet training issues, stress (secondary enuresis), inability to concentrate urine, altered smooth muscle physiology, small bladder capacity, or dysfunction of the arousal system.
- Diurnal enuresis associated with a higher rate of urinary tract infections.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- The pathophysiology of primary enuresis involves the inability to awaken from sleep in response to full bladder, or a decreased functional capacity of the bladder with possible excessive nighttime urine production.
- May be associated with encopresis and sleep disorders such as sleep terrors; much less likely to be a primary psychological disorder.
- Organic causes of enuresis include diabetes mellitus, diabetes insipidus, bladder outlet obstruction, small bladder capacity, detrusor instability, urethral valves, meatal stenosis, cerebral palsy, spina bifida, pelvic mass, impacted stool, sedating medications, nocturnal seizures, urinary tract infections, kidney disease, hyperthyroidism, pinworms, and obstructive sleep apnea.

WORKUP

- History and physical examination to rule out anatomic abnormalities, look for signs of obstructive sleep apnea. Fluid intake, voiding diaries, and stooling histories may be useful. Family history of enuresis, particularly for nocturnal enuresis.
- Children frequently experience shame, so gentleness and care must be exercised when questioning or examining the child.
- Observation of voiding is useful to assess for weak stream.

LABORATORY TESTS

- Urinalysis with specific gravity and urine culture if white cells or nitrites to rule out infection
- Serum studies to rule out diabetes, electrolyte abnormalities, or renal dysfunction

IMAGING STUDIES

- In complicated cases, or if there is evidence of obstructive sleep apnea, sleep studies may be useful.
- If an anatomic abnormality is suspected, urologic imaging, including voiding cystourethrogram and renal sonogram is possibly indicated: An abdominal x-ray may demonstrate stool retention; MRI of the spine if evidence of abnormalities of lower spine or perineum is found on examination.

TREATMENT

NONPHARMACOLOGIC THERAPY

Behavioral treatment:

- Scheduled voiding to reduce the frequency of enuretic episodes.
- Motivational therapy including sticker or star charts to reward child for dry nights.
- Alarm and pad technique: 66% response rate (compared with 4% of control participants), although about half relapse.
- Punishment for enuresis is not effective.

ACUTE GENERAL Rx

Education and motivational therapy

CHRONIC Rx

- Alarm pad is first-line treatment.
- Desmopressin (DDAVP) administered orally at bedtime significantly reduces the incidence of bedwetting with complete response in 30% of patients and another 40% with dramatic reduction in symptoms. Relapse rate is as high as 70% after discontinuation. Of note, the intranasal preparation is associated with a greater risk for water intoxication and is not recommended.
- Tricyclic antidepressants (imipramine): Efficacy supported by randomized control trials. Use with care in children, given the side effect profile.
- Serotonin reuptake inhibitors: Lack of adequate trials is notable.
- Indomethacin suppositories may reduce normal prostaglandin inhibitory effects on antidiuretic hormone.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Weak or limited evidence for complementary treatment interventions, including psychotherapy, hypnosis, chiropractic care, acupuncture, and medicinal herbs

DISPOSITION

- After age 5 yr, the rate of spontaneous remissions is approximately 12% to 15% per yr.
- The disorder usually resolves by adolescence. However, effective treatment spares considerable misery.
- Fewer than 1% will have enuresis as adults.

REFERRAL

- If coexisting, a psychiatric condition complicates the course of treatment.
- Referral to a pediatric urologist is indicated for primary enuresis refractory to therapy and for selected secondary causes (e.g., urinary tract malformations, neurologic disorders).

PEARLS & CONSIDERATIONS

Illness, hospitalization, and family stressors may precipitate recurrent enuresis after a period of dryness.

PATIENT & FAMILY EDUCATION

- American Academy of Pediatrics: www.healthychildren.org/English/ages-stages/toddler/toilet-training/Pages/default.aspx
- Kidshealth: http://kidshealth.org/parent/general/sleep/enuresis.html

RELATED CONTENT

Bedwetting (Patient Information)

AUTHOR: **Marta Majczak, MD**

SUGGESTED READINGS

Baird DC, Seehusen DA, Bode DV: Enuresis in children: a case-based approach, *Am Fam Physician* 90(8):560-568, 2014.

Joinson C: Childhood incontinence: risk factors and impact, *Nurs Times* 112(20):15-16, 2016.

Eosinophilic Esophagitis (EoE) PTG

BASIC INFORMATION

DEFINITION

Eosinophilic esophagitis is a chronic, antigen- and immune-mediated disease, which requires these inclusion criteria after secondary causes of esophageal eosinophilia are excluded:

1. Inflammation secondary to eosinophilic infiltration within the esophagus (confirmed with at least 15 eosinophils per high power field (HPF) detected on biopsy of mucosa taken at mid and distal esophagus)
2. Symptoms related to esophageal dysfunction Mucosal eosinophilia is isolated to the esophagus and persists after a proton pump inhibitor (PPI) trial

SYNONYMS

Esophageal eosinophilia
EoE
EE

ICD-10CM CODE
K20.0 Eosinophilic esophagitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): One to 20 new cases per 100,000 inhabitants per yr, increased from last year
PREVALENCE: Between 13 and 49 cases per 100,000 inhabitants
PREDOMINANT SEX: Male predominance (ratio ~3:1)
PREDOMINANT AGE: Peak of disease activity at age 35 to 39
PEAK INCIDENCE: Older children; in adults, ages 30 to 50
GENETICS:

- Association between thymic stromal lymphopoietin *(TSL)* gene mutation and risk for EoE
- Higher risk in those with homozygous pattern for the mutation
- *TSL* gene found on Yp11.3 chromosome
- Association with polymorphism on eotaxin-3 (CCL-26)

RISK FACTORS/ETIOLOGY: Genetic, host immune, and environmental

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Adults: Dysphagia to solid foods, food impaction, heartburn, noncardiac chest pain, increased time to consume meals, concurrent allergic disease (asthma, eczema, rhinitis, atopic dermatitis, seasonal/food allergies)
- Children: Vomiting, regurgitation, nausea, epigastric/abdominal pain, chest pain, water brash, globus, decreased appetite, gagging, choking, refusal of food, possible atopy
- Often associated with asthma, rhinitis, dermatitis, and other atopic conditions

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gastroesophageal reflux disease
- PPI-responsive esophageal eosinophilia (PPI-REE)—see "Acute General Rx"
- Celiac disease
- Eosinophilic gastroenteritis
- Crohn disease
- Hypereosinophilic syndrome
- Achalasia
- Vasculitis/pemphigus/connective tissue diseases
- Infectious (fungal/viral)
- Graft-versus-host disease
- Pemphigus
- Connective tissue disease

WORKUP

- Esophagogastroduodenoscopy (EGD) with at least two to four biopsies from distal and mid/proximal esophagus after a PPI trial
- Confirmation: Persistence of symptoms *and* ≥15 eosinophils/HPF on pathology (Fig. 1) although esophagus is normal in ~5% to 10% of patients
- Other histological findings can include basal zone hyperplasia, dilated intracellular spaces, and subepithelial fibrosis
- Endoscopic findings can include white mucosal papules, which represent eosinophilic microabscesses, linear furrows, esophageal narrowing with stricture, mucosal tearing, and esophageal trachealization (Fig. 2), esophageal rings, felinization of esophagus. Felinization of the esophagus is a radiologic term used to describe 1 to 2 mm transverse folds found circumferentially along the entire lumen of the esophagus that appear transiently on EGD and barium studies, possibly attributed to thickened and contracted muscularis mucosae

LABORATORY TESTS

- Forty percent to 50% have elevated peripheral eosinophilia
- Fifty percent to 60% have elevated serum immunoglobulin E (IgE) levels

IMAGING STUDIES

Esophagram can reveal rings and strictures.

TREATMENT

NONPHARMACOLOGIC THERAPY

Three strategies of dietary therapy:

- Empiric six-food elimination diet (eliminates milk, soy, egg, wheat, nuts, and seafood) For patients with response, foods can be reintroduced one at a time for 6 wk
- Total elimination of all food allergens with elemental or amino acid–based formula

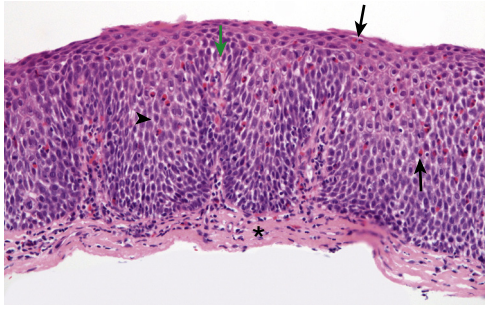

FIG. 1 H&E staining of an esophageal specimen from a patient with eosinophilic esophagitis. *Arrows* point to eosinophils, including some at the surface. *Arrowhead* points to dilated intercellular spaces. *Asterisk* marks the lamina propria, showing inflammation and fibrosis. *Green arrow* points to elongated papillae. There is also marked basal layer hyperplasia, with the basal layer reaching almost to the luminal surface. *H&E*, hematoxylin and eosin. (From Feldman M et al *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

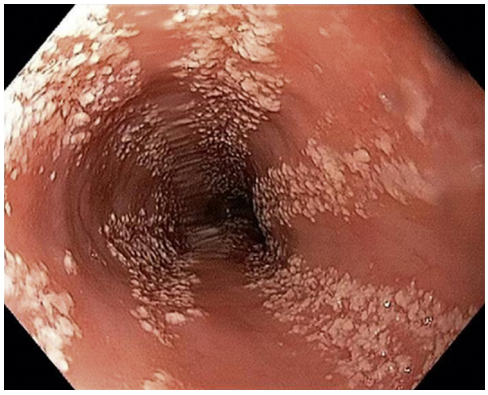

FIG. 2 Endoscopic view of eosinophilic esophagitis with furrowing and exudates. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

- Targeted elimination diet guided by allergy testing, typically skin prick testing or patch testing
- Dilation if stricture is present and/or patient is refractory to therapy with the goal of creating a tear in the mucosa

ACUTE GENERAL Rx

- An 8-wk trial of PPI therapy to exclude PPI-responsive esophageal eosinophilia should be initiated after an initial EGD with biopsy based on clinical symptoms with subsequent EGD (with biopsies).
  1. If eosinophilia persists on biopsy despite PPI use, diagnosis is EoE
  2. If eosinophilia is reduced on repeat biopsies, patient is considered to have proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE), not EoE
- An EGD (with biopsies) should be performed initially if a critical stricture is present (e.g., patient presents with food impaction).
- If EoE is confirmed, patient should be tried on aerosolized topical glucocorticoids (fluticasone or budesonide) and/or dietary elimination.
  1. Topical steroids shown to be most effective:
     a. Swallowed fluticasone 880 to 1760 mcg/day in a divided dose bid (adult dosing)
        (1) Delivered by meter-dosed inhaler without a spacer.
        (2) Medication is sprayed into the patient's mouth and then swallowed.
        (3) Patient should **not** inhale when the medication is being delivered.
        (4) Patient should not eat or drink for 30 to 60 min following administration.
     b. Swallowed budesonide 2 mg daily, typically in divided doses
        (1) Administered using a nebulizer: Patient then instructed to swallow accumulated liquid
        (2) Administered as viscous slurry: Mixing 1 mg/2 ml nebulizer ampules with sucralose (5 1-g packets per 1 mg of budesonide)
        (3) Patient should not eat or drink for 30 to 60 min after taking the budesonide suspension

CHRONIC Rx

- If patient is responsive to PPI therapy, EoE has been excluded and patient can be continued on PPI therapy with surveillance of symptoms.
- If patient is responsive to aerosolized topical steroids and/or dietary modification, continue steroids at lowest dose and/or continue dietary elimination.
- If lack of response to initial therapy:
  1. Assess compliance.
  2. Restrict diet further.
  3. Increase steroid dose or consider alternative steroid.
  4. Switch from dietary modification to steroid therapy and vice versa.
  5. Consider second-line agents or clinical trials.
  6. Reevaluate diagnosis and secondary causes of esophageal eosinophilia (see "Differential Diagnosis" earlier).
- Chronic histologic and symptomatic surveillance is recommended.
- If dysphagia persists, endoscopic dilation is recommended for amelioration of symptoms.

DISPOSITION

Follow-up by gastroenterologist is important to gauge progression or regression of disease.

REFERRAL

Referrals to gastroenterologists, allergists, and dieticians allow for a multidisciplinary approach to diagnosis and management of EoE.

PEARLS & CONSIDERATIONS

COMMENTS

- EoE can be confused with PPI-REE, and patients should undergo a PPI trial before confirmation of EoE and utilization of topical steroids, step-up elimination diet, or esophageal dilation.
- Endoscopic surveillance of disease with or without symptoms is important.
- While esophageal dilation is the mainstay of therapy in patients with esophageal strictures, narrowing of esophagus, and esophageal rings, dilation will not reduce the risk of recurrence as eosinophilic burden is unaffected.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Gastroesophageal Reflux Disease (Related Key Topic)

AUTHOR: **Zilla Hussain, MD**

SUGGESTED READINGS

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Souza RF: Eosinophilic esophagitis: what if elimination diet does not work? *Digestive Disease Week* 2, 2018. Washington, D.C.

Eosinophilic Fasciitis

BASIC INFORMATION

DEFINITION

Eosinophilic fasciitis (EF) is a rare inflammatory disease of the skin and subcutaneous tissue characterized by erythema, edema, and eosinophilia in peripheral blood that was first described by Lawrence Shulman in 1974. This condition starts with acute onset of symmetrical erythema, edema, and induration of the trunk or an extremity and later may progress to sclerosis of the dermis and subcutaneous fascia leading to contractures.

SYNONYMS

Shulman syndrome
Diffuse fasciitis with eosinophilia

ICD-10CM CODE
M35.4 Diffuse (eosinophilic) fasciitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Exact incidence of EF is unknown.
- Women are 1.3 to 2.1 times as likely as men to be affected.
- Mean age of onset: 47 to 57 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Early stage:
  1. Acute onset of limb (typically symmetrical) or trunk erythema and edema
  2. Peripheral eosinophilia
- Late stage:
  1. Indurated collagenous thickening of the subcutaneous fascia
  2. Peripheral eosinophilia often absent
- Cutaneous: Peau d'orange, Groove sign (visible indentation of superficial vein; Fig. E1)
  1. Face, hands, and feet are typically spared
- Musculoskeletal: Limited joint mobility (joint contractures in 50% to 60% of patients)
- Neuropathies: Cranial and peripheral neuropathies (carpal tunnel syndrome, mononeuritis multiplex)
- Constitutional: Myalgia, muscle weakness, fatigue, weight loss
- Hematologic: Up to 10% of EF cases have been associated with hematologic disorders such as aplastic anemia, myeloproliferative disorders, lymphoma, leukemia, and multiple myeloma
- Patients with EF often lack visceral involvement or history of Raynaud phenomenon

ETIOLOGY

The etiology is unknown. A proposed mechanism of disease is a nonspecific immune-mediated inflammation of the fascia triggered by stress (exercise, trauma), exposures (medications, radiation therapy, burns), infection (*Borrelia burgdorferi*), autoimmune disease, or hematologic disorder. Most cases are considered idiopathic.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Localized scleroderma: Morphea, linear
- Systemic scleroderma
- Scleroderma-like disorders: Nephrogenic systemic fibrosis, scleromyxedema, scleredema
- Hypereosinophilic syndrome
- Deep vein thrombosis
- Cellulitis
- Graft-versus-host disease

WORKUP

- Diagnosis by histopathology with fascial thickening and fibrosis is considered gold standard.
- Universally accepted, validated diagnostic criteria are lacking.
- Proposed diagnostic criteria (two major or one major and two minor) by Pinal-Fernandez et al (2014):
  1. Major:
     a. Swelling, induration, and thickening of the skin and subcutaneous tissue that is symmetrical or nonsymmetrical, diffuse (extremities, trunk, and abdomen), or localized (extremities)
     b. Fascial thickening with accumulation of lymphocytes and macrophages with or without eosinophilic infiltration (determined by full-thickness wedge biopsy of clinically affected skin)
  2. Minor:
     a. Eosinophilia $>0.5 \times 10^9$/L
     b. Hypergammaglobulinemia >1.5 g/L
     c. Muscle weakness and/or elevated aldolase levels
     d. Groove sign and/or peau d'orange
     e. Hyperintense fascia on MR T2-weighted images
- Exclusion criteria: Diagnosis of systemic sclerosis

LABORATORY TESTS

- Peripheral eosinophilia in 64% to 86% of cases in early stage
- Elevated erythrocyte sedimentation rate and/or elevated aldolase usually correlates with disease activity
- Creatinine kinase usually normal
- Hypergammaglobulinemia (35%) of unclear significance

IMAGING STUDIES

- Consider MRI during initial work-up:
  1. Noninvasive
  2. Identifies presence of fascia edema and inflammation
  3. Can guide appropriate site for biopsy or be used if biopsy nondiagnostic
- Consider PET-CT (though limited data based on case reports)

TREATMENT

ACUTE GENERAL Rx

- Given the rarity of EF, no randomized controlled trials have been performed to date.
- Corticosteroids (prednisone 0.5 to 1 mg/kg/d) are considered mainstay of treatment.
- Based on a recent retrospective review from 2016 of the largest cohort of EF patients to date, complete response is more likely with combination of corticosteroids and methotrexate compared to other treatment combinations, corticosteroid therapy, or treatment without corticosteroids.
- Other potential agents based on case reports include mycophenolate mofetil (MMF), intravenous immunoglobulin (IVIG), cyclosporine, azathioprine, infliximab, rituximab, and sirolimus as well as UVA phototherapy or extracorporeal photochemotherapy.

CHRONIC Rx

- Treatment duration is unknown. Patients are monitored for clinical response, and medications are decreased/discontinued accordingly.
- Patients with incomplete response may require increased doses of corticosteroids.

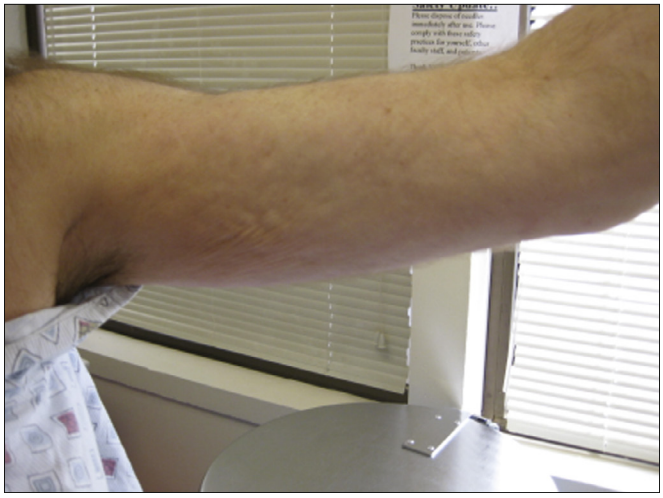

FIG. E1 The "groove sign" of eosinophilic fasciitis. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

DISPOSITION

- Improved outcomes with early treatment.
- Long-term prognosis is unknown but is generally good.
- Relapse can occur after cessation of steroids.

REFERRAL

Dermatology should be consulted for full skin-to-muscle biopsy. May require surgical evaluation to reduce contracture and maintain function.

PEARLS & CONSIDERATIONS

COMMENTS

- Physical therapy is a crucial, but often overlooked, part of managing EF.
- Patients should be started on prophylaxis for opportunistic infections when on long-term corticosteroids or immunosuppression.

AUTHORS: **Alexandra Abrams-Downey, MD,** and **Erna Milunka Kojic, MD**

SUGGESTED READINGS

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Jinnin M et al: Diagnostic criteria, severity classification and guidelines of eosinophilic fasciitis, *J Dermatol* 45:881-890, 2018.

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Pinal-Fernandez I et al: Diagnosis and classification of eosinophilic fasciitis, *Autoimmun Rev* 13:379-382, 2014.

Wright NA et al: Epidemiology and treatment of eosinophilic fasciitis: an analysis of 63 patients from 3 tertiary care centers, *JAMA Dermatol* 152:97-99, 2016.

Eosinophilic Granulomatosis with Polyangiitis

BASIC INFORMATION

DEFINITION

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome (CSS) and also as allergic granulomatosis and angiitis, refers to a multisystem granulomatous vasculitis characterized by severe asthma, chronic rhinosinusitis, and hypereosinophilia. Classification criteria and definition for EGPA are described in Table E1.

SYNONYMS

Allergic angiitis
Allergic granulomatosis
Allergic granulomatosis and angiitis
Churg-Strauss syndrome (CSS)
EGPA

ICD-10CM CODES

M31.30 Wegener granulomatosis without renal involvement

EPIDEMIOLOGY & DEMOGRAPHICS

- Overall incidence of 2.4 cases per 1 million persons in the U.S. Among patients with asthma, the annual incidence of EPGA is estimated to average 34.6 per 1 million patients.
- Usually occurs at a mean age of 40 yr, and is uncommon in those ≥65 yr. It is rare in children but presents in an aggressive form with cardiopulmonary involvement when it does occur.
- No gender predominance.
- Rarest of the ANCA-associated vasculitis but most common of the p-ANCA vasculitides.
- Cardiac or GI involvement and age ≥65 yr are indicators of worse prognosis.
- With treatment, 1-yr survival rate is approximately 90%, and 5-yr survival is 62%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The clinical picture of EPGA typically consists of three partially overlapping phases, which may or may not be sequential:

- Prodromal phase:
  1. Severe adult-onset asthma, with or without allergic rhinitis, atopic dermatitis, sinusitis, headache, cough, and wheezing
  2. Precedes development of systemic vasculitis by several yrs
- Eosinophilic/tissue infiltration phase:
  1. Peripheral eosinophilia and eosinophilic infiltration of the lungs, myocardium, and GI tract, with or without granulomas
  2. Signs and symptoms of cough, fever, anorexia, weight loss, sweats, malaise, nausea, vomiting, abdominal pain, and diarrhea
  3. Forty percent of EGPA patients present with asthma, pulmonary opacities, and hypereosinophilia in this phase
- Systemic vasculitic phase:
  1. Development of necrotizing vasculitis that is clinically apparent primarily in peripheral nerves, skin, and kidneys, although any organ can be affected
  2. Signs and symptoms include fever, fatigue, weight loss
- Skin involvement is common and seen in >50% of patients. It can be divided into three categories:
  1. Erythematous maculopapules (can resemble erythema multiforme)
  2. Hemorrhagic lesions (associated with wheals)
  3. Cutaneous and subcutaneous nodules on extensor surfaces

ETIOLOGY

Etiology unknown but believed to be an autoimmune-mediated process (see "Comments")

DIAGNOSIS

- Clinical findings and biopsy showing eosinophilic vasculitis.
- The American College of Rheumatology (ACR) has established the criteria for EGPA diagnosis in patients without vasculitis (Table E1). The presence of any four or more of the six criteria yields a sensitivity of 85% and a specificity of 99.7%. For patients with vasculitis, the presence of asthma and eosinophilia is 90% sensitive and 99% specific for EGPA.

DIFFERENTIAL DIAGNOSIS

- Polyarteritis nodosa (PAN)
- Granulomatosis with polyangiitis and microscopic polyangiitis (GPA, formerly known as Wegener granulomatosis)
- Goodpasture syndrome
- Loeffler syndrome
- Hypereosinophilia syndrome
- Rheumatoid arthritis
- Leukocytoclastic vasculitis

Although similar and at times grouped with patients with PAN or GPA, EGPA differs in that:

- EGPA vasculitis involves small-sized arteries, veins, and venules.
- EGPA, unlike PAN, predominantly involves the lung.
- Kidney involvement is much less common in EGPA than in GPA. Pulmonary lesions in GPA usually involve the upper respiratory tract rather than the peripheral lung parenchyma in EGPA.
- EGPA shows necrotizing vasculitis along with eosinophilic granulomas.

LABORATORY TESTS

- Complete blood count with differential: Eosinophilia >10% is an American College of Rheumatology (ACR) diagnostic criterion.
- Blood urea nitrogen and creatinine may be mildly elevated, suggesting renal involvement.
- Urinalysis may show mild hematuria and proteinuria.
- 24-hour urine for protein; >1 g/day is a poor prognostic factor.
- Perinuclear antineutrophilic cytoplasmic antibody (P-ANCA) is found in 40% to 60% of patients. Negative ANCA does not rule out EGPA.
- Antiproteinase 3 (PR3) antibody positivity.
- IgE is commonly elevated.
- Elevation of aspartate aminotransferase, alanine aminotransferase, and creatinine phosphokinase may indicate liver or muscle (skeletal or cardiac) involvement.
- Rheumatoid factor may be positive.
- Biopsy helps confirm the diagnosis. Surgical lung biopsy is the gold standard. Transbronchial biopsy is rarely helpful. Necrotizing vasculitis and extravascular necrotizing granulomas, usually with eosinophilic infiltrates, are suggestive of EGPA. The presence of eosinophils in extravascular tissues is most specific for EGPA.

IMAGING STUDIES

- Chest radiograph is abnormal in eosinophilic and vasculitic phases: Asymmetrical bilateral patchy migratory infiltrates, interstitial lung disease, small pleural effusions, or nodular infiltrates (Fig. E1).
- Lung lesions in EGPA are noncavitating, as opposed to those in GPA.
- Paranasal sinus films may reveal sinus opacification, which is an ACR diagnostic criterion.
- Angiography is sometimes done in patients with mesenteric ischemia or renal involvement.

TABLE E1 Classification Criteria and Definition for Churg-Strauss Syndrome

Diagnosis Criteria	
American College of Rheumatology (Preferred; Requires 4 of 6)	**Lanham (Requires All 3)**
Asthma	Asthma
Eosinophilia (>10% total WBC count)	Eosinophilia (>10% WBC count or >1.5 × 10^9)
Neuropathy (mono- or polyneuropathy)	Systemic vasculitis affecting at least two or more extrapulmonary sites
Pulmonary infiltrates (migratory or transitory)	
Paranasal sinus abnormality (pain, tenderness, or radiologic abnormality)	
Extravascular eosinophils (in a biopsy containing an artery, arteriole, or venule)	

WBC, White blood cell.
From Hochberg MC, et al: *Rheumatology,* ed 5, St. Louis, 2011, Mosby.

TREATMENT

NONPHARMACOLOGIC THERAPY

Oxygen therapy in severe asthmatic exacerbations

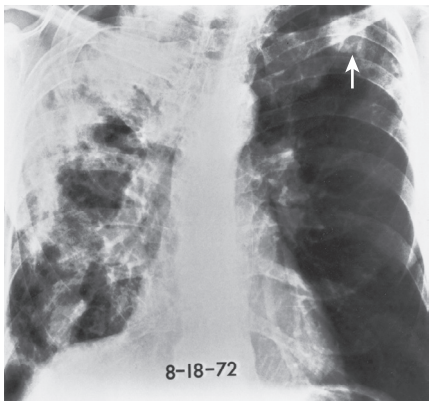

FIG. E1 Allergic angiitis and granulomatosis. Posteroanterior chest radiograph demonstrates peripheral air space consolidation in the right lung and a nodule *(arrow)* in the left upper lobe in this asthmatic patient. (From McLoud TC [ed]: *Thoracic radiology: the requisites,* St Louis, 1998, Mosby.)

PHARMACOLOGIC THERAPY

The following five factors suggest poor prognosis (five-factor score) and determine the aggressiveness of the immune suppressive therapy:

1. Proteinuria >1 g/day
2. Creatinine >1.58 mg/dl
3. Cardiovascular involvement
4. GI tract involvement
5. CNS involvement

ACUTE GENERAL Rx

- Corticosteroids are the treatment of choice if no poor prognostic factors are present. Prednisone 0.5 to 1.5 mg/kg/day is the starting dose and is continued for 6 to 12 wk and then tapered to 10 mg/day at 1 yr as clinical disease resolves. Response to steroids may be dramatic. Patients with extensive disease may require IV corticosteroids.
- A drop in the patient's eosinophil count and the ESR indicates a response to treatment. P-ANCA does not reliably correspond with disease activity.
- For severe disease, cyclophosphamide is used in combination with corticosteroids.

CHRONIC Rx

- In patients with one or more poor prognostic factors, immunosuppressant agents (cyclophosphamide 1 to 2 mg/kg/day) are used with corticosteroids as first-line therapy. The ideal duration of cyclophosphamide ranges from 6 to 12 mo.
- In patients who do not respond to corticosteroid treatment or in EGPA relapse, cyclophosphamide therapy is indicated as a second-line therapy.
- Azathioprine (2 mg/kg/day) or high-dose IV immunoglobulin has shown benefit in patients with severe disease and in patients unresponsive to corticosteroids.
- Corticosteroids, in combination with interferon-alpha, have also been used in refractory cases but may be difficult to tolerate.
- Patients with persistent symptoms of asthma will require long-term corticosteroids even if vasculitis is no longer present.
- Maintenance therapy using methotrexate (15 to 25 mg/wk) or azathioprine (2 mg/kg/day) is an alternative to cyclophosphamide.

DISPOSITION

- Clinical remission is obtained in more than 90% of patients after treatment. Relapse is common on cessation of therapy (~26%).
- Five-yr survival rate with treatment is between 60% and 90% and decreases to 50% at 7 yr. Asthma generally remains persistent, and ischemic damage to peripheral nerves can be permanent.
- The 5-yr survival rate of untreated EPGA is 25%.
- Death usually occurs from progressive refractory vasculitis, myocardial involvement (~50% of deaths), or severe GI involvement (mesenteric ischemia, pancreatitis).

REFERRAL

- A pulmonary referral for diagnosis and management is appropriate.
- Patients should be followed up closely by rheumatology. Patients usually need long-term immunosuppressive medications.

PEARLS & CONSIDERATIONS

COMMENTS

- EGPA is distinguished from other vasculitides by the nearly universal presence of adult-onset asthma that typically precedes all other symptoms. Family history is often negative for allergies or asthma.
- Vasculitis may not present until several yrs after the prodromal phase.
- Up to 77% of patients in the prodromal phase of EGPA require oral steroids for asthma control.
- Patients often have constitutional symptoms of weight loss, fever, and malaise before specific organ involvement is clinically evident.
- Peripheral nerve involvement from vasculitis of the vasa vasorum commonly manifests as mononeuritis multiplex. Patients may present with sudden foot or wrist drop, along with sensory deficits in the distribution of one or more distal nerves.
- Most patients with GI involvement are symptomatic. Gastroenteritis, acute abdomen, cholecystitis, hemorrhage, bowel perforation, and mesenteric ischemia have all been reported in patients with EGPA.
- Most patients with EGPA respond to corticosteroid treatment and do not require cytotoxic therapy.
- Symptoms of GPA typically appear as oral corticosteroids are being decreased or discontinued for the treatment of asthma and not triggered by leukotriene receptor-1 antagonists, as previously reported.
- Compared with GPA, patients more often present with history of atopy, asthma, or allergic rhinitis. When present, eosinophilia in EGPA is often >1000 eosinophils/mm^3 compared with GPA, in which eosinophilia is much milder (<500 eosinophils/mm^3).
- The heart is involved in up to 60% of patients with EGPA and represents a major cause of mortality.

AUTHOR: **Kachiu C. Lee, MD, MPH**

SUGGESTED READINGS

Baldini C et al: Clinical manifestations and treatment of Churg-Strauss syndrome, *Rheum Dis Clin North Am* 36(3):527-543, 2010.

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BASIC INFORMATION

DEFINITION

Eosinophilic pneumonias (EPs) are a group of disorders characterized by pulmonary infiltrates, eosinophilia of the pulmonary parenchyma or airways, and in some cases, peripheral blood eosinophilia. They manifest by different radiologic and clinical syndromes.

SYNONYMS

EP
Simple pulmonary eosinophilia
Chronic eosinophilic pneumonia
Acute eosinophilic pneumonia
Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)
Idiopathic hypereosinophilic syndrome
Allergic bronchopulmonary aspergillosis
Parasite-induced, fungal-induced, and drug-induced pulmonary eosinophilia

ICD-10CM CODE

J82 Pulmonary eosinophilia, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

Vary depending on the specific cause

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever, cough, and shortness of breath
- Vary depending on the specific cause

ETIOLOGY

SIMPLE PULMONARY EOSINOPHILIA (LÖFFLER SYNDROME):

- Often associated with helminth infections, which can cause pulmonary eosinophilia by transpulmonary passage of larvae, pulmonary parenchymal invasion, or hematogenous spread.
- Can also be seen as the result of a hypersensitivity reaction to infectious organisms or drugs.
- Presents as transient pulmonary infiltrates and peripheral eosinophilia.
- Symptoms are usually mild and self-limited and include fever, cough, and dyspnea.
- Treatment includes removing the offending agent and antimicrobial therapy if appropriate.

IDIOPATHIC ACUTE EP:

- Acute onset of fever, cough, dyspnea (<1 mo).
- Often presents with acute respiratory failure (PaO_2 <60%), requiring intensive care.
- Bilateral diffuse infiltrates on chest radiograph.
- High-resolution computed tomography (CT) scan of the chest typically demonstrates patchy ground glass and reticular opacities; small bilateral pleural effusions are also common.
- Bronchoalveolar lavage (BAL) eosinophilia >25%.
- Absence of infection or other known causes of eosinophilic pneumonia.
- Associations: Recent onset of tobacco smoking, drugs, occupational exposures, exposure to World Trade Center dust, and military exposures in the Middle East.
- Steroids lead to rapid improvement, although there is no consensus about ideal dosing strategy.
- Relapse is uncommon, and prognosis is excellent if promptly treated.

IDIOPATHIC CHRONIC EP:

- Often occurs in middle age and is more commonly seen in women and nonsmokers.
- Associated with asthma.
- Absence of infection or other cause.
- Presentation over weeks to months.
- Symptoms include productive cough, dyspnea, weight loss, night sweats, and fever.
- Chest radiograph typically shows bilateral pulmonary infiltrates.
- "Photographic negative" pulmonary edema (peripheral or pleural based opacities) is highly suggestive but only present in 25% of cases.
- High-resolution CT of the chest may reveal atelectasis, pleural effusions, lymphadenopathy, and septal thickening.
- Pulmonary function tests are nonspecific and often show mixed restrictive and obstructive pattern. Reduced diffusion capacity is also common.
- Peripheral blood eosinophilia is almost always present.
- Diagnose by BAL (almost all cases have >25% eosinophils). Lung biopsy is rarely needed but typically shows interstitial and alveolar infiltrate with eosinophils.
- Treatment with glucocorticoids is typically rapidly effective.
- Relapses are common when glucocorticoids are tapered or discontinued and prolonged steroid courses are often required.
- Case reports suggest inhaled steroids and omalizumab may be helpful in patients with prolonged steroid dependence.
- Prognosis is typically excellent.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA):

- Hypersensitivity reaction to *Aspergillus fumigatus*
- Frequently associated with asthma and cystic fibrosis
- Often presents as severe, persistent asthma, resistant to treatment. Symptoms also include fever, myalgias, cough, wheezing, expectoration of brown-black mucous plugs, and rarely hemoptysis
- A patient with chronic asthma with a component of bronchiectasis and pulmonary infiltrates should be evaluated carefully for ABPA
- Imaging typically shows recurrent (sometimes migratory) infiltrates, central bronchiectasis, and endobronchial mucous impaction ("finger in glove")
- Laboratory tests commonly show peripheral eosinophilia, elevated serum IgE, and elevated sputum and BAL eosinophilia
- Pulmonary function tests commonly show reversible airflow obstruction
- Major diagnostic criteria:
  1. History of asthma or cystic fibrosis
  2. Positive skin test to *Aspergillus* or increased *Aspergillus fumigatus*–specific IgE
  3. Precipitating serum antibodies to *Aspergillus*
  4. Radiographic opacities consistent with ABPA
  5. Serum eosinophilia >500 cells/ml

The disease has been characterized by a staging system. Patients do not necessarily proceed from one stage to another.

Stage I	Acute phase
Stage II	Remission
Stage III	Exacerbation
Stage IV	Glucocorticoid-dependent ABPA
Stage V	End-stage (fibrotic) ABPA

- Treatment: Systemic corticosteroids are the mainstay of treatment. Antifungals may provide additional benefit in modulating airway fungal burden and are recommended for use in patients with relapse or glucocorticoid-dependent disease.
- Development of bronchiectasis portends a worse prognosis.
- Response to therapy and activity of disease may be monitored by measuring IgE levels, which typically will decrease by 35% to 50% when a patient is in remission.

TROPICAL PULMONARY EOSINOPHILIA:

- Onset of asthma, fever, paroxysmal cough and bronchospasm, marked peripheral blood eosinophilia
- Basilar reticulonodular and interstitial infiltrates
- High serum IgE levels
- Presumed etiology: Filariasis *(Wuchereria bancrofti* and *Brugia malayi)*
- Treatment is with diethylcarbamazine

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA):

- Formerly known as Churg-Strauss syndrome.
- Eosinophilic granulomatous inflammation and necrotizing vasculitis of small- to medium-size vessels that involves many organ systems in the setting of asthma.
- Patients present with signs of asthma and atopy including cough, dyspnea, wheezing, sinusitis, and allergic rhinitis; other symptoms depend on other organs involved.
- Labs reveal peripheral blood eosinophilia, elevated IgE.
- 40% of patients will have a positive ANCA (p-ANCA more common than c-ANCA).
- Imaging may show patchy opacities, consolidation, or nodules.
- Pulmonary function test may reveal airflow obstruction.
- Organ systems involved include lungs, heart, skin, peripheral nervous system, GI tract, and kidneys.

- Pathogenesis is not clearly known.
- Untreated mortality is high, but remission is common with treatment.
- Treatment includes steroids and other immunosuppressive agents.

HYPEREOSINOPHILIC SYNDROME:

- A disease of persistently elevated peripheral eosinophils (>6 mo) of unknown etiology with tissue hypereosinophilia, resulting in end organ damage.
- Can involve multiple organs, including the heart, lungs, nervous system, and GI tract.
- Cardiac disease can be severe, including valvular disease and myocardial fibrosis.
- Presentation often depends on the organ systems involved but can include fever, cough, weight loss, wheezing, or CNS abnormalities.
- In addition to the idiopathic form, may have a myeloproliferative etiology.
- Lungs are affected in 25% of patients.
- Chest imaging may show opacities, consolidation, or lymphadenopathy.
- Diagnosis of exclusion.
- Check echocardiogram.
- Treat with steroids if symptomatic or evidence of end-organ dysfunction (particularly cardiac disease).
- Patients with myeloproliferative disease associated hypereosinophilic syndrome with *FIP1L1-PDGFRA* fusion gene mutations typically have an aggressive course and are treated with imatinib.

DRUG- OR TOXIN-INDUCED EOSINOPHILIC PNEUMONIA:

- Can have several different clinical presentations, including simple pulmonary eosinophilia, chronic eosinophilic pneumonia, acute eosinophilic pneumonia, or drug reaction with eosinophilia and systemic symptoms (DRESS).
- Described causes of drug- or toxin-induced EP: Most commonly associated with antibiotics and NSAIDs. Others include amiodarone, bleomycin, captopril, iodine, methotrexate, venlafaxine, sulfa-containing drugs, illicit drugs, dust exposure, and so on.
- Consider DRESS when pulmonary symptoms are also associated with skin eruption and fevers.
- Imaging findings are nonspecific and can include bilateral infiltrates.
- Diagnostic evaluation often includes BAL to exclude infection or other lung disease.
- Laboratory evaluation rarely diagnostic.
- Treatment includes removal of the offending agent and sometimes steroids.

Dx DIAGNOSIS

- Diagnosis varies depending on specific cause of pneumonia.
- Usually involves chest radiograph (Fig. E1), CT, peripheral eosinophil count, BAL, and possibly lung biopsy.

DIFFERENTIAL DIAGNOSIS

- Bacterial pneumonia
- Tuberculosis

FIG. E1 Chest radiograph shows pattern of peripheral pulmonary infiltrates characteristic of chronic eosinophilic pneumonia. (From Weinberger SE: *Principles of pulmonary medicine,* ed 7, Philadelphia, 2019, Elsevier.)

- Fungal pneumonia
- Parasitic infection *(Ascaris, Strongyloides)*
- Idiopathic pulmonary fibrosis
- Bronchiolitis obliterans and organizing pneumonia
- Hypersensitivity pneumonitis
- Radiation pneumonitis
- Bronchogenic carcinoma
- Rheumatoid lung disease
- Sarcoidosis

WORKUP

Physical examination, laboratory tests, imaging, bronchoscopy

LABORATORY TESTS

- WBC counts are often normal
- Often peripheral blood eosinophilia
- Elevated eosinophil count on BAL
- Consider ANCA, stool O+P, parasite serologies, IgE, *Aspergillus* precipitins, rheumatologic serologies as appropriate based on history and examination

IMAGING STUDIES

Chest radiograph may show a variety of infiltrates depending on the cause of EP. CT demonstrates a more characteristic pattern and distribution of parenchymal opacities than chest radiography.

Rx TREATMENT

- Varies depending on the cause.
- Remove offending agent or treat with appropriate antibiotic.
- Steroids may be helpful in many cases; doses and length of treatment depend on etiology of symptoms and response to treatment.
- There have been recent case reports of successful use of omalizumab (Xolair) as a steroid-sparing agent in the treatment of chronic eosinophilic pneumonia, although this practice is not well examined in the literature to date.
- Supportive respiratory care.

DISPOSITION

Depends on etiology. Prognosis is good if offending agent can be removed or an infectious etiology treated. Glucocorticoids have a good effect, but relapse often recurs with tapering in chronic idiopathic cases.

REFERRAL

To pulmonologist if a BAL or lung biopsy is needed to establish the diagnosis

! PEARLS & CONSIDERATIONS

- History (including travel) and physical examination are most important. Temporal association of eosinophilia and pulmonary abnormalities is an important diagnostic clue.
- Coccidioidomycosis and *Aspergillus* can present as eosinophilic lung disease and are important to recognize because steroid therapy can produce progressive infection.
- *Aspergillus* from respiratory specimens does not always indicate true infection and may be colonization.

- Blood eosinophilia >1 × 10^9 eosinophils/L or BAL >25% is helpful in narrowing diagnosis.
- Integrating the clinical, radiologic, and pathologic findings facilitates the initial and differential diagnoses of various eosinophilic lung diseases.

RELATED CONTENT

Aspergillosis (Related Key Topic)
Drug-Induced Parenchymal Lung Disease (Related Key Topic)
Eosinophilic Granulomatosis with Polyangiitis (Related Key Topic)
Hypereosinophilic Syndrome (Related Key Topic)

AUTHOR: **Melissa H. Tukey, MD, MS**

SUGGESTED READINGS

Cottin V et al: Eosinophilic lung diseases, *Immunol Allergy Clin North Am* 32:557, 2012.
Kaya H et al: Omalizumab as a steroid-sparing agent in chronic eosinophilic pneumonia, *Chest* 142(2):513, 2012.
Simon HU et al: Refining the definition of hypereosinophilic syndrome, *J Allergy Clin Immunol* 126:45-49, 2010.
Wechsler ME et al: Novel targeted therapies for eosinophilic disorders, *J Allergy Clin Immunol* 130:563-567, 2012.

BASIC INFORMATION

DEFINITION

Epicondylitis is an overuse injury of the common extensor tendon origin at the lateral epicondyle (tennis elbow) and common flexor tendon origin at the medial epicondyle (golfer elbow). The term *epicondylitis* is a misnomer because the tendon, rather than the epicondyle, is primarily involved in this degenerative process, and histologic changes are characterized by angiofibroblastic hyperplasia, rather than inflammatory changes.

SYNONYMS

Tennis elbow (lateral epicondylitis)
Golfer elbow (medial epicondylitis)
Elbow tendinosis
Elbow tendinopathy
Epicondylalgia
Elbow tendinitis

ICD-10CM CODES

M77.00	Medial epicondylitis, unspecified elbow
M77.10	Lateral epicondylitis, unspecified elbow
M77.01	Medial epicondylitis, right elbow
M77.02	Medial epicondylitis, left elbow
M77.11	Lateral epicondylitis, right elbow
M77.12	Lateral epicondylitis, left elbow
M77.0	Medial epicondylitis
M77.1	Lateral epicondylitis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE

- 1% to 3% of the general population.
  1. 90% of cases of tennis elbow are not related to playing tennis. Recreational tennis players who play >2 h/d have two to four times greater risk of developing epicondylitis compared with the general population.
  2. Smoking, obesity, repetitive movement for more than 2 h daily, and forceful activity are risk factors in the general population.
- The lateral side is involved more often than the medial.

PREDOMINANT AGE AND SEX:

- Affects middle-aged women more often than men.
- More common in individuals 40 to 60 yr old.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Main symptom is pain in lateral or medial elbow.
  1. Pain is typically related to activity.
  2. Physical examination maneuver to provoke pain: Wrist extension against resistance tests for lateral epicondylitis and wrist flexion against resistance for medial epicondylitis. Local tenderness is experienced over the affected epicondyle (Figs. E1 and E2).

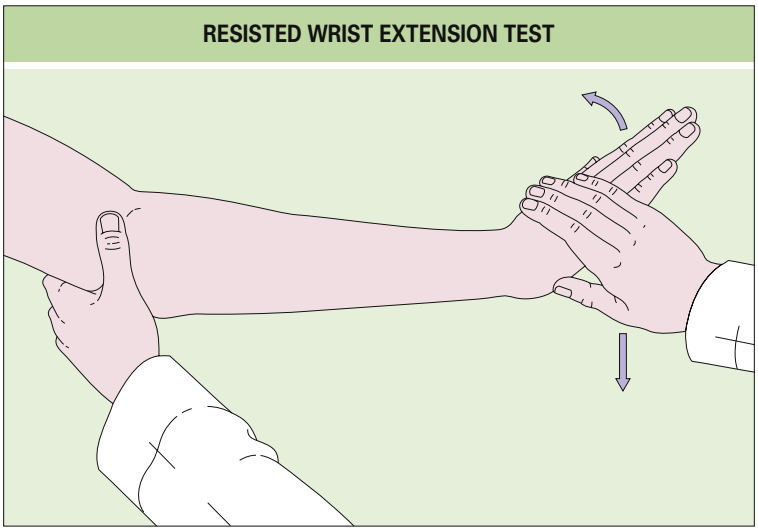

FIG. E1 Resisted wrist and long finger extension. Patients with lateral epicondylitis normally experience increased pain as this test is performed. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

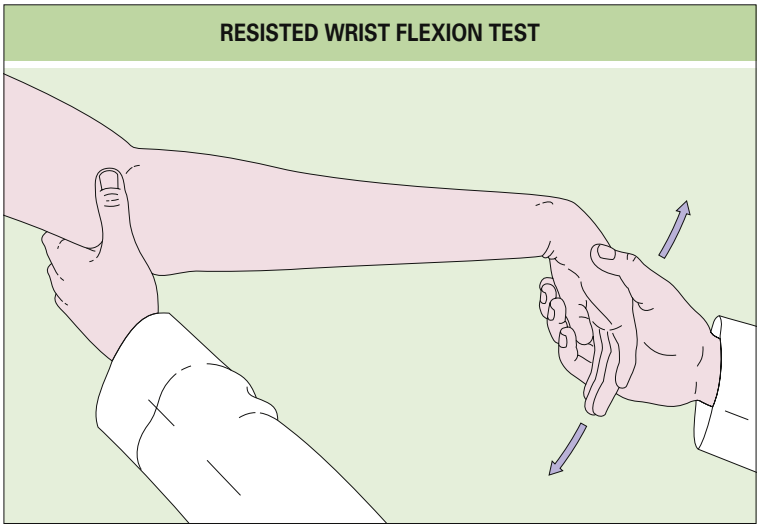

FIG. E2 Resisted wrist flexion with the elbow in extension. This normally increases medial elbow pain in patients with medial epicondylitis. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

ETIOLOGY

- Epicondylitis is thought to be secondary to repetitive microtrauma, leading to degeneration, tendinosis, and possibly tendon tear, which results in a robust angiogenic and fibroblastic response.
- The pathology is defined by a disorganization of normal collagen by invading fibroblasts in association with an immature vascular reparative response and the **absence of inflammatory cells,** which is termed *angiofibroblastic tendinosis.*
- Although classic inflammatory changes are not present, cytokines have been shown to play a role in the cause of epicondylitis.

GENETICS

Patients with BstUI and DpnII variants of the *COL5A1* gene are at increased risk for development of lateral epicondylitis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Intraarticular elbow pathology (osteoarthritis, osteochondritis dissecans, loose body)
- Radial tunnel syndrome (compression of the posterior interosseous nerve)
- Cubital tunnel syndrome (compression of the median nerve)
- Medial collateral ligament instability
- Valgus extension overload
- Ulnar neuritis
- Tumors
- Avascular necrosis
- Thoracic outlet syndrome
- Cervical radiculopathy

IMAGING STUDIES

- Plain radiography is useful for chronic cases to evaluate for osteoarthritis, exostosis, or other bony abnormalities.

- Ultrasound may show tendinosis as hypoechoic swelling of the involved tendon, possible hyperechoic calcification, and bony abnormality. Power or color Doppler signal is variable.
- MRI is the gold standard in detecting epicondylitis. MRI is the most sensitive test, showing tendon thickening and high T2 signal intensity.

Rx TREATMENT

- Rest, activity modification, and overuse prevention.
- Athletes may benefit from technique modifications.
- Ice packs and heat may be beneficial.
- Nonsteroidal antiinflammatory drugs (NSAIDs) can be used topically or orally but usually provide only short-term relief.
- Local steroid/lidocaine injection (Fig. E3) can be considered, but recent trials have called into question the long-term efficacy of corticosteroid injections for epicondylitis.
- Wrist brace or splint.
- Physical therapy with isometric strengthening exercises. Tendon fenestration (tenotomy or dry needling) has been deployed in ultrasound-guided treatment of lateral epicondylitis with some success. A recent small study reports short-term benefit of Kinesiotaping and extracorporeal shock wave therapy (ESWT) in treatment of lateral epicondylitis.
- Acupuncture has been found to be beneficial in some cases.
- Local injection of platelet-rich plasma has been investigated to a limited extent for use in the treatment of lateral epicondylitis with some evidence of improvement in pain and function.
- Autologous blood and prolotherapy are also currently used in clinical practice.
- Injection of botulinum toxin A at the myotendinous junction has been found to be helpful in a small randomized controlled trial.
- Patients with refractory symptoms after 6 mo of nonoperative management may benefit from surgical intervention.

DISPOSITION

- Epicondylitis is self-limited in most cases. Resolution of symptoms may take months to years.
- Prognosis is worse in the following situations:
  1. The dominant hand is involved.
  2. Patient experiences high physical strain at work.
  3. Duration of symptoms is more than 3 mo.
  4. Patient experiences severe pain at presentation and concomitant neck pain.

REFERRAL

If symptoms do not respond to a 6-mo trial of conservative therapy, surgical referral is appropriate.

PEARLS & CONSIDERATIONS

- The lateral epicondyle may be harder to localize than bony medial epicondyle.
- The diagnosis can frequently be made with physical examination and history alone.
- The majority of cases are self-resolving.

RELATED CONTENT

Golfer Elbow (Patient Information)
Tennis Elbow (Patient Information)

AUTHORS: **Manuel F. DaSilva, MD,** and **Nicholas J. Lemme, MD**

FIG. E3 Injection for right tennis elbow (lateral epicondylar syndrome). (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

SUGGESTED READINGS

Eraslan L et al: Does Kinesiotaping improve pain and functionality in patients with newly diagnosed lateral epicondylitis? *Knee Surg Sports Traumatol Arthrosc* 2017.

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Riff AJ et al: Open vs percutaneous vs arthroscopic surgical treatment of lateral epicondylitis: an updated systematic review, *Am J Orthop* 47(6), 2018.

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Shiri R et al: Lateral and medial epicondylitis: role of occupational factors, *Best Pract Res Clin Rheumatol* 25:43-57, 2011.

Tosti R et al: Lateral epicondylitis of the elbow, *Am J Med* 126(4):357, 2013. e1-e6.

Vaquero-Picado A et al: Lateral epicondylitis of the elbow, *EFFORT Open Rev* 1(11):391-397, 2017.

Von Hofwegen C et al: Epicondylitis in the athlete's elbow, *Clin Sports Med* 29(4):577-597, 2010.

Walz DM et al: Epicondylitis: pathogenesis, imaging, and treatment, *Radiographics* 30:167, 2010.

BASIC INFORMATION

DEFINITION

Epidermolysis bullosa (EB) is a rare disorder presenting in adults with the development of blisters on the hands, feet, elbows, knees, and other body regions after mild trauma. It represents a group of genetic disorders characterized by mechanically fragile skin with a propensity to develop blisters and/or erosions. There are four major types: dystrophic (DEB), junctional (JEB), simplex (EBS), and ***Kindler syndrome.*** They differ in the ultrastructural site within which cutaneous blisters form. Kindler syndrome is an extremely rare form characterized by trauma-induced blistering, photosensitivity, progressive poikiloderma, cutaneous atrophy, and mucosal inflammation. Characteristics of major forms of EBS, basal are summarized in Table E1. The characteristics of the major forms of JEB are described in Table E2.

SYNONYMS

EB
Kindler syndrome

ICD-10CM CODES

L12.30	Acquired epidermolysis bullosa, unspecified
Q81.2	Epidermolysis bullosa dystrophica
Q81.0	Epidermolysis bullosa simplex
Q81.9	Epidermolysis bullosa, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE AND INCIDENCE: The estimated overall prevalence and incidence of EB in the U.S. are 11.1 per 1 million population and 19.6 per 1 million live births, respectively. The approximate prevalences and incidences, respectively, of the major types of EB are as follows: EB simplex, 6.0 and 7.9; junctional EB, 0.5 and 2.7; dominant dystrophic EB, 1.5 and 2.1; and recessive dystrophic EB, 1.4 and 3.0.

GENETICS: The most common forms of EB simplex (EBS) are transmitted in an autosomal dominant manner. Table E3 summarizes the various clinical phenotypes and inheritance.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

EB is marked by development of painful blisters on the hands, feet (Fig. E1), elbows, and knees after mild trauma. Extensive blistering (Fig. E2) may occur. EB may also be complicated by atrophic scarring, milia formation, and nail dystrophy. Fig. E3 illustrates helpful cutaneous findings in patients with EB.

Table E4 summarizes major extracutaneous complications of EB.

ETIOLOGY

This is an inherited disorder (see Table E3).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bullous pemphigoid
- Pemphigus vulgaris
- Linear IgA bullous dermatosis

TABLE E1 Characteristics of Major Forms of Epidermolysis Bullosa Simplex, Basal

Type	Clinical Manifestations
EBS, localized (formerly Weber-Cockayne)	Easy blistering on palms and soles
	May be focal keratoderma of palms and soles in adults
	25% show oral mucosal erosions
	Rarely show reticulated pigmentation, especially on arms and trunk and punctate keratoderma (EBS with mottled pigmentation)
EBS, generalized, intermediate (formerly Koebner)	Generalized blistering
	Variable mucosal involvement
	Focal keratoderma of palms and soles
	Nail involvement in 20%
	Improves with advancing age
EBS, generalized, severe (formerly Dowling-Meara)	Most severe in neonate, infant; improves beyond childhood
	Large, generalized blisters; later, smaller (herpetiform) blisters
	Mucosal blistering, including esophageal
	Nails thickened, shed but regrow
	May have natal teeth
EBS with mottled pigmentation	Reticulated hyperpigmentation, especially on arms and trunk
	Punctate keratoses and keratoderma

EBS, Epidermolysis bullosa simplex.
From Paller AS, Mancini AJ (eds): *Hurwitz clinical pediatric dermatology,* ed 5, Philadelphia, 2016, Elsevier, Table 13.2, p. 319, in Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

TABLE E2 Characteristics of Major Forms of Junctional Epidermolysis Bullosa

Type	Clinical Manifestations
JEB, generalized severe (formerly Herlitz)	50% of patients die by 2 yr old
	Blisters heal with atrophic scarring but no milia
	Periungual and fingerpad blistering, erythema
	Blistering of oral and esophageal mucosae
	Laryngeal and airway involvement with early hoarseness
	Later, perioral granulation tissue with sparing of lips
	Anonychia
	Dental enamel hypoplasia, excessive caries
	Growth retardation
	Anemia
JEB, generalized, intermediate (formerly non-Herlitz)	Less severe, but similar manifestations to Herlitz type, including dental, nail, and laryngeal involvement
	Granulation tissue is rare
	Perinasal cicatrization
	Less mucosal involvement
	Alopecia
	Anemia, but not as severe as JEB, generalized severe
JEB, localized	Localized blisters without residual scarring or granulation tissue
	Minimal mucosal involvement
	Dental and nail abnormalities as in JEB, generalized severe
JEB, generalized with pyloric atresia	Usually lethal in neonatal period
	Generalized blistering, leading to atrophic scarring
	May be born with large areas of cutis aplasia
	No granulation tissue
	Nail dystrophy or anonychia
	Pyloric atresia, genitourinary malformations
	Rudimentary ears
	Dental enamel hypoplasia (survivors)
	Variable anemia, growth retardation, mucosal blistering

JEB, Junctional epidermolysis bullosa.
From Paller AS, Mancini AJ (eds): *Hurwitz clinical pediatric dermatology,* ed 5, Philadelphia, 2016, Elsevier, Table 13.4, p. 321, in Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

TABLE E3 Epidermolysis Bullosa: Simplex, Junctional, and Dystrophic Subtypes and Kindler Syndrome

Entities with a lighter background represent rare variants.

EPIDERMOLYSIS BULLOSA: SIMPLEX, JUNCTIONAL AND DYSTROPHIC SUBTYPES AND KINDLER SYNDROME		
Subtype	**Inheritance**	**Defective protein(s)**
Suprabasal intraepidermal cleavage		
Acral peeling skin syndrome	AR	Transglutaminase 5
EB superficialis	Unknown	Unknown
Acantholytic EBS	AR	Desmoplakin; plakoglobin
Skin fragility syndromes		
Desmoplakin deficiency (skin fragility–woolly hair syndrome)	AR	Desmoplakin
Plakoglobin deficiency	AR	Plakoglobin
Plakophilin deficiency (skin fragility–ectodermal dysplasia syndrome)	AR	Plakophilin 1
Basal intraepidermal cleavage		
EBS, localized (formerly Weber–Cockayne)	AD	Keratins 5 and 14
EBS, generalized severe (formerly Dowling–Meara)		
EBS, generalized intermediate		
EBS with mottled pigmentation	AD	Keratin 5
EBS, migratory circinate		
EBS, AR-KRT14	AR	Keratin 14
EBS due to KLHL24	AD	Kelch-like protein 24
EBS with muscular dystrophy	AR	Plectin
EBS with pyloric atresia	AR	Plectin; $\alpha_6\beta_4$ integrin
EBS-Ogna	AD	Plectin
EBS, AR-BP230 deficiency	AR	Bullous pemphigoid antigen 1 (BP230)
EBS, AR-exophilin 5 deficiency	AR	Exophilin 5
Intra-lamina lucida cleavage		
JEB, generalized severe (formerly Herlitz)	AR	Laminin 332
JEB, generalized intermediate	AR*	Laminin 332; collagen XVII
JEB with pyloric atresia	AR	$\alpha_6\beta_4$ integrin
JEB, late onset	AR	Collagen XVII
JEB with respiratory and renal involvement	AR	α_3 integrin subunit
JEB, localized	AR	Collagen XVII; $\alpha_6\beta_4$ integrin
JEB, inversa	AR	Laminin 332
JEB-laryngo-onycho-cutaneous syndrome	AR	Laminin α3 chain (an isoform)
Sublamina densa cleavage		
DDEB, generalized	AD	Collagen VII
Other DDEB variants: acral, pretibial, pruriginosa, nails only		
DDEB, bullous dermolysis of the newborn		
RDEB, generalized severe (formerly Hallopeau–Siemens)	AR	
RDEB, generalized intermediate		
RDEB, inversa		
Other RDEB variants: localized, pretibial, pruriginosa, centripetalis		
RDEB, bullous dermolysis of the newborn		
Mixed cleavage planes		
Kindler syndrome	AR	Kindlin-1
*One case with AD inheritance has been reported.		

AD, Autosomal dominant; *AR,* autosomal recessive; *DDEB,* dominant dystrophic EB; *EB,* epidermolysis bullosa; *EBS,* epidermolysis bullosa simplex; *JEB,* junctional epidermolysis bullosa; *RDEB,* recessive dystrophic EB.

From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

FIG. E1 Localized epidermolysis bullosa simplex. A and **B,** Bullae arising on the toes and plantar surfaces at sites of lateral or rotary traction. The majority of blisters occur in acral sites. (**A,** From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier. **B,** Courtesy Julie V. Schaffer, MD)

- Porphyria cutanea tarda
- Chemical burn
- Thermal burn
- Blisters due to trauma (friction blisters)
- Cicatricial pemphigoid

WORKUP

An approach to the laboratory diagnosis of EB is illustrated in Fig. E4.

LABORATORY TESTS

Skin biopsy and serum for direct and indirect immunofluorescence can detect skin basement membrane–specific autoantibodies.

Rx TREATMENT

ACUTE GENERAL Rx

- Nutritional support, avoidance of trauma
- Topical antibiotics, sterile dressing
- Dressings frequently used in patients with EB are described in Table E5
- Systemic corticosteroids
- Dapsone
- Azathioprine
- Colchicine
- Cyclosporine

CHRONIC Rx

The management of long-term complications of EB is summarized in Table E6.

REFERRAL

Dermatology in all cases

PEARLS & CONSIDERATIONS

COMMENTS

Workup for inflammatory bowel disease and ELISA for type VII collagen-specific autoantibodies should also be considered.

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READING

Fine JD, Mellerio JE: Epidermolysis bullosa. In Bolognia JL et al: *Dermatology*, ed 4, Philadelphia, 2018, Elsevier, pp. 538-553.

FIG. E2 Generalized intermediate epidermolysis bullosa simplex. Extensive blistering on the buttocks **(A)** and blistering in association with focal keratoderma on the soles **(B)** of a 2-yr-old girl. (From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier; Courtesy, Julie V. Schaffer, MD)

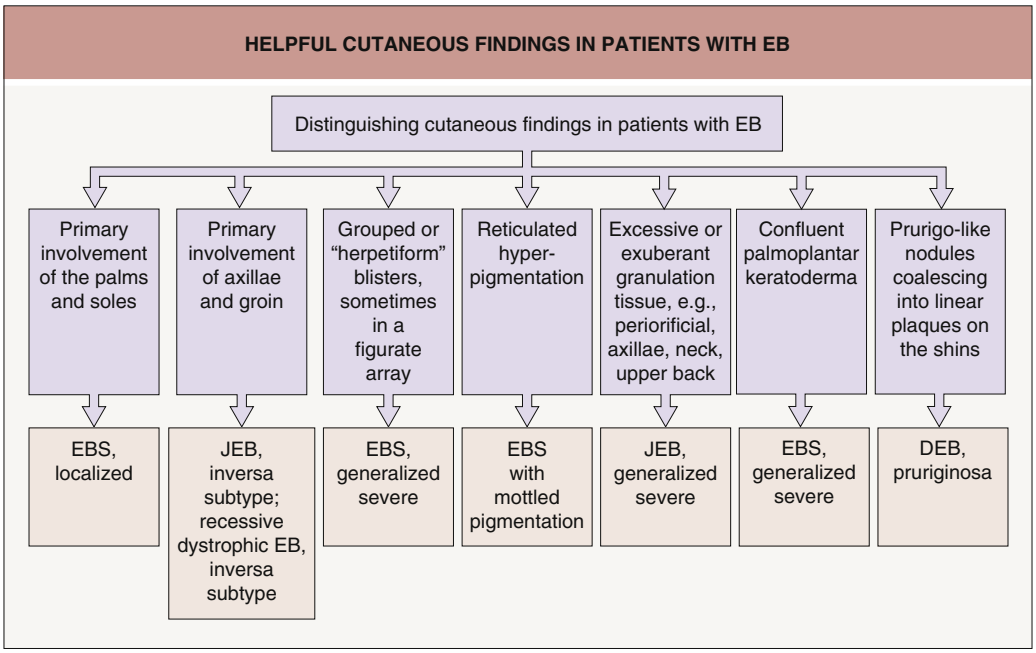

FIG. E3 Helpful cutaneous findings in patients with epidermolysis bullosa *(EB).* *DEB,* Dystrophic EB; *EBS,* EB simplex; *JEB,* junctional EB. (From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.)

TABLE E4 Major Extracutaneous Complications of Epidermolysis Bullosa

	EB Subtype(s) Most Commonly Affected	
Complications	**≥50% of Patients**	**<50% of Patients**
Eyes		
Corneal blisters, ulcers, and scarring	RDEB-gen/sev	JEB-gen/sev > RDEB-gen/intermed, RDEB-inv, JEB-gen/intermed
Ectropion formation		JEB-gen/sev; Kindler
Oral Cavity and Upper Airway (Excluding Blisters)		
Microstomia	RDEB-gen/sev	JEB-gen/sev, RDEB-inv
Enamel hypoplasia	JEB (all subtypes)	
Excessive caries and premature loss of teeth	RDEB gen/sev, JEB-gen/sev	
Tracheolaryngeal stenosis	JEB-gen/sev	JEB-gen/intermed
Gastrointestinal Tract		
Esophageal strictures	RDEB-gen/sev, RDEB-inv	RDEB-gen/intermed, Kindler > JEB-gen/sev
Pyloric atresia	JEB-PA, EBS-PA	
Malnutrition/failure to thrive	RDEB-gen/sev, JEB-gen/sev	JEB-gen/intermed
Severe constipation	RDEB-gen/sev	JEB-gen/sev, EBS-gen/sev
GERD	RDEB	JEB, EBS-gen/sev
Colitis		Kindler, RDEB-gen/sev
Genitourinary Tract		
Urethral meatal stenosis		RDEB-gen/sev, JEB-gen/sev, Kindler
Chronic renal failure*		RDEB-gen/sev
Hydroureter and hydronephrosis		JEB-PA, JEB-gen/sev
Nephrotic syndrome	JEB-resp/renal	JEB-gen/sev
Heart		
Dilated cardiomyopathy		RDEB-gen/sev > JEB, RDEB-gen/intermed
Musculoskeletal System		
Pseudosyndactyly	RDEB-gen/sev	RDEB-gen/intermed, Kindler
Osteoporosis or osteopenia	RDEB-gen/sev	RDEB-gen/sev, JEB-gen/sev
Muscular dystrophy	EBS-MD	
Bone Marrow		
Severe multifactorial anemia	RDEB-gen/sev, JEB-gen/sev	

*Causes include renal amyloidosis and glomerulonephritis.
EB, Epidermolysis bullosa; *EBS,* EB simplex; *gen/intermed,* generalized intermediate; *gen/sev,* generalized severe; *GERD,* gastroesophageal reflux disease; *inv,* inversa; *JEB,* junctional EB; *MD,* muscular dystrophy; *PA,* pyloric atresia; *RDEB,* recessive dystrophic EB; *resp/renal,* respiratory and renal involvement.
From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

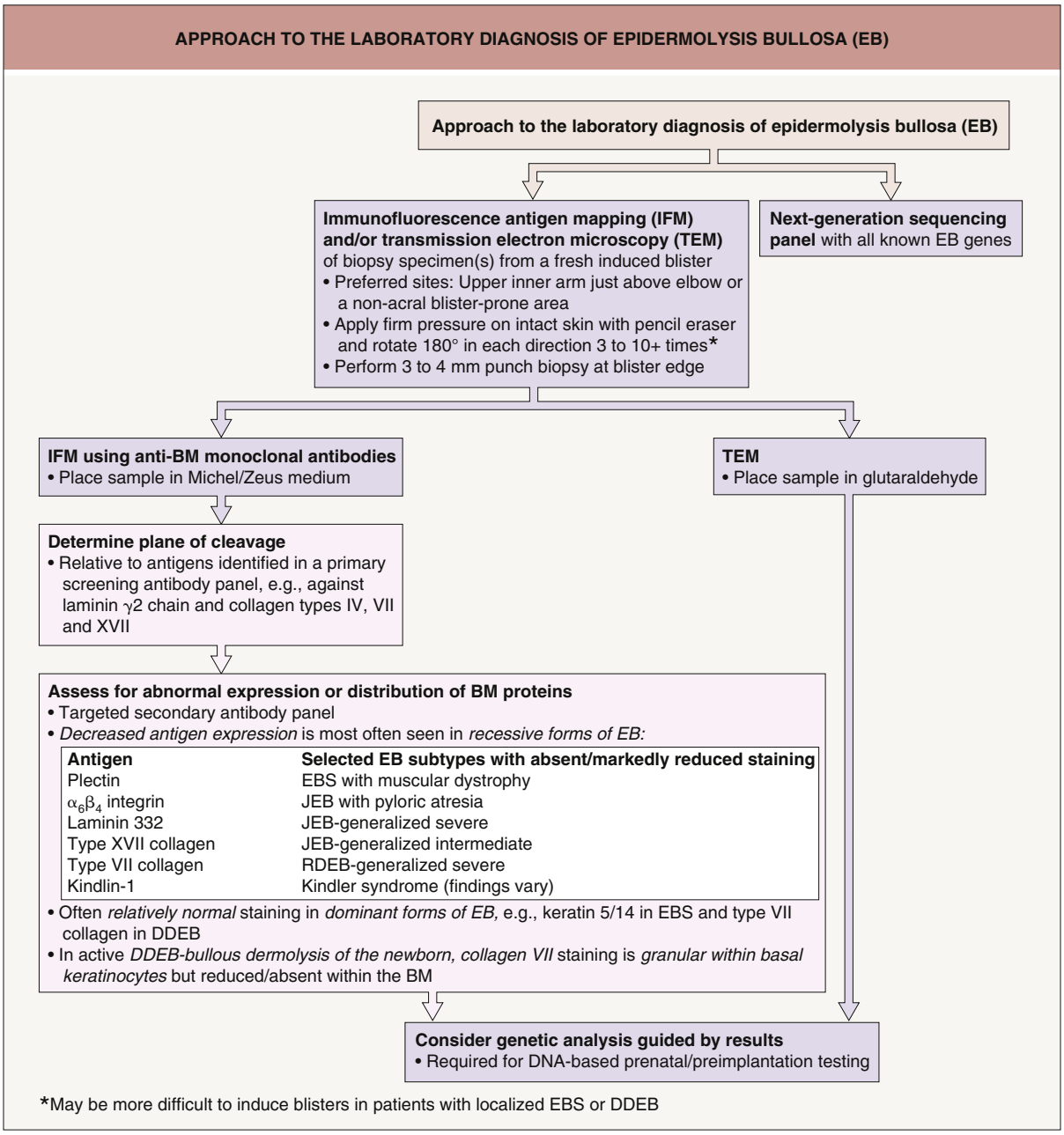

FIG. E4 Approach to the laboratory diagnosis of epidermolysis bullosa *(EB)*. *BM,* Basement membrane; *DDEB,* dominant dystrophic EB; *DNA,* deoxyribonucleic acid; *EBS,* EB simplex; *JEB,* junctional EB; *RDEB,* recessive dystrophic EB. (From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.)

TABLE E5 Dressings Frequently Used in Patients with Epidermolysis Bullosa

Dressing Type	Use	Examples®,™
Soft silicone dressings ("low-tack")	• Suitable as primary or secondary dressings in many types of EB • May have a foam backing for mechanical protection or to wick exudate away from the wound	Mepitel, Mepilex, Mepilex Transfer, Mepilex Border
Nonadherent lipido-colloid dressings	• Suitable for primary contact	UrgoTul
Hydrogel dressings	• Provide moisture to drier wounds to facilitate healing • May provide relief from pain or itch	Flexigel, Curagel, ActiFormCool
Foam dressings	• Useful to absorb moderate amounts of wound exudate	Mepilex, Allevyn
Absorptive dressings	• Useful to absorb heavy amounts of wound exudate	Eclypse, Sorbion Sana
Silver-containing dressings	• Clinically infected or highly colonized wounds • Avoid prolonged use due to risk of silver absorption	UrgoTul SSD, Mepilex AG
Other antimicrobial dressings	• Clinically infected or highly colonized wounds	PolyMem, Cutimed Sorbact, Activon Tulle, Suprasorb X + PHMB

EB, Epidermolysis bullosa.
From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

TABLE E6 Management of Long-Term Complications of Epidermolysis Bullosa

Complication	Prevention and Monitoring/Detection	Management
Oral and Gastrointestinal		
Excessive caries	• Diligent oral hygiene • Antiseptic and fluoride mouthwashes • Periodic evaluation and cleaning by a dentist	• Restorative dentistry
Microstomia		• Physical therapy • "Mouth expanding" devices
Oral ulceration		• Topical antiseptics, topical NSAIDs, barrier preparations (e.g., sucralfate suspension)
Esophageal strictures	• Evaluate dysphagia with contrast studies	• Dietary modification (soft foods/purées, caloric supplementation) • Fluoroscopically guided balloon dilatation; repeated procedures are often required • In severe and recalcitrant cases, surgical options include colonic interposition
Gastroesophageal reflux disease		• Proton pump inhibitors, H_2 blockers, prokinetic agents (e.g., metoclopramide, domperidone [not available in the U.S.])
Constipation	• Ensure adequate fluid intake and dietary fiber	• Osmotic laxatives (e.g., containing polyethylene glycol), mineral oil • Avoid suppositories and enemas
Nutritional		
Growth retardation/inadequate intake to meet nutritional needs	• Monitor height, weight, and body mass index • Periodically assess serum zinc, selenium, iron, vitamin D, and carnitine levels (e.g., yearly) • Oral supplements to optimize intake of calories, protein, vitamins, and minerals	• Consider gastrostomy feedings
Hematologic		
Anemia due to iron deficiency and chronic inflammation	• Monitor CBC and measures of iron stores	• Iron supplementation (oral or IV) • Consider erythropoietin or darbepoetin alpha • Consider blood transfusion if hemoglobin ≤7-8 g/dl and/or symptomatic
Genitourinary and Renal		
Urinary outflow obstruction (e.g., urethral or ureteral strictures)	• Consider annual ultrasound of the urinary tract and urodynamic studies (especially for JEB)	• Dilatation procedures as needed to treat obstruction • Avoid unnecessary instrumentation
Renal disease (e.g., hydronephrosis, postinfectious glomerulonephritis, renal amyloidosis, IgA nephropathy)	• Blood urea nitrogen and serum electrolyte levels, urinalysis, and blood pressure evaluation every 6 mo in RDEB patients • Adequately treat streptococcal infections	• Hemodialysis or peritoneal dialysis if renal failure develops
Musculoskeletal		
Osteopenia and osteoporosis	• Annual DEXA scan and spinal radiographs beginning at age 5 yr in RDEB and JEB patients • Calcium and vitamin D supplementation	• Consider IV bisphosphonate therapy
Pseudosyndactyly of hands/feet	• Cushioned splints on hands/forearms and individual wrapping of fingers in RDEB patients	• Surgery to release contractures and webbing

Continued

TABLE E6 Management of Long-Term Complications of Epidermolysis Bullosa—cont'd

Complication	Prevention and Monitoring/Detection	Management
Oncologic		
Cutaneous squamous cell carcinoma	• Periodic total-body skin examinations; for RDEB patients, approximately every 3-6 mo beginning at age 10 yr and every 3 mo after age 16 yr • Biopsy or monitor nonhealing ulcers • Consider taking serial photographs	• Excision ± skin grafting (sometimes amputation); consider MRI to assess extent of local disease • Consider staging with CT, PET-CT, sentinel lymph node biopsy
Ocular		
Chronic complications include corneal scarring, symblepharon, ectropion	• Periodic ophthalmologic evaluation for patients with eye involvement • Lubricating eye drops	• Surgical procedures, e.g., division of symblepharon, amniotic membrane transplantation
Cardiac		
Dilated cardiomyopathy	• Consider annual echocardiography beginning in late childhood for RDEB patients	• Medical management • Supplement selenium and carnitine if deficient
Psychological and Psychiatric		
Disrupted family unit (e.g., via divorce)	• Consider family counseling, support groups	• Psychological/family counseling
Depression and suicidal ideation/ attempts	• Consider psychological counseling, support groups	• Psychiatric evaluation, antidepressant therapy

CBC, Complete blood count; *CT,* computed tomography; *DEXA,* dual-energy x-ray absorptiometry; *EB,* epidermolysis bullosa; *Ig,* immunoglobulin; *IV,* intravenous; *JEB,* junctional EB; *MRI,* magnetic resonance imaging; *NSAID,* nonsteroidal antiinflammatory drug; *PET-CT,* positron emission tomography and computed tomography; *RDEB,* recessive dystrophic EB.
Modified from Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

Epididymitis PTG

BASIC INFORMATION

DEFINITION

- Epididymitis is an inflammatory reaction of the epididymis caused by either an infectious agent or local trauma. In most cases of acute epididymitis, the testis is also involved (orchitis).
- Epididymitis is considered chronic if lasting ≥6 wk. Chronic epididymitis has been subcategorized into inflammatory chronic epididymitis, obstructive chronic epididymitis, and chronic epididymalgia.

SYNONYMS

Nonspecific bacterial epididymitis
Sexually transmitted epididymitis

ICD-10CM CODES

N45.1	Epididymitis
A54.00	Gonococcal infection of lower genitourinary tract, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Cause of >600,000 visits to physicians per yr
PEAK INCIDENCE: Sexually active yrs
PREDOMINANT SEX: Exclusive to males
PREDOMINANT AGE: All ages affected but usually in sexually active men or older males
CONGENITAL: Congenital urologic structural disorders possibly predisposing to infections

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Tender swelling of the scrotum with erythema, usually unilateral testicular pain and tenderness
- Dysuria and/or urethral discharge
- Fever and signs of systemic illness (less common)
- Pain and redness on scrotal examination
- Hydrocele or even epididymo-orchitis, especially late
- Chronic draining scrotal sinuses with a "beadlike" enlargement of the vas deferens in tuberculous disease

ETIOLOGY

- In young, sexually active men (<35 yr of age), the most common causes of infections are *Neisseria gonorrhoeae* and *Chlamydia trachomatis.*
- In older men (>35 yr of age) or those with underlying urologic disease:
  1. Gram-negative aerobic rods are predominant (i.e., *Escherichia coli*).
  2. Similar organisms are found in men following invasive urologic procedures.
  3. Gram-positive cocci are rarely seen in these groups.
  4. Mycobacteria may also be a cause of epididymitis.
- Acute epididymitis caused by sexually transmitted enteric organisms (e.g., *Escherichia coli*) also occurs among men who are the insertive partner during anal intercourse.
- Young, prepubertal boys may present with epididymitis caused by coliform bacteria; almost always a complication of underlying urologic disease such as reflux.
- In AIDS patients, CMV and *Salmonella* epididymitis have been described. CMV may have a negative urine culture. Toxoplasmosis and *Cryptococcus* should also be considered as a cause of epididymitis in AIDS patients.
- Chronic infectious epididymitis is most frequently seen in conditions associated with granulomatous reaction; mycobacterium tuberculosis is the most common granulomatous disease affecting the epididymis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Orchitis
- Testicular torsion, trauma, or tumor
- Epididymal cyst
- Hydrocele
- Varicocele
- Spermatocele
- Testicular torsion should be considered in all cases (Table E1).

WORKUP

- Consideration of a full assessment of the urologic tract in patients with bacterial infection, especially if recurrent
- If discharge is present, cultures and Gram stain smear of urethral exudate. Gram stain should demonstrate ≥5 WBC per oil immersion field
- In sexually active men: Gonococcal cultures of the throat and rectum possibly of value
- If testicular torsion a consideration: Radionuclear imaging
- Examination of first void uncentrifuged urine for leukocytes if the urethral Gram stain is negative. Positive leukocyte esterase test on first-void urine or microscopic examination of first-void urine sediment will demonstrate ≥10 WBC per high power field. A culture and Gram-stained smear of this urine specimen should be obtained along with nucleic acid amplification testing (NAAT) from urine samples for gonorrhea and chlamydia
- Imaging with sonogram (Fig. E1)

LABORATORY TESTS

- All suspected cases of acute epididymitis should be tested for *C. trachomatis* and for *N. gonorrhoeae* by NAAT. Urine is the preferred specimen for NAAT testing.
- Urinalysis and urine culture if dysuria is present or if urinary tract infection is suspected.
- HIV testing and counseling.
- PPD placed and chest x-ray viewed if TB suspected (rare cases).
- Rarely, biopsy to ensure the diagnosis of tuberculous epididymitis.

TREATMENT

ACUTE GENERAL Rx

- Ice packs and scrotal elevation for relief of pain
- Analgesia with acetaminophen with or without codeine or NSAIDs
- Antibiotics to cover suspected pathogens. Empiric therapy is indicated before laboratory test results are available
- Recommended regimens are ceftriaxone 250 mg IM in a single dose plus doxycycline 100 mg bid for 10 days. For acute epididymitis most likely caused by enteric organisms, treatment options are levofloxacin 500 mg qd × 10 days or ofloxacin 300 mg bid × 10 days. Add ceftriaxone 250 mg IM single dose to levofloxacin or ofloxacin in men who practice insertive anal sex and are suspected to have chlamydia and gonorrhea and enteric organisms
- Best treatment for older men with gram-negative bacteriuria: Ofloxacin 300 mg PO bid for 10 days or levofloxacin 500 mg PO qd for 10 days
- *Pseudomonas* covered by ciprofloxacin PO or IV or cefepime (2 g IV q8h)
- Consider ampicillin-sulbactam, third-generation cephalosporin, ticarcillin-clavulanate, or piperacillin-tazobactam in toxic-appearing patients
- Surgical aspiration of local abscesses or even open surgical drainage
- Diabetics: Especially prone to develop more extensive scrotal infections, including Fournier gangrene
- Reinforcement of compliance with antibiotics to avoid partial treatment

CHRONIC Rx

- Repair of underlying structural defects is considered especially if infections are severe or recur.
- Surgical repair of reflux in young boys should be undertaken promptly and at a young age when possible.
- Sex partners of patient should be referred for evaluation and treatment.

REFERRAL

- If abscess or chronic structural problems suspected
- If another diagnosis, such as testicular torsion, is suspected

PEARLS & CONSIDERATIONS

- Recurrent epididymitis in sexually active men is usually related to failure to simultaneously treat sexual partners for STDs.
- Recurrent epididymitis in nonsexually active men is generally related to structural-anatomic defects in the genitourinary system or relapsing disease from inadequate initial treatment or antimicrobial resistance.
- Tuberculous epididymitis fails to respond to seemingly adequate antimicrobial therapy even without characteristic radiographic changes on chest films.

RELATED CONTENT

Epididymitis (Patient Information)
Orchitis (Related Key Topic)
Testicular Torsion (Related Key Topic)

AUTHORS: **Philip A. Chan, MD, MS,** and **Glenn G. Fort, MD, MPH**

TABLE E1 Differentiation among Causes of the Acute Scrotum

Feature	Testicular Torsion	Appendix Torsion	Epididymitis
Age	<1 yr, puberty	7-14 yr	Adult
Onset	Hours	1-2 days	Days to weeks
Location of pain	Entire testicle	Upper pole	Epididymis
Systemic symptoms	Nausea	None	Fever
Cremasteric reflex	No	Intact	Intact
Pyuria	Rare	No	Yes
Ultrasound findings	Diffusely hypoechoic Asymmetrical testicles Normal or decreased flow Spermatic cord knot	Focally hypoechoic Symmetrical testicles Normal flow	Hypoechoic epididymis Symmetrical testicles Increased flow
Treatment	Surgery	Supportive	Antibiotics; prepuberty: Supportive only

NOTE: No single finding in patients with an acute scrotum can reliably differentiate torsion from other causative disorders. When torsion is a diagnostic possibility, prompt urology consultation is mandatory.

From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.

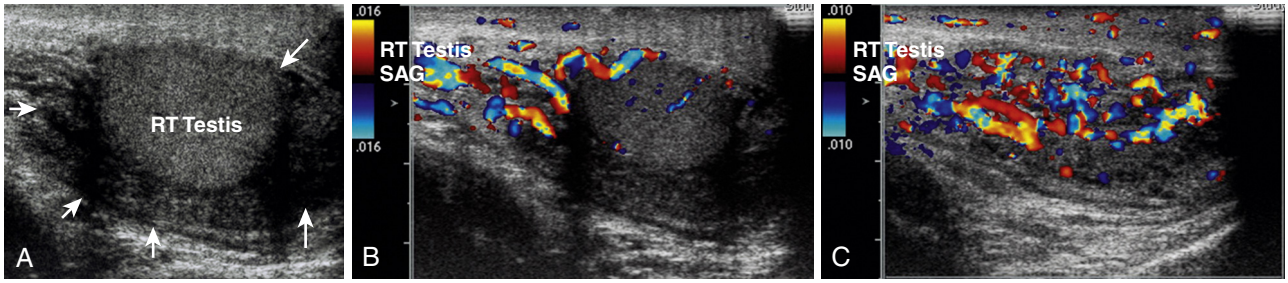

FIG. E1 Acute epididymitis in 8-year-old boy with right scrotal pain. A, Gray-scale sagittal sonogram of the right testis shows a normal-appearing testis surrounded posterolaterally by a prominent, hypoechoic heterogeneous epididymis. **B,** Longitudinal color flow Doppler image of the scrotum reveals increased flow in the head of the epididymis with normal flow in the testis. **C,** Marked hypervascularity is noted throughout the body and tail of the epididymis. Skin thickening is noted on all three images. (From Rumack CM et al: *Diagnostic ultrasound*, ed 4, Philadelphia, 2011, Elsevier.)

BASIC INFORMATION

DEFINITION

Epidural abscess is a suppurative infection of the central nervous system localized between the dura mater and the overlying skull or vertebral column. There are two types of epidural abscess: spinal epidural abscess (SEA) and intracranial epidural abscess (IEA), depending on the location within the central nervous system.

SYNONYMS

SEA
Spinal epidural abscess
IEA
Intraspinal abscess

ICD-10CM CODE
G06.2 Extradural and subdural abscess, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Spinal epidural abscess: 2 to 25 patients per 100,000 admissions; spinal epidural abscess is 9 times more common than intracranial abscess
PEAK INCIDENCE: Median age at onset of spinal epidural abscess: 50 yr old
PREVALENCE: Greatest between 50 and 70 yr of age
PREDOMINANT SEX: More common in men
RISK FACTORS: Bacteremia, secondary to distant infection; epidural catheter placement (0.5% to 3% risk), paraspinal injections of glucocorticoids or for pain management, contiguous bone or soft tissue infection, intravenous drug abuse, diabetes, immunosuppressive therapy, HIV

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Initially nonspecific, such as fever and malaise
- Classic triad: Fever, spinal pain, and neurologic deficits are not common
- More commonly:
  1. Localized and significant back pain is present.
  2. Nerve root pain is present ("shooting" or "electrical" from involved nerve root).
  3. Motor weakness, sensory changes, and even paralysis can occur.
  4. Fever may not be a prominent sign.

ETIOLOGY

- Bacteria enter the epidural space most often secondary to hematogenous spread from foci elsewhere in the body (25% to 50% of cases) or by direct extension from nearby infected tissues such as vertebral body or psoas muscle. A local intervention such as injection can also cause infection.
- Hematogenous foci include furuncles, cellulitis, urinary tract infection, pharyngitis, and pneumonia.
- Microbiology:
  1. *Staphylococcus aureus*, including methicillin-resistant S. *aureus* (MRSA), accounts for 50% to 90% of cases.
  2. Aerobic and anaerobic streptococci account for 8% to 17% of cases.
  3. Aerobic gram-negative rods *(Escherichia coli* and *Pseudomonas)* account for 10% to 17% of cases.
  4. Coagulase-negative staphylococci can be seen with spinal procedures.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Disc and degenerative bone disease
- Metastatic tumors
- Vertebral discitis and osteomyelitis

WORKUP

Includes a combination of physical exam with neurologic evaluation, blood work, and radiographic studies

LABORATORY TESTS

- Blood cultures
- Culture of fluid or pus for bacteria aerobically and anaerobically by CT-guided aspiration if possible. Fungal stain and cultures and AFB stain and culture should also be obtained to exclude more unusual pathogens.
- Erythrocyte sedimentation rate and/or C-reactive protein
- CBC with differential

IMAGING STUDIES

- MRI with gadolinium is the diagnostic test of choice (Fig. E1) and imperative if diagnosis is considered.
- CT is an alternative but not as good as MRI for visualizing spinal cord and epidural space.
- CT myelography can be performed if MRI is not available.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Immediate surgery is required if neurologic deficits occur or the patient worsens with medical therapy.
- CT-guided aspiration of abscess with antimicrobial therapy is an alternative treatment to surgery for patients without neurologic deficits.

ACUTE GENERAL Rx

- Empiric antibiotic regimen should include antibiotics effective against staphylococci (including MRSA), streptococci, and gram-negative rods.
- Examples are vancomycin: 30 to 60 mg/kg daily divided in q12h doses adjusted for creatinine clearance *plus* metronidazole (500 mg IV q8h) *plus* ceftriaxone (2 g IV q12h) or ceftazidime (2 g IV q8h) if *Pseudomonas* is suspected. Meropenem: 1 g IV q8h with vancomycin as an alternative, especially if penicillin allergic.
- If cultures reveal methicillin-sensitive *S. aureus*, use nafcillin 2 g IV q4h.

CHRONIC Rx

Antimicrobial therapy tailored to culture results may have to be continued for 4 to 6 weeks depending on whether or not there was surgical or CT-guided drainage. If osteomyelitis is suspected, treat for 6 to 8 weeks.

DISPOSITION

- Mortality rates vary from 5% to 32%. Irreversible paralysis can affect 4% to 22% of patients.
- Complete recovery is more likely if neurologic signs are present less than 24 hours before the start of treatment.
- Final functional capacity may continue to improve for up to 1 yr after the end of treatment.

REFERRAL

- Neurosurgery should be involved early when this diagnosis is considered.
- Refer to an interventional radiologist for possible aspiration.
- An infectious diseases evaluation is needed for antimicrobial therapy.

PEARLS & CONSIDERATIONS

COMMENTS

It is important to think of spinal epidural abscess early to permit early treatment and prevent permanent neurologic deficits.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Brain Abscess (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Allison B, Farrinn AM: Spinal epidural abscess: a review with special emphasis on earlier diagnosis, *Biomed Res Int* 2016:1614328, 2016.

Artenstein AW et al: Spinal epidural abscess in adults: a 10-year clinical experience at a tertiary academic medical center, *Open Forum Infect Dis* 3:191, 2016.

Patel AR, et al.: Spinal epidural abscesses: risk factors, medical vs surgical management, a retrospective review of 128 cases, *Spine J* 14:326-330, 2014.

Tompkins M, et al.: Spinal epidural abscess, *J Emerg Med* 39(3):384-390, 2010.

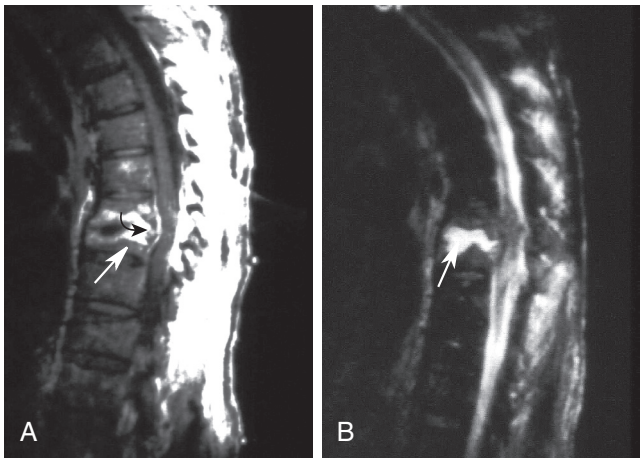

FIG. E1 Discitis with epidural abscess. Sagittal postcontrast T1-weighted **(A)** and T2-weighted **(B)** magnetic resonance imaging scans demonstrate features of discitis and adjacent osteomyelitis. Vertebral bodies and disc space are of low signal intensity on T1-weighted image and of bright signal intensity on T2-weighted image *(straight arrows).* Epidural abscess surrounding and compressing cord is also identified *(curved arrow).* (From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.)

Epidural Hematoma

BASIC INFORMATION

DEFINITION

Epidural hematoma (EDH) is the accumulation of blood in the potential space surrounding the brain, between the dura mater and the inner surface of the skull.

SYNONYMS

Extradural hematoma/hemorrhage
EDH

ICD-10CM CODES	
S06.4	Epidural hemorrhage
I62.1	Non-traumatic extradural hemorrhage
S06.4X0A	Epidural hemorrhage without loss of consciousness, initial encounter
S06.4X1A	Epidural hemorrhage with loss of consciousness of 30 minutes or less, initial encounter
S06.4X9A	Epidural hemorrhage with loss of consciousness of unspecified duration, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Exact incidence is unknown; however, it is found in 1% to 4% of traumatic head injury cases and 5% to 15% of autopsy series.
PREDOMINANT SEX AND AGE: Male > female
PEAK INCIDENCE: Peak incidence is among adolescents and young adults. It is rarely found in patients older than 50 to 60 yr old.
GENETICS: There is a role for genetics in spontaneous (nontraumatic) EDH caused by coagulopathies and vascular malformations.
RISK FACTORS: Head trauma, especially in cases involving skull fracture

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History of head trauma is present.
- Signs and symptoms vary depending on severity.
- Symptoms: Altered mental status, nuchal rigidity, headache, vomiting, drowsiness, confusion, aphasia, photophobia, and paralysis.
- Signs: Transient loss of consciousness, followed by a "lucid interval" in 47% of cases, in which the patient is free of any neurologic signs or symptoms. This is followed by clinical deterioration including vomiting, lethargy, confusion, or seizures. Other signs may include focal neurologic deficits such as paralysis of limbs, unequal pupils, and coma. Signs of increased intracranial pressure could be found including the Cushing reflex of hypertension, bradycardia, and respiratory distress. External signs of skull fracture—lacerations, ecchymoses, cerebrospinal fluid (CSF) rhinorrhea or otorrhea—may be observed. Skull fractures can be found in 75% to 95% of EDH patients.
- Coma or stupor with ipsilateral cranial nerve III palsy and contralateral hemiparesis may indicate transtentorial (uncal) herniation.

ETIOLOGY

- Traumatic: Commonly caused by arterial injury (the middle meningeal artery) from a temporal bone fracture (Fig. 1) but may also be injury of the anterior meningeal artery, a dural arteriovenous (AV) fistula at the vertex, or from venous bleeding
- Nontraumatic: Caused by an infection/eroding abscess, coagulopathy, hemorrhagic tumors, vascular malformations, postsurgical procedures, and in special populations (e.g., pregnant women, patients receiving hemodialysis)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

In the setting of head trauma: Subdural hematoma, subarachnoid hemorrhage, cerebral contusion, brain laceration, diffuse brain swelling

WORKUP

- Imaging is the mainstay of diagnosis.
- Serial head CT is the test most commonly used due to its simplicity, widespread use, and availability. Typical appearance is a "lens shaped," or "lentiform" hyperdensity (Fig. 2). Box 1 describes CT findings of EDH.
- Note: Head CT is not conclusive in 8% of cases possibly due to severe anemia, early scanning (before blood has time to accumulate), and severe hypotension.
- Brain MRI: More sensitive. Indicated in situations in which there is a strong clinical suspicion but no evidence of EDH on head CT (Fig. 3).
- Angiography: Rarely necessary but may be used to evaluate an underlying vascular lesion.
- NOTE: Lumbar puncture (LP) is contraindicated in EDH due to risk of brain stem herniation.

LABORATORY TESTS

- Laboratory tests are helpful as adjunct to diagnosis but are not the mainstay of diagnosis or treatment.
- CBC may be helpful to evaluate for anemia, although in an acute onset of bleeding hemoglobin levels can be normal.
- Other tests: Renal functions, electrolytes, liver functions, INR may be helpful depending on the case scenario.

TREATMENT

Acute symptomatic EDH is a neurologic emergency that requires surgical treatment to prevent permanent brain injury.

NONPHARMACOLOGIC THERAPY

- Immediate surgical decompression, ideally within 1 to 2 hr after traumatic event

FIG. 2 Head computed tomography showing two epidural hematomas in a 23-year-old involved in a motor vehicle accident. Note air bubbles that are a result of linear fracture in the left temporal bone *(short arrow).*

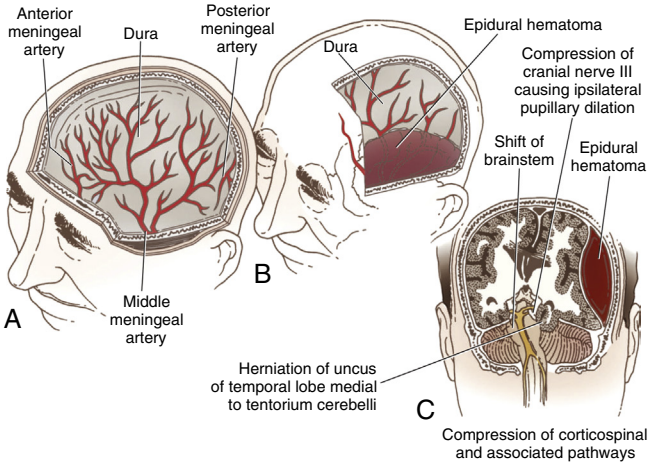

FIG. 1 Epidural hematoma is typically caused by trauma resulting in laceration of the middle meningeal artery. A, The middle meningeal artery. The typical traumatic epidural hematoma is caused by a laceration of this vessel. **B** and **C,** A linear fracture of the squamous portion of the temporal bone has torn the middle meningeal artery, which has resulted in an epidural hematoma. (From Rothrock JC: Neurosurgery. In Rothrock JC [ed.]: *Alexander's care of the patient in surgery,* ed 13, Philadelphia, 2007, Elsevier.)

BOX 1 Computed Tomography (CT) Findings of Epidural Hematoma

- CT appearance: variable white to gray on brain windows
- Location: peripheral to brain, variable but usually temporal region
- Shape: biconvex disc or lens
- Pearl: does not cross suture lines
- White swirl sign means active bleeding
- Significance: may cause mass effect and herniation
- Look for midline shift
- Look for effacement of ventricles and sulci
- Surgical indications: 15-mm thickness or 5-mm midline shift

From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.

FIG. 3 Epidural hematoma on magnetic resonance image. Coronal T2-weighted images show hypointense biconvex extraaxial collection in the left temporal region.

- Craniotomy and hematoma evacuation is the treatment of choice. When indicated, identify and ligate the bleeding vessel.
- Burr hole evacuation: This involves drilling a hole in the skull to evacuate the hematoma. It is a lifesaving procedure that is indicated if surgical expertise is limited.

ACUTE GENERAL Rx

- Cardiopulmonary resuscitation and assessment for disability.
- Medical resuscitation maneuvers: Head elevation, hyperventilation, monitoring of vital signs and avoidance of hypotension and hyperthermia, sedation if necessary.
- Medications: Osmotic diuresis with IV mannitol, cerebrosedating medications, antiepileptics may be used to treat or, in some situations, prevent seizures. The patient should also be started on a proton pump inhibitor to decrease risks of developing an upper gastrointestinal bleed.
- Reversing anticoagulation should be weighed in terms of advantages versus disadvantages.
- NOTE: Glucocorticoid therapy is *not* indicated following head injury and may be related to increased mortality.
- Evaluation for surgery: The best available evidence points toward advantages of decompression procedures. Nonoperative treatment may only be indicated if the patient has no symptoms, no focal neurologic deficit, no coma (Glasgow coma score >8), and EDH volume is less than 30 ml by CT scan, with clot thickness <15 mm and midline shift of less than 5 mm.
- Nonoperative treatment involves close monitoring, hourly neurologic checks, and serial head CT scans.

CHRONIC Rx

- There is a risk of permanent brain damage whether the disorder is treated or not. Most recovery occurs in the first 6 months with some improvement over 2 yr.
- Children have a tendency to recover more quickly.
- Patients should be educated on rehabilitative exercises and to alert medical professionals in the event of new neurologic symptoms.
- Support and encouragement to patient and family should always be provided.

REFERRAL

Neurosurgery should be the first service consulted. If not available, then general surgery needs to be called. Clinical nurse practitioners, pastoral care staff, and social workers to help patients and families are also appropriate.

PEARLS & CONSIDERATIONS

- Acute symptomatic EDH is a neurologic emergency. Urgent surgical evacuation is necessary in patients with Glasgow coma score less than 9, hematoma greater than 30 ml in volume, or presence of anisocoria.
- EDH should be suspected in any patient with a history of blow to the head leading to a period of loss of consciousness.
- Initial resuscitation is extremely important, but surgery is the mainstay of treatment for acute symptomatic EDH.

PREVENTION

Should be directed toward preventing head trauma: Use of appropriate safety equipment (e.g., helmets, hard hats, safe driving, avoiding diving into unknown depths)

PATIENT & FAMILY EDUCATION

Online head injury support groups are helpful: www.headinjury.com/linktbisup.htm, www.headinjury.com/, www.dailystrengthorg/c/Brain-Injury/support-group.

AUTHOR: **Fred F. Ferri, MD**

Epiglottitis PTG ALG

BASIC INFORMATION

DEFINITION

Epiglottitis is a rapidly progressive cellulitis of the epiglottis and adjacent soft tissue structures with the potential to cause abrupt airway obstruction, which can be life-threatening.

SYNONYMS

Supraglottitis
Cherry-red epiglottitis

ICD-10CM CODE
J05.1 Acute epiglottitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Due to vaccination against *Haemophilus influenzae* type B, this is a rare infection in children estimated at between 0.6 to 0.8 per 100,000 in one study and for adults at 1.6 per 100,000.
PEAK INCIDENCE: Now highest in children ages 6 to 12
PREDOMINANT SEX: Males

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Irritability, fever, dysphonia, and dysphagia
- Respiratory distress, with child tending to lean up and forward
- Often, drooling or oral secretions
- Often, presence of tachycardia and tachypnea
- On visualization, edematous and cherry-red epiglottis
- Often, no classic barking cough as seen in croup
- Possibly fulminant course (especially in children), leading to complete airway obstruction

ETIOLOGY

- In children, *Haemophilus influenzae* type b, still most common cause but now rare due to vaccination, *Streptococcus pyogenes,* (group A Streptococcus) *Streptococcus pneumoniae, and Staphylococcus aureus* (includes MRSA).
- In adults, *Streptococcus pyogenes* (group A Streptococcus), *H. influenzae* (can be isolated from blood and/or epiglottis [about 26% of cases]).
- Pneumococci, streptococci, and staphylococci are also implicated.
- Role of viruses in epiglottitis unclear.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Croup (Table E1)
- Angioedema
- Retropharyngeal or peritonsillar abscess
- Diphtheria
- Foreign body aspiration
- Lingual tonsillitis
- Bacterial tracheitis

WORKUP

- Cultures of blood and urine.
- Lateral neck radiograph to show an enlarged epiglottis, ballooning of the hypopharynx, and normal subglottic structures (Fig. 1).
  1. Radiographs are of only moderate sensitivity and specificity and take time to perform.
  2. Visualization of the epiglottis may be safer in adults than in children.
- Cultures of the epiglottis.

LABORATORY TESTS

- CBC: May reveal a leukocytosis with a shift to the left.
- Chest radiograph examination: May reveal evidence of pneumonia in close to 25% of cases.
- Cultures of blood, urine, and the epiglottis, as noted previously.

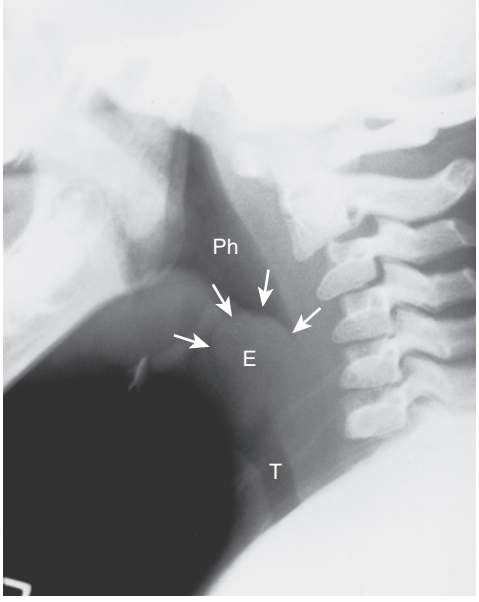

FIG. 1 Epiglottitis. A lateral soft tissue view of the neck shows a ballooned pharynx *(Ph)* with swollen epiglottis *(E)* in the shape of a large thumbprint *(arrows). T,* Trachea. (From Mettler FA [ed]: *Primary care radiology,* Philadelphia, 2000, Saunders.)

TREATMENT

ACUTE GENERAL Rx

- Maintenance of adequate airway is critical. Fig. E2 describes the optimal assessment and management of upper airway obstruction caused by epiglottitis or severe croup. It is crucial to have a tracheostomy set "at bedside."
- Early placement of an endotracheal or nasotracheal tube in a child is advised.
- Closely follow the adult patient, if no signs of airway obstruction, and defer intubation.
- In children, visualization and intubation are best done in the most controlled environment.
- *H. influenzae* in children is much less common in large part due to the HIB vaccine.

Empiric antibiotics:

- **In children:** Use cefotaxime 50 mg/kg IV q8h or ceftriaxone 50 mg/kg IV q24h *plus* vancomycin for its coverage of MRSA. If penicillin allergy, use levofloxacin 10 mg/kg IV q24h *plus* clindamycin 7.5 mg/kg IV q6h.
- **In adults:** Ceftriaxone 2 g IV q24h or cefotaxime *plus* vancomycin.
- If possible, obtain cultures before initiating antibiotics.
- If there is an unvaccinated child for *H. influenzae* at home (or in a day care center) who is >4 yr and living with an index case, give close family contacts of the patient (including adults) rifampin 20 mg/kg/day for 4 days (up to 600 mg/day) for prophylaxis.
- Role of epinephrine or corticosteroids in the management of epiglottitis is not firmly established.

DISPOSITION

Invasive *H. influenzae* infections and epiglottitis are reportable illnesses; this may be particularly important in recognizing an outbreak in a day care center with unvaccinated children.

REFERRAL

- Close cooperation between the pediatrician or internist, anesthesiologist, and otorhinolaryngologist, especially when epiglottis is visualized and when the patient requires endotracheal intubation.
- Best managed in a critical care setting or ICU.

PEARLS & CONSIDERATIONS

The incidence of epiglottitis has diminished markedly since the introduction of the protein conjugate vaccine against *H. influenzae* serotype B into routine childhood immunization.

The mortality rate now in children is about 1% but still remains at about 7% in adults.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Epiglottitis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READING

Chen C et al: Acute epiglottitis in the immunocompromised host: case report and review of the literature, *Open Forum Infect Dis* 5:ofy038, 2018.

Westerhuis B, Bietz MG, Lindemann J: Acute epiglottitis in adults: an underrecognized and life-threatening condition, *S.D Med* 66(8):309-311, 2013.

TABLE E1 Comparison of Croup, Epiglottitis, and Bacterial Tracheitis

	Croup	Epiglottitis	Bacterial Tracheitis
Peak age	6 mo-3 yr	5-7 yr but can be seen throughout childhood	3-5 yr but seen throughout childhood
Pathologic features	Subglottic inflammation, edema	Inflammation and edema of the epiglottis, aryepiglottic folds	Bacterial superinfection with inflammation of the tracheal mucosa, copious mucopurulent secretions obstructing the trachea
Organisms	Parainfluenza virus, RSV, adenovirus	Group A beta-hemolytic streptococcus, *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae*	*Staphylococcus aureus* or mixed flora
Clinical features	Onset follows URI prodrome consisting of croupy cough, hoarse voice, low-grade fever, inspiratory stridor	Rapid progression of high fever, toxicity, drooling, stridor	Several-day prodrome of crouplike illness progressing to toxicity, inspiratory and expiratory stridor, marked distress
Laboratory and radiographic findings	Steeple sign on PA view of the neck, or normal	Thumbprint sign on lateral aspect of the neck, thickened aryepiglottic folds, loss of air in the vallecula	Normal upper airway structures, shaggy tracheal air column
Management	Steroids uncommon, aerosolized epinephrine	Intubation, antibiotics	Intubation common, antibiotics rare, intubation

PA, Posteroanterior; *RSV,* respiratory syncytial virus; *URI,* upper respiratory infection.
From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Saunders.

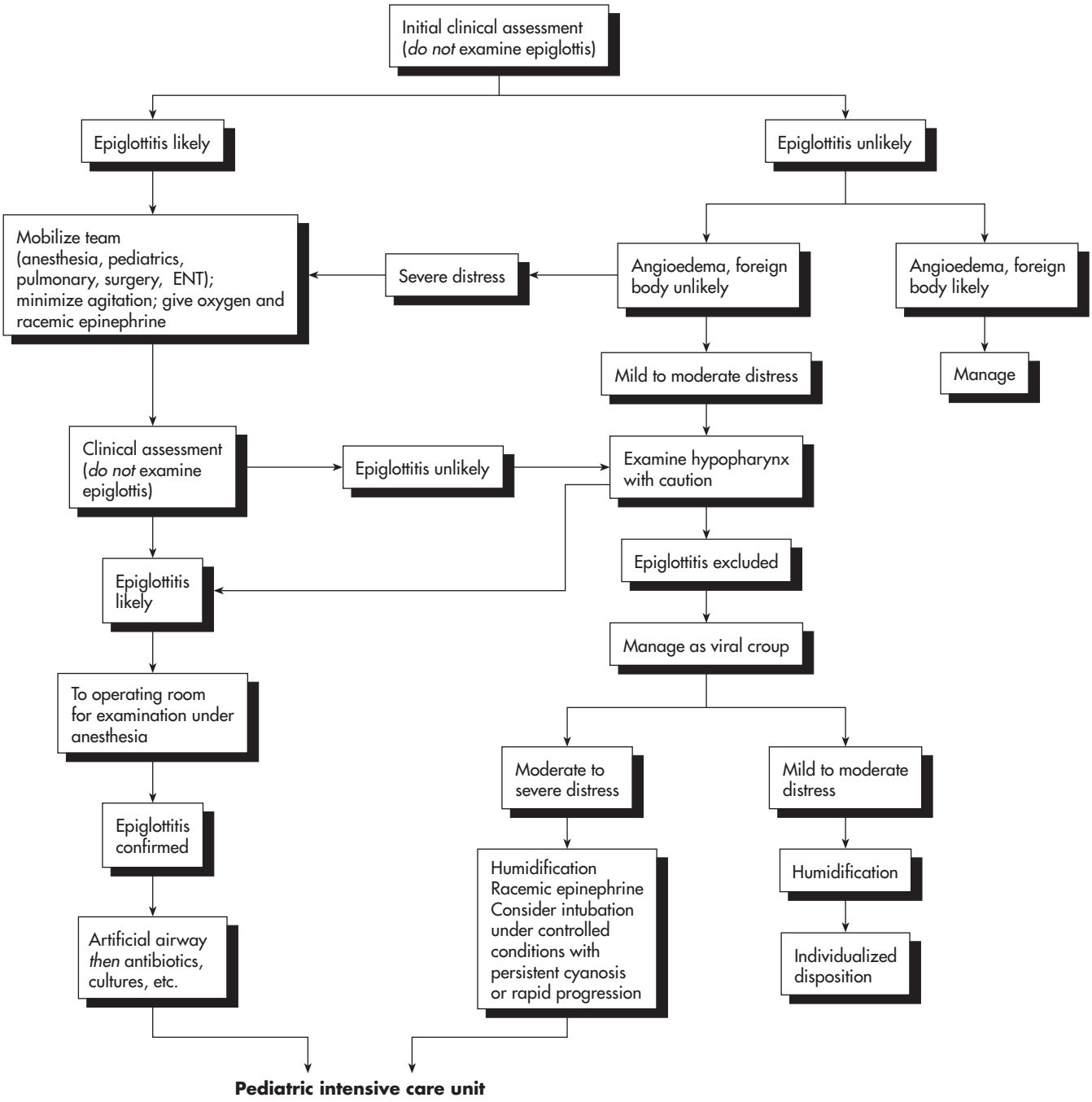

FIG. E2 Optimal assessment and management of upper airway obstruction caused by epiglottitis or severe croup. Care must be individualized to reflect resources and logistic issues within a given institution. *ENT,* Ear, nose, throat. (From Barkin RM et al: *Emergency pediatrics,* St Louis, 1999, Mosby.)

BASIC INFORMATION

DEFINITION

Epiploic appendagitis is an ischemic infarction of an epiploic appendage caused by the torsion or spontaneous thrombosis of the epiploic appendage central draining vein. Epiploic appendages are fat-containing, peritoneum-bounded sites containing blood vessels that extend from the serosa of the colon. They vary in size from 5 mm to 5 cm and occur throughout the colon but are most numerous in the sigmoid colon. Epiploic appendagitis is usually a benign self-limited condition but can mimic other causes of acute abdomen such as diverticulitis or acute appendicitis.

SYNONYMS

Appendicitis epiploica
Epiplopericolitis
Hemorrhagic epiploitis
Appendagitis

ICD-10CM CODE
K55.0 Acute vascular disorders of the intestine

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Reported in 2% to 7% of patients suspected of diverticulitis and 0.3% to 1% of patients suspected of appendicitis
PEAK INCIDENCE: Reported age range of 12 to 82 yr with a peak incidence in the fifth decade of life
PREDOMINANT SEX AND AGE: Four times higher in men than women
RISK FACTORS: Obesity and strenuous exercise

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients present with acute or subacute onset of lower abdominal pain.
- Pain is left sided in 60% to 80% of cases and is nonmigratory, but worsens with cough and abdominal stretching.
- Less frequent are nausea and vomiting, low-grade fever, diarrhea, and bloating.
- Patients do not appear acutely ill, rebound tenderness is not common, and a mass is only palpable in 10% to 30% of patients.

ETIOLOGY

- Epiploic appendage: Small, fat-filled, serosa-covered sacs, attached on the external surface of the colon by vascular stalks, from cecum to rectosigmoid junction. There are about 50 to 100 of these, they measure 1 to 2 cm thick and 2 to 5 cm long, and they may serve as a protective and defensive mechanism
- Primary epiploic appendagitis: Ischemic infarction of an epiploic appendage either by torsion or spontaneous thrombosis of the epiploic appendage central draining vein, causing vascular occlusion and focal inflammation
- Secondary epiploic appendagitis: Inflammation of the epiploic appendage is caused by an external process such as diverticulitis, appendicitis, pancreatitis, or cholecystitis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Appendicitis
- Diverticulitis
- Ovarian torsion, ovarian cyst rupture, ectopic pregnancy
- Secondary epiploic appendagitis: Pancreatitis, and cholecystitis are predisposing conditions

WORKUP

- Physical exam, bloodwork, and radiology

LABORATORY TESTS

Complete blood count, erythrocyte sedimentation rate, C-reactive may be normal or mildly elevated

IMAGING STUDIES

- Abdominal CT: Characteristic finding of round or ovoid lesions of fatty density measuring 1.5 to 3 cm in diameter with a hyperattenuating rim (Fig. E1) and ill-defined fat stranding are seen in mesenteric fat adjacent to the colon. At times the thrombosed vein can be seen as a high attenuated dot within the appendage.
- Abdominal ultrasound: At the site of maximum tenderness, a noncompressible hyperechoic small ovoid or round solid mass of adipose tissue is identified between the colon and abdominal wall.

TREATMENT

PHARMACOLOGIC THERAPY

- Ibuprofen: 600 mg PO q8h for 4 to 6 days
- Opiates for pain for 4 to 6 days if needed

ACUTE GENERAL Rx

Epiploic appendagitis is usually a self-limited, benign condition lasting 3 to 14 days.

DISPOSITION

- Patients usually do not require hospitalization or antibiotics.
- Recurrence rates are low.

REFERRAL

Surgery is only required for patients who do not improve or who have a complication such as abscess or bowel obstruction.

PEARLS & CONSIDERATIONS

- It is important to consider this entity in patients with abdominal pain because the correct diagnosis could avoid unnecessary use of further diagnostic studies, antibiotic therapy, and even surgical therapy.
- Although symptoms of epiploic appendagitis generally resolve within 2 weeks, CT findings may persist for 6 months.

RELATED TOPICS

Appendicitis (Related Key Topic)
Diverticular Disease (Diverticulosis, Diverticulitis, Diverticular Hemorrhage) (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

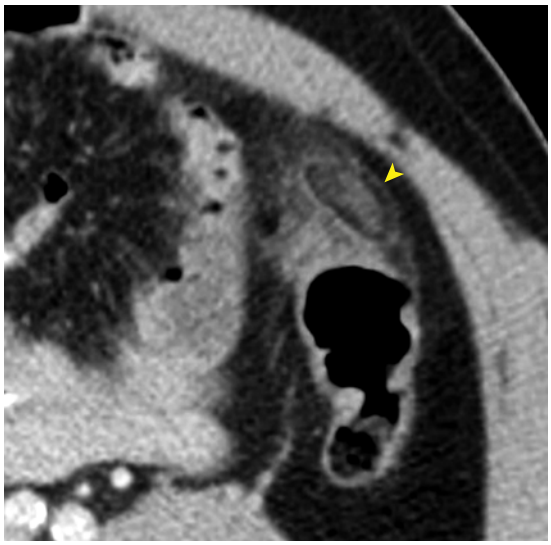

FIG. E1 Epiploic appendagitis. Axial computed tomography shows a pericolonic focus of inflammation enveloping a focus of fat *(arrowhead)*. This finding is characteristic of epiploic appendagitis. (From Webb WR, et al.: *Fundamentals of body CT,* ed 4, Philadelphia, 2015, Saunders.)

Episcleritis PTG

BASIC INFORMATION

DEFINITION

Episcleritis is an inflammation of the episclera, the thin layer of vascular elastic tissue between the sclera and conjunctiva.

ICD-10CM CODE
H15.1 Episcleritis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Relatively rare in an ophthalmologic practice
PEAK INCIDENCE: Most common in middle and old age
PREDOMINANT SEX: None
PREDOMINANT AGE: 40s

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Red, vascular injection of conjunctiva with engorged and enlarged blood vessels beneath the conjunctiva (Fig. E1)
- Pain in area of inflammation that is usually localized (severe pain suggests deeper inflammation; see Scleritis)
- Can be diffuse or nodular inflammation

ETIOLOGY

Associated with collagen-vascular diseases, vasculitis, trauma; usually idiopathic

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute glaucoma.
- Conjunctivitis and blepharoconjunctivitis.
- Scleritis.
- Subconjunctival hemorrhage.
- Congenital or lymphoid masses.
- The differential diagnosis of "red eye" is described in Section II.
- Table E1 compares immunologic diseases of the eye.

WORKUP

Eye examination, general check-up for collagen-vascular disease or other autoimmune diseases

LABORATORY TESTS

Studies for collagen-vascular disease (e.g., antinuclear antibody, erythrocyte sedimentation rate, rheumatoid factor)

TREATMENT

NONPHARMACOLOGIC THERAPY

Warm compresses

ACUTE GENERAL Rx

- Topical steroids, 1% prednisolone if no glaucoma; nonsteroidal eye drops if there is a tendency for glaucoma.
- Nonsteroidal antiinflammatory drugs (NSAIDs): Treat underlying systemic disease.

CHRONIC Rx

NSAID eye drops (diclofenac eye drops, ketorolac ophthalmic solution)

DISPOSITION

Close follow-up needed

REFERRAL

To ophthalmologist if patient unresponsive to treatment after a few days

PEARLS & CONSIDERATIONS

COMMENTS

- Can rarely be associated with collagen-vascular disease.
- Episcleritis has a tendency to recur.
- May occur with systemic autoimmune disease. Workup for autoimmune disease is often negative, more likely with scleritis (50%). Ask about other symptoms to find autoimmune disorders, helps to guide workups.
- Episcleritis is a benign and self-limiting condition; loss of vision only occurs with steroid-induced cataracts. Prolonged topical steroid treatment is worse than the condition itself.

RELATED CONTENT

Episcleritis (Patient Information)
Scleritis (Related Key Topic)

AUTHOR: **R. Scott Hoffman, MD**

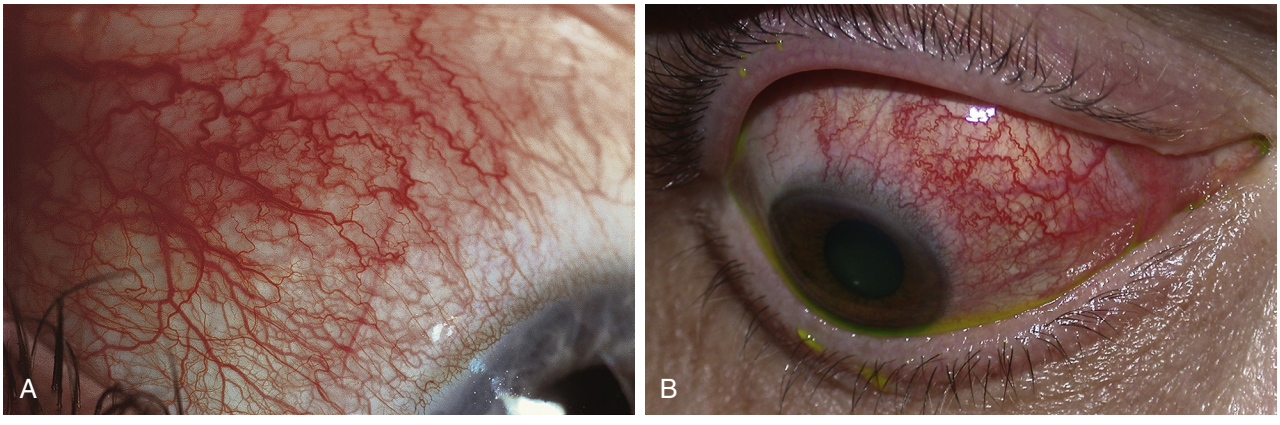

FIG. E1 A, Diffuse episcleritis with maximal vascular congestion in the superficial episcleral plexus. **B,** Scleritis with congestion of the deep vascular plexus. (*Fig. A,* Courtesy of P Watson. *Fig. B,* In Bowling B: *Kanski's clinical ophthalmology, a systemic approach,* ed 8, Philadelphia, 2016, Elsevier.)

TABLE E1 Immunologic Diseases of the Eye

Disease	Clinical Parameters	Signs/Symptoms	Treatment
Ocular cicatricial pemphigoid	Systemic pemphigoid Females predominate Peak incidence: 60-70 yr of age	Severe conjunctival redness Chronic conjunctivitis Mucous discharge Conjunctival scarring Inturning eyelids and eyelashes Breakdown of corneal and conjunctival epithelium Sight threatening	*Mild:* Dapsone *Severe:* Systemic steroids Immunosuppressive drugs
Peripheral ulcerative keratitis	*Mild:* Both females and males affected Any age Example: Associated with staphylococcal blepharitis *Necrotizing:* Mooren ulcer Both females and males affected Adults Unilateral involvement (worldwide) Bilateral involvement (males of African descent) History of infectious ocular disease History of rheumatic disease	*Mild:* Pain Photophobia Tearing Redness Peripheral infiltrate on ocular examination Not sight-threatening *Necrotizing:* Pain Photophobia Tearing Redness Perilimbal ulceration Sight-threatening	*Mild:* Topical steroids and antibiotics *Necrotizing:* Topical steroids Systemic steroids and other immunosuppressive drugs Surgical intervention
Episcleritis	Females predominate Peak incidence: 40 yr of age	Conjunctival redness Diffuse or nodular Minimal pain Not sight threatening	Cool compress Treat associated blepharitis Artificial tears Topical NSAIDs Topical steroids
Scleritis	Females predominate Peak incidence: 40 yr of age; rare in children *Anterior scleritis:* diffuse, nodular, necrotizing *Posterior scleritis:* Scleritis associated with systemic disease, rarely with ocular infection (40%)	*Anterior scleritis:* Deep, boring pain Diffuse ocular redness Raised nodules Scleral ulceration *Necrotizing scleritis:* Sight threatening *Posterior scleritis:* Pain with eye movement Sight threatening	Topical steroids ineffective Periocular steroid injection acceptable Oral NSAIDs, systemic steroids, immunosuppressive drugs
Uveitis	Associated with systemic and infectious disease (40%) All ages Occurrence rates: *Anterior uveitis:* 70% *Intermediate uveitis*: 20% *Posterior uveitis:* 10%	*Anterior:* Redness Pain Photophobia Anterior chamber cells and fibrin Pupil miotic *Intermediate:* Bilateral involvement Mildly hazy/blurry vision *Posterior:* Photophobia Pain Sight threatening	*Anterior:* Topical steroids *Intermediate:* Periocular steroids Systemic steroids *Posterior:* Systemic steroids Immunosuppressive drugs

NSAIDs, Nonsteroidal antiinflammatory drugs.
From Adkinson NF et al*: Middleton's allergy principles and practice*, ed 8, Philadelphia, 2014, Saunders.

BASIC INFORMATION

DEFINITION

Epistaxis is defined as bleeding from the nose or nasal hemorrhage and is classified as either anterior or posterior.

SYNONYM

Nosebleed

ICD-10CM CODE
R04.0 Epistaxis

EPIDEMIOLOGY & DEMOGRAPHICS

- Epistaxis accounts for one of every 200 emergency department visits in the U.S. annually.
- It increases in frequency after age 20 yr and reaches the highest levels among the elderly population.
- More than 80% of cases of epistaxis are anterior in origin (Little area) and occur from Kiesselbach plexus.
- Only 5% of patients with epistaxis have posterior bleeds.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Nosebleed
- Hypotension and hemodynamic instability with acute, severe epistaxis

ETIOLOGY

- Approximately 90% of epistaxis events are idiopathic.
- Common identifiable causes are:
  1. Cold, dry environment
  2. Trauma (nose picking, accidents, and physical altercations)
  3. Structural deformities (septal deviations or spurs, chronic perforations)
  4. Inflammatory (rhinosinusitis, nasal polyposis)
  5. Allergies
  6. Foreign bodies in the nasal cavity
  7. Tumors (juvenile angiofibroma)
  8. Irritants
  9. Hypertension
  10. Coagulopathy (hemophilia, von Willebrand disease, thrombocytopenia)
  11. Osler-Weber-Rendu disease
  12. Renal failure
  13. Drugs: Aspirin, nonsteroidal antiinflammatory drugs, warfarin, alcohol, sildenafil, and tadalafil
  14. Blood vessel disorders (connective tissue disease, hereditary hemorrhagic telangiectasia)
  15. Pseudoaneurysm and aneurysm of the internal carotid artery might present as epistaxis

DIAGNOSIS

A good attempt should be made to directly visualize the source of bleeding to confirm the diagnosis and determine the best treatment. Fig. E1 illustrates anatomical sites for epistaxis.

DIFFERENTIAL DIAGNOSIS

Pseudoepistaxis must be ruled out. Common extranasal sites of bleeding that can simulate epistaxis include:

- Pulmonary hemoptysis
- Bleeding esophageal varices
- Tumor bleeding from the pharynx, larynx, or trachea

WORKUP

The workup should include laboratory blood testing to exclude obvious causes. Type and cross in anticipation of transfusion if the bleeding is severe.

LABORATORY TESTS

- Hemoglobin and hematocrit
- Platelet count
- Blood urea nitrogen and creatinine
- Coagulation studies (prothrombin time and partial thromboplastin time)
- Type and crossmatching of blood products

IMAGING STUDIES

Radiographic studies are usually not helpful.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Digital compression or pinching of the lower soft cartilaginous part of the nose for 10 min is the method of choice.
- Use cotton or tissue plug.
- The patient should be sitting and leaning forward, breathing through the mouth, allowing blood to flow out of the nostrils as opposed to bending backward, which would allow the blood to flow down the throat.
- Application of cold compresses to the bridge of the nose to cause a vasoconstrictive effect; the patient may also suck on ice to achieve this effect.

ACUTE GENERAL Rx

Anterior epistaxis:

- Local vasoconstriction is performed by moistening a cotton pledget with either:
  1. 4% lidocaine with 1:1000 epinephrine
  2. 4% lidocaine with 1% phenylephrine (Neo-Synephrine)
  3. 4% lidocaine with 0.05% oxymetazoline (Afrin)

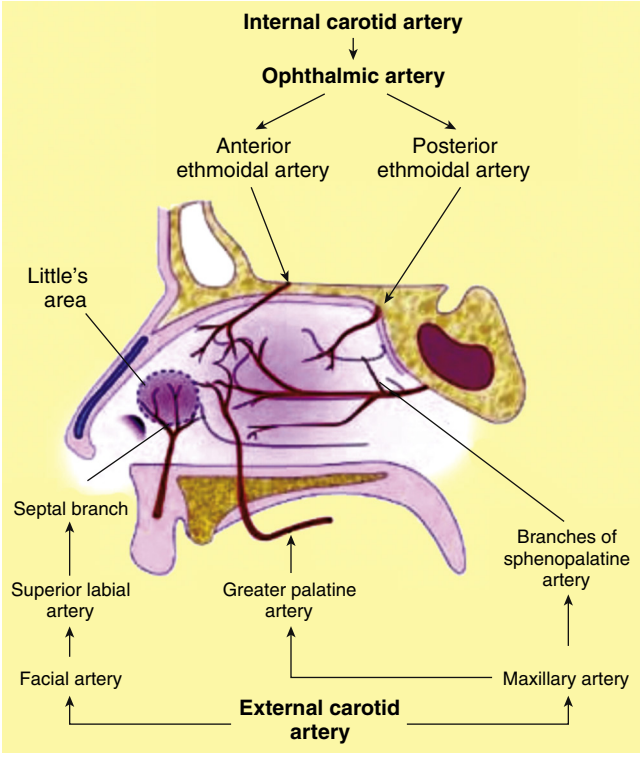

FIG. E1 Anatomical sites for epistaxis. (From McLarnon CM, Carrie S: Epistaxis, *Surgery (Oxford)* 30(11):584-589, 2012.)

4. 4% cocaine or cocaine 25% in paraffin base ointment and inserting the pledget into the nasal cavity with bayonet forceps
- Cauterization with silver nitrate or trichloroacetic acid is performed once hemostasis is achieved.
- Anterior nasal packing is needed when local measures are unsuccessful. Nasal packing is performed under local anesthesia and is done by inserting Vaseline gauze strips in layers from the floor of the nasal cavity to the front entrance of the nasal orifice. Enough pressure is placed to tamponade the epistaxis.
- Other commercially available nasal packing uses sponge packs that expand when exposed to blood or moisture and can be used for anterior epistaxis.

Posterior epistaxis:
- Posterior nasal packing:
  1. Commercially available nasal sponge packing can be applied
  2. Rolled gauze technique
- Foley catheter balloon insertion into the nasopharynx can be tried in patients with posterior epistaxis.

Newer agents in the treatment of epistaxis:
- Quick clot hemostatic agent, available OTC. When it comes in contact with blood in and around a wound, it absorbs the smaller water molecules from the blood to promote rapid clotting
- FloSeal hemostatic matrix, a combination of human thrombin, gelatin matrix, and calcium chloride, which are mixed together and placed at bleeding site
- Recombinant factor VIIa, generally reserved for uncontrolled epistaxis

CHRONIC Rx

- If acute treatment fails to stop the bleeding or the site of bleeding cannot be located, electrocautery or endoscopic cauterization can be used.
- Electrocautery is performed after suitable anesthesia, such as application of a topical anesthetic followed by local anesthetic injection. Only one side of the nasal septum should be cauterized at a time because perforation can result from bilateral cauterization.
- Arterial ligation or embolization has been used in refractory posterior epistaxis.
- For cases involving irritated or inflamed mucosa, a conservative regimen of triamcinolone 0.025%, Nemdyn, Nasalate, or equivalent cream should be applied once a week, combined with nightly application of a small quantity of petroleum jelly to the septum before bedtime.

DISPOSITION

- Most cases of anterior epistaxis from Kiesselbach plexus can be stopped by nasal compression and local vasoconstriction or cauterization.
- Nasal packing with gauze or sponge can control 90% of anterior epistaxis.
- Anterior and posterior packs are removed in 2 to 3 days. Hospital admission should be considered in patients who cannot be expected to return for prompt follow-up because prolonged packing increases the risk of pressure necrosis, toxic shock syndrome, sinus infections, and other complications.
- Although rare, epistaxis can lead to death by aspiration of blood, hemodynamic compromise from rapid excessive blood loss, or toxic shock syndrome.

REFERRAL

- If epistaxis cannot be controlled, an ear-nose-throat (ENT) specialist should be called for assistance.
- ENT specialist should be consulted in any patient with posterior epistaxis requiring posterior packing.

PEARLS & CONSIDERATIONS

COMMENTS

- Silver nitrate cauterization, if done on both sides of the nasal septum, can lead to septal perforation and should be discouraged.
- If anterior nasal packing is done, broad-spectrum antibiotics (e.g., amoxicillin-clavulanate 250 mg PO tid or trimethoprim-sulfamethoxazole 1 tablet PO bid) are used until the anterior packs are removed. Although it is customary to place patients on antibiotics to prevent sinusitis from obstruction, there is no proof that this is effective.
- Complications of nasal packing include:
  1. Aspiration
  2. Dislodged packing
  3. Infection
  4. Nasal trauma
- Traditional risk factors for epistaxis, including nasal perforation, nasal septum deviation, rhinitis, sinusitis, and upper respiratory tract infection, do not increase the risk of recurrent epistaxis. Significant risk factors for recurrent epistaxis include congestive heart failure, diabetes mellitus, hypertension, and a history of angina. Warfarin use also increases risk of recurrence, independent of INR. Aspirin and clopidogrel do not increase the risk of recurrent epistaxis.[1]

RELATED CONTENT

Nosebleeds (Patient Information)

AUTHOR: **Tanya Ali, MD**

[1]Abrich V et al: Risk factors for recurrent spontaneous epistaxis, *Mayo Clin Proc* 89(12):1636-1643, 2014.

BASIC INFORMATION

DEFINITION

Epstein-Barr virus infection refers to a disease caused by Epstein-Barr virus (EBV), a human herpesvirus.

SYNONYMS

Infectious mononucleosis (IM)
Kissing disease

ICD-10CM CODES

B27.80	Other infectious mononucleosis without complication
B27.81	Other infectious mononucleosis with polyneuropathy
B27.82	Other infectious mononucleosis with meningitis
B27.89	Other infectious mononucleosis with other complication
B27.90	Infectious mononucleosis, unspecified without complication
B27.91	Infectious mononucleosis, unspecified with polyneuropathy
B27.92	Infectious mononucleosis, unspecified with meningitis
B27.99	Infectious mononucleosis, unspecified with other complication

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 5 cases/100,000 persons per yr of IM
PREDOMINANT SEX: Neither, although peak incidence occurs about 2 yr earlier in women
PREDOMINANT AGE:

- Clinical evidence of IM: Occurs most commonly at ages 15 to 24 yr
- EBV infection: Occurs earlier in life in lower socioeconomic groups

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most EBV infections either are asymptomatic or cause a nonspecific viral illness.
- Incubation period is 1 to 2 mo, possibly followed by a prodrome of anorexia, low-grade fever, malaise, headache, and chills; after several days, clinical triad of pharyngitis, moderate to high fever, and adenopathy may appear, accompanied by fatigue and malaise.
- Pharyngitis is usually the most severe symptom; white or necrotic exudates are common.
- Symmetrical lymphadenopathy is most prominent in the posterior more than anterior cervical region but may be diffuse.
- Splenomegaly (50% of cases) is possible, most commonly during the second week of illness.
- Maculopapular or morbilliform rash is uncommon but will often occur in patients who receive ampicillin (Fig. E1). Patients may have palatal petechiae, periorbital, or palpebral edema. Mucocutaneous oral hairy leukoplakia (OHL), which is associated with intense EBV replication and the action of EBV-encoded proteins such as latent membrane protein-1, may occur.
- Possible IM presentation: Fever and adenopathy without pharyngitis.
- Nausea, vomiting, and anorexia are frequent in patients with IM, probably reflecting mild hepatitis encountered in 90% of infected individuals.
- Although complications such as spleen rupture, airway obstruction, and malignancy may be severe and fatal, they are uncommon and tend to resolve completely.
- Hematologic involvement includes hemolytic or aplastic anemia, thrombocytopenia, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome, and disseminated intravascular coagulation (DIC). Pneumonia, myocarditis, pancreatitis, mesenteric adenitis, myositis, and glomerulonephritis may occur as well. Nervous system involvement includes Guillain-Barré syndrome, facial nerve palsy, meningoencephalitis, aseptic meningitis, transverse myelitis, peripheral neuritis, and optic neuritis.
- IM is usually a self-limited illness. Acute symptoms resolve in 1 to 2 wk, but symptoms of malaise and fatigue often persist for months.
- EBV is related to lymphoproliferative syndromes in transplant recipients and in AIDS patients.
- Increasing evidence showing an association between EBV infection and African Burkitt, B-cell or T-cell lymphoma, and nasopharyngeal carcinoma. Table 1 describes EBV-associated malignancies.

ETIOLOGY

- EBV is a ubiquitous virus.
- Infection during childhood is much less likely to cause significant illness.
- Frequency of IM in late adolescence is attributed to the onset of social contact between the sexes.
- Close personal contact is usually necessary for transmission, although EBV is occasionally transmitted by blood transfusion; transfer via saliva while kissing may be responsible for many cases.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Heterophile-negative IM caused by cytomegalovirus (CMV)
- Although clinical presentation similar, CMV more frequently follows transfusion
- Bacterial and viral causes of pharyngitis
- Toxoplasmosis
- Acute retroviral syndrome of HIV
- Lymphoma
- Lyme disease

WORKUP

Heterophile antibody and CBC with blood smear. Table 2 describes frequently determined EBV-specific antibodies.

LABORATORY TESTS

- Increased WBC common, with a relative lymphocytosis of more than 50% and neutropenia identified.
- Hallmark of IM: Atypical lymphocytes of more than 10% (not pathognomonic) are found.
- Mild thrombocytopenia is present.
- Falling hematocrit signals the possibility of splenic rupture or immune hemolytic anemia.
- Elevated hepatocellular enzymes and cryoglobulins are found in most cases.
- Heterophile antibody:
  1. As measured by the monospot test, may be positive at presentation or may appear later in the course of illness. Its accuracy is 71% to 90% but has a 25% false-negative rate in the first week of illness.
  2. A negative test should be repeated in 1 wk if clinical suspicion is high.
  3. A false-positive test has been reported with primary HIV infection.
- Viral capsid antigen (VCA) IgG and IgM are rarely used for diagnosis, but better value in children because heterophile antibody is negative in most children younger than 8 yr.

TABLE 1 Epstein-Barr Virus (EBV)-Associated Malignancies

Malignancy	EBV Frequency (%)
Hodgkin disease	~40
Non-Hodgkin lymphomas	
Burkitt lymphoma	20-95
Diffuse large B-cell lymphoma and CD30$^+$ Ki-1$^+$ anaplastic large cell lymphoma	10-35
Lymphomatoid granulomatosis	80-95
T-cell–rich B-cell lymphoma	20
Angioimmunoblastic lymphoma	>80
T-cell, NK-cell, and T/NK-cell lymphomas	30-90
Nasopharyngeal carcinoma	>95
Gastric adenocarcinoma	5-10
Pyothorax-associated lymphoma	>95
Leiomyosarcoma in immunocompromised patients	>95

NK cell, Natural killer cell; *T cell,* T lymphocyte cell.
From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

TABLE 2 Frequently Determined EBV-Specific Antibodies

Antibody Specificity	Positive in IM (%)	Time of Appearance in IM	Persistence	Comments
Viral Capsid Antigen				
VCA-IgM	100	At clinical presentation	4-8 weeks	Highly sensitive and specific; of major diagnostic utility
VCA-IgG	100	At clinical presentation	Lifelong	Useful for documentation of past EBV infection
Early Antigen				
Anti-D	70	Peaks 3-4 weeks after onset	3-6 months	Correlates with disease severity; seen in NPC patients
Anti-R	Low	2 weeks to several months after onset	2 months to >3 yr	Occasionally seen with unusually severe cases; seen in African Burkitt lymphoma patients
EBNA	100	3-4 weeks after onset	Lifelong	Presence excludes primary EBV infection

EBNA, EBV nuclear antigen; *EBV,* Epstein-Barr virus; *Ig,* immunoglobulin; *IM,* infectious mononucleosis; *NPC,* nasopharyngeal carcinoma; *VCA,* viral capsid antigen.
Adapted from Schooley RT: Epstein-Barr virus (infectious mononucleosis). In Mandell GL et al (eds): *Principles and practice of infectious diseases,* Philadelphia, 2010, Churchill Livingstone.

- PCR DNA for CMV is the test of choice in transplant recipients who develop lymphoproliferative syndromes.

IMAGING STUDIES

Chest radiograph examination:
- May rarely show infiltrates
- Possible elevated left hemidiaphragm with splenic rupture

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive including rest
- Splenectomy if rupture occurs
- Transfusions for severe anemia or thrombocytopenia

ACUTE GENERAL Rx

- Pharmacologic therapy is not indicated in uncomplicated illness.
- Avoid aspirin due to the risk of Reye syndrome.
- Avoid ampicillin and amoxicillin as their use can frequently precipitate a nonallergic rash. Azithromycin has also been implicated.
- Use of steroids is suggested in patients who have severe thrombocytopenia, hemolytic anemia, impending airway obstruction resulting from enlarged tonsils, or fulminant liver failure. Prednisone 60 to 80 mg PO qd for 3 days, then tapered over 1 to 2 wk.
- Although it may reduce initial viral shedding, there is little evidence to support the use of antiviral agents such as acyclovir in the management of IM.

CHRONIC Rx

An extremely rare, chronic form of IM with persistent fevers and fatigue has been described and should be differentiated from chronic fatigue syndrome, which is not related to EBV.

DISPOSITION

Eventual resolution of all symptoms

REFERRAL

If more than mild illness

PEARLS & CONSIDERATIONS

- Epstein-Barr infection will occur in 95% of the world population at some point in life.
- It is felt the antibiotic-induced rash in IM is a transient virus-mediated immune alteration that sets the stage for loss of antigenic tolerance and the development of a reversible, delayed-type hypersensitivity reaction to the antibiotic

COMMENTS

Avoidance of contact sports during the first month of illness because splenic rupture can occur even in the absence of clinically detectable splenomegaly in 0.1% to 0.5% of patients.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Epstein-Barr Virus Infection (Patient Information)
Mononucleosis (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Shepard RJ: Exercise and the athlete with infectious mononucleosis, *Clin J Sport Med* 27:168-178, 2017.

Thompson DF, Ramos CL: Antibiotic-induced rash in patients with infectious mononucleosis, *Ann Pharmacother* 51:154-162, 2017.

Womack J, Jimenez M: Common questions about infectious mononucleosis, *Am Fam Physician* 91(6):372-376, 2015.

FIG. E1 Patient with infectious mononucleosis and ampicillin-induced rash. Maculopapular rash extends over the trunk and extremities. Rash frequently has a violaceous hue and is often accompanied by pruritus. (Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.)

BASIC INFORMATION

DEFINITION

Erectile dysfunction (ED) is the persistent inability to achieve or sustain a penile erection of adequate rigidity to make sexual penetration possible or satisfactory.

SYNONYMS

ED
Impotence
Male erectile disorder
Sexual dysfunction (a nonspecific term)

ICD-10CM CODES

N48.4	Impotence of organic origin
F52.2	Failure of genital response
F52.9	Unspecified sexual dysfunction, not caused by organic disorder or disease
N52.01	Erectile dysfunction due to arterial insufficiency
N52.02	Corporo-venous occlusive erectile dysfunction
N52.03	Combined arterial insufficiency and corporo-venous occlusive erectile dysfunction
N52.1	Erectile dysfunction due to diseases classified elsewhere
N52.2	Drug-induced erectile dysfunction
N52.31	Erectile dysfunction following radical prostatectomy
N52.32	Erectile dysfunction following radical cystectomy
N52.33	Erectile dysfunction following urethral surgery
N52.34	Erectile dysfunction following simple prostatectomy
N52.39	Other post-surgical erectile dysfunction
N52.8	Other male erectile dysfunction
N52.9	Male erectile dysfunction, unspecified

DSM-5 CODE

302.72	Failure of genital response

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.):

- Increases with age and presence of specific medical comorbidities
- Approximately 8% in the 20s to 30s, 18% in the 50s, 25% in the 60s, 37% in the 70s, 80% in the 80s

PREDOMINANT SEX: By definition, only in males

PREDOMINANT AGE: Increases with age

RISK FACTORS: Age, coronary artery disease, peripheral vascular disease, hypertension, hypogonadism, diabetes mellitus, hypercholesterolemia, prostate surgery, neurologic injury, numerous medications, alcohol, smoking or drug abuse, obesity, obstructive sleep apnea, systemic sclerosis; psychological: performance anxiety

ETIOLOGY

- A classification of male erectile dysfunction is described in Box 1.
- Most cases involving men older than 50 yr are caused by organic problems related to neurologic, hormonal, or vascular abnormalities or prescription or recreational drugs. In organic ED, nocturnal penile tumescence is generally diminished or absent, and ED is also experienced during private masturbation and across partners.
- Psychogenic ED results from mental stress, depression, a stressful partner relationship, a partner's sexual and mental health problems, and performance anxiety. Performance anxiety is extremely common and is characterized by a focus on the performance outcome of sex (i.e., obtaining and maintaining an erection) rather than a focus on the process and enjoyment of sex. Psychogenic ED is characterized by normal nocturnal penile tumescence and/or erections associated with erotic material or other partners, and by otherwise negative medical test results.
- Vascular disease: History of hypertension (HTN), peripheral vascular disease, ischemic heart disease, diabetes, smoking. In approximately 40% of men >50 yr, the primary cause of ED is related to atherosclerotic disease, diabetes mellitus (DM), neuropathy, or vascular disease.
- Obesity and metabolic syndrome.
- Medication side effects: Antihypertensives such as thiazides and clonidine, guanethidine or methyldopa (consider change to ACE inhibitors and calcium channel blockers with lower reported incidence of ED); antiandrogens such as spironolactone, finasteride, ketoconazole; cimetidine (but not ranitidine or famotidine); antidepressants such as selective serotonin reuptake inhibitors [SSRIs]; and antipsychotics. Table 1 summarizes drug-induced erectile dysfunction and suggested alternatives.

BOX 1 Classification of Male Erectile Dysfunction

Organic
- I. Vasculogenic
  - A. Arteriogenic
  - B. Cavernosal
  - C. Mixed
- II. Neurogenic
- III. Anatomic
- IV. Endocrinologic

Psychogenic
- I. Generalized
  - A. Generalized unresponsiveness
    1. Primary lack of sexual arousability
    2. Aging-related decline in sexual arousability
  - B. Generalized inhibition
    1. Chronic disorder of sexual intimacy
- II. Situational
  - A. Partner-related
    1. Lack of arousability in specific relationship
    2. Lack of arousability owing to sexual object preference
    3. High central inhibition owing to partner conflict or threat
  - B. Performance-related
    1. Associated with other sexual dysfunction (e.g., rapid ejaculation)
    2. Situational performance anxiety (e.g., fear of failure)
  - C. Psychological distress or adjustment related
    1. Associated with negative mood state (e.g., depression) or major life stress (e.g., death of partner)

From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

TABLE 1 Drug-Induced Erectile Dysfunction and Suggested Alternatives

Class	Known to Cause Erectile Dysfunction	Suggested Alternatives
Antihypertensives	Thiazide diuretics General β blockers	α-Blockers Calcium channel blockers Specific β-blockers Angiotensin-converting enzyme inhibitors Angiotensin II receptor antagonists
Psychotropics	Antipsychotics Antidepressants Anxiolytics	Anxiolytic (buspirone); antidepressant (bupropion)
Antiandrogen	Androgen receptor antagonists Luteinizing hormone–releasing hormone agonists 5α-Reductase inhibitors	
Opiates		
Antiretroviral agents		
Tobacco		Quit smoking
Alcohol	Large amount	Small amount

From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

- Excessive alcohol and nicotine use.
- Recreational drugs, including cocaine, heroin, amphetamines, and marijuana. These may increase libido but impair performance.
- Hormonal dysfunction such as testosterone deficiency (decreases libido and erection), hypothyroidism or hyperthyroidism, hyperprolactinemia, and adrenal insufficiency.
- Neurogenic causes including spinal cord lesions, cortical lesions, and peripheral neuropathies.
- Trauma or pelvic surgeries such as radical prostatectomy or cystectomy.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- A useful tool to diagnose/evaluate ED severity is the Sexual Health Inventory for Men (SHIM).
- Distinguish psychogenic and organic contributions to ED.
- Evaluate for underlying etiology of organic ED and comorbid psychiatric condition.

WORKUP

- Clinical history should include time course (abrupt onset may correlate with reversible cause such as medications, psychosocial stress, psychiatric complaint, trauma; nonsustained erection may be secondary to anxiety or vascular steal syndrome), cause (psychogenic vs. organic), and change in libido. Box 2 describes symptoms suggesting neurologic sexual impairment.
- Report of spontaneous nocturnal or morning erections indicate intact neurologic reflexes and penile blood flow.
- Decreased libido may indicate endocrinologic or psychogenic cause.
- If possible, interview partner regarding partner's sexual function, relationship satisfaction, and mental health history.
- Medical and social history should address cardiac disease symptoms and risk factors (HTN, DM, hyperlipidemia, smoking, and substance abuse), pelvic surgery, medications, and mental health. Coronary artery calcium score (CAC) is best indicator of subclinical coronary artery disease.

BOX 2 Symptoms Suggesting Neurologic Sexual Impairment

- Continual erectile dysfunction
  - Absence of morning erections
  - No erection or orgasm during masturbation or sex with different partners
- Related somatic complaints
- Sensory loss in genitals, pelvis, or legs
- Urinary incontinence
- Certain neurologic conditions
  - Spinal cord injury
  - Diabetic neuropathy
  - Multiple sclerosis
  - Herniated intervertebral disk
- Use of many medications

From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.

- Physical examination to check blood pressure, visual field defects to evaluate for pituitary tumors; femoral and peripheral pulses, femoral bruits; gynecomastia; neuronal damage (genital sensation, cremasteric reflex); direct penile damage (e.g., plaque formation such as Peyronie disease); prostate examination; or testicular atrophy and other secondary sexual characteristics. Signs of neurologic sexual impairment are summarized in Box 3.

LABORATORY TESTS

Screen for diabetes mellitus with fasting glucose. Consider lipid panel, thyroid-stimulating hormone, morning serum testosterone (free and total). If decreased testosterone, check prolactin, follicle-stimulating hormone, and luteinizing hormone.

IMAGING STUDIES

Imaging studies are rarely performed except in situations of pelvic trauma or surgery.

OTHER STUDIES

- Nocturnal penile tumescence testing is very specific for distinguishing psychogenic versus organic causes.
- Neurogenic etiologies examined by the cremasteric reflex (inner-thigh touch elicits scrotal contraction), the bulbocavernosus reflex, or the pudendal-evoked response.
- Intracorporeal injection of prostaglandin E_1 to distinguish vascular and nonvascular etiologies (erection is achieved in patients with normal vascular systems). If no erection with direct injection of vasoactive substance, consider duplex ultrasound of penile vasculature.
- In patients without an obvious cause of ED, consider screening for cardiovascular disease prior to starting treatment.

Rx TREATMENT (FIG. 1)

NONPHARMACOLOGIC THERAPY

- Various psychotherapeutic approaches: Cognitive-behavioral therapy preferred; success rates decrease with advancing age and duration of symptoms.

BOX 3 Signs of Neurologic Sexual Impairment

- Signs of spinal cord injury
  - Paraparesis or quadriparesis
  - Leg spasticity
  - Urinary incontinence
- Signs of autonomic nervous system injury
  - Orthostatic hypotension or lightheadedness
  - Anhidrosis in groin and legs
  - Urinary incontinence
  - Retrograde ejaculation
- Signs of peripheral nervous system injury
  - Loss of sensation in the genitals, "saddle area," and legs
  - Paresis and areflexia in legs
  - Scrotal, cremasteric, and anal reflex loss

From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.

- Psychosexual therapy is first line for psychogenic ED. Psychosexual therapy may be used as for adjunctive therapy in ED from any cause to address contributing, performance anxiety, social, and relationship issues.
- Performance anxiety is best addressed by sensate focus in which a couple is asked to refrain from sexual penetration but enjoy erotic touching.
- Mechanical vacuum devices (function by drawing blood into corpus cavernosum) are 70% to 90% effective but are difficult to use and subject to noncompliance.
- Incorporate vascular risk factor reduction including counsel on diet, exercise, smoking cessation, ETOH intake and screening/treatment for HTN, insulin resistance, and hypercholesterolemia as appropriate. Trials have shown that lifestyle modification and pharmacotherapy for cardiovascular risk factors are effective in improving sexual function in men with ED.

ACUTE GENERAL Rx

- First-line treatment: In setting of sexual stimulation, four selective phosphodiesterase type 5 (PDE5) inhibitors (Table 2) prolong nitric oxide–induced vasodilation by increase of intracavernosal cyclic guanosine monophosphate levels. Sildenafil (Viagra) and vardenafil (Levitra, Staxyn) can be taken 30 to 60 min before sexual activity, and both are effective for about 4 hr. Avanafil (Stendra) can be taken 15 to 30 min before sexual activity and is effective for about 6 hr. Tadalafil (Cialis) can be taken several hours before sexual activity (although 50% respond within 30 min) and lasts up to 36 hr. All four PDE5 inhibitors have similar efficacy and tolerability, but tadalafil has a longer duration of action and is less affected by high-fat meals and alcohol. Counsel patients to avoid high-fat meals and excessive alcohol when taking PDE5 inhibitors, as they may impede effectiveness.
- With PDE5 inhibitors, avoid concomitant use of nitrates (absolute contraindication), drugs that inhibit or induce cytochrome P450 CYP3A4, and drugs that prolong the QT interval. Caution in men on alpha-adrenergic blocker therapy because of concern for hypotension; start the lowest dose of PDE5 inhibitor. Caution in men who have had myocardial infarction in the past 6 mo, resting hypotension or uncontrolled hypertension, unstable angina, positive exercise stress test or poor exercise tolerance. Counsel on side effects of headache, flushing, dyspepsia, nasal congestion, changes in color perception (including blue vision for sildenafil and vardenafil but not tadalafil), sudden hearing loss, and priapism (rare). Nonarteritic anterior ischemic optic neuropathy is also a rare association with sildenafil and tadalafil. Consider counseling on safe sexual practices when prescribing PDE5 inhibitors.
- Second-line treatment if PDE5 inhibitors fail: Self-injection with intraurethral alprostadil (prostaglandin E_1 [medicated urethral suppository]) applied into meatus of penis before intercourse; or intracavernosal injections of vasodilators (e.g., papaverine or prostaglandin E_1). Consider combining intraurethral

alprostadil with PDE5 inhibitor. Relatively high success with self-injection, but attrition is high (Table E3).
- Second-line treatment alternative: Vacuum constriction pump; has variable satisfaction rate.

CHRONIC Rx

- Psychosexual therapy is helpful as an adjunctive treatment.
- Psychogenic impotence: PDE5 inhibitors are effective in patients with depression because tissues, nerves, hormones, and vasculature are normal. PDE5 inhibitors are also effective as a way of providing positive experiences and building sexual confidence. Full psychological evaluation is recommended before starting treatment.
- For men not responding to other approaches: Surgical implantation of penile prosthesis may be considered. Full psychological evaluation is recommended to evaluate the possibility of unrealistic expectations or partner problems contributing to ED.
- Testosterone therapy in men with low testosterone (i.e., hypogonadal); evaluate for prostate cancer before prescribing testosterone.
- Aerobic exercise may improve ED along with pharmacologic treatment.

DISPOSITION

- Psychogenic-acquired ED will remit spontaneously in 15% to 30% of cases.
- Lifelong ED is usually a chronic and unremitting condition.
- Situational ED may remit with changes in social environment and reducing performance anxiety.

REFERRAL

- Refer if psychotherapy, sexual focused therapy, or invasive organic treatment required
- Refer to urology if PDE5 inhibitors fail or sudden onset occurs after penile trauma

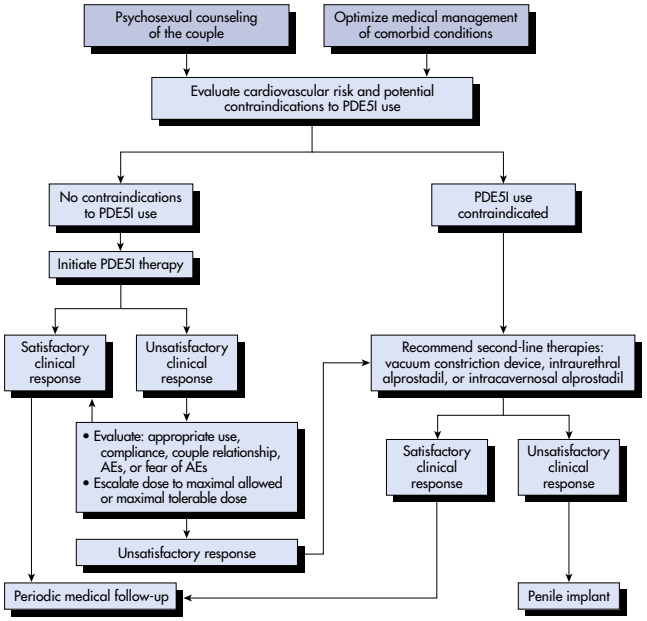

FIG. 1 An algorithmic approach to the treatment of erectile dysfunction in men. *AE,* Adverse effects; *PDE5I,* phosphodiesterase 5 inhibitor. (From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders.)

PEARLS & CONSIDERATIONS

- ED is commonly evaluated and treated by primary care physician; refer to urologist if oral therapy fails or surgery is required.
- PDE5 inhibitors are treatment of choice for most causes of ED. Main contraindications are nitrate use and decompensated cardiac disease. Caution in patients on alpha-adrenergic blockers and with blood pressures at extreme ends (significant hypotension or hypertension).
- For optimal response, patients should be appropriately informed of proper use, precautions, and adverse effects of PDE5 inhibitors. Try six to eight times at optimal doses before declaring PDE5 inhibitors a failure. Consider switching among the four PDE5 inhibitors if one fails.
- Men with ED are at increased risk of coronary, cerebrovascular, and peripheral vascular diseases. Screen for cardiovascular risk factors in these patients.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Erectile Dysfunction (Patient Information)
Ejaculation and Orgasm Disorders (Related Key Topic)
Hypogonadism, Male (Related Key Topic)

AUTHOR: **John P. Wincze, PhD**

TABLE 2 Comparison of Four Phosphodiesterase Type 5 Inhibitors Currently Available in the United States

	Sildenafil	Vardenafil	Tadalafil	Avanafil
C_{max} (ng/ml)	450	20.9	378	2153
T_{max} (hr)	0.8	0.7-0.9	2	0.3-0.5
Onset of action (min)	15-60	15-60	15-120	15-60
Half-life (hr)	3-5	4-5	17.5	3-5
Bioavailability	40%	15%	Not tested	30%
Fatty food	Reduced absorption	Reduced absorption	No effect	Reduced absorption
Recommended dosage	25, 50, 100 mg	5, 10, 20 mg	5, 10, 20 mg	50, 100, 200 mg
Side effects				
Headache, dyspepsia, facial flushing	Yes	Yes	Yes	Yes
Backache, myalgia	Rare	Rare	Yes	Rare
Blurred/blue vision	Yes	Rare	Rare	No
Precaution with antiarrhythmics	No	Yes	No	No
Contraindication with nitrates	Yes	Yes	Yes	Yes

C_{max}, Maximal plasma concentration; *half-life,* time required for elimination of one half of the medication from plasma; *T_{max},* time required to attain C_{max}.
From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

SUGGESTED READINGS

Chung JH et al: Safety and efficacy of once daily administration of 50 mg mirodenafil in patients with erectile dysfunction: a multicenter, double-blind, placebo controlled trial, *J Urol* 189:1006-1013, 2013.

Gupta BP et al: The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction, *Arch Intern Med* 171(20):1797-1803, 2011.

Rew KT, Heidelbaugh JJ: Erectile dysfunction, *Am Fam Phys* 94(10):820-827, 2016.

Shah N et al: Cardiovascular disease prevention in men with vascular erectile dysfunction: the view of the preventive cardiologist, *Am J Med* 129:251-259, 2016.

Wincze JP, Weisberg RB: *Sexual dysfunction: a guide for assessment and treatment*, ed 3, NY, 2015, Guilford Press.

TABLE E3 Guidelines for Intracavernosal Therapy

1. Do not prescribe intracavernosal therapy to men who have psychiatric disorders, hypercoagulable states, or sickle cell disease; who are receiving anticoagulant therapy; or who are unable to comprehend the risks or take appropriate action should complications occur.
2. Designate a physician or a urologist to be available to handle emergencies related to complications of intracavernosal injections, such as prolonged erection and priapism.
3. Instruct the patient in the injection technique, the risks of intracavernosal therapy, and the steps to be taken in the event of prolonged erection or priapism.
4. Administer the first injection in the office, and observe the blood pressure and heart rate response. This provides an excellent opportunity for educating the patient, observing adverse effects, and determining whether the patient will respond to intracavernosal therapy.
5. Start with a low dose of alprostadil and titrate the dose based on the erectile response and the duration of erection. Adjust the dose of alprostadil to achieve an erection that is sufficient for sexual intercourse but does not last more than 30 min.
6. If the erection does not abate in 30 min, the patient should be instructed to take a tablet of pseudoephedrine or terbutaline (Brethine) or an intracavernosal injection of phenylephrine. If this is not effective, the patient should call the designated physician or urologist and go to the emergency department.

From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders, Elsevier.

Erysipelas PTG

BASIC INFORMATION

DEFINITION

Erysipelas is a type of cellulitis caused by infection of the superficial layers of the skin and cutaneous lymphatics. Erysipelas is characterized by redness, induration, lymphangitis, lymphadenopathy, and a sharply demarcated, raised border.

SYNONYM

St. Anthony's fire

ICD-10CM CODE
A46 Erysipelas

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT AGE: Occurs most often in the young or old
RISK FACTORS: Patients with impaired lymphatic or venous drainage (mastectomy, saphenous vein harvesting) and immunocompromised patients. Athlete's foot is a common portal of entry.
RECURRENCE RATE: Relatively common

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Distinctive red, warm, tender skin lesion with induration and a sharply defined, advancing, raised border (Fig. E1).
- Most common sites are lower extremities and face.
- Systemic signs of infection (fever) are often present.
- Vesicles or bullae may develop.
- After several days, lesions may appear ecchymotic.
- After 7 to 10 days, desquamation of affected area may occur.

ETIOLOGY

- Usually group A β-hemolytic streptococci (GABHS)
- Less often group B, C, or G streptococci
- Rarely *Staphylococcus aureus*

COMPLICATIONS

- Abscess
- Necrotizing fasciitis
- Thrombophlebitis
- Gangrene
- Metastatic infection

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other types of cellulitis
- Necrotizing fasciitis
- Deep vein thrombosis
- Stasis dermatitis
- Erythema nodosum
- Contact dermatitis
- Erythema migrans (Lyme disease)
- Insect bite
- Herpes zoster
- Erysipeloid
- Acute gout
- Pseudogout

WORKUP

History, physical examination, and laboratory evaluation

LABORATORY TESTS

Diagnosis is usually made by characteristic clinical setting and appearance.

- Complete blood count: White blood cell count often elevated
- Blood cultures positive in 5% of patients. Septic, or there is a history of animal bites for immersion injury and are not routinely indicated unless the host is immunocompromised
- Gram stain and culture of any drainage from skin lesions has low yield
- Culture of aspirated fluid from leading edge of skin lesion has low yield

IMAGING STUDIES

- Not routinely indicated
- Duplex ultrasound for patients suspected of having deep vein thrombosis
- CT scan or MRI for patients with suspected necrotizing fasciitis

TREATMENT

NONPHARMACOLOGIC THERAPY

- Elevation of the affected limb
- Warm compresses

ACUTE GENERAL Rx

Typical erysipelas of extremity in nondiabetic patient:

- PO: Penicillin V 500 mg q6h. Use clindamycin in patients who are allergic to penicillin.
- IV: Penicillin G (aqueous) 1 to 2 million units q6h. Use vancomycin 15 mg/kg IV q12h in penicillin-allergic patients.

Facial erysipelas (include coverage for *Staphylococcus aureus*):

- PO dicloxacillin 500 mg q6h
- IV nafcillin or oxacillin 2 g q4h
- IV vancomycin 1 g q12h
- Daptomycin 4 mg/kg IV q24h
- Linezolid 600 mg IV q12h

DISPOSITION

Prognosis is good with antibiotic treatment but recurrence is common.

REFERRAL

For surgical debridement for patients with necrotizing fasciitis or for drainage of abscess

PEARLS & CONSIDERATIONS

- Consider early surgical referral when necrotizing fasciitis suspected. Consider skin biopsy when not responding to appropriate antibiotics.
- Look for tinea pedis as portal of entry in erysipelas of lower extremities, and treat if present.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Erysipelas (Patient Information)
Cellulitis (Related Key Topic)

AUTHOR: **Gail M. O'Brien, MD**

SUGGESTED READING

Smith E et al: Which outcomes are reported in cellulitis trials? *Br J Dermatol* 178(5):1028-1034, 2018.

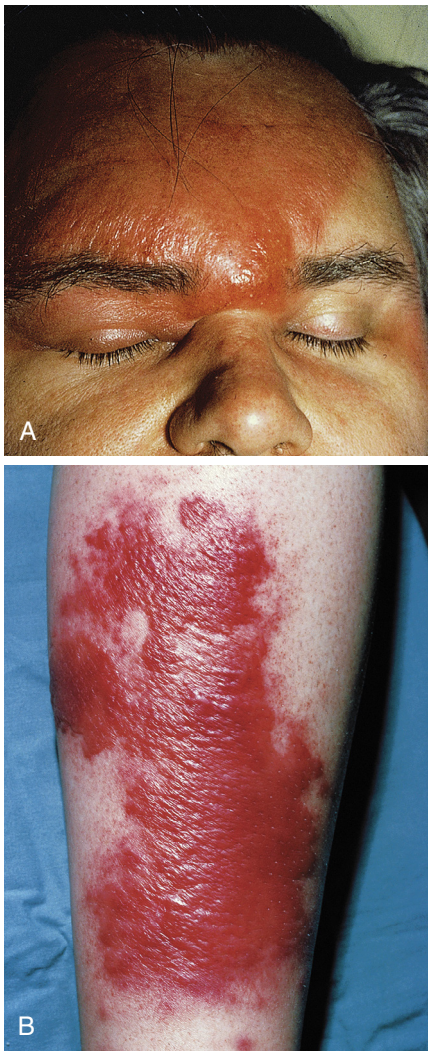

FIG. E1 A and B, Erysipelas. (From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

Erythema Elevatum Diutinum

BASIC INFORMATION

DEFINITION

Erythema elevatum diutinum (EED) is a chronic form of leukocytoclastic vasculitis consisting of violaceous, red-brown, or yellowish papules, plaques, or nodules that favor the extensor surfaces.

EED may occur in association with infections, hematologic abnormalities, autoimmune diseases, or other conditions.

SYNONYM

EED

ICD-10CM CODE
L951 Erythema elevatum diutinum

EPIDEMIOLOGY & DEMOGRAPHICS

- EED is a rare disease.
- It most frequently affects young and middle-aged adults between the ages of 30 and 60 yr.
- There is no known sex or racial predilection.

ASSOCIATED FACTORS

- Infections: HIV infection, beta-hemolytic streptococcal infections, hepatitis, and tuberculosis.
- Hematologic disorders: Plasma cell dyscrasias (particularly IgA monoclonal gammopathies), myelodysplasia, myeloproliferative disorders, B-cell lymphoma, and hairy cell leukemia. EED may appear yrs after the diagnosis of the hematologic disease.
- Autoimmune disease: Inflammatory bowel disease, rheumatoid arthritis, celiac disease, relapsing polychondritis, lupus erythematosus, granulomatous polyangiitis, and dermatomyositis.
- Other sporadic reports of disease associations include breast carcinoma and dermatitis herpetiformis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- EED most commonly manifests as a bilateral eruption of violaceous, red-brown, or yellowish papules, plaques, or nodules.
- Early EED tends to be soft and erythematous.
- Older lesions are often more firm secondary to fibrosis.
- EED is most frequently found on acral skin and periarticular skin.
- The extensor surfaces of the elbows (Fig. E1), knees, ankles, hands, and fingers (Fig. E2) are commonly involved.
- Less frequently involved sites include the face, retroauricular area, trunk, axillae, buttocks, and genitalia.
- Nodular lesions progressing to bulky masses appear to be more common in patients with EED associated with human immunodeficiency virus (HIV) infection.
- Additional reported presentations of EED include annular plaques with raised borders, verrucous plaques on the soles, and vesicobullous presentations.
- The cutaneous manifestations of EED may be asymptomatic or associated with a burning or stinging sensation or pruritus (especially in early stages).
- Extracutaneous symptoms include arthralgia, fever, or other constitutional symptoms.
- Ocular abnormalities such as peripheral keratitis, nodular scleritis, panuveitis, and blindness also have been reported.

ETIOLOGY

- The pathogenesis of EED is not well understood.
- It appears to be a form of immune complex–mediated vasculitis.
- The cutaneous findings may result from the deposition of immune complexes in small blood vessels in the skin, leading to complement activation, neutrophilic infiltration, and the release of destructive enzymes.
- Direct immunofluorescence studies reveal perivascular deposition of complement, IgG, IgM, IgA, and fibrin in EED.
- In vitro studies suggest that activation of cytokines such as interleukin-8 contributes to selective recruitment of leukocytes to affected skin.
- Antineutrophil cytoplasmic antibodies (ANCA) may also be pathogenic in EED.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Granuloma faciale
- Sweet syndrome
- Rheumatoid neutrophilic dermatitis
- Palisaded neutrophilic and granulomatous dermatitis
- Rheumatoid nodules
- Multicentric reticulohistiocytosis
- Sarcoidosis
- Leprosy

FIG. E1 Erythema elevatum diutinum. Nodules typically form over the extensor surfaces of the knuckles and other joints. (Firestein GS et al: *Kelley's textbook of rheumatology,* Philadelphia, 2013, WB Saunders.)

WORKUP/LABORATORY TESTS/ IMAGING STUDIES

- Complete blood count, comprehensive metabolic panel
- Human immunodeficiency virus (HIV) test
- Immunofixation electrophoresis
- Streptozyme test
- Hepatitis B and C serology
- Antinuclear antibody (ANA)
- Antineutrophil cytoplasmic antibodies
- Anti-nDNA antibody, antiphospholipid antibodies
- Chest radiograph, urinalysis
- Specific testing for other infections or autoimmune diseases should be based upon the presence of suggestive signs, symptoms, or patient history

TREATMENT

NONPHARMACOLOGIC THERAPY

Local surgical excision can be beneficial for localized fibrotic nodules of EED.

ACUTE GENERAL Rx

Dapsone (with or without glucocorticoids) is the medical treatment of choice for EED.

CHRONIC Rx

Dapsone, colchicine, methotrexate, tetracycline

DISPOSITION

- EED usually has a prolonged course, characterized by fluctuating periods of exacerbation and stability.
- The disease may resolve spontaneously after 5 to 10 yr; however, persistence up to 40 yr has occurred.
- EED does not progress to systemic vasculitis.
- Recurrence is common after cessation of dapsone.

PEARLS & CONSIDERATIONS

- EED is a rare form of leukocytoclastic vasculitis consisting of violaceous, red-brown, or yellowish papules, plaques, or nodules that favor the extensor surfaces.
- It may occur in association with infections, hematologic disorders, or autoimmune diseases.
- The diagnosis of EED is made based upon correlation of the clinical and histologic findings.
- Treatments for EED have included local medications, systemic medications, and surgery.
- In addition, the associated underlying disease (when present) should be treated.
- Erythema elevatum diutinum exhibits a prolonged relapsing-remitting course.

REFERRAL

Ophthalmology, dermatology, rheumatology

AUTHOR: **Catherine E. Najem, MD**

FIG. E2 Erythema elevatum diutinum. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

Erythema Multiforme PTG

BASIC INFORMATION

DEFINITION

Erythema multiforme is an inflammatory disease characterized by eruption of annular, maculopapular lesions with dark raised, erythematous, or vesiculobullous center surrounded by a pale zone. It is believed to be caused by immune complex formation and subsequent deposition in the skin and mucous membranes. It is considered a hypersensitivity reaction to infection or drugs.

SYNONYM

EM

ICD-10CM CODES

L51.0 Nonbullous erythema multiforme
L51.8 Other erythema multiforme
L51.9 Erythema multiforme, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT AGE: 20 to 40 yr
RISK FACTORS: Often associated with herpes simplex and other infectious agents, drugs, or connective tissue diseases

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Prodromal symptoms are mild or absent. Itching or burning at the site of eruption may occur.
- Symmetric skin lesions (Fig. E1) with a classic "target" appearance (caused by the centrifugal spread of red maculopapules to circumference of 1 to 3 cm with a purpuric, cyanotic, or vesicular center) are present (Fig. E2). The papules may enlarge into plaques measuring a few centimeters in diameter with a dark or red central portion (Fig. E3). Target lesions may not be apparent for several days and generally heal in 1 to 2 wk without scarring.
- EM lesions are most common on the face, back of the hands and feet, and extensor aspect of the forearms and legs (EM minor). Trunk involvement can occur in severe cases (EM major).
- Urticarial papules, vesicles, and bullae may also be present and generally indicate EM major.
- EM major bullae and erosions may also be present in the oral cavity. The most common sites are the lips and buccal mucosa.

ETIOLOGY

- Immune complex formation and subsequent deposition in the cutaneous microvasculature may play a role in the pathogenesis of erythema multiforme.
- The majority of cases follow outbreaks of herpes simplex virus 1 and 2.
- *Mycoplasma pneumoniae,* fungal infections, medications (bupropion, sulfonamides, penicillins, nonsteroidal antiinflammatory drugs, barbiturates, phenothiazines, hydantoins).
- In >50% of patients no specific cause is identified.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Chronic urticaria
- Pityriasis rosea
- Contact dermatitis
- Pemphigus vulgaris
- Lichen planus
- Serum sickness
- Drug eruption
- Granuloma annulare
- Polymorphic light eruption
- Viral exanthema
- Stevens-Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)
- Bullous pemphigoid
- Viral exanthems
- Leukocytoclastic vasculitis
- Lupus erythematosus
- Secondary syphilis

WORKUP

- Medical history with emphasis on drug ingestion.
- Laboratory evaluation in patients with suspected collagen-vascular diseases.
- Skin biopsy when diagnosis is unclear.

LABORATORY TESTS

- Complete blood count with differential, elevated ESR
- Antinuclear antibody
- Serology for *Mycoplasma pneumoniae,* HSV-1, HSV-2
- Biopsy for atypical cases
- Direct immunofluorescence if suspecting bullous diseases

TREATMENT

NONPHARMACOLOGIC THERAPY

- Mild cases generally do not require treatment; lesions resolve spontaneously within 1 mo.
- Potential drug precipitants should be removed.

ACUTE GENERAL Rx

- Treatment of associated diseases (e.g., valacyclovir or famciclovir for herpes simplex, erythromycin for *Mycoplasma* infection).
- Dapsone, antimalarials, or azathioprine for severe or resistant cases.
- Prednisone 40 to 80 mg/day for 1 to 3 wk is effective for decreasing inflammation and pain and may be tried in patients with many target lesions; however, the role of systemic steroids remains controversial.
- Levamisole, an immunomodulator, may be effective in the treatment of patients with chronic or recurrent oral lesions (dose is 150 mg/day for 3 consecutive days used alone or in combination with prednisone).
- IV immunoglobulins in severe cases.
- Antimicrobial therapy is indicated if *M. pneumoniae* is the trigger of EM.

DISPOSITION

The rash generally evolves over a 2-wk period and resolves within 3 to 4 wk without scarring. A severe bullous form can occur (see entry for "Stevens-Johnson Syndrome").

REFERRAL

Hospital admission in patients with suspected Stevens-Johnson syndrome

PEARLS & CONSIDERATIONS

COMMENTS

The risk of recurrence of erythema multiforme exceeds 30%. Recurrence may be treated with valacyclovir 500 to 1000 mg/day, famciclovir 125 to 250 mg/day, or acyclovir 400 mg bid. Dapsone, antimalarials, azathioprine, or cyclosporine use is reserved for cases resistant to antivirals.

RELATED CONTENT

Erythema Multiforme (Patient Information)
Stevens-Johnson Syndrome (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

FIG. E1 Erythema multiforme (EM). Round erythematous swollen plaques and target lesions on the palms. This girl developed EM in association with her systemic lupus erythematosus. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E2 Erythema multiforme. Classic target lesions and marginated wheals with central vesicles are characteristic. (From Paller AS, Mancini, AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E3 Erythema multiforme. Extensive target lesions on the thighs of a 12-yr-old girl. The recurrent reaction was suppressed by administration of oral acyclovir. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Erythema nodosum (EN) is an acute, tender, erythematous, nodular skin eruption resulting from inflammation of subcutaneous fat, often associated with bruising. It is the most common form of panniculitis.

SYNONYM

EN

ICD-10CM CODE
L52 Erythema nodosum

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: It is the most common form of panniculitis. Two to three cases/100,000 persons per yr.
PREDOMINANT SEX: Female:male ratio of 3 to 4:1
PREDOMINANT AGE: 25 to 40 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Prodromal symptoms of fatigue, malaise, upper respiratory infection symptoms may precede eruption by 1 to 2 wk.
- Acute onset of tender nodules typically located on the shins and occasionally seen on the thighs and forearms (Fig. E1).
- The nodules are usually 1/8 to 1 inch in diameter but can be as large as 4 inches; they begin as light red lesions, then become darker and often ecchymotic. The nodules heal within 8 wk without ulceration.
- Associated findings:
  1. Fever (60%)
  2. Lymphadenopathy (<50%)
  3. Arthralgia (64%)
  4. Signs of the underlying illness

ETIOLOGY

Cell-mediated hypersensitivity reaction is seen more frequently in persons with human leukocyte antigen (HLA) B8. The lesion results from an exaggerated interaction between an antigen and cell-mediated immune mechanisms leading to granuloma formation. Up to 55% of cases of EN are idiopathic.
Infections:
- Bacteria:
  1. Campylobacter
  2. Streptococcal pharyngitis (28% to 48%)
  3. *Salmonella* enteritis
  4. *Yersinia* enteritis
  5. Psittacosis
  6. *Chlamydia pneumoniae* infection
  7. *Mycoplasma* pneumonia
  8. Meningococcal infection
  9. Gonorrhea
  10. Syphilis
  11. Lymphogranuloma venereum
  12. Tularemia
  13. Cat-scratch disease
  14. Leprosy
  15. Tuberculosis
- Fungi:
  1. Histoplasmosis
  2. Coccidioidomycosis
  3. Blastomycosis
  4. *Trichophyton verrucosum*
- Viruses:
  1. Cytomegalovirus
  2. Hepatitis B
  3. Epstein-Barr virus
- Drugs (3% to 10%):
  1. Sulfonylureas
  2. Sulfonamides
  3. Penicillins
  4. Oral contraceptives
  5. Gold salts
  6. Prazosin
  7. Aspirin
  8. Bromides
- Sarcoidosis (11% to 25%)
- Inflammatory bowel disease
- Hodgkin disease, non-Hodgkin lymphoma
- Ankylosing spondylosis and reactive arthropathies (e.g., associated with inflammatory bowel disease)
- Behçet disease
- Löfgren syndrome
- Acute myelogenous leukemia

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Insect bites
- Posttraumatic ecchymoses
- Vasculitis
- Weber-Christian disease
- Fat necrosis associated with pancreatitis
- Necrobiosis lipoidica
- Scleroderma
- Lupus panniculitis
- Subcutaneous granuloma

WORKUP

- Physical examination
- Diagnosis of underlying illness by history, physical examination, and laboratory tests as indicated

LABORATORY TESTS

- Erythrocyte sedimentation rate
- Throat culture and antistreptolysin O titer
- Purified protein derivative
- Others depending on index of suspicion (e.g., stool culture and evaluation for ova and parasites in patients with diarrhea and gastrointestinal symptoms)
- Skin biopsy in doubtful cases:
  1. Early lesion: Inflammation and hemorrhage in subcutaneous tissue
  2. Late lesion: Giant cells and granulomata

IMAGING STUDIES

Chest radiograph to rule out sarcoidosis and tuberculosis

TREATMENT

- The disease is self-limited and treatment is symptomatic. EN nodules develop in pretibial locations and resolve spontaneously over several weeks without scarring or ulceration.
- Treatment of underlying disorders.
- Avoidance of contact irritation of affected areas.
- Nonsteroidal antiinflammatory drugs for pain.
- Systemic steroids (prednisone 1 mg/kg of body weight/day, tapered over several days) may be useful in severe cases if underlying risk of sepsis and malignancy have been excluded.
- Potassium iodide given as tablet 300 mg tid or as a supersaturated solution (five drops three times/day in orange juice) has been reported as effective for symptom control.
- Intralesional corticosteroid injections for persistent lesions.

PROGNOSIS

Typical case:
- Pain for 2 wk
- Resolution within 8 wk

RELATED CONTENT

Erythema Nodosum (Patient Information)
Sarcoidosis (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

FIG. E1 Erythema nodosum. Tender, red, oval nodules on the extensor aspect of the legs. Note that several have darkened and resemble bruises. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

Esophageal Tumors ALG PTG

BASIC INFORMATION

DEFINITION

Esophageal tumors include benign and malignant neoplasms of the esophageal mucosa and wall. Carcinomas of the esophageal epithelium, both squamous cell carcinoma and adenocarcinoma (including adenoacanthoma, mucoepidermoid, and adenoid cystic), are the most common tumors of the esophagus. Rare esophageal tumors include both malignant (spindle cell, small cell, sarcoma, lymphoma, melanoma, and choriocarcinoma) and benign neoplasms (leiomyoma, papilloma, and fibrovascular polyps). One can also develop metastatic disease from a cancer that originated in another organ, but this is very rare. Breast cancer, lung cancer, and melanoma would be the most likely culprits. Approximately 15% of esophageal tumors arise in the proximal esophagus, 50% in the middle third of the esophagus, and 35% in the lower third. Tumors involving the esophageal-gastric junction are usually staged and treated as esophageal cancers if the tumor epicenter is no more than 2 cm into the proximal stomach. Tumors in the upper two thirds are usually squamous cell cancers, and tumors in the lower third are usually adenocarcinomas. The incidence of superficial esophageal cancers is increasing. These invade no deeper than the submucosa.

ICD-10CM CODES

C15.X	Malignant neoplasm of the esophagus (X defines location)
C15.3	Malignant neoplasm of upper third of esophagus
C15.4	Malignant neoplasm of middle third of esophagus
C15.5	Malignant neoplasm of lower third of esophagus
D00.2	Carcinoma of esophagus, in situ

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: It is the eighth most common cancer worldwide and the seventh leading cause of cancer deaths. Rates are increasing every decade and are highest in the Asian esophageal cancer belt, extending from the Caspian Sea to northern China, with certain high-incidence pockets in Finland, Ireland, southeast Africa, and northwest France. Incidence has increased six-fold since 1975. Foods including cured meats and spicy regional fare likely play a role in certain areas. Rates of squamous cell carcinoma are decreasing while those of adenocarcinomas are dramatically increasing. The causes of squamous cell carcinoma most commonly include tobacco and alcohol abuse. Epithelial dysplasia usually occurs, which progresses to carcinoma in situ. Adenocarcinomas are usually the result of GERD and obesity. The mucosa of the esophagus undergoes intestinal metaplasia. Genetic alterations occur, which perpetuate the cell changes during proliferation.

PREVALENCE: In the U.S., there was an estimated 16,000 new cases and 15,000 deaths are reported yearly, making it the seventh leading cause of death by cancer among men. The majority of cases are diagnosed at an advanced stage (unresectable or metastatic disease).

RACE, AGE, & SEX PREDOMINANCE: In the U.S., squamous cell esophageal cancer is more common among those of African descent than whites, whereas adenocarcinoma is more common in whites than in those of African descent. The overall male:female ratio is 3 to 4:1; the highest male/female ratio is in the Hispanic population. It usually develops in the fifth to seventh decades and is associated with lower socioeconomic status.

GENETICS: Increasing evidence shows that genetics may play a role by increasing susceptibility to esophageal cancer. One well-identified disease associated with esophageal cancer is tylosis (focal non-epidermolytic palmoplantar keratoderma), linked to loss of heterozygosity on chromosome 17q. Familiar clustering of Barrett esophagus and the recent identification of germline mutations in affected sibling pairs support a genetic link to esophageal adenocarcinoma. Also, up to 35% of esophageal adenocarcinomas can have overexpression of HER2, which can lead to the use of targeted therapy (trastuzumab) in the treatment plan.

CLINICAL PRESENTATION

Symptoms and signs:

- Dysphagia (74%): Initially with solid foods, gradually progresses to semisolids and liquids; the latter signs usually indicate incurable disease with tumor involving more than 60% of the esophageal circumference. It may be felt as chest pain
- Unintentional weight loss: Usually of short duration. Losing >10% of body mass predicts poor outcome
- Hoarseness: Suggests recurrent laryngeal nerve involvement
- Odynophagia and halitosis: Unusual symptoms
- Cervical adenopathy: Usually involving supraclavicular lymph nodes
- Dry cough: Suggests tracheal involvement
- Aspiration pneumonia: Caused by fistula between the esophagus and trachea
- Iron deficiency anemia: Related to chronic GI blood loss
- Massive hemoptysis or hematemesis from the invasion of vascular structures
- Advanced disease spreads to lymph nodes, liver, lungs, peritoneum, and pleura
- Hypercalcemia: Associated with squamous cell carcinoma from secretion of a parathyroid-like tumor peptide

Clinical findings:

- 50% to 60% of patients present with the inoperative stage of their disease (locally advanced, regional, or metastatic).

ETIOLOGY

The pathogenesis of esophageal cancers is attributable to chronic recurrent oxidative damage from any of the following etiologic agents, which cause inflammation, and esophagitis, increased cell turnover, and, ultimately, initiation of the carcinogenic process.

ETIOLOGIC AGENTS: Squamous cell carcinoma

- Excess alcohol consumption is strongly associated with squamous cell esophageal cancer in the United States; hard liquor is associated with a higher incidence than wine or beer.
- Tobacco and alcohol synergistically increase risk for squamous cell cancer
- Other ingested carcinogens:
  1. Nitrates (converted to nitrites): South Asia, China
  2. Smoked opiates: Northern Iran
  3. Fungal toxins in pickled vegetables
  4. Betel nut chewing
- Mucosal damage:
  1. Long-term exposure to extremely hot tea (>70 °C [158 °F])
  2. Lye ingestion
- Radiation-induced strictures
- Achalasia: Incidence of esophageal cancer is seven times greater in this population
- Host susceptibility as a result of precancerous lesions:
  1. Plummer-Vinson syndrome (Paterson-Kelly): Glossitis with iron deficiency
  2. Congenital hyperkeratosis and pitting of palms and soles (tylosis)
- Human papillomavirus infection (particularly types 16 and 18) has been variably detected in squamous cell carcinoma of the esophagus, sometimes associated with p53 tumor suppressor gene mutations
- Questionable relationship with prolonged bisphosphonate use (≥10 prescriptions, or use >3 yr)
- Possible association with celiac sprue or dietary deficiencies of molybdenum, selenium, zinc, vitamin A

ADENOCARCINOMA: The incidence of adenocarcinoma is continually rising, whereas that of squamous cell carcinoma is unchanged.

- Smoking increases the risk of developing adenocarcinoma, particularly in patients with Barrett.
- Obesity, hiatal hernia, and diets lacking in fresh fruit and vegetables and high in fat (particularly from red meat and processed foods).
- Chronic GERD leading to Barrett metaplasia and adenocarcinoma via immune cell infiltration and production of inflammatory mediators and reactive oxygen species. The annual rate of transformation from Barrett to adenocarcinoma is <0.5%.
- *H. pylori* infection may reduce the risk of adenocarcinoma.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Achalasia
- Scleroderma of the esophagus
- Diffuse esophageal spasm
- Esophageal rings and webs

LABORATORY TESTS

Complete blood cell count, blood chemistry, and liver enzymes should be obtained at diagnosis. No biomarkers are currently recommended to

diagnose, monitor, or predict outcomes. While both the CEA and CA-19-9 can be elevated in patients with esophageal cancer (up to 70%), the sensitivity is low (18 % to 35%) and there is no proven predictive value.

IMAGING STUDIES

Imaging studies are important not only for diagnosis but for accurate staging:

- Esophagogastroduodenoscopy (EGD) (Fig. E1) should be performed initially to visualize smaller tumors, which may be missed by esophagogram, and to allow histopathologic confirmation.
- Endoscopic inspection of the larynx, trachea, and bronchi may identify concomitant cancers of head, neck, and lung ("triple endoscopy").
- Endoscopic ultrasound (EUS) (Fig. E1) appears to be the most accurate method for locoregional staging: to determine the depth of tumor invasion and to assess for and possibly obtain fine needle aspiration biopsies of suspicious lymph nodes.
- PET CT has become the standard of care, along with EUS, for the most accurate staging. These modalities can determine tumor spread for preoperative staging. CT scans of the chest (Fig. E2) and abdomen are more useful for restaging patients after initial therapy.
- Staging laparoscopy may alter treatment plans in 20% to 30% of cases by more accurately staging regional lymph nodes and detecting occult peritoneal metastases.
- Double-contrast esophagogram effectively identifies large esophageal lesions.
  1. In contrast to benign esophageal leiomyomata, which cause narrowing with preservation of normal mucosal pattern, esophageal carcinomas cause ragged ulcerating mucosal changes in association with deeper infiltration.

STAGING

Table 1 describes the TNM staging system for cancer of the esophagus from the American Joint Committee on Cancer Criteria. Fig. 3 illustrates an algorithm for staging thoracic esophageal cancer.

TABLE 1 TNM Staging System for Cancer of the Esophagus (American Joint Committee on Cancer Criteria)

Primary Tumor (T)*	
T_X	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_{is}	High-grade dysplasia†
T_1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T_{1a}	Tumor invades lamina propria or muscularis mucosae
T_{1b}	Tumor invades submucosa
T_2	Tumor invades muscularis propria
T_3	Tumor invades adventitia
T_4	Tumor invades adjacent structures
T_{4a}	Resectable tumor invading pleura, pericardium, or diaphragm
T_{4b}	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.
Lymph Node (N)‡	
N_X	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Metastasis in 1-2 regional lymph nodes
N_2	Metastasis in 3-6 regional lymph nodes
N_3	Metastasis in 7 or more regional lymph nodes
Distant Metastasis (M)	
M_X	Metastasis cannot be assessed
M_0	No distant metastasis
M_1	Distant metastasis

TNM, tumor, node, metastases.
*(1) At least maximal dimension of the tumor must be recorded and (2) multiple tumors require the T(m) suffix.
†High-grade dysplasia includes all noninvasive neoplastic epithelia that was formerly called carcinoma in situ.
‡Number must be recorded for total number of regional nodes sampled and total number of reported nodes with metastasis.
From Edge S et al (eds): *AJCC cancer staging manual,* ed 7, New York, 2010, Springer.

Rx TREATMENT

TREATMENT OF ALL STAGES OF ESOPHAGEAL CANCER:

Although the histology of esophageal cancer can differ, most studies have combined tissue types in exploring treatment options. The histology develops secondary to differing pathogenesis and causative agents with tumor biology likely playing a role through varying mutations. The likelihood of response and prognosis can differ as well. However, as there is a lack of data on how histology should dictate the treatment approach, we therefore generally attack this cancer in a uniform manner as most studies have suggested the optimum benefit be obtained through a neoadjuvant chemoradiation approach followed by surgery when applicable in up to stage III disease.

COMBINATION THERAPY: CHEMORADIOTHERAPY FOLLOWED BY SURGICAL RESECTION: Induction chemotherapy that occurs before chemoradiation for patients with locally advanced but still possibly resectable disease has been given with good results. However, no studies have shown this being superior to chemoradiation alone. It can, however, provide relief of dysphagia. Standard fractionation 3D-RT is used in chemoradiotherapy.

- Chemotherapy is most often given with concurrent radiotherapy. Chemotherapy acts as a radiosensitizer and makes tumor cells more vulnerable to the effects of ionizing radiation, thus improving tumoricidal effects on cancer. Neoadjuvant chemoradiotherapy followed by surgery is the most common approach for patients with resectable disease but is employed primarily for patients with stage IIA or higher disease. Five-yr survival is improved with neoadjuvant approach (39%) versus surgery alone (16%). Several trials have now shown that preoperative therapy improves survival among patients with potentially curable esophageal or esophagogastric junction cancer. Neoadjuvant chemotherapy alone is another option for locally advanced disease, but results are not as good as with neoadjuvant chemoradiotherapy.
- Chemoradiotherapy followed by surgery should be offered to late stage I ($T_{1b}N_0$ or higher), stage II, and stage III esophageal cancer patients as the current standard of care. In several studies, this approach significantly improved local control, reduced recurrence, and reduced mortality compared with surgery alone in patients with resectable esophageal cancer. Trimodality therapy is the preferred treatment for most esophageal cancers.
- Chemoradiotherapy alone may be offered as the definitive treatment for patients who are not surgical candidates, and some of these patients may be cured.
- Combination chemotherapy using a platinum doublet (platinum agent plus second agent) can achieve significant tumor reduction in 30% to 60% of patients. Cisplatin, oxaliplatin, or carboplatin is usually given with 5-FU (5-fluorouracil) or paclitaxel to obtain the desired tumoricidal effects. Other chemotherapeutic agents with activity in esophageal cancer include irinotecan, epirubicin, and docetaxel.
- Capecitabine in combination with either cisplatin or oxaliplatin is as effective as 5FU in the neoadjuvant or definitive treatment setting.
- Complications of chemoradiotherapy primarily include mucositis, nausea, vomiting, diarrhea, myelosuppression, nephrotoxicity, ototoxicity, neurotoxicity with peripheral neuropathy, esophageal stricture, esophageal rupture, trachea-esophageal fistula (6%), and radiation pneumonitis. These can occur to varying degrees and are certainly more significant in the elderly and those with significant comorbidities.
- Postoperative adjuvant chemoradiotherapy should be offered to node-positive patients who underwent initial surgery alone.

SURGICAL RESECTION:

- Surgical resection of squamous cell carcinoma and adenocarcinoma of the middle esophagus and lower third of the esophagus is an acceptable initial modality for local and resectable disease in the absence of widespread metastases detected by CT-PET and transesophageal ultrasound (T_1 and T_2 tumors). Gastric pull-through or colonic interposition typically is used to provide luminal continuity.
- Endoscopic mucosal resection may replace radical surgical resection in patients with dysplasia and some small early tumors with no lymph node involvement (T_{is} or T_{1a}), but a recent Cochrane review found no studies comparing endoscopic treatment vs. surgery. Endoscopic mucosal resection may be beneficial for patients who are poor surgical candidates. It may be performed in conjunction with ablative therapies, including radiofrequency ablation, thermal ablation techniques, laser ablation, argon plasma coagulation,

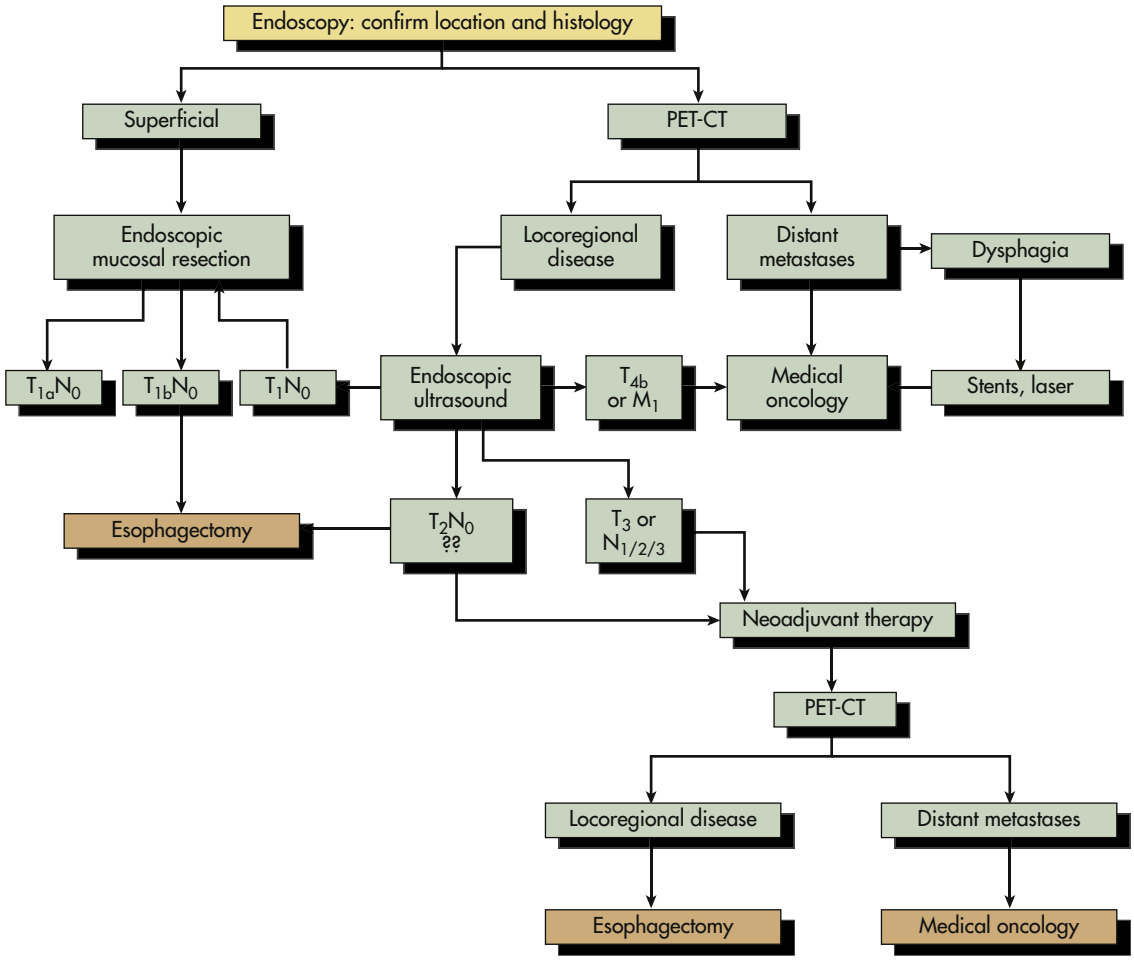

FIG. 3 An algorithm for staging a thoracic esophageal cancer patient. Metastatic disease must always be confirmed by pathologic evaluation of the tissue in question. *PET-CT,* Positron emission tomography–computed tomography. (From Sellke FW et al: *Sabiston & Spencer surgery of the chest,* ed 9, Philadelphia, 2016, Elsevier.)

or photodynamic therapy. Electrocoagulation (electrofulguration) is also being used and may aid in the relief of esophageal blockage.

- Complications of surgery:
  1. Anatomic fistula (usually with colon interposition, subphrenic abscesses).
  2. Respiratory complications.
  3. Cardiovascular complications are most common, including MI, CVA, and PE.
  4. Mortality is lower and clinical outcomes are better at high-volume hospitals and with minimally invasive surgery.
  5. Hybrid minimally invasive esophagectomy has been reported to have a lower incidence of intraoperative and postoperative major complications, specifically pulmonary complications, than open esophagectomy, without compromising overall and disease-free survival over a 3-yr period.[1]

Despite adequate preoperative staging, 25% of patients initially treated with surgical resection will have microscopically positive resection margins and are upstaged at the time of surgery. This has led to the majority of patients receiving neoadjuvant chemoradiotherapy as demonstrated in the CROSS Trial. The median disease-free survival for this group of patients was significantly prolonged as compared with the surgery-alone group. Death from recurrent cancer was decreased by 9% in the neoadjuvant group as well. The benefit of neoadjuvant therapy on survival was consistent regardless of histologic subtype.

PRE-TREATMENT PATIENT PREPARATION

The patient needs to stop smoking and drinking alcohol if at all possible. Before neoadjuvant or definitive chemoradiotherapy, the patient should have placement of an intravenous access device and a feeding tube (J-tube is preferable before surgical resection).

RADIATION THERAPY:

- Squamous cell carcinomas are more radiosensitive. Radiotherapy achieves good local control but is generally only used as monotherapy in a palliative mode for obstructive symptoms in patients with unresectable or advanced cancer or those with multiple comorbidities that limit treatment. It is best used for cervical esophageal tumors, but response rates are best when combined with chemotherapy.
- Radiotherapy in the preoperative/neoadjuvant setting is taken to a total dose of 40 to 50 Gy. For definitive therapy, the dose range is 50 to 55 Gy.
- Palliative radiotherapy for bone metastasis is also effective.
- Complications of radiotherapy: Can best be avoided by 3D conformal therapy.
  1. Esophageal stricture, fistula formation, radiation-induced pulmonary fibrosis, and transverse myelitis are the most common.
  2. Radiotherapy-induced cardiomyopathy and skin changes are rare.

IMRT can also be used for the treatment of esophageal cancers. It is associated with a more favorable toxicity profile. Very few studies have been completed to date using chemotherapy with IMRT and is therefore not considered a standard approach at this time for neoadjuvant therapy.

[1]Mariette C et al: Hybrid minimally invasive esophagectomy for esophageal cancer, *N Engl J Med* 380(2):152-162, 2019.

Brachytherapy: This is also an option for patients in a palliative mode. It provides high-dose radiation to a localized area and may prevent the need for a stent in patients with dysphagia. Its use is very limited in prior irradiated tissue for fear of fistula and perforation of the esophagus.

TREATMENT OF UNRESECTABLE, LOCALLY ADVANCED, OR METASTATIC DISEASE

- Combination chemotherapy regimens as a rule have a higher response rate than single-agent therapy. Response rates can be as high as 50% but that does not always translate into prolonged survival.
- Neoadjuvant chemotherapy regimens can also be utilized in locally advanced or metastatic settings. Cisplatin is probably the most active agent, and this combined with 5FU can yield response rates shown in several studies of 20% to 50%. If a taxane is added to this regimen in the metastatic setting, the triple drug regimen can lead to a prolongation in disease progression by about 2 mo, which may translate into prolonged survival. However, the patients have to be carefully chosen for this triple drug regimen because of increased toxicity. Other active double regimens can combine cisplatin with irinotecan, etoposide, or gemcitabine. Again, capecitabine can be substituted for 5FU in these regimens.

TARGETED MOLECULAR THERAPY

This is only applicable in adenocarcinoma of the esophagus that has overexpression of HER2. There is no apparent role for this treatment in squamous cell carcinoma.

- Ramucirumab is a recombinant monoclonal IgG1 antibody that is a vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist. It inhibits ligand proliferation and migration of endothelial cells and ultimately inhibits angiogenesis. It is indicated for second-line therapy in conjunction with paclitaxel or as third line as monotherapy.
- Trastuzumab, in combination with cisplatin and 5FU, can be used as first-line therapy for metastatic esophageal cancer in patients with HER-2 overexpressing adenocarcinoma. Approximately 22% of adenocarcinomas will overexpress the type II epidermal growth factor receptor HER2. The overall response rate is 47%.

IMMUNOTHERAPY IN ESOPHAGEAL CANCER

- This involves an immune checkpoint inhibitor that targets PD-1.
- Studies have been done using nivolumab and pembrolizumab with varying response rates of 10% to 30% in patients who have progressive disease and failed traditional therapy with at least two previous chemotherapy regimens. Currently, only pembrolizumab is approved in the U.S. for treatment of esophageal cancer.

FOLLOW-UP CARE

The majority of recurrences develop within 12 months. Clinical monitoring, lab tests, imaging, and endoscopic evaluation where appropriate (particularly Barrett), are performed for postoperative surveillance, without clear benefit in earlier detection or decreased mortality. For patients who have undergone definitive therapy, it is recommended that endoscopic surveillance be performed every 3 mo for the first yr, and then annually. Palliative procedures such as repeated endoscopic dilation, endoscopic ablation, endoscopic mucosal resection, photodynamic therapy, brachytherapy, feeding tube insertion, or placement of expandable metal stents or polyvinyl prostheses to bypass tumors have been used for unresectable patients. The morbidity and mortality associated with resection in patients with advanced disease and/or for palliation argues against offering this modality to most of these patients.

SURVIVORSHIP

- Overall 5-yr survival for all stages at presentation is 15% (39% for localized disease, 21% for regional disease, and 4% for distant disease).
- Endoscopic therapy for highly selected stage 0 or stage I patients with disease limited to the submucosa may have 5-yr survival rates of 70% to 90%.
- Surgical resection without neoadjuvant treatment: 5-yr survival rate is 5% to 30%, with higher survival (up to 45% to 50%) in early-stage cancers.
- Radiation therapy without chemotherapy or surgery: 5-yr survival rate of 6% to 20%.
- Chemoradiotherapy without surgery: 5-yr survival up to 30%.
- Combined trimodality treatment: Up to 45% to 50% 5-yr survival rates (all stages of disease treated).
- Patients with metastatic disease have median survivals of less than 1 yr with palliative chemotherapy.

REFERRAL

- To gastroenterologist for endoscopy for patients with dysphagia, odynophagia, or unexplained weight loss, or for palliative care
- To medical oncologist for evaluation of preoperative chemotherapy and care of the metastatic patient
- To radiation oncologist for palliative therapy if tumor is actively bleeding, unresectable, or if obstruction is present
- To hospice if appropriate

PEARLS & CONSIDERATIONS

COMMENTS

More than 50% of patients with esophageal cancer are diagnosed when the disease is metastatic or unresectable.

PREVENTION

- A diet high in fruits, vegetables, and antioxidants may be associated with lower risk of esophageal cancer.
- Avoid tobacco and excessive alcohol use.
- Avoid ingested toxins known to cause esophageal cancers.
- Aspirin may have a chemopreventive role in Barrett but is only currently recommended for patients with other (e.g., cardiac) indications.
- There is no evidence that vitamins, Chinese herbal regimens, or green tea prevent esophageal cancer.
- Screening the general population is not recommended. If Barrett esophagus is detected, regularly scheduled surveillance endoscopies are necessary, with consideration for radiofrequency or other ablation therapy if dysplasia is detected.

PATIENT & FAMILY EDUCATION

Provide education and support about the likely prognosis because most esophageal cancers are diagnosed at an advanced stage.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Esophageal Cancer (Patient Information)
Barrett Esophagus (Related Key Topic)

AUTHOR: **Anthony G. Thomas, DO, FACP**

SUGGESTED READINGS

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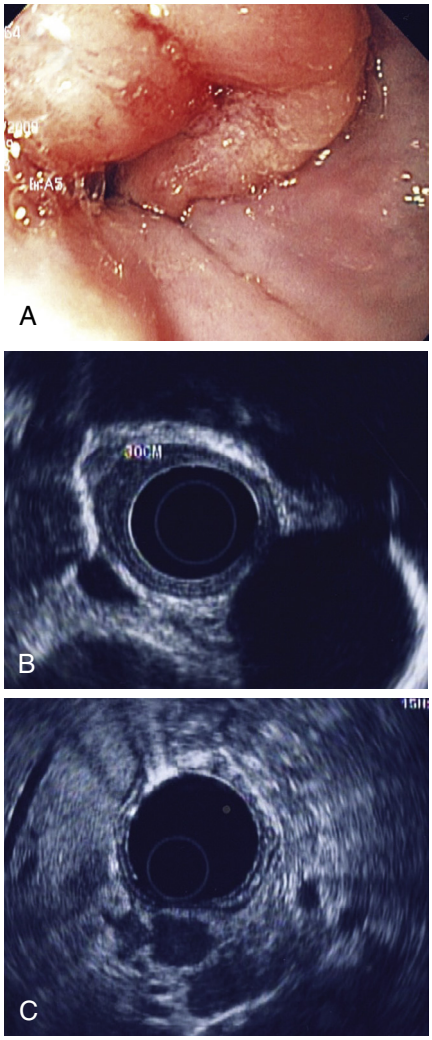

FIG. E1 Esophageal cancer. A, Endoscopic picture of malignant esophageal stricture. **B,** EUS image showing T_3 lesion. **C,** Malignant celiac lymphadenopathy. *EUS,* Endoscopic ultrasound. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, WB Saunders.)

FIG. E2 Computed tomography of the chest showing abnormal thickening of the esophagus suggestive of malignancy. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

Esophageal Varices ALG

BASIC INFORMATION

DEFINITION

Esophageal varices are dilated submucosal veins that occur in patients with underlying portal hypertension, function as a shunt between the portal venous and systemic venous circulation, and can result in severe upper GI hemorrhage.

ICD-10CM CODES

I85.00 Esophageal varices without bleeding
I85.01 Esophageal varices with bleeding

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Esophageal varices: 5% to 15% per yr in patients with cirrhosis
- Hemorrhage:
  1. One third of all patients with varices will develop hemorrhage.
  2. Variceal hemorrhage occurs in 25% to 40% of patients with cirrhosis.
  3. The risk of bleeding from varices is approximately 15% at 1 yr.
  4. Survivors of an episode of active bleeding have a 70% risk of recurrent hemorrhage within 1 yr.

PREVALENCE: Approximately 50% of patients with cirrhosis have varices at the time of diagnosis.

RISK FACTORS: Cirrhosis, low platelet count and advanced Child-Pugh class, hepatitis C with advanced fibrosis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Often asymptomatic until acute upper GI hemorrhage: Hematemesis, hypovolemia
- No physical findings specific for esophageal varices
- Stigmata of cirrhosis and portal hypertension may be evident: palmar erythema, telangiectasias, gynecomastia, testicular atrophy, jaundice, caput medusae, lower extremity edema, ascites, splenomegaly, hemorrhoids, asterixis

ETIOLOGY

- Portal hypertension results from obstruction to portal venous outflow, and varices subsequently develop in order to decompress the hypertensive portal vein and return blood to the systemic circulation.
- Varices may appear when portal vein pressures rise above 10 to 12 mm Hg.
- Cirrhosis is the most common cause of portal hypertension.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Budd-Chiari syndrome, cirrhosis, portal vein thrombosis, schistosomiasis, Wilson disease
- Other causes of upper GI bleeding: Duodenal or gastric ulcers, gastric cancer, Mallory-Weiss tear

WORKUP

Upper endoscopy, laboratory tests, and imaging

LABORATORY TESTS

- CBC:
  1. Anemia (blood loss, nutritional deficiencies, alcohol myelosuppression)
  2. Thrombocytopenia (hypersplenism, alcohol myelosuppression)
- Renal function panel:
  1. BUN: Often increased in setting of upper GI bleeding
  2. Creatinine: Often elevated by hypovolemia, monitor for hepatorenal syndrome
  3. Sodium: Dilutional hyponatremia
- Heme-positive stools
- Type and crossmatch: In preparation for blood transfusion
- INR/PT and PTT: Coagulation factors produced in liver and may be prolonged in liver disease or impairment
- Liver function tests: ALT/AST may be normal in cirrhotic patients due to longstanding fibrosis; elevated alkaline phosphatase and a direct hyperbilirubinemia may be present if cholestatic liver disease is present
- Serum albumin: Severe liver disease results in hypoalbuminemia

IMAGING STUDIES

Invasive:

- Esophagogastroduodenoscopy (EGD) (upper endoscopy):
  1. In all patients with cirrhosis, screen for the presence or absence of varices and determine subsequent risk for variceal hemorrhage.
  2. In patients with small varices (<5 mm) repeat EGD in 2 yr (unless decompensation occurs).
  3. In patients with compensated cirrhosis who do not have varices, screening is repeated every 2 to 3 yr.
  4. In patients with decompensated cirrhosis (ascites, hepatic encephalopathy, variceal hemorrhage, or jaundice), it is repeated every yr or at the time of first decompensation.
  5. Emergently performed if there is evidence of acute upper GI bleeding to diagnose and treat variceal hemorrhage.

Noninvasive:

- Esophagography with barium can diagnose esophageal varices (Fig. E1).
- Capsule endoscopy can also diagnose esophageal varices, although sensitivity is not yet established.
- CT scan (Fig. E2).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Endoscopic variceal ligation (Fig. E3) is an alternative to nonselective beta-blockers for primary prophylaxis against variceal hemorrhage. It is also used in patients unable to tolerate beta-blockers.
  1. Typically for patients with medium or large varices at highest risk for hemorrhage (Child-Pugh B/C or red wale markings viewed on endoscopy)
  2. Usually two to four sessions
  3. May not be a permanent solution because varices can recur after initial eradication
  4. Associated with significant complications, including hemorrhage from banding-induced ulcerations
     a. Therefore should be performed by endoscopists with expertise in prophylactic banding
     b. First surveillance endoscopy 1 to 3 mo after obliteration, then every 6 to 12 mo indefinitely

ACUTE GENERAL Rx

- Variceal hemorrhage: Acute hemodynamic resuscitation with packed red blood cell transfusion, correct coagulopathy and thrombocytopenia, airway protection and intubation as necessary, antibiotics (ceftriaxone or norfloxacin) for SBP prophylaxis, octreotide maintained for 2 to 5 days in conjunction with endoscopic therapy. The use of balloon tamponade in the control of active variceal bleeding should be a last resort when other forms of therapy are not available or fail to achieve hemostasis. Balloon tamponade (Fig. E4) should be used only as a temporary means of stabilization and a bridge to a more definitive form of therapy.
- EGD to treat bleeding esophageal varices by esophageal band ligation or sclerotherapy (Fig. 5).

CHRONIC Rx

Primary prophylaxis (Fig. 6):

- Nonselective beta-blockers such as propranolol (20 mg twice daily), nadolol (40 mg once daily) or carvedilol (6.25 mg twice daily)
  1. Increase as tolerated for goal heart rate of approximately 55 beats/min
  2. Blocks the adrenergic dilatory tone in mesenteric arterioles, resulting in unopposed alpha-adrenergic mediated vasoconstriction and therefore a decrease in portal inflow

Secondary prophylaxis (Fig. E7):

- All patients with compensated cirrhosis who have bled from esophageal varices should receive esophageal band ligation and beta-blockers, unless beta-blockers are contraindicated.
  1. Transjugular intrahepatic portosystemic shunt or surgical shunt may be performed if bleeding from esophageal varices continues or recurs despite this dual therapy.
- For patients with decompensated cirrhosis there is evidence, although limited, against the use of prophylactic beta-blockers due to the risk for increased mortality.

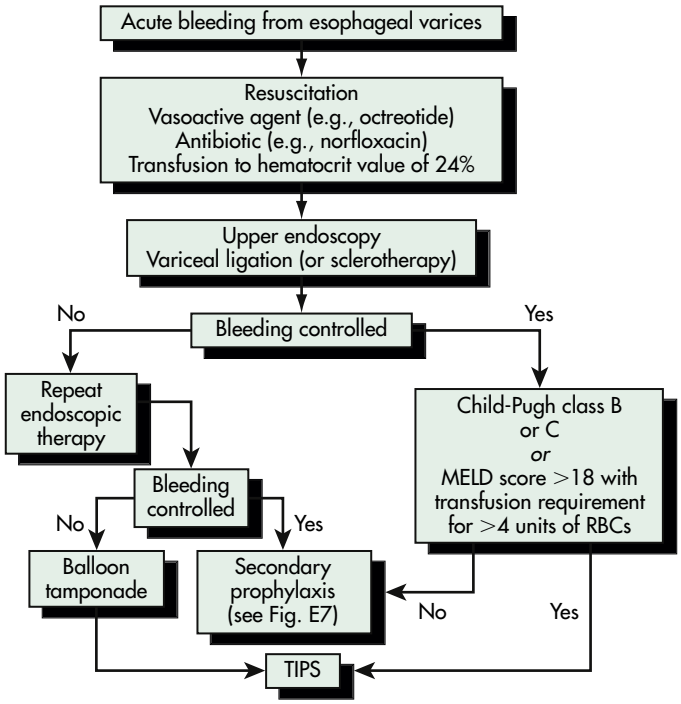

FIG. 5 Algorithm for the management of bleeding esophageal varices. *RBC,* Red blood cell; *MELD,* model end state liver disease; *TIPS,* transjugular intrahepatic portosystemic shunt. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

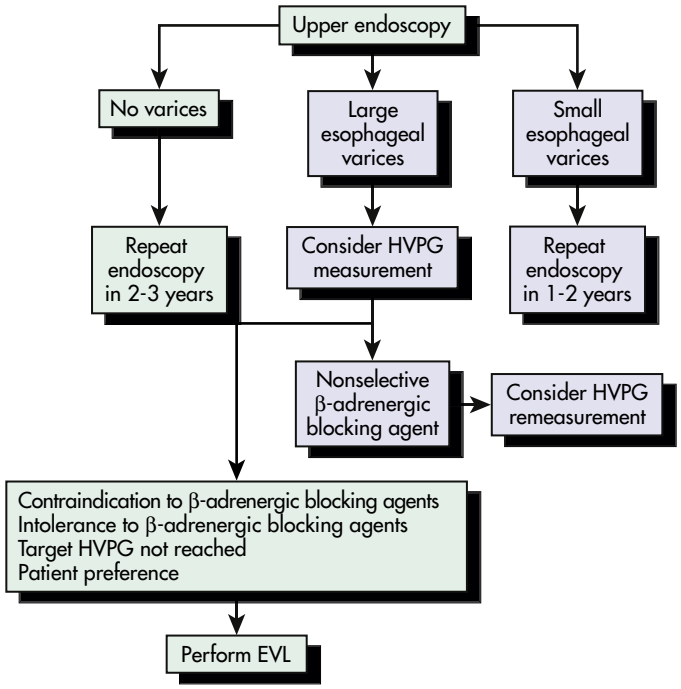

FIG. 6 Algorithm for the primary prophylaxis of esophageal variceal hemorrhage in patients with cirrhosis. The hepatic vein pressure gradient *(HVPG)* may be measured in patients with large varices before a nonselective β-adrenergic blocking agent is started and remeasured 1 mo after the maximum tolerated dose of the beta-blocker is reached. The goal of treatment is to reduce the HVPG to <12 mm Hg or by ≥20%. *EVL,* Endoscopic variceal ligation. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

REFERRAL

Consultation with a gastroenterologist is recommended in all patients with cirrhosis or portal hypertension in order to screen for esophageal varices.

PEARLS & CONSIDERATIONS

Besides variceal size, risk factors for variceal hemorrhage include Child-Pugh class B/C or variceal red wale markings on endoscopy.

RELATED CONTENT

Cirrhosis (Related Key Topic)
Portal Hypertension (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

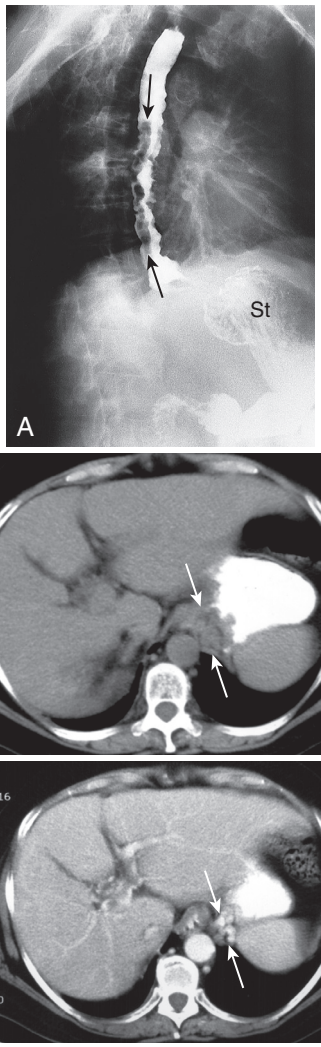

FIG. E1 Esophageal varices. In an oblique view from an upper gastrointestinal examination **(A)** performed on an alcoholic patient, a large, dark, wormlike filling density *(arrows)* is seen in the distal esophagus. It is caused by varices protruding into the lumen of the esophagus. The stomach *(St)* also is seen. Varices also can be seen on computed tomography (CT) scan. On a CT scan without intravenous contrast **(B),** they are seen as small, rounded structures *(arrows)*, and they may indent the fundus of the stomach. When intravenous contrast is given **(C),** they enhance and become whiter *(arrows)*. (From Mettler FA: *Essentials of radiology,* ed 3, Philadelphia, 2014, WB Saunders.)

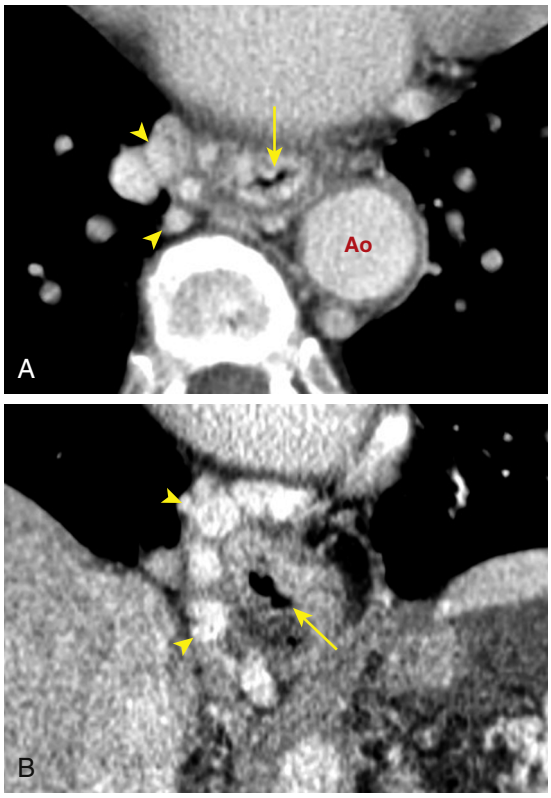

FIG. E2 Esophageal varices. Numerous large enhancing varices *(arrowheads)* resulting from cirrhosis and portal hypertension surround and indent the distal esophagus *(arrow).* **A,** Axial postcontrast computed tomography (CT). **B,** Coronal postcontrast CT in the same patient. *Ao,* Descending thoracic aorta. (From Webb WR et al: *Fundamentals of body CT,* ed 4, Philadelphia, 2015, WB Saunders.)

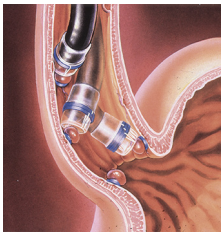

FIG. E3 Esophageal varices. Endoscopic band ligation performed with a multiple-band ligating device. The endoscopist makes circumferential contact between the end of the ligating device and the varix to be ligated. Endoscopic suction draws the varix into the device, after which the elastic band is ejected to ensnare the varix. The ligated tissue sloughs after 3 to 5 days, leaving a shallow ulceration that generally heals within 1 wk. (Courtesy Bard Endoscopic Technologies, Billerica, Mass.)

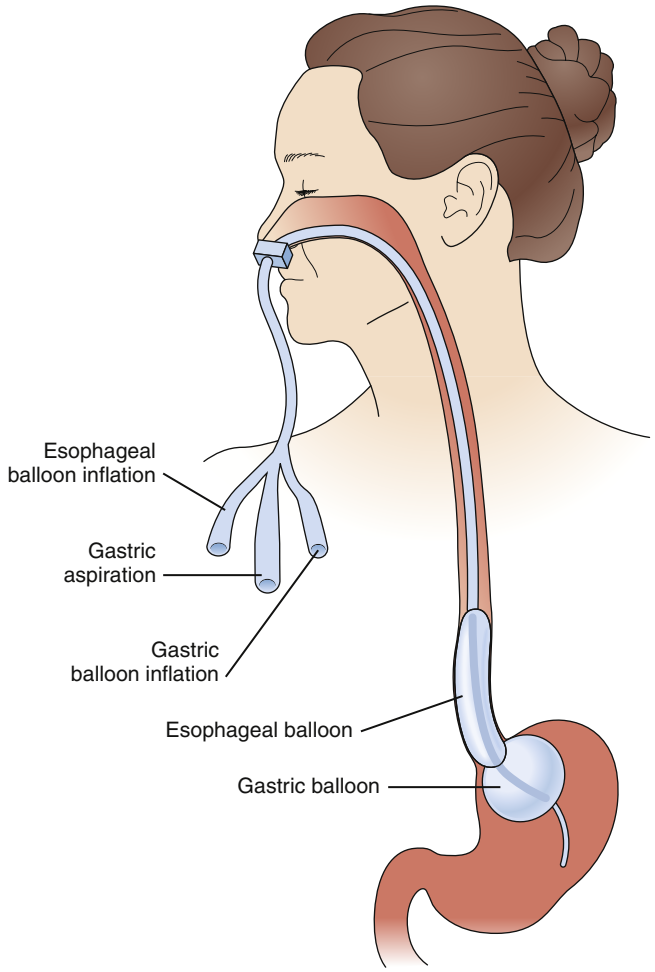

FIG. E4 Sengstaken-Blakemore tube. The tube is passed to at least the 50-cm mark. The gastric balloon is then inflated with the full recommended volume of air (usually 450 to 500 ml). A portable chest radiograph should be obtained to check for proper placement. The tube is pulled back gently until resistance is felt against the diaphragm. If bleeding persists from the aspiration port, the esophageal balloon is inflated to the lowest pressure needed to stop bleeding (usually 30 to 45 mm Hg). (From Parrillo JE, Dellinger RP: *Critical care medicine: principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

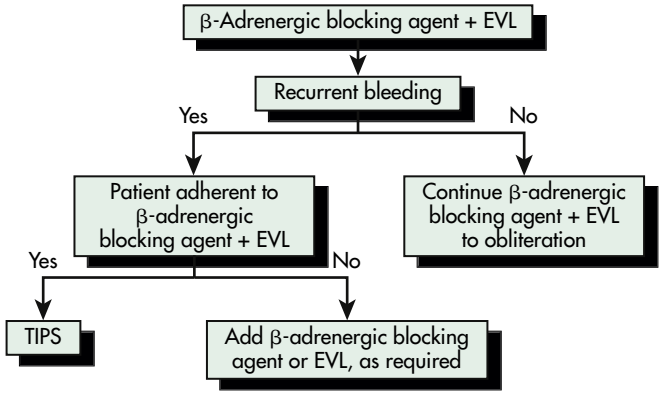

FIG. E7 Algorithm for the prevention of recurrent variceal bleeding (secondary prophylaxis). *EVL,* Endoscopic variceal ligation; *TIPS,* transjugular intrahepatic portosystemic shunt. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

Essential Tremor PTG

BASIC INFORMATION

DEFINITION

A tremor is an oscillatory movement of a body part. Essential tremor is a predominantly postural and action tremor that is bilateral and tends to progress slowly over the years in the absence of other neurologic abnormalities.

SYNONYMS

Benign essential tremor
Familial tremor

ICD-10CM CODE
G25.0 Essential tremor

EPIDEMIOLOGY & DEMOGRAPHICS

Essential tremor is one of the most prevalent neurologic diseases. It affects nearly 7 million persons in the U.S. It is the most common movement disorder.

PREDOMINANT AGE: Can begin at any age, but incidence increases after age 40 yr. Prevalence is 6% to 9% for those >60 yr of age.

GENETICS: Positive family history is found in 50% of patients. No gender or racial predominance.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Tremor (Fig. 1), 4 to 12 Hz, bilateral postural and action tremor of the upper extremities (90% to 95%), head (30%), legs (10% to 15%), and voice (20%). Typically, it is the same amplitude throughout the action, such as bringing a cup to the mouth.
- No other neurologic abnormalities on examination except difficulty with tandem gait.
- Symptoms worsen under emotional distress with fatigue or use of caffeine or other stimulants and improve with intake of small amounts of alcohol.

ETIOLOGY

Often an inherited disease in an autosomal dominant pattern. Sporadic cases without a family history can occur.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS (SEE TABLE 1)

- Parkinson disease: The tremor is usually asymmetric, especially early on in the disease, and is predominantly a resting tremor. Patients with Parkinson disease will also have increased tone, decreased facial expression, slowness of movement, and shuffling gait.
- Cerebellar tremor: This is an intention tremor that increases at the end of a goal-directed movement (such as finger to nose testing). Other associated neurologic abnormalities include ataxia, dysarthria, and difficulty with tandem gait.
- Drug-induced: Many drugs enhance normal, physiologic tremor. These include caffeine, nicotine, lithium, levothyroxine, β-adrenergic bronchodilators, amiodarone, valproate, and SSRIs.
- Wilson disease: This is often characterized by a wing-beating tremor that is most pronounced with shoulders abducted, elbows flexed, and fingers pointing toward each other. Usually there are other neurologic abnormalities including dysarthria, dystonia, and Kayser-Fleischer rings on ophthalmologic examination.
- Physiologic tremor.

WORKUP

- Essential tremor is a clinical diagnosis. Review of medications is essential.
- All imaging studies (MRI, CT) are unnecessary unless other neurologic abnormalities are present.

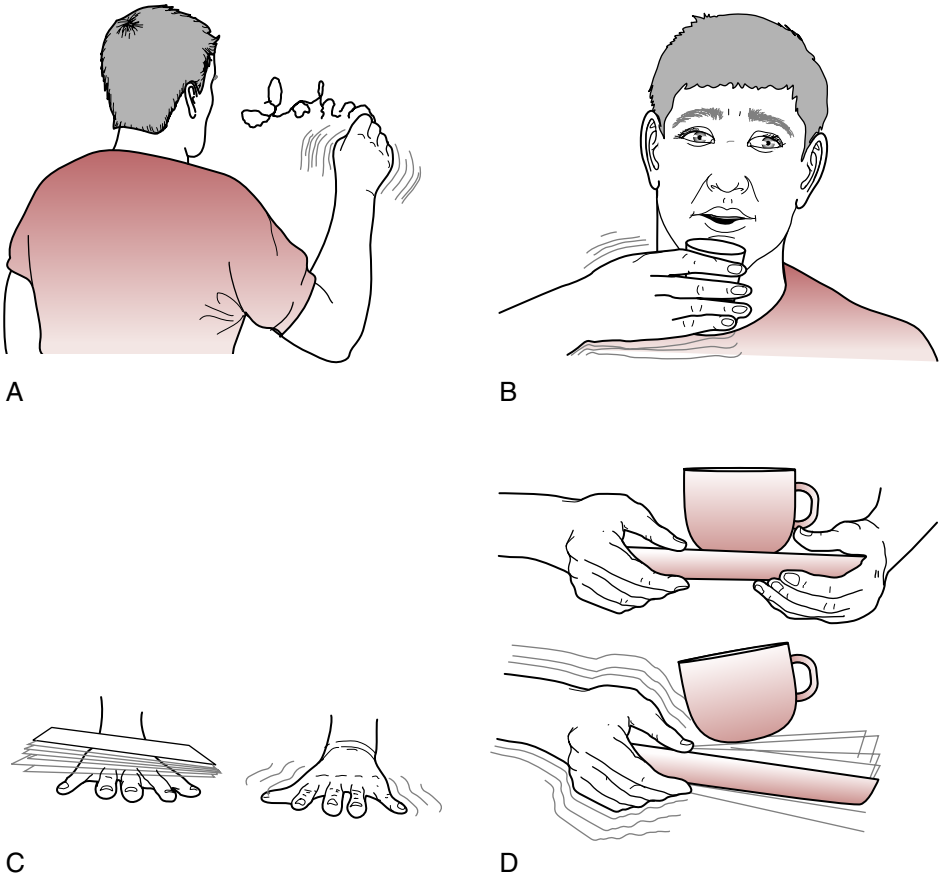

FIG. 1 Physicians elicit this 34-year-old gentleman's essential tremor by having him write his name **(A),** drink from a filled glass **(B),** support an envelope on his outstretched and pronated hand **(C),** or transfer a cup and saucer from one hand to the other **(D).** When his hands rest in his lap, the tremor completely subsides. Essential tremor is a prime example of an action tremor. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.)

TABLE 1 Overlapping Features of Various Types of Tremor

Feature	Parkinson Syndrome	Cerebellar Tremor	Essential Tremor
Present at rest	Yes	No	Yes
Increased tone	Yes	No	No
Decreased tone	No	Yes	No
Postural abnormality	Yes	Yes	No
Head involvement	Yes	Yes	Yes
Intentional component	No	Yes	Yes
Incoordination	No	Yes	No

From Remmel KS et al: *Handbook of symptom-oriented neurology,* ed 3, St Louis, 2002, Mosby.

- Obtain TSH to rule out hyperthyroidism.
- In patients younger than 40 yr old with other neurologic abnormalities, send ceruloplasmin, serum copper, and 24-hr urine copper to evaluate for Wilson disease.

Rx TREATMENT

Treat essential tremor when it is functionally impairing. Treatments are up to 75% effective.

NONPHARMACOLOGIC THERAPY

- Stress management
- Minimization of caffeine use if consumption is correlated with worsened symptoms
- Wrist weights and use of weighted utensils may be helpful in reducing tremor amplitude during feeding. Consumption of small quantities of alcohol at social functions, although relief may be short in duration and may be followed by tremor rebound
- A recent trial using MRI-guided focus ultrasound thalamotomy found it effective in reducing hand tremor in patients with essential tremor. Side effects included sensory and gait disturbances[1]

[1] Elias WJ et al: A randomized trial of focused ultrasound thalamotomy for essential tremor, *N Engl J Med* 375:730-739, 2016.

ACUTE GENERAL Rx

Propranolol (20 to 40 mg) may be used in preparation for specific event.

CHRONIC Rx

First-line agents:

- Propranolol/Inderal LA: Typical starting dose is 30 mg/day. The usual therapeutic dose is 160 mg/day. Although not contraindicated, this medication must be used with caution in those with asthma, depression, cardiac disease, and diabetes. Atenolol or sotalol are also effective.
- Primidone: Typical starting dose is 12.5 to 25 mg qhs. Usual therapeutic dose is between 62.5 and 750 mg daily (assuming side effects are tolerated). Sedation and nausea are common at treatment initiation.
- Topiramate: 25 mg qhs, may titrate up to about 400 mg.

Other (second-line) agents:

- Gabapentin: Typical starting dose is 300 mg tid. Usual therapeutic dose is 1200 to 3600 mg daily in divided doses.
- Pregabalin: Typical starting dose is 50 mg twice a day. Usual therapeutic dose is 150 to 600 mg per day in divided doses.
- Benzodiazepines (i.e., alprazolam): 0.125 to 3 mg daily in divided doses.
- Focal botulinum toxin injections.

SURGICAL Rx

Thalamic deep brain stimulation (or possibly thalamotomy) contralateral to side of tremor is reserved for resistant tremor or for patients who do not tolerate drug therapy. Surgical ablation of the neutral intermediate nucleus or the thalamus with use of magnetic resonance-guided focused ultrasound was recently FDA approved.

DISPOSITION

Patients should be reassured that the condition is not associated with other neurologic disabilities; however, it can become quite functionally disabling over time.

REFERRAL

This is a condition that usually can be treated by the primary care physician; however, if patient fails first-line therapies, the patient should be referred to a neurologist for other drug trials and discussion of possible surgical options.

PEARLS & CONSIDERATIONS

- Essential tremor is the most common of all movement disorders.
- In addition to motor dysfunction, essential tremor can cause significant psychological impact on patients in social situations.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Essential Tremor (Patient Information)

AUTHORS: **Chloe Mander Nunneley, MD, Joseph S. Kass, MD, JD, FAAN,** and **U. Shivraj Sohur, MD, PhD**

SUGGESTED READINGS

Abboud H et al: Essential tremor: choosing the right management plan for your patient, *Cleve Clin J Med* 78:821, 2011.

Elias WS, Shah BB: Tremor, *JAMA* 311(9):948-954, 2014.

Elias WJ et al: A randomized trial of focused ultrasound thalamotomy for essential tremor, *N Engl J Med* 375:730-739, 2016.

Exocrine Pancreatic Insufficiency

BASIC INFORMATION

DEFINITION

Exocrine pancreatic insufficiency (EPI) is a serious condition characterized by a deficiency in pancreatic digestive enzymes resulting in inadequate digestion of fats, carbohydrates, and proteins. The most common cause of EPI is chronic pancreatitis (CP) in adults and cystic fibrosis (CF) in children. Clinically, EPI commonly results in fat malabsorption and is characterized by steatorrhea, weight loss, and maldigestion.

SYNONYMS

Pancreatic insufficiency
EPI
Fat malabsorption

ICD-10CM CODE
K86.81 Exocrine pancreatic insufficiency

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Approximately 40% in patients with CP and 90% in patients with CF
PREDOMINANT SEX & AGE: More common in males than females
RISK FACTORS:

- Excessive alcohol consumption, leading to recurrent pancreatitis and CP
- Smoking
- Bile ductal abnormalities
- Pancreatitis
- Genetic predisposition
- Intestinal surgery
- History of inflammatory bowel disease
- History of celiac disease

PHYSICAL FINDINGS & CLINICAL PRESENTATION

EPI manifests as a malabsorption syndrome. The clinical features may mimic and coexist with common gastrointestinal conditions (i.e., irritable bowel syndrome [IBS], small-intestinal bacterial overgrowth [SIBO], celiac disease), which may delay diagnosis. Patients often limit dietary fat intake to avoid or reduce steatorrhea. Severity depends on the degree of pancreatic loss and can be categorized into mild or moderate-to-severe disease as follows:

- *Mild disease*
  1. Asymptomatic
  2. Normal bowel movements
  3. Mild abdominal discomfort
  4. Bloating
- *Moderate-to-severe disease*
  1. Chronic diarrhea
  2. Excessive weight loss
  3. Excessive flatulence
  4. Abdominal pain/bloating
  5. Voluminous and foul-smelling stools
  6. Fatty food intolerance
  7. Failure to thrive in children
  8. Steatorrhea (stool fat >6 g/day) when >90% of pancreatic glandular function is loss
- Edema (as a result of protein malnutrition and hypoalbuminemia)
- Fat-soluble vitamins deficiencies (rare):
  1. Vitamin A (impaired night vision)
  2. Vitamin D (osteoporosis, metabolic bone disease, hyperparathyroidism, hypocalcemia)
  3. Vitamin E (neuropathy, anemia)
  4. Vitamin K (ecchymosis)

ETIOLOGY (TABLE 1)

EPI usually results from CP in adults or CF in children. Pancreatic exocrine insufficiency is also a common occurrence in patients recovering from severe acute pancreatitis, with the severity of symptoms correlating with the degree of pancreatic necrosis. Causative factors can generally be classified into pancreatic and extrapancreatic conditions.

DIAGNOSIS

The diagnosis of EPI is challenging because patients often present with nonspecific signs and symptoms, and reliable diagnostic tests are lacking.

DIFFERENTIAL DIAGNOSIS

With the exception of voluminous and foul-smelling stools, the following conditions may present in a manner similar to EPI:

- Celiac disease
- IBS
- Inflammatory bowel disease
- SIBO
- Short bowel syndrome

WORKUP

- A complete history, physical examination, and laboratory evaluation are essential to making the diagnosis and excluding other common causes of diarrhea and weight loss.
- Complete electrolyte panel to detect hypokalemia, hypocalcemia (in setting of vitamin D deficiency), hypomagnesemia, and metabolic acidosis from malabsorption and gastrointestinal losses.
- Complete blood count (CBC) may reveal anemia from iron, vitamin B_{12}, or folate deficiencies.
- Prolonged prothrombin times may be elevated because of vitamin K malabsorption.
- Alternative causes of maldigestion should be investigated, such as infection with *Giardia lamblia,* celiac serology, liver disease, and SIBO tests.

LABORATORY TESTS

Direct and indirect pancreatic function tests are available to diagnose EPI.

- **Indirect:** Measures the level of pancreatic enzymes or the consequences of exocrine insufficiency. Used to monitor the effectiveness of pancreatic enzyme replacement therapy (PERT).
  1. **Fecal fat quantification:** Considered the gold standard for evaluating fat digestion. However, it does not distinguish between maldigestion and malabsorption.
  2. **Fecal elastase-1 (FE-1):** The most sensitive and specific test of pancreatic function. This enzyme is minimally degraded during intestinal transit. The test measures enzymatic production of FE-1 and can be used to screen for moderate-to-severe EPI with high sensitivity. FE-1 levels >200 μg/g are normal, levels of 100 to 200 μg/g are considered mild, and levels <100 μg/g are severe for EPI. Liquid stool can lead to falsely low results because of dilution.
  3. **Fecal chymotrypsin:** Sensitive and specific test of pancreatic function. Variably degraded during transit in the intestinal lumen. Accurate levels require an interruption of PERT for several days.
  4. **Serum trypsinogen:** Reflects pancreatic acinar cell mass. Highly sensitive for severe EPI when levels <20 ng/ml. This test is not commonly employed in clinical practice.
  5. **^{13}C-Triglyceride breath test:** Monitors the digestion of isotope-labeled fat meal to reflect absorption and metabolization of product. It is used to measure the efficacy of PERT.
- **Direct:** Most sensitive and specific diagnostic tests for the diagnosis of EPI. Tests use hormonal secretagogues to stimulate the pancreas and then collect duodenal fluid to measure secretory content. Tests use CCK, secretin, and CCK-secretin.
  1. Endoscopic pancreatic function tests
  2. Secretin test

TABLE 1 Etiologiesof Exocrine Pancreatic Insufficiencies

Pancreatic	Extrapancreatic
Acute/chronic pancreatitis (alcohol abuse, trauma, hereditary, idiopathic)	Celiac disease
Pancreatic cancer	Inflammatory bowel disease
Pancreatic, ampullary, and duct obstruction	Autoimmune pancreatitis
Cystic fibrosis	Zollinger-Ellison syndrome
Diabetes mellitus type 1 or 2	Gastrointestinal surgeries (gastrectomy, gastric bypass, extensive small-bowel surgery)
Shwachman-Diamond syndrome (EPI with anemia, neutropenia, and bony abnormalities)	
Hemochromatosis	

IMAGING STUDIES

- Computed tomography (CT): First-line imaging study of choice. Permits visualization of calcifications, cysts, deformation/obstruction of bile ducts, pancreatic/peripancreatic tumors, fibrosis, and parenchyma loss.
- Magnetic resonance cholangiopancreatography: Provides 3D-imaging of the pancreaticbiliary ductal system.

Rx TREATMENT

The management of EPI includes dietary and lifestyle modifications, as well as PERT and vitamin supplementation, to relieve maldigestion-related symptoms and restore normal nutritional health. Underlying diseases leading to EPI should also be treated.

NONPHARMACOLOGIC THERAPY

Nutritional therapy aims to relieve maldigestion-related symptoms and ensure normal nutritional status. Patients should be encouraged to consume small and frequent meals. In addition, patients should abstain from consuming alcohol and smoking. Limiting dietary fat has not been shown to improve outcomes.

PHARMACOLOGIC THERAPY

Oral administration of pancreatic enzyme replacements (Table 2) is the method of choice for treatment of EPI. It is indicated for patients with weight loss, symptomatic steatorrhea, or steatorrhea of >15 g/day. The aim of PERT is to compensate for the deficiencies of normal pancreatic enzyme secretion and increase fat absorption. Doses are individually tailored but usually start at 25,000 to 40,000 IU of lipase in the form of enteric-coated mini-microspheres per main meal. Inadequate responses can be managed by either dose escalation or the addition of proton pump inhibitors or H_2 antagonists to prevent acid inactivation of lipase.

TABLE 2 Enzyme Products for the Treatment of Chronic Pancreatitis

Product	Formulation	Lipase Content per Pill or Capsule (USP units)
Creon	Enteric-coated capsule	3000; 6000; 12,000; 24,000; 36,000
Zenpep	Enteric-coated capsule	3000; 5000; 10,000; 15,000; 20,000; 25,000
Pancreaze	Enteric-coated capsule	4200; 10,500; 16,800; 21,000
Ultresa	Enteric-coated capsule	13,800; 20,700; 23,000
Pertzye	Enteric-coated with bicarbonate	8000; 16,000
Viokase	Non–enteric-coated tablet*	10,440; 20,880

The total dose of lipase per meal should be titrated based on response but usually requires at least 60,000 and usually 90,000 USP units (30,000 IU) of lipase per meal and half that amount with snacks. The dose should be split equally during the meal and immediately after the meal.

*Non–enteric-coated agents require cotreatment with an H_2 receptor antagonist or proton pump inhibitor to avoid denaturation of the enzymes by gastric acid.

USP, United States Pharmacopeia.

From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

DISPOSITION

- Consider further evaluation in patients with persistent weight loss and steatorrhea.

REFERRAL

- Consultation with a gastroenterologist can help expedite diagnosis and rule out alternate diagnoses.
- Referral to a nutritionist can aid the patient with malnutrition and alleviate symptoms.

PEARLS & CONSIDERATIONS

- The pancreas has an important role in the digestion of all nutrients, but fats in particular.
- EPI is a condition related to decreased pancreatic enzyme release resulting from loss of pancreatic parenchyma, inadequate pancreatic stimulation, pancreatic duct obstruction, or pancreatic enzyme inactivation.
- Common symptoms of EPI include weight loss, steatorrhea, and abdominal bloating.
- Timely diagnosis is crucial because delay may impair the child's growth, lead to adverse outcomes of malnutrition, and increase morbidity and mortality.
- Individualized dietary advice together with the appropriate PERT are the cornerstones of EPI therapy.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED TOPICS

Chronic Pancreatitis (Related Key Topic)
Pancreatitis, Acute (Related Key Topic)
Cystic Fibrosis (Related Key Topic)
Celiac Disease (Related Key Topic)
Crohn Disease (Related Key Topic)
Ulcerative Colitis (Related Key Topic)

AUTHORS: **Erick A. Argueta, MD,** and **Dominick Tammaro, MD**

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Factitious Disorder (Including Munchausen Syndrome)

BASIC INFORMATION

DEFINITION

Factitious disorder, according to the DSM-5, occurs when an individual feigns physical or psychological signs or symptoms or induces injury or disease with identified deception. Individuals present to others as ill, impaired, or injured and create signs or symptoms by lying, simulating (e.g., putting drops of blood into a urine sample), or actually creating disease (e.g., injecting bacteria or taking medications). The primary aim is to achieve the patient role, and the behavior persists even in the absence of apparent external rewards such as monetary gain or obtaining narcotics. While the behavior itself is engaged in consciously, the underlying motivation is unconscious. More is known about factitious physical disorder.

The individual may seek examination and treatment including invasive diagnostic testing or surgery. The term *Munchausen syndrome* is reserved for the most severe variant of factitious physical disorder and is characterized by exaggerated lying (pseudologia fantastica), sociopathy, geographic wandering (peregrinating) from hospital to hospital, and seeking the role of a patient.

SYNONYMS

Munchausen syndrome (severe form of factitious disorder)
Munchausen by proxy (factitious disorder created in another person, usually a child)
Hospital addiction syndrome
Surreptitious illness

ICD-10CM CODE
F68.10 Intentional production or feigning of symptoms or disabilities, either physical or psychological (factitious disorder)
DSM-5 CODE
300.19 Factitious disorder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Unknown
PREVALENCE (IN U.S.): Likely underdiagnosed because of the role of deception, but estimates range between 0.5% and 2%
PREDOMINANT SEX: Variable. With psychological subtype M > F; with predominant physical symptoms F > M by a ratio of 3:1. Munchausen syndrome M > F, and Munchausen by proxy mostly younger females
PREDOMINANT AGE: 30 to 40 yr of age
PEAK INCIDENCE: Approximately 30 to 40 yrs of age
GENETICS: No genetic predisposition known

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patient is inconsistent or intentionally misleading and resistant to allowing providers to obtain outside records.
- Clinical picture is atypical for the natural history of disease (e.g., an infection that does not respond to multiple courses of appropriate antibiotics).
- Tests, consultations, and medical and surgical treatments done to no avail and often contradicting history provided by the patient.
- Presentation may be acute and dramatic and in excess of what might be expected.
- The patient may predict deterioration or report exacerbation just before scheduled discharge.
- Opposition to psychiatric consultation.

ETIOLOGY

- A history of significant childhood illness; traumatic experiences such as having witnessed violence and physical, emotional, or sexual abuse can predispose.
- Personality disorders and psychodynamic factors often play a significant role in the development and maintenance of this disorder.

DIAGNOSIS

This is a diagnosis of exclusion. It requires demonstrating that the individual is taking surreptitious actions to misinterpret, simulate, or cause signs or symptoms of illness or injury in the absence of any obvious external reward. Early diagnosis is helpful to prevent extensive and unnecessary testing, which can cause iatrogenic injury.

There may be direct observation of fabrication, the presence of signs or symptoms that contradict laboratory testing, nonphysiologic response to treatment, physical evidence of fabrication (e.g., syringes at the bedside), recurrent patterns of illness exacerbation, or failure to follow the expected natural history of disease. Box E1 describes clues that increase the likelihood of subtle forms of factitious disease.

DIFFERENTIAL DIAGNOSIS

- Primary medical condition
- Somatic symptoms disorder: Not intentionally produced
- Conversion disorder
- Conditions in which self-injurious behavior is common such as borderline personality disorder. The goal is self-injury and not to attain the sick role
- Malingering: Clear secondary gain with conscious motivation (e.g., financial gain or avoidance of unwanted duties)

WORKUP

- Dictated by the presenting complaints. A reasonable index of suspicion when presentation is not consistent with known pathology.
- Methods that have been used to bolster or confirm a suspicion of self-induced or factitious disease are summarized in Box E2.

LABORATORY TESTS

- Laboratory testing often reveals inconsistencies.
- Laboratory abnormalities may reflect the underlying factitious behavior (e.g., hypokalemia in an individual surreptitiously taking furosemide or a clean urine sample obtained by straight catheterization in someone complaining of hematuria).

TREATMENT

NONPHARMACOLOGIC THERAPY

Two approaches may be considered:

- Nonpunitive constructive confrontation by the primary physician and a psychiatrist in collaboration. A supportive stance should be maintained and an offer for ongoing support and follow-up made. Box E3 summarizes consensus opinions on the treatment of factitious disease.
- Avoid overt confrontation with patient but provide him or her with a face-saving way to recover. For example, a therapeutic double bind would involve saying, "There are two possibilities here: one is that you have a medical problem that should respond to the next intervention we do, or two, you have a factitious disorder. The outcome will give us the answer." Features of supportive confrontation are described in Box E4.
- Munchausen syndrome is the most severe variant and may be virtually impossible to treat except to avoid further invasive and iatrogenic intervention.

BOX E1 Clues That Increase the Likelihood of Subtle Forms of Factitious Disease

Predominantly women
Previous experience in the medical field, which provides an unusual grasp of terminology and access to medical supplies
Multiple surgeries, multiple procedures
Inexplicable laboratory test results
Inconsistency and implausibility of certain aspects of the history
Visits to three or more medical centers previously for the same symptoms, or to a nationally known referral center such as the Mayo Clinic or Cleveland Clinic, despite residing far away
History of substance abuse or prior psychiatric disorder
Vagueness in regard to details of past history and/or reluctance to allow release of previous medical records

From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

BOX E2 Methods That Have Been Used to Bolster or Confirm a Suspicion of Self-Induced or Factitious Disease

Review old medical records and discuss case with previous doctors and family members if appropriate. Identify discrepancies and inconsistencies, and estimate influence of gain derived from the sick role. Inquire about psychosomatic illness, previous psychiatric treatment, suicide attempts, stress in the patient's life, childhood abuse, marital/sexual problems, eating disorders, and so on. A forensic consultant with access to multiple records can be uniquely helpful in identifying conflicting stories.
Review previous biopsy slides, looking for foreign body material in wounds, melanosis coli, and other clues, as appropriate for the patient's symptoms.
Obtain a psychiatric evaluation to help determine whether the patient has a personality disorder or psychiatric disease, absence of which would argue against factitious disease. Psychiatrists should not attempt initially to discover the underlying unconscious motivation that may have impelled the patient to assume the sick role.
If symptoms and signs may be explained by surreptitious ingestion of medications and poisons, obtain appropriate medication and toxicology screens. Consider obtaining a urine test for diuretics even in the absence of renal or electrolyte disorders. Evaluate results of such screens in light of the sensitivity and specificity of the tests employed.
Test biological fluids collected under direct observation and compare results with fluids collected privately by the patient. For example, compare fecal material obtained at "unprepped" sigmoidoscopy with fecal material submitted by the patient.
Have nursing staff observe the patient to detect tampering behavior.
Search the patient's personal belongings.
Conduct covert videotape surveillance, especially in suspected Munchausen syndrome by proxy.

From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

BOX E3 Consensus Opinions on the Treatment of Factitious Disease

Achievement of insight should not be the principal early goal of treatment, because it can weaken the patient's defenses.
One person should have primary responsibility for patient management.
There should be a comprehensive psychiatric evaluation of the patient, including assessment for suicide risk.
All members of a multidisciplinary team should be aware of the psychiatric assessment and treatment plan.
The treatment plan should be individualized.
Comorbid illness should be treated appropriately.
If confrontational techniques are used, they should be nonpunitive and supportive.

From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

BOX E4 Features of Supportive Confrontation

Tell the patient what you suspect without outright accusation.
Support the diagnosis of factitious disease with facts.
Provide empathetic and face-saving comments.*
Avoid probing to uncover the patient's underlying feelings and motivations.†
Assure the patient that the physician will not release the diagnosis to others without the patient's permission unless required to do so by law.‡
Ensure that the staff demonstrates continued acceptance of the patient.
Encourage psychiatric help, but do not force the issue.

*"Maybe you didn't know what you were taking—this medication could cause you to be sick"; "Maybe you took it in your sleep"; "What you did was a cry for help, and we understand"; "We realize you must be in great distress"; "We want to continue to take care of you."
†This is done to minimize disruption of essential emotional defenses.
‡Later it may be decided to break this promise in patients with potentially fatal factitious disease, such as patients who are creating sepsis by injecting contaminated material into their bodies. This promise should only be broken after consultation and consensus opinion has been obtained by an ethics committee, legal personnel, and others, as described in the text.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

ACUTE GENERAL Rx

- Treatment of comorbid psychiatric disorders may be helpful with medications and/or psychotherapy, which may ameliorate the factitious behavior.
- Multidisciplinary staff meetings can be useful to ventilate feelings and develop cohesive treatment plans.

CHRONIC Rx

- Attempt to engage the patient in some form of psychotherapy or at least a harm-reduction strategy.
- Establishment of a central reporting register has been proposed to aid development of evidence-based guidelines.

DISPOSITION

- After being confronted with their behavior, patients may cease factitious behavior, but they may also seek other physicians or hospitals, as in the Munchausen variant.
- Some patients may enter psychotherapy, particularly when they have been given a face-saving approach with avoidance of a humiliating confrontation.

REFERRAL

Always obtain psychiatric referral. Risk management attorneys and hospital ethicists may contribute to challenging decision making in these patients.

PEARLS & CONSIDERATIONS

- Think of factitious disorders whenever there is an unexplained medical course that continues to repeat itself despite appropriate treatment.
- Patients may have a history of working in the health care field.
- Gratuitous, self-aggrandizing deception may be noted.

AUTHORS: **Christina D. Scully, MD,** and **Dwayne R. Heitmiller, MD, FAPM**

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BASIC INFORMATION

DEFINITION

Failure to thrive (FTT) describes a delay in growth and development among children. FTT is a cluster of symptoms rather than a specific disease.

CLINICALLY

The term (FTT) is often used for infants and children with weight below the 5th percentile for sex and corrected age.

SYNONYMS

Pediatric undernutrition
Faltering growth
Weight faltering
Growth failure
FTT

ICD-10CM CODE
R62.51 Failure to thrive (child)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: FTT is a common problem, though its incidence in the community is unclear. A total of 1% to 5% of inpatient pediatric admissions are for evaluation of FTT.
PREDOMINANT SEX AND AGE: FTT most commonly occurs among children ages 6 to 12 mo, with 80% presenting before 18 mo of age. Most FTT patients present before 3 yr of age. Males and females are equally affected.
RISK FACTORS: Poverty is the single greatest risk factor. Nonmedical: Poverty, food insecurity, social isolation, neglect, and physical or emotional abuse. Medical: Intrauterine growth restriction (IUGR), prematurity, medical conditions leading to inadequate food intake, food malabsorption, or increased metabolic demand.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Children have blunted growth in height, weight, head circumference, or any combination of these. Children may have pallid, dry, or cracked skin, sparse hair growth, poorly developed musculature, lack of subcutaneous fat, swollen abdomen, or evidence of vitamin deficiencies.

ETIOLOGY

FTT is the result of inadequate nutrition, which may be due to a wide range of medical or psychosocial causes. FTT can be thought of as stemming from inadequate nutritional intake, malabsorption of nutrients, or increased caloric expenditure, though the actual cause is commonly multifactorial.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Inadequate nutritional intake: Food insecurity, poor parent knowledge of child's needs, formula dilution, excessive juice, breastfeeding difficulties, neglect, behavioral feeding problem, oromotor dysfunction, developmental delay, emesis, gastroesophageal reflux, volvulus, increased intracranial pressure, genetic disease (trisomy 13, 18, 21), and psychiatric conditions
- Malabsorption: Cystic fibrosis, celiac disease, eosinophilic esophagitis, food protein insensitivity or intolerance, and inflammatory bowel disease
- Increased metabolic demand: Insulin resistance, congenital infection, other infection, genetic syndrome, hyperthyroidism, chronic disease, and malignancy

WORKUP

- Evaluation should include the child's eating habits, caloric intake, parent-child interactions, psychosocial history, past medical history, medications, family history to include parent stature and weight, review of systems, and physical exam. Fig. E1 illustrates an algorithm for management of a child with FTT.
- Height, weight, and weight-to-length measurements are most sensitive, whereas head circumference and body mass index (BMI) may be useful. Common FTT criteria for children younger than 2 yr are below, but clinical judgment should be used because normal causes and biologic variants may exist.
  1. Length, weight, or BMI below the 3rd or 5th percentile on more than one consecutive visit
  2. Weight that drops below two major percentile lines
  3. Weight less than 80% of the ideal weight for age
  4. Weight-to-length below the 5th percentile or weight-for-length less than 70% to 79% of the median
  5. Weight velocity below the 3rd or 5th percentile
  6. Weight less than 70% of the 50th percentile; may require hospitalization
- Obtain caliper measurements of skinfold thickness and midarm muscle circumference.
- Observation of a meal being taken to assess potential feeding difficulties.
- A 3-day food diary is helpful, as well as consultation by a nutritionist, to calculate the child's intake of energy, protein, vitamins, and minerals.
- Assess stool frequency, consistency, quantity, as well as fat, blood, or mucus content.
- Routine hospitalization for FTT evaluation is not recommended. Rarely, hospitalization for observed feedings and further workup is warranted.

LABORATORY TESTS

- Laboratory tests should be based on medical history and physical exam findings and should consider the risk for refeeding syndrome and other medical complications.
- Consider CBC with red blood cell indices, complete chemistry panel including phosphorus, thyroid function, urinalysis, HIV

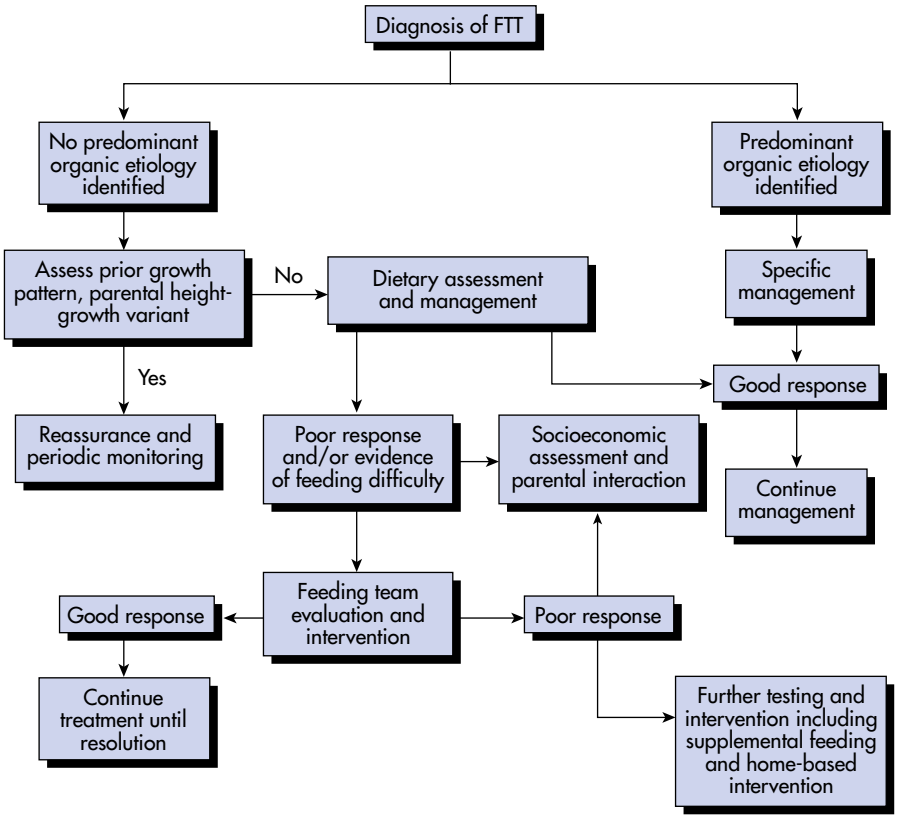

FIG. E1 Algorithm for management of a child with failure to thrive *(FTT).* (Shashidhar H, Tolia V: Failure to thrive. In Wyllie R, Hyams JS [eds], *Pediatric gastrointestinal and liver disease,* ed 4, Philadelphia, 2011, Elsevier, pp 136-145.e3.)

testing, C-reactive protein or erythrocyte sedimentation rate, celiac screening, stool examination for fats or reducing substances, or sweat chloride testing. If clinically indicated, growth hormone level and genetic sequencing can be checked.

IMAGING STUDIES

Imaging tests are not routinely performed but may be warranted depending on underlying medical cause.

Rx TREATMENT

Identification and management of underlying causes should be implemented. In cases in which there is no underlying medical condition, providing nutrition repletion will, by definition, correct FTT. A multidisciplinary team (including, but not limited to, social workers, occupational/speech therapists, nutritionists/dietitians, nurses, advanced practice nurses, and pediatricians) should be used.

NONPHARMACOLOGIC THERAPY

- Add calorie-dense foods or increase the number of feedings.
- Enteral feeding, percutaneous endoscopic gastrostomy (PEG), and nasogastric feeding tubes can be used to accelerate weight gain, and results should be seen within 2 to 7 days. Caloric intake should be titrated up to goal over 5 to 7 days. Caloric goals by age group: 0 to 6 mo: 108 kcal/kg/day, 6 to 12 mo: 98 kcal/kg/day, and 1 to 3 yr: 102 kcal/kg/day.
- Swift restoration of nutrition can lead to life-threatening refeeding syndrome, where shifts in electrolyte balance (low phosphate, magnesium, potassium), fluid balance (edema), hypoglycemia, gastroparesis or ileus, impaired heart function or arrhythmia, and sudden death can occur. Calories must therefore be titrated slowly to goal with close monitoring.
- Treat underlying medical conditions, including mental health disorders.
- Assist with family psychosocial stressors.
- Follow up closely, including home nursing visits.
- In cases where economic, psychosocial, or parental issues are suspected and the child's growth is not maintained, state and federal legislation regarding reporting to child protection services must be followed.

ACUTE GENERAL Rx

Multivitamins including iron and zinc

CHRONIC Rx

Nutrient repletion with the goal of accelerated growth should be continued for 4 to 9 months

DISPOSITION

Children with FTT commonly remain small in height and weight. Studies consistently find that children with FTT are more prone to long-term cognitive, learning, and behavioral abnormalities.

REFERRAL

- Indicated based on the cause of FTT
- Hospitalization should be considered in cases of FTT in which a child is less than 70% of predicted weight for length, where outpatient management has failed, when a suspicion of abuse or neglect exists, where signs of traumatic injury are present, where serious impairment of the child's caregiver is evident, or for close observation and treatment for refeeding syndrome.

PEARLS & CONSIDERATIONS

COMMENTS

- FTT is a common childhood symptom encountered in the outpatient and inpatient pediatric populations, is caused by undernutrition, and is associated with inadequate nutritional intake, malabsorption, or increased metabolic demand.
- A thorough multidisciplinary approach to assessment, diagnosis, and management should be used to manage nutrient status and any underlying cause(s).
- Child height/length, weight, and weight-for-length measurements with comparison to standard growth curves are useful in the identification of potential cases of FTT.
- FTT treatment should include restoration of nutrition along with treatment of the underlying cause(s), including psychosocial factors.
- Although FTT can usually be managed effectively in the outpatient setting, specific indications for inpatient treatment should be considered.

PREVENTION

Nutritional counseling and anticipatory guidance should be provided at each well-child visit. Growth parameters should be measured during serial clinical assessments and compared with growth standards. Enlist dietitians and visiting nurses to provide support to families with children at high risk of FTT.

AUTHOR: **Fred F. Ferri, MD**

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BASIC INFORMATION

DEFINITION

A "primary" fallopian tube tumor is defined as a tumor that is restricted to or mainly affects the fallopian tube.

SYNONYMS

Fallopian tube cancers, serous tubal intraepithelial carcinomas

ICD-10CM CODES

C57.00	Malignant neoplasm of unspecified fallopian tube
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Primary fallopian tube tumors make up 0.3% to 1.1% of all gynecologic cancers.

Highest incidence in white, non-Hispanic women aged 60 to 79 yr.

GENETICS: Patients with BRCA mutations have a 0% to 12% incidence of serous tubal intraepithelial carcinomas (STIC). Women with hereditary nonpolyposis colorectal cancer also have a higher risk of STIC than the general population.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Physical exam findings are similar to those of ovarian and primary peritoneal cancers. Patients can have abdominal bloating, early satiety, abdominal distention, and weight loss. However, many early fallopian tube cancers are detected at time of risk-reducing bilateral salpingoophorectomy.

ETIOLOGY

Etiology is unknown at this time. STIC is believed to be the precursor lesion to high-grade serous carcinomas (HGSC) of the ovary.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ovarian cancer
- Primary peritoneal cancer

WORKUP

LABORATORY TESTS:

- Complete blood count, basic metabolic panel
- CA125
- Pathology:
  1. Until recently, grossly positive tubal mass was required to assign the tumor origin to the fallopian tube.
  2. Fimbrial carcinoma is unlikely to cause tubal dilation.
  3. More recently the SEE-FIM protocol for pathologic evaluation of fallopian tubes has been used to better evaluate the potential for primary fallopian tube cancers.
  4. SEE-FIM involves sectioning and extensively examining the fimbriated end. Fimbrial carcinoma is unlikely to cause tubal dilation.
  5. Fimbrial carcinomas contain TP53 mutations.

IMAGING STUDIES

- Pelvic ultrasonography
- CT abdomen/pelvis

STAGING

See Table E1.

TREATMENT

Approach mirrors treatment for ovarian cancers

NONPHARMACOLOGIC THERAPY

Surgery: Generally, total hysterectomy with removal of both tube and ovaries is the first-line treatment with goal of complete resection of all visible tumors; pelvic and para-aortic lymph node resection is often also performed.

ACUTE GENERAL Rx

Medications to control nausea and vomiting, constipation associated with tumor burden

CHRONIC Rx

- Adjuvant chemotherapy:
  1. Usually with platinum-based combination chemotherapy regimens, usually platinum-taxane combination
- Radiotherapy is no longer recommended

DISPOSITION

SURVIVAL:

- 5-yr survival is about 65% or higher.
- Stage of disease at time of diagnosis is the most important prognostic indicator.
- Overall survival is 30% to 50%.

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TABLE E1 International Federation of Gynecology and Obstetrics Staging

- **Stage 0.** Carcinoma in situ (limited to tubal mucosa)
- **Stage I.** Growth limited to the fallopian tubes
  1. **Stage I_A.** Growth limited to one tube with extension into submucosa and/or muscularis, but not penetrating the serosal surface. No malignant calls in ascites or peritoneal washings.
  2. **Stage I_B.** Growth limited to both tubes with extension into submucosa and/or muscularis but not penetrating the serosal surface. No malignant calls in ascites or peritoneal washings.
  3. **Stage 1_C.** Tumor either stage I_A or I_B with tumor extension through or onto the tubal serosa OR with ascites containing malignant cells OR with positive peritoneal washings.
- **Stage II.** Growth involving one or both fallopian tubes with pelvic extension.
  1. **Stage II_A.** Extension and/or metastasis to the uterus and/or ovaries
  2. **Stage II_B.** Extension to other pelvic tissues
  3. **Stage II_C.** Tumor either stage II_A or II_B AND with ascites containing malignant cells OR with positive peritoneal washing
- **Stage III.** Tumor involving one or both fallopian tubes with peritoneal implants outside of the pelvis, involvement of the small bowel, omentum, or liver surface, and/or positive retroperitoneal or inguinal nodes. Peritoneal implants are studs of tumors implanted in the abdominal wall
  1. **Stage III_A.** Tumor grossly limited to the true pelvis with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces (small bowel, omentum, or liver surface)
  2. **Stage III_B.** Tumor involving one or both tubes with histologically confirmed implants visualized on the abdominal peritoneal surfaces (small bowel, omentum, liver surface), none exceeding 2 cm in diameter. Lymph nodes negative for tumor
  3. **Stage III_C.** Abdominal implants greater than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes
- **Stage IV.** Growth invading one or both fallopian tubes with distant metastases, including parenchymal liver metastases. Parenchymal liver disease refers to cancer inside the liver; it differs from disease on the liver surface, which may qualify as stage III disease. Fluid on the lungs (pleural effusion) may classify as stage IV disease, but only if cancer cells are found to be present in the fluid

BASIC INFORMATION

DEFINITION

A fall is an "event which results in a person coming to rest inadvertently on the ground and other than a consequence of the following: loss of consciousness, sudden onset of paralysis, or epileptic seizure."

SYNONYMS

Syncope
Collapse

ICD-10CM CODES	
E880-E888.9	Accidental fall
R29.6	Repeated falls

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Trauma is the fifth leading cause of death in persons >65 yr of age, and falls are responsible for 70% of accidental deaths in persons ≥75 yr.
- The incidence of falls among community-dwelling older adults is 30% to 40%. Two thirds of falls in the community are preventable; 6% to 7% of these falls result in fracture.
- The incidence of falls for nursing home and hospitalized older adults is three times the rate of community-dwelling older adults. Over 50% of nursing home residents fall during their stay.
- 20% to 30% of older adults who fall suffer significant injury leading to immobility, dependence, and an increased risk of early death.

HEALTH CARE COST: In 2006, patients ≥65 had over 2.1 million visits to the ED for injurious falls, which was 10.5% of all ED visits among the elderly and 29.6% of these visits required hospital admission. In those that were admitted, the mean length of stay was 5.5 days with a mean cost of $10,800. The aggregate hospital cost for those requiring admission in 2006 was $6.8 billion. (Source: Healthcare Cost and Utilization Project.)

PREDOMINANT SEX & AGE:

- Fall-related mortality is highest among older white men followed by white women, African American men, and African American women.
- The incidence rates of falls increase with advancing age.
- Older adults ≥85 yr are 10 to 15 times more likely to have a fracture compared with those aged 60 to 65 yr.

RISK FACTORS: Four groups of risk factors for falls have been identified (Table 1):

- Intrinsic factors inherent in the older adult who falls.
- Extrinsic factors circumstantial to the older adult who falls.
- Falls in nursing homes.
- Situational or the activity in which the older adult is engaged in when a fall occurs.

CLINICAL PRESENTATION

- Older adults who fall may present with minor soft tissue injuries, such as lacerations or bruising, hip fracture, or head trauma; however, most falls are not reported unless an injury has occurred.
- If an older adult presents for medical attention for a fall or reports recurrent falls in the past year or difficulties in walking or balance, a multifactorial fall risk assessment should be completed.
- The multifactorial fall risk assessment should include:
  1. Focused history: A detailed history of events and circumstances surrounding fall, relevant risk factors including review of medications, acute and chronic medical problems (e.g., osteoporosis, urinary incontinence, and cardiovascular disease), and whether the fall was witnessed
  2. Physical examination:
     a. Vital signs including orthostatics.
     b. Cardiovascular examination assessing for arrhythmias, carotid bruits, or new murmurs.
     c. Neurologic examination including vision assessment, evaluation of lower-extremity strength, peripheral nerves, proprioception, and testing of cortical, extrapyramidal, and cerebellar function.
     d. Gait and balance assessment: Multiple screening tools are available for fall risk screening and balance assessment (Tables 2 and 3). "Get up and go test" is a rapid assessment that will quickly tell you if the patient needs rehabilitation and what to work on. (Ask patient to stand from a seated position without use of hands, walk 10 feet forward, turn around, and return to chair and sit).
     e. Musculoskeletal exam with attention to joints of lower extremity, feet, and footwear.
  3. Functional assessment including the older adult's activities of daily living skills, use of adaptive equipment, and fear of falling
  4. Environmental assessment of home safety

TABLE 1 Risk Factors for Falls in the Elderly

Intrinsic

Aging

Age-related decline in vestibular function might lead to loss of balance, dizziness, and falls. Aging of the vision system (e.g., glaucoma, cataracts, retinopathy) may result in decreased visual acuity, inability to discriminate dark/light, and decreased spatial perception.

Cardiac

Cardiac arrhythmias, carotid sinus hypersensitivity, neurocardiogenic syncope.

Neurologic

Parkinson disease, normal pressure hydrocephalus (NPH), sensory neuropathy, dementia/impaired cognition, cervical myelopathy, senile gait disorder, prior stroke. (One third of the elderly have abnormal position sense.)

Musculoskeletal

Lower extremity weakness, impaired knee extension and ankle plantar flexion strength contribute to abnormalities in gait velocity and step length, deconditioning, arthritis, foot abnormalities (such as bunions, calluses, or nail abnormalities).

Vascular

Vertebrobasilar insufficiency, postural hypotension, postprandial hypotension.

Metabolic

Hypoglycemia, hypothyroidism, hyponatremia.

Psychiatric

Depression.

Medications

Use of more than four medications may be associated with an increased risk of falls. Medications that may increase fall risk include benzodiazepines, sleeping medications, neuroleptics, antidepressants, anticonvulsants, class I antiarrhythmics, and antihypertensives.

Extrinsic

Environmental

Environmental hazards cause >50% of falls in the elderly (cords, furniture, small objects, ill-fitting shoes, slippery surfaces, loose rugs, uneven steps, optical patterns on escalators). Majority occurs with mild-moderate activity (walking, stepping up/down, changing position); 70% occur at home and 10% on stairs (descending > ascending).

Nursing Home Falls

20% have a cardiovascular cause (hypotension: drug induced, postprandial, postural, or bradycardia) 5% are the result of an acute illness such as PNA, febrile illness, UTI, CHF.

3% are from an overwhelming intrinsic event such as syncope, seizure, stroke, psychoactive drugs.

Situational

Tripping over obstacles, carrying heavy items, descending/ascending stairs, rapid turning, reaching overhead, climbing ladders, ill-fitting shoes, lack of assistive devices.

CHF, Congestive heart failure; *PNA,* pneumonia; *UTI,* urinary tract infection.

TABLE 2 Scales Used for Fall Risk Screening and Balance Assessment

Instrument	Items	Setting		
		Community	Acute	Chronic
Multifactorial Reports				
STRATIFY	Five items—history of falls, agitation, visual impairment, frequent toileting, able to stand but needs assistance with moving		X	X
Morse Fall Scale	Six items—history of falls, secondary diagnoses, parenteral therapy, use of ambulation aids, gait, mental status		X	X
FROP-Com	13 risk factors in 26 items—fall and fall injury history, medications, medical conditions, sensory loss, feet, cognitive status, toileting, nutrition, environment, function, behavior, balance, gait; total score, 0 to 60; fall risk high with score >24	X		
Fall risk for residential care	Among persons who can stand without assistance—poor balance or two of three the following: Fall history, nursing home residence, urinary incontinence Among persons who cannot stand without assistance—one of three of the following: fall history, hostel residence, use of nine or more medications			X
Functional Mobility				
Berg Balance test	14 tasks scored 0 to 4; total range 0 to 56; fall risk increases as score decreases	X	X	X
Functional reach	Distance reached in inches without moving the feet; fall risk <7 inches	X	X	X
Performance-oriented mobility and balance	Balance subscale score 0 to 16, gait subscale 0 to 12, summary score 0 to 28; summary score <19 indicates high fall risk	X		X
Timed up and go	Time in seconds to rise from a chair, walk 3 m, turn, walk back, and sit down; <10 sec normal; fall risk increases with time >13.5 sec	X		X
Dynamic gait index	Eight walking tasks scored 0 to 3, total score 0 to 24; <18 or 19 indicates fall risk	X		
Functional mobility tests	Time to complete eight step ups (alternate step test) >10 sec, timed sit to stand five times >12 sec, 6-m walk time >6 sec increased fall risk	X		
Physiologic profile assessment	Performance in five domains: Sway, reaction time, strength, proprioception, contrast sensitivity; total score 0 to >3; fall risk increased with score ≥2	X		

FROP-Com, Falls Risk for Older People in the Community; *STRATIFY,* St. Thomas Risk Assessment Tool in Falling elderly inpatients.
From Fillit HM et al: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

TABLE 3 Clinical Assessment Based on Components of Postural Control

Organ System	Impairment	Clinical Evaluation	Potential Cause
Eye	Decreased acuity	Vision chart	Presbyopia, macular degeneration, cataracts
	Reduced visual fields	Confrontation, perimetry	Glaucoma, posterior circulation stroke
	Decreased depth perception	Stereo or depth testing	Monocular vision
	Decreased dark adaptation	Self-report—inability to dilate pupil in low light	Aging, miotic agents for glaucoma
Vestibular apparatus	Otoliths	Ability to detect true vertical, Hallpike maneuver	Benign positional vertigo
	Semicircular canals	Ability to detect position during rotation with eyes closed, nystagmus, visual acuity during head motion	Meniere disease, vestibular hypofunction
Peripheral nerve	Peripheral neuropathy	Light touch, filaments, two-point discrimination, vibratory sense	Diabetes, peripheral vascular disease, vitamin B_{12} deficiency
Circulation	Reduced cerebral perfusion	Low blood pressure, altered level of consciousness, light-headedness	Medications, arrhythmias, postprandial hypotension
	Orthostatic hypotension	Positional change in blood pressure	Medications, autonomic dysfunction, dehydration
Brain	Reduced attention	Ability to perform dual tasks like timed up and go with cup of water, executive function tasks	Mild cognitive impairment, dementia, medications
	Psychomotor slowing	Timed tapping, timed finger to nose test, trails A test (connect the dots)	Medications, degenerative and vascular brain diseases
	Altered postural reflexes	Absent or slowed righting reflexes	Parkinson disease, other extrapyramidal and degenerative brain diseases
Muscle	Reduced strength	Manual muscle testing, strength-based functional performance (chair rise, squat)	Generalized—inactivity, sarcopenia, vitamin D deficiency, myopathies
			Focal deficits, spinal cord and peripheral motor nerve conditions
Musculoskeletal pain	Loss of flexibility	Contractures, decreased range of motion	Arthritis, inactivity
	Bone and joint deficits	Weight-bearing pain	Arthritis, fractures, periarticular conditions, foot problems
	Disturbance of spinal cord, roots, nerves	Leg and back pain with activity	Spinal stenosis, radiculopathies, peripheral neuropathies

From Fillit HM et al: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

ETIOLOGY

- Falls are a multifactorial syndrome resulting from the cumulative effects of impaired gait and balance, aging, polypharmacy, depression, cognitive impairment, acute medical illness, or environmental factors (Fig. E1).
- Most falls among community-dwelling older adults are due to environmental factors, whereas falls among nursing home residents are a result of confusion, gait impairment, or postural hypotension.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Falls are often a nonspecific symptom of an acute illness (such as delirium, urinary tract infection, acute anemia, or pneumonia) or an exacerbation of a chronic disease (chronic heart failure [CHF] or chronic obstructive pulmonary disease [COPD]). The mnemonic "DELIRIUMS" can be used to assess the differential diagnosis in acute delirium. (**D**rugs, **E**motional [depression], **L**ow PaO_2 [CHF, COPD], **I**nfection, **R**etention [urinary, fecal], **I**ctal status, **U**nder nutrition/hydration, **M**etabolic, **S**ubdural/Sensory [all neurologic causes] workup).

WORKUP

- Older adults presenting with a noninjurious fall need a detailed history and physical exam to identify acute medical illnesses and potential modifiable risk factors. Laboratory and neuroimaging studies may be necessary if the history and physical exam indicate a specific problem. ECG and Holter monitoring may be considered if cardiac arrhythmia is suspected.
- See Fig. E1.

LABORATORY TESTS

CBC, stool guaiac, blood chemistries, thyroid function, liver function, vitamin B_{12} level, folate level, erythrocyte sedimentation rate, vitamin D level, drug levels, and urinalysis depending on physical/historical findings.

IMAGING STUDIES

- CT or MRI of the brain or cervical spine films in the presence of neurologic or gait impairment.
- Chest x-ray if pulmonary pathology (pneumonia, pulmonary edema) is suspected.
- Consider ECG, echocardiography, or Holter monitor if suspicious for structural cardiac abnormality or syncope.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical therapy evaluation for gait and balance training, evaluation of appropriate assisted devices (e.g., cane, walker), the use of fall prevention equipment (e.g., low beds, bed alarms).
- Home safety assessment: Studies show that 50% of recurrent fallers fell doing the same activity that caused them to fall the first time. This can be prevented by creating a home safety evaluation checklist (preferably done by family member to improve compliance) or arranging for a home safety inspection by a visiting nurse or occupational therapist.
- Minimization or discontinuation of certain medications associated with falls (psychotropics).
- Customized exercise program to improve strength, gait, and balance.
- Evaluation of proper footwear, hard sole, and low heel height.

ACUTE GENERAL Rx

Hospitalization may be necessary for treatment of hip fracture, subdural hematoma, lacerations, or trauma as well as the treatment of underlying cause of the fall such as infection, metabolic disturbances, cardiovascular (e.g., carotid sinus hypersensitivity, vasovagal syndrome, bradyarrhythmias, and tachyarrhythmias) or neurologic abnormality.

CHRONIC Rx

- Screen and treat for osteoporosis as low bone density increases the risk of hip or other fractures.
- Optimize treatment of chronic illnesses such as CHF, COPD, osteoarthritis, Parkinson disease, dementia, postural hypotension, and visual problems.
- Vitamin D supplementation of at least 800 IU per day. Epidemiological studies reveal that compared with usual care, short-term intervention with oral nutritional supplementation and dietetic counseling significantly decrease falls in malnourished older adults.
- Table 4 summarizes the management of impairments that contribute to instability and falls.

COMPLEMENTARY & ALTERNATIVE MEDICINE

T'ai chi has been shown to reduce the risk of falls in community-dwelling study participants.

DISPOSITION

Falls increase the older adult's risk of hospitalization, institutionalization, and mortality.

REFERRAL

- Referral may be appropriate to cardiologist, ophthalmologist, neurologist, or podiatrist depending on the presence of a specific condition.
- Consider referral to physical therapist for gait and balance training, evaluation for assisted device, or strengthening program.

PEARLS & CONSIDERATIONS

COMMENTS

- Fear of falling may lead to restriction of activities, social isolation, and dependence.
- Older adults with four or more risk factors have a 78% chance of falling.
- Mortality from falls has increased by 42% over the past decade.

PREVENTION

The U.S. Preventive Services Task Force recommends exercise or physical therapy and vitamin D supplementation to prevent falls in community-dwelling adults aged ≥65 who are at increased risk for falls. It does not recommend automatically performing an in-depth multifactorial risk assessment in conjunction with comprehensive management of identified risks to prevent falls in community-dwelling adults aged 65 or older because the likelihood of benefit is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of the circumstances of prior falls, comorbid medical conditions, and patient values.

SCREENING

The "get up and go test" is a quick assessment of balance and gait. A more in-depth screening tool for falls is the Tinetti gait and balance assessment, which evaluates normal and adaptive ability to maintain balance when rising from a chair, standing with eyes closed, turning, and receiving a sternal nudge. It also evaluates several components of gait (step height, postural sway, path deviation). The test is scored on the patient's ability to perform specific tasks. Scoring is done on a 3-point scale with a range of 0 to 2. Individual scores are combined to form three measures: an overall gait assessment score (maximum score = 12), an overall balance assessment score (maximum score = 16), and a gait and balance score (maximum score = 28). In general, patients who score below 19 are at high risk for falls, and those who score 19 to 24 are at risk for falls.

PATIENT & FAMILY EDUCATION

Providing education and information for the patient and caregiver regarding fall prevention strategies in addition to multifactorial risk reduction strategies

SUGGESTED READINGS

Available at ExpertConsult.com

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TABLE 4 Management of Impairments That Contribute to Instability and Falls

Organ System	Impairment	Medical Management	Restorative Services	Environmental Modifications
Eye	Decreased acuity	Corrective lenses	Low vision rehabilitation	Lighting
	Reduced visual fields	Prisms in spectacles	Low vision rehabilitation, teach to scan using head rotation	
	Loss of depth perception	Cataract removal, if indicated	Teach to use shadows to detect depth	Lighting to accent shadows, contrast
	Poor dark adaptation	Switching to glaucoma medications that do not cause miosis		Lighting
Vestibular system	Benign paroxysmal positional vertigo (BPPV)	Epley maneuver	Vestibular rehabilitation	
	Meniere disease	Cautious use of meclizine, diuretics; rarely, surgery	Vestibular rehabilitation	
Peripheral nerve	Neuropathy	Footwear to protect foot and maximize sensation	Assistive devices for haptic enhancement	Hand holds, railings
Central circulation	Reduced brain perfusion	Treatment varies by cause Arrhythmias—medications to control rate and rhythm, pacemakers Postprandial hypotension—frequent small meals		
	Orthostatic hypotension	Treatment varies by cause Adjust offending medications Autonomic neuropathy—salt loading, fluorinated corticosteroids Dehydration—hydration, reduce diuretic dose	Compression hose, calf muscle contractions	
Brain	Reduced attention	Medication adjustment	Practice dual tasks	
	Psychomotor slowing	Medication adjustment	Practice movement speed	
	Abnormal righting reflexes	Antiparkinsonian medication helps bradykinesia more than balance	Assistive devices, practice getting up after a fall	Protective clothing
Effector muscle	Weakness	Reduced activity—treat contributing causes (e.g., CHF, anemia, COPD, arthritis)	Strength-training exercises	Raise chair height
		Focal motor deficit due to spinal stenosis—sometimes surgery Myopathy—adjust offending medications, possibly steroids for myositis	Orthotics, exercise, assistive devices	
Musculoskeletal	Decreased range of m motion		Active and passive range of motion exercise, orthotics	
Pain	Bone and joint	Analgesics, injections	Physical modalities (e.g., heat, massage, assistive devices, orthoses, adaptive equipment)	Place items within easy reach
	Spinal cord, roots, nerves	Injections, surgery, analgesics	Orthoses, assistive devices	Place items within easy reach

CHF, Congestive heart failure; *COPD,* chronic obstructive pulmonary disease.
From Fillit HM et al: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

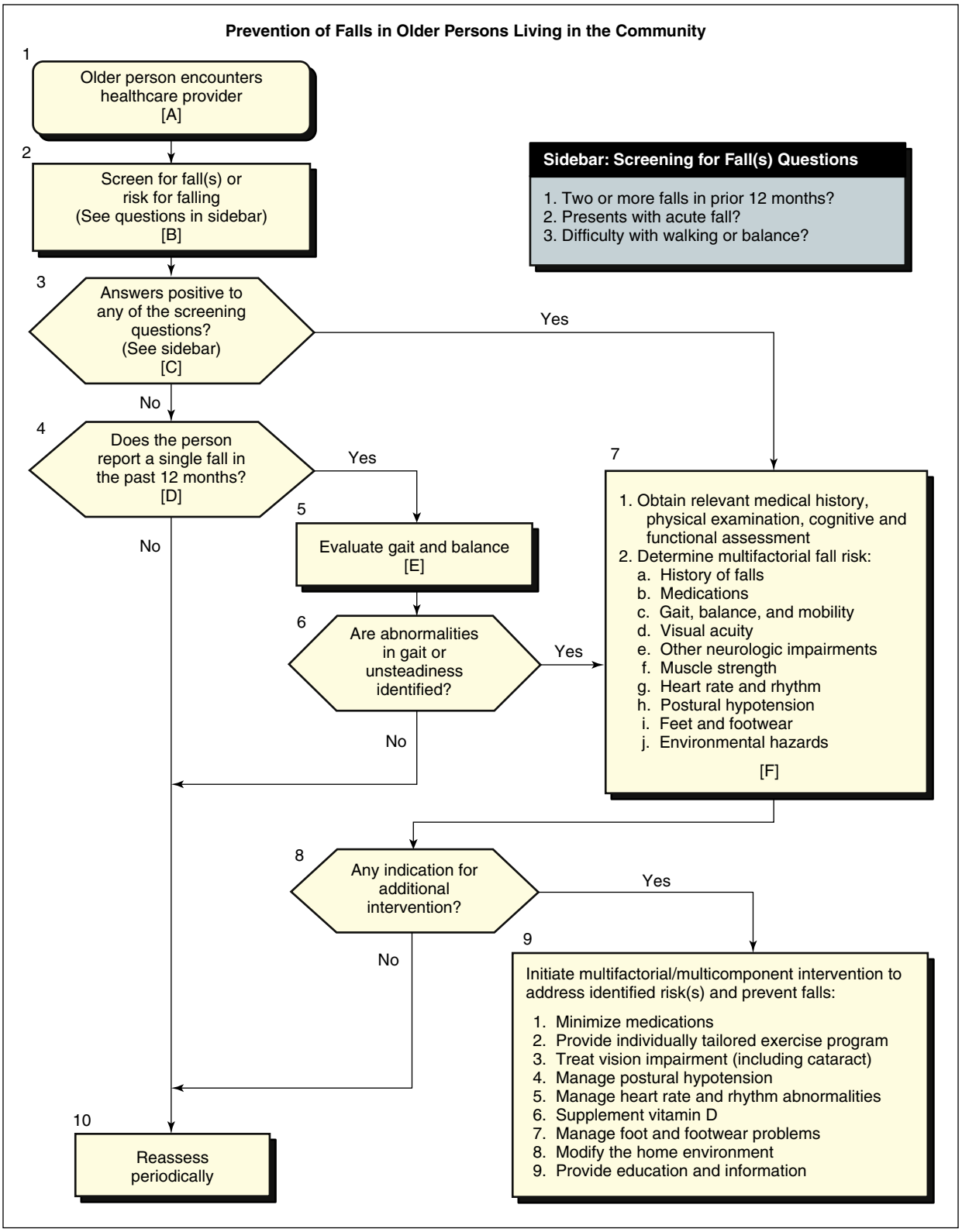

FIG. E1 Guideline for the prevention of falls in older persons living in the community. (From Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society: Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons, *J Am Geriatr Soc* 59:148-157, 2011.)

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Familial Adenomatous Polyposis and Gardner Syndrome PTG

BASIC INFORMATION

DEFINITION

Familial adenomatous polyposis (FAP) is a highly penetrant, autosomal-dominant condition characterized by hundreds of colorectal adenomatous polyps that inevitably progress to cancer (Fig. E1). *Gardner syndrome* is a subset of FAP, with prominent extraintestinal manifestations including dental abnormalities, soft tissue lesions, desmoid tumors, and osteomas.

ICD-10CM CODES

D12.2 Benign neoplasm of ascending colon
D12.3 Benign neoplasm of transverse colon
D12.4 Benign neoplasm of descending colon
D12.5 Benign neoplasm of sigmoid colon
D12.6 Benign neoplasm of colon, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- FAP occurs in approximately 1 in 10,000 births worldwide.
- FAP accounts for <1% of all colorectal cancers.
- Individuals develop hundreds to thousands of adenomatous colorectal polyps.
- Polyps usually present in adolescence.
- 100% lifetime risk for colorectal cancer; most diagnosed by 40 yr of age.
- Gastric, duodenal, periampullary, and small bowel polyps occur but have lower malignant potential.
- Increased risk for other tumors: Desmoid (15%), duodenal/periampullary (7%), thyroid (2%), brain (1%), childhood hepatoblastoma (1%), nasopharyngeal angiofibroma (benign), pancreatic (2%), adrenal adenoma (10%), and gastric (1%).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Phenotypic variability is seen in individuals and families with the same mutation. Extraintestinal manifestations may precede intestinal disease. These findings are reported in at least 20% of individuals with FAP.

- Congenital hypertrophy of the retinal pigment epithelium (CHRPE): Benign fundus lesions, usually present at birth
- Dental abnormalities: Supernumerary or unerupted teeth
- Soft tissue lesions: Epidermal or sebaceous cysts, fibromas, lipomas, desmoid tumors (benign, locally invasive, aggressive connective tissue tumor)
- Osteomas (benign bone growths): Skull, mandible, long bone
- Anemia, occult blood in stool, bowel obstruction, weight loss

ETIOLOGY

- FAP is caused by mutations of the tumor suppressor gene adenomatous polyposis coli *(APC)* on chromosome 5q21 to q22; more than 1000 disease-causing mutations identified. The site of the mutation often correlates with the extraintestinal findings.
- De novo mutations are responsible for approximately 20% of FAP cases. These may be due to germline mutations or somatic cell mosaicism, which is seen when a new mutation occurs in the APC gene post-fertilization and is present in only a subset of cell types or tissues.
- Table E1 summarizes the genetics of colonic polyposis.

DIAGNOSIS

In individuals with a family history, more than 100 adenomatous colorectal polyps, CHRPE lesions, or positive genetic testing confirms diagnosis. In those without a family history, more than 100 adenomatous colorectal polyps suggest the diagnosis, and genetic testing confirms it. The diagnosis should be considered in individuals with ≥10 adenomatous colorectal polyps or fewer polys in the presence of extraintestinal findings.

DIFFERENTIAL DIAGNOSIS

- Turcot syndrome
- Attenuated FAP (also APC gene mutation, but presents with fewer polyps [<100], at a later age, and has lower cancer risk than FAP [~80% lifetime risk])
- MUTYH-associated polyposis
- Peutz-Jeghers syndrome
- Juvenile polyposis syndrome
- Cowden disease
- Lynch syndrome
- Hereditary mixed polyposis syndrome
- Polymerase proofreading-associated polyposis
- Hyperplastic polyposis
- Table 2 compares various adenomatous polyposis syndromes

WORKUP

History, physical examination, laboratory tests, imaging studies

DIAGNOSTIC SCREENING OPTIONS

GENETIC TESTING: NOTE: Genetic counseling should be performed, and written informed consent obtained before testing. Refer to a specialized center for counseling and evaluation.

- Should be offered to first-degree relatives of affected individuals (with an identified mutation) at age 10 to 12 yr and clinically suspected individuals.
- Able to identify a mutation in approximately 80% of families. To ensure that the family has a detectable mutation, test an affected family member first.
- If positive in the affected individual, the test can differentiate with 100% accuracy affected and unaffected family members. If negative in the affected individual, screening family members will not be useful in determining disease status.
- If no known family history exists, screening the clinically suspected individual is reasonable. A positive test rules in FAP but a negative test does not rule it out.
- Numerous testing techniques available; may require multiple tests to identify the mutation.

SIGMOIDOSCOPY:

- Individuals with a positive genetic test, untested at-risk family members, or patients from families with an unidentified *APC* mutation: Annual flexible sigmoidoscopy or colonoscopy beginning at 10 to 12 yr of age.
- Once adenomatous polyps are detected, patients should undergo colonoscopy and evaluation for colectomy.
- Negative genetic test in patients from families with an identified mutation: Average risk screening.
- Screening with upper endoscopy should begin at age 25 and should include visualization of duodenal papilla. Additional annual screening should include thyroid ultrasound.

CHRPE: Lesions occur in up to 80% of families and are a reliable indicator of affected status in these families.

TREATMENT

- Prophylactic colectomy or proctocolectomy: Timing determined by polyp number, size, and degree of dysplasia. Postsurgical endoscopic surveillance annually.
- Additional screening:
  1. Annual physical examination: History, examination (including thyroid), and blood tests
  2. Upper endoscopy to screen for gastric/duodenal polyps: Baseline at age 25 yr (earlier if colon polyps detected) and repeated every 3 mo to 4 yr based on findings
  3. Annual thyroid ultrasound: Begin in teenage yrs
  4. Other possible cancer sites imaged if symptoms occur or if these cancers have occurred in relatives
- Treat soft tissue lesions and osteomas for symptoms or cosmetic concerns. Treat desmoid tumors if they pose a risk to adjacent structures.

DISPOSITION

- 100% chance of colorectal cancer in untreated individuals. Many other neoplasms occur at higher rates.
- Metastatic colorectal cancer is the leading cause of death (58%), followed by desmoid tumors (11%), and duodenal/periampullary adenocarcinoma (8%).

REFERRAL

- Patients should be managed at centers with expertise in FAP, including a gastroenterologist, medical geneticist, and surgeon.
- Genetic counselors can be found at www.nsgc.org.
- Genetic clinics and laboratories can be found at www.ncbi.nlm.nih.gov/gtr.

TABLE 2 Adenomatous Polyposis Syndromes

Syndrome	Gene Mutation	Polyps	Extraintestinal Abnormalities
Classic FAP	*APC* (usually truncated protein)	Colonic adenomas (thousands) Duodenal, periampullary adenomas Gastric fundic gland polyps Jejunal and ileal adenomas Ileal lymphoid polyps	Mandibular osteomas Dental abnormalities
Gardner variant of FAP	*APC*	Same as FAP	Osteomas (mandible, skull, long bones) CHRPE Desmoid tumors Epidermoid and sebaceous cysts Fibromas, lipomas Thyroid, adrenal tumors
Turcot variant of FAP	*APC* DNA MMR*	Colonic adenomas (sometimes fewer than in classic FAP)	Medulloblastoma Glioblastoma multiforme CHRPE
Attenuated FAP	*APC* 5′ and 3′ regions	Colonic adenomas (<100; proximal colon) Duodenal, periampullary adenomas Gastric fundic gland polyps	Mandibular osteomas (rare)
Familial tooth agenesis	*Axin2* (APC pathway)	Colonic adenomas Hyperplastic polyps	Agenesis of teeth
Bloom syndrome	*BLM*	Colonic adenomas	Small stature Facial erythema/telangiectasia Male sterility Adenocarcinomas, leukemia, lymphoma
MUTYH polyposis	*MUTYH (MYH)*	Colonic adenomas (5-100) Duodenal polyposis Gastric cancer	CHRPE Osteomas

*May be more appropriately classified under hereditary nonpolyposis colon cancer.
APC, Adenomatous polyposis coli; *CHRPE,* congenital hypertrophy of the retinal pigment epithelium; *DNA,* deoxyribonucleic acid; *FAP,* familial adenomatous polyposis; *MMR,* mismatch repair.
From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, WB Saunders.

PEARLS & CONSIDERATIONS

- Management should be individualized based on genotype, phenotype, and individual preferences.
- Sulindac (NSAID) and celecoxib (COX-2 inhibitor) can cause duodenal and colorectal polyp regression in individuals with FAP. Preliminary studies with other agents also show polyp regression. Their ability to reduce cancer risk remains unknown; they do not replace colon resection for cancer prevention.
- Desmoid tumors usually present in the 30s, frequently occur in the abdomen, and are difficult to treat with high rates of recurrence. Growth and recurrence are stimulated by surgery.
- Screen children of affected parents (from infancy to age 7 yr) biannually with alpha-fetoprotein level and liver ultrasound to rule out hepatoblastoma.
- Preimplantation and prenatal genetic testing is available.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Familial Adenomatous Polyposis and Polyposis Syndromes (Patient Information)
Colorectal Cancer (Related Key Topic)
Lynch Syndrome (Related Key Topic)
Peutz-Jeghers Syndrome and Other Polyposis Syndromes (Related Key Topic)

AUTHOR: **Sudeep K. Aulakh, MD**

SUGGESTED READINGS

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FIG. E1 Familial adenomatous polyposis with innumerable adenomatous polyps, increasing in size and density from proximal *(upper left)* to distal *(lower right)*. (From Skarin AT: *Atlas of diagnostic oncology*, ed 4, St Louis, 2010, Mosby.)

TABLE E1 Genetics of Colonic Polyposis

Syndrome (Abbreviation, Synonym)	Gene(s)	Molecular Phenotype	Noncolonic Organs Affected
Sporadic adenomatous polyp	Unknown	Chromosomal instability (aneuploidy)	None known
Familial adenomatous polyposis (FAP)	*APC*	Chromosomal instability (aneuploidy)	Duodenum, stomach, pancreas, thyroid, liver, central nervous system
Attenuated familial adenomatous polyposis (AFAP)	*APC*	Chromosomal instability (aneuploidy)	Duodenum, thyroid, liver, central nervous system
Hereditary nonpolyposis colon cancer (HNPCC, Lynch syndrome)	*hMLH1, hMSH2, hMSH6, hPMS2*	MSI	Endometrium, stomach, ovary, biliary and urinary tracts, small bowel, central nervous system
MUTYH-linked adenomatous polyposis (MAP)	*MUTYH*	Chromosomal instability (aneuploidy)	Duodenum
Peutz-Jeghers syndrome (PJS)	*STK1* (70%)	Unknown	Breast, pancreas, stomach, ovary, lung, small bowel, uterus, testis
Juvenile polyposis syndrome	*SMAD4, BMPR1A*	Unknown	Blood vessels (hereditary hemorrhagic telangiectasia)
Hyperplastic polyposis	*SMAD4, BMPR1A* (40%), *PTEN*	Unknown	Stomach, pancreas, small bowel

MSI, Microsatellite instability.
From Niederhuber JE: *Abeloff's Clinical Oncology*, ed 6, Philadelphia, 2020, Elsevier.

Familial Mediterranean Fever (FMF)

BASIC INFORMATION

DEFINITION

Familial Mediterranean fever (FMF) is a hereditary periodic fever syndrome. FMF type 1 is characterized by recurrent short episodes of inflammation and serositis, while FMF type 2 is characterized by amyloidosis as the first clinical manifestation.

SYNONYMS

Non-neuropathic heredofamilial amyloidosis
Benign paroxysmal peritonitis
Familial paroxysmal polyserositis
Recurrent polyserositis
Periodic fever
FMF

ICD-10CM CODE

E85.0 Non-neuropathic heredofamilial amyloidosis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Varies depending on the ethnic background of the population. FMF affects primarily eastern Mediterranean populations (e.g., Armenian, Arab, Turkish, Jewish) but is not restricted to these ethnic groups. In Armenians, the prevalence is 1 in 500, and in people of Turkish descent, estimates are 1 per 1000. As many as 1 in 5 people of these ethnic backgrounds is a carrier of FMF.
PREDOMINANT SEX AND AGE: Male:female ratio is 1.5 to 2:1. Disease onset is typically before age 20, with the vast majority of initial attacks occurring before age 10. Very rare to have onset after age 40.
GENETICS: Pattern of inheritance is primarily autosomal recessive. Mutations in the *MEFV* gene, which encodes the pyrin protein, causes the disease in many cases. There are more than 80 known mutations, and in 10% to 20% of cases no mutation is found, although FMF diagnostic criteria fulfilled.
RISK FACTORS: Affected first-degree relatives, consider offering genetic testing

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Sporadic, recurrent attacks of fever and severe pain, abrupt in onset, usually lasting 1 to 3 days, with spontaneous resolution.
- Almost all patients have episodic abdominal pain. On exam may have tenderness, guarding, rebound and rigidity; may be mistaken for an acute surgical abdomen.
- Attacks localized to chest in up to half of patients due to pleural inflammation or referred from subdiaphragmatic inflammation.
- Arthritis is usually mono- or oligoarticular, involving large joints (e.g., knee, ankle, hip). Pain is usually out of proportion to swelling.
- Up to 50% of patients can have an erysipelas-like rash, usually on lower extremities (Fig. E1).
- Rarer manifestations include prolonged febrile myalgias, pericarditis, orchitis, aseptic meningitis, migratory polyarthritis, Henoch-Schönlein purpura, sacroiliitis, infertility.

ETIOLOGY

MEFV is the only gene in which pathogenic variants are known to cause FMF, and it encodes pyrin, a protein that plays a role in the innate immune system and helps regulate the inflammasome. The exact mechanism that triggers acute FMF attacks remains unclear.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other periodic fever syndromes (Table E1)
- Systemic rheumatic diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, adult onset Still disease, abdominal vasculitis)
- Infection

WORKUP

The diagnosis is based on a detailed history with suggestive clinical symptoms and is supported by ethnic origin and family history; the diagnosis is not excluded by negative genetic testing. If genetic testing is negative but clinical suspicion remains high, can consider trial of colchicine; would expect a favorable response.

LABORATORY TESTS

- CBC: Leukocytosis with neutrophil predominance
- Elevated acute phase reactants: erythrocyte sedimentation rate, c-reactive protein, fibrinogen, serum amyloid A protein
- Sterile, inflammatory synovial fluid if arthrocentesis conducted
- Urinalysis with proteinuria should raise concern for renal amyloidosis
- *MEFV* gene mutation (75% are V726A, M694V, M694I, M680I, E148Q)
- If undergoing abdominal surgery, a negative laparotomy is expected

FIG. E1 Familial Mediterranean fever rash. A, Erysipelas-like erythema (ELE) of familial Mediterranean fever (FMF): erythematous plaques on the foot. **B,** ELE of FMF: erythematous plaques on the lower extremity. (From Callen JP et al: *Dermatologic signs of systemic disease,* ed 5, 2017, Elsevier.)

TABLE E1 Hereditary Periodic Fever Syndromes

	Hereditary Periodic Fever Syndromes					
				Cryopyrin-associated periodic syndromes (CAPS)		
	FMF	**HIDS**	**TRAPS***	**MWS**	**FCAS† (1 and 2)**	**NOMID (CINCA)**
Ethnicity	Sephardic Jewish, Arab, Turkish, Italian, Armenian	Predominantly Dutch, Northern European	Any ethnic group	Any ethnic group	Any ethnic group	Any ethnic group
Inheritance	AR	AR	AD	AD	AD	AD
Gene	*MEFV*	*MVK* ‡	*TNFRSF1A*	*NLRP3 (CIAS1)*	*NLRP3 (CIAS1); NLRP12*	*NLRP3 (CIAS1)*
Chromosome	16p13.3	12q24	12p13	1q44	1q44	1q44
Protein	Pyrin	Mevalonate kinase	TNF receptor-1A	Cryopyrin	Cryopyrin; monarch-1	Cryopyrin
Attack length	1-3 days	3-7 days	Often >7 days	1-2 days	Minutes – 3 days	Continuous + flares
Mucocutaneous lesions	Erysipeloid erythema and edema	Erythematous macules and edematous papules, which may become purpuric; occasional oral and vaginal ulcers	Erythematous patches and edematous plaques (often annular or serpiginous); later ecchymotic in appearance; rarely oral ulcers	Urticarial papules and plaques	Cold-induced urticarial papules and plaques	Urticarial papules and plaques; occasional oral ulcers
Distribution of skin lesions	Favor lower leg, foot	Widespread on face, trunk, and extremities	Migrate distally on an extremity with underlying myalgia; may be more widespread	Widespread on face, trunk, and extremities	Extremities > trunk, face	Widespread on face, trunk, and extremities
Abdominal pain and serositis	Peritonitis > pleuritis > pericarditis	Abdominal pain, but rarely serositis	Peritonitis > pleuritis, pericarditis	Abdominal pain, but rarely serositis	Rare	Rare
Musculoskeletal findings	Monoarthritis > exercise-induced myalgia	Arthralgia > oligoarticular arthritis > myalgia	Migratory myalgia > arthralgia > monoarthritis	Myalgia ("lancinating limb pain"), arthralgia > large-joint oligoarticular arthritis	Arthralgia > myalgia	Epiphyseal and patellar overgrowth, arthritis, deforming arthropathy
Ocular findings	Uncommon	Uncommon	Periorbital edema, conjunctivitis, rarely uveitis	Conjunctivitis, episcleritis, optic disc edema	Conjunctivitis	Conjunctivitis, uveitis, optic disc edema, blindness
Neurologic findings	Rarely aseptic meningitis	Headache	Headache	Sensorineural hearing loss; headache	Headache	Sensorineural hearing loss; aseptic meningitis, seizures
Other clinical findings	Acute scrotal swelling; splenomegaly	Cervical LAN, HSM	Scrotal pain; splenomegaly, occasional LAN			LAN, HSM; dysmorphic facies—frontal bossing, protruding eyes
Amyloidosis	Most common in M694V homozygotes	Rare	~15% of cases	~25% of cases	Uncommon	Late complication
Dermal infiltrate in typical skin lesions	Neutrophils	Neutrophils and/or lymphocytes; mild vasculitis common	Lymphocytes, monocytes, and a few neutrophils	Neutrophils and/or lymphocytes (sparse)	Neutrophils (perivascular)	Neutrophils (perivascular + periadnexal)
Cutaneous vasculitis	LCV/HSP (5%-10%), PAN (~1%)	LCV/HSP	Lymphocytic small vessel (rare)			

TABLE E1 Hereditary Periodic Fever Syndromes—cont'd

	Hereditary Periodic Fever Syndromes					
				Cryopyrin-associated periodic syndromes (CAPS)		
	FMF	HIDS	TRAPS*	MWS	FCAS† (1 and 2)	NOMID (CINCA)
Laboratory abnormalities§	Low C5a inhibitor in serosal fluids	High serum IgD‖ (>100 IU/ml) and IgA1; mevalonate in urine during attacks; low lymphocyte mevalonate kinase	Low serum soluble TNF receptor-1 (<1 ng/ml between attacks)			
Treatment	Colchicine prophylaxis; NSAIDs, TNF inhibitors, thalidomide, herbal remedies	Corticosteroids for acute attacks; anakinra; TNF inhibitors (e.g., etanercept); simvastatin	Corticosteroids; TNF inhibitors (e.g., etanercept)	Corticosteroids; IL-1/IL-1R antagonists: rilonacept, canakinumab, anakinra	IL-1/IL-1R antagonists	IL-1/IL-1R antagonists

AD, Autosomal dominant; *AR*, autosomal recessive; *CINCA*, chronic infantile neurologic, cutaneous, and articular syndrome; *FCAS*, familial cold autoinflammatory syndrome; *FMF*, familial Mediterranean fever; *HIDS*, hyperimmunoglobulinemia D with periodic fever syndrome; *HSM*, hepatosplenomegaly; *HSP*, Henoch-Schönlein purpura; *Ig*, immunoglobulin; *IL*, interleukin; *LAN*, lymphadenopathy; *LCV*, leukocytoclastic vasculitis; *MWS*, Muckle–Wells syndrome; *NOMID*, neonatal-onset multisystem inflammatory disease; *NSAID*, nonsteroidal antiinflammatory drug; *PAN*, polyarteritis nodosa; *TNF*, tumor necrosis factor; *TRAPS*, TNF receptor-associated periodic syndrome.
*Includes familial Hibernian fever.
†Also referred to as familial cold urticaria.
‡Allelic with mevalonic aciduria, which is characterized by dysmorphology, psychomotor retardation, and progressive cerebellar ataxia as well as periodic fevers and other features of HIDS.
§Genetic analysis can be performed to confirm the diagnosis.
‖IgD levels are occasionally normal; elevated IgD may also be observed in FMF and TRAPS.
Courtesy, Julie V Schaffer, M.D. In Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

IMAGING STUDIES

During an acute attack, depending on manifestations such as peritonitis, pleuritis, or arthritis, may see air-fluid levels, pleural effusions, and/or synovial effusions.

Rx TREATMENT

The main goals of treatment are to (1) prevent acute attacks and (2) prevent the development of amyloidosis.

ACUTE GENERAL AND CHRONIC Rx

- Supportive care during acute episodes with IVF, NSAIDs, pain control.
- To prevent attacks first-line Rx is colchicine, 0.6 to 1.8 mg daily.
  1. If colchicine unresponsive, possibility of noncompliance, or reconsider diagnosis.
  2. Should continue colchicine in pregnant FMF patients, and it is safe to breastfeed.
- If truly colchicine unresponsive, IL-1 inhibition (anakinra, rilonacept, canakinumab) is second-line; 5% to 10% of patients are colchicine resistant. There are also successful reports of using thalidomide, TNF inhibitors, and tocilizumab.

DISPOSITION

Since the usage of colchicine, most treated patients are asymptomatic and do not commonly see development of AA amyloidosis.

REFERRAL

Rheumatology

PEARLS & CONSIDERATIONS

COMMENTS

- Most patients have disease onset before age 20, and attacks typically last 1 to 3 days. Colchicine is the standard of care for prophylaxis of attacks and prevention of amyloidosis. Should continue treatment with colchicine during pregnancy. Should question diagnosis if there is no response to colchicine. Type AA amyloidosis is the most frequent complication of FMF, with the kidneys being the most affected organ.
- Contrary to expectations, the incidence of cancer in patients with FMF is significantly lower than the general population.

PREVENTION

Should consider referring all first-degree relatives of FMF patients for genetic testing, whether or not they have symptoms.

PATIENT & FAMILY EDUCATION

https://rarediseases.info.nih.gov/diseases/6421/disease

AUTHOR: **Daphne Scaramangas-Plumley, MD**

SUGGESTED READINGS

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De Benedetti S et al: Canakinumab for the treatment of autoinflammatory recurrent fever syndromes, *NEJM* 378(20):1908-1919, 2018.

Ozen S et al: EULAR recommendations for the management of familial Mediterranean fever, *Ann Rheum Dis* 75:644-651, 2016.

Padeh S, Berkun Y: Familial Mediterranean fever, *Curr Opin Rheumatol* 28:523-529, 2016.

Fatty Liver of Pregnancy, Acute

BASIC INFORMATION

DEFINITION

Acute fatty liver of pregnancy (AFLP) is characterized histologically by microvesicular fatty cytoplasmic infiltration of hepatocytes with minimal hepatocellular necrosis.

SYNONYMS

Acute fatty metamorphosis
Acute yellow atrophy
AFLP
Acute fatty liver of pregnancy

ICD-10CM CODES

026.611	Liver and biliary tract disorders in pregnancy, first trimester
026.612	Liver and biliary tract disorders in pregnancy, second trimester
026.613	Liver and biliary tract disorders in pregnancy, third trimester
026.619	Liver and biliary tract disorders in pregnancy, unspecified trimester

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Rare: 1 in 10,000 to 1 in 20,000 pregnancies
- Equal frequencies in all races and at all maternal ages

AVERAGE GESTATIONAL AGE: 37 wk (range 28 to 42 wk)

- 20% present postnatally

RISK FACTORS:

- Primiparity
- Multiple gestation
- Male fetus
- History of type 2 diabetes mellitus
- Preeclampsia

GENETICS: Some with a familial deficiency of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Initial manifestations:
  1. Nausea and vomiting (70%)
  2. Pain in right upper quadrant or epigastrium (50% to 80%)
  3. Malaise and anorexia
- Jaundice often in 1 to 2 wk
- Hypoglycemia
- Late manifestations:
  1. Fulminant hepatic failure
  2. Encephalopathy
  3. Renal failure
  4. Pancreatitis
  5. Gastrointestinal and uterine bleeding
  6. Disseminated intravascular coagulation (10%)
  7. Seizures
  8. Coma
- Liver:
  1. Usually small
  2. Normal or enlarged in preeclampsia, eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), and acute hepatitis
  3. Coexistent preeclampsia in up to 46% of patients

ETIOLOGY

- Fetal long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) deficiency results in transplacental passage of excess fetal fatty acids and subsequent accumulation in the maternal liver.
- Postulated that inhibition of mitochondrial oxidation of fatty acids may lead to microvesicular fatty infiltration of liver.
- Fatty metamorphosis of preeclamptic liver disease believed to be of different etiology.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute gastroenteritis
- Preeclampsia or eclampsia with liver involvement
- HELLP syndrome
- Acute viral hepatitis
- Fulminant hepatitis
- Drug-induced hepatitis caused by halothane, phenytoin, methyldopa, isoniazid, hydrochlorothiazide, or tetracycline
- Intrahepatic cholestasis of pregnancy
- Gallbladder disease
- Reye syndrome
- Hemolytic-uremic syndrome
- Budd-Chiari syndrome
- Systemic lupus erythematosus

WORKUP

- A clinical diagnosis is based predominantly on physical and laboratory findings (Swansea criteria).
- Most definitive diagnosis is through liver biopsy with oil red O staining and electron microscopy.
- Liver biopsy is reserved for atypical cases only and only after any existing coagulopathy is corrected with fresh frozen plasma because of concerns for excessive bleeding.

LABORATORY TESTS

Tests to determine the following:

- Hypoglycemia (often profound <60 mg/dl)
- Hyperammonemia
- Elevated aminotransferases (usually <500 U/ml)
- Thrombocytopenia
- Leukocytosis (white blood cell count >15,000)
- Hyperbilirubinemia (usually <10 mg/dl)
- Low albumin
- Hypofibrinogenemia (<300 mg/dl)
- Disseminated intravascular coagulation (DIC) (in 75%)

IMAGING STUDIES

- Ultrasound: Best used to rule out other diseases in the differential diagnosis such as gallbladder disease
- CT scan: Plays minimal role because of a high false-negative rate

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient is admitted to intensive care unit for stabilization.
- Fetus is delivered; spontaneous resolution usually follows delivery.
- Mode of delivery is based on obstetric indications and clinical assessment of disease severity.

ACUTE GENERAL Rx

- Decrease in endogenous ammonia through dietary protein restriction; neomycin 6 to 12 g/day PO to decrease presence of ammonia-producing bacteria; magnesium citrate 30 to 50 ml PO or enema to evacuate nitrogenous wastes from colon.
- Administration of IV fluids with glucose to keep glucose levels >60 mg/dl.
- Coagulopathy corrected with fresh frozen plasma.
- Avoidance of drugs metabolized by liver.
- Aggressive avoidance and treatment for nosocomial infections; consideration of prophylactic antibiotics.
- Monitor closely for development of complications such as hepatic encephalopathy, pulmonary edema, DIC, and respiratory arrest.
- Plasma exchange after delivery may result in a lower maternal mortality.

CHRONIC Rx

Orthotopic liver transplantation is the only treatment for irreversible liver failure.

DISPOSITION

- Before 1980, both maternal and fetal mortality rates were approximately 85%.
- Since 2008, maternal mortality rates have been less than 10%.
- Usually rapid return of liver function to normal after delivery.
- Minimal risk of recurrence with future pregnancies.

REFERRAL

- To tertiary health care facility as soon as diagnosis is suspected.
- Twenty percent of infants born to mothers with AFLP have LCHAD; after birth, all infants should be evaluated for the deficiency.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Eclampsia (Related Key Topic)
Preeclampsia (Related Key Topic)
HELLP Syndrome (Related Key Topic)

AUTHOR: **Kelly Ruhstaller, MD**

SUGGESTED READINGS

Goel A et al: Pregnancy-related liver disorders, *J Clin Exp Hepatol* 4(2):151-162, 2014.

Kamimura K et al: Advances in understanding and treating liver diseases during pregnancy: a review, *World J Gastroentesterol* 21(17):5183-5590, 2015.

Westbrook RH et al: Pregnancy and liver disease, *J Hepatol* 64:933-945, 2016.

Wolfe JL et al: Acute fatty liver disease of pregnancy, *Am J Gastroenterol* 112:838-846, 2017.

BASIC INFORMATION

DEFINITION

Febrile seizures are seizures that occur in febrile children (fever of at least 100.4° F [38° C]) between the ages of 6 and 60 mo in the absence of infection of the central nervous system (CNS), metabolic disturbance, or history of neonatal seizures or a previous unprovoked seizure. Febrile seizures are subdivided into two categories: Simple and complex. Simple febrile seizures last <15 min, are generalized (without a focal component), and occur once in a 24-hr period, whereas complex febrile seizures are prolonged (>15 min), show focal neurologic signs, or occur more than once in 24 hr.

SYNONYMS

Febrile convulsions
Seizures, febrile

ICD-10CM CODE
R56.0 Febrile convulsions

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Febrile seizures are the most common seizures of childhood. 2% to 5% of children will have a febrile seizure by age 60 mo. Simple febrile seizures represent 65% to 90% of febrile seizures.
PREVALENCE: Represents up to 18% of all pediatric epilepsy syndromes
PREDOMINANT SEX AND AGE: Slightly more common in boys than girls
PEAK INCIDENCE: 6 to 60 mo

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Children with febrile seizures have normal physical and neurologic examinations.
- Viral illnesses are the predominant cause of febrile seizures.

ETIOLOGY

- Viral infections are a common cause of a fever that triggers febrile seizures.
- Febrile seizures tend to occur in families. Although clear evidence exists for a genetic basis of febrile seizures, the mode of inheritance is unknown.
- Febrile seizures are likely multifactorial with genetic and environmental factors.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- CNS infection (i.e., meningitis)
- Epilepsy

WORKUP

- It is important to first investigate whether an underlying infection exists. Fig. 1 describes guidelines for febrile seizure evaluation.
- In patients with simple self-limited febrile seizures with rapid return to consciousness and a normal neurologic examination, further workup is not routinely recommended.
- In patients with complex febrile seizures, laboratory workup and brain imaging are recommended.
- Electroencephalogram (EEG) is not routinely recommended in the evaluation of a neurologically healthy child with simple febrile seizures.

LABORATORY TESTS

- Routine blood workup (CBC with differential, complete metabolic panel (CMP), electrolytes), blood and urine cultures are often performed, but there is no evidence that these tests are necessary for identifying the cause of a simple febrile seizure.
- Cerebrospinal fluid (CSF) analysis: Follow lumbar puncture guidelines of the American Academy of Pediatrics.
- Lumbar puncture should be performed in children with febrile seizures and signs and symptoms of meningitis (e.g., neck stiffness, Kernig sign, Brudzinski sign), or if the patient history or examination suggests the presence of meningitis or other intracranial infection.
- In infants 6 to 12 mo of age with febrile seizures, lumbar puncture is an option if they have not received the recommended *Haemophilus influenza* type b (Hib) or pneumococcal vaccinations, or if their immunization status is unknown.
- Lumbar puncture is also considered an option in children with febrile seizures pretreated with antibiotics.

IMAGING STUDIES

- MRI of the brain is not required in the routine evaluation of patients with simple febrile seizures.
- Imaging of the brain should be considered in children with complex febrile seizures and in children with focal neurologic deficits.
- CT scans of the head should be avoided in children, if possible, due to exposure to radiation and the relative low yield of the test compared with MRI. CT scans of the head are reserved for neurologic emergencies and are adjusted for weight in children.

TREATMENT

Febrile seizures do not usually require antiepileptic drug treatment.

NONPHARMACOLOGIC THERAPY

Not applicable

GENERAL Rx

Symptomatic treatment of fever

CHRONIC Rx

No chronic treatment for febrile seizures is recommended.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Not applicable

DISPOSITION

- Treatment is not recommended.
- Febrile seizures should stop by age 60 mo.
- Risk of recurrence in the first 2 yr after an initial febrile seizure is 15% to 70%.

REFERRAL

Patients with recurrent febrile seizures need to be referred for a consultation by a pediatric neurologist.

PEARLS & CONSIDERATIONS

COMMENTS

- It is crucial to find out the etiology of the fever and to treat it appropriately.
- Patient with seizures and fever after age 60 mo are not classified as febrile seizures.

PREVENTION

Antipyretics do not reduce the recurrence risk of febrile seizures. However, fever should be treated and worked up independently of the diagnosis of febrile seizures.

PATIENT & FAMILY EDUCATION

- Children with febrile seizures do not need antiepileptic drug treatment.
- Patient education and information can be obtained at the Epilepsy Foundation: www.epilepsyfoundation.org. Parents should be reassured that children without underlying developmental problems will usually not have lasting neurologic effects from febrile seizures.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Fever Seizures (Patient Information)

AUTHOR: **Patricio Sebastian Espinosa, MD, MPH**

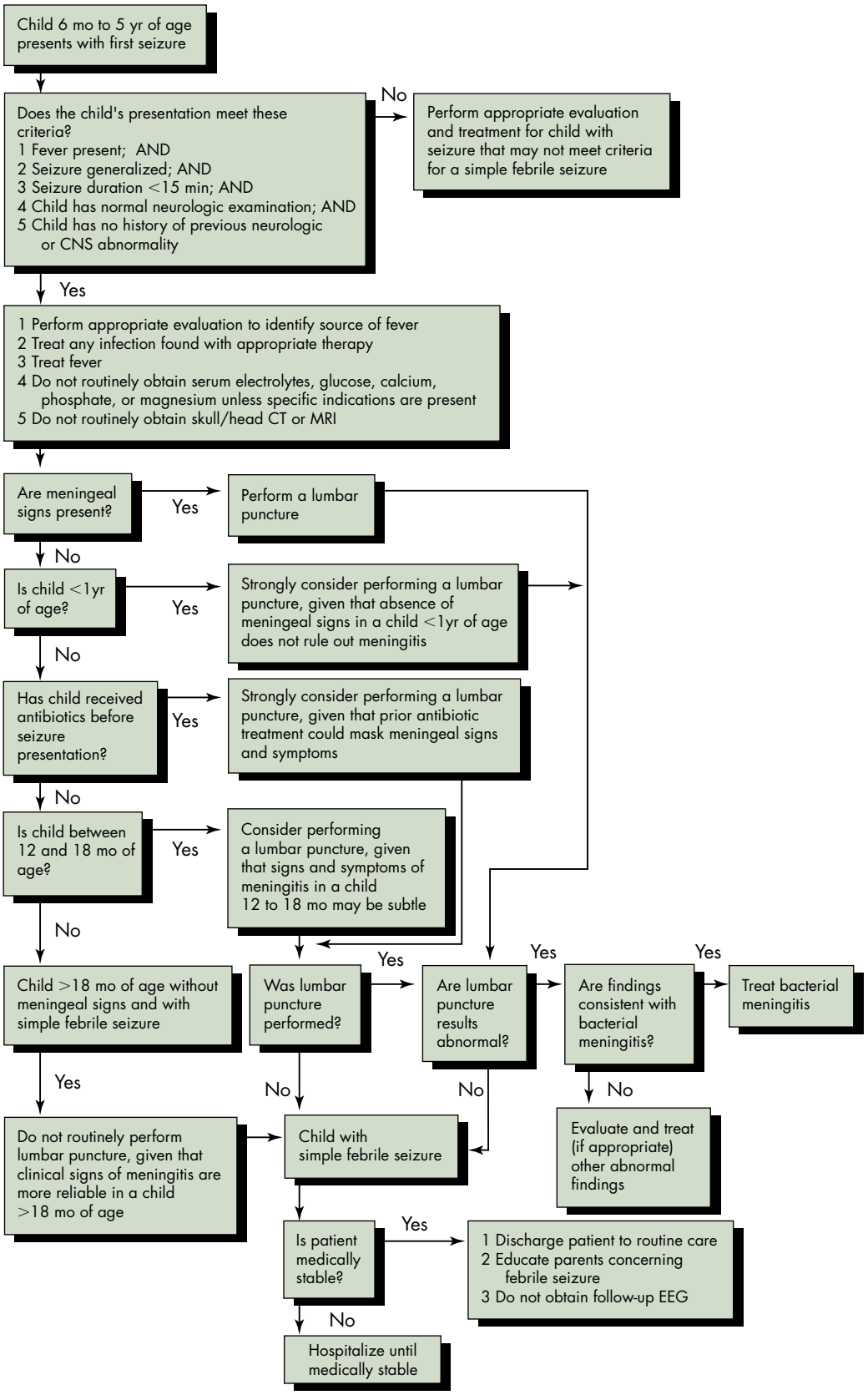

FIG. 1 Guidelines for febrile seizure evaluation. *CNS,* Central nervous system; *CT,* computed tomography; *EEG,* electroencephalogram; *MRI,* magnetic resonance imaging. (From Custer JW, Rau RE: *The Harriet Lane handbook,* ed 18, St Louis, 2009, Mosby.)

SUGGESTED READINGS

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Subcommittee on Febrile Seizures; American Academy of Pediatrics: Neurodiagnostic evaluation of the child with a simple febrile seizure, *Pediatrics* 127(2):389-394, 2011.

Felty Syndrome

BASIC INFORMATION

DEFINITION

Felty syndrome (FS) is originally defined as the triad of seropositive rheumatoid arthritis (RA), splenomegaly, and neutropenia. The hallmark of FS is a persistent, idiopathic neutropenia. Splenomegaly is extremely variable in its extent and is no longer an absolute diagnostic requirement; it is an extraarticular manifestation of seropositive RA.

SYNONYM

FS

ICD-10CM CODES

M05.00	Felty syndrome, unspecified site
M05.011	Felty syndrome, right shoulder
M05.012	Felty syndrome, left shoulder
M05.019	Felty syndrome, unspecified shoulder
M05.021	Felty syndrome, right elbow
M05.022	Felty syndrome, left elbow
M05.029	Felty syndrome, unspecified elbow
M05.031	Felty syndrome, right wrist
M05.032	Felty syndrome, left wrist
M05.039	Felty syndrome, unspecified wrist
M05.041	Felty syndrome, right hand
M05.042	Felty syndrome, left hand
M05.049	Felty syndrome, unspecified hand
M05.051	Felty syndrome, right hip
M05.052	Felty syndrome, left hip
M05.059	Felty syndrome, unspecified hip
M05.061	Felty syndrome, right knee
M05.062	Felty syndrome, left knee
M05.069	Felty syndrome, unspecified knee
M05.071	Felty syndrome, right ankle and foot
M05.072	Felty syndrome, left ankle and foot
M05.079	Felty syndrome, unspecified ankle and foot
M05.09	Felty syndrome, multiple sites

EPIDEMIOLOGY & DEMOGRAPHICS

- The lifetime risk of FS for a patient initially diagnosed with RA is estimated to be 1%. The prevalence has been steadily declining over the past two decades.
- Demographics are similar to RA, affecting 60% to 80% women.
- FS patients tend to have a family history of RA and be HLA-DR4 positive.
- Recognized in patients in their late 40s or early 50s who have had RA for >10 yr.
- FS is rare in African Americans because of the infrequency of HLA-DR4 in this population.

CLINICAL PRESENTATION

- Felty syndrome (FS) is an uncommon extraarticular manifestation of rheumatoid arthritis (RA) with neutropenia (absolute neutrophil counts <2000/μl) and splenomegaly.
  1. RA is typically severe, long-standing (at least >10 yr) with seropositive rheumatoid factor (RF) or anti-citrullinated peptide antibodies (ACPA).
- Extraarticular manifestations (rheumatoid nodules, vasculitis, skin lesions, pleuropericarditis, and other) are more frequently found in patients with FS than RA.
- One third of patients may have relatively inactive synovitis. Erythrocyte sedimentation rate (ESR) is almost always significantly elevated even in patients with inactive synovitis.
- Splenomegaly and neutropenia are rarely present before the arthritis.
- Mild hepatomegaly is common (up to 68%).
- The degree of splenomegaly varies and may be detectable only by imaging studies; the degree of splenomegaly has no correlation with the degree of neutropenia.
- Patients with FS have a twentyfold increased frequency of bacterial infections compared with other RA patients.
- FS patients have greater risk of developing non-Hodgkin lymphoma than RA patients. Similarly, FA patients are at increased risk of lung disease. Differentiation between large granular lymphocyte (LGL) leukemia and FS is necessary because both can present with neutropenia and are associated with RA.

ETIOLOGY

The pathogenesis of FS is probably multifactorial, including immune dysfunction resulting from an imbalance between granulocyte production and destruction from the circulatory pool.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Systemic lupus erythematosus
- LGL leukemia
- Drug reaction (conventional disease-modifying anti-rheumatic drugs [DMARDs] or biologic DMARDs)
- Myeloproliferative disorders
- Lymphoma or reticuloendothelial malignancies
- Cirrhosis with portal hypertension
- Sarcoidosis
- Tuberculosis
- Amyloidosis
- HIV infection
- Epstein-Barr virus infection
- Malaria

LABORATORY TESTS

- There is no single diagnostic test for patients with FS.
- CBC with differential to detect neutropenia <2000/μl, mild to moderate anemia, and mild to moderate thrombocytopenia.
- Elevated ESR, C-reactive protein.
- Elevated rheumatoid factor and/or anticyclic citrullinated peptide (anti-CCP) antibody titers, positive in 94% and 77%, respectively, with typically higher titers.
- Autoantibody levels are more frequently elevated in FS.
  1. Antinuclear antibody (ANA) positive in 67%
  2. Antihistone antibody positive in 83%
  3. Antineutrophil cytoplasmic antibody (ANCA) positive in 77%
  4. Anti-glucose-6-phosphate isomerase antibody positive in 92%
- HLA-DR4: positive in 98%.
- Immunoglobulin levels may be higher and complement levels lower in FS patients than in RA patients.
- Peripheral smear morphology and immunophenotypic analysis is essential to exclude LGL leukemia.
- Bone marrow examination, which typically shows myeloid hyperplasia with maturation arrest, is often necessary to exclude other causes of neutropenia.

IMAGING STUDIES

Ultrasonography or CT scan may be useful in diagnosing splenomegaly but is not necessary.

TREATMENT

ACUTE GENERAL Rx

The principal treatment interventions include nonpharmacologic measures to reduce the risk for infection and medications to control RA disease and alleviate the granulocytopenia.

- Splenectomy:
  1. Usually reserved for patients with profound neutropenia (<1000/mm^3) and severe recurrent infections despite treatment with synthetic disease-modifying antirheumatic drugs (cs-DMARDs) and/or biologic disease-modifying antirheumatic drugs (bDMARDs).
  2. Acutely reverses hematologic abnormalities.
  3. 25% to 30% have recurrent neutropenia, but the granulocyte count usually remains above the pre-splenectomy level.
  4. Improvement in frequency of recurrent infection is variable and not correlated with degree of hematologic improvement.
- DMARDs (conventional synthetic [csDMARDs] and biologic [bDMARDs]):
  1. Methotrexate (MTX) and rituximab (RTX) are the DMARDs that are preferred in patients with FS, as their benefits have been described in case reports and case series. Leflunomide may be used as an alternative to MTX in patients unable to take MTX. Abatacept is recommended for patients with inadequate response to MTX and RTX, and who require prednisone at dosages greater than 10 to 15 mg daily for control of arthritis and granulocytopenia.
  2. Tumor necrosis factor (TNF) inhibitors are avoided because they have been found to be an ineffective treatment for FS. Tocilizumab and tofacitinib have not been studied, but are avoided because each may cause neutropenia.
  3. Penicillamine, sulfasalazine, hydroxychloroquine, gold salt: Limited experience; infrequently used; not the first choice for FS.
- Corticosteroids:
  1. Overwhelming infection is the main barrier to the use of corticosteroids.

2. Prednisone 30 mg/day or more can elevate the neutrophil count, but this effect is often not sustained when the dose is reduced.
3. Pulse dosing is a potential alternative for short-term elevation of neutrophils.

- Granulocyte colony-stimulating factor/granulocyte-macrophage colony-stimulating factor:
  1. Improves neutrophil count but not arthritis and anemia of FS
  2. May be useful as adjunctive therapy during serious infection or in preparation for surgery

DISPOSITION

- Poor prognosis with recurrent infections because of neutropenia. The average mortality rate after diagnosis is 25% in 5 yr.
- Articular involvement can be severe in FS.

REFERRAL

- To a hematologist for treatment of neutropenia
- To a rheumatologist for treatment of RA

PEARLS & CONSIDERATIONS

COMMENTS

- Recurrent infections are the major cause of death.
- Neutropenia of FS can be effectively treated with DMARDs, the greatest experience with MTX.

RELATED CONTENT

Hypersplenism (Related Key Topic)
Rheumatoid Arthritis (Related Key Topic)

AUTHOR: **Anthony M. Reginato, PhD, MD**

SUGGESTED READINGS

Hamada-Ode K, Taniguchi Y, Shimamura Y, Kagawa T, Terada Y: Efficacy of abatacept for Felty's syndrome, *Rheumatology (Oxford)* 2019.

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Sarp U et al: A beneficial long-term and consistent response to rituximab in the treatment of refractory neutropenia and arthritis in a patient with Felty syndrome, *J Clin Rheumatol* 20(7):398, 2014.

Fertility Preservation in Women

BASIC INFORMATION

DEFINITION

Fertility preservation is the process of preserving eggs, sperm, or reproductive tissue for future use.

Patients typically seek fertility preservation techniques before undergoing sterilizing therapies for cancer treatment or for elective delay of childbearing.

SYNONYMS

Oncofertility
In vitro fertilization
Cryopreservation

ICD-10CM CODES

Z31.84	Encounter for fertility preservation procedure
Z31.62	Encounter for fertility preservation counseling (before cancer therapy) (before removal of gonads)
Z31.41	Encounter for fertility testing
Z31.9	Other special procreative management

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Given the emergence and novelty of fertility preservation techniques, the epidemiology has not been well established. Currently, little is known regarding the perceptions and prevalence of elective fertility preservation. However, there is a growing need for discussions regarding fertility options among cancer patients. In 2006, the American Society of Clinical Oncology published guidelines for oncologists to discuss the possibility of infertility and offer referral for fertility preservation consultation and treatment.

In 2017, nearly 12% of men and women found to have cancer were younger than 45 yr Furthermore, the prevalence of nonsurgical premature menopause in female cancer survivors was 9.1% by age 40, nearly tenfold higher than baseline. Recent literature shows that, among adolescent females with malignancies, 81% of them and 93% of parents were interested in fertility preservation, even if options were described as experimental.

PREDOMINANT SEX AND AGE: Fertility declines with age in both men and women, but the effects of age are more pronounced in women, particularly after age 35.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- An increasing proportion of women are choosing to delay childbearing to pursue educational degrees or for professional achievement.
- For women seeking to delayed childbearing, a thorough history and physical should be performed. A thorough reproductive history including previous pregnancies, spontaneous/elective abortions, and pregnancy complications; a gynecologic history including cysts, fibroids, sexually transmitted diseases, and endometriosis also needs to be included.
- A complete assessment of past medical diagnoses, illicit drug use, and family history is indicated. Specifically, age is a determining factor guiding management. The older a woman is at the time of oocyte cryopreservation, the lower the probability of live birth in the future. The highest probability of live birth after oocyte cryopreservation occurs for women ≤35 yr of age, whereas the maximum age for attempting oocyte cryopreservation may be as high as 45 yr.
- For patients undergoing sterilizing therapies, chemotherapy, or radiation, physicians should discuss the risk of treatment-induced infertility and possible interventions to preserve fertility. Ultimately, the optimal preservation approach depends on the type of gonadotoxic treatment (radiation vs. chemotherapy), time available, patient age, cancer type, partner status, costs, and storage.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Elective delay
- Gonadotoxic treatment with radiation
- Gonadotoxic treatment with chemotherapy

WORKUP

Initial workup requires a discussion of patient goals, ideal family size, and timeline. Physicians should set realistic expectations for their patients' most likely outcome. Factors such as age and number of retrieved oocytes can predict the probability of achieving a live birth. Online calculators are available to guide clinical management.

LABORATORY TESTS

Assessment of markers of ovarian reserve:

- Anti-Müllerian hormone concentration (>2.7 ng/ml is associated with improved oocyte quality)
- Day 3 follicle-stimulating hormone (<10 to 15 mIU/ml is normal)
- Day 3 estradiol concentration (<80 pg/ml is normal)
- Inhibin B (>45 pg/ml is normal)

IMAGING STUDIES

Consider an ultrasound-guided assessment of ovarian reserve:

- Antral follicle count (>3 to 4 is normal)
- Ovarian volume (>3 cc is normal)

TREATMENT

There exist a multitude of methods for fertility preservation:

- Cryopreservation:
  1. Embryo: This method is an established technique for fertility preservation; the percentage of live birth after embryo transfer is similar to the natural fecundity rate of 20% to 30%. Women undergo ovarian stimulation with gonadotropins followed by office oocyte retrieval via needle aspiration under ultrasound guidance. Oocytes are fertilized in vitro with partner or donor sperm. The subsequent embryos that arise are cryopreserved using either slow freezing or vitrification, and stored for future use; there is no time limit for embryo storage. Cryopreserved embryos are not associated with poor obstetrical outcomes. However, for women undergoing chemotherapy, certain time constraints make oocyte retrieve unfeasible. Additionally, ovarian stimulation may not be possible with estrogen-sensitive tumors.
  2. Oocytes: Oocyte cryopreservation is technically more challenging than embryo preservation. Given the increased water content in oocytes, cryopreservation risks ice crystals, excessive osmotic pressure, and electrolyte toxicity. Although the success rates tend to be lower than embryo cryopreservation, harvesting oocytes are more appealing for women without partners at the time of fertility preservation. Patient should be counseled extensively on their risk of transfer success and live birth. Large retrospective cohorts have shown that approximately 5% of thawed oocytes will successfully implant and 4% will result in a live birth in women whose average age was 33.
  3. Ovarian tissue: This technique remains in its infancy and is currently experimental. The advantages of this technique include faster time, preservation of many oocytes, and no ovarian stimulation necessary. The ovarian tissue can remain either in the pelvis or other locations throughout the body. Retrieval is often invasive, typically with laparoscopy.
- Transposition via oophoropexy: This technique can be useful in patients with planned radiation. The ovary can be removed from the field of radiation and transposed elsewhere in the pelvis.
- Gonadotropin-releasing hormone (GnRH) agonists: This technique is useful in women undergoing chemotherapy. GnRH agonists suppress ovarian function and are speculated to prevent toxic damage to oocytes caused by chemotherapy. This technique remains in its infancy. The efficacy and success have not been established, and this is therefore not the first-line therapy for fertility preservation.

Ultimately, a complete evaluation of patient goals, time available, and cancer type is necessary before selecting a method of fertility preservation.

DISPOSITION

Fertility preservation via cryopreservation of embryos or oocytes is completed in an outpatient setting. GnRH agonist therapy is also managed in an outpatient setting. Harvesting ovarian tissue and transposing via oophoropexy are more invasive procedures, requiring surgical management.

REFERRAL

The American Society of Clinical Oncology and the American Society of Reproductive Medicine recommend early referral to a reproductive endocrine and infertility specialist if fertility is a concern before treatment.

PEARLS & CONSIDERATIONS

COMMENTS

- Two major indications for fertility preservation include prior cancer treatment and elective delay of childbearing.
- Early referral to a reproductive endocrinology and infertility specialist is essential.
- A discussion of patient-centered reproductive goals should be initiated.
- Fertility preservation techniques should be reviewed, and the best option selected for each patient, specific to the situation and reproductive goals.

PATIENT & FAMILY EDUCATION

- Fertility Preservation for Cancer Patients: A patient education video sponsored by the American Society of Reproductive Medicine. www.reproductivefacts.org/
- Egg Freezing Counseling Tool (EFCT): Predicts likelihood of live birth for elective egg freezing in women. www.mdcalc.com/bwh-egg-freezing-counseling-tool-efct

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Fetal Alcohol Spectrum Disorder

BASIC INFORMATION

DEFINITION

- Adverse effects of alcohol on developing humans represent spectrum of structural anomalies and behavioral and neurocognitive disabilities, most accurately termed fetal alcohol spectrum disorder (FASD) (Table E1).
- Children at severe end of spectrum defined as having fetal alcohol syndrome (FAS).

SYNONYMS

Fetal alcohol spectrum disorder
FAS
FASD

ICD-10CM CODES

Q86.0	Fetal alcohol syndrome (dysmorphic)
P04.3	Newborn (suspected to be) affected by maternal use of alcohol

EPIDEMIOLOGY & DEMOGRAPHICS

- Alcohol considered to be most common teratogen to which the fetus is liable to be exposed. The percentage of pregnant women who consume alcohol has increased from 7.6% in 2012 to 10.2% in 2015.
- 10% report drinking alcohol during pregnancy and 2% to 4% admit to binge drinking. Binge drinking is associated with the development of behavioral problems and physical deformities.
- Most common cause of inheritable intellectual disability in the U.S.
- Prevalence is 1 to 2/1000 live births across the U.S. It is least prevalent in Hispanic children and most prevalent in Native American and Alaskan Natives.
- Each yr 40,000 babies are born with FASD.

RISK FACTORS

- Advanced maternal age (>30 yr)
- High parity
- African American, Alaskan Native, or Native Indian descent
- Binge drinking (>4 drinks per occasion)
- History of prior affected child
- Genetic susceptibility
- Undernutrition
- Low socioeconomic group

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Typical features:

- Growth retardation
  1. Prenatal or postnatal
  2. Height and/or weight <10%
- Facial dysmorphia (Fig. E1)
  1. Smooth philtrum
  2. Thin vermilion border
  3. Small palpebral fissure (<10%)
  4. Others: Epicanthic folds, ptosis of eyelids, flat nasal bridge and midface, upturned nose, railroad track ears, and so forth
- CNS abnormalities
  1. Structural
     a. Head circumference, 10%
     b. Clinically significant brain abnormalities observable through imaging
  2. Neurologic
     a. Neurologic problems not due to a postnatal insult or fever
  3. Functional
     a. Intellectual deficit
     b. Cognitive or developmental deficits
     c. Executive function deficits
     d. Motor function delays
     e. Problem with attention and hyperactivity
     f. Social skills
     g. Other problems such as sensory, pragmatic language, and memory

Rare birth defects:

- Cardiac
  1. Ventricular septal defect (VSD)
  2. Atrial septal defect (ASD)
  3. Tetralogy of Fallot
  4. Aberrant great vessels
- Skeletal
  1. Radioulnar synostosis
  2. Hypoplastic nails
  3. Clinodactyly (curved fifth finger)
  4. Shortened fifth digit
  5. Pectus excavatum and carinatum
  6. Klippel-Feil syndrome
  7. Hemivertebrae
  8. Camptodactyly
  9. Scoliosis
- Renal
  1. Aplastic kidneys
  2. Dysplastic kidneys
  3. Ureteral duplication
  4. Hypoplastic kidneys
  5. Hydronephrosis
  6. Horseshoe kidneys
- Ocular
  1. Strabismus
  2. Refractive problems
  3. Retinal vascular abnormalities
- Auditory
  1. Conductive hearing loss
  2. Neurosensory hearing loss
- Others
  1. Hockey stick–like palmar crease

ETIOLOGY

- Prenatal damage comes about primarily by direct action of ethanol or its metabolites (e.g., acetaldehyde) on the fetus.
- Exact damaging mechanism is unclear.
- Although the damaging effect of alcohol is different in the various phases of pregnancy, it is by no means limited to first trimester.
- No exact dose-response relationship between alcohol consumed during prenatal period and extent of damage inflicted on infant.
- An occasional drink during pregnancy carries no risk to the fetus, but no level of drinking is known to be safe during pregnancy.
- The least significant effect recognized at 2 drinks/day is smaller birth weight (160 g less than average).
- Until 4 to 6 drinks/day are consumed, no additional subtle clinical features are evident.
- Most children who have FAS have been born to frankly alcoholic mothers whose intake is ≥8 to 10 drinks/day, and those who engage in binge drinking.
- The risk of serious problem in the offspring of a chronically alcoholic woman is ~30% to 50%; the greatest risk is mental retardation.

SECONDARY DISABILITIES

- Mental health problems
- Dependent living
- Employment problems
- Disruptive school problems
- Trouble with law
- Confinement
- Inappropriate sexual behavior
- Alcohol or drug problems

TABLE E1 Institute of Medicine's Diagnostic Criteria for Fetal Alcohol–Related Abnormalities

Category 1	
FAS with confirmed maternal alcohol exposure	Presence of classic triad of growth retardation, characteristic facial dysmorphology, and neurodevelopmental abnormalities. This is often defined as full-blown FAS
Category 2	
FAS without confirmed maternal alcohol exposure	Triad in category 1 is present without confirmed maternal drinking
Category 3	
Partial FAS with confirmed maternal alcohol exposure	Presence of some of the characteristic facial anomalies plus growth retardation or CNS neurodevelopmental abnormalities or behavioral/cognitive abnormalities
Category 4	
FAS with confirmed maternal alcohol exposure and alcohol-related birth defects	Some congenital anomalies as a result of alcohol toxicity
Category 5	
FAS with confirmed maternal alcohol exposure and alcohol-related neurodevelopmental disorder	Evidence of CNS neurodevelopmental abnormalities, a complex pattern of behavioral/cognitive abnormalities, or both, but not necessarily any obvious physical changes

CNS, Central nervous system; *FAS,* fetal alcohol syndrome.

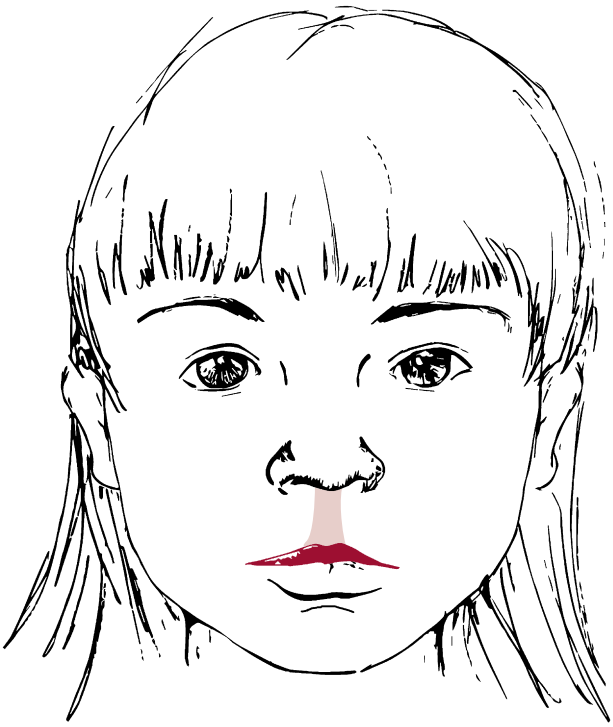

FIG. E1 The three most prominent and consistent facial abnormalities of fetal alcohol syndrome occur in the midface and give this 6-yr-old girl the distinctive appearance: short palpebral fissures that hide the medial and lateral portions of her eyes, smooth philtrum (the normally indented vertical groove between the bottom of the nose and the upper lip), and a thin upper lip. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists*, ed 8, Philadelphia, 2017, Elsevier.)

Dx DIAGNOSIS

- It is a diagnosis of exclusion.
- Diagnosis is difficult prenatally and at birth. Most cases are not diagnosed until school age.
- As the characteristic facial features tend to become decreasingly recognizable as the child reaches adolescence, the diagnosis becomes increasingly difficult with advancing age.
- Prenatal exposure to alcohol is not sufficient to warrant a diagnosis. According to the CDC, diagnosis of FAS requires three specific findings and history of prenatal alcohol exposure:
  1. Growth restriction (intrauterine or postnatal)
  2. CNS involvement
  3. Documentation of all three facial abnormalities (smooth philtrum, thin vermilion border, and short palpebral fissure)
- Imaging recommendation during pregnancy with alcohol exposure:
  1. High-risk anatomy scan
  2. Serial growth scan
  3. Fetal echocardiogram at 22 to 24 weeks' intrauterine pregnancy
- Measurement of the ethyl esters of fatty acids in the meconium and hair of the newborn can substantiate maternal alcohol exposure.
- In school-aged children, the diagnostic process should include a thorough psychological evaluation that assesses multiple domains. Also, supplement the observation by obtaining standardized testing through early intervention programs, public schools, and psychologists in private practice.

DIFFERENTIAL DIAGNOSIS

- Other causes of symmetric growth retardation including intrauterine infection and aneuploidy.
- Aneuploidy (T21, T18, T13).
- Syndromes with overlapping features of FAS:
  1. Fetal anticonvulsant syndrome
  2. Maternal phenylketonuria
  3. Toluene embryopathy
  4. Velocardiofacial syndrome (deletion 22q11)
  5. Williams syndrome
  6. Dubowitz syndrome
  7. Cornelia de Lange syndrome

Rx TREATMENT

- As there is no cure for FAS, we need to emphasize prevention.
- For women who are planning pregnancy or who could become pregnant, the United States Surgeon General recommends the safest course: to avoid alcohol entirely during pregnancy.
- Women of childbearing age who are not pregnant should drink ≤7 alcoholic drinks/wk and ≤3 drinks on any one occasion.
- Preconception counseling should be offered to women of childbearing age who are at risk for an alcohol-exposed pregnancy.

TABLE E2 T-ACE Questions*

T (tolerance)	How many drinks does it take to make you feel high? (3 or more drinks = 2 points)
A (annoyed)	Have people annoyed you by criticizing your drinking? (Yes = 1 point)
C (cut down)	Have you felt you ought to cut down on your drinking? (Yes = 1 point)
E (eye opener)	Have you ever had to drink first thing in the morning to steady your nerves or to get rid of a hangover? (Yes = 1 point)

*A score of 2 or more indicates heavy or problem drinker. Its sensitivity is 70% and specificity is 85%.

TABLE E3 TWEAK*

T (tolerance)	How many drinks does it take before you begin to feel the first effects of alcohol? (3 or more drinks = 2 points)
W (worried)	Have close friends or relatives worried about your drinking in the past year? (Yes = 2 points)
E (eye opener)	Do you sometimes take a drink in the morning when you first get up? (Yes = 1 point)
A (amnesia)	Has a friend or family member ever told you about things you said or did while you were drinking that you could not remember? (Yes = 1 point)
K (kut down)	Do you sometimes feel the need to cut down on your drinking? (Yes = 1 point)

*A total of 3 or more points indicates that the woman is likely to be a heavy or problem drinker. Its sensitivity is 79% and specificity is 83%.

- Screen all pregnant women for alcohol use.
- The National Institute on Alcohol Abuse and Alcoholism recommends that any woman who reports drinking >7 drinks/wk or >3 drinks on a given day be further assessed for alcohol-related problems.
- The T-ACE (Table E2) and TWEAK (Table E3) questionnaires are used to identify women drinking enough to potentially damage the fetus. The CAGE questionnaire is less sensitive for screening pregnant women.
- Effective treatment alternatives for women who screen positive for hazardous alcohol use include brief interventions to promote reductions in alcohol use and that facilitate referral to specialized treatment programs.
- Discontinuation or reduction of alcohol consumption at any point in pregnancy may be beneficial.

- The use of alcohol-containing tonics and medications should be avoided. This applies to medications with an alcohol base when the concentration exceeds 10%.
- Alcoholism is one of the few situations in which pregnancy interruption may be discussed with the patient as it may result in FAS.
- Early diagnosis and appropriate treatment may decrease secondary disabilities and recurrence in future pregnancies.
- A child should be referred for full FAS evaluation when substantial prenatal alcohol use by the mother has been confirmed (>7 drinks/wk, >3 drinks on multiple occasions, or both).
- If substantial prenatal exposure is known, with no other positive criteria, the physician should document exposure and closely monitor the child's growth and development.
- When information about prenatal exposure is unknown, a child should be referred for full FAS if any of the following conditions are present: (1) all three dysmorphic facial features (smooth philtrum, thin vermilion border, and small palpebral fissure), (2) one or more of these facial features with growth deficit, (3) one or more facial features with one or more CNS abnormalities, (4) one or more dysmorphic facial features with growth deficit and one or more CNS abnormalities, or (5) any report of concern by a caregiver or parent that a child has or may have FAS.
- Infants and children who are diagnosed with FAS should be evaluated by a physician who is knowledgeable and competent in the evaluation of neurodevelopment and psychosocial problems associated with the diagnosis.
- A multidisciplinary team including a clinical geneticist, developmental pediatrician, mental health professional, social worker, and education specialist is often necessary for management.
- Treatment options include:
  1. Medications to help with symptoms
  2. Behavior and education therapy
     a. Friendship training
     b. Specialized math training
     c. Executive function training
     d. Parent-child interaction training
     e. Parenting and behavior management training
  3. Parenting training
     a. Concentrate on child's strengths and talents.
     b. Accept child's limitations.
     c. Be consistent with everything.
     d. Use concrete language and examples.
     e. Use stable routine that does not change daily.
     f. Keep everything simple.
     g. Be specific (i.e., say exactly what you mean).
     h. Structure your child's world to provide a foundation for daily living.
     i. Use visualized aids, music, and hands-on activities to help your child learn.
     j. Use positive reinforcement often.
     k. Supervise.
     l. Repeat, repeat, and repeat.
  4. Emphasis on the following protective factors helps reduce the effects and also assists people with this condition to reach their full potential:
     a. Diagnosing before 6 yr
     b. Living in stable nurturing home environment in school yrs
     c. Absence of violence
     d. Involvement in special education and social services
  5. Alternative approaches such as biofeedback, auditory training, relaxation therapy, visual imagery, yoga/exercise, acupuncture/acupressure, massage, Reiki, energy healing, animal-assisted therapy, and so forth may play a role.

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BASIC INFORMATION

DEFINITION

A traveler who returns from a foreign country with a fever or develops a fever within a month of returning.

ICD10-CM CODES

A50	Fever of other and unknown origin
A95	Yellow fever
A90	Dengue fever
A01	Typhoid and paratyphoid fever
B54	Malaria, malarial (fever)
A98.8	Other specified viral hemorrhagic fever

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Fever was the chief complaint in 28% of travelers who reported to a travel clinic. Mortality is between 0.2% and 0.5%. According to the CDC, the specific cause of fever may not be diagnosed in up to 25% or more of returned travelers.

PEAK INCIDENCE: Location and timing of travel influences the incidence of fever.

RISK FACTORS: Morbidity and mortality increased among elderly and young travelers.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- A detailed history on the trip must be obtained, including areas of travel, activities, sleeping arrangements, pre-trip immunizations, comorbidities, and use of malaria prophylaxis.
- If the incubation period is <21 days, the most common diseases include malaria, typhoid fever, and dengue. Also consider Japanese encephalitis, meningococcemia, plague, typhus, yellow fever, and viral hemorrhagic fevers.
- If incubation period is >21 days, the most common diseases include malaria, tuberculosis (TB), and hepatitis A. Consider acute HIV infection, acute systemic schistosomiasis, borreliosis, other viral hepatitis, and West African trypanosomiasis (Table 1).

If there is fever accompanied by any of the following syndromes, CDC recommends further investigation because of a high risk of a disease that affects public health and immediate infection control and containment/isolation procedures are indicated:

- Skin rash with or without conjunctivitis (e.g., measles, meningococcemia, hemorrhagic fevers such as Ebola)
- Rapid respiratory rate (e.g., influenza, Middle East respiratory syndrome [MERS], pneumonic plague)
- Persistent cough (e.g., tuberculosis, pertussis)
- Decreased consciousness (e.g., meningococcal meningitis, rabies)
- Bruising or unusual bleeding without previous injury (e.g., hemorrhagic fevers)
- Persistent voluminous diarrhea (e.g., cholera)
- Persistent vomiting other than air or motion sickness (e.g., norovirus infection)
- Jaundice (e.g., hepatitis A)
- Flaccid paralysis of recent onset (e.g., polio)

Common causes of fever in returning travelers:

- Malaria: Most common cause of fever after travel in endemic areas. Presents with abrupt rigors, relapsing high fevers, diaphoresis, malaise, headaches, myalgias, abdominal pain, nausea, vomiting, diarrhea.
- Enteric fevers (typhoid fever, paratyphoid fever): Clinical syndrome of sustained fever, anorexia, abdominal pain, malaise. Diarrhea usually precedes other symptoms. May see hepatosplenomegaly and rose spots on physical exam. Vaccines are 70% effective. Patient will have traveled to a developing nation. Diagnoses by identification of organism in blood, stool, or urine.
- Dengue fever ("breakbone fever"): Abrupt fever, severe myalgia, headaches with retroorbital pain, maculopapular blanching rash, petechial fever similar to meningococcus.

Hemorrhagic fevers:

- Yellow fever: Classic presentation of jaundice, black emesis, albuminuria. Patients may also have conjunctival injection, facial flushing, relative bradycardia.
- Ebola: Recent large outbreaks in West Africa with recurring smaller outbreaks. Symptoms of fever, myalgia, and abdominal pain that progress to hemorrhage, shock, and end organ failure.

Fever with central nervous system involvement:

- Consider malaria, meningococcal meningitis, tuberculosis, rabies.
- Japanese encephalitis: Asian distribution, associated with rural rice fields. High fevers, headache, nuchal rigidity, and seizures.

Chronic fevers: Relapsing or constant fever >3 wk:

- African trypanosomiasis (African sleeping sickness): Bite from the tsetse fly, painless chancre that grows for 2 to 3 wk. Fever unresponsive to antimalarials, malaise, wasting, behavioral and neurologic changes, encephalitis, coma occur.
- American trypanosomiasis (Chagas disease): Spread by reduviid bug (kissing or assassin bug). Painful edema at wound near mouth, unilateral periorbital edema, lymphadenopathy for 2 to 4 wk. Latent phase with nerve destruction causing cardiac and GI manifestations.
- Middle East respiratory syndrome (travel to or near the Arabian Peninsula): Fever, acute respiratory distress syndrome, or pneumonia.

ETIOLOGY

Table 2 summarizes the constellations of exposures and clinical presentations suggestive of particular diagnoses in returning travelers.

TABLE 1 Incubation Periods of Common Travel-Related Infections*

Short Incubation (<10 days)	Medium Incubation (10-21 days)	Long Incubation (>21 days)
Malaria	Malaria	Malaria
Arboviruses including dengue, yellow fever, Japanese encephalitis	Flaviviruses: Tick-borne encephalitis and Japanese encephalitis	Schistosomiasis
Hemorrhagic fevers: Lassa, ebola, South American arenaviruses	Hemorrhagic fevers: Lassa, ebola, Crimean-Congo	Tuberculosis
Respiratory viruses including severe acute respiratory syndrome	Acute HIV infection	Acute HIV infection
Typhoid and paratyphoid	Typhoid and paratyphoid	Viral hepatitis
Bacterial enteritis	*Giardia*	Filariasis
Rickettsia: Spotted fever group—Rocky Mountain spotted fever, African tick typhus, Mediterranean spotted fever, scrub typhus, Q fever	*Rickettsia*: Flea-borne, louse-borne, and scrub typhus, Q fever, spotted fevers (rare)	*Rickettsia:* Q fever
Bacterial pneumonia including *Legionella*	Cytomegalovirus	Secondary syphilis
Relapsing fever	*Toxoplasma*	Epstein-Barr virus including mononucleosis
Amebic dysentery	Amebic dysentery	Amebic liver disease
Meningococcemia	Histoplasmosis	Leishmaniasis
Brucella (rarely)	*Brucella*	*Brucella*
Leptospirosis	Leptospirosis	Bartonellosis (chronic)
Fascioliasis	Babesiosis	Babesiosis
Rabies (rarely)	Rabies	Rabies
African trypanosomiasis (acute), East African (rarely)	East African trypanosomiasis (acute)	West African trypanosomiasis (chronic)
	Hepatitis A (rarely)	Cytomegalovirus
	Measles	

*Diseases that commonly have variable incubation periods are shown more than once. However, most diseases may rarely have an atypical incubation period, and this is not shown here.
HIV, Human immunodeficiency virus.
From Bennet et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.

TABLE 2 Constellations of Exposures and Clinical Presentations Suggestive of Particular Diagnoses in Returned Travelers*

Exposure Scenario	Distinctive Findings	Diagnosis
Any exposure in any area with documented malaria transmission	Fever with or without any other finding	Malaria
Most tropical countries	Fever and altered mental status	Malaria, meningococcal meningitis, rabies, West Nile virus
Budget travel to India, Nepal, Pakistan, or Bangladesh	Insidious onset, high unremitting fever, toxic patient, paucity of physical findings	Enteric fever due to *Salmonella typhi* or *Salmonella paratyphi*
Freshwater recreational exposure in Africa	Fever, eosinophilia, hepatomegaly, negative malaria smear	Acute schistosomiasis (Katayama fever)
Bitten by *Aedes aegypti* in Central America, Southeast Asia, or the South Pacific	Fever, headache, myalgia, diffuse macular rash, mild to moderate thrombocytopenia	Dengue
Bitten by *A. aegypti* or *Aedes albopictus* in India, Malaysia, Singapore, the Caribbean, or an island in the Indian Ocean	Fever, headache, myalgia, diffuse macular rash, arthralgia, tenosynovitis often followed by chronic polyarthritis after the fever resolves	Chikungunya fever
Hunting or visiting game reserves in southern Africa	Fever, eschar, diffuse petechial rash	African tick typhus due to *Rickettsia africae*
Travel to Southeast Asia	Fever, eschar, diffuse petechial rash	Scrub typhus due to *Orientia tsutsugamushi*
Hiking, biking, swimming, rafting with exposure to fresh surface water	Fever, myalgia, conjunctival suffusion, mild to severe jaundice, variable rash	Leptospirosis
Cruise, elderly traveler	Influenza-like illness	Influenza A or B
Outdoor exposure anywhere in the Americas	Large, single furuncular lesion anywhere on body, with sense of movement inside	Myiasis due to *Dermatobia hominis* (botfly)
Clothing washed or dried out of doors in Africa	Multiple furuncular lesions around clothing contact points with skin	Myiasis due to *Cordylobia anthropophaga* (tumbu fly)
New sexual partner during travel	Fever, rash, mononucleosis-like illness	Acute human immunodeficiency virus infection
Travel to any developing country or to Western Europe	Coryza, conjunctivitis, Koplik spots, rash	Measles
Longer visit to humid areas of Africa, the Americas, or Southeast Asia	Asymptomatic eosinophilia or with periodic cough or wheezing	Strongyloidiasis
Sand fly bite in either New or Old World tropical area	Painless skin ulcer with clean, moist base in exposed area	Cutaneous leishmaniasis
Resort hotel in southern Europe, ± exposure to whirlpool spas	Pneumonia	Legionnaires' disease
Explored a cave in the Americas	Fever, cough, retrosternal chest pain, hilar adenopathy	Histoplasmosis
Ingestion of unpasteurized goat cheese	Chronic fever, fatigue	*Brucella melitensis*
Long trip to West/Central Africa	Afebrile, intensely pruritic, evanescent truncal maculopapular rash	Onchocerciasis
Long trip to West/Central Africa	Migratory localized angioedema or swellings over large joints, eosinophilia	Loiasis
Safari to game parks of East Africa	Fever, nongenital chancre, fine macular rash	East African trypanosomiasis
Travel to Australia	Fever, fatigue, polyarthritis	Ross River virus
Farming areas of India and Southeast Asia	Fever, altered mental status, paralysis	Japanese encephalitis
Forested areas of central and eastern Europe and across Russia	Fever, altered mental status, paralysis	Tick-borne encephalitis
Rodent exposure in West Africa	Fever, sore throat, jaundice, hemorrhagic manifestations	Lassa fever
Ingestion of sushi, ceviche, or raw freshwater fish	Migratory nodules in truncal areas with overlying erythema or mild hemorrhage	Gnathostomiasis
Returning Hajj pilgrim or family contact	Fever, meningitis	Meningococcal meningitis
Ingestion of snails, fish, or shellfish in Asia or Australia	Eosinophilic meningitis	Angiostrongyliasis, gnathostomiasis
Diabetic or compromised host with exposure to moist terrain in Asia or Australia	Fever, sepsis, pneumonia or multifocal abscesses	Melioidosis
Summertime exposure to rodent droppings in Scandinavia	Fever with decreased renal function	Puumala virus
Ingestion of undercooked meat of any animal in any country	Fever, facial edema, myositis, increased creatine phosphokinase, massive eosinophilia, normal erythrocyte sedimentation rate	Trichinosis
Unvaccinated, returning from sub-Saharan Africa or forested areas of Amazonia	Fever, jaundice, proteinuria, hemorrhage	Yellow fever
Exposure to farm animals	Pneumonia, mild hepatitis	Q fever
Possible tick exposure almost anywhere	Fever, headache, rash, conjunctival injection, hepatosplenomegaly	Tick-borne relapsing fever
Poor hygienic conditions with possible body louse exposure in Ethiopia or Sudan	Fever, headache, rash, conjunctival injection, hepatosplenomegaly	Louse-borne relapsing fever

*The table includes illnesses of travelers (listed first) as well as less common diseases with presentations that should suggest the possibility of the appropriate diagnosis. Many diseases have a spectrum of presentation, and the table describes the most common presentations of these diseases. Many diseases have a spectrum of geographic origins, and the table describes the most common exposures seen in daily practice.

From Bennet et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Table 3 is a table from CDC with clinical findings and infections to consider. Table 4 is also from the CDC, pairing regions with common tropical diseases that may be causing fever.

- Malaria
- Dengue
- Hemorrhagic fevers: Yellow fever, Ebola
- Enteric fever: Typhoid, paratyphoid
- Meningococcemia
- TB
- Acute HIV
- Trypanosomiasis
- Viral hepatitis
- Common nontravel causes of fever: Urinary tract infection, upper respiratory tract infections

WORKUP

Must consider travel location, activities, endemic diseases

LABORATORY TESTS

Consider:

- CBC
- Comprehensive metabolic panel
- Prothrombin time/international normalized ratio, partial thromboplastin time
- Urinalysis
- Blood, urine stool cultures
- Cerebrospinal fluid analysis, gram stain, culture
- Rapid HIV screen
- Serial blood smears q8 to 12h over 2 days
- Specific serology for suspected infections

IMAGING STUDIES

Not usually required, but consider as clinically indicated:

- Chest x-ray
- Upright abdominal x-ray
- CT: Head
- CT: Abdomen and pelvis

TABLE 3 CDC: Clinical Findings and Select Associated Infectious Diseases

Common Clinical Findings	Infections to Consider after Tropical Travel
Fever and rash	Dengue, chikungunya, Zika, measles, spotted fever or typhus group rickettsioses, enteric fever (skin lesions may be there or not), meningococcemia, acute HIV infection, varicella
Fever and abdominal pain	Enteric fever, amebic or pyogenic liver abscess
Fever and normal or low WBC count	Dengue, malaria, rickettsial infection, enteric fever, chikungunya Zika, acute HIV
Fever and hemorrhage	Viral hemorrhagic fevers (e.g., dengue, yellow, Ebola, Lassa fever), meningococcemia, leptospirosis, spotted fever group rickettsial infections)
Fever and arthralgia or myalgia (sometimes persistent)	Chikungunya, dengue, Zika, Ross River virus, muscular sarcocystosis, trichinellosis
Fever and eosinophilia	Acute schistosomiasis, drug hypersensitivity reaction, fascioliasis, sarcocystosis, trichinellosis, angiostrongyliasis, and other parasitic infections
Fever and respiratory symptoms / pulmonary infiltrates	Influenza and other common bacterial and viral pathogens, legionellosis, tuberculosis, acute schistosomiasis, Q fever, leptospirosis, Middle East respiratory syndrome, acute histoplasmosis, or coccidioidomycosis, psittacosis, melioidosis, pneumonic plague
Fever and altered mental status/ CNS involvement	Cerebral malaria, arboviral encephalitides (Jap. Encephalitis, West Nile virus), meningococcal meningitis, rabies, African trypanosomiasis, scrub typhus, angiostrongyliasis, tickborne encephalitis, rabies
Fever and jaundice	Acute viral hepatitis (A, B, C, E), yellow fever and other viral hemorrhagic fevers, severe malaria, leptospirosis
Mononucleosis syndrome	EBV, CMV, toxoplasmosis, acute HIV
Fever persisting >2 weeks	Malaria, enteric fever, EBV, CMV, toxoplasmosis, acute HIV, acute schistosomiasis, brucellosis, tuberculosis, Q fever, visceral leishmaniasis
Fever with onset >6 weeks after travel	Plasmodium vivax or ovale malaria, acute hepatitis (B, C, E), tuberculosis, amebic liver abscess, melioidosis, African trypanosomiasis

CMV, Cytomegalovirus; *CNS,* central nervous system; *EBV,* Epstein-Barr virus; *HIV,* human immunodeficiency virus; *WBC,* white blood cells.

TABLE 4 Regions with Common Tropical Disease

Geographic Area	Common Tropical Disease Causing Fever	Other Infections Causing Outbreaks or Clusters in Travelers
Caribbean	Chikungunya, dengue, malaria, Zika	Acute histoplasmosis, leptospirosis
Central America	Chikungunya, dengue, malaria (primarily Plasmodium vivax), Zika, enteric fever	Leptospirosis, histoplasmosis, coccidioidomycosis, leishmaniasis
South America	Chikungunya, dengue, malaria (primarily *P. vivax*), Zika	Bartonellosis, leptospirosis, enteric fever, histoplasmosis
South Central Asia	Dengue, enteric fever, malaria (primarily non-falciparum)	Chikungunya, scrub typhus
Southeast Asia	Dengue, malaria (primarily non-falciparum)	Chikungunya, leptospirosis
Sub-Saharan Africa	Malaria (primarily P. falciparum), tickborne rickettsiae, acute schistosomiasis, Dengue fever	African trypanosomiasis, chikungunya enteric fever, meningococcal meningitis

(CDC last update 6/2019)

Rx TREATMENT

Pretravel prevention should focus on proper vaccinations and prophylactic antimalarial antibiotics. Posttravel treatment depends on diagnosing or ruling out specific, known causes of fever in the returning traveler. Treatment ranges from supportive care to IV antibiotics, as with malaria and Dengue fever.

- Malaria (pediatric dosing, refer to CDC treatment table)
  Uncomplicated *Plasmodium falciparum* or species not identified:
  1. Artemether-lumefantrine (Coartem) 1 tab is 20 mg artemether/120 mg lumefantrine 3 day treatment schedule, 6 doses total
     Day 1: 1 dose and the second dose 8 hr later
     Day 2 and 3: 1 dose PO bid
     5 to <15 kg: 1 tab per dose
     15 to <25 kg: 2 tabs per dose
     25 to <35 kg: 3 tabs per dose
     35 kg and up: 4 tabs per dose
  2. Malarone (atovaquone/proguanil): 250 mg Atovaquone/100 mg Proguanil
     Malarone 4 tabs PO qd for 3 days
  3. Quinine sulfate 542 mg base (650 mg salt) PO q8h for 3 to 7 days *plus*
     Doxycycline 100 mg PO q12h for 7 days *or*
     Tetracycline: 250 mg PO QID for 7 days *or*
     Clindamycin: 20 mg base/kg/day PO divided tid for 7 days
  4. Mefloquine (not suggested unless the others cannot be taken because of high incidence of neuropsychiatric side effects, high resistance in Southeast Asia): 684 mg base (750 mg salt) PO initial dose, 456 mg base (500 mg salt) PO 6 to 12 hr after the first dose; total dose: 1250 mg salt
- Severe malaria:
  1. IV artesunate: Give 2.4 mg/kg per dose; administer 1 dose at 0, 12, 24, and 48 hr for a total of 4 doses
  Followed by 1 of the following:
     a. Coartem: treatment as above
     b. Doxycycline (clindamycin in pregnant patients): Treatment as above if patient can tolerate PO, otherwise give 100 mg IV q12h and then switch to oral doxycycline as soon as patient can take oral medication; for IV use, avoid rapid administration; treatment course = 7 days

Clindamycin: Treatment as above, unless patient cannot tolerate PO, 10 mg base/kg loading dose IV followed by 5 mg base/kg IV q8h; switch to PO clindamycin as soon as possible; avoid rapid administration for IV use; treatment course is 7 days

c. Mefloquine if there is no other option

- Dengue: Supportive care, fever and pain control, prevent dehydration
  1. NSAIDs and aspirin contraindicated due to increased bleeding risk
  2. Acetaminophen or paracetamol q6h
  3. Cool compresses, ice compresses, bath if necessary
- Typhoid fever: Fluoroquinolone (ciprofloxacin), third-generation cephalosporins (cefixime or ceftriaxone), azithromycin. Duration varies based on severity.
- Hemorrhagic viruses: Supportive care
- Meningococcus: Standard bacterial meningitis care

DISPOSITION

- Depending on the specific disease, severity of disease, and possibility of transmission.
- Patients may have outpatient or inpatient medical treatment.
- The most severe cases may need ICU and/or isolation.

REFERRAL

- Infectious disease consult
- Contact the CDC for recommendations pertaining to endemic diseases and treatment
- Some medical treatments and diagnostic testing must be sent from the CDC
- Mandatory reporting of some diseases to CDC

PEARLS & CONSIDERATIONS

COMMENTS

- The differential depends on the geography. Also consider travel to endemic areas, pretrip immunizations, comorbidities, non-travel-related diseases, sleeping arrangements, activities, and immunocompromised status.
- Until demonstrated otherwise, some travel medicine experts recommend assuming that all febrile travelers coming from malaria endemic regions have malaria.

PREVENTION

Check the CDC website and the Yellow Book for pretrip vaccinations.

PATIENT & FAMILY EDUCATION

Visit www.cdc.gov for further information.

RELATED CONTENT

Brucellosis (Related Key Topic)
Dengue Fever (Related Key Topic)
Histoplasmosis (Related Key Topic)
Human Immunodeficiency Virus (Related Key Topic)
Leishmaniasis (Related Key Topic)
Malaria (Related Key Topic)
Measles (Rubeola) (Related Key Topic)
Q Fever (Related Key Topic)
Rabies (Related Key Topic)
Salmonellosis (Related Key Topic)
Trichinellosis (Related Key Topic)
West Nile Virus Infection (Related Key Topic)
Yellow Fever (Related Key Topic)
Zika Virus (Related Key Topic)

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Samantha Ni, MD,** and **Ana Castaneda-Guarderas, MD**

SUGGESTED READINGS

Centers for Disease Control and Prevention: Travelers' Health: Available at www.cdc.gov/travel/.

Thwaites GE et al: Approach to fever in the returning traveler, *N Engl J Med* 376(6):548-560, 2017.

BASIC INFORMATION

DEFINITION

Fever of undetermined origin (FUO) was first defined by Petersdorf and Beeson in 1961 as an illness characterized by temperatures >38.3° C (101° F) on several occasions for >3 wk with an uncertain diagnosis after 1 wk of study in the hospital. With the increased availability of outpatient evaluation, the requirement of hospitalization for diagnosis was removed. As of 2017, the widely accepted definition of FUO is:

- Temperature ≥38.3° C (101° F) on at least two occasions
- Duration of illness ≥3 wk or multiple febrile episodes in ≥3 wk
- Not immunocompromised
  1. Neutropenic >1 wk in last 3 mo
  2. Known HIV
  3. Hypogammaglobulinemia
  4. 10 mg prednisone or equivalent for at least 2 wk

FUO can be classified into classic, nosocomial (health care associated), neutropenic (immune deficient), and HIV-associated. Table 1 provides a summary of definitions and major features of subtypes of FUO.

SYNONYMS

Fever of unknown origin
Pyrexia of unknown origin

ICD-10CM CODE
R50.9 Fever, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Due to advances in medical knowledge and technology, the distribution of causes of FUO has changed.
- Improved imaging and culture techniques have led to decreased diagnosis secondary to malignancy or infection.
- In recent yrs, more FUOs have no identified cause and eluded diagnosis:
  1. In prospective study of 73 immunocompetent patients with FUO, 51% had no identified cause.

CLINICAL PRESENTATION

Significant fever (≥38.3° C [101° F]) that has persisted for longer than an acute self-limiting illness would be expected to and without identified etiology despite reasonable investigations in whatever setting is appropriate.

ETIOLOGY

FUO can be divided into four categories:

- Infectious (17% to 35%)
  1. Localized:
     a. Abscess (intraabdominal, pelvic, renal, dental, intracranial)
     b. Endocarditis (including subacute and culture negative)
     c. Infected peripheral vessels
     d. Osteomyelitis
     e. Urinary tract infection
     f. Sinusitis
     g. *Clostridium difficile* colitis
  2. Generalized:
     a. Bacterial: Typhoid fever, bartonellosis, brucellosis, Q fever
     b. Viral: HIV, cytomegalovirus (CMV), Epstein-Barr virus (EBV), multicentric Castleman disease
     c. Fungal: Histoplasmosis, blastomycosis, cryptococcosis, coccidioidomycosis
     d. Mycobacterial: Tuberculosis (extrapulmonary, military)
     e. Parasitic: Malaria, toxoplasmosis, visceral leishmaniosis, amoebic abscess
- Noninfectious inflammatory (24% to 36%)
  1. Adult Still disease
  2. Giant cell arteritis, temporal arteritis, polymyalgia rheumatics
  3. Other vasculitides: Polyarteritis nodosa, Takayasu arteritis, granulomatosis with polyangiitis, mixed cryoglobulinemia
  4. Other rheumatologic disorders: Systemic lupus erythematous, rheumatoid arthritis
- Malignancy (10% to 20%)
  1. Lymphoma
  2. Leukemia
  3. Myelodysplastic syndrome
  4. Solid tumors: Renal cell carcinoma, hepatocellular carcinoma, metastatic disease

TABLE 1 Summary of Definitions and Major Features of the Four Subtypes of Fever of Undetermined Origin

Feature	Classic FUO	Health Care–Associated FUO	Immune-Deficient FUO	HIV-Related FUO
Definition	>38.0° C, (100.4° F) >3 wk, >2 visits or 1 wk in hospital	≥38.0° C (100.4° F), >1 wk, not present or incubating on admission	≥38.0° C (100.4° F), >1 wk, negative cultures after 48 hr	≥38.0° C (100.4° F), >3 wk for outpatients, >1 wk for inpatients, HIV infection confirmed
Patient location	Community, clinic, or hospital	Acute care hospital	Hospital or clinic	Community, clinic, or hospital
Leading causes	Cancer, infections, inflammatory conditions, undiagnosed, habitual hyperthermia	Health care–associated infections, postoperative complications, drug fever	Majority due to infections, but cause documented in only 40%-60%	HIV (primary infection), typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis, immune reconstitution inflammatory syndrome (IRIS)
History emphasis	Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder	Operations and procedures, devices, anatomic considerations, drug treatment	Stage of chemotherapy, drugs administered, underlying immunosuppressive disorder	Drugs, exposures, risk factors, travel, contacts, stage of HIV infection
Examination emphasis	Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower limb deep veins	Wounds, drains, devices, sinuses, urine	Skinfolds, IV sites, lungs, perianal area	Mouth, sinuses, skin, lymph nodes, eyes, lungs, perianal area
Investigation emphasis	Imaging, biopsies, sedimentation rate, skin tests	Imaging, bacterial cultures	CXR, bacterial cultures	Blood and lymphocyte count; serologic tests; CXR; stool examination; biopsies of lung, bone marrow, and liver for cultures and cytologic tests; brain imaging
Management	Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments	Depends on situation	Antimicrobial treatment protocols	Antiviral and antimicrobial protocols, vaccines, revision of treatment regimens, good nutrition
Time course of disease	Mos	Wks	Days	Wks to mos
Tempo of investigation	Wks	Days	Hours	Days to wks

CMV, Cytomegalovirus; *CXR,* chest radiograph; *FUO,* fever of undetermined origin; *HIV,* human immunodeficiency virus; *IV,* intravenous.
Adapted from Mandell GL et al (eds): *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Churchill Livingstone. Borrowed from Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, WB Saunders.

- Miscellaneous (3% to 15%)
  1. Drug-induced fever
  2. Inflammatory bowel disease
  3. Sarcoidosis
  4. Pulmonary embolism/deep vein thrombosis
  5. Alcoholic hepatitis
  6. Familial Mediterranean fever
  7. Factitious fever
- No diagnosis in 16% to 39% of cases

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Over 200 possible diagnoses for FUO

WORKUP

- By definition, FUO is a diagnostic challenge. As the list of possible causes is extensive, there is no useful, clear-cut algorithmic approach.
- Accurate history and careful physical examination are essential. Table E2 describes an approach to the patient with FUO based on history and physical findings.
- Laboratory tests and imaging dependent on medical history clues and physical findings.
- When in doubt, perform another complete history and physical examination. Examples of subtle physical findings in patients with FUO are described in Table 3.

MEDICAL HISTORY CLUES

- Duration, accompanying symptoms (rigor, drenching sweats)
  1. Degree of fever, nature of fever curve, apparent toxicity, and response to antipyretic have not be found to be helpful.
- Unintentional weight loss
- Drenching night sweats
- Rash
- Myalgias
- Joint pain
- Unilateral retro-orbital headache or jaw claudication
- History of immunosuppression
- Thromboembolic risk factors (previous episodes, prolonged immobility, oral contraceptive pills recent surgeries)
- Medications
- Sick contacts
- Social history:
  1. Alcohol intake
  2. Occupational exposures
  3. Animal exposures
  4. Insect bites
  5. Sexual exposures
  6. Travel history
- Family history:
  1. Autoimmune disorders
  2. Malignancies
  3. Familial Mediterranean fever

PHYSICAL FINDINGS

- HEENT (head, ears, eyes, nose, throat): Sinus tenderness, dental abscesses, funduscopic lesions
- Neck: Adenopathy, palpable thyroid
- Lungs: Auscultate for rales
- Heart: Murmur
- Abdomen: Organomegaly
- Rectal: Prostate tenderness
- Pelvic: Cervical motion tenderness, fundal or adnexal masses or pain, inguinal adenopathy
- Extremities: Clubbing, splinter hemorrhages, tenderness or fluctuance at IV access site
- Musculoskeletal: Joint effusions
- Skin: Rashes, wounds

LABORATORY TESTS

- Initial laboratory testing:
  1. Complete blood count with differential
  2. Comprehensive metabolic panel
  3. Inflammatory markers (erythrocyte sedimentation rate [ESR], C-reactive protein)
  4. Urinalysis
  5. Lactate dehydrogenase
  6. Blood cultures
  7. Thyroid-stimulating hormone
  8. HIV antibody testing
- Consider:
  1. HIV viral load
  2. Hepatitis serologies
  3. TB testing (purified protein derivative or interferon gamma release assay)
  4. Testing for endemic fungal infections (based on geographic location and exposure)
  5. Peripheral smear (thick and thin)
  6. Creatine kinase
  7. Ferritin
  8. Antinuclear antibody testing
  9. Rheumatoid factor
  10. Serum protein electrophoresis
  11. Lumbar puncture
  12. Biopsy (based on clinical and laboratory findings)
- May need to repeat tests at regular intervals until diagnosis is established

IMAGING STUDIES

- Initial:
  1. CXR
  2. Abdominal imaging (CT or ultrasound [US])
- Consider:
  1. Venous duplex imaging
  2. Fluorodeoxyglucose (FDG)-PET
     a. Anatomic localization of focally increased FDG uptake
     b. Consider when initial workup negative and no clear diagnostic clues

TABLE 3 Examples of Subtle Physical Findings Having Special Significance in Patients with Fever of Undetermined Origin

Body Site	Physical Finding	Diagnosis
Head	Sinus tenderness	Sinusitis
Temporal artery	Nodules, reduced pulsations	Temporal arteritis
Oropharynx	Ulceration	Disseminated histoplasmosis
	Tender tooth	Periapical abscess
Fundi or conjunctivae	Choroid tubercle	Disseminated granulomatosis*
	Petechiae, Roth spot	Endocarditis
Thyroid	Enlargement, tenderness	Thyroiditis
Heart	Murmur	Infective or marantic endocarditis
Abdomen	Enlarged iliac crest lymph nodes, splenomegaly	Lymphoma, endocarditis, disseminated granulomatosis*
Rectum	Perirectal fluctuance, tenderness	Abscess
	Prostatic tenderness, fluctuance	Abscess
Genitalia	Testicular nodule	Periarteritis nodosa
	Epididymal nodule	Disseminated granulomatosis
Lower extremities	Deep venous tenderness	Thrombosis or thrombophlebitis
Skin and nails	Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing	Vasculitis, endocarditis

*Includes tuberculosis, histoplasmosis, coccidioidomycosis, sarcoidosis, and syphilis.
From Mandell GL et al (eds): *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 7, Philadelphia, 2010, Churchill Livingstone.

Rx TREATMENT

- Therapy should be tailored once etiology of FUO has been established.
- When the cause of FUO remains unknown, empiric treatment with broad spectrum antibiotics should be reserved for patients who are severely ill.

DISPOSITION

- Prognosis is determined primarily by the underlying disease.
- FUO patients who remain undiagnosed after an extensive evaluation generally have a favorable outcome.

REFERRAL

To an infectious disease specialist, hematologist, or rheumatologist if no diagnosis after thoughtful workup

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Fever of Unknown Origin (Patient Information)

AUTHORS: **Alexandra Abrams-Downey, MD,** and **Erna Milunka Kojic, MD**

TABLE E2 Approach to Management of Fever and Neutropenia

History and Physical Findings	Indicated Modifications in Antimicrobial Coverage or Diagnostic Test
Fever during neutropenia, stable patient	*Escalation approach:* Antibiotic monotherapy with an antipseudomonal β-lactam agent in hemodynamically stable patients with mild to moderate burden of illness; if the patient is receiving antibiotic prophylaxis, then empiric therapy must be based on an agent of a class different from that used for prophylaxis (e.g., if the patient is receiving fluoroquinolone-based prophylaxis, then switch to a β-lactam–based regimen)
Hypotension, signs of severe sepsis or septic shock	*Deescalation approach:* Initial broad-spectrum antimicrobial coverage with a triple-antibiotic regimen (e.g., carbapenem plus vancomycin plus an aminoglycoside) is recommended; if cultures are negative for gram-positive organisms, consider discontinuing vancomycin after 3 days
Fever that is persistent or recrudescent on or after day 5 of antibiotic therapy	Empiric antifungal therapy: Add an amphotericin B product, an echinocandin, or voriconazole if the patient is not already receiving prophylaxis with a mold-active agent; a CT scan of the chest may help identify fungal infection; consider a CT scan of the chest and frequent galactomannan testing during neutropenia to guide preemptive treatment as an alternative strategy to empiric antifungal treatment
Severe oral or esophageal mucositis	Send a swab for viral (HSV) culture; add antiviral coverage if not already being given; consider antiviral resistance to prophylaxis if esophagitis occurs late in the course of neutropenia; add an antifungal agent for possible *Candida* esophagitis; switch streptococcal coverage to vancomycin; esophagoscopy may be indicated
Catheter exit site or tunnel erythema, tenderness, discharge or cellulitis at any site	Culture any discharge; add vancomycin; for tunnel infection (erythema and tenderness 2 cm above exit site), catheter removal and surgical debridement generally are required
Possible anaerobic infection	Add metronidazole if broad-spectrum antibiotics without activity against anaerobes are being used
Abdominal pain, especially right lower quadrant, suggestive of neutropenic enterocolitis; oropharyngeal, neck or soft tissue swelling	Perform a CT scan of the affected area Supportive care: Avoid surgical intervention if possible in a neutropenic patient
New pulmonary infiltrate	Bronchoscopy (with or without biopsy) is the preferred method for evaluating new infiltrates in high-risk patients Nodular: Add mold coverage with voriconazole, posaconazole, or amphotericin B preparation Alveolar: Broaden gram-negative coverage and add *Legionella* coverage (quinolone or macrolide) Interstitial: Send specimen for diagnostic studies for respiratory viruses, PCP, and herpes viruses, particularly CMV Review patient history for risk factors for tuberculosis or infection with endemic fungi
Upper respiratory symptoms of coryza, congestion during fall or winter	Send nasal wash or swab for respiratory viral studies (e.g., culture, PCR, rapid antigen testing)
Hemorrhagic cystitis	Indicated studies include urine viral culture and BK virus PCR assay (for hematopoietic stem cell transplant recipients)

CMV, Cytomegalovirus; *CT,* computed tomography; *HSV,* herpes simplex virus; *PCP, Pneumocystis jirovecii* pneumonia; *PCR,* polymerase chain reaction.
From Niederhuber JE: *Abeloff's Clinical Oncology*, ed 6, Philadelphia, 2020, Elsevier.

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BASIC INFORMATION

DEFINITION

Fibrocystic breast disease (FBD), now called "fibrocystic breast changes" (FBC), includes benign breast lesions including:

- Microcystic and macrocystic changes
- Fibrosis
- Mild and moderate hyperplasia
- Sclerosing adenosis
- Apocrine metaplasia
- Fibroadenoma
- Papilloma
- Papillomatosis
- Radial scar

Nonmalignant breast lesions can be divided into nonproliferative, proliferative without atypia, and atypical hyperplasia. Nonproliferative lesions such as simple breast cysts are considered not to be at increased risk for breast cancer. Proliferative lesions, including ductal hyperplasia, intraductal papillomas, sclerosing adenosis, radial scars, and fibroadenomas, are considered markers for a small increased risk of progressing to breast cancer, and patients should be counseled on risk reduction.

SYNONYMS

Cystic changes
Chronic cystic mastitis
Fibrocystic breast changes
Mammary dysplasia
Fibrocystic mastopathy
Diffuse cystic mastopathy

ICD-10CM CODES

N60.01 Solitary cyst of right breast
N60.02 Solitary cyst of left breast
N60.09 Solitary cyst of unspecified breast
N60.11 Diffuse cystic mastopathy of right breast
N60.12 Diffuse cystic mastopathy of left breast
N60.19 Diffuse cystic mastopathy of unspecified breast
N60.3 Fibrosclerosis

EPIDEMIOLOGY & DEMOGRAPHICS

- FBC affects 30% to 60% of reproductive-age women.
- Most commonly seen in women ages 30 to 50 yr.

ETIOLOGY

The cause of FBC is unknown but is thought to be influenced by reproductive hormones, estrogen in particular.

- Because it is found in the majority of healthy breasts, it is regarded as a nonpathologic process.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

See Table E1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Lumpy or ropey breast texture
- Nodular areas
- Tenderness of breasts and/or nipples
- Dominant mass more often in the upper outer quadrants
- Symptoms tend to be affected by changes in the menstrual cycle.
- Symptoms can be aggravated in postmenopausal women who initiate hormone therapy
- Nipple discharge

For differentiation of breast masses, see Table 2. Characteristics of breast masses suspect for cancer (90% sensitivity, 40% to 60% specificity) are:

- Fixed mass
- Poorly defined mass
- Hard (scirrhous) mass

WORKUP

- Rule out breast carcinoma if breast mass, thickening, discharge, and/or pain are present.
- Perform biopsy of suspected area for histologic confirmation.

IMAGING STUDIES

Mammography and ultrasound studies required:

- For mammographic changes (suspicious densities, microcalcifications [Fig. E1], architectural distortion): Careful evaluation, including possibly biopsy to exclude breast cancer
- Ultrasound study (Fig. E2): To evaluate the presence of a solid vs. cystic mass
- MRI is not recommended for routine evaluation of breast pain or fibrocystic changes

TABLE 2 Differentiation of Breast Masses

Characteristic	Cystic Disease	Benign Adenoma	Malignant Tumor
Patient age	25-60 yr	10-55 yr	25-85 yr
Number	One or more	One	One
Shape	Round	Round	Irregular
Consistency	Elastic, soft to hard	Firm	Stony hard
Delimitation	Well delimited	Well delimited	Poorly delimited
Mobility	Mobile	Mobile	Fixed
Tenderness	Present	Absent	Absent
Skin retraction	Absent	Absent	Present

From Swartz MH: *Textbook of physical diagnosis,* ed 7, Philadelphia, 2014, WB Saunders.

TREATMENT

NONPHARMACOLOGIC THERAPY

Treatment is symptomatic:

- Reassurance
- Supportive bra
- OTC pain medications including NSAIDs and Tylenol
- Reduced intake of methylxanthines (coffee, chocolate), although this is not as effective as previously thought
- Decreasing vitamin E or salt has not proved to be effective
- Periodic physician examination to monitor patients with FCD who have pronounced nodular features
- Aspiration for palpable or symptomatic cysts (NOTE: Cysts often recur; repeat aspiration is not always required unless pain is a problem)

PHARMACOLOGIC TREATMENT

For breast pain:

- Danocrine (Danazol): This is the only FDA-approved drug for breast pain. Moderate success has been reported, but the side effect profile is significant due to androgenic effects.
- Bromocriptine: The medication inhibits prolactin, and its effects are better than a placebo, but side effects such as lightheadedness and gastrointestinal symptoms limit its use.
- Tamoxifen: This has been found to reduce breast pain in 70% of affected women with cyclic breast pain, but the side effects of hot flashes and vaginal dryness interfere with compliance.
- Pharmacologic therapy is usually tapered down after 3 to 6 mo of treatment.

FOLLOW-UP

- Evaluate carefully to exclude breast cancer; then offer reassurance and periodic reevaluation as required.
- Regular self-examination, annual physician examination.

REFERRAL TO BREAST SURGEON

- For further evaluation and/or biopsy if suspicious changes are associated with FBC (including progression of dominant mass or thickening, persistent or bloody nipple discharge, or suspicious mammographic changes or lesions)
- To alleviate anxiety associated with breast symptoms or changes

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Fibrocystic Breast Changes (Patient Information)
Breast Cancer (Related Key Topic)
Mastodynia (Related Key Topic)
Mastitis (Related Key Topic)

AUTHORS: **Estelle H. Whitney, MD,** and **Anthony Sciscione, DO**

SUGGESTED READINGS

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The American Society of Breast Surgeons: *Consensus guideline on diagnostic and screening magnetic resonance imaging of the breast*, Available at: www.breastsurgeons.org/about/statements/PDF_Statements/MRI.pdf, June 22, 2017.

TABLE E1 Typical US characteristics of solid breast lesions

	Benign	Malignant
Shape	Oval/ellipsoid	Variable
Alignment	Wider than deep aligned parallel to tissue planes	Deeper than wide
Margins	Smooth/thin echogenic pseudocapsule with 2-3 gentle lobulations	Irregular or spiculated echogenic "halo"
Echotexture	Variable-to-intense hyperechogenicity	Low-level Marked hypoechogenicity
Homogeneity of internal echoes	Uniform	Non-uniform
Lateral shadowing	Present	Absent
Posterior effect	Minimum attenuation/posterior enhancement	Attenuation with obscured posterior margins
Other signs		Calcification Microlobulation Intraductal extension Infiltration across tissue planes and increased echogenicity of surrounding fat

From Sutton D: *Textbook of radiology and imaging*, ed 7, 1998, Churchill Livingstone; and Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, 2019, Elsevier.

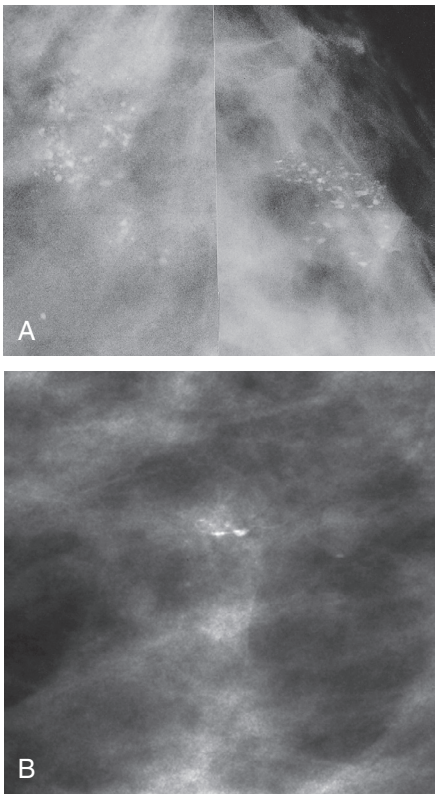

FIG. E1 Fibrocystic change. A, On the CC view, the calcifications appear as round "smudge" shadows. **B,** On the lateral view, 'teacups' representing the layering of calcific material in the dependent portion of microcysts are seen. (From Adam A et al: *Grainger & Allison's diagnostic radiology*, ed 5, 2007, Churchill Livingstone; Sutton D: *Textbook of radiology and imaging*, ed 7, 1998, Churchill Livingstone; and Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, 2019, Elsevier.)

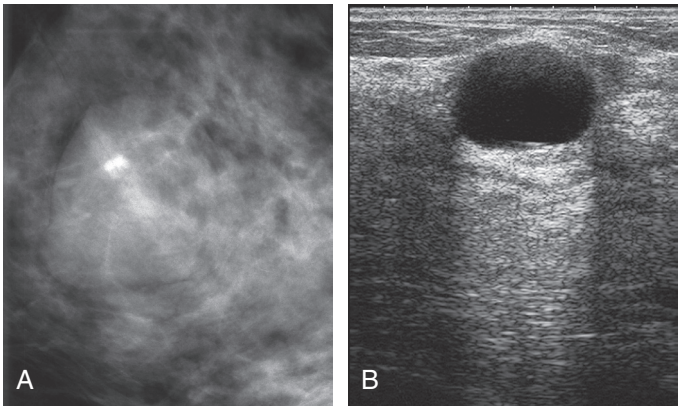

FIG. E2 Cyst. A, A well-defined, rounded mass with an associated lucent halo. **B,** Ultrasound. The absence of internal echoes and posterior enhancement is diagnostic of a cyst. (From Adam A et al: *Grainger & Allison's diagnostic radiology*, ed 5, 2007, Churchill Livingstone; and Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Fibromyalgia (FM) is a syndrome characterized by chronic, widespread musculoskeletal pain without evidence of soft tissue inflammation. Key features include fatigue, sleep disruption, cognitive disturbance, and psychiatric and somatic symptoms. Research suggests that FM is a disorder of pain regulation, which is often classified as a form of central sensitization.

SYNONYMS

"Fibrositis" is a term that is no longer used, because there is no evidence of connective tissue inflammation in FM.

FM

ICD-10CM CODE
M79.7 Fibromyalgia

EPIDEMIOLOGY & DEMOGRAPHICS

Worldwide, the prevalence of FM is estimated to be between 2% and 8%, and it increases with age. In the U.S., FM is the most common cause of musculoskeletal pain in women aged 20 to 55 yr. Using the 2010 American College of Rheumatology (ACR) diagnostic criteria for FM, the female:male ratio is approximately 2:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients with FM often report the following symptoms:

- Chronic (>3 mo) widespread (affecting both sides of the body, above and below the waist, and involving the axial spine) musculoskeletal pain
- Cognitive disturbances
- Fatigue and sleep disturbances (e.g., unrefreshed sleep, easy fatigability)
- Psychiatric symptoms (e.g., anxiety, depression)
- Headache (present in more than half of patients with FM; this includes migraine and tension-type headaches)
- Paresthesias
- Associated disorders: Irritable bowel syndrome, interstitial cystitis/painful bladder syndrome

On physical examination, patients with FM may have tenderness in particular soft tissue locations called tender points. Examination of tender points requires that the examiner be familiar with the areas to palpate and that they apply enough pressure (4 kg/cm^2 or enough pressure to whiten the nail bed of the fingertips of the examiner).

ETIOLOGY

Although the exact cause of FM is unknown, its etiology is thought to be multifactorial:

- Genetic and environmental factors may play a role. Evidence suggests that both the ascending and descending pain pathways operate abnormally, resulting in central amplification of pain signals. Familial associations of FM provide strongest evidence that reflect both these factors.
- In those predisposed, FM may be precipitated by stressful events such as abuse, injury from accidents, illnesses (including autoimmune disorders), infections, surgical procedures, and psychological stressors.
- Psychosocial, neuroendocrine, hormonal, and sociocultural factors also influence symptom expression.

PATHOGENESIS

Much remains to be discovered about the pathogenesis of FM, even though significant advances have been made in our understanding of this syndrome over the past few decades. Researchers have shown that biochemical, metabolic, and immunoregulatory abnormalities exist in patients with FM. Hence, this condition is now believed to be neurosensory in nature.

- Augmented pain and sensory processing is a hallmark, resulting in diffuse pain, allodynia (pain brought on by nonpainful stimuli), and hyperalgesia (more intense and prolonged pain perception).
- Afflicted persons show altered physiologic responses to painful stimulation at spinal and supraspinal levels.
- Brain neuroimaging studies found differences in brain structure, neurochemical concentrations, and functional brain networks in FM compared with control subjects. PET scans have revealed widespread activation of glial cells in the cortex, particularly in the frontal and parietal lobes.
- Pain augmentation may also result from a loss of tonic inhibition by descending inhibitory pathways from the brain to the spinal cord.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The presence of any of the disorders mentioned below does not necessarily exclude a diagnosis of FM because it may coexist with many conditions:

- Other functional somatic or "central sensitivity" syndromes: Myofascial pain, chronic fatigue syndrome, irritable bowel syndrome, headache/migraines, chronic pelvic and bladder pain disorders, and temporomandibular disorder
- Disorders that can mimic FM and must be ruled out include metabolic (e.g., hypothyroidism), infectious, and neurologic disorders. Arthritis and rheumatic diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, Sjögren syndrome)
- Myalgias and other muscle disease (e.g., inflammatory and metabolic myopathies)
- Mood and anxiety disorders
- Sleep disorders (e.g., sleep apnea, restless leg syndrome)
- Neurologic disorders
- Medications: Statin-induced muscle pain, opioid-induced hyperalgesia

WORKUP

A thorough history, physical examination, and appropriately selected laboratory or imaging studies can usually differentiate FM from connective tissue or other systemic diseases.

- Chronic (>3 mo) widespread pain is the hallmark symptom of FM, but fatigue, tenderness, depression/anxiety, nonrestorative sleep, cognitive difficulties (the so-called "fibrofog"), and functional impairment are other key symptoms.
- The 1990 ACR FM Classification Criteria were used for clinical studies:
  1. Chronic, widespread pain in all four quadrants of the body and the axial skeleton
  2. Pain on digital palpation of at least 11 of 18 tender points
- The 2010 ACR diagnostic criteria for FM do not require a tender point examination; other disorders that would otherwise explain the musculoskeletal pain must be excluded (Table 1).
- A diagnostic screening tool (Fibromyalgia Diagnostic Screen) developed by Arnold and colleagues was found to accurately screen for FM. This tool includes a patient self-reported questionnaire and an abbreviated physical examination with targeted lab tests.
- The most recent FM diagnostic criteria are by ACTION-APS Pain Taxonomy (AAPT), an international working group. To fulfill AAPT criteria for FM, a patient is required to have a history of at least 3 mo of widespread pain in at least 6 of 9 possible pain sites, and moderate to severe sleep disturbance or fatigue.

LABORATORY TESTS

- Selective use of ancillary tests complements the history and physical examination in the diagnosis of FM. Testing should be highly focused on the exclusion of FM mimickers or suspected concurrent diseases.
- Complete blood cell count, routine chemistries, thyroid-stimulating hormone (TSH), 25-hydroxy vitamin D level (low levels can cause muscle pain), vitamin B^{12} level (low levels can cause fatigue and pain), iron studies (low levels can cause fatigue and depressive symptoms), and magnesium levels (low levels can cause muscle spasms).
- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are generally normal.
- Routine testing for antinuclear antibody (ANA) and/or rheumatoid factor should be avoided unless history and physical examination suggest an autoimmune disease.

TREATMENT

GENERAL RX

The goal in treating patients with fibromyalgia is to reduce the main symptoms of the syndrome (musculoskeletal pain, fatigue, depression, anxiety, poor sleep).

- Challenging to treat; best approach may be combination of drug and nondrug therapies.

TABLE 1 2010 Fibromyalgia Diagnostic Criteria

Criteria

A patient satisfies diagnostic criteria for fibromyalgia if the following three conditions are met:

1. Widespread pain index (WPI) 7 and symptom severity (SS) scale score of 5 or WPI 3-6 and SS scale score of 9.
2. Symptoms have been present at a similar level for at least 3 mo.
3. The patient does not have a disorder that would otherwise explain the pain.

Ascertainment

1. WPI: Note the number of areas in which the patient has had pain over the past wk. In how many areas has the patient had pain?

Score will be between 0 and 19.

Shoulder girdle, left	Hip (buttock, trochanter), left	Jaw, left	Upper back
Shoulder girdle, right	Hip (buttock, trochanter), right	Jaw, right	Lower back
Upper arm, left	Upper leg, left	Chest	Neck
Upper arm, right	Upper leg, right	Abdomen	
Lower arm, left	Lower leg, left		
Lower arm, right	Lower leg, right		

2. SS scale score:
   Fatigue
   Waking unrefreshed
   Cognitive symptoms

For the each of the three symptoms above, indicate the level of severity over the past week using the following scale:
0, No problem
1, Slight or mild problems, generally mild or intermittent
2, Moderate, considerable problems, often present at a moderate level
3, Severe: Pervasive, continuous, life-disturbing problems

Considering somatic symptoms in general, indicate whether the patient has:*
0, No symptoms
1, Few symptoms
2, A moderate number of symptoms
3, A great deal of symptoms

The SS scale score is the sum of the severity of the three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12.

*Somatic symptoms that might be considered include muscle pain, irritable bowel syndrome, fatigue or tiredness, thinking or remembering problem, muscle weakness, headache, pain or cramps in the abdomen, numbness or tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud phenomenon, hives or welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of or change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

Adapted from Wolfe F et al: The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity, *Arthritis Care Res* 62:600-610, 2010.

- Nonpharmacologic (Table 2): Strong evidence to support exercise (aerobic, strengthening, and stretching exercises; tai chi; yoga), cognitive behavioral therapy, physical therapy, and patient education (e.g., regarding the disease, importance of good sleep and hygiene).
- FM can be due to abnormalities in many different neurotransmitter systems; thus, approaches and treatment responses may vary.
- Pharmacologic therapies for fibromyalgia are summarized in Table 3.
- Best evidence for tricyclics (low-dose amitriptyline, cyclobenzaprine), serotonin-norepinephrine reuptake inhibitors (milnacipran, duloxetine), gabapentinoids (gabapentin, pregabalin).
- Second-tier drug classes include SSRIs.
- "Start low, go slow" approach is best to avoid side effects, which are common. Medication adherence is generally poor.
- There is no evidence that acetaminophen, NSAIDs or corticosteroids are effective in FM.
- The only analgesic that has demonstrated some efficacy in FM has been tramadol; can consider for treatment-resistant cases.
- Avoid narcotic use. Opioid use and abuse may aggravate chronic widespread pain.

DISPOSITION

- The pain and symptoms of FM can wax and wane, vary in physical location and in intensity day-to-day; many patients continue to have chronic pain and fatigue regardless of therapy.
- Disability rates vary from 10% to 30%.

REFERRAL

Referral to rheumatology, neurology, mental health professionals, physical medicine and rehabilitation, including PT. Multidisciplinary team approach is generally most helpful.

PEARLS & CONSIDERATIONS

- Fibromyalgia is a neurosensory disorder whereby affected individuals have abnormal central nociceptive processing.
- Diagnosis is based on the presence of chronic musculoskeletal pain in the absence of physical or laboratory evidence of inflammation and in the absence of any other condition that would explain the symptoms.
- Treatment options are varied, but a combination of drug and nondrug options is likely to provide optimal results.
- Myofascial pain syndrome may represent a localized form of FM. It is associated with trigger points (rather than tender points as seen in FM). Some patients with myofascial pain syndrome may progress to FM.

COMMENTS

FM occurs frequently in patients with some rheumatic diseases, such as rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus, in which prevalence of FM may reach 20%.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Fibromyalgia (Patient Information)

AUTHOR: **Nadine Mbuyi, MD**

TABLE 2 Nonpharmacologic Therapies for Fibromyalgia

Treatment	Cost	Specifics	Evidence Level	Side Effects	Suggestions
Patient education	Low	Incorporate principles of self-management, including a multimodal approach.	1, A		• After initial diagnosis, spend several visits (or use separate educational sessions) to explain the condition and set treatment expectations.
Graded exercise	Low	Aerobic exercise has been best studied, but strengthening and stretching also have been shown to be of value.	1, A	Worsening of symptoms when program is begun too rapidly	• Counsel patients to "start low, go slow." • For many patients, focusing first on increasing daily "activity" is more helpful before actually starting exercise.
Cognitive behavioral therapy (CBT)	Low	Pain-based CBT programs have been shown to be effective in one-on-one settings, small groups, and via the Internet.	1, A	No significant side effects of CBT per se, but patients' acceptance is often poor when they view this as a "psychological" intervention	• Internet-based programs are gaining acceptance and are more convenient for working patients.
Complementary and alternative medicine (CAM) therapies	Variable	Most CAM therapies have not been rigorously studied.	1, A	Generally safe	• There is emerging evidence that CAM treatments such as tai chi, yoga, balneotherapy, and acupuncture might be effective. • Allowing patients to choose which CAM therapies to incorporate into an active treatment program can increase self-efficacy.
CNS neurostimulatory therapies		Several different types of CNS neurostimulatory therapies have been shown to be effective in FM and other chronic pain states.		Headache	• These treatments continue to be refined as we learn about optimal stimulation targets, "dosing," and so on.

CNS, Central nervous system; *FM,* fibromyalgia.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE 3 Pharmacologic Therapies for Fibromyalgia

Treatment	Cost	Specifics	Evidence level	Side Effects	Suggestions
Pharmacologic therapies		Pharmacologic therapy is best chosen based on the predominant symptoms and initiated in low dose with slow dose escalation.	5, Consensus		• Some practitioners find that getting patients on a drug regimen that helps improve symptoms before initiating nonpharmacologic therapies can help improve compliance.
Tricyclic compounds		• Amitriptyline 10-70 mg qhs • Cyclobenzaprine 5-20 mg qhs	1, A	Dry mouth, weight gain, constipation, "groggy" or drugged feeling	• When effective, can improve a wide range of symptoms, including pain, sleep, bowel, and bladder symptoms. • Taking these drugs several hours before bedtime improves side effect profile.
Serotonin norepinephrine reuptake inhibitors	Duloxetine is generic, milnacipran not	• Duloxetine, 30-120 mg/day • Milnacipran, 100-200 mg/day	1, A	Nausea, palpitations, headache, fatigue, tachycardia, hypertension	• Warning patients about transient nausea, taking with food, and slowly increasing dose can increase tolerability. • Milnacipran might be slightly more noradrenergic than duloxetine and thus potentially more helpful for fatigue and memory problems, but it is also more likely to cause HTN.

TABLE 3 Pharmacologic Therapies for Fibromyalgia—cont'd

Treatment	Cost	Specifics	Evidence level	Side Effects	Suggestions
Gabapentinoids	Gabapentin is generic, pregabalin not	• Gabapentin 800-2400 mg/day in divided doses • Pregabalin up to 600 mg/day in divided doses	1, A	Sedation, weight gain, dizziness	• Giving most or all of the dose at bedtime can increase tolerability.
γ-Hydroxybutyrate	Available for treating narcolepsy, cataplexy	GHB 4.5-6.0 g per night in divided doses	1, A	Sedation, respiratory depression, and death	• Shown to be efficacious but not approved by U.S. FDA because of safety concerns.
Low-dose naltrexone	Low	4.5 mg/day	Two small single center RCTs		
Cannabinoids	NA	Nabilone 0.5 mg PO qhs-1.0 mg bid	1, A	Sedation, dizziness, dry mouth	• No synthetic cannabinoid is approved in the U.S. for treatment of pain.
Selective serotonin reuptake inhibitors (SSRIs)	SSRIs that should be used in FM (see Suggestions) are all generic	Fluoxetine, sertraline, paroxetine	1, A	Nausea, sexual dysfunction, weight gain, sleep disturbance	• Older, less selective SSRIs may have some efficacy in improving pain, especially at higher doses that have more prominent noradrenergic effects. • Newer SSRIs (citalopram, escitalopram, desvenlafaxine) are less effective or ineffective as analgesics.
NSAIDs		• No evidence of efficacy • Can be helpful to treat comorbid "peripheral pain generators"	5, D	GI, renal, and cardiac side effects	• Use the lowest dose for the shortest period of time to reduce side effects.
Opioids		• Tramadol with or without acetaminophen, 50-100 mg every 6 hours • No evidence of efficacy for stronger opioids	5, D	Sedation, addiction, tolerance, opioid-induced hyperalgesia	• There is increasing evidence that opioids are less effective for treating chronic pain than previously thought, and their risk-benefit profile is worse than other classes of analgesics.

bid, Twice a day; *FDA,* U.S. Food and Drug Administration; *FM,* fibromyalgia; *GHB,* gammahydroxybutyrate; *GI,* gastrointestinal; *HTN,* hypertension; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PO,* oral; *qhs,* at bedtime; *RCT,* randomized controlled trial.

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

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Fifth Disease (Parvovirus B19 Infection) PTG

BASIC INFORMATION

DEFINITION

Parvovirus B19 is a small, nonenveloped ssDNA virus that belongs to the *Erythrovirus* genus of the Parvoviridae family. It was first discovered in 1975 when units of blood were being screened for hepatitis B and was read as a false-positive result (sample 19 in panel B). It causes a spectrum of human disease, ranging from asymptomatic to fatal depending on the underlying host. Classically, it has been associated with erythema infectiosum (EI), or "fifth disease," the fifth in a series of six viral exanthems that commonly affect school-aged children and are named in order of the dates they were first described. In addition, parvovirus B19 causes a variety of clinical manifestations in fetuses, adults, and the immunocompromised.

SYNONYMS

Parvovirus B19
Erythema infectiosum
Fifth disease

ICD-10CM CODE
B08.3 Erythema infectiosum [fifth disease]

EPIDEMIOLOGY & DEMOGRAPHICS

Parvovirus B19 infection occurs worldwide. Humans are the only known hosts.

INCIDENCE: Between 1% and 9% of pregnancies are affected by B19 infection. During B19 epidemics, approximately 20% of susceptible school staff members or child care personnel will become infected. The infection rate of household contacts may be as high as 50%.

PEAK INCIDENCE: In the U.S., B19 infection occurs more frequently between late winter and early summer, often in cycles of local epidemics that peak every 4 to 10 yr.

PREVALENCE: The percentage of people with protective IgG antibodies to parvovirus B19 increases with age. Approximately 15% of school-aged children and 50% to 80% of adults have protective antibody titers. Half of women of childbearing age lack antibodies to B19, as do 30% to 40% of pregnant women.

PREDOMINANT AGE: 5 to 18 yr old

RISK FACTORS:

- Exposure to school-aged children
- Immunosuppression
- Congenital or acquired hematologic abnormalities
- Blood transfusion
- Tissue transplantation
- Vertical transmission from infected mother to fetus

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The clinical presentation comprises a wide spectrum and is influenced by the infected person's age and hematologic and immunologic status. Among immunocompetent individuals, approximately 25% of those infected are asymptomatic, 50% have nonspecific flulike symptoms, and 25% have the classic symptoms of B19 infection, including rash and/or arthralgias.

Five typical clinical syndromes are associated with parvovirus B19 infection:

- Fifth disease/erythema infectiosum (EI)
  1. EI is most often seen in children, although it can also occur in adults. EI is characterized by a bright red, nontender rash most prominent on the cheeks, with a circumoral pallor producing the classic "slapped face" appearance (Fig. E1), which is often followed by a reticular, lacelike rash on the trunk and extremities (Figs. E2 and E3). This is typically a transient, self-limited illness that begins with a prodrome of flulike symptoms such as fever, malaise, myalgias, coryza, headache, nausea, and diarrhea. The malar rash occurs once viremia has resolved and antibody production has occurred, as it is thought to be secondary to immune complex deposition.
- Arthropathy
  1. Acute polyarthralgias and polyarthritis are more commonly seen in adults (especially women) and typically involve symmetric small joints of the extremities. The arthritis is nonerosive. Joint symptoms usually resolve within 3 wk but may rarely become persistent or recurrent. A rash develops in 75% of infected adults, but less than 20% have the classic "slapped face" rash seen in EI. The rash may be exacerbated by changes in temperature, sunlight, exercise, or emotional stress.
- Transient aplastic crisis (TAC)
  1. TAC occurs in individuals with hematologic disorders causing increased red blood cell destruction (e.g., sickle cell disease) or decreased red cell production (e.g., iron deficiency anemia). Patients with TAC present with pallor, weakness, and lethargy due to severe anemia, often requiring transfusion. TAC is most often self-limited and usually resolves in 1 to 2 wk.
- Fetal infection leading to nonimmune hydrops fetalis, intrauterine fetal death, or miscarriage
  1. Pregnant women with B19 infection have a 30% chance of fetal transmission. The risk of fetal loss is 5% to 10% and greatest when fetal infection occurs in the first 20 wk of gestation. Parvovirus has not been shown to cause congenital anomalies.
- Pure red cell aplasia in immunocompromised individuals
  1. Chronic infection and severe, sometimes life-threatening anemia have been described in immunocompromised patients, including those with leukemia and other cancers, HIV, congenital immunodeficiency, and tissue transplantation.

Other manifestations:

- Additional skin findings have been reported, including petechial, papular-purpuric gloves-and-socks syndrome (PPGSS), which is an uncommon manifestation of B19 infection. It begins with painful erythema and induration of the hands and feet that then progresses to an erythematous exanthem with a distinct margin at the wrist and ankle joints. Skin changes may further progress to petechia, purpura, and bulla with skin sloughing. PPGSS is seen mainly in young adults and usually resolves in 1 to 3 wk.
- B19 has also been reported in association with a wide range of diseases and clinical manifestations including chronic arthritis, vasculitis, myocarditis, immune thrombocytopenia, neutropenia, nephritis, lymphadenitis, meningitis, encephalitis, hemophagocytic syndrome, and fulminant liver disease. A causal role for B19 in these illnesses has yet to be established.

ETIOLOGY, INFECTIVITY, & TRANSMISSION

- B19 preferentially infects, replicates in, and is directly cytotoxic to erythroid progenitor cells, which may result in profound anemia or pure red cell aplasia.
- Viremia and the period of greatest infectivity occur 5 to 10 days after exposure and last about 1 wk in immunocompetent individuals,

FIG. E1 Erythema infectiosum. Erythema of the bilateral cheeks, which has been likened to a "slapped cheeks" appearance. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E2 Erythema infectiosum. Reticulate erythema on the upper arm of a patient with erythema infectiosum. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E3 Erythema infectiosum. Patchy erythema with reticulate changes of the inner thigh in a patient with erythema infectiosum. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

after which time antibody production begins and typical symptoms of rash and arthralgias manifest.
- Modes of transmission include contact with respiratory tract secretions, vertical transmission from mother to fetus, percutaneous exposure to blood, and transfusion of blood products.
- Because of its nonenveloped capsid, parvovirus B19 is heat stable and difficult to inactivate with solvent detergents, leading to its potential to contaminate blood products.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Depending on the clinical presentation, differential includes:

- Erythema infectiosum
- Roseola, rubella, measles, group A strep, and other childhood viral exanthems
- Infectious mononucleosis
- Acute HIV infection
- Drug eruption
- Acute polyarthritis
- Juvenile rheumatoid arthritis (Still disease)
- Transient arthritis secondary to an acute viral infection

WORKUP

- Most patients with parvovirus B19 infection do not require laboratory testing because symptoms are mild and resolve over 5 to 7 days.
- Diagnosis can be made by the typical clinical presentation of EI in well children.
- Laboratory tests may be required for confirmation in immunosuppressed populations, those with severe anemia or transient aplastic crisis (TAC), and pregnant women.
- People who are at risk for severe parvovirus complications and are at high risk for exposure might benefit from antibody testing to determine whether they are immune to parvovirus.

LABORATORY TESTS

- Complete blood count (CBC) and reticulocyte count: Reticulocyte count and hematocrit indicate the clinical severity of infection. CBC classically shows a normocytic normochromic anemia. Reticulocytes are markedly decreased or absent in pure red blood cell aplasia, rising once neutralizing antibody is produced. White blood cell and platelet counts are typically unchanged.
- Parvovirus B19 IgM and IgG: Parvovirus B19 IgM enzyme immunoassay is widely available and the preferred method of diagnosis in immunocompetent individuals. IgM can be detected within 7 to 10 days of exposure and may persist for several mo. IgG antibodies are detectable about 15 days after exposure and persist for life.
- Parvovirus B19 viral DNA polymerase chain reaction (PCR) is the most sensitive method of detection and is the preferred method for diagnosis in immunocompromised individuals, fetuses, and immunocompetent patients with suspected persistent infection. High titers of viral DNA in serum are indicative of active infection. Rare B19 variants can be under-quantified by some PCR methods. Low levels of B19 DNA may be detected in serum by PCR for mo to yrs after treatment or resolution of disease, and low levels of viral DNA may be found in tissues in patients without active disease.
- Bone marrow biopsy: Bone marrow examination in patients with pure red cell aplasia demonstrates complete or near-complete absence of red cell precursors. Characteristic giant proerythroblasts containing large eosinophilic nuclear inclusions can be seen.
- Fig. E4 illustrates investigations for parvovirus B19 infection in pregnancy.
- Prenatal testing: Fetal nuchal translucency measurement and ductus venosus Doppler velocimetry may indicate the presence of severe fetal anemia. Ultrasound may show fetal edema, ascites, pleural effusions, and cardiomegaly in hydrops fetalis.

Rx TREATMENT

Treatment for fifth disease is generally supportive because the majority of B19 infections are asymptomatic or mild and self-limited. This includes nonsteroidal antiinflammatory drugs for relief of joint symptoms, antipyretics such as acetaminophen for fever, and adequate hydration.

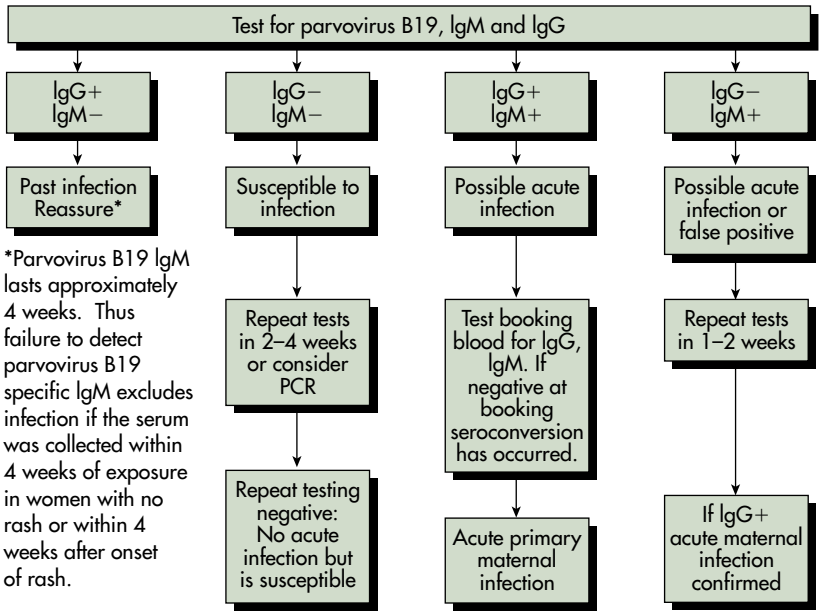

FIG. E4 Investigations for parvovirus B19 infection. (From Stephen G, Gillham J: Fetal infection: a pragmatic approach to recognition and management, *Obstet Gynecol Reprod Med* 22:299-303, 2012.)

- No antiviral drug is available.
- Blood transfusion is often required in cases of severe anemia and pure red cell aplasia until red blood cell (RBC) production returns; intrauterine transfusion may be required in fetal infection.
- Initiation of antiretroviral therapy (ART) has been associated with resolution of B19-induced anemia in HIV-infected patients.
- Bone marrow transplantation has been used in individuals with nonresolving aplastic crisis.
- The mainstay of therapy for fetal hydrops is delivery, which may be followed by resuscitation and ventilation in cases of severe hydrops.

IV immunoglobulin (IVIG) treatment may be considered for immunocompromised patients with chronic B19 infection and chronic anemia and has also been used in certain cases of acute, severe infection.

DISPOSITION

- B19 infection is typically self-limited, with symptoms usually resolving within a few wk and most often only requiring supportive care.
- The illness is contagious in the wk before the rash appears. Once the rash appears, the person with the illness is no longer considered contagious and does not require isolation.
- Patients in whom persistent arthritis with or without joint erosion develops should be evaluated by a rheumatologist.
- In immunocompetent patients, anemia is typically transient with spontaneous resolution and return of RBC production in days to wk. In patients with hematologic abnormalities, however, anemia may be severe and may be the result of transient aplastic crisis or pure red cell aplasia, which warrants immediate hematologic evaluation and transfusion.
- Patients with TAC or chronic parvovirus B19 infection pose a risk for nosocomial spread and, when hospitalized, should be isolated with droplet precautions.
- Patients with chronic infection and anemia may require evaluation for possible IVIG treatment.
- Pregnant women with B19 infection have a 30% risk of fetal transmission; they should undergo close monitoring of fetal health and development and may require fetal transfusion or referral to a tertiary care center for delivery in the case of hydrops fetalis.

REFERRAL

- To hematologist if signs of marrow suppression
- To rheumatologist if signs of severe or erosive arthritis

PEARLS & CONSIDERATIONS

- Generally self-limited disease lasting up to 3 wk in immunocompetent individuals.
- Symmetric arthritis involving small joints is common in adults, whereas facial rash is common in children.
- Can cause severe anemia with or without transient aplastic crisis that may become chronic in patients with hematologic abnormalities, immunocompromise, malignancy, or a history of organ transplantation.
- Infection during pregnancy can cause fetal anemia, hydrops fetalis, or fetal loss.

PREVENTION

- Personal infection control practices including hand hygiene; covering the mouth while sneezing and coughing; not touching the eyes, mouth, or nose; not sharing food and drinks; and avoiding contact with sick persons.
- Droplet isolation precautions for infected immunocompromised patients or those with TAC.
- Testing of plasma pools and blood products: In June 2009, the FDA issued guidance requiring manufacturers to perform parvovirus B19 nucleic acid testing to reduce the possible risk of parvovirus B19 transmission by plasma-derived products.
- Vaccines have not progressed beyond phase I/II clinical trials.

RELATED CONTENT

Fifth Disease (Patient Information)

AUTHORS: **Rebecca Cangemi, MD,** and **Dominick Tammaro, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Filariasis is a general term for an infection caused by subcutaneous nematodes (roundworms) of the genera *Wuchereria* and *Brugia,* found in the tropical and subtropical regions of the world. The disease is characterized by acute lymphatic inflammation or chronic lymphatic obstruction associated with intermittent fevers or recurrent episodes of dyspnea and bronchospasm.

SYNONYMS

Lymphatic filariasis
Elephantiasis
Tropical pulmonary eosinophilia

ICD-10CM CODES

B74.0 Filariasis due to *Wuchereria bancrofti*
B74.1 Filariasis due to *Brugia malayi*
B74.9 Filariasis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): In the U.S., the last locale with endemic lymphatic filariasis was Charleston, South Carolina, with no infections seen since the early twentieth century. Zoonotic infections from other *Brugia* spp. have been sporadically reported in North America.
INCIDENCE (GLOBAL): Thanks to mass drug administration campaigns targeted at stopping transmission of infection, prevalence is steadily decreasing globally. However, lymphatic filariasis is endemic in 73 countries; 40 million people have clinical manifestations, 15 million have elephantiasis, and 25 million men have genital swelling (usually hydrocele) from filariasis.
PREDOMINANT SEX: Male
PREDOMINANT AGE: For both males and females, risk is greatest between the ages of 15 and 35 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical manifestations result from acute lymphatic inflammation or chronic lymphatic obstruction.
- Many patients are asymptomatic despite the presence of microfilaremia.
- Episodes of lymphangitis and lymphadenitis are associated with fever, headache, and back pain with painful swellings. Painful localized swelling or acute adenolymphangitis is usually caused by the death of an adult worm.
- Acute funiculitis and epididymitis or orchitis may also be present; all usually resolve within days to wks but tend to recur.
- Chronic infections may be associated with lymphedema, most commonly manifested by hydrocele.
- It is a progressive disease, leading to nonpitting edema and brawny changes that may involve a whole limb.
- Elephantiasis occurs in about 10% of patients, with skin of the scrotum or leg becoming thickened and fissured; the patient is thereafter plagued by recurrent ulceration and infection.
- Chyluria, a condition that develops when lymphatic vessels rupture into the urinary tract, or chylocele may occur.
- Tropical pulmonary eosinophilia can also occur; it is caused by high IgE in response to microfilariae in the lungs and results in nocturnal asthma, fatigue, and weight loss with pulmonary infiltrates on imaging and eosinophilia.

ETIOLOGY

Caused by one of three types of nematode parasite transmitted to humans by mosquitoes:

- *W. bancrofti* (>90% of cases; Fig. E1): Africa (including Egypt), areas of Central and South America, the Pacific Islands, and the Caribbean Basin.
- *B. malayi:* Restricted to India, Malaysia, and other parts of Southeast Asia.
- *B. timori:* Confined to the Indonesian archipelago. After bite of an infected mosquito:
  1. Filarial larvae move into lymphatic vessels and nodes and mature into adult male (2- to 4-cm) and female (4- to 10-cm) worms (Fig. E2). *Wolbachia* bacteria are needed for filarial development.
- After fertilization, the female nematode produces 10,000 or more microfilariae that enter into the bloodstream via the lymphatics.
- Nocturnal periodicity, an increased presence of microfilariae in the circulation during the night when mosquitos are active, is important for diagnosis by blood smear.
- Humans are the definitive hosts.

Acute and chronic inflammatory and granulomatous changes in the lymphatic channels:

- Result from complex interaction of adult worms and host's immune systems

FIG. E1 Microfilaria of *Wuchereria bancrofti* in peripheral blood. (Courtesy Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention. From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

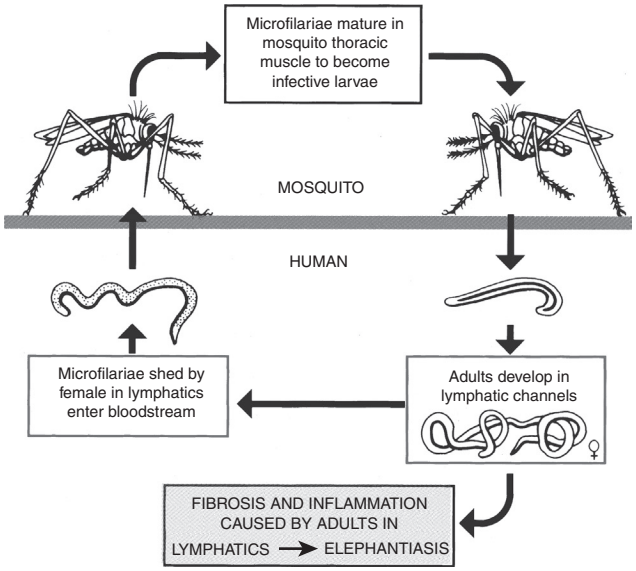

FIG. E2 Lifecycle of lymphatic filariasis. (From Souhami RL, Moxham J: *Textbook of medicine,* ed 4, London, 2002, Churchill Livingstone.)

- Eventually lead to fibrosis and obstruction
- Most likely to develop into obstructive lymphatic disease with recurrent exposure over many yrs, with approximately 30% of those infected going on to develop lymphedema/hydrocele

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Milroy disease, postoperative scarring, and lymphedema of malignancy

WORKUP

Diagnosis is suspected in individuals who have resided in endemic areas for at least 3 to 6 mo or more and complain of recurrent episodes of lymphangitis, lymphadenitis, scrotal edema, or thrombophlebitis, with or without fever.

LABORATORY TESTS

- Demonstration of microfilariae on a blood smear via Giemsa or Wright Stain for definitive diagnosis. Samples drawn at night, especially between 10 PM and 2 AM, have the greatest yield.
- Occasionally, microfilaremia in chylous urine or hydrocele fluid.
- Prominent eosinophilia only during periods of acute lymphangitis or lymphadenitis.
- Serologic tests for antibody, including enzyme-linked immunosorbent assay and indirect fluorescent antibody (often unable to distinguish among the various forms of filariasis or between acute and remote infection).
- Immunoassays (e.g., circulating filaria antigen [CFA]): More successful in antigen detection in patients who are microfilaremic than in those who are amicrofilaremic.

IMAGING STUDIES

- Chest radiography: Reticular nodular infiltrates (tropical pulmonary eosinophilia syndrome).
- In men proven to be microfilaremic, scrotal ultrasonography to aid in the detection of adult worms and "filarial dance sign" may be seen.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Standard of care for elephantiasis:
  1. Elevation of the affected limb
  2. Use of elastic stockings
  3. Local foot care
- General wound care for chronic ulcers and prevention of secondary infection
- Surgical intervention may be necessary for hydrocele

ACUTE GENERAL Rx

- Diethylcarbamazine citrate (DEC) to reduce microfilaremia by 90%.
  1. Effect on adult worms, especially those of the *Wuchereria* species, less certain.
  2. Given in an oral dose of 6 mg/kg PO qd in 3 divided doses × 14 days or 6 mg/kg/day as single PO dose daily × 14 days *plus* doxycycline 200 mg/day × 6 wk (to decrease number of *Wolbachia* and number of microfilaria).
  3. DEC should not be used if coinfection with Loa loa or onchocerciasis is suspected, because of severe adverse reactions, including blindness and death.
- Ivermectin alone or in combination with DEC to decrease microfilaremia. Ivermectin kills the microfilariae but does not kill adult worms.
- Side effects of these drugs include severe hypotensive reactions with dizziness, headache, fever, and vomiting, especially in patients with high microfilarial loads.
- World Health Organization (WHO) recommendation: DEC given as a single dose, alone or (preferably) in combination with ivermectin as treatment in endemic areas.
- Antibacterial agents (a penicillin or cephalosporin) may be indicated to treat coexisting bacterial soft tissue infection (cellulitis or lymphangiitis), which frequently complicates filariasis of the lower extremities.
- Doxycycline for 1 to 2 mo may decrease the number of adult worms and improve lymphatic pathology.
- A recent trial revealed that a single dose of a three-drug regimen of ivermectin, diethylcarbamazine, and albendazole results in a greater clearance of microfilariae than a single dose of a two-drug regimen of diethylcarbamazine plus albendazole.[1]

CHRONIC Rx

- Surgical drainage of hydroceles
- No satisfactory therapy for patients with chyluria

DISPOSITION

Rarely fatal, but the psychological impact of limb and scrotal deformities associated with elephantiasis is substantial

REFERRAL

To a surgeon for management of hydrocele; to a lymphedema therapist when appropriate

PREVENTION

Individuals who intend to travel or reside in endemic areas should be advised to institute preventive measures such as the use of netting and insect repellents containing DEET, especially at night when mosquitos transmitting disease are most active.

AUTHORS: **Tara C. Bouton, MD, MPH, TM, Philip A. Chan, MD, MS,** and **Glenn G. Fort, MD, MPH**

[1] King CL et al: A trial of a triple-drug treatment for lymphatic filariasis, *N Engl J Med* 379:1807-1810, 2018.

SUGGESTED READINGS

Fox LM: Lymphatic filariasis. In *CDC Yellow book 2018: health information for international travel*, New York, 2017, Oxford University Press.

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BASIC INFORMATION

DEFINITION

Focal seizures are characterized by focal cortical discharges that provoke seizure symptoms related to the area of the brain involved. Focal aware seizures (previously known as simple partial seizures) do not cause impairment of consciousness. However, focal aware seizures can evolve into focal impaired awareness (previously known as complex partial) and/or tonic clonic seizures. In the revised International League Against Epilepsy (ILAE) classification of seizures, the name "partial seizures" has been replaced with "focal seizures."

SYNONYMS

Simple partial seizures
Seizures, partial
Partial seizures

ICD-10CM CODES

G40.0	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset
G40.109	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, without status epilepticus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 30 to 50 cases per 100,000 person per yr
PREVALENCE: 5 to 8 cases per 1000 persons
PREDOMINANT SEX AND AGE: No gender preference

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with focal seizures usually have normal physical and neurologic examinations unless secondary due to a structural abnormality such as a stroke, where the patient will have a neurologic exam consistent with the area of CNS structural damage.
- During focal seizures the patients are conscious, but they may have an alteration of awareness. However, if there is spread of the epileptic focus causing secondary generalization, the patient will then lose consciousness and evolve into a generalized tonic clonic seizure. Clues to this progression include a subjective aura before the onset of convulsion, unilateral shaking, and head turning to one side (versive head turning).
- Patients with focal seizures can experience postictal weakness/paralysis that usually resolves within 24 hr (Todd paralysis). However, focal neurologic deficits may also be indicative of a new structural brain lesion.
- Manifestations of focal impaired awareness seizures may include automatisms (semipurposeful behaviors) such as fumbling of fingers or lip smacking.

ETIOLOGY

- Seizures in general are a cardinal sign of cortical neurologic injury.
- The etiology of focal seizures can be either genetic or due to a neurologic injury.
- Frequent causes of focal seizures are tumors, stroke, CNS infections (neurocysticercosis among others), arteriovenous malformations (AVMs), cavernous malformations, traumatic brain injury, cortical dysplasia, and structural abnormalities.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Transient ischemic attack
- Movement disorders
- Psychogenic nonepileptic spells
- Migraines
- The differential diagnosis of nonepileptic events is summarized in Table 1. Table 2 summarizes clinical characteristics that help distinguish epileptic from nonepileptic events

WORKUP

EEG. Ambulatory EEG and/or video EEG recommended for patients with diagnostic uncertainty

LABORATORY TESTS

Routine blood workup (CBC, CMP, glucose, electrolytes) may be considered in appropriate clinical situations.

IMAGING STUDIES

- In the acute setting, a CT scan of the head is high yield to rule out space-occupying lesions.
- MRI of the brain with a defined epilepsy protocol should be performed in all patients with recurrent seizures.

TREATMENT

- Almost all antiepileptic drugs are approved for focal seizures, either in monotherapy or in adjunct. Carbamazepine traditionally has been the standard initial drug treatment for focal seizures. However, newer antiepileptic drugs have better side effect profiles.
- Lamotrigine, levetiracetam, and oxcarbazepine are effective and well-tolerated antiepileptic drugs for treating focal seizures.
- Eslicarbazepine is indicated for the treatment of focal-onset seizures as monotherapy or adjunctive therapy. The recommended initial dose of eslicarbazepine is 400 mg once daily. Increase the dose in weekly increments of 200 mg, based on clinical response and tolerability, to a recommended maintenance dose of 800 to 1600 mg once daily.
- Lacosamide is indicated as monotherapy or adjunctive therapy in patients with focal-onset seizures. The initial recommended dose is 50 mg twice daily; increase at weekly intervals by 50 mg twice daily, up to a recommended maintenance dose of 100 to 200 mg twice daily.
- Patients who continue to have seizures despite a trial of two antiepileptic drugs and adequate doses should be referred for evaluation for epilepsy surgery. Surgical treatments (e.g., temporal lobectomy in mesial temporal sclerosis) may be indicated in refractory cases of focal seizures.

GENERAL Rx

- After a first unprovoked seizure with normal examination, imaging, and EEG, no treatment may be necessary, although patients may elect to undergo treatment.
- According to a recent joint American Academy of Neurology and American Epilepsy Society evidence-based guideline on the management of a first unprovoked seizure in adults, there is strong evidence that the risk of a second seizure is highest in the first 2 yr and ranges from 21% to 45%. This risk is higher for patients with prior brain insults such a traumatic brain injury or stroke or those with epileptiform abnormalities on EEG. Significant brain imaging abnormalities and nocturnal seizures also indicate a more elevated risk of recurrent seizures. Chronic treatment with antiepileptic drugs is indicated for more than

TABLE 1 Differential Diagnosis of Nonepileptic Events

General Medical Conditions
- Transient ischemic attack (TIA)
- Complicated migraine
- Syncope
- Hypoglycemia
- Parasomnia (e.g., rapid eye movement [REM], behavior disorder, or night terrors)
- Narcolepsy
- Myoclonus (from metabolic disturbance)

Psychiatric Causes
- Conversion disorder
- Somatic symptom disorder
- Dissociative disorder
- Panic disorder (simulating focal seizures)

Volitional Deception
- Factitious disorder (goal is to maintain the sick role)
- Malingering (goal is to obtain secondary gain, e.g., disability income)

From Stern TA et al: *Massachusetts General Hospital handbook of general hospital psychiatry,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 2 Clinical Characteristics That Help Distinguish Epileptic from Nonepileptic Events

	Epileptic Seizures	Nonepileptic Seizures/Events
Onset	Sudden onset and offset	Often gradual
Duration	Often <3 minutes	Variable
Perception	May experience olfactory, gustatory, visual hallucination; déjà vu; derealization	May experience auditory hallucinations; paranoia
Eyes during event	Open	Closed
Incontinence	Common	Rare
Awareness	Often impaired; can stay aware during some focal seizures	Variable; may be responsive during parts of the event
Recall of event	None or limited (e.g. aura)	Usually intact
Ictal EEG	Almost always abnormal	Unchanged from baseline
Interictal EEG	Normal or abnormal	Often normal
Tongue bite	Lateral tongue	None or tip of tongue
Injury	May be present	Rarely present (suggestive of serious psychopathology)
Incontinence	May be present	Rare
Postictal state	Confusion or drowsiness is common	Rare
Prolactin	Elevated; or normal	Normal; rarely elevated from baseline

From Stern TA et al: *Massachusetts General Hospital handbook of general hospital psychiatry,* ed 7, Philadelphia, 2018, Elsevier.

two unprovoked seizures or in patients with one seizure with abnormal workup. However, moderate evidence supports advising the patient that immediate antiepileptic therapy, compared with delaying treatment until a second unprovoked seizure, is likely to reduce the risk of a seizure recurrence in the next 2 yr. Furthermore, the risk of adverse events with antiepileptic drugs ranges from 7% to 31%, with most of these adverse events being mild and reversible. Thus, the practice guideline suggests that under certain circumstances, adults with one provoked seizure even without high-risk EEG or MRI findings can be treated with antiepileptic drugs because, at least over the next 2 yr, the risk of a recurrent seizure is reduced. Although there is no strong evidence that such treatment improves quality of life, even one seizure can have negative consequences on social and occupational functioning such as driving, making treatment an attractive option for many.

- Recurrent seizures and seizures with abnormal studies require treatment in the form of medicines, consideration of surgery, or with approved medical devices.

DISPOSITION

- Response to treatment often depends on the etiology of the focal seizures.
- Forty-seven percent of patients become seizure free with monotherapy and 67% with polytherapy.
- Patients who do not respond to two drugs should be referred to an epilepsy center for consideration of surgical treatment.
- No driving until seizure free in accordance with local laws and regulations.
- Patients should avoid situations that may cause injuries or accidents in the event of a seizure, such as climbing ladders, swimming unsupervised, or taking baths (rather than showers).
- Many antiepileptic drugs also affect vitamin D absorption or metabolism, prompting attention to patients' bone health.
- All patients with epilepsy are at higher risk for depression and should be screened.

REFERRAL

Patients with epilepsy and seizures should be referred for a consultation by a neurologist, preferably one with a special interest in epilepsy.

PEARLS & CONSIDERATIONS

COMMENTS

- Successful treatment depends on the correct choice of antiepileptic drugs based on patient's gender and comorbidities.
- Valproic acid should be avoided in girls and women with childbearing potential due to the risk of teratogenicity.
- All women of childbearing age taking antiepileptic drugs should take folic acid supplementation (1 to 4 mg/day) for the prevention of neural tube defects. Many antiepileptic drugs interact with oral contraception.

PREVENTION

- Sleep deprivation and alcohol consumption should be avoided.
- Drug compliance is compulsory to prevent seizure recurrence.

PATIENT & FAMILY EDUCATION

- Patient education and information can be obtained at the Epilepsy Foundation: www.epilepsyfoundation.org.
- Patients should be counseled on general seizure precautions such as swimming, bathing, and heights.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Focal Motor Seizures (Patient Information)

AUTHORS: **Patricio Sebastian Espinosa, MD, MPH,** and **Corey Goldsmith, MD**

SUGGESTED READINGS

Fisher RS et al: Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE commission for classification and terminology, *Epilepsia* 58(4):522-530, 2017.

Krumhold A et al: Evidence-based guideline: management of an unprovoked first seizure in adults. Report of the guideline development subcommittee of the American Academy of Neurology and the American Epilepsy Society, *Neurology* 84(16):1705-1713, 2015.

BASIC INFORMATION

DEFINITION

Folliculitis is inflammation of the hair follicle as a result of infection, physical injury, or chemical irritation.

SYNONYM

Sycosis barbae

ICD-10CM CODES

L72.9	Follicular cyst of skin and subcutaneous tissue, unspecified
L73.1	Pseudofolliculitis barbae
L73.8	Other specified follicular disorders
L66.2	Folliculitis decalvans
L66.4	Folliculitis ulerythematosa reticulata
L66.3	Perifolliculitis capitis abscedens

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Staphylococcal folliculitis is the most common form of infectious folliculitis; it occurs most commonly in persons with diabetes. Gram-negative folliculitis occurs in patients who have had moderately inflammatory acne for long periods and have been treated with long-term antibiotics such as tetracycline.
PREDOMINANT SEX: Sycosis barbae occurs most frequently in men who have commenced shaving.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The lesions generally consist of painful yellow pustules surrounded by erythema; a central hair is present in the pustules. Furuncles with pus may be present.
- Patients with sycosis barbae may initially present with small follicular papules or pustules that increase in size with continued shaving; deep follicular pustules may occur surrounded by erythema and swelling; the upper lip is frequently involved.
- "Hot tub" folliculitis occurs within 1 to 4 days after the use of a hot tub with poor chlorination. It is characterized by papules and pustules (Fig. E1) with surrounding erythema generally affecting the torso, buttocks, and limbs (Fig. E2).

ETIOLOGY

- Staphylococcus infection (e.g., sycosis barbae), *Pseudomonas aeruginosa* ("hot tub" folliculitis)
- Gram-negative folliculitis (*Klebsiella, Enterobacter, Proteus*) associated with antibiotic treatment of acne
- Chronic irritation of the hair follicle (use of cocoa butter or coconut oil, chronic irritation from workplace)
- Initial use of systemic corticosteroid therapy (steroid acne), eosinophilic folliculitis (AIDS patients), *Candida albicans* (immunocompromised patients)
- *Pityrosporum orbiculare*

FIG. E1 Papules and pustules in hot tub folliculitis. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pseudofolliculitis barbae (ingrown hairs)
- Acne vulgaris
- Dermatophyte fungal infections
- Keratosis pilaris
- Cutaneous candidiasis
- Superficial fungal infections
- Miliaris

WORKUP

- Physical examination and medical history (e.g., use of hot tub: "hot tub" folliculitis; adolescent patients who have started shaving: sycosis barbae; use of occlusive topical steroid therapy: *Staphylococcus* folliculitis).
- Gram-negative folliculitis in acne patients on prolonged antibiotic treatment manifests with superficial pustules 3 to 6 mm in diameter flaring out from anterior nares or fluctuant, deep-seated nodules.

LABORATORY TESTS

- Generally not necessary.
- Gram stain is useful to identify the infective organisms in infectious folliculitis and to differentiate infectious folliculitis from noninfectious.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Prevention of chemical or mechanical skin irritation
- Glycemic control in diabetics
- Proper chlorination of hot tubs and spas
- Shaving with a clean razor

ACUTE GENERAL Rx

- Cleansing of the area with chlorhexidine and application of saline compresses to involved area.
- Application of 2% mupirocin ointment or 1% retapamulin ointment for bacterial folliculitis affecting a limited area (e.g., sycosis barbae).
- Treatment of severe cases of *Pseudomonas* folliculitis with ciprofloxacin.
- Treatment of *S. aureus* folliculitis with dicloxacillin 250 mg qd for 10 days.
- Isotretinoin is the treatment of choice in gram-negative folliculitis. Amoxicillin or TMS-SMX can be used when isotretinoin is contraindicated or cannot be tolerated.

CHRONIC Rx

- Chronic nasal or perineal *S. aureus* carriers with frequent folliculitis can be treated with rifampin 300 mg bid for 5 days.
- Mupirocin or retapamulin ointment applied to nares bid is also effective for nasal carriers.

DISPOSITION

- Most cases of bacterial folliculitis resolve completely with proper treatment.
- Steroid folliculitis responds to discontinuation of steroids.

PEARLS & CONSIDERATIONS

COMMENTS

Patients should be instructed in good personal hygiene and avoidance of sharing razors, towels, and washcloths.

RELATED CONTENT

Folliculitis (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

FIG. E2 *Pseudomonas* hot foot syndrome. Tender papules and papulopustules on the plantar aspect of the foot. Culture of a swab from one of the pustules grew *P. aeruginosa.* (Courtesy John J. Van Aalst, M.D. From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Food allergies are divided into IgE-mediated and immunologically mediated non-IgE reactions. They include a spectrum of disorders that involve adverse immunologic responses to dietary antigens.

ICD-10CM CODES

T78.0	Adverse food reaction (including anaphylactic shock)
T78.1	Other adverse food reactions, not elsewhere classified
L27.2	Dermatitis due to ingested food
Z91.010	Allergy to peanuts
Z91.011	Allergy to milk products
Z91.012	Allergy to eggs
Z91.013	Allergy to seafood
Z91.018	Allergy to other foods
Z91.02	Food additives allergy status

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Food allergies have a cumulative incidence of 6% to 8% for the first 3 yr of life.

PREVALENCE:

- Overall prevalence is 1% to 2% in general population, ~3.9% to 8% in children.
- Patient self-reported food allergies have a prevalence of 12% to 13%, demonstrating the importance of objective measures in assessing food allergies.
- Nearly 40% of children with food allergy have a history of severe reactions that, if not treated immediately with proper medication, can lead to hospitalization or even death.[1]
- There is insufficient evidence to conclude a racial predilection (Greenhawt, 2013).

GENETICS: Children with parents or close relatives with allergies may have a tendency to become allergic to foods.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- IgE-mediated reactions: (within minutes to a few hours): Pruritus, urticaria or angioedema, atopic dermatitis, GI symptoms, conjunctival injection, sneezing, nasal congestion, rhinorrhea, bronchospasm, and anaphylaxis
- Non–IgE-mediated reactions: Food-induced enterocolitis, celiac disease, Crohn disease, dermatitis herpetiformis, and pulmonary reactions such as Heiner syndrome. These illnesses are discussed separately.
- Signs, symptoms, and presentation reflect specific allergic manifestation, but in food allergies there is a reproducible temporal relationship to ingested food allergens.

ETIOLOGY

Failure to establish tolerance to food antigens. IL-33 mediated epithelial permeability and Th2 skewing result in sensitization to food proteins which are presented to primed T cells. Food processing conditions that may affect allergenic activity are described in Table 1.

[1] Gupta RS et al: The prevalence, severity, and distribution of childhood food allergy in the United States, *Pediatrics* 128(l):e9-e17, 2011.

DIAGNOSIS

- Thorough history (to identify specific food[s], quantity consumed, timing, and nature of reaction) and physical exam should be performed.
- The temporal relationship and reproducibility of the symptoms are most important to establishing the diagnosis.
- A review of ingredient labels may be helpful.
- Confirmatory testing can include skin testing or in vitro testing.
- Skin prick testing (SPT): Positive predictive value <50%, but negative predictive value >95%. Thus a negative skin test effectively rules out an IgE-mediated process.
- In vitro testing: RAST testing: Historically it is less sensitive than skin testing, but sensitivity has improved with cut off points indicating a positive predictive value of 95% for allergies to eggs, milk, peanuts, wheat, and fish.
- Atopy patch test: Used in conjunction with RAST and skin testing in multiallergic children to plan widening the elimination diet. However, it is not recommended in the routine evaluation of food allergies.
- Double-blind, placebo-controlled food challenges are the gold standard test for determining food allergies. These need to be done in a supervised and controlled setting.
- In summary, if the history and lab tests are suggestive of a specific food allergy, that food should be confirmed by SPT, RAST, or food challenge and, once confirmed, eliminated from the diet.

DIFFERENTIAL DIAGNOSIS

- Gastrointestinal disorders
- Irritable bowel syndrome
- Carcinoid syndrome
- Giardiasis
- Structural abnormalities like hiatal hernia, pyloric stenosis, Hirschsprung disease, tracheoesophageal fistula
- Disaccharidase deficiencies: Lactase, sucrase-isomaltase complex, glucose-galactose complex
- Pancreatic insufficiency: Cystic fibrosis
- Gallbladder disease
- Peptic ulcer disease
- Malignancy
- Metabolic disorders
- Galactosemia
- Phenylketonuria
- Pharmacologic-related conditions
- Gustatory rhinitis
- Auriculotemporal syndrome (facial flush from tart food)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Elimination diet should be used in conjunction with nutritional counseling. Fig. 1 illustrates an algorithm for the management of food allergy
- Formula-fed infants: Brief trial of hydrolyzed milk formula as most children with milk allergy–induced skin symptoms will respond to the change of formula. Nonresponders may require amino acid–based formula.
- In older children: Elimination of one to two suspected foods is appropriate for 2 wk or longer and then reintroducing the foods to determine if symptoms recur.

ACUTE GENERAL Rx

- Antihistamines (both H1 and H2 antihistamines), albuterol if wheezing, epinephrine and glucocorticoids in patients with anaphylaxis.
- Patients with documented IgE-mediated reactions should receive and be counseled on the use of epinephrine autoinjector.

NEW TREATMENTS FOR FOOD ALLERGIES

- Oral and sublingual immunotherapy may play a role in management of food allergies, but this is currently under investigation.
- Recombinant vaccines and other immunomodulatory strategies are under development, although monoclonal anti-IgE antibody has shown benefit in adults with peanut allergy.

PEARLS & CONSIDERATIONS

- Eczema that develops in first 6 to 12 mo of life is usually the first manifestation of atopy.
- Egg allergy or sensitization is the strongest recognized predictor of respiratory allergies in children and asthma in adults.
- Consultation with trained dietitian is critical to avoid potentially adverse nutritional consequences in children with multiple food allergies.
- Skin testing is the preferred method for identifying food-specific IgE. RAST is useful if there is chance of severe food reaction causing risk to the patient.
- American Academy of Pediatrics no longer recommends avoiding the influenza and MMR vaccines in patients with severe systemic allergic reactions to egg.

COMMENTS

- Milk allergy usually resolves by age 5. Risk factors for persistence are early cutaneous manifestations following milk ingestion, development of other atopic conditions, and persistence of milk-specific high IgE titers. Soy milk is recommended for these children, keeping in mind that about 15% of these children can develop soy allergy.
- Egg allergy has been thought to resolve in 66% of children by 5 yr of age and in 75% of children by 7 yr of age. Trials have shown that oral immunotherapy can desensitize a high proportion of children with egg allergy and induce sustained unresponsiveness in a clinically significant subset.

TABLE 1 Food Processing Conditions That May Affect Allergenic Activity

Processing Stage	Nature of Processing	Impact of Processing on Allergens	Food-Level Evidence	Clinical Implications
Post-harvest treatments	Modified atmosphere for storage of fruit and vegetables	Expression of Bet v 1 homologs is upregulated during storage; levels are higher in fruit stored for 4-5 mo compared with fresh fruit. Expression of LTP allergens is downregulated during storage; levels are higher in fresh fruit and decrease during storage.	Apple	Individuals with birch pollen–related fruit allergies may tolerate freshly picked but not stored fruit. LTP-allergic individuals may experience reverse symptoms, although severity of LTP allergies may completely preclude consumption of problem fruit.
Primary processing	Removal of outer layers by physical or chemical peeling	Loss of allergens such as LTPs located in the outer layers.	Peach	Peeling fruits can make them safe for consumption by certain individuals with LTP allergies.
Secondary processing	Fruit purees and fresh juices	Labile Bet v 1 homologs are modified. Prolamin superfamily fruit LTPs retain a native-like structure.	Peach, apple	Individuals with Bet v 1–related fruit allergies usually can consume pureed fruit products. These foods can still trigger reactions in individuals with LTP fruit allergies.
	Preparation of pasteurized, UHT fruit juices and milk	Labile Bet v 1 homologs are modified. Prolamin superfamily fruit LTPs retain a native-like structure. Milk allergens retain much of their native structure.	Peach, apple, milk	Individuals with Bet v 1–related fruit allergies usually can consume UHT-processed fruit products. Processing is insufficient to make UHT juices safe for individuals with LTP fruit allergies. The allergenic potential of UHT milk resembles that of pasteurized and raw milk.
	Boiling	The prolamin superfamily LTPs and 2S albumin retain a native-like structure after boiling, although when seeds are boiled, much of the protein is lost into cooking water. Boiling alters the structure of milk, egg, and fish allergens. Boiling alters the structure of cupin allergens (7S and 11S seed storage proteins) and can render them insoluble.	Maize, wheat, peanut, lentil, fish, milk, egg	Boiling seeds (e.g., peanuts) and milk reduces their allergenicity but does not abolish it. For some foods (e.g., polenta), the extent of cooking affects the residual level of allergenic activity.
	Roasting and frying	Thermostable allergens, notably the prolamin superfamily 2S albumin allergens, retain their native structure and solubility after roasting and frying. Some cupin allergens (7S and 11S seed storage proteins) are altered by roasting and become insoluble. Maillard modification of allergens may take place under these processing conditions.	Peanut	The major peanut 2S albumin allergens retain their allergenic activity, explaining why roasted peanuts possess significant allergenic activity. Allergenic activity of the 7S and 11S globulins is retained to some extent after roasting. Maillard modifications may further contribute to the allergenic activity of roasted peanuts.
	Preparation of powdered ingredients, such as celery spice, skimmed milk, and pasteurized egg white powder	Major allergens retain their three-dimensional structure and activity in dry-processed goods. Maillard modifications take place under these processing conditions when residual sugars are present (e.g., lactose in skimmed milk powder).	Celery spice, milk	Powdered food ingredients have allergenic activity similar to unprocessed foods and can promote trigger reactions when included in recipes or through cross-contact in other foods (e.g., residual milk powder in foods otherwise free from milk).
	Deamidation	Acidic conditions are used to treat food ingredients (notably gluten) to improve their food functional properties through deamidation.	Gluten	Induces formation of novel IgE epitopes through glutamine deamidation, which results in individuals reacting to foods prepared with deamidated gluten ingredients who can otherwise safely consume wheat flour–containing foods.

Continued

TABLE 1 Food Processing Conditions That May Affect Allergenic Activity

Processing Stage	Nature of Processing	Impact of Processing on Allergens	Food-Level Evidence	Clinical Implications
	Hydrolyzed food ingredients	Enzymatic (usually microbial proteases) and chemical treatments are used to hydrolyze protein ingredients to change their functional properties. Ingredients may originate from soy, milk (e.g., caseinates, whey protein), gluten, and other sources.	Milk, egg, gluten	Hydrolysis reduces IgE reactivity but does not abolish it completely, which may in part result from the presence of residual intact protein. Evidence is largely limited to in vitro IgE binding studies and animal models with little direct in vivo evidence for allergic humans.
	Oil refining	Proteins are removed during the refining process, and residual protein levels in highly refined oils are very low.	Soybean, peanut	In the EU, highly refined soybean oils are considered safe for consumption by individuals with soy allergies. Highly refined peanut oils do not appear to cause adverse reactions in peanut-allergic individuals, but these oils do not have an EU labeling derogation.
Complex foods	Fining agents added to alcoholic beverages	Certain beverages contain residual levels of fining agents based on isinglass, fish gelatin, milk casein, egg albumin, or lysozyme. Fining agents and their residues in beverages usually are highly modified compared with the raw, unprocessed foods.	Beer, wine, and spirits	Individuals with allergies to fish triggered by collagen or egg can react to alcoholic beverages when they are used as fining agents, although this depends on the nature of the individual's allergy and whether fining agents are used in conjunction with other agents, such as bentonite. Reactions to fining agents are rare, and many individuals with egg, milk, or fish allergy can safely consume these beverages.
	Fermented foods	Lactic acid fermentations can cause proteins to unfold and precipitate or form gelled networks due to the reduced pH. Fermentative organisms secrete proteases that can hydrolyze proteins.	Milk, soybean	Although fermented milk and yogurt may retain some allergenic activity, other highly modified foods, such as soy sauce, may have substantially reduced allergenic activity and may not present a hazard to certain allergic patients.
	Baked foods	Food ingredients may be included that are raw or have already been processed (e.g., skimmed milk powder, pasteurized egg white). Complex interactions between different food ingredients coupled with further cooking modify allergens and result in their becoming part of the insoluble food matrix, but data are limited because of the poor solubility of allergens in physiologic buffers.	Milk	Evidence from oral food challenge studies indicates that baking reduces the allergenic activity of milk, and foods with baked milk may be given to children whose infantile cow's milk allergy is beginning to resolve.

EU, European Union; *LTP*, lipid transfer protein; *UHT*, ultrahigh temperature.
From Adkinson NF et al: *Middleton's allergy principles and practice*, ed 8, Philadelphia, 2014, Saunders.

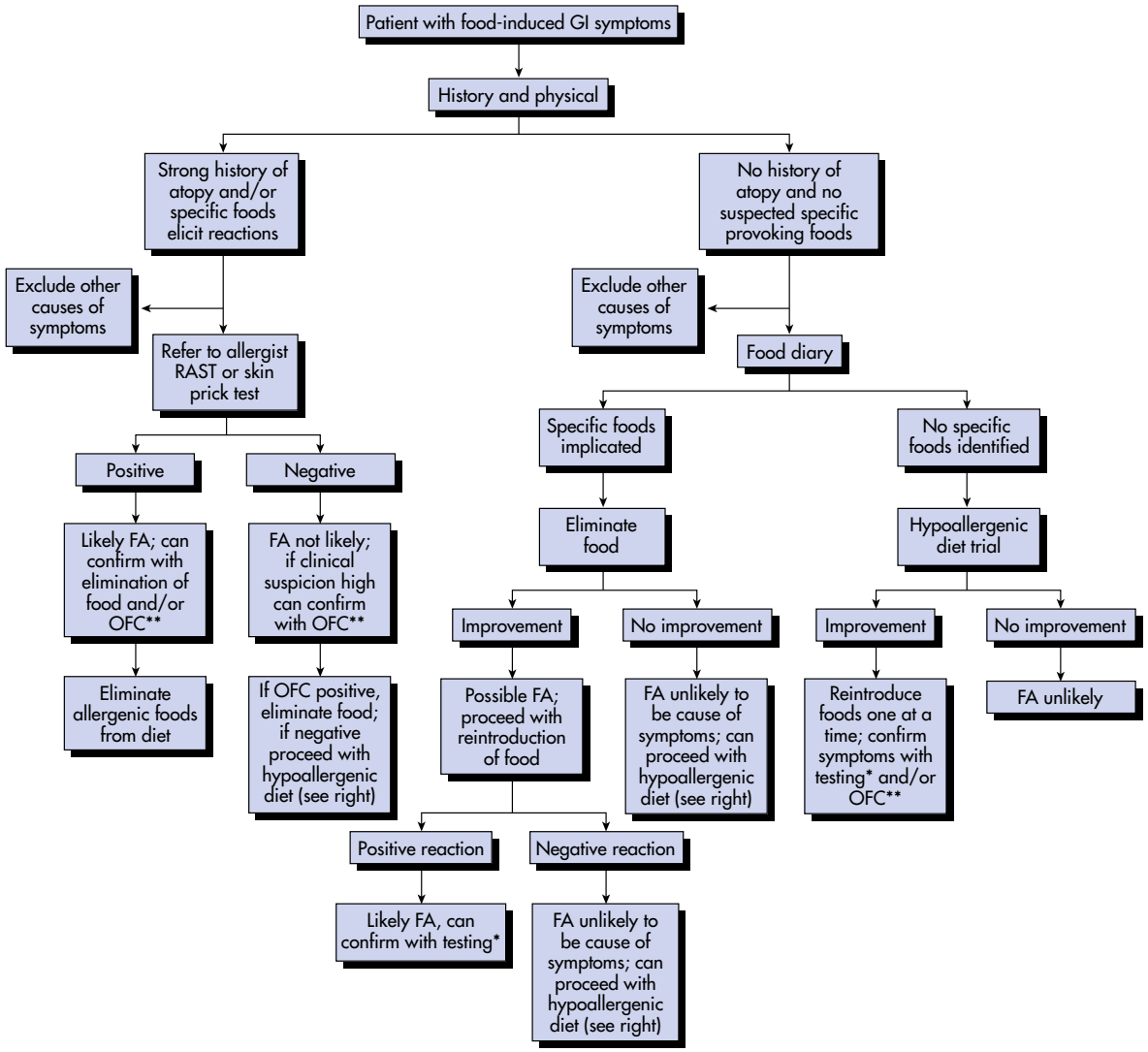

FIG. 1 Algorithm for the management of food allergy *Testing indicates skin-prick testing, radioallergosorbent tests *(RAST),* IgG_4 assay, and/or patch testing. Note that clinical symptoms must be associated with the food(s) that test positive before the food(s) should be eliminated from the diet. **Oral food challenge *(OFC)* involves reintroducing the food and observing for signs/symptoms of food allergy *(FA).* Treatment of food allergy involves elimination of the causative food(s) from the diet.

- Wheat allergy found to resolve by 5 yr of age and soybean allergy by 2 yr of age.

PREVENTION

- There is conflicting evidence regarding the protective effect of breastfeeding on food allergies.
- There is no evidence to suggest that exclusive breastfeeding for 6 mo or more is superior to exclusive breastfeeding for 4 to 6 mo in terms of developing food allergies.
- In high-risk infants who are not exclusively breastfed, there is limited evidence to suggest that feeding with hydrolyzed formula compared to cow's milk formula reduces allergies.
- Currently, there is no evidence to support the use of prebiotics and/or probiotics for the prevention of allergic diseases.
- No current evidence exists to support delaying the introduction of solid foods beyond 4 to 6 mo.
- The early introduction of peanuts significantly decreases the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts.[2] Early peanut introduction (ages 4 to 11 months) lowers the risk of developing peanut allergy by 80% compared with peanut introduction after age 5 yr.
- In recent phase 3 trials of oral immunotherapy in children and adolescents who were highly allergic to peanut, treatment with AR101 resulted in higher doses of peanut protein that could be ingested without dose-limiting symptoms.

PATIENT & FAMILY EDUCATION

Information can be found on American Academy of Allergy, Asthma and Immunology (www.aaaai.org), the Food Allergy and Anaphylaxis Network (www.foodallergy.org), and the Anaphylaxis Campaign (www.anaphylaxis.org.uk).

REFERRAL

Patients may be referred to an allergy/immunology specialist when the diagnosis is uncertain or if avoidance measures are not successful.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Food Allergies (Patient Information)

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[2] Gupta RS et al: The prevalence, severity, and distribution of childhood food allergy in the United States, *Pediatrics* 128(l):e9-e17, 2011.

SUGGESTED READINGS

Boyce JA et al: Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-Sponsored Expert Panel, *J Allergy Clin Immunol* 126(Suppl):S1-S58, 2010.

Burks AW et al: Oral immunotherapy for treatment of egg allergy in children, *N Engl J Med* 367:233-243, 2012.

DuToit G et al: Randomized trial of peanut consumption in infants at risk for peanut allergy, *N Engl J Med* 372(9):803-813, 2015.

Greenhawt ME: Racial and ethnic disparity in food allergy in the United States: a systematic review, *J Aller Clin Immunol* 1(4):378–386, 2013.

Gupta RS et al: Childhood food allergies: current diagnosis, treatment, and management strategies, *Mayo Clin Proc* 88(5):512-526, 2013.

Jones SM, Burks AW: Food allergy, *N Engl J Med* 377:1168-1176, 2017.

NIAID-Sponsored Expert Panel: Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-Sponsored Expert Panel, *J Allergy Clin Immunol* 126(6):S1-S68, 2010.

The PALISADE group of clinical investigators: AR101 oral immunotherapy for peanut allergy, *N Engl J Med* 379:1991-2001, 2018.

BASIC INFORMATION

DEFINITION

Food poisoning is an illness caused by ingestion of food contaminated by bacteria and/or bacterial toxins. A foodborne disease outbreak is defined as two or more cases of a similar illness resulting from ingestion of a common food.

SYNONYMS

Enterotoxin-poisoning
Epidemic vomiting disease

ICD-10CM CODE
A05.9 Bacterial foodborne intoxication, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- CDC estimates that each yr one in six Americans will experience a foodborne illness.
- Approximately 800 foodborne disease outbreaks are reported in the U.S. each yr, accounting for approximately 15,000 illnesses, 800 hospitalizations, and 20 deaths. Outbreak-associated foodborne illnesses are only a small subset of the estimated 9.4 million foodborne illnesses that occur annually in the U.S.[1]
- Majority of identifiable causes are bacterial, although more than 250 known diseases can be transmitted through food.

PEAK INCIDENCE: Varies with specific organism

- Summer: *Staphylococcus aureus, Salmonella, Shigella* spp.
- Summer and fall: *Clostridium botulinum, Vibrio parahaemolyticus*
- Spring and fall: *Campylobacter jejuni*
- Winter: *Clostridium perfringens, Yersinia enterocolitica*

PREDOMINANT AGE: Varies with specific agent
NEONATAL INFECTION: Rare but severe with *Shigella* and *Salmonella* spp.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Any combination of GI symptoms and fever. Orthostatic pulse and blood pressure changes should be noted
- Specific organisms suspected on the basis of the incubation period and predominant symptoms (Table 2), although a great deal of overlap exists
  1. Short incubation period (1 to 6 hr): Involve the ingestion of preformed toxin; noninvasive.
     a. *S. aureus:* Nausea, profuse vomiting, and abdominal cramps common; diarrhea possible, but fever uncommon; usually resolves within 24 hr; foods implicated in outbreaks include meats, mayonnaise, and cream pastries.
     b. *B. cereus:* Two forms, a short incubation (emetic) form (characterized by vomiting and abdominal cramps in virtually all patients, diarrhea in one third of patients, fever uncommon) and a long incubation (diarrheal) form; illness usually mild, resolves within 12 hr; unrefrigerated rice most often implicated as vehicle. Other sources include gravy, meats, stews, vanilla, and sauces.
  2. Moderate incubation period (8 to 16 hr): Involves the in vivo production of toxin; noninvasive.
     a. *C. perfringens:* Severe crampy abdominal pain and watery diarrhea common; fever and vomiting unlikely; symptoms usually resolving within 24 hr; outbreaks invariably related to cooked meat or poultry that is allowed to cool without refrigeration; most cases in the fall and winter months. *C. perfringens* is the third most common cause of foodborne illness in the United States.
     b. *B. cereus:* Diarrheal (or long incubation) form most commonly beginning with diarrhea, abdominal cramps, and occasionally vomiting; fever uncommon; usually resolves within 24 hr; the responsible food is usually fried rice.
  3. Long incubation period (>16 hr): Some toxin-mediated, some invasive.
- Toxin-producing organisms include:
  1. *C. botulinum:* Should be considered when a diarrheal illness coincides with or precedes paralysis; severity of illness related to the quantity of toxin ingested; characteristic cranial nerve palsies progressing to a descending paralysis; fever usually absent; usually associated with home-canned foods.
  2. Enterotoxigenic *E. coli* (ETEC): Most common cause of travelers' diarrhea; after 1- to 2-day incubation period, abdominal cramps and copious diarrhea occur; vomiting and fever uncommon; usually resolves after 3 to 4 days; vehicle usually unbottled water or contaminated salad or ice.
  3. Enterohemorrhagic *E. coli* (EHEC): Can cause severe abdominal cramps and watery diarrhea, which may eventually become bloody; bacteria (strain O157:H7) are noninvasive; no fever; illness may be complicated by hemolytic-uremic syndrome; associated with contaminated beef (especially hamburger), unpasteurized milk or juice. Table 3 summarizes the various strains of diarrheagenic *E. coli.*
  4. *V. cholerae:* Varies from a mild, self-limited illness to life-threatening cholera; diarrhea, nausea, and vomiting, abdominal cramps, and muscle cramps; no fever; severe cases may progress to shock and death within hours of onset; survivors usually have resolution of symptoms in 1 wk; U.S. cases are either imported or result from ingestion of imported food.
- Invasive organisms include:
  1. *Salmonella:* Associated most often with nontyphoidal strains; incubation period generally 12 to 48 hr; nausea, vomiting, diarrhea, and abdominal cramps typical; fever possible; outbreaks of gastroenteritis related to contaminated poultry, meat, and dairy products.
  2. *Shigella:* Asymptomatic infection possible, but some with fever and watery diarrhea that may progress to bloody diarrhea and dysentery; with mild illness, usually self-limited, resolves in a few days; with severe illness, may develop complications; transmission usually from person to person but can occur via contaminated food or water.
  3. *C. jejuni:* The most common foodborne bacterial pathogen; incubation period is about 1 day, then a prodrome of fever, headache, and myalgias; intestinal phase marked by diarrhea associated with fever, malaise, and abdominal pain; diarrhea mild to profuse and bloody; usually resolves in about 7 days, but relapse is possible; associated with undercooked meats and poultry, unpasteurized dairy products, and drinking from freshwater streams.
  4. *Y. enterocolitica* and *Y. pseudotuberculosis:* Infrequent causes of enteritis

[1] Dewey-Mattia D et al: Surveillance for foodborne disease outbreaks–United States 2009-2015, *MMWR Surveill Summ* 67(10):1-11, 2018.

TABLE 1 Pathogenic Mechanisms in Bacterial Foodborne Disease

Preformed Toxin	Toxin Production in Vivo	Tissue Invasion	Toxin Production and/or Tissue Invasion
Staphylococcus aureus	*Clostridium perfringens*	*Campylobacter jejuni*	*Vibrio parahaemolyticus*
Bacillus cereus (short incubation)	*B. cereus* (long incubation)	*Salmonella*	*Yersinia enterocolitica*
Clostridium botulinum	*C. botulinum* (infant botulism)	*Shigella*	
	Enterotoxigenic *Escherichia coli*	Invasive *E. coli*	
	Vibrio cholerae 01 or 0139		
	V. cholerae non-01		
	Shiga toxin–producing *E. coli*		

From Mandell GL et al: *Principles and practice of infectious diseases,* ed 6, Philadelphia, 2005, Churchill Livingstone.

TABLE 2 Foodborne Disease Agents and Clinical Presentation

Usual Incubation Periods	Causative Agent	Clinical Illness			Epidemiologic and Laboratory Diagnosis
		Fever	Diarrhea	Vomiting	
5 min-6 h (usually <3 h)	Chemical or toxin	Rare	Occasional	Common	Demonstration of toxin or chemical from food or epidemiologic incrimination of food
1-6 h (usually <1 h)	*Staphylococcus aureus* enterotoxin	Rare	Occasional	Profuse	Isolation of organisms in food (>10^5/g)/vomitus/stool; detection of enterotoxin in food
	Bacillus cereus emetic toxin	Rare	Occasional	Profuse	Isolation of organisms in food (>10^5/g)/vomitus/stool
6-24 h	*Clostridium perfringens* enterotoxin	Rare	Typical	Occasional	Isolation of organisms or toxin from food (10^5/g) or stools of ill persons, epidemiologic incrimination of food; detection of enterotoxin in food
	B. cereus enterotoxin	Rare	Typical	Occasional	
12-72 h	*Clostridium botulinum*	Clinical sydrome compatible with botulism	Constipation more common		Isolation of organism or toxin from food (10^5/g) or stools; demonstration of toxin in serum or food
16-96 h	*Shigella*	Common	Typical, often bloody	Occasional	Isolation of organism from clinical specimens from two or more ill persons; isolation of organism from epidemiologically implicated food
	Nontyphoidal *Salmonella*	Common	Typical	Occasional	
	Enteroinvasive *E. coli* (EIEC)	Common	Typical, may be bloody	Occasional	
	Enteropathogenic *E. coli* (EPEC)	Occasional	Typical	Occasional	
	Enterotoxigenic *E. coli* (ETEC)	Rare	Typical	Rare	
	Vibrio parahaemolyticus; V. cholerae enterotoxin	Occasional	Typical	Occasional	
1-3 days	Caliciviruses (noroviruses) Rotavirus	Occasional	Typical	Common	Antigen detection (enzyme immunoassay) in stool; immune electron microscopy of stool; detection of viral RNA in stool or vomitus by PCR
1-10 days	*Yersinia*	Uncommon	Typical, severe abdominal pain	Uncommon	Isolation of organisms from food or clinical specimens of ill persons
2-10 days	*Campylobacter jejuni*	Common	Typical, often bloody	Uncommon	Isolation of organisms from food or clinical specimens of ill persons
1-11 days	*Cryptosporidium*	Occasional	Common	Occasional	Demonstration of oocysts in stool or in small bowel biopsy of ill persons; demonstration of organism in epidemiologically implicated food
	Cyclospora	Occasional	Common	Occasional	Demonstration of parasite in stool or in small bowel biopsy of ill persons; demonstration of organism in epidemiologically implicated food
	Giardia intestinalis	Occasional	Common	Occasional	Demonstration of parasite in stool or in small bowel biopsy of ill persons; demonstration of organism in epidemiologically implicated food
2 days-wks	*Bacillus anthracis*	Common	Typical	Frequent	Isolation of organism from blood or contaminated meat
1-7 days	*E. coli* O157:H7 and other Shiga toxin–producing *E.coli*	Uncommon	Typical	Frequent	Isolation of organism from food or stool or identification of toxin in stools of ill persons
3-60 days, usually 7-14	*Salmonella typhi*	Common	Diarrhea or constipation	Uncommon	Isolation of organisms from food or clinical specimens of ill persons
7-21 days	*Brucella* spp.	Common	Common	Rare	Isolation of organisms from blood or bone marrow culture of ill persons; fourfold increase in standard agglutination titer overall several wks or single titer 1:160 in person with compatible clinical syndrome
1-4 wk	*Giardia lamblia*	Rare	Common	Rare	Stool for ova and parasite examination enzyme immunoassay
2 days-8 wk	*Trichinella spiralis*	Common	Common	Common	Serology, muscle biopsy

PCR, Polymerase chain reaction; *RNA*, ribonucleic acid.
From Cherry JD et al: Feigin and Cherry's *Pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

in the United States; children affected more often than adults; fever, diarrhea, and abdominal pain lasting 1 to 3 wk; some with mesenteric adenitis that mimics acute appendicitis; contaminated food or water is usually responsible.

5. *V. parahaemolyticus:* In the United States, most outbreaks in coastal states or on cruise ships during the summer months; incubation period usually >1 day, followed by explosive watery diarrhea in the majority of cases; nausea, vomiting, abdominal cramps, and headache also common; fever less common; usually resolves by 1 wk; related to ingestion of seafood.
6. Enteroinvasive *E. coli* (EIEC): A rare cause of disease in the United States; high incidence of fever and bloody diarrhea; may resemble bacillary dysentery.

TABLE 3 Diarrheagenic *Escherichia coli*

Strains	Pathogenic Mechanisms	Persons Affected	Clinical Features
DAEC	Diffuse adherence to Hep-2 cells	Children in developing countries	Watery diarrhea (acute) and persistent diarrhea
EAEC	Aggregative adherence to Hep-2 cells	Children in developing countries	Watery diarrhea (acute) and persistent diarrhea
STEC O157:H7 Non-O157:H7 O104:H4*	Shiga toxins 1 and 2	Children and adults Persons who ingest contaminated food, especially hamburger (outbreaks)	Watery diarrhea Bloody diarrhea (classic)
EIEC	Epithelial cell invasion	Children and adults	Watery diarrhea Dysentery
EPEC Typical Atypical	Attaching and effacing Bundle-forming pilus, attachment and effacement lesions or atypical adherence pattern	Children	Watery diarrhea (acute) Persistent diarrhea
ETEC	Heat-labile and/or heat-stable toxin Adherence	Children in developing countries; travelers	Watery diarrhea

DAEC, Diffusely adhering *Escherichia coli*; *EAEC,* enteroaggregative *E. coli*; *EIEC,* enteroinvasive *E. coli*; *EPEC,* enteropathogenic *E. coli*; *ETEC,* enterotoxigenic *E. coli*; *STEC,* Shiga toxin–producing *E. coli.*
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

7. *V. vulnificus:* May cause serious, often fatal illness in persons with chronic liver disease; GI symptoms usually absent, but fever, chills, hypotension, and hemorrhagic skin lesions possible; patients with liver disease or at increased risk of developing liver disease should avoid eating raw oysters.

ETIOLOGY

- Table 1 describes pathogenic mechanisms in bacterial foodborne disease.
- Classically categorized as either inflammatory (invasive) or noninflammatory:
  1. *Noninflammatory: B. cereus, S. aureus, C. botulinum, C. perfringens, V. cholerae, enterotoxigenic E. coli (ETEC), and enterohemorrhagic E. coli (EHEC); toxin-producing organisms that are noninvasive; fecal leukocytes are not seen.*
  2. Inflammatory: *Campylobacter,* enteroinvasive *E. coli* (EIEC), *Salmonella, Shigella, V. parahaemolyticus,* and *Yersinia;* cause disease by invasion of intestinal tissue; fecal leukocytes are seen.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Gastroenteritis caused by viruses (Norwalk, Noro, or rotavirus), parasites *(Amoeba histolytica, Giardia lamblia),* or toxins (ciguatoxins, mushrooms, heavy metals).

LABORATORY TESTS

- Watchful waiting is often the most appropriate option and ancillary testing is usually not necessary.
- In severe or persistent cases stool test for fecal leukocytes may help narrow the differential diagnosis:
  1. Send stool for culture and for ova and parasites.
  2. Send stool for *C. difficile* toxin in patients with current or recent antibiotic use.
  3. Note: Some pathogens are not identified on routine stool culture; laboratory should be advised if *Yersinia, C. botulinum, Vibrio,* or enterohemorrhagic *E. coli* (O157:H7) are suspected.
  4. Finding *B. cereus, C. perfringens,* or *E. coli* in stool is of little value, because these may be part of the normal bowel flora.
  5. Stool cultures are positive in less than 40% of cases.
  6. Newer techniques such as polymerase chain reaction (PCR) testing provide a more rapid and reliable determination of specific pathogens.
- If botulism suspected, send food, serum, and stool for toxin assay.
- Blood cultures should be considered for all febrile patients.
- Consider toxic megacolon (identified on plain abdominal sonography).
- Consider sigmoidoscopy to obtain tissue and histology in hospitalized patients with bloody diarrhea.
- Consider lactoferrin measurement if an inflammatory etiology is suspected.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Adequate rehydration is the mainstay of therapy.

ACUTE GENERAL Rx

- Most cases of acute infectious diarrhea are viral and antibiotics are not indicated.
- Gastroenteritis caused by the following bacterial organisms requires no antimicrobial treatment: *B. cereus, S. aureus, C. perfringens, V. parahaemolyticus, Yersinia,* and enterohemorrhagic and enteroinvasive *E. coli.*
- The usual cause of travelers' diarrhea is enterotoxigenic *E. coli.* Although usually a self-limited illness, antibiotics can shorten the course in patients with fever or dysentery.
  1. Azithromycin 1000 mg in a single oral dose or
  2. SMX/TMP one DS tab bid for 3 days or
  3. Ciprofloxacin 500 mg PO bid for 3 days
- The mainstay of therapy for cholera is fluid replacement. Antibiotics should be given to decrease shedding and duration of illness.
  1. Doxycycline 300 mg in a single dose or 100 mg PO bid for 3 days
  2. SMX/TMP one DS tab bid for 3 days
- Treatment is not indicated for *Salmonella* gastroenteritis. Patients who are at high risk of developing bacteremia may be treated for 48 to 72 hr (see "Salmonellosis").
- Although shigellosis tends to be a self-limited illness, antibiotics shorten the course of illness and may limit transmission of the illness (see "Shigellosis").
- Those with moderate or severe *Campylobacter* diarrhea may benefit from treatment.
  1. Azithromycin 500 mg qd for 3 days or
  2. Erythromycin 500 mg PO qid for 5 days or
  3. Ciprofloxacin 500 mg PO bid for 5 days
- *V. vulnificus* sepsis should be treated with:
  1. Doxycycline 100 mg IV bid for 2 wk
  2. Ceftazidime 2 g IV q8h for 2 wk
- For suspected botulism, antitoxin should be administered early (see "Botulism").
- Table 4 summarizes antibiotic therapy for nonsevere infections with common bacterial enteropathogens in immunocompetent adults.

CHRONIC Rx

Patients with *Salmonella* infections may become carriers and may require treatment (see "Salmonellosis").

DISPOSITION

- Most infections are self-limited and do not require therapy.
- In immunocompromised host or patient with underlying disease, serious complications are possible.
- Postinfectious syndromes are important with some infections:
  1. Reiter syndrome: *Salmonella, Shigella, Campylobacter, Yersinia* spp.; more common in genetically susceptible host (HLA-B27+)
  2. Guillain-Barré syndrome: *Campylobacter* spp

TABLE 4 Antibiotic Therapy for Nonsevere Infections with Common Bacterial Enteropathogens in Immunocompetent Adults

Organism	Recommended Antibiotic(s)	Alternative Antibiotic(s)
***Shigella* Species**		
Shigella infection (non-*dysenteriae*; for *Shigella dysenteriae* type 1, see text)	Ciprofloxacin 500 mg twice daily (or levofloxacin 500 mg daily) × 3 days	Azithromycin 500 mg-1 g daily × 3-5 days TMP/SMX 160 mg/800 mg twice daily, if sensitive, × 3 days
***Salmonella* Species**		
Enterocolitis, uncomplicated	Not usually recommended (see text)	Can consider in areas of high fluoroquinolone quinolone resistance; Azithromycin 1 g daily × 5 days
Typhoid and enteric fevers*	Ciprofloxacin 500 mg twice daily (or ofloxacin 400 mg twice daily) × 7-14 days Ceftriaxone 2-3 g IV daily × 7-14 days	
***Campylobacter* Species**		
Campylobacter jejuni	Not usually required Ciprofloxacin 500 mg twice daily × 3 days	Azithromycin 500 mg-1 g × 3-5 days
Yersinia enterocolitica		
Enterocolitis, uncomplicated	Not usually required	An aminoglycoside (parenteral)Tetracycline 500 mg 4 times daily × 5 days TMP/SMX 160 mg/800 mg twice daily × 5 days Ciprofloxacin 500 mg twice daily × 5 days Doxycycline 100 mg twice daily × 5 days
Escherichia coli†		
Enterotoxigenic	Endemic disease; usually self-limited, supportive care (see text). Travelers' diarrhea: ciprofloxacin 500 mg twice daily × 3 days Rifaximin 200 mg 3 times daily × 3 days	Azithromycin 500 mg-1 g daily × 3-5 days TMP/SMX 160 mg/800 mg twice daily, if sensitive, × 3 days
Shiga toxin–producing	Unclear if antibiotics are effective; may be harmful	
***Vibrio* Species**		
Vibrio cholera	Doxycycline 300 mg × 1 dose	Ciprofloxacin 1 g × 1 dose Azithromycin 1 g × 1 dose Tetracycline 500 mg every 6 hours × 3 days
Vibrio parahaemolyticus	Usually not required; no controlled trials	As for *V. cholerae*

TMP/SMX, Trimethoprim/sulfamethoxazole.

NOTE: All antibiotics are administered orally unless otherwise indicated. Recommendations are given for treatment of mild/moderate infections only. Treatments for complicated infections or severely ill, bacteremic, or immunocompromised patients are not listed above and may differ from treatments for mild disease.

*For severe typhoid fever, consider the addition of glucocorticoids (dexamethasone 3 mg/kg × 1, then 1 mg/kg every 6 hours × 48 hours) to parenteral antimicrobial therapy. Antimicrobial sensitivity testing is required. Fluoroquinolones (e.g., ciprofloxacin) should not be used as empiric therapy in Asia or other areas with high fluoroquinolone resistance.

†Enteropathogenic, enteroaggregative, and diffusely enteroadherent *E. coli* are omitted from this table because these types are defined in research laboratories and are not diagnosed in routine clinical practice. Enteroinvasive *E. coli* presenting as inflammatory diarrhea should be treated empirically as for *Shigella* spp.

From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

REFERRAL

If more than a mild illness

PEARLS & CONSIDERATIONS

COMMENTS

- Grossly underreported and undiagnosed
- All cases to be reported to the local health department
- Table 5 summarizes control and prevention measures of foodborne diseases

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Bacterial Food Poisoning (Patient Information)
Salmonellosis (Related Key Topic)
Botulism (Related Key Topic)
Shigellosis (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

TABLE 5 Control and Prevention of Foodborne Diseases

General Recommendations for All Persons

- Thoroughly cook raw food from animal sources, such as beef, pork, poultry, fish, and eggs, to temperatures that eliminate most pathogens.*
- Wash raw fruits and vegetables before eating.
- Keep uncooked meats separate from fruits, vegetables, cooked foods, and ready-to-eat foods.
- Do not thaw meat, poultry, or fish on the counter (instead, thaw in a refrigerator, in cold water, or in a microwave oven).
- Wash hands before, during, and after preparing food and before eating food.
- Wash knives, other utensils, and cutting boards after handling uncooked foods.
- Keep refrigerators set to below 40° F and freezers set to 0° F or lower and verify with a thermometer.
- Refrigerate perishable foods within 2 hr (or within 1 hr if left out at temperatures >90°F).
- Read and follow all cooking and storage instructions on food product packaging. This is especially important for foods prepared in microwave ovens because these ovens heat foods unevenly. Even foods that may appear ready to eat may require thorough cooking.
- Persons with diarrhea or vomiting possibly caused by an infectious agent should not prepare foods for others.
- Keep all animals, including reptiles and amphibians, away from surfaces where foods or drinks are prepared.
- Do not drink unpasteurized (raw) milk or eat foods made from unpasteurized milk. (Exception: Hard cheeses made from raw milk that have been aged >60 days are generally safe to eat.)
- Do not eat home-canned foods that were not known to be adequately heat processed during canning.

Recommendations for Persons at High Risk, Such as Pregnant Women and People With Weakened Immune Systems, in Addition to the Recommendations Listed Above

Measures to Prevent a Variety of Bacterial Infections

- Do not eat uncooked sprouts.
- Do not drink prepackaged juice or juice-containing beverages that have not been processed to reduce or eliminate microbial contamination (e.g., by pasteurization).

Listeriosis Prevention Measures

- Do not eat soft cheeses, such as feta, Brie, and Camembert; blue-veined cheeses; and Mexican-style cheeses, such as queso blanco, queso fresco, and panela, unless the package has a label that clearly states that the cheese is made from pasteurized milk.
- Do not eat refrigerated pâtés or meat spreads. Canned or shelf-stable pâtés and meat spreads are safe to eat.
- Do not eat refrigerated smoked seafood unless it is contained in a cooked dish, such as a casserole. Refrigerated smoked seafood, such as salmon, trout, whitefish, cod, tuna, and mackerel, is most often labeled as "nova-style," "lox," "kippered," "smoked," or "jerky." The fish is found in the refrigerator section or sold at delicatessen counters of grocery stores and delicatessens. Canned or shelf-stable smoked seafood is safe to eat.
- Do not eat hot dogs, luncheon meats, or delicatessen meats unless they are reheated until steaming hot.
- Avoid getting fluid from hot dog packages on other foods, utensils, and food preparation surfaces, and wash hands after handling hot dogs, luncheon meats, and delicatessen meats.

Salmonellosis Prevention Measures

- Choose pasteurized eggs.

Vibriosis, Toxoplasmosis, and Norovirus Prevention Measures

- Do not eat raw or lightly steamed oysters, clams, or other raw shellfish (especially important for patients with liver disease).

More food safety information can be found at www.foodsafety.gov/keep/index.html.

*Poultry: 165°F (73.9°C); ground meats: 160°F (71.1°C); intact cuts of beef, pork, ham, veal, and lamb: 145°F (62.8°C) and allow to rest for at least 3 minutes before eating; fish and shellfish: 145°F (62.8°C); egg dishes: 160°F (71.1°C).

From Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.

SUGGESTED READINGS

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DuPont HL: Acute infectious diarrhea in immunocompetent adults, *N Engl J Med* 370:1532-1540, 2014.

Kalyoussef S, Feja KN: Foodborne illnesses, *Adv Pediatr* 61:287-312, 2014.

Switaj TL, Winter KJ, Christensen SR: Diagnosis and management of foodborne illness, *Am Fam Physician* 92:358-365, 2015.

BASIC INFORMATION

DEFINITION

Friedreich ataxia is the most common hereditary neurodegenerative ataxic disorder. It results in degeneration of the dorsal root ganglia, posterior columns, spinocerebellar and corticospinal tracts, and large sensory peripheral neurons.

ICD-10CM CODE
G11.1 Early-onset cerebellar ataxia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Estimated at 1 in 30,000 Caucasians
PEAK INCIDENCE: 8 to 15 yr
PREVALENCE (IN U.S.): 2 to 4 per 100,000. Carrier rate 1:120 to 1:160; lower prevalence in people of Asian or African descent
PREDOMINANT SEX: Males and females affected equally
GENETICS: Autosomal recessive; 96% of affected patients are homozygous and 4% are compound heterozygous (two different mutations). Trinucleotide repeat expansion accounts for 94% to 98% of cases, whereas point mutations account for 2% to 6% of cases.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Onset of progressive appendicular and gait ataxia, with absent muscle stretch reflexes in the lower extremities
- With disease progression (within 5 yr): Dysarthria, distal loss of position and vibration sense, pyramidal leg weakness, areflexia in all four limbs, and extensor plantar responses
- Common findings: Progressive scoliosis, distal atrophy, pes cavus, and cardiomyopathy (symmetric concentric hypertrophic form in most cases)
- Insulin-requiring diabetes mellitus may occur in 10% of patients with glucose intolerance occurring in an additional 10% to 20%

ETIOLOGY

- Genetic: Frataxin gene is localized to the centromeric region of chromosome 9q13.
- Normal sequence has 6 to 27 repeats; abnormal sequence has 120 to 1700 GAA repeats.
- Frataxin deficiency leads to impaired mitochondrial iron homeostasis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Charcot-Marie-Tooth disease type 2
- Abetalipoproteinemia
- Severe vitamin E deficiency with malabsorption
- Early-onset cerebellar ataxia with retained reflexes
- Autosomal-dominant cerebellar ataxia (spinocerebellar ataxia)

WORKUP

- Specific gene testing for the expanded GAA trinucleotide repeat (only required test). Other tests, listed below, support the diagnosis but are not specific like genetic testing.
- Diagnostic criteria include electrophysiologic evidence for a generalized axonal sensory or sensorimotor neuropathy.
- ECG may show widespread T-wave inversion and evidence of left ventricular hypertrophy. ECG abnormalities are present in 65% of patients.
- Sural nerve biopsy shows loss of large myelinated fibers.

LABORATORY TESTS

- Genetic testing
- Electromyography or nerve conduction study
- ECG and echocardiogram
- Peripheral blood smear for acanthocytes
- Lipid profile
- 2-hour glucose tolerance test
- Vitamin E levels (if necessary)

IMAGING STUDIES

MRI of the spinal cord may demonstrate spinal cord atrophy with essentially normal cerebrum, brainstem, and cerebellum (Fig. E1).

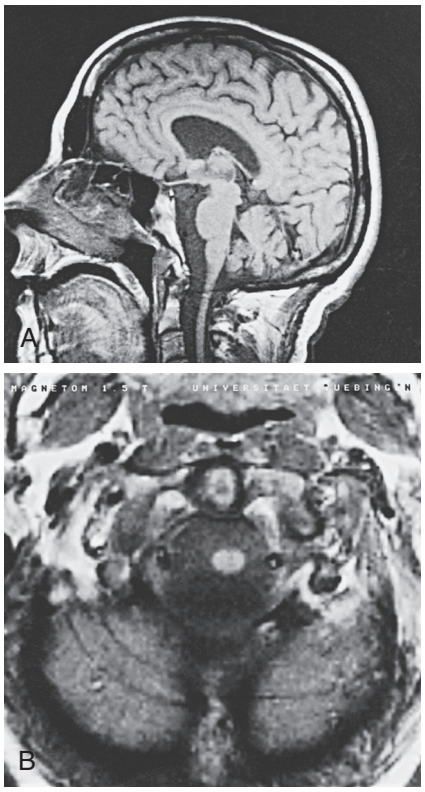

FIG. E1 T1 magnetic resonance image of the brain (midsagittal section) and spinal cord (axial slice at level of the dens) showing severe shrinkage of the cervical cord, but the cerebellum and brain stem are of normal size. (From Goetz CG: *Textbook of clinical neurology,* Philadelphia, 1999, Saunders.)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Surgical correction of scoliosis and foot deformities in selected patients
- Prosthetic devices as required (e.g., ankle-foot orthosis for footdrop)
- Physical therapy
- Communication devices for patients with severe dysarthria

ACUTE GENERAL Rx

None established.

- An antioxidant, idebenone (short-chain analogue of coenzyme Q10), administered orally at 5 to 20 mg/kg/day with or without vitamin E has demonstrated inconsistent effects on neurologic, cardiac, and psychosocial outcome measures in clinical trials.
- Further research with various antioxidants and iron chelators is ongoing. An open-label pilot study of antioxidants (coenzyme Q10, 400 mg/day, and vitamin E, 2100 U/day) in a small cohort demonstrated slowing in progression of generalized ataxia and kinetic dysfunction and significant improvement in cardiac function with unaltered deterioration in posture, gait, and hand dexterity.

CHRONIC Rx

Chronic management of congestive heart failure is required. Cardiac arrhythmias will warrant pacemaker implantation.

DISPOSITION

- Loss of ambulation typically occurs within 15 yr of symptom onset, and 95% are wheelchair bound by age 45 yr.
- Life expectancy is reduced, particularly if heart disease is present.

REFERRAL

- Neurologist for evaluation and diagnosis
- Genetic counseling (recommended if available)
- Cardiologist to manage cardiomyopathy and electrophysiologic abnormalities

PEARLS & CONSIDERATIONS

Friedreich ataxia should be considered in all preadolescent and adolescent children presenting with progressive ataxia. Early recognition of cardiac failure and arrhythmias and institution of appropriate therapy helps prolong survival.

RELATED CONTENT

Friedreich Ataxia (Patient Information)

AUTHORS: **Joseph S. Kass, MD, JD, FAAN,** and **Fariha Jamal, MD**

BASIC INFORMATION

DEFINITION

Frontotemporal dementia (FTD) is an umbrella term that encompasses three distinct syndromes: behavioral variant FTD (bvFTD), semantic dementia (SD), and progressive nonfluent aphasia (PNFA). All three syndromes are marked by frontal and/or temporal lobe atrophy; however, they manifest with different clinical presentations. The most common subtype is bvFTD, which is marked by changes in behavior and personality with disinhibition and the breaking of social norms. SD is characterized by a loss of word comprehension and meaning, and PNFA presents with agrammatic, nonfluent speech.

SYNONYMS

- FTD
- FTLD
- Frontotemporal lobar degeneration (FTLD) is the term used for the neuropathologic findings seen in the different FTD syndromes.
- Pick disease: This term was historically used to refer to FTD. However, it is now strictly a neuropathologic diagnosis for patients found to have Pick bodies at autopsy, as very few diagnoses of FTD are associated with these neuropathologic findings.

ICD-10CM CODES

G31.0 Frontotemporal dementia
G31.01 Pick disease
G31.09 Other frontotemporal dementia

EPIDEMIOLOGY & DEMOGRAPHICS

The current data on epidemiology of FTD are variable due to misdiagnosis and underreporting. The following data are estimations obtained through systematic reviews.

INCIDENCE: The estimated annual incidence is 2.7 to 4.1 per 100,000 persons.

PREVALENCE: The estimated point prevalence is 15 to 22 per 100,000 persons.

PREDOMINANT SEX AND AGE: There is a nearly equal distribution by sex, and the average age of presentation is 58 yr.

GENETICS: Approximately 40% of FTD cases have a positive family history, and several genes (Table 1) have been associated with the development of familial FTD. The most common are mutations in *C9ORF72, MAPT,* and *GRN* (Table 2).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The early stage of bvFTD is characterized by changes in behavior and personality. Patients display a lack of insight into these changes, and family members may initially think they are suffering a midlife crisis or a new-onset psychiatric disorder. Therefore, careful history-taking is required.
- Behavioral changes include disinhibition, impulsivity, distractibility, violation of social norms (such as offensive, insensitive, or inappropriate sexual remarks; inappropriate behaviors; inappropriately explicit or personal conversations; or encroachment on the personal space of others), as well as increased irritability and impulsive criminal behavior (such as shoplifting or violating traffic laws).
- Patients also display decreased ability to empathize with others, insensitivity to the needs and emotions of their loved ones, and distance/detachment in their personal relationships.
- Apathy and inertia are also common symptoms, with possible development of immobility as the disorder progresses.
- Other associated symptoms that may develop are changes in language and speech (verbal aspontaneity, stereotyped phrases, mutism in late stages), repetitive motor movements, or hyperphagia.
- Physical exam findings for bvFTD can include upper and/or lower motor neuron signs, dysarthria, dysphagia, and pseudobulbar affect. Some patients meet criteria for both FTD and amyotrophic lateral sclerosis.
- Although behavioral changes can also occur in the other FTD syndromes SD and PNFA, these two primarily have language deficits that precede the behavioral changes.
  1. SD is characterized by a gradual loss of the knowledge of words, objects, and concepts, with preservation of speech fluency and syntax.
  2. PNFA is characterized by effortful, nonfluent speech, word-finding difficulties, and agrammatism, with preservation of single-word comprehension.

DIAGNOSIS

Diagnosis of bvFTD is primarily clinical, with neuroimaging and pathology/genetics required for further confirmation. In 2011, the International Behavioral Variant FTD Consortium (FTDC) developed revised criteria for the diagnosis of bvFTD (Table 3).

- In summary, six core symptoms that can be seen in bvFTD were identified. The presence of any three is sufficient to diagnose *possible* bvFTD.
- Diagnosis of *probable* bvFTD requires meeting the following three conditions: (1) patient has diagnosed possible bvFTD, (2) significant functional decline, and (3) frontal and/or anterior temporal atrophy/hypoperfusion seen on imaging.
- Diagnosis of *definitive* bvFTD can be made only when the patient has possible or probable bvFTD, plus either (1) pathologic evidence of FTLD on biopsy or postmortem, or (2) presence of a known causal genetic mutation.

DIFFERENTIAL DIAGNOSIS

- Other neurodegenerative disorders, including Alzheimer disease (AD), idiopathic Parkinson disease, dementia with Lewy bodies, corticobasal syndrome, progressive supranuclear palsy, and chronic traumatic encephalopathy

TABLE 1 Clinical, Genetic, and Pathologic Correlations in Frontotemporal Lobar Degeneration

Clinical Presentation	% of FTLD	Associated Genes		Comorbidities				Neuropathologic Subtypes			
				Parkinsonism	MND	IBM PDB	FTLD-tau	FTLD-TDP	FTLD-FUS	FTLD-UPS	FTLD-ni
bvFTD	57%			+	+	+/–	++	++	+	+/–	+/–
		C9orf72	++	+	++			Type B > A		+/–	
		GRN	+	+				Type A			
		MAPT	+	+			+				
		VCP	+/–		+/–	+		Type D			
		CHMP2B	+/–	+/–	+/–					+	
nfvPPA	24%			+	+/–		++	+			
		C9orf72	+								
		GRN	++	+				Type A			
		MAPT	+	+			+				
svPPA	19%			+/–	+/–		+/–	++ (Type C)			
		Rarely genetic									

Number of plus signs (+) signifies relative frequency of the observation; +/– indicates rare observation.
bv, Behavioral variant; *FTLD,* frontotemporal lobar degeneration; *FUS,* fused in sarcoma; *IBM,* inclusion body myopathy; *MND,* motor neuron disease; *nfv,* agrammatic or nonfluent variant; *ni,* no inclusions; *PDB,* Paget disease of the bone; *PPA,* primary progressive aphasia; *sv,* semantic variant; *TDP,* TAR DNA-binding protein; *UPS,* ubiquitin-proteasome system.
From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

TABLE 2 Gene Mutations Associated with Frontotemporal Dementia

Gene	Chromosome	Protein	Protein Function	Mode of Inheritance	Mutation Frequency in Familial FTD	Mutation Frequency in Sporadic FTD	Age of Onset (Mean, Range)
C9ORF72	9p21.2	Unknown	Unknown	AD	21%	6%	50s (mid 20-80s)
MAPT	17q21.31	Microtubule-associated tau protein	Microtubule stabilization and assembly	AD	6.3%	1.5%	Mid-50s (20-80s)
GRN	17q21.31	Progranulin	Activates signaling cascades for development, inflammation, and wound repair	AD	5%-15%	5%	60s (mid 30-80s)

AD, Autosomal dominant; *FTD,* frontotemporal dementia.
From Deleon J, Miller BL: Frontotemporal dementia. In Daniel CK, Geschwind H, Paulson HL (eds), *Handbook of clinical neurology,* ed 148, Philadelphia, 2018, Elsevier, pp 409-430.

TABLE 3 International Consensus Criteria for Behavioral Variant FTD

Must be present for any FTD clinical syndrome:
- Shows progressive deterioration of behavior and/or cognition by observation or history

Possible bvFTD
- Three of the features (A-F) must be present; symptoms should occur repeatedly, not just as a single instance:
  - A. Early (3 yr) behavioral disinhibition
  - B. Early (3 yr) apathy or inertia
  - C. Early (3 yr) loss of sympathy or empathy
  - D. Early (3 yr) perseverative, stereotyped, or compulsive/ritualistic behavior
  - E. Hyperorality and dietary changes
  - F. Neuropsychological profile: executive function deficits with relative sparing of memory and visuospatial functions

Probable bvFTD
- All the following criteria must be present to meet diagnosis:
  - A. Meets criteria for possible bvFTD
  - B. Significant functional decline
  - C. Imaging results consistent with bvFTD (frontal and/or anterior temporal atrophy on CT or MRI or frontal hypoperfusion or hypometabolism on SPECT or PET)

Definite bvFTD
- Criteria A and either B or C must be present to meet diagnosis:
  - A. Meets criteria for possible or probable bvFTD
  - B. Histopathological evidence of FTLD on biopsy at post mortem
  - C. Presence of a known pathogenic mutation

Exclusion criteria for bvFTD
- Criteria A and B must both be answered negatively; criterion C can be positive for possible bvFTD but must be negative for probable bvFTD:
  - A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders
  - B. Behavioral disturbance is better accounted for by a psychiatric diagnosis
  - C. Biomarkers strongly indicative of Alzheimer disease or other neurodegenerative process

Additional features
- Presence of motor neuron findings suggestive of motor neuron disease
- Motor symptoms and signs similar to corticobasal degeneration and progressive supranuclear palsy
- Impaired word and object knowledge
- Motor speech deficits
- Substantial grammatical deficits

bvFTD, Behavioral variant frontotemporal dementia; *FTD,* frontotemporal dementia; *FTLD,* frontotemporal lobar degeneration; *SPECT,* single-photon emission computed tomography.
From Rascovsky K et al: Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia TT, *Brain* 2011;134:1-22.

- Psychiatric disorders (bipolar disorder, schizophrenia, obsessive-compulsive disorder, depression, personality disorders)
- Metabolic disturbances or nutritional deficiencies (hypothyroidism, B_{12} deficiency)
- Substance abuse/toxicities (ethanol, drugs of abuse, heavy metal poisoning)
- Infections (meningitis, HIV-associated dementia, neurosyphilis)
- Cerebrovascular disease (stroke, vascular dementia, lacunar infarctions)
- CNS tumors

WORKUP

- Careful history-taking with specific attention paid to initial symptoms, time course, progression of symptoms, family history, psychiatric history, and other medical history
- Comprehensive neurologic physical exam to help rule out other CNS etiologies
- Use of the International Behavioral Variant FTD Criteria for diagnosis (Table 3).
- Genetic testing for causal mutations of FTD *(C9ORF72, MAPT,* and *GRN).*
- Medication review (especially drugs that may alter mental status, such as anticholinergics, opiates, benzodiazepines, barbiturates, and neuroleptics)
- Neuropsychological tests of executive function, memory, and social cognition to rule out other neurodegenerative disorders
- Psychiatric evaluation to rule out psychiatric disorders

LABORATORY TESTS

- CBC, serum electrolytes, glucose, BUN/creatinine, liver function tests
- Cerebrospinal fluid (CSF) analysis for infection and measurement of CSF tau and amyloid (which can help differentiate between FTD and AD)
- Vitamin B_{12}, thyroid function tests, HIV, and syphilis screening
- Urine toxicity screen
- In vivo histopathology:
  1. Almost all cases of FTLD have one of the following protein inclusions found on pathologic examination: TAR DNA-binding protein with molecular weight 43 kDa (TDP-43), microtubule-associated protein tau (MAPT), or fused-in-sarcoma protein (FUS). If feasible and as medical technology advances, in vivo histopathologic testing can confirm the diagnosis.

IMAGING STUDIES

- In general, structural MRI and CT will show gray matter atrophy in the frontal and/or temporal lobes, anterior cingulate cortex, and insula with variation in distribution between the different FTD subtypes.
  1. Patients with bvFTD specifically will usually show atrophy in the orbitofrontal, anterior cingulate, anterior insular, and anterior temporal cortices.
  2. SD is associated with atrophy in the temporal poles, and PNFA with atrophy in the left perisylvian region.
- A normal MRI scan does not exclude FTD, however, because changes may not be seen in early stages of the disorder. In these cases, PET or SPECT can be used to visualize areas of hypoperfusion/hypometabolism.

Rx TREATMENT

- No disease-modifying drugs currently exist for the treatment of FTD. With advances in the understanding of FTD pathophysiology and genetics, however, new therapies such as antisense oligonucleotides and tau-specific antibodies are being investigated for their efficacy in treating or altering the progression of the syndrome and may see eventual clinical application.
- Current management of FTD is aimed at management of behavioral symptoms through both pharmacologic and nonpharmacologic means.

NONPHARMACOLOGIC THERAPY

- Due to the impulsivity and the risk for injury seen in bvFTD, discussions with family members about driving, the patient's access to finances, and safety of the physical environment should be conducted early in management.
- For patients with motor symptoms, regular exercise and physical therapy are helpful.
- Speech therapy is helpful for patients with language deficits.
- Diet counseling can aid in prevention of weight gain in patients with hyperphagia.

ACUTE GENERAL Rx

None

CHRONIC Rx

- There are conflicting reports of the efficacy of several medications in the symptomatic treatment of FTD. These include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors, and antipsychotics.
- SSRIs have the most consensus on their benefit in the management of FTD. They have been shown to help decrease the severity of disinhibition, impulsivity, eating disorders, and repetitive behaviors.
- The use of antipsychotics is controversial, but they are sometimes given to control symptoms of aggression, agitation, and psychosis. However, patients with FTD are also at an increased risk for extrapyramidal side effects due to poorly functioning dopaminergic pathways, and thus are usually used only when SSRIs are not successful.

DISPOSITION

- Patients with FTD benefit from having the social support and specialized care offered in dementia-focused care homes and skilled nursing facilities.
- The range and severity of behaviors seen in FTD can put great burden on family and friends. Education, counseling, and connection with social support or referral to a dementia-focused care home can help reduce caregiver stress.

REFERRAL

Patients who have severe or complex presentations should be referred to a neurologist with expertise in dementia or neurodegenerative disorders.

PEARLS & CONSIDERATIONS

FTD is a complex neurologic disorder with a wide variety of presenting symptoms. The most common syndrome seen is bvFTD; therefore, patients with gradual-onset changes in personality, disinhibition, and increased impulsivity should be investigated for FTD. Therapy is aimed at management of the behavioral symptoms, most commonly through the use of SSRIs. Social support and dementia-specific care facilities are helpful for both patients and family members.

PATIENT & FAMILY EDUCATION

The Association for Frontotemporal Degeneration (http://www.theaftd.org; 866-507-7222)

RELATED CONTENT

Alzheimer Disease (Related Key Topic)
Parkinson Disease (Related Key Topic)
Dementia with Lewy Bodies (Related Key Topic)

AUTHORS: **Marco Pares, BS, MD Candidate,** and **Joseph S. Kass, MD, JD, FAAN**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Frostbite represents tissue injury (or death) from freezing and vasoconstriction induced by severe environmental cold exposure.

SYNONYM

Cold-induced tissue injury

ICD-10CM CODES

T35.0	Superficial frostbite involving multiple body regions
T34	Frostbite with tissue necrosis
T345	Frostbite with tissue necrosis of wrist and hand
T34.8	Frostbite with tissue necrosis of ankle and foot
T34.9	Frostbite with tissue necrosis of other and unspecified sites
T35.4	Superficial frostbite involving multiple body regions
T33.9	Superficial frostbite of unspecified sites, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

- Environmental factors include windchill factor, temperature, duration of exposure, altitude, and degree of wetness. Hands and feet account for >90% of injuries; nose, cheeks, ears, and male genitalia are also more susceptible.
- Host factors include psychiatric illness and neuroleptic and sedative drugs (especially alcohol, which, in addition to impairing judgment, inhibits shivering and causes cutaneous vasodilation). Other risk factors include immobility, previous frostbite, malnutrition, tobacco use, peripheral neuropathy, peripheral vascular disease, diabetes, exhaustion, and constricting clothing and footwear.
- Patients at the extremes of age are at greatest risk, but frostbite is more common in adults between 30 and 49 yrs of age with a strong male predominance (10:1)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Frostbite may be classified into four degrees of injury severity or, more practically, into *superficial* (corresponding to first and second degree) and *deep* (corresponding to third and fourth degree) groups. In both cases, the degree of frostbite can only be accurately determined after rewarming as initially most frostbite injuries appear similar.
- *Superficial* frostbite involves the skin and subcutaneous tissue. The frozen part is waxy, white (or mottled), and firm but soft and resilient below the surface when gently depressed. After rewarming, there is an initial hyperemia that may be followed by swelling and formation of superficial blisters with clear or milky fluid within 6 to 24 hr. There is no ultimate tissue loss.
- *Deep* frostbite extends into the dermis and may involve muscles, nerves, tendons, or bones. The skin may be hard or wooden, without tissue resilience. Nonblanching cyanosis, hemorrhagic blisters, tissue necrosis (Fig. E1), and gangrene may develop. Affected tissue has a poor prognosis and debridement or amputation is generally required.
- Patients initially feel numbness, prickling, and itching. More severe injury can produce paresthesias and stiffness, with burning or throbbing pain upon thawing.

PATHOPHYSIOLOGY

Two phases of tissue injury:

1. The actual freezing of the tissues, during which cellular damage is caused by the formation of extracellular ice crystals, which cause osmotic shifts, cellular dehydration, cell membrane lysis, and cell death.
2. The reperfusion injury, during which the thawing of damaged endothelial cells releases a cascade of inflammatory mediators (e.g., prostaglandin F, thromboxane A2, bradykinins, histamine), resulting in capillary compression, vascular stasis, progressive ischemic injury, and thrombus formation. These conditions ultimately lead to the destruction of the microcirculation and to cell death.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Frostnip: A superficial nonfreezing cold injury associated with intense vasoconstriction and characterized by frost forming on the surface of the skin. Transient numbness, tingling, and pallor resolve quickly with warming
- Pernio (chilblains): Self-limited, cold-induced vasculitis associated with purple plaques or nodules, often affecting dorsum of hands and feet; seen with prolonged cold exposure to above-freezing temperatures
- Cold immersion (trench foot): Caused by ischemic injury resulting from sustained, severe vasoconstriction in appendages exposed to wet cold at temperatures above freezing

WORKUP

- Laboratory workup is not indicated unless the patient has systemic hypothermia.
- Early presentation (<24 hr from thawing): If there is deep frostbite with potential significant morbidity, perfusion evaluation with angiography (or Tc-99m or MRA) should be done emergently in anticipation of potential thrombolysis treatment.
- Late presentation (>24 hr from thawing): Noninvasive imaging with MRA or multiphase bone scintigraphy (ideally with SPECT/CT) can be used to predict the likely levels of tissue viability for future reconstruction after amputation.

TREATMENT (3 PHASES)

1. FIELD MANAGEMENT

- Prioritize treatment of hypothermia (core body temperature <35° C; 95° F) with systemic and adjunctive rewarming measures if available (e.g., warmed, humidified oxygen, heated IV saline [45° C; 113° F], and warming blankets) before thawing frostbitten extremities.
  1. Shelter patient out of wind and give warm fluids.
- Remove constricting or wet clothing and jewelry from affected digits.
  1. Place cold extremity in a companion's axilla or groin for 10 min, then replace dry gloves/boots.
- Insulate, splint, and elevate affected areas if practical to do so.
  1. Never rub or massage the affected area. Avoid dry heat (e.g., fires and heaters).
- Avoid thawing if there is any risk of refreezing and if possible avoid ambulation on thawed lower extremities (unless only distal toes affected).
- Box 1 describes the Alaska State Guidelines for prehospital treatment of frostbite.

2. REWARMING

- Rapid rewarming (with warm water) limits the freezing injury and yields better outcomes than slow rewarming (e.g., moving to a warmer location).
- Rapid rewarming is achieved by immersing the affected area in a circulating warm water bath with or without a mild antibacterial agent (e.g., chlorhexidine or povidone-iodine) maintained at 37° to 39° C for at least 15 to 30 min up to 1 hour, until all tissues are thoroughly rewarmed and pliable with a red-purple color. Active motion during rewarming is advisable; massage is not.
- Administer analgesics during rewarming (ibuprofen and possibly narcotics).

3. POST-THAW TREATMENT

- Tetanus prophylaxis and topical antibiotics if potentially contaminated skin wound.
- Consider systemic antibiotics for patients with significant trauma or signs of infection.
- Debride broken clear vesicles and avoid disrupting intact blisters (especially hemorrhagic ones) unless they interfere with mobility.
- Topical aloe vera (a potent anti-prostaglandin agent) q6h and ibuprofen (a thromboxane inhibitor) 400 to 600 mg bid to tid (or daily aspirin) can be given until wounds are healed or surgery occurs.
- Thrombolytic therapy: May consider if <24 hr from thawing in a patient with severe frostbite and poor prognostic indicators (e.g., cool skin after rewarming, numb, dusky or blue digits, hemorrhagic blisters). First, evaluate perfusion with angiography (or possibly MRA)

BOX 1 Alaska State Guidelines for Prehospital Treatment of Frostbite

First Responder/Emergency Medical Technician—I, II, III/Paramedic/Small Bush Clinic
Evaluation and Treatment

A. Anticipate, assess, and treat the patient for hypothermia, if present.
B. Assess the frostbitten area carefully because the loss of sensation may cause the patient to be unaware of soft tissue injuries in that area.
C. Obtain a complete set of vital signs and the patient's temperature.
D. Remove jewelry and clothing, if present, from the affected area.
E. Obtain a patient history, including the date of the patient's last tetanus immunization.
F. If there is frostbite distal to a fracture, attempt to align the limb unless there is resistance. Splint the fracture in a manner that does not compromise distal circulation.
G. Determine whether rewarming the frostbitten tissue can be accomplished in a medical facility. If it can, transport the patient while protecting the tissue from further injury from cold or impacts.
H. If the decision is made to rewarm frostbitten tissue in the field, you should prepare a warm water bath in a container large enough to accommodate the frostbitten tissues without them touching the sides or bottom of the container. The temperature of the water bath should be 99° to 102° F (37° to 39° C).
   1. Generally, patients with frostbite do not require opiates for pain relief; they occasionally need non-opiate pain medication or anxiolytics. If possible, consult a physician regarding the administration of oral analgesics, such as acetaminophen, ibuprofen or aspirin. Aspirin or ibuprofen may help improve outcomes by blocking the arachidonic acid pathway.
   2. Immersion injury or frostbite with other associated injuries may produce significant edema and high pain levels. These patients may need opiate pain medications for initial treatment. In this case, advanced life support personnel should administer morphine or other analgesics in accordance with physician-signed standing orders or online medical control.
I. A source of additional warm water must be available.
J. Water should be maintained at approximately at 99° to 102° F (37° to 39° C) and gently circulated around the frostbitten tissue until the distal tip of the frostbitten part becomes flushed.
K. Pain after rewarming usually indicates that viable tissue has been successfully rewarmed.
L. After rewarming, let the frostbitten tissues dry in the warm air. Do **not** towel dry.
M. After thawing, tissues that were deeply frostbitten may develop blisters or appear cyanotic. Blisters should not be broken and must be protected from injury.
N. Pad between affected digits and bandage affected tissues loosely with a soft, sterile dressing. Avoid putting undue pressure on the affected parts.
O. Rewarmed extremities should be kept at a level above the heart, if possible.
P. Protect the rewarmed area from refreezing and other trauma during transport. A frame around the frostbitten area should be constructed to prevent blankets from pressing directly on the injured area.
Q. Do not allow an individual who has frostbitten feet to walk except when the life of the patient or rescuer is in danger. Once frostbitten feet are rewarmed, the patient becomes nonambulatory.

to assess for arterial compromise. Next, administer intraarterial (or intravenous) tPA if perfusion defects are demonstrated and there is no contraindication to thrombolysis. Tissue salvage rate appears to correlate with elapsed time to treatment from time of rewarming and best outcomes seen within the first 12 hours. Although the use of early thrombolytic therapy appears to limit reperfusion injury and reduce subsequent digit amputation significantly, high-quality studies are lacking, and this treatment is not yet U.S. FDA-approved.

- Some protocols include heparin or prostacyclin in addition to tPA to prevent recurrent thrombosis.
- Vasodilator therapy: Various vasodilators (NTG, pentoxifylline, phenoxybenzamine, nifedipine, reserpine, and buflomedil) have been tried, with the best evidence favoring prostacyclin (or iloprost, an injectable available in Europe that has vasodilatory, fibrinolytic-enhancing, and antiplatelet activity). If iloprost is available, at least one study has shown superior efficacy to tPA, and it is easier to administer, has a better safety profile, has fewer contraindications, and can be managed on a general ward.
- Daily dressing changes with dry, sterile, noncompressive, and nonadherent dressings. Splint and elevate hands and feet to reduce edema and separate digits with cotton gauze. Avoid any abrasion to limit risk of infection.
- Whirlpool hydrotherapy: 1 to 2 times per day for 30 min with warm water (37° to 39° C), with or without an antiseptic solution if severe edema is present, until there is a clear demarcation of necrotic tissues or evidence of tissue healing.
- Gentle, progressive physical therapy after edema resolves.
- Keep site warm, and avoid all vasoconstrictors, including nicotine.
- Adjunctive treatments including dextran, warfarin, sympathectomy, and hyperbaric oxygen are of potential but unproven benefit.

DISPOSITION

A majority of patients have long-term residual symptoms, including cold hypersensitivity, neuropathic pain, sensory deficits, hyperhidrosis, secondary Raynaud disease, localized osteoporosis, edema, hair or nail deformities, and (rarely) arthritis. Treatment with tricyclics, gabapentin, calcium channel blockers, and careful protection from further cold exposure may be helpful.

REFERRAL

- Hospitalize for hypothermia or deep frostbite; a burn unit is best.
- Surgical decisions regarding amputation should be deferred until demarcation of viable tissue is clear. Traditionally, this can take 6 to 12 wk by clinical examination. Triple phase Tc-99m bone scan with SPECT/CT in the days after injury can be used to predict level of amputation accurately. Early surgical intervention is indicated if refractory pain, sepsis, or gangrene occurs.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Frostbite (Patient Information)

AUTHOR: **Michael P. Johnson, MD**

SUGGESTED READINGS

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FIG. E1 Third- and fourth-degree frostbite with tissue death. Note demarcation beyond the interphalangeal joint. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, WB Saunders.)

Functional Gallbladder Disorder

BASIC INFORMATION

DEFINITION

Biliary pain caused by gallbladder dysmotility in the absence of gallstones, sludge, or microlithiasis. It is a diagnosis of exclusion with no evidence of structural disease seen with normal hepatobiliary and pancreatic laboratory and diagnostic imaging modalities.

SYNONYMS

Biliary dyskinesia
Gallbladder dyskinesia
Gallbladder spasm
Acalculous biliary disease
Chronic acalculous cholecystitis
Chronic acalculous
Gallbladder dysfunction
Cystic duct syndrome

ICD-10CM CODE
K82.9 Disease of gallbladder, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Biliary dyspepsia has an incidence rate of 1% to 6%.
PREVALENCE: Ten percent to 45% of total population report dyspepsia.
PREDOMINANT SEX AND AGE: There is a 3:1 female-to-male predominance.
RISK FACTORS: There is no consistent relationship to meals or fatty meal intake.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

These patients present with typical biliary pain that fulfills the Rome III criteria:

- Patients present with sporadic epigastric or right upper quadrant pain lasting for 30 min but less than 6 hours.
- Episodes are recurrent and occur in sporadic intervals (but not daily).
- The pain is not relieved by bowel movements.
- The pain is not relieved by postural movements.
- The pain is not relieved by antacids.
- The pain builds up to a steady level.
- The pain is severe enough it impedes daily activities and may even require an emergency department visit.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary gallbladder disorders: Gallstones, cholecystitis
- Pancreatobiliary disorders: Cholelithiasis, choledocholithiasis, pancreatitis, pancreatic neoplasm
- Gastrointestinal disorders: Gastroesophageal reflux disorder, peptic ulcer disease, inflammatory bowel disease, irritable bowel syndrome, gastric or esophageal neoplasm
- Metabolic disorders: Obesity, diabetes mellitus
- Cholecystokinin deficiency: Celiac disease

WORKUP

This is a diagnosis of exclusion in a patient with biliary pain. Patients will have normal blood test results and hepatobiliary and pancreatic enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, amylase, and lipase. Imaging, including abdominal ultrasound, is essentially normal without evidence of gallstone or gallbladder sludge pathology.

LABORATORY TESTS

Laboratory tests, including serum AST, ALT, ALP, bilirubin, gamma-glutamyl transferase, amylase, and lipase, are within normal limits.

IMAGING STUDIES

- To exclude gallstone pathology, a transabdominal ultrasound is initial choice for imaging. Transabdominal ultrasound is capable of detecting gallstones up to 3 to 5 mm in size. Patients should fast for at least 8 hours before ultrasound to optimize visualization of the gallbladder.
- If gallstones or gallbladder are not found on ultrasound but still suspected, endoscopic ultrasound (EUS) may be used to detect microlithiasis or gallstones smaller than 3 mm.
- Assessing gallbladder emptying through cholecystokinin (CCK)–stimulated cholescintigraphy is essential in the diagnosis. CCK-stimulated cholescintigraphy allows for the calculation of gallbladder ejection fraction (GBEF). Normal GBEF is >38%. Patients with a GBEF <35% to 40% with reproducible pain on CCK stimulation is suggestive of functional gallbladder disorder.

TREATMENT

In patients with appropriate evaluation for suspected functional gallbladder disorder, surgical management with cholecystectomy is the preferred method of treatment.

NONPHARMACOLOGIC THERAPY

Surgical cholecystectomy is the preferred method of treatment. Studies have shown symptomatic relief in up to 98% of patients postcholecystectomy.

ACUTE GENERAL Rx

- Initial management should include adequate analgesic control for abdominal pain.
- Opioid analgesics should be avoided because they may exacerbate symptoms involved in a hypofunctioning gallbladder.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Turmeric (Curcuma) has been known to alleviate biliary dyspepsia by stimulating gallbladder contractions.

DISPOSITION

Patients with functional gallbladder disorder are often misdiagnosed. These patients require appropriate evaluation to exclude other hepatobiliary etiology. After they are properly diagnosed, these patients have a favorable prognosis after surgical intervention.

REFERRAL

- Gastroenterology consultation may be considered to rule out microlithiasis via EUS.
- Surgical consultation should be considered for possible cholecystectomy in select patients.

PEARLS & CONSIDERATIONS

COMMENTS

Functional gallbladder disorder is a diagnosis of exclusion. It is essential that other hepatobiliary pathology be ruled out first. CCK-stimulation scintigraphy showing a reduced GBEF without any other pathology is suggestive of this disorder. Patients fare well with surgical intervention.

RELATED TOPICS

Cholangiocarcinoma (Related Key Topic)
Cholecystitis (Related Key Topic)
Choledocholithiasis (Related Key Topic)
Cholelithiasis (Related Key Topic)

AUTHORS: **Rosann Cholankeril, MD,** and **George Cholankeril, MD**

BASIC INFORMATION

DEFINITION

Galactorrhea can be defined as inappropriate lactation (in the absence of pregnancy or postpartum state) as a result of nonphysiologic augmentation of prolactin release.

ICD-10CM CODES

N64.3	Galactorrhea not associated with childbirth
O92.6	Galactorrhea in pregnancy

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Milky discharge from nipples (Fig. E1), usually occurring bilaterally
- Evidence of chest wall irritation from ill-fitting clothing, herpes zoster, or atopic dermatitis may be present
- Visual field defects (bitemporal hemianopsia) may be present with prolactinomas, particularly if large, such as macroadenomas
- Headaches may also occur in cases of large pituitary adenomas
- Evidence of acromegaly, Cushing syndrome, or hypothyroidism when galactorrhea is caused by these disorders

ETIOLOGY

- Medications (phenothiazines, metoclopramide, selective serotonin reuptake inhibitors, anxiolytics, buspirone, risperidone, atenolol, valproic acid, conjugated estrogen and medroxyprogesterone, methyldopa, verapamil, H_2 receptor blockers [cimetidine], octreotide, danazol, tricyclic antidepressants, isoniazid, amphetamine, reserpine, opiates, sumatriptan, rimantadine, oral contraceptive formulations): After infancy, galactorrhea is often medication induced
- Pituitary tumors (prolactinomas, craniopharyngiomas)
- Hypothyroidism (diminished feedback inhibition increases thyroid-releasing hormone [TRH], which increases prolactin)
- Breast stimulation: Prolonged suckling or during sexual intercourse
- Chest wall irritation from ill-fitting clothing, herpes zoster, atopic dermatitis, burns
- Breast surgery
- Chronic renal failure (decreased prolactin clearance)
- Cushing syndrome
- Herbs (e.g., fennel, red clover, anise, red raspberry, marshmallow)
- Cocaine
- Cannabis
- Spinal cord surgery or injury, or tumors
- Severe gastroesophageal reflux disease, esophagitis (stimulation of thoracic nerves by the cervical and thoracic ganglia)
- Neonatal ("witch's milk" produced by 2% to 5% of neonates because of precipitous drop in maternal estrogen and progesterone postdelivery)
- Cancer: Lymphomas, Hodgkin disease, bronchogenic carcinoma, renal adenocarcinomas
- Sarcoidosis and other infiltrative disorders
- Tuberculosis affecting pituitary gland
- Pituitary stalk resection
- Multiple sclerosis
- Empty sella syndrome
- Acromegaly
- Increased stress, including major trauma
- Exercise
- Idiopathic, diagnosis of exclusion

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Intraductal papilloma
- Breast cancer
- Paget disease of breast
- Breast abscess

WORKUP

- Complete history focusing on menstrual irregularity, infertility, previous pregnancies, duration of galactorrhea, medications, visual complaints, fatigue. Age of onset is also significant (e.g., prolactinoma most common between ages 20 and 35 yr; neonatal galactorrhea is usually secondary to transplacental transfer of maternal estrogen)
- Physical examination: Height, weight, vital signs. Evidence of hirsutism, acne, obesity, visual field defects, goiter, neurologic deficits
- Breast examination for presence of nodules, evaluation of discharge (milky versus serosanguineous versus purulent). Inspection of chest wall
- Laboratory testing and imaging studies (see "Laboratory Tests")

LABORATORY TESTS

- β-Human chorionic gonadotropin (HCG) test (positive in pregnancy)
- Prolactin level (elevated, often >200 ng/ml in prolactinoma but may occur at any prolactin level). Confirm with repeat fasting test (avoid exercise and breast stimulation)
- Thyroid-stimulating hormone (TSH) (elevated in hypothyroidism)
- Basic metabolic panel (BMP): Blood urea nitrogen, creatinine (elevated in renal failure), glucose (elevated in Cushing syndrome)
- Urinalysis (hematuria in renal cell carcinoma)
- Microscopic examination of nipple discharge (scant cellular material, numerous fat globules, can be seen without specific staining)

IMAGING STUDIES

- MRI of brain if prolactin level is elevated, amenorrhea is present, or visual field defects are detected on physical examination.
- High-resolution CT of brain with special coronal cuts through the pituitary region may be helpful in patients with contraindications to MRI; however, it may miss small lesions.

TREATMENT

- Discontinuation of potential offending agents
- Avoidance of excessive breast stimulation
- Galactorrhea resulting from prolactinoma can be managed medically or with careful surveillance depending on size and growth of tumor, associated symptoms, and prolactin level. Surgical treatment of prolactinomas is usually reserved for medication failures. Please refer to the topic "Prolactinoma" in Section I for additional information
- No treatment is necessary for normoprolactinemic patients with idiopathic nonbothersome galactorrhea. Provide reassurance
- Normoprolactinemic patients with bothersome galactorrhea may respond to low dose dopamine agonist (e.g., cabergoline 0.25 mg twice weekly)
- If patient is experiencing anovulatory dysfunction, consider treatment with bromocriptine (discontinue with confirmation of pregnancy)

REFERRAL

Endocrine and neurosurgical consultation if prolactinoma is detected

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Galactorrhea (Patient Information)
Pituitary Adenoma (Related Key Topic)
Prolactinoma (Related Key Topic)

AUTHORS: **Siri M. Holton, MD,** and **Rachel Wright Heinle, MD, FACOG**

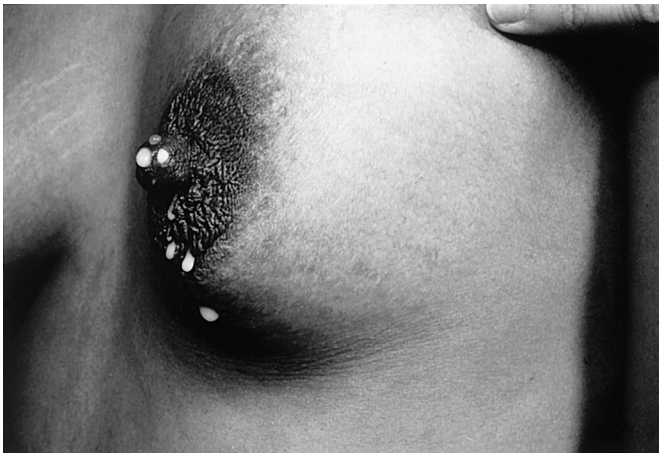

FIG. E1 Galactorrhea. Milk production in a nonpregnant woman resulting from a prolactinoma. (From Haines DE: *Fundamental neuroscience for basic and clinical applications,* ed 3, Philadelphia, 2006, Churchill Livingstone.)

SUGGESTED READING

Huang W, Molitch ME: Evaluation and management of galactorrhea, *Am Fam Physician* 85(11):1073-1080, 2012.

BASIC INFORMATION

DEFINITION

Gallbladder cancer (GBC) is a rare malignancy that originates from the epithelial lining of the gallbladder. Nearly all of these cancers are adenocarcinomas. Rare pathological types include adenosquamous carcinoma, squamous cell carcinoma, small-cell carcinoma, and carcinosarcoma.

ICD-10CM CODE
C23 Malignant neoplasm of gallbladder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- The fifth most common gastrointestinal cancer in the U.S. Over 12,000 new cases of gallbladder cancer and cancers of large bile ducts will be diagnosed in 2020, and fewer than 4 in 10 will be gallbladder cancers.
- Incidence of new cases estimated at 1 to 2 cases per 100,000 population in the U.S.
- Most prevalent in South American countries and some Asian counties, such as Japan and Korea, due to high incidence of cholelithiasis.

PREDOMINANT SEX AND AGE: Female:male ratio 2.5:1 to 3.1:1. Incidence increases with age.

GENETICS: Increased incidence occurs in hereditary syndromes such as Gardner syndrome, neurofibromatosis type I, and hereditary nonpolyposis colon cancer (HNPCC).

RISK FACTORS (BOX E1):

- Gallstone disease
- Porcelain gallbladder
- Female gender
- Older age
- Gallbladder polyps (size >1 cm)
- Primary sclerosing cholangitis
- Chronic infection from salmonella or helicobacter
- Obesity

BOX E1 Risk Factors for Gallbladder Carcinoma

Anomalous union of the pancreaticobiliary ductal system
Carcinogens*
Cholangiocarcinoma
Cholelithiasis (stone size >1 cm)
Chronic *Salmonella typhi* or *paratyphi* carrier status
First-degree relative with gallbladder cancer
IBD
Intrahepatic biliary dysplasia
Lynch syndrome
Porcelain gallbladder
PSC
Segmental adenomyomatosis in patients ≥60 yr of age

*Methylcholanthrene, O-aminoazotoluene, nitrosamines, and possibly others.
IBD, Inflammatory bowel disease; *PSC,* primary sclerosing cholangitis.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Early stage: Most patients are asymptomatic.
- Late stage: Right-upper-quadrant pain, weight loss, malaise, nausea, vomiting, and obstructive jaundice. Patients can also present with symptoms of cholecystitis including fever and pain.
- Physical exam may reveal Courvoisier law (palpable gallbladder and mild painless jaundice).
- Can often be misdiagnosed as biliary colic or cholecystitis, resulting in delayed diagnosis

ETIOLOGY/PATHOGENESIS

Chronic inflammation of gallbladder from any cause can predispose to evolution from dysplasia to carcinoma in situ to invasive cancer subsequently.

- Gallbladder cancer can spread early by hematogenous or lymphatic route or by direct invasion into the liver.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cholangiocarcinoma
- Acalculous cholecystitis
- Carcinoma of the ampulla of Vater
- Gallbladder mucocele
- Gallstones
- Gallbladder volvulus

WORKUP

- Initial work consists of laboratory evaluation and sonogram of abdomen.
- Liver function tests might reveal bile duct obstruction with an elevated serum bilirubin or alkaline phosphatase.
- Cancer antigen 19-9 (CA 19-9) or carcinoembryonic antigen (CEA) is frequently elevated, but they both have low sensitivity and specificity for diagnostic purposes.
- Suspicious ultrasonographic findings, including calcification, thickened gallbladder wall, gallbladder polyps ≥10 mm, and protruding mass, are warranted for additional imaging studies with computed tomography (CT) of abdomen (Fig. E1), magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP), or endoscopic ultrasonography (EUS).
- Chest CT should be done to complete staging work-up. PET/CT has limited sensitivity but high specificity in the detection of regional lymph node metastases. PET/CT may be considered when there is an equivocal finding on CT/MRI.
- Staging laparoscopy is very useful to determine resectability state.
- Staging (Table E1).

TREATMENT

- Surgery (Table E2) is the mainstay of treatment for curative intent. Incidental GBC is often operated by laparoscopic cholecystectomy and detected by pathology review postoperatively. In these cases, a radical re-resection is indicated depending on tumor stage.
- Extended cholecystectomy is the preferred approach when GBC is suspected pre-operatively.
- Adjuvant therapy:
  1. T_{1a} with negative margins: No adjuvant chemotherapy.
  2. T_{1b} or higher: Adjuvant chemotherapy with fluoropyrimidine-based or gemcitabine-based chemotherapy alone or fluoropyrimidine chemoradiotherapy.
- Unresectable or metastatic disease: Gemcitabine/cisplatin is considered first-line standard of care. Taxanes and fluoropyrimidine-containing regimens can be used upon disease progression. The role of immunotherapy and targeted agents is investigational. Pembrolizumab (PD-1 inhibitor) is appropriate for microsatellite instability high (MSI-H) tumors.
- Neoadjuvant chemotherapy may downstage select patients with unresectable disease. Reevaluation by a surgeon should be considered.
- Role of chemoradiotherapy can be considered in select cases in the adjuvant setting or as definitive management for unresectable disease.

SURVEILLANCE

- Consider imaging every 6 mo for 2 yr if clinically indicated, and then annually up to 5 yr.
- Consider CEA and CA 19-9 as clinically indicated.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Sonali Harchandani, MD,** and **Patan Gultawatvichai, MD**

SUGGESTED READINGS

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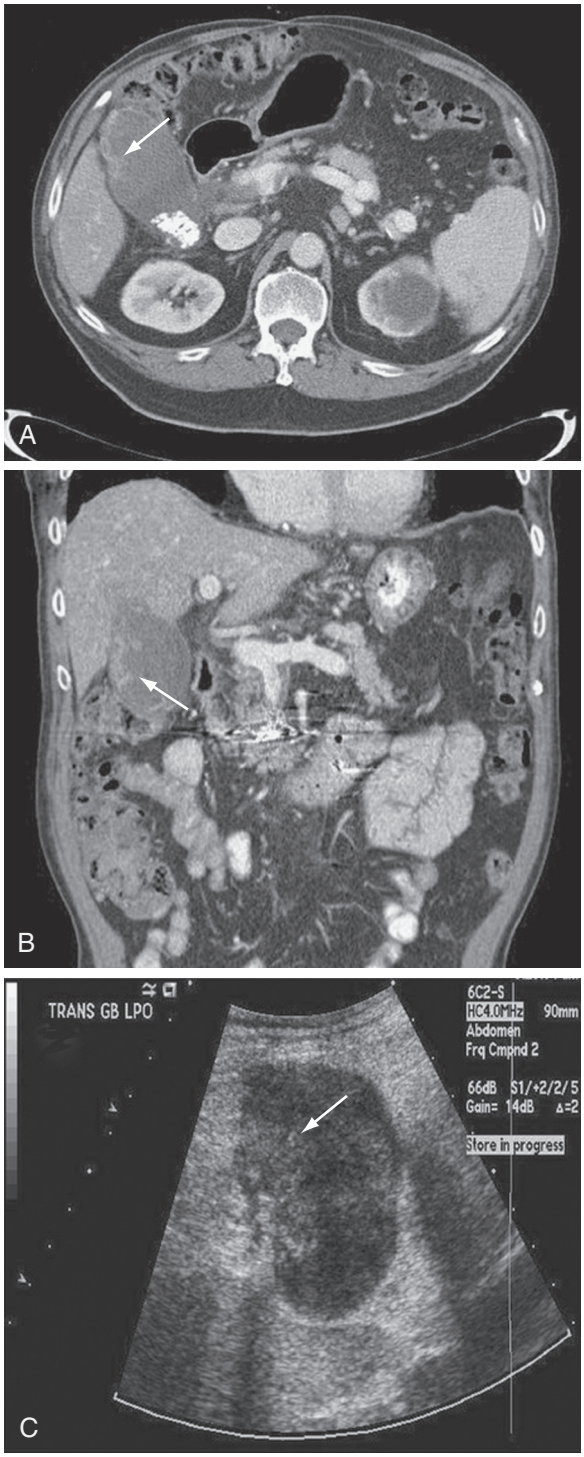

FIG. E1 Imaging of gallbladder carcinoma. A, Axial computed tomography view of the abdomen. Cholelithiasis is seen inferior to the gallbladder mass *(arrow)*. **B,** Coronal view of the same patient. **C,** Ultrasonography in the same patient showing a large mass *(arrow)* originating from the gallbladder wall and protruding into the lumen. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

TABLE E1 TNM and American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) Staging Systems for Gallbladder Carcinoma

TNM Stage	Criteria
T_x	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_{is}	Carcinoma in situ
T_{1a}	Tumor invades lamina propria
T_{1b}	Tumor invades muscularis propria
T_2	Tumor invades perimuscular connective tissue without extension beyond serosa or into liver
T_3	Tumor perforates the serosa AND/OR Tumor directly invades the liver AND/OR Tumor invades one other adjacent organ (i.e., stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts)
T_4	Tumor invades the portal vein or hepatic artery OR Tumor invades ≥2 extrahepatic organs or structures
N_x	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastases
N_1	Lymph node metastases along the cystic duct, bile duct, hepatic artery, AND/OR portal vein
N_2	Metastases to periaortic, pericaval, superior mesenteric artery, AND/OR celiac artery lymph nodes
M_0	No distant metastases
M_1	Distant metastases

AJCC/UICC Stage	Tumor	Node	Metastasis
0	T_{is}	N_0	M_0
I	T_1	N_0	M_0
II	T_2	N_0	M_0
III_A	T_3	N_0	M_0
III_B	T_{1-3}	N_1	M_0
IV_A	T_4	N_{0-1}	M_0
IV_B	Any T	N_2	M_0
	Any T	Any N	M_1

TNM, Tumor, node, metastasis.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE E2 Recommended Management by Stage

Stage	Surgical Management	Postoperative Management
T_{1a}	Simple cholecystectomy	Review pathology report to confirm negative cystic duct margins No routine follow-up advised
T_{1b}	Radical cholecystectomy (i.e., segment IV_b/V resection [preferred], hepatic wedge resection, right hepatic lobectomy, or trisectionectomy with R0 resection) and portal lymphadenectomy	Staging workup with CT chest/abdomen/pelvis (or CT chest and MRI abdomen/pelvis) Adjuvant fluoropyrimidine chemoradiation versus gemcitabine-based or fluoropyrimidine-based chemotherapy Surveillance imaging
II	See earlier for T_{1b} tumors	See earlier for T_{1b} tumors
III	Consider diagnostic staging laparoscopy followed by operation for T_{1b} tumors if no metastatic disease is identified	See earlier for T_{1b} tumors
IV_A	Stage IV_A (T4 N_{0-1} M_0) disease may be amenable to resection (see stage III)	Adjuvant fluoropyrimidine chemoradiation versus gemcitabine-based or fluoropyrimidine-based chemotherapy
IV_B	N_2 and M_1 disease is a contraindication to attempts at curative resection. Patients may require palliative operation for relief of biliary obstruction but attempts at endoscopic/ percutaneous drainage should be considered first-line treatment	Unresectable disease: Combined gemcitabine/cisplatin therapy, fluoropyrimidine-based or gemcitabine-based chemotherapy regimens current

CT, Computed tomography; *MRI*, magnetic resonance imaging.
From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.

BASIC INFORMATION

DEFINITION

A fluid-filled sac (cyst) overlying a tendon sheath or joint

SYNONYM

Ganglion

ICD-10CM CODE
M67.4 Ganglion

EPIDEMIOLOGY & DEMOGRAPHICS

- Ganglia are more common in women than men (3:1).
- Can occur at any age, but usually between the second and fourth decades of life.
- Most common soft tissue tumor of the hand and wrist.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most ganglia occur on the dorsum of the wrist (50% to 70%) (Fig. E1).
- The volar wrist (18% to 20%) is the next most common site.
- Can also involve the proximal digital flexor tendons and the distal interphalangeal joints.
- Left and right hands are equally affected.
- Ganglia are usually solitary, firm, smooth, round, and fluctuant.
- Pain from mass effect or compression against nearby structure may be present (e.g., median nerve and radial nerve).

FIG. E1 Dorsal wrist ganglion. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

- Hand numbness may be present.
- Patient may have hand muscle weakness.
- Ganglia usually develop over a period of months but may arise suddenly.

ETIOLOGY

Ganglia are believed to derive from synovial herniation or expansion from the joint capsule or tendon sheath. Repetitive movement as an etiology is uncertain, although it may cause enlargement of the lesion or worsen symptoms.

DIAGNOSIS

Direct inspection and localization of the cyst often are enough to make the diagnosis of ganglia. Transillumination is an easy method of differentiating ganglia from solid tumors; ganglia transilluminate, but solid tumors do not.

DIFFERENTIAL DIAGNOSIS

- Lipoma
- Fibroma
- Epidermoid inclusion cyst
- Osteochondroma
- Hemangioma
- Infection (tuberculosis, fungi, and secondary syphilis)
- Gout
- Rheumatoid nodule
- Radial artery aneurysm

WORKUP

The workup of ganglia usually consists of history, physical examination, and occasionally radiography.

LABORATORY TESTS

Blood tests are not specific in the diagnosis of ganglia.

IMAGING STUDIES

- Radiographs of the hand and wrist are taken to rule out other bone or joint abnormalities.
- Ultrasound studies are helpful in the diagnosis of ganglia by demonstrating smooth cystic walls that may be septated.
- CT scan can be done if the ultrasound is equivocal.
- MRI helps differentiate malignant bone lesions from cystic structures.
- Arthrography may demonstrate a communication between the joint and ganglia (not commonly done).

TREATMENT

Expectant treatment is appropriate if the mass is not painful or interfering with motor function.

NONPHARMACOLOGIC THERAPY

- Attempts to rupture the cyst by sharp blows with a book or with finger compression are not recommended.
- Aspiration, heat, and sclerotherapy have been tried but have met with high recurrence rates (60%).

ACUTE GENERAL Rx

- Aspiration at the base with a large-bore needle (18-gauge) followed by injection of 20 to 40 mg of triamcinolone acetonide can be tried.
- This may be repeated if the ganglia recurs (35% to 40%).

CHRONIC Rx

Total ganglionectomy and repair of the defect after tracing its connection to the tendon sheath is effective and the surgical procedure of choice.

DISPOSITION

- Ganglia spontaneously resolve in approximately 40% to 50% of cases.
- Aspiration with steroid injection is successful in approximately 65% of cases.
- Surgery provides cure in 85% to 95% of the cases.
- Complications of ganglia include:
  1. Carpal tunnel syndrome with pain and muscle atrophy
  2. Radial nerve impingement
  3. Radial artery compression
- Complications of ganglion surgery include:
  1. Infection
  2. Recurrence (5% to 15%), usually from inadequate excision
  3. Reflex sympathetic dystrophy
  4. Scar formation

REFERRAL

It is best to refer patients with symptomatic ganglia to a hand surgeon.

PEARLS & CONSIDERATIONS

- Dorsal ganglia usually originate from the scapholunate ligament.
- Volar ganglia typically originate between the tendons of the flexor carpi radialis and brachioradialis.

COMMENTS

A ganglion's synovial membrane maintains its secretory function. Aspiration of ganglia often demonstrates a viscous, mucinous, clear fluid containing albumin, globulin, and hyaluronic acid.

RELATED CONTENT

Ganglia (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

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Nahra ME, Bucchieri JS: Ganglion cysts and other tumor related cysts of the hand and wrist, *Hand Clin* 20(3):249, 2004.

Wang AA, Hutchinson DT: Longitudinal observation of pediatric hand and wrist ganglia, *J Hand Surg* 26(4):599, 2001.

BASIC INFORMATION

DEFINITION

Gastric cancer is an adenocarcinoma arising from the stomach. Cancers in the cardia arising within 5 cm of the gastroesophageal junction (GEJ) are typically classified as GEJ cancers. It is subdivided into intestinal and diffuse histology. The diffuse form of gastric cancer is more common in women and young patients, whereas the intestinal type is predominantly related to environmental factors (smoking, diet high in smoked, salted, and pickled food, nitrates and nitrites) and ethnicity (Asian and Pacific descent). The classification of gastric adenocarcinoma by depth of invasion is illustrated in Fig. 1.

SYNONYMS

Gastric adenocarcinoma
Stomach cancer
Linitis plastica

ICD-10CM CODES

C16	Malignant neoplasm of stomach
C16.0	Malignant neoplasm of cardia of stomach
C16.1	Malignant neoplasm of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach

EPIDEMIOLOGY & DEMOGRAPHICS

- Gastric cancer is the fourth commonest cancer in the world, with an annual incidence of approximately 950,000 cases annually; of these, 70% occur in developing countries. The highest incidence is in Asia and the lowest in North America. Annual estimated deaths due to gastric cancer are 723,000 worldwide.
- In the U.S., an estimated 27,510 new cases and 11,140 deaths were expected in 2019.
- The incidence of gastric cancer is 6.7 in 100,000 persons in the U.S. Mortality rate is 3.4 per 100,000 persons. Although the incidence of distal stomach tumors has greatly declined over the past 30 yr, that of proximal tumors of the cardia and fundus is on the rise.
- Gastric cancer is more common in male patients >65 yr (70% of patients are >50 yr).
- Male/female ratio is 3:2.
- Hereditary diffuse gastric cancer (HDGC) has an autosomal-dominant inheritance, and cancer develops at a young age (average age 37 yr). Germline truncating mutations in the tumor-suppressor E-cadherin gene *(CDH1)* are found in up to 50% of these families. It is associated with an 80% lifetime risk of gastric cancer.
- Increased risk of gastric cancer is also seen with Lynch syndrome, FAP, Peutz-Jeghers, juvenile polyposis syndrome, and hyperplastic gastric polyps.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Medical history may reveal complaints of postprandial fullness with significant weight loss (70% to 80%), nausea/vomiting (20% to 40%), dysphagia (20%), and dyspepsia, usually unrelieved by antacids; epigastric discomfort, usually lessened by fasting and exacerbated by food intake, is also common.
- Epigastric or abdominal mass (30% to 50%), epigastric pain.
- Iron deficiency anemia is typically seen from tumor bleeding, and hemoccult-positive stools are detected.
- Hard, nodular liver: May indicate metastatic disease to the liver.
- Ascites, lymphadenopathy, or pleural effusions: May indicate metastases.

ETIOLOGY

RISK FACTORS:

- Chronic *Helicobacter pylori* gastritis. Gastric cancer develops in persons infected with *H. pylori* but not in uninfected persons. Those with histologic findings of severe gastric atrophy, corpus-predominant gastritis, or intestinal metaplasia are at increased risk. Persons with *H. pylori* infection and duodenal ulcer are not at risk, whereas those with gastric ulcers, nonulcer dyspepsia, and gastric hyperplastic polyps are. Eradication of *H. pylori* reduces gastric cancer risk
- Tobacco abuse, heavy alcohol consumption
- Food additives (nitrosamines), smoked foods, occupational exposure to heavy metals, rubber, asbestos
- Chronic atrophic gastritis with intestinal metaplasia, hypertrophic gastritis, and pernicious anemia
- Box 1 summarizes risk factors for gastric adenocarcinoma

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gastric lymphoma (5% of gastric malignancies)
- Hypertrophic gastritis
- Peptic ulcer
- Reflux esophagitis

WORKUP

Upper endoscopy (Fig. E2) with biopsy will confirm diagnosis. Endoscopic ultrasonography in combination with PET/CT scanning and operative lymph node dissection can be used in staging of the tumor. Table 1 and Fig. 1 describe staging systems for gastric carcinoma.

LABORATORY TESTS

- Complete blood count reveals microcytic anemia.
- Hemoccult-positive stools are detected.
- Chemistry tests can reveal hypoalbuminemia or abnormal liver enzymes in patients with metastasis to the liver.

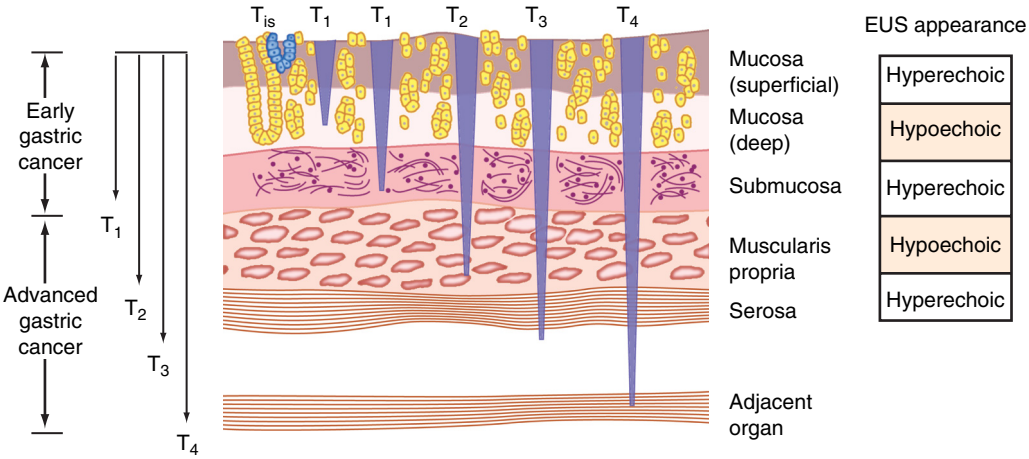

FIG. 1 Classification of gastric adenocarcinoma by depth of invasion (T classification). In the TNM classification, T denotes depth of invasion: T_{is} designates carcinoma in situ; T_1 tumors are confined to the mucosa (T_{1a}) and submucosa (T_{1b}); T_2 tumors invade the muscularis propria but not the serosa; T_3 tumors penetrate the subserosal connective tissue without involving the visceral peritoneum or contiguous structures; and T_4 tumors invade the serosa (visceral peritoneum) and may involve adjacent organs and tissues. In early gastric cancer, the disease is confined to the mucosa and submucosa (T_1), regardless of nodal involvement. (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Saunders.)

BOX 1 Risk Factors for Gastric Adenocarcinoma

Definite
H. pylori infection
Chronic atrophic gastritis
Intestinal metaplasia
Dysplasia*
Adenomatous gastric polyps
Cigarette smoking
History of gastric surgery (especially Billroth II)
Genetic factors:
- Family history of gastric cancer (first-degree relative)
- Familial adenomatous polyposis (with fundic gland polyps)
- Hereditary nonpolyposis colorectal cancer
- Peutz-Jeghers syndrome
- Juvenile polyposis

Probable
High salt intake
Obesity (adenocarcinoma of the cardia only)
Snuff tobacco use
History of gastric ulcer
Pernicious anemia
Regular aspirin or other NSAID use (protective)

Possible
Statin use (protective)
Heavy alcohol use
Low socioeconomic status
Ménétrier disease
High intake of fresh fruits and vegetables (protective)
High ascorbate intake (protective)

Questionable
Hyperplastic and fundic gland polyps
Diet high in nitrates
High green tea consumption (protective)

*Surveillance for cancer is recommended in patients with this risk factor.
From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Saunders.

TABLE 1 TNM Staging Criteria and Stages for Gastric Carcinoma Based on AJCC 8th Edition

T Category	T Criteria
T_X	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_{is}	Carcinoma *in situ*: Intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia
T_1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T_{1a}	Tumor invades the lamina propria or muscularis mucosae
T_{1b}	Tumor invades the submucosa
T_2	Tumor invades the muscularis propria
T_3	Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures
T_4	Tumor invades the serosa (visceral peritoneum) or adjacent structures
T_{4a}	Tumor invades the serosa (visceral peritoneum)
N Category	**N Criteria**
N_X	Regional lymph node(s) cannot be assessed
N_0	No regional lymph node metastasis
N_1	Metastasis in one or two regional lymph nodes
N_2	Metastasis in three to six regional lymph nodes
N_3	Metastasis in seven or more regional lymph nodes
N_{3a}	Metastasis in 7 to 15 regional lymph nodes
M Category	**M Criteria**
M_0	No distant metastasis
M_1	Distant metastasis

Stage	pT	pN	M
Stage 0	T_{is}	N_0	M_0
Stage IA	T_1	N_0	M_0
Stage IB	T_1	N_1	M_0
	T_2	N_0	M_0
Stage IIA	T_1	N_2	M_0
	T_2	N_1	M_0
	T_3	N_0	M_0
Stage IIB	T_1	N_{3a}	M_0
	T_2	N_2	M_0
	T_3	N_1	M_0
	T_{4a}	N_0	M_0
Stage IIIA	T_2	N_{3a}	M_0
	T_3	N_2	M_0
	T_{4a}	N_1 or N_2	M_0
	T_{4b}	N_0	M_0
Stage IIIB	T_1	N_{3b}	M_0
	T_2	N_{3b}	M_0
	T_3	N_{3a}	M_0
	T_{4a}	N_{3a}	M_0
	T_{4b}	N_1 or N_2	M_0
Stage IIIC	T_3	N_{3b}	M_0
	T_{4a}	N_{3b}	M_0
	T_{4b}	N_{3a} or N_{3b}	M_0
Stage IV	Any T	Any N	M_1

- Up to 25% of gastric cancers overexpress the HER2/neu growth factor receptor, and it is now standard practice to evaluate gastroesophageal tumors for HER2 overexpression.
- Mutation-specific predictive genetic testing by polymerase chain reaction amplification followed by restriction: Enzyme digestion and DNA sequencing for truncating mutations in *CDH1* is recommended in families of patients with familial diffuse cancer because gastric cancer develops in three of every four carriers of a mutant *CDH1* gene. Genetic abnormalities in gastric adenocarcinoma are summarized in Table E2.

IMAGING STUDIES

Chest and abdomen PET/CT scan (Fig. E3) to evaluate for metastases

Rx TREATMENT

ACUTE GENERAL Rx

- Gastrectomy: Most curable tumors can be removed with adequate margins by subtotal gastrectomy; total gastrectomy is used when mandated by proximal cancer location or disease extent. The preferred treatment for lesions arising in the body or antrum of the stomach is a radical distal subtotal resection (Fig. E4). This procedure removes approximately 80% of the stomach, along with the first portion of the duodenum, the gastrohepatic and gastrocolic omenta, and the nodal tissue adjacent to the three branches of the celiac axis. Extensive or proximal cancers require a total gastrectomy to achieve an adequate proximal gastric margin (Fig. E5). If total gastrectomy is necessary, a splenectomy is sometimes performed, particularly in gastric cancers of the proximal third of the stomach and tumors of the body near the greater curvature. These cancers are more apt to metastasize to lymph nodes in the splenic hilum that cannot be completely excised without a splenectomy. Routine splenectomy is no longer practiced because of

the increased complications. A splenectomy should be performed when worrisome, palpable nodes are present in the splenic hilum.
- In advanced cases, palliative gastrectomy (bleeding, obstruction) can be performed. Outlet obstruction can be addressed by performing a gastrojejunostomy.
- In patients with operable gastric cancer, the perioperative regimen chemotherapy can decrease tumor size and stage while improving progression-free and overall survival. The current standard neoadjuvant regimen in use is the FLOT (5-fluorouracil [5-FU], leucovorin, oxaliplatin, docetaxel) regimen.
- Postoperative adjuvant chemoradiotherapy using the older 5-FU and leucovorin regimen is an option for stage II to III patients. Alternatively, the modern approach is combination chemotherapy with FOLFOX (5-FU, leucovorin, oxaliplatin) or CAPOX (capecitabine, oxaliplatin) regimens with radiotherapy reserved for high-risk patients only.
- In metastatic gastric cancer, the use of chemotherapy with triplet or doublet regimens results in improved overall survival. In the subset of patients with gastric cancer expressing *HER2-2/neu* oncogene (20% to 25% of patients), the addition of trastuzumab to platinum plus 5-FU or capecitabine prolongs overall survival.
- Patients progressing after first-line chemotherapy can derive a survival benefit with the use of chemotherapy in combination with antivascular endothelial growth factor receptor-2 antibody ramucirumab. Immunotherapy with program death receptor-1 antibodies (nivolumab, pembrolizumab) has been shown to improve survival in previously treated patients with high-MSI tumors.
- Treatment algorithms for newly diagnosed gastric or gastroesophageal junction cancer are illustrated in Figs. 6 and 7.

DISPOSITION

- Median survival rate of metastatic or recurrent gastric carcinoma is 10 to 15 mo overall.
- The 5-yr survival for early gastric cancers is >35%.

PEARLS & CONSIDERATIONS

COMMENTS

- Gastrectomy patients will need vitamin B_{12} replacement. They are also at risk for dumping syndrome and should be advised to ingest frequent, small meals.
- Prophylactic gastrectomy should be considered in young, asymptomatic carriers of germ-line truncating *CDH1* mutations who belong to families with highly penetrant heredity diffuse gastric cancer.
- Gastric cancer screening for average-risk patients is not recommended in the U.S.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Stomach Cancer (Patient Information)

AUTHOR: **Ritesh Rathore, MD**

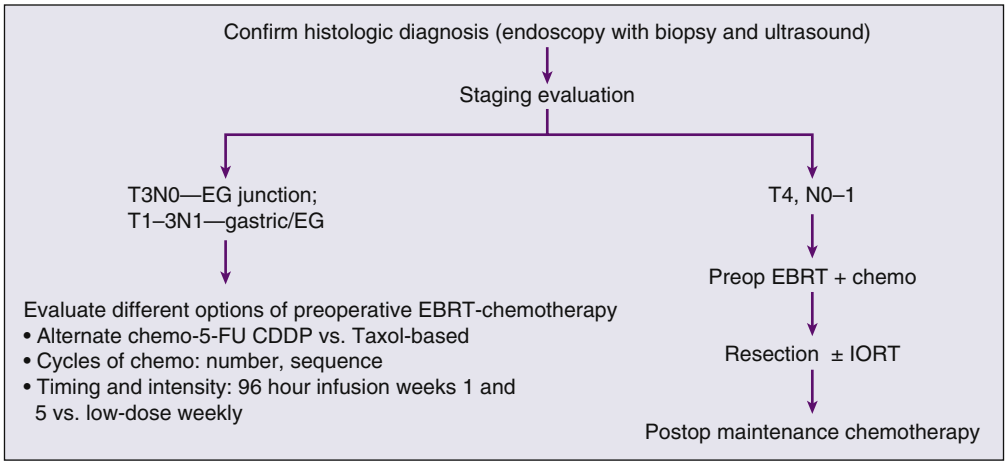

FIG. 6 Treatment algorithm: newly diagnosed gastric or gastroesophageal junction cancer. Adjuvant therapy precedes surgery. *CDDP, Cis*-diamminedichloroplatinum; *chemo,* chemotherapy; *EBRT,* external-beam radiation therapy; *EG,* esophagogastric; *5-FU,* 5-fluorouracil; *IORT,* intraoperative radiation therapy; *postop,* postoperative; *preop,* preoperative. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

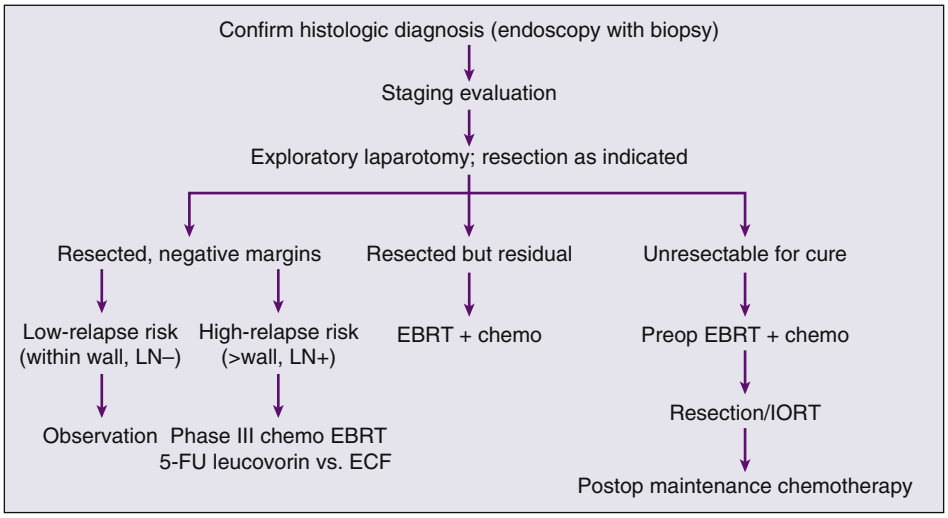

FIG. 7 Treatment algorithm: newly diagnosed gastric or gastroesophageal junction cancer. Surgery precedes adjuvant therapy. *chemo,* Chemotherapy; *EBRT,* external-beam radiation therapy; *ECF,* epirubicin, cisplatin, 5-fluorouracil; *5-FU,* 5-fluorouracil; *IORT,* intraoperative radiation therapy; *LN,* lymph node; *postop,* postoperative; *preop,* preoperative. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

SUGGESTED READINGS

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Shum H, Rajdev L: Multimodality management of resectable gastric cancer: a review, *World J Gastrointest Oncol* 6(10):393-402, 2014.

Siegel RL et al: Cancer statistics, *CA Cancer J Clin* 69(1):7-34, 2019.

FIG. E2 Polypoid gastric cancer. A trilobed polyp is apparent at the angularis. (From Feldman M et al [eds]: *Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management,* ed 8, Philadelphia, 2006, Saunders.)

TABLE E2 Genetic Abnormalities in Gastric Adenocarcinoma

Abnormalities	Approximate Gene Frequency (%)
Microsatellite instability	15-50
DNA aneuploidy	60-75
Deletion/Suppression	
p53 (tumor protein 53)	60-70
FHIT (fragile histidine triad gene)	60
APC (adenomatous polyposis coli gene) loss of heterozygosity	50
DCC (deleted in colorectal cancer gene) loss of heterozygosity	50
Decreased Expression Due to Hypermethylation	
p16	≈50
TFF1 (human trefoil factor 1 gene)	≈50
p27	<50
MLH1 (human mutL homolog 1 gene)	15-20
E-cadherin	50
Amplification/Overexpression	
COX-2 (cyclooxygenase-2)	70
HGF (hepatocyte growth factor)	60
VEGF (vascular endothelial growth factor)	50
c-met	50
AIB-1 (amplified in breast cancer-1)	40
beta-Catenin	25
EGFR (EGF receptor gene)	15
Mutations	
PI3K (phosphatidylinositol 3-kinase gene)	25
PTPRT (protein-tyrosine phosphatase receptor type gene)	17

From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Saunders.

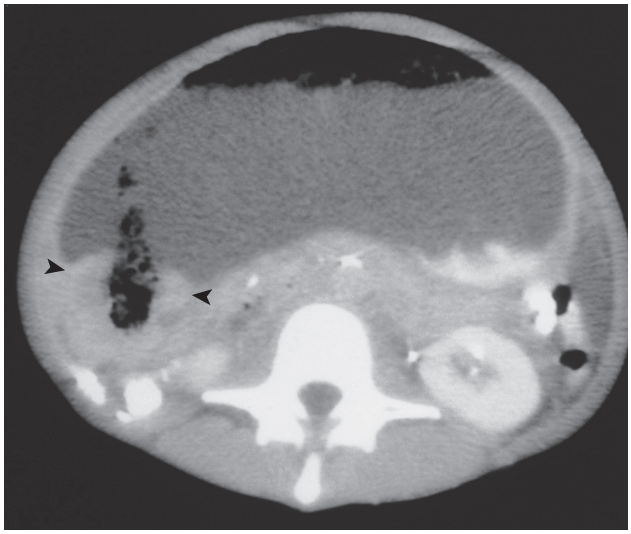

FIG. E3 Gastric outlet obstruction: cancer of the antrum. A markedly distended stomach with an air-fluid level is seen on computed tomography. In this case, a mass in the distal end of the antrum is apparent *(arrowheads).* (From Grainger RG et al [eds]: *Grainger & Allison's diagnostic radiology: a textbook of medical imaging,* ed 4, St Louis, 2001, Churchill Livingstone.)

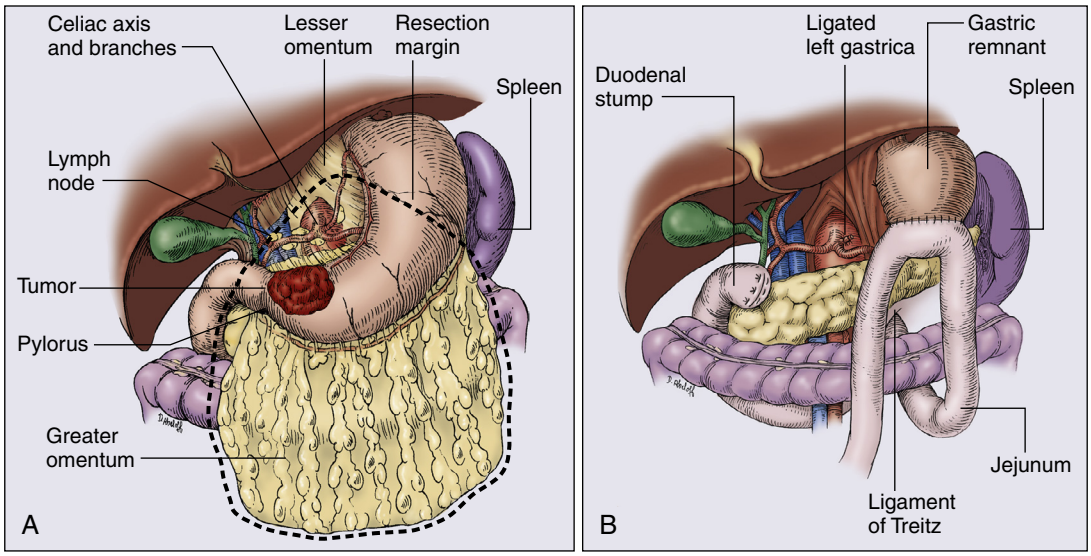

FIG. E4 A, Radical subtotal gastrectomy. The extent of resection for this tumor of the antrum includes the distal 80% of the stomach; the lesser and greater omenta; the perigastric lymph nodes (Japan N1); and lymph nodes along the left gastric, celiac, and common hepatic arteries (Japan N2). **B,** Radical subtotal gastrectomy reconstruction. After closure of the duodenal stump and lesser curvature of the stomach, the gastric remnant and proximal jejunum are anastomosed end to side in an antecolic position. The spleen and distal pancreas have been left in situ. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

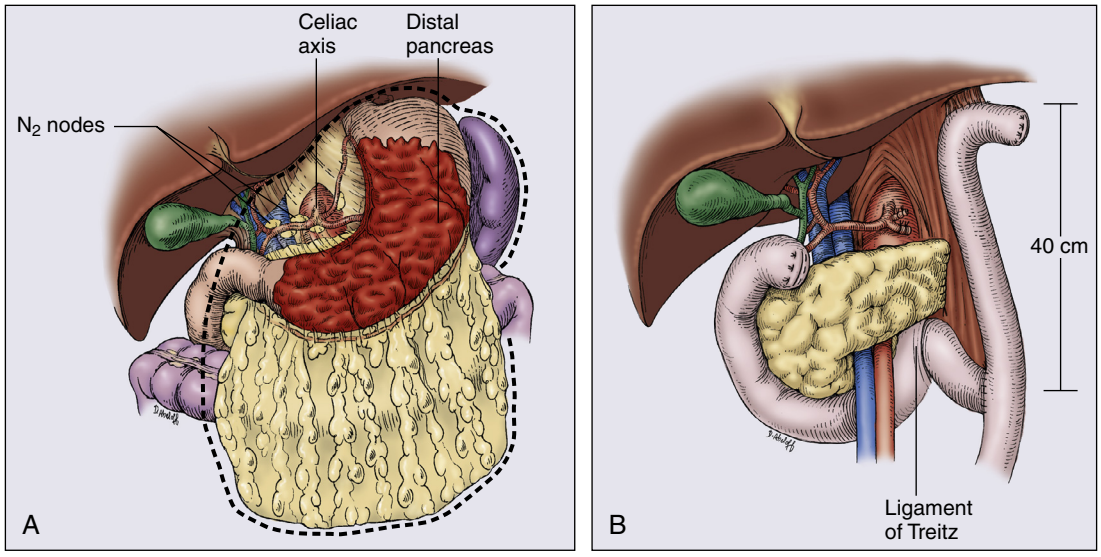

FIG. E5 A, Radical total gastrectomy. A total gastrectomy is indicated for this extensive tumor of the stomach. Both omenta, the spleen, distal pancreas, and Japan N_2 lymph nodes are to be included with the operative specimen. **B,** Radical total gastrectomy reconstruction. Although a variety of anastomoses and jejunal pouches have been described, no benefit seems to accrue from any approach, except to keep the biliary and pancreatic secretions away from the esophageal mucosa. The Cohn end-to-side Roux-en-Y esophagojejunostomy with a 40-cm limb is depicted. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

Gastrinoma ALG PTG

BASIC INFORMATION

DEFINITION

A gastrinoma is a neuroendocrine tumor that secretes gastrin with a resultant hypergastrinemic state, which results in severe peptic ulcer disease with diarrhea, and this is also known as Zollinger-Ellison syndrome (ZES).

SYNONYMS

Zollinger-Ellison (ZE) syndrome
Zes

ICD-10CM CODES

C25.4	Malignant neoplasm of endocrine pancreas
E16.4	Abnormal secretion of gastrin

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence is unknown, but there is consensus that approximately 0.5 to 3 persons per million develop gastrinoma each yr in most geographical areas.
- Females have a slightly greater preponderance for developing the disease, and gastrinoma is most frequently diagnosed between the ages of 20 and 50 yr.
- Two thirds of gastrinomas are sporadic, and one third are associated with multiple endocrine neoplasia type 1 (MEN-1), an autosomal-dominant genetic disorder that also includes hyperparathyroidism and pituitary tumors.
- Approximately 60% of gastrinomas are malignant.
- The incidence and prevalence of pancreatic neuroendocrine tumors are increasing. They represent 1.3% of all cases of pancreatic cancer.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The majority of patients (95%) present with symptoms of peptic ulcer (see Section I, "Peptic Ulcer Disease").
- 60% of patients have symptoms related to gastroesophageal reflux disease (see Section I, "Gastroesophageal Reflux Disease").
- One third of patients with ZE have diarrhea and, less commonly, steatorrhea.

The following circumstances warrant suspicion of ZE syndrome:

- Ulcers distal to the first portion of the duodenum
- Multiple peptic ulcers
- Ineffective treatment for peptic ulcer disease with the usual drug doses and schedules
- Peptic ulcer and diarrhea
- Familial history of peptic ulcer
- Patients with a personal or family history suggesting parathyroid or pituitary tumors or dysfunction
- Peptic ulcer and urinary tract calculi
- Patients with peptic ulcer who are negative for *Helicobacter pylori* and do not have a history of nonsteroidal antiinflammatory drug use

ETIOLOGY

- Gastrinomas are derived from the enteroendocrine cells that arise from the embryologic endoderm and form tumors mainly in the pancreas but also in the proximal small intestine. They are classified as well-differentiated neuroendocrine tumors (NETs).
- The pathophysiologic manifestations of ZE syndrome are related to the effects of hypergastrinemia. Gastrin stimulates gastric acid secretion, which in turn is responsible for the development of duodenal ulcers and diarrhea. Gastrin also promotes gastric mucosal epithelial cell growth and resulting parietal cell hyperplasia.
- Gastrinomas are usually small (0.1 to 2 cm) but sometimes large (>20 cm) tumors.
- 60% of gastrinomas are malignant, with liver and regional lymph nodes the most common site of metastases. Histology is not a good predictor of the biology of gastrinomas.
- 60% of patients with MEN-1 have gastrinomas.
- 10% of patients with ZE syndrome have islet cell hyperplasia rather than gastrinomas; in 10% to 20% of patients, tumors cannot be located because of their small size.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Peptic ulcer disease (see Section I, "Peptic Ulcer Disease")
- Gastroesophageal reflux disease (see Section I, "Gastroesophageal Reflux Disease")
- Other endocrine tumors of the pancreas (see Table E1)

WORKUP

- Fig. E1 illustrates an algorithm for the diagnosis of ZES. Sensitivities of gastrinoma

TABLE E1 Characteristics of Endocrine Tumors of the Pancreas

Tumor Type	Major Clinical Symptoms	Predominant Hormone	Islet Cell Type	Malignant (%)	Localization	Other Clinical Features
Insulinoma	Hypoglycemia (fasting or nocturnal)	Insulin	β	10	Usually pancreatic; rarely extrapancreatic	Catecholamine excess
Glucagonoma	1. Diabetes mellitus 2. Migratory necrolytic erythema	Glucagon	α	90	Usually pancreatic; rarely extrapancreatic	Panhypoaminoaciduria Thromboembolism Weight loss
Gastrinoma	Recurrent peptic ulcer disease	Gastrin	γ	90	Usually pancreatic but frequently extrapancreatic	Diarrhea/steatorrhea
Somatostatinoma	1. Diabetes mellitus 2. Diarrhea, steatorrhea	Somatostatin	δ	80	Pancreatic and duodenal	Hypochlorhydria Weight loss Gallbladder disease
VIPoma	Watery diarrhea, hypokalemia, achlorhydria (WDHA syndrome)	Vasoactive intestinal polypeptide (VIP)	δ	50	Usually pancreatic but frequently extrapancreatic	Metabolic acidosis Hyperglycemia Hypercalcemia Flushing
PPoma	1. Hepatomegaly 2. Abdominal pain	Pancreatic polypeptide (PP)	PP cells	80	Usually pancreatic; rarely extrapancreatic	Occasional watery diarrhea

From Besser GM, Cudworth AG: *Clinical endocrinology,* Philadelphia, 1987, Lippincott/Gower Medical Publishing, p. 20.

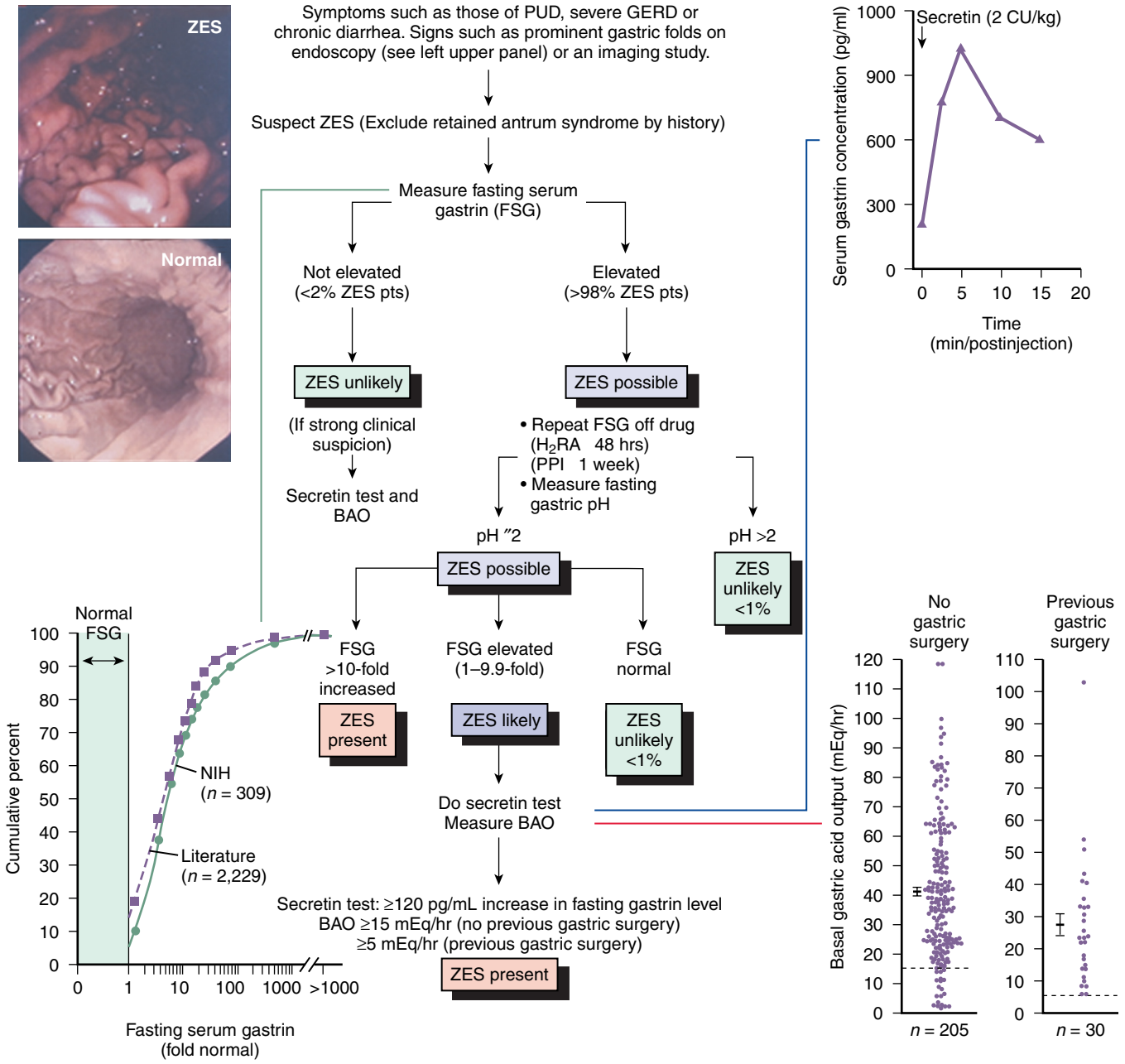

FIG. E1 Algorithm for the diagnosis of Zollinger-Ellison syndrome *(ZES).* *Right upper,* Typical ZES patient with a positive secretin test result (i.e., ≥120-pg/ml increase in fasting gastrin level). *Right lower,* Marked elevations in mean basal acid output (BAO) with or without previous gastric acid–reducing surgery. The dotted horizontal lines show the proposed criterion of >15 mEq/hr or >5 mEq/hr proposed to distinguish patients with ZES from those without ZES. *Left upper,* Prominent gastric folds found on endoscopy in a ZES patient, compared with a normal subject. *Left lower,* Fasting serum gastrin levels in ZES expressed as a multiple of the upper limit of normal on the horizontal axis. Very few patients had normal values; 60% had less than tenfold serum gastrin increases. *CU,* Clinical units. (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Saunders.)

localization studies are summarized in Table E2

- Diagnosis of peptic ulcer:
  1. Endoscopy
- Gastric acid secretion:
  1. Serum gastrin level (fasting) >150 pg/ml (criterion for diagnosis is serum gastrin >1000 pg/ml) (causes of false-positive results: Pernicious anemia, renal failure, retained gastric antrum syndrome, diabetes mellitus, rheumatoid arthritis)
- Provocative gastrin level tests:
  1. Secretin stimulation
  2. Calcium stimulation
  3. Standard test meal stimulation
- Gastrinoma localization:
  1. Arteriography
  2. Abdominal sonography
  3. Abdominal CT scan
  4. Abdominal MRI/PET scan
  5. Selective portal vein branch gastrin level
  6. Octreotide scan

Rx TREATMENT

- Surgical resection of the gastrinoma (note: 90% of gastrinomas can be located, resulting in a 40% overall cure rate).
- Total gastrectomy or vagotomy (palliative in some patients).
- Medical treatment:

TABLE E2 Sensitivities of Gastrinoma Localization Studies

Study	% of Tumors Localized			
	Overall	Pancreas	Duodenum	Liver Metastases
Preoperative				
Noninvasive				
Transabdominal ultrasonography	20-30			14
Abdominal computed tomography	50	80	35	50
Abdominal magnetic resonance imaging	25			83
Octreoscan	71-90		50	
DOTA scan	>90	>90	>60-90	>90
Invasive				
Endoscopic ultrasonography	85	75-100	28-57	
Intraoperative				
Palpation	65	91	60	
Intraoperative ultrasonography	83	95	58	
Duodenotomy	–	–	100	

From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.

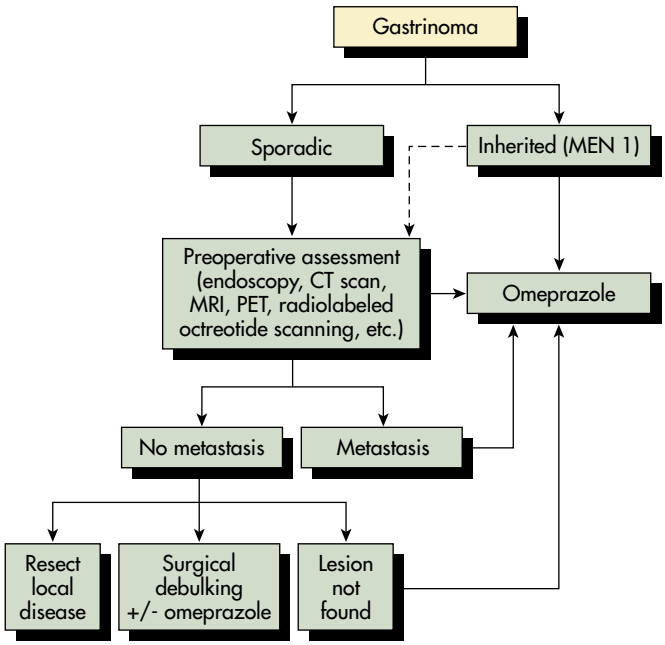

FIG. E2 Treatment algorithm for the management of a patient with gastrinoma. In some circumstances, patients with familial gastrinoma may also be candidates for surgical resection if disease is highly limited *(dotted line)*. *CT,* Computed tomography; *MEN 1,* multiple endocrine neoplasia type 1; *MRI,* magnetic resonance imaging; *PET,* positron emission tomography. (From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

1. Proton pump inhibitors (e.g., omeprazole, lansoprazole) is the mainstay of therapy.
2. Somatostatin or octreotide has an antiproliferative effect and controls diarrhea symptoms.
3. Targeted therapy: Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), has shown a survival benefit in patients with advanced pancreatic neuroendocrine tumors, with low rates of severe adverse events. Another oral tyrosine kinase inhibitor, sunitinib, has also shown encouraging results on prolongation of survival in this setting.
4. The use of a radioactive-labeled isotope lutetium Lu 177-dotatate has demonstrated a survival benefit in gastroenteric-pancreatic neuroendocrine tumors. It binds to somatostatin receptors to deliver radiation directly into tumor cells and is superior to octreotide depot in this setting.
5. Chemotherapy for metastatic gastrinoma with streptozotocin, 5-fluorouracil, and doxorubicin is of limited benefit.

- Fig. E2 describes a treatment algorithm for gastrinoma.

PROGNOSIS

Five-yr survival:

- Two thirds of all patients
- 20% with liver metastases
- 90% without liver metastases

REFERRAL

To gastroenterologist, surgeon, and medical oncologist (upon development of metastatic disease)

RELATED CONTENT

Gastrinoma (Zollinger-Ellison Syndrome) (Patient Information)

AUTHOR: **Bharti Rathore, MD**

SUGGESTED READINGS

Cives M, Strosberg JR: Gastroenteropancreatic neuroendocrine tumors, *CA Cancer J Clin* 68(6):471-487, 2018.

Epelboym I et al: Zollinger-Ellison syndrome: classical considerations and current controversies, *Oncologist* 19(1):44-50, 2014.

Raymond E et al: Sunitinib malate for the treatment of pancreatic neuroendocrine tumors, *N Engl J Med* 364:501-513, 2011.

Strosberg J et al: Phase 3 trial of 177Lu-dotatate for midgut neuroendocrine tumors, *N Engl J Med* 376(2):125-135, 2017.

Yao JC et al: Everolimus for advanced neuroendocrine tumors, *N Engl J Med* 364:514-523, 2011.

BASIC INFORMATION

DEFINITION

Histologically, *gastritis* refers to inflammation in the stomach. Endoscopically, gastritis refers to a number of abnormal features such as erythema, erosions, and subepithelial hemorrhages. Gastritis can also be subdivided into erosive, nonerosive, and specific types of gastritis with distinctive features both endoscopically and histologically.

SYNONYMS

Erosive gastritis
Hemorrhagic gastritis
Helicobacter pylori gastritis

ICD-10CM CODES

K29.00	Acute gastritis without bleeding
K29.01	Acute gastritis with bleeding
K29.20	Alcoholic gastritis without bleeding
K29.21	Alcoholic gastritis with bleeding
K29.30	Chronic superficial gastritis without bleeding
K29.31	Chronic superficial gastritis with bleeding
K29.40	Chronic atrophic gastritis without bleeding
K29.41	Chronic atrophic gastritis with bleeding
K29.50	Unspecified chronic gastritis without bleeding
K29.51	Unspecified chronic gastritis with bleeding
K29.60	Other gastritis without bleeding
K29.61	Other gastritis with bleeding
K29.70	Gastritis, unspecified, without bleeding
K29.71	Gastritis, unspecified, with bleeding
K52.81	Eosinophilic gastritis or gastroenteritis

EPIDEMIOLOGY & DEMOGRAPHICS

- Erosive and hemorrhagic gastritis is most commonly seen in patients taking nonsteroidal antiinflammatory drugs (NSAIDs), alcoholics, and critically ill patients (usually on ventilator support).
- *H. pylori* infection with gastritis is believed to be present in 30% to 50% of the population; however, the majority are asymptomatic.
- The prevalence of *H. pylori* infection increases with age from <10% in whites <40 yr to >50% in patients >50 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with gastritis generally present with nonspecific clinical signs and symptoms (e.g., epigastric pain, abdominal tenderness, bloating, anorexia, nausea [with or without vomiting]). Symptoms may be aggravated by eating
- Epigastric tenderness in acute alcoholic gastritis (may be absent in chronic gastritis)
- Foul-smelling breath
- Hematemesis ("coffee grounds" emesis)

ETIOLOGY

- Alcohol, NSAIDs, stress (critically ill patients usually on mechanical respiration), hepatic or renal failure, multiorgan failure
- *H. pylori* infection
- Bile reflux, pancreatic enzyme reflux
- Gastric mucosal atrophy, portal hypertension gastropathy
- Irradiation

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Peptic ulcer disease
- Gastroesophageal reflux disease
- Nonulcer dyspepsia
- Gastric lymphoma or carcinoma
- Pancreatitis
- Gastroparesis

WORKUP

Diagnostic workup includes a comprehensive history and endoscopy with biopsy.

LABORATORY TESTS

- *H. pylori* testing by urea breath test, stool antigen test (*H. pylori* stool antigen), endoscopic biopsy, or specific antibody test is recommended.
  1. The urea breath test documents active infection (sensitivity and specificity >90%). It uses a flat breath card read by a small analyzer.
  2. The stool antigen test is an enzymatic immunoassay (ELISA) that identifies *H. pylori* antigen in a stool specimen with a polyclonal anti–*H. pylori* antibody. It is as accurate as the urea breath test for diagnosis of active infection and follow-up evaluation of patients treated for *H. pylori.* A negative result on the stool antigen test 8 wk after completion of therapy identifies patients in whom eradication of *H. pylori* was successful.
  3. Histologic evaluation of endoscopic biopsy samples is considered by many the gold standard for accurate diagnosis of *H. pylori* infection. However, detection of *H. pylori* depends on the site and number of biopsy samples, the method of staining, and experience of the pathologist.
  4. Serologic testing for antibodies to *H. pylori* is easy and inexpensive; however, the presence of antibodies demonstrates previous but not necessarily current infection. Antibodies to *H. pylori* can remain elevated for months to yrs after infection has cleared; therefore antibody levels must be interpreted in light of patient's symptoms and other test results (e.g., peptic ulcer disease [PUD] seen on upper gastrointestinal series).
- Vitamin B_{12} level in patients with atrophic gastritis.
- Hematocrit (low if significant bleeding has occurred).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of mucosal irritants such as alcohol and NSAIDs
- Lifestyle modifications with avoidance of tobacco and foods that trigger symptoms

ACUTE GENERAL Rx

- Eradication of *H. pylori,* when present, can be accomplished with various regimens:
  1. Quadruple therapy: Proton pump inhibitor (PPI) (omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, rabeprazole 20 mg) bid *plus* clarithromycin 500 mg BID plus amoxicillin 1000 mg bid *plus* metronidazole 500 mg BID for 14 days.
  2. Triple therapy: PPI bid *plus* clarithromycin 500 mg bid *and* metronidazole 500 mg bid for 14 days. This regimen is useful in those with penicillin allergy.
  3. Triple therapy: Clarithromycin 500 mg BID plus amoxicillin 1 g BID plus PPI BID for 14 days. Useful only in areas with clarithromycin resistance <15%.
  4. Bismuth quadruple therapy: Bismuth subsalicylate (e.g., Pepto-Bismol) 525 mg QID plus metronidazole 500 mg QID plus tetracycline 500 mg QID plus PPI BID for 14 days.
- Prophylaxis and treatment of stress gastritis with sucralfate suspension 1 g orally q4 to 6h, H_2-receptor antagonists, or PPIs in patients on ventilator support.

CHRONIC Rx

- Omeprazole, H2RB, or sucralfate in patients receiving long-term NSAIDs.
- Avoidance of alcohol, tobacco, and prolonged NSAID or corticosteroid use.

DISPOSITION

- Patients should be tested for eradication ≥4 weeks after completion of therapy. Undetectable stool antigen tested at least 4 wk after therapy accurately confirms cure of *H. pylori* infection in initially seropositive healthy subjects with reasonable sensitivity. PPI therapy should be stopped at least 2 wk prior to testing.
- Surveillance gastroscopy in patients with atrophic gastritis (increased risk of gastric cancer).

RELATED CONTENT

Gastritis (Patient Information)
Helicobacter pylori Infection (Related Key Topic)
Peptic Ulcer Disease (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

BASIC INFORMATION

DEFINITION

- Gastroenteritis is a broad term used for various gastrointestinal pathologic states. The main manifestation is diarrhea, defined as daily stool of at least 200 g, often accompanied by nausea, vomiting, malaise, anorexia, fever, abdominal pain, and dehydration. Gastroenteritis is usually self-limited, but if it is not managed properly, it can lead to a prolonged course. It usually lasts less than 7 days and not longer than 2 weeks. Diarrhea lasting more than 14 days is chronic or persistent.
- May be caused by viruses, bacteria, or parasites. Viruses are responsible for acute gastroenteritis in most patients.
- Gastroenteritis is a common cause of morbidity/mortality around the world. In the developing world, it is a leading cause of death.

ICD-10CM CODES

K52.9	Non-infective gastroenteritis and colitis
558.3	Allergic gastroenteritis and colitis
K52.1	Infectious gastroenteritis and colitis
K52.0	Gastroenteritis and colitis due to radiation

EPIDEMIOLOGY & DEMOGRAPHICS

- Frequency is difficult to determine. Gastroenteritis is underreported in adults. It accounts for about 250,000 hospitalizations each yr.
- Statistics on sporadic cases of adult viral gastroenteritis are not known. Norovirus is the leading cause of medically attended acute gastroenteritis in U.S. children and is associated with nearly 1 million health care visits annually.
- It is estimated that there are 1.5 billion cases a yr worldwide.
- It is the leading cause of death in many developing countries. Children under the age of 5 yr are most vulnerable.
- Viral gastroenteritis may be transmitted by the fecal-oral route, by asymptomatic carriers, or by symptomatic patients before the symptoms start.
- Traveler diarrhea affects 20% to 50% of residents of industrialized countries who travel to developing countries.

PREDOMINANT SEX:

- No sexual predilection
- Higher mortality seen in women
- Females have a higher incidence of *Campylobacter* infections

PREDOMINANT AGE:

- May occur at any age
- High morbidity and mortality in the very young (younger than 5 yr), the elderly (people aged 65 or older), and the immunosuppressed

RISK FACTORS

- Use of proton pump inhibitors (PPI) may increase the risk of developing gastroenteritis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Diagnosis is made clinically. Laboratory studies are not routinely necessary.
- A well-taken history is important. The onset, duration, and frequency of diarrhea should be noted. The aim of the physical examination is to assess the patient's degree of hydration. This also helps to identify the cause of diarrhea and identify patients at risk of complications.
- Viral gastroenteritis has a short prodrome with vomiting, mild fever, and nonbloody and watery diarrhea, usually for 1 to 4 days.
- Bacterial gastroenteritis presents with high fever, bloody diarrhea, severe abdominal pain, and at least 6 stools in a 24-hour period.
- Patients usually present with:
  1. Diarrhea: Usually more than 6 stools a day indicates bacterial cause of gastroenteritis.
  2. Vomiting.
  3. Abdominal pain.
  4. Mucus and/or blood in stool: Indicating bacterial or parasitic infection.
  5. Fever.
  6. Dehydration: This is the main cause of morbidity and mortality. Check for lethargy, dry mucous membrane, poor skin turgor, sunken eyes as signs of dehydration.
  7. Malnutrition: This occurs when diarrhea is chronic. There is reduced muscle and fat mass.
  8. Abdominal pain: This is a very common symptom in gastroenteritis.
  9. Borborygmi: There is significantly increased peristaltic activity, which may cause audible or palpable bowel activity.
  10. Perianal erythema: Secondary to constantly wet area. Wet buttock and perianal area may result in redness and skin breakdown.

ETIOLOGY

- Viral gastroenteritis (in adults)
  1. The caliciviruses, such as *Norovirus* genogroup I (e.g., Norwalk), *Norovirus* genogroup II (e.g., South Hampton), *Sapovirus* (e.g., Sapporo)
  2. Nongroup A *Rotavirus*
  3. *Astrovirus*
  4. Adenovirus
- Bacterial gastroenteritis: The top three leading causes of bacterial diarrhea worldwide are *Salmonella, Shigella,* and *Campylobacter* spp.
  1. *Salmonella* (eggs, dairy)
  2. *Shigella*
  3. *Campylobacter* (dairy, poultry)
  4. *Aeromonas species* (seafood, oysters)
  5. *Yersinia* (pork)
  6. Enterohemorrhagic *Escherichia coli* (ground beef)
  7. E. coli
  8. *Clostridium perfringens* (pork, vegetables)
- Parasitic gastroenteritis
  1. *Giardia*
  2. *Cryptosporidium*
  3. *Microsporidia*
  4. *Cyclospora*
- Traveler diarrhea
  1. Usually caused by Enterotoxigenic *E. coli,* but other organisms implicated include *Salmonella, Shigella,* and *Campylobacter*.
  2. Risk is highest in travelers to Africa, but it is also common in travelers to Portugal, Spain, and some Eastern European countries.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Amebiasis
- Appendicitis
- Celiac disease
- Inflammatory bowel disease (ulcerative colitis, Crohn disease)
- Colon cancer
- Bowel obstruction
- Botulism
- Hemolytic uremic syndrome
- Food poisoning
- Intraabdominal abscess
- Cholera

WORKUP

- In most cases laboratory tests are not indicated.
- Further workup is indicated in patients who:
  1. Have persistent diarrhea
  2. Are extremely dehydrated
  3. Appear seriously ill
  4. Have high fever
  5. Present with severe abdominal pain
  6. Have bloody diarrhea
  7. Have persistent nausea

LABORATORY TESTS

- Routine laboratory tests:
  1. Tests such as CBC and BMP may not be indicated in making a diagnosis. However, electrolytes and BUN are indicated in patients with severe diarrhea or dehydration.
  2. CBC is indicated with severe diarrhea or toxicity. WBC is increased in *Salmonella* infection; eosinophilia is present in parasitic infections.
- Stool studies:
  1. Presence of blood/leukocytes in stool may indicate inflammatory diarrhea.
  2. In *Salmonella* or *Shigella* infections there is an increased fecal leukocyte.
  3. Stool leukocytes are absent in viral diarrhea.
- Stool culture:
  1. Are only useful when positive
  2. Usually not necessary in most cases of diarrhea
  3. Indications for stool cultures include: Bloody stools; prolonged, untreated diarrhea; fever; leukocytes in stool; immunosuppressed patients; immunocompromised patients; and patients who have traveled to remote, exotic, or developing nations. It should also be considered in patients with concurrent or very recent use of antibiotics to rule out *Clostridium difficile* infection as a cause of the diarrhea

- Examination for ova and parasites (O&P) is indicated in immunosuppressed patients, immunocompromised patients, and patients who have traveled to remote, exotic, or developing nations.

IMAGING STUDIES

- In patients with suspected bowel obstruction, perforation, or toxic megacolon, abdominal series is warranted.
- Consider CT scan of the abdomen in older patients with severe abdominal pain.

Rx TREATMENT

GENERAL CONSIDERATIONS

- Most infectious diarrhea is self-limited. Medical care is mainly supportive. Fig. E1 describes an approach to the management of gastroenteritis.
- It is important to assess the degree of dehydration by checking BP, pulse, HR, skin turgor, mucous membrane, thirst, urine output, and mental status change.
- Oral rehydration therapy is very important in diarrhea treatment.
- Consider intravenous rehydration when oral rehydration fails. Watch out for potassium depletion.
- Early re-feeding decreases recovery time.

Principles of treatment include:

- Rehydration: Orally or intravenously, PRN
- Treatment of symptoms such as fever, abdominal pain, nausea, vomiting as needed
- Identify and treat complications

REHYDRATION:

- Oral hydration products include Naturalyte, Rehydralyte.
- Intravenous solutions used include dextrose 5% in 0.5 isotonic NaCl with 50 mEq $NaHCO_3$ and 10 to 20 mEq KCl.
  1. Indications for IV hydration include intractable vomiting, severe dehydration, change in mental status or consciousness, and ileus.
  2. Oral hydration is not appropriate due to environmental conditions.

TREATMENT OF SYMPTOMS:

- Infectious diarrhea sometimes requires empiric treatment with antibiotics. Foodborne toxigenic diarrhea usually does not.
- Traveler diarrhea: Patients without fever or dysentery may be treated with rifaximin 200 mg thrice daily for 3 days, or ciprofloxacin 500 mg twice daily or 750 mg daily for 1 to 3 days; patients with fever or dysentery can be treated with azithromycin 1000 mg in a single dose.
- *C. difficile* diarrhea and parasitic infestations with *Giardia* or *Entamoeba* are treated with metronidazole or vancomycin. For *C. difficile*, it is important to discontinue the causative antibiotic.
- Treat severe nausea and vomiting with antiemetics.
- Antidiarrheal agents may be useful for systemic relief in mild to moderate diarrhea.
- Loperamide (Imodium) or bismuth subsalicylate (Pepto-Bismol) may provide limited relief in traveler or nonbloody diarrhea.

Dietary measures may include:

- Start with banana, rice, applesauce, toast diet (BRAT diet)
- As early as possible introduce lean meats and clear liquid

In recent yrs the use of probiotics (nonpathogenic live microorganism) has increased; however, recent multicenter trials of combination probiotic (combined *L. rhamnosus-L. helveticus* given twice/day) for children with gastroenteritis did not show any significant benefit and should not be recommended in young children with acute gastroenteritis.[1]

REFERRAL

Referral to infectious disease or gastroenterologist specialist may be indicated in patients:

- With diarrhea lasting more than 7 days
- Hypernatremia
- Severe dehydration associated with cardiovascular symptoms
- In whom a parasitic etiology is suspected
- With *C. difficile* resistant to treatment with metronidazole and vancomycin
- With HIV/AIDS, immunocompromised
- With clinical features indicating extraintestinal involvement (e.g., meningitis, sepsis, pneumonia) or another etiology (e.g., hemolytic uremic syndrome)
- Who relapse

[1]Freedman SB et al: Multicenter trial of a combination probiotic for children with gastroenteritis, *N Engl J Med* 379:2015-26, 2018.

PEARLS AND CONSIDERATIONS

PREVENTION

- Perform proper hand washing before and after eating and after each bowel movement to prevent spread to family members.
- Avoid (raw) shellfish served in certain unregulated places.
- Avoid raw or undercooked eggs and/or poultry.
- Wash all produce before consumption.
- For travelers to high-risk areas:
  1. Eat only cooked foods.
  2. Drink hot or carbonated beverages.
  3. Avoid water, raw peeled fruits/vegetables, green leafy vegetables, and street food sold by street vendors.
  4. Vaccines are available for *Salmonella typhi* and *Vibrio cholerae* (the latter provides about 50% protection for 3 to 6 months).

PATIENT & FAMILY EDUCATION

- Stress the importance of oral rehydration.
- Stress the need for early appropriate feeding.
- Relapse occurs due to dietary noncompliance.
- Travelers to developing areas should be educated on proper avoidance measures and treatment.
- Also stress the importance of good hygiene, hand washing, safe food preparation, and access to clean water as key in preventing gastroenteritis.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Clostridium difficile Infection (Related Key Topic)
Gastroenteritis (Patient Information)
Giardiasis (Related Key Topic)
Traveler Diarrhea (Related Key Topic)

AUTHOR: **Daniel K. Asiedu, MD, PhD, FACP**

SUGGESTED READINGS

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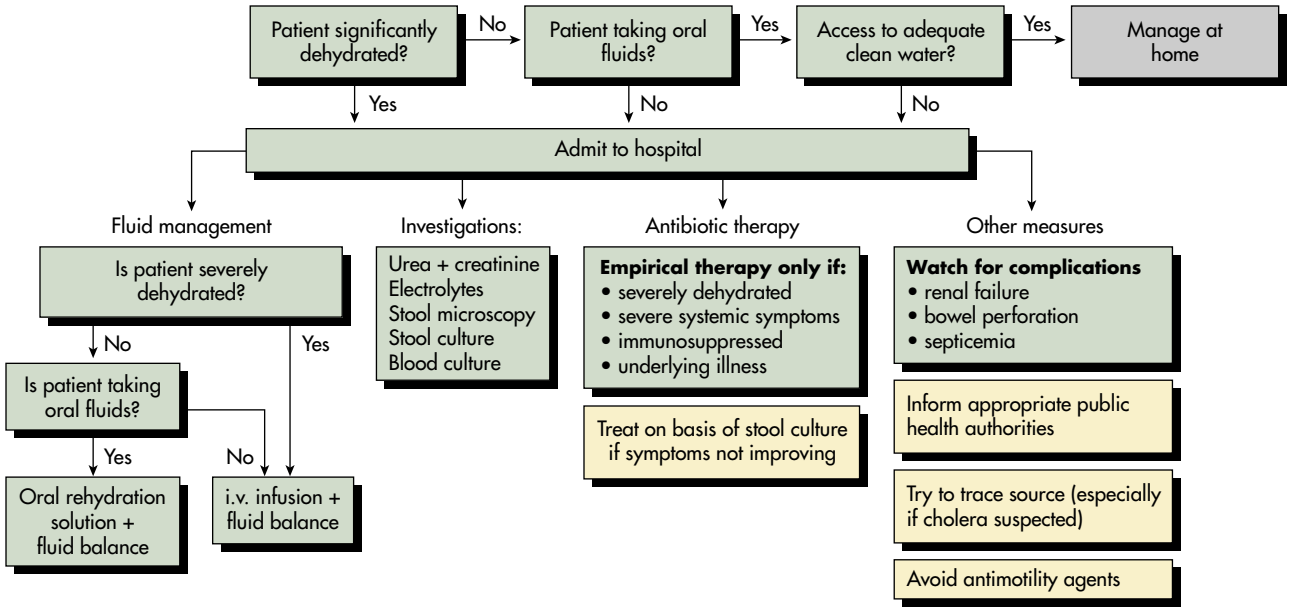

FIG. E1 Management of gastroenteritis. (From Currie G, Douglas G: *Flesh and bones of medicine,* St Louis, 2011, Mosby, pp 8-9.)

BASIC INFORMATION

DEFINITION

Gastroesophageal reflux disease (GERD) is a motility disorder characterized primarily by heartburn and caused by the reflux of gastric contents into the esophagus. A current definition is a condition that develops when the reflux of stomach contents causes at least two heartburn episodes per week and/or complications. Table 1 describes a classification system for esophagitis.

SYNONYMS

Peptic esophagitis
Reflux esophagitis
GERD

ICD-10CM CODES

K21.9 Gastroesophageal reflux disease without esophagitis
R12 Heartburn

EPIDEMIOLOGY & DEMOGRAPHICS

- GERD is one of the most prevalent gastrointestinal disorders. It is the most common GI diagnosis recorded during visits to outpatient clinics. From 14% to 20% of adults are affected.
- Nearly 7% of persons in the United States have heartburn daily, 20% have it monthly, and 60% have it intermittently. Incidence in pregnant women exceeds 80%.
- Nearly 20% of adults use antacids or over-the-counter H_2 blockers at least once a week for relief of heartburn.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination: Generally unremarkable
- Clinical signs and symptoms: Heartburn, dysphagia, sour taste, regurgitation of gastric contents into the mouth
- Chronic cough and bronchospasm
- Chest pain, laryngitis, early satiety, abdominal fullness, and bloating with belching
- Dental erosions in children

TABLE 1 Los Angeles Endoscopic Classification System for Esophagitis

Grade A	One or more mucosal breaks confined to folds, ≤5 mm
Grade B	One or more mucosal breaks >5 mm confined to folds but not continuous between the tops of mucosal folds
Grade C	Mucosal breaks continuous between tops of two or more mucosal folds but not the circumferential
Grade D	Circumferential mucosal break

From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

ETIOLOGY

- Incompetent lower esophageal sphincter (LES) (see Fig. E1)
- Medications that lower LES pressure (calcium channel blockers, alpha-adrenergic antagonists, nitrates, theophylline, anticholinergics, sedatives, prostaglandins).
- Foods that lower LES pressure (chocolate, yellow onions, peppermint). Table 2 summarizes modulators of lower esophageal sphincter (LES) pressure
- Tobacco abuse, alcohol, coffee
- Pregnancy
- Gastric acid hypersecretion
- Hiatal hernia (controversial) present in >70% of patients with GERD; however, most patients with hiatal hernia are asymptomatic
- Obesity is associated with a statistically significant increase in the risk for GERD symptoms, erosive esophagitis, and esophageal carcinoma

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Peptic ulcer disease
- Unstable angina
- Esophagitis (from infections such as herpes, *Candida*), medication induced (doxycycline, potassium chloride), eosinophilic esophagitis
- Esophageal spasm (nutcracker esophagus)
- Cancer of esophagus

WORKUP

- Aimed at eliminating the conditions noted in the differential diagnosis and documenting the type and extent of tissue damage. Generally, when symptoms of GERD are typical and the patient responds to therapy, there is no need for further diagnostic tests to verify the diagnosis.
- Upper GI endoscopy (Fig. E2) is useful to document the type and extent of tissue damage in persistent GERD and to exclude eosinophilic esophagitis and potentially malignant conditions such as Barrett esophagus. The American College of Physicians recommends endoscopy in the setting of GERD in people with heartburn and alarm symptoms (dysphagia, bleeding, anemia, weight loss, and recurrent vomiting). It is also indicated in people with GERD symptoms that persist despite a therapeutic trial of 4 to 8 wk of bid proton pump inhibitor (PPI) therapy in patients with severe erosive esophagus after a 2-mo course of PPI therapy to assess healing and rule out Barrett esophagus.

LABORATORY TESTS

- 24-hr esophageal pH monitoring with transnasal catheter or a 48-hr wireless capsule are sensitive diagnostic tests to assess the degree of acid exposure in the esophagus in patients not responding to acid-reducing therapy; however, they are not practical and generally not done. They are useful in patients with atypical manifestations of GERD, such as chest pain or chronic cough.
- High-resolution esophageal manometry (HRM) is indicated in patients with refractory reflux in whom surgical therapy is planned.
- *Helicobacter pylori* testing is not indicated in GERD.

IMAGING STUDIES

An upper GI series is useful in patients unwilling to have endoscopy or with medical contraindications to the procedure. It can identify ulcerations and strictures; however, it may

TABLE 2 Modulators of Lower Esophageal Sphincter (LES) Pressure

	Increase LES Pressure	Decrease LES Pressure
Hormones/peptides	Gastrin	CCK
	Motilin	Secretin
	Substance P	Somatostatin
		Vasoactive intestinal peptide
Neural agents	α-Adrenergic agonists	α-Adrenergic antagonists
	β-Adrenergic antagonists	β-Adrenergic agonists
	Cholinergic agonists	Cholinergic antagonists
Foods and nutrients	Protein	Chocolate
		Fat
		Peppermint
Other factors	Antacids	Barbiturates
	Baclofen	Calcium channel blockers
	Cisapride	Diazepam
	Domperidone	Dopamine
	Histamine	Meperidine
	Metoclopramide	Morphine
	Prostaglandin $F_2\alpha$	Prostaglandins E_2 and I_2
		Serotonin
		Theophylline

CCK, Cholecystokinin.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

miss mucosal abnormalities. Only one third of patients with GERD have radiographic signs of esophagitis on an upper GI series.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Lifestyle modifications with avoidance of foods (e.g., citrus- and tomato-based products, onions, spicy foods, carbonated beverages, mint, chocolate, fried foods) and drugs that exacerbate reflux (e.g., caffeine, β-blockers, calcium channel blockers, α-adrenergic agonists, theophylline)
- Avoidance of tobacco and alcohol use
- Elevation of head of bed (4 to 8 in) with blocks
- Avoidance of lying down directly after late or large evening meals, consumption of smaller and more frequent meals
- Weight reduction to BMI <25, decreased fat intake
- Avoidance of clothing that is tight around the waist

GENERAL Rx

- PPIs (esomeprazole 40 mg qd, omeprazole 20 mg qd, lansoprazole 30 mg qd, rabeprazole 20 mg qd, or pantoprazole 40 mg qd, or dexlansoprazole 30 mg) are generally safe, tolerated, and highly effective in most patients (Table E3). Omeprazole and esomeprazole are inhibitors of CYP2C19 and can increase serum concentrations of phenytoin and diazepam. Concomitant use of clopidogrel should also be avoided with omeprazole and esomeprazole. Increased risk of pneumonia has been documented in hospitalized patients. Long-term use of PPIs has been associated with increased risk of osteoporosis and patients should be warned about an increased risk of fractures with long-term use. Use of PPIs in patients with cirrhosis increases risk of spontaneous bacterial peritonitis and hepatic encephalopathy. Rare side effects of PPIs include acute interstitial nephritis, hypomagnesemia, and QT prolongation.
- H_2 blockers (nizatidine 300 mg qhs, famotidine 40 mg qhs) can be used but are generally much less effective than PPIs.
- Antacids (may be useful for relief of mild symptoms; however, they are generally ineffective in severe cases of reflux).
- Prokinetic agents (metoclopramide) are indicated only when PPIs are not fully effective. They can be used in combination therapy; however, side effects limit their use.
- Combination of PPE with an agent that reduces esophageal sphincter relaxation (baclofen) plus a neuromodulator (desipramine) may be tried in patients with refractory heartburn before considering surgery.
- For refractory cases: Think first, cut last. Surgery with Nissen fundoplication (Fig. E3). Potential surgical candidates should have reflux esophagitis documented by esophagogastroduodenoscopy and normal esophageal motility as evaluated by manometry. Surgery generally consists of reduction of hiatal hernia when present and placement of a gastric wrap around the gastroesophageal (GE) junction (fundoplication). Although laparoscopic fundoplication is now widely used, long-term medical therapy is a better choice for most patients who are willing to remain on daily acid-reduction medication. In patients preferring surgical intervention, surgery should not be advised with the expectation that patients with GERD will no longer need to take antisecretory medications or that the procedure will prevent esophageal cancer among those with GERD and Barrett esophagus. Approximately 17.7% of patients who undergo primary laparoscopic antireflux surgery will experience recurrent gastroesophageal reflux requiring long-term medication use or secondary antireflux surgery. Risk factors for recurrence are older age, female sex, and comorbidity.
- Endoscopic radiofrequency heating of the GE junction (Stretta procedure) is a treatment modality for GERD patients unresponsive to traditional therapy. Its mechanism of action remains unclear. Endoscopic gastroplasty (EndoCinch procedure) is also aimed at treating GERD. Initial results appear encouraging; however, long-term studies are needed before recommending these procedures. A newer surgical approach to GERD is the LINX antireflux device (Figs. E4 and E5).
- Lifestyle modification must be followed for life because GERD is generally an irreversible condition in most patients.

DISPOSITION

- Recurrence of reflux is common if treatment is discontinued. Preliminary trials have shown that in patients with severe reflux esophagitis successfully treated with PPI therapy, stopping PPI medication was associated with T lymphocyte–predominant esophageal inflammation and basal cell and papillary hyperplasia without loss of surface cells.
- The majority of patients respond well to therapy. In patients with chronic GERD, long-term outcomes are similar between medical therapy with PPIs and anti-reflux surgery. Prolonged use of PPIs is associated with increased risk of fractures of hip, wrist, and spine; increased risk of diarrhea from *Clostridium difficile;* pneumonia; and possible iron deficiency from impaired iron absorption. PPIs also block the effects of clopidogrel by inhibiting cytochrome P450 2C19 isozyme. Therefore all PPIs (other than pantoprazole) should be avoided in patients using clopidogrel. H_2 blockers can be used for patients with GERD taking clopidogrel.
- Postsurgical complications occur in nearly 20% of patients (dysphagia, gas, bloating, diarrhea, nausea). Long-term follow-up studies also reveal that within 3 to 5 yr, 52% of patients who had undergone antireflux surgery are taking antireflux medications again.

REFERRAL

- There is a strong and probably causal relation between symptomatic prolonged and untreated GERD, Barrett esophagus, and esophageal adenocarcinoma. GI referral for upper endoscopy is needed when there are concerns about associated peptic ulcer disease, Barrett esophagus, or esophageal cancer.
- Patients with Barrett esophagus should undergo surveillance endoscopy with mucosal biopsy every 2 yr or less because the risk of developing adenocarcinoma of esophagus is at least 30 times greater than that of the general population.
- Testing and treating for *Helicobacter pylori* in patients with GERD has not been shown to improve symptoms.
- All children with dental erosions should be evaluated for GERD.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Gastroesophageal Reflux Disease (GERD) (Patient Information)
Achalasia (Related Key Topic)
Dysphagia (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

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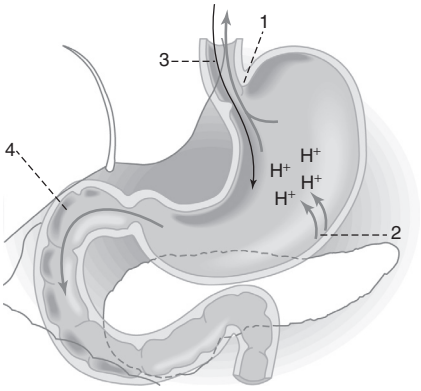

FIG. E1 Pathogenesis of gastroesophageal reflux disease: *(1)* impaired lower esophageal sphincter—low pressures or frequent transient lower esophageal sphincter relaxation; *(2)* hypersecretion of acid; *(3)* decreased acid clearance resulting from impaired peristalsis or abnormal saliva production; *(4)* delayed gastric emptying or duodenogastric reflux of bile salts and pancreatic enzymes. (From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, WB Saunders.)

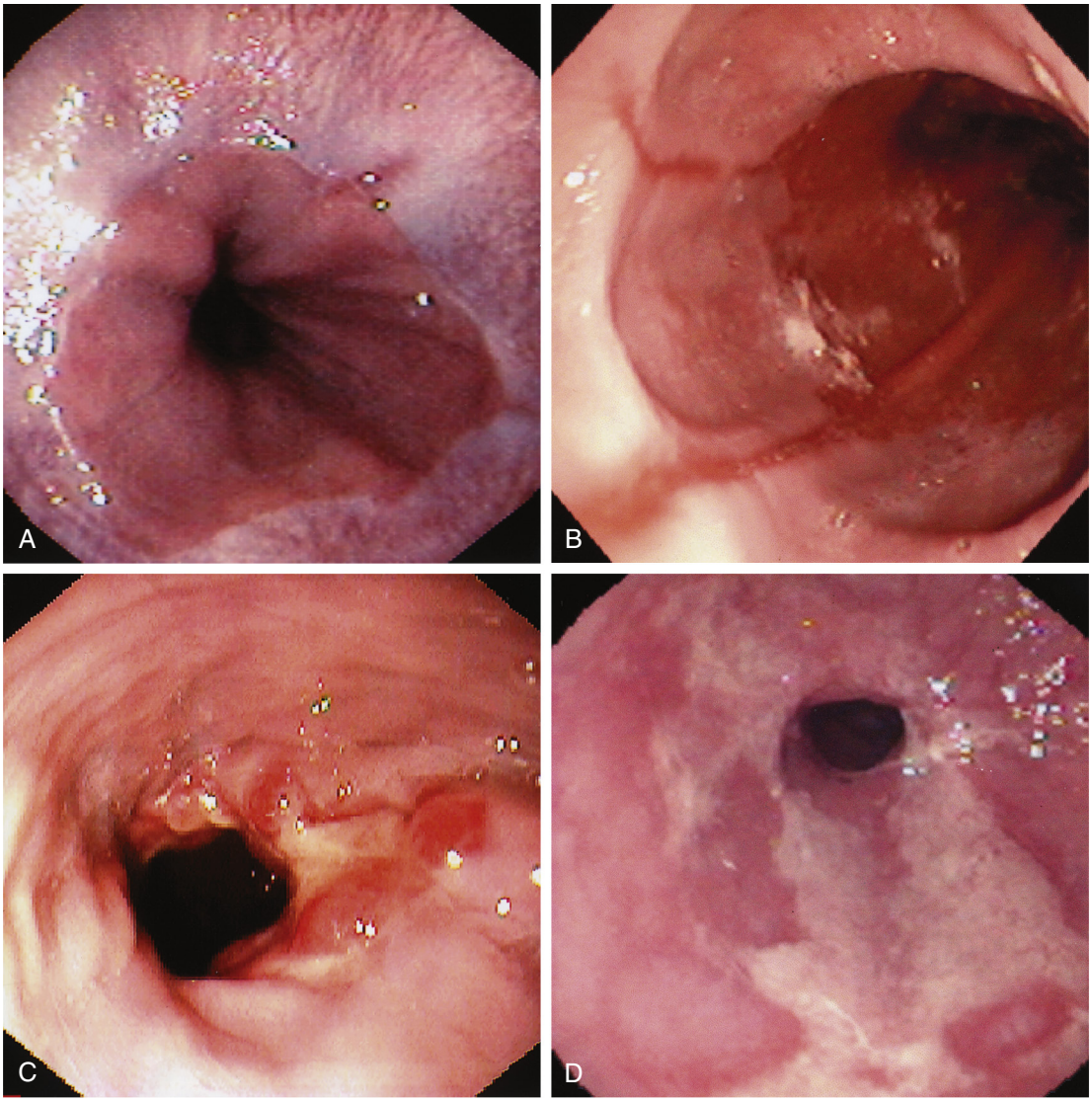

FIG. E2 Endoscopic photographs of the four grades of esophagitis (A to D) using the Los Angeles classification system as outlined in Table 1. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

TABLE E3 Drug Therapy for Esophageal Disorders

Agent	Dose
Antacids: Liquid (to Buffer Acid and Increase LESP)	
For example, Mylanta II/Maalox TC (acid-neutralizing capacity, 25 mEq/5 ml)*	15 ml qid 1 hr after meals and at bedtime or as needed
Gaviscon (to Decrease Reflux via a Viscous Mechanical Barrier and Buffer Acid)	
$Al(OH)_3$, $NaHCO_3$, Mg trisilicate, alginic acid	2-4 tablets qid at bedtime or as needed
H_2-Receptor Antagonists (to Decrease Acid Secretion)	
Famotidine	20-40 mg bid or 2.5-5 ml bid
Nizatidine	150 mg bid
Proton Pump Inhibitors (to Decrease Acid Secretion and Gastric Volume)†	
Omeprazole	20 mg/day; maintenance dose, 20 mg/day
Lansoprazole	30 mg/day; maintenance dose, 15 mg/day
Pantoprazole	40 mg/day; maintenance dose, 40 mg/day
Rabeprazole	20 mg/day; maintenance dose, 20 mg/day
Esomeprazole	20-40 mg/day; maintenance dose, 20 mg/day
Dexlansoprazole	30-60 mg/day; maintenance dose, 30 mg/day

*Patients with reflux are not generally hypersecretors of gastric acid, so the therapeutic doses of antacids are based on their capacity to buffer (normal) basal acid secretion rates of approximately 1 to 7 mEq/hr (mean, 2 mEq/hr) and peak meal-stimulated acid secretion rates of about 10 to 60 mEq/hr (mean, 30 mEq/hr).
†High-dose therapy is a twice-daily administration of the usual daily dose.
bid, Twice a day; *LESP,* lower esophageal sphincter pressure; *mEq,* milliequivalent; *qid,* four times a day.
Modified from Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.

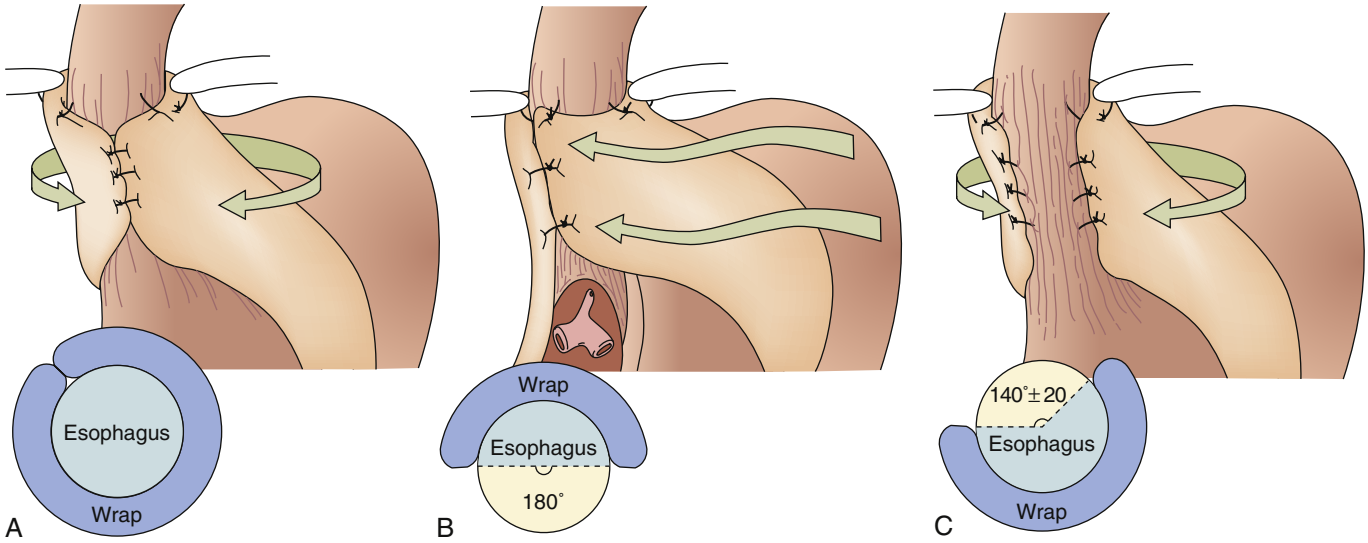

FIG. E3 Three types of fundoplication. A, A 360-degree fundoplication. **B,** Partial anterior fundoplication. **C,** Partial posterior fundoplication. (From Yates RB et al: Gastroesophageal reflux disease and hiatal hernia. In Townsend CM et al [eds]: *Sabiston textbook of surgery,* ed 20, Philadelphia, 2017, Elsevier.)

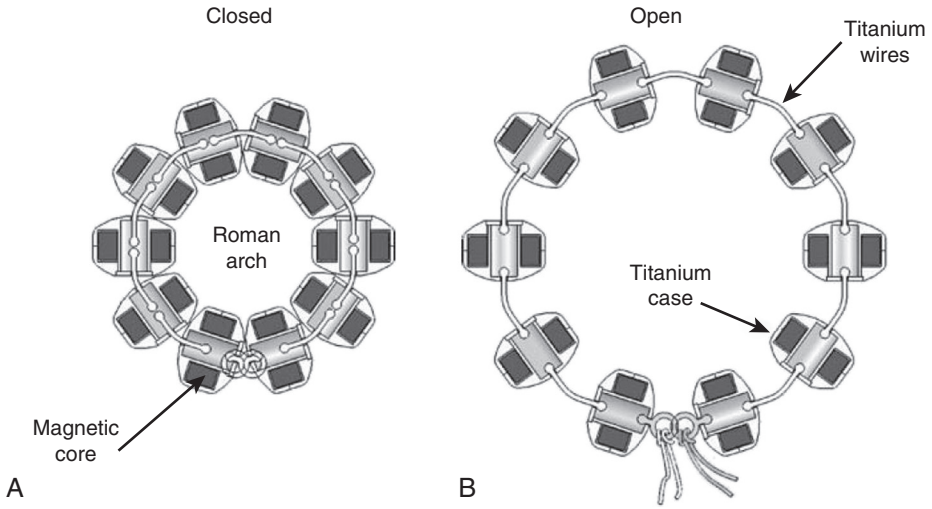

FIG. E4 An engineering schematic of the magnetic sphincter augmentation device. The device consists of an expansible bracelet of magnetic beads designed to be placed surgically around the exterior surface of the distal end of the lower esophageal sphincter (LES). Each bead is composed of a titanium case containing a magnetic core of small, disk-shaped magnets. The beads are connected by titanium wires of specific lengths that limit the distance any two individual beads can move apart. When the device is closed **(A),** the magnetic force is sufficient to prevent effacement and opening of the LES yet is weak enough to allow the device to open **(B)** with the esophageal peristalsis. When the device is closed, the Roman arch construction prevents compression of the esophageal tissues. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

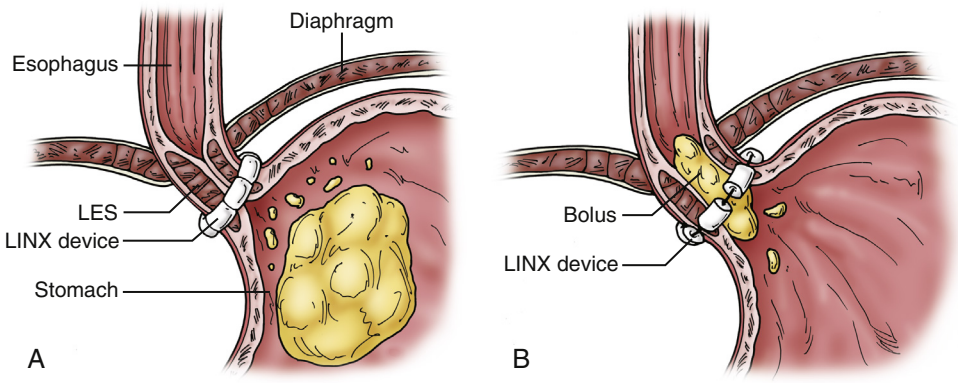

FIG. E5 The LINX magnetic sphincter augmentation device is implanted around the inferior border of the lower esophageal sphincter *(LES)* as shown. A, The magnetic device in the closed position, which prevents effacement and opening of the LES and subsequent reflux. Each magnetic bead rests on the adjacent beads to prevent compression of the esophageal tissues. **B,** The device in the open position, which allows transport of food by esophageal peristalsis, belching of an overdistended stomach, and vomiting when necessary. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

Gender Dysphoria and Gender Nonconformity

BASIC INFORMATION

DEFINITION

Transgender or *gender diverse (TGD) identity* is an umbrella term when a person's perceived and innate sense of being male or female (i.e., gender identity) is at odds with the natal assigned gender based on chromosomes, hormones, organs, and eventually secondary sexual characteristics. For some TGD persons, gender dysphoria may result when an individual's gender identity is incongruent with the person's assigned gender, with discomfort and dislike of one's external gender characteristics and a desire to be physically different from the gender born into or assigned at birth. Other TGD persons may not experience dysphoria or distress but understand their gender in a way that varies from a male-female binary. Transition is a social, medical, and surgical process, whereby TGD persons present in the gender with which they identify. Transition is typically divided into three types (reversible, partially reversible, and irreversible), but should be tailored to the individual throughout the life span while also providing comprehensive medical care.

SYNONYMS

Gender dysphoria/gender incongruence
GD/GI
TGD
Transgender–Gender diverse; gender dysphoria in children, adolescents, adults
Transgender-gender diverse identity
Transsexual

ICD-10CM CODES
For the purposes of medical care for transgender individuals, ICD-10 codes are already inaccurate and do not represent and reflect current standards and understanding of gender development. The diagnostic entity of gender identity disorder has been rejected as pathologizing and inappropriate per DSM-5 psychiatric coding.

F64.0	Transsexualism
F64.2	Gender identity disorder of childhood
F64.9	Gender identity disorder, unspecified
F64.8	Other gender identity disorder
E34.9	Endocrine, Hormones Disease of, Disorder(s), Dysfunction(s), Disturbance, Complication(s) from

DSM-5: See note above regarding DSM-5.

EPIDEMIOLOGY & DEMOGRAPHICS

DEVELOPMENT & BACKGROUND: Gender development begins as early as 18 mo. By age 2 to 4 yr, children understand gender differences and use pronouns such as "him" and "her." Toddlers identify their own gender, and most consider gender a stable personal trait at age 5 to 6 yr. All children partake in gender play and explore gender activities, behaviors, and roles. Gender play does not mean a child is dysphoric, dislikes his or her gender, or identifies as the other gender. Gender diversity in prepubertal yrs is more than gender play; nonconforming prepubertal children exhibit *consistent, persistent, and insistent* play, dress, attributes, and activities of the other gender. Some of these children, but not all, experience dysphoria regarding their genitalia or express mild to intense discomfort and dislike of their biologic gender. Some, but not all, gender nonconforming prepubertal children may verbally assert that they are or need to be the other gender. Some TGD children, adolescents, and adults have more fluid interpretations of gender and do not easily fit into a masculine versus feminine binary. As we talk more with patients, we learn more and more about the inherent diversity of gender.

PREDOMINANT AGE: Incidence may be heavily associated with cultural expectations. It is generally less acceptable to be a feminized boy than a prepubertal girl who is a "tomboy." At puberty there appears to be a spike in gender dysphoria, with the onset of discordant secondary gender characteristics.

PREVALENCE: Overall, it is estimated that 0.6% of people identify as transgender, or approximately 1.4 million U.S. citizens per the 2016 CDC-based Behavioral Risk Factor Surveillance System and the UCLA School of Law Williams Institute. Accurate data are absent and likely underestimate prevalence. Additionally, it appears that younger age and geography are associated with increased TGD representation.

GENETICS: There is no known single or specific genetic basis for TGD identity or gender dysphoria. There appear to be no specific relationships between transgender identity with socioeconomic status, race, or ethnicity. TGD identity may be more common in those with autistic spectrum disorders.

RISK FACTORS: Most children and adults benefit from medical care and social systems that do not pathologize their innate sense and experience of self. However, children and teens who are TGD have historically experienced higher rates of child abuse, bullying, mental health concerns (e.g., anxiety, depression, suicidality, eating disorders), and substance use. Historically, transgender adult populations have poorer health outcomes, such as depression, anxiety, self-harm and suicide, substance use, underemployment, homelessness, incarceration, and positive HIV status. Poorer health outcomes are explained by using minority stress theory (chronic stress related to stigma and dysphoria) rather than gender variance as a pathology itself.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

TGD prepubertal children may present with *consistent, persistent, and insistent* interest and expression of other or opposite-gendered activities and behaviors, or they may present with a more gender-fluid identity. Many gender dysphoric children may initially present with more normative gender play and expression, however, still experience underlying problems with their internal gender identity.

Adolescents and adults may present clinically at any point along the life span, though many express having cross-gender feelings and identities earlier in life. For some patients, the physical changes of puberty become an unbearable reminder of internal vs. external gender dissonance. Research suggests that when gender dysphoria is increased by the onset of puberty it rarely subsides. Some gender dysphoric persons will not present initially with gender dysphoria but with mood, behavior, or social problems.

DIAGNOSIS

- TGD identity is not considered pathologic or requiring psychiatric evaluation and care. Developmental models instead view gender along a biologic spectrum with diverse presentations and expression. Persons may assert TGD identity without severe self-hatred or significant dysphoric presentation. Psychiatric evaluations are no longer required or essential to "diagnose" gender nonconforming persons; however, mental health and social work services may help support individuals or their families in their transition plan.
- Changes in DSM-5 focus on "gender dysphoria" and inherent distress in one's natal gender and biologic gender characteristics reflecting a shift from a "disorder" of identity. For an individual to be diagnosed with gender dysphoria, marked differences between the individual's natal or assigned gender and expressed/experienced gender must exist for at least 6 mo; cause clinically significant distress or impairment in social, occupational, or other important areas of functioning; with strong and consistent desire to be the other gender.

WORKUP

- Ideally, this assessment begins with interviewing the individual as a part of a holistic health assessment. Persons with various degrees and experience in behavioral health can perform these interviews. Mental health and social support may help patients cope with body dysphoria, treat comorbid mental health concerns, assist with social and emotional skill building, and create a safe and successful transition plan. Parents of a TGD child may benefit from counseling services so that they may address their own parental reactions to transition and successfully focus on the child's issues and needs. Consistently, research demonstrates that early family support of a child's authentic gender identity is linked to positive mental health outcomes.
- Clinical interview includes assessment of gender experience from childhood until present; desired name, pronouns, and past and current place on the gender spectrum; past and current attempts to feminize or masculinize with clothing, hair, makeup, hormones (both prescribed and nonprescribed), and surgeries; future goals of transitioning,

gender identity, and expression. Transition goals, gender identity, and expression will vary among each individual and may not fit into traditional binaries. For many children, parents may provide insight as to early childhood gender identity and expression. For some children, parental distress and denial of a consistent cross-gender identity is the most problematic aspect of providing care.

- Review for known comorbidities by asking mental health specific questions about: depression, anxiety, eating disorders, self-harm (cutting, suicidal ideation, suicide attempts), psychiatric hospitalization, and substance use. Patient history should also include: sexual attraction and behaviors and risk for sexually transmitted infections and pregnancy; social history, experience of bullying, hate crimes, physical or emotional/verbal abuse, homelessness, joblessness, and survival sex. Resiliency theory also promotes focusing on patient strengths and identifying social support systems.
- An initial visit may include a physical examination, depending on the provider and patient goals. Many gender dysphoric persons are exquisitely uncomfortable with their genitalia and genital examination. If the evaluation is a consultation for information and counseling, an exam may be deferred until the patient is more comfortable and familiar with the provider. Tanner staging of genitalia, along with hormonal measures, can estimate pubertal stage and appropriateness for puberty blockers or gender-affirming hormones.
- Luteinizing hormone is a preferred lab for evaluating prepubertal children and Gonadotropin releasing hormone (GnRH) analogue use, but additional laboratory studies may include follicle stimulating hormone, testosterone, or estradiol. For older youth or adults starting gender affirming hormones (GAH), baseline laboratory values may include CBC, lipid panel, and liver function tests. GAH may affect hematopoiesis, cholesterol levels, and irritate the liver. More recent data suggest that extensive laboratory testing is likely unnecessary for most patients, as there do not seem to be clinically significant changes in these laboratory values over time. Testosterone may be useful to measure androgen suppression in asserted women receiving estrogen therapy or in asserted men aiming for physiologic male levels. Evaluating levels of estradiol or testosterone may be useful only if clinical goals are not being achieved. Potassium and blood pressure monitoring is useful in transwomen starting spironolactone to block male pattern hair growth.
- Screening for sexually transmitted infections (urine, rectal, and oral *Chlamydia* and gonorrhea; syphilis; herpes simplex virus; HIV; hepatitis B and C), and pregnancy is indicated according to sexual practices. Transwomen, including transwomen of color, have some of the highest rates of HIV; consider offering pre-exposure prophylaxis for HIV (PREP) if consistent with sexual practices.
- Attention to regular routine health needs (vaccines, lab work, and screenings) should be addressed in all TGD individuals. Over time, patients should receive typical preventive and screening tests for both natal and asserted gender in accordance with what hormones and anatomy are present.

Rx TREATMENT

Treatment recommendations are flexible and should be individualized to the specific goals expressed by the patient. Treatment is determined by patient age and development (including Tanner stage) and desired place on the gender spectrum. A diagnosis of gender dysphoria/gender incongruence (GD/GI) should be confirmed before proceeding with gender-affirming hormone therapy.

REVERSIBLE TRANSITION

- Social transition includes taking a name and pronouns in the identified gender, as well as clothing, shoes, hair, make-up, and other gender identifying social cues. For prepubertal, androgynous children, social transition does not require hormones, but does require extensive planning for disclosure, social support, and peer- and school-based activities Timing for social transition varies, but many individuals are beginning the social transition process long before medical therapies.
- GnRH agonists act to block the hypothalamic pituitary gonadal axis and put a "pause" on endogenous gender hormone secretion. Puberty blockers are completely reversible and best when used at very early Tanner stage II breast and testicular development. When used in early puberty, blockers stop puberty and permit regression to prepubertal hormone levels to allow a patient to remain at his or her current androgynous physical gender characteristics. Stopping puberty "buys time" for the patient and family to explore their gender goals and to determine safe and healthy next steps.
- GnRH analogues may be used for patients who are later in puberty (Tanner 3-5 genital exam) but who are still androgynous in regard to secondary gender characteristics, such as voice, facial and body hair, bone, muscle, and fat deposition. Blockers can also be used to stop erectile function or menses, which can be highly distressing to some gender dysphoric persons.
- GnRH analogues are *completely reversible.* If stopped, a person can continue into biologic puberty with no impact on future gender characteristics or fertility.
- Most teens who opt to start GnRH agonists to block puberty continue to create a transition plan and eventually move to GAH and puberty in their asserted gender. The current literature from the past 30 or more yrs demonstrates that it is unlikely that an adolescent who is consistently, persistently, and insistently gender nonconforming or transgender will return to his or her assigned natal gender or regret either blockers or GAH. This can be both of concern and relief to parents as they determine how to best to support their child.

PARTIALLY REVERSIBLE TRANSITION:

- GAH therapies include testosterone for masculinization and estradiol for feminization. Both hormones may have reversible effects on skin, fat deposition, and muscle mass. Irreversible testosterone effects may include lower voice, male pattern face and body hair, and clitoromegaly. Irreversible estradiol effects include areolar enlargement and breast tissue growth. These changes are usually desired by transgender individuals and desired for continued transition into their asserted gender. It is also important to address the limitations of GAH.
- Estradiol creates softer skin, female body fat deposition (hips/thighs), and breast development. It may impair erectile function, which may or may not be desired because some male-to-female persons still want or depend on penile function (masturbation, sexual relationships, and/or sex work). Estradiol is typically administered sublingually but can be taken intramuscularly, orally, or topically.
- Testosterone masculinizes by deepening the voice and inducing male-pattern hair, fat, and muscle deposition (bulk and abdominal girth) and clitoromegaly.
- Both gender hormones should not be used in lieu of contraception, as current evidence suggests that estrogen or testosterone is not sufficiently effective as a contraceptive. Persons taking testosterone who are having unprotected egg–sperm sex should be counseled about the chance of pregnancy and offered birth control in addition to testosterone. Alternatively, fertility may be impaired, and individuals who feel strongly about having future genetic children or childbearing may wish to consult reproductive endocrinology and infertility specialists to discuss sperm- and oocyte-preservation strategies before initiating GAH.
- Consent to what we know and do not know is an important part of beginning the cross-gender hormone process. We currently do not have strong guidelines or outcome studies for ongoing preventive care and anticipatory guidance.

IRREVERSIBLE TRANSITION: The U.S. Department of Health and Human Services Departmental Appeals Board ruled Medicare's categorical exclusion of gender confirmation medical and surgical treatments was unreasonable and contrary to medical standards of care. Several states have adopted legislation that should prevent insurers from excluding transgender care services; however, there is as yet no consensus or plan for universal coverage for transgender health services.

Surgical options for masculinization include mastectomy and male chest reconstruction, hystero-oophorectomy, and orchi-penoplasty; for feminization they include orchiectomy-penectomy with vulvovaginal reconstruction, breast implants, and other cosmetic surgeries.

Some patients do not want surgery, while others opt for partial surgical transition.

ADDITIONAL THERAPIES: Antiandrogens such as spironolactone or finasteride prevent male-pattern hair growth, while laser treatment and electrolysis offer permanent hair removal. Female patients may desire vocal coaching, tracheal shaving, and facial feminizing surgeries. Progesterone may promote increased breast development, although there is no evidence pointing to effectiveness or risk. Topical androgen therapies do not seem to improve clitoral growth.

Individual, family, and marital counseling and therapies can be important, as can psychiatric medications for comorbid conditions as persons and families negotiate the process of transition. Reparative therapy is *universally* rejected as *unethical and harmful* by all the national medical and psychological boards and associations.

DISPOSITION

- Younger prepubertal gender nonconforming patients may grow up and be cisgender or transgender, hetero or homosexual. Patients who have early consistent, persistent, insistent dysphoria or cross-gender identification are more likely to continue this into puberty and eventually transition. There is also a growing population of gender-fluid patients who do not easily fit into dichotomous gender binaries.
- "Passing" in one's asserted gender can have significant and demonstrated protective effects for victimization from hate crimes and interpersonal violence, low socioeconomic status, underemployment, and isolation. Early identification and early transition in a person's identified gender, along with a better likelihood of acceptance, offers significant psychosocial benefits to many gender dysphoric persons.

REFERRALS

There are few contraindications to transitioning for most transgender or gender dysphoric persons. Active psychosis and inability to consent to care would require further psychiatric evaluation but are extremely rare. For older persons, some medical issues involving cardiac, liver, and thromboembolic risks complicate hormone use and need to be taken into consideration.

PEARLS & CONSIDERATIONS

- Periodic assessment of a person's place on the gender spectrum can begin in toddler age children and can continue into adulthood as a potentially effective way of helping identify and support TGD or gender dysphoric persons earlier. Earlier identification and parental support for gender dysphoric and TGD persons may lead to improved mental and physical health outcomes.
- Hormone blockers and GAH typically offer far more benefit than risk in the treatment of gender dysphoria when a person desires to transition to the opposite gender.
- Affirming treatment of TGD-identified persons will vary depending on patient-specific goals and gender expression. Treatment should be individualized but also comprehensive, including appropriate screening and preventative tests, social and legal support, and mental health resources.
- Federal and state changes in mandated insurer coverage of gender care, including gender affirming surgeries, may offer substantial benefit for a growing population of transgender identified persons.

PATIENT & FAMILY EDUCATION

- The World Professional Association for Transgender Health promotes the highest standards of health care for individuals through the articulation of Standards of Care (SOC) for the Health of Transsexual, Transgender, and Gender Nonconforming People. The SOC are based on the best available science and expert professional consensus: www.wpath.org/publications/soc
- Center of Excellence for Transgender Health, the mission of which is to increase access to comprehensive, effective, and affirming health care services for trans communities: http://transhealth.ucsf.edu/
- The Trans Health Program at Fenway helps to ensure access to high-quality, informed care for trans women, trans men, genderqueer, gender nonconforming, nonbinary individuals, affirmed men and women, people with trans histories, and anyone with health needs unique to their diverse gender expressions and identities: http://fenwayhealth.org/care/medical/transgender-health/

AUTHORS: **Caroline Golski, MD,** and **Michelle Forcier, MD, MPH**

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BASIC INFORMATION

DEFINITION

Genitopelvic pain/penetration disorder, previously referred to as the separate conditions of "vaginismus" or "dyspareunia," is described in DSM-5 as encompassing persistent or recurrent difficulty in having intercourse, marked vulvovaginal or pelvic pain associated with attempts at intercourse, marked fear or anxiety associated with the pain of intercourse, or tensing or tightening the pelvic floor muscles while attempting vaginal intercourse. Symptoms must have persisted for a minimum of 6 mo and cause clinically significant distress to the individual. The condition may be lifelong or acquired.

SYNONYMS

Vaginismus
Dyspareunia

ICD-10CM CODES

N94.1	Unspecified dyspareunia
N94.2	Vaginismus
F52.5	Vaginismus not due to a substance or known physiological condition
F52.6	Dyspareunia not due to a substance or known physiological condition

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Estimated at 11.7% to 42% of women presenting to sexual dysfunction clinics
PREVALENCE: Affects 14% to 34% of younger women and 6.5% to 45% of older women
PREDOMINANT SEX: Affects people with vulvas
RISK FACTORS: Any previous sexual trauma, including incest or rape

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Tightening of the vaginal muscle with decreased ability or inability to accommodate penetration
- Tension, pain, or burning felt when penetration is attempted
- Decrease in or no desire to have intercourse
- Avoidance of sexual activity
- Intense phobia or fear of pain

ETIOLOGY

- Learned conditioned response (Fig. E1) to real or imagined painful vaginal experience (e.g., traumatic speculum examination, incest, rape)
- Vaginitis
- Pelvic inflammatory disease
- Endometriosis
- Anatomic anomalies
- Atrophic vaginitis
- Mucosal tears
- Inadequate lubrication
- Focal vulvitis
- Painful hymenal tags
- Scarring secondary to episiotomy
- Skin disorders
- Topical allergies
- Postherpetic neuralgia

DIAGNOSIS

WORKUP

- Thorough history (including sexual and psychological history)
- Careful pelvic examination

TREATMENT

An individualized, multidisciplinary approach must be taken to treat the underlying and exacerbating physical and emotional aspects of this condition.

NONPHARMACOLOGIC THERAPY

- Pelvic floor physical therapy, including deconditioning the response by systematic self-administered progressive dilation techniques using fingers or dilators
- Behavioral and/or psychosexual therapy

PHARMACOLOGIC THERAPY

- Intravaginal prasterone, low-dose vaginal estrogen, and ospemifene can be used in postmenopausal women
- Lubricants, topical anesthesia, and moisturizers may help reduce or alleviate dyspareunia

ACUTE GENERAL Rx

- Cause should be determined by history and explained to the patient so that she understands the possible mechanics of this disorder.
- Patient must be motivated to desire painless vaginal insertion for such reasons as pleasurable coitus, tampon insertion, or gynecologic examination.
- Patient (and her partner) must be willing to patiently undergo the process of systematic desensitization and counseling.

DISPOSITION

A high percentage of successfully treated patients

REFERRAL

To a gynecologist or sex therapist

PEARLS & CONSIDERATIONS

RELATED CONTENT

Dyspareunia (Related Key Topic)

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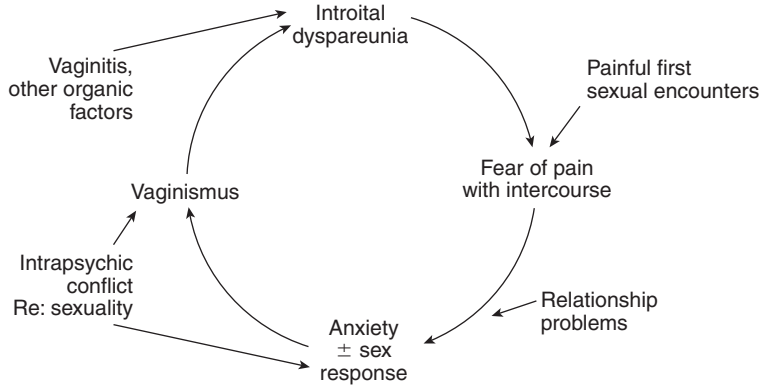

FIG. E1 Dyspareunia and vaginismus cycle. (From Lentz GM: *Emotional aspects of gynecology sexual dysfunction, eating disorders, substance abuse, depression, grief, loss; comprehensive gynecology*, St Louis, 2007, Mosby. Reference: Bergeron S et al: Female sexual pain disorders: a review of the literature on etiology and treatment, *Curr Sex Health Rep* 7:3, 2015.)

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BASIC INFORMATION

DEFINITION

Genitourinary syndrome of menopause (GSM) is a collection of chronic, progressive symptoms and signs related to menopause, which include changes to vulvovaginal and bladder-urethral areas due to a decrease in estrogen and other sex steroids. The symptoms and signs include vaginal dryness, burning, soreness, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of frequency, urgency, urge incontinence, and recurrent urinary tract infection.

SYNONYMS

Vulvovaginal atrophy (VVA)
Atrophic vaginitis
Urogenital atrophy
GSM

ICD-10CM CODES

N95.1	Menopausal and female climacteric states
N95.2	Postmenopausal atrophic vaginitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: GSM can occur at any time in a woman's life; however, it is more common during the postmenopausal phase, affecting >50% of women at this age versus ~15% of premenopausal women.

PREVALENCE: According to a cross-sectional population-based study, GSM and its features affect 57% of sexually active women in the United States aged 40 to 65 yr.

RISK FACTORS:

- Menopause
- Nonmenopause hypoestrogenism
- Bilateral oophorectomy
- Cigarette smoking
- Alcohol abuse
- Decreased sexual frequency and abstinence
- Ovarian failure
- Lack of exercise
- Absence of vaginal childbirth
- Estrogen deficient because of cancer treatments

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Principal symptoms include vaginal dryness, dyspareunia, burning, itching, and dysuria.
- Atrophy of the labia majora and vaginal introitus are observed, include labial thinning, narrowing of the introitus, decreased width and depth of the vagina, along with observed pale and dry vulvar and vaginal tissues with loss of rugae and elasticity.
- Laboratory studies may suggest an increase in vaginal pH (>5.0) with loss of superficial cells on vaginal maturation index.
- A thin, watery, yellowish vaginal discharge may be noticed. A urethral caruncle may develop.
- GSM symptoms are also reported to negatively affect sexual satisfaction in >50% of patients, as well as in their personal relationships.

ETIOLOGY

- The etiology of GSM is secondary to hypoestrogenism, which is predominantly caused by decreased levels of endogenous estrogen during the transition between perimenopausal and postmenopausal yr in the female body.
- Other etiologies of hypoestrogenism include postpartum and lactation, use of medications with antiestrogenic effects, bilateral oophorectomy, hypothalamic amenorrhea or amenorrhea combined with glucocorticoid therapy, primary ovarian insufficiency, breast cancer treatments including chemotherapy, pelvic surgery, radiation, and aromatase inhibitors (AIs).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Vaginal infections, including *Candida* vulvovaginitis, bacterial vaginosis, trichomoniasis, and desquamative inflammatory vaginitis
- Irritant dermatitis in response to perfumes, deodorants, soaps, lubricants, spermicides, perineal pads, or panty liners
- Vulvovaginal dermatoses, including lichen sclerosus, lichen planus, and lichen simplex chronicus
- Cancer and precancerous lesions, including vulvar intraepithelial neoplasm, vulvar cancer, and extramammary Paget disease
- Vulvodynia
- Other etiologies of frequent urinary tract infection or associated symptoms

WORKUP

- Complete medical history focusing on use of medications with antiestrogenic effects and cancer treatments, which include chemotherapy, pelvic surgery, and radiation therapy
- Pelvic examination: Changes in shape and color in external labia majora and minora; atrophy in clitoral hood and the clitoris; changes in vulvar and vaginal tissue; some patients may also experience inflammation with potential vaginal bleeding
- Laboratory testing (see "Laboratory Tests")

LABORATORY TESTS

- Vaginal pH may reach above 4.6 in the absence of other causes.
- Vaginal maturation index (VMI): Microscopic findings on a smear of the vaginal epithelium may include increase of parabasal cells with a significant decrease of intermediate and superficial cells (<5%).

TREATMENT

SYSTEMIC HORMONE THERAPY: Use of estrogen only or estrogen plus progestogen for the management of vulvovaginal symptoms. Systemic hormone therapy is preferred if vasomotor symptoms are also present and require treatment. This therapy is usually combined with other types of treatments.

LOCAL ESTROGEN TREATMENT: Local vaginal estrogen treatment is suggested as the main treatment for GSM, combined with nonhormonal lubricants and vaginal moisturizers. This treatment can work as short-term therapy in improving vulvovaginal symptoms and lower urinary tract symptoms. Treatment options include estrogen creams, vaginal rings, estrogen tablets, vaginal inserts, and intravaginal dehydroepiandrosterone (DHEA). Vaginal estrogen products with suggested low dosage have been U.S. Food and Drug Administration (FDA) approved in the U.S. for the treatment of GSM (Table 1).

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS): Certain SERMs with estrogen agonistic effect have shown improvement in VMI, vaginal pH, vaginal dryness, and dyspareunia (e.g., daily use of ospemifene 60 mg orally).

BAZEDOXIFENE (BZA) AND CONJUGATED ESTROGENS (CES): BZA (20 mg) combined with CE (0.45 or 0.625 mg) has shown significant improvement in vasomotor and vulvovaginal symptoms and dyspareunia, while preventing bone loss and being safe for the endometrium and breast.

NONPHARMACOLOGIC THERAPY

NONHORMONAL TREATMENT: Vulvovaginal symptoms can be improved by use of nonhormonal lubricants during intercourse and regular use of long-acting vaginal moisturizers.

FRACTIONAL CO_2 LASER TREATMENT: Fractional CO_2 laser treatment has been reported in an Australian study to be significantly effective in improving sexual function, relieving symptoms of dyspareunia, and delivering positive changes in bladder function and prolapse symptoms in the long-term (12 to 24 months). However, the laser or energy-based devices have not been approved by the FDA for the treatment of vulvovaginal symptoms.

ACUTE GENERAL Rx

Ospemifene (daily 60 mg orally)

CHRONIC Rx

Vaginal estrogen with prescribed dose (Table 1)

COMPLEMENTARY & ALTERNATIVE MEDICINE

Vaginal hyaluronic acid–based moisturizers are reported to improve vulvovaginal symptoms as effectively as estrogen-based treatment.

REFERRAL

- Postcoital bleeding should be evaluated for cervical cancer.
- Systemic disease (e.g., Crohn disease) consultation if genital tract ulcers or fissures

TABLE 1 Hormonal Therapy for Treatment of Genitourinary Syndrome of Menopause

Treatment	Product	Dosage		Comments
		Initial	Maintenance	
Vaginal Cream				
Estradiol-17b	Estrace (Allergan, Irvine, CA)	0.5-1.0 g, daily for 2 wk	0.5-1.0 g, 1-3 times weekly	FDA-approved dose is higher (loading dose = 2.0-4.0 g, daily; maintenance dose = 1.0 g, 1-3 times weekly)
Conjugated estrogens	Premarin (Pfizer, New York, NY)	0.5-1.0 g, daily for 2 wk	0.5-1.0 g, 1-3 times weekly	FDA-approved dose is higher and administration is cyclic (for GSM, 0.5-2.0 g, daily for 21 days and then off for 7 days; for dyspareunia, [A] 0.5 g, daily for 21 days and then off for 7 days, or [B] 0.5 g, twice weekly)
Vaginal Insert				
Estradiol hemihydrate	Vagifem (Novo Nordisk, Bagsværd, Denmark), Yuvafem (Amneal, Bridgewater, NJ)	10-mcg insert, once daily for 2 wk	1 twice weekly	—
Estradiol-17b softgel capsules	TX-004HR	4, 10, or 25 mcg, daily for 2 wk	1 twice weekly	This product is not yet FDA approved
DHEA (prasterone)	Intrarosa (AMAG Pharmaceuticals, Waltham, MA)	6.5 mg, once daily	6.5 mg, once daily	—
Vaginal Ring				
Estradiol-17b	Estring (Pfizer, New York, NY)	Insert for 90 days (2-mg releases approximately 7.5 mcg daily)	Change every 90 days	—
Estradiol acetate	Femring (Warner Chilcott UK Limited, Larne, Northern Ireland, UK)	Insert for 90 days (12.4-mg or 24.8-mg releases 0.05 mg or 0.1 mg daily, respectively)	Change every 90 days	This product is delivered vaginally but it provides systemic hormone levels to treat VMS and GSM
Selective Estrogen Receptor Modulator				
Ospemifene	Osphena (Duchesnay USA, Rosemont, PA)	60 mg, daily	60 mg, daily	FDA approved for dyspareunia

FDA, U.S. Food and Drug Administration; *VMS,* vasomotor symptoms.
From Faubion SS et al: Genitourinary syndrome of menopause: management strategies for the clinician, *Mayo Clin Proc* 92:1842-1849, 2017.

are detected combined with abdominal pain, blood in stool, and unexplained weight loss.
- Recurrent urinary tract infection with other associated symptoms may require genitourinary workup and/or cystoscopy.

PEARLS & CONSIDERATIONS

COMMENTS

- The estradiol ring may dislodge with bowel movement, sexual intercourse, douching, or Valsalva maneuvers. Vaginal ring users are encouraged to remove or replace the vaginal ring on their own.
- The safety of systemic hormone therapy in women with breast cancer should be carefully considered.
- With the use of local estrogen cream, dosing at least 12 hours before vaginal sexual activity is recommended to prevent estrogen absorption by a sexual partner.

PATIENT & FAMILY EDUCATION

Clinicians should discuss the concept of maintaining sexual function for postmenopausal women. For women with a sexual partner, regular vaginal intercourse or stimulation helps to maintain vaginal health, as well as provide comfort and satisfaction during sexual activities in the future. For women without a sexual partner, regular use of vaginal vibrator or other stimulators should be recommended to maintain healthy vaginal function.

RELATED TOPICS

Genitourinary Syndrome of Menopause (Patient Information)
Vaginitis, Estrogen-Deficient (Related Key Topic)

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BASIC INFORMATION

DEFINITION

Gestational diabetes mellitus is hyperglycemia occurring during the second or third trimester in absence of a prepregnancy diagnosis of type 1 or type 2 diabetes.

Screening for gestational diabetes mellitus in asymptomatic pregnant women after 24 weeks' gestation is a grade B recommendation by the U.S. Preventive Services Task Force (USPSTF). In the U.S., a two-step approach to screening is commonly used and is currently endorsed by the American College of Obstetricians and Gynecologists (ACOG) and the National Institutes of Health (NIH). The International Association of Diabetes in Pregnancy Study Group has recommended a simplified one-step approach for screening and diagnosing GDM, which has been endorsed by the American Diabetes Association since 2011, with the acknowledgment that the one-step approach increases the prevalence of GDM without clear evidence of benefit. Pregnant women with diabetes mellitus (DM) (gestational or preexisting) are classified according to White classification (Table 1).

SYNONYMS

Gestational diabetes
Diet-controlled gestational diabetes (A1)
Medication-treated gestational diabetes (A2)

ICD-10CM CODES

O24.410	Gestational diabetes mellitus in pregnancy, diet controlled
O24.414	Gestational diabetes mellitus in pregnancy, insulin controlled
O24.419	Gestational diabetes mellitus in pregnancy, unspecified control
O99.810	Abnormal glucose complicating pregnancy

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Approximately 5% of pregnant women in the U.S. will be diagnosed with GDM using the two-step approach and 18% using the one-step approach.

PREDOMINANT SEX AND AGE: Women of childbearing age; increased risk is observed in women over the age of 35 yr.

GENETICS: Higher rate in women with a family history of GDM or type 2 diabetes in a first-degree relative; specific HLA alleles (DR3 or DR4) predispose to the development of DM type 2 after pregnancy.

RISK FACTORS

- Overweight or obesity
- Family history of GDM or type 2 diabetes, particularly in first-degree relatives
- Polycystic ovarian syndrome
- Multiple gestation
- Hypertensive disorder of pregnancy or chronic hypertension
- Chronic systemic steroid use
- History of macrosomia in prior pregnancy
- Personal history of abnormal glucose tolerance or GDM in previous pregnancy
- Hispanic, Native American, African American, Asian, or Pacific Islander ethnicity
- Advanced maternal age (over age 25)
- Unexplained perinatal loss or malformation in previous or current pregnancy may be suggestive of preexisting diabetes

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Suspect GDM if:

- Fetal size greater than dates on Leopold or increased fundal height measurement
- Ultrasound findings of fetal macrosomia (especially enlarged abdominal circumference) or polyhydramnios
- Marked maternal obesity or weight gain above expected range
- Acanthosis nigricans (as underlying insulin resistance increases risk)
- Symptoms of diabetes
- Glucosuria
- Hemoglobin A1C greater than or equal to 5.7 in the first trimester

ETIOLOGY

During normal pregnancy several mechanisms contribute to increased insulin resistance. Placental secretion of human placental lactogen (hPL) decreases maternal insulin sensitivity, decreases maternal glucose utilization, and increases lipolysis, all to ensure adequate glucose availability to the growing fetus. Maternal pancreatic beta cells are increased in order to secrete additional insulin to compensate for the increased circulating blood glucose. Insulin resistance is also exacerbated by an increase in maternal adipose deposition, decreased exercise, and increased caloric intake. GDM occurs when maternal insulin secretion cannot meet the increased glucose burden, resulting in carbohydrate intolerance and hyperglycemia.

TABLE 1 White Classification for Pregnant Women with Diabetes (Gestational or Preexisting)

Class	Description
A1	DM diagnosed during pregnancy and controlled by diet
A2	DM diagnosed during pregnancy and requiring medication
B	Insulin-requiring DM diagnosed before pregnancy, age >20 yr, lasting <10 yr
C	Insulin-requiring DM, onset at age 10 to 19 yr, with a duration 10 to 19 yr
D	Onset >10 yr or duration >20 yr, or associated with hypertension or background retinopathy
F	DM with renal disease
H	DM with coronary artery disease
R	DM with proliferative retinopathy
T	DM with renal transplant

DM, Diabetes mellitus.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Preexisting type 1 or 2 DM not previously diagnosed

WORKUP

- History with focus on personal medical history, prior pregnancy history, and family history
- Routine prenatal examination
- Laboratory evaluation (see the following)

LABORATORY TESTS

- Exclude preexisting diabetes
- For women with risk factors (see above), order a 1-hr glucose tolerance test at the first prenatal visit, then repeat at 24 to 28 weeks if initial screen was normal. If abnormal at intake, consider the probability of undiagnosed preexisting DM or underlying insulin resistance and check hemoglobin A1c. A diagnosis of diabetes is made if a woman meets any of the following criteria: Fasting plasma glucose >126 mg/dl, A1c >6.5%, random plasma glucose >200 mg/dl. The authors consider a first-trimester A1c of ≥5.7 suggestive of preexisting insulin resistance, and would be inclined to monitor closely for hyperglycemia.
- Two-step approach:
  1. For screening without risk factors, a 1-hr, nonfasting 50-g oral glucose tolerance test (OGTT) is appropriate. If the result is abnormal (≥130 mg/dl, as defined by Carpenter and Coustan), a 3-hr, 100-g oral glucose tolerance test is performed. The diagnosis of GDM is made if two or more of the following glucose values are met or exceeded:
     a. Fasting: 95 mg/dl
     b. 1-hr plasma glucose: 180 mg/dl
     c. 2-hr plasma glucose: 155 mg/dl
     d. 3-hr plasma glucose: 140 mg/dl
  2. If one of four values on 3-hr glucose tolerance test is abnormal, consider repeat testing in 1 month and recommend a low-carbohydrate diet immediately and consultation with a nutritionist. At least one study has demonstrated increased perinatal risk in women with only one of four abnormal values on 3-hr OGTT
- One-step approach:
  1. Like the two-step, a one-step screening is performed at 24 to 28 weeks on all pregnant patients who have not already been diagnosed with diabetes. This is a 2-hr, 75-g oral glucose tolerance test performed after an overnight, 8-hr fast. A diagnosis of GDM is made if one or more of the following values are met or exceeded:

   a. Fasting: ≥92 mg/dl
   b. 1-hr plasma glucose ≥180 mg/dl
   c. 2-hr plasma glucose ≥153 mg/dl
- After pregnancy, women with GDM have an increased risk of developing diabetes during their lifetime. Women with GDM should be screened at or after 6 weeks postpartum with a 75-g 2-hour GTT to diagnose type 2 diabetes using the same criteria as nonpregnant patients. Alternatively, an HgbA1c can be performed at or after 12 weeks postpartum.

IMAGING STUDIES

Ultrasound for fetal size is performed in women with GDM. It may be initiated at the time of diagnosis and repeated every 3 to 4 weeks if macrosomia is suspected. Clinicians should consider local standards of care.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Glucose monitoring:
  1. Four times daily: Fasting and 2-hr postprandial (defined as 2 hr after the start of each meal).
  2. Goals: Fasting <95 mg/dl; 2-hr postprandial <120 mg/dl.
  3. Can also use 1-hr postprandial goal of <140 mg/dl.
- Dietary modifications for glycemic control:
  1. Follow a low-carbohydrate diet; avoid sugar and concentrated sweets; and eat small, frequent meals (three meals with two snacks is often recommended).
  2. Complex carbohydrates should be consumed over simple carbohydrates to prevent glucose fluctuations.
  3. Diet should adequately meet the needs of pregnancy (below) while restricting carbohydrates to 33% to 40% of daily calories. Caloric needs in pregnancy:
     a. BMI <30: 30 kcal/kg/day.
     b. BMI >30: 25 kcal/kg/day.
     c. BMI >40: 12 to 14 kcal/kg/day.
  4. Regular moderate exercise, defined as 30 minutes five times per week.
  5. Ongoing nutrition counseling throughout pregnancy.

PHARMACOLOGIC Rx

Initiate if >20% of glucose values are elevated after trial of diet control:

- Insulin: Considered the gold standard in GDM management.
  1. There are no randomized controlled trials on insulin regimens, and therapy is largely guided by expert opinion.
  2. Insulin is the only FDA-approved medication for GDM (Pregnancy Class B) and does not cross placenta.
  3. Insulin may be started first line or added when oral medications have failed to achieve glycemic control. The authors consider factors such as the degree of hyperglycemia, obstacles to medication adherence, and gestational age at time of diagnosis (with early-onset diagnosis more likely to progress and require insulin) when initiating therapy. The ADA recommends insulin as first-line pharmacotherapy for GDM, and ACOG (2017) mirrors this recommendation (Level A).
  4. Regardless of insulin regimen initiated, blood glucose values should be reviewed frequently, and the regimen adjusted and customized to optimize each woman's blood glucose levels; using a single agent or combination of long, intermediate and/or short-acting insulins.
  5. One commonly used regimen:
     a. Insulin 0.7 to 1.0 U/kg/day SQ (based on current pregnant weight), with two thirds of the total daily dose given in the morning and one third of the total daily dose given in the evening.
     b. One third of each dose is given as short-acting insulin and the remaining two thirds as long-acting insulin.
- Oral hypoglycemics:
  1. Oral antidiabetic agents continue to be used in the management of GDM, despite a lack of FDA approval for this indication.
  2. Several recent studies have examined the potential benefits and harms of metformin and glyburide, comparing them with the gold-standard insulin and with each other. Metformin (compared with insulin) has been demonstrated to decrease maternal glucose levels, maternal weight gain, and the risk of gestational hypertension. Evidence grows that it may decrease the risk of preeclampsia as well. Although known to cross the placenta, concerns about the long-term risk in exposed offspring have been mitigated by at least one recent study showing no neurodevelopmental differences with intrauterine exposure to metformin versus insulin. Meanwhile, recent meta-analyses have demonstrated worse neonatal outcomes with the use of glyburide compared with insulin. With both metformin and glyburide, many women go on to require insulin therapy.
  3. As of 2017, ACOG recommends "in women who decline insulin therapy or for those women whom the obstetrician or obstetric care provider believes the patient will be unable to safely administer insulin, metformin is a reasonable second-line choice" (Level B); while suggesting that glyburide should not be recommended as a first-line agent due to a failure to achieve equivalent outcomes to insulin in most studies (also Level B).
  4. Metformin: Begin at 500 mg PO nightly or bid, and titrate up to a maximum of 2500 mg daily in divided doses.
  5. Glyburide: Begin at 2.5 mg qd, and titrate up to a maximum of 20 mg qd (10 mg bid). Increase dose as needed by 2.5 to 5 mg/wk.

ANTENATAL TESTING

Antepartum testing is recommended for women with pregestational diabetes and gestational diabetes. There is no consensus regarding initiation, frequency or modality of antepartum testing in gestational diabetes, and this should be guided by local standards.

ONE COMMONLY USED REGIMEN

- Weekly NST/AFI beginning at 32 weeks or when medications are initiated in women with GDMA2. Less frequent testing or delayed initiation of testing may be considered in women who maintain glycemic control with diet alone (GDMA1), as increased rates of stillbirth have not been observed in these women before 40 weeks' gestation.
- Preexisting or poorly controlled diabetes, vascular complications, or concomitant hypertension: Twice weekly NST/AFI beginning at 28 weeks. Consider hospital admission to obtain glycemic control.

TIMING AND ROUTE OF DELIVERY

- Women with preexisting diabetes should be induced at 39 weeks.
- Women with GDMA2 may also be induced at 39 weeks unless otherwise indicated, with decisions regarding induction guided by local standards of care.
- In women with GDMA1, ACOG supports expectant management of up to 40 and 6/7 weeks with appropriate antepartum testing.
- Counsel regarding elective cesarean section at or after 39 weeks if estimated fetal weight is over 4500 g.
- Consider delivery earlier than 39 weeks if poor glycemic control or other medical indications such as growth restriction or preeclampsia.

INTRAPARTUM MANAGEMENT

- Goal is normoglycemia (80 to 120 mg/dl) using insulin and D5 lactated Ringer IV fluid if needed.
- Monitor glucose every 1 to 2 hours in active labor.
- Preparation for shoulder dystocia.
- If on glyburide, discontinue in labor or 12 hr before a scheduled induction.
- If on insulin consider decreased long-acting insulin by one third to one half before scheduled induction. Most experts recommend holding insulin entirely the morning of a scheduled cesarean delivery.

POSTPARTUM MANAGEMENT

- Class A2: Check fasting blood glucose level before discharge; if abnormal, continue checking at home and schedule early follow-up with primary care physician to confirm diagnosis of DM.
- 6-wk postpartum visit: Screen for impaired glucose tolerance and diabetes with a 75 g, 2-hr glucose tolerance test. Alternatively, an HgbA1c may be performed at or after 12 weeks postpartum.

- If no evidence of DM, screen annually for DM and counsel on risk factor modification.

REFERRAL

- Nutritionist
- Maternal-fetal medicine
- Diabetes educator
- Nurse care manager, when available

COMPLICATIONS

- Maternal: Preeclampsia, future type 2 DM or GDM, operative delivery
- Fetal: Polyhydramnios, macrosomia, congenital malformations, shoulder dystocia, birth trauma, IUFD
- Neonatal: Hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia, perinatal death, respiratory distress, future obesity, and DM

PEARLS & CONSIDERATIONS

- Trials have shown that although treatment of mild gestational DM did not significantly reduce the frequency of a composite outcome that included stillbirth or perinatal death and several neonatal complications, it did reduce the risks of fetal overgrowth, shoulder dystocia, cesarean delivery, and hypertensive disorders.
- Lactation improves maternal glucose metabolism and may prevent or delay the development of type 2 DM following GDM. Higher lactation intensity and longer duration are independently associated with lower 2-yr incidences of DM after a GDM-affected pregnancy.

PREVENTION

Regular exercise, maintenance of ideal body weight, and high-fiber low-glycemic diet

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Gestational Diabetes (Patient Information)
Diabetes Mellitus (Related Key Topic)

AUTHORS: **Ashley Lakin, DO, MA, Susanna R. Magee, MD, MPH, Anthony Sciscione, DO,** and **Helen B. Gomez, MD**

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Giant Cell Arteritis ALG PTG

BASIC INFORMATION

DEFINITION

Giant cell arteritis (GCA) is a segmental systemic granulomatous arteritis affecting medium and large arteries in individuals >50 yr. Inflammation primarily targets branches of the extracranial head and neck blood vessels (external carotids, temporal arteries, ciliary and ophthalmic arteries). The aorta and subclavian and brachial arteries can also be affected. Intracranial arteritis is rare.

SYNONYMS

Temporal arteritis
Cranial arteritis
GCA
Horton disease

ICD-10CM CODES

M31.5 Giant cell arteritis with polymyalgia rheumatica
M31.6 Other giant cell arteritis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Approximately 20 new cases per 100,000 persons >50 yr; peak incidence is in patients ages 60 to 80 yr.
PREVALENCE: 200 cases per 100,000 persons; it is the most common primary vasculitis; female/male predominance of twofold to fourfold; more common in Caucasians.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

GCA can present with the following clinical manifestations:

TABLE 1 Atypical Manifestations of Giant Cell Arteritis

Fever of unknown origin
Respiratory symptoms (especially cough)
Otolaryngeal manifestations
Glossitis
Lingual infarction
Throat pain
Hearing loss
Large-artery disease
Aortic aneurysm
Aortic dissection
Limb claudication
Raynaud phenomenon
Neurologic manifestations
Peripheral neuropathy
Transient ischemic attack (TIA) or stroke
Dementia
Delirium
Myocardial infarction
Tumorlike lesions
Breast mass
Ovarian and uterine mass
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Microangiopathic hemolytic anemia

From Harris ED et al: *Kelly's textbook of rheumatology,* ed 7, Philadelphia, 2005, Saunders.

- Headache, often associated with marked scalp tenderness—noticed while brushing hair (hair comb allodynia)
- Constitutional symptoms (fever, weight loss, anorexia, fatigue)
- Polymyalgia rheumatica (aching and stiffness of the trunk and proximal muscle groups)
- Visual disturbances (transient or permanent monocular or binocular visual loss)
- Intermittent claudication of jaw and tongue on mastication that is especially prominent when solid food such as steak is chewed
- Table 1 describes atypical manifestations of GCA

Important physical findings in GCA:

- Vascular examination: The temporal artery demonstrates tenderness, decreased pulsation, and nodularity (ropy) (Fig. E1); diminished or absent pulses in upper extremities may be seen.

ETIOLOGY

Vasculitis of unknown etiology. An association with HLA-DRB*04 has been identified. Recent demonstration of varicella zoster virus virion, antigen, and DNA within the vessel walls of the temporal arteries on histopathologic specimens of giant cell arteritis suggest an association.

DIAGNOSIS

Clinical history and vascular examination remain cornerstones of diagnosis. An algorithm for diagnosing GCA is described in Fig. 2. The American College of Rheumatology has proposed classification criteria to aid in the diagnosis of GCA. Presence of three or more of these criteria in a patient with suspected vasculitis is considered to be suggestive of GCA:

- Age of onset of symptoms >50 yr
- New-onset of or new type of localized headache
- Temporal artery abnormalities including tenderness or decreased pulsation
- Westergren erythrocyte sedimentation rate (ESR) elevated (typically >50 mm/hr)
- Temporal artery biopsy with vasculitis and mononuclear cell infiltrate or granulomatous changes

DIFFERENTIAL DIAGNOSIS

- Other vasculitic syndromes
- Nonarteritic anterior ischemic optic neuropathy (NAION)
- Pituitary apoplexy
- Primary amyloidosis
- Transient ischemic attack, stroke
- Infections
- Occult neoplasm, multiple myeloma

LABORATORY TESTS

- ESR elevated although up to 22% of patients with GCA have normal ESR before treatment.
- C-reactive protein (CRP) is typically included in laboratory investigation; it may have greater sensitivity than ESR. CRP typically rises before the ESR.
- Mild to moderate normochromic normocytic anemia, elevated platelet count.

IMAGING STUDIES

Imaging studies do not play a major role in diagnosing GCA and are rarely indicated:

- Color duplex ultrasonography (CDUS) of temporal artery produces three characteristic features—periluminal "halo" over the temporal artery involved, segmental arterial stenosis, and arterial luminal occlusion in severe cases. CDUS of the temporal artery has 40% to 75% sensitivity and 79% to 83% specificity for diagnosis of GCA. Clinical utility is not superior to clinical examination with biopsy.

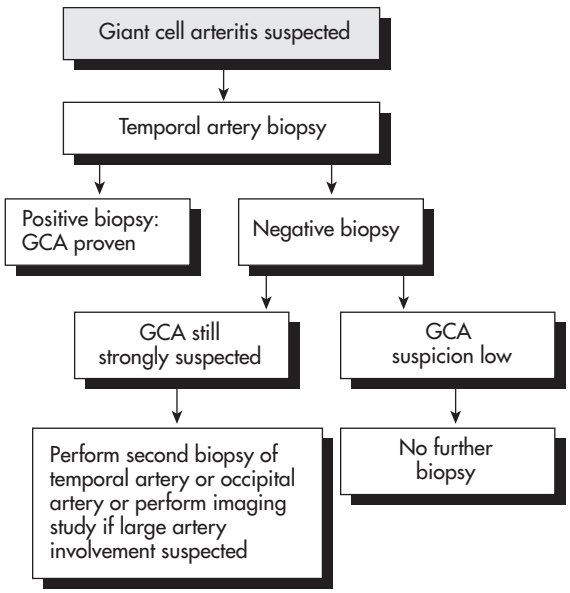

FIG. 2 Algorithm for diagnosing giant cell arteritis *(GCA).* (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

- Contrasted MRI of temporal artery may be performed in patients with contraindications to surgical biopsy of the superficial temporal artery if treatment with steroids has not been initiated. MRI has a 78.4% sensitivity and 90.4% specificity in detecting temporal artery involvement in patients with a clinical diagnosis of GCA.
- Angiography of the arms is indicated in patients with peripheral vascular insufficiency.
- Fluorine-18-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (18F-FDG PEA/CT) imaging may be used to detect large-vessel inflammation in GCA. Sensitivity is 64% in the maxillary or temporal arteries and increases to 82% if vertebral arteries and increases specificity is 100%.

Rx TREATMENT

ACUTE GENERAL Rx

- If there is clinical suspicion of GCA, treatment should be initiated without waiting for results of laboratory or imaging studies.
- IV methylprednisolone (250 to 1000 mg for 1 to 3 days) is considered standard of care in patients with severe clinical manifestations such as visual loss from ischemic optic neuropathy.
- Oral prednisone (1 mg/kg/day): High-dose oral regimen should be continued at least until symptoms resolve and ESR returns to normal; usually 3 to 4 wk after treatment initiation. Steroid taper is very slow (10% to 20% per mo) with monitoring of clinical features as well as ESR and CRP. When dose <10 mg/day, taper by 1 mg/mo. Treatment may last up to 2 yr or more.
- Although corticosteroids have traditionally been the treatment of choice, tocilizumab, an IL-6 receptor blocker, was recently approved by the FDA for the treatment of GCA. Patients treated with tocilizumab and prednisone achieved remission faster, had a greater reduction in steroid dosage, and had prolonged maintenance of remission when compared with those treated with prednisone alone.
- There is no evidence for the role of other steroid-sparing agents.

DISPOSITION

- With steroid therapy there is a dramatic improvement of systemic symptoms, but not vision in patients with ischemic optic neuropathy. In one study only 4% of eyes improved in both visual acuity and central visual field.
- Management of flares: Repeat prednisone induction if patient experiences severe flare. If mild flare, increase prednisone by 10% to 20% and slow down prednisone taper.

REFERRAL

- Surgical or ophthalmologic referral for biopsy of temporal artery
- Rheumatology referral for long-term immunosuppressive treatment management

PEARLS & CONSIDERATIONS

- Treatment of GCA should be started if there is clinical suspicion of the disease. This usually includes patients above the age of 50 presenting with a severe headache and systemic features that suggest GCA as well. Physicians should not wait for laboratory or pathologic confirmation before starting treatment as the risk of visual loss increases. Blindness from untreated GCA is permanent.
- Temporal artery biopsy should be performed as soon as possible, but within 2 wk of initiating treatment with steroids. The biopsy may remain positive for 2 to 6 wk after initiation of corticosteroids.
- Treatment should not be withheld pending temporal artery biopsy.

COMMENTS

- The relation between polymyalgia rheumatica and GCA is unclear, but the two frequently coexist. They are considered to be different points along the gradient or spectrum of the same disease.
- Clinical picture rather than ESR should be the prime yardstick for continuing prednisone therapy. A rising ESR in a clinically asymptomatic patient with normal hematocrit should raise suspicion for alternate explanations (e.g., infections, neoplasms).
- GCA is associated with a markedly increased risk for the development of aortic aneurysm, which is often a late complication and may cause death. Annual chest radiograph in chronic CGA patients has been suggested, as well as emergent chest CT or MRI for clinical suspicion.
- GCA is also associated with increased risk of myocardial infarction, stroke, and peripheral vascular disease.
- Coadministration of low dose aspirin (81 mg/day) has been reported by some as effective for further reduction of risk of blindness. Additional trials may be needed before it can be recommended as standard therapy.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Giant Cell Arteritis (Patient Information)
Vasculitis, Systemic (Related Key Topic)

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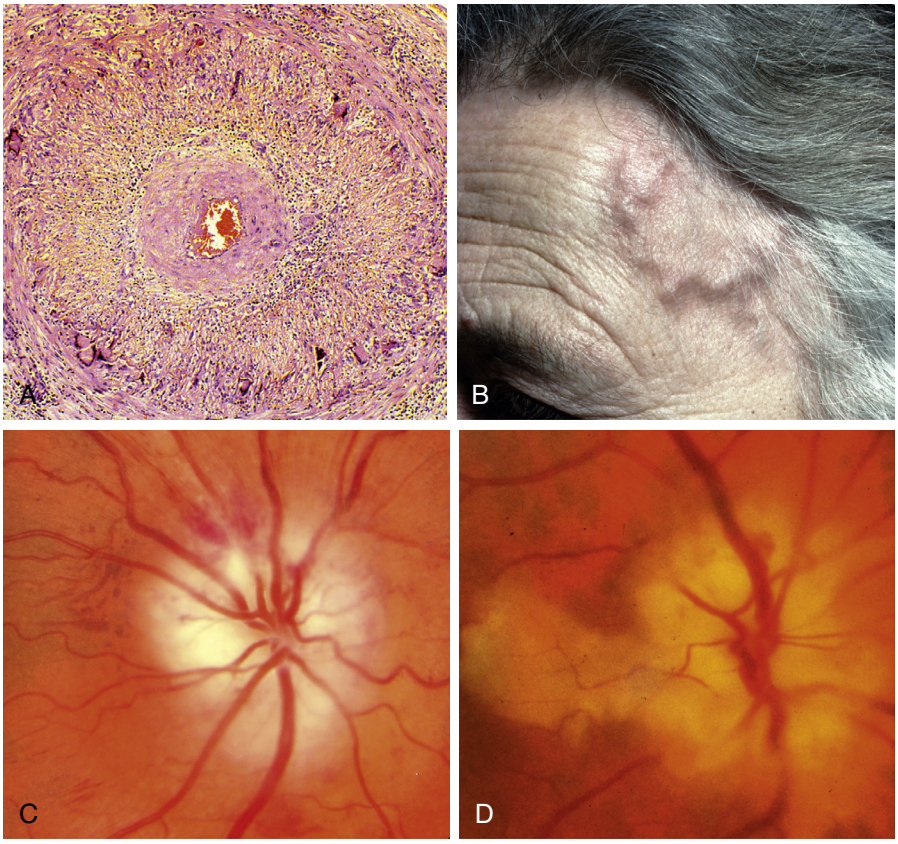

FIG. E1 Giant cell arteritis. A, Histology shows transmural granulomatous inflammation, disruption of the internal elastic lamina, proliferation of the intima, and gross narrowing of the lumen. **B,** The superficial temporal artery is pulseless, nodular, and thickened. **C,** Ischemic optic neuropathy. **D,** Ischemic optic neuropathy and cilioretinal artery occlusion. (From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

Giant Cell Myocarditis

BASIC INFORMATION

DEFINITION

Giant cell myocarditis (GCM) is a rare but frequently fatal inflammatory disorder that affects the myocardium characterized by widespread infiltration in the myocardial tissue of multinucleated giant cells and myocardiocyte necrosis that is not secondary to ischemic events or cardiac rejection in the setting of transplantation. Giant cells are abnormal masses produced by the fusion of inflammatory cells called macrophages. Patients may develop acute or fulminant deterioration in left ventricular systolic function despite standard heart failure treatment, ventricular arrhythmias, and heart block.

SYNONYMS

GCM
Idiopathic myocarditis
Isolated myocarditis

ICD-10CM CODE
I40.1 Giant Cell Myocarditis (acute or subacute); Isolated Myocarditis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Overall, the incidence of GCM is low. Autopsy series report an incidence of GCM ranging from 0.007% to 0.051%.
PREDOMINANT SEX AND AGE: In a large multicenter registry of GCM cases ($n = 63$) patients ranged in age from 16 to 69 yr at the time of symptom onset, with an average patient age of 42.6 yr. GCM affects males and females in equal numbers.
GENETICS: Gene expression analysis of GCM shows that altered expression of T-cell activation genes (immune response genes), such as chemokine receptor 4; chemokine ligans 5, 9, 13, and 19; interleukin-1 receptor alpha to interleukin-10 receptor alpha; and beta-2 integrin, may play a role in its pathogenesis. Additional studies are required in order to further elucidate potential therapeutic targets for GCM.
RISK FACTORS: Approximately 20% of patients who develop GCM have a history of an autoimmune disorder, including ulcerative colitis or Crohn disease and hyperthyroidism.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Approximately 75% of patients present with congestive heart failure (CHF). Shortness of breath/dyspnea on exertion accompanied by fatigue and decreased exercise capacity can be the initial manifestations of CHF
- Increased jugular venous pressure, an S3 murmur, hepatomegaly, and peripheral edema may present in worsening heart failure, specifically right ventricular failure
- Signs of inadequate perfusion with acute progression of heart failure leading to cardiogenic shock, including hypotension, low pulse pressure, cool extremities, persistent tachycardia, and mental status changes
- Ventricular arrhythmia (14%): Ventricular tachycardia with possible deterioration to ventricular fibrillation or sudden cardiac death (SCD)
- Heart block (5%): Ranging from first-degree to complete atrioventricular block
- Initial symptoms resembling an acute myocardial infarction, such as chest pain, present in up to 6% of patients with GCM
- Syncope/presyncope, dizziness, palpitations, or lightheadedness secondary to heart block or ventricular arrhythmia

ETIOLOGY

- The etiology of giant cell myocarditis is insufficiently known but commonly attributed to immune dysregulation mediated by T lymphocytes.
- The strong association of GCM with autoimmune disorders, as well as tumors of immune cells such as thymoma and lymphoma, would also suggest a process of dysregulated immunity.
- Recent gene expression profiling of patients with GCM has revealed upregulation of genes involved in the T-cell immune response.
- Other rarely reported conditions in association with the development of GCM include drug hypersensitivity reaction and infection such as parvovirus B19 (diagnosed via DNA polymerase chain reaction [PCR]) or coxsackie B2 virus (diagnosed via serology and cardiac immunoblotting). However, no microbiologic agent has been directly identified in cardiac tissue by microscopy, tissue culture, or inoculation in experimental animals.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ischemic or nonischemic cardiomyopathy
- Acute coronary syndrome
- Other infiltrative diseases of the myocardium, such as sarcoidosis, lymphocytic, and hypersensitivity myocarditis (Table 1)

WORKUP

- Medical history to determine various etiologies of myocarditis, specifically history of autoimmune disorders.
- Diagnostic workup includes chest x-ray, ECG, laboratory evaluation, echocardiogram, cardiac catheterization, cardiac MRI with late gadolinium enhancement, and endomyocardial biopsy.

LABORATORY TESTS

- N-terminal brain natriuretic propeptide (NT-pro BNP) is recommended if heart failure symptoms are present.
- Increased levels of CKMB, troponin I or T, lactate dehydrogenase, and aspartate aminotransferase are present in the setting of myocardial necrosis.

IMAGING STUDIES

- Chest x-ray: Enlargement of the cardiac silhouette with or without pulmonary congestion.
- ECG: Sinus tachycardia with nonspecific ST-T wave changes, intraventricular conduction defects, and bundle branch blocks are common manifestations in idiopathic giant cell myocarditis. Ventricular arrhythmias or heart blocks may also be present.
- Echocardiogram: Acute severe myocarditis is associated with global systolic dysfunction and decreased ejection fraction. The left ventricle may be dilated or hypokinetic. Abnormal tissue Doppler signal can provide additional evidence for the presence of myocarditis.
- Cardiac catheterization and angiography: Used to rule out coronary artery disease and valvular disease. Patients with GCM will most commonly have a normal coronary arteries.
- Cardiac MRI can be used to detect myocardial edema and myocyte injury in myocarditis. It has the sensitivity and specificity of approximately 80% for diagnosing acute myocarditis. Late gadolinium enhancement (LGE) demonstrates myocardial damage from inflammation or fibrosis. Combining T2 imaging with LGE can help distinguish acute inflammation from chronic injury.
- F-18 fluorodeoxyglucose combined with positron emission tomography (FDG-PET) can assess the severity of myocardial inflammation, as well as likelihood of disease progression to fibrosis, dilated cardiomyopathy, and heart failure.
- Endomyocardial biopsy (EMB) is considered the gold standard for diagnosis. The sensitivity of right ventricular EMB for GCM is 80% to 85%; it is 93% with repeated biopsy, or with combined right and left ventricular biopsies. Histopathology reveals the presence of giant cells, granulomas (less frequently), the character of inflammation (lymphocytes, eosinophils, macrophages), and the presence of myocyte hypertrophy and interstitial fibrosis (Fig. E1).
- It is important to distinguish between various types of inflammatory myocarditis because survival among patients in whom GCM is diagnosed on the basis of endomyocardial biopsy or apical wedge sampling is worse than patients with either cardiac sarcoid or lymphocytic myocarditis.
- GCM usually has diffuse or multifocal involvement of the endocardium; therefore EMB tends to have a higher diagnostic sensitivity in GCM than in cardiac sarcoidosis (35%) or lymphocytic myocarditis (25%).

TREATMENT

Cyclosporine-based combined immunosuppression may be able to reduce myocardial inflammation and improve clinical outcome. The goal of immunosuppression therapy is to delay heart transplantation and delay transplant. Cessation or sometimes reduction of immunosuppression is associated with GCM recurrence as far as 8 yr after diagnosis. Heart transplantation is frequently inevitable. The rate of death or cardiac transplantation was 89% with a median survival

TABLE 1 Features of Select Causes of Inflammatory Myocarditis

Inflammatory Disorder	Histologic Features	Common Presentations	Diagnosis	Treatment Monitoring
CS	Granulomas, in the absence of infection. Eosinophils and necrosis rare or absent.	Heart block, ventricular arrhythmias, more indolent cardiomyopathy	Clinical, electrocardiographic, and advanced imaging with ^{18}F-FDG PET or CMR. EMB sensitivity increased by ventricular voltage mapping. Basal septal aneurysm is rare but specific.	Clinical status, arrhythmia monitoring, natriuretic peptides, LV function, and possibly serial PET imaging.
Idiopathic GCM	Necrotizing inflammation with lymphocytes, eosinophils, histiocytes, and multinucleated giant cells often near the region of myocyte damage. No well-formed granulomas.	Ventricular tachycardia in the setting of acute or fulminant systolic heart failure with/without heart block. Progressive course over wks to mos, requiring inotropic and/or mechanical circulatory support.	EMB	Clinical status, assessment of ventricular function, repeat EMB indicated for suspected recurrent disease.
Eosinophilic myocarditis	Endocardial or perivascular forms. Extensive myocyte damage suggests necrotizing eosinophilic myocarditis or very early GCM.	Heart failure related to valvular involvement. Thrombi with peripheral emboli are common.	CMR. Disease may be isolated to the LV, decreasing the diagnostic use of right ventricular EMB.	Clinical status, assessment of ventricular function, CMR for tissue characterization, peripheral eosinophil count if initially elevated.
Lymphocytic myocarditis	Lymphocyte predominant, nonischemic infiltrate with or without myocyte necrosis (borderline if no myocyte damage).	Heart failure with a dilated LV. Fulminant disease associated with a smaller ventricular size and thicker walls.	CMR	Clinical status, natriuretic peptides, assessment of ventricular function.

CMR, Cardiac magnetic resonance; *CS,* cardiac sarcoidosis; *EMB,* endomyocardial biopsy; *GCM,* giant cell myocarditis; *LV,* left ventricle; *PET,* positron emission tomography; *^{18}F-FDG,* ^{18}F-fluorodeoxyglucose.

From Kadkhodayan A et al: Imaging of inflammation in unexplained cardiomyopathy, *JACC Cardiovasc Imaging* 9(5):603-617, 2016.

of 5.5 mo from the onset of symptoms to the time of death or transplantation.

The prognosis of GCM with no or limited immunosuppressive therapy is poor. Without appropriate immunosuppressive therapy, the median survival from GCM symptom onset to death or transplant is only 3 mo. With appropriate immunosuppressive therapy, the 5-yr survival rate free of transplant ranges from 52% to 72%.

NONPHARMACOLOGIC THERAPY

Mechanical circulatory support may be required for acute decompensated heart failure. Cardiac transplantation is often required.

ACUTE GENERAL Rx

- Immunosuppressive therapy: Usually involves a combination of muromonab-CD3, cyclosporine, azathioprine, and corticosteroids with mycophenolate mofetil a potential substitute for azathioprine.
- Antiarrhythmic drugs (AADs) for ventricular arrhythmias including amiodarone, sotalol, and mexiletine. Sustained arrhythmias should be treated with urgent cardioversion.
- Treatment for heart failure with reduced ejection fraction includes angiotensin-converting enzyme inhibitor (or angiotensin receptor blocker) and evidence-based beta blocker.
- Catheter or surgical ablation for VT.
- Mechanical circulatory support and cardiac transplant: Potential options for patients with refractory heart failure or cardiogenic shock include ventricular assist device (VAD) or extracorporeal membrane oxygenation (ECMO). Cardiac transplant needs to be considered soon after diagnosis. GCM can recur in ~25% of transplanted hearts.

DISPOSITION

- GCM has a significantly worse prognosis compared with lymphocytic or presumed viral myocarditis.
- Immunosuppression must be continued long term as GCM can recur up to 8 yr after diagnosis if immunosuppressive therapy is tapered or terminated.
- Even with long-term immunosuppression, patients remain at risk of developing ventricular arrhythmias and may require ICD.
- Rate of death or cardiac transplant was 89% and the median survival from onset of symptoms was 5.5 mo.

REFERRAL

- Implantation of a cardiac defibrillator should be considered (class IIa indication) in GCM, with this diagnosis as the sole criterion in patients who have reasonable expectation of survival with a good functional status for more than 1 yr. Permanent ICD is not recommended until the resolution of the acute phase and a wearable external defibrillator may be considered during recovery.
- Endomyocardial biopsy is the gold standard and should be performed when there is clinical suspicion present.
- Most patients will require heart transplant despite aggressive treatment with immunosuppressive therapy.
- Catheter or surgical VT ablation may be considered in patients with recurrent ventricular arrhythmias; however, success rate in this population is unknown.
- Complete heart block and symptomatic bradycardia are indications for pacing during acute phase of GCM.

PEARLS & CONSIDERATIONS

- Rapid diagnosis is critical, as the management differs from that of other myocardial processes containing giant cells, and early institution of combined cyclosporine-based immunosuppression can dramatically affect the disease course by reducing inflammation and improving transplant-free survival.
- Owing to advancements in diagnostic and therapeutic options, it is now increasingly diagnosed on the basis of endomyocardial biopsies, explanted hearts, or apical wedge sections removed at the time of ventricular assist device placement.

RELATED TOPICS

Myocarditis (Related Key Topic)

AUTHOR: **Jennifer Bell, MD**

SUGGESTED READINGS

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Cooper LT et al: Usefulness of immunosuppression for giant cell myocarditis, *Am J Cardiol* 102(11):1535-1539, 2008, https://doi.org/10.1016/j.amjcard.2008.07.041.

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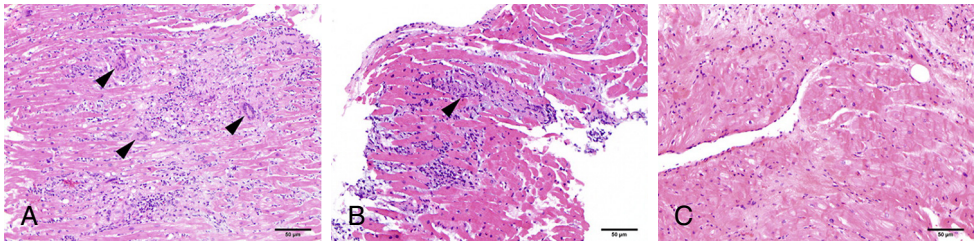

FIG. E1 Histopathologic presentation of giant cell myocarditis (GCM). A, Active GCM characterized by an intense lymphoplasmacytic and eosinophilic infiltrate with scattered multinucleated giant cells *(arrowheads),* associated with myocyte injury and necrosis (hematoxylin and eosin staining, 100× original magnification). **B,** Recurrent GCM, characterized by a lymphoplasmacytic infiltrate with rare multinucleated giant cell *(arrowhead)* (hematoxylin and eosin staining, 100× original magnification). **C,** Moderate myocyte hypertrophy with moderate interstitial (replacement-type) fibrosis, likely representing myocarditis-associated injury (hematoxylin and eosin staining, 100× original magnification). (From Maleszewski J et al: Long-term risk of recurrence, morbidity and mortality in giant cell myocarditis, *Am J Cardiol* 115(12):1733-1738, 2015.)

BASIC INFORMATION

DEFINITION

Giardiasis is an intestinal and/or biliary tract infection caused by the noninvasive protozoal parasite *Giardia intestinalis* (also known as *G. lamblia* or *G. duodenalis*). The organism is a widespread zoonotic parasite and frequently contaminates fresh water sources worldwide.

SYNONYMS

Giardiasis
Giardia duodenalis (accepted species name by the CDC)
Giardia intestinalis

ICD-10CM CODE
A07.1 Giardiasis [lambliasis]

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):
- Exact incidence unknown. CDC estimates 20,000 cases a yr in the U.S.
- Frequently occurs as waterborne outbreaks in international adoptees, travelers, immunocompromised patients, and those with cystic fibrosis.
- *G. lamblia* has been demonstrated in 4% to 7% of submitted stool specimens, making it the most commonly identified intestinal parasite.

PREVALENCE (IN U.S.): 4%
PREDOMINANT SEX: Male = female
PREDOMINANT AGE:
- Preschool children, especially if in day care
- 20 to 40 yr of age, especially among sexually active homosexual men (oral-anal contact)

PEAK INCIDENCE:
- Varies with risk factors, outbreaks, but peak onset from early summer through early fall
- All age groups affected

GENETICS: Familial disposition: Patients with common variable immunodeficiency or X-linked agammaglobulinemia are at increased risk of infection.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- More than 70% with one or more intestinal symptoms (diarrhea, flatulence, cramps, bloating, nausea). Table 1 summarizes clinical signs and symptoms of giardiasis
- Incubation period averages 7 to 21 days
- Fever in <30%
- Chronic diarrhea, malabsorption, and weight loss, which can be up to 10% of body weight, are common
- GI bleeding is unusual
- Continuous or intermittent symptoms, lasting for 2 to 4 wk
- Of infected patients, 20% to 25% are asymptomatic and can shed cysts for months

TABLE 1 Symptoms of Giardiasis

Symptom	Frequency (%)
Flatulence	56-74
Anorexia	40-64
Abdominal cramps	55-80
Foul-smelling stool	57-72
Abdominal distention	31
Bloating	55-69
Nausea	58-68
Malaise	84
Diarrhea	89
Belching	30
Weight loss	48-64
Fever	17-28

From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

ETIOLOGY

Infection is acquired by ingestion of viable cysts of the organism (Fig. 1), typically in contaminated water or food or by fecal-oral contact. *Giardia* cysts are resistant to chlorination and survive well in cold mountain streams.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other agents of infective diarrhea (amebae, *Salmonella* sp., *Shigella* sp., *Staphylococcus aureus, Cryptosporidium*, etc.)
- Noninfectious causes of malabsorption

WORKUP

- Stool specimen (three specimens yield 90% sensitivity) as a saline suspension or duodenal aspirate for microscopic examination to establish diagnosis and exclude other pathogens
- Immunoassays for *Giardia* sp. Antigens in stool samples such as the DFA or ELISA are now routinely used in most clinical laboratories. These assays are 85% to 98% sensitive and 90% to 100% specific. They are more sensitive than stool microscopy for confirming the diagnosis. They also have a faster turnaround time.

LABORATORY TESTS

Serum albumin, vitamin B_{12} levels, and stool fat test to exclude malabsorption

IMAGING STUDIES

- Not necessary unless biliary obstruction is suspected
- In detection of organism, possible interference by barium in stool from radiographic studies

TREATMENT

NONPHARMACOLOGIC THERAPY

Avoidance of milk products to reduce symptoms of transient lactase deficiency that occur in many patients and can last for wk to mo

GENERAL Rx

Adult and pediatric (Table E2):
- Metronidazole 250 mg PO three times daily for 5 to 10 days. Pediatric dose: 5 mg/kg tid × 7 days (metronidazole should be avoided in pregnancy)
- Alternative regimen: Tinidazole: 2 g single dose (50 mg/kg in children over 3 yr of age)
- Nitazoxanide: aged 12 to 47 mo: 100 mg bid × 3 days. Aged 4 to 11 yr: 200 mg bid × 3 days
- Quinacrine: 100 mg po tid × 5 to 7 days
- Albendazole 400 mg PO qd × 5 days
- Paromomycin 25 to 35 mg/kg/day in three doses for 5 to 10 days. Safe for pregnancy

DISPOSITION

Reinfection is possible. Postinfection lactose intolerance is common and is frequently mistaken for recurrent infection.

PEARLS & CONSIDERATIONS

COMMENTS

Travelers to endemic areas (developing world, wilderness areas) should be cautioned to boil drinking water or use water purification tablets (for iodine-containing products, chlorination is not effective). Chronic giardiasis as seen in developing nations can cause delays in growth and development in children due to malabsorption and diarrhea.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Giardiasis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

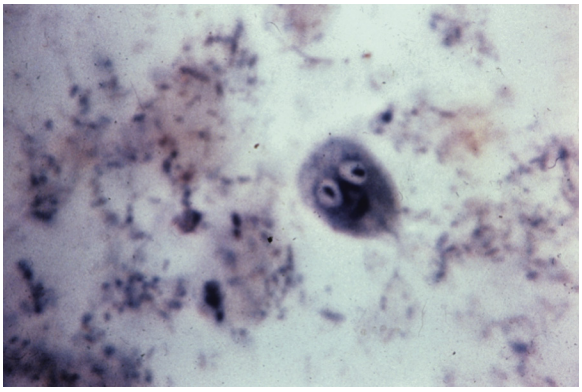

FIG. 1 *Giardia lamblia* trophozoite is demonstrated in a trichrome stain of fecal material. Note the prominent nuclei in the trophozoite. (From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.)

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Muhsen K, Levine MM: A systematic review and meta-analysis of the association between *Giardia lamblia* and endemic pediatric diarrhea in developing countries, *Clin Infect Dis* 55(Suppl 4):S271-S293, 2012.

Nash TE: Unraveling how Giardia infections cause disease, *J Clin Invest* 123:2346, 2013.

TABLE E2 Drugs for the Treatment of Giardiasis

Drug	Dose	Efficacy (%)	Side Effects
Metronidazole	15 mg/kg/day orally divided 3 times a day for 5-10 days (maximum, 750 mg/day)	80-100	Metallic taste, headache, nausea, vomiting, rash, peripheral neuropathy, neutropenia, disulfiram-like effects
Tinidazole	50 mg/kg, single dose (maximum, 2 g)	80-96	Metallic taste, nausea, vomiting, headache, rash, peripheral neuropathy, neutropenia, disulfiram-like effects
Ornidazole[a]	40-50 mg/kg, single dose (maximum, 2 g)	96-100	Metallic taste, nausea, vomiting, headache, rash, peripheral neuropathy, neutropenia, disulfiram-like effects
Secnidazole	2 g, single dose	90	Nausea, anorexia, abdominal pain
Albendazole[b]	15 mg/kg per day for 5-7 days (maximum, 400 mg/day)	94-100	Anorexia, constipation, neutropenia, elevated liver function test results
Furazolidone	6 mg/kg per day orally divided 4 times a day for 10 days	81-96	Allergic reactions, headache, nausea, vomiting, diarrhea, brown discoloration of urine, hemolysis, disulfiram-like effects
Paromomycin	30 mg/kg per day divided 3 times a day for 5-10 days (maximum, 1.5 g/day)	55-88	Nausea, vomiting, ototoxicity, nephrotoxicity
Quinacrine[a]	6 mg/kg per day divided 3 times a day for 7 days	92-95	Nausea, vomiting, dizziness, headache, yellow or orange skin and mucous membrane discoloration, hemolysis, toxic psychosis
Nitazoxanide	1-3 yr: 200 mg/day divided 2 times a day for 3 days 4-11 yr: 400 mg/day divided 2 times a day for 3 days ≥12 yr: 1000 mg/day divided 2 times a day for 3 days	85-90	Nausea, abdominal pain, diarrhea, anorexia, flatulence, headache, yellow eyes, discolored urine, increased creatinine and serum glutamic-pyruvic transaminase levels

[a]No longer produced in the U.S. Can be obtained from Panorama Pharmacy, Panorama City, CA.
[b]Not approved by the U.S. Food and Drug Administration for this indication in the U.S.
From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

BASIC INFORMATION

DEFINITION

Gilbert syndrome is an autosomal-dominant disorder characterized by indirect hyperbilirubinemia caused by impaired glucuronyl transferase activity.

SYNONYM

Gilbert disease

ICD-10CM CODE
E80.4 Gilbert syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Probable autosomal-dominant disease affecting >5% of the U.S. population
PREDOMINANT SEX: Male:female ratio of 3:1
GENETICS: Most common hereditary hyperbilirubinemia (genotypic prevalence 12%)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- No abnormalities on physical examination other than mild jaundice when bilirubin exceeds 3 mg/dl.
- A family history of unconjugated hyperbilirubinemia may be present.

ETIOLOGY

- Decreased elimination of bilirubin in bile is caused by inadequate conjugation of bilirubin.
- Alcohol consumption and starvation diet can increase bilirubin level.
- The pathogenesis of Gilbert syndrome has been linked to a reduction in the bilirubin UGT-1 gene *(HUG-Brl)* transcription, resulting from a mutation in the promoter region.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hemolytic anemia
- Liver disease (chronic hepatitis, cirrhosis)
- Crigler-Najjar syndrome

WORKUP

- Most patients are diagnosed during or after adolescence, when isolated hyperbilirubinemia is detected as an incidental finding on routine biochemical testing.
- Laboratory evaluation to exclude hemolysis and liver diseases as a cause of the elevated bilirubin level (Table 1 and Fig. 1).

LABORATORY TESTS

Elevated indirect (unconjugated) bilirubin (rarely exceeds 5 mg/dl)

TABLE 1 Characteristic Patterns of Liver Function Tests

Disorder	Bilirubin	Alkaline Phosphatase	AST	ALT	Prothrombin Time	Albumin
Gilbert syndrome (abnormal bilirubin metabolism)	↑	NL	NL	NL	NL	NL
Bile duct obstruction (pancreatic cancer)	↑↑↑	↑↑↑	↑	↑	↑-↑↑	NL
Acute hepatocellular damage (toxic, viral hepatitis)	↑-↑↑↑	↑-↑↑	↑↑↑	↑↑↑	NL-↑↑↑	NL-↓↓
Cirrhosis	NL-↑	NL-↑	NL-↑	NL-↑	NL-↑↑	NL-↓↓

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase; *NL,* normal; ↑, increase; ↓, decrease (arrows indicate extent of change: ↑-↑↑↑, slight to large).
From Andreoli TE (ed): *Cecil essentials of medicine,* ed 6, Philadelphia, 2005, WB Saunders.

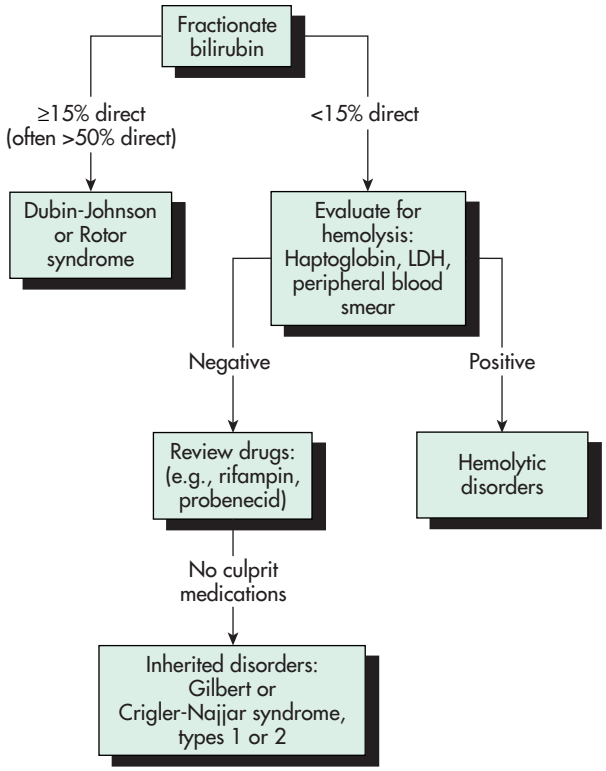

FIG. 1 Evaluation of an isolated elevation of the serum bilirubin level. *LDH,* Lactic dehydrogenase. (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, WB Saunders.)

TREATMENT

ACUTE GENERAL Rx

Treatment is generally unnecessary. Phenobarbital (if clinical jaundice is present) can rapidly decrease serum indirect bilirubin level.

DISPOSITION

Prognosis is excellent. Treatment is generally unnecessary.

REFERRAL

Referral is generally not necessary.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients should be reassured about the benign nature of the condition.
- Fasting for 2 days or significant dehydration may raise the bilirubin level and result in the clinical recognition of jaundice.

AUTHOR: **Fred F. Ferri, MD**

BASIC INFORMATION

DEFINITION

Inflammation of the gums covering the maxilla and mandible

ICD-10CM CODES

K05.0	Acute gingivitis
K05.1	Chronic gingivitis
K05.6	Other disorders of gingiva and edentulous alveolar ridge

EPIDEMIOLOGY & DEMOGRAPHICS

Gingivitis generally occurs in adults.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Inflammation is usually painless. Red velvety gingiva may be present (Fig. E1).
- Bleeding may occur with minor trauma such as brushing teeth.
- A bluish discoloration of the gums and halitosis are sometimes present.
- Subgingival plaque may be seen on close examination, and in time, there is detachment of soft tissue from the tooth surface.
- Long-standing infection may lead to destructive periodontal disease, which may involve teeth and bones.
- A dramatic form of gingivitis called acute ulcerative necrotizing gingivitis (ANUG or "trench mouth") can occur. This is manifested by acute, painful inflammation of the gingivae, with bleeding, ulceration, and halitosis. At times this is accompanied by fever and lymphadenopathy.
- Linear gingival erythema ("HIV gingivitis") presents as a brightly inflamed band of marginal gingiva. It may be painful, with easy bleeding and rapid destruction.
- Severe periodontitis can occur in patients with diabetes mellitus or HIV infection and in primary HIV infection (acute retroviral syndrome).
- Pregnancy may be associated with an acute form of gingivitis. Gingivae become inflamed and hypertrophic; this is likely the result of hormonal shifts.

ETIOLOGY

- A variety of organisms may be found in the environment of plaque. Anaerobes play a predominant role in periodontal disease.
  1. Bacteria playing a role in chronic disease include *Tannerella forsythia, Porphyromonas gingivalis,* and *Treponema denticola.*
  2. Porphyromonas gingivalis is considered the keystone pathogen as it secretes enzymes known as gingipains that cause tissue damage and immune disruption and changes to the normal oral commensal microbiota.
- Improper hygiene and poorly fitting dentures may contribute to the development of gingivitis.
- Excessive use of tobacco and alcohol may predispose individuals to gingival disease.
- In patients with HIV infection, gram-negative anaerobes, enteric organisms, and yeast predominate.
- Appropriate oral hygiene, such as flossing and tooth brushing, can prevent the accumulation of bacterial plaque; once dense plaque is present, adequate hygiene becomes more difficult.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Gingival hyperplasia, which may be caused by long-term use of phenytoin or nifedipine

WORKUP

Oral examination

LABORATORY TESTS

Elevated serum glucose in diabetics

IMAGING STUDIES

Radiographs of the teeth and facial bones may reveal extension of infection to these structures.

TREATMENT

NONPHARMACOLOGIC THERAPY

Removal of plaque, and at times, debridement of soft tissue

ACUTE GENERAL Rx

- Penicillin VK, 500 mg PO qid for 1 to 2 wk
- Clindamycin, 300 mg PO qid for 1 to 2 wk
- For linear gingival erythema, chlorhexidine gluconate rinses at a concentration of 0.2% and nystatin rinses or troches may be used

CHRONIC Rx

Extensive or recurrent infection may require periodic evaluation and debridement.

DISPOSITION

Continued inflammation can eventually lead to destruction of teeth and bone.

REFERRAL

Patients should be referred to a dentist or periodontist.

PEARLS & CONSIDERATIONS

COMMENTS

- Presence of periodontal disease is associated with an increased incidence of anaerobic pleuropulmonary infections.
- Existing data support the recommendation to change a toothbrush every 3 mo. Worn brushes seem to be less effective in plaque reduction.

RELATED CONTENT

Gingivitis (Patient Information)
Gingivitis, Necrotizing Ulcerative (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

FIG. E1 Gingivitis in a patient with cicatricial pemphigoid. This pattern of periodontal, chronic, red, velvety gingivitis is very suggestive of this disorder but may occur in other blistering diseases. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

SUGGESTED READINGS

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Hodgdon A: Dental and related infections, *Emerg Med Clin North Am* 31(2):465-480, 2013.
Slots J: Human viruses in periodontitis, *Periodontol 2000* 53(1):89-110, 2010.
Khan SA et al: Periodontal diseases: bug induced, host promoted, *PLoS Pathog* 11:e1004952, 2015.

Gingivitis, Necrotizing Ulcerative (NUG)

BASIC INFORMATION

DESCRIPTION

Necrotizing ulcerative gingivitis (NUG) is a distinct painful infectious disease primarily of the interdental and marginal gingiva. It is characterized by a symptom triad that includes gingival pain, ulcer, and bleeding.

SYNONYMS

NUG
Trench mouth
Acute necrotizing ulcerative gingivitis (ANUG)
Vincent stomatitis
Fusospirochetal gingivitis
Acute ulcerative gingivitis

ICD-10CM CODE
A69.0 Necrotizing ulcerative stomatitis

EPIDEMIOLOGY

INCIDENCE: Unlike in the developing world, NUG is seen rarely in developed countries.
PREDOMINANT AGE:

- Occurs in the second and third decades of life in the developed world.
- In contrast, it affects young children more often in developing countries.

PREDOMINANT SEX: Slightly more prevalent in males than in females because the latter group tend to have better oral hygiene.

RISK FACTORS

- Poor oral hygiene
- Smoking/chewing tobacco
- Alcohol use
- Drug addiction
- Poor socioeconomic status
- Psychological stress
- Preexisting gingivitis
- Lack of sleep
- Malnutrition
- Overcrowding
- Living near livestock
- History of prior NUG
- Recent illness
- Underlying systemic diseases
- Acatalasia
- Various infections such as measles, malaria, and infestation with intestinal parasites
- Trauma
- Immunosuppression:
  1. Dermatomyositis (DM)
  2. Steroid use
  3. HIV/AIDS
  4. Use of chemotherapeutic drugs
  5. Leukemia and other malignancies

ETIOLOGY

- Polymicrobial
- Often caused by both *Fusobacterium* and spirochetes

PATHOGENESIS

- Unknown.
- For the most part, it appears to result from an opportunistic infection in a host with lowered resistance.

CLINICAL FEATURES

- Onset of the disease is usually sudden.
- Severe gingival pain.
- Gingival tissue is inflamed, edematous, friable, and necrotic; the normal pointed interdental papillae are blunted, but there is no loss of attachment.
- Gingival bleeding with little or no provocation.
- Punched out ulcerations are seen along the interdental papillae around the anterior incisors and posterior molars. A grayish-white pseudomembrane often covers these ulcers. These punched out ulcers along the pseudomembrane are pathognomonic of NUG.
- Other features include:
  1. Halitosis
  2. Alteration in taste, such as a metallic flavor
  3. Wooden teeth feeling
  4. Odynophagia
  5. Fever and fatigue
  6. Cervical lymphadenopathy

DIAGNOSIS

- Based on the clinical features
- WBC may be elevated
- Gram stain and aerobic/anaerobic culture
- Dental x-ray or x-ray of face to check on the extent of the disease
- HIV testing is recommended for patients refractory to antibiotic therapy

DIFFERENTIAL DIAGNOSIS

- Gingivitis
- Acute herpetic gingivostomatitis
- Aphthous stomatitis
- Chronic periodontal disease
- Desquamative gingivitis
- Gonococcal and streptococcal gingivostomatitis
- Oral candidiasis
- Ludwig angina
- HIV-associated idiopathic ulcerations

TREATMENT

- Improve oral hygiene by flossing and brushing at least twice a day.
- Improve nutrition and hydrations.
- Eliminate contributing factors such as smoking, alcohol, carbonated beverages, spicy/hot foods, poor nutrition, stress, and so on.
- Antibiotic coverage for 5 to 10 days. Most recommend oral penicillin V 250 to 500 mg orally every 6 to 8 hr and metronidazole 250 to 500 mg orally every 8 hr. Tetracycline is given instead of penicillin in patients allergic to the latter. As an alternative one could give only clindamycin instead of the drug combination of penicillin and metronidazole.
- Rinsing the mouth at least twice a day with warm saline (1/2 teaspoon of salt in 1 cup of water), 0.12% chlorhexidine, or dilute 3% hydrogen peroxide (mixed half and half with water).
- Pain is controlled with oral pain medications and topical application of 2% viscous lidocaine (15 ml oral rinse every 6 to 8 hr as needed) to the inflamed gum.
- Surgical debridement is needed in severe cases.
- Scaling and root planing following the resolution of infection and the acute inflammation.
- At times reconstructive surgery may be needed.

COMPLICATIONS

- Cancrum oris (noma) results when NUG involves the deeper tissue
- Vincent angina from the involvement of tonsils and pharynx
- Necrotizing ulcerative periodontitis
- Loss of teeth
- Periodontal abscess
- Alveolar bone destruction
- Disfigurement
- Cellulitis
- Dehydration/malnutrition

PROGNOSIS

- Dramatic relief of symptoms within 24 hr of initiating antibiotics and supportive treatment is characteristic.
- Risk of recurrence is high.

PEARLS & CONSIDERATIONS

PREVENTION

- Good oral hygiene
- Use of power toothbrush is better than a manual brush
- Good general health including proper nutrition, sleep, and exercise
- Routine dental checks
- Avoidance of smoking and alcohol
- Stress management

PATIENT EDUCATION

Not a communicable disease

AUTHOR: **Hemant K. Satpathy, MD**

Glaucoma, Open-Angle PTG

BASIC INFORMATION

Glaucoma is a chronic degenerative optic neuropathy (or the high potential for such degeneration due to risk factors) in which the neuroretinal rim of the optic nerve becomes progressively thinner, thereby enlarging the optic-nerve cup. The classification of glaucoma is based on the appearance of the iridocorneal angle (open angle vs. narrow or closed angle) and is further subdivided into primary and secondary types. Fig. 1 and Table 1 illustrate the difference between open-angle and narrow-angle glaucoma. Primary open-angle glaucoma can occur with or without elevated intraocular pressure (IOP). Normal tension glaucoma refers to primary open-angle glaucoma without elevated intraocular pressure.

SYNONYMS

Primary open-angle glaucoma (POAG)
Open-angle glaucoma or chronic open-angle glaucoma (OAG, COAG)
Secondary open-angle glaucoma (e.g., pseudoexfoliation, pigment dispersion, trauma, inflammatory)
Ocular hypertension (elevated intraocular pressure with no evidence of optic nerve damage)
Optic nerve cupping, glaucoma suspect

ICD-10CM CODES

H40.10X0	Unspecified open-angle glaucoma, stage unspecified
H40.10X1	Unspecified open-angle glaucoma, mild stage
H40.10X2	Unspecified open-angle glaucoma, moderate stage
H40.10X3	Unspecified open-angle glaucoma, severe stage
H40.10X4	Unspecified open-angle glaucoma, indeterminate stage
H40.11X0	Primary open-angle glaucoma, stage unspecified
H40.11X1	Primary open-angle glaucoma, mild stage
H40.11X2	Primary open-angle glaucoma, moderate stage
H40.11X3	Primary open-angle glaucoma, severe stage
H40.11X4	Primary open-angle glaucoma, indeterminate stage

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Third most common cause of vision loss (75% to 95% of all forms of glaucoma are open angle)

PEAK INCIDENCE:
- Increases after age 40 yr
- Three million cases expected by 2020 because of the rapid increase in aging population

PREVALENCE (IN U.S.):
- Overall prevalence in U.S. population aged >40 yr is estimated to be 1.86%, with 1.57 million white and 398,000 black patients affected. By 2020, we may expect more than 3 million cases in the U.S.
- 150,000 patients have bilateral blindness.
- Prevalence is higher in diabetics, those with high myopia, and older persons.
- More common in African-American population (three times the age-adjusted prevalence than whites). There is a genetic tendency to OAG; multiple genes have been isolated that are associated with development of high IOP and optic nerve damage.

PREDOMINANT AGE:
- Persons >50 yr
- Can occur in 30s and 40s, and juvenile forms are rare

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- High intraocular pressures and/or large optic nerve cup (Fig. E2). Ocular Hypertension Treatment Study results help to delineate important risk factors, including high eye pressure, thin corneal central thickness, age, and visual field results.
- Abnormal visual fields (with advanced glaucoma damage to the optic nerve).
- Open anterior chamber angle—evaluated with gonioscopy at slit lamp
- Figs. E3 and E4 illustrate stages of open-angle glaucoma.
- Since early treatable stages of OAG normally have no symptoms, it's important to have routine eye exams, especially patients with family history and patients over 60 yr.
- Secondary forms of OAG may exhibit ocular findings such as pseudo-exfoliation, pigment dispersion, blood in anterior chamber, inflammation.

ETIOLOGY

- Uncertain hereditary tendency (multifactorial genetics)
- Topical steroids can induce high IOP and cause glaucoma
- Trauma
- Inflammatory (e.g., history of uveitis)
- High-dose oral corticosteroids taken for prolonged periods

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other optic neuropathies (previous retinal vascular disorders, optic nerve pits, or coloboma).
- Physiologic cupping of the optic nerve: The optic nerve may appear similar to glaucoma damage but does not progress. This is followed for any signs of progression.
- Ocular hypertension: IOP is chronically elevated, but not causing optic nerve damage, must monitor closely.
- Secondary glaucoma from inflammation and steroid therapy.
- Trauma

WORKUP

- Comprehensive eye examination
- Intraocular pressure
- Slit lamp examination
- Visual fields
- Gonioscopy: To determine the type of glaucoma (narrow, open, or closed angles)
- Nerve fiber analysis (e.g., OCT, and HRT)
- Corneal thickness (thick central cornea will result in possible overestimation of the true physiologic IOP, and vice versa, so this is

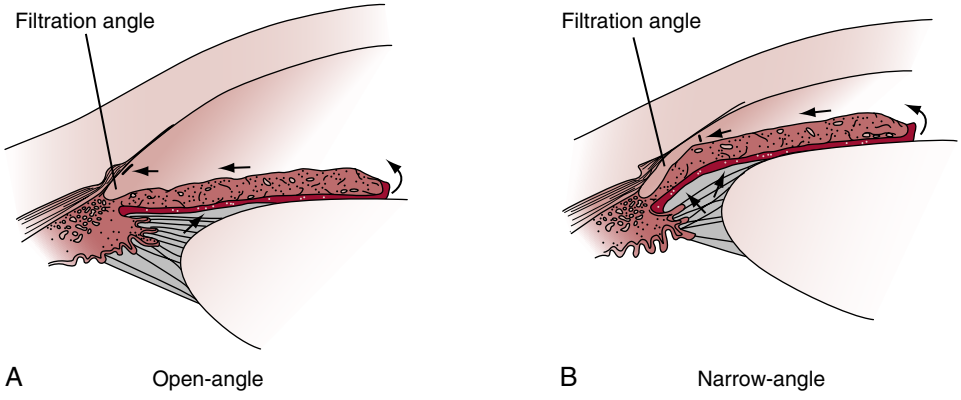


FIG. 1 A, Open-angle glaucoma: Drainage of the aqueous humor becomes obstructed, and impaired flow from the eye leads to gradually increased intraocular pressure. **B,** Narrow-angle glaucoma: When the iris moves forward, as may occur during pupil dilation, the angle is narrowed or even closed. Obstruction of aqueous humor flow leads to angle-closure glaucoma. (From Kaufman DM, Geyer HL, Milstein MJ: *Kaufman's clinical neurology for psychiatrists*, ed 8, Philadelphia, 2017, Elsevier.)

TABLE 1 Characteristics of Glaucoma

Feature	Primary Open-Angle Glaucoma	Narrow-Angle Glaucoma
Occurrence	85% of all glaucoma cases	15% of all glaucoma cases
Cause	Unclear*	Closed angle prevents aqueous drainage
Age at onset	Variable	50 to 85 yr
Anterior chamber	Usually normal	Shallow
Chamber angle	Normal	Narrow
Symptoms	Usually none Decreased vision, late	Headache Seeing halos around lights Sudden onset of severe eye pain Vomiting during attack
Cupping of disc	Progressive if not treated	After one or more untreated attacks
Visual fields	Peripheral fields are involved early Central involvement is a very late sign	Involvement is a late sign
Ocular pressure	Progressively higher if not medically controlled Late: High	Early: Detected with provocative tests only
Other signs		Fixed, partially dilated pupil Conjunctival injection "Steamy" cornea†
Treatment	Medical Laser surgery	Surgical
Prognosis	Good if recognized early Very dependent on patient compliance	Good

*Thought to be a defect in the trabecular network ultrastructure.
†Like looking through a steamy window.
From Swartz MH: *Textbook of physical diagnosis, history and examination,* ed 7, Philadelphia, 2014, Elsevier.

important information in diagnosis and treatment of OAG)

LABORATORY TESTS

Blood sugar

IMAGING STUDIES

- Optic nerve photography—stereo photographs
- Visual field testing
- Laser scan of nerve fiber layer, OCT, HRT. Rarely, MRI of orbits if the glaucoma findings are atypical or suspicious of other causes of optic nerve atrophy.

Rx TREATMENT

ACUTE GENERAL Rx

- β-Blockers (e.g., timolol) qd to bid depending on individual response to drug.
- Carbonic anhydrase inhibitors (e.g., Diamox 250 mg qid or 500 mg bid).
- Prostaglandin analogues (latanoprost, bimatoprost, travoprost, tafluprost) are commonly used as first-line treatment. They lower intraocular pressure by 25% to 30% by increasing uveoscleral outflow and reducing aqueous production.
- Alpha-2 agonists and cholinergic agonists.
- Hyperosmotic agents (mannitol) in acute treatment (IV).
- Selective laser trabeculoplasty (SLT) may delay or forestall need for second eye drop. The effect may be temporary but the laser can be repeated.

CHRONIC Rx

- At least biannual checks of intraocular pressure and adjustment of medication.
- Surgical trabeculectomy and filter valve surgeries can be considered for glaucoma that progresses (optic nerve changes or visual field progression) despite maximal tolerated medical therapies. Recently, minimally invasive glaucoma surgeries (MIGS) have been advocated for IOP control. Some are performed at the time of cataract procedures and some are independent procedures. The effort is to reduce the risks associated with traditional trabeculectomy.

DISPOSITION

Must be followed by ophthalmologist

REFERRAL

Immediately to ophthalmologist

PEARLS & CONSIDERATIONS

COMMENTS

- Glaucoma is a serious blinding disease that must be monitored professionally by an ophthalmologist. It is mostly asymptomatic until late in the disease when visual problems arise. Even in developed countries half of glaucoma cases are undiagnosed.
- Risk factors that should prompt referral to an ophthalmologist for evaluation of glaucoma are high intraocular pressure, family history of glaucoma, use of systemic or topical corticosteroids, older age, and black race.
- Vision loss from glaucoma cannot be recovered. Early diagnosis and treatment may minimize visual loss.
- Glaucoma is not solely caused by increased intraocular pressure because approximately 20% of patients with glaucoma have normal intraocular pressure. However, high pressure is definitely a risk factor to be considered.

SUGGESTED READINGS

Available at ExpertConsult.com

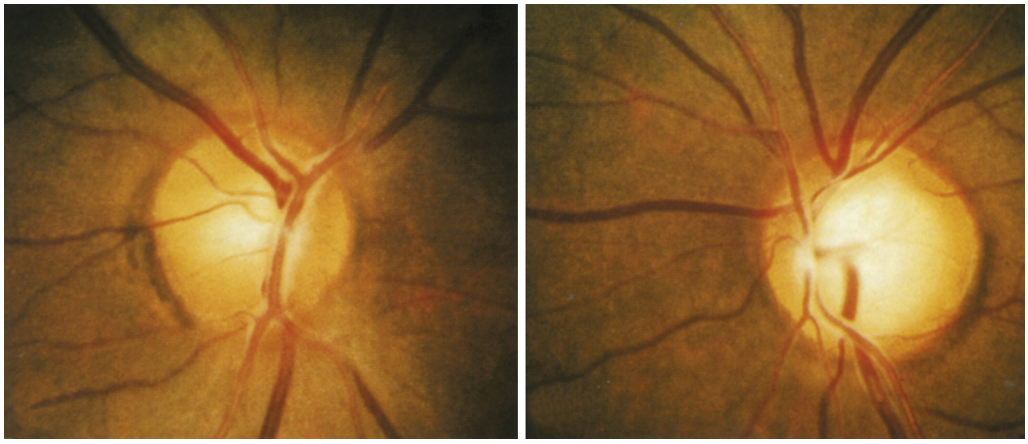
RELATED CONTENT

Glaucoma (Patient Information)

AUTHOR: **R. Scott Hoffman, MD**

SUGGESTED READINGS

Gupta D, Chen PP: Glaucoma, *Am Fam Physician* 93(8):668-674, 2016.
Quigley HA: Glaucoma, *Lancet* 377:1367-1377, 2011.
Weinreb RN et al: The pathophysiology and treatment of glaucoma, *JAMA* 311(18):1901-1911, 2014.



A B

FIG. E2 A and **B,** Optic cup asymmetry in glaucoma. The cup-disc ratio is approximately 30% in **A** *(right eye)* and 70% in **B** *(left eye).* (Swartz MH: *Textbook of physical diagnosis, history and examination*, ed 7, Philadelphia, 2014, Elsevier.)

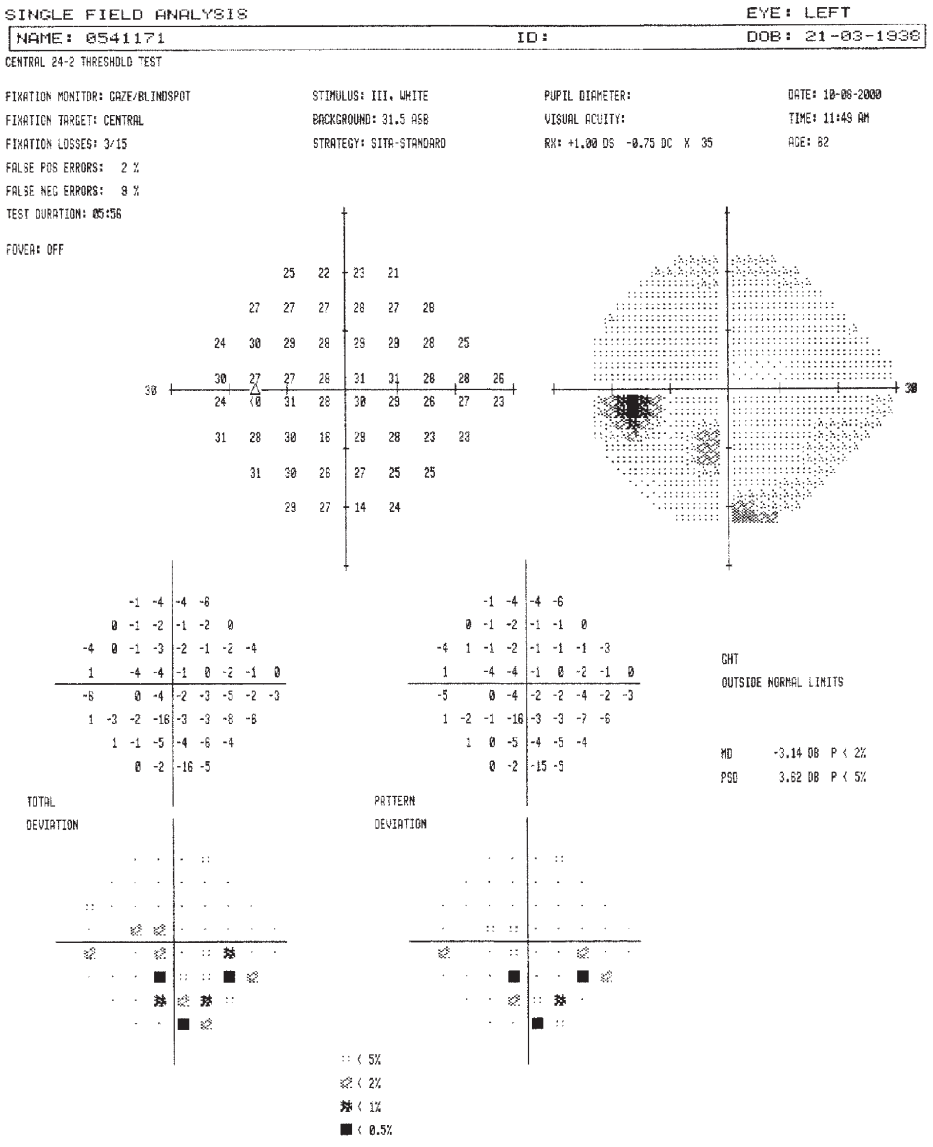


FIG. E3 Small paracentral scotoma in mild to moderate glaucoma. (From Bowling B: *Kanski's clinical ophthalmology: a systematic approach,* ed 8, Philadelphia, 2016, Elsevier.)

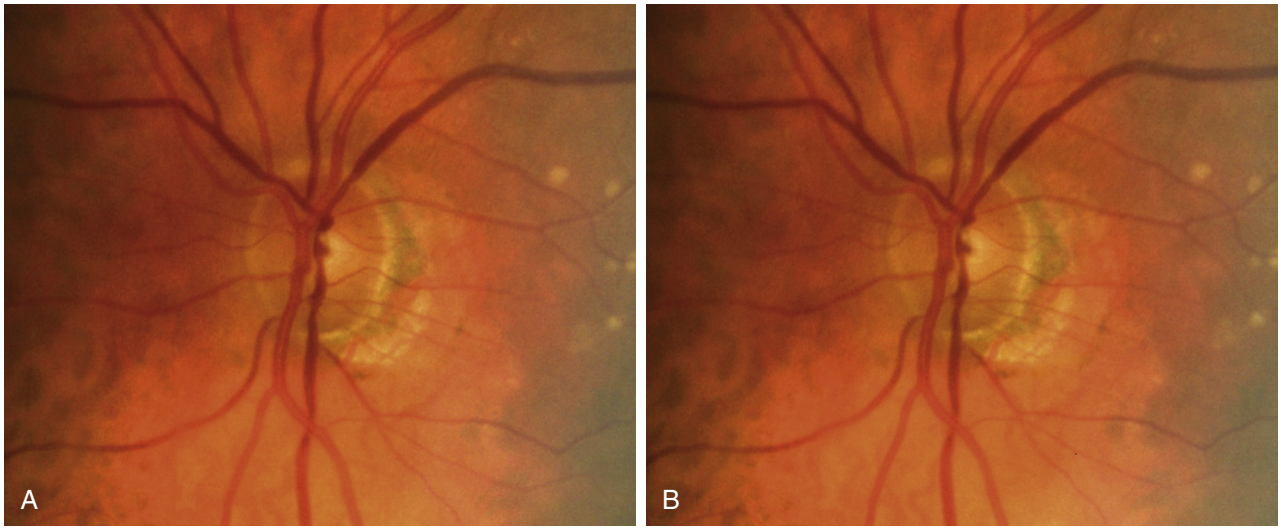


FIG. E4 Moderate to marked glaucoma. A and **B,** Stereo disc photographs showing inferior neuro-retinal rim shelving.

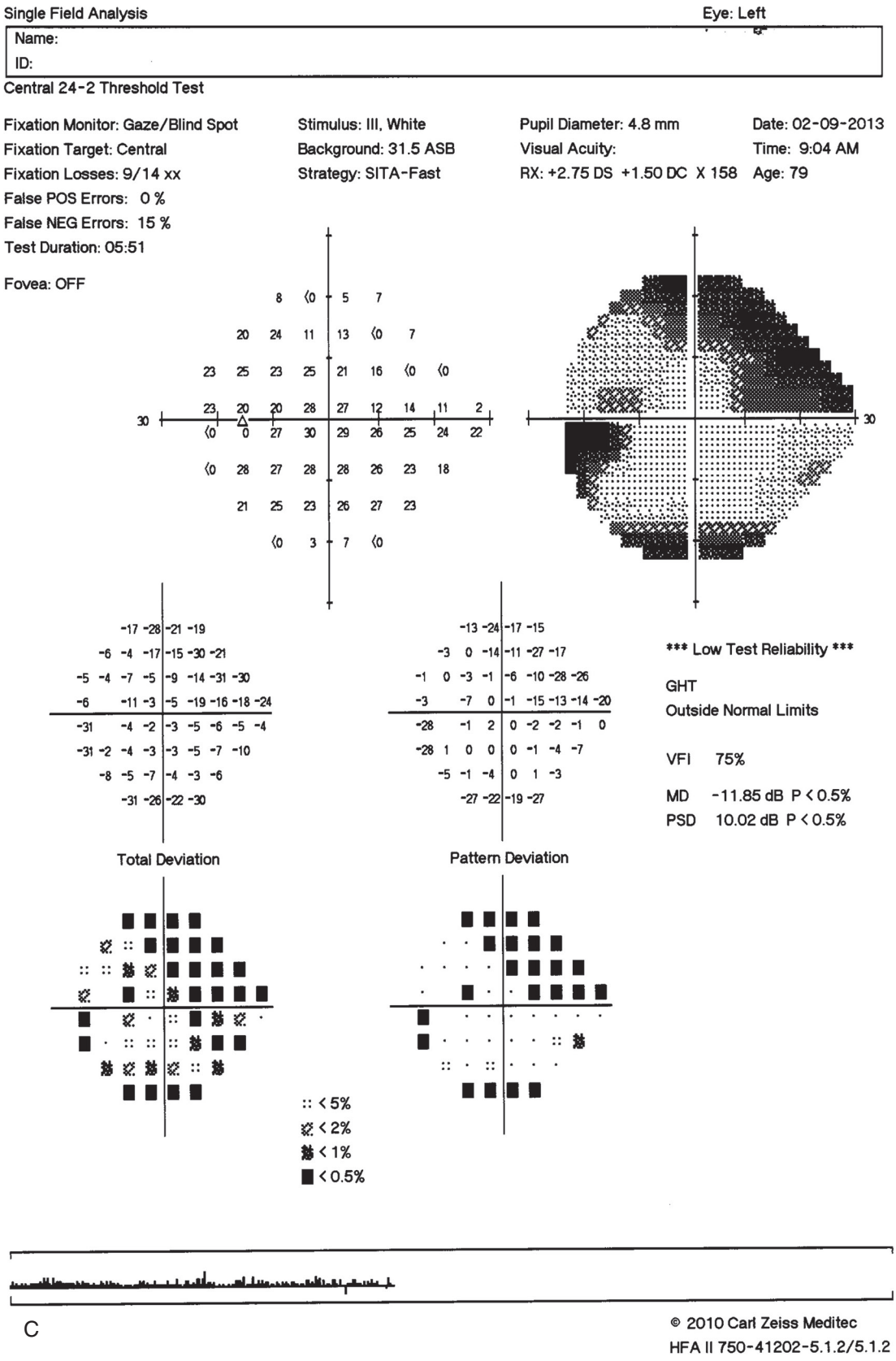


FIG. E4, cont'd C, Visual field from the same eye showing superior arcuate scotoma and nasal step (but note suboptimal reliability).

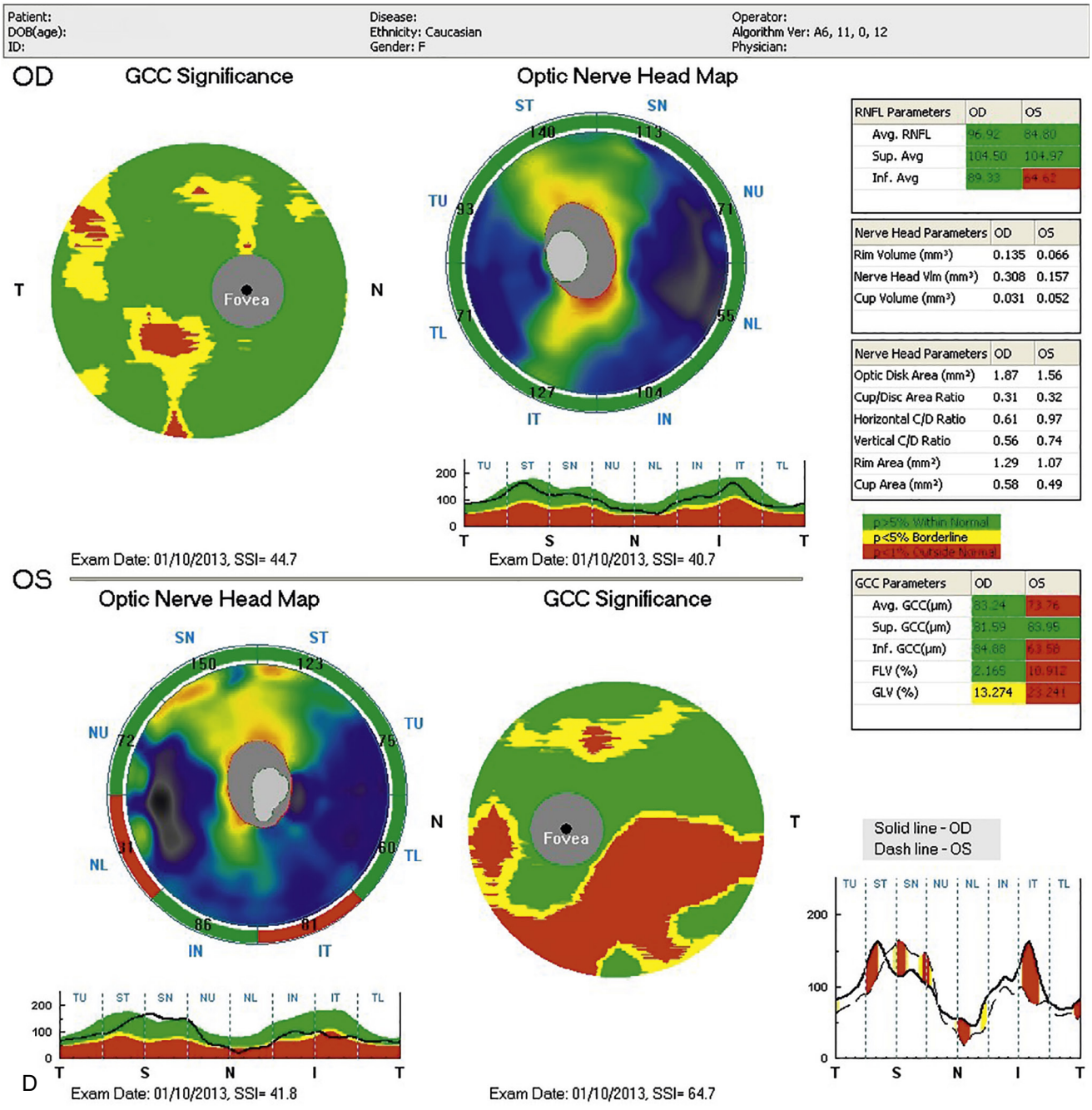


FIG. E4, cont'd D, OCT from the same patient—note inferior abnormality on ganglion cell complex analysis of the left eye corresponding to the superior nasal step. (From Bowling B: *Kanski's clinical ophthalmology: a systematic approach*, ed 8, Philadelphia, 2016, Elsevier.)

Glaucoma, Primary Angle-Closure PTG

BASIC INFORMATION

DEFINITION

Primary angle-closure glaucoma occurs when elevated intraocular pressure is associated with closure of the filtration angle or obstruction in the circulating pathway of the aqueous humor.

SYNONYMS

Acute glaucoma, angle-closure glaucoma (ACG)
Pupillary block glaucoma
Narrow-angle glaucoma
Angle-closure glaucoma

ICD-10CM CODES

H40.061	Primary angle closure without glaucoma damage, right eye
H40.062	Primary angle closure without glaucoma damage, left eye
H40.063	Primary angle closure without glaucoma damage, bilateral
H40.069	Primary angle closure without glaucoma damage, unspecified eye

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- 2% to 8% of all patients with glaucoma.
- Higher incidence among those with hyperopia, small eyes, dense cataracts, shallow anterior chambers.

PEAK INCIDENCE: Greater >50 yr; high association with hyperopia, cataracts, and eye trauma
PREDOMINANT SEX: Females are affected more often than males.
PREDOMINANT AGE: 50 to 60 yr
GENETICS: Family history is not particularly helpful; far-sighted (hyperopes) individuals with thickening lenses (i.e., cataracts) are often those with angle-closure attacks.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Although angle-closure glaucoma can present with an acute painful crisis associated with blurred vision, more than 75% of patients present with an asymptomatic course with progressive loss of the visual field (similar to that in patients with primary open-angle glaucoma; referred to as intermittent, subacute, or chronic angle closure)
- Hazy cornea
- Narrow angle
- Pain may be present (supraorbital headache is typical)
- Injection of conjunctiva, red eye (often severe limbal conjunctival injection with very high intraocular pressure [IOP])
- Shallow anterior chamber (one can shine a light from the side to perceive the forward position of the iris with narrow AC angles)
- Thick cataract
- Pupil may be mid-dilated and nonreactive to light
- Figs. E1 and E2 illustrate gonioscopy in primary angle-closure glaucoma

ETIOLOGY

- Narrow angles with acute closure: Blockage of circulatory path of the aqueous humor (Fig. E3) causing increase in IOP. ACG (primary angle closure glaucoma) occurs more commonly in eyes with shorter axial length (far-sightedness), shallower anterior chamber, and a relatively larger lens (enlarging cataract).
- Secondary angle-closure glaucoma (more rare) resulting from neovascularization of iris, iris tumors, lens induced, iris scarring, trauma, chronic inflammation with scarring, malignant glaucoma with aqueous misdirection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Open-angle glaucoma: Angle-closure glaucoma is distinguished from open-angle glaucoma by the closure of the angle between the iris and cornea, obstructing outflow of aqueous humor
- High intraocular pressure (normal IOP is usually 8 to 21 mm Hg)
- Optic nerve cupping
- Shallow chamber
- Open-angle glaucoma
- Conjunctivitis
- Corneal disease, keratitis
- Uveitis
- Scleritis
- Allergies
- Contact lens wearing with irritation

WORKUP

Comprehensive eye examination: If one suspects narrow angle or angle closure, avoid pupil dilation, as this may exacerbate the attack.

- Intraocular pressure (with ACG, IOP can be extremely high, >60 mm Hg)
- Gonioscopy for direct visualization of the chamber angle
- Slit lamp examination
- Visual field examination
- Laser scan of nerve fiber layer and optic nerve, optical coherence tomography (OCT)
- Optic nerve evaluation
- Anterior chamber depth

LABORATORY TESTS

- Blood sugar and complete blood count (if diabetes or inflammatory disease is suspected)
- Visual field
- Nerve fiber analysis, OCT, Heidelberg retinal tomography

IMAGING STUDIES

- Fundus photography (optic nerve photos)—very helpful for comparing changes in optic nerve shape
- Fluorescein angiography for neovascular disease such as diabetic retinopathy, retinal vein occlusions
- Ultrasound biomicroscopy and anterior OCT can show relationships of anterior eye structures

TREATMENT

The goal of treatment is to acutely lower pressure on the eye and keep it down.

NONPHARMACOLOGIC THERAPY

Laser iridotomy early in disease process

ACUTE GENERAL Rx

- IV mannitol
- Pilocarpine
- β-Blockers
- Diamox
- Laser iridotomy
- Anterior chamber paracentesis (as emergency treatment)

CHRONIC Rx

- Iridotomy: When there is an adequate peripheral hole in the iris, the chance for future angle closure is usually eliminated unless there are rare other angle anomalies (i.e., plateau iris or peripheral synechiae).
- Lens removal (cataract extraction) can also eliminate the possibility of ACG.
- Trabeculectomy and filter valve procedures for nonresponsive cases.
- Other laser procedures, such as gonioplasty for atypical angle closures.

DISPOSITION

Refer to ophthalmologist immediately.

REFERRAL

If acute angle-closure episode is suspected, should refer emergently to ophthalmologist.

PEARLS & CONSIDERATIONS

COMMENTS

- Do not use antihistamines or vasodilators with narrow-angle glaucoma.
- After iridotomy, the majority of patients will be totally cured and will need no further medication and have no visual loss.
- Lower socioeconomic status and higher levels of social deprivation are risk factors for delayed detection and probable worse outcomes in glaucoma.
- Risk factors that should prompt referral to an ophthalmologist for evaluation of glaucoma are high intraocular pressure, family history of glaucoma, use of systemic or topical corticosteroids, older age, and black race.
- Glaucoma is undiagnosed in 9 out of 10 affected people worldwide and is undiagnosed in 50% of those in developed countries.
- Angle closure has become rarer because most people have cataract extractions at an earlier stage than in the past.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Glaucoma (Patient Information).
Glaucoma, Open Angle (Related Key Topic)

AUTHOR: **R. Scott Hoffman, MD**

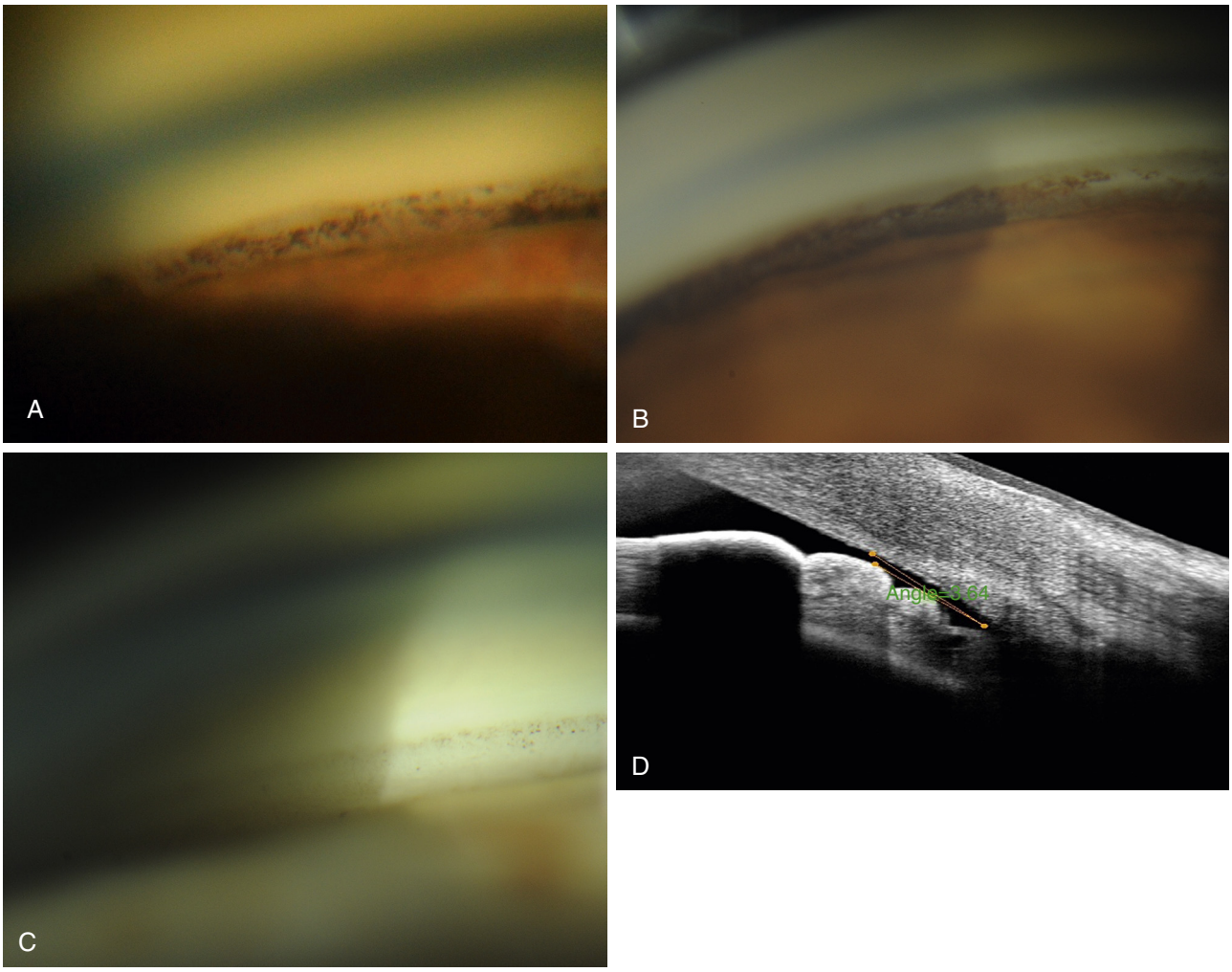


FIG. E1 Primary angle closure suspect. A, On gonioscopy, only a double Schwalbe line and part of the nonpigmented trabecular meshwork are visible—the iris is apposed to the pigmented meshwork. **B,** Pigment smudging of the nonpigmented meshwork seen on indentation gonioscopy. **C,** Moderately but not critically narrow angle for comparison—sparsely pigmented Schwalbe line, nonpigmented meshwork, and pigmented meshwork. **D,** Very narrow angle on dark-room anterior segment optical coherence tomography (OCT). (From Bowling B: *Kanski's clinical ophthalmology, a systematic approach*, ed 8, Philadelphia, 2016, Elsevier.)

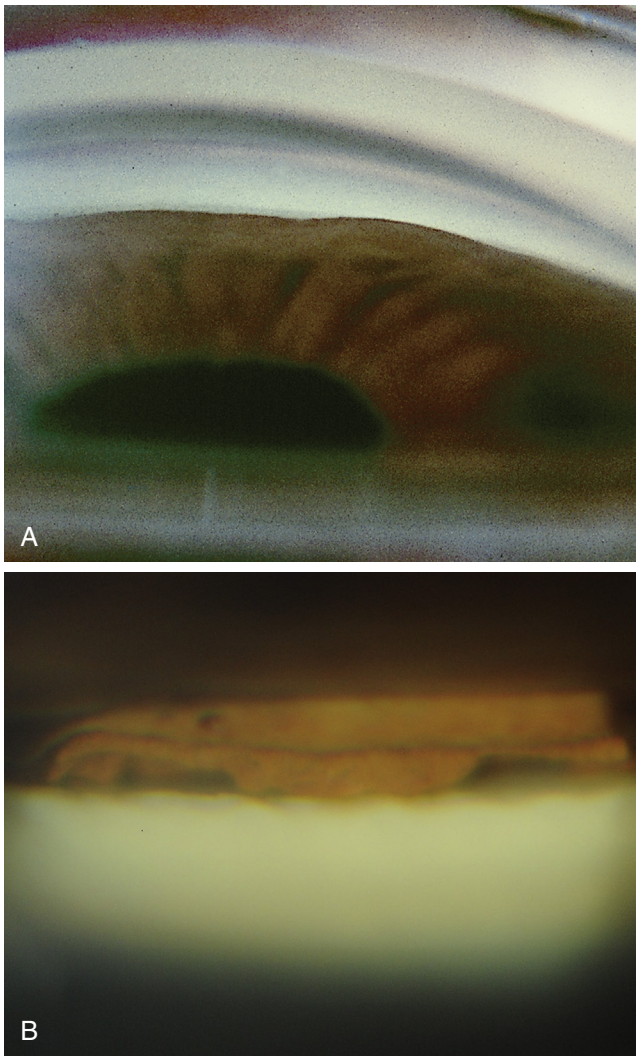


FIG. E2 Primary angle closure. A, Closed inferior angle on gonioscopy. **B,** Peripheral anterior synechiae (PAS) on indentation gonioscopy—superior angle. (*A,* Courtesy L. MacKeen.) (From Bowling B: *Kanski's clinical ophthalmology, a systematic approach,* ed 8, Philadelphia, 2016, Elsevier.)

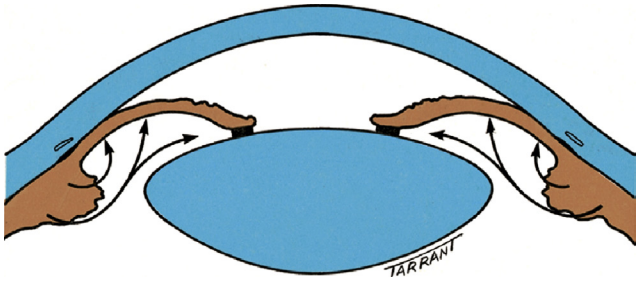


FIG. E3 Angle closure due to pupillary block, with anterior iris bowing and iridocorneal contact. (From Bowling B: *Kanski's clinical ophthalmology, a systematic approach*, ed 8, Philadelphia, 2016, Elsevier.)

SUGGESTED READINGS

Gupta D, Chen PP: Glaucoma, *Am Fam Physician* 93(8):668-674, 2016.
Quigley HA: Glaucoma, *Lancet* 377:1367-1377, 2011.
Weinreb RN et al: The pathophysiology and treatment of glaucoma, *JAMA* 311(18):1901-1911, 2014.

Glenohumeral Dislocation

BASIC INFORMATION

DEFINITION

Glenohumeral dislocation occurs when the humeral head exceeds its physiologic limitations, causing it to translate beyond the glenoid rim. It often requires some form of reduction in order to relocate the humeral head. Lesser events that are self-limited are termed *subluxation* or *subjective instability.* During these events, the humeral head translates too, but not past the glenoid rim.

Often, the cause of dislocation is traumatic, with the most common direction of humeral head translation being anteriorly and inferiorly. Some anterior dislocations may cause a tear of the anteroinferior glenoid labrum (Bankart lesion). Less commonly the head may dislocate posteriorly, such as during seizures or electrocution.

Multidirectional instability predisposes patients to dislocation and is present in a small number of patients. Frequent subluxations or dislocations may occur in multiple directions and result in excessive joint laxity. They may occur with minimal trauma and are often bilateral.

ICD-10CM CODES	
M24.419	Recurrent dislocation, unspecified shoulder
M24.819	Other specific joint derangements of unspecified shoulder, not elsewhere classified
S43.016A	Anterior dislocation of unspecified humerus, initial encounter
S43.026A	Posterior dislocation of unspecified humerus, initial encounter
S43.036A	Inferior dislocation of unspecified humerus, initial encounter

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Traumatic:

- The arm is held in external rotation with anterior dislocation and internal rotation with posterior dislocation.
- Slight movement is possible without pain.
- The acromion may appear more prominent, and there may be an absence of the normal "fullness" beneath the acromion.
- Status of the axillary nerve must always be checked before and after reduction (sensation to the lateral shoulder and ability to gently activate the deltoid).
- Fractures of the humeral head or glenoid rim may occur and predispose patients to future instability and dislocation events.

Multidirectional:

- Often present after minimal trauma or with recurrent episodes of "giving out," weakness, and popping.
- Sulcus sign may be positive (as the arm is pulled inferiorly with the patient upright, an indentation forms between the acromion and humeral head, indicating excessive inferior movement of the head).
- Other signs of generalized joint laxity may be present, such as elbow hyperextension, extension of the small finger metacarpophalangeal joint >90 degrees, or flexion of the thumb down to the volar forearm (Beighton criteria).

ETIOLOGY

- Anterior: Due to trauma, often with the arm abducted and externally rotated
- Posterior: Often secondary to seizure or electrical shock
- Multidirectional: Secondary to generalized joint laxity

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Proximal humerus fracture
- Grade 3 or greater acromioclavicular (AC) joint injury: Presents with pain and prominent AC joint

IMAGING STUDIES

- Acute shoulder injury: True anteroposterior (AP) (aimed 15 degrees across the body for a perpendicular view of the glenohumeral joint), scapular "Y" view, and an axillary lateral
  1. Internal/external rotation variations in the true AP image may reveal bony injury to the proximal humerus.
- CT: Useful to evaluate fractures of the glenoid and/or humerus. May include contrast arthrogram to evaluate labrum and rotator cuff
- MRI: Useful to evaluate soft tissue only, including labral injury or rotator cuff tear

TREATMENT

- Reduction of the acute dislocation by gentle distal traction in the relaxed patient should be followed by brief immobilization with a sling (less than 1 wk for simple dislocations).
- Posterior dislocations, inferior dislocations, or fracture-dislocations should be reduced by an experienced practitioner.
- Gentle limited range-of-motion exercises as pain subsides followed by strengthening exercises at 2 wk.

DISPOSITION

- Recurrence of anterior dislocation is common in the young population; patients under 30 should be referred to an orthopedist for further evaluation.
- Primary dislocations in patients >40 yr old are not generally complicated by recurrence but may result in shoulder stiffness and associated rotator cuff tears.
- There is an almost 100% recurrence after the third dislocation.

REFERRAL

Surgical reconstruction may be required in patients with recurrent dislocations.

PEARLS & CONSIDERATIONS

COMMENTS

- X-rays in two orthogonal planes are always indicated to confirm dislocation or reduction. A single radiograph is never acceptable.
- It is important to know if there was an injury involved in the first episode and if a radiograph was taken to determine direction of the dislocation.
- Up to 50% of posterior dislocations are missed by the first examiner, usually the result of an inadequate lateral radiograph of the glenohumeral joint.
- "Voluntary" dislocators should typically be treated nonsurgically.
- Sports activities may be resumed when there is pain-free full motion with normal strength.
- Multidirectional instabilities are usually treated nonsurgically with strengthening exercises, and rehabilitation.
- Dislocations in either direction are occasionally overlooked. If the injury is over 2 to 4 wk old, enough tissue healing will have occurred to make closed reduction nearly impossible. Open surgical reduction may then be needed.

AUTHORS: **Stephen E. Marcaccio, MD,** and **Brett D. Owens, MD**

SUGGESTED READINGS

Gil JA et al: Current concepts in the diagnosis and management of traumatic, anterior glenohumeral subluxations, *Orthop J Sport Med* 5(3), 2017. https://doi.org/10.1177/2F2325967117694338.

Owens B et al: Pathoanatomy of first-time, traumatic, anterior glenohumeral subluxation events, *J Bone J Surg Am* 92(7):1605-1611, 2010.

Reinold MM, Gill TJ: Current concepts in the evaluation and treatment of the shoulder in overhead-throwing athletes, part 1: physical characteristics and clinical examination, *Sport Heal A Multidiscip Approach* 2(1):39-50, 2010.

BASIC INFORMATION

DEFINITION

Glossitis is an inflammation of the tongue that can lead to loss of filiform papillae.

ICD-10CM CODES
K14.0 Glossitis
K14.2 Median rhomboid glossitis

EPIDEMIOLOGY & DEMOGRAPHICS

Glossitis is seen more frequently in patients of lower socioeconomic status, malnourished patients, alcoholics, smokers, elderly patients, immunocompromised patients, and patients with dentures.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The appearance of the tongue varies depending on the etiology of the glossitis (Fig. E1). Loss of filiform papillae results in a red, smooth-surfaced tongue.
- The tongue may appear pale in patients with significant anemia.
- Pain and swelling of the tongue may be present when glossitis is associated with infections, trauma, or lichen planus.
- Ulcerations may be present in patients with herpetic glossitis, pemphigus, or streptococcal infection.
- Excessive use of mouthwash may result in a "hairy" appearance of the tongue (Fig. E2).

ETIOLOGY

- Nutritional deficiencies (vitamin E, riboflavin, niacin, vitamin B_{12}, iron)
- Infections (viral, candidiasis, tuberculosis, syphilis)
- Trauma (generally caused by poorly fitting dentures)
- Irritation of the tongue from toothpaste, medications, alcohol, tobacco, citrus
- Lichen planus, pemphigus vulgaris, erythema multiforme
- Neoplasms

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infections
- Use of chemical irritants
- Neoplasms
- Skin disorders (e.g., Behçet syndrome, erythema multiforme)

WORKUP

- Laboratory evaluation to exclude infectious processes, vitamin deficiencies, and systemic disorders
- Biopsy of lesion only when there is no response to treatment

LABORATORY TESTS

- Complete blood count: Decreased hemoglobin and hematocrit, low mean corpuscular volume (MCV) (iron-deficiency anemia), elevated MCV (vitamin B_{12} deficiency)
- Vitamin B_{12} level
- 10% potassium hydroxide (KOH) scrapings in patients with white patches suspect for candidiasis

TREATMENT

NONPHARMACOLOGIC THERAPY

Avoidance of primary irritants such as hot foods, spices, tobacco, and alcohol

ACUTE GENERAL Rx

Treatment varies with the etiology of the glossitis.

- Malnutrition with avitaminosis: Multivitamins
- Candidiasis: Fuconazole 200 mg on day 1, then 100 mg/day for at least 2 wk or nystatin 400,000 U suspension qid for 10 days or 200,000 pastilles dissolved slowly in the mouth 4 to 5 times qd for 10 to 14 days
- Painful oral lesions: Rinsing of the mouth with 2% lidocaine viscous, 1 to 2 tablespoons q4h prn; triamcinolone 0.1% applied to painful ulcers prn for symptomatic relief

CHRONIC Rx

- Lifestyle changes with elimination of tobacco, alcohol, and other primary irritants
- Dental evaluation for correction of ill-fitting dentures
- Correction of associated metabolic abnormalities such as hyperglycemia from diabetes mellitus

DISPOSITION

Most patients experience prompt improvement with identification and treatment of the cause of the glossitis.

REFERRAL

Surgical referral for biopsy of solitary lesions unresponsive to treatment to rule out neoplasm.

PEARLS & CONSIDERATIONS

COMMENTS

If the primary cause of glossitis is not identified or cannot be corrected, enteric nutritional replacement therapy should be considered in malnourished patients.

RELATED CONTENT

Glossitis (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

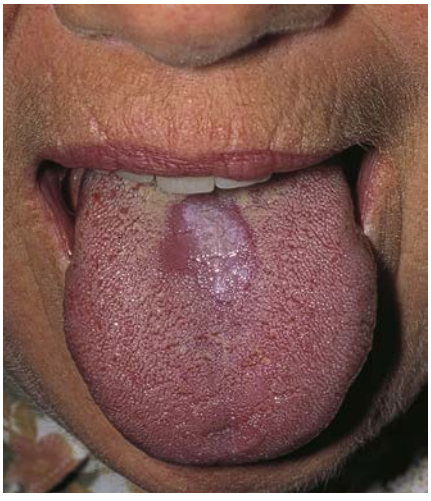


FIG. E1 Median rhomboid glossitis. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

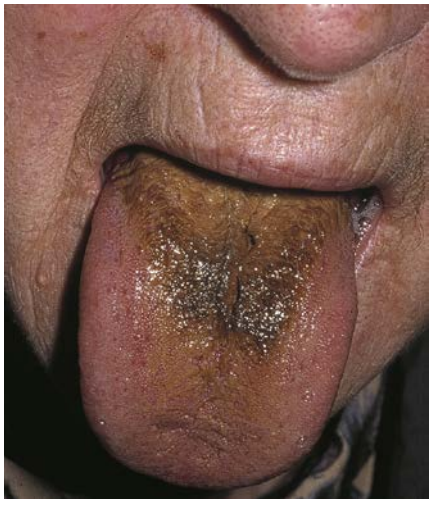


FIG. E2 Black hairy tongue. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

BASIC INFORMATION

DEFINITION

Gonorrhea is a sexually transmitted bacterial infection with a predilection for columnar and transitional epithelial cells. It commonly manifests as urethritis, cervicitis, or salpingitis. Infection may be asymptomatic. It differs between males and females in course, severity, and ease of recognition.

SYNONYMS

Gonococcal urethritis
Gonococcal vulvovaginitis
Gonococcal cervicitis
Gonococcal bartholinitis
GC

ICD-10CM CODES

A54.9	Gonococcal infection, unspecified
O98.211	Gonorrhea complicating pregnancy, first trimester
O98.212	Gonorrhea complicating pregnancy, second trimester
O98.213	Gonorrhea complicating pregnancy, third trimester
O98.219	Gonorrhea complicating pregnancy, unspecified trimester
O98.22	Gonorrhea complicating childbirth
O98.23	Gonorrhea complicating the puerperium
A54.03	Gonococcal cervicitis, unspecified
A54.00	Gonococcal infection of lower genitourinary tract, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- The disease is common worldwide, affects both sexes and all ages, especially younger adults; highest incidence is in inner-city areas. Per CDC reports, approximately 470,000 new cases were found in the U.S. in 2016 with over 60% found in metropolitan statistical centers. Gonorrhea is the second most commonly reported communicable disease.
- Asymptomatic anterior urethral carriage may occur in 12% to 50% of cases in men.
- Asymptomatic in 50% to 80% of cases in women. Most common dissemination is by mucosal passage to fallopian tubes, resulting in pelvic inflammatory disease (PID) in 10% to 15% of infected women. Hematogenous spread may result in septic arthritis and skin lesions. Conjunctivitis rarely occurs, but may result in blindness if not rapidly treated. Infection can occur in both men and women in oropharynx and anorectally.
- The World Health Organization (WHO) reports that there were 78 million new cases of gonorrhea worldwide among adults in 2012.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Males: Purulent discharge from anterior urethra (Fig. E1), with dysuria appearing 2 to 7 days after infecting exposure. May have rectal infection causing pruritus, tenesmus, and discharge, or may be asymptomatic.
- Females: Initial urethritis or cervicitis may occur a few days after exposure, frequently mild. Infections may be asymptomatic or may not produce recognizable symptoms until complications have occurred. In approximately 20% of cases uterine invasion occurs after menstrual period with signs and symptoms of endometritis, salpingitis, or pelvic peritonitis. The patient may have purulent discharge or inflamed Skene or Bartholin glands.
- Classic presentation of acute gonococcal PID is fever, abdominal and adnexal tenderness, and, often, absence of purulent discharge. Physical examination may be normal if asymptomatic. Disseminated gonococcal infection (DGI) may manifest with petechial or pustular acral skin lesions (Fig. E2), asymmetric polyarthralgia, tenosynovitis, or oligoarticular septic arthritis. The infection is occasionally complicated by perihepatitis and, rarely, endocarditis or meningitis.

ETIOLOGY

- *Neisseria gonorrhoeae* is also known as gonococcus. Plasmids coding for β-lactamase render some strains resistant to penicillin or tetracycline. There is an increasing frequency of chromosomally mediated resistance to penicillin, tetracycline, fluoroquinolones, and cefoxitin. In the Far East, high-level resistance to spectinomycin is endemic.
- There is a rising number of cases of quinolone-resistant *N. gonorrhoeae* worldwide, with the expected number to rise in the U.S. from importation.
- Men who have sex with men are vulnerable to the emerging threat of antimicrobial-resistant *N. gonorrhoeae.*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Nongonococcal urethritis (NGU)
- Nongonococcal mucopurulent cervicitis
- *Chlamydia trachomatis*

WORKUP

Diagnosis depends on bacteriologic investigation. Culture and nucleic acid amplification tests (NAAT) are available for the detection of genitourinary infection with *N. gonorrhoeae.*

- NAATs are preferred testing modalities for the detection of genitourinary infection with *N. gonorrhoeae.* The performance of NAATs with respect to overall sensitivity, specificity, and ease of specimen transport is better than that of any of the other tests available for the diagnosis of gonococcal infections. NAATs should be used to detect gonorrhea except in cases of child sexual assault involving boys and rectal and oropharyngeal infections in prepubescent girls. When evaluating a potential gonorrhea treatment failure, case culture and susceptibility testing might be required. NAATs allow testing of the widest variety of specimen types, including endocervical swabs, vaginal swabs, urethral swabs (men), and urine (from both men and women).
- Culture: Gonorrhea culture on Thayer-Martin medium (organism is fastidious; requires aerobic conditions with increased carbon dioxide atmosphere; incubate ASAP). Culture has a sensitivity of 95% or more for urethral specimens from men with symptomatic urethritis and 80% to 90% for endocervical infection in women. Gram-negative intracellular diplococci are diagnostic in male urethral smears (Fig. E3). There is a false-negative rate of 60% to 70% in female cervical or urethral smears.
  1. Concomitant serologic testing for syphilis for all patients
  2. Concomitant *Chlamydia* testing for all patients
  3. Offer of HIV testing and counseling to all patients

LABORATORY TESTS

- First-catch urine (or genital swab) sample NAAT is the preferred screening and diagnostic test for gonorrhea. These tests have largely replaced culture in many settings where persons are screened for asymptomatic genital infection. They are not more sensitive than culture for detecting *N. gonorrhoeae* in cervical or urethral specimen; however, they have specificities >99% and retain sensitivity when used to test voided urine or self-collected vaginal swabs.
- Gonorrhea culture on Thayer-Martin medium (organism is fastidious; requires aerobic conditions with increased carbon dioxide atmosphere; incubate ASAP). Culture has a sensitivity of 95% or more for urethral specimens from men with symptomatic urethritis and 80% to 90% for endocervical infection in women.
- Nonamplified DNA probe tests are less sensitive than culture or NAATs and are not useful in the diagnosis of rectal or pharyngeal infection or for testing urine; however, they are inexpensive, readily available and offered in many laboratories in combination assays for *C. trachomatis.*
- Concomitant serologic testing for syphilis on all patients.
- Concomitant *Chlamydia* testing on all patients.
- Offer of HIV testing and counseling to all patients.

TREATMENT

ACUTE GENERAL Rx

Uncomplicated infections of the cervix, urethra, and rectum. Critical for the practitioner to know local resistance characteristics to best treat the patient:

- Ceftriaxone 250 mg IM × 1 dose *plus* azithromycin 1 g PO single dose. Doxycycline 100 mg PO bid for 7 days can be substituted for

azithromycin in patients with azithromycin allergy.

Alternative regimens if ceftriaxone is not available:

- Ceftizoxime, cefoxitin with probenecid, and cefotaxime. None of these injectable cephalosporins offer any advantage over ceftriaxone.
- Cefixime 400 mg PO × 1 dose *plus* azithromycin 1 g orally single dose. Doxycycline 100 mg PO bid for 7 days can be substituted for azithromycin in patients with azithromycin allergy.
- If the patient has severe cephalosporin allergy, then azithromycin 2 g PO single dose *plus* single-dose gemifloxacin 320 mg PO or gentamicin 240 mg IM.
- A test-of-cure is not needed for persons who receive a diagnosis of uncomplicated urogenital or rectal gonorrhea who are treated with any of the recommended or alternative regimens.

Uncomplicated gonococcal infections of the pharynx:

- Ceftriaxone 250 mg IM × 1 dose *plus* azithromycin 1 g PO single dose. Doxycycline 100 mg PO bid for 7 days can be substituted for azithromycin in patients with azithromycin allergy.
- Treatment of the cephalosporin-allergic patient: Oral azithromycin 2 g *plus* single dose gemifloxacin 320 mg PO *or* 240 mg IM of gentamicin is effective.
- Any person with pharyngeal gonorrhea who is treated with an alternative regimen should return 14 days after treatment for a test-of-cure using either culture or NAAT.

Treatment of arthritis and arthritis-dermatitis syndrome:

- Recommended regimen: Ceftriaxone 1 g IM or IV every 24 hours plus azithromycin 1 g orally as a single dose.
- Alternative regimens: Cefotaxime 1 g IV every 8 hours or ceftizoxime 1 g IV every 8 hours *plus* azithromycin 1 g orally in a single dose.

Pregnancy

- Pregnant women infected with *N. gonorrhoeae* should be treated with dual therapy consisting of ceftriaxone 250 mg in a single IM dose or azithromycin 1 g PO as a single dose. When cephalosporin allergy or other considerations preclude treatment and spectinomycin is not available, consultation with an ID specialist is recommended.

DISPOSITION

- To reduce development of drug resistance, reculture should be done for patients who show continued symptoms despite treatment. These patients should be tested with a culture-based gonorrhea test that can detect antibiotic resistance.
- All sexual partners should be identified, examined, tested, and receive presumptive treatment.
- Patients should be counseled to avoid unprotected intercourse with partners for 1 wk after all partners have completed treatment.

REFERRAL

PID requiring hospitalization, disseminated gonococcal infection

PEARLS & CONSIDERATIONS

COMMENTS

- This is a reportable disease.
- The proportion of gonorrhea cases in heterosexual men who are fluoroquinolone resistant (QRNG) has reached 6.7%, an elevenfold increase from 0.6% in 2001. Fluoroquinolone antibiotics are no longer recommended to treat gonorrhea in the U.S.
- The use of azithromycin as the second antimicrobial is preferred over doxycycline due to the high prevalence of tetracycline resistance.
- The U.S. Preventive Services Task Force (USPSTF) recommends screening for gonorrhea in sexually active females younger than 25 yrs and in older women who are at increased risk for infection (multiple partners, new partner, partner who has concurrent partners). The USPSTF also concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for gonorrhea in men.
- High-intensity counseling on sexual risk reduction has been shown to reduce sexually transmitted infections (STIs) in primary care and related settings.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Gonorrhea (Patient Information)
Cervicitis (Related Key Topic)
Chlamydia Genital Infections (Related Key Topic)
Pelvic Inflammatory Disease (Related Key Topic)

AUTHORS: **Anthony Sciscione, DO,** and **Ella Stern, MD**

SUGGESTED READINGS

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Kirkcaldy RD et al: *Neisseria gonorrhoeae* antimicrobial resistance among men who have sex with men and men who have sex exclusively with women: the gonococcal isolate surveillance project, 2005-2010, *Ann Intern Med* 158:321-328, 2013.

O'Connor EA et al: Behavioural sexual risk-reduction counseling in primary care to prevent sexually transmitted infections: a systematic review for the U.S. Preventive Services Task Force, *Ann Intern Med* 161(12):874-883, 2014.

FIG. E1 Purulent urethral discharge from a man with gonococcal urethritis. (From Mandell GL et al: *Principles and practice of infectious diseases,* ed 6, Philadelphia, 2005, Churchill Livingstone.)

FIG. E2 Disseminated gonococcal infection: Skin lesions. A, Macules, papules, and pustules over an ankle. **B,** Hemorrhagic papules localized in trunk. **C,** Hemorrhagic vessel over a distal interphalangeal joint. (**C** Courtesy of Dr. Peter Schlessinger. From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

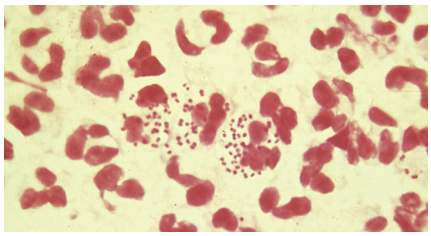

FIG. E3 ***Neisseria gonorrhoeae.*** Gram stain of urethral exudate in gonorrhea, showing intracellular gram-negative reniform diplococci. (Courtesy of Dr. S.E. Thompson. From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

BASIC INFORMATION

DEFINITION

Anti-glomerular basement membrane disease (anti-GBM disease), also known as Goodpasture disease, is a rare, autoimmune, small-vessel vasculitis affecting blood vessels of the lungs and kidneys that results in a pulmonary-renal syndrome. A pulmonary-renal syndrome is defined as the coexistence of pulmonary alveolar hemorrhage (i.e., triad of hemoptysis, diffuse alveolar infiltrates, and anemia) and acute kidney injury (AKI) from rapidly progressive glomerulonephritis (RPGN). Notably, a pulmonary-renal syndrome may affect only the kidneys (AKI and RPGN) or kidneys and lungs simultaneously. Rarely, only the lungs are involved.

SYNONYMS

Anti-glomerular basement membrane disease
Goodpasture syndrome

ICD-10CM CODES

N01.7	Rapidly progressive nephritic syndrome with diffuse crescentic glomerulonephritis
N00.7	Acute nephritic syndrome with diffuse crescentic glomerulonephritis

EPIDEMIOLOGY & DEMOGRAPHICS

- Anti-GBM disease has a bimodal age distribution, predominantly affecting young, white, male smokers, and, next most commonly, affecting older adults (>50 yr old, women more than men)
- Goodpasture disease accounts for 5% to 15% of all cases of RPGN
- HLA-DR2 locus is positive in 80% of patients.
- Approximately 20% to 40% of patients with anti-GBM antibody have positive antineutrophil cytoplasmic auto-antibodies (ANCAs)
- Anti-GBM disease can also occur with other glomerular diseases, such as ANCA- vasculitis, lupus, and membranous nephropathy
- Anti-GBM disease may occur posttransplant due to newly formed antibodies in up to 5% of patients with Alport disease who undergo kidney transplantation
- Secondary anti-GBM disease may occur in patients treated with immunomodulatory agents or in other autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, celiac disease, ulcerative colitis, and infective endocarditis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Dyspnea, cough, hemoptysis
- Skin pallor, fever, arthralgias (may be mild or absent at the time of initial presentation)
- Hematuria may be noted
- Frothy urine due to proteinuria, although nephrotic syndrome is uncommon

ETIOLOGY

Anti-GBM disease is caused by autoantibodies directed against the alpha-3 chain of type IV collagen, a primary component of the glomerular basement membrane (GBM). The presentation of the disease is due to the distribution of the antigen. Antibody deposition leads to immune cell- and complement-mediated tissue inflammatory damage resulting in pulmonary hemorrhage and glomerulonephritis. With appropriate treatment, there is eventual decline in antibody titers, and relapse with antibody production is rare.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Granulomatosis with polyangiitis
- Systemic lupus erythematosus
- Eosinophilic granulomatosis with polyangiitis (eGPA), formerly Churg-Strauss syndrome
- Essential mixed cryoglobulinemia
- Idiopathic rapidly progressive glomerulonephritis
- Drug-induced renal pulmonary disease (e.g., penicillamine)

WORKUP

Laboratory and clinical evaluation, diagnostic imaging, and kidney biopsy

LABORATORY & CLINICAL TESTS

- Serum anti-GBM antibodies (commercial enzyme-linked immunosorbent assay (ELISA) has 95% sensitivity and 95% to 99% specificity)
- Normal serum complement (C3 and C4) levels
- Absence of circulating immune complexes, antineutrophil cytoplasmic antibodies (except with overlap), and cryoglobulins
- Urinalysis with microscopic hematuria, proteinuria, and red blood cell casts
- Urine protein–to–creatinine ratio to quantify proteinuria
- Elevated blood urea nitrogen and creatinine
- Immunofluorescence studies of kidney biopsy specimens with anti-GBM antibody demonstrate linear staining pattern, often with C3 deposition
- Complete blood count and serum iron studies demonstrate iron-deficiency anemia from urinary and pulmonary blood losses
- Bronchoalveolar lavage may demonstrate presence of alveolar hemorrhage and exclude an infection

IMAGING STUDIES

Chest radiograph with airspace disease composed of alveolar infiltrates or evidence of pulmonary hemorrhage (Fig. E1)

TREATMENT

ACUTE GENERAL Rx

- Plasmapheresis with albumin replacement for 1 to 2 wk (fresh frozen plasma used if bleeding risk present), with immunosuppression typically consisting of prednisone (1 mg/kg per day) and oral cyclophosphamide (2 mg/kg per day). Intravenous cyclophosphamide has been used at some institutions. Rituximab has not been studied in trials but is used in patients who may not be good candidates for cyclophosphamide.
- Hemodialysis if kidney failure occurs.
- Factors influencing treatment decisions in Goodpasture disease are described in Table E1.

DISPOSITION

Life-threatening pulmonary hemorrhage and irreversible glomerular damage are major causes of death.

REFERRAL

- Referral for kidney biopsy to guide management
- Consider kidney transplantation in patients with end-stage renal disease

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Goodpasture Syndrome (Patient Information)

AUTHORS: **Dhruti P. Chen, MD,** and **Koyal Jain, MD**

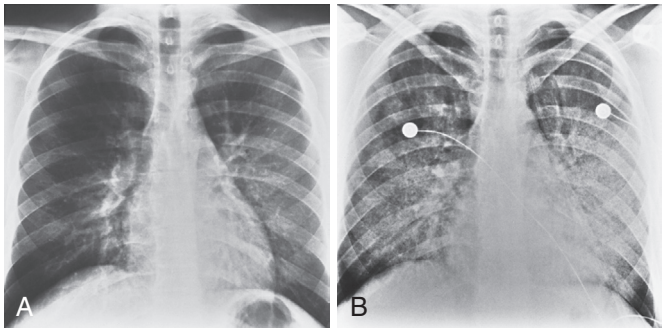

FIG. E1 Lung hemorrhage. A, Patient with early pulmonary hemorrhage. The chest radiograph still appears normal. **B,** Radiograph taken 4 days later shows the evolution of alveolar shadowing caused by lung hemorrhage. (From Floege J et al: *Comprehensive clinical nephrology,* ed 5, Philadelphia, 2015, Saunders, Figure 24–4).

TABLE E1 Factors Influencing Decision to Treat Aggressively in Goodpasture Disease

	Factors Favoring Aggressive Treatment	Factors Against Aggressive Treatment (predictors of poor renal outcomes)
Pulmonary hemorrhage	Present	Absent
Oliguria	Absent	Present
Creatinine	<5.5 mg/dl (~500 μmol/L)	>5.5-6.5 mg/dl (~500-600 μmol/L) and ANCA negative Severe damage on kidney biopsy No desire for early kidney transplantation
Other factors	Creatinine >5.5-6.5 mg/dl (~500-600 μmol/L) *but* Rapid and recent progression ANCA-positive Glomerular damage less severe than expected Crescents recent, nonfibrous Early renal transplantation is optimal	
Associated disease	Absent	Unusually high risk from immunosuppression

ANCA, Antineutrophil cytoplasmic auto-antibodies.
From Floege J et al: *Comprehensive Clinical Nephrology,* ed 5, Philadelphia, 2015, Saunders.

SUGGESTED READINGS

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Pedchencko V et al: Molecular architecture of the goodpasture autoantigen in anti-GBM nephritis, *N Engl J Med* 363:343-354, 2010.

BASIC INFORMATION

DEFINITION

Gout is a term used to refer to a group of disease states caused by tissue deposition of monosodium urate due to prolonged hyperuricemia. Clinical manifestations of gout include acute and chronic arthritis, soft tissue inflammation, tophus formation, gouty nephropathy, and nephrolithiasis. Untreated hyperuricemia in patients with gout may lead to chronic destructive deforming arthritis.

ICD-10CM CODES

M10	Gout
M10.0	Idiopathic gout
M10.1	Lead-induced gout
M10.2	Drug-induced gout
M10.3	Gout due to impairment of renal function
M10.4	Other secondary gout
M10.9	Gout, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Self-reported prevalence in the U.S. is estimated at 3.9% of adults.
PREDOMINANT SEX: Male:female ratio ~4:1
PREDOMINANT AGE: 30 to 50 yr in men; older than 60 yr in women

ETIOLOGY

- Gout is induced by inflammation from monosodium urate (MSU) crystal deposition. The primary risk factor for MSU deposition is hyperuricemia, though local factors such as temperature, pH, and mechanical stress may play a role. Fig. E1 illustrates the pathophysiology of gout.
- Hyperuricemia and gout develop from excessive uric acid production, a decrease in the renal excretion of uric acid, or both.
- Primary hyperuricemia results from an inborn error of metabolism and may be attributed to several biochemical defects.
- Secondary hyperuricemia may develop as a complication of acquired disorders (e.g., leukemia) or as a result of the use of certain drugs (e.g., diuretics). Consumption of alcohol, especially beer, increases the risk of gout, and fructose-rich beverage intake is associated with hyperuricemia. Gout promoters and inhibitors are summarized in Table 1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

ACUTE GOUT:

- Rapid onset of pain and swelling and erythema of a distal joint and/or periarticular soft tissue. Box 1 summarizes clinical pearls in acute gout attacks.
- May present as monoarthritis of any joint. Acute gout of the first metatarsophalangeal (MTP) joint is known as *podagra.*
- 10% to 15% of attacks are polyarticular.
- Spontaneous resolution occurs over days to wks.

CHRONIC TOPHACEOUS GOUT (FIG. E2):

- Insidious onset of painless arthritis and soft tissue swelling
- Distal small joints characteristic
- May be confused with nodal osteoarthritis
- Box 2 summarizes clinical pearls in chronic gout

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS OF ACUTE GOUT

- Septic arthritis, cellulitis
- Pseudogout, calcium pyrophosphate crystal deposition disease
- Trauma

DIFFERENTIAL DIAGNOSIS OF CHRONIC GOUT

- Osteoarthritis (especially nodal OA in women)
- Rheumatoid arthritis
- Psoriatic arthritis

Section II describes the differential diagnosis of acute monoarticular and oligoarticular arthritis.

WORKUP

Arthrocentesis and examination of synovial fluid

LABORATORY TESTS

- Uric acid: All patients with gout are hyperuricemic at some time, but during an acute attack the serum uric acid may be normal or low.
- Synovial aspirate: Usually cloudy and markedly inflammatory in nature. Urate crystals in fluid are needle shaped and strongly negatively birefringent under polarized microscopy (Fig. E3).
- CBC: Neutrophilic leukocytosis often present.
- Inflammatory markers: ESR and CRP often elevated.

IMAGING STUDIES

- Plain radiography for diagnosis and evaluation. No typical findings in early gouty arthritis, but late disease is associated with characteristic punched-out marginal erosions (Fig. E4) and overhanging edges.
- Musculoskeletal ultrasound has been shown to be an effective means of detecting monosodium urate crystal deposition. Ultrasound can differentiate urate crystals that are found on the surface of articular cartilage from CPPD crystals that are seen within the substance of the cartilage (Fig. E5). Double contour sign can be seen.

TREATMENT

TREATMENT OPTIONS FOR ACUTE GOUT (TABLE 2)

- Nonsteroidal antiinflammatory medication (see Table 3).
  1. Indomethacin 75 mg bid
  2. Ibuprofen 800 mg tid
  3. Naproxen 500 mg bid
  4. Celecoxib 20 mg bid
- Low-dose colchicine (less toxic, as effective as traditional high-dose colchicine): 1.2 mg PO, followed by 0.6 mg PO 1 h later, then 0.6 mg daily or bid. Dose for renal function.
- Intraarticular corticosteroid injection (treatment of choice for monoarticular large joint attack): Triamcinolone acetonide 40 mg or equivalent for knee.
- Systemic corticosteroid therapy: prednisone 40 mg PO for 3 days, then taper over 10 days (effective and safe, but evidence is lacking).

TABLE 1 Gout Promoters and Inhibitors*

Crystal formation	Seed nucleus (particulate) Immunoglobulin Phagocytes Low temperature Low pH Cation concentration Intraarticular dehydration Other (unknown) macromolecules
Triggering the acute flare (local factors)	Rapid change in urate level Microcrystal release IgG coat (apolipoproteins B, E inhibitory) Complement activation (classical, alternate, MAC) Inflammasome activation Cytokine and chemokine release Endothelial activation (e-selectin, ICAM-1, VCAM-1) Local trauma?
Presence of susceptible phagocytes, mast cells (systemic events)	Surgery, trauma Infections, other intercurrent systemic illness Alcohol, dietary intake Drugs that raise or lower circulating urate level

*A diverse array of proteins and other mediators have been identified on the surfaces of urate crystals. In addition to their proinflammatory effect through opsonizing existing crystals, immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies may promote crystal formation by providing a stable molecular platform for crystal nucleation and growth. Apolipoproteins are the best characterized of the antiinflammatory molecules that coat crystals. The characteristics of the phagocytes encountering the crystals may be crucial; macrophages that are more differentiated are less likely to elicit proinflammatory cytokines.

ICAM-1, Intercellular adhesion molecule 1; *Ig,* immunoglobulin; *MAC,* membrane attack complex; *VCAM-1,* vascular cell adhesion molecule 1.

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

BOX 1 Acute Gout: Clinical Pearls

- Abrupt and rapid onset
- Maximal symptom intensity at 8-12 hours
- Attacks often come on at night or early morning
- Most commonly monoarticular in men during first attack
- Metatarsophalangeal joint is first affected in 50% of cases; other commonly affected joints: ankle, heel, knee, wrists, and hands
- Joints are red, hot, swollen, and exquisitely tender
- Attacks resolve within days to wks without treatment

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

BOX 2 Chronic Gout: Clinical Pearls

- Pattern of symptoms changes: Time between attacks shortens; more joints may be involved
- Tophaceous disease may result in a destructive arthropathy
- Tophaceous deposits may be bothersome and cause marked reduction in quality of life
- Increased risk for nephrolithiasis
- Associated with comorbidities such as metabolic syndrome, diabetes mellitus, chronic kidney disease, cardiovascular disease, hyperlipidemia, and obesity

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TREATMENT OF HYPERURICEMIA IN PATIENTS WITH GOUT

The American College of Rheumatology and most international rheumatology guidelines recommend that every patient with gout who has tophi, more than two attacks of gout per yr, chronic kidney disease, or nephrolithiasis be treated with pharmacologic urate-lowering therapy. Serum uric acid should be monitored on a regular basis and urate-lowering therapy intensified until a target of less than 6 mg/dl is reached. In most cases, urate-lowering therapy should be continued for life. Fig. 6 summarizes pharmacologic serum urate–lowering treatment.

The American College of Physicians Guidelines recommends a more conservative approach based on recurrence of symptoms. These guidelines have been criticized as ignoring the progressive nature of gout and perpetuating the well-documented underutilization and under-dosing of urate-lowering therapy.

NONPHARMACOLOGIC THERAPY

Lifestyle and dietary modification should always be a component of therapy for patients with gout, but this is rarely effective without concomitant pharmacologic urate-lowering therapy, as dietary modification can lower uric acid only about 1 mg/dl. Recommendations include reducing ingestion of red meat, kidney, liver, yeast extract, shellfish, and overall protein along with restricting alcohol intake. Discontinuation of diuretic therapy may help lower serum uric acid.

PHARMACOLOGIC TREATMENT OF SYMPTOMATIC HYPERURICEMIA

ALLOPURINOL: Allopurinol is very effective and safe when used properly. Correct dosing and patient compliance are essential elements in the prevention of erosive and tophaceous gout. Patients with renal insufficiency are at increased risk for allopurinol hypersensitivity, which manifests as fever, rash, and hepatitis occurring most commonly in the first 3 mo of therapy. The rash may progress to life-threatening toxic epidermal necrolysis if not recognized early.

Traditionally, therapy with allopurinol is initiated several wks after the acute attack has resolved. However, initiation of allopurinol at presentation may improve long-term compliance without reducing the efficacy of acute treatment. The initial dose should be low (≤100 mg/day depending on creatinine clearance) in patients with renal insufficiency and those with very high uric acid levels. High initial doses are associated with increased incidence of allopurinol hypersensitivity. The serum uric acid should be reevaluated after 4 to 6 wk of therapy, and the allopurinol dose adjusted to reduce the serum uric acid to less than 6 mg/dl. The most common therapeutic dosage of allopurinol is 300 mg/day, but dose may be increased by 50 to 100 mg every 2 to 3 wk until the target serum uric acid level is achieved. There is evidence that increasing allopurinol doses in patients with renal insufficiency does not result in significant toxicity, but concurrent use with statins and colchicine is associated with a higher incidence of adverse effects. Some authors have reported using doses as high as 800 mg daily without excess toxicity. It is recommended that patients of Han Chinese, Thai, and Korean ancestry be tested for HLA-B*5801 before initiating allopurinol as these individuals are at high risk of allopurinol hypersensitivity if this allele is present.

FEBUXOSTAT: Febuxostat is a xanthine oxidase inhibitor that has been shown to be more potent than allopurinol 300 mg daily for reducing serum uric acid. The chemical structure of febuxostat is different from allopurinol, making cross-reactive allergy unlikely. The metabolism of febuxostat is primarily hepatic, which obviates the need for dose adjustments due to renal insufficiency. Some cases of hepatic toxicity have been reported, and it is recommended that liver function tests be monitored. Febuxostat may help preserve renal function in patients with chronic kidney disease (CKD) but has not been tested in patients with severe renal failure.

The primary indication for febuxostat is demonstrated allergy to allopurinol. The cost of febuxostat may be as much as 40 times that of allopurinol, and there is some evidence suggesting that febuxostat may be associated with higher cardiovascular and all-cause mortality than allopurinol in patients with cardiovascular risk factors. In 2019, the FDA added a boxed warning for increased risk of death with febuxostat.

PROBENECID: Uricosuric agents may be used in patients with good renal function and urinary uric acid less than 600 mg in a 24-h collection. Probenecid can be used in patients with intolerance to xanthene-oxidase inhibitors. Compliance is poor due to the necessity of taking the drug more often than once daily.

LESINURAD: Lesinurad is a URAT1 and OAT4 inhibitor approved by the FDA in 2015 for gout-associated hyperuricemia unresponsive to xanthine oxidase inhibitor monotherapy, to be taken in combination with a xanthene oxidase inhibitor. This drug was withdrawn in 2019 because of business-related reasons without safety concerns noted.

PEGLOTICASE: Intravenous PEGylated uricase is FDA approved for treatment of severe refractory tophaceous gout. It is a PEGylated recombinant mammalian uricase that rapidly degrades urate when given intravenously. Use is limited by very high cost and potential toxicities, including frequent gout flares and anaphylaxis. Rasburicase is a nonpegylated uricase used in tumor lysis syndrome and is not indicated for gout treatment.

PATIENT & FAMILY EDUCATION

It is essential that patients, families, physicians, and other members of the health care team appreciate the importance of compliance with a daily allopurinol regimen if recurrent flares and progression to chronic arthritis and tophi are to be avoided. Allopurinol should be discontinued only for symptoms suggesting hypersensitivity; otherwise it should be continued during flares, medical illnesses, and surgical procedures.

REFERRAL

- Rheumatologist if diagnosis is not clear or therapy is complicated
- Podiatrist for management of pedal complications

PEARLS & CONSIDERATIONS

- The interleukin-1 receptor antagonist anakinra (Kineret) is an effective off-label agent for treatment of gout in complex patients with contraindications to standard therapies.
- Do not stop allopurinol during hospitalizations, surgery, or acute attacks unless there is evidence of drug allergy. The dosage of allopurinol should be adjusted in patients with acute kidney injury.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Gout (Patient Information)
Hyperuricemia (Related Key Topic)

AUTHOR: **Kevin V. Plumley, MD, MPH**

TABLE 2 Therapeutic Options for Acute Gouty Inflammation

Drug Option	Level of Evidence	Typical Regimens
COX-nonselective NSAIDs	Grade A evidence for each regimen listed	Naproxen, 750-1000 mg PO daily in divided doses for 3 days; then 500-750 mg total daily for 4-7 days Sulindac, 300-400 mg/day in divided doses for 7-10 days Indomethacin, 150-200 mg PO daily in divided doses for 3 days; then 100 mg PO daily in divided doses for 4-7 days
COX-2–selective NSAIDs	Grade A	For example: celecoxib, 800 mg; then 400 mg on day 1 followed by 400 mg bid for 7 days
Systemic corticosteroids	Grade A evidence for oral prednisolone, 35 mg/day for five or six doses; lower evidence grades for other regimens	Prednisone, 30-60 mg/day for 3 days; then taper every 3 days by 10-15 mg less as a daily dose until discontinuation Oral prednisolone, 35 mg/day for 5-7 days Medrol dose pack (for less severe flares) or to initiate therapy In an NPO patient: • Triamcinolone, 60 mg IM once with additional corticosteroid treatment as needed • Methylprednisolone, 100-150 mg IV for 1-2 days
Intraarticular corticosteroids	Grade C evidence	Particularly useful for flares in a single large joint Triamcinolone acetonide preparations are especially useful Dose titrated to the size of the joint
ACTH	Grade C evidence	25 USP units of synthetic ACTH SC for less severe flares; 40 USP units IM or IV once for more severe flares (including larger joint flares and polyarticular gout) One or two repeated doses of synthetic ACTH at intervals of 12 hr are often required with each of these regimens
Oral colchicine	Grade A evidence for U.S. FDA-approved regimen	In the U.S.: To treat an early acute gout flare: 1.2 mg once followed by 0.6 mg in 1 hr and then 12 hr later; oral low-dose colchicine at prophylaxis doses until the acute gout flare resolves Outside the U.S.: 0.5 mg tid for several days is the EULAR-recommended dosing regimen Oral colchicine treatment of acute gout should be limited to once every 2 wk in those already taking a maintenance low dose of colchicine
Off-label use in U.S.: IL-1 antagonism	Grade C for anakinra; grade A for canakinumab	Use of anakinra (e.g., 100 mg SC daily for 3 days) or canakinumab (150 mg SC as single dose) for acute gout flare is not approved by the FDA, but canakinumab is approved by the EMA for this indication

ACTH, Adrenocorticotropic hormone; *bid,* twice a day; *COX,* cyclooxygenase; *EMA,* European Medicines Agency; *EULAR,* European League Against Rheumatism; *FDA,* U.S. Food and Drug Administration; *IL-1,* interleukin-1; *IM,* intramuscularly; *IV,* intravenously; *NPO,* nothing by mouth; *NSAID,* nonsteroidal antiinflammatory drug; *PO,* by mouth; *SC,* subcutaneously; *tid,* three times a day; *USP,* U.S. Pharmacopeia.

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE 3 Treatment of Gout

Acute Gout	Interval Gout	Treatment of Hyperuricemia
NSAIDs (preferred): Indomethacin 50 mg qid or ibuprofen 800 mg tid (or other NSAID in full doses). Contraindicated in patients with renal insufficiency and gastrointestinal disorders. *Or* **Colchicine, oral:** 1.2 mg followed by a second dose of 0.6 mg 1 hr later. Contraindicated in patients with renal insufficiency and gastrointestinal disorders *Or* **Intraarticular steroids** (Treatment of choice for large joint monoarthritis): Triamcinolone 40 mg or equivalent for knee *Or* Systemic steroid therapy (for patients in whom NSAIDs and colchicine are contraindicated) Prednisone 30-50 mg PO daily or in divided doses. May use lower dose in diabetic or postsurgical patients.	**Colchicine, oral:** 0.6-1.2 mg/day as prophylaxis against recurrent attacks. **NSAIDs may also be used for prophylaxis.** **Hypouricemic agent:** Indicated for patients with recurrent attacks despite prophylaxis, severe hyperuricemia, presence of tophi, urolithiasis, or gouty arthritis **Other:** Weight loss, reduce alcohol (especially beer), diet low in seafood, red meat, organ meat, and fructose	**Colchicine, oral:** 0.6-1.2 mg/day for 4-6 wk before initiating hypouricemic therapy and for several mo afterward to prevent recurrent attacks during initiation of hypouricemic therapy. *And* **Allopurinol:** Initial dose 100 mg/day in patients with renal insufficiency or very high uric acid levels. Increase dose as needed to attain uric acid less than 6 mg/dl. *Or* **Uricosuric agent** (Use only in patients with good renal function and <600 mg uric acid in a 24-hr collection): probenecid, 0.5-1 g bid, or sulfinpyrazone 100 mg tid or qid. **Other:** Consider febuxostat for patients allergic to allopurinol and the addition of lesinurad in patients resistant to xanthine oxidase inhibitors. Pegloticase may be useful for selected patients with severe tophaceous gout.

NSAID, nonsteroidal antiinflammatory drug; *PO,* by mouth; *qid,* four times a day; *tid,* three times a day.

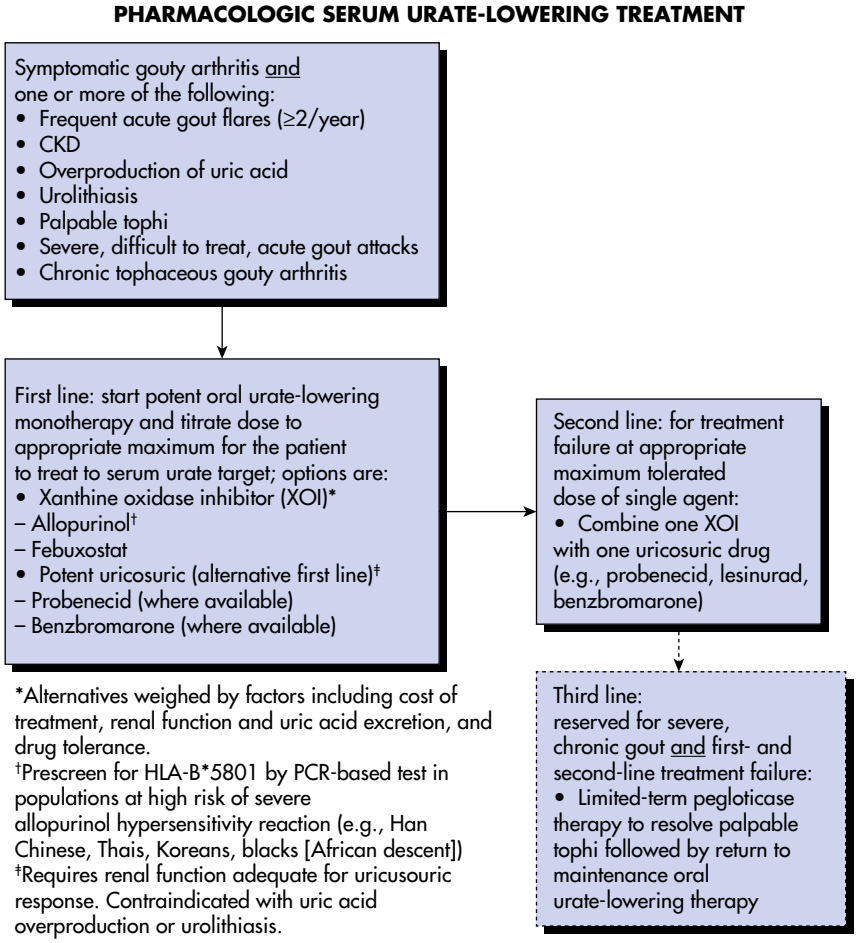

FIG. 6 Algorithm for pharmacologic serum urate–lowering treatment of hyperuricemia in patients with a confirmed diagnosis of gout. The algorithm, discussed in the text, summarizes the first-, second-, and third-line approaches to pharmacologic urate-lowering therapy, including management of refractory hyperuricemia in difficult gout. *CKD*, Chronic kidney disease; *PCR*, polymerase chain reaction. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

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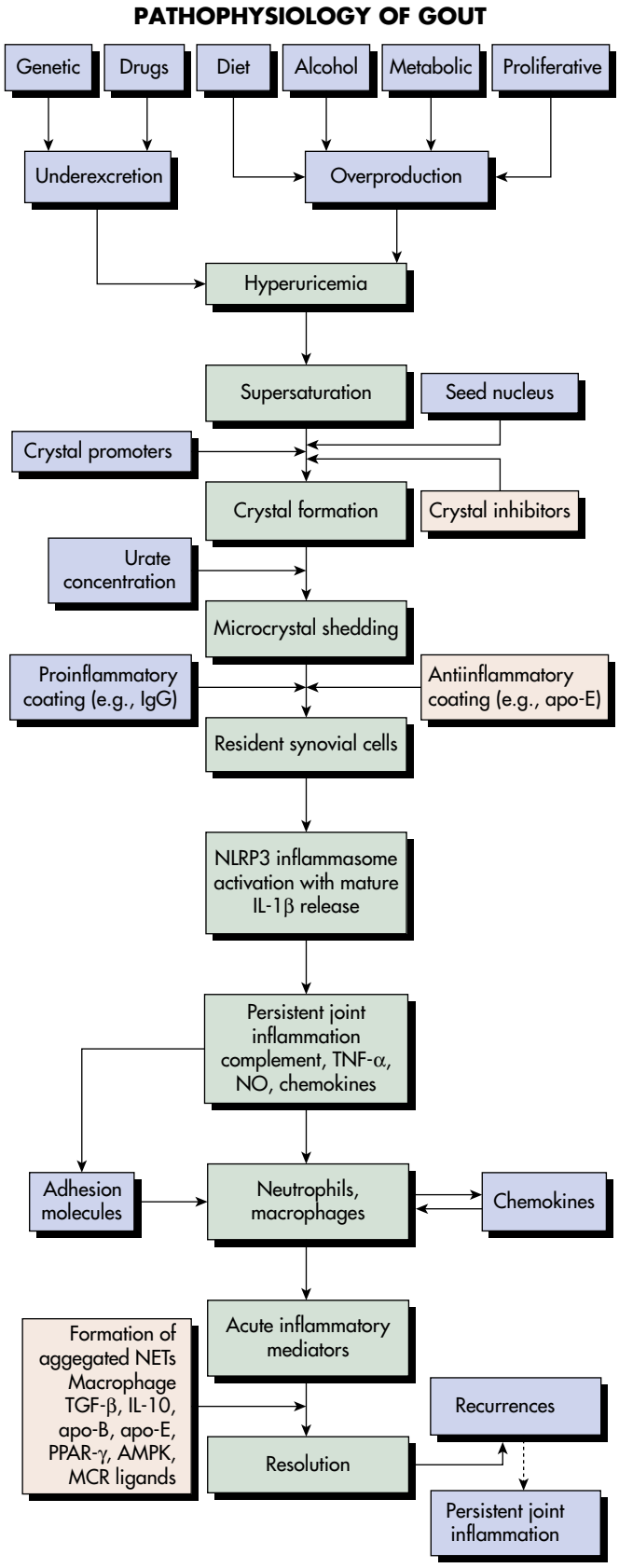

FIG. E1 Many signals impact at the critical points in this pathway. Patients with hyperuricemia do not necessarily form urate crystals. Crystals ingested by phagocytes sometimes elicit remarkably little inflammation, and inflammation is often low grade or clinically inapparent in advanced gout, indicating robust regulation of the pathways shown. The factors leading to the spontaneous termination of the acute gout flare are incompletely understood. *AMPK,* Adenosine monophosphate–activated protein kinase; *apo,* apolipoprotein; *IgG,* immunoglobulin G; *IL,* interleukin; *MCR,* melanocortin receptor; *NET,* neutrophil extracellular trap; *NLRP3,* nucleotide-binding oligomerization domain-like receptor 3; *NO,* nitric oxide; *PPAR,* peroxisome proliferator–activated receptor; *TGF-β,* transforming growth factor-β; *TNF-α,* tumor necrosis factor-α. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

FIG. E2 Advanced tophaceous gout with multiple intraarticular and periarticular tophi. Tophi observed on bilateral first metatarsophalangeal joints **(A)** (right greater than left) and the hand **(B)** in a patient with severe tophaceous gout. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

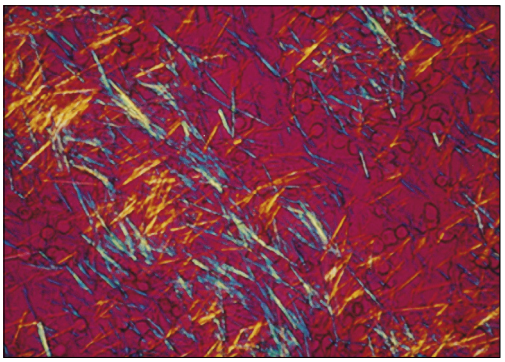

FIG. E3 Monosodium urate crystals from tophus. Crystals aspirated from a subcutaneous tophus. Polarized transmission white (halogen) light; 90-degree extinction filter; 530-nm first-order compensator. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

FIG. E4 Chronic tophaceous gout. Asymmetric large eccentric soft tissue lumps (tophi). Underlying gouty erosions are seen at several sites, particularly the distal interphalangeal joint of the right little finger and the carpometacarpal joint of the thumb. (From Adam A et al: *Grainger & Allison's diagnostic radiology,* ed 5, London, 2007, Churchill Livingstone; in Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia 2019, Elsevier.)

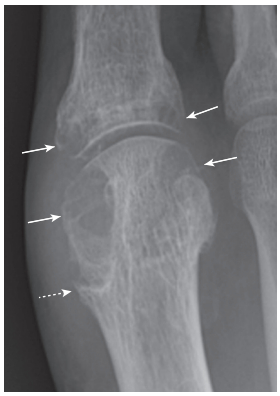

FIG. E5 Classic radiographic findings of gout in a 69-year-old man. Note the asymmetric, well-marginated erosions in the head of the first metatarsal and lesser erosions in the opposing phalanx *(solid arrows).* The medial erosions are characteristically larger than the lateral erosions. There is a "hook" sign on the inferior margin of the large medial erosion of the head of the metatarsal *(dashed arrow).* The joint space is preserved, and there is no osteopenia. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2014, WB Saunders.)

Graft-versus-Host Disease

BASIC INFORMATION

DEFINITION

Graft-versus-host disease (GVHD) is a complication of allogeneic hematopoietic stem cell transplantation (HSCT) in which a patient's bone marrow is replaced by a donor's, and the donor cells recognize the patient's organs as foreign and launch an immunologic attack on them. GVHD is reported rarely after autologous bone marrow transplant and blood transfusion. GVHD that occurs between the time of engraftment and up to 100 days afterward is termed *acute GVHD.* GVHD that occurs beyond 100 days is termed *chronic GVHD*.

SYNONYM

GVHD

ICD-10CM CODE

D89.813 Graft-versus-host disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The incidence of acute GVHD is 25% to 35% in recipients of fully matched sibling donor grafts and 40% to 50% in recipients of matched unrelated donor grafts. The incidence of chronic GVHD is 30% in recipients of fully histocompatible transplants and 60% to 70% in mismatched or unrelated donor recipients.

PREDOMINANT AGE AND SEX: Older age and female donor-to-male recipient transplant are risk factors for GVHD.

GENETICS: Degree of HLA mismatch is a risk factor for GVHD.

RISK FACTORS:

- Degree of HLA mismatches is the strongest risk factor
- Source of graft (peripheral blood or bone marrow greater than umbilical cord blood)
- Female donor-to-male recipient
- Multiparous donors
- Intensity of the transplant conditioning regimen
- Acute GVHD prophylactic regimen
- Transplants that achieve full donor chimerism
- CMV mismatch
- Older patients, those with poor functional status

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute GVHD: Median onset is 21 to 25 days post-HSCT.
- Skin is affected in approximately 80% of patients, gastrointestinal (GI) tract in 50%, and liver in 50%.
- Chronic GVHD primarily occurs within the first yr after HSCT, but 5% to 10% of patients develop HSCT after 1 yr. About 30% of chronic GVHD is de novo without history of acute GVHD. The median time to diagnosis of chronic GVHD is 4.5 mo. Common clinical manifestations of chronic GVHD are summarized in Table E1.
- Skin lesions include maculopapular rash commonly involving the neck, shoulders, palms, and soles.
- More severe lesions include blisters, ulcers, and bullae.
- GI manifestations include anorexia, nausea, vomiting, abdominal pain, ileus, secretory diarrhea that is often copious, and hematochezia. The diarrheal volume determines the severity of disease.
- Liver involvement occurs as a result of damage to biliary canaliculi, causing cholestasis with hyperbilirubinemia and elevated alkaline phosphatase. Severity of liver disease is evaluated based on serum bilirubin levels.

ETIOLOGY

GVHD occurs when immune cells transplanted from a donor (the graft) recognize the transplant recipient (the host) as foreign, and initiate an immune attack against the recipient organs. The pathophysiology of GVHD is illustrated in Fig. E1.

TABLE E1 Common Clinical Manifestations of Chronic Graft-versus-Host Disease

Organ System	Clinical Manifestations
Cutaneous	Poikiloderma, lichen planus, dermal sclerosis, morphea-like features, hypopigmentation or hyperpigmentation, ichthyosis, nail dystrophy, onycholysis
Ocular	Keratoconjunctivitis sicca, conjunctivitis, corneal ulcerations
Oral	Lichen planus, hyperkeratotic plaques, xerostomia, mucosal atrophy, ulcers, restriction of mouth opening from sclerosis
Pulmonary	Bronchiolitis obliterans, bronchiolitis obliterans–organizing pneumonia
Gastrointestinal	Esophageal web and strictures, malabsorption syndrome, exocrine pancreatic insufficiency
Hepatic	Cholestasis
Genitourinary	Vaginal stenosis or scarring, lichen planus
Musculoskeletal	Fasciitis, joint contractures from sclerosis, myositis or polymyositis, arthritis
Hematopoietic	Thrombocytopenia, eosinophilia, lymphopenia, hemolytic anemia, hypogammaglobulinemia

From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

DIAGNOSIS

The National Institutes of Health (NIH) consensus criteria used to diagnose GVHD classify manifestations of GVHD as "diagnostic" or "distinctive" of chronic GVHD, or as common to both acute and chronic GVHD.

Common diagnostic criteria sufficient to establish a diagnosis of chronic GVHD:

- Poikiloderma
- Lichen planus–like features
- Esophageal web
- Strictures or stenosis in the upper to middle third of the esophagus
- Bronchiolitis obliterans diagnosed with lung biopsy

Common distinctive criteria that are encountered in chronic GVHD but are insufficient by themselves to establish a diagnosis include the following:

- Depigmentation
- Cicatricial conjunctivitis
- Keratoconjunctivitis sicca
- Bronchiolitis obliterans diagnosed with pulmonary function tests (PFTs) and radiology
- Myositis or polymyositis

To make a diagnosis of chronic GVHD, at least one diagnostic clinical sign of chronic GVHD must be present or at least one distinctive manifestation must be confirmed by pertinent biopsy or other relevant tests in the same or another organ. The clinical features, staging, and grading of acute GVHD are summarized in Table E2.

DIFFERENTIAL DIAGNOSIS

- Engraftment syndrome
- Erythema multiforme
- Malignancy
- Hepatic sinusoidal obstructive syndrome
- Drug eruptions and toxicities
- Dermatomyositis
- Systemic sclerosis

WORKUP

Although the diagnosis of GVHD is mostly made based on clinical signs and symptoms, biomarkers and organ-specific histology may help establish diagnosis.

LABORATORY TESTS

A panel of plasma biomarkers, including IL-2-receptor-α, TNF receptor-1, IL-8, and hepatocyte growth factor, has been suggested as a confirmatory tool for the diagnosis of GVHD at the onset of clinical manifestations. However, biomarker identification remains an active area of investigation.

IMAGING STUDIES

Positron emission tomography (PET) scanning may be used to distinguish intestinal GVHD from other diagnoses in patients with intestinal GVHD.

TREATMENT

Treatment of GVHD:

- Treatment depends on the organs involved and the severity of GVHD. Commonly administered drugs for GVHD are summarized in Table E3.

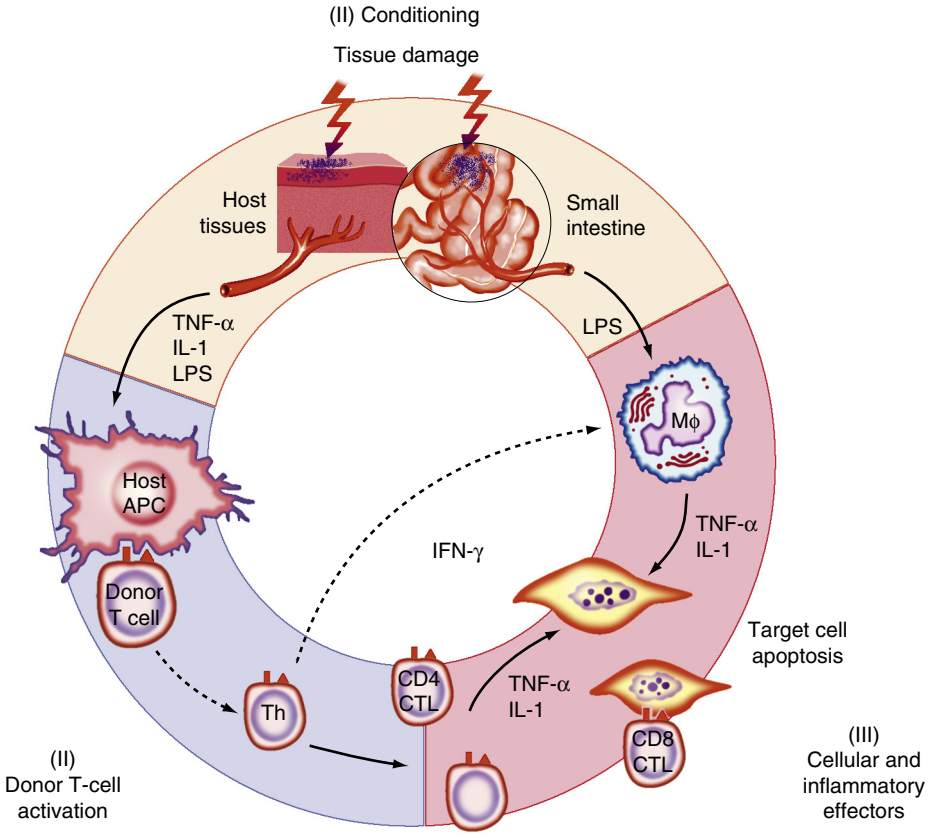

FIG. E1 Pathophysiology of graft-versus-host-disease (GVHD). During step 1, both irradiation and chemotherapy damage and activate host tissues, including intestinal mucosa, liver, and the skin. Activated host cells subsequently secrete inflammatory cytokines (e.g., TNF-α and IL-1) that can be measured in the systemic circulation. The cytokine release has important effects on host antigen-presenting cells (APCs), including increased expression of intercellular and vascular cell adhesion molecules and MHC class II antigens. These changes in the APCs enhance the recognition of host MHC and/or minor H antigens by mature donor T cells. During step 2, donor T-cell activation is characterized by proliferation of GVHD T cells and secretion of the Th1 cytokines IL-2 and IFN-γ. Both of these cytokines play central roles in clonal T-cell expansion, induction of CTL and NK cell responses, and priming of mononuclear phagocytes. In step 3, mononuclear phagocytes primed by IFN-γ are triggered by a second signal such as endotoxin LPS to secrete cytopathic amounts of IL-I and TNF-α. LPS can leak through the intestinal mucosa damaged by the conditioning regimen to stimulate gut-associated lymphoid tissue or Kupffer cells in the liver; LPS that penetrates the epidermis may stimulate keratinocytes, dermal fibroblasts, and macrophages to produce similar cytokines in the skin. This mechanism results in the amplification of local tissue injury and further production of inflammatory effectors such as nitric oxide, which, together with CTL and NK effectors, leads to the observed target tissue destruction in the stem cell transplant host. CTL effectors use Fas/FasL, perforin/granzyme B, and membrane-bound cytokines to lyse target cells. *APC,* Antigen-presenting cell; *CTL,* cytotoxic T lymphocyte; *ICAM,* intercellular adhesion molecule; *IFN,* interferon; *IL,* interleukin; *LPS,* lipopolysaccharide; *MHC,* major histocompatibility complex; *NK,* natural killer; *TNF,* tumor necrosis factor. (From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

TABLE E2 Clinical Manifestations and Staging of Acute Graft-versus-Host Disease

Organ	Clinical Manifestations	Staging
Skin	Erythematous, maculopapular rash involving palms and soles; may become confluent Severe disease: Bullae	Stage 1: <25% rash Stage 2: 25%-50% rash Stage 3: Generalized erythroderma Stage 4: Bullae
Liver	Painless jaundice with conjugated hyperbilirubinemia and increased alkaline phosphatase	Stage 1: Total bilirubin 2-3 mg/dl Stage 2: Total bilirubin 3.1-6 mg/dl Stage 3: Total bilirubin 6.1-15 mg/dl Stage 4: Total bilirubin >15 mg/dl
Gastrointestinal tract	Upper: Nausea, vomiting, anorexia Lower: Diarrhea, abdominal cramps, distension, ileus, bleeding	Stage 1: Diarrhea >500 ml/day Stage 2: Diarrhea >1000 ml/day Stage 3: Diarrhea >1500 ml/day Stage 4: Ileus, bleeding

From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

- In mild cutaneous GVHD, topical steroids may be used along with optimization of prophylactic regimen.
- Systemic methyl prednisone 2 mg/kg per day in divided doses should be used for grade 2 or higher GVHD, in addition to the optimization of prophylactic measures. Corticosteroid treatment can be tapered over several mo.
- In GVHD with gastrointestinal involvement, systemic glucocorticoids plus oral nonabsorbable steroids should be used. In addition, octreotide may reduce diarrhea.
- Patients who demonstrate progression of disease by day 5 of therapy or no response by day 7 are considered to have glucocorticoid resistance. There is no standard therapy for steroid refractory GVHD. Second-line agents in treatment of GVHD include mycophenolate mofetil, etanercept, pentostatin,

TABLE E3 Commonly Administered Drugs for Graft-versus-Host Disease Prophylaxis and Treatment

Drug	Mechanism	Adverse Effects
Corticosteroids	Direct lymphocyte toxicity; suppress proinflammatory cytokines such as TNF-α	Hyperglycemia, acute psychosis, severe myopathy, neuropathy, osteoporosis, cataract development
Methotrexate (MTX)	Antimetabolite: inhibits T-cell proliferation	Significant renal, hepatic, and gastrointestinal toxicities
Cyclosporine A (CSA)	IL-2 suppressor; blocks Ca^{2+}-dependent signal transduction distal to TCR engagement	Renal and hepatic insufficiency, hypertension, hyperglycemia, headache, nausea and vomiting, hirsutism, gum hypertrophy, seizure with severe toxicity
Tacrolimus (FK506)	IL-2 receptor; blocks Ca^{2+}-dependent signal transduction distal to TCR engagement	Similar to cyclosporine A
Mycophenolate mofetil (MMF)	Inhibits de novo purine synthesis	Body aches, abdominal pain, nausea and vomiting, diarrhea, neutropenia
Sirolimus	mTOR inhibitor	Thrombocytopenia, hyperlipidemia, TTP
Antithymocyte globulin (ATG)	Polyclonal immunoglobulin	Anaphylaxis, serum sickness

Ca^{2+}, Calcium ion; *IL-2,* interleukin-2; *mTOR,* mammalian target of rapamycin; *TCR,* T-cell receptor; *TNF-α,* tumor necrosis factor-α; *TTP,* thrombotic thrombocytopenic purpura.
From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE E4 Glucksberg Criteria for Staging of Acute Graft-versus-Host Disease[a]

Overall Grade	Skin	Liver		Gut
I	1-2	0		0
II	1-3	1	*and/or*	1
III	2-3	2-4	*and/or*	2-3
IV	2-4	2-4	*and/or*	2-4

[a]See Table E2 for individual organ staging. Traditionally, individual organs are staged without regard to attribution. The overall grade of graft-versus-host disease, however, reflects the actual extent of graft-versus-host disease. To achieve each overall grade, skin disease, liver, and/or gut involvement are required.
From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

alpha-1 antitrypsin, sirolimus, ruxolitinib antithymocyte globulin, and extracorporeal photopheresis.

ACUTE GENERAL Rx

Acute treatment involves topical or systemic corticosteroids. Second-line agents can be used in steroid-resistant cases.

CHRONIC Rx

Corticosteroids, tapered over several mo, can be used in chronic treatment of GVHD.

DISPOSITION

Patients should be directed to individuals who originally initiated organ or bone marrow transplantation surgery.

REFERRAL

Physicians with expertise in immunosuppression

PEARLS & CONSIDERATIONS

COMMENTS

GVHD is a potentially fatal disorder that occurs after an allogeneic transplant of bone marrow, peripheral blood stem cells, or solid organs. The donor bone marrow or peripheral blood stem cells attack the recipient's organs. Immunosuppression is required to prevent and treat this disorder.

GRADING OF GVHD: Severity is defined by the International Blood and Marrow Transplant Research (IBMTR) grading system:

- Grade A: stage 1 skin involvement alone (maculopapular rash over <25% of the body) with no liver or gastrointestinal involvement
- Grade B: stage 2 skin involvement; stage 1 to 2 gut or liver involvement
- Grade C: stage 3 involvement of any organ system (generalized erythroderma; bilirubin 6.1 to 15.0 mg/dl; diarrhea 1500 to 2000 ml/day)
- Grade D: stage 4 involvement of any organ system (generalized erythroderma with bullous formation; bilirubin >15 mg/dl; diarrhea >2000 ml/day or pain or ileus)

Glucksberg criteria for staging of acute GVHD are summarized in Table E4.

PREVENTION

- Prophylactic regimen should be decided based on underlying disease, the degree of HLA disparity, the conditioning regimen, and patient characteristics.
- Mycophenolate and calcineurin inhibitors should be used in patients undergoing reduced intensity allogeneic HSCT.
- For patients who receive myeloablative or reduced intensity conditioning, antithymocyte globulin can be added to the prophylactic regimen.

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SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Granuloma annulare (GA) is a chronic, usually self-limited, inflammatory disorder of the dermis that classically presents as arciform to annular plaques located on the extremities.

SYNONYMS

Pseudorheumatoid nodule—subcutaneous granuloma annulare
GA

ICD-10CM CODE
L92.0 Granuloma annulare

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common in children and young adults; most cases of localized GA are diagnosed in patients <30 yr
- Female predominance (2:1)
- Disseminated form associated with diabetes mellitus
- Recurrent in 40% of affected individuals
- A generalized form of GA can occur in up to 15% of patients

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The main clinical variants of GA are localized (75%), disseminated (>10 lesions), subcutaneous (occurring primarily in children aged 2 to 5 yr), patch-type or macular GA, and perforating (rare form manifesting with 1- to 4-mm papules with a central crust usually appearing on the dorsal hands).
- Localized GA starts as a small ring of colored skin or pale erythematous papules. More common in children and young to middle-age adults. Usually, only one or a few lesions occur at any one time.
- Lesions coalesce and evolve into annular plaques over several wk.
- Plaques undergo central involution and increase in diameter over several mo (0.5 to 5 cm).
- Most frequently found on the lateral and dorsal surfaces of the hands and feet (Fig. E1 and Fig. E2).
- Most lesions resolve spontaneously after several mo.
- The generalized form of GA is characterized by hundreds of small (lesions rarely exceed 5 cm in diameter), flesh-colored papules in a symmetric distribution on the trunk and extremities. It most commonly affects women in the fifth or sixth decades but can also be seen in adolescents and children. Some patients are completely asymptomatic, whereas others complain of severe pruritus.
- Macular GA is more common in women between ages 30 to 70 and manifests with flat or slightly palpable erythematous or red-brown lesions on upper medial thighs and in bathing-trunk distribution.
- Deep dermal GA (subcutaneous GA) presents as large, painless, skin-colored nodules that are frequently mistaken for rheumatoid nodules.

ETIOLOGY

Unknown, but may be related to vasculitis, trauma, monocyte activation, or delayed hypersensitivity.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Tinea corporis
- Lichen planus
- Necrobiosis lipoidica diabeticorum
- Sarcoidosis
- Rheumatoid nodules
- Late secondary or tertiary syphilis
- Arcuate and annular plaques of mycosis fungoides
- Papular GA can simulate insect bites, secondary syphilis, xanthoma
- Annular elastolytic giant cell granuloma

WORKUP

- Diagnosis based on clinical appearance and presentation
- Biopsy when diagnosis is unclear

LABORATORY TESTS

- No laboratory tests will help confirm the diagnosis.
- Biopsy shows focal degeneration of collagen and elastic fibers, mucin deposition, and perivascular and interstitial lymphohistiocytic infiltrate in the upper and middle dermis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Reassurance, given the self-limited and benign nature of GA

CHRONIC Rx

High-potency topical corticosteroids with or without occlusion and intralesional steroid injection into elevated border with triamcinolone 2.5 to 10 mg/ml are useful first-line local therapies.

- Cryosurgery, psoralen ultraviolet-A (UVA) range or UVA-1 therapy, and carbon dioxide laser treatment can also be used.
- Systemic agents (e.g., niacinamide, hydroxychloroquine, chloroquine, cyclosporine, dapsone) are generally reserved for severe cases. Recent case reports indicate positive outcomes with tacrolimus and pimecrolimus and the tumor necrosis factor infliximab.

DISPOSITION

Most lesions resolve spontaneously within 2 yr.

REFERRAL

Dermatology referral recommended for symptomatic, disseminated disease

PEARLS & CONSIDERATIONS

COMMENTS

GA has been described as a paraneoplastic granulomatous reaction to Hodgkin disease, non-Hodgkin lymphoma, solid organ tumors, and mycosis fungoides.

RELATED CONTENT

Granuloma Annulare (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

FIG. E1 Granuloma annulare. Annular, flesh-colored, nonscaly plaques. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Edinburgh, 2016, Elsevier.)

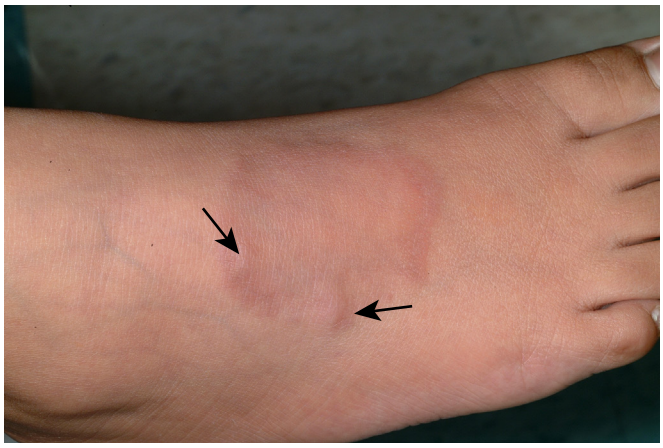

FIG. E2 Granuloma annulare. This patient's plaque reveals both cutaneous and subcutaneous (*arrows*) involvement. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Edinburgh, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Granuloma inguinale is a genital ulcerative disease caused by a gram-negative bacterium, *Klebsiella granulomatis,* which may be sexually transmitted. It can also be spread through close, long-term, nonsexual contact.

SYNONYMS

Donovanosis
Calymmatobacterium granulomatis

ICD-10CM CODE
A58 Granuloma inguinale

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Rare in the U.S. (<100 cases reported annually) and other developed countries
PREVALENCE: Endemic in some tropical and developing areas, including India, Papua New Guinea, the Caribbean, Central Australia, and southern Africa; incubation period is variable (1 to 2 wk)
PREDOMINANT SEX: Can affect both males and females

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinically, the disease is commonly characterized as painless, slowly progressive ulcerative lesions on the genitals or perineum without regional lymphadenopathy; subcutaneous granulomas (pseudobuboes) might also occur. The lesions are highly vascular (i.e., beefy red appearance [Fig. E1]) and bleed easily on contact.
- Extragenital infection can occur with extension of infection to the pelvis, or it can disseminate to bones, intraabdominal organs, or the mouth.
- Pathogenic features:
  1. Large, infected mononuclear cell containing many Donovan bodies
  2. Intracytoplasmic location

ETIOLOGY

K. granulomatis is a gram-negative bacillus that reproduces within polymorphonuclear cells, plasma cells, and histiocytes, causing the infected cells to rupture, releasing 20 to 30 organisms.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Carcinoma
- Secondary syphilis: Condylomata lata
- Amebiasis: Necrotic ulceration
- Concurrent infections
- Lymphogranuloma venereum
- Chancroid
- Genital herpes

WORKUP

- Check for clinical manifestations.
  1. Lesions bleed easily.
  2. Lesions are sharply defined and painless.
  3. Secondary infection may ensue.
  4. Inguinal involvement may cause pseudobuboes.
  5. Elephantiasis can result from obstruction of lymphatics.
  6. Suppuration and sinus formation are rare in female patients.
- Screen for other sexually transmitted diseases.
- Exclude other causes of lesions.
- Obtain stained, crushed prep from lesion.

LABORATORY TESTS

- The causative organism is difficult to culture and diagnosis requires visualization of dark-staining Donovan bodies with Wright stain (observation of Donovan bodies [intracellular bacteria]; organisms in vacuoles within macrophages) via biopsy of the ulcer or tissue crush prep. No FDA-cleared molecular tests for the detection of *K. granulomatis* DNA exist.
- HIV testing of all patients.

TREATMENT

ACUTE GENERAL Rx

Recommended regimen:
- Azithromycin 1 g PO once per wk or 500 mg daily for at least 3 wk and until all lesions have completely healed

Alternative regimens:
- Doxycycline 100 mg PO bid for at least 3 wk and until all lesions have completely healed
- Ciprofloxacin 750 mg PO bid for at least 3 wk and until all lesions have completely healed
- Erythromycin base 500 mg PO qid for at least 3 wk and until all lesions have completely healed
- Trimethoprim/sulfamethoxazole, one double-strength tablet (160 mg/800 mg) PO bid for at least 3 wk and until all lesions have completely healed
- Add gentamicin 1 mg/kg IV q8h if no improvement within the first few days of therapy

CHRONIC Rx

If there is a poor initial response, extend treatment. Treatment of relapses is often necessary. Patients should be counseled to avoid risky sex practices and to abstain from intercourse until infection is cleared.

DISPOSITION

Follow up clinically until signs and symptoms have resolved, then routine annual or semiannual visits.

REFERRAL

If response is poor, consider referral to an infectious disease specialist.

PEARLS & CONSIDERATIONS

COMMENTS

- Sexual partners within 60 days before onset of patient's symptoms should be examined and offered therapy.
- Pregnant women should be treated with erythromycin regimen.
- Patient education material can be obtained from local and state health clinics and also from American College of Obstetricians and Gynecologists.

RELATED CONTENT

Granuloma Inguinale (Patient Information)
Chancroid (Related Key Topic)
Lymphogranuloma Venereum (Related Key Topic)
Syphilis (Related Key Topic)

AUTHORS: **Stefani Bissonette, MD,** and **Anthony Sciscione, DO**

FIG. E1 **A** and **B,** Granuloma inguinale. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Elsevier.)

SUGGESTED READING

Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, *MMWR Morb Mortal Wkly Rep* 64, 2015. June 5, 2015. No. 3.

BASIC INFORMATION

DEFINITION

Granulomatosis with polyangiitis (GPA), formerly known as "Wegener granulomatosis," is a multisystem necrotizing vasculitis that generally affects the upper and lower respiratory tracts and the kidneys. It is characterized as an ANCA-associated granulomatous small-vessel vasculitis. Clinical manifestations depend on the tropism of blood vessel involvement and organ systems commonly affected beyond the respiratory tract and kidneys and can include neurologic and skin involvement, and the musculoskeletal systems as well as the gastrointestinal tract.

The disease can also present in a limited form that is generally confined to the upper respiratory tract and can be managed less aggressively than the more diffuse systemic form.

SYNONYMS

GPA
Wegener granulomatosis (WG)

ICD-10CM CODE
M31.3 Wegener granulomatosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 3/100,000 in recent U.S. epidemiologic studies, equal in men and women, more common in whites
MEAN AGE AT ONSET: 41 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical manifestations often vary with the stage of the disease and degree of organ involvement; localized disease often has upper respiratory tract involvement without systemic vasculitis, whereas systemic disease stages include early systemic, generalized, and severe disease.
- Frequent manifestations are:
  1. Upper respiratory tract: Chronic sinusitis, chronic otitis media, mastoiditis, nasal crusting, obstruction and epistaxis, nasal septal perforation, nasal lacrimal duct stenosis, saddle nose deformities (Fig. E1), and tracheal and subglottic stenosis. Up to 90% of patients with GPA have one or more nasal manifestations.
  2. Eyes: Conjunctivitis, ulcerative keratosis, episcleritis or scleritis, optic neuropathy, nasolacrimal duct obstruction, retinal vasculitis, uveitis, proptosis.
  3. Ears: Sensorineural and conductive hearing loss, otorrhea, and polychondritis.
  4. Mouth: Chronic ulcerative lesions of the oral mucosa, "mulberry" gingivitis.
  5. Lung: Nodules, pulmonary infiltrates or effusions, cavitary lesions, and frank hemoptysis (6% to 85%).
  6. Kidney: Rapidly progressive glomerulonephritis (38% to 70%), microscopic hematuria with or without red cell casts, and proteinuria.
  7. Skin: Cutaneous nodules over extensor surfaces of joints, necrotizing skin lesions (Fig. E2), palpable purpura (30% to 46%), urticaria, and livedo reticularis.
  8. Nervous system: Mononeuritis multiplex and peripheral neuropathies (15% to 40%), meningeal inflammation (pachymeningitis), headaches, and CNS involvement (7% to 11%).
  9. Musculoskeletal: Monoarthritis or polyarthritis (nondeforming), usually affecting large joints (60%).
  10. Constitutional: Fever (23% to 30%), weight loss (50%), and fatigue (61%).

ETIOLOGY

Unknown; complex immune-mediated disorder, believed to begin with granulomatous inflammation that progresses to systemic vasculitis. Various risk factors, including genetic, infectious and environmental triggers, have been considered.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other granulomatous lung diseases (e.g., sarcoidosis, lymphomatoid granulomatosis, eosinophilic granulomatosis with polyangiitis [EGPA, formerly Churg-Strauss syndrome]), necrotizing bronchocentric granulomatosis). The differential diagnosis of granulomatous lung disease is described in Section II. Table E1 describes differential diagnostic features of ANCA-associated vasculitis.
- Other ANCA-associated vasculitides, including microscopic polyangiitis (MPA).
- Goodpasture disease, other causes of glomerulonephritis (e.g., poststreptococcal nephritis).
- Neoplasms (especially lymphoproliferative disease).

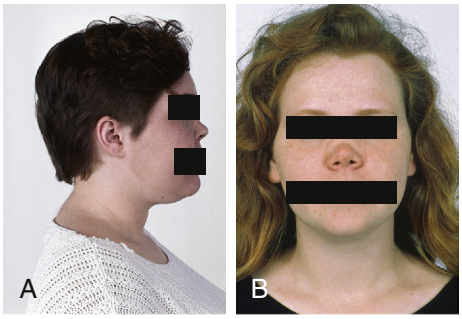

FIG. E1 Saddle-nose deformity in a patient with Wegener granulomatosis. (From *Kelley's textbook of rheumatology*, ed 8, Philadelphia, 2009, Elsevier.)

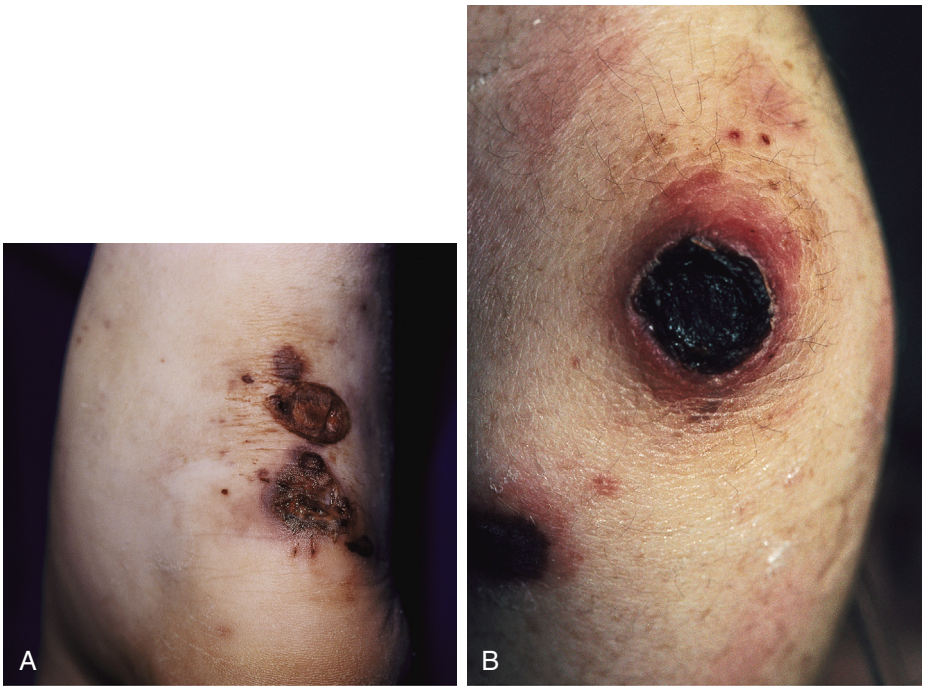

FIG. E2 Granulomatosis with polyangiitis (GPA; formerly known as Wegener granulomatosis). Painful, ulcerative, necrotic plaques on the ankle **(A)** and elbow **(B)** of a female with GPA. (From Paller AS, *Mancini AJ: Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Edinburgh, 2016, Elsevier.)

- Bacterial or fungal sinusitis.
- Viral infections.
- Cocaine-induced midline destructive lesions and levamisole-induced vasculitis.

WORKUP

- Granulomatosis with polyangiitis should be suspected in a patient presenting with sinus disease that is unresponsive to conventional treatment and/or pulmonary hemorrhage, glomerulonephritis, mononeuritis multiplex resulting in wrist drop or foot drop or progressive migratory arthralgias or arthritis.
- Chest x-ray, laboratory evaluation, PFTs, and tissue biopsy for granulomatous lesions (Fig. E3).

TABLE E1 Differential Diagnostic Features of the Antineutrophil Cytoplasm Antibody–Associated Vasculitides

Feature	Microscopic Polyangiitis (MPA)	GPA (Wegener Granulomatosis)	EGPA (Churg-Strauss Syndrome)	Comments
Glomerulonephritis	+++	+++	+	Progressive renal failure uncommon in EGPA
Pulmonary infiltrates or nodules	++	+++	+++	Asthma and eosinophilia in EGPA
Alveolar hemorrhage	++	++	+	
Upper airway disease	+	+++	++	Ear, nose, and throat disease usually favors GPA
Skin, purpura	+++	+	++	
Peripheral nerve involvement	+	++	+++	Often a prominent feature of EGPA
Central nervous system involvement	+	+	+	

+++, Very commonly seen; ++, seen often; +, uncommon finding; *EGPA*, eosinophilic granulomatosis with polyangiitis; *GPA*, granulomatosis with polyangiitis.
From Firestein GS et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, WB Saunders.

LABORATORY TESTS

- ANCA serology: Most patients with GPA have a positive test result for cytoplasmic pattern of ANCA (c-ANCA). In GPA, ANCAs are predominantly directed against proteinase 3 (anti-PR3), which is the confirmatory test in a patient with positive ANCA staining on immunofluorescence. However, between 10% and 15% of patients with GPA are positive for p-ANCA (usually MPO), and up to 10% are ANCA negative.
- CBC: Anemia, leukocytosis, thrombocytosis (>400,000/μL).
- Chemistry: Elevated serum creatinine, decreased creatinine clearance.
- Urinalysis: May reveal hematuria, RBC casts, and proteinuria.
- Inflammatory markers: Increased ESR, positive rheumatoid factor, and elevated C-reactive protein may be found.
- Liver function, hepatitis serologies, cryoglobulins, HIV screens, ANA, C3, C4, anti-GBM, and cultures to exclude other processes with similar constitutional symptoms.

IMAGING STUDIES

- Chest x-ray: May reveal bilateral multiple nodules, cavitary mass lesions, pleural effusion (20%). Up to one third of patients without pulmonary signs or symptoms have an abnormal chest x-ray (Fig. E4).
- Computed tomography of sinuses, (Fig. E5), computed tomography of chest, MRI of brain (Fig. E6) depending on symptoms

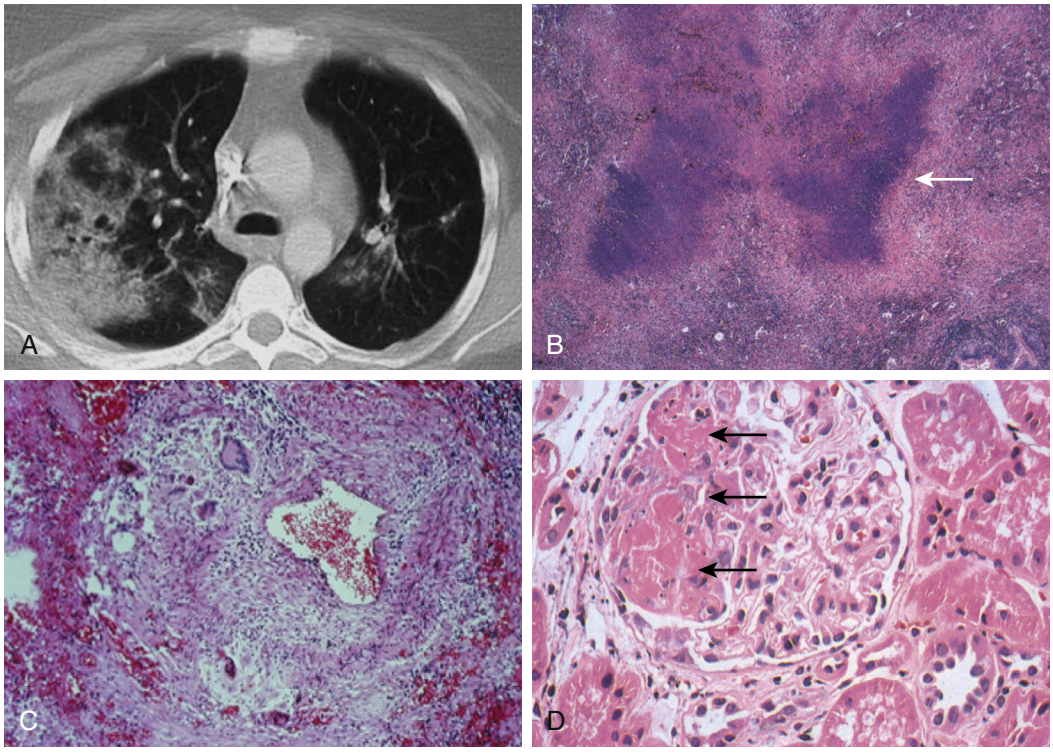

FIG. E3 **A,** Chest computed tomographic scan of a patient with granulomatosis with polyangiitis (GPA) shows typical nodular lung infiltrate with cavitation. **B,** Low-power view of granulomatous inflammation and geographic necrosis (*arrow*) in a lung biopsy from a patient with GPA. **C,** Granulomatous vasculitis involving a small pulmonary artery in the lung of a patient with GPA. The vessel wall is markedly thickened with an inflammatory infiltrate that includes multinucleated giant cells. **D,** Glomeruli showing segmental necrosis with early crescent formation (*arrows*). (From Adkinson NF et al: *Middleton's allergy principles and practice*, ed 8, Philadelphia, 2014, WB Saunders.)

FIG. E4 Chest radiograph shows multiple cavitary pulmonary nodules in patient with Wegener granulomatosis. (From Weinberg SE et al: *Principles of pulmonary medicine,* ed 5, Philadelphia, 2008, WB Saunders.)

- PFTs: Useful in detecting stenosis of the airways.
- Fiber optic bronchoscopy with BAL and endoscopic ENT examination: Nasal crusting ("golden crusts") are typical on evaluation (Fig. E7).
- Biopsy of one or more affected organs should be attempted; the most reliable source for tissue diagnosis is the lung. Lesions in the nasopharynx can be easily biopsied, but biopsy yield is only 20%. Biopsy of radiographically abnormal pulmonary parenchyma provides the highest yield (>90%).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Ensure proper airway drainage.
- Give nutritional counseling.

ACUTE GENERAL Rx

- Immunosuppressive therapy should be considered in all patients with GPA.
- Induction therapy in GPA consists of glucocorticoid with either cyclophosphamide or rituximab. Selected patients with severe disease may benefit from the addition of plasma exchange to this regimen.
- Historically, the gold standard for treatment is pulse methylprednisolone followed by prednisone 60 to 80 mg/day and pulse cyclophosphamide (1 g/m^2 every 4 wk) or daily oral cyclophosphamide (2 mg/kg/day). This was generally effective and used to control clinical manifestations. MESNA can be used with cyclophosphamide for the prevention of cyclophosphamide-induced hemorrhagic cystitis.
- Based on the RAVE trial, rituximab (375 mg/m^2/wk ×4 wk) appears to be more effective than traditional therapy in treating GPA that presents with disease flares and is at least as effective as traditional therapy for the induction of remission. The RITUXVAS trial concluded that a combined cyclophosphamide-rituximab regimen was not inferior to pulse cyclophosphamide alone. Both of these studies used concurrent methylprednisolone followed by prednisone.
- Methotrexate and glucocorticoids alone may be used with mild extrarenal disease or little to no renal involvement, or with limited sinus and upper airway involvement.
- For severe active renal disease, the MEPEX trial demonstrated that plasma exchange in addition to cyclophosphamide and glucocorticoids may enhance renal function recovery.
- Potentially useful agents for maintenance therapy include rituximab, methotrexate, azathioprine, and mycophenolate mofetil. The MAINRITSAN trial showed that rituximab may be preferable for maintenance therapy, and the CYCAZAREM (for azathioprine) and LEM (for leflunomide) trials showed that these agents can also be used. The WEGENT study showed oral methotrexate and azathioprine were noninferior for maintenance than intravenous cyclophosphamide.

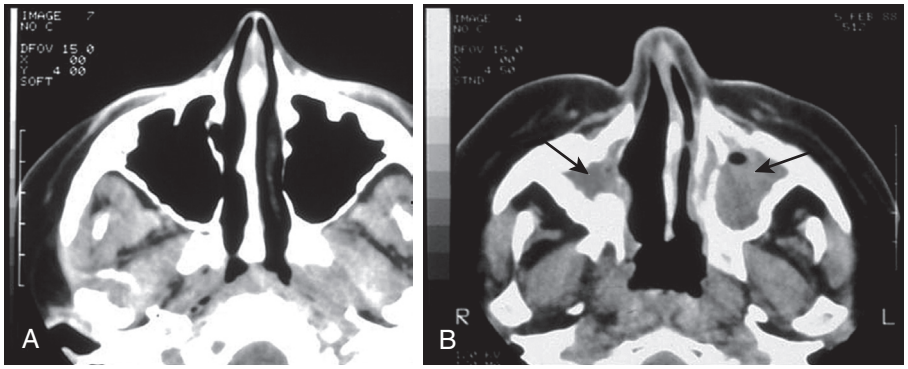

FIG. E5 Computed tomography (CT) scans of the sinuses. A, Normal maxillary sinuses in a recently diagnosed Wegener granulomatosis (WG) patient. **B,** Sinus CT scan of a patient with long-standing WG: Nasal septal deviation to the left, destruction of the medial walls of the right maxillary sinus, opacification of both sinuses with soft tissue densities *(arrows),* and neo-ossification of all maxillary bony structures due to chronic inflammation. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

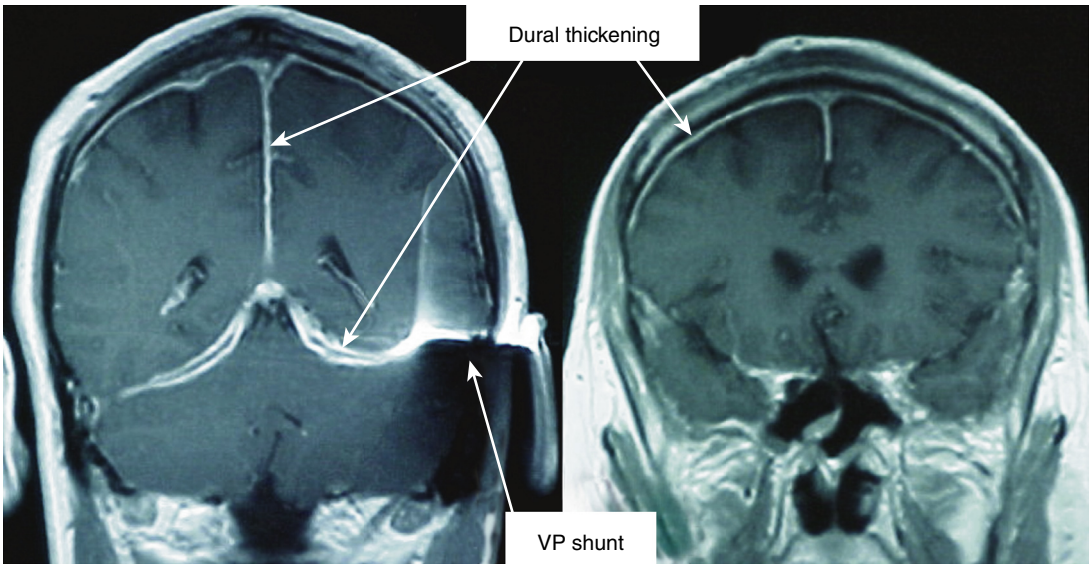

FIG. E6 Pachymeningitis in a patient with granulomatosis with polyangiitis. Magnetic resonance imaging findings. *VP,* Ventriculoperitoneal. (From Firestein GS et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, WB Saunders.)

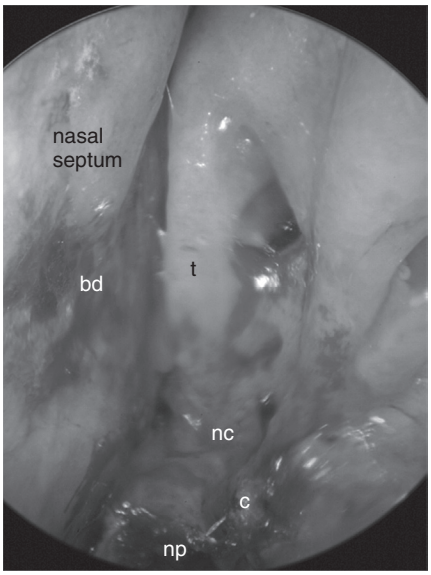

FIG. E7 Endoscopic view of nasal cavity of granulomatosis with polyangiitis patient showing crusting and bloody discharge. (From Holle et al: *Rheum Dis Clin North Am* 36[3]:507-526, 2010.)

- Maintenance therapy should generally be continued for at least 18 to 24 mo, and ultimate duration of immunosuppression is decided on a case-by-case basis.
- Treatment with TMP-SMX (160 mg/800 mg bid) may reduce the incidence of relapses in patients with granulomatosis with polyangiitis in remission. It is also useful in preventing *Pneumocystis jiroveci* pneumonia (PJP), which occurs in 10% of patients receiving induction therapy. Dose of TMP-SMX (160 mg/800 mg) for prophylaxis is 1 tablet three times/wk. If the patient is unable to tolerate TMP-SMX, PJP prophylaxis can also be achieved with dapsone, atovaquone, or inhaled pentamidine.

DISPOSITION

- Five-yr survival with aggressive treatment is approximately 80%; without treatment 2-yr survival is 20%.
- Age >50 yr, impaired renal function, pulmonary involvement at diagnosis, and lack of ENT changes at diagnosis are all associated with worse outcomes and increased mortality rate.
- With standard therapy, remission is achieved by 90% to 94% of patients, but relapse is frequent (from 18% to 40% at 24 mo).

REFERRAL

- Rheumatology referral for continued treatment
- ENT, surgical referral for biopsy

PEARLS & CONSIDERATIONS

COMMENTS

- Granulomatosis with polyangiitis is characterized by granulomatous lesions and vasculitis involving the respiratory tract, lung, and kidneys.
- C-ANCA levels should not dictate changes in therapy, because they correlate erratically with disease activity.
- The incidence of venous thrombotic events in patients with granulomatosis with polyangiitis is significantly higher than in the general population. Clinicians should maintain a heightened awareness of the risks of venous thrombosis and a lower threshold for evaluating patients for possible DVT or pulmonary embolism.
- Disease relapse remains a major problem in the course of the disease.

RELATED CONTENT

Granulomatosis with Polyangiitis (Patient Information)

AUTHORS: **Nicole B. Yang, MD,** and **Anthony M. Reginato, PhD, MD**

SUGGESTED READINGS

Berti A et al: The epidemiology of antineutrophil cytoplasmic autoantibody-associated vasculitis in Olmsted County, Minnesota (USA): a twenty-year population-based study, *Arthritis Rheumatol* 69(12):2338-2350, 2017.

Bossuyt X et al: Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis, *Nat Rev Rheumatol* 13(11):683-692, 2017.

Charles P et al: Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: Results of a multicenter, randomized controlled, phase III trial (MAINRITSAN2), *Annals rheum dis* 77(8):1143-1149, 2018.

Hiemstra TF et al: Mycophenate mofetil vs. azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis, *JAMA* 304(21):2381-2388, 2010.

Holle JU et al: Clinical manifestations and treatment of Wegener's granulomatosis, *Rheum Dis Clin North Am* 36(3):507-526, 2010.

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Kallenberg CG: Key advances in the clinical approach to ANCA-associated vasculitis, *Nat Rev Rheumatol* 10(8):484-493, 2014.

Singer O, McCune JW: Update on maintenance therapy for granulomatosis with polyangiitis and microscopic polyangiitis, *Current opinion in rheum* 29(3): 248-253, 2017.

Stone JH et al: Rituximab versus cyclophosphamide for ANCA-associated vasculitis, *N Engl J Med* 363:221-232, 2010.

Walsh M et al: Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: a meta-analysis, *Am J Kidney Dis* 57:566, 2011.

BASIC INFORMATION

DEFINITION

The prototype of granulomatous arthritis is tuberculous arthritis. Atypical mycobacteria, sarcoidosis, and sporotrichosis can cause granulomatous involvement of the synovium, but these entities are much less common.

SYNONYMS

Tuberculous arthritis
Pott disease

ICD-10CM CODES

M01.1 Tuberculous arthritis (A18.0+)
M01.6 Arthritis in mycoses (B35-B49+)
M01.8 Arthritis in other infections and parasitic diseases classified elsewhere
M00.9 Pyogenic arthritis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: No seasonal predilection
PREVALENCE (IN U.S.): Unknown
PREDOMINANT SEX: Male = female
PREDOMINANT AGE: Rare in childhood

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Often no constitutional symptoms (fever and weight loss)
- Possibly no clinical or radiographic evidence of pulmonary tuberculosis (TB)
- Spinal infection most often in the thoracic or upper lumbar area, with back pain as the most common symptom
- Considerable local muscle spasm possible
- Kyphosis and neurologic symptoms resulting from spinal cord compression in advanced disease
- Chronic monoarticular arthritis in the peripheral joints
- Single joint involved in 85% of patients
- Pain, swelling, limitation of motion, and joint stiffness less dramatic than in acute bacterial arthritis; possibly present for mos to yrs
- Seen more often in persons from developing countries, elderly patients, and hemodialysis patients

ETIOLOGY

- Hematogenous spread of organisms from a distant site of infection or by direct spread from bone
- Most commonly affected area: 50% of cases in the spine; next most commonly affected area: Large joints (knee and hip)
- Primary infection beginning in the lungs and spreading to the highly vascular synovium
- Tuberculous osteomyelitis commonly involving an adjacent joint
- In peripheral joints, a granulomatous reaction in the synovium causing joint effusion and eventual destruction of underlying bone
- In the spine, infection of the intervertebral disk spreading to adjacent vertebrae
- Osteomyelitis of vertebrae causing collapse, kyphosis, or gibbous deformity, and possibly paraspinal "cold" abscess

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Sarcoidosis
- Fungal arthritis
- Metastatic cancer
- Primary or metastatic synovial tumors

WORKUP

- High index of suspicion needed
- Gold standard: Synovial biopsy and culture for bacteria, including acid-fast bacilli, and fungi
- Joint aspiration and culture of the synovial fluid performed while awaiting biopsy
- Positive synovial fluid smear for acid-fast bacilli in 20% of cases; positive culture in 80%
- Elevated synovial fluid protein, low glucose
- Considerable variation in synovial fluid WBC count, but values of 10,000 to 20,000 cells/mm^3 typical; may be predominantly polymorphonuclear leukocytes
- Usually positive tuberculin skin test result implies exposure to TB, not necessarily active disease. Interferon-gamma release assays also can detect exposure to TB but not active disease (QuantiFERON TB Gold Test, TB T-Spot test)
- Anergy in elderly patients or in advanced disease
- In spinal infections, percutaneous or open biopsy to obtain accurate C&S data

LABORATORY TESTS

Peripheral WBC count and ESR are elevated but nonspecific.

IMAGING STUDIES

- Plain radiographs of the affected joint.
  1. Typically demonstrate bony destruction with little new bone formation
  2. Osteopenia and soft tissue swelling in early infections
  3. Later, erosions at the joint margins
  4. In the spine, disk space narrowing with vertebral collapse (wedging) causing characteristic kyphosis
- CT scan: Useful in early diagnosis of infections of the spine and to detect paraspinal abscess.
- Technetium and gallium scintigraphic scans: Findings may be positive but do not permit differentiation from inflammation or osteoarthritis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Encourage range of motion exercises of the affected joint to prevent contractures.

ACUTE GENERAL Rx

- Combination chemotherapy
  1. If sensitive TB suspected, give isoniazid 5 mg/kg/day (maximum 300 mg/day) plus rifampin 10 mg/kg/day (maximum 600 mg/day) for at least 6 mo and pyrazinamide 15 to 30 mg/kg/day (maximum 2 g/day) for at least the first 2 mo plus ethambutol 15 to 25 mg/kg/day until sensitivity results are available.
  2. Most patients are treated successfully with chemotherapy alone.
  3. Urgent surgical intervention is necessary if spinal cord compression causes neurologic changes.
- Surgical debridement in cases of extensive bone involvement

CHRONIC Rx

In long-standing extensive disease, arthrodesis of weight-bearing joints

DISPOSITION

Loss of cartilage and destruction of underlying bone if treatment is not initiated promptly

REFERRAL

- To a physician experienced in the management of TB
- For consultation with an infectious diseases specialist if drug resistance is suspected or documented
- For neurosurgical and/or orthopedic consultation if neurologic impairment suspected

PEARLS & CONSIDERATIONS

COMMENTS

As TB has become less prevalent in the U.S. in the past 10 yr, TB arthritis and osteomyelitis have also become less common. However, because of an increase in patients receiving antitumor necrosis factor-alpha therapy, there has been an increase of granulomatous diseases with nontuberculous mycobacteria such as *Mycobacterium avium.*

RELATED CONTENT

Tuberculosis, Miliary (Related Key Topic)
Tuberculosis, Pulmonary (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READING

Hogan JI et al: Mycobacterial musculoskeletal infections, *Infect Dis Clin North Am* 31:369-382, 2017.

BASIC INFORMATION

DEFINITION

Graves disease is a hypermetabolic state caused by circulating immunoglobulin G (IgG) antibodies that bind to and activate the G-protein–coupled thyrotropin receptor. This activation stimulates follicular hypertrophy and hyperplasia, causing thyroid enlargement as well as increases in thyroid hormone production. It affects the thyroid, ocular muscles and shin. It is characterized by thyrotoxicosis, diffuse goiter, and infiltrative ophthalmopathy (edema and inflammation of the extraocular muscles and an increase in orbital connective tissue and fat); infiltrative dermopathy characterized by lymphocytic infiltration of the dermis; accumulation of glycosaminoglycans; and occasionally edema.

SYNONYM

Thyrotoxicosis

ICD-10CM CODES

E05.00	Thyrotoxicosis with diffuse goiter without thyrotoxic crisis or storm
E05.01	Thyrotoxicosis with diffuse goiter with thyrotoxic crisis or storm

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE: Graves disease is the most common cause of hyperthyroidism. It affects 3% of women and 0.5% of men during their lifetime. There is a slight increased incidence among young African Americans. The annual incidence of Graves disease-associated ophthalmopathy is 16 cases per 100,000 women and 3 cases per 100,000 men. It is more common in whites than Asians. Cigarette smoking is a risk factor.

PREDOMINANT AGE: Peak incidence is between 30 and 60 yr.

GENETICS: Patients often report a family history of Hashimoto thyroiditis, Graves disease, or other autoimmune conditions. Increased prevalence of *HLA-B8* and *HLA-DR3* in whites with Graves disease. Concordance rate is 20% among monozygotic twins.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Diffusely enlarged thyroid. Thyroid bruit may be present. Cervical lymphadenopathy may also be present
- Elevated systolic blood pressure with a widened pulse pressure
- Tachycardia, palpitations, tremor, hyperreflexia
- Exophthalmos (50% of patients) (Fig. 1), lid retraction (lid lag), in which contraction of the levator palpebrae muscles of the eyelids shows immobility of the upper eyelid with downward rotation of the eye
- Nervousness, weight loss (weight gain in 10% of patients), heat intolerance, pruritus, muscle weakness, atrial fibrillation
- Increased sweating, brittle nails, clubbing of fingers
- Localized infiltrative dermopathy (1% to 2% of patients) is most frequent over the anterolateral aspects of the legs, commonly over the pretibial area (pretibial myxedema) but can be found at other sites (especially after trauma). It is non-pitting and indurated. It is typically patchy with a peau d'orange appearance to the skin
- Men may have gynecomastia, reduced libido, and erectile dysfunction. Women often have irregular menses

ETIOLOGY

Autoimmune etiology: Thyrotropin receptor antibodies (TRAb) mediated activation of TSH receptor (TSHR). The activity of the thyroid gland is stimulated by the action of T cells, which induce specific B cells to synthesize antibodies against thyroid-stimulating hormone (TSH) receptors in the follicular cell membrane.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Anxiety disorder
- Premenopausal state
- Thyroiditis
- Other causes of hyperthyroidism (e.g., toxic multinodular goiter, toxic adenoma)
- Other: Metastatic neoplasm, diabetes mellitus, pheochromocytoma

WORKUP

- The diagnosis is made clinically on most instances.
- The diagnostic workup includes a detailed medical history followed by laboratory and imaging studies and ECG. Patients often present with anxiety, heat intolerance, menstrual dysfunction, increased appetite, and weight loss. Elderly patients can have an atypical presentation (apathetic hyperparathyroidism). For additional information, refer to the topic "Hyperthyroidism."
- Table 1 describes the clinical assessment of the patient with Graves ophthalmopathy.

FIG. 1 Proptosis seen in the setting of Graves disease. A, Eye signs in Graves disease. **B,** Severe proptosis in Graves disease. (**A** and **B,** Courtesy Dr. Meir H. Kryger.) (From Kryger M et al: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.)

LABORATORY TESTS

- Increased free thyroxine (T_4) and free triiodothyronine (T_3)
- Decreased TSH
- Measurement of thyroid-stimulating antibodies (TSI) and TRAb

IMAGING STUDIES

- 24-hr radioactive iodine uptake (RAIU): Increased homogeneous uptake.
- CT or MRI of the orbits (Fig. E2) is useful if there is uncertainty about the cause of ophthalmopathy.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient education and discussion of therapeutic options.
- Smoking cessation: Smoking is associated with an increased risk of progression of Graves ophthalmopathy.

ACUTE GENERAL Rx

- Antithyroid drugs (thionamides, ATDs) to inhibit thyroid hormone synthesis or peripheral conversion of T_4 to T_3:
  1. Methimazole or propylthiouracil (PTU) are available. Methimazole is generally preferred because it has a longer half-life, allowing for once-daily dosing. PTU is preferred during pregnancy.
  2. Side effects: Skin rash (3% to 5%), arthralgias, myalgias, granulocytopenia (0.5%); rare side effects: Aplastic anemia, hepatic necrosis (PTU), cholestatic jaundice.
  3. Thionamide antithyroid drug therapy results in a remission in 40% to 50% of patients treated for 12 to 18 mo.
- Radioactive iodine (RAI):
  1. Treatment of choice for patients >21 yr and younger patients who have not achieved remission after 1 yr of ATD therapy
  2. Contraindicated during pregnancy and lactation
  3. Following radioactive therapy there may be an acute elevation of thyroid antibody titers and exacerbation of ocular symptoms in 15% to 20% of patients.
- Surgery: Near-total thyroidectomy. Indications: Obstructing goiters despite RAI and ATD therapy, patients who refuse RAI and cannot be adequately managed with ATDs, and pregnant women inadequately managed with ATDs. Complications of surgery include hypoparathyroidism (4%) and vocal cord paralysis (1%).
- Adjunctive therapy: Beta-adrenergic receptor blockers (e.g., atenolol 50 to 100 mg/day) to alleviate the beta-adrenergic symptoms of

TABLE 1 Clinical Assessment of the Patient with Graves Ophthalmopathy

Activity Measures*
Spontaneous retrobulbar pain
Pain on attempted up or down gaze
Redness of the eyelids
Redness of the conjunctiva
Swelling of the eyelids
Inflammation of the caruncle and/or plica
Conjunctival edema
Severity Measures
Lid aperture: Distance between lid margins in millimeters with the patient looking in the primary position, sitting relaxed, and with distant fixation
Swelling of the eyelids (absent/equivocal, moderate, severe)
Redness of the eyelids (absent/present)
Redness of the conjunctivae (absent/present)
Conjunctival edema (absent, present)
Inflammation of the caruncle or plica (absent, present)
Exophthalmos: Measured in millimeters using the same Hertel exophthalmometer and the same intercanthal distance for an individual patient
Subjective diplopia score†
Eye muscle involvement (ductions in degrees)
Corneal involvement (absent/punctate keratopathy/ulcer)
Optic nerve involvement: Best-corrected visual acuity, color vision, optic disk, relative afferent pupillary defect (absent/present), plus visual fields if optic nerve compression is suspected

*Based on the seven classic features of inflammation in Graves ophthalmopathy. The clinical activity score (CAS) is the total number of items present; a CAS ≥3 indicates active ophthalmopathy.
†Subjective diplopia score: 0 = no diplopia; 1 = intermittent (i.e., diplopia in primary position of gaze, when tired, or when first awakening); 2 = inconstant (i.e., diplopia at extremes of gaze); 3 = constant (i.e., continuous diplopia in primary or reading position).
From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders.

hyperthyroidism (tachycardia, tremor); contraindicated in patients with bronchospasm.

- Graves ophthalmopathy: Methylcellulose eye drops to protect against excessive dryness, sunglasses to decrease photophobia, intraocular and systemic high-dose corticosteroids for severe exophthalmos. Worsening of ophthalmopathy after RAI therapy is often transient and can be prevented by the administration of prednisone. Other treatment options include antiinflammatory and immunosuppressive agents, radiation, and corrective surgical procedures. The administration of the antioxidant selenium (100 μg PO bid) has been recently reported as effective in improving quality of life, reducing ocular involvement, and slowing progression of the disease in patients with mild Graves orbitopathy. Its mechanism of action is believed to be an effect on the oxygen free radicals and cytokines that play a pathogenic role in Graves orbitopathy. Inhibition of the insulin-like growth factor I receptor (IGF-IR) is a new therapeutic strategy to combat the underlying autoimmune etiology of ophthalmopathy. Trials with teprotumumab, a human monoclonal antibody inhibitor of IGF-IR, in patients with active, moderate-to-severe ophthalmopathy have shown effectiveness in reducing proptosis.[1]
- Dermopathy and acropachy: Topical corticosteroids are often used but are generally ineffective. Trials using rituximab infusion for dermopathy have shown striking improvement.

[1]Douglas RS et al: Teprotumumab for the treatment of active thyroid eye disease, N Engl J Med 382(4):341-352, 2020.

CHRONIC Rx

Patients undergoing treatment with ATDs should be seen every 1 to 3 mo until euthyroidism is achieved and every 3 to 4 mo while they are receiving ATDs.

DISPOSITION

- ATDs induce sustained remission in <60% of cases.
- The incidence of hypothyroidism after RAI is >50% within the first yr and 2% per yr thereafter.
- Complications of surgery include hypothyroidism (28% to 43% after 10 yr), hypoparathyroidism (4%), and vocal cord paralysis (1%).
- Successful treatment of hyperthyroidism requires lifelong monitoring for the onset of hypothyroidism or the recurrence of thyrotoxicosis.
- RAI therapy is followed by the appearance or worsening of ophthalmopathy more often than is therapy with methimazole, particularly in patients who are cigarette smokers. It can be prevented with the administration of prednisone 0.5 mg/kg body weight per day starting 2 to 3 days after RAI, continued for 1 mo, then tapered off over 2 mo.
- Mild to moderate ophthalmopathy often improves spontaneously. Severe cases can be treated with high-dose glucocorticoids, orbital irradiation, or both. Orbital decompression may be used in patients with optic neuropathy and exophthalmos (see "Hyperthyroidism").

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Graves Disease (Patient Information)
Hyperthyroidism (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Bahn RS: Graves' ophthalmopathy, *N Engl J Med* 362:726-738, 2010.
Burch HB, Cooper DS: Management of Graves disease: a review, *J Am Med Assoc* 314(23):2544-2554, 2015.
Marsocci C et al: Selenium and the course of mild Graves' orbitopathy, *N Engl J Med* 364:1920-1931, 2011.
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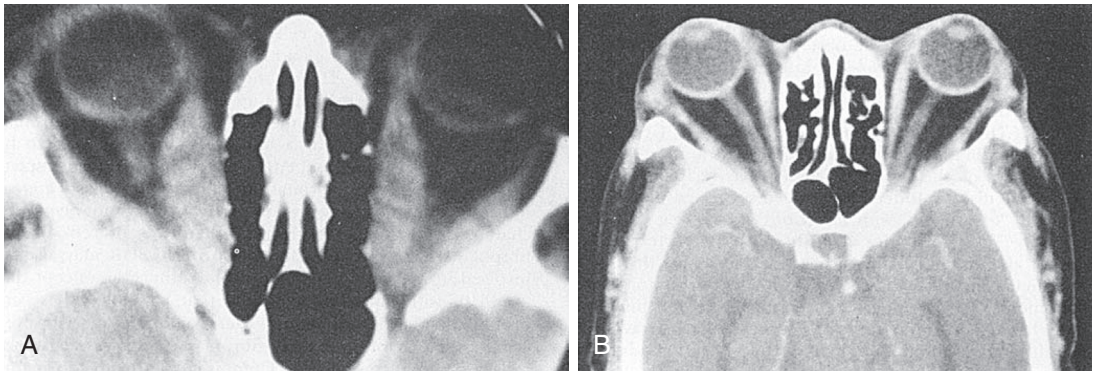

FIG. E2 Computed tomography scans of orbits in two patients with Graves orbitopathy. A, Notice the obviously grossly swollen medial rectus extraocular muscles in both orbits and the resulting proptosis. **B,** The patient shows considerable proptosis with only minimal muscle enlargement, suggesting the presence of a large amount of retroorbital fat. (Courtesy Dr. Peter Som, New York, NY.)

Grief, Complicated or Prolonged

BASIC INFORMATION

DEFINITION

Bereavement is a universal human experience, and grieving after the loss of a loved one is recognized as a normal and healthy response to loss. Normal grieving typically resolves on its own over time. In a small proportion of bereaved individuals, the process of grieving does not resolve on its own. In complicated or prolonged grief, intense grieving symptoms significantly impair functioning. Complicated grief was proposed as a diagnosis for DSM-5, and prolonged grief disorder has been recommended for inclusion in the ICD-11. Persistent complex bereavement disorder is included in the DSM-5 appendix in the section for conditions needing further study.

SYNONYMS

Prolonged grief disorder
Persistent complex bereavement disorder

ICD-10CM CODES
Complicated grief and prolonged grief are not included as diagnoses in the DSM-5 or the ICD-10.

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Studies indicate that of bereaved individuals, around 10% experience bereavement symptoms that grow or persist with the passage of time and significantly impair functioning.

PREDOMINANT SEX AND AGE: Prolonged grief is more common among women than men, and more common in the elderly, who are exposed to more losses as they age.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The key feature of prolonged or complicated grief is impaired functioning in occupational, social, or other contexts beyond 6 to 12 mo after the loss, with symptoms that center around feelings of loss. Individuals struggling with prolonged or complicated grief may present with intense longing for the deceased, feelings of emptiness, prolonged reactivity to reminders of the loss, unwillingness to adopt new roles, difficulty engaging in social relationships, isolation and social disengagement, and fixation on the past and on reminders of the past. They may have difficulty envisioning life without the deceased person and may experience suicidal ideation or intent as a result.

ETIOLOGY

The etiology is not known, but complications such as isolation or attentional biases impede normal resolution of grief and lead to prolonged or intensified grief symptoms. Risk factors include a history of trauma or loss, a history of mood or anxiety disorders, insecure attachment style, low perceived social support, increased stress, having been a caregiver for the deceased, pessimistic temperament, and violent cause of death of the deceased.

DIAGNOSIS

Proposed criteria for prolonged difficulties with bereavement differ, but commonalities include having been bereaved (loss of a loved one) and experiencing a constellation of the symptoms listed below for at least 6 mo (different sets of criteria propose different minimum lengths of time ranging from 6 to 12 mo):

- Experiencing intense yearning, sorrow, or pain, or preoccupation with the deceased
- Feeling stunned or having difficulty accepting the death of the loved one
- Feelings of emptiness or lack of self
- Emotional numbness
- Bitterness about the loss
- Avoidance of reminders of the loss
- Difficulty moving on with life and forging new friendships or pursuing hobbies or interests
- Difficulty engaging in relationships
- Difficulty imagining life without the deceased
- Impairment in social, occupational, or other areas of functioning

DIFFERENTIAL DIAGNOSIS

- Major depression: Whereas in major depression, wherein a globally pessimistic outlook prevails, with prolonged or complicated grief, negative feelings tend to be specifically centered on the loss of the loved one.
- PTSD: Whereas PTSD is characterized predominantly by fear, horror, anger, guilt, shame, and hyperarousal, prolonged or complicated grief is characterized by yearning, loss, and emptiness.

WORKUP

A comprehensive clinical interview should assess when symptoms began, whether symptoms and negative feelings center on the loss of the loved one, impairment in functioning, and hopelessness or suicidal ideation or intent. The assessment should also explore attachment history and the history or presence of other psychiatric disorders.

IMAGING STUDIES

Imaging studies have shown activation of the nucleus accumbens on exposure to cues of the deceased in cases of complicated grief but not in cases of normal grief.

TREATMENT

Studies have demonstrated the efficacy of various grief-specific therapies. Commonalities across treatments that have demonstrated efficacy include:

- Psychoeducation about grief
- A focus on processing the loss of the loved one, including feelings of loss and positive reminiscing about the loved one
- A focus on restoring functioning and purposeful engagement in life
- A focus on challenging thoughts that worsen negative feelings

Some studies have found that antidepressant medications are not effective for prolonged grief symptoms, but more research is needed on psychopharmacology and prolonged grief. For example, some studies report that a subset of bereaved individuals (20%) meet criteria for MDD and have a course and treatment response similar to nonbereaved patients with MDD. A recent study found that among suicide-bereaved individuals, complicated grief therapy enhances compliance with antidepressant medication, improves functioning, and reduces suicidal ideation.

Psychotherapies for depression, including interpersonal psychotherapy, have not been effective for prolonged or complicated grief.

DISPOSITION

Compared with normal grief, prolonged or complicated grief is associated with debilitating distress and disability, suicidal ideation, and negative health outcomes.

PEARLS & CONSIDERATIONS

- It is important to assess patients 6 to 12 mo after a loss of a loved one and to determine whether they might be experiencing prolonged or complicated grief.
- For patients with prolonged or complicated grief, grief-specific therapy has demonstrated efficacy and should be encouraged.
- Treatments for depression that do not specifically address the loss have not been shown to be effective for complicated grief.
- Suicidality must be assessed.

AUTHOR: **Abigail K. Mansfield, PhD**

SUGGESTED READINGS

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Kendler et al: Does bereavement related major depression differ from major depression related to other stressful life events? *Am J Psychiatry* 165:1449-1455, 2008.

Shear MK: Complicated grief, *N Engl J Med* 372:153-160, 2015.

Zisook S et al: Treatment of complicated grief in survivors of suicide loss: a HEAL report, *J Clin Psychiatry* 79(e1-e7), 2018.

BASIC INFORMATION

DEFINITION

Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy (affects nerve roots and peripheral nerves), with predominant motor involvement. It is the most common cause of acute flaccid paralysis in the Western hemisphere and probably worldwide. By definition, maximal clinical weakness, the clinical nadir, occurs within 4 wk of disease onset.

SYNONYMS

AIDP (acute inflammatory demyelinating polyradiculoneuropathy)
Acute polyneuropathy
Ascending paralysis
GBS
Postinfectious polyneuritis

ICD-10CM CODE
G61.0 Guillain-Barré syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.6 to 1.9 cases/100,000 persons annually without geographic variation. Incidence increases with age. A slight peak in incidence occurs between late adolescence and early adulthood. A slight male preponderance (1.25:1) also exists.

PREDISPOSING FACTORS: Viral (HIV, CMV, EBV, influenza) and bacterial *(Campylobacter jejuni, Mycoplasma pneumoniae)* infections; systemic illness (Hodgkin lymphoma, immunizations). Major antecedents of GBS are described in Box E1.

ETIOLOGY

- Unknown, but believed to be caused by infection-induced aberrant immune response.
- Preceding infectious illness 1 to 4 wk before disease onset has been noted. The most frequent antecedent infection is *C. jejuni* infection (associated with 30% of cases of GBS and 20% of cases of Miller Fisher syndrome).
- Humoral and cell-mediated immune attack of peripheral nerve myelin, Schwann cells; sometimes with primary axonal involvement.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symmetric weakness, most commonly involving proximal muscles initially, subsequently involving both proximal and distal muscles; difficulty in ambulating, getting up from a chair, or climbing stairs (Box E2)
- Depressed or absent reflexes bilaterally
- Minimal to moderate glove and stocking paresthesias/dysesthesia/anesthesia or back pain
- Pain (caused by involvement of posterior nerve roots) may be prominent
- Autonomic abnormalities (bradyarrhythmias or tachyarrhythmias, hypotension or hypertension)
- Respiratory insufficiency (caused by weakness of bulbar/intercostal muscles)
- Facial paresis, ophthalmoparesis, dysphagia (secondary to cranial nerve involvement)
- GBS consists of several clinical variants based on the pattern of clinical involvement and electrophysiologic findings. These include:
  1. AIDP (most common form in Europe and North America)
  2. Acute motor axonal neuropathy (AMAN; most prevalent form in China and Japan)
  3. Acute motor and sensory axonal neuropathy (AMSAN; has more severe sensory involvement and is associated with more severe clinical course and poorer prognosis)
  4. Miller Fisher syndrome (MFS; triad of ophthalmoplegia, ataxia, and areflexia)
  5. Acute pandysautonomia (rapid onset of parasympathetic and sympathetic failure without motor or sensory involvement)
  6. Regional variants (e.g., pharyngeal-cervical-brachial GBS, pure ataxic GBS)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Toxic peripheral neuropathies: Heavy metal poisoning (lead [microcytic anemia], thallium [alopecia], arsenic [typically accompanied by acute GI illness]), medications (vincristine, disulfiram), organophosphate poisoning, hexacarbon (glue sniffer's neuropathy)
- Nontoxic peripheral neuropathies: Acute intermittent porphyria, fulminant vasculitic polyneuropathy, infectious (poliomyelitis, diphtheria, Lyme disease, West Nile virus), tick paralysis
- Neuromuscular junction disorders: Myasthenia gravis, botulism, snake envenomation
- Myopathies such as polymyositis and acute necrotizing myopathies caused by drugs
- Metabolic derangements such as hypermagnesemia, hypokalemia, hypophosphatemia
- Acute CNS disorders such as basilar artery thrombosis with brainstem infarction, brainstem encephalomyelitis, transverse myelitis, or spinal cord compression
- Conversion disorder
- Malingering
- Table 1 differentiates clinical patterns of acute neuromuscular weakness

WORKUP

- Exclude other causes based on clinical history, examination, and laboratory tests.
- Lumbar puncture (may be normal in the first 1 to 2 wk of the illness). Typical findings include elevated CSF protein with few mononuclear leukocytes (albuminocytologic dissociation) in 80% to 90% of patients. Elevated CSF cell counts is an expected feature in cases associated with HIV seroconversion.
- EMG/nerve conduction study (NCS) may be normal in the first 10 to 14 days of the disease. The earliest electrodiagnostic abnormality is prolongation or absence of H-reflexes. NCS evidence of demyelination (prolonged distal latency, conduction velocity slowing, conduction block, temporal dispersion, and prolonged F-waves) in two or more motor nerves confirms diagnosis of AIDP in the appropriate clinical context.

LABORATORY TESTS

- CBC may reveal early leukocytosis with left shift. Electrolytes are tested to exclude metabolic causes of weakness.
- Heavy metal testing; urine porphyria screen; creatine kinase; HIV testing, including tests for HIV seroconversion, especially if CSF demonstrates lymphocytic pleocytosis. MRI brain and spinal cord with and without contrast may be indicated if diagnosis is uncertain. In GBS, a gadolinium-enhanced MRI of the lumbosacral spine may reveal nerve root enhancement.
- Antibodies against ganglioside GQ1b may be present in up to 90% of patients with MFS. IgG antibodies against ganglioside GM1 may be associated with AMAN. There are no antiganglioside antibodies commonly associated with AIDP.
- In equivocal cases, especially if peripheral nerve vasculitis is a concern, nerve biopsy may aid in confirming a diagnosis of GBS. Sensory nerve biopsy demonstrates segmental demyelination with infiltration of monocytes and T cells into the endoneurium. Axonal loss is commonly seen in sensory nerve biopsy specimens in GBS.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Close monitoring of respiratory function (frequent measurements of vital capacity, negative inspiratory force, and tidal volume) and pulmonary toilet should be done because respiratory failure is the major complication in GBS
- Frequent repositioning of patient to minimize formation of pressure sores
- Prevention of venous thromboembolism with antithrombotic stockings as a supplement to pharmacologic venous thromboembolism prevention
- Emotional support and social counseling for patient and family
- Pain control
- Cardiac monitoring to detect arrhythmias
- Physical and occupational therapy once patient is medically stable and able to participate.
- Avoidance of drugs that may worsen myasthenia gravis or interfere with neuromuscular transmission

ACUTE GENERAL Rx

- Option 1: Infusion of IV immunoglobulins (IVIG; 0.4 g/kg/day for 5 days). Always check serum IgA levels before infusion to prevent anaphylaxis in IgA-deficient patients.
- Option 2: Early therapeutic plasma exchange (TPE or plasmapheresis: 200 to 250 ml/kg over five sessions every other day), started within 7 days of onset of symptoms, is beneficial in reducing the need for mechanical ventilation in patients with rapidly progressive disease and results in improved rate of recovery. It is contraindicated in patients with cardiovascular disease (recent

TABLE 1 Clinical Patterns of Acute Neuromuscular Weakness

Cause	Cranial Nerve Involvement	Limb Weakness	Reflexes	Sensory	Autonomic Changes
Guillain-Barré syndrome	Common, facial diplegia	Distal (ascending)	Absent	Common	Possible (20%)
Miller Fisher syndrome	Hallmark: Ophthalmoplegia	Variable hallmark: Ataxia	Absent	Rare	Rare
Myasthenia gravis	Common, ptosis, facial, oculomotor	Proximal (shoulders and thighs)	Normal	Present	Present
Botulism	Symmetric diplopia, ptosis, dysarthria, dysphagia	Descending	Absent or decreased	No	Yes (e.g., ileus, mydriasis, reduced salivation, urinary retention)
Organophosphate poisoning	Bulbar dysfunction, dysarthria, dysphagia	Diffuse	Decreased	Late	Yes (e.g., bradycardia, sialorrhea, bronchorrhea, lacrimation, diarrhea, miosis causing blurry vision)
Brainstem	Common, ocular movement	Crossed findings (face/limbs)	Increased	Common	Rare
Spinal cord	No	Quadriparesis or paraparesis	Decreased then increased	Loss below level	If above thoracic level

From Parrillo JE, Dellinger RP: *Critical care medicine: principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.

MI, unstable angina), active sepsis, and autonomic dysfunction.
- Both therapies are equally effective and may shorten recovery time by 50%. There is no proven benefit from combining IVIG and plasma exchange. Glucocorticoids are contraindicated.
- Mechanical ventilation may be needed if FVC is <12 to 15 ml/kg, vital capacity is rapidly decreasing or is <1000 ml, negative inspiratory force is <20 cm H_2O, PaO_2 is <70, or the patient is having significant difficulty clearing secretions or is aspirating.

CHRONIC Rx

- Ventilatory support may be necessary in 10% to 20% of patients. Adequate fluid/electrolyte support and nutrition are necessary, especially in patients with dysautonomia or bulbar dysfunction.
- Aggressive nursing care to prevent decubitus, infections, fecal impactions, and pressure nerve palsies.
- Monitoring and treatment of autonomic dysfunction (bradyarrhythmias or tachyarrhythmias, orthostatic hypotension, systemic hypertension).
- Treatment of back pain and dysesthesia with low-dose tricyclics, gabapentin, and so on. Opiate narcotics can be used cautiously in the short term but may compound dysautonomia.
- Pharmacologic venous thromboembolism prevention with agents such as heparin (5000 U SC q12h) or enoxaparin (40 mg SC daily) in poorly ambulating and nonambulatory patients.
- Stress ulcer prevention in patients receiving ventilator support.
- Physical and occupational therapy rehabilitation, including supportive devices.

DISPOSITION

- Mortality rate is approximately 5% to 10% worldwide. Causes of death include cardiac arrest, pulmonary embolism, and fulminant infections. A recent study showed 62% complete motor recovery, 14% mild weakness, 9% moderate weakness, 4% bed-bound or ventilated, and 8% dead at 1 yr. Another study suggested that about 33% of patients were free from sensory symptoms at 1 yr, with residual sensory loss present in the lower extremities in 67% and 36% in the upper extremities. About 32% had to change their work, 30% were unable to function at home as well as they could before the disease, and 52% had to alter their leisure activities 1 yr after GBS onset. Excessive fatigue is a common complaint in patients during the recovery phase of GBS. This may be treated with exercise therapy (e.g., bicycle exercise training).
- Predictors for poor recovery (inability to walk independently at 1 yr): Age >60 yr, preceding diarrheal illness, recent CMV infection, fulminant or rapidly progressing course, ventilatory dependence, reduced motor amplitudes (<20% normal), or unexcitable nerves on NCS. Outcomes may also be influenced by complications of medical therapy.
- GBS is typically a monophasic illness. Recurrence may occur in <5% of patients following full recovery.

REFERRAL

- Neurology to aid in diagnosis and direct treatment
- Pulmonary/critical care for ICU management
- Otolaryngology or general surgery for tracheostomy in patients requiring prolonged ventilatory support
- Gastroenterology for percutaneous endoscopic gastrostomy for patients with prolonged inability to obtain nutrition orally

PEARLS & CONSIDERATIONS

- GBS is the most common cause of acute flaccid paralysis.
- Close monitoring of ventilatory function with respiratory mechanics (FVC and NIF) is of paramount importance in all patients with suspected GBS.
- Glucocorticoids are not indicated in GBS and may even slow recovery.

PATIENT & FAMILY EDUCATION

Patient education information may be obtained from the Guillain-Barré Foundation International, The Holly Building, 104 1/2 Forrest Avenue, Narberth, PA 19072; phone: (610) 667-0131; fax: (610) 667-7036; toll-free: (866) 224-3301; E-mail: info@gbs-cidp.org

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Guillain-Barré Syndrome (Patient Information)

AUTHOR: **Divya Singhal, MD**

SUGGESTED READINGS

Dimachkie MM et al: Guillain-Barré syndrome, *Curr Treat Options Neurol* 15(3):338-349, 2013.

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Yuki N, Hans-Peter H et al: Guillain-Barré syndrome, *N Engl J Med* 366:2294-3011, 2012.

BOX E1 Major Antecedents of Guillain-Barré Syndrome

Frequent
Upper respiratory tract infections
Campylobacter jejuni enteritis
Cytomegalovirus infection
Epstein-Barr virus infection
Hepatitis A infection
Hepatitis B infection
Hepatitis C infection
HIV infection

Infrequent
Mycoplasma pneumoniae infection
Haemophilus influenzae infection
Leptospira icterohaemorrhagiae infection
Salmonellosis
Rabies vaccine
Tetanus toxoid
Bacille Calmette-Guérin immunization
Sarcoidosis
Systemic lupus erythematosus
Lymphoma
Trauma
Surgery

Questionable
Hepatitis B vaccine
Influenza vaccine
Hyperthermia
Epidural anesthesia

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

BOX E2 Findings Suggesting Guillain-Barré Syndrome

Relative symmetry of symptoms
Mild sensory signs and symptoms
Cranial nerve involvement
Autonomic dysfunction
Absence of fever at onset
Cytoalbuminologic dissociation of cerebrospinal fluid
Typical electrodiagnostic findings
Progression over days to wks
Recovery beginning 2 to 4 wk after cessation of progression

From Adams JG: *Emergency medicine: clinical essentials,* Philadelphia, 2013, Saunders.

Gynecomastia ALG PTG

BASIC INFORMATION

DEFINITION

Gynecomastia is a benign enlargement of male breast resulting from proliferation of glandular breast tissue.

ICD-10CM CODE
N62 Hypertrophy of breast

EPIDEMIOLOGY

- Most common reason for male breast evaluation.
- Seen in patients of all age groups.
- 60% to 90% of infants have transient gynecomastia due to high estrogenic state of pregnancy.
- Prevalence during adolescence ranges from 4% to 69%. It results from transient increase of estradiol concentration at the onset of puberty.
- Higher incidence in body builders due to use of anabolic steroids.
- 24% to 65% of older men have gynecomastia. It is secondary to decreased testosterone production with advanced age, increased peripheral conversion of testosterone to estrogen, and at times from side effects of medications.

PATHOPHYSIOLOGY

Altered estrogen-androgen balance, in favor of estrogen

ETIOLOGY

- Physiologic
- Infancy
- Puberty
- Persistent pubertal gynecomastia seen in 25% of cases
- Elderly
- Pathologic
- Idiopathic (25%)
- Increased estrogen production or action
- Testicular tumors (3%)
- Chronic liver disease
- Malnutrition
- Hyperthyroidism
- Adrenal tumors
- Familial gynecomastia
- Decreased testosterone production or action (10%)
- Testicular trauma
- Testicular torsion
- Viral orchitis
- Congenital anorchia
- Renal failure (1%)
- Hyperthyroidism (1.5%)
- Malnutrition
- Androgen insensitivity syndrome
- Five-alpha reductase deficiency
- Pituitary tumors
- Kallmann syndrome
- Klinefelter syndrome
- Medications (10% to 25%)
- Estrogen, gonadotropins, clomiphene, phenytoin, ketoconazole, metronidazole, metoclopramide, alkylating agents, busulfan, methotrexate, cisplatin, cimetidine, ranitidine, omeprazole, flutamide, finasteride, etomidate, HAART therapy, INH, tricyclic antidepressants, phenothiazines, diazepam, haloperidol, calcium channel blocker, ACE inhibitors, spironolactone, digoxin, amiodarone, methyldopa, alcohol, marijuana, heroin, methadone, amphetamine, anabolic steroids. Table E1 summarizes the various causes of gynecomastia.

CLINICAL FEATURES

- Although gynecomastia is usually bilateral, it could be unilateral.
- Characterized by concentric rubbery to firm disk of tissue, which is often mobile and located directly beneath the areola (Fig. E1).
- Pain is usually not severe. Varying degree of tenderness and nipple sensitivity are more common than pain, usually in the first 6 mo.

DIAGNOSIS

- Good history and physical examination including review of all medications the patient is taking is helpful.
- Mammogram is recommended for suspected breast cancer.

FIG. E1 Gynecomastia. (From Swartz MH: *Textbook of physical diagnosis*, ed 7, Philadelphia, 2014, Saunders.)

- Serum concentration of hCG, LH, testosterone, and estradiol should be measured, preferably in the morning, unless the cause is clearly apparent. There is no uniformity of opinion regarding what biochemical evaluation, if any, should be performed in patients with asymptomatic gynecomastia. Fig. E2 describes an algorithm for evaluation of gynecomastia.

DIFFERENTIAL DIAGNOSIS

- Breast cancer
  1. Mass is usually firm to hard
  2. Unilateral
  3. Eccentric in location
  4. Could be associated with nipple discharge and retraction, lymphadenopathy, and skin dimpling
- Pseudogynecomastia or lipomastia
  1. Characterized by fat deposition without glandular proliferation
  2. Seen in obese men
  3. Bilateral
  4. Remain unchanged over time

TREATMENT

- Observation is recommended for most patients with physiologic gynecomastia. They often regress spontaneously. Reassurance and follow-up examination in 3 to 6 mo usually suffice.
- Treat the underlying cause, and stop the offending medications.
- Treatment is most effective in the early stages (first 6 mo). Medical therapy often fails when given for longstanding (>12 mo) cases because of the presence of fibrosis.
- Potential indications of early therapy include severe breast enlargement, pain, tenderness, and psychological embarrassment. Consider giving tamoxifen 10 mg orally twice a day to these patients for up to 3 mo. It is not FDA-approved for this purpose. It results in regression of gynecomastia in approximately 80% of patients and, of which, only 60% had complete regression. As far as breast symptoms, such as pain and tenderness, some improvement is usually seen within a month of therapy.
- Surgery is offered for symptomatic gynecomastia that does not respond to medical therapy. However, for adolescents, surgery is deferred until puberty is completed. The different surgical options include subcutaneous mastectomy, ultrasound-guided liposuction, and suction-assisted lipectomy.
- For prevention of gynecomastia in patients with prostate cancer using antiandrogen therapy, one could offer tamoxifen or radiotherapy.

RELATED CONTENT

Gynecomastia (Patient Information)

AUTHOR: **Hemant K. Satpathy, MD**

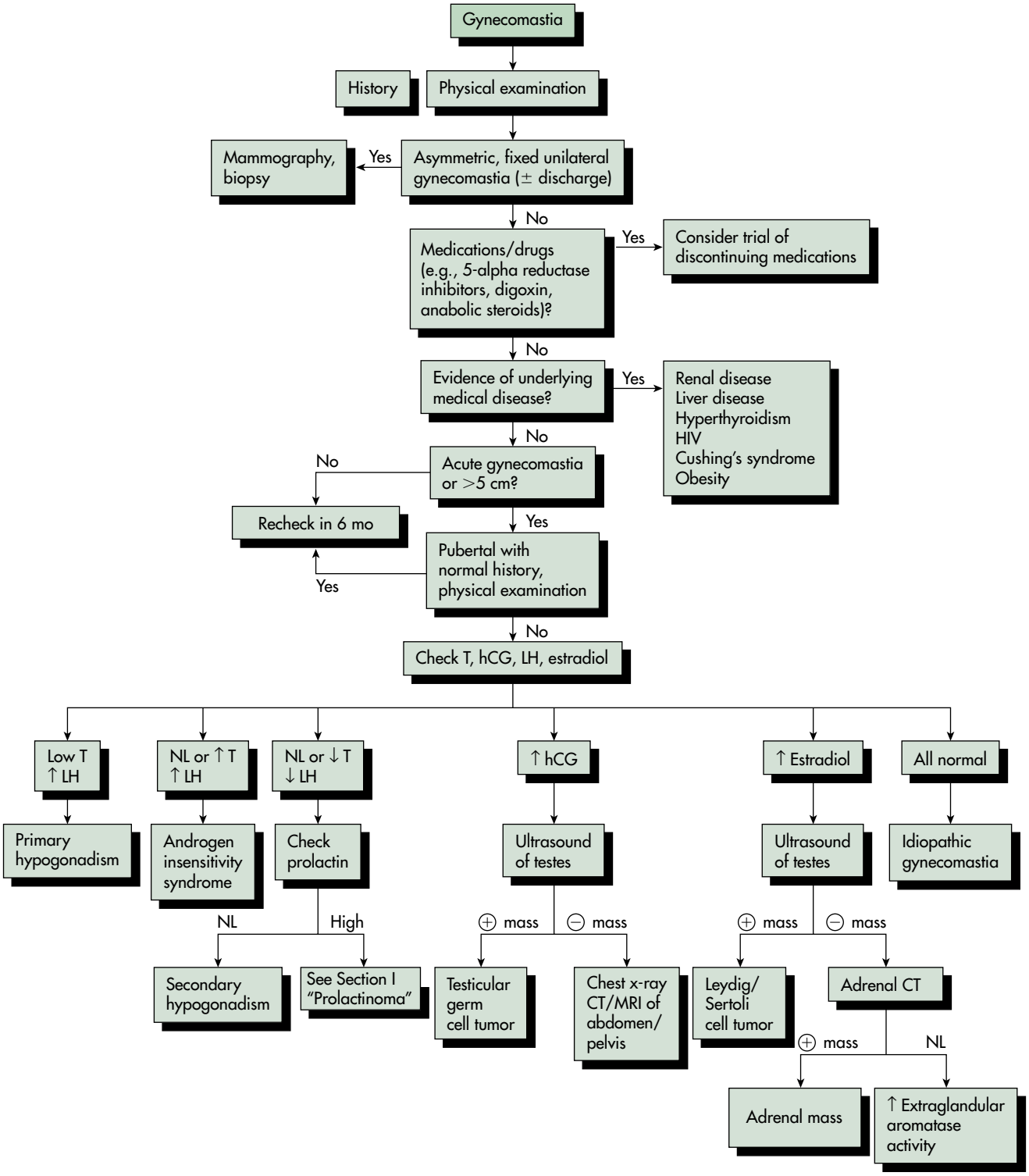

FIG. E2 Evaluation of gynecomastia. *CT,* Computed tomography; *hCG,* human chorionic gonadotropin; *HIV,* human immunodeficiency virus; *LH,* luteinizing hormone; *MRI,* magnetic resonance imaging; *NL,* normal limits; *T,* testosterone.

TABLE E1 Causes of Gynecomastia

Cause	Examples
Physiologic Causes	
Maternal estrogen exposure	Neonatal gynecomastia
Transient increase in estrogen to androgen concentrations	Pubertal gynecomastia
Estrogen Excess	
Estrogens or estrogen receptor agonists	Estrogens, marijuana smoke, digitoxin, testosterone or other aromatizable androgens
Increased peripheral aromatase activity	Obesity, aging, familial
Estrogen-secreting tumors	Adrenal carcinoma, Leydig or Sertoli cell tumor
hCG-secreting tumors	Germ cell, lung, hepatic carcinoma
hCG treatment	
Androgen Deficiency or Resistance	
Androgen deficiency	Primary or secondary hypogonadism
Hyperprolactinemia causing androgen deficiency	
Androgen resistance disorders	Congenital and acquired androgen resistance
Drugs that interfere with androgen action	Spironolactone, androgen receptor antagonists, marijuana, 5α-reductase inhibitors, histamine 2 receptor antagonists
Systemic Disorders	
Organ failure	Hepatic cirrhosis, chronic kidney disease
Endocrine disorders	Hyperthyroidism, acromegaly, growth hormone treatment, Cushing syndrome
Nutritional disorders	Refeeding, recovery from chronic illness (hemodialysis, insulin, isoniazid, antituberculous medications, ART)
Idiopathic Causes	
Drugs	ART, calcium channel antagonists, amiodarone, antidepressants (SSRIs, tricyclic antidepressants), alcohol, amphetamines, penicillamine, sulindac, phenytoin, omeprazole, theophylline
Adult-onset idiopathic gynecomastia	
Persistent prepubertal macromastia	

ART, Antiretroviral therapy; *hCG,* human chorionic gonadotropin; *SSRIs,* selective serotonin reuptake inhibitors.
From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

SUGGESTED READING

Dickson G: Gynecomastia, *Am Fam Physician* 85(7):716-722, 2012.

BASIC INFORMATION

DEFINITION

Hairy cell leukemia is a lymphoid neoplasm characterized by diffuse infiltration of the spleen and bone marrow by small mature B cells with prominent cytoplasmic "hairy" projections.

SYNONYMS

HCL
Leukemic reticuloendotheliosis

ICD-10CM CODES

C91.40	Hairy cell leukemia not having achieved remission
C91.41	Hairy cell leukemia, in remission
C91.42	Hairy cell leukemia, in relapse

EPIDEMIOLOGY & DEMOGRAPHICS

- Rare disease with incidence of 3 cases per 1 million person-yr, about 900 new cases per yr in the U.S.
- Affects predominantly white men (male to female ratio of 4:1) with median age of 55 yr
- Accounts for about 2% of all leukemias in adults
- No known risk factors, although association with exposure to Agent Orange, industrial and agricultural chemicals has been suggested

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most patients present with fatigue and weakness, infections, or easy bruising.
- Physical findings include pallor, ecchymoses.
- Peripheral lymphadenopathy is uncommon.
- Splenomegaly due to infiltration by HCL is a salient feature present in >90% of cases (Fig. E1); hepatomegaly may be present in up to 58% (Table E1).
- Rarely, autoimmune complications (vasculitis, hemolytic anemia), extramedullary infiltration or spontaneous splenic rupture may occur.

ETIOLOGY

- HCL is a malignancy of mature B cells of unknown etiology.
- A molecular hallmark of HCL is the *BRAF* V600E gene mutation, which is present in almost all cases of HCL, but absent in other B-cell lymphomas.

DIAGNOSIS

The diagnosis of HCL requires demonstration of malignant B cells with characteristic immunophenotype and morphology in the blood, bone marrow and/or spleen. Table E1 describes major diagnostic features of HCL.

DIFFERENTIAL DIAGNOSIS

- Other lymphomas involving the spleen and bone marrow: Splenic marginal zone, follicular, or mantle cell lymphoma, CLL, as well as rare entities like HCL-variant and splenic diffuse red pulp small B-cell lymphoma. The distinction between HCL and these other disorders is facilitated by using the characteristic morphologic and immunotypic findings characteristic of these disorders (Table E2).
- HCL variant is a distinct entity characterized by worse prognosis, poor response to purine analogue chemotherapy, lack of *BRAF* mutation, lack of CD25 and CD123, expression of the *VH4-34* immunoglobulin rearrangement, and lymphocytosis.
- Myelofibrosis and bone marrow failure syndromes, including aplastic anemia.
- Other medical causes of splenomegaly and pancytopenia, including cirrhosis and type 1 Gaucher disease.

WORKUP (TABLE E3)

History and physical examination with attention to liver and spleen

LABORATORY TESTS AND IMAGING STUDIES (TABLE E4)

- Complete blood count shows pancytopenia; anemia may vary from minimal to severe; severe monocytopenia is characteristic.
- Peripheral blood smear for identification of hairy cells (Fig. E2) which can account for 5% to 80% of cells in the peripheral blood.
- Peripheral blood or bone marrow flow cytometry is necessary to rule out other lymphoproliferative disorders, including HCL-variant.
- A bone marrow biopsy (Fig. E3) is essential for diagnosis. Marrow aspiration may not be feasible because of increased reticulin fibrosis, resulting in a "dry tap."
- Pretreatment assessment of renal, liver function, lactate dehydrogenase and hepatitis B testing.
- Immunohistochemistry can detect the *BRAF* V600E mutation, but molecular testing for the mutation is recommended.
- Imaging is not essential, but computed tomography may be obtained to evaluate the spleen and internal adenopathy.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Asymptomatic patients with incidentally diagnosed HCL (10% of cases) may be observed without therapy.
- Fertility counseling is important prior to starting chemotherapy.

ACUTE GENERAL Rx

- HCL is typically treated with a single course of chemotherapy leading to a durable (median 8 yr) complete remission for up to 90% of patients. Blood counts typically normalize within 2 to 4 mo of treatment.
- Drugs of choice are the purine analogues: Cladribine (2-chloro-2-deoxyadenosine) or pentostatin (2-deoxycoformycin, DCF).
- Cladribine can be administered as an intravenous infusion or subcutaneous injection (0.10 to 0.14 mg/kg daily for 5 to 7 days, or weekly for 6 wk) and has little toxicity, except for the risk of neutropenic infections (20%) and septic death (2%). Patients with only partial remission may receive a second course at least 6 mo later.
- Infectious prophylaxis (*P. jirovecii* pneumonia, herpes zoster) may be used during immunosuppressive chemotherapy; G-CSF support does not decrease the risk of fever or hospitalization after standard therapy.
- Patients who have minimal residual disease after cladribine may receive additional treatment with the monoclonal antibody rituximab.
- A treatment algorithm for HCL is illustrated in Fig. E4.

CHRONIC Rx

- Patients require long-term follow-up and laboratory surveillance because approximately 40% eventually will experience a recurrence.
- Recurrent or refractory HCL may be treated with a repeat course of a purine analogue, rituximab, the anti-CD22 immunotoxin moxetumomab pasudotox, *BRAF* V600E inhibitors (vemurafenib or dabrafenib), interferon alpha, ibrutinib (oral Bruton tyrosine kinase inhibitor), or other chemotherapy.
- Survivorship principles include adherence to adult vaccination schedule (with the exception of live vaccines) and surveillance for secondary cancers (lymphomas, skin cancers, and some solid tumors).

DISPOSITION

HCL has a favorable prognosis with most patients achieving long-term survival.

REFERRAL

Hematology consultation is mandatory in all patients.

PEARLS & CONSIDERATIONS

COMMENTS

The diagnosis of hairy cell leukemia is occasionally missed and subsequently made by the pathologist after removal of the spleen for diagnostic purposes.

RELATED CONTENT

Hairy Cell Leukemia (Patient Information)

AUTHOR: **Adam J. Olszewski, MD**

SUGGESTED READINGS

Grever MR et al: Consensus guidelines for the diagnosis and management of patients with classic hairy cell leukemia, *Blood* 129:553-560, 2017.

Kreitman RJ et al: Moxetumomab pasudotox in relapsed/refractory hairy cell leukemia, *Leukemia* 32:1768-1777, 2018.

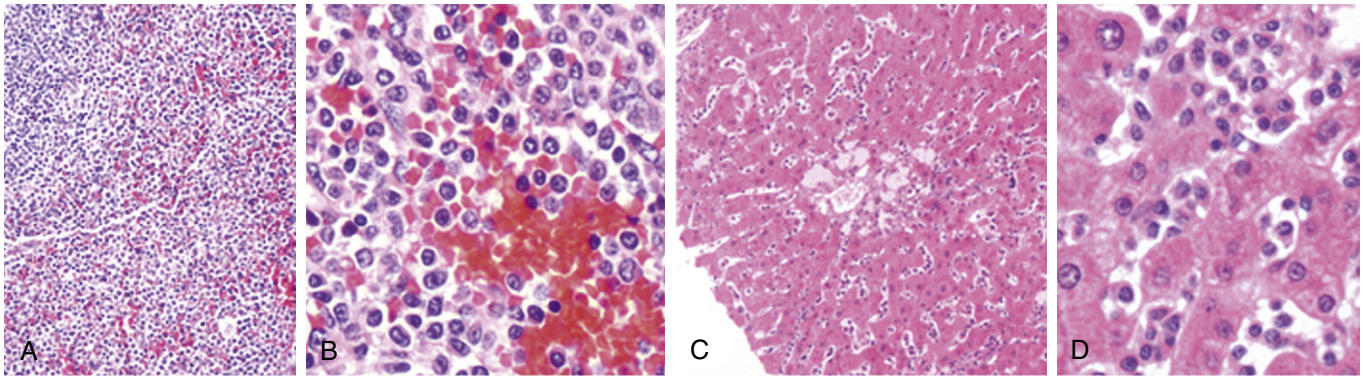

FIG. E1 Histopathology of the spleen and liver in hairy cell leukemia. The spleen **(A, B)** shows a massive and diffuse infiltrate in the red pulp and depletion of the white pulp. The infiltrate is associated with hemorrhage, which results in red blood cell "lakes" **(B)** (*lower right*). The liver **(C, D)** is frequently involved, and the pattern of infiltration is predominantly sinusoidal. (From Hoffman R et al: *Hematology: basic principles and practice*, ed 7, Philadelphia, 2018, Churchill Livingstone.)

TABLE E1 Major Diagnostic Features of Hairy Cell Leukemia

Study	Findings
Morphology of hairy cells	Oval or indented nuclei and abundant pale blue cytoplasm Absent or inconspicuous nucleoli Circumferential cell surface with "ruffled" projections
Bone marrow biopsy morphology	Diffuse or interstitial bone marrow infiltration, without discrete nodular aggregates Clear cells with "fried egg" or spindled appearance Reticulin fibrosis
Flow cytometry	Clonal B cells expressing CD11c, CD20, CD25, CD103, and CD200 and lacking CD5, CD10, and CD23 expression
Immunohistochemistry	Positive for cyclin D1, DBA.44, tartrate-resistant acid phosphatase (TRAP), and annexin-A1
Molecular studies	*BRAF* V600E mutation

Adapted from Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.

TABLE E2 Immunophenotype of Hairy Cell Leukemia and Other Indolent Lymphoid Neoplasms

Disease	sIg	CD5	CD10	CD11c	CD20	CD22	CD23	CD25	CD103
HCL	+/–	–/+	–	++	+	+	–/+	+	++
CLL	+/–	++	–	–/+	+/–	–/+	++	–/+	–
B-PLL	++	+	–	–/+	+/–	+	+/–	–	–
HCLv	+/–	–	–	++	+	+	–	–	–/+
MCL	+	++	–	–	+	+	–/+	–	–
SMZL	+	–/+	–/+	+	+	+/–	–/+	–	–
FL	+	–	+	–	++	+	–/+	–	–

B-PLL, B-prolymphocytic leukemia; *CLL*, chronic lymphocytic leukemia; *FL*, follicular lymphoma; *HCL,* hairy cell leukemia; *HCLv*, variant form of hairy cell leukemia; *MCL*, mantle cell lymphoma; *sIg*, surface immunoglobulin; *SMZL*, splenic marginal zone lymphoma.

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE E3 Initial Workup of a Patient with Suspected Hairy Cell Leukemia

- History and physical examination
- Complete blood count with differential counts
- Review of peripheral blood smear
- Serum chemistries
- Bone marrow aspirate and biopsy with immunostains
- Immunophenotyping by flow cytometry of peripheral blood and bone marrow
- ? Serum soluble markers such as CD25 and CD22
- ? Immune status analysis with CD4/CD8 lymphocyte subsets
- Appropriate imaging, if febrile, to rule out infections

From Hoffman R, et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE E4 Clinical and Laboratory Findings of Hairy Cell Leukemia at Presentation

Finding	% of Patients With Finding	Comments
Splenomegaly	86	Massive in 25% of patients
Hepatomegaly	73	If biopsied at presentation, the liver is nearly always involved.
Lymphadenopathy	13	Mostly abdominal and retroperitoneal; peripheral lymphadenopathy is uncommon.
Anemia (hemoglobin ≤12.0 g/dl)	77	
Neutropenia (1500×10^9/L)	79	
Monocytopenia (500×10^9/L)	98	Marked monocytopenia (150×10^9/L) is present in 90% of patients.
Thrombocytopenia ($100{,}000 \times 10^9$/L)	73	
Hairy cells detected on peripheral smear examination	85	Often few in number; identification may require careful examination by an experienced observer.

From Jaffe ES: *Hematopathology*, Philadelphia, 2011, WB Saunders.

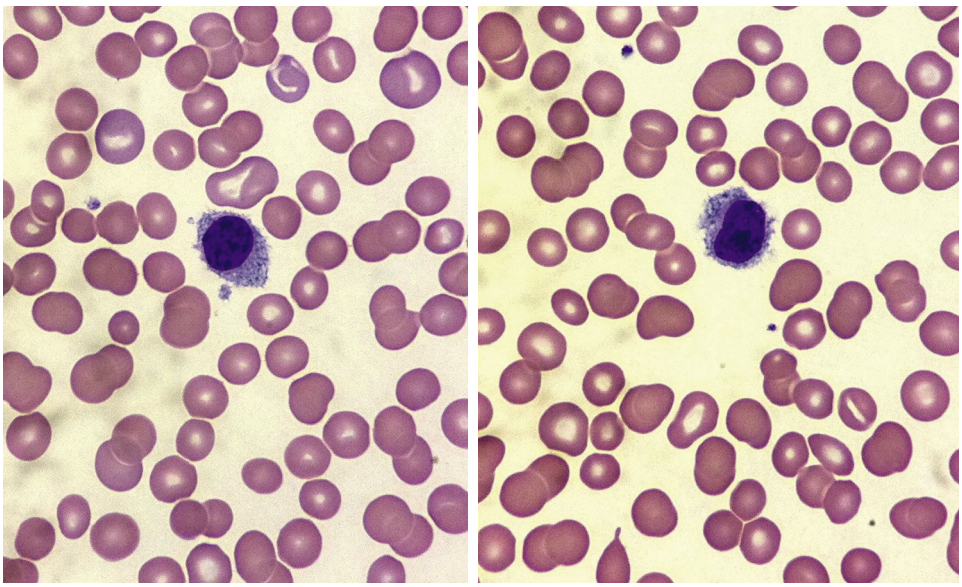

FIG. E2 Peripheral blood smear in hairy cell leukemia. Note the lymphocytes with hair-like cytoplasmic projections surrounding the nucleus. (Courtesy Adam J. Olszewski, M.D.)

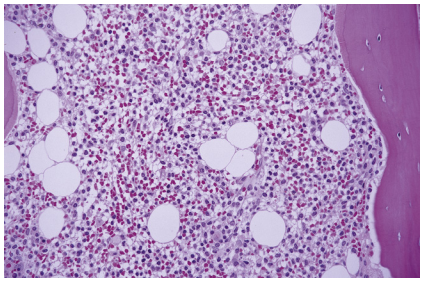

FIG. E3 Bone marrow trephine biopsy section from a patient with hairy cell leukemia. The bone marrow is hypercellular with a diffuse infiltration by hairy cells. The hairy cell nuclei are widely spaced, separated from each other by a pale, lightly eosinophilic cytoplasm. Many extravasated red blood cells are present between the hairy cells (hematoxylin and eosin stain, 630×). (From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Churchill Livingstone.)

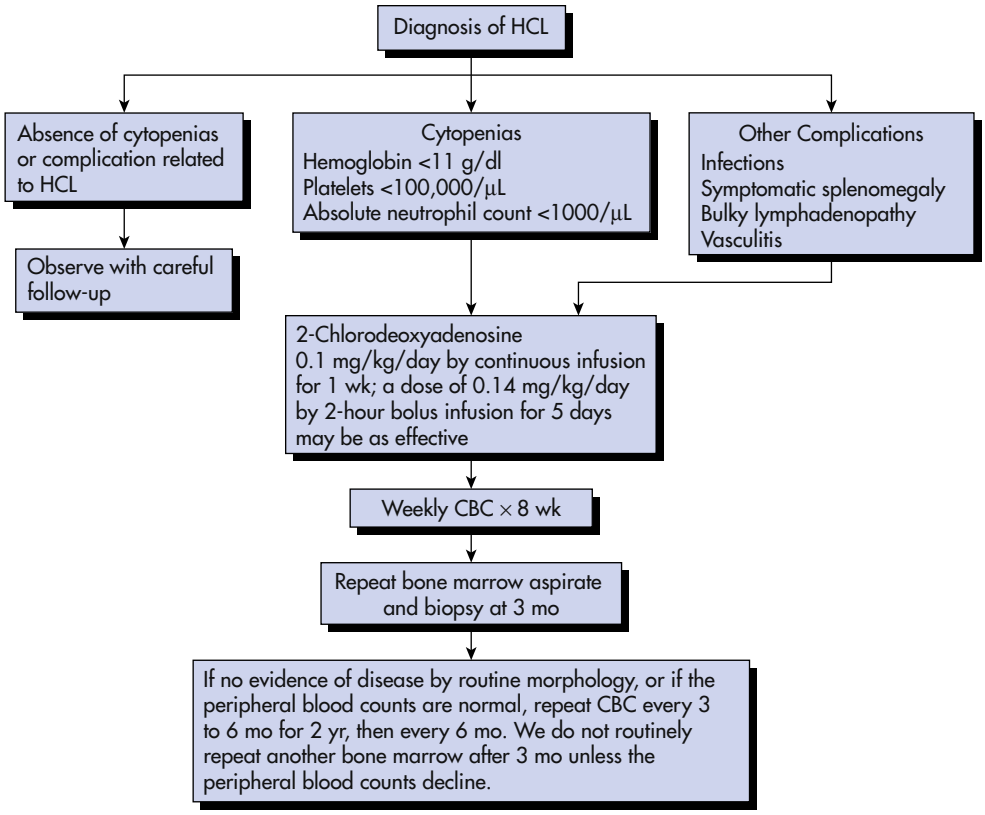

FIG. E4 An algorithm of a proposed strategy for the treatment of hairy cell leukemia (HCL). *CBC,* Complete blood count; *HCL,* hairy cell leukemia. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

BASIC INFORMATION

DEFINITION

Hallucinations are false perceptions that have no basis in the external environment. Overdoses of hallucinogenic drugs cause symptoms including anxiety, dysphoria, tachycardia, fever, hypertension, seizure, and rhabdomyolysis. Commonly used drugs that cause hallucinations include lysergic acid diethyl amide (LSD), psilocybin (hallucinogenic mushrooms, "magic mushrooms"), mescaline, peyote, methylenedioxymethamphetamine (ecstasy), phencyclidine (PCP, angel dust), cathinone derivatives ("bath salts"), salvia, *Datura* genus (Jimson weed, angel's trumpet), dextromethorphan, and ketamine ("special K," "vitamin K").

SYNONYMS

Overdose, "OD"
Psychedelics
Entheigeon (substance that generates the god/spirit within)
Enactogens (awareness of "the touch within")

ICD-10CM CODES

F16.20	Hallucinogen dependence, uncomplicated
F16.90	LSD reaction (acute) (without dependence)
T40.901	A poisoning by unspecified psychodysleptics [hallucinogens], accidental (unintentional), initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Used by people of all ages. The drugs commonly are used in group settings such as raves, parties, and college events.
PEAK INCIDENCE: Most commonly between the ages of 17 and 25 yr old
PREVALENCE:

- LSD lifetime prevalence of use >12 yr old: 9.5%.
- Hallucinogens prevalence of use >12 yr old: 15.3%.
- Overdose or seeking medical treatment is rare.
- Table 1 (shows the prevalence of various drugs for 8th, 10th, and 12th graders in 2018.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical presentation varies by amount and type of drug used.
- Overall presentation includes distortions in body image and sensory perception, as well as rapid, intense alterations in mood; emotions; and suggestibility.
- Overdose symptoms may range from acute anxiety, agitation, tachycardia, hypertension, hyponatremia, hyperthermia, severe agitation, rhabdomyolysis, seizure, cardiac dysrhythmia, respiratory failure, and death.
- Classic pure hallucinogens: Lysergic acid diethyl amide (LSD), psilocybin (hallucinogenic mushrooms, "magic mushrooms"). Individuals rarely present for medical treatment. The patient usually is conscious, alert, and can provide history of drug ingestion. Serious medical problems have been reported to include seizures, hyperthermia, rhabdomyolysis, and acute renal failure. New trends in self-administered "microdosing" of psilocybin or LSD for treatment of depression or other psychological disorders may present as inadvertent overdose.
- Mescaline: Found in many cacti. Similar structure to LSD; however, there have not been reports of medically significant adverse effects directly from the drug.
- Peyote: Legal for use by the Native American Church. Adverse effects occur first, prior to hallucinations, and within 1 hour of ingestion include severe nausea, vomiting, abdominal pain, dizziness, ataxia, nystagmus, and headache. Mild adrenergic effects of increased temperature, pulse, and blood pressure occurs after the initial symptoms. Hallucinations begin several hours later.
- Methylenedioxymethamphetamine (ecstasy): Not a true hallucinogenic but with similar effects of increased stimulation. Mild increase in temperature, pulse, hypertension, nausea, bruxism, jaw-clenching, dry mouth, muscle aches, ataxia. Severe effects include significant increases in blood pressure leading to intracranial hemorrhage, brain or heart ischemia, arrhythmia, sudden cardiac death, hyponatremia, malignant hyperthermia, DIC, seizures, and rhabdomyolysis. Symptoms are similar to serotonin syndrome.
- Phencyclidine (PCP, angel dust): Similar to ketamine with multiple effects that include features of hallucinations. Patients may have CNS stimulation or depression. The most common signs are mild hypertension and vertical nystagmus in 60% of patients. Other important warning signs for the safety of staff and physicians include severe agitation, physical violence, unpredictable behavior, and decreased response to pain. Disassociation, seizures (up to 3%), rhabdomyolysis with resulting acute renal failure, dystonic reactions, hyperthermia causing hepatic necrosis, and multiorgan failure are also possible.
- Cathinone derivatives (bath salts): Similar to PCP, with sympathomimetic effects of elevated temperature, blood pressure, pulse, sweating. Patients also may be severely agitated, aggressive, and violent toward staff. Severe medical effects include severe hyperthermia, hyponatremia, seizures, and rhabdomyolysis.
- Salvia: Adverse effects are mild and may include slurred speech, dysphoria, headache, nausea, vomiting, dizziness.
- *Datura* genus (Jimson weed, angel's trumpet): Anticholinergic alkaloids with symptoms consistent with anticholinergic poisoning: Hyperthermia, delirium, hallucinations, mydriasis, blurry vision, dry mouth, tachycardia, urinary retention.
- Dextromethorphan: Most commonly used by adolescents due to availability in over-the-counter cold and flu products; likely to be associated with salicylate, antihistamine, and acetaminophen overdose due to combination of cold and flu product ingredients.

ETIOLOGY

Usually caused by stimulation of various receptors in the brain, including serotonin type 2, dopamine, norepinephrine, acetylcholine, beta$_2$-adrenergic, NMDA, opioids, and voltage-gated electrolyte channels.

TABLE 1* Trends in Prevalence of Various Drugs for 8th Graders, 10th Graders, and 12th Graders; 2018 (in percent)

Drug	Time Period	8th Graders	10th Graders	12th Graders
Hallucinogens	Lifetime	2.20	3.90	6.60
	Past yr	1.40	2.70	4.30
	Past mo	0.60	0.80	1.40
Ketamine	Past yr	-	-	0.70
LSD	Lifetime	1.40	2.80	5.10
	Past yr	0.90	2.00	3.20
	Past mo	0.40	0.50	1.00
PCP	Past yr	-	-	1.10
Salvia	Past yr	0.60	0.70	0.90

*www.drugabuse.gov/drug-abuse/hallucinogens
LSD, Lysergic acid diethyl amide; *PCP,* phencyclidine.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Alcohol use or withdrawal
- Benzodiazepine withdrawal
- Anticholinergic poisoning
- Serotonin syndrome
- Neuroleptic malignant syndrome
- Thyrotoxicosis
- Central nervous system infections
- Anti-NMDA encephalitis
- Structural brain lesions
- Acute psychosis
- Hypoglycemia
- Hypoxia
- Sepsis
- Acute ischemic or hemorrhagic stroke
- Polysubstance use
- Incidental trauma

WORKUP

- Must rule out nontoxic causes of altered mental status. Vital signs should be examined immediately. History of drug use, dementia, delirium,

and risk factors for CNS infection should be considered. Patients should also be examined for occult and incidental trauma that occurred while under the influence of the drugs.

LABORATORY TESTS

- Consider:
  1. Complete blood count
  2. Glucose level
  3. Comprehensive metabolic panel
  4. Thyroid-stimulating hormone
  5. Creatine phosphokinase
  6. Arterial blood gas
  7. Toxicologic screening for other illegal drugs (urine and serum), acetaminophen, salicylate
  8. Lumbar puncture

IMAGING STUDIES

- Consider:
  1. ECG
  2. CT of head
  3. MRI of brain

Rx TREATMENT

Because most symptoms are not life or limb threatening, most treatment revolves around supportive treatment.

NONPHARMACOLOGIC THERAPY

- Place patient in a calm and quiet area with limited auditory and visual stimulation.
- Patients may benefit from a sitter to reorient him or her and provide a calming presence.
- Physical restraints should be used only if absolutely necessary due to the increased risk of agitation, hyperthermia, and rhabdomyolysis. Severely violent patients may require chemical restraint in addition to physical restraint.
- Severe hyperthermia may require active cooling measures.
- Supplemental oxygen should be considered.
- Bowel irrigation not usually recommended after 60 min of ingestion; unlikely to be beneficial for most compounds.

ACUTE GENERAL Rx

- Benzodiazepines are the mainstay of medical treatment
- Aggressive intravenous hydration with isotonic crystalloids
- Naloxone
- Dextrose
- Dantrolene if refractive hyperthermia
- Hypertonic saline if hyponatremic
- Cyproheptadine for serotonin syndrome
- IV nitroprusside or nicardipine for blood pressure control
- Propofol, barbiturate for refractive seizure
- Paralytics for hyperthermia secondary to dystonic reactions
- Physostigmine for severe anticholinergic poisoning

DISPOSITION

- Patients should be monitored for several hours for improvement of symptoms. If symptoms improve, patients who are mentally lucid and steady on their feet may be discharged under the close supervision of family or friends.
- Patients not improving may require further workup.
- If no organic cause is found, patients may require psychiatric evaluation.
- Patients may need to be admitted until resolution of organ injury.

REFERRAL

- Psychiatric referral may be required.
- Substance abuse or rehab.

PEARLS & CONSIDERATIONS

COMMENTS

- Actual substance used may be unclear.
- Most treatment is supportive care.
- Treat symptoms of hyperthermia, severe hypertension, and possible rhabdomyolysis.
- Chemical restraint with benzodiazepines is safe and effective.

RELATED CONTENT

Alcohol Use Disorder (Related Key Topic)
Delirium (Related Key Topic)
Delirium Tremens (Related Key Topic)
Opioid Overdose (Related Key Topic)
Serotonin Syndrome (Related Key Topic)

AUTHORS: **Samantha Ni, MD,** and **Craig Blakeney, MD**

SUGGESTED READINGS

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National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services: Hallucinogens. Available at: www.drugabuse.gov/drugs-abuse/hallucinogens

Sutter ME et al: Alternative drugs of abuse, *Clin Rev Allerg Immunol* 46(1):3-18, 2014.

BASIC INFORMATION

DEFINITION

Hand-foot-mouth disease (HFMD) is a viral illness characterized by superficial lesions of the oral mucosa and skin of the extremities. HFMD is primarily caused by coxsackie or enterovirus infection and can be transmitted by either respiratory droplet contact or fecal-oral contact. Although young children are predominantly affected, adults are also at risk. This disease is usually self-limited and benign, although outbreaks in the Asia Pacific region have been increasingly complicated by neurologic and cardiopulmonary sequelae.

SYNONYMS

HFMD
Vesicular stomatitis with exanthema
Coxsackie virus infection
Enterovirus infection

ICD-10CM CODE

B08.4	Enteroviral vesicular stomatitis with exanthem

EPIDEMIOLOGY & DEMOGRAPHICS

- HFMD most often affects children <10 yr.
  1. Children <5 yr are at the highest risk of infection and have the most severe cases.
- HFMD is contagious. Close contacts of affected children, including family members and health care workers, are the most commonly infected adults. Outbreaks can also occur in clustered populations of young adults (a recent outbreak at a military base affected 4.7% of the exposed population).
- Infection is spread from person to person by direct contact with saliva, respiratory secretions, fluid in vesicles, or stool.
- Outbreaks in daycares, schools, summer camps, hospital cohorts, and other groups with close contact are common.
- A person is most contagious during the first wk of illness.
- Outbreaks tend to occur during the summer.
- Infection leads to immunity, but a subsequent episode may occur after infection with a different etiologic virus or type.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms:

- After a 3- to 5-day incubation period (range 2 to 7 days), patients may report odynophagia, sore throat, malaise, and fever (38.3° to 40° C; 101° to 104° F).
- 1 to 2 days later, the characteristic oral lesions appear (small red spots that blister and may ulcerate). The fluid from these lesions is infectious, and disease can be transmitted through contact with the fluid.
- In 75% of cases, skin lesions on the extremities accompany these oral manifestations (small flat or raised red bumps, sometimes with blisters—they can be macular, maculopapular, or vesicular), but the lesions may be absent. The skin lesions are usually not painful or pruritic, but can be painful.
- Only 11% of adults have cutaneous findings.
- Lesions appear over the course of 1 or 2 days and resolve over 3 to 4 days.

Physical findings:

- Oral lesions are common and are usually found on the tongue, buccal mucosa, gingivae, and hard palate.
- Oral lesions initially start as 1- to 3-mm erythematous macules and evolve into gray vesicles on an erythematous base.
- Vesicles are frequently broken by the time of presentation and appear as superficial, gray ulcers with surrounding erythema.
- Skin lesions of the palms of the hands and soles of the feet are common and start as linear erythematous papules (3 to 10 mm in diameter) that evolve into gray vesicles that may be mildly painful (Fig. E1). These vesicles are usually intact at presentation and remain so until they desquamate within 2 wk. They are nonpruritic.
- Involvement of the buttocks and genital area is also common (present in 31% of cases).
- Although rare, atypical findings such as fingernail or toenail loss (nail separation from the nail matrix, otherwise known as onychomadesis) after HFMD (notably with the A6 strain of coxsackie virus) has been reported in children. The nail loss is temporary, and nails grow back without intervention.
- Another atypical skin manifestation is that of "eczema coxsackium," which is described as the typical skin lesions of coxsackie virus but with a more extensive distribution involving the trunk and extremities, localized to areas of active or past atopic dermatitis.
- In rare cases, encephalitis, meningitis, myocarditis, poliomyelitis-like paralysis, and pulmonary edema may develop. Sporadic acute paralysis and long-term neurologic sequelae have been reported with enterovirus 71.
- Although information is limited, there is no clear evidence that pregnancy outcomes are affected in the setting of maternal infection. There are case reports of potential adverse outcomes such as spontaneous abortion or serious neonatal morbidity attributed to coxsackie virus infection, although these outcomes are rare.

ETIOLOGY

- Coxsackie virus group A, type 16, was the first and is the most common cause of HFMD.
- Enterovirus 71 is the second leading cause of HFMD. Enterovirus 71 is neurotropic and has a predilection for the brainstem, leading to more severe cases of the disease and more complications than with other strains or viruses. Clusters of severe disease have been reported in the Asia Pacific region.
- Coxsackie virus strains A5, A6, A7, A9, A10, B1, B2, B3, and B5 have also been implicated.
- Coxsackie A6 has been known to cause a severe skin rash and self-limited nail abnormalities (onychomadesis). Patients with this strain may lack oral lesions.
- Epidemic outbreaks have been reported with coxsackie A16 and enterovirus 71.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Aphthous stomatitis
- Herpes simplex infection
- Herpangina
- Behçet syndrome
- Erythema multiforme
- Pemphigus
- Gonorrhea
- Acute leukemia
- Lymphoma
- Allergic contact dermatitis

WORKUP

The diagnosis is made on the basis of typical history and characteristic physical examination.

LABORATORY TESTS

- Not indicated unless the diagnosis is in doubt such as for a suspected case with an atypical presentation.
  1. Oropharyngeal specimen, stool specimen, or vesicular fluid may be obtained

FIG. E1 Hand-foot-mouth disease. Deep-seated vesicles with erythema involving the palmar surface of the fingers. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence*, ed 5, Edinburgh, 2016, Elsevier.)

to identify the presence of enterovirus or coxsackie virus by polymerase chain reaction (PCR) (preferred due to rapidity of results compared with culture) or by culture, but may take from 2 to 4 wk for results. Due to prolonged shedding of the virus (wks to mos), detection of virus in secretions may not be responsible for current symptoms.

- Identification of a certain strain is only available in public health laboratories.

Rx TREATMENT

ACUTE GENERAL Rx

- Symptomatic therapy is given for this usually self-limited disease and usually resolves completely within 7 to 10 days.
- There are currently no available approved therapies for more severe cases. Antivirals and IV immunoglobulin have been evaluated for enterovirus 71 infections, but these treatments have not been evaluated in randomized, placebo-controlled studies.
- Systemic steroids should be avoided because they have been associated with more severe disease and higher viral loads.

DISPOSITION

Prognosis is excellent except in rare cases of central nervous system or cardiac involvement. Most are managed as outpatients. Hospitalization should be considered if the patient is unable to maintain adequate hydration due to painful oral lesions and in cases of neurologic manifestations such as meningitis, encephalitis, or flaccid paralysis, or cardiac complications such as myocarditis.

REFERRAL

Not usually needed, although dermatology or infectious disease consultation can be considered for diagnostic or therapeutic input for an atypical or severe case

PEARLS & CONSIDERATIONS

- Frequent handwashing, disinfection of contaminated surfaces, and washing of soiled articles of clothing can help reduce transmission.
- HFMD has no relation to hoof and mouth disease in cattle.

RELATED CONTENT

Hand, Foot, and Mouth Disease (Patient Information)

AUTHOR: **Erica Hardy, MD, MMS**

SUGGESTED READINGS

Banta J et al: Outbreak of hand, foot, and mouth disease caused by coxsackievirus A6 among basic military trainees-Texas 2015, *MMWR (Morb Mortal Wkly Rep)* 65:678-680, 2016.

Centers for Disease Control and Prevention: Notes from the field: severe hand, foot, and mouth disease associated with coxsackievirus a6 – Alabama, Connecticut, California, and Nevada, *MMWR (Morb Mortal Wkly Rep)* 61:213-214, 2012.

Hubiche T et al: Dermatological spectrum of hand, foot and mouth disease from classical to generalized exanthema, *Pediatr Infect Dis J* 33:e92-e98, 2014.

Nassef N et al: Hand-foot-and-mouth disease: a new look at a classic viral rash, *Curr Opin Pediatr* 27(4):486-491, 2015.

Repass GL et al: Hand, foot and mouth disease: identifying and managing an acute viral syndrome, *Cleve Clin J Med* 81(9):537-543, 2014.

BASIC INFORMATION

DEFINITION

Hantavirus pulmonary syndrome (HPS) is a severe infectious cardiopulmonary illness usually caused by the Sin Nombre virus (SNV), whose main vector is the deer mouse.

SYNONYMS

Four Corners disease
Hantavirus cardiopulmonary syndrome (HCPS)
HPS

ICD-10CM CODE
B33.4 Hantavirus (cardio)-pulmonary syndrome (HPS) (HCPS)

EPIDEMIOLOGY & DEMOGRAPHICS

- First identified in the U.S. in 1993, hantavirus has been found throughout the Americas, with most U.S. cases occurring in the Western half of the U.S.
- The number of HPS cases reported in the U.S. through December 31, 2012, was 616. Of these, 585 cases occurred from 1993 onward, following the initial identification of HPS, whereas 31 cases were retrospectively identified. 36% of all reported cases have resulted in death.
- The peak incidence to date was in June and July 1993 in the Four Corners region of the U.S.
- HPS is more common in the spring and summer.
- HPS is more prevalent among males, most likely because of increased environmental exposure.
- Mean age is 37 yr (range, 8 to 83). It has not been found at the extremes of age.
- Risk factors include exposure to rodent populations, rural locales, occupations with increased exposure to rodents, and entering infrequently opened structures.

CLINICAL PRESENTATION

- The most common symptoms are fever, headache, nausea, vomiting, cough, shortness of breath, and myalgia. It is not associated with rhinorrhea or nasal congestion.
- The most common signs on physical examination include fever, hypoxemia, and tachypnea. Rash, mucosal bleeding, and peripheral edema are not found with HPS.
- There are two phases of HPS, the prodromal phase and the cardiopulmonary phase, each of which lasts 2 to 7+ days. The prodromal phase is characterized by:
  1. Fever, chills, headache, and myalgias, especially in the legs and back
  2. Cough, nausea, vomiting, diarrhea, abdominal pain, and general malaise
  3. Tachypnea, tachycardia, and hypoxemia
- The cardiopulmonary phase has the following characteristics:
  1. Dry cough and dyspnea
  2. Acute pulmonary edema
  3. Hypotension
  4. Decreased cardiac output
  5. Coagulopathy

ETIOLOGY

- HPS is most often caused by SNV.
- The main vector is the deer mouse.
- It is transmitted by inhalation of aerosolized feces, urine, or saliva from infected rodents.
- No cases of person-to-person transmission have been reported in the U.S.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute respiratory distress syndrome
- Pneumonia, especially atypical
- Congestive heart failure
- Pulmonary edema
- Acute bacterial endocarditis
- Gastroenteritis, appendicitis, or cholelithiasis
- Plague
- Tularemia ("rabbit fever")
- Histoplasmosis
- Coccidioidomycosis
- Cardiogenic shock
- HIV/AIDS
- Myocardial infarction
- Goodpasture syndrome or granulomatosis with polyangiitis (Wegener granulomatosis)
- Other viral hemorrhagic fevers (see Table E1)

TABLE E1 Pathobiologic and Clinical Aspects of Viral Hemorrhagic Fevers

Disease	Incubation Period (days)	Onset	Bleeding	Rash	Jaundice	Heart	Lung	Kidney	CNS	Eye
Filoviridae										
Ebola HF	3-21	Abrupt	++	+++	+	++?	+	+	+	+
Marburg HF	3-21	Abrupt	++	+++	+	++?	+	+	+	+
Arenaviridae										
Lassa fever and Lujo HF[a]	5-16	Gradual	+	++	0	++	+	0	+	0
South American HFs[a]	7-14	Gradual	+++	0	0	++	+	0	+++	0
Bunyaviridae										
HF with renal syndrome	9-35	Abrupt	+++	0	0	++	+	+++	+	0
Hantavirus pulmonary syndrome	7-35	Gradual	0 (except for Andes virus infection)	0	0	+++	+++	+	+	0
Rift Valley fever[b]	2-5	Abrupt	+++	+	++	+?	0	+	++	++
Crimean-Congo HF	3-12	Abrupt	+++	0	++	+?	+	0	+	0
Flaviviridae										
Yellow fever	3-6	Abrupt	+++	0	+++	++	+	++	++	0
Dengue HF	3-15	Abrupt	++	+++	+	++	+	0	+	0
Kyasanur Forest disease	3-8	Abrupt	++	0	0	+	++	0	+++	+
Omsk HF	3-8	Abrupt	++	0	0	+	++	0	+++	+

CNS, Central nervous system; *HF,* hemorrhagic fever; 0, sign not typically noted/organ not typically affected; +, sign occasionally noted/organ occasionally affected; ++, sign commonly noted/organ commonly affected; +++, sign characteristic/organ involvement severe.
[a]Data are insufficient to distinguish between the syndromes produced by the various Old and New World arenaviruses.
[b]Hemorrhagic fever, encephalitis, and retinitis may be seen in Rift Valley fever independently of each other.

WORKUP

- Diagnosis is made on the basis of clinical criteria (fever, hypoxemia, and bilateral interstitial edema) or autopsy evidence of idiopathic noncardiogenic pulmonary edema, as well as confirmatory laboratory testing.
- Laboratory testing: Rapid strip immunoblot assay (RIBA), Western blot, or ELISA to detect IgM antibodies to SNV or other hantaviruses.
- Complete blood count q8h initially.
  1. All patients manifest thrombocytopenia, and its progression is the most consistent indicator heralding the cardiopulmonary phase of HPS.
  2. Differential usually reveals a left shift with atypical, enlarged lymphocytes. White blood cell counts are an unreliable indicator of severity of infection.
- Lactate level >4 mg/dl is associated with a high mortality rate.
- Elevated serum LDH level.
- Rapid immunoblot strip assay for SNV antibodies.
- Diagnosis is confirmed by identification of immunoglobulin M and G antibodies to SNV.

IMAGING STUDIES

Chest radiography: Bilateral diffuse interstitial edema

Rx TREATMENT

There is no known specific treatment or therapy, only supportive therapy.

NONPHARMACOLOGIC THERAPY

- Intensive care unit admission in tertiary care center
- Mechanical ventilation with high pulmonary end-expiratory pressure and high Fio_2
- Pulmonary artery catheterization
- Extracorporeal membrane oxygenation (ECMO)

ACUTE GENERAL Rx

- Supportive measures
- Supplemental oxygen
- Intubation when indicated
- Hemodynamic monitoring
- Cautious fluid resuscitation because of potential capillary leak syndrome
- Early use of vasopressors
- Initial broad-spectrum antibiotics
- No definitive antiviral therapy for SNV
- Glucocorticoids have no effect on reducing mortality and therefore cannot be recommended

DISPOSITION

- Patients who survive cardiopulmonary phase of HPS have rapid clinical improvement.
- There are no serious sequelae.

REFERRAL

University of New Mexico Hospital is one of the few facilities with experience in ECMO for treatment of HPS. This modality is only for hemodynamically unstable, critically ill patients who do not respond to conventional therapies.

BOX E1 Centers for Disease Control and Prevention Recommendations for Preventing Hantavirus Pulmonary Syndrome

- Eliminate rodent harborage.
  1. Keep cooking, eating, and food storage areas clean.
  2. Cover human food and animal feed.
  3. Contain and elevate garbage.
  4. Seal holes and cracks in dwellings to prevent entrance by rodents.
  5. Clear brush and trash from around homes and outbuildings.
- Control rodent populations by maintaining snap traps and using rodenticides; in areas where plague occurs, control fleas with insecticides.
- Safely clean up rodent-infested areas.
  1. Air out infested spaces before cleanup.
  2. Spray areas of infestation and all excreta, nesting, and other materials with household disinfectant or 10% bleach solution. Then clean up, seal in bags, and dispose.
  3. Avoid sweeping, vacuuming, or stirring dust until the area is thoroughly wet with disinfectant.
  4. Wear rubber gloves; disinfect gloves before removal, and wash hands afterward.
  5. In areas where plague occurs, spray insecticide on trapped rodents and nesting materials to prevent fleas from abandoning rodents to find new hosts.
- Avoid rodents when outdoors.
  1. Do not disturb rodent droppings or camp or sleep near burrows or areas where trash is present.
  2. Avoid feeding or handling rodents even if they appear friendly.

From Auerbach P: *Wilderness medicine, Expert Consult premium edition—enhanced online features and print,* Philadelphia, 2012, WB Saunders.

PEARLS & CONSIDERATIONS

COMMENTS

- Although rare, HPS should be a consideration in those with acute respiratory illness and a history suggestive of HPS exposure. The combination of thrombocytopenia, left shift granulocytes, and circulating immunoblasts >10% of the total lymphoid series (diagnostic triad) is rare in other viral illnesses.
- Testing for hantavirus should always be considered in cases of thrombocytopenia and fever of unknown origin, especially in areas endemic for the infection.

PREVENTION

Rodent control is the primary way to prevent hantavirus infection. Box E1 describes CDC recommendations for preventing hantavirus pulmonary syndrome. No prophylactic vaccine is available.

AUTHOR: **Maher Tabba, MD, FACP, FCCP**

SUGGESTED READINGS

Centers for Disease Control and Prevention: Reported cases of HPS: HPS in the United States. Available at: www.cdc.gov/hantavirus/surveillance/index.html.

Denecke B et al: Hantavirus infection: a neglected diagnosis in thrombocytopenia and fever? *Mayo Clin Proc* 85(11):1016-1020, 2010.

BASIC INFORMATION

DEFINITION

Head and neck squamous cell carcinoma is a malignant disease entity that arises from the epithelium of the mucosal surfaces of the upper aerodigestive tract and accounts for about 90% of head and neck cancers. This disease results from exposure to carcinogens and from the accumulation of genetic alterations. The workup and management of these patients depends upon the specific subsite of the aerodigestive tract in the head and neck from which the primary tumor arises. These subsites are the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx. Cutaneous malignancies, thyroid neoplasms, and salivary gland neoplasms also occur in the head and neck but are beyond the scope of this chapter.

SYNONYMS

HNC
Head and neck cancer
HNSCC
Head and neck squamous cell carcinoma

ICD-10CM CODES

C00-C14	Malignant neoplasms of lip, oral cavity, and pharynx
C30	Malignant neoplasm of nasal cavities, middle ear, and accessory sinuses
C32	Malignant neoplasm of larynx
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face, and neck

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- U.S. annual incidence of head and neck cancer (90% of which is squamous cell carcinoma) is approximately 62,000 persons per yr.
- Annual mortality is approximately 13,000 persons per yr.
- Accounts for approximately 3% of all cancers in the U.S.
- Human papilloma virus (HPV)-associated squamous cell carcinoma of the head and neck accounts for 5% to 20% of all HNSCCs, and 40% to 90% of those arise in oropharynx.
- Incidence of all forms of HNSCC is on the decline, except oropharyngeal squamous cell carcinoma, which is increasing in incidence, likely related to the rise in human papilloma virus (HPV) associated HNSCC.

PEAK INCIDENCE: Sixth decade of life

PREDOMINANT SEX AND AGE: Male:female ratio is about 3:1. Risk increases significantly over the age of 40.

GENETICS: Research is ongoing in genetic factors that lead to the development and progression of HNSCC. Tumor suppressor genes including *p53, NOTCH1,* and *CDKN2A,* among others, have been shown to harbor mutations in patients with HNSCC.

RISK FACTORS: The two most strongly implicated risk factors associated with HNSCC are tobacco and alcohol use. These carcinogens place the entire epithelium of the upper respiratory tract at risk for multiple primary tumors via a process known as field cancerization. More recently, a new subset of HNSCC caused by the HPV has been increasing in prevalence. HPV 16 is the most common genotype detected. Patients are more likely to be white middle-aged men, nonsmokers, with minimal alcohol use and higher socioeconomic status.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presenting signs and symptoms are related to local effects of the primary tumor, regional spread, metastatic disease, or paraneoplastic phenomena:
  1. Oral cavity, oropharynx, hypopharynx: Painful mass or ulceration (Fig. E1), dysphagia, odynophagia, weight loss
  2. Larynx: Hoarseness, voice change, shortness of breath, stridor
  3. Nasal cavity, paranasal sinus, nasopharynx—referred otalgia, conductive hearing loss from middle ear effusion, epistaxis, cranial nerve palsies
  4. All sites: Cranial nerve palsies, painless neck mass from regional metastases to cervical lymph nodes. Most common site of distant metastases is the lung, with bone and liver being much less common
- Physical exam: A thorough examination of the head and neck, including cranial nerve exam, otoscopy, inspection and palpation of oral cavity, oropharynx, and neck, and general physical exam:
  1. Concerning exam findings: Unilateral middle ear effusion, ulcerated mass of the oral cavity (Fig. E2) or oropharynx, trismus, painless neck mass

ETIOLOGY

Exposure to carcinogens including tobacco and alcohol causes genetic alterations in the epithelium of mucosal surfaces lining the upper aerodigestive tract, leading to malignant transformation of epithelial cells. HPV-associated HNSCC is a direct result of the carcinogenic effects of the virus and is not related to alcohol and tobacco use. Primary nasopharyngeal carcinoma has a weak association with tobacco and alcohol and is endemic to southern China, Southeast Asia, and northern Africa. There is a strong association between Epstein-Barr virus infection and primary nasopharyngeal carcinoma.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Lymphoma, primary salivary gland malignancy, thyroid malignancy, benign tumors of the upper aerodigestive tract, metastases

WORKUP

- Initial workup includes a full physical examination, indirect and/or direct laryngoscopy, imaging studies of the head and neck as well as the chest and/or body to assess for metastases, laboratory tests as indicated, and referral to a head and neck cancer specialist.
- Additional workup by head and neck cancer specialist:
  1. Flexible fiber-optic laryngoscopy or mirror laryngoscopy
  2. Biopsy of the tumor in office or under anesthesia
  3. Fine-needle aspiration (FNA) and biopsy for patient who presents with a suspicious neck mass
  4. Panendoscopy with biopsy under anesthesia, which may include direct laryngoscopy, esophagoscopy, and/or bronchoscopy

LABORATORY TESTS

Complete blood count (CBC), coagulation studies, electrolytes, ECG, liver function tests (albumin, transaminases, alkaline phosphatase), TSH

IMAGING STUDIES

- CT scan of the neck with contrast: Necessary to evaluate extent of primary tumor and nodal metastases in neck (Fig. E3)
- MRI of head and neck (optional): Useful for nasopharyngeal, infratemporal fossa, temporal bone, parotid, parapharyngeal, skull base, or intracranial involvement
- Chest x-ray or CT chest with contrast: To evaluate for lung metastases
- PET/CT (Fig. E4): Highlights areas in the body with increased metabolic uptake. Useful initially to assess extent of primary tumor, location of unknown primary tumor, cervical metastases, distant metastases, and second primary tumors. Can be used to monitor for recurrence in the posttreatment setting

STAGING

Staging is based on the tumor, node, metastasis (TNM) staging system provided by the AJCC (Table 1). Staging varies depending on the head and neck subsite that is involved. Any nodal metastasis in the neck automatically classifies as advanced disease (Stage III or IV). Distant metastases place patients at Stage IVC. The exception to this is HPV-positive cancer of the oropharynx, in which the most recent staging system allows for a patient to be classified as low as Stage II even with cervical nodal metastases given the excellent response to treatment and prognosis for these tumors.

TREATMENT

- Treatment consists of surgery, radiation, chemotherapy, or a combination of any or all of the three modalities. The goal is to use as few modalities as possible to minimize side effects of treatment without compromising oncologic success.
  1. Surgery (Fig. E5): Complete surgical resection of the primary tumor along with unilateral or bilateral neck dissections to

TABLE 1 TNM Staging System for Cutaneous Squamous Cell Carcinoma of the Head and Neck

T: Primary Tumor

T_X	Primary tumor cannot be assessed
T_{is}	Carcinoma in situ
T_1	Tumor <2 cm in greatest dimension
T_2	Tumor ≥2 cm, but <4 cm in greatest dimension
T_3	Tumor ≥4 cm in maximum dimension or minor bone erosion or perineural invasion*
T_4	Tumor with gross cortical bone/marrow, skull base invasion and/or skull base foramen invasion
T_{4a}	Tumor with gross cortical bone/marrow invasion
T_{4b}	Tumor with skull base invasion and/or skull base foramen involvement

*Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T_3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm in caliper, or manifesting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

N: Regional Lymph Nodes

Clinical N (cN)

N_X	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Metastasis in single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(–)
N_2	Metastasis in single ipsilateral lymph node, >3 cm but not >6 cm in greatest dimension and ENE(–); or in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension; or in bilateral or contralateral lymph nodes and ENE(–), none >6 cm in greatest dimension and ENE(–)
N_{2a}	Metastasis in single ipsilateral lymph node, >3 cm but no >6 cm in greatest dimension and ENE(–)
N_{2b}	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
N_{2c}	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
N_3	Metastasis in lymph node, >6 cm in greatest dimension and ENE(–); *or* metastasis in any node(s) and clinically overt ENE [ENE(+)]
N_{3a}	Metastasis in a lymph node >6 cm in greatest dimension and ENE(–)
N_{3b}	Metastasis in any node(s) and ENE(+)

Pathologic N (pN)

N_X	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Metastasis in single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(–)
N_2	Metastasis in single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(+), or >3 cm but not >6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
N_{2a}	Metastasis in single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(+), *or* a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE(–)
N_{2b}	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
N_{2c}	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
N_3	Metastasis in lymph node, >6 cm in greatest dimension and ENE(–); *or* in a single ipsilateral node >3 cm in greatest dimension and ENE(+), *or* multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)
N_{3a}	Metastasis in a lymph node >6 cm in greatest dimension and ENE(–)
N_{3b}	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+), *or* multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)

NOTE: A designation of *U* or *L* may be used for any N category to indicate metastasis above the lower border of the cricoid *(U)* or below the lower border of the cricoid *(L)*.

Similarly, clinical and pathologic ENE should be recorded as ENE(–) or ENE(+).

M: Metastasis

M_0	No distant metastasis
M_1	Present distant metastasis

Staging for Cutaneous Squamous Cell Carcinoma

Stage 0	T_{is}	N_0	M_0
Stage I	T_1	N_0	M_0
Stage II	T_2	N_0	M_0
Stage III	T_3	N_0	M_0
Stage III	T_1	N_1	M_0
Stage III	T_2	N_1	M_0
Stage III	T_3	N_1	M_0
Stage IV	T_1	N_2	M_0
Stage IV	T_2	N_2	M_0
Stage IV	T_3	N_2	M_0
Stage IV	Any T	N_3	M_0
Stage IV	T_4	Any N	M_0
Stage IV	Any T	Any N	M_1

ENE, Extranodal extension.

From American Joint Committee on Cancer staging manual, ed 8, 2017.

remove involved or potentially involved lymph nodes as clinically indicated.
2. Radiation: Allows for easier access to poorly exposed tumors such as those of the larynx, oropharynx, nasopharynx, or hypopharynx. Disadvantages include lengthy, time-intensive treatment course, xerostomia, pain, and higher surgical morbidity if salvage surgery is needed.
3. Chemotherapy: Useful only as an adjuvant to radiation therapy or for palliation. Single-agent cisplatin therapy is widely accepted in the U.S. as a standard for chemoradiation regimens for head and neck cancers of any site. Major toxicities include nausea, vomiting, renal toxicity, ototoxicity, and myelosuppression.
4. Reconstruction: Performed with the goal of optimizing functional and cosmetic outcomes. Options include primary closure, local flaps, regional flaps, skin grafts, and microvascular free flaps from other parts of the body (e.g., radial forearm, fibula, anterolateral thigh, latissimus, etc.).

ACUTE GENERAL Rx

- Early-stage disease (Stage I or II):
  1. Single-modality treatment with surgery or radiation alone may be appropriate for early-stage head and neck cancer. The choice between one or the other depends on the specific subsite of the head and neck that is involved and the side effects profile for each modality.
  2. Treatment of the potentially involved lymph nodes in the neck with either neck dissection or radiation is controversial and depends on the clinical scenario and the judgment of the treatment team.
- Locoregionally advanced disease (Stage III or IV):
  1. In general, these patients have large tumors >4 cm and/or cervical nodal metastases. Treatment typically involves multimodality therapy with either surgery followed by radiation therapy or upfront chemoradiation alone. Depending on the presence of certain adverse pathologic features of the surgical specimen, adjuvant chemoradiation may be necessary. If chemoradiation is the initial treatment modality, surgery may be needed in the adjuvant setting for residual or recurrent disease.
  2. Laryngeal cancers are the exception where select advanced disease with T_3 or N_1 tumors can be managed with single-modality therapy with surgery or radiation alone.
  3. Nasopharyngeal cancer is also an exception. This is not a surgical disease. Managed primarily by radiation to primary site and neck for early-stage disease. Chemoradiation is primary treatment for advanced disease. Surgery is reserved for recurrent or residual disease of primary site or neck following radiation therapy.
- Metastatic disease (Stage IVC):
  1. Palliation of symptoms is the primary goal of treatment.
- All patients should be counseled on smoking cessation and avoidance of alcohol.

DISPOSITION

- Prognosis depends on the specific subsite of the head and neck that is involved. Overall 5-yr survival rate for head and neck squamous cell carcinoma is about 55%. This varies with 5-yr survival rates for carcinoma of the lip as high as 89.7% and carcinomas of the hypopharynx as low as approximately 30%.
- Patients are followed on a regular basis multiple times a yr by a head and neck cancer specialist. After a 5-yr disease-free survival, patients are followed on a yearly basis.

REFERRAL

Referral should be made to an otolaryngologist or oral surgeon who specializes in head and neck cancer.

PEARLS & CONSIDERATIONS

PREVENTION

- Encourage all patients to cease using tobacco and to limit alcohol consumption.
- Examine the oral cavity and palpate the neck during the annual physical examination. Work up any suspicious masses or lesions.

PATIENT & FAMILY EDUCATION

www.entnet.org/content/head-and-neck-cancer
www.cancer.gov/types/head-and-neck

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Laryngeal Carcinoma (Related Key Topic)
Oral Cancer (Related Key Topic)

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SUGGESTED READINGS

Boscolo-Rizzo P et al: New insights into human papillomavirus-associated head and neck squamous cell carcinoma, *Acta Otorhinolaryngol Ital* 33(2):77-87, 2013.

Cooper JS et al: National cancer database report on cancer of the head and neck: 10-year update, *Head Neck* 31(6):748-758, 2009.

Marur S, Forastiere AA: Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and diagnosis, and treatment, *Mayo Clin Proc* 91(3):386-396, 2016.

Mehanna H et al: PET-CT surveillance versus neck dissection in advanced head and neck cancer, *N Engl J Med* 374:1444-1454, 2016.

Siegel RL et al: Cancer statistics 2016, *CA Cancer J Clin* 66(1):7, 2016.

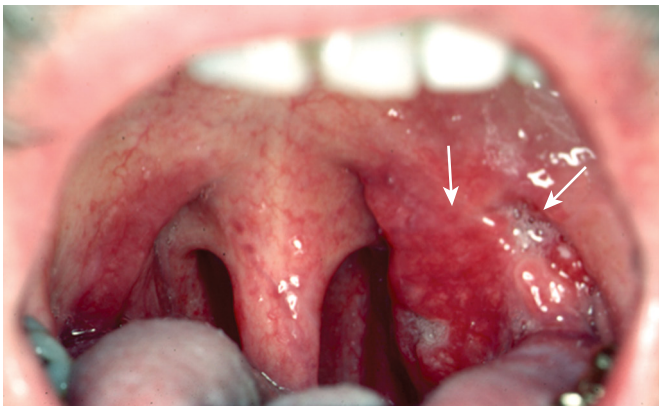

FIG. E1 Squamous cell carcinoma of the left tonsil *(arrows).* (From Richardson MA et al: *Cummings otolaryngology–head and neck surgery,* ed 5, Philadelphia, 2010, Mosby, pp. 1358-1374, Figure 100-8.)

FIG. E2 Oral squamous cell carcinoma. (From James WD et al: *Andrews' diseases of the skin: clinical dermatology,* ed 12, Philadelphia, 2016, Elsevier.)

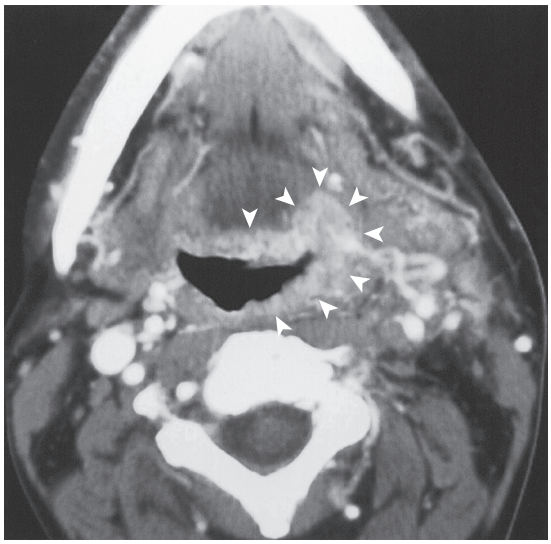

FIG. E3 Computed tomography scan with contrast showing tumor of the base of the left oropharynx *(arrowheads).* (From Richardson MA et al: *Cummings otolaryngology–head and neck surgery,* ed 5, Philadelphia, 2010, Mosby, pp. 1393-1420, Figure 102-47.)

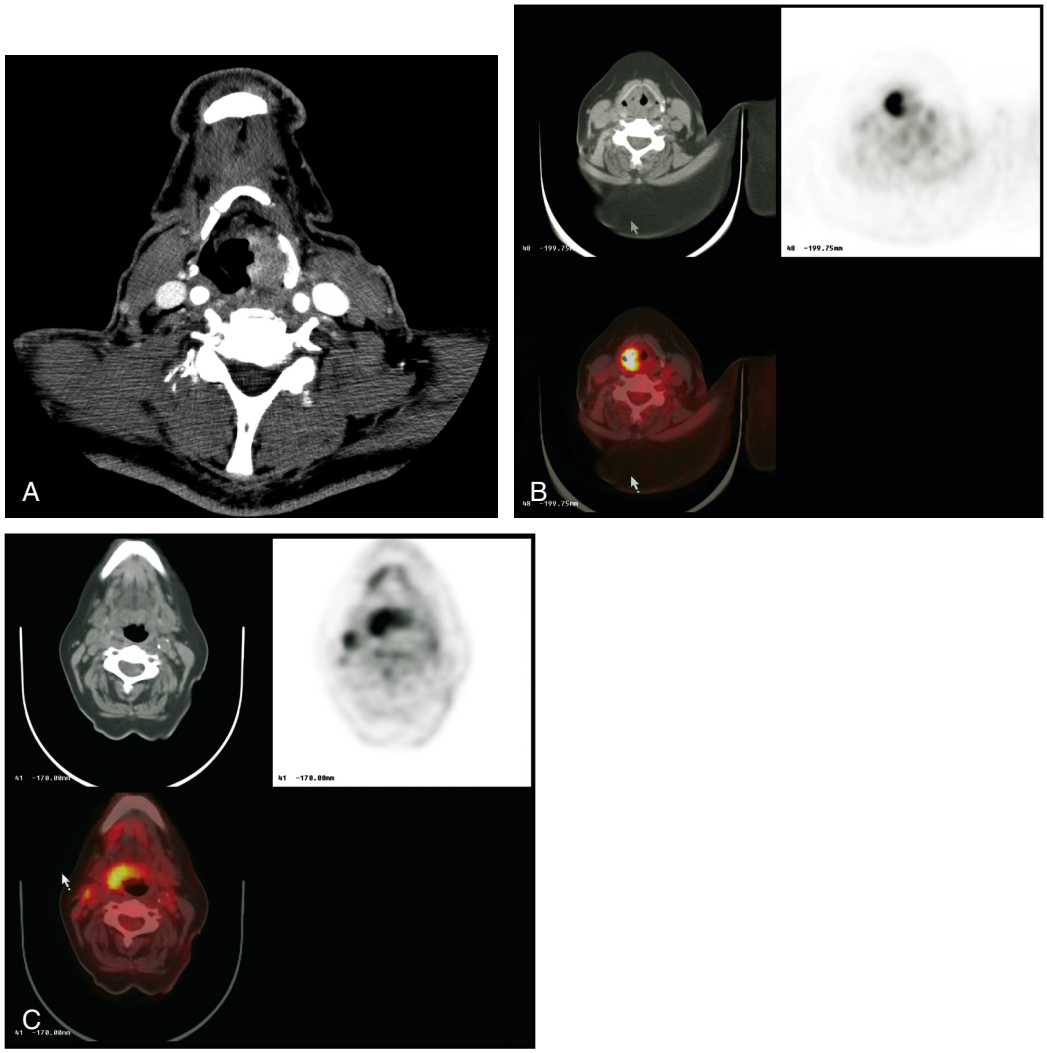

FIG. E4 Head and neck tumors. A, Axial computed tomography (CT) image of the neck with intravenous contrast agent shows a mass in the left piriform sinus. **B,** Positron emission tomography (PET) and PET-CT images show right vocal cord cancer with intense tracer uptake. **C,** PET and PET-CT images from the lower level of the neck show nodal tracer uptake consistent with metastases. (Courtesy Dr. David Yousem, The Johns Hopkins University; in Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

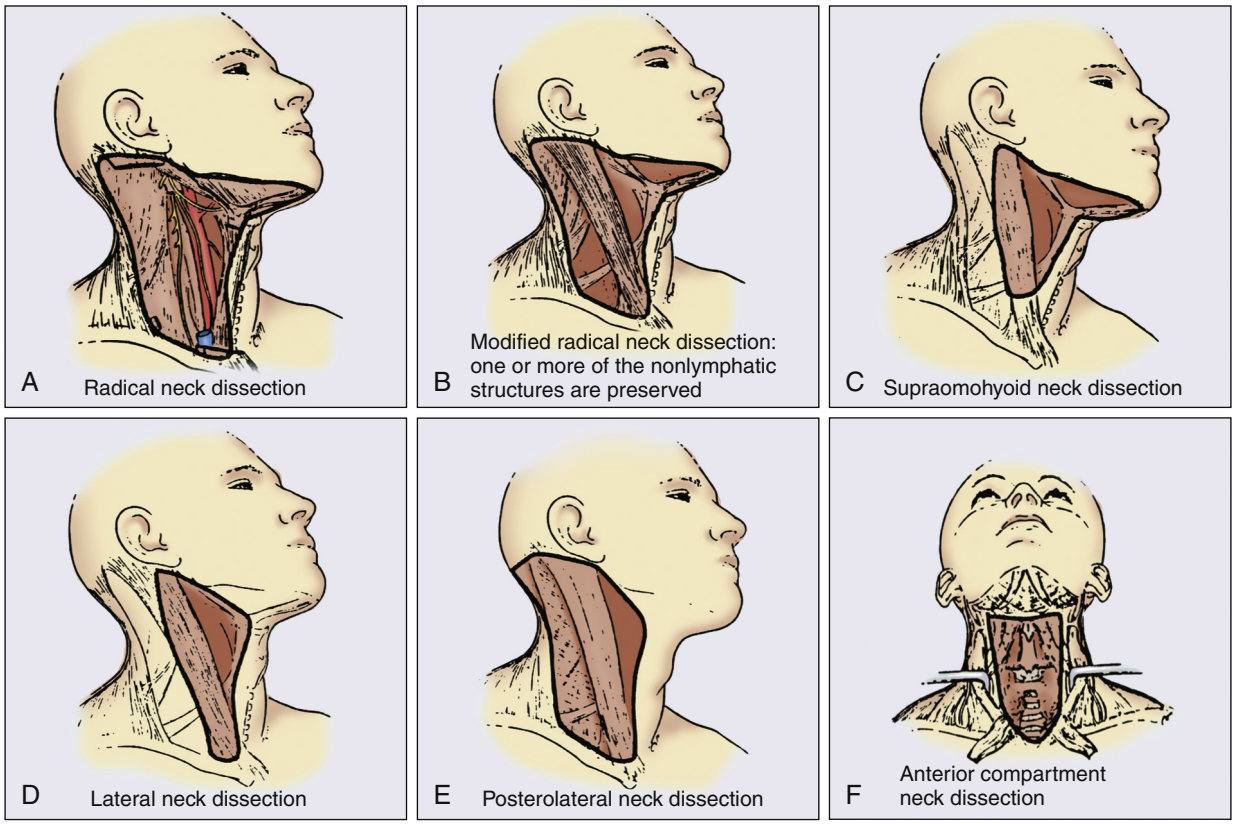

FIG. E5 Types of neck dissection. A, Radical. **B,** Modified radical: one or more of the nonlymphatic structures are preserved. **C,** Supraomohyoid. **D,** Lateral. **E,** Posterolateral. **F,** Anterior compartment. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

Health Care–Associated Infections (HAIs)

BASIC INFORMATION

DEFINITION

Health care–associated infections (HAIs) are infections associated with health care, generally occurring on or after the third calendar day of admission to a hospital. Surveillance classification criteria are established by the Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN). The definitions related to vascular catheter–related infections are summarized in Table E1.

SYNONYMS

Hospital-acquired condition (HAC)–CMS defines certain HAIs as HACs
Nosocomial infections
Hospital acquired infections

ICD-10CM CODES

A04.71	Enterocolitis due to *Clostridium difficile,* recurrent
A04.72	Enterocolitis due to *Clostridium difficile*, not specified as recurrent
B95.62	Methicillin-resistant *Staphylococcus aureus* infection as the cause of diseases classified elsewhere
J15.212	Pneumonia due to methicillin-resistant *Staphylococcus aureus*
A41.02	Sepsis due to methicillin-resistant *Staphylococcus aureus*
K68.11	Postprocedural retroperitoneal abscess
T81.41XA	Infection following a procedure, superficial incisional surgical site, initial encounter
T81.42XA	Infection following a procedure, deep incisional surgical site, initial encounter
T81.43XD	Infection following a procedure, organ and space surgical site, initial encounter
T80.219A	Unspecified infection due to central venous catheter, initial encounter
J95.851	Ventilator-associated pneumonia
T83.091A	Other mechanical complication of indwelling urethral catheter, initial encounter
T88.0XXA	Infection following immunization, initial encounter
T80.29XA	Infection following other infusion, transfusion and therapeutic injection, initial encounter
T80.211A	Bloodstream infection due to central venous catheter, initial encounter
T83.098A	Other mechanical complication of other urinary catheter, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Develop in at least 4% of hospitalized patients; over 1.7 million patients previously estimated.
- In 2011:
  1. HAIs accounted for more than 75,000 deaths.
  2. HAIs in the U.S. cost between $28 and $33 billion annually.
- At least one third of hospital-acquired infections are preventable.
- Leads to increased morbidity and mortality.
- Progress is tracked nationally to reduce HAIs.

PREVALENCE (IN U.S.): Estimated 648,000 patients with at least one HAI/yr in 2011

PREDOMINANT SEX:

- Overall, approximately equal
- Elderly women: Predominantly nosocomial urinary tract infections

PREDOMINANT AGE: Newborns and elderly patients (>60 yr) at highest risk

PEAK INCIDENCE: Varies widely with infection site

RISK FACTORS: Patients with the following conditions can develop HAIs at any age:

- In ICU
- Intubation
- Chronic lung disease
- Renal disease
- Comatose
- Chronic urethral or vascular catheterization
- Malnutrition
- Postoperative state
- Diabetes

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Vary with specific HAIs

ETIOLOGY

- Bacteria (gram-negative bacteria are responsible for >30% of HAIs)
- Fungi
- Viruses

SOURCES AND MODES OF TRANSMISSION:

- Patient's own flora
  1. Comprises resistant organisms associated with hospitalization
  2. Frequently maintained thereafter by persistent GI colonization
- Unwashed hands of staff
  1. Physicians
  2. Nurses
- Invasion of protective defenses (intact skin, respiratory cilia, urinary sphincters, and mucosa)
  1. IV lines/central lines
  2. Catheters
  3. Respiratory equipment
  4. Surgical wounds
  5. Scopes and other imaging devices. CP-CRE outbreaks occurred in recent yrs from difficult-to-clean duodenoscopes
- Failure to provide adequate negative pressure, high-volume air flow chambers for airborne infection isolation of patients with TB or disseminated herpes zoster or chickenpox
- Failure to rapidly identify and provide appropriate care (with isolation or precautions) for patients with communicable diseases
- Food
- Fomites
- Personnel attire can become contaminated. Although studies have not yet verified the link

TABLE E1 Definitions

	Definition	Comments
Catheter tip colonization	Positive culture of the catheter tip that grew to ≥15 cfu/ml (semi-quantitative), 10^2 cfu/ml (quantitative sonication), or 10^3 cfu/ml quantitative vortexing	Qualitative culture should no longer be used
Exit-site infection	Tenderness, erythema of site induration >2 cm	Positive culture of exudate confirms the exit-site infection microbiologically
Catheter-related bloodstream infection (CR-BSI)	One positive blood culture obtained from a peripheral vein and clinical manifestation of infection and (1) catheter tip colonization or (2) a differential time to positivity of more than 120 min and no obvious source of bacteremia except the catheter	Simultaneous quantitative culture from a peripheral vein and the catheter of 5:1 ratio is rarely used. NB: Exclusion of other sources of infection reveals important variability in the final classification in ICU patients. Purulence of the catheter exit site strongly implicates the catheter as the source of infection
Central line–associated bloodstream infection (CLA-BSI)	One positive blood culture and clinical manifestation of infection in a patient with a catheter in place with no other source of bacteremia except the catheter	Easy-to-collect definitions for epidemiologic purposes. Exposed to an overestimation of the BSI due to catheter infection, especially in ICU and oncohematologic patients
Catheter-related clinical sepsis	Clinical manifestation of infection that disappears within 48 h of catheter removal and a positive catheter tip culture and no other obvious treated source of infection	Represent 30%-50% of catheter-related infections with general manifestations. Not easy to collect routinely but may need antimicrobial treatment (see text)

BSI, Bloodstream infection; *ICU,* intensive care unit.
From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

between attire contamination and disease transmission, cross-contamination of previously washed hands can occur
- Inattention to safe injection practices has led to outbreaks of hepatitis and fungal meningitis
  1. Do not administer medications from a syringe to multiple patients even if the needle is changed.
  2. Use fluid infusion and administration sets (e.g., IV bags or bottles, tubing, connectors) for one patient only and dispose after each use. Do not use bags or bottles as a common source of supply for multiple patients.
  3. Use single-dose vials for parenteral medications whenever possible and do not administer medications from single-dose vials to multiple patients or combine leftover contents for later use.
  4. Single-dose, single-use vials do not have preservative and should be used for a single patient and a single case, procedure, and injection.
  5. When a single dose or single vial is accessed or opened, discard as per manufacturer or at the end of the case or procedure (whichever comes first).
  6. Insulin pens should be used for one single designated person only even if the needle is changed.

RISKS AMPLIFIED:
- Use of broad-spectrum antibiotics
  1. Select highly resistant bacteria.
  2. Establish multidrug-resistant bacteria as endemic flora in microenvironments within the hospital.
  3. Consider antibiotic stewardship programs to reduce these risks.
- May be required by accrediting agency or government
- Highly vulnerable patients with specific risk factors
  1. Immunosuppression (as a result of therapy, transplantation, AIDS)
  2. Old age
  3. Postsurgery
  4. Prolonged surgery
  5. Chronic lung disease
  6. Ventilator dependence
  7. Antacid therapy
  8. Vascular lines
  9. Hyperalimentation
  10. ICU stay
  11. Recent antibiotic therapy
- Clustering of seriously ill patients
  1. Often with wounds or contaminated drainage
  2. Intensifying probability of cross-infection

PREVENTION STRATEGIES: Handwashing and hand hygiene between all patient contacts is the single most important method of decreasing HAI:
- Regular soap and water for at least 15 sec.
- Chlorhexidine (particularly good for gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* [MRSA]), alcohol hand rub, or other antiseptic for resistant organisms.
- Purpose of soap and water handwashing:
  1. Degrease hand surfaces.
  2. Flush away oils and associated bacteria, removal of visible dirt or body fluids.
- Procedure:
  1. Lukewarm water
  2. Must include all surfaces
  3. Special attention to areas between fingers and to the dirtier dominant hand (most people reflexively wash the cleaner, nondominant hand more vigorously)
- Alcohol hand sanitizers:
  1. Improve handwashing frequency (less drying to hands, faster, and no need for wash basin and towels for drying)
  2. Significantly reduce HAIs
  3. Now recommended in essentially all routine health care settings
  4. Rub hands until dry, approximately 15 sec
- Environmental cleaning:
  1. New supplemental no-touch technologies such as hydrogen peroxide vapor or mist or ultraviolet irradiation appear to reduce environmental contamination from *Clostridium difficile* spores, *Norovirus*, and resistant microorganisms.
  2. Clinical equipment should be properly disinfected or sterilized per manufacturer's instructions.
  3. High-touch items in patient environment should undergo frequent, thorough disinfection.
  4. Follow manufacturer written instructions for required contact time with disinfectant.

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS:
- MRSA bacteremia decreased 13% between 2011 and 2014 in the U.S.
- Health care–associated MRSA strains are typically resistant to many antibiotics, remaining susceptible to vancomycin and trimethoprim–sulfamethoxazole.
- High-risk factors include dialysis, recent stay in acute or long-term care facilities.
- Control measures include hand hygiene, disinfection of equipment, protective attire for isolation, and standard precautions.
- Community-acquired MRSA (CA-MRSA) is associated with soft tissue, presenting as boils, rash, or so-called spider bite, and typically occurs in patients who have no recent health care or hospital interaction.
- CA-MRSA often not found in nares.
- CA-MRSA can be sensitive to fluoroquinolones, clindamycin, and/or erythromycin in addition to vancomycin and trimethoprim/sulfamethoxazole.

Refer to the topic "Methicillin-Resistant *Staphylococcus aureus*" for more information.

VANCOMYCIN-RESISTANT ENTEROCOCCUS FAECIUM (VREF):
- The percentage of HAIs caused by VREF increased more than twentyfold between 1989 and 1993, rising from 0% to 9%. By 2005, VREF, vancomycin-resistant *E. faecalis,* and other vancomycin-resistant species of enterococci had become common and endemic nosocomial pathogens accounting for 15% to 40% of all enterococci isolated in the hospital setting.
- A high percentage of VREF isolated, 80%, are also ampicillin resistant.
- Factors predisposing to VREF colonization or infection include a high percentage of hospital days receiving antibiotic therapy, use of IV, underlying disease, immunosuppression, and abdominal surgery.
- Evidence suggests that the vehicle is the hands of health care workers (HCWs).
- Control measures:
  1. Aggressive isolation of colonized or infected patients.
  2. Restraint in using broad-spectrum antibiotics.
  3. Compliance with hand-hygiene best practices.

Refer to the topic "Vancomycin-Resistant Enterococcus" for more information.

CLOSTRIDIUM DIFFICILE:
- Causes diarrhea as a result of pseudomembranous colitis.
- Accounts for 15% to 25% of health care–associated diarrhea. Recent survey found *C. difficile* was the third most common HAI and accounted for 70% of gastrointestinal HAIs.
- Warrants contact precautions and disinfection against spores, for example, properly diluted bleach, supplemental no-touch technology (silver, hydrogen peroxide vapor or mist, ultraviolet light, hypochlorous acid).
- Alcohol hand sanitizer likely does not eliminate spores of this organism: Can use soap and water to wash hands at sink.
- Spores can be dispersed in the air or room environment surrounding patients.
- Treatment is tiered based on severity. Vancomycin or fidaxomicin is recommended to treat initial onset.
- Rising incidence of *C. difficile* infection with emerging strains that have up to twenty-threefold more toxin production.
- Toxin assays vary widely in ability to detect toxin.
- Only unformed stool specimens should be submitted for laboratory *C. difficile* testing.
- Polymerase chain reaction (PCR) and nucleic acid amplification test/loop mediated isothermal DNA amplification (NAAT/LAMP) are more sensitive test methods than enzyme immunoassay (EIA).
- Antibiotics can predispose persons by altering their normal gut flora.
- Can present in healthy patients with no known risk factors.
- Sometimes causes toxic megacolon or fulminant colitis.

NOROVIRUS:
- Patients present with sudden onset of nausea, vomiting, and/or diarrhea
- Now considered yr round rather than seasonal
- Disinfection with bleach or agent with efficacy against norovirus.
- Often need to isolate exposed persons for average incubation period, such as 3 days, to prevent outbreak

SURVEILLANCE
- Crucial for early identification of infections. Enables:
  1. Immediate intervention
  2. Education
- Prospective, concurrent, hospital surveillance:
  1. Electronic data mining provides accurate review

2. Feasible with sophisticated computerized data collection and analysis
- Targeted surveillance addresses high-risk procedures and patient populations.
  1. May be mandated by state or federal government
- Routine rate calculations and statistical analyses:
  1. Use device-specific days, procedure-specific cases, or patient-days as denominators.
  2. Enhance early recognition of infections by body site and by organism.
  3. Facilitate proper early control of potential outbreaks.
- Active surveillance or screening cultures for multidrug-resistant organisms (MDROs); for example, high-risk populations for MRSA

Dx DIAGNOSIS

MOST COMMON HEALTH CARE–ASSOCIATED INFECTIONS:
- Device-associated infections (26%) (central line–associated bloodstream infections, catheter-associated urinary tract infections, and ventilator-associated pneumonias)
- Surgical site and other soft tissue infections (22%)
- Pneumonia (22%)
- GI infections (17%)

HEALTH CARE–ASSOCIATED UTIS:
- General associations:
  1. Indwelling urinary (e.g., Foley) catheters
  2. Inappropriate catheter care (including opening catheter junctions)
  3. Female sex
  4. Absence of systemic antibiotics
- Physical findings:
  1. Fever
  2. Dysuria
  3. Leukocytosis
  4. Pyuria
  5. Flank or costovertebral angle tenderness
- Usual organisms:
  1. *E. coli*
  2. *Candida* spp.
  3. *Enterococcus* spp.
  4. *Pseudomonas* spp.
  5. *Klebsiella* spp.
  6. *Enterobacter* spp.
- Sepsis in 1% to 3% of hospital-associated UTIs
- Prevention bundle to eliminate catheter-associated UTIs (CAUTIs):
  1. Use meticulous aseptic technique during insertion and daily perineal care.
  2. Avoid unnecessary urinary catheters; remove promptly.
  3. Never open the catheter-collection tubing junction (keep system closed).
  4. Obtain all specimens using sterile syringe.
  5. Secure the Foley.
  6. Remove Foley catheters as soon as possible.
  7. Substitute intermittent catheterization for Foley catheters.

HEALTH CARE–ASSOCIATED BLOODSTREAM INFECTIONS:
- General associations:
  1. IV lines
  2. Arterial lines
  3. Central venous pressure (CVP) lines: Lead to catheter-associated bloodstream infection (CLABSI)
  4. Phlebitis
  5. Hyperalimentation
  6. Lack of safe injection best practices
- Fever possibly only presenting sign
- Exit site of all vascular lines carefully evaluated for:
  1. Erythema
  2. Induration
  3. Tenderness
  4. Purulent drainage
- Usual organisms for device-associated bacteremia:
  1. *S. aureus* (including MRSA)
  2. *Staphylococcus epidermidis* for long-term IV lines
  3. *Enterobacter* spp.
  4. *Klebsiella* spp.
  5. *Candida* spp.
  6. *Pseudomonas aeruginosa* may come from a water source or reflect cutaneous bacteria
- Phlebitis in 1.3 million patients yearly
- Approximately 10,000 annual deaths from IV sepsis
- Prevention bundle to eliminate central line-associated bloodstream infections (CLABSIs):
  1. Meticulous sterile technique during central catheter line insertion.
  2. Emphasis should be placed on attention to detail, including handwashing, adherence to guidelines for catheter insertion and maintenance, appropriate use of antiseptic solutions such as chlorhexidine (CHG) to prepare the skin before central line insertion.
  3. Modified catheter, for example, antiseptic-coated line, may reduce risk for endoluminal colonization and catheter-related sepsis in subclavian lines.
  4. Decrease use of routine IVs and encourage PO intake.
  5. Avoid using a femoral vein insertion site. Subclavian central line site is associated with lower infection rate than jugular.
  6. Bundle to prevent CLABSIs includes hand hygiene, CHG skin prep for insertion of central lines, full barrier protection for insertion of central lines, removal of unnecessary lines, insertion checklist.
  7. Consider daily CHG baths in ICUs.
  8. In the U.S., 50% decrease in CLABSI between 2014 and 2018.
  9. Table E2 summarizes recommended strategies for prevention of catheter-related bloodstream infections (CR-BSI) in ICU patients.

TABLE E2 Main Recommended Strategies for Prevention of CR-BSI in ICU

Structure and Process of Care
Adequate nurse-to-patient ratio
Use only trained personnel who demonstrate competence for catheter insertion and maintenance
Educate, assess knowledge, and audit adherence to guidelines of ICU HCWs
Conduct a continuous quality-improvement program based on recommendations and adapted locally
Organize a follow-up of the institution's process of care and CR-BSI rate
Participate in a surveillance network
Catheter Insertion
Hand hygiene
Full barrier precautions for CVC insertion
Preparation of cutaneous site with chlorhexidine
Subclavian rather than jugular or femoral access (should be weighed against the risk of mechanical complications)
Avoid subclavian access for dialysis catheters
Subcutaneous tunneling for internal jugular or femoral short-term CVCs
Ultrasound guidance to reduce number of cannulation attempts and mechanical complications for jugular and femoral access
Use a sterile sleeve for all pulmonary artery catheters
Do not routinely replace CVCs (even using guidewire exchange procedure)
Chlorhexidine-sulfadiazine impregnated for short-term CVCs only if the level of CR-BSI is high despite implementation of a comprehensive strategy to reduce the rate of CR-BSI
Catheter Maintenance
Immediate dressing change if loosened, soiled, or moistened
Remove catheters as soon as possible after intended use
Daily visual inspection of the catheter site
Sterile transparent or gauze dressings for CVCs
Gauze when blood is oozing from the insertion site
Chlorhexidine-impregnated gels or chlorhexidine sponge dressings should be used to reduce CR-BSI from arterial catheters and CVCs
Replace tubing used to administer blood products and lipid emulsions (including propofol) within 24 hours of initiating the infusion
Replace administration sets no more frequently than at 4-day intervals, but at least every 7 days

CR-BSI, Catheter-related bloodstream infection; *CVC,* central venous catheter; *ICU,* intensive care unit; *HCW,* health care worker.
From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

HEALTH CARE–ASSOCIATED PNEUMONIAS:
- More common in ICUs
- General associations:
  1. Aspiration
  2. Intubation: Leads to ventilator-associated events (VAE) or ventilator-associated pneumonia (VAP)
  3. Altered consciousness
  4. Old age
  5. Chronic lung disease
  6. Postsurgery
  7. Antacids
  8. Head of bed not elevated
- Signs of pneumonia common among patients on general wards:
  1. Cough
  2. Sputum
  3. Fever
  4. Leukocytosis
  5. New infiltrate on chest x-ray examination
- Signs more subtle in ICUs because many patients have purulent sputum because of chronic intubation:
  1. Change in sputum character or volume
  2. Small changes on chest x-ray examination
- Usual organisms:
  1. *S. aureus* (including MRSA)
  2. *Pseudomonas aeruginosa*
  3. *Enterobacter* spp.
  4. *Acinetobacter* spp.
  5. *Klebsiella* spp.
- Less common organisms:
  1. *Stenotrophomonas* spp.
  2. *Legionella* spp., *Flavobacterium* spp.
  3. Respiratory syncytial virus (infants)
  4. Adenovirus
- 1% of hospitalized patients affected
- Mortality rate high (40%)
- Prevention bundle:
  1. Use meticulous sterile technique during suctioning and handling airway.
  2. Do not routinely change ventilator breathing circuits and components. For heat and moisture exchangers, no more frequently than every 48 hr.
  3. Drain respirator tubing without allowing fluid to return to respirator.
  4. Wash hands routinely to prevent colonization of patients and transfer of organisms among patients.
  5. Use of a bundle to prevent VAEs and VAPs to include elevate the head of bed, provide deep vein thrombosis (DVT) prophylaxis, provide peptic ulcer disease (PUD) prophylaxis, hold sedation, test for ability to extubate, control glucose, gastric decontamination.
  6. Consider oral mouth care with CHG for vented patients in ICUs.

SURGICAL AND HEALTH CARE–ASSOCIATED SOFT TISSUE INFECTIONS:
- Associations:
  1. Decubitus ulcers
  2. Surgical site risks: Contaminated or dirty or infected, the American Society of Anesthesiologists' (ASA) physical status classification of ASA 3 or 4, duration of surgery over national average, usually 3 hr
  3. Abdominal surgery
  4. Presence of drain
  5. Preoperative length of stay
  6. Surgeon
  7. Presence of other infection
- Physical findings:
  1. Decubitus ulcer with fluctuance at margin or under firm eschar
  2. Erythema extending >2 cm beyond margin of surgical wound
  3. Tenderness
  4. Induration
  5. Erythema
  6. Fluctuance
  7. Purulent drainage
  8. Dehiscence of sutures
- Usual organisms:
  1. *S. aureus* (including MRSA)
  2. *Enterococcus* spp.
  3. *Enterobacter* spp.
  4. *Acinetobacter* spp.
  5. *E. coli* spp.
- Prevention:
  1. Use careful skin care and frequent, proper positioning of patient to prevent decubitus ulcer.
  2. Use meticulous sterile surgical technique.
  3. Use properly washed and sterilized instruments, processed in accordance with manufacturer's instructions. Minimize immediate-use steam sterilization (formerly known as flash sterilization).
  4. Wash hands to decrease colonization when handling postoperative wound.
  5. Limit prophylactic antibiotics to 24 hr perioperatively.
  6. Double wrap contaminated dressings (hold in gloved hand and evert gloves over dressings) before disposal.
  7. Surgical Care Improvement Project (SCIP) bundle to include antibiotic prophylaxis selection, receipt of antibiotic within 1 hr before surgery, discontinuation of antibiotic within 24 hr of surgery end time, cardiac surgery patients with controlled 6 A.M. postoperative blood glucose, clip rather than shave prep, postoperative normothermia for colorectal surgery patients, removal of Foley catheter by end of postoperative day 2 (except for urologic, gynecologic, or perineal procedures, or on paralytics, vasopressors/inotropics during ICU stay).
  8. Preadmission nares MRSA screening often beneficial for open heart and orthopedic implants when time is allowed for decolonization, chlorhexidine showers, and appropriate antibiotic prophylaxis selection.
  9. Often, preadmission nares MRSA screening is also performed.
  10. Consider antiseptic shower the night before and the morning of surgery.

LABORATORY TESTS
- Appropriate to specific HAI and specific patient's condition
- Cultures generally indicated for proper confirmation of responsible pathogens:
  1. Urine
  2. Blood
  3. Sputum
  4. Soft tissue
- Molecular analysis of health care–associated epidemics:
  1. Plasmid fingerprinting
  2. Restriction endonuclease digestion (plasmid and genomic DNA)
  3. Peptide analysis
  4. Immunoblotting
  5. Ribosomal RNA (rRNA) typing
  6. DNA probes
  7. Multilocus enzyme electrophoresis
  8. Restriction fragment length polymorphism (RFLP)
  9. PCR
  10. Provide confirmation of point-source or common strains and corroboration of hypotheses reached using classic epidemiology

IMAGING STUDIES
Rarely needed for diagnosis of HAI; helpful for deep surgical site infection

Rx TREATMENT

ACUTE GENERAL Rx
- Appropriate to etiologic organism:
  1. Antibiotic
  2. Antifungal
  3. Antiviral
- Specific therapy determined after careful consideration of resident flora within the microenvironment in which the patient was hospitalized.
  1. Empiric therapy.
  2. Frequently difficult to fashion accurately.
  3. Often undesirable unless the patient's clinical condition requires urgent treatment.
- Consultation for expert advice regarding antibiotic selection in view of known epidemiologic risks within the hospital (hospital epidemiologist or infectious disease specialist).
- Avoid unnecessary treatment for organisms that are colonizing (no signs or symptoms of infection) but not infecting patients.
- Prevention of spread of communicable diseases.
  1. Isolation or precautions (airborne, droplet, contact isolation precautions, and combinations thereof).
  2. Classic schema (strict, respiratory isolation and contact [skin and wound] precautions) have been replaced by more streamlined revised guidelines (airborne, droplet, contact isolation precautions, and combinations thereof).
  3. Less careful response to some diseases (e.g., hemorrhagic fevers) inadvertently induced by removal of strict isolation category.
  4. Universal or standard precautions to protect HCWs against splash or splatter of blood or body fluids.
  5. Tracking roommates of patients with communicable disease, such as norovirus

or influenza, and using precautions during the incubation period.

- Universal or standard precautions used for all patients during all anticipated contacts with blood, body fluids, or secretions.
  1. Gloves.
  2. Goggles or eye shield.
  3. Gowns that prevent blood or potentially infectious materials from passing through.
- Consider aggressive isolation to restrict spread of multidrug-resistant organisms and their plasmids.
  1. MRSA.
  2. VREF.
  3. MDR-GNRs (multidrug-resistant gram-negative rods) can include extended-spectrum β-lactamases (ESBL), carbapenem-resistant Enterobacteriaceae (CP-CRE), and some *Acinetobacter baumannii.* New microbiology interpretive criteria (breakpoints) can result in no longer reporting mechanism of resistance.
  4. New Delhi metallo-β-lactamase 1 (NDM-1): These are gram-negative Enterobacteriaceae with a new type of carbapenem-resistance gene.
  5. Colistin-resistant *E. coli.* The *mcr-1* gene that makes bacteria resistant to colistin was found twice in the U.S. Most recently, an *mcr-9* gene was also found in a patient in the U.S. This resistance could move to other bacteria. Colistin is a last-resort antibiotic for treating patients with infection from multidrug-resistant organisms.
  6. VIM- and IMP-type metallo-ß-lactamase producers.

Refer to the topic "Multidrug-Resistant Gram Negative Rods" for more information.

DISPOSITION

The infection prevention and control service or hospital epidemiologist should be notified when infectious complications occur in the hospital setting; most, but not all, HAIs are potentially avoidable, and every effort should be taken to minimize the risk of infections associated with health care. Nationwide success in achieving and sustaining zero CLABSIs, zero CAUTIs, and zero VAPs warrants widespread use of infection prevention bundles to target zero HAIs.

REFERRAL

- To infection preventionist
- To hospital epidemiologist

PEARLS & CONSIDERATIONS

COMMENTS

- Sharp and splash injuries to staff are relatively rare, but nearly all are preventable.
  1. Nurses incur most injuries.
  2. Usual causes:
     a. Needle sticks
     b. Scalpel and surgical needle injuries
     c. Blood splashes
  3. Prevention:
     a. Never recap needles.
     b. Dispose of needles only in rigid, impermeable plastic containers.
     c. Clearly announce instrument passes in the operating room and during procedures. Use passing trays.
     d. Use needleless systems for vascular access and neutral displacement central line connectors.
     e. Use gloves, mask, and goggles/eye shield if aerosol or splash is likely.
     f. Never leave needles or other sharp items in beds.
     g. Never dispose of sharp items in regular trash bags.
  4. Infection prevention and control or employee health staff should be consulted immediately after exposure to determine need for prophylaxis for hepatitis B or HIV.
  5. All clinical staff should be immune to hepatitis B (natural or vaccine).
- Fungi previously considered to be contaminants are now risks for patients with cancer and organ transplantation.
  1. *Candida* spp.
     a. *C. auris*
     b. *C. guilliermondii*
     c. *C. krusei*
     d. *C. parapsilosis*
     e. *C. tropicalis*
     f. Note that *Candida auris* has emerged with resistance, sometimes to all three major classes of antifungal drugs. The fungus has spread quickly, causing outbreaks and resulting in invasive infection with higher risk of death. These multidrug-resistant isolates are often misidentified by automated lab systems. Contact precautions in a private room are recommended, with attention to thorough daily and terminal environmental disinfection. Current recommendation is for a disinfectant effective against spores.
  2. *Aspergillus* spp.
  3. *Curvularia* spp.
  4. *Bipolaris* spp.
  5. *Exserohilum* spp.
  6. *Alternaria* spp.
  7. *Fusarium* spp.
  8. *Scopulariopsis* spp.
  9. *Pseudallescheria boydii*
  10. *Trichosporon beigelii*
  11. *Malassezia furfur*
  12. *Hansenula* spp.
  13. *Microsporum canis*
- Focused, committed efforts by the entire health care staff continuously directed toward prevention:
  1. Each HAI addressed as an opportunity to improve the delivery of safe patient care always using best practices
  2. Essential for individual staff members to understand that small risks applied to large populations result in a large number of total events (i.e., HAIs)
- Antibiotic stewardship:
  1. Choose appropriate antibiotic.
  2. Minimize vancomycin use.
  3. Consider procalcitonin to guide antibiotic use for sepsis.
  4. Follow CDC core elements and checklist.
- The Centers for Medicare & Medicaid Services denies inpatient payments for certain HAIs. Total reimbursement is linked to performance by comparing HAI outcome with national benchmark, top percentile, and achieved standardized infection ratios (SIR).
  1. The number of surgical-site *S. aureus* infections acquired in the hospital, particularly cardiac or orthopedic, has been reduced by rapid screening and decolonizing of nasal carriers of *S. aureus* before surgery.
  2. Universal decolonization of ICU patients for MRSA has been advocated without nares screening as a model to reduce bloodstream infection and MRSA clinical isolates.

RELATED CONTENT

Clostridium difficile Infection (Related Key Topic)
Methicillin-Resistant *Staphylococcus aureus* (Related Key Topic).
Multidrug-Resistant Gram Negative Rods (Related Key Topic)
Vancomycin-Resistant Enterococcus (Related Key Topic)

AUTHOR: **Marlene Fishman Wolpert, MPH, CIC, FAPIC**

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Heart Block, Complete (PTG)

BASIC INFORMATION

DEFINITION

Complete heart block (CHB) is the absence of electrical impulse transmission from the atria to the ventricles when atrioventricular (AV) junction is not physiologically refractory, due to a functional or anatomical impairment of the conduction system, resulting in a bradycardia characterized by AV dissociation. It may be acquired or congenital. CHB can be permanent or reversible.

SYNONYMS

Third-degree AV block
CHB
Complete AV block

ICD-10CM CODE
I44.2 Atrioventricular block, complete

EPIDEMIOLOGY & DEMOGRAPHICS

- The prevalence of CHB is 0.04%.
- The prevalence of CHB increases with age.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Physical examination may be normal. Cannon A waves may appear in the jugular vein periodically due to the right atrium contracting during ventricular systole. Patients may present with the following clinical manifestations:

- Dizziness, palpitations
- Syncope or presyncope (due to reduced cardiac output)
- Fatigue, impaired exercise tolerance
- Mental status changes
- Congestive heart failure
- Angina pectoris
- Some patients may be asymptomatic (e.g., congenital CHB)

ETIOLOGY

- Fibrosis or sclerosis of the conduction system, Lenegre and Lev disease
- Acute myocardial infarction—inferior (14%) or anterior (2%) wall of patients, usually within 24 hours
- Drug effect (digitalis, calcium channel blockers, beta-blockers, amiodarone)
- Cardiomyopathy and myocarditis
- Infiltrative processes of the myocardium (amyloidosis, sarcoidosis, scleroderma, tumor)
- Metabolic abnormalities (hyperkalemia, hypoxia, hypothyroidism)
- Lyme carditis, rheumatoid nodules, polymyositis, Chagas disease
- Neuromuscular disorders (Becker muscular dystrophy, myotonic muscular dystrophy)
- Congenital (birth from mothers with systemic lupus)
- Hyperkalemia
- Familial: SCN5 sodium channel mutations have been associated with CHB
- Iatrogenic (cardiac surgery, catheter ablation of arrhythmias, percutaneous coronary intervention). Transcatheter aortic valve implantation (TAVI) is shown to be frequently associated with new conduction abnormalities; patients with preexisting right bundle branch block are at increased risk of CHB (resolves over time in most patients).
- Paroxysmal due to phase 4 block of the His-Purkinje system

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis includes lesser degree of AV block, automatic accelerated junctional rhythms, and nonconducted premature atrial contractions.
- The atrial rate must be faster than the ventricular rate (more As than Vs), and the junctional or ventricular rate is regular. Episodes of AV dissociation with an accelerated ventricular or junctional pacemaker overtaking the sinus node can often look like heart block on a single electrocardiogram.

WORKUP

- Workup such as routine labs, cardiac biomarkers, and cardiac imaging should be dictated by the clinical circumstances.
- ECG: Diagnostic of the disease (Figs. 1 and 2):
  1. P waves are present with a regular atrial rate that is faster than the ventricular rate.
  2. P waves are not related to the QRS complexes. The PR intervals are variable.
  3. RR intervals are regular.
  4. QRS complexes may be narrow with a rate of 40 to 60 beats/min (block proximal to His bundle) or wide with a rate of <40 beats/min (block distal to His bundle), depending on the location of the block in the conduction system.
  5. Complete AV block can result from block at the level of AV node, within the His bundle, or distal to it, in the Purkinje system.

TREATMENT

ACUTE GENERAL Rx

- Initial treatment should focus on the hemodynamic stability and symptoms of the patient.
- Fig. 3 illustrates the evaluation and management of third degree AV block.
- Consider temporary pacemaker insertion if ventricular escape rate is slow (<40 beats/min) and associated with symptoms or hemodynamic compromise as well as wide QRS escape rhythms, which can be unstable, and QT prolongation above 500 ms, increasing the risk of torsade de pointes ventricular tachycardias.
- CHB as a complication of inferior MI usually only requires temporary pacing; however, a CHB as a result of anterior MI often requires permanent pacing (Table 1).
- Acquired CHB usually requires pacing, but patients with congenital CHB often have sufficiently rapid escape rhythm to prevent symptoms and avoid permanent pacemaker implantation.
- Withdraw AV-nodal blocking agents if any.
- Short-term therapy (until adequate pacing therapy is established):
  1. Vagolytic agents such as atropine may be used to increase the rate of the escape rhythm (for AV nodal level blocks).
  2. Catecholamines such as isoproterenol transiently used for a CHB at any site (use with extreme caution or not at all in patients with coronary artery disease or in patients with digitalis toxicity).
  3. Percutaneous external cardiac pacing (uncomfortable for patients and not always reliably capturing the ventricle).
- Drugs cannot be relied on to increase HR for more than several hours or days without side effects; therefore, temporary or permanent pacemaker insertion is indicated.
- Symptomatic CHB in the absence of a condition that is likely to resolve is an ACC/AHA/HRS Class I indication for permanent pacemaker (PPM) placement.
- Class I indications for PPM placement in asymptomatic patients according to the ACC/AHA guidelines include:
  1. Patients in sinus rhythm, with documented asystolic pauses greater than or equal to 3.0 sec or an escape rate <40 beats/min, or with an escape rhythm that is below the AV node
  2. Patients with atrial fibrillation and bradycardia with one or more pauses of at least 5 sec or longer
  3. After catheter ablation of the AV junction
  4. If cardiomegaly or LV dysfunction is present with ventricular rates of 40 beats/min or faster
  5. Postoperative CHB that is not expected to resolve
  6. When it is associated with neuromuscular diseases, such as Erb dystrophy (limb-girdle muscular dystrophy), Kearns-Sayre syndrome, myotonic muscular dystrophy, and peroneal muscular atrophy
  7. CHB present during exercise in the absence of myocardial ischemia
- Therapy is directed toward the underlying etiology if there is a reversible source (i.e., IV antibiotics for Lyme disease).
- Table 2 summarizes the management of complete heart block.

CHRONIC Rx

Dual-chamber pacemaker implantation. Patients with a pacemaker need regular follow-up and pacemaker monitoring to ensure proper device functioning. Interest has developed recently in placing the ventricular pacing lead in the His bundle region, which can result in a narrow-paced QRS and may prevent ventricular dyssynchrony associated with traditional RV pacing.

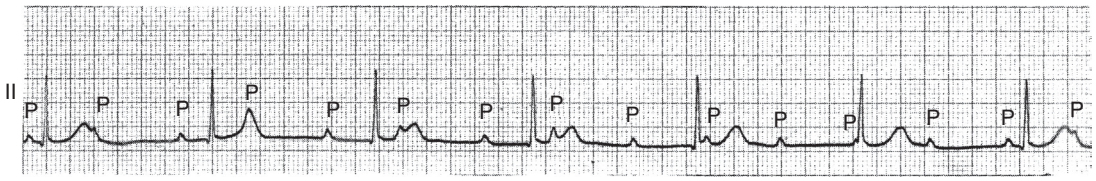

FIG. 1 Third-degree (complete) atrioventricular heart block is characterized by independent atrial (P) and ventricular (QRS) activity. The atrial rate is always faster than the ventricular rate. The PR intervals are completely variable. Some P waves fall on the T wave, distorting its shape. Others may fall in the QRS complex and be "lost." Notice that the QRS complexes are of normal width, indicating that the ventricles are being paced from the atrioventricular junction. (From Goldberger AL, [ed]: *Clinical electrocardiography,* ed 5, St Louis, 1994, Mosby.)

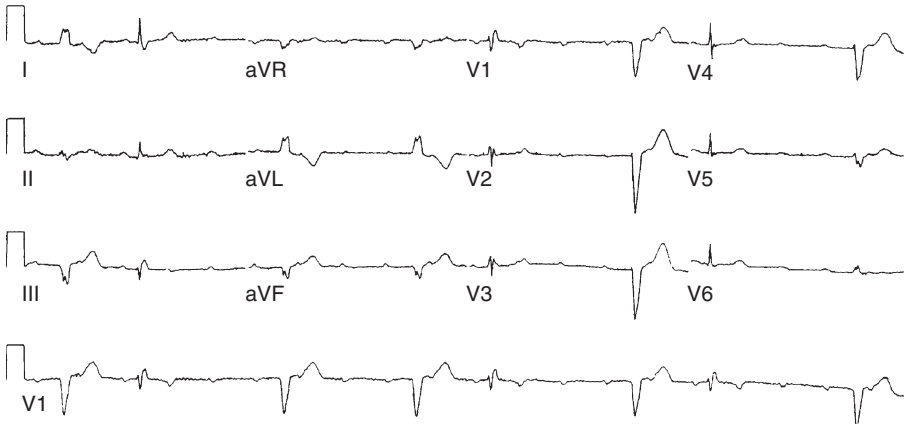

FIG. 2 High-grade atrioventricular block. Note that only three P waves conducted to the ventricle in the whole tracing. Conducted P waves were associated with normal PR intervals and right bundle branch block, a finding suggesting infranodal block. All other P waves were blocked, and ventricular escape rhythm with a left bundle branch block pattern is observed. Note that the block is not caused by retrograde concealment in the atrioventricular node or His-Purkinje system from the ventricular escape complexes because the conducted P waves occurred at a short cycle following the escape complexes. *aVF,* Augmented vector foot; *aVL,* augmented vector left; aVR, augmented vector right. (From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, WB Saunders.)

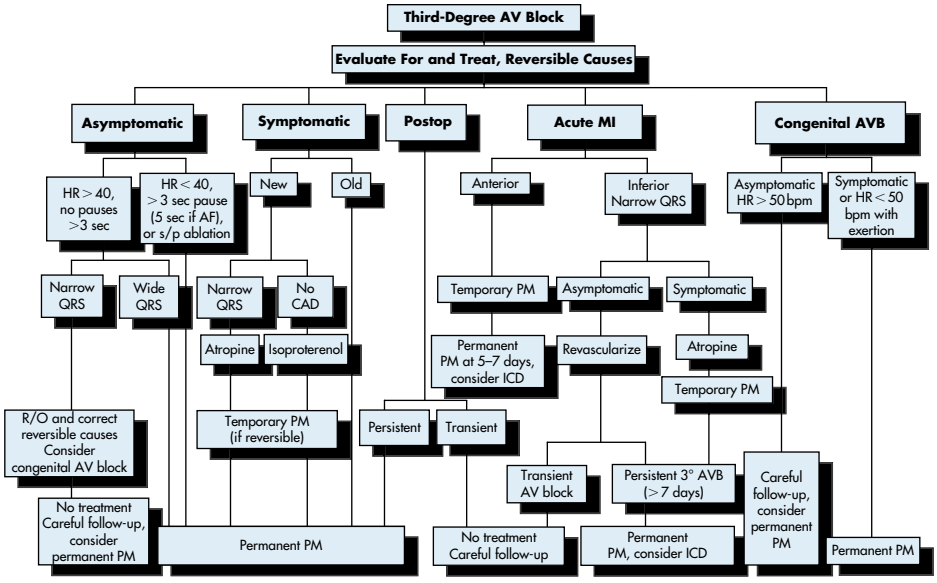

FIG. 3 Evaluation and management of third-degree atrioventricular *(AV)* block. *AF,* Atrial flutter; *AVB*, atrioventricular block; *bpm,* beats per minute; *CAD*, coronary artery disease; *HR,* heart rate; *ICD*, implantable cardioverter defibrillator; *MI*, myocardial infarction; *PM*, pacemaker; *R/O,* rule out; *s/p,* after. (From Olshansky B et al: *Arrhythmia essentials*, ed 2, Philadelphia, 2017, Elsevier.)

TABLE 1 Indications for Pacing in AV Block

Class I

1. Third-degree or advanced second-degree AV block at any anatomic level associated with any one of the following conditions:
   a. Symptoms (including heart failure) attributable to AV block *(Level of Evidence: C)*
   b. Arrhythmias and other medical conditions that require drugs that result in symptomatic bradycardia *(Level of Evidence: C)*
   c. Documented periods of asystole >3.0 seconds, any escape rate <40 beats/min, or any escape rhythm below the AV junction (e.g., a wide QRS morphology) in awake, asymptomatic patients in sinus rhythm *(Level of Evidence: C)*
   d. A documented period of asystole >5 seconds in awake, asymptomatic patients in atrial fibrillation *(Level of Evidence: C)*
   e. After catheter ablation of the AV junction *(Level of Evidence: C)*
   f. Postoperative AV block that is not expected to resolve after cardiac surgery *(Level of Evidence: C)*
   g. Neuromuscular diseases, such as myotonic muscular dystrophy, Kearns–Sayre syndrome, Erb (limb-girdle) dystrophy, and peroneal muscular atrophy, with or without symptoms of bradycardia *(Level of Evidence: B)*
2. Asymptomatic third-degree AV block at any anatomic site with an average awake ventricular rate >40 beats/min in patients with cardiomegaly or left ventricular dysfunction
3. Second-degree or third-degree AV block during exercise in the absence of myocardial ischemia (*Level of Evidence: C*)
4. Symptomatic second-degree AV block regardless of type or site of block (*Level of Evidence: B*)

Class IIa

1. Advanced second-degree or third-degree AV block at any anatomic site with an average ventricular rate >40 beats/min in the absence of cardiomegaly (*Level of Evidence: C*)
2. Asymptomatic second-degree AV block at intra- or infra-His levels found at electrophysiologic study (*Level of Evidence: B*)
3. First-degree or second-degree AV block with symptoms similar to those of pacemaker syndrome (*Level of Evidence: B*)
4. Asymptomatic type II second-degree AV block with a narrow QRS. When type II second-degree AV block occurs with a wide QRS, including isolated right bundle branch block, pacing becomes a Class I recommendation. (*Level of Evidence: B*)

Class IIb

1. AV block due to drug use or toxicity when the block is expected to recur even after withdrawal of the drug (*Level of Evidence: B*)
2. Neuromuscular diseases, such as myotonic muscular dystrophy, Kearns–Sayre syndrome, Erb (limb-girdle) dystrophy, and peroneal muscular atrophy with any degree of AV block (including first-degree AV block), with or without symptoms of bradycardia (*Level of Evidence: B*)

Class III

1. Asymptomatic first-degree AV block (*Level of Evidence: B*)
2. Asymptomatic type I second-degree AV block at a site above the His (i.e., the AV node) level or not known to be intra- or infra-Hisian by electrophysiologic study (*Level of Evidence: B*)
3. AV block expected to resolve and unlikely to recur (e.g., drug toxicity, Lyme disease, nocturnally in sleep apnea, early postoperative status, transient increases in vagal tone) (*Level of Evidence: B*)

AV, Atrioventricular.
From Bonow RO et al: *Braunwald's heart disease: a textbook of cardiovascular medicine,* ed 9, Philadelphia, 2012, WB Saunders.

DISPOSITION

- Mortality is highest in the neonatal period in congenital CHB.
- Prognosis is favorable after insertion of a pacemaker and is related to the underlying etiology of complete AV block (e.g., myocardial infarction, cardiomyopathy).
- Nonrandomized studies have shown that PPM insertion improves survival in patients with CHB.

REFERRAL

All patients with CHB should be referred to a cardiologist for consideration of temporary and/or PPM implantation.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients should be instructed to avoid activities that may damage the pacemaker (e.g., contact sports).
- Pacemaker manufacturers do not recommend any special restrictions regarding proximity to typical household items.
- All pacemaker manufacturers offer pacemakers that are MRI compatible. Older pacemaker models and leads may have a strong relative contraindication for MRI.
- Leadless pacemakers that are implanted directly into the right ventricle using a special delivery system are available for special indications and are primarily used for patients who are at high risk for traditional pacemakers and do not require dual-chamber pacing.
- Some medical procedures, such as lithotripsy, hyperbaric chamber, and electrocautery used during surgery, may require pacemaker programming and testing perioperatively.
- Table 3 describes the five-letter pacemaker code, and Table 4 summarizes common permanent pacemakers.

RELATED CONTENT

Complete Heart Block (Patient Information)

AUTHOR: **John Wylie, MD, FACC**

TABLE 2 Complete Heart Block Management

Setting	Therapy
Asymptomatic–Acquired	• Rule out reversible causes, including: Hyperkalemia Acute inferior MI Digoxin toxicity Excess calcium channel blocker therapy Lyme disease • If HR <40 bpm, first-line therapy is a permanent DDD pacemaker. • Temporary pacing is indicated if heart rate <40 bpm. The patient has impaired hemodynamics, and if permanent, pacing cannot be accomplished expeditiously. The CHB has an identifiable and reversible cause, while awaiting recovery. Temporary transvenous pacing must be used with caution in patients with any escape rhythm, particularly if wide QRS complex and slow. Overdrive suppression can occur rapidly. • If the rate of escape rhythm >40 bpm, permanent pacemaker insertion is controversial. • Temporary pacing is to be avoided in asymptomatic patients whose ventricular rates are >40 bpm, especially if the QRS complex is narrow. • CHB due to radio frequency ablation of the AV junction to control ventricular response rate in atrial fibrillation requires permanent pacing. May occur even if the patient is asymptomatic from a slow ventricular rate (40 bpm) that may be quite stable over time. Acquired CHB is associated with a poor short-term prognosis (>50% mortality in the first 6-12 mo after diagnosis). If irreversible, pacing is indicated.
Symptomatic	• A permanent pacemaker is indicated. • Temporary pacing is indicated if permanent pacing cannot be done expeditiously or if CHB has an identifiable and reversible cause (e.g., drug overdose).
Congenital	• Usually associated with a narrow QRS complex with an escape rhythm arising in the AVN. • Patients are usually asymptomatic. • In patients who are asymptomatic, the indications for a pacemaker are controversial. • Patients will need close follow-up, at least annually, for evaluation of symptoms suggesting chronotropic incompetence. • If symptomatic bradycardia, a permanent pacemaker is indicated. • If rate is consistently <50 bpm and does not increase with exercise (chronotropic incompetence), a permanent pacemaker is indicated.
MI	• If symptomatic bradycardia, a temporary pacemaker is indicated. • If CHB block occurs in the setting of an anterior infarction, permanent pacing is indicated if AVB persists. • CHB in inferior MI is generally in the AVN. There is usually no need for a permanent pacemaker, as it usually resolves. If it does not resolve, a permanent pacemaker may be indicated in some cases.
Preoperative	• Permanent pacemaker first, unless the surgery is emergent. • If surgery is emergent, insert a temporary pacemaker pre-op with the plan for a permanent pacemaker after surgery.
Postoperative	• Transcutaneous or temporary transvenous pacing. • A permanent pacemaker is indicated if there is permanent damage to the AV conduction system (e.g., after aortic valve surgery or VSD repair).

AV, Atrioventricular; *AVB,* atrioventricular block; *AVN,* atrioventricular node; *bpm,* beats per minute; *CHB,* complete atrioventricular block; *HR,* heart rate; *MI,* myocardial infarction; *VSD,* ventricular septal defect.
From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.

TABLE 3 Five-Letter Pacemaker Code

Letter 1 Chamber Paced	Letter 2 Chamber Sensed	Letter 3 Sensing Response	Letter 4 Programmability	Letter 5 Antitachycardia Functions
A = atrium	A = atrium	T = triggered*	P = simple	P = pacing
V = ventricle	V = ventricle	I = inhibited	M = multiprogrammable	S = shock
D = dual	D = dual	D = dual (A and V inhibited)	R = rate adaptive	D = dual (shock pace)
O = none	O = none	O = none	C = communicating	
			O = none	

*In the triggered response mode, the pacemaker discharges or fires when it recognizes an intrinsic depolarization. As a result, pacemaker spikes occur during inscription of the QRS complex. Because this mode results in high energy consumption and a shortened battery life and because the sensing response can be misinterpreted as pacemaker malfunction, this sensing mode is not used with modern pacemakers.
From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, WB Saunders.

TABLE 4 Common Permanent Pacemakers

Code	Indication	Advantages	Disadvantages
VVI	Intermittent backup pacing; inactive patient	Simplicity; low cost	Fixed rate; risk of pacemaker syndrome
VVIR	Atrial fibrillation	Rate responsive	Requires advanced programming
DDD	Complete heart block	Atrial tracking restores normal physiology	No rate responsiveness; requires two leads and advanced programming
DDDR	Sinus node dysfunction; for rate responsiveness atrioventricular block and need	Universal pacer; all options available by programming	Complexity, cost, programming, and follow-up evaluation

From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, WB Saunders.

Heart Block, Second-Degree PTG

BASIC INFORMATION

DEFINITION

Second-degree heart block or second-degree atrioventricular (AV) heart block is characterized by a failure of one or more, but not all, atrial impulses to conduct to the ventricles. The block may be at any level of the AV conduction system. In both types of second-degree heart block, the sinus rate will continue at regular intervals, resulting in a constant sinus rate. When more than one atrial impulse is present for each ventricular complex, the rhythm may be described as a ratio of the number of atrial impulses to the number of ventricular complexes. Electrocardiographically there are three types of second-degree block:

- Mobitz I (Wenckebach):
  1. Characterized by a progressive prolongation of the PR interval prior to a blocked nonconducted beat and a shorter PR interval after that blocked beat; the conducted impulse will generally be narrow. The cycle may repeat periodically, leading to "grouped beating."
  2. Site of block is usually AV node (proximal to the His bundle).
- Mobitz type II:
  1. Characterized by fixed PR intervals before and after blocked beats and may be associated with a wide QRS morphology (right bundle branch block [RBBB] or left bundle branch block [LBBB] patterns).
  2. Site of block is usually infranodal, especially when QRS is wide.
  3. It has a greater propensity for progressing to third-degree AV block.
- Pure 2:1 conduction patterns cannot be reliably classified as Mobitz type I or type II because there are not enough P waves to characterize prolongation of the PR interval.

SYNONYMS

Wenckebach block (Mobitz type I block)
Mobitz type II block
AV block

ICD-10CM CODES

I44.1	Atrioventricular block, second degree
I45.5	Other specified heart block
Q24.6	Congenital heart block

EPIDEMIOLOGY & DEMOGRAPHICS

Mobitz type I block is more common and may occur in individuals with heightened vagal tone or as a side effect of medications, such as β-blockers or calcium channel blockers.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with Mobitz type I are usually asymptomatic. Patients with either type may feel palpitations or the feeling of "missing a beat." Sudden loss of consciousness without warning (Adams-Stokes attack) can occur in patients with Mobitz type II; however, it is much more common in patients with complete heart block.
- Type I block: There is gradual decrease in the intensity of the first heart sound with widening of the a-c interval in the central venous waveform, ending in a pause, and an a wave not followed by a v wave in the neck along with an irregular pulse.
- Type II block: The first heart sound retains a constant intensity, with intermittent ventricular pauses and a waves not followed by v waves in the neck. There is an irregular pulse for most times with intermittent pauses.

ETIOLOGY

- High vagal tone (young patients, athletes at rest)
- Degenerative changes in the AV conduction system
- Ischemia at the AV nodes (type I with inferior wall myocardial infarction [MI] and type II with anterior wall MI)
- Drugs (digitalis, quinidine, procainamide, adenosine, calcium channel blockers [nondihydropyridines], β-blockers)
- Cardiomyopathies, collagen vascular diseases, infiltrative diseases (amyloidosis, sarcoidosis, hematochromatosis)
- Myocarditis/endocarditis (infectious, e.g., Lyme disease, Chagas disease; and noninfectious, e.g., systemic lupus erythematosus)
- Hyperkalemia, hypermagnesemia
- Hypothyroidism
- Prior cardiac valve surgery
- Catheter trauma, catheter ablation for arrhythmias

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The ECG easily and reliably distinguishes Mobitz type I from Mobitz type II block and from other conduction abnormalities. It should be distinguished from the less common phenomenon of second-degree sinoatrial node exit block.

Mobitz type I block with a normal QRS complex tends to be benign and usually does not progress to more advanced forms of AV conduction within a short period of time because the disease is mostly confined to within the AV node. Mobitz type II block often precedes the development of Adams-Stokes syncope, symptoms are frequent, prognosis is compromised, and progression to third-degree AV block is common and sudden. Thus, type II second-degree AV block with a wide QRS typically indicates diffuse conduction system disease involving even the infranodal His-Purkinje system.

WORKUP

ECG, ambulatory monitoring (Holter or external loop recorders) in selected patients

- Mobitz type I (Fig. 1) ECG shows:
  1. Sequential and gradual prolongation of PR interval leading to a nonconducted P wave
  2. Shortened PR interval following the pause as compared with the pre-pause PR interval
  3. Progressive shortening of the R-R interval prior to nonconducted atrial impulse
  4. Usually see "grouped beating" pattern
- Mobitz type II ECG shows (Fig. 2):
  1. Fixed duration of PR interval with constant P-P and R-R intervals
  2. Sudden nonconducted P wave
  3. Abnormal QRS duration or fascicular blocks are common
- In 2:1 AV block (Fig. 3), it cannot be determined based on the 12-lead ECG whether there is Mobitz type I or type II AV block, although a wide QRS complex is suggestive of Mobitz type II.
  1. Administering atropine can improve AV conduction if the AV block is type I or within the AV node; however, if it is infranodal (i.e., type II), the increased sinus rate caused by atropine may worsen the ratio of AV conduction, resulting in worsening bradycardia.
  2. Exercise stress testing may function in the same way as atropine above. If the disease is confined to the AV node, it may improve with exercise, but in cases of Mobitz type II AV block, the degree of AV block will worsen.
  3. Carotid sinus stimulation and other vagal maneuvers may worsen the AV block if it is at the level of the AV node (i.e., Mobitz type I) but will paradoxically improve the ratio of AV conduction by slowing down the sinus rate if it is a Mobitz type II or infranodal AV block.
  4. An algorithm for evaluation of patients with 2:1 AV block is illustrated in Fig. 4.

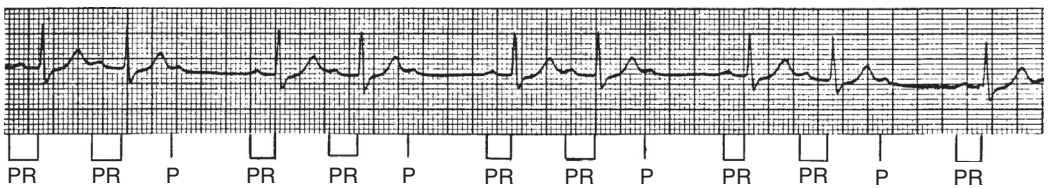

FIG. 1 Wenckebach (Mobitz type I) second-degree atrioventricular block. Notice the progressive increase in PR intervals, with the third P wave in each sequence not followed by a QRS. Wenckebach block produces a characteristically syncopated rhythm with grouping of the QRS complexes (group beating).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Elimination of drugs that may induce AV block such as digoxin, beta-blockers, and calcium channel blockers

ACUTE GENERAL Rx

- Treatment is usually not necessary unless the resting heart rate is <40 beats per min (bpm) while awake.
- If symptomatic (e.g., dizziness), atropine 1 mg (may repeat once after 5 min) may be tried to increase AV conduction; if no response, trial of dobutamine or isoproterenol may be helpful prior to insertion of a pacemaker.
- Atropine:
  1. Reduces heart block due to hypervagotonia but not due to AV node ischemia
  2. Does not increase infranodal conduction (third-degree and second-degree AV block that is below the AV node)
  3. Should be used with caution in Mobitz type II AV block due to possible paradoxical decrease in heart rate (as atrial rate increases, AV conduction decreases)
  4. Is ineffective in heart transplantation patients
- If associated with anterior wall MI and wide QRS complex, consider insertion of a temporary pacemaker.
- Indications for permanent pacemaker (PPM) implantation by ACC/AHA/HRS 2008 guidelines:
  1. Second-degree AV block with associated symptomatic bradycardia regardless of the type or site of the block (class I; level of evidence: B)
  2. Second-degree AV block provoked by exercise in the absence of myocardial ischemia (class I; level of evidence: C)
  3. Asymptomatic second-degree AV block at intra- or infra-His levels found at electrophysiologic study (class IIa; level of evidence: B)
  4. First- or second-degree AV block with symptoms similar to those of pacemaker syndrome or hemodynamic compromise (class IIa; level of evidence: B)
  5. Asymptomatic type II second-degree AV block with a wide QRS, including isolated right bundle branch block (class I; level of evidence: B)

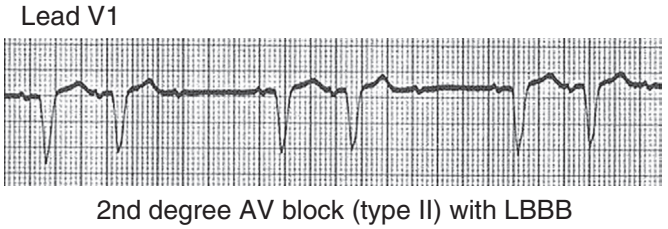

FIG. 2 Mobitz type II atrioventricular (AV) block with left bundle branch block (LBBB). Note the fixed P-P intervals with no change in PR intervals followed by a sudden nonconducted P wave. The LBBB indicates infranodal disease in the His-Purkinje system that is suggestive of Mobitz type II block.

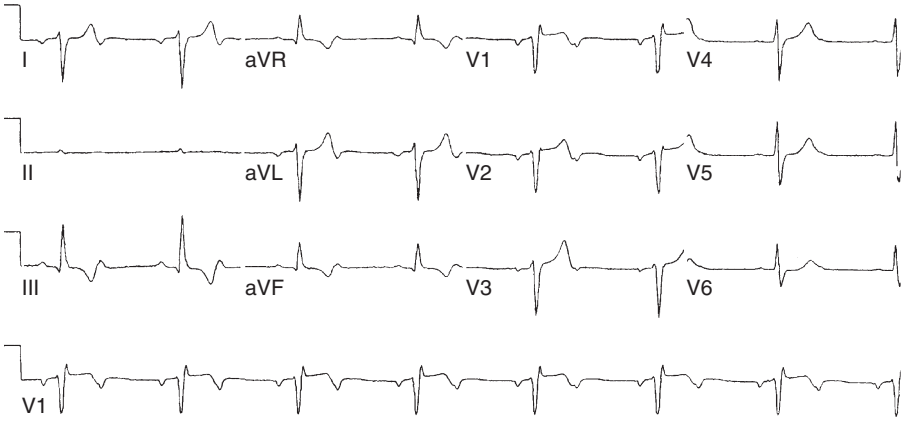

FIG. 3 Second-degree 2:1 atrioventricular block. Notice the short PR interval during conducted complexes and the wide QRS complexes, suggesting block in the His-Purkinje system. (From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, WB Saunders.)

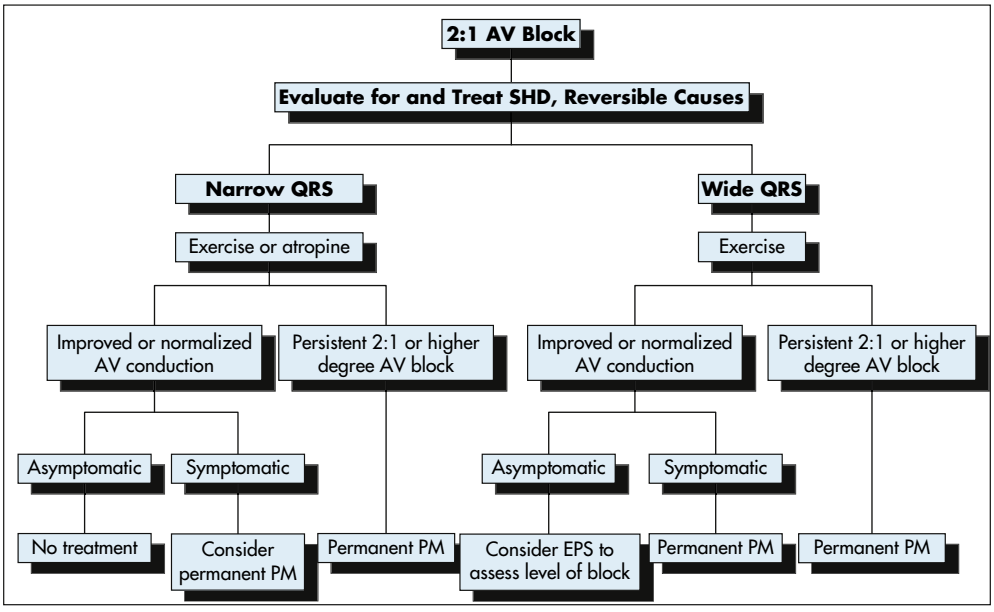

FIG. 4 Evaluation and management of 2:1 AV block. *AV*, Atrioventricular; *EPS*, electrophysiology study; *PM*, pacemaker; *SHD*, structural heart disease (no overt evidence of myocardial, valvular, congenital, or coronary heart disease.) (From Olshansky B et al: *Arrhythmia essentials*, ed 2, Philadelphia, 2017, Elsevier.)

6. PPM is not indicated for asymptomatic type I second-degree AV block at supra-His (AV node) level or that which is not known to be intra- or infra-Hisian (class III; level of evidence: C)

- Table 1 summarizes the management of Mobitz type I second-degree AV block.
- Table 2 summarizes the management of Mobitz type II second-degree AV block.

DISPOSITION

Prognosis is good with insertion of a pacemaker.

REFERRAL

Referral for pacemaker insertion (see "Acute General Rx")

PEARLS & CONSIDERATIONS

COMMENTS

Patients with symptomatic Mobitz type II should be referred for a pacemaker. Asymptomatic patients should be referred if the AV block worsens with exercise and should be followed up routinely for potential development of high-grade AV block.

RELATED CONTENT

Second-Degree Heart Block (Patient Information)

AUTHOR: **Aleem I. Mughal, MD**

TABLE 1 Mobitz Type I Second-Degree Atrioventricular Block Management

Setting	Therapy

Outpatient—Asymptomatic	• Treadmill testing will help assess chronotropic competence (if this rhythm is not related to myocardial ischemia), as well as enhance AVN conduction, thereby reducing the degree of Wenckebach block (e.g., from 5:4 to 8:7 or producing first-degree AVB only).
	• Holter monitoring can assess the degree and level of AVB and the persistence of the problem during activities of daily living and any diurnal variation.
	• If the QRS duration is wide and Holter monitoring or stress testing suggests infranodal block, an electrophysiology study may help to confirm the level of AVB.
	• If block is demonstrated to be intra- or infra-Hisian, permanent pacemaker implantation is reasonable, even in an asymptomatic patient. On occasion, intra-Hisian block can be demonstrated in a patient with a narrow, normal-appearing QRS complex by the production of higher degrees of AV block during treadmill testing with the increase in sinus rate.
	• No therapy.
	  • If not due to reversible cause (e.g., drugs or transient damage to the AV node from Lyme disease) and the QRS duration is normal, as more advanced or complete heart block rarely develops.
	  • There may be increased risk of syncope and symptoms in the future.

Outpatient—Symptomatic	• Some AV nodal blocking drugs (digoxin, β-adrenergic blockers, calcium blockers) may be the cause and should be reduced or stopped, if possible, and then only if severe symptomatic bradycardia occurs.
	• If older or at high risk for structural heart disease, consider an echocardiogram to assess LV function (even if no physical findings are present).
	• If due to a correctable cause such as AV nodal blocking drugs, stop the drug, if possible.
	• If there is a wide QRS or bundle branch block, it is possible that Wenckebach can be due to a block below the AV node (in the His-Purkinje system).
	  • In this case, permanent pacemaker implantation is indicated.
	  • Acutely, intravenous atropine or oral theophylline usually increases conduction through the AV node.
	  • These may paradoxically decrease ventricular rate and increase the degree of block if the block is below the bundle of His.
	• Permanent pacemaker implantation is indicated if symptomatic second-degree AVB is not otherwise correctable.

MI	• Is often reversed during thrombolysis or angioplasty.
	• May also appear for the first time concomitantly with these procedures.
	• Transient in nature
	• Temporary DDD pacing for the following:
	  • Persistent low heart rate (<40 bpm)
	  • Low cardiac output
	  • Ischemia
	  • Refractory hypotension
	  • Symptoms of light-headedness and dizziness
	• Atropine or theophylline may reverse the block but can cause unwanted tachycardia during drug administration.
	• These drugs are only rarely indicated except at the time of presentation of the patient.
	• Atypical AV block is more common in inferior-posterior MIs due to the Bezold-Jarisch reflex and the effect of increased vagal tone on the AV node.
	  • This is usually transient, and unless there is hemodynamic collapse, there is no need for a temporary pacemaker.
	  • Rarely is there a need for a permanent pacemaker. This is true even if transient third-degree (complete) AV block occurs, as high degrees of block tend to resolve over 5-7 days.
	  • If the AV block does not resolve but the ventricular rate is >40 bpm, no therapy is required if patient is asymptomatic.
	  • If the block does not resolve after 7 days and/or the ventricular rate is <40 or if patient is symptomatic, a permanent pacemaker is indicated.

Preoperative	• Assess drugs given and their need; stop offending drugs that enhance vagal tone, if possible. • If no symptoms, no therapy. • If symptomatic and no reversible causes, provide temporary pacing before surgery. • Need for permanent pacing can be accomplished in the postoperative setting. • Atropine or isoproterenol may be given to increase AV node conduction if symptomatic or hemodynamically significant.
Postoperative	• Rare after CABG but, if it occurs, consider an offending drug or transient ischemia to the AV node. • No therapy is generally needed. • If associated with wide QRS complex, consider block below the His. • If it persists, consider an EP study to assess the level of the block. • If patient is asymptomatic and block is above His, no need for permanent pacemaker. • If patient is symptomatic or block is below the His, permanent pacemaker is indicated. • If the block is associated with valve (especially aortic) surgery, consider direct damage to the AV node. • If persistent, a pacemaker is indicated for symptoms or persistent slow rate (<40 bpm or no increase in rate with exercise).

AV, Atrioventricular; *AVB*, atrioventricular block; *AVN*, atrioventricular node; bpm, beats per minute; *CABG*, coronary artery bypass graft; *DDD*, dual-chamber; *EP*, electrophysiology; *LV*, left ventricular; *MI*, myocardial infarction.

From Olshansky B et al: *Arrhythmia essentials*, ed 2, Philadelphia, 2017, Elsevier.

TABLE 2 Mobitz Type II Second-Degree Atrioventricular Block Management

Setting	Therapy

Outpatient—Asymptomatic	• Risk for complete heart block and death is significant (approximately 50%).
	• A dual-chamber permanent pacemaker is recommended as the pacing system of choice.
	  • Admit the patient for a permanent pacemaker and place on a cardiac monitor.
	  • In the absence of symptoms or progressive (higher-degree AVB), there is no need for a temporary pacemaker before permanent pacemaker implantation.
	  • Avoid atropine.
	  • Evaluate for the presence of underlying cardiac disease, such as infiltrative processes (e.g., amyloid) or MI.

Outpatient—Symptomatic	• Dual-chamber permanent pacemaker implantation is indicated.
	• Admit the patient and place on a cardiac monitor.
	  • If symptomatic or hemodynamically detrimental ventricular bradycardia is present, a temporary pacemaker is indicated if a permanent system cannot be placed expeditiously.
	  • Do not give atropine because this may worsen the AVB and produce a slower ventricular rate.
	  • Exercise, sinus tachycardia, and catecholamines also can worsen the degree of block by enhancing AV nodal conduction and impinging on the refractory period of the His-Purkinje system.

MI	• Place temporary pacemaker.
	  • Mobitz type II second-degree AVB is associated with a high rate of heart failure in this setting.
	  • A permanent pacemaker is indicated if the AVB is persistent because the risk of complete heart block is >50%.
	  • Long-term prognosis may not be improved.
	  • Avoid the use of antiarrhythmic drugs (including lidocaine) in the absence of a pacemaker, unless there is sustained ventricular tachyarrhythmia, as these drugs may worsen the degree of AVB.
	  • Do not give atropine.
	  • Mobitz type II second-degree AVB has a lower (albeit not known with certainty) incidence in the current early revascularization era, but if present or of new onset may improve with time, but this is rare. After being present and persistent, a pacemaker will likely be needed.

Preoperative	• Place permanent pacemaker.
	  • If urgent or emergent surgery, place a temporary pacemaker with the plan for a permanent pacemaker after surgery.
	  • If CABG, epicardial atrial and ventricular wires can be placed, with temporary pacing as standby, until a permanent transvenous pacemaker can be placed.
	  • It is best to place the permanent pacemaker after CABG or other cardiac surgery as leads otherwise tend to dislodge.
	  • If endocarditis, temporary pacemaker until infection resolves and after cardiac surgery.
	  • Avoid antiarrhythmic drugs and atropine.

Postoperative	• If bradycardia, temporary pacing (via epicardial wires, if present, after cardiac surgery).
	• Temporary Mobitz type II AV block may resolve after cardiac surgery.
	  • It may be due to trauma near the His-Purkinje system (e.g., with aortic valve surgery, where left bundle branch block is a not-infrequent accompaniment).
	  • Persistent (e.g., more than 3-5 days) Mobitz type II block will require permanent pacing.
	  • No antiarrhythmic drugs should be given unless an adequate backup ventricular pacing is available.
	  • Endocarditis with abscess near the septum can destroy the His-Purkinje system.
	  • Despite surgical repair, permanent pacing will likely be required.
	  • For patients having tricuspid valve replacement, an endocardial lead can occasionally be placed across a porcine bioprosthesis without producing tricuspid regurgitation but should be avoided if there is a mechanical valve.
	  • Tricuspid valve repair (e.g., annuloplasty) should not pose a problem in positioning a right ventricular lead.

AV, Atrioventricular; *AVB*, atrioventricular block; *CABG*, coronary artery bypass graft; *MI,* myocardial infarction. From Olshansky B et al: *Arrhythmia essentials*, ed 2, Philadelphia, 2017, Elsevier.

BASIC INFORMATION

DEFINITION

Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The cardinal manifestations of heart failure are dyspnea, fatigue, and fluid retention. The pathophysiology of HF (Fig. E1) is related to progressive activation of the neuroendocrine system to compensate for decreased effective circulating volume (Table 1), leading to total body volume overload and circulatory insufficiency. These events culminate in the development of pulmonary congestion as well as peripheral edema. Specifically, the renin-angiotensin-aldosterone system (RAAS) is implicated; once activated, it can lead to volume expansion (sodium retention) and cardiac fibrosis (mediated through angiotensin II). Another recognized mechanism is disordered adrenergic stimulation as a key component of progression of disease. The term *congestive heart failure* (CHF) usually denotes a volume-overloaded status as a result of HF. Given that not all patients have volume overload at the time of the evaluation, *congestive heart failure* should be distinguished from the broader term *heart failure*.

CLASSIFICATION: The American College of Cardiology/American Heart Association (ACC/AHA) describes the following four stages of HF. This staging model was designed to emphasize the evolution and progression of HF over a continuum and the preventability of HF in at-risk patients.

Stage A: Patients at high risk (e.g., with hypertension, atherosclerotic disease, diabetes mellitus, metabolic syndrome, cytotoxin, family history) for HF but without structural heart disease or symptoms of HF

Stage B: Patients with structural heart disease (e.g., left ventricular [LV] dysfunction) but without symptoms of HF

Stage C: Patients with structural heart disease with prior or current symptoms of HF

Stage D: Patients with refractory HF requiring specialized interventions

In addition to the ACC/AHA stages described above, the New York Heart Association (NYHA) defines four functional classes of HF designed to describe the symptoms of stage C and D HF. The functional classes are intended to assess the symptoms of HF and may fluctuate with therapy. It should be noted that current guidelines employ the functional classes to aid in determination of appropriate treatment.

I. Asymptomatic or symptomatic only at activity levels that would limit normal individuals

II. Symptomatic with ordinary exertion (e.g., 2 city blocks or 1 flight of stairs in a faster than usual pace)

III. Symptomatic with less than ordinary exertion (e.g., less than 2 city blocks or 1 flight of stairs)

IV. Symptomatic at rest

Table 2 compares the ACC/AHA and the NYHA classification. Table 3 describes a simplified classification and common clinical characteristics of patients with acute heart failure.

TERMINOLOGY: Although HF has traditionally been classified as systolic vs. diastolic, this was dependent on the imaging modality used. With noted variation in the observed systolic function between studies, the ejection fraction serves as a better marker. HF is now categorized into *HF with reduced ejection fraction* (HFrEF) and HF with *preserved ejection fraction* (HFpEF). Other common classifications include right-sided vs. left-sided and high-output vs. low-output. Systolic HF or HFrEF is defined by the presence of impaired contractility of the LV, as measured by ejection fraction (EF) ≤40% with clinical signs or symptoms of HF. In contrast, HFpEF has been described as evidence (clinical) of HF with an EF ≥50% with or without evidence of diastolic dysfunction. There are two further classifications of HFpEF: HFpEF borderline, used to describe patients with an EF 41% to 49%, and HFpEF improved, used to describe patients who previously had HFrEF with an improvement in their EF.

Right-sided HF denotes peripheral signs and symptoms of HF without evidence of pulmonary congestion, as opposed to left-sided HF, which typically manifests with pulmonary congestion and subsequent signs and symptoms of right-sided HF. The most common cause of right-sided HF is left-sided HF. High-output HF involves signs and symptoms of HF but features an elevated cardiac output unable to meet the abnormally high metabolic demands of peripheral tissues and is the result of myriad systemic disorders (e.g., systemic arteriovenous fistulas, hyperthyroidism, anemia). The term *acute decompensated HF* (ADHF) refers to worsening of signs or symptoms of HF due to a wide range of causes. Of note, HF is not equivalent to cardiomyopathy or LV dysfunction. These latter terms describe the possible structural or functional reasons for the development of HF, whereas HF is a clinical syndrome characterized by specific symptoms and signs.

SYNONYMS

HF
Congestive heart failure
CHF
Cardiac failure
Cardiogenic shock
Cardiogenic pulmonary edema

ICD-10CM CODES

I50.20	Unspecified systolic (congestive) heart failure
I50.21	Acute systolic (congestive) heart failure
I50.22	Chronic systolic (congestive) heart failure
I50.23	Acute on chronic systolic (congestive) heart failure
I50.30	Unspecified diastolic (congestive) heart failure
I50.31	Acute diastolic (congestive) heart failure
I50.32	Chronic diastolic (congestive) heart failure
I50.33	Acute on chronic diastolic (congestive) heart failure
I50.40	Unspecified combined systolic (congestive) and diastolic (congestive) heart failure
I50.41	Acute combined systolic (congestive) and diastolic (congestive) heart failure
I50.42	Chronic combined systolic (congestive) and diastolic (congestive) heart failure
I50.43	Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure
I50.9	Heart failure, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- There is variability in the reported demographics of HF due to heterogeneous definitions and classifications of HF. Incidence rate is lowest among white women and highest among black men. African Americans have the highest risk for HF of the demographic groups with blacks having a higher 5-yr mortality rate than whites.
- The lifetime risk of developing HF is 20% for Americans ≥40 yr of age.
  1. In the U.S., HF incidence has largely remained stable over the past several decades, with >650,000 new HF cases diagnosed annually.
  2. There has been an increase in the prevalence of HF in the population over time. This is primarily due to improved treatment of hypertension and valvular and coronary disease, allowing patients to survive an early death only to later develop HF.
- HF is primarily a condition of the elderly. Approximately 80% of patients hospitalized with HF are older than 65 yr. HF is the most common inpatient diagnosis in the U.S. for patients aged >65 yr.
- HF incidence increases with age, rising from approximately 20 per 1000 individuals 65 to 69 yr to >80 per 1000 individuals among those >85 yr. Before age 75, the incidence of HF is higher in males, but both sexes are equally affected after this age cutoff.
- In the U.S., 1.1 million hospital discharges and 3.2 million hospitalizations/ambulatory care visits were associated with HF in 2007.
- Prevalence: 5.1 million persons in the U.S. and an estimated 23 million persons worldwide. The prevalence of HF is rising, especially in the elderly, particularly due to aging of the population and improved survival from other conditions.
- The estimated (direct and indirect) cost of HF in the U.S. was >$40 billion in 2012, with over half of these costs spent on hospitalizations. The mean cost of HF-related hospitalizations is $23,077 per patient and is higher when HF was a secondary rather than the primary diagnosis.
- HFrEF and HFpEF each make up about half of the overall HF burden.
- Among patients with HF in one large population study, hospitalizations were common

TABLE 1 Compensatory Mechanisms in Heart Failure

Compensatory Response	Stimuli	Beneficial Effects	Adverse Effects	Potential Pharmacologic Interventions
Renin-angiotensin system activation	↓CO/BP ↓Renal blood flow ↑β-adrenergic activity	Maintain vital organ perfusion through vasoconstriction and sodium retention	↑Afterload → worsened LV function Adverse LV remodeling (apoptosis, myocyte hypertrophy)	ACE inhibitors ARBs
Adrenergic activation	↓CO/BP	↑CO through ↑ in heart rate and contractility ↑BP	↑Ischemia ↑Afterload → worsened LV function ↑LVEDP → pulmonary congestion Adverse LV remodeling (apoptosis, myocyte hypertrophy)	β-adrenergic blocking agents
Renal salt and water retention	↑Antidiuretic hormone ↑Norepinephrine ↑Angiotensin II ↑Aldosterone ↓Renal blood flow	↑Preload → ↑stroke volume and CO	Pulmonary and systemic congestion Adverse LV remodeling	Diuretics Aldosterone inhibitors ACE inhibitors, ARBs β-adrenergic blocking agents
↑Natriuretic peptide secretion	Volume expansion (atrial stretch)	Diuresis Natriuresis Partial inhibition of renin-angiotensin system and norepinephrine	None known	Natriuretic peptides

ACE, Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CO,* cardiac output; *LV,* left ventricular; *LVEDP,* left ventricular end-diastolic pressure.
From Sellke FW et al: *Sabiston & Spencer surgery of the chest,* ed 9, 2016, Elsevier.

TABLE 2 American College of Cardiology/American Heart Association (ACC/AHA) Stages of Heart Failure (HF) Compared to the New York Heart Association (NYHA) Functional Classification

ACC/AHA Stages		NYHA Functional Classification	
A	At high risk for HF but without structural heart disease or symptoms of HF.	None	
B	Structural heart disease but without signs or symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF.	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
D	Refractory HF requiring specialized interventions.	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

after HF diagnosis, with 83% of patients hospitalized at least once and 43% hospitalized at least 4 times. More than half of the hospitalizations were related to noncardiovascular causes.

RISK FACTORS

Several conditions are associated with an increased risk of developing heart failure. If these are identified and treated appropriately, it may be possible to delay, if not prevent, the onset of HF.

- Hypertension: The incidence of HF is higher in patients with higher blood pressures, older age of the hypertensive patient, and in patients who have been hypertensive for longer.
- Diabetes mellitus: The incidence of HF is increased in patients with diabetes mellitus, independent of the presence of structural heart disease.
- Metabolic syndrome: Appropriately treating hypertension, diabetes mellitus, and dyslipidemia can decrease the incidence of HF.
- Atherosclerotic disease: Patients with atherosclerotic disease are likely to develop HF.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The clinical and physical exam findings should be given the highest priority when determining the diagnosis of HF. These signs and symptoms are dependent on the severity of disease, precipitant factors, comorbid conditions, and whether the HF symptoms are predominantly right-sided or left-sided. Clues in the patient's history when evaluating HF are summarized in Table 4.

- Common clinical manifestations are:
  1. Dyspnea on exertion, that can progress to dyspnea at rest, caused by increasing pulmonary vascular congestion
  2. Orthopnea, caused by increased venous return in the recumbent position and further elevated pulmonary venous pressure
  3. Paroxysmal nocturnal dyspnea (PND) resulting from multiple factors including increased venous return in the recumbent position, decreased PaO_2, and decreased adrenergic stimulation of myocardial function during sleep
  4. Nocturnal angina resulting from increased myocardial oxygen demand (secondary to increased venous return in the recumbent position causing increased preload) in patients with concomitant coronary artery disease (CAD)
  5. ***Cheyne-Stokes respiration*** (alternating phases of apnea and hyperventilation) caused by prolonged circulation time from lungs to brain as a result of impaired cardiac output
  6. Fatigue, lethargy, and decreased functional capacity resulting from low cardiac output and hypoperfusion of peripheral tissues
  7. Table 5 summarizes common presenting symptoms and signs of decompensated heart failure.
- Physical examination (Table 6):
  1. Fine pulmonary crackles, wheezes, tachypnea, hypoxia (due to elevated pulmonary pressures). Crackles may be absent in chronic and longstanding high pulmonary venous pressure because it allows for lymphatic drainage in the lungs to increase.

TABLE 3 Simplified Classification and Common Clinical Characteristics of Patients with Acute Heart Failure

Clinical Classification	Symptom Onset	Triggers	Signs and Symptoms	Clinical Assessment	Course
Decompensated heart failure	Usually gradual	Noncompliance, ischemia, infections	Peripheral edema, orthopnea, dyspnea on exertion	SBP: Variable CXR: Often clear despite elevated filling pressures	Variable, high rehospitalization rate
Acute hypertensive heart failure	Usually sudden	Hypertension, atrial arrhythmias, ACS	Dyspnea (often severe), tachypnea, tachycardia, rales common	SBP: High (>180/100 mm Hg) CXR with pulmonary edema Hypoxemia common	High acuity, but patient often responds quickly to therapy with vasodilators, noninvasive ventilation Postdischarge mortality is low
Cardiogenic shock	Variable	Progression of advanced HF or major myocardial insult (e.g., large AMI, acute myocarditis)	End-organ hypoperfusion; Oliguria, confusion, cool extremities	SBP: Low or low normal LV function usually severely depressed RV dysfunction common Laboratory evidence of end-organ dysfunction (renal, hepatic)	High inpatient mortality Poor prognosis unless readily reversible cause or mechanical support, transplantation

ACS, Acute coronary syndrome; *AMI,* acute myocardial infarction; *CXR,* chest x-ray film; *LV,* left ventricular; *RV,* right ventricular; *SBP,* systolic blood pressure.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

2. Tachycardia and narrowed pulse pressure (due to increased sympathetic tone)
3. S_3 gallop, paradoxical splitting of S_2, jugular venous distention, peripheral edema in dependent tissues, congestive hepatomegaly, ascites, and hepatojugular reflux (due to volume overload)
4. Perioral and peripheral cyanosis, decreased capillary refill, pulsus alternans, and cool extremities (due to decreased cardiac output)

- Six common clinical presentations identified by European Society of Cardiology of Acute Heart Failure Syndromes:
  1. ADHF presenting with hypertension (SBP >160): The hypertension leads to increased afterload causing pulmonary vascular congestion
  2. Worsening or decompensation of chronic HF
  3. Flash pulmonary edema
  4. Cardiogenic shock
  5. Acute coronary syndrome (ACS) and ADHF
  6. Isolated RV failure
- Each of these scenarios may require different therapies to effectively stabilize and treat the patient.

Acute precipitants of HF decompensation include noncompliance with salt restriction or medications (most common cause), any acute systemic illness, infection, arrhythmias (e.g., atrial fibrillation), ischemia or infarction, uncontrolled hypertension, new medications (e.g., negative inotropic agents such as calcium channel blockers/antiarrhythmic agents), nonsteroidal antiinflammatory drugs (NSAIDs), renal dysfunction, toxins (e.g., ethanol and anthracyclines), surgery, or valvular catastrophe.

TABLE 4 Using the Medical History to Assess the Heart Failure Patient

Symptoms Associated with HF Include:

Fatigue
Shortness of breath at rest or during exercise
Dyspnea
Tachypnea
Cough
Diminished exercise capacity
Orthopnea
Paroxysmal nocturnal dyspnea
Nocturia
Weight gain/weight loss
Edema (of extremities, scrotum, or elsewhere)
Increasing abdominal girth or bloating
Abdominal pain (particularly if confined to right upper quadrant)
Loss of appetite or early satiety
Cheyne-Stokes respirations (often reported by family rather than patient)
Somnolence or diminished mental acuity

Historical Information Helpful in Determining if Symptoms Are Caused by HF

A past history of HF
Cardiac disease (e.g., coronary artery disease, valvular or congenital disease, previous myocardial infarction)
Risk factors for heart failure (e.g., diabetes, hypertension, obesity)
Systemic illnesses that can involve the heart (e.g., amyloidosis, sarcoidosis, inherited neuromuscular diseases)
Recent viral illness or history of HIV infection or Chagas disease
Family history of HF or sudden cardiac death
Environmental and/or medical exposure to cardiotoxic substances
Substance abuse
Noncardiac illnesses that could affect the heart indirectly, including high-output states (e.g., anemia, hyperthyroidism, arteriovenous fistulas)

HIV, Human immunodeficiency virus.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

ETIOLOGY

LEFT VENTRICULAR FAILURE: The dichotomy of whether HF occurs in the setting of preserved or reduced LV systolic function plays an important role in treatment strategies. Patients with HFpEF may have significant abnormalities in active relaxation and passive stiffness of the LV as well as valvular disease. HFrEF denotes poor pump function.

- Abnormal LV systolic function:
  1. CAD (acute or chronic ischemia, myocardial infarction [MI], LV aneurysm), the most common cause of cardiomyopathy in the U.S., comprising 50% to 75% of HF patients.
  2. Increased afterload or pressure overload (severe hypertension, aortic stenosis)
  3. Increased preload or volume overload (mitral regurgitation, aortic regurgitation)
  4. Cardiomyopathy: Idiopathic, infiltrative (nonischemic)
  5. Infectious (Chagas, myocarditis)
  6. Infiltrative (amyloidosis, sarcoidosis, hemochromatosis)
  7. Toxins (ethanol, cocaine, anthracyclines)
  8. Tachycardia induced (e.g., with atrial fibrillation)
- Preserved LV systolic function (Table 7):
  1. Impaired relaxation (myocardial ischemia, diabetes mellitus, metabolic syndrome)
  2. Tachyarrhythmia (featuring reduced diastolic filling time)
  3. Restrictive cardiomyopathy (myocardial stiffness, such as hypereosinophilic syndrome, amyloidosis, hemochromatosis)

TABLE 5 Common Presenting Symptoms and Signs of Decompensated Heart Failure

Symptoms	Signs
Predominantly Related to Volume Overload	
Dyspnea (exertional, paroxysmal nocturnal dyspnea, orthopnea, or at rest), cough, wheezing	Rales, pleural effusion
Foot and leg discomfort	Peripheral edema (legs, sacral)
Abdominal discomfort/bloating; early satiety or anorexia	Ascites/increased abdominal girth; right upper quadrant pain or discomfort; hepatomegaly/splenomegaly; scleral icterus
	Increased weight
	Elevated jugular venous pressure, abdominojugular reflux
	Increasing S_3, accentuated P_2
Predominantly Related to Hypoperfusion	
Fatigue	Cool extremities
Altered mental status, daytime drowsiness, confusion, or difficulty concentrating	Pallor, dusky skin discoloration, hypotension
Dizziness, presyncope, or syncope	Pulse pressure (narrow) Proportional pulse pressure (low)
Other Signs/Symptoms of Acute Heart Failure	
Depression	Orthostatic hypotension (hypovolemia)
Sleep disturbances	S_4
Palpitations	Systolic/diastolic cardiac murmurs

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 6 Physical Findings of Heart Failure

Tachycardia
Extra beats or irregular rhythm
Narrow pulse pressure or thready pulse*
Pulses alternans*
Tachypnea
Cool and/or mottled extremities*
Elevated jugular venous pressure
Dullness and diminished breath sounds at one or both lung bases
Rales, rhonchi, and/or wheezes
Apical impulse displaced leftward and/or inferiorly
Sustained apical impulse
Parasternal lift
Third and/or fourth heart sound (either palpable and/or audible)
Tricuspid or mitral regurgitant murmur
Hepatomegaly (often accompanied by right upper quadrant discomfort)
Ascites
Presacral edema
Anasarca*
Pedal edema
Chronic venous stasis changes

*Indicative of more severe disease.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

4. High cardiac output (thiamine deficiency, anemia, thyrotoxicosis, arteriovenous malformations)
5. Increased afterload (uncontrolled hypertension, aortic stenosis, hypertrophic obstructive cardiomyopathy)
6. Hypervolemia (oliguric renal failure, iatrogenic)

RIGHT VENTRICULAR FAILURE:

- Left-sided HF
- Chronic hypoxemic pulmonary disease
- Valvular heart disease (mitral stenosis or regurgitation)
- Pulmonary embolism
- Primary pulmonary hypertension
- Right-to-left shunts that cause systemic hypoxemia (e.g., large patent foramen ovale and tetralogy of Fallot)
- Left-to-right shunts that cause volume overload (e.g., atrial and ventricular septal defects)
- Bacterial endocarditis (right-sided)
- Right ventricular infarction

DX DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- COPD, asthma
- Cirrhosis
- Nephrotic syndrome
- Venous insufficiency
- Pulmonary embolism
- ARDS (adult respiratory distress syndrome)
- Pneumonia
- Heroin overdose

WORKUP

- ACC/AHAA guidelines for initial and serial evaluation of heart failure are summarized in Table 8.
- Blood work (to diagnose potentially reversible causes, identify comorbidities, and assess disease severity):
  1. CBC (to evaluate for anemia, infections), urinalysis, blood urea nitrogen (BUN), creatinine, electrolytes (worsening hyponatremia is a marker of disease severity and is associated with higher mortality rates), liver enzymes (hepatic congestion), thyroid function (especially in the elderly or patients with comorbid atrial fibrillation or known thyroid disease).
  2. Fig. 2 illustrates the use of biomarkers in HF. B-type natriuretic peptide (BNP) is a cardiac neurohormone secreted from the ventricles in response to elevated LV end-diastolic pressure. While the sensitivity is low in asymptomatic patients, low BNP level has a negative predictive value up to 90% in symptomatic patients. An elevated BNP correlates with severity of disease and parallels closely morbidity and mortality outcome measures. N-terminal-pro-BNP (NT-pro-BNP) is the cleavage remnant of BNP. It has a longer half-life and is renally cleared, making it susceptible to alterations in renal function. A level of <300 pg/ml has an age-independent 98% negative predictive value. There are new data to suggest that BNP screening and early intervention with risk factor modification in patients at risk of developing heart failure may prevent development of left ventricular dysfunction (class IIa recommendation). Natriuretic peptide biomarkers are also useful (class IA recommendation) both for diagnosis in patients presenting with dyspnea and for prognosis in patients with acute decompensated heart failure and chronic heart failure. Measurement of baseline levels of natriuretic peptide biomarkers on admission to the hospital is useful to establish a prognosis in acutely decompensated HF, and predischarge natriuretic peptide level can be useful to establish a postdischarge prognosis. There are insufficient data to recommend natriuretic peptide biomarker–guided therapy or serial measurements for the purpose of reducing hospitalization or deaths. ACC/AHA/HFSA guidelines for the use of biomarkers in HF are summarized in Table 9.
  3. Cardiac biomarkers may be elevated if ischemia is the precipitant factor. However, slight elevations are very common and may not always be due to obstructive coronary artery disease. These elevations could be due to subendocardial ischemia (due to increased end-diastolic pressure resulting in decreased perfusion) and necrosis, or cardiomyocyte damage from the inflammatory cytokines or oxidative stress. Impaired renal function is very common, and decreased clearance of the biomarkers can contribute to their elevation. Therefore these elevations should be interpreted in the context of the clinical setting. Despite that, in patients with acute decompensated heart failure (ADHF), a positive cardiac troponin test (from whatever mechanism) is associated with worse prognosis.
  4. Screening for dyslipidemia and glucose intolerance, which are risk factors for CAD.
  5. If hemochromatosis is suspected (specifically in Northern European patients), consider checking a transferrin saturation and ferritin level.

TABLE 7 Mechanisms/Factors Contributing to the Pathophysiology of Heart Failure with Preserved Ejection Fraction

Cardiovascular

LV Structure

Concentric remodeling, LV hypertrophy

LV Function

Diastolic dysfunction: Abnormal relaxation, decreased recoil, abnormal filling, decreased distensibility, increased diastolic pressure
Systolic dysfunction: Abnormal midwall and long-axis shortening, decreased twist
Hemodynamic load
  Increased afterload and filling load
Heterogeneity
  Dyssynergy, dyssynchrony
Left atrial structure and function
  Increased LA volume and stiffness, decreased LA reservoir function, passive conduit function and active booster pump function
Ischemia
  Subendocardial and microvascular disease, impaired coronary, pulmonary, and peripheral flow reserve
Rate and rhythm abnormalities
  Chronotropic incompetence, atrial fibrillation, supraventricular tachycardia
Vascular dysfunction
  Arterial stiffening, endothelial dysfunction

Cardiomyocyte

Abnormal calcium homeostasis (↑ diastolic calcium or ↓ rate of calcium reuptake → incomplete or impaired relaxation)
  Sarcolemmal calcium channels (Na^+/Ca^{2+} exchanger and calcium pump)
  Sarcoplasmic reticulum Ca^{2+}ATPase (SERCA) abundance and function
  Proteins modifying SERCA activity: Phospholamban, calmodulin, calsequestrin abundance, and phosphorylation state
  Sarcoplasmic reticulum calcium release channels
Energetics (↓ ATP or ↑ ADP slows actin-myosin cross-bridge release)
  ADP/ATP ratio, ADP and P_i concentration, phosphocreatine shuttle function
Proteins regulating cross-bridge formation and calcium sensitivity
  Troponin C: Calcium binding
  Troponin I: Phosphorylation state
Cytoskeletal proteins
  Microtubules (increased density) → ↑ diastolic stiffness
  Titin isoforms (↑ noncompliant isoform and phosphorylation state) → ↑ diastolic stiffness

Extracellular Matrix

Collagen structure, geometry, content, collagen I/III ratio
Collagen homeostasis, synthesis, postsynthetic processing, posttranslational crosslinking, degradation
Basement membrane proteins
Bioactive proteins and peptides: MMP/TIMP, SPARC, TGF-β
Fibroblast structure, function, phenotype
Myofibroblast transdifferentiation

Extra Cardiac

Extrinsic forces (RV-LV interaction and pericardial constraint)
Peripheral muscle and ergoreflex dysfunction
Pulmonary hypertension (secondary to chronic pulmonary venous hypertension)
Neurohormonal activation
Comorbid conditions (renal dysfunction, anemia, chronic lung disease)

ADP, Adenosine diphosphate; *ATP,* adenosine triphosphate; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle; *SPARC*, secreted protein, acidic and rich in cysteine [osteonectin]; *TGF,* transforming growth vector.
From Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.

6. Consider HIV testing in high-risk patients.

- Electrocardiogram (ECG):
  1. Look for signs of prior MI, chamber enlargement, hypertrophy, heart block, arrhythmia, and evidence of pericardial effusion.
  2. More than 25% of patients with HF have some form of intraventricular conduction abnormality that manifests as an increased QRS duration. The most common pattern seen is left bundle-branch block.
- Chest x-ray (Fig. 3):
  1. Evaluate for pulmonary venous congestion, pulmonary edema, pleural effusion, cardiomegaly, chamber dilation, and Kerley B lines.
- Echocardiography:
  1. Plays a critical diagnostic role in patients with HF and is useful in assessment of systolic, diastolic function in addition to assessment of valvular structure and function
- Exercise stress testing:
  1. May be useful in evaluating concomitant ischemic etiologies and assessment of degree of disability in stable compensated patients.
- Cardiac catheterization:
  1. Left heart catheterization can help to identify coronary artery disease as a cause of HF. Right heart catheterization can help to evaluate intracardiac filling pressures, estimates of valvular areas, presence of intracardiac shunts, and calculation of hemodynamic properties such as cardiac output, systemic vascular resistance, and pulmonary artery wedge pressure to further guide management.
- Cardiac MRI:
  1. Useful modality in accurately estimating EF (with less variability than conventional 2D echocardiography). MRI is also useful in excluding pericardial disease, identifying infiltrative disease, and assessing viability in cases of HF caused by underlying ischemic heart disease.

Rx TREATMENT

NONPHARMACOLOGIC GENERAL MEASURES

- Assess the etiology and severity of disease. Educate the patient and family about the nature of the disorder. Assess the home setting and if patient has social support to ensure compliance, especially for patients with dementia.
- Identify and correct precipitating factors (e.g., increased sodium load, medication noncompliance, ischemia, infections, anemia, thyrotoxicosis) and address lifestyle modification (e.g., smoking and alcohol cessation, weight reduction, avoiding use of nonsteroidal antiinflammatory drugs [NSAIDs]). Anemia is common in patients with HF. In patients with NYHA class II and III symptoms and iron deficiency, IV iron replacement may be reasonable to improve functional status and quality of life (class IIb recommendation). Treatments with erythropoiesis-stimulating agents (ESAs) have not shown improved clinical outcomes in patients with systolic HF and mild-to-moderate anemia and are thus not recommended. Table 10 describes ACC/AHA guidelines for treating patients at high risk for development of heart failure.
- Review list of medications and discontinue the ones that can contribute to HF (e.g., NSAIDs, antiarrhythmic drugs, calcium channel blockers, thiazolidinediones).
- Dietary sodium restriction of <2 g/day is commonly recommended to patients with HF and is endorsed by many guidelines.
- Restrict fluid intake to <2 L/day in patients with hyponatremia.
- Caloric supplementation should be provided to patients with advanced HF with weight loss and muscle wasting due to cardiac cachexia. Weight loss may reflect cachexia caused by the higher total energy expenditure associated with HF compared with that of healthy sedentary subjects. The diagnosis of cardiac cachexia independently predicts a worse prognosis.
- For patients with coexisting obstructive sleep apnea, continuous positive airway pressure (CPAP) may be reasonable after polysomnography (class IIb recommendation).

TABLE 8 ACC/AHA Guidelines for Initial and Serial Evaluation of Heart Failure

Class	Indication: History, Physical Examination, and Risk Scoring	Level of Evidence
I	A thorough history and physical examination should be obtained/performed in patients presenting with HF to identify cardiac and noncardiac disorders or behaviors that might cause or accelerate the development or progression of HF.	C
	In patients with idiopathic DCM, a three-generational family history should be obtained to aid in establishing the diagnosis of familial DCM.	C
	Volume status and vital signs should be assessed at each patient encounter. This includes serial assessment of weight, as well as estimates of jugular venous pressure and the presence of peripheral edema or orthopnea.	B
IIa	Validated multivariable risk scores can be useful to estimate subsequent risk of mortality in ambulatory or hospitalized patients with HF.	C
Indication: Diagnostic Tests and Biomarkers (also see below)		
I	Initial laboratory evaluation of patients presenting with HF should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone.	C
	Serial monitoring, when indicated, should include serum electrolytes and renal function.	C
	A 12-lead ECG should be performed initially on all patients presenting with HF.	C
	In ambulatory patients with dyspnea, measurement of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) is useful to support clinical decision making regarding the diagnosis of HF, especially in the setting of clinical uncertainty, and measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF.	A
IIa	Screening for hemochromatosis or HIV is reasonable in select patients who present with HF.	C
	Diagnostic tests for rheumatologic diseases, amyloidosis, or pheochromocytoma are reasonable in patients presenting with HF in whom there is a clinical suspicion of these diseases.	C
	BNP-guided or NT-proBNP–guided HF therapy can be useful to achieve optimal dosing of GDMT in select, clinically euvolemic patients followed in a well-structured HF disease management program.	B
IIb	The usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with HF is not well established. The measurement of other clinically available tests, such as biomarkers of myocardial injury or "fibrosis," may be considered for additive risk stratification in patients with chronic HF.	B
Indication: Noninvasive Cardiac Imaging		
I	Patients with suspected or new-onset HF, or those presenting with acute decompensated HF, should undergo a chest radiograph to assess heart size and pulmonary congestion and to detect alternative cardiac, pulmonary, and other diseases that may cause or contribute to the patient's symptoms.	C
	A two-dimensional echocardiogram with Doppler should be performed during initial evaluation of patients presenting with HF to assess ventricular function, size, wall thickness, wall motion, and valve function.	C
	Repeat measurement of EF and measurement of the severity of structural remodeling are useful to provide information in patients with HF who have had a significant change in clinical status; who have experienced or recovered from a clinical event; who have received treatment, including GDMT, that might have had a significant effect on cardiac function; or who may be candidates for device therapy.	C
IIa	Noninvasive imaging to detect myocardial ischemia and viability is reasonable in patients presenting with de novo HF who have known CAD and no angina, unless the patient is not eligible for revascularization of any kind.	C
	Viability assessment is reasonable in select situations when planning revascularization in HF patients with CAD.	B
	Radionuclide ventriculography or MRI can be useful to assess LVEF and volume when echocardiography is inadequate.	C
	MRI is reasonable when assessing myocardial infiltrative processes or scar burden.	B
III: No benefit	Routine repeat measurement of LV function assessment in the absence of clinical status change or treatment interventions should not be performed.	B
Indication: Invasive Evaluation		
I	Invasive hemodynamic monitoring with a pulmonary artery catheter should be performed to guide therapy in patients who have respiratory distress or clinical evidence of impaired perfusion in whom the adequacy or excess of intracardiac filling pressures cannot be determined from clinical assessment.	C
IIa	Invasive hemodynamic monitoring can be useful for carefully selected patients with acute HF who have persistent symptoms despite empiric adjustment of standard therapies and (a) whose fluid status, perfusion, or systemic or pulmonary vascular resistance is uncertain; (b) whose systolic pressure remains low, or is associated with symptoms, despite initial therapy; (c) whose renal function is worsening with therapy; (d) who require parenteral vasoactive agents; or (e) who may need consideration for mechanical circulatory support or transplantation.	C
	When ischemia may be contributing to HF, coronary arteriography is reasonable for patients eligible for revascularization.	C
	Endomyocardial biopsy can be useful in patients presenting with HF when a specific diagnosis is suspected that would influence therapy.	C
III: No benefit	Routine use of invasive hemodynamic monitoring is not recommended in normotensive patients with acute decompensated HF and congestion with symptomatic response to diuretics and vasodilators.	B
III: Harm	Endomyocardial biopsy should not be performed in the routine evaluation of patients with HF.	C

ACC, American College of Cardiology; *AHA,* American Heart Association; *BNP,* B-type natriuretic peptide; *CAD,* coronary artery disease; *DCM,* dilated cardiomyopathy, *ECG,* electrocardiogram; *EF,* ejection fraction; *GDMT,* guideline-directed medical therapy; *HIV,* human immunodeficiency virus; *LVEF,* left ventricular ejection fraction; *MRI,* magnetic resonance imaging.

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

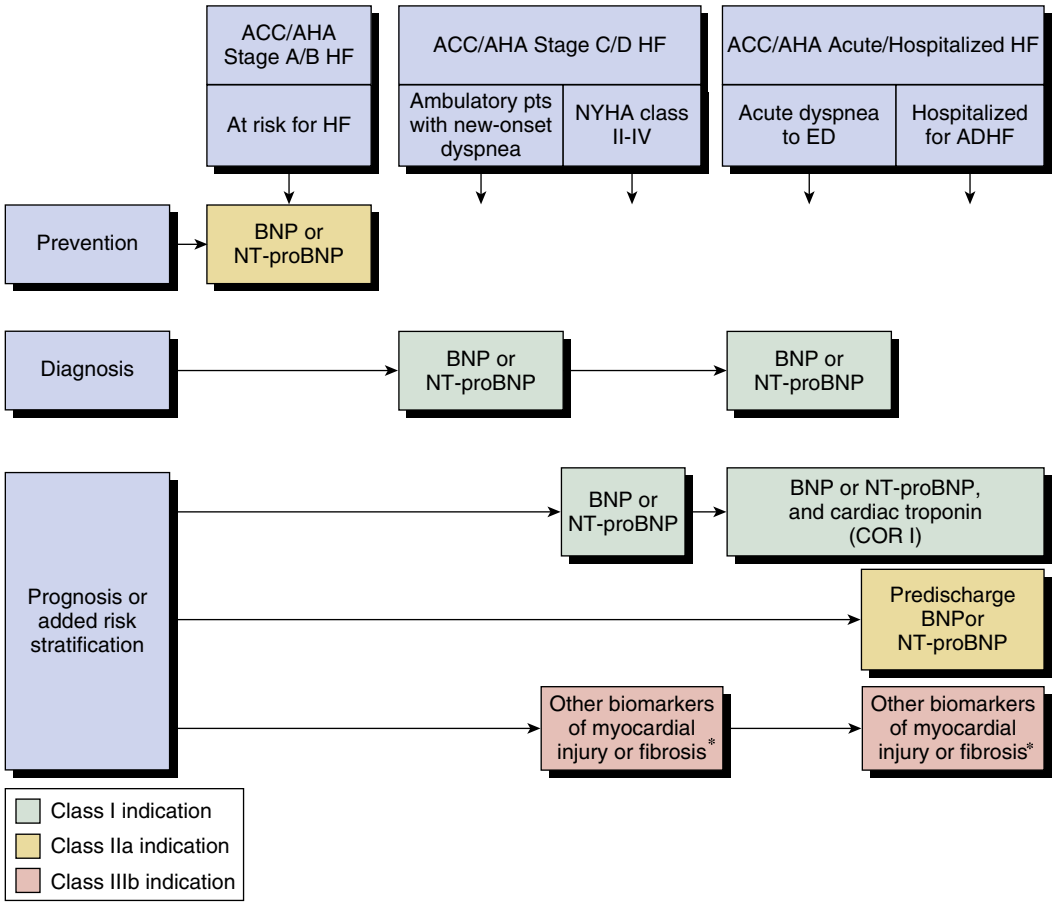

FIG. 2 Indications for the use of biomarkers in heart failure. *Other biomarkers of injury or fibrosis include soluble ST2 receptor, galectin-3, and high-sensitivity troponin. *ACC,* American College of Cardiology; *AHA,* American Heart Association; *ADHF,* acute decompensated heart failure; *BNP,* B-type natriuretic peptide; *COR,* class of recommendation; *ED,* emergency department; *HF,* heart failure; *NT-proBNP,* N-terminal pro-B-type natriuretic peptide; *NYHA,* New York Heart Association; *pts,* patients. (Modified from Yancy CW et al: 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America, *J Am Coll Cardiol* 2017;70[6]:776; in Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

- Exercise training (or regular physical activity) is recommended as safe and effective for patients with class I to III HF who are able to participate to improve functional status (class I recommendation). Cardiac rehabilitation is unfortunately an underused preventive measure, although it has been shown to reduce morbidity and mortality. Cardiac rehabilitation can be useful in clinically stable patients with HF to improve functional capacity, exercise duration, health-related quality of life, and mortality (class IIa recommendation).
- Pneumococcal vaccination and annual influenza vaccination.
- ACC/AHA guidelines for treatment of asymptomatic left ventricular systolic dysfunction are summarized in Table 11.

TREATMENT OF ADHF

- Four phases in treatment of ADHF:
  1st phase: Initial stabilization and management (Table 12)
  2nd phase: Inpatient hospital care (Table 13)
  3rd phase: Early discharge planning and care
  4th phase: Early postdischarge care
- 1st phase: Initial stabilization and management
- Short-term goals: Hemodynamic stabilization, stabilization of respiratory status, symptom relief, optimization of tissue perfusion, and recognition of more immediately life-threatening conditions (e.g., arrhythmias, valvular catastrophe, MI, cardiac tamponade). Initial therapy of ADHF is contingent on appropriate determination of clinical scenario.
- Management as per clinical scenario:
  1. ADHF-associated hypertension: Goal is afterload reduction and decrease of systemic hypervolemia. Mode of treatment: Diuresis (IV loop diuretics) and vasodilators (acutely nitrates and morphine followed by treatment with ACE inhibitors or angiotensin receptor blockers [ARBs])
  2. Worsening or decompensation of chronic HF (HFrEF or HFpEF): Goal is control of volume status. Treatment is accomplished with vasodilators and diuretics.
  3. Flash pulmonary edema: Goal is afterload reduction (vasodilators such as nitrates acutely), respiratory status stabilization, and diuresis (IV loop diuretics). Rate control can be initiated in patients with atrial fibrillation or tachyarrhythmias as it may improve cardiac filling and function.
  4. Cardiogenic shock: Goal is hemodynamic stabilization. Treatment consists of inotropes + vasopressors ± mechanical circulatory support ± emergent revascularization if indicated.
  5. ACS and ADHF: Goal is hemodynamic stabilization + emergent restoration of coronary perfusion. See "Acute Coronary Syndrome."
  6. Isolated RV failure: Goals are identification of etiology: (1) valvular, (2) pulmonary hypertension, and (3) primary RV failure secondary to ischemia. Treatment: depends on etiology, either corrective surgery vs. treatment of pulmonary hypertension (endothelin antagonists, calcium channel blockers, phosphodiesterase inhibitors) vs. coronary reperfusion therapies.

TABLE 9 ACC/AHA/HFSA Guidelines for Use of Biomarkers in Heart Failure

Class	Biomarkers for Prevention of HF	Level of Evidence
IIa	For patients at risk of developing HF, natriuretic peptide biomarker–based screening can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF.	B-R
Biomarkers for Diagnosis		
I	In patients presenting with dyspnea (acute or chronic), measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclusion of HF.	A
Biomarkers for Prognosis or Added Risk Stratification		
I	Measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF.	A
I	Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated HF.	A
IIa	During a HF hospitalization, a predischarge natriuretic peptide level can be useful to establish a postdischarge prognosis.	B-NR
IIb	In patients with chronic HF, measurement of other clinically available tests, such as biomarkers of myocardial injury or fibrosis, may be considered for additive risk stratification.	B-NR

ACC, American College of Cardiology; *AHA,* American Heart Association; *BNP,* B-type natriuretic peptide; *HF,* heart failure; *HFSA,* Heart Failure Society of America; *NT-proBNP,* N-terminal pro-B-type natriuretic peptide.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

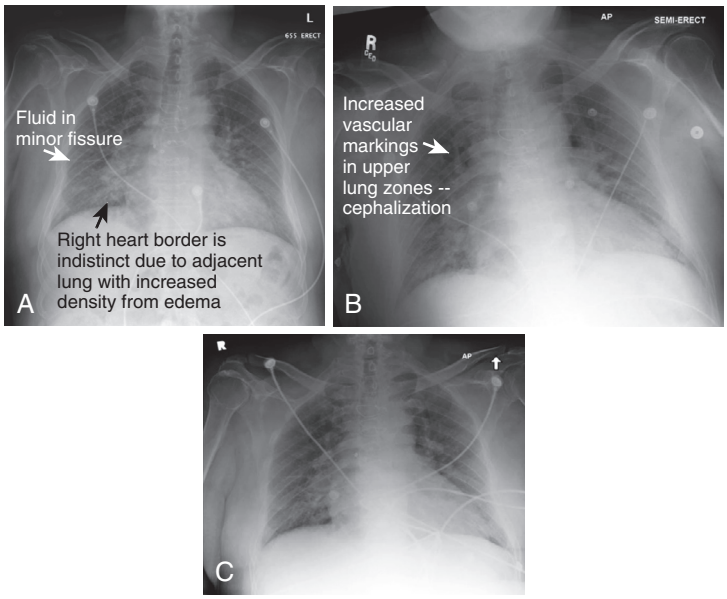

FIG. 3 Congestive heart failure. Mild left ventricular hypertrophy with restricted filling, ejection fraction >55%, and no pericardial effusion. This 63-year-old man with coronary artery disease, chronic renal insufficiency, and diastolic heart failure (ejection fraction >55%) presented multiple times for dyspnea (**A, B,** and **C,** first through third clinical presentations). Each of these three radiographs shows signs of moderate pulmonary edema. The diaphragms and costophrenic angles are clear, suggesting no pleural effusion. The right heart border in all three images is indistinct because of interstitial edema in these locations. Portions of the left heart border are also indistinct. The upper lung fields have a hazy appearance indicating mild edema. Fluid is visible in the minor fissure on all three images. Does the similarity of these radiographs mean that edema is not the cause of the patient's dyspnea? No, he simply presented with pulmonary edema on all three occasions. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, WB Saunders.)

ACUTE PHARMACOLOGIC TREATMENTS:

- Vasodilators (Table 14) are appropriate in most patients with ADHF (contraindicated in cardiogenic shock and severe aortic stenosis)
  1. Nitroglycerin (0.4 to 0.8 mg sublingually every 3 to 5 min, or by intravenous infusion starting at 0.2 to 0.4 mcg/kg/min with subsequent up titration) may be administered in the emergency setting until relative hypotension ensues. Nitrates are contraindicated after use of phosphodiesterase inhibitors such as sildenafil due to risk of hypotension.
  2. Sodium nitroprusside (0.1 to 0.2 mcg/kg/min as an intravenous infusion) is a potent vasodilator with balanced venous and arteriolar effects that usually requires hemodynamic monitoring with an arterial line and may precipitate coronary steal and thiocyanate toxicity (elevated risk in renal failure).
  3. When given intravenously, loop diuretics have an immediate vasodilator effect that provides clinical relief of symptoms before diuresis begins. Due to gut edema and unpredictable patterns of absorption, oral formulation may become less effective. Therefore intravenous formulation should be used in the acute setting. Studies showed no difference in outcome when using bolus dosing vs. continuous IV infusion. Administration of smaller doses of short-acting loop diuretics multiple times daily is preferable to a single large dose because the kidneys can avidly reabsorb sodium after the initial diuresis. However, if a certain dose is not adequate to force diuresis, the dose, rather than the frequency, should be increased until a single effective dose is reached; more frequent doses can be added as needed. Therefore monitoring of urine output, renal function, and electrolytes is key. The addition of a distal tubule inhibitor such as metolazone 30 min prior to loop diuretic dosing has a synergistic effect and often enhances diuresis because it inhibits sodium reabsorption in the distal segment in the face of increased sodium delivery from the loop. Diuretics should be used with caution in patients with aortic stenosis.
- Inotropic agents are used for temporary hemodynamic support in cardiogenic shock, but have not been shown to improve survival. Many of these agents have serious associated adverse events including myocardial necrosis and malignant arrhythmias.
  1. Dobutamine (starting at 2.5 to 5 mcg/kg/min) can be used for inotropic support but is associated with increased myocardial oxygen demand and cardiac arrhythmias and may result in hypotension from decreased systemic vascular resistance.
  2. Milrinone (37.5 to 75 mcg/kg loading dose, followed by 0.375 to 0.75 mcg/kg/min) can be used as a vasodilator and inotropic agent, but is associated with increased oxygen demand and cardiac arrhythmias, and may result in hypotension from decreased systemic vascular resistance.
- Renal replacement therapy or ultrafiltration (can be used as an alternative to pharmacologic diuresis in ADHF when renal function is significantly compromised).
- ACE inhibitors or ARBs, if part of a patient's chronic medication regimen, should be continued in the absence of hypotension, acute renal failure, or hyperkalemia.
- Beta-blockers, if part of a patient's chronic medication regimen, may be continued or reduced in dosage in mild exacerbations of

TABLE 10 ACC/AHA Guidelines for Treating Patients at High Risk of Developing Heart Failure (Stage A)

Class	Indication	Level of Evidence
I	Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines to lower the risk of HF.	A
I	In patients at increased risk, stage A, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg.	B-R
I	Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided.	C
II	For patients at risk of developing HF, natriuretic peptide biomarker–based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF.	B-R

ACC, American College of Cardiology; *AHA,* American Heart Association; *GDMT,* guideline-directed medical therapy; *HF,* heart failure. From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 11 ACC/AHA Guidelines for Treatment of Asymptomatic Left Ventricular Systolic Dysfunction (Stage B)

Class	Indication	Level of Evidence
I	In all patients with a recent or remote history of MI or ACS and reduced EF, ACE inhibitors should be used to prevent symptomatic HF and reduce mortality. In patients intolerant of ACE inhibitors, ARBs are appropriate unless contraindicated.	A
	In all patients with a recent or remote history of MI or ACS and reduced EF, evidence-based beta blockers should be used to reduce mortality. Beta blockade and ACE inhibition should be used in all patients with a recent or remote history of MI regardless of EF or presence of HF.	B
	In all patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and cardiovascular events.	A
	Blood pressure should be controlled in accordance with clinical practice guidelines for hypertension to prevent symptomatic HF.	A
	ACE inhibitors should be used in all patients with a reduced EF to prevent symptomatic HF.	A
	Beta blockers should be used in all patients with a reduced EF to prevent symptomatic HF.	C
IIa	To prevent sudden death, placement of an ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of 30% or less, are on appropriate medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 yr.	B
III: Harm	Nondihydropyridine calcium channel blockers with negative inotropic effects may be harmful in asymptomatic patients with low LVEF and no symptoms of HF after MI.	B

ACC, American College of Cardiology; *ACE,* angiotensin-converting enzyme; *ACS,* acute coronary syndrome; *AHA,* American Heart Association; *ARB,* angiotensin receptor antagonist; *EF,* ejection fraction; *HF,* heart failure; *ICD,* implantable cardioverter-defibrillator; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

HF but should be discontinued in patients with hypotension or those requiring inotropic support. Beta-blockers should not be initiated in patients who are not on chronic beta-blocker therapy until euvolemia is achieved unless used for rate control.

- Morphine sulfate can cause venodilation and thus reduce cardiac preload. It may be used to reduce patient work of breathing and anxiety, but recent retrospective studies have suggested increased incidence of mechanical ventilation and in-hospital mortality in patients who received morphine.
- If ADHF with preserved EF is suspected, therapy is usually aimed at relief of symptoms and correction of any potential precipitating etiologies (e.g., tachycardia, hypertension, ischemia). Treatment generally involves diuretics to reduce pulmonary congestion with caution to not overdiurese given the need for elevated filling pressures in these patients to ensure adequate stroke volume and cardiac output. Nitrates may be useful in providing symptomatic relief but may precipitate hypotension. Ventricular rate should be controlled in the presence of atrial fibrillation, which, at rapid rates, is poorly tolerated in patients with impaired diastolic filling. Negative inotropic agents such as beta-blockers and calcium channel blockers can be used with caution. ACC/AHA/HSFA guidelines for treatment of patients with stage C HF and preserved left ventricular ejection fraction are summarized in Table 15.
- Nesiritide (recombinant brain natriuretic protein) does not reduce morbidity or mortality (ASCEND-HF trial).
- 2nd phase: Inpatient hospital care.
  1. This phase of treatment includes further diuresis and stabilization of volume status (Table 16). The patient should be carefully brought to euvolemia with daily volume status and electrolyte monitoring. The patient should also be transitioned to oral diuretics when stabilized. While inpatient, the patient should have his/her medical and device management optimized with the therapies discussed later.
- 3rd phase: Early discharge planning and care.
  1. The patient should be transitioned to oral diuretics and be placed on optimum outpatient maintenance therapy. If the patient was on IV inotropic therapy, oral regimens should be adjusted while these infusions are tapered off. Prolonged physiologic effects of these IV inotropic agents after their discontinuation before discharge may mask the inadequate diuretic regimen and intolerance to the vasodilator doses. This can result in readmission, especially with milrinone due to its long half-life that can be further prolonged by the common coexisting impaired renal function. Therefore it may be recommended that patients who received inotropic infusions remain hospitalized for at least 48 hours after inotropic agents are discontinued and optimize the oral regimen.
- 4th phase: Early postdischarge care
  1. The patient will require reevaluation and constant monitoring in order to avoid another episode of ADHF. Emphasis should be placed on importance of compliance with instructions regarding dietary restrictions and daily body weight monitoring. Early follow-up should be scheduled as well as outpatient electrolyte monitoring if required after medication adjustments.

CHRONIC TREATMENT OF HFREF: The goals of HF therapy are clinical improvement followed by stabilizing, slowing, or even reversing deterioration in myocardial function, and ultimately a reduction in risk of morbidity (including hospitalization rates) and mortality.

- ACE inhibitors:
  1. Reduce morbidity and mortality.
  2. Produce both venous and arterial vasodilation acutely, thereby reducing both preload and afterload.
  3. Potential mechanism of long-term benefit is attenuation of RAAS activation and decreased myocardial remodeling and fibrosis.

TABLE 12 ACC/AHA Guidelines for Treatment of Symptomatic Left Ventricular Systolic Dysfunction (Stage C)

Class	Indication	Level of Evidence
	Nonpharmacologic Interventions	
I	Patients with HF should receive specific education to facilitate HF self-care.	B
	Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional status.	A
IIa	Cardiac rehabilitation can be useful in clinically stable patients with HF to improve functional capacity, exercise duration, HRQOL, and mortality.	B
	Sodium restriction is reasonable for patients with symptomatic HF to reduce congestive symptoms.	C
	Continuous positive airway pressure (CPAP) can be beneficial to increase LVEF and improve functional status in patients with HF and sleep apnea.	B
	Pharmacologic Interventions	
I	Measures listed as class I recommendations for patients in stages A and B are recommended where appropriate.	A, B, C
	GDMT should be the mainstay of pharmacologic therapy for HFrEF.	A
	Diuretics	
I	Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to ameliorate symptoms.	C
	Angiotensin-Converting Enzyme Inhibitors/Adrenergic Receptor Blockers	
I	ACE inhibitors are recommended in patients with HFrEF and current or previous symptoms, unless contraindicated, to reduce morbidity and mortality.	A
	ARBs are recommended in patients with HFrEF with current or previous symptoms who are ACE inhibitor–intolerant, unless contraindicated, to reduce morbidity and mortality.	A
IIa	ARBs are a reasonable choice to reduce morbidity and mortality as alternatives to ACE inhibitors for first-line therapy in patients with HFrEF, especially in those already taking ARBs for other indications, unless contraindicated.	A
IIb	Addition of an ARB may be considered in persistently symptomatic patients with HFrEF who are already being treated with an ACE inhibitor and a beta-blocker in whom an aldosterone antagonist is not indicated or tolerated.	A
III: Harm	Routinely combining an ACE inhibitor, an ARB, and an aldosterone antagonist.	C
	Beta-Blockers	
I	Use of one of the three beta-blockers proven to reduce mortality (i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or previous symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality.	A
	Aldosterone Receptor Antagonists	
I	Aldosterone receptor antagonists (or mineralocorticoid receptor antagonists) are recommended in patients with NYHA class II-IV and LVEF of ≤35%, unless contraindicated, to reduce morbidity and mortality.	A
I	Aldosterone receptor antagonists are recommended to reduce morbidity and mortality after an acute MI in patients with LVEF of ≤40% who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated.	B
III: Harm	Inappropriate use of aldosterone receptor antagonists is potentially harmful because of life-threatening hyperkalemia or renal insufficiency when serum creatinine is >2.5 mg/dl in men or >2.0 mg/dl in women (or estimated glomerular filtration rate <30 ml/min/1.73 m^2), and/or potassium >5.0 mEq/liter.	B
	Hydralazine and Isosorbide Dinitrate	
I	The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III-IV HFrEF receiving optimal therapy with ACE inhibitors and beta-blockers, unless contraindicated.	A
IIa	A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or previous symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated.	B
	Digoxin	
IIa	Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF.	B
	Anticoagulation	
I	Patients with chronic HF with permanent/persistent/paroxysmal atrial fibrillation and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 yr of age) should receive chronic anticoagulant therapy.	A
I	The selection of an anticoagulant agent (warfarin, dabigatran, apixaban, or rivaroxaban) for permanent/persistent/paroxysmal atrial fibrillation should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in the international normalized ratio therapeutic range if the patient has been taking warfarin.	C
IIa	Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal atrial fibrillation but no additional risk factor for cardioembolic stroke.	B
III: No benefit	Anticoagulation is not recommended in patients with chronic HFrEF without atrial fibrillation, a previous thromboembolic event, or a cardioembolic source.	B
	Statins	
III: No benefit	Statins are not beneficial as adjunctive therapy when prescribed solely for HF.	A
	Omega-3 Fatty Acids	
IIa	Omega-3 PUFA supplementation is reasonable to use as adjunctive therapy in patients with NYHA class II-IV symptoms and HFrEF or HFpEF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations.	B

Continued

TABLE 12 ACC/AHA Guidelines for Treatment of Symptomatic Left Ventricular Systolic Dysfunction (Stage C)—cont'd

Class	Indication	Level of Evidence
	Drugs of Unproven Value or That May Cause Harm	
III: No benefit	Nutritional supplements as treatment for HF are not recommended in patients with current or previous symptoms of HFrEF.	B
	Hormonal therapies other than to correct deficiencies are not recommended for patients with current or previous symptoms of HFrEF.	C
III: Harm	Drugs known to adversely affect the clinical status of patients with current or previous symptoms of HFrEF are potentially harmful and should be avoided or withdrawn whenever possible (e.g., most antiarrhythmic drugs, most calcium channel blocking drugs [except amlodipine], NSAIDs, or thiazolidinediones).	B
	Long-term use of infused positive inotropic drugs is potentially harmful for patients with HFrEF, except as palliation for patients with end-stage disease who cannot be stabilized with standard medical treatment (see recommendations for stage D).	C
	Calcium Channel Blockers	
III: No benefit	Calcium channel blocking drugs are not recommended for routine therapy in patients with HFrEF.	A

ACC, American College of Cardiology; *ACE,* angiotensin-converting-enzyme; *AHA,* American Heart Association; *ARB,* angiotensin-receptor blocker; *GDMT,* guideline-directed medical therapy; *HF,* heart failure; *HFpEF,* heart failure with preserved ejection fraction; *HFrEF,* heart failure with reduced ejection fraction; *HRQOL*, health-related quality of life; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction; *NYHA,* New York Heart Association; *NSAID,* nonsteroidal antiinflammatory drug; *PUFA,* polyunsaturated fatty acid.
From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

TABLE 13 ACC/AHA Recommendations for the Hospitalized Patient with Heart Failure (HF)

Class	Indication	Level of Evidence*
I	Thorough history and physical examination to evaluate for adequacy of systemic perfusion, volume status, contribution of precipitating factors and/or comorbidities, and whether HF is associated with preserved ejection fraction.	C
	Concentrations of B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) to evaluate dyspnea if the contribution of heart failure is not known.	A
	Acute coronary syndrome should be promptly identified by electrocardiogram and cardiac troponin testing, and treated, as appropriate to the overall condition and prognosis of patient.	C
	Oxygen therapy should be administered to relieve symptoms related to hypoxemia.	C
	Improve systemic perfusion in patients who present with rapid decompensation and hypoperfusion associated with decreasing urine output and other manifestations of shock.	C
	Treatment of significant fluid overload with intravenous loop diuretics. The diuretic dose should be titrated to relieve symptoms and to reduce extracellular fluid volume excess.	B, C
	Monitor the effects of therapy with careful measurement of fluid intake and output; vital signs; body weight, and symptoms of systemic perfusion and congestion.	C
	Intensify the diuretic regiment when the diuresis is inadequate to relieve congestion.	C
	Intravenous inotropic or vasopressor drugs should be administered to maintain systemic perfusion and preserve end-organ performance in patients with clinical evidence of hypotension associated with hypoperfusion and elevated cardiac filling pressures.	C
	Invasive hemodynamic monitoring to guide therapy in patients who are in respiratory distress or with clinical evidence of impaired perfusion if filling pressures cannot be determined from clinical assessment.	C
	Medications should be reconciled and adjusted as appropriate on admission to and discharge from the hospital.	C
	Maintenance treatment with oral therapies known to improve outcomes (ACE inhibitors or ARBs and beta-blocker therapy) in the absence of hemodynamic instability or contraindications.	C
	Initiation of treatment with oral therapies known to improve outcomes (ACE inhibitors or ARBs and beta-blocker therapy) in stable patients prior to hospital discharge.	B
	During transition from intravenous to oral diuretic therapy, patient should be monitored carefully for supine and upright hypotension, worsening renal function, and HF signs/symptoms.	C
	Comprehensive written discharge instructions for patients and their caregivers is strongly recommended.	C
	Postdischarge systems of care, if available, should be used to facilitate the transition to effective outpatient care.	B
IIa	Urgent cardiac catheterization and revascularization in patients with acute HF with known or suspected acute myocardial ischemia due to occlusive coronary disease when there are signs and symptoms of inadequate systemic perfusion and revascularization is likely to prolong meaningful survival.	C
	Intravenous nitroglycerin, nitroprusside, or nesiritide for patients with evidence of severely symptomatic fluid overload in the absence of systemic hypotension.	C
	Ultrafiltration for patients with refractory congestion not responding to medical therapy.	B
IIb	Intravenous inotropic drugs (dopamine, dobutamine, or milrinone) for patients presenting with documented severe systolic dysfunction, low blood pressure, and evidence of low cardiac output, with or without congestion, to maintain systemic perfusion and preserve end-organ performance.	C
III	Use of parenteral inotropes in normotensive patients with acute decompensated HF without evidence of decreased organ perfusion.	B
	Routine use of invasive hemodynamic monitoring in normotensive patients with acute decompensated HF and congestion with symptomatic response to diuretics and vasodilators.	B

*See guidelines text for definition of level of evidence categories.
ACC, American College of Cardiology; *ACE,* angiotensin-converting enzyme; *AHA,* American Heart Association; *ARB,* angiotensin-receptor blocker.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 14 Intravenous Vasoactive Agents for Treatment of Acute Heart Failure

Intravenous Medication	Initial Dose	Effective Dose Range	Comments
Vasodilators			
Nitroglycerin; glyceryl trinitrate	20 μg/min	40-400 μg/min	Hypotension, headache Tolerance with continuous use after 24 hours
Isosorbide dinitrate	1 mg/hr	2-10 mg/hr	Hypotension, headache Tolerance with continuous use within 24 hours
Nitroprusside	0.3 μg/kg/min	0.3-5 μg/kg/min (usually <4 μg/kg/min)	Caution in patients with active myocardial ischemia Hypotension; cyanide side effects (nausea, dysphoria); thiocyanate toxicity; light sensitive
Nesiritide	2 μg/kg bolus with 0.010-0.030 μg/kg/min infusion*	0.010-0.030 μg/kg/min†	Uptitration: 1 μg/kg bolus, then increase infusion rate by 0.005 μg/kg/min no more frequently than every 3 hours, up to maximum of 0.03 μg/kg/min Hypotension, headache (less than with organic nitrates)
Inotropes			
Dobutamine	1-2 μg/kg/min	2-20 μg/kg/min	For inotropy and vasodilation; hypotension, tachycardia, arrhythmias; ?mortality
Dopamine	1-2 μg/kg/min	2-4 μg/kg/min	For inotropy and vasodilation; hypotension, tachycardia, arrhythmias; ?mortality
	4-5 μg/kg/min	5-20 μg/kg/min	For inotropy and vasoconstriction; tachycardia, arrhythmias; ?mortality
Milrinone	25-75 μg/kg bolus over 10-20 min* followed by infusion	0.10-0.75 μg/kg/min	For vasodilation and inotropy; hypotension, tachycardia, arrhythmias; renal excretion; ?mortality
Enoximone††	0.25-0.75 mg/kg	1.25-7.5 μg/kg/min	For vasodilation and inotropy; hypotension, tachycardia, arrhythmias; ?mortality
Levosimendan††	12-24 μg/kg bolus over 10 min followed by infusion	0.5-2.0 μg/kg/min	For vasodilation and inotropy; active metabolite present for ~84 hours; hypotension, tachycardia, arrhythmias; ?mortality
Epinephrine		0.05-0.5 μg/kg/min	For vasoconstriction and inotropy; tachycardia, arrhythmias, end-organ hypoperfusion; ?mortality
Norepinephrine		0.2-1.0 μg/kg/min	For vasoconstriction and inotropy; tachycardia, arrhythmias, end-organ hypoperfusion; ?mortality

*Some clinicians do not administer a bolus dose to decrease the risk of hypotension. Bolus not recommended in patients with hypotension.
†Lower doses have also been effective in some small studies.
††Not approved for use in all countries.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 15 ACC/AHA/HFSA Guidelines for Treatment of Patients with Stage C Heart Failure and Preserved Left Ventricular Ejection Fraction (HFpEF)

Class	Indication	Level of Evidence
I	Systolic and diastolic blood pressure should be controlled in accordance with published clinical practice guidelines to prevent morbidity.	B
	Diuretics should be used for relief of symptoms due to volume overload.	C
IIa	Coronary revascularization is reasonable in patients with coronary artery disease in whom symptoms (angina) or demonstrable myocardial ischemia is judged to be having an adverse effect on symptomatic heart failure.	C
	Management of atrial fibrillation according to published clinical practice guidelines is reasonable to improve symptomatic heart failure.	C
	The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure.	C
IIb	In appropriately selected patients with HFpEF (with EF ≥45%, elevated BNP levels or heart failure admission within 1 yr, estimated glomerular filtration rate >30 ml/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.	B-R
IIb	The use of ARBs might be considered to decrease hospitalizations.	B
III: No benefit	The routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is ineffective.	B-R
III: No benefit	Routine use of nutritional supplements is not recommended.	C

ACC, American College of Cardiology; *ACE,* angiotensin-converting enzyme; *AHA,* American Heart Association; *ARB,* angiotensin receptor blocker; *BNP,* B-type (brain) natriuretic peptide; *HFSA,* Heart Failure Society of America. From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

4. Used as first-line therapy for asymptomatic LV dysfunction (LVEF <40%) and symptomatic systolic HF (ACC/AHA grades A-D).
5. Therapy should be initiated at low doses to prevent hypotension and rapidly titrated to higher doses as tolerated.
6. Contraindications to the use of ACE inhibitors are renal insufficiency (creatinine clearance <30 ml/min), bilateral renal artery stenosis, hyperkalemia, hypotension, or adverse reactions (e.g., angioedema).

- ARBs:
  1. Receptor antagonists to the angiotensin II receptor.
  2. Clinical trials have not shown any superiority compared to ACE inhibitors in patients with systolic HF (LVEF <40%).
  3. Reserved for patients who are ACE inhibitor intolerant.
  4. Combination therapy with ARBs and ACE inhibitors is generally not recommended.
  5. Have a similar contraindication profile to ACE inhibitors. Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful for patients with HFrEF.

TABLE 16 Therapeutic Approaches for Volume Management in Acute Heart Failure (AHF)

Severity of Volume Overload	Diuretic	DOSE (mg)	Comments
Moderate	Furosemide, or	20-40, or up to 2.5 times oral dose	IV administration preferable in symptomatic patients
	Bumetanide, or	0.5-1.0	Titrate dose according to clinical response.
	Torsemide	10-20	Monitor Na^+, K^+, creatinine, BP
Severe	Furosemide, or	40-160, or 2.5 times oral dose 5-40 mg/hr infusion	Intravenously
	Bumetanide, or	1-4/0.5-2 mg/hr infusion (max, 2-4 mg/hr, limit 2-4 hr)	Bumetanide and torsemide have higher oral bioavailability than furosemide, but IV administration preferable in AHF.
	Torsemide	20-100/5-20 mg/hr	
	Ultrafiltration	200-500 ml/hr	Adjust ultrafiltration rate to clinical response; monitor for hypotension; consider hematocrit sensor.
Refractory to loop diuretics	Add HCTZ, *or*	25-50 twice daily	Combination with loop diuretic may be better than very high dose of loop diuretics alone.
	Metolazone, *or*	2.5-10 once daily	Metolazone more potent if creatinine clearance <30 ml/min
	Chlorothiazide, *or*	250-500 mg IV 500-1000 mg PO	
	Spironolactone	25-50 once daily	Spironolactone best choice if patient not in renal failure and normal or low serum K^+, although may not be very potent
In case of alkalosis	Acetazolamide	0.5	Intravenously
Refractory to loop diuretics and thiazides	Add dopamine (renal vasodilation), *or* dobutamine or milrinone (inotropic agent)		
	Ultrafiltration, or hemodialysis if coexisting renal failure		

BP, Blood pressure; *IV,* intravenous; *HCTZ,* hydrochlorothiazide; *PO,* by mouth.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

- Angiotensin receptor–neprilysin inhibitor (ARNI) (valsartan/sacubitril):
  1. Neprilysin is an enzyme that degrades natriuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides.
  2. In a randomized controlled trial (PARADIGM-HF) that compared valsartan/sacubitril with enalapril in symptomatic patients with HFrEF tolerating an adequate dose of either ACE inhibitor or ARB, the ARNI reduced the composite end point of cardiovascular death or HF hospitalization significantly, by 20%. Additionally, in another randomized controlled trial (PIONEER – HF), in HFrEF patients hospitalized with decompensated HF, initiation of valsartan/sacubitril caused a greater reduction in NT-proBNP concentration than enalapril. Rates of adverse effects did not significantly differ between the two groups.
  3. In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (class I).
  4. ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (class III: Harm).
  5. ARNI should not be administered to patients with a history of angioedema (class III: Harm).
  6. ARNI has not shown additional benefit over ARB in patients with preserved ejection fraction and is not indicated in this group of patients.
- Beta-adrenergic blockers (beta-blockers):
  1. Reduce morbidity and mortality. Such benefits observed with bisoprolol (CIBIS II trial), metoprolol succinate (MERIT-HF trial), and carvedilol (COPERNICUS trial).
  2. Benefit is believed to be conferred by blockade of sympathetic effects of neurohormonal stimulation due to HF.
  3. Are considered first-line therapy for symptomatic patients with systolic HF (NYHA class ≥II and LVEF <35%).
  4. Only carvedilol, bisoprolol, and metoprolol succinate (long acting) have been approved for the medical treatment of chronic HF; these agents are generally started in patients judged to be euvolemic and dosage is to be slowly uptitrated as tolerated.
  5. Adverse effects include worsening HF (due to negative inotropic effects), fatigue, dizziness, bradycardia, hypotension, and bronchospasm.
- Aldosterone receptor antagonists:
  1. Reduce morbidity and mortality.
  2. Indicated in patients with NYHA class II-IV HF, with LVEF ≤35%, already treated with ACE inhibitors and beta-blockers without significant renal insufficiency or hyperkalemia. Patients with NYHA class II should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be ≤2.5 mg/dl in men or ≤2.0 mg/dl in women (or estimated glomerular filtration rate >30 ml/min/1.73 m2), and potassium should be <5.0 mEq/L. They are also indicated for post-MI patients with EF ≤40% who have either symptomatic HF or diabetes mellitus.
  3. Spironolactone may cause gynecomastia, galactorrhea, and hyperkalemia (especially in patients with baseline renal insufficiency or type 4 renal tubular acidosis). It has been best studied in chronic HF with NYHA class III to IV symptoms (RALES study).
  4. Eplerenone is associated with fewer endocrine side effects and has especially been studied in postmyocardial infarction left ventricular dysfunction (EPHESUS trial) and in chronic systolic HF with only class II symptoms (EMPHASIS-HF trial).
  5. Inappropriate use of aldosterone receptor antagonists is potentially harmful because of life-threatening hyperkalemia or renal insufficiency when serum creatinine is >2.5 mg/dl in men or >2.0 mg/dl in women (or estimated glomerular filtration rate <30 ml/min/1.73 m2), and/or potassium >5.0 mEq/L.
- Diuretics:
  1. They are used to maintain euvolemia and to improve symptoms as discussed previously.
  2. Although data on diuretic efficacy are limited, a meta-analysis of a few small trials

found that they were associated with reduction in mortality as well as reduced hospitalization for HF.
3. Of note, loop diuretics with better bioavailability, such as torsemide and bumetanide, may be used in diuretic-resistant patients but are generally more expensive.

- Combination of isosorbide dinitrate and hydralazine:
  1. Cause venous (nitrates) and arteriolar (hydralazine) vasodilation resulting in decreased preload and afterload.
  2. The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and beta-blockers, unless contraindicated.
  3. A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated.
  4. Adverse effects of nitrates include hypotension, headaches, and tolerance as well as reflex tachycardia and lupus-like syndrome with hydralazine.
- Digoxin:
  1. Positive inotropic and negative chronotropic drug that works by inhibition of the sodium-potassium transmembrane exchange pump and through its vagomimetic action.
  2. Commonly used in patients with concomitant atrial fibrillation.
  3. Has been shown to reduce HF-related hospitalizations but does not confer any mortality benefit (DIG trial). However, there is evidence suggesting that digoxin may actually have an effect on survival that varies with the serum digoxin level; survival was improved when the level was between 0.5 and 0.8 ng/ml (most often in men) and significantly worsened when it was ≥1.2 ng/ml and >0.9 mg/ml in women.
  4. Caution must be used in patients with abnormal renal function to avoid digoxin toxicity and life-threatening arrhythmia. Avoid hypokalemia because potassium competes with digoxin on the same site of the Na^+-K^+-ATPase pump.
- I_f channel inhibitor (ivabradine):
  1. Ivabradine is a new therapeutic agent that selectively inhibits the I_f current in the sinoatrial node, providing heart rate reduction.
  2. Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline-directed therapy, including a beta-blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (class IIa).
- Cardiac resynchronization therapy (CRT):
  1. Improves morbidity and mortality rates in selected patients.
  2. The presence of a bundle-branch block or other intraventricular conduction delay (IVCD) can cause ventricular dyssynchrony, which induces regional loading disparities and reduces the efficiency of ventricular contraction, thereby further impairing the systolic function of a failing ventricle.
  3. CRT is indicated for patients who have LVEF ≤35%, sinus rhythm, left bundle-branch block with a QRS duration of 150 ms or greater, and NYHA class II, III, or ambulatory IV symptoms on guideline-directed medical therapy. CRT is NOT indicated in patients whose functional status and life expectancy are limited predominantly by chronic noncardiac conditions. Life expectancy should be >1 yr.
  4. In the appropriate subset of patients, CRT in addition to optimal medical therapy has been shown in numerous clinical trials to improve symptoms by at least one NYHA class, improve 6-min walk distance and quality of life, reduce rate of HF-related hospitalization, and reduce rate of all-cause and cardiovascular mortality.
  5. ACC/AHA guidelines for cardiac resynchronization therapy are summarized in Table 17.
- Implantable cardioverter-defibrillators (ICDs):
  1. Sudden cardiac death (SCD) is a common cause of death in patients with HF in both ischemic and nonischemic cardiomyopathies. Ventricular tachycardia (VT) degenerating into ventricular fibrillation (VF) is the culprit in the majority of patients with SCD, although bradyarrhythmias do also occur with less frequency.
  2. ICD therapy is recommended for primary prevention of SCD to reduce total mortality in selected patients with nonischemic dilated cardiomyopathy or ischemic heart disease at least 40 days post-MI with LVEF ≤35% and NYHA class II or III symptoms on chronic guideline-directed medical therapy, who have reasonable expectation of meaningful survival for >1 yr.
  3. Patients with HF who survive an episode of sudden cardiac arrest or experience sustained VT in the presence of

TABLE 17 ACCF/AHA Guidelines for Cardiac Resynchronization Therapy (CRT)

Class	Indication	Level of Evidence
I	CRT is indicated for patients who have LVEF of 35% or less, sinus rhythm, LBBB with QRS duration of 150 msec or greater, and NYHA Class II, III, or ambulatory IV symptoms on GDMT.	A for NYHA Class III/I B for Class II
IIa	CRT can be useful for patients who have LVEF of 35% or less, sinus rhythm, non-LBBB pattern with QRS duration of 150 msec or greater, and NYHA Class III/ambulatory Class IV symptoms on GDMT.	A
	CRT can be useful for patients who have LVEF of 35% or less, sinus rhythm, LBBB with QRS duration of 120 to 149 msec, and NYHA Class II, III, or ambulatory IV symptoms on GDMT.	B
	CRT can be useful in patients with atrial fibrillation and LVEF of 35% or less on GDMT if (a) the patient requires ventricular pacing or otherwise meets CRT criteria and (b) atrioventricular nodal ablation or pharmacologic rate control will allow near-100% ventricular pacing with CRT.	B
	CRT can be useful for patients on GDMT who have LVEF of 35% or less and are undergoing placement of new or replacement device with anticipated requirement for significant (>40%) ventricular pacing.	C
IIb	CRT may be considered for patients who have LVEF of 35% or less, sinus rhythm, non-LBBB pattern with QRS duration of 120 to 149 msec, and NYHA Class III/ambulatory Class IV on GDMT.	B
	CRT may be considered for patients who have LVEF of 35% or less, sinus rhythm, non-LBBB pattern with QRS duration of 150 msec or greater, and NYHA Class II symptoms on GDMT.	B
	CRT may be considered for patients who have LVEF of 30% or less, ischemic etiology of HF, sinus rhythm, LBBB with QRS duration of 150 msec or greater, and NYHA Class I symptoms on GDMT.	C
III: No benefit	CRT is not recommended for patients with NYHA Class I or II symptoms and non-LBBB pattern with QRS duration less than 150 msec.	
	CRT is not indicated for patients whose comorbidities and/or frailty limit survival with good functional capacity to less than 1 yr.	

ACCF, The American College of Cardiology Foundation; *AHA,* American Heart Association; *GDMT,* guideline-directed medical therapy; *LBBB,* left bundle-branch block; *LVEF,* left ventricular ejection fraction; *NYHA,* New York Heart Association.

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

LVEF <35% are at high risk for future arrhythmic events and SCD and obtain a mortality benefit from ICD placement for secondary prevention, with or without adjunctive therapies such as antiarrhythmic drugs, radiofrequency ablation, surgery, or transplant.

4. ACC/AHA guidelines for indications for implantable cardioverter-defibrillators are summarized in Table 18.

- In the absence of an indication (e.g., atrial fibrillation), routine use of anticoagulation is currently not recommended in patients with HF. Even with the increased risk for LV thrombus formation in dilated cardiomyopathy and subsequent thromboembolization, data are conflicting about benefits of antithrombotic (antiplatelet or anticoagulant) therapy for primary prevention to reduce thromboembolic events or mortality in patients with systolic HF who are in sinus rhythm (SOLVD, V-HeFT, SAVE, HELAS, and WASH trials). It may be reasonable to consider anticoagulation for secondary prevention in patients with HF who had a prior thromboembolic event; however, risks and benefits should be carefully assessed.
- Antiplatelet agents are recommended for patients with concomitant CAD.
- Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use.
- Calcium channel blocking drugs are not recommended as routine treatment for patients with HFrEF.
- Omega-3 polyunsaturated fatty acid supplementation is reasonable to use as adjunctive therapy in patients with NYHA class II-IV symptoms and HFrEF or HFpEF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations.
- Percutaneous coronary intervention (PCI) or surgical revascularization should be considered in patients with HF and significant CAD who are revascularization candidates.
- In general, the following sequence of drugs is recommended:
  1. Loop diuretics to provide symptom relief and achieve a euvolemic state.
  2. ACE inhibitor or ARB started at low doses, then increased to a moderate dose in 1-2 wk. Replace with ARNI in those tolerating ACE inhibitor or ARB.
  3. Beta-blockers after the patient is stable on ACE/ARB treatment. Start a low dose, then uptitrate to goal based on trial data or maximal dose tolerated. Once achieved, uptitration of ACE or ARB to goal doses can be completed.
- The following drugs can be added in selected patients in the absence of contraindications:
  1. Aldosterone antagonists improve survival in NYHA class II with LVEF <30% or NYHA class III-IV with EF <35%. Kidney function should be stable with eGFR ≥30 ml/min and potassium <5 mEq/L.
  2. Combination of hydralazine with a nitrate in patients (particularly African Americans) with a reduced EF.
  3. Digoxin reduces hospitalizations for HF and controls HR in atrial fibrillation. It can also help control symptoms.

CHRONIC TREATMENT OF HFPEF:

- To date, there is a relative dearth of clinical trials examining effective chronic treatment strategies in this subset of patients with HFpEF. Current therapies are mainly for symptomatic relief. ACC/AHA guidelines for treatment of patients with end-stage heart failure are summarized in Table 19.
- Therapy centers on relief of volume overload with judicious diuretic use, treatment of ischemia via coronary revascularization (Table 20), management of atrial fibrillation, controlling heart rate and blood pressure to prevent acute decompensation, and restriction of sodium and fluid to prevent volume overload.
- Diuretics should be used for relief of symptoms due to volume overload in patients with HFpEF.
- The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF.
- The use of ARBs might be considered to decrease hospitalizations for patients with HFpEF.
- Aldosterone antagonists may be used in appropriate patients with HFpEF (EF >45%, elevated BNP or HF admission in the past yr, potassium <5.0 mEq/L, estimated glomerular filtration rate >30 and creatinine <2.5 mg/dl) to decrease hospitalizations (class IIb recommendation).
- Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life in patients with HFpEF is not recommended as there is no benefit.
- There is no evidence to support routine use of nutritional supplements, and they are not recommended for patients with HFpEF.
- Surgical options (Table 21) for contributing critical aortic stenosis, constrictive pericarditis, and hypertrophic cardiomyopathy (HCM) should be entertained in appropriate patients.
- In patients with comorbidities including anemia, hypertension, and sleep apnea, the following recommendations are made:
  1. Intravenous iron replacement in patients with NYHA class II and III HF and iron deficiency (ferritin <100 ng/ml or 100-300 ng/ml with transferrin saturation <20%) to improve functional status and quality of life (class IIb recommendation).
  2. Titration of medical therapy to attain systolic blood pressure <130 mm Hg is recommended in patients with HFrEF and hypertension, as well as in patients with HFpEF and persistent hypertension after treatment of volume overload (class I recommendation).
  3. A formal sleep assessment should be obtained in patients with NYHA class II-IV HF with suspicion of sleep-disordered breathing. Continuous positive airway pressure should be used in patients with HF and obstructive sleep apnea to improve sleep quality and daytime sleepiness (class IIb recommendation).

DISPOSITION

- Coordination of care (Table 22) is essential in patients with chronic heart failure.
- Annual mortality of systolic HF ranges from 10% in stable patients with mild symptoms to 50% in patients with NYHA class IV disease (a mortality rate rivaling some malignancies).

TABLE 18 ACCF/AHA Guidelines for Indications for Implantable Cardioverter-Defibrillators (ICDs)

Class	Indication	Level of Evidence
I	ICD therapy is recommended for primary prevention of SCD in selected patients with HFrEF at least 40 days post-MI with LVEF less than 35% and NYHA Class II or III symptoms receiving chronic GDMT, who are expected to live more than 1 yr.	A
I	ICD therapy is recommended for primary prevention of SCD in selected patients with HFrEF at least 40 days post-MI with LVEF less than 30% and NYHA Class I symptoms receiving GDMT, who are expected to live more than 1 yr.	B
IIa	To prevent SCD, placement of ICD is reasonable in patients with asymptomatic ischemic cardiomyopathy who are at least 40 days post-MI, have an LVEF of 30% or less, are on appropriate medical therapy, and have reasonable expectation of survival with a good functional status for more than 1 yr.	B
IIb	ICD therapy to prevent SCD in patients with nonischemic cardiomyopathy who are at least 40 days post-MI, have LVEF less than 35%, with NYHA Class II or III symptoms while undergoing chronic optimal medical therapy, and have reasonable expectation of survival for more than 1 yr with good functional status.	B
	Usefulness of implantation of ICD is of uncertain benefit to prolong meaningful survival in patients with high risk of non-SCD, as predicted by frequent hospitalizations, advanced frailty, or comorbidities such as systemic malignancy or severe renal dysfunction.	B

HFrEF, Heart failure with reduced ejection fraction; *MI,* myocardial infarction; *SCD,* sudden cardiac death; see **Table 17** for other abbreviations.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 19 ACC/AHA Guidelines for Treatment of Patients with End-Stage Heart Failure (Stage D)

Class	Indication	Level of Evidence
	Nonpharmacologic Interventions	
IIa	Fluid restriction (1.5-2 L/day) is reasonable in stage D, especially in patients with hyponatremia.	B
	Inotropic Support	
I	Until definitive therapy (e.g., coronary revascularization, MCS, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary IV inotropic support to maintain systemic perfusion and preserve end-organ performance.	C
IIa	Continuous IV inotropic support is reasonable as "bridge therapy" in patients with stage D refractory to GDMT and device therapy who are eligible for and awaiting MCS or cardiac transplantation.	B
IIb	Short-term, continuous IV inotropic support may be reasonable in those hospitalized patients presenting with documented severe systolic dysfunction who present with low blood pressure and significantly depressed cardiac output, to maintain systemic perfusion and preserve end-organ performance.	B
	Long-term, continuous IV inotropic support may be considered as palliative therapy for symptom control in select patients with stage D despite optimal GDMT and device therapy who are not eligible for either MCS or cardiac transplantation.	B
III: Harm	Long-term use of either continuous or intermittent, IV parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, is potentially harmful in the patient with HF.	B
	Use of parenteral inotropic agents in hospitalized patients without documented severe systolic dysfunction, low blood pressure, or impaired perfusion, and evidence of significantly depressed cardiac output, with or without congestion, is potentially harmful.	B
	Mechanical Circulatory Support (MCS)	
IIa	MCS is beneficial in carefully selected patients with stage D HFrEF in whom definitive management (e.g., cardiac transplantation) or cardiac recovery is anticipated or planned.	B
	Nondurable MCS, including the use of percutaneous and extracorporeal ventricular assist devices (VADs), is reasonable as a "bridge to recovery" or "bridge to decision" for carefully selected patients with HFrEF with acute, profound hemodynamic compromise.	B
	Durable MCS is reasonable to prolong survival for carefully selected patients with stage D HFrEF.	B
	Cardiac Transplantation	
I	Evaluation for cardiac transplantation is indicated for carefully selected patients with stage D HF despite GDMT, device, and surgical management	C

ACC, American College of Cardiology; *AHA,* American Heart Association; *GDMT,* Guideline-directed medical therapy; *HF,* heart failure; *HFrEF,* heart failure with reduced ejection fraction; *IV,* intravenous.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 20 ACC/AHA Guidelines for Surgical/Percutaneous/Transcatheter Interventional Treatments of Heart Failure

Class	Indication	Level of Evidence
I	Coronary artery revascularization via CABG or percutaneous intervention is indicated for patients (HFpEF and HFrEF) on GDMT with angina and suitable coronary artery anatomy, especially for a left main artery stenosis (>50%) or left main–equivalent disease.	C
IIa	CABG to improve survival is reasonable in patients with mild to moderate LV systolic dysfunction (EF 35%-50%) and significant (≥70% diameter stenosis) multivessel CAD or proximal left anterior descending coronary artery stenosis when viable myocardium is present in the region of intended revascularization.	B
	CABG or medical therapy is reasonable to improve morbidity and cardiovascular mortality for patients with severe LV dysfunction (EF <35%), HF, and significant CAD.	B
	Surgical aortic valve replacement is reasonable for patients with critical aortic stenosis and a predicted surgical mortality of no greater than 10%.	B
	Transcatheter aortic valve replacement after careful candidate consideration is reasonable for patients with critical aortic stenosis who are deemed inoperable.	B
IIb	CABG may be considered with the intent of improving survival in patients with ischemic heart disease with severe LV systolic dysfunction (EF <35%) and operable coronary anatomy whether or not viable myocardium is present.	B
	Transcatheter mitral valve repair or mitral valve surgery for functional mitral insufficiency is of uncertain benefit and should only be considered after careful candidate selection and with a background of GDMT.	B
	Surgical reverse remodeling or LV aneurysmectomy may be considered in carefully selected patients with HFrEF for specific indications, including intractable HF and ventricular arrhythmias.	B

ACC, American College of Cardiology; *AHA,* American Heart Association; *CABG,* coronary artery bypass grafting, *CAD,* coronary artery disease; *EF,* ejection fraction; *GDMT,* guideline-directed medical therapy; *HF,* heart failure; *HFpEF,* heart failure with preserved ejection fraction; *HFrEF,* HF with reduced ejection fraction; *LV,* left ventricle.
From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

The Seattle Heart Failure Model provides an accurate estimate of 1-, 2-, and 3-yr survival before and after different therapies. This model can be useful to assess the need for LV assist device implantation or urgent transplantation. The calculator is available online at http://depts.washington.edu/shfm/.

- Cardiac transplantation has a 5-yr survival rate of ~70% and represents a viable option in selected patients. Fig. E4 describes an algorithm for evaluation of potential heart transplant recipient.
- The use of an LV assist device (LVAD) in patients with advanced HF can result in a clinically meaningful survival benefit and improve quality of life in patients who are not candidates for cardiac transplantation. There are two approved uses of LVADs specifically as a bridge to transplant and as destination therapy. There are two major categories of LVAD pulsatile flow devices vs. continuous

TABLE 21 Surgery for Management of Heart Failure (HF): Guideline Recommendations

2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure

Recommendations for Myocardial Revascularization in Patients with Chronic HF

- Myocardial revascularization is recommended when angina persists despite antiangina drugs; *class I, level of evidence A.*
  The choice between CABG and PCI should be made by the heart team after careful review.
  CABG is recommended for patients with angina and significant LM or LM-equivalent stenosis to improve prognosis.
  CABG is recommended for patients with HFrEF, significant CAD (LAD or multivessel disease), and LVEF <35%.

2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease*

- A heart team approach to revascularization is recommended in patients with diabetes mellitus and complex multivessel CAD; *class 1, level of evidence C.*
- CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and multivessel CAD for which revascularization is likely to improve survival (3-vessel CAD or complex 2-vessel CAD involving the proximal LAD); *class 1, level of evidence B.*

2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease†

Indications for Aortic Valve Surgery in Aortic Stenosis (as) with Left Ventricular Dysfunction

- AVR is recommended for asymptomatic patients with severe AS and LVEF <50%; *class I, level of evidence B.*
- AVR is reasonable in symptomatic patients with low-flow/low-gradient severe AS with reduced LVEF with a low-dose dobutamine stress study that shows an aortic velocity ≥4.0 m/sec or mean pressure gradient ≥40 mm Hg with a valve area of ≤1.0 cm^2; *class IIa, level of evidence B.*
- AVR is reasonable for patients with moderate AS who are undergoing other cardiac surgery; *class IIa, level of evidence C.*
- TAVR is recommended in patients who meet an indication for AVR for AS and who have a prohibitive surgical risk and post-TAVR survival >12 mo; *class I, level of evidence B.*
- TAVR is a reasonable alternative to surgical AVR in patients who meet an indication for AVR and who have a high surgical risk; *class IIa, level of evidence B.*

Indications for Aortic Valve Surgery in Aortic Regurgitation (AR) with LV Dysfunction

- AVR is recommended for symptomatic patients with severe AR; *class I, level of evidence B.*
- AVR is indicated for patients with severe AR and LV systolic dysfunction; *class I, level of evidence B.*

Indications for Mitral Valve Surgery in Functional Mitral Regurgitation (MR)

- Mitral valve surgery is reasonable for patients with chronic severe functional MR who are undergoing CABG or AVR; *class IIa, level of evidence C.*
- Mitral valve surgery may be considered for severely symptomatic patients (NYHA Class III/IV) with chronic severe functional MR; *class IIb, level of evidence B.*
- Mitral valve repair may be considered for patients with chronic moderate functional MR who are undergoing other cardiac surgery; *class IIb, level of evidence C.*

ESC/EACTS Guidelines on the Management of Valvular Heart Disease (Version 2012)‡

Indications for Mitral Valve Surgery in Chronic Secondary Mitral Regurgitation (MR)

- Surgery is indicated in patients with severe MR undergoing CABG and LVEF >30%; *class I, level of evidence C.*
- Surgery should be considered in patients with moderate MR undergoing CABG; *class IIa, level of evidence C.*
- Surgery should be considered in symptomatic patients with severe MR, LVEF <30%, option for revascularization, and evidence of viability; *class IIa, level of evidence: C.*
- Surgery may be considered in patients with severe MR, LVEF >30%, who remain symptomatic despite optimal medical management (including CRT if indicated) and have low comorbidity, when revascularization is not indicated; *class IIb, level of evidence C.*

*Fihn SD et al: 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, *Circulation* 2014;130:1749-67.

†Nishimura RA et al: 2014 AHA/ACC guideline for the management of patients with valvular heart disease: *J Thorac Cardiovasc Surg* 2014;148:E1-E132.

‡Vahanian A et al: Guidelines on the management of valvular heart disease (version 2012), *Eur Heart J* 2012;33:2451-96.

AATS, Americation Assocation for Thoracic Surgery; *ACC,* American College of Cardiology; *AHA,* American Heart Association; *AS,* aortic stenosis; *AVR,* Aortic valve replacement; *CABG,* coronary artery bypass grafting; *CAD,* coronary artery disease; *CRT,* cardiac resynchronization therapy; *EACTS,* European Association for Cardio-Thoracic Surgery; *ESC,* European Society of Cardiology; *HFrEF,* heart failure with reduced ejection fraction; *LAD,* left anterior descending coronary artery; *LCx,* left circumflex coronary artery; *LM,* left main coronary artery; *LV,* left ventricle; *LVEF,* left ventricular ejection fraction; *NYHA,* New York Heart Association; *PCI,* percutaneous coronary intervention; *PCNA,* Preventive Cardiovascular Nurses Association; *SCAI,* Society for Cardiovascular Angiography and Interventions; *STS,* Society of Thoracic Surgeons; *TAVR,* transcatheter aortic valve replacement.

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 22 Coordinating Care for Patients with Chronic Heart Failure

Class	Indication	Level of Evidence
I	Effective systems of care coordination with special attention to care transitions should be deployed for every patient with chronic HF that facilitate and ensure effective care that is designed to achieve GDMT and prevent hospitalization.	B
	Every patient with HF should have a clear, detailed, and evidence-based plan of care that ensures the achievement of GDMT goals, effective management of comorbid conditions, timely follow-up with the health care team, appropriate dietary and physical activities, and compliance with secondary prevention guidelines for cardiovascular disease. This plan of care should be updated regularly and made readily available to all members of the patient's health care team.	C
	Palliative and supportive care is effective for patients with symptomatic advanced HF to improve quality of life.	B

GDMT, Guideline directed medical therapy; *HF,* heart failure.

From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

flow devices. Continuous flow devices are associated with increased survival as destination therapy as compared to medically managed controls (REMATCH trial).

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Heart Failure (Patient Information)

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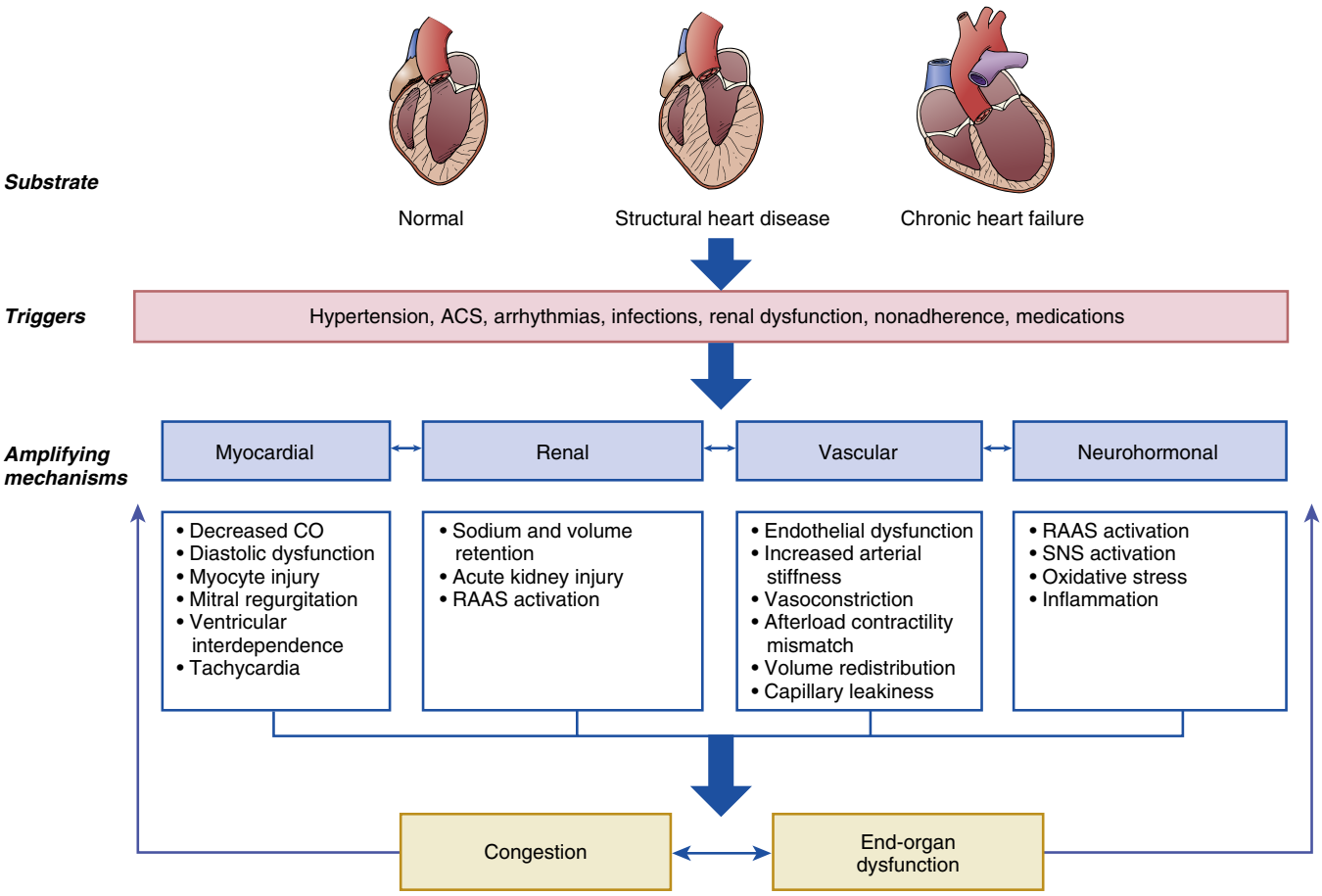

FIG. E1 A schematic representation of the pathophysiology of acute heart failure. *ACS,* Acute coronary syndrome; *CO,* cardiac output; *RAAS,* renin-angiotensin-aldosterone system; *SNS,* sympathetic nervous system. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

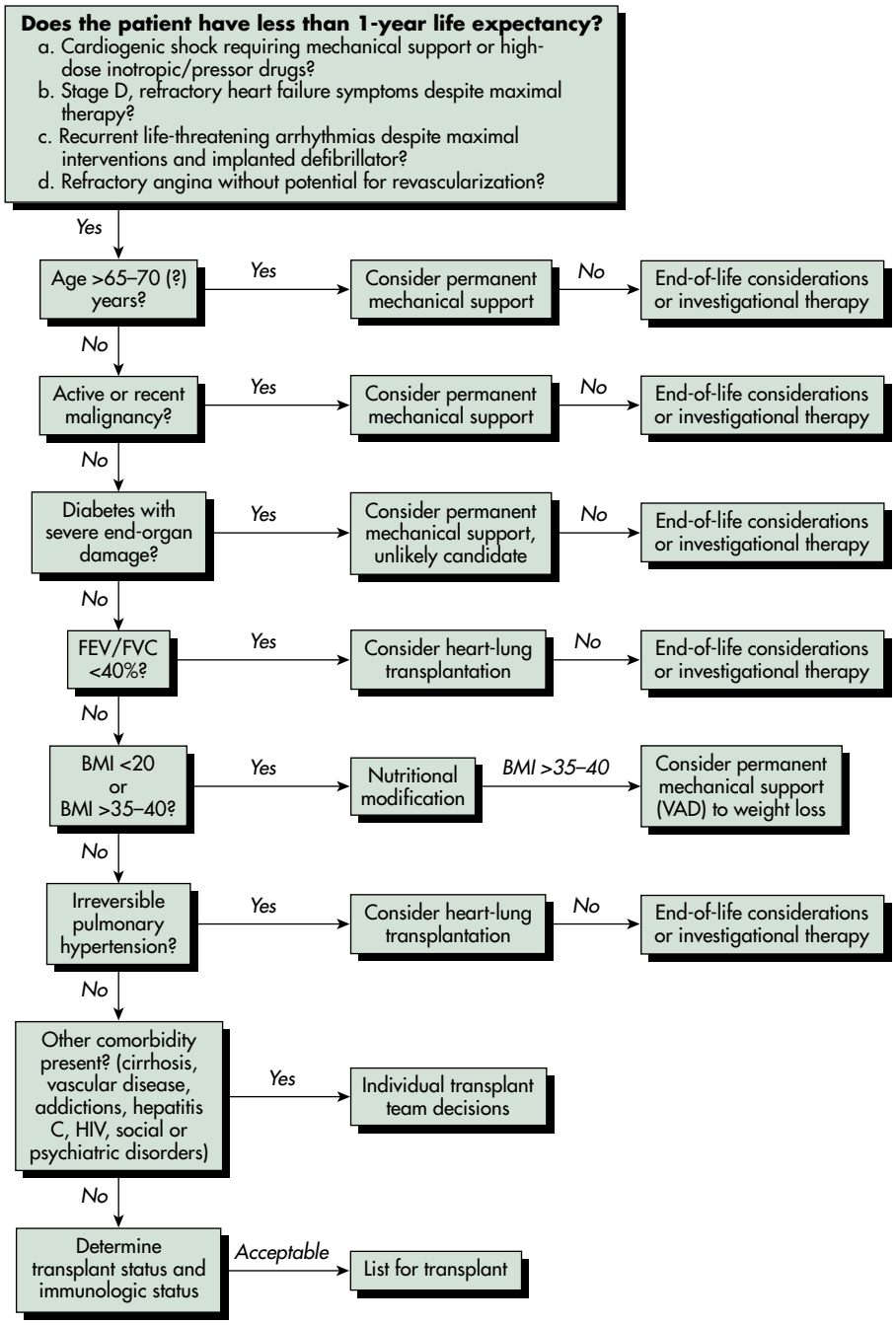

FIG. E4 Algorithm for evaluation of the potential heart transplant recipient. *BMI,* Body mass index; *FVC,* forced vital capacity; *FEV,* forced expiratory volume; *HIV,* human immunodeficiency virus; *VAD,* ventricular assist device. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

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BASIC INFORMATION

DEFINITION

Heat exhaustion and heat stroke are part of a continuum of heat-related illness, and unless factors leading to heat exhaustion are corrected swiftly, affected patients can progress to heat stroke.

- ***Heat exhaustion:*** An illness resulting from prolonged, heavy activity in a hot environment with subsequent dehydration, electrolyte depletion, and rectal temperature >37.8° C (100° F) but ≤40° C (104° F).
- ***Heat stroke:*** A life-threatening heat illness characterized by extreme hyperthermia (core temperature >40° C [104.0° F]), dehydration, and neurologic manifestations. Heat stroke can be further subdivided into "exertional heat stroke" occurring in generally healthy individuals undergoing strenuous physical activity in warm conditions and "non-exertional heat stroke" often seen in elderly and/or debilitated patients with impaired thermal regulations due to illness or medications (see Etiology).

SYNONYMS

Heat illness
Hyperthermia

ICD-10CM CODES

T67.5 Heat exhaustion, unspecified
T67.0 Heatstroke and sunstroke
T67.1 Heat syncope
T67.2 Heat cramp
T67.3 Heat exhaustion, anhydrotic
T67.6 Heat fatigue, transient

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Incidence of heat stroke is approximately 20 cases/100,000 population.
PREDOMINANT AGE: Heat exhaustion and stroke occur more frequently in elderly patients, especially those taking diuretics or medications that impair heat dissipation (e.g., phenothiazines, anticholinergics, antihistamines, beta-blockers). Table 1 describes factors predisposing to serious heat illness.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Heat exhaustion:

- Generalized malaise, weakness, headache, muscle and abdominal cramps, nausea, vomiting, hypotension, tachycardia.
- Rectal temperature is usually normal.
- Sweating is usually present.

Heat stroke:

- Neurologic manifestations (seizures, tremor, hemiplegia, coma, psychosis, other bizarre behavior)
- Evidence of dehydration (poor skin turgor, sunken eyeballs)
- Tachycardia, hyperventilation
- Skin is hot, red, and flushed
- Sweating is often (not always) absent, particularly in elderly patients
- Classic heat stroke generally develops slowly over days and occurs predominantly in older persons and in those with chronic illness. Exertional heat stroke is more common in young, healthy persons, has a more rapid onset, and is associated with higher core temperatures. Table 2 compares classic and exertional heat stroke. Box 1 summarizes organ dysfunction seen in patients with heat stroke

ETIOLOGY

- Exogenous heat gain (increased ambient temperature)
- Increased heat production (exercise, infection, hyperthyroidism, drugs)
- Impaired heat dissipation (high humidity, heavy clothing, neonatal or elderly patients, drugs [phenothiazines, anticholinergics, antihistamines, butyrophenones, amphetamines, cocaine, alcohol, β-blockers])

TABLE 1 Factors Predisposing to Serious Heat Illness

Individual Factors

Lack of acclimatization
Low physical fitness
Excessive body weight
Dehydration
Advanced age
Young age

Health Conditions

Inflammation and fever
Viral infection
Cardiovascular disease
Diabetes mellitus
Gastroenteritis
Rash, sunburn, and previous burns to large areas of skin
Seizures
Thyroid storm
Neuroleptic malignant syndrome
Malignant hyperthermia
Sickle cell trait
Cystic fibrosis
Spinal cord injury

Drugs

Anticholinergic properties (atropine)
Antiepileptic (topiramate)
Antihistamines
Glutethimide (Doriden)
Phenothiazines
Tricyclic antidepressants
Amphetamines, cocaine, "ecstasy"
Ergogenic stimulants (e.g., ephedrine, ephedra)
Lithium
Diuretics
β-Blockers
Ethanol

Environmental Factors

High temperature
High humidity
Little air motion
Lack of shade
Heat wave
Physical exercise
Heavy clothing
Air pollution (nitrogen dioxide)

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.

- Diuretics, laxatives
- Fig. E1 describes an algorithm of the pathophysiology of heat stroke

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infections (meningitis, encephalitis, sepsis)
- Head trauma
- Epilepsy
- Thyroid storm
- Acute cocaine intoxication
- Malignant hyperthermia
- Heat exhaustion can be differentiated from heat stroke by the following:
  1. Essentially intact mental function and lack of significant fever in heat exhaustion
  2. Mild or absent increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and alanine aminotransferase (ALT) in heat exhaustion

WORKUP

- Heat stroke: Comprehensive history, physical examination, and laboratory evaluation.
- Heat exhaustion: In most cases, laboratory tests are not necessary for diagnosis.

LABORATORY TESTS

Laboratory abnormalities may include the following:

- Elevated blood urea nitrogen (BUN), creatinine, hematocrit
- Hyponatremia or hypernatremia, hyperkalemia or hypokalemia
- Elevated LDH, AST, ALT, CPK, bilirubin
- Lactic acidosis, respiratory alkalosis (from hyperventilation)
- Myoglobinuria, hypofibrinogenemia, fibrinolysis, hypocalcemia

TREATMENT

- Treatment of heat exhaustion consists primarily of placing the patient in a cool, shaded area and providing rapid hydration and salt replacement.
  1. Fluid intake should be at least 2 L q4h in patients without history of CHF.
  2. Salt replacement can be accomplished by using one-quarter teaspoon of salt or two 10-grain salt tablets dissolved in 1 L of water.
  3. If IV fluid replacement is necessary, young athletes can be given normal saline IV (3 to 4 L over 6 to 8 hr); in elderly patients, consider using D5½NS IV with the rate titrated to cardiovascular status.
- Patients with heat stroke should undergo rapid cooling.
  1. Remove the patient's clothes and place the patient in a cool and well-ventilated room.
  2. If patient is unconscious, position on his or her side and clear the airway. Protect airway and augment oxygenation (e.g., nasal O_2 at 4 L/min to keep oxygen saturation >90%).

TABLE 2 Comparison of Classic and Exertional Heat Stroke

Patient Characteristics	Classic	Exertional
Age	Young children or elderly	15-55 yr
Health	Chronic illness	Usually healthy
Fever	Unusual	Common
Prevailing weather	Frequent in heat waves	Variable
Activity	Sedentary	Strenuous exercise
Drug use	Diuretics, antidepressants, anticholinergics, phenothiazines	Ergogenic stimulants or cocaine
Sweating	Often absent	Common
Acid-base disturbances	Respiratory alkalosis	Lactic acidosis
Acute renal failure	Uncommon	Common (≈15%)
Rhabdomyolysis	Uncommon	Common (≈25%)
CK	Mildly elevated	Markedly elevated (500-1000 U/L)
ALT, AST	Mildly elevated	Markedly elevated
Hyperkalemia	Uncommon	Common
Hypocalcemia	Uncommon	Common
DIC	Mild	Marked
Hypoglycemia	Uncommon	Common

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase; *CK,* creatine kinase; *DIC,* disseminated intravascular coagulation.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.

BOX 1 Organ Dysfunction Seen in Patients with Heat Stroke

Encephalopathy
Rhabdomyolysis
Acute renal failure
Acute respiratory distress syndrome
Myocardial injury
Hepatocellular injury
Intestinal ischemia and infarction
Pancreatic injury
Hemorrhagic complication (e.g., disseminated intravascular coagulation)

From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

3. Monitor body temperature every 5 min. Measurement of the patient's core temperature with a rectal probe is recommended. The goal is to reduce the body temperature to 39° C (102.2° F) in 30 to 60 min. Advantages, disadvantages, and efficacy of various cooling methods are described in Table E3.
4. Spray the patient with a cool mist and use fans to enhance airflow over the body (rapid evaporation method).
5. Immersion of the patient in ice water, stomach lavage with iced saline solution, intravenous administration of cooled fluids, and inhalation of cold air are advisable only when the means for rapid evaporation are not available. Immersion in tepid water (15° C, 59° F) is preferred over ice water immersion to minimize risk of shivering.
6. Use of ice packs on axillae, neck, and groin is controversial because they increase peripheral vasoconstriction and may induce shivering.
7. Antipyretics are ineffective because the hypothalamic set point during heat stroke is normal despite the increased body temperature.
8. Intubate a comatose patient, insert a Foley catheter, and start nasal O_2. Continuous ECG monitoring is recommended.
9. Insert at least two large-bore IV lines and begin IV hydration with normal saline (NS) or Ringer lactate.
10. Draw initial laboratory studies: Electrolytes, complete blood count, blood urea nitrogen, creatinine, AST, ALT, CPK, LDH, glucose, PT (INR), PTT, platelet count, Ca^{2+}, lactic acid, and arterial blood gases.
11. Treat complications as follows:
    a. Hypotension: Vigorous hydration with normal saline or Ringer lactate
    b. Convulsions: Diazepam 5 to 10 mg IV (slowly)
    c. Shivering: Chlorpromazine 10 to 50 mg IV
    d. Acidosis: Use bicarbonate judiciously (only in severe acidosis)

- Observe for evidence of rhabdomyolysis and hepatic, renal, or cardiac failure and treat accordingly.

DISPOSITION

Most patients recover completely within 48 hr. Central nervous system injury is permanent in 20% of cases. Mortality rate can exceed 30% in patients with prolonged and severe hyperthermia. Delayed access to cooling is the leading cause of morbidity and mortality in persons with heat stroke.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Heat Exhaustion and Heat Stroke (Patient Information)
Acute Kidney Injury (Related Key Topic)
Rhabdomyolysis (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Becker J, Stewart LK: Heat-related illness, *Am Fam Physician* 83(11):1325-1330, 2011.

Centers for Disease Control and Prevention: Heat illness among high school athletes, U.S. 2005–2009, *MMWR Morb Mort Wkly Rep* 59(32), 2010.

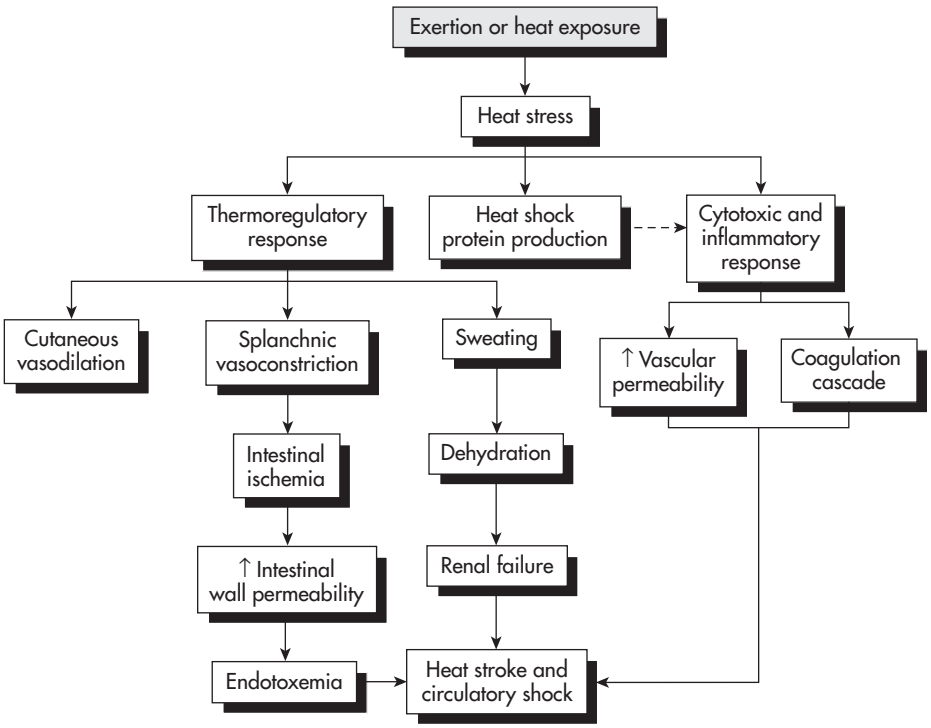

FIG. E1 Algorithm of the pathophysiology of heat stroke. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

TABLE E3 Advantages, Disadvantages, and Efficacy of Various Cooling Methods

Cooling Method	Advantages	Disadvantages	Effectiveness
Antipyretics		Can worsen liver or renal injury	Not effective (the temperature set-point is not elevated in hyperthermia) Not effective in controlling pathologic inflammation
Evaporative cooling	Noninvasive, easy to monitor, readily available	Labor-intensive—requires constant moistening of skin	Comparison studies show the cooling rate on average to be slower than immersion Published rate range: 0.05-0.31° C/min (32.09-32.56° F/min)
Immersion	Noninvasive, rapid	Cumbersome, poorly tolerated, safety questionable if comorbid conditions present, monitoring difficult, shivering and vasoconstriction	Comparison studies show the cooling rate on average to be faster than evaporation Published rate range: 0.04-0.35° C/min (32.07-32.63° F/min)
Immersion of the hands and forearms	Noninvasive, easy to perform in the field	Shivering and vasoconstriction	Slower cooling but appropriate for mildly ill patients, such as those with heat exhaustion
Ice packing	Noninvasive, readily available	Shivering and vasoconstriction, poorly tolerated	Less effective than immersion or evaporation Some authorities recommend using both evaporation and ice
Cold gastric or peritoneal lavage	Very rapid	Invasive, cumbersome (cold sterile saline needed for peritoneal lavage)	In canine studies, questionably faster than evaporation or immersion
Dantrolene	In theory, decreases heat production by inhibiting muscle contraction		No clear efficacy; it may be more effective for exertional than for classic heat stroke
Benzodiazepines	Treatment of shivering to decrease heat production and heat-induced seizures	Sedation	Whether treatment increases cooling is unknown but may make cooling treatments tolerable Also effective for heat-related seizures

From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

BASIC INFORMATION

DEFINITION

Abnormal uterine bleeding (AUB) is a broad term for variations in normal menses. Normal duration of menstrual flow is 5 days; normal menstrual cycle is 21 to 35 days. Heavy menstrual bleeding, or menorrhagia, is a large volume of menstrual blood loss (i.e., >80 ml per cycle). Bleeding may also be prolonged, intermenstrual, frequent, and irregular. This language replaces prior terms such as *metrorrhagia, polymenorrhea,* or *oligomenorrhea.*

PALM-COEIN classification of abnormal uterine bleeding was adopted in 2011 to standardize terminology and reflect etiology: Polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified. AUB-P would refer to abnormal uterine bleeding due to polyps.

SYNONYMS

Menometrorrhagia
Dysfunctional uterine bleeding
Irregular menstrual cycle

ICD-10CM CODES

N92.0	Excessive and frequent menstruation with regular cycle
N92.1	Excessive and frequent menstruation with irregular cycle
N92.2	Excessive menstruation at puberty
N92.4	Excessive bleeding in the premenopausal period
N92.6	Irregular menstruation, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 10% to 15% of reproductive-aged women; 30% of outpatient office visits; 70% of all gynecologic consults
PEAK INCIDENCE: Reproductive-aged women, ages 13 to 50
PREVALENCE: 9% to 14% of all women
PREDOMINANT SEX AND AGE: Female; peak in adolescence and perimenopausal periods
GENETICS: Hereditary coagulopathy (most commonly von Willebrand disease, platelet dysfunction disorders) in 20% of women with heavy menstrual bleeding
RISK FACTORS: Genetic predisposition, anticoagulation treatment, obesity, endocrinopathies, autoimmune disease, liver disease, renal disease

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History: Age, age at menarche or menopause, menstrual bleeding patterns, severity of bleeding, pain, underlying medical conditions, surgical history, medications, family history, hirsutism, acne, symptoms of thyroid dysfunction or other endocrinopathy
  1. If heavy bleeding since menarche, screen for signs and symptoms of hemostatic disorder, including postpartum hemorrhage, surgery-related bleeding, bleeding from dental work, easy bruising, epistaxis, and frequent gum bleeding
- Physical exam: Weight, hirsutism, acne, thyroid nodules, signs of insulin resistance (acanthosis nigricans), signs of bleeding disorder (petechiae, ecchymoses, pallor, swollen joints), pelvic examination including external, speculum, and bimanual exam of uterus

ETIOLOGY

- Pregnancy/miscarriage
- Endometrial polyps
- Adenomyosis
- Uterine leiomyoma
- Endometrial hyperplasia or carcinoma
- Coagulopathy, inherited or acquired
- Ovulatory dysfunction, most likely PCOS
- Endometrial
- Arteriovenous malformation
- Infection
- Iatrogenic

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Pregnancy, sexually transmitted infection, polycystic ovary syndrome (PCOS), thyroid dysfunction, anovulation due to immature hypothalamic-pituitary-ovarian axis or perimenopausal transition, uterine pathology including endometrial hyperplasia or carcinoma, leiomyoma, adenomyosis, or endometrial polyp, coagulopathy, iatrogenic due to medications including oral contraceptives or anticoagulants (warfarin), nonuterine bleeding (urinary, gastrointestinal, vaginal, or cervical source)

WORKUP

- History
- Physical exam
- Laboratory, pathology, and imaging studies to determine etiology

LABORATORY TESTS

- Pregnancy test
- Complete blood count (CBC)
- Thyroid-stimulating hormone (TSH)
- *Chlamydia trachomatis* testing if high risk
- Pap smear if indicated
- Targeted screening for bleeding disorders
- Endometrial sampling by endometrial biopsy or hysteroscopic sampling for women >45 yr or <45 yr with history of unopposed estrogen (PCOS, obesity), failed medical management, or persistent abnormal bleeding
- Iron studies if anemia is suspected

IMAGING STUDIES

- Pelvic ultrasound, transabdominal and transvaginal
- Sonohysterography or hysteroscopy if ultrasound is not adequate or further evaluation of the cavity is required
- MRI if needed for surgical planning or further evaluation of structural abnormality

TREATMENT

SURGICAL MANAGEMENT

- Dilation and curettage
- Hysteroscopic resection of uterine pathology including endometrial polyps and submucosal leiomyoma
- Myomectomy
- Endometrial ablation
- Uterine artery embolization
- Hysterectomy

ACUTE GENERAL Rx

Acute severe bleeding may be managed medically with oral progestins, combined oral contraceptive pills, IV estrogen, tranexamic acid, and/or blood transfusion as indicated. Surgical management includes dilation and curettage, uterine artery embolization, or hysterectomy.

CHRONIC Rx

- Combined hormonal contraceptives (pill, transdermal patch, vaginal ring) in a cyclic or continuous regimen
- Progesterone intrauterine device
- Oral or injected progesterone
- Gonadotropin-releasing hormone analog
- Nonsteroidal antiinflammatory drugs
- Tranexamic acid, aminocaproic acid
- Danazol (significant side-effect profile requires justification for use; this is rare)
- Selective progesterone receptor modulators (investigational for bleeding related to leiomyomas)
- Surgery for anatomic causes, including polypectomy or myomectomy
- Uterine artery embolization for leiomyomatous uterus
- Endometrial ablation or hysterectomy if completed childbearing
- Replacement of or treatment for any abnormal bleeding factors (i.e., DDAVP)

REFERRAL

- If unresponsive to initial hormonal management, referral to gynecologist is warranted.
- If concern for a structural etiology or malignancy, referral to a gynecologist for surgical management is indicated.
- If endometrial sampling reveals endometrial hyperplasia or malignancy, referral to a gynecologist or gynecologic oncologist is indicated. Resampling is necessary with progestin therapy for hyperplasia. If endometrial hyperplasia associated with complex glands or atypia, consultation with gynecologic oncologist is warranted due to high degree of progression to malignancy.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Heavy Menstrual Bleeding (Menorrhagia) (Patient Information)
Abnormal Uterine Bleeding (Related Key Topic)

AUTHORS: **Christina M. Johnson, MD,** and **Nima R. Patel, MD, MS**

SUGGESTED READINGS

Bradley LD, Gueye NA: The medical management of abnormal uterine bleeding in reproductive aged women, *Am J Obstet Gynecol* 214(1):31-44, 2016.

Committee on Practice Bulletins-Gynecology: Practice bulletin no. 128: diagnosis of abnormal uterine bleeding in reproductive-aged women, *Obstet Gynecol* 120:197-206, 2012.

Committee on Practice Bulletins-Gynecology: Practice bulletin no. 136: management of abnormal uterine bleeding associated with ovulatory dysfunction, *Obstet Gynecol* 122:176-185, 2013.

BASIC INFORMATION

DEFINITION

Infection of the human gastric mucosa with the organism *Helicobacter pylori,* a spiral-shaped gram-negative organism with unique features that allow it to survive in the hostile gastric environment.

SYNONYM

Previously known as *Campylobacter pylori*

ICD-10CM CODE

B96.81 *Helicobacter pylori* [*H. pylori*] as the cause of diseases classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

H. pylori is the most common chronic bacterial infection in human beings, probably affecting 50% of the Earth's population in all age groups as well as 30% to 40% of the U.S. population. In developing nations, infection is acquired at an earlier age and occurs more frequently.

CLINICAL PRESENTATION

- *H. pylori* causes histologic gastritis in all affected individuals. The majority of cases are asymptomatic and unlikely to proceed to serious consequences.
- *H. pylori* is a causative agent in peptic ulcer disease (PUD), gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma, as well as a risk factor for iron-deficiency anemia and likely chronic idiopathic thrombocytopenic purpura. It may present with the signs and symptoms of these disorders, including abdominal pain, bloating, anorexia, and early satiety. Fig. 1 describes association of *H. pylori* infection and disease states.
- "Alarm symptoms" that should prompt more immediate and aggressive workup include weight loss, dysphagia, protracted nausea or vomiting, anemia, melena, and palpable abdominal mass, particularly in older individuals.

ETIOLOGY

- Route of acquisition is unknown but is presumed to be person to person by fecal-oral or possibly oral-oral transmission.
- The majority of cases are acquired in childhood. Socioeconomic status and living conditions in childhood affect risk of acquisition of infection. These factors include housing density, number of siblings, overcrowding, sharing a bed, and lack of running water.
- Iatrogenic transmission has been documented.
- *H. pylori* does not invade gastroduodenal tissue, but disrupts the mucous layer, causing the underlying mucosa to be more vulnerable to acid peptic damage.
- It is unclear what differentiates the subset of patients with *H. pylori* who go on to develop ulcers or cancer.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infection with *H. pylori* should be considered in the face of PUD, gastric cancer, gastritis, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma.
- *H. pylori* should be considered in the differential diagnosis of upper gastrointestinal (GI) tract disease, along with nonulcer dyspepsia, reflux esophagitis, biliary tract disease, gastroparesis, pancreatitis, ischemic bowel, and unexplained iron deficiency anemia.

WORKUP

- Workup is indicated in patients with active PUD, a past history of documented peptic ulcer, or gastric MALT lymphoma, as well as those with immune thrombocytopenic purpura (ITP), and otherwise unexplained iron deficiency. The role of routine screening in high-risk populations is not clear. However, numerous studies suggest that *H. pylori* eradication is protective against progression of premalignant gastric lesions. Consider testing those starting long-term NSAID, low-dose aspirin, or proton pump inhibitor (PPI) therapy. Routine identification and treatment of *H. pylori* in cases of nonulcer dyspepsia, gastroesophageal reflux disease (GERD), and in asymptomatic individuals in populations at high risk for gastric cancer is considered controversial. There is insufficient evidence to advocate screening in asymptomatic first-degree relatives of gastric cancer patients. A test-and-treat strategy may be used in patients younger than 55 with uncomplicated dyspepsia who have no alarm symptoms.
- Results of testing must be interpreted in relation to the individual patient's likelihood of *H. pylori* infection based on demographic risk factors. In the U.S. population, increased probability of infection exists in African Americans, Hispanics/Latinos, immigrants from developing nations, patients with poor socioeconomic status, Native Americans from Alaska, and persons >50 yr.
- Routine screening for *H. pylori* is not indicated in asymptomatic patients who are at low risk of infection.
- Infected patients with functional dyspepsia often benefit from treatment and should be evaluated for *H. pylori.*

LABORATORY TESTS

- Testing may be invasive or noninvasive depending on the need for endoscopy for other indications. There is no indication for endoscopy solely to diagnose *H. pylori.*
- Tests for *H. pylori* are differentiated as active or passive. Active tests provide direct evidence that *H. pylori* infection is currently present and include urea breath testing and stool antigen testing. Passive testing, which includes all serologic testing for *H. pylori,* detects the presence of antibodies to the organism. It is limited by its inability to distinguish between active current infection and prior infection that has resolved.
- Tests that use urease as a marker (urea breath and stool antigen tests and biopsy for urease activity) may result in false-negative results in patients taking antibiotics, bismuth, or antisecretory therapy, as well as those with active ulcer bleeding. Patients should be off antibiotics for 4 wk and off protein pump inhibitors for 2 wk before urea breath or stool antigen testing.

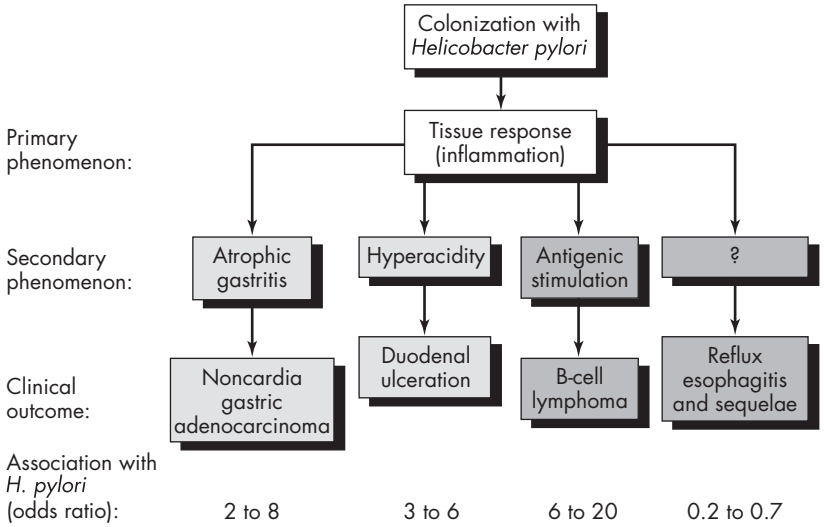

FIG. 1 Association of *Helicobacter pylori* colonization and disease states. After *H. pylori* acquisition, virtually all persons develop persistent colonization that lasts for life. Colonization induces tissue responses termed *chronic gastritis.* This process affects gastric physiology, including glandular structure, acid secretion, and antigen processing, which in turn affect disease risk. Colonization with *H. pylori* increases the risk for certain diseases (duodenal ulcer, gastric ulcer, noncardiac gastric adenocarcinoma, and B-cell lymphomas) but appears to decrease the risk for gastroesophageal reflux disease and its complications, including Barrett esophagus, and adenocarcinoma of the esophagus or gastric cardia. (From Mandell GL et al: *Principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Churchill Livingstone.)

- When diagnostic endoscopy is indicated (for suspicion or follow-up of PUD or gastric MALT), antral biopsy should be tested for urease activity. If urease testing is likely to show a false-negative result because of recent proton pump inhibitor (PPI), bismuth, or antibiotic use or active ulcer bleeding, the sample should undergo histologic examination.
- In cases in which biopsy is not indicated, urea breath testing or stool antigen testing is indicated to evaluate for active infection. Urea breath testing is slightly more expensive than stool antigen testing, but both costs are in the modest range. Choice can be made based on patient preference and availability. The sensitivities and specificities of these two tests are similar (>90%), but sensitivity may be reduced in the face of active upper GI bleed or recent PPI use.
- Serologic testing should be avoided, although it may be useful in low-risk patients in areas with low prevalence to confirm lack of infection. In this situation, positive results should be confirmed with an active testing method.

Rx TREATMENT

ACUTE GENERAL Rx

- Test only patients whom you intend to treat if positive (see "Workup"). At this time, the value of eradicating *H. pylori* infection has been clearly demonstrated in patients with PUD or gastric MALT lymphoma.
- The optimal antibiotic regimen remains undefined. In addition to efficacy, side effects, cost, and ease of administration must be considered.
- Due to increasing resistance to clarithromycin, decisions regarding appropriate regimens should take into account local rates of clarithromycin resistance, as well as any prior macrolide exposure for the patient. Clarithromycin resistance can be assumed to be >15% in the U.S., unless local resistance information is available.
- The following regimens may be considered for first-line therapy:
  1. Quadruple therapy: PPI (esomeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, omeprazole 40 mg, or rabeprazole 20 mg, all given bid), with twice-daily clarithromycin (500 mg) amoxicillin (1 g bid), and metronidazole 500 mg bid for 10 to 14 days.
  2. Bismuth quadruple therapy: PPI twice daily (see earlier) combined with bismuth subsalicylate (Pepto-Bismol and others) 262 or 525 mg four times daily, as well as tetracycline (500 mg qid) and metronidazole (250 mg qid or 500 mg tid-qid) for 10 to 14 days. This is now recommended as first-line therapy in areas of high clarithromycin resistance and in patients with penicillin allergy.
- Current guidelines recommend extended treatment of 10 to 14 days. Use of combination capsules may improve compliance but is likely to be more expensive.
- Recent guidelines suggest multiple other regimens that can be considered based on local resistance patterns and patient's allergy profile.
- Prior exposure to a macrolide or metronidazole, for any reason, is associated with increased resistance. A preferable regimen would include medications to which the patient has not been previously exposed.
- Diarrhea and abdominal cramping are commonly observed with many of the regimens. (Probiotics may diminish this effect.) Other side effects may include a metallic taste with metronidazole or clarithromycin, neuropathy, seizures, and disulfiram-like reaction with metronidazole, diarrhea with amoxicillin, photosensitivity with tetracycline, and *Clostridium difficile* infection with any antibiotic exposure. Bismuth may cause black stool and constipation. Tetracycline is contraindicated in pregnant patients.
- 20% of patients may not respond to initial therapy. It is important to reinforce compliance. Second-line therapy should avoid antibiotics used in initial treatment and should include either bismuth-containing quadruple therapy or levofloxacin-containing triple therapy (regardless of local clarithromycin resistance patterns). When possible, management of those who do not respond to two courses of therapy should be guided by antimicrobial sensitivity testing (endoscopy with biopsy for cultures and sensitivity).

CHRONIC Rx

- It is essential to document clearance of infection after the completion of treatment. Repeat testing is generally performed 1 mo after completion of antibiotics and at least 2 wk after cessation of PPI therapy.
- Active tests such as urea breath test and stool antigen testing should be used. They are equally accurate in confirming eradication, and either may be used depending on availability and patient preference.
- Serology does not reliably revert to undetectable levels after treatment and should not be used to determine eradication.

DISPOSITION

Consider further evaluation in patients with recurrent symptoms after appropriate treatment.

REFERRAL

- Patients with gastric MALT lymphoma should be followed by a gastroenterologist and oncologist with expertise in the care of lymphoid neoplasms.
- Patients with dyspepsia who have tested positive for *H. pylori* and failed two courses of treatment should be referred for endoscopy and biopsy for culture and sensitivity.

PEARLS & CONSIDERATIONS

- It remains unclear whether *H. pylori* eradication reduces the risk of progression to gastric cancer.
- Outcomes in PUD and gastric MALT lymphoma are improved with treatment of associated *H. pylori* infection.
- Tests that provide direct evidence of active *H. pylori* infection (urea breath and stool antigen testing) are preferred. These may result in false-negative results in patients taking antibiotics, bismuth, or antisecretory agents, which should be stopped at an appropriate time interval before testing.
- Serologic testing does not differentiate active from prior infection. If performed, positive results should be confirmed with active testing.
- Be aware of high-risk populations in low-prevalence settings, including immigrants from Mexico, South America, Southeast Asia, and Eastern Europe.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Helicobacter pylori Infection (Patient Information)
Gastritis (Related Key Topic)
Peptic Ulcer Disease (Related Key Topic)

AUTHOR: **Margaret Tryforos, MD**

SUGGESTED READINGS

Chey WD et al: ACG Clinical Guideline: treatment of *Helicobacter pylori* infection, *Am J Gastroenterol* 112(2):212-239, 2017.

Crowe SE: *Helicobacter pylori* infection, *N Engl J Med* 380(12):1158-1165, 2019.

Malfertheiner P et al: For the European Helicobacter Study Group. Management of *Helicobacter pylori* infection—the Maastricht IV/Florence consensus report, *Gut* 61(5):646-664, 2012.

McColl KEL: *Helicobacter pylori* infection, *N Engl J Med* 362:1597-1604, 2010.

BASIC INFORMATION

DEFINITION

The HELLP syndrome is a serious variant of preeclampsia. HELLP is an acronym for ***h***emolysis, ***e***levated ***l***iver enzymes, and ***l***ow ***p***latelet count. It is the most frequently encountered microangiopathy of pregnancy. Two classification systems exist (Mississippi Classification and Tennessee Classification); degree of maternal thrombocytopenia is a primary indicator of disease severity:

	Tennessee	Mississippi
Class 1:	Platelets <100,000/mm^3 AST or ALT >70 IU/L	Platelets <50,000/mm^3 AST or ALT >70 IU/L
Class 2:		Platelets >50,000/mm^3 to <100,000/mm^3 AST or ALT >70 IU/L
Class 3:		Platelets >100,000/mm^3 to <150,000/mm^3 AST or ALT ≥70 IU/L

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase. All criteria require LDH ≥600 IU/L.

SYNONYMS

HELLP
Hemolysis
Elevated liver enzymes
Low platelet syndrome

ICD-10CM CODES

O14.2	HELLP syndrome
O26.892	Other specified pregnancy related conditions, second trimester
O26.893	Other specified pregnancy related conditions, third trimester
O26.899	Other specified pregnancy related conditions, unspecified trimester
O26.90	Pregnancy related conditions, unspecified, unspecified trimester
O26.91	Pregnancy related conditions, unspecified, first trimester
O26.92	Pregnancy related conditions, unspecified, second trimester
O26.93	Pregnancy related conditions, unspecified, third trimester

EPIDEMIOLOGY & DEMOGRAPHICS

- HELLP is a rare complication occurring in <1% of total pregnancies.
- Among women with severe preeclampsia, 6% will manifest with one abnormality suggestive of HELLP syndrome, 12% will develop two abnormalities, and approximately 10% will develop all three.
- The HELLP syndrome, like preeclampsia, is rare before 20 wk of gestation and the majority of cases occur during the third trimester.
- One third of all cases occur postpartum; of these, only 80% are typically diagnosed with preeclampsia before delivery.
- Younger age, headache, bilirubin >2.0, LDH >1290, and platelets <50k are predictive of worse maternal outcomes.

RISK FACTORS: Women >35 yr, white, multiparity, heritable genetics
RECURRENCE RATE: 3% to 25%

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Definitive laboratory criteria remain to be validated prospectively.
- Most commonly used criteria include hemolysis defined by the presence of an abnormal peripheral smear with schistocytes, lactate dehydrogenase (LDH) >600 U/L, and total bilirubin >1.2 mg/dl; elevated liver enzymes (serum aspartate aminotransferase (AST) >70 U/L); low platelet count as less than 100,000/ml.
- Although many women with HELLP syndrome are asymptomatic, 80% report right upper quadrant pain, and 50% to 60% present with excessive weight gain and worsening edema.

ETIOLOGY

As with other microangiopathies, endothelial dysfunction, with resultant activation of the intravascular coagulation cascade, has been proposed as the central pathogenesis of HELLP syndrome.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute fatty liver of pregnancy
- Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome
- Appendicitis
- Gallbladder disease
- Peptic ulcer disease
- Enteritis
- Hepatitis
- Pyelonephritis
- Systemic lupus erythematosus
- Box E1 summarizes medical and surgical disorders often confused with HELLP syndrome

WORKUP

Because HELLP syndrome is a disease entity based on laboratory values, initial assessment is detailed below.

LABORATORY TESTS

- Initial assessment of suspected HELLP syndrome should include a complete blood count to evaluate platelets, urinalysis, serum creatinine, LDH, uric acid, indirect and total bilirubin levels, and AST/alanine aminotransferase (ALT).
- Tests of prothrombin time, partial thromboplastin time, fibrinogen, and fibrin split products are reserved for women with a platelet count well below 100,000/mm^3.

IMAGING STUDIES

Imaging should be considered in the setting of severe abdominal pain and transaminitis to evaluate for hepatic hematoma and rupture.

TREATMENT

Treatment depends on gestational age of the fetus, severity of condition, and maternal status. Stabilization of the mother is the first priority. Fig. E1 describes an algorithm for the management of HELLP syndrome.

ACUTE GENERAL Rx

- Assess gestational age thoroughly. Fetal status should be monitored with nonstress tests, contraction stress tests, and/or biophysical profile.
- Maternal status should be evaluated by history, physical examination, and laboratory testing.
- Magnesium sulfate is administered for seizure prophylaxis regardless of blood pressure.
- Blood pressure control is achieved with agents such as hydralazine or labetalol.
- Indwelling Foley catheter to monitor maternal volume status and urine output.
- Eculizumab has also been proposed as a possible therapy in case reports.

CHRONIC Rx

- In pregnancies of 34 wk or with class 1 HELLP syndrome, delivery, either vaginal or abdominal, within 48 hr is the goal.
- In the preterm fetus, corticosteroid therapy to enhance fetal lung maturation is indicated.
- Some reports have shown temporary amelioration of HELLP severity with the administration of high-dose steroids measured by increased urine output, improvement in platelet count, and liver function test. A 2015 meta-analysis of multiple studies

BOX E1 Medical and Surgical Disorders Often Confused with HELLP Syndrome

- Acute fatty liver of pregnancy
- Appendicitis
- Gallbladder disease
- Glomerulonephritis
- Hemolytic uremic syndrome
- Hepatic encephalopathy
- Hyperemesis gravidarum
- Idiopathic thrombocytopenia
- Pyelonephritis
- Systemic lupus erythematosus
- Antiphospholipid antibody syndrome
- Thrombotic thrombocytopenic purpura
- Viral hepatitis
- HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome

From Gabbe SG: *Obstetrics*, ed 6, Philadelphia, 2012, WB Saunders.

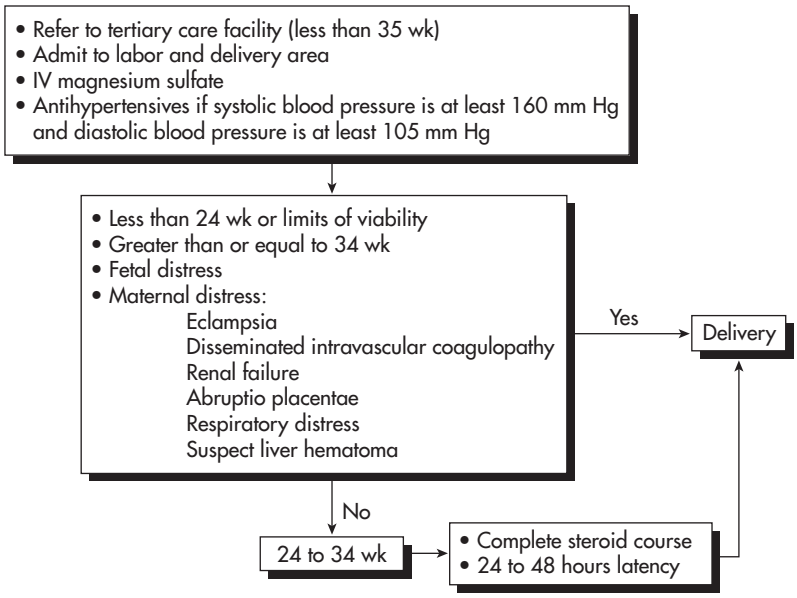

FIG. E1 An algorithm for the management of HELLP syndrome. IV, intravenous. (From Gabbe SG: *Obstetrics*, ed 6, Philadelphia, 2012, WB Saunders.)

suggested improvement in lab parameters and decreased length of ICU stay with steroid administration. However, there was not better maternal mortality and morbidity.
- Judicious use of blood products, especially in those requiring surgery.
- The patient requires intensive observation. Laboratory levels may worsen immediately postpartum but should begin to improve within 48 hr.

DISPOSITION

The natural history of this disorder is a rapidly deteriorating condition requiring close monitoring of maternal and fetal well-being.

REFERRAL

Preterm patients with HELLP syndrome should be stabilized hemodynamically and transferred to a tertiary care center. Term patients can be treated at a local hospital depending on the availability of obstetric, neonatal, and blood banking services.

PEARLS & CONSIDERATIONS

- Not all women with HELLP have hypertension or proteinuria.
- Life-threatening hemorrhage is a rare event in HELLP syndrome. Identifiable risk factors predictive of a major hemorrhage are thrombocytopenia (<100,000/mm^3), AST >70 IU/L, and previous gestations.
- The most effective therapy for HELLP is emergent delivery of the fetus.

RELATED CONTENT

Eclampsia (Related Key Topic)
Preeclampsia (Related Key Topic)

AUTHORS: **Robert Matera, MD,** and **John L. Reagan, MD**

SUGGESTED READINGS

Aloizos S et al: HELLP syndrome: understanding and management of a pregnancy-specific disease, *J Obstet Gynaecol* 33(4):331-337, 2013.

del-Rio-Vellosillo M, Garcia-Medina JJ: Anesthetic considerations in HELLP syndrome, *Acta Anaesthesiol Scand* 60:144-157, 2016. PMID 2644688.

Woudstra DM et al: Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy, *Cochrane Database Syst Rev* 9:CD008148, 2010.

Hemochromatosis PTG ALG

BASIC INFORMATION

DEFINITION

Hemochromatosis is an autosomal-recessive disorder that disrupts the body's regulation of iron and is characterized by increased accumulation of iron in various organs (adrenals, liver, pancreas, heart, testes, kidneys, pituitary) and eventual dysfunction of these organs if not treated appropriately.

SYNONYMS

Bronze diabetes
Hereditary hemochromatosis HH

ICD-10CM CODES

E83.110	Hereditary hemochromatosis
E83.111	Hemochromatosis due to repeated red blood cell transfusions
E83.118	Other hemochromatosis
E83.119	Hemochromatosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: In whites, approximately 1 in 385 persons
PREDOMINANT SEX AND AGE: Generally diagnosed in males in their fifth decade. Diagnosis in females is generally not made until 10 to 20 yr after menopause.
GENETICS: Most common genetic disorder in North European ancestry. Homozygosity for the *C282Y* mutation is now found in approximately 5 of every 1000 persons of European descent.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- In earlier stages patients completely asymptomatic and diagnosed due to abnormal laboratory tests
- Hepatic dysfunction leading to hepatomegaly, fibrosis, and eventually cirrhosis
- Noninflammatory arthropathy (Fig. E1)
- Gonadal insufficiency leading to loss of libido and testicular atrophy
- Diabetes mellitus: Risk greater in patients with family history
- Iron-induced cardiac disease resulting in cardiomyopathy, heart failure, and arrhythmias
- Skin pigmentation

ETIOLOGY

- The majority of the patients diagnosed with hemochromatosis have mutation in the *HFE* gene and are either homozygous for the *C282Y* mutation *(C282Y/C282Y)* or compound heterozygote for the *C282Y* mutation and either the mutation *H63D (C282Y/H63D)* or less commonly the *S65C (C282Y/S65C).*
- The remainder of the patients are classified as non–*HFE*-associated hemochromatosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hereditary anemias with defect of erythropoiesis
- Cirrhosis, chronic liver disease, porphyria cutanea tarda
- Repeated blood transfusions
- Table 1 summarizes hereditary causes of iron overload

WORKUP

Medical history, physical examination, and laboratory evaluation should be focused on affected organ systems (see "Physical Findings & Clinical Presentation"). Fig. E2 outlines evaluation for possible hereditary hemochromatosis in an individual with negative family history. Liver biopsy is the gold standard for diagnosis; it reveals iron deposition in hepatocytes, bile ducts, and supporting tissues.

LABORATORY TESTS

- Transferrin saturation is the best screening test. Values >45% are an indication for further testing.
- Elevated serum ferritin is good evidence of iron overload, but other causes like chronic inflammatory conditions, malignancy, and so forth need to be ruled out as ferritin is also an acute phase reactant.
- Genotypical screening for *C282Y* and *H63D* mutation in *HFE* gene should be done in patients with high transferrin saturation, elevated ferritin, or both.
- Liver biopsy (Fig. E3) is the gold standard but is not needed in somebody who has a persistently elevated transferrin saturation, elevated ferritin, or both.
- Hepatic iron index can help differentiate between various causes of iron overload.
- Elevated aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase are seen.
- Hyperglycemia is found.
- Endocrine abnormalities (decreased testosterone, luteinizing hormone, follicle-stimulating hormone) are noted.
- Table 2 describes laboratory findings in patients with hereditary hemochromatosis.

IMAGING STUDIES

Routine radiologic imaging is not needed. MRI (Fig. E4) may show low signal intensity in the liver and can be used to estimate hepatic iron concentration.

TREATMENT

The goal of therapy is the removal of excess iron and maintaining it at a normal or near-normal level. Phlebotomy is first line treatment. The goal is to reduce serum ferritin to 50 to 100 mg/ml. Box E1 summarizes the treatment of *HFE*-related hereditary hemochromatosis.

NONPHARMACOLOGIC THERAPY

Phlebotomy is the treatment of choice.

ACUTE GENERAL Rx

- The timing and frequency of phlebotomy needs to be individualized for each patient.
- For patients with heavy iron overload, twice-weekly phlebotomies should be started. In most patients, weekly phlebotomy is adequate.
- The effectiveness of treatment is monitored by periodic ferritin measurement. The goal is to bring ferritin level below 50 ng/ml.
- Patients with iron overload due to transfusion-dependent anemias may not tolerate phlebotomy. For these patients, iron chelation may be needed.
- The chelating agent deferoxamine has to be given daily as a 9- to 12-hr IV or SC infusion, and compliance is difficult.
- The oral chelating agent deferasirox (Exjade) is effective, but should not be used in patients with high-risk myelodysplastic syndrome because it can cause renal impairment, hepatic impairment, or gastrointestinal hemorrhage, which can be fatal.

CHRONIC Rx

After the ferritin has been brought to less than 50 ng/ml, phlebotomy is needed on an as-needed basis to keep the ferritin at that level.

DISPOSITION

- Serum ferritin measurement is the most useful prognostic indicator of disease severity.
- Prognosis is good if phlebotomy is started early (before onset of cirrhosis or diabetes mellitus); women can have the full phenotypic expression of the disease, including cirrhosis, and should also be aggressively treated.

REFERRAL

For liver biopsy if diagnosis is uncertain

PEARLS & CONSIDERATIONS

COMMENTS

- Persons who are homozygous for the *HFE* gene mutation *C282Y* comprise 85% to 90% of phenotypically affected individuals. Patients who are heterozygous for both *C282Y* and *H63D* generally do not have clinically evident disease unless coexisting factors (e.g., excessive alcohol intake) are present.
- Patients with hemochromatosis and serum ferritin levels <1000 ng/ml are unlikely to have cirrhosis. Liver biopsy to screen for cirrhosis may be unnecessary in such patients.
- Cirrhotic patients must be periodically monitored (ultrasound or CT scan) because of their increased risk of hepatocellular carcinoma.
- *HFE* gene testing for *C282Y* mutation is a cost-effective method of screening relatives of patients with hereditary hemochromatosis. The American College of Gastroenterology recommends genotyping persons who have abnormal iron screening tests and first-degree relatives of those identified with *C282Y* homozygosity.
- Established cirrhosis, hypogonadism, destructive arthritis, and insulin-dependent diabetes mellitus secondary to hemochromatosis cannot be reversed with repeated phlebotomy, but their progress can be slowed.

TABLE 1 Hereditary Iron Overload Disorders

Disorder	Gene, Chromosome Location	Inheritance	Plasma Transferrin Saturation	Plasma Ferritin	Iron Deposition Sites	Clinical Manifestations
Hereditary hemochromatosis, *HFE*-associated (type 1; OMIM235200)	*HFE,* 6p21	Autosomal recessive	Early increase; >45%	Later increase after third decade of life	Parenchymal iron overload affecting hepatocytes, heart, pancreas, other organs	Liver and heart disease, diabetes, gonadal failure, arthritis, skin pigmentation
Hereditary hemochromatosis, *TFR2*-associated (type 3; OMIM604250)	*TFR2,* 7q22	Autosomal recessive	Early increase; >45%	Later increase after third decade of life	Parenchymal iron overload affecting hepatocytes, heart, pancreas, other organs	Liver and heart disease, diabetes, gonadal failure, arthritis, skin pigmentation
Juvenile hemochromatosis, hemojuvelin-associated (type 2A; OMIM 602390)	*HJV,* 1q21	Autosomal recessive	Early increase; >45%	Increased by second decade of life	Parenchymal iron overload affecting hepatocytes, heart, pancreas, other organs	As for hereditary hemochromatosis, but liver involvement less prominent
Juvenile hemochromatosis, hepcidin-associated (type 2B; OMIM613313)	*HAMP,* 19q13	Autosomal recessive	Early increase; >45%	Increased by second decade of life	Parenchymal iron overload affecting hepatocytes, heart, pancreas, other organs	As for hereditary hemochromatosis, but liver involvement less prominent
Hemochromatosis, *DMT1*-associated (OMIM 206100)	*SCL11A2,* 12q13	Autosomal recessive	Early increase; >45%	Normal to moderately elevated	Hepatic iron overload, predominantly in hepatocytes	Severe microcytic anemia, liver dysfunction
Atransferrinemia (OMIM 209300)	*TF,* 3q22	Autosomal recessive	No plasma transferrin	Increased	Parenchymal iron overload affecting hepatocytes, heart, pancreas; no iron stores in bone marrow or spleen	Transfusion-dependent iron-deficiency anemia, growth retardation, poor survival
Aceruloplasminemia (OMIM 604290)	*CP,* 3q24-q25	Autosomal recessive	Decreased	Increased	Marked iron accumulation in basal ganglia, liver, pancreas	Diabetes, progressive neurologic disease, retinal degeneration
Hemochromatosis, ferroportin-associated, with impaired iron export (type 4A; OMIM606069)	*SLC40A1,* 2q32	Autosomal dominant	Remains normal or low	Early increase	Predominantly macrophage iron deposition	None
Hemochromatosis, ferroportin-associated, with hepcidin resistance (type 4B; OMIM606069)	*SLC40A1,* 2q32	Autosomal dominant	Early increase; >45%	Early increase	Parenchymal iron overload affecting hepatocytes, heart, pancreas, other organs	Similar to *HFE*-associated hemochromatosis

From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 2 Laboratory Findings in Patients with Hereditary Hemochromatosis

Measurements	Normal Subjects	Patients with Hereditary Hemochromatosis	
		Asymptomatic	Symptomatic
Blood (Fasting)			
Serum iron level (μg/dl)	60-180	150-280	180-300
Serum transferrin level (mg/dl)	220-410	200-280	200-300
Transferrin saturation (%)	20-45	45-100	80-100
Serum ferritin level (ng/ml)			
Men	20-200	150-1000	500-6000
Women	15-150	120-1000	500-6000
Genetic (*HFE* Mutation Analysis)			
C282Y/C282Y	wt/wt‡	*C282Y/C282Y*	*C282Y/C282Y*
*C282Y/H63D**	wt/wt	*C282Y/H63D*	*C282Y/H63D*
Liver			
Hepatic iron concentration			
μg/g dry weight	300-1500	2000-10,000	8000-30,000
μmol/g dry weight	5-27	36-179	140-550
Hepatic iron index†	<1	1 to >1.9	>1.9
Liver histology			
Perls Prussian blue stain	0, 1+	2+ to 4+	3+, 4+

*Compound heterozygote.
†Calculated by dividing the hepatic iron concentration (in μmol/g dry weight) by the age of the patient (in yr). With the increased use of genetic testing in patients with iron overload, the specificity of the hepatic iron index has diminished.
‡wt/wt: wild type (normal).
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

- In patients who are heterozygous for *C282Y* or *H63D* mutation, clinically meaningful iron overload does not develop.
- Screening for hepatocellular carcinoma is reserved for those with hereditary hemochromatosis and cirrhosis.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hemochromatosis (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Bacon BR et al: Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases, *Hepatology* 54(1):328-343, 2011.

Crownover BK, Covey CJ: Hereditary hemochromatosis, *Am Fam Physician* 87(3):183-190, 2013.

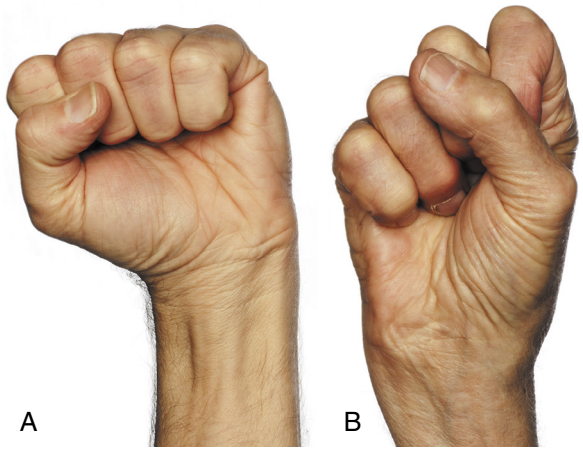

FIG. E1 The iron fist sign in hereditary hemochromatosis (HH) arthropathy. (A) A normal hand. **(B)** Hand in a patient with HH arthropathy. The poor flexion in the index and middle fingers in HH arthropathy is caused by a lack of flexion in the "damaged" metacarpophalangeal 2,3 joints. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

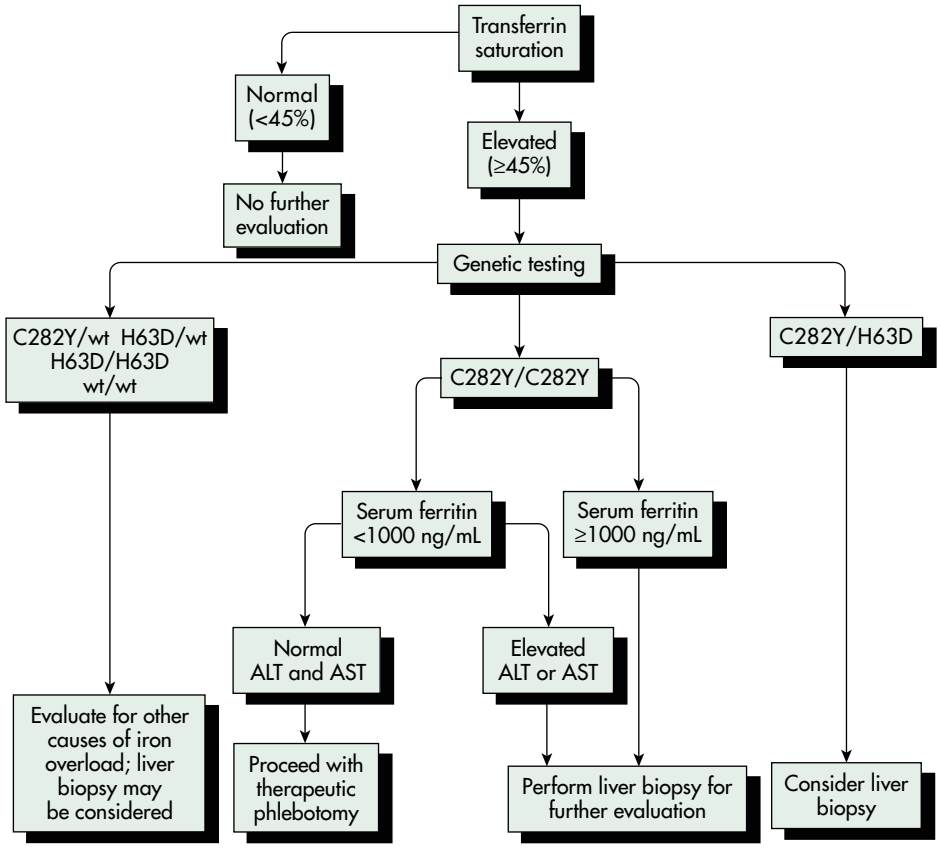

FIG. E2 Algorithm for the evaluation of possible *HFE*-related hereditary hemochromatosis in a person with a negative family history. *ALT,* Alanine aminotransferase; *AST,* aspartate aminotransferase; *wt*, wild-type. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

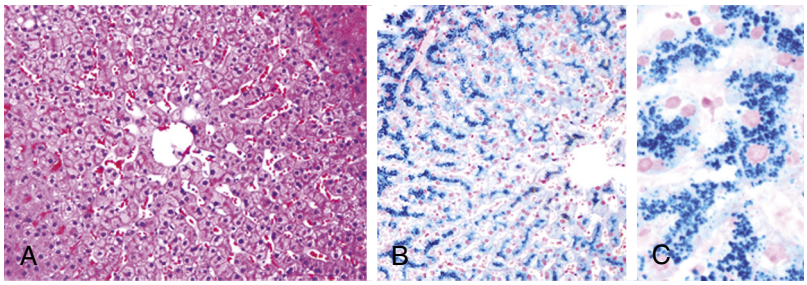

FIG. E3 *HFE* hemochromatosis. Liver biopsy sample from a 46-year-old man with homozygous *HFE* hemochromatosis. Hematoxylin and eosin stain of the liver **(A)** shows intact hepatic architecture. Iron stain **(B, C)** shows marked diffuse iron deposits in the hepatocytes throughout the lobules. A normal liver would show essentially no iron in the hepatocytes. (From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

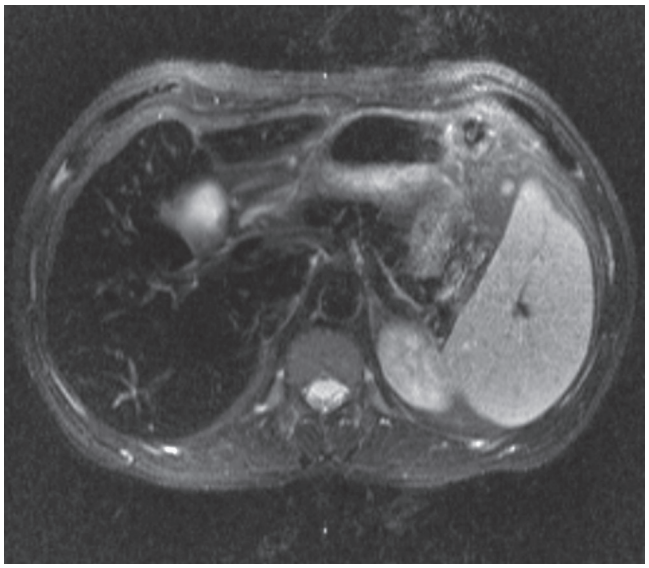

FIG. E4 Magnetic resonance image of a patient with hemochromatosis. This T2-weighted image shows low signal intensity in the liver due to the magnetic susceptibility effects of iron compared with normal signal intensity in the spleen. In secondary iron overload, the spleen would also have low signal intensity due to increased iron deposition in reticuloendothelial cells. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

BOX E1 Treatment of *HFE*-Related Hereditary Hemochromatosis

Perform phlebotomy of 500 ml (1 unit) of whole blood weekly unless the hematocrit value drops below 37%.
Check the transferrin saturation and ferritin levels at 2- to 3-mo intervals to monitor response (optional).
When the iron stores are depleted (ferritin between 50 and 100 ng/ml and transferrin saturation <50%), proceed to maintenance phlebotomy of 1 unit of whole blood every 2-3 mo. Aim to keep the transferrin saturation below 50%; if successful, the ferritin level should remain between 50 and 100 ng/ml.

From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

BASIC INFORMATION

DEFINITION

Hemolytic uremic syndrome (HUS) is a life-threatening disorder characterized by microangiopathic hemolytic anemia (MAHA) and severe acute kidney injury. HUS is one of numerous disorders of the broader syndrome known as thrombotic microangiopathy (TMA). HUS, as opposed to some other forms of TMA, is notable for the severity of kidney injury. Although lacking a widely accepted definition, HUS is commonly defined by the presence of acute kidney injury, anemia (hemoglobin < lower limit of normal), hemolysis (lactate dehydrogenase > upper limit of normal), and thrombocytopenia (platelets < lower limit of normal). Shiga toxin–producing *E. coli* infection (STEC-HUS) and hereditary or acquired complement dysregulation (atypical HUS) are two important causes of HUS and are the foci of this chapter.

SYNONYMS

HUS
STEC-HUS (Shiga toxin-producing *E. coli*-hemolytic uremic syndrome)
aHUS (atypical hemolytic uremic syndrome)
TMA (thrombotic microangiopathy)

ICD-10CM CODES
D59.3 Hemolytic-uremic syndrome
M31.1 Thrombotic microangiopathy

EPIDEMIOLOGY & DEMOGRAPHICS

Diarrhea-associated HUS, commonly due to STEC-HUS, is largely a disease of children and the most common etiology of HUS in children <5 yr of age. The incidence is estimated at 2 to 3 per 100,000 persons. It is more common in summer and fall months and in rural areas.

The incidence of atypical HUS (aHUS) is far less common, estimated at approximately 0.1 per million in children <17 yr of age and <0.5 per million in adults. The disease may be more common in adult women than men, without an apparent sex difference in pediatrics. Although germline mutations in the complement cascade are common, a positive family history is present in <30%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

In children with Shiga toxin–producing *E. coli*-hemolytic uremic syndrome (STEC-HUS), fever, abdominal pain, vomiting, and nonbloody diarrhea begin a median of 3 days after ingestion of infected material. Bloody diarrhea ensues 1 to 3 days later, and STEC-HUS typically develops within a wk of the onset of diarrhea. Fever is often absent at clinical presentation, and fatigue, dehydration, oliguria, and pallor are commonly presenting signs. Seizures can develop with severe disease. Leukocytosis is associated with a worse prognosis.

The onset of aHUS may be preceded by an identifiable "second hit" event such as infection or pregnancy in 50% of patients or fewer. Acute kidney injury is particularly severe in aHUS, with 70% to80% of patients requiring kidney replacement therapy (e.g., hemodialysis) shortly after presentation. The absence of severe AKI should prompt consideration of an alternative diagnosis. Thrombocytopenia is modest and often >60,000 cells/mm^3. Schistocytes may be present on peripheral blood smear, but are often fewer than expected. Notably, gastrointestinal symptoms may be present in 30% of patients, potentially mimicking STEC-HUS. Multi-organ system involvement with cardiovascular and neurological complications is common. C3 levels are low in approximately 50% of cases. Therefore, normal C3 concentration does not exclude aHUS. Proteinuria, potentially in the nephrotic range, and microscopic hematuria are frequently found.

ETIOLOGY

Endothelial activation and injury with subsequent microvascular thrombosis underlie the pathophysiology of HUS.

STEC-HUS is commonly attributed to ingestion of beef infected with the enterohemorrhagic O157:H7 strain of *E. coli*. However, non-O157 strains now account for approximately 50% of cases, and sources include contaminated water, milk, cider, fish, and vegetables. Endothelial injury is initiated by binding of Shiga toxin, followed by leukocyte recruitment, increased thrombin generation, impaired fibrinolysis, and small vessel thrombosis. Secondary activation of complement may contribute to endothelial injury early in the disease.

In aHUS, a germline mutation in the alternative pathway of complement or an acquired autoantibody directed against complement factor H is identified in 60% to 80% of patients. A second-hit, or "complement amplifying condition" (e.g., infection, pregnancy, inflammation), may be present. Endothelial injury results from the terminal membrane attack complex (C5b–9) and leukocyte recruitment, leading to activation of the coagulation system and small vessel thrombosis. The genes most commonly implicated in aHUS are complement factors H (CFH), I (CFI), and B (CFB); membrane cofactor protein (MCP); complement component 3 (C3); thrombomodulin (THBD); and complement factor H related protein 5 (CFHR5). Homozygous deletion of the gene region encompassing complement factor H-related protein 1 (CFHR1) is associated with the development of autoantibodies against factor H (FH). Mutations of the diacylglycerol kinase ε (DGKE) and methylmalonic aciduria cblC type with homocystinuria (MMACHC) genes cause aHUS. However, the roles of complement dysregulation in these disorders remains unclear.

DIAGNOSIS

Diagnosis requires recognition of the presence of a thrombotic microangiopathy associated with significant kidney injury. While STEC-HUS and aHUS are important causes, many other diseases have similar presentations (Table E1). In particular, thrombotic thrombocytopenic purpura (TTP) and infection by *S. pneumoniae* or human immunodeficiency virus (HIV) should be excluded. Severely depressed activity of ADAMTS13 (**a** **d**isintegrin **a**nd **m**etalloproteinase

TABLE E1 Differential Diagnosis of Etiologies of Hemolytic-Uremic Syndrome

ADAMTS13 Deficiency <5% to 10%	Drugs
Thrombotic thrombocytopenic purpura (TTP)	Quinine
Infection Associated	$P2Y_{12}$ antagonists
Shiga toxin–producing *E. coli*	Tacrolimus, cyclosporine A
Streptococcus pneumoniae	Sirolimus, everolimus
Campylobacter jejuni	Muromonab-CD3 (OKT3)
Human immunodeficiency virus	Gemcitabine
Cytomegalovirus	Mitomycin C
Epstein-Barr virus	Interferon
Influenza	Vascular endothelial growth factor inhibitors
Parvovirus B19	Tyrosine kinase inhibitors
Primary Abnormality in Complement Regulation	Cocaine
Atypical HUS	Oxymorphone
Immune Dysregulation	***Malignant Hypertension***
Monoclonal light chain	***Disseminated Intravascular Coagulation***
Systemic lupus erythematosus	***Pregnancy***
Antiphospholipid antibody syndrome	Severe preeclampsia / HELLP Syndrome
Scleroderma renal crisis	***Malignancy***
Metabolic/Cell Signaling	***Post-Bone Marrow Transplant***
MMACHC gene mutation	***Other***
Diacylglycerol kinase ε gene mutation	Castleman disease
	POEMS
	Hemophagocytic lymphohistiocytosis (HLH)

HELLP, Hemolysis, elevated liver enzymes, and low platelet count; *HUS,* hemolytic uremic syndrome.

with a **t**hrombo**s**pondin type 1 motif, member **13**) on the order of <5% to 10% is consistent with TTP.

DIFFERENTIAL DIAGNOSIS

Diagnostic considerations are shown in Table E1. Occasionally, C3 glomerulopathy may demonstrate histology compatible with chronic microangiopathy. Typically, overt small vessel thrombosis is absent, and peripheral hemolysis is rarely present.

WORKUP

The workup for suspected HUS includes blood, urine, and stool testing.

LABORATORY TESTS

- Routine: Peripheral blood smear, lactate dehydrogenase level, haptoglobin level, prothrombin and partial thromboplastin times, fibrinogen, ADAMTS13 activity, C3 and C4 levels, complement CH50 test, direct antiglobulin test (i.e., Coombs), vitamin B_{12} level, methylmalonic acid level, and β-HCG (beta human chorionic gonadotropin) level
- Infection associated: Stool Shiga toxin assay, blood/urine/stool cultures, HIV antibody, and urine pneumococcal antigen if indicated
- Acquired: Antiphospholipid antibody testing (Russell viper venom time, β2-glycoprotein antibodies, anti-cardiolipin antibodies), ANA, serum free light chains, and FH autoantibody
- In-born: aHUS genetic testing

IMAGING STUDIES

There is no specific imaging study for HUS, and imaging should be performed as required for diseases under consideration.

Rx TREATMENT

The local health department should be notified if STEC is isolated; an epidemiological investigation may be required to prevent or mitigate a larger foodborne outbreak.

The mainstay of therapy for STEC-HUS is supportive care. Stabilization and maintenance of the extracellular fluid volume status is a major determinant of outcome, and patients should be aggressively but carefully volume resuscitated. Hypertension should be controlled. Antibiotics, especially fluoroquinolones, are generally contraindicated in STEC infection as they may precipitate HUS or worsen established disease. Plasma exchange and anti-complement C5 therapy (eculizumab) are not routinely recommended and have an unclear role in managing this disease. There is no established role for corticosteroids or anticoagulation.

The standard of care for aHUS is eculizumab. As aHUS is often a diagnosis of exclusion, it is important to promptly exclude other conditions for which treatment may differ (e.g., antibiotics for *S. pneumoniae* infection, plasma exchange for TTP). Plasma exchange may initially stabilize aHUS, but long-term outcomes of aHUS are poor when managed only with plasma exchange. Plasma exchange, however, may be initially beneficial in the setting of deficient levels of complement factors H, B, or I, or in the presence of FH autoantibody-associated disease. Hypertension should be managed with an angiotensin–converting enzyme inhibitor similar to scleroderma renal crisis. Kidney replacement therapy (e.g., hemodialysis) may be required.

Any clearly associated triggering condition should be addressed. For example, in gemcitabine-associated HUS, the drug should be discontinued if feasible.

OUTCOME

The vast majority of pediatric patients with STEC-HUS recover. Death occurs in approximately 3% of afflicted individuals. In survivors, albuminuria develops in 20% to 40%, abnormal kidney function in 10% to 20%, and hypertension in 5% to 15%.

Historically, in aHUS, 40% to 60% of plasma exchange–treated patients either died or developed end-stage renal disease by 1 yr. With eculizumab, mortality is low, 50% develop chronic kidney disease, and 3% to 10% have cardiovascular complications. Approximately 80% of patients requiring hemodialysis regain sufficient kidney function to discontinue kidney replacement therapy. Many patients are able to withdraw eculizumab treatment under expert guidance. Most forms of aHUS may recur in the transplanted kidney.

PEARLS & CONSIDERATIONS

- STEC-HUS is the most common cause of HUS in children, although many different infectious and other etiologies exist.
- aHUS is more common than STEC-HUS in adults, but etiologies such as TTP, infection, antiphospholipid antibody syndrome, and others must be excluded.
- Prompt diagnosis and treatment is necessary to reduce morbidity and mortality.
- Immediate nephrology and hematology consultations are recommended.

RELATED CONTENT

Hemolytic-Uremic Syndrome (Patient Information)

Thrombotic Thrombocytopenic Purpura (Related Key Topic)

AUTHOR: **C. John Sperati, MD, MHS**

SUGGESTED READINGS

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Sperati CJ, Moliterno AR: Thrombotic microangiopathy—focus on atypical hemolytic uremic syndrome, *Hematol Oncol Clin N Am* 29:541-559, 2015.

Tarr PI et al: Shiga-toxin-producing Escherichia coli and haemolytic uraemic syndrome, *Lancet* 365:1073-1086, 2005.

BASIC INFORMATION

DEFINITION

Hemophilia is a hereditary bleeding disorder caused by low levels of factor VIII (hemophilia A) or factor IX coagulant activity (hemophilia B).

SYNONYMS

Hemophilia A: Classic hemophilia, factor VIII deficiency hemophilia
Hemophilia B: Christmas disease, factor IX hemophilia

ICD-10CM CODES	
D66	Hereditary factor VIII deficiency
D67	Hereditary factor IX deficiency
D68.311	Acquired hemophilia
Z14.01	Asymptomatic hemophilia A carrier
Z14.02	Symptomatic hemophilia A carrier

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE (IN U.S.): Hemophilia A: 100 cases per 1 million males; it is the most common severe inherited bleeding disorder in humans. Hemophilia B: 20 cases per 1 million males. There are approximately 400,000 patients with severe hemophilia worldwide.
GENETIC: Both hemophilias have an X-linked recessive pattern of inheritance with only males affected.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The clinical features of hemophilia A and B are generally indistinguishable from each other. The clinical symptoms are determined by the baseline factor activity in each patient. Spontaneous bleeding can occur with those with *severe* hemophilia (<1% factor VIII or IX activity). Trauma-induced bleeding can occur in those with *moderate* hemophilia (factor levels 1% to 5%) and *mild* hemophilia (factor levels >5%).
- Bleeding is most commonly seen in joints (knees, ankles, elbows), resulting in hot, swollen, painful joints (Fig. E1) and subsequent crippling joint deformity (Fig. E2).
- Bleeding can also occur into the muscles and the gastrointestinal tract.
- Compartment syndrome can occur from large hematomas.
- Hematuria may be present.

ETIOLOGY

- Both disorders are congenital X-linked recessive disorders of hemostasis. An overview of the coagulation cascade relevant to hemophilia and von Willebrand disease (vWD) is provided in Fig. E3.
- Hemophilia A: Low factor VIII coagulant (VIII:C) activity; can be classified as mild if factor VIII:C levels are >5%, moderate if levels are 1% to 5%, and severe if levels are <1%.
- Hemophilia B: Low levels of factor IX coagulant activity.
- Spontaneous acquisition of factor VIII inhibitors (acquired hemophilia) is rare.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other clotting factor deficiencies
- Platelet function disorders
- Vitamin K deficiency

WORKUP

Patients with mild hemophilia bleed only in response to major trauma or surgery and may not be diagnosed until young adulthood. Diagnostic workup includes laboratory evaluation, as below:

- Partial thromboplastin time (aPTT) is prolonged. Prothrombin time (PT) is normal, and the aPTT mixing study will fully correct.
- Factor VIII (Table E1) reduced factor VIII:C level distinguishes hemophilia A from other causes of prolonged PTT.
- Factor VIII antigen, fibrinogen level, and bleeding time are normal.
- Factor IX coagulant activity levels are reduced in patients with hemophilia B.
- Coagulation factor activity measurement is useful to correlate with disease severity. Normal range is 50 to 150 U/dl; 5 to 20 U/dl indicates mild disease, 2 to 5 U/dl indicates moderate disease, and <2 U/dl indicates severe disease with spontaneous bleeding episodes.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of contact sports
- Patient education regarding the disease; promotion of exercises such as swimming
- Avoidance of aspirin or other NSAIDs
- Orthopedic evaluation and physical therapy evaluation in patients with joint involvement
- Hepatitis vaccination

ACUTE GENERAL Rx

(*See* Box E1, Box E2)

HEMOPHILIA A:

- Reversal and prevention of acute bleeding in hemophilia A and B are based on adequate replacement of deficient or missing factor protein. Table E2 summarizes recommendations for clotting factor replacement.
- The choice of the product for replacement therapy is guided by availability, capacity, concerns, and cost. Recombinant factors cost two to three times as much as plasma-derived factors, and the limited capacity to produce recombinant factors often results in periods of shortage. In the United States, the majority of patients with severe hemophilia use recombinant products.
- Factor VIII concentrates are effective in controlling spontaneous and traumatic hemorrhage in severe hemophilia. The new recombinant factor VIII is stable without added human serum albumin (decreased risk of transmission of infectious agents).
- Emicizumab is a bispecific monoclonal antibody that bridges activated factor IX and factor X to replace the function of missing activated factor VIII, thereby restoring

FIG. E1 Acute hemarthrosis of the knee is a common complication of hemophilia. It may be confused with acute infection unless the patient's coagulation disorder is known because the knee is hot, red, swollen, and painful. (From Forbes CD, Jackson WF: *Color atlas and text of clinical medicine,* ed 3, London, 2003, Mosby.)

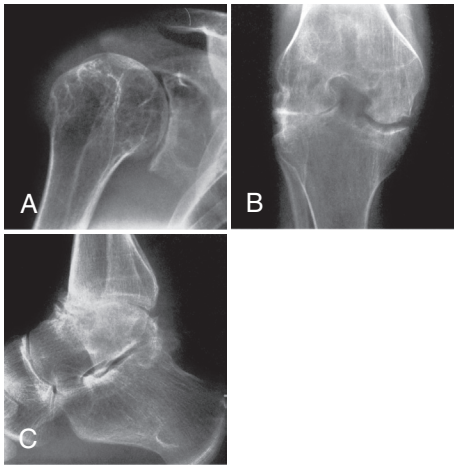

FIG. E2 Radiographic changes associated with hemophilic arthropathy. A, Radiograph of the shoulder showing multiple subchondral cysts in the head of the humerus, an early finding in hemophilic arthropathy. The glenohumeral joint space is fairly well preserved, and range of motion is normal. **B,** Widening of the intercondylar notch and near fusion of the femur and medial tibial condyle in the knee joint affected by hemophilic arthropathy. **C,** Narrowing and fusion of the tibiotalar joint in the ankle. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

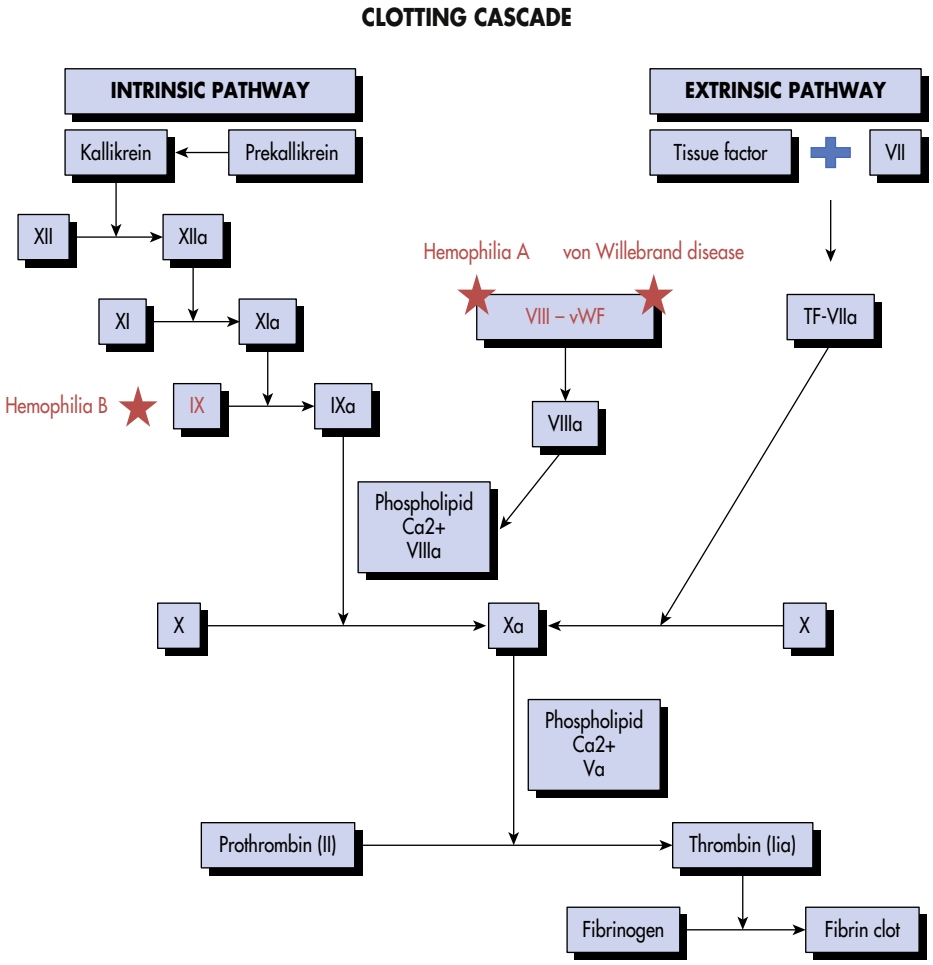

FIG. E3 Factor VIII in plasma is mostly noncovalently bound to von Willebrand factor *(vWF),* which protects it from metabolism. A number of factors including thrombin act to dissociate VIII from vWF to provide cofactors for the conversion of X to Xa. An absolute deficiency in VIII, a functional change, or a deficiency in vWF will result in reduced VIIIa to act as a cofactor. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

TABLE E1 Differential Diagnosis of a Low Factor VIII Level

- FVIII <10%
  1. Severe or moderately severe hemophilia A
  2. Severe type 1 VWD
  3. Type 3 VWD
  4. Type 2N VWD
  5. Acquired hemophilia A
  6. Acquired VWD
- FVIII: 10% to 50%
  1. Mild hemophilia A
  2. Type 1 VWD
  3. Type 2N VWD
  4. Combined FVIII and FV deficiency

FV, Factor V; *FVIII,* factor VIII; *VWD,* von Willebrand disease. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

hemostasis. Emicizumab prophylaxis administered subcutaneously once weekly or every 2 weeks led to a significantly lower bleeding rate than no prophylaxis among persons with hemophilia A without inhibitors; emicizumab is not recommended for treatment of bleeding.

- Alloantibodies (inhibitors) that neutralize factor VIII clotting function occur in nearly 30% of patients with severe hemophilia A after exposure to factor VIII. In these patients, bypassing agents (antiinhibitor coagulant complex [AICC] and recombinant activated factor VII [rFVIIa]) can be used to treat bleeding. AICC can also be used prophylactically to decrease the frequency of joint and other bleeding events in patients with severe hemophilia A and factor VIII inhibitors. Trials with emicizumab have shown that prophylaxis with it significantly lowers the rate of bleeding events among patients with hemophilia A who have developed inhibitors.
- Recombinant activated factor VII is useful to stop spontaneous hemorrhages and prevent excessive bleeding during surgery in 75% of patients with inhibitors. Recommended dose is 90 μg/mg of body weight every 2 to 3 hr for treatment of life-threatening hemorrhage.
- Desmopressin acetate 0.3 μg/kg q24h (causes release of factor VIII:C) may be used in preparation for minor surgical procedures in mild hemophiliacs.
- Aminocaproic acid (EACA, Amicar) 4 g PO q4h can be given for persistent bleeding that is unresponsive to factor VIII concentrate or desmopressin.
- *Valoctocogene roxaparvovec is an investigational adeno-associated virus vector containing the B-domain-deleted FVIII gene. The 3-yr follow-up results from an ongoing phase I/II study of patients with severe hemophilia A showed significantly reduced annual bleeding rates and increased factor VIII (FVIII) activity levels. This therapy is awaiting approval from regulatory agencies.*

HEMOPHILIA B:

- Infuse factor IX concentrates. It is important to remember that factor IX concentrates contain other proteins that may increase the risk of thrombosis with recurrent use; thus factor IX concentrates must be used only when clearly indicated.
- Daily administration of oral cyclophosphamide and prednisone without empirical factor VIII therapy is an effective and well-tolerated treatment for acquired hemophilia.

BOX E1 Treatment Options for Bleeding in a Patient with Factor VIII Deficiency and an Inhibitor

- Low Titer, Low Responder
- Mild Bleeding
  1. Local and conservative measures, such as rest, ice, compression, and elevation
  2. If the patient is known to respond to DDAVP (i.e., mild hemophilia A), 0.3 μg/kg IV or 300 μg intranasal (150 μg per nostril; 150 μg for patients <50 kg) for minor bleeding or treatment before minor surgery
  3. Oral antifibrinolytic therapy (ε-aminocaproic acid or tranexamic acid) for mucosal bleeding
  4. FVIII dosing to raise the level to 50%
  5. Recombinant FVIIa (90 to 120 μg/kg, followed by 90 μg/kg every 2 to 3 hours)
  6. Activated prothrombin complex concentrates (50 to 100 units/kg, with maximum daily dose of 200 units/kg)
  7. Concurrent treatment with antifibrinolytics should be administered with caution
- Life- or Limb-Threatening Bleeding
  1. FVIII dosing to maintain FVIII activity levels at 100%
  2. Recombinant FVIIa (270 μg/kg for one dose may be considered with caution versus 90 μg/kg every 2 to 3 hours)
  3. Activated prothrombin complex concentrates (100 units/kg, with maximum daily dose of 200 units/kg)
  4. Concurrent treatment with antifibrinolytics should be administered with caution
- Low Titer, High Responder
- Mild Bleeding
  1. Local and conservative measures, such as rest, ice, compression, and elevation
  2. If the patient is known to respond to DDAVP (i.e., mild hemophilia A), 0.3 μg/kg IV or 300 μg intranasal (150 μg for patients <50 kg) for minor bleeding or treatment before minor surgery
  3. Oral antifibrinolytic therapy (ε-aminocaproic acid or tranexamic acid) for mucosal bleeding
  4. Recombinant factor VIIa (270 μg/kg, bolus may be considered with caution versus 90 μg/kg every 2 to 3 hours)
  5. Activated prothrombin complex concentrates (100 units/kg, with a maximum daily dose of 200 units/kg, may induce anamnesis)
- Life- or Limb-Threatening Bleeding
  1. FVIII in high doses to maintain levels of 100%
  2. Frequent monitoring for an anamnestic response, usually within 5 to 7 days
  3. After the anamnestic response develops:
     a. Recombinant FVIIa (270 μg/kg, may be considered with caution versus 90 μg/kg every 2 to 3 hours)
     b. Activated prothrombin complex concentrates (50 to 100 units/kg, with a maximum daily dose of 200 units/kg)
- High Titer, High Responder
- Mild Bleeding
  1. Local and conservative measures, such as rest, ice, compression, and elevation
  2. Oral antifibrinolytic therapy (ε-aminocaproic acid or tranexamic acid) for mucosal bleeding
  3. Recombinant FVIIa (270 μg/kg, should be considered with caution versus 90 μg/kg every 2 to 3 hours)
  4. Activated prothrombin complex concentrates (100 units/kg, with a maximum daily dose of 200 units/kg)
  5. Concurrent treatment with antifibrinolytics should be administered with caution
- Life- or Limb-Threatening Bleeding
  1. Recombinant FVIIa (270 μg/kg, should be considered with caution versus 90 μg/kg IV every 2 to 3 hours)
  2. Activated prothrombin complex concentrates (100 units/kg, with a maximum daily dose of 200 units/kg)
  3. If available, immunoadsorption can be attempted to rapidly lower the inhibitor titer so as to allow use of FVIII
- Main Features of the Agents Effective for Inhibitor Treatment/Prophylaxis
  1. **Content** APCC: Activated vitamin k–dependent clotting factors; rFVIIa: Recombinant FVIIa alone
  2. **Mechanism of action** APCC: Activate plasma FX and FII; rFVIIa: Activates FX on platelets
  3. **Half-Life** APCC: Putatively 8 to 12 hours; rFVIIa: 2 to 3 hours
  4. **Efficacy** APCC: About 80%; rFVIIa: About 80%

APCC, activated prothrombin complex concentrate; *DDAVP,* desmopressin acetate; *FII,* factor II; *FIII,* factor III; *FVIIa,* activated factor VIIa; *FX,* factor X; *IV,* intravenous; *rFVIIa,* recombinant activated clotting factor VII.
(From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

CHRONIC Rx

- The aim of chronic treatment is to prevent spontaneous bleeding and excessive bleeding during any surgical intervention. Monitoring and treatment of patients with hemophilia at comprehensive hemophilia treatment centers is cost-effective and decreases morbidity and mortality.
- Prophylaxis with recombinant factor VIII can prevent joint damage and decrease the frequency of joint and other hemorrhages in young boys with severe hemophilia A. The estimated annual cost for treatment of one patient with recombinant factor VIII is $300,000.
- Implantation of genetically altered fibroblasts that produce factor VIII is safe and well tolerated. This form of therapy is feasible in patients with severe hemophilia. Hemophilia will likely be the first common, severe genetic disease to be cured by gene therapy.
- Table E3 summarizes alternative, nonclotting factor concentrate therapies for treating hemophilia.

DISPOSITION

- In the 1980s, approximately 90% of patients with hemophilia were infected with the hepatitis C virus (HCV), and more than 55% of this cohort was coinfected with HIV. The development of genetically engineered recombinant factor therapy in the 1990s virtually eliminated the risk of acquiring HCV and HIV from factor replacement therapy.
- Despite the advent of virally safe blood products and blood treatment programs, many hemophiliacs are HCV and HIV seropositive.
- Intracranial bleeds are a common cause of death in hemophiliacs. They are fatal in 30% of patients, occur in 10% of patients, and are generally the result of trauma.

REFERRAL

To a specialized center with multidisciplinary teams that can treat the disease and comorbidities

RELATED CONTENT

Hemophilia (Patient Information)

AUTHOR: **Bharti Rathore, MD**

BOX E2 Treatment of Life-Threatening Bleeding Episodes in Patients with Inhibitors Against Factor VIII or Factor IX

Concentrates
- Factor VIII containing concentrates in high doses (as high as 150-200 IU/kg) if inhibitor titer is low (<5-10 BU). High-dose continuous infusion of factor VIII (≈10 IU/kg per hour) after a high-dose bolus may be useful.
- Recombinant factor VIIa. Dose is 90 μg/kg (or a dose up to 320 μg/kg) administered every 2 hours. Risk of thrombosis exists with this product.
- Activated PCCs at a dose of 50-75 IU/kg every 8-12 hours. Risk of thrombosis exists with this product.

Immunomodulation
- Antibody depletion
  1. Plasmapheresis
  2. Extracorporeal immunoadsorption of plasma (staphylococcal protein A column therapy and other methods)
- Suppression of antibody production
  1. High-dose steroids (equivalent of prednisone 80 mg/day)
  2. Cyclophosphamide (10-15 mg/kg load and 2-3 mg/kg per day)
  3. Intravenous immunoglobulin (1 g/kg daily for 2 days)
  4. More aggressive regimens that may include vincristine, azathioprine, cyclosporine, or interferon-γ

Conservative Measures
- Immobilization
- Compression
- Local application of hemostatic agents
- Antifibrinolytics
- Avoid venipunctures, intramuscular injections, arterial puncture, and lumbar punctures
- Avoid use of medications that inhibit platelet function (ASA, NSAIDs)
- DDAVP may be effective in some patients with low-titer inhibitors

ASA, Aspirin; *BU,* Bethesda unit; *DDAVP,* desmopressin acetate; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PCC,* prothrombin complex concentrate.
(From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

TABLE E2 Recommendations for Clotting Factor Replacement

Site of Bleed	Level Desired (%)	Hemophilia A (rFVIII) (U/kg)	Hemophilia B (rFIX) (U/kg)
Oral mucosa	>30	20	40
Epistaxis	>30	20	40
Joint or muscle	>50	30	50
GI	>50	30	50
GU	>50	50	75
CNS	>100	75	125
Trauma or surgery	>100	75	125

CNS, Central nervous system; *GI,* gastrointestinal; *GU,* genitourinary; *rFIX,* recombinant factor IX; *rFVIII,* recombinant factor VIII.
(From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

TABLE E3 Alternative, Nonclotting Factor Concentrate Therapies for Treating Hemophilia

- Rebalancing hemostasis strategies:
- TFPI Inhibition approaches: Anti-TFPI aptamer, antibody and peptide.
- Antithrombin siRNA biosynthesis inhibition.
- Both approaches can be delivered by infrequent (weekly or less often) subcutaneous injections.
- Factor VIII mimetic molecule: Bispecific antibody to FIXa and FX.
- Can be administered by subcutaneous injection and has shown activity in FVIII inhibitor patients.

FX, Factor X; *FIXa,* Factor IXa; *FVIII,* factor VIII; *siRNA,* small interfering ribonucleic acid; *TFPI,* tissue factor pathway inhibitor.
(From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

SUGGESTED READINGS

Bauer KA: Current challenges in the management of hemophilia, *Am J Manag Care* 21(6 Suppl):S112-S122, 2015.

George LA: Hemophilia gene therapy comes of age, *Hematology Am Soc Hematol Educ Program* 2017(1):587-594, 2017.

Kempton CL et al: Toward optimal therapy for inhibitors in hemophilia, *Blood* 124(23):3365-3372, 2014.

Leissinger C et al: Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors, *N Engl J Med* 365:1684-1692, 2011.

Mahlangu J et al: Emicizumab prophylaxis in patients who have hemophilia A without inhibitors, *N Engl J Med* 379(9):811-822, 2018.

Manco-Johnson MJ et al: Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia, *N Engl J Med* 357:535, 2007.

Oldenburg J et al: Emicizumab prophylaxis in hemophilia A with inhibitors, *N Engl J Med* 377:809-818, 2017.

BASIC INFORMATION

DEFINITION

Hemoptysis is coughing up of blood originating from the lower respiratory tract, ranging from blood-streaked sputum to gross blood. If greater than 400 to 600 ml in 24 hours or if the bleeding rate is >100 ml/hr, it is considered massive hemoptysis.

ICD-10CM CODE
R04.2 Hemoptysis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown, varies based on underlying pathology
RISK FACTORS: Tobacco smoking predisposes to lung cancer, a common cause of hemoptysis. Systemic processes (rheumatologic, renal, hematologic) may contribute to alveolar hemorrhage or vasculitis. Anticoagulation can worsen bleeding.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presentation of hemoptysis is variable (Table 1) and can range from minimal blood-tinged sputum to more than 500 ml of gross blood in 24 hr. Other symptoms depend on the underlying etiology and can include cough, sputum production, fever, shortness of breath, weight loss, night sweats, wheezing, and chest pain.
- There are no specific exam findings, but clues to the etiology may be present, for example, focal wheezing, rhonchi or rales on pulmonary exam, murmur of mitral stenosis on cardiac exam.

ETIOLOGY

- There are many potential causes of hemoptysis including airway disease (bronchitis, bronchiectasis, lung neoplasm), infection (necrotizing pneumonia, lung abscess, tuberculosis, fungal infection), inflammatory diseases (granulomatosis with polyangiitis, Goodpasture syndrome, lupus), cardiac disease (mitral stenosis after rheumatic heart disease, congenital heart diseases), and others (pulmonary embolism, cocaine use, foreign body, airway trauma, iatrogenic and cryptogenic).
- Acute respiratory tract infections, asthma, chronic obstructive pulmonary disease (COPD), malignancy, and bronchiectasis are the most common diagnoses in outpatient primary care.
- Worldwide, tuberculosis accounts for 7% to 85% of cases of massive hemoptysis. Highest incidence is in South Africa; lowest incidence is in the U.S.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Various potential causes of lower respiratory tract bleeding
  1. Airway disease (bronchitis, bronchiectasis, lung neoplasm)
  2. Infection (necrotizing pneumonia, lung abscess, tuberculosis, fungal infection)
  3. Inflammatory diseases (granulomatosis with polyangiitis, Goodpasture syndrome, lupus)
  4. Cardiac disease (mitral stenosis after rheumatic heart disease, congenital heart diseases)
  5. Pulmonary embolism
  6. Cocaine use
  7. Foreign body
- Bleeding from upper respiratory tract
- Hematemesis or epistaxis
- Coagulopathy

WORKUP

- The initial history should focus on determining the anatomic origin of the bleeding and on quantifying the volume of the hemoptysis in order to triage appropriately.
- Complete history and physical exam may suggest a particular etiology; important to ask about duration and quantity of hemoptysis and smoking history.

LABORATORY TESTS

- Complete blood count
- Coagulation profile
- Serum chemistries, including creatinine, urinalysis
- If indicated, consider vasculitis serologies (i.e., antinuclear antibody [ANA], antineutrophil cytoplasmic antibodies [ANCA], anti-glomerular basement membrane [anti-GBM])
- Arterial blood gas to assess oxygenation
- Sputum for cultures and cytologic studies
- Purified protein derivative (PPD)

IMAGING STUDIES

- Chest x-ray: All patients with hemoptysis should have a chest x-ray but will likely need additional studies to localize site of bleeding.
- Chest CT: Chest CT scan combined with flexible bronchoscopy has the highest yield for localizing the site of bleeding.

TABLE 1 Features of Hemoptysis and Patient Presentation

Hemoptysis Feature	Clinical Presentation
Blood usually bright red	Often dyspneic
Portion of blood usually frothy	Hypoxemia
Alkaline pH	
Blood usually mixed with sputum	Preceding cough common
Alveolar macrophages may be present in sputum smear	Anemia and melena uncommon

From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

TREATMENT

Varies based on underlying etiology and nonmassive versus massive hemoptysis

NONPHARMACOLOGIC THERAPY

Massive hemoptysis:
- Arteriographic embolization of bronchial arteries and/or collateral systemic vessels
- Surgical resection of affected lung

ACUTE GENERAL Rx

Massive hemoptysis (Fig. 1):
- Stabilize hemodynamic status and oxygenation.
- Reverse any coagulopathy.
- Bronchoscopy can be used to identify cause of hemoptysis (e.g., neoplasm), as well as to help isolate a site/segment of bleeding.
- If site of bleeding is known, place patient with bleeding lung in dependent position to prevent blood from spilling into nonaffected lung, and consider selective intubation with large-bore, single-lumen endotracheal tube or double-lumen endotracheal tube.
- Bronchoscopic lavage with iced saline or topical application of epinephrine can be tried as a temporizing measure.
- Bronchoscopic balloon tamponade of bleeding site can be used as temporizing measure.
- Early consultation with interventional radiology, interventional pulmonology, and/or thoracic surgery for definitive intervention is recommended.

Submassive hemoptysis:
- For submassive hemoptysis, identify and treat underlying condition. Refer to pulmonologist or hematologist if indicated.

CHRONIC Rx

For patients requiring anticoagulation or antiplatelet therapy for another disorder, consider risks/benefits of continued anticoagulation or antiplatelet therapy.

DISPOSITION

Generally, patients have a good prognosis after an episode of hemoptysis, but those with massive bleeding and/or malignancy tend to have a poorer prognosis.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Evaluation of hemoptysis (Algorithm, Section III)

AUTHOR: **Gaetane Michaud, MD**

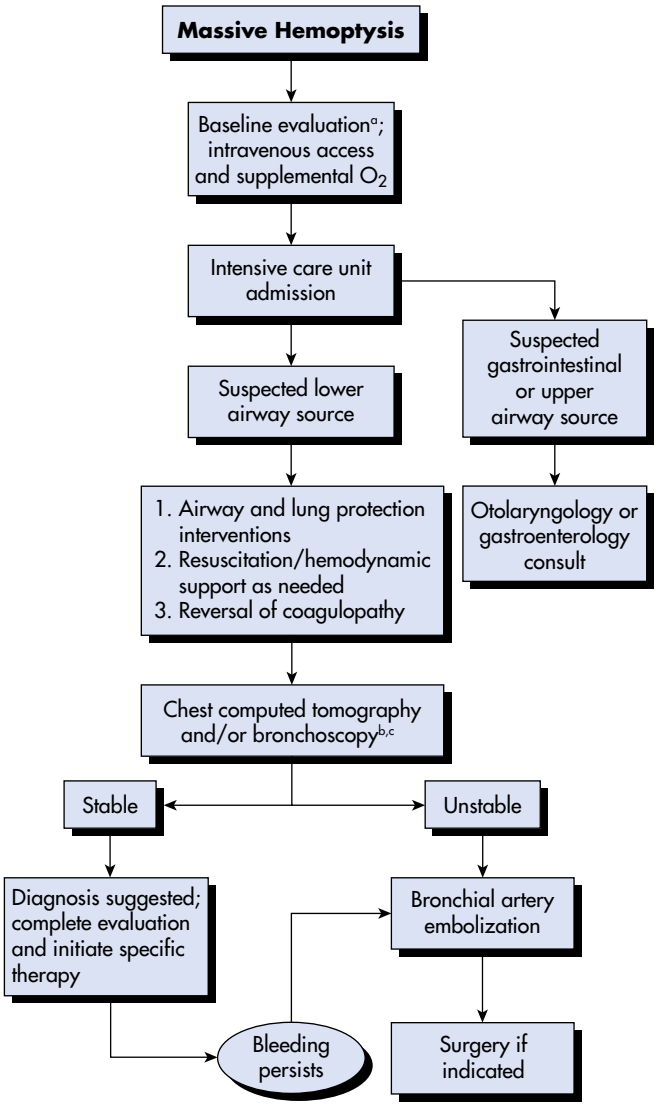

FIG. 1 Massive hemoptysis. [a]History and physical examination, complete blood cell count, coagulation studies, type and cross-match, chest radiograph, arterial blood gas levels. [b]Local availability and patient stability should guide choice; computed tomography is preferred in initial evaluation in stable patients. [c]Local measures, including topical vasoconstrictors, bronchial blockers, laser photocoagulation, electrocautery, and hemostatic agents, can be used endobronchially. *O_2,* Oxygen. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

SUGGESTED READING

Earwood JS, Thompson TD: Hemoptysis: evaluation and management, *Am Fam Physician* 91(4):243-249, 2015.

BASIC INFORMATION

DEFINITION

A hemorrhoid is a varicose dilation of a vein of the superior or inferior hemorrhoidal plexus, resulting from a persistent increase in venous pressure. External hemorrhoids are distal to the pectinate or dentate line (inferior plexus), are covered in stratified squamous epithelium, and have sensory innervation. Internal hemorrhoids are proximal to the pectinate or dentate line (superior plexus), are covered in columnar epithelium, and do not have sensory innervation. Mixed hemorrhoids are located both distal and proximal to the dentate line. Internal hemorrhoids can prolapse to various degrees, and both internal and external hemorrhoids can thrombose.

SYNONYM

Piles

ICD-10CM CODES

K64.0 First degree hemorrhoids
K64.1 Second degree hemorrhoids
K64.2 Third degree hemorrhoids
K64.3 Fourth degree hemorrhoids
K64.8 Other hemorrhoids
K64.9 Unspecified hemorrhoids

EPIDEMIOLOGY & DEMOGRAPHICS

Potential for development of symptomatic hemorrhoids in all adults

PREVALENCE:

- Self-reported prevalence in the U.S. is around 5% of the general population, with 50% of the population reported experiencing them within their lifetime
- Hemorrhoids are identified in nearly 40% of patients undergoing screening colonoscopy.
- Increased predominance in white and higher socioeconomic populations

PREDOMINANT SEX: Males and females affected equally

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- 40% of individuals are asymptomatic
- Painless bleeding with defecation; bleeding is bright red with staining seen on toilet paper or droplets in toilet (most common complaint in those who are symptomatic)
- Pressure in the perianal area
- Perianal irritation
- Mucofecal staining of underclothes
- Fecal incontinence
- Acute external hemorrhoids: Painful, swollen, and often thrombosed; red, deep purple tense bulge; can become necrotic or infected (Fig. E1)
- Pain on sitting, standing, or defecating often associated with thrombosed hemorrhoid
- Prolapse (Fig. E2)
- Constipation
- A classification of internal hemorrhoids is described in Table E1

ETIOLOGY

- Low-fiber, high-fat diet
- Chronic constipation and straining with defecation
- Diarrhea
- Advancing age
- High resting anal sphincter pressures
- Pregnancy
- Obesity
- Rectal surgery (i.e., episiotomy)
- Prolonged sitting
- Anal intercourse
- Pelvic tumors

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Fissure
- Abscess
- Anal fistula
- Condylomata acuminata
- Hypertrophied anal papillae
- Rectal prolapse (Fig. E3)
- Rectal polyp
- Neoplasm (anal cancer, colorectal cancer)
- Inflammatory bowel disease

WORKUP

- Inspection
- Digital rectal examination: At rest and with Valsalva
- Anoscopy
- Endoscopy (dependent on age and associated symptoms)

TABLE E1 Classification of Internal Hemorrhoids

Grade	Location	Symptoms
1	Bulge into anal canal	Painless bleeding
2	Prolapse, reduce spontaneously	Bleeding, burning, itching
3	Prolapse, must be manually reduced	Bleeding, itching, mucoid drainage
4	Prolapse and cannot be reduced	Pain, bleeding, mucoid drainage

From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.

FIG. E1 Thrombosed external hemorrhoid. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

FIG. E2 Prolapsed and thrombosed internal hemorrhoids. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

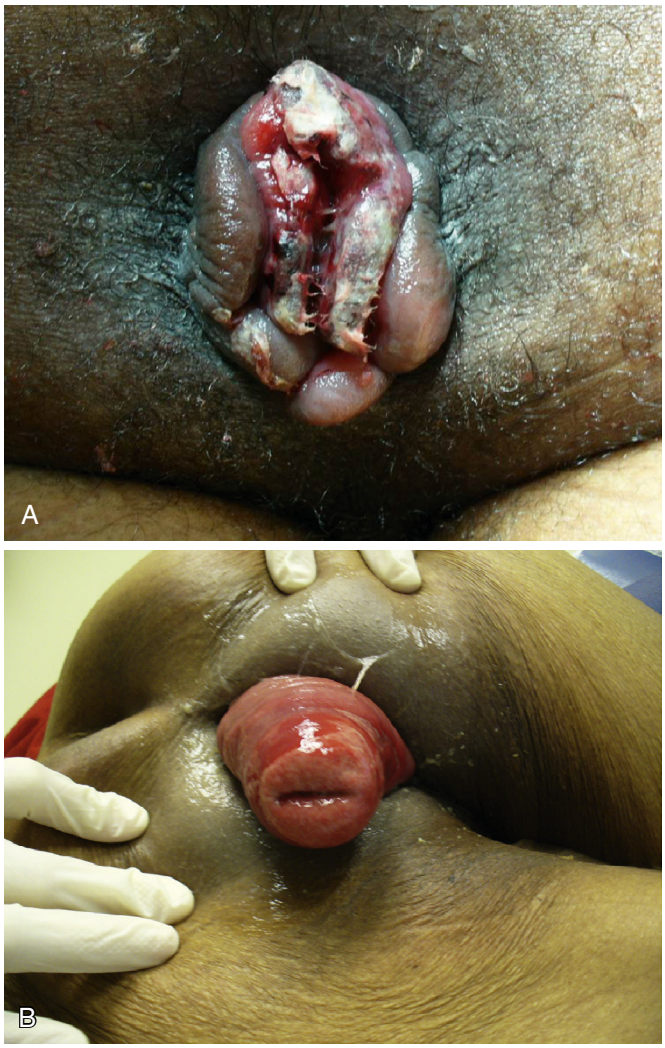

FIG. E3 Differentiating hemorrhoidal prolapse from true rectal prolapse. A, Incarcerated, strangulated internal hemorrhoids with visible radial folds. **B,** True rectal prolapse with visible circular folds. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

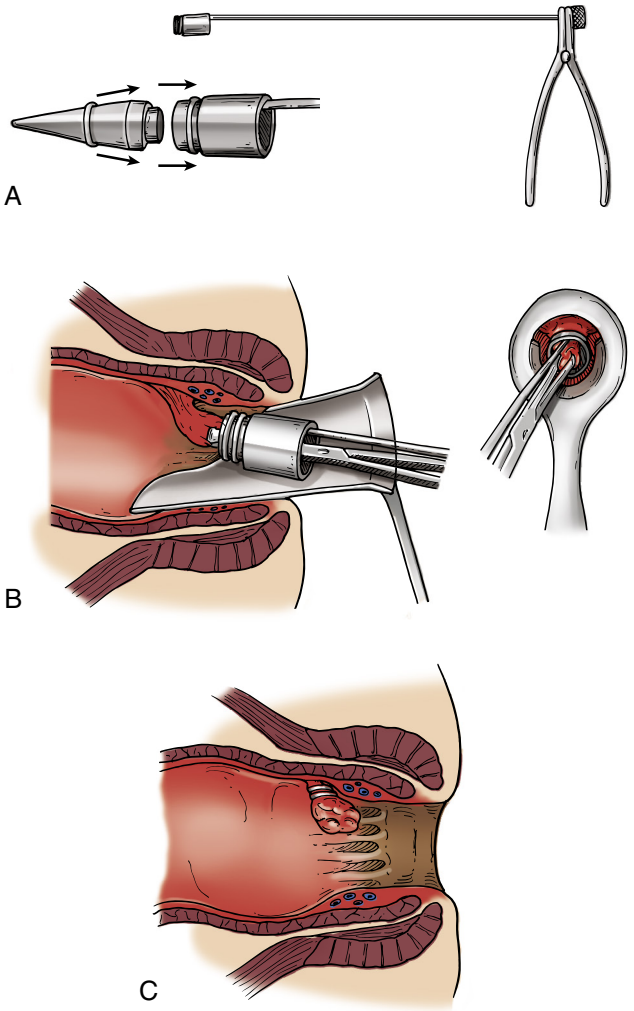

FIG. E4 Rubber band ligation of internal hemorrhoids. A, Rubber band placed onto banding gun. **B,** Hemorrhoid is grasped 2 cm above the dentate line and the band advanced over the hemorrhoid. **C,** Band in correct position after ligation. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of constipation and straining with defecation
- Avoidance of prolonged sitting on toilet (consider decreased screen time on toilet)
- High-fiber diet (20 to 30 g/day)
- Increased fluid intake (six to eight glasses of water per day)
- Exercise
- Cleaning with mild soap and water after defecation
- Warm soaks (15 min TID and after defecation) or ice to soothe
- Sitz baths

ACUTE GENERAL Rx

- Fiber supplements to provide bulk (psyllium extracts or mucilloids)
- Medicated compresses with witch hazel
- Topical hydrocortisone (1% to 3% cream or ointment)
- Topical anesthetic (lidocaine)
- Glycerin suppositories
- Stool softeners
- Surgically remove during first 72 hr after onset

CHRONIC Rx

- Rubber band ligation (Fig. E4)
- Injection sclerotherapy
- Photocoagulation
- Cryodestruction
- Hemorrhoidectomy
- Fig. E5 illustrates the technique for excision of thrombosed external hemorrhoids. Fig. E6 illustrates the anatomy of the rectosigmoid region
- Anal dilation
- Laser (Fig. E7) or cautery hemorrhoidectomy
- Observance for complications: Thrombosis, bleeding, infection, anal stenosis, or weakness
- Stapled hemorrhoidopexy, a newer technique for the treatment of patients with Grade III or IV internal disease, involves the use of a circular stapler to resect mucosal tissue, interrupt arterial and venous flow, and simultaneously affix the remaining tissue in situ about the dentate line[1]
- Table E2 summarizes treatment options for internal hemorrhoids

DISPOSITION

Should resolve, but high rate of recurrence

REFERRAL

To colorectal or general surgeon for any hemorrhoid that does not respond to conservative therapy

[1] Jacobs D: Hemorrhoids, *N Engl J Med* 371:944-951, 2014..

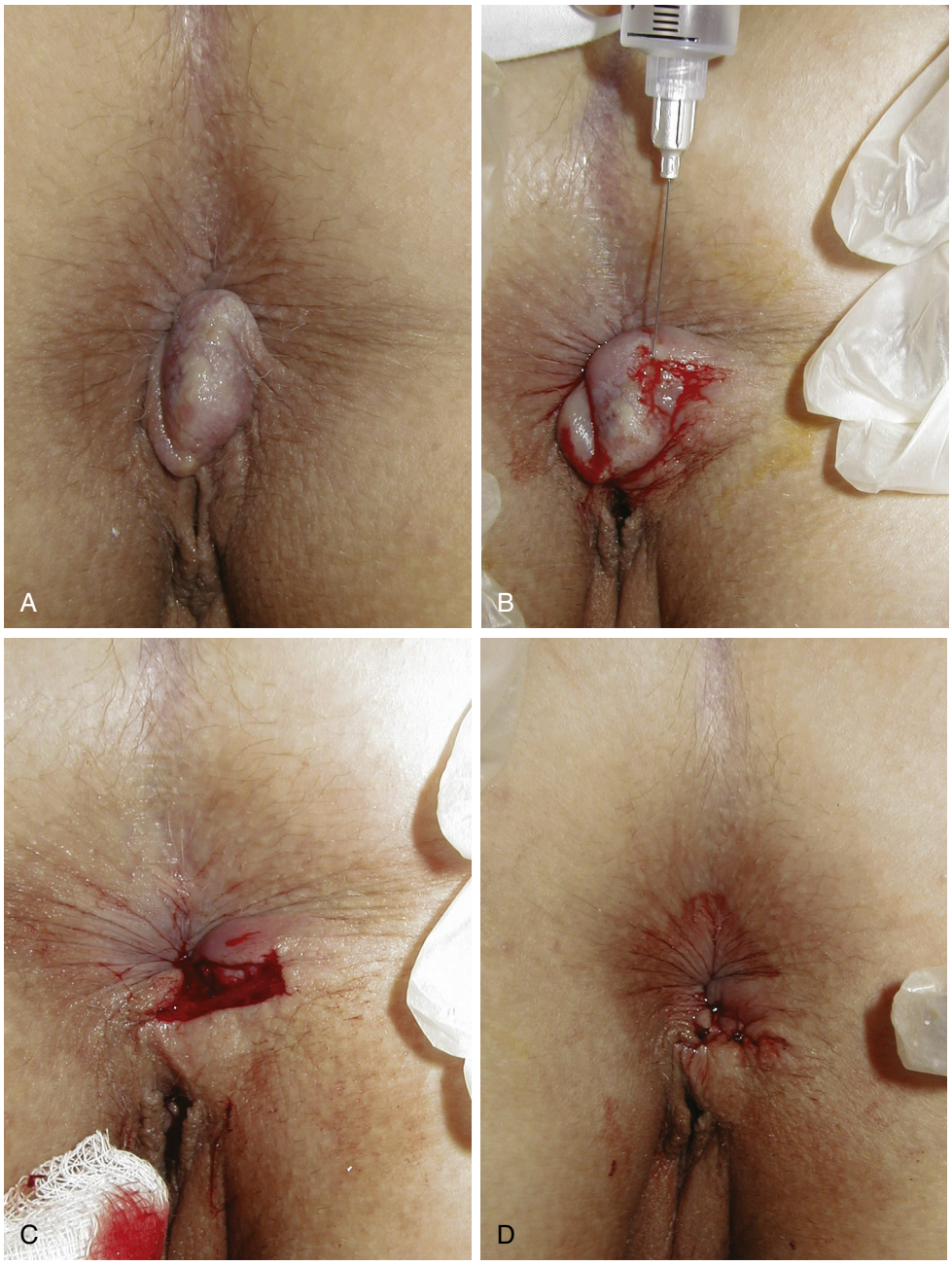

FIG. E5 Office excision of a thrombosed external hemorrhoid. A, Thrombosed right anterior external hemorrhoid. **B,** Injection of 1% lidocaine with epinephrine. **C,** Excision of external component. **D,** Closure with two or three interrupted absorbable sutures. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

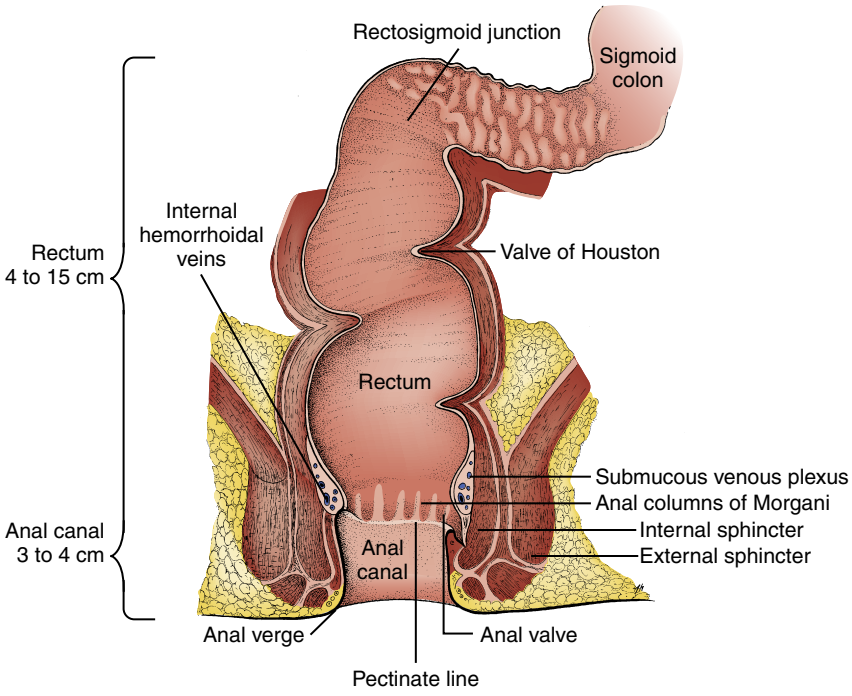

FIG. E6 Anatomy of the retrosigmoid region. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

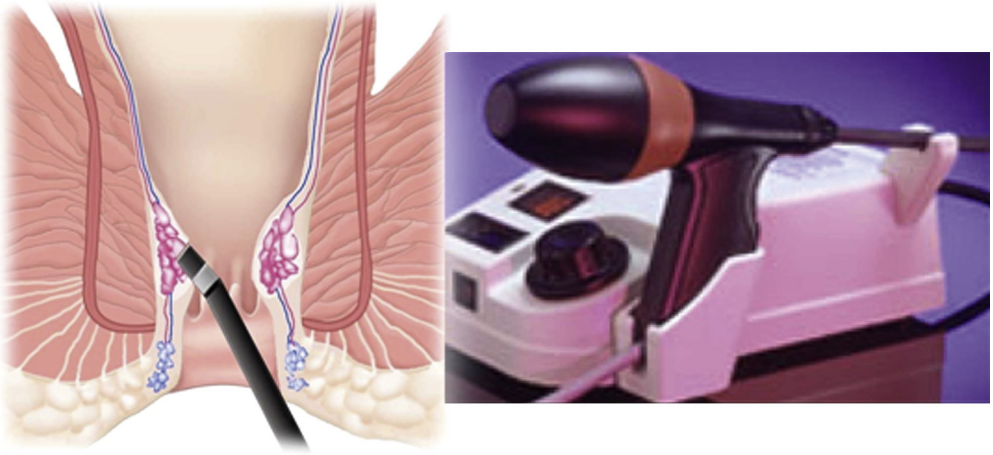

FIG. E7 Ferguson hemorrhoidectomy. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

TABLE E2 Treatment Options for Internal Hemorrhoids

Type of Treatment	Hemorrhoid Grades	Success Rate	Comments
General			
Diet (increase in fiber and fluids) and bowel habit modification	1-4	Unknown	Patients with all grades of hemorrhoids should use these measures (see text). Patients with high grades of hemorrhoids will need additional therapy.
Endoscopic			
Sclerosing agent	1-4	75%	May be the favored treatment of patients with AIDS (successful results even with grades 3 and 4 hemorrhoids). Life-threatening sepsis rarely complicates therapy.
Rubber band ligation	2 and 3	65%-75%	Grade 1 hemorrhoids are too small, and grade 4 hemorrhoids are usually too large for this procedure. The most commonly performed office procedure for hemorrhoids Life-threatening sepsis rarely complicates therapy; 1% risk of severe hemorrhage when band sloughs.
Infrared coagulation	1 and 2	Less than for rubber band ligation	Equipment for the procedure is expensive. Rare complications
Surgical			
Excisional hemorrhoidectomy	3 and 4	>85% on 10-yr follow-up	External tags may be removed at the time of the surgical procedure. Postoperative pain is pronounced.
Procedure for prolapsing hemorrhoids (PPH)*	3 and 4	>75%; several studies show higher long-term recurrence rates than with excisional hemorrhoidectomy	Newer procedure Overall, significantly less postoperative pain than with excisional hemorrhoidectomy, but some patients experience severe, persistent postoperative pain or defecation urgency Pelvic sepsis and death have been reported after this procedure.

AIDS, Acquired immune deficiency syndrome.
*Also called *stapled hemorrhoidopexy.*
(From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

PEARLS & CONSIDERATIONS

COMMENTS

- Patients need to understand the importance of a healthy diet, regular exercise, and rectal hygiene.
- Stress the importance of avoiding prolonged sitting and straining on the toilet.
- Stress the need not to defer the urge to defecate.
- Surgical treatment with excisional hemorrhoidectomy recommended within 24 to 72 hours of initial symptoms of thrombosed hemorrhoid.
- Patients with red flag symptoms such as melena, dark blood from the rectum, constitutional symptoms, change in bowel habits, and fecal occult blood positive stools without gross blood per rectum require further investigation with endoscopy and referral as necessary.

RELATED CONTENT

Hemorrhoids (Patient Information)
Hemorrhoids (Primary Care Procedures in Appendix)
Anal Fissure (Related Key Topic)

AUTHORS: **Tess Crouss, MD,** and **Emily Saks, MD, MSSCE**

SUGGESTED READINGS

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Heparin-Induced Thrombocytopenia

BASIC INFORMATION

DEFINITION

There are two forms of heparin-induced thrombocytopenia (HIT). Type I HIT is a mild, transient decrease in platelet count that occurs during the first 2 days of heparin exposure due to non–immune-mediated platelet aggregation. This is a benign reaction, and the platelet count will return to normal while heparin is continued. This chapter will address Type II HIT, an antibody-mediated thrombocytopenia with risk of thrombosis.

SYNONYMS

Type II heparin-induced thrombocytopenia
Heparin-induced thrombocytopenia and thrombosis (HITT)
Heparin-associated immune thrombocytopenia

ICD-10CM CODE
D75.82 Heparin-induced thrombocytopenia (HIT)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Occurs in 0.2% to 5% of patients exposed to heparin in various clinical settings. Initially, there was an overwhelming underdiagnosis of HIT; however, since the introduction of HIT antibody ELISA test, there is a propensity to overdiagnose HIT irrespective of the clinical scenario.
PREDOMINANT SEX AND AGE: Females are at slightly higher risk than males. More common in adults, but may also occur in children.
RISK FACTORS: Heparin type (unfractionated heparin has up to 10 times greater risk than low–molecular-weight heparin), dose (therapeutic dose may have a greater risk than prophylactic dose, though no dose is considered too low to cause HIT), and duration (longer duration of exposure confers greater risk); type of patient (surgical patients, especially cardiac and orthopedic, are at higher risk than medical patients). Risk factors for HIT are summarized in Table 1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Suspect in a patient with:
- Exposure to heparin in the last 5 to 10 days OR exposed to heparin in the prior 3 mo
- Unexplained platelet count decrease to 50% below pretreatment baseline
- Onset of thrombocytopenia 5 to 10 days after heparin initiation
- Venous or arterial thrombosis (e.g., DVT or phlegmasia cerulea dolens, pulmonary embolism, skin necrosis at heparin injection sites, limb gangrene, adrenal hemorrhage, stroke or cavernous sinus thrombosis, myocardial infarction)
- Acute anaphylaxis during administration of heparin bolus

ETIOLOGY

Occurs when IgG antibodies bind to complexes of heparin and platelet factor 4 (PF4), a prothrombotic cytokine released from platelets during their activation. The resulting immune complexes activate adjacent platelets, leading to further PF4 release, additional antibody production, and eventual platelet aggregation with premature removal from circulation (causing thrombocytopenia). This process also leads to increased thrombin generation, though the full mechanism of thrombosis in HIT is not completely understood.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Thrombocytopenia due to other causes including:
- Sepsis or infection
- Disseminated intravascular coagulation
- Immune thrombocytopenia
- Thrombocytopenic thrombotic purpura
- Hemolytic uremic syndrome
- Drug-induced thrombocytopenia (other than heparin)
- Antiphospholipid antibody syndrome
- Liver failure
- Splenic sequestration
- Intravascular devices

WORKUP

HIT is, first and foremost, a clinical diagnosis that is confirmed with laboratory testing. See Table 2 for workup based on pretest probability. If the patient has a low pretest probability score, heparin can be safely continued, and there is no need to send further testing for HIT. A patient with moderate-to-high pretest probability requires HIT testing (Table 3), imaging studies for lower-extremity deep venous thrombosis (also consider imaging of upper extremities if swelling is present or venous catheters are in place), cessation of heparin products, and initiation of alternative anticoagulation. Patients with moderate-to-high pretest probability without HIT antibodies or intermediate pretest probability with only weakly positive HIT antibodies (based on optical density, discussed below) can resume heparin, as HIT is unlikely in these scenarios. Patients with high pretest probability with weakly positive antibodies or moderate-to-high pretest probability with moderate to strongly positive antibodies likely have HIT and should be treated as such.

LABORATORY TESTS

These can be broadly divided into two categories: Immunoassays (high sensitivity) and functional assays (high specificity).

In the appropriate clinical setting, testing for HIT antibodies with an ELISA can be useful. This test is very sensitive, but not specific. The majority of patients with positive testing for HIT antibodies will not develop clinical HIT. Thus, HIT antibody testing is more effective for ruling out rather than confirming the diagnosis of HIT.

HIT antibody optical density (OD) can be used as a correlate for HIT antibody concentration. OD range is defined as weakly positive (0.4 to 1.0), moderately positive (1.0 to 2.0), or strongly positive (>2.0). A weakly positive OD (0.4 to 1.0) is only rarely associated with functional assay positivity (1% to 5%), whereas an OD >2.0 almost always shows functional assay positivity (89% to 100%). A higher OD is also associated with a higher pretest probability score and increased risk of thrombosis. Of note, the HIT antibody IgG subtype is the pathologic antibody for HIT, and thus the use of IgG-specific ELISA kits increases the test specificity over the polyspecific (IgA/M/G) antibody. In general, patients with low pretest probability via the 4T clinical prediction score should not have HIT antibody testing performed because it has a more than 99% negative predictive value, while all patients with intermediate and high pretest probability of HIT benefit from HIT antibody testing.

The gold standard test for HIT is to measure heparin-dependent platelet activation via the functional serotonin release assay (14C-SRA). This is both a highly sensitive and specific test. Donor platelets are radiolabeled with serotonin and then incubated with patient serum and heparin. If antibodies to the platelet factor 4-heparin complex are present in the patient's serum, the platelets react and release the radiolabeled serotonin, which is then measured. Availability and turnaround time of this test is dependent on the institution, which can influence the test's clinical utility. Cases where there is intermediate pretest probability with only a weakly positive HIT antibody OD most benefit from confirmatory SRA testing.

Overall, the diagnosis of HIT can be considered confirmed by (1) a positive ELISA with OD >2.00 or (2) a positive functional assay.

IMAGING STUDIES

Doppler ultrasonography of the extremities in the correct clinical setting.

TREATMENT

- For patients with a moderate or high pretest probability, discontinue all heparin

TABLE 1 Risk Factors for Heparin-Induced Thrombocytopenia

Heparin Type	Unfractionated > Low-Molecular-Weight Heparin > Fondaparinux
Patient type	Postoperative (major > minor surgery) > medical > obstetric/pediatric
Dose[a]	Prophylactic dose > therapeutic dose > flushes
Duration	11-14 days[b] > 5-10 days > 4 days or fewer
Sex	Female > male

[a]Importance of heparin dose is uncertain because of compounding effect of patient type (e.g., postoperative patients tend to receive prophylactic-dose heparin whereas medical patients [e.g., with venous thromboembolism] are more likely to receive therapeutic-dose heparin); nevertheless, reported frequencies of heparin-induced thrombocytopenia (HIT) are relatively high in patients given postoperative prophylactic-dose heparin.
[b]Heparin exposure beyond 14 days does not usually increase the risk of HIT beyond that of an 11- to 14-day exposure.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 2 The 4Ts Score for Estimating the Pretest Probability of Heparin-Induced Thrombocytopenia

	POINTS (0, 1, or 2 for each of the four parameters; maximum points = 8)		
	2	**1**	**0**
Thrombocytopenia (acute)	>50% platelet count fall to nadir ≥20 × 10^9/L	30%-50% platelet count fall; or nadir 10-19 × 10^9/L	<30% platelet count fall; or nadir ≤10 × 10^9/L
Timing of fall in platelet count or other sequelae	Onset day 5-10 or <1 day (if heparin exposure within 30 days)	>Day 10, timing unclear, or <day 1 with recent heparin 31-100 days	Platelet count fall <day 4 (without recent heparin exposure)
Thrombosis or other sequelae	New thrombosis; skin necrosis; post-heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis—not confirmed	None
Other cause for thrombocytopenia	No other cause for platelet count fall is evident	Possible other cause is evident	Definite other cause is present
Pretest probability score: 6-8 = High; 4-5 = Intermediate; 0-3 = Low			

From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

TABLE 3 Laboratory Assays for Heparin-Induced Thrombocytopenia

Assay	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Functional assay (e.g., serotonin release assay)	88	~100	~100	81
PF4/heparin enzyme immunoassay (ELISA)	95-98	86	93	95

ELISA, Enzyme-linked immunosorbent assay; *PF4,* platelet factor 4.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

TABLE 4 Treatment Schedules for Bivalirudin and Argatroban

Anticoagulant	Dosing Protocol for HIT-Associated Thrombosis	Anticoagulant Monitoring[a]	Clearance	Half-Life (min)	Comment
Bivalirudin	No bolus; initial infusion rate: 0.15-0.20 mg/kg per hour	1.5-2.5 × baseline aPTT	Enzymic (80%); renal (20%)	25	Off-label treatment for HIT (although approved for PCI in patient with HIT); minor prolongation of INR (compared with argatroban)
Argatroban	No bolus; initial infusion rate: 2 μg/kg per minute	1.5-3.0 × baseline aPTT	Hepatobiliary	40-50	Initial dose 0.5 μg/kg per minute in hepatic insufficiency[b]; moderate or marked prolongation of INR, which complicates overlap with warfarin anticoagulation

Dosing protocols shown are appropriate for most patients with strongly suspected or confirmed HIT whether or not complicated by thrombosis. (Dosing for bivalirudin and argatroban is substantially different when given for PCI.) *aPTT,* Activated partial thromboplastin time; *HIT,* heparin-induced thrombocytopenia; *INR,* international normalized ratio; *PCI,* percutaneous coronary intervention.
[a]In general, the patient's baseline aPTT should be used for calculating target range when appropriate; otherwise the mean laboratory normal range can be used.
[b]Reduced initial dosing (e.g., 0.5-1.2 μg/kg per minute) is also appropriate in patients in intensive care units, with cardiac failure, or postcardiac surgery).
Modified from Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

exposure. Even if the patient does not have a clinically evident thrombosis, there is a significant risk of developing an incident clot within the subsequent 30 days. Thus, the patient must be started on an alternative anticoagulant.

- Two agents, both direct thrombin inhibitors, are approved for this indication (Table 4):
  1. Argatroban (preferred agent in renal failure and in hemodialysis patients; avoid in liver dysfunction).
  2. Bivalirudin (approved only for patients with HIT or at risk of HIT who are undergoing PCI; dose adjustment is required in renal failure).
- NOTE: Lepirudin is no longer available. Outside of the U.S., the factor Xa inhibitor danaparoid may be used.
- Platelet transfusion in the absence of life-threatening hemorrhage or extreme thrombocytopenia should be avoided. Risk of bleeding is low, and platelet transfusions in HIT can increase risk of arterial thrombosis.
- A direct thrombin inhibitor should be continued as a single agent until the platelet count returns to baseline (generally 150 × 109/L, but consider the individual patient's baseline).
- Warfarin can be added after platelet recovery (maximum dose of 5 mg/day to reduce risk of warfarin-induced skin necrosis and venous limb gangrene). This overlap therapy should continue until the platelet count has reached a stable plateau, the INR has reached goal (typically 2 to 3, though guidelines may vary with argatroban as it artificially elevates the INR), and after a minimum overlap of 5 days with both the direct thrombin inhibitor and warfarin.
- The length of treatment is controversial, but most clinicians agree that at least 1 mo of alternative anticoagulation is required in the absence of thrombosis, while at least 3 to 6 mo of treatment are required in the presence of thrombosis.

TABLE 5 Treatment Schedules for Danaparoid and Fondaparinux

Anticoagulant	Therapeutic Dosing Protocol for HIT-Associated Thrombosis[a]	Anticoagulant Monitoring	Clearance	Half-Life (h)	Comment
Danaparoid	Initial bolus, 2250 units[b] IV; accelerated infusion (400 units/h × 4 h, 300 units/h × 4 h; then 200 units/h IV, subsequently adjusted by antifactor Xa levels)	Antifactor Xa levels (target, 0.5-0.8 units/ml)	Renal (minor)	25	Widely approved for HIT treatment (although not in the U.S.); not available in the U.S.; low risk for in vivo cross-reactivity; prophylactic-dose therapy[c] may be appropriate when clinical suspicion for HIT is low.
Fondaparinux	7.5 mg[d] subcutaneous once daily	Anti–Xa factor levels (target levels not well established)	Renal (major)	17	Not approved for HIT treatment (although increasingly used as off-label therapy). Prophylactic-dose therapy[e] may be appropriate when clinical suspicion for HIT is low, or if there is renal insufficiency.

HIT, Heparin-induced thrombocytopenia; *IV,* intravenous.
[a]Therapeutic dosing is usually appropriate for strongly suspected or confirmed HIT (including "isolated" HIT, i.e., HIT without apparent thrombosis), or when thrombosis is documented.
[b]Adjust IV danaparoid bolus for body weight: <60 kg, 1500 units; 60-75 kg, 2250 units; 75-90 kg, 3000 units; >90 kg, 3750 units.
[c]Prophylactic-dose regimen, 750 units subcutaneous every 8 h (for renal failure, reduce to 750 units every 12 h).
[d]Five milligrams for body weight <50 kg and 10 mg for body weight >100 kg; the author sometimes gives 10 mg as the first and/or second dose (rather than 7.5 mg) for severe HIT. Because HIT treatment is usually started in the afternoon, the author usually gives the second dose (and subsequent doses) at 8 a.m. (i.e., the interval between first and second doses is often only 14-20 h rather than 24 h), which helps to achieve steady-state therapy more quickly. Dose reduction and antifactor Xa monitoring (if available) is appropriate if being used in a patient with renal insufficiency.
[e]Prophylactic-dose regimen, 2.5 mg subcutaneous every day (assumes normal renal function).
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.-

- Fondaparinux, a synthetic pentasaccharide that inhibits factor X but not thrombin, is being increasingly used for treatment of HIT despite not yet being FDA approved (Table 5). Emerging data suggest it has similar efficacy as direct thrombin inhibitors, with the additional advantages of lower bleeding risk, easier administration (subcutaneous), and lower cost. Rare cases of fondaparinux-induced HIT have been reported, however.
- The use of direct oral anticoagulants (e.g., rivaroxaban, dabigatran, apixaban) is being studied. Retrospective reviews have shown DOACs to be safe and effective for the treatment of HIT, though randomized prospective data remain lacking.
- In patients with confirmed HIT, all heparin products should be avoided for life. A possible exception is in patients who require brief intraoperative anticoagulation such as cardiac bypass surgery.

REFERRAL

Request a hematology consultation.

PEARLS & CONSIDERATIONS

COMMENTS

- HIT paradoxically causes thrombocytopenia and *clotting,* not bleeding.
- It is unclear whether patients with HIT should be considered heparin allergic lifelong. Risk of recurrent HIT with heparin rechallenge years later is relatively low, about 5% in one small study (though recurrence risk is higher perioperatively). If such a patient requires surgery with heparin (e.g., on-pump cardiac bypass), consider perioperative argatroban.
- Consult the coagulation laboratory and/or hematology when bridging patients on argatroban to warfarin, as argatroban concomitantly raises the INR in most assays. Some clinicians will use a higher target than 2 to 3 during the bridging period for this reason.
- Be alert to heparin exposure in the absence of anticoagulation or DVT prophylaxis: Hospitalized patients are often exposed to heparin lock flushes, heparin-coated catheters, or heparin-coated guidewires—any of which could precipitate HIT.

PREVENTION

Strongly consider the use of low-molecular-weight heparin in place of unfractionated heparin in hospitalized patients with a stable creatinine clearance of 30 ml/min or greater. Such a preventive strategy can reduce the risk of HIT by over 90% and yield cost savings in testing and treatment.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Robert Matera, MD,** and **John L. Reagan, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Hepatic encephalopathy is a neuropsychiatric syndrome occurring in patients with severe impairment of liver function and consequent accumulation of toxic products not metabolized by the liver. It is characterized by gradual impairment of the ability to perform mental tasks and to react to external stimuli. Fig. 1 illustrates the hepatic encephalopathy grades in acute liver failure. ***Minimal hepatic encephalopathy*** refers to patients with hepatic cirrhosis and mild cognitive impairment, but no history of overt encephalopathy.

SYNONYMS

Hepatic coma
Portal systemic encephalopathy
HE

ICD-10CM CODES

G92	Toxic encephalopathy
G93.40	Encephalopathy, unspecified
G93.41	Metabolic encephalopathy
K70.40	Alcoholic hepatic failure without coma
K70.41	Alcoholic hepatic failure with coma
K72.0	Acute and subacute hepatic failure
K72.00	Acute and subacute hepatic failure without coma
K72.01	Acute and subacute hepatic failure with coma
K72.1	Chronic hepatic failure
K72.10	Chronic hepatic failure without coma
K72.11	Chronic hepatic failure with coma
K72.9	Hepatic failure, unspecified
K72.90	Hepatic failure, unspecified without coma
K72.91	Hepatic failure, unspecified with coma
K91.82	Postprocedural hepatic failure

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE: Hepatic encephalopathy occurs in >40% of all cases of cirrhosis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Hepatic encephalopathy can be classified by clinical stages described in Table 1. Other widely used scales are the four score criteria and the West Haven criteria. The West Haven criteria for grading hepatic encephalopathy is as follows:

- Grade (0): No abnormalities noted
- Grade (1): Unawareness (mild), euphoria or anxiety, shortened attention span, impairment of calculation ability, lethargy, or apathy
- Grade (2): Disorientation to time, obvious personal change, inappropriate behavior
- Grade (3): Somnolence to stupor, responsiveness to stimuli, gross disorientation, bizarre behavior
- Grade (4): Coma

The physical examination in hepatic encephalopathy varies with the stage and may reveal the following abnormalities:

- Skin: Jaundice, palmar erythema, spider angiomata, ecchymosis, dilated superficial periumbilical veins (caput medusae) in patients with cirrhosis
- Eyes: Scleral icterus, Kayser-Fleischer rings (Wilson disease)
- Breath: Fetor hepaticus
- Chest: Gynecomastia in men with chronic liver disease
- Abdomen: Ascites, small nodular liver (cirrhosis), tender hepatomegaly (congestive hepatomegaly)
- Rectal examination: Hemorrhoids (portal hypertension), guaiac-positive stool (alcoholic gastritis, bleeding esophageal varices, peptic ulcer disease, bleeding hemorrhoids)
- Genitalia: Testicular atrophy in males with chronic liver disease
- Extremities: Pedal edema from hypoalbuminemia
- Neurologic: Flapping tremor (asterixis), obtundation, coma with or without decerebrate posturing

ETIOLOGY

- Hepatic encephalopathy is thought to be caused mainly by accumulation of unmetabolized ammonia. The shunting of ammonia into the systemic circulation results in neuronal dysfunction leading to hepatic encephalopathy
- Precipitating factors in patients with underlying cirrhosis (upper gastrointestinal bleeding, hypokalemia, hypomagnesemia, analgesic and sedative drugs, sepsis, alkalosis, increased dietary protein)
- Acute fulminant viral hepatitis
- Drugs and toxins (e.g., isoniazid, acetaminophen, diclofenac and other NSAIDs, statins, methyldopa, loratadine, propylthiouracil, lisinopril, labetalol, halothane, carbon tetrachloride, erythromycin, nitrofurantoin, troglitazone, herbal products, flavocoxid)
- Reye syndrome
- Shock and/or sepsis
- Fatty liver of pregnancy
- Metastatic carcinoma, hepatocellular carcinoma
- Other: Autoimmune hepatitis, ischemic venoocclusive disease, sclerosing cholangitis, heat stroke, amebic abscesses

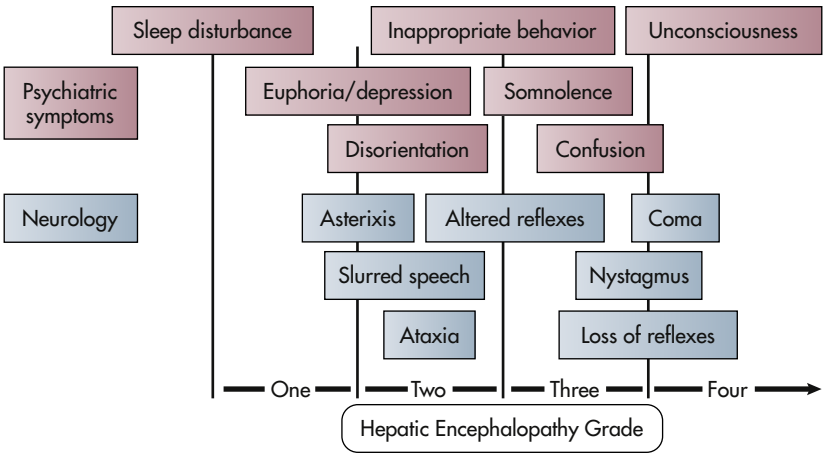

FIG. 1 Hepatic encephalopathy grade in acute liver failure. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Elsevier.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Delirium caused by medications or illicit drugs
- Cerebrovascular accident, subdural hematoma
- Meningitis, encephalitis
- Hypoglycemia
- Uremia
- Cerebral anoxia
- Hypercalcemia
- Metastatic neoplasm to brain
- Alcohol withdrawal syndrome/Wernicke-Korsakoff syndrome
- Hyponatremia
- Postictal state

WORKUP

Hepatic encephalopathy should be considered in any patient with cirrhosis who presents with neuropsychiatric manifestations. Exclude other etiologies with comprehensive history (obtained from patient, relatives, and others), physical examination, and laboratory and imaging studies. A pertinent history should include exposure to hepatitis, ethanol intake, drug history, exposure to toxins, IV drug abuse, measles or influenza with aspirin use (Reye syndrome), and history of carcinoma (primary or metastatic). Minimal hepatic encephalopathy may not be obvious on clinical examination, but can be detected with neurophysiologic and neuropsychiatric testing.

LABORATORY TESTS

- Alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, glucose, calcium, electrolytes, blood urea nitrogen, creatinine, albumin
- Complete blood count, platelet count, prothrombin time, partial thromboplastin time
- Serum and urine toxicology screen in suspected medication or illegal drug use

TABLE 1 Clinical Stages of Hepatic Encephalopathy

Stage	Asterixis	EEG Changes	Clinical Manifestations
I (prodrome)	Slight	Minimal	Mild intellectual impairment, disturbed sleep-wake cycle
II (impending)	Easily elicited	Usually generalized	Drowsiness, confusion, coma/inappropriate behavior, disorientation, mood swings
III (stupor)	Present if patient cooperative	Grossly abnormal slowing of rhythm	Drowsy, unresponsive to verbal commands, markedly confused, delirious, hyperreflexia, positive Babinski sign
IV (coma)	Usually absent	Appearance of delta waves, decreased amplitudes	Unconscious, decerebrate or decorticate response to pain present (stage IVA) or absent (stage IVB)

EEG, Electroencephalogram.
From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, WB Saunders.

- Blood and urine cultures, urinalysis
- Venous ammonia level. Measurement of serum ammonia level is useful in the evaluation of acute liver failure because levels correlate with the severity of encephalopathy and elevated levels are predictive of severe encephalopathy and cerebral edema. It is not useful for the evaluation or screening of hepatic encephalopathy in patients with chronic liver disease because it can neither rule in nor rule out hepatic encephalopathy, and levels do not correlate with the degree of encephalopathy
- Arterial blood gases

IMAGING STUDIES

CT scan or MRI of the brain may be useful in selected patients to exclude other etiologies when diagnosis is unclear.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Identification and treatment of precipitating factors.
- Restriction of protein intake is ill-advised and not necessary, since normal protein intake does not appear to exacerbate hepatic encephalopathy.

ACUTE GENERAL Rx

The approach to patients with high grade hepatic encephalopathy is shown in Fig. 2. Table 2 summarizes the management of fulminant hepatic failure.

Reduction of colonic ammonia production:

- Lactulose 25 ml twice daily initially; dose is subsequently adjusted depending on clinical response to achieve production of 3 bowel movements daily. IV ornithine aspartate should be considered for those not responding to lactulose.
- The oral antibiotic rifaximin (550 mg PO bid) is effective in reducing the risk of recurrent hepatic encephalopathy in patients with cirrhosis. It can be taken with lactulose, and the combination of lactulose and rifaximin is superior to lactulose alone in reversing hepatic encephalopathy. Rifaximin has also been shown to be effective in improving psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy. It is well tolerated but expensive.
- Probiotics (e.g., 1 capsule containing 112.5 billion viable lyophilized bacteria tid) might also be beneficial in altering gut flora to reduce ammonia production.

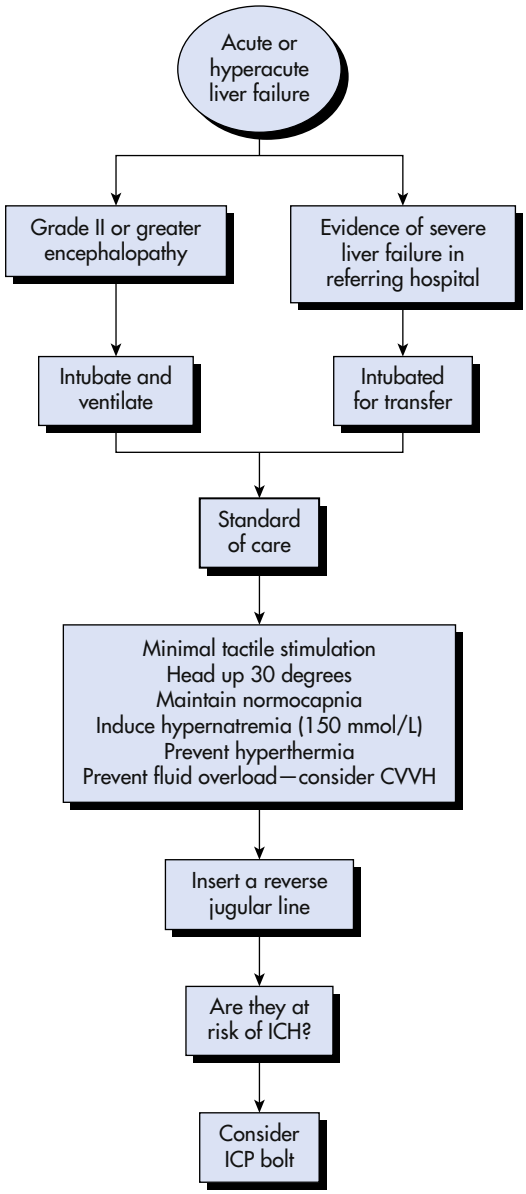

FIG. 2 Initial management of patient with high-grade encephalopathy. CVVH, Continuous venovenous hemofiltration; ICH, intracranial hypertension; ICP, intracranial pressure. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

Treatment of cerebral edema:

- Cerebral edema is often present in patients with acute liver failure, and it accounts for nearly 50% of deaths. Monitoring intracranial pressure by epidural, intraparenchymal, or subdural transducers and treatment of cerebral edema with mannitol (100 to 200 ml of 20% solution [0.3 to 0.4 g/kg of body weight]) given by rapid IV infusion are helpful

TABLE 2 Management of Fulminant Hepatic Failure

No sedation except for procedures
Minimal handling
Enteric precautions until infection ruled out
Monitor:
1. Heart and respiratory rate
2. Arterial BP, CVP
3. Core/toe temperature
4. Neurologic observations
5. Gastric pH (>5.0)
6. Blood glucose (>4 mmol/L)
7. Acid-base
8. Electrolytes
9. PT, PTT

Fluid balance:
1. 75% maintenance
2. Dextrose 10%-50% (provide 6-10 mg/kg/min)
3. Sodium (0.5-1 mmol/L)
4. Potassium (2-4 mmol/L)

Maintain circulating volume with colloid/FFP coagulation support only if required

Drugs:
1. Vitamin K
2. H2 antagonist
3. Antacids
4. Lactulose
5. N-acetylcysteine for acetaminophen toxicity
6. Broad-spectrum antibiotics
7. Antifungals

Nutrition:
1. Enteral feeding (1-2 g protein/kg/day)
2. PN if ventilated

BP, Blood pressure; *CVP,* central venous pressure; *FFP,* fresh frozen plasma; *PN,* parenteral nutrition; *PT,* prothrombin time; *PTT,* partial thromboplastin time.
From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, WB Saunders.

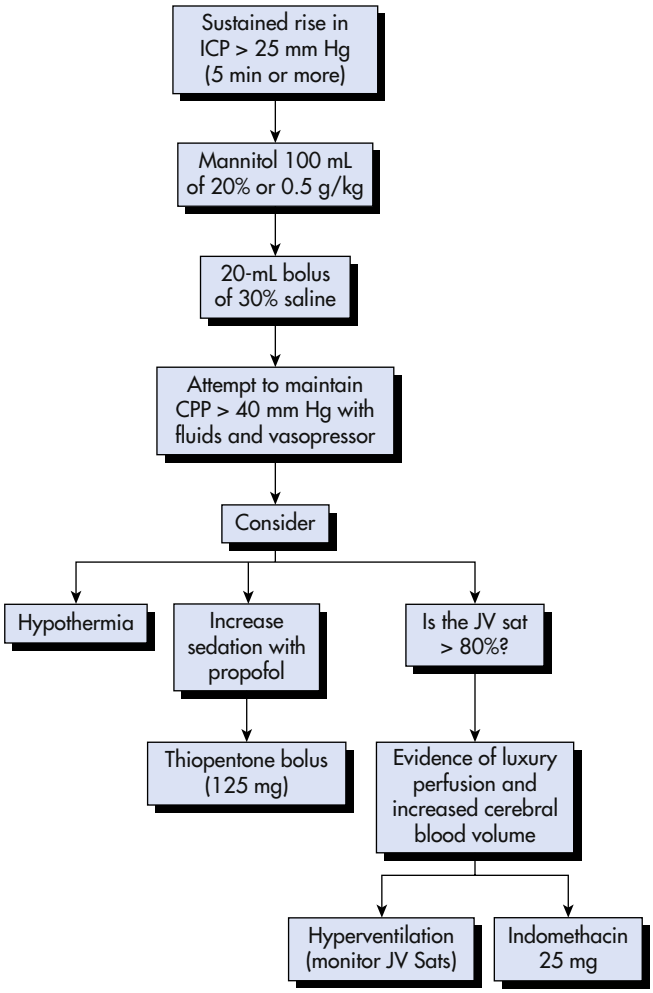

FIG. 3 Management of a sustained rise in intracranial pressure. *CPP,* Cerebral perfusion pressure; *ICP,* intracranial pressure; *JV,* jugular venous; *Sats,* saturation. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

in selected patients (e.g., potential transplantation patients).
- Fig. 3 illustrates the management of a sustained rise in intracranial pressure in liver failure.
- Dexamethasone and hyperventilation (useful in head injury) are of little value in treating cerebral edema from liver failure.

CHRONIC Rx

- Avoidance of any precipitating factors (e.g., high-protein diet, medications).
- Consideration of liver transplantation in selected patients with progressive or recurrent encephalopathy (Box E1). Liver transplantation remains the only curative therapeutic option.

DISPOSITION

Prognosis varies with the underlying etiology of the liver failure and the grade of encephalopathy (generally good for grades 1 or 2; poor for grades 3 or 4). Without proper therapy, the survival rate at 1 yr is 42% and decreases to 23% at 3 yr.

REFERRAL

The early stages of hepatic encephalopathy can be managed in the outpatient setting, whereas stages III or IV require hospital admission.

PEARLS & CONSIDERATIONS

COMMENTS

- Trials have shown that adding IV albumin to lactulose may improve outcomes in severe hepatic encephalopathy by reducing oxidative stress through reduction of levels of circulating cytokines and endotoxins.
- Long-acting benzodiazepines should not be used to treat anxiety and sleep disorders in patients with cirrhosis, as they may precipitate encephalopathy.
- Patients not responding to supportive therapy should be evaluated for liver transplantation.
- Not all patients with cirrhosis develop hepatic encephalopathy. It has been shown that 40% of persons with cirrhosis and minimal hepatic encephalopathy do not develop overt hepatic encephalopathy in long-term follow-up. There are genetic factors associated with development of hepatic encephalopathy in patients with cirrhosis. Genetic analyses have shown that glutaminase TACC and CACC haplotypes are linked to the risk for overt hepatic encephalopathy.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Encephalopathy (Patient Information)
Cirrhosis (Related Key Topic)
Hepatic Encephalopathy (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

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BOX E1 Various Prognostic Criteria Used for Liver Transplantation in Patients with Fulminant Hepatic Failure

King's College Criteria

Acetaminophen overdose:

- Arterial pH <7.3 (irrespective of grade of encephalopathy) or
- PT >100 sec (INR >6.5)
- Serum creatinine >3.4 mg/dl (>300 μmol/L)
- Patients with grade III and IV hepatic encephalopathy

Nonacetaminophen liver injury:

- PT >100 sec (INR >6.5) (irrespective of grade of encephalopathy) or any three of the following variables:
  1. Age <10 or >40 yr
  2. Non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions
  3. Jaundice >7 days before onset of encephalopathy
  4. Serum bilirubin 17.4 mg/dl (300 μmol/L)
  5. PT >50 sec

Cliché Criteria

Factor V <20% in persons <30 yr or both of the following:

- Factor V <30% in patients >30 yr
- Grade III or IV encephalopathy

Serum Gc Globulin Levels

Decreasing Gc levels due to dying hepatocytes

Serum α-Fetoprotein Level

Serial increase from day 1 to day 3 has shown correlation with survival

Liver Biopsy

70% necrosis is discriminant of 90% mortality

Gc, Plasma group-specific component protein; *INR,* international normalized ratio; *PT,* prothrombin time.
From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.

Hepatitis A PTG

BASIC INFORMATION

DEFINITION

Hepatitis A is generally an acute self-limiting infection of the liver by an enterically transmitted picornavirus, hepatitis A virus (HAV). Infection may range from asymptomatic to fulminant hepatitis.

SYNONYMS

Infectious hepatitis
Short incubation hepatitis
Type A hepatitis
HAV (hepatitis A virus)

ICD-10CM CODES

B15.9 Hepatitis A without hepatic coma
B15.0 Hepatitis A with hepatic coma

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Hepatitis A occurs worldwide, affecting 1.4 million people annually and accounting for 20% to 40% of cases of viral hepatitis in the U.S. It is the most common cause of viral hepatitis worldwide
- The seroprevalence increases with age, ranging from 10% in individuals aged <5 yr to 74% in those aged >50 yr
- In the U.S., average disease rate was ~15 cases/100,000 persons/yr before routine vaccination of all children in certain states. The incidence after 2005 is about 1 case/100,000
- The incidence is relatively higher in some regions in the U.S., including Arizona, Alaska, California, Idaho, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, and Washington
- At-risk groups include:
  1. Residents and staff of group homes
  2. Children and employees of day care centers
  3. People who engage in oral-anal contact, regardless of sexual orientation
  4. IV drug abusers
  5. Travel to endemic areas
  6. Areas of overcrowding, poor sanitation, inadequate sewage treatment

PREVALENCE:

- Approximately three fourths of the U.S. population has serologic evidence of prior infection.
- Anti-HAV prevalence has an inverse relation to income and household size.

PREDOMINANT SEX: None, except higher infection rates seen in men who have sex with men who engage in oral–anal contact.

PREDOMINANT AGE/PEAK INCIDENCE:

- In areas of high rates of hepatitis A, virtually all children are infected while younger than 10 yr, but disease is rare.
- In areas of moderate rates of hepatitis A, disease occurs in late childhood and young adults.
- In areas of low rates of hepatitis A, most cases occur in young adults.

INCUBATION PERIOD: Averages 30 days (15 to 50)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Infection with HAV may have acute or subacute presentation, icteric or anicteric. Severity of illness seems to increase with age (90% of infection in children aged <5 yr may be subclinical).
- The incubation period of HAV is 2 to 6 wk.
- A preicteric, prodromal phase of approximately 1 to 14 days; 15% no apparent prodrome. Symptoms are usually abrupt in onset and may include anorexia, fatigue, malaise, nausea, vomiting, fever, headache, and mild abdominal pain.
- Less common symptoms are chills, myalgias, arthralgias, upper respiratory symptoms, constipation, diarrhea, pruritus, urticaria.
- Jaundice occurs in >70% of patients. Patients older than 30 yr are more likely than younger individuals to have jaundice.
- The icteric phase is preceded by dark urine.
- Bilirubinuria is typically followed a few days later by clay-colored stools and icterus.

PHYSICAL EXAMINATION

- Jaundice: Peaks in severity 2 wk after onset
- Hepatomegaly
- Splenomegaly
- Cervical lymphadenopathy
- Evanescent rash
- Petechiae
- Cardiac arrhythmias

COMPLICATIONS

- Cholestasis
- Fulminant hepatitis
- Arthritis
- Myocarditis
- Optic neuritis
- Transverse myelitis
- Thrombocytopenic purpura
- Aplastic anemia
- Red cell aplasia
- Henoch-Schönlein purpura
- IgA dominant glomerulonephritis

ETIOLOGY

- Caused by HAV, a 27-nm, nonenveloped, icosahedral, positive-stranded RNA virus.
- Transmission is fecal-oral route, from person to person. Transmission occurs with close contact or with food- or water-borne outbreaks with inadequately purified water or cooked foods. Recent outbreaks have involved green onions and tomatoes.
- Parenteral transmission is considered rare.
- Vertical transmission has also been reported.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other hepatitis virus (B, C, D, E): Table 1 summarizes serology and PCR test results
- Infectious mononucleosis
- Cytomegalovirus infection
- Herpes simplex virus infection
- Leptospirosis
- Brucellosis
- Drug-induced liver disease
- Ischemic hepatitis
- Autoimmune hepatitis

WORKUP

- IgM antibody specific for HAV
- Liver function tests; ALT and AST elevations are sensitive for liver damage but not specific for HAV
- Elevated ESR
- CBC; may find mild lymphocytosis

TABLE 1 Diagnostic Blood Tests: Serology and Viral Polymerase Chain Reaction

HAV	HBV	HCV	HDV	HEV
Acute/Active Infection				
Anti-HAV IgM (+)	Anti-HBc IgM (+)	Anti-HCV (+)	Anti-HDV IgM (+)	Anti-HEV IgM (+)
Blood PCR positive*	HBsAg (+) Anti-HBs (–) HBV DNA (+) (PCR)	HCV RNA (+) (PCR)	Blood PCR positive HBsAg (+) Anti-HBs (–)	Blood PCR positive*
Past Infection (Recovered)				
Anti-HAV IgG (+)	Anti-HBs (+) Anti-HBc IgG (+)†	Anti-HCV (+) Blood PCR (–)	Anti-HDV IgG (+) Blood PCR (–)	Anti-HEV IgG (+) Blood PCR (–)
Chronic Infection				
N/A	Anti-HBc IgG (+) HBsAg (+) Anti-HBs (–) PCR (+) or (–)	Anti-HCV (+) Blood PCR (+)	Anti-HDV IgG (+) Blood PCR (–) HBsAg (+) Anti-HBs (–)	N/A
Vaccine Response				
Anti-HAV IgG (+)	Anti-HBs (+) Anti-HBc (–)	N/A	N/A	N/A

*Research tool.
†Still poses a risk for reactivation.
HAV, Hepatitis A virus; *HBc,* hepatitis B core; *HBs,* hepatitis B surface; *HBsAg,* hepatitis B surface antigen; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HDV,* hepatitis D virus; *HEV,* hepatitis E virus; *Ig,* immunoglobulin; *N/A,* not applicable; *PCR,* polymerase chain reaction.
From Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

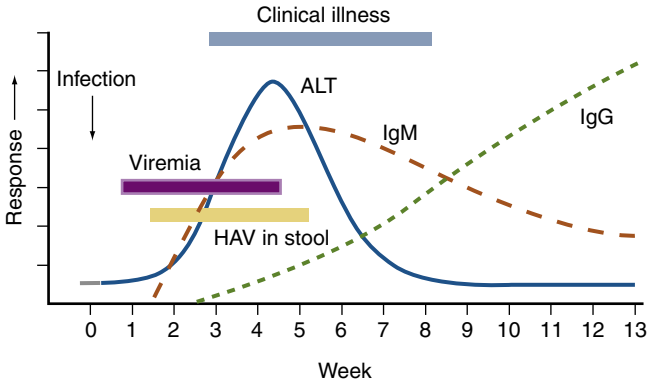

FIG. 1 Immunologic, virologic, and biochemical events during the course of a typical hepatitis A virus (HAV) infection. *ALT,* Alanine transaminase; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M. (From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.)

TABLE 2 Recommendations for Routine Preexposure Use of Hepatitis A Virus Vaccine

Group	Comments
Children	Vaccine should be given to all children at age 1 yr (12-23 mo).* Vaccination of children 2-18 yr may also be warranted.†
International travelers‡	IG may be given in addition to or instead of vaccine; children <12 mo should receive IG.
Close contacts of newly arriving international adoptees	All persons who anticipate close personal contact (e.g., household contact or regular babysitter) during the first 60 days after arrival
Men who have sex with men	Includes adolescents
Illicit drug users	Includes adolescents
Persons with chronic liver disease, such as those with hepatitis B or C	Increased risk of fulminant hepatitis A with HAV infection
Persons receiving clotting factor concentrates	
Persons who work with HAV in research laboratory settings	

*Hepatitis A vaccine is not licensed for children <12 mo.
†States and communities with existing vaccination programs for children aged 2 to 18 yr are encouraged to maintain these programs. Catch-up vaccination for this age group may be warranted elsewhere in the context of ongoing outbreaks among children.
‡Persons traveling to Canada, Western Europe, Japan, Australia, or New Zealand are at no greater risk than in the U.S.
HAV, Hepatitis A virus; *IG,* immunoglobulin.
From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 8, Philadelphia, 2015, Saunders.

LABORATORY TESTS

- Diagnosis confirmed by IgM anti-HAV; it is detectable in almost all infected patients at presentation and remains positive for 3 to 6 mo.
- A fourfold rise in titer of total antibody (IgM and IgG) to HAV confirms acute infection.
- HAV detection in stool and body fluids by electron microscopy.
- HAV RNA detection in stool, body fluids, serum, and liver tissue.
- ALT and AST usually more than 8 times normal in acute infection.
- Bilirubin usually 5 to 15 times normal.
- Alkaline phosphatase minimally elevated, but higher level in cholestasis.
- Albumin and prothrombin time are generally normal; if elevated, they may herald hepatic necrosis.
- Fig. 1 illustrates the typical course of hepatis A.

IMAGING STUDIES

- Rarely useful
- Sonogram (fulminant hepatitis)

Rx TREATMENT

- Usually self-limited
- Supportive care
- Those with fulminant hepatitis may require hospitalization and treatment of associated complications
- Activity as tolerated
- Advise to avoid alcohol and hepatotoxic drugs
- Patients with fulminant hepatitis should be assessed for liver transplantation

CHRONIC Rx

No chronic HAV and no chronic carrier state. The majority of patients have resolution of symptoms and liver abnormalities within 3 mo.

DISPOSITION

- Follow-up as outpatient.
- Most patients recover within 3 mo of infection, although 5% to 10% of patients will experience a relapse in the first 6 mo.
- HAV is a self-limited infection and does not cause chronic hepatitis.

REFERRAL

- To a hepatologist if severe, fulminant hepatitis develops
- To a transplant surgeon if liver transplant becomes a consideration for fulminant hepatitis and liver failure

PEARLS & CONSIDERATIONS

- All cases of hepatitis A should be reported to the public health authorities because foodborne or water-borne outbreaks may occur, and public health efforts (mass vaccination or immunoglobulin therapy) may prevent secondary cases.
- Hepatitis A is a common illness in internationally traveled and developing countries. Pretravel vaccination is strongly recommended for travelers who are HAV susceptible. Table 2 summarizes recommendations for preexposure use of hepatitis A virus vaccine. Updated dosage recommendations are described in Table 3.
- Handwashing is important because the hepatitis A virus may survive for up to 4 hours on the fingertips.
- There have been significant recent outbreaks of hepatitis A in the U.S. In 2016-2018 there was an increase of cases by 294% vs. cases in 2013-2015. This was mostly among the homeless, IV drug abusers, men having sex with men, and individuals who consumed certain imported food items.

PREVENTION

- Improvement in hygiene and sanitation
- Heating food
- Avoidance of water and foods from endemic area

PASSIVE IMMUNIZATION

- Immunoglobulin provides protection against HAV through passive transfer of antibody.
- Preexposure prophylaxis indicated for people traveling to endemic areas with immune globulin (Ig 0.02 or 0.06 ml/kg given IM) who have not received or cannot receive the hepatitis A vaccine before departure. The lower dose is effective for up to 3 mo, and the higher dose is effective for up to 5 mo.
- Postexposure prophylaxis (PEP): For individuals with a recent exposure to hepatitis A who have not received the vaccine, post-exposure prophylaxis is warranted with either immunoglobulin (Ig 0.02 ml/kg given IM) or a single dose of the hepatitis A vaccine within 2 wk of the exposure. For healthy persons ages 12 mo to 40 yr of age, a single dose of the hepatitis

TABLE 3 Indications and Updated Dosage Recommendations for GamaSTAN S/D Human Immune Globulin for Preexposure and Postexposure Prophylaxis against Hepatitis A Infection

Indication	Updated Dosage Recommendation
Preexposure prophylaxis	
Up to 1 mo of travel	0.1 ml/kg
Up to 2 mo of travel	0.2 ml/kg
2 mo of travel or longer	0.2 ml/kg (repeat every 2 mo)
Postexposure prophylaxis	0.1 ml/kg

From Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

A vaccine should be given. Children <12 mo, adults >40 yr of age, and persons who have chronic liver disease and who are immunocompromised should receive immunoglobulin.

ACTIVE IMMUNIZATION

- There are several inactivated and attenuated hepatitis vaccines; only the inactivated vaccines are currently available for use and they have been found to be safe and highly immunogenic: HAVRIX or VAQTA. These can be used in adults and children older than 12 mo. They are given as a two-dose regimen 6 mo to 1 yr apart. A combined hepatitis A and hepatitis B vaccine called TWINRX is also available.
- Protective antibody levels were reached in 94% to 100% of adults 1 mo after the first dose; similar results have been found for children and adolescents.
- Theoretic analyses of antibody levels estimate duration of immunity to be 10 to 20 yr.
- Vaccine should be considered for persons who are at risk. Those traveling to or working in endemic areas, men who have sex with men, illegal drug users, persons with chronic liver disease, and children in areas with high rates of hepatitis A infection.
- The Advisory Committee on Immunization Practices recommends routine hepatitis A vaccination for all children beginning at 12 to 23 mo of age. Simultaneous administration of MMR and HCPA vaccines is recommended for infants aged 6 to 11 mo traveling internationally. The travel-related dose for infants aged 6 to 11 mo should not be counted towards the routine 2-dose series.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hepatitis A (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Aggarwal R, Goel A: Hepatitis A: Epidemiology in resource-poor countries, *Curr Opin Infect Dis* 28:488-496, 2015.

Foster MA et al: Increase in hepatitis A virus infections - United States, 2013-2018, *MMWR Morb Mortal Wkly Rep* 68(18):413-515, 2019.

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Nelson N et al: Update: recommendations of the advisory committee on immunization practices for use of hepatitis A vaccine for postexposure prophylaxis and for pre-exposure prophylaxis for international travel, *MMWR (Morb Mortal)* 67(43):1216-1220, 2018.

Wu D, Guo CY: Epidemiology and prevention of hepatitis A in travelers, *J Travel Med* 20(6):394-399, 2013.

BASIC INFORMATION

DEFINITION

Hepatitis B is an acute infection of the liver parenchymal cells caused by the hepatitis B virus (HBV).

SYNONYMS

Serum hepatitis
Long incubation (30 to 180 days) hepatitis HBV
HBV

ICD-10CM CODES

B16	Acute hepatitis B
B16.0	Acute hepatitis B with delta-agent with hepatic coma
B16.1	Acute hepatitis B with delta-agent without hepatic coma
B16.2	Acute hepatitis B without delta-agent with hepatic coma
B16.9	Acute hepatitis B without delta agent and without hepatic coma
B18.0	Chronic viral hepatitis B with delta-agent
B18.1	Chronic viral hepatitis B without delta-agent
B19.1	Unspecified viral hepatitis B
B19.10	Unspecified viral hepatitis B without hepatic coma
B19.11	Unspecified viral hepatitis B with hepatic coma

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- The CDC estimated that in 2015 there were 21,900 cases of acute hepatitis B, with an overall incidence of 1.1 cases per 100,000.
- Much higher incidence in Europe (~1 million new cases annually) and in areas of high endemicity.
- In the U.S., transmission is mainly horizontal (percutaneous and mucous membrane exposure to infectious blood and other body fluids [e.g., sexual transmission, either homosexual or heterosexual]); also from needle sharing among drug abusers; occupational exposure to contaminated blood and blood products; persons receiving transfusions of blood and blood products; and hemodialysis patients.

NOTE: Improved screening of blood and blood products has greatly reduced, although not eliminated, the risk of posttransfusion HBV infection.

- In areas of high endemicity, transmission is largely vertical (perinatal): HBV exists in the blood and body fluids. Perinatal transmission from HBsAg-positive mothers is as high as 90% unless immunoprophylaxis is given.

PREVALENCE:

- The WHO estimates that 400 million people worldwide (6% of the population) are chronic HBV carriers. North America, Western Europe, and Australia are areas of low prevalence, <2%. In the U.S. an estimated 800,000 to 2.2 million people have chronic HBV infection. About two thirds of them are unaware that they are infected.
- Africa, Asia, and the Western Pacific region are areas of high prevalence, ≥8%.
- Southern and Eastern Europe have intermediate rates, 2% to 7%.
- Chronically infected persons, those with positive HBsAg for >6 mo, represent the major source of infection.
- As many as 95% of infants and children aged <5, who typically have subclinical acute infection, will become chronic HBV carriers.
- Adults are more likely to have clinically evident acute infection, but only 1% to 5% will develop chronic infection.
- ~0.1% of patients with acute infection will develop fulminant acute hepatitis resulting in death.

PREDOMINANT SEX:

- Predominant in males because of increased IV drug abuse, homosexuality.
- Females more commonly terminate in chronic carrier state.

PREDOMINANT AGE: 20 to 45 yr
PEAK INCIDENCE: 30 to 45 yr of age, at rates of 5% to 20%
GENETICS: Neonatal infection:

- Rare in the U.S.
- High (up to 90%) in areas of high endemicity (only 5% to 10% of perinatal infections occur in utero).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The incubation period of HBV infection is 4 to 24 wk. HBV infection presents as acute hepatitis in a minority of patients
- Patients often present with nonspecific symptoms
- Profound malaise (Fig. E1)
- Many asymptomatic cases
- Prodrome:
  1. 15% to 20% serum sickness (urticaria, rash, arthralgia) during early HBsAg
  2. HBsAg-Ab complex disease (polyarteritis nodosa–arthritis, arteritis, glomerulonephritis)
- Hepatomegaly (87%) with right upper quadrant (RUQ) tenderness:
  1. Hepatic punch tenderness
  2. Splenomegaly: Rare (10% to 15%)
- Jaundice (30% of patients), dark urine, with occasional pruritus
- Variable fever (when present, generally precedes jaundice and rapidly declines following onset of icteric phase)
- Spider angiomata: Rare; resolves during recovery
- Rare polyarteritis nodosa, cryoglobulinemia

ETIOLOGY

- Caused by HBV (42-nm hepadnavirus with an outer surface coat [HBsAg], inner nucleocapsid core [HBcAg; HBeAg]; DNA polymerase; and partially double-stranded DNA genome). There are eight genotypes (A to H) based on nucleotide sequence. The prevalence of each genotype varies widely.
- Transmission by parenteral route (needle use, tattooing, ear piercing, acupuncture, transfusion of blood and blood products, hemodialysis, sexual contact), perinatal transmission.
- Infection may result from contact of infectious material with mucous membranes and open skin breaks (e.g., HBV is stable and can be transmitted from toothbrushes, utensils, razors, baby toys, assorted medical equipment [respirators, endoscopes]).
- Oral intake of infectious material may result in infection through breaks in the oral mucosa.
- Food or water are virtually never found to be sources of HBV infection.
- Infection occurs primarily in liver, where necrosis probably results from cytotoxic T-cell response, direct cytopathic effect of HBcAg (core antigen), high-level HBsAg (surface antigen) expression, or coinfection with delta (D) hepatitis virus (RNA delta core within HBsAg envelope).
- Recovery (>90%):
  1. Fulminant hepatitis occurring in <1% (especially if coinfected with hepatitis D); 80% fatal
  2. Unusual (5%) prolonged acute disease for 4 to 12 mo, with recovery
  3. Overall fatality increases with age and viral inoculation (e.g., transfusions)
- Chronic hepatitis B (CHB) infection (1% to 2%), four phases:
  1. Immune-tolerant phase: A highly replicative/low-inflammatory phase where HBV DNA levels are high (typically >1 million IU/ml), ALT levels are normal, and biopsies have minimal signs of significant inflammation or fibrosis.
     a. This phase can persist for yrs, especially in those infected prenatally.
     b. With age there is a likely transformation to an HBeAg-positive immune-active phase.
  2. HBeAg-positive immune-active phase: Elevated ALT and HBV DNA levels in conjunction with liver injury (≥20,000 IU/ml). Median age of onset is 30 yr in those infected at a young age. Biopsy will show moderate to severe inflammation or fibrosis.
  3. Inactive CHB phase: HBV DNA levels are low or undetectable (<2000 IU/ml), ALT levels are normal, and anti-HBe is present. Biopsy shows minimal necroinflammation but variable fibrosis.
  4. HBeAg-negative immune reactivation phase: Elevated ALT and elevated HBV DNA (≥2000 IU/ml). Biopsy will show moderate to severe necroinflammation and fibrosis.
- Table 1 summarizes causes of hepatitis flares in patients with CHB.
- The most feared complications of CHB are cirrhosis and hepatocellular carcinoma (HCC), which kill more than 300,000 people/yr

TABLE 1 Causes of Hepatitis Flares in Patients with Chronic Hepatitis B

Cause of Flare	Comment
Spontaneous	Factors that precipitate viral replication are unclear
Immunosuppressive therapy	Flares are often observed during withdrawal of the agent; preemptive antiviral therapy is required
Antiviral therapy for HBV	
Interferon	Flares are often observed during the second to third mo of therapy in 30% of patients; may herald virologic response
Nucleoside analog	
During treatment	Flares are no more common than with placebo
Drug-resistant HBV	Severe consequences can occur in patients with advanced liver disease
On withdrawal	Flares are caused by the rapid reemergence of wild-type HBV; severe consequences can occur in patients with advanced liver disease
HIV treatment	Flares can occur as a result of the direct toxicity of HAART or with immune reconstitution; HBV increases the risk of antiretroviral drug hepatotoxicity
Genotypic variation	
Precore and core promoter mutants	Fluctuations in serum ALT levels are common with precore mutants
Superinfection with other hepatitis viruses	May be associated with suppression of HBV replication

ALT, Alanine aminotransferase; *HAART,* highly active antiretroviral therapy; *HBV,* hepatitis B virus; *HIV,* human immunodeficiency virus.
From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, WB Saunders.

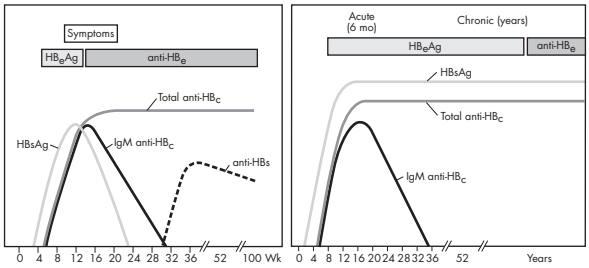

FIG. 2 Typical course of hepatitis B. *Left,* Typical course of acute hepatitis B. *Right,* Chronic hepatitis B. *HBc,* Hepatitis B core; *HBe,* hepatitis B early; *HBeAg,* hepatitis B early antigen; *HBs,* hepatitis B surface; *HBsAg,* hepatitis B surface antigen; *IgM,* immunoglobulin M. (From Mandell GL et al: *Principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, WB Saunders.)

globally. One quarter to one third of patients will go on to develop these complications. The risk of developing HCC appears to be greatest among individuals with the highest serum levels of HBV DNA.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute disease confused with other viral hepatitis infections (A, C, D, E).
- Any viral illness producing systemic disease and hepatitis (e.g., yellow fever, EBV, CMV, HIV, rubella, rubeola, coxsackie B, adenovirus, herpes simplex or zoster).
- Nonviral causes of hepatitis (e.g., leptospirosis, toxoplasmosis, alcoholic hepatitis, drug-induced [e.g., acetaminophen, INH], toxic hepatitis [carbon tetrachloride, benzene]).

WORKUP

- Acute serum specimen for hepatitis B serology (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb), HBDNA by PCR
- LFTs
- CBC
- Liver biopsy: Rarely indicated for diagnosis of fulminant viral hepatitis, chronic hepatitis, cirrhosis, carcinoma

LABORATORY TESTS

- Diagnosis of acute HBV infection is best confirmed by IgM HBcAb in acute or early convalescent serum or by HBDNA by PCR.
  1. Generally, IgM present during onset of jaundice
  2. Coexisting HBsAg
- HBsAg and IgG-HBcAb during acute jaundice are strongly suggestive of remote HBV infection and another cause for current illness (Fig. 2).
- HBsAb alone is suggestive of immunization response.
- With recovery, HBeAg is rapidly replaced by HBeAb in 2 to 3 mo, and HBsAg is replaced by HBsAb in 5 to 6 mo.
- In chronic HBV hepatitis, HBsAg and HBeAg are persistent without corresponding Ab.
- In chronic carrier state, HBsAg is persistent, but HBeAg is replaced by HBeAb.
- HBcAb develops in all outcomes.
- HBeAg correlation with highest infectivity; appearance of HBeAb heralds recovery.
- LFTs:
  1. ALT and AST: Usually more than eight times normal (often 1000 U/L) at onset of jaundice (minimal acute ALT/AST rises often followed by chronic hepatitis or hepatocellular carcinoma).
  2. Bilirubin: Variably elevated in icteric viral hepatitis.
  3. Alkaline phosphatase: Minimally elevated (one to three times normal) acutely.
- Albumin and prothrombin time:
  1. Generally normal.
  2. If abnormal, possible harbinger of impending hepatic necrosis (fulminant hepatitis).
- WBC and ESR: Generally normal.

IMAGING STUDIES

- Sonogram to document rapid reduction in liver size during fulminant hepatitis or mass in hepatocellular carcinoma
- FibroScan (transient elastography): A noninvasive specialized ultrasound test to quantify liver fibrosis without liver biopsy

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Symptomatic treatment as necessary
- Activity as tolerated
- High-calorie diet preferred; often best tolerated in morning

ACUTE GENERAL Rx

- In most cases of acute HBV infection, no treatment is necessary; >90% of adults will spontaneously clear infection.

TABLE 2 Indications for Prompt or Urgent Treatment of Hepatitis B

	Indications	Preferred Agent	Principal Supportive Data
Cirrhosis*			
Decompensated	Clinical stabilization; minimizing risk for recurrence after transplant	Entecavir (0.5 mg) or tenofovir (300 mg)†	Open label; multiple large case series
Borderline compensated	Forestalling disease progression; avoidance of transplantation	As above	Undefined
Well compensated	As above	As above	Randomized controlled trials
Acute Liver Failure			
HBV reactivation	Minimizing further liver injury; reducing risk of recurrence after liver transplantation, if needed	Entecavir (0.5 mg) or tenofovir (300 mg)†	Open label with comparison with historical controls
Severe acute hepatitis	Minimizing further liver injury and enhancing full recovery	Consider lamivudine or telbivudine‡	Small case series

*It has been the author's (RP) practice to use maintenance antiviral therapy for all hepatitis B surface antigen (HBsAg)-positive patients with cirrhosis to prevent reactivation of hepatitis B.
†Daily dose should be adjusted according to the patient's renal function, as indicated in the manufacturer's recommendations.
‡Either agent can be used if the anticipated duration of therapy is 6 mo or less.
HBV, Hepatitis B virus.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

- Hospitalization advisable for any patient in danger from dehydration caused by poor oral intake, whose PT is prolonged, who has rising bilirubin level >15 to 20 μg/dl, or who has any clinical evidence of hepatic failure. Table 2 summarizes indications for prompt or urgent treatment of hepatitis B.
- IV therapy needed (rarely) for hydration during severe vomiting.
- Avoid hepatically metabolized drugs.
- No therapeutic measures are beneficial.
- Steroids not shown helpful.

CHRONIC Rx

- Treatment of chronic HBV infection is dependent on which phase the patient is found to be in:
  1. Therapy is warranted for patients in immune-active CHB stage (HBeAg negative or HBeAg positive) to decrease the risk of liver-related complications. Treatment options include:
     a. Pegylated interferon 2a: 180 mcg subcutaneously weekly for 48 wk. This will lead to seroconversion rates of 20% to 30% (HBeAg to anti-HBe), and 65% of patients will have HBV DNA <2000 IU/ml off therapy but cure rates remain low at 3% to 7% and has significant side effects: Bone marrow suppression and exacerbation of existing neuropsychiatric symptoms, including depression. Candidates for interferon therapy should not have significant psychiatric disease, cardiac disease, cytopenia, seizure disorder, autoimmune disease, or pregnancy.
     b. Entecavir: A nucleotide analogue. Dose 0.5 to 1 mg daily, suppresses HBV DNA replication and improves liver inflammation and fibrosis.
     c. Tenofovir disoproxil: 300 mg daily, is another nucleotide analogue. A newer formulation, tenofovir alafenamide (Vemlidy) 25 mg a day, has less renal and bone toxicity in long-term use.
     d. Other nucleotide agents: Lamivudine, telbivudine, and adefovir are less frequently used due to issues of resistance.
     e. Cure rates with nucleotide agents are between 1% and 12%, and thus most patients will require treatment indefinitely but are considered first line of therapy.
  2. Therapy is not warranted in adults with immune-tolerant CHB. LFTs should be checked every 6 mo to look for conversion to immune-active or inactive status.
     a. Therapy may be warranted for select adults >40 with normal ALT and elevated HBV DNA (≥1 million IU/ml) with liver biopsy showing significant necroinflammation or fibrosis.
  3. HBeAg-positive adults without cirrhosis who seroconvert to anti-HBe on therapy with entecavir or tenofovir disoproxil can discontinue treatment after a period of treatment consolidation.
  4. It is recommended that patients receive indefinite therapy with entecavir or tenofovir disoproxil if HBeAg-negative immune-active CHB is present, unless there is a competing rationale for treatment discontinuation.
  5. Adults with compensated cirrhosis and low levels of viremia (<2000 IU/ml) should be treated with entecavir or tenofovir disoproxil to reduce the risk of decompensation, regardless of ALT level.

DISPOSITION

- Follow-up as outpatient
- Acute disease: Infection will resolve (defined as clearance of hepatitis B surface antigen within 6 mo) in 90% of adult patients
- Rare fatalities (fulminant hepatitis)
- Possible chronic carrier state, cirrhosis, hepatocellular carcinoma
- Cure of HBV is an unrealistic goal for most patients with chronic infection since only a few patients will become HBsAb with current treatment modalities

REFERRAL

To infectious disease specialist and gastroenterologist for consultation regarding fulminant hepatitis or prolonged cholestasis, for cases of uncertain etiology, or for treatment of CAH

PEARLS & CONSIDERATIONS

COMMENTS

- Virus and HBsAg in high titers in blood for 1 to 7 wk before jaundice and for a variable time thereafter.
- Screening (HBV surface antigen [HBsAg], HBV core antigen antibody, antibody to HBsAg) should be offered to high-risk groups.
- Transmission is possible during entire period of HBsAg (and especially during HBeAg) in serum.
- Universal precautions should be followed for all contacts with blood or secretions/excretions contaminated with blood.
- Antiviral therapy is recommended in pregnancy to reduce perinatal transmission if HBsAg positive and HBV DNA >200,000 IU/ml. Can use tenofovir disoproxil, lamivudine, or telbivudine. Tenofovir may be preferred because it has a better resistance profile and there are more safety data in pregnany women with hepatitis B. Fig. 3 describes an algorithm for the treatment of hepatitis B surface antigen (HBsAg)-positive mothers during pregnancy.
- Preventing before exposure:
  1. Lifestyle changes.
  2. Meticulous testing of blood supply (although some chronically infected, infectious donors are HBsAg negative).
  3. Sterilization via steam or hypochlorite.
  4. Hepatitis B vaccine for high-risk groups given IM in deltoid to induce HBsAb (response should be confirmed) is protective (>90% effective). The FDA has recently approved a two-dose hepatitis B virus vaccine (HEPLISAV-B) for use in adults ≥18 yr old, administered at 0 and 1 mo.
  5. Recommendation for universal childhood immunization with doses at birth, 1 mo, and 6 mo.

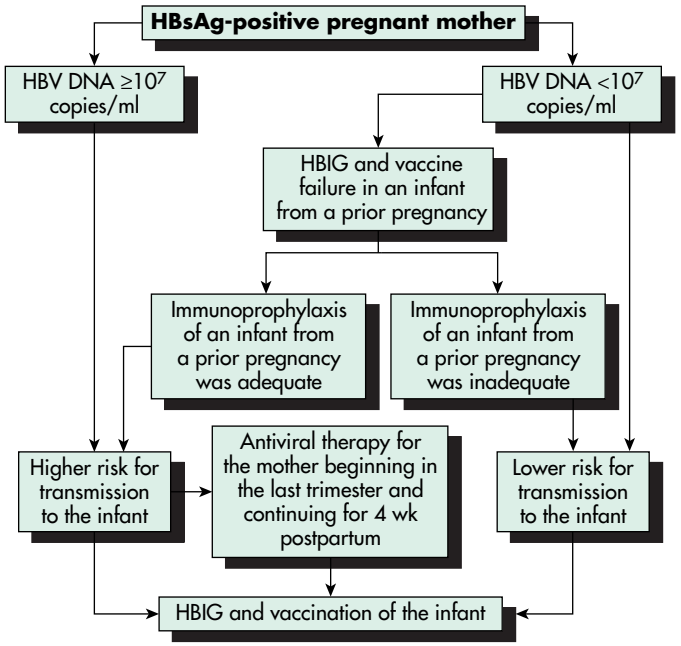

FIG. 3 Algorithm for the treatment of hepatitis B surface antigen (HBsAg)-positive mothers during pregnancy. The goal of treatment in highly viremic mothers is to lower the serum HBV DNA level by several $\log_{10}$ IU/ml by the time of delivery to minimize the chance of newborn infection. The choice of antiviral agent is less important if treatment of the mother is not needed long term. In the event that the treatment needs to be continued after delivery, the patient should be started on a high-genetic-barrier drug initially or switched to one immediately after delivery. See text for further details about drug selection. *HBIG,* hepatitis B immune globulin; *HBV,* hepatitis B virus. (From Feldman M et al. [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, WB Saunders.)

- Prevention after exposure:
  1. HBV hyperimmune globulin (HBIG) (0.06 ml/kg IM) given immediately after needlestick, within 14 days of sexual exposure, or at birth, followed by HBV vaccination. A second dose of HBIG is given in 28 days for those refusing vaccine or vaccine nonresponders.
  2. Standard immune globulin: Nearly as effective as HBIG.
- Preventive therapy with entecavir or tenofovir disoproxil for patients who test positive for HBsAg and are undergoing chemotherapy may reduce the risk for HBV reactivation and HBV-associated morbidity and mortality.
- Hepatitis B prophylaxis is described in Section V.
- Table 3 summarizes interpretation of serologic markers and serum DNA in hepatitis B.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hepatitis B (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

TABLE 3 Interpretation of Serologic Markers and Serum DNA in Hepatitis B

	HBsAg	HBeAg	Anti-HBc IgM	Anti-HBc IgG	Anti-HBs	Anti-HBe	HBV DNA*
Acute hepatitis	+	+/–	+				+
Acute hepatitis, window period			+				
Recovery from acute hepatitis			+	+	+	+/–	
Chronic hepatitis	+	+					+
Chronic hepatitis (precore mutant)	+					+	+
Inactive carrier	+					+/–	
Vaccinated					+		

*HBV DNA $>10^5$ copies/ml.

anti-HBc IgG, Hepatitis B core antibody (IgG type); *anti-HBc IgM,* hepatitis B core antibody (IgM type); *anti-HBe,* hepatitis B early antibody; *anti-HBs,* hepatitis B surface antibody; *HBeAg,* hepatitis Be antigen; *HBsAg,* hepatitis B surface antigen; *HBV DNA,* hepatitis B viral DNA.

From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, WB Saunders.

SUGGESTED READINGS

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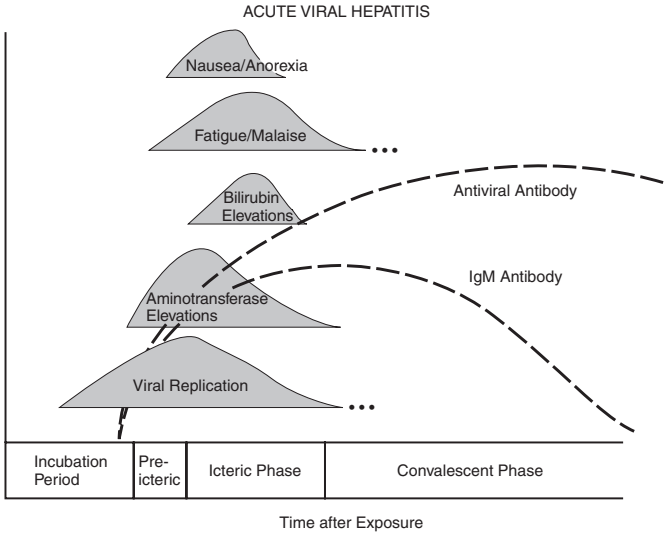

FIG. E1 The typical course of acute viral hepatitis. *IgM,* Immunoglobulin M. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, WB Saunders.)

BASIC INFORMATION

DEFINITION

Hepatitis C is an acute liver parenchymal infection caused by hepatitis C virus (HCV).

SYNONYM

Transfusion-related non-A, non-B hepatitis (incubation period averages 6 wk, intermediate between hepatitis A and B)

ICD-10CM CODES

B17.1	Acute hepatitis C
B18.2	Chronic viral hepatitis C
B17.10	Acute hepatitis C without hepatic coma
B17.11	Acute hepatitis C with hepatic coma
B19.20	Unspecified viral hepatitis C without hepatic coma
B19.21	Unspecified viral hepatitis C with hepatic coma

EPIDEMIOLOGY & DEMOGRAPHICS

Hepatitis C infection is the most common chronic blood-borne infection in the United States. About 3% of baby boomers test positive for the virus. The CDC now recommends testing for hepatitis C for anyone born from 1945 to 1965.

INCIDENCE: HCV infects more than 185 million individuals worldwide. Approximately 20% of patients chronically infected with HCV progress to cirrhosis.

- 150,000 new cases/yr (37,500 symptomatic; 93,000 later chronic liver disease; 30,700 cirrhosis). The incidence of acute HCV has declined substantially over the past 30 yr (from 7.4/100,000 to 0.7/100,000).
- ~9000 of these ultimately die of HCV infection; most common (40%) cause of nonalcoholic liver disease in the United States

PREVALENCE (IN U.S.):

- Overall prevalence of anti-HCV antibody is 1% to 1.2% (an estimated 2.7 million persons nationwide).
- Highest prevalence in hemophiliacs transfused before 1987 and users of injection drugs, 72% to 90%. Over past 30 yr, blood transfusion as a risk factor declined from 15% of cases to 1.9%.
- Among low-risk groups, prevalence 0.6%.

PREDOMINANT SEX: Slight male predominance.

PREDOMINANT AGE: Highest prevalence in 30- to 49-yr age group (65%).

PEAK INCIDENCE:

- 20 to 39 yr of age.
- African Americans and whites have similar incidence of acute disease; Hispanics have higher rates.
- Prevalence is substantially higher among non-Hispanic blacks than among non-Hispanic whites.

GENETICS: Neonatal infection is rare; increased risk with maternal HIV-1 coinfection.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms usually develop 7 to 8 wk after infection (range of 2 to 26 wk), but 70% to 80% of cases are subclinical.
- 10% to 20% report acute illness with jaundice and nonspecific symptoms (abdominal pain, anorexia, malaise).
- Fulminant hepatitis may rarely occur during this period.
- After acute infection, 15% to 25% have complete resolution (absence of HCV RNA in serum, normal ALT).
- Progression to chronic infection is common, 50% to 84%. 74% to 86% have persistent viremia; spontaneous clearance of viremia in chronic infection is rare. 60% to 70% of patients will have persistent or fluctuating ALT levels; 30% to 40% with chronic infection have normal ALT levels.
- 15% to 20% of those with chronic HCV will develop cirrhosis over a period of 20 to 30 yr; in most others, chronic infection leads to hepatitis and varying degrees of fibrosis. Table 1 summarizes factors associated with progression of hepatic fibrosis in patients with chronic HCV infection. Table 2 describes factors associated with cirrhosis in persons with hepatitis C infection.
- 0.4% to 2.5% of patients with chronic infection develop hepatocellular carcinoma (HCC).
- 25% of patients with chronic infection continue to have an asymptomatic course with normal LFTs and benign histology.
- In chronic HCV infection, extrahepatic sequelae include a variety of immunologic and lymphoproliferative disorders (e.g., cryoglobulinemia, membranoproliferative glomerulonephritis, and possibly Sjögren syndrome, autoimmune thyroiditis, polyarteritis nodosa, aplastic anemia, lichen planus, porphyria cutanea tarda, B-cell lymphoma, others).
- Fig. 1 illustrates the natural history of HCV infection.

ETIOLOGY

- Caused by HCV (single-stranded RNA flavivirus). HCV genotype 1 accounts for about 75% of HCV in the US. Genotypes 2 and 3 account for about 20-25% of infections, genotype 4 for 6%, and genotypes 5 and 6 for about 1%.
- Most HCV transmission is parenteral.
- In the United States, advances in screening of blood and blood products have made transfusion-related HCV infection rare (the risk is estimated to be 0.001% per unit transfused).
- Injecting-drug use accounts for most HCV transmission in the United States (60% of newly acquired cases, 20% to 50% of chronically infected persons).
- Occupational needlestick exposure from an HCV-positive source has a seroconversion rate of 1.8% (range 0% to 7%).
- Nosocomial transmission rates (from surgery and procedures such as colonoscopy and hemodialysis) are extremely low.
- Sexual transmission and maternal-fetal transmission are infrequent (estimated at 5%).
- No identifiable risk in 40% to 50% of community-acquired hepatitis C, but snorting of cocaine by shared use of straw or rolled-up paper has been identified as a risk factor because it causes microscopic bleeding of nasal mucosa.
- HCV infection may stimulate production of cytotoxic T lymphocytes and cytokines (INF-γ), which probably mediate hepatic necrosis.

TABLE 1 Factors Associated With Progression of Hepatic Fibrosis in Patients With Chronic Hepatitis C Virus Infection

Established	Possible	Not Associated
Age >40 yr	Increased hepatic iron concentration	Viral genotype
Alcohol consumption	Male gender	Viral load
Hepatitis B virus coinfection	Serum ALT level	
HIV coinfection		
Immunosuppressed state		
Insulin resistance		
Marijuana use		
Obesity		
Schistosomiasis		
Severe hepatic necroinflammation		
Smoking		
White race		

ALT, Alanine aminotransferease; *HIV,* human immunodeficiency virus.
From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other hepatitis viruses (A, B, D, E).
- Other viral illnesses producing systemic disease (e.g., yellow fever, EBV, CMV, HIV, rubella, rubeola, coxsackie B, adenovirus, HSV, HZV).
- Nonviral hepatitis (e.g., leptospirosis, toxoplasmosis, alcoholic hepatitis, drug-induced hepatitis [acetaminophen, INH], toxic hepatitis).

WORKUP

- Acute hepatitis C antibody, viral genotyping, viral titers.
- LFTs; CBC.

NOTE: ALT is an easy and inexpensive test to monitor infection and efficacy of therapy. However, ALT levels may fluctuate or even be

TABLE 2 Factors Associated With Cirrhosis in Persons With Hepatitis C Infection

Factor	Impact	Comment
Environmental		
Alcohol use	+4	The importance of minimal alcohol ingestion (<20 g/day) has not been established
Host		
HIV infection	+4	Increasingly important as HIV-related survival improves; may be masked by competing mortality
HBV infection	+3	Strong effect when HBsAg positive; relatively uncommon
Age	+4	Strong effect; increases as low as 40 yr. Hard to distinguish from infection duration
Body mass index	+2	Associated with metabolic syndrome
Duration of HCV infection	+3	Cirrhosis is rare before 10 yr
HLA type	+1?	HLA B54 is correlated with increased risk of cirrhosis; DRB1*0301 with lack of cirrhosis
Viral		
Quasispecies complexity	+1	Cross-sectional studies cannot assess causality, and complexity may be confounded by duration of infection
HCV genotype 1	+1?	Genotype 1b in some, but not other studies, could be confounded by longer duration of 1b infections
Quantitative measures of viremia (serum or plasma HCV RNA level)	+2	Not always detected or lost in multivariate analysis of age or HIV

HCV, Hepatitis C virus; *HIV,* human immunodeficiency virus; *HLA,* human leukocyte antigen; *RNA,* ribonucleic acid.
From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.

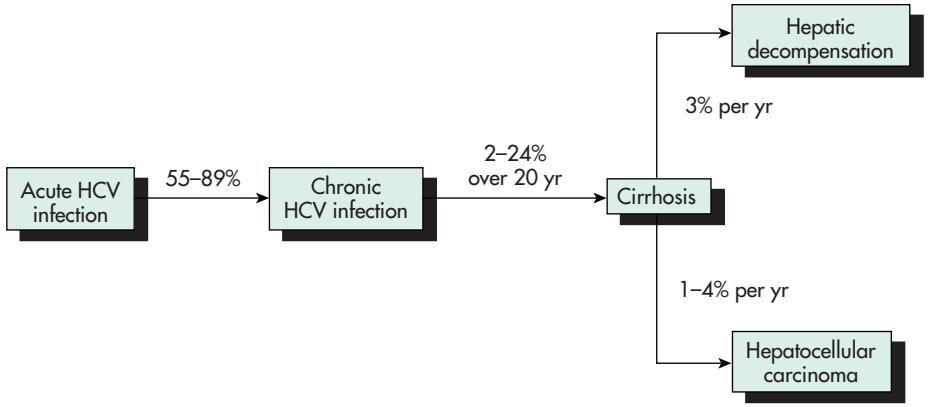

FIG. 1 Natural history of HCV infection. Hepatic decompensation includes ascites, hepatic encephalopathy, variceal hemorrhage, hepatorenal syndrome, or hepatic synthetic dysfunction. *HCV,* Hepatitis C virus. (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.)

normal in active or chronic infection and even with cirrhosis, and ALT may remain elevated even after clearance of viremia.

- Liver biopsy with histologic staging had been the gold standard for assessing the degree of disease activity and the likelihood of disease progression, and also to help rule out other causes of liver disease.
- Transient elastography (FibroScan) is a non-invasive specialized ultrasound assessment that quantifies liver fibrosis and corresponds it to the equivalent in the METAVIR scoring system traditionally used in liver biopsies. It is being increasingly used in place of liver biopsy in many institutions.

LABORATORY TESTS

- Diagnosis is often by exclusion, because it takes 6 wk to 12 mo to develop anti-HCV antibody (70% positive by 6 wk, 90% positive by 6 mo).
- Diagnostic tests include serologic assays for antibodies and molecular tests for viral particles.
  1. Enzyme immunoassay is the test for anti-HCV antibody:
     a. The current version can detect antibody within 4 to 10 wk after infection.
     b. False-negative rate in low-risk populations is 0.5% to 1%.
     c. False negatives also occur in immune-compromised persons, HIV-1, renal failure, HCV-associated essential mixed cryoglobulinemia.
     d. False positives in autoimmune hepatitis, paraproteinemia, and persons with no risk factors.
- The recombinant immunoblot assay that was previously recommended as a follow-up to positive antibody test is no longer available. The CDC now recommends that anyone who tests positive for HCV antibodies receive a follow-up HCV RNA test.
- Qualitative and quantitative HCV RNA tests using PCR: Lower limit of detection is <43 IU/ml.
- Used to confirm viremia and to assess response to treatment.
- Qualitative polymerase chain reaction (PCR) useful in patients with negative enzyme immunoassay in whom infection is suspected.
- Quantitative tests use either branched-chain DNA or reverse transcription PCR; the latter is more sensitive.
- Viral genotyping can distinguish among genotypes 1, 2, 3, 4, 5, and 6, which is helpful in choosing therapy; most of these tests use PCR. Genotypes 1, 2, 3, and 4 predominate in the United States and Europe (genotype 1 is especially common in North America [60% to 75% of Hep C infections in the United States]).
- FibroSure score uses a combination of six serum markers of liver function plus age and gender in a patented algorithm to generate a measure of fibrosis and necroinflammatory activity in the liver as a quantitative surrogate marker for the corresponding METAVIR scoring system.
- LFTs: ALT and AST may be elevated to more than eight times normal in acute infection; in chronic infection ALT may be normal or fluctuate.
- Bilirubin may be five to 10 times normal.
- Albumin and prothrombin time generally normal; if abnormal, may be harbinger of impending hepatic necrosis.
- WBC and erythrocyte sedimentation rate (ESR) are generally normal.

- HIV testing. Infection with HCV is seen in 15% to 30% of individuals with HIV infection due to shared risk factors.
- All patients infected with HCV should be tested for Hepatitis B. HBV vaccination is recommended for susceptible individuals, because HBV reactivation may occur during treatment of HCV with direct-acting antiviral therapy.

IMAGING STUDIES

- Transient elastography (FibroScan) to quantify liver fibrosis as an absolute score. Some insurance companies use this score as a basis to determine eligibility for treatment.
- Sonogram: Rapid liver size reduction during fulminant hepatitis or mass in HCC.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Activity and diet as tolerated; avoid saw palmetto and green tea leaf herbs.

ACUTE GENERAL Rx

- Supportive care.
- Avoid hepatically metabolized drugs.

CHRONIC Rx

Response to therapy is influenced by HCV genotype. Recommendations for the treatment of hepatitis C in adults are changing constantly as new therapies come to the market. The advent of direct-acting antiviral agents (DAAs) has drastically changed treatment options and improved cure rates to greater than 95%. The most up-to-date guidance is available at the website www.hcvguidelines.org. The following is a brief summary of the guidelines based on genotype. Newer agents containing fixed-dose combinations of direct-acting antiviral (DAA) drugs have been approved for HCV infections caused by any of the six major HCV genotypes in patients without cirrhosis or with compensated cirrhosis. These agents are Mavyret (combination of glecaprevir, an HCV NS3/4A protease inhibitor, and pibrentasvir, an NS5A inhibitor) and Vosevi (combination of the NS5B nucleotide polymerase inhibitor sofosbuvir, the NS5A inhibitor velpatasvir, and the NS3/4A protease inhibitor voxilaprevir). Both agents are approved for use in treatment-experienced patients and Mavyret is also approved for treatment-naïve patients. Currently, these treatment regimens are extremely expensive.

Genotype 1a: Options for treatment-naïve patients without cirrhosis, listed by level of evidence:

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) (Zepatier) for 12 wk and in those who do not have baseline NS5A RAVs (amino acid substitutions at 28, 30, 31, or 93 that confer resistance to elbasvir). Rating: Class I, Level A.
- Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) (Mavyret) for 8 wk. Rating: Class I, Level A.
- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) (Harvoni) for 12 wk. Rating: Class I, Level A. (Can also use this regimen for only 8 wk for patients who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/ml. Rating: Class I, Level B.)
- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) (Epclusa) for 12 wk. Rating: Class I, Level A.
- Alternative regimens:
  1. Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg) with weight-based ribavirin for 12 wk. Rating: Class I, Level A.
  2. Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 wk. Rating: Class I, Level A.
  3. Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) daily for 12 wk. Rating: Class I, Level B.
  4. Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) (Zepatier) with weight-based ribavirin for patients with baseline NS5A RADs for elbasvir for 16 wk. Rating; Class IIa, Level B.

Genotype 1a: Options for treatment-naïve patients with compensated cirrhosis:

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) [Zepatier] and in those in whom no baseline NS5A RAVs for elbasvir are detected for 12 wk. Rating: Class I, Level A.
- Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) [Mavyret] for 12 wk. Rating: Class I, Level A.
- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) [Harvoni] for 12 wk. Rating: Class I, Level A.
- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) [Epclusa] for 12 wk. Rating: Class I, Level A.
- Alternative regimen:
  1. Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) [Zepatier] with weight-based ribavirin for 16 wk for patients who have baseline NS5A RASs. Rating: Class IIa, Level B.

Genotype 1b: Treatment-naïve patients without cirrhosis:

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) [Zepatier] for 12 wk. Rating: Class I, Level A.
- Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) [Mavyret] for 8 wk. Rating: Class I, A.
- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) [Harvoni] for 12 wk. Rating: Class I, Level A. (Can treat for 8 wk in patients who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/ml. Class I, Level B.)
- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) [Epclusa] for 12 wk. Rating: Class I, Level A.
- Alternative regimens:
  1. Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg) for 12 wk. Rating: Class I, Level A.
  2. Daily simeprevir (150 mg) plus sofosbuvir (400 mg) daily for 12 wk. Rating: Class I, Level A.
  3. Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 wk. Rating: Class I, Level B.

Genotype 1b: Treatment-naïve patients with compensated cirrhosis:

- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) [Zepatier] for 12 wk. Rating: Class I, Level A.
- Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) [Mavyret] for 12 wk. Rating: Class I, Level A.
- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir [Harvoni] for 12 wk. Rating: Class I, Level A.
- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) [Epclusa] for 12 wk. Rating: Class I, Level A.
- Alternative regimens:
  1. Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg) with weight-based ribavirin for 12 wk Rating: Class I, Level A.

Genotype 2: Treatment-naïve regimens without cirrhosis:

- Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) [Mavyret] for 8 wk. Rating: Class I, Level A.
- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) [Epclusa] for 12 wk. Rating: Class I, Level A.
- Alternative regimen: Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 wk. Rating: Class IIa, Level B.

Genotype 2: Treatment-naïve patients with compensated cirrhosis:

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) [Epclusa] for 12 wk. Rating: Class I, Level A.
- Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for 12 wk. Rating: Class I, Level B.
- Alternative regimen: Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 16 to 24 wk. Rating: Class IIa, Level B.

Genotype 3: Treatment-naïve patients without cirrhosis:

- Daily fixed-dose of glecaprevir (300 mg)/pibrentasvir (120 mg) for 8 wk. Rating: Class I, Level A.
- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) [Epclusa] for 12 wk. Rating: Class I, Level A.
- Alternative regimen: Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 wk. Rating: Class I, Level A.

Genotype 3: Treatment-naïve patients with compensated cirrhosis:

- Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) [Mavyret] for 12 wk. Rating: Class I, Level A.
- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) [Epclusa] for 12 wk. Rating: Class I, Level A.
- Alternative regimens:
  1. Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) [Vosevi] when Y93H amino acid substitution is present for 12 wk. Rating: IIa, Level B.
  2. Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) with or without weight-based ribavirin for 24 wk. Rating: Class IIa, Level B.

Genotype 4: Treatment-naïve patients without cirrhosis:

- Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) {Mavyret] for 8 wk. Rating: Class I Level A.
- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) [Epclusa] for 12 wk. Rating: Class I, Level A.
- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) [Zepatier] for 12 wk. Rating: Class IIa, Level B.
- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) [Harvoni] for 12 wk. Rating: Class IIa, Level B.
- Alternative regimen: Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin for 12 wk. Rating: Class I, Level A.

Genotype 4**:** Treatment-naïve patients with compensated cirrhosis:

- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) [Epclusa] for 12 wk. Rating: Class I, Level A.
- Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) [Mavyret] for 12 wk. Rating: Class I, Level B.
- Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) [Zepatier] for 12 wk. Rating: Class IIa, Level B.
- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) [Harvoni] for 12 wk. Rating: Class IIa, Level B.
- Alternative regimen: Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin for 12 wk. Rating: Class I, Level A.

Genotypes 5 and 6: Treatment-naïve patients with and without cirrhosis:

- Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for 8 wk with no cirrhosis. Rating: Class I, Level A and 12 wk with compensated cirrhosis. Rating: Class I, Level A.
- Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) [Epclusa] for 12 wk. Rating: Class I, Level B.
- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) [Harvoni] for 12 wk. Rating: Class IIa, Level B.

Drug interactions can be significant with these regimens (http://www.hepdruginteractions.org). With DAA regimens, viral loads are measured at 4 wk into the therapy to monitor success and at the end of therapy. A final viral load is measured 12 wk after completing the treatment, and if undetectable, the patient is considered to have a sustained virologic response (SVR), which equates to a cure.

For *treatment-experienced* patients there are guidelines per genotype as well (www.hcvguidelines.org). Treatment is based on genotype and whether the patient is without cirrhosis or with compensated cirrhosis. Regimen will depend on whether the patient had been exposed in the past to interferon/ribavirin-based regimens, NS3 protease inhibitors regimens (telaprevir, boceprevir, simeprevir), or DAA agents.

In 2017, a new salvage regimen was approved: Once-daily Vosevi (fixed-dose combination of 100 mg voxilaprevir (HCV NS3/4A protease inhibitor) plus 400 mg sofosbuvir and 100 mg velpatasvir. Eligible patients include:

- Genotypes 1, 2, 3, 4, 5, or 6 in patients previously treated with a regimen containing an NS5A inhibitor for 12 wk (NOTE: In clinical trials, prior experience with NS5A inhibitors included daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir)
- Genotype 1a or 3 in patients previously treated with sofosbuvir without an NS5A inhibitor for 12 wk. (NOTE: In clinical trials, prior treatment experience included sofosbuvir with or without any of the following: Peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitors: Boceprevir, simeprevir, or telaprevir.)
- Liver transplantation:
  1. Hepatitis C is the main indication for liver transplantation in the United States.
  2. It is the only option for patients with deteriorating HCV-related cirrhosis and for some patients with HCC.
  3. Recurrent infection occurs in almost all patients with progressive fibrosis and cirrhosis; as many as 20% progress to cirrhosis within 5 yr posttransplant.

DISPOSITION

- The absence of HCV RNA in blood 12 wk after completion of treatment is considered a cure. There is no need to check HCV antibodies since they will remain positive indefinitely.
- SVR after treatment among HCV-infected persons at any stage of fibrosis is associated with reduced HCC.
- Periodic abdominal ultrasonography for HCC screening.
- Recent guidelines recommend against measurement of alpha-fetoprotein (AFP) to screen for HCC in patients with chronic hepatitis C due to lack of sensitivity, specificity, and predictive values.

REFERRAL

- To a hepatologist or infectious disease specialist for treatment for hepatitis C in patients who have been previously treated or for treatment failures with DAA agents.
- To a transplant surgeon for consideration of liver transplant if indicated.

PEARLS & CONSIDERATIONS

- More rapid progression of disease in persons who drink alcohol regularly, persons of advanced age at time of infection, and those coinfected with other viruses (HIV, hepatitis B). All persons with identified HCV infection should receive a brief alcohol screening and intervention as clinically indicated.
- Regression of cirrhosis has been demonstrated after antiviral therapy in some patients with chronic hepatitis C. Regression is associated with decreased disease-related morbidity and improved survival.
- The presence of interleukin (IL)-28B and HLA class II is independently associated with spontaneous resolution of HCV infection, and single nucleotide polymorphism IL-28B and DQB1*03:01 may explain approximately 15% of spontaneous resolution of HCV infection.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hepatitis C (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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Hepatitis D

BASIC INFORMATION

DEFINITION

- A defective RNA virus
- Depends on hepatitis B virus (HBV) for its active viral replication
- Most severe form of viral hepatitis
- Results in severe liver disease often causing cirrhosis and liver failure

SYNONYMS

HDV
Delta virus
Delta agent

ICD-10CM CODES

B16.0 Acute hepatitis B with delta-agent with hepatic coma
B16.1 Acute hepatitis B with delta-agent without hepatic coma
B18. 0 Chronic viral hepatitis B with delta-agent

EPIDEMIOLOGY & DEMOGRAPHICS

- The least common cause of chronic viral hepatitis worldwide.
- Endemic in the Mediterranean Basin and Pacific Islands.
- The rates of occurrence in the tropical and subtropical areas were higher compared with those in northern Europe or North America due to the increased HBV in those locations.
- Immigration from endemic areas to northern Europe and the U.S. has increased HDV in these areas (Fig. E1).

INCIDENCE:

- Increasing in developed countries due to immigration and higher rates of HBV.
- Remains a major health concern in developing countries.

PEAK INCIDENCE: Peak incidence was in the 1980s.

PREVALENCE:

- 15 to 20 million people affected worldwide.
- The highest prevalence is in the Middle East, Central Africa, northern parts of South America, and the Mediterranean basin (Fig. E2).

PREDOMINANT SEX AND AGE:

- Occurs in both sexes
- Age varies
- Historically, the disease is most severe in children and drug addicts, who are often co-infected with hepatitis C or HIV

GENETICS:

- There are eight identified genotypes of HDV.
- The genotype has no influence on management.
- It is unclear whether the genotypes carry substantial clinical or prognostic significance.
- Genotype does have an important role when studying epidemiology.
- Different HBV genotypes may interact with different genotypes of HDV.
- Table E1 illustrates the individual genotypes, their geographical distribution, and the few associated clinical observations.

RISK FACTORS

- Transmitted by parenteral routes.
- Shares the same risk factors as HBV.
- Highest rates of infection are in intravenous drug users.
- Sexual transmission through heterosexual contact can occur.
- Its spread among men who have sex with men has not been evident.
- Vertical transmission can also occur but is rare.
- Box E1 describes persons who should be clinically suspected of having HDV infection.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical manifestations can vary. Because of the obligate relationship of HDV to HBV infection, the natural history of HDV infection depends on the clinical course of HBV. Two distinct types of HDV infections are possible: *Primary infection* (or coinfection), in which infection of HBV and HDV occur simultaneously, and *superinfection*, in which HDV infection is superimposed on established chronic HBV infection. These two different disease states can usually be distinguished by serologic and genomic testing for both viruses (Fig. E3).
- Symptoms can include nausea, lethargy, and abdominal pain.
- The presentation depends on whether it occurs as a coinfection with HBV or as a superinfection in a chronic HBV carrier.
- HBV/HDV coinfection is usually a self-limited acute hepatitis.
- Superinfection can cause a severe acute hepatitis with a drastic clinical course.
- Severe infection can result in liver cirrhosis, liver cancer, liver failure, and even death.
- Coinfection with HBV, HCV, and HIV has increased risk of liver cirrhosis.

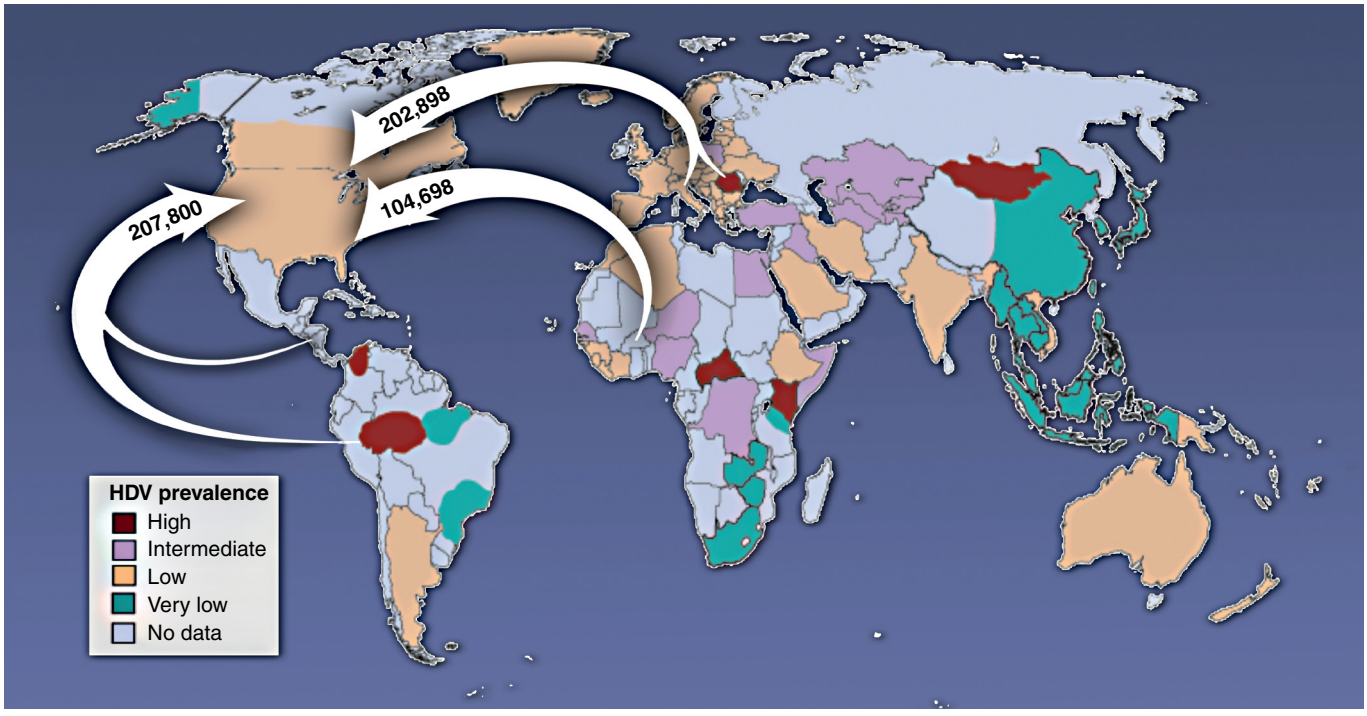


FIG. E1 Worldwide prevalence of hepatitis D virus (HDV) infection and immigration patterns to the U.S. from endemic regions of the world (1974 to 2008). The numbers within the *arrows* indicate the total number of hepatitis B surface antigen-positive immigrants who are estimated to have come to the U.S. from various regions during this period. Changing immigration patterns are likely to account for a greater prevalence of HDV infection in the U.S. than previously considered. (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, WB Saunders.)

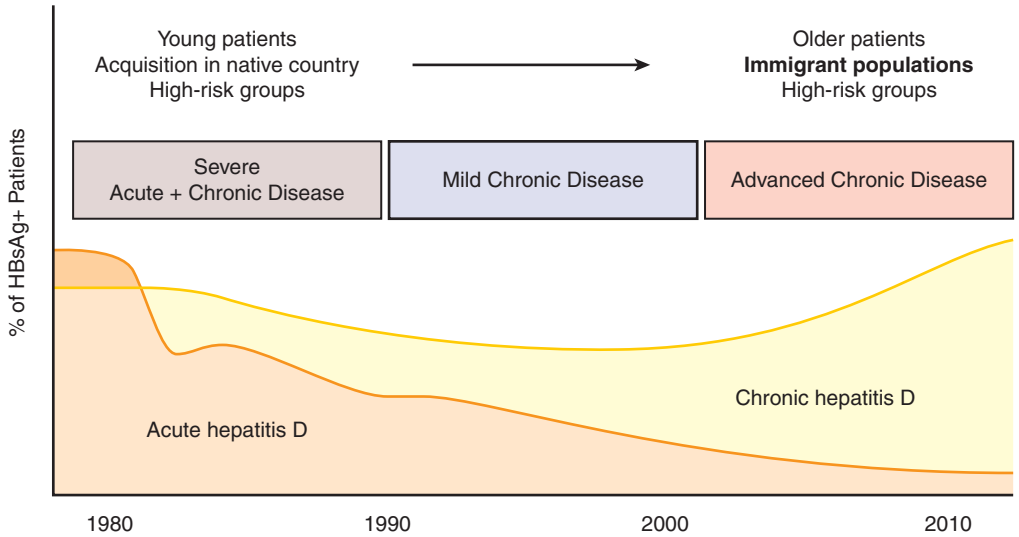


FIG. E2 Timeline of the changing epidemiology of hepatitis D virus (HDV) infection since the late 1970s. HDV had a dramatic, acute appearance in the early to mid-1980s, and many of the patients were young, from countries with a high prevalence of HDV infection, or identified as being in high-risk groups (e.g., people who inject drugs). Since that time, many of the patients with severe liver injury have died because of the infection, and many of those with initially mild hepatitis have developed advanced liver disease and its complications. With changing immigration patterns in Europe and the U.S. (see Fig. E1), more cases of chronic HDV infection are being seen in persons who have relocated from high-prevalence areas. *HBsAg,* Hepatitis B surface antigen. (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, WB Saunders.)

TABLE E1 Hepatitis D Virus Genotypes

Genotype	Geography	Clinical Observations
1 (Most common)	North America, Europe, Middle East, North Africa, Mediterranean, and Taiwan	Lower remission rates and more adverse events compared to genotype 2 in Taiwan
2	North and East Asia	Milder disease (in East Asia)
3	South America (Northern)	Fulminant hepatitis
4	Japan and Taiwan	Milder disease (in East Asia)
5-8	West and Central Africa	N/A

N/A, Not applicable.

BOX E1 Persons Who Should Be Clinically Suspected of Having Hepatitis D Virus Infection*

HBsAg-positive immigrants from regions that are moderately to highly endemic for HDV
HBsAg carriers with a history of injection drug use
Persons with chronic hepatitis B and rapid evolution to cirrhosis or hepatocellular carcinoma
HBsAg carriers who are persistently HBV DNA negative but have active liver disease
Persons with an unexplained acute flare of chronic hepatitis B that is not due to acute hepatitis A or C or reactivation of hepatitis B

*Initial screening with anti-HDV is recommended.
Anti-HDV, Antibody to HDV; *DNA,* deoxyribonucleic acid; *HBsAg,* hepatitis B surface antigen; *HDV,* hepatitis D virus.* From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, WB Saunders.

ETIOLOGY

- HDV requires the hepatitis B surface antigen (HBsAg) for hepatocyte adherence and virion assembly.
- HBsAg carriers serve as the main reservoirs for hepatitis D infection and often become chronic carriers of the virus.
- At least 5% of HBV carriers worldwide are infected with HDV.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

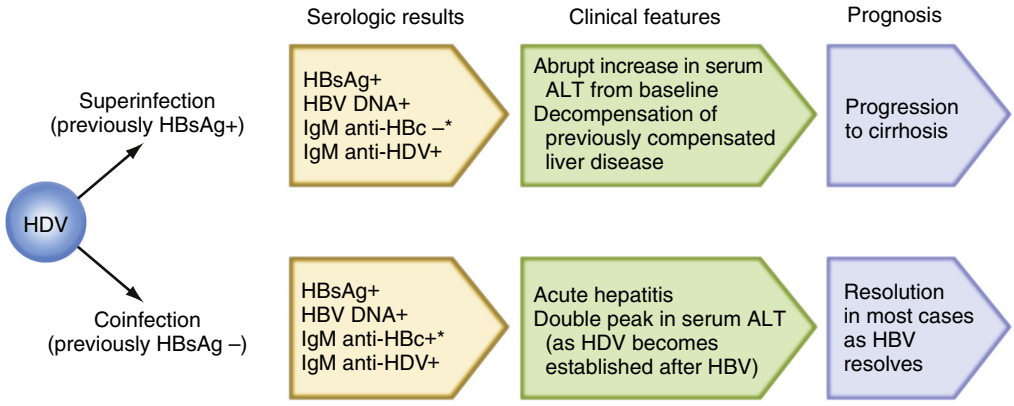
- Acute hepatitis B infection
- Recrudescence of HBV infection in a known HBV carrier

WORKUP

- The first step is to measure the immunoglobulin (Ig) G antibodies to HDV, also known as anti-HD.
- Antibody response may be diminished in immunocompromised individuals, such as those with HIV.
- The most sensitive and specific test is the HDV-RNA measured by polymerase chain reaction (PCR).
- Level of viremia does not correlate with the severity of disease.
- There are no distinct histological characteristics from biopsy when compared to findings from isolated HBV infection.

LABORATORY TESTS

- Patients with coinfection can experience a biphasic course with two peaks of alanine aminotransferase (ALT) elevations several wk apart.
- The first peak occurs during HBV replication, and the second peak occurs during delayed HDV replication.
- Key serological markers in acute co-infection include HDV-RNA, HBV-DNA, HBsAg, immunoglobulin (Ig) M antibody to hepatitis B core antigen (HBcAb), and IgM anti-HDV.
- HDV-RNA and HBV-DNA titers decrease as the infection resolves.
- Hepatitis B surface antibody (HbSAb) is formed as HBsAg disappears.
- IgM anti-HDV can persist even after HbSAb appears and aminotransferases normalize.
- Superinfection with HDV is differentiated from an acute HBV flare by detecting the presence of HDV-RNA and IgM anti-HDV along with measuring HBV-DNA titers, which are elevated in acute HBV infection.



*Distinguishing feature between superinfection and coinfection.

FIG. E3 Serologic results, clinical features, and prognosis of hepatitis D virus *(HDV)* superinfection and coinfection with HDV and hepatitis B virus *(HBV). ALT*, Alanine aminotransferase; *anti-HBc*, antibody to hepatitis B core antigen; *anti-HDV*, antibody to hepatitis D virus; *DNA*, deoxyribonucleic acid; *HBsAg*, hepatitis B surface antigen; *HBV*, hepatitis B virus; *HDV*, hepatitis D virus; *IgM*, immunoglobulin M. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

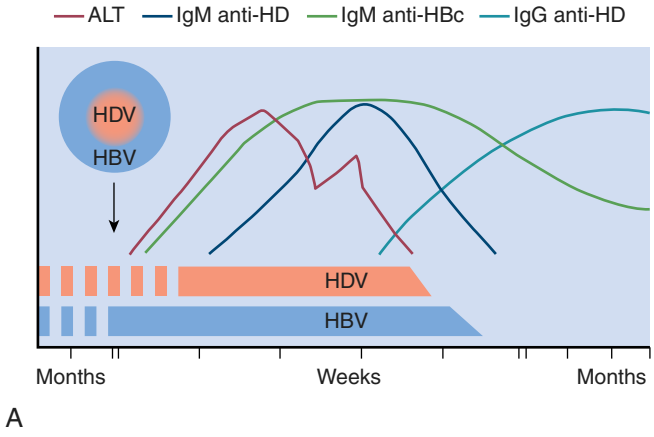


FIG. E4 A, Course of hepatitis B virus *(HBV)* and hepatitis D virus *(HDV)* coinfection. **B,** Course of hepatitis D virus superinfection in chronic hepatitis B carriers. *ALT,* Alanine aminotransferase; *anti-HBc,* antibody to hepatitis B core antigen; *anti-HD,* antibody to delta antigen; *Ig,* immunoglobulin. (From Boyer TD et al: *Zakim & Boyer's hepatology: a textbook of liver disease*, ed 6, Philadelphia, 2012, WB Saunders.)

TABLE 2 Diagnostic Markers for Hepatitis D Virus Infection, Their Importance, and Potential Weaknesses

Diagnostic Markers and Their Importance	Potential Weaknesses
IgG anti-HDV	
Positive in all persons exposed to HDV; persists long term, even after viral clearance May indicate active or past infection; not a neutralizing antibody	May not be elevated in immunocompromised persons.
IgM anti-HDV	
Positive in acute infection; negative in past infection May be used as a surrogate marker for HDV replication Decrease in titers and subsequent clearance in chronic HDV infection is a predictor of spontaneous or therapy-induced remission	Often persists in chronic infection, particularly with active liver disease. Neither 100% sensitive nor specific for HDV replication.
HDAg	
Can be demonstrated in hepatocytes by immunohistochemical staining	The reliability of immunochemistry decreases as the disease becomes chronic. The presence of high titers of neutralizing antibodies (anti-HDV) interferes with detection of HDAg. Less sensitive than molecular assays.
HDV RNA (qualitative)	
Marker of HDV replication Positive in all patients with chronic HDV infection Negative in spontaneous or treatment-induced viral clearance	Variability in the HDV genome and assay primers influences the sensitivity of HDV RNA detection. No WHO standardized assay.
HDV RNA (quantitative)	
Used to measure the level of HDV RNA in serum Useful method for predicting and monitoring treatment response	HDV RNA may be present at a lower titer than the limit of detection (as low as 10 copies/ml). Levels do not reflect the grade or stage of liver disease. May be useful for monitoring patients during therapy with interferon, but there is no WHO standardized assay. Results may differ significantly among laboratories.
HBsAg (quantitative)	
May be useful for predicting or monitoring treatment response during therapy with interferon, because a falling titer heralds HBsAg loss and hence HDV RNA clearance	Confined to research laboratories in the U.S. but commercially licensed in Asia and Europe.

anti-HDV, Antibody to hepatitis D virus; *HBsAg,* hepatitis B surface antigen; *HDAg,* hepatitis D antigen; *HDV,* hepatitis D virus; *Ig,* immunoglobulin; *RNA,* ribonucleic acid; *WHO,* World Health Organization.

From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, WB Saunders.

- The lack of IgM to HBcAb also suggests superinfection in a chronic HBV carrier, rather than acute HBV infection.
- See Fig. E4, *A* and *B*, which illustrate the natural course in coinfection and superinfection, respectively. Table 2 describes diagnostic markers for HDV infection, their importance, and potential weaknesses.

IMAGING STUDIES

Imaging studies are not used in diagnosis.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive care
- Management of symptoms

ACUTE GENERAL TREATMENT

- No current FDA-approved therapy
- Interferon-alpha is the only therapeutic option, which has shown minimal benefit. (Cure rates 25% to 45%). Treatment is indicated in infected patients with progressive liver disease.
- Antivirals against HBV that do not affect HbSAg do not treat HDV.

CHRONIC TREATMENT

- Interferon-alpha should be continued for at least 12 mo.
- Response is determined by the loss of HBsAg.
- Response is often delayed.
- Treatment should be given for at least 1 yr before the individual is determined to be a nonresponder.
- Longer-term therapy is associated with a sustained disappearance of HDV-RNA and HBsAg along with regression of liver fibrosis.
- Relapse after interferon therapy completion is common.
- Investigations of other therapies, such as prenylation inhibitors, are currently ongoing.

DISPOSITION

- HBV/HDV coinfection is usually a self-limited illness that resolves after a few wk.
- 2% of patients with coinfection progress to chronic HDV infection.
- Superinfection can cause a severe acute hepatitis sometimes leading to cirrhosis, liver failure, and death, but usually results in chronic infection.

REFERRAL

Patients should be referred to a hepatologist or someone who is experienced in treating liver disease.

PEARLS & CONSIDERATIONS

COMMENTS

- Consider HDV infection in patients with underlying HBV and progressive liver disease.
- Superinfection can lead to cirrhosis, liver failure, and death.
- Interferon-alpha is the only current therapeutic option, but has severe limitations secondary to side effects and significant relapse rates after treatment completion.

PREVENTION

- Aimed at modifying risk factors.
- No vaccine available for HDV.
- Vaccinating against HBV helps prevent HDV.
- High-risk populations, such as intravenous drug users, should be vaccinated against HBV.

RELATED CONTENT

Hepatitis B (Related Key Topic)

AUTHOR: **Hiresh D. Trivedi, MD**

Hepatitis E

BASIC INFORMATION

DEFINITION

Hepatitis E is an RNA virus transmitted mostly by the fecal-oral route that is among the most frequent causes of acute hepatitis worldwide, with an estimated 20 million cases annually and 70,000 deaths.

SYNONYMS

Previously known as enterically transmitted non-A non-B hepatitis
HEV
Hepatitis E virus
Epidemic non-A, non-B hepatitis

ICD-10CM CODE
B17.2 Acute hepatitis E

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Considered hyperendemic in India, Bangladesh, China, and Mexico (Fig. E1). It is probably the most common cause of acute hepatitis and jaundice in the world.
- In developed nations usually associated with travelers returning from endemic countries (Table E1).
- Large outbreaks can occur and are associated with fecal-contaminated water.
- Person-to-person transmission is thought not to contribute to morbidity in epidemics.

PEAK INCIDENCE:

- Some waterborne outbreaks are more common in summer months.
- Foodborne transmission through raw or undercooked meat of wild deer, boar and domestic pigs, and probably rabbit contributes to cases of hepatitis E in developed nations.

PREVALENCE:

- In endemic countries, HEV prevalence of 25% for all non-A and non-B acute hepatitis cases.
- In endemic countries among blood donors, IgG antibodies are found in as high as 45% of donors.
- In developing countries, prevalence of IgG antibodies is 1% to 4% among blood donors.

PREDOMINANT SEX AND AGE:

- High attack rates are found in adults 15 to 40 yr of age. In developed countries HEV is more common in males over the age of 40.
- Fulminant hepatic failure occurs more frequently during pregnancy, with mortality rates of 15% to 25%.
- Vertical transmission commonly occurs via intrauterine and perinatal routes and can lead to severe liver disease and high mortality in fetuses and neonates.
- Men are more frequently affected than women.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- After an incubation period of 15 to 60 days, most cases are self-limited and asymptomatic (80%). Clinical features of acute hepatitis E are summarized in Box E1.
- Symptomatic patients will experience nonspecific findings:
  1. Flulike myalgia, arthralgia, anorexia
  2. Hepatomegaly, fever, weakness, vomiting, diarrhea
  3. Jaundice, pale stools, darkened urine can also occur, as in other hepatitis infections
- Elevated liver function tests: Total bilirubin, ALT, AST occur 1 to 6 wk after onset of illness.
- Case fatality rate is very low: 0.5% to 4%, except in pregnancy: 15% to 25%.
- Rare complications include pancreatitis, encephalitis, proximal myopathy.

ETIOLOGY

- HEV is the sole member of the *Orthohepevirus* genus of the Hepeviridae family.
- HEV is an icosahedral, nonenveloped, single-stranded RNA virus about 27 to 34 nm in diameter.
- There are four genotypes, of which humans are the host for all four genotypes, and swine and other mammals may also be the hosts for genotypes 3 and 4. Box E2 summarizes features of HEV genotypes 1 and 2. Table E2 compares epidemiologic and clinical features associated with HEV genotypes 1 and 3.

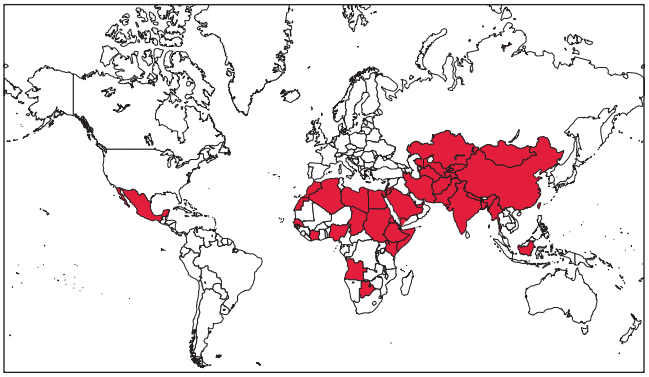


FIG. E1 Geographic distribution of areas where infection with HEV genotypes 1 and 2 is highly endemic *(red areas).* (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.)

TABLE E1 HEV Genotypes and Their Geographic Distribution

Genotype	Human Cases	Animal Cases
1	South, Southeast and Central Asia, Africa	—
2	Mexico, Western Africa	—
3	U.S., South America, Europe (France, Spain, U.K., the Netherlands), Japan	U.S., China, Japan, Southeast Asia, Australia, New Zealand, South America
4	China, Taiwan, Japan, Vietnam	India, China, Taiwan, Japan

From Feldman M et al. (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hepatitis A: Another fecal-oral hepatitis virus with low mortality and low chronic state rate
- Hepatitis B, hepatitis C, hepatitis D
- Drug-induced liver injury such as from isoniazid
- Dengue fever, malaria
- Typhoid fever

WORKUP

- Consists of tests on blood and feces on a clinical-compatible patient/travel to endemic areas.
- Patients will shed detectable virus in stool 1 wk prior to start of illness and persist for up to 2 wk afterward.
- Diagnosis is made by detection of HEV IgM or RNA.

LABORATORY TESTS

- Anti-HEV IgM antibodies can be detected 4 days after onset of jaundice and persist for 5 mo.
- Anti-HEV IgG antibodies are detectable shortly after appearance of the IgM antibodies.
- PCR on blood and feces.
- Fig. E2 illustrates the typical course of HEV infection.

PATHOLOGY

- On liver biopsy will demonstrate a cholestatic picture and classic types of acute viral hepatitis.
- In fulminant cases, there is massive hepatic necrosis.

TREATMENT

- Treatment is supportive, as most cases are self-limited in normal hosts.
- Solid-organ transplant patients benefit from ribavirin treatment with chronic hepatitis E (70% response rate).

BOX E1 Clinical Features of Acute Hepatitis E

Incubation period of 2–10 wk
Varying clinical manifestations:
Anicteric hepatitis
Icteric hepatitis
Severe hepatitis leading to fulminant hepatic failure
Inapparent, asymptomatic infection
Clinical illness similar to that with other types of acute viral hepatitis (except among pregnant women)
Milder illness in children
Low mortality rate (0.07%–0.6%) except in pregnant women

From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

BOX E2 Features of HEV Genotypes 1 and 2

Acute infection with no evidence of chronicity
Large outbreaks involving up to several thousand persons in developing countries
Frequent sporadic cases
More common among young adults
Fecal-oral transmission, usually through contaminated water
Highest attack rates are among young adults aged 15 to 40 yr, with relative sparing of children
Infrequent person-to-person transmission
No evidence of parenteral or sexual transmission
Greater likelihood of severe disease (liver failure) with high mortality rates (15% to 25%) in pregnant women, especially in the third trimester
Mother-to-newborn (transplacental) transmission is known to occur

From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.

REFERRAL

To gastroenterologist or infectious diseases for correct diagnosis

PEARLS & CONSIDERATIONS

COMMENTS

HEV can become chronic in organ transplant patients on immunosuppressive therapy, and ribavirin appears to produce a sustained virologic response.

PREVENTION

Hepatitis E vaccines are available and appear to be 96% effective.

PATIENT & FAMILY EDUCATION

Travelers to endemic areas should take precautions and drink only potable water and not eat uncooked shellfish, fruits, and vegetables.

RELATED CONTENT

Hepatitis A (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

TABLE E2 Comparison of Epidemiologic and Clinical Features Associated with HEV Genotypes 1 and 3

Characteristic	Genotype 1	Genotype 3
Epidemiologic patterns of human disease	Large epidemics, small outbreaks, and frequent sporadic cases	A small proportion of cases with sporadic acute hepatitis
Persons affected	Young, otherwise healthy persons; males > females	Mostly elderly, often with other comorbid conditions; males > females
Animal-to-human transmission	Not reported	Demonstrated; a likely mode of transmission through consumption of undercooked meat or close contact with animals
Water-borne transmission	Well known to occur; most common route	Unknown
Animal reservoir	No	Yes (pigs, wild boars, deer)
Severity	Variable severity, including fulminant hepatic failure; severe disease is particularly common in pregnant women	Severity and poor outcome are related to comorbid conditions.
Chronic infection	Not known to occur after acute infection	Immunosuppressed persons; transplant recipients receiving immunosuppressive drugs

From Feldman M et al (eds): *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.

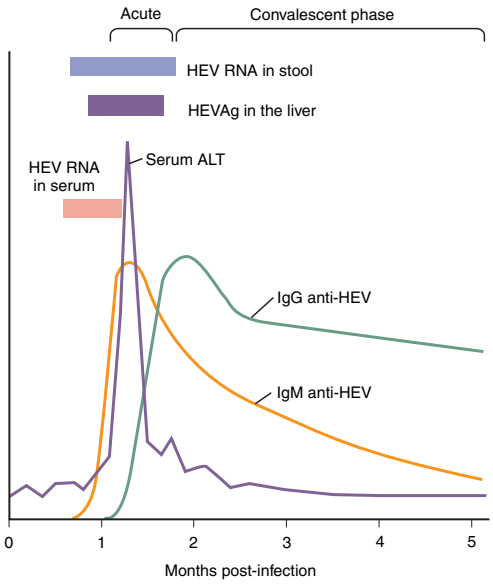


FIG. E2 Typical course of HEV infection (based on studies with human subjects and experimentally infected primates). *anti-HEV,* Antibody to HEV; *Ag,* antigen; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M. (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.)

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BASIC INFORMATION

DEFINITION

Hepatocellular carcinoma (HCC) is a malignant neoplasm of the hepatocytes.

SYNONYMS

Hepatoma
HCC

EPIDEMIOLOGY & DEMOGRAPHICS

HCC is the fifth most common cancer worldwide (~600,000 new cases/yr) and the fourth most common cause of cancer deaths. Incidence varies worldwide:

- 85% of patients with hepatocellular carcinoma have cirrhosis
- Areas with high rates of hepatitis B and C (East Asia, sub-Saharan Africa) have highest incidence
- Males more affected than females, with ratios between 2:1 and 4:1
- Peak incidence: Fifth and sixth decades in Western countries, earlier in areas with perinatal transmission of hepatitis B
- Incidence has grown in the U.S. due to chronic hepatitis C, increasing nonalcoholic fatty liver disease (NAFLD), metabolic syndrome, obesity, and diabetes mellitus
  1. During the past two decades, the incidence in the U.S. doubled. In 2013, an estimated 25,600 cases were recorded. The greatest proportional increase has been among Hispanics and whites between 45 and 60 yr of age.
  2. Mean age of diagnosis approximately 65 yr.
  3. HCC is the fastest-rising cause of cancer-related deaths in the U.S.
  4. The incidence in the U.S. is expected to increase to 38,350 cases by 2020 and 56,200 cases by 2030.
- Risk factors:
  1. Chronic hepatitis B infection accounts for 50% of all cases and most childhood cases
  2. Chronic hepatitis C infection markers are found in 80% to 90% of patients with HCC in Japan and 30% to 50% in the U.S.
  3. Cirrhosis from other causes: Alcoholic liver disease, nonalcoholic steatohepatitis, primary biliary cirrhosis, hemochromatosis, α1-antitrypsin deficiency, and autoimmune hepatitis
  4. Hepatotoxins: Aflatoxin B1
  5. Systemic diseases affecting the liver: Tyrosinemia
  6. Obesity and diabetes mellitus

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- One third of patients are asymptomatic.
- Abdominal pain may be the initial presentation.
- Signs of underlying cirrhosis and portal hypertension are often present.
- Previously compensated cirrhosis with new ascites, encephalopathy, jaundice, or bleeding.
- Paraneoplastic syndromes (hypoglycemia, erythrocytosis, hypercalcemia, severe diarrhea, dermatomyositis) may be present. Box 1 summarizes paraneoplastic syndromes associated with hepatocellular carcinoma.
- Table 1 summarizes symptoms and signs of hepatocellular carcinoma.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Metastatic cancers to liver
- Intrahepatic cholangiocarcinoma
- Benign liver neoplasms (adenomas, focal nodular hyperplasia, and hemangiomas)
- Focal fatty infiltration

WORKUP

- History regarding risk factors

BOX 1 Paraneoplastic Syndromes Associated with Hepatocellular Carcinoma

Carcinoid syndrome
Hypercalcemia
Hypertension
Hypertrophic osteoarthropathy
Hypoglycemia
Neuropathy
Osteoporosis
Polycythemia (erythrocytosis)
Polymyositis
Porphyria
Sexual changes—isosexual precocity, gynecomastia, feminization
Thyrotoxicosis
Thrombophlebitis migrans
Watery diarrhea syndrome

(From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

TABLE 1 Symptoms and Signs of Hepatocellular Carcinoma

Symptom	Frequency (%)
Abdominal pain	59-95
Weight loss	34-71
Weakness	22-53
Abdominal swelling	28-43
Nonspecific GI symptoms	25-28
Jaundice	5-26
Sign	
Hepatomegaly	54-98
Ascites	35-61
Fever	11-54
Splenomegaly	27-42
Wasting	25-41
Jaundice	4-35
Hepatic bruit	6-25

GI, Gastrointestinal. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

- Physical examination with attention to signs of chronic liver disease
- Laboratory evaluation and imaging studies
- Imaging studies: Ultrasound for initial testing; 3-phase CT scan or dynamic contrast-enhanced MRI

LABORATORY TESTS

- Liver function tests.
- α-Fetoprotein (AFP) levels can be elevated in 70% of patients. An AFP level >400 ng/ml is highly suggestive of HCC; however, elevations may not be seen in up to 40% of patients with small lesions (1 to 2 cm).
- Paraneoplastic syndromes associated with HCC may cause hypercalcemia, hypoglycemia, and polycythemia.
- Elevated serum HBV DNA level (≥10,000 copies/ml) is a strong risk predictor of HCC independent of HBeAg, serum aminotransferase level, and liver cirrhosis.

IMAGING STUDIES

Ultrasound (US), CT scan (Fig. E1), or MRI. Ultrasound is most commonly used as a screening test for HCC in high-risk patients every 6 mo. Fig. E2 shows a laparoscopic view of a cirrhotic liver with a nodular hepatoma.

The following imaging modalities are recommended based on US findings:

- Hepatic lesion <1 cm needs to be followed with a repeat US every 3 mo to ensure the lesion does not change in size. If stable for 24 mo, the interval for US can be increased to every 6 mo.
- Hepatic lesion >1 cm needs further confirmatory imaging with either a CT scan or an MRI scan. If the chosen imaging modality shows characteristics typical of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phase) the diagnosis of HCC is confirmed with no need for additional diagnostic testing or biopsy. If the imaging modality is inconclusive or atypical for HCC, then the alternate imaging test must be performed. If the second imaging modality is also inconclusive, an image-guided biopsy is recommended.

BIOPSY: Percutaneous biopsy under ultrasound or CT scan is obtained in the event that imaging studies are nondiagnostic or atypical for HCC, or if no cirrhosis is present. Negative biopsy results should be followed and the hepatic nodule reassessed every 3 to 6 mo until it is no longer seen, enlarges, or shows diagnostic characteristics.

SCREENING: Screening high-risk patients with US every 6 mo is currently recommended to identify early-stage HCC. The use of AFP in addition to US is debatable; though it does increase detection rate it also increases false-positive results. The use of AFP alone should be discouraged due to limited sensitivity and specificity. Patients on transplant waiting lists should be regularly screened for HCC because in the U.S. the development of HCC gives increased priority for liver transplantation. Screening for HCC is recommended in the following groups:

- Hepatitis B carriers (HBsAg positive): Asian males >40 yr, Asian females >50 yr, all cirrhotic hepatitis B carriers, family history

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of HCC and North American blacks/Africans older than age 20 yr
- Cirrhosis (nonhepatitis B): Hepatitis C, alcoholic cirrhosis, hemochromatosis, primary biliary cirrhosis, and possibly α1-antitrypsin deficiency, autoimmune hepatitis, and nonalcoholic steatohepatitis

STAGING: The commonly used Barcelona Clinic Liver Cancer (BCLC) staging system includes patient performance status, cancer symptoms, number and size of nodules, and liver function. The TNM staging classification is described in Table 2.

Treatment is determined according to stage (Fig. 3):
- Early stage (A): Asymptomatic single tumor 5 cm or 3 nodules, each ≤3 cm
- Intermediate stage (B): Patients with tumors that exceed early criteria but do not yet show cancer-related symptoms, vascular invasion, or metastases
- Advanced stage (C): Patients with mild cancer-related symptoms and/or vascular invasion or extrahepatic spread
- End-stage (D): Patients with advanced, symptomatic disease

Rx TREATMENT

- Treatment options for hepatocellular carcinoma are summarized in Table 3. Fig. 4 describes a treatment algorithm for HCC.
- Early stage: Curative treatment (surgical resection or liver transplantation). Patients who have a single lesion can be offered surgical resection if they are noncirrhotic or have cirrhosis with well-preserved liver function, normal bilirubin, and no significant portal hypertension. Liver transplantation is an effective option for patients with HCC corresponding to the Milan criteria (Table 4). Living donor transplantation can be offered for HCC if the waiting time is expected to be long. Local ablation is safe and effective therapy for patients who cannot undergo resection or as a bridge to transplantation. With these options, survival at 5 yr ranges from 50% to 70%. Radiofrequency ablation (RFA) is used in patients with early HCC who are not surgical candidates, and very high local control rates at 2 yr are obtained (>90%), but eventual recurrence rates can approach 70% at 5 yr.
- Intermediate stage: Transarterial chemoembolization (TACE) is recommended as first-line, noncurative therapy for nonsurgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread. More recently, transarterial use of selective internal radiation therapy (SIRT) with yttrium-90 radiolabeled glass microspheres is an alternative to traditional TACE approaches in this setting. Median survivals exceed 2 yr.
- Advanced stage: Palliative targeted therapy, immunotherapy, or clinical trials are used in this stage. Sorafenib and lenvatinib are oral multikinase inhibitors, which are both approved as standard first-line therapy options.
- In patients who have previously received first-line targeted therapy, the oral multikinase inhibitors regorafenib and cabozantinib have shown improved survival. In addition, the immune checkpoint inhibitors nivolumab and pembrolizumab have demonstrated improved survival when used in the second-line setting.
- The antiangiogenic agent ramucirumab was recently approved in the second-line treatment of HCC patients previously treated with sorafenib.

DISPOSITION

- For resectable HCC, the 5-yr survival after liver transplantation is 50% to 70% and 30% to 50% with surgical resection. For unresectable HCC, the overall prognosis is poor.
- Tumor size is an independent prognostic factor for resected small HCC (≤50 mm in diameter). Patients with tumors of 0 to 35 mm diameter have a better 60-mo HCC specific survival rate than do those with larger tumors (36 to 50 mm).[1]
- In the U.S. the 5-yr overall survival rate for HCC is approximately 10%.

REFERRAL

Multidisciplinary gastrointestinal cancer team for treatment planning

PEARLS & CONSIDERATIONS

- Universal hepatitis B vaccination in children in endemic areas has been shown to decrease the incidence of HCC.
- Treatment of patients with chronic hepatitis B–associated cirrhosis with lamivudine reduces the incidence of HCC. Treatment with entecavir in chronic hepatitis B-HCC can improve hepatic function and MELD score.
- Treatment with interferon-based therapy in patients with noncirrhotic hepatitis C reduces risk of HCC in patients demonstrating a sustained viral response.
- HCC screening is recommended in high-risk patients because curative therapies are available only for small and early HCC.

[1] Zhang W et al: Effect of tumor size on cancer-specific survival in small hepatocellular carcinoma, *Mayo Clin Proc* 90(9):1187-1195, 2015.

TABLE 2 Hepatocellular Carcinoma TNM Staging Classification and Milan Criteria for Liver Transplantation

	T stage
T_x	The primary tumor is not assessable
T_0	No tumor is present
T_1	A single tumor (of any size) without blood vessel invasion
	T_{1a}: Solitary tumor <2 cm (greatest dimension) without vascular invasion
	T_{1b}: Solitary tumor >2 cm (greatest dimension) without vascular invasion
T_2	A single tumor >2 cm *with* vascular invasion or multiple tumors (none >5 cm)
T_3	Multiple tumors, any more >5 cm
T_4	Tumor(s) invading a major branch of the portal or hepatic vein with direct invasion of adjacent organs including the diaphragm (other than gallbladder) or with perforation of the visceral liver peritoneum
	N stage
N_x	The lymph nodes are not assessable
N_0	There is no regional nodal involvement
N_1	There is regional nodal involvement
	M stage
M_0	There is no distant tumor spread
M_1	There is distant tumor spread

Milan criteria for liver transplantation

1 tumor ≤5 cm in diameter, or
Up to 3 tumors ≤3 cm in diameter
+ No vascular invasion
+ No extrahepatic disease

Note

The TNM staging classification does not consider the background liver function, which is often impaired in cirrhosis and will affect treatment options and prognosis. Other staging systems consider both disease extent and liver function, but have not been compared accurately against one another:
- Barcelona Clinic Liver Cancer (BCLC) system
- Cancer of the Liver Italian Program (CLIP) system
- Okuda system

From Grant, LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.

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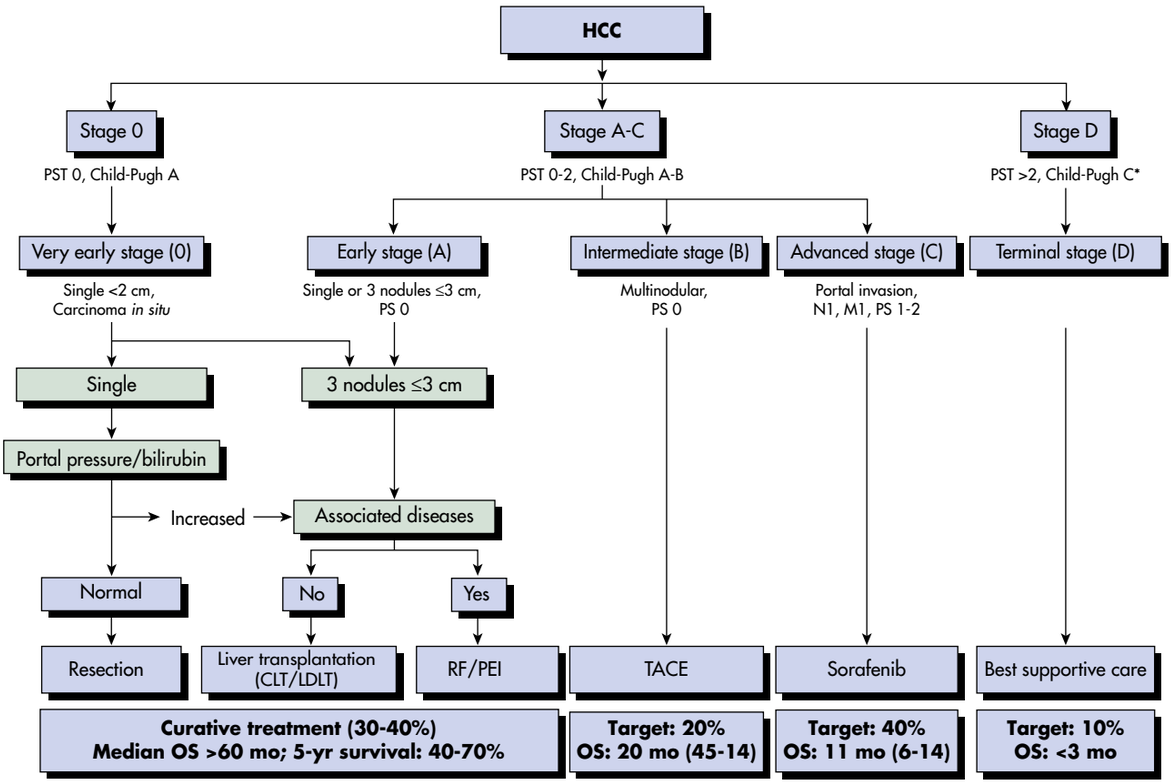

FIG. 3 Updated Barcelona Clinic Liver Cancer staging system and treatment strategy, 2011. (From Grant, LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

TABLE 3 Treatment Options for Hepatocellular Carcinoma

Treatment Modality	Comments
Surgical resection	Curative but limited to noncirrhotic patients and cirrhotic patients without portal hypertension
Liver transplantation	Successful in selected patients with limited disease; requires lifelong immunosuppression
Radiofrequency ablation or ethanol injection	Potentially curative for small tumors, including multiple tumors
Transarterial chemoembolization (TACE)	Prolongs survival in unresectable tumors if hepatic function is preserved; not curative
Immunotherapy	Checkpoint inhibitors improve survival in previously treated patients
Targeted molecular therapies	Sorafenib and lenvatinib improve patient survival in previously untreated patients Regorafenib and cabozantinib improve patient survival in previously treated patients

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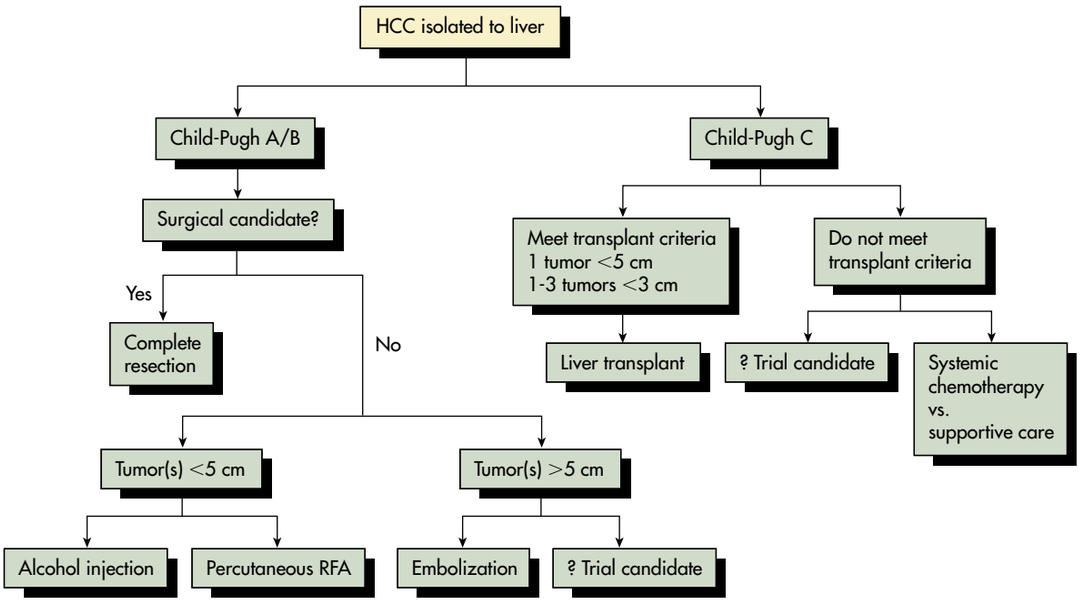

FIG. 4 Treatment algorithm for hepatocellular carcinoma *(HCC).* *RFA,* Radiofrequency ablation. (From Bruix J, Sherman M; AASLD: Management of hepatocellular carcinoma: an update, *Hepatology* 53(3):1020-1022, 2011.)

TABLE 4 Milan Criteria of Eligibility for Liver Transplantation

Presence of a tumor ≤5 cm in diameter in patients with single hepatocellular carcinomas
Or
≤3 tumor nodules, each 3 cm or less in diameter, in patients with multiple tumors

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

- Patients diagnosed with HCC with an AFP >1000 are at increased risk for recurrence after transplantation regardless of tumor size.
- There are numerous ongoing trials with tyrosine kinase inhibitors and monoclonal antibodies for advanced HCC in patients who are intolerant or resistant to sorafenib. The future of therapy for advanced HCC will likely lead to the personalized combination of multiple agents targeting different oncogenic pathways to optimize treatment success.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Liver Cancer (Patient Information)

AUTHOR: **Bharti Rathore, MD**

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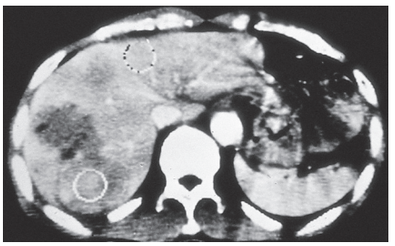


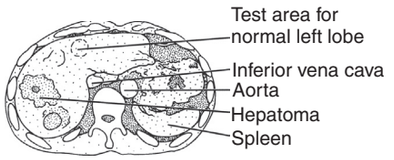
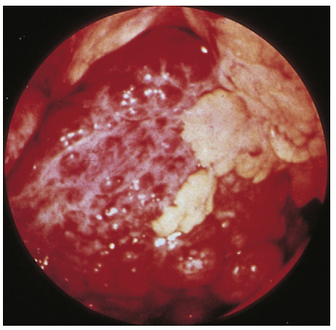


FIG.E1 Hepatoma. Computed tomography scan shows a diffuse lesion in the right lobe of an otherwise normal liver. (From Skarin AT: *Atlas of diagnostic oncology,* ed 3, St Louis, 2003, Mosby.)



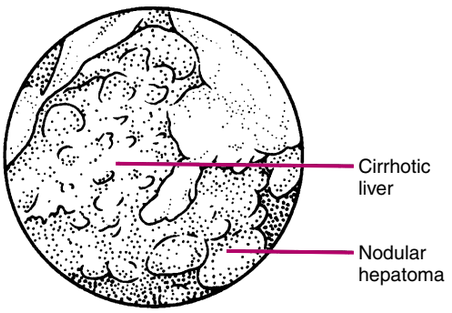


FIG. E2 Hepatocellular carcinoma. Laparoscopic view shows a cirrhotic liver with a nodular hepatoma. (From Skarin AT: *Atlas of diagnostic oncology,* ed 4, St Louis, 2010, Mosby.)

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Hepatopulmonary Syndrome ALG

BASIC INFORMATION

DEFINITION

Hepatopulmonary syndrome (HPS) is defined by the presence of (1) liver disease (usually chronic), (2) reduced arterial oxygenation, and (3) evidence of intrapulmonary vascular dilations (IPVDs).

SYNONYM

HPS

ICD-10CM CODE
K76.81 Hepatopulmonary syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Between 4% and 47% of patients with cirrhosis; the wide range is due to lack of diagnostic criteria
PREDOMINANT SEX AND AGE: No data on age or gender prevalence
GENETICS: New data suggest that polymorphisms in genes involved in the regulation of angiogenesis are associated with increased HPS risk.
RISK FACTORS: HPS occurs with any degree or etiology of liver disease but is more prevalent in patients with established cirrhosis and portal hypertension. There is no clear relationship between severity of hepatic dysfunction and level of systemic hypoxemia.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Dyspnea
- Platypnea: Worsened dyspnea when sitting upright compared with supine position due to further ventilation-perfusion mismatch
- Orthodeoxia: Decreased Pa_{O_2} when the patient is sitting upright compared with supine position due to ventilation-perfusion mismatch
- Increased spider angiomata
- Signs of severe hypoxemia (e.g., cyanosis and clubbing of the digits)

ETIOLOGY

Dilation of intrapulmonary arterioles and dilated vascular channels between pulmonary arteries and veins leads to a ventilation-perfusion mismatch and right-to-left shunting. Research shows that nitric oxide (NO) plays a role in vasodilation. The relationship of vasodilation to liver disease is unclear. Fig. E1 illustrates a proposed pathophysiology of hepatopulmonary syndrome. New areas of research include endothelin-1, which is produced by proliferating cholangiocytes, pulmonary angiogenesis, and opiate receptors' influence on NO production.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Portopulmonary hypertension
- Cavopulmonary anastomosis
- Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome)
- Chronic lung disease (e.g., COPD or pulmonary fibrosis) with coexisting liver disease

WORKUP

- Diagnosis should be suspected in patients with cirrhosis who develop hypoxemia in the absence of other causes (e.g., COPD, thromboembolism).
- Workup includes lab testing and imaging studies (see following), but diagnosis is based on clinical findings.

LABORATORY TESTS

- Arterial blood gas while breathing room air, both supine and erect; Pa_{O_2} <80 mm Hg in the absence of an alternative cause or A-a gradient ≥15 mm Hg (or ≥20 mm Hg in those ≥65 yr old).
- Pulmonary function tests will show nonspecific reduction in DLco.

IMAGING STUDIES

- The most effective screening tool is a transthoracic echocardiogram with bubble study to rule out right-to-left cardiac shunt; microbubble opacification in the left atrium after three to eight heartbeats suggests vasodilation of the pulmonary vascular bed.
- Chest x-ray may show nonspecific bibasilar interstitial pattern.
- Scintigraphic perfusion scanning: Technetium-99m–labeled albumin found in the brain or spleen indicates dilated pulmonary vasculature or cardiac right-to-left shunt.
- Pulmonary angiography is rarely used unless there is a potential to embolize arteriovenous malformations (AVM).

TREATMENT

Ideal treatment would be targeted against pulmonary vasodilation. Most medications have targeted NO production, the activity of NO synthase or endothelin-1, pulmonary angiogenesis, or even bacterial translocation, but no controlled trials exist. Liver transplantation is the only successful treatment, which leads to improvement in gas exchange or complete resolution in gas exchange in the majority of patients. However, severe hypoxemia with Pa_{O_2} <50 mm Hg has been associated with high posttransplant mortality. Some studies have shown benefit of transjugular intrahepatic portosystemic shunting (TIPS), although it is not currently an established treatment. Coil embolization in the setting of pulmonary AVMs is another possible area of treatment.

NONPHARMACOLOGIC THERAPY

Oxygen to correct hypoxemia; Pa_{O_2} will partially correct with administration of supplemental O_2.

ACUTE GENERAL Rx

Correct hypoxemia with supplemental O_2

CHRONIC Rx

- Liver transplantation is the only successful treatment; the majority of patients show improvement in oxygenation at 1 yr after transplant. There are some data showing

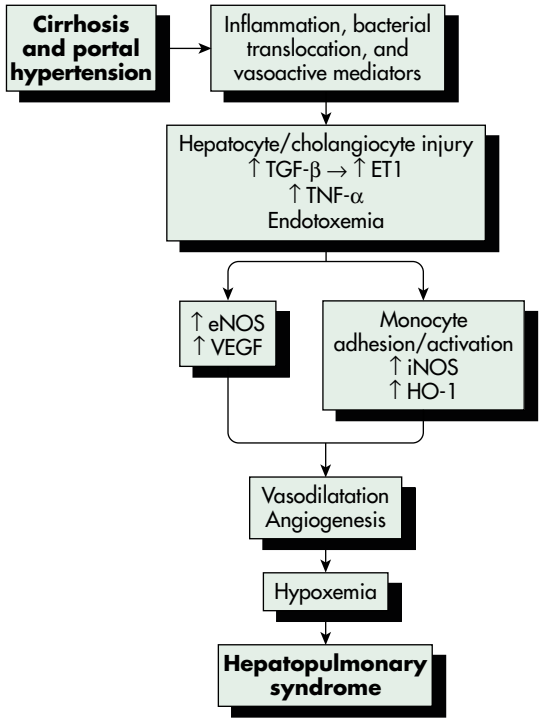

FIG. E1 Proposed pathophysiology of hepatopulmonary syndrome. *eNOS*, Endothelial nitric oxide synthase; *ET1,* endothelin-1; *HO-1,* heme oxygenase; *iNOS,* inducible nitric oxide synthase; *TGF-β,* transforming growth factor-β; *VEGF*, vascular endothelial growth factor. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

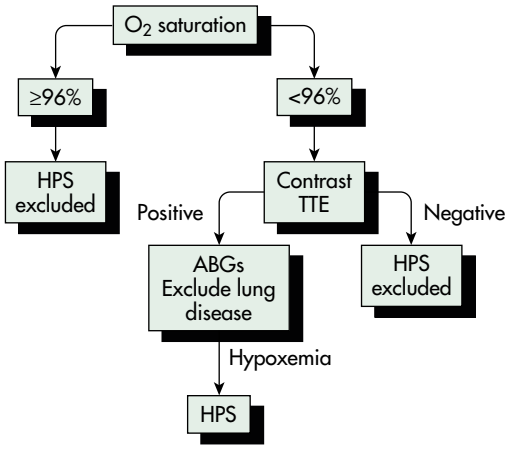

FIG. E2 Approach to screening for hepatopulmonary syndrome *(HPS)* in potential candidates for liver transplantation. *ABG*, Arterial blood gas; *TTE*, transthoracic echocardiography. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

worse outcomes for patients with severe HPS (Pao_2 <50 mm Hg), but mortality appears to be improving. Fig. E2 illustrates an approach to screening for hepatopulmonary syndrome in potential candidates for liver transplantation.

COMPLEMENTARY & ALTERNATIVE MEDICINE

One study suggested that garlic supplements might reduce the A-a gradient in patients with HPS. Studies of diets containing low amounts of L-arginine have not shown benefit.

DISPOSITION

The diagnosis of HPS confers a poor prognosis. Patients with HPS have high mortality and shorter median survival than other patients with liver disease, even after adjusting for the severity of liver disease. According to one natural history study, compared to patients with similar severities of liver disease and comorbidities whose 5-yr survival was estimated at 63%, patients with HPS had a 5-yr survival rate of only 23%.

REFERRAL

- Referral to pulmonologist to help in establishing diagnosis
- Referral to a liver transplant center

PEARLS & CONSIDERATIONS

COMMENTS

Consider the diagnosis of HPS in patients with cirrhosis who present with dyspnea without signs of pulmonary edema from fluid overload.

RELATED CONTENT

Cirrhosis (Related Key Topic)

AUTHORS: **Kathleen Doo, MD,** and **Samaan Rafeq, MD**

BASIC INFORMATION

DEFINITION

Hepatorenal syndrome (HRS) is a functional cause of acute kidney injury (AKI) that occurs in the setting of severe acute or chronic liver disease, most commonly with cirrhosis and portal hypertension. HRS develops as a result of reduced renal perfusion caused by hemodynamic alterations in arterial circulation, as well as overactivity of endogenous vasoactive systems.

In HRS, liver dysfunction leads to increased production or activity of vasodilators. Vasodilation is most pronounced in the splanchnic circulation and, combined with cardiac dysfunction, results in systemic hypotension. Disturbed vasoconstrictor-vasodilator balance in the kidney favoring vasoconstrictors precipitates intense renal arteriolar vasoconstriction, renal cortical hypoperfusion, and AKI. (see Fig. E1). Fig. E2 illustrates the proposed pathophysiology and triggers of HRS. It is now recognized that HRS not only involves circulatory dysfunction but also systemic inflammation.

There are two types of HRS (see Table E1). The International Club of Ascites (ICA) recently revised the nomenclature and diagnosis of type 1 HRS (HRS-1), renaming it HRS-acute kidney injury (HRS-AKI), and type 2 HRS (HRS-2), renaming it HRS–nonacute kidney injury (HRS-NAKI).

- Type 1: Acute and rapid deterioration in kidney function (see Table E2)
- Type 2: Moderate stable chronic kidney disease (CKD) (average serum creatinine, 1.5 mg/dl [133 μmol/L])

SYNONYMS

Hepatorenal failure
Hepatic nephropathy
HRS
Oliguric renal failure of cirrhosis

ICD-10CM CODES

K76.7	Hepatorenal syndrome, hepatorenal failure
Z87.19	History of hepatorenal syndrome
Z84.1	Family history of hepatorenal syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

The probability of HRS in patients with cirrhosis is 18% at 1 yr and 39% at 5 yr. HRS is associated with poor prognosis. HRS type 1 is associated with >90% mortality in 3 mo, with higher mortality conferred by a Model for End-stage Liver Disease (MELD) score >30 and higher stages of AKI. HRS type 2 is associated with 30% mortality in 3 mo and 60% in 1 yr. Although the cause of liver failure or MELD score does not predict the development of HRS, MELD score predicts mortality when HRS has occurred. Dilutional hyponatremia is an independent risk factor for HRS.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

There are no specific physical findings associated with HRS, although it is usually associated with signs and symptoms of acute or chronic decompensated liver failure, such as hypotension, jaundice, spider angiomata, splenomegaly, ascites, fetor hepaticus, edema, asterixis, encephalopathy, or coma. Usually, HRS is accompanied by oliguria and a bland urine sediment. However, a nonoliguric state or an active urine sediment (blood, casts, and/or protein) does not exclude the diagnosis of HRS.

PRECIPITANTS

Precipitating events are identified in 70% to 100% of cases of HRS. Contributory factors include bacterial infection, alcoholic hepatitis, excessive laxative or NSAID use, GI bleeding, or large-volume paracentesis without albumin administration. Unlike HRS, prerenal azotemia, irrespective of its etiology (diuresis or other fluid removal), improves with cessation of diuretic therapy and/or volume resuscitation. Nevertheless, HRS may present in the absence of a clear precipitating factor. Recent studies suggest that, among those not listed for liver transplant, mortality rates are extremely high in patients with either HRS or acute tubular necrosis (ATN).

DIAGNOSIS

HRS is a diagnosis of exclusion. The revised diagnostic criteria for HRS are summarized in Table E3.

DIFFERENTIAL DIAGNOSIS

- Prerenal azotemia: Must be excluded or treated appropriately before establishing a diagnosis of HRS. Prerenal azotemia typically responds to volume expansion and cessation of diuretic therapy. Both prerenal azotemia and HRS are often associated with fractional excretion of sodium (FE_{Na}) <1%.
- ATN: Urine sodium >30 mEq/L, FE_{Na} >1.5%, urine-to-plasma creatinine ratio <30, urine-to-plasma osmolality ratio = 1; urine sediment reveals muddy brown casts and cellular debris. There is no significant response to sustained plasma expansion.
- Other: Renal artery or vein thrombosis; cardiorenal syndrome; urinary tract obstruction; glomerulonephritis; and toxicity from drugs, organic solvents, heavy metals, heme pigments, and intravenous contrast medium.

WORKUP

Acute azotemia and oliguria in the setting of liver disease requires laboratory evaluation to differentiate HRS from ATN. Extracellular fluid volume challenge may be required to differentiate HRS from prerenal azotemia. Diagnostic paracentesis should be done to rule out spontaneous bacterial peritonitis (SBP). Serum creatinine and BUN are poorly sensitive markers of kidney function in cirrhosis. Serum creatinine in patients with cirrhosis is also affected by the following factors:

- Decreased formation of creatinine from creatine in muscles, secondary to muscle wasting
- Increased renal tubular secretion of creatinine
- Increased volume of distribution causing dilution of SCr
- Interference with assays for SCr by elevated bilirubin

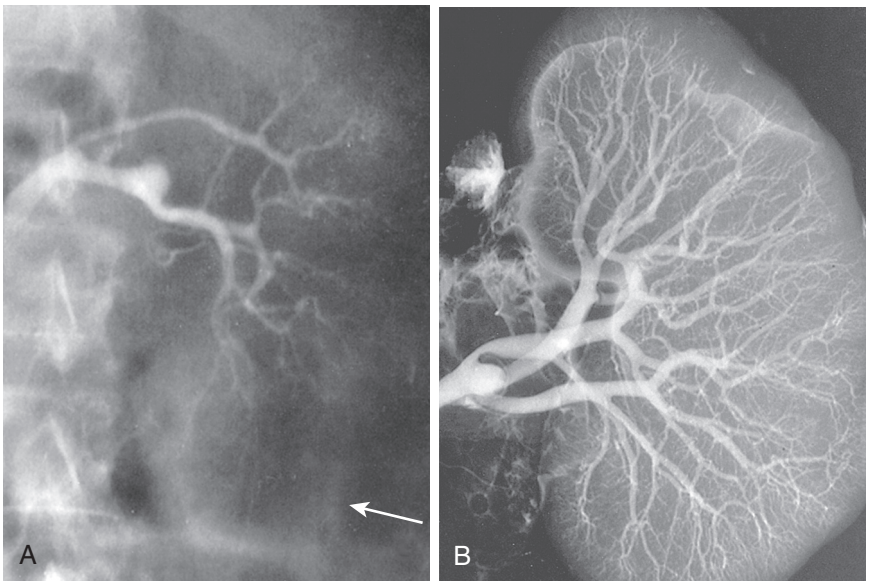

FIG. E1 Circulatory dysfunction in hepatorenal syndrome (HRS). A, Renal angiogram (the *arrow* marks edge of the kidney). **B,** The angiogram carried out in the same kidney at autopsy. Note complete filling of the renal arterial system throughout the vascular bed to the periphery of the cortex. The vascular attenuation and tortuosity seen previously **(A)** are no longer present. The vessels are also histologically normal. This finding indicates the functional nature of the vascular abnormality in HRS. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, St Louis, 2010, Saunders.)

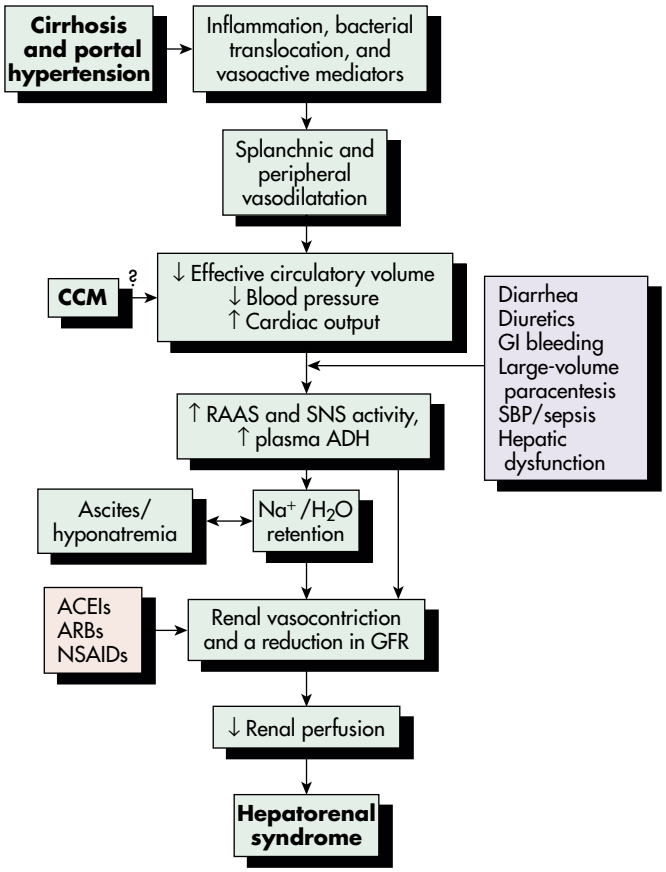

FIG. E2 Proposed pathophysiology and triggers of hepatorenal syndrome. *ACEI,* Angiotensin-converting enzyme inhibitor; *ADH,* antidiuretic hormone; *ARB,* angiotensin receptor blocker; *CCM,* cirrhotic cardiomyopathy; *GFR,* glomerular filtration rate; *NSAID,* nonsteroidal anti-inflammatory drug; *RAAS,* renin-angiotensin-aldosterone system; *SBP,* spontaneous bacterial peritonitis; *SNS,* sympathetic nervous system. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

TABLE E1 Definition of Hepatorenal Syndrome

Type 1 HRS: HRS-AKI

Acute and rapid deterioration in kidney function: An acute increase in serum creatinine of ≥0.3 mg/dl within 48 hours or ≥50% from a stable baseline serum creatinine within 3 mo (presumed to have developed within the past 7 days when no prior readings are available).
Occurs in parallel with the cirrhosis-associated failure of other organs or systems (e.g., coagulopathy, hepatic encephalopathy).
In cirrhosis, is a form of acute-on-chronic liver failure.
Frequently follows a precipitating event, mainly bacterial infection; rapidly fatal without treatment.
Mean survival of 2 to 3 wk. Renal replacement therapy does not prolong life without liver transplantation.

Type 2 HRS: HRS-NAKI

HRS-AKD	Hepatorenal syndrome-acute kidney disease: a) eGFR <60 ml/min per 1.73 m^2 for <3 mo in the absence of other (structural) causes; *or* b) SCr increase <50% using the last available outpatient value within 3 mo
HRS-CKD	Hepatorenal syndrome-chronic kidney disease: eGFR <60 ml/min per 1.73 m^2 for 3 mo in the absence of other (structural) causes

Moderate stable CKD.
Mean survival of 6 mo.

AKI, Acute kidney injury; *CKD,* chronic kidney disease; *eGFR,* estimated glomerular filtration rate; *HRS,* hepatorenal syndrome; *NAKI,* nonacute kidney injury; *SCr,* serum creatinine.
From Fernández J, Arroyo V: Hepatorenal syndrome. In Johnson RJ et al (eds): *Comprehensive clinical nephrology,* ed 5, Philadelphia, 2015, Saunders, pp 873-882.

LABORATORY TESTS

- Serum electrolytes (serum sodium <135 mEq/L), blood urea nitrogen, creatinine, and osmolality
- Urinalysis, urine sodium, urine creatinine, urine osmolality
- Urine sodium <10 mEq/L, FE_{Na} <1%, urine-to-plasma creatinine ratio >30, urine plasma-to-urine osmolality ratio >1.5, bland urine sediment. FE_{Na} does not adequately differentiate HRS from other common etiologies of AKI in liver dysfunction, but only a minority of patients with HRS have high urine sodium concentrations

IMAGING STUDIES

Kidney, bladder, and ureter ultrasound may be indicated if obstructive uropathy is suspected. Duplex Doppler ultrasonography may show increased renal resistive indices (RI) in hilar, medullary, and cortical areas and disappearance of the RI gap (difference between interlobar and cortical RI), indicating reduction of renal blood flow. CT may be required to diagnose occult infection(s), and prophylaxis directed at preventing contrast-associated nephropathy is recommended.

Rx TREATMENT

ACUTE GENERAL Rx

- Box E1 summarizes the management of HRS. Avoidance of precipitating factors (Table E4) and their appropriate therapy are cornerstones of HRS management.
- Patients who have survived an episode of SBP should receive long-term prophylaxis with daily norfloxacin or trimethoprim/sulfamethoxazole.
- Improvement in liver function due to partial resolution of the primary disorder or successful liver transplantation is the optimal treatment. Liver transplantation leads to resolution of HRS type 1 in 76% of cases.
- Splanchnic vasoconstrictor agents (e.g., terlipressin, norepinephrine, and midodrine combined with octreotide). Note that terlipressin, a vasopressin analog, has not yet been approved for prescription in the United States or Canada.
- Dopamine and prostaglandins are generally ineffective in treating patients with HRS.

PHARMACOLOGIC THERAPY

Most therapy is centered on the use of vasoconstrictor therapy and albumin resuscitation targeted at the reversal of splanchnic arterial vasodilation.

NONPHARMACOLOGIC THERAPY

- Liver transplantation alone for candidates with type I HRS for <4 wk, and simultaneous liver-kidney transplantation for those at risk of nonrecovery of kidney function.
- Transjugular intrahepatic portosystemic shunt (TIPS) for patients with HRS-2 and refractory ascites.
- Renal replacement therapy as a bridge to liver transplantation.

REFERRAL

Referral for hepatology, nephrology, and liver transplantation as indicated

PEARLS & CONSIDERATIONS

- Serum creatinine remains a main biomarker in diagnosis of HRS; there is a potential role

of new urinary biomarkers in the differential diagnosis for AKI in patients with cirrhosis.
- Outcomes are poor in both HRS-AKI and ATN-AKI. Differentiation between these two diagnoses is of questionable clinical importance.
- The mortality of patients with liver failure who require renal replacement therapy is high and is similar in HRS and ATN. However, renal recovery and patient survival 1 and 5 yr after liver transplantation are significantly worse for patients with AKI secondary to ATN versus HRS.
- Vasopressor agents and volume resuscitation with albumin remain a mainstay of medical management.
- In severely ill patients who are not candidates for liver transplantation, dialysis does not improve outcomes.

RELATED CONTENT

Hepatorenal Syndrome (Patient Information)

AUTHORS: **Maria Andrievskaya, MD,** and **James E. Novak, MD, PhD**

TABLE E2 Hepatorenal Syndrome Type 1 Classified by Acute Kidney Injury (AKI) Stage according to the International Club of Ascites (ICA) and Acute Kidney Injury Network (AKIN) Criteria

Risk/Stage 1	Increase in SCr >1.5- to 2-fold from baseline; or by >0.3 mg/dl (26.5 μmol/L) Increase in SCr of 50% or more to a final value of >1.5 mg/dl (133 μmol/L)
Injury/Stage 2	Increase in SCr >2- to 3-fold from baseline
Failure/Stage 3	Increase in SCr >3-fold from baseline; or SCr >4 mg/dl (353.6 μmol/L) with an acute increase of ≥0.5 mg/dl (44 μmol/L); or initiation of renal replacement therapy

SCr, Serum creatinine.
From Angeli P et al: Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites, *J Hepatol* 62:968-974, 2015.

TABLE E3 Revised Diagnostic Criteria for Hepatorenal Syndrome Type of Acute Kidney Injury (HRS-AKI) in Patients with Cirrhosis

- **Cirrhosis; acute liver failure; acute on chronic liver failure**
- Diagnosis of AKI according to International Club of Ascites criteria*
- No improvement in kidney function after 48 consecutive hours of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg body weight per day (maximum dose, 100 g per day)
- Absence of shock
- No current or recent use of nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory drugs, aminoglycosides, iodinated contrast media)
- No macroscopic signs of structural kidney injury, defined as:
  - Absence of proteinuria (>500 mg/day)
  - Absence of microhematuria (>50 red blood cells per high-power field)
  - Normal findings on renal ultrasonography

*This criterion would not be included in cases of known pre-existing structural chronic kidney disease (e.g., diabetic or hypertensive nephropathy).
From Angeli P et al: Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites, *J Hepatol* 62:968-974, 2015.

BOX E1 Management of Hepatorenal Syndrome (HRS)

- Measures to prevent variceal bleeding (e.g., beta blockers, band ligation)
- Treatment of severe alcoholic hepatitis
- Prevention of HRS
  - Avoid intravascular volume depletion (diuretics, excessive lactulose, GI bleeding, large-volume paracentesis without adequate volume repletion)
  - Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be avoided or used with caution in patients with cirrhosis and ascites. Judicious management of nephrotoxins (NSAIDs, antibiotics). Prompt diagnosis and treatment of infections (SBP, sepsis)
  - SBP prophylaxis: Long-term use of norfloxacin (or trimethoprim/sulfamethoxazole) can be justified if the ascitic fluid protein <1.5 g/dl along with CKD (creatinine >1.2 mg/dl, BUN >25 mg/dl or serum Na <130 mmol/L) or liver failure (Child score >9 and bilirubin >3 mg/dl) (Class I, Level A)
  - Avoid use of proton pump inhibitors without indications as can precipitate SBP.
- Treatment of HRS
  - Stop all nephrotoxic or volume-depleting agents (ACEIs, ARBs, NSAIDs, diuretics)
  - Antibiotics for infections
  - IV albumin—bolus of 1 g/kg/day on presentation (maximum dose, 100 g daily). Continue at dose of 20–60 g daily as needed to maintain central venous pressure 10–15 cm H_2O
  - Vasopressor therapy (in addition to albumin):
    - Terlipressin*—start at 1 mg IV every 4 h and increase up to 2 mg IV every 4 h if baseline serum creatinine level does not improve by 25% at day 3 of therapy

    OR
    - Midodrine and octreotide—begin midodrine at 2.5–5 mg orally 3 times daily and increase to a maximum dose of 15 mg 3 times daily. Titrate to a MAP increase of at least 15 mm Hg; begin octreotide at 100 μg subcutaneously 3 times daily and increase to a maximum dose of 200 μg subcutaneously 3 times daily, or begin octreotide as a 25-μg IV bolus and continue at a rate of 25 μg/h

    OR
    - Norepinephrine—0.1 to 0.7 μg/kg per minute as an IV infusion. Increase by 0.05 μg/kg per minute every 4 h and titrate to a MAP increase of at least 10 mm Hg
    - Duration of vasopressor treatment is generally a maximum of 2 wk until reversal of hepatorenal syndrome or liver transplantation
- Evaluate patient for liver transplantation

*Not available in the U.S.
ACEI, Angiotensin-converting enzyme inhibitor; *ARB,* angiotensin receptor blocker; *BUN,* blood urea nitrogen; *CKD,* chronic kidney disease; *GI,* gastrointestinal; *IV,* intravenous; *MAP,* mean arterial pressure; *NSAID,* nonsteroidal anti-inflammatory drug; *SPB,* spontaneous bacterial peritonitis.
From Feldman M et al: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

TABLE E4 Prevention of Acute Kidney Injury in Patients with Cirrhosis

Risk Factors	Preventive Approaches
Hepatorenal syndrome development	Judicious use of diuretics and lactulose to avoid hypovolemia Antibiotic prophylaxis following GI bleeding Albumin administration during large volume paracentesis (6 to 8 g/L of ascitic fluid removed) Spontaneous bacterial peritonitis (SBP) prophylaxis in patients with low-protein ascites Early recognition and treatment of SBP with antibiotics and albumin at the dose of 1.5 g per kg of body weight at the time of diagnosis of SBP and 1 g per kg of body weight at the third day of treatment
Nephrotoxic medication exposure	Avoid nephrotoxic medications if possible Appropriate drug dosing based on pharmacokinetics and close monitoring of drug toxicity, early recognition of drug-induced AKI, and discontinuation of offending agent if possible Use of lipid formulations of amphotericin B rather than conventional formulations of amphotericin B Use of azole antifungal agents and/or the echinocandins rather than conventional amphotericin B, if equal therapeutic efficacy can be assumed
Radiocontrast exposure	Consider alternative imaging methods or avoidance of IV contrast if possible Use of low or iso-osmolar agents with lowest volume possible IV volume replacement prior to contrast exposure
Intraabdominal hypertension	Paracentesis, with coadministration of albumin, in patients with tense ascites

AKI, Acute kidney injury; *IV,* intravenous.
From Ronco C et al: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Hereditary breast and ovarian cancer syndrome (HBOC) patients carry a significant cancer-associated alteration in the *BRCA1* and/or *BRCA2* gene. These genetic mutations can confer a heightened risk of malignancy in the breast, ovary, fallopian tube, and peritoneum in women and an elevated risk of prostate and breast cancer in men. Additionally, the risk of pancreatic cancer and skin cancer are elevated for both men and women. Another condition, Lynch syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC), is associated with an increased risk of endometrial cancer and ovarian cancer in women and cancer of the colon, stomach, pancreas, and small bowel in both women and men. Patients with Lynch syndrome carry significant pathogenic alterations in five genes, as noted below.

The risk for a particular verified genetically associated cancer is significantly greater than the cancer risk associated with the general population or with one's personal and/or family cancer history alone, without a positive genetic test. Frequently, a cancer that is associated with a heritable genetic mutation presents at a younger age than that seen in the general population is a relatively rare type of cancer and/or affects multiple same-side family members. Identifying carriers can significantly reduce the morbidity and mortality of the patient and her/his close family members.

SYNONYMS

Hereditary breast and ovarian cancer syndrome (HBOC)
Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC)
Hereditary cancer syndrome

ICD-10CM CODES

Z84.81	Family history of carrier of genetic disease
Z80.3	Family history of malignant neoplasm of breast
Z80.41	Family history of malignant neoplasm of ovary
Z80.49	Family history of malignant neoplasm of other genital organs (uterus, vagina, for example)
Z15.01	Genetic susceptibility to malignant neoplasm of breast
Z15.02	Genetic susceptibility to malignant neoplasm of ovary

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Overall, an estimated 6% to 10% of gynecologic cancers are heritable. Approximately 7% to 10% of the estimated 235,000 new breast cancer cases are likely to be associated with heredity. Inherited pathogenic *BRCA 1, 2* mutations account for an estimated 11% to 15% of ovarian cancer cases. Less than 1% of the general population has a pathogenic mutation in the *BRCA 1* or *2* gene. As noted above, Lynch syndrome–associated mutations increase ovarian and uterine cancer as well as colorectal (up to 5% of colorectal cancers are considered heritable), pancreatic, and gastric cancers. This article will, however, focus on gynecologic disease. Tables 1 and 2 summarize genes associated with hereditary breast and ovarian cancer predisposition.

PREDOMINANT SEX AND AGE: Although females are predominantly affected, males who carry deleterious mutations in *BRCA 1, 2* are at a significantly higher risk for cancer. Both sexes can transmit the altered gene to their offspring.

GENETICS: The transmission pattern is autosomal dominant. A child whose father or mother has a *BRCA* mutation has a 50% chance of inheriting that genetic mutation.

RISK FACTORS: *BRCA1* and *BRCA2* mutations can generate a greater risk of breast cancer than other such well-established factors as increased breast density, history of atypical ductal or lobular hyperplasia, nulliparity, obesity, and family history.

Up to 37% of breast cancer patients and 100% of ovarian/tubal/peritoneal cancer patients are at risk for hereditary breast and ovarian cancer syndrome.

Hereditary Breast and Ovarian Cancer Syndrome (HBOC):

- Individuals with *BRCA1*, *BRCA2* mutations (Fig. 1)
- Red flags (not an exhaustive list) for possible HBOC include personal or family history of:
  1. Personal breast cancer diagnosed at ≤45 yr old
  2. Triple-negative breast cancer (ER-, PR-, Her2-)
  3. Ovarian cancer: Very important factor (mostly papillary serous)
  4. Male breast cancer
  5. Two primary breast cancers
  6. Ashkenazi Jewish ancestry
  7. Breast cancer with ≥2 relatives with an HBOC-associated cancer (breast, ovary, prostate, pancreatic cancers)
  8. A previously identified HBOC mutation
  9. Two or more close relatives with breast cancer, one of whom was diagnosed at age 50 yr or younger

TABLE 1 Genes Associated with Hereditary Breast Cancer Predisposition

Gene	Syndrome	Relative Risk of BC	BC Risk by Age 80 Yr	Associated Cancers
High Penetrance				
BRCA1	HBOC	~15-30	70%	Ovarian, other
BRCA2	HBOC	~10-20	70%	Ovarian, pancreatic, prostate, other
p53	Li-Fraumeni syndrome	100	50% by 60 yr	Soft tissue sarcoma, osteosarcoma, brain tumors, adrenocortical carcinoma, leukemia, other
PTEN	Cowden syndrome	No reliable estimate	70%-80%	Thyroid (follicular and rarely papillary) endometrial, genitourinary, other
	Bannayan-Riley-Ruvalcaba syndrome			
	Proteus			
	Proteus-like syndrome			
STK11	Peutz-Jeghers syndrome	No reliable estimate	30% by age 60	Small intestine, colorectal, uterine, testicular and ovarian sex chord tumors, other
CDH1	Hereditary diffuse gastric carcinoma	~3.25	39%	Lobular breast, diffuse gastric, other
Lower or Moderate Penetrance				
ATM (heterozygote)	Ataxia-telangiectasia in homozygotes	~3	30	Undefined in heterozygotes
CHK2 (CHEK2)	Li-Fraumeni variant	1.5-3	20%-30%	Undefined
PALB2	None known	5	~40	Undefined in heterozygotes

BC, Breast cancer; *HBOC,* hereditary breast and ovarian cancer syndrome.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

10. Three or more HBOC-associated cancers at any age

NOTE:

- One half of *BRCA* carriers inherit the mutation from their father.
- Early onset of cancer may be a more important red flag than the number of affected family members, especially if the number of family members is small to begin with.
- Testing criteria (Tables 3 and 4), as per National Comprehensive Cancer Network (NCCN) guidelines, may differ from the red flags noted previously.
- Family history extends to first-, second-, and third-degree relatives.
- Consider Lynch syndrome–associated cancers (e.g., colorectal, gastric, brain, pancreas, small bowel, skin, ureter, renal pelvis, GI polyps), as Lynch syndrome is associated also with ovarian and uterine (endometrial) cancer.
- *BRCA* stands for BReast CAncer.
  1. The majority (84%) of the approximately 7% of breast cancers and 14% of ovarian cancers that result from a heritable mutation are due to a *BRCA1* (52%) and *BRCA2* (32%) gene mutation.
  2. By age 70, in comparison to the 7.3% risk of breast cancer in the general population, or approximately double that risk if one has an affected first-degree relative, *BRCA1* and *BRCA2* mutation carriers have up to an 87% reported risk of developing breast cancer. As opposed to a general-population risk of 2% for developing a second breast primary within 5 yr of a first diagnosis, women with HBOC mutations have a 12% to 27% risk. This risk climbs to a reported 50% (*BRCA2*) and up to 64% (*BRCA1*) by age 70.
  3. By age 70, in contrast to the 0.7% risk of ovarian cancer in the general population, there is a reported risk of up to 27% to 63% for *BRCA2* and *BRCA1* mutation carriers, respectively. The risk for ovarian cancer within 10 yr of a breast cancer diagnosis is 6.8% (*BRCA2*) to 12.7% (*BRCA1*) as opposed to a general-population risk of less than 1.0%.
  4. Men with HBOC have an up to tenfold increased risk for breast cancer and a more than twofold increase in prostate cancer in comparison to the general-population risk. In men, the *BRCA2* mutation increases the cancer risk more than the *BRCA1* mutation. In fact, the breast cancer risk for a male with a *BRCA2* mutation is up to 80 times the risk seen in the general population.
  5. Both men and women have an elevated risk (up to sevenfold) for pancreatic cancer (*BRCA2* >1) and for melanoma (2.5-fold increase with *BRCA2*).
  6. Ashkenazi Jewish ancestry is associated with founder mutations 187delAG (*BRCA1*), 5382insC (*BRCA1*), and 6174delT (*BRCA2*), which confer a significantly elevated risk for breast and ovarian cancer. As opposed to the 1 in 400 risk in the general population, 1 in 40 individuals of Ashkenazi Jewish descent have a *BRCA 1* or *2* mutation.

Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer):

- Individuals with *MLH1, MSH2, MSH6, PMS2, EPCAM* mutations.
- By age 70, Lynch syndrome carriers have—in addition to an increased risk for colorectal, gastric, hepatobiliary, urinary tract, small bowel, brain, skin, and pancreatic cancers—up to an approximately twentyfold increase in ovarian cancer (4% to 12% risk vs. the general-population risk of 0.7%) and up to an approximately fortyfold increase in uterine cancer (25% to 60+% risk vs. the general-population risk of 1.6%).
- The previously listed genes and others (e.g., *PTEN, TP53, CDH1, STK11*) that are found less frequently are considered high-penetrance genes, as they can increase the relative risk of their respective syndromes by greater than four- to fivefold.
- Other, more moderate-penetrant genes (e.g., *CHEK2, ATM, PALB2, BRIP1, RAD51C, RAD51D*), that is, those that are associated with a two- to fourfold increase in the relative risk of cancer, should be considered when assessing risk and ordering genetic tests.

TABLE 2 Genes Associated with Hereditary Ovarian Cancer Predisposition

Gene	Syndrome	Relative Risk of OC	OC Risk by Age 80 Yr	Associated Cancers
High Penetrance				
BRCA1	Hereditary breast ovarian cancer syndrome	~50	~40%	Breast, other
BRCA2	Hereditary breast ovarian cancer syndrome	~8	11%-26%	Breast, pancreas, prostate, other
MLH1 *MSH2* *MSH6* *PMS2* *EPCAM*	Lynch syndrome	~4	~20%	Colon Uterine Stomach Small intestine Urinary tract Pancreatic Possible other sites
Lower or Moderate Penetrance				
RAD51C	None	~5	~6%	Undefined Autosomal recessive Fanconi anemia
RAD51D	None	~12	~14%	Undefined Autosomal recessive Fanconi anemia

OC, Ovarian cancer.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

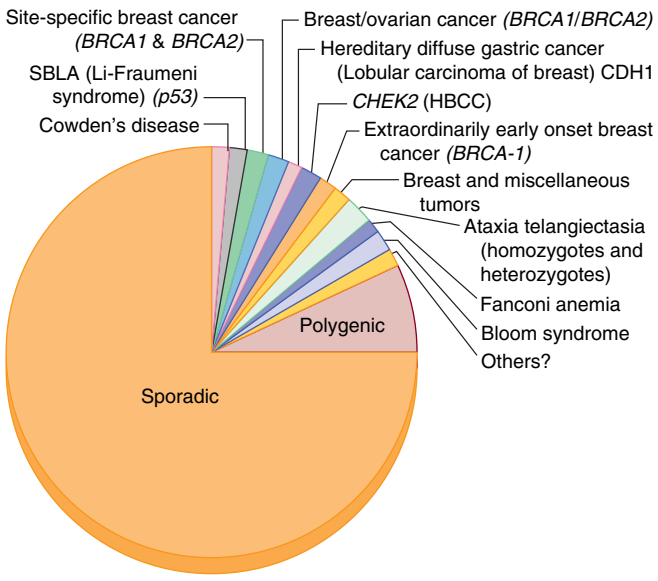

FIG. 1 Schematic depicting heterogeneity in breast cancer. *HBCC*, Hereditary breast and colorectal cancer; *SBLA*, sarcoma, breast and brain tumors, leukemia, laryngeal and lung cancer, and adrenal cortical carcinoma. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.)

TABLE 3 Testing Criteria for Breast Ovarian Cancer Syndrome*

Individual from a family with a known deleterious *BRCA1* or *BRCA2* gene mutation
Personal history of breast cancer plus one or more of the following:
- Diagnosed at ≤45 yr of age
- Diagnosed at ≤50 yr of age with
  - An additional breast cancer primary
  - At least one close blood relative with breast cancer at any age
  - At least one close relative with pancreatic cancer
  - At least one close relative with prostate cancer
  - An unknown or limited family history
- Diagnosed at age 60 with
  - Triple-negative breast cancer
- Diagnosed at any age with
  - At least one close blood relative with breast cancer before 50 yr of age
  - At least two close blood relatives with breast cancer at any age
  - At least one close blood relative with ovarian cancer
  - At least one close blood relative with pancreatic cancer
  - At least two close blood relatives with prostate cancer
  - A close female blood relative with ovarian cancer
  - An individual of ethnicity associated with a higher mutation frequency
- Personal history of ovarian cancer
- Personal history of male breast cancer
- Personal history of prostate cancer at any age with a close relative with breast, ovarian, or pancreatic cancer at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- Family history meeting any of the above criteria

See NCCN guidelines for the most up-to-date and detailed description for counseling and testing.

*For more detailed information, see the National Comprehensive Cancer Network (NCCN) guidelines.
From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2017, Elsevier.

TABLE 4 National Comprehensive Cancer Network (NCCN) Guidelines for Recommending Genetic Testing for *BRCA1* or *BRCA2* Mutations*

Personal history of breast cancer and one or more of the following:
- Diagnosed at age ≤45 yr
- Diagnosed with at least two breast cancer primaries (bilateral, separate ipsilateral), the first at age 50 yr
- Diagnosed at age ≤50 yr with one or more close relatives† with breast cancer (prostate or pancreatic) at any age
- Diagnosed with triple-negative breast cancer at age ≤60 yr
- Diagnosed at any age with one or more close relatives with breast cancer at age ≤50 yr
- Diagnosed at any age with two or more close relatives at any age
- Diagnosed at any age with one or more close relatives with invasive ovarian cancer (including fallopian tube and primary peritoneal) at any age
- Diagnosed at any age with two or more close relatives with pancreatic and/or prostate cancer
- Having a close male relative with breast cancer at any age

*Individuals with a limited or unknown family history may have an underestimated probability of a familial gene mutation detection.
†Close relative pertains to first-, second-, or third-degree blood relatives on the same side (either maternal or paternal) of the family.
From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2017, Elsevier.

- More than 12 known gene mutations are associated with an elevated risk for breast cancer, and a similar number are associated with an elevated risk for ovarian cancer. As such, screening for *BRCA1, BRCA2* alone will miss these mutations.
- In addition to established deleterious mismatch repair gene mutations, gene alterations that are categorized in the literature as emerging risk mutations are also associated with hereditary gynecologic and other cancers.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Present at a younger age
- Bilaterality more likely
- Multiple primaries in one individual

ETIOLOGY

Hereditary cancers are typically due to a genetic mutation in a tumor suppression gene that interferes with DNA repair and allows an otherwise potentially avoidable cancer to develop. This is distinct from familial cancers in which there is no isolated gene mutation but, nonetheless, cancers appear in the family to a degree more than that which would be statistically seen in the general population. Nongenetic factors such as lifestyle habits and environmental influences contribute to cancer risk as well.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- General (sporadic) population or familial basis for the cancer in question.
- Hereditary cancer is more likely to present at a younger age, to span a number of generations, to affect more family members than would be expected (if a large enough family), especially in a suspicious pattern, and to include some rare (ovary, male breast cancer, for example) presentations.
- In addition to the more common syndromes listed previously, consider Cowden *(PTEN),* Peutz-Jeghers *(STK11),* Li-Fraumeni *(TP53),* and others.

WORKUP

Family history questionnaire, patient and family interviews, genetic counseling/risk assessment (including tools such as Tyrer-Cuzick/Gail/Claus models), and tailored genetic testing.

LABORATORY TESTS

- A simple blood or saliva sample drawn in the office or a lab, after informed consent, is needed. This specimen should be sent to a reliable laboratory recognized nationally for its genetic cancer testing accuracy (technologic and interpretative), reporting format, and the support staff ability and availability for consultation, office counseling, and testing integration. Look for a laboratory that has published peer-reviewed data and has an accurate classification methodology that relies on an extensive database. Realize that these labs are not FDA approved and that CLIA certification, while needed, relies on just in-house data. Remember also that most patients get tested only once in their lifetime, and so accuracy is imperative.
- Options include:
  1. Syndrome specific: For example, HBOC-*BRCA* testing (including large rearrangement detection); Lynch syndrome; founder mutation testing (187delAG, 5382insC, 6174delT)—Ashkenazi Jewish population (often recommended as the first test for this population); single-site testing (if a previously identified gene mutation is known in the family); cancer specific, for example, breast cancer panel—*BRCA 1, 2* with/without reflex to broader panel (i.e., sequential testing).
  2. Comprehensive panel testing (can include HBOC syndrome *BRCA1*, *BRCA2*), Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*), Li-Fraumeni (*TP53*), Cowden (*PTEN*), Peutz-Jeghers (*STK11*), *PALB2, CHEK2, ATM, BRIP1, RAD51C*, and others [upward of 28+ genes]).
- Choice of the test is generally based on personal/family history, although thoroughness of the risk assessment may be limited by

attempting to choose a gene test based on history/phenotype alone.
- Comprehensive panel testing has been shown to increase mutation detection and to aid in test selection when patients qualify for more than one syndrome/cancer-specific test, or it can be used to capture a potentially broader view of risk. There is a concern, however, for detecting mutations that are not clinically actionable, at this time.
- Categories of results include (1) positive or negative for a deleterious mutation or (2) a genetic variant of uncertain significance, in which a cancer risk is not yet established or ruled out. It is critical that the classification of these variants is accurate.

IMAGING STUDIES

Screening transvaginal ultrasonography, annual mammography, annual MRI (when breast cancer risk is 20% or more based on Tyrer-Cuzick or other breast cancer risk screening models)

Rx TREATMENT/RISK REDUCTION

- Heightened surveillance, judicious chemoprevention, and prophylactic surgery have been associated with improved outcomes.
- Surveillance includes patient breast awareness, clinical breast exam, mammography, MRI, transvaginal ultrasonography, and CA-125 blood testing, for example.
- Chemopreventive approaches have been shown to reduce the risk of ovarian cancer by up to 60% (with an oral contraceptive) and risk of contralateral breast cancer by as much as 53% (with tamoxifen).
- In HBOC patients, prophylactic total mastectomy can reduce the risk for breast cancer by 90%, and a bilateral salpingo-oophorectomy, after childbearing or by age 40, can reduce the risk of ovarian cancer by up to 96% and the risk of breast cancer by up to 68%.
- Consider preimplantation genetic diagnosis in conjunction with in vitro fertilization.

REFERRAL

If services are needed beyond one's practice or comfort level, consider consulting with knowledgeable genetic counselors, gynecologists, gynecologic oncologists, breast surgeons, and gastroenterology specialists, among others.

! PEARLS & CONSIDERATIONS

- Be vigilant. Be motivated by the risks: Women with these mutations are approximately 10 times more likely to develop breast cancer and 20 to 30 times more likely to develop ovarian cancer. Look for red flags during every encounter, regardless of the patient's chief complaint or scheduled visit type, and inquire and regularly update information about the patient's personal and family history of cancer. Consider that approximately 10% of general practice patients have a significant family history. Supply a printed family history questionnaire. Always consider your patient's cancer risk, especially when charting a new treatment course or planning a surgical procedure. Oftentimes, a more comprehensive approach may be taken if a patient proves to be a mutation carrier.
- Adjust the age at which screening/treatment is initiated and the frequency of the visits depending on the age of the youngest affected family member, the at-risk cancer site, and the carrier status of the patient.
- Encourage input from the patient during the screening, workup, follow-up, and treatment.
- Recommend that the patient verify any questionable family history, collect appropriate family documentation/testing, and involve her family in the process; this involvement can include advising, counseling, and testing for close relatives.
- Try to counsel and test (if appropriate) those family member(s) who, if tested, would render testing of progeny/other family members less necessary. Testing an affected family member is oftentimes the most appropriate, efficient, cost-effective, and informative approach.
- Genetic testing can more accurately predict risk and enable a more tailored management approach than relying on one's family history alone. Be mindful that there may be other, although as yet unidentified, mutations at the root of one's patient's personal or family cancer history.
- Refer to your professional societies and the NCCN for screening and surveillance/imaging/treatment guidelines. Don't hesitate to engage the assistance of a genetic counselor, gynecologist, oncologist, breast surgeon, and/or a gastroenterologist during this initial phase.
- Involve other appropriate specialists in the patient's short- and long-term care, depending on the at-risk anatomic systems.
- Remember that *BRCA1*- and *BRCA2*-positive men are at a significantly higher risk for breast and prostate cancer.
- Consider prophylactic bilateral mastectomy or bilateral salpingo-oophorectomy.
- Encourage high-risk patients to complete childbearing at a younger age and consider, as appropriate, subsequent prophylactic bilateral salpingo-oophorectomy and menopause hormone therapy options.
- Recommend prophylactic bilateral salpingectomy for at-risk patients during any other surgical procedure—once childbearing is complete. Consider such assistive reproductive options as preimplantation genetic diagnosis.
- Genetic information cannot be used as the basis for a "preexisting condition" with regard to health insurance or employment, according to federal and state laws. It may play a role in life insurance, disability insurance, and long-term care insurance.
- While insurance coverage generally is available, panel testing reimbursement may occasionally be challenged. Vocalize and document your support of the appropriate testing and management, with both your patient and her/his insurance company. Enlist the assistance of your local professional society, as needed.
- There may be a medical-legal risk if a failure to identify and/or genetically counsel or test a high-risk patient and/or her family results in a delay in the diagnosis of breast or ovarian cancer. The provider, laboratory, insurance company, and the employer may have legal exposure for failing to order testing, for providing inaccurate results, or for denial of coverage, respectively.
- Being aware of a patient's cancer risk facilitates initiation of those preventive screenings and management strategies that have been shown to reduce the likelihood of cancer and improve early cancer detection rates. This can be of tremendous benefit for the patient's family members as well as the patient.

PREVENTION

Consider appropriate screening and surveillance (awareness/physical exam by patient and health care provider, imaging studies, diagnostic procedures, counseling, and genetic testing) as well as prophylactic surgery and chemopreventive measures.

PATIENT & FAMILY EDUCATION

Always encourage patients to revisit their personal and family history and to update this information with all of their health care providers and their family members. Recommend that patients initiate discussions with their family members and other health care providers in an ongoing effort to reduce their and their loved ones' risk of heritable cancer.

Refer to NCCN guidelines (www.nccn.org) and national specialty society recommendations.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Breast Cancer (Related Key Topic)
Lynch Syndrome (Related Key Topic)
Ovarian Cancer (Related Key Topic)

AUTHOR: **David I. Kurss, MD, FACOG, NCMP**

SUGGESTED READINGS

Hartmann LC, Lindor NM: The role of risk-reducing surgery in hereditary breast and ovarian cancer, *N Engl J Med* 374:454-468, 2016.

Heemskerk-Gorritsen BA et al: Breast cancer risk after salpingo-oophorectomy in health *BRCA1/2* mutation carriers: revisiting the evidence for risk reduction, *J Natl Cancer Inst* 107:107, 2015.

Hereditary Hemorrhagic Telengiectasia

BASIC INFORMATION

DEFINITION

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Rendu-Weber syndrome, is a hereditary vascular disorder characterized by the development of arteriovenous malformations throughout the body.

SYNONYMS

Osler-Rendu-Weber syndrome
HHT
Osler disease

ICD-10CM CODE
I78.0 Hereditary hemorrhagic telangiectasia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1 in 8,000 to 16,500
PREVALENCE: Approximately 1.2 million people worldwide
PREDOMINANT SEX AND AGE:
- Men = women
- Individual variability

GENETICS: Inherited dominant mutation. Mutations in the endoglin gene, a cell surface component of the transforming growth factor–β (TGF-β) receptor complex, causes this syndrome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Recurrent epistaxis and gastrointestinal (GI) bleeds due to lesions in the oropharyngeal epithelium and gut. The most common manifestation is recurrent and spontaneous epistaxis occurring in 90% to 95% of patients due to fragile telangiectasia on the nasal mucosa.
- 40% to 50% of patients develop GI bleeding sometime during the course of their disease.
- Telangiectasia lesions may be present on the lips, tongue (Fig. E1), nasal mucosa, retina, hands, chest, and lower extremities. There may be many erythematous macules and papules.
- Telangiectasias either are round and mildly raised or are stellate without a well-defined border.
- Mucocutaneous lesions are 1 to 4 mm, sharply demarcated red to purple macules, or spiderlike projections. They usually develop at puberty.

FIG. E1 Hereditary hemorrhagic telangiectasia. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Elsevier.)

- Arteriovenous (AV) malformations of the lungs, central nervous system, or liver.
- Multiple AV malformations causing liver involvement or atypical cirrhosis are rare but can occur. Liver left-to-right shunting can predispose patients to high-output heart failure.

ETIOLOGY

- Autosomal dominant disorder with incomplete penetrance.
- Mutations in *ENG* and *ACVRLK1* that code for endoglin and ALK, which are TGF-β receptors that function in integrity of vessel structures.
- Type 1 (HHT_1) is due to loss of function gene mutation of *ENG* (9q3).
- Type 2 (HHT_2) is due to loss of function gene mutation of *ALK1* (12q13).
- There is a third type of HHT associated with juvenile polyposis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Generalized essential telangiectasia
- Unilateral nevoid telangiectasia
- Scleroderma with CREST syndrome
- Rosacea
- Actinic keratosis
- Ataxia telangiectasia
- Venous hypertension
- Cushing syndrome

WORKUP

Diagnosis can generally be made from a detailed history and physical exam if at least three of these four criteria are present:
1. Spontaneous recurrent epistaxis
2. Multiple telangiectasias (in multiple sites such as face, mouth, and lips)
3. Visceral lesions such as arteriovenous malformations (AVMs) may result in GI bleeding or hepatic, pulmonary, cerebral, or spinal hemorrhage
4. First-degree relative with diagnosed HHT

If two criteria are present, there is a possible diagnosis.

LABORATORY TESTS

- Complete blood cell count (CBC), including platelet count, to evaluate anemia and rule out thrombocytopenia; coagulation profile. Patients with this disorder have normal levels of clotting factors and an intact clotting mechanism
- Ferritin level, stool for occult blood
- Endoscopy (upper and lower), angiography

IMAGING STUDIES

- Electron microscopy shows lack of pericytes.
- Chest radiograph.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Laser ablation of symptomatic lesions
- GI bleeding prophylaxis
- Angiographic embolization
- Segmental bowel resection
- Surgical correction of AV malformations
- Dermoplasty of the bleeding nasal septum

ACUTE GENERAL Rx

- Optimal therapy remains elusive. Trials comparing topical intranasal treatment with bevacizumab vs. estriol vs tranexamic acid vs. nasal saline spray showed that there was no advantage to topical therapy with these medications compared with frequent saline sprays for reducing the frequency of epistaxis in patients with HHT.
- In those without a history of pulmonary AV malformations, tamoxifen 20 mg/day (antiestrogen) or aminocaproic acid (antifibrinolytic) therapies may be considered.
- In severe cases may consider use of agents such as thalidomide or lenalidomide to block VEGF (high VEGF levels lead to disorganized and tortuous vessels).
- Trials suggest some potential use of phosphoinositide 3-kinase inhibitor BKM120.

CHRONIC Rx

Iron replacement for anemia due to blood loss

DISPOSITION

Prognosis depends on areas affected by AV malformations.

REFERRAL

To ENT and vascular surgeon for correction of vascular malformations, gastroenterologist for esophagogastroduodenoscopy

PEARLS & CONSIDERATIONS

- Primary manifestations usually occur before puberty and are characterized as epistaxis. Later, hemorrhages of GI and genitourinary (GU) tracts occur.
- Vascular abnormalities may result in portal hypertension, pulmonary AV malformations with hemoptysis, cerebrovascular accidents, and hematuria in addition to GI bleeding and anemia.
- Genetic screening of first-degree relatives should be performed.
- 5% to 10% of patients have pulmonary AV malformations.
- In two thirds of individuals who have neurologic symptoms, the source is pulmonary AV malformations.
- Those with history of pulmonary AV malformations require antibacterial prophylaxis for surgical or dental operations.
- Approximately 15% to 20% of patients with AV malformations in the lungs present with stroke due to embolic abscesses.

COMMENTS

Affected children may experience recurrent epistaxis before detection of the characteristic skin and mucous membrane lesions.

PREVENTION

Seek genetic counseling if one has a family history of Osler-Rendu-Weber syndrome.

PATIENT & FAMILY EDUCATION

HHT Foundation International: http://hht.org

AUTHORS: **Fred F. Ferri, MD,** and **Heather Ferri, DO**

SUGGESTED READINGS

Dupuis-Girod S et al: Effect of bevacizumab nasal spray on epistaxis duration in hereditary hemorrhagic telangiectasia, *JAMA* 316(9):934-942, 2016.

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Herpangina PTG

BASIC INFORMATION

DEFINITION

Herpangina is a self-limited upper respiratory tract infection associated with a characteristic vesicular rash on the soft palate.

SYNONYMS

Vesicular stomatitis
Acute lymphonodular pharyngitis

ICD-10CM CODE
B08.5 Enteroviral vesicular pharyngitis

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: Male = female
PREDOMINANT AGE: 3 to 10 yr

PHYSICAL FINDINGS & CLINICIAL PRESENTATION

- Characterized by ulcerating lesions typically located on the soft palate (Fig. E1)
- Usually fewer than six lesions that evolve rapidly from a diffuse pharyngitis to erythematous macules and subsequently to vesicles that are moderately painful
- Fever, vomiting, and headache in the first few days of illness but subsiding spontaneously
- Pharyngeal lesions typical for several more days

ETIOLOGY

- Most cases caused by coxsackie A viruses (most frequently A8, A10, and A16).
- Occasional cases caused by other enteroviruses (echovirus and enterovirus 71).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Herpes simplex
- Bacterial pharyngitis
- Tonsillitis
- Aphthous stomatitis
- Hand-foot-mouth disease

WORKUP

Diagnosis is typically based on characteristic lesions on the soft palate.

LABORATORY TESTS

- Viral and bacterial cultures of the pharynx to exclude herpes simplex infection and streptococcal pharyngitis if the diagnosis is in doubt.
- The type-specific antibodies appear in the blood about 1 wk after infection has occurred and attain their maximum titer in 3 wk.

FIG. E1 Herpangina with shallow ulcers in the roof of the mouth. (From Bennett JE et al [eds]: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.)

TREATMENT

- Give symptomatic treatment for sore throat: Saline gargles and analgesics, and encourage oral fluids.
- No antiviral therapy indicated; avoid antibacterial agents because they are ineffective, increase cost, might result in side effects, and promote antibiotic resistance.

NONPHARMACOLOGIC THERAPY

Analgesic throat lozenges are helpful in some cases.

ACUTE GENERAL Rx

Antipyretics when indicated

CHRONIC Rx

Self-limited infection

DISPOSITION

- Generally, resolution of symptoms within 1 wk
- Persistence of fever or mouth lesions beyond 1 wk suggestive of an alternative diagnosis (see "Differential Diagnosis")

REFERRAL

For consultation with otolaryngologist or infectious disease specialist if the diagnosis is in doubt.

PEARLS & CONSIDERATIONS

COMMENTS

Household outbreaks may occur, especially during the summer months.

RELATED CONTENT

Herpangina (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

BASIC INFORMATION

DEFINITION

Herpes simplex is a viral infection caused by the herpes simplex virus (HSV). HSV-1 is associated primarily with oral infections, and HSV-2 causes mainly genital infections. However, either type can infect any site. After the primary infection, the virus enters the nerve endings in the skin directly below the lesions and ascends to the dorsal root ganglia, where it remains in a latent stage until it is reactivated.

SYNONYMS

Genital herpes
Herpes labialis
Herpes gladiatorum
Herpes digitalis
Oral herpes

ICD-10CM CODES	
A60	Anogenital herpesviral (herpes simplex) infections
A60.04	Herpesviral vulvovaginitis
B00	Herpesviral (herpes simplex) infections
B00.1	Herpesviral vesicular dermatitis
B00.82	Herpes simplex myelitis
B00.9	Herpesviral infection, unspecified
P35.2	Congenital herpesviral (herpes simplex) infection

EPIDEMIOLOGY & DEMOGRAPHICS

- More than 85% of adults have serologic evidence of HSV-1 infection. The seroprevalence of adults with HSV-2 in the U.S. is 25%; however, only approximately 20% of these persons recall having symptoms of HSV infection.
- Most cases of eye or digital herpetic infections are caused by HSV-1.
- Worldwide, more than 400 million persons have genital herpes caused by HSV-2. In the U.S., 1 in 5 adults is infected with HSV-2, and 1 million new infections occur yearly.
- Frequency of recurrence of HSV-2 genital herpes is higher than HSV-1 oral labial infection.
- The frequency of recurrence is lowest for oral labial HSV-2 infections.
- The incidence of complications from herpes simplex (e.g., herpes encephalitis) is highest in immunocompromised hosts.
- Male circumcision significantly reduces the incidence of HSV-2.

PHYSICAL FINDINGS & CLINICIAL PRESENTATION

PRIMARY INFECTION:

- Symptoms occur from 3 to 7 days after contact (respiratory droplets, direct contact).
- Constitutional symptoms include low-grade fever, headache and myalgias, regional lymphadenopathy, and localized pain.
- Pain, burning, itching, and tingling last several hours.
- Grouped vesicles, usually with surrounding erythema, appear and generally ulcerate or crust within 48 h (Fig. E1).
- The vesicles are uniform in size (differentiating it from herpes zoster vesicles, which vary in size). Scattered erosions covered with exudate may be noted on genitals (Fig. E2).
- During the acute eruption the patient is uncomfortable; involvement of lips and inside of mouth (Fig. E3) may make it unpleasant for the patient to eat; urinary retention may complicate involvement of the genital area.
- Lesions generally last from 2 to 6 wk and heal without scarring.

RECURRENT INFECTION:

- Generally caused by alteration in the immune system; fatigue, stress, menses, local skin trauma, and exposure to sunlight are contributing factors.
- The prodromal symptoms (fatigue, burning and tingling of the affected area) last 12 to 24 hr.
- A cluster of lesions generally evolves within 24 hr from a macule to a papule and then vesicles surrounded by erythema; the vesicles coalesce and subsequently rupture within 4 days, revealing erosions covered by crusts.
- The crusts are generally shed within 7 to 10 days, revealing a pink surface.
- The most frequent location of the lesions is on the vermilion border of the lips (HSV-1), the penile shaft or glans penis and the labia (HSV-2), buttocks (seen more frequently in women), fingertips (herpetic whitlow), and trunk (may be confused with herpes zoster).
- Rapid onset of diffuse cutaneous herpes simplex (eczema herpeticum) may occur in certain atopic infants and adults. It is a medical emergency, especially in young infants, and should be promptly treated with acyclovir.
- Herpes encephalitis, meningitis, and ocular herpes can occur in patients with immunocompromised status and occasionally in normal hosts.

ETIOLOGY

HSV-1 and HSV-2 are both DNA viruses.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Impetigo
- Behçet syndrome
- Coxsackie virus infection
- Syphilis
- Stevens-Johnson syndrome
- Herpangina
- Aphthous stomatitis
- Varicella
- Herpes zoster

WORKUP

Diagnosis is based on clinical presentation. Laboratory evaluation confirms diagnosis.

LABORATORY TESTS

- Direct immunofluorescent antibody slide tests provide a rapid diagnosis.
- Viral culture is the most definitive method for diagnosis; results are generally available in 1 or 2 days. The lesions should be sampled during the vesicular or early ulcerative stage; cervical samples should be taken from the endocervix with a swab.
- Pap smear will detect HSV-infected cells in cervical tissue from women without symptoms.
- Serologic tests for HSV: Immunoglobulin (Ig) G and IgM serum antibodies. Antibodies to HSV occur in 50% to 90% of adults. The presence of IgM or a fourfold or greater rise in IgG titers indicates a recent infection (convalescent sample should be drawn 2 to 3 wk after the acute specimen is drawn).
- Tzanck smear is a readily available test that will demonstrate multinucleated giant cells. However, it is not a highly sensitive test.

TREATMENT

- Table 1 summarizes antiviral chemotherapy for HSV infection.
- Topical acyclovir, penciclovir, and docosanol are optional treatments for recurrent herpes labialis, but they are less effective than oral treatments.

DISPOSITION

Most patients recover from the initial episode or recurrences without complications; immunocompromised hosts are at risk for complications (e.g., disseminated herpes simplex infection, herpes encephalitis).

REFERRAL

- Hospital admission in patients with herpes encephalitis or herpes meningitis and in immunocompromised hosts with diffuse herpes simplex infection
- Ophthalmology referral in patients with suspected ocular herpes

PEARLS & CONSIDERATIONS

COMMENTS

- Provide patient education regarding transmission of HSV.
- Condom use offers significant protection against HSV-1 infection in susceptible women.
- Patients should be instructed on the use of condoms for sexual intercourse and on avoiding kissing or sexual intercourse until lesions are crusted. Pericoital application of tenofovir gel, an antiretroviral vaginal gel, has also been shown to reduce the risk of HSV-2 in women. This may be useful in regions of the world where use of condoms is shunned.
- Patients should also avoid contact with immunocompromised hosts or neonates while lesions are present.

TABLE 1 Topical and Oral Antiviral Medications Used for Herpes Simplex Virus Infections*

Drug	Formulation	Regimen	Indication/Comment
Topical			
Acyclovir	5% cream (2 g, 5 g)	Apply 5 times/day	Recurrent HL; A: ≥12 yr; 4 days; Rx
	5% ointment (15 g, 30 g)	Apply 6 times/day	Initial GH, localized HSV; A: adults; 7 days; Rx
Penciclovir	1% cream (1.5 g, 5 g)	Apply q2h (awake)	Recurrent HL; A: ≥12 yr; 4 days; Rx
Docosanol	10% cream (2 g)	Apply 5 times/day	HL; A: ≥12 yr; treat until healed; OTC
Oral (all Rx)			
Acyclovir	200 mg capsule		A: ≥2 yr
	400 mg, 800 mg tablet		
	200 mg/5 ml susp		
		200 mg 5 times/day	Initial GH; 10 days
		200 mg 5 times/day	Recurrent GH; 5 days
		400 mg 2 times/day	Suppression, recurrent GH; up to 12 mo, then reevaluate
Famciclovir	125, 250, 500 mg tablet		A: ≥18 yr
		1500 mg single dose	Recurrent HL
		1000 mg 2 times/day	Recurrent GH; 1 day
		250 mg 2 times/day	Suppression, recurrent GH; up to 12 mo
Valacyclovir	500 mg, 1 g caplet		A: adults and ≥12 yr for HL
		1 g 2 times/day	Initial GH; 10 days
		500 mg 2 times/day	Recurrent GH; 3 days
		500 mg-1 g once daily	Suppressive GH
		2 g 2 times/day	HL; 1 day; both adults and children ≥12 yr

*Approved indications and regimens listed; often used off-label.
A, Approved; *GH,* genital herpes; *HL,* herpes labialis; *HSV,* herpes simplex virus; *OTC,* over-the-counter; *Rx,* by prescription.
From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.

- Proper handwashing techniques should be explained.
- Patients with herpes gladiatorum (cutaneous herpes in athletes involved in contact sports) should be excluded from participation in active sports until lesions have resolved.
- Many new HSV-2 infections are asymptomatic. Since HSV-2 antibody tests have become commercially available, an increasing number of persons have learned that they have genital herpes through serologic testing. Persons with asymptomatic HSV-2 infection shed virus in the genital tract less frequently than persons with symptomatic infection, but much of the difference is attributable to less frequent genital lesions because genital lesions are accompanied by frequent viral shedding. The U.S. Preventive Services Task Force (USPSTF) recommends against routine serologic screening for genital HSV infection in asymptomatic adolescents and adults, including those that are pregnant.
- Suppressive treatment of HSV-2 infection lowers the incidence of genital lesions by 70% to 80%, but cuts the rate of HSV-2 transmission to uninfected partners by only 50%.
- Pregnancy: Antiviral prophylaxis with acyclovir is recommended from 36 wk of gestation until delivery in women with a history of genital herpes. Elective cesarean delivery should be performed in laboring patients with active lesions to decrease the risk of neonatal herpes.
- Trials involving investigational herpes simplex vaccine have found it to be effective in preventing HSV-1 genital disease and infection, but not in preventing HSV-2 disease or infection.

RELATED CONTENT

Genital Herpes (Patient Information)
Oral Herpes (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

FIG. E1 Herpetic gingivostomatitis. Multiple erosions with crusting. Note the associated lesions involving the chin. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence*, ed 5, 2016, Elsevier.)

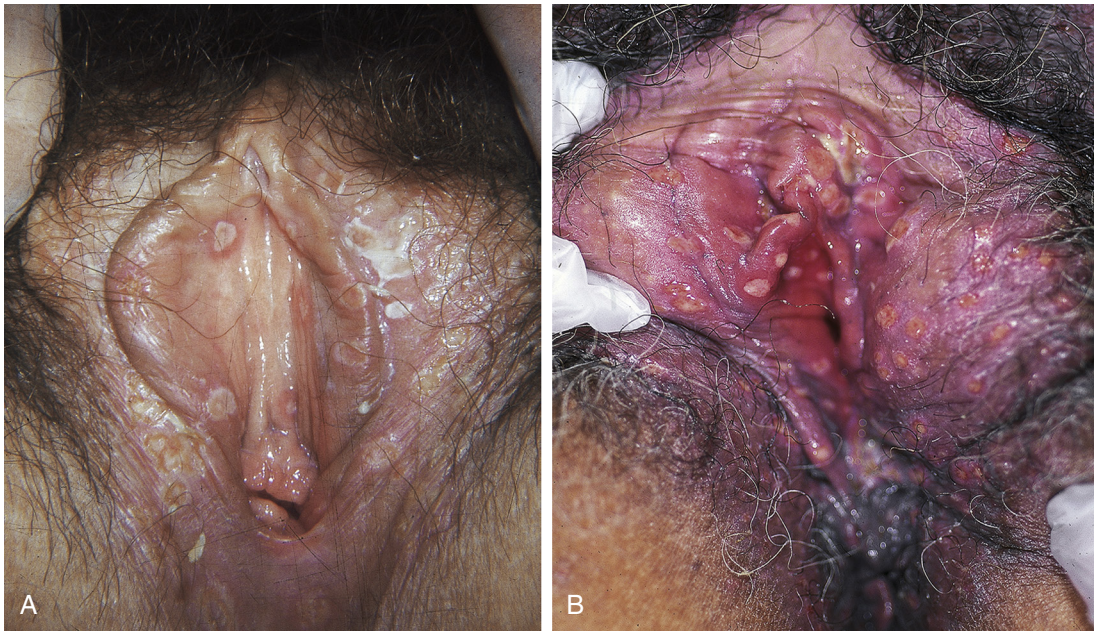

FIG. E2 Primary herpes simplex. A, Scattered erosions covered with exudate. **B,** Numerous erosions appeared 4 days after contact with an asymptomatic carrier. (From Habif TP: *Clinical dermatology*, ed 4, Philadelphia, 2004, Mosby.)

FIG. E3 Herpes labialis. Erythematous erosions clustered on the right lower lip in a patient with labial herpes. This young girl also had herpes-associated erythema multiforme. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence*, ed 5, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Corneal infection with herpes simplex virus (HSV-1 or HSV-2).

SYNONYMS

Herpes simplex keratoconjunctivitis
Herpes simplex dendritic keratitis
Herpes simplex stromal keratitis
Herpetic keratitis

ICD-10CM CODE
B00.52 Herpes viral keratitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 5/100,000 to 15/100,000 per yr
PEAK INCIDENCE: After an episode of ocular HSV, there is a 30% chance of a recurrence within a 1-yr period.
PREVALENCE: 149/100,000 people
PREDOMINANT SEX & AGE: Equal, although some studies report a slight male predominance. There are no known patterns of age of presentation.
GENETICS: There are no known patterns of genetic inheritance.
RISK FACTORS: Risk factors include close physical contact with an HSV disease carrier and primary or latent infection with HSV-1 or HSV-2. Neonatal ocular HSV can result from direct maternal transmission. The landmark Herpetic Eye Disease Study (HEDS) found that prior stromal keratitis increases the chances of recurrent stromal keratitis, but prior epithelial keratitis does not increase the chance of recurrent epithelial keratitis. That study also found that proposed triggers of recurrent disease, including psychological stress, systemic infection, sunlight exposure, menstruation, contact lens wear, and eye injury, are not associated with an increased recurrence rate.

PHYSICAL FINDINGS & CLINCIAL PRESENTATION

- Ocular manifestations of HSV infection include periocular vesicular skin lesions, conjunctival injection, follicular conjunctivitis, iridocyclitis, elevated intraocular pressure, and keratitis.
- Patients commonly present with a red eye, ocular pain, tearing, and/or photophobia.
- HSV can affect any part of the cornea and present as epithelial keratitis, stromal keratitis, or endotheliitis. Corneal findings are best visualized using slit-lamp microscopy. Classic dendritic lesions in epithelial keratitis can be seen with a cobalt blue light or a Wood's light following administration of topical fluorescein.
- Presentation is usually unilateral and may occur in the setting of a concurrent upper respiratory infection or other systemic conditions. Recurrent HSV infections may occur in a patient with a history of prior "eye infections."

ETIOLOGY

HSV keratitis results from HSV-1 or (less commonly) HSV-2 infection of the cornea and the subsequent host immune and inflammatory response. HSV keratitis most often represents reactivation of a latent infection in the trigeminal ganglion. Primary infection is rarely clinically evident.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Herpes zoster ophthalmicus, corneal abrasion, recurrent corneal erosion, viral conjunctivitis, allergic conjunctivitis, acanthamoeba keratitis

WORKUP

Ocular HSV disease is most often a clinical diagnosis, although diagnosis may be aided by cytologic, molecular, and immunologic assays described in the following.

LABORATORY TESTS

Culture of corneal or vesicular skin lesion scrapings or cytologic examination with Giemsa stain. PCR and a variety of immunologic assays can also aid with diagnosis but are of limited availability. Serologic antibody testing can help exclude HSV as a diagnosis with a negative result, but positive results are of limited value given the high seroprevalence of HSV.

TREATMENT

The treatment of ocular herpetic disease is determined by the location and extent of disease involvement, with several recommendations resulting from the HEDS study. Oral antivirals and topical antivirals are the mainstay of treatment. Topical antivirals are typically reserved for epithelial keratitis. Oral antivirals are preferred for stromal and endothelial disease. Topical antibiotics and topical corticosteroids are also used in select cases.

NONPHARMACOLOGIC THERAPY

- Corneal epithelial involvement may benefit from the addition of epithelial debridement, and nonhealing epithelial defects may be addressed with bandage contact lenses or tarsorrhaphy.
- After resolution of keratitis, corneal stromal scars may be managed surgically with partial-thickness (i.e., deep anterior lamellar keratoplasty) or full-thickness penetrating keratoplasty (corneal transplantation).

ACUTE GENERAL Rx

- Systemic antiviral treatment options: Acyclovir 400 mg PO five times daily, valacyclovir 500 mg PO bid, famciclovir 125 to 250 mg PO bid for 7 to 14 days
- Eyelid involvement only: Systemic antiviral, antibiotic ointment bid, and warm or cool compresses PRN for comfort
- Eyelid margin, corneal epithelial, and/or conjunctival involvement: Systemic antiviral or topical antiviral (ganciclovir 0.15% gel, trifluridine 1% drops) five times daily, topical antibiotic qid (i.e., fourth-generation fluoroquinolone)
- Corneal stromal involvement: Systemic antiviral, topical steroid (i.e., prednisolone acetate 1% qid), cycloplegic (i.e., cyclopentolate 1% bid)
- Iridocyclitis/trabeculitis: Systemic antiviral, topical steroids with or without systemic steroids

CHRONIC Rx

- When used, topical antivirals are typically continued for 1 to 2 wk until the epithelial defect is healed.
- Topical steroids for corneal stromal involvement are tapered slowly over wks to mos.
- Prophylactic oral antivirals (acyclovir 400 mg or famciclovir 125 mg PO bid) may be used indefinitely for severe cases and have been shown to reduce the rate of recurrences.

DISPOSITION

Patients with ocular HSV require referral and close follow-up with ophthalmology, initially every 1 to 2 days, with extended follow-up based on clinical course.

REFERRAL

A patient with suspected ocular herpetic disease should be started on systemic antivirals and then referred promptly for evaluation by an ophthalmologist.

PEARLS & CONSIDERATIONS

COMMENTS

Herpes simplex is one of the most common causes of corneal blindness. Physicians from all specialties should be aware of the high seroprevalence of the herpes simplex virus and maintain a high index of suspicion for ocular herpetic disease when patients with or without a known history of herpes simplex present with ocular complaints such as red eye, ocular pain, and photophobia. Treatment with systemic antiviral medication and prompt referral to an ophthalmologist are crucial early steps in the management of suspected disease.

PREVENTION

Despite significant interest, there is currently no HSV vaccine available. Given the high prevalence of HSV in the community, it is difficult to prevent systemic and ocular HSV infection. In

patients who have a history of ocular HSV, there is evidence to support the efficacy of maintenance systemic antiviral medication to prevent disease recurrences.

PATIENT & FAMILY EDUCATION

American Academy of Ophthalmology: http://www.aao.org/eye-health/diseases/herpes-keratitis

RELATED CONTENT

Herpes Simplex (Related Key Topic)
Herpes Zoster (Related Key Topic)

AUTHOR: **Thomas H. Dohlman, MD**

SUGGESTED READING

White ML, Chodosh J: Herpes simplex virus keratitis: a treatment guideline 2014, *Ophthalmology* 2014. Available at https://www.aao.org/clinical-statement/herpes-simplex-virus-keratitis-treatment-guideline.

BASIC INFORMATION

DEFINITION

Herpes zoster is a disease caused by reactivation of the varicella-zoster virus, with spread of the virus alone from the sensory nerve to the dermatome. After the primary infection (chickenpox), the virus becomes latent in the dorsal root ganglia and reemerges when there is a weakening of the immune system (as a result of disease or advanced age). Over 90% of the adult U.S. population is latently infected with varicella zoster virus.

SYNONYMS

Shingles
HZ

ICD-10CM CODES

B02	Herpes zoster
B02.0	Zoster encephalitis
B02.1	Zoster meningitis
B02.30	Zoster ocular disease, unspecified
B02.31	Zoster conjunctivitis
B02.32	Zoster iridocyclitis
B02.33	Zoster keratitis
B02.34	Zoster scleritis
B02.39	Other herpes zoster eye disease
B02.7	Disseminated zoster
B02.8	Zoster with other complications
B02.9	Zoster without complications

EPIDEMIOLOGY & DEMOGRAPHICS

- Herpes zoster occurs during the lifetime of 10% to 20% of the population. There are approximately 1 million cases annually in the U.S. The incidence of herpes zoster has increased fourfold over the past six decades.
- There is an increased incidence in immunocompromised patients (chemotherapy, radiotherapy, immunosuppression due to corticosteroids, AIDS, DM, malignancy), the elderly (most common after age 60) (Fig. E1), and children who acquired chickenpox when younger than 2 mo.

PHYSICAL FINDINGS & CLINICIAL PRESENTATION

- Pain generally precedes skin manifestation by 3 to 5 days and is generally localized to the dermatome that will be affected by the skin lesions.
- Constitutional symptoms are often present (malaise, fever, headache).
- The initial rash consists of erythematous maculopapules generally affecting one dermatome (thoracic region in majority of cases [Fig. E2]). Typically the rash does not cross the midline. Some patients (<30%) may have scattered vesicles outside the affected dermatome. In rare cases the rash can be generalized (Fig. E3).
- The initial maculopapules evolve into vesicles and pustules by the third or the fourth day.
- The vesicles have an erythematous base (Fig. E4), are cloudy, of various sizes (a distinguishing characteristic from herpes simplex, in which the vesicles are of uniform size), and may have a classic appearance of grouped vesicles (Fig. E5).
- The vesicles subsequently become umbilicated and then form crusts that generally fall off within 3 wk; scarring may occur.
- Pain during and after the rash is generally significant. Postherpetic neuralgia occurs after herpes zoster in approximately one third of patients aged 60 yr and older and can persist for mos or yrs.
- Secondary bacterial infection with *Staphylococcus aureus* or *Streptococcus pyogenes* may occur.
- Regional lymphadenopathy may occur.
- Herpes zoster may involve the trigeminal nerve (most frequent cranial nerve involved); involvement of the first division of the trigeminal nerve is known as "herpes zoster ophthalmicus" and can result in blindness. The appearance of blisters on the tip of the nose (Hutchinson sign) is a common manifestation of herpes zoster ophthalmicus. Involvement of the geniculate ganglion can cause facial palsy and a painful ear, with the presence of vesicles on the pinna and external auditory canal (Ramsay Hunt syndrome).
- Pain typical of herpes zoster in the absence of cutaneous lesions, known as "Zoster sine herpete," is rare.

ETIOLOGY

Reactivation of varicella virus (human herpes virus III)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rash: Herpes simplex and other viral infections, contact dermatitis
- Pain from herpes zoster: May be confused with acute myocardial infarction, pulmonary embolism, pleuritis, pericarditis, renal colic

WORKUP

The diagnosis of herpes zoster is usually made by the characteristic dermatomal presentation.

LABORATORY TESTS

Laboratory tests are generally not necessary. In cases where the clinical diagnosis is not obvious, PCR testing for varicella zoster virus is has high sensitivity and specificity. It is readily available and results can usually be obtained in less than 24 hours. Other laboratory studies for diagnosis of herpes zoster include viral culture, DFA, and serologic testing.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Wet compresses (using Burow solution or cool tap water) applied for 15 to 30 min five to ten times a day may be useful to break vesicles and remove serum and crust. Then carefully pat dry.
- Care must be taken to prevent any secondary bacterial infection by keeping cutaneous lesions clean and dry.

ACUTE GENERAL Rx

- Oral antiviral agents can shorten the disease course and help prevent post-herpetic neuralgia. They can decrease acute pain, inflammation, and vesicle formation when treatment is begun within 72 hr of onset of rash. Treatment options are:
  1. Valacyclovir 1000 mg tid for 7 days
  2. Famciclovir 500 mg tid for 7 days
  3. Acyclovir 800 mg 5 times daily for 7 to 10 days
- The role of corticosteroids in herpes zoster is controversial. Many physicians prescribe them to improve rash healing and reduce pain severity; however, a Cochrane review failed to show sufficient evidence to support the use of corticosteroids for the prevention of postherpetic neuralgia. Corticosteroids can be considered in older patients within 72 hr of clinical presentation or if new lesions are still appearing if there are no contraindications to their use. Initial dose is prednisone 60 mg/day decreased by 5 mg/day until finished.
- Immunocompromised patients and patients with herpes zoster complicated by CNS involvement should be treated with IV acyclovir 10 to 15 mg/kg q8h in 1-hr infusions for 7 days, with close monitoring of renal function and adequate hydration; vidarabine (continuous 12-hr infusion of 10 mg/kg/day for 7 days) is also effective for treatment of disseminated herpes zoster in immunocompromised hosts.
- Patients with AIDS and transplant recipients may develop acyclovir-resistant varicella-zoster; these patients can be treated with foscarnet (40 mg/kg IV q8h) continued for at least 10 days or until lesions are completely healed.
- Postherpetic neuralgia:
  1. Gabapentin 100 to 600 mg tid is effective in the treatment of pain and sleep interference associated with postherpetic neuralgia. Other effective agents are pregabalin, duloxetine, and tricyclic antidepressants.
  2. Lidocaine patch 5% is also effective in relieving postherpetic neuralgia. Patches are applied to intact skin after resolution of blisters and crusts to cover the most painful area for up to 12 hr within a 24-hr period.
  3. Capsaicin cream can be useful for treatment of postherpetic neuralgia. It is generally applied 3 to 5 times daily for several weeks after the crusts have fallen off. A topical 8% patch formulation of capsaicin is now available by prescription for postherpetic neuralgia.
  4. Sympathetic blocks (stellate ganglion or epidural) with 0.25% bupivacaine and rhizotomy are reserved for severe cases unresponsive to conservative treatment.

DISPOSITION

- The incidence of postherpetic neuralgia (defined as pain that persists more than 90 days after onset of rash) increases with age (<30% by age 40 yr, >70% by age 70 yr); antivirals reduce the risk of postherpetic neuralgia.
- Incidence of disseminated herpes zoster is increased in immunocompromised hosts (e.g., 15% to 50% of patients with active Hodgkin disease).
- Immunocompromised hosts are also more prone to neurologic complications (encephalitis, myelitis, cranial and peripheral nerve palsies, acute retinal necrosis). The mortality rate is 10% to 20% in immunocompromised hosts with disseminated zoster.
- Motor neuropathies occur in 5% of all cases of zoster; complete recovery occurs in >70% of patients.
- Rates of HZ recurrence are more frequent than previously reported and are comparable to rates of first HZ occurrence in immunocompetent individuals.

REFERRAL

- Hospitalization for IV acyclovir in patients with disseminated herpes zoster.
- Patients with herpes zoster ophthalmicus should be referred to an ophthalmologist.
- Consultation with an otolaryngologist is advisable in patients with Ramsey Hunt syndrome.
- Vaccination: In the absence of the herpes zoster vaccine, persons who live to 85 yr of age have a 50% risk of herpes zoster. Immunocompetent adults ≥50 yr (including those who have already received Zostavax) are appropriate candidates for recombinant varicella zoster virus vaccine (Shingrix). It consists of 2 doses 2 to 6 mo apart and is preferred over Zostavax for herpes zoster prevention. Adults who are VZV seronegative (never had varicella) should be immunized against varicella with two doses of varicella vaccine (Varivax). Despite its efficacy and safety, use of this vaccine remains low (<8% of potential recipients).

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Shingles (Patient Information)
Postherpetic Neuralgia (Related Key Topic)
Ramsey Hunt Syndrome (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

FIG. E1 Herpes zoster, involvement of the V1 dermatome. (From James WD et al: *Andrews' diseases of the skin: clinical dermatology,* ed 12, Philadelphia, 2016, Elsevier.)

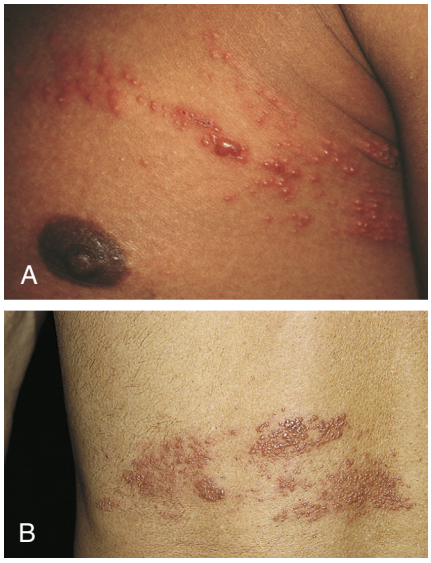

FIG. E2 A and **B,** Herpes zoster lesions in T3 distribution. (From Swartz MH: *Textbook of physical diagnosis,* ed 7, Philadelphia, 2014, WB Saunders.)

FIG. E3 Herpes zoster, generalized. (From Swartz MH: *Textbook of physical diagnosis,* ed 7, Philadelphia, 2014, WB Saunders.)

FIG. E4 Herpes zoster occurred in this 3-year-old. She had chickenpox at age 18 mo. The varicella-zoster virus causes both conditions. Spontaneous resolution can be expected. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

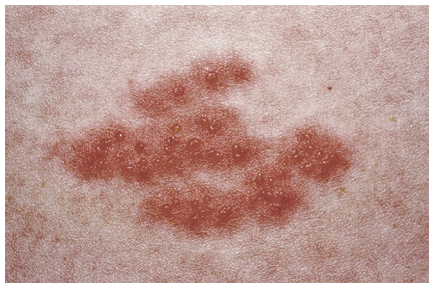

FIG. E5 Herpes zoster. Classic appearance of grouped vesicles. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

SUGGESTED READINGS

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Schmader K: In the clinic: herpes zoster, *Ann Intern Med ITC* 17-30, August 7, 2018.

Tseng HF et al: Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease, *J Am Med Assoc* 305(2):160-166, 2011.

Yawn B et al: Herpes zoster recurrences more frequent than previously reported, *Mayo Clin Proc* 86(2):88-93, 2011.

Hiatal Hernia PTG

BASIC INFORMATION

DEFINITION

Protrusion of a portion of the stomach into the thoracic cavity through the diaphragmatic esophageal hiatus

SYNONYMS

Hiatus hernia
Diaphragmatic hernia

ICD-10CM CODES

K44.9	Diaphragmatic hernia without obstruction or gangrene
Q40.1	Congenital hiatus hernia
Q79.0	Congenital diaphragmatic hernia
K44.0	Diaphragmatic hernia with obstruction, without gangrene
K44.1	Diaphragmatic hernia with gangrene

EPIDEMIOLOGY & DEMOGRAPHICS

- Found in 50% of patients older than 50 yr.
- Prevalence increases with age.
- More prevalent in Western countries than in Africa and Asia.
- Paraesophageal hiatal hernias are more common in women than in men (4:1).
- Associated with diverticulosis (25%), esophagitis (25%), duodenal ulcers (20%), and gallstones (18%).
- Saint triad: Hiatal hernia, diverticular disease, cholelithiasis.
- More than 90% of patients with endoscopic documentation of esophagitis have hiatal hernias.

PHYSICAL FINDINGS & CLINICIAL PRESENTATION

Most patients are asymptomatic. If symptoms are present, they resemble those of gastroesophageal reflux disease (GERD):

- Heartburn
- Dysphagia
- Regurgitation of gastric contents
- Chest pain
- Postprandial fullness
- GI bleed
- Dyspnea
- Hoarseness
- Wheezing with bowel sounds heard over the left lung base

ETIOLOGY

- The repetitive stretching of the gastroesophageal (GE) junction with swallowing and actions (e.g., vomiting, coughing) or states (e.g., obesity, pregnancy) that increase intraabdominal pressure may cause widening of the hiatus, rupture of the phrenoesophageal ligament, and onset of the hernia.
- Hiatal hernias are classified as:
  1. Type I: Sliding (Fig. E1), axial, or concentric hiatal hernia (most common type, 99%). Only the GE junction protrudes into the thoracic cavity, and the phrenoesophageal ligament remains intact.
  2. Type II: Paraesophageal or rolling hernia (Fig. E2) (1%). The GE junction stays at the level of the diaphragm, but part of the stomach bulges into the thoracic cavity through a defect in the phrenoesophageal ligament.
  3. Type III (Fig. E3): Mixed (rare), a combination of type I and type II.
  4. Type IV (Fig. E4): Large defect in hiatus that allows other intraabdominal organs to enter the hernia sac.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Peptic ulcer disease
- Unstable angina
- Esophagitis (caused by *Candida,* herpes, NSAIDs, etc.)
- Esophageal spasm
- Barrett esophagus
- Schatzki ring
- Achalasia
- Zenker diverticulum
- Esophageal cancer

WORKUP

Exclude conditions noted in the differential diagnosis and document the presence of a hiatal hernia. Upper endoscopy may also be needed to exclude abnormal metaplasia, dysplasia, or neoplasia.

LABORATORY TESTS

- Blood tests are not specific.
- Esophageal manometry, although not commonly done, can be used in establishing a diagnosis (low sensitivity, but high specificity when compared with endoscopy).

IMAGING

- Upper gastrointestinal (UGI) barium contrast swallow series: Best defines the anatomic abnormality. Demonstration that the gastric cardia is herniated 2 cm above the hiatus is diagnostic. UGI may also reveal a tortuous

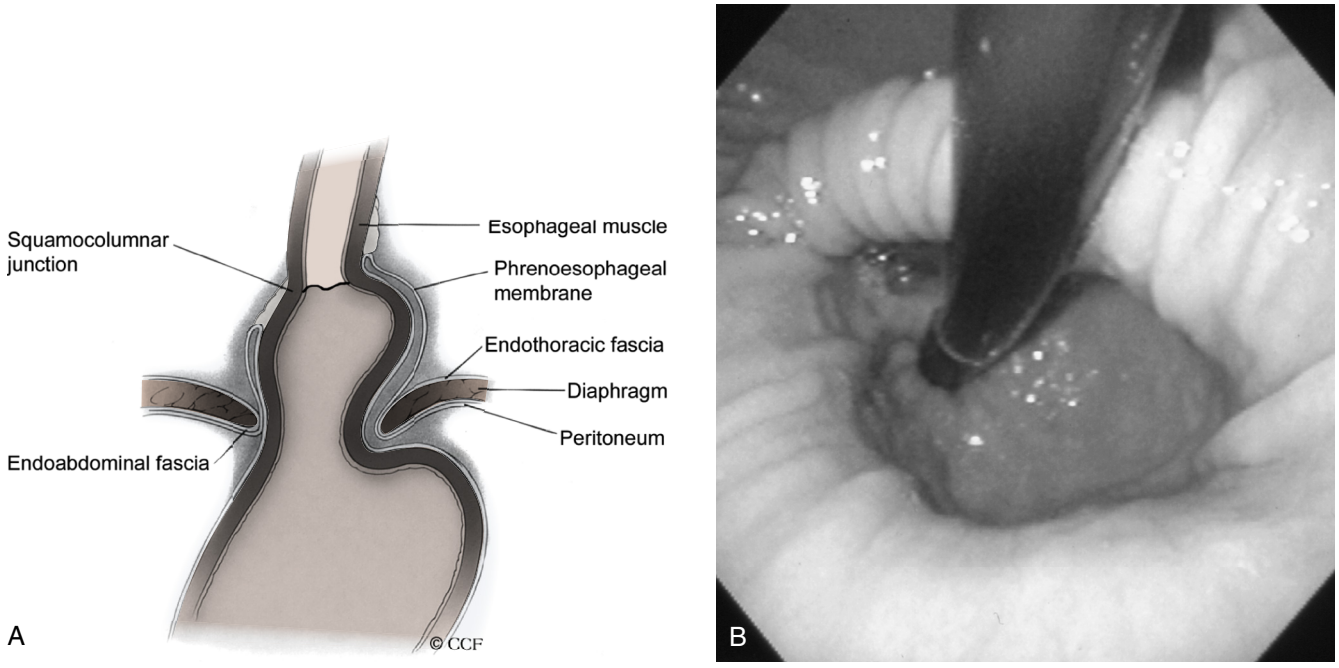

FIG. E1 Type I hiatal hernia. A, Pictorial presentation. **B,** Retroflexed view from the intraabdominal stomach at esophagoscopy. Diaphragmatic impression and intrathoracic stomach can be seen. (From Sellke FW et al: *Sabiston & Spencer surgery of the chest,* ed 9, Philadelphia, 2016, Elsevier.)

esophagus. If endoscopy is performed preoperatively, a barium swallow is generally not necessary.
- UGI endoscopy: Documents the presence of a hiatal hernia and excludes commonly associated findings of esophagitis and Barrett esophagus (recommended at least once during the workup). The >2 cm of gastric rugal fold seen above the margins of the diaphragmatic crura is diagnostic.
- Abdominal ultrasonography: Simple, well tolerated. A transdiaphragmatic esophageal diameter of ≥18 mm is highly suggestive of the presence of a sliding hiatal hernia.
- Computed tomography: Hiatal hernia is often seen as an incidental finding on CT scans done for other reasons.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Lifestyle modifications: Avoid foods and drugs that decrease lower-esophageal pressure (e.g., caffeine, chocolate, mint, calcium channel blockers, and anticholinergics).
- Weight loss, decrease in abdominal circumference.
- Avoid large meals.
- Sleep with the head of the bed elevated 6 inches.

ACUTE GENERAL Rx

- Antacids may be useful to relieve mild symptoms.
- H2 antagonists (e.g., ranitidine 150 mg bid or 300 mg qd, or famotidine 20 mg bid).
- If significant GERD is present with documented esophagitis, proton pump inhibitors (PPIs, e.g., omeprazole 20 mg qd or lansoprazole 30 mg qd) are used. Refractory symptoms may require higher doses (e.g., bid dosing).
- Prokinetic agents (e.g., metoclopramide 10 mg taken 30 min before each meal) can be added to an H2 antagonist or PPI.

CHRONIC Rx

- When indicated, surgery (laparoscopic or open) can be done in patients with refractory symptoms impairing quality of life or causing intestinal (e.g., recurrent GI bleeds) or extraintestinal complications (e.g., aspiration pneumonia, asthma, or ear, nose, and throat complications).
- Prophylactic surgery is a consideration in all paraesophageal hernias because they have a higher incidence of strangulation.

DISPOSITION

- More than 90% of patients with GERD symptoms respond well to medical therapy.
- Complications of hiatal hernias are similar to complications occurring in patients with GERD:
  1. Erosive esophagitis
  2. Ulcerative esophagitis
  3. Barrett esophagus
  4. Peptic stricture
  5. GI hemorrhage
  6. Extraintestinal complications
  7. Lung collapse or heart failure (severe cases)

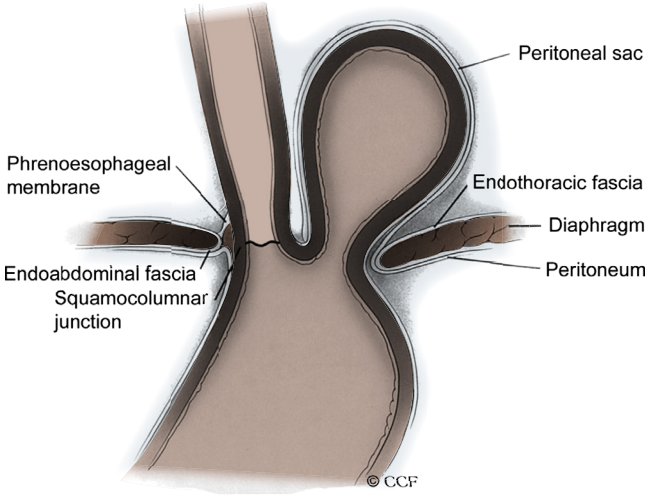

FIG. E2 Type II hiatal hernia. (From Sellke FW et al: *Sabiston & Spencer surgery of the chest,* ed 9, Philadelphia, 2016, Elsevier.)

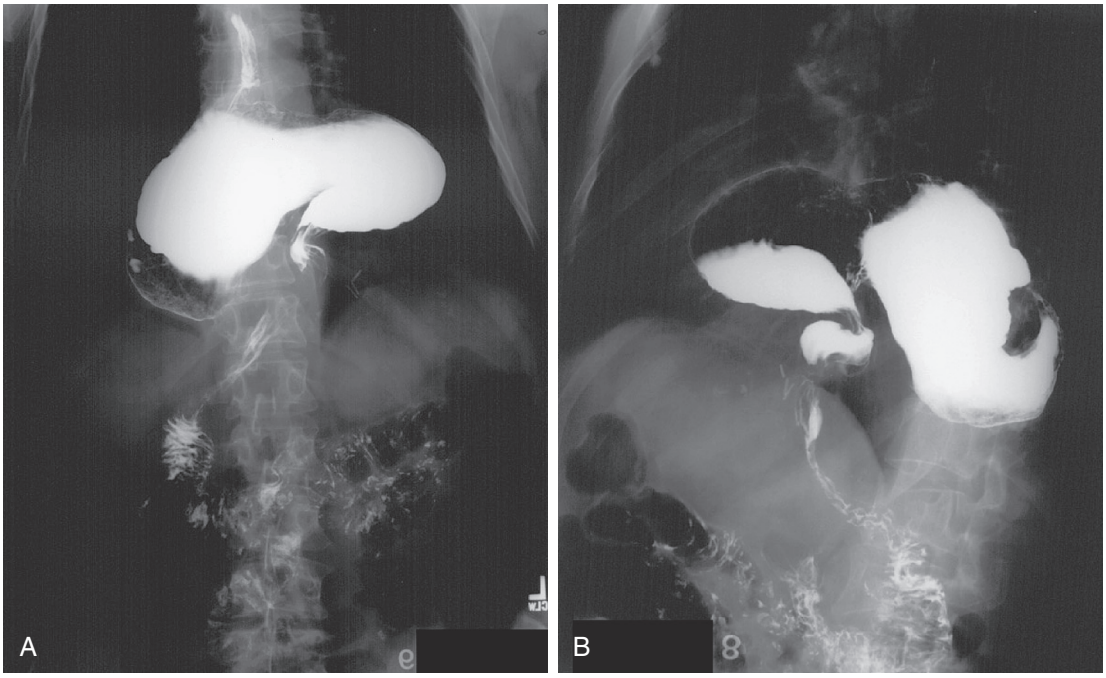

FIG. E3 Type III hiatal hernia. Barium esophagram demonstrates a type III hiatal hernia with organoaxial rotation. **A,** Posteroanterior view. **B,** Lateral view. (From Sellke FW et al: *Sabiston & Spencer surgery of the chest,* ed 9, Philadelphia, 2016, Elsevier.)

REFERRAL

- Gastroenterologist for symptoms refractory to conventional therapy (H_2 antagonists, antacids, and PPIs) or having complications previously mentioned.
  - General surgery evaluation for large hiatal hernia or severe complications.
  - Indications for emergent surgical evaluation include acute volvulus, uncontrolled bleeding, obstruction, strangulation, perforation, or respiratory compromise.

PEARLS & CONSIDERATIONS

COMMENTS

- Gastric ulceration and erosions (*Cameron lesion*) can occur in the paraesophageal hernia pouch and are an uncommon cause of UGI bleeding.
- May cause iron deficiency anemia.
- Gastric volvulus or torsion can also occur and presents as dysphagia and postprandial pain.
- High incidence of esophagitis even after the eradication of *Helicobacter pylori*.
- The appearance of hiatal hernia may resemble a left atrial mass by echocardiography.

RELATED CONTENT

Hiatal Hernia (Patient Information)

AUTHORS: **Ana Castaneda-Guarderas, MD,** and **Caleb Cantrell, BS**

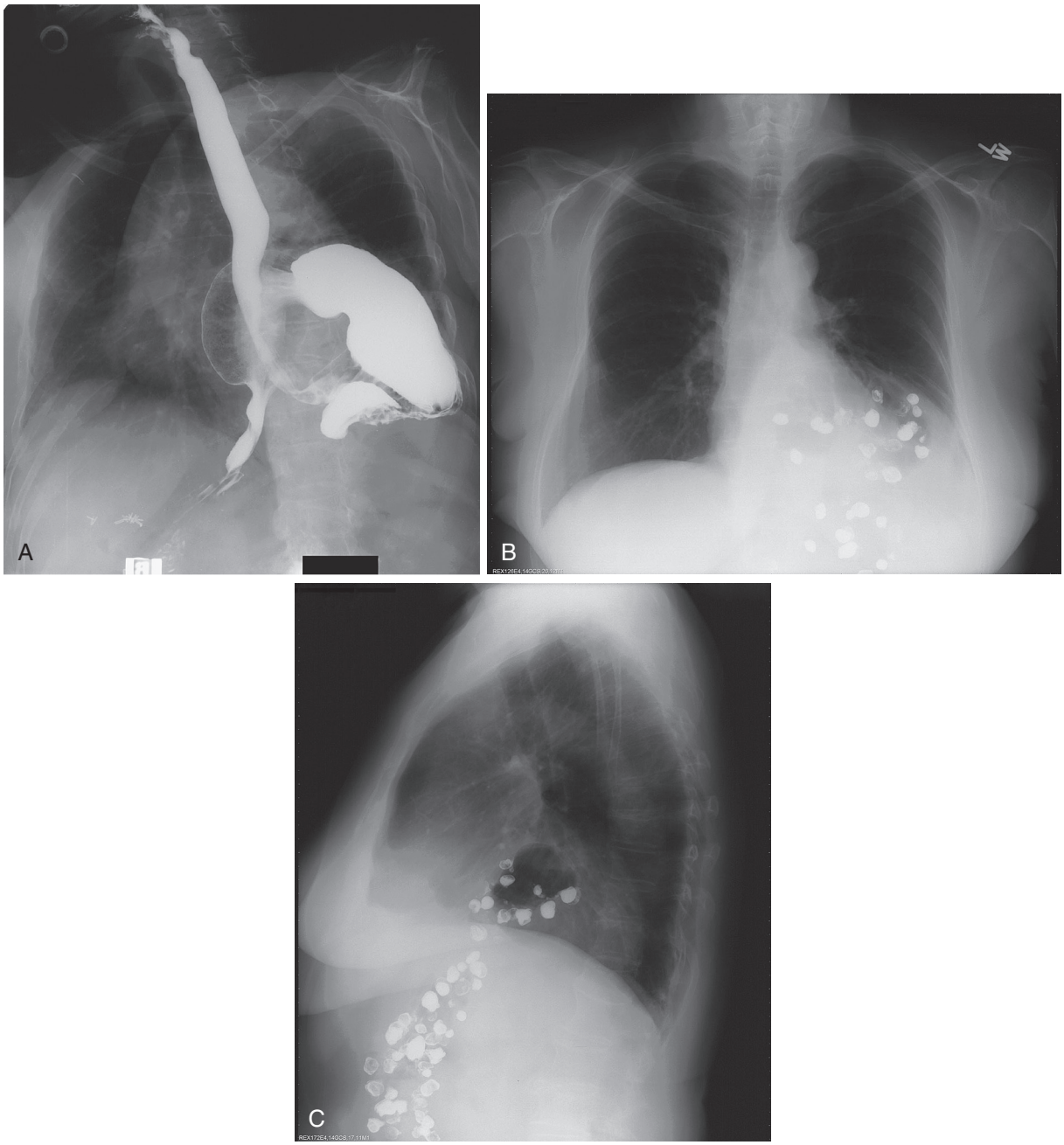

FIG. E4 Type IV hiatal hernia. A, Barium esophagram demonstrates a type III hiatal hernia with organoaxial rotation. Three days later, barium is seen in colonic diverticulum on preoperative chest radiograph. **B,** Posteroanterior view. **C,** Lateral view. Therefore, this is a type IV hiatal hernia. (From Sellke FW et al: *Sabiston & Spencer surgery of the chest,* ed 9, Philadelphia, 2016, Elsevier.)

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Siegal SR et al: Modern diagnosis and treatment of hiatal hernias, *Langenbecks Arch Surg*, 2017.

Hidradenitis Suppurativa

BASIC INFORMATION

DEFINITION

Hidradenitis suppurativa (HS) is a chronic, relapsing suppurative cutaneous disease affecting skin that bears apocrine glands and is manifested by abscesses, fistulating sinus tracts, and chronic infection leading to scarring.

SYNONYMS

Acne inversa
Apocrinitis
Verneuil disease
HS

ICD-10CM CODE
L73.2 Hidradenitis suppurativa

EPIDEMIOLOGY & DEMOGRAPHICS

Onset is postpubertal, with an average age of onset of 23 yr; rates decline after age 55 yr.
PREVALENCE: Overall prevalence in the United States is ~1% to 2%.
PREDOMINANT SEX: Female: male ratio is 3:1.
PREDOMINANT AGE: HS most often manifests after puberty, usually in the second or third decade of life. It is rare in the elderly.
RISK FACTORS:

- Obesity and metabolic syndrome
- Family history (approximately 30%)
- Hyperandrogenism in women
- Cigarette smoking

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The diagnosis is primarily clinical, based on the development of typical lesions in a characteristic distribution, with a relapsing nature. The course of HS is prolonged and marked by intermittent periods of activity and remission.

- Early symptoms include pain, itching, burning, erythema, and hyperhidrosis.
- Typical lesions include:
  1. Painful erythematous papules and nodules leading to painful abscesses with foul-smelling discharge.
  2. Dermal contractures and ropelike elevation of the skin.
  3. Comedones in the apocrine, gland-bearing skin.
- Classified into Hurley Stages (Table E1):
  1. Stage I: Abscesses without sinus tracts or scarring.
  2. Stage II: Multiple abscesses plus sinus tracts and scarring.
  3. Stage III: Diffuse involvement of entire area with abscesses, sinus tracts, and scarring.
- The axilla is the most common site (Fig. E1).
- Less common sites include the inguinal region, the breasts (more often in women), and the perineal or perianal skin (more often in men).
- There is a strong tendency toward relapse and recurrence.

TABLE E1 Hidradenitis Suppurativa—Grading Systems and Therapeutic Ladder

Hurley Staging System

- Stage I—one or more abscesses with no sinus tract or scar formation
- Stage II—one or more widely separated recurrent abscesses, with sinus tract and scar formation
- Stage III—multiple interconnected sinus tracts and abscesses throughout an affected region; more extensive scarring

Sartorius Grading System

- Anatomical regions involved: Axilla (left and/or right), groin (left and/or right), gluteal (left and/or right), or other region (e.g., inframammary): 3 points per region involved
- Number and scores of lesions for each region: Nodules = 1; fistulae = 6
- The longest distance between two relevant lesions* (i.e., nodules and fistulae) in each region: <5 cm = 1; 5-10 cm = 3; >10 cm = 9
- Are all lesions clearly separated by normal skin? In each region—yes 0/no (Hurley III) 9

Therapeutic Ladder

Indication	Therapeutic Interventions
General measures	• If obese or overweight, weight reduction • Reduce friction and moisture via loose undergarments, absorbent powders, and topical aluminum chloride • Antiseptic soaps • Smoking cessation
Hurley Stage I	• Intralesional triamcinolone (5 mg/ml) injections into early inflammatory lesions • Topical clindamycin • Eradication of *S. aureus* carriage with topical mupirocin in nose, axillae, umbilicus, and perianal regions • Oral antibiotics tailored to results of bacterial cultures from pustular discharge or abscess contents • Oral antibiotic therapy (alone or in combination) for its anti-inflammatory effect (rifampin + clindamycin, tetracycline, doxycycline, minocycline, dapsone, trimethoprim–sulfamethoxazole) • Oral anti-androgen therapy (e.g., finasteride)
Hurley Stage II	• Oral antibiotic therapy (see Stage I) • Acitretin • Systemic immunosuppressive agents including adalimumab,† infliximab, and cyclosporine • Surgical treatments‡ • Limited local excisions with second intention healing • CO_2 laser ablation with second intention healing • Nd:YAG laser treatments, at least 3-4 monthly sessions
Hurley Stage III	Medical treatments outlined for Stages I and II Surgical treatments‡ • Early wide surgical excision of involved areas • CO_2 laser ablation with second intention healing

†FDA-approved dosing regimen: 160 mg (four 40 mg injections) on day 1, *or* 80 mg daily on days 1 and 2 followed by 80 mg on day 15 and then 40 mg on day 29 and weekly thereafter.
‡Incision and drainage are discouraged given high rate of recurrence.
From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

- There is often a poor response to conventional antibiotics and no pathogens isolated from cultures of lesions.
- The disease is often mistaken for a simple infection and a long delay in diagnosis is common.
- Three clinical subtypes of HS have been recently proposed[1]:
  1. A classic axillary-mammary HS subtype, representing 48% of cases and characterized by breast and axillary involvement and hypertrophic scarring.
  2. A follicular HS subtype, representing 26% of cases manifesting primarily in male smokers with a family history of HS and characterized by follicular lesions, including epidermal cysts, pilonidal sinus, comedones, and severe acne.
  3. A gluteal HS subtype, representing 26% of cases, most often seen in smokers with lower body mass index (BMI) and with a morphology characterized by follicular papules, folliculitis, and gluteal involvement.

[1]Woodruff CM, Charlie AM, Leslie KS: Hidradenitis suppurative: a guide for the practicing physician, *Mayo Clin Proc* 90(12):1679-1693, 2015.

ETIOLOGY

- Keratinous materials plug apocrine glands in hair follicles leading to stasis, dilation, rupture, and re-epithelialization. Fig. E2 illustrates the pathogenesis of hidradenitis suppurativa.

FIG. E1 Hidradenitis suppurativa. A and **B,** Papulopustules, nodules, sinus tracts, and scarring in the axilla (Hurley stage II [A] and III [B]). **C,** Superficial sinus tracts that serve as a clue to the diagnosis, even in the absence of active disease. **D,** Severe disease with inflammatory nodules, hypertrophic scarring, draining fistulae, and sinus tract formation of the perianal region, buttocks, and upper thighs. This is the type of patient who is at risk for the development of squamous cell carcinoma and secondary amyloidosis. (**A,** Courtesy, Kalman Watsky, MD; **B,** Courtesy, Marco Romanelli, MD. In Bolognia J: *Dermatology,* ed 4, 2018, Elsevier.)

- Bacteria are trapped and multiply, leading to gland rupture with surrounding inflammation and local bacterial infection.
- Over time, repeated nodules and infections cause scarring, which can lead to deep tissue damage and sinus tracts.
- Infectious agents such as *Streptococcus, Staphylococcus,* and *Escherichia coli,* and enteric flora have been identified in cultures but are likely a secondary component of the disease.
- There is likely a significant genetic component to the disease. 35% to 40% of patients report a family history of HS. An HS spectrum of different phenotypes has been characterized involving genetic factors that are not yet well described but may be important for future therapy.
- HS has been associated with other endocrine and autoimmune disorders such as diabetes, Cushing syndrome, acromegaly, Crohn disease, and inflammatory arthritis.
- Metabolic syndrome affects as many as 50% of patients with HS and may exacerbate the associated inflammation.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Follicular pyodermias such as folliculitis, furuncles, carbuncles, and pilonidal cysts
- Noduloulcerative syphilis
- Cat scratch disease
- Granuloma inguinale
- Perianal and vulvar manifestations of Crohn disease
- Actinomycosis
- Lymphogranuloma venereum
- Dermoid, epidermoid, or Bartholin cysts
- Tuberculous inflammation of the skin
- Lymphadenitis
- Erysipelas

WORKUP

Primarily a clinical diagnosis based on typical lesions (see "Physical Findings & Clinical Presentation").

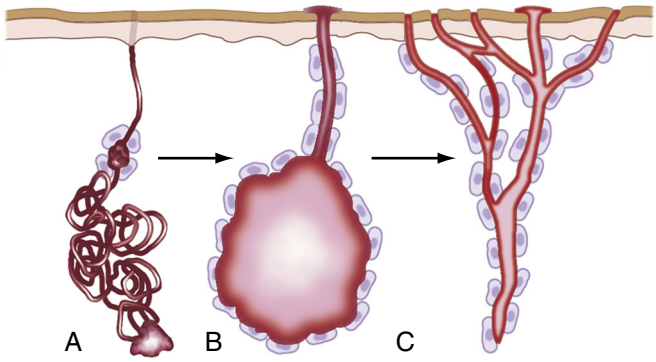

FIG. E2 Pathogenesis of hidradenitis suppurativa, an inflammatory disease of the apocrine sweat glands and adjacent connective tissue. A, The initiating event is occlusion of the apocrine duct by a keratinous plug. **B,** Bacteria are trapped beneath the keratinous plug and multiply to form an abscess, which can rupture into adjacent tissue. **C,** The end result is recurrent abscesses, chronic draining sinuses, and indurated scarred skin and subcutaneous tissues. Often, multiple tracts are interconnected and lead to the skin. (From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

LABORATORY TESTS

- Patients with acute lesions may have an elevated erythrocyte sedimentation rate or WBC.
- Febrile and toxic-appearing patients should have complete blood count, chemistries, and blood cultures.
- Any pus should be sampled for bacterial culture and sensitivity.

Rx TREATMENT

There is no definitive cure for hidradenitis.

NONPHARMACOLOGIC THERAPY

- Weight loss and control of metabolic syndrome
- Smoking cessation
- Avoidance of shaving, depilatory creams, deodorants
- Avoidance of tight-fitting clothing
- Warm compresses
- Incision and drainage of nonpurulent lesions is *not* recommended due to recurrence and scarring
- Laser therapy, radiotherapy, and cryotherapy currently under study
- Wide local excision for stage III disease with or without vacuum-assisted closure device

ACUTE AND CHRONIC Rx

- NSAIDs for inflammation and pain, consider gabapentin, pregabalin, SSRIs for chronic pain management.
- Antibiotics never proven to be effective; however, they are a mainstay of treatment. Can base treatment on the basis of aspirate culture and sensitivities or empirically.
  1. Clindamycin is the only topical antibiotic proven to be effective in randomized controlled trial and is appropriate for stage I disease.
  2. For oral therapy in stage II: Consider clindamycin and rifampin in combination. Cephalosporins, dicloxacillin, erythromycin, minocycline, and tetracycline have also been used.
  3. Severe, recurrent disease can require up to 3 to 6 mo of antibiotics.
- Oral contraceptives with low androgenic progesterone (norgestimate, desogestrel, or gestodene) for women show mixed effectiveness. They are especially advantageous for female patients of childbearing age who also require some form of birth control.
- Isotretinoin has been used with mixed effectiveness. It should be avoided in women of childbearing age.
- Metformin has mixed effectiveness, possibly due to related metabolic syndrome and hyperandrogenism.
- Trials using zinc gluconate 75 to 118 mg/day in patients with mild (grade 1) disease have shown mixed effectiveness.
- Corticosteroids and other immune suppressants such as cyclosporin, infliximab, and etanercept have been used for stage II disease, with mixed results.
- Adalimumab, an antitumor necrosis factor-α antibody given once per week (dose 40 mg/wk) has shown significantly higher clinical response as compared to placebo in phase 3 trials. Infliximab has also been used in trials with variable success rates, with most patients exhibiting clinical improvement within 8 wk.

COMPLICATIONS

- Squamous cell carcinoma
- Scarring leading to restricted limb mobility or lymphedema
- Rectal or urethral fistulas
- Psychological effects related to disfiguring nature of disease

REFERRAL

- Referral to dermatology during stage I to II disease.
- Referral to a surgeon is indicated for stage III disease.
- Surgical approaches include laser surgery and excisional surgery.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients with hidradenitis are at risk for severe depression, social isolation, and negatively impacted sexuality as a result of their disease.
- There is an average delay in diagnosis of 12 yr and most patients are diagnosed in stage II of the disease.
- It is important to maximize nonmedical treatment, start medical treatment, and refer to a surgeon early in the disease course to ensure the best quality of life for patients.
- The only definitive treatment for hidradenitis is wide excision of the involved skin.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Fred F. Ferri, MD**

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BASIC INFORMATION

DEFINITION

High-altitude illness refers to a spectrum of cerebral and pulmonary syndromes related to hypoxemia occurring during rapid ascent to high altitudes in unacclimatized individuals. Common acute syndromes include high-altitude pulmonary edema (HAPE), acute mountain sickness (AMS), and high-altitude cerebral edema (HACE). The latter two are thought to represent different points of severity along the same pathophysiologic process in the brain.

SYNONYMS

Altitude sickness
High-altitude headache
Acute mountain sickness
AMS
High-altitude pulmonary edema
High-altitude cerebral edema

ICD-10CM CODES

T70.29	Other and unspecified effects of high altitude
W94	Exposure to high and low air pressure and changes in air pressure

EPIDEMIOLOGY & DEMOGRAPHICS

- Millions of people worldwide are at risk of developing altitude sickness annually.
- 80% of people who ascend to high altitudes have high-altitude headache (HAH_2).
- AMS is the most common of the altitude diseases. It affects approximately 40% to 50% of people ascending to 14,000 ft (4200 m) from lowland and 25% of visitors to an altitude of 2000 m (6560 ft).
- The incidence of HACE is reported to be 0.1% to 2% at elevations in excess of 12,000 ft (3000 m). HACE is often complicated by concomitant HAPE.
- Men are five times more likely to develop HAPE than are women.
- AMS and HACE affect men and women equally.
- Some studies have suggested that climbers with a prior history of HAPE have a roughly 60% chance of recurrence if they ascend to the same elevation at the same rate.

PHYSICAL FINDINGS & CLINICIAL PRESENTATION (TABLE E1)

HAH_1
- Headache that develops within 24 hr of ascent.
- Bilateral, frontal or frontotemporal, dull or pressing quality.
- Mild to moderate intensity and aggravated by exertion, movement, straining, coughing, or bending.
- Headache resolves within 8 hr of descent.
- HAH should resolve with analgesics and/or 10 to 15 min of supplementary oxygen.
- Difficult to distinguish from headaches secondary to dehydration.

AMS
- AMS is thought to be a progression of HAH_2.
- Occurs within 6 to 12 hours after rapid ascent to 8000 ft (2500 m) in 10% to 25% of unacclimatized persons.
- Headache is the most common symptom.
- Dizziness and light-headedness.
- Nausea, vomiting, and loss of appetite.
- Fatigue.
- Sleep disturbance from an exaggerated hyperventilatory phase of Cheyne-Stokes respiration in response to hypoxemia and alkalosis.
- AMS can evolve into HAPE and HACE.
- Retinal hemorrhages can be present from increased blood flow or breakdown in the blood-retinal barrier.
- Supplemental oxygen may be used to support the clinical diagnosis.

HACE
- Usually presents several days after AMS.
- Headache, nausea, vomiting, mild fever, confusion, irritability, drowsiness, stupor, hallucinations, seizures, and paralysis.
- Truncal ataxia and encephalopathy.
- Coma and death from brain herniation may develop within hours of the first symptoms.

HAPE (Fig. E1)
- Typically occurs 2 to 4 days after ascent to more than 8000 ft (2500 m)
- It can occur at a lower elevation in patients with pulmonary hypertension
- Dyspnea out of proportion to the level of exertion, loss of stamina
- Dry cough or cough with frothy rust- or pink-tinged sputum
- Chest tightness
- Tachycardia, tachypnea, rales, cyanosis

ETIOLOGY

- During ascent to altitudes above sea level, the atmospheric pressure decreases. Although the percentage of oxygen in the air remains the same, the partial pressure of oxygen decreases with increased altitude, and can cause hypoxemia. Fig. E2 illustrates the effect of altitude on alveolar Pao_2 and oxygen saturation.
- Increased cerebral blood flow and the loss of autoregulation of intracranial pressure may contribute to increased cerebral vascular permeability and subsequent brain edema (HACE).
- Hypobaric hypoxia can trigger elevated pulmonary pressures, resulting in protein-rich, hemorrhagic exudates into the lung alveoli due to a breakdown in the pulmonary blood-gas barrier (HAPE).
- The body responds to low oxygen partial pressures through a process of acclimatization (see "Comments").

DIAGNOSIS

Made by clinical presentation and physical findings

DIFFERENTIAL DIAGNOSIS

- Dehydration
- Carbon monoxide poisoning
- Hypothermia
- Infection
- Substance abuse
- Congestive heart failure
- Pulmonary embolism
- Cerebrovascular accident
- Box E1 summarizes the differential diagnosis of high-altitude illnesses

WORKUP

Typically the diagnosis is self-evident after history and physical examination. Laboratory tests and imaging studies help monitor cardiopulmonary and central nervous system status in patients admitted to the intensive care unit for pulmonary and/or cerebral edema. In patients with HAPE occurring at lower altitudes (<8000 ft), an evaluation of preexisting pulmonary hypertension or a left-to-right shunt should be considered.

LABORATORY TESTS

Not useful, unless to rule out an alternative diagnosis

IMAGING STUDIES

- Chest x-ray showing Kerley B-lines and patchy edema (see Fig. E1)
- CT scan of the head showing diffuse or patchy edema
- MRI of the head showing characteristic intense T2 signal in the white matter

TREATMENT

NONPHARMACOLOGIC THERAPY

- Stop the ascent to allow acclimatization or start to descend until symptoms have resolved.
- Patient with AMS can stay at the same height and may ascend once symptoms resolve but should strongly consider using acetazolamide for the remainder of the trip.
- If the symptoms recur or fail to resolve after 2 to 3 days, descent is indicated.
- Descent is the definitive treatment and should begin immediately at the first suspicion of HACE.
- Oxygen 4 to 6 L/min is used for severe AMS, HAPE, and HACE.
- Portable hyperbaric bags are useful if available at the site.
- Altitude can cause diuresis that may be mediated by enhanced release of atrial natriuretic peptide. When coupled with the increased fluid loss through increased ventilation, there is a higher risk for dehydration, and adequate hydration should be maintained.

ACUTE PHARMACOLOGIC Rx

- Nonsteroidal antiinflammatory drugs (e.g., ibuprofen 600 mg every 6 hours, beginning 6 hours before ascending) are often used for prophylaxis of traditional altitude sickness and in treating headaches in AMS. However trials have shown that ibuprofen is slightly inferior to acetazolamide for acute mountain sickness prevention, and should not be recommended over acetazolamide for rapid ascent.[1]

[1] Burns P et al: Altitude sickness prevention with ibuprofen relative to acetazolamide, *Am J Med* 132(2):247-251, 2019.

- Acetazolamide 125 to 250 mg PO bid is the preferred agent and has been effective for both prevention and acute therapy in patients with AMS and HACE. Dexamethasone is equally effective to reduce symptoms of AMS and can be used as an alternative to acetazolamide. It should also be added to acetazolamide in patients with HACE.
- Nifedipine 10 mg sublingual followed by long-acting nifedipine 30 mg bid is used for patients with HAPE who cannot descend immediately. Salvage therapy in absence of supplemental oxygen and descent also includes phosphodiesterase-5 inhibitors (sildenafil or tadalafil).
- Dexamethasone 4 mg PO every 6 hr is used in patients with severe AMS, HAPE, or HACE.

CHRONIC Rx

Prevention is the most prudent therapy.

- Slow, staged ascent to avoid altitude sickness.
- Start the ascent below 8000 ft.
- Ascend 1000 ft/day (300 m/day).
- Spend two nights at the same altitude every 3 days.
- Sleep at lower heights than the altitude climbed ("climb high, sleep low").
- Prophylactic therapy with NSAIDs (ibuprofen 600 mg every 6 hours, beginning 6 hours before ascending) or acetazolamide up to 750 mg daily and/or dexamethasone 8 to 16 mg daily decreases the risk of developing AMS (combination may have additive benefit). The drugs should be used until acclimatization occurs.
- Prophylactic inhalation of a β-adrenergic agonist, salmeterol 125 mcg q12h, or the use of slow-release nifedipine 20 mg bid have both been shown to reduce the risk of HAPE in susceptible individuals.
- Tadalafil, a long-acting phosphodiesterase inhibitor, has recently been shown to decrease the incidence of HAPE in susceptible individuals.
- Box 2 summarizes field treatment of high-altitude illness.

DISPOSITION

- AMS improves over a period of 2 to 3 days.
- HAPE is the most common cause of death among patients with altitude illnesses.
- More than 60% of patients with HAPE will have recurrence of symptoms on subsequent climbs.
- In HACE, neurologic deficits may persist for wks but eventually resolve. If coma occurs, prognosis is poor.

REFERRAL

Cardiology and neurology referrals are made in patients with pulmonary edema and central nervous system findings, respectively.

PEARLS & CONSIDERATIONS

COMMENTS

- Acclimatization is the process in which an individual who normally resides at low altitudes adapts to hypobaric hypoxia to improve tolerance and performance at higher altitudes. These mechanisms include:
  1. An increase in respiratory rate and tidal volume. This hyperventilation allows lowering of arterial carbon dioxide to preserve oxygen delivery, even at extreme altitudes.
  2. An early increase in heart rate and stroke volume to improve oxygen delivery. After 1 wk, both parameters decrease because of diuresis and lower catecholamine levels.
  3. Pulmonary hypertension develops in response to hypoxemia, resulting in improvement of the ventilation-perfusion mismatch but may be maladaptive and lead to the development of HAPE.
  4. Cerebral vasodilation to increase blood flow to the brain.
  5. Rise in hemoglobin and hematocrit. This is a long-term process that takes up to 1 wk to occur in response to the need for improved oxygen delivery.
- Adaptation to altitude is different from acclimatization and refers to physiologic differences in permanent residents at high altitude (e.g., an increased oxygen diffusion capacity).
- High-altitude illness can generally be prevented by ascending to 300 to 500 m/day at altitudes above 3000 m and including a rest day every 3 to 4 days.
- Risk factors for the development of altitude sicknesses are:
  1. Rapid ascent
  2. Previous history of altitude sickness
  3. Strenuous exertion on arrival
  4. Obesity
  5. Male gender
- Physical fitness is not protective against high-altitude illness.
- Both dexamethasone and tadalafil decrease systolic pulmonary artery pressure and may reduce the incidence of HAPE in adults with a history of HAPE. Dexamethasone prophylaxis may also reduce the incidence of AMS in these adults.
- Descent is mandatory for all persons with HACE or HAPE.
- The American College of Chest Physicians has released a primer on caring for passengers with a variety of health conditions who are traveling to high-altitude places or areas (http://www.accpstorage.org/newOrganization/patients/TravelingwithOxygen.pdf). Specific indications for supplemental oxygen are provided in the document.

BOX 2 Field Treatment of High-Altitude Illness

High-Altitude Headache and Mild Acute Mountain Sickness
- Stop ascent, rest, acclimatize at same altitude
- Symptomatic treatment as necessary with analgesics and antiemetics
- Consider acetazolamide, 125 to 250 mg bid, to speed acclimatization
- OR descend 500 m (1640 ft) or more

Moderate to Severe Acute Mountain Sickness
- Low-flow oxygen, if available
- Acetazolamide, 125 to 250 mg bid, with or without dexamethasone, 4 mg PO, IM, or IV q6h
- Hyperbaric therapy
- OR immediate descent

High-Altitude Cerebral Edema
- Immediate descent or evacuation
- Oxygen, 2 to 4 L/min
- Dexamethasone, 8 mg PO, IM, or IV, then 4 mg q6h
- Hyperbaric therapy

High-Altitude Pulmonary Edema
- Minimize exertion and keep warm
- Immediate descent or hyperbaric therapy
- Oxygen, 4 to 6 L/min until improving, then 2 to 4 L/min

If above unavailable, one of the following:
- Nifedipine, 30 mg extended release q12h
- Sildenafil 50 mg q8h
- Tadalafil 10 mg q12h
- β-agonists may be helpful

Periodic Breathing
- Acetazolamide, 62.5 to 125 mg at bedtime as needed

bid, Twice a day; *IM,* intramuscularly; *IV,* intravenously; *PO,* orally.
From Auerbach P: *Wilderness medicine, expert consult,* premium edition—enhanced online features and print, Philadelphia, 2012, WB Saunders.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Altitude Sickness (Patient Information)

AUTHORS: **Javeryah Safi, MD,** and **Samaan Rafeq, MD**

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TABLE E1 Clinical Characteristics of High-Altitude Illnesses

	Clinical Classification			
	HAH	**Mild AMS**	**Moderate to Severe AMS**	**HACE**
Symptoms	Headache only	Headache plus one more symptom (nausea/vomiting, fatigue/lassitude, dizziness, or difficulty sleeping) All symptoms of mild severity	Headache plus one or more symptoms (nausea/vomiting, fatigue/lassitude, dizziness, or difficulty sleeping) Symptoms of moderate to severe intensity	±Headache Worsening of symptoms seen in moderate to severe AMS
LL-AMS score*	1-3, headache only	2-4	5-15	
Physical signs	None	None	None	Ataxia Altered mental status
Findings	None	None	Slightly increased body temperature Slight desaturation Widened A-a gradient Elevated ICP White matter edema (CT, MRI)	HAPE common: Positive chest radiograph, rales, dyspnea at rest Elevated ICP White matter edema (CT, MRI)
Pathophysiology	Unknown; cerebral vasodilation, trigeminal vascular system?	Unknown; same as HAH?	Vasogenic edema; cytotoxic edema?	Advanced vasogenic cerebral edema; cytotoxic edema?

*The self-reported Lake Louise AMS score.

AMS, Acute mountain sickness; *CT,* computed tomography; *HACE,* high-altitude cerebral edema; *HAH,* high-altitude headache; *HAPE,* high-altitude pulmonary edema; *ICP,* intracranial pressure; *LL-AMS,* Lake Louise AMS; *MRI,* magnetic resonance imaging.

From Auerbach P: *Wilderness medicine, expert consult,* premium edition—enhanced online features and print, Philadelphia, 2012, WB Saunders.

FIG. E1 Chest radiograph showing high-altitude pulmonary edema. (From Strauss RH [ed]: *Sports medicine,* ed 2, Philadelphia, 1991, WB Saunders.)

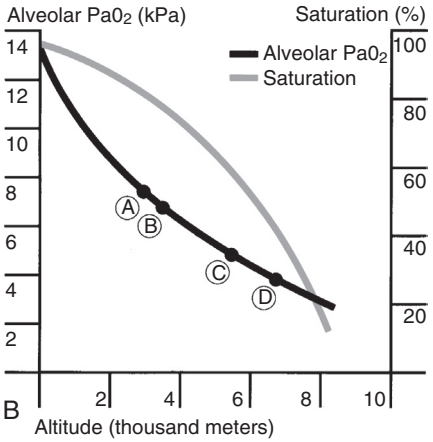

FIG. E2 Effect of altitude on alveolar PaO_2 and oxygen saturation. Because of the steep slope of the oxygen dissociation curve, increasing altitude to greater than 5000 m causes abdominal cramps and nausea. **A,** 3500 m (12,000 ft)—headache, nausea, diminished visual acuity, and possible precipitous fall in saturation. In an unacclimated person, acute change occurs at **(B)** 3000 m (10,000 ft)—slightly impaired memory and judgment, increased heart rate, and pulmonary edema. **C,** 5500 m (18,000 ft)—impaired consciousness after several hours in many people. **D,** 6750 m (22,000 ft)—loss of consciousness. (From Souhami RL, Moxham J: *Textbook of medicine,* ed 4, London, 2002, Churchill Livingstone.)

BOX E1 Differential Diagnosis of High-Altitude Illnesses

Acute mountain sickness and high-altitude cerebral edema	Dehydration, exhaustion, viral or bacterial infection, alcohol hangover, hypothermia, carbon monoxide poisoning, migraine, hyponatremia, hypoglycemia, diabetic ketoacidosis, CNS infection, transient ischemic attack, arteriovenous malformation, stroke, seizures, brain tumors, ingestion of toxins or drugs, acute psychosis
High-altitude pulmonary edema	Asthma, bronchitis, pneumonia, mucus plugging (secondary to previous), idiopathic hyperventilation syndrome, pulmonary embolism, heart failure, myocardial infarction

CNS, Central nervous system.
From Auerbach P: *Wilderness medicine, expert consult,* premium edition—enhanced online features and print, Philadelphia, 2012, WB Saunders.

BASIC INFORMATION

DEFINITION

Hip fractures refer to fractures of the proximal part of the femur and can be classified as intracapsular or extracapsular. Intracapsular fractures include fractures of the femoral head and femoral neck (Fig. E1, Table E1). Extracapsular fractures include intertrochanteric fractures, subtrochanteric fractures and, less commonly, greater or lesser trochanteric fractures. These fractures can be further categorized by the fracture pattern and stability.

SYNONYMS

Hip fracture
Proximal femur fracture
Intracapsular fracture: Femoral neck fractures (subcapital vs. transcervical vs. basicervical)
Extracapsular fracture: Intertrochanteric, peritrochanteric, or subtrochanteric fractures

ICD-10CM CODES
Code x Y (Y = encounter type: A [initial], D [subsequent with routine healing], G [subsequent with delayed healing], K [subsequent with nonunion], P [subsequent with malunion], S [sequelae]).

S72.0	Fracture of neck of femur
S72.1	Pertrochanteric fracture
S72.2	Subtrochanteric fracture
S72.3	Fracture of shaft of femur
S72.4	Fracture of lower end of femur
S72.7	Multiple fractures of femur
S72.8	Fractures of other parts of femur
S72.009	Fracture of unspecified part of neck of unspecified femur
M84.359xY	Stress fracture hip, unspecified
M84.459xY	Pathologic fracture of the hip, unspecified
M85.353xY	Stress fracture unspecified femur

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Lifetime risk in women ~16%
INCIDENCE: 350,000 hip fractures annually in the U.S.
EPIDEMIOLOGY:
- Female > male
- Caucasian > African American
- 90% >65 yr old
- Mean age, 80 yr old

MORTALITY: 20% to 25% mortality within the first yr following the fracture

RISK FACTORS

- Osteoporosis
- Age >75 yr old
- Gait instability, foot deformities, and muscular weakness
- Sensory impairment such as neuropathy
- Polypharmacy
- Impaired cognition, depression
- Use of alcohol or benzodiazepines
- Orthostatic hypotension
- Environmental hazards at home (e.g., loose rugs, exposed cords)
- Subclinical hyperthyroidism

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hip or groin pain
- Displaced fractures: Affected extremity may be shortened and externally rotated (less often internally rotated)
- Impacted/stressed/nondisplaced fracture: Pain with motion or ambulation; often without obvious deformity
- Ecchymosis or bruising about the hip
- Inability to bear weight and tenderness to palpation

ETIOLOGY

- Trauma
- Age-related bone fragility secondary to osteoporosis or decreased bone mineral density
- Increased risk of fractures in elderly (decline in muscle function, reduced bone quality, polypharmacy, or use of psychotropic medication, etc.)
- Stress fractures

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Osteoarthritis/rheumatoid arthritis of the hip
- Hip dislocation
- Pathologic fracture
- Muscle strain or tendonitis
- Lumbar disk syndrome with radicular pain
- Insufficiency fracture of pelvis or pubic ramus fracture
- Trochanteric bursitis
- Septic hip joint
- Pelvic fracture
- Lateral femoral cutaneous nerve entrapment (meralgia paresthetica)
- Labral tear or pathology
- Paget disease
- Neoplasm

WORKUP

In most cases, the diagnosis is based on clinical presentation and plain radiographs (Figs. E2 and E3). Fig. E4 illustrates the Garden classification of femoral neck fractures, which classifies the fracture based on the amount of displacement or gapping between the fracture fragments and relative stability of the fracture pattern. Additional imaging may be required to aid in the diagnosis of subtle hip fractures not evident on plain radiographs (e.g., MRI for stress or occult fractures).

IMAGING STUDIES

- Standard radiographs should include an anteroposterior view of the pelvis and hip, and a cross-table lateral view of the hip to confirm the diagnosis. Full-length femur and knee films should also be obtained.
- If initial radiographs are negative, then computed tomography (CT) or MRI may be indicated. Stress fractures can be diagnosed

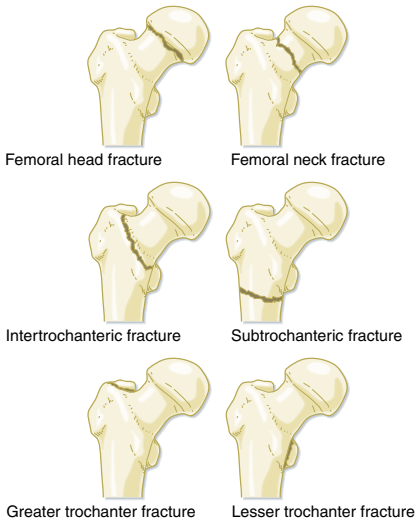

FIG. E1 Types of hip fractures. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

TABLE E1 Garden Classification of Femoral Neck Fractures

Type I	Nondisplaced, slightly impacted, incomplete fracture line The medial trabeculae of the femoral head and neck form an angle of 180 degrees The femoral head is tilted into valgus The distal fragment lies in external rotation
Type II	Nondisplaced, complete fracture line The medial trabeculae of the femoral head and neck form an angle of 160 degrees Nondisplaced femoral head Normal distal alignment
Type III	Complete fracture line, with displacement <50% The femoral head trabeculae are not in alignment with those of the pelvis The femoral head is tilted into varus and medially rotated The distal fragment lies in external rotation
Type IV	Complete fracture line, with displacement >50% and dissociation The femoral head trabeculae lie in alignment with those of the pelvis The femoral head is detached and frequently realigns with the acetabulum The distal fragment is proximally displaced and lies in external rotation

From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2014, Saunders.

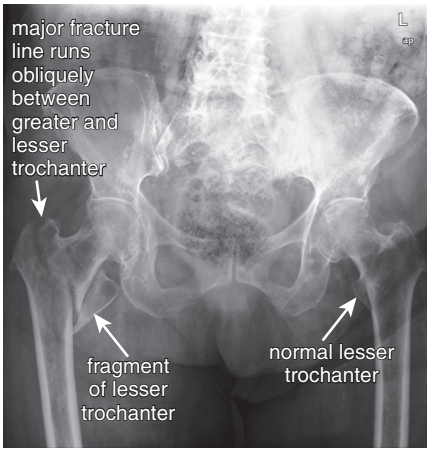

FIG. E2 Intertrochanteric femur fracture: Three parts (proximal, distal, and one trochanter). Intertrochanteric femur fractures are common, with the mechanism often being a fall from standing in an elderly patient. The major fracture line usually runs obliquely between the greater and the lesser trochanters. These fractures may have two, three, or four parts classically, although severely comminuted combinations are also possible. Two-part fractures consist of the proximal and distal fragments. Three-part fractures also include a fragment of one trochanter. Four-part fractures include fragments of both trochanters. This 86-yr-old woman had an unwitnessed fall. She has a typical three-part fracture, with a fragment of the lesser trochanter visible. Note her generalized severe osteopenia. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

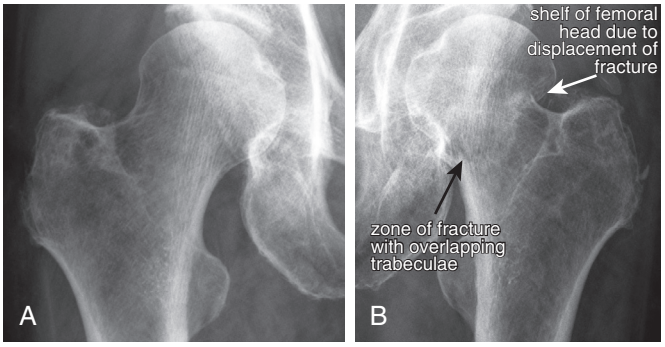

FIG. E3 Femoral neck fracture. This 84-yr-old woman had an unwitnessed fall. **A,** Normal right hip, osteoporotic. **B,** Left hip, another relatively subtle femoral neck fracture. Note the smudging of the trabeculae of the femoral neck. In addition, the distal fragment has shifted medially, creating an overhanging ledge of the femoral head not seen on the opposite normal side. Some femoral neck fractures are more obvious. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

with CT scan; however, MRI is the preferred study for the diagnosis of occult fractures. Bone scanning may also be used to identify fractures.

Rx TREATMENT

- Orthopedic consultation: The majority of hip fractures are treated surgically, with nonoperative management reserved for patients with significant medical comorbidities, severe dementia, or patients who are nonambulatory preinjury.
- Preoperative workup: CBC, BMP, type and screen, coagulation panel, chest radiograph, ECG, and urinalysis.
- Surgery is indicated in most cases, with the goal of surgical fixation within 24 to 48 h. Repair within 24 h is associated with lower complication rates and lower 30-day mortality. Treatment depends on fracture pattern and stability:
  1. Femoral neck, nondisplaced/valgus impacted: Internal fixation with 3 cannulated screws
  2. Displaced femoral neck: <65 yr old: Urgent anatomic reduction, cannulated screws or dynamic hip screw (DHS)
  3. Displaced femoral neck >65 yr old: Total hip arthroplasty for healthy, active patients and hemiarthroplasty for frail or sick patients
  4. Intertrochanteric fractures: Intramedullary nail (IMN) or dynamic hip screw (DHS)
  5. Unstable intertrochanteric/reverse obliquity: IMN, blade plate, dynamic condylar screw (not DHS)
- Deep vein thrombosis (DVT) prophylaxis (enoxaparin, fondaparinux, heparin). Mechanical DVT prophylaxis in the nonaffected limb. Pharmacologic DVT prophylaxis is usually continued for 14 to 30 days postoperatively.
- Pain management: Effective pain management is a primary goal in hip fracture. Opioid analgesics have a high incidence of delirium and constipation. Nerve blockade is effective in reducing acute pain following a hip fracture. A bowel regimen and adequate hydration are recommended in patients taking narcotics.
- Prophylactic antibiotics should be administered before surgery and continued for 24 hours after surgical repair.
- Rehabilitation is a major component of hip fracture treatment and should be initiated on the first day postoperatively.
- Conservative therapy and pain control should be considered in patients who are not surgical candidates (e.g., significant medical risk, bed-/wheelchair-bound, or severe dementia).

DISPOSITION

- Mortality associated with surgery typically ranges from 2% to 4% but varies based on the patient's risk profile. Elderly patients have a fivefold to eightfold increased risk for all-cause mortality during the first 3 mo after a hip fracture.
- Mortality rate within 1 yr in elderly patients is 20% to 30%.
- Increased annual mortality persists over time for both women and men, but at any given age, the annual mortality following a hip fracture is higher in men than in women.
- Dementia is a particularly poor prognostic sign.

REFERRAL

To orthopedic surgeon for surgical consideration when the diagnosis is made

PEARLS & CONSIDERATIONS

COMMENTS

- Complications: Nonunion, malunion, infection, avascular necrosis, DVT, delirium, decubitus ulcers, persistent pain, loosening of prosthesis, and periprosthetic fractures.
- Nonoperative management:
  1. Should be considered for nonambulatory patients, patients with severe dementia, or patients who are at high risk of complications associated with surgery (e.g., severe cardiac or pulmonary disease).
  2. Early bed-to-chair mobilization and vigilant nursing care to avoid skin breakdown and decubitus ulcers.
  3. Patients may experience pain relief prior to physiologic union of the fracture.
- Severe groin pain or inability to ambulate may be the only finding associated with an occult fracture of the femoral neck. If suspected, MRI can be obtained.
- In the U.S., hip fracture rates and subsequent mortality among persons aged ≥65 yr old are declining, and comorbidities among patients with hip fractures are very expensive ($40,000 in the first yr following hip fracture for direct medical costs and $5000 in subsequent yrs). The estimated cost related to hip fractures was >$20 billion in 2007.
- Fragility (or low-energy) hip fractures are common in elderly patients with reduced bone quality. These types of fractures are associated with a 1-yr mortality of 26% and 58% of patients requiring long-term care in a nursing facility. Diagnosis of a fragility fracture of the hip is associated with a second fragility fracture within the next 5 yr.
- Concurrent prolonged use of proton-pump inhibitors (≥1 yr) is associated with reduced effectiveness of alendronate for preventing hip fractures in older adults.

PREVENTION

- The rate of hip fracture could be reduced by:
  1. Elimination of environmental hazards (e.g., poor lighting, loose rugs, low sitting furniture)
  2. Regular exercise for balance and strength
  3. Patient education about fall prevention
  4. Medication review to minimize side effects and polypharmacy
  5. Prevention and treatment of osteoporosis (e.g., calcium/vitamin D, resistance exercise, reversal of underlying pathology)

RELATED CONTENT

Hip Fracture (Patient Information)

AUTHOR: **James H. Dove, MD**

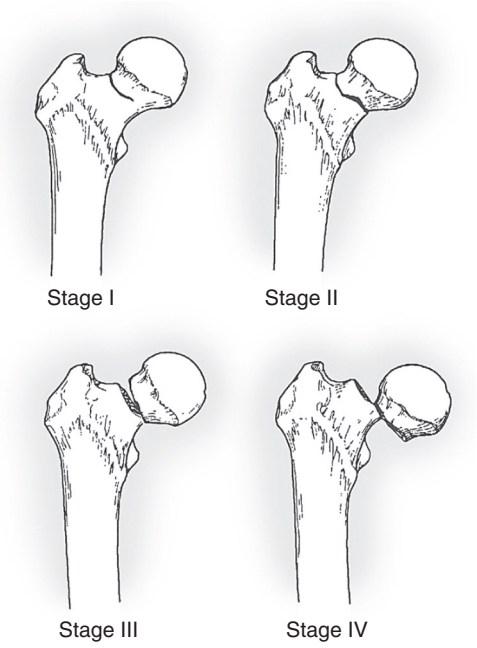

FIG. E4 Garden classification of femoral neck fractures. (From Kyle RF: Fractures of the hip. In Gustilo RB et al [eds]: *Fractures and dislocations,* St Louis, 1993, Mosby.)

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BASIC INFORMATION

DEFINITION

Hirsutism is the development of stiff, pigmented (terminal) facial and body hair (male distribution) in women as a result of excess androgen production.

SYNONYM

Excessive hair growth

ICD-10CM CODE
L68.0 Hirsutism

EPIDEMIOLOGY & DEMOGRAPHICS

- Overall prevalence unknown, estimated 5% to 10% in reproductive age women.
- Race and genetics should be considered. Some distinct ethnic populations have minimal body hair and others (Mediterranean, Middle Eastern, South Asian) have moderate to large amounts of body hair while serum androgen levels are similar.
- Social norms and culture also determine how much body hair is cosmetically acceptable.
- Half of all cases of mild hirsutism do not have hyperandrogenemia. "Patient-important hirsutism" refers to hirsutism causing woman sufficient distress to seek care.
- Incidence and presentation of hirsutism is dependent on underlying cause of androgen excess (see "Differential Diagnosis").
- Most women with hirsutism have polycystic ovary syndrome (PCOS). PCOS accounts for 95% of cases of hirsutism.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Timing of symptoms: Abrupt onset, short duration, rapid progression, progressive worsening, more severe signs of virilization (Fig. E1), or later age of onset suggest androgen-producing tumor, late-onset congenital adrenal hyperplasia, or Cushing syndrome. Weight increases may produce increased androgen production.
- Menstrual history: Menarche, cycle regularity and symptoms of ovulation, fertility, and contraception use. Anovulatory cycles are the most common underlying cause of androgen excess.
- Medication use history: Some drugs cause hirsutism or produce androgenic effects (danazol, phenytoin, valproic acid, androgenic progestins [e.g., norgestrel], cyclosporin, minoxidil, metoclopramide, phenothiazines, methyldopa, diazoxide, and penicillamine).
- Family history: Known or suspected family history of hirsutism, congenital adrenal hyperplasia, insulin resistance, polycystic ovary syndrome (PCOS), infertility, obesity, menstrual irregularity may be found.
- Physical exam reveals deepening voice, body habitus, increased muscle mass, galactorrhea; abdominal and pelvic exam.
- Associated cutaneous manifestations (Fig. E2) are acne, acanthosis nigricans, striae, hair distribution, location and quantity, frontotemporal balding, muscle mass, clitoromegaly.
- Ferriman-Gallwey scale, a simple, pictorial system of scoring nine body areas, is the most common tool used to quantify hirsutism. It may be unreliable in non-Caucasian women of other ethnicities.

ETIOLOGY

- Presence of hirsutism indicates androgen excess. Total testosterone may be normal, but free testosterone is elevated.
- Androgens induce vellus hair follicles (soft, unpigmented hair) in sex-specific areas (upper lip, chin, midsternum, upper abdomen, back, buttocks) to develop into thicker, more heavily pigmented terminal hairs.
- Anovulatory ovaries are usual source of excess androgens through thecal cell steroidogenesis and conversion of androstenedione to testosterone. The most common cause of hirsutism is polycystic ovary syndrome, which accounts for three out of every four cases.
- Conditions that decrease hepatic production of sex hormone binding globulin (SHBG) decrease protein-bound testosterone and increase free testosterone fraction (e.g., low estrogen, high androgen, and hyperinsulinemic states).
- Late-onset, congenital adrenal hyperplasia enzyme deficiency (most commonly 21-hydroxylase deficiency) produces excess 17 hydroxyprogesterone (17-OHP) and overproduction of androstenedione.
- Rare ovarian tumors primarily derived from Sertoli-Leydig cells, granulosa theca cells, or hilus cells produce excess androgens.
- Rare adrenal tumors produce excess androgens.
- Rare pituitary or hypothalamic tumors produce excess prolactin and can lead to anovulation.
- Box E1 summarizes causes of androgen excess in women of reproductive age.

FIG. E1 Hirsutism. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, WB Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Androgen-independent vellus hair: Soft, unpigmented hair that covers entire body
- Hypertrichosis: Diffusely increased total body hair (vellus or lanugo-type) not restricted to androgen-dependent areas often an adverse response to a medication or systemic illness (e.g., anorexia nervosa, porphyria, malnutrition, hypothyroidism)
- PCOS 75%
- Idiopathic 5% to 15%
- Congenital adrenal hyperplasia 1% to 8%
- Insulin resistance syndrome 3% to 4%
- Cushing syndrome <1%
- Drug induced <1%
- Ovarian tumor <1%
- Adrenal tumor <1%
- Hyperthecosis <1%
- Hyperprolactinemia <1%

WORKUP

- Hirsutism is a clinical diagnosis.
- Management of hirsutism is largely independent of the etiology.
- Workup in selected hirsute women is directed to determine underlying cause of androgen excess.
- See specific conditions for more detailed workup of individual diagnoses.

LABORATORY TESTS

Establishing laboratory evidence of excess androgens in women with moderate or severe hirsutism, sudden onset, rapid progression, or associated menstrual dysfunction, central obesity, clitoromegaly, or acanthosis nigricans is an approach consistent with guidelines from the Endocrine Society, the American College of Obstetricians and Gynecologists, the Androgen Excess and Polycystic Ovary Syndrome Society, and the American Association of Clinical Endocrinologists.

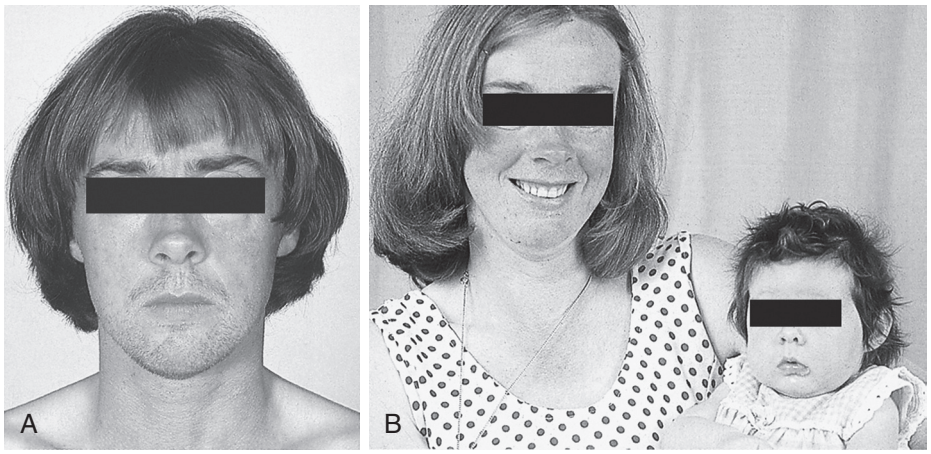

FIG. E2 A patient with an arrhenoblastoma with associated polycystic ovaries before and after treatment. A, Before treatment, the patient had marked facial hirsutism. **B,** The patient is shown successfully treated. The tumor was resected and ovulation ensued with clomiphene and human chorionic gonadotropin therapy. (From Besser CM, Thorner MO: *Comprehensive clinical endocrinology,* ed 3, St Louis, 2002, Mosby.)

BOX E1 Causes of Androgen Excess in Women of Reproductive Age

Ovarian
Polycystic ovary syndrome (PCOS)
Hyperthecosis (a severe PCOS variant)
Ovarian tumor (e.g., Sertoli-Leydig cell tumor)

Adrenal
Nonclassic adrenal hyperplasia
Cushing syndrome
Glucocorticoid resistance
Adrenal tumor (e.g., adenoma, carcinoma)

Specific Conditions of Pregnancy
Luteoma of pregnancy
Hyperreaction luteinalis
Aromatase deficiency in fetus

Other
Hyperprolactinemia, hypothyroidism
Medications (danazol, testosterone, anabolizing agents)
Idiopathic hirsutism (normal serum testosterone in an ovulatory woman)
Idiopathic hyperandrogenism (patients who do not fall into any of the other categories listed)

From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders.

- Total plasma testosterone (normal range 20-60 ng/dl [0.69-2.1 nmol/L]) or free testosterone: Early morning on day 4 to 10 of menstrual cycle to screen for testosterone-secreting tumors. If moderately or markedly elevated (total testosterone >150 ng/dl [5.2 nmol/L], free testosterone >2 ng/dl [0.07 nmol/L]) may image adrenals and ovaries for androgen-secreting tumors

Other laboratory test considerations if appropriate:

- Prolactin: Moderately elevated values should prompt imaging of pituitary-hypothalamic region.
- 17-OHP (17 α-hydroxyprogesterone): Screen for adrenal enzyme deficiencies. Morning value >200 ng/dl in early follicular phase suggests nonclassic (late onset) congenital adrenal hyperplasia due to 21-hydroxylase deficiency and may be confirmed with high-dose (250 mcg) ACTH stimulation test.
- Thyroid-stimulating hormone (TSH): Rule out hypothyroidism.
- Dehydroepiandrosterone sulfate (DHEA-S): Screen for adrenal androgen production as almost entirely produced by adrenals. Levels >700 mcg/dl (13.6 nmol/L) raise suspicion for adrenal androgen-secreting tumor.

Additional laboratory test considerations if appropriate:

- Follicle-stimulating hormone (FSH): Rule out hypoestrogenic state (perimenopausal)
- Luteinizing hormone (LH): Typically elevated in PCOS with low or normal FSH
- 24-hour urinary free cortisol: Rule out Cushing syndrome and overproduction of cortisol
- Overnight single-dose dexamethasone suppression test: Rule out Cushing syndrome and adrenal hyperfunction
- Fasting blood sugar (FBS), 2-hr 75-g oral glucose tolerance test, fasting insulin levels: Rule out insulin resistance syndrome
- Table E1 summarizes laboratory tests for the differential diagnosis of androgen excess

IMAGING STUDIES

Imaging study considerations if appropriate:

- Pelvic ultrasound (high resolution, transvaginal): Rule out ovarian tumor if total testosterone is elevated.
- Abdominal CT/MRI: Rule out adrenal tumor if elevated DHEAS.
- Pituitary-hypothalamic region CT/MRI: Rule out pituitary tumor if prolactin elevated.
- Laparoscopy/laparotomy: Rule out small ovarian tumor in cases of elevated testosterone levels without radiologic evidence of adrenal or ovarian pathology.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Weight reduction: Can reduce androgen production indirectly by reducing insulin-stimulated theca cell androgen production and improve menstrual function, and slow hair growth in obese women
- Cosmetic: Temporary:
  1. Shaving: Does not stimulate hair growth; lasts days, leaves stubble
  2. Epilation: Electronic plucking
  3. Bleaching: Removes hair pigment. May cause skin irritation
  4. Mechanical waxing/plucking
  5. Depilatories: Gels, lotions, or creams that chemically disrupt sulfide bonds of hair causing dissolution of hair shaft. No stubble
  6. Photoepilation (laser and intense pulsed light [IPL]): Hair follicles destroyed by wavelengths of light absorbed by melanin. Good for pigmented hair; laser treatment is more effective than shaving, waxing, and electrolysis. It lasts 3 to 6 mo as vellus follicles remain and can be converted to terminal pigmented hair under excess androgens
- Cosmetic: Permanent. Electrolysis: Destroys individual hair follicles. May be expensive and time consuming

ACUTE GENERAL Rx

See "Pharmacologic Therapy."

CHRONIC Rx

See "Pharmacologic Therapy."

PHARMACOLOGIC THERAPY

- Usually second-line treatment following nonpharmacologic, physical methods of hair control, and in consideration of patient's comorbidities and risk factors, patient preferences, area of excess hair amenable to treatment, and access and affordability of treatments
- Pharmacologic treatments categorized as topical, oral contraceptive pills (OCPs), antiandrogens (potential adverse effects on a developing male fetus, so use with reliable contraception), other treatments directed at specific underlying etiology

TABLE E1 Laboratory Tests for the Differential Diagnosis of Androgen Excess

Initial Testing

Total testosterone
Prolactin
Thyroid-stimulating hormone

Further Testing Based on Clinical Presentation

17-Hydroxyprogesterone (8:00 A.M.)
17-Hydroxyprogesterone 60 min after IV ACTH
Cortisol (8:00 a.m.) after 1 mg dexamethasone at midnight
DHEAS
Androstenedione
Imaging of ovaries (transvaginal ultrasonography)
Imaging of adrenals (abdominal ultrasonography, CT, MRI)
Nuclear imaging after IV administration of radiolabeled cholesterol

ACTH, Adrenocorticotropic hormone; *CT,* computed tomography; *DHEAS,* dehydroepiandrosterone sulfate; *IV,* intravenous; *MRI,* magnetic resonance imaging.
From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders.

- Topical: Eflornithine topical cream 13.9%: Unclear mechanism of action; may inhibit ornithine decarboxylase, retarding hair growth. Temporary cosmetic treatment for facial hair. Applied directly to unwanted facial hair bid with at least 8-hr spaced applications. Does not remove hair, rather slows growth. Slow response over 4 to 8 wk. Hair growth returns upon discontinuation of treatment
- OCPs: Suppress ovarian steroidogenesis and LH through low-dose estrogen and low androgenic progestational agents. Slow response to treatment. Suppresses new hair growth. Established hair unaffected. Low-dose OCPs with low androgenic progestational agents, for example, desogestrel, drospirenone, norgestimate. Avoid norgestrel and levonorgestrel (higher androgenic progestational agents)
- Antiandrogens: Spironolactone: When OCPs unacceptable or may be added for disappointing results after 6 mo of OCP treatment:
  1. Aldosterone-antagonist diuretic inhibits adrenal and ovarian biosynthesis of androgens. May result in ovulation, so consider contraception needs
  2. Slow response usually 6 mo or more
  3. 200 mg PO qd, then decrease to 25 to 50 mg qd maintenance
  4. May cause hyperkalemia
  5. Anovulatory, unopposed estrogen states require progestin management

REFERRAL

- To endocrinologist if difficulty in determining diagnosis, achieving therapeutic goals, or resistant to first-line therapies. Prepubertal and postmenopausal hirsutism is suspicious for neoplastic or secondary endocrine causes and should be referred for further evaluation
- Consider referral or consultation for following therapies:
  1. Finasteride: Antiandrogen, in hair follicle blocks 5α-reductase conversion of testosterone to intranuclearly active 5α-dihydrotestosterone (DHT):
     a. Use only with reliable contraception because DHT necessary for normal male fetus urogenital development
     b. Not FDA approved for treatment of hirsutism
     c. 1 to 5 mg PO qd
  2. Flutamide: Inhibits androgen uptake and receptor binding:
     a. Not recommended by Endocrine Society Clinical Practice Guidelines and not FDA approved for treatment of hirsutism, but used by some European endocrinologists
     b. Use only with reliable contraception
     c. Reserved for women with severe, resistant hirsutism because of risk of hepatic dysfunction
  3. Cyproterone acetate: Antiandrogen that competes with DHT for binding androgen receptors. Used as progestin component of OCPs outside the U.S.
- Other treatments directed at specific underlying etiology:
  1. Metformin/thiazolidinediones: Therapy reserved for documented insulin-resistant states
  2. GnRH agonists: Recommended only in women with severe hyperandrogenemia (e.g., ovarian hyperthecosis) with suboptimal response to combination low-dose estrogen/progestin pills and antiandrogen treatment. Inhibits gonadotropin and consequently ovarian androgen and estrogen secretion
  3. Dexamethasone: Adrenal glucocorticoid suppression is reserved for diagnosis of adrenal enzyme deficiency
  4. Total abdominal hysterectomy/bilateral salpingo-oophorectomy reserved for recalcitrant hirsutism in older female with hyperthecosis and undesired fertility

PEARLS & CONSIDERATIONS

COMMENTS

- Hirsutism is both an endocrine and cosmetic problem for patients.
- Ovulation induction therapy is indicated in women desiring pregnancy.
- Delay checking serum androgens until oral contraceptives have been discontinued for 2 to 3 mo.
- Evaluation of incidental adrenal mass is always warranted.

RELATED CONTENT

Hirsutism (Patient Information)
Polycystic Ovary Syndrome (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Bode D et al: Hirsutism in women, *Am Fam Physician* 85(4):373-380, 2012.
Escobar-Morreale HF et al: Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society, *Hum Reprod Update* 18:146, 2012.

BASIC INFORMATION

DEFINITION

Langerhans cell histocytosis (LCH) is a clonal neoplastic proliferation of Langerhans-type dendritic cells that express CD1a, CD207, langerin, and S100 protein along with an accompanying inflammatory infiltrate. This leads to formation of granulomatous lesions (Box E1) that result in varying degrees of organ involvement and dysfunction (Table E1).

SYNONYMS

Eosinophilic granuloma (if solitary lesion)
Hand-Schüller-Christian disease (if multiple lesions)
LCH
Letterer-Siwe disease (if disseminated or visceral involvement)
Langerhans cell histiocytosis

ICD-10CM CODES

C96.0	Multifocal and multisystemic (disseminated) Langerhans-cell histiocytosis
C96.6	Unifocal Langerhans-cell histiocytosis
D76.3	Other histiocytosis syndromes
C96.5	Multifocal and unisystemic Langerhans-cell histiocytosis

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence is about 5 per million persons per yr, with most cases occurring in childhood.
- LCH is the most common histiocytic disorder.
- LCH affects males more often than females, with ratio of about 3.7:1.
- More common in whites of Northern European descent; rare in those of African descent.
- Disseminated LCH usually occurs before 2 yr of age.
- Primary Langerhans cell histocytosis of the lung is almost always a disease of smokers, usually nonclonal, and thought to represent a reactive process.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical presentation is highly variable.
- Patients with unifocal disease are usually older children and adults who most commonly present with a lytic bone lesion that is eroding the cortex of the bone (Fig. E1). Solitary lesion at other sites present as mass lesions or enlarged lymph nodes.
- Patients with unisystem multifocal disease (Hand-Schüller-Christian disease) are usually young children who present with multiple or sequential destructive bone lesions often associated with adjacent soft tissue masses. Skull and mandibular involvement is common. A benign isolated bony lesion (eosinophilic granuloma) is most often found in children younger than 15 yr of age.
- An aggressive disseminated disease infiltrating organs and causing organ dysfunction (Letterer-Siwe disease). This is the rarest form of LCH, affecting mostly children younger than 2 yr.
- Bone lesions (seen in about 80%):
  1. May be isolated or multiple
  2. Although some bone lesions may be asymptomatic, patients may complain of pain in the localized area of the bone
  3. The common sites of bone involved differ depending on the patient's age. In children, the most common bone involvement is the skull (~40%), followed by the femur, rib, vertebra, and humerus. In contrast, in adults, the primary sites of bone involvement are the jaw (30%), skull, vertebra, pelvis, and extremities
  4. Proptosis
  5. Mastoiditis
  6. Loose teeth
  7. Gingival hypertrophy
- Skin is involved in 40% of the patients (Fig. E2, Fig. E3), and common manifestations are brown to purplish papules or eczematous rash. Common sites: Scalp, neck, trunk, groin, and extremities. Cutaneous clues to Langerhans cell histiocytosis are summarized in Box E2.
- Lymphadenopathy is present in nearly 20% of patients. Cervical nodes are commonly involved. Involved lymph nodes are usually soft and matted on physical examination. Pulmonary disease is seen in approximately 10% of cases. More common in adults than in children. Patients with lung involvement may present with spontaneous pneumothorax or nonproductive cough, dyspnea, chest pain, or constitutional symptoms such as fever or weight loss. Diffuse emphysema associated with pulmonary fibrosis is the end stage of a mixed restrictive and obstructive pattern of disease.
- Liver involvement is seen in 15% to 20% of cases and presents as tumor-like or cystic lesions or as hepatomegaly. It can be accompanied by liver function abnormalities such as hyperbilirubinemia, elevated liver enzymes, or clotting factor deficiencies. Involvement of the biliary tree may present as progressive sclerosing cholangitis.
- Involvement of the spleen may present as massive splenomegaly (5% to 10%) with or without hypersplenism.
- Histocytosis X involves CNS in approximately 6% of the patients at the time of diagnosis. However, lesions of facial bone and those in the cranial fossa can have CNS involvement in approximately 25% of patients. The most common site affected is the hypothalamic-neurohypophyseal region, where infiltration and destruction usually manifest as diabetes insipidus, which manifests as insatiable thirst and urination. The other common CNS manifestations are symptoms of neurodegeneration (ataxia, cognitive dysfunction). Involvement of the thymus, parotid glands, and GI tract has been reported in rare cases.

ETIOLOGY

Historically, LCH has been presumed to arise from transformed or pathologically activated epidermal dendritic cells called Langerhans cells. New evidence suggests that LCH occurs as a consequence of misguided differentiation of myeloid dendritic cell precursors. Genetic, molecular, and functional data implicate activation of the ERK signaling pathway at critical stages in myeloid differentiation as an essential and universal driver of LCH pathology. A recent meta-review comprising 653 patient samples assessed an overall frequency of 48.5% for the *BRAF* V600E point mutation in LCH.

DIAGNOSIS

The diagnosis of LCH is made based on the biopsy of the involved organ. The key biopsy feature is identification of the LCH cells, which

BOX E1 Histiocytoses

Langerhans cell histiocytosis
Juvenile xanthogranuloma
Xanthoma disseminatum
Benign cephalic histiocytosis
Necrobiotic xanthogranuloma
Generalized eruptive histiocytoma
Progressive nodular histiocytoma
Indeterminate cell histiocytosis
Multicentric reticulohistiocytosis
Sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease)
Hemophagocytic syndromes
Malignant histiocytic syndromes

From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.

TABLE E1 Organ Involvement in Langerhans Cell Histiocytosis

Organ	Comment
Skin	Often the initial presenting sign
Bone	Painful swelling common; incidence: Skull > long bones > flat bones (ribs, pelvis, vertebrae)
Lymph nodes	Cervical most common
Liver	
Spleen	
Lungs	Diffuse micronodular pattern on radiography
Gastrointestinal tract	
Thymus	
Bone marrow	Pancytopenia portends a poor prognosis
Gingivae, buccal mucosa	Swelling, erythema, erosions, petechiae
Kidney	
Endocrine glands	Diabetes insipidus most common
Central nervous system	

From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.

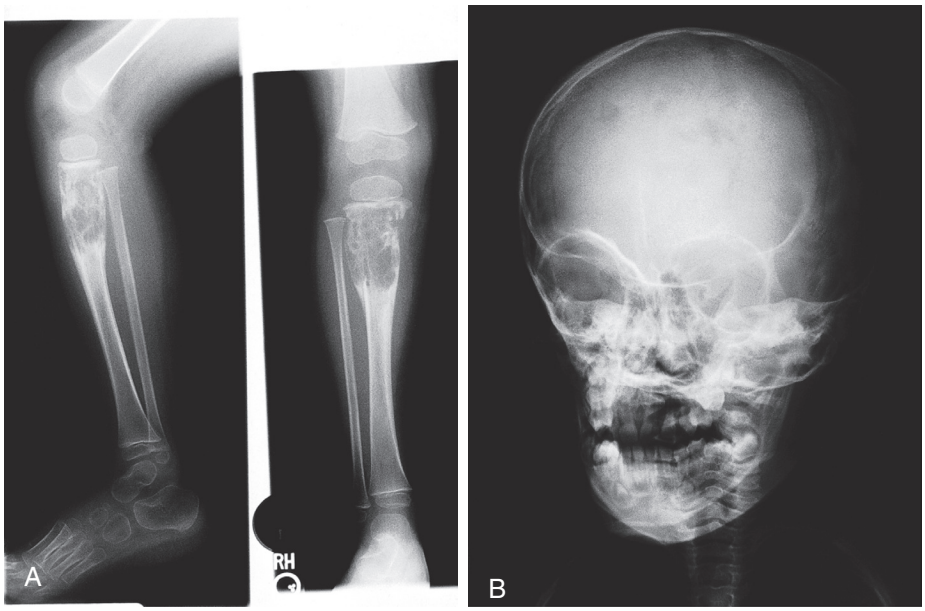

FIG. E1 Langerhans cell histiocytosis. Plain radiography reveals multiple lytic lesions in the tibia **(A)** and the skull **(B)** of a 4-yr-old child with disseminated disease. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

FIG. E2 Langerhans cell histiocytosis (LCH). Erythematous, crusted papules on the palm in this newborn with congenital multisystem LCH. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

FIG. E3 Neonatal Langerhans cell histiocytosis (LCH). These crusted, vesicular lesions were initially felt to be suggestive of neonatal varicella in this 10-day-old female. Biopsy confirmed LCH. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

BOX E2 Cutaneous Clues to Langerhans Cell Histiocytosis

Recalcitrant seborrheic dermatitis-like eruption
Localization of rash to scalp, posterior auricular regions, perineum, axillae
Eroded papules in flexural areas
Petechial or purpuric papules
Crusted papules on palms and/or soles (scabies preparation negative)
Any of the above lesions in combination with lymphadenopathy

From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.

TABLE E2 Distinguishing Characteristics of the Reactive Lymphohistiocytoses

	Genetic History	Virus Infection	Cellular Immune Function	Miscellaneous
HLH, genetic	Autosomal recessive	Possibly associated	↓ CMI ↓ NK cell activity ↓ Monocyte killing ↓ CMI	Perforin deficiency Hypertriglyceridemia, perforin (PRF1), Munc 13-4 mutations
Secondary infection–associated	Sporadic	Yes	↓ CMI NL or ↑ NK cell in instances associated with EBV ↓ Anomalous EBV-related killing	Coagulopathy early in the course of the disease
XLP	X-linked sporadic	EBV	NL or ↑ NK cell NL or ↑ anomalous EBV-related killing	*SH2DIA* mutation Severe, often fatal hepatitis
SHML	Sporadic	?EBV	Not reported	Autoimmune phenomena
LG	Sporadic	EBV	↓ CMI	Lymphoma development

CMI, Cell-mediated immunity; *EBV,* Epstein-Barr virus; *HLH,* hemophagocytic lymphohistiocytosis; *LG,* lymphomatoid granulomatosis: *NK,* natural killer; *NL,* normal; *SHML,* sinus histiocytosis with massive lymphadenopathy; *XLP,* X-linked lymphoproliferative syndrome.

From Nathan DG et al [eds]: *Nathan and Oski's hematology of infancy and childhood,* ed 6, Philadelphia, 2003, WB Saunders.

are oval with grooved, folded, indented, or lobulated nuclei with fine chromatin, inconspicuous nucleoli, and thin nuclear membranes. The characteristic milieu includes a variable number of eosinophils, histiocytes, neutrophils, and small lymphocytes. Occasionally, eosinophilic abscesses with central necrosis, rich in Charcot-Leyden crystals, may be found. The ultrastructure hallmark is the cytoplasmic Birbeck granules. Langerhans cells consistently express CD1a, CD207, langerin, and S100 protein.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of LCH is extensive because it is an uncommon disease that can affect multiple organ systems. LCH in bone, lymph nodes, thymus, and spleen can be confused with lymphoma, solid tumors, or CNS tumors, including germinoma and meningioma. Cutaneous involvement can mimic vasculitis and cutaneous lymphoma, and pulmonary involvement can mimic multiple diseases that cause interstitial lung disease. Histologically and immunophenotypically, LCH must be distinguished from other histiocytic and dendritic cell disorders, metastatic solid or hematopoietic neoplasms, and hemophagocytic lymphohistiocytic and macrophage activation syndromes. The common differential diagnoses are:

1. Erdheim Chester disease (ECD): Rare multisystem histiocytic disorder seen in adults.
2. Juvenile xanthogranuloma: Benign proliferative disorder of the histiocytic cells of the dermal dendrocytic phenotype.
3. Multiple myeloma.
4. Hemophagocytic lymphohistiocytiosis (HLH): HLH and related macrophage activation syndrome are systemic disorders with tissue infiltration by nonneoplastic histocytes.
5. Rosai Dorfman disease: A disease characterized by sinus histiocytosis with massive lymphadenopathy.

Histiocytosis syndromes of childhood are three classes based on histopathologic findings. Class I histiocytosis (also known as LCH) includes the clinical entities of eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease. Class II histiocytoses are nonmalignant proliferative disorders that are characterized by accumulation of macrophages. The two major diseases among the class II histiocytoses are hemophagocytic lymphohistiocytosis (FHLH) and infection-associated hemophagocytic syndrome (IAHS). These diseases are grouped together under the term *hemophagocytic lymphohistiocytosis* (HLH) (see Table E2). Class III histiocytoses are malignancies of cells of monotype-macrophage lineage (acute monocytic leukemia) and true malignant histiocytoses.

WORKUP

Baseline evaluation should include:

- Routine laboratory tests: CBC with differentials, chemistries with liver and renal functions, ESR, LDH, ferritin, uric acid, and urinalysis.
- Unilateral bone marrow aspiration and biopsy is indicated in patients with liver and spleen involvement, for patients with unexplained cytopenias, and for children younger than 2 yr of age.
- *BRAF* V600E mutation testing. This mutation is positive in about 65% of the pathologic dendritic cells.
- Radiographic evaluation should include a skeletal survey, skull series, bone scan, and chest radiograph. PET scan is also helpful in measuring the initial extent of disease.
- Other laboratory testing or radiologic imaging should be done depending on the symptoms and laboratory abnormalities.

LABORATORY TESTS

- CBC may reveal cytopenias in patients with bone marrow involvement or those with hypersplenism.
- Electrolytes, BUN, creatinine, urinalysis, and urine and serum osmolality are helpful in the diagnosis of diabetes insipidus.
- Results of liver function tests (LFTs) may be abnormal in patients with liver involvement.
- Bronchoalveolar lavage may show increased numbers of CD1a-positive histiocytes or Langerhans cells in patients with pulmonary LCH.

IMAGING STUDIES

- Radiograph studies of affected areas show lytic lesions with or without sclerotic margins.
- Panoramic dental view of the mandible and maxilla for children with oral involvement.
- Chest radiograph can show interstitial reticulonodular infiltrates. This pattern typically progresses toward frank honeycombing fibrosis later in the course of the disease (Fig. E4).
- High-resolution CT scan of the chest confirms interstitial lung scarring, nodules, and cysts and represents an excellent noninvasive means for diagnosis and follow-up of pulmonary LCH. Pulmonary cysts are bilateral and symmetric, showing slight upper-lobe predominance with relative sparing of the costophrenic angles.
- CT scan of the temporal bone is indicated for evaluation of mastoid and inner and middle ear involvement.
- Ultrasound of the abdomen is helpful for evaluation of hepatosplenomegaly.
- Conventional cholangiography or MRI cholangiopancreatography can confirm the presence of biliary involvement.
- MRI of the brain is indicated to visualize the hypothalamic-hypophyseal region in patients suspected of having diabetes insipidus.

Rx TREATMENT

Treatment is based on organ involvement and the extent of disease. LCH is usually stratified into single or multisystem LCH based on the organ system involvement. Single-system LCH patients typically do not have systemic symptoms. Multisystem LCH have two or more organ or system involvement.

- Single-system disease:
  Patients with truly limited single-site disease such as skin or bone may not need upfront intervention. The commonly available topical therapies for single organ or system involvement are as follows:
  1. Isolated bone lesions:
     a. Curettage of affected site and implantation of allograft bone chips or polymethylmethacrylate
     b. Intralesional prednisone
     c. Bisphosphonates
     d. NSAIDs
     e. Radiation therapy is useful for vertebrae or femoral neck lesions at risk of collapse
  2. Single skin lesions are treated with:
     a. Topical steroid (e.g., triamcinolone acetonide) applied bid
     b. Nitrogen mustard in 20% solution
     c. Surgery
     d. Intralesional interferon
     e. Isotretinoin

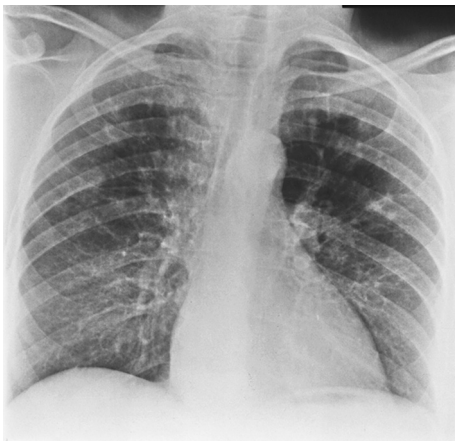

FIG. E4 Langerhans cell histiocytosis (LCH; histiocytosis X). There is a reticular nodular pattern in the upper lobes. The lung volumes are preserved.

3. Treatment of solitary lymph node involvement:
   a. Excision at the time of diagnosis
   b. Systemic oral prednisone

- Multisystem disease:
  Treatment of multisystem disease includes systemic chemotherapy (vinblastine and prednisone with mercaptopurine added for high-risk patients). Typically induction therapy is given for 6 wk, and if there is a response to therapy, the therapy is continued for a total of 1 yr. Patients with multisystem disease and risk of organ involvement (i.e., liver, spleen, and bone marrow) seem to benefit from combination chemotherapy regimens. Approximately 50% of patients fail to respond to standard systemic chemotherapy, justifying continued need for clinical trials.
  1. For severe, high-risk, disseminated cases not responding within 6 wk of initial treatment, salvage therapy, including high dose of the purine analogue cladribine along with high-dose cytosine arabinoside followed by allogeneic blood stem cell transplantation, should be considered. Additionally, liver or lung transplantation might be the treatment of choice for terminal liver and lung failure patients.
  2. Targeted therapy using vemurafenib has resulted in clinical responses in the majority of cases with the BRAF mutation.
  3. Diabetes insipidus is treated with DDAVP.
  4. Adults with isolated pulmonary LCH do not require aggressive treatment and benefit from smoking cessation.
  5. Empirical steroids, in either short pulses or longer exposures, has been used in the treatment of pulmonary disease; however, data regarding effectiveness are limited.
  6. Lung transplantation has been tried in both children and adults with advanced pulmonary disease and limited lung function, but failure rates are high because of local recurrence after transplantation.

PROGNOSIS & PREDICTIVE FACTORS

- Clinical course is related to staging of the disease at presentation, with 99% or greater survival for unifocal disease and 66% mortality for younger children with multisystem involvement who do not respond promptly to therapy.
- Involvement of bone marrow, liver, and lung are regarded as high-risk factors.
- Progression from initial focal disease to multisystem involvement can occur, most commonly in infants.
- Systemic and (rarely) multifocal disease can be complicated by hemophagocytic syndrome.

REFERRAL

Multidisciplinary approach: Pediatric oncologist, radiation oncologists, oral maxillary surgeons, ear-nose-throat specialists, audiology, dermatology, endocrinology, and family counseling

PEARLS & CONSIDERATIONS

COMMENTS

- The course of LCH is often unpredictable and varies from spontaneous resolution to rapid progression and death or multiple recurrences and regressions with risk for permanent sequelae.
- The association of LCH with other malignancies (e.g., acute lymphocytic leukemia, acute myeloid leukemia, and solid tumors) has been cited.

PATIENT & FAMILY EDUCATION

- Instruct patients to promptly report the development of hemoptysis. This symptom may indicate malignancy or superimposed bacterial–fungal infection, such as *Aspergillus* species infection.
- Educate about the likely etiologic role of cigarette smoking.

AUTHOR: **Bharti Rathore, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Histoplasmosis is caused by the fungus *Histoplasma capsulatum* and characterized by a primary pulmonary focus with occasional progression to chronic pulmonary histoplasmosis (CPH) or various forms of dissemination. Progressive disseminated histoplasmosis (PDH) may present with a diverse clinical spectrum, including adrenal necrosis, pulmonary and mediastinal fibrosis, and ulcerations of the oropharynx and GI tract. In those patients coinfected with HIV, it is a defining disease for AIDS.

SYNONYMS

- North American histoplasmosis
- Ohio Valley fever
- Vanderbilt disease

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Unknown for acute pulmonary disease
- For CPH, estimated at 1/100,000 cases in endemic areas
- For PDH in immunocompetent adults, estimated at 1/2000 cases of histoplasmosis

PREVALENCE: Unknown

PREDOMINANT SEX: Clinically evident disease is most common in males; male:female ratio of 4:1

PREDOMINANT AGE:

- CPH is most often seen in males >50 yr old with an associated history of COPD.
- Presumed ocular histoplasmosis syndrome (POHS) is seen between ages of 20 and 40 yr.

PEAK INCIDENCE: Unknown

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Conidia are deposited in alveoli then converted to yeast forms where they spread to regional lymph nodes and other organs, especially liver and spleen.
- 1 to 2 wk later, a granulomatous inflammatory response begins to contain the yeast in the form of discrete granulomas.
- Delayed-type hypersensitivity to *Histoplasma* antigens occurs 3 to 6 wk after exposure.
- Clinical disease manifests in various forms (Box E1), depending on host cellular immunity and inoculum size:
  1. **Acute primary pulmonary histoplasmosis:**
     a. An overwhelming number of patients are asymptomatic.
     b. Most clinically apparent infections manifest by complaints of fever, headache, malaise, pleuritic chest pain, nonproductive cough, and weight loss.
     c. Less than 10%, mainly women, complain of arthralgias, myalgias, and skin manifestations such as erythema multiforme or erythema nodosum (Fig. E1).
     d. Acute pericarditis presents in a smaller percentage of patients.
     e. Hepatosplenomegaly is most commonly observed in children.
     f. With particularly heavy exposure, there is severe dyspnea, marked hypoxemia, impending respiratory failure.
     g. Most patients are asymptomatic within 6 wk.
  2. **CPH:**
     a. Presents insidiously with low-grade fever, malaise, weight loss, cough, sometimes with blood-streaked sputum or frank hemoptysis.
     b. Most patients with cavitary lesions present with associated COPD or chronic bronchitis, masking underlying fungal disease.

BOX E1 Clinical Manifestations of Histoplasmosis

- Asymptomatic infection
- Pneumonia
- Progressive disseminated infection (HIV, immunocompromise, infancy)
- Mediastinal lymphadenopathy
- Cavitary pneumonia[a]
- Asthma-like illness
- Pleural effusion or granulomatous pleuritis[a]
- Obstruction or dysfunction of contiguous mediastinal structures (bronchi, esophagus) by granulomatous inflammation of lymph nodes (mediastinal granuloma)
- Isolated cervical or supraclavicular lymphadenopathy[a]
- Superior vena cava syndrome[a]
- Mediastinal fibrosis[a]
- Vocal cord granuloma
- Vocal cord paralysis
- Hemoptysis
- Broncholithiasis with lithoptysis[a]
- Chylothorax[a]
- Diaphragmatic weakness or paralysis
- Esophageal diverticulum or fistula
- Pericarditis
- Erythema nodosum
- Meningitis or focal cerebritis[a]
- Arthritis or arthralgias
- Parotitis
- Nephrocalcinosis
- Interstitial nephritis[a]
- Hypercalcemia
- Gastrointestinal tract ulceration or hemorrhage
- Gastrointestinal tract pseudomalignancy
- Crohn disease–like illness
- Biliary obstruction[a]
- Ocular histoplasmosis, choroiditis[a]
- Endocarditis[a]
- Adrenal mass[a]

[a]Rare in children.
From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

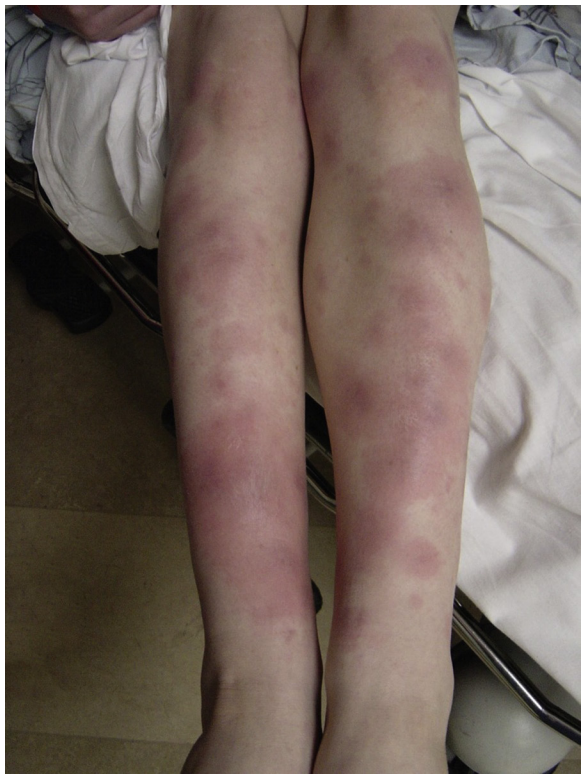

FIG. E1 Erythema nodosum in an adolescent boy with pulmonary histoplasmosis. (From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.)

c. Tends to worsen preexisting pulmonary disease and further contribute to eventual respiratory insufficiency.

3. **PDH:**
   a. In both acute and subacute forms, constitutional symptoms of fever, fatigue, malaise, and weight loss are common.
   b. Acute form (seen in infants and children) presents with respiratory symptoms, fever ≥101° F(38.3° C), generalized lymphadenopathy, marked hepatosplenomegaly, and fulminant course resembling septic shock associated with a high fatality rate.
   c. Subacute form is more common in adults and associated with lower temperatures, hepatosplenomegaly, oropharyngeal ulceration, focal organ involvement (including adrenal destruction, endocarditis, chronic meningitis, and intracerebral mass lesions).
   d. Course of subacute form is relentless, with untreated patients dying within 2 yr.
   e. Chronic PDH is found in adults and marked by gradual symptoms of weight loss, weakness, easy fatigability; low-grade fever when present; oropharyngeal ulcerations and hepatomegaly and/or splenomegaly in one third of patients.
   f. Less clinical evidence of focal organ involvement in chronic form than in subacute form.
   g. Natural history of chronic form is protracted and intermittent, spanning mos to yrs.

- **Histoplasmoma:**
  1. A healed area of caseation necrosis surrounded by a fibrous capsule
  2. Usually asymptomatic
- **Mediastinal fibrosis:**
  1. A rare consequence of a fibroblastic process that encases caseating mediastinal lymph nodes producing severe retraction, compression, and distortion of mediastinal structures
  2. Constriction of the bronchi resulting in bronchiectasis, also esophageal stenosis associated with dysphagia, and superior vena cava syndrome
- **POHS:**
  1. Diagnosis characterized by distinct clinical features, including atrophic choroidal scars and maculopathy in patients with histories suggestive of exposure to the fungus (e.g., residence in an endemic area)
  2. Patient complains of distortion or loss of central vision without pain, redness, or photophobia
  3. Usually no evidence of infection except for a positive skin reaction to histoplasmin
- **In patients with AIDS:**
  1. Possible presentation as overwhelming infection similar to acute PDH seen in children
  2. Constitutional symptoms: Fever, weight loss, malaise, cough, dyspnea
  3. About 10% with cutaneous maculopapular, erythematous eruptions or purpuric lesions on face, trunk, and extremities
  4. Up to 20% with CNS involvement, manifesting as intracerebral mass lesions, chronic meningitis, or encephalopathy

ETIOLOGY

- *H. capsulatum* is a dimorphic fungus present in temperate zones and river valleys worldwide.
- In the U.S., it is highly endemic in southeastern, mid-Atlantic, and central states (Ohio and Mississippi River valleys). Outside the U.S. it is distributed in Central and South America, the Caribbean, and in regions of Australia, India, and Africa.
- Exists as mold at ambient temperature and favors soils enriched with bird or bat droppings.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute pulmonary histoplasmosis:
  1. Mycobacterium tuberculosis
  2. Community-acquired pneumonias caused by *Mycoplasma* and *Chlamydia*
  3. Other fungal diseases, such as those caused by *Blastomyces dermatitidis* and *Coccidioides immitis*
- Chronic cavitary pulmonary histoplasmosis: *M. tuberculosis*
- Histoplasmomas: True neoplasms
- Sarcoidosis

WORKUP

- Suspect diagnosis in patients who present with a history of residence or travel in an endemic area, especially if engaged in occupations (e.g., outside construction or street cleaning) or hobbies (e.g., cave exploring) that increase the likelihood of exposure to fungal spores.
- Suspect diagnosis in immunosuppressed patients with remote history of exposure, especially if associated with characteristic calcifications on chest x-ray.

LABORATORY TESTS

- Detection of *Histoplasma* antigen in serum and urine. Urine antigen is 75% accurate in normal hosts and 95% in immunocompromised patients with disseminated disease. The sensitivity and specificity of the urinary antigen is also dependent on the stage of infection exceeding 80% in acute and disseminated infection but decreasing to less than 50% in chronic infection. The serum test is close to 100% accurate, but with *Blastomyces* and *Coccidioides*, tests may cross-react with infections. Tests can also be performed on bronchoalveolar lavage.
- Demonstration of organism on culture from body fluid or tissues biopsy (Fig. E2) will confirm the diagnosis in clinically suspected cases and negative urinary antigen.
  1. Especially high yield in patients with AIDS
  2. Characteristic oval yeast cells in neutrophils with Giemsa stain from peripheral smear
  3. Preparations of infected tissue with Gomori silver methenamine for revealing yeast forms, especially in areas of caseation necrosis
- Serologic tests, including complement-fixing (CF) antibodies and immunodiffusion assays.
- In PDH:
  1. Pancytopenia
  2. Marked elevations in alkaline phosphatase and alanine aminotransferase (ALT) common
- In chronic meningitis (majority of cases):
  1. CSF pleocytosis with either lymphocytes or neutrophils predominating
  2. Elevated CSF protein levels
  3. Hypoglycorrhachia

IMAGING STUDIES

- Chest x-ray in acute pulmonary histoplasmosis:
  1. Singular or multiple patchy infiltrates, especially in the lower lung fields
  2. Hilar or mediastinal lymphadenopathy with or without pneumonitis
  3. Diffuse nodular or confluent bilateral miliary infiltrates characteristic of heavier exposure
  4. Infrequent pleural effusions, except when associated with pericarditis
- Chest x-ray in histoplasmoma: Coin lesion displaying central calcification, ranging from 1 to 4 cm in diameter, predominantly located in the subpleural regions
- Chest x-ray in CPH (Fig. E3):
  1. Upper lobe disease frequently associated with cavities

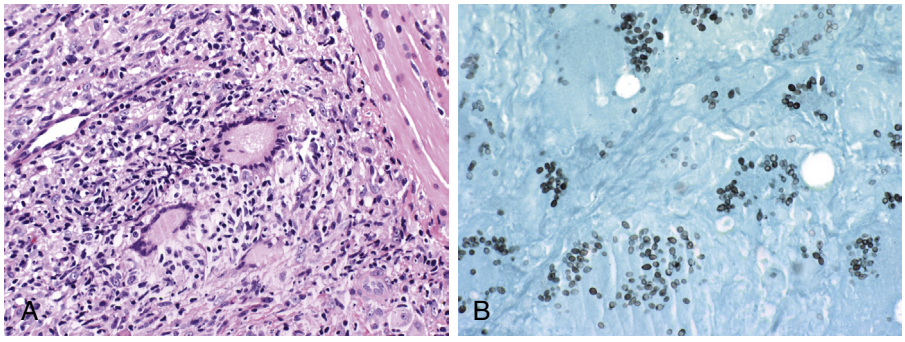

FIG. E2 A, Photomicrograph shows a tissue biopsy specimen from a patient with slowly progressing disseminated histoplasmosis. Granulomas are well formed, and no organisms are seen. Hematoxylin and eosin stain, ×450. **B,** Special stains better demonstrate yeast in tissue sections. Silver methenamine stain, ×450. (From Mason RJ: *Murray & Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, WB Saunders.)

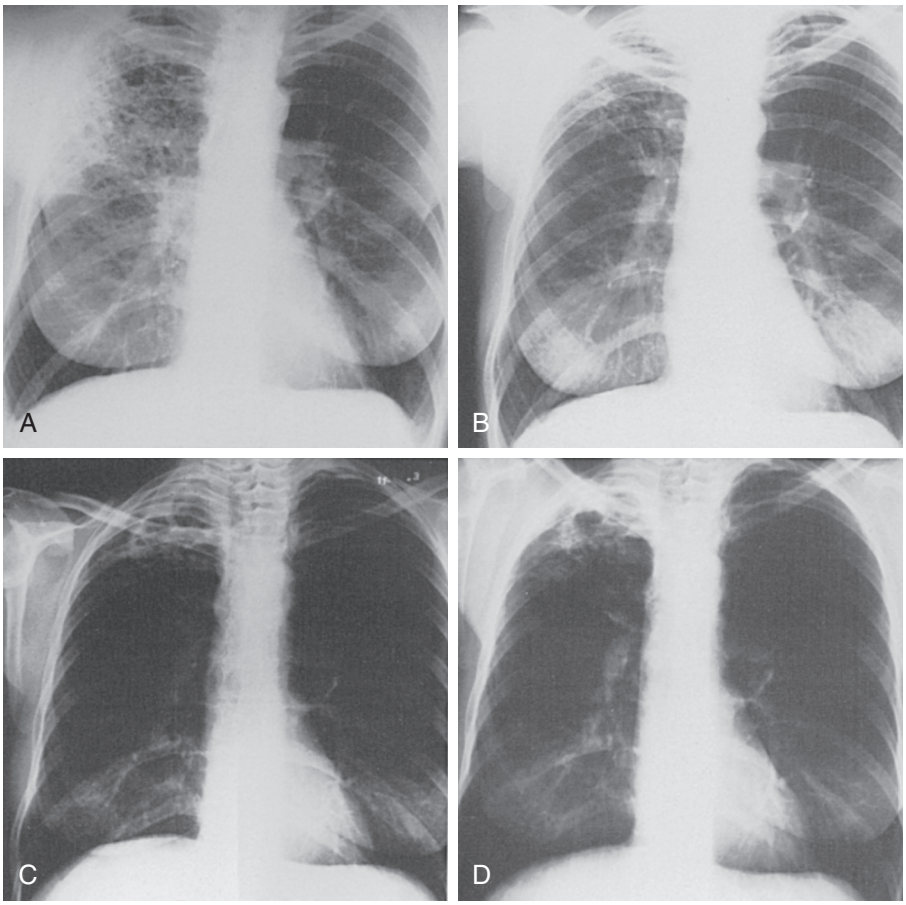

FIG. E3 The evolution of chronic pulmonary histoplasmosis in a smoker. A, At the onset of the illness, the chest radiograph shows multiple cavity-like air spaces. **B,** 2.5 yr later, fibrosis has occurred with volume loss of the lobe and retraction of the hilum. **C,** A further 17 mo later, the entire right upper lobe appears to be destroyed. **D,** There are signs of continued activity and a residual cavity at the time of diagnosis. The sputum culture was positive for *Histoplasma capsulatum*. (From Mason RJ: *Murray & Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, WB Saunders.)

2. Preexisting calcifications in the hilum associated with peribronchial streaking extending to the parenchyma
- Chest x-ray in acute PDH: Hilar adenopathy and/or diffuse nodular infiltrates
- CT scan of adrenals to reveal bilateral enlargement and low-attenuation centers

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

For life-threatening disease seen in acute disseminated disease or infection in patients with AIDS: Supportive therapy with IV fluids

ACUTE GENERAL Rx

- No drug therapy is required for asymptomatic pulmonary disease.
- A course of therapy with itraconazole 200 mg PO tid for 3 days, then 200 mg/day PO for 6 to 12 wk may be beneficial in some patients with acute pulmonary distress. Avoid fluconazole because it is not as active.
- Same therapy appropriate for immunocompetent, mild to moderately symptomatic patients with CPH and subacute and chronic forms of PDH, but duration for 6 to 12 mo.
- Use amphotericin B 0.7 to 1 mg/kg IV q day for initial therapy in moderate to severe disease and then transition to oral itraconazole within 1 to 2 wk. Lipid formulations of amphotericin can be used to avoid nephrotoxicity of amphotericin B, and they produce better outcomes in terms of mortality, rates of culture conversion, and side effects.
- Liposomal amphotericin: 3 mg/kg/day IV or amphotericin B lipid complex: 5 mg/kg/day.
- Posaconazole is highly effective as well, but voriconazole is less active in vitro than itraconazole and posaconazole. Isavuconazole is also active in vitro, but echinocandins such as micafungin are not effective.
- Chronic cavitary pulmonary histoplasmosis: Itraconazole 200 mg PO tid for 3 days, then once or twice daily for at least 12 mo.
- CNS histoplasmosis: Liposomal amphotericin B, 5 mg/kg/day for a total of 175 mg/kg over 4 to 6 wk, then itraconazole 200 mg 2 to 3×/day for at least 12 mo.
- Endocarditis: Surgical treatment with excision of infected valve or graft combined with amphotericin for a total dose of 35 mg/kg or 2.5 g.
- For pericardial disease:
  1. Antifungal therapy: No apparent benefit
  2. Best managed with NSAIDs
- For POHS:
  1. Antifungal therapy: No apparent benefit
  2. May respond to laser therapy

CHRONIC Rx

- In patients with AIDS: Lifelong suppressive therapy with either itraconazole, given 200 mg PO q day, or IV amphotericin B at a dose of 50 mg once weekly; a triazole compound posaconazole (400 mg PO bid) may be useful in refractory cases, but clinical experience is limited at this point
- Prophylaxis in HIV-infected patients with <150 CD4 cells/mm^3: Itraconazole 200 mg PO qd

DISPOSITION

For those with chronic or progressive disease, especially if immunocompromised, prognosis is dependent on prompt recognition and timely administration of appropriate antifungal drugs.

REFERRAL

- To an infectious disease specialist in suspected cases of disseminated disease, especially if immunocompromised
- To a pulmonologist for patients with CPH form because of progressive respiratory compromise
- To a thoracic surgeon for decompression procedures for progressive mediastinal fibrosis

PEARLS & CONSIDERATIONS

- *H. capsulatum*, variety *duboisii*, also known as African histoplasmosis, is restricted to Senegal, Nigeria, Zaire, and Uganda.
- Unlike *H. capsulatum*, pulmonary forms of *duboisii* are not seen, and the disease is limited to the skin, soft tissues, and bone.

COMMENTS

- Patients living in endemic areas, especially if immunocompromised, should take appropriate respiratory precautions when disposing of bird waste from rooftop or home aviaries.
- Appropriate respiratory precautions should also be taken when leisure traveling to areas that act as a natural haven for the fungus, such as bat caves.

RELATED CONTENT

Histoplasmosis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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Hage CA et al: Histoplasmosis: up-to-date evidence-based approach to diagnosis and management, *Semin Respir Crit Care Med* 36:729-745, 2015.

Wheat LJ et al: Histoplasmosis, *Infect Dis Clin North Am* 30:207-227, 2016.

BASIC INFORMATION

DEFINITION

Patients with histrionic personality disorder (HPD) present with a pervasive pattern of excessive emotionality and attention-seeking behavior that generally begins in early adulthood. The individual must meet five or more of the following criteria:

1. Is uncomfortable in situations where he or she is not the center of attention
2. Interaction with others is often characterized by inappropriate sexually seductive or provocative behavior
3. Displays rapidly shifting and shallow expression of emotions
4. Consistently uses physical appearance to draw attention to self
5. Has a style of speech that is excessively impressionistic and lacking in detail
6. Shows self-dramatization, theatricality, and exaggerated expression of emotion
7. Is suggestible (i.e., easily influenced by others or circumstances)
8. Considers relationships to be more intimate than they actually are

SYNONYMS

Hysterical personality disorder
Psycho-infantile personality disorder
Personality disorder (nonspecific)
Personality disorder (trait specified)

ICD-10CM CODE	
F60.4	Histrionic personality disorder
DSM-5 CODE	
301.5	Histrionic personality disorder

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.):

- Diagnosed more often in women (85%); rarely found in men
- Prevalence: 1% to 3%

PREDOMINANT SEX: Female. Cultural factors (e.g., attention-seeking behavior not as acceptable in men) may lead to more common diagnosis in women.

PREDOMINANT AGE: Generally begins in early adulthood.

GENETICS: Limited research using interview and self-report methods suggests that histrionic personality disorder has a moderate genetic component.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- No specific physical findings
- Exaggerated emotionality
- Clinical presentation:
  1. Exaggerated, shallow, and/or rapidly shifting emotions
  2. A pattern of repeated attention-seeking behavior, often suggestive or provocative
  3. Theatrical

ETIOLOGY

- Unknown
- Hypothesized that childhood events, psychosocial adversity, and genetics are contributory
- A two-generation study by Cloninger and Guze (1975), showed that the daughters of fathers with sociopathy had a higher prevalence of hysteria than did daughters of other fathers. The differences were significant both for daughters with hysteria comorbid with sociopathy and for daughters with hysteria alone

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other cluster B personality disorders (narcissistic, borderline personality disorder especially hysteroid dysphoria, antisocial personality disorder) share some common features
- Other personality disorders (e.g., dependent personality disorder)
- Personality change attributable to general medical condition
- Symptoms in association with chronic substance abuse

WORKUP

There is no formal test to establish diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Long-term individual psychotherapy is treatment of choice.
- One controlled study exists, suggesting that patients in schema therapy experience greater functional improvement and symptom reduction compared with treatment-as-usual and clarification-oriented psychotherapy.
- Unlike other people who have personality disorders, these individuals often seek treatment and exaggerate their symptoms and difficulties in functioning.
- Patients tend to be more emotionally needy and are often reluctant to terminate therapy.

ACUTE GENERAL Rx

- No placebo-controlled trials.
- Impulsive-aggressive variants can occasionally benefit from selective serotonin reuptake inhibitor (SSRI) antidepressants.
- Care should be given when prescribing medications because of the potential for self-destructive or otherwise harmful behaviors.

DISPOSITION

- Therapeutic approaches should not focus on the long-term personality change but rather short-term alleviation of specific difficulties and deficits within the person's life.
- Therapeutic approaches that emphasize vague somatic, anxious, or depressive symptoms often fail.
- Patients are likely to be intolerant or drop out of treatment approaches that use delayed gratification.
- Symptoms are moderately stable over adulthood and may remit or decrease in intensity with age.

REFERRAL

Primarily treated by mental health professionals

PEARLS & CONSIDERATIONS

- This disorder is difficult to treat.
- Like most personality disorders, patients present for treatment primarily when stress or other situational factors within their lives have made their ability to function and cope effectively impossible.
- Suicidality and risk of self-injury should be assessed on a regular basis, and suicidal threats and self-mutilation should not be ignored or dismissed. Patients may present with a higher risk for (or history of) suicidal gestures.
- Patients may report high rates of impulsive behavior motivated by sensation- or novelty-seeking.
- An alternative model in DSM-5, section III, reconceptualizes histrionic personality disorder as "Personality Disorder, Trait Specified," which rates (1) impairment in personality functioning (identity, self-direction, empathy, and/or intimacy) and (2) pathologic trait domains such as attention seeking, grandiosity, and manipulativeness.

PATIENT & FAMILY EDUCATION

Group and family therapy approaches are generally not recommended because individuals with this disorder often try to draw attention to themselves and exaggerate every action and reaction.

AUTHORS: **Mark Zimmerman, MD,** and **Theresa A. Morgan, PhD**

SUGGESTED READINGS

Bamelis L et al: Results of a multicenter randomized controlled trial of the effectiveness of schema therapy for personality disorder, *Am J Psych* 171:305-322, 2014.

Cloninger CR, Guze SB: Hysteria and parental psychiatric illness, *Psychol Med* 5:27-31, 1975.

Torgersen S et al: The heritability of cluster B personality disorders assessed both by personal interview and questionnaire, *J Pers Disord* 17:848-866, 2012.

BASIC INFORMATION

DEFINITION

HIV-associated cardiomyopathy (HIVAC) encompasses several distinct types of heart failure with different etiologies. Before widespread use of antiretroviral therapy (ART), HIVAC manifested as symptomatic systolic dysfunction, with or without ventricular dilatation, in patients with end-stage AIDS. This condition is now mostly seen in regions where patients do not have easy access to ART. It is considered a Stage IV HIV-defining illness and indicates a poor prognosis. With the use of ART, the definition of HIVAC is evolving and includes a growing prevalence of diastolic dysfunction in asymptomatic individuals with adequate viral suppression.

SYNONYM

HIVAC

ICD-10CM CODES

I42.9 Cardiomyopathy, unspecified
B20 Human immunodeficiency disease

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE & PREVALANCE:

- The rate of systolic heart failure increases with decreasing CD4 counts and is especially prevalent with CD4 counts of less than 100 cells/mm^3. Before the use of ART, studies indicate that up to two thirds of AIDS patients had myocarditis on autopsy and half of all hospitalized patients with HIV had cardiomyopathy.
- In sub-Saharan Africa, 2.6% of all patients presenting to the hospital with decompensated heart failure have HIVAC. The mortality from HIVAC in some of these areas is as high as 15% to 20%.
- In high-income countries, the use of ART has decreased the risk of systolic dysfunction significantly to less than 10%. Conversely, the rate of subclinical diastolic dysfunction has increased to more than 40%.
- Risk factors include high viral load, low CD4 count, low selenium count, increased duration of HIV infection, and low socioeconomic status.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients typically present with new-onset heart failure in the setting of late-stage HIV. They display classic features of heart failure, including respiratory distress from pulmonary edema.
- Patients who are treated with ART may develop signs and occasional symptoms of subclinical cardiac dysfunction, whether systolic or diastolic. They can have abnormal ventricular filling, pulmonary hypertension, and decreased exercise capacity.

ETIOLOGY

There are multiple etiologies of systolic dysfunction in HIV patients. These include:

- Direct cardiotoxic effects of HIV infection causing cardiomyocyte apoptosis and myocardial infiltration with macrophages, starting as early as the acute phase of HIV infection
- Myocarditis via opportunistic infections, both viral and nonviral, including tuberculous myopericarditis, or toxoplasma and cryptococcal myocarditis
- Cardiac autoimmunity with HIV infection leading to increased risk for coronary artery disease
- Micronutrient deficiency, particularly of selenium, due to malnutrition and HIV wasting
- Zidovudine therapy, which causes myocardial damage through pathologic changes in mitochondria, an effect that is dose dependent and reversible on discontinuation of this medication:
  1. Note that there is a high prevalence of zidovudine use in low-income countries due to economic constraints, despite the availability of other, less cardiotoxic ART regimens.
- Many antiretroviral medications cause myocardial fibrosis and steatosis, which may impair contractility and lessen ventricular compliance
- An increased risk of ischemic cardiomyopathy

The diastolic dysfunction more prevalent in high-income countries is most likely due to a combination of chronic inflammation and the use of ART.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Ischemic cardiomyopathy: Patients receiving ART have an increased risk for atherosclerotic disease because of metabolic syndrome, likely caused by many HIV medications and greater life expectancy.

WORKUP

- Echocardiogram is the only test used to diagnose HIV-associated cardiomyopathy.
- There is currently no routine screening that is recommended.

TREATMENT

- Management is essentially the same as that for other cardiomyopathies. The treatment for acute decompensated heart failure is diuresis. Long-term care of systolic dysfunction would require the use of beta-blockers and ACEi/ARBs, as tolerated, to prevent progression of disease.
- ART should be started immediately in diagnosed individuals, despite the risk of cardiotoxicity from these medications.
- If a patient is already on ART, which includes zidovudine, changing ART regimen could be considered, as the cardiotoxic effects of this medication may be reversible.
- For end-stage heart failure, mechanical assist devices or cardiac transplant are options, although less available to HIV-infected individuals.

DISPOSITION & REFERRAL

- Infectious disease specialist: Referral to ensure treatment with the most appropriate ART regimen
- Cardiology: As with other forms of cardiomyopathy, depending on the degree of heart failure

PEARLS & CONSIDERATIONS

- Management of patients with HIV-associated cardiomyopathy should prioritize identification and correction of other concomitant causes of cardiomyopathy that may require specific therapies, including opportunistic infections, cardiotoxic drugs, and CAD.
- Left ventricular function is an independent predictor of death in adults infected with HIV.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Acquired Immunodeficiency Syndrome (Related Key Topic)
Cardiomyopathy, Dilated (Related Key Topic)
Human Immunodeficiency Virus (Related Key Topic)

AUTHORS: **Anshul Parulkar, MD,** and **Dominick Tammaro, MD**

SUGGESTED READINGS

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Lumsden RH, Bloomfield GS: The causes of HIV-associated cardiomyopathy: a tale of two worlds, *Biomed Res Intl* 2016:8196560, 2016, https://doi.org/10.1155/2016/8196560.

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Schuster C et al: Acute HIV infection results in subclinical inflammatory cardiomyopathy, *J Infect Dis* 218(3):466-470, 2018, https://doi.org/10.1093/infdis/jiy183.

Vachiat A et al: HIV and ischemic heart disease, *J Am Coll Cardiol* 69(1):73-82, 2017, https://doi.org/10.1016/j.jacc.2016.09.979.

BASIC INFORMATION

DEFINITION

- HIV-associated cognitive dysfunction covers a spectrum of disorders ranging from asymptomatic (asymptomatic neurocognitive impairment) to mild (mild neurocognitive disorder) to severe (including HIV-associated dementia).
- Cognitive, motor, and behavioral abnormalities.

SYNONYMS

HAD
HAND
HIV-associated neurocognitive disorder (HAND)
HIV dementia
HIV-associated dementia
Mild neurocognitive disorder
AIDS dementia complex
HIV-1 encephalopathy

ICD-10CM CODES

B20	Human immunodeficiency virus [HIV] disease
R41.8	Other and unspecified symptoms and signs involving cognitive functions and awareness
B97.35	Human immunodeficiency virus, type 2 [HIV 2] as the cause of diseases classified elsewhere

EPIDEMIOLOGY

- According to the CHARTER study, approximately 52% of HIV-infected individuals have HAND. The largest group has asymptomatic neurocognitive impairment (approximately 33%), followed by minor neurocognitive disorder (12%), and HIV-associated dementia (2%).
- The epidemiology has changed in the era of antiretroviral therapy (ART), with the number of cases of HIV-associated dementia (HAD) falling from 15% in the pre-ART era to 2% now, but the proportion of mildly affected patients is increasing.
- As HIV-infected patients live longer, the prevalence of HAND may be increasing.

CLINICAL FEATURES

- The 2007 Frascati Criteria for HAND require assessment of five cognitive domains: Verbal/language ability, attention and working memory, abstraction and executive function, speed of information processing, sensory perceptual skills, and motor skills. The criteria define three levels of HAND:
  1. Asymptomatic neurocognitive disorder: An acquired impairment in at least two cognitive domains as defined by a performance on neuropsychological testing of more than 1 SD below expected age and education-adjusted norms. This impairment does not impact daily functioning, and the patient may be unaware of its existence.
  2. Mild neurocognitive disorder: An acquired impairment in at least two cognitive domains as defined by a performance on neuropsychological testing of more than 1 SD below expected age and education-adjusted norms. This impairment does impact daily functioning to a mild degree. For example, work efficiency is decreased, but the patient can compensate for the deficits.
  3. HIV-associated dementia: An acquired impairment in at least two cognitive domains as defined by a performance on neuropsychological testing of more than 2 SD below expected age and education-adjusted norms. This impairment does impact daily functioning to a significant degree.
- Cognitive changes: Forgetfulness, poor attention and concentration, increased difficulty performing complex tasks, slowed psychomotor speed.
- Behavioral changes: Apathy, lack of initiative, social withdrawal, irritability, occasionally agitation, psychosis, or obsessive-compulsive disorder.
- Motor problems: Clumsiness, unsteady gait, poor balance, tremor, leg weakness.
- Progressive/later stages: Bedbound, severe dementia, bowel/bladder incontinence.
- Classically HIV-associated dementia was described as a classic subcortical dementia (attention, concentration, working memory, and executive function difficulties being prominent features). However, in the ART era, more patients are developing cortical features.
- Results from inflammation triggered by HIV itself (not related to opportunistic infection) and immune activation of microglia and brain macrophages.
- In children: Developmental delay, microcephaly, and spasticity are common.
- Table E1 summarizes features of HIV-associated neurocognitive disorder.

RISK FACTORS

- Low CD4 count (less than 200 cells/mm^3)
- High viral load
- Anemia
- Injection drug use
- Hepatitis C
- Female gender
- Older age

DIAGNOSIS

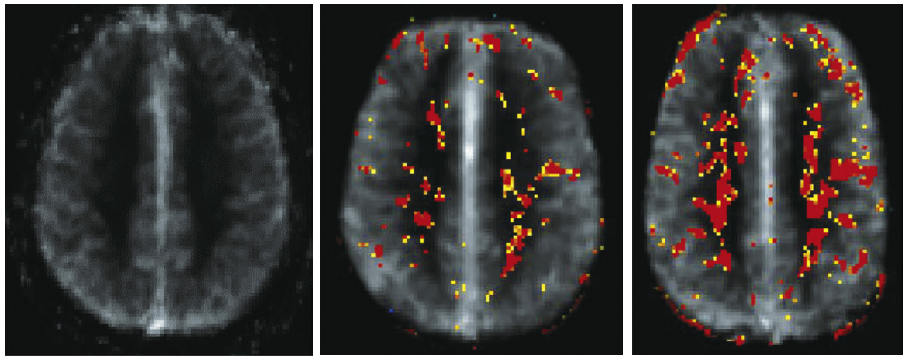
WORKUP

- Diagnosis is based on clinical examination and neuropsychologic tests and exclusion of opportunistic processes.
- CT of brain may show subcortical hypodensities, enlarged ventricles, and cortical atrophy greater than expected for age.
- MRI head (Fig. E1, Fig. E2): Diffuse, confluent, periventricular white matter hyperintensities on T2-weighted images with cortical atrophy and enlarged ventricles. The white matter hyperintensities are not mandatory for the diagnosis.
- Lumbar puncture: CSF analysis helps to rule out opportunistic infections. In HIV-related cognitive dysfunction, the CSF may show a nonspecific increase in cell count and protein but may also be normal.
- Subtle electrophysiologic abnormalities can be found in early HIV-1 infection (on

TABLE E1 Clinical Triad in Human Immunodeficiency Virus Type 1–Associated Neurocognitive Disorder

Cognition	Behavioral	Motor
Forgetfulness	Apathy	Gait instability
Mental slowing	Social withdrawal	Poor coordination
Decreased concentration	Lack of spontaneity	Leg weakness

From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 8, Philadelphia, 2015, Saunders.



Asymptomatic MCMD HAD

FIG. E1 Perfusion MRI (pMRI) maps showing regions of increasing cerebral blood volume (CBV) with advancing HIV groups: Asymptomatic, minor cognitive–motor disorder (MCMD), and HIV-associated dementia (HAD). Areas of red indicate >2 standard deviations elevation in CBV. (Tucker KA et al: Neuroimaging in human immunodeficiency virus infection, *J Neuroimmunol* 157[1-2]:153-162, 2004.)

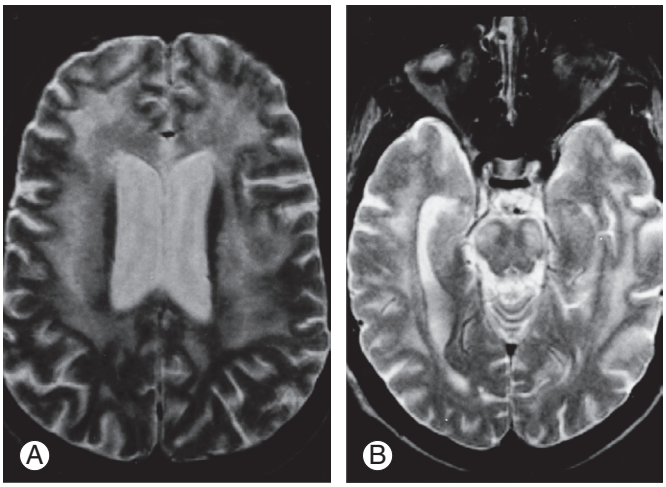


FIG. E2 Advanced HIV encephalopathy. Axial T2WI. There is diffuse confluent and symmetrical abnormal high signal returned from the white matter of the cerebral hemispheres **(A),** which is also extending into the brainstem to involve the cerebral peduncles **(B).** In this patient there is also generalized atrophy. Features that help to differentiate HIV from PML are the symmetry of the changes and the lack of signal abnormalities on T1WI. (From Adam A, Dixon AK, Grainger RG, Allison DJ. Grainger & Allison's diagnostic radiology, 5th ed. Churchill Livingstone, 2007, in Grant, LA: *Grainger & Allison's Diagnostic Radiology Essentials,* ed 2, 2019, Elsevier.)

electroencephalography, evoked potentials, nerve conduction studies), but they do not seem to have a predictive value for the later onset of HIV-associated dementia, which correlates most with a history of the CD4+ T-lymphocyte nadir of less than 200 cells/microliter.

- Potential causes for cognitive impairment that must be ruled out include:
  1. Opportunistic central nervous system (CNS) processes (e.g., toxoplasmosis, primary CNS lymphoma, progressive multifocal leukoencephalopathy, cytomegalovirus encephalitis, cryptococcal meningitis)
  2. HIV-mediated CD8 encephalitis
  3. General paresis of the insane due to syphilis
  4. Vitamin B_{12} deficiency resulting in subacute combined degeneration
  5. Substance use
  6. Alcoholism
  7. Psychiatric disorders such as depression, anxiety, bipolar disorder, or schizophrenia
  8. Side effects of prescribed medications

Rx TREATMENT

Early treatment with antiretroviral therapy (ART) may lead to clinical improvement in some patients, but in many cases, cognitive dysfunction persists despite ART.

Maintaining high CD4 count and not allowing CD4 count to nadir below 200 cells/microliter may protect against the development of HAND.

PEARLS & CONSIDERATIONS

- Initiation of ART can lead to rapid improvement in cognitive function in early stages
- Untreated, life span of patient with HIV-associated dementia is typically 4 to 6 mo.
- Most common presenting complaint in children infected with HIV.
- Patients may have other medical or psychiatric conditions or a social history that seriously confounds the diagnosis of HIV-associated neurocognitive disorder.
- Five HIV-related opportunistic infections that commonly cause cognitive impairment are toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy, primary CNS lymphoma, and cytomegalovirus encephalitis.
- HIV-associated CD8 encephalitis is subacute, progressive encephalopathy characterized by diffuse perivascular and intraparenchymal CD8+ lymphocytic infiltration. MRI shows hyperintensity of the white matter on T2 sequences and linear or punctate enhancement in a perivascular distribution on T1 post-gadolinium sequences. CSF analysis reveals elevated protein and a CD8+ T-cell-predominant pleocytosis. Treatment is with high-dose corticosteroids and can result in a good outcome despite an initially poor neurological status.

REFERRALS

- Upon diagnosis/clinical suspicion for HIV-associated cognitive dysfunction, referral to neurology is recommended.
- Referral to neuropsychology may be considered.
- Referral to infectious disease specialist to manage HIV infection.

AUTHOR: **Joseph S. Kass, MD, JD, FAAN**

SUGGESTED READINGS

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Zarkali A, Gorgoraptis N, Miller R et al: CD8+ encephalitis: a severe but treatable HIV-related acute encephalopathy, *Practical Neurology* 17:42-46, 2017.

BASIC INFORMATION

DEFINITION

Compulsive hoarding is defined as the acquisition of and failure to discard a large number of possessions that appear to be useless or of limited value, with living spaces sufficiently cluttered so as to preclude activities for which those spaces were designed and significant distress or impairment in functioning caused by the hoarding. Hoarding has historically been a criterion of obsessive-compulsive personality disorder. With the publication of the DSM-5 (2013), compulsive hoarding is now recognized as a distinct form of psychopathology.

- Persistent difficulty discarding or parting with possessions, regardless of the value others may attribute to these possessions. (The Work Group is considering alternative wording: "Persistent difficulty discarding or parting with possessions, regardless of their actual value.")
- This difficulty is due to strong urges to save items and/or distress associated with discarding.
- The symptoms result in the accumulation of a large number of possessions that fill up and clutter active living areas of the home or workplace to the extent that their intended use is no longer possible. If all living areas become decluttered, it is only because of the interventions of third parties (e.g., family members, cleaners, authorities).
- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning (including maintaining a safe environment for self and others).
- The hoarding symptoms are not due to a general medical condition (e.g., brain injury, cerebrovascular disease).
- The hoarding symptoms are not restricted to the symptoms of another mental disorder (e.g., hoarding due to obsessions in obsessive-compulsive disorder, decreased energy in major depressive disorder, delusions in schizophrenia or another psychotic disorder, cognitive deficits in dementia, restricted interests in autism spectrum disorder, food storing in Prader-Willi syndrome).

Specify if:

- With excessive acquisition: If discarding possessions is accompanied by excessive acquisition of items that are not needed or for which there is no available space

Specify if:

- With good or fair insight
- With poor insight
- With absent insight/delusional beliefs

SYNONYMS

Hoarding
Obsessive-compulsive disorder
Obsessive-compulsive personality disorder
Anankastic personality disorder
Saving
Collecting
Clutter

ICD-10CM CODE
F42.9 Obsessive compulsive disorder, unspecified
DSM-5 CODE
300.3 Obsessive compulsive disorder

EPIDEMIOLOGY, PREVALENCE & DEMOGRAPHIC

- Community surveys suggest that the prevalence of clinically significant compulsive hoarding is estimated to be somewhere between 2% and 6%. National studies on prevalence are not yet available.
- Clinical samples suggest a higher prevalence among females, but some epidemiologic studies suggest a higher prevalence among males.
- Hoarding onset typically starts in early adolescence.
- Late-onset hoarding is rare.
- Available data outside of the U.S. suggest that hoarding is a universal phenomenon.
- Hoarding tendencies tend to begin in childhood or adolescence and become clinically significant by middle age.
- Hoarding may have a sudden onset in adulthood after experiencing a traumatic event.
- A large percentage of individuals who hoard report having at least one first-degree relative who experiences hoarding problems. The link appears to be stronger among first-degree female relatives (e.g., mothers, sisters).
- It is estimated that one in four people with OCD are hoarders.
- Hoarding tends to be a chronic condition with spontaneous remission a rarity.

Associated with Axis I (Major Depressive Disorder, Social Phobia, Obsessive-Compulsive Disorder, Generalized Anxiety Disorder, and Attention-Deficit Hyperactivity Disorder) and Axis II (Borderline Personality Disorder and Avoidant Personality Disorder).

RISK FACTORS

- Genetic vulnerabilities and early attachment experiences are thought to contribute to hoarding behavior.
- Social isolation can lead to hoarding behavior as a way to provide comfort.
- A sudden traumatic event can lead to hoarding behavior as a coping mechanism.
- Family history.
- Age.

ETIOLOGY

Although the etiology is unknown, hoarders share a number of characteristics, including problems with emotional attachments to possessions (i.e., viewing their possessions as extensions of themselves), behavioral avoidance (i.e., a fear of making a decision about what to do with a possession), beliefs about the nature of possessions (i.e., an exaggerated desire for control over possessions and a sense of responsibility to take care of the possessions and to be prepared for the future), perfectionism (i.e., possessions must be used perfectly such as a belief that a newspaper must be thoroughly read), information-processing deficits (i.e., deficits in decision making, difficulty in memory functions, and deficits in categorization and organization), and an avoidance of waste. Physical abuse and sexual trauma have been associated with greater acquiring tendencies but not with saving. Intense negative emotional reactions (sadness) may also play a role in the etiology. Hoarding in children has been associated with behavioral and emotional dysregulation.

DIAGNOSIS

WORKUP

Hoarding disorder is not diagnosed if the hoarding behavior is determined to be the direct consequence of another medical condition, including traumatic brain injuries, surgery for seizure control, cerebrovascular disease, infections of the central nervous system, neurogenetic conditions, autism, schizophrenia, major depressive episode, obsessive-compulsive disorder, or neurocognitive disorders.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Frost and Hartl developed a cognitive-behavioral model of hoarding, which conceptualizes hoarding as a consequence of (1) information-processing deficits, (2) problems in forming emotional attachments, (3) behavioral avoidance, and (4) erroneous beliefs about the nature of possessions.
- Steketee and Frost published a specialized cognitive-behavioral therapy (CBT) compulsive hoarding treatment manual that uses cognitive-behavioral strategies to address these areas. The authors recommend 26 therapy sessions over a period of 1 yr. Treatment can be individual or group therapy with a combination of office and in-home sessions. Family consultation is recommended, with an emphasis on education and the treatment of hoarding behavior.
- Specific variables, including female gender, younger age, a greater number of CBT sessions, and a greater number of home visits, have been associated with a better clinical outcome.

ACUTE GENERAL Rx

Antidepressants may be helpful for underlying mood or anxiety disorders.

CHRONIC Rx

- CBT is the preferred treatment for hoarding disorder, but selective serotonin reuptake inhibitors (SSRIs) are the preferred pharmacologic intervention for severe cases.
- A recent review of CBT, pharmacologic, and family-based interventions yielded modest statistically significant improvements.
- A systematic review of treatment with cognitive-behavioral therapy for hoarding that compared therapy traditionally used to treat

obsessive-compulsive disorder with therapy specifically designed for hoarding disorder suggested improvement in hoarding symptoms with both interventions. However, when compared to each other, the efficacy of these treatments is inconclusive.
- New research suggests the potential benefit of Internet-based CBT for hoarding disorder.

DISPOSITION

Long-term follow-up is essential for recurring hoarding behavior and to address underlying mood disorders.

REFERRAL

- CBT is the preferred treatment.
- If underlying mood symptoms such as depression and anxiety interfere with treatment, a referral for medication is encouraged.

PEARLS & CONSIDERATIONS

Patients with hoarding disorder can be challenging to treat because many with the disorder do not recognize that they have a problem nor do they understand the negative impact hoarding has on their lives and the lives of their loved ones. They often do not believe that they need treatment, and they take great comfort in their possessions. Patient and family education is an important first step in the treatment of hoarding disorder. Family members are often frustrated and angry at the individual who hoards because of a perception that the hoarder is simply "messy," "lazy," etc. Psychoeducation helps family members understand the complicated nature of the illness. They can be instructed on how to become "surrogate therapists" rather than distress the family member who hoards by taking it upon themselves to throw items away. It is essential that they work with a therapist who has expertise with hoarding behavior.

PATIENT & FAMILY EDUCATION

International OCD Foundation: http://208.88.128.33/hoarding/

AUTHOR: **Jeffrey P. Wincze, PhD**

SUGGESTED READINGS

Fitzpatrick M et al: "Blended" therapy: the development and pilot evaluation of an Internet-facilitated cognitive behavioral intervention to supplement face-to-face therapy for hoarding disorder, *Internet Interv* (12)16-25, 2018.

Ivanov VZ et al: Enhancing group cognitive-behavioral therapy for hoarding disorder with between-session Internet-based clinician support: a feasibility study, *J Clin Psychol* 74(7):1092-1105, 2018, https://doi.org/10.1002/jclp.22589. Epub.

Muroff J et al: Pilot trial of cognitive and behavioral treatment for hoarding disorder delivered via webcam: feasibility and preliminary outcomes, *J Obsessive Compuls Relat Disord* (18)18-24, 2018.

Thompson C et al: A systematic review and quality assessment of psychological, pharmacological, and family based interventions for hoarding disorder, *Asian J Psychiatr* 27:53-66, 2017.

Wincze JP et al: Categorization in compulsive hoarding, *Behav Res Ther* 45:63, 2007.

BASIC INFORMATION

DEFINITION

Hodgkin lymphoma is a malignant disorder arising from germinal center B cells and characterized histologically by the presence of multinucleated giant cells (Reed-Sternberg cells) in a mixed inflammatory background.

ICD-10CM CODES

C81.90	Hodgkin lymphoma, unspecified, unspecified site
C81.00	Nodular lymphocyte predominant Hodgkin lymphoma, unspecified site
C81.10	Nodular sclerosis classical Hodgkin lymphoma, unspecified site
C81.20	Mixed cellularity classical Hodgkin lymphoma, unspecified site
C81.30	Lymphocyte depleted classical Hodgkin lymphoma, unspecified site
C81.79	Other classical Hodgkin lymphoma, extranodal and solid organ sites
C81.90	Hodgkin lymphoma, unspecified, unspecified site
C81.91	Hodgkin lymphoma, unspecified, lymph nodes of head, face, and neck
C81.92	Hodgkin lymphoma, unspecified, intrathoracic lymph nodes
C81.93	Hodgkin lymphoma, unspecified, intra-abdominal lymph nodes
C81.94	Hodgkin lymphoma, unspecified, lymph nodes of axilla and upper limb
C81.95	Hodgkin lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C81.96	Hodgkin lymphoma, unspecified, intrapelvic lymph nodes
C81.97	Hodgkin lymphoma, unspecified, spleen
C81.98	Hodgkin lymphoma, unspecified, lymph nodes of multiple sites
C81.99	Hodgkin lymphoma, unspecified, extranodal and solid organ sites

EPIDEMIOLOGY & DEMOGRAPHICS

- There is a bimodal age distribution (15 to 34 yr and >50 yr).
- Incidence is 4 in 100,000 cases; >8000 new cases of Hodgkin lymphoma diagnosed annually in the U.S.
- Concordance for Hodgkin lymphoma in identical twins suggests that a genetic susceptibility underlies Hodgkin lymphoma in young adulthood.
- There is association between certain HLA haplotypes, especially HLA-A1.
- The disease is more common in males (in childhood Hodgkin lymphoma, >80% occur in males), whites, and higher socioeconomic groups.
- There is an increased risk in smokers and HIV-infected individuals.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Painless palpable lymphadenopathy is the most common presenting symptom
- The most common site of involvement is the neck region
- Fever and night sweats: Fever in a cyclical pattern (days or wks of fever alternating with afebrile periods) is known as Pel-Ebstein fever
- Unexplained weight loss, generalized malaise
- Persistent, nonproductive cough
- Lymph node pain associated with alcohol ingestion often because of heavy eosinophil infiltration of the tumor sites is relatively uncommon
- Generalized pruritus
- Hepatosplenomegaly
- Other: Superior vena cava syndrome, spinal cord compression (rare), erythema nodosum (very rare), ichthyosis (very rare)

ETIOLOGY

- Evidence implicating Epstein-Barr virus remains controversial.
- Cigarette smoking has also been implicated.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Non-Hodgkin lymphoma
- Sarcoidosis
- Infections (e.g., cytomegalovirus, Epstein-Barr virus, toxoplasmosis, HIV, tuberculosis)
- Drug reaction

WORKUP

Diagnosis is confirmed by lymph node biopsy. The World Health Organization classifies Hodgkin lymphoma into two groups: Classical Hodgkin lymphoma (92% to 97%) and nodular lymphocyte-predominant Hodgkin lymphoma (3% to 8%). Classical Hodgkin lymphoma has four main histologic subtypes based on the number of lymphocytes, Reed-Sternberg cells, and the presence of fibrous tissue (Table 1):

- Nodular sclerosis (Fig. E1)
- Mixed cellularity (Fig. E2)
- Lymphocyte rich
- Lymphocyte depleted

Nodular sclerosis occurs mainly in young adulthood, whereas the mixed cellularity type is more prevalent after age 50 yr. Table 2 summarizes key features of Hodgkin lymphomas.

Staging: Table 3 describes the Cotswolds Staging Classification.

Proper staging requires the following:

- Detailed history (with documentation of "B symptoms" and physical examination)
- Excisional biopsy with histologic, immunophenotypic and immunohistochemical analysis
- Laboratory evaluation (complete blood count, erythrocyte sedimentation rate [ESR], blood urea nitrogen, creatinine, liver function tests, albumin, lactate dehydrogenase, HIV test), immunophenotypic markers (see Table 4)
- Positron emission tomography (PET)/computed tomography (CT) scan of the chest, abdomen, and pelvis
- Unilateral bone marrow biopsy in selected patients

Box 1 summarizes recommended staging procedures for Hodgkin lymphoma.

TREATMENT

ACUTE GENERAL Rx

The main therapeutic modality includes chemotherapy with or without radiotherapy depending on stage and other risk factors (Table 5). In general, chemotherapy plus involved-site radiotherapy is standard treatment for Hodgkin lymphoma in the early stages; however, recent data suggest that chemotherapy alone is appropriate for a significant proportion of patients. Chemotherapy (Table 6) is used for advanced stage disease with radiotherapy in selected patients, such as those with bulky disease.

Most oncologists prefer the combination of adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine (ABVD). ABVD does not cause infertility or stem cell damage and has also shown to be effective in patients with HIV infection and Hodgkin lymphoma. Table 7 describes characteristics of the ABVD regimen.

Recent trials have shown that in patients with early-stage Hodgkin lymphoma and favorable prognosis, defined by fewer than three nodal sites without bulky or extranodal disease in the absence of ESR >50 without symptoms or 30 with symptoms, treatment with two cycles of ABVD followed by 20 Gy of involved-field radiation therapy may be as effective as, and less toxic than, four cycles of ABVD followed by 30 Gy of involved-field radiation therapy. For patients with early stage disease who do not meet these criteria, options include three or four cycles of ABVD plus involved site radiotherapy

TABLE 1 Frequency of Histologic Subtypes of Hodgkin Lymphoma According to the 2008 WHO Classification

Classic Hodgkin Lymphoma (cHL)	95%
• Nodular sclerosis classic Hodgkin lymphoma (NSCHL)	70%
• Mixed cellularity classic Hodgkin lymphoma (MCCHL)	20%-25%
• Lymphocyte-rich classic Hodgkin lymphoma (LRCHL)	5%
• Lymphocyte-depleted classic Hodgkin lymphoma (LDCHL)	<1%
Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)	5%

From Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 2 Key Features of Hodgkin Lymphoma

Lymphoma	Demographics, Clinical Presentation	Morphology	Cell Surface Markers	Prognosis
Nodular, lymphocyte predominant (NLPHL)	M > F, 30-50 yr, with peripheral lymphadenopathy	Mononuclear cells with convoluted nuclei (popcorn or L&H cells) loosely aggregated in nodules of small B cells	CD45, CD20, bcl-6, J-chain, Oct-2, BOB.1, EBV absent in LP cells	Excellent for stages I, II
Nodular sclerosis	M = F, <30 yr with mediastinal mass, occasional spleen or lung involvement; 40% have B symptoms; most patients present with stage II disease	Broad bands of collagen, nodules of lymphoid tissue with aggregates of HRS cells and lacunar cells, multinucleated variants	CD15, CD30, CD45-EBV in 1%-40%	Good with systemic therapy
Mixed cellularity	M > F; median age, 38 yr; peripheral lymphadenopathy common, spleen, BM; B symptoms common; patients often stage III or IV	Classic HRS cells in mixture of lymphocytes, plasma cells, eosinophils, histiocytes	CD15, CD30, CD45-EBV in 75%	Good with systemic therapy
Lymphocyte depletion	M > F; median age, 30-37 yr; B symptoms, advanced stage common; associated with HIV	Classic HRS cells common with paucity of background lymphocytes; pleomorphic HRS cells mimic sarcoma	CD15, CD30, CD45-EBV positive in HIV-affected patients	Associated with advanced stage
Lymphocyte-rich classical	M > F, older age; peripheral lymphadenopathy; B symptoms rare; most patients with stage I or II disease	Scattered classic HRS cells among numerous small lymphocytes; nodular growth pattern	CD15, CD30; Oct2 and BOB.1 vary; J-chain absent; EBV in 40%-75%	Good, similar to NLPHL

BM, Bone marrow; *EBV,* Epstein-Barr virus; *F,* female; *HIV,* human immunodeficiency virus; *HRS,* Hodgkin Reed-Sternberg; *L&H,* lymphocytic and histiocytic; *LP,* lymphoplasmacytic; *M,* male.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

TABLE 3 Cotswolds-Modified Ann Arbor Staging System for Hodgkin Lymphoma

Stage	Criteria
I	Disease affecting a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer ring)
II	Disease affecting two or more discrete lymph node regions confined to the same side of the diaphragm
III	Disease affecting two or more discrete lymph node regions or lymphoid structures on both sides of the diaphragm
IV	Disease that has spread to one or more extranodal sites (that do not meet the criteria for E) or extralymphatic structure including involvement of the bone marrow, liver, or lungs
Designation	**Criteria**
A	Absence of B symptoms[a]
B	Presence of B symptoms[a]
S	Involvement of the spleen
E	Single extranodal site or involvement of an extranodal site that is contiguous to an involved nodal region
X	Bulky disease as defined as >1/3 mediastinum at its widest part or a nodal mass >10 cm at its greatest diameter

[a]B symptoms: Constitutional symptoms including night sweats, fevers, or weight loss (>10% over 6 mo).
From Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 4 Selected Immunophenotypic Markers and Histologic Characteristics of Use in the Differential Diagnosis of Hodgkin Lymphoma and Other Lymphoid Neoplasms

Marker	Classical HL	Nodular Lymphocyte Predominant HL	TCRBCL	ALCL
CD30	+	–	–	+
CD15	+	–	–	–
CD20	–/+*	+	+	–
CD45	–	+	+	+/–
CD79a	–	+	+	–
ALK	–	–	–	+/–
EMA	–	+	+	+
Nodular growth protein	+/–†	+	–	–

*CD20 positivity in classical Hodgkin lymphoma is quite heterogeneous, with a wide range in brightness of staining.
†In classical Hodgkin lymphoma, a nodular growth pattern is confined to the nodular sclerosing subtype.
+, >90% of cases positive; +/–, majority of cases positive; –/+, minority of cases positive; –, <10% of cases positive; *ALCL,* anaplastic large cell lymphoma; *HL,* Hodgkin lymphoma; *TCRBCL,* T-cell rich B-cell lymphoma.
From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, WB Saunders.

to 30 Gy. In addition, chemotherapy alone, in the absence of bulky disease, is an alternative approach, especially in women younger than 30 yr given the increased risk of including breast cancer, as well as cardiac and thyroid disease. Although the risk of disease recurrence is slightly higher in patients who receive chemotherapy alone, there is no difference in overall survival.

BEACOPP, an intensified regimen consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, has been advocated by some as the new standard for treatment of advanced Hodgkin lymphoma in place of ABVD. Recent trials have shown that treatment with BEACOPP, as compared with ABVD, results in better initial tumor control, but the long-term clinical outcome does not differ significantly between the two regimens. In addition, with the use of the escalated BEACOPP regimen, the rate of complications is higher (3% treatment-related death, 20% rate of hospitalization, and 3% rate of secondary leukemia, and near-universal infertility). Thus, if the goal is cure with the least overall toxic effects, it is best to favor ABVD therapy, reserving rescue therapy with high-dose chemotherapy and autologous hematopoietic stem-cell transplantation for the small number of patients in whom the primary treatment fails.

In March 2018, the FDA approved the combination of brentuximab vedotin and doxorubicin, vinblastine and dacarbazine (AVD) for previously untreated, stage III or IV Hodgkin lymphoma patients. The combination of brentuximab vedotin and AVD was associated with a longer median modified progression-free survival than ABVD, but also was associated with higher rates of neutropenia and neuropathy.

- Definitions of treatment groups are described in Table 8.
- Recommendations for the primary treatment of Hodgkin lymphoma outside of clinical trials are described in Table 9.

BOX 1 Recommended Staging Procedures for Hodgkin Lymphoma

The following staging procedures are recommended for the initial workup of Hodgkin lymphoma:

1. Adequate surgical biopsy reviewed by an experienced hematopathologist
2. Cytologic examination of any effusion in selected cases
3. Detailed history, with attention to the presence or absence of systemic symptoms, and a careful physical examination, emphasizing node chains, size of the liver and spleen, and inspection of Waldeyer ring
4. Routine laboratory tests: Complete blood cell count, erythrocyte sedimentation rate, and liver function tests
5. Neck, chest, and abdominal CT imaging fused with 18-FDG PET scan (Fig. E3)

From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

TABLE 5 Standard Treatment Approach According to Prognostic Group

Early-favorable HL	Combined modality therapy • 2-4 cycles of chemotherapy followed by involved-field radiotherapy
Early-unfavorable HL (intermediate-stage)	Combined modality therapy • 4-6 cycles of chemotherapy followed by involved-field radiotherapy
Advanced HL	Extensive chemotherapy • 6-8 cycles of chemotherapy ± consolidation with localized radiotherapy

CT, Computerized tomography; *HL*, Hodgkin lymphoma.
From Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 6 Standard Chemotherapy Regimens for the Treatment of Advanced Hodgkin Lymphoma

Regimen	Drugs	Route	Schedule
ABVD	Adriamycin 25 mg/m^2	IV	Day 1 and 15
	Bleomycin 10 mg/m^2	IV	Day 1 and 15
	Vinblastine 6 mg/m^2	IV	Day 1 and 15
	Dacarbazine 375 mg/m^2	IV	Day 1 and 15
			Every 28 days
BEACOPP (escalated)	Bleomycin 10 mg/m^2	IV	Day 8
	Etoposide 200 mg/m^2	IV	Day 1-3
	Adriamycin 35 mg/m^2	IV	Day 1
	Cyclophosphamide 1250 mg/m^2	IV	Day 1
	Vincristine 1.4 mg/m^2	IV	Day 8
	Procarbazine 100 mg/m^2	PO	Days 1-7
	Prednisolone 40 mg/m^2	PO	Days 1-14
	G-CSF	SC	From day 8
			Every 21 days

ABVD, Adriamycin, bleomycin, vinblastine, and dacarbazine; *BEACOPP,* bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, and prednisone; *G-CSF*, granulocyte colony-stimulating factor; *IV,* intravenous; *PO,* by mouth; *SC,* subcutaneous.
From Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 7 Characteristics of the ABVD Regimen

Agents: Doxorubicin, bleomycin, vinblastine, dacarbazine
All intravenous, total compliance
80% complete response rate
10% primary refractory disease
60%-65% overall disease-free survival
Most relapses occur within the first 4 yr; however, about 10% of all relapses occur beyond 5 yr
Major side effects are nausea, phlebitis, myelosuppression, less cumulative myelotoxicity than MOPP
No infertility
No leukemia

ABVD, Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine; *MOPP,* mechlorethamine, Oncovin (vincristine), procarbazine, prednisone.
From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, WB Saunders.

- In 2011, the FDA approved the use of the anti-CD30 antibody drug conjugate brentuximab vedotin for the treatment of patients with Hodgkin lymphoma who have relapsed after autologous stem cell transplant and for patients who have relapsed but are not candidates for transplant. Brentuximab vedotin is associated with an overall response rate of 75%.
- In August 2015, brentuximab vedotin was approved as consolidation therapy after autologous transplant in patients at high risk for relapse. The median progression-free survival with brentuximab vedotin was 43 mo vs. 24 mo in patients who received placebo.
- In May 2016, the FDA approved the anti-PD-1 monoclonal antibody nivolumab for patients with Hodgkin lymphoma who relapsed after autologous stem cell transplant and post-transplant brentuximab vedotin. The overall response rate to nivolumab was 65%, and the complete response rate was 7%.
- In March 2017, the FDA approved the anti-PD-1 monoclonal antibody pembrolizumab in patients with refractory disease or those who have relapsed after three or more lines of therapy. The overall response rate was 69%, and the complete response rate was 22%.

DISPOSITION

- Cure rates as high as 85% to 90% in early stage patients and 75% in stage III/V disease are now possible with appropriate initial therapy.
- Poor prognostic features (Table 10, Table 11) include presence of B symptoms, advanced age, advanced stage at initial presentation, male sex, low albumin, high ESR, lymphocyte depletion histology, and increased number of tumor-associated macrophages.
- Unlike escalated BEACOPP, ABVD is not associated with a risk of leukemia.
- Mediastinal irradiation increases the risk of subsequent cardiac disease, including valvular and pericardial disease, accelerated coronary artery disease, and conduction abnormalities.
- Radiation therapy increases the risk of developing secondary solid tumors, especially breast cancer in women younger than age 30 yr (Table 12).
- Table 13 describes potential late complications of Hodgkin lymphoma treatment and appropriate clinical responses and preventive strategies.

REFERRAL

- To surgery for lymph node biopsy
- Fertility clinic for sperm banking
- Hematology/oncology
- Radiation oncology, in selected cases

PEARLS & CONSIDERATIONS

COMMENTS

- Young male patients should consider sperm banking before the initiation of therapy even

TABLE 8 Definition of Treatment Groups According to the EORTC/GELA and GHSG

Treatment Group	EORTC/GELA	GHSG	NCIC/ECOG
Early-stage favorable	CS I-II without risk factors (supradiaphragmatic)	CS I-II without risk factors	Standard risk group: Favorable CSD I-II (without risk factors)
Early-stage unfavorable (intermediate)	CS I-II with ≥1 risk factors (supradiaphragmatic)	CS I, CSIIA ≥1 risk factors; CS IIB with C/D but without A/B	Standard risk group: Unfavorable CS I-II (at least one risk factor)
Advanced stage	CS III-IV	CS IIB with A/B; CS III-IV	High-risk group: CS I or II with bulky disease; intraabdominal disease; CS III, IV
Risk factors (RF)	A large mediastinal mass B age ≥50 yr C elevated ESR* D ≥4 involved regions	A large mediastinal mass B extranodal disease C elevated ESR* D ≥3 involved areas	A ≥40 yr B not NLPHL or NS histology C ESR ≥50 mm/h D ≥4 involved nodal regions

CS, Clinical stage; *ECOG,* Eastern Cooperative Oncology Group; *EORTC,* European Organization for Research and Treatment of Cancer; *ESR,* erythrocyte sedimentation rate; *GELA,* Groupe d'Etude des Lymphomes de l'Adulte; *GHSG,* German Hodgkin Study Group; *NCIC,* National Cancer Institute of Canada. *NLPHL,* nodular lymphocyte predominant Hodgkin lymphoma; *NS,* nodular sclerosis.
*Erythrocyte sedimentation rate (ESR) (≥50 mm/h without or ≥30 mm/h with B-symptoms).
From Hoffman R et al: *Hematology, basic principles and practice*, ed 5, New York, 2009, Churchill Livingstone.

TABLE 9 Recommendations for the Primary Treatment of Hodgkin Lymphoma Outside of Clinical Trials

Group	Stage	Recommendation
Early stages (favorable)	CS I-II A/B, no RFs	2 cycles ABVD + ISRT (20 Gy)
	Early stages (unfavorable, intermediate)	4-6 cycles ABVD ±30 Gy for nonbulky disease
	CS I-II A/B + RFs	4-6 cycles ABVD + 30 Gy for bulky disease
Advanced stages	CS IIB + RFs, CS III A/B, CS IV A/B	6 cycles ABVD; BEACOPP-escalated *or* BEACOPP-14 ± RT, 20-30 Gy for residual tumor (PET positive) and/or bulky disease

ABVD regimen, Adriamycin (doxorubicin), vinblastine, bleomycin, and dacarbazine; *BEACOPP-escalated* regimen, bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone, and G-CSF; *BEACOPP-14* regimen, bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone, and G-CSF; *CS,* clinical stage; *ISRT,* involved site radiation therapy; *PET,* positron emission tomography; *RF,* risk factors; *RT,* radiation therapy;
From Hoffman R et al: *Hematology, basic principles and practice*, ed 5, New York, 2009, Churchill Livingstone.

TABLE 10 Prognostic Factors in Early and Advanced-Stage Hodgkin Lymphoma

Prognostic Group	EORTC	GHSG	NCCN
Early-favorable	CS I-II without risk factors (supradiaphragmatic)	CS I-II without risk factors	CS IA-IIA without risk factors
Early-unfavorable (Intermediate)	CS I-II with ≥1 risk factor (supradiaphragmatic)	CS I-IIA with ≥1 risk factor C/D but not A/B	CS I-II with ≥1 risk factor
Advanced	CS III-IV	CS IIB with risk factors A/B CS III/IV	CS III-IV
Prognostic factors	(A) Bulky mediastinal mass[a] (B) Age ≥50 yr (C) Elevated ESR (>50 mm/h without B symptoms; >30 mm/h with B symptoms)[b] (D) ≥4 nodal areas (out of 5 supra-diaphragmatic EORTC areas)	(A) Bulky mediastinal mass[a] (B) Extranodal disease (>1 lesion) (C) Elevated ESR (>50 mm/h without B symptoms; >30 mm/h with B symptoms)[b] (D) ≥3 nodal areas (out of 11 GHSG areas)	(A) Bulky mediastinal mass[a] (B) Bulk >10 cm (C) Elevated ESR (>50 mm/h without B symptoms) (D) B symptoms (E) ≥4 nodal areas (out of 17 Ann Arbor regions)

[a]Bulky mediastinal mass: Ratio ≥0.035 of the maximum horizontal chest diameter (*EORTC*); ratio ≥1/3 of the maximum horizontal chest diameter (*GHSG*); ratio >1/3 of the maximum horizontal chest diameter (*NCCN*).
[b]B symptoms: Night-sweats, fever, weight loss (unexplained, >10% over 6 mo).
CS, Clinical stage; *EORTC*, European Organization for Research and Treatment of Cancer; *ESR*, estimated sedimentation rate; *GHSG*, German Hodgkin Study Group; *NCCN*, National Comprehensive Cancer Network.
From Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 11 International Prognostic Score (IPS) for Advanced Hodgkin Lymphoma

No. of Prognostic Factors	% of patients	5-yr FFP (%)	5-yr OS (%)
0-1 (low-risk)	29	79	90
2-3 (intermediate-risk)	52	64	80
4-7 (high-risk)	19	47	59

FFP, Freedom from progression; *OS*, overall survival.
From Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 12 Second Neoplasms Seen With Increased Frequency After Successful Hodgkin Lymphoma Treatment

Acute myelogenous leukemia/myelodysplasia (BEACOPP)
Non-Hodgkin lymphoma
Melanoma
Soft tissue sarcoma
Adenocarcinoma:
Breast
Thyroid
Lung
Stomach and esophagus:
Squamous cell carcinoma
Skin
Uterine cervix
Head and neck

BEACOPP, Bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, and prednisone.
From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, Saunders.

though the risk of infertility with ABVD is low. Symptomatic males, particularly with advanced stage Hodgkin lymphoma, may have disease-related oligospermia at diagnosis.

- Chemotherapy with or without involved-field radiotherapy should be the standard treatment for Hodgkin lymphoma with early stage disease. Chemotherapy with radiation in selected cases should be the standard of care for advanced stage.
- After failure of ABVD therapy, more than 60% of patients who have had a relapse and about 30% of patients with initially refractory lymphoma can be reliably cured with high-dose chemotherapy and autologous hematopoietic stem-cell transplantation.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hodgkin Lymphoma (Patient Information)

AUTHORS: **Jorge J. Castillo, MD,** and **Ann S. LaCasce, MD, MMSc**

TABLE 13 Potential Late Complications of Hodgkin Lymphoma Treatment and Appropriate Clinical Responses and Preventive Strategies

Risk/Problem	Incidence/Response
Dental caries	Neck or oropharyngeal irradiation can cause decreased salivation. Patients should have careful dental care follow-up and should make their dentist aware of the previous irradiation.
Hypothyroidism	After external beam irradiation that encompasses the thyroid with doses sufficient to cure Hodgkin lymphoma, at least 50% of patients will eventually become hypothyroid. All patients whose TSH level becomes elevated should be treated with lifelong thyroxine replacement in doses sufficient to suppress TSH levels to low normal. This is also necessary to ensure that the radiation-damaged thyroid is not subjected to long-term stimulation by thyroid-stimulating hormone, which can increase the risk of thyroid neoplasm.
Infertility	ABVD is not known to cause any permanent gonadal toxicity, although oligospermia for 1-2 yr after treatment is common. Direct or scatter radiation to gonadal tissue can cause infertility, amenorrhea, or premature menopause, but this seldom occurs with the current fields used for the treatment of Hodgkin lymphoma. Thus, with the current chemotherapy regimens and radiation fields used, most patients will not develop these problems. In general, after treatment, women who continue menstruating are fertile, but men require semen analysis to provide a specific answer. High-dose chemoradiotherapy and hematopoietic stem cell transplantation almost always cause permanent infertility in both genders, although some young women occasionally recover fertility.
Impaired immunity to infections	Hodgkin lymphoma and its treatment can lead to lifelong impairment of full immunity to infection. All patients should be given annual influenza immunization and pneumococcal immunization every 5 yr. Patients whose spleen has been irradiated or removed should also be immunized against meningococcal types A and C and *Haemophilus influenza* type B. As for all adults, diphtheria and tetanus immunizations should be kept up-to-date.
Secondary neoplasms	Although uncommon, certain secondary neoplasms occur with increased frequency in patients who have been treated for Hodgkin lymphoma. These include acute myelogenous leukemia, thyroid, breast, lung, and upper gastrointestinal carcinoma and melanoma, and cervical carcinoma in situ. It is appropriate to screen for these neoplasms for the rest of the patient's life because they might have lengthy induction periods.

ABVD, Adriamycin, bleomycin, vinblastine, dacarbazine; *TSH,* thyroid-stimulating hormone.
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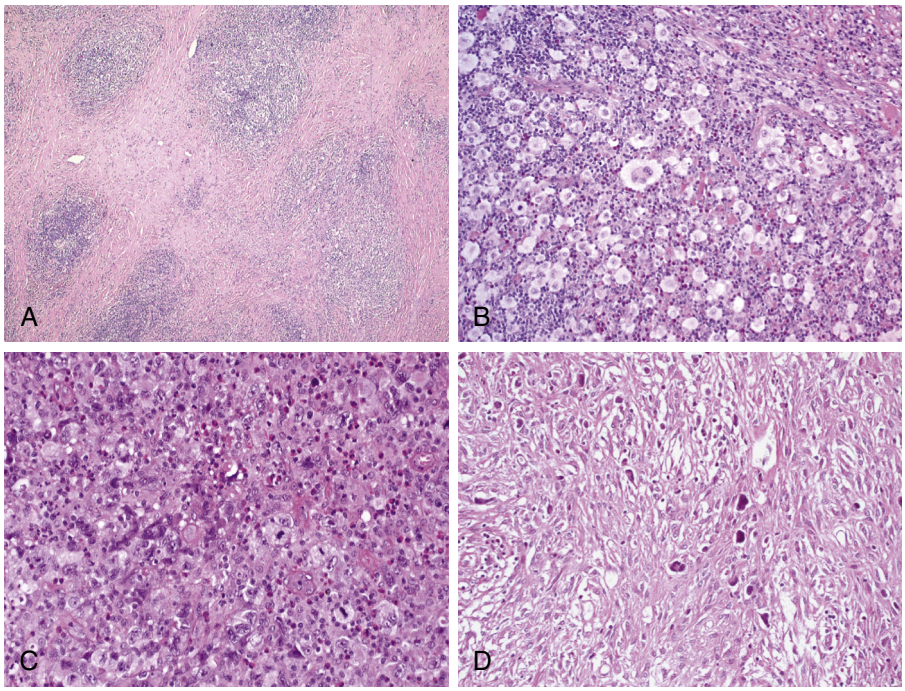

FIG. E1 Hodgkin lymphoma. Morphology of classical Hodgkin lymphoma (CHL). **A,** Nodular sclerosis CHL. Cellular nodules are separated by concentric bands of mature collagen. **B,** Close-up of cellular nodule shows numerous lacunar cells with clear cytoplasm intermingled with lymphocytes, neutrophils, and eosinophils. Note collagen bands rimming the nodule. **C,** Nodular sclerosis CHL grade II. Confluent sheets of neoplastic cells with partly anaplastic features intermingled with a minority of inflammatory cells. This morphology is consistent with the so-called syncytial variant of CHL. **D,** Lymphocyte-depleted CHL, diffuse fibrosis subtype. Neoplastic Reed-Sternberg and Hodgkin cells in a hypocellular background with histiocytes and fibroblasts. This case lacks nodularity and ordered collagen bands. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.)

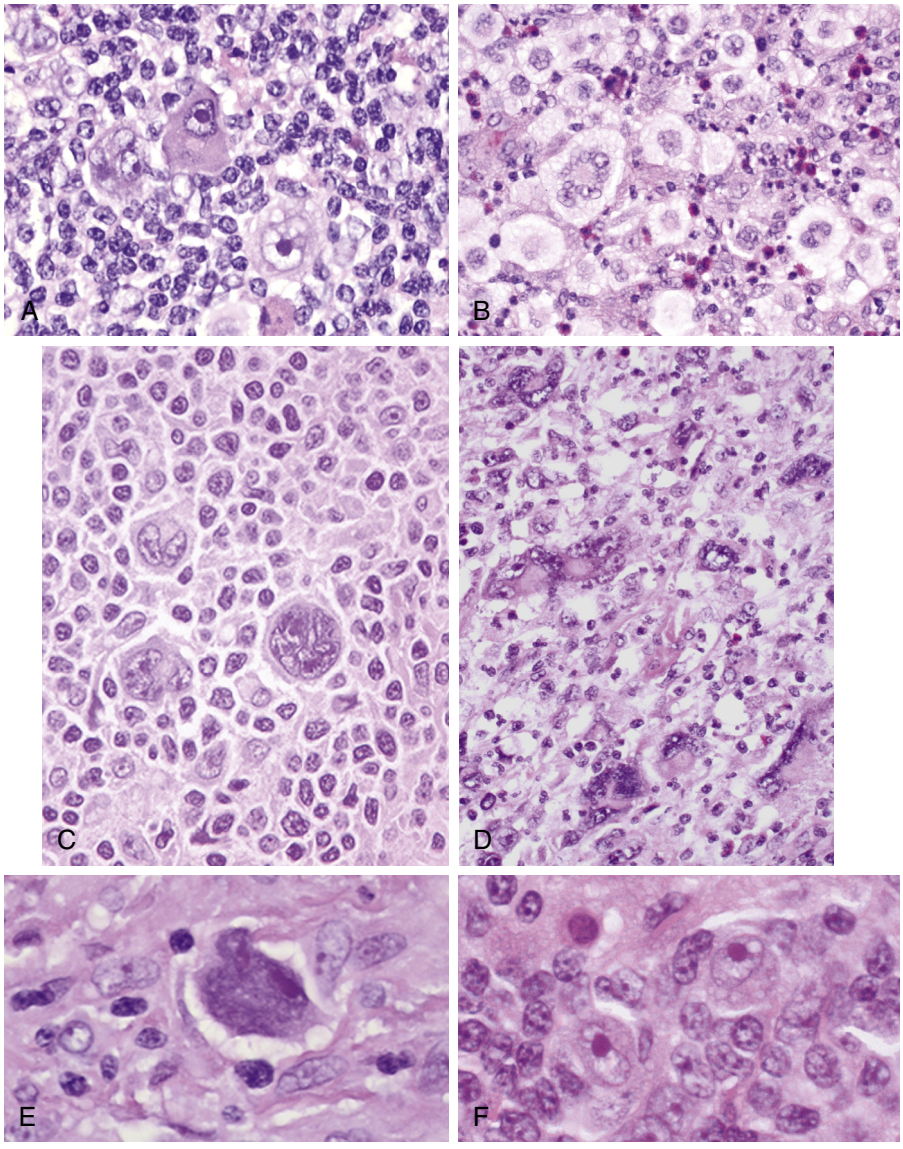

FIG. E2 Hodgkin lymphoma. Cytologic features of Reed-Sternberg (RS) cells and Hodgkin cells. **A,** Classic RS cells and variants in mixed cellularity—classical Hodgkin lymphoma (CHL), with amphophilic cytoplasm, large nuclei with clear karyoplasm, and huge viral inclusion-like nucleoli. **B,** Typical lacunar cells in a case of nodular sclerosis CHL. Note the delicate folded nuclear membranes, less conspicuous nucleoli, and ample clear cytoplasm with threadlike protrusions. **C,** Typical RS cells, including a binuclear variant, in mixed cellularity CHL. **D,** Abundant, sometimes bizarre multinucleated tumor cells in a case of nodular sclerosis grade II. **E,** So-called mummified RS cell with condensed, deeply basophilic cytoplasm. **F,** Two classic mononuclear Hodgkin cells in a case of mixed cellularity CHL. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.)

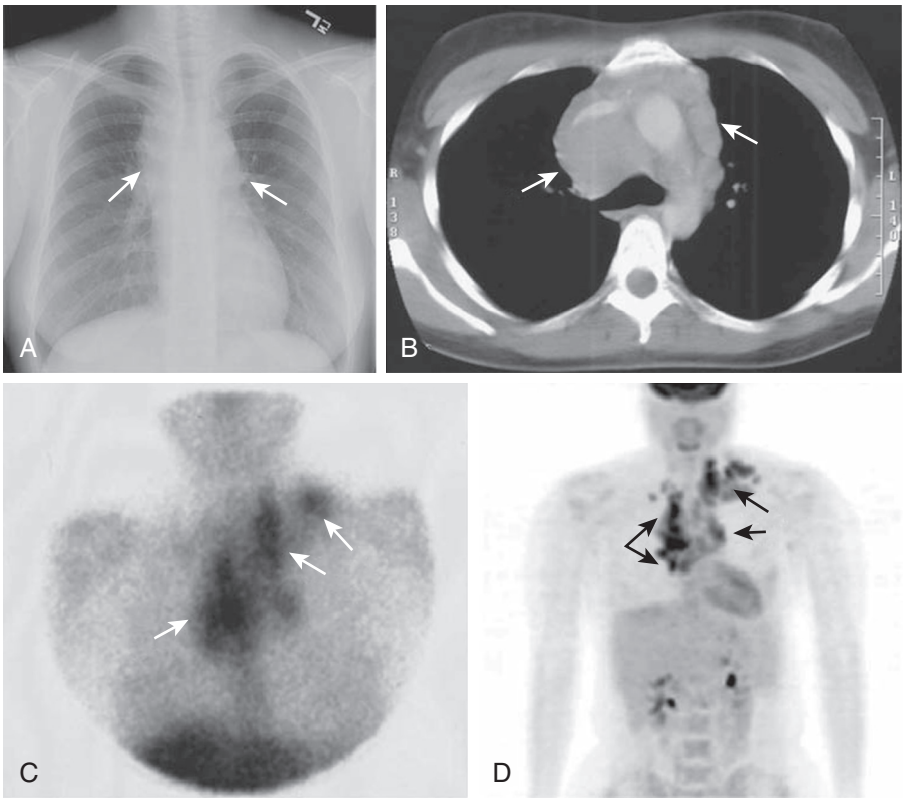

FIG. E3 Imaging of Hodgkin lymphoma. Bulky Hodgkin disease as seen on chest radiograph **(A)**, computed tomography (CT) of the chest **(B)**, gallium scan **(C)**, and positron emission tomography (PET) **(D)**. The *arrows* indicate sites of disease. Note that the PET and CT scans provide more detailed information than the chest radiograph and gallium scan. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.)

BASIC INFORMATION

DEFINITION

Hookworm is a parasitic infection of the intestine caused by the soil helminths *Necator americanus* (North and South America, Central Africa and parts of Asia) and *Ancylostoma duodenale* (Mediterranean nations, India, Iran, Far East). The hookworm of dogs and cats, *Ancylostoma ceylanicum*, (India, Southeast Asia) also can affect humans.

SYNONYMS

Ground itch
Ancylostoma duodenale infection
Necator americanus infection

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Varies greatly in different areas of the U.S.
- Most common in rural areas of southeastern U.S.
- Poor sanitation and increased rainfall increase incidence.

PREVALENCE (IN U.S.): Varies from 10% to 90% in regions where it is found.
PREDOMINANT AGE: Schoolchildren

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Nonspecific abdominal complaints
- Symptoms related to iron deficiency anemia depending on the amount of iron in the diet and worm burden (these organisms consume host's RBCs)
- Fatigue, tachycardia, dyspnea, and high-output failure
- Hypoproteinemia and edema from loss of proteins into the intestinal tract
- Unusual for pulmonary manifestations to occur when the larvae migrate through the lungs
- Skin rash at sites of larval penetration in some individuals without prior exposure: Ground itch

ETIOLOGY

Two main species can cause this disease: *N. americanus* and *A. duodenale. N. americanus* is the predominant cause of hookworm in the U.S. They are soil nematodes (geohelminthic infections) that are acquired by skin contact (i.e., bare feet) with contaminated soils in moist, warm climate. Worldwide, over 700 million people are infected.

- Infection occurs via penetration of the skin by the larval form, with subsequent migration via the bloodstream to the alveoli, up the respiratory tract, then into the GI tract (Fig. 1).
- *Ancylostoma* spp. infection can also occur via the oral route through ingestion of contaminated water supplies.
- Sharp mouth parts allow for attachment to intestinal mucosa.
- *Ancylostoma* spp. are more likely to cause iron deficiency anemia because they are larger and remove more blood daily from the bowel wall than the other hookworm species, *N. americanus.*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Strongyloidiasis
- Ascariasis
- Other causes of iron deficiency anemia and malabsorption

WORKUP

Examine stool for hookworm eggs. Shedding of eggs starts around 8 wk after skin penetration in *N. americanus* infections and longer with *A. duodenale,* but eggs are indistinguishable between the two species. PCR stool assays are available in reference labs.

LABORATORY TESTS

CBC to show hypochromic, microcytic anemia; possible mild eosinophilia and hypoalbuminemia

IMAGING STUDIES

Chest x-ray: Generally not helpful, occasionally shows opacities

TREATMENT

NONPHARMACOLOGIC THERAPY

- Prevention of disease by not walking barefoot and by improving sanitary conditions.
- Vaccines are in development.

ACUTE GENERAL Rx

- Albendazole 400 mg PO as a single dose or daily for 3 days is the preferred treatment.
- Mebendazole 100 mg PO bid for 3 days is more effective than as a 500-mg single dose.
- Pyrantel pamoate 11 mg/kg (to max dose of 1 g) PO qd × 3 days.
- Iron supplementation may be helpful in patients with iron deficiency.

DISPOSITION

Easily treated

REFERRAL

To gastroenterologist and infectious disease specialist if diagnosis uncertain

PEARLS & CONSIDERATIONS

COMMENTS

- Appropriate disposal of human waste is important in controlling the disease in areas with a high prevalence of hookworm infestation.
- Wearing shoes will avoid contact with contaminated soil, and the provision of safe water and sanitation for disposing human excreta is important in control of hookworm.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hookworm Infection (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

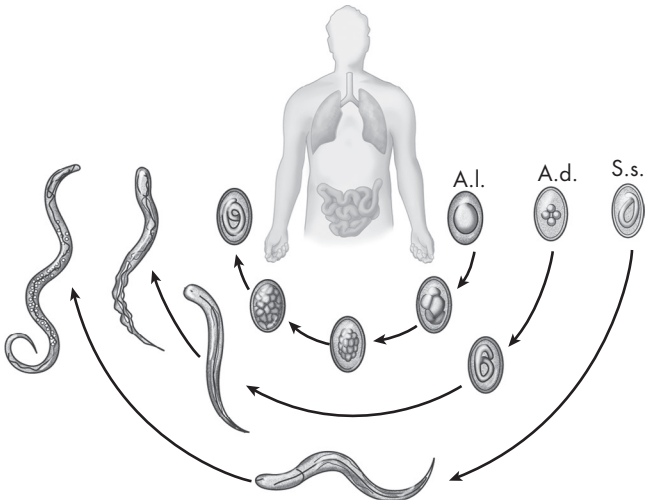

FIG. 1 Life cycle of intestinal nematodes with a migratory phase through the lungs. Eggs are passed with stools in *Ascaris lumbricoides (A.l.), Necator americanus,* or *Ancylostoma duodenale (A.d.),* or they hatch on their way out in *Strongyloides stercoralis (S.s.).* Ascaris eggs mature in soil, and humans are infected upon ingestion of these eggs. With hookworm and strongyloidiasis, humans are infected via skin penetration by filariform larvae. In all three infections, larvae pass through a migratory phase via the lungs before reaching maturity at their final habitat in the small intestine. (From Mandell GL et al: *Principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Churchill Livingstone.)

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Horner Syndrome (PTG)

BASIC INFORMATION

DEFINITION

Horner syndrome is the clinical triad of ipsilateral ptosis, miosis, and sometimes facial anhidrosis. Disruption of any of the three neurons in the oculosympathetic pathway (first-order, second-order, or third-order) can cause Horner syndrome.

SYNONYMS

Oculosympathetic paresis

Raeder paratrigeminal syndrome: Horner syndrome of the third-order neuron associated with pain in the trigeminal nerve distribution

ICD-10CM CODE	
G90.2	Horner syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

Congenital or acquired

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Ptosis is usually mild. It results from loss of sympathetic tone to Müller muscle, which contributes approximately 2 mm of upper eyelid elevation. Weakness of the corresponding muscle in the lower eyelid causes it to elevate slightly. This combination causes narrowing of the palpebral fissure. Levator function of the eyelid is preserved.
- Miosis results from loss of sympathetic innervation to the iris dilator muscle. The affected pupil reacts normally to bright light and accommodation. Anisocoria is greater in dim light.
  1. Dilation lag: Horner pupil dilates more slowly than the normal pupil when lights are dimmed (20 vs. 5 sec) because it dilates passively as a result of relaxation of the iris sphincter.
- Presence of facial anhidrosis is variable and depends on the site of injury. It occurs with lesions affecting first-order or second-order neurons.
- Congenital Horner syndrome may result in heterochromia. The affected eye has a lighter-colored iris.
- Acute cases may also present with facial flushing, conjunctival injection, and nasal stuffiness from the loss of sympathetic vasoconstriction.

ETIOLOGY

Disruption of the ipsilateral sympathetic innervation to the eye and face. Lesions can damage any of the three neurons in the oculosympathetic pathway (Fig. E1). First-order neuron lesions are least common but are usually caused by pathology in the hypothalamus, brain stem, or cervicothoracic spinal cord. Second-order neuron lesions are often caused by disease involving the cervicothoracic spinal cord, lung apex, or anterior neck. Third-order neuron lesions are usually seen with disease in the internal carotid artery, skull base, cavernous sinus, or orbital apex. Location is often suggested by the presence of associated findings. Vascular disease and neoplasm must be considered.

One large study found that 65% of patients with Horner syndrome had an identifiable cause, 13% had a first-order neuron lesion, 44% had a second-order neuron lesion, and 43% had a third-order neuron lesion.

Mechanical:

- Syringomyelia
- Trauma
- Tumors: Benign, malignant head and neck cancers (thyroid, apical lung, mediastinal)
- Cervical rib

Vascular (ischemia, hemorrhage or arteriovenous malformation):

- Brain stem lesion: Commonly occlusion of the posterior inferior cerebellar artery but other arteries may be responsible (vertebral; superior, middle or inferior lateral medullary arteries; superior or anterior inferior cerebellar arteries)
- Carotid artery aneurysm, dissection, arteritis: Can also be from injury to other major vessels (internal carotid artery, subclavian artery, ascending aorta)
- Jugular venous ectasia
- Cavernous sinus thrombosis
- Cluster headache, migraine

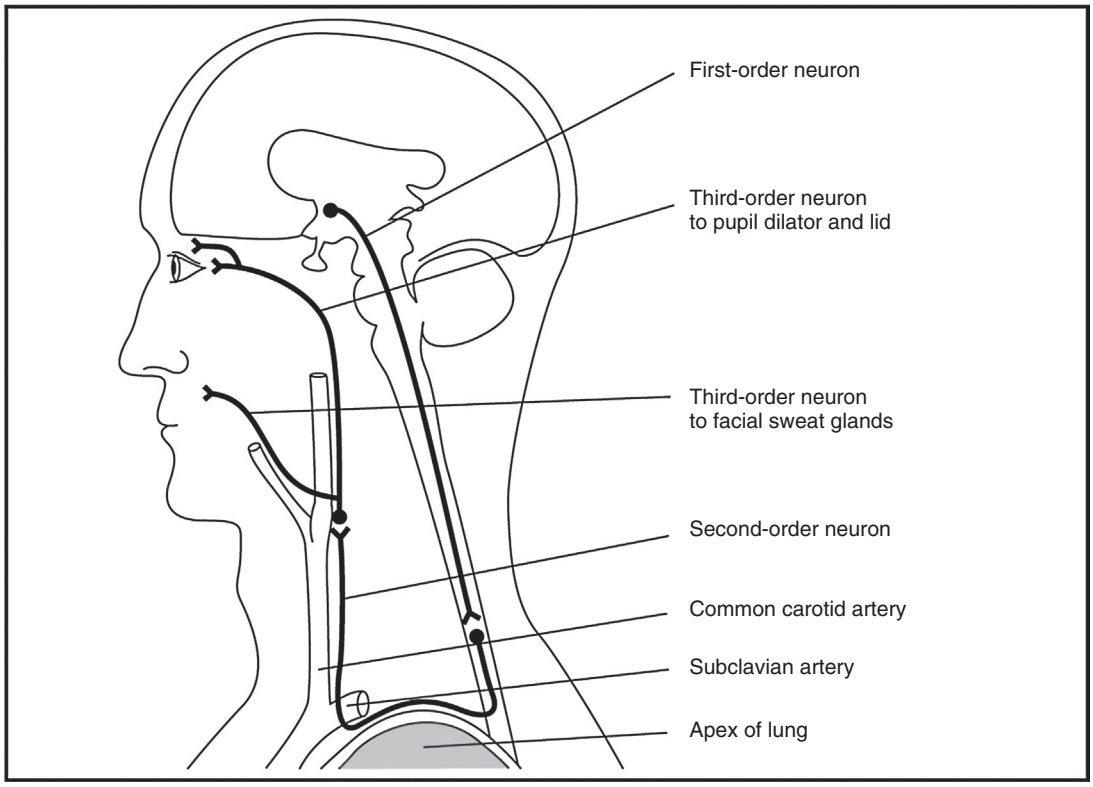


FIG. E1 Anatomy of sympathetic pathways to the eye. The sympathetic innervation of the eye consists of three neurons connected in a series: first-order neurons, second-order neurons, and third-order neurons. The first-order neurons (central neurons) extend from the posterior hypothalamus to the C8 to T2 level of the spinal cord. The second-order neurons (preganglionic neurons) leave the spinal cord and travel over the lung apex, around the subclavian artery, and along the carotid artery to the superior cervical ganglion. The third-order neurons (postganglionic neurons) diverge and take two paths: those to the pupil and lid muscles travel along the internal carotid artery through the cavernous sinus to reach the orbit; those to the facial sweat glands travel with the external carotid artery to the face. Lesions in any of these neurons cause Horner syndrome and distinct associated physical signs. (From McGee [ed]: *Evidence-based physical diagnosis,* ed 3, Philadelphia, 2012, WB Saunders.)

Miscellaneous:
- Idiopathic
- Congenital
- Demyelination (multiple sclerosis)
- Infection (apical tuberculosis, herpes zoster, Lyme disease)
- Myelitis
- Pneumothorax
- Iatrogenic (angiography, internal jugular/subclavian catheter, chest tube, neck or upper thoracic surgery, epidural spinal anesthesia)

DX DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Causes of anisocoria (unequal pupils):
- Normal variant
- Mydriatic use, medications
- Prosthetic eye
- Prior eye surgery, trauma
- Iritis
- Acute angle-closure glaucoma
- Adie tonic pupil
- Third nerve palsy

Causes of ptosis are described in Section II.

WORKUP

History, physical examination, pharmacologic testing, imaging

PHARMACOLOGIC TESTING

These medications may not be readily available. Pharmacologic testing should not delay evaluation in acute, painful, or traumatic cases or in patients with a history of malignancy.
- Topical cocaine test (Fig. E2): Confirms diagnosis (drops increase anisocoria by dilating normal pupil but not Horner pupil).
- Topical apraclonidine test: Confirms diagnosis (drops reverse anisocoria by causing dilation of Horner pupil and slight constriction of normal pupil). Less reliable than topical cocaine in acute Horner syndrome (Box E1).
- Topical hydroxyamphetamine test: Distinguishes first- and second-order neuron lesions from third-order sympathetic lesions (drops dilate normal pupil and first- or second-order Horner pupil, but not third-order Horner pupil). Testing must be delayed >48 hr after topical cocaine or apraclonidine testing.

IMAGING STUDIES

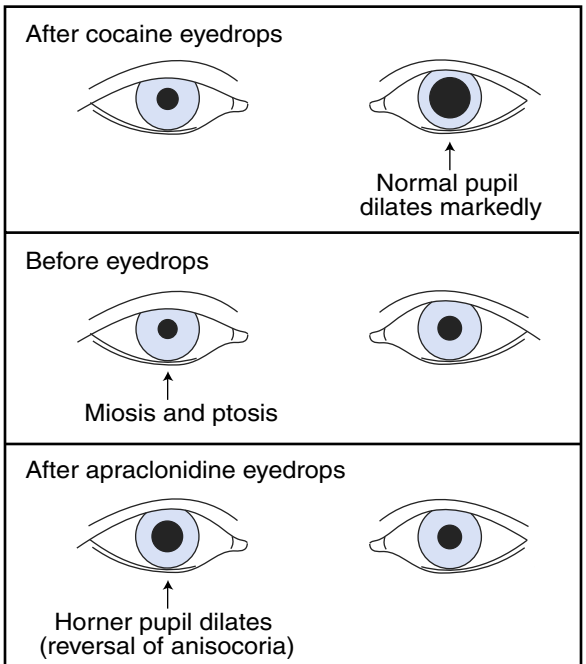
- One approach is to image the entire oculosympathetic pathway with an MRI of the brain to the upper chest and an MRA of the neck (or CT/CTA if acute presentation or MR not possible)
- Other approaches suggest using results of pharmacologic testing, as well as accompanying signs and symptoms to guide imaging
- MRI brain: Brain stem (diplopia, eye movement abnormalities, vertigo, ataxia, lateral medullary syndrome); cavernous sinus (sixth nerve palsy)
- MRI cervical and upper thoracic spinal cord: Sensory changes/weakness of extremities, bowel/bladder dysfunction
- MRI/MRA or CTA neck: Carotid artery dissection (acute Horner syndrome with face or neck pain)
- CT chest and neck: Evaluate lung apex, perivertebral areas, mediastinum if symptoms do not localize to the central nervous system; brachial plexus lesion (arm/hand pain or weakness)

RX TREATMENT

- Treatment depends on underlying cause.
- Ptosis can be surgically corrected or treated with medication (phenylephrine drops).

REFERRAL

Ophthalmologist for pharmacologic testing to confirm diagnosis and localize lesion



Eyedrop	Horner pupil	Normal pupil
Cocaine	No change	Dilates
Apraclonidine	Dilates	No change

FIG. E2 Confirmation of Horner syndrome: the cocaine and apraclonidine eyedrop tests. This patient has a right Horner syndrome with right miosis and ptosis *(middle row).* 45 min after installation of cocaine drops into each eye *(top row),* the Horner pupil fails to dilate, but the normal pupil dilates, markedly aggravating the anisocoria and confirming the diagnosis of Horner syndrome. 45 min after installation of apraclonidine drops into each eye (performed on a different day than the cocaine test; *bottom row*), the right Horner pupil dilates, but there is no response in the normal pupil, thus reversing the anisocoria and also confirming the diagnosis of Horner syndrome. Cocaine eyedrops block the reuptake of norepinephrine at the myoneural junction of the iris dilator, causing the pupil to dilate unless norepinephrine is absent because of sympathetic denervation. Apraclonidine eyedrops have no effect on normal pupils, but after sympathetic denervation from Horner syndrome, the affected pupil is supersensitive to their effect. Apraclonidine may also cause elevation of the lid in Horner syndrome *(bottom row),* although only the response of the pupil is used when interpreting the test. (From McGee S: *Evidence-based physical diagnosis,* ed 4, Philadelphia, 2018, Elsevier.)

BOX E1 Horner Syndrome, Eyedrop Tests

Finding (Reference)	Sensitivity (%)	Specificity (%)	LIKELIHOOD RATIO IF FINDING IS	
			Present	Absent
Detecting Horner Syndrome				
Anisocoria ≥1 mm after topical cocaine	95	99	**96.8**	**0.1**
Reversal of anisocoria after topical apraclonidine	95	90-95	**14.0**	**0.1**
Diagnosing First- or Second-Order Nerve Lesion in Horner Syndrome				
Small pupil dilates with topical hydroxyamphetamine (Paredrine)	83-92	79-96	**9.2**	**0.2**
Small pupil fails to dilate with dilute phenylephrine	88	79	**4.2**	NS
Asymmetric facial sweating	53	78	NS	0.6

NS, Not significant.
From McGee S: *Evidence-based physical diagnosis,* ed 4, Philadelphia, 2018, Elsevier.

PEARLS & CONSIDERATIONS

- May be the presentation of a life-threatening condition. Horner syndrome presenting acutely or associated with head/neck pain, trauma, or history of malignancy should be evaluated urgently.
- Normal variant anisocoria:
  1. Occurs in 20% of people
  2. Usually <1 mm difference between pupils
  3. Pupils are round and display a normal, brisk constriction and dilation response to light
- Infants with Horner syndrome may present with Harlequin sign, contralateral hemifacial flushing

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Horner Syndrome (Patient Information)
Lung Neoplasms, Primary (Related Key Topic)

AUTHOR: **Sudeep K. Aulakh, MD**

SUGGESTED READINGS

Davagnanam I et al: Adult Horner's syndrome: a combined clinical, pharmacological and imaging algorithm, *Eye* 27:291, 2013.
Gross JR et al: An approach to anisocoria, *Curr Opin Ophthalmol* 27:486, 2016.
Martin TJ: Horner syndrome: a clinical Review, *ACS Chem Neurosci* 9:177, 2018.

BASIC INFORMATION

DEFINITION

Hot flashes are sudden onset of intense warmth that begins in the neck or face, or in the chest and progresses to the neck and face; often associated with profuse sweating, flushing, clamminess, anxiety, and palpitations.

SYNONYMS

HFs
Vasomotor symptoms (VMSs)
Hot flushes
Night sweats

ICD-10CM CODES

N95.1 Menopausal and female climacteric states
R23.2 Flushing

EPIDEMIOLOGY & DEMOGRAPHICS

- Hot flashes affect up to 75% of women who are in the menopausal transition.
- Hot flashes typically start during late perimenopause, increase in frequency and severity throughout the menopausal transition, and finally decline over time after the final menstrual period.
- Median total duration of hot flashes is 7 yr, with symptoms lasting for a median of 4.5 yr after the last menstrual period. Women who have hot flashes early in the menopause transition can experience symptoms for more than 12 yr.
- Prevalence of hot flashes differs among racial and ethnic groups in the U.S. with highest frequency among African American women and lowest frequency among Chinese and Japanese women.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Profuse sweating and red blotching of skin may be noted during the vasomotor event.
- Palpitations and hyperreflexia may be present during the hot flash.
- Hot flashes typically last 1 to 5 min.
- Each hot flash is associated with increase in temperature, increased pulse rate, and increased blood flow into the hands and face.
- Hot flashes during sleep are common and are referred to as *night sweats*.
- There is considerable variation in the frequency of hot flashes. One third of women report more than 10 flashes per day.

ETIOLOGY

- Dysfunction of central thermoregulatory centers caused by reduction of estrogen levels at the time of menopause
- Tamoxifen use
- Chemotherapy-induced ovarian failure
- Androgen ablation therapy for prostate carcinoma

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Carcinoid syndrome
- Anxiety disorder
- Idiopathic flushing
- Malignancy (lymphoma, solid tumors)
- Hyperthyroidism
- Hyperhidrosis
- Infection

WORKUP

Evaluation of hot flashes is aimed at excluding the conditions listed in the differential diagnosis.

LABORATORY TESTS

- Follicle-stimulating hormone (FSH), luteinizing hormone, estradiol level. The serum FSH levels rather than estradiol levels are associated with greater severity of hot flashes in older postmenopausal women, suggesting that nonestrogen feedback systems may be important in modulating the severity of hot flashes. It is not necessary to obtain an FSH to make the diagnosis of menopausal status, however. An amenorrheic woman over age 50 with vasomotor symptoms is assumed to have made the menopausal transition, and serum markers of menopause are not required to complete the diagnosis.
- Thyroid-stimulating hormone (TSH).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Behavioral interventions such as relaxation training and paced respiration have been reported effective in reducing symptoms in some women.
- Lifestyle changes such as maintaining a healthy body weight, exercising regularly, and avoiding caffeine, alcohol, tobacco, and spicy foods may be beneficial.

ACUTE GENERAL Rx

- Systemic hormone therapy with estrogen alone or in combination with progestin is the most effective way to manage menopausal hot flashes with up to a 75% reduction in weekly episodes. Women receiving hormone therapy are at increased risk of thromboembolic disease and breast cancer; therefore, use should be limited to the shortest duration and smallest possible dose to control symptoms, and only after considering potential risks and benefits for each individual patient.
- While there is some evidence that progestin-only medications may improve hot flashes, it is not considered first-line treatment for vasomotor symptom management.
- The only nonhormonal method that is FDA-approved for management of hot flashes is the SSRI paroxetine (7.5 mg daily). Other antidepressants shown to be effective for treatment of hot flashes include escitalopram (10 mg to 20 mg per day), venlafaxine (37.5 mg to 75 mg per day), and desvenlafaxine (100 mg to 150 mg per day). Caution should be taken in prescribing SSRIs and SNRIs in women taking tamoxifen, as these antidepressants interfere with the cytochrome P-450 metabolism of tamoxifen, reducing its efficacy.
- Duavee is a new FDA-approved treatment of moderate to severe vasomotor menopausal symptoms. It consists of a combination of conjugated estrogens and bazedoxifene, a new selective estrogen receptor modulator (SERM).
- The anticonvulsant gabapentin (300-1200 mg/day) represents another nonhormonal alternative in the treatment of hot flashes. It can be used alone or in combination with an antidepressant; however, combining the two medications does not appear to be more effective than just gabapentin alone.
- The antihypertensive clonidine is also somewhat effective in reducing the frequency of hot flashes in mild cases. Adverse effects include dry mouth, sedation, and dizziness.
- Recent trials with the anti-cholinergic drug oxybutynin have shown effectiveness in reducing the frequency and severity of hot flashes in women with a history of breast cancer.
- Vitamin E (800 IU/day) may be effective in patients with mild symptoms that do not interfere with sleep or daily function.
- Soy protein (use of soy extracts that contain plant-derived estrogens [phytoestrogens]) is often used; however, clinical trials have not shown clear efficacy.
- Several classes of herbal remedies are available to patients and are commonly used, generally without significant benefit. Frequently used agents are *Cimicifuga racemosa* (black cohosh, snakeroot, bugbane), *Angelica sinensis,* and evening primrose (evening star). Recent trials using the isopropanolic extract of black cohosh rootstock (Remifemin) did show some improvement in controlling menopausal symptoms. Such alternative medications may be used to treat mild to moderate symptoms, but it is possible that symptomatic improvements may derive in part from a placebo effect. Acupuncturists are the second most consulted therapists by menopausal women. Evidence of acupuncture efficacy as an HF treatment is conflicting. A recent randomized trial[1] revealed that Chinese medicine acupuncture was not superior to noninsertive sham acupuncture for women with moderately severe menopausal HFs.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hot Flashes (Patient Information)
Menopause (Related Key Topic)

AUTHOR: **Helen Toma, MD, MSPH**

[1]Ee C et al: Acupuncture for menopausal hot flashes: a randomized trial, *Ann Intern Med* 164:146-154, 2016.

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

The human immunodeficiency virus (HIV) is a retrovirus that is responsible for causing acquired immunodeficiency syndrome (AIDS). HIV infection does not necessarily mean a person has AIDS. Table 1 summarizes surveillance case definition for HIV.

SYNONYMS

HIV

AIDS: The result of progressive HIV infection in which a person has a weakened immune system and meets specific diagnostic criteria (See "Acquired Immunodeficiency Syndrome" in Section I and Table 2.)

EPIDEMIOLOGY & DEMOGRAPHICS (IN U.S.)

- An estimated 1.1 million people in the United States are infected with HIV, and approximately 14% of them do not know they are infected.
- In 2018, there were approximately 38,000 new HIV diagnoses, according to the Centers for Disease Control and Prevention (CDC).
- Incidence is highest among gay, bisexual, and other men who have sex with men (MSM) and in minority racial and ethnic populations.

PREDOMINANT RISK GROUPS:

- Gay, bisexual, and other MSM is the group most affected by HIV.
- In 2017, MSM accounted for approximately 67% of all new diagnoses, according to the CDC.
- HIV disproportionately affects MSM of younger age and black/African American and Hispanic/Latino background.
- Heterosexual transmission and injection drug use accounted for 24% and 6%, respectively, of new HIV diagnoses in 2017.
- Table 3 summarizes risk factors associated with sexual transmission of HIV.

RACIAL DATA:

- In 2017, individuals of African American descent accounted for 43% of new HIV diagnoses despite being 12% of the U.S. population.
- In 2016, Hispanics/Latinos accounted for 26% of new HIV diagnoses despite being 18% of the U.S. population.

GENETICS:

Familial Disposition:

Individuals with deletions in the *CCR5* gene are immune from infection with macrophage tropic virus (the predominant virus in sexual transmission). Other genetic variants may contribute to rapid progression or long-term control of the virus once infected. One in 300 individuals infected with HIV is an "elite controller," which means they are able to maintain a normal CD4 count and undetectable viral load through immune control.

Congenital Infection:

- In 2017, 73 children younger than 13 yr received a diagnosis of perinatally acquired HIV, according to the CDC, which may occur in utero, during delivery, or after delivery via breastfeeding.
- No specific congenital abnormalities are associated with HIV infection, although there is a higher risk of spontaneous abortion and low birth weight.

Neonatal Infection:

- May occur during delivery or via breastfeeding.
- Typically asymptomatic.
- All pregnant women should be tested for HIV and, if positive, take antiretrovirals (ARVs).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Signs and symptoms are variable with stage of disease.
- Acute HIV infection (0 to 3 mo, usually within several weeks):
  1. Causes a self-limited mononucleosis-like illness in 50% to 80% of individuals, characterized by fever, sore throat, lymphadenopathy, headache, and a rash resembling roseola. Individuals may also be asymptomatic.
  2. In a minority of acute cases, aseptic meningitis, Bell palsy, or peripheral neuropathy may occur.
  3. Opportunistic infections such as thrush or *Pneumocystis jiroveci* pneumonia (PJP) may occur.
- Chronic HIV infection is usually characterized by a prolonged asymptomatic "latent" phase without symptoms followed by nonspecific symptoms of lymphadenopathy, fatigue, weight loss, diarrhea, and skin changes,

TABLE 1 Surveillance Case Definition for HIV Infection in Adults and Adolescents (Age >13 yr)

Stage	Laboratory Evidence	Clinical Evidence
Stage 1	Laboratory confirmation of HIV infection and CD4+ T-lymphocyte count of ≥500 cells/μL or CD4+ T-lymphocyte percentage of ≥ 29%[a]	No AIDS-defining condition (see Table 2)
Stage 2	Laboratory confirmation of HIV infection and CD4+ T-lymphocyte count of 200-499 cells/μL or CD4+ T-lymphocyte percentage of 14%-28%[a]	No AIDS-defining condition (see Table 2)
Stage 3	Laboratory confirmation of HIV infection and CD4+ T-lymphocyte count of <200 cells/μL or CD4+ T-lymphocyte percentage of <14%[a]	Documentation of an AIDS-defining condition with laboratory confirmation of HIV infection (see Table 2)
Stage unknown	Laboratory confirmation of HIV infection and no information on CD4+ T-lymphocyte count or percentage	No information on presence of an AIDS-defining condition

[a]The CD4+ T-lymphocyte percentage is a percentage of the total lymphocyte count.

From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 2 Surveillance Definitions of AIDS-Defining Conditions

Opportunistic Infections:

- *Pneumocystis jiroveci (carinii)*
- *Mycobacterium avium* complex
- *Mycobacterium tuberculosis*
- Toxoplasmosis
- Candidiasis: Esophageal and systemic
- Histoplasmosis
- Cryptococcosis
- Cryptosporidiosis and isosporiasis
- Leishmaniasis
- Cytomegalovirus disease
- Recurrent bacterial infections (≥2 episodes/yr)

Lymphomas

Kaposi Sarcoma

Cervical Cancer

AIDS Dementia Syndrome

Wasting Syndrome

From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 3 Risk Factors Associated with Sexual Transmission of HIV

- Sexually transmitted infections
  - Ulcerative or nonulcerative diseases
- Genital tract inflammation
- HIV disease
  - Higher viral loads
  - Lower CD4+ levels
  - Acute HIV infection
  - Lack of effective antiretroviral therapy
  - Lack of heterozygosity or homozygosity for the inactivating 32-base pair deletion in the chemokine receptor gene *(CCR5)*
- Anatomic factors
  - Lack of circumcision
  - Cervical ectopy
  - Leukocytospermia
  - Hormonal contraception
- Sexual practices
  - Receptive anal intercourse
  - Sexual activity during menses
  - Bleeding during intercourse (disruption of vaginal mucosa through trauma)
  - Lack of barrier protection
- HIV viral features
  - Syncytium formation
  - Certain viral clades

From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

TABLE 4 Etiology of Anemia in Human Immunodeficiency Virus

HIV Related

HIV Infection

- Anemia of chronic disease
- Blunted production/response to erythropoietin
- Suppression of CFU-GEMM (HIV/inflammatory cytokines)

Neoplasms Infiltrating BM

Non-Hodgkin lymphoma, KS, Hodgkin lymphoma

Infections of the BM

- Parvovirus B19
- Atypical mycobacteria (MAI/MAC)
- M. TB
- Histoplasma
- CMV

Medications Causing Decreased Production	Medications Causing Hemolysis
• RT inhibitors • Ganciclovir • Bactrim • Amphotericin B	• Indinavir • Bactrim and Dapsone in G6PD deficiency

HIV Unrelated

- B_{12} and/or folic acid deficiencies
- Iron deficiency caused by chronic blood loss

BM, Bone marrow; *CFU-GEMM,* colony-forming unit–granulocyte, erythrocyte, macrophage, megakaryocyte; *CMV,* cytomegalovirus; *G6PD,* glucose-6-phosphate dehydrogenase; *KS,* Kaposi sarcoma; *MAC,* mycobacterium avium complex; *MAI,* mycobacterium avium-intracellulare; *M. TB, Mycobacterium tuberculosis*; *RT,* reverse transcriptase.

From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

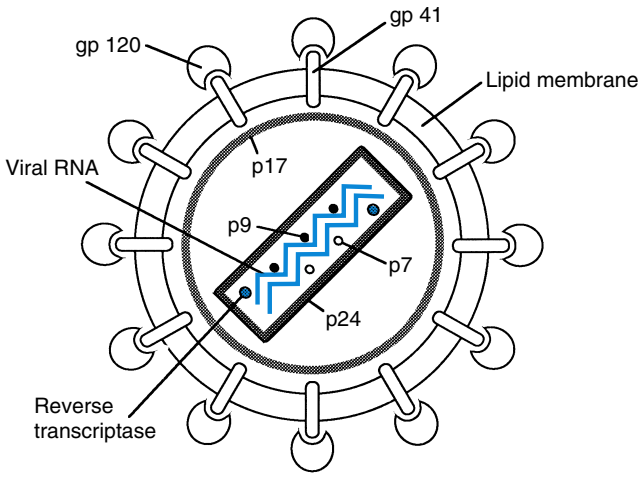

FIG. 1 Structure of the human immunodeficiency virus virion. Two coding strands of genomic ribonucleic acid (RNA) are packaged in the nucleoid core with p7, p9, and p24 proteins and reverse transcriptase. The core is surrounded by the p17 matrix protein lining the inner surface of the envelope. The envelope consists of a lipid bilayer derived from the infected cell and glycoprotein spikes that consist of the outer glycoprotein (GP) 120 molecule, which contains the binding site for CD4, and GP41, which anchors the glycoprotein complex to the envelope and mediates fusion of the viral membrane with the cell membrane during viral penetration. (From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

including seborrheic dermatitis, localized herpes zoster, and/or fungal infection.

- Advanced disease is characterized by AIDS-associated diseases, including infections and malignancies (see specific disorders). Anemia may be multifactorial (Table 4).
- HIV infection in women may be associated with lower levels of viral load at comparable degrees of immunosuppression when compared with men. Furthermore, women may, on average, have higher CD4 counts at the time of HIV diagnosis.
- Another special consideration in women infected with HIV is the high incidence of human papillomavirus (HPV) co-infection and risk for cervical cancer. HIV-positive women should be screened for cervical cancer at time of initial HIV diagnosis and annually thereafter if pap testing is normal. If the results of three consecutive Pap tests are normal, then follow-up testing can occur every 3 yr. HPV vaccination is also recommended in men and women 9- to 26-yr-old who are HIV positive.
- Co-infection with HIV and hepatitis C virus is common because of similar transmission risk. Hepatitis C is most commonly transmitted by contaminated needles or blood exposure. Hepatitis C can be transmitted sexually, but the risk is low. Patients with HIV and hepatitis C progress faster to cirrhosis. Patients may already have signs of advanced liver disease at the time of diagnosis.

ETIOLOGY

- HIV is a single-stranded RNA retrovirus (Fig. 1) that is categorized as type 1 or 2.
- HIV-1 was derived from transmission of a simian immunodeficiency virus (SIV) from chimpanzees in Central Africa; HIV-2 was derived from an SIV found in sooty mangabey monkeys from West Africa.
- HIV-1 is the predominant pathogenic retrovirus in human populations; HIV-2 has limited distribution (primarily West Africa) and tends to progress less rapidly than HIV-1. HIV-2 should be considered in individuals from West Africa or whose sexual partners are from West Africa.
- HIV is transmitted by sexual contact, shared needles, blood transfusion, or from mother to child during pregnancy, delivery, or breastfeeding.
- Primary target of infection: CD4 lymphocytes.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute HIV infection: Often diagnosed or confused with mononucleosis or other respiratory viral infections.
- Late symptoms: Similar to those produced by other wasting/chronic illnesses such as neoplasms, tuberculosis (TB), disseminated fungal infection (such as *Candida*), malabsorption, or depression.
- HIV-related encephalopathy: Confused with Alzheimer disease or other causes of chronic dementia (cognitive impairment in HIV infection is described in another chapter in Section I); myelopathy and neuropathy possibly resembling other demyelinating diseases such as multiple sclerosis.
- Direct central nervous system (CNS) involvement: Manifests as encephalopathy, myelopathy, or neuropathy in advanced cases. Table 5 summarizes neuromuscular syndromes in HIV infection.
- Renal failure, rheumatologic disorders, thrombocytopenia, or cardiac abnormalities (Table 6) may be seen in association with HIV-1.

WORKUP

Diagnosis is established by testing for HIV antibodies in the blood. The CDC recommends routine testing for patients in all health care settings unless the patient declines (opt-out screening). This includes routine testing of pregnant women. It is also recommended that separate written consent should no longer be required, although by law this is being addressed on a state-by-state basis. Generally, all persons aged 13 to 64 yr should undergo HIV testing at least once, and more frequently (at least once a yr) if sexually active. For individuals who may be at higher risk (e.g., men who are having sex with multiple other men), 3 to 6 mo is recommended.

An FDA-approved at-home rapid HIV screening test is available. It uses swabs of oral fluids from upper and lower gums. A positive test requires confirmatory testing.

LABORATORY TESTS

HIV antibodies are detected by a two-step technique:

- An initial screening test (i.e., enzyme-linked immunosorbent assay [ELISA]).
- Confirmation of an initial positive screening test with more specific assays. The classic confirmatory test is the western blot, but other modalities may be used. Fig. E2 summarizes the laboratory diagnosis of HIV infection.

TABLE 5 Neuromuscular Syndromes in Human Immunodeficiency Virus Type 1 Infection

Diagnosis	Disease Stage	Clinical Features	Diagnostic Studies	Treatment
AIDP	Early > late	Weakness more than sensory loss	CSF: ↑ WBCs	Early: IVIG, steroids, plasmapheresis
CIDP			↑↑ Protein	Late: Consider ganciclovir/foscarnet
			NCS: Demyelination	
MM	Early or late	Multiple painful mononeuropathies	NCS: Multifocal axonal neuropathy	Early: None
			Biopsy: Inflammation/vasculitis	Late: Steroids/cyclophosphamide
			CMV	Ganciclovir/foscarnet
Nucleoside	Any stage	Distal sensory loss	NCS: Distal axonopathy	Nucleoside withdrawal
Neuropathy		Neuropathic pain	Increased serum lactate	
DSPN	Late	Distal sensory loss	NCS: Distal axonopathy	NSAIDs, capsaicin
		Neuropathic pain		AED, tricyclics
PP	Late	Progressive flaccid paraparesis, urinary dysfunction, LS pain	CSF: Increased WBCs (PMNs), CMV PCR+	Ganciclovir/foscarnet Cidofovir
DILS	Late	Sjögren syndrome, distal motor and sensory loss, pain	NCS: Axonal neuropathyBiopsy: $CD8^+$ T cells, HIV-1	Zidovudine/ART Steroids
Zidovudine	Any stage	Proximal weakness	EMG: ± irritative	Zidovudine withdrawal
Myopathy		Myalgias	Biopsy: Ragged red fibers	
Polymyositis	Any stage	Proximal weakness	EMG: ± irritative	Steroids, IVIG
		Myalgias	Biopsy: Inflammatory infiltrates	Immunosuppressants
ALS-like	Late	Weakness, dysphagia	EMG: Neurogenic	ART

AED, Antiepileptic drug; *AIDP,* acute inflammatory demyelinating polyneuropathy; *ALS,* amyotrophic lateral sclerosis; *ART,* antiretroviral therapy; *CIDP,* chronic inflammatory demyelinating polyneuropathy; *CMV,* cytomegalovirus; *CSF,* cerebrospinal fluid; *DILS,* diffuse infiltrative lymphocytosis syndrome; *DSPN,* distal sensory polyneuropathy; *EMG,* electromyography; *IVIG,* intravenous immunoglobulin; *LS,* lumbosacral; *MM,* mononeuritis multiplex; *NCS,* nerve conduction studies; *NSAID,* nonsteroidal antiinflammatory drug; *PCR,* polymerase chain reaction; *PMNs,* polymorphonuclear leukocytes; *PP,* progressive polyradiculopathy; *WBCs,* white blood cells.

From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

TABLE 6 Summary of HIV-Associated Cardiovascular Diseases

Disease	Possible Causes	Incidence/Prevalence	Diagnosis	Treatment
Accelerated atherosclerosis	Protease inhibitors, atherogenesis with virus-infected macrophages, chronic inflammation, glucose intolerance, dyslipidemia, endothelial dysfunction	Up to 8%	ECG, stress testing, echocardiography, lipid profile, CT angiography, calcium scoring	Smoking cessation, low-fat diet, aerobic exercise, blood pressure control, guideline-based statin use, percutaneous coronary intervention, coronary artery bypass surgery
Dilated cardiomyopathy	Coronary artery disease	Up to 8% of asymptomatic patients	Chest radiographic findings	Diuretics, digoxin, ACE inhibitors, beta blockers
LV systolic dysfunction	Drug related: Cocaine, AZT, IL-2, doxorubicin, interferon Infectious: HIV, *Toxoplasma*, coxsackievirus group B, EBV, CMV, adenovirus Metabolic or endocrine: selenium or carnitine deficiency, anemia, hypocalcemia, hypophosphatemia, hyponatremia, hypokalemia, hypoalbuminemia, hypothyroidism, growth hormone deficiency, adrenal insufficiency, hyperinsulinemia Cytokines: TNF-β, nitric oxide, TGF-β, endothelin-1, interleukins Immunodeficiency: CD4 count <100 Autoimmune	Up to 25% of autopsy cases	ECG: Nonspecific conduction abnormalities, PVCs, PACs Echocardiographic findings: Low to normal LV wall thickness, increased LV mass, LV dilation, systolic LV dysfunction Possible laboratory studies: Troponin T, brain natriuretic peptide concentration, CD4 count, viral load, viral PCR, *Toxoplasma* serology, thyroid-stimulating hormone, cortisol, carnitine, selenium, serum ACE, stress testing, myocardial biopsy, cardiac catheterization	Adjunctive treatment in HIV patients Treatment of infection Nutritional replacement IVIG Intensify antiretroviral therapy Follow-up serial echocardiograms
LV diastolic dysfunction	TNF, IL-6 Hypertension Chronic viral infection	Up to 37% asymptomatic	Echocardiography Tissue Doppler imaging	Treat hypertension Intensify antiretroviral therapy

TABLE 6 Summary of HIV-Associated Cardiovascular Diseases—cont'd

Disease	Possible Causes	Incidence/Prevalence	Diagnosis	Treatment
Primary pulmonary hypertension	Plexogenic pulmonary arteriopathy	0.5%	ECG, echocardiography, right-heart catheterization	Anticoagulation, vasodilators, prostacyclin analogues Endothelin antagonists PDE-5 inhibitors
Pericardial	Bacteria: *Staphylococcus*, *Streptococcus*, *Proteus*, *Klebsiella*, *Enterococcus*, *Listeria*, *Nocardia*, *Mycobacterium* Viral pathogens: HIV, HSV, CMV, adenovirus, echovirus Other pathogens: *Cryptococcus*, *Toxoplasma*, *Histoplasma* Malignancy: Kaposi sarcoma, lymphoma, capillary leak/wasting/malnutrition Hypothyroidism Immunodeficiency Uremia	11%/yr, markedly reduced in post-HAART studies Spontaneous resolution in 42% of affected patients Approximately 30% increase in 6-mo mortality	Pericardial rub on examination Echocardiography Fluid analysis for Gram stain, culture, and cytology ECG—low voltage/PR depression Associated pleural and peritoneal fluid analysis Pericardial biopsy	Treat the cause Follow-up: Serial echocardiograms Intensify antiretroviral therapy Pericardiocentesis or window
Infective endocarditis	Autoimmune Bacteria: *Staphylococcus aureus* or *Staphylococcus epidermidis*, *Salmonella*, *Streptococcus*, *Haemophilus parainfluenzae*, *Pseudallescheria boydii*, HASEK organisms Fungal: *Aspergillus fumigatus*, *Candida*, *Cryptococcus neoformans*	6% increased incidence in IVDAs, regardless of HIV status	Blood cultures; echocardiography	Intravenous antibiotics, valve replacements
Nonbacterial thrombotic endocarditis	Valvular damage, vitamin C deficiency, malnutrition, wasting, DIC, hypercoagulable state, prolonged acquired immunodeficiency	Rare condition, but clinically relevant emboli in 42% of cases	Echocardiography	Anticoagulation Treat vasculitis or underlying illness
Malignancy	Kaposi sarcoma, non-Hodgkin lymphoma, leiomyosarcoma, low CD4 count, prolonged immunodeficiency HHV-8, EBV	Approximately 1% Usually metastatic in HIV-positive patients	Echocardiography, biopsy	Chemotherapy possible
Right ventricular disease	Recurrent pulmonary infections, pulmonary arteritis, microvascular pulmonary emboli, COPD		ECG, echocardiography, right-heart catheterization	Diuretics, treat underlying lung infection or disease, anticoagulation as clinically indicated
Vasculitis	Drug therapy with antibiotics and antivirals	Increasing incidence	Clinical diagnosis	Systemic corticosteroids, withdrawal of drug
Autonomic dysfunction	CNS disease, drug therapy, prolonged immunodeficiency, malnutrition, sedentary lifestyle	Increased in patients with CNS disease	Tilt-table test, Holter or event monitoring	Procedural precautions
Arrhythmias	Drug therapy, pentamidine, autonomic dysfunction, acidosis electrolyte abnormalities		ECG—long QT, Holter monitoring, exercise stress testing	Discontinue drug, procedural precautions, electrolyte replacement
Lipodystrophy	Drug therapy: Protease inhibitors		Echocardiography, lipid profile, cardiac catheterization, coronary calcium score	Lipid therapy (beware of drug interactions), aerobic exercise, altered antiretroviral therapy, cosmetic surgery/fat implantation

ACE, Angiotensin-converting enzyme; *AZT,* zidovudine (azidothymidine); *CMV,* cytomegalovirus; *CNS,* central nervous system; *COPD,* chronic obstructive pulmonary disease; *CT,* computed tomography; *DIC,* disseminated intravascular coagulation; *EBV,* Epstein-Barr virus; *ECG,* electrocardiogram; *HAART,* highly active antiretroviral therapy; *HASEK, Haemophilus* species (*Haemophilus parainfluenzae*, *Haemophilus aphrophilus*, *Haemophilus paraphrophilus*), *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; *HHV,* human herpesvirus; *HSV,* herpes simplex virus; *IL,* interleukin; *IVDA,* intravenous drug abuser; *IVIG,* intravenous immunoglobulin; *LV,* left ventricle; *PAC,* premature atrial complex; *PCR,* polymerase chain reaction; *PDE,* phosphodiesterase; *PVC,* premature ventricular complex; *TGF,* transforming growth factor; *TNF,* tumor necrosis factor.

From Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.

- Screening antibody tests generally measure HIV-1 and HIV-2 antibodies. Confirmatory tests will generally differentiate between HIV-1 and HIV-2 as well. However, the viral load assays (HIV RNA PCR) are specific only for HIV-1.
- Fourth-generation antibody/antigen tests can detect the "p24" antigen, which is present early in HIV infection and can be used to diagnose HIV earlier than previous generations. An HIV RNA PCR should still be sent if acute HIV is suspected.
- Baseline viral resistance testing (e.g., genotype) is recommended for all newly diagnosed patients with HIV to guide choice of ART.
- The CD4 count and HIV viral load (e.g., HIV RNA PCR) should be measured in all patients.
- The CD4 count is a marker of current immune status. Table 7 describes the World Health Organization (WHO) immunologic classification for established HIV infection.
- The HIV RNA PCR (viral load) is predictive of disease progression.

- Rapid serologic tests have been increasingly used and are useful in specific settings: Occupational exposures, pregnant women in labor without previous testing, and patients in high seroprevalence areas (for immediate results). Specimens are either blood or saliva and results are given within 1 to 20 min. Although sensitivity is high (99%), false-positive tests are more common in low seroprevalence populations. Thus, all positive results must be confirmed with standard serology.
- Early during infection (i.e., acute HIV infection), standard antibody tests may be negative ("window period"). The fourth-generation antibody/antigen test reduces this window period. The standard for diagnosing HIV during acute infection is by testing for HIV RNA (viral load).
- In 2014, the CDC released a revised surveillance case definition for HIV infection. This information has been added in the EBM section of this topic. Table 8 describes the WHO clinical staging of HIV/AIDS for adults and adolescents with confirmed HIV infection. Table 9 compares the WHO and CDC staging systems.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Maintenance of adequate nutrition

ACUTE GENERAL Rx

Acute management of opportunistic infections and malignancies (see AIDS-associated disorders, "Pneumonia, Pneumocystis jiroveci (carinii);" "Cryptococcosis;" "Tuberculosis, Pulmonary;" "Cryptosporidium Infection;" "Toxoplasmosis;" etc., elsewhere in this text)

TABLE 7 World Health Organization Immunologic Classification for Established HIV Infection

HIV-Associated Immunodeficiency	Age-Related CD4 Values			
	<11 mo (% $CD4^+$)	12-35 mo (% $CD4^+$)	36-59 mo (% $CD4^+$)	>5 yr (Absolute No./mm^3 or % $CD4^+$)
None or not significant	>35	>30	>25	>500
Mild	30-35	25-30	20-25	350-500
Advanced	25-29	20-24	15-19	200-349
Severe	<25	<20	<15	<200 or <15%

From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

TABLE 8 World Health Organization Clinical Staging of HIV/AIDS for Adults and Adolescents with Confirmed HIV Infection

Clinical Stage 1
Asymptomatic
Persistent generalized lymphadenopathy
Clinical Stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight)*
Recurrent respiratory tract infections (e.g., sinusitis, tonsillitis, otitis media, pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruptions
Seborrheic dermatitis
Fungal nail infections
Clinical Stage 3
Unexplained* severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhea for longer than 1 month
Unexplained persistent fever (>37.6 °C [99.7 °F]), intermittent or constant, for longer than 1 mo
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis (current)
Severe bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, or bacteremia)
Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis
Unexplained anemia (<8 g/dl), neutropenia ($<0.5 \times 10^9$/L), or chronic thrombocytopenia ($<50 \times 10^9$/L)
Clinical Stage 4†
HIV wasting syndrome
Pneumocystis jiroveci
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal, longer than 1 month's duration, or visceral at any site)
Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)

TABLE 8 World Health Organization Clinical Staging of HIV/AIDS for Adults and Adolescents with Confirmed HIV Infection—cont'd

Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis, including meningitis
Disseminated nontuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis (with diarrhea)
Chronic isosporiasis
Disseminated mycosis (coccidioidomycosis or histoplasmosis)
Recurrent nontyphoidal *Salmonella* bacteremia
Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumors
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

AIDS, Acquired immunodeficiency syndrome.
*Unexplained refers to when the condition is not explained by other causes.
†Some additional specific conditions can also be included in regional classifications (e.g., reactivation of American trypanosomiasis [meningoencephalitis or myocarditis]) in the World Health Organization region of the Americas and disseminated penicilliosis in Asia.
From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

TABLE 9 Comparison of WHO and CDC Staging Systems*

WHO Stage†	WHO T-Lymphocyte Count and Percentage‡	CDC Stage§	CDC T-Lymphocyte Count and Percentage
Stage 1 (HIV infection)	$CD4^+$ T-lymphocyte count of ≥500 cells/mm^3	Stage 1 (HIV infection)	$CD4^+$ T-lymphocyte count of ≥500 cells/mm^3 or $CD4^+$ T-lymphocyte percentage of ≥29
Stage 2 (HIV infection)	$CD4^+$ T-lymphocyte count of 350-499 cells/mm^3	Stage 2 (HIV infection)	$CD4^+$ T-lymphocyte count of 200-499 cells/mm^3 or $CD4^+$ T-lymphocyte percentage of 14-28
Stage 3 (advanced HIV disease [AHD])	$CD4^+$ T-lymphocyte count of 200-349 cells/mm^3	Stage 2 (HIV infection)	$CD4^+$ T-lymphocyte count of 200-499 cells/mm^3 or $CD4^+$ T-lymphocyte percentage of 14-28
Stage 4 (acquired immunodeficiency syndrome [AIDS])	$CD4^+$ T-lymphocyte count of <200 cells/mm^3 or $CD4^+$ T-lymphocyte percentage of <15	Stage 3 (AIDS)	$CD4^+$ T-lymphocyte count of <200 cells/mm^3 or $CD4^+$ T-lymphocyte percentage of <14

CDC, Centers for Disease Control and Prevention; *WHO,* World Health Organization.
*For reporting purposes only.
†Among adults and children aged ≥5 yr.
‡Percentage applicable for stage 4 only.
§Among adults and adolescents (ages ≥13 yr). CDC also includes a fourth stage, stage unknown; laboratory confirmation of HIV infection but no information on $CD4^+$ T-lymphocyte count or percentage and no information on AIDS-defining conditions.
From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

CHRONIC Rx

All HIV-infected patients should be considered for ART regardless of CD4 cell count. The benefit of ART is well established in preventing progression to AIDS and associated comorbidities. Furthermore, individuals who are on ART and undetectable are highly unlikely to transmit HIV to others. Identifying individuals with HIV as soon as possible and administering ART is the basis of effective public health approaches to addressing HIV (i.e., "Treatment as Prevention").

- Therapy is strongly recommended for all patients with symptomatic established HIV disease regardless of the CD4 count. Symptomatic HIV disease is defined as the presence of any of the following: thrush, vaginal candidiasis, herpes zoster, peripheral neuropathy, bacillary angiomatosis, cervical dysplasia in situ, constitutional symptoms such as fever or diarrhea for more than 1 month, ITP, PID, or listeriosis.
- In asymptomatic individuals, ART is recommended regardless of CD4 cell counts. The recommendations are due to the safety and benefit of newer antivirals in preventing AIDS and decreasing both morbidity and mortality. Earlier treatment may also help reduce transmission of the virus to others due to reductions in viral loads.
- ART generally consists of using a 3-drug regimen to treat HIV infection. Classes of antiretrovirals include:
  1. Nucleoside/nucleotide reverse transcriptase inhibitor (NRTI): Zidovudine (AZT), lamivudine (3TC), emtricitabine (FTC), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), abacavir (ABC), stavudine (D4T), or didanosine (DDI).
  2. Protease inhibitors (PI): Lopinavir/ritonavir, atazanavir, fosamprenavir, darunavir, saquinavir, amprenavir, tipranavir, nelfinavir, and indinavir. These PIs may be "boosted" by ritonavir or cobicistat to increase levels.
  3. Non-nucleoside reverse transcriptase inhibitors (NNRTI): Nevirapine, efavirenz, etravirine, delavirdine, or rilpivirine.
  4. Integrase inhibitors (II): Raltegravir, elvitegravir, bictegravir, and dolutegravir.
  5. Fusion inhibitors: Enfuvirtide (T-20). This drug is administered through subcutaneous injections and is only used as part of a salvage regimen for individuals who have failed multiple other regimens.
  6. CCR5 inhibitors: Maraviroc. Before using this drug, a viral trophism assay should be checked to determine if the virus uses the CCR5 co-receptor to infect cells. If the virus uses the CXCR4 co-receptor, this drug will not be effective.
  7. Post-attachment inhibitors: Ibalizumab. Blocks CD4 receptors that HIV needs to enter cells with.

TABLE 10 What Antiretroviral Regimen to Choose for Initial Therapy

Preferred Regimens	Comments
Integrase inhibitor-based regimen Bictegravir/TAF/FTC Raltegravir + TDF/FTC or TAF/FTC Dolutegravir + TDF/FTC or TAF/FTC Dolutegravir/ABC/3TC	Use abacavir only in individuals who are HLA-B*5701 negative.
PI-based regimen Darunavir/r or Darunavir/c (once daily) + TDF/FTC or TAF/FTC	Use if there is a concern for drug resistance.
Preferred regimen for pregnant women ABC/3TC or TDF/FTC plus Raltegravir or Darunavir/r or Atazanavir/r	TDF should be avoided in renal impairment.
Alternative Regimens	**Comments**
INSTI-based regimens Elvitegravir/cobicistat/TDF/FTC Elvitegravir/cobicistat/TAF/FTC RAL + ABC/3TC	
NNRTI-based regimens (in alphabetical order) EFV/TDF/FTC or EFV + TAF/FTC EFV + ABC/3TC RPV/TDF/FTC or RPV/TAF/FTC RPV + ABC/3TC	EFV should not be used with caution in the first trimester of pregnancy or in women trying to conceive. NVP should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or C) Should not be used in women with pre-treatment CD4 >250 cells/mm^3 or men with CD4 >400 cells/mm^3
PI-based regimens (in alphabetical order) ATV/r or ATV/c + ABC/3TC ATV/r or ATV/c + TDF/FTC or TAF/FTC DRV/c or DRV/r + ABC/3TC	ABC should not be used in patients who test positive for HLA-B*5701 Use with caution in patients with high risk of cardiovascular disease or with pretreatment HIV RNA >100,000 copies/ml Once-daily LPV/r is not recommended in pregnant women.

3TC, Lamivudine; *ABC,* abacavir; *ATV,* atazanavir; *DRV,* darunavir; *EFV,* efavirenz; *FPV,* fosamprenavir; *FTC,* emtricitabine; *INSTI,* integrase strand transfer inhibitor; *LPV,* lopinavir; *MRV,* maraviroc; *NNRTI,* nonnucleoside reverse transcriptase inhibitor; *NRTI,* nucleos(t)ide reverse transcriptase inhibitor; *NVP,* nevirapine; *PI,* protease inhibitor; *r,* low dose ritonavir; *RAL,* raltegravir; *RNA,* ribonucleic acid; *RVP,* rilpivirine; *TAF,* tenofovir alafenamide; *TDF,* tenofovir disoproxil fumarate. The following combinations in the recommended list are available as fixed-dose combination formulations: ABC/3TC, EFV/TDF/FTC, LPV/r, TDF/FTC, RPV/TDF/FTC, and ZDV/3TC.

Modified from DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Department of Health and Human Services 1-161, 2018. www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

- Adding a fourth drug to the three-drug regimen does not improve viral suppression or outcomes and is not recommended. Treatment interruptions based upon CD4 responses appear harmful in recent comparative studies versus standard continuous treatment protocols and should be avoided. Antiretroviral regimens for initial therapy are summarized in Table 10.
- Typical dosing regimen consists of two NRTIs and either a NNRTI, PI, or II. IIs are now the preferred third drug because of tolerability. Data support inclusion of lamivudine or emtricitabine as one of the two NRTIs.
- Individuals with drug resistant HIV may be on more complex and atypical regimens. Consultation with an HIV specialist is recommended.

Standard NRTIs include:

- Tenofovir disoproxil fumarate/emtricitabine 1 tablet once daily. Individuals with underlying renal dysfunction or requiring other nephrotoxic agents may be at increased risk of renal toxicity while taking tenofovir. TDF may also be associated with reductions in bone mineral density.
- Tenofovir alafenamide/emtricitabine 1 tablet once daily. TAF is a newer formulation of TDF with less nephrotoxicity and bone mineral density effects. Both TDF/FTC, and TAF/FTC are recommended components of the initial regimen (with a "backbone" medication). TDF should be avoided in patients with a creatinine clearance (CrCl) <60 ml/min. TAF should be avoided in patients with a CrCl <30 ml/min.
- Abacavir/lamivudine 1 tablet once daily. Abacavir may be associated with increased risk of myocardial infarction. Before using this drug, individuals should be checked for HLA-B*5701. Individuals with this allele are at higher risk of serious hypersensitivity reactions, and this drug should be avoided.
- Zidovudine/lamivudine 1 tablet twice daily. Once widely prescribed; now rarely used due to lower efficacy compared with tenofovir-emtricitabine; zidovudine is associated with lipoatrophy and anemia, as well as GI and CNS side effects.

Standard backbone regimens include:

- IIs (these are now considered first line):
  1. Bictegravir (50 mg once daily): Fixed-dose combination of bictegravir with the NRTIs TAF and FTC.
  2. Dolutegravir (50 mg once daily): Fixed-dose combination of dolutegravir and the NRTIs abacavir and lamivudine for once-daily treatment of HIV-1 infection. HLA-B*5701 should be checked first.
  3. Elvitegravir: Given with cobicistat (booster) and tenofovir/emtricitabine in a fixed-dose combination.
  4. Raltegravir (400 mg twice a day).
- NNRTIs:
  1. Efavirenz 600 mg daily: Should be used in caution in women in the first trimester or those who are contemplating pregnancy.
  2. Rilpivirine: Given with tenofovir and emtricitabine as part of a fixed-dose combination.
  3. Nevirapine 200 mg two times a day: Avoid with CD4 count >250 in men and >350 cells per cubic millimeter in women because of the risk of hepatitis. The newer agent rilpivirine had higher virologic failures and should be considered an alternative agent.
  4. Etravirine 200 mg two times a day: This drug is generally used in patients for whom other regimens have failed. Etravirine retains activity in many patients who have developed resistance against efavirenz and nevirapine.
- PIs (ritonavir boosted):
  1. Darunavir and ritonavir (800 mg and 100 mg a day): This is considered a preferred PI regimen within the U.S. Department of Health and Human Services (DHHS) guidelines with either tenofovir disoproxil fumarate or TAF and emtricitabine.
  2. Atazanavir and ritonavir (300 mg and 100 mg) 2 tablets a day: Lower pill burden, but use with caution with acid-reducing agents (can alter absorption).
  3. Lopinavir and ritonavir (200 mg/50 mg) 2 tablets twice a day (or 4 tablets once a day): Most likely to cause diarrhea and has the greatest negative effect on triglyceride levels.
  4. Fosamprenavir and ritonavir (700 mg and 100 mg) 2 tablets twice a day (or 4 tablets once a day): Cannot take fosamprenavir with sulfa allergy.
  5. Saquinavir and ritonavir: Saquinavir is no longer recommended for initial treatment of any patient and should be prescribed only in consultation with a specialist.
- All these drugs have their own unique, as well as class-specific, side effects and require careful follow-up to achieve optimal antiviral effects. Compliance with the drug regimen and tolerance of common side effects are critically important to maintain drug efficacy. Antiviral response should be monitored by baseline HIV viral load and CD4 count and repeat measurement at 2 and 4 weeks into treatment and then periodically (every 3-6 months) to ensure viral suppression.
- All patients should have genotypic resistance testing upon entry into medical care and before initiation of ART.
- In experienced patients, an antiretroviral regimen should be constructed based on past antiretroviral use and the results of genotypic or phenotypic testing.

- Patients with a CD4 count <200/mm^3 should be given preventive therapy for PJP (Table 11).
- Evaluation of chronic diarrhea in patients with HIV is described in the AIDS topic in Section I.
- Criteria for discontinuing and restarting opportunistic infection prophylaxis for adults and adolescents with HIV infection is described in Table 12.
- HIV infection in a pregnant woman poses special challenges and considerations. Appropriate and timely ART given to mother and newborn has been shown to dramatically reduce the risk of perinatal transmission of HIV. The goal of therapy is to achieve an undetectable viral load. For HIV-infected pregnant women who are already receiving ART: (1) Continue therapy if suppressing viral replication, but avoid use of efavirenz in the first trimester (substitution is recommended in the first trimester); (2) if viremia on therapy, genotypic testing is recommended. For HIV-infected pregnant women who have never received ART: (1) All women should start on ART as soon as possible. Most antiretrovirals are safe in pregnancy; however, efavirenz should be avoided because of possible teratogenicity (Class D), DDI and D4T should be avoided (potential of lactic acidosis), and some protease inhibitors may be dose-altered in pregnancy. Importantly, dolutegravir (DTG) should be avoided in the first trimester because of an increased risk for neural tube defects. Nevirapine should not be initiated in an antiretroviral-naive pregnant patient with CD4 counts >250 cells/mm^3 because of the risk of hepatotoxicity. (2) Women who do not need ART for their own health should also initiate three-drug therapy, but may do so at the end of the first trimester.

TABLE 11 Criteria for Discontinuing and Restarting Opportunistic Infection Prophylaxis for Adults and Adolescents with Human Immunodeficiency Virus Infection

Opportunistic Infection	Criteria for Discontinuing Primary Prophylaxis	Criteria for Restarting Primary Prophylaxis	Criteria for Discontinuing Secondary Prophylaxis/Chronic Maintenance Therapy	Criteria for Restarting Secondary Prophylaxis/ Chronic Maintenance Therapy
Pneumocystis pneumonia (PJP)	CD4$^+$ count >200 cells/mm^3 for >3 mo in response to ART	CD4$^+$ count <200 cells/mm^3	CD4$^+$ count increased from <200 cells/mm^3 to >200 cells/mm^3 for ≥3 mo in response to ART If PJP is diagnosed when CD4$^+$ count >200 cells/mm^3, prophylaxis should probably be continued for life regardless of CD4$^+$ count rise in response to ART.	CD4$^+$ count <200 cells/mm^3, or if PCP recurred at a CD4$^+$ count >200 cells/mm^3
Toxoplasma gondii encephalitis (TE)	CD4$^+$ count >200 cells/mm^3 for >3 mo in response to ART	CD4$^+$ count <100-200 cells/mm^3	Successfully completed initial therapy, remain asymptomatic of signs and symptoms of TE, and CD4$^+$ count >200 cells/mm^3 for >6 mo in response to ART	CD4$^+$ count <100 cells/mm^3
Microsporidiosis	Not applicable	Not applicable	No signs and symptoms of non-ocular microsporidiosis and CD4$^+$ count >200 cells/mm^3 for >6 mo in response to ART Patients with ocular microsporidiosis should be on therapy indefinitely regardless of CD4$^+$ count.	No recommendation
Disseminated *Mycobacterium avium* complex (MAC) disease	CD4$^+$ count >100 cells/mm^3 for ≥3 mo in response to ART	CD4$^+$ count <50 cells/mm^3	If fulfill the following criteria Completed ≥12 mo therapy, and No signs and symptoms of MAC, and Have sustained (≥6 mo) CD4$^+$ count >100 cells/mm^3 in response to ART	CD4$^+$ count <50 cells/mm^3
Bartonellosis	Not applicable	Not applicable	If fulfill the following criteria Received 3-4 mo of treatment CD4$^+$ count >200 cells/mm^3 for ≥6 mo Certain specialists would discontinue therapy only if *Bartonella* titers have also decreased by fourfold.	No recommendation
Mucosal candidiasis	Not applicable	Not applicable	If used, reasonable to discontinue when CD4$^+$ count >200 cells/mm^3	No recommendation
Cryptococcal meningitis	Not applicable	Not applicable	If fulfill the following criteria Completed course of initial therapy Remain asymptomatic of cryptococcosis CD4$^+$ count ≥200 cells/mm^3 for >6 mo in response to ART Certain specialists would perform a lumbar puncture to determine if cerebrospinal fluid is culture and antigen negative before stopping therapy.	CD4$^+$ count <100 cells/mm^3
Histoplasma capsulatum infection	If used, CD4$^+$ count >150 cells/mm^3 for 6 mo on ART	For patients at high risk for acquiring histoplasmosis, restart at CD4$^+$ count ≤150 cells/mm^3.	If fulfill the following criteria received itraconazole for ≥1 yr Negative blood cultures CD4$^+$ count >150 cells/mm^3 for ≥6 mo in response to ART Serum *Histoplasma* antigen <2 units	CD4$^+$ count ≤150 cells/mm^3

Continued

TABLE 11 Criteria for Discontinuing and Restarting Opportunistic Infection Prophylaxis for Adults and Adolescents with Human Immunodeficiency Virus Infection—cont'd

Opportunistic Infection	Criteria for Discontinuing Primary Prophylaxis	Criteria for Restarting Primary Prophylaxis	Criteria for Discontinuing Secondary Prophylaxis/Chronic Maintenance Therapy	Criteria for Restarting Secondary Prophylaxis/ Chronic Maintenance Therapy
Coccidioidomycosis	If used, $CD4^+$ count ≥250 cells/mm^3 for ≥6 mo	If used, restart at $CD4^+$ count <250 cells/mm^3	**Only for patients with focal coccidioidal pneumonia:** Clinically responded to ≥12 mo of antifungal therapy $CD4^+$ count >250 cells/mm^3 Receiving ART Suppressive therapy should be continued indefinitely, even with increase in $CD4^+$ count on ART for patients with diffuse pulmonary, disseminated, or meningeal diseases.	No recommendation
Cytomegalovirus retinitis	Not applicable	Not applicable	$CD4^+$ count >100 cells/mm^3 for >3-6 mo in response to ART. Therapy should be discontinued only after consultation with an ophthalmologist, taking into account magnitude and duration of $CD4^+$ count increase, anatomic location of the lesions, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring. Routine (every 3 mo) ophthalmologic follow-up is recommended for early detection of relapse or immune restoration uveitis.	No recommendation
Isospora belli infection	Not applicable	Not applicable	Sustained increase in $CD4^+$ count to >200 cells/mm^3 for >6 mo in response to ART and without evidence of *I. belli* infection	No recommendation

ART, Antiretroviral therapy.

Modified from Centers for Disease Control and Prevention: Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Disease Society of America, *MMWR* 58(RR-4), 2009.

TABLE 12 Prophylaxis to Prevent First Episode of HIV-related Opportunistic Disease

Pathogen	Indication	First Choice	Alternative
Pneumocystis jiroveci pneumonia (PJP, previously referred to as *Pneumocystis carinii,* PCP)	$CD4^+$ count <200 cells/mm^3 or oropharyngeal candidiasis$CD4^+$ <14% or history of AIDS-defining illness $CD4^+$ count >200 but <250 cells/mm^3 if monitoring $CD4^+$ count every 1-3 mo is not possible	Trimethoprim-sulfamethoxazole (TMP-SMX) double-strength PO daily; *or* single-strength daily	TMP-SMX 1 double-strength PO 3 times weekly; *or* Dapsone 100 mg PO daily or 50 mg PO bid; *or* Aerosolized pentamidine 300 mg via Respirgard II nebulizer every month; *or* Atovaquone 1500 mg PO daily
Toxoplasma gondii encephalitis	*Toxoplasma* IgG–positive patients with $CD4^+$ count <100 cells/mm^3Seronegative patients receiving PCP prophylaxis not active against toxoplasmosis should have *Toxoplasma* serology retested if $CD4^+$ count declines to <100 cells/mm^3. Prophylaxis should be initiated if seroconversion occurred.	TMP-SMX, 1 double-strength PO daily	TMP-SMX 1 double-strength PO 3 times weekly; *or* TMP-SMX 1 single-strength PO daily; *or* Dapsone 50 mg PO daily + pyrimethamine 50 mg PO weekly + leucovorin 25 mg PO weekly; *or* Dapsone 200 mg PO weekly + pyrimethamine 75 mg PO weekly + leucovorin 25 mg PO weekly
Mycobacterium tuberculosis infection (TB) (treatment of latent TB infection or LTBI)	(1) Diagnostic test for LTBI, no evidence of active TB, and no prior history of treatment for active or latent TB (2) Diagnostic test for LTBI, but close contact with a person with infectious pulmonary TB and no evidence of active TB (3) A history of untreated or inadequately treated healed TB (i.e., old fibrotic lesions) regardless of diagnostic tests for LTBI and no evidence of active TB	Isoniazid (INH) 300 mg PO daily or 900 mg PO twice weekly for 9 mo—both plus pyridoxine 25 mg PO daily; *or* For persons exposed to drug-resistant TB, selection of drugs after consultation with public health authorities	Rifampin (RIF) 600 mg PO daily × 4 mo; or Rifabutin (dosage depends on ART regimen). Be careful of drug interactions with these medications (PIs and NNRTIs) Isoniazid (15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum) and rifapentine (10-14.0 kg 300 mg; 14.1-25.0 kg 450 mg; 25.1-32.0 kg 600 mg; 32.1-49.9 kg 750 mg; ≥50.0 kg 900 mg maximum) once weekly for a total of 3 mo

TABLE 12 Prophylaxis to Prevent First Episode of HIV-related Opportunistic Disease—cont'd

Pathogen	Indication	First Choice	Alternative
Disseminated *Mycobacterium avium* complex (MAC) disease	$CD4^+$ count <50 cells/mm^3—after ruling out active MAC infection	Azithromycin 1200 mg PO once weekly; *or* Clarithromycin 500 mg PO bid; *or* Azithromycin 600 mg PO twice weekly	RFB 300 mg PO daily (dosage adjustment based on drug-drug interactions with antiretroviral therapy); rule out active TB before starting RFB
Streptococcus pneumoniae infection	$CD4^+$ count >200 cells/mm^3 and no receipt of pneumococcal vaccine in the past 5 yr. $CD4^+$ count <200 cells/mm^3—vaccination can be offered In patients who received polysaccharide pneumococcal vaccination (PPV) when $CD4^+$ count <200 cells/mm^3 but has increased to >200 cells/mm^3 in response to antiretroviral therapy	A single dose of PCV13 followed by a single dose of PPSV23 at least 8 wk later. A second dose of PPSV23 should be given 5 yr after the initial PPSV23 dose.	
Influenza A and B virus infection	All HIV-infected patients	Inactivated influenza vaccine 0.5 ml IM annually	
Histoplasma capsulatum infection	$CD4^+$ count ≤150 cells/mm^3 and at high risk because of occupational exposure or live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-yr)	Itraconazole 200 mg PO daily	
Coccidioidomycosis	Positive IgM or IgG serologic test result in a patient from a disease-endemic area; and $CD4^+$ count <250 cells/mm^3	Fluconazole 400 mg PO daily itraconazole 200 mg PO bid	
Varicella-zoster virus (VZV) infection	*Pre-exposure prevention:* Patients with $CD4^+$ count ≥200 cells/mm^3 who have not been vaccinated, have no history of varicella or herpes zoster, or who are seronegative for VZV NOTE: Routine VZV serologic testing in HIV-infected adults is not recommended. *Postexposure—close contact with a person who has active varicella or herpes zoster* For susceptible patients (those who have no history of vaccination or of either condition, or are known to be VZV seronegative)	*Pre-exposure prevention:* Primary varicella vaccination (Varivax), 2 doses (0.5 ml SC) administered 3 mo apart. If vaccination results in disease because of vaccine virus, treatment with acyclovir is recommended. *Postexposure therapy:* Varicella-zoster immune globulin (VariZIG) 125 IU per 10 kg (maximum of 625 IU) IM, administered within 96 hr after exposure to a person with active varicella or herpes zoster NOTE: As of June 2007, VariZIG can be obtained only under a treatment IND (1-800-843-7477, FFF Enterprises).	VZV-susceptible household contacts of susceptible HIV-infected persons should be vaccinated to prevent potential transmission of VZV to their HIV-infected contacts. Alternative postexposure therapy: Postexposure varicella vaccine (Varivax) 0.5 ml SC × 2 doses, 3 mo apart if $CD4^+$ count >200 cells/mm^3; *or* Preemptive acyclovir 800 mg PO 3×/day for 5 days These two alternatives have not been studied in the HIV population.
Human papillomavirus (HPV) infection	Women aged 11-26 yr. Men aged 11-26 yr	HPV quadrivalent vaccine 0.5 ml IM mo 0, 2, and 6	
Hepatitis A virus (HAV) infection	HAV-susceptible patients with chronic liver disease or who are injection-drug users, or men who have sex with men. Certain specialists might delay vaccination until $CD4^+$ count >200 cells/mm^3.	Hepatitis A vaccine 1 ml IM × 2 doses—at 0 and 6-12 mo IgG antibody response should be assessed 1 mo after vaccination; nonresponders should be revaccinated	
Hepatitis B virus (HBV) infection	All HIV patients without evidence of prior exposure to HBV should be vaccinated with HBV vaccine, including patients with $CD4^+$ count <200 cells/mm^3. *Patients with isolated anti-HBc:* Consider screening for HBV DNA before vaccination to rule out occult chronic HBV infection	Hepatitis B vaccine IM (Engerix-B 20 μg/ml or Recombivax HB 10 μg/ml) at 0, 1, and 6 mo Anti-HBs should be obtained 1 mo after completion of the vaccine series.	Some experts recommend vaccinating with 40-μg doses of either vaccine.
	Vaccine nonresponders: Defined as anti-HBs <10 IU/ml 1 mo after a vaccination series For patients with low $CD4^+$ count at the time of first vaccination series, certain specialists might delay revaccination until after a sustained increase in $CD4^+$ count with antiretroviral therapy.	Revaccinate with a second vaccine series.	Some experts recommend revaccinating with 40-μg doses of either vaccine.

ART, Antiretroviral therapy; *HB,* hepatitis B; *IG,* immunoglobulin; *IM,* intramuscular; *IND,* investigational new drug; *NNRTI,* nonnucleoside analog reverse transcriptase inhibitor; *PI,* protease inhibitors; *PO,* by mouth; *RFB,* rifabutin.

Modified from Centers for Disease Control and Prevention: Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Disease Society of America, *MMWR* 58(RR-4), 2009.

- Preferred ART medications during pregnancy include:
  1. NRTIs: TDF/FTC, TDF/3TC, or ABC/3TC
  2. INSTI: Raltegravir; dolutegravir can be used after the first trimester; limited data with bictegravir
  3. PIs: ATV/r or DRV/r
- ART should continue through the baby's birth. Zidovudine should also be given intravenously to the woman at the time of labor if the woman has an HIV RNA >1000 copies/ml or there is a concern for poor adherence, regardless of whether it is an existing component of her three-drug regimen. In women with viral loads persistently >1000 copies/ml despite appropriate ART, cesarean section may further lower risk of transmission. For women with HIV RNA <1000 copies/ml zidovudine (AZT) should also be given to the newborn for the first 6 weeks of life. If HIV RNA levels are >1000 copies/ml, infants should receive combination ART, which may include zidovudine, lamivudine and nevirapine for 6 weeks. Mothers should completely avoid nursing.

DISPOSITION

- Ongoing care consisting of frequent medical evaluations and monitoring of CD4 counts and HIV viral loads.
- Long-term care focused on providing up-to-date ART and prophylaxis of PJP and other opportunistic infections, as well as early detection of complications.
- Ongoing assessment for cardiovascular risk and other primary prevention interventions.
- Screening for hepatitis A, B, and C. Treatment when indicated. Drugs such as TDF and lamivudine have activity against both HIV and hepatitis B and may be used in patients with co-infection.
- Vaccinations including hepatitis A and B (when susceptible), pneumococcus (PCV13 and PPSV23), tetanus/diphtheria/pertussis, meningococcal, and influenza. Box 1 summarizes vaccinations in HIV-positive adults.
- Yearly screening for other sexually transmitted infections (chlamydia, gonorrhea, and syphilis). This includes trichomonas in women and extragenital testing for chlamydia and gonorrhea (i.e., pharyngeal and rectal) in MSM.

BOX 1 Vaccination in HIV-Positive Adults

Generally Avoid
- BCG
- Oral polio
- Oral typhoid

Avoid if CD4+ Cells <200
- Yellow fever
- Measles
- Varicella-zoster virus (VZV)

Give Routinely
- Tetanus/diphtheria (or Tdap)
- Hepatitis A/B
- *Streptococcus pneumoniae*
- Hib
- Meningococcal
- Influenza, yearly

Give if Indicated for Travel
- Typhoid Vi
- Meningococcal
- Polio, IPV
- Rabies
- Japanese encephalitis
- Tick-borne encephalitis

From Auerbach P: *Wilderness medicine, expert consult,* premium edition—enhanced online features and print, Philadelphia, 2012, WB Saunders.

- Consideration of AIDS (lymphomas, HPV) and non-AIDS related (screening for general population, age-specific cancers).

REFERRAL

To a physician knowledgeable and experienced in the management of HIV infection and its complications.

PREVENTION

- TDF/FTC may be used as pre-exposure prophylaxis (PrEP). Individuals who are HIV negative may take TDF/FTC once a day to prevent HIV infection. PrEP has been demonstrated to be effective in MSM, heterosexuals, and injection drug users. Individuals on PrEP should be monitored every three months for renal dysfunction, HIV status, and adherence.
- Post-exposure prophylaxis (PEP) is an effective prevention intervention for individuals exposed to HIV infection, either occupationally or through a sexual exposure. PEP should be taken within 72 hours of an exposure and continued for 28 days. Baseline HIV status, renal function, hepatitis B/C, and liver function should be assessed. The recommended first-line regimen is tenofovir-emtricitabine 300/200 mg once daily plus raltegravir 400 mg orally twice daily or Dolutegravir 50mg once daily. Dolutegravir should be avoided in women of childbearing potential or who are pregnant.

PEARLS & CONSIDERATIONS

COMMENTS

- ART should be initiated in all HIV-infected individuals regardless of CD4 cell counts.
- ART in combination with avoidance of breastfeeding and elective cesarean section in women with viremia reduces risk for mother-to-child transmission.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Human Immunodeficiency Virus (HIV) Infection (Patient Information)

Acquired Immunodeficiency Syndrome (Related Key Topic)

AUTHOR: **Philip A. Chan, MD, MS**

SUGGESTED READINGS

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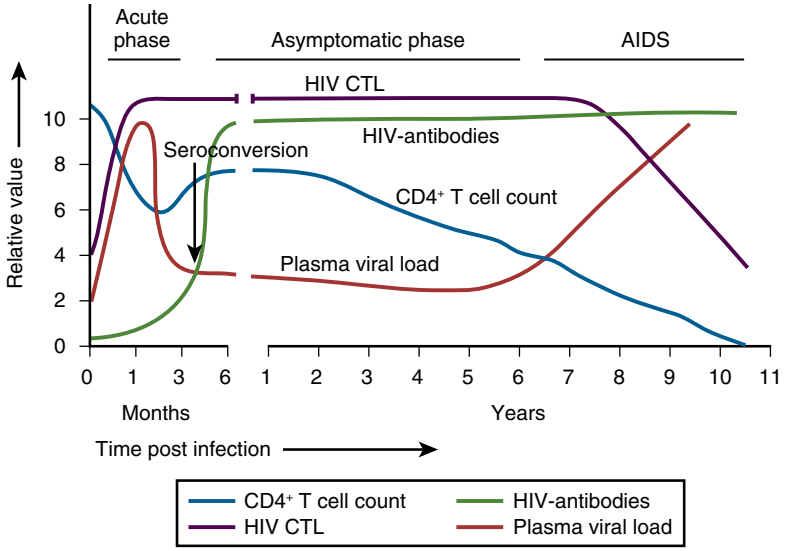
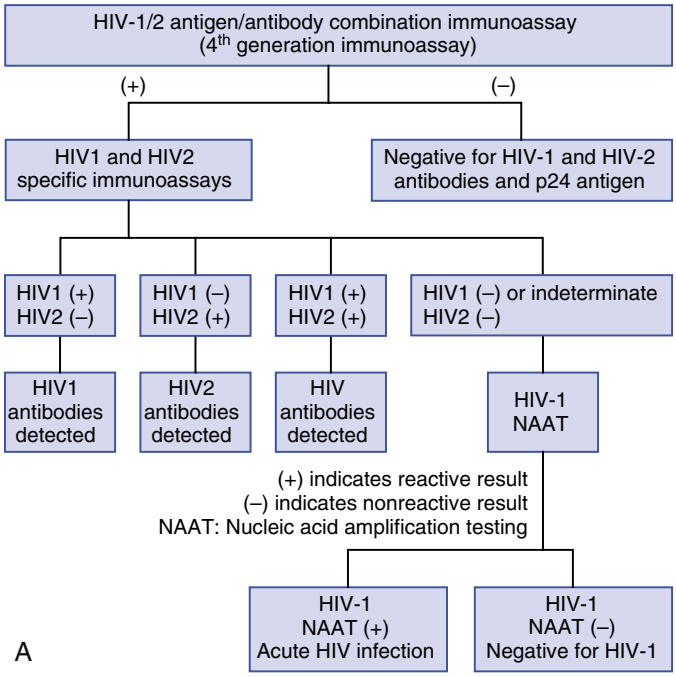


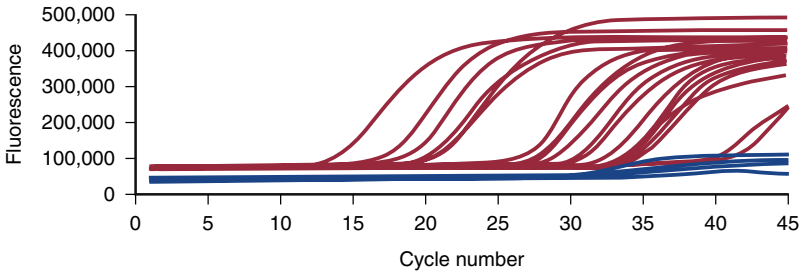


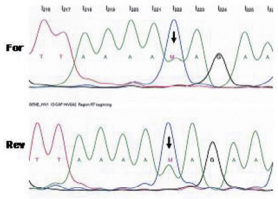
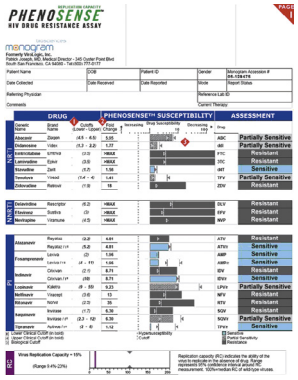
A

1. Screen with an HIV-1/2/p24 antibody/antigen assay. If negative, chances of an established HIV-1 or HIV-2 infection are low.
2. Test screen positive samples with immunoassay that differentiates between HIV-1 and HIV-2.
3. Specimens with a reactive screen and negative or indeterminate for HIV-1/HIV-2 differentiation need to be confirmed by HIV-1 NAAT.
    1. A reactive HIV-1 NAAT result and a nonreactive HIC-1/HIV-2 antibody differentiation immunoassay are consistent with laboratory evidence of acute HIV-1 infection.
    2. A reactive HIV-1 NAAT result and indeterminate HIV-1/HIV-2 antibody differentiation immunoassay indicate a false positive on the initial screen immunoassay.
    3. A negative HIV-1 NAAT results and nonreactive or indeterminate HIV-1?HIV-2 antibody differentiation immunoassay result are consistent with a false positive result on the initial screening immunoassay.
4. Laboratories should use this same testing algorithm, beginning with the antigen/antibody combination screen immunoassay, with serum or plasma specimens submitted for testing after a reactive result from any rapid HIV test.
5. No further testing is required for specimens that are nonreactive on the initial screening immunoassay.
6. Inconsistent or conflicting results should be investigated with follow-up testing on a newly collected specimen.

FIG. E2 Laboratory diagnosis of human immunodeficiency virus *(HIV)* infection. *CTL,* Cytotoxic T lymphocytes; *DNA,* deoxyribonucleic acid; *RNA,* ribonucleic acid. (From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, Philadelphia, 2017, Elsevier.)

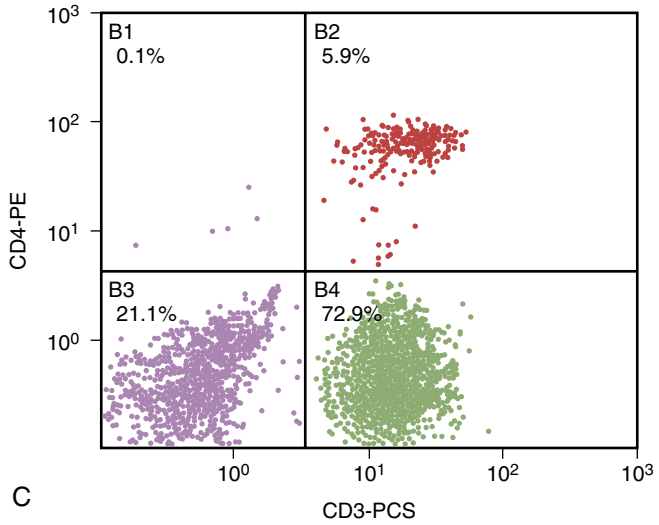
Assay	Comments
Prognosis/Monitoring Treatment	

HIV viral load
 
 	
	• The same method should be used for monitoring individual patients to minimize technical variation in HIV blood levels.
	• HIV viral load testing is used to
	  • Diagnose acute retroviral syndrome before seroconversion develops.
	  • Assess prognosis and progression of HIV disease.
	  • Guide antiretroviral therapy.
	  • Define a baseline level so that response to therapy can be measured.
	  • Monitor response to therapy.
	• Greater than 0.5 log (3-fold) change in blood HIV load is considered clinically significant.

Genotypic HIV assays  	• Genotypic assays are helpful in antiretroviral-naive patients for initial assessment of treatment options. Genotyping is also useful for patients who develop virologic failure with rising HIV viral load during highly active antiretroviral therapy, and need guidance for treatment modification. • Genotyping detects changes in the nucleic acid sequence of the relevant HIV1 gene and identifies drug resistance by detecting mutations in the HIV1 genome that lead to specific amino acid substitutions in the HIV1 RT or protease enzymes.
Resistance-associated reverse transcriptase (RT) mutation K103N Resistance to nevirapine and efavirenz	
Phenotypic assays  	• Phenotypic assays amplify RT and protease genes from the patient's HIV predominant quasi-species virus RNA or proviral DNA. These amplicons are then inserted into a laboratory virus that lacks the genes, creating a hybrid virus. The hybrid virus is then propagated in cell culture, and its ability to propagate in the presence of varying concentrations of the anti-HIV agent is measured. Results are expressed as concentrations of drug required to inhibit 50% of growth (IC50) compared with a wild-type control strain.
Virtual phenotypes	• The patient's HIV genotype is compared with a database containing many known HIV drug-resistant and susceptible genotypes to predict the patient's response to therapy.

B

Assay	Comments
Immune Status	

CD4 cell counts
(% CD4 and absolute number)
 
 	
	• CD4 cell count and CD4/CD8 ratio are used to
	  • Stage HIV disease.
	  • Help establish the risk of specific HIV-associated infectious or neoplastic complications.
	  • Determine the need for prophylaxis against opportunistic infections.
	  • Determine the need for and response to antiretroviral therapy.

C

FIG. E2, cont'd.

BASIC INFORMATION

DEFINITION

Huntington disease (HD) is a trinucleotide repeat autosomal dominant neurodegenerative disorder characterized by involuntary movements, psychiatric disturbance, and cognitive decline. The disease exhibits the genetic phenomenon of anticipation, such that subsequent generations have longer repeats and a younger age of onset (Table E1).

SYNONYMS

Huntington chorea
HD

ICD-10CM CODE
G10 Huntington disease

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Late 30s and 40s, with onsets from ages 2 to 70 yr.

Age of onset, but not necessarily disease severity, correlates with CAG repeat numbers.
PREVALENCE (IN U.S.): 4.1 to 8.4 cases/100,000 persons. Most common neurodegenerative cause of generalized chorea.
PREDOMINANT SEX: Female = male
PREDOMINANT AGE: Adulthood
GENETICS: Autosomal dominant

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Chorea: Irregular, rapid, flowing, nonstereotyped involuntary movements (Fig. E1). When there is a writhing quality, it is referred to as choreoathetosis. Chorea is present early on and tends to decrease in end stages of disease.
- Dancelike, lurching gait (Fig. E2), often caused by chorea.
- Westphal variant: Cognitive dysfunction, bradykinesia, and rigidity. This variant is more commonly seen in juvenile-onset Huntington.
- Oculomotor abnormalities are common early on and include increased latency of response and insuppressible eye blinking.
- Psychiatric disorders (can be present early on): Depression is commonly seen, as well as obsessive-compulsive behaviors and aggression associated with impaired impulse control.

ETIOLOGY

- Trinucleotide repeat disorder; repeat of CAG, which codes for glutamine
- The responsible gene is the *huntingtin* gene (*HTT*), located on chromosome 4. Its function is not known.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Drug-induced chorea: Dopamine, stimulants, anticonvulsants, antidepressants, and oral contraceptives have all been known to cause chorea.
- Sydenham chorea: Decreased incidence with decline of rheumatic fever.
- Benign hereditary chorea: Autosomal dominant with onset in childhood; nonprogressive and without associated dementia or behavioral problems.
- Senile chorea: Possibly vascular in origin.
- Wilson disease: Autosomal recessive; tremor, dysarthria, and dystonia are more common presentations than chorea. A total of 95% of patients with neurologic manifestations will have Kayser-Fleischer rings.
- Postinfectious.
- Systemic lupus erythematosus: Can be the presenting feature of lupus (rare).
- Chorea gravidarum: Presents during first 4 to 5 mo of pregnancy and resolves after delivery.
- Paraneoplastic: Seen most commonly in small-cell lung cancer and lymphoma.
- *C9orf72* mutation: Originally described as a leading cause of frontotemporal dementia-amyotrophic lateral sclerosis; it is also the most common phenocopy of HD in people of European origin.
- Huntington disease–like syndrome 2: This is the most common Huntington disease–like syndrome caused by GTC/CAG triplet expansions in the JPH3 gene encoding junctophilin-3 and found exclusively in people of African descent.

WORKUP

Onset of symptoms in an individual with an established family history requires no additional investigation.

LABORATORY TESTS

- Genetic testing for CAG repeat numbers. Genetic testing should be ordered only with appropriate pretesting and posttesting genetic counseling.
- If no CAG repeat is in the *huntingtin* gene, other genetic mutations may be producing a phenocopy of Huntington disease. Consider additional genetic tests, such as spinocerebellar ataxia type 17, the *C9orf2* hexanucleotide repeat (in people of European descent), the GTC/CAG triplet expansions in the JPH3 gene encoding junctophilin-3 (in people of African descent).
- Also obtain complete blood count with smear, erythrocyte sedimentation rate, electrolytes, serum ceruloplasmin, 24-h urinary copper excretion, thyroid panel, antinuclear antibody, liver function tests, HIV, and ASO titer. Consider paraneoplastic markers.

IMAGING STUDIES

CT scan or MRI scan (Fig. E3) will show atrophy, most notably in the caudate and putamen. In some cases, the striatal atrophy causes a characteristic appearance of the lateral ventricles on imaging termed "boxcar ventricles." The cortex is involved to a lesser extent. A normal scan does not exclude the diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive counseling
- Physical and occupational therapy
- Home health care
- Genetic counseling

CHRONIC Rx

- Chorea does not need to be treated unless it is disabling.
- Tetrabenazine and deutetrabenazine are both approved by the FDA for the symptomatic treatment of chorea seen in Huntington disease. They are both a reversible inhibitor of the vesicle monoamine transporter type 2 (VMAT-2), inhibiting primarily dopamine and to a lesser degree serotonin and norepinephrine. Side effects include parkinsonism and severe depression. Deutetrabenazine appears to have a lower incidence of neuropsychiatric adverse effects than tetrabenazine. Both drugs are expensive and have no effect on disease progression.
- Neuroleptics, typical or atypical, can be used for symptomatic management of neuropsychiatric issues and chorea at low doses (e.g., haloperidol 1 to 10 mg/day).
- Amantadine (up to 300 to 400 mg divided tid).
- Depression with suicidal ideation is common; may improve with tricyclic antidepressants or SSRIs.
- Recent trials[1] involving intrathecal administration of IONIS-HTT_{Rx}, an antisense oligonucleotide designed to inhibit HTT messenger RNA and thereby reduce concentration of mutant *huntingtin* in patients with early Huntington disease, have shown

TABLE E1 CAG Repeats and Disease Risk

CAG Repeat #	Allele Classification	Disease Risk	Risk to Offspring
≤26	Normal	No symptoms	None
27-35	Intermediate	No symptoms	Low
36-39	Disease	At risk for HD	Moderate
≥40	Disease	HD imminent	High

HD, Huntington disease.

[1]Tabrizi SJ et al: Targeting huntingtin expression in patients with Huntington's disease, *N Engl J Med* 380(24):2307-2316, 2019.

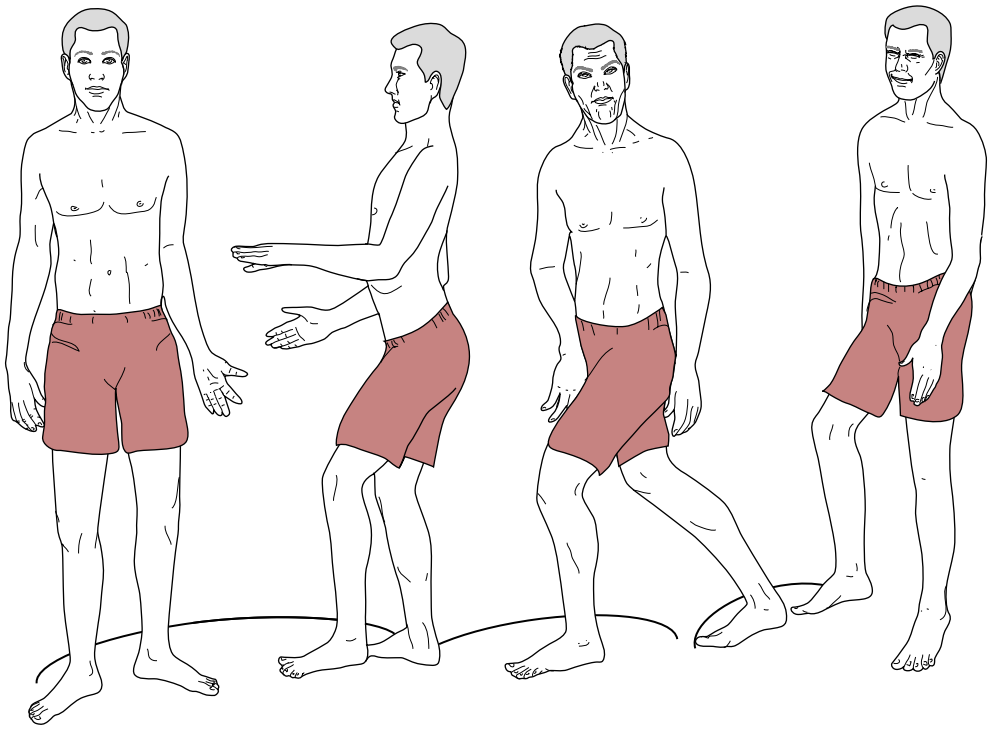


FIG. E1 The signature of Huntington disease is a jerky gait that results from intermittent, unexpected trunk and pelvic motions, spontaneous knee flexion and extension, lateral swaying, variable cadence, and unequal stride length. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.)

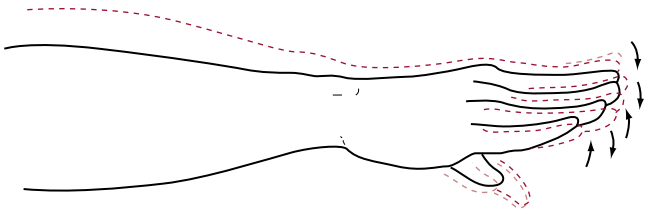


FIG. E2 With their arms and hands extended, Huntington disease patients fidget with their fingers and wrists. Neurologists label these movements "piano playing." (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.)

dose-dependent reductions in concentration of mutant *huntingtin* without serious side effects.

DISPOSITION

Relentless course of variable duration leading to progressive disability and death

REFERRAL

- Should refer to psychiatry and neurology for treatment of mood disorders and movement disorders
- Genetic counseling

PEARLS & CONSIDERATIONS

- Suicide rate is fivefold that of the general population.
- Generational transmission is often associated with the phenomenon of "anticipation," with disease starting at an earlier age in a child because of increased repeat length compared with that of the parent.
- Childhood-onset HD presents with parkinsonism rather than with chorea.
- The number of repeats does correlate with age of onset but does not clearly correlate with disease severity. Interpretation of number of repeats is still difficult at this time; therefore, it is debatable whether to disclose this information to patients.

RELATED CONTENT

Huntington Disease (Patient Information)

AUTHORS: **Angad Jolly, PhD, Joseph S. Kass, MD, JD, FAAN,** and **Fariha Jamal, MD**

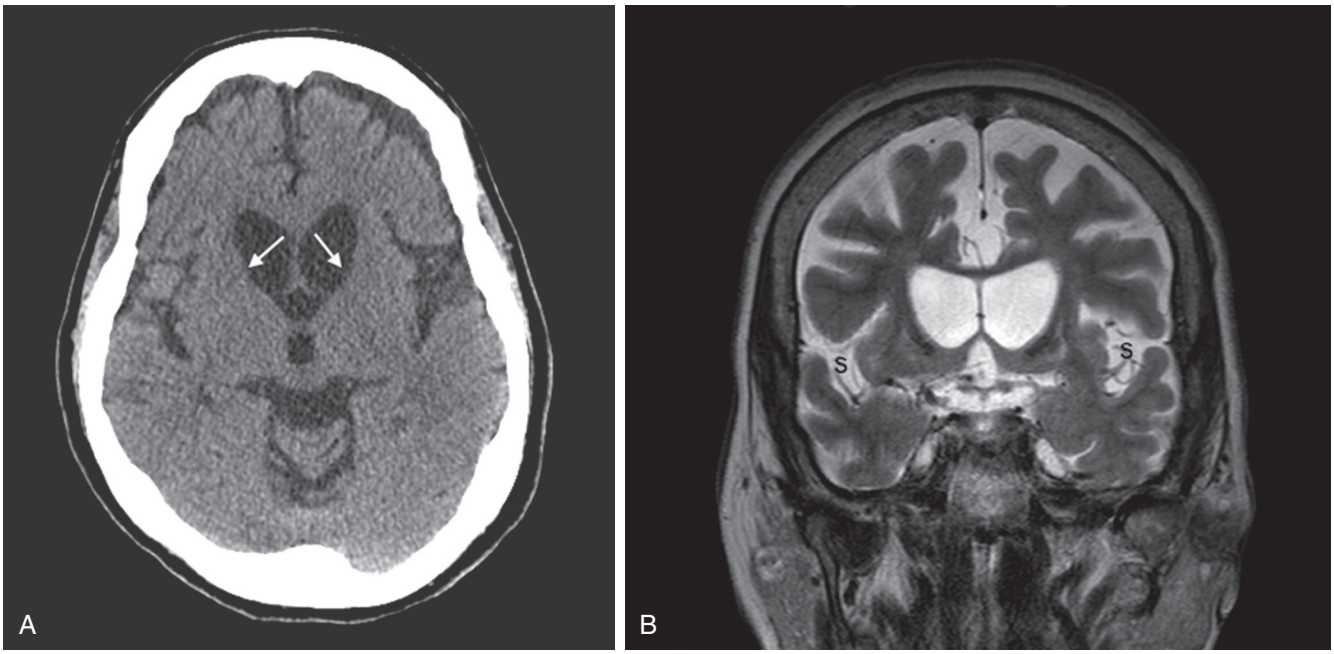


FIG. E3 A, This computed tomography scan shows the characteristic abnormality of Huntington disease: The anterior horns of the lateral ventricles are convex (bowed outward) because of atrophy of the caudate nuclei *(arrows).* The convex shape of the ventricles in Huntington disease contrasts with the concave shape seen in normal individuals and in those with cerebral atrophy and hydrocephalus ex vacuo. In addition to the caudate atrophy, Huntington disease, like many other neurodegenerative illnesses, is associated with cortical atrophy with widened sulci and enlarged ventricles. **B,** This *coronal* view of the magnetic resonance image of the same patient also shows the convex expansion of the lateral ventricles, large sulci, and widened Sylvian fissures *(S).* (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.)

SUGGESTED READINGS

Eddy CM et al: Change in mental state and behaviour in Huntington's disease, *Lancet Psychiatry* 3:1079-1086, 2016.

Termsarasab P: Chorea, *Continuum (Minneap Minn)* 25 (4, Movement Disorders): 1001-1035, 2019.

BASIC INFORMATION

DEFINITION

A hydrocele is a fluid collection in a serous scrotal space, usually between the layers of the tunica vaginalis (Fig. E1). A hydrocele that fills with fluid from the peritoneum is termed *communicating*. This is distinguished from a *noncommunicating* hydrocele by history of variation in size throughout the day and palpation of a thickened cord above the testicle on the affected side. A communicating hydrocele is a small inguinal hernia in which fluid, but not peritoneal structures, traverses the processus vaginalis. In noncommunicating hydrocele, the processus vaginalis was obliterated during development. An abdominoscrotal hydrocele is a rare variant of a hydrocele in which there is a large, tense hydrocele that extends into the lower abdominal cavity.

ICD-10CM CODES

N43.3	Hydrocele, unspecified
N43	Hydrocele and spermatocele
N43.0	Encysted hydrocele
N43.1	Infected hydrocele
N43.2	Other hydrocele
P83.5	Congenital hydrocele

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms:

- Scrotal enlargement (Fig. E2)
- Scrotal heaviness or discomfort radiating to the inguinal area
- Back pain

Physical findings:

- Most hydroceles are smooth and nontender. Scrotal distention may make it difficult to palpate the testis, but it is important to palpate the testis because some young men develop a hydrocele in association with a testis tumor.
- Transillumination of the scrotum confirms the fluid-filled nature of the mass (Fig. E3).

ETIOLOGY

Hydroceles may occur as a congenital abnormality in which the processus vaginalis fails to close. In this case an inguinal hernia is virtually always associated with the malformation. Congenital hydroceles are most common in infants (1% to 2% of neonates have hydroceles) and children. In adults, hydroceles are more frequently caused by infection, tumor, or trauma. Infection of the epididymis often results in the development of a secondary hydrocele. Tropical infections such as filariasis may produce hydroceles.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Spermatocele
- Inguinoscrotal hernia
- Testicular tumor
- Varicocele
- Epididymitis

IMAGING STUDIES

Scrotal ultrasound is useful to rule out a testicular tumor as the cause of the hydrocele (Fig. E4). The acute development of a hydrocele might be associated with the onset of epididymitis, testicular tumor, trauma, and torsion of a testicular appendage. An ultrasound of the scrotum may provide important diagnostic information.

TREATMENT

- No treatment if asymptomatic and testis is believed to be normal. Most congenital hydroceles resolve by 12 mo of age following reabsorption of the hydrocele fluid.
- Surgical repair should be considered if the hydrocele is tense and large. Communicating hydroceles should be repaired in the same manner as an indirect hernia. The indications for repair of a noncommunicating hydrocele include failure to resolve and increase in size to one that is large and tense.
- Surgical correction is similar to a herniorrhaphy: An inguinal incision is made, the spermatic cord is identified, the hydrocele fluid is drained, and a high ligation of the processus vaginalis is performed.

PEARLS & CONSIDERATIONS

- The long-term risk of a communicating hydrocele is the development of an inguinal hernia.
- An inguinal hernia/hydrocele is likely if compression of the fluid-filled mass completely reduces the hydrocele.

RELATED CONTENT

Hydrocele (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

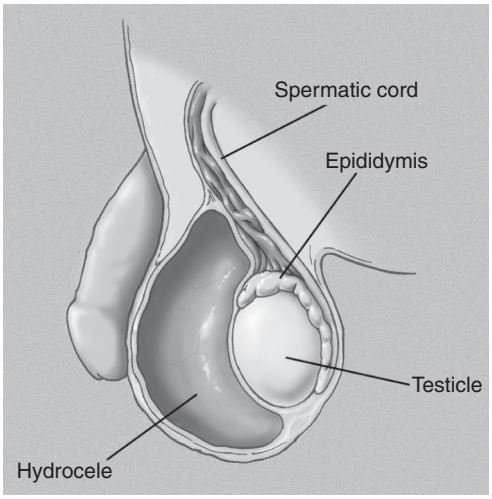


FIG. E1 Schematic representation of the testicle, epididymis, spermatic cord, and a hydrocele. (From Lipshultz LI et al: *Urology and the primary care practitioner,* ed 3, Philadelphia, 2008, Elsevier.)

FIG. E2 Hydrocele. (From Grainger RG et al [eds.]: *Grainger & Allison's diagnostic radiology,* ed 4, London, 2001, Harcourt.)

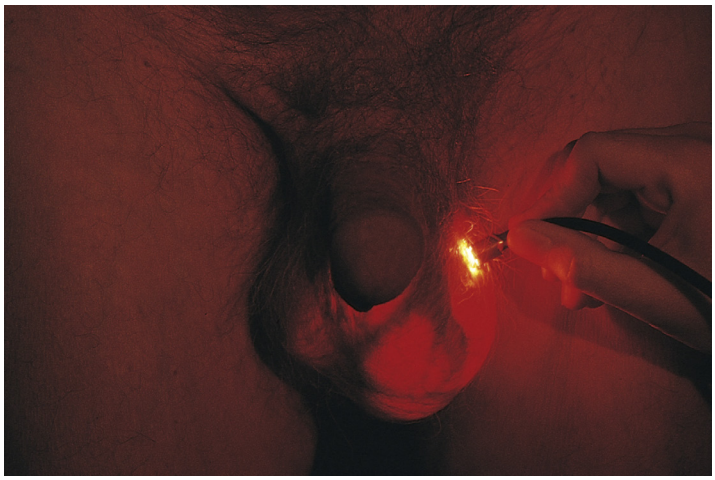


FIG. E3 Transilluminated hydrocele. (From Swartz MH: *Textbook of physical diagnosis, history and examination,* ed 7, Philadelphia, 2014, Elsevier.)

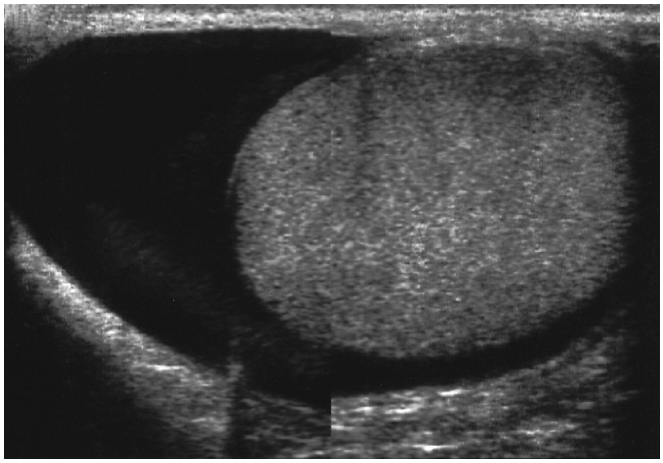


FIG. E4 Longitudinal ultrasound view of normal testis and moderate hydrocele. (From Swartz MH: *Textbook of physical diagnosis, history and examination,* ed 7, Philadelphia, 2014, Elsevier.)

BASIC INFORMATION

DEFINITION

Normal pressure hydrocephalus (NPH) is a syndrome of symptomatic hydrocephalus in the setting of normal cerebrospinal fluid (CSF) pressure. The classic clinical triad of NPH includes gait disturbance, cognitive decline, and incontinence.

SYNONYMS

Normal pressure hydrocephalus
NPH
Occult hydrocephalus
Extraventricular obstructive hydrocephalus
Chronic hydrocephalus

ICD-10CM CODES
G91.2 Normal pressure hydrocephalus
G91.8 Other hydrocephalus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The exact incidence is not known. In one study the incidence was found to be 5.5 per 100,000, but it may account for up to 5% of dementia in the U.S. Hospital discharge data suggest approximately 11,500 new cases diagnosed annually (may be overestimated). The prevalence of NPH may be as high as 14% among extended care facility patients.
PREDOMINANT SEX: Males = females
PREDOMINANT AGE: NPH is more common with increasing age. In one study of 1238 patients who had undergone a head CT and neuropsychiatric evaluation, 0.2% of patients between 70 and 79 had probable NPH, and 5.9% of those 80 yr old and older had probable NPH.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Gait difficulty: A "magnetic" gait in which patients have difficulty initiating ambulation, and the gait may be broad-based and shuffling, with the appearance that the feet are stuck to the floor.
- Cognitive decline: Mental slowing, forgetfulness, and inattention, typically without agnosia, aphasia, or other cortical disturbances.
- Incontinence: Initially may have urinary urgency; incontinence later develops. Fecal incontinence also occasionally occurs. In one prospective study of 55 consecutive patients with idiopathic NPH, nocturia was the most common symptom, urge incontinence was the most bothersome, and 100% had detrusor overactivity on urodynamic studies.
- *Gegenhalten* (paratonia or involuntary resistance with passive movement) or other frontal lobe signs may be seen.

ETIOLOGY

- Approximately 50% of cases are idiopathic; the remaining cases have a variety of causes, including prior subarachnoid hemorrhage, meningitis, head trauma, or intracranial surgery.
- Symptoms are presumed to result from stretching of sacral motor and limbic fibers that lie near the ventricles as dilation occurs.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Alzheimer disease with extrapyramidal features
- Cognitive impairment in the setting of Parkinson disease or parkinsonism-plus syndromes
- Dementia with Lewy bodies
- Frontotemporal dementia
- Cervical spondylosis with cord compromise in the setting of degenerative dementia
- Multi-infarct dementia
- HIV-associated dementia
- Table 1 differentiates MRI findings between hydrocephalus and atrophy

WORKUP

- Large-volume lumbar puncture:
  1. Time to walk a prespecified distance (usually 25 feet) is measured, followed by removal of 40 to 50 ml of CSF.
  2. Retest of timed walking is done later (sometimes at 1 and 4 hr). Patients who have significant improvement in gait are more likely to be shunt-responsive; those with mild or negative response can have variable outcomes.
  3. Opening and closing pressure are measured; if pressure is elevated, alternative causes must be considered. Higher *normal* pressure may predict a good outcome from CSF shunting (normal CSF pressure: 8 to 15 mm Hg or 10 to 18 cm H_2O).
- Measurement of CSF outflow resistance by an infusion test or CSF pressure monitoring is sometimes used to help predict surgical outcome. External lumbar drainage (ELD) is being used more commonly.

LABORATORY TESTS

- CSF should be sent for routine fluid analysis to exclude other pathologies.
- CSF biomarkers may be useful in excluding Alzheimer disease (e.g., Tau/A-beta 42).

IMAGING STUDIES

- CT scan or MRI (Fig. 1) can be used to document ventriculomegaly. The distinguishing feature of NPH is ventricular enlargement out of proportion to sulcal atrophy (Fig. E2), and typically the frontal horn ratio (Evans ratio) exceeds 0.40. An algorithm for evaluation of patients with enlarged ventricles is described in Fig. 3.
- MRI has advantages over CT, including better ability to visualize structures in the posterior fossa, visualize transependymal CSF flow (seen as periventricular T2 FLAIR hyperintensity), and document extent of white matter lesions. On MRI a flow void in the aqueduct and third ventricle ("jet sign"), thinning and elevation of the corpus callosum on sagittal images, rounding of the frontal horns, and a narrow CSF space at the high convexity/midline areas relative to Sylvian fissure size may be seen. MRI time-resolved 2D phase contrast imaging with velocity encoding can also be used to visualize CSF flow.
- Isotope cisternography and dynamic MRI studies have not been shown to be superior in predicting shunt outcome.

TREATMENT

There is no evidence that NPH can be effectively treated with medications. CSF diversion via a ventriculoperitoneal shunt is a definitive treatment.

NONPHARMACOLOGIC THERAPY

Response to ventriculoperitoneal shunting is variable. Some patients (variable depending on series reported) show significant improvement from shunting; however, effectiveness of shunting has never been demonstrated in a randomized controlled trial. Gait is most likely to improve.

TABLE 1 Differentiation between Hydrocephalus and Atrophy

	Hydrocephalus	Atrophy
Temporal horns	Enlarged	Normal (except in Alzheimer disease)
Third ventricle	Convex ▸ distended anterior recess	Concave ▸ normal anterior recess
Fourth ventricle	Normal or enlarged	Normal
Transependymal CSF migration	Presents acutely	Absent
Sulci	Flattened	Enlarged out of proportion to age

From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.

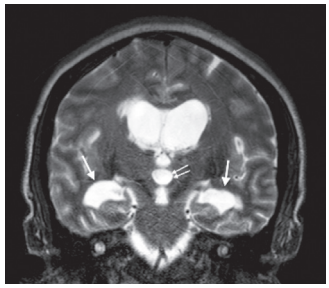


FIG. 1 This MRI study shows a coronal view of the brain of a patient with NPH. It demonstrates the classic findings: Dilation of the lateral ventricles, their temporal horns (*large arrows*), and the third ventricle (*pair of arrows*), and absence of cerebral atrophy. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.)

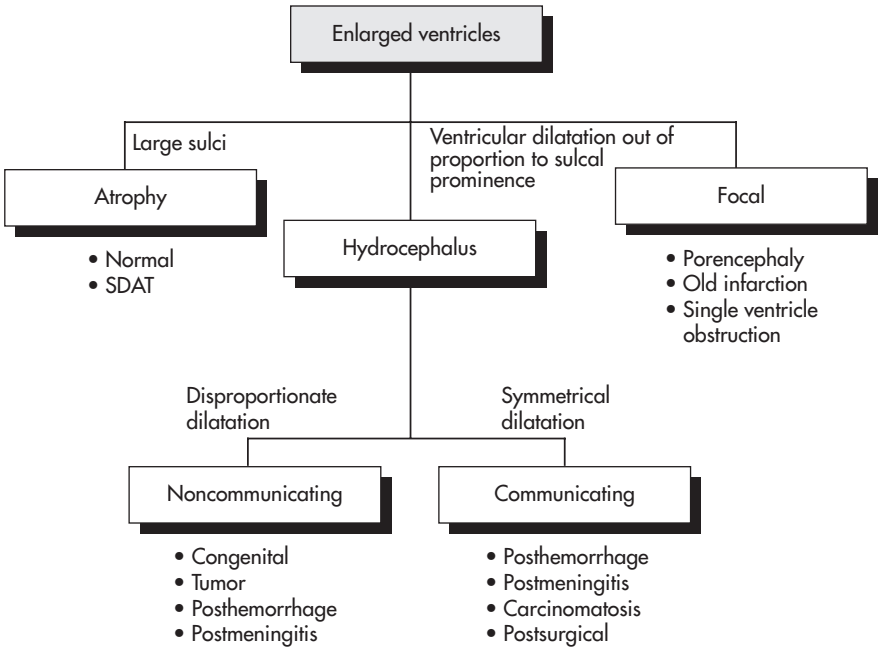


FIG. 3 Radiographic differential diagnosis of enlarged ventricles. *SDAT,* Senile dementia of the Alzheimer type. (From Weissleder R et al: *Primer of diagnostic imaging,* ed 5, St Louis, 2011, Mosby.)

Factors that may predict positive outcome with surgery:
- NPH caused by prior trauma, subarachnoid hemorrhage, or meningitis
- History of mild impairment in cognition <2 yr duration
- Onset of gait abnormality before cognitive decline
- Imaging demonstrates hydrocephalus without sulcal enlargement, including normal-size sylvian fissures and cortical sulci, and absent or mild white matter lesions
- Transependymal CSF flow visualized on MRI
- Large-volume tap or ELD produces dramatic but temporary relief of symptoms
- High *normal* opening pressure

Factors that may predict negative outcome with surgery:
- Extensive white matter lesions or diffuse cerebral atrophy on MRI
- Moderate to severe cognitive impairment
- Onset of cognitive impairment before gait disorder
- History of alcohol abuse

ACUTE GENERAL Rx

Shunting in selected patients

DISPOSITION

Symptoms of NPH may progress over time. Prompt diagnosis may improve chances for treatment success.

REFERRAL

To neurologist for initial evaluation, including lumbar puncture, followed by neurosurgeon for shunting in appropriate patients

PEARLS & CONSIDERATIONS

Each of the cardinal symptoms of NPH is commonly seen in the elderly and occurs in multiple disease processes; therefore, differential diagnoses should always be considered carefully.

CAUTION

Shunt complications, including subdural or intracerebral hematoma, may occur in 30% to 40% of patients. In one retrospective study spanning 10 yr, which included patients with idiopathic as well as other forms of adult hydrocephalus, the shunt failure rate was 32%.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Normal Pressure Hydrocephalus (Patient Information)

AUTHORS: **Tamara G. Fong, MD, PhD,** and **Irina A. Skylar-Scott, MD**

SUGGESTED READINGS

Jaraj D et al: Prevalence of idiopathic normal-pressure hydrocephalus, *Neurology* 82(16):1449-1454, 2014.

Krzastek SC et al: Characterization of lower urinary tract symptoms in patients with idiopathic normal pressure hydrocephalus, *Neurourol Urodyn*, 4, 2016.

Reddy GK et al: Management of adult hydrocephalus with ventriculoperitoneal shunts: long-term single institution experience, *Neurosurgery* 69(4):774-781, 2011.

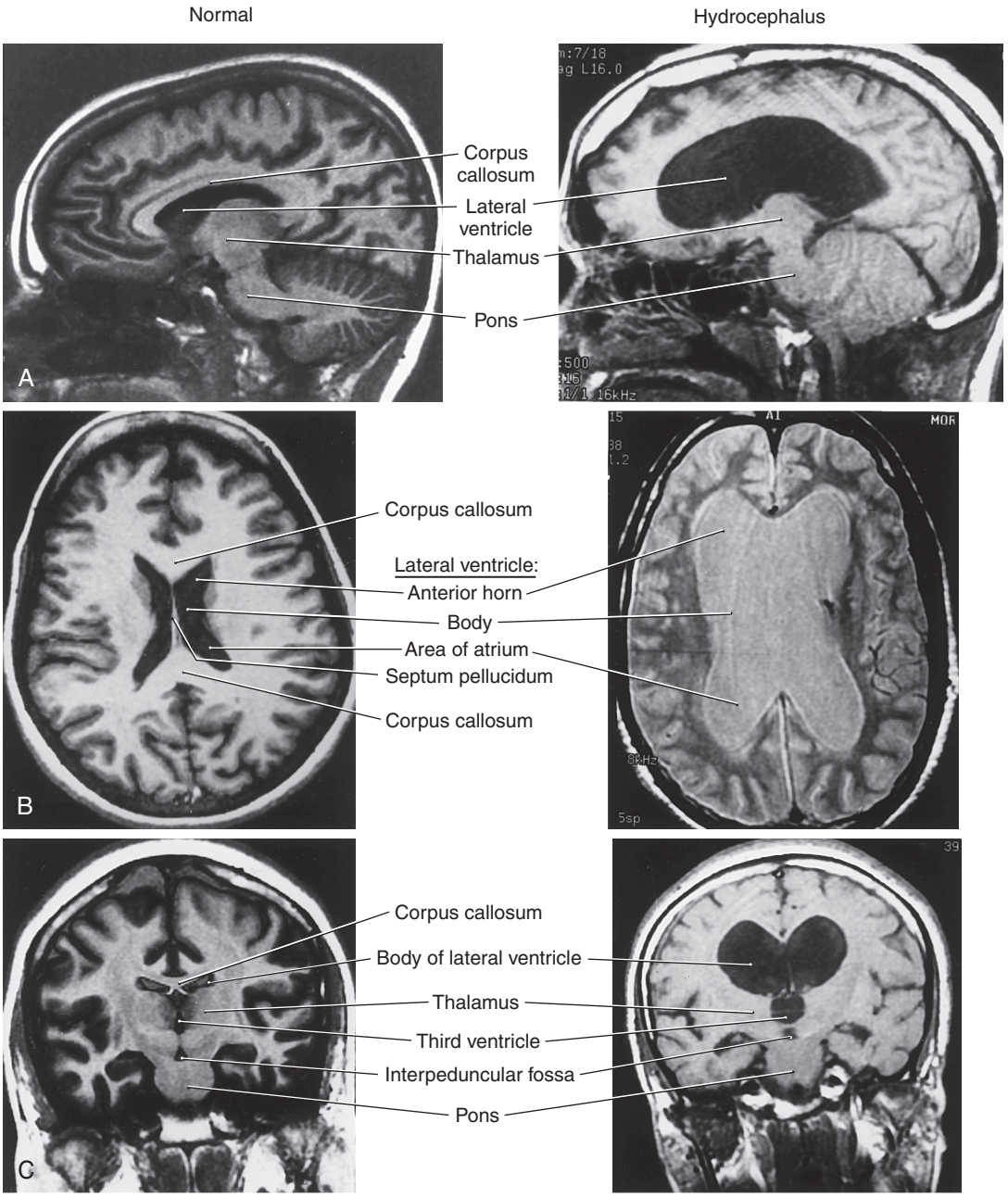


FIG. E2 Comparison of normal and hydrocephalic brains in sagittal **(A),** axial **(B),** and coronal **(C)** planes as seen on MR images. (From Haines DE: *Fundamental neuroscience for basic and clinical applications,* ed 3, Philadelphia, 2006, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Hydronephrosis in Greek means "water inside the kidney" and is an anatomic dilation of the collecting system of the kidneys (renal pelvis and/or calyces). When combined with dilation of the ureters, this is known as hydroureteronephrosis. Hydronephrosis is not a specific diagnosis and is *not* synonymous with obstruction. Hydronephrosis can occur with complete, partial, or no obstruction of urine flow.

SYNONYMS

Pelviectasis
Caliectasis
Pelvocaliectasis
Pyelocaliectasis

ICD-10CM CODES

N13.0	Hydronephrosis with ureteropelvic junction obstruction
N13.1	Hydronephrosis with ureteral stricture, not elsewhere classified
N13.2	Hydronephrosis with renal and ureteral calculous obstruction
N13.30	Unspecified hydronephrosis
N13.39	Other hydronephrosis
Q62.0	Congenital hydronephrosis

EPIDEMIOLOGY & DEMOGRAPHICS

Prevalence from multiple autopsy series ranges from 2% to 4%, with subjects ranging in age from neonates to geriatric patients. Antenatal hydronephrosis is one of the most common findings in prenatal ultrasound scans, affecting up to 5% of pregnancies, with 30% to 40% persisting postnatally. Of these, 40% will resolve spontaneously. Hydronephrosis in children is often caused by congenital and structural abnormalities of the kidneys and ureters, such as ureteropelvic junction obstruction (UPJO) or vesicoureteral reflux (VUR). Hydronephrosis in adults is often a result of obstruction of one or both kidneys, usually caused by stones, tumors, infections, and trauma. Stones remain the commonest cause overall of upper urinary tract obstruction. In adults 20 to 60 yr in age, hydronephrosis is more common in women, secondary to pregnancy/gynecologic causes. During pregnancy, physiologic hydronephrosis (more commonly on the right) occurs in up to 90% of cases and is often asymptomatic. In older patients (age >60 yr), obstruction from prostate enlargement or malignancy is the most common cause.

CLINICAL PRESENTATION

Hydronephrosis may present as an asymptomatic, incidental finding during imaging performed for another purpose. Symptoms often indicate an element of obstruction, and the presentation will depend on the *degree* of obstruction (complete or partial), *chronicity* of obstruction (acute or chronic), and *anatomic* factors (unilateral, bilateral and intrinsic or extrinsic in the ureter).

HISTORY:

- Pain is usually present along the flank with radiation toward the ipsilateral groin or lower abdominal quadrant. If onset is sudden and severe, consider a ureteral stone. If the pain is induced by diuresis (e.g., following consumption of alcohol), consider UPJO ("Dietl crisis"). When obstruction is subacute to chronic, symptoms may be vague, less intense, or absent, and may wax and wane in severity (colic). Extrinsic compression (e.g., malignancy-associated compression of ureters) usually has a more insidious onset compared with intrinsic obstruction (e.g., ureteral stone or blood clot).
- Nausea and vomiting are typically associated with acute obstruction, most often from an intrinsic obstructing process.
- Oliguria/anuria may occur with complete, bilateral obstruction, or with an obstructed solitary kidney.
- Urinary symptoms are often absent, unless there is an associated condition, including urinary tract infection, distal ureteral stone, or urinary retention. These voiding symptoms include dysuria, urinary urgency and frequency, pelvic pressure, and discomfort.
- Hematuria: May indicate a stone, urinary tract infection, or malignancy.
- Site of obstruction can relate to the presentation: Upper tract obstruction will frequently present with flank pain, but lower tract obstruction is often associated with voiding symptoms.

PHYSICAL EXAMINATION: A complete physical examination is warranted, but may not be helpful in the assessment of hydronephrosis. Areas to pay special attention to include the following:

- Blood pressure measurement.
- Palpable abdominal masses are rare, except in children or very thin patients with massive hydronephrosis. Costovertebral angle tenderness is not a particularly helpful finding. Palpate and percuss for an enlarged bladder.
- Complete genitourinary and pelvic exams:
  1. Pelvic exam will assess for pelvic masses or pelvic organ prolapse, which is rarely associated with ureteral obstruction.
  2. Digital rectal exam will assess for prostatic abnormality or rectal mass.
  3. Residual urine volume may demonstrate incomplete emptying of the bladder. Residual urine volume can be evaluated indirectly by bedside ultrasonography or directly by catheterization.

ETIOLOGY

Hydronephrosis can be caused by extrinsic or intrinsic factors relative to the urinary tract (Table 1). Causes may be grouped as congenital or acquired.

DIAGNOSIS

Diagnostic workup will depend on the age of the patient, acuity of presentation, if hydronephrosis was diagnosed incidentally, and if associated symptoms are present.

DIFFERENTIAL DIAGNOSIS

- Extrarenal pelvis where no true obstruction exists, but is confused with obstruction
- Urinary stones
- Neoplastic disease: Kidney, ureter, bladder, urethra
- Prostatic hyperplasia
- Urethral stricture
- Neurologic disease producing voiding dysfunction
- Urinary reflux
- Urinary tract infection

TABLE 1 Causes of Hydronephrosis

Obstructive	
Intrinsic to the Urinary Tract	Ureter: Ureteropelvic junction obstruction, ureterovesical junction obstruction, stricture, tumor, ureterocele, stone, blood clot, sloughed papilla, infection, hyperplastic polyp
	Bladder: Malignancy, stone, bladder neck obstruction, urine retention
	Prostate: Benign prostatic enlargement, prostatitis, calculus, abscess, malignancy
	Urethra: Stricture, stone, diverticulum, malignancy, posterior urethral valves, phimosis
Extrinsic to the Urinary Tract	Reproductive system:
	Uterus: Pregnancy, prolapse, fibroids, malignancy
	Ovary: Malignancy, cyst, abscess
	Vascular system:
	Aneurysm: Abdominal aorta, iliac vessel
	Aberrant vessels: Ureteropelvic junction
	Venous: Retrocaval ureter, ovarian vein syndrome
	Gastrointestinal system:
	Inflammatory bowel disease, GI malignancy, abscesses, cysts
	Diseases of the retroperitoneum
	Retroperitoneal fibrosis
	Retroperitoneal malignancy (primary or metastatic deposits)
	Hematoma
	Lymphocele
	Iatrogenic injury
Nonobstructive	
	Vesicoureteral reflux
	Extrarenal pelvis
	Megaureter/megacalycosis
	Pyelonephritis

GI, Gastrointestinal.

- Medication effects
- Trauma
- Congenital abnormality of urinary tract
- Urinary retention
- Retroperitoneal fibrosis
- Urinary trauma
- Iatrogenic injuries

LABORATORY TESTS

- **Evaluation of kidney function** by blood urea nitrogen and creatinine. If azotemia is present, bilateral obstruction or unilateral obstruction of a solitary kidney has occurred.
- **Evaluation of electrolyte abnormalities** including hypo- or hypernatremia, hyperkalemia, and low bicarbonate concentration.
- **Urinalysis and sediment examination** may reveal white blood cells, red blood cells, or bacteria in the appropriate setting (e.g., infection, stones). Urine microscopy facilitates crystal identification, which may suggest urinary stone disease. The sediment may be normal in obstructive renal disease.
- **Urine culture** should be sent when urinalysis or presentation suggests urinary tract infection.
- **Urine cytology** when urothelial cancer is suspected.

IMAGING STUDIES

- Ultrasound is an excellent initial test, especially for children and pregnant women. It is a screening test that permits evaluation of the kidneys, portions of the ureters, bladder wall, and bladder volume, and contour of the collecting system and ureters. Point-of-care ultrasound provides early, rapid imaging and aids patient triage and justification for additional imaging. Ultrasound is >90% sensitive and specific for hydronephrosis. The absence of ureteral jets on ultrasound may be an indirect sign of obstruction, but is not definitive (Fig. E1).
- Abdominal, plain film, or kidney, ureter and bladder (KUB) radiographs are of limited value in isolation. These tests complement ultrasound and may be helpful in diagnosing radiopaque kidney or ureteral stones.
- Abdominal CT scan without intravenous contrast medium provides excellent localization of sites of obstruction (Figs. E2 and E3), especially if a ureteral calculus is the cause of obstruction. A normal ureter on an unenhanced CT is considered 2 to 3 mm wide in adults. If kidney function is normal, CT urography (without and then with contrast, and with delayed images of the ureters), provides excellent anatomic information, and is the modality of choice for assessment of possible upper tract tumors or evaluation of incidental hydronephrosis.
- MRI is an alternative to CT. MRI provides detail but cannot directly detect a stone and is expensive. Impaired renal function may preclude gadolinium administration. MRI is considered after other tests are inconclusive or contraindicated, such as in pregnant patients, those with renal insufficiency, and those with contrast allergy.
- Antegrade or retrograde ureterograms/pyelograms are invasive procedures, but can be used if there are contraindications to CT or MRI scans with contrast (e.g., contrast allergy, renal impairment).
- Voiding cystourethrography, frequently used in pediatric patients, can diagnose vesicoureteral reflux and bladder neck or urethral obstruction.
- Diuretic renography (MAG3 renogram) is a functional radioisotopic test that provides differential function of each kidney, and determines if functional obstruction is present.

Rx TREATMENT

ACUTE GENERAL Rx

- Analgesics, antiemetics, and fluids for treatment of pain, nausea, and vomiting
- Antibiotics for urinary tract infection/pyelonephritis

Definitive management:

- Management depends on presence of obstruction, etiology, and location of hydronephrosis. Prompt treatment of infection and relief of obstruction prevent long-term loss of kidney function. Chronic renal obstruction from any cause may produce permanent functional deterioration.
- General principles include the following:
  1. Routine outpatient evaluation for hydronephrosis in asymptomatic or minimally symptomatic patients with no infection, electrolyte derangements, or acute kidney injury.
  2. Surgical treatment is aimed at relieving obstruction when hydronephrosis is associated with urinary tract infection, acute kidney injury, uncontrollable pain, or nausea and vomiting. Surgical treatment is also indicated with complete urinary obstruction from a bilateral obstructing process or unilateral obstruction in a solitary kidney.
  3. Urethral catheter or suprapubic catheter placement is indicated for bladder outlet obstruction.
  4. Ureteral stenting is carried out for decompression of one or both kidneys.
  5. Percutaneous nephrostomy tubes may be required in the setting of extrinsic ureteral compression or when ureteral stenting is not possible or fails.

REFERRAL

Prompt, emergent referral is paramount in the setting of severe symptoms, infection, or impaired renal function.

- Urology for diagnostic and/or therapeutic procedures (pediatric urologist for antenatal or postnatal hydronephrosis)
- Oncology for diagnosed neoplasm
- Gynecology for pregnancy or if female pelvic anatomy is involved
- Nephrology for electrolyte/acid-base disturbances

PEARLS & CONSIDERATIONS

COMMENTS

- Hydronephrosis is not a primary disorder; an underlying etiology must be sought.
- Children often have congenital causes; adults generally have acquired intrinsic or extrinsic causes.
- There are obstructive and nonobstructive causes of hydronephrosis. Further evaluation can be performed without specialty consultation with a computed tomography urogram, magnetic resonance urogram, or diuretic renogram.
- Prompt renal decompression is critical when hydronephrosis is associated with infection, severe kidney injury, and/or electrolyte abnormalities.

PREVENTION

Timely and appropriate management of acute kidney obstruction prevents long-term kidney damage. Hydronephrosis may persist after relief of the obstructing cause.

SUGGESTED READINGS

Available at ExpertConsult.com

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SUGGESTED READINGS

Davenport MT et al: Antenatally diagnosed hydronephrosis: current postnatal management, *Pediatr Surg Int* 29:207-214, 2013.

Pathan SA et al: Emergency physician interpretation of point-of-care ultrasound for identifying and grading of hydronephrosis in renal colic compared with consensus interpretation by emergency radiologists, *Acad Emerg Med*, 2018.

Wein AJ: Pathophysiology of urinary tract obstruction. In *Campbell-Walsh Urology*, ed 11, Philadelphia, 2016, Elsevier WB Saunders.

Wein AJ: Management of upper urinary tract obstruction. In *Campbell-Walsh Urology*, ed 11, Philadelphia, 2016, Elsevier WB Saunders.

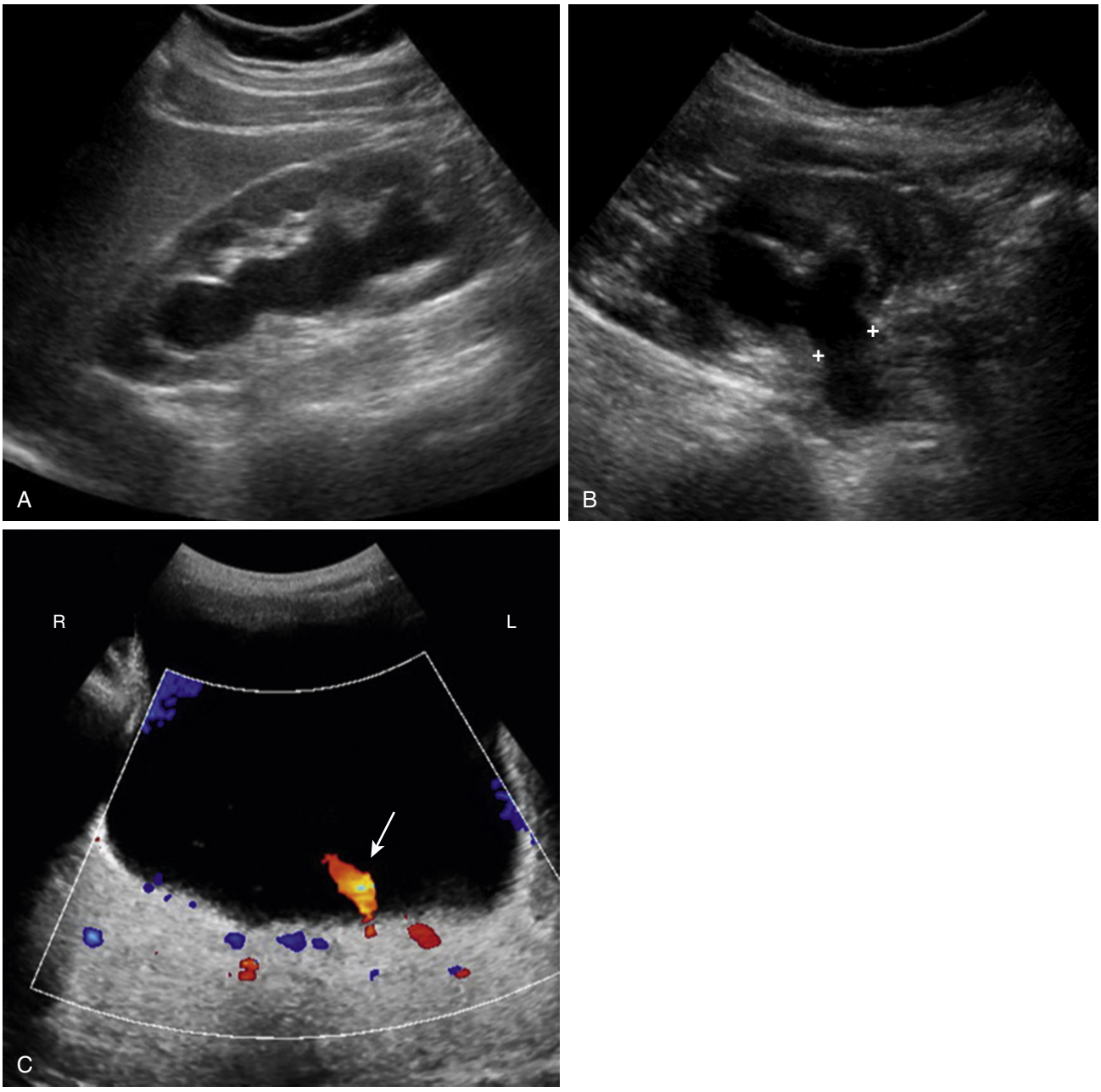

FIG. E1 Renal ultrasound demonstrating hydronephrosis of the right kidney. A, Sagittal image. **B,** Transverse image demonstrating a dilated renal pelvis. **C,** Transverse image of the bladder demonstrating a ureteral jet *(arrow)* on the left side but no ureteral jet on the right, which may suggest obstruction on that side.

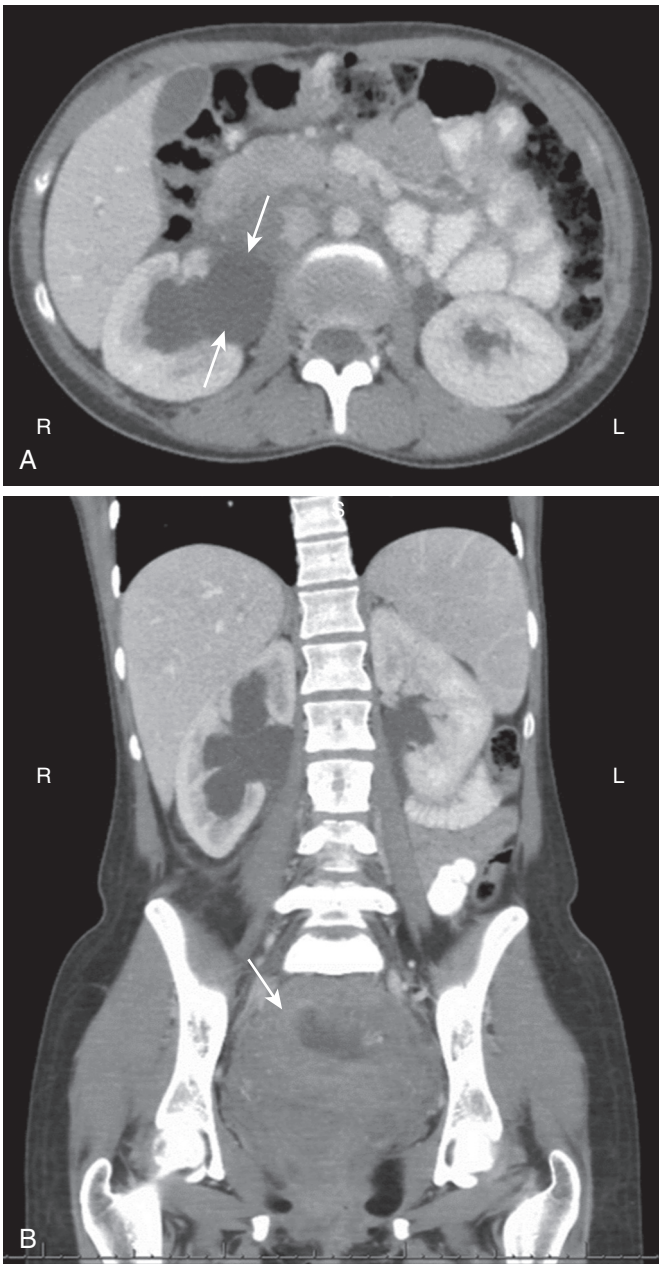

FIG. E2 Computed tomography scan of the abdomen showing a grossly hydronephrotic kidney on the right. A, Cross-sectional image. Arrows highlight the dilated renal pelvis. Sequential sections demonstrate that the ureter was dilated along its length to the distal ureter, where it was being compressed by a large pelvic mass. **B,** Coronal image. This again shows the right-sided hydronephrosis and the large pelvic mass *(arrow).*

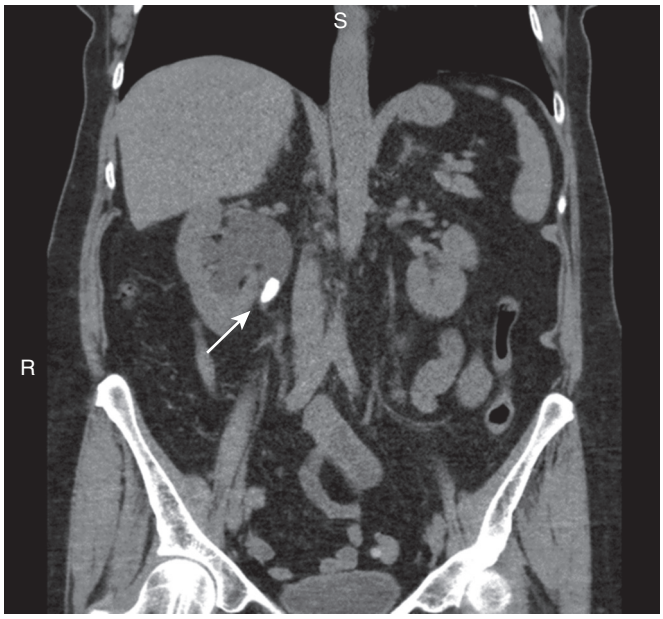

FIG. E3 Coronal computed tomography scan of abdomen showing a grossly hydronephrotic kidney on the right secondary to a large (1.5 cm × 0.9 cm) ureteropelvic junction stone *(arrow).*

BASIC INFORMATION

DEFINITION

Hypercholesterolemia refers to a blood cholesterol measurement ≥200 mg/dl.

SYNONYMS

Hyperlipidemia
Hypercholesteremia
Dyslipidemia
Type II familial hyperlipoproteinemia

ICD-10CM CODE
E78.0 Pure hypercholesterolemia

EPIDEMIOLOGY & DEMOGRAPHICS

- Over 105 million (37%) adults in the U.S. have total blood cholesterol levels higher than 200 mg/dl. Of this group, more than 36 million adults have extremely high-risk cholesterol levels over 240 mg/dl (13%).
- For men over the age of 20 yr, approximately 48% of white men, 45% of black men, and 50% of Hispanic men have high blood cholesterol.
- For women over the age of 20, approximately 50% of white women, 42% of black women, and 50% of Hispanic women have hypercholesterolemia.
- Prevalence of hypercholesterolemia increases with increasing age.
- According to NHANES data for 2009 to 2010, about 47% of adults had at least one of three risk factors for cardiovascular disease—uncontrolled high blood pressure, uncontrolled high levels of low-density lipoproteins (LDL) cholesterol, or current smoking.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- A detailed medication history should be performed because some medications may affect lipid levels (e.g., thiazides, corticosteroids, beta-blockers, and estrogens).
- The physical examination should include measurements of BMI and BP, thyroid and liver assessments, and examining peripheral pulses including carotids for bruits.
- Physical findings, particularly in the familial forms may include:
  1. Tendon xanthomas
  2. Xanthelasma
  3. Arcus corneae
  4. Arterial bruits (young adulthood)

ETIOLOGY

Primary:
- Genetics
- Obesity
- Dietary intake

Secondary:
- Hypothyroidism
- Diabetes mellitus
- Nephrotic syndrome
- Obstructive liver disease: Hepatoma, extrahepatic biliary obstruction, primary biliary cirrhosis
- Alcohol or tobacco use
- Dysgammaglobulinemia (multiple myeloma, SLE)
- Drugs: Oral contraceptives, progesterone, corticosteroids, thiazide diuretics, β-blockers, androgenic steroids, retinoic acid derivatives, protease inhibitors

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Always consider underlying secondary causes for the elevated cholesterol.
- Patients with very high LDL cholesterol usually have genetic forms of hypercholesterolemia (see "Hyperlipoproteinemia, Primary"). Early detection of these cases and family testing to identify similarly affected relatives is important.
- Metabolic syndrome:
  1. A constellation of lipid and nonlipid risk factors of a metabolic origin
  2. Diagnosed when three or more of the following are present: abdominal obesity (waist circumference >40 in in men and >35 in in women); fasting triglycerides >150 mg/dl; HDL <40 mg/dl in males and <50 mg/dl in females; systolic BP >130 mmHg and diastolic BP >85 mmHg; fasting glucose >110 mg/dl

WHO SHOULD BE SCREENED:
- AACE recommends screening of patients >20 yr of age for elevated cholesterol every 5 yr, males >45 yr and females >55 yr of age every 1 to 2 yr, and >65 yr of age every yr up to 75 yr of age regardless of CAD risk status. Patients above 75 yr of age with multiple CAD risk factors should still continue to get screened annually.
- The USPSTF supports routine screening for men aged >35 yr and women aged >45 yr by measurement of nonfasting total and HDL cholesterol alone.
- In 2010, the USPSTF recommended routine screening for overweight and obesity in persons aged <20 yr.
- In 2011, ACC/AHA recommended screening for hypertriglyceridemia by a nonfasting measurement. A nonfasting level of <200 mg/dl is commensurate with an optimal level of <100 mg/dl and no further testing is required. However, a nonfasting level of >200 mg/dl warrants further testing with a fasting lipid profile.

LABORATORY TESTS

- Obtain a lipid profile. A fasting lipid panel has been traditionally preferred over a nonfasting lipid profile; however, this recommendation has come into question, and expert consensus statements from Canada and Europe recommend nonfasting lipid testing as the new standard for lipid measurement. In nonfasting patients, triglyceride levels ≥175 mg/dl should be considered elevated as compared with <150 mg/dl for fasting panels. Fasting lipid panels are preferred for patients with triglycerides over 400 mg/dl.
- Perform a workup for secondary causes if clinically indicated, such as TSH, metabolic profile, LFTs, and fasting glucose.

TREATMENT

NONPHARMACOLOGIC THERAPY

- First line of treatment: Dietary therapy can result in 5% to 15% reduction in LDL cholesterol level.
- Composition of the **TLC diet:**
  1. Total fat 25% to 30% of total calories
  2. Polyunsaturated fat up to 10% of total calories
  3. Monounsaturated fat up to 20% of total calories
  4. Saturated fats <7% of total calories
  5. Carbohydrate 50% to 60% of total calories
  6. Protein 15% of total calories
  7. No more than 200 mg/day of cholesterol
  8. Fiber 20 to 30 g/day
- Increased physical activity: Encourage 30 min of moderately intense physical activity, four to six times a wk (e.g., brisk walking, riding stationary bike, water aerobics)
- Maintenance of a healthy weight
- Avoidance of tobacco products
- Counseling on CAD risk factors (Table 1)
- Plant-based diets (including stanol-containing margarines, oat bran, and nuts) have shown effectiveness in controlling lipids.

ACUTE GENERAL Rx

No acute treatment needed

CHRONIC Rx

- Box 1 summarizes the key recommendations for the treatment of blood cholesterol to reduce ASCVD (atherosclerotic cardiovascular disease) risk in adults.
- The guidelines identify four high-risk groups that benefit from statin therapy:
  1. Patients with clinical ASCVD (Table 2, Fig. 1)
  2. LDL ≥190 mg/dl
  3. DM aged 40 to 75 yr and LDL 70 to 189 mg/dl
  4. 10-yr risk for ASCVD ≥7.5% and LDL 70 to 189 mg/dl

TABLE 1 Risk Factors for Heart Disease

1. Cigarette smoking
2. Hypertension (BP ≤140/90 mm Hg or on medications)
3. Low HDL cholesterol (<40 mg/dl)*
4. Family history of premature CHD (<55 yr in first-degree male relative or <65 yr in first-degree female relative)
5. Age (men ≥45 yr, women ≥55 yr)

*HDL cholesterol >60 mg/dl counts as a negative risk factor; its presence removes one risk factor from the total count.
BP, Blood pressure; *CHD,* congenital heart disease; *HDL,* high-density lipoprotein cholesterol.

BOX 1 2013 ACC/AHA Summary of Key Recommendations for the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults

A. Heart-healthy lifestyle habits should be encouraged for all individuals
B. The appropriate intensity of statin therapy should be initiated or continued
   1. Clinical ASCVD*
      a. Age 75 yr or less and no safety concerns: High-intensity statin (class I, level A)
      b. Age 75 yr or safety concerns: Moderate-intensity statin (class I, level A)*
   2. Primary prevention: Primary LDL-C 190 mg/dl or greater
      a. Rule out secondary causes of hyperlipidemia (class I, level B)
      b. Age 21 yr or older: High-intensity statin (class I, level B)
      c. Achieve at least a 50% reduction in LDL-C (class IIa, level B)
      d. LDL-C lowering nonstatin therapy may be considered to further reduce LDL-C (class IIb, level C)
   3. Primary prevention: Diabetes, 40 to 75 yr of age, and LDL-C 70 to 189 mg/dl
      a. Moderate-intensity statin (class I, level A)
      b. Consider high-intensity statin when 7.5% or greater 10-yr ASCVD risk using the Pooled Cohort Equations (class IIa, level B)†‡
   4. Primary prevention: No diabetes, 40 to 75 yr of age, and LDL-C 70 to 189 mg/dl
      a. Estimate 10-yr ASCVD risk using the Risk Calculator based on the Pooled Cohort Equations in those *not* receiving a statin; estimate risk every 4 to 6 yr (class I, level B)
      b. To determine whether to initiate a statin, engage in a clinician-patient discussion of the potential for ASCVD risk reduction, adverse effects, drug-drug interactions, and patient preferences
      c. Reemphasize heart-healthy lifestyle habits and address other risk factors (class IIa, level C)
         i. 7.5% or greater 10-yr ASCVD risk: Moderate- or high-intensity statin (class I, level A)
         ii. 5% to 7.5% 10-yr ASCVD risk: Consider moderate-intensity statin (class IIa, level B)
         iii. Other factors may be considered: LDL-C 160 mg/dl or greater, family history of premature ASCVD, hs-CRP 2.0 mg/L or greater, CAC score 300 Agatston units or greater, ABI less than 0.9, or lifetime ASCVD risk (class IIb, level C)
   5. Primary prevention when LDL-C is less than 190 mg/dl and age is less than 40 or more than 75 yr, or less than 5% 10-yr ASCVD risk
      a. Statin therapy may be considered in selected individuals (class IIb, level C)
   6. Statin therapy is not routinely recommended for individuals with NYHA class II-IV heart failure or who are receiving maintenance hemodialysis
C. Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments
   1. Assess adherence, response to therapy, and adverse effects within 4 to 12 wk following statin initiation or change in therapy (class I, level A)
      a. Measure a fasting lipid panel (class I, level A)
      b. Do not routinely monitor ALT or CK unless symptomatic (class IIa, level C)
      c. Screen and treat type 2 diabetes according to current practice guidelines. Heart-healthy lifestyle habits should be encouraged to prevent progression to diabetes (class I, level B)
      d. Anticipated therapeutic response: Approximately 50% or greater reduction in LDL-C from baseline for high-intensity statin and 30% to 50% for moderate-intensity statin (class IIa, level B)
         i. Insufficient evidence for LDL-C or non–HDL-C treatment targets from RCTs
         ii. For those with unknown baseline LDL-C, an LDL-C less than 100 mg/dl was observed in RCTs of high-intensity statin therapy
      e. Less than anticipated therapeutic response:
         i. Reinforce improved adherence to lifestyle and drug therapy (class I, level A)
         ii. Evaluate for secondary causes of hyperlipidemia if indicated (class I, level A)
         iii. Increase statin intensity, or if on maximally tolerated statin intensity, consider addition of nonstatin therapy in selected high-risk individuals (class IIb, level C)§
      f. Regularly monitor adherence to lifestyle and drug therapy every 3 to 12 mo once adherence has been established. Continue assessment of adherence for optimal ASCVD risk reduction and safety (class I, level A)
D. In individuals intolerant of the recommended intensity of statin therapy, use the maximally tolerated intensity of statin (class I, level B). If there are muscle or other symptoms, establish that they are related to the statin (class IIa, level B)

*Clinical ASCVD includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.
†Estimated 10-yr or "hard" ASCVD risk includes first occurrence of nonfatal MI, CHD death, and nonfatal and fatal stroke as used by the Risk Assessment Work Group in developing the Pooled Cohort Equations on the basis of age, sex, smoking status, total cholesterol level, HDL-C level, systolic blood pressure, and the use of antihypertensive therapy.
‡These factors may include primary LDL-C of 160 mg/dl or greater or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset at less than 55 yr of age in a first-degree male relative or at less than 65 yr of age in a first-degree female relative; hs-CRP 2 mg/L or greater; CAC score 300 Agatston units or greater or 75th percentile or greater for age, sex, and ethnicity; ABI less than 0.9; or lifetime risk of ASCVD. Additional factors that might aid in individual risk assessment could be identified in the future.
§High-risk individuals include those with clinical ASCVD, an untreated LDL-C 190 mg/dl or greater, suggesting genetic hypercholesterolemia, or individuals with diabetes 40 to 75 yr of age and LDL-C 70 to 189 mg/dl.
ABI, Ankle-brachial index; *ACC,* American College of Cardiology; *AHA,* American Heart Association; *ALT,* alanine aminotransferase, a test of hepatic function; *ASCVD,* atherosclerotic cardiovascular disease; *CAC,* coronary artery calcium; *CHD,* coronary heart disease; *CK,* creatine kinase, a test of muscle injury; *HDL-C,* high-density lipoprotein cholesterol; *hs-CRP,* high-sensitivity C-reactive protein; *LDL-C,* low-density lipoprotein cholesterol; *MI,* myocardial infarction; *NYHA,* New York Heart Association; *RCTs,* randomized controlled trials; and *TIA,* transient ischemic attack.
From 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 63(25 Pt B):2889-2934, 2014.

TABLE 2 Atherosclerotic Cardiovascular Disease

1. Coronary heart disease: Acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization
2. Stroke or transient ischemic attack
3. Peripheral arterial disease

- The 10-yr risk of ASCVD is calculated with the risk calculator available at http://my.americanheart.org/cvriskcalculator
- ASCVD events are reduced by using the maximum tolerated statin intensity in the above groups shown to benefit the most (Tables 3 and 4).
- Additional factors such as CRP >2 mg/L, primary LDL >160, genetic hyperlipidemias, family history of premature CHD, ABI <0.9, and coronary artery calcium score (CAD) assessed with CT may be used in patients who are not in one of four statin benefit groups and for whom a decision to initiate statin therapy is otherwise unclear. Statins are generally beneficial in patients at intermediate risk and selected patients with borderline risk who have a calcium score that is 100 or higher or who are in

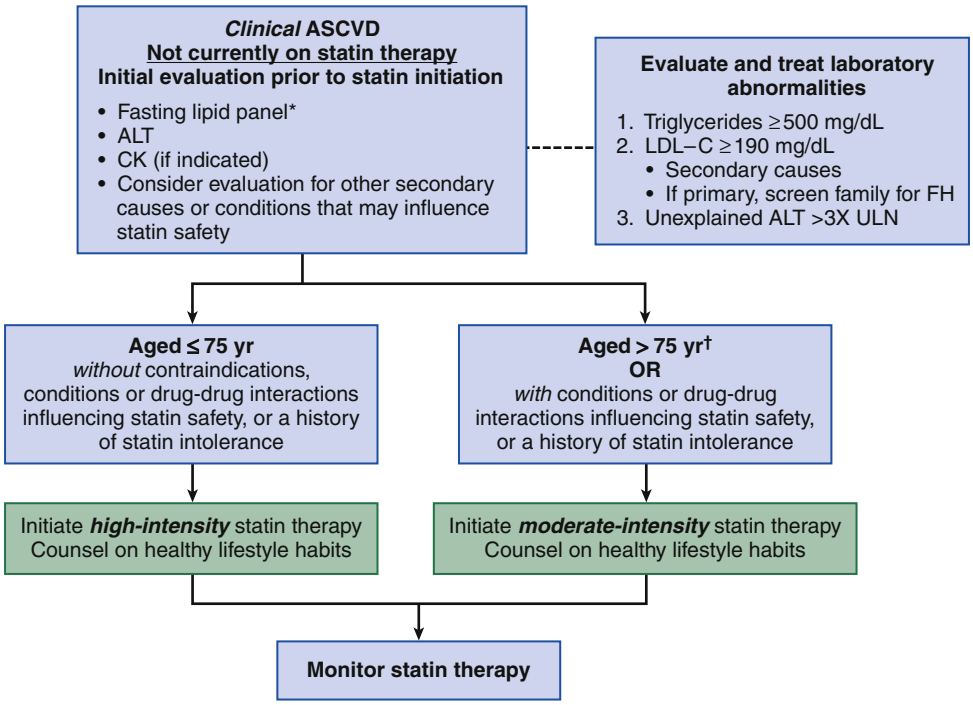

FIG. 1 Initiating statin therapy in individuals with clinical ASCVD. *Fasting lipid panel is preferred. In a nonfasting individual, a nonfasting non-HDL–C >220 mg/dl may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are >500 mg/dl, a fasting lipid panel is required. †It is reasonable to evaluate the potential for ASCVD benefits and for adverse effects and to consider patient preferences in initiating or continuing a moderate- or high-intensity statin in individuals with ASCVD >75 yr of age. *ALT,* Alanine transaminase; *ASCVD,* atherosclerotic cardiovascular disease; *CK,* creatine kinase; *FH,* familial hypercholesterolemia; *HDL–C,* high-density lipoprotein cholesterol; *LDL–C,* low-density lipoprotein cholesterol; *ULN,* upper limit of normal. (Modified from Stone NJ et al: 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol,* 2013. In Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.)

TABLE 3 Statin Intensity Therapies

High Intensity (Decrease LDL-C ≥50%)	Moderate Intensity (Decrease LDL-C 30%-49%)
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg
—	Simvastatin 20-40 mg
—	Pravastatin 40-80 mg
—	Lovastatin 40 mg
—	Fluvastatin XL 80 mg
—	Fluvastatin 40 mg bid
—	Pitavastatin 2-4 mg

bid, Twice a day; *LDL-C,* low-density lipoprotein cholesterol.
From Stone N et al: 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 63(25 Pt. B):2889, 2014.

TABLE 4 Statin Benefit Groups and Recommended Therapy

Statin Benefit Group	High Intensity	Moderate Intensity	Additional Testing
Clinical ASCVD	Yes	Consider†	None
Primary LDL-C >190 mg/dl	Yes	Consider†	None
Diabetes without ASCVD and 10-yr risk ≥7.5%*	Yes	Consider†	None
Diabetes without ASCVD and 10-yr risk <7.5%*	Consider‡	Yes	Case-by-case
Primary prevention and 10-yr risk ≥7.5%*	Consider‡	Yes	Case-by-case
Primary prevention and 10-yr risk <7.5%*	Consider‡	Consider‡	Case-by-case

*Based on Pooled Cohort Risk Equations.
†If age >75 yr or not candidate for high intensity.
‡If abnormal high-sensitivity C-reactive protein, coronary artery calcium, ankle-brachial index, lifetime risk.
ASCVD, Atherosclerotic cardiovascular disease; *LDL-C,* low-density lipoprotein cholesterol.
From Boyden TF et al: Implementing new guidelines in the management of blood cholesterol, *Am J Med* 127:705, 2014.

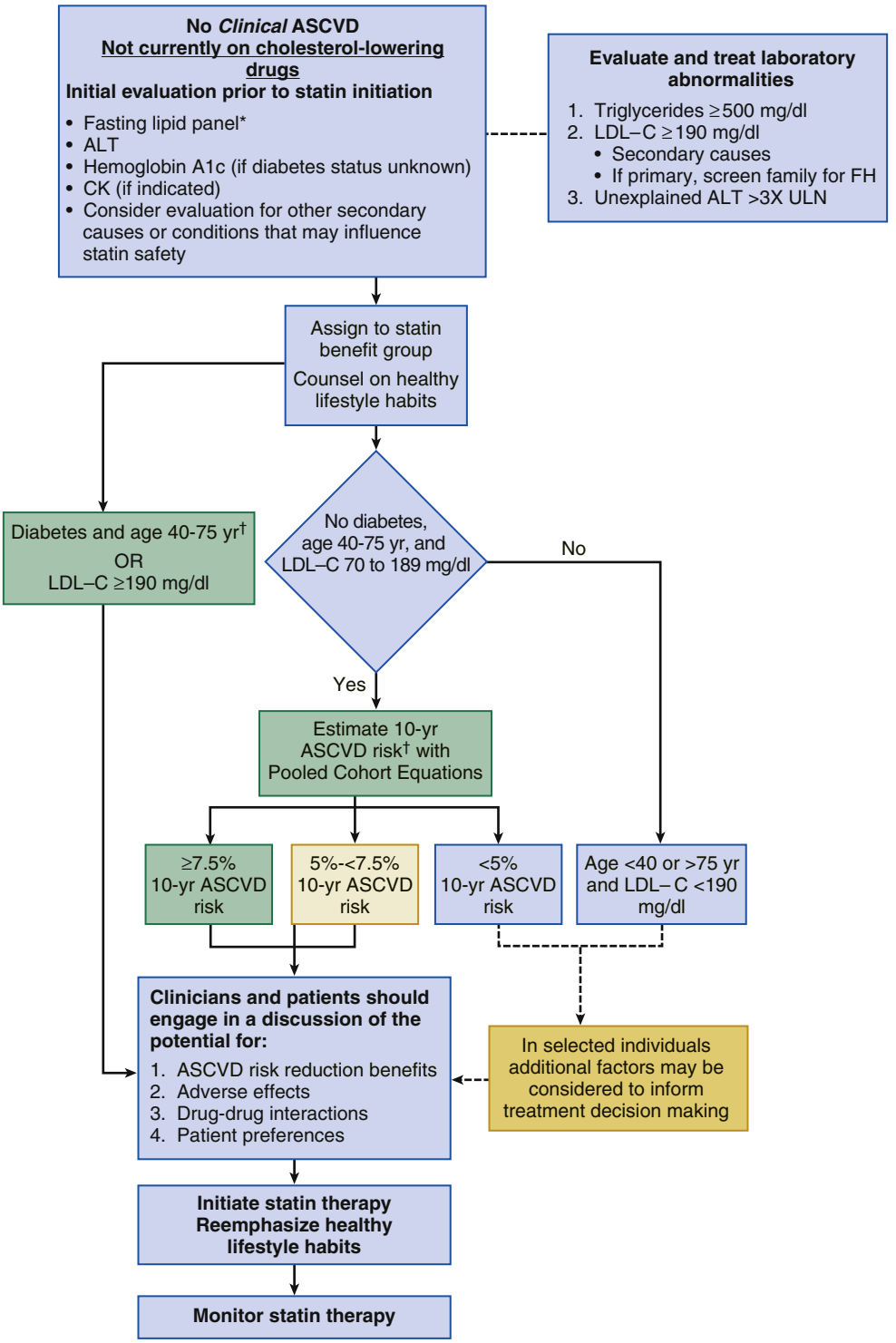

FIG. 2 Initiating statin therapy in individuals without clinical ASCVD. *Fasting lipid panel is preferred. In a nonfasting individual, a nonfasting non-HDL–C>220 mg/dl may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are >500 mg/dl, a fasting lipid panel is required. †The Pooled Cohort Equations can be used to estimate 10-yr ASCVD risk in individuals with and without diabetes. *ALT,* Alanine transaminase; *ASCVD,* atherosclerotic cardiovascular disease; *CK,* creatine kinase; *FH,* familial hypercholesterolemia; *LDL–C,* low-density lipoprotein cholesterol; *ULN,* upper limit of normal. (Modified from Stone NJ et al: 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol,* 2013. In Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015. Elsevier.)

the 75th percentile or higher for their age, sex, and race. Statins should also be considered in persons with scores of 1 to 99, particularly if they are 55 yr of age or older.[1]

- Percent reduction in LDL cholesterol is used as a guide to compliance and adherence to therapy in the 2018 AHA/ACC Revised Clinical Practice Guidelines. Studies have shown that compared with less-intensive LDL-C lowering, more intensive lowering reduces all-cause mortality and cardiovascular mortality; patients with higher baseline LDL-C have greater benefit.
- Moderate-intensity statin therapy should be continued for individuals >75 yr of age for secondary prevention. However, factors such as comorbidities, safety, and priorities of care should be considered before initiating statins for primary prevention of ASCVD.
- Fig. 2 illustrates initiating statin therapy in individuals without clinical ASCVD.
- Adherence to lifestyle and to statin therapy should be reiterated with patients before the addition of a nonstatin drug.
- High-risk patients with a suboptimal response to statins who are unable to tolerate a recommended intensity or who are completely statin intolerant may benefit from the addition of a nonstatin cholesterol-lowering agent such as ezetimibe.
- Table E5 summarizes oral drugs affecting lipoprotein metabolism.
- PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (alirocumab [Praluent], evolocumab [Repatha]) are indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL cholesterol. PCSK9 inhibitors lower risk for ischemic cardiovascular events in persons with stable CAD and elevated atherogenic lipoproteins despite statin therapy. These medications are administered by subcutaneous injection and are expensive.
- The management of metabolic syndrome includes weight reduction, increased physical activity, and treatment of hypertension, elevated triglycerides, and low HDL cholesterol.
- According to recent studies, each 40 mg/dl reduction in LDL cholesterol by statin therapy confers a 20% reduction in ASCVD. In other words, a relative risk reduction of 30% in ASCVD by moderate-intensity therapy and 45% by high-intensity therapy has been approximated.
- Recent trials have shown that bempedoic acid, an inhibitor of ATP citrate lyase, reduces LDL cholesterol. The addition of bempedoic acid to maximally tolerated statin therapy did not lead to a higher incidence of overall adverse events than placebo and led to significant lowering of LDL cholesterol.[2]

DISPOSITION AND FOLLOW-UP

- Baseline LFT testing should be done before initiation of statin therapy and as clinically indicated thereafter.
- CK level monitoring is not recommended unless a patient reports muscle weakness or myalgias.
- Statin therapy should be monitored by repeating a lipid profile within 4 to 12 wk after initiation of therapy.
- Counseling about behavioral lifestyle changes and risk factors for CHD should be provided at every follow-up visit.
- Adverse effects of statin-associated diabetes varies by statin intensity: 1 excess case of diabetes per 1000 treated individuals with moderate-intensity statin and 3 excess cases of diabetes per 1000 treated individuals with high-intensity statin per yr has been reported. Myopathy and hemorrhagic stroke incidence is around 1 excess case per 10,000 treated individuals.
- Per new guidelines, those who develop diabetes during statin therapy should be advised to continue it to reduce their risk of ASCVD events and should adhere to a heart-healthy diet, engage in physical activity, cease tobacco use, and maintain a healthy body weight (Table E5).
- Maintain patients on simvastatin 80 mg only if they have been taking this dose for 12 or more mo without evidence of muscle toxicity.
- Do not start new patients on simvastatin 80 mg.
- Place patients who do not meet their LDL goal on simvastatin 40 mg on alternative LDL-C-lowering treatment(s) to reach goal.

REFERRAL

Patients with rare lipid disorders, hyperlipoproteinemias, patients resistant to treatment, on complex regimens, and with evidence of disease progression despite treatment should be referred to a lipid specialist.

PEARLS & CONSIDERATIONS

COMMENTS

- New features in the 2018 clinical practice guidelines compared to the 2013 guidelines support the addition of nonstatin medications (ezetimibe or PCSK9 inhibitors) to statin therapy for secondary prevention in patients at very high risk. In primary prevention, a clinical patient risk discussion is strongly recommended before a decision is made about statin treatment. Among intermediate-risk patients, identification of risk-enhancing factors and coronary calcium testing is recommended when considering the use of a statin.[3]
- Familial hypercholesterolemia (FH) is characterized by elevated cholesterol concentrations early in life. Untreated FH is associated with premature cardiovascular disease in adulthood. Screening can detect FH in children, and lipid-lowering treatment in childhood can reduce lipid concentrations in the short term, with little evidence of harm. A 20-yr follow-up study of statin therapy has shown that initiation of statin therapy during childhood in patients with FH slows the progression of carotid intima media thickness and reduces the risk of cardiovascular disease in adulthood.[4]
- The American Academy of Pediatrics (AAP) guideline (*Pediatrics* 122:198, 2008) recommends consideration toward pharmacologic treatment for children with LDL >190 mg/dl or >160 mg/dl if other risk factors are present.
- *HDL cholesterol efflux capacity* refers to the ability of HDL to accept cholesterol from macrophages, which is a key step in reverse cholesterol transport. It is inversely associated with the incidence of cardiovascular events and may be a useful biomarker when added to traditional risk factors.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

High Cholesterol (Patient Information)
Coronary Artery Disease (Related Key Topic)
Hyperlipoproteinemia, Primary (Related Key Topic)
Statin-Induced Muscle Syndrome (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

[1]Michos ED et al: Lipid management for the prevention of atherosclerotic cardiovascular disease, *N Engl J Med* 381(16):1557-1567, 2019.

[2]Ray KK et al: Safety and efficacy of bempedoic acid to reduce LDL cholesterol, *N Engl J Med* 380:1022-1032, 2019.

[3]Grundy SM et al: 2018 Cholesterol Clinical Practice Guidelines: Synopsis of the 2018 American Heart Association/American College of Cardiology/Multisociety Cholesterol Guideline, *Ann Intern Med* 170(11):779-783, 2019.

[4]Luirink IK et al: 20-year follow-up of statins in children with familial hypercholesterolemia, *N Engl J Med* 381(16):1547-1556, 2019.

SUGGESTED READINGS

Chou R et al: Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US Preventive Services Task Force, *J Am Med Assoc* 316(19):2008-2024, 2016.

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Last AR et al: Hyperlipidemia: drugs for cardiovascular risk reduction in adults, *Am Fam Physician* 95(2):78-87, 2017.

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Pletcher MJ et al: Non-optimal lipids commonly present in young adults and coronary calcium later in life: the CARDIA (Coronary Artery Risk Development in Young Adults) study, *Ann Intern Med* 153:137-146, 2010.

Rohatgi A et al: HDL cholesterol efflux capacity and incident cardiovascular events, *N Engl J Med* 371:2383-2393, 2014.

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TABLE E5 Drugs Affecting Lipoprotein Metabolism

Drug Class	Agents and Daily Doses	Lipid/Lipoprotein Effects	Side Effects	Contraindications
HMG-CoA reductase inhibitors (statins)	Lovastatin (10-40 mg) Pravastatin (10-80 mg) Simvastatin† (5-80 mg) Fluvastatin (20-40 mg) Atorvastatin (10-80 mg) Rosuvastatin (5-40 mg) Pitavastatin (2-4 mg)	LDL↓ 20%-60% HDL↑ 5%-15% TG↓ 7%-30%	Myalgias, myositis Increased liver enzymes New-onset diabetes (with intensive therapy) Unproven concerns about memory loss	Active or chronic liver disease Pregnancy Concomitant use of certain drugs*
Bile acid sequestrants	Colestipol (5-20 g) Colesevelam‡ (2.6-3.8 g) Cholestyramine (4-16 g)	LDL↓ 15%-30% HDL↑ 3%-5% TG No change or increase	Gastrointestinal distress, constipation, drug interaction, hypertriglyceridemia Decreased absorption of fat-soluble vitamins	TG >300 mg/dl GI motility disorder
Omega-3 fatty acids	Fish oils (4-6 g)	TG↓ 45% HDL↑ 13%	Increased bleeding time Nausea	Caution with anticoagulant therapy
Nicotinic acid	Immediate release (niacin) (1.5-3 g) Extended release (Niaspan) (1-2 g)	LDL↓ 5%-25% HDL↑ 15%-35% TG↓ 20%-50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Chronic liver disease Severe gout Diabetes Peptic ulcer disease Pregnancy/lactation
Fibric acids	Gemfibrozil (600 mg bid) Fenofibrate (45-145 mg)	LDL↓ 5%-20% HDL↑ 10%-20% TG↓ 20%-50%	Dyspepsia Gallstones Myopathy (especially with concomitant use of gemfibrozil and statins)	Severe renal disease (dose adjustment for fenofibrate) Severe hepatic disease Caution with statins Can worsen LDL cholesterol
Ezetimibe (cholesterol absorption inhibitor)	Ezetimibe (10 mg)	LDL↓ 18% HDL↑ 1% TG↓ 8%	Abdominal pain; myalgias	Liver disease Avoid with resins and fibrates

*Cyclosporine, macrolide antibiotics, various antifungal agents, and cytochrome P-450 inhibitors (fibrates and niacin should be used with appropriate caution).
†Dosages of 80 mg of simvastatin are no longer recommended. Potential interactions with amlodipine and ranolazine warrant doses ≤2 mg daily.
‡Colesevelam reduces glucose and A1c ~0.5% and has been approved for treatment of diabetes with dyslipidemia.
GI, Gastrointestinal; *HDL,* high-density lipoprotein cholesterol; *HMG-CoA,* 3-hydroxy-3-methylglutaryl coenzyme A; *LDL,* low-density lipoprotein cholesterol; *TG,* triglyceride.
Modified from The National Cholesterol Education Program, *JAMA* 285:2486, 2001. In Boyden TF et al: Implementing new guidelines in the management of blood cholesterol, *Am J Med* 127:705, 2014.

Hypercoagulable State PTG

BASIC INFORMATION

DEFINITION

Hypercoagulable state is an inherited or acquired condition associated with an increased risk of thrombosis. A classification of hypercoagulable states is described in Table 1.

SYNONYM

Thrombophilia

ICD-10CM CODES

D68.5 Primary thrombophilia
D68.6 Other thrombophilia
D68.8 Other specified coagulation defects
D68.9 Coagulation defect, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE, PREVALENCE, PREDOMINANT SEX, AND AGE: See Table 2. Significant variations in the prevalence rates and thrombotic risks for hypercoagulable states are reported. This may reflect geographic variation in the prevalence of genetic defects, different populations, or the presence of other unidentified thrombophilic risk factors. When thrombosis occurs, it is often associated with an acquired risk factor (e.g., surgery, pregnancy, oral contraceptive [OC] use).

GENETICS:

- Most people with a genetic defect will not have thrombotic disease.
- Approximately half of patients with unprovoked thrombosis have an identifiable inherited thrombophilia. There is a low risk of recurrent thrombosis in patients with a single genetic defect. Multiple genetic defects are not uncommon (1% to 2% prevalence in patients with idiopathic venous thromboembolism [VTE]); a strong synergistic effect occurs when multiple defects are present.

RISK FACTORS: Family history of thrombosis, increasing age, tobacco use, immobility, surgery, prior history of deep vein thrombosis (DVT) pregnancy, hormone replacement therapy, trauma, connective tissue disease, underlying malignancy, medications (megestrol acetate, tamoxifen, oral contraceptives). Potential prothrombotic states are summarized in Table 3.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Inherited thrombophilia is usually associated with VTE, most commonly DVT
- Some acquired thrombophilias are associated with arterial thrombosis. Table 2 describes sites of thrombosis according to coagulation defect
- Pregnancy complications
- Medical conditions associated with increased risk of thrombosis

ETIOLOGY

- Thrombosis is often a multifactorial process with genetic, environmental, and acquired factors. Table E4, Table E5, Table E6, and Table E7 describe causes of acquired and inherited deficiencies in antithrombin, protein C, and protein S.
- Thrombotic risk increases with use of OCs or hormone replacement therapy (HRT) and during the pregnancy/postpartum period.
- Adverse pregnancy outcomes may be caused by thrombosis of the uteroplacental circulation.

TABLE 1 Classification of Hypercoagulable States

Hereditary	Mixed	Acquired
Loss of Function		
Antithrombin deficiency	Hyperhomocysteinemia	Previous venous thromboembolism
Protein C deficiency	Obesity	Pregnancy, puerperium
Protein S deficiency	Cancer	
		Drug-induced:
		Heparin-induced thrombocytopenia
		Prothrombin complex concentrates
		L-asparaginase
		Hormonal therapy
Gain of Function		
Factor V Leiden	Postoperative	
Prothrombin FII G20210A	Myeloproliferative disorders	
Elevated factor VIII, IX, or XI		

Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 3 Potential Prothrombotic States

Congenital

Deficiency of anticoagulants
AT-III, protein C or protein S, plasminogen
Resistance to cofactor proteolysis
Factor V Leiden
High levels of procoagulants
Prothrombin 20210 mutation
Damage to endothelium

Acquired

Obstruction to flow indwelling lines
Pregnancy
Polycythemia/dehydration
Immobilization
Injury
Trauma, surgery, exercise
Inflammation
IBD, vasculitis, infection, Behçet syndrome
Hypercoagulability
Pregnancy
Malignancy
Antiphospholipid syndrome
Nephrotic syndrome
Oral contraceptives L-Asparaginase

Rare Other Entities

Congenital dysfibrinogenemia
Acquired
Paroxysmal nocturnal hemoglobinuria
Thrombocythemia
Vascular grafts

AT-III, Antithrombin III; *IBD,* inflammatory bowel disease.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, WB Saunders.

TABLE 2 Hypercoagulable Conditions

	Prevalence in General Population (%)	Prevalence in Population with Thrombosis (%)	A/V Events	Relative Risk of Thrombosis
FVL mutation	5% of whites; rare in nonwhites	12%-40%	V	Heterozygous: 3-7; homozygous: 80
Prothrombin G20210A mutation	3% of whites; rare in nonwhites	6%-18%	V	3
AT deficiency	0.02%	1%-3%	V	20-50
PC deficiency	0.2%-0.4%	3%-5%	V	7-15
PS deficiency	0.03%-0.1%	1%-5%	V	5-11
Antiphospholipid antibody syndrome	1%-2%	5%-21%	V + A	2-11

A, Arterial; *AT,* antithrombin; *FVL,* factor V Leiden; *PC,* protein C; *PS,* protein S; *V,* venous.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

INHERITED: Factor V Leiden (FVL) mutation:

- Autosomal-dominant mutation with low penetrance
- Causes activated protein C resistance (APCR); 90% of APCR is caused by FVL mutation
- Most common inherited thrombophilia; accounts for 40% to 50% of cases
- OC use in heterozygous carriers is associated with an eightfold increased risk of VTE compared with noncarriers and a thirty-fivefold increased risk of VTE compared with noncarriers not using OCs
- May be associated with cardiovascular disease in select high-risk subgroups

Prothrombin G20210A mutation:

- Autosomal-dominant mutation with low penetrance
- OC use in heterozygous carriers is associated with a sixteenfold increased risk of VTE compared with noncarriers not using OCs
- May be associated with cardiovascular disease in select high-risk subgroups and young patients with ischemic stroke
- Causes increased mRNA accumulation and protein synthesis, leading to elevated prothrombin plasma concentrations

Protein C, protein S, antithrombin (AT) deficiency:

- Autosomal-dominant inheritance; many mutations identified for each of these conditions
- Decreased level (type I deficiency) or abnormal function (type II deficiency)
- First episode of thrombosis is usually in young adults

Protein C and protein S:

- Homozygous condition is very rare; usually associated with lethal thrombosis in infancy
- Associated with warfarin-induced skin necrosis, which occurs secondary to depletion of vitamin K–dependent anticoagulant factors sooner than procoagulant factors in the first few days of therapy

AT deficiency:

- Most thrombogenic of the inherited thrombophilias; 50% lifetime risk of thrombosis.
- Homozygous condition is very rare, probably not compatible with normal fetal development.
- Arterial thrombosis can occur rarely.
- Can cause heparin resistance.

Other possible causes: Non-O blood group, dysfibrinogenemia, elevated thrombin-activatable fibrinolysis inhibitor, elevated factor IX and factor XI levels

ACQUIRED: Antiphospholipid antibody syndrome (APS):

- Most common cause of acquired thrombophilia
- Can present as arterial or venous thrombosis, recurrent pregnancy loss, and adverse pregnancy outcomes
- Thromboembolic events occur in up to 30% of population; high risk of recurrent thrombosis (up to 70% reported)
- See "Antiphospholipid Antibody Syndrome" for more information

Conditions associated with increased risk of thrombosis:

- Prior thrombosis
- Trauma
- Medical illness: Heart failure, respiratory failure, infection, diabetes mellitus, obesity, nephrotic syndrome, inflammatory bowel disease
- Chronic hemolysis–paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, sickle cell anemia
- Pregnancy (sixfold increased risk of VTE), postpartum, OC use (fourfold increased risk, higher risk with third-generation OCs), transdermal contraceptive patch, HRT (twofold increased risk), tamoxifen, raloxifene
- Immobilization, travel
- Surgery (especially orthopedic), central venous catheters
- Hyperviscosity syndromes
- Myeloproliferative disorders
- Malignancy: Disease or treatment related
- Heparin-induced thrombocytopenia and thrombosis
- Smoking

WORKUP

- History (presence of conditions or use of medications predisposing to thrombosis, family history of thrombosis), physical examination, laboratory tests, imaging studies. Routine investigations to evaluate a patient with thrombosis are summarized in Box 1.
- Age-appropriate cancer screening.
- No consensus exists regarding screening for thrombophilia; few cost-effectiveness or outcomes data are available. Thrombophilia screening is probably overused, as results usually do not change management.
- Thrombophilia screening is not recommended for primary prevention of VTE; some advocate testing prior to OC use or pregnancy in women with a strong family history of thrombosis or thrombophilia. Box 2 summarizes recommendations regarding when to perform a thrombophilia screen. Essential tests for thrombophilia screening are described in Box 3.
- Screening not recommended if VTE was associated with an identified risk factor. A possible exception is thrombosis associated with pregnancy, the postpartum period, or with OC use.
- Provoked by weak triggers in a patient with a strong family history and female family members of childbearing age; consider testing for FVL, prothrombin *G20210A* mutation, protein C, protein S, and AT deficiency. Consider testing for APS if extensive DVT or pulmonary embolism (PE).
- Unprovoked VTE:
  1. Screen individuals for APCR, prothrombin *G20210A* mutation, protein C, protein S, AT deficiency, and APS if any of the following are present: <50 yr of age at first episode of thrombosis + strong family history of thrombosis or female family member of childbearing age, thrombosis in unusual anatomic location (cerebral veins or splanchnic veins; if splanchnic veins, consider testing as well for myeloproliferative neoplasms [MPN] and paroxysmal nocturnal hemoglobinuria [PNH]).
  2. Screen all others for APS.
- Arterial thrombosis: Screen for APS.
- NOTE: Routine screening for factor VIII level or hyperhomocysteinemia is not recommended.

BOX 1 Routine Investigations to Evaluate a Patient with Thrombosis

Test	Abnormality	Diagnostic Information
Complete blood count	Elevated hematocrit Increased white count Increased platelet count Leukopenia Thrombocytopenia	Myeloproliferative disorder (e.g., essential thrombocythemia, polycythemia vera); may be found in paroxysmal nocturnal hemoglobinuria; if associated with heparin administration, consider heparin-induced thrombocytopenia
Blood film	Leukoerythroblastic changes	Underlying neoplasm invading bone marrow
Liver function tests	Abnormal tests	May point to malignancy
Renal function	Impaired renal function	Assess prior to anticoagulation with heparin, low-molecular-weight heparin or new oral anticoagulants
Urinalysis	Proteinuria	Nephrotic syndrome; may be associated with venous thromboembolism or renal vein thrombosis
PT and aPTT	Prolonged PT and aPTT	To enable safe anticoagulation to proceed if required Need to exclude lupus anticoagulant

aPTT, Activated partial thromboplastin time; *PT,* prothrombin time.
Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

BOX 2 When to Perform a Thrombophilia Screen

Clinical Scenario
- First episode of unprovoked venous thromboembolism in individuals younger than 40 yr of age
- Thrombosis in an unusual site (e.g., cerebral or mesenteric thrombosis)
- Two or more first-degree relatives with unprovoked thrombosis
- Three or more early pregnancy losses, or one or more fetal deaths after 10 wk gestation

Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

BOX 3 Essential Tests for Thrombophilia Screening

- Basic coagulation screen
  1. International normalized ratio (INR): To exclude warfarin effect—warfarin will lower protein C and S levels
  2. Activated partial thromboplastin time (aPTT): To exclude heparin effect—heparin will lower antithrombin levels
- Functional assay for antithrombin (with heparin to detect type II defects)
- Functional assay for protein C
- Functional assay for protein S (immune assays for total and free protein S)
- APC resistance assay: With genetic test for factor V Leiden for confirmation of abnormal results
- Genetic test for *FIIG 20210A* gene mutation
- Anticardiolipin and β_2 -glycoprotein-1 antibodies (IgG and IgM) and lupus anticoagulant assay

APC, Activated protein C; *Ig,* immunoglobulin.
Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TIMING OF WORKUP:
- Ideally >3 wk after discontinuation of vitamin K antagonists (VKA) and >2 days after discontinuation of direct oral anticoagulant (DOAC) (except for APS, which requires prolonged anticoagulation).
- NOTE: Acute thrombosis, anticoagulation, pregnancy, and many medical conditions can affect the results and must be considered in the timing and interpretation of the workup.

LABORATORY TESTS
- CBC with peripheral smear, electrolytes, calcium, creatinine, blood urea nitrogen (BUN) and liver function tests, prothrombin time/partial thromboplastin time, prostate-specific antigen (in men aged >50 yr), urinalysis.
- Note: Genetic counseling and written informed consent should be obtained before genetic testing. Abnormal nongenetic tests should be repeated after 6 wk to decrease false-positive results.
- APCR: APC-resistance assay (using factor V–deficient plasma). Presence of lupus anticoagulant causes false positives. Follow-up positive APCR assay with genetic test for FVL.
- Prothrombin G20210A mutation testing.
- AT, protein C, and protein S deficiency: Functional assays; if decreased perform antigenic assay to determine type of deficiency. Antigenic assays for protein S should measure free and total levels. In protein C and protein S deficiency, the functional assay may be falsely low in the presence of APCR or elevated factor VIII level and falsely high if lupus anticoagulant is present.
- APS: Any one of the following found on two occasions at least 12 wk apart: Lupus anticoagulant, anticardiolipin antibodies, or anti–B_2-glycoprotein-I antibodies.

IMAGING STUDIES
Chest radiograph and other tests as appropriate to diagnose thrombosis and rule out associated conditions

Rx TREATMENT

NONPHARMACOLOGIC THERAPY
OC/HRT use and smoking should be avoided.

PROPHYLAXIS
- Prophylactic anticoagulation in high-risk situations.
- Patients with AT deficiency may benefit from antithrombin concentrates in high-risk situations.
- Pregnancy prophylaxis: Timing and intensity of therapy is based on the patient's risk (genetic or acquired defect and clinical history). Women with thrombophilia and recurrent adverse pregnancy outcomes may benefit from prophylaxis with heparin (low-molecular-weight heparin most commonly used) and low-dose aspirin.

ACUTE GENERAL Rx
Initial therapy is the same as for individuals with and without thrombophilia, with exceptions for protein C, AT, and APS deficiency as detailed in the following.

Venous thrombosis:
- DOACs such as Xa inhibitors (rivaroxaban and apixaban) have been FDA-approved for treatment in acute DVT and are currently recommended as first-line therapy. They have been found to be noninferior to warfarin, appear easier to use with fewer drug interactions, and have a trend toward less major bleeding.
- In patients unable to take DOACs, begin low-molecular-weight heparin (LMWH) and warfarin simultaneously. Continue heparin for at least 5 days and until international normalized ratio (INR) is therapeutic for 2 consecutive days; continue warfarin for at least 3 mo. Aim for INR of 2 to 3. Unfractionated heparin (UH) or fondaparinux (factor Xa inhibitor) may be used as alternatives to LMWH. LMWH is preferred over UH (except in patients with massive pulmonary embolism, increased risk of bleeding, or renal failure) because of equivalent or superior effectiveness and a better safety profile.
- Thrombophilia is not associated with a higher risk of recurrent VTE during warfarin therapy, with the exception of cancer patients in whom LMWH for 3 to 6 mo is associated with lower rates of recurrence than warfarin therapy.
- In pregnancy, anticoagulate with heparin throughout pregnancy and for at least 6 wk postpartum. Minimum duration of anticoagulation should be 6 mo. LMWH is preferred over UH. Warfarin may be used postpartum.
- Consider thrombolysis or thrombectomy in patients with massive pulmonary embolism or large proximal lower extremity DVT.

Protein C deficiency:
- Warfarin-induced skin necrosis: Discontinue warfarin, give vitamin K, and start heparin anticoagulation. Consider protein C replacement with protein C concentrate or fresh frozen plasma. Warfarin may be restarted at a low dose (2 mg daily for 3 days and increase by 2 to 3 mg daily until target INR is reached). Continue heparin for at least 5 days and until warfarin-induced anticoagulation is achieved.

AT deficiency:
- AT concentrates may be used if difficulty achieving anticoagulation (heparin resistance), severe thrombosis, or recurrent thrombosis despite adequate anticoagulation.

APS:
- Warfarin is superior to rivaroxaban in patients with APS. The RAPS trial randomized patients with APS to receive either rivaroxaban or warfarin and found significantly higher rates of thrombosis in the rivaroxaban group. A subsequent trial noted increased endogenous thrombin potential (a marker of less effective anticoagulation) in APS patients switched to rivaroxaban following initial VKA therapy compared to those continued on warfarin. This studied was not powered to assess clinical efficacy.

Arterial thrombosis:
- Anticoagulation and evaluation for thrombolysis or surgery

CHRONIC Rx
- Optimal duration of anticoagulation remains unknown. Length of therapy may be individualized by assessing the risk of recurrence. Residual thrombosis (on ultrasonography) or elevated D-dimer levels after completion of anticoagulation are associated with an increased risk of recurrence. With these findings, consider prolonging anticoagulation.

TABLE 8 Management of Women with a History of Venous Thrombosis during Pregnancy and the Puerperium

Clinical History	Thrombophilia	Antepartum	Postpartum[a]
Prior VTE due to a transient risk factor	No	Surveillance	Yes
Prior VTE due to pregnancy or estrogens	Yes or no	Prophylactic LMWH	Yes
Prior idiopathic VTE	Yes or no	Prophylactic LMWH	Yes
Recurrent VTE	Yes or no	Treatment dose LMWH	Resume long-term anticoagulation
No prior VTE Positive family history	Antithrombin deficiency; homozygous FII G20210A; or Factor V Leiden; or dual heterozygosity for both mutations	Prophylactic or intermediate dose LMWH	Yes

LMWH, Low-molecular-weight heparin; *VTE,* venous thromboembolism.
[a]Postpartum prophylaxis involves a 6-wk course of prophylactic doses of LMWH or dose-adjusted warfarin (target INR: 2.0 to 3.0).
Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

- Must consider risk and benefit; risk of major bleeding 2% to 3% annually in general population on anticoagulation but higher in the elderly (7% to 9% per yr). Long-term anticoagulation is usually not indicated given the low risk of recurrent thrombosis for most conditions and the bleeding risk associated with anticoagulation.
- Indefinite anticoagulation considered if any of the following:
  1. Life-threatening thrombosis or thrombosis at an unusual site
  2. More than a single genetic defect
  3. Presence of AT deficiency or APS
  4. Unprovoked DVT or PE with low bleeding risk
  5. >1 Provoked DVT or PE with low bleeding risk
- Patients with active cancer may benefit from indefinite anticoagulation.

DISPOSITION

Depends on underlying condition

REFERRAL

Hematology, maternal-fetal medicine, obstetric medicine

PEARLS & CONSIDERATIONS

COMMENTS

- Women with thrombophilic defects but no prior history of venous thromboembolism, or family history of the same, likely do not require antepartum prophylaxis or postpartum treatment, but definitive data are lacking. A summary of these recommendations is provided in Table 8.
- DOACs and warfarin therapy effectively reduce the risk of recurrent VTE; when therapy is discontinued VTE risk increases.
- Rivaroxaban is inferior to warfarin in patients with APS.
- Previous episode of VTE is a major risk factor for recurrence regardless of the presence of thrombophilia. Risk is greatest in the first 2 yr after thrombosis. 20% of all patients with unprovoked VTE have recurrence within 5 yr.
- Genetic risk factors for thrombosis in nonwhites remain largely unknown.
- Interpreting workup: Many medical conditions cause acquired abnormalities.
  1. Acute thrombosis may be associated with lupus anticoagulant, increased anticardiolipin antibodies, and elevated factor VIII levels
  2. Heparin therapy: Antithrombin levels decrease by up to 30%; can affect lupus anticoagulant testing
     a. Warfarin therapy: Cannot measure protein C and protein S (levels and function decrease); antithrombin levels may increase; can affect lupus anticoagulant testing
  3. Protein C, protein S, and antithrombin levels decrease with acute thrombosis (<2 wk), surgery, liver disease, disseminated intravascular coagulation, and chemotherapy. Protein C level also decreases with severe infection but levels increase with age and hyperlipidemia. Protein S and antithrombin levels also decrease with nephrotic syndrome, pregnancy, and estrogen therapy (HRT, OCs)
  4. APCR is increased with pregnancy, estrogen therapy (HRT, OCs), and certain cancers; elevated factor VIII level and antiphospholipid antibodies can cause APCR

PREVENTION

Risk of postthrombotic syndrome decreases if compression stockings are worn for at least 1 yr, starting in the first month after the DVT.

PATIENT & FAMILY EDUCATION

National Blood Clot Alliance
120 White Plains Road, Suite 100
Tarrytown, NY 10591
www.stoptheclot.org/contact.htm

National Collaborative Outreach Project of the Blood Clot Outreach Program at the Hemophilia and Thrombosis Center University of North Carolina at Chapel Hill
www.clotconnect.org/about-clot-connect/about

Factor V Leiden Resources
www.fvleiden.org/resources/index.html

APS Foundation of America, Inc.
P. O. Box 801
LaCrosse, WI 54602-0801
www.apsfa.org/

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Thrombophilia (Patient Information)
Antiphospholipid Antibody Syndrome (Related Key Topic)
Deep Vein Thrombosis (Related Key Topic)
Pulmonary Embolism (Related Key Topic)

AUTHORS: **Robert Matera, MD,** and **John L. Reagan, MD**

TABLE E4 Types of Inherited Antithrombin Deficiency

Type	Antigen	Activity (No Heparin)	Activity (with Heparin)
I	Low	Low	Low
II (active site defect)	Normal	Low	Low
II (heparin-binding site defect)	Normal	Normal	Low

Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE E5 Causes of Acquired Antithrombin Deficiency

Decreased Synthesis	Increased Consumption	Enhanced Clearance
Hepatic cirrhosis	Major surgery	Heparin
Severe liver disease	Acute thrombosis	Nephrotic syndrome
L-asparaginase	Disseminated intravascular coagulation	
	Severe sepsis	
	Multiple trauma	
	Malignancy	
	Prolonged extracorporeal circulation	

Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE E6 Types of Inherited Protein C Deficiency

Type	Antigen	Activity
I	Low	Low
II	Normal	Low

Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE E7 Types of Inherited Protein S Deficiency

Type	Total Protein S	Free Protein S	Protein S Activity
I	Low	Low	Low
II	Normal	Normal	Low
III	Normal	Low	Low

Hoffman R et al: *Hematology, basic principles, and practice* ed 7, Philadelphia, 2018, Elsevier.

SUGGESTED READINGS

Andrade D et al: 15th international Congress on antiphospholipid antibodies Task Force on Antiphospholipd syndrome treatment trends report. In Erkan D, Lockshin M, (eds): *Antiphospholipid syndrome,* ed 1, 2017, Springer International Publishing, p. 317.

Baglin T et al: Clinical guidelines for testing for heritable thrombophilia, *Br J Haematol* 149:209-220, 2010.

Connors JM: Thrombophilia testing and venous thrombosis, *New Engl J Med* 377:1177-1187, 2017.

Couturaud F et al: Factors that predict thrombosis in relatives of patients with venous thromboembolism, *Blood* 124:2124-2130, 2014.

Kearon C et al: Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report, *Chest* 149:315-352, 2016.

Kunk PR et al: Direct oral anticoagulants in hypercoagulable states, *J Thromb Thrombolysis* 43(1):79-85, 2017.

Hyperemesis Gravidarum PTG

BASIC INFORMATION

DEFINITION

Hyperemesis gravidarum refers to a severe and persistent form of nausea and vomiting in pregnancy. While no precise criteria exist to define the severity, it may be characterized by at least a 5% weight loss from prepregnancy weight, dehydration, ketonuria, and electrolyte imbalance. Typical onset occurs at wk 4 to 8 of pregnancy, continuing through wk 14 to 16 of pregnancy.

ICD-10CM CODES

O21.0 Mild hyperemesis gravidarum
O21.1 Hyperemesis gravidarum with metabolic disturbance

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.5% to 2% of pregnancies
GENETICS: A genetic predisposition may exist; hyperemesis gravidarum is more common among first-degree relatives of those diagnosed with the condition.
RISK FACTORS: Women with increased placental mass, including molar pregnancy or multiple gestation, family history or personal history of hyperemesis gravidarum, prior miscarriage, nulliparity, young age, hyperthyroidism, gastrointestinal disorders, vestibular disease, motion sickness, long interpregnancy interval, and supertaster status. Alcohol use, smoking, and anosmia may be protective. A female fetus increases the risk by 1.27-fold.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Weight loss of more than 5% from pre-gravid weight
- Symptoms: Nausea, vomiting, spitting, enhanced olfactory senses, food and/or fluid intolerance, lethargy
- Signs: Poor skin turgor, dry mucous membranes, hypotension, tachycardia
- Complications include inadequate caloric and nutritional intake, dehydration, and electrolyte abnormalities, including hyponatremia, hypocalcemia, hypokalemia, and, in severe cases, hypochloremic metabolic acidosis or Wernicke encephalopathy from thiamine deficiency. Severe hyperemesis gravidarum also has been shown to correlate with higher rates of anxiety and depression

ETIOLOGY

Unknown, but likely multifactorial. Theories include interactions between hCG and the thyroid, gestational hyperestrogenemia, and gastric dysrhythmias.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gastrointestinal conditions: Gastroenteritis, gastroparesis, biliary tract disease, hepatitis, intestinal obstruction, peptic ulcer disease, appendicitis, inflammatory bowel disease
- Genitourinary tract conditions: Pyelonephritis, nephrolithiasis
- Metabolic disease: Hyperthyroidism, hyperparathyroidism, diabetic ketoacidosis, cannabinoid hyperemesis syndrome, porphyria, adrenal insufficiency
- Neurologic conditions: Pseudotumor cerebri, vestibular lesions, migraines, tumors of the central nervous system, cyclic vomiting syndrome
- Miscellaneous: Drug toxicity or intolerance, psychogenic
- Pregnancy-related conditions: Acute fatty liver of pregnancy, preeclampsia

WORKUP

Diagnosis is one of exclusion. History and physical examination along with laboratory tests to rule out other causes of vomiting should be performed.

LABORATORY TESTS

- BMP may reveal hyponatremia, hypokalemia, low serum urea.
- Urinalysis may show elevated specific gravity, ketonuria, or proteinuria.
- Liver enzymes (ALT typically more elevated than AST, both usually reaching only two to three times the upper limit of normal).
- Serum bilirubin (<4 mg/dl).
- Serum amylase or lipase (up to 5× greater than normal).
- CBC may show an increase in hematocrit from volume depletion.
- Magnesium and calcium may be low.
- TSH and free T4 (transient hyperthyroidism occurs in 2/3 of women with hyperemesis gravidarum; this is biochemical hyperthyroidism that usually resolves by 18 wk of gestation; testing and treatment should not be undertaken without additional clinical evidence of intrinsic thyroid disease).

IMAGING STUDIES

- Ultrasound to evaluate for multiple gestation or molar pregnancy
- If the patient is having associated pain, a right upper quadrant ultrasound may be indicated to evaluate biliary tract disease

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of foods and smells that trigger nausea
- Ginger (200 to 500 mg q8h)
- Protein-heavy meals
- Reassurance and support, in some cases intensive cognitive-behavioral therapy

ACUTE GENERAL Rx

- Pyridoxine (vitamin B_6) 10 to 25 mg PO q8h
- Doxylamine 12.5 to 25 mg qhs
- Pyridoxine (10 mg)/doxylamine (10 mg) combination, starting with 2 tablets qhs and adding an additional 1 tablet q A.M. and 1 tablet q P.M. if needed
- Antiemetics including promethazine, prochlorperazine, metoclopramide, and ondansetron have been shown to be generally safe and effective in improving pregnancy outcome
- Corticosteroids (methylprednisolone, prednisone) may be considered after 10 wk of gestation
- IV fluid and electrolyte administration if evidence of deficiency is found
- Thiamine prior to dextrose administration to avoid Wernicke encephalopathy
- Restart oral intake gradually no less than 48 hr after vomiting has stopped

CHRONIC Rx

- If unable to tolerate oral intake, consider replacing with enteral or parenteral feeding
- Repeated IV fluid and electrolyte replacement can be conducted through outpatient visits

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Supportive psychotherapy
- Acupuncture
- Acupressure with use of a wrist band

DISPOSITION

- Infants born from pregnancies complicated by hyperemesis may have a higher risk of being small for gestational age or low birth weight than those not; however, this may be limited to infants of women who have experienced significant weight loss in the setting of hyperemesis.
- Women with hyperemesis gravidarum should be counseled that they have a higher risk than other women of developing similar symptoms in future pregnancies.

PEARLS & CONSIDERATIONS

COMMENTS

Nausea and vomiting in early pregnancy are associated with psychosocial morbidity.

RELATED CONTENT

Hyperemesis Gravidarum (Patient Information)

AUTHORS: **T. Caroline Bank, MD,** and **Anthony Sciscione, DO**

BASIC INFORMATION

DEFINITION

Hypereosinophilic syndrome (HES) refers to overproduction of eosinophils with sustained eosinophil counts over 1500/ml (1.5×10^9/L), in which eosinophilic infiltration of tissues (skin, lungs, heart, liver, spleen, lymph nodes) and mediator release cause organ dysfunction. HES may be primary or have a reactive cause.

SYNONYMS

Idiopathic hypereosinophilic syndrome (IHES)
HES

ICD-10CM CODE
D72.1 Eosinophilia

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: Occurs in men more often than women (9:1)
PREDOMINANT AGE: Usually occurs between the ages of 20 and 50 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical presentation of HES may vary from an incidental finding of eosinophilia to sudden onset of cardiac or neurologic symptoms.
- Early presentation includes fatigue, cough, breathlessness, muscle pain, angioedema, rash, and fever.
- Cardiac manifestations (58%) include dyspnea, orthopnea, and signs and symptoms of congestive heart failure (CHF). Includes three stages: Acute necrotic stage secondary to endocardial infiltration of eosinophils, thrombus formation, and fibrotic stage. This may result in a restrictive or dilated cardiomyopathy and/or valvular heart disease.
- Neurologic manifestations (54%) may be of three types:
  1. Thromboembolic (e.g., cardiac emboli or local vascular thrombosis)
  2. CNS dysfunction: Confusion, loss of memory, ataxia, upper motor neuron signs, seizures, and behavior changes
  3. Peripheral neuropathy (most common) may be symmetric or asymmetric, sensory or mixed sensory, and motor deficits
- Pulmonary manifestations (40%) include a chronic persistent nonproductive cough, shortness of breath, and dyspnea on exertion. Diffuse or focal infiltrate may present in 20% of cases. Complications may include pulmonary fibrosis, CHF, or pulmonary embolus.
- Cutaneous manifestations (56%) usually include eczema, lichenifications, urticaria, angioedema, or erythematous pruritic papules and nodules.
- GI manifestations (23%) include diarrhea, but findings of gastritis, colitis, pancreatitis, cholangitis, and hepatitis can occur.
- Ocular manifestations (23%) are thought to be the result of retinal microemboli.
- Vascular manifestations include venous or arterial thrombosis of unknown mechanism such as femoral artery occlusion, intracranial sinus thrombosis, and digital gangrene.

ETIOLOGY

- Primary HES is a myeloproliferative neoplasm (MPN) with molecular activation of platelet-derived growth factor receptor (PDGER). Secondary (reactive) HES occurs in response to an identified stimulus (see "Differential Diagnosis").
- In some cases, a fusion event generating an abnormal and oncogenic tyrosine kinase (FIP1L1-PDGFRA) appears to be causative, especially in males.

DIAGNOSIS

Criteria for the diagnosis of idiopathic HES include:

- Persistent eosinophilia of >1500 eosinophils/mm^3 for more than 6 mo
- Exclusion of other conditions causing eosinophilia (Box E1)
- Signs and symptoms of organ system dysfunction (e.g., heart, liver, lung)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes all causes of peripheral blood eosinophilia: Parasitic infections, coccidioidomycosis, cat-scratch disease, asthma, Churg-Strauss syndrome, allergic rhinitis, atopic dermatitis, drug-induced eosinophilia, aspergillosis, eosinophilic pneumonia, hypersensitivity pneumonitis, HIV, eosinophilic gastroenteritis, inflammatory bowel disease, leukemias (CML and CMML), and systemic mastocytosis with eosinophilia.

WORKUP

The workup of a patient who is suspected of having HES should exclude other causes mentioned in the "Differential Diagnosis" section leading to peripheral eosinophilia.

LABORATORY TESTS

- CBC with differential; often the total WBC ranges from 10,000 to 30,000/mm^3 with eosinophilia of 30% to 70%, anemia is present in 50% of the cases, and either thrombocytopenia or thrombocytosis may be noted
- Erythrocyte sedimentation rate (ESR) and rheumatoid factor
- Liver function tests (LFTs), electrolytes, urinalysis, BUN, and creatinine
- HIV assay
- Stools for ova and parasites ×3
- Serologic blood tests for parasitic infections (e.g., *Strongyloides*)
- Total IgE level
- Bone marrow aspirate and biopsy (Fig. E1)
- Duodenal aspirate
- ECG
- Tissue biopsies as indicated
- Serum levels of vitamin B_{12}
- Serum levels of tryptase

IMAGING STUDIES

- Chest radiograph may be clear or show infiltrates, effusions, or fibrotic scarring.
- CT scan of chest, abdomen, and pelvis.
- Echocardiogram (or cardiac MRI for early cardiac involvement) can assess for ventricular function and valvular pathology including regurgitation and thrombi formation.

TREATMENT

Treatment is initiated only if there is evidence of organ involvement. In primary (neoplastic) HES, treatment of underlying disorders can improve eosinophilia.

NONPHARMACOLOGIC THERAPY

In patients with hypereosinophilia without organ involvement, serial echocardiograms, blood chemistries, and pulmonary function tests are recommended at 6-mo intervals.

ACUTE GENERAL Rx

- In patients with organ involvement without FIP1L1-PDGFRA fusion, initial therapy is with prednisone 1 mg/kg/day or 60 mg/day in adults.
- Patient's symptoms and peripheral eosinophil counts are monitored.
- Doses may be tapered to alternate-day prednisone use in patients whose eosinophil counts have been suppressed.

CHRONIC Rx

- Steroid-refractory patients with FIP1L1-PDGFRA fusion can be treated with imatinib.
- If the disease continues to progress, vincristine, etoposide, interferon-α, cyclosporine, and leukapheresis are alternative choices.
- Anticoagulation and/or antiplatelet agents are often used in patients with HES.
- If all else fails, bone marrow transplantation may be considered.

DISPOSITION

- Before the use of cardiac imaging (echo) and cardiac surgeries (valve replacement), patients with HES had a poor prognosis with a mean survival time of 9 mo and a 3-yr survival rate of 12%.
- Deaths usually result from CHF, endocarditis, and systemic emboli.
- 5-yr and 15-yr survival rates are 80% and 42%, respectively.

REFERRAL

HES is a rare and complicated disorder requiring a multidisciplinary approach.

AUTHOR: **Fred F. Ferri, MD**

BOX E1 Diseases, Syndromes, and Conditions Commonly Associated with Peripheral Blood Eosinophilia or Tissue Eosinophilia

Infectious Agents

Parasitic

- Tropical eosinophilia
- Visceral larval migrans (VLM, toxocariasis)
- Helminth infections
- Filariasis *(Wuchereria bancrofti, Brugia malayi)*
- Onchocerciasis
- Schistosomiasis
- Fascioliasis
- Paragonimiasis
- Strongyloidiasis
- Trichinosis
- Hookworm
- Ascariasis
- Echinococcosis/hydatid disease

Nonparasitic

- Coccidioidomycosis
- Chlamydial pneumonia of infancy
- Scarlet fever and pneumococcal pneumonia (convalescent phase)
- Cat-scratch disease
- Cryptococcosis (CSF eosinophilia) in HIV

Allergic Diseases

- Asthma (atopic and intrinsic, nasal polyps, aspirin intolerance syndromes)
- Bronchopulmonary aspergillosis
- Allergic rhinitis
- Urticarias (acute allergic and chronic idiopathic)
- Atopic dermatitis
- Acute drug (hypersensitivity) reactions (interstitial nephritis, cholestatic hepatitis, exfoliative dermatitis)

Respiratory Tract Disorders

- Hypersensitivity pneumonitis (rare)
- Allergic bronchopulmonary aspergillosis
- Eosinophilic pneumonia
- Transient pulmonary infiltrates (Löffler syndrome)
- Prolonged pulmonary infiltrates with eosinophilia (PIE syndromes)
- Tropical pulmonary eosinophilia (TPE)
- Bronchiectasis
- Cystic fibrosis

Endocrinologic Disorders

- Addison disease

Gastrointestinal Diseases

- Inflammatory bowel disease (IBD)
- Eosinophilic gastroenteritis, eosinophilic esophagitis (EE)
- Allergic gastroenteritis (young children)
- Celiac disease (when associated with EE)

Toxic Reactions to Ingested Agents

- Eosinophil myalgia syndrome (L-tryptophan)
- Toxic oil syndrome

Reactions to Cytokine Therapies

- IL-2 and IL-2 plus lymphokine-activated killer (LAK) cells
- GM-CSF for chemotherapy-induced neutropenia

Cutaneous Disorders

- Atopic dermatitis
- Immunologic skin diseases
- Scabies
- Eosinophilic cellulitis (Wells syndrome)
- Episodic angioedema with eosinophilia
- Chronic idiopathic urticaria
- Bullous pemphigoid
- Herpes gestationis

Immunodeficiency Syndromes

- Wiskott-Aldrich syndrome
- Selective IgA deficiency with atopy
- Hyper-IgE recurrent infection syndrome (Job syndrome)
- Swiss-type and sex-linked combined immunodeficiency
- Nezelof syndrome
- Graft-versus-host disease (GVHD)

Connective Tissue Diseases

- Vasculitis or collagen vascular disorders
- Hypersensitivity vasculitis
- Allergic granulomatosis with angiitis (Churg-Strauss syndrome)
- Serum sickness
- Eosinophilic fasciitis
- Sjögren syndrome
- Rheumatoid arthritis (severe)

Neoplastic and Myeloproliferative Diseases and Syndromes

- Ovarian carcinoma
- Solid tumors (mucin secreting, epithelial cell origin)
- Eosinophilic leukemia
- Idiopathic hypereosinophilic syndrome (HES)
- Systemic mastocytosis
- Lymphomas (T cell, Hodgkin)
- Chronic myelogenous leukemia, acute myelogenous leukemia, MDS (myelodysplastic syndrome)
- T-cell lymphocytic leukemia
- Myelomonocytic leukemia with bone marrow eosinophilia (M4Eo, inversion 16)
- Angioimmunoblastic lymphadenopathy
- Angioblastic lymphoid hyperplasia (Kimura disease)

Rare Causes

- Chronic active hepatitis
- Chronic dialysis
- Acute pancreatitis
- Postirradiation
- Hypopituitarism

CSF, Cerebrospinal fluid; *GM-CSF,* granulocyte-macrophage colony-stimulating factor; *HIV,* human immunodeficiency virus; *Ig,* immunoglobulin; *IL,* interleukin.

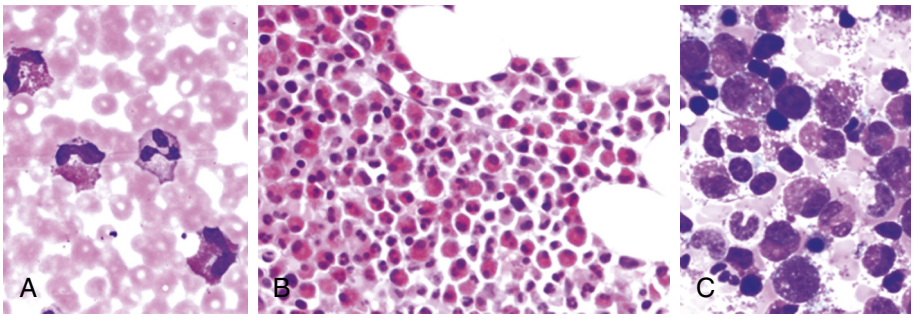

FIG. E1 Hypereosinophilic syndrome. The illustration is from the case of a 38-yr-old woman who was found to have a marked eosinophilia when she presented with headaches, nausea, and vomiting. The white blood cell count was 16,900/μl, with 36% eosinophils **(A).** The bone marrow was hypercellular and showed sheets of eosinophils **(B).** On the aspirated material **(C),** eosinophils and eosinophilic precursors accounted for more than 70% of the cells. The patient had no obvious infectious process and no allergies. There was no malignancy associated with eosinophilia, such as T-cell lymphoma, Hodgkin lymphoma, or other myeloid disease. Peripheral blood lymphocyte phenotyping showed no abnormal T-cell subset. Cytogenetic analysis showed a normal female karyocyte, and fluorescence in situ hybridization analysis for del 4q12 showed no deletion of CHIC2. (From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Hyperglycemic hyperosmolar syndrome (HHS) is a life-threatening complication of diabetes mellitus characterized by marked hyperglycemia, dehydration, and hyperosmolality with or without mental obtundation, in the absence of significant ketoacidosis.

SYNONYMS

HHS
Hyperosmolar hyperglycemic syndrome
Diabetic hyperosmolar syndrome
Hyperglycemic hyperosmolar nonketotic syndrome
Hyperglycemic hyperosmolar nonketotic coma
Hyperosmolar hyperglycemic state
Nonketotic hyperosmolar syndrome

ICD-10CM CODES

E08.00	Diabetes mellitus due to underlying condition with hyperosmolarity without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)
E08.01	Diabetes mellitus due to underlying condition with hyperosmolarity with coma
E09.00	Drug or chemical induced diabetes mellitus with hyperosmolarity without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)
E09.01	Drug or chemical induced diabetes mellitus with hyperosmolarity with coma
E11.00	Type 2 diabetes mellitus with hyperosmolarity without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)
E11.01	Type 2 diabetes mellitus with hyperosmolarity with coma
E13.00	Other specified diabetes mellitus with hyperosmolarity without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)
E13.01	Other specified diabetes mellitus with hyperosmolarity with coma

EPIDEMIOLOGY & DEMOGRAPHICS

HHS is a rare condition that most commonly affects patients with type 2 diabetes mellitus. Approximately 20% of patients have no history of diabetes. Elderly individuals with new-onset diabetes or those with poorly controlled type 2 diabetes predisposed to extracellular fluid volume depletion (so-called dehydration) are at increased risk for HHS. Mortality from HHS is estimated at 5% to 20%, a greater mortality rate than for diabetic ketoacidosis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Polyuria, polydipsia, weight loss, weakness
- Mental status changes that can range from full alertness to coma
- Focal neurologic signs (e.g., hemiplegia, hemianopsia) or seizures (focal or generalized), aphasia, visual hallucinations
- Symptoms of coexisting illnesses or comorbidities that may have precipitated the event
- Signs of extracellular fluid volume depletion, including dry mucous membranes, poor skin turgor, sunken eyes, hypotension, and tachycardia
- Normothermia or hypothermia despite the presence of infection, due to peripheral vasodilation

ETIOLOGY

HHS can be precipitated by various conditions:

- Infection (most common precipitant)
- Insulin deficiency (undiagnosed diabetes, inadequate insulin, or medication nonadherence)
- Inflammatory conditions (e.g., acute pancreatitis, acute cholecystitis)
- Ischemia/infarction (e.g., myocardial infarction, stroke, bowel ischemia)
- Kidney failure
- Severe dehydration (e.g., burns, heatstroke)
- Drugs (e.g., steroids, thiazides, atypical antipsychotics, sympathomimetics including cocaine, alcohol, pentamidine)

A relative insulin deficiency provides enough insulin to inhibit ketogenesis but is insufficient to inhibit hepatic gluconeogenesis, glycogenolysis, or peripheral glucose uptake, with consequent hyperglycemia. With underlying illness, counterregulatory hormone excess leads to further blood glucose elevation. The resultant extreme hyperglycemia leads to osmotic diuresis. If adequate hydration is not maintained, dehydration and worsening renal function ensue. Diminished renal filtration further impairs glucose excretion, thus exacerbating the hyperglycemia, dehydration, and hyperosmolality.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diabetic ketoacidosis
- Stroke (especially in the elderly with neurologic abnormalities)
- Hypovolemic or septic shock
- Encephalopathy

WORKUP

After the initial history is obtained, perform a physical exam that includes immediate evaluation of airway, breathing, circulation, mental status, volume status, and signs suggestive of precipitating event including infection, myocardial infarction, or stroke.

LABORATORY TESTS

- Hyperglycemia: Blood glucose >600 mg/dl (Box 1)
- Serum osmolality: >320 mOsm/kg, typically
- Complete metabolic panel, including serum creatinine, blood urea nitrogen (BUN), electrolytes, glucose
- Serum sodium: May be low, normal, or high. Hyperglycemia increases plasma osmolality that translocates intracellular water to the extracellular compartment, decreasing serum sodium. Serum sodium can be corrected by adding 1.6 mmol/L to the measured serum sodium for each 100 mg/dl rise in serum glucose above 100 mg/dl. Marked osmotic diuresis induced by hyperglycemia may cause the serum sodium level to be normal or high
- Serum potassium and phosphate: Total body potassium and phosphate deficits typically occur due to urinary losses from osmotic diuresis. However, these levels may be acutely normal or high due to extracellular shift secondary to insulin deficiency and hyperosmolality
- Anion gap and serum lactate: Anion gap may be normal or elevated in the setting of lactic acidosis
- Arterial blood gas: pH >7.3
- Serum and urine ketones: Negative or small
- Serum bicarbonate: >15 mmol/L
- Hemoglobin A_{1c} (if not performed in past 3 mo)
- Complete blood count with differential (may indicate presence of underlying infection [leukocytosis >25,000 mm^3], inflammatory condition, hemoconcentration. A leukocytosis of 10,000 to 15,000 mm^3 is expected from the stress of illness alone)
- Urinalysis, urine/sputum/blood cultures as indicated based on physical exam findings to evaluate the precipitating illness and other comorbidities

IMAGING STUDIES

ECG, chest radiograph, and other imaging studies as indicated to evaluate the precipitating causes

BOX 1 Diagnostic Testing Criteria for Patients with Hyperglycemic Hyperosmolar State

Glucose higher than 600 mg/dl
Normal pH (classically, however, patients are often mildly acidotic)
No significant ketosis*
Serum osmolarity
- >320 mOsm/L with any mental status changes, *or*
- >350 mOsm/L

*Serum acetoacetate is often present, typically an absent or low β-hydroxybutyrate level.
From Adams JG et al (eds): *Emergency medicine: clinical essentials,* ed 2, Philadelphia, 2013, WB Saunders.

Rx TREATMENT

ACUTE GENERAL Rx Aggressive fluid resuscitation, intravenous insulin, and electrolyte correction are the mainstays of treatment. Patients with HHS are very ill, and many are elderly. Elderly patients may require slower correction of osmolality to limit cerebral edema.

AGGRESSIVE INTRAVENOUS FLUID REPLACEMENT: Due to trivial ketonemia and the insulin sensitivity of most HHS patients, initial treatment is intravenous fluid alone without insulin. Insulin used prior to intravenous hydration or early in resuscitation risks a precipitous drop in serum osmolality. In the absence of cardiac compromise or end-stage renal disease, infuse 0.9% normal saline (NS) at an initial rate of 1 L/h. A lower rate of 250 to 500 ml/hr may be adequate in the absence of severe dehydration. If the corrected serum sodium is elevated, 0.45% NS may be infused instead. Reassess corrected sodium needs by frequent checks and calculation. Recommended sodium decline is 0.5 mmol/L/hr and should not surpass 10 to 12 mmol/L per day. Use measured or calculated osmolality to guide the rate of fluid resuscitation for gradual normalization of osmolality. Once serum glucose decreases to 300 mg/dl, change the intravenous fluid to 5% dextrose with 0.45% NS at 150 to 250 ml/hr.

INSULIN: Once glucose is no longer significantly improving with fluids alone, reassess patient's fluid status and initiate intravenous insulin. Administer initial bolus of intravenous regular insulin 0.1 units/kg followed by 0.1 units/kg/hr infusion or a continuous infusion of 0.14 units/kg/hr without initial bolus. If serum glucose declines by less than 50 to 75 mg/dl in the first hour, increase the insulin infusion rate. Once the serum glucose reaches 300 mg/dl, decrease the insulin infusion rate to 0.02 to 0.05 units/kg/hr to maintain serum glucose between 200 to 300 mg/dl until resolution of HHS.

POTASSIUM REPLACEMENT: Insulin therapy shifts potassium intracellularly, frequently causing hypokalemia. If serum potassium at presentation is between 3.3 and 5.2 mmol/L, infuse 20 to 30 mmol of potassium chloride (KCl) with each liter of intravenous fluid to maintain serum potassium between 4 and 5 mmol/L. If the serum potassium concentration at presentation is <3.3 mmol/L, replace potassium by administering KCl infusion at 20 to 30 mmol/h, and withhold insulin until the serum potassium concentration is >3.3 mmol/L. If the serum potassium at presentation is >5.2 mmol/L, monitor serum potassium level every 2 hours without intravenous potassium supplementation.

PHOSPHORUS AND MAGNESIUM REPLACEMENT:

- Phosphorus and magnesium replacement are not routinely recommended. There are no studies of the utility of phosphate administration during treatment of HHS. Very low phosphorus levels may limit adenosine triphosphate (ATP) generation, thus limiting adequate diaphragm function. In patients with cardiac dysfunction, respiratory depression, or anemia and serum phosphate <1 mg/dl, add 20 to 30 mmol/L potassium phosphate to intravenous fluids.
- Monitor serum glucose hourly and serum electrolytes, BUN, and creatinine every 2 to 4 hours until resolution of HHS.

TRANSITION TO SUBCUTANEOUS INSULIN: Normalization of serum osmolality and mental status indicates resolution of HHS. At this point, a transition to subcutaneous insulin should be performed. Overlap the initiation of subcutaneous intermediate- or long-acting insulin and discontinuation of intravenous insulin by 2 to 4 hours to ensure adequate insulin levels and prevent rebound hyperglycemia. In patients with a known history of diabetes, their home insulin regimen may be initiated if adequate prior to presentation. In patients with poorly controlled diabetes, the subcutaneous insulin dose can be determined based on their stable insulin drip requirement. Insulin-naive patients may be started on basal-bolus insulin therapy either by calculation of total daily dose of 0.5 to 0.8 units/kg (split as half-basal and half-bolus; administer one-third total bolus for each meal) or by their individual stable insulin drip requirements. Further subcutaneous insulin dose titration is based on subsequent blood glucoses. Resolution of glucotoxicity and inciting condition(s) will decrease insulin requirements. The underlying infection/inflammatory condition or precipitating event must be adequately treated.

CHRONIC THERAPY: Most patients will need insulin at discharge, at least short term. Patients whose diabetes was previously well controlled on oral agents may resume oral therapy after blood glucose stabilization by insulin.

DISPOSITION Most patients require management in an emergency care setting, such as the intensive care unit or in a step-up facility.

PEARLS & CONSIDERATIONS

COMMENTS

- When patients with ESRD experience development of HHS, special management considerations are needed. Aggressive fluid resuscitation is unnecessary in anuric ESRD patients, because most patients cannot produce the osmotic diuresis associated with normal kidney function. Note that urinary potassium and phosphorus losses will not occur, thereby limiting the need for supplementation. Lower continuous insulin infusion rates are required in ESRD patients because of decreased insulin clearance. Hemodialysis is typically delayed until serum glucoses are corrected. Precipitous decreases in serum glucose from insulin administration and hemodialysis may result in rapid shifts in tonicity, predisposing cerebral edema.
- Education of the patient, family, and caregivers at chronic care facilities regarding optimal glycemic control, limiting modifiable risk factors for HHS, and prevention of dehydration is paramount.

AUTHORS: **Jessica E. Shill, MD,** and **Stanley Linder, DO**

BASIC INFORMATION

DEFINITION

- Hyperhidrosis is the excessive production of sweat beyond the body's physiologic need for thermoregulation.
- There are two types of hyperhidrosis: primary and secondary. Primary hyperhidrosis is the idiopathic, bilateral, and symmetric sweating from focal areas. Secondary hyperhidrosis is either generalized or focal excessive sweating due to an underlying cause (e.g., diet, medication, or medical condition).
- Primary hyperhidrosis affects many aspects of daily life, which can be detrimental to emotional well-being, self-esteem, interpersonal relationships, as well as work and productivity. Despite this, only one third of those affected consult a physician about their problem. Primary care physicians are essential in the initial diagnosis and treatment of this condition. Early detection and treatment can significantly improve a patient's quality of life, with treatment efficacy between 90% and 95%.

SYNONYM

Excessive perspiration

ICD-10CM CODES

L74.513 Primary hyperhidrosis
L74.52 Secondary focal hyperhidrosis

EPIDEMIOLOGY & DEMOGRAPHICS

According to recent epidemiologic data, hyperhidrosis affects approximately 4.8% of the U.S. population (15.3 million people), and prevalence in both genders is approximately equal. However, women are more likely to discuss the condition with their physician.

PEAK INCIDENCE: The average age of onset is 25 yr.

PREVALENCE: The condition is most common among people aged 25 to 64 yr.

PREDOMINANT SEX AND AGE: Equal proportions male and female.

GENETICS: Unknown.

RISK FACTORS: None known for primary, but secondary has numerous causes (see Table 1).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History:
  1. Pattern of sweating: Frequency, stress exacerbation, volume, duration, body areas involved, symmetry, triggers, and presence or absence during sleep
  2. Impact on daily life
  3. Family history
  4. Medications that could induce sweating
  5. Excessive intake of coffee or other stimulants
  6. Review of systems to evaluate for systemic disease: Fever; weight loss; anorexia; palpitations; other signs of thyroid, malignant, or neurologic diseases
- Physical examination: Evidence of excessive sweating and location on patient's body

DIAGNOSIS

The initial diagnostic step is to evaluate whether the patient's symptoms represent primary or secondary hyperhidrosis.

- Primary: Greater than 90% of cases are primary. Criteria for diagnosis include focal and visible excessive sweating for greater than 6 months without any apparent cause, as well as at least two of the following:
  1. Impairment of daily activities
  2. Bilateral and symmetric sweating (axilla [most common], palms, soles, face, or scalp)
  3. Occurrence at least once per week
  4. Onset younger than 25 yr
  5. No abnormal nocturnal sweating
  6. Positive family history

  NOTE: If four criteria are met, the discrimination between primary and secondary increases (positive predictive value, 0.99; negative predictive value, 0.85)
- Secondary: Less than 10% of cases but with numerous underlying causes, which can be divided between focal and generalized sweating patterns.

Focal:

- Neurologic (neuropathy, spinal injury, Horner syndrome, Arnold-Chiari malformation)
- Gustatory sweating after eating spicy foods

Generalized:

- Medications (cholinergic agents, selective serotonin reuptake inhibitors/serotonin–norepinephrine reuptake inhibitors, selective estrogen receptor modulators, insulin, sulfonylureas, niacin, sildenafil, etc.)
- Toxicity (recreational drugs, alcohol, drug/alcohol withdrawal)
- Endocrine (hypoglycemia, hyperthyroidism, hyperpituitarism, pheochromocytoma, menopause, pregnancy, acromegaly)
- Neurologic (Parkinson disease, cerebrovascular accident)
- Malignancy (lymphoma, carcinoid)
- Psychiatric (panic attack, social anxiety, generalized anxiety disorder)
- Cardiopulmonary (acute respiratory failure, congestive heart failure, chronic obstructive pulmonary disease, myocardial infarction)
- Infection and fever
- Table 1 summarizes all causes of hyperhidrosis

TABLE 1 Causes of Hyperhidrosis

Cortical
Emotional
Familial dysautonomia
Congenital ichthyosiform erythroderma
Epidermolysis bullosa
Nail-patella syndrome
Jadassohn-Lewandowsky syndrome
Pachyonychia congenita
Palmoplantar keratoderma
Stroke

Hypothalamic
Drugs:
Alcohol
Antipyretics
Cocaine
Emetics
Insulin
Opiates (including withdrawal)
Ciprofloxacin
Exercise

Infection:
Defervescence
Chronic illness

Metabolic:
Carcinoid syndrome
Debility
Diabetes mellitus
Hyperpituitarism
Hyperthyroidism
Hypoglycemia
Obesity
Pheochromocytoma
Porphyria
Pregnancy
Rickets
Infantile scurvy

Cardiovascular:
Heart failure
Shock
Vasomotor
Cold injury
Raynaud phenomenon
Rheumatoid arthritis

Neurologic:
Abscess
Familial dysautonomia
Postencephalitic
Tumor

Miscellaneous:
Chédiak-Higashi syndrome
Compensatory
Lymphoma
Phenylketonuria
Vitiligo
Frey syndrome

Medullary
Physiologic gustatory sweating
Encephalitis
Granulosis rubra nasi
Syringomyelia
Thoracic sympathetic trunk injury

Spinal
Cord transection
Syringomyelia

Changes in Blood Flow
Maffucci syndrome
Arteriovenous fistula
Klippel-Trénaunay syndrome
Glomus tumor
Blue rubber-bleb nevus syndrome

From Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

Hyperhidrosis

DIFFERENTIAL DIAGNOSIS

- Primary hyperhidrosis
- Fever
- Anxiety disorder
- Heart attack
- Hyperthyroidism
- Hypoglycemia
- Malignancy
- Menopause
- Heat exposure
- Obesity

WORKUP

No further workup is necessary to diagnose primary hyperhidrosis; secondary hyperhidrosis will require more specific testing to evaluate the underlying cause.

LABORATORY TESTS

There are no specific laboratory tests for primary hyperhidrosis. Underlying causes of secondary hyperhidrosis might dictate further laboratory workup.

IMAGING STUDIES

None

Rx TREATMENT

- Primary hyperhidrosis:
  1. Topical:
     a. Aluminum chloride 20% to 25% (first line in mild cases) can produce mild localized burning at application sites.
     b. Glycopyrronium cloth (Qbrexza) is a premoistened cloth containing the long-acting anticholinergic agent glycopyrronium. It is applied once daily for the treatment of excessive underarm sweating (primary axillary hyperhydrosis). It is an expensive alternative first-line treatment useful in severe cases.
     c. Aldehyde agents (formaldehyde, glutaraldehyde) can cause allergic sensitization and localized skin irritation.
  2. Botulinum toxin A injection (first line in severe cases) is safe and effective but expensive; preferred option for axillary hyperhidrosis.
  3. Systemic treatments (oral anticholinergics, beta-blockers, clonazepam).
- Secondary hyperhidrosis:
  1. Diagnose and treat the underlying condition.

NONPHARMACOLOGIC THERAPY

- Electrical current (iontophoresis): Introduction of charged ions into skin to disrupt eccrine gland secretion
- Microwave therapy: Destroys eccrine glands through cellular thermolysis
- Surgery (endoscopic sympathectomy): Destruction of the sympathetic ganglia innervating areas of excessive sweating

DISPOSITION

Hyperhidrosis is a chronic medical condition that will need long-term treatment with either topical medications, oral medications, or surgical intervention. Discuss with the patient which treatment option is best for the patient.

REFERRAL

If initial treatments are ineffective, referral to a dermatologist can be considered.

SUGGESTED READINGS

Available at ExpertConsult.com

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SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Abnormal elevation of potassium (K^+) in the blood associated with either normal or altered total body stores of potassium. Normal K^+ level in the blood is 3.5 to 5.0 milliequivalents per liter (mEq/L). Hyperkalemia can be defined as mild (levels 5.1 to 6.0 mEq/L), moderate (levels 6.0 to 7.0 mEq/L), and severe (levels >7.0 mEq/L). Levels higher than 7 mEq/L can lead to significant hemodynamic and neurologic consequences, whereas levels exceeding 8.5 mEq/L can cause respiratory paralysis or cardiac arrest and quickly be fatal.

SYNONYM

High potassium

ICD-10CM CODE
E87.5 Hyperpotassemia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE & PREVALENCE:

- Overall incidence and prevalence of hyperkalemia is unknown. The rate is low in uncomplicated hypertensives on the inhibitors of renin-angiotensin-aldosterone system (RAASi), but it rises in the setting of other comorbidities listed below.
- Rarely detected in the general population, it is seen in only 2.6% of emergency room visits and 3.5% of hospital admissions in a Canadian study, with similar results in two U.S. studies.
- Chronic kidney disease (CKD) patients are most prevalent at 10%. Increased risk depends on the underlying conditions present. Is also seen with end-stage kidney disease (ESKD), acute kidney injury (AKI), cardiovascular disease (CVD), diabetes mellitus (DM), or metabolic acidosis (especially associated with non-gap inorganic acidosis), and on medications such as RAASi and mineralocorticoid receptor inhibitors (MRA) and other potassium-sparing diuretics.
- The prevalence of ICD-10 diagnosis for hyperkalemia was found to be very low (14.6%).

PREDOMINANT SEX & AGE:

- More common with increasing age due to increased prevalence of etiological factors such as CKD, DM, CVD, and concomitant use of medications that predispose to hyperkalemia.
- Lower socioeconomic groups also have an increased prevalence, where monitoring of drug therapy and control of DM and hypertension are often inadequate.

GENETICS: Other syndromes that may be associated with hyperkalemia include:

- Pseudohypoaldosteronism type II (familial hyperkalemic hypertension, also known as Gordon syndrome):
  1. Rare inherited form of hyperkalemia characterized by hypertension, hyperchloremic metabolic acidosis, and hyperkalemia with normal GFR.
  2. Mutations of several genes can be seen affecting sodium, potassium, and chloride transport in the tubule of the kidney.
  3. All forms respond to treatment with thiazide-like diuretics.
- Hyperkalemic periodic paralysis:
  1. Autosomal dominant mutation resulting in flaccid generalized weakness and hyperkalemia
- Glomerulopathy with fibronectin deposits (GFND):
  1. Autosomal dominant disorder manifested by proteinuria, hypertension, and type IV RTA
- Disorders of steroid metabolism and mineralocorticoid receptors:
  1. 21-hydroxylase deficiency and aldosterone synthase deficiency both associated with low aldosterone levels
- Congenital hypoaldosteronism:
  1. Autosomal recessive mutation associated with low aldosterone and salt wasting
  2. Increased serum ratio of 18-hydroxycorticosterone-to-aldosterone
- Nephronophthisis:
  1. Manifested by enlargement of kidneys, inflammatory portal fibrosis, and development of ESKD. Results in progressive interstitial fibrosis and tubulopathy.
- Disorders of chloride homeostasis:
  1. Autosomal recessive mutation causing isolated hyperchlorihidrosis with excessive salt wasting in sweat resulting in severe hyponatremic dehydration and hyperkalemia.

RISK FACTORS: Primary risk factor is CKD, especially if eGFR is <45 ml/min/1.73m^2 more commonly associated with diabetes mellitus type 1 or 2, or urinary tract obstruction with obstructive nephropathy (especially if associated with chronic interstitial nephritis).

Medications associated with hyperkalemia:

- Potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride, eplerenone)
- Nonsteroidal antiinflammatory drugs (NSAIDs)
- Angiotensin-converting enzyme inhibitors (ACEIs)
- Angiotensin receptor blockers (ARBs)
- Direct renin inhibitors
- Calcineurin inhibitors (cyclosporine and tacrolimus)
- Pentamidine
- Digoxin (toxicity especially in CKD)
- Trimethaphan-sulfamethoxazole
- Heparin
- Ketoconazole
- Metyrapone
- Herbs

Clinical risk factors:

- Male sex
- Non-black
- DM
- CVD
- CHF
- AKI
- CKD
- Acidosis (nonorganic)
- Urinary obstruction

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Most patients presenting with hyperkalemia are asymptomatic, with the abnormal laboratory study discovered inadvertently. The symptoms when present are nonspecific and mostly related to muscular or cardiac dysfunction.

- Muscle paralysis
- Dyspnea
- Palpitations
- Chest pain
- Nausea or vomiting
- Paresthesias

The physical exam typically does not alert the physician to a diagnosis of hyperkalemia, other than bradycardia, if present, or muscle tenderness accompanied by muscle weakness, suggesting rhabdomyolysis. Flaccid paralysis and/or depressed or absent deep tendon reflexes may be present.

ETIOLOGY

- Potassium is maintained in a narrow range of normal (3.8 to 5.0 mEq/L) by redundant and highly efficient homeostatic mechanisms that simultaneously control internal K^+ redistribution while regulating net K^+ excretion especially in the face of increased K^+. When a defect occurs in one or both of these two processes, a net rise in extracellular K^+ concentration occurs, resulting in hyperkalemia. We often see a blunting of the redistribution process with insulin deficiency, decrease in aldosterone production or action, decreased adrenergic activity, and osmolar disturbances associated with an increase in extracellular osmolality such as with hyperglycemia.
- The kidney is responsible for most of the regulation of potassium absorption and excretion (95%), which is dependent on the functional renal mass, thus the prominent association with CKD and reduced renal mass. Kidney failure or failure of the renal tubule to augment K^+ secretion plays a role in the maintenance of hyperkalemia. The importance of cell shifts is illustrated by the observation that if only 2% of potassium is shifted out of the cells to the extracellular fluid, it would raise the level from 4 mEq/L to 8 mEq/L, which would be critical.
- CKD is the single most important condition predisposing to hyperkalemia due to progressively decreasing GFR (falling clearance) and development of tubulointerstitial dysfunction (lower tubular secretion). Patients with progressive CKD are commonly associated with CVD, DM, HBP, and proteinuria, and they therefore are instructed to consume a diet very low in sodium, typically associated with a higher potassium intake. Low-sodium diets may be compensated for by an increase in salt-substitute intake, in many cases without the patients realizing that potassium chloride may further increase potassium intake. Another condition not uncommonly associated with CKD acutely increasing the risk of hyperkalemia is AKI, which, in addition to acutely reducing the capacity of the kidney to excrete a potassium load, can be associated

with an acute potassium load, especially if in the presence of tissue breakdown (e.g., rhabdomyolysis), gastrointestinal bleeding, or transfusions with outdated blood. Metabolic acidosis commonly acutely worsens in AKI, facilitating shift of potassium out of cells. These processes can often result in the development of severe and life-threatening hyperkalemia.

- DM (characterized by insulin deficiency and hypertonicity when uncontrolled, both of which shift potassium out of cells) and CVD (especially myocardial infarctions, left ventricular hypertrophy, and congestive heart failure, often associated with various pharmacologic interventions that may induce or worsen hyperkalemia). CVD often clusters with CKD and hence their concomitant presence may contribute to a higher prevalence of hyperkalemia. Among the relevant CVD medications, recall that β_2-2 receptor blockers inhibit renin production (decreasing ability of potassium to shift into cells); heparin inhibits aldosterone production (decreasing ability to excrete a potassium load); and digitalis impairs potassium excretion (by blocking Na-K-ATPase, which is important in potassium secretion by the tubule). The magnitude of impact on potassium by these medications, however, is limited, typically in the range of ~0.2 to 0.5 mEq/L. A much more relevant class is RAASi and potassium-sparing diuretics (Amiloride), with hyperkalemia seen in <2 % of patients without CKD, increasing to 5% with dual RAASi therapy, and up to 10% in the presence of CKD (especially stages >3b). In those patients at risk for hyperkalemia, it is recommended not to use dual RAASi therapy and to be very cautious with the use of RAASi and MRA.
- Congestive heart failure (CHF). Almost 4 out of 10 CHF patients in a population-based cohort study in Denmark developed hyperkalemia, many with recurrent episodes. Hyperkalemia risk was strongly associated with stage of CKD and use of spironolactone especially in addition to a renin-angiotensin system blocking medication.

TABLE 1 Differential Diagnosis of Hyperkalemia

- Pseudohyperkalemia
- Cellular redistribution from intra- to extracellular space
  1. Mineral acid acidosis (not endogenous organic acidosis)
     a. Hyperkalemia inhibits ammoniagenesis, reducing net acid secretion and compounding metabolic acidosis
  2. Hypertonicity (hyperglycemia, sucrose, mannitol)
  3. DM: Insulin deficiency
  4. Hyperkalemic periodic paralysis
  5. β2-adrenergic antagonists
  6. α-adrenergic agonists
  7. Drugs
     a. Glucagon
     b. Digoxin overdose
     c. Aminocaproic acid-A
     d. Tetrodotoxin
     e. Succinyl choline
  8. Rebound after labile
  9. Extreme exercise
  10. Crush and tissue injury
     a. Rhabdomyolysis
     b. Hemolysis
     c. Tumor lysis syndrome
- Decreased renal excretion
  1. CKD
     a. Use of nonsteroidal antiinflammatory drugs (NSAIDs)
  2. ESKD
  3. Type 4 renal tubular acidosis
     a. Diabetes mellitus
     b. Obstructive nephropathy
     c. Amiloride
     d. Trimethoprim
     e. Pentamidine
     f. Suxamethonium
     g. Volume depletion
     h. HIV infections
- Excess intake (rare except in advanced CKD or ESKD)
  1. Salt substitute (typically KCl)
  2. Potassium-enriched foods (melons, citrus juice, raw coconut juice has 44.3 mEq/L [44.3 mmol/L], noni juice has 56 mEq/L [56 mmol/L] K)
  3. River bed clay (red clay) very enriched, with 100 mEq K/100 g clay
- Mineralocorticoid deficiency (Addison disease)
  1. Hypoaldosteronism: Primary or secondary
  2. HIV infection
- Defect of tubular function or voltage defect resulting in hyperkalemia and hypertension:
  1. Genetic
     a. Pseudohyperaldosteronism type 2
- Also known as familial hyperkalemic hypertension or Gordon syndrome
  1. Acquired
     a. Calcineurin inhibitors (tacrolimus and cyclosporine)

CKD, Chronic kidney disease; *DM,* diabetes mellitus; *ESKD,* end-stage kidney disease; *KCl,* potassium chloride.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Hyperkalemia develops due to three mechanisms: redistribution, decreased secretion, and increased intake. (In the presence of normal renal and adrenal function, it is very difficult to ingest enough potassium to become hyperkalemic, so hyperkalemia is rarely seen in people without advanced CKD.) The differential diagnosis is listed in Table 1.

WORKUP

Fig. 1 illustrates a clinical approach to hyperkalemia. The following steps should be followed in the workup of hyperkalemia:

- R/O pseudohyperkalemia: An in vitro phenomenon caused by mechanical release of potassium from cells during phlebotomy or specimen processing. This may be seen with severe leukocytosis (>70,000/cm^3 or thrombocytosis (platelet count >500,000 cm^3), severe fist clenching during phlebotomy, prolonged application of a tight tourniquet, and use of a small-bore needle. The diagnosis is made when serum potassium concentration exceeds the plasma potassium concentration by >0.5 mEq/L (>0.5 mmol/L). Contamination with potassium EDTA in certain tubes can spuriously increase plasma potassium concentration accompanied by a very low plasma calcium concentration.
- If no predisposition to hyperkalemia, repeat the blood test before taking action, unless ECG changes are present.
- Perform an ECG to look for the hallmark changes seen with hyperkalemia, which commonly have a sequential progression that historically seemed to correlate with the potassium level, if present. Some studies seem to indicate inconsistent findings of the ECG in hyperkalemia, especially with K^+ levels <6.5 mEq/L and more predictive at levels >7.2 to 9.4 mEq/L.
  1. Early ECG changes seen with serum potassium level of 5.5 to 6.5 mEq/L: Peaked T waves (Fig. E2), especially in the precordial leads; shortened QT interval; and occasionally ST segment depression.
  2. K >6.5 mEq/L: Widening of the QRS complex (nonspecific intraventricular conduction delay [IVCD]) of >120 milliseconds that does not meet the criteria for right or left bundle branch block. If you see an IVCD, think hyperkalemia. May also see amplified R waves.

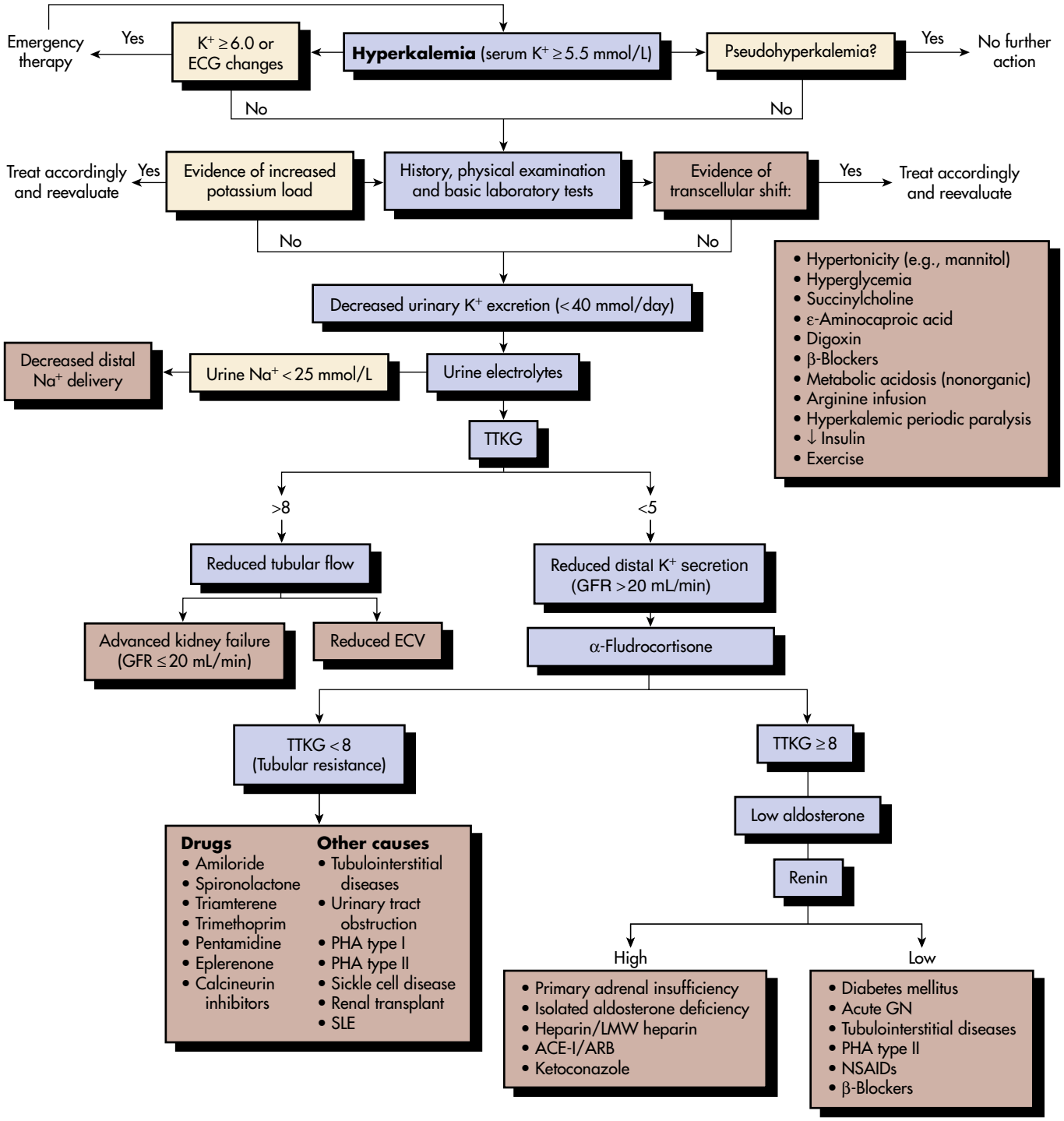


FIG. 1 Clinical approach to hyperkalemia. *ACE-I,* Angiotensin-converting enzyme inhibitor; *ARB,* angiotensin II receptor blocker; *CCD,* cortical collecting duct; *ECG,* electrocardiogram; *ECV,* effective circulatory volume; *GFR,* glomerular filtration rate; *GN,* glomerulonephritis; *HIV,* human immunodeficiency virus; *LMW heparin,* low-molecular-weight heparin; *NSAID,* nonsteroidal antiinflammatory drug; *PHA,* pseudohypoaldosteronism; *SLE,* systemic lupus erythematosus; *TTKG,* transtubular potassium gradient. (From Skorecki K et al: *Brenner & Rector's the kidney,* ed 10, Philadelphia, 2016, Elsevier.)

3. K >7 mEq/L: Associated with decreased amplitude of P waves with increase in PR interval and development of bradycardia, which is associated with atrioventricular blocks.
4. K >8.0 mEq/L: Develops absence of P waves and the progressively widened QRS eventually merges with the T waves, forming a sine wave pattern followed by ventricular fibrillation or asystole.

In hemodialysis patients with hyperkalemia, T wave "tenting" was nonpredictive of serum K^+ level, especially in the elderly and diabetics. There have even been case reports of severe hyperkalemia with no ECG changes.

- Look for the symptoms or physical findings noted above and then do the basic studies:
  1. ECG
  2. Urine potassium, sodium, and osmolality
  3. Complete blood count and platelet count
  4. Basic metabolic profile with a calculated estimated GFR (eGFR) (CKD alone should

not develop hyperkalemia until eGFR is <20 to 25 ml/min.)

5. Depending on the history and results of the initial blood tests, the following may be indicated:
   a. Glucose to r/o hypertonicity in uncontrolled diabetics
   b. Digoxin level if patient is on digoxin
   c. Arterial or venous blood gas if acidosis is suspected
   d. Urinalysis if renal insufficiency is present to r/o AKI or acute glomerulonephritis
   e. Serum cortisol and aldosterone levels to check for deficiency when other causes are eliminated
   f. Serum uric acid and phosphorus to r/o tumor lysis syndrome
   g. Serum creatinine phosphokinase (CPK) and calcium measurements for rhabdomyolysis
   h. Urine myoglobin test (if you see a very + dipstick of urine for blood and no RBCs, be suspicious of this) for crush injury and rhabdomyolysis

- Accurately assess kidney function with a serum creatinine and calculated GFR to define the risk of hyperkalemia as well as the acid base status, especially identifying the presence of a non-anion gap mineral metabolic acidosis.
- Look for the presence of a non-anion gap mineral metabolic acidosis associated with the hyperkalemia typically diagnosing a type 4 RTA. This is typically seen with a hyporeninemic hypoaldosterone state (seen in diabetic nephropathy of chronic interstitial nephropathy) or obstructive nephropathy.
- Determine the presence of a renal origin for hyperkalemia using the urine potassium concentration.

This will determine the presence of a renal tubule dysfunction in a hyperkalemic patient. There are four types of urine chemistry analysis available to determine this: (1) Urine potassium (K) concentration, (2) the fractional excretion of potassium, (3) the urine potassium/creatinine ratio, and (4) the "transtubular potassium gradient" (TTKG). See Table 2 for the expected values of each in both renal and nonrenal causes of hyperkalemia.

LABORATORY TESTS

- Serum electrolytes, BUN, and creatinine
- Urinalysis and urine protein–creatinine ratio
- Serum and plasma potassium
- Plasma and urine osmolality
- Serum and urine creatinine
- Cortisol level
- Aldosterone level
- 18-hydroxycorticosterone

IMAGING STUDIES

- Ultrasound of the kidneys and bladder
- CT scan of the abdomen

Rx TREATMENT

- Supportive measurements such as fluids, pacing, and pressers do not work in the setting of hyperkalemia. In acute, severe, life-threatening hyperkalemia, the approach is divided into two components. First stabilize the myocardium to prevent a fatal arrhythmia. Giving IV calcium is cardioprotective in the setting of hyperkalemia, commonly reversing all hyperkalemic ECG changes within seconds of administration. However, it does not decrease the potassium levels; therefore, other therapies are needed to reduce the potassium level.
- Before giving calcium, make sure digoxin toxicity is not present, as calcium administration can be fatal in the face of digoxin-induced hyperkalemia.
- The aggressiveness of the treatment should be directly related to the rapidity with which the hyperkalemia developed, the absolute level of the potassium, and the evidence of toxicity by symptoms and/or examination and ECG changes. The more rapid the rise in potassium, the higher the level; and the more severe the cardiotoxicity depicted by the ECG changes, the more aggressive the therapy should be.

TABLE 2 Defining Renal Origin of Hyperkalemia

Application of TTKG, FE_K, and Urine K:Cr Ratio
Expected values for TTKG* or FE_K
Nonrenal forms of hyperkalemia
TTKG >5-7, FE_K >10%
Urine K:Cr ratio >30 mEq/L
Spot urine $[K^+]$ >25 mEq/L
Renal hyperkalemia
TTKG <5 or FE_K <10% (inappropriately low)
Urine K:Cr ratio <30 mEq/g Cr
Urine $[K^+]$ <25 mEq/24 h

*Prerequisites for use: UNa >25 mEq/L and urine not dilute.
Cr, Creatinine; *FE_K,* fractional excretion of K^+; *TTKG,* transtubular potassium gradient.
Formulae:
TTKG = (Urine K ÷ [Urine osmolality/Plasma osmolality]) ÷ Plasma K
FE_K = ([urine K^+]/[serum K^+])/(urine creatinine/serum creatinine)
Multiply by 100 for percentage

NONPHARMACOLOGIC THERAPY

- The mainstay of therapy should be educating the patient and the family regarding a low-potassium diet (<3 g/day), as well as providing a list of high-potassium foods to avoid.
- Maintaining adequate hydration and preventing volume depletion, which limits potassium excretion by the kidney.

ACUTE GENERAL Rx

In patients with severe hyperkalemia, treatment (Fig. 3) is as follows:

- IV calcium (Fig. 4) to ameliorate cardiac toxicity (if not digoxin toxic).
- Identify and remove sources of potassium intake.
- IV glucose and insulin infusion to enhance cellular uptake of potassium.
  1. Make sure to monitor closely for several hours for hypoglycemia, especially in advanced CKD patients.
- Correct severe acidosis with IV sodium bicarbonate.
- Consider beta-adrenergic agonist therapy (e.g., nebulized albuterol, 10 mg via venti mask), which is preferred over alkali therapy in patients with renal failure.
- Increase potassium excretion with administration of loop diuretic IV or cation-exchange medications mentioned previously.
  1. Medications that increase potassium excretion in addition to IV saline and loop diuretics include use of an aldosterone analogue (e.g., 9-alpha fludrocortisone acetate [Florinef]) in patients with hyporeninemia or hypoaldosteronism or patients with solid organ transplant on CNI and hyperkalemia.
- Emergency dialysis in potentially lethal hyperkalemia unresponsive to conservative measures or with acute kidney failure.
- Once the hyperkalemia has been corrected chronic management should be initiated to maintain a normal potassium with dietary restriction, adjusting/stopping medications associated with hyperkalemia, or use of the newer ion exchange resins sodium zirconium cyclosilicate and patiromer that are more palatable and better tolerated than sodium polystyrene sulfate.

CHRONIC Rx

In the presence of a moderate elevation of potassium and no ECG abnormalities:

- Correct the source of increase potassium (e.g., inhibited excretion or increased intake)
- Increase potassium excretion using cation exchange resin (Table 3) or diuretics:
  1. Historical therapy is sodium polystyrene sulfate with or without sorbitol. This may fall to the wayside in the face of the newer therapies with more consistent results and less potential toxicity (dose is 15 g to 30 g orally and may be repeated in 3 to 4 hours). *Caution:* Using large doses repeatedly may cause sodium overload and can potentially decompensate a patient with congestive heart failure. Do not give as an enema (especially with sorbitol). Rare cases of intestinal necrosis have been reported with use.
  2. Patiromer is a non-reabsorbed oral calcium-containing potassium-binding polymer suspension (dose 8.4 to 25.2 g daily).
     a. Shown to lower serum potassium in hyperkalemia associated with diabetic nephropathy and CHF on RAASi.
     b. Calcium is the ion exchanger (not sodium), and it can form calcium carbonate in the colon and affect absorption of some medications, especially ciprofloxin, levothyroxine, and metformin. Administer at least 3 hours before or after all oral medications.
     c. Can bind magnesium and be associated with hypomagnesemia; recommend monitoring magnesium levels intermittently in chronic use.
  3. Sodium zirconium cyclosilicate is a non-absorbed inorganic polymer selectively exchanging potassium for sodium and hydrogen ions (dose 10 g tid for up to 48

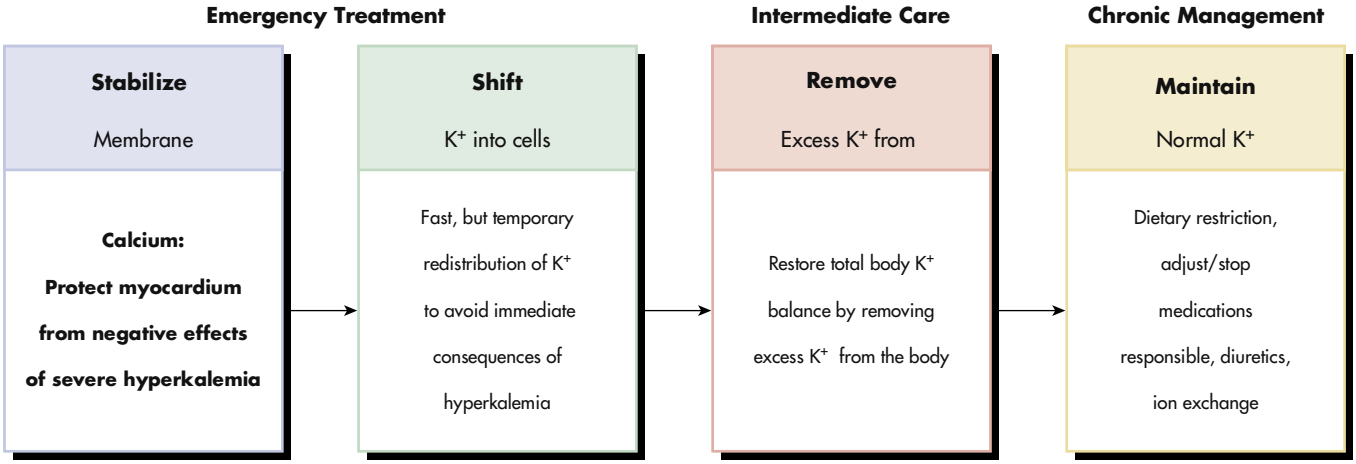
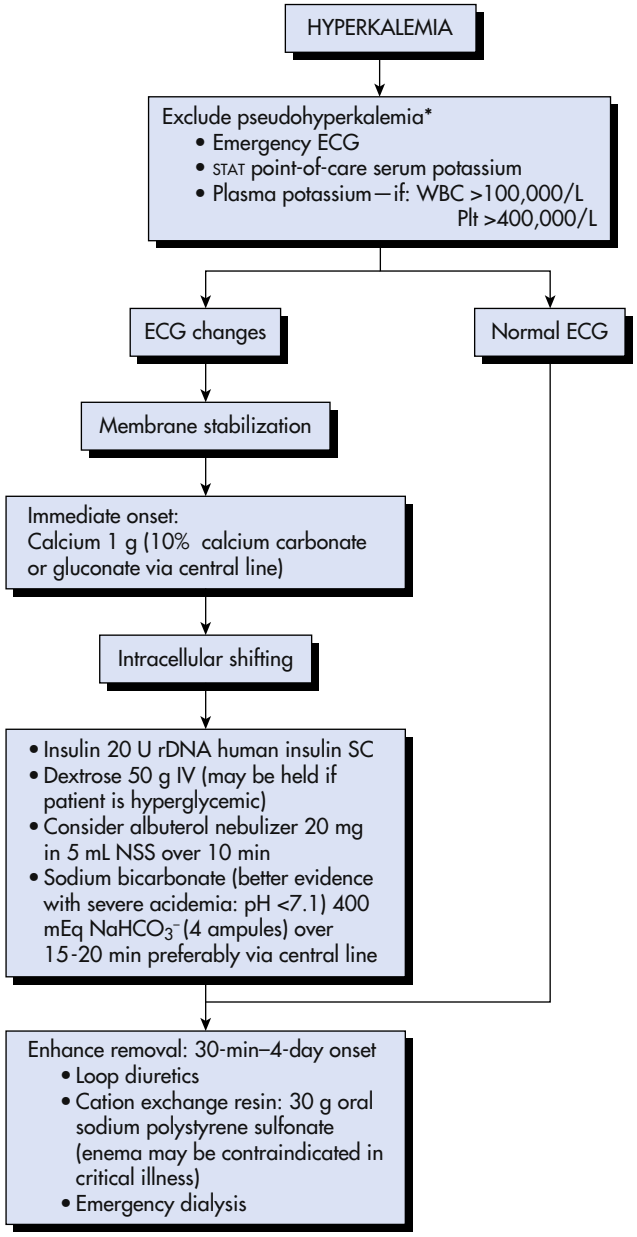


FIG. 3 Management of hyperkalemia.



*May be unnecessary in appropriate clinical situation

FIG. 4 Algorithm for treatment of hyperkalemia. *ECG,* Electrocardiogram; *IV,* intravenously; *NSS,* normal saline solution; *Plt,* platelet count; *rDNA,* ribosomal deoxyribonucleic acid; *SC,* subcutaneously; *stat,* at once; *WBC,* white blood cell count. (From Ronco C et al: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.)

TABLE 3 Available Potassium Ion Exchange Resins

	Sodium Polystyrene Sulfate	Patiromer	Sodium Zirconium Cyclosilicate
Dosage	15-30 g 1-4 times/day	8.4 g, 16.8 g, or 25.2 g Once daily	10 g, 3 times daily for up to 48 hr; then 5 g every other day to 15 g daily
Counterion	Sodium	Calcium	Sodium
Average daily sodium load	495-1980 mg	0 mg	400-2400 mg
Concomitant dose separation with other oral medications	3 hours separation (6 hours in patients with gastroparesis)	3 hours separation	2 hours separation

hours followed by 5 g every other day to 15 g daily for chronic use).
   a. Sodium is the ion exchanger and can be associated with sodium overload if large doses are used for prolonged time.
   b. Also must be administered at least 2 hours before or after all oral medications.

Management of nonurgent hyperkalemia:
- Discontinue or reduce medications that interfere with potassium excretion.
  1. Stop RAASi (special care if in combination)
  2. Stop spironolactone, eplerenone, amiloride, triamterene
  3. Stop all NSAIDs (including OTC) and COX-2 inhibitors
  4. Herbal medicine: stop Chan su and Noni juice
  5. If possible, address whether patient is on a calcineurin inhibitor (CNI)
- Prescribe a low-potassium diet (70 mEq/day).
- Give a loop diuretic (or thiazide of CNI-induced hyperkalemia).
- If bicarbonate <22, give $NaHCO_3$ tablets (650 mg tablet [7.6 mEq] or Shohl solution (sodium citrate) (3 to 60 ml tid).
- Patiromer or sodium zirconium cyclosilicate avoids use of SPS for chronic hyperkalemia.
  1. None of the ion exchange resins should be used for urgent hyperkalemia, some ongoing studies looking at sodium zirconium cyclosilicate
- May be able to continue RAASi with either patiromer or sodium zirconium cyclosilicate.

DISPOSITION
- Patients with acute symptomatic hyperkalemia with ECG changes should be admitted to a hospital in a monitored bed/intensive care unit.
- Asymptomatic patients with no ECG changes can be treated as outpatients and educated extensively regarding a low-potassium diet with close follow-up including a repeat potassium in 24 to 48 hr, depending on the severity, and a wk later.

REFERRAL
Patients with associated hypertension, proteinuria, CKD, or persistent hyperkalemia should be referred to a nephrologist for more intensive evaluation and to assess for a genetic etiology.

PEARLS & CONSIDERATIONS

COMMENTS
- Ensure that specimen is not hemolyzed.
- When in doubt, repeat the test.
- Rule out pseudohyperkalemia.
- Risk associated with comparable levels of hyperkalemia is higher in individuals with normal kidney function compared with those with increasingly severe CKD.
- Do not give IV calcium or insulin/dextrose if no ECG changes for hyperkalemia.
- Don't forget to educate and encourage dietary restriction of potassium. (Avoid salt substitutes.)
- Evaluate for urinary obstruction, especially in diabetics (neurogenic bladder) and in elderly males (prostatic hypertrophy).

PREVENTION
- Avoid dual therapy with ARB and ACEI or direct renin inhibitor.
- In patients with type 4 RTA, educate to reduce high-potassium food intake during their seasons (e.g., tomatoes, citrus fruits), avoid travel to areas where these foods are endemic and avoid volume depletion.
- In CKD patients or in patients with type 4 RTA, avoid using a salt substitute (which is potassium chloride).

PATIENT & FAMILY EDUCATION
Education regarding potassium content of foods is of high, practical importance. A renal nutritionist should review the patient's medical records for potential dietary interventions.

SUGGESTED READINGS
Available at ExpertConsult.com

RELATED CONTENT
Chronic Kidney Disease (Related Key Topic)

AUTHORS: **Nelson Kopyt, DO,** and **Jerry Yee, MD**

SUGGESTED READINGS

Kovesdy CP: Updates in hyperkalemia: outcomes and therapeutic strategies, *Rev Endocr Metab Disord* 18:41-47, 2017.

Montford JR, Linas S: How dangerous is hyperkalemia? *J Am Soc Nephrol* 2017. ASN.2016121344v1-ASN.2016121344.

Palmer BF: A physiologic-based approach to the evaluation of a patient with hyperkalemia, *AJKD* 56(2):387-393, 2010.

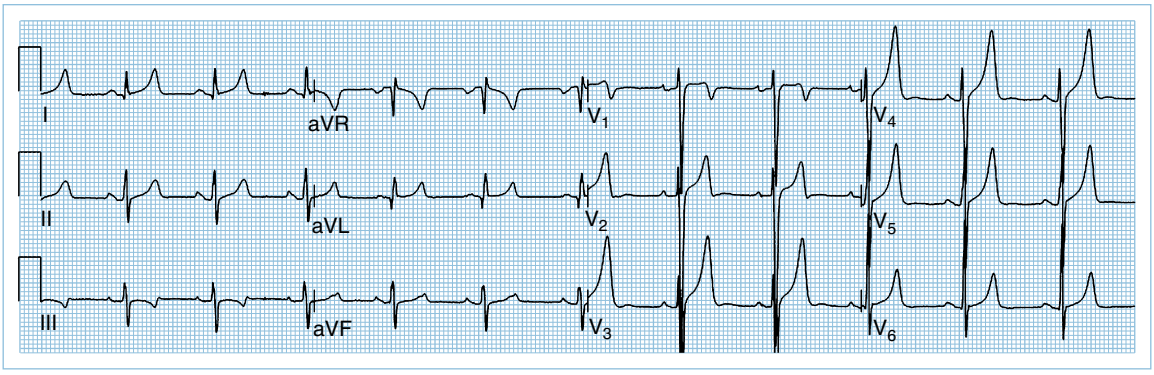


FIG. E2 Tall peaked T waves with hyperkalemia. This 12-lead electrocardiogram shows the tented T waves that are commonly seen in mild to moderate degrees of hyperkalemia. Tented T waves of hyperkalemia need not be tall, although in this case they are. *aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right. (From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

BASIC INFORMATION

DEFINITION

- Primary hyperlipoproteinemia is a group of genetic disorders of the lipid transport proteins in the blood that manifests as abnormally elevated levels of cholesterol, triglycerides, or both in the serum of affected patients.
- Usually defined as total cholesterol, LDL, triglycerides, or lipoprotein A levels above 90th percentile or HDL or apo A-1 levels below the 10th percentile for the general population. Fig. E1 illustrates the structure of lipoproteins. Plasma lipoprotein composition is described in Table E1.

SYNONYM

Hyperlipidemia

ICD-10CM CODES

E78.0	Pure hypercholesterolemia
E78.2	Mixed hyperlipidemia
E78.1	Pure hyperglyceridemia
E78.4	Other hyperlipidemia
E78.3	Hyperchylomicronemia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The most common types are lipoprotein A excess, hypertriglyceridemia, and combined hyperlipidemia.

- Incidence of heterozygous familial hypercholesterolemia: 1:500
- Incidence of homozygous familial hypercholesterolemia: 1:1 million
- Familial hypercholesterolemia: Autosomal-dominant disorder
- Familial combined hyperlipidemia: Possibly an autosomal-dominant disorder
- Multifactorial predilection: Apparent in majority of affected individuals

GENETICS:

- Familial lipoprotein lipase deficiency: Autosomal recessive, resulting in an elevation in the plasma chylomicrons and triglycerides
- Familial apoprotein CII deficiency: Autosomal recessive, resulting in increased serum chylomicrons, very low-density lipoprotein (VLDL), and hypertriglyceridemia
- Familial type 3 hyperlipoproteinemia: Single-gene defect requiring contributory factors to manifest
- Familial hypercholesterolemia: Autosomal-dominant defect of the LDL receptor, resulting in an elevated serum cholesterol level and normal triglycerides
- Familial hypertriglyceridemia: Common, autosomal-dominant defect resulting in elevated VLDL and triglycerides
- Multiple lipoprotein–type hyperlipidemia: Autosomal dominant, manifesting as isolated hypercholesterolemia, isolated hypertriglyceridemia, or hyperlipidemia
- Polygenic hypercholesterolemia: Multifactorial
- Polygenic hyperalphalipoproteinemia: Autosomal dominant or polygenic, causing an elevated high-density lipoprotein
- A classification of lipoprotein disorders and their clinical findings and management are summarized in Table 2

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Familial lipoprotein lipase deficiency: Recurrent bouts of abdominal pain in infancy, eruptive xanthomas, hepatomegaly, splenomegaly, lipemia retinalis
- Familial apoprotein CII deficiency: Occasional eruptive xanthomas
- Familial type 3 hyperlipoproteinemia: Xanthoma striata palmaris or tuberoeruptive xanthomas, xanthelasmas, arterial bruits at a young age, gangrene of the lower extremities at a young age
- Familial hypercholesterolemia: Tendon xanthomas, arcus corneae, xanthelasma
- Familial hypertriglyceridemia: Associated obesity; eruptive xanthomas can develop with exacerbations

ETIOLOGY

- Genetic defects causing lipid abnormalities
- Environmental influences, including diet, drugs, and alcohol intake

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Secondary causes of hyperlipoproteinemias:

- Hypothyroidism
- Diabetes mellitus
- Pancreatitis
- Autoimmune hyperlipoproteinemia
- Nephrotic syndrome
- Biliary obstruction; Table E3 describes the differential diagnosis of hyperlipidemia and dyslipidemia

WORKUP

- Family history for premature cardiac disease
- Personal history of recurrent pancreatitis
- Detailed physical examination

LABORATORY TESTS

- Standard lipid profile; Table 4 summarizes laboratory findings in lipid disorders
- If normal, further testing with measurement of lipoprotein A, apo B, and apo A-1
- Lipoprotein electrophoresis and ultracentrifugation (for phenotypic classification)
- Workup for secondary causes: TSH, fasting glucose, liver function, renal function, urinary protein

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cornerstone of treatment: Dietary therapy
  1. TLC diet (**t**herapeutic **l**ifestyle **c**hanges): See "Hypercholesterolemia" topic
- Risk factor reduction includes smoking cessation, treatment of hypertension, exercise
- Familial lipoprotein lipase deficiency and familial apoprotein CII deficiency: Fat-free diet
- Remainder of cases, except those with polygenic hyperalphalipoproteinemia: Fat- and cholesterol-restricted diets

ACUTE GENERAL Rx

No acute treatment is needed.

CHRONIC Rx

- Familial lipoprotein lipase deficiency, polygenic hyperalphalipoproteinemia, or familial apoprotein CII deficiency: No chronic drug therapy.
- Familial type 3 hyperlipoproteinemia: Usually responds well to secondary causes being treated and diet therapy; if not, fibric acids may be tried.
- Familial hypercholesterolemia: Statins, bile acid sequestrants, or niacin. Ezetimibe can be added to statins to achieve LDL goals. Alirocumab and evolocumab are subcutaneously injected PCSK9 (protein convertase subtilisin kexin type 9) inhibitors available as an adjunct diet and maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia (HeFH). They can be added to statins and ezetimibe.
- Familial hypertriglyceridemia: Fibric acids (fenofibrate), niacin, omega-3 PUFA-containing fish oil capsules. Icosapent ethyl, a highly purified eicosapentaenoic acid ester, has been shown to lower triglyceride levels and cardiovascular risk in patients with hypertriglyceridemia.
- Multiple lipoprotein–type hyperlipidemia: Drug therapy aimed at the predominant lipid abnormality noted.
- Recent data suggest in patients with lipoprotein abnormalities that treatment goals should be based on non-HDL cholesterol rather than LDL cholesterol.
- The FDA has approved mipomersen and lomitapide in patients with homozygous familial hypercholesterolemia already taking maximum doses of other lipid-lowering drugs. Both medicines are hepatotoxic and very expensive.
- Recent trials with bempedoic acid, an inhibitor of ATP citrate lyase that lowers LDL cholesterol, have shown to significantly lower LDL when bempedoic acid was added to maximally tolerated statin therapy.

DISPOSITION

- Those with polygenic hyperalphalipoproteinemia: Excellent prognosis for longevity
- Those with familial hypercholesterolemia, familial type 3 hypercholesterolemia, or multiple lipoprotein–type hyperlipidemia: Even with aggressive treatment, at high risk for accelerated atherosclerosis and coronary artery disease

PEARLS & CONSIDERATIONS

COMMENTS

- Patient information is available through the American Heart Association.
- Lipid-lowering drug therapy is recommended for children ≥10 yr whose LDL-C levels remain extremely elevated after 6 mo to 1 yr of dietary modification. Drug therapy also can be considered for children with LDL-C levels of ≥190 mg/dl.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hypercholesterolemia (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

TABLE 2 Disorders of Lipids: Clinical Findings and Management

Disorder	Xanthomas	Cardiovascular	Gastrointestinal	Neurologic	Ophthalmologic	Other Findings	Management
Type I	Eruptive, tendinous, xanthelasmas	None	Acute abdomen, hepatosplenomegaly, pancreatitis	None	Lipemia retinalis, retinal vein occlusion	Diabetes, lipemic plasma	Diet, plasmapheresis
Type II	Planar, especially intertriginous, tendinous, tuberous	Generalized atherosclerosis	None	None	Arcus cornea	None	Type IIa: bile acid sequestrants, statins, niacin, fish oil Type IIb: statins, niacin, fibrate
Type III	Planar, especially palmar, tuberous	Atherosclerosis	None	None	None	Abnormal glucose tolerance, hyperuricemia	Statins, fibrate
Type IV	Eruptive, tuberous	Atherosclerosis	Acute abdomen, hepatosplenomegaly, pancreatitis	None	Lipemia retinalis	Obesity	Statins, fibrate, niacin
Type V	Eruptive, tuberous	Atherosclerosis	Acute abdomen, hepatosplenomegaly, pancreatitis	None	Lipemia retinalis	Obesity, hyperinsulinemia	Niacin, fibrate
Tangier	Macular rash, foam cells in biopsies	Atherosclerosis	Acute abdomen, hepatosplenomegaly	Peripheral neuropathy	Corneal infiltration	Enlarged orange tonsils, lymphadenopathy	
Apolipoprotein A-I and C-III deficiency	Planar and tendon xanthomas, foam cells in biopsies	Atherosclerosis	Normal	Normal	Corneal clouding	None	
HDL deficiency with planar xanthomas	Planar xanthomas, foam cells in biopsies	Atherosclerosis	Hepatomegaly	Normal	Corneal opacity	None	

HDL, High-density lipoprotein.
From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.

TABLE 4 Laboratory Findings in Lipid Disorders

Disorder	Inheritance	OMIM No.	Prevalence	Cholesterol	Triglycerides	VLDL	Chylomicrons	LDL	HDL	Serum	Cause
Type I	AR		1/million	↑	↑↑↑	↑	↑	↓	↓↓↓	Creamy top	
a: Familial hyperchylomicronemia		239600, 246650, 615947									a. Deficiency from mutations in lipoprotein lipase; *LMF1*; *GPIHBP1*
b: Familial apoprotein C2 or A-V deficiency		207750, 133650									b. Deficient ApoC2 or ApoA5 (see Type V)
c: —		118830									c. LP lipase inhibitor in blood
Type II			1 in 500 for heterozygotes	↑	NI or ↑	↑	NI	↓	↓	Clear	
a: Familial hypercholesterolemia	AD	143890, 144010, 603776									LDL receptor defect in 60%-80%; *APOB, PCSK9,* each <5%
	AR	603813									*LDLRAP1*
b: Familial combined hyperlipidemia	AD, AR	144250	1 in 100							Clear	Polygenic Decreased LDL receptor and ApoB100 dysfunction
Type III Familial dysbetalipoproteinemia	AR	107741	1 in 10,000	↑	↑	↑	↑	↓	NI	Turbid	ApoE2 synthesis
Type IV Familial hypertriglyceridemia	AD	144600	1 in 100	↑	NI ↑	↑	NI	↓	↓↓	Turbid	Renal disease, diabetes
Type V	AR	144650	Very rare	↑	↑↑↑	↑	↑	↓	↓↓↓	Creamy top, turbid bottom	Apo A-V (ApoA5) deficiency

AD, Autosomal dominant; *Apo,* apolipoprotein; *AR,* autosomal recessive; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *LP,* lipoprotein; *NI,* normal; *OMIM,* Online Mendelian Inheritance in Man; *VLDL,* very low-density lipoprotein; *↑,* increased; *↓,* decreased.

From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.

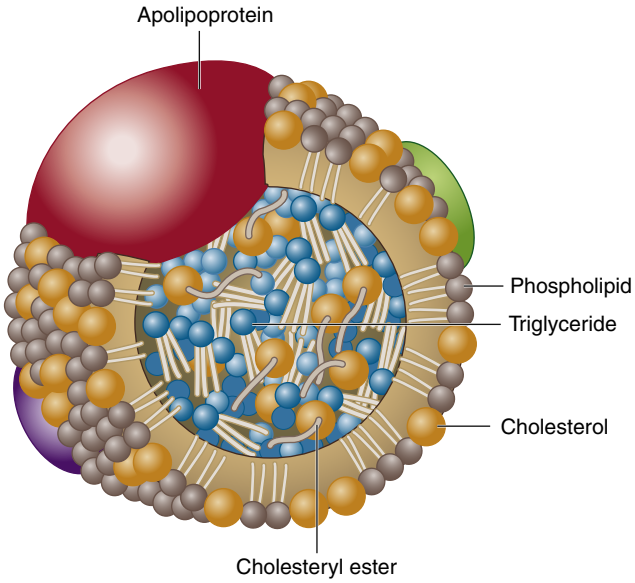


FIG. E1 Structure of lipoproteins. Phospholipids are oriented with their polar group toward the aqueous environment of plasma. Free cholesterol is inserted within the phospholipid layer. The core of the lipoprotein is made up of cholesteryl esters and triglycerides. Apolipoproteins are involved in the secretion of the lipoprotein, provide structural integrity, and act as cofactors for enzymes or as ligands for various receptors. (From Bonow RO et al: *Heart disease,* ed 9, Philadelphia, 2012, WB Saunders.)

TABLE E1 Plasma Lipoprotein Composition

Component	Origin	Density (g/ml)	Size (nm)	Protein (%)	Cholesterol in Plasma (mmol/L)†	Triglyceride in Fasting Plasma (mmol/L)‡	Apoprotein	
							Major	Other
Chylomicron*	Intestine	<0.95	100-1000	1-2	0.0	0.0	B48	A-I, Cs
Chylomicron remnants*	Chylomicron metabolism	0.95-1.006	30-80	3-5	0.0	0.0	B48, E	A-I, A-IV, Cs
VLDL	Liver	<1.006	40-50	10	0.1-0.4	0.2-1.2	B100	AI, Cs
IDL	VLDL	1.006-1.019	25-30	18	0.1-0.3	0.1-0.3	B100, E	
LDL	IDL	1.019-1.063	20-25	25	1.5-3.5	0.2-0.4	B100	
HDL	Liver, intestine	1.063-1.210	6-10	40-55	0.9-1.6	0.1-0.2	A-I, A-II	A-IV
Lipoprotein(a)	Liver	1.051-1.082	25	30-50			B100, (a)	

HDL, High-density lipoprotein; *IDL,* intermediate-density lipoprotein; *LDL,* low-density lipoprotein; *VLDL,* very low-density lipoprotein.
*In the fasted state, serum (or plasma) should not contain chylomicrons or their remnants.
†In mmol/L. For mg/dl, multiply by 38.67.
‡In mmol/L. For mg/dl, multiply by 88.5.
From Bonow RO et al: *Heart disease,* ed 9, Philadelphia, 2012, WB Saunders.

TABLE E3 Differential Diagnosis of Hyperlipidemia and Dyslipidemia

Hypertriglyceridemia	Hypercholesterolemia	Increased Cholesterol and Triglycerides	Low HDL
Primary Disorders			
LPL deficiency	Familial hypercholesterolemia	Familial combined hyperlipidemia	Familial hypoalphalipoproteinemia
ApoCII deficiency	Familial defective apoB100	Dysbetalipoproteinemia	ApoAI mutations
Familial hypertriglyceridemia	Polygenic hypercholesterolemia	Diabetes mellitus	LCAT deficiency
Dysbetalipoproteinemia	Sitosterolemia	Hypothyroidism	ABCA1 deficiency
Secondary disorders	Hypothyroidism	Glucocorticoids	Anabolic steroids
Diabetes mellitus	Obstructive liver disease	Immunosuppressives	Retinoids
Hypothyroidism	Nephrotic syndrome	Protease inhibitors	
High-carbohydrate diets	Thiazides	Nephrotic syndrome	
Renal failure		Lipodystrophies	
Obesity/insulin resistance			
Estrogens			
Ethanol			
β-Blockers			
Protease inhibitors			
Glucocorticoids			
Retinoids			
Bile acid-binding resins			
Antipsychotics			
Lipodystrophies			
Thiazides			

ABCA1, Adenosine triphosphate-binding cassette transporter 1; *apo,* apolipoprotein; *HDL,* high-density lipoprotein; *LCAT,* lecithin:cholesterol acyltransferase; *LPL,* lipoprotein lipase.
From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders.

SUGGESTED READINGS

Bhatt DL et al: Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia, *N Engl J Med* 380(1):11-22, 2019.

Last AR et al: Hyperlipidemia: drugs for cardiovascular risk reduction in adults, *Am Fam Physician* 95(2):7887, 2017.

Lozano P et al: Lipid screening in childhood and adolescence for detection of familial hypercholesterolemia: evidence report and systematic review for the US Preventive Services Task Force, *J Am Med Assoc* 316(6):645-655, 2016.

Ray KK et al: Safety and efficacy of bempedoic acid to reduce LDL cholesterol, *N Engl J Med* 380(11):1022-1032, 2019.

Hypernatremia

BASIC INFORMATION

DEFINITION

Hypernatremia is a clinical disorder that results from net water deficit (i.e., dehydration). It is identified when the serum sodium concentration (S_{Na}) exceeds the upper limit of normal (145 mEq/L). Hypernatremia does not reflect the net total body sodium content or extracellular fluid volume status. Consequently, patients may be hypovolemic, hypervolemic, or euvolemic when hypernatremic.

SYNONYMS

Hyperosmolality
Hypertonicity
High serum sodium concentration

ICD-10CM CODES

E87.0	Hyperosmolality and/or hypernatremia
E86.0	Dehydration

EPIDEMIOLOGY & DEMOGRAPHICS

The prevalence of hypernatremia varies based on the defined population and clinical setting. In the outpatient setting, it is reported at the extremes of age. Sixty percent of hypernatremia cases develop in hospitalized patients, and about 80% of these cases occur in intensive care units.

Among noncritical hospitalized patients, the prevalence rate of hypernatremia is 0.2% to 2.5%. The incidence is greater in critically ill and elderly patients, and the prevalence rate ranges from 10% to 26% in this population. Hypernatremia is independently associated with mortality.

RISK FACTORS:

- Age >60 yr
- Acute kidney injury on admission
- Altered mental status
- Mechanical ventilation
- Enteral tube feeding
- Negative fluid balance
- Hyperglycemia/uncontrolled diabetes mellitus
- Hypertonic bicarbonate or mannitol administration
- Hypokalemia
- Hypercalcemia
- Underlying polyuric disorders

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms generally correlate with the severity of hypernatremia, rapidity of development, and underlying cause. In the elderly, symptoms do not generally develop until the S_{Na} is >160 mEq/L.
- In mild hypernatremia, symptoms can include generalized muscle weakness, restlessness, anorexia, nausea, and vomiting.
- With severe hypernatremia, symptoms can begin with lethargy and irritability with progression to confusion, seizures, and, rarely, coma.
- In extreme scenarios, particularly in infants, hypernatremia-induced brain cell shrinkage can lead to intracranial bleeding from vascular stretching and consequent vessel rupture.
- Polydipsia and polyuria may be present in certain types of hypernatremia such as diabetes insipidus.
- Key elements of the history should focus on respective fluid and water intakes and losses, urine output, insensible losses, thirst response, and accessibility to water and fluids.
- Clinicians should evaluate the extracellular fluid volume status of patients. Classifying volume status will assist in determining the etiology and management of hypernatremia (Fig. 1).

ETIOLOGY

The etiology of hypernatremia is understood through the Edelman equation (refer to "Hyponatremia"). As a result, hypernatremia can be a clinical end-result of either net water deficit or excessive sodium intake. Renal water regulation and thirst stimuli are key physiologic components that prevent hypernatremia.

- To prevent hypernatremia, water is retained and urine concentrated by the kidneys under the influence of antidiuretic hormone or arginine vasopressin (AVP). Impairment of AVP secretion, reduction of the medullary concentration gradient, or an inability of AVP

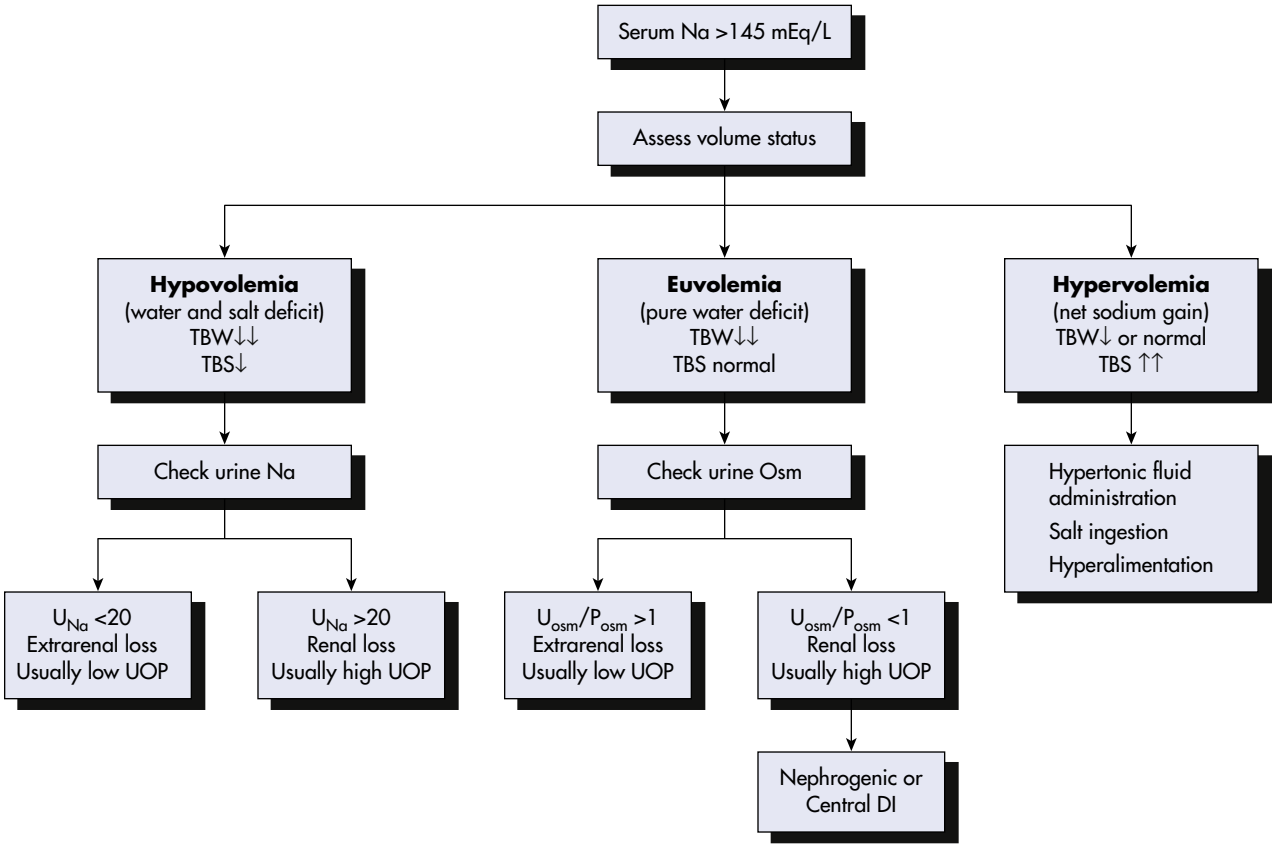


FIG. 1 Diagnostic approach to hypernatremia. *DI,* Diabetes insipidus; *Na,* sodium; *Osm,* osmolality; *TBS,* total body salt; *TBW,* total body water; *UOP,* urine output. (Adapted from Gilbert SJ, Weiner DE: *National Kidney Foundation primer on kidney disease,* ed 6, Philadelphia, 2017, WB Saunders.)

to stimulate insertion of aquaporin channels into the luminal membranes of collecting duct cells leads to excessive renal water losses and hypernatremia.

- Elevated plasma osmolality from hypernatremia triggers a thirst response by the hypothalamus. If water intake exceeds water loss or net solute gain, hypernatremia is avoided. Hypernatremia develops when the thirst response is impaired or when there is a lack of access to water, a common circumstance for mechanically ventilated patients and the elderly with cognitive impairments and physical limitations.

Hypernatremia can be classified in the following manner:

- Excessive water loss
  1. Gastrointestinal losses
     a. Vomiting or nasogastric losses
     b. Ileostomy
     c. Pancreaticobiliary fistula
     d. Diarrhea
     e. Laxatives
  2. Renal losses
     a. Osmotic diuresis
        (1) Osmotic diuretics (mannitol, sorbitol, glycine)
        (2) Glucosuria (hyperglycemia, SGLT2 inhibitor administration)
        (3) Urea diuresis (e.g., steroid use, high-protein diet, hypercatabolic state)
        (4) Postobstructive and post–acute tubular necrosis (post-ATN) diuresis
     b. Water diuresis
        (1) Central diabetes insipidus (CDI)
           (a) Genetic
              i. Autosomal dominant
              ii. Autosomal recessive
           (b) Acquired (e.g., post trauma, iatrogenic, craniopharyngioma, metastatic cancers, encephalitis)
           (c) Sarcoidosis
           (d) Multifocal Langerhans cell histiocytosis
           (e) Eosinophilic granulomatosis
        (2) Nephrogenic diabetes insipidus (NDI)
           (a) Genetic
              i. Arginine vasopressin receptor 2 (AVPR2) or aquaporin 2 (AQP2) gene mutations
              ii. Autosomal dominant polycystic kidney disease
              iii. Familial hypocalciuric hypercalcemia: Mutated calcium-sensing receptor
           (b) Acquired
              i. Chronic kidney disease
              ii. Post-ATN diuresis
              iii. Hypokalemia
              iv. Hypercalcemia (diverse causes)
              v. Drugs (e.g., lithium, amphotericin, ifosfamide, demeclocycline)
              vi. Gestation (increased placental vasopressinase)
- Impaired water intake
  1. Adipsia or hypodipsia
     a. Septooptic dysplasia
     b. Craniopharyngioma
  2. Impaired access to water
     a. Mechanical ventilation
     b. Dementia
     c. Cognitive impairment (e.g., dementia)
- Excessive sodium intake
  1. Hypertonic saline or sodium bicarbonate administration
  2. Salt tablet ingestion
  3. Salt-water drowning

An alternative classification based on the volume status of the patient is provided in Table 1.

TABLE 1 Causes of Hypernatremia

Hypovolemic Hypernatremia

Renal Loss
- Loop diuretics
- Post-AKI diuresis
- Postobstructive diuresis
- Osmotic diuresis (hyperglycemia, mannitol, urea)

Extrarenal Loss
- Gastrointestinal (diarrhea, nasogastric suctioning, vomiting)
- Skin (sweating, burns)

Euvolemic Hypernatremia

Renal Loss
- Diabetes insipidus (ADH-dependent mechanism)
  1. Central DI (complete or partial)
  2. Nephrogenic DI (X-linked recessive with defect in V2 receptor or aquaporin, unresponsive to ADH)
  3. Gestational DI
- Acquired Nephrogenic DI
  1. Electrolyte disturbances (hypercalcemia, hypokalemia)
  2. Drug-induced (amphotericin B, lithium, foscarnet)
  3. Chronic kidney disease (medullary cystic disease, sickle cell anemia, amyloidosis, Sjögren syndrome)
  4. Malnutrition

Extrarenal Loss
- Increased insensible loss (fevers, sweating, tachypnea)
- Decreased intake
  1. Primary hypodipsia
  2. Reset osmostat
  3. Decreased access to water (altered mental status, iatrogenic)
- Water loss into cells (seizures, exercise)

Hypervolemic Hypernatremia
- Excessive sodium administration (saline or bicarbonate)
- Hyperalimentation
- Salt ingestion
- Mineralocorticoid excess
- Hypertonic dialysis

ADH, Antidiuretic hormone; *AKI,* acute kidney injury; *DI,* diabetes insipidus.

Adapted from Gilbert SJ, Weiner DE: *National Kidney Foundation primer on kidney disease,* ed 6, Philadelphia, 2017, WB Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Dehydration refers to net water deficits, and its clinical result is hypernatremia. Conversely, volume depletion occurs as a result of net loss of total body sodium and water, which results in decreased intravascular volume. Recognizing dehydration and volume depletion as distinct entities that may coexist has management implications. For example, euvolemic hypernatremia is due to pure water loss, and replacing water deficit is adequate therapy. This strategy is not appropriate in hypovolemic hypernatremia because volume (sodium and potassium) and water losses require replacement.

WORKUP

- Workup of hypernatremia begins with a detailed history and physical examination. Historical features that reveal volume depletion and/or dehydration are crucial and include a family history of diabetes insipidus and medication or drug use.
- In hospitalized patients, careful assessments of cumulative fluid intake and fluid losses must be made.
- In adults, hypernatremia usually develops from net water loss and inability to access water (e.g., altered mentation, mechanical ventilation). If access to water is not restricted, etiologies that impair thirst center function should be considered.
- In the presence of polyuria, the underlying etiology should be sought.

LABORATORY TESTS

- Serum chemistry: S_{Na} with serial repetition based on clinical scenario (e.g., 2 to 12 h). Frequent monitoring facilitates an appropriate correction rate of S_{Na} and evaluation of the response to therapy. Derangements of other electrolyte and renal parameters frequently accompany hypernatremia.
- Urine osmolality (U_{osm}): In the presence of a functioning hypothalamic-pituitary axis, a rise in plasma osmolality results in AVP-mediated urinary concentration (U_{osm} exceeds P_{osm}, typically >600 to 700 mOsm/kg). Thus, U_{osm} may signal the presence of DI.
  1. Low U_{osm} (<300 mOsm/kg) suggests hypernatremia from CDI or NDI. After an initial diagnostic workup is conducted, differentiation between CDI and NDI is required, as outlined in the "Diabetes Insipidus" section.
  2. High U_{osm} is usually from extrarenal water losses.
- Urine sodium (U_{Na}) and urine potassium (U_K): U_{NA} assists in the determination of intravascular volume (Fig. 1). Together, U_{NA} and U_K help to quantify urine electrolyte-free water clearance to guide therapy as explained later. Electrolyte-free water has no effective osmolality at equilibrium and is water comprised of no electrolytes with or without urea. Urinary parameters should be monitored every 12 to 24 h until S_{Na} is adequately corrected.

TREATMENT

- Treatment of hypernatremia requires the replacement of the existing water deficit and ongoing daily electrolyte-free water losses.
- Volume replacement may be required, and may take precedence when volume depletion is present.

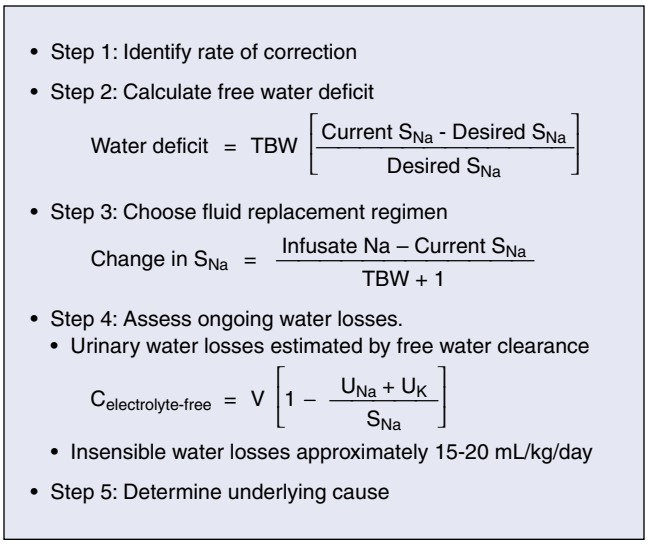


FIG. 2 Approach to treatment of hypernatremia. $C_{electrolyte\text{-}free}$, Electrolyte-free water clearance; *Na,* sodium; S_{Na}, serum sodium; *TBW,* total body water; U_K, urine potassium; U_{Na}, urine sodium; *V,* urine volume. (Adapted from Gilbert SJ, Weiner DE: *National Kidney Foundation primer on kidney disease,* ed 6, Philadelphia, 2017, WB Saunders.)

- A stepwise approach to the therapy of hypernatremia is depicted in Fig 2.
  1. Step 1: Identify the rate of correction, rate of rise of S_{Na}.
     a. Although the exact risk is unknown, too-rapid correction of chronic hyponatremia (>48 h) can have deleterious neurologic consequences, namely cerebral edema.
     b. Based on clinical data from infants and critically ill adults, chronic hypernatremia should not be corrected faster than 10 to 12 mEq/L per day or an average of 0.5 mEq/L per hour. This rate would apply to most nonhospitalized elderly patients, because hypernatremia develops over several days.
     c. In rare individuals with acute hypernatremia (e.g., intentional or accidental massive sodium ingestions), the S_{Na} may be rapidly corrected (within 24 h) to normal S_{Na} levels.
  2. Step 2: Calculate free water deficit.
     a. Free water deficit is the volume of free water required to correct the current S_{Na} to the target S_{Na}. This is estimated with the following formula:
        (1) Water deficit = TBW × [(current S_{Na}/target S_{Na}) – 1].
     b. In the preceding formula, TBW is the estimated total body water. Target S_{Na} is the S_{Na} that should be achieved in a 24-h period as determined in step 1.
     c. As a general estimate, TBW estimates are 50% to 60% of lean body weight in men and women.
  3. Step 3: Choose fluid replacement regimen.
     a. In patients with a pure water deficit, the calculated water deficit in step 2 should be replaced as either enteral water or intravenous D_5W. Do not infuse pure water by the intravenous route to prevent hemolysis.
     b. When possible, the enteral route should be used during hydration therapy to avoid overly rapid glucose infusions that may induce hyperglycemia, which promotes an osmotic diuresis. This pathophysiologic sequence may occur as D_5W infusion rates are increased to greater than 300 ml/h.
     c. The rate of replacement (ml/h) of the water deficit is obtained by dividing the calculated water deficit volume by 24 h. However, the ongoing rate of water losses must be addressed simultaneously.
     d. Because hypovolemia is present in more than 50% of cases of hypernatremia, concurrent volume replacement with isotonic fluid should be administered (0.9% sodium chloride [NaCl]) when appropriate. An alternative strategy is to use a single infusion of 0.45% saline solution that replaces salt and water. For example, 1 L of 0.45% NaCl adds 500 ml of water and 500 ml of 0.9% NaCl to the total body water.
     e. The change in S_{Na} with 1 L of a particular replacement fluid can be predicted by the following formula:
        (1) Change in S_{Na} = ($Na_{Infusate}$ – current S_{Na}) / (TBW + 1).
     f. This formula applies to the one-time administration of a 1-L infusate with a sodium concentration ($Na_{Infusate}$). $Na_{Infusate}$ concentrations for 0.45% saline, 0.9% saline, and 3% saline are, respectively, 77, 154, and 513 mEq/L.
  4. Step 4: Assess ongoing water losses.
     a. Ongoing daily water losses must be determined and added to the water deficit volume. Water losses occur from urinary water excretion and insensible losses from the skin, stool, and respiratory tract. Failure to account for these losses will result in undercorrection of hypernatremia.
     b. Urinary losses can be estimated by the electrolyte-free water clearance equation in Fig. 2.
     c. Insensible water losses can be estimated as 15 to 20 ml/kg/day.
- If hypernatremia is due to hypervolemia, consider the addition of loop diuretics to remove excess sodium.
- Evaluate for any underlying cause of hypernatremia and treat accordingly.
- Replace other electrolyte deficits such as potassium, and potassium deficits generally should be addressed before correction of hypernatremia.
- Repeat steps 1 through 4 until S_{Na} is reduced to approximately 140 to 145 mEq/L.
- The preceding formulas represent only guidance. Largely due to errors intrinsic to TBW estimation and fluid losses, underestimation or overestimation is common. Therefore, trend analysis of S_{Na} is critical. Serial measurements of S_{Na} must be evaluated with subsequent treatment based on results. Laboratory evaluations may be required at relatively brief intervals, that is, every 2 h during initial management.

DISPOSITION

Management of hypernatremia generally warrants inpatient admission because patients have underlying conditions that impair the thirst response.

REFERRAL

Nephrology consultation for management of hypernatremia and evaluation of underlying causes is appropriate. Endocrinology consultation may be warranted if diabetes insipidus is suspected.

PEARLS & CONSIDERATIONS

COMMENTS

- Hypernatremia is a problem of water deficit that is associated with an impaired thirst mechanism.
- Volume deficits may be present simultaneously.
- The rate of correction of S_{Na} includes determination of ongoing water losses and the water deficit.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Diabetes Insipidus (Related Key Topic)

AUTHORS: **Lalathaksha Kumbar, MD,** and **Reem Yusufani, MD**

SUGGESTED READINGS

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Arora SK: Hypernatremia disorders in the intensive care unit, *J Intensive Care Med* 28:37, 2011.

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BASIC INFORMATION

DEFINITION

Hyperparathyroidism is an endocrine disorder caused by excessive secretion of parathyroid hormone (PTH) from the parathyroid glands. Autonomous production of PTH resulting in hypercalcemia defines primary hyperparathyroidism. Secondary hyperparathyroidism occurs when the parathyroid glands appropriately increase PTH production in response to low calcium or vitamin D states. Primary hyperparathyroidism is the focus of this section.

ICD-10CM CODES

E21.0	Primary hyperparathyroidism
E21.1	Secondary hyperparathyroidism, not elsewhere classified
E21.2	Other hyperparathyroidism
E21.3	Hyperparathyroidism, unspecified
N25.81	Secondary hyperparathyroidism of renal origin

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Four cases per 100,000 persons per yr. Although malignancy is the most common cause of hypercalcemia in hospitalized patients, primary hyperparathyroidism is the most common cause of hypercalcemia in the outpatient setting.

PREVALENCE: Varies by country and race with approximately nine cases/1000 persons in the United States.

PREDOMINANT SEX AND AGE: Higher prevalence in women (female:male ratio 3 to 4:1) and older age (peaks in the seventh decade of life).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The majority of patients with primary hyperparathyroidism are asymptomatic. Diagnosis is usually considered in patients after an incidental discovery of elevated calcium or PTH levels on biochemical screening or during the evaluation for decreased bone mass. The development of symptoms varies with severity and rapidity of disease progression and reflects both the hypercalcemic and hyperparathyroid components of the disease process.

- Cardiovascular: Hypertension, shortened QT interval, bradycardia, arrhythmia, valvular calcification, left ventricular hypertrophy, increased mean carotid intima-media thickness
- GI: Anorexia, nausea, vomiting, constipation, abdominal pain, peptic ulcer disease, pancreatitis
- Genitourinary (GU): Nephrolithiasis, nephrocalcinosis, renal insufficiency, polydipsia, polyuria, nocturia, nephrogenic diabetes insipidus, renal tubular acidosis
- Musculoskeletal: Weakness, myopathy, bone pain, osteopenia, osteoporosis, gout, pseudogout, chondrocalcinosis, osteitis fibrosa cystica, subperiosteal bone resorption (Fig. E1)
- CNS: Confusion, anxiety, fatigue, lethargy, obtundation, depression, coma
- Other: Pruritus, metastatic calcifications, band keratopathy

ETIOLOGY

- Most cases of primary hyperparathyroidism are sporadic, but hyperparathyroidism can be associated with rare familial conditions such as multiple endocrine neoplasia (MEN-1 and MEN-2). Mutations in certain genes have been linked to tumor development in both sporadic and familial cases such as hyperparathyroidism-jaw tumor syndrome. Higher prevalence of hyperparathyroidism is noted with head and neck irradiation, chronic low calcium or vitamin D status, and lithium therapy.
- Pathologic characteristics include adenoma (80%), hyperplasia (15% to 20%), or carcinomas (<1%).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary hyperparathyroidism:
  1. Adenoma (80%)
  2. Hyperplasia (15% to 20%)
  3. Carcinomas (<1%)
- Secondary hyperparathyroidism precipitated by conditions that result in hypocalcemia:
  1. Renal calcium loss (i.e., medication: Loop diuretics and hypercalciuria)
  2. Calcium deficiency
  3. Vitamin D deficiency
  4. Malabsorption
  5. Chronic kidney disease (most common)
  6. Pseudohypoparathyroidism (PTH resistance)
  7. Inhibition of bone resorption (i.e., bisphosphonates and denosumab)
- Other causes of hypercalcemia include:
  1. Medications: Thiazide diuretics, lithium therapy
  2. Vitamin D intoxication, milk-alkali syndrome
  3. Familial hypocalciuric hypercalcemia (FHH)
  4. Renal failure (tertiary hyperparathyroidism)
  5. Thyrotoxicosis
  6. Granulomatous disorders (e.g., sarcoidosis)
  7. Malignancy (e.g., lung cancer, lymphoma, multiple myeloma, bone metastasis)
  8. Prolonged immobilization

WORKUP

- Typically, primary hyperparathyroidism is confirmed with an elevated serum calcium and PTH level.
  1. Two measurements of serum calcium are required for the confirmation of hypercalcemia. Total calcium should be corrected for low albumin utilizing the formula: Corrected Calcium = Serum Calcium + 0.8 × 4 − serum albumin. If a reliable laboratory is available, ionized calcium should be considered, especially in conditions associated with acid-base disturbances or low albumin states. Patients with primary hyperparathyroidism can also present with normal calcium levels (normocalcemic primary hyperparathyroidism).
  2. The serum intact PTH (iPTH) level is the single best test to evaluate the etiology of hypercalcemia. PTH is elevated or in the high normal range (i.e., inappropriately normal for an elevated calcium state) in primary hyperparathyroidism. PTH is decreased in most other conditions associated with elevated calcium.
- Other causes of hypercalcemia should be ruled out. These are typically associated with low PTH levels. Exceptions include lithium use and FHH.
  1. Review medication history to determine lithium, thiazide, vitamin D, or calcium intake.
  2. Check 24-hour urine calcium:creatinine to rule out FHH. Urine calcium is very low (<100 mg) and calcium clearance/creatinine clearance ratio is <0.01 in FHH. PTH can be normal or high in FHH.
  3. Consider PTH-related peptide (PTHrP) to evaluate hypercalcemia related to malignancies and vitamin D 1,25 to assess hypercalcemia secondary to granulomatous diseases or lymphomas.
  4. Multiple myeloma and bone metastasis can also result in a high calcium state and therefore must be appropriately evaluated.
- Rule out other causes of elevated PTH (i.e., secondary hyperparathyroidism). Serum calcium is typically low or low-normal in secondary hyperparathyroidism.
  1. Check calcium and 25 OH-vitamin D to rule out deficiency states.
  2. Check serum creatinine to assess renal function and 24-hour urine calcium and creatinine to evaluate renal loss.

LABORATORY TESTS

- Serum calcium (ionized or corrected calcium): Normal or elevated in primary hyperparathyroidism
- Serum phosphorus: Low or low-normal in primary hyperparathyroidism
- PTH: Elevated or high-normal in primary hyperparathyroidism
- Serum creatinine and estimated glomerular filtration rate (eGFR)
- 24-hour urine calcium and creatinine
- PTHrP and 1,25 OH-vitamin D levels 25 OH-vitamin D level
- ECG may reveal shortening of the QT interval secondary to severe hypercalcemia (>12 mg/dl)

IMAGING STUDIES

- Parathyroid localization with technetium-99m sestamibi (Figs. E2 and 3) can identify potential adenomas to help with surgical planning.
- Parathyroid ultrasound (Fig. 4) and computed tomography (CT) are also used to localize the parathyroid adenoma.

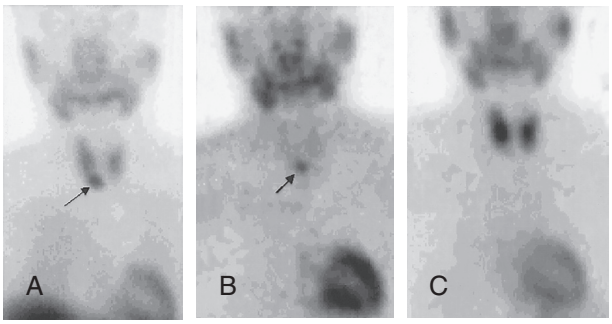

FIG. 3 Parathyroid adenoma. 99m Tc-MIBI images at 10 min **(A)** and 3 h **(B)** showing a persistent focus of activity inferior to the right lobe of the thyroid; 99m TcO 4 image **(C)** shows normal thyroid uptake but the adenoma is not visualized. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

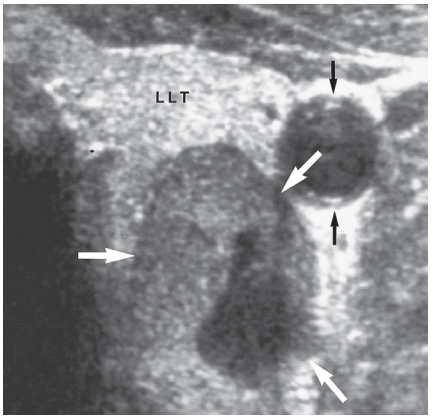

FIG. 4 High-resolution US of the left lobe of the thyroid (LLT) anterior to a parathyroid adenoma *(white arrows).* There is a small area of cystic degeneration within the posterior aspect of the adenoma. Carotid artery *(black arrows).* (From Adam A et al: *Grainger & Allison's diagnostic radiology,* ed 5, 2007, Churchill Livingstone; in Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

FIG. 6 Secondary hyperparathyroidism. Lateral radiograph of the thoracic spine demonstrating increased sclerosis along the end-plates and increased lucency of the central part, giving a "rugger jersey" spine appearance. Also note deformity of the vertebral bodies, with loss of height and increased diameter, in addition to wedge-shaped deformities at the upper thoracic spine related to decreased stability and weakness of the abnormal bone. (From Adam A et al: *Grainger and Allison's diagnostic radiology,* ed 6, 2015, Elsevier; in Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

- Bone mineral density (BMD) imaging of the spine, hip, and forearm (distal third of radius) is recommended for all patients with hyperparathyroidism in order to assess the risk for osteoporosis and fragility fractures. Plain radiographic abnormalities are illustrated in Figs. E5 and 6. Cortical bone loss (i.e. forearm) is greater than trabecular bone loss (i.e. hip and spine) in hyperparathyroidism.
- Renal ultrasound can be considered to assess asymptomatic renal stones.

Rx TREATMENT

Modality of treatment depends on disease progression and which patients are more likely to suffer end-organ effects of hyperparathyroidism or benefit the most from surgery. Fig. 7 illustrates an algorithm for managing persistent or recurrent hyperparathyroidism.

- Surgery is the only definitive treatment for symptomatic primary hyperparathyroidism. Surgery can normalize calcium levels, decrease the risk for kidney stones, improve bone mineral density and fracture risk, and enhance quality of life measures.
  1. Indications for parathyroidectomy (Box 1):
     a. All patients younger than 50 yr
     b. Hypercalcemia (Ca >1 mg/dl above upper limit normal)
     c. Creatinine clearance <60 ml/min
     d. 24-h urine for calcium >400 mg/dl (>10 mmol/dl)
     e. Presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or CT
     f. Osteoporosis
        (1) Bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA): T-score ≤2.5 at lumbar spine, total hip, femoral neck, or distal third of radius
        (2) Vertebral fracture by x-ray, CT, MRI, vertebral fracture assessment (VFA) by DXA
  2. Surgical approaches include:
     a. Minimally invasive parathyroidectomy has increased in popularity. The surgeon will identify and remove the abnormal gland that was identified on preoperative imaging. This technique has limited dissection and has improved recovery time. Intraoperative monitoring of PTH level is done to ensure the removal of the abnormal gland. Fall of PTH level by 50%, into the normal range, is expected within 10 to 15 min after removal of the abnormal gland.
     b. Bilateral neck exploration under general anesthesia is the traditional surgical approach. All parathyroid glands are identified and compared. An experienced endocrine surgeon cures >95% of patients undergoing bilateral neck exploration. Potential complications include transient and permanent hypocalcemia secondary to hypoparathyroidism and recurrent laryngeal nerve injury.
- Ablation therapy (e.g., ethanol, angiographic, radiofrequency) can be considered in patients who are not surgical candidates. Limited data are available on efficacy and side effects. Repeat ablations may be required if hypercalcemia persists.
- Medical management:
  1. Avoid medications that precipitate hypercalcemia (e.g., thiazide or lithium)
  2. Because inadequate calcium and vitamin D status stimulates PTH, it is not necessary to significantly restrict calcium and vitamin D intake. Vitamin D replacement safely improves vitamin D level and decreases PTH level without significantly increasing serum calcium level and urinary calcium excretion. Repletion of vitamin D is recommended in patients whose levels are <30 mg/dl (75 mmol/L). Dietary calcium intake should be approximately 1000 mg/day.
  3. Encourage physical activity since immobilization increases bone resorption.
  4. Recommend adequate hydration (at least 2 L) to minimize the risk of nephrolithiasis.
     a. For patients who are not surgical candidates or who refuse surgery, pharmacologic options are available. The choice of pharmacologic agents is dependent on the desired goal. Cinacalcet (Sensipar) is an oral calcimimetic agent that activates the calcium sensing receptor in the para-

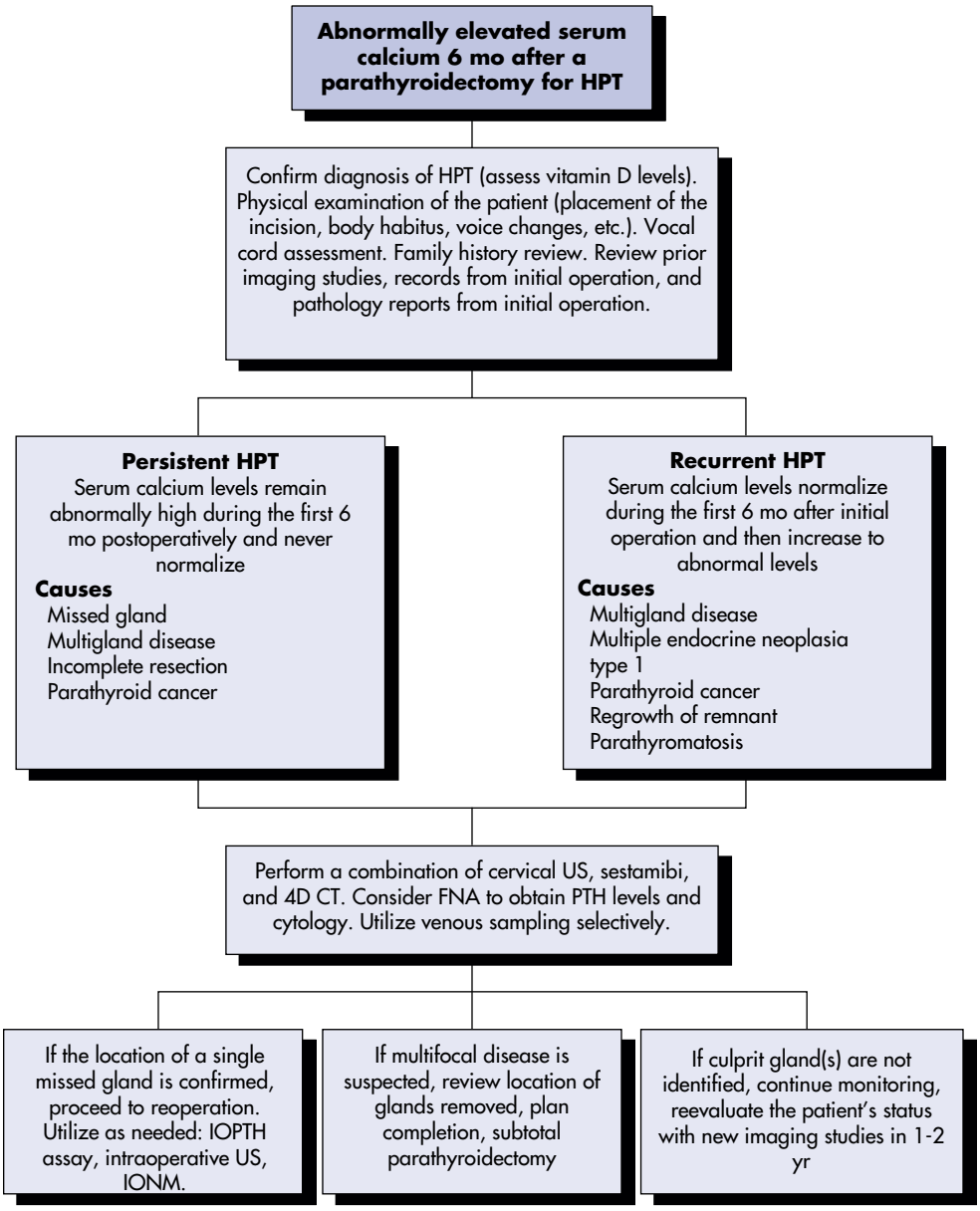

FIG. 7 Algorithm for managing persistent or recurrent hyperparathyroidism (HPT). *4D CT*, Four-dimensional computed tomography; *FNA*, fine-needle aspiration; *IONM*, intraoperative neurophysiologic monitoring; *IOPTH*, intraoperative parathyroid hormone; *PTH*, parathyroid hormone; *sestamibi*, technetium (^{99m}Tc) sestamibi imaging; *US*, ultrasonography. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

BOX 1 Indications for Parathyroidectomy in Patients With Secondary and Tertiary Hyperparathyroidism

Indications for Parathyroidectomy in Patients with Secondary Hyperparathyroidism (SHPT)

SHPT refractory to medical therapy:
- Parathyroid hormone >1000 pg/ml
- Calcium × Phosphorus product >55

Renal osteodystrophy
Calciphylaxis
Other retractable symptoms, including uremic pruritus, persistent anemia, bone pain, muscle pain, abdominal pain, fatigue, and weakness

Indications for Parathyroidectomy in Patients With Tertiary Hyperparathyroidism

Severe hypercalcemia (calcium >12.5 mg/dl)
Persistent hypercalcemia ≥2 yr after renal transplantation, associated with:
- Decline in renal function, without graft rejection
- Nephrolithiasis
- Progressive bone disease
- Pancreatitis

From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.

thyroid gland. It decreases PTH production and subsequently normalizes or decreases serum calcium levels, without significant BMD changes. It is indicated for the treatment of severe hypercalcemia in patients with primary hyperparathyroidism who are unable to undergo surgery. It is also indicated for the treatment of secondary hyperparathyroidism associated with chronic kidney disease and for hypercalcemia associated with parathyroid carcinoma.

b. Agents such as bisphosphonates (e.g., alendronate, zoledronate) that inhibit bone resorption and increase BMD should be considered when improvement in BMD is the primary goal in patients with hyperparathyroidism.

- Medical monitoring is recommended for asymptomatic primary hyperparathyroidism. The majority of patients do not manifest disease progression during observation. However, approximately 25% of asymptomatic patients require surgery over a 10-yr follow-up period.
  1. Indications for medical monitoring:
     a. Clinically asymptomatic and >50 yr old
     b. Serum calcium level only mildly elevated (<1 mg/dl above upper limit normal)
     c. GFR >60 ml/min and no nephrolithiasis or nephrocalcinosis
     d. No evidence of osteoporosis
     e. Medically unfit for surgery or refusing surgery
- Symptoms should be assessed regularly. Serum calcium, PTH, creatinine, and eGFR should be checked semiannually. DXA performed at three sites every 1 to 2 yr or vertebral fracture assessment of the spine is clinically indicated (e.g., height loss, back pain).

ACUTE GENERAL Rx

Severe and/or symptomatic hypercalcemia may require hospitalization, especially if serum calcium >12 mg/dl. Acute management of hypercalcemia includes:

- Vigorous hydration with IV normal saline (2 to 4 L/day). Fluid status must be monitored in patients with cardiac dysfunction or renal insufficiency in order to avoid fluid overload.
- Bisphosphonates can effectively decrease calcium levels. Zoledronate (4 mg IV over 15 min) or pamidronate (60 to 90 mg IV over 4 hours) are both effective. Onset of action is 24 to 48 hours.
- Calcitonin (4 units/kg IM/SC every 12 hours) may be used with bisphosphonates to achieve a more rapid reduction of calcium levels. Onset of action is within hours.

PEARLS & CONSIDERATIONS

COMMENTS

- Parathyroidectomy should be considered for all patients with symptomatic hyperparathyroidism. If surgery is contraindicated or not desired, cinacalcet and bisphosphonates can be used.
- Asymptomatic patients can be monitored with serial calcium, creatinine, eGFR, and bone mineral density measurements. Disease progression may result in surgery.
- Most patients can be managed medically by limiting factors that result in hypercalcemia (e.g., dehydration, immobilization, thiazide diuretics) and maintaining normal calcium and vitamin D intake.
- Patients with osteopenia and high fracture risk may require antiresorptive therapy such as bisphosphonates.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hyperparathyroidism (Patient Information)

AUTHOR: **Vicky Cheng, MD**

SUGGESTED READINGS

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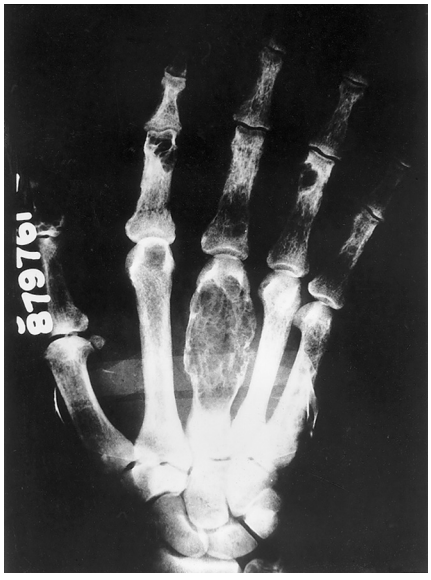

FIG. E1 Radiograph of hand from a patient with severe primary hyperparathyroidism. Note the dramatic remodeling associated with the intense region of high bone turnover in the third metacarpal, in addition to widespread evidence of subperiosteal and trabecular resorption. (Courtesy Fuller Albright Collection, Massachusetts General Hospital. From Larsen PR et al [eds]: *Williams textbook of endocrinology,* ed 10, Philadelphia, 2003, WB Saunders.)

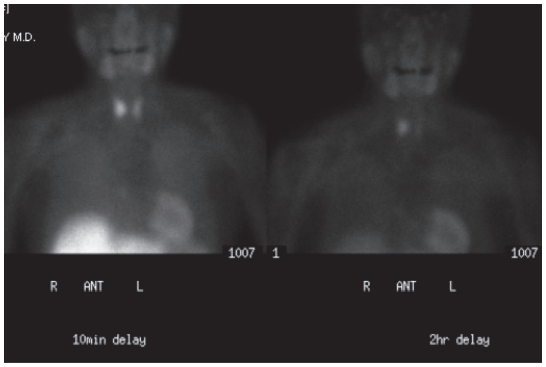

FIG. E2 Role of scintigraphy in detecting parathyroid adenomas. A 66-yr-old woman with hypercalcemia. CT (not shown) did not reveal a parathyroid adenoma. 99m Tc-sestamibi radionuclide imaging demonstrates uptake in both thyroid and parathyroid parenchyma in the 10-min delayed image (left); however, at 2-hour delay, imaging (right) demonstrates persistent uptake in the right lobe of the thyroid gland, representing the parathyroid adenoma (From Adam A, Dixon AK, Gillard JH, Schaefer-Prokop CM: Grainger and Allison's *diagnostic radiology,* ed 6, Elsevier, 2015, in Grant LA: Grainger & Allison's *diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

FIG. E5 Hyperparathyroidism. Chondrocalcinosis in the knee menisci **(A)** and **(B)** the symphysis pubis. **(C)** Subperiosteal erosions along the radial side of the middle phalanx of the 2nd finger. Acro-osteolysis is also present. Metastatic calcification of the digital artery confirms this is secondary hyperparathyroidism. **(D)** cortical "tunneling" in the proximal phalanges. **(E)** Brown tumor within the distal tibia. **(F)** Precipitation of amorphous calcium phosphate in the soft tissues of the shoulder (hyperparathyroidism secondary to chronic renal disease. (From Adam A et al: *Grainger & Allison's diagnostic radiology,* ed 5, 2007, Churchill Livingstone; in Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Hypersensitivity pneumonitis (HP) is a group of immunologically mediated pulmonary diseases, with or without systemic manifestations (e.g., fever, weight loss), caused by the inhalation of an antigen to which the patient is sensitized and hyperresponsive. Sensitization and exposure alone in the absence of symptoms do not define the disease.

SYNONYMS

HP - Extrinsic allergic alveolitis (EAA)
Bird fancier's lung
Farmer's lung
Malt worker's lung
"Ventilation" pneumonitis
Maple bark-stripper's lung
Sauna taker's lung
Hot tub lung

ICD-10CM CODES

J67.x Hypersensitivity pneumonitis due to specific organic dusts
J67.9 Hypersensitivity pneumonitis due to unspecified organic dust

EPIDEMIOLOGY & DEMOGRAPHICS

- Estimates of the prevalence and incidence of HP vary considerably and depend on the definition and methods used to establish the diagnosis.
- Clinical presentation depends on the intensity of exposure, environmental conditions, and genetic risk factors that remain poorly understood.
- More than 300 causative agents have been identified, and the number continues to grow.
- Causative agents in residential and occupational exposures include birds, mold, humidifiers, fountains, steam irons, dry sausage molds, moldy cheese, contaminated wood, biofilm contained within wind instruments (e.g., trombone, saxophone), and organic and inorganic chemicals, including metalworking fluids.
- It is likely that genetic factors are also involved that result in an exaggerated lung response to an offending agent. The major histocompatibility complex is the most studied thus far.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Vary depending on frequency and intensity of antigen exposure.

- Acute: Fever, cough, malaise, and dyspnea 4 to 6 hours after an intense exposure. Symptoms resolve with removal of the inciting agent, typically within 12 to 24 hours
- Often misdiagnosed initially as a viral illness or asthma
- Subacute: Insidious onset of productive cough, dyspnea on exertion, anorexia, and weight loss, usually from a heavy, sustained exposure
- Chronic: Gradually progressive cough, dyspnea, malaise, and weight loss, usually from low-grade or recurrent exposure
- Physical examination: Hypoxemia, cyanosis, rales, possible fever

ETIOLOGY

- Numerous environmental agents, often encountered in occupational settings.
- Common sources of antigens: "Moldy" hay, silage, grain, or vegetables; bird droppings or feathers (including those found commonly in down pillows, blankets, and upholstered furniture); low-molecular-weight chemicals (e.g., isocyanates); pharmaceutical products.
- Fig. E1 illustrates the pathogenesis of hypersensitivity pneumonitis.

DIAGNOSIS

- Accurate diagnosis is important for differentiating HP from other interstitial lung diseases because the prognosis and treatment may differ.
- The clinical syndrome of acute HP is indistinguishable from an acute respiratory infection with a history of illness occurring within hours of exposure to an antigen.
- Need high index of suspicion.
- Detailed occupational and home exposure history is required.
- Lung biopsy is often necessary for diagnosis.

DIFFERENTIAL DIAGNOSIS

Acute Stages	Chronic Stages
Allergic bronchopulmonary aspergillosis	Idiopathic pulmonary fibrosis (IPF)
Pulmonary embolism	Bronchiectasis
Asthma	Chronic bronchitis
Aspiration pneumonia	Nonspecific interstitial pneumonia (NSIP)
Bacterial pneumonia	Connective tissue–related lung disease
Fungal or mycobacterial pneumonia	Sarcoidosis
Bronchiolitis obliterans–organizing pneumonia	
Eosinophilic pneumonia	
Churg-Strauss syndrome	
Wegener granulomatosis	

WORKUP

No single radiologic, physiologic, or immunologic test is specific for the diagnosis of HP. HP must be suspected in any patient presenting with cough, dyspnea, fever, and malaise. A thorough history focusing on potential exposures is essential. Table 1 describes examples of occupational causes of HP.

Environmental and occupational history questions should ask about grain dusts, animal handling, food processing, cooling towers, fountains, metal-working fluids, symptom improvement away from exposure, pets (particularly

TABLE 1 Examples of Occupational Causes of Hypersensitivity Pneumonitis

Occupation	Cause
Farmer	Thermophilic actinomycetes in moldy hay
Metal worker	Contamination of metal-working fluids with microorganisms such as *Mycobacteria immunogens* or fungi
Worker exposed to humidifiers	Contamination with microorganisms such as protozoa or fungi
Sugarcane worker	Moldy sugarcane (bagassosis)
Maple bark stripper	Fungi
Chicken or turkey worker	Avian proteins
Pharmaceutical worker	Penicillin
Food handler	Soybeans
Office worker	Microorganisms contaminating air conditioners or humidifiers
Swimming pool attendant	Fungal contamination in sprays around pool area
Animal worker	Rat proteins
Mushroom worker	Fungi
Wheat farmer or handler	Weevil-infested flour
Greenhouse worker	Fungi
Workers spraying urethane paint or adhesives/sealants (or less often, other workers using diisocyanate)	Methylene diphenyl diisocyanate, hexamethylene diisocyanate, toluene diisocyanates
Chemical worker using plastics, resins, paints	Trimellitic anhydride

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.

birds), hobbies involving chemicals, feathers, or fur, organic dusts, presence of humidifiers, dehumidifiers, or hot tubs/saunas, leaking or flooding indoors, visible fungal growth in living or working environment, feather pillows, bedding, or upholstered furniture.

Major diagnostic criteria:

- History of compatible clinical symptoms, physical exam, changes on chest radiograph or high-resolution CT (HRCT) of the chest, and pulmonary function tests. Particularly suspicious if symptoms appear to worsen within hours after antigen exposure
- Confirmation of exposure to the offending agent by history, investigation of the environment, serum precipitin tests to potential agents (often referred to as a "hypersensitivity panel" by many labs)
- BAL fluid lymphocytosis (if performed)
- Compatible histologic changes by lung biopsy (if performed): Poorly formed granulomas or mononuclear cell infiltrate
- Positive natural challenge (reproduction of symptoms and laboratory abnormalities after exposure to the suspected environment) or controlled inhalation challenge

LABORATORY TESTS

- Routine laboratory tests do not make the diagnosis, but typically the erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, and leukocyte count are increased; elevated immunoglobulins IgG and IgM are nonspecific; rheumatoid factor (RF) and immune complexes are often positive; peripheral eosinophil count and serum IgE are generally normal.
- Lactate dehydrogenase (LDH) is increased and tends to decrease with improvement.
- Pulmonary function tests: Restrictive ventilatory pattern is typically seen. Decreased FEV_1, decreased forced vital capacity, decreased total lung capacity, decreased diffusion capacity, and decreased static compliance.
- Arterial blood gases show mild hypoxemia (worsens with exercise).
- A-a gradient shows slight increase.
- Serum precipitin test for IgG antibodies against offending antigen may be positive in serum. Precipitins are sensitive but not specific for HP (asymptomatic patients may have IgG antibodies in serum). HP may also be present without a positive precipitin test.
- Skin testing is generally not helpful in establishing a diagnosis.

IMAGING STUDIES

Chest x-ray: Nonspecific; may be normal in early stage.

- Acute/subacute: Bilateral interstitial and alveolar nodular infiltrates in a patchy or homogeneous distribution.
- Chronic: Diffuse reticulonodular infiltrates and fibrosis.

High-resolution chest CT scan (Fig. 2): No pathognomonic features but demonstrates airspace and interstitial patterns in the acute and subacute stage. The chronic stage reveals honeycombing, air trapping, and bronchiectasis.

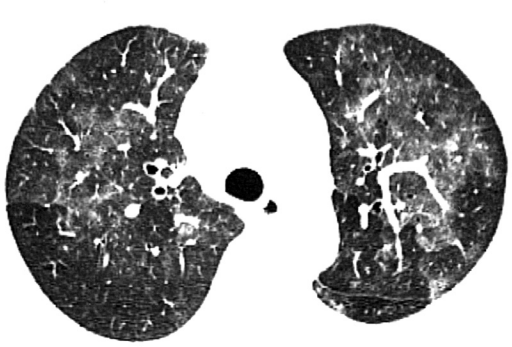

FIG. 2 In this patient with hypersensitivity pneumonitis, patchy ground-glass opacity is visible bilaterally. (From Mason RJ: *Murray & Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, WB Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Early recognition and avoidance of the causative antigen

ACUTE GENERAL Rx

- Glucocorticoids accelerate initial lung recovery but may have no effect long term (from a controlled study in farmer's lung). No prospective, randomized, placebo-controlled trials for other types of HP or subacute and chronic stages.
- Prednisone 0.5 to 1 mg/kg usually over 1 to 2 wk then tapered over 4 wk. Some patients, particularly those with subacute or chronic presentation, may require a longer course of therapy.

DISPOSITION/PROGNOSIS

Prognosis is generally better in patients with acute or subacute HP. Prognosis is worse in those with older age, desaturation during exercise, and findings of severe fibrosis by lung biopsy.

Acute: 4 to 48 hours

- Clinical: Fever, chills, cough, hypoxia, malaise
- HRCT: Ground-glass infiltrates
- Immunopathology: Poorly formed, noncaseating granulomas or mononuclear cell infiltration in a peribronchial distribution, frequently with giant cells
- Prognosis: Good

Subacute: Wks to 4 mo

- Clinical: Dyspnea, cough, episodic flares
- HRCT: Micronodules, air trapping
- Immunopathology: More well-formed, noncaseating granulomas, bronchiolitis, organizing pneumonia, and interstitial fibrosis
- Prognosis: Good

Chronic: 4 mo to yr

- Clinical: Dyspnea, cough, fatigue, weight loss
- HRCT: Fibrosis (possible), honeycombing, emphysema
- Immunopathology: Granulomatous inflammation may be seen in addition to bronchiolitis obliterans (with or without organizing pneumonia) and honeycombing and fibrosis, lymphocytic infiltration, centrilobular and bridging fibrosis, neutrophil-mediated air space destruction, giant cells
- Prognosis: Generally poor

REFERRAL

- Bronchoscopy: BAL provides useful supportive data in the diagnosis of HP. Usually reveals intense lymphocytosis (typically T cells >50%) of predominantly CD8+ suppressor cells. In the acute stage, neutrophils predominate, but as the disease progresses to chronic form, the ratio of CD4+ to CD8+ cells increases. When fibrosis is present the number of neutrophils increases.
- Lung biopsy: The histopathologic features of HP are distinctive but not pathognomonic. Bronchiolitis and interstitial pneumonitis with granuloma formation typically is seen. Variable degrees of interstitial fibrosis are seen in the chronic form. Chronic HP may be difficult to distinguish from IPF or NSIP pathologically.
- Laboratory inhalation challenge: Testing to prove a direct relation between a suspected antigen and disease; extract of antigen is inhaled by nebulizer.

PEARLS & CONSIDERATIONS

A clinical prediction rule using six features has high specificity and sensitivity for the diagnosis of acute and subacute HP:

- Exposure to a known offending agent
- Positive specific precipitating antibody
- Recurrent episodes of symptoms
- Inspiratory crackles
- Symptoms occurring 4 to 8 hr after exposure
- Weight loss

HP occurs more frequently in smokers than nonsmokers (likely from an immunosuppressive effect).

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hypersensitivity Pneumonitis (Patient Information)

AUTHOR: **Melissa H. Tukey, MD, MS**

SUGGESTED READINGS

Churg A: Chronic hypersensitivity pneumonitis, *Am J Surg Pathol* 30(2):201, 2006.
Costabel U et al: Chronic hypersensitivity pneumonitis, *Clin Chest Med* 33:151-163, 2012.
Fishwick D et al: New occupational and environmental causes of asthma and extrinsic allergic alveolitis, *Clin Chest Med* 33:605-616, 2012.
Lacasse Y et al: Recent advances in hypersensitivity pneumonitis, *Chest* 142:208-217, 2012.
Metzger F et al: Hypersensitivity pneumonitis due to molds in a saxophone player, *Chest* 138(3), 2010.

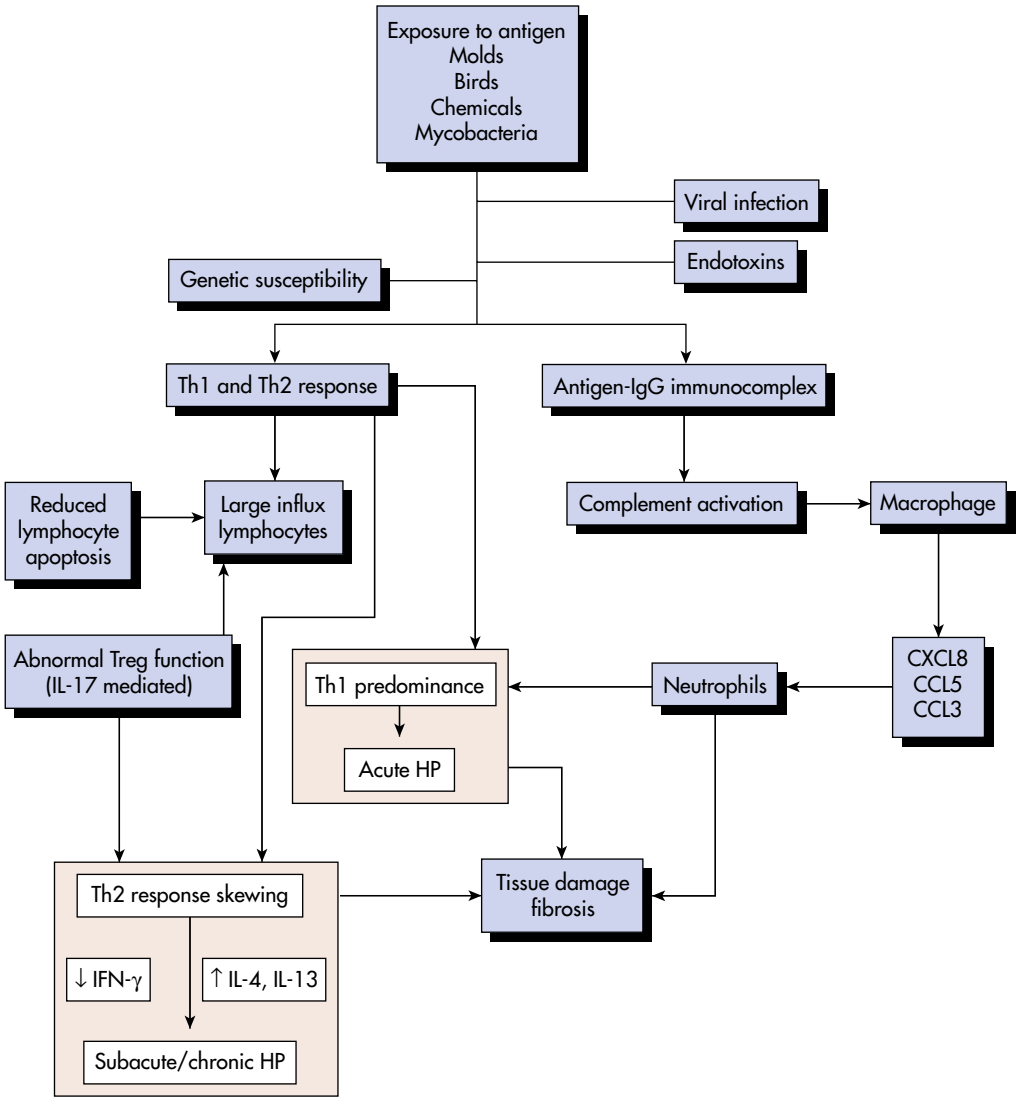

FIG. E1 Pathogenesis of hypersensitivity pneumonitis (HP). Chronic and repeated exposure to antigens in genetically susceptible individuals triggers an inflammatory process. A T-helper (Th) 1 response predominates in the early stages, whereas Th2 skewing occurs in later stages, both leading to tissue damage from inflammatory propagation and cytokine release. Lung tissue lymphocytes are increased because of decreased lymphocyte apoptosis and impaired regulatory T cell (Treg) function (mediated by interleukin [IL]-17). Early inflammatory changes include IgG binding to antigen and complement pathways with macrophage activation and secretion of chemoattractants (CXCL8, CCL5, CCL3) that induce neutrophilic airway infiltration and tissue destruction. *IFN,* Interferon; *Ig,* immunoglobulin. (From Adkinson NF et al: *Middleton's allergy principles and practice,* ed 8, Philadelphia, 2014, WB Saunders.)

BASIC INFORMATION

DEFINITION

Hypersplenism is a syndrome characterized by splenomegaly, cytopenias (one or more of the following: Anemia, thrombocytopenia, or leukopenia), and compensatory hyperplastic bone marrow. These cytopenias are correctable with splenectomy.

ICD-10CM CODE
D73.1 Hypersplenism

EPIDEMIOLOGY & DEMOGRAPHICS

Most often seen in patients with liver disease, hematologic malignancy, and infection.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms depend on the size of the spleen, rate of growth, and underlying disease
- History: Early satiety, abdominal discomfort or fullness, acute left upper quadrant (LUQ) pain (infarction, sequestration crisis), referred pain to left shoulder
- Physical examination: Splenomegaly (normal spleen usually not palpable), LUQ tenderness, presence of a rub in LUQ (suggestive of splenic infarct), stigmata of cytopenias

ETIOLOGY

- The spleen is an important component of the hematologic and immune systems (antigen processing and antibody synthesis). The spleen is responsible for the modification (removal of particles and parasites) and clearance of senescent or poorly deformable red blood cells (RBCs). It also filters blood, removing foreign particles (microorganisms) and other particulates (e.g., complement- or antibody-coated cells) from the circulation. The spleen is a platelet reservoir, storing 30% of platelet mass. It can become the site of hematopoiesis in certain disease states. The spleen's normal activities are augmented when enlarged.
- Splenomegaly increases the proportion of blood channeled through the red pulp, causing inappropriate splenic pooling of both normal and abnormal blood cells. The size of the spleen determines the amount of cell sequestration. Up to 90% of platelets may be pooled in an enlarged spleen. Prolonged sequestration leads to increased destruction of RBCs. Platelets and white blood cells (WBCs) have about normal survival time even when sequestered and may be available if needed.
- Splenomegaly exacerbates cytopenias by dilution, possibly due to plasma volume expansion.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Hypersplenism can be caused by splenomegaly of almost any cause.

- Splenic congestion: Cirrhosis (portal hypertension); congestive heart failure; portal, splenic, or hepatic vein thrombosis
- Hematologic causes: Hemolytic anemia, spherocytosis, elliptocytosis, sickle cell anemia, thalassemia, extramedullary hematopoiesis, chronic transfusions, following use of granulocyte colony-stimulating factor
- Infections: Viral (hepatitis, infectious mononucleosis, cytomegalovirus, HIV/AIDS), bacterial (endocarditis, sepsis, tuberculosis, salmonella, brucella), parasitic (babesiosis, malaria, leishmaniasis, schistosomiasis, toxoplasmosis), fungal
- Malignancy: Acute or chronic leukemia, lymphoma, myeloproliferative diseases (polycythemia vera, essential thrombocythemia, myelofibrosis), splenic or metastatic tumors
- Inflammatory diseases: Rheumatic fever, rheumatoid arthritis (Felty syndrome), systemic lupus erythematosus, sarcoid, serum sickness
- Infiltrative diseases: Amyloidosis, Gaucher disease, Niemann-Pick disease, glycogen storage disease

WORKUP

History (including travel), physical examination, laboratory tests, imaging studies

LABORATORY TESTS

- CBC with differential: Cytopenias, neutrophilia (infection)
- Peripheral smear: RBC and WBC morphology (abnormal cells may suggest infection, malignancy, bone marrow disease, rheumatologic disease), organisms (bacteria, malaria, babesiosis)
- Bone marrow aspiration/biopsy: Hyperplasia of cytopenic cell lines; hematologic, infiltrative, or infectious disorders
- Tests to diagnose suspected cause of splenomegaly: Liver function, hepatitis serology, HIV, rheumatoid factor, antinuclear antibody, tissue biopsy
- NOTE: Red cell mass (^{51}Cr assay) may be used to assess severity of anemia. RBC mass measurement will differentiate true anemia (decrease in RBCs) from dilutional anemia (plasma volume expansion)

IMAGING STUDIES

Choice of imaging study depends on suspected underlying pathology.

- Ultrasound: Splenic size, presence of cyst or abscess
- CT with contrast: Estimate volume, obtain structural information: Cyst, abscess, malignancy
- MRI: Most useful for assessing vascular lesions and infections
- Nuclear medicine: Liver-spleen scan: Assess anatomy and function; may suggest presence of portal hypertension
- Consider additional tests as suggested by history and exam: Chest radiograph, echocardiogram, PET scan

TREATMENT

ACUTE GENERAL Rx

- Treat underlying disease
- Splenectomy is considered if:
  1. Indicated for the management of the underlying cause
  2. Persistent symptomatic disease (severe cytopenia) not responding to therapy
  3. Necessary for diagnosis

RISKS:

- Infections (especially encapsulated organisms): Risk greatest in the first 2 yr after splenectomy. Asplenic patients have a twofold to threefold increase of sepsis and infection-related mortality. Attempts to decrease risk include:
  1. Immunization with pneumococcal (PCV13 and PPSV23), meningococcal (MenACWY and MenB), and *Haemophilus influenza* type b (Hib) vaccines (if not previously vaccinated) at least 2 wk before splenectomy. Preferred: PCV13 vaccination followed by PPSV23 vaccination at least 8 wk later. If already immunized with PPSV23, PCV13 vaccine should be given at least 1 yr later. Revaccination with PPSV23 in 5 yr and again after age 65 yr (and 5 yr after most recent dose). Revaccination for meningococcal (MenACWY) every 5 yr. Annual inactivated or recombinant influenza vaccination. NOTE: If unable to vaccinate 2 wk before splenectomy, vaccinate 2 wk after surgery. Ensure all age-appropriate vaccinations are up to date.
  2. Prophylactic antibiotics after splenectomy in highest-risk patients.
  3. Patient education regarding the importance of rapid initiation of antibiotics and seeking emergent care at the first sign of infection.
- Thromboembolic complications, especially high risk of portal vein thrombosis.
- Possible increased risk of atherosclerotic heart disease and cancer.
- Splenectomy should not be performed if the spleen is the main site of hematopoiesis as a result of bone marrow failure (e.g., myelofibrosis).
- Other options include partial splenectomy, partial splenic artery embolization, radiofrequency ablation, portosystemic shunting (for congestive splenomegaly).

DISPOSITION

- Cytopenias are usually correctable with splenectomy; normal cell counts return within a few weeks.
- Splenectomy may alleviate portal hypertension.
- Prognosis depends on the underlying disease.

REFERRAL

Hematology

PEARLS & CONSIDERATIONS

Thrombocytopenia in hypersplenism is usually moderately severe (>50 × 10^9/L) and asymptomatic; severe thrombocytopenia (<20 × 10^9/L) suggests another diagnosis.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hypersplenism (Patient Information)
Felty Syndrome (Related Key Topic)

AUTHOR: **Sudeep K. Aulakh, MD**

SUGGESTED READINGS

Centers for Disease Control and Prevention: *Recommended immunization schedule for adults aged 19 years or older, United States*. www.cdc.gov/vaccines/schedules.

Kristinsson SY et al: Long-term risks after splenectomy among 8,149 cancer-free American veterans: a cohort study with up to 27 years follow-up, *Haematologica* 99(2):392, 2014.

Lv Y et al: Causes of peripheral cytopenia in hepatitic cirrhosis and portal hypertensive splenomegaly, *Exp Biol Med* 242(7):744, 2017.

Wang YB et al: Partial splenic artery embolization to treat hypersplenism secondary to hepatic cirrhosis: a meta-analysis, *Am Surg* 83(3):274, 2017.

BASIC INFORMATION

DEFINITION

Normal blood pressure (BP) in adults can be defined as systolic BP <120 mm Hg and diastolic BP <80 mm Hg. Elevated blood pressure is defined as systolic BP between 120 and 129 mm Hg or diastolic BP <80 mm Hg. Hypertension can be divided into stage 1: systolic BP from 130 to 139 mm Hg or diastolic BP from 80 to 89 mm Hg and stage 2: systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg. This definition is based on accurate measurements and average of ≥2 readings on ≥2 occasions.

SYNONYMS

Essential hypertension
Idiopathic hypertension
High BP

ICD-10CM CODES	
I10	Essential (primary) hypertension
I15.0	Renovascular hypertension
I15.1	Hypertension secondary to other renal disorders
I15.2	Hypertension secondary to endocrine disorders
I15.8	Other secondary hypertension
I15.9	Secondary hypertension, unspecified
O10.919	Unspecified pre-existing hypertension complicating pregnancy, unspecified trimester
I67.4	Hypertensive encephalopathy

EPIDEMIOLOGY & DEMOGRAPHICS

- In the U.S., 50% of people age 60 to 69 yr and approximately 75% of people >70 yr of age are affected. Worldwide, it is estimated that 41% of people ages 35 to 70 yr have hypertension, and only 46.5% of them are aware of it.
- Peak prevalence increases with age and is highest among non-Hispanic black adults in the U.S.
- Hypertension is linked with a higher risk of heart attack, stroke, heart failure, and kidney disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Physical examination may be entirely within normal limits except for the presence of elevated BP. A proper initial physical examination on a hypertensive patient should include the following:

- The BP should be measured with an appropriately sized cuff (bladder of the cuff should cover at least two thirds of the circumference of the arm) and in both arms (the higher of the readings being used). Table 1 describes blood pressure cuff size and error in measurement.
- The BP should be measured twice on each visit, and separated by at least 1 to 2 min to allow the return of trapped blood.
- The patient should be seated in a calm environment for at least 5 min with the arm in which BP is measured rested on support level with the heart.
- Postural BP change should always be recorded in the elderly to diagnose postural hypotension. This is assessed by taking BP in supine (after 5-min rest) and standing (after 2 min) positions. A drop of ≥20 mm Hg in systolic, a drop of ≥10 mm Hg diastolic BP, or symptoms of cerebral hypoperfusion is suggestive of postural (orthostatic) hypotension.
- A diagnosis of hypertension (HTN) may be established if the BP is markedly elevated (>180/110 mm Hg) or has evidence of end organ damage; otherwise such a diagnosis should wait until BP is found elevated on >2 readings on >2 different occasions.
- Nonoffice (home, workplace, 24-hr ambulatory) BP determination to establish the pattern of HTN (sustained, "white coat," or "masked" HTN) in selected patients.
- Measure heart rate, height, weight, body mass index, and waist circumference.
- Some general clinical clues for when to screen for secondary HTN include:
  1. Severe or resistant HTN
  2. An acute rise in BP developing in a patient with previous stable BP
  3. Age less than 30 yr, non-obese, non-black with no family history of HTN
  4. Sudden onset or accelerated hypertension
  5. Age of onset before puberty. If above is suspected, additional tests for secondary HTN should be done including renin, aldosterone, cortisol levels, 24-hr urine metanephrines, and serum catecholamines
- Physical examination should include searching for secondary causes, and sequelae of hypertension.
- Examine skin for the presence of café-au-lait spots (neurofibromatosis), uremic appearance (renal failure), and violaceous striae (Cushing syndrome).
- Perform careful funduscopic examination; check for papilledema, retinal exudates, hemorrhages, arterial narrowing, arteriovenous compression.
- Examine neck for carotid bruits, distended neck veins, and enlarged thyroid gland.
- Perform extensive cardiopulmonary examination: Check for a laterally displaced point of maximal intensity, an S3 or S4, and valvular murmurs.
- Palpate abdomen for renal masses (pheochromocytoma, polycystic kidneys), and auscultate for bruit over the aorta and renal arteries.
- Examine arterial pulses (dilated or absent femoral pulses and BP greater in upper extremities than lower extremities suggest aortic coarctation).
- Look for truncal obesity (Cushing syndrome) and pedal edema (congestive heart failure [CHF]).
- Table 2 provides a guide to evaluation of identifiable causes of HTN.
- Table 3 summarizes clinical clues to guide the investigation in young patients with hypertension that has a potentially hereditary cause.

ETIOLOGY

- Essential (primary) HTN (85%)
- Drug induced or drug related (5%)
  1. NSAIDs
  2. Oral contraceptives
  3. Corticosteroids
- Renal HTN (5%)
  1. Renal parenchymal disease (3%)
  2. Renovascular HTN (RVH) (<2%)
- Endocrine (<2%)
  1. Primary aldosteronism (at least 5%)
  2. Pheochromocytoma (0.2%)
  3. Cushing syndrome and long-term steroid therapy (0.2%)
  4. Hyperparathyroidism or thyroid disease (0.2%)
- Coarctation of the aorta (0.2%)

DIAGNOSIS

WORKUP

- The objective for the initial evaluation of HTN is to establish the diagnosis and stage of HTN. Table 4 summarizes initial laboratory evaluation of the hypertensive patient.
- Gather office and nonoffice BP readings, assess presence of target organ damage

TABLE 1 Blood Pressure Cuff Size and Error in Measurement*

	Arm Circumference		
Cuff Bladder Size	**28 cm or less**	**29-42 cm**	**43 cm or more**
Regular (12 × 23 cm)	Accurate	Overestimates SBP by 4-8 mm Hg DBP by 3-6 mm Hg	Overestimates SBP by 16-17 mm Hg DBP by 10-11 mm Hg
Large (15 × 33 cm)	Underestimates SBP by 2-3 mm Hg DBP by 1-2 mm Hg	Accurate	Overestimates SBP by 5-7 mm Hg DBP by 2-4 mm Hg
Thigh (18 × 36 cm)	Underestimates SBP by 5-7 mm Hg DBP by 1-3 mm Hg	Underestimates SBP by 5-7 mm Hg DBP by 2-4 mm Hg	Accurate

DBP, Diastolic blood pressure reading; *SBP,* systolic blood pressure reading.
**Overestimation* means that hypertension may be diagnosed in someone with normal blood pressure; *underestimation* means that the blood pressure reading may be normal in someone who actually has high blood pressure. See text for further discussion.
From McGee S: *Evidence-based physical diagnosis,* ed 4, Philadelphia, 2018, Elsevier.

TABLE 2 Guide to Evaluation of Identifiable Causes of Hypertension

Suspected Diagnosis	Clinical Clues	Diagnostic Testing
Chronic kidney disease	Estimated GFR <60 ml/min/1.73 m^2 Urine albumin-to-creatinine ratio ≥30 mg/g	Renal sonography
Renovascular disease	New elevation in serum creatinine, marked elevation in serum creatinine with ACEI or ARB, drug-resistant hypertension, flash pulmonary edema, abdominal, or flank bruit	Renal sonography (atrophic kidney), CT or MR angiography, invasive angiography
Coarctation of the aorta	Arm pulses > leg pulses, arm BP > leg BP, chest bruits, rib notching on chest radiography	MR angiography, TEE, invasive angiography
Primary aldosteronism	Hypokalemia, drug-resistant hypertension	Plasma renin and aldosterone, 24-hr urine aldosterone and potassium after oral salt loading, adrenal vein sampling
Cushing syndrome	Truncal obesity, wide and blanching purple striae, muscle weakness	1 mg dexamethasone-suppression test, urinary cortisol after dexamethasone, adrenal CT
Pheochromocytoma	Paroxysms of hypertension, palpitations, perspiration, and pallor; diabetes	Plasma metanephrines, 24-hr urinary metanephrines and catecholamines, abdominal CT or MR imaging
Obstructive sleep apnea	Loud snoring, large neck, obesity, somnolence	Polysomnography

ACEI, Angiotensin-converting enzyme inhibitor; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CT,* computed tomography; *GFR,* glomerular filtration rate; *MR,* magnetic resonance; *TEE,* transesophageal echocardiography.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.

TABLE 3 Clinical Clues to Guide the Investigation in Young Patients with Hypertension That Has a Potentially Hereditary Cause

Specific Conditions	Possible Causes of Familial Hypertension	Clinical Clues
Catecholamine-Producing Tumors		
Pheochromocytoma/paraganglioma	Familial cases are responsible for <30% of cases, including MEN2A and MEN2B, von Hippel-Lindau disease, neurofibromatosis, and familial paraganglioma syndromes (SDH complex mutations)	Paroxysmal palpitations, headaches, diaphoresis, pale flushing; syndromic features of any of the associated disorders
Neuroblastomas (adrenal) Aortic or renovascular lesions	1%-2% of neuroblastomas are familial	
Coarctation of the aorta	Overrepresented in families but no familial distribution	Asymmetry between upper- and lower-extremity BP, radial-formal pulse delay; associated with Turner syndrome, Williams syndrome, and bicuspid aortic valve
Renal artery stenosis caused by fibromuscular dysplasia or inherited arterial wall lesions	<10% familial with AD pattern	Abnormal renal vascular imaging results; vascular disease in the carotid territory at an early age; common in neurofibromatosis and Williams syndrome; also present in tuberous sclerosis, Ehlers-Danlos syndrome, and Marfan syndrome
Parenchymal kidney disease GN	Alport disease (X-linked, AR, or AD), familial IgA nephropathy (AD with incomplete penetrance)	Proteinuria, hematuria, low eGFR
PKD	ADPKD type 1 or 2, ARPKD	Multiple renal cysts (as few as three in patients under 30 yr)
Adrenocortical disease Glucocorticoid-remediable aldosteronism (familial hyperaldosteronism type I)	AD chimeric fusion of the 11β-hydroxylase and aldosterone synthase genes	Cerebral hemorrhages at young age, cerebral aneurysms; mild hypokalemia; high plasma aldosterone, low renin
Familial hyperaldosteronism	AD; unknown defect	Severe type 2 hypertension in early adulthood; high plasma aldosterone, low renin; no response to glucocorticoid treatment
Familial hyperaldosteronism type III	AD; unknown defect	Severe hypertension in childhood with extensive target-organ damage; high plasma aldosterone, low renin; marked bilateral adrenal enlargement
Congenital adrenal hyperplasia	AR mutations in 11β-hydroxylase or 21-hydroxylase	Hirsutism, virilization; hypokalemia and metabolic alkalosis; low plasma aldosterone and renin
Monogenic Primary Renal Tubular Defects		
Gordon syndrome	AD mutations of *KLHL3, CUL3, WNK1,* and *WNK4;* AR mutations of *KLHL3*	Hyperkalemia and metabolic acidosis with normal renal function
Liddle syndrome	AD mutations of the epithelial sodium channel	Hypokalemia and metabolic alkalosis; low plasma aldosterone and renin
Apparent mineralocorticoid excess	AD mutation in 11β-hydroxysteroid dehydrogenase type 2	Hypokalemia and metabolic alkalosis; low plasma aldosterone and renin
Geller syndrome Hypertension-brachydactyly syndrome	AD mutation in the mineralocorticoid receptor AD mutations in the phosphodiesterase E3A enzyme	Hypokalemia and metabolic alkalosis; low plasma aldosterone and renin; increased BP during pregnancy or exposure to spironolactone
Unknown Mechanisms		
Hypertension-brachydactyly syndrome	AD	Short fingers (small phalanges) and short stature; brainstem compression from vascular tortuosity in the posterior fossa
Essential Hypertension		
	Polygenic	When obesity or metabolic syndrome is present, the likelihood of essential hypertension is higher

AD, Autosomal dominant; *ADPKD,* autosomal dominant polycystic kidney disease; *AR,* autosomal recessive; *ARPKD,* autosomal recessive polycystic kidney disease; *BP,* blood pressure; *eGFR,* estimated glomerular filtration rate; *GN,* glomerulonephritis; *IgA,* immunoglobulin A; *MEN,* multiple endocrine neoplasia; *PKD,* polycystic kidney disease; *SDH,* succinate dehydrogenase.
From Skorecki K et al: *Brenner and Rector's the kidney,* ed 10, Philadelphia, 2016, Elsevier.

TABLE 4 Initial Laboratory Evaluation of the Hypertensive Patient to Investigate the Presence of Comorbid Conditions, Secondary Causes, or Established Target-Organ Damage

Test	Clinical Usefulness
Serum creatinine (and estimated glomerular filtration rate)	Assessment of renal function. Identifies parenchymal kidney disease as a possible secondary cause as well as established TOD.
Serum potassium	Low potassium (of renal origin) suggests mineralocorticoid excess (primary or secondary), glucocorticoid excess, Liddle syndrome. High potassium with normal renal function suggests Gordon syndrome. Low levels raise caution about the use of thiazides and loop diuretics. High levels preclude the use of ACEIs, ARBs, renin inhibitors, and potassium-sparing diuretics.
Serum sodium	If high, suggests primary aldosteronism. If low, alerts to the need to avoid thiazide diuretics.
Serum bicarbonate	If high, suggests aldosterone excess (primary or secondary). If low with normal renal function, suggests Gordon syndrome (with high potassium) or primary hyperparathyroidism (with high calcium).
Serum calcium	If high, suggests primary hyperparathyroidism.
Serum glucose	Identifies prediabetes or diabetes. In the appropriate setting, suggests glucocorticoid excess, pheochromocytoma, or acromegaly.
Lipid profile	Identifies hyperlipidemia.
Hemoglobin/hematocrit	If high, in the absence of other hematologic abnormalities or underlying lung disease, suggests sleep apnea.
Urinalysis*	Proteinuria and hematuria identify a possible secondary cause (glomerulonephritis). Proteinuria can also be a marker of TOD.
Electrocardiogram	Identifies left ventricular hypertrophy, old myocardial infarction, or other ischemic changes. Identifies conduction abnormalities that may preclude the use of β-blockers or nondihydropyridine CCBs.

The most recent guidelines do not recommend blood urea nitrogen (BUN) measurement alone.
*Some organizations recommend screening microalbuminuria as a more sensitive tool to identify early renal injury.
ACEI, Angiotensin-converting enzyme inhibitor; *ARB,* angiotensin receptor blocker; *CCB,* calcium channel blocker; *TOD,* target-organ damage.
From Skorecki K et al: *Brenner and Rector's the kidney,* ed 10, Philadelphia, 2016, Elsevier.

(TOD), assess the level of global cardiovascular disease risk, and produce a plan for individualized monitoring and therapy
- Patient counseling and education should be prominent features of the initial evaluation
- Pertinent history:
  1. Age of onset of HTN, previous antihypertensive therapy
  2. Family history of HTN, stroke, cardiovascular disease
- Diet, salt intake, caffeine, alcohol, drugs (e.g., oral contraceptives, NSAIDs, decongestants, steroids)
- Occupation, lifestyle, pain, socioeconomic status, psychologic factors
- Other cardiovascular risk factors: Hyperlipidemia, obesity, diabetes mellitus
- Symptoms of secondary HTN:
  1. Headache, palpitations, excessive perspiration (possible pheochromocytoma)
  2. Weakness, polyuria (consider hyperaldosteronism)
  3. Claudication of lower extremities (seen with coarctation of aorta)
  4. Loud snoring, daytime somnolence, morning confusion (may warrant evaluation for sleep apnea)

LABORATORY TESTS

- Routine laboratory tests recommended before initiating therapy include:
  1. Urinalysis with microscopic evaluation; for signs of glomerulopathy
  2. Basic metabolic panel and calcium; for signs of kidney damage, hypokalemia (primary aldosteronism and Cushing syndrome), hypercalcemia (hyperparathyroid)
  3. Complete blood count
  4. Screening for coexisting diseases that may adversely affect prognosis; hemoglobin A1c or fasting glucose level, serum lipid panel
  5. Optional tests include measurement of urinary albumin or albumin/creatinine ratio

IMAGING STUDIES

- ECG: Check for presence of left ventricular hypertrophy (LVH) with strain pattern.
- Renal duplex ultrasonography, CT angiography or magnetic resonance angiography of the renal arteries in suspected renovascular hypertension (renal artery stenosis) may be considered.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Lifestyle modifications (the initial treatment of hypertension should focus on lifestyle modifications):
- Weight loss if overweight (target body mass index [BMI] <25).
- Limit alcohol intake to 1 oz of ethanol per day (<2 drinks/day) in men or 0.5 oz (<1 drink/day) in women.
- Regular aerobic exercise (at least 30 min/day on most days).
- Reduce sodium intake to <100 mmol/day (<1.5 g of sodium/day).
- Maintain adequate dietary potassium (>3500 mg/day) intake in patients with normal kidney function.
- Smoking cessation.
- The BP reduction seen ranges from 2 to 20 mm Hg, most significant with substantial weight loss and the implementation of the Dietary Approaches to Stop Hypertension (DASH) eating plan, which relies on a diet high in fruits and vegetables, moderate in low-fat dairy products, and low in animal protein but with substantial amount of plant protein from legumes and nuts.

ACUTE GENERAL Rx

- Multiple recent consensus documents regarding blood pressure goals and when to initiate treatment have been published.
- According to the 2017 *ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults*, goals of treatment are as follows[1]:
  1. For adults with confirmed hypertension and known cardiovascular disease (CVD) or 10-yr atherosclerotic cardiovascular disease (ASCVD) event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended.
  2. For adults with confirmed hypertension without additional markers of increased CVD risk, a BP target of less than 130/80 mm Hg may be reasonable.
- In addition, initiation of therapy recommendations is as follows:
  1. Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-yr ASCVD risk <10% and stage 2 hypertension.
  2. Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and for primary prevention in adults with an estimated 10-yr ASCVD risk of 10% or higher and stage 1 hypertension.
  3. Initiate antihypertensive drug therapy with two first-line agents of different classes for adults with stage 2 hypertension and BP more than 20/10 mm Hg higher than their target.
  4. It is reasonable to initiate therapy with a single agent for adults with stage 1 hypertension and a goal less than 130/80 mm Hg.

[1]Whelton P et al: 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical guidelines, *J Am Coll Cardiol* 2017.

5. Patients with diabetes mellitus and chronic kidney disease are considered high risk.

- Additional guidance may be taken from the writers of the JNC 8 guidelines, published in 2014[2]:
  1. In the general non-black population, preferred initial agents are thiazide-type diuretics, angiotensin-converting enzyme inhibitors (ACEI), calcium channel blockers (CCBs), or angiotensin receptor blockers (ARBs). ACEI or ARBs are preferred initial agents in diabetics and those with chronic kidney disease (CKD) in this population.
  2. Preferred initial agents in the black population (including diabetics) are thiazide-type diuretics or CCBs.
  3. When selecting drugs, try to give once per day dosages to improve compliance. Also consider the cost of the medication, metabolic and subjective side effects, and drug-drug interactions.
- The major advantages and limitations of each class of drugs are described as follows:
  1. Thiazide diuretics:
     a. Advantages: Inexpensive, once-daily dosing. Useful in edematous states, CHF, chronic renal disease, elderly patients (decreased incidence of hip fractures in elderly patients)
     b. Disadvantages: Significant adverse metabolic effects (hypokalemia), increased risk of cardiac arrhythmias, sexual dysfunction, gout flares, possible adverse effects on lipids and glucose levels
  2. Beta-blockers:
     a. Advantages: Ideal in hypertensive patients with ischemic heart disease or status post myocardial infarction (MI); favored in hyperkinetic, young patients (resting tachycardia, wide pulse pressure, hyperdynamic heart) and stable CHF patients
     b. Disadvantages: Adverse effect on quality of life (increased incidence of fatigue, depression, impotence), bronchospasm, hypoglycemia, peripheral vascular disease, adverse effects on lipids, masking of signs and symptoms of hypoglycemia in diabetics
  3. Calcium antagonists:
     a. Advantages: Helpful in hypertensive patients with ischemic heart disease. Generally favorable effect on quality of life; can be used in patients with bronchospastic disorders, renal disease, peripheral vascular disease, metabolic disorders, and salt sensitivity. CCBs BP-lowering effect is independent of Na^+ intake.
     b. Disadvantages: Diltiazem and verapamil should be avoided in patients with CHF due to systolic dysfunction because of their negative inotropic effects; pedal edema may occur with nifedipine and amlodipine; constipation can be severe in elderly patients receiving verapamil. CCB-related edema is positional in nature, it improves with lying position; additional strategies include switching CCB classes, reducing dosage, giving the medication later in the day, and adding a venodilator (nitrates, an ACE, or an ARB); diuretics may improve edema, but at the expense of a reduction in plasma volume.
  4. ACE inhibitors:
     a. Advantages: First-line therapy for patients with left ventricular dysfunction, helpful in prevention of diabetic renal disease; effective in decreasing LVH, and remodeling.
     b. Disadvantages: Dry cough is a frequent side effect (5% to 20% of patients); hyperkalemia may occur in patients with diabetes or severe renal insufficiency; hypotension may occur in volume-depleted patients; increased risk of renal failure in patients with renal artery stenosis; contraindicated in pregnancy.
  5. ARBs:
     a. Advantages: Well tolerated, favorable impact on quality of life; useful in patients unable to tolerate ACE inhibitors because of persistent cough and in CHF and diabetic patients; single daily dose. An episode of renal insufficiency with ACE inhibitors does not rule out future therapy with an ARB unless high-grade bilateral renal artery stenosis exists.
     b. Disadvantages: Hypotension may occur in volume-depleted patients; hyperkalemia; risk of renal failure in renal artery stenosis; contraindicated in pregnancy.
  6. Alpha-adrenergic blockers:
     a. Advantages: No adverse effect on blood lipids or insulin sensitivity; helpful in benign prostatic hypertrophy.
     b. Disadvantages: Postural hypotension, sedation; syncope can be avoided by giving an initial low dose at bedtime. Generally considered third- or fourth-line agent.
  7. Central alpha-antagonists:
     a. Oral clonidine mainstay of therapy for hypertensive urgencies because of the ease of administration and relative safety.
     b. Transdermal clonidine; useful in management of labile HTN, the hospitalized patient who cannot take medications by mouth, and patients subject to early-morning BP surges. At equivalent doses, transdermal clonidine is more apt to precipitate salt and water retention than is the case with oral clonidine.
     c. Dose beyond 0.4 mg causes fatigue, sedation, dry mouth, salt and water retention, and rebound HTN upon abrupt termination of the medication.
  8. Combined alpha- and beta-adrenergic receptor blockers:
     a. Labetalol, nebivolol, and carvedilol: Use is reserved to treat complicated hypertensive patient when an antihypertensive effect beyond beta-blockade is sought. IV labetalol is used for hypertensive emergencies. Carvedilol is shown to have less adverse effect on glycemic control than metoprolol and to reduce urinary protein excretion in hypertensive diabetic patients.
  9. Direct-acting smooth muscle relaxant: Hydralazine
     a. Advantages: Beneficial in black patients when used with isosorbide dinitrate.
     b. Disadvantages: May lead to reflex tachycardia, worsening ischemia (best used with nitrates), at higher doses or with renal failure can lead to a reversible drug-induced lupus.
  10. Renin inhibitors: Newest class of antihypertensives (Aliskiren):
      a. Advantages: Generally well tolerated; once-daily dosing; can be used alone or in combination with other antihypertensive agents (avoid combining with ACEI or ARBs given increase of hyperkalemia).
      b. Disadvantages: Contraindicated in pregnancy; should not be used in patients with impaired renal function; excessive cost; paucity of cardiovascular outcomes data showing benefit.

TREATMENT OF RENOVASCULAR HYPERTENSION: The therapeutic approach varies with the cause of the renovascular hypertension (RVH) (refer to "Renal Artery Stenosis" for additional information).

- Young patients with fibromuscular dysplasia refractory to medical therapy can be treated with percutaneous transluminal renal angioplasty (PTRA).
- Medical therapy is advisable in elderly patients with atheromatous RVH; useful agents are:
  1. Beta-blockers: Highly effective in patients with elevated plasma renin
  2. ACE inhibitors: Highly effective; however, should be avoided in patients with bilateral renal artery stenosis or with a solitary kidney and renal artery stenosis
  3. Diuretics: Often used in combination with ACE inhibitors
- Surgical revascularization: A recent trial revealed that renal-artery stenting does not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal-artery stenosis and hypertension or CKD.[3]

[2]James PA et al: 2014 Evidence-based guidelines for the management of high blood pressure in adults. Report from the panel members appointed to the eighth Joint National Committee (JNC8), *JAMA* 311(5):507-520, 2014.

[3]Cooper CJ et al: Stenting and medical therapy for atherosclerotic renal-artery stenosis, *N Engl J Med* 370:13-22, 2014..

TABLE 5 Drugs Used to Treat Hypertension in Pregnancy

Drug	Starting Dose	Maximum Dose	Comments
Acute Treatment of Severe Hypertension			
Hydralazine	5-10 mg IV every 20 min	20 mg*	Avoid in cases of tachycardia and persistent headaches
Labetalol	20-40 mg IV every 10-15 min	220 mg*	Avoid in women with asthma or congestive heart failure
Nifedipine	10-20 mg oral every 30 min	50 mg*	Avoid in case of tachycardia and palpitations
Long-Term Treatment of Hypertension			
Methyldopa	250 mg bid	4 g/day	
Labetalol	100 mg bid	2400 mg/day	
Nifedipine	10 mg bid	120 mg/day	
Thiazide diuretic	12.5 mg bid	50 mg/day	

*If desired blood pressure levels are not achieved, switch to another drug.
From Gabbe SG: *Obstetrics,* ed 6, Philadelphia, 2012, WB Saunders.

HTN DURING PREGNANCY:
- HTN complicates 5% to 12% of all pregnancies.
- The American Obstetrical Committee defines BP of 130/80 mm Hg as the upper limit of normal at any time during pregnancy.
- A rise of 30 mm Hg systolic or 15 mm Hg diastolic is also considered abnormal regardless of the absolute values obtained.
- Hypertension during pregnancy can be from chronic HTN, gestational HTN, preeclampsia or preeclampsia superimposed on chronic HTN. It is important to distinguish the etiology because the risk to mother and fetus is much greater in preeclampsia.
- Treatment of chronic HTN during pregnancy is as follows:
  1. Initial treatment with conservative measures (proper nutrition, limited physical activity).
  2. When drug therapy is necessary, initiation of methyldopa, hydralazine, labetalol or nifedipine is preferred. Table 5 summarizes drugs used to treat hypertension in pregnancy.
  3. ACE inhibitors can cause fetal and neonatal complications; their use should be avoided in pregnancy.
  4. The safety of CCBs remains unclear.
  5. Diuretics should be used only if there is a specific reason for initiating and maintaining their use (e.g., HTN associated with severe fluid overload or left ventricular dysfunction).

MALIGNANT HTN, HYPERTENSIVE EMERGENCIES, AND HYPERTENSIVE URGENCIES: Definitions:
- Malignant HTN occurs with HTN when there are grades III and IV retinopathy (exudates, hemorrhages, and papilledema).
  1. The rate of BP rise is a critical factor in the development of malignant HTN.
  2. Complications and mortality rates are much higher in malignant HTN compared with essential HTN.
  3. Requires immediate BP reduction (not necessarily into normal ranges) to prevent or limit target organ disease.
- Hypertensive emergencies occur when the BP elevation is >180 mm Hg systolic and/or >120 mm Hg diastolic without evidence of new or progressive organ dysfunction. It requires rapid lowering of BP to prevent end-organ damage.
- Hypertensive urgencies are BP elevations >180 mm Hg systolic and/or >120 mm Hg diastolic with end-organ damage that should be corrected within 24 hr of presentation.
  1. Most clinicians suggest lowering the BP to <160 mm Hg/<100 mm Hg or to a level no more than 30% lower than the patient's baseline BP.

Therapy: The choice of therapeutic agents varies with the cause. IV medications are preferred in hypertensive emergencies.
- Nitroprusside is the drug of choice in hypertensive encephalopathy, HTN and intracranial bleeding, malignant HTN, HTN and heart failure, dissecting aortic aneurysm (used in combination with propranolol); its onset of action is immediate. Because it is metabolized to cyanide, patients should be carefully monitored for toxicity (mental status changes, acidemia).
- Fenoldopam is a vasodilator agent useful for the short-term (up to 48 hr) management of severe HTN when rapid but quickly reversible reduction of BP is required. It should be avoided in patients with glaucoma.
- Other commonly used agents are the IV CCBs nicardipine and clevidipine (useful for urgent treatment of HTN in the intensive care unit or operating room), the beta-blocker esmolol (useful in aortic dissection or postoperative HTN), labetalol (combined β-adrenergic and α-blocker useful in patients with coronary disease), phentolamine (useful for catecholamine-related emergencies), IV nitroglycerin (used in patients with cardiac ischemia and hypertensive crisis), and hydralazine (used for hypertensive emergencies in pregnancy.
- Table 6 summarizes IV medications useful in hypertensive crisis.

The following are important points to remember when treating hypertensive emergencies:
- Introduce a plan for long-term therapy at the time of the initial emergency treatment.
- Agents that reduce arterial pressure can cause the kidney to retain sodium and water; therefore, the judicious administration of diuretics should accompany their use.
- The initial goal of antihypertensive therapy is not to achieve a normal BP, but rather to gradually reduce the BP; cerebral hypoperfusion may occur if the mean BP is hypertension in patients with CKD.

PEARLS & CONSIDERATIONS

COMMENTS
- "Masked hypertension" refers to the detection of hypertension with home or ambulatory monitoring. Up to 40% of patients with BP less than 140/90 mm Hg in the office may have masked hypertension. Automated blood pressure monitors are useful to screen for masked hypertension.
- "White coat hypertension" is defined as an elevated BP during medical office exam with BP in the normal range at home. Its prevalence is as high as 30% among patients with an elevated BP in the office. These patients are at increased risk for overt hypertension.
- For patients with hypertension, every 20/10 mm Hg increase in BP doubles the risk of cardiovascular events.
- Most patients will require at least two medications for BP control.
- If BP is greater than 20/10 mm Hg above goal, therapy should be initiated with two drugs.
- Resistant HTN: HTN is considered resistant if the BP cannot be reduced below target levels in patients who are compliant with an optimal triple-drug regimen that includes a diuretic. Terms *refractory* and *resistant* are used interchangeably. Causes include pseudohypertension, measurement artifact, medication nonadherence, volume overload, and secondary HTN.
  1. Pseudohypertension in elderly: Hardened and sclerotic artery is not compressible hence falsely elevates BP measurement artifact.
  2. Measurement artifact: BP taken incorrectly (small cuff, improper support).
- Renal sympathetic denervation: A recent blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 mo after renal artery denervation as compared with a sham control.
- Barriers to BP control: System issues, provider issues; patient issues, and behavior issues. The rate at which physicians adopt recommended changes based on evidence-based findings can be quite slow and has been properly described as "clinical inertia."
- Indications for specialist referral for patients with HTN are described in Table 7.
- New U.S. guidelines for the treatment of hypertension recommend the following:
  1. Use of blood pressure-lowering medication for secondary prevention in patients with cardiovascular disease and average systolic blood pressure (SBP) ≥130 mm

TABLE 6 Treatment of Hypertensive Crisis: Intravenous Medications

Drug Name and Mechanism of Action	Indications/Advantages/Dose	Disadvantages/Adverse Effects/Metabolism Cautions
Sodium Nitroprusside		
Nitric oxide compound; vasodilation of arteriolar and venous smooth muscle Increases cardiac output by decreasing afterload	Useful in most hypertensive emergencies Onset of action immediate, duration of action 1-2 min Dose: 0.25 μg/kg/min Maximum dose: 8-10 μg/kg/min	Contraindicated in high-output cardiac failure, congenital optic atrophy. Anemia and liver disease at risk of cyanide toxicity: Acidosis, tachycardia, change in mental status, almond smell on breath. Risk of thiocyanate toxicity with renal disease: Psychosis, hyperreflexia, seizure, tinnitus. Cautious use with increased intracranial pressure. Do not use maximum dose for more than 10 min. Crosses the placenta.
Nitroglycerin		
Directly interacts with nitrate receptors on vascular smooth muscle Primarily dilates venous bed Decreases preload	Use with symptoms of cardiac ischemia, perioperative hypertension in cardiac surgery Initial dose: 5 μg/min Maximum dose: 100 μg/min	Contraindicated in angle-closure glaucoma, increased intracranial pressure. Blood pressure decreased secondary to decreased preload, cardiac output—avoid when cerebral or renal perfusion compromised. Caution with right ventricular infarct.
Labetalol		
β- and α-Adrenergic blockade α:β-Blocking ratio is 1:7	Onset of action 2-5 min, duration 3-6 hr Bolus 20 mg, then 20-80 mg every 10 min for maximum dose 300 mg Infuse at 0.5-2 mg/min	Avoid in bronchospasm, bradycardia, congestive heart failure, greater than first-degree heart block, second/third trimester pregnancy. Use caution with hepatic dysfunction, inhalational anesthetics (myocardial depression). Enters breast milk.
Esmolol		
Cardioselective β1-adrenergic blocking agent	Use with aortic dissection Use during intubation, intraoperative, and postoperative hypertension Onset of action 60 sec, duration 10-20 min, 200-500 μg/kg/min for 4 min, then infuse 50-300 μg/kg/min	See labetalol. Not dependent on renal or hepatic function for metabolism (metabolized by hydrolysis in red blood cells).
Fenoldopam		
Postsynaptic dopamine-1 agonist; decreases peripheral vascular resistance; 10 times more potent than dopamine as vasodilator	May be advantageous in kidney disease, increases renal blood flow, increases sodium excretion, no toxic metabolites Initial dose: 0.1 μg/kg/min, with titration every 15 min No bolus	Contraindicated in glaucoma (may increase intraocular pressure) or allergy to sulfites; hypotension, especially with concurrent β-blocker. Check serum potassium every 6 hr. Concurrent acetaminophen may significantly increase blood levels. Dose-related tachycardia.
Hydralazine		
Primarily dilates arteriolar vasculature	Primarily used in pregnancy/eclampsia Dose: 10 mg every 20-130 min; maximum dose 20 mg Decreases blood pressure in 10-20 min Duration of action 2-4 hr	Reflex tachycardia; give β-blocker concurrently. May exacerbate angina. Half-life 3 hr, affects blood pressure for 100 hr. Depends on hepatic acetylation for inactivation.
Phentolamine		
α-Adrenergic blockade	Used primarily to treat hypertension from excessive catecholamine excess (e.g., pheochromocytoma) Dose: 5-15 mg Onset of action 1-2 min, duration 3-10 min	β-Blockade is generally added to control tachycardia or arrhythmias. As in all catecholamine excess states, β-blockers should never be given first, as the loss of β-adrenergically mediated vasodilatation will leave α-adrenergically mediated vasoconstriction unopposed and result in increased pressure.
Nicardipine		
Dihydropyridine calcium channel blocker; inhibits transmembrane influx of calcium ions into cardiac and smooth muscle	Onset of action 10-20 min, duration 1-4 hr Initial dose: 5 mg/hr to maximum of 15 mg/hr	Avoid with congestive heart failure, cardiac ischemia. Adverse effects include tachycardia, flushing, headache.
Clevidipine		
Short-acting dihydropyridine calcium channel antagonist	Initial dose: 1 mg/hr; can be increased to 21 mg/hr	Reduces blood pressure without affecting cardiac filling pressures or causing reflex tachycardia.
Enalaprilat		
Angiotensin-converting enzyme inhibitor	Onset of action 15-20 min, duration 12-24 hr Dose: 1.25-5 mg every 6 hr	Response not predictable, with high renin states may see acute hypotension. Hyperkalemia in setting of reduced glomerular filtration rate. Avoid in pregnancy.
Trimethaphan		
Nondepolarizing ganglionic blocking agent; competes with acetylcholine for postsynaptic receptors	Used in aortic dissection Dose: 0.5-5 mg/min	Does not increase cardiac output. No inotropic cardiac effect. Disadvantages include parasympathetic blockade, resulting in paralytic ileus and bladder atony and development of tachyphylaxis after 24-96 hr of use.

From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

TABLE 7 Indications for Specialist Referral for Patients with Hypertension

Urgent Treatment Needed
Accelerated hypertension (severe hypertension with grade III-IV retinopathy)
Particularly severe hypertension (>220/120 mm Hg)
Impending complications (e.g., transient ischemic attack, left ventricular failure)
Possible Underlying Cause
Any clue in history or examination of a secondary cause (e.g., hypokalemia with increased or high–normal plasma sodium)
Elevated serum creatinine
Proteinuria or hematuria
Sudden onset or worsening of hypertension
Young age (any hypertension <20 yr; needing treatment <30 yr)
Therapeutic Problems
Multiple drug intolerances
Multiple drug contraindications
Persistent nonadherence or nonconcordance
Special Situations
Unusual blood pressure variability
Possible white coat hypertension
Hypertension in pregnancy

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, WB Saunders.

Hg or diastolic blood pressure (DBP) ≥80 mm Hg, and for primary prevention in adults with an estimated 10-yr ASCVD risk of >10% and an average SBP ≥130 mm Hg or DBP ≥80 mm Hg.

2. In patients with no history of cardiovascular disease and an estimated 10-yr ASCVD risk <10%, blood pressure lowering medication is recommended for those with an average SBP ≥140 mm Hg or an average DBP ≥90 mm Hg.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

High Blood Pressure (Patient Information)
High Blood Pressure—Child (Patient Information)
Eclampsia (Related Key Topic)
Pheochromocytoma (Related Key Topic)
Preeclampsia (Related Key Topic)
Renal Artery Stenosis (Related Key Topic)

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BASIC INFORMATION

DEFINITION

Hyperthyroidism is a hypermetabolic state resulting from excess thyroid hormone.

SYNONYM

Thyrotoxicosis

ICD-10CM CODES

E05.00	Thyrotoxicosis with diffuse goiter without thyrotoxic crisis or storm
E05.01	Thyrotoxicosis with diffuse goiter with thyrotoxic crisis or storm
E05.10	Thyrotoxicosis with toxic single thyroid nodule without thyrotoxic crisis or storm
E05.11	Thyrotoxicosis with toxic single thyroid nodule with thyrotoxic crisis or storm
E05.20	Thyrotoxicosis with toxic multinodular goiter without thyrotoxic crisis or storm
E05.21	Thyrotoxicosis with toxic multinodular goiter with thyrotoxic crisis or storm
E05.30	Thyrotoxicosis from ectopic thyroid tissue without thyrotoxic crisis or storm
E05.31	Thyrotoxicosis from ectopic thyroid tissue with thyrotoxic crisis or storm
E05.40	Thyrotoxicosis factitia without thyrotoxic crisis or storm
E05.41	Thyrotoxicosis factitia with thyrotoxic crisis or storm
E05.80	Other thyrotoxicosis without thyrotoxic crisis or storm
E05.81	Other thyrotoxicosis with thyrotoxic crisis or storm
E05.90	Thyrotoxicosis, unspecified without thyrotoxic crisis or storm
E05.91	Thyrotoxicosis, unspecified with thyrotoxic crisis or storm
E06.2	Chronic thyroiditis with transient thyrotoxicosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE:

- Hyperthyroidism affects 2% of women and 0.2% of men in their lifetimes.
- Toxic multinodular goiter usually occurs in women >55 yr and is more common than Graves disease in the elderly.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with hyperthyroidism generally present with tachycardia, tremor, hyperreflexia, anxiety, irritability, emotional lability, panic attacks, heat intolerance, sweating, increased appetite, diarrhea, weight loss, menstrual dysfunction (oligomenorrhea, amenorrhea). Presentation may be different in elderly patients (see the following).
- Patients with Graves disease may present with exophthalmos, lid retraction, and lid lag (Graves ophthalmopathy). The following signs and symptoms of ophthalmopathy may be present: blurring of vision, photophobia, increased lacrimation, double vision, and deep orbital pressure. Clubbing of fingers associated with periosteal new bone formation in other skeletal areas (Graves acropachy) and pretibial myxedema may also be noted.
- Clinical signs of hyperthyroidism in the elderly may be masked by manifestations of coexisting disease (e.g., new-onset atrial fibrillation, exacerbation of congestive heart failure).

ETIOLOGY

- Graves disease (diffuse toxic goiter): 80% to 90% of all cases of hyperthyroidism
- Toxic multinodular goiter (Plummer disease)
- Toxic adenoma
- Iatrogenic and factitious
- Transient hyperthyroidism (subacute thyroiditis, Hashimoto thyroiditis)
- Rare causes: Hypersecretion of thyroid-stimulating hormone (TSH) (e.g., pituitary neoplasms), struma ovarii, ingestion of large amount of iodine in a patient with preexisting thyroid hyperplasia or adenoma (Jod-Basedow phenomenon), hydatidiform mole, carcinoma of thyroid, amiodarone therapy

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Anxiety disorder
- Pheochromocytoma
- Metastatic neoplasm
- Diabetes mellitus
- Premenopausal state

WORKUP

Suspected hyperthyroidism requires laboratory confirmation and identification of its etiology because treatment varies with cause. A detailed medical history will often provide clues to the diagnosis and etiology of the hyperthyroidism. Fig. E1 describes a diagnostic approach to suspected hyperthyroidism.

LABORATORY TESTS

- Elevated free thyroxine (T_4)
- Elevated free triiodothyronine (T_3): Generally not necessary for diagnosis
- Low TSH (unless hyperthyroidism is a result of the rare hypersecretion of TSH from a pituitary adenoma)
- Thyroid autoantibodies useful in selected cases to differentiate Graves disease from toxic multinodular goiter (absent thyroid antibodies)

IMAGING STUDIES

- 24-hour radioactive iodine uptake (RAIU) is useful to distinguish hyperthyroidism from iatrogenic thyroid hormone synthesis (thyrotoxicosis factitia) and from thyroiditis.
- An overactive thyroid shows increased uptake, whereas a normal underactive thyroid (iatrogenic thyroid ingestion, painless or subacute thyroiditis) shows normal or decreased uptake.
- The RAIU results also vary with the etiology of the hyperthyroidism:
  1. Graves disease: Increased homogeneous uptake
  2. Multinodular goiter: Increased heterogeneous uptake
  3. Hot nodule: Single focus of increased uptake
- RAIU is also generally performed before the therapeutic administration of radioactive iodine to determine the appropriate dose.

TREATMENT

NONPHARMACOLOGIC THERAPY

Patient education regarding thyroid disease and discussion of the therapeutic options. Patients should be informed that radioiodine, antithyroid drugs, and surgery are all reasonable treatment options for hyperthyroidism. It is crucial for the physician to have a detailed discussion with the patient about the benefits and risks relative to lifestyle, patients' values, and coexisting conditions.

ACUTE GENERAL Rx

ANTITHYROID DRUGS (THIONAMIDES): Propylthiouracil (PTU) and methimazole inhibit thyroid hormone synthesis by blocking production of thyroid peroxidase (PTU and methimazole) or inhibit peripheral conversion of T_4 to T_3 (PTU). Methimazole is favored by most endocrinologists because of the potential for hepatic failure with PTU. PTU is preferred in pregnant women during the first trimester because methimazole has been associated with aplasia cutis and with choanal and esophageal atresia. Complete blood count and differential should be obtained before their use.

- Dosage: Methimazole 15 to 30 mg/day given as a single dose; PTU 50 to 100 mg PO q8h.
- Antithyroid drugs can be used as the primary form of treatment or as adjunctive therapy before radioactive therapy or surgery or afterward if the hyperthyroidism recurs.
- Side effects: Skin rash (3% to 5% of patients), arthralgias, myalgias, granulocytopenia (0.5%). Rare side effects are aplastic anemia, hepatic necrosis from PTU, cholestatic jaundice from methimazole.
- When antithyroid drugs are used as primary therapy, they are usually given for 6 to 18 mo; prolonged therapy may cause hypothyroidism. Monitor thyroid function every 2 mo for 6 mo, then less frequently.
- The use of antithyroid drugs before radioiodine therapy is best reserved for patients in whom exacerbation of hyperthyroidism after radioactive iodine therapy is hazardous (e.g., elderly patients with coronary artery disease or significant coexisting morbidity). In these patients the antithyroid drug can be stopped 2 days before radioactive iodine therapy, resumed 2 days later, and continued for 4 to 6 wk.

RADIOIODINE THERAPY (RADIOACTIVE IODINE [RAI; ^{131}I]):
- RAI is the treatment of choice for patients aged >21 yr and younger patients who have not achieved remission after 1 yr of antithyroid drug therapy. RAI is also used in hyperthyroidism caused by toxic adenoma or toxic multinodular goiter.
- Contraindicated during pregnancy (can cause fetal hypothyroidism) and lactation. Pregnancy should be excluded in women of childbearing age before RAI is administered.
- A single dose of RAI is effective in inducing a euthyroid state in nearly 80% of patients.
- There is a high incidence of post-RAI hypothyroidism (>50% within first yr and 2%/yr thereafter); these patients should be frequently evaluated for the onset of hypothyroidism (see "Chronic Rx").

SURGICAL THERAPY (SUBTOTAL THYROIDECTOMY):
- Indicated in obstructing goiters, in any patient who refuses RAI and cannot be adequately managed with antithyroid medications (e.g., patients with toxic adenoma or toxic multinodular goiter), and in pregnant patients who cannot be adequately managed with antithyroid medication or develop side effects to them. Thyroidectomy can also be considered as primary therapy in refractory cases of amiodarone-induced hyperthyroidism. Thyroidectomy is not indicated for low RAIU hyperthyroidism.
- Patients should be rendered euthyroid with antithyroid drugs before surgery.
- Complications of surgery include hypothyroidism (28% to 43% after 10 yr), hypoparathyroidism, and vocal cord paralysis (1%).
- Most patients should be started on replacement doses of levothyroxine (1.7 mcg/kg/day) before discharge from hospital.
- Hyperthyroidism recurs after surgery in 10% to 15% of patients.

ADJUNCTIVE THERAPY: Propranolol alleviates the beta-adrenergic symptoms of hyperthyroidism; initial dose is 20 to 40 mg PO q6h; dosage is gradually increased until symptoms are controlled. Major contraindications to propranolol are congestive heart failure and bronchospasm. Diagnosis and treatment of thyrotoxic storm are also discussed in Section I.

CHRONIC Rx

- Patients undergoing treatment with antithyroid drugs should be seen every 1 to 3 mo until euthyroidism is achieved and every 3 to 4 mo while they remain on antithyroid therapy. After treatment is stopped, periodic monitoring of thyroid function tests with TSH is recommended every 3 mo for 1 yr, then every 6 mo for 1 yr, then annually.
- Orbital decompression surgery can be used to correct Graves orbitopathy (Fig. E2). The administration of the antioxidant selenium (100 mcg PO bid) has been recently reported as effective in improving quality of life, reducing ocular involvement, and slowing progression of the disease in patients with mild Graves orbitopathy. Its mechanism of action is believed to be an effect on the oxygen free radicals and cytokines that play a pathogenic role in Graves orbitopathy.

DISPOSITION

Successful treatment of hyperthyroidism requires lifelong monitoring for the onset of hypothyroidism or the recurrence of thyrotoxicosis.

REFERRAL

- Endocrinology referral is recommended at the time of initial diagnosis and during treatment.
- Surgical referral in selected patients (see "Surgical Therapy").
- Hospitalization of all patients with thyroid storm.

PEARLS & CONSIDERATIONS

COMMENTS

- Elderly hyperthyroid patients may have only subtle signs (weight loss, tachycardia, fine skin, brittle nails). This form is known as ***apathetic hyperthyroidism*** and manifests with lethargy rather than hyperkinetic activity. An enlarged thyroid gland may be absent. Coexisting medical disorders (most commonly cardiac disease) may also mask the symptoms. These patients often have unexplained congestive heart failure, worsening of angina, or new-onset atrial fibrillation resistant to treatment. See the topic "Graves Disease" for additional information on diagnosis and treatment.
- **Subclinical hyperthyroidism** is defined as a normal serum-free thyroxine and free triiodothyronine levels with a TSH level suppressed below the normal range and usually undetectable. Prevalence in the general population is 1% to 2%. These patients usually do not present with signs or symptoms of overt hyperthyroidism. Subclinical hyperthyroidism is associated with an increased risk of atrial fibrillation and heart failure in older adults. Treatment options include observation or a therapeutic trial of low-dose antithyroid agents for 6 mo to attempt to induce remission. The American Thyroid Association and the American Association of Clinical Endocrinologists recommend treatment of patients with TSH levels <0.1 mIU if they are older than 65 or have associated comorbidities (osteoporosis, heart failure).
- ***Thyrotoxic periodic paralysis (TPP)*** is a hyperthyroidism-related hypokalemia and muscle-weakening condition resulting from a sudden shift of potassium into cells. Many patients do not have other symptoms of hyperthyroidism. Typical presentation involves an Asian adult male with acute fatigue and muscle weakness initially presenting in the lower extremities. Physical examination reveals decreased deep tendon reflexes, hypertension, and tachycardia. ECG often reveals U waves, high QRS voltage, and first-degree atrioventricular block. Additional laboratory testing reveals normal acid-base state, hypokalemia with low urinary potassium excretion (spot urinary potassium concentration <20 mEq/L from potassium shift into cells), hypophosphatemia, hypophosphaturia, and hypercalciuria. Electromyography during attacks shows low-amplitude compound muscle action potential of the tested muscle. Therapy consists of cautious potassium supplementation (increased risk of rebound hyperkalemia). Use of nonselective beta-blockers (e.g., propranolol) to counteract hyperadrenergic activity, which may be causing TPP, may also be useful.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hyperthyroidism (Patient Information)
Graves Disease (Related Key Topic)
Thyrotoxic Storm (Related Key Topic)

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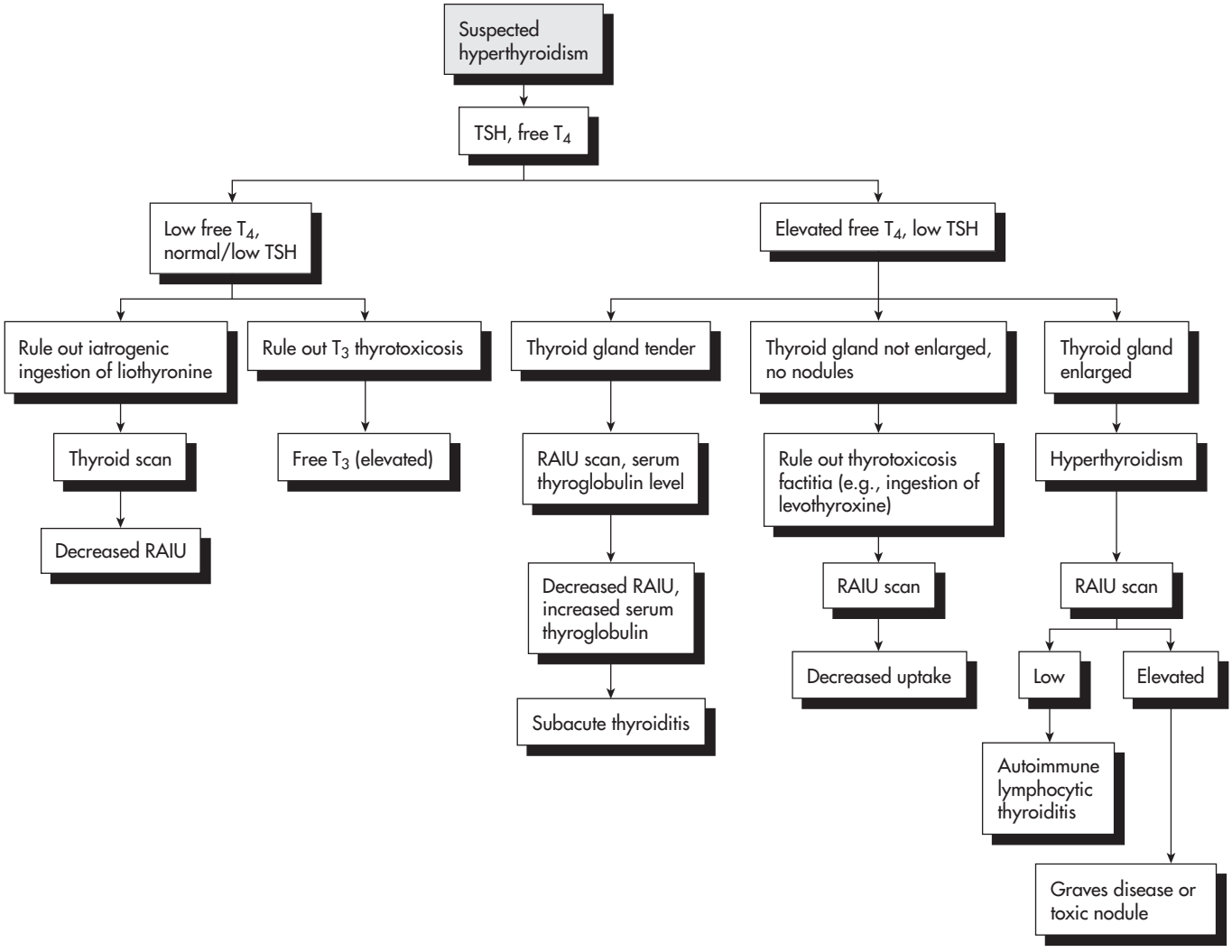

FIG. E1 Hyperthyroidism. *RAIU,* Radioactive iodine uptake; *TSH,* thyroid-stimulating hormone.

FIG. E2 Characteristic signs of Graves orbitopathy. A, Graves orbitopathy was subsequently corrected by orbital decompression surgery. **B,** Note the thyroid stare, asymmetry, proptosis, and periorbital edema before correction. (Courtesy Dr. Jack Rootman, University of British Columbia, Vancouver, Canada, from Larsen PR et al [eds]: *Williams textbook of endocrinology,* ed 10, Philadelphia, 2003, WB Saunders.)

BASIC INFORMATION

DEFINITION

Hypertrophic osteoarthropathy (HOA) is a syndrome of abnormal proliferation of the skin and osseous tissues. Clubbing of the digits, periostitis of long bones, and synovial effusions can be seen. Clubbing may be asymptomatic, but patients with periostitis often have deep aching in long bones. HOA may be primary or secondary to other underlying disease processes such as cancer.

SYNONYMS

Primary hypertrophic osteoarthropathy
Pachydermoperiostosis
Idiopathic clubbing
Touraine-Solente-Golé syndrome
Secondary hypertrophic osteoarthropathy
HOA

ICD-10CM CODES

M89.3	Hypertrophy of bone
M89.40	Other hypertrophic osteoarthropathy, unspecified site
M89.411	Other hypertrophic osteoarthropathy, right shoulder
M89.412	Other hypertrophic osteoarthropathy, left shoulder
M89.419	Other hypertrophic osteoarthropathy, unspecified shoulder
M89.421	Other hypertrophic osteoarthropathy, right upper arm
M89.422	Other hypertrophic osteoarthropathy, left upper arm
M89.429	Other hypertrophic osteoarthropathy, unspecified upper arm
M89.431	Other hypertrophic osteoarthropathy, right forearm
M89.432	Other hypertrophic osteoarthropathy, left forearm
M89.439	Other hypertrophic osteoarthropathy, unspecified forearm
M89.441	Other hypertrophic osteoarthropathy, right hand
M89.442	Other hypertrophic osteoarthropathy, left hand
M89.449	Other hypertrophic osteoarthropathy, unspecified hand
M89.451	Other hypertrophic osteoarthropathy, right thigh
M89.452	Other hypertrophic osteoarthropathy, left thigh
M89.459	Other hypertrophic osteoarthropathy, unspecified thigh
M89.461	Other hypertrophic osteoarthropathy, right lower leg
M89.462	Other hypertrophic osteoarthropathy, left lower leg
M89.469	Other hypertrophic osteoarthropathy, unspecified lower leg
M89.471	Other hypertrophic osteoarthropathy, right ankle and foot
M89.472	Other hypertrophic osteoarthropathy, left ankle and foot
M89.479	Other hypertrophic osteoarthropathy, unspecified ankle and foot
M89.48	Other hypertrophic osteoarthropathy, other site
M89.49	Other hypertrophic osteoarthropathy, multiple sites

EPIDEMIOLOGY & DEMOGRAPHICS

- Fig. 1 provides a classification of HOA.
- Primary HOA is a familial autosomal-dominant disease affecting the age group between 1 and 20 yr and is rare.
- There is a male:female ratio of 9:1.
- Secondary HOA is more common, typically occurs in adults 55 to 75 yr. 80% to 90% of secondary HOA is associated with non–small cell lung cancer, most frequently adenocarcinoma; other associated illnesses include:
  1. Pulmonary: Mesothelioma, bronchogenic carcinoma, lung abscesses, empyema, bronchiectasis, cystic fibrosis, pulmonary fibrosis, sarcoidosis, arteriovenous malformations
  2. Gastrointestinal: Carcinoma of esophagus or colon, biliary atresia, peptic ulcer disease, inflammatory bowel disease, hepatocellular carcinoma, liver cirrhosis, amebiasis, laxative abuse, achalasia
  3. Cardiac: Infective endocarditis, right-to-left cardiac shunts, aortic aneurysms, infected aortic bypass graft
  4. Hematologic: Thalassemia, myelofibrosis, Hodgkin lymphoma
  5. Endocrine: Thyroid acropachy, POEMS syndrome
  6. Connective tissue diseases
  7. Thymoma
  8. HIV infection
  9. Osteosarcoma
  10. Nasopharyngeal sarcoma

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Primary HOA typically presents with the insidious onset of clubbing of the hands and feet, described as "spade-like." Finger clubbing is diagnosed by measurement of the digital index (Fig. 2). Other signs and symptoms of HOA include:
  1. Joint pain and swelling
  2. Sensation of warmth or burning in the hands and feet
  3. Coarsening of facial features with grooves or depressions in the scalp, ptosis of the lids
  4. Thickening of the arms and legs
  5. Oily skin, diaphoresis, gynecomastia, and acne
  6. Thin and shiny appearance of the skin around the nail bed
  7. Nail convexity with nail "floating" sensation within the soft tissue is noticed on palpation of the base of the nail bed
  8. Elephant legs: Nonpitting soft tissue swelling with tenderness can be seen
- Secondary HOA patients may present with clinical symptoms before the underlying disorder can be detected. Signs and symptoms are similar to those seen in primary HOA, but there may be findings related to the underlying disease (e.g., lung carcinoma, infective endocarditis).
- Patients presenting with painful joints prior to developing clubbing can be misdiagnosed as having inflammatory arthritis.

ETIOLOGY

The pathogenesis of HOA (Fig. 3) is not fully understood; current knowledge suggests that HOA results from the activation of one or more growth factors and inflammatory mediators. Levels of vascular endothelial growth factor (VEGF) have been found to be elevated in both primary and secondary HOA. Platelet-derived growth factor secreted by megakaryocytes that normally are inactivated in the lungs and systemic circulation have been implicated in the etiology of HOA in the setting of pulmonary conditions and right-to-left shunts. Primary HOA likely has a genetic basis. Mutations in the HPGD gene that encodes for prostaglandin synthesis have been identified in some patients with this condition. The finding of hyperestrogenism in patients with HOA and simple clubbing led to a new hypothesis on the pathogenesis of HOA involving estrogens, prostaglandin E2, prostaglandin A2, and the inflammatory reflex.

DIAGNOSIS

Diagnosis is primarily clinical; radiographs and bone scans can help confirm the diagnosis.

DIFFERENTIAL DIAGNOSIS

Paget disease, reactive arthritis, psoriatic arthritis, syphilitic periostitis, osteoarthritis, rheumatoid arthritis, osteomyelitis, scleromyxedema, and acromegaly.

WORKUP

HOA warrants an investigation into finding a possible secondary association.

LABORATORY TESTS

- Routine laboratory studies such as blood count, electrolytes, and urine studies are typically normal in primary and secondary HOA.
- Erythrocyte sedimentation rate is usually elevated in secondary HOA.
- Liver function tests may be abnormal in patients with secondary HOA from gastrointestinal pathology.
- Alkaline phosphatase may be elevated as a result of periostitis of long bones.
- Analysis of the synovial fluid from joint effusions reveals a low white blood cell count with normal viscosity, color, and complement levels.

IMAGING STUDIES

- A chest radiograph should be obtained to rule out underlying lung cancer.
- Radiographs of the long bones show periosteal new bone formation (Fig. E4).
- Doppler ultrasound may be useful in identifying periostitis.

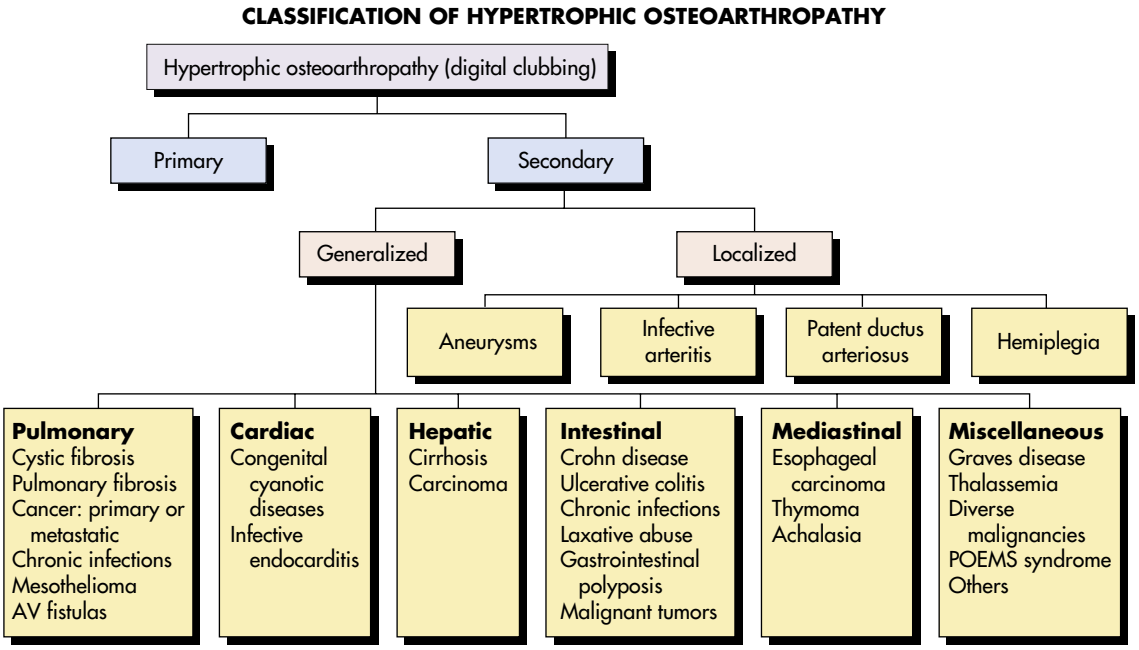

FIG. 1 Various forms of hypertrophic osteoarthropathy (HOA). *AV,* Arteriovenous; *POEMS,* polyneuropathy, organomegaly, endocrinopathy, monoclonal proteins, and skin changes. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

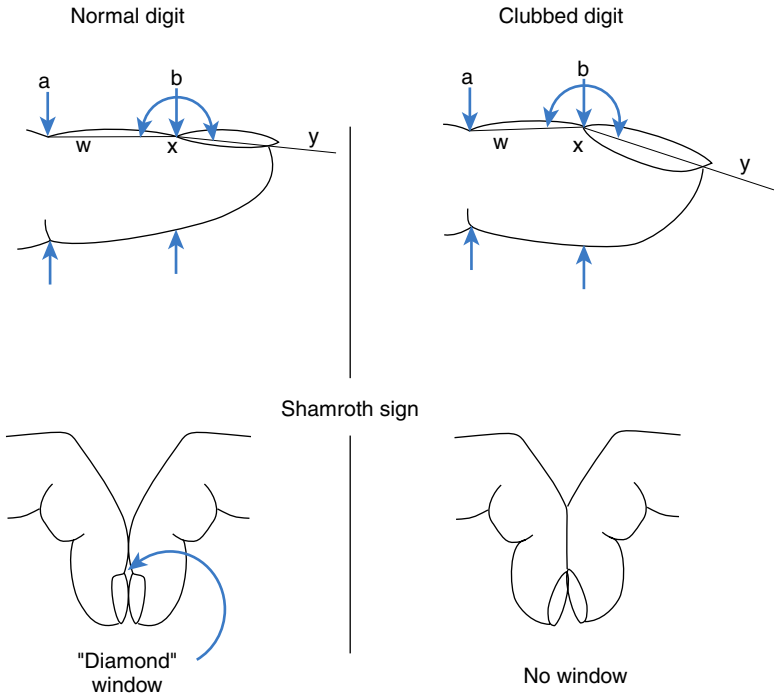

FIG. 2 Clubbing. The normal digit is on the left; the clubbed one, on the right. The distal interphalangeal joint is denoted by **A;** the junction of the nail and skin at the midline is denoted by **B.** The interphalangeal depth ratio is the ratio of the digit's depth measured at **B** divided by that at **A.** The hyponychial angle is the angle *wxy.* In the figure, the depth ratio is 0.9 for the normal digit and 1.2 for the clubbed digit (a ratio >1 indicates clubbing), and the hyponychial angle is 185 degrees for the normal digit and 200 degrees for the clubbed digit (a hyponychial angle >190 degrees indicates clubbing). The Shamroth sign refers to the absence of the diamond-shaped window that normally appears when the terminal phalanges of similar digits are opposed to each other. (From McGee S: *Evidence-based physical diagnosis,* ed 4, Philadelphia, 2018, Elsevier.)

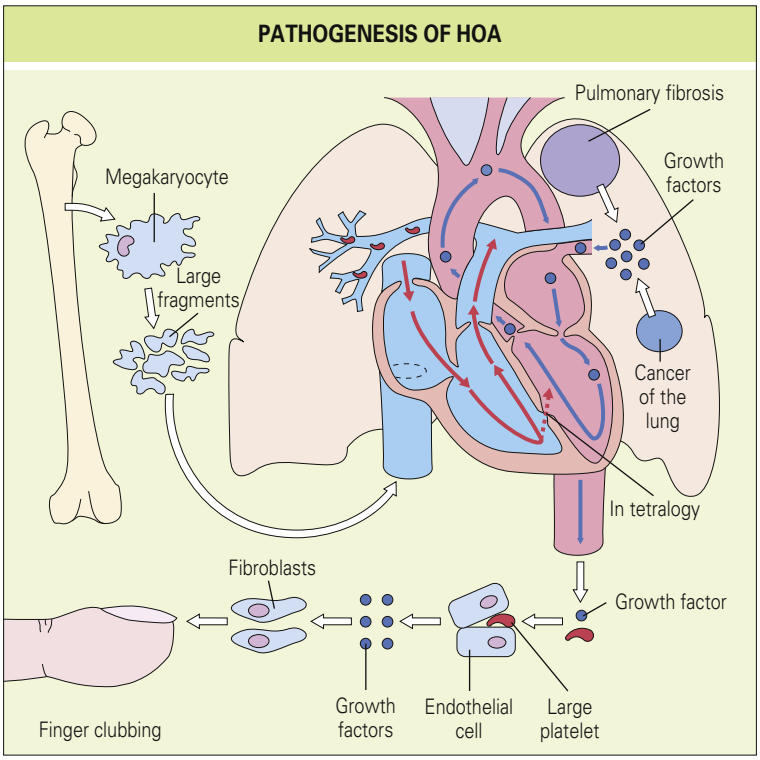

FIG. 3 Theoretic explanation for the development of hypertrophic osteoarthropathy (HOA). Megakaryocytes emerge from the bone marrow and, in normal circumstances, are fragmented in the lung microvasculature. In individuals with cyanotic heart disease (in this case, tetralogy of Fallot), the large fragments would not enter the pulmonary circulation; instead, they would directly enter the systemic circulation, reach its most distal sites, release growth factors, activate endothelial cells, and thus induce finger clubbing. In individuals with lung cancer, a growth factor derived from abnormal tissue would enter the systemic circulation and induce clubbing. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

- Bone scan with technetium-99m reveals cortical uptake.
- Single photon emission computed tomography (SPECT)/CT can increase specificity by excluding bony metastasis.
- Angiography findings may demonstrate hypervascularization of the finger pads.

Rx TREATMENT

ACUTE GENERAL Rx

- Treatment of primary HOA is symptomatic. Nonsteroidal antiinflammatory medications, corticosteroids, tamoxifen citrate, or retinoids can be used.
- Colchicine can be helpful for the pain due to subperiosteal new bone formation.
- Reconstructive surgery is indicated for correction of gross disfigurement.
- Case reports of improvement in symptoms of primary HOA with infliximab and arthroscopic synovectomy.
- Treatment of secondary HOA is to treat the underlying disease. Correction of heart malformation or removal of an underlying tumor can be followed by regression of HOA. NSAIDs for symptomatic relief, joint aspiration/injection.

CHRONIC Rx

In patients with secondary HOA refractory to NSAIDs and aspirin, octreotide (100 mcg subcutaneously twice daily) and bisphosphonates, including pamidronate (1 mg/kg intravenously to a maximum of 60 mg) and zoledronic acid, which inhibit VEGF expression, have been found to be highly effective. Vagotomy has been tried with some success. Definitive treatment remains to treat the underlying disease.

REFERRAL

Referral should be made to rheumatology when the diagnosis of HOA is suspected and the cause remains unclear.

PEARLS & CONSIDERATIONS

- Symptoms of joint pain and swelling in patients with primary HOA often improve with time.
- Prognosis and disease course in patients with secondary HOA will depend on the underlying cause.
- The insidious development of clubbing suggests an infectious process, whereas the rapid progression of clubbing may suggest underlying malignancy.

COMMENTS

Infections and intrathoracic malignancies are the most common causes of secondary HOA. HOA secondary to infection of an arterial graft has been reported.

SUGGESTED READINGS

Available at ExpertConsult.com

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FIG. E4 Hypertrophic osteoarthropathy. Wrist radiograph showing periostosis at the distal ends of the radius and ulna. The coarse, layered appearance is most evident along the diaphyses. The relative sparing of the radial epiphyses is characteristic. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

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BASIC INFORMATION

DEFINITION

Hyperuricemia may be defined as serum uric acid >7.0 mg/dl in males or >6.0 mg/dl in females. Some persons, who are not hyperuricemic by this definition, will have levels of uric acid that exceed the limit of solubility of uric acid in tissue. Data from the Framingham study indicate that hyperuricemia increased from 4.8% of the population in the early 1970s to 9.3% in the mid-1980s. Age is an important risk factor in the increasing incidence of hyperuricemia and gout. Women become hyperuricemic at an older age than men due to the uricosuric effect of estrogen. Most people with hyperuricemia are asymptomatic and will remain so; however, 20% of those with serum uric acid >9 mg/dl will develop gout in 5 yrs. Hyperuricemia is strongly associated with gout, obesity, diabetes, hypertension, and cardiovascular disease but has not been proven to cause any of these conditions.

ASYMPTOMATIC HYPERURICEMIA

Definition: Laboratory evidence of elevated serum uric acid without clinical disease known to be caused by hyperuricemia

ICD-10CM CODE

E79.0 Hyperuricemia without signs of inflammatory arthritis and tophaceous disease

ETIOLOGY

Factors associated with urate variation are summarized in Table E1. Overproduction of uric acid accounts for a minority of cases of hyperuricemia. Most cases are due to decreased renal clearance of uric acid and high dietary purine consumption. Fig. E1 describes factors affecting urate balance. Table E2 describes classification of hyperuricemia and gout.

DIAGNOSIS

EVALUATION

The finding of hyperuricemia should prompt a thorough evaluation of potential causes and related diseases. Fig. E2 describes the evaluation of patients with hyperuricemia. If there is no clinical evidence of gout, nephrolithiasis, or acute kidney injury, the patient may be said to have asymptomatic hyperuricemia. Potential causes of elevated uric acid include malignancy, renal insufficiency, toxins, lead toxicity, and dietary indiscretion. If a careful history and physical exam do not reveal an evident cause of persistent hyperuricemia, a 24-hour urine collection for uric acid and creatinine may be considered. Patients with urinary excretion of uric acid >800 mg/24 hours are likely to be overproducers of uric acid and should be investigated more thoroughly for the underlying cause of their hyperuricemia.

LABORATORY TESTS

- CBC with differential
- CMP (blood urea nitrogen [BUN]/creatinine)
- Urinalysis
- Lipid profile
- Consider 24-hour urine collection for uric acid

TREATMENT

No specific therapy is indicated for most patients with asymptomatic hyperuricemia. Lifestyle and dietary modification are often advisable.

NONPHARMACOLOGIC THERAPY

- Weight loss, regular exercise
- Reduce alcohol intake, especially beer

TABLE E1 Factors associated with urate variation

Genetic factors	Dietary influences	Clinical associations
Male sex Common variants associated with hyperuricemia (replicated) • *SLC2A9* • *ABCG2* • *PDZK1* • *GCKR* • *RREB1* • *SLC17A3* ■ *SLC16A9* • *SLC22A11* • *SLC22A12* • *INHBC* Rare monogenic causes • HPRT deficiencies: Complete (Lesch-Nyhan syndrome), partial (Kelley-Seegmiller syndrome) • PRPP synthetase overactivity • Glucose-6-phosphatase deficiency • Fructose-1-P aldolase deficiency • Myogenic glycogenoses (types III, V, VII) • Uromodulin-associated kidney disease: FJHN, MCKD types 1 and 2	Associated with increased urate • High purine foods (e.g., red meat, liver, offal, shellfish) • Fructose- and sugar-sweetened drinks • Alcohol (beer and spirits) Associated with lower urate • Low-fat dairy products • Cherries • Vitamin C • Coffee	Older age Postmenopause in women Medical comorbidities • Hemolytic disorders • Hemopoietic malignancies; tumor lysis • Lactic or ketoacidosis; hypoxemic states • Lead nephropathy, chronic low-level exposure • Preeclampsia • Renal impairment • Psoriasis • Vasopressin-resistant diabetes insipidus • Bartter and Gitelman syndromes • Down syndrome • Hypertriglyceridemia • Hypertension • Obesity • Cardiovascular disease Medications associated with hyperuricemia • Aspirin (low dose) • Chemotherapeutic cytotoxics • Diuretics • Pyrazinamide • Ethanol • Levodopa • Nicotinic acid • Cyclosporine and tacrolimus Medications associated with reduced serum urate Losartan • Fenofibrate • Leflunomide • Calcium channel blockers • Atorvastatin • Sevelamer

FJHN, Familial juvenile hyperuricemic nephropathy; *HPRT,* hypoxanthine-guanine phosphoribosyltransferase; *MCKD,* medullary cystic kidney disease; *PRPP,* 5-phosphoribosyl 1-pyrophosphate.
From Hochberg MC: Rheumatology, ed 7, Philadelphia, 2019, Elsevier.

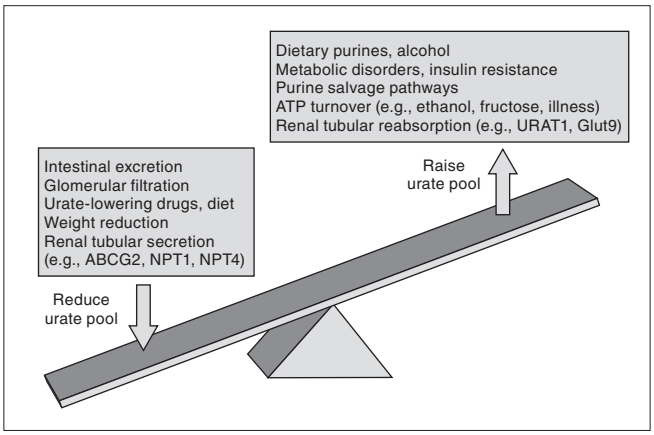

FIG. E1 Factors affecting urate balance. The systemic urate pool and the likelihood of gout are determined by the dynamic balance among dietary purines, endogenous synthesis and recycling, and disposal by the kidney and gut. *ATP,* Adenosine triphosphate. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

TABLE E2 Classification of Hyperuricemia and Gout

Impaired Uric Acid Excretion
Primary gout with decreased uric acid clearance
Secondary gout
Clinical conditions
Reduced glomerular filtration rate
Hypertension
Obesity
Systemic acidosis
Familial juvenile hyperuricemic nephropathy
Medullary cystic kidney disease
Lead nephropathy
Drugs
Diuretics
Ethanol
Low-dose salicylates (0.3-3.0 g/day)
Cyclosporine
Tacrolimus
Levodopa
Excessive urate production
Primary metabolic disorders
HPRT deficiency
PRPP synthetase overactivity
Glucose-6-phosphatase deficiency
Fructose-1-phosphate aldolase deficiency
Secondary causes
Clinical conditions
Myelo- and lymphoproliferative disorders
Obesity
Psoriasis
Glycogenoses III, V, VII
Drugs and dietary components
Nicotinic acid
Pancreatic extract
Cytotoxic drugs
Red meat, organ meat, shellfish
Alcoholic beverages (especially beer)
Fructose

HPRT, Hypoxanthine-guanine phosphoribosyltransferase; *PRPP,* phosphoribosyl pyrophosphate.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.

- Reduce consumption of foods known to be high in purines such as red meat, organ meat, and high-fructose soft drinks

PEARLS & CONSIDERATIONS

- Research suggests there may be a causal relationship between hyperuricemia and early hypertension.
- If drug can be used to decrease hyperuricemia for an alternative condition, should consider this (hypertension: Use losartan or CCB, avoid diuretic if possible)
- Very high levels of serum uric acid may warrant treatment even if asymptomatic.
- Patients with hyperuricemia and a family history of gout should be followed closely for the development of gouty arthritis.
- Hyperuricemia in patients with gout should almost always be treated with urate-lowering medication (see "Gout"). The presence of gouty tophi or arthritis due to gout is generally an absolute indication for urate-lowering therapy.

There is evidence from several sources suggesting that treatment of hyperuricemia slows the progression of chronic kidney disease (CKD) in patients without gout. However, one large randomized controlled study of febuxostat therapy in stage 3 CKD conducted in Japan was unable to replicate this finding. Current recommendations do not support the use of urate-lowering therapy in CKD unless there is concomitant gout, but the issue needs further study.

Recent studies have suggested that allopurinol use is associated with a reduced risk of myocardial infarction and reduction in all-cause mortality. These preliminary studies have sparked renewed research interest.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Gout (Related Key Topic)

AUTHOR: **Bryant Uy, MPH, PA-C**

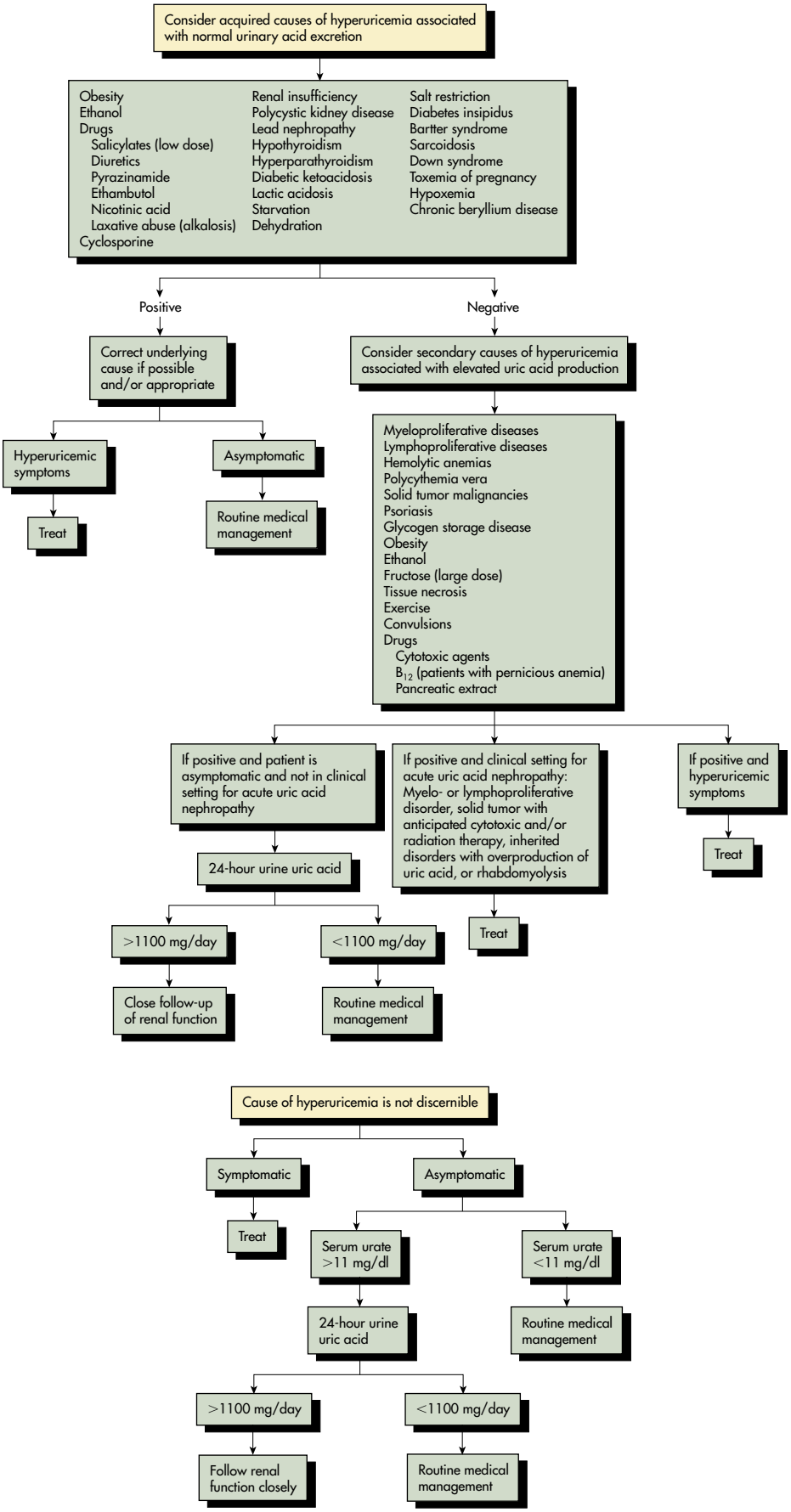

FIG. E2 Evaluation of patients with hyperuricemia. (From Harris ED et al [eds]: *Kelley's textbook of rheumatology,* ed 7, Philadelphia, 2005, WB Saunders.)

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Hypoactive Sexual Desire Disorder (HSDD)

BASIC INFORMATION

DEFINITION

- Persistently or recurrently diminished or absent sexual/erotic thoughts or fantasies and desire for sexual activity.
- The judgment of deficiency is made by the clinician taking into account factors related to age, social context, and general contexts of the individual's life.
- Symptoms must have been present for a minimum of 6 mo, the majority of the time, and be distressing to the individual.
- The lack of desire must not be better explained by a nonsexual mental disorder or by severe relationship distress or other significant stressor.
- Must also not be better attributable to substance/medication or another medical condition.

SYNONYMS

Subsumed in female sexual interest/arousal disorder
Hypoactive sexual desire disorder, situational
Psychosexual desire disorder, situational hypoactive
Psychosexual dysfunction associated with inhibited libido
Psychosexual dysfunction with inhibited libido
Situational hypoactive sexual desire disorder
HSDD

ICD-10CM CODES
F52.0 Hypoactive sexual desire disorder
F52.22 Female sexual arousal disorder
DSM-5 CODES
302.71
302.72

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Prevalence of low sexual desire increases with age. Middle-aged women (45 to 65 yr old) and men over 60 appear at greatest risk of experiencing qualifying distress.
PREVALENCE:

- Among males, rates of HSDD vary depending on country of origin and means of assessment. Generally, 6% of men 18 to 24 and 41% of men 66 to 74 report problems with sexual desire. Persistent lack of sexual interest that lasts longer than 6 mo is seen in approximately 1.8% of men 16 to 44.
- For women, rates of HSDD are more uncertain, especially given the new inclusion of HSDD into female sexual interest/arousal disorder. Prior studies with less stringent criteria suggest approximately 36% of women endorse low sexual desire, but roughly only 8% report experiencing clinical levels of related distress. These rates also vary by country of origin and method of assessment (Fig. E1).

PREDOMINANT SEX & AGE: HSDD appears to be more prevalent in women; however, men are more likely to be underdiagnosed or misdiagnosed with another sexual dysfunction.
GENETICS: There appears to be a strong influence of genetics in the vulnerability of women to sexual dysfunction. Specifically, women with the ll genotype for the SCL6A4 promoter region (5HTTLPR) appear to be eight times more likely to have selective serotonin reuptake inhibitor (SSRI) associated sexual dysfunction if they are also taking oral contraceptives. Men with the ll genotype have also been found to be at greater risk of sexual dysfunction. Similarly, dopamine (D4) receptor polymorphisms influence all phases of the sexual response cycle.
RISK FACTORS: Temperamental and environmental risk factors for HSDD include mood and anxiety symptoms, negative cognitions about sexuality or relationship, alcohol use, early childhood trauma, interpersonal problems, and lack of adequate sex education. Physiologic risk factors include age, medical conditions such as diabetes mellitus, thyroid dysfunction, hyperprolactinemia, coronary disease, renal failure, and androgen deficiency, as well as other neuroendocrine changes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- HSDD can be lifelong or acquired as well as generalized or situational.
- Men appear more likely to present with the acquired, situational subtype.
- For women, lack of pleasure is a common presenting clinical complaint.
- Consideration of initiation of sexual activity and receptivity to sexual activity initiated by the partner should be assessed. Men are often more likely to initiate sexual encounters, and noninitiation may be a signifier of a possible problem, but any shift in pattern of initiation should be investigated further.
- Other sexual activities such as masturbation or partnered sexual activity may still occur even in the context of low sexual desire.
- The interpersonal context of HSDD should be taken into account, as often a desire discrepancy between partners leads to discussions of possible HSDD, but this is not sufficient for diagnosis.
- Symptoms should be present for approximately 6 mo, but clinical judgment can be used if symptoms are of lesser duration.

ETIOLOGY

Best evidence suggests a multifactorial etiology, including factors along the biopsychosocial continuum, including genetic vulnerability, interpersonal distress, cultural factors, mental health, medical conditions, and medical treatments.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

If low sexual desire can be attributed largely to one of these factors, HSDD should not be diagnosed, and the underlying factor should be addressed.

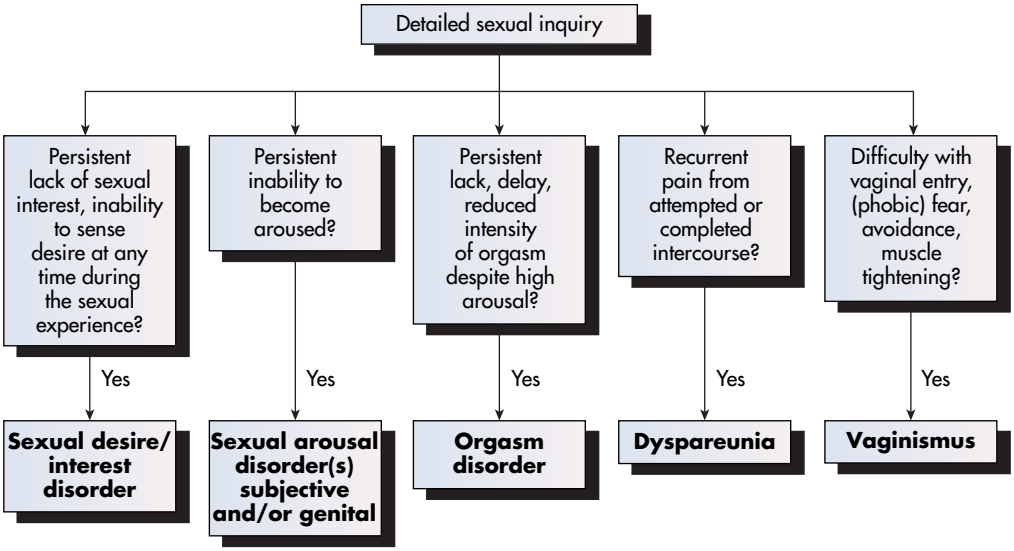

FIG. E1 Currently recommended definitions for women's sexual dysfunction. Comorbidity is usual, especially sexual desire/interest disorder with one of the sexual arousal disorders. (From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders.)

- Nonsexual mental disorder: Depression, anxiety, posttraumatic stress disorder, and schizophrenia
- Substance/medication use: Drugs of abuse (e.g., alcohol), anticonvulsants (e.g., carbamazepine), cardiovascular and antihypertensive agents (e.g., clonidine), hormonal medications (e.g., oral contraceptives), and psychotropic medications (e.g., SSRIs)
- Another medical condition: Endocrine disorders (e.g., diabetes mellitus), coronary artery disease, cancer, central nervous system disease, hypertension, and arthritis
- Interpersonal factors: Relationship discord, partner sexual problems, dissatisfaction with partner or relationship, communication deficits, and intimate partner violence
- Other sexual dysfunctions: Erectile disorder, female orgasmic disorder, and genitopelvic pain/penetration disorder

WORKUP

- Clinical interview should include a sexual history, medical history, and psychosocial history. The sexual history should include questions about prior sexual issues, sexual behavior and practices, and patient's treatment goals.
- A physical examination may be warranted for some female patients to identify possible contributing factors to low desire such as vulvovaginal atrophy, genital sensory changes, and pelvic floor prolapse.
- Symptoms of depression and anxiety should be assessed. This can be done with brief screeners such as the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7).
- Adequate endocrine functioning can be assessed through a combination of history taking (e.g., menstrual patterns) and laboratory tests when warranted by history.
- Self-rating scales and standardized symptom-specific checklist may be helpful in diagnosis and determining treatment. Example screeners include the Brief Sexual Symptom Checklist (BSSC), the Decreased Sexual Desire Screener (DSDS), and Female Sexual Function Index (FSFI).

LABORATORY TESTS

- Laboratory tests should be undertaken if indicated by history or physical exam.
- Common tests include:
  1. Thyroid function, serum total testosterone, prolactin, follicle-stimulating hormone (FSH), and luteinizing hormone (LH)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Multimodal interventions are often needed to address the complex etiology of HSDD.
- Basic sex education can be a valuable in-office intervention that can alleviate distress that arises from unrealistic norms or misunderstandings related to basic reproductive anatomy and physiology.
- Simple suggestions related to reducing stress, increasing communication with partner, and leading a healthy lifestyle can help to improve sexual function for some.
- Patients should be referred for psychological intervention when medical rule-outs have been completed. Therapist should have experience with treating sexual problems.
- The number of controlled trials studying the efficacy of psychological treatment for HSDD is limited; however, available evidence suggests significant improvements with the use of cognitive behavioral therapy, mindfulness-based approaches, traditional sex therapy, or a combination.
- There is support for both individual- and couple-based treatments.

ACUTE GENERAL Rx

- Currently, only one FDA-approved treatment exists for premenopausal women with HSDD: Flibanserin (Addyi). Addyi is a multifunctional serotonin agonist/antagonist that passes through the blood-brain barrier and selectively affects the prefrontal cortex. Addyi has been shown to increase the number of satisfying sexual events per mo.
- Addyi is contraindicated for use with moderate and strong CYP3A4 inhibitors, with alcohol, and in patients with hepatic impairments. Side effects include dizziness, somnolence, fatigue, and nausea.
- The FDA has required a Risk Evaluation and Mitigation Strategy (REMS) for Addyi, which requires prescribers and pharmacies to be certified in the REMS program to prescribe and dispense. More information is available at: https://addyirems.com/AddyiUI/rems/home.action.
- Bupropion hydrochloride is a mild dopamine and norepinephrine reuptake inhibitor and nicotinic acetylcholine receptor antagonist that is used as an antidepressant and smoking cessation aid. There is some empirical evidence for off-label use suggesting that bupropion significantly increases sexual desire in nondepressed women. It has also been shown to be effective in reversing SSRI-induced sexual dysfunction.
- Buspirone is a serotonin 1A partial agonist and is used off-label for treatment of HSDD. It has been shown to reduce low-desire side effects of SSRIs when coadministered.
- Testosterone is widely prescribed off-label for postmenopausal women, with substantial evidence suggesting testosterone therapy improves sexual well-being among postmenopausal women. There is limited evidence for similar effects among premenopausal women.
- Testosterone is a well-established treatment for men with HSDD secondary to low testosterone.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Recent studies have shown good preliminary efficacy of treating both sexual arousal and desire disorders with mindfulness, yoga, and meditation as a complement to psychotherapy.

DISPOSITION

- HSDD is a common sexual dysfunction that affects both men and women across the life span. With appropriate identification and treatment, many patients will experience improvement in sexual desire; however, finding appropriate referrals and support for patients may be challenging.
- Specific types of HSDD can resolve in time untreated if a patient's contextual factors change (e.g., new partner), but for others HSDD will persist or worsen without treatment.
- Patients may be at higher risk for relationship discord and other psychiatric disorders such as depression and anxiety.

REFERRAL

- Most patients presenting with HSDD would benefit from referral to a therapist skilled in treating sexual problems.
- Patients with unresolved physical or sexual trauma should be promptly referred to a specialist.
- Establishing a referral network of specialists in sexual medicine and therapy is important.

PEARLS & CONSIDERATIONS

- Biologic and psychological factors often comingle and contribute to the individual picture of HSDD.
- Linguistic and cultural variations can heavily impact the presentation of HSDD and the associated distress as well as treatment.
- New FDA-approved medication Addyi remains controversial among sexual medicine specialists.
- Discussions of potential sexual side effects of medications and of general sexual health with all patients will allow for more open conversations when problems do arise.

RELATED CONTENT

Ejaculation and Orgasm Disorders (Related Key Topic)

Sexual Dysfunction in Women (Related Key Topic)

AUTHOR: **Karlene Cunningham, PhD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Hypoaldosteronism is defined as an aldosterone deficiency or impaired aldosterone function.

ICD-10CM CODES

E27.40	Unspecified adrenocortical insufficiency
E27.3	Drug-induced adrenocortical insufficiency
E27.9	Disorder of adrenal gland, unspecified
E27.1	Primary adrenocortical insufficiency
E27.40	Unspecified adrenocortical insufficiency
E27.49	Other adrenocortical insufficiency

EPIDEMIOLOGY & DEMOGRAPHICS

Selective hypoaldosteronism accounts for as many as 10% of cases of unexplained hyperkalemia.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination may be entirely within normal limits.
- Hypertension may be present in some patients.
- Profound muscle weakness and cardiac arrhythmias may be present.

ETIOLOGY

- Hyporeninemic hypoaldosteronism (renin-angiotensin dependent): Decreased aldosterone production as a result of decreased renin production; the typical patient has renal disease attributable to various factors (e.g., diabetes mellitus, interstitial nephritis, multiple myeloma, HIV infection, urinary tract obstruction, aging) and medications (NSAIDs, COX-2 inhibitors, ACEI/ARBs).
- Hyperreninemic hypoaldosteronism (renin-angiotensin independent): Renin production by the kidneys is intact; the defect is in aldosterone biosynthesis or in the action of angiotensin II. Common causes of this form of hypoaldosteronism are medications (ketoconazole, heparin), lead poisoning, aldosterone enzyme defects, and severe illness.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Pseudohypoaldosteronism: Renal unresponsiveness to aldosterone. In this condition both renin and aldosterone levels are elevated. Pseudohypoaldosteronism can be caused by medications (spironolactone), chronic interstitial nephritis, systemic disorders (systemic lupus erythematosus, amyloidosis), or primary mineralocorticoid resistance.

WORKUP

Measurement of plasma renin activity after 4 hr of upright posture can differentiate hyporeninemic from hyperreninemic causes. Renin levels in the normal or low range identify cases that are renin-angiotensin dependent, whereas high renin levels identify cases that are renin-angiotensin independent. The diagnosis and etiology of hypoaldosteronism can be confirmed with the renin-aldosterone stimulation test:

- Hyporeninemic hypoaldosteronism: Low stimulated renin and aldosterone levels
- End-organ refractoriness to aldosterone action: High stimulated renin and aldosterone levels
- Adrenal gland abnormality: High stimulated renin and low aldosterone levels

LABORATORY TESTS

- Increased potassium, normal or decreased sodium
- Hyperchloremic metabolic acidosis (caused by the absence of hydrogen-secreting action of aldosterone)
- Increased BUN and creatinine (secondary to renal disease)
- Hyperglycemia (diabetes mellitus is common in these patients)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Low-potassium diet with liberal sodium intake (at least 4g of sodium chloride per day)
- Avoidance of ACE inhibitors and potassium-sparing diuretics

ACUTE GENERAL Rx

- Judicious use of fludrocortisone (0.05 to 0.1 mg PO every morning) in patients with aldosterone deficiency associated with deficiency of adrenal glucocorticoid hormones
- Furosemide 20 to 40 mg qd to correct hyperkalemia of hyporeninemic hypoaldosteronism

DISPOSITION

Prognosis varies with the etiology of hypoaldosteronism and presence of associated disorders.

REFERRAL

Endocrinology referral for renin-aldosterone stimulation test

PEARLS & CONSIDERATIONS

COMMENTS

Treatment of pseudohypoaldosteronism is the same as for hypoaldosteronism; however, effect is limited because of impaired renal sensitivity.

RELATED CONTENT

Hyperkalemia (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

Hypochondriasis (Illness Anxiety Disorder) PTG

BASIC INFORMATION

DEFINITION

Illness anxiety disorder is a newly defined diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders,* ed 5 (DSM-5). In the DSM-5, hypochondriasis and related conditions were replaced by two new concepts: Illness anxiety disorder (somatic symptoms absent or minimal; concern focused on the idea of illness) and somatic symptom disorder (somatic symptoms present, with significant related distress and impairment)—both diagnostic subtypes of the DSM-5 Somatic Symptom and Related Disorders category (Somatoform disorders in DSM-IV).

Illness anxiety disorder, referred to more generally as *health anxiety*, is marked by the preoccupation with the fear of having, or the idea that one has, a serious undiagnosed disease, despite a lack of significant corresponding somatic symptoms or medical evidence. Whether or not a medical diagnosis is present, the severity of health-related anxiety is clearly disproportionate to the individual's health status. Most medical literature explores the previously defined disorder hypochondriasis; it is unknown exactly how that evidence applies to illness anxiety disorder.

SYNONYMS

Hypochondriasis
Illness anxiety disorder
Somatoform disorder (DSM-IV)
Health anxiety

ICD-10CM CODE
F45.21 Hypochondriasis
DSM-5 CODE
300.7 Illness anxiety disorder

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 1% to 5% (based on estimates of DSM-III and DSM-IV disorder hypochondriasis) but may be higher (3% to 10%) in primary care outpatient settings
PREDOMINANT SEX: Equal frequency in men and women
PREDOMINANT AGE: Onset at any age, but most commonly between ages 20 and 30 yr

GENETICS/RISK

No known genetic component. May be more common in less-educated individuals. A comorbid mental disorder (e.g., generalized anxiety, obsessive-compulsive disorder, or depression) may affect over two thirds of individuals with illness anxiety disorder; personality disorders and other somatic symptom disorders may also be more common.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Somatic symptoms or signs are not present or are only mild; the focus of anxiety is the suspected medical diagnosis itself (i.e., concern for illness rather than symptoms per se).
- Mild somatic symptoms, if present, often include nonpathologic physical signs or sensations (e.g., belching, orthostatic light-headedness).
- High health-related anxiety persists despite reassuring clinical evaluation (without the intensity of a delusion).
- Illness anxiety symptoms often correlate with psychosocial stressors.
- Illness preoccupation lasts at least 6 mo (the specific illness feared may vary).
- Disruption in health-related quality of life and/or social, occupational, or other important areas of functioning.
- Two presentation types: Care-seeking (medical attention frequently sought) and care-avoidant (maladaptive avoidance of health care).
- No specific physical examination findings.

ETIOLOGY

Unknown neurobiologic etiology. Serious childhood illness or trauma may be associated with illness anxiety disorder in adulthood.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Underlying medical condition
- Delusional disorder (somatic type—fixed delusion of illness despite evidence to the contrary)
- Adjustment disorder (health-related anxiety in response to identifiable or documented medical illness)
- Somatic symptom disorder (excessive distress related to somatic symptom[s]) (medically unexplained symptoms)
- Body dysmorphic disorder (restricted to a circumscribed concern about appearance)
- Generalized anxiety disorder with health concerns as one worry among others
- Major depressive disorder with health concerns occurring only during depressive episodes
- Psychosis, as may occur with depression and schizophrenia
- Factitious disorder (formerly Munchausen syndrome)
- Malingering

WORKUP

- History, physical examination, age-appropriate screenings, and laboratory and imaging tests, as appropriate, to exclude underlying medical condition
- Symptom measures (e.g., Health Anxiety Inventory) may be used for detection and monitoring of severity over time
- Evaluation for other psychiatric disorders associated with illness anxiety, such as depression and generalized anxiety

TREATMENT

NONPHARMACOLOGIC THERAPY

- Psychotherapy, specifically cognitive behavioral therapy (CBT), is the mainstay of treatment, with techniques to alter or restructure maladaptive thinking and behavior and to improve coping with health anxiety. Individual or group CBT, acceptance and commitment therapy (ACT), behavioral stress management, and mindfulness-based approaches, including Internet-based treatments, have demonstrated success
- Regularly scheduled brief medical appointments not contingent on symptoms
- Emphasis on care coordination
- Avoidance of the suggestion that symptoms are "all in your head"
- Education about illness anxiety diagnosis and framing of psychosomatic experience (on a spectrum of normal to excessive)
- Emphasis on optimization of function (rather than cure) as the goal of treatment
- Avoidance of repeated or nonmedically indicated diagnostic testing, referrals, or treatments
- Limit on reading medical texts or websites
- Benign interventions to reduce stress and build resilience (e.g., exercise, massage, meditation, social support, sleep hygiene, etc.)

CHRONIC Rx

- Antidepressants may be helpful even in individuals without features of depression: Placebo-controlled trials of fluoxetine and paroxetine suggest benefit. Norepinephrine-serotonin reuptake inhibitors (NSRIs) such as duloxetine have documented efficacy in the treatment of pain related to depression and associated with medical conditions (fibromyalgia, diffuse musculoskeletal pain [osteoarthritis]) often comorbid with psychiatric illness.
- Treatment of comorbid psychiatric conditions, if present.

DISPOSITION

Waxing and waning course over decades; recovery rates between 30% and 85%. Positive prognostic factors include shorter duration of illness anxiety and lack of comorbid psychiatric disorder.

REFERRAL

Referral for CBT is the mainstay of treatment; referral to a psychiatrist may be needed in the case of comorbid psychiatric condition.

PEARLS & CONSIDERATIONS

- The primary goal in treating illness anxiety is to improve patients' ability to cope with health fears.
- Psychotherapy and pharmacotherapy may be helpful treatment modalities for individuals open to treatment not directed at the perceived illness.
- In the updated DSM-5, hypochondriasis and related somatoform disorders were replaced by two new concepts: Somatic symptom disorder (somatic symptoms present, with significant related distress) and illness anxiety disorder (somatic symptoms absent or minimal; concern focused on the idea of illness).

RELATED CONTENT

Hypochondria (Patient Information)
Somatic Symptom Disorder (Related Key Topic)
Somatization Disorder (Patient Information)

AUTHOR: **Colin J. Harrington, MD**

SUGGESTED READINGS

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Hypocomplementemic Urticarial Vasculitis

BASIC INFORMATION

DEFINITION

- Hypocomplementemic urticarial vasculitis (HUV) is the term used to describe patients with urticarial vasculitis and hypocomplementemia who do not meet diagnostic criteria for hypocomplementemic urticarial vasculitis syndrome.
- In general, patients with HUV have cutaneous disease and few or no systemic manifestations.

SYNONYMS

Urticarial vasculitis
Hypocomplementemic urticarial vasculitis syndrome
HUV

ICD-10CM CODE
M31.8 Hypocomplementemic vasculitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Urticarial vasculitis (UV) is a rare diagnosis.
- The incidence and prevalence of the disorder are uncertain.

PEAK INCIDENCE: The peak reported incidence is in the fourth decade of life.

PREVALENCE: The prevalence of UV in patients with chronic urticaria varies from 5% to 20%.

PREDOMINANT AGE AND SEX:

- Women comprise 60% to 80% of reported patients.
- UV has also been described in children; the youngest reported case occurred in a patient 1 yr of age.

GENETICS: A study including two families with autosomal-recessive HUVS found that mutations in *DNASE1L3* were associated with a familial form of HUVS and HUVS associated with SLE.

RISK FACTORS:

- The association with some disorders in which the antigen-antibody complexes are well defined (e.g., hepatitis B, hepatitis C), and the observation that removal of immune complexes by plasmapheresis is temporally associated with the resolution of the urticarial lesions.
- Medications and viruses (particularly hepatitis B and C) have been implicated as the target antigen in some cases.
- There have also been reports demonstrating the development of UV in association with infliximab, glatiramer acetate, and the injection of hyaluronic acid.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- **Dermatologic:** The urticarial lesions (or wheals) of urticarial vasculitis (UV) can be found anywhere on the body. Urticarial lesions are typically more pruritic than painful and can be associated with angioedema, purpura, and livedo reticularis.
- **Musculoskeletal:** Arthralgias and arthritis are the most common systemic manifestation of UV. Joint pain is usually migratory and transient, frequently affecting the hands, elbows, feet, ankles, and knees.
- **Renal:** Renal disease is characterized by proteinuria and hematuria. The renal disease of UV includes proliferative glomerulonephritis, focal necrotizing vasculitis, crescentic glomerulonephritis, membranoproliferative glomerulonephritis, and tubulointerstitial nephritis. The renal involvement of UV tends to be more severe in children.
- **Pulmonary:** Pulmonary involvement is a leading cause of morbidity and mortality in UV and may include cough, dyspnea, hemoptysis, chronic obstructive pulmonary disease (COPD), asthma, pleuritis, and pleural effusions. The most common pulmonary manifestations are COPD and asthma.
- Smoking accelerates pulmonary parenchymal destruction by helping to recruit neutrophils. Thus, patients with UV should not smoke and should avoid secondhand smoke.
- **Gastrointestinal:** GI symptoms include substernal pain, abdominal pain, nausea, vomiting, and diarrhea. Hepatomegaly and splenomegaly have been reported.
- **Ophthalmologic:** Ophthalmologic symptoms include episcleritis, uveitis, and conjunctivitis. A rare case of serpiginous choroidopathy with subsequent blindness was reported; optic atrophy has been reported also.
- **Cardiovascular:** Symptoms include pericarditis, tamponade, valvular disease, and pericardial effusion.
- **Neurologic:** Central nervous system (CNS) involvement includes pseudotumor cerebri (the most common CNS manifestation), aseptic meningitis, cranial nerve palsies, peripheral neuropathy, and transverse myelitis.

ETIOLOGY

- HUV results from the formation of immune complexes in the blood that then deposit in vessel walls.
- In some patients with UV (particularly those with hypocomplementemic urticarial vasculitis), a collagen-like region on C1q has been implicated as the antigenic target.
- The autoantibody is referred to as a C1q precipitin.
- Once antigen-antibody complexes have formed, they can activate the classical complement pathway. This generates C3a and C5a, which cause mast cell degranulation resulting in urticarial eruptions. C3a and C5a also cause increased vessel permeability and chemotaxis of neutrophils.
- Infiltrating neutrophils release proteolytic enzymes, causing further tissue destruction and edema.
- IL-1 may play a role in the pathogenesis of UV.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Common urticarial
- Erythema multiforme
- Neutrophilic urticarial dermatosis
- Acquired angioedema

LABORATORY TESTS

The most common abnormal laboratory results associated with urticarial vasculitis (UV) include:

- Elevated erythrocyte sedimentation rate (ESR)
- Hypocomplementemia (usually decreased C1q, C3, and C4)
- Circulating immune complexes by the C1q solid phase test and/or anti-C1q antibody assay
- Positive antinuclear antibodies (ANA)
- Antidouble stranded DNA (ds-DNA)
- Anti-Ro, -La, -Sm, and -RNP antibodies
- Antineutrophil cytoplasmic antibodies (ANCA), particularly enzyme immunoassays for antibodies to proteinase-3 and myeloperoxidase (PR3- and MPO-ANCA)
- Rheumatoid factor and/or anticyclic citrullinated peptides (anti-CCP)
- Immunofixation electrophoresis
- Cryoglobulins and cryofibrinogens

Skin biopsy: Leukocytoclasis, or fragmentation of leukocytes with nuclear debris, and fibrinoid deposits are important histopathologic findings that represent direct signs of vessel damage. Immunofluorescence reveals deposits of immunoglobulins, complement, or fibrin around blood vessels in most patients.

TREATMENT

GENERAL Rx

- UV is often difficult to treat, and therapy is based upon case reports and small series.
- Systemic glucocorticoids are considered the mainstay of therapy for UV, and additional agents are typically added.
- Antihistamines are used to manage pruritus.
- Glucocorticoids in combination with either dapsone, colchicine, or hydroxychloroquine are typically used as initial therapy for patients with mild to moderate disease.
- For patients with refractory symptoms or those with organ- or life-threatening disease manifestations, other agents in combination with glucocorticoids are recommended: mycophenolate mofetil, methotrexate, azathioprine, and cyclosporine; rarely, cyclophosphamide, rituximab, anakinra, canakinumab, and omalizumab are used.
- The assistance of a rheumatologist with experience in the management of vasculitides is suggested for patients with evidence of significant systemic disease.

DISPOSITION

- Patients with hypocomplementemia have severe disease and may experience significant morbidity and mortality; however, they rarely die as a direct result of the disease, even in the setting of multisystem involvement.
- Pulmonary involvement is a leading cause of morbidity and mortality, due largely to complications of COPD.

Hypocomplementemic Urticarial Vasculitis

REFERRAL

Rheumatology, dermatology, pulmonary critical care, cardiology, nephrology

PEARLS & CONSIDERATIONS

- UV is a clinicopathologic entity consisting of urticaria and evidence of leukocytoclastic vasculitis on skin biopsy.
- UV predominantly involves the skin but may affect other organs, particularly the lungs, kidney, and gastrointestinal tract.
- Hypocomplementemia, when present, may be associated with extensive vasculitis and systemic features.
- The pathophysiology of UV is believed to involve the deposition of immune complexes in vessel walls, complement activation, and mast cell degranulation due to C3a and C5a with resultant urticaria.
- The diagnosis of UV requires the presence of urticaria with leukocytoclastic vasculitis (LCV) on skin biopsy.
- If LCV is present, further testing is indicated to define the presence and extent of systemic disease and to evaluate for associated conditions.
- UV is a benign and self-limited disease for the majority of patients, although symptoms can last for decades in some individuals.

AUTHOR: **Catherine E. Najem, MD**

SUGGESTED READING

Jachiet M et al: The clinical spectrum and therapeutic management of hypocomplementemic urticarial vasculitis: data from a French nationwide study of fifty-seven patients, *Arthritis Rheumatol* 67:527, 2015.

BASIC INFORMATION

DEFINITION

Hypoglycemia refers to abnormally low blood glucose levels in circulating plasma. It is defined as a glucose value less than 70 mg/dl (3.9 mmol/L). "Serious hypoglycemia" refers to values <54 mg/dl (3.0 mmol/L). "Severe hypoglycemia" is any glucose value necessitating external assistance to correct it. "Reactive hypoglycemia" refers to symptoms of hypoglycemia with plasma glucose value greater than 70 mg/dl. A multitude of scenarios can lead to this potentially fatal condition.

SYNONYMS

Glycopenia
Low blood glucose
Low blood sugar
HG

ICD-10CM CODES

E10.641	Type 1 diabetes mellitus with hypoglycemia with coma
E10.649	Type 1 diabetes mellitus with hypoglycemia without coma
E11.641	Type 2 diabetes mellitus with hypoglycemia with coma
E11.649	Type 2 diabetes mellitus with hypoglycemia without coma
E13.641	Other specified diabetes mellitus with hypoglycemia with coma
E13.649	Other specified diabetes mellitus with hypoglycemia without coma
E16.1	Other hypoglycemia
E16.2	Hypoglycemia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- More frequent in type 1 diabetes mellitus (DM). Estimated that glucose levels may be as low as 50 to 60 mg/dl ~10% of the time in type 1 DM.
- HG occurrence 62 to 320 episodes per 100 patient yr in type 1 diabetes vs. 35 episodes per 100 patient yr in type 2 diabetes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms are often nonspecific.
- Early symptoms include sweating, pallor, anxiety, palpitations, hunger, and tremor.
- Late symptoms with lower plasma glucose levels include seizures, altered mental status, and coma.
- Profound or prolonged hypoglycemic episodes can cause irreversible brain injury, cardiopulmonary arrest, and death.

ETIOLOGY

- Medications are the most common cause of hypoglycemia. Most common causes include exogenous insulin, insulin secretagogues (sulfonylureas [SU] and meglitinides [MG]), and alcohol
- Critical illness
  1. Organ failure (hepatic, cardiac, or renal)
  2. Sepsis
- Hormone deficiency (cortisol, glucagon, and epinephrine)
- Endogenous hyperinsulinism (insulinoma, functional beta-cell disorders, insulin autoimmune hypoglycemia)
- Rare fatal episodes thought to be secondary to ventricular arrhythmias

DIAGNOSIS

Characterized by Whipple triad:

- Symptoms potentially explained by hypoglycemia
- Low blood glucose levels during the symptoms
- Relief of symptoms with administration of glucose or glucagon

DIFFERENTIAL DIAGNOSIS

Hypoglycemic symptoms in the presence of normal plasma glucose levels (>70 mg/dl) point to other etiologies: Postprandial syndrome, cardiac disease, psychiatric disease, metabolic disorders (hyperthyroidism, pheochromocytoma)

WORKUP

- If Whipple triad is positive, the next step is to consider a patient's medical status.
- Iatrogenic causes are the most common causes of hypoglycemia in hospitalized patients (review the timing of glucose-lowering medications and interactions between medications).
- Detailed history, including past medical history, a thorough medication history, and timing of hypoglycemia (in regard to meals and medications).

LABORATORY TESTS

- An algorithm for recognition and evaluation of hypoglycemia is described in Fig. 1.
- If the cause is not apparent after a thorough history, the following is appropriate:

FASTING: If symptoms witnessed when fasting, with verified low blood glucose levels, draw the following labs: Plasma glucose, β-hydroxybutyrate (BHOB), insulin, C-peptide, proinsulin, screen for SU and MG metabolites.

POSTPRANDIAL:

- Plasma glucose, insulin, C-peptide, and proinsulin prior to ingestion of the meal and every 30 min thereafter for 5 hr.

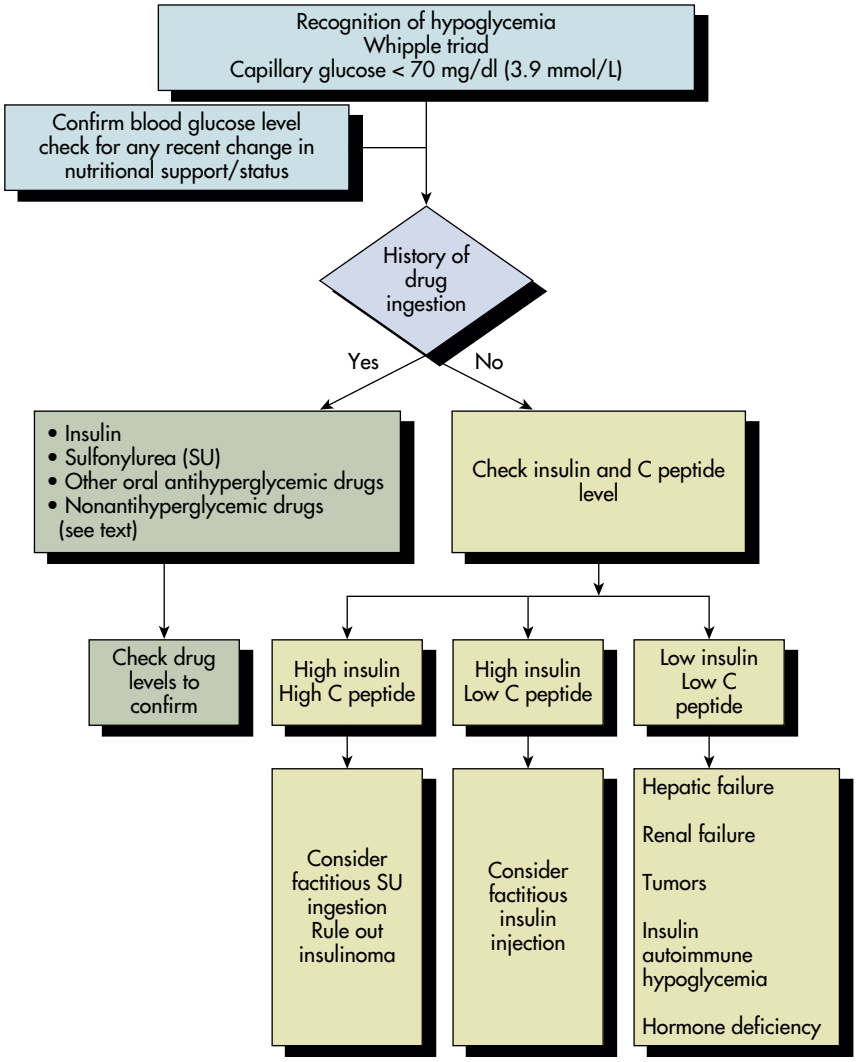

FIG. 1 Recognition and evaluation of hypoglycemia. (From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.)

- Only evaluate the samples drawn when glucose levels are <60 mg/dl.
- If a patient has a presentation consistent with Whipple triad, then measure SU, MG, and antibodies to insulin.

72-HR FAST:

- Collect blood specimens for measurement of plasma glucose, insulin, C-peptide, proinsulin, and BHOB every 6 hr until the glucose concentration is <60 mg/dl.
- Increase frequency of sampling to every 1 to 2 hr.
- Insulin, C-peptide, and proinsulin are only relevant in those specimens in which the plasma glucose concentration is <60 mg/dl.
- The fast should be ended when any of the following occurs:
  1. The plasma glucose concentration is <45 mg/dl.
  2. The patient has symptoms or signs of hypoglycemia.
  3. 72 hr have elapsed.
  4. The plasma glucose concentration is <55 and Whipple triad has been documented on a prior occasion.
- Insulin antibodies are also measured but do not need to be measured during the hypoglycemic state.

IMAGING STUDIES

If hypoglycemia is suspected secondary to an insulinoma or malignancy, transabdominal ultrasound (US), CT scan, or endoscopic US can be used to help with diagnosis as well as for staging purposes.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Recognition of signs and symptoms, and self-monitoring of blood glucose are especially important in insulin-deficient patient.
- Avoiding drugs that can exacerbate condition (e.g., alcohol) if it occurs on repeated occasions.
- Bedtime snacks if hypoglycemia occurs at night.
- In situations caused by tumor etiologies (e.g., islet cell, insulinoma, and nonislet cell), definitive treatment may require surgical removal.

PHARMACOLOGIC THERAPY

- Treating the underlying etiology that exacerbates hypoglycemia (e.g., infection, proper diabetic regimen)
- Fast-acting carbohydrates (e.g., glucose tablets, hard candy, IV dextrose infusion)
- Pure glucose (dextrose) if caused by insulin secretagogue in addition with alpha-glucosidase inhibitor
- In severe hypoglycemia with seizure activity, 25 g of 50% dextrose IV or 0.5 to 1.0 mg IM/subcutaneous glucagon
- Fig. 2 describes a management algorithm for hypoglycemia

REFERRAL

- Most scenarios of hypoglycemia can be managed by primary care physicians by adjusting medications.
- If the cause is not clear, then endocrinology referral is recommended.

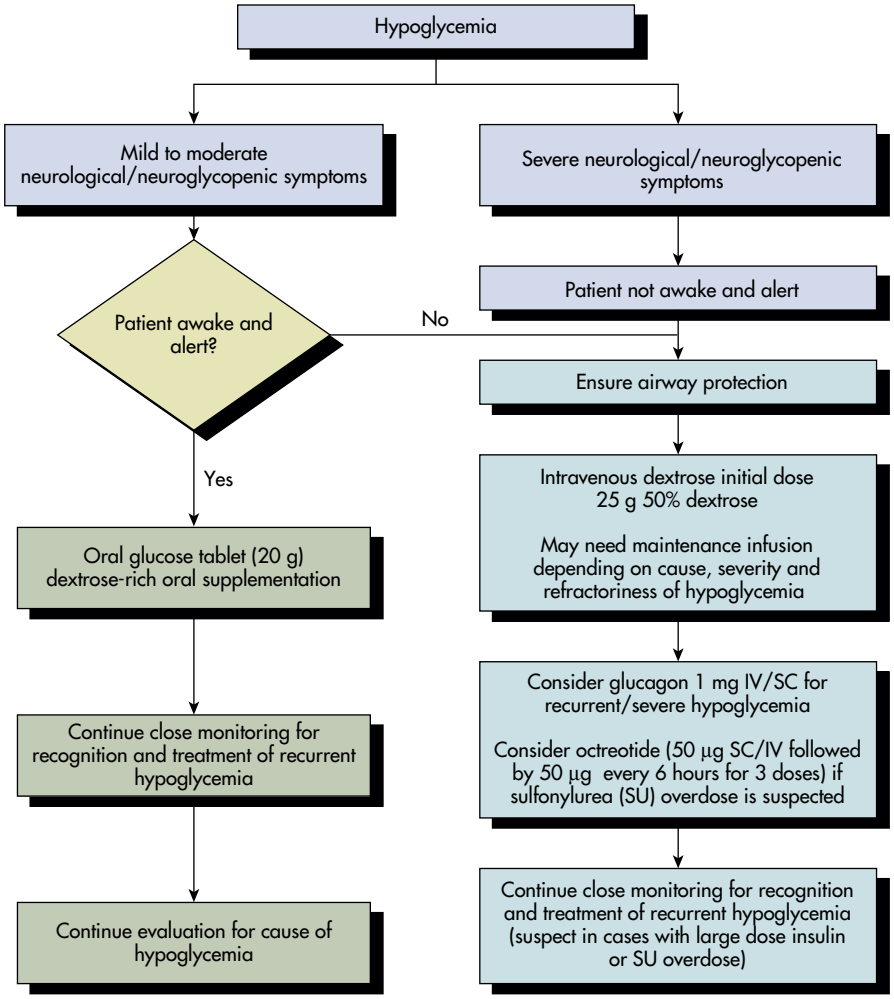

FIG. 2 Management of hypoglycemia. *IV,* Intravenous; *SC,* subcutaneous. (From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.)

PEARLS & CONSIDERATIONS

- Hypoglycemia can cause severe morbidity and death if not dealt with promptly and effectively.
- Hypoglycemia is very common in patients with DM, especially type 1 DM, and most commonly it is a side effect of medications.
- In patients who are hospitalized, the etiology is often multifactorial.
- Clinically important hypoglycemia is uncommon in nondiabetic patients, and evaluation for a hypoglycemic disorder in these patients should only occur if the Whipple triad is met.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Diabetes Mellitus (Related Key Topic)
Insulinoma (Related Key Topic)

AUTHORS: **Mark F. Brady, MD, MPH, MMSc,** and **Brittany N. Mertz, PA-C, MMSc-PA**

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BASIC INFORMATION

DEFINITION

Male hypogonadism is a clinical syndrome involving subnormal testosterone levels and/or impaired sperm production due to dysfunction at one or both levels of the hypothalamic-pituitary-testicular axis.

SYNONYM

Testicular dysfunction

ICD-10CM CODES

E23.0 Hypopituitarism
E23.1 Drug-induced hypopituitarism
E29 Testicular dysfunction
E29.1 Testicular hypofunction
E29.8 Other testicular dysfunction
E29.9 Testicular dysfunction, unspecified
E89.3 Postprocedural hypopituitarism

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Hypogonadism is the most common clinical disorder of the testis. Incidence is unclear due to the many possible underlying factors, nonspecificity of symptoms, and questions relating to the adequacy of a diagnostic serum total testosterone threshold.

PREVALENCE: Prevalence of hypogonadism increases with aging, obesity, diabetes mellitus, and other comorbidities. The average decrease in serum total testosterone levels in aging men is 1% to 2% per yr. Prevalence rises to 23% among men in their 70s. However, in population-based surveys of community-dwelling middle-aged and older males, prevalence of hypogonadism is approximately 6%.

GENETICS: Genetic abnormalities underlie a number of hypogonadal disorders including Klinefelter syndrome, Noonan syndrome, hemochromatosis, Kallmann syndrome, and Prader-Willi syndrome.

RISK FACTORS: These are many and include genetic abnormalities; the aging process; pituitary and testicular lesions and disorders; medications; drug abuse; HIV disease; acute illnesses; chronic cardiac, hepatic, renal, and pulmonary diseases; cancer; ionizing radiation; chemotherapy; obesity; and malnutrition.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Sexual (specific)
- Decrease in frequency of erections
- Erectile dysfunction
- Decrease in libido
- Decreased fertility
- Small or shrinking testes
- Gynecomastia
- Diminished sexual hair
- Hot flushes and sweats

Neuropsychologic (less specific)
- Depression
- Inability to concentrate
- Diminished motivation and vitality
- Decrease in self-confidence
- Diminished energy and stamina
- Sleep disturbances

Physical features and findings
- Diminished capacity for physical activity
- Decrease in physical endurance and performance
- Diminished muscle mass and strength
- Increase in body fat
- Decrease or loss of axillary and pubic hair and decrease in shaving frequency
- Fine wrinkling over the lateral aspects of the face
- Breast enlargement with or without tenderness
- Change in consistency and decrease in size of testes
- Fragility fractures
- Anemia

ETIOLOGY

- The importance of a careful history and examination cannot be overstated to determine the etiology of possible hypogonadism. Primary hypogonadism is a result of a decrease in testicular testosterone secretion and/or a decrease in spermatogenesis with an associated increase in gonadotropin levels as in Klinefelter syndrome, cryptorchidism, and following orchitis, testicular trauma, chemotherapy, and irradiation.
- Secondary hypogonadism is due to hypothalamic-pituitary dysfunction, which results in a decrease in testosterone levels and/or spermatogenesis with gonadotropin levels that are subnormal or inappropriately within the normal range.
- Combined primary and secondary hypogonadism is a result of deficits at both the level of the hypothalamic-pituitary axis and testes with variable gonadotropin levels depending upon the predominance of the level of the defect.

DIAGNOSIS (Fig. 1)

DIFFERENTIAL DIAGNOSIS

Hypogonadotropic or secondary hypogonadism
- Pituitary dysfunction: Hypopituitarism, functioning or nonfunctioning pituitary tumor, lymphocytic hypophysitis, infiltrative disease as with sarcoidosis, hemochromatosis, and histiocytosis X
- Hyperprolactinemia: Prolactinoma, medication-related, chronic kidney disease
- Genetic: Kallmann syndrome with anosmia, Prader-Willi syndrome with morbid obesity
- Acute and chronic illnesses, malnutrition, emotional disorders, HIV, sleep apnea, aging, malignancies, obesity, and renal, hepatic, pulmonary, and cardiac diseases
- Opioids, CNS: Active medications, glucocorticoid excess, and GnRH analogues (androgen deprivation therapy)

Hypergonadotropic or primary hypogonadism
- Genetic: Klinefelter syndrome, Noonan syndrome, myotonic dystrophy
- Gonadal damage due to drugs, alcohol, radiation, chemotherapy, trauma
- Congenital anorchia (vanishing testis syndrome)
- Cryptorchidism
- Mumps orchitis, HIV orchitis
- Diabetes mellitus
- Hodgkin disease
- Aging

Combined primary and secondary hypogonadism
- Hemochromatosis, sickle cell disease, thalassemia
- Alcoholism, glucocorticoid therapy, aging
- Chronic cardiac, hepatic, renal, pulmonary diseases, and HIV disease

WORKUP

- Determine the presence or absence of male hypogonadism on the basis of history, clinical manifestations and findings, and documentation of consistently low serum total testosterone levels and/or abnormal seminal fluid analysis.
- Morning serum total testosterone levels should be measured on at least 2 or 3 occasions for confirmation of diagnosis and when necessary followed by measurement of serum free or bioavailable testosterone.
- Serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels are measured to determine whether hypogonadism is primary, secondary, or a result of combined defects of the hypothalamic-pituitary axis and testis. The case of testosterone deficiency should be definitively determined before initiation of testosterone replacement therapy.
- Hormonal assessment of gonadal status should not be done during an acute or subacute illness.

LABORATORY TESTS

- Serum total testosterone is tightly bound to sex hormone binding globulin (SHBG) and weakly bound to circulating albumin. 0.5% to 3% of serum total testosterone is unbound or free.
- Liquid chromatography tandem mass spectrometry assays for total serum testosterone are more accurate than immunoassays.
- Bioavailable testosterone refers to unbound testosterone plus the testosterone that is loosely bound to albumin.
- Free testosterone, if necessary, is best measured by equilibrium dialysis or centrifugal ultrafiltration.
- An SHBG measurement is helpful in determining the adequacy or normality of a serum total testosterone measurement. Conditions that lower SHBG include obesity, protein-losing states, androgens, hypothyroidism, and familial SHBG deficiency. Increases in SHBG occur in those with hyperthyroidism, hepatitis, cirrhosis, and HIV disease, aging, and by estrogens.
- The lower limit of normal for serum total testosterone in a healthy young male is approximately 240 to 950 ng/dl and a low-normal serum free testosterone in a young normal male is 5 to 20 ng/dl.
- Serum total testosterone levels can vary from day to day and there is a diurnal rhythm in young normal males with morning levels that are higher by approximately 20% to 25% as compared with levels in the afternoon.

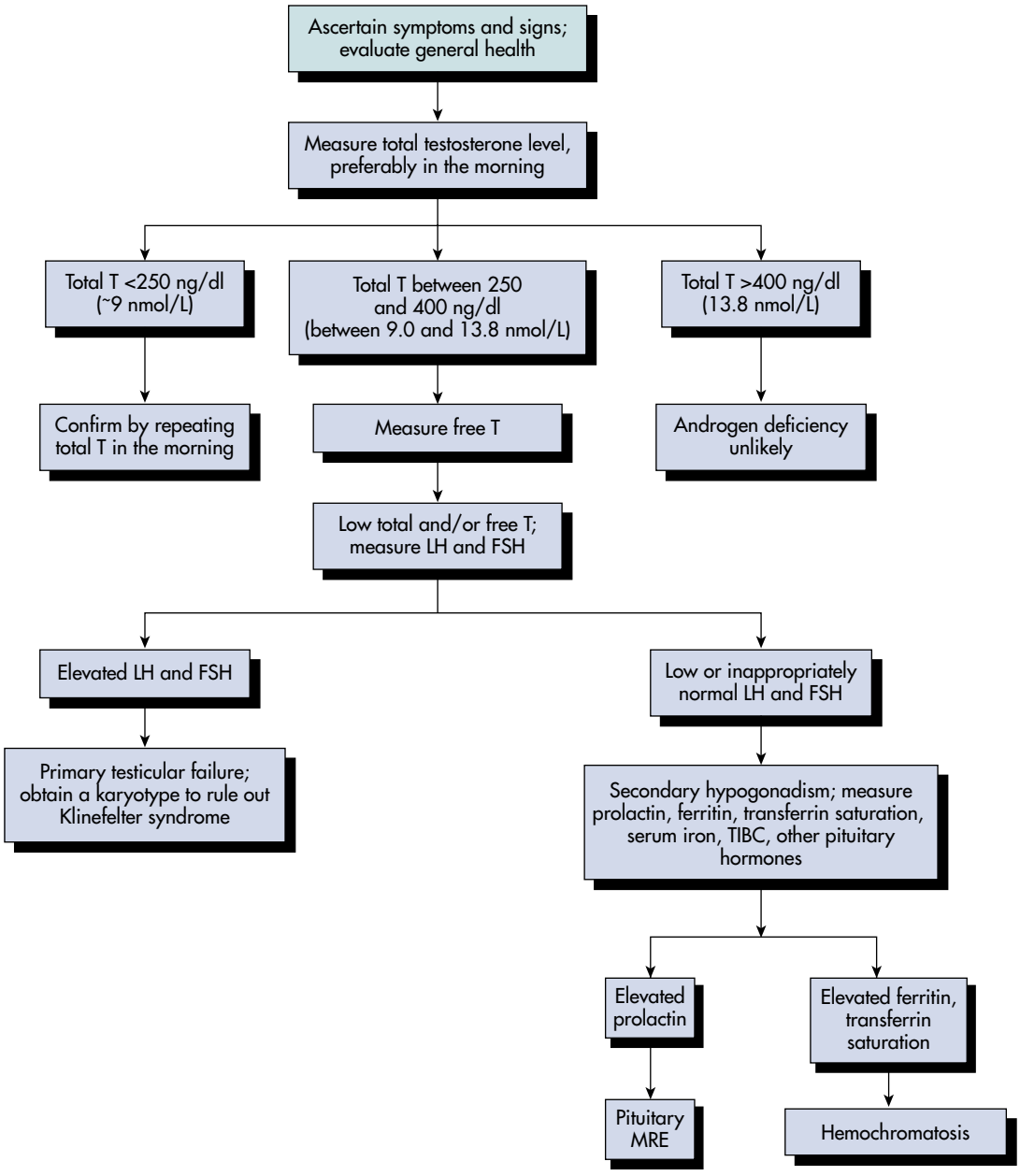

FIG. 1 Algorithm showing an approach for the diagnostic evaluation of adult men suspected of having androgen deficiency. *FSH,* Follicle-stimulating hormone; *LH,* luteinizing hormone; *T,* testosterone; *TIBC,* total iron-binding capacity. (From Shalender B, Shehzad B: Diagnosis and treatment of hypogonadism in men, *Best Pract Res Clin Endocrin* 25:251-270, 2011.)

- In elderly males, the diurnal rhythm is diminished with levels approximately 10% lower in the afternoon as compared with morning levels.
- Serum FSH and LH measurements are important in delineating primary, secondary, and combined hypogonadism.
- Hypogonadal symptoms are more likely to be seen in those with total serum testosterone level below the lower limit of values for young normal males. Serum total testosterone levels of <150 ng/dl are unequivocally low.
- Transient suppression of total serum testosterone may occur during acute illness, in males that are being treated with glucocorticoid, in those taking opiates or CNS-active medications, in those with malnutrition or poor eating habits, and during excessive physical exercise.
- Quantity and quality of sperm counts and activity can vary in a significant way for a variety of reasons. Therefore, in assessing fertility, seminal fluid analysis should be done on two or more occasions, each separated by 2 or more wk, and on semen collected within an hour of ejaculation after more than 2 days of abstinence.
- Depending on the clinical picture and examination, other studies may be necessary, including a karyotype analysis, for example, for Klinefelter syndrome, or serum prolactin measurement for patients with possible hyperprolactinemia, which may be drug-induced, related to a prolactinoma, or to chronic renal disease.

IMAGING STUDIES

In males with severe androgen deficiency with low serum gonadotropin levels, increased serum prolactin levels, hypopituitarism, severe headaches, and visual defects, an MRI of the pituitary would be appropriate. In males with hypogonadism and a history of fractures, dual energy x-ray absorptiometry (DXA) measurements of spine and hip should be obtained to further delineate the status of the skeletal system.

Rx TREATMENT

Testosterone replacement therapy is indicated when patients have symptoms and signs of hypogonadism and serum testosterone levels

that are consistently subnormal with levels of <250 ng/dl. The goal of replacement therapy is to restore serum testosterone levels to within the normal range of values and to have a positive effect on the constellation of hypogonadal symptoms and signs. Subnormal spermatogenesis, if present in such patients, is not affected by testosterone therapy. In patients with hypogonadotropic or secondary hypogonadism, chorionic gonadotropin and/or GnRH therapy can optimize spermatogenesis, whereas, generally in patients with primary hypogonadism, subnormal spermatogenesis and infertility are irreversible.

NONPHARMACOLOGIC THERAPY

- Weight reduction, especially when it appears to be a major factor underlying male hypogonadism
- Discontinuation of anabolic steroids, CNS-active medications, and narcotic abuse
- Surgery or radiation therapy for patients with a pituitary functioning or nonfunctioning tumor with visual field abnormality and headaches who are not candidates for further medical therapy or have been unsuccessfully treated with medication
- Surgery indicated for chronic gynecomastia and, occasionally, in cases with recent-onset gynecomastia that has not responded to testosterone replacement therapy

CHRONIC Rx

Testosterone formulations:

- Parenteral testosterone preparations: Testosterone enanthate (generic) and testosterone cypionate (Depo-Testosterone and generic) 150 to 200 mg are injected intramuscularly every 2 wk. Following injections, there are appreciable fluctuations in serum testosterone, with levels rising within the first several days and a subsequent decrease to normal and in some cases to below normal at the end of the 2 wk. As a result of the varying levels of testosterone, patients may have related symptoms. Adjustments in dose and dosing interval may help to alleviate the serum fluctuations and clinical symptoms. Testosterone undecanoate (AUEFD-ENDO) is an injectable depot formulation FDA-approved for male hypogonadism. The recommended dosage is 750 mg injected IM at 0 and 4 wk, and then every 10 wk thereafter.
- Topical testosterone preparations:
  1. Testosterone adhesive patch (Androderm) delivers 2.5 or 5 mg of testosterone when applied nightly to the back, abdomen, upper arms, or thighs. Serum testosterone levels rise to within normal range in a few hours after application and, thereafter, are relatively stable. Daily doses of up to 10 mg may be necessary.
  2. Testosterone 1% gels (AndroGel and Testim). AndroGel is available in 2.5 g and 5 g gel units that deliver 2.5 mg and 5 mg of testosterone, respectively. The gel is applied daily in the morning by hand over the shoulder, upper arms, or abdomen. Adjustments in dose to 7.5 g or 10 g of gel may be necessary to optimize serum testosterone levels. AndroGel (1.62%) pump is also available for daily application. Testim is available in 5-g and 10-g tubes and with morning applications over the shoulders or arms delivers 5 mg and 10 mg of testosterone, respectively. Both AndroGel and Testim provide relatively stable serum testosterone levels. Two new transdermal formulations, Fortesta and Axiron, are now available and are applied daily by metered dose pumps. With these preparations, care is necessary to avoid skin-to-skin contact exposure with others.
- Testosterone pellets: 3 to 6 pellets of testosterone each containing 75 mg of testosterone are surgically inserted subcutaneously every 3 to 6 mo and provide relatively stable serum testosterone levels.

RISKS & ADVERSE EFFECTS

- Contraindications to testosterone therapy include prostate cancer and breast cancer. Relative contraindications include severe benign prostatic hyperplasia, hematocrit ≥50% at baseline, sleep apnea, and severe congestive heart failure.
- Patients on chronic testosterone therapy need to be followed carefully with prostate and prostate-specific antigen (PSA) assessments and hematocrit measurements for possible excessive induction of erythrocytosis, initially at 3 to 6 mo and at regular intervals thereafter.
- Current testosterone use for 6 mo or shorter is associated with 63% higher risk for venous thromboembolism (VTE). VTE risk peaks during the first 6 mo and declines to 25% thereafter.[1]

REFERRAL

Endocrinology for full endocrine and metabolic assessment and therapy. Urology for further assessment and follow-up of the prostate and for evaluation and therapy of erectile dysfunction. Neurosurgery for evaluation and possible surgery for a pituitary lesion. Plastic surgery for chronic gynecomastia. Reproductive endocrinology for those with an infertility problem.

[1]Martinez C et al: Testosterone treatment and risk of venous thromboembolism: population based case-control study, *BMJ* 355:596-598, 2016.

PEARLS & CONSIDERATIONS

COMMENTS

- Do not screen men "routinely" for hypogonadism. Screening men with nonspecific symptoms of hypogonadism (e.g., decreased energy) is also not recommended. Screening should be limited to men with specific signs and symptoms of hypogonadism.
- Male hypogonadism is an important and frequently encountered problem that requires a complete medical history, examination, and hormonal assessment to determine whether a patient has hypogonadism and requires testosterone replacement therapy. Treated patients need to be seen on a regular basis to avoid possible testosterone adverse effects. Patients requiring testosterone replacement should have testosterone, prostate specific antigen, and hematocrit levels monitored.
- Trials to evaluate the effects of testosterone treatment in older men revealed that in symptomatic men 65 yr of age or older, raising testosterone concentrations for 1 yr from moderately low to the mid-normal range had a moderate benefit with respect to sexual function and some benefit with respect to mood and depressive symptoms but no benefit with respect to vitality or walking distance.[2]
- Controversy exists regarding the safety of testosterone replacement therapy following reports of increased risk of cardiovascular events. However, a recent trial among men with androgen deficiency dispensed testosterone prescriptions revealed lower risk of cardiovascular outcomes over a median follow-up of 3.4 yr.[3]
- Clinical trials have also demonstrated that testosterone replacement in men with low testosterone increases volumetric bone mineral density (vBMD) and estimated bone strength more in trabecular than peripheral bone and more in the spine than the hip.[4]

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Joseph R. Tucci, MD, FACP, FACE**

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Hypokalemic Periodic Paralysis

BASIC INFORMATION

DEFINITION

Hypokalemic periodic paralysis (HPP) constitutes a variety of disorders resulting in the common pathway of muscle ion channel defects, resulting in painless muscle weakness. Total-body muscle weakness may occur periodically with either a true potassium deficit or, more commonly, a potassium shift intracellularly.

SYNONYMS

Periodic paralysis
Hypokalemic nonperiodic paralysis
Cavare disease
HPP

ICD-10CM CODE
G72.3 Familial periodic paralysis (Cavare's disease)

EPIDEMIOLOGY & DEMOGRAPHICS

- HPP has an incidence of 1:100,000.
- Autosomal-dominant inheritance.
- One third of cases are new mutations.
- Most new cases develop in patients with thyrotoxicosis.
- Anderson syndrome is a rare variant of HPP and has an incidence of 1:1,000,000. Patients are at risk for cardiac arrhythmias because the potassium-channel mutation is also expressed in cardiac muscle.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usual onset is during adolescence as transient episodes of generalized weakness without muscle-tone loss following exercise or carbohydrate intake.
- Attacks usually last several hours but can last up to days.
- Attacks may be provoked by rest after vigorous exercise, stress, or high-carbohydrate meals. The resulting increase in epinephrine and/or insulin leads to an intracellular shift of potassium and low serum potassium.
- Attacks have also been known to be provoked by cold, alcohol, lack of sleep, emotional stress, beta-2 receptor agonists, diuretics, corticosteroids, insulin, glucocorticoids, viral illness, menstruation, and pregnancy.
- Legs are generally affected more than arms, and proximal more than distal muscles.
- Most commonly symptoms occur in the morning after waking.
- Ocular, bulbar, and respiratory muscles are spared.

ETIOLOGY

- Caused by mutations in transmembrane voltage-gated ion channels of the skeletal muscle or endoplasmic reticulum.
- Most common mutation is in the alpha-1 subunit of the dihydropyridine-sensitive calcium channel in skeletal muscle. Exact mechanism for causing hypokalemia is not currently known.
- The final common pathway is low extracellular potassium concentration. This causes a transient membrane depolarization, which inactivates voltage-gated sodium and calcium channels. These channels are no longer capable of generating action potential essential for muscular contraction.

DIAGNOSIS

- Hypokalemia during an attack and the exclusion of alternative syndromes is sufficient to establish the diagnosis.
- Serum potassium will normalize between attacks in HPP.
- If there is familial history of HPP, no further diagnostic tests apart from hypokalemia during an attack are necessary.

DIFFERENTIAL DIAGNOSIS

- Hyperkalemic periodic paralysis
- Normokalemic periodic paralysis
- Thyrotoxicosis
- Myasthenia gravis
- Secondary hypokalemia unrelated to channelopathy
- Anderson syndrome
- Guillain-Barré syndrome
- Transverse myelitis
- Tick paralysis
- Botulism
- Barium poisoning

WORKUP

Serum potassium levels establish the diagnosis and guide treatment.

LABORATORY TESTS

- Mean serum potassium level during attacks has been reported as 2.4 mmol/L.
- T3, T4, TSH levels to exclude thyrotoxic periodic paralysis resulting from hyperthyroidism.
- Rule out secondary causes of hypokalemia (thyrotoxicosis, diuretic use, vomiting, diarrhea, hyperaldosteronism, distal tubular renal acidosis).
- Serum electrolyte measurement.
- Genetic testing is available for the majority of common mutations.
- Provocative testing with ACTH, exercise, or insulin and glucose are high-risk options when genetic testing does not produce results.
- Electromyography may help distinguish the etiology of hypokalemia during an attack.

OTHER TESTS

EKG may demonstrate ST depression, T wave depression, increased U wave. Arrhythmias are uncommon with HPP but have been reported.

TREATMENT

ACUTE GENERAL Rx

- Potassium chloride, 60 to 120 mEq PO given in increments of 15 to 30 every 20 to 30 min is usually sufficient to relieve acute attacks.
- PO potassium is preferred to IV form.
- Carbonic anhydrase inhibitors, specifically acetazolamide and dichlorphenamide, have shown utility in relieving symptoms. However, there is potential for exacerbating hypokalemic attack in patients with diabetes via intracellular potassium shift.

CHRONIC Rx

- Patients may develop chronic progressive proximal myopathy around age 50 yr. Most pronounced in proximal upper and lower extremities as well as pelvic girdle.
- Frequency of attacks and weakness begin to decrease around age 50 yrs.
- Avoidance of potassium-lowering pharmaceuticals, high-carbohydrate foods, bicarbonate and potassium-lowering diuretics, and strenuous physical exercise has been demonstrated to prevent attacks.
- Some patients may need potassium supplements, potassium-sparing diuretics, and carbonic anhydrase inhibitors chronically to maintain sufficient serum potassium levels to prevent attacks.

DISPOSITION

- Patients treated with oral potassium are at risk for hyperkalemia following an attack as intracellular potassium redistributes into the extracellular space. Potassium levels may be monitored intermittently for 24 hr after treatment.
- Patients with new-onset hypokalemia or suspected new-onset HPP may be admitted for further diagnostic workup.

PEARLS & CONSIDERATIONS

Serum potassium levels reflect extracellular potassium, which is only 2% of total body potassium stores. Low serum potassium levels during an attack typically represent intracellular shift rather than total-body depletion.

SUGGESTED READING

Available at ExpertConsult.com

AUTHOR: **Craig Blakeney, MD**

SUGGESTED READING

Sung CC et al: Etiologic and therapeutic analysis in patients with hypokalemic nonperiodic paralysis, *Am J Med* 128:289-296, 2015.

BASIC INFORMATION

DEFINITION

Magnesium (Mg), after potassium, is the second most abundant intracellular and fourth most cation in living organisms. This ion plays a vital role in nearly every major metabolic and biochemical process within cells. Magnesium is a critical cofactor of the ubiquitous cellular Na^+-K^+-ATPase and is notable to have coexisting secondary electrolyte disorders when deranged. Serum magnesium concentration is tightly regulated by a dynamic balance among three organ systems: Gut, kidney, and bone. Most of the total body magnesium is found in bone, muscle, and skin. Serum magnesium represents only 0.3% of the total body magnesium. Magnesium has been implicated in and used as treatment for several diseases. Although its importance is widely acknowledged, routine serum magnesium levels are generally not evaluated in clinical medicine.

Magnesium deficiency is defined as a decrease in total body magnesium content. The recommended daily allowance of magnesium is 420 mg for males and 320 mg for females. Fig. 1 illustrates magnesium homeostasis in healthy adults. Magnesium is mainly absorbed through the jejunum and ileum. Poor dietary intake of magnesium usually does not lead to severe magnesium deficiency because normal kidney function prevents magnesium loss through renal conservation of magnesium maintaining homeostasis. Fig. 2 depicts the renal handling of magnesium by the kidney. Hypomagnesemia is typically defined as a total serum magnesium concentration below 1.8 mg/dl and is categorized as mild (1.5 to 1.8 mg/dl), moderate (1 to 1.4 mg/dl), or severe (<1 mg/dl). Serum magnesium levels do not fully correlate with total body magnesium levels given that the different compartments that magnesium is found in do not easily equilibrate like sodium does. Thus normal magnesium levels in patients where hypomagnesemia would be expected may still need magnesium supplementation, such as in cases of hypocalcemia, hypokalemia, or malnutrition.

SYNONYMS

Magnesium deficiency
Low magnesium

ICD-10CM CODES

E83.40 Disorders of magnesium metabolism, unspecified
E83.42 Hypomagnesemia

EPIDEMIOLOGY & DEMOGRAPHICS

Hypomagnesemia has been estimated to occur in more than 10% of hospitalized patients and is especially common among the critically ill, with an incidence as high as 65%. It may be encountered in 25% to 35% of patients with acute pancreatitis. Low magnesium levels frequently are encountered in chronic alcoholics and poorly controlled diabetics. The incidence and prevalence of hypomagnesemia are similar across sexes, races, and ethnicities, but may be greater in the elderly. This observation may be explained by poorer nutritional intake, greater use of certain medications (e.g., diuretics, laxatives, proton pump inhibitors), or comorbidities.

RISK FACTORS

- Alcoholism
- Volume expansion (including pregnancy)
- Poorly controlled diabetes mellitus
- Chronic diuretic use
- Chronic laxative use
- Chronic use of proton pump inhibitors
- Subarachnoid hemorrhage
- Severe sepsis
- Acute phase after liver transplantation
- Large transfusions with citrate-rich blood products
- Postsurgical patients
- Leptospirosis
- Pancreatitis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Mild hypomagnesemia is most frequently asymptomatic. Clinical manifestations appear with more severe deficiency.
- Signs and symptoms are not unique and frequently difficult to determine if caused by hypomagnesemia or its complications of hypokalemia or hypocalcemia.
- Symptoms of hypomagnesemia have been reported at modest degrees of depletion, but generally they are more common when serum magnesium levels fall below 1.2 mg/dl.
- Neuromuscular effects include weakness, cramps, and paresthesias. Manifestations may include Trousseau and Chvostek signs. More severe depletion can cause vertical nystagmus, tetany, and seizures.
- Metabolic effects include hypokalemia from renal potassium wasting that may be refractory to potassium supplementation until magnesium deficiency is repaired. Hypocalcemia is also common in hypomagnesemia, which suppresses release of parathyroid hormone (PTH), and end-organ resistance to PTH with low 1, 25 vitamin D levels may occur.
- Cardiovascular effects: Hypomagnesemia is associated with a variety of atrial and ventricular arrhythmias.
- ECG findings: Flattened T-waves, prolonged QT interval, ST depression, and widened QRS complexes and concerns for *torsades de pointes*.
- The role of magnesium deficiency in the clinical development of seizures and cardiac arrhythmias requires treatment of these conditions with magnesium.

ETIOLOGY

Causes (Table 1)

DIAGNOSIS

WORKUP

- Comprehensive history including medication and dietary history, alcohol use, prior magnesium measurements, and history of disorders associated with hypomagnesemia (e.g., disorders of gastrointestinal tract, vomiting, diarrhea)
- Physical examination and review of vital signs, intake, and output

LABORATORY TESTS

The total serum concentration of magnesium should be measured in hospitalized patients with acute illness to screen for hypomagnesemia. This is indicated for critically ill patients

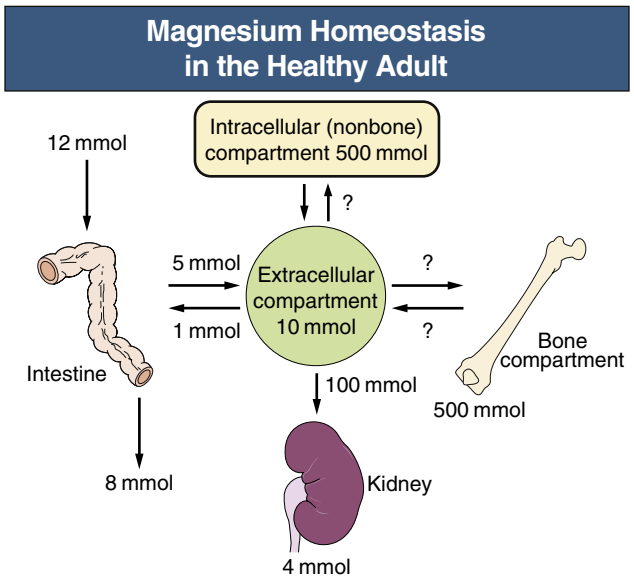

FIG. 1 Magnesium homeostasis in healthy young adults. Net zero balance results from net intestinal uptake (absorption minus secretion) equaling urinary loss. After its passage into the extracellular fluid, Mg^{2+} enters the intracellular space and is deposited in bone or soft tissue or eliminated via the kidneys. Entry and exit fluxes between the extracellular and intracellular spaces (skeletal and nonskeletal compartments) are also of identical magnitude; however, precise values of exchange are still debated. (From Johnson RJ: *Comprehensive clinical nephrology,* ed 6, Philadelphia, 2019, Elsevier.)

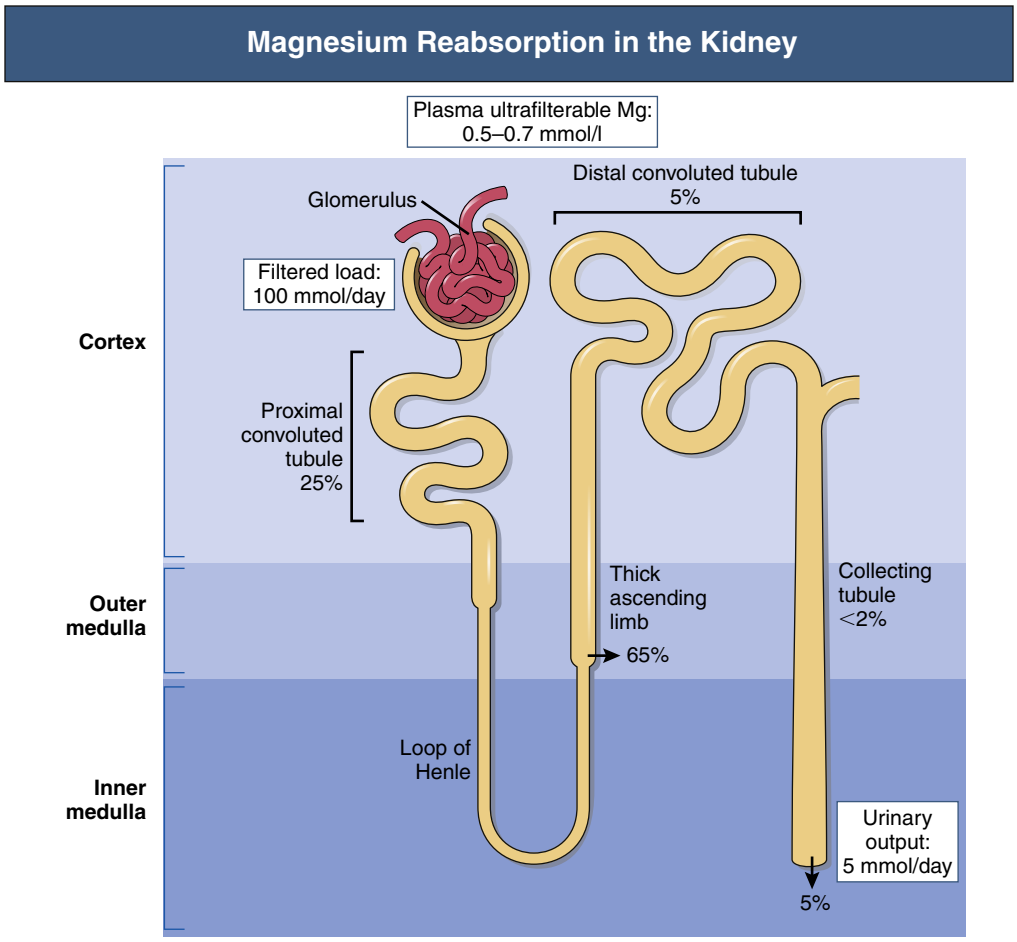

FIG. 2 Sites of magnesium reabsorption in various segments. Percentage absorbed in various segments of the renal tubule from the glomerular ultrafiltrate. (Redrawn from Quamme GA: Control of magnesium transport in the thick ascending limb, *Am J Physiol* 256:F197-F210, 1989. In Johnson RJ: *Comprehensive clinical nephrology,* ed 6, Philadelphia, 2019, Elsevier.)

and those deemed at risk of cardiac arrhythmias or seizures. Although the ionized fraction of serum magnesium (typically two-thirds of the total concentration) is the physiologically active form of the cation, measurement of serum ionized magnesium is not recommended because this measurement does not influence clinical management. The etiology of magnesium deficiency is often obvious from the history. When the cause is unknown, the fractional excretion of magnesium (FE_{Mg}) may facilitate diagnosis. With extrarenal magnesium loss from malabsorption or laxative abuse, the FE_{Mg} should be appropriately reduced (<4%). If FE_{Mg} exceeds 4%, renal magnesium wasting is present, often secondary to surreptitious diuretic use or familial magnesium-wasting disorders.

IMAGING STUDIES

Not routinely recommended

Rx TREATMENT

It is unclear whether mild, asymptomatic hypomagnesemia requires treatment. However, symptomatic hypomagnesemia is treated with intravenous magnesium, typically magnesium sulfate. For treatment of *torsades de pointes,* 1 to 2 g of intravenous magnesium sulfate as a bolus over 5 minutes is recommended.

Magnesium repletion in patients with acute or chronic renal insufficiency must be carried out cautiously. Evaluation for depressed deep tendon reflexes, periodic monitoring of serum magnesium levels, and dose reductions from 50% to 75% are recommended.

Oral magnesium supplementation may treat mild cases of hypomagnesemia successfully. In the outpatient setting, oral magnesium salts such as magnesium oxide (250 to 500 mg four times daily) can be used for repletion. However, these agents frequently cause diarrhea, particularly at high doses. Patients with gastrointestinal magnesium-wasting who do not achieve normal levels of repletion with one formulation may respond to an alternative formulation. Potassium-sparing diuretics may be used for renal magnesium-wasting states, provided hyperkalemia does not occur. Intravenous magnesium supplementation causes an abrupt rise in serum magnesium levels, which leads to reduced reabsorption of magnesium by the kidneys in patients with normal renal function and will limit magnesium repletion. In most cases, oral supplementation of magnesium should suffice.

DISPOSITION

- Potential contributing factors should be evaluated and treated appropriately.
- Patients with symptomatic or severe hypomagnesemia require monitoring in an intensive care setting until the serum magnesium concentration and associated electrolyte abnormalities are corrected and stabilized at safe levels.
- The risk of recurrence depends primarily on the nature of the underlying disorder. Hypomagnesemia has less chance of recurrence if the offending medication is discontinued and/or when gastrointestinal and renal losses are not chronic. Inherited disorders may necessitate prolonged supplementation.
- In patients with self-limited reasons for magnesium deficiency, repletion therapy can be accomplished easily. However, in patients with persistent magnesium wasting, treatment by oral magnesium therapy may not correct the serum level to normal. Nevertheless, these individuals adapt to their chronic hypomagnesemia and tolerate it fairly well.

REFERRAL

- Outpatient referral to nephrology or endocrinology may be indicated to help manage

TABLE 1 Causes of Magnesium Deficiency

Poor intake	Dietary deprivation or malnutrition
	Insufficient magnesium in tube-feeding formulas
	Parenteral nutrition preparations with insufficient magnesium
Redistribution of magnesium from extracellular to intracellular space or bone	Treatment of diabetic ketoacidosis
	Refeeding syndrome
	Hungry bone syndrome following parathyroidectomy
	Correction of metabolic acidosis
	Acute and chronic pancreatitis (soft tissue sequestration and gastrointestinal loss)
	Severe burns (sequestration in necrotic tissue)
	Hyperthyroidism
Poor intestinal absorption/increased intestinal loss	Diarrhea
	Inflammatory bowel disease (*e.g.*, Crohn disease, ulcerative colitis)
	Intestinal fistula
	Laxative use
	Nasogastric suction
	Proton pump inhibitor administration
	Severe malabsorption
	Short bowel syndrome
	Steatorrhea
Excessive renal loss	Diuretics:
	Loop diuretics (loss of magnesium and calcium)
	Thiazide-like diuretics (loss of magnesium with calcium retention)
	Hypercalciuria
	Metabolic acidosis
	Osmotic diuretics (hypertonic solutions)
	Poorly controlled diabetes and diabetic ketoacidosis (especially during recovery phase after phosphorus replacement)
	Primary hyperaldosteronism
	Renal tubular acidosis
	Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
	Other drugs:
	Aminoglycosides
	Amphotericin B
	Cisplatin, carboplatin
	Cyclosporine
	Foscarnet
	Monoclonal antibodies that target the epidermal growth factor receptor (*e.g.*, cetuximab, panitumumab)
	Pentamidine
	Tacrolimus
Inherited causes	Autosomal-dominant hypocalcemia with hypercalciuria (ADHH)
	Bartter syndrome
	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
	Gitelman syndrome
	Hypomagnesemia with secondary hypocalcemia (HSH)
	Isolated dominant hypomagnesemia
	Isolated recessive hypomagnesemia

patients with chronic hypomagnesemia that does not warrant hospital admission.
- Inpatient referral to specialists in nephrology, endocrinology, and /or critical care medicine is recommended in cases of severe or symptomatic hypomagnesemia.
- Consultation with a dietitian can help increase dietary magnesium intake and protein supplementation in malnourished patients.

PEARLS & CONSIDERATIONS

COMMENTS

Serum magnesium measurement is the most available and most commonly employed test to evaluate magnesium status.

Routine correction of underlying etiologies and electrolyte and metabolic derangements is recommended for hypomagnesemia while increasing dietary magnesium intake and/or supplementing magnesium. Chronic hypomagnesemia may be associated with various micro- and macrovascular complications.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hypokalemia (Section II Differential Diagnosis)
Hypoparathyroidism (Related Key Topic)

AUTHORS: **Stanley Linder, DO,** and **Snigdha T. Reddy, MD**

SUGGESTED READINGS

de Baaij JH et al: Magnesium in man: implications for health and disease, *Physiol Rev* 95(1):146, 2015.

Quamme GA: Magnesium homeostasis and renal magnesium handling, *Miner Electrolyte Metab* 19(4-5):218-225, 1993.

Topf JM, Murray PT: Hypomagnesemia and hypermagnesemia, *Rev Endocr Metab Disord* 4(2):195-206, 2003.

BASIC INFORMATION

DEFINITION

Hyponatremia is defined as a measured serum sodium concentration (S_{Na}) less than the lower limit of normal (i.e., <130 to135 mmol/L). Since the clinical manifestations of hyponatremia are due to hypotonicity, appropriate clinical management depends on correctly distinguishing between most patients with hypotonic hyponatremia from patients who are hypertonic or isotonic or who have pseudohyponatremia (low measured S_{Na} due solely to laboratory artifact). For this chapter, hyponatremia will be used synonymously with hypotonic hyponatremia. Pseudohyponatremia and hypertonic/isotonic hyponatremia will be identified specifically by those names.

SYNONYMS

Low serum sodium concentration
Hypoosmolality

ICD-10CM CODE
E87.1 Hypo-osmolality and hyponatremia

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: The prevalence of hyponatremia varies widely according to setting and population age. In the general U.S. population dataset of the National Health and Nutrition Examination Survey (NHANES), the overall prevalence was 1.72%. One study of emergency department patients reported a prevalence of 2.3% in patients 16 to 21 yr and 16.9% in patients >80 yr. Following surgery for traumatic hip fracture, the incidence of moderate (<135 mmol/L) and severe (<130 mmol/L) postoperative hyponatremia was 27% (95% CI, 21.7% to 32.5%) and 9% (95% CI, 5.7% to 12.8%), respectively. The prevalence in stable, older outpatients has been reported to be approximately 8% and as great as 18% to 20% in sick or frail populations. The overall incidence at or during hospital admission is comparable, with even higher rates in patients admitted for congestive heart failure (CHF), cirrhosis, or elderly patients admitted for fragility fracture.

PREDOMINANT SEX AND AGE: Prevalence of hyponatremia was significantly higher in women in the NHANES dataset (2.09%; *P*=0.004) and increased with age.

GENETICS: The hyponatremic disorder, nephrogenic syndrome of inappropriate antidiuresis (NSIAD), is caused by rare familial gain-of-function mutations of the arginine vasopressin receptor-2. Activation of a mutated receptor located in the renal collecting duct produces overt hyponatremia in infancy.

RISK FACTORS: In NHANES, hyponatremia was more common in subjects with hypertension, diabetes, coronary artery disease, stroke, chronic obstructive pulmonary disease, cancer, and psychiatric disorders, and less common in those with no comorbidities (1.04%, *P* <0.001). A significant risk of death was associated with hyponatremia in unadjusted Cox models (hazard ratio [HR], 3.61; *P* <0.001) and adjusted (HR 2.43; *P* <0.001). The incidence in outpatients using thiazide diuretics was 15.1%, with an HR of 4.95 (95% CI, 4.12 to 5.96). Reported frequencies of hyponatremia of outpatients using selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine reuptake inhibitors (SNRIs) has varied widely between 0.5% and 32%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Critical history includes detailed documentation of fluid consumption and diet, gastrointestinal and insensible losses of fluid and electrolytes, urine outputs, changes in weight, medication use, changes in behavior or cognition. Recent medical procedures involving irrigation of tissue beds (e.g., transurethral prostatectomy or hysteroscopy with endometrial resection), participation in marathons or other strenuous endurance exercise or attendance at "rave" parties where illicit use of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") is common should be noted. Comorbid conditions that increase the risk of hyponatremia include malignancy, CNS or pulmonary disease, adrenal or thyroid disease, CHF, liver disease, or nephrotic syndrome.
- The etiology of hyponatremia may affect the clinical presentation both directly and/or by its effect on the extracellular fluid volume (ECFV). Hypovolemia and hypervolemia (decreased or increased ECFV, respectively) are identified by conventional clinical criteria. If available, vector bioimpedance analysis has been shown to further increase accuracy. Specific manifestations of the precipitating cause or underlying diseases may be evident (e.g., fever and delirium following the use of MDMA, stigmata of alcoholism or malnutrition, fever and/or localizing symptoms related to pneumonia or other pulmonary disease, or headaches and visual field defects from an intracranial mass).
- Neurologic symptoms predominate as the direct clinical manifestations of hyponatremia due to cerebrocyte swelling. Compensatory processes that reduce cerebral edema by extrusion of electrolytes, amino acids, and carbohydrates from brain cells take 24 hours to become fully active and up to 7 days to reach completion. Therefore, patients who develop hyponatremia over less than 24 to 48 hours have the highest degree of brain swelling, the most severe neurologic symptoms, and greatest risk of permanent or fatal brain injury. Post-pubertal, premenopausal women appear to undergo cerebral compensation more slowly, placing them at greater risk from acute hyponatremia.
- Acute hyponatremia may result in nausea and malaise as S_{Na} becomes 130 mmol/L or less. Headache, lethargy, obtundation, neurogenic pulmonary edema, and/or seizures may occur when the S_{Na} is <120 mmol/L. In the most severe cases, death from brain stem herniation can occur.
- Chronic hyponatremia almost never presents with life-threatening clinical manifestations. However, subtler neurologic disturbances such as ataxia, short-term memory deficits, fatigue, lethargy and nausea have been commonly reported. Muscular weakness and elevated creatine kinase and even rhabdomyolysis may occur. Chronic hyponatremia has also been associated with increased risk of falls, fractures, and osteoporosis in elderly patients. In addition, hyponatremia has been associated with increased risk of cardiovascular complications and mortality in a diverse group including elderly outpatients, general hospital admissions, and patients admitted for stroke, subarachnoid hemorrhage, CHF, cirrhosis, pneumonia, hip fracture and liver transplantation.

ETIOLOGY

- In patients with hypotonic hyponatremia, S_{Na} is closely approximated by the ratio, $(TBNa_e + TB_K)/TBW$ (TB_{Na} and TB_K are total body compartments of exchangeable sodium and potassium, respectively; TBW represents total body water). Hypotonic hyponatremia results from decreases of the numerator, increases of denominator, or both. TB_{Na} is the main determinant of ECFV.
- ECFV depletion (with proportionately greater decrease in TBNa and possibly TBK than in TBW).
  1. GI losses with intake of hypotonic fluids
  2. Renal losses (diuresis, tubulopathies) with intake of hypotonic fluid
  3. Cerebral salt wasting
- Normovolemic (normal ECFV and TB_{Na}).
  1. Syndrome of inappropriate antidiuresis (SIAD; see "Syndrome of Inappropriate Antidiuresis")
  2. Medications (thiazide diuretics, SSRIs and SNRIs, narcotics, MDMA/"Ecstasy," carbamazepine, cyclophosphamide, nicotine, DDAVP, phenothiazines, terlipressin)
  3. Pain, nausea, stress
  4. Marathon running or other endurance exercise
  5. Primary polydipsia
  6. Solute-limited water excretion (tea-and-toast diet, beer potomania)
  7. Severe potassium deficiency with normal total body sodium
  8. Adrenal insufficiency or hypothyroidism
  9. Reset osmostat
- Hypervolemic (increased ECFV and TB_{Na}) with decreased effective arterial blood volume (EABV). Hyponatremia results from proportionately greater increase in TBW than in TB_{Na} and TB_K.
  1. CHF
  2. Nephrotic syndrome
  3. Cirrhosis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- *Pseudohyponatremia.* Clinical laboratories report and to some extent measure the concentration of sodium (mmol) per liter of

plasma, not plasma water. Consequently, conditions (severe hypertriglyceridemia, hypercholesterolemia and hyperproteinemia) that significantly reduce the aqueous fraction of plasma (normally 0.93) may lead to a decrease in the reported S_{Na} despite the presence of serum normal osmolality (S_{osm}). However, since the condition can coexist with preexisting hypernatremia or hypotonic hyponatremia that also affects S_{osm}, a more reliable method for identifying the disorder is the presence of an increased serum osmolal gap (i.e., difference between measured and calculated serum osmolalities is >10 mOsm/kg H_2O) and a low S_{Na}. Calculated $S_{osm\ (mOsm/L)} = 2 \times S_{Na}$ (mmol/L) + S_{Glu} (mg/dl)/18 + BUN (mg/dl)/2.8. In brief, pseudohyponatremia is isotonic hyponatremia.

- *Hypertonic hyponatremia.* Small solutes such as glucose (in the absence of insulin), mannitol, and sorbitol accumulate in higher concentrations in the ECF than ICF and shift water from the ICF to ECF compartment. Since the ICF is virtually sodium free, the ECF sodium concentration declines producing hyponatremia. In the case of glucose, a decrease in S_{Na} of 1.6 mmol/L occurs for each increment of serum glucose of 100 mg/dl. The property of a solute to shift fluid from ICF to ECF is known as tonicity, which is of clinical importance because increases and decreases in tonicity also result in brain cell shrinkage and edema, respectively. In contrast, solutes such as urea or ethanol that equilibrate across cell membranes increase total serum osmolality (measured by freezing point depression) but neither tonicity nor S_{Na}.

WORKUP

- Comprehensive history including medication and drug abuse history, psychiatric history, exercise history, prior serum sodium measurements, dietary history, history of external fluid losses, volume and composition of oral and IV fluid intake, and history suggestive of disorders associated with hyponatremia (e.g., disorders of the lungs, CNS, heart, kidney, liver, adrenal gland, or thyroid; malignancies; diabetes mellitus; nausea; vomiting; pain; or stress)
- Comprehensive physical examination including careful review of vital signs, weights, intake and outputs; evidence of increased ECFV (e.g., edema, ascites, or pleural effusions) or depletion and evidence of comorbid diseases listed previously (e.g., abnormal pulmonary, neurologic or cardiovascular exam, hepatomegaly, thyromegaly or nodular thyroid)

LABORATORY TESTS

- Serum glucose to adjust for influence on serum sodium (serum sodium decreases approximately 1.6 mmol/L for every additional 100 mg/dl increase in serum glucose).
- Serum potassium: Because $S_{Na} = (TB_{Na} + TB_K)/TBW$, decreases in TB_K lower S_K and S_{Na}.
- Random urine osmolality and 24-hour urine volume. U_{osm} <100 mOsm/kg H_2O usually indicates appropriate suppression of ADH, suggesting diagnoses of solute-limited water excretion, primary polydipsia, or a reset osmostat (if S_{Na} is below the patient's altered setpoint). U_{osm} ≥100 mOsm/kg H_2O usually implies the presence of ADH. However, U_{osm} ~290 mOsm/kg is seen in patients using loop diuretics while even higher osmolalities can be seen during osmotic diuresis. The latter is characterized by total urine osmolar excretion >900 mOsm/day), while in both cases urinary ([Na] + [K]) ~60 to 90 mmol/L.
- Random urine sodium (U_{Na}), and urine potassium (U_K). U_{Na} <20 mmol/L suggests either decreased ECFV or decreased EABV. U_K must be considered when prescribing and monitoring therapy (see the following).
- Specific testing for comorbid diseases listed previously as clinically indicated (e.g., fasting morning cosyntropin-stimulated serum cortisol level, BNP, and TSH).

IMAGING STUDIES

- Not routinely required. Computed tomography or magnetic resonance imaging may be indicated to diagnose associated etiologies or evaluate associated delirium that may be present in acute hyponatremia.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Hyponatremic patients excrete less electrolyte-free water than input. Moderate fluid restriction (10 to 15 ml/kg) is indicated while patients are hyponatremic, especially if free water excretion capacity remains impaired. Diets high in protein, sodium, and potassium increase urine osmolar generation, thereby increasing free water excretion.

ACUTE GENERAL Rx

- Acute (hypotonic) hyponatremia is defined as developing over <24 hours. Acute hyponatremia results in larger increases in brain water than equivalent changes in S_{Na} developing over longer durations due to lack of cellular adaptation to hypotonic stress. Consequently, correction of acute hyponatremia is a medical emergency and mandates an increase in S_{Na} of 4 to 6 mmol/L within the initial 1 to 3 hours of therapy, depending on severity of symptoms and acuity of S_{Na} elevation. Iatrogenic cases, classically children or premenopausal women receiving perioperative hypotonic fluids, are fortunately rare now. These circumstances can present with headache or nausea prior to severe symptoms and require emergent correction. Acute hyponatremia is rare in patients with high ECFV because the increased TB_{Na} partially offsets the decreased $(TB_{Na} + TB_K)/TBW$ ratio, due to the increased TBW.
- Controlled increases of S_{Na} at this rapid rate nearly always requires hypertonic (3%) saline. The recommended rate of correction in severe acute hyponatremia is an increase in S_{Na} of 4 to 6 mmol/L in the first hour. In normovolemic patients (i.e., having normal TB_{Na}), furosemide 20 to 40 mg IV has been used in conjunction with hypertonic saline to lessen the expansion of ECFV while maintaining the rapid increase in S_{Na} by increasing free water excretion.
- Regardless of the therapies employed, patients with acute hyponatremia require monitoring in an ICU setting with frequent measurements of S_{Na}, urine volume, and U_{osm} until patients are neurologically stable and the S_{Na} approaches the lower normal range.

CHRONIC Rx

- Chronic hyponatremia develops over >24 to 48 hours, during which time brain cell adaptation occurs by the extrusion of electrolytes and organic osmolytes such as amino acids. Consequently, the possibility of cerebral edema is minimized while the risks of rapid correction increase. Precipitous increases in S_{Na} in this setting have been associated with demyelinating injuries. The appropriate target for correction of hyponatremia in this setting is 6 to 8 mmol/L per day.
- In hypovolemic patients with chronic hyponatremia the usual clinical practice is to administer 0.9% saline until patients are normovolemic. The 0.9% saline results in very little direct change in S_{Na} because it increases total body cation and TBW proportionately, but indirectly can eventually trigger a rapid increase in S_{Na} after patients become normovolemic and ADH is suppressed. The simultaneous use of desmopressin (1 to 2 mcg IV every 12 hours) is a recommended adjuvant to therapy in these patients to postpone the risk of overly rapid correction until the patient is clinically normovolemic and IV fluids may be discontinued, and the patient monitored. If the rate or magnitude of S_{Na} correction starts exceeds recommended targets, desmopressin may be re-dosed as needed. Desmopressin may provide protection against overly rapid elevations of S_{Na} in patients with unrecognized solute-limited water diuresis (see later).
- The risk of overly rapid correction is highest in hyponatremic patients with tea-and-toast diets or beer potomania. These patients are recognized primarily by a U_{osm} < 100 mOsm/kg H_2O, thereby demonstrating suppression of ADH. The preferred treatment of this situation is fluid restriction and dietary supplementation to supply appropriate quantities of protein and electrolytes. Reflex administration of IV saline is contraindicated: 1 L of IV 0.9% saline (308 mOsm/L) supplies enough osmoles to excrete 3 to 6 L of hypotonic urine in the absence of ADH. If saline has already been given, rapid urinary water loss may be blunted by desmopressin.
- The treatment of normovolemic patients is covered in detail in the "Syndrome of Inappropriate Antidiuresis" and thus is only briefly reviewed here. The goal of therapy in these patients is to reduce TBW in controlled fashion maintaining TBNa and TBK. Some patients with chronic normovolemic

hyponatremia (e.g., drug-induced etiologies or primary polydipsia) have self-limited abnormalities and primarily require monitoring to prevent excessively rapid correction. Active therapy as described below can be started to avoid delays. If required, desmopressin can be administered intermittently to temporarily block further losses of free water to slow the overall rate of correction. If overcorrection has occurred oral and/or IV hypotonic fluids may be quantitatively administered to lower the serum sodium actively. Other disorders may only slowly resolve and require more active therapy as delineated in "Syndrome of Inappropriate Antidiuresis," consisting of either a direct V2 receptor antagonist or a loop diuretic combined with replacement of electrolytes lost during diuresis.

DISPOSITION

- Patients with symptomatic or severe hyponatremia require monitoring in an ICU setting until the S_{Na} has stabilized at a safe level. Frequent monitoring of serum sodium, urine volume, and urine osmolality and electrolytes is required, with adjustments in therapy as outlined previously as needed.
- All potential contributing causes should be evaluated and treated appropriately. Aside from obvious disorders, less apparent conditions such as adrenal insufficiency and hypothyroidism should be ruled out.
- The risk of recurrence depends primarily on the nature of the underlying disorders present. Hypovolemic hyponatremia (e.g., diarrheal or diuretic-induced electrolyte and water losses) or drug-induced SIAD may have little chance of recurrence if the offending medication is discontinued or if gastrointestinal losses are not chronic. Elderly patients with solute-limited diuresis due to low electrolyte and protein intake may be resistant to major changes in diet but may agree to NaCl tablets and/or protein supplements. In addition to disease-specific management, incurable conditions (e.g., chronic CNS or pulmonary disease, CHF, or cirrhosis) may require life-long fluid restriction (10 to 15 ml/kg/day), high protein and electrolyte diets as tolerated, and periodic monitoring of the S_{Na} to reduce the risk of recurrence.

REFERRAL

- Referral to specialists in nephrology, endocrinology, and/or critical care medicine are recommended in cases of severe or symptomatic hyponatremia to aid in setting appropriate rates of correction and to recommend, monitor, and adjust therapeutic regimens to achieve those target rates.
- Outpatient referral to nephrology or endocrinology may be required to facilitate the management of patients with mild hyponatremia or recurrent hyponatremia that does not warrant hospitalization.

PEARLS & CONSIDERATIONS

COMMENTS

PREVENTION: Well-meaning family members, friends, news media, and health care providers often encourage patients with chronic kidney disease or who are taking diuretics to drink large amounts of water. When these patients consume more free water than they can excrete, hyponatremia may develop. Similarly, participants in marathons or other high-intensity endurance activities may ingest so much water that in place of TBW depletion they develop high TBW and hyponatremia. Patients at risk for hyponatremia should receive a specific fluid prescription that avoids both extremes. Conversely, patients with diarrheal losses or who develop decreased ECFV from loop diuretics or combination diuretics must be counseled that intake of water or other hypotonic fluids alone will lead to hyponatremia but not effectively restore ECFV. Safe outpatient correction of ECFV requires the consumption of electrolyte-containing solutions such as those marketed for infants. A more recent alternative is the use of commercial electrolyte tablets or packets. Standard sports drinks have high sugar content but relatively low quantities of electrolytes and may be inadequate for electrolyte replacement.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Syndrome of Inappropriate Antidiuresis (Related Key Topic)

AUTHORS: **Mark D. Faber, MD,** and **Jerry Yee, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

A decrease in parathyroid hormone (PTH) secretion or function results in hypoparathyroidism. In **primary hypoparathyroidism,** absence or dysfunction of the parathyroid gland results in inadequate PTH secretion and subsequent hypocalcemia and hyperphosphatemia. Surgical hypoparathyroidism is the most common etiology, followed by autoimmune disorders. Individuals with autoimmune polyglandular syndrome 1 typically present in childhood/adolescence with candidiasis, hypoparathyroidism, and adrenal insufficiency. Impaired function of PTH (i.e., PTH resistance) can also cause hypocalcemia and hyperphosphatemia, but the measured PTH level is elevated in this circumstance. A maternally transmitted mutation in the *GNAS1* gene results in PTH resistance (i.e., pseudohypoparathyroidism). It is associated with characteristic features that include developmental delay, short stature, round facies, and short 4th metacarpal known as Albright hereditary osteodystrophy (AHO). Paternal transmission manifests with AHO without PTH resistance (i.e., pseudopseudohypoparathyroidism; Table 1). **Secondary hypoparathyroidism,** a condition in which PTH levels are low in response to hypercalcemic states, is discussed in Section IV (see hypercalcemia discussion in the "Calcium" topic).

ICD-10CM CODES

E20.0	Idiopathic hypoparathyroidism
E20.1	Pseudohypoparathyroidism
E20.8	Other hypoparathyroidism
E20.9	Hypoparathyroidism, unspecified
E89.2	Postprocedural hypoparathyroidism
P71.4	Transitory neonatal hypoparathyroidism

EPIDEMIOLOGY & DEMOGRAPHICS

The incidence and prevalence of primary hypoparathyroidism depends on the etiology of the condition. Estimated prevalence in the United States is between 23 to 37 cases per 100,000 person-yr. Postoperative hypoparathyroidism is the most common etiology (75%). This occurs in the setting of thyroid or parathyroid surgery as a result of removal of, or vascular compromise of, the parathyroid glands during surgery. Transient hypoparathyroidism (<6 mo) can be as high as 20% postoperatively, but permanent dysfunction (>6 mo) is less common (3%). Autoimmune disorders are the second most common cause of hypoparathyroidism in adults (female/male ratio of 1.4:1.0). Autoimmune polyglandular syndrome type I is reported to have an incidence worldwide of 1:1,000,000. Other etiologies of hypoparathyroidism are very rare.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The symptoms of hypoparathyroidism are primarily related to hypocalcemia. The presentation of symptoms varies with the severity and duration of illness.

- Cardiovascular: Prolonged QT intervals, QRS and ST segment changes, ventricular arrhythmias
- Musculoskeletal: Muscle cramps, laryngospasm, osteomalacia (adults), rickets (children), weakened tooth enamel, osteosclerosis
- CNS: Tetany (Chvostek sign and Trousseau sign), seizures, paresthesias, visual impairment from cataract formation, altered mental status, papilledema, and basal ganglia calcifications with longstanding disease
- GI: Abdominal pain
- Renal: Hypercalciuria and nephrolithiasis
- Other: Dry scaly skin, brittle nails, dry hair

In addition to the hypocalcemia-related symptoms, syndromes associated with hypoparathyroidism can have distinct clinical findings. Conditions associated with hypoparathyroidism include:

- Autoimmune polyglandular syndrome type 1: Mucocutaneous candidiasis and adrenal insufficiency
- DiGeorge syndrome: Dysmorphic facies, cleft palate
- Pseudohypoparathyroidism: Developmental delay, short stature, round face, short fourth metacarpal (Albright hereditary osteodystrophy)
- Hypoparathyroidism-retardation-dysmorphism syndrome: Short stature, microcephaly, microphthalmia, small hands and feet, abnormal teeth
- Hypoparathyroidism-deafness-renal dysplasia syndrome: Sensorineural deafness
- Kenny-Caffey syndrome: Short stature
- Kearns-Sayre syndrome: Paralysis of eye muscles and pigmentary retinopathy

ETIOLOGY

There are several etiologies of hypoparathyroidism:

- Postoperative hypoparathyroidism; most common cause (78% of cases)
- Destruction of the parathyroid glands:
  1. Autoimmune polyglandular syndrome type 1
  2. Radiation to the neck
  3. Infiltrative diseases (e.g., metastatic carcinoma, Wilson disease, hemochromatosis, thalassemia, granulomatous disease)
- Developmental defects of the parathyroid glands:
  1. Isolated hypoparathyroidism
  2. Branchial dysembryogenesis (DiGeorge syndrome)
  3. Hypoparathyroidism-retardation-dysmorphism syndrome
  4. Hypoparathyroidism-deafness-renal dysplasia syndrome
  5. Mitochondrial dysfunction associated with hypoparathyroidism
  6. Kearns-Sayre syndrome
  7. Mitrochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome
  8. Mitochondrial trifunctional protein (MTP) deficiency syndrome
- Functional and secretory defects of the parathyroid glands:
  1. Activating mutation of the calcium-sensing receptor alters the set point of the receptor and decreases PTH secretion
  2. Activating antibodies to calcium-sensing receptor alters the set point of the receptor and decreases PTH secretion
  3. PTH resistance (i.e., target organs unresponsive to PTH action)
     a. Pseudohypoparathyroidism (PHP): Heterogeneous disorder presenting in childhood characterized by hypocalcemia, hyperphosphatemia, and elevated PTH levels. Table 2 summarizes the various types of PHP
     b. Hypermagnesemia and hypomagnesemia

TABLE 1 Types of Hypoparathyroidism

Type	Calcium	PO_4	PTH	Comments
Hypoparathyroidism	↓	↑	↓	Surgical removal (most common cause)
Pseudohypoparathyroidism	↓	↑	Ø↑	End-organ resistance to parathyroid hormone and Albright hereditary osteodystrophy
Pseudo-pseudohypoparathyroidism	Normal	Normal	Normal	Only Albright hereditary osteodystrophy

PO_4, Phosphate; *PTH,* parathyroid hormone.
(Adapted from Weissleder R et al: *Primer of diagnostic imaging,* ed 5, St Louis, 2011, Mosby.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Secondary hypoparathyroidism as a result of hypercalcemia.
- Other conditions associated with hypocalcemia. These conditions are usually associated with an elevated PTH hormone level.

WORKUP

- Hypoparathyroidism is characterized by hypocalcemia and hyperphosphatemia as a result of inadequate PTH secretion.
  1. Two measurements of serum calcium are required for the confirmation of hypocalcemia. Total calcium should be corrected for low albumin utilizing the formula: Corrected calcium = measured calcium + [(4 – albumin) × 0.8]. If a reliable laboratory is available, ionized calcium should be considered especially in conditions associated with acid-base disturbances or low albumin states.

TABLE 2 Types of Pseudohypoparathyroidism (PHP)

Disorder	Urinary cAMP Response to PTH	Urinary PO_4 Response to PTH	Other Hormonal Resistance	AHO	Pathophysiology
PHP type 1A	Decreased	Decreased	Yes	Yes	$G_s\alpha$ mutation
Pseudo-PHP	Normal	Normal	No	Yes	$G_s\alpha$ mutation
PHP type 1B	Decreased	Decreased	No	No	*GNAS1* imprinting mutations
PHP type 1C	Decreased	Decreased	Yes	Yes	$G_s\alpha$ activity normal
PHP type 2	Normal	Decreased	No	No	Vitamin D deficiency or myotonic dystrophy in some cases

AHO, Albright hereditary osteodystrophy; *cAMP*, cyclic adenosine monophosphate; *GNAS1,* portion of the *GNAS* complex locus encoding $G_s\alpha$; $G_s\alpha$, α-subunit of the stimulatory G protein; PO_4, phosphate; *PTH*, parathyroid hormone.
(From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

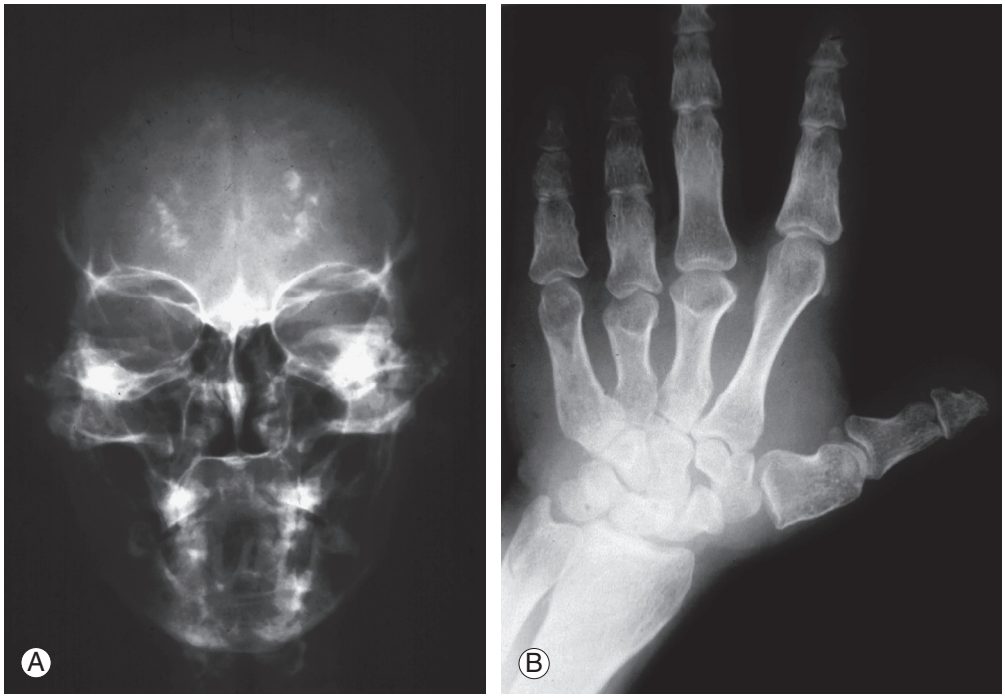

FIG. 1 Hypoparathyroidism. (A) Soft tissue calcification may be present, seen here in the basal ganglia. **(B)** In pseudohypoparathyroidism there are shortened metacarpals, particularly the 4th and 5th. (From Adam A, Dixon AK, Grainger RG, Allison DJ: *Grainger & Allison's diagnostic radiology,* 5e. Churchill Livingstone, 2007, in Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

2. Serum phosphorus is usually high-normal or elevated in primary hypoparathyroidism.
3. Serum intact PTH (iPTH) level is the single best test to evaluate the etiology of hypocalcemia. Typically, PTH is low or inappropriately normal in primary hypoparathyroidism and elevated in most other conditions associated with low calcium levels. However, PTH is also elevated in disorders associated with impaired PTH function (i.e., pseudohypoparathyroidism). Genetic studies as indicated if medical or family history is suggestive.

The diagnosis is established by concurrent measurements of ionized calcium or corrected calcium that is within the lower limit of normal range and low or undetectable levels of PTH on two separate occasions at least 2 wk apart.

LABORATORY TESTS

- Total and ionized calcium: Low in hypoparathyroidism
- PTH: Low in hypoparathyroidism and high in PTH resistance states like pseudohypoparathyroidism
- Phosphorus: High-normal or high in hypoparathyroidism
- Magnesium: Both hypomagnesemia and hypermagnesemia can cause hypoparathyroidism
- 24-hr urine calcium and creatinine to evaluate the risk for renal stones
- ECG should be considered. Hypocalcemia is associated with prolonged QT interval, rarely ST-segment elevations

IMAGING

- Renal ultrasonography to detect the presence of nephrocalcinosis
- Soft tissue calcifications may be noted on plain x-rays (Fig.1)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Diet:

- Consumption of calcium-enriched food (i.e. dairy)
- Restriction of phosphate intake (i.e. commercially prepared foods)

Parathyroid autotransplantation:

- Hypoparathyroidism and subsequent hypocalcemia are common problems after neck exploration for total or near-total thyroidectomy or parathyroidectomy. In cases where there is concern for postoperative hypoparathyroidism, parathyroid autotransplantation of one or two parathyroid glands into the forearm or sternocleidomastoid muscle should be performed to prevent postoperative hypoparathyroidism.

PHARMACOLOGIC THERAPY

The mainstay of treatment for primary hypoparathyroidism is pharmacologic therapy with calcium and vitamin D supplementation. The goals of therapy are to control symptoms and minimize complications of therapy. The aim should be to achieve low-normal serum calcium level (8.0 to 8.5 mg/dl), high-normal serum phosphorus level, 24-hr urinary calcium <300 mg/day, and a calcium-phosphorus product $<55\ mg^2/dl^2$.

- Vitamin D:
  1. There are several vitamin D preparations available on the market, but the treatment of choice for patients with primary hypoparathyroidism is calcitriol. It is an active metabolite that does not require hydroxylation in the liver or kidney and therefore bypasses the PTH-mediated 1-α hydroxylation defect that occurs with hypoparathyroidism.
  2. Dose of 0.25 to 1 μg once or twice daily is usually required to correct hypocalcemia and improve symptoms. Its maximal effect is seen after 10 h and it lasts for 2 to 3 days.
  3. High doses of vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol) may also be used.
- Calcium:
  1. Calcium carbonate or calcium citrates are common oral agents used for treatment of hypocalcemia associated with hypoparathyroidism. Calcium carbonate contains 40% elemental calcium, and calcium citrate contains 21% elemental calcium. Calcium carbonate requires an acidic environment for effective absorption, and as a result, it must be taken with food. Its effectiveness is decreased with concomitant use of H_2 blockers or proton pump inhibitors. Calcium citrate does not require an acidic environment for effective absorption.
  2. Start with a dose of 500 to 1000 mg of elemental calcium two to three times daily and adjust the dose for a desired calcium in the low-normal range.
- Magnesium:
  1. Hypocalcemia is difficult to correct without normalizing magnesium levels.
  2. Magnesium sulfate IV 2 g over 20 min followed by 1 g/hr infusion can be considered in severe deficiency states. Milder deficiencies can be managed with oral magnesium 100 mg three times a day.
- Thiazide diuretics:
  1. Thiazide diuretics (25 to 100 mg daily) decrease urine calcium excretion and decrease kidney stones. They should be considered in individuals with urine calcium >250 mg/day.
- PTH replacement:
  1. Injectable synthetic human PTH (1-84) decreases urinary calcium excretion and maintains serum calcium in the normal range with reduced requirements for calcium and vitamin D supplementation.
  2. PTH (1-84, Natpara, an 84-amino acid single-chain polypeptide identical to native parathyroid hormone) is the first FDA-approved product for use in the treatment of hypoparathyroidism as an adjunct to calcium and vitamin D. PTH (1-84) is recommended for patients who cannot be well controlled on conventional therapy alone. The cost for a 4-wk supply of Natpara exceeds $7000.

ACUTE GENERAL Rx

Severe and/or symptomatic hypocalcemia requires hospitalization. Acute management of hypocalcemia includes:

- Telemetry monitoring for arrhythmias associated with severe hypocalcemia
- IV infusion of calcium gluconate 10 ml of 10% solution to receive a bolus of 90 mg of elemental calcium followed by an infusion of 0.5 to 2 mg/kg/hr until calcium levels are in the low-normal range

PEARLS & CONSIDERATIONS

COMMENTS

- The mainstay of treatment for primary hypoparathyroidism is calcitriol and calcium supplementation to maintain a goal serum calcium level in the low-normal range. IV calcium should be considered if calcium <7.0 mg/dl.
- Treatment of hypothyroidism is commonly associated with hypercalciuria, nephrocalcinosis, nephrolithiasis, and renal insufficiency. It is recommended to target blood calcium levels to the lower end of the normal range in order to reduce hypercalciuria. Urinary calcium levels should also be monitored periodically.
- Hypomagnesemia causes functional, reversible parathyroid hypofunction. Magnesium levels should be assessed and appropriately replaced in all patients with hypocalcemia before a low PTH level is attributed to hypoparathyroidism.
- In patients undergoing neck exploration, consideration should be given to the parathyroid glands. Autotransplantation of one or more parathyroid glands should be considered when appropriate to prevent postoperative hypoparathyroidism.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Vicky Cheng, MD**

SUGGESTED READINGS

Bilezikian JP et al: Management of hypoparathyroidism, *J Clin Endocrinol Metab* 101(6):2313-2324, 2016.

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Hypopituitarism (PTG)

BASIC INFORMATION

DEFINITION

Hypopituitarism (from the Latin *pituita,* meaning "phlegm") is the deficiency of one or more of the hormones of the anterior or posterior pituitary gland resulting from diseases of the hypothalamus or pituitary gland. Panhypopituitarism indicates the loss of all the pituitary hormones but is often used in clinical practice to describe patients deficient in growth hormone (GH), gonadotropins, corticotropin, or thyrotropin in whom posterior pituitary function remains intact.

SYNONYMS

Panhypopituitarism
Pituitary insufficiency

ICD-10CM CODES

E23.0 Hypopituitarism
E23.1 Drug-induced hypopituitarism
E89.3 Postprocedural hypopituitarism

EPIDEMIOLOGY & DEMOGRAPHICS

Incidence of 4.2 cases per 100,000 persons

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms depend on type of onset, number and severity of hormone deficiencies, their target organs, and age of onset.

- Mass effect of a pituitary tumor can cause headaches and visual disturbances (typically as bitemporal hemianopsia).
- Rhinorrhea.
- Corticotropin deficiency:
  1. Fatigue and weakness, no appetite, abdominal pain, nausea, vomiting, failure to thrive in children, and hyponatremia. If the onset is abrupt, hypotension and shock.
- Thyrotropin deficiency:
  1. Fatigue and weakness, weight gain, cold intolerance, anemia, constipation
  2. Bradycardia, hung-up reflexes, pretibial edema, change in voice, and hair loss
- Gonadotropin deficiency:
  1. Loss of libido, erectile dysfunction, amenorrhea, hot flashes, dyspareunia, infertility, gynecomastia, decreased muscle mass, and anemia
- GH deficiency:
  1. Growth retardation in children
  2. Easy fatigue, hypoglycemia
  3. Lean mass is reduced and fat mass is increased, leading to obesity
  4. Decreased bone mineral density, increased low-density lipoprotein cholesterol, obesity, increased inflammatory cardiovascular markers (interleukin-6 and C-reactive protein)
- Hyperprolactinemia:
  1. Galactorrhea, hypogonadism, inability to lactate after delivery
  2. Posterior pituitary (vasopressin; antidiuretic hormone [ADH] deficiency): Diabetes insipidus with polyuria, polydipsia, nocturia, hypotension, and dehydration

ETIOLOGY

It can be congenital or acquired:

- Congenital: Mutations in transcription factors produce multiple hormonal deficiencies. Mutations in genes produce single hormonal deficiency.
- Acquired (Table 1): The result of destruction of pituitary cells caused by:
  1. Pituitary apoplexy: Hemorrhage or infarction of the pituitary gland. Predisposing factors include diabetes mellitus, anticoagulation therapy, head trauma, and radiation therapy. Sheehan syndrome: Postpartum necrosis, a rare complication after pregnancy.
  2. Infiltrative disease, including sarcoidosis, hemochromatosis, histiocytosis X, Wegener granulomatosis, lymphocytic hypophysitis, and infection of the pituitary (tuberculosis, mycosis, syphilis).
  3. Primary empty sella syndrome: Flattening of the pituitary gland caused by extension of the subarachnoid space and filling of cerebrospinal fluid into the sella turcica.
  4. Pituitary tumors: Classified by size (microadenomas, <10 mm; macroadenomas, >10 mm) and function. Prolactin-secreting tumors and nonfunctioning tumors account for the majority of pituitary adenomas.
  5. Suprasellar tumors: Craniopharyngiomas are the most common.

DIAGNOSIS

The diagnosis of hypopituitarism is suspected by clinical history and physical findings and is established by blood tests to confirm the presence of hormone deficiency.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is as outlined under "Etiology."

WORKUP

Includes baseline determination of each anterior pituitary hormone followed by dynamic provocative stimulation tests, radiograph imaging, and formal visual field testing. Table 2 summarizes testing for assessment of anterior pituitary function.

LABORATORY TESTS

- Corticotropin deficiency:
  1. The presence of a 9:00 am cortisol level >20 mcg/dl or <4 mcg/dl usually confirms sufficiency or deficiency, respectively.
  2. Corticotropin stimulation test using 250 mcg of corticotropin given IV and measuring serum cortisol before and 30 and 60 min after administration. A normal response is an increase in serum cortisol level >20 mcg/dl.
  3. With pituitary disease these test results may be indeterminate, and more dynamic testing such as an insulin-tolerance or metyrapone test may be necessary.
- Thyrotropin deficiency:
  1. Thyroid-stimulating hormone (TSH) and free T_4 measurements
  2. Primary hypothyroidism shows elevated TSH with low free T_4. Secondary hypothyroidism shows normal or low TSH with low free T_4 and low T_3 resin uptake.
- Gonadotropin deficiency:
  1. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), estrogen, and testosterone measurements.
  2. In men, hypogonadotropic hypogonadism is seen with low testosterone levels and normal or low FSH and LH levels (ideally measured at 9:00 A.M. because of diurnal rhythm). Check free testosterone if patient is obese.
  3. In premenopausal women with amenorrhea, low estrogen with normal or low FSH and LH levels is typically seen.
- GH deficiency:
  1. Insulin-induced hypoglycemia stimulation test using 0.1 to 0.15 unit/kg regular insulin given IV and measuring GH 30, 60, and 120 min after administration. A normal response is a GH level >3 mcg/dl. This test is contraindicated in seizure disorder or ischemic heart disease.
  2. Combination of GH-releasing hormone plus arginine is an alternative test, with a diagnostic threshold of 9 mcg/L.
  3. Because the relation between serum insulin-like growth factor (IGF)-1 and GH levels blurs with age, a normal serum IGF-1 does not exclude the diagnosis in older adults.
- Hyperprolactinemia: Prolactin levels may be elevated in prolactin-secreting pituitary adenomas.
- Vasopressin deficiency:
  1. Urinalysis shows low specific gravity.
  2. Urine osmolality is low.
  3. Serum osmolality is high.
  4. Fluid deprivation test over 18 hr with inability to concentrate the urine.
  5. Serum vasopressin level is low.
  6. Electrolytes may show hyponatremia and exclude hyperglycemia.

IMAGING STUDIES

- Imaging is the first step in identifying an underlying cause.
- MRI (Fig. E1) is more sensitive than CT in visualizing the pituitary fossa, sella turcica, optic chiasm, pituitary stalk, and cavernous sinuses. It is also more sensitive in detecting pituitary microadenomas. CT with contrast can be used if MRI is not available.
- Surveillance scan at baseline and 12 mo thereafter depending on protocol and clinical symptoms.

TABLE 1 Causes of Acquired Pituitary Insufficiency

Traumatic
- Surgical resection
- Radiation damage
- Traumatic brain injury

Infiltrative/Inflammatory
- Primary hypophysitis
- Lymphocytic
- Granulomatous
- Xanthomatous
- Secondary hypophysitis
- Sarcoidosis
- Langerhans cell histiocytosis
- Infections
- Granulomatosis with polyangiitis
- Takayasu disease
- Hemochromatosis

Infections
- Tuberculosis
- *Pneumocystis jirovecii* infection
- Fungal (histoplasmosis, aspergillosis)
- Parasites (toxoplasmosis)
- Viral (cytomegalovirus)

Vascular
- Pregnancy related
- Aneurysm
- Apoplexy
- Diabetes
- Hypotension
- Arteritis
- Sickle cell disease

Neoplastic
- Pituitary adenoma
- Parasellar mass
- Rathke cyst
- Dermoid cyst
- Meningioma
- Germinoma
- Ependymoma
- Glioma
- Craniopharyngioma
- Hypothalamic hamartoma, gangliocytoma
- Pituitary metastatic deposits
- Hematologic malignancy
- Leukemia
- Lymphoma

Functional
- Nutritional
- Caloric restriction
- Malnutrition
- Excessive exercise
- Critical illness
- Acute illness
- Chronic renal failure
- Chronic liver failure
- Hormonal
- Hyperprolactinemia
- Hypothyroidism
- Drugs
- Anabolic steroids
- Glucocorticoid excess
- GnRH agonists
- Estrogen
- Dopamine
- Somatostatin analog
- Thyroid hormone excess

Modified from Kaiser U, Ho KKY: Pituitary physiology and diagnostic evaluation. In Melmed S, et al eds: *Williams textbook of endocrinology*, ed 13, Philadelphia, 2016, Elsevier. Table 8.5, p. 193, in Kliegman RM: *Nelson Textbook of Pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

Rx TREATMENT

Threefold: Removing underlying cause (surgery or radiation), treating hormonal deficiencies, and addressing any other repercussions from deficiency. Table 3 summarizes replacement therapy for adult hypopituitarism.

NONPHARMACOLOGIC THERAPY

- IV fluid resuscitation, correction of electrolyte and metabolic abnormalities with potassium bicarbonate, and oxygen therapy.
- Transsphenoidal surgery for tumors causing specific symptoms.
- Radiation or stereotactic radiosurgery ("gamma knife") for medically unresponsive, surgically unresectable tumors and tumors for which other modalities are contraindicated. It is both safe and effective for recurrent or residual pituitary adenomas.

ACUTE GENERAL Rx

Acute situations such as adrenal crisis or myxedema coma can occur in untreated hypopituitarism and should be treated accordingly with IV corticosteroids (e.g., hydrocortisone 100 to 250 mg bolus followed by hydrocortisone 100 mg IV q6h for 24 hr) and levothyroxine (e.g., 5 to 8 mcg/kg IV over 15 min, then 100 mcg IV q24h).

CHRONIC Rx

Treatment is lifelong:
- Adrenocorticotropic hormone (ACTH) deficiency: Hydrocortisone 10 mg PO every morning and 5 mg PO every evening or prednisone 5 mg PO every morning and 2.5 mg PO every evening. Dexamethasone or prednisone is often preferred because of longer duration of action.
- LH and FSH deficiency:
  1. In men, testosterone enanthate or propionate 200 to 300 mg IM every 2 to 3 wk, or transdermal testosterone scrotal patches can be tried.
  2. In women who are not interested in fertility, conjugated estrogen 0.3 to 1.25 mg/day and held the last 5 to 7 days of each mo with the addition of medroxyprogesterone 10 mg/day given during days 15 to 25 of the normal menstrual cycle. In those who have secondary hypogonadism and wish to become pregnant, pulsatile gonadotropic-releasing hormone may be of benefit.
- TSH deficiency: Levothyroxine 0.05 to 0.2 mg/day. Only free thyroxine should be used to monitor appropriate dosing to maintain thyroxine level in the mid to upper half of normal range.
- GH deficiency:
  1. GH replacement in children is universally accepted.
  2. GH replacement in adults is not generally recommended and requires careful consideration of each individual case. It may have effects on quality of life, body composition, bone density, and cardiovascular risk factors.
  3. Side effects of replacement include peripheral edema, arthralgia, and headaches.
  4. Usual GH dose is between 0.2 and 0.4 mg, determined by the age and gender of a patient and increments of 0.1 mg every 2 to 4 wk until serum IGF-1 is in the upper part of the normal range. Young adults and women taking estrogen require a higher dose.
- ADH deficiency:
  1. Desmopressin (DDAVP) 10 to 20 mcg by intranasal spray or 0.05 to 0.1 mg PO bid is used in patients with diabetes insipidus.
  2. Vasopressin: 5 to 10 U given IM or SC q6h.

DISPOSITION

- Hormone replacement therapy is adjusted according to serum hormone monitoring.
- If untreated can lead to adrenal crisis, severe hyponatremia and hypothyroidism, metabolic abnormalities, and death.
- Complications: Visual deficit, adrenal crisis, susceptibility to infection and other stressors.
- Prognosis: Stable patients have a favorable prognosis with replacement hormone therapy. Patients with acute decompensation are in critical condition with a high mortality rate.

REFERRAL

Consultation with an endocrinologist and neurosurgeon for surgical treatment

PEARLS & CONSIDERATIONS

- All patients sustaining moderate to severe head injury should undergo assessment of anterior pituitary function during the acute phase and at 6 mo.
- IGF-1 can be used as a marker of GH deficiency.
- All tests of GH secretion are more likely to give false-positive results in obese patients.
- The GH axis is the most vulnerable to the effects of radiotherapy; doses as low as 18 Gy in children have caused GH deficiency.
- Sequence of hormonal disruption: GH secretion then gonadotropin secretion. TSH and adrenocorticotropic hormone secretion are somewhat resistant.
- Thyroxine supplementation increases the rate of cortisol metabolism and can lead to adrenal crisis, so corticosteroids should be replaced first.
- All patients receiving glucocorticoid replacement therapy should wear proper identification stating the need for this therapy.

TABLE 2 Assessment of Anterior Pituitary Function

Test	Dose	Normal Response	Side Effects
ACTH			
Insulin tolerance	0.1-0.15 U/kg IV	Peak cortisol response >18 μg/dl, or ≥5 μg/dl	Sweating, palpitation, tremor
Metyrapone	30 mg/kg PO at 11 P.M.	Peak 11-DOC ≥7 μg/dl Peak cortisol ≤7 μg/dl Peak ACTH >75 pg/ml	Nausea, insomnia, adrenal crisis
CRH stimulation	100 μg IV	Peak ACTH ≥2-4-fold Peak cortisol ≥20 μg/dl or ↑ ≥7 μg/dl	Flushing
ACTH stimulation	250 μg IV or IM, or 1 μg IV	Peak cortisol ≥20 μg/dl	Rare
TSH			
Serum T_4 (free T_4) Total T_3 TSH—third-generation TRH stimulation	200-500 μg IV	Peak TSH ≥2.5-fold, or ↑ ≥5-6 mU/L (females) or ≥2-3 mU/L (males)	Flushing, nausea, urge to micturate
PRL			
Serum PRL TRH stimulation	200-500 μg IV	PRL ↑ ≥2.5-fold	Flushing, nausea, urge to micturate
LH/FSH			
Serum LH and FSH Serum testosterone GnRH stimulation	100 μg IV	Elevated in menopause and in men with primary testicular failure (otherwise normal) 300-900 ng/ml LH ≥2-3-fold, or ↑ by 10 IU/L FSH ≥1.5-2-fold, or ↑ ≥2 IU/L	Rare
GH			
Insulin tolerance	0.1-0.15 U/kg	GH peak >5 μg/L	Sweating, palpitation, tremor
L-Arginine	Arginine 0.5 g/kg (maximum, 30 g) IV over 30-120 min	GH peak >0.4 μg/L	Nausea
Plus			
GHRH	GHRH 1-5 μg/kg	GH peak >4 μg/L	Flushing

ACTH, Adrenocorticotropic hormone; *CRH,* corticotropin-releasing hormone; *11-DOC,* 11-deoxycorticosterone; *FSH,* follicle-stimulating hormone; *GH,* growth hormone; *GHRH,* growth hormone–releasing hormone; *GnRH,* gonadotropin-releasing hormone; *IM,* intramuscular; *IV,* intravenous; *LH,* luteinizing hormone; *PO,* by mouth; *PRL,* prolactin; T_3, triiodothyronine; T_4, thyroxine; *TRH,* thyrotropin-releasing hormone; *TSH,* thyroid-stimulating hormone; *TRH,* thyrotropin-releasing hormone.
From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders, Elsevier Inc.

TABLE 3 Replacement Therapy for Adult Hypopituitarism*

Deficient Hormone

Treatment

ACTH

Hydrocortisone: 10-20 mg/day in divided doses
Cortisone acetate: 15-25 mg/day in divided doses

TSH

L-Thyroxine: 0.05-0.2 mg/day according to T_4 levels

FSH/LH (in males)

Testosterone enanthate: 200 mg IM q2-3 wk
Testosterone skin patch: 2.5-5.0 mg/day (or up to 7.5 mg/day)
Testosterone gel: 3-6 g/day

For fertility: hCG three times weekly, or hCG + either FSH or menopausal gonadotropin or GnRH

FSH/LH (in females)

Conjugated estrogen: 0.3-0.625 mg/day
Micronized estradiol: 1 mg/day
Estradiol valerate: 2 mg
Piperazine estrone sulfate: 1.25 mg
Estradiol skin patch: 4-8 mg twice weekly

All of the estrogens are administered with progesterone or progestin sequentially or in combination if uterus is present
For fertility: Menopausal gonadotropin, and hCG, or GnRH

Growth hormone

Somatotropin (in adults): 0.2-1.0 mg/day SC
Somatotropin (in children): 0.02-0.05 mg/kg per day

Vasopressin

Intranasal desmopressin: 10-20 μg bid
Oral DDAVP: 300-600 μg/day, usually in divided doses

ACTH, Adrenocorticotropic hormone; *bid,* twice per day; *DDAVP,* desmopressin acetate; *FSH,* follicle-stimulating hormone; *GnRH,* gonadotropin-releasing hormone; *hCG,* human chorionic gonadotropin; *IM,* intramuscular; *LH,* luteinizing hormone; *SC,* subcutaneous; T_4, thyroxine; *TSH,* thyroid-stimulating hormone.
From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders, Elsevier Inc.

- Stress doses of corticosteroids are indicated before surgery or for any medical emergency (e.g., sepsis, acute myocardial infarction).
- Antidiuretic hormone deficiency may be masked if there is ACTH deficiency with symptoms only appearing when cortisol has been replaced.

COMMENTS

- Mineralocorticoid replacement is not necessary in secondary adrenal insufficiency because the renin-angiotensin-aldosterone system is unaffected by pituitary failure.
- Patients with adult-acquired GH deficiency must meet at least two criteria before replacement therapy: A poor GH response to at least two standard stimuli and hypopituitarism from pituitary or hypothalamic damage. The criteria are different in children in whom GH is required for normal growth.
- Prevention of acute decompensation can be accomplished by reminding patients to increase the dose of hydrocortisone in response to stress.
- Medical therapy should precede surgical therapy.

RELATED CONTENT

Hypopituitarism (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

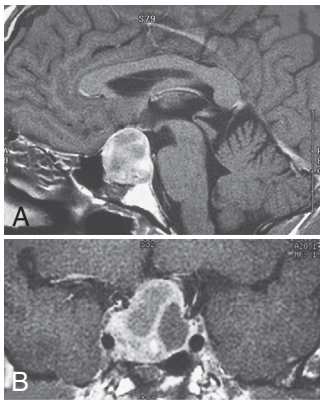

FIG. E1 T1-weighted gadolinium-enhanced MR of a pituitary adenoma. **(A)** Sagittal and **(B)** coronal images. (Courtesy of D. Thomas. From Bowling B: *Kanski's clinical ophthalmology*, ed 8, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Hypospadias is a developmental abnormality of the penis characterized by:

- Abnormal ventral opening of the urethral meatus anywhere from the ventral aspect of the glans penis to the perineum
- Ventral curvature of the penis (chordee)
- Dorsal foreskin hood

ICD-10CM CODES

Q54.1 Hypospadias, penile
Q54.2 Hypospadias, penoscrotal
Q54.3 Hypospadias, perineal
Q54.4 Congenital chordee
Q54.8 Other hypospadias
Q54.9 Hypospadias, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- One of the most common congenital anomalies in males
- Prevalence is highest in North America at 34.2 per 10,000 births, and lowest in Asia at 0.6 per 10,000 births

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Genetics: Normal karyotypes are seen with glanular hypospadias; abnormal karyotypes are noted in more severe forms of hypospadias
- Cryptorchidism: 8% to 9% occurrence
- Inguinal hernia: 9% to 10% occurrence
- Hydrocele: 9% to 16% occurrence

PENILE CURVATURE (CHORDEE): Three theories:

- Abnormal development of the urethral plate
- Abnormal fibrotic mesenchymal tissue at the urethral meatus
- Corporal disproportion

ETIOLOGY

Multifactorial:

- Genetic predisposition:
  1. There is a 9% to 17% recurrence rate in male siblings and an 8% recurrence rate in male offspring of men who have hypospadias.
  2. Only 30% of hypospadias cases have a clear genetic cause.
  3. The condition has an estimated 57% to 77% heritability and is equally transmitted through maternal and paternal sides of the family.
- Maternal and other influences:
  1. There is increased incidence in small for gestational age infants and monochorionic twins.
  2. Severe hypospadias is seen in patients with maternal hypertension, oligohydramnios, and preterm delivery, suggesting placental insufficiency may play a role.
  3. Males conceived by in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) may have a fivefold increased risk of hypospadias, according to some studies.
- Hormonal factors:
  1. Disruption in prenatal androgen exposure
  2. Fetal exposure to maternal estrogenic compounds (progestin or diethylstilbestrol)
  3. Possible link to disturbed testicular development as seen in testicular dysgenesis syndrome

DIAGNOSIS

WORKUP

Made by observation and examination (Fig. E1)

LABORATORY TESTS

The clinician always should consider a disorder of sex development (DSD) if there is associated cryptorchidism. The evaluation should include ultrasound; genitographic studies; and chromosomal, gonadal, biochemical, and molecular studies.

TREATMENT

ACUTE GENERAL Rx

CLASSIFICATION BASED ON MEATAL POSITION:

- Distal (glandular, coronal, subcoronal): 60%
- Middle (distal shaft, midshaft, posterior penile): 25%
- Proximal (penoscrotal, scrotal, perineal): 15%

SPECIAL CONSIDERATIONS:

- The major reason for operating on any patient with hypospadias is to correct deformities that interfere with the function of urination and procreation.
- Another reason for intervention is cosmetic concern.
- The American Academy of Pediatrics recommends the best time for surgical intervention to be 6 to 12 mo.

HORMONAL MANIPULATION:

- Controversial.
- Human chorionic gonadotropin (hCG) administration is given before repair of proximal hypospadias.
- The effect of hCG administration is decreased hypospadias and chordee severity in all patients and increased vascularity and thickness of the proximal corpus spongiosum.
- Application of topical testosterone increases mean penile circumference and length without any lasting side effects.
- Prepubertal exogenous testosterone does not adversely affect ultimate penile growth.

CHRONIC Rx

Surgical procedures:

- Orthoplasty (correcting penile curvature)
- Urethroplasty
- Meatoplasty
- Glanuloplasty
- Skin coverage

There is no single universally acceptable applicable technique for hypospadias repair.

Complications may occur up to 5 yr after the procedure, and therefore the patients should be monitored beyond the first yr, particularly in cases of middle or proximal hypospadias.

TYPES OF REPAIR

- Urethral plate tubularization: Makes a new urethra by rolling a ventral strip of skin from the penile shaft in glandular and penile shaft repairs
- Urethral plate augmentation: Used for more severe hypospadias where a urethra is created using a vascular strip of inner foreskin that is transferred to the ventral skin
- Urethral plate substitution (two stage repair): Used in the most extreme/severe cases
  1. Stage one: Corrects the penile curvature and transfers dorsal foreskin to the ventral side of the penis
  2. Stage two: Urethroplasty that occurs 6 mo after the first operation

COMPLICATIONS OF REPAIR: Hematoma, meatal stenosis, fistula, urethral stricture, urethral diverticulum, wound infection, impaired healing, balanitis xerotica obliterans, penile curvature

PEARLS & CONSIDERATIONS

- Apparent simple isolated hypospadias may be the only visible indication of an underlying abnormality.
- The dorsal hood of redundant foreskin is used in the repair of hypospadias, so the patient with hypospadias and a dorsal hood should not be circumcised.

RELATED CONTENT

Hypospadias (Patient Information)

AUTHORS: **Helen Toma, MD, MSPH,** and **Anthony Sciscione, DO**

FIG. E1 Varying forms of hypospadias. A through **F** illustrate various degrees of hypospadias. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, WB Saunders.)

SUGGESTED READING

Van der Horst HJR, de Wall LL: Hypospadias, all there is to know, *Eur J Pediatrics* 176:435-441, 2017.

BASIC INFORMATION

DEFINITION

Hypothermia is a rectal temperature <35° C (95.8° F). "Accidental hypothermia" is an unintentionally induced decrease in core temperature in the absence of preoptic anterior hypothalamic conditions.

ICD-10CM CODES

R68.0	Hypothermia, not associated with low environmental temperature
T68	Hypothermia

EPIDEMIOLOGY & DEMOGRAPHICS

- Hypothermia occurs most frequently in the following groups: Alcoholics; homeless; learning-impaired; patients with cardiovascular, cerebrovascular, or pituitary disorders; those using sedatives or tranquilizers; and elderly patients.
- >700 persons in the U.S. die from hypothermia annually.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The clinical presentation varies with the severity of hypothermia. Shivering may be absent if body temperature is <33.3° C (92° F) or in patients taking phenothiazines.

Hypothermia may masquerade as cerebrovascular accident, ataxia, or slurred speech, or the patient may appear comatose or clinically dead. Signs of hypothermia are summarized in Box E1. Physiologic stages of hypothermia:

- Stage HT I: Mild hypothermia (typical core temperature 32.2° C to 35 °C [90° F to 95° F]): Arrhythmias, ataxia
- Stage HT II: Moderate hypothermia (core temperature 28° C to 32.2° C [82.4° F to 90° F]):
  1. Progressive decrease of level of consciousness, pulse, cardiac output, and respiration
  2. Fibrillation, dysrhythmias (increased susceptibility to ventricular tachycardia)
  3. Elimination of shivering mechanism for thermogenesis
- Stage HT III: Severe hypothermia (core temperature ≤28° C to 24° C [82.4° F to 75° F]):
  1. Absence of reflexes or response to pain
  2. Decreased cerebral blood flow, decreased CO_2
  3. Increased risk of ventricular fibrillation or asystole
  4. Vital signs present
- Stage IV: No vital signs (core temperature <24° C [75° F])

ETIOLOGY

Exposure to cold temperatures for a prolonged period. Contributing factors include:

- Drugs: Ethanol, phenothiazines, sedative-hypnotics
- Skin disorders: Extensive burns, severe psoriasis, exfoliative dermatitis
- Metabolic disorders: Hypopituitarism, hypothyroidism, hypoadrenalism
- Neurologic abnormalities: Stroke, head trauma, acute spinal cord transection, impaired shivering
- Other: Lack of acclimatization, aggressive fluid resuscitation, sepsis, heat stroke treatment
- Box E2 summarizes factors predisposing to hypothermia

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- It is crucial to determine an accurate core temperature measurement. Advantages and considerations of various methods to determine core temperature are summarized in Table 1. Core temperature is best monitored with an esophageal probe. Rectal and bladder temperature generally lag behind core temperatures during the rewarming process
- Cerebrovascular accident
- Myxedema coma
- Drug intoxication
- Hypoglycemia

LABORATORY TESTS

- Metabolic and respiratory acidosis are usually present.
  1. When blood cools, the arterial pH increases, oxygen tension (Po_2) increases, and the pCO_2 falls. Temperature correction factors for arterial blood gas specimens are summarized in Box 3.
  2. Blood gas analyzers warm the blood to 37° C (98.6° F), increasing the partial pressure of dissolved gases, resulting in higher oxygen and carbon dioxide levels and a lower pH than the patient's actual values. A decrease in K^+ initially, then an increase in K^+ with increasing hypothermia; extreme hyperkalemia indicates a poor prognosis.
- Hematocrit increases (caused by hemoconcentration), decreasing leukocytes and platelets (caused by splenic sequestration).
- Blood viscosity, increased clotting time.

IMAGING STUDIES

- Chest x-ray: Generally not helpful; may reveal evidence of aspiration (e.g., intoxicated patient with aspiration pneumonia).

TABLE 1 Core Temperature Measurements

Type	Advantages	Considerations
Rectal	Convenient	Insert 15 cm (6 inches)
	Continuous monitoring	Lags during transition from cooling to rewarming
		Falsely elevated with peritoneal lavage
		Falsely low if probe is in cold feces or when lower extremities are frozen
Esophageal	Convenient	Insert 24 cm (9.5 inches) below larynx
	Continuous monitoring	Tracheal misplacement
		Aspiration
		Falsely elevated with heated inhalation
Tympanic	Approximates hypothalamic temperature via internal carotid artery	Probe: Tympanic membrane perforation; canal hemorrhage Infrared: Unreliable; cerumen effect
Bladder	Convenient	Unreliable
	Continuous monitoring	Falsely elevated with peritoneal lavage
		Falsely low with cold diuresis

From Auerbach P: *Wilderness medicine, expert consult premium edition—enhanced online features and print,* Philadelphia, 2012, WB Saunders.

BOX 3 Temperature Correction Factors for Arterial Blood Gas Specimens*

ABG Component Correction Factor

$pH + 0.015 (37 - T_c)$

$Pa_{O_2} - 0.072 (37 - T_c) \times Pa_{O_2}$

$Pa_{CO_2} - 0.044 (37 - T_c) \times Pa_{CO_2}$

Example

A patient presents with a core temperature of 32° C with the following ABG values: pH 7.12, Pa_{CO_2} 52 mm Hg, and Pa_{O_2} 52 mm Hg. Corrections for temperature are as follows:

$pH = 7.12 + [0.015 (37 - 32)] = 7.195$

$Pa_{O_2} = 52 - [0.072 (37 - 32) \times 52] = 33.28$ mm Hg

$Pa_{CO_2} = 52 - [0.044 (37 - 32) \times 52] = 40.56$ mm Hg

These corrections also may be used for hyperthermia.

*Arterial blood gas values not corrected for temperature in significantly hypothermic patients yield falsely low pH and falsely elevated Pa_{CO_2} and Pa_{O_2} values.

ABG, Arterial blood gas; Pa_{O_2}, partial pressure of oxygen; Pa_{CO_2}, partial pressure of arterial carbon dioxide; T_c, core temperature.

From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

FIG. 1 Hypothermic J waves (Osborne waves) *(arrows)* in an 80-yr-old man with core temperature of 86° F (30° C). These waves disappeared with rewarming.

BOX 4 Preparing Hypothermic Patients for Transport

1. The patient must be dry. Gently remove or cut off wet clothing and replace it with dry clothing or a dry insulation system. Keep the patient horizontal, and do not allow exertion or massage of the extremities.
2. Stabilize injuries (i.e., the spine; place fractures in the correct anatomic position). Open wounds should be covered before packaging.
3. Initiate heated intravenous infusions (IVs) if feasible; bags can be placed under the patient's buttocks or in a compressor system. Administer a fluid challenge.
4. Active rewarming should be limited to heated inhalation and truncal heat. Insulate hot water bottles in stockings or mittens, and then place them in the patient's axillae and groin.
5. The patient should be wrapped. Begin building the wrap by placing a large plastic sheet on the available surface (floor, ground), and on it place an insulated sleeping pad. A layer of blankets, a sleeping bag, or bubble wrap insulating material is laid over the sleeping pad. The patient is then placed on the insulation. Heating bottles are put in place along with IVs, and the entire package is wrapped layer over layer, with the plastic as the final closure. The patient's face should be partially covered, but a tunnel should be created to allow access for breathing and monitoring.

From Auerbach P: *Wilderness medicine, expert consult premium edition—enhanced online features and print,* Philadelphia, 2012, Elsevier.

- ECG: Prolonged PR, QT, and QRS segments, depressed ST segments, inverted T waves, atrioventricular block, and hypothermic J waves (Osborne waves) may appear at temperatures less than 33.0° C (91.4° F); characterized by notching of the junction of the QRS complex and ST segments (Fig. 1).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- The first critical step in management of accidental hypothermia is initiating passive external rewarming by removing wet clothing and covering the patient with insulating material.
- Specific treatment of hypothermia varies with the following:
  1. Degree of hypothermia.
  2. Existence of concomitant diseases (e.g., cardiovascular insufficiency).
  3. Patient's age and medical condition (e.g., elderly, debilitated patients vs. young, healthy patients).
- General measures:
  1. Secure an airway before warming all unconscious patients; precede endotracheal intubation with oxygenation (if possible) to minimize the risk of arrhythmias during the procedure.
  2. Peripheral vasoconstriction may impede placement of a peripheral intravenous catheter; consider femoral venous access as an alternative to the jugular or subclavian sites to avoid ventricular stimulation.
  3 A Foley catheter should be inserted, and urinary output should be monitored and maintained >0.5 to 1 ml/kg/hr with intravascular volume replacement.
  4. Box 4 summarizes measures for preparing hypothermic patients for transport.

ACUTE GENERAL Rx

- Continuous ECG monitoring of patients is recommended. Ventricular arrhythmias can be treated with bretylium; lidocaine is generally ineffective, and procainamide is associated with an increased incidence of ventricular fibrillation in hypothermic patients.
- Correct severe acidosis and electrolyte abnormalities.
- Hypothyroidism, if present, should be promptly treated (see "Myxedema Coma").
- If clinical evidence suggests adrenal insufficiency, administer IV methylprednisolone.

In patients unresponsive to verbal or noxious stimuli or with altered mental status, 100 mg of thiamine, 0.4 mg of naloxone, and 1 ampule of 50% dextrose may be given.

Warm (104° F to 113° F [40° C to 45° C]), humidified oxygen should also be given if available.

- Specific treatment:
  1. Mild hypothermia (rectal temperature <32.3° C [90° F]): Passive external rewarming is indicated. Place the patient in a warm room (temperature >21° C [69.8° F]), and cover with insulating material after gently removing wet clothing; recommended rewarming rates vary between 0.5° C/hr and 20° C/hr (32.9° F/hr and 68° F/hr) but should not exceed 0.55° C/hr (32.99° F/hr) in elderly persons
  2. Moderate to severe hypothermia:
     a. Active core rewarming
        (1) Delivery of heat by way of fluids: Warm gastrointestinal irrigation (with saline enemas and by nasogastric tube); IV fluids (usually D_5NS without potassium) warmed to 104° F to 107.6° F (40° C to 42° C), peritoneal dialysis with dialysate heated to 40.5° C to 42.5° C (104.9° F/hr to 108.5° F/hr)
        (2) Inhalation of heated, humidified oxygen (warmed to 40° C [104° F]) increases core temperature by 1° C (1.8° F) per hr and decreases evaporative heat loss from respiration
  3. Active external rewarming: Immersion in a bath of warm water (40° C to 41° C); active external rewarming may produce shock because of excessive peripheral vasodilation. Ideal candidates are previously healthy, young patients with acute immersion hypothermia.
  4. Extracorporeal blood warming with cardiopulmonary bypass appears to be an efficacious rewarming technique in young, otherwise healthy persons.
  5. Patients with cardiac instability and those in cardiac arrest should be transported to a center capable of providing extracorporeal membrane oxygenation (ECMO) unless other conditions (e.g., trauma) require transport to a closer facility.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Hypothermia (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READING

Brown DJA et al: Accidental hypothermia, *N Engl J Med* 367:1830-1838, 2012.

BOX E1 Signs of Hypothermia

Head, Eye, Ear, Nose, Throat
- Mydriasis
- Decreased corneal reflexes
- Extraocular muscle abnormalities
- Erythropsia
- Flushing
- Facial edema
- Epistaxis
- Rhinorrhea
- Strabismus

Cardiovascular
- Initial tachycardia
- Subsequent tachycardia
- Arrhythmias
- Decreased heart tones
- Hepatojugular reflux
- Jugular venous distention
- Hypotension
- Peripheral vasoconstriction

Respiratory
- Initial tachypnea
- Adventitious sounds
- Bronchorrhea
- Progressive hypoventilation
- Apnea

Gastrointestinal
- Ileus
- Constipation
- Abdominal distention or rigidity
- Poor rectal tone
- Gastric dilation in neonates or in adults with myxedema
- Vomiting

Genitourinary
- Anuria
- Polyuria
- Oliguria
- Testicular torsion

Neurologic
- Depressed level of consciousness
- Ataxia
- Dysarthria
- Amnesia
- Anesthesia
- Areflexia
- Poor suck reflex
- Hypoesthesia
- Antinociception
- Initial hyperreflexia
- Hyporeflexia
- Central pontine myelinolysis

Psychiatric
- Impaired judgment
- Perseveration
- Mood changes
- Peculiar "flat" affect
- Altered mental status
- Paradoxical undressing
- Neuroses
- Psychoses
- Suicide
- Organic brain syndrome
- Anorexia nervosa
- Depression
- Apathy
- Irritability

Musculoskeletal
- Increased muscle tone
- Shivering
- Rigidity or pseudo-rigor mortis
- Paravertebral spasm
- Opisthotonos
- Compartment syndrome

Dermatologic
- Erythema
- Pallor
- Cyanosis
- Icterus
- Scleral edema
- Ecchymosis
- Edema
- Pernio
- Frostnip
- Frostbite
- Panniculitis
- Cold urticaria
- Necrosis
- Gangrene

From Auerbach P: *Wilderness medicine, expert consult premium edition—enhanced online features and print,* Philadelphia, 2012, WB Saunders.

BOX E2 Factors Predisposing to Hypothermia

Decreased Heat Production
Endocrinologic Failure
- Hypopituitarism
- Hypoadrenalism
- Hypothyroidism
- Lactic acidosis
- Diabetic and alcoholic ketoacidosis

Insufficient Fuel
- Hypoglycemia
- Malnutrition
- Marasmus
- Kwashiorkor
- Extreme physical exertion

Neuromuscular Physical Exertion
- Age extremes
- Impaired shivering
- Inactivity
- Lack of adaptation

Impaired Thermoregulation
Peripheral Failure
- Neuropathies
- Acute spinal cord transection
- Diabetes

Central or Neurologic Failure
- Cardiovascular accident
- Central nervous system trauma
- Toxicologic effects
- Metabolic failure
- Subarachnoid hemorrhage
- Pharmacologic effects
- Hypothalamic dysfunction
- Parkinson disease
- Anorexia nervosa
- Cerebellar lesion
- Neoplasm
- Congenital intracranial anomalies
- Multiple sclerosis
- Hyperkalemic periodic paralysis

Increased Heat Loss
Environmental
- Immersion
- Nonimmersion

Induced Vasodilation
- Pharmacologic effects
- Toxicologic effects

Erythrodermas
- Burns
- Psoriasis
- Ichthyosis
- Exfoliative dermatitis

Iatrogenic
- Emergency childbirth
- Cold infusions
- Heatstroke treatment

Miscellaneous Associated Clinical States
- Multisystem trauma
- Recurrent hypothermia
- Episodic hypothermia
- Shapiro syndrome
- Infections: Bacterial, viral, parasitic
- Pancreatitis
- Carcinomatosis
- Cardiopulmonary disease
- Vascular insufficiency
- Uremia
- Paget disease
- Giant cell arteritis
- Sarcoidosis
- Shaken baby syndrome
- Systemic lupus erythematosus
- Wernicke-Korsakoff syndrome
- Hodgkin disease
- Shock
- Sickle cell anemia
- Sudden infant death syndrome

From Auerbach P: *Wilderness medicine, expert consult premium edition-enhanced online features and print,* Philadelphia, 2012, WB Saunders.

BASIC INFORMATION

DEFINITION

Hypothyroidism is a disorder caused by the inadequate secretion of thyroid hormone.

SYNONYM

Myxedema

ICD-10CM CODES

E00.9	Congenital iodine-deficiency syndrome, unspecified
E02	Subclinical iodine-deficiency hypothyroidism
E03.0	Congenital hypothyroidism with diffuse goiter
E03.1	Congenital hypothyroidism without goiter
E03.2	Hypothyroidism due to medicaments and other exogenous substances
E03.3	Postinfectious hypothyroidism
E03.8	Other specified hypothyroidism
E03.9	Hypothyroidism, unspecified
E89.0	Postprocedural hypothyroidism

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE & PREVALENCE: 1.5% to 2% of women and 0.2% of men. Overall, about 1 in 300 persons in the U.S. has hypothyroidism.

PREDOMINANT AGE: Incidence of hypothyroidism increases with age; among persons older than 60 yr, 6% of women and 2.5% of men have laboratory evidence of hypothyroidism (thyroid-stimulating hormone [TSH] more than twice normal level).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hypothyroid patients generally present with the following signs and symptoms: Fatigue, lethargy, weakness, constipation, weight gain, cold intolerance, muscle weakness, slow speech, slow cerebration with poor memory
- Skin: Dry, coarse, thick, cool, sallow (yellow color caused by carotenemia); nonpitting edema in skin of eyelids and hands (myxedema) secondary to infiltration of subcutaneous tissues by a hydrophilic mucopolysaccharide substance (Fig. E1, *A* and *B*)
- Hair: Brittle and coarse; loss of outer third of eyebrows
- Faces: Dulled expression, thickened tongue, thick and slow-moving lips
- Thyroid gland: May or may not be palpable (depending on the cause of the hypothyroidism)
- Heart sounds: Distant, possible pericardial effusion
- Pulse: Bradycardia
- Neurologic: Delayed relaxation phase of the deep tendon reflexes, cerebellar ataxia, hearing impairment, poor memory, peripheral neuropathies with paresthesia
- Musculoskeletal: Carpal tunnel syndrome, muscular stiffness, weakness

ETIOLOGY

- Primary hypothyroidism (thyroid gland dysfunction): The cause of >90% of the cases of hypothyroidism
  1. Hashimoto thyroiditis is the most common cause of hypothyroidism after age 8 yr
  2. Idiopathic myxedema (nongoitrous form of Hashimoto thyroiditis)
  3. Previous treatment of hyperthyroidism (radioiodine therapy, subtotal thyroidectomy)
  4. Subacute thyroiditis
  5. Radiation therapy to the neck (usually for malignant disease)
  6. Iodine deficiency or excess
  7. Drugs (lithium, para-aminosalicylate, sulfonamides, phenylbutazone, amiodarone, thiourea)
  8. Congenital (approximately one case per 2000 to 4000 live births)
  9. Prolonged treatment with iodides
- Secondary hypothyroidism: Pituitary dysfunction, postpartum necrosis, neoplasm, infiltrative disease-causing deficiency of TSH
- Tertiary hypothyroidism: Hypothalamic disease (granuloma, neoplasm, or irradiation causing deficiency of thyrotropin-releasing hormone)
- Tissue resistance to thyroid hormone: Rare

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Depression
- Dementia from other causes
- Systemic disorders (e.g., nephrotic syndrome, congestive heart failure, amyloidosis)

LABORATORY TESTS

- TSH, free T4, thyroid peroxidase antibodies (TPOAB).
- Increased TSH: TSH may be normal if patient has secondary or tertiary hypothyroidism, is receiving dopamine or corticosteroids, or the level is obtained after severe illness.
- Decreased free T4 in hypothyroidism, normal free T4 in subclinical hypothyroidism.
- Other common laboratory abnormalities: Hyperlipidemia, hyponatremia, and anemia.
- Increased antimicrosomal and antithyroglobulin antibody titers: Useful when autoimmune thyroiditis is suspected as the cause of the hypothyroidism. The American Thyroid Association recommends treatment of pregnant patients with subclinical hypothyroidism and anti-thyroid peroxidase (anti-TPO) antibody positivity.
- Fig. 2 describes a strategy for the laboratory evaluation of patients with suspected hypothyroidism.

TREATMENT

NONPHARMACOLOGIC THERAPY

Patients should be educated regarding hypothyroidism and its possible complications. Patients should also be instructed about the need for lifelong treatment and monitoring of their thyroid abnormality.

ACUTE GENERAL Rx

Start replacement therapy with levothyroxine (L-thyroxine) 25 to 100 μg/day, depending on the patient's age and the severity of the disease. Physiologic combinations of L-thyroxine plus liothyronine do not offer any objective advantage over L-thyroxine alone. The levothyroxine dose may be increased every 6 to 8 wk, depending on the clinical response and serum TSH level. Elderly patients and patients with coronary artery disease should be started with 12.5 to 25 μg/day (higher doses may precipitate angina). The average maintenance dose of levothyroxine is 1.7 μg/kg/day (100 to 150 μg/day in adults). The elderly may require <1 μg/kg/day, whereas children generally require higher doses (up to 3 to 4 μg/kg/day). Pregnant patients also have increased requirements. Estrogen therapy may also increase the need for thyroxine. Women with hypothyroidism should increase their levothyroxine dose by approximately 30% as soon as pregnancy is confirmed. Close monitoring of serum thyrotropin levels and adjustment of levothyroxine dose to maintain a TSH level of 4.0 mU/L as upper limit is recommended throughout pregnancy. Table 1 summarizes conditions that alter levothyroxine requirements.

CHRONIC Rx

- Periodic monitoring of TSH level is an essential part of treatment. Patients should be evaluated initially with office visit and TSH levels every 6 to 8 wk until the patient is clinically euthyroid and the TSH level is normalized. The frequency of subsequent visits and TSH measurement can then be decreased to every 6 to 12 mo. Pregnant patients should be checked every trimester.
- For monitoring therapy in patients with central hypothyroidism, measurement of serum free thyroxine (free T4 level) is appropriate and should be maintained in the upper half of the normal range.

REFERRAL

Admission to the hospital intensive care unit is recommended in all patients with myxedema coma. Additional information on the diagnosis and treatment of this life-threatening complication of hypothyroidism is available under "Myxedema Coma" in Section I.

PEARLS & CONSIDERATIONS

COMMENTS

Subclinical hypothyroidism occurs in as many as 20% of elderly patients and is characterized by an elevated serum TSH and a normal free T_4 level. Subclinical hypothyroidism can progress to overt hypothyroidism, especially if antithyroid antibodies are present. It is associated with an increased risk of coronary heart disease events and mortality, particularly in those with a TSH concentration of 10 mU/L or greater. Treatment is individualized and controversial.

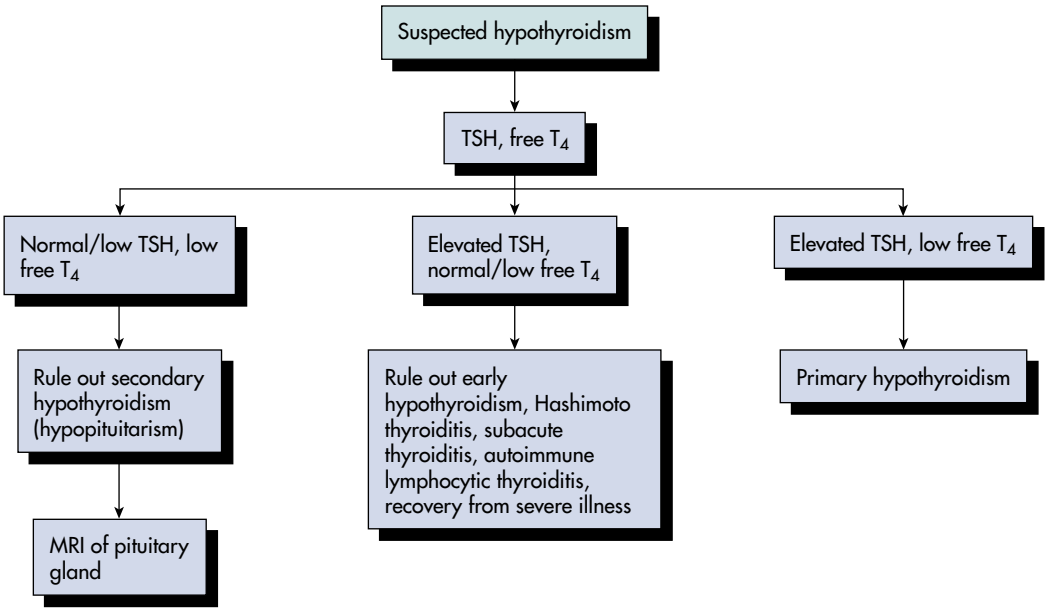

FIG. 2 Strategy for the laboratory evaluation of patients with suspected hypothyroidism. The principal differential diagnosis is between primary and central hypothyroidism. The serum thyrotropin *(TSH)* concentration is the critical laboratory determination that, in general, allows recognition of the cause of the disease. An exception is the individual with a recent history of thyrotoxicosis (and suppressed TSH), in whom a low free thyroxine (T_4) level may be associated with a reduced TSH level for several mo after relief of the thyrotoxicosis. In patients with primary hypothyroidism, the absence of thyroid peroxidase (TPO) antibodies raises a possible diagnosis of transient hypothyroidism after an undiagnosed episode of subacute or postviral thyroiditis. In such patients, a trial of levothyroxine in reduced dosage after 4 mo may reveal recovery of thyroid function, thus avoiding permanent levothyroxine replacement. *MRI,* Magnetic resonance imaging. (From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders.)

TABLE 1 Conditions That Alter Levothyroxine Requirements

Increased Levothyroxine Requirements
Pregnancy
Gastrointestinal Disorders
Mucosal diseases of the small bowel (e.g., sprue)
After jejunoileal bypass and small-bowel resection
Impaired gastric acid secretion (e.g., atrophic gastritis)
Diabetic diarrhea
Drugs That Interfere with Levothyroxine Absorption
Cholestyramine
Sucralfate
Aluminum hydroxide
Calcium carbonate
Ferrous sulfate
Drugs That Increase the Cytochrome P450 Enzyme (CYP3A4) Activity
Rifampin
Carbamazepine
Estrogen
Phenytoin
Sertraline
Drugs That Block T_4-to-T_3 Conversion
Amiodarone
Conditions That May Block Deiodinase Synthesis
Selenium deficiency
Cirrhosis
Decreased Levothyroxine Requirements
Aging (≥65 yr)
Androgen therapy in women

T_3, Triiodothyronine; *T_4,* thyroxine.
(From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders.)

Some trials[1] have shown that levothyroxine provides no apparent benefit in older persons with subclinical hypothyroidism. The management of subclinical hypothyroidism should be individualized on the basis of TSH level, comorbid conditions, risk factors, and patient preference. In general, replacement therapy is recommended by most physicians for patients with serum TSH >10 mU/L and with presence of goiter or thyroid autoantibodies or patient has risk factors.

Congenital hypothyroidism is a pediatric disorder with an observed prevalence of one in 2000 to 4000 live births in the U.S. Screening is conducted in all newborns in all states and accomplished by measuring TSH from dried whole blood spots collected on a newborn by heel stick within the first 24 to 48 hours of life. Currently 14 states perform a routine second screen at approximately 2 wk of age. A two-screen approach is preferred because retrospective analysis found that 20% of congenital hypothyroidism cases were in infants who had normal TSH on the first screen but elevated TSH concentrations on the second screen.

[1]Stott DJ et al: Thyroid hormone therapy for older adults with subclinical hypothyroidism, *N Engl J Med* 376:2534-2544, 2017.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hypothyroidism (Patient Information)
Myxedema Coma (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

FIG. E1 **A** and **B,** Typical appearance of patients with moderately severe primary hypothyroidism or myxedema. Notice the dry skin and sallow complexion; absence of scleral pigmentation differentiates the carotenemia from jaundice. Both individuals demonstrate periorbital myxedema. The patient in **B** illustrates the loss of the lateral aspect of the eyebrow, sometimes termed *Queen Anne sign.* That finding is not unusual in the age group that is commonly affected by severe hypothyroidism and should not be considered a specific sign of the condition. (From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders.)

SUGGESTED READINGS

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ID Reaction

BASIC INFORMATION

DEFINITION

ID reaction refers to an acute dermatitis developing at cutaneous sites distant from a primary inflammatory focus (Fig. E1) and is not explained by the inciting primary inflammation.

SYNONYM

Autoeczematization

ICD-10CM CODES

L30.2	Cutaneous autosensitization
L30.8	Other specified dermatitis
L30.9	Dermatitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Exact prevalence in the U.S. is unknown.
- Seen in all ages.
- Males and females are equally affected.
- No particular race or ethnicity is more vulnerable.

ETIOLOGY

Infection with dermatophytes, mycobacterium, histoplasma, viruses, bacteria, or parasites (e.g., lice):

- Dermatitis such as contact, stasis, or eczematous.
- Other causes include retained sutures, ionizing radiation, and blunt trauma.

PATHOGENESIS

Unknown but possible explanations include:

- Abnormal immune recognition of autologous skin antigens
- Stimulation of normal T cells by altered skin constituents
- Lowering of the threshold for skin irritation
- Dissemination of infectious antigen resulting in a secondary response
- Hematogenous dissemination of cytokines from the primary site of inflammation

CLINICAL FEATURES

- Usually associated with exacerbation of primary dermatitis.
- Characteristics of the rash in ID reaction include:
  1. Sudden onset of rash appearing within 1 or 2 wk of primary inflammation
  2. The rash could not be identified as a common dermatosis
  3. Lesions are most commonly seen in the side of the fingers. However, ID reaction could be generalized. Particularly in patients with stasis dermatitis, it appears in forearms, thighs, legs, trunk, face (Fig. E2), hands, neck, and feet in descending order of frequency
  4. Extremely pruritic
  5. Often symmetric in distribution
  6. Most of the time it is vesicular
- It resolves upon treatment of primary inflammation.

FIG. E1 ID reaction. Papular eruption of the face associated with severe tinea infection of the hand. (From Kliegman RM: *Nelson Textbook of Pediatrics,* ed 21, Philadelphia, 2020, Elsevier.)

DIAGNOSIS

- It is a clinical diagnosis. The diagnosis should not be made conclusively unless there is an acute inflammatory process at a distant site and the ID reaction disappears shortly after the acute inflammation is controlled.
- Fungus, when suspected, could be isolated only from the primary site by using potassium hydroxide or by using fungal culture.
- At times, skin biopsy is done. The biopsy findings are not pathognomonic for ID reaction. These include spongiotic epidermal vesicles associated with superficial perivascular lymphocytic infiltration of dermis, which may also contain scattered eosinophils. Whereas most of the lymphocytes in the epidermis are CD3 and CD8 T cells, those in the dermis are primarily CD4 cells.
- Patch testing may be considered to exclude primary or secondary allergic contact dermatitis.

DIFFERENTIAL DIAGNOSIS

- Atopic dermatitis
- Contact dermatitis
- Drug eruptions
- Dyshidrotic eczema
- Folliculitis
- Scabies
- Dermatophytic infection
- Viral exanthema

TREATMENT

- The treatment is best directed toward the inciting cause.
- Medications used for symptomatic treatment of ID reaction include:
  1. Local or systemic steroids
  2. Local or systemic antihistamines
  3. Topical or systemic antibiotics for secondary bacterial infection
  4. Aluminum sulfate or calcium acetate for weeping skin lesions
  5. Rarely, local or systemic macrolactams (e.g., cyclosporine)

COMPLICATION

Secondary bacterial infection

PROGNOSIS

It almost always resolves within days when the primary dermatitis is adequately treated.

PATIENT & FAMILY EDUCATION

Treat primary dermatitis promptly.

AUTHOR: **Fred F. Ferri, MD**

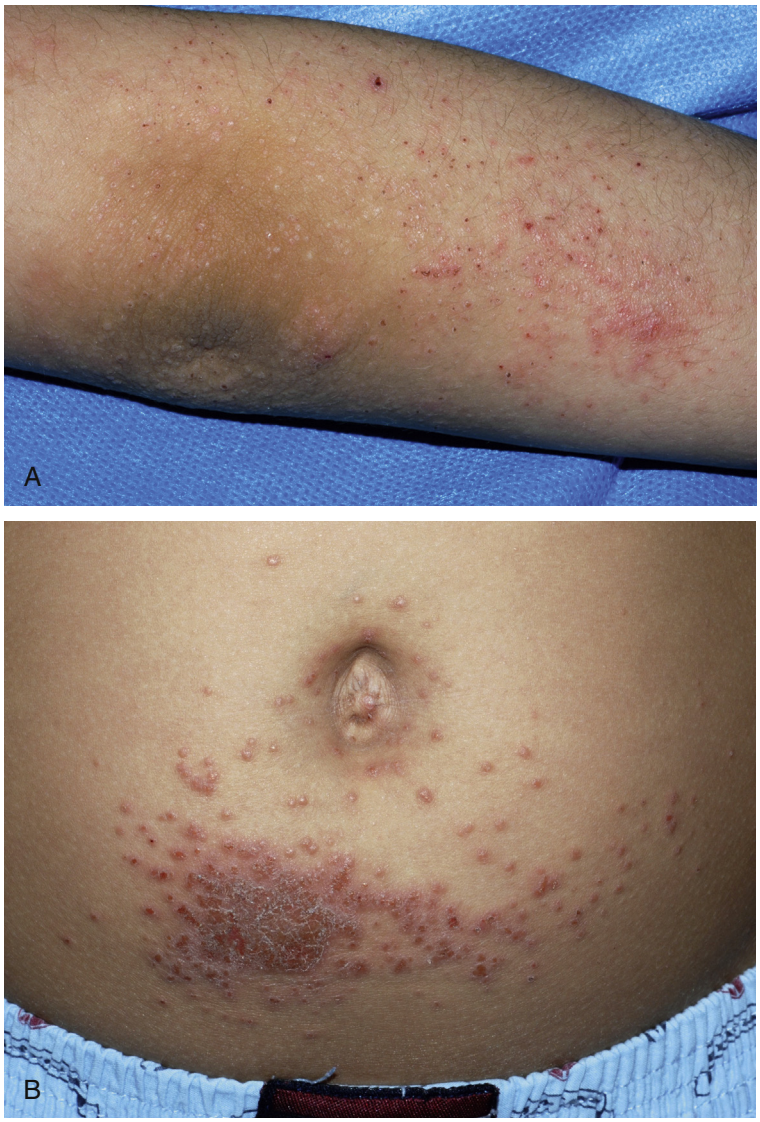

FIG. E2 ID reactions in children due to allergic contact dermatitis (ACD) to nickel. A, Multiple flat-topped papules, several of which have been excoriated, in addition to patches of eczema. **B,** Square-shaped area of ACD due to nickel in a buckle with an associated ID reaction. The latter consists of edematous crusted papules that are separate from the area of direct nickel contact. (From Bolognia JL et al: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.)

Idiopathic Intracranial Hypertension

BASIC INFORMATIONS

DEFINITION

Idiopathic intracranial hypertension (IIH) is a syndrome of increased intracranial pressure (ICP) without either underlying hydrocephalus or mass lesion and with normal cerebrospinal fluid analysis.

SYNONYMS

Pseudotumor cerebri
IIH
Benign intracranial hypertension

ICD-10CM CODE
G93.2 Benign intracranial hypertension

EPIDEMIOLOGY & DEMOGRAPHICS

- 90% of affected persons are women of childbearing age with elevated body mass index (BMI).

INCIDENCE:

- General population: 1 to 2 per 100,000 (including children)
- Women (obese females in reproductive age group): 20 per 100,000
- Men: 0.3 to 1.5 cases per 100,000
- Female:male ratio 9:1
- More than 90% of IIH patients are obese
- Mean age at diagnosis is 30 yr

RISK FACTORS:

- Obesity
- Medications: Vitamin A and retinoids (used in treatment of acne and leukemia), chronic oral medications used for acne (tetracycline, minocycline), glucocorticoid use or withdrawal
- Systemic conditions: Chronic kidney disease, polycystic ovarian syndrome, obstructive sleep apnea

PHYSICAL FINDINGS & CLINICAL PRESENTATION

SYMPTOMS:

- Headaches: Generalized, throbbing, slowly progressive, worse with straining maneuvers, worse in the morning
- Transient visual obscuration: A brief blurring of vision or scotomata lasting <30 sec; occurs with postural changes, Valsalva maneuver; may be monocular
- Double vision: Usually due to sixth nerve palsy
- Pulsatile tinnitus: Described as a "whooshing sound" that is synchronous with heartbeat; classic symptom that indicates raised ICP
- Photopsia: Lights, sparkles in the eyes
- Pain: Mainly retroorbital. Pain may also be located in the shoulders or neck. Could be present without a headache. Low back pain with radiation along the lower extremities (radicular) may be seen

SIGNS:

- Papilledema: Seen in virtually all cases; usually bilateral but may be asymmetric
- Sixth nerve palsy: Seen in approximately 10% to 20% of patients; considered to be a nonlocalizing neurologic sign
- Visual field defects: Include enlarged physiologic blind spot, nasal field defects, and constricted visual fields. Up to 90% of patients exhibit some form of visual loss on perimetry
- Loss of central vision: End result of longstanding and untreated IIH

ETIOLOGY

- The exact etiology remains unknown.
- Proposed pathophysiologic mechanisms underlying the raised ICP include increased brain water content, excess cerebrospinal fluid (CSF) production, reduced CSF absorption, and increased cerebral venous pressure either alone or in combination.
- Another proposed mechanism includes abnormal vitamin A metabolism leading to increased CSF retinol levels and decreased CSF absorption at the arachnoid granulations.

DIAGNOSIS

DIAGNOSTIC CRITERIA

MODIFIED DANDY CRITERIA FOR DIAGNOSIS OF IIH:

- Signs and symptoms of raised ICP (listed above)
- Absence of localizing focal neurologic signs (except sixth nerve palsy)
- CSF opening pressure of 25 cm H_2O or more with normal CSF composition
- Normal neuroimaging studies (MRI and magnetic resonance venography [MRV] brain) including absence of cerebral venous thrombosis; stenosis of transverse sinuses may be seen in IIH without thrombosis

DIFFERENTIAL DIAGNOSIS

- IIH is a diagnosis of exclusion and criteria listed above have to be satisfied.
- Causes of papilledema include intracranial space-occupying lesions such as tumors, abscesses, hematoma; venous sinus thrombosis; low CSF pressure; carcinomatous meningitis; chronic meningitides such as neurosarcoidosis, central nervous system (CNS) lupus, neurosyphilis, cryptococcal meningitis, and tuberculous meningitis.

WORKUP

- Neuroimaging studies: MRI of brain with MR head venogram; CT head and CT head venogram when MRI of brain cannot be obtained.
- Lumbar puncture: CSF opening pressure (OP) should be obtained in the lateral decubitus position with the legs stretched and patient relaxed. Diagnosis is confirmed by a CSF opening pressure >250 mm H_2O with normal fluid composition.
- Ophthalmologic examination: All patients with IIH need an ophthalmologic examination including visual fields at baseline and follow-up visits. Enlargement of the blind spot and reduction in peripheral fields are commonly seen.

LABORATORY TESTS

CSF analysis shows normal protein, glucose, and cell count.

IMAGING STUDIES

- MRI of the brain to rule out underlying structural lesions
  1. Absence of specific causes of raised ICP listed previously
  2. Empty sella sign often associated with chronic raised ICP but not pathognomonic
- MR or CT venography to exclude cortical venous thrombosis
  1. May show transverse sinus stenosis in IIH without thrombosis. Absence of specific causes of raised ICP listed previously
- CT head
  1. May show slit-like ventricles

TREATMENT

NONPHARMACOLOGIC THERAPY

- Treatment is aimed primarily at preservation of vision
- Weight loss in obese patients
- Continuous positive airway pressure if obstructive sleep apnea is suspected

ACUTE GENERAL Rx

- Acetazolamide 250 mg to 4 g per day: Reduces CSF production by inhibition of carbonic anhydrase, occasionally causing anorexia and resultant weight loss. Dose can be increased to a maximum of 4 g a day in resistant cases with visual loss.
- Furosemide 40 to 120 mg/day in divided doses: Apparent mechanism of action is by reduced sodium transport, leading to decreased total CSF volume.
- Topiramate 100 to 400 mg/day: Reported to be effective in treatment of IIH. It is a weak carbonic anhydrase inhibitor with weight loss as one of its primary side effects.
- Serial lumbar punctures (LP): SHOULD NOT BE CONSIDERED AS STANDARD TREATMENT OF IIH. LP should be attempted in patients with severe headaches resistant to medical therapy. Goal is to reduce spinal fluid pressure to allow immediate reduction in headache severity. This treatment should be reserved for the most resistant cases and should be used as a conduit to future surgical intervention. Serial LP should not be used as treatment for IIH with progressive visual loss.

CHRONIC Rx

Surgical intervention is indicated in cases of treatment failure and progressive visual loss.

- Optic nerve fenestration: Preferred for patients with visual loss and easily controlled headaches. Proposed mechanism is decompression of the optic nerve. Highly effective; however, has been associated with significant number of failure rates
- CSF shunting: Neurosurgical procedure; performed in patients with significant visual deterioration and difficult-to-control headaches. Provides rapid improvement in

symptoms; however, reported to have significant rates of shunt revisions because of shunt malfunction

DISPOSITION

- IIH is a potentially blinding condition, with severe vision loss in 5% to 10% of patients; patients should be co-managed by neurologists and ophthalmologists (preferably by a neuro-ophthalmologist). Monthly follow-up is essential until visual fields stabilize. More frequent follow-up is needed in patients with severe papilledema or visual loss at presentation.
- All patients with IIH should undergo MR or CT venography to rule out the possibility of venous sinus thrombosis.

REFERRAL

- Neuroophthalmology for serial evaluation of visual fields and fundus photographs
- Nutritionist for weight loss
- General neurologist for the initial workup and eventual treatment of raised ICP

PEARLS & CONSIDERATIONS

COMMENTS

- IIH is a potentially blinding condition.
- IIH is a diagnosis of exclusion.
- IIH is a disease of young obese women of childbearing age (90% of affected patients).

PREVENTION

Maintenance of ideal body weight is one of the best preventive mechanisms for avoidance of IIH. However, it does occur in patients with normal body weight. In these cases there are no known preventable risk factors.

PATIENT & FAMILY EDUCATION

The combination of weight loss and medical therapy is highly effective in treatment of IIH. Given that most patients with IIH are young and otherwise healthy, high success rates can be accomplished.

RELATED CONTENT

Diplopia (Section II, Differential Diagnosis)
Optic Atrophy (Related Key Topic)

AUTHOR: **Sachin Kedar, MBBS, MD**

SUGGESTED READINGS

Biousse V et al: Update on the pathophysiology and management of idiopathic intracranial hypertension, *J Neurol Neurosurg Psychiatry* 83:488, 2012.

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BASIC INFORMATION

DEFINITION

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic fibrosing interstitial pneumonia with histopathologic characteristics of usual interstitial pneumonia (UIP) occurring in the absence of an identifiable cause of lung injury. Clinically, it is characterized by progressive parenchymal scarring and loss of pulmonary function.

SYNONYMS

Cryptogenic fibrosing alveolitis
IPF
Pulmonary fibrosis
Usual interstitial pneumonia

ICD-10CM CODE
J84.112 Idiopathic pulmonary fibrosis

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence: 7 to 16 cases/100,000 persons worldwide. Clinically IPF affects >50,000 people in the U.S. and accounts for 20% to 30% of interstitial lung diseases. It is the most common idiopathic interstitial pneumonia
- Most commonly presents in sixth and seventh decades
- More common in men than women
- More common in current and past smokers
- Familial forms account for 3% to 25% of cases. Genetic variants: Include mutations in surfactant protein C and telomerase as well as polymorphisms of the *MUC5B* gene
- No distinct geographic distribution; no clear racial predilection

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most present with gradual onset (>6 mo) of exertional dyspnea and nonproductive cough. Progressive dyspnea is usually the most prominent symptom. Cough affects up to 80% of patients with IPF, is frequently disabling, and lacks effective therapy.
- Fine bibasilar inspiratory crackles, "velcro inspiratory crackles" in >80% of patients, with progression upward as the disease advances.
- Clubbing is found in 25% to 50% of patients.
- Cyanosis and right heart failure (cor pulmonale) may occur late in the disease course.
- There are no extrapulmonary manifestations beyond clubbing and complications of right heart failure. Fever and wheezing are rare and suggest alternative diagnosis.
- Fig. E1 is a chest radiograph showing diffuse bilateral lower lung predominant reticular opacities in a patient with IPF.

ETIOLOGY

- Unknown. Fig. 2 illustrates a proposed pathogenetic sequence in IPF.
- Cigarette smoking, environmental exposures, gastroesophageal reflux, and microaspiration have been associated with IPF.
- Aberrant tissue repair and fibrosis are believed to play a greater role in the pathogenesis than generalized inflammation. Immune system activation and increased vascular permeability contribute to the underlying pathology.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Sarcoidosis
- Drug-induced interstitial lung disease
- Pulmonary manifestations of collagen vascular diseases (e.g., rheumatoid arthritis [RA], systemic sclerosis); ILD may be an initial sign of disease
- Hypersensitivity pneumonitis (HP)
- Occupational exposures (e.g., asbestos, silica) may cause pneumoconiosis that mimics IPF
- Other idiopathic interstitial pneumonias:
  1. Desquamative interstitial pneumonia (DIP)
  2. Respiratory bronchitis–interstitial lung disease (RB-ILD)
  3. Acute interstitial pneumonia (AIP)
  4. Nonspecific interstitial pneumonia (NSIP)
  5. Cryptogenic organizing pneumonia (COP)
- IPF is considered a diagnosis of exclusion

WORKUP

- Almost all patients have abnormal chest radiograph at presentation, with bilateral reticular opacities most prominent in the periphery and lower lobes. Peripheral honeycombing may be seen.
- High-resolution CT scan (Fig. 3) is the best diagnostic test. It shows patchy peripheral reticular abnormalities with intralobular linear opacities, irregular septal thickening, subpleural honeycombing, and minimal, if any, ground-glass opacities.
- Pulmonary function testing shows restrictive pattern and reduced carbon monoxide diffusion into the lung.
- Six-minute walk test may show reduced exercise tolerance and/or exertional hypoxia.
- Laboratory abnormalities (nondiagnostic): Mild anemia; increases in erythrocyte sedimentation rate, lactate dehydrogenase, C-reactive protein; low titer antinuclear antibody seen in up to 30% of patients.
- The need for autoimmune serologies is not well defined. Any signs or symptoms that might suggest underlying autoimmunity should be evaluated fully.

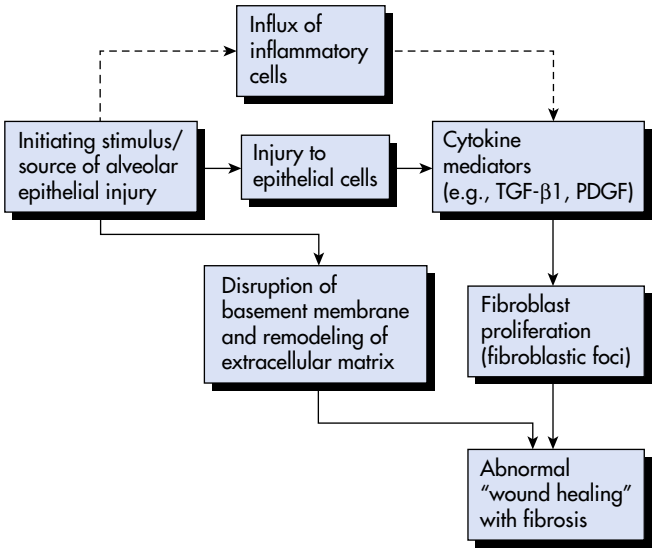

FIG. 2 Proposed pathogenetic sequence in idiopathic pulmonary fibrosis. Dotted lines indicate that although there is an influx of inflammatory cells, this is not thought to be a primary component of pathogenesis. *PDGF,* Platelet-derived growth factor; *TGF-β1,* transforming growth factor-β1. (From Weinberger SE: *Principles of pulmonary medicine,* ed 7, Philadelphia, 2019, Elsevier.)

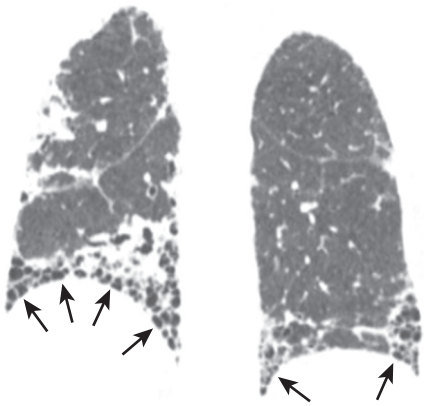

FIG. 3 Pulmonary fibrosis, honeycombing, and a usual interstitial pneumonia (UIP) pattern in idiopathic pulmonary fibrosis (IPF). Coronal high-resolution computed tomography reconstruction shows honeycombing *(arrows)* with a basal and subpleural predominance. This is typical of a UIP pattern. (Webb WR, Brant WE, Major NM: *Fundamentals of body CT,* ed 4, Philadelphia, 2015, Saunders.)

TABLE 1 Summary of Histologic Findings for Immunologic Lung Diseases

Disease	Histology
Granulomatous	
Foreign body, inorganic dust	Simple granuloma
Hypersensitivity pneumonitis	Granulomas with $CD4^+$/$CD8^+$ T cells; interstitial edema; fibrosis in later stages
Infections	
Tuberculosis	Caseating granulomas
Sarcoidosis	Noncaseating granulomas
Granulomatous Vasculitides	
Wegener granulomatosis	Necrotizing granulomas involving vasculature
Churg-Strauss syndrome	Necrotizing granulomas involving vasculature
Eosinophilic pneumonias	Granulomas with eosinophilic predominance; interstitial edema
Histiocytosis X	Granulomas with Langerhans cells
Alveolitic	
Drug-associated injury	Interstitial edema with inflammatory cells
Goodpasture syndrome	Linear staining of basement membrane with anti-IgG antibodies typically seen on renal biopsy; interstitial edema with inflammatory cells
Idiopathic Interstitial Pneumonias	
Idiopathic pulmonary fibrosis	Interstitial edema and/or fibrosis with inflammatory cells; patchy fibrotic change
Desquamative interstitial pneumonia	Interstitial edema with sparse inflammatory cells; mild diffuse fibrotic change
Idiopathic nonspecific interstitial pneumonia	Thickened interstitium with inflammatory cells; some patchy fibrosis
Acute interstitial pneumonia	Diffuse alveolar damage with thickened fibrotic interstitium; proliferating fibroblasts
Respiratory bronchiolitis–associated interstitial lung disease	Macrophages infiltrating distal bronchioles
Cryptogenic organizing pneumonia	Chronically inflamed alveoli with granulation tissue in bronchioles and macrophages in alveoli
Lymphocytic interstitial pneumonia	Diffuse lymphocytic and plasma cell infiltration; minimal alveolar injury
Idiopathic pleuroparenchymal fibroelastosis	Diffuse alveolar damage with fibrosis

From Sellke FW et al: *Sabiston & Spencer surgery of the chest,* ed 9, 2016, Elsevier.

- There is a limited role for bronchoalveolar lavage either in diagnosis or monitoring IPF.
- Gold standard for diagnosis is lung biopsy (open thoracotomy or video-assisted thoracoscopy). Hallmark features: Heterogeneous distribution of parenchymal fibrosis against background of mild inflammation (UIP). In patients with characteristic chest CTs, lung biopsies can be avoided.
- When there is uncertainty, lung biopsy is critical to distinguish IPF from diseases with better prognosis and different treatment options.
- Table 1 summarizes histologic findings for immunologic diseases.
- A multidisciplinary approach involving the collaboration of pulmonology, radiology, and pathology to secure a diagnosis is considered standard of care.

Rx TREATMENT

- Two FDA-approved oral therapies have similar proven efficacy in slowing disease progression, but neither elevates patients' perceived quality of life, and both are associated with substantial side effects. Combination therapy with both medications has not been investigated. Pirfenidone is an antifibrotic medication without a known mechanism of action. It is taken three times a day with food. Its major side effects are nausea, abdominal discomfort, and photosensitivity. LFTs require periodic surveillance.
- Nintedanib is a tyrosine kinase inhibitor taken twice daily. Its major side effect is diarrhea, which often resolves. LFTs also need to be followed.
- Additional new therapies are being investigated and are in phase I, II and III testing. Recent trials have shown that adding sildenafil to nintedanib did not improve quality of life or lessen 24-week mortality.[1]
- In patients with advanced disease, treatment options include supportive care (pulmonary rehabilitation, supplemental oxygen, influenza and pneumococcal vaccination) and potential lung transplantation.
- Treatment of asymptomatic gastroesophageal reflux may be reasonable given association between pulmonary fibrosis and reflux or microaspiration.
- Lung transplantation is the only therapy shown to prolong survival in IPF. Guidelines for transplantation by pulmonary disease are summarized in Box 1. Box 2 summarizes absolute contraindications to lung transplantation. Posttransplant 5-yr survival for IPF patients is approximately 50% to 60%. Median survival time is longer after bilateral lung transplantation than single lung transplantation but is associated with more complications during the first yr.
- Acute exacerbation of IPF, defined as worsening dyspnea (<1 mo), the presence of new opacities on radiograph, and the lack of evidence of infection, has a yearly incidence of 10% to 20%. Progressive respiratory failure may require mechanical ventilation; however, a palliative care approach is often chosen instead. Treatment for exacerbations typically includes high-dose corticosteroids and broad-spectrum antibiotics, although the efficacy of this approach is unproven and questionable.

[1]Peljto AL et al: Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis, *JAMA* 309(21):2232-2239, 2013.

DISPOSITION

- Spontaneous remissions do not occur, although long periods of stability can occur.
- Natural history includes progressive loss of pulmonary function. Predictors of poor outcome include older age, male gender, moderately to severely abnormal PFTs and presence of pulmonary hypertension.
- There is an increased risk of lung cancer.
- Mean survival after the diagnosis of biopsy-confirmed IPF is 3 to 5 yr, although with new therapies available, survival is less defined.
- Respiratory failure is the most common cause of death.

REFERRAL

- To pulmonologist for review of abnormal chest imaging and establishing diagnosis.
- Encouraging participation in clinical trials is a priority.
- Early referral for lung transplant.
- Later stage management should include palliative care or hospice services.

PEARLS & CONSIDERATIONS

- The course is progressive, with a high mortality rate. The most common cause of death in IPF is respiratory failure.
- Critical to differentiate IPF from other interstitial lung diseases because prognosis and treatment approaches differ.
- Two oral therapies shown to slow disease progression are available. Combination therapy has not been investigated. Additional novel treatments are being investigated.[2]

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Idiopathic Pulmonary Fibrosis (Patient Information)

AUTHOR: **Peter LaCamera, MD**

[2]Kolb M et al: Nintedanib plus sildenafil in patients with idiopathic pulmonary fibrosis, *N Engl J Med* 379:1722-31, 2018.

BOX 1 Guidelines for Transplantation by Pulmonary Disease

Chronic Obstructive Pulmonary Disease
Patients with a BODE index* of 7 to 10 or at least one of the following:
- History of hospitalization for exacerbation associated with acute hypercapnia (P_{CO_2} >50 mm Hg)
- Pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy
- FEV_1 <20% predicted and either DLCO <20% predicted or homogeneous distribution of emphysema

Cystic Fibrosis and Other Causes of Bronchiectasis
Oxygen-dependent respiratory failure
Hypercapnia
Pulmonary hypertension

Idiopathic Pulmonary Fibrosis and NSIP
Histologic or radiographic evidence of usual interstitial pneumonia and any of the following:
- DLCO <39% predicted
- 10% or greater decrement in FVC during 6 months of follow-up
- A decrease in pulse oximetry below 88% during a 6-MWT
- Honeycombing on high-resolution computed tomography (fibrosis score >2)

Histologic evidence of NSIP and any of the following:
- DLCO <35% predicted
- 10% or greater decrement in FVC or 15% decrease in DLCO during 6 months of follow-up

Pulmonary Arterial Hypertension
Persistent New York Heart Association class III or IV on maximal medical therapy
Low (<350 m) or declining 6-MWT
Failing therapy with intravenous epoprostenol or equivalent
Cardiac index <2 L/min/m^2
Right atrial pressure >15 mm Hg

*BODE index includes body mass index, degree of airflow obstruction (assessed by percent predicted FEV_1), degree of dyspnea (assessed by the modified Medical Research Council [MMRC] dyspnea scale), and exercise capacity (assessed by the 6-minute walk distance). The index increases as body mass index, FEV_1, and distance walked decrease and as the MMRC scale increases.
6-MWT, 6-minute walk test; *DLCO*, diffusing capacity of the lungs for carbon monoxide; *FVC,* forced vital capacity; *NSIP,* nonspecific interstitial pneumonia.
From Sellke FW, del Nido PJ, Swanson SJ: *Sabiston & Spencer surgery of the chest,* ed 9, Philadelphia, 2016, Elsevier.

BOX 2 Absolute Contraindications to Lung Transplantation

- Malignancy within the last 2 yr, with the exception of cutaneous squamous and basal cell carcinomas; the role of lung transplantation in patients with focal pulmonary adenocarcinoma in situ (formerly known as *bronchoalveolar carcinoma*)
- Untreatable advanced dysfunction of another organ system (heart, liver, kidney); coronary artery disease not amenable to percutaneous intervention or bypass grafting, or associated with significant impairment of left ventricular function, is an absolute contraindication to lung transplantation, but heart-lung transplantation could be considered in some cases
- Incurable chronic extrapulmonary infection, including chronic active viral hepatitis B, hepatitis C, and human immunodeficiency virus
- Significant chest-wall or spinal deformity
- Nonadherence or inability to follow through with medical therapy or office follow-up
- Untreatable psychiatric or psychological condition associated with the inability to cooperate or comply with medical therapy
- Absence of a consistent or reliable social support system
- Substance addiction (alcohol, tobacco, or narcotics) that is either active or has been within the last 6 mo

From Sellke FW, del Nido PJ, Swanson SJ: *Sabiston & Spencer surgery of the chest,* ed 9, Philadelphia, 2016, Elsevier.

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Raghu G: An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management, *Am J Respir Crit Care Med* 183:788-824, 2011.

Richeldi L: Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis, *N Engl J Med* 365:1179-1187, 2011.

Richeldi L: Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis, *N Engl J Med* 370:2071-2082, 2014.

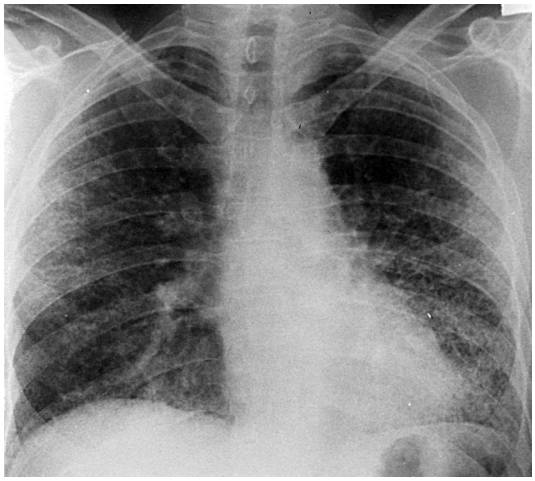

FIG. E1 Chest radiograph shows diffuse bilateral lower lung predominant reticular opacities in a patient with idiopathic pulmonary fibrosis (IPF). (From Mason RJ: *Murray & Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, Saunders.)

IgA Nephropathy ALG

BASIC INFORMATION

DEFINITION

Immunoglobulin A (IgA) nephropathy is a proliferative glomerulonephritis associated with predominant deposition of IgA in the mesangium. IgA deposition may occur in isolation or with IgG, IgM, or both, and often with complement protein C3.

SYNONYMS

Berger disease
IgAN
IgA vasculitis

ICD-10CM CODES

N02.1	Recurrent and persistent hematuria with focal and segmental glomerular lesions
N02.3	Recurrent and persistent hematuria with diffuse mesangial proliferative glomerulonephritis
N02.5	Recurrent and persistent hematuria with diffuse mesangiocapillary glomerulonephritis
N02.7	Recurrent and persistent hematuria with diffuse crescentic glomerulonephritis
N02.8	Recurrent and persistent hematuria with other morphologic changes

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: IgA nephropathy (IgAN) is the most common primary glomerulopathy worldwide. The annual incidence of IgAN in the U.S. is about 1 to 4 cases per 100,000 person-yr. There is a West-to-East increase in incidence and prevalence. There is a very low incidence in Africa relative to the U.S. and a higher incidence in East Asia. In Japan, the incidence is 10 times as high as in the U.S. In Europe, there is a South-to-North increase in incidence, with Nordic populations having more than a twofold greater risk than southern Europeans. Because IgA is the primary gut antibody, the increased incidence and prevalence in Asia has been postulated to be related to geographic differences in dietary exposure to antigens and genetic factors as discussed below.
PREVALENCE: Prevalence data ranges from 1.3% to 16% in the general population based on autopsy studies that demonstrate renal IgA deposits. In most reports, prevalence rates are expressed as a percentage of cases of primary glomerulonephritis or as a percentage of total series of renal biopsies. The prevalence rate in kidney biopsies is lowest in the Middle East (5%), 10% to 35% in Europe, 20% in the U.S., and 32% to 54% in Japan and China, reflecting the West-to-East increase in incidence and prevalence. Lower rates may be biased by a more conservative approach by U.S. nephrologists reluctant to perform kidney biopsies in asymptomatic patients with minimal renal abnormalities compared with screening programs in Japan.
PREDOMINANT SEX AND AGE: IgAN is most prevalent in the second and third decades of life with a male:female ratio of 2:1 in the U.S. and 3:1 ratio in Europe. In East Asia, the male:female ratio is closer to 1:1.
GENETICS AND PATHOGENESIS: The primary defect is systemic aberrant glycosylation resulting in galactose-deficient IgA1 (Gd-IgA1) in the serum, a heritable trait in diverse racial and ethnic groups. The genetic predisposition is confirmed by the presence of elevated Gd-IgA1 serum levels in a quarter of relatives of patients with IgAN . The Gd-IgA1 binds autoantibody IgG generating nephritogenic immune complexes.

Although a sporadic disease in more than 90% of cases, recent genome-wide association studies have identified 6% to 8% of cases with at least 15 susceptibility loci, with the strongest signal from the major histocompatibility complex (MHC) region of chromosome 6. Certain loci are more prevalent in Asia compared with the U.S. and Europe. Geospatial analysis of the genetic risk in 85 worldwide populations mirrors the West-to-East worldwide pattern and South-to-North European distribution of the disease. In addition, Asian Americans have a fourfold higher end-stage renal disease incidence than European Americans and a seven fold higher end-stage renal disease incidence than African Americans, reflecting the genetic basis for this disease. An interesting theory is that the greater prevalence of risk alleles in East Asians may have been selected to protect against intestinal helminthic infestation.

There is abnormal alternative pathway complement activation in IgAN. Recent studies have examined factor H-related (FHR) proteins that interfere with factor H, a major negative regulator of C3 activation. FHR-1 proteins are elevated in IgAN and associated with progressive disease. Patients with two copies of the CFHR1 gene had greater FHR-1 levels, implicating potential genetics of factor H dysregulation causing or worsening IgA nephropathy. More recently the role of B-cell activation factor (BAF) of the tumor necrosis factor family and T-cell cytokine APRIL are considered important to disease pathogenesis.
RISK FACTORS: There are greater associations in Asians, whites, and Native Americans, but IgAN is relatively rare in African Americans. IgAN is more common in males outside East Asia.

Renal outcomes: The most robust risk factors and predictors of poor renal outcomes include older age, hypertension, proteinuria >1 g/day, and decreased glomerular filtration rate (GFR) at time of diagnosis. Lower hemoglobin and albumin recently have been shown as robust poor outcome risk factors. Pathologic risk factors for poor renal outcomes include increased mesangial cellularity, segmental glomerulosclerosis, and tubular atrophy and interstitial fibrosis (see Box E1).

BOX E1 Prognostic Markers in IgA Nephropathy

Clinical
Poor prognosis
- Increasing age
- Severity of proteinuria
- Hypertension (increased systolic blood pressure)
- Renal impairment (decreased GFR)
- Decreased serum albumin
- Decreased hemoglobin
- Persistent microscopic hematuria

Good prognosis
- Recurrent macroscopic hematuria

Histopathologic (Oxford Classification)
Poor prognosis
- Increased mesangial cellularity
- Segmental glomerulosclerosis
- Tubular atrophy/interstitial fibrosis
- Crescents

No impact on prognosis
- Endocapillary hypercellularity

GFR, Glomerular filtration rate.
From Canetta PA et al: Glomerular diseases: emerging tests and therapies for IgA nephropathy, *Clin J Am Soc Nephrol* 9:617, 2014; and Lv J et al: Evaluation of the Oxford Classification of IgA nephropathy: a systematic review and meta-analysis, *Am J Kidney Dis* 62(5):891, 2013.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- 75% of children and young adults present with macroscopic hematuria often associated with upper respiratory infection or gastrointestinal illness. Older adults present with microscopic hematuria, proteinuria, and hypertension.
- Loin pain may be associated with macroscopic hematuria. This symptom should not be confused with the much more rare disorder termed "loin pain hematuria syndrome."
- Physical findings are usually unremarkable. Hypertension is present in 20% to 30% of patients with chronic kidney disease and edema is seen in the 5% of patients with nephrotic-range proteinuria.
- IgAN presents as acute kidney injury due to hemoglobin toxicity from macroscopic hematuria in 5% of patients and as chronic kidney disease in 10% to 20% of patients.

ETIOLOGY

- Most cases are idiopathic/primary. IgA vasculitis (formerly Henoch-Schönlein purpura) may represent a more systemic, vasculitic form of IgAN.
- Secondary causes of IgAN (Table E1): Hepatitis B; alcoholic cirrhosis; celiac disease; inflammatory bowel disease (IBD); psoriasis; sarcoidosis; cystic fibrosis; cancer of the lungs, larynx, or pancreas; HIV infection; systemic lupus erythematosus; rheumatoid arthritis; diabetic nephropathy; Sjögren syndrome; and Reiter syndrome. Given the role of IgA in the gut, aside from IBD, infections in the GI tract have been associated with IgAN or flares of the disease.
- The four-hit pathogenesis model is demonstrated in Fig. E1. The first hit with high heritability is abnormal glycosylation that produces galactose-deficient IgA1 (Gd-IgA1). This abnormal glycosylation is mediated by changes in the activity of a key enzyme,

TABLE E1 Classification of Immunoglobulin A (IgA) Nephropathy

Primary IgA nephropathy
Secondary IgA nephropathy
Associated Disorders
IgA vasculitis
HIV infection
Toxoplasmosis
Seronegative spondyloarthropathy
Celiac disease
Dermatitis herpetiformis
Crohn disease
Liver disease
Alcoholic cirrhosis
Ankylosing spondylitis
Reiter syndrome
Neoplasia
Mycosis fungoides
Lung carcinoma
Mucin-secreting carcinoma
Cyclic neutropenia
Immunothrombocytopenia
Gluten-sensitive enteropathy
Scleritis
Sicca syndrome
Mastitis
Pulmonary hemosiderosis
Berger disease
Leprosy
Familial IgA nephropathy

HIV, Human immunodeficiency virus.
From Skorecki K et al: *Brenner and Rector's the kidney,* ed 10, Philadelphia, 2016, Elsevier.

C1GALT1. In turn, this enzyme is regulated by microRNAs. The second hit is production of anti-glycan antibodies that recognize epitopes on Gd-IgA1, forming immune complexes that deposit in the mesangium as the third hit. IgA also stimulates production of growth factors such as PDGF and IGF-1, leading to mesangial expansion. The activation of complement and release of inflammatory cytokines from activated leukocytes represents the fourth and final hit.

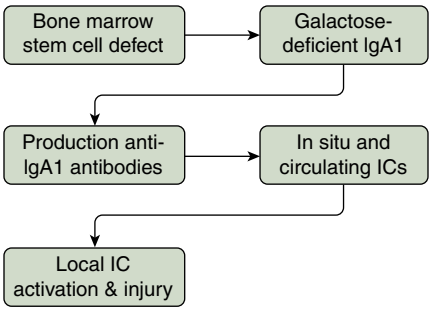

FIG. E1 Pathogenesis of IgA nephropathy. *IgA,* Immunoglobulin A; *IC,* immune complex.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is the group of glomerular, hematuric diseases.

- IgA vasculitis (Henoch-Schönlein purpura)
- Hereditary nephritis
- Thin glomerular basement membrane disease
- Lupus nephritis
- Vasculitis
- Post infectious nephritis
- Secondary causes associated with IgA nephropathy as mentioned above

WORKUP

- Diagnosis is suspected based on clinical history and laboratory data. Episodes of gross hematuria with upper respiratory infections and urinalysis demonstrating dysmorphic hematuria and RBC casts with negative serologies for other glomerulonephritides (e.g., lupus and vasculitis) strongly point to the diagnosis. Although serum IgA levels are elevated in 50% of patients, their sensitivity and specificity are low; diagnosis is confirmed by kidney biopsy showing predominant or codominant IgA deposits in the mesangium.
- To standardize diagnosis and provide prognostication, the pathology is scored via the Oxford IgAN MEST classification that evaluates **M**esangial hypercellularity, **E**ndocapillary hypercellularity, **S**egmental glomerulosclerosis, and **T**ubular atrophy/interstitial fibrosis.
- Prognosis is excellent with normal renal function and low proteinuria; accordingly, kidney biopsy is restricted to patients with sustained proteinuria >1 g/day or worsening kidney function.

LABORATORY TESTS

- Urinalysis variably demonstrates protein, dysmorphic red blood cells, and red blood cell casts.
- Serum creatinine may be elevated.
- Urine protein-to-creatinine ratio reveals mild increases in proteinuria.
- Serum IgA is elevated in only 50% of patients, but has little clinical utility.

Rx TREATMENT

Although initially considered a benign disease, IgAN is recognized as a common cause of kidney failure. Currently there is no cure.

NONPHARMACOLOGIC THERAPY

- Weight reduction in overweight or obese patients
- Smoking cessation

ACUTE & CHRONIC GENERAL Rx

- Antihypertensive therapy, preferably with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). The goal blood pressure is <125/75 mm Hg if proteinuria is >1 g/day and <130/80 if <1 g/day, per international guidelines. Dual RAAS blockade is not recommended due to risk of hyperkalemia.
- Patients with recurrent gross hematuria, isolated microscopic hematuria, no or minimal proteinuria (<1 g/day), normal blood pressure, and normal kidney function should be monitored every 6 to 12 mo to evaluate disease progression. Fish oil may be considered but has limited supporting data.
- If bouts of recurrent macroscopic hematuria are associated with tonsillitis, tonsillectomy may benefit these patients; however, this treatment is controversial..
- Patients with persistent proteinuria >1 g/day with or without hypertension are treated with ACE inhibitors or ARBs.
- Based on three randomized, controlled trials, a 6-mo regimen of glucocorticoid steroids was advocated for patients with good kidney function with persistent proteinuria of >1 g/day, despite ACE inhibitor or ARB administration and fish oil after 6 mo. However, a recent, prospective, randomized, controlled trial (STOP-IgAN) showed no difference in decline in GFR with corticosteroids in subnephrotic patients followed for 3 yr, with increased infections, glucose intolerance, and obesity. Another recent multicenter study (TESTING) of 262 subnephrotic patients randomized to steroids versus placebo showed potential renal benefit of steroid treatment, but was stopped early due to excess infections in the steroid group (14.7% vs 3.2%). Thus, definite conclusions regarding steroid treatment have not been established. Patients with nephrotic syndrome and relatively preserved kidney function on maximal RAAS blockade are treated with steroids for a 6-mo course, especially if there is disease progression. Steroid treatment is not indicated if significant chronic disease is demonstrated on renal biopsy or if the GFR is <20 ml/min per 1.73 m^2.
- Rapidly progressive glomerulonephritis, in the absence of severe fibrosis on kidney biopsy, is treated with pulse steroids followed by oral steroids, combined with cyclophosphamide for the first 2 to 3 mo. This initial regimen is followed by oral steroids and azathioprine for 2 yr as a maintenance treatment.

- Patients with acute kidney injury require a kidney biopsy to differentiate acute tubular necrosis from pigment nephropathy that requires only supportive therapy from crescentic IgA nephropathy that is treated with aggressive medical management.
- Kidney transplantation is the treatment of choice for end-stage renal disease. Although the recurrence rate of IgA nephropathy in the transplant is 50%, allograft loss from recurrent IgA nephropathy is only 5%.
- Statins are indicated for all IgA nephropathy patients with dyslipidemia, hypertension, and other cardiovascular risks.
- The roles of mycophenolate, rituximab, and plasmapheresis are not clearly defined given lack of evidence.
- A phase 2b clinical trial (NEFIGAN) showed potential benefit from use of budesonide.
- Future treatments may include targeted immunosuppression of the gut and modification of abnormal complement activation.

COMPLEMENTARY & ALTERNATIVE MEDICINE

The role of fish oil is controversial. One large, randomized, placebo-controlled study showed benefit, although many small, randomized studies showed no benefit. The recommendation for mild disease is that fish oil is optional for patients. International consensus guidelines recommend fish oil along with ACE inhibitors/ARBs if proteinuria is >1 g/day.

DISPOSITION/PROGNOSIS

- Complete remission occurs in <10% of patients.
- End-stage renal failure develops in 12% of patients followed for 5 yr, in 15% to 20% within 10 yr, and in 20% to 40% within 20 yr. Prognostic markers in IgAN are described in Box E1.
- Poor prognostic indicators include hypertension, extent of renal insufficiency, extent of proteinuria, and certain histologic changes seen in renal biopsy such as crescents, increased mesangial cells, glomerulosclerosis, and tubulointerstitial fibrosis or atrophy.
- Potential future biomarkers include increased serum levels of glycan-specific IgG antibodies that predict progression to end-stage kidney disease or death, elevated serum levels of galactose-deficient IgA1 correlated with risk of progressive kidney deterioration, FHR proteins associated with more rapid decline in kidney function, and selected urine microRNAs that potentially may diagnose IgA nephropathy or determine disease severity.

REFERRAL

Patients with suspected IgAN are commonly referred to nephrologists for diagnosis and treatment, typically presenting with gross hematuria and urinalysis with blood and proteinuria.

PEARLS & CONSIDERATIONS

COMMENTS

- Gross hematuria (red urine) is uncommon with intrinsic kidney diseases but is commonly encountered in IgA nephropathy and cyst rupture in autosomal dominant polycystic kidney disease.
- IgA nephropathy is not an entirely benign condition, even when microhematuria is the only clinical presentation. Nearly 40% of patients reach end-stage kidney disease after 20 yr of illness.
- Episodic gross hematuria that occurs during upper respiratory infections is a classic presentation for IgA nephropathy. Angiotensin-converting enzyme inhibitors or ARB is initiated.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **Dhruti P. Chen, MD,** and **Koyal Jain, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

IgA vasculitis (IgAV, formerly known as Henoch-Schönlein purpura [HSP]) is a systemic, small-vessel, IgA immune complex–mediated leukocytoclastic vasculitis characterized by a tetrad of palpable purpura, colicky abdominal pain, renal disease, and arthritis/arthralgias. It may also present with gastrointestinal (GI) bleeding.

SYNONYMS

Henoch-Schönlein purpura
Anaphylactoid purpura
Allergic purpura
HSP

ICD-10CM CODE
D69.0 Allergic purpura

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Annual incidence of 3 to 27 cases/100,000 population in children. Approximately 1/100,000 in adults.
PREVALENCE: Most common vasculitis seen in children and younger age groups; seen in white and Asian populations (primarily from Korea and Japan); 3 to 4 times more commonly than in black patients.
PREDOMINANT SEX AND AGE: Approximately 2:1 male:female ratio. Seen mostly from ages 3 to 12 with peak incidence between 4 and 6 yr, although this disorder can be seen in older adolescents and young adults; 90% of all patients are <10 yr old. Older age prognosticates a worse outcome with malignancy found in some.
PEAK INCIDENCE: Late autumn to early spring, rarely in summer. Seasonal variation is not seen in adults.
GENETICS: Recent studies have identified genetic susceptibility factors, but familial recurrence is very rare. There appears to be a strong genetic predisposition with HLA class 2 region related to HLA-DRB1*01 allele. There may also be protective genetic associations of HLA genes that may reduce the risk of acquiring the disease and explain ethnic differences. The ACE, IL*, and HLA-B*35 genes are associated with worse renal phenotype.
RISK FACTORS: There are no formally identified risk factors; however, viral precipitants have been theorized to trigger onset of the disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Palpable purpura (Fig. E1) of dependent areas, especially lower extremities (palms and soles) and areas subjected to pressure, such as the beltline in adults or buttocks in toddlers. Facial involvement is rare.
- GI symptoms are seen in up to two thirds of patients. Common findings are abdominal pain, nausea, vomiting, diarrhea, cramping, hematochezia, and melena. Complications include GI bleeding (20% to 30%), bowel ischemia, intussusception (1% to 5%), and bowel perforation (<1%). Pancreatitis and acalculous cholecystitis are rare complications.
- Subcutaneous edema.
- Arthralgias and arthritis in 60% to 85%. Typically oligoarticular, affecting lower extremity and large joints. Periarticular swelling and tenderness also noted.
- Renal involvement is seen in as many as 80% of older children, usually within the first month of illness. Fewer than 5% progress to end-stage renal failure, a major cause of morbidity. Renal manifestations may range from isolated hematuria or proteinuria to severe crescentic glomerulonephritis.
- 10% to 20% of male children can present with pain and swelling of the scrotum that can mimic testicular torsion.
- Central nervous system (CNS) involvement is rare, but can manifest as confusion, weakness, visual deficits, or impaired consciousness.

ETIOLOGY

- Presumptive etiology is exposure to a trigger antigen that causes antibody formation.
- Antigen-antibody (immune) complex deposition then occurs in arteriole and capillary walls of skin, renal mesangium, and GI tract. Immunoglobulin A (IgA) deposition is most common.
- Abnormal IgA1 glycosylation is a leading cause of the elevated serum galactose-deficient IgA1 levels seen in the disease.
- Antigen triggers postulated include drugs, foods, immunization, and upper respiratory and other viral illnesses. Group A streptococcal infection is the most common precipitant in children, seen in up to one third of cases. Of childhood cases, 30% to 65% are preceded by an unspecified upper respiratory infection. Various precipitants have been described in case reports including parvovirus B19, *Helicobacter pylori*, and intravesical BCG (used for treatment of bladder cancer), to name a few.
- Case reports have been published describing development of IgA vasculitis after treatment with a variety of medications including immunosuppressive agents (e.g., etanercept, infliximab, adalimumab) and more widely used medications such as vancomycin, pantoprazole, and ibuprofen. There is no correlation between vaccinations and development of IgAV.

DIAGNOSIS

- Diagnosis is generally clinical. Nonthrombocytopenic purpura (see Fig. E2) is essential to the diagnosis. Skin or renal biopsy demonstrating IgA deposition in vessel walls can help narrow the differential diagnosis
- Skin manifestations are most common and primarily affect small superficial vessels. See Box E1 for common clinical manifestations of IgA vasculitis
- Skin biopsy shows leukocytoclastic vasculitis. Renal biopsy shows mesangial IgA deposition

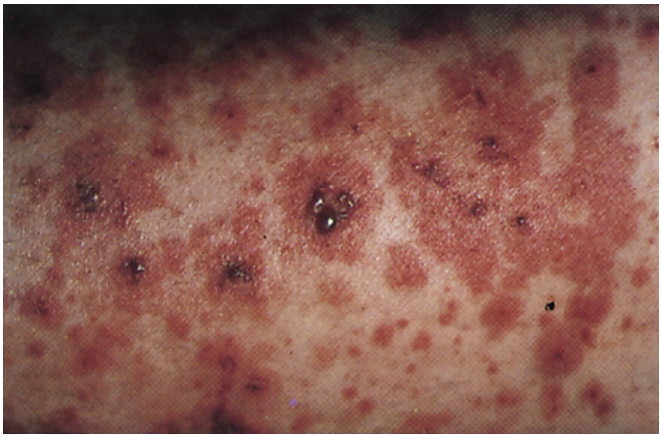

FIG. E1 Palpable purpura in a patient with IgA vasculitis. (From Hoffman R et al [eds]: *Hematology: basic principles and practice,* ed 4, Philadelphia, 2005, Saunders.)

FIG. E2 Extensive palpable purpura over the lower extremities in a 7-year-old girl with IgA vasculitis. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

BOX E1 Clinical Characteristics of Patients with Henoch-Schönlein Purpura/Immunoglobulin A Vasculitis*

Skin (Involvement Is Present in all Patients)
Palpable purpura
Petechiae
Ecchymoses
Bullae
Ulceration
Maculopapular lesions
Urticarial lesions
Subcutaneous edema

Joints (up to 82%)
Arthritis or arthralgia

Gastrointestinal System (50%-75%)
Abdominal pain
Gastrointestinal hemorrhage
Bowel infarction
Bowel perforation
Duodenal obstruction
Intussusception
Acute pancreatitis
Hepatobiliary involvement
Protein-losing enteropathy

Renal (20%-60%)
Microscopic hematuria
Proteinuria
Macroscopic hematuria
Acute nephritic or nephritic syndrome
Hypertension
Acute renal failure

Urogenital
Orchitis
Scrotal edema
Ureteral stenosis
Testicular torsion

Neurologic
CNS vasculitis
Headache
Seizures
Visual abnormalities and verbal disability
Facial palsy
Peripheral neuropathy

Pulmonary
Alveolar hemorrhage
Intestinal infiltrates

CNS, Central nervous system.
*Listed sttarting from the most frequent to the most rare.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE E1 Laboratory Features of Henoch-Schönlein Purpura/ Immunoglobulin A Vasculitis

Investigations	Possible Findings
Initial Investigations	
Complete blood count	May reveal leukocytosis or anemia
Acute-phase reactions (ESR or CRP)	Normal or elevated
Urinalysis	Normal, hematuria, or proteinuria
Stool guaiac examination	Normal, positive
Secondary Investigations (Indicated According to Clinical Features and Abnormal Results of the Above)	
Urine protein/creatinine	Normal, increased, nephrotic range
Renal functional tests	Normal, elevated creatinine, hypoalbuminemia
Plain abdominal supine radiography and chest radiography	Normal, air leak
Abdominal ultrasonography	Thickened bowel wall, intussusception
Tests for Differential Diagnosis	Diseases to be Differentiated
Blood culture	Specific infections
Imaging procedures and relevant biopsies	To differentiate from PAN
ANCA	ANCA-associated vasculitis
Antinuclear antibodies, anti–double-stranded DNA, complement 3	SLE, hypocomplementemic urticarial vasculitis

ANCA, Antineutrophil cytoplasmic antibody; *CRP,* C-reactive protein; *ESR,* erythrocyte sedimentation rate; *PAN,* polyarteritis nodosa; *SLE,* systemic lupus erythematosus.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

- The presence of two of the following four American College of Rheumatology criteria yields a diagnostic sensitivity of 87.1% and specificity of 87.7%:
  1. Palpable purpura unrelated to thrombocytopenia
  2. Age <20 yr at onset of first symptoms
  3. Bowel angina
  4. Granulocytic infiltration of arteriole or venule walls on biopsy
- In 2010, a European consortium (European League Against Rheumatism/Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society) published a set of validated diagnostic criteria that showed 100% sensitivity and 87% specificity. Their criteria described purpura or petechiae and one or more of the following:
  1. Abdominal pain
  2. Predominant IgA deposits on histopathology
  3. Arthritis or arthralgia
  4. Renal involvement

DIFFERENTIAL DIAGNOSIS

- Polyarteritis nodosa
- Acute abdomen
- Meningococcemia
- Rocky Mountain spotted fever
- Cryoglobulinemia thrombocytopenic purpura
- Hypersensitivity vasculitis
- Microscopic polyangiitis
- Granulomatosis with polyangiitis (Wegener granulomatosis)

WORKUP

History, physical examination, laboratory testing, skin or renal biopsy

LABORATORY TESTS (TABLE E1)

- Laboratory abnormalities are not specific for IgA vasculitis but may help identify complications and rule out other diseases.
  1. Electrolytes, blood urea nitrogen, and creatinine.
  2. Urinalysis.
  3. Complete blood count.
  4. Prothrombin time, fibrinogen, and fibrin degradation products.
  5. Blood cultures.
  6. Skin or renal biopsy.
- Leukocytosis and eosinophilia may be seen.
- IgA levels are elevated in approximately 50% of patients.
- Glomerulonephritis may be present (microscopic hematuria, proteinuria, and red blood cell casts).
- Pathologic examination may aid diagnosis.
  1. Characteristic skin biopsy findings include hemorrhage below the epidermis, as well as necrotic thickened small vessels with IgA/C3 deposits.
  2. There is no one characteristic renal lesion, although mesangial IgA deposition is often seen.

IMAGING STUDIES

Imaging studies are generally not diagnostic of IgA vasculitis, although certain studies may be useful to narrow the differential diagnosis and/or screen for complications.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Supportive care with pain management, adequate hydration, and nutrition is the primary intervention as up to 94% of cases in children and 87% cases in adults will resolve spontaneously.

ACUTE GENERAL Rx

- Prednisone 1 to 2 mg/kg PO daily for 2 wk is typically given for severe arthritis and/or abdominal pain. An equivalent dose of methylprednisolone can be used with same efficacy.

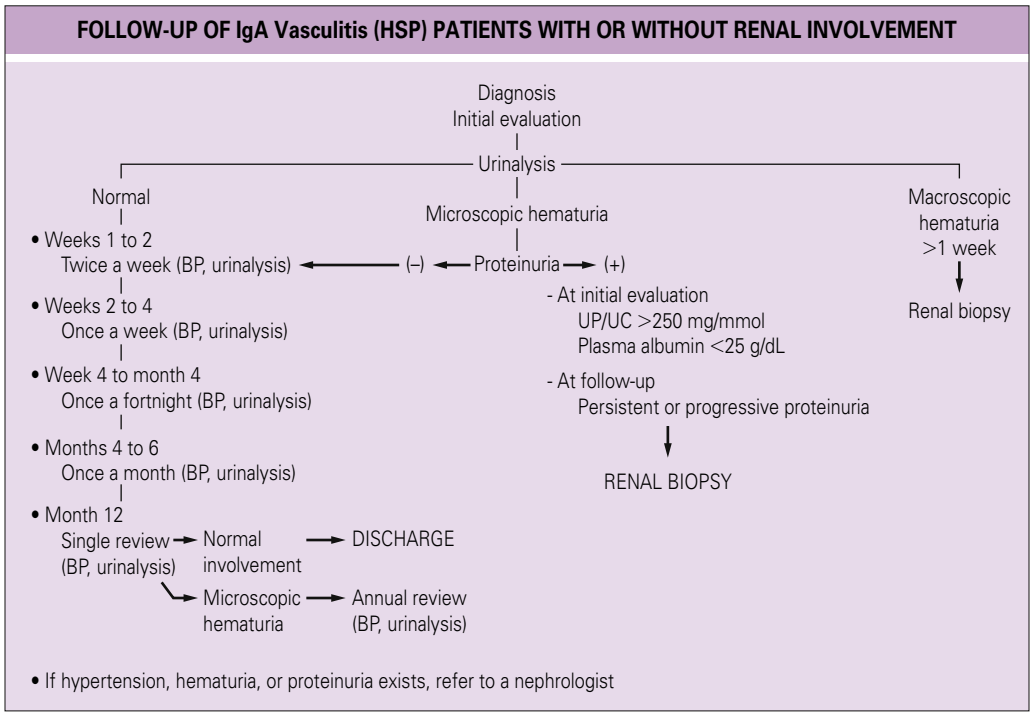

FIG. E3 A practical approach for patients with renal involvement. *BP,* Blood pressure; *UC,* urinary creatinine; *UP,* urinary protein. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

1. A double-blind, randomized, controlled trial (RCT) found that early treatment with prednisone reduced abdominal pain and joint symptoms but did not prevent development of renal disease. It was effective in the treatment of renal disease once it was established.

- Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend the same treatment for nephritis related to IgA vasculitis in children and adults.
  1. ACE inhibitor or ARB therapy is suggested for nephritis with persistent proteinuria.
  2. If unsuccessful and GFR >50 ml/min/1.73m^2, treatment similar to that for IgA nephritis with a prolonged (6-mo) glucocorticoid regimen is suggested.
  3. Patients with crescentic glomerulonephritis with deteriorating renal function or nephrotic syndrome related to IgA vasculitis should be treated as if they have crescentic IgA nephritis; such treatment includes corticosteroids and cyclophosphamide.
  4. Recent case series and case reports on a total of 12 patients with biopsy-proven renal involvement who failed steroids +/- immunosuppressives had improvement in kidney function or proteinuria or hematuria with rituximab therapy.
  5. Mycophenolate mofetil has been shown to be useful in glucocorticoid-resistant children with nephrotic range proteinuria, but a recent review that included RCTs did now show strong benefit.
  6. An RCT of 24 children with nephrotic range proteinuria or crescentic HSPN on biopsy, comparing methylprednisolone with cyclosporine, revealed resolution of proteinuria in all 11 patients treated with cyclosporine A within 3 mo vs. 7 of 13 from the methylprednisolone group. The 6 from the methylprednisolone group without resolution were treated with cyclosporine with 5 showing response.
  7. Not all patients with nephritis or nephrotic-range proteinuria respond to these treatments; they eventually may require renal transplantation.
  8. Fig. E3 illustrates follow-up of IgA vasculitis patients with or without renal involvement.
- Severe gastrointestinal involvement (defined by intense pain, GI bleeding, and protein losing enteropathy) improved with intravenous immunoglobulin (IVIG) in eight pediatric patients with IgA vasculitis. IVIG was found to slow or stop effects on eGFR in patients with nephritis. A case series postulated an efficacious addition of plasma exchange to adults with severe renal and extrarenal complications.

CHRONIC Rx

- Even if renal involvement is not present after initial episode, urinalysis and blood pressure should be checked every 2 to 4 wk for first 6 mo to detect development and progression of kidney disease.
- Azathioprine may allow earlier corticosteroid discontinuation in patients with relapsing symptoms of IgA vasculitis.

COMPLEMENTARY & ALTERNATIVE MEDICINE

No complementary or alternative treatment modalities proven to be effective for IgA vasculitis.

DISPOSITION

- Prognosis excellent, with spontaneous recovery within 4 wk in most patients.
- Hospitalization is required for significant GI or renal involvement.
- Increased age of onset generally correlates with morbidity. While end-stage renal disease (ESRD) occurs in 10% to 30% of adult patients with IgA vasculitis at 15 yr, chronic renal insufficiency is the most common long-term morbidity and affects adults more than children.
- Recurrences in up to one third of patients, especially within first 4 to 6 mo after initial episode and most commonly in patients with renal involvement. Recurrences are characteristically less severe than initial episode. For those with relapsing course, immunosuppression may be required depending on the severity of the symptoms.

REFERRAL

Rheumatology, nephrology, or general surgery consultation based on clinical manifestations

PEARLS & CONSIDERATIONS

- Organ systems involved in IgA vasculitis are skin, joints, GI tract, and kidneys.

- Palpable purpura, abdominal pain, arthritis, and renal involvement are common clinical manifestations.
- GI symptoms and arthritis may precede rash. Skin and renal manifestations occur at the same time.
- Most with spontaneous recovery within 4 wk of onset of symptoms.
- End-stage renal disease occurs in only 5% of all patients with IgA vasculitis.

RELATED CONTENT

Henoch-Schönlein Purpura (Patient Information)

AUTHORS: **Valerie Carter, MD,** and **Dominick Tammaro, MD, FACP**

SUGGESTED READINGS

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IgG4-Related Disease

BASIC INFORMATION

DEFINITION

IgG4-related disease (IgG4-RD) is a fibroinflammatory condition that can lead to tumefactive and tissue-destructive lesions in nearly every organ (Table 1).

SYNONYMS

Type 1 autoimmune pancreatitis
Mikulicz syndrome

ICD-10CM CODE
D89.89 Other specified disorders involving the immune mechanism

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE AND PREVALENCE: Exact incidence and prevalence are unknown. Most epidemiologic information comes from Japanese studies of autoimmune pancreatitis (AIP).
PREDOMINANT SEX/AGE: Among two study cohorts of 765 patients, mean age of symptom onset was 57.7 and 59.5 yr. There may be a slight predilection for males, about 3:2.
RISK FACTORS: Tobacco, asbestos exposure, atopy, history of malignancy

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with IgG4-RD experience 1.8 yr mean average time to diagnosis.
- Clinical manifestations depend on the distribution of organ involvement, and nearly every organ system may be involved.
- Presentations are subacute and may include constitutional symptoms such as fatigue and weight loss. Arthralgias and enthesopathy may be present; however, frank synovitis is atypical.
- IgG4-RD may involve lacrimal glands, salivary glands, orbits, sinuses, thyroid (Reidel thyroiditis), lymph nodes, aorta and surrounding connective tissue (aortitis, periaortitis), lung (nodules, GGOs, pleural thickening, ILD), kidney (tubulointerstitial nephritis), pancreas (autoimmune pancreatitis), biliary system, skin (cutaneous pseudolymphoma), and lymph nodes.
- Nervous system involvement includes pachymeningitis, hypophysitis, and peripheral nerve inflammation or enlargement.
- IgG4-RD may also cause retroperitoneal fibrosis (RPF), which can manifest with poorly localized pain in back, abdomen, thighs; hydronephrosis and lower extremity edema.

ETIOLOGY

Remains unknown, and disease has only been recognized for a short time. Disease thought to be autoimmune in nature, with CD4+ and T-follicular helper cells playing a role. IgG4 antibodies are not thought to be pathogenic.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Broad, dependent on which organ system is involved:

- Lymphoma, malignancy (i.e., pancreatic cancer)
- Primary sclerosing cholangitis
- Sarcoidosis
- Large-vessel vasculitis, ANCA-associated vasculitis
- Erdheim-Chester disease
- Sjögren syndrome
- Orbital pseudotumor

WORKUP

- Diagnosis based on combination of history, clinical findings, laboratory tests, and radiographic and histopathologic findings.
- Umehara et al proposed diagnostic criteria (see Table 1), which divides IgG4-RD into three categories: definite, probable, and possible. Definitive diagnosis requires fulfillment of clinical, hematologic, and histopathologic criteria. Clinical evidence includes presence of swelling or masses in one or more organ

TABLE 1 Nomenclature of IgG4-Related Disease and Allied Conditions

Organ	Preferred Name	Previously Called
Pancreas	IgG4-related pancreatitis	Type 1 autoimmune pancreatitis
Eye:	IgG4-related ophthalmic disease	Eosinophilic angiocentric fibrosis, multifocal fibrosclerosis
Lacrimal glands	IgG4-related dacryoadenitis	Mikulicz syndrome
Orbital soft tissue	IgG4-related orbital inflammation	
Orbital pseudotumor	IgG4-related orbital pseudotumor	Orbital pseudotumor
Extraocular muscle disease	IgG4-related orbital myositis	
Salivary glands:	IgG4-related sialadenitis	Mikulicz syndrome
Parotid glands	IgG4-related parotitis	Mikulicz syndrome
Submandibular glands	IgG4-related submandibular gland disease	Mikulicz syndrome, Kuttner tumor
Pachymeninges	IgG4-related pachymeningitis	
Hypophysis	IgG4-related hypophysis	Autoimmune hypophysitis
Thyroid	IgG4-related thyroiditis	Riedel thyroiditis, multifocal fibrosclerosis
Aorta or arteries	IgG4-related aortitis or periaortitis	Lymphoplasmacytic aortitis, inflammatory aortic aneurysm
Mediastinum	IgG4-related mediastinitis	Multifocal fibrosclerosis, mediastinal fibrosis
Retroperitoneum	IgG4-related retroperitoneal fibrosis	Multifocal fibrosclerosis, Ormond disease
Mesentery	IgG4-related mesenteritis	
Skin	IgG4-related skin disease	Cutaneous pseudolymphoma
Lymph node	IgG4-related lymphadenopathy	
Bile ducts	IgG4-related sclerosing cholangitis	Sclerosing cholangitis
Gallbladder	IgG4-related cholecystitis	
Liver	IgG4-related hepatopathy	
Lung	IgG4-related lung disease	Eosinophilic angiocentric fibrosis, interstitial pneumonia
Pleura	IgG4-related pleuritis	
Pericardium	IgG4-related pericarditis	
Kidney	IgG4-related kidney disease	
Breast	IgG4-related mastitis	
Prostate	IgG4-related prostatitis	Prostatitis

From Hochberg MC et al: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

BOX 1 Comprehensive Diagnostic Criteria for IgG4-Related Disease

1. Clinical study shows characteristic diffuse or localized swelling or masses in single or multiple organs.
2. Hematologic study shows elevated levels of serum IgG4 (≥135 mg/dl).
3. Histopathologic study shows the following two findings.
   (1) Histologic findings: marked lymphocyte and plasmacyte infiltration and fibrosis.
   (2) IgG4-positive plasma cell infiltration: ratio of IgG4 to IgG positive cells >40% and IgG4-positive plasma cells/hpf >10

Of the above: When (1) + (2) + (3) are fulfilled, it is definite.
When (1) + (3) are fulfilled, it is probable.
When (1) + (2) are fulfilled, it is possible.

However, it is important to differentiate from malignant tumors of each organ (e.g., cancer, lymphoma) and similar diseases (e.g., SS, PSC, Castleman disease, secondary retroperitoneal fibrosis, Wegener granulomatosis with polyangiitis, sarcoidosis, eosinophilic granulomatosis with polyangiitis, etc.) with additional histopathologic examination as much as possible.

Even when a patient cannot be diagnosed with CCD criteria for IgG4-RD, she or he may be diagnosed using organ-specific diagnostic criteria for IgG4-RD.

CCD, Comprehensive clinical diagnostic; *IgG4-RD,* IgG4-related disease; *PSC,* primary sclerosing cholangitis; *SS,* Sjögren syndrome.
From Umehara H et al: Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Modern Rheumatol* 22:21-30, 2012. In Hochberg MC et al.: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

systems. A serum IgG4 >135 mg/dl fulfills the hematologic requirement. Histology shows marked lymphocyte and plasmacyte infiltration and fibrosis; it should also show IgG4 positive plasma cell infiltration >40% and more than 10 IgG4 positive plasma cells per hpf.

- An analysis of cross-sectional cohorts recently demonstrated four mutually exclusive groups to which IgG4-RD may be clustered:
  1. Group 1 is characterized by pancreatohepatobiliary disease such as AIP.
  2. Group 2 includes RPF and aortic involvement.
  3. Group 3 encompasses disease limited to the head and neck structures.
  4. Group 4 is characterized by head and neck involvement along with extraglandular, systemic involvement.

LABORATORY TESTS

- Serum IgG4 is neither sensitive nor specific and has been reported as low as 51% in disease population. IgG4 elevation is also seen in vasculitides and malignancies. IgG4 is unreliable as a biomarker because it may remain normal during disease relapse or elevated despite clinical response.
- Measurement of blood plasmablast concentration if available.
- Other laboratory tests may include peripheral eosinophil count, serum IgE, C3, C4, and UA.
- Serologies can be considered, including SSA, SSB, and ANCA.

IMAGING STUDIES

- Imaging frequently reveals organ enlargement and tumefactive lesions in areas involved (Fig. E1 and Fig. E2).
- Storiform (swirling) fibrosis and obliterative phlebitis are characteristic histopathologic lesions. Histology is consistent across organ systems (Fig. E3).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Patients who are asymptomatic or who have limited disease may be approached with expectant management (watchful waiting).

ACUTE GENERAL Rx

- Glucocorticoids are first line for remission induction. Optimal treatment is unknown and approaches are based on small case series. Steroids typically result in symptom improvement within 2 wk and remission within 2 mo.
- Suggested initial doses of prednisone include 0.6 mg/kg/day and/or prednisone 40 mg/day for 4 wk with taper over 3 to 6 mo.
- Urgent therapy is recommended when there is serious organ involvement such as aortitis, retroperitoneal fibrosis, proximal biliary strictures, tubulointerstitial nephritis, pachymeningitis, pancreatic enlargement, and pericarditis.

CHRONIC Rx

Not all patients require steroid-sparing agents; however, azathioprine, methotrexate, mycophenolate mofetil, 6-mercaptopurine, tacrolimus, cyclophosphamide, and rituximab have been used. Rituximab (1000 mg at day 1, 15) has been shown to be effective even without concomitant glucocorticoid therapy in a prospective study.

REFERRAL

- Rheumatology
- Gastroenterology or to specialty with suspected organ involved

PEARLS & CONSIDERATIONS

- Challenges to recognizing the IgG4-RD include failure to consider the diagnosis.
- IgG4-RD may affect nearly every organ and/or anatomic site.
- IgG4-RD may mimic malignancy, infections or other inflammatory and vasculitic conditions.

SUGGESTED READING

Available at ExpertConsult.com

AUTHOR: **Long Pham, MD**

SUGGESTED READINGS

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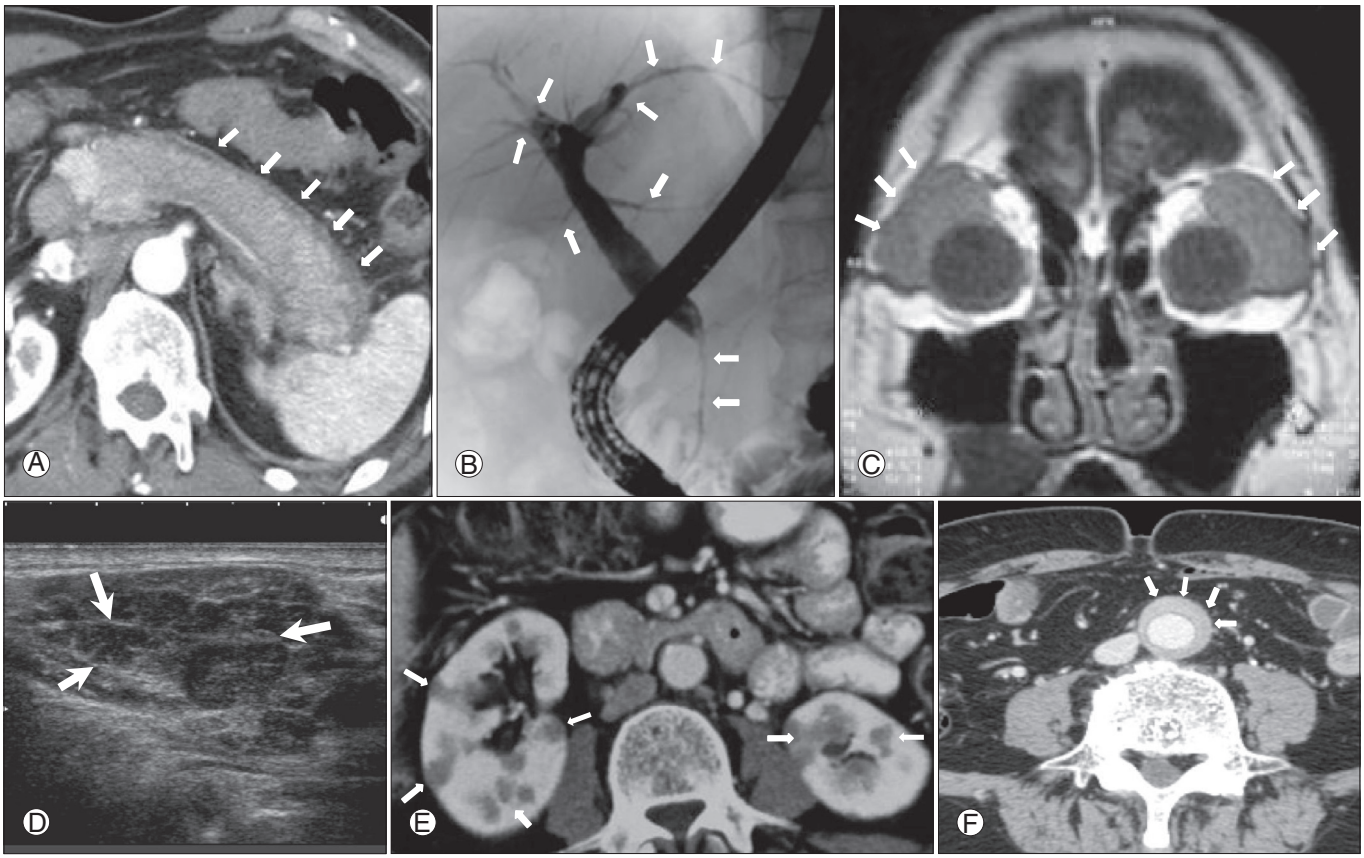

FIG. E2 Radiologic images in IgG4-related disease (IgG4-RD). (A) Diffuse pancreatic swelling and capsule-like rim *(arrows)* in type I autoimmune pancreatitis. **(B)** Endoscopic retrograde cholangiopancreatography findings of IgG4-related sclerosing cholangitis indicate stricture of lower common and intrahepatic bile duct *(arrows).* **(C)** Magnetic resonance imaging of IgG4-related ophthalmic disease shows enlargement of bilateral lacrimal glands *(arrows).* **(D)** Ultrasonographic image of IgG4-related submandibular gland disease shows multiple low echoic areas surrounded by linear high echoic structures in submandibular glands *(arrows).* **(E)** Enhanced computed tomography (CT) image of IgG4-related kidney disease reveals multiple poorly enhanced lesions *(arrows).* **(F)** Enhanced CT image of IgG4-related aortitis indicates marked wall thickening of abdominal aorta *(arrows).* (From Hochberg MC et al: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

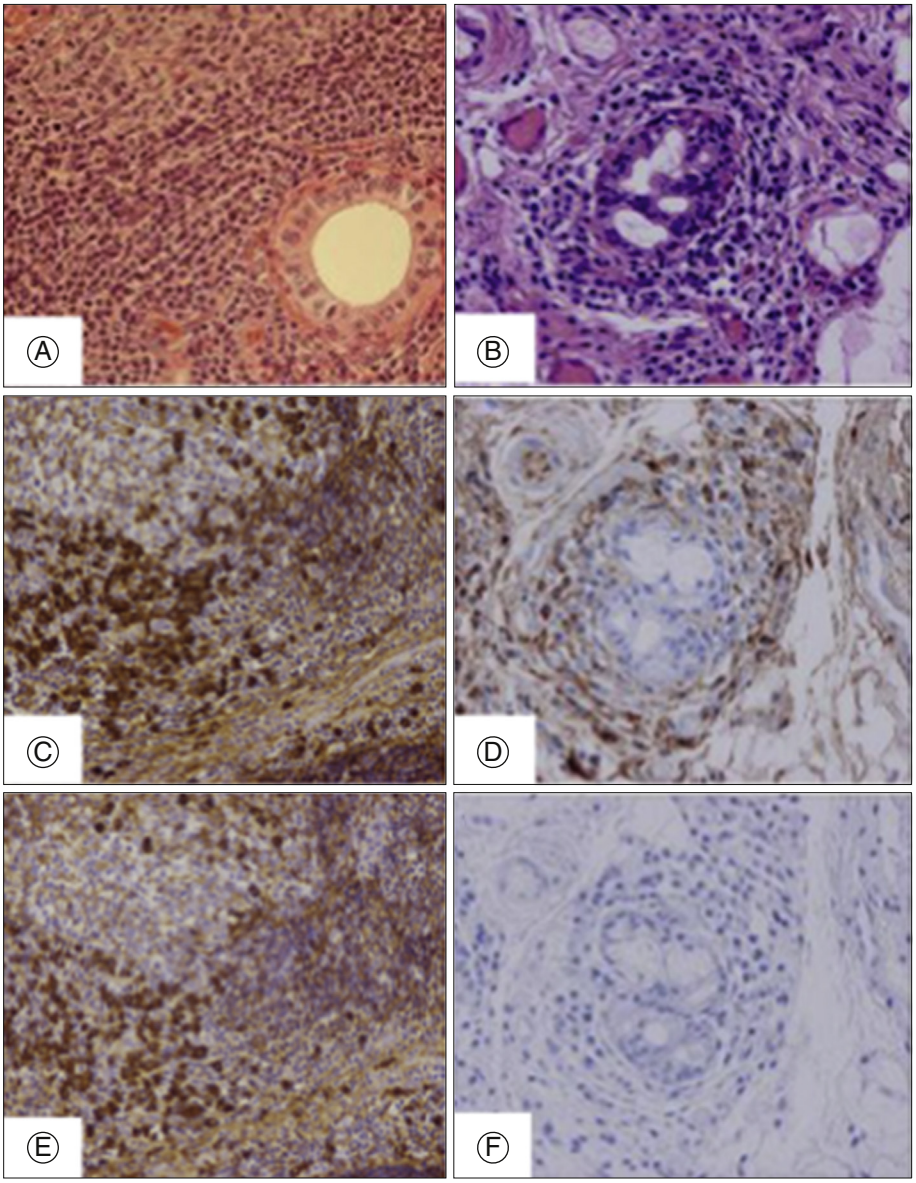

FIG. E3 Histopathology of IgG4-related disease. Panel ***D*** shows plasma cells staining for IgG4; panel ***F*** shows the characteristic storiform fibrosis. (From Hochberg MC et al: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

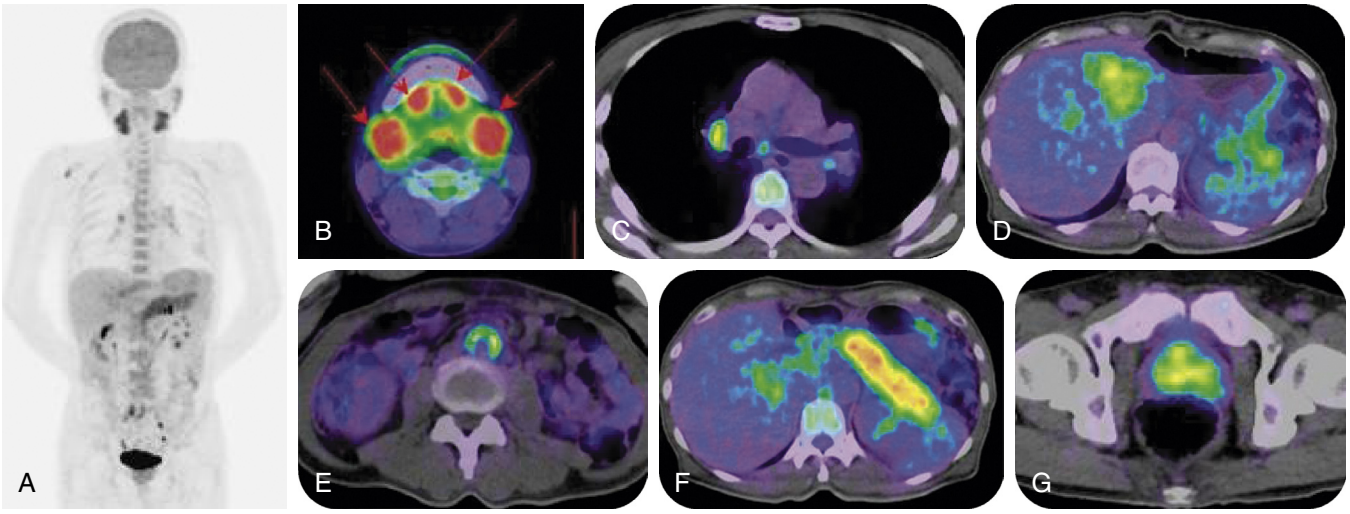

FIG. E1 Multiorgan involvements in IgG4-related disease (IgG4-RD). (A) Imaging with 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) enables mapping of multiorgan involvements in IgG4-RD. Increased uptake of 18F-FDG in the bilateral submandibular glands **(B)**, mediastinum lymph node **(C)**, liver pseudotumor **(D)**, periaortitis **(E)**, autoimmune pancreatitis **(F)**, and prostatitis **(G)**. (From Hochberg MC et al: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

Immune Thrombocytopenic Purpura ALG PTG

BASIC INFORMATION

DEFINITION

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder in which antibody-coated or immune complex-coated platelets are destroyed prematurely, producing defects in cellular immunity that result in peripheral thrombocytopenia. In primary ITP, the thrombocytopenia is isolated, whereas in secondary ITP, the condition is associated with other disorders (e.g., systemic lupus erythematosus [SLE], HIV, chronic lymphocytic leukemia [CLL], lymphomas).

SYNONYM

ITP

ICD-10CM CODE
D69.3 Immune thrombocytopenic purpura

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Primary ITP occurs in 10 in 100,000 adults and 5 in 100,000 children.
PREVALENCE: Five to 10 cases per 100,000 persons.
PREDOMINANT SEX: 72% of patients >10 yr are female; among children, males are more commonly affected.
PREDOMINANT AGE: Children ages 1 to 6 yr and young women (70% are <40 yr). New onset of ITP after age 60 yr is uncommon; comprehensive workup for secondary ITP may be required.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The presentation of ITP is different in children and adults:

- Children generally present with sudden onset of bruising and petechiae from severe thrombocytopenia.
- In adults, the presentation is insidious; a history of prolonged purpura may be present; many patients are diagnosed incidentally on the basis of automated laboratory tests that now routinely include platelet counts.
- The physical examination may be entirely normal.
- Patients with severe thrombocytopenia may have petechiae, purpura, epistaxis, or heme-positive stool from gastrointestinal bleeding. Life-threatening bleeding is uncommon and generally confined to patients with platelets <10,000/mm^3.
- Splenomegaly is unusual; its presence should alert to the possibility of other etiologies of thrombocytopenia.
- The presence of dysmorphic features (skeletal anomalies, auditory abnormalities) may indicate a congenital disorder as the cause of the thrombocytopenia.

ETIOLOGY

Increased platelet destruction is caused by autoantibody targets to platelet-membrane antigens, in particular, antibodies against platelet GPIIb/IIIa or GPIb/IX. The spleen has a major role in ITP by producing autoantibodies in the white pulp and removing autoantibody-coated platelets in the red pulp. Production of antibodies could be triggered either by immunogenicity of membrane glycoproteins (GPs) on the platelet surface or by external factors such as infections or medications.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Falsely low platelet count due to aggregation (resulting from EDTA-dependent or cold-dependent agglutinins). Platelet count is corrected by using heparin or citrate anticoagulated tube
- Viral infections (e.g., HIV, hepatitis C, mononucleosis, rubella)
- Drugs commonly implicated are quinidine, heparin, antibiotics (linezolid, vancomycin, sulfonamides, rifampin), platelet inhibitors (tirofiban, abciximab, eptifibatide), cimetidine, NSAIDs, thiazide diuretics, antirheumatic agents (gold salts, penicillamine), and many chemotherapeutic agents (cyclosporine, fludarabine, carboplatin, oxaliplatin)
- Hypersplenism resulting from liver disease
- Myelodysplastic and lymphoproliferative disorders
- Pregnancy, hypothyroidism
- SLE, thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome
- Congenital thrombocytopenia (e.g., Fanconi syndrome, May-Hegglin anomaly, Bernard-Soulier syndrome)

LABORATORY TESTS

- Complete blood count, platelet count, and peripheral smear: Platelets are decreased. The peripheral smear should show large platelets and no schistocytes (Fig. E1). Red blood cells and white blood cells have a normal morphology. Unless the patient has been bleeding, the hemoglobin level and leukocyte count should be normal.
- Additional tests may be ordered to exclude other causes of the thrombocytopenia when clinically indicated (e.g., HIV, antinuclear antibody [ANA], thyroid-stimulating hormone [TSH] [hypothyroidism and hyperthyroidism can cause thrombocytopenia], liver enzymes, Hep C ab).
- Direct assay of platelet-bound antibodies has an estimated positive predictive value of only 80% to 83%. A negative test cannot be used to rule out the diagnosis.
- Bone marrow aspiration and biopsy are recommended in adults older than 60 yr if there is evidence of immature cells on peripheral smear or persistent neutropenia.

IMAGING STUDIES

CT scan of abdomen/pelvis in patients with splenomegaly to exclude other disorders causing thrombocytopenia

TREATMENT

NONPHARMACOLOGIC THERAPY

- Minimize activity to prevent injury or bruising (e.g., contact sports should be avoided).
- Stop any potentially offending drugs (see "Etiology"). Avoid medications that increase the risk of bleeding (e.g., aspirin and other NSAIDs).

ACUTE GENERAL Rx

- Treatment varies with the platelet count, patient's age, and bleeding status. For newly diagnosed patients with minimal bleeding treatment consists of corticosteroids vs. observation when platelet counts are <30,000 mm^3 and hospital admission when platelet counts are <20,000 mm^3 (Fig. 2).
- Outpatient observation and frequent monitoring of platelet count are needed in asymptomatic established ITP patients with platelet counts >20,000/mm^3.
- Oral prednisone: 1 mg/kg/day in a tapering course for 4 to 6 wk is the most common initial regimen. Prolonged (>6 wk) courses of prednisone are not recommended. Response rates range from 50% to 75%, and most responses occur within the first 3 wk.
- IV methylprednisolone: 30 mg/kg/day (maximum dose of 1 g/day for 2 or 3 days) infused over 20 to 30 min plus IV immunoglobulin (1 g/kg/day for 2 or 3 days).
- Pulsed-dose oral dexamethasone: Given at a dose of 40 mg/day for 4 consecutive days when given for three to four cycles every 4 wk results in a high response rate (80% to 85%) and has been shown to have fewer side effects when compared to longer courses of prednisone. A meta-analysis of nine randomized trials revealed no major increase in efficacy but confirmed less toxicity and faster increases in platelet counts using high-dose dexamethasone.
- Continuation of corticosteroids is limited by long-term complications associated with its use (osteoporosis, weight gain, opportunistic infections, emotional lability).
- Infusion of platelets should only be given to patients with life-threatening hemorrhage or those undergoing emergent surgery.
- IV immunoglobulin (typically 1 to 2 g/kg in divided doses) is used in two settings: corticosteroid-refractory patients and pregnant patients. It rapidly increases platelet count in nearly 80% of patients, but its effect is transient.
- Anti-D immunoglobulin, a pooled IgG product derived from the plasma of Rh(D)-negative donors, is also effective. It can be given only to patients who are Rh(D) positive with hemoglobin >8 mg/dl and the usual dose is 50 to 75 mcg/kg.
- Rituximab, a monoclonal antibody directed against the CD20 antigen, is used as a second-line agent. Usual dose is 375 mg/m^2 weekly × 4 wk.
- Splenectomy is considered a subsequent option in case of rituximab failure. Previously, it was considered in adults with platelet count <20,000/mm^3 after 6 wk of medical treatment or after 6 mo if more than 10 to 20 mg of prednisone per day is still required to maintain a platelet count >30,000/mm^3. In children, splenectomy is generally reserved for persistent thrombocytopenia

(>1 yr) and clinically significant bleeding. Appropriate immunizations (pneumococcal vaccine in adults and children, *Haemophilus influenzae* vaccine, meningococcal vaccine in children) should be administered earlier than 2 wk before planned splenectomy. Postsplenectomy vaccinations should be performed in all cases.

- Additional second-line agents are thrombopoietin receptor agonists (TPO-RA), azathioprine, cyclosporin A, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, and *Vinca* alkaloids.
- Romiplostim, a recombinant fusion protein, and the oral TPO-RA eltrombopag are effective in increasing platelet count in adult patients with chronic ITP refractory to corticosteroids and/or splenectomy. American Society of Hematology guidelines, revised in 2011, recommend the use of TPO-RA for adult patients with ITP at risk for bleeding who have a contraindication to splenectomy, or who have not responded to at least one other therapy.

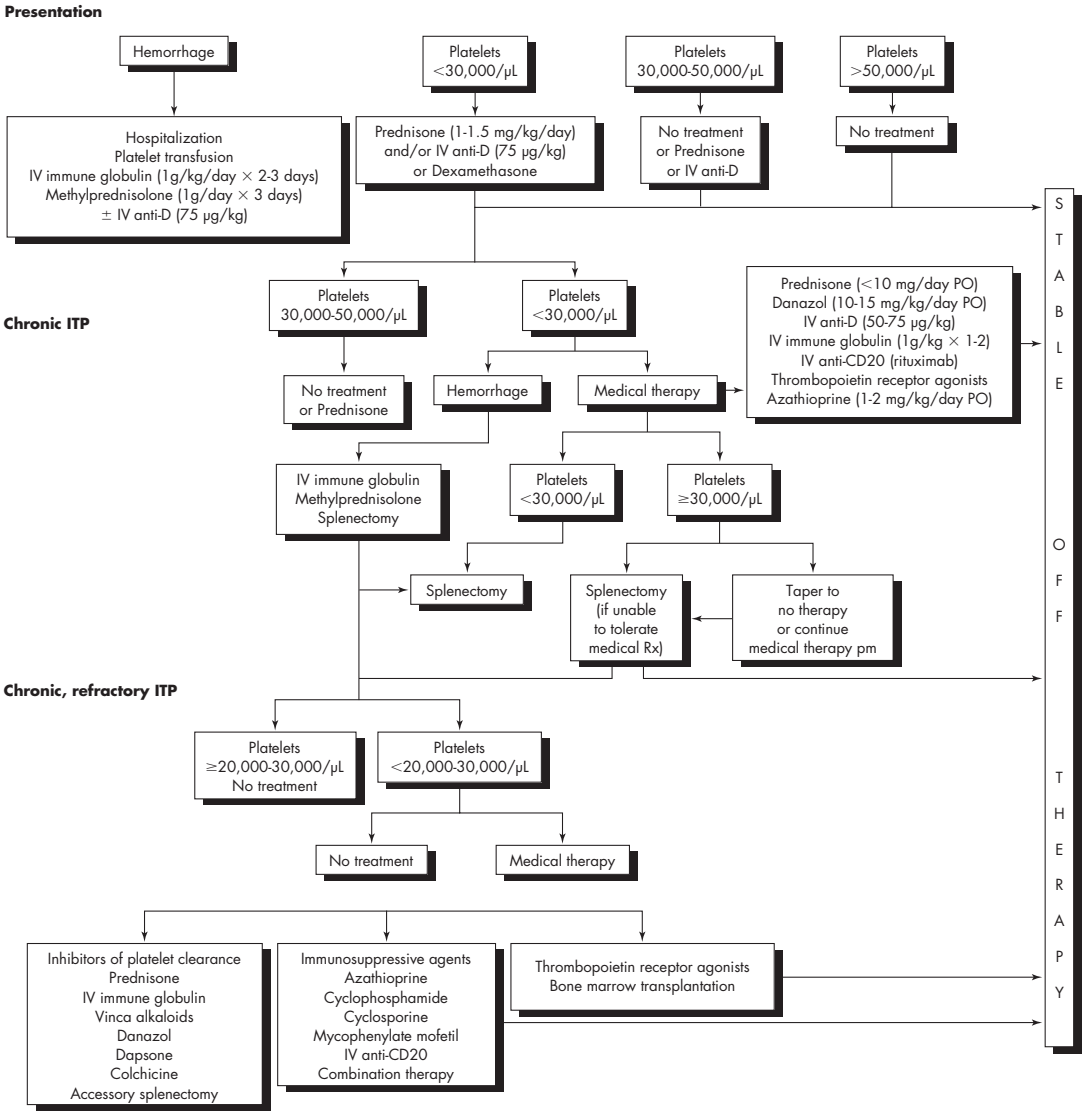

FIG. 2 Treatment algorithm for management of adult-onset immune thrombocytopenic purpura. Some advocate the use of 20,000/mm^3 as a guideline for therapy. The decision to treat patients with platelet counts lower than 50,000/mm^3 is based in part on evidence of bleeding, a history of bleeding, comorbid risk factors, lifestyle, and tolerance of therapy. There is no consensus as to duration of steroid therapy. The use of anti-D as initial therapy is appropriate only for Rh(D)-positive individuals who are not markedly anemic or hemolyzing. The goal of medical therapy is to attain a hemostatic platelet count, generally >20,000 to 30,000/mm^3. The threshold for treatment depends on comorbid risk factors for bleeding and risk of trauma. Higher platelet counts may be appropriate for surgery or after trauma. Medications can be used individually, but combinations of azathioprine and danazol (or corticosteroids) may provide added benefit and allow lower doses to be used. IVIG and anti-D are generally reserved for severe thrombocytopenia unresponsive to oral agents. The decision to proceed to splenectomy depends on intensity of therapy required, tolerance to side effects, risk of surgery, and patient preference. IVIG and/or methylprednisolone may help to increase the platelet count immediately before splenectomy. Laparoscopic and open splenectomy have comparable outcomes. The decision to treat patients who have platelet counts lower than 20,000 to 30,000/mm^3 after splenectomy involves an assessment of the risk of hemorrhage versus the side effects of each form of therapy. *ITP,* Immune thrombocytopenic purpura; *IV,* intravenous; *pm,* precision medicine; *PO,* by mouth; *Rx,* prescription. (Modified from Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Churchill Livingstone.)

- Fostamatinib is an inhibitor of the enzyme spleen tyrosine kinase (Syk). Syk plays an important role in phagocytosis of FcγR-mediated signal transduction and inflammatory propagation. It received FDA approval of chronic ITP in adults who had an insufficient response to previous treatment including corticosteroids, intravenous immunoglobulin (IVIG), splenectomy and/or a TPO-RA. The recommended initial dose is 100 mg oral twice daily. It can be increased to 150 mg twice daily if the platelet count has not responded to at least 50 $\times 10^9/mm^3$ at 1 mo.

PREGNANCY Rx

- No treatment is required when platelet count is >30,000/mm^3 or higher until 36 weeks' gestation, or earlier in case of premature labor.
- Oral corticosteroids and IVIG.
- Refractory ITP may require splenectomy in the second trimester.

DISPOSITION

- More than 80% of children have a complete remission within 8 wk.
- In adults, the course of the disease is chronic; only 5% of adults have spontaneous remission.
- The principal cause of death from ITP is intracranial hemorrhage (1% of children, 5% of adults).

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Immune Thrombocytopenic Purpura (Patient Information).

AUTHORS: **Kittika Poonsombudlert, MD,** and **Patan Gultawatvichai, MD**

SUGGESTED READINGS

Cooper N, Ghanima W: Immune thrombocytopenia, *N Engl J Med* 381(10):945-955, 2019.

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Imbach P, Crowther M: Thrombopoietin-receptor agonists for primary immune thrombocytopenia, *N Engl J Med* 365:734-741, 2011.

Kuter DJ et al: Romiplostim or standard of care in patients with immune thrombocytopenia, *N Engl J Med* 363:1889, 2010.

Mithoowani S et al: High-dose dexamethasone compared with prednisone for previously untreated primary immune thrombocytopenia: a systematic review and meta-analysis, *Lancet Haematol* 3(10):e489-e496, 2016.

Neunert C et al: American Society of Hematology 2019 guidelines for immune thrombocytopenia, *Blood Adv* 3(23):3829-3866, 2019.

Rajasekhar A et al: 2013 clinical practice guide on thrombocytopenia in pregnancy, *Am Soci Hematol*, 2013.

Thota S et al: Immune thrombocytopenia in adults: an update, *Cleve Clin J Med* 79:641, 2012.

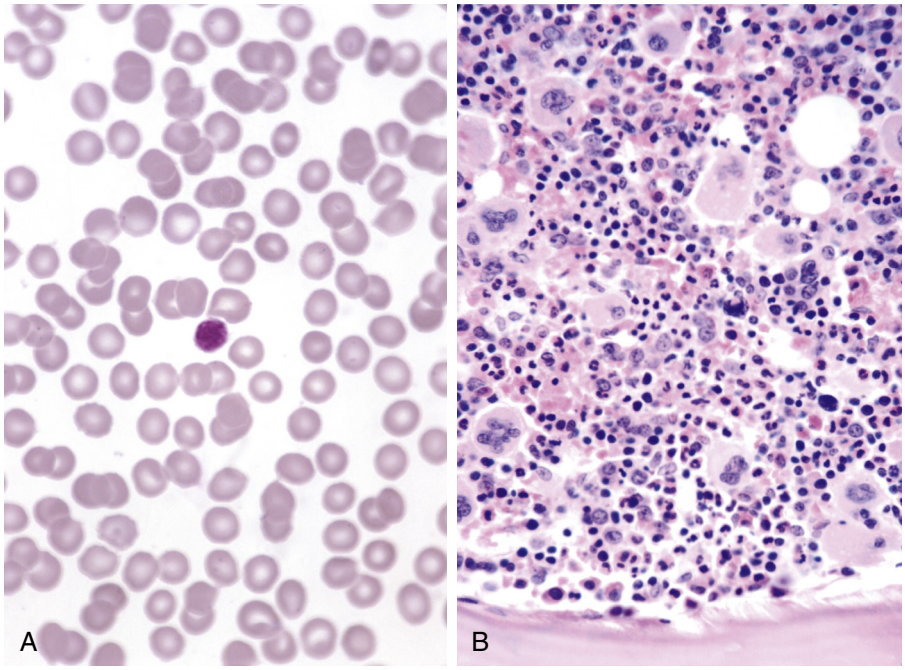

FIG. E1 Immune thrombocytopenic purpura. A, Peripheral blood smear of immune thrombocytopenic purpura. A single large platelet is seen at the center. Large platelets reflect early release from the bone marrow. **B,** The bone marrow trephine biopsy section contains increased numbers of megakaryocytes. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.)

BASIC INFORMATION

DEFINITION

Impetigo is a highly contagious superficial skin infection generally caused by *Staphylococcus aureus* and/or *Streptococcus* spp.

Common presentations are bullous impetigo (generally caused by staphylococcal disease) and nonbullous impetigo (from streptococcal infection and possible staphylococcal infection); the bullous form is caused by an epidermolytic toxin produced at the site of infection.

SYNONYMS

Impetigo vulgaris
Pyoderma
Impetigo contagiosa
Bullous impetigo

ICD-10CM CODES

L01.00 Impetigo, unspecified
L01.01 Nonbullous impetigo
L01.02 Bockhart impetigo
L01.03 Bullous impetigo
L01.09 Other impetigo

EPIDEMIOLOGY & DEMOGRAPHICS

- Impetigo is the most common bacterial skin infection in children 2 to 5 yr of age. Bullous impetigo accounts for 30% of cases and nonbullous for 70% of cases. Impetigo is most common in temperate zones, mostly during the summer in hot, humid weather. Common sources for children are dirty fingers, pets, and other children in school or day care centers. Impetigo often complicates insect bites, pediculosis, scabies, eczema, and poison ivy.
- Bullous impetigo is most common in infants and children. The nonbullous form is most common in children ages 2 to 5 yr with poor hygiene in warm climates.
- The overall incidence of acute nephritis with impetigo varies between 2% and 5%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Nonbullous impetigo begins as a single red macule or papule that quickly becomes a vesicle. Rupture of the vesicle produces an erosion of which the contents dry to form honey-colored crusts. Multiple lesions with golden yellow crusts (Fig. E1) and weeping areas are often found on the skin around the nose, mouth, and limbs.
- Bullous impetigo is manifested by the presence of vesicles that enlarge rapidly to form bullae with contents that vary from clear to cloudy. There is subsequent collapse of the center of the bullae (Fig. E2); the peripheral areas may retain fluid, and a honey-colored crust may appear in the center (Fig. E3). As the lesions enlarge and become contiguous with the others, a scaling border replaces the fluid-filled rim; there is minimal erythema surrounding the lesions.
- Regional lymphadenopathy is most common with nonbullous impetigo.
- Constitutional symptoms are generally absent.

ETIOLOGY

- *S. aureus* coagulase positive is the dominant microorganism (50% to 70% of cases).
- *S. pyogenes* (group A β-hemolytic streptococci): M-T serotypes of this organism associated with acute nephritis are 2, 49, 55, 57, and 60. Group B streptococci are associated with newborn impetigo.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Atopic dermatitis
- Herpes simplex infection
- Ecthyma
- Folliculitis
- Dermatitis herpetiformis
- Insect bites
- Scabies, pediculosis
- Tinea corporis, cutaneous candidiasis
- Pemphigus vulgaris and bullous pemphigoid
- Chickenpox
- Thermal burns
- Contact dermatitis
- Stevens-Johnson syndrome, Sweet syndrome

WORKUP

Diagnosis is clinical.

LABORATORY TESTS

- Generally not necessary
- Gram stain and culture and sensitivity to confirm the diagnosis when the clinical presentation is unclear
- Sedimentation rate parallel to activity of the disease

FIG. E1 Nonbullous (crusted) impetigo. Erythematous papules with honey yellow–colored crusting. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

FIG. E2 Bullous impetigo. Thin-walled vesicles and shallow erosions with peripheral collarettes and mild crusting on the buttock and posterior thigh. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

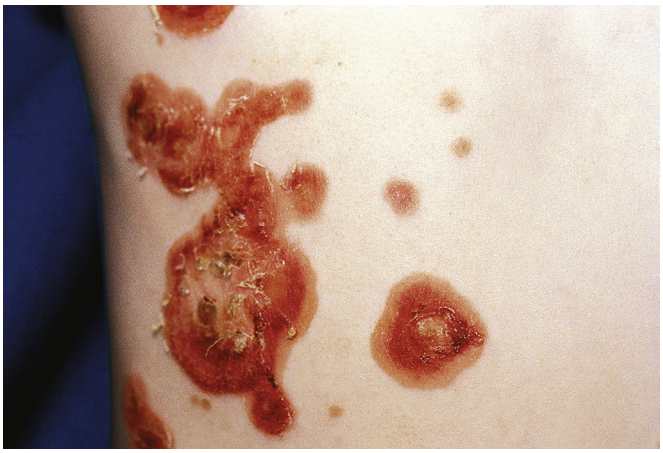

FIG. E3 Bullous impetigo. Multiple tender, erythematous patches with a peripheral collarette, representing remnants of the blister roof. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

- Increased anti-DNAse B and antihyaluronidase
- Urinalysis revealing hematuria with erythrocyte casts and proteinuria in patients with acute nephritis (most frequently occurring in children between ages 2 and 4 yr in the southern part of the U.S.)
- If recurrent staphylococcal impetigo develops, a culture of the anterior nares should be done to rule out a carrier state

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Remove crusts by soaking with wet cloth compresses (crusts block the penetration of antibacterial creams).

GENERAL Rx

- Treatment consists of topical or oral antibotics that are active against both *S. aureus* and β-hemolytic streptococci.
- Application of 2% mupirocin ointment tid for 10 days or retapamulin 1% applied bid for 5 days to the affected area or until all lesions have cleared.
- Ozenoxacin is a topical nonfluorinated quinolone antibiotic recently FDA-approved for treatment of impetigo in patients 2 mo old. Cost is a limiting factor.
- Oral antibiotics are used in severe cases: Commonly used agents are dicloxacillin 250 mg qid for 7 to 10 days, cephalexin 250 mg qid for 7 to 10 days, azithromycin 500 mg on day 1, 250 mg on days 2 through 5, amoxicillin/clavulanate 500 mg q8h.
- Impetigo can be prevented by prompt application of mupirocin or triple-antibiotic ointment (bacitracin, Polysporin, and neomycin) to sites of skin trauma.
- Patients who are carriers of *S. aureus* in their nares should be treated with mupirocin ointment applied to their nares bid for 5 days or a 10-day course of rifampin, 600 mg/day, combined with dicloxacillin (for methicillin-sensitive *Staphylococcus aureus* [MSSA]) or trimethoprim-sulfamethoxazole [TMP-SMX] (for methicillin-resistant *Staphylococcus aureus* [MRSA]).
- Fingernails should be kept short, and patients should be advised not to scratch any lesions to avoid spread of infection.

DISPOSITION

Most cases of impetigo resolve promptly with appropriate treatment. Both bullous and nonbullous forms of impetigo heal without scarring.

REFERRAL

Nephrology referral in patients with acute nephritis

PEARLS & CONSIDERATIONS

COMMENTS

- Patients should be instructed on use of antibacterial soaps and avoidance of sharing of towels and washcloths because impetigo is extremely contagious.
- Children attending day care should be removed until 48 to 72 hr after initiation of antibiotic treatment.
- Bullous impetigo may be an early manifestation of HIV infection.

RELATED CONTENT

Impetigo (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Bangert S et al: Bacterial resistance and impetigo trend: a review, *Pediatr Dermatol* 29(3):431-434, 2012.

Hartman-Adams H et al: Impetigo: diagnosis and treatment, *Am Fam Physician* 90(4):229-235, 2014.

Inclusion Body Myositis

BASIC INFORMATION

DEFINITION

Inclusion body myositis (IBM) is the most common acquired idiopathic myopathy with onset after the age of 50. The idiopathic inflammatory myopathies include polymyositis (PM), dermatomyositis (DM), autoimmune necrotizing myopathy, and inclusion body myositis. They are associated with inflammatory involvement of muscle fibers and recurrent weakness. Although IBM is classified among the inflammatory myopathies, its underlying pathophysiology has not yet been delineated, and antiinflammatory medications do not improve weakness.

SYNONYM

IBM

ICD-10CM CODE
G72.41 Inclusion body myositis [IBM]

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.22 to 0.79 cases/100,000 persons; uncommon in Asians and African Americans
PREVALENCE: 0.5 to 7.1 cases/100,000 persons
PREDOMINANT SEX: Male:female ratio: 1.3:1
PREDOMINANT AGE: 87% older than 50 yr; mean age of 60 yr
PEAK INCIDENCE: Seventh decade
RISK FACTORS: None known
GENETICS: Less than 10% of cases familial

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Insidious onset of slowly progressive proximal leg and distal arm weakness.
- Time to diagnosis from symptom onset often lags by yrs to a decade. Most patients report a history of preexisting weakness averaging 5 to 7 yr.
- Functional loss of strength in the legs most often precedes arm weakness.
- The cardinal clinical features include early weakness and atrophy of quadriceps muscles (difficulty climbing stairs, rising from chairs, and getting out of cars) along with wrist and finger flexor muscles (difficulty grasping, opening jars, and turning doorknobs). Ankle dorsiflexion weakness may also be prominent leading to foot drop and tripping.
- When examining strength, side-to-side asymmetries are seen in one or more muscle groups in the majority of patients. This stands in contrast to the symmetrical, proximal involvement of polymyositis and most muscular dystrophies.
- Dysphagia and/or mild facial weakness are present in about one third to one half of cases. Dysphagia may be the presenting symptom.
- Although sensory symptoms are usually lacking, one third have evidence of peripheral neuropathy on physical examination and/or electrodiagnostic testing.
- 10% to 15% of patients have concomitant autoimmune disorders such as systemic lupus erythematosus, Sjögren syndrome, scleroderma, sarcoidosis, or thrombocytopenia. However, unlike polymyositis and dermatomyositis, IBM does not portend an increased risk of heart disease, lung disease, or cancer.

ETIOLOGY

The pathogenesis of IBM is not known. Inflammatory, degenerative, viral, and prion etiologies have been postulated, but none substantiated.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Polymyositis (Table E1)
- Dermatomyositis
- Amyotrophic lateral sclerosis
- Late-onset muscular dystrophies
- Acid maltase deficiency

WORKUP

- Thorough neurologic examination with emphasis on the motor exam.
- Nerve conduction studies should be performed to exclude other causes and EMG to document a myopathy.
- The diagnosis of definite IBM requires the following features on muscle biopsy (Fig. E1): (1) Inflammation, (2) inflammatory cells invading healthy muscle fibers, (3) vacuoles, and (4) amyloid deposits by Congo red staining, TDP-43 sarcoplasmic staining, or tubulofilaments on electron microscopy.

LABORATORY TESTS

- Creatine kinase level (mildly elevated early in disease but less than 10× normal levels; creatine kinase levels may normalize as the disease progresses).
- Complete blood count and coagulation studies should be drawn in anticipation of the muscle biopsy.

IMAGING STUDIES

MRI may reveal atrophy and signal abnormalities in volar forearm muscle groups and quadriceps atrophy with relative preservation of the rectus femoris muscle.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical therapy and occupational therapy with the use of assistive mobility devices such as canes, walkers, and wheelchairs are the mainstay of therapy.
- Occasionally knee orthoses or ankle-foot orthoses may improve and prolong ambulation.

ACUTE GENERAL Rx

None

CHRONIC Rx

- Experts have not found clinically significant improvement in functional strength with any pharmacologic therapy. Clinical trials of corticosteroids, methotrexate, intravenous immunoglobulin, anti-T lymphocyte globulin, etanercept, interferon β-1a, and oxandrolone have all failed to demonstrate functional improvements in limb strength.
- A short, small trial of a home exercise program demonstrated mild improvements in strength.
- IBM is generally refractory to therapy.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Some patients choose to self-treat with creatine supplementation, coenzyme Q10, or lithium. There is no evidence supporting these treatments.

REFERRAL

- Patients with suspected IBM should be referred to a neurologist with subspecialty expertise in neuromuscular medicine.
- Physical therapy and occupational therapy consultations help the patient optimize ambulation and fine motor tasks, respectively.
- Speech therapy consultations can assist with symptomatic dysphagia.

PROGNOSIS

Life expectancy is not significantly altered in this late-onset, slowly progressive disorder. Some patients require wheelchair use 10 to 20 yr after disease onset.

PEARLS & CONSIDERATIONS

COMMENTS

- In contrast to PM and DM, muscle weakness in IBM generally affects both distal and proximal muscles. Although typically symmetric, muscle distribution may be asymmetric.
- A key to diagnosis rests in finding weakness of wrist and/or finger flexors (especially the deep finger flexors at the DIP joints) on examination.

PREVENTION

None known

PATIENT & FAMILY EDUCATION

Patient information and support groups can be found at: www.ninds.nih.gov/Disorders/All-Disorders/Inclusion-Body-Myositis-Information-Page and www.myositis.org.

RELATED CONTENT

Inflammatory Myopathies (Related Key Topic)

AUTHORS: **Emma H. Weiss, MD, Matthew P. Wicklund, MD,** and **Joseph S. Kass, MD, JD, FAAN**

SUGGESTED READING

Greenberg SA: Inclusion body myositis, *Curr Opin Rheumatol* 23:574, 2011.

TABLE E1 Clinical and Laboratory Features of Idiopathic Inflammatory Myopathy Subgroups

Clinical Features	Dermatomyositis	Polymyositis	Inclusion Body Myositis
Age	Children and adults	Adults[a]	Adults >50 yr
Disease onset	Subacute	Subacute	Chronic
Muscle weakness	Proximal	Proximal	Selective pattern[b]
Symmetry	Symmetric	Symmetric	Asymmetric
Systemic features	Yes[c]	Yes[c]	Yes[d]
Skin changes	Yes[e]	No	No
Calcinosis	Yes[f]	Rarely	No
Associated connective tissue disease	Yes[g]	Yes[g]	Yes[h]
Associated malignancy	Yes	Yes	Yes
Laboratory features			
Serum enzymes[i]	Normal to high	Normal to high	Normal to high
Abnormal EMG[j]	Yes	Yes	Yes
Abnormal muscle biopsy	Perifascicular atrophy, capillary depletion, patchy MHC class I expression and microinfarcts	$CD8^+$ T cell invasion of nonnecrotic fibers and MHC class I expression on fibers	$CD8^+$ T cell invasion, MHC expression, vacuolated fibers, and tubulofilamentous inclusions in fibers

$CD8^+$ T cell, cytotoxic T lymphocyte cell; *EMG,* electromyogram; *MHC,* major histocompatibility complex.
[a]Rarely in children.
[b]Early involvement of finger flexor, wrist flexor or wrist extensor weakness, and involvement of quadriceps femoris.
[c]Some patients have dysphagia, synovitis, and interstitial lung disease.
[d]Some patients have dysphagia.
[e]Gottron sign and heliotrope rash.
[f]Especially in children.
[g]Overlap with scleroderma, systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, and mixed connective tissue disease.
[h]Associated with Sjögren syndrome but less frequently associated with other connective tissue diseases.
[i]Serum creatine kinase, aspartate transaminase, lactate dehydrogenase, and aldolase vary from normal to very high levels.
[j]Myopathic motor unit potentials with spontaneous discharges in dermatomyositis, with and without spontaneous discharges in polymyositis, and mixed pattern of short- and long-duration motor unit potentials in inclusion body myositis.
From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, WB Saunders.

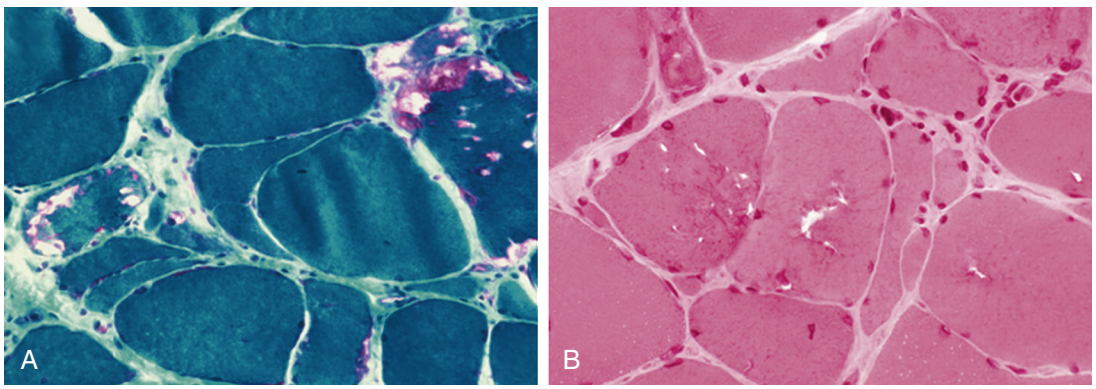

FIG. E1 Trichrome, hematoxylin, and eosin staining of inclusion body myositis biopsy. Note the red-rimmed inclusions **(A)** and marked variation in muscle fiber size **(A** and **B).** (Courtesy Dr. Paul Plotz.)

BASIC INFORMATION

DEFINITION

Fecal incontinence is defined as the involuntary loss of gas or liquid stool (minor incontinence) or the involuntary loss of solid stool (major incontinence).

SYNONYMS

Anal or bowel incontinence
Accidental bowel leakage
Fecal incontinence

ICD-10CM CODES
R15.9 Full incontinence of feces
F98.1 Encopresis not due to a substance or known physiological condition

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Affects 0.5% to 1.5% of the population younger than age 65, but >10% older than 65. More common in institutionalized patients.
PREVALENCE: Varies widely depending on definition used and population studied; often underreported. In community-based studies, ranges from 1% to 24%. Increases with age and BMI in women.
PREDOMINANT SEX AND AGE: Slightly more common in females than males and those of advanced age (older than 65 yr).

RISK FACTORS:
- Cognitive or behavioral dysfunction
- Structural anorectal abnormalities (e.g., rectal prolapse)
- Neurologic disorders, comorbidities (e.g., diabetes mellitus), inflammatory bowel disease (IBD)
- Poor mobility in female gender, advanced age
- Anal sphincter trauma (surgery, obstetrical injury)
- Fecal impaction from constipation or diarrhea

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Inspect perianal area to evaluate for the presence of fecal material, prolapsing hemorrhoids, chemical dermatitis, scars, fistula or rectal prolapse.
- Assess for anocutaneous reflex. This may be elicited by stroking skin in each perianal quadrant (normal response is a brisk anal wink). Absent reflex is suggestive of nerve damage.
- Digital rectal examination to assess for impaction, mass, and resting to squeezing anal tone by asking the patient to bear down. Ask patient to bear down to assess for rectal prolapse or excessive perianal descent.

ETIOLOGY

- Usually multifactorial. Table 1 summarizes the mechanisms, causes, and pathophysiology of fecal incontinence. Common types of anorectal dysfunction causing rectal outlet delay in the elderly are summarized in Table 2
- Overflow due to fecal impaction
- Anal sphincter weakness:
  1. Trauma (e.g., anorectal surgery, childbirth).
  2. Nontraumatic (e.g., neurologic, spinal cord lesions, diabetes, scleroderma).
- Anorectal inflammation:
  1. Radiation, IBD
- CNS disorders (e.g., dementia, multiple sclerosis, stroke)
- Anatomic disturbance of pelvic floor:
  1. Fistula, prolapse
- Idiopathic

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Fecal encopresis
- Irritable bowel syndrome or IBD

WORKUP

- Requires detailed history taking that includes the onset and precipitating events, duration and severity, stool consistency and urgency. Important to evaluate for history of urinary incontinence, anorectal surgery or radiation, neurologic disorders, or prior vaginal deliveries and complete a thorough physical exam. An algorithm for the evaluation and management of patients with fecal incontinence is illustrated in Fig. 1.
- Diagnostic workup may include endoscopy, anorectal manometry, endorectal ultrasound (simple and economical), MRI, defecography,

TABLE 1 Mechanisms, Causes, and Pathophysiology of Fecal Incontinence

Mechanism	Causes	Pathophysiology
Abnormal Anorectal or Pelvic Floor Structures		
Anal sphincter muscles	Hemorrhoidectomy, neuropathy, obstetric injury	Sphincter weakness, loss of sampling reflex
Puborectalis muscle	Aging, excessive perineal descent, trauma	Obtuse anorectal angle, sphincter weakness
Pudendal nerve	Excessive straining, obstetric or surgical injury, perineal descent	Sphincter weakness, sensory loss, impaired reflexes
Nervous system, spinal cord, autonomic nervous system	Avulsion injury, spine surgery, diabetes mellitus, head injury, multiple sclerosis, spinal cord injury, stroke	Loss of sensation, impaired reflexes, secondary myopathy, loss of accommodation
Rectum	Aging, IBD, IBS, prolapse, radiation	Loss of accommodation, loss of sensation, hypersensitivity
Abnormal Anorectal or Pelvic Floor Function		
Impaired anorectal sensation	Autonomic nervous system disorders, central nervous system disorders, obstetric injury	Loss of stool awareness, rectoanal agnosia
Fecal impaction	Dyssynergic defecation	Fecal retention with overflow, impaired sensation
Altered Stool Characteristics		
Increased volume and loose consistency	Drugs, bile salt malabsorption, infection, IBD, IBS, laxatives, metabolic disorders	Diarrhea and urgency, rapid stool transport, impaired accommodation
Hard stools, retention	Drugs, dyssynergia	Fecal retention with overflow
Miscellaneous		
Physical mobility, cognitive function	Aging, dementia, disability	Multifactorial changes
Psychosis	Willful soiling	Multifactorial changes
Drugs*	Anticholinergics Antidepressants Caffeine Laxatives Muscle relaxants	Constipation Altered sensation, constipation Relaxation of sphincter tone Diarrhea Relaxation of sphincter tone
Food intolerance	Fructose, lactose, or sorbitol malabsorption	Diarrhea, flatus

*Pathophysiology is noted for each class of drugs.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

TABLE 2 Types of Anorectal Dysfunction Causing Rectal Outlet Delay in Older People

Pathophysiology	Clinical Picture	
Rectal dysmotility	Reduced rectal motility and contractions Increased rectal compliance Variable degree of rectal dilation Impaired rectal sensation with blunting of urge to pass stool Over time, increasing rectal distention required to reflexively trigger the defecation mechanism	Rectal hard or soft stool retention on digital examination of which patient may be unaware Chronic rectal distention leads to relaxation of the internal sphincter and fecal soiling One postulated cause is diminished parasympathetic outflow as a result of impaired sacral cord function (e.g., from ischemia or spinal stenosis); may also develop through persistent disregard or suppression of the urge to defecate as a result of dementia, depression, immobility, or painful anorectal conditions
Pelvic floor dyssynergia	Paradoxical contraction or failure to relax the pelvic floor and external anal sphincter muscles during defecation Manometric studies show paradoxical increases in anal canal pressure on straining	Severe and long-standing symptoms of rectal outlet delay Parkinson disease More common in younger women
Irritable bowel syndrome	Increased rectal tone and reduced compliance Lower pain threshold on distending the rectum during anorectal function tests	Usually constipation-predominant in older people Rome criteria symptoms: Abdominal distention or pain relieved by defecation, passage of mucus, and feeling of incomplete emptying

From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, 2017, Elsevier.

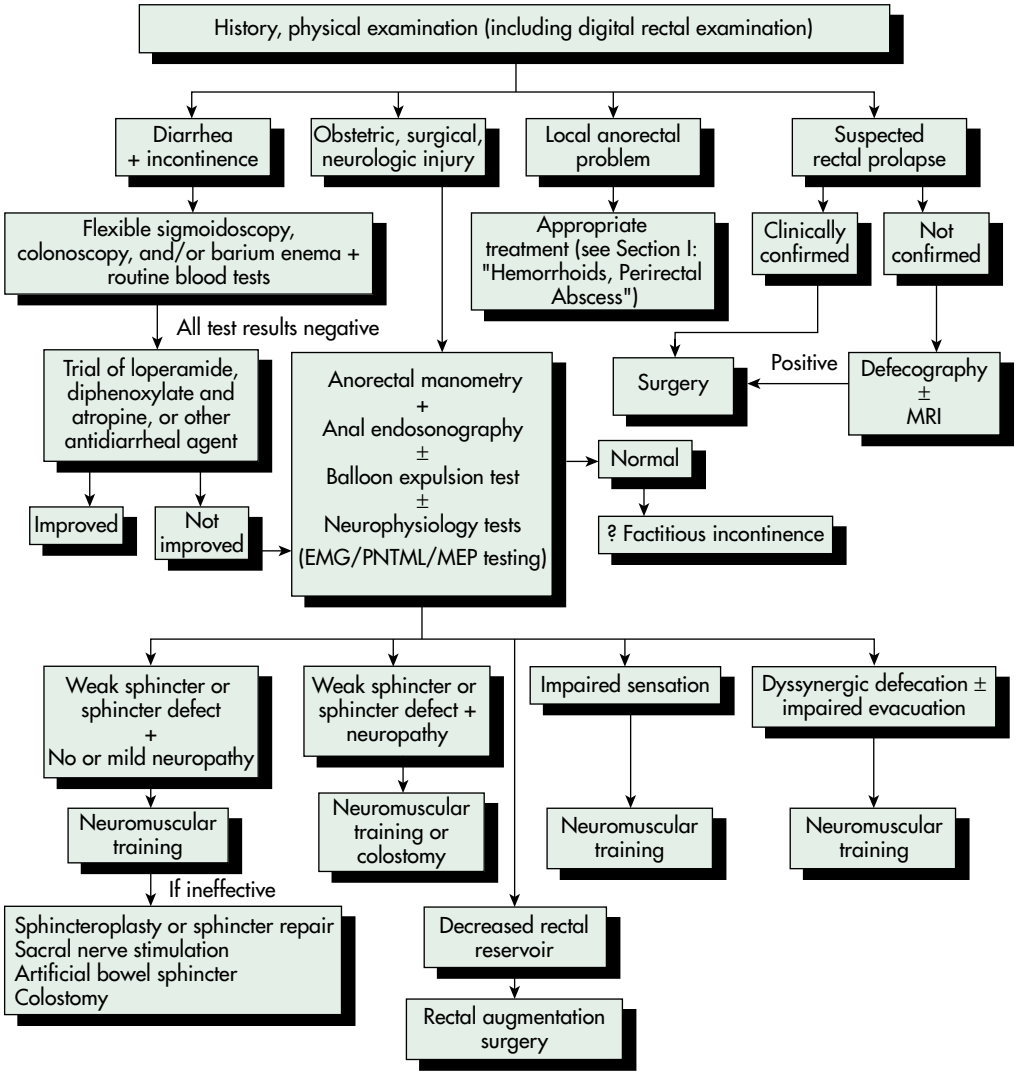

FIG. 1 Algorithm for the evaluation and management of patients with fecal incontinence. *EMG,* Electromyography; *MEP,* motor-evoked potential; *PNTML,* pudendal nerve terminal motor latency. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

pudendal nerve terminal latency, balloon expulsion test, and anal electromyography (EMG), depending on signs and symptoms. Diagnostic tests for fecal incontinence are summarized in Table 3.

Rx TREATMENT

- Therapy is focused on patient education (Table E4), supportive care, medications, biofeedback, and surgery. Table 5 summarizes bowel preparation in the elderly prior to colonoscopy.
- Medications focus on decreasing stool frequency and improving consistency.
  1. Fiber supplements (e.g., methylcellulose)
  2. Antidiarrheals: Loperamide, diphenoxylate/atropine sulfate, cholestyramine
  3. Topical phenylephrine, oral valproate sodium to increase smooth muscle tone
  4. Injectable anal bulking agent: Dextranomer -hyaluronic acid gel is FDA approved for the treatment of fecal incontinence in adults who fail conservative therapy. Given as four 1-ml injections into the deep submucosal layer of the anal canal. If inadequate response after at least 4 wk, a second course can be attempted.

NONPHARMACOLOGIC THERAPY

- Supportive therapy:
  1. Education, behavioral training, pelvic floor exercises
  2. Dietary modifications (e.g., increased fiber/fluid intake, less caffeine), food diary
  3. Incontinence pads, barrier cream (e.g., zinc oxide)
- Biofeedback therapy
- Electrical stimulation:

TABLE 3 Diagnostic Tests for Fecal Incontinence

Test	Clinical Use: Advantages	Clinical Use: Disadvantages	Quality of Evidence	Comments
Physiologic				
Anorectal manometry	Quantifies EAS and IAS pressures; identifies rectal hyposensitivity, rectal hypersensitivity, impaired rectal compliance, dyssynergic defecation	Lack of standardization	Good	Useful for detecting anal sphincter weakness, altered rectal sensation and accommodation, and dyssynergia
Needle EMG	Quantifies spike potentials and re-innervation pattern indicating neuropathy or myopathy	Invasive, painful; not widely available	Fair	Useful but used largely in research laboratories
Surface EMG	Displays EMG activity; can provide information on normal or weak muscle tone	Inaccurate, frequent artifacts	Fair	Used largely for neuromuscular training
Pudendal nerve terminal motor latency (PNTML)	Measures latency of the terminal portion of the pudendal nerve, simple to perform	Minimally invasive, low sensitivity, interobserver differences	Fair	Conflicting data; correlation with other tests and surgical outcome unclear
Translumbar and transsacral motor-evoked potentials	Quantifies the nerve conduction time of the entire spinoanal and spinorectal pathways; minimally invasive	Lack of standardization, training, controlled studies, and availability	Fair	Promising noninvasive test; more objective and higher yield than PNTML
Colonic transit study with radiopaque markers	Evaluates the presence of fecal retention; inexpensive and widely available	Inconsistent methodology, validity has been questioned	Good	Useful for identifying patients with fecal seepage and older persons with impaction
Balloon expulsion test (BET)	Simple, inexpensive, bedside assessment of ability to expel a simulated stool; identifies dyssynergic defecation	Lack of standardization	Good	Normal BET does not exclude dyssynergia; should be interpreted in the context of other anorectal test results
Imaging				
Anorectal US	Visualizes IAS and EAS defects, thickness, and atrophy and puborectalis muscles	Interobserver bias; scars difficult to identify	Good	Most widely available
Defecography	Detects prolapse, intussusception, obtuse anorectal angle, and pelvic floor weakness, as well as rectoceles and megarectum	Radiation exposure, embarrassment, availability, interobserver bias, inconsistent methodology	Fair	Useful and complementary with other tests
MRI	Simultaneously evaluates global pelvic floor anatomy and dynamic motion; reveals sphincter morphology and pathology outside the anorectum	Expensive, lack of standardization and availability	Fair	Used as an adjunct to other tests
Plain abdominal film	Identifies excessive amount of stool in the colon; simple, inexpensive, widely available	Lack of standardization of interpretation, lack of controlled studies	Poor	Not recommended for routine evaluation but useful in older adults and children with incontinence and fecal impaction
Barium enema	Identifies megacolon, megarectum, stenosis, diverticulosis, extrinsic compression, and intraluminal masses	Lack of standardization, embarrassment, radiation exposure, lack of controlled studies	Poor	Not recommended as part of routine evaluation
Endoscopy				
Flexible sigmoidoscopy and colonoscopy	Directly visualizes the colon to exclude mucosal lesions (e.g., solitary rectal ulcer syndrome, inflammation, malignancy)	Invasive, risks related to procedure (perforation, bleeding) and sedation	Poor	Indicated in patients with unexplained diarrhea and seepage and patients >age 50

EAS, External anal sphincter; *EMG,* electromyography; *IAS,* internal anal sphincter.

Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

TABLE 5 Bowel Preparation in Older People

- Older age, constipation, reported laxative use, tricyclic antidepressants, stroke, diabetes, and dementia are associated with inadequate preparation and taking longer to perform full colonoscopy.
- Even when patients take 75% to 100% of their prescribed treatments, bowel preparation is satisfactory only 50% of the time.

Guidance

- Give regular laxatives (e.g., Movicol 2 sachets daily) and enemas or suppositories for at least 1 wk before the procedure, with a longer run-up period in patients known to have constipation and those with comorbidities such as diabetes.
- Individualize the cathartic regimen (e.g., 1 to 2 L of GoLYTELY daily over 2 to 3 days in those unable to drink 4 L, or use of alternative preparations such as sodium picosulfate).
- Identify potential nonadherence. ("Can the patient drink 4 L of GoLYTELY in 24 hours?")
- Preempt unpleasant side effects. ("Will the patient be able to reach the toilet in time to avoid fecal leakage?")
- Use oral phospho soda with caution as administration in older people increases serum phosphate, even in patients with normal creatinine clearance.
- Consider preprocedure plain abdominal x-ray for evaluation of persistent fecal loading.
- Where possible, give a clear fluid diet before administration of bowel preparation.

From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, 2017, Elsevier.

1. Anal electrodes
2. Sacral nerve stimulation
3. Posterior tibial nerve stimulation

- Surgery:
  1. Anal sphincteroplasty
  2. Implanted devices (e.g., artificial anal sphincter).
  3. Colostomy (if intractable symptoms and/or failed all other therapies)
  4. Miscellaneous: Radiofrequency ablation, anal sling

REFERRAL

Colorectal surgery

PEARLS & CONSIDERATIONS

COMMENTS

The shame, embarrassment, and stigma associated with fecal and urinary incontinence pose significant barriers to seeking professional treatment, resulting in many people suffering from these conditions without help. Therefore, during routine office visits, asking all patients older than 70 about incontinence may be helpful.

PREVENTION

- Reduce constipation and avoid straining during bowel movements.
- Routine episiotomy is the most easily preventable risk factor for fecal incontinence in females.

PATIENT & FAMILY EDUCATION

https://www.niddk.nih.gov/health-information/digestive-diseases/bowel-control-problems-fecal-incontinence

SUGGESTED READINGS

Available at ExpertConsult.com

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TABLE E4 Patient Education

Toilet Habits and Positioning

- Do not delay having a bowel movement when you feel the urge.
- Put aside a particular time each day (we would advise after breakfast) when you can sit on the toilet without being in a hurry.
- A relaxed attitude to bowel evacuation will help, especially if you have problems with straining or a feeling of anal blockage.
- If straining is a problem, place a footstool under your feet while sitting on the toilet because this increases the ability of your abdominal muscles to help evacuate stool.

Abdominal Massage

- Lie on the bed with pillows under your head and shoulders.
- Bend your knees, and place a pillow underneath them for support.
- Cover your abdomen with a light sheet.
- Massage your abdomen with firm but gentle circular movements, starting at the right side and working across to the left side.
- Continue the massage for about 10 min.
- This massage should be a pleasant experience; if you feel any discomfort, stop.

Diet

- To help prevent constipation, you should eat more of the food from list A and less of the food from list B. Foods from list A tend to make the stool softer and easier to pass because they are high in fiber. Foods from list B tend to make the stool harder because they bind together the contents of the bowel.
  1. List A: Fresh fruit, prunes and other dried fruit, whole meal bread, bran cereals, porridge, salad, cooked vegetables (with skin where possible), beans, lentils
  2. List B: Milk, hard cheese, yogurt, white bread or crackers, refined cereals, cakes, pancakes, noodles, white rice, chocolate, creamed soups
- You should increase your fiber intake gradually because sudden change in fiber content may cause temporary bloating and irregularity. It is important to eat food that contains fiber throughout the day and not just at one meal such as breakfast.
- Increase the amount of fluid you drink gradually, up to 10 glasses a day. Try to drink more water, fruit juices, and carbonated drinks.

Sphincter Strengthening

Learning to Do Your Exercises

- Sit in a comfortable position with your knees slightly apart. Now imagine that you are trying to stop yourself from passing wind from the rectum. To do this, you must squeeze the muscle around the back passage. Try squeezing and lifting that muscle as tightly as you can. You should be able to feel the muscle move. Your buttocks, abdomen, and legs should not move at all. You should be aware of the skin around the back passage tightening and being pulled up and away from your chair. Really try to feel this. You now are exercising your anal sphincter muscles. (You do not need to hold your breath when you tighten the muscles.)

Practicing Your Exercises

- Tighten and pull up the anal sphincter muscles as much as you can. Hold tightened for at least 5 seconds, then relax for at least 10 seconds.
- Repeat the exercise at least 5 times. This will improve the strength of your muscles.
- Next, pull the muscles to about half of their maximum squeeze and see how long you can hold this. Then relax for at least 10 seconds.
- Repeat at least 5 times. This will improve the endurance, or staying power, of your muscles.
- Pull up the muscles as quickly and tightly as you can, relax, then pull up again. See how many times you can do this before you get tired. Try for at least 5 quick pull-ups. Try this quick exercise at least 10 times each day.
- Do all these exercises as hard as you can several times a day. As the muscles get stronger, you will find that you can do more pull-ups each time without getting tired.
- It takes time for exercises to make muscle stronger. You may need to exercise regularly for several mo before the muscles reach their full strength.

Instructions for Using Suppositories

- These may be inserted into your rectum by your nurse or caregiver, or yourself if you are physically able.
- If necessary, first go to the toilet and empty your bowels if you can.
- Wash your hands.
- Remove any foil or wrapping from the suppository.
- Either squat or lie on your side with your lower leg straight and your upper leg bent toward your waist.
- Gently but firmly insert the suppository, narrow end first, into the rectum using a finger. Push far enough (about 1 inch) so that it does not come out again.
- You may find your body wanting to push out the suppository. Close your legs and keep still for a few minutes.
- Try not to empty your bowels for at least 10 to 20 min.

From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, 2017, Elsevier.

SUGGESTED READINGS

Bharucha AE et al: Epidemiology, pathophysiology, and classification of fecal incontinence: state of the science summary for the National Institute of Diabetes and Digestive Kidney Diseases (NIDDK) workshop, *Am J Gastroenterol* 110:127-136, 2015.

Van Koughnett JA, Wexner SD: Current management of fecal incontinence: choosing amongst treatment options to optimize outcomes, *World J Gastroenterol* 19(48):9216-9230, 2013.

Wald A: Update on the management of fecal incontinence for the gastroenterologist, *Gastroenterol Hepatol* 12(3):155-164, 2016.

Whitehead WE et al: Treatment of fecal incontinence: state of the science summary for the National Institute of Diabetes and Digestive and Kidney Diseases workshop, *Am J Gastroenterol* 110:138-146, 2015.

BASIC INFORMATION

DEFINITION

Urinary incontinence is the involuntary loss of urine.

SYNONYMS

Urinary incontinence
UI

ICD-10CM CODES

R32	Unspecified urinary incontinence
N39.3	Stress incontinence (female) (male)
N39.41	Urgency urinary incontinence
N39.46	Mixed incontinence
N39.49	Disorder of urinary system, unspecified
R39.81	Functional urinary incontinence

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE: In the general population between the ages of 15 and 64 yr, 1.5% to 5% of men and 25% to 57% of women have urinary incontinence. In the nursing home population, 75% of the population has some degree of incontinence. Nearly 20% of children through the mid-teenage yrs have episodes of urinary incontinence.

CLINICAL, PSYCHOLOGICAL, & SOCIAL IMPACT

Fewer than 50% of women living with incontinence in the U.S. consult health care professionals for care, resulting in significant physical and psychological limitations. Many women choose to turn to home remedies, commercially available absorbent materials, and supportive aids. As the incontinence worsens, many women become depressed, limit social interaction, refrain from sexual intimacy, and become homebound. It is estimated that $19.5 billion in direct costs is spent annually on incontinence in the U.S. Urinary incontinence contributes to approximately 6% of nursing home admissions in the older population, leading to a cost of $3 billion per yr. With aging populations around the world, this cost is dramatically increasing every yr.

The continence mechanisms are complex and include multiple levels of control—central and peripheral nervous systems, detrusor muscle, urethra, and pelvic floor muscle. Normal function depends on multiple levels of control and dysfunction at any of these levels can lead to incontinence.

MAJOR TYPES OF INCONTINENCE (FIG. 1)

- **Stress urinary incontinence (SUI)** (Table E1) is the complaint of involuntary loss of urine with effort or physical exertion (sporting activities), or on sneezing or coughing (any activity that increases intraabdominal pressure). SUI may be demonstrated in the office with a simple cough stress test during examination. The cotton swab test can determine the degree of urethral mobility, which may be helpful in determining which type of surgical procedure to perform, but this test is not useful for diagnosing SUI.
- **Intrinsic sphincter deficiency (ISD)** is the most severe form of SUI and indicates a urethra that cannot remain closed even at rest. Urodynamically, this is diagnosed with a maximal urethral closure pressure <20 cm H_2O and leak point pressure <60 cm H_2O.
- **Urgency urinary incontinence (UUI)** is the complaint of involuntary loss of urine associated with urgency, a sudden compelling desire to pass urine that is difficult to defer. The diagnosis is often made clinically based on patient's report of symptoms but may also be associated with involuntary detrusor contractions on urodynamic investigation. May be idiopathic or neurogenic.
- **Overactive bladder (OAB)** is described as a constellation of symptoms (Figs. E2 and E3) including urgency, with or without urgency urinary incontinence, usually with urinary frequency and nocturia. It should be distinguished from excessive fluid intake and must exclude urinary tract infection. Can occur in up to 27% of men and up to 43% of women.
- **Mixed urinary incontinence** is the complaint of involuntary leakage of urine associated with urgency and also with exertion, effort, sneezing or coughing (see Fig. E4).
- **Overflow incontinence** is the leakage of urine resulting from urinary retention with resultant overflow or spilling of the urine. Causes include hypotonic bladder resulting from age, neurologic conditions such as diabetes or spinal cord injury, prior surgery, drug effects (e.g., intravesical Botox), or fecal impaction. It may also be caused by obstruction at the bladder neck and urethra, such as from prior anti-incontinence surgery, pelvic organ prolapse, urethral stenosis, or detrusor-sphincter dyssynergia.
- **Functional urinary incontinence** is the complaint of involuntary leakage of urine resulting from chronic impairments of physical and/or cognitive functioning. This is a diagnosis of exclusion and may be cured by improving the patient's functional status, treating comorbidities, changing medications, and reducing environmental barriers.
- **Extraurethral urinary incontinence** is leakage that bypasses the urethral meatus (i.e., vesicovaginal fistula or ectopic ureter).

DIAGNOSIS

HISTORY

- Since many women are hesitant to bring up symptoms of incontinence, these symptoms should be elicited through simple screening.
- History of present illness, psychosocial factors, congenital disorders, access issues for the physically challenged, neurologic disorders, and medication use are coexistent disorders that may affect the urinary tract.
- Urinary incontinence may be characterized by frequency of incontinence episodes, severity, and extent of bother.
- Voiding diary to assess total voided volume, frequency of micturition, mean volume voided, largest single volume, diurnal distribution, nature and severity of incontinence.
- Assessments of the severity of symptoms and goals for treatment are important parts of the history.

WORKUP

- General physical examination:
  1. Confounding conditions including mobility issues. Comorbid conditions that can cause or contribute to urinary incontinence in elderly patients are summarized in Table 2. Table 3 describes medications that can cause or contribute to urinary incontinence
  2. Neuromuscular deficits (gait of the patient)
- Pelvic exam:
  1. Concurrent pelvic organ prolapse
  2. Vaginal discharge
  3. Estrogen status
  4. Pelvic floor strength assessment

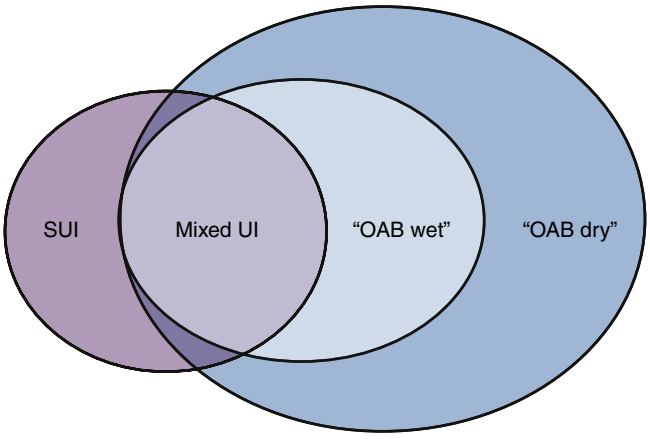

FIG. 1 Incontinence may be stress urinary incontinence *(SUI),* mixed urinary incontinence *(UI),* or urgency urinary incontinence ("overactive bladder *[OAB]* wet"), especially in women. SUI can coexist with "OAB dry," giving rise to mixed symptoms of stress incontinence and urgency. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

TABLE 2 Comorbid Conditions that Can Cause or Contribute to Urinary Incontinence in Frail Older Adults

Conditions	Comments	Implications for Management
Comorbid Medical Illnesses		
Diabetes mellitus	Poor control can cause polyuria and precipitate or exacerbate incontinence; also associated with increased likelihood of urgency incontinence and diabetic neuropathic bladder	Better control of diabetes can reduce osmotic diuresis and associated polyuria, improve incontinence
Degenerative joint disease	Can impair mobility and precipitate urgency UI	Optimal pharmacologic and nonpharmacologic pain management can improve mobility, toileting ability
Chronic pulmonary disease	Associated cough can worsen stress UI	Cough suppression can reduce stress incontinence and cough-induced urgency UI
Congestive heart failure Lower extremity venous insufficiency	Increased nighttime urine production can contribute to nocturia and UI	Optimizing pharmacologic management of congestive heart failure, sodium restriction, support stockings, leg elevation, and late afternoon dose of rapid-acting diuretic may reduce nocturnal polyuria, associated nocturia, nighttime UI
Sleep apnea	May increase nighttime urine production by increasing production of atrial natriuretic peptide	Diagnosis and treatment of sleep apnea, usually with continuous positive airway pressure devices, may relieve UI, reduce nocturnal polyuria and associated nocturia
Severe constipation and fecal impaction	Associated with "double" incontinence (urine and fecal)	Appropriate use of stool softeners Adequate fluid intake and exercise Disimpaction if necessary
Neurologic and Psychiatric Conditions		
Stroke	Can precipitate urgency UI and, less often, urinary retention; also impairs mobility	UI after acute stroke often resolves with rehabilitation; persistent UI should be further evaluated. Regular toileting assistance essential for those with persistent mobility impairment
Parkinson disease	Associated with urgency UI; also causes impaired mobility and cognition in late stages	Optimizing management may improve mobility, improve UI Regular toileting assistance essential for those with mobility and cognitive impairment in late stages
Normal-pressure hydrocephalus	Presents with UI, along with gait and cognitive impairments	Patients presenting with all three symptoms should be considered for brain imaging to rule out this condition; may improve with a ventricular-peritoneal shunt
Dementia (Alzheimer, multi-infarct, others)	Associated with urgency UI; impaired cognition and apraxia interfere with toileting and hygiene	Regular toileting assistance essential for those with mobility and cognitive impairment in late stages
Depression	May impair motivation to be continent; may also be a consequence of incontinence	Optimizing pharmacologic and non-pharmacologic management of depression may improve UI Discontinuation or modification of drug regimen
Medications		
Functional Impairments		
Impaired mobility, impaired cognition	Impaired cognition and/or mobility due to a variety of conditions (listed above) and others can interfere with ability to toilet independently and can precipitate UI	Regular toileting assistance essential for those with severe mobility and/or cognitive impairment
Environmental Factors		
Inaccessible toilets Unsafe toilet facilities No contrasting color between toilet and seat Caregivers unavailable for toileting assistance	Frail, functionally impaired persons require accessible and safe toilet facilities and, in many cases, human assistance to be continent	Environmental alterations may be helpful; supportive measures such as pads may be necessary if caregiver assistance not regularly available

UI, Urinary incontinence.
From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

5. Neurologic examination to assess sacral nerves with anal wink and bulbocavernosus reflex

- Rectal examination to assess sphincter tone and stool impaction
- Simple cough stress test
- Urethral hypermobility
- Postvoid residual check with bladder scan or catheter to exclude retention
- 3-day bladder diary to assess frequency, timing, and volume of voids

LABORATORY TESTS

It is important to rule out urinary tract infection and microscopic hematuria with urinalysis and/or culture prior to more invasive testing for other causes for incontinence.

SPECIALIZED STUDIES

- **Urodynamic testing:** Measures different facets of urine storage and evacuation; usually necessary only if basic office evaluation does not elicit the cause of incontinence, if incontinence is persistent despite treatments, or if there are confounding contributors to incontinence including prior surgery
  1. Simple cystometrogram: Graph of bladder and abdominal pressures related to fluid volume during filling/storage/voiding to assess sensation and capacity; also assesses presence of detrusor contractions, whether voluntary or involuntary
  2. Uroflowmetry and pressure-flow studies: Measure the mechanism of bladder emptying and rate of urine flow
  3. Urethral mechanism and pressure studies
  4. Electromyography: Studies the neuromuscular activity of pelvic muscles and striated urethral sphincter during filling and micturition
- **Cystourethroscopy:** Procedure that can be done in the office or the operating room in which an endoscope is inserted into the urethra to view the inside of the bladder and urethra. This procedure is not routinely used

TABLE 3 Medications that Can Cause or Contribute to Urinary Incontinence in Frail Older Adults

Medications	Effects on Continence
α-Adrenergic agonists	Increased smooth muscle tone in urethra and prostatic capsule may precipitate obstruction, urinary retention, related symptoms
α-Adrenergic antagonists	Decreased smooth muscle tone in urethra may precipitate stress urinary incontinence in women
Angiotensin-converting enzyme inhibitors	Cause cough that can exacerbate UI
Anticholinergics	May cause impaired emptying, urinary retention, and constipation, which can contribute to UI; may cause cognitive impairment, reduce effective toileting ability
Calcium channel blockers	May cause impaired emptying, urinary retention, and constipation, which can contribute to UI; may cause dependent edema, which can contribute to nocturnal polyuria
Cholinesterase inhibitors	Increase bladder contractility, may precipitate urgency UI
Diuretics	Cause diuresis and precipitate UI
Lithium	Polyuria due to diabetes insipidus
Opioid analgesics	May cause urinary retention, constipation, confusion, immobility, all of which can contribute to UI
Psychotropic drugs Sedatives Hypnotics Antipsychotics Histamine-1 receptor antagonists	May cause confusion and impaired mobility and precipitate UI; anticholinergic effects; confusion
Selective serotonin reuptake inhibitors	Increase cholinergic transmission, may lead to urinary UI
Others—gabapentin, glitazones, nonsteroidal antiinflammatory drugs	Can cause edema, which can lead to nocturnal polyuria and cause nocturia and nighttime UI

UI, Urinary incontinence.
From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

to evaluate incontinence unless hematuria is present or prior pelvic surgery is noted on history

IMAGING STUDIES

- These are usually ordered only if history and/or physical findings suggest other, less common causes of incontinence (i.e., genitourinary fistula) or if microscopic hematuria is present.
- Renal ultrasound may be used to assess for hydronephrosis.
- CT urogram may be used to assess upper tract abnormalities, congenital anomalies, genitourinary fistula, and microscopic hematuria etiologies.

Rx TREATMENT

- The recommended approach to urinary incontinence is a stepped care plan first offering noninvasive behavioral modifications such as bladder training, weight loss, and fluid management. Fig. E5 summarizes the diagnosis and treatment of overactive bladder
- **Pelvic floor muscle training,** including Kegel exercises and often augmented with biofeedback or electrical stimulation, is an important component of first-line therapy for stress, urge, and mixed incontinence. Women should perform 45 to 50 exercises per day to achieve good results (60% to 85% reduction in incontinence if biofeedback is also used)
- **Estrogen,** oral or vaginal, increases the concentration of alpha-adrenergic receptors in the urethra and bladder, which improves vascularity and subsequently increases thickness of the urethral epithelium in women with urogenital atrophy
- **Pharmacotherapy** is usually reserved for urgency urinary incontinence:
  1. Antimuscarinic (anticholinergic) medications: Block parasympathetic muscarinic receptors (detrusor M2/M3 receptors) to inhibit involuntary detrusor contractions:
     a. Agents available: Darifenacin, fesoterodine, oxybutynin (available orally and as a transdermal patch), solifenacin, tolterodine, and trospium
     b. Efficacy: Shown to improve symptoms and continence but only modestly compared with placebo
     c. Side effects: High rates of discontinuation due to side effects, most often dry mouth and constipation. May also exacerbate urinary retention, blurred vision, dyspepsia, and impaired cognitive function, with some studies now showing an association with dementia if used for >2 yr; contraindicated in narrow-angle glaucoma
     d. Of note, trospium may have a lower risk of cognitive impairment give the size of the molecule as it is less likely to cross the blood-brain barrier
  2. Beta-agonists: Stimulate β3-adrenergic receptor in the detrusor muscle to cause relaxation and increase bladder capacity
     a. Agent available: Mirabegron
     b. Efficacy: Significant reductions in urgency incontinence in randomized trials
     c. Side effects: Tachycardia, hypertension, headache, and diarrhea (similar to placebo); not recommended in uncontrolled hypertension
  3. OnabotulinumtoxinA (Botox A): Inhibits the presynaptic release of acetylcholine from motor neurons at the neuromuscular junction to paralyze the muscle; given by cystoscopic intravesical injection every 6 to 12 months:
     a. Efficacy: Similar rates of improvement seen when compared with antimuscarinic medications, but more women reporting complete resolution of urgency urinary incontinence with Botox A (35% to 50% reporting "total continence" in clinical trials); third-line treatment due to adverse effects
     b. Adverse effects: Urinary retention or incomplete bladder emptying (5% requiring catheterization) and urinary tract infections (33%)
- **Peripheral tibial nerve stimulation:** 30-minute session of tibial nerve stimulation once per week for 12 weeks followed by a customized maintenance plan to treat OAB. Compared with placebo, pooled success rate was 60% in a guideline published by American Urological Association; fewer adverse events noted when compared with anti-muscarinic medication
- **Sacral neuromodulation:** Stimulation of bladder and pelvic floor nerves to treat OAB, UUI, and idiopathic urinary retention. The mechanism is unknown. The procedure occurs in a two-stage process: first the electrode is placed near S3 to determine if symptoms are improved by 50%; if so, then next the pulse generator is implanted. Evidence suggests 70% of women experience significant improvement in their symptoms with sacral neuromodulation
- **Augmentation cystoplasty:** Older procedure that was used before introduction of sacral neuromodulation in patients with poorly compliant bladders who were at risk for upper tract deterioration, completed by using a gastrointestinal segment
- **Devices:**
  1. Continence pessaries: For women with SUI who wish to defer or avoid surgery; help increase urethral resistance during increased intraabdominal pressure. A large randomized controlled trial demonstrated similar outcomes among women who underwent pessary, behavioral therapy, or a combination of both for incontinence; at 12 months, approximately 50% of women still using the

assigned treatment reported improvement in symptoms
2. Over-the-counter vaginal or urethral inserts: Disposable devices used to support the urethra, especially in women with situational stress incontinence (i.e., only when exercising); however, urethral inserts have been associated with a high rate of urinary tract infection

- **Surgery:** Indicated for women with SUI without symptom control after conservative management or as first-line treatment in appropriately counseled women who decline more conservative treatment:
  1. Synthetic slings are the most common primary surgical treatment for SUI. Cure rates of 62% to 98% have been reported in a recent systematic review:
     a. Transvaginal/retropubic: Trocars are passed through the retropubic space from the midurethra to the abdomen (or vice versa). Short-term cure rates range from 73% to 82% according to a 2009 Cochrane meta-analysis, with de novo urgency in approximately 6% of patients
     b. Transobturator: Trocars are passed from the vagina behind the ischium (or vice versa), with similar cure rates as the retropubic slings
     c. Single-incision slings: Only one vaginal incision is needed beneath the urethra; ends of the sling are secured in the internal obturator muscle
  2. Autologous fascial slings: Usually considered second line after the failure of synthetic slings due to length and morbidity of the operation. Cure rates estimated to be 50% to 75% depending on definition of cure
  3. Cadaveric slings: Usually second line; use has declined more recently due to concerns with early failure and declining success rate over time. Cure rates of 74% at 12 to 23 months and 80% at 48 months or greater
  4. Retropubic urethropexy, i.e., Burch procedure (open abdominal or laparoscopic): A large meta-analysis estimated cure rates to be 82% at 12 to 23 months and 73% at 48 months or longer for open procedures
- **Bulking Agents:** For treatment of stress incontinence, without hypermobility or in poor surgical candidates:
  1. Available agents: Carbon-coated zirconium beads, calcium hydroxyapatite, cross-linked polydimethylsiloxane
  2. Effectiveness: Relatively noninvasive but less effective than surgical intervention; cure rate at 63% to 80% at 1 yr
- Treatment for urinary retention and overflow incontinence focuses on reversal of modifiable factors and drainage of urine from the bladder:
  1. Clean intermittent self-catheterization
  2. Sacral neuromodulation

PEARLS & CONSIDERATIONS

COMMENTS

- Weight loss and exercise are helpful for urinary incontinence in obese women. Overweight and obese women with urinary incontinence also have a high prevalence of monthly fecal incontinence (16% found to be associated with low dietary fiber intake after adjustment for other known risk factors for fecal incontinence)
- Transient causes of urinary incontinence in the elderly are described in Table 4.
- Other forms of incontinence:
  1. Nocturnal enuresis: Loss of urine occurring during sleep; can occur as idiopathic or neurogenic
  2. Postvoid dribble: A postsphincteric collection of urine seen with urethral diverticulum; can be idiopathic
  3. Extraurethral incontinence: Enterovesical, urethral; also known as *fistula*
- Conditions that predispose to surgical failure: Advanced age, prior failed incontinence surgery, concurrent detrusor instability, abnormal perineal electromyography, pelvic radiation
- The Women's Preventive Services Initiative (WPSI) recommends screening women for urinary incontinence annually

TABLE 4 Transient Causes of Urinary Incontinence (DIAPPERS)

D	Delirium/confusional state
I	Infection—urinary (symptomatic)
A	Atrophic urethritis/vaginitis
P	Pharmaceuticals (diuretics, and so on)
P	Psychological, especially depression
E	Endocrine (hypercalcemia, hypokalemia, glycosuria)
R	Restricted mobility
S	Stool impaction

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Urinary Incontinence (Patient Information)
Pelvic Organ Prolapse (Related Key Topic)

AUTHORS: **Meagan S. Cramer, MD,** and **Emily Saks, MD, MSSCE**

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TABLE E1 Surgical Treatment of Stress Incontinence

- Abdominal retropubic urethropexy (suspension)
- Marshall-Marchetti-Krantz
  - Burch operation
- Sling procedure:
  - Pubovaginal (bladder neck) sling
    - Autologous:
      - Rectus abdominis fascia
      - Tensor fascia lata
      - Anterior vaginal wall sling
  - Allograft (cadaveric fascia lata fascia)
  - Xenograft:
    - Porcine dermis
    - Small intestinal submucosa
  - Synthetic mesh (polypropylene)
- Tension-free midurethral sling (polypropylene):
  - Retropubic
  - Transobturator
  - Single incision
- Urethral-bulking agents–
  - Carbon-coated zirconium beads
  - Calcium hydroxyapatite
  - Cross-linked polydimethylsiloxane

From Lipshultz LI et al: *Urology and the primary care practitioner,* ed 3, Philadelphia, 2008, Elsevier.

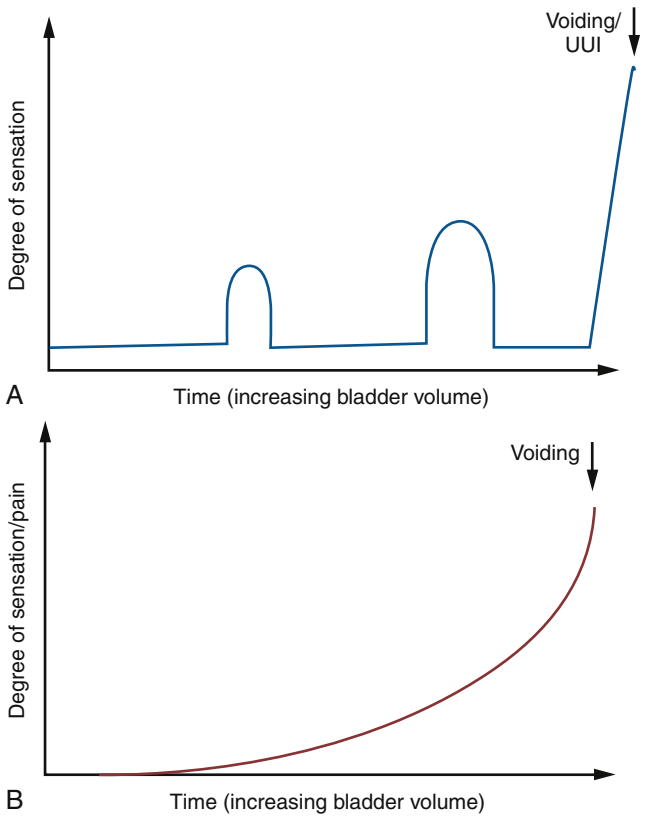

FIG. E2 The differences in the development of bladder sensation in overactive bladder (OAB) and bladder pain syndrome (BPS). A, In OAB, phasic increases in urgency arise and recede as filling progresses, until severe urgency compels the patient to void or an urgency urinary incontinence (UUI) episode sets in. **B,** In BPS, pain increases throughout filling, accelerating as filling progresses. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

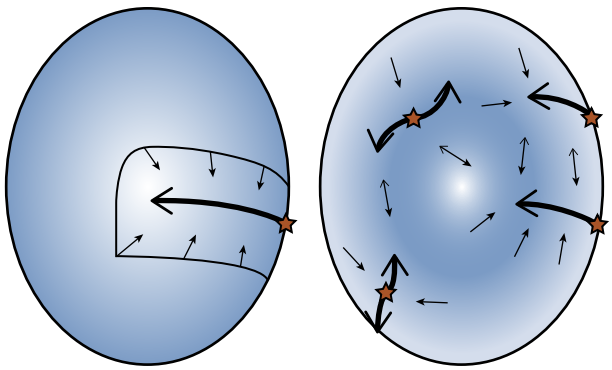

FIG. E3 *Left,* Schematic representation of a whole bladder during urinary storage, illustrating a localized "micromotion" contraction, starting from an initiation point *(star),* and spreading to a limited part of the bladder wall. Such activity is characteristic of the normal isolated bladder in all species tested (including human), and it is associated with only small fluctuations in bladder pressure, presumably because the noncontracting part of the bladder stays relaxed. In the overactive bladder *(right),* multifocal trigger points lead to continuous activity; this enhances the effect on bladder pressure (as the bulk of the bladder is active) and stimulates afferents by the extensive distorting movements. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

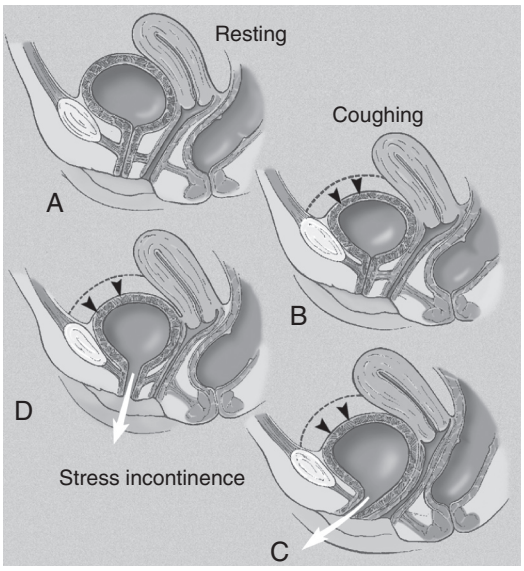

FIG. E4 A, Bladder and urethra in normal position. **B,** Intraabdominal pressure transmitted to the bladder *(arrowheads).* **C,** Bladder and urethra in abnormal position with loss of support (hypermobile). **D,** Loss of urethral closure *(arrow).* (From Lipshultz LI et al: *Urology and the primary care practitioner,* ed 3, Philadelphia, 2008, Elsevier.)

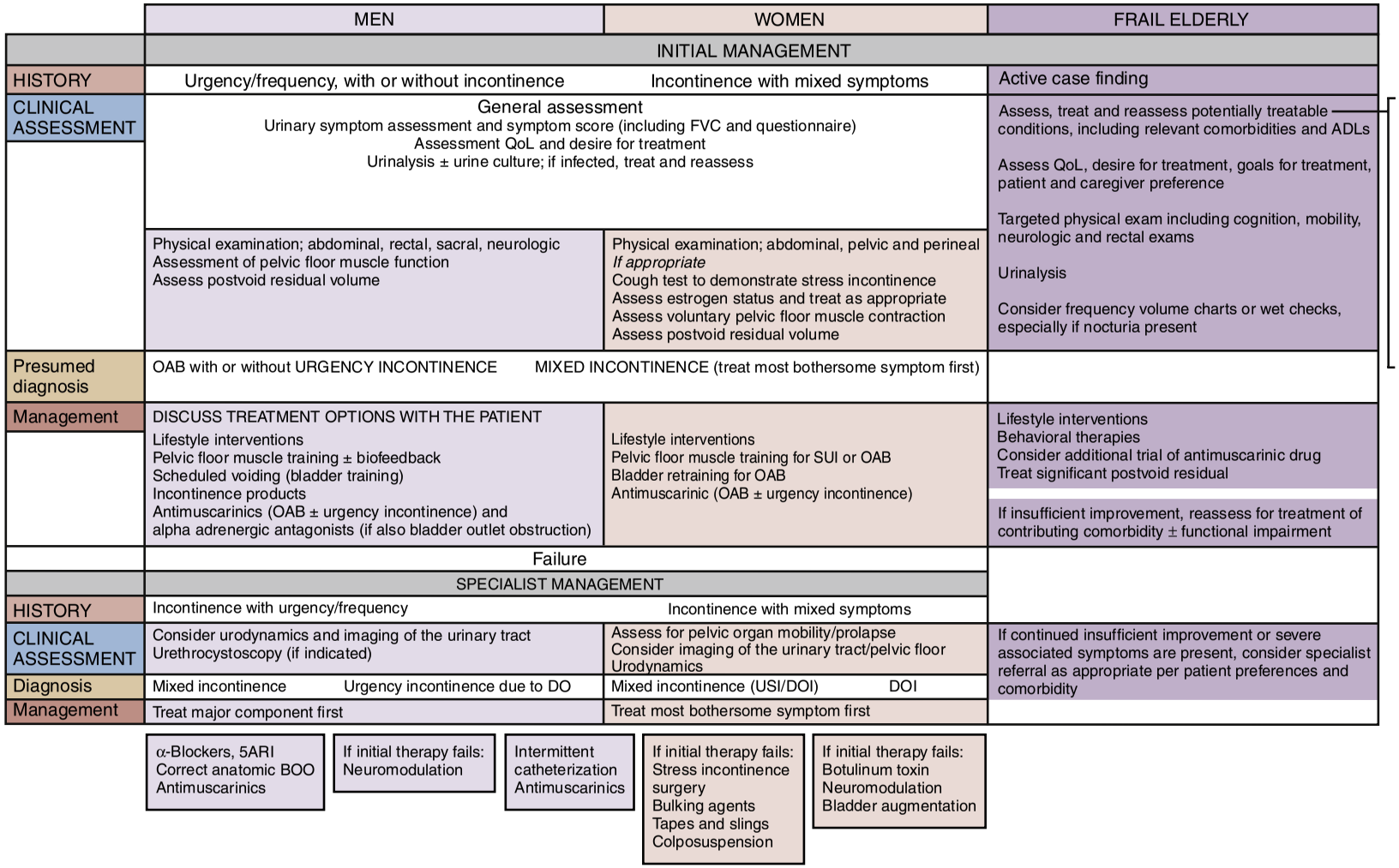

FIG. E5 Overactive bladder in men, women, and the frail elderly; assessment and management derived from the respective algorithms of the fifth International Consultation on Incontinence. *ADLs,* Activities of daily living; *5ARI,* 5α-reductase inhibitor; *BOO,* bladder outlet obstruction; *DO,* detrusor overactivity; *DOI,* detrusor overactivity incontinence; *FVC,* frequency volume chart; *OAB,* overactive bladder; *QoL,* quality of life; *SUI,* stress urinary incontinence; *USI,* urodynamic stress incontinence. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Hypotonia is diminished muscular resistance against passive stretching of the body. Infantile hypotonia refers to hypotonia present in the newborn or infant.

SYNONYM

Floppy infant

ICD-10CM CODES

P94.2	Congenital hypotonia
P94.8	Other disorders of muscle tones of newborn
P94.9	Disorders of muscle tone of newborn, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

The incidence of infantile hypotonia is difficult to assess, as it can be a symptom of multiple disorders. Central causes for hypotonia are approximately four times more common than peripheral causes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

A detailed history and physical exam are the key tools to localizing the lesion because the cause can be at any level in the neuraxis, providing an extensive differential.

- Assess tone by observing the fully awake child for body movements, body posture, and signs of decreased in utero movements (hip dislocation, arthrogryposis, plagiocephaly, pectus excavatum).
- When supine, hypotonic infants lie with their extremities extended and abducted, termed the frog-leg position.
- When pulled gently by the hands from supine toward sitting position, hypotonic infants have significant head lag and very little resistance to the examiner.
- When held under the arms by the axillae in vertical suspension, hypotonic infants start to slip through the examiner's hands unlike infants with normal tone.
- If held prone with support under the torso in horizontal suspension, hypotonic infants fall limply into an "inverted U"position.
- Signs of hypotonia of central origin include abnormal head shape or size, decreased level of consciousness, dysmorphic features, hyperreflexia, seizures, apnea, or abnormal sleep-wake cycles (Table E1). Signs of hypotonia of peripheral origin (i.e., a lesion in the motor unit) include an alert and profoundly weak infant with hyporeflexia and atrophic muscles. Tongue fasciculations and intention tremor may be seen in anterior horn disease.
- The rest of the neurologic and general exams can provide pertinent clues to specific diagnoses. Cardiac murmurs, skin lesions, hepatosplenomegaly, and other systemic features help narrow the differential.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Common central causes:

- Acquired brain insult
  1. Infection
  2. Hypoxic encephalopathy
  3. Intracranial hemorrhage
- Brain anomalies: Neuromigrational disorders
- Genetic disorders:
  1. Prader-Willi syndrome
  2. Down syndrome
  3. Kabuki syndrome
  4. Williams syndrome
  5. MECP2 duplication syndrome
  6. Fragile X syndrome
  7. Peripheral causes
- Anterior horn cell disease:
  1. Spinal muscular atrophy
  2. Hypoxic injury
  3. Neurogenic arthrogryposis
- Polyneuropathies (motor or sensory):
  1. Hereditary motor-sensory neuropathy
  2. Charcot-Marie-Tooth disease
  3. Congenital hypomyelinating disorder
- Neuromuscular junction disorders:
  1. Infantile botulism
  2. Congenital myasthenia gravis
  3. Transient neonatal myasthenia
- Congenital myopathies:
  1. Central core disease
  2. Nemaline rod myopathy
  3. Fiber-type disproportion myopathy
  4. Multi-minicore disease
  5. Myotubular myopathy
- Muscular dystrophies:
  1. Dystrophinopathies (Becker and Duchenne)
  2. Congenital myotonic dystrophy
  3. Walker-Warburg disease
  4. Fukuyama disease
  5. Muscle-eye-brain disease
- Metabolic disorders:
  1. Acid maltase deficiency (Pompe disease)
  2. Cerebrohepatorenal syndrome (Zellweger)
  3. Cytochrome-c oxidase deficiency
  4. Mitochondrial myopathies
  5. Neonatal adrenoleukodystrophy

TABLE E1 Localizing Examination Findings

Site of Lesion	Strength	Reflexes	Muscle Mass	Fasciculations
Central nervous system	Normal or slightly impaired	Brisk (decreased after acute injury)	Normal	None
Anterior horn cell	Weak	Decreased	Significant atrophy	Prominent (but not in neonatal period)
Peripheral nerve	Weak	Decreased	Atrophy	None
Neuromuscular junction	Weak	Normal	Normal	None
Muscle	Weak	Decreased or absent	Atrophy or pseudohypertrophy	None

LABORATORY TESTS

- Evaluate neonate for sepsis
- Electrolytes including glucose, creatinine, calcium
- Liver function tests
- Ammonia level
- Creatinine kinase level
- Lactate
- Consider TORCH titers
- Karyotype or specific genetic testing
- Serum amino acids
- Urine organic acids
- Acylcarnitine/carnitine panel
- Very long chain fatty acids
- EMG/nerve conduction velocity (NCV)
- Muscle biopsy

IMAGING STUDIES

MRI of brain for structural brain abnormality detection. MRI of spine if spinal morphology needs evaluation.

TREATMENT

Most of these disorders have no specific treatment; supportive care is offered.

However, infantile spinal muscular atrophy (Werdnig-Hoffman disease) now has an FDA-approved therapy, nusinersen, which has been shown to promote achievement of motor milestones and increase event-free survival dramatically compared with placebo. The mechanism of action is an antisense oligonucleotide that promotes production of full-length SMN (survival motor neuron) protein, which is lacking in this disease.

CHRONIC Rx

- Physical therapy, occupational therapy, and other therapies tailored to the patient's specific needs can provide significant improvement in quality of life and ability to function.
- Respiratory illnesses are common in these children, so vaccinations should be kept up to date.

DISPOSITION

- Long-term outcome varies greatly among different diseases.
- As a general rule, a hypotonic infant who requires mechanical ventilation cannot survive extubation (unless the cause is neonatal myasthenia).

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BASIC INFORMATION

DEFINITION

Infertility in a reproductive-age couple is the inability to conceive after unprotected intercourse for ≥1 yr. When a female is greater than 35 yr of age, an evaluation is justified after 6 mo without successful pregnancy. Earlier evaluation at any age is warranted with preexisting symptoms or medical conditions.

SYNONYM

Sterility

ICD-10CM CODES	
N46	Male infertility
N46.8	Other male infertility
N46.9	Male infertility, unspecified
N97.0	Female infertility associated with anovulation
N97.1	Female infertility of tubal origin
N97.2	Female infertility of uterine origin
N97.8	Female infertility of other origin
N97.9	Female infertility, unspecified
O09.00	Supervision of pregnancy with history of infertility, unspecified trimester
O09.01	Supervision of pregnancy with history of infertility, first trimester
O09.02	Supervision of pregnancy with history of infertility, second trimester
O09.03	Supervision of pregnancy with history of infertility, third trimester
Z31.81	Encounter for male factor infertility in female patient

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: One in eight reproductive age couples experience infertility. This prevalence is consistent in all developed countries and there is evidence that it is historically stable.

PREDOMINANT SEX AND AGE: By definition this is a diagnosis of reproductive age couples. Infertility increases with aging in both males and females, but more dramatically in women. Male factor is responsible in ~40% of couples and the female factor is responsible in ~40% of couples. The remainder of the cases are either combined male and female, or unexplained infertility, meaning a clear cause is not identified.

PEAK INCIDENCE: The incidence of infertility increases with age. Subtle decreases in female fertility start as early as age 30. The rate of infertility increases dramatically after age 37, and unassisted pregnancies become extremely uncommon as women reach the mid-40s. There is also a subtle, but still detectable, decrease in male fertility that may start as early as age 30.

RISK FACTORS: Aging is among the most common risk factors, predominantly among females, although there is evidence that aging affects male fertility as well. Women are increasingly deferring pregnancy due to the lack of a partner or career, which is likely associated with increasing prevalence in certain sectors of the population. Tubal factor infertility can be a result of endometriosis, prior tubal surgery, prior ruptured appendix, or sexually transmitted diseases such as chlamydia and gonorrhea. Extremes of weight, particularly obesity, are associated with ovulatory dysfunction. Other causes include polycystic ovarian syndrome (PCOS), hypothalamic dysfunction, thyroid disorders and hyperprolactinemia. Male factor infertility may be idiopathic or due to trauma, infection, varicocele, obstruction, hypothalamic dysfunction, or exposure to environmental toxins. Smoking is the most common lifestyle choice that impairs fertility.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Age
- Previous fertility, particularly if no pregnancy has occurred in another relationship despite absence of contraception
- Absence of secondary sexual characteristics
- Abnormal uterine bleeding or absent menstruation
- Clinical signs of androgen excess: Hirsutism, acne, alopecia
- Abnormal pelvic exam: Enlarged uterus, adnexal masses, pelvic/abdominal tenderness
- History of urological surgery in male or trauma to testes

ETIOLOGY

- Female factor:
  1. Advanced age
  2. Tubal factor: Pelvic inflammatory disease, endometriosis, prior pelvic surgery, history of ruptured appendicitis, prior elective sterilization
  3. Anatomic: Uterine fibroids, polyps, intrauterine adhesions, uterine anomalies
  4. Oligo-/anovulation: Most frequently due to polycystic ovarian syndrome (PCOS), but also due to thyroid abnormalities, hyperprolactinemia, nonclassic congenital adrenal hyperplasia, hypothalamic dysfunction
- Male factor:
  1. Abnormal semen analysis
  2. Elective sterilization
- Idiopathic: Both male and female

DIAGNOSIS

WORKUP

- Confirmation of ovulation: History of regular menstrual cycles, mid-luteal serum progesterone, basal body temperature testing, urinary luteinizing hormone predictor kits
- Complete transvaginal pelvic ultrasound
- Ovarian reserve testing: Anti-müllerian hormone, follicle-stimulating hormone (FSH), and estradiol obtained on cycle day 2 to 4 and antral follicle count
- Fallopian tube evaluation: Hysterosalpingogram (HSG) (Fig. 1)
- Uterine cavity evaluation: HSG, saline infusion sonohysterography, hysteroscopy, or 3D ultrasound of uterus
- Male factor: Semen analysis

LABORATORY TESTS

- Semen analysis, using Kruger strict morphology. Abstain 2 to 5 days prior to test.
- FSH and estradiol collected cycle day 2, 3, or 4 and anti-müllerian hormone as a measure of ovarian reserve.
- Mid-luteal progesterone (ideally 7 days prior to expected menses). Given variability of serum progesterone measurements throughout the day and absence of a reliable threshold, most practitioners use clinical criteria to diagnose ovulatory dysfunction.
- Urinary luteinizing hormone measurement.
- Thyroid-stimulating hormone (TSH).
- In patients with oligo- or anovulation: Prolactin, testosterone, 17-hydroxyprogesterone.

IMAGING STUDIES

- Day 2 or 3 transvaginal pelvic ultrasound to assess uterine or adnexal abnormalities and to count the number of small antral follicles (2 to 9 mm) as a measure of ovarian reserve. If oligo- or anovulatory, to assess for polycystic-appearing ovary
- Hysterosalpingogram (early follicular phase after menses complete but before ovulation, typically between days 5 and 12 of the menstrual cycle)
- Also used for imaging of uterine cavity: Saline infusion sonohysterography, 3D ultrasound of uterus, hysteroscopy

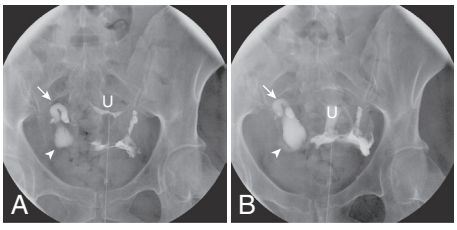

FIG. 1 Hysterosalpingogram spot radiographs early **(A)** and late **(B)** demonstrate a rounded collection of contrast material *(arrowhead)* adjacent to the dilated ampullary portion of the right fallopian tube *(arrow),* caused by peritubal pelvic adhesions related to previous pelvic inflammatory disease. Normal patient left fallopian tube. *U,* Uterus. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, WB Saunders.)

Rx TREATMENT

Once the patient presents for evaluation, testing should be completed as quickly as possible, ideally within one menstrual cycle. The couple should follow up with the evaluating provider once all testing is completed and treatment initiated as abnormalities are found.

ACUTE GENERAL Rx

- Fertility preservation options among females are summarized in Table E1. Oligo- or anovulation should be treated with ovulation induction agents, such as clomiphene citrate or aromatase inhibitors. A recent multicenter trial found that aromatase inhibitors achieved higher live birth rates than clomiphene citrate.[1] Historically, clomiphene citrate has been used, but a very well done randomized controlled trial convincingly demonstrated that letrozole is superior. Far less commonly, ovulatory dysfunction is the result of hypothalamic dysfunction. In these patients, once hypothalamic or pituitary abnormalities are excluded with MRI, ovulation can be achieved using injectable gonadotropins.
- Tubal factor infertility may be treated surgically if mild, and if the female patient is young and can afford the time to attempt pregnancy over multiple menstrual cycles. If the patient is older or if the tubal pathology is moderate to severe, in vitro fertilization (IVF) is recommended.
- Uterine anatomic abnormalities such as submucosal fibroids, polyps, intrauterine adhesions, or septate uterus should be corrected if they are identified. Fibroids that do not impact the uterine cavity probably do not interfere with fertility. Removal of intramural or subserosal fibroids is reserved for situations in which these cause excessive vaginal bleeding, pain, or pressure.
- Male infertility: Referral to urologist for complete evaluation. Fertility preservation options for males are summarized in Table E2. If semen analysis is severely abnormal, the following laboratory testing is recommended: Testosterone, FSH, estradiol, luteinizing hormone, TSH and prolactin, karyotype and Y-chromosome microdeletion.
  1. Mild male factor infertility may be treated with intrauterine insemination (IUI), but severe male factor will usually require assisted reproductive technologies (ART) with intracytoplasmic sperm injection (ICSI) in the laboratory, where sperm is injected directly into the oocyte. Some men may require epididymal aspiration or testicular biopsy to obtain sperm for IVF/ICSI. Donor sperm may be necessary in cases of azoospermia due to testicular failure, if male partner has a genetic disorder, or if couple is unable to proceed with IVF/ICSI.
- Unexplained infertility can be treated empirically using superovulation with clomiphene citrate, aromatase inhibitors, or gonadotropins combined with intrauterine insemination with partner's or donor sperm. Most providers recommend using an oral ovulation induction agent with insemination as a first-line superovulatory agent because it is inexpensive. After three to four such cycles, few pregnancies occur and the couple should be advised to become more aggressive. Controversy exists as to whether gonadotropins with insemination or IVF should be used after clomiphene citrate superovulation induction. There is evidence suggesting that moving to IVF after 3 mo of clomiphene citrate and insemination shortens the time interval to achieving pregnancy.[2] A randomized trial in women with unexplained infertility revealed ovarian stimulation with letrozole resulted in a significantly lower frequency of multiple gestation but also a lower frequency of live birth, as compared with gonadotropin but not as compared with clomiphene.
- Donor egg or embryo may be required in cases of premature ovarian insufficiency or due to age factor. Some couples may elect to pursue adoption.
- For LGBT couples, many family building options are available, including IUI or IVF utilizing donor sperm, donor oocytes, and/or gestational carrier, depending on the needs of the couple.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Acupuncture is widely used by women being treated for infertility. Limited data suggest some benefit, with possible mechanisms of action including increasing blood flow to the uterus and/or ovaries. Despite these studies, it is unproven whether acupuncture definitely improves IVF outcomes. Patients may additionally benefit from the stress relief that acupuncture provides.

DISPOSITION

- Most couples will achieve a pregnancy, provided that they are willing to proceed with treatment including ovulation induction, superovulation, IUI, IVF, or gamete donation.
- Adoption is also a worthwhile and viable possibility for couples unable to conceive.

REFERRAL

Couples should be referred to a reproductive endocrinologist once the complexity of treatment exceeds the comfort level of the provider, whether a family physician, internist, or general gynecologist. Complex ovulation and superovulation induction and ART are best managed by a board-certified reproductive endocrinologist.

[1]Legro RS et al: Letrozole versus clomiphene for infertility in the polycystic ovary syndrome, *N Engl J Med* 371:119-129, 2014.

[2]Reindollar RH et al: A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial, *Fertil Steril* 94:888-899, 2010.

PEARLS & CONSIDERATIONS

COMMENTS

- The incidence of heterotopic pregnancy in patients who have undergone ART is relatively common; identification of a patient with ultrasound-proved intrauterine pregnancy who used ART to conceive should NOT necessarily exclude the possibility of an ectopic gestation.
- Single-embryo transfer is becoming more common in IVF cycles to reduce the rate of multiple gestation.
- Preimplantation genetic testing for monogenic/single-gene defects (PGT-M) or preimplantation genetic testing for chromosomal structural rearrangement (PGT-SR) is used in selected IVF cycles when one or both parents has one or more known genetic abnormalities or chromosomal rearrangements to test embryos for these specific genetic abnormalities prior to implantation.
- Preimplantation genetic testing for aneuploidy (PGT-A) is used in IVF cycles to screen embryos for aneuploidy prior to implantation.

PREVENTION

- Techniques that reduce the incidence of pelvic inflammatory disease, such as condom use, can reduce pelvic adhesions that are associated with tubal factor infertility.
- Women should be made aware of the fact that delaying pregnancy into the later reproductive yrs reduces the likelihood for successful pregnancy. Many women are electing to cryopreserve oocytes or embryos for future use.
- Oocyte, embryo, or sperm cryopreservation is recommended for patients undergoing gonadotoxic chemotherapy or radiation treatment as a means of fertility preservation. Ovarian or testicular tissue cryopreservation may also be performed under a research protocol. All patients should be referred to a reproductive endocrinologist before planned treatment to discuss fertility preservation options.

PATIENT & FAMILY EDUCATION

Patient support groups such as *Resolve* (www.resolve.org) are available to help couples during evaluation and treatment of infertility, which can be extraordinarily stressful.

RELATED CONTENT

Infertility (Patient Information)
Amenorrhea (Related Key Topic)
Pelvic Inflammatory Disease (Related Key Topic)
Polycystic Ovary Syndrome (Related Key Topic)

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Emelia Argyropoulos Bachman, MD**

SUGGESTED READINGS

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TABLE E1 Fertility Preservation Options Among Females

	Option						
	Embryo Freezing	**Egg Freezing**	**Ovarian Tissue Freezing**	**Radiation Shielding of Gonads**	**Ovarian Transposition**	**Radical Trachelectomy**	**Ovarian Suppression**
Medical status	Standard	Experimental	Experimental	Standard	Standard	Standard	Experimental
Definition	Harvesting eggs, in vitro fertilization, and freezing of embryos for later implantation	Harvesting and freezing of unfertilized eggs	Freezing of ovarian tissue and reimplantation after cancer treatment	Use of shielding to reduce scatter radiation to the reproductive organs	Surgical repositioning of ovaries away from the radiation field	Surgical removal of the cervix with preservation of the uterus	Gonadotropin-releasing hormone analogues or antagonists used to suppress ovaries
Pubertal status	After puberty	After puberty	Before or after puberty	Before or after puberty	Before or after puberty	After puberty	After puberty
Time requirement	10-14 days from menses; outpatient surgical procedure	10-14 days from menses; outpatient surgical procedure	Outpatient surgical procedure	In conjunction with radiation treatments	Outpatient procedure	Inpatient surgical procedure	In conjunction with chemotherapy
Success rates	Approximately 40% per transfer; varies by age and center; thousands of babies born	Approximately 21.6% per embryo transfer; 200+ live births	Case reports of two live births	Only possible with selected radiation fields and anatomy	Approximately 50% because of altered blood flow and scattered radiation	No evidence of higher cancer recurrence rates in appropriate candidates	Unknown; conflicting results reported; larger randomized trials in progress
Cost	Approx. $12,000/cycle; storage fees and pregnancy costs additional	Approx. $12,000/cycle; storage fees and pregnancy costs additional	$12,000 for procedure; storage fees and reimplantation costs additional	Generally included in cost of radiation	Unknown; may be covered by insurance	Generally included in the cost of cancer treatment	$500/mo
Timing	Before or after treatment	Before or after treatment	Before or after treatment	During treatment	Before treatment	During treatment	During treatment
Special considerations	Need partner or donor sperm	May be attractive to single women or those opposed to embryo creation	Not suitable if high risk of ovarian metastases; only preservation option for prepubescent girls	Expertise required; does not protect against effects of chemotherapy	Expertise required	Limited to early-stage cervical cancer; offered at a limited number of centers	Does not protect from radiation effects

Modified from www.livestrong.org/fertility. In Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE E2 Fertility Preservation Options for Males

	Option				
	Sperm Banking (Masturbation)	**Sperm Banking (Alternative Collection Methods)**	**Radiation Shielding of Gonads**	**Testicular Tissue Freezing**	**Testicular Sperm Extraction**
Medical status	Standard	Experimental	Standard	Experimental	Standard
Definition	Sperm is obtained through masturbation, then frozen	Sperm obtained through testicular extraction or electroejaculation under sedation	Use of shielding to reduce the dose of radiation delivered to the testes	Tissue obtained through biopsy and frozen for future use	Use of biopsy to obtain individual sperm from testicular tissue
Pubertal status	After puberty	After puberty	Before and after puberty	Before and after puberty	After puberty
Time requirement	Outpatient procedure	Outpatient procedures	In conjunction with radiation treatments	Outpatient procedure	Outpatient procedure
Success rates	Generally high; the most established technique for men	If sperm is obtained, similar to standard sperm banking	Possible with select radiation fields and anatomy	No available human success rates	30%-70% in postpubescent patients
Cost	Approximately $1500 for three samples; storage fees average $500/yr	Varies greatly based on collection method	Generally included in the cost of radiation treatments	$500-$2500 for surgery; $300-$1000 for freezing; $500/yr for storage	$4000-$16,000 (in addition to costs for in vitro fertilization)
Timing	Before treatment	Before treatment	During treatment	Before treatment	Before or after treatment
Special considerations	Deposits can be made every 24 hours	Can be considered if male cannot ejaculate	Expertise required; does not protect against effects of chemotherapy	May be only option for prepubescent boys	Center should be able to freeze sperm found at time of biopsy

Modified from www.livestrong.org/fertility. In Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

BASIC INFORMATION

DEFINITION

Inflammatory myopathies are idiopathic diseases of muscle characterized clinically by muscle weakness and pathologically by inflammation and muscle fiber breakdown. The four most common are dermatomyositis (DM), necrotizing autoimmune myositis, polymyositis (PM), and inclusion body myositis (IBM). See separate topics on "Inclusion Body Myositis" and "Necrotizing Autoimmune Myopathy" for details regarding these topics.

SYNONYMS

Immune-mediated myopathies
Idiopathic inflammatory myopathies
Myositis syndromes
Polymyositis
Dermatomyositis
IMM

ICD-10CM CODES

M33.02	Juvenile dermatopolymyositis with myopathy
M33.12	Other dermatopolymyositis with myopathy
M33.20	Polymyositis, organ involvement unspecified
M33.22	Polymyositis with myopathy
M33.90	Dermatopolymyositis, unspecified, organ involvement unspecified
M33.92	Dermatopolymyositis, unspecified with myopathy

EPIDEMIOLOGY & DEMOGRAPHICS

Inflammatory myopathies are the largest group of potentially treatable myopathies in children and adults.

DM:

- Occurs in children and in adults (bimodal age peak).
- Average age at diagnosis is 40 yr in adults. Age range in children: 5 to 14 yr.
- More common in females than in males (2:1).
- Incidence 1:100,000.
- Prevalence 1 to 10 cases/million in adults and 1 to 3.2 cases/million in children.
- Up to one third of patients older than 50 with DM have an associated malignancy.

PM:

- Occurs mostly in adults, very rare in children
- Average age at diagnosis >20 yr
- More common in females
- Least common inflammatory myopathy
- Exact incidence unknown

PHYSICAL FINDINGS & CLINICAL PRESENTATION

DM and PM:

- Most patients have a subacute onset over wks to mos.
- Pattern is typically symmetric proximal muscle weakness involving the proximal limbs (shoulder and pelvic girdles).
- Weakness of neck flexion and extension is common.
- Difficulty getting up from a chair, climbing stairs, reaching for objects above head, or combing hair.
- Distal muscle involvement and ocular involvement are uncommon.
- Sensation is preserved.
- Reflexes may be preserved or diminished.
- Dysphagia and dysphonia result from involvement of striated muscle of the pharynx and proximal esophagus.
- Esophageal dysmotility is common in DM.
- Respiratory failure from associated pulmonary fibrosis.
- Cardiac conduction abnormalities can be seen with DM.
- Systemic autoimmune disease occurs frequently in PM, and rarely in DM.
- Skin findings in DM:
  1. Heliotrope rash on the upper eyelids (Fig. E1)
  2. Erythematous rash on the face
  3. May also involve the back and shoulders (shawl sign), neck and chest (V-shape), knees (Fig. E2), and elbows
  4. Photosensitivity
  5. Gottron papules (violaceous papules overlying dorsal interphalangeal or metacarpophalangeal areas, elbow or knee joints [Fig. E3])
  6. Nail cracking, thickening, and irregularity (Fig. E4) with periungual telangiectasia
  7. Mechanic's hand: Fissured, hyperpigmented, scaly, and hyperkeratotic; also associated with increased risk of interstitial lung disease

ETIOLOGY

DM: Complex, immune-mediated microangiopathy. Adaptive immune response via humorally mediated complement attack

PM: Unknown:

- Cell-mediated immune major histocompatibility-I (MHC-1) process directed against muscle fibers is likely, given biopsy features.
- A viral etiology has been proposed secondary to the presence of autoantibodies to histidyl transferase, anti-Jo-1, and signal recognition particle.

DIAGNOSIS

- The diagnosis of each subtype of inflammatory myopathy is based on clinical history, pattern of muscle involvement, electromyographic findings, muscle biopsy, and presence of certain antibodies.
- Myopathic pattern of muscle weakness.
- Characteristic rash in DM.
- Electromyography (EMG) shows myopathic (small-amplitude, short-duration, polyphasic) motor potentials with early recruitment.
- Majority of patients have "irritable" features (fibrillations and positive sharp waves) on EMG.
- See "Laboratory Tests."
- Biopsy is required for diagnosis and should confirm inflammation before treatment is started. Table 1 describes histologic features of idiopathic inflammatory myopathies. In idiopathic inflammatory myopathies, myopathic features (variation in fiber size, fiber splitting, fatty replacement of muscle tissue, and increased endomysial connective tissue) should be seen in addition to the following:
  1. DM: Perifascicular atrophy, membrane attack complex (MAC) deposition along capillaries
  2. PM: Endomysial infiltrates composed of CD8+ T cells and macrophages invading nonnecrotic muscle fibers that express MHC-I antigen

DIFFERENTIAL DIAGNOSIS

- IBM
- Muscular dystrophies
- Amyloid myoneuropathy
- Amyotrophic lateral sclerosis
- Myasthenia gravis
- Eaton-Lambert syndrome
- Drug-induced myopathies (e.g., quinidine, NSAIDs, penicillamine, HMG-CoA-reductase inhibitors)
- Diabetic amyotrophy
- Guillain-Barré syndrome
- Hyperthyroidism or hypothyroidism
- Lichen planus
- Amyopathic DM (rash without weakness)
- DM sine rash (weakness with characteristic biopsy, but no rash)
- Systemic lupus erythematosus (SLE)
- Contact atopic or seborrheic dermatitis
- Psoriasis

LABORATORY TESTS

- Creatine kinase (CK) is the most sensitive muscle enzyme test for muscle breakdown. It should be checked at onset, and serially monitored several times during treatment.
- CK is typically elevated (5 to 50× normal) in active PM.
- CK may be normal or only slightly elevated in DM.
- Aldolase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and lactate dehydrogenase (LDH) may be elevated.
- Anti-Jo-1 antibodies are seen in myositis with associated interstitial lung disease but are not specific for either DM or PM.
- Myositis-specific and myositis-associated autoantibodies in adult polymyositis and dermatomyositis and juvenile dermatomyositis are summarized in Table E2.
- DM: Anti-MDA-5, anti-Mi-2, anti-TIF-1, and anti-NXP2 (implicated in cancer-associated dermatomyositis).
- PM: Antisynthetase antibodies (often seen in overlap myositis) associated with interstitial lung disease, arthritis, fever, and "mechanic's hands."
- Electrolytes, thyroid-stimulating hormone (TSH), Ca, and Mg should be evaluated to exclude other causes of weakness.
- Check ECG for cardiac involvement.

IMAGING STUDIES

- Chest x-ray is used to rule out pulmonary involvement. If suspicious for pulmonary interstitial disease, a high-resolution CT scan of the chest may be helpful.
- Radiography is an efficient means of identifying and characterizing soft-tissue calcinosis (Fig. E5).
- Although MRI arguably has greater diagnostic value than electromyography or serum enzyme

TABLE 1 Histologic Features of Idiopathic Inflammatory Myopathies

Feature	Dermatomyositis	Polymyositis	Inclusion Body Myositis
Necrosis of muscle fibers	+	+	+
Variation in fiber diameter	+	+	+
Regeneration of muscle fibers	+	+	+
Proliferation of connective tissue	+	+	+
Infiltration of mononuclear cells*	+	+	+
Perivascular and perimysial inflammation	+	–/+	–/+
Endomysial inflammation	–/+	+	+
Perifascicular atrophy	+	–	–
Abnormally dilated capillaries	+	–/+	–
Reduced capillary density	+	–/+	–
Deposition of complement on vessel walls	+	–/+	–
Microinfarcts	+	–	–
Invasion of non-necrotic fibers by cytotoxic T lymphocytes and macrophages	–	+	+
Expression of major histocompatibility complex class I on muscle fibers	–/+	+	+
Rimmed vacuoles with amyloid deposits and tubulofilaments†	–	–	+
Angulated or atrophic and hypertrophic fibers	–	–	+
Ragged red or cytochrome oxidase–negative fibers	–	–	+

*Inflammation is absent in a small proportion of polymyositis and dermatomyositis biopsies.
†Also seen in chronic neurogenic conditions and distal myopathies.
From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders, Elsevier.

measurements in cases of suspected idiopathic inflammatory myopathy, MRI findings have not been formalized as a diagnostic criterion for idiopathic inflammatory myopathy. The acceptance of MRI as a diagnostic tool in myositis may be inhibited by the high cost and the need for more reliable and validated methods of summarizing the findings of MRI. MRI evaluation before biopsy, however, has become routine at many tertiary care centers. Fascial disease is manifested on MRI by fascial or perifascial hyperintensity on fluid-sensitive sequences. The edema-like signal in the deep subcutis may accompany fasciitis and can indicate associated panniculitis.

- Video fluoroscopy or barium swallow study to look for upper esophageal dysfunction in patients with dysphagia and DM.
- Table E3 summarizes affected organs and their evaluation in inflammatory muscle disease.

Rx TREATMENT

Goal: Maintain function, minimize disease/iatrogenic sequelae

NONPHARMACOLOGIC THERAPY

- Sun-blocking agents with SPF 15 or greater for skin protection in patients with DM
- Physical therapy beneficial for gait training and increasing muscle tone and strength
- Occupational therapy assists with activities of daily living
- Speech therapy to monitor patients with swallowing dysfunction

ACUTE GENERAL Rx

- Corticosteroids are the mainstay of therapy. Start prednisone 1 to 2 mg/kg per day, up to a maximum dose of 100 mg/day. Continue until muscle strength improves or muscle enzymes have normalized for at least 4 wk. Begin tapering by 10 mg/mo until 60 mg/day, then slowly taper by 5 mg/mo. Consider every-other-day prednisone treatment at same dose (may decrease side effects).
- Consider IV immunoglobulin (IVIG) if patient fails to improve on prednisone, or muscle enzymes begin rising when tapering off prednisone. See "Chronic Rx" for specific dosage.
- Hydroxychloroquine can be used to treat the cutaneous lesions of DM.
- A treatment algorithm for adult patients with inflammatory myopathies is illustrated in Fig. 6.

CHRONIC Rx

- Chronic prednisone therapy may be needed for yrs, but other immunosuppressive ("steroid-sparing") agents may be added early to decrease long-term steroid side effects.
- Azathioprine 2 to 3 mg/kg per day tapered to 1 mg/kg per day once steroid is tapered to 15 mg/day. Reduce dosage monthly by 25-mg intervals. Maintenance dosage is 50 mg/day.
- Methotrexate 7.5 to 10 mg PO/wk, increased by 2.5 mg/wk to total of 25 mg/wk; consider IM dosing if PO is ineffective.
- IV immunoglobulin 2 g/kg total dose over 2 to 5 days.
- IV cyclophosphamide 1 g/M^2 monthly for 6 mo is preferred to oral dosing for refractory cases. However, oral dosing of cyclophosphamide is 1 to 3 mg/kg per day PO or 2 to 4 mg/kg per day in conjunction with prednisone.
- Cyclosporine A: Initial dose 2.0 to 2.5 mg/kg bid; long-term maintenance is lowest effective dose.
- Mycophenolate mofetil 500 mg PO bid, titrate to 1500 mg PO bid over 1 to 2 mo.
- Hydroxychloroquine 200 mg PO daily; monitor for visual changes.

DISPOSITION

- 30% to 40% of patients achieve clinical remission with treatment.
- In patients with residual weakness, deficits typically remain stable over long-term follow-up.
- 10% experience recurrent disease.
- Serum CK often returns to normal before symptoms improve.
- During exacerbations, enzymes may rise before clinical symptoms appear.
- Poor prognostic indicators include delay in diagnosis, older age, recalcitrant disease, malignancy, interstitial pulmonary fibrosis, dysphagia, leukocytosis, fever, and anorexia.
- Infection, malignancy, and cardiac and pulmonary dysfunction are the most common causes of death.
- With early treatment, 5- and 8-yr survival rates of 80% and 73%, respectively, have been reported.

REFERRAL

Neurology or rheumatology referral should be made to help establish the diagnosis and implement treatment.

PEARLS & CONSIDERATIONS

- Do not implement treatment before muscle biopsy.
- When assessing response to treatment, clinical muscle strength is more important than muscle enzyme tests.
- The concern for malignancies (ovary, lung, breast, GI) associated with DM is legitimate and merits screening in patients older than age 40 at time of diagnosis and every 2 to 3 yr thereafter.
- No association exists between juvenile DM and malignancy.

- Overlap syndrome refers to patients with DM who also meet criteria for a connective tissue disorder (e.g., rheumatoid arthritis, scleroderma, SLE).
- In any patient taking steroids, closely monitor for:
  1. Diabetes or glucose intolerance (2-hr oral glucose tolerance test)
  2. Osteopenia/osteoporosis (DEXA scan q6mo)
  3. Cataracts (yearly ophthalmologic appointment)
  4. Hypertension
  5. Psychiatric side effects including depression or psychosis
  6. Poor sleep
  7. Peptic ulcer disease (prescribe H_2 antagonist or proton pump inhibitor)
- Clinical and immune response features can be used for categorizing heterogeneous myositis syndromes and mutually exclusive and stable phenotypes and are useful for predicting clinical signs and symptoms, associated environmental and genetic risk factors, and responses to therapy and prognosis.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Dermatomyositis and Polymyositis (Patient Information)
Inclusion Body Myositis (Related Key Topic)
Necrotizing Autoimmune Myopathy (Related Key Topic)

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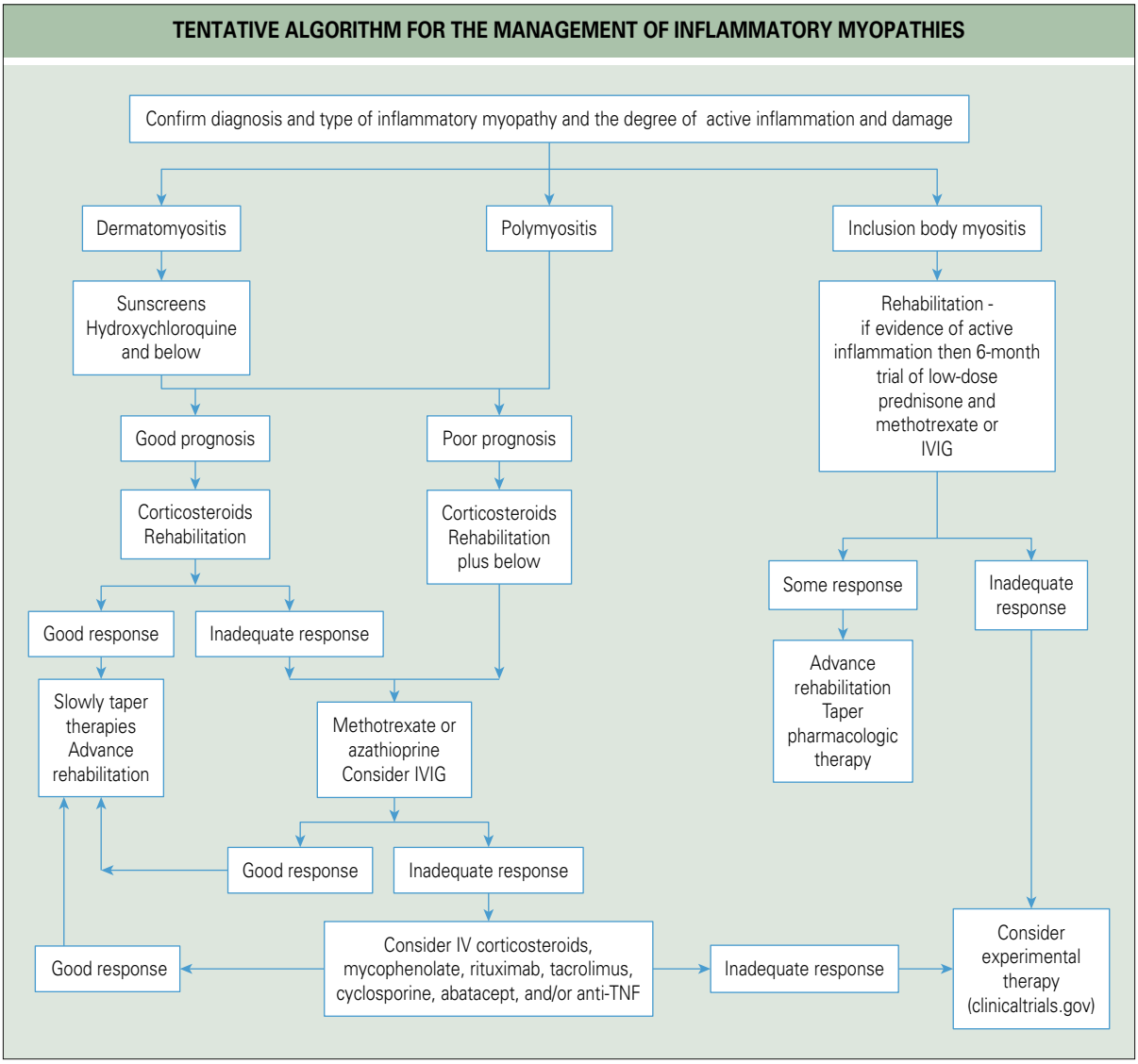

FIG. 6 Tentative algorithm for the management of inflammatory myopathies. *anti-TNF,* Anti–tumor necrosis factor; *IVIG,* intravenous immunoglobulin. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

SUGGESTED READINGS

Dalakas MC: Inflammatory muscle diseases, *N Engl J Med* 372:1734–1747, 2015.
Milone M: Diagnosis and management of immune-mediated myopathies, *Mayo Clin Proc* 92(5):826–827, 2017.

FIG. E1 Dermatomyositis—eyelid edema and heliotrope sign. A, Inflammation of the upper eyelid can be more subtle in darkly pigmented skin; note involvement of the lateral nasal root and cheeks. Eyebrow alopecia is due to chemotherapy. **B,** The characteristic pink-violet color is seen with involvement of the hairline, lower forehead, upper eyelids, and cheeks; the edema is striking and involves the nasal root as well as the eyelids. (From Bolognia J: *Dermatology,* ed 4, 2018, Elsevier.)

FIG. E2 Violaceous plaques on the knees in a patient with dermatomyositis (Gottron sign). (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

FIG. E3 Dermatomyositis—Gottron papules. A, Only a few Gottron papules are present, but there is definite accentuation of the pink-violet inflammation over the metacarpophalangeal (MCP) joints and proximal and distal interphalangeal (PIP, DIP) joints as well as the proximal nail folds. Note the ragged cuticles. **B,** The flat-topped (lichenoid) papules overlying the DIP, PIP, and MCP joints (knuckles) are subtle and were misdiagnosed as verrucae vulgares in this child. **C,** More obvious disease in which the multiple pink-violet lichenoid papules are coalescing and there is some involvement of the interphalangeal skin. (**A,** Courtesy Kalman Watsky, MD; **B**, Courtesy Julie V Schaffer, MD. In Bolognia J: *Dermatology,* ed 4, 2018, Elsevier.)

FIG. E4 Enlarged nail fold capillaries in a patient with dermatomyositis. (From Hochberg MC et al: *Rheumatology,* ed 5, St.Louis, 2011, Mosby.)

TABLE E2 Myositis-Specific and Myositis-Associated Autoantibodies in Adult Polymyositis and Dermatomyositis and Juvenile Dermatomyositis

Autoantibody	Autoantigen	Clinical Features
Jo-1, non–Jo-1 (PL7, PL12, EJ, OJ, KS, Tyr, Zo)	Amino-acyl-tRNA synthetase	Fever, Raynaud phenomenon, mechanic's hands, myositis, polyarthritis, ILD
SRP	Signal recognition particle (cytoplasmic protein translocation)	Severe necrotizing myopathy; predominantly PM
Mi-2	Helicase	DM (adult > children); "shawl" sign and other DM rashes
PM-Scl	Nucleolar macromolecular complex	Overlap features of myositis and SSc (or either disease alone); mechanic's hands
U1RNP	Small nuclear ribonucleoprotein	Overlap syndromes (MCTD)
SUMO-1 (small ubiquitin-like modifier 1)	Small ubiquitin-like modifier enzyme (posttranslational modification)	Adult DM, ILD
TIF1-γ (p155/140)	Transcriptional intermediary factor 1-γ (TIF1-γ)	Cancer-associated myositis in adults; >20% frequency in JDM cohorts; severe cutaneous disease in adult DM and JDM
NXP2/MJ (p140)	NXP-2 (SUMO target; possible role in SUMO-mediated transcriptional repression)	20%-25% frequency in JDM cohorts; calcinosis; severe disease (atrophy or contractures)
MDA-5 (cADM-140)	RNA helicase	ADM, ILD; palmar papules and cutaneous ulcerations
PMS1	PMS1 (DNA mismatch repair enzyme)	Myositis (specifics not known)
Ku[1]	70- and 80-kDa nuclear/nucleolar protein complex (DNA break repair and recombination)	UCTD and overlap syndromes (Raynaud phenomenon, ILD, myositis, arthritis)
HMGCR (200/100 kDa)[2,3]	HMG CoA reductase	Necrotizing myopathy

ADM, Amyopathic dermatomyositis; *DM,* dermatomyositis; *HMG CoA,* hydroxymethylglutaryl–coenzyme A; *ILD,* interstitial lung disease; *JDM,* juvenile DM; *MCTD,* mixed connective tissue disease; *PM,* polymyositis; *SSc,* systemic sclerosis; *UCTD,* undifferentiated connective tissue disease.

(1)Rozelle A, Trieu S, Chung L: Malignancy in the setting of the anti-synthetase syndrome, *J Clin Rheumatol* 14:285-288, 2008.
(2)Zhang L et al: Cardiac involvement in adult polymyositis or dermatomyositis: a systematic review, *Clin Cardiol* 35(11):686-691, 2012.
(3)Oddis CV et al: International consensus guidelines for trials of therapies in the idiopathic inflammatory myopathies, *Arthritis Rheum* 52(9):2607-2615, 2005.

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

FIG. E5 Advanced calcinosis. Radiograph of the arm in a girl with juvenile dermatomyositis, showing extensive amorphous and wispy calcification corresponding to subcutaneous calcinosis. Sheetlike calcification outlining muscles corresponds to deep fascial calcification. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, Saunders.)

TABLE E3 Affected Organs and Their Evaluation in Inflammatory Muscle Disease

Organ or System	Modalities of Evaluation	Pathologic Processes	Findings
Muscle	Biopsy	Myofiber degeneration and regeneration	Myofiber size variation; vacuolated, necrotic fibers Large central nuclei, basophilic sarcoplasm
		Inflammation	Mononuclear cell infiltration
		Fibrosis	Increased interstitium and fatty replacement of muscle
	EMG	Myofiber destruction	Low-amplitude, short, polyphasic potential; spontaneous fibrillations; irritability
	MRI		
	T1 image	Fibrosis	Atrophy of muscle, scarring
	STIR image	Inflammation	Bright signal in inflamed muscle
Heart	ECG, echo	Myocarditis, fibrosis	Arrhythmias, left ventricular hypertrophy
	Biopsy	Myocarditis, fibrosis	Myofiber size variation, mononuclear cell infiltrates, fibrosis
Lungs	CXR, HRCT	Inflammation, fibrosis	Interstitial markings
	PFTs	Inflammation, fibrosis, restrictive lung disease	Decreased TLV, FVC, and D_{LCO}
	Radionuclide scan	Inflammation, fibrosis	Ventilation–perfusion mismatches
	BAL	Inflammation, fibrosis	Abnormal leukocyte numbers and differentials
	Biopsy	Inflammation, fibrosis	Mononuclear cell infiltration, destruction of alveolar space and fibrosis
Skin	Biopsy	Inflammation	Vacuolization of the basal layer; mononuclear cell infiltration
GI system	Radiographic studies	Inflammation, fibrosis	Reflux and uncoordinated peristalsis

BAL, Bronchoalveolar lavage; *CXR,* chest radiography; *echo,* echocardiography; D_{LCO}, diffusion capacity for carbon monoxide; *ECG,* electrocardiography; *EMG,* electromyography; *FVC,* forced vital capacity; *GI,* gastrointestinal; *HRCT,* high-resolution computed tomography; *MRI,* magnetic resonance imaging; *PFT,* pulmonary function tests; *STIR,* short tau inversion recovery; *TLV,* total lung volume.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

BASIC INFORMATION

DEFINITION

Influenza is an acute febrile illness caused by infection with influenza type A or B virus. Seasonal influenza can include the H1N1 virus. A similar respiratory illness is severe acute respiratory syndrome (SARS) caused by a coronavirus called SARS-associated coronavirus (SARS-CoV). A new novel coronavirus was recognized in two patients in September 2012. This is a very different virus from the SARS agent; the two patients exhibited acute respiratory distress syndrome, renal failure, consumptive coagulopathy, and/or pericarditis. Now called the Middle East respiratory syndrome (MERS-CoV) virus, it has affected more than 2,200 persons in 27 countries since 2012. Patients have fever and pneumonia requiring hospitalization. Transmission spread in 2015 from the Middle East to Korea and China, resulting in more than 185 cases. There were 558 cases in Saudi Arabia from January 2015 through early June 2016, and 75 in 2018. Persons who are immunocompromised or have diabetes, renal failure, or chronic lung disease are thought to be at greater risk of severe illness. Dromedary camels and their milk are documented to harbor MERS-CoV.

Refer to the "Influenza, Avian" topic for more information.

SYNONYMS

Flu
Influenza-like illness (ILI)

ICD-10CM CODES

J10.00	Influenza due to other identified influenza virus with unspecified type of pneumonia
J10.1	Influenza due to other identified influenza virus with other respiratory manifestations
J11.1	Influenza due to unidentified influenza virus with other respiratory manifestations
J12.9	Viral pneumonia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Winter outbreaks lasting 5 to 6 wk
PREDOMINANT SEX: Male = female
PREDOMINANT AGE: Attack rates are usually higher among children than adults, although children are less prone to pulmonary complications. The severity of the 2017 to 2018 flu season was described by the Centers for Disease Control and Prevention (CDC) as high for all age groups: children, adults and older adults. Of the 171 reported pediatric deaths in the 2017 to 2018 season, 22% of the vaccine-eligible children had received vaccine.
INCIDENCE (IN U.S.): Annual incidence of influenza-related deaths is between 12,000 and 51,000 deaths/yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- "Classic flu" is characterized by abrupt onset of fever, headache, myalgias, anorexia, and malaise after a 1- to 2-day incubation period.
- Clinical syndromes are similar to those produced by other respiratory viruses, including pharyngitis, common colds, tracheobronchitis, bronchiolitis, and croup.
- Respiratory symptoms such as cough, sore throat, and nasal discharge are usually present at the onset of illness, but systemic symptoms predominate.
- Elderly patients may experience fever, weakness, and confusion without any respiratory complaints.
- Acute deterioration to status asthmaticus may occur in patients with asthma.
- Influenza pneumonia: Rapidly progressive cough, dyspnea, and cyanosis may occur after typical flu onset. This may be caused by primary influenza pneumonia or secondary bacterial pneumonia (often pneumococcal or staphylococcal co-infection).
- For influenza A (H3N2v), children younger than 10 yr lack immunity. People ≥65 yr and those with morbid obesity are at high risk.

ETIOLOGY

- Variation in the surface antigens of the influenza virus, hemagglutinin (HA) and neuraminidase (NA), leading to infection with variants to which immunity is inadequate in the population at risk
- Droplet transmission by small-particle aerosols and deposited on the respiratory tract epithelium

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Respiratory syncytial virus, adenovirus, parainfluenza virus infection
- Secondary bacterial pneumonia or mixed bacterial-viral pneumonia

WORKUP

- The accuracy of clinical diagnosis of influenza on the basis of symptoms alone is limited because symptoms from illness caused by other pathogens can overlap considerably with influenza. Diagnostic tests available for influenza include viral cultures, serology, rapid influenza diagnostic tests (RIDTs), reverse transcription-polymerase chain reaction (RT-PCR), and immunofluorescence assays.
- Virus isolation from nasal or throat swab or sputum specimens is the most rapid diagnostic method in the setting of acute illness.
- Specimens are placed into virus transport medium and processed by a reference laboratory.
- For serologic diagnosis:
  1. Paired serum specimens, acute and convalescent, the latter obtained 10 to 20 days later.
  2. Fourfold rises or falls in the titer of antibodies (various techniques) considered diagnostic of recent infection.
  3. Commercial rapid influenza diagnostic tests (RIDTs) are available. They can detect influenza virus antigens within 15 min of testing. Rapid flu test should be collected as early as possible, ideally within 4 days of onset. False-negative results are common during the flu season. A negative test result does NOT exclude diagnosis of influenza.
  4. Commercial RIDTs cannot determine if an H3N2 is a variant virus; when suspect H3N2v virus infection, send nasopharyngeal swab or aspirate in viral transport medium to state public health laboratory for rRT-PCR testing using Centers for Disease Control and Prevention (CDC) FLU rRT-PCR diagnostic panel assay. Novel digital immunoassay (DIAs) and rapid nucleic amplification tests (NAATs) have a markedly higher sensitivity for influenza A and B than traditional RIDTs.

LABORATORY TESTS

Septic syndrome presentation: CBC, ABG analysis, blood cultures

IMAGING STUDIES

- Chest x-ray examination when suspecting viral pneumonia: Peribronchial and patchy interstitial infiltrates in multiple lobes with atelectasis. Table 1 describes x-ray pulmonary findings based on virus type.
- Possible progression to diffuse interstitial pneumonitis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Bed rest
- Hydration

ACUTE GENERAL Rx

- Supportive care: Antipyretics; avoid use of aspirin in children because of the association with Reye syndrome.
- Antibiotics if bacterial pneumonia is proved or suspected.
- Amantadine is NOT recommended due to resistant isolates.
- Neuraminidase inhibitors block release of virions from infected cells, resulting in shortened duration of symptoms and decrease in complications; effective against both influenza A and B, including A (H3N2v) for all hospitalized patients, those with severe and progressive illness, and high-risk patients with suspected or confirmed H3N2v.
  1. Oseltamivir, administered orally:
     a. For treatment, 75 mg PO twice daily for 5 days
     b. For prevention, 75 mg PO once daily for a minimum of 2 wk in an outbreak setting or 7 days after exposure for an adult
  2. Zanamivir, administered via inhaler:
     a. For treatment, 10 mg (2 inhalations of 5 mg each) twice daily for 5 days.

TABLE 1 Pulmonary Radiographic Findings Based on Virus Type

Virus	Centrilobular Nodules	Lobar Ground-Glass	Diffuse Ground-Glass	Thickened Interlobular Septa	Consolidation
Influenza	+++	+++	+		+
Epstein-Barr	+	+	+		+
Cytomegalovirus	++	++	++	+	+
Varicella-zoster	+++	+	+		
Herpes simplex	+	+++	+		+++
Measles	++	+	+		+
Hantavirus			+++	+	++
Adenovirus	++	+			+++

From Weissleder R et al: *Primer of diagnostic imaging,* ed 5, St Louis, 2011, Mosby.

   b. For prevention in households, 10 mg (2 inhalations of 5 mg each) once daily for 7 days. Not recommended in persons with underlying airways disease such as asthma or chronic obstructive pulmonary disease.
   c. Adjust dosing in patients with renal impairment or end-stage renal disease.
3. Baloxavir (Xofluza) was approved by the FDA in 2018 for acute uncomplicated influenza infection in patients ≥ 12 yr of age. Its mechanism of action is through inhibition of an endonuclease involved in viral RNA replication. It is a single dose drug.

- Placebo-controlled studies have suggested that antiviral therapy with any of the previously mentioned agents must ideally be initiated within 1 to 2 days of the onset of symptoms and reduces the duration of illness by ~1 day.
- Oseltamivir resistance developed on therapy in individuals with avian flu (H5N1) in Asia, and this is associated with poor outcome.
- Amantadine and rimantadine resistance are documented for novel (H1N1) influenza and H3N2 influenza virus.
- Systemic corticosteroids should not be routinely administered to patients with suspected or confirmed influenza, including H3N2v virus infection, except for patients on chronic corticosteroid therapy for COPD, asthma.
- Recent trials[1] have shown that in patients hospitalized with severe influenza infection, triple therapy with clarithromycin 500 mg, naproxen 200 mg, and oseltamivir 75 mg bid for 30 days reduced mortality and did not increase complications compared with oseltamivir (75 mg bid for 5 days) alone.

DISPOSITION

Patients are hospitalized if signs of pneumonia are present.

REFERRAL

Infectious disease and/or pulmonary consultation when influenza pneumonia is suspected

[1]Hung IFN et al: Efficacy of clarithromycin-naproxen-oseltamivir combination in the treatment of patients hospitalized for influenza (H3N2) infection: an open-lab, randomized, controlled, phase IIb/III trial, *Chest* 151:1069-1080, 2017.

PEARLS & CONSIDERATIONS

COMMENTS

- Prevention of influenza in patients at high risk is an important goal of primary care.
- Vaccines reduce the risk of infection and the severity of illness.
   1. Antigenic composition of the vaccine is updated annually. The northern hemisphere's 2019 to 2020 season trivalent vaccine includes an A/Brisbane/02/2018 (H1N1) pdm09-like virus (updated), an A/Kansas/14/2017 (H3N2)-like virus (updated), and a B/Colorado/06/2017-like (Victoria lineage) virus.
   2. Quadrivalent vaccines contain these three vaccine viruses, plus a second influenza B vaccine virus strain called B/Phuket/3073/2013-like (Yamagata lineage) virus.
   3. Revaccination is recommended annually before onset of influenza activity in the community, even for those who received the vaccine in the previous season.
   4. Delaying vaccination to ensure persistence of vaccine-induced protection during flu season could result in missed opportunities to vaccinate.
   5. Seasonal influenza vaccine does not provide protection against the influenza A (H3N2v) virus that is associated with agricultural fairs.
   6. Vaccination should be given at the start of the flu season (September-October) for all persons aged ≥6 mo who do not have contraindications. Vaccination is particularly important for persons who are at high risk and their contacts/caregivers. When vaccine supply is limited, vaccination efforts should focus on the following groups:
      a. All children aged 6 mo to 4 yr (59 mo)
      b. People 50 yr and older
      c. Adults and children with chronic cardiac (except hypertension) or pulmonary (including asthma), renal, hepatic, neurologic, hematologic or metabolic disease (including diabetes mellitus)
      d. Immunocompromised patients (including HIV-infected persons or patients immunosuppressed due to medications)
      e. Women who are or will be pregnant during the influenza season
      f. Children aged 6 mo to 18 yr who are receiving long-term aspirin therapy
      g. Residents of nursing homes and other long-term care facilities
      h. American Indians/Alaska Natives
      i. Persons who are morbidly obese (BMI ≥40)
      j. Health care workers (HCWs)
      k. Household contacts and caregivers of persons in the previous groups
   7. Vaccination precautions include:
      a. Guillain-Barré syndrome within 6 wk following a previous dose of influenza vaccine
      b. Moderate or severe acute illness with or without fever
      c. Asthma in persons >5 yr (LAIV4)
      d. Other underlying medical conditions that might predispose to complications after wild-type influenza infection (e.g., chronic pulmonary, cardiovascular [excluding isolated hypertension], renal, hepatic, neurologic, hematologic, or metabolic disorders [underlying diabetes mellitus]) (LAIV4)
   8. Contraindication to receiving vaccine:
      a. Previous severe allergic reaction to influenza vaccine
      b. For LAIV4: Concomitant aspirin- or salicylate-containing therapy in children and adolescents
      c. For LAIV4: Children 2 to 4 yr with asthma Dx in past 12 mo
      d. For LAIV4: Immunocompromised due to any cause including medications or HIV infection
      e. For LAIV4: Close contacts and caregivers of severely immunosuppressed persons who require a protected environment
      f. For LAIV4: Pregnancy
      g. For LAIV4: Received influenza antiviral medication within past 48 hr
   9. Special efforts should be made to vaccinate high-risk patients <65 yr, only 10% to 15% of whom are vaccinated each yr.

TABLE 2 Antiviral Agents for Influenza

	Amantadine	Rimantadine	Zanamivir	Oseltamivir
Protein target	M2	M2	Neuraminidase	Neuraminidase
Activity	A only (H1N1 and H3N2 are resistant)	A only (H1N1 and H3N2 are resistant)	A and B	A and B
Side effects	CNS (13%) GI (3%)	GI (6%)	? Bronchospasm	GI (9%)
Metabolism	None	Multiple (hepatic)	None	Hepatic
Excretion	Renal	Renal, + others	Renal	Renal (tubular secretion)
Drug interactions	Antihistamines, anticholinergics	None	None	Probenecid (increased levels of oseltamivir)
Dose adjustments needed	≥65 yr old CrCl <50 ml/min	≥65 yr old CrCl <10 ml/min	None	CrCl <30 ml/min Severe liver dysfunction
Contraindications	Acute-angle glaucoma	Severe liver dysfunction	Underlying airway disease, asthma	
FDA-Approved Indications				
Therapy	Adults and children ≥1 yr old	Adults only	Adults and children ≥7 yr old	Adults and children ≥1 yr old*
Prophylaxis	Yes	Yes	Adults and children ≥5 yr old	Adults and children ≥13 yr old†

*FDA has authorized treatment of S-OIV (novel H1N1) virus with oseltamivir in children ≥3 mo of age.
†FDA has authorized prophylaxis for S-OIV (novel H1N1) virus with oseltamivir in children ≥1 yr.
CNS, Central nervous system; *CrCl,* creatinine clearance; *FDA,* U.S. Food and Drug Administration; *GI,* gastrointestinal.
From Mandell GL et al: *Principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Churchill Livingstone.

10. HCW vaccination minimizes transmission to patients and coworkers. Some states mandate vaccination of HCWs; some healthcare facilities and other states require the wearing of face masks by unvaccinated HCWs during the influenza season, particularly when there is widespread flu.
11. Vaccine efficacy varies by age and by type of circulating virus. Efficacy varies each yr and has ranged from 23% to 60% overall; 2018 to 2019 efficacy varied by age group. Even with low efficacy, hospitalizations are reduced.
12. Alternate vaccine formulations:
    a. Intradermal vaccine for injection via a small needle into skin instead of muscle has not been available for every flu season.
    b. The CDC's Advisory Committee on Immunization Practices (ACIP) found no measurable protective benefit from using nasal spray, live-attenuated influenza vaccine (LAIV) during the 2015 to 2016 flu season. ACIP recently reviewed more data and found LAIV4 effective against influenza B and influenza A (H3N2). Effectiveness of the updated LAIV4 against currently circulating influenza A (H1N1) pdm09-like viruses is unknown. ACIP recommends any licensed, age-appropriate influenza vaccine, including LAIV4, for the 2019 to 2020 season.
    c. Give TIV if recipient has egg allergy or asthma or cares for immunosuppressed persons who require a protective environment.
    d. Thimerosal-free vaccine is available.
    e. IIV can be trivalent or quadrivalent, and egg-based or non–egg-based (cell culture or recombinant hemagglutinin).
    f. There is no preference for standard dose IIV or high dose IIV (age 65 or over).
    g. ACIP guidance for egg allergies:
        (1) If a person with egg allergy experiences only hives, then administer trivalent recombinant hemagglutinin influenza vaccine (RIV3) if ages 18 to 49, or IIV and observe for at least 30 min for reaction following vaccine.
        (2) If a person with egg allergy experiences other symptoms such as cardiovascular (e.g., hypotension), respiratory distress (e.g., wheezing), gastrointestinal (e.g., nausea/vomiting), reaction requiring epinephrine or emergency medical attention, administer RIV3 if age 18 to 49, or refer to a physician with expertise in management of allergic conditions.
        (3) If there is no known history of exposure to egg, but the person is suspected of having egg allergy, consult with a physician who has expertise in the management of allergies before vaccinating, or give RIV3 (if ages 18 to 49).
        (4) If person reports past reactions to egg involving symptoms other than urticaria (e.g., angioedema or swelling, respiratory distress, lightheadedness, recurrent emesis) or who required epinephrine or other medical intervention, should be vaccinated in a medical setting with supervision of vaccine administration by health care provider able to recognize and manage severe allergic reactions.

- Storage of vaccines:
    1. Maintain storage temperatures with adequate refrigeration and temperature monitoring.
    2. Do not use beyond expiration date or manufacturer's beyond use date.
    3. Do not access single-dose vial for more than one dose.
- Chemoprophylaxis:
    1. Table 2 describes antiviral agents for influenza. Oseltamivir and zanamivir are recommended in the U.S. during the influenza season. Baloxavir marboxil was recently (2018) FDA approved and may eventually replace the other agents as a preferred drug (single-dose treatment for persons 12 to 65 yr old weighing over 40 kg, low side-effects profile).
    2. Consider (after the current circulating strain of influenza has been shown to be sensitive):
        a. For high-risk patients in whom vaccination is contraindicated
        b. When the available vaccine is known not to include the circulating strain
        c. To provide added protection to immunosuppressed patients likely to have a diminished response to vaccination
        d. In the setting of an outbreak, when immediate protection of unvaccinated or recently vaccinated patients at high risk of complications is desired
    3. Chemoprophylaxis with antiviral drugs is not recommended for healthy persons exposed to seasonal influenza.
    4. Give for 2 wk in the case of late vaccination and for the duration of the flu season in all other patients.
    5. Treatment should not wait for laboratory confirmation of influenza.
    6. Do not give aspirin or aspirin-containing products to children with influenza-like illness due to the risk of Reye syndrome.

- Other prevention strategies:
  1. Hand hygiene, cough etiquette (cover your cough), respiratory hygiene (use of tissues, facemasks for the ill and proper disposal).
  2. Seasonal flu personal protective equipment (PPE)—wear gloves and gowns as per universal/standard precautions. Per the CDC, wear a facemask, adhering to Droplet Precautions for 7 days after illness onset or until 24 hr after fever and respiratory symptoms are resolved, whichever is longer. Patient placement in a negative pressure room and N95 respirator for health care workers are recommended when conducting aerosol-generating procedures.
  3. Highly pathogenic Asian avian influenza (HPAI) includes H5N1, H7N9, H5N2, and H5N8. CDC recommends wearing eye protection, N95 respirator, gown, and gloves as for airborne and contact precautions.
  4. Management of ill health care workers—exclude from work until at least 24 hr after they no longer have a fever (without the use of fever-reducing medication). Extended exclusion time period when caring for severely immunocompromised patients.
  5. Standard cleaning and disinfection procedures.
- The Centers for Medicare and Medicaid Services links health care worker vaccine acceptance with payment for performance.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Influenza (Flu) (Patient Information)

AUTHOR: **Marlene Fishman Wolpert, MPH, CIC, FAPIC**

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Influenza, Avian

BASIC INFORMATION

DEFINITION

Avian influenza is a virus originating in birds that has the capacity to infect humans. The prior influenza pandemics of the 20th century (from the devastating 1918 pandemic [H1N1], in which 40 to 100 million people died, to the lesser pandemics of 1957 [H2N2] and 1968 [H3N3], of 1 to 6 million deaths) were caused by highly virulent, efficiently transmitted influenzas that evolved from avian strains.

The highly pathogenic avian influenza A (H5N1), which emerged in 1997 in Hong Kong and is capable of only incidentally infecting humans, had threatened to bring another pandemic flu. It has infected over 850 persons worldwide and has a high case fatality rate of 55% (62 total cases in 2011) as it spread via migrating waterfowl from Asia to Europe and Africa.

However, the worldwide epidemic of a novel influenza strain in 2009 to 2010 with millions of cases was not with this virus but with the influenza A (H1N1) virus, which was a reassortment human–swine–avian virus.

In 2013, a new novel avian influenza emerged in China: H7N9, of which there were >1300 lab-confirmed cases. To date, there is no evidence of sustained transmission among humans for this virus, but there have been a few small clusters. The number of new cases was only 3 in 2017 to 2018. See related topic "Influenza."

SYNONYMS

Bird flu
Pandemic flu

ICD-10CM CODE

J09 Influenza due to certain identified influenza virus

EPIDEMIOLOGY & DEMOGRAPHICS

Avian influenza A H5N1 is an influenza virus related to those that bring our yearly influenzas, against which populations are routinely vaccinated. Influenza viruses are enveloped RNA viruses with segmented genomes and great antigenic diversity. They are categorized by their core proteins (A, B, C), species of origin (avian, swine, human), geographic site of isolation, serial number, and influenza subtypes based on the major antigenic surface glycoproteins, hemagglutinin (HA), and neuraminidase (NA). Example: H5N1 refers to hemagglutinin subtype 5 and neuraminidase subtype 1.

Often human and avian viruses meet and re-sort in a pig respiratory system. Southeast Asia is often the birthplace of new flu strains because birds, pigs, and people live in close proximity. It is where avian influenza A H5N1 and H7N9 emerged, first infecting domestic poultry and then wild birds that migrated across Eurasia. It is transmitted directly from birds to their keepers. Antigenic drift or shift may eventually allow avian influenza A H5N1 to gain the ability to be easily transmissible from human to human, transforming it from a highly virulent influenza strain to a pandemic flu.

PREDOMINANT SEX AND AGE: Children and young adults

RISK FACTORS: Poultry work, possibly swine work (in case of reassortment), travel to affected areas

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presenting features include fever of at least 100.4° F (38° C) with leukopenia or lymphopenia nearly always followed by viral pneumonia with escalating respiratory distress.
- Ventilatory support is often required within 48 hr of hospitalization for acute respiratory distress syndrome (ARDS).
- Symptom onset is 2 to 5 days after exposure, longer than with human influenza.
- Respiratory symptoms may also be accompanied by watery diarrhea.
- Complications include respiratory failure, renal dysfunction, cardiac compromise, pulmonary hemorrhage, pneumothorax, and multiorgan failure. A common cause of death is superinfection with bacterial pneumonias.

ETIOLOGY

H5N1 resists host antiviral cytokines, inducing excessive host proinflammatory responses. It may cause death by "cytokine storm" rather than by inherent pathogenicity. It attaches to sialic acid molecules via an α2-3 galactose receptor (common in birds) also found in human alveoli, leading to heavy damage to lower lungs. It causes severe pulmonary injury with diffuse alveolar damage. In the bone marrow, there is a reactive histiocytosis with hemophagocytosis that may lead to pancytopenia.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Atypical pneumonia, typical respiratory virus infections (e.g., influenza, respiratory syncytial virus), severe acute respiratory syndrome, upper respiratory infection with conjunctivitis (e.g., adenovirus). Clinical symptoms are indistinguishable from those of other illnesses.

WORKUP

Comprehensive travel, occupational, and epidemiologic history

LABORATORY TESTS

- Aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, complete blood count should be performed.
- Throat swab within 3 days of onset of symptoms to be sent for viral culture and polymerase chain reaction assay for avian influenza A (H5N1) RNA with appropriate biosafety precautions. The throat swab is more effective than nasal swabs because avian influenza preferentially infects the throat and lower respiratory tract. In the U.S., the FDA has approved the release of influenza H/A5 (Asian lineage) Virus real-time reverse transcription-PCR primer and probe set for more than 140 labs in 50 states, which will return preliminary results in 4 hr. An rRT-PCR has also been developed for the influenza A H7N9 virus.
- High-risk patients who must be tested include those with history of travel within 10 days of symptom onset to a country with documented H5N1 avian flu as well as patients with radiographically confirmed pneumonia, ARDS, or severe respiratory illness without an alternate etiology.
- Low-risk patients are those who have contact with domestic poultry or contact with people who have traveled to a country with documented H5N1 avian flu who have fever >38° C (>100.4° F) and cough, sore throat, and shortness of breath.

IMAGING STUDIES

- Chest radiography detects infiltrates a median of 7 days after onset of fever. They may be diffuse, multifocal or patchy infiltrates, or interstitial infiltrates or segmental or lobular consolidation. Progression to respiratory failure is indicated by diffuse bilateral ground-glass infiltrates.
- See "Imaging Studies" in the "Acute Respiratory Distress Syndrome" topic.

TREATMENT

- Vaccines and antivirals are the usual means for preventing and treating flu, but there are limited supplies worldwide. A subvirion H1N1 vaccine was approved by the FDA in 2007. The traditional means of vaccine production using embryonated hens' eggs has been limited because the bird flu kills the eggs. Promising new vaccine production methods are advancing through the experimental stages, including adenovirus vectors that have the possibility of allowing rapid large-scale production of vaccines.
- Beginning in the 2015 to 2016 flu season, an H1N1 component was added to the seasonal flu vaccine, which traditionally had been a bivalent vaccine (one strain of influenza A and one of influenza B) into a trivalent vaccine (two influenza A strains, including an H1N1 stain and an influenza B strain). See "Influenza."

NONPHARMACOLOGIC THERAPY

- N95 particulate masks prevent person-to-person transmission of H5N1. Surgical masks also likely prevent transmission of the virus as was seen in the H1N1 pandemic.
- In preparation for pandemic flu, increase worldwide surveillance and disease reporting, kill infected birds, increase the numbers of available intensive care unit beds with mechanical ventilators and increase emergency capacity, educate medical personnel and the public, and produce vaccines.
- In response, use influenza surveillance, social distancing (school closures), travel restrictions, quarantine, respirator masks, communications networking, and international teamwork to cordon off affected areas.

ACUTE GENERAL Rx

- The neuraminidase inhibitor oseltamivir can reduce the severity and duration of symptoms if treatment is initiated in the first 48 hr after symptom onset.
  1. Treatment: Adults: 75 mg PO twice daily for 5 days
  2. Postexposure prophylaxis: 75 mg PO daily for 7 to 10 days
- H5N1 demonstrates amantadine and rimantadine resistance.
- Peramivir: An IV neuraminidase inhibitor was FDA approved in December 2014. It has a long half-life, allowing for once daily dosing. It is effective against a variety of influenza A and B subtypes.

PEARLS & CONSIDERATIONS

PREVENTION

See "Nonpharmacologic Therapy."

PATIENT & FAMILY EDUCATION

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AUTHOR: **Glenn G. Fort, MD, MPH**

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Inguinal Hernia

BASIC INFORMATION

DEFINITION

Inguinal hernias are characterized by their location and reducibility. An ***indirect*** inguinal hernia courses from the internal inguinal ring, toward the external inguinal ring, and into the scrotum. A ***direct*** inguinal hernia bulges directly outward and is medial to the internal inguinal ring. An irreducible (i.e., not able to be pushed back into the abdominal cavity) inguinal hernia is ***incarcerated*** and may be associated with moderate to severe pain, tenderness to palpation and/or overlying erythema. A ***strangulated*** inguinal hernia is an incarcerated hernia with a compromised blood supply and ischemia resulting in moderate to severe pain, tenderness to palpation, overlying erythema, +/- fever, and/or nausea and vomiting.

SYNONYMS

Groin hernia
Indirect hernia
Direct hernia

ICD-10CM CODES

K40	Inguinal hernia
K40.9	Inguinal hernia without obstruction or gangrene

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Incidence is unknown.
PREVALENCE: Approximately 5% of the population experiences an abdominal hernia, and 75% of these are inguinal hernias. Two thirds of inguinal hernias are indirect, and the rest are direct.
PREDOMINANT SEX AND AGE: Male gender and increasing age are associated with increased incidence of inguinal hernias.
PEAK INCIDENCE: Increases with age
RISK FACTORS: History of hernia repair, older age, male sex, Caucasian race, family history, smoking

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with asymptomatic or mildly symptomatic inguinal hernias often present with a complaint of groin bulging, discomfort or both.
- Patients with incarcerated or strangulated inguinal hernias present with moderate to severe groin pain and tenderness to palpation and may have overlying erythema, fever, nausea or vomiting.
- The most common physical exam findings are palpable groin bulging within the scrotum (indirect hernia) (Fig. E1) or inguinal region (direct hernia); this may be best appreciated in the standing position. In males, an asymptomatic indirect hernia may be detected by invaginating the scrotal tissue, following the spermatic cord into the external femoral ring and instructing the patient to perform the Valsalva maneuver.

ETIOLOGY

Inguinal hernias are caused by a defect in the abdominal wall that is present at birth or develops with age.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other hernias: Femoral, abdominal (Fig. E2)
- Testicular: Testicular torsion, epididymitis
- Pregnant patient: Round ligament varicosity
- Vascular: Femoral aneurysm or pseudoaneurysm
- Lymphatic: Inguinal lymphadenitis, lymphogranuloma venereum

WORKUP

- Uncomplicated inguinal hernias may be diagnosed based on history or physical examination.
- If the diagnosis is unclear and the patient is asymptomatic or mildly symptomatic (mild discomfort), proceed to imaging.
- If the patient is moderately or severely symptomatic, or incarcerated or strangulated hernia is suspected, refer the patient to an emergency department.

LABORATORY TESTS

- Asymptomatic and mildly symptomatic patients require no laboratory testing.
- All other patients should be referred to an emergent setting for a complete blood count, basic metabolic panel, lactate, prothrombin time/international normalized ratio and type and screen.

IMAGING STUDIES

- If there is low concern for incarcerated or strangulated hernia (e.g., groin bulging with mild discomfort), yet the diagnosis remains unclear, obtain a groin ultrasound.
- If there is clinical concern for incarcerated or strangulated hernia (e.g., moderate to severe pain, overlying redness, nausea, vomiting, fever, increased bowel sounds), refer to the emergency department for CT abdomen/pelvis with IV contrast.

TREATMENT

- Asymptomatic and mildly symptomatic inguinal hernias can be referred on an outpatient basis to a general surgeon for expectant management.
- Suspected incarcerated or strangulated hernias should be referred to an emergency department for reduction and/or emergent surgical consultation.

NONPHARMACOLOGIC THERAPY

Although spring trusses are more commonly used in Europe, a surgeon may fit the patient with one during a period of watchful waiting.

ACUTE GENERAL Rx

- Patients with suspected incarcerated hernias need emergent reduction. This is best accomplished in an emergency department setting given the frequent need for intravenous medications.
- Incarcerated hernias sometimes can be reduced with firm direct pressure when the patient is in the Trendelenburg position; most require intravenous analgesia.

CHRONIC Rx

Patients with easily reducible, mildly symptomatic hernias can be referred to a general surgeon for expectant management.

DISPOSITION

- Patients without suspected incarcerated or strangulated hernia can be dispositioned home.
- Patients with moderate or severely symptomatic hernias or suspected incarcerated or strangulated hernias should be dispositioned to an emergent setting.

REFERRAL

- Mildly symptomatic patients should be referred to a general surgeon on an outpatient basis for watchful waiting.
- Moderately symptomatic patients (with no signs or symptoms of incarceration) should be referred urgently to a general surgeon for consideration of elective repair.
- Patients who present with potential incarceration or strangulation should be referred to an emergency department for reduction and emergent surgical consultation.

SUGGESTED READINGS

Available at ExpertConsult.com

FIG. E1 Left indirect inguinal hernia. (From Swartz MH: *Textbook of physical diagnosis, history and examination*, ed 7, 2014, Elsevier.)

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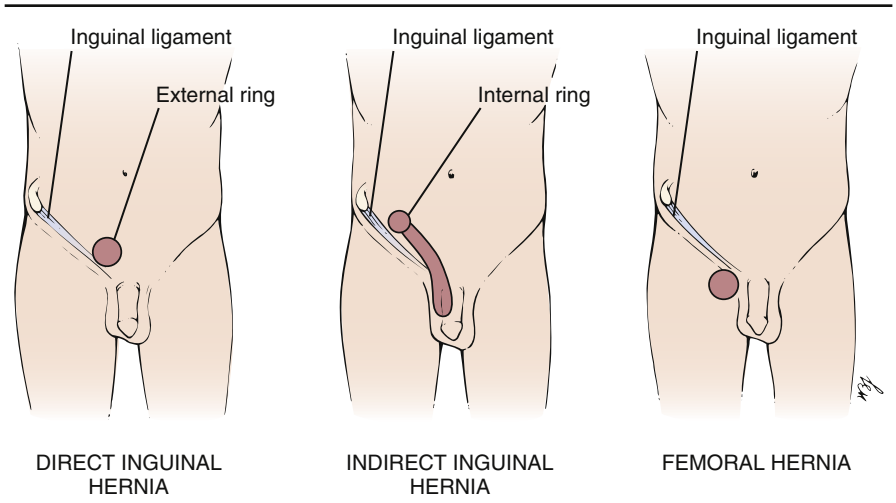

Feature	Direct Inguinal	Indirect Inguinal†	Femoral
Occurrence	Middle-aged and elderly men	All ages	Least common: more frequently found in women
Bilaterality	55%	30%	Rarely
Origin of swelling	Above inguinal ligament; directly behind and through external ring	Above inguinal ligament; hernial sac enters inguinal canal at internal ring and exits at external ring	Below inguinal ligament
Scrotal involvement	Rare	Common	None
Impulse location	At side of examining finger in inguinal canal	At tip of examining finger in inguinal canal	Not felt by examining finger in inguinal canal; mass below canal

†See Fig. E1.

FIG. E2 Differential diagnosis of hernias. (From Swartz MH: *Textbook of physical diagnosis, history and examination,* ed 7, 2014, Elsevier.)

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BASIC INFORMATION

DEFINITION

Insomnia is a disturbance of initiating or maintaining sleep. Restless, nonrestorative sleep may also be described as another specified insomnia. The disturbance occurs despite adequate circumstances and opportunity for sleep and is accompanied by significant distress or impairment in daytime functioning.

In the new DSM-5, the diagnosis of primary insomnia has been replaced with **insomnia disorder** in order to avoid the distinction between primary and secondary forms of the disorder. This paradigm shift relates to widely accepted research in the field suggesting that there is a bidirectional and interactive relationship between insomnia and any coexisting medical and/or mental disorders.

SYNONYMS

Sleeplessness
Sleep disorder, sleep disturbance, dyssomnia (NOTE: The terms *sleep disorder, sleep disturbance,* and *dyssomnia* are generic and can refer to disorders of wakefulness [hypersomnia] or sleep-related behavior disorders [parasomnias])
Insomnia disorder
Chronic insomnia disorder

ICD-10CM CODES

F51.01	Primary insomnia
F51.02	Adjustment insomnia
F51.03	Paradoxical insomnia
F51.04	Psychophysiologic insomnia
F51.05	Insomnia due to other mental disorder
F51.09	Other insomnia not due to a substance or known physiological condition
G47.00	Insomnia, unspecified
G47.01	Insomnia due to medical condition
G47.09	Other insomnia
Z73.810	Behavioral insomnia of childhood, sleep-onset association type
Z73.811	Behavioral insomnia of childhood, limit setting type
Z73.812	Behavioral insomnia of childhood, combined type
Z73.819	Behavioral insomnia of childhood, unspecified type

DSM-5 CODES
Depends on specific diagnosis.

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 20% to 30% of adults experience occasional bouts of acute insomnia.
PREVALENCE (IN U.S.): The prevalence of chronic insomnia disorder ranges from 6% to 10%.
PREDOMINANT SEX: More common in women
PREDOMINANT AGE: Transient insomnia can occur at any age; persistent insomnia can also occur at any age but is more common after age 60 yr.
GENETICS: Can run in families and may be genetically influenced. Circadian rhythm disorders and narcolepsy have been traced to specific genes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Difficulty initiating sleep, inability to maintain sleep, and/or early morning awakening.
- Significant distress or impairment in daytime functioning such as fatigue or low energy, sleepiness, cognitive impairments, mood disturbances, and/or physiologic or behavioral problems.
- Difficulty occurs despite adequate opportunity for sleep.
- Symptoms may be acute and self-limited, chronic but intermittent, or chronic and frequent.

ETIOLOGY

- Transient insomnia:
  1. Any stressful biopsychosocial change in life circumstance (e.g., marriage, divorce, birth of a child, loss of a loved one, illness, retirement, etc.)
  2. Travel (across time zones)
  3. Environmental disruptions (noise, heat, cold, poor bedding, bed partners, unfamiliar surroundings, etc.)
- Persistent insomnia (Fig. 1):
  1. Mood and anxiety disorders (depression, hypomania/mania, PTSD)
  2. Psychophysiologic insomnia (conditioned arousal, extended sleep opportunity, sleep effort, poor sleep hygiene)
  3. Sleep-related breathing disorders (e.g., obstructive apnea and hypopnea, increased upper airway resistance)
  4. Chronobiologic (also known as circadian rhythm) disorder (delayed sleep phase, advanced sleep phase, shift work, non-24-hr sleep-wake disorder secondary to blindness)
  5. Drug and alcohol abuse
  6. Restless legs syndrome and periodic leg movements
  7. Neurodegenerative (Alzheimer disease, Parkinson disease, etc.)
  8. Medical (pain, GERD, nocturia, orthopnea, menopause, medications, etc.)

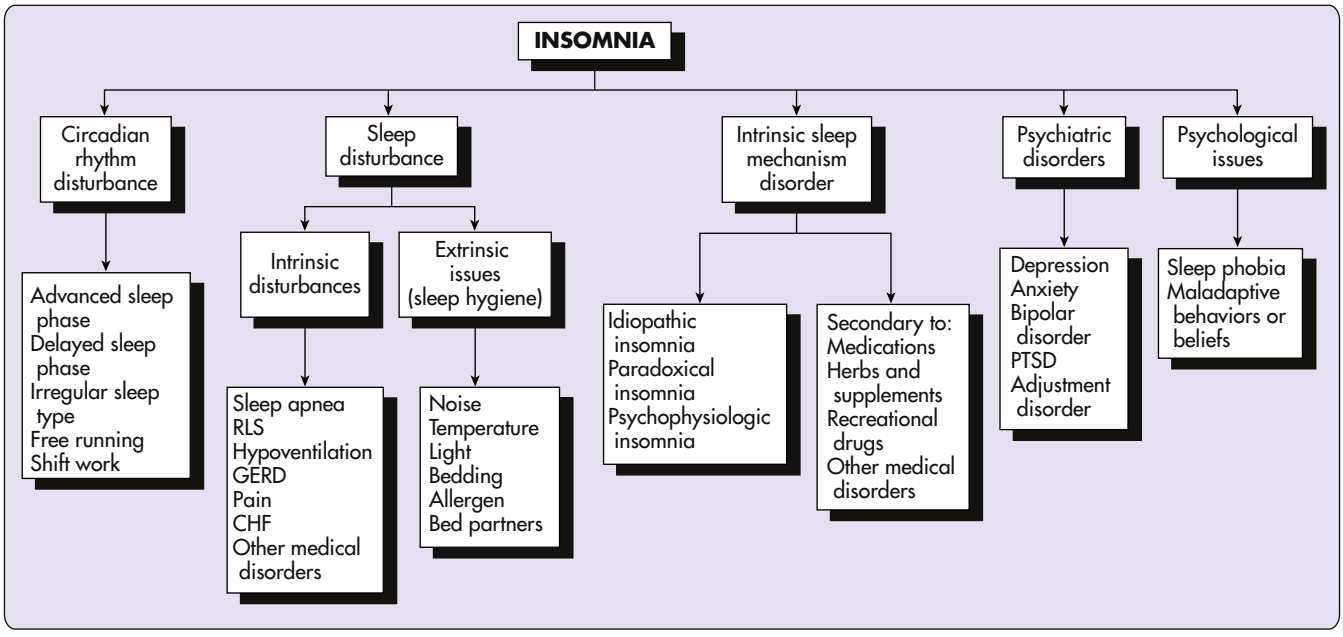

FIG. 1 Diagnostic flowchart to approach insomnia. *CHF,* Congestive heart failure; *GERD,* gastroesophageal reflux disease; *PTSD,* posttraumatic stress disorder; *RLS,* restless legs syndrome. (From Kryger MH et al: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.)

DIAGNOSIS

Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for the diagnosis of insomnia disorder is as follows[1]:

- Dissatisfaction with sleep quantity or quality, with one or more of the following symptoms:
  1. Difficulty initiating sleep
  2. Difficulty maintaining sleep, characterized by frequent awakenings or trouble returning to sleep after awakenings
  3. Early-morning awakening with inability to return to sleep
- The sleep disturbance causes clinically significant distress or impairment in daytime functioning, as evidenced by at least one of the following:
  1. Fatigue or low energy
  2. Daytime sleepiness
  3. Impaired attention, concentration, or memory
  4. Mood disturbance
  5. Behavioral difficulties
  6. Impaired occupational or academic function
  7. Impaired interpersonal or social function
  8. Negative effect on caregiver or family functioning
- The sleep difficulty occurs at least 3 nights per wk, is present for at least 3 mo, and occurs despite adequate opportunity for sleep

DIFFERENTIAL DIAGNOSIS

Insomnia disorder is only ruled out when the disorder is seen exclusively during other etiologies (see "Etiology"). It can be precipitated by a "primary" medical, mental health, or other sleep-wake disorder, but often continues as a comorbid condition even after the "primary disorder" has been treated. For medical disorders such as obesity, diabetes mellitus, and renal disease, obstructive sleep apnea is a frequent complication and must be ruled out. Insomnia remains the most resistant symptom following the treatment of depression. Its continued expression complicates the treatment of depression, reduces remission rates, and increases the likelihood of relapse of depression. Once evidence has been established of ongoing perpetuating factors such as conditioned arousal, sleep extension, worry and rumination about sleep, and sleep effort, this predicts that the insomnia will not likely remit even with the remission of the original precipitating stressor or disorder. It is also important to note that sleep dysregulation is a frequent early sign of a manic episode. Restoring sleep will often help reduce manic symptoms.

Circadian rhythm disturbances such as those seen in shift workers, blind individuals who lack a light-dark cycle to synchronize the body clock, adolescents and young adults with delayed sleep phase syndrome, and people with jet lag can mimic signs and symptoms of insomnia, especially initial and late insomnia. These disorders can be treated with chronobiologic therapies such as chronotherapy, bright light exposure, melatonin, or melatonin agonists. However, the timing of these interventions can be critical to outcome and constitutes therapies that are very different from standard medical and/or behavioral treatment for insomnia.

[1]American Psychiatric Association: *Diagnostic and statistical manual of mental disorders,* 5th ed, American Psychiatric Publishing, Arlington, VA, 2013.

BOX 1 Sleep Habits (Sleep Hygiene Measures) That May Improve Sleep

1. Reduce caffeine, alcohol, or tobacco late in the day or especially evening.
2. Avoid heavy meals at night, but consider a light snack before bed such as toast or a handful of nuts.
3. Increase daytime activity, but avoid exercise within 3-5 hours of bedtime.
4. Increase daytime exposure to natural light.
5. Reduce liquids in the last 4 hours before bedtime.
6. Consider white noise as background sound for the sleep environment.
7. Maintain regular bed and wake times.
8. Go to bed with calm mind; resolve arguments or set a time earlier in the day to review problems and perhaps write down plans, solutions, or things to do.
9. Keep light exposure in the middle of the night to a minimum when awake and attenuate morning light in the bedroom.
10. Avoid pets in the bed.

WORKUP

- History (with bed partner interview, if possible)
- Medication review (e.g., steroids can disrupt sleep)
- Sleep diary for 2 wk (Consider the Consensus Sleep Diary [Carney CE et al in Suggested Readings])
- Wrist actigraphy (detects gross limb movements and can distinguish wake from sleep states) as an adjunct to a sleep diary provides some objective verification of the diary data and provides prospective measurement of sleep and wake across the 24-hr day. Actigraphy should not be considered an alternative to prospective sleep diary data
- Validated sleep-quality rating scale (optional).
  1. Insomnia Severity Index
  2. Pittsburgh Sleep Quality Index
  3. Epworth Sleepiness Scale (see Daytime Sleepiness Test at www.sleepfoundation.org)

LABORATORY TESTS

- Evaluate for anemia (especially low ferritin level), uremia (for restless legs), thyroid function (if other signs present).
- Polysomnography (in home or in sleep laboratory) is not standard for insomnia but should be reserved for patients whose history suggests specific sleep-related breathing or movement disorders. It is indicated for symptoms suggestive of daytime sleepiness (obstructive sleep apnea, narcolepsy), nonrestorative sleep (periodic leg movements, chronic pain conditions), or sleep behavior suggesting parasomnia (somnambulism, REM sleep behavior).

IMAGING STUDIES

- Not generally helpful
- Brain CT or MRI for severe daytime sleepiness or acute onset

TREATMENT

NONPHARMACOLOGIC THERAPY

- Sleep hygiene measures (Box 1) as a monotherapy are not very effective in cases of persistent insomnia. More useful if combined with procedures described next.
- Cognitive-behavioral therapy (CBT-I) has been shown to reduce time to fall asleep and time awake during the night, can reduce reliance on sleep medications, and has shown lasting effects after treatment has been discontinued. It should be the initial treatment option in persons with chronic insomnia.
- The standard components that comprise CBT-I are as follows:
  1. Stimulus control, which addresses the conditioned cues that create arousal when attempting to sleep by restricting activity in bed to sleep and sex and not permitting sleep effort, worrying, watching TV, reading, etc., in bed (reconditioning of this type can take several days or wks—patients should not come to expect positive changes on the first night).
  2. Sleep restriction therapy reduces sleep opportunity to the average amount of total sleep time the patient is getting as determined by baseline sleep diary data. Sleep time is increased incrementally, based on improving sleep efficiency. Note that restricted time in bed should never be <5 hr. For the elderly and infirm, average total sleep time plus 30 min is sometimes considered. For patients whose estimated average total sleep time is <4 hr, a diagnosis of paradoxical insomnia should be considered and CBT-I would be contraindicated. Caution should also be exercised when using sleep restriction therapy in bipolar disorder and seizure disorders, as sleep deprivation early in treatment can precipitate a manic episode and lower seizure threshold, respectively.
  3. Cognitive therapy targets unhelpful beliefs and worries about sleep, negative and unwanted thoughts, sleep effort, selective attention bias and monitoring, misperception of sleep and daytime deficits, and counterproductive safety behaviors that are thought to maintain insomnia.
  4. Sleep hygiene is aimed at improving sleep habits (e.g., initiating or maintaining exercise, avoiding heavy meals at night, and altering the timing of or eliminating caffeine, nicotine, and alcohol intake). Environmental factors should also be addressed (e.g., using white noise and/or light attenuating bedroom). Caffeine sometimes can prove useful when used judiciously in the morning and early

afternoon to combat the increased fatigue and somnolence that are produced early in therapy with sleep restriction and stimulus control. In addition, exercise contingently applied to daytime fatigue can also help to improve alertness during the day and increase sleep pressure at bedtime.

5. Relaxation exercises (e.g., progressive muscle relaxation, diaphragmatic breathing) may be good adjunctive therapy, especially in highly anxious patients, but are not thought to be essential in CBT-I. Increasingly, mindfulness-based practices are being effectively utilized alone and in combination with other elements of CBT-I. Mindfulness may help patients to adopt a more flexible and accepting stance toward insomnia.

ACUTE GENERAL Rx

- Benzodiazepine receptor agonists zolpidem 5 mg and zaleplon 5 mg for sleep-onset insomnia, and zolpidem continuous-release formulation 6.25 to 12.5 mg and eszopiclone 1 to 3 mg for maintenance insomnia.
- Suvorexant is an orexin receptor antagonist FDA approved for insomnia. Signaling of orexin neuropeptides sustains wakefulness. Suvorexant promotes sleep by blocking orexin neuropeptides from binding to their receptors. The initial dose is 10 mg once daily within 30 min of bedtime. Most common side effect (10%) is next-day somnolence.
- Benzodiazepine sedative-hypnotics (e.g., temazepam 7.5 to 30 mg, triazolam 0.125 to 0.25 mg).
- A low-dose formulation (6 mg) of the tricyclic antidepressant doxepin, brand name Silenor, is also FDA approved for treatment of insomnia associated with sleep maintenance. This dose retains the hypnotic effect of doxepin without the typical tricyclic effects. A generic 10 mg/ml liquid formulation of doxepin is also available.
- In critical care: Lorazepam 0.25 to 0.5 mg PO, SL, or IV as needed for sleep. In patients with acute delirium, haloperidol 0.25 to 0.5 mg IV as needed up to 2 mg/day may be less likely to worsen confusion.
- Melatonin 3 to 5 mg has been used for delayed phase insomnia with shortening of sleep initiation time but no real change in sleep efficiency. There can be side effects, especially at higher doses.
- Melatonin agonist ramelteon 8 mg for sleep-onset insomnia when a mild agent without benzodiazepine side effects is desired.
- Avoid antihistamines except for occasional use.
- Optimize treatment of medical symptoms, especially pain.
- Most prescription and over-the-counter medications carry significant risk of adverse events and drug interactions, especially in the geriatric patient. Preferred pharmacotherapeutic agents in the elderly are zolpidem, zaleplon, eszopiclone, and ramelteon.

CHRONIC Rx

- Considerable research supports the efficacy of CBT-I, with acute treatment outcomes equivalent to pharmacotherapy, and better long-term outcomes and maintenance of treatment gains. Although there is limited availability of CBT-I specialists, especially in certain geographic areas, there are now online interactive evidence-based self-help programs that can serve as an effective base for a stepped model of care. Patients who fail these attempts should still be encouraged to seek more tailored treatment with a specialist, especially when the insomnia is comorbid with other conditions.
- When CBT-I is applied to patients with related comorbidities (e.g., depression, chronic pain), evidence suggests that targeted treatment for insomnia not only results in significant improvement of the insomnia but, in many cases, influences the course of the related comorbidities. For example, when CBT-I is applied concurrently with antidepressants, it has the effect of doubling remission rates in depression and reduces suicidal ideation by up to 65%. In a recent study of patients with comorbid depression and insomnia, head-to-head comparison of Internet-based treatments for depression (dCBT-D) and insomnia (dCBT-I) demonstrated that dCBT-I outperformed dCBT-D for insomnia and matched its efficacy in depression.
- Note that the American College of Physicians recently published clinical guidelines for the management of chronic insomnia disorder, suggesting that CBT-I be the first-line treatment for insomnia and recommending that it be attempted before pharmacologic approaches when possible.
- Three sedative-hypnotics—zolpidem continuous release, eszopiclone, and ramelteon—FDA approved for long-term use.
- Some evidence shows that benzodiazepines and benzodiazepine receptor agonists can be used for chronic insomnia on either intermittent or nightly use with moderate risk of tolerance and dependence but low risk of addiction.
- Sedating antidepressants (e.g., trazodone 25 to 150 mg, mirtazapine 7.5 to 30 mg, amitriptyline 25 to 50 mg, doxepin 10 mg) are in widespread use, with limited data on safety and efficacy. Amitriptyline should be avoided in older adults.
- Sedating antipsychotics (e.g., quetiapine 25 to 200 mg, olanzapine 2.5 to 10 mg at night) considered for severe mood or psychotic disorders associated with insomnia.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Melatonin may shorten sleep-onset latency in some individuals. It may have more clinical utility in the management of circadian rhythm disorders. Timing of administration in these types of cases requires careful consideration and would not be often administered at bedtime.

DISPOSITION

- Transient (acute) insomnia: Usually self-limited. May require follow-up if stress-related or illness-related because of risk of depression or persistence. Prophylactic education regarding maladaptive sleep practices such as extending time in bed, and/or remaining in bed when unable to sleep, might be helpful in avoiding a more protracted course of insomnia.
- Persistent insomnia: Patients who respond well to CBT-I often continue to maintain gains at 1- and 2-yr follow-ups. Patients may need periodic follow-up to reinforce good sleep hygiene and stimulus control and for reevaluation of pharmacologic therapies. There is now a compelling amount of evidence that insomnia, if left untreated, is associated with significant negative mental and health effects over time.

REFERRAL

- A referral to a behavioral medicine specialist may be required for CBT-I or for circadian rhythm disturbances (find a directory at https://www.behavioralsleep.org)
- Excessive daytime sleepiness not obviously caused by insomnia (e.g., narcolepsy, sleep-related breathing disorder)
- Nighttime behavior suggestive of a parasomnia (e.g., somnambulism, REM behavior disorder)
- Severe insomnia not responsive to basic interventions

PEARLS & CONSIDERATIONS

COMMENTS

CBT-I often results in worse sleep and more fatigue in the short run. Patients often respond to initial worsening of symptoms as a sign of failure; however, they should be encouraged to see this as an important piece of the therapy and to stay the course as new conditioned patterns begin to emerge, sleep efficiency improves, and total sleep time gradually increases.

Patients should avoid compensating for lost sleep by extending sleep opportunity in the form of going to bed early, sleeping in, or napping. Therefore, early treatment should focus on helping patients to manage daytime fatigue and sleepiness by engaging in activities that help patients stay awake and maintain set bed and wake times.

PREVENTION

It is estimated that 50% to 70% of individuals demonstrating the syndrome of insomnia (e.g., insomnia symptoms more than 3 days per wk for a mo along with deleterious daytime sequelae) are still syndromic 1 to 5 yr later. Therefore, early intervention with medication or education to prevent the development of maladaptive compensatory behaviors (e.g., napping, sleeping late, tossing and turning in bed, avoiding or decreasing daytime activity) may help to reduce the risk of developing persistent insomnia.

PATIENT & FAMILY EDUCATION

The National Sleep Foundation (http://www.sleepfoundation.org) is a comprehensive resource for health care providers and patients.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Fatigue, Chronic (Differential Diagnosis in Section II)
Insomnia (Patient Information)

AUTHOR: **Donn Posner, PhD**

SUGGESTED READINGS

Blom LP: Three-year follow-up comparing cognitive behavioral therapy for depression to cognitive behavioral therapy for insomnia, for patients with both diagnoses, *Sleep* 40(8):1-5, 2017.

Brasure M: Psychological and behavioral interventions for managing insomnia disorder: an evidence report for a clinical practice guideline by the American College of Physicians, *Ann Int Med* 165:113-124, 2016.

Carney CE: The Consensus Sleep Diary: standardizing prospective sleep self-monitoring, *Sleep* 35(2):287-302, 2012.

Manber R: A step towards stepped care: delivery of CBT-I with reduced clinician time, *Sleep Med Rev* 19(3-5), 2015.

Maness DL, Khan M: Non-pharmacologic management of chronic insomnia, *Am Fam Physician* 92(12):1058-1064, 2015.

Mysliwiec V et al: The management of chronic insomnia disorder and obstructive sleep apnea: synopsis of the 2019 U.S. Department of Veterans Affairs and U.S. Department of Defense clinical practice guidelines, *Ann Intern Med* 172(5):325-336, 2020.

Qaseem A: Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians, *Ann Intern Med* 165(2):125-133, 2016.

Trauer JM: Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis, *Ann Intern Med* 163(3):191-204, 2015.

Wilt TJ: Pharmacologic treatment of insomnia disorder: an evidence report for a clinical practice guideline by the American College of Physicians, *Ann Int Med* 165:103-121, 2016.

Winkelman JW: Clinical practice, insomnia disorder, *N Engl J Med* 373:1437-1444, 2015.

BASIC INFORMATION

DEFINITION

Insulinoma is a pancreatic insulin-secreting tumor that leads to inappropriately elevated plasma insulin or proinsulin levels with suppression of hepatic glucose output and subsequent hypoglycemia, especially during periods of fasting.

ICD-10CM CODES

C25.4 Malignant neoplasm of endocrine pancreas
D13.7 Benign neoplasm of endocrine pancreas
D37.7 Neoplasm of uncertain or unknown behavior of other digestive organs (pancreas)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: One case per 250,000 persons annually. 90% of insulinomas are benign.
PREDOMINANT SEX AND AGE: Insulinomas occur in both sexes (approximately 60% in women) and at all ages. In a Mayo Clinic series, the median age at diagnosis was 50 yr in sporadic cases, but 23 yr in patients with multiple endocrine neoplasia, type 1 (MEN-1).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms typically occur in the morning before breakfast (i.e., fasting hypoglycemia as opposed to reactive hypoglycemia, which is not commonly associated with insulinoma).

Neuroglycopenic Symptoms	**%**
Various combinations of diplopia, blurred vision, sweating, palpitations, or weakness	85
Confusion or abnormal behavior	80
Unconsciousness or amnesia	53
Grand mal seizures	12
Adrenergic Symptoms	**%**
Sweating	43
Tremulousness	23
Hunger, nausea	12
Palpitations	10

ETIOLOGY, PATHOLOGY, & PATHOPHYSIOLOGY

- Insulinomas are almost always solitary. Malignant insulinomas account for 5% of the total; they tend to be larger (6 cm). Metastases are usually to the liver (47%), regional lymph nodes (30%), or both.
- Insulinomas are evenly distributed in the head, body, and tail of the pancreas; ectopic insulinomas are rare (1% to 3%). Tumor size: 5% are ≤0.5 cm, 34% are 0.5 to 1 cm, 53% are 1 to 5 cm, and 8% are >5 cm.
- Histologic classification includes insulinoma in 86% of patients, adenomatosis in 5% to 15%, nesidioblastosis in 4%, and hyperplasia in 1%. Adenomatosis consists of multiple macroadenomas or microadenomas and occurs especially in patients with MEN-1. Nesidioblastosis is also a diffuse lesion in which islet cells form as buds on ductular structures.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS (OF FASTING HYPOGLYCEMIA)

Hyperinsulinism:
- Insulinoma
- Nonpancreatic tumors
- Severe congestive heart failure
- Severe renal insufficiency in non–insulin-dependent diabetes

Hepatic enzyme deficiencies or decreased hepatic glucose output (primarily in infants and children):
- Glycogen storage diseases
- Endocrine hypofunction
- Hypopituitarism
- Addison disease
- Liver failure
- Alcohol abuse
- Malnutrition

Exogenous agents:
- Sulfonylureas, biguanides
- Insulin
- Other drugs (aspirin, pentamidine)

Functional fasting hypoglycemia:
- Autoantibodies to insulin receptor or insulin

LABORATORY TESTS

- An overnight fasting blood sugar level combined with a simultaneous plasma insulin, proinsulin, and/or C peptide level will establish the existence of fasting organic hypoglycemia in 60% of patients. Table E1 describes biochemical patterns in patients with various causes of hyperinsulinemic hypoglycemia.
- If single overnight fasting glucose and insulin levels are nondiagnostic, a 72-hr fast is usually done with blood glucose and insulin levels determined at 2- to 4-hr intervals. A total of 75% of patients with insulinoma develop symptoms and a blood sugar level of <40 mg/dl by 24 hr, 92% to 98% develop these by 48 hr, and virtually all patients develop them by 72 hr. The test is considered positive for insulinoma if the plasma insulin/glucose ratio is more than 0.3. If at any point the patient becomes symptomatic, plasma insulin and glucose values should be obtained and IV glucose should be administered.
- The Endocrine Society guidelines for diagnosis of hypoglycemic disorders is based on glucose level <55 mg/dl (<3.1 mmol/L), elevated C-peptide level ≥0.61 ng/ml (≥0.2 nmol/L). Elevated insulin level ≥18 pmol/L, proinsulin level >5 pmol/L, and suppressed β-hydroxy-butyric acid level.
- An "amended" insulin-glucose ratio that accounts for the normal variation in insulin secretion according to prevailing glycemia has been shown to improve diagnostic accuracy of insulinomas. The "amended" insulin-glucose ratio is derived from the simple insulin-glucose ratio by subtracting 30 mg/dl (1.7 mmol/L) from the measured glucose concentrations.

IMAGING STUDIES

- Abdominal CT scan or MRI (Fig. E1) detects half to two thirds of insulinomas (abdominal ultrasound is not effective); should be done only after laboratory tests for insulinoma have confirmed the diagnosis
- Intraoperative ultrasound
- Arteriography
- Octreotide scan (Fig. E2)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Enucleation of single insulinoma
- Partial pancreatectomy for multiple adenomas

ACUTE GENERAL Rx

- Carbohydrate administration
- Diazoxide directly inhibits insulin release and has an extrapancreatic, hyperglycemic effect that enhances glycogenolysis
- Lanreotide and octreotide (somatostatin analogues)
- Streptozotocin

REFERRAL

To an endocrinologist and then to an endocrine surgeon

RELATED CONTENT

Hypoglycemia (Algorithm in Section III)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READING

Nauck MA, Meier JJ: Diagnostic accuracy of an "amended" insulin-glucose ratio for the biochemical diagnosis of insulinomas, *Ann Intern Med* 157:767-775, 2012.

TABLE E1 Biochemical Patterns in Patients with Various Causes of Hyperinsulinemic Hypoglycemia

Insulin	C Peptide	Proinsulin	Sulfonylurea	Insulin Antibody	Diagnosis
↑	↓	↓	–	–	Exogenous insulin
↑	↑	↑*	–	–	Insulinoma, congenital hyperinsulinism
↑	↑	↑	+	–	Sulfonylurea
↑	↑†,‡	↑†,‡	–	+	Insulin autoimmune
±↑	↓	↓	–	–	Insulin receptor autoimmune‡

*>20% of insulin value.
†Free C peptide and proinsulin ↓.
‡Insulin receptor antibody +.
From Larsen PR et al: *Williams textbook of endocrinology,* ed 10, Philadelphia, 2003, Saunders.

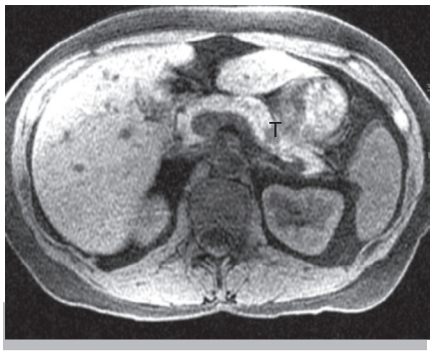

FIG. E1 Magnetic resonance image shows an insulinoma tumor *(T)* in the tail of the pancreas. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

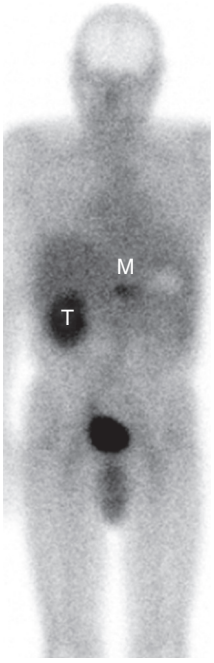

FIG. E2 Somatostatin receptor scintigraphy demonstrates primary tumor *(T)* and liver metastasis *(M).* (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

Intermittent Explosive Disorder (IED)

BASIC INFORMATION

DEFINITION

Multiple episodes of impulsive verbal or physical aggression out of proportion to perceived stressors or threats

SYNONYM

IED

ICD-10CM CODES

F63.81 Intermittent explosive disorder
F63.8 Other habit and impulse disorders
F63.9 Habit and impulse disorder, unspecified

DSM-5 CODE

312.34 Intermittent explosive disorder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown
PEAK INCIDENCE: Occurs earlier in life
PREVALENCE: Lifetime prevalence of 6% to 7%
PREDOMINANT SEX AND AGE: Occurs more so in males and in people under the age of 50.
GENETICS: Patients with intermittent explosive disorder (IED) are more likely to have first-degree relatives with the disorder. In addition, adoption and twin studies point to a >50% of the variance in aggression related to genetic factors.
RISK FACTORS: Prior history of violence, exposure to trauma, comorbid depression, anxiety, substance abuse or dependence, or cluster B personality disorders. There is evidence that substance use disorders place patients at risk of developing this condition, as opposed to the other way around.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Several episodes of verbal or physical aggression; the latter may include attacks on others or destruction of physical property.
- The aggression is out of proportion to any perceived stressors or threats.
- The aggression is impulsive.
- The aggression causes distress.
- The aggression is not accounted for by another disease process.
- The patient is at least 6 yr of age.

ETIOLOGY

- Potentially an imbalance between aggression, originating from the amygdala and other limbic structures, and orbitofrontal, and anterior cingulate cortices. The temporoparietal junction, an area involved in empathy and social cognitive processes, seems to be activated in treatment with Lexapro (see the following). This view is supported by multiple studies involving functional neuroimaging, specifically fMRI.
- From a neurochemical basis, a deficiency in the neurotransmitter serotonin appears involved. PET imaging shows a decrease in serotonergic innervation in the anterior cingulate cortex and serotonergic agents treat IED (see the following).
- Endocannabinoids may play a role. One study showed that circulating levels of anandamide were inversely related to affect regulation.
- Inflammation may play a role. Numerous markers of oxidative stress and aggression are more increased in patients with IED than in controls.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Psychiatrically, patients may suffer from mood, anxiety, psychotic, and personality disorders (primarily antisocial and borderline). In addition, patients may be under the effects of substances, or in withdrawal from them.
- Neuropsychiatrically, dementia, delirium, temporal lobe epilepsy, cardiovascular disease, multiple sclerosis, and brain lesions can all cause similar behavior. IED is often thought of as part of a frontal network syndrome related to impairment in prefrontal cortical functioning, which can sometimes present with neurologic soft signs (frontal release signs).
- If delirium is expected, a wider, more systemic differential diagnosis should be explored.

WORKUP

A thorough mental status and neurologic examination should be performed. In addition, there should be careful consideration for other neuropsychiatric conditions if the history points in that direction.

LABORATORY TESTS

- Urine toxicology screen, as substance abuse is highly comorbid.
- Dementia workup when appropriate: CBC, brain MRI or at least a head CT, Chem 7, B_{12}, TSH, Folate, RPR.
- Delirium workup when appropriate; associated signs and symptoms may be helpful for guidance, especially in clinical settings.

IMAGING STUDIES

- Brain MRI or head CT, in cases where dementia, delirium, neurovascular disease, or brain lesions are expected. The appropriate test should be ordered depending on the particulars of the case (i.e., MRI to evaluate for MS and subcortical disease).
- EEG is indicated to evaluate for seizure-related conditions.

TREATMENT (TABLE E1)

- Selective serotonin reuptake inhibitors (SSRIs) are considered first-line therapy. Multiple studies have been performed on fluoxetine, up to 60 mg per day, though it is not unreasonable to try other SSRIs given similar mechanisms of action. Cost, side effects, drug half-life, and drug-drug interactions need to be considered. Starting at 20 mg per day, and increasing by 10 mg every other wk, for a total of a 12-wk trial, is recommended.
- Multiple large trials and meta-analyses also point to the efficacy of phenytoin, lamotrigine, topiramate, and valproate. Unless there is a contraindication to SSRIs, AEDs should be considered second line, given their potential side effects and toxicities.
- Lithium has also shown to be helpful.
- See Table E1 for details related to particular medications.

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral therapy has been shown to be helpful for patients with IED.
- Patients are taught to examine their thoughts in relation to stressful circumstances.
- Patients can be taught to examine their somatic sensations and change these through relaxation techniques.
- Relapse prevention is focused on helping patients avoid explosive behaviors in the future.

ACUTE GENERAL Rx

See previous

COMPLEMENTARY & ALTERNATIVE MEDICINE

There is no evidence on the use of complementary or alternative medicine for this disorder.

REFERRAL

Referral to an outpatient mental health provider may be helpful.

PEARLS & CONSIDERATIONS

PREVENTION

No prevention measures have been identified.

PATIENT & FAMILY EDUCATION

Psychoeducation to the patient and family may be helpful, especially in helping to identify triggers and supporting the use of coping skills.

RELATED CONTENT

Abuse, Drug (Related Key Topic)
Attention Deficit-Hyperactivity Disorder (Related Key Topic)
Bipolar Disorder (Related Key Topic)
Conduct Disorder (Related Key Topic)
Paranoid Personality Disorder (Related Key Topic)

AUTHOR: **Anthony Gallo, MD**

TABLE E1 Medications for Intermittent Explosive Disorder

Medication	Starting Dose	Blood Level	Adverse Outcomes	Cautionary Notes
Fluoxetine	10 mg PO q A.M.	N/A	Mania, sexual dysfunction, SIADH	Caution in patients with bipolar disorder
Phenytoin	100 mg PO tid	10-20 mcg/ml	Hepatotoxicity, gingival hyperplasia	Caution in patients with hepatic dysfunction
Topiramate	50 mg daily	N/A	Sedation	
Lamotrigine	25 mg daily	N/A	Rash, SJS	Slow titration schedule
Valproate	250 mg PO bid	75-125 mcg/ml	Hyperammonemia, pancreatitis, hepatic impairment	Caution in patients with hepatic impairment
Carbamazepine	200 mg PO bid	4-12 mcg/ml	Hepatic failure, SJS, blood dyscrasias, SIADH	Caution in patients with hepatic impairment
Lithium	300 mg PO bid	0.6-1.2 mEq/L	Hypothyroid, nephrotoxicity	Caution in patients with renal impairment

bid, Twice per day; *PO,* by mouth;*SIADH,* syndrome of inappropriate antidiuretic hormone secretion; *SJS,* Stevens-Johnson syndrome; tid, three times per day.

SUGGESTED READINGS

Bernice YY et al: Management of Morgellons disease with low-dose trifluoperazine, *JAMA Dermatol* 154(2):216-218, 2018.

Coskun F et al: Treatment of intermittent explosive disorder with carbamazepine, *Clin Neuropharmacol* 41:82-83, 2018.

BASIC INFORMATION

DEFINITION

The interstitial lung diseases (ILDs) include more than 150 nonmalignant disorders, characterized by varying degrees of damage to the lung parenchyma or interstitium via inflammation and fibrosis. The term "ILD" can be confusing as processes affecting the alveolar space (e.g., pulmonary alveolar proteinosis) are also lumped under the title. A clinical classification of the interstitial lung diseases is summarized in Table 1. The diseases can generally be divided into three subgroups—those that are caused by an identifiable or suspected trigger, those that are associated with an underlying, more systemic disorder, and those that are idiopathic.

SYNONYMS

Interstitial pulmonary disease
ILD
Diffuse parenchymal lung disease (DPLD)
Interstitial pneumonia

ICD-10CM CODES

J84.17	Other interstitial pulmonary diseases with fibrosis in diseases classified elsewhere
J84.89	Other specified interstitial pulmonary diseases
J84.9	Interstitial pulmonary disease, unspecified
J84.115	Respiratory bronchiolitis interstitial lung disease
J84.848	Other interstitial lung diseases of childhood

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE AND PREVALENCE: Varies widely with type of ILD. The most common ILDs are sarcoidosis, cryptogenic organizing pneumonia, and idiopathic pulmonary fibrosis. The prevalence of these syndromes varies widely across different populations as defined by age, gender, and race.
PREDOMINANT SEX & AGE: Some ILDs are more common in women, such as those resulting from connective tissue disorders. Lymphangiomyomatosis occurs exclusively in premenopausal women. ILD caused by occupational exposures are more common in men. Most ILDs occur in people >50 yr; however, sarcoidosis most often presents in younger populations.
RISK FACTORS: Although many ILDs are categorized as idiopathic, the most common identifiable risk factors include environmental exposures such as silicone, asbestos, or bird droppings; reactions to drugs such as chemotherapeutic agents; radiation therapy; cardiac medications; and finally some history of connective tissue disease such as rheumatoid arthritis or scleroderma. Both tobacco and drug use can result in an ILD.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Shortness of breath (especially with exertion)
- Cough (dry)
- Tachypnea
- Bibasilar end-inspiratory dry crackles
- Pulmonary hypertension
- Cyanosis, clubbing

Hallmarks of ILD include a restrictive pattern and decreased diffusing capacity for carbon monoxide (DLCO) as demonstrated by pulmonary function testing. The restrictive process can be the result of a number of factors depending on the type of ILD. Different types of ILD are characterized by varying degrees of acute inflammatory changes, which are potentially reversible, and fibrosis, which is largely irreversible.

- Specific changes may be seen:
  1. Granulomatous: Accumulation of T lymphocytes, macrophages, and epithelioid cells into granulomas in lung parenchyma
  2. Inflammation and fibrosis: Injury to epithelium causes inflammation; if chronic, inflammation spreads to interstitium and vascular areas

TABLE 1 Clinical Classification of the Interstitial Lung Diseases

Connective Tissue Diseases
Scleroderma
Polymyositis-dermatomyositis
Systemic lupus erythematosus
Rheumatoid arthritis
Mixed connective tissue disease
Ankylosing spondylitis

Treatment-Related or Drug-Induced Diseases
Antibiotics (nitrofurantoin, sulfasalazine)
Antiarrhythmics (amiodarone, tocainide, propranolol)
Antiinflammatories (gold, penicillamine)
Anticonvulsants (Dilantin)
Chemotherapeutic agents (mitomycin C, bleomycin, busulfan, cyclophosphamide, chlorambucil, methotrexate, azathioprine, BCNU [carmustine], procarbazine)
Therapeutic radiation
Oxygen toxicity
Narcotics

Primary and Idiopathic Diseases
Sarcoidosis
Primary pulmonary Langerhans cell histiocytosis (eosinophilic granuloma)
Amyloidosis
Pulmonary vasculitis
Gaucher disease
Niemann-Pick disease
Hermansky-Pudlak syndrome
Neurofibromatosis
Lymphangioleiomyomatosis
Tuberous sclerosis
Idiopathic pulmonary fibrosis
Nonspecific interstitial pneumonia
Cryptogenic organizing pneumonia
Respiratory bronchiolitis ILD or desquamative interstitial pneumonia
Acute interstitial pneumonia
Lymphocytic interstitial pneumonia
Pleuroparenchymal fibroelastosis
Bone marrow transplantation
Eosinophilic pneumonia
Alveolar proteinosis
Alveolar microlithiasis
Metastatic calcification

Occupational and Environmental Diseases
Inorganic
Silicosis
Asbestosis
Hard-metal pneumoconiosis
Coal worker's pneumoconiosis
Berylliosis
Talc pneumoconiosis
Siderosis (arc welder)
Stannosis (tin)

Organic (hypersensitivity pneumonitis)
Bird breeder's lung
Farmer's lung

ILD, Interstitial lung disease.
Modified from Mason RJ: *Murray & Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, WB Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Congestive heart failure
- Pneumonia: Viral, bacterial, mycobacterial, fungal
- Pulmonary embolism
- COPD
- Pulmonary hypertension
- Vasculitis
- Metastatic malignancy manifesting as lymphangitic carcinomatosis

WORKUP

- Well-defined patterns in pulmonary function tests are usually consistent with restrictive defect (decreased FVC, FRC, RV, and TLC) owing to decreased lung compliance caused by alveolar wall thickening as a result of inflammation and fibrosis. Diffusion capacity is usually reduced also because of inflammation and thickening of alveolar walls, though nonspecific. FEV_1/FVC is usually normal or increased because lung stiffness keeps small airways open, although some conditions (e.g., sarcoidosis, hypersensitivity pneumonitis) may result in air trapping.
- Bronchoscopy and bronchoalveolar lavage (BAL) may help identify type of ILD. However, their role in defining stage of disease and response to therapy is controversial. Histologic patterns in the interstitial lung diseases and their disease associations are summarized in Table 2.
- If laboratory studies and imaging including HRCT fail in yielding a diagnosis, a surgical biopsy may be required. A common objective of performing a biopsy is to evaluate the possibility of idiopathic pulmonary fibrosis, which has a unique approach to treatment.
- Fig. 1 illustrates an algorithm for the approach to a patient with interstitial lung disease.

LABORATORY TESTS

- ABGs may be normal or show respiratory alkalosis and widened Aa gradient.
- Blood tests for connective tissue diseases, such as antinuclear antibodies,

TABLE 2 Histologic Patterns in the Interstitial Lung Diseases and Their Disease Associations

Histologic Patterns	Clinical Associations
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis; connective tissue diseases (uncommon); asbestosis; chronic hypersensitivity pneumonitis; chronic aspiration pneumonia; chronic radiation pneumonitis; Hermansky-Pudlak syndrome
Nonspecific interstitial pneumonia	Idiopathic; connective tissue diseases; drugs; AIDS
Diffuse alveolar damage	Acute interstitial pneumonia (Hamman-Rich syndrome); acute respiratory distress syndrome (ARDS); drugs (cytotoxic agents, heroin, paraquat, ethchlorvynol, aspirin); toxic gas inhalation; radiation therapy; oxygen toxicity; connective tissue disease; infections
Organizing pneumonia	Cryptogenic organizing pneumonia; organizing stage of diffuse alveolar damage; drugs (amiodarone, cocaine); infections; connective tissue diseases
Desquamative interstitial pneumonia/respiratory bronchiolitis	Cigarette smoking; idiopathic DIP of childhood
Lymphocytic interstitial pneumonia	Idiopathic; hypogammaglobulinemia; autoimmune diseases, including Hashimoto thyroiditis, lupus erythematosus, primary biliary cirrhosis, Sjögren syndrome, myasthenia gravis, chronic active hepatitis; AIDS; allogeneic bone marrow transplantation
Eosinophilic pneumonia	Idiopathic acute and chronic; tropical filarial eosinophilia; parasitic infections; allergic bronchopulmonary aspergillosis; allergic granulomatosis of Churg and Strauss; hypereosinophilic syndrome; AIDS
Alveolar proteinosis	Pulmonary alveolar proteinosis; acute silicosis; aluminum dust; AIDS; myeloproliferative disorder
Diffuse alveolar hemorrhage	
with capillaritis	Wegener granulomatosis; microscopic polyangiitis; systemic lupus erythematosus; polymyositis; scleroderma; rheumatoid arthritis; mixed connective tissue disease; lung transplantation; drugs (retinoic acid, propylthiouracil, Dilantin); Behçet disease; cryoglobulinemia; Henoch-Schönlein purpura; pauci-immune glomerulonephritis; immune complex glomerulonephritis
without capillaritis	Idiopathic pulmonary hemosiderosis; systemic lupus erythematosus; Goodpasture syndrome; diffuse alveolar damage; pulmonary venoocclusive disease; mitral stenosis; lymphangioleiomyomatosis
Amyloid deposition	Primary amyloidosis; multiple myeloma; lymphocytic interstitial pneumonia
Granuloma	Sarcoidosis; hypersensitivity pneumonitis; pulmonary Langerhans cell histiocytosis; silicosis; intravenous talcosis; berylliosis; lymphocytic interstitial pneumonia; infections

AIDS, Acquired immunodeficiency syndrome; *DIP,* desquamative interstitial pneumonia.
Modified from Mason RJ: *Murray & Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, WB Saunders.

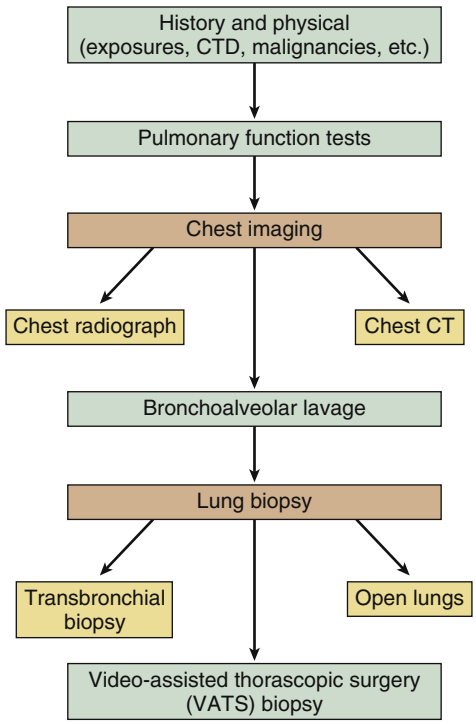

FIG. 1 Algorithm for the approach to a patient with interstitial lung disease. *CT,* computed tomography; *CTD,* connective tissue disease. (From Sellke FW et al: *Sabiston & Spencer surgery of the chest,* ed 9, Philadelphia, 2016, Elsevier.)

anti-immunoglobulin antibodies (rheumatoid factors), LDH. Laboratory findings in the interstitial lung diseases are summarized in Table 3.
- Serum precipitins confirm exposure if hypersensitivity pneumonitis is suspected.
- Antineutrophil cytoplasmic antibodies or antibasement membrane antibodies if vasculitis is suspected.
- Angiotensin-converting enzyme testing (ACE levels) in sarcoidosis is of unclear value.

IMAGING STUDIES

- Chest x-ray may be normal but commonly shows a bibasilar reticular pattern. Table 4 summarizes radiographic features of the interstitial lung diseases.
- High-resolution CT (HRCT) (Fig. 2) is the gold standard for evaluating parenchymal opacities seen on chest x-ray; it is also useful for determining potential biopsy sites.
- Echocardiography may be useful to evaluate cardiac function/dilation or to evaluate for pulmonary hypertension, which can complicate advanced ILDs.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Avoidance of tobacco and occupational exposures

ACUTE GENERAL Rx

- Supplemental oxygen in patients with hypoxemia is helpful short and long term.
- Glucocorticoids are the mainstay of therapy for many of the ILDs. Patients should be continuously reevaluated after the initiation of treatment to gauge response. If they are improved or stable, steroids may be tapered. If not, the same course may be maintained 4 additional wk. If patient's condition is unresponsive to steroids or declines as the steroids are tapered, may consider adding second agent (cyclophosphamide, azathioprine, mycophenolate, among other options).
- ILD is a common manifestation of systemic sclerosis and a leading cause of systemic

TABLE 3 Radiographic Features of the Interstitial Lung Diseases

Feature	Diseases
Upper zone–predominant disease	Radiation pneumonitis; neurofibromatosis; chronic sarcoidosis; pulmonary Langerhans cell histiocytosis; silicosis; chronic hypersensitivity pneumonitis; chronic eosinophilic pneumonia; ankylosing spondylitis; nodular rheumatoid arthritis; berylliosis; drug induced (amiodarone, gold, BCNU [carmustine]); radiation
Increased lung volumes	Lymphangioleiomyomatosis; chronic sarcoidosis; chronic pulmonary Langerhans cell histiocytosis; tuberous sclerosis; neurofibromatosis
Radiographic honeycomb lung	Idiopathic pulmonary fibrosis; connective tissue disease; asbestosis; drug induced; lymphocytic interstitial pneumonia; chronic aspiration pneumonia; hemosiderosis; Hermansky-Pudlak syndrome; alveolar proteinosis
Pneumothorax	Pulmonary Langerhans cell histiocytosis; lymphangioleiomyomatosis; tuberous sclerosis; neurofibromatosis, IPF
Kerley B lines	Lymphangitic carcinomatosis; lymphangioleiomyomatosis; left atrial hypertension (mitral valve disease, venoocclusive disease); lymphoma; amyloidosis
Lymphadenopathy	Sarcoidosis; lymphoma; lymphangitic carcinomatosis; lymphoid interstitial pneumonia; berylliosis; amyloidosis; Gaucher disease
Pleural disease	Lymphangitic carcinomatosis; connective tissue disease; asbestosis (pleural calcification); lymphangioleiomyomatosis (chylous effusion); drug induced (nitrofurantoin, radiation); sarcoidosis
Eggshell calcification of lymph nodes	Silicosis; sarcoidosis; radiation

IPF, Idiopathic pulmonary fibrosis.
From Mason RJ: *Murray & Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, WB Saunders.

TABLE 4 Laboratory Findings in the Interstitial Lung Diseases

Finding	Diseases
Leukopenia	Sarcoidosis; connective tissue disease; lymphoma; drug induced
Leukocytosis	Systemic vasculitis; hypersensitivity pneumonitis; lymphoma
Eosinophilia	Eosinophilic pneumonia; sarcoidosis; systemic vasculitis; drug induced (sulfa, methotrexate)
Thrombocytopenia	Sarcoidosis; connective tissue disease; drug induced; Gaucher disease; idiopathic pulmonary fibrosis
Hemolytic anemia	Connective tissue disease; sarcoidosis; lymphoma; drug induced; idiopathic pulmonary fibrosis
Normocytic anemia	Diffuse alveolar hemorrhage syndromes; connective tissue disease; lymphangitic carcinomatosis
Urinary sediment abnormalities	Connective tissue disease; systemic vasculitis; drug induced
Hypogammaglobulinemia	Lymphocytic interstitial pneumonia
Hypergammaglobulinemia	Connective tissue disease; sarcoidosis; systemic vasculitis; idiopathic pulmonary fibrosis; asbestosis; silicosis; lymphocytic interstitial pneumonia; lymphoma
Serum autoantibodies	Connective tissue disease; systemic vasculitis; sarcoidosis; idiopathic pulmonary fibrosis; silicosis; asbestosis; lymphocytic interstitial pneumonia
Serum immune complexes	Idiopathic pulmonary fibrosis; lymphocytic interstitial pneumonia; systemic vasculitis; connective tissue disease; pulmonary Langerhans cell histiocytosis
Serum angiotensin-converting enzyme	Sarcoidosis; hypersensitivity pneumonitis; silicosis; acute respiratory distress syndrome; Gaucher disease
Antibasement membrane antibody	Goodpasture syndrome
Antineutrophil cytoplasmic antibody	Systemic vasculitis

From Mason RJ: *Murray & Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, WB Saunders.

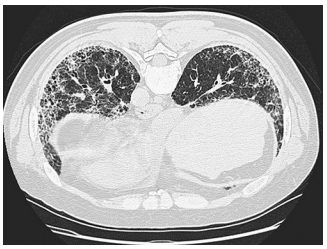

FIG. 2 High-resolution computed tomography scan of the chest shows fibrotic changes in a subpleural distribution with honeycombing consistent with usual interstitial pneumonia. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

sclerosis–related death. Nintedanib, a tyrosine kinase inhibitor, has been shown to have antifibrotic and antiinflammatory effects in early trials with resulting lower annual rate of decline in FVC in patients using nintedanib than placebo.

CHRONIC GENERAL Rx

- Outpatient pulmonary rehabilitation may be of value.
- Lung transplantation may be considered in appropriate patients in severe stages of the disease.

DISPOSITION

The prognosis is highly variable and depends on the cause, severity of illness, and initial response to treatment.

REFERRAL

- Pulmonary referral for workup and management
- Surgical referral for biopsy

PEARLS & CONSIDERATIONS

COMMENTS

It is very important when working up an ILD to take a thorough history of tobacco and drug use, prior medications, workplace and environmental exposures and pets, as well as a review of systems, including signs and symptoms that might suggest an underlying connective tissue disease.

PREVENTION

Proper industrial hygiene from a respiratory perspective is important as well as close surveillance when patients are given medications with known pulmonary toxicity. Symptoms of an ILD in the setting of an autoimmune condition need to be evaluated thoroughly.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Interstitial Pulmonary Disease (Patient Information)

AUTHOR: **Peter LaCamera, MD**

SUGGESTED READINGS

Diestler O et al: Nintedanib for systemic sclerosis –associated interstitial lung disease, *N Engl J Med* 380:2518-2528, 2019.

Raghu G et al: An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management, *Am J Respir Crit Care Med* 183:788-824, 2011.

Raghu G: Idiopathic pulmonary fibrosis: new evidence and an improved standard of care in 2012, *Lancet* 380(9842):699-701, 2012.

Travis WD et al: An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias, *Am J Respir Crit Care Med* 188(6):733-748, 2013.

Interstitial Nephritis PTG

BASIC INFORMATION

DEFINITION

Can be classified into two broad categories:

1. Acute interstitial nephritis (AIN):
   a. Decrease in kidney function resulting from delayed hypersensitivity immune-mediated injury, most often drug-induced
   b. Characterized on kidney biopsy by edema and leukocyte infiltration of the renal interstitium and tubules (referred to as *tubulitis*), which classically spares glomeruli and blood vessels
2. Chronic interstitial nephritis:
   a. Final common pathway of many chronic kidney diseases including diabetic kidney disease, hypertensive kidney disease, unresolved AIN, chronic obstruction, high-grade vesicoureteral reflux, and chronic bacterial infections
   b. Characterized on renal biopsy by interstitial fibrosis with mononuclear leukocyte infiltration and tubular atrophy

SYNONYMS

Acute tubulo-interstitial nephritis
Contracted kidney
Cirrhosis of the kidney
Granular kidney
Gouty kidney
Renal sclerosis
Chronic productive nephritis without exudation

ICD-10CM CODES

N05.8	Unspecified nephritic syndrome with other morphologic changes
N05.9	Unspecified nephritic syndrome with unspecified morphologic changes
N10	Acute tubulo-interstitial nephritis
N11	Chronic tubulo-interstitial nephritis
N11.8	Other chronic tubulo-interstitial nephritis
N11.9	Chronic tubulo-interstitial nephritis, unspecified
N12	Tubulo-interstitial nephritis, not specified as acute or chronic
N15	Other renal tubulo-interstitial diseases
N16	Renal tubulo-interstitial disorders in diseases classified elsewhere
N17.8	Other acute kidney failure

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- Prevalence is significantly underestimated.
- AIN is found in 0.5% to 2.6% of all kidney biopsies but may be as high as 5% to 18% in patients biopsied with acute kidney injury (AKI).

DEMOGRAPHICS:

- Increasing incidence in the elderly, attributed to reduced glomerular filtration rate (GFR), immune-mediated dysfunction, increasing medication use, and comorbidities.
- Median age at presentation is 65 yr.

RISK FACTORS:

- Advanced age (>65 yr)
- Volume depletion
- Underlying kidney disease
- Congestive heart failure
- Diabetes
- HIV infection

PHYSICAL FINDINGS & CLINICAL PRESENTATION

SIGNS AND SYMPTOMS:

- For AIN, the most common presentation is a rise in serum creatinine and blood urea nitrogen (BUN) levels that is asymptomatic. When AIN is advanced, it is associated with nonspecific symptoms of AKI from any cause, including the following:
  1. Malaise
  2. Anorexia
  3. Nausea and vomiting
  4. Oliguria or polyuria
  5. Hematuria
  6. Flank pain
- Classic triad (fever, maculopapular rash, and eosinophilia) is present in only 5% of cases:
  1. When present, the rash is usually a truncal maculopapular morbilliform eruption.
  2. Triad was characteristic of methicillin-related AIN, which has not been used in the U.S. for decades.
- A small minority present with tubulo-interstitial nephritis and uveitis (TINU) syndrome. The uveitis may be symptomatic or subclinical and may develop before, during, or after the renal injury. Adolescent females are most often affected by TINU.
- For chronic interstitial nephritis, there may be a subacute to protracted subtle rise in creatinine without any obvious symptoms as seen with AIN.

ETIOLOGY

ACUTE INTERSTITIAL NEPHRITIS:

- **Drug-induced** (70%). More than 150 agents have been implicated. AKI usually develops 10 to 14 days after exposure to the drug, but may develop sooner if there was a previous exposure.
  1. Antibiotics (beta-lactams, sulfonamides, rifampin, fluoroquinolones)
  2. NSAIDs (including selective COX-2 inhibitors)
  3. Proton pump inhibitors and H2 blockers (primarily cimetidine)
  4. Loop diuretics (furosemide, bumetanide)
  5. Antineoplastic agents
  6. Anticonvulsants
  7. Allopurinol (particularly common cause of drug rash or reaction with eosinophilia and systemic symptoms [DRESS] with AIN)
  8. Immunotherapy: Checkpoint pathway inhibitors
- **Infection** (10% to 15%). May be systemic or localized to genitourinary system.
  1. Bacteria: *Streptococci, Corynebacterium diphtheria, Legionellae, Yersinia, Mycobacteria, Mycoplasmas, Rickettsiae*
  2. Viruses: Cytomegalovirus, Epstein-Barr virus, hantaviruses, hepatitis C virus, herpes simplex virus, HIV, mumps, polyomavirus, influenza A virus
  3. Other: *Treponema pallidum, Toxoplasma gondii, Babesia* species
- **Other Causes** (15% to 20%)
  1. Idiopathic (10%)
  2. Immune disorders: Systemic lupus erythematosus, Sjögren syndrome, small-vessel vasculitides, autoimmune pancreatitis
  3. Neoplastic disorders (multiple myeloma)
  4. DRESS syndrome
  5. IgG4-related disease
  6. Hypocomplementemic tubulointerstitial nephritis (likely related to IgG4 disease)

CHRONIC INTERSTITIAL NEPHRITIS:

- Metabolic diseases (urate nephropathy, hypercalcemic nephropathy, hypokalemic nephropathy, oxalate nephropathy)
- Sarcoidosis
- Heavy metals
- Chronic urinary tract obstruction
- Aristolochic acid
- Diabetic kidney disease
- Hypertensive kidney disease

OVERLAP OF ACUTE AND CHRONIC INTERSTITIAL NEPHRITIS: Some metabolic processes and autoimmune disorders can present either as acute or chronic interstitial nephritis. For example, oxalate nephropathy can present with acute interstitial nephropathy in the setting of ethylene glycol ingestion, or with chronic interstitial nephritis in patients with prior bariatric surgery and a high oxalate-containing diet.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other causes of AKI or chronic kidney disease (CKD), including acute tubular necrosis (ATN), atheroembolic disease, glomerulonephritis, hypertensive nephrosclerosis, prerenal azotemia, obstructive nephropathy, and renal vascular disease

WORKUP

- Diagnosis is most often made by defining the temporal relationship between onset and resolution of an AKI episode with use and discontinuation of a known culprit drug.
- Gold standard for diagnosis is kidney biopsy. This is reserved for clinical situations with an unclear diagnosis, when removal of the offending agent does not result in improvement or may impact medical care, or when steroid initiation is being considered.

LABORATORY TESTS

- No single laboratory test has sufficient positive or negative predictive value to be useful in diagnosing interstitial nephritis.
- Diagnosis may be made based on clinical history, constellation of urine and serum abnormalities, and clinical course.

URINE TESTS:

- Urine eosinophilia historically was considered a marker of AIN, but this urinary finding is neither sensitive nor specific for AIN and has a low positive and negative predictive value, i.e., urine eosinophils do not establish or rule out AIN. Eosinophiluria may be found in a variety of kidney diseases.
- Urinalysis findings may include sterile pyuria, microhematuria, glucosuria, and proteinuria. Nephrotic syndrome is present in less than 1% of patients.
- Urine sediment analysis may include leukocytes, leukocyte casts, red cells, and tubular epithelial cells (Fig. E1). However, a bland urine sediment can also be seen in interstitial nephritis, especially if chronic. A lack of pyuria does not exclude AIN. Additionally, granular casts may be noted when tubulitis is present.

BLOOD TESTS:

- Serum chemistry profile: Elevated BUN, elevated creatinine, low serum phosphorus, low serum urate may be seen.
- Complete blood count with differential may reveal the following:
  1. Eosinophilia (not sensitive; if present, this finding greatly increases clinical suspicion for a systemic drug reaction. Eosinophilia may also occur in other causes of AKI including cholesterol emboli, vasculitis, and hematologic or solid organ malignancy).
  2. A hemoglobin level that is disproportionately low compared with the degree of AKI. This is attributed to loss of interstitial erythropoietin-producing cells, which may be impacted by the inflammatory cellular congestion).
- If drug-related AIN is not suspected, laboratory workup for infection, vasculitis, and autoimmune disorders may be warranted depending on the clinical context.

IMAGING STUDIES

Gallium scintigraphy, positron emission tomography, and computed tomography have been used to evaluate AIN in patients. These tests may distinguish between AIN and other forms of AKI in patients too unstable for a renal biopsy.

KIDNEY BIOPSY

Critical in diagnosis of interstitial nephritis in patients in whom the differential of AKI is broad. Biopsy findings include (Fig. E2):

- Predominant lymphocytic and monocytic infiltrate (Fig. E2, B).
- Presence of eosinophils is suggestive of drug-induced AIN (Fig. E2, C).
- Tubulitis (renal tubular invasion by inflammatory cells) is suggestive of AIN.
- Early on, inflammation is associated with edema, but may transition to fibrosis with underlying tubular atrophy as the process becomes more chronic (Fig. E2, D).
- Granuloma formation may be more suggestive of infectious AIN, especially in regions where the infectious etiologies described earlier are endemic.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Largely supportive; removal of offending agent, if known, will resolve 60% of cases.

ACUTE GENERAL Rx

- Maintain adequate hydration and urine output and avoid volume overloading.
- Identify and treat infection if present.
- Avoid nephrotoxins and medications that impair renal blood flow.
- Uveitis in TINU syndrome may be asymptomatic. Ophthalmologic exam is recommended in idiopathic AIN.
- Retrospective studies and anecdotal literature have shown that steroid treatment, initiated within 7 days of diagnosis, may reduce the requirement for chronic dialysis in patients with drug-induced AIN who have not responded to drug withdrawal alone. Steroids are the basis of treatment in idiopathic AIN, AIN associated with systemic disease, and TINU. Regimens vary. Some include an initial steroid pulse of methylprednisolone, 250 to 500 mg for 3 consecutive days, followed by 1 mg/kg prednisone. Others start with 1 mg/kg of prednisone with no intravenous, with tapering over 4 to 6 wk. Steroids are not administered to patients with significant kidney fibrosis on histologic examination.
- Cyclophosphamide, cyclosporine, and mycophenolate mofetil have all been used anecdotally as therapy in steroid-resistant disease. Among these, mycophenolate mofetil has the largest body of evidence for use as a steroid-sparing agent, if AKI recurs when steroids are tapered or discontinued, or when patients develop adverse effects from steroid therapy.

CHRONIC Rx

- Limit exposure to known nephrotoxic agents.
- Adjust dosages of all medications as indicated by glomerular filtration rate.
- Rigorous control of blood pressure, diabetes, and cholesterol.
- Relieve any sources of chronic obstruction.

DISPOSITION

With AIN:

- Complete recovery with return to baseline creatinine occurs in 60% to 65% of cases.
- Partial recovery is seen in 10% to 20%.
- Irreversible damage in 5% to 10%.
- Relapse is common with repeated exposure to offending agents.

REFERRAL

Renal consultation is often necessary, especially if the diagnosis is unclear, biopsy is required, or there is treatment-resistant disease.

PEARLS & CONSIDERATIONS

COMMENTS

Acute interstitial nephritis is most often due to drugs started in the preceding 30 days. The most common drug classes are beta-lactam antibiotics, NSAIDs, and proton pump inhibitors (PPIs). In contrast to ATN, which is often associated with oliguria, early AIN may be associated with polyuria; therefore, a high index of suspicion in this clinical setting is essential for early diagnosis.

PREVENTION

Use known offending agents with care, especially in the elderly and those with known underlying kidney disease.

PATIENT & FAMILY EDUCATION

www.nlm.nih.gov/medlineplus/ency/article/000464.htm

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Interstitial Nephritis (Patient Information)

AUTHORS: **Evan Zeitler, MD,** and **Koyal Jain, MD**

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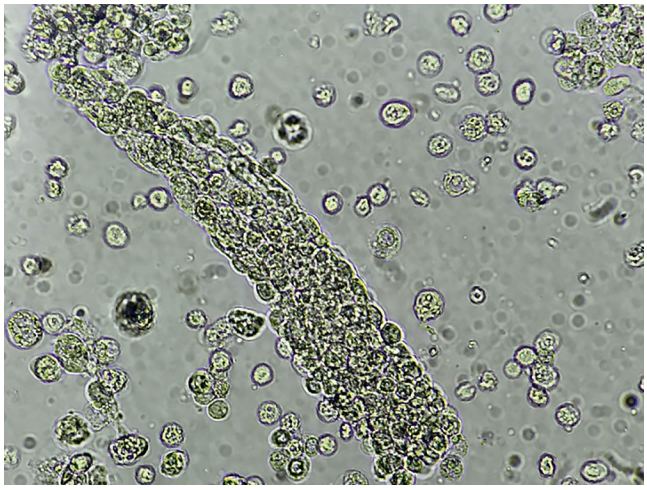

FIG. E1 Urinary sediment showing white blood cells and white blood cell cast. (Courtesy Randy L. Luciano, MD.)

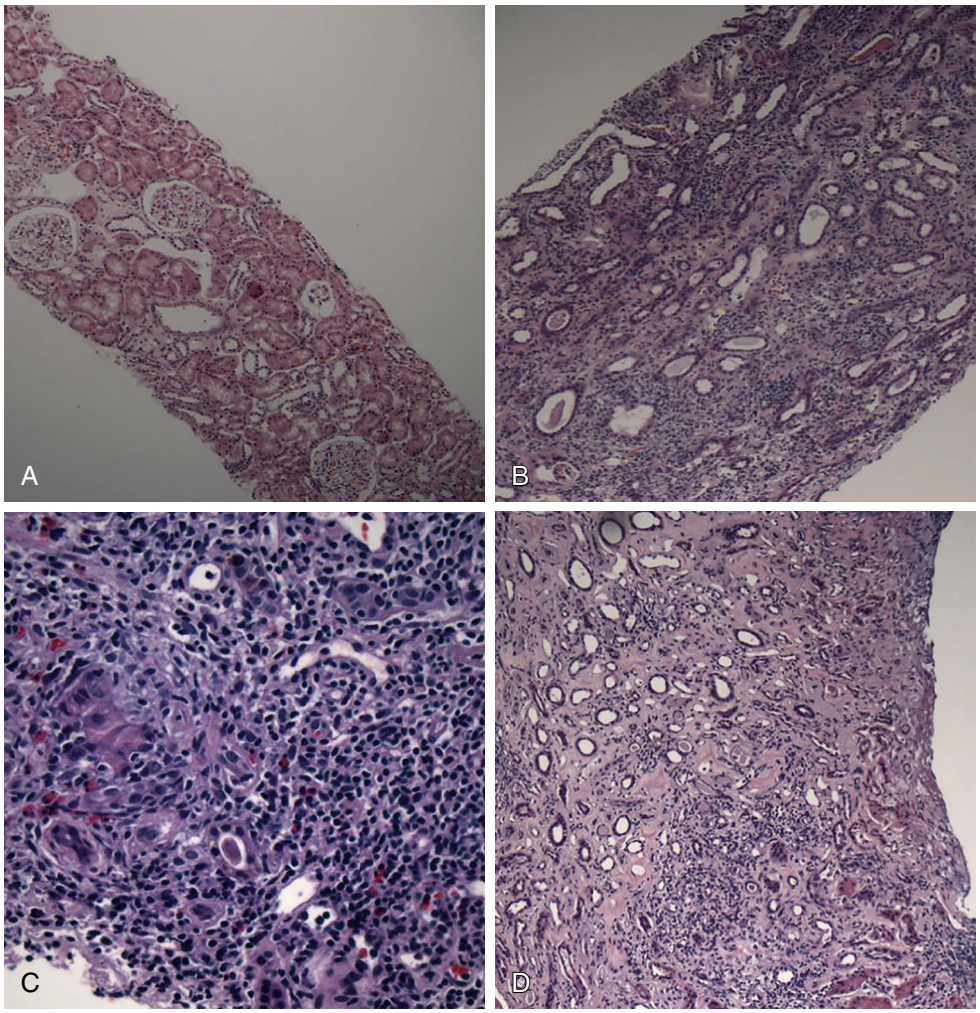

FIG. E2 **A,** Normal biopsy showing tubular lumen with no cells in interstitium. **B,** Acute interstitial nephritis with significant interstitial infiltrate and compressed tubules. **C,** High-power view of cellular infiltrate showing lymphocytes, monocytes, and eosinophils (cells with red cytoplasm). **D,** Chronic interstitial nephritis with areas of fibrosis (pink, cell-sparse areas). (Courtesy Randy L. Luciano, MD.)

BASIC INFORMATION

DEFINITION

Provided that criteria for right bundle branch block (RBBB), left bundle branch block (LBBB), or hemifascicular block (Fig. E1) are not met, intraventricular conduction delay (IVCD) is defined by a QRS >110 ms in adults, >90 ms in children 8 to 16 yr, and >80 ms in children younger than 8 yr. It is a common clinical abnormality related to a conduction disturbance that occurs at various levels in the His-Purkinje system. Abnormal activation of the local myocardium can coexist. It can be caused by anatomic abnormalities and the physiologic properties of cardiac tissue. It may occur between ventricles (interventricular), within Purkinje fibers or ventricular myocardium (intraventricular), or between layers of the myocardium (intramural). Parietal block occurs in the terminal Purkinje system and presents with prolonged QRS in leads V1 to V3 compared with V4 to V6. This particular type of IVCD is associated with right ventricular arrhythmogenic dysplasia. It is considered to take place beyond the Purkinje myocardial gates and is due to an abated cell-to-cell conduction.

SYNONYMS

IVCD
Nonspecific/unspecified intraventricular conduction disturbance
Intraventricular conduction delay/defect/block
Fragmented QRS complex
Prolonged/wide QRS

ICD-10CM CODES

I45.4 Non-specific intraventricular block
I45.8 Other specified conduction disorders
I45.9 Conduction disorder, unspecified

EPIDEMIOLOGY

- The prevalence of IVCD in the general population increases with age.
- A Finnish Social Security study, on 10,899 subjects with baseline ECGs, showed a prevalence of IVCD in 0.6% of the total population. 45.6% of subjects with QRS ≥110 ms without evidence of cardiac disease or bundle branch block, had an increased risk of all-cause mortality with relative risk 1.75.
- IVCD has a consensus prevalence of 30% in patients with heart failure (HF) ranging between 14% and 47% in various studies.
- The reported prevalence in military aviators was similar to RBBB at 0.2%.

ETIOLOGY

IVCD is usually the result of abnormal ventricular activation caused by delay in one or more levels of the conduction system. Activation abnormalities of the local myocardium can coexist and further alter the pattern of ventricular excitation.

Patients with IVCD are not a homogeneous group but rather reflect the underlying causative conditions such as dilated cardiomyopathy, hypertensive cardiomyopathy, ischemic cardiomyopathy, or other conditions. Therefore grouping patients on the basis of IVCD is not clinically meaningful.

The most common clinical conditions associated with IVCD are the following:

- Coronary artery disease
- Infiltrative cardiomyopathy: Amyloidosis, sarcoidosis, hemosiderosis, etc.
- Cardiomyopathies of other etiologies
- Left ventricular hypertrophy
- Endocarditis of the aortic valve
- Myocarditis
- Chagas disease (parasitic)
- Primary conduction diseases: Lenegre disease, Lev disease
- Congenital anomalies
- Progressive systemic scleroderma
- Pulmonary embolism
- Cyclic antidepressants
- Hyperkalemia
- Hypothermia
- Intracardiac catheter manipulation

Antiarrhythmic drugs, class IA (e.g., procainamide, disopyramide, quinidine), and class IC (e.g., flecainide, encainide, and propafenone), amantadine, carbamazepine, cocaine, diphenhydramine, mesoridazine, and thioridazine may cause IVCD. In addition, propoxyphene and propranolol can also cause IVCD by sodium channel blockade in older adults due to myocardial fibrosis caused by apoptosis.

Etiology can be unknown in many cases.

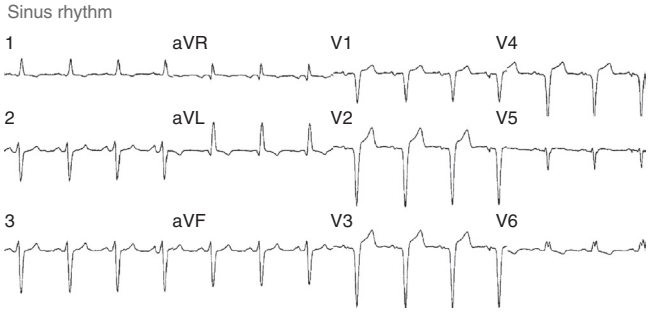

FIG. E1 Normal sinus rhythm baseline with intraventricular conduction delay resembling left bundle branch block (LBBB). *aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right. (From Issa ZF: *Clinical arrhythmology and electrophysiology: a companion to Braunwald's heart disease,* ed 2, Philadelphia, 2012, Saunders.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

IVCD per se is asymptomatic and is recognizable only with a 12-lead ECG.

DIAGNOSIS

Intraventricular conduction delay is usually an incidental ECG finding. By definition, this defect does not meet criteria for RBBB, LBBB, or hemifascicular block.

DIFFERENTIAL DIAGNOSIS

- Unifascicular block
- Bifascicular block
- Wolff-Parkinson-White (WPW) pattern and variants
- LBBB
- RBBB

EVALUATION

The evaluation of the patient with IVCD should be oriented toward the cause of the ECG abnormality to implement appropriate therapy and counseling. Thorough history and physical exam must be performed to implement adequate laboratory and imaging testing based on the level of suspicion for the causes of IVCD listed earlier. Such tests could include but are not limited to:

- Standard laboratory testing appropriate for age, gender, and metabolic abnormalities
- Resting ECG
- Exercise ECG, with or without imaging
- Ambulatory ECG
- Echocardiogram
- Specialized studies based on known comorbidities and risk assessment or suspicion of them such as heart failure, myocardial infarction, or cardiomyopathies

TREATMENT

Optimize the treatment of the underlying contributing conditions. In selected patients at risk for sudden cardiac death due to significant coronary artery disease or arrhythmogenic right ventricular dysplasia, appropriate referral should be made.

Although cardiac resynchronization therapy has been effective in reducing clinical events in patients with LBBB, patients with IVCD have not demonstrated similar benefit. In the absence of LBBB, cardiac resynchronization therapy offers no benefit for the management of patients with IVCD. In fact there may be an increased risk of ventricular tachycardia for this group when receiving defibrillator devices with or without cardiac resynchronization.

However, intraventricular dyssynchrony has been found to be directly related to IVCD and to have major implications in the identification of adequate electronic pacing sites in patients who require device implantation therapy.

PROGNOSIS

Different studies have shown that IVCD is associated with increased all-cause mortality

with relative risk (RR) 1.75 to 2.01, increased cardiac mortality with RR 1.87 to 4.25, and a markedly elevated risk of sudden arrhythmic death with RR 2.9 to 3.11. A Finnish study in a community cohort, published in 2015, showed that IVCD had a notably high hazard ratio for cardiovascular mortality at 4.25 (95% CI 1.95 to 9.26).

Prognosis depends on the underlying associated clinical conditions. The presence of IVCD constitutes a prognostic marker for cardiac events in CAD, hypertrophic cardiomyopathy, structural heart disease with implanted cardiac defibrillators, Chagas disease, arrhythmogenic right ventricular dysplasia, Brugada syndrome, and acquired long QT syndrome. It is associated with heart failure hospitalization in patients with hypertrophic cardiomyopathy.

An area of increasing interest is the presence of intra- and interatrial conduction delay as it relates to the generation of atrial fibrillation. It is more reliable than left atrial volume and dimension in the prediction of atrial fibrillation and ischemic stroke. It has a direct correlation with aortic strain in patients with hypertension, and it correlates with increased symptoms and mortality in patients with systolic heart failure.

REFERRAL

Refer to a cardiologist if there is history of palpitations, dizziness, heart failure, myocardial infarction, or an abnormal cardiac exam.

PEARLS & CONSIDERATIONS

- IVCD can be due to drugs such as Class I antiarrhythmic drugs.
- IVCD can be a normal variant and is not always associated with cardiac pathology.
- Clinical correlation is needed to identify associated cardiac abnormalities.
- In patients with heart failure, cardiac resynchronization for IVCD in the absence of LBBB is not associated with clinical benefit.

AUTHORS: **John Wylie, MD, FACC,** and **Ioannis Koulouridis, MD, MS**

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Irritable Bowel Syndrome PTG ALG

BASIC INFORMATION

DEFINITION

Irritable bowel syndrome (IBS) is a chronic functional disorder manifested by alteration in bowel habits and recurrent abdominal pain and bloating. IBS is a symptom complex influenced by a variety of physiologic determinants from gut to brain and back. The ROME IV criteria for diagnosis of IBS are:

- Patient has recurrent abdominal pain ≥1 day per wk, on average, in the previous 3 mo, with an onset ≥6 mo before diagnosis
- Abdominal pain is associated with at least two of the following three symptoms:
  1. Pain related to defecation
  2. Change in frequency of stool
  3. Change in form (appearance) of stool
- Patient has none of the following warning signs:
  1. Age ≥50 yr, no previous colon cancer screening, and presence of symptoms
  2. Recent change in bowel habit
  3. Evidence of overt GI bleeding (e.g., melena or hematochezia)
  4. Nocturnal pain or passage of stool
  5. Unintentional weight loss
  6. Family history of colorectal cancer or inflammatory bowel disease
  7. Palpable abdominal mass or lymphadenopathy
  8. Evidence of iron-deficiency anemia on blood testing
  9. Positive test for fecal occult blood
- The criteria must be fulfilled for at least the past 3 mo with symptom onset at least 6 mo before the diagnosis.
- Table 1 subtypes IBS by predominant stool pattern.

SYNONYMS

Irritable colon
Spastic colon
IBS

ICD-10CM CODES

K58	Irritable bowel syndrome
K58.9	Irritable bowel syndrome without diarrhea
K58.0	Irritable bowel syndrome with diarrhea

EPIDEMIOLOGY & DEMOGRAPHICS

- IBS is the most common functional bowel disorder. An estimated 15 million people in the U.S. have IBS.
- IBS occurs in 7% to 21% of the general population of industrialized countries and is responsible for >50% of gastrointestinal (GI) referrals. Worldwide adult prevalence is 12%. Incidence increases during adolescence and peaks in third and fourth decades of life.
- Female:male ratio is 2:1. Peak prevalence is from 20 to 39 yr of age.
- Nearly 50% of patients have psychiatric abnormalities, with anxiety disorders being most common.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The clinical presentation of IBS consists of abdominal pain and abnormalities of defecation, which may include loose stools, usually after meals and in the morning, alternating with episodes of constipation.
- Physical examination is generally normal.
- Nonspecific abdominal tenderness and distention may be present.

ETIOLOGY

- Unknown, believed to be multifactorial. Fig. 1 illustrates a biopsychological model of IBS pathophysiology
- Associated pathophysiology includes altered GI motility, alteration in gut flora, and increased gut sensitivity
- Risk factors: Anxiety, depression, personality disorders, history of childhood sexual abuse, and domestic abuse in women

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Inflammatory bowel disease (IBD)
- Diverticulitis
- Colon malignancy
- Endometriosis
- Peptic ulcer disease
- Biliary liver disease
- Chronic pancreatitis
- Constipation caused by medications (opiates, calcium channel blockers, anticholinergics)
- Diarrhea caused by medications (metformin, colchicine, proton pump inhibitors, antacids, antibiotics)
- Small-bowel overgrowth
- Celiac disease
- Parasites
- Lymphoma of GI tract
- Pelvic floor dyssynergia

TABLE 1 Subtyping Irritable Bowel Syndrome by Predominant Stool Pattern

- IBS with constipation (IBS-C)—hard or lumpy stools* ≥25% and loose (mushy) or watery stools† ≥25% of bowel movements‡
- IBS with diarrhea (IBS-D)—loose (mushy) or watery stools† ≥25% and hard or lumpy stool* ≥25% of bowel movements‡
- Mixed IBS—hard or lumpy stools* ≥25% and loose (mushy) or watery stools† ≥25% of bowel movements‡
- Unsubtyped IBS (IBS unclassified)—insufficient abnormality of stool consistency to meet criteria for IBS with constipation, diarrhea, or mixed‡

IBS, Irritable bowel syndrome.
*Bristol Stool Form Scale 1-2 (separate hard lumps like nuts [difficult to pass] or sausage-shaped but lumpy).
†Bristol Stool Form Scale 6-7 (fluffy pieces with ragged edges, a mushy stool or watery, no solid pieces, entirely liquid).
‡In the absence of use of antidiarrheals or laxatives.
Adapted from Sayuk GS, Gyawali CP: Irritable bowel syndrome: modern concepts and management options, *Am J Med* 128(8):817-827, 2015.

WORKUP

Diagnostic workup (Table 2) is aimed primarily at excluding the conditions listed in the differential diagnoses. A step-wise approach is critical. It is important to identify red flags of other diseases, such as weight loss, rectal bleeding, onset in patients >50 yr, fever, nocturnal pain, and family history of malignancy or IBD. Additional red flags include abnormal examination (e.g., mass, enlarged lymph nodes, stool positive for occult blood, muscle wasting) and abnormal laboratory values (anemia, leukocytosis, abnormal chemistry).

LABORATORY TESTS

- Blood work is generally normal. CBC is reasonable to evaluate for anemia. The presence of anemia should alert to the possibility of a colonic malignancy or IBD.
- Other reasonable tests include C-reactive protein, tissue transglutaminase antibody (rule out celiac disease) and TSH (rule out thyroid abnormalities).
- Fecal calprotectin level is useful to differentiate IBS from inflammatory bowel disease in patients who have IBS with diarrhea or with both diarrhea and constipation. Fecal calprotectin levels less than 40 mcg/g exclude IBD in patients with IBS.
- Testing of stool for ova and parasites should be considered only in patients with chronic diarrhea. Evaluation of stool for *Clostridium difficile* may be helpful in patients with predominant diarrhea symptoms who have recently taken antibiotics.

IMAGING STUDIES

- Imaging studies (e.g., flat and upright abdominal radiograph, small-bowel series, sonogram or CT of abdomen and pelvis) are normal and not necessary for diagnosis.
- Lower endoscopy is generally normal except for the presence of some spasms. Colonoscopic imaging should be performed only in persons who have alarm features to rule out organic disease and in persons older than 50 yr to screen for colorectal cancer.

TREATMENT

NONPHARMACOLOGIC THERAPY

- The patient should be encouraged to maintain an adequate fiber intake and to eliminate foods that aggravate symptoms. Avoidance of caffeine, dairy products, fatty foods, and dietary excesses is also helpful. Several clinical trials have shown that a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) improves symptoms in nearly 70% of patients with IBS.
- Cognitive-behavioral therapy is also recommended, particularly in younger patients because psychosocial stressors are important triggers of IBS. Reassurance that the disorder is benign and education about trigger avoidance and stress management are important.
- Importance of regular exercise and adequate fluid intake should be stressed.

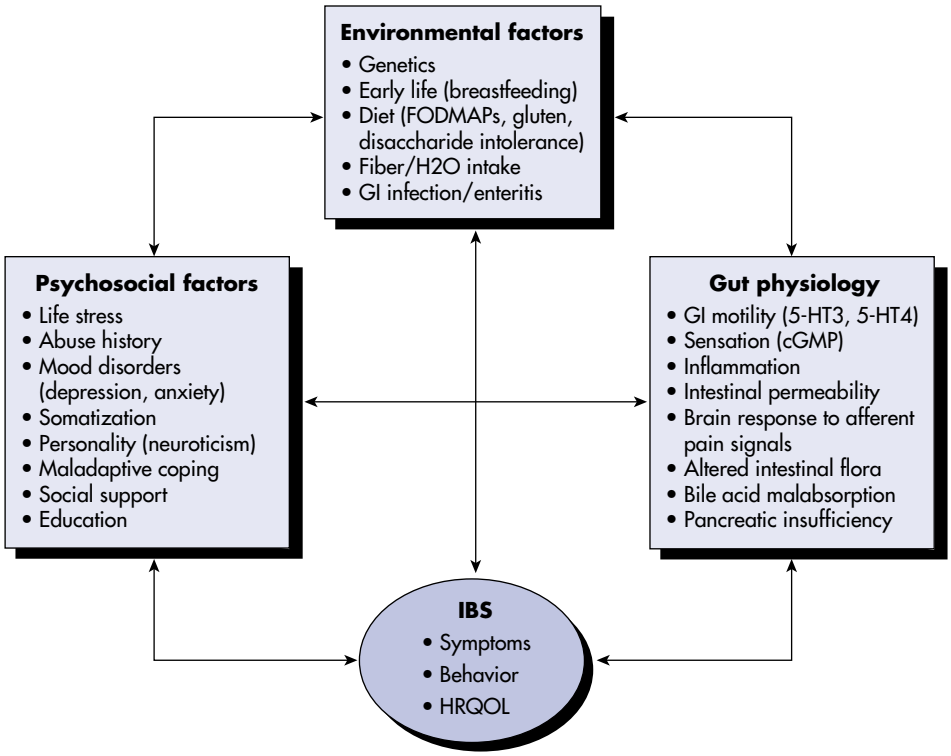

FIG. 1 A biopsychosocial model of irritable bowel syndrome pathophysiology. Irritable bowel syndrome is thought to be a multifactorial disorder, deriving from a potential multitude of etiopathogenic factors, including environmental, psychological, and physiologic factors. This model highlights the complex, often bidirectional interplay of these factors in the experience of irritable bowel syndrome symptoms. *cGMP,* Cyclic guanosine monophosphate; *5-HT3,* serotonin type 3; *5-HT4,* serotonin type 4; *FODMAPS,* fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; *HRQOL,* health-related quality of life; *IBS,* irritable bowel syndrome. (Modified from Sayuk GS, Gyawali CP: Irritable bowel syndrome: modern concepts and management options, *Am J Med* 128(8):817-827, 2015.)

- Fig. E2 illustrates the management of irritable bowel syndrome.

GENERAL Rx

- The mainstay of treatment of IBS is a high-fiber diet. Fiber is helpful for relief of constipation but not for relief of pain. Because symptoms are chronic, the use of laxatives should generally be avoided.
- Soluble fiber (psyllium) is more effective in symptom relief than insoluble fiber (bran). Fiber supplementation with psyllium 1 tbsp bid or calcium polycarbophil (FiberCon) 2 tablets one to four times daily followed by 8 oz of water may be necessary in some patients.
- Patients should be instructed that there might be some increased bloating on initiation of fiber supplementation, which should resolve within 2 to 3 wk. It is important that patients take these fiber products on a regular basis and not only as needed. Fiber is not effective in patients with diarrhea-predominant IBS and may worsen symptoms in these patients.
- Patients who appear anxious can benefit from use of sedatives or selective serotonin reuptake inhibitors (SSRIs). Tricyclic antidepressants in low doses are also effective in some patients with diarrhea-predominant IBS.
- C-2 chloride channel activators: Lubiprostone (Amitiza) is a chloride channel activator that stimulates chloride-rich intestinal fluid secretion and accelerates small intestine and colonic transmit time. It may be effective in chronic constipation-predominant IBS unresponsive to conventional treatment. Usual dose is 8 to 24 mcg bid with food. Side effects include headache and nausea.
- Linaclotide (Linzess) is a guanylate cyclase-C (GC-C) agonist FDA approved for IBS with constipation. It stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the CFTR ion channel, resulting in increased intestinal fluid and accelerated transit. Usual dose for IBS is 290 mcg 30 min before eating. The most common adverse effects are diarrhea, abdominal pain, flatulence, and abdominal distension.
- Eluxadoline (Viberzi) is a μ-opioid receptor agonist and Δ-opioid receptor antagonist FDA approved for IBS with diarrhea. It decreases muscle contractility, inhibits water and electrolyte secretion, and increases rectal sphincter tone. Usual dose is 100 mg PO bid taken with food.
- Loperamide is effective for diarrhea. Alosetron, a serotonin type-3 receptor antagonist previously withdrawn because of severe constipation and ischemic colitis, has been reintroduced with limited availability. It is indicated only for women with severe chronic diarrhea-predominant IBS unresponsive to conventional therapy and not caused by anatomic or metabolic abnormality. Starting dose is 1 mg qd.
- Alterations in gut flora have been identified as potentially contributing to IBS (84% of IBS patients have an abnormal lactulose breath test, suggesting small-intestinal bacterial overgrowth). Rifaximin, a gut-selective antibiotic, has been used in recent trials to eradicate bacterial overgrowth (70% eradication rate). A dose of 400 mg tid for 10 days was reported effective in improving IBS symptoms up to 10 wk after discontinuation of therapy. Until additional evidence is available, use of rifaximin or other antibiotics in IBS should be reserved for patients with proven bacterial overgrowth.
- Antispasmodics-anticholinergics (e.g., dicyclomine, hyoscyamine) are often used, but efficacy data from clinical trials are inconclusive.
- Probiotics: Bifidobacteria and some combinations of probiotics have shown some limited efficacy. Lactobacilli do not appear to be

TABLE 2 Irritable Bowel Syndrome Treatment Strategy: A Way Forward

1. Evaluation
   a. Consider conditions that mimic IBS (e.g., celiac disease, microscopic colitis, bile acid diarrhea, pancreatic insufficiency, carbohydrate intolerances, medication side effects, postsurgical neoanatomy)
   b. Assess for the presence of alarm symptoms
   c. Evaluate for symptom triggers (e.g., stressors, diet)
   d. Explore presence of other functional GI (e.g., functional dyspepsia) and non-GI disorders (e.g., fibromyalgia), psychiatric comorbidity, and drug intolerances
   e. Understand previous IBS treatment experiences
2. Selection of treatment approach
   a. Predicated on symptom severity and dominant symptoms
   b. Symptom severity (intensity, bother, effects on quality of life)
      i. Mild symptoms, intermittent symptoms, low symptom burden: Symptomatic or peripheral therapy
      ii. Moderate symptoms: Centrally acting neuromodulators, especially if symptomatic therapy does not provide adequate benefit
      iii. Severe symptoms and those with comorbidities (non-GI functional disorders, psychiatric): Both centrally acting neuromodulators and peripheral therapy
         a. Concurrent affective disorders need to be managed.
         b. Other central therapies (cognitive and behavioral therapy, hypnosis, stress reduction) may need to be considered.
   c. Dominant symptoms (diarrhea, constipation, pain, other GI symptoms)
      i. Constipation predominant
         a. Laxatives, fiber
         b. Novel agents (linaclotide, lubiprostone)
      ii. Diarrhea predominant
         a. Antidiarrheals
         b. Alosetron
         c. Address dysbiosis (rifaximin, probiotics)
         d. Diet (low FODMAP)
         e. Bile binders (cholestyramine, colesevelam)
         f. Disaccharidases (lactase)
      iii. Pain predominant
         a. Antidepressants (TCAs and SNRIs preferred)
         b. Linaclotide when constipation present
         c. Avoid narcotics
3. Education and therapeutic alliance
   a. Inform patient about etiopathogenesis.
   b. Reaffirm legitimacy of diagnosis; allay concerns about organic disease.
   c. Provide information about support organizations (International Foundation for Functional Gastrointestinal Disorders).

FODMAP, Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; *GI,* gastrointestinal; *IBS,* irritable bowel syndrome; *SNRI,* serotonin-norepinephrine reuptake inhibitor; *TCA,* tricyclic antidepressant.

effective for the treatment of IBS. Additional data showing efficacy is needed before probiotics can be endorsed for treatment of IBS.

- Antidepressants: SSRIs are more effective than placebo for relief of global IBS symptoms.

DISPOSITION

More than 60% of patients respond successfully to treatment over the initial 12 mo; however, IBS is a chronic, relapsing condition and requires prolonged therapy.

REFERRAL

GI referral is recommended in patients with rectal bleeding, fever, nocturnal diarrhea, anemia, weight loss, or onset of symptoms >40 yr. Consultation is also necessary if specialized diagnostic procedures such as endoscopy are necessary.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients should be educated regarding maintenance of a high-fiber diet and elimination of stressors, which can precipitate attacks of IBS. They should be reassured that their condition does not lead to cancer.
- Recent drug efforts (alosetron, tegaserod) are aimed at serotonergic receptors in the gut because most of the serotonin in the body is found in the GI tract and is believed to be involved in the mediation of visceral sensation and motility.
- Cognitive-behavioral therapy is effective in the treatment of patients with IBS and should be considered as part of the armamentarium against this disorder.
- Some patients with IBS but without celiac disease show symptom improvement on a wheat-free diet. A 2- to 3-wk trial of wheat avoidance may be reasonable in patients with treatment-resistant IBS.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Irritable Bowel Syndrome (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

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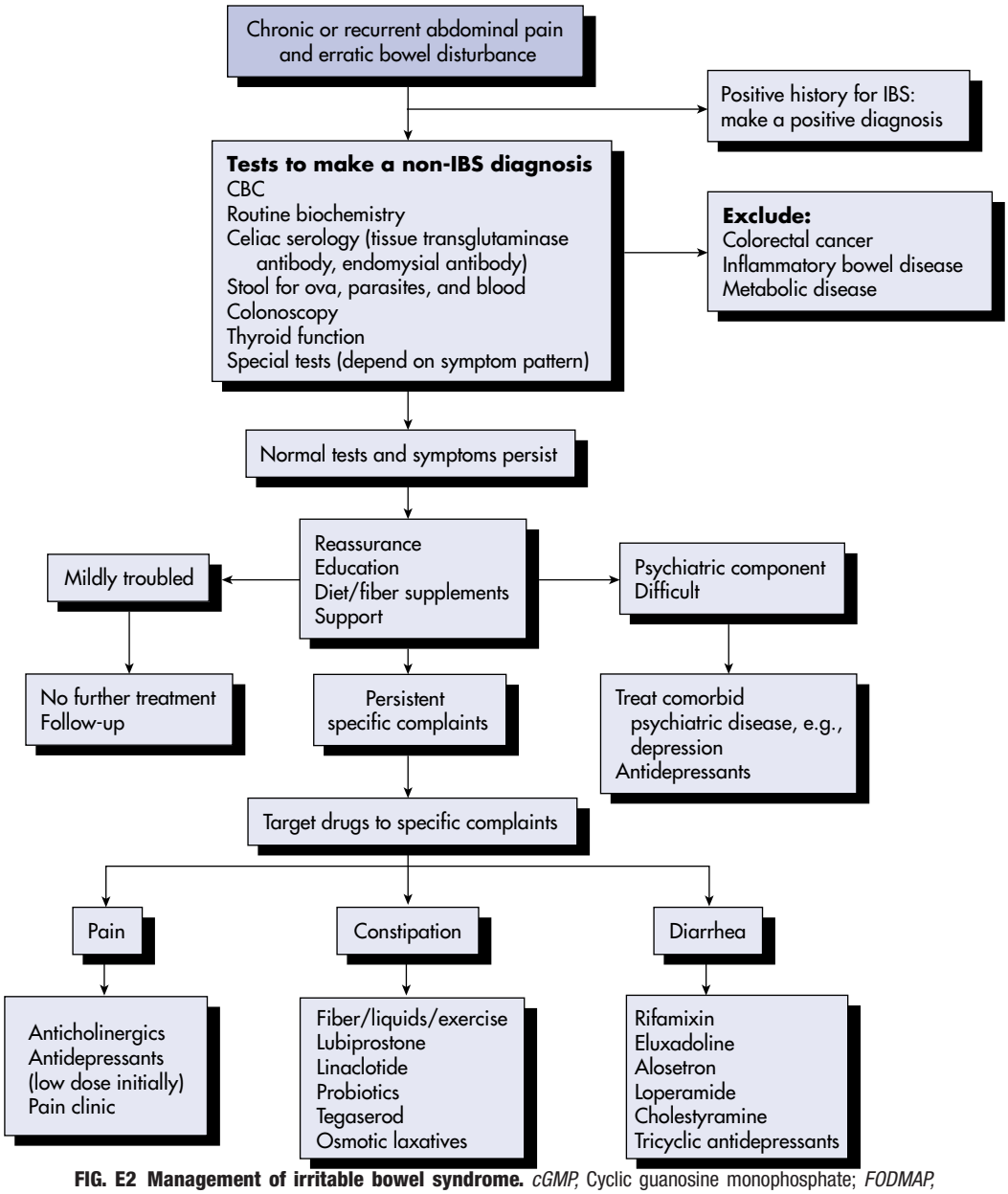

FIG. E2 Management of irritable bowel syndrome. *cGMP,* Cyclic guanosine monophosphate; *FODMAP,* fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; *GI,* gastrointestinal; *H_2O,* water; *HRQOL,* health-related quality of life. (Modified from Palmer KR, Penman ID: 22 Alimentary tract and pancreatic disease. In Colledge NR, Walker BR, Ralston SH: *Davidson's principles and practice of medicine,* Philadelphia, 2010, Elsevier.)

BASIC INFORMATION

DEFINITION

Ischemic colitis (IC) is tissue damage and inflammation of the large intestine due to a reduction in blood flow.

SYNONYMS

Intestinal ischemia
Colonic ischemia
IC

ICD-10CM CODES

K51.50	Left-sided colitis without complications
K51.51	Left-sided colitis with complications
K51.511	Left-sided colitis with rectal bleeding
K51.512	Left-sided colitis with intestinal obstruction
K51.513	Left-sided colitis with fistula
K51.514	Left-sided colitis with abscess
K51.518	Left-sided colitis with other complication
K51.519	Left-sided colitis with unspecified complications
K52.3	Indeterminate colitis
K55.0	Acute vascular disorders of intestine
K55.031	Focal (segmental) acute (reversible) ischemia of large intestine
K55.032	Diffuse acute (reversible) ischemia of large intestine
K55.039	Acute (reversible) ischemia of large intestine, extent unspecified
K55.9	Vascular disorder of intestine, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: It is the most common type of intestinal ischemia with an annual incidence of 15.6 to 17.7 per 100,000.
PEAK INCIDENCE: Unknown
PREVALENCE: Unknown
PREDOMINANT SEX AND AGE:
- More common among older patients (60s to 70s)
- Female predominance

RISK FACTORS:
- Older age (60s to 70s)
- Atherosclerotic disease
- Hemodialysis
- Hypertension
- Atrial fibrillation
- Diabetes
- Small vessel disease
- Sickle cell disease
- Infection (CMV, *E. coli*)
- Aortic surgery, endovascular intervention, cardiopulmonary bypass surgery
- Long-distance running, extreme exercise
- Hypercoagulable state
- Myocardial ischemia
- Mechanical obstruction
- Hypoalbuminemia
- Pharmacologic
- Shock

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Key historical points:
  1. Rapid-onset cramping and abdominal pain (classically thought to involve the left side more often, but newer literature suggests that no one region is affected predominantly). Pain secondary to large intestine ischemia is often not as severe as pain associated with small intestine ischemia
  2. Urge to defecate may accompany developing abdominal pain
  3. Hematochezia (usually within 24 hrs). More commonly associated with ischemic colitis of the large bowel compared with small bowel involvement
- Physical exam findings suggestive of ischemic colitis:
  1. Abdominal exam may be nonspecific early on
  2. May have peritoneal signs in severe illness or bowel perforation
  3. Hypotension and tachycardia in severe cases
  4. Guaiac positive stool

ETIOLOGY

GENERAL:
- Caused by a reduction in blood flow, usually sudden, to a segment of the large intestine. The resulting blood flow is not enough to provide the oxygen and nutrients necessary for normal cellular metabolism.
- Particularly affected are the watershed regions of the colon (Fig. E1), which have limited collateral circulation (splenic flexure and sigmoid colon).
- Medical and surgical conditions associated with ischemic colitis are summarized in Box 1.

SPECIFIC:
- Nonocclusive disease:
  1. Hypoperfusion: Cardiac failure, septic shock, hemorrhagic shock, hemodialysis
  2. Iatrogenic: Drugs (especially constipation-inducing). Medications associated with ischemic colitis are summarized in Box 2
  3. Colonic obstruction: Colon cancer, constipation, volvulus
  4. Long-distance running
- Occlusive disease:
  1. Arterial: Thrombus/emboli, cholesterol emboli, small vessel disease (atherosclerosis, diabetes, vasculitis, rheumatoid arthritis, radiation, amyloidosis), trauma
  2. Surgical: Aortic aneurysm repair, cardiac catheterization, cardiopulmonary bypass, colectomy, endoscopy, renal transplant
  3. Venous: Mesenteric venous thrombosis, hypercoagulable state, sickle cell disease, pancreatitis, portal hypertension, lymphocytic phlebitis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infectious colitis (e.g., *Clostridium difficile, Salmonella, Shigella*)

BOX 1 Medical and Surgical Conditions Associated with Ischemic Colitis

Cardiovascular/Pulmonary
Atherosclerosis*
Atrial fibrillation
Chronic obstructive pulmonary disease
Hypertension

Gastrointestinal
Constipation
Diarrhea
Irritable bowel syndrome

Low Flow State
Septic shock
Congestive heart failure
Hemorrhagic shock
Hypotension

Surgery
Abdominal surgery
Aortic surgery
Cardiovascular surgery

Invasive Interventions
Postendovascular abdominal manipulations (e.g., chemoembolization)
Postcolonoscopy

Metabolic/Rheumatoid
Diabetes mellitus
Dyslipidemia
Rheumatoid arthritis
Systemic lupus erythematosus

Miscellaneous
Hypercoagulable states†
Sickle cell disease
Long-distance running

*For example, ischemic heart disease, cerebrovascular disease, peripheral vascular disease.
†Antiphospholipid syndrome, factor V Leiden deficiency, protein C and S deficiency.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

BOX 2 Drugs Associated with Ischemic Colitis

Constipation-inducing drugs (opioids and nonopioids)
Immunomodulator drugs (anti-TNFα, type 1 interferon-α, type 1 interferon-β)
Chemotherapeutic drugs (e.g., Taxanes)
Cocaine and methamphetamines
Female hormones
Oral contraceptive medications
Antibiotics
Pseudoephedrine
Serotoninergic (e.g., Alosetron, Sumatriptan)
Diuretics

TNF, Tumor necrosis factor.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

- Inflammatory bowel disease, inflammatory bowel syndrome, celiac disease
- Small bowel ischemia
- Constipation
- Diverticulitis
- Bowel obstruction
- Pancreatitis
- Malignancy
- Radiation enteritis

WORKUP

The clinical presentation is often vague and can be variable from patient to patient. A high index of suspicion must be maintained in any patient presenting with abdominal pain and bloody stool. In addition to the physical exam, the following are key to confirming the diagnosis:

- Lab studies
- Computed tomography
- Lower endoscopy

LABORATORY TESTS

- General:
  1. CBC (may see leukocytosis)
  2. Metabolic panel
  3. Liver function panel
- Specific markers: There are no specific laboratory tests for ischemic colitis. However, elevated levels of certain markers suggest inadequate global perfusion:
  1. Lactate
  2. Lactate dehydrogenase
  3. CK
  4. Amylase
- Coagulation studies
- Stool studies: Stool culture, ova and parasite, *C. difficile* toxin assay, tests for *Salmonella, Shigella, Campylobacter,* and *E. coli*

IMAGING STUDIES

- Abdominal CT with contrast: Although findings can be nonspecific, the value of CT is in distinguishing ischemic colitis from nonischemic causes of abdominal pain. It also can assess the degree of ischemia and gauge the need for surgical intervention. It may identify arterial emboli or venous obstruction. Specific findings suggestive of ischemic colitis include, but are not limited to, intestinal wall thickening, thumbprinting, pericolonic stranding, and peritoneal free fluid or free air. Pneumatosis (the presence of gas in the colonic wall), portal venous gas, and the presence of megacolon usually indicate severe disease favoring immediate surgical intervention.
- Abdominal radiograph: X-rays are rarely helpful in diagnosing ischemic colitis. Findings may be subtle or absent unless transmural necrosis and perforation have occurred, causing pneumoperitoneum.
- Lower endoscopy: This is the gold standard for confirming diagnosis of ischemic colitis. In the absence of peritoneal signs, colonoscopy is the test of choice to evaluate the degree of ischemia. If ischemia is suspected, lower endoscopy should be performed within the first 24 to 48 hrs. In most cases, visual inspection of the colonic wall using this technique will confirm the diagnosis and dictate the need for conservative versus surgical management. However, endoscopy should not be performed in patients with acute peritonitis or evidence of irreversible ischemic damage on CT.

Rx TREATMENT

- Treatment depends on the severity of disease and the specific etiology of colonic ischemia. However, the mainstay of therapy consists of optimizing blood flow to ischemic regions of bowel and removing any potential exacerbating factors. Initial supportive care consists of aggressive IV crystalloid resuscitation, bowel rest, and broad-spectrum antibiotics with aerobic and anaerobic coverage. A treatment algorithm is illustrated in Fig. 2.
- In mild cases where patients are hemodynamically stable and do not have signs of peritonitis, colonoscopy should be performed. Patients with nonviable bowel seen on endoscopy require immediate operative intervention. However, the remainder of patients should be managed medically with continued IV fluids, bowel rest, and broad-spectrum antibiotics. Consider the use of a nasogastric tube in patients with abdominal distention or signs of ileus or bowel obstruction. Avoid vasoconstrictive medications as these can exacerbate colonic hypoperfusion. Monitor signs of adequate end organ perfusion (e.g., mental status, abdominal pain, urine output). Management of underlying causes (e.g., heart failure, vascular disease, sepsis) should be considered.
- In severe cases not responding to supportive therapy, where patients are exhibiting acute peritonitis, sepsis, hypotension, or pain out of proportion to clinical exam, surgical abdominal exploration is warranted. Resection of gangrenous segments of bowel may be necessary. Colonoscopy should be avoided in these patients.

NONPHARMACOLOGIC THERAPY

- Open or laparoscopic abdominal exploration to identify necrotic bowel. Box 3 summarizes indications for surgical intervention in patients with ischemic colitis
- NG tube for bowel decompression if ileus is present

ACUTE GENERAL Rx

- Supportive care:
  1. IV fluids
  2. Bowel rest
  3. Broad-spectrum antibiotics (aerobic and anaerobic coverage)
- Anticoagulation (not indicated in nonocclusive ischemia but may be considered in proven arterial occlusion or mesenteric vein thrombosis)
- Abdominal exploration:
  1. Bowel prep should be given
  2. Bowel resection may be indicated in severe colitis
  3. Repeat surgical exploration normally is performed within 12 to 24 hrs, especially after colonic resection, to assess the viability of colonic tissue and state of the anastomosis. Intraoperative infrared angiography based on IV injection of indo cyanine green (Fig. E3) can be used as an adjunct for decisions of whether to resect in determining margins and the integrity of intestinal anastomoses
  4. Note that primary anastomosis after colonic resection is contraindicated in certain cases (e.g., presence of aortic or iliac grafts; or when tissue is too friable for stable anastomosis)

CHRONIC Rx

- Avoid overly aggressive hypertension treatment.
- Avoid dehydration.
- Avoid extreme exercise.

DISPOSITION

- Most cases of acute ischemic colitis are nongangrenous and resolve completely with medical care in 1 to 2 days. However, the need for surgery in more severe cases portends a worse prognosis and is associated with increased morbidity and mortality. Any risk factors for ischemic colitis should be identified and mitigated as much as possible.

REFERRAL

Prompt general surgery consultation is indicated in patients with the following:

- Hemodynamic instability and peritoneal signs on examination
- CT showing signs of bowel infarction or perforation
- Endoscopy showing nonviable bowel or peritoneal signs

PEARLS & CONSIDERATIONS

COMMENTS

Ischemic colitis typically occurs in older patients who have multiple comorbidities. A high index of suspicion should be maintained for patients with recent endovascular procedures. These patients require close outpatient follow-up and management by a primary care provider.

PREVENTION

Avoid overly aggressive hypertension treatment, dehydration, and extreme exercise.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Mesenteric Venous Thrombosis (Related Key Topic)
Acute Mesenteric Ischemia (Related Key Topic)

AUTHORS: **Paul White, MD,** and **Mark F. Brady, MD, MPH, MMSc**

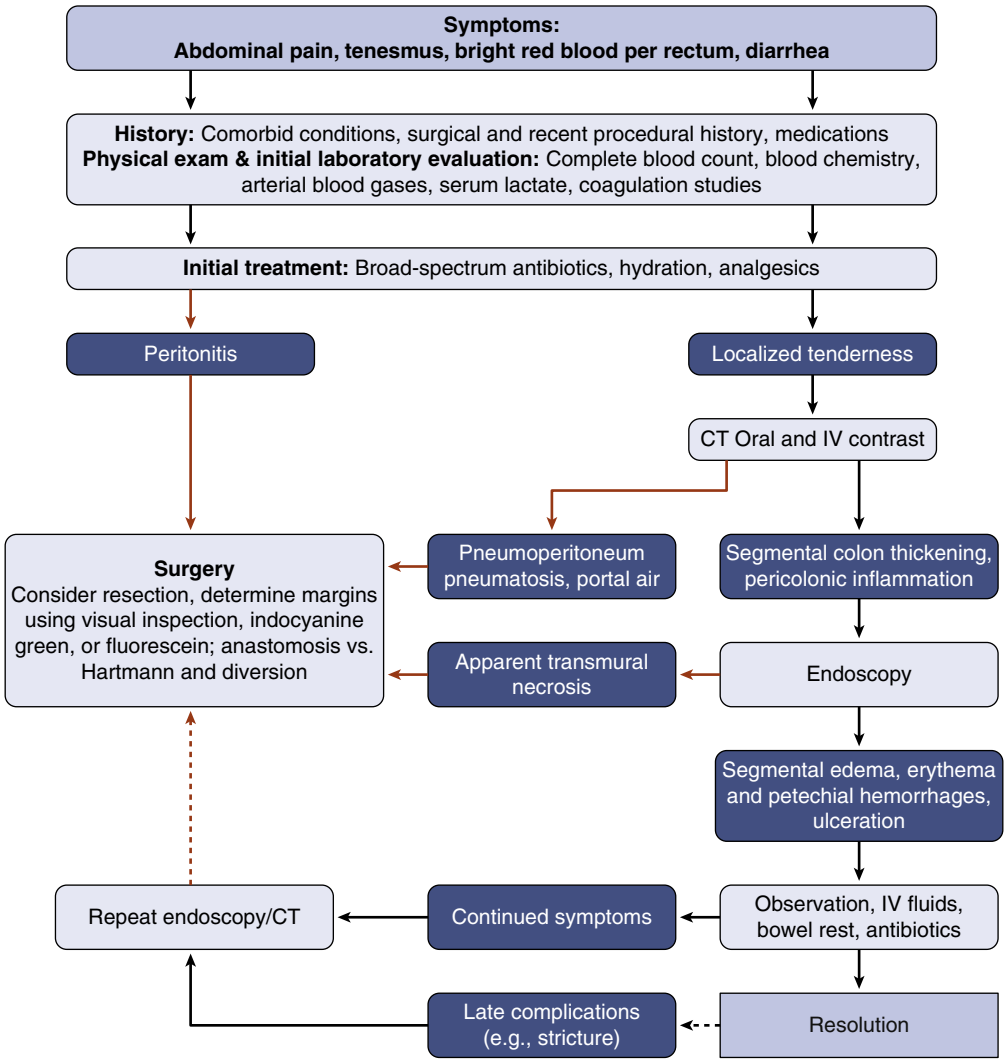

FIG. 2 Treatment algorithm for ischemic colitis. *CT,* Computed tomography; *IV,* intravenous. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

BOX 3 Indications for Surgical Intervention in Patients with Ischemic Colitis

Acute
Peritonitis
Bowel perforation
Bowel necrosis
Fulminant colitis
Massive hemorrhage
Sepsis

Chronic
Intractable symptoms (abdominal pain, bloody diarrhea, etc.) lasting >2 weeks
Recurrent sepsis
Chronic colitis
Ischemic stricture
Malnutrition from protein-losing enteropathy

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

SUGGESTED READINGS

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Washington C et al: Management of ischemic colitis, *Clin Colon Rectal Surg* 25:228-235, 2012.

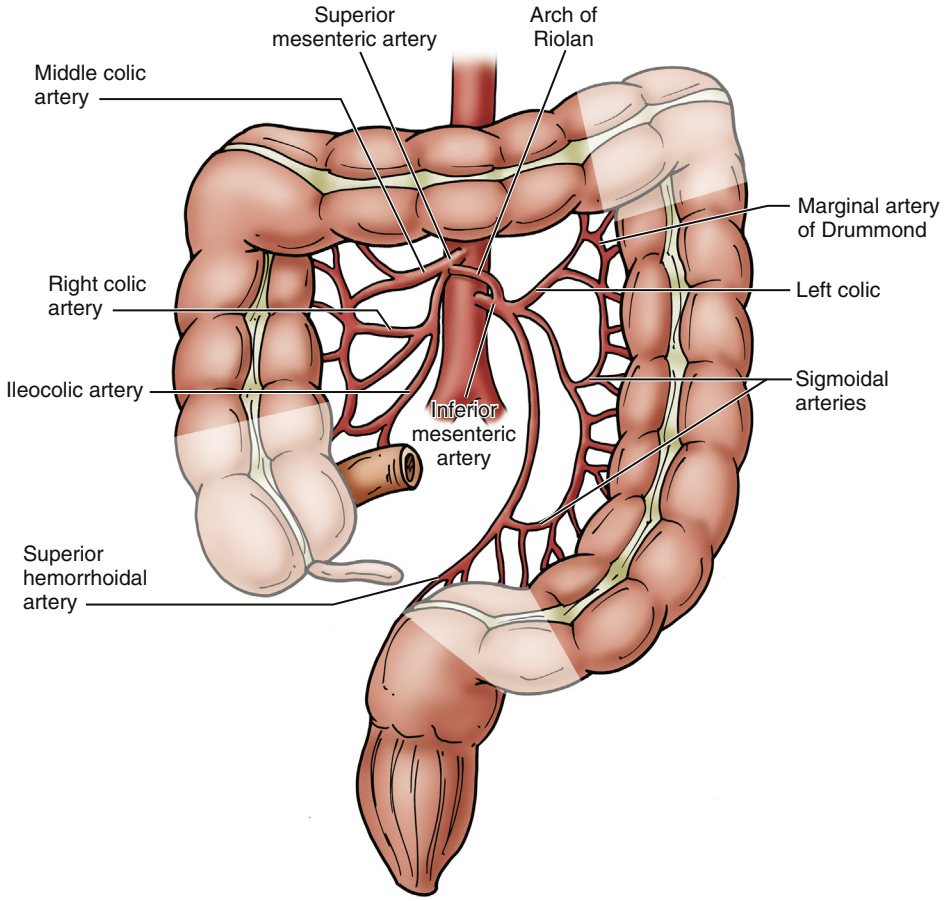

FIG. E1 Arterial supply to the colon. Shaded areas depicting potential watershed regions. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

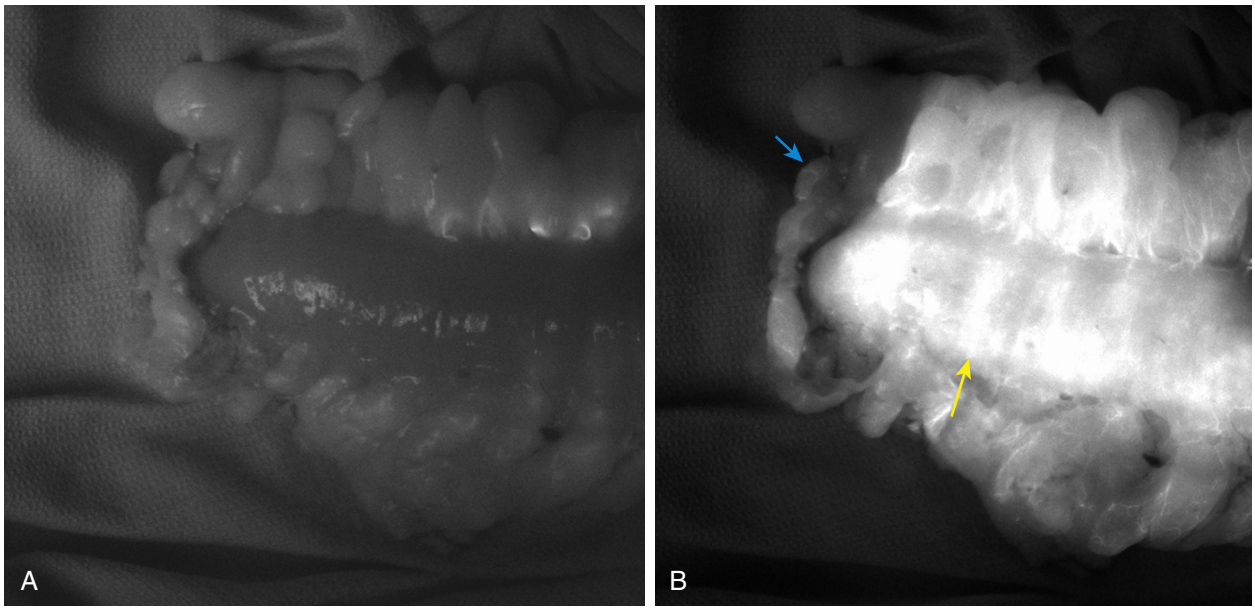

FIG. E3 Indocyanine green-based infrared angiography. A, Colon before injection. **B,** Colon after injection: *(short blue arrow)* Ischemia of resection margin; *(yellow arrow)* normal perfusion of colon. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

Ischemic Hepatitis

BASIC INFORMATION

DEFINITION

- A common form of vascular liver disease
- Occurs when a severe systemic disturbance leads to decreased perfusion to the liver resulting in tissue hypoxia

SYNONYMS

Hypoxic hepatitis
Shock liver
Ischemic hepatopathy
Hepatic necrosis

ICD-10CM CODES

K76.2	Central hemorrhagic necrosis of liver
K75.89	Other specified inflammatory liver disease

EPIDEMIOLOGY & DEMOGRAPHICS

- Occurs worldwide

INCIDENCE:

- Less than 1% on the inpatient medical wards
- Incidence is higher (2.5%) in intensive care unit

PEAK INCIDENCE: Highest in the cardiac care units

PREVALENCE:

- Recognized as most frequent cause of acute liver injury
- 57% of patients with liver enzymes >1000 IU/L have ischemic hepatitis
- Prevalence up to 10% in the intensive care setting

PREDOMINANT AGE AND SEX:

- Can occur in all ages
- Most common in elderly

GENETICS: No genetic predisposition

RISK FACTORS:

- Most common is cardiovascular disease
- Chronic heart failure
- Cirrhosis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Altered mental status may be present due to decreased cerebral perfusion.
- Other symptoms are often masked by the overall disease state.
- Hepatic synthetic function is usually preserved in ischemic hepatitis.

ETIOLOGY

- Cardiac disease in the most common (Fig. E1)
- This includes myocardial infarction, arrhythmias, cardiac tamponade, and cardiogenic shock
- Majority of patients have markedly increased cardiac filling pressures
- Respiratory failure and sepsis are the second and third most common
- Hypovolemic shock from hemorrhage, dehydration, and heat stroke
- Hypotension (only 1 in 2 patients have documented low blood pressures)
- See Table 1 for a brief summary of the different causes of ischemic hepatitis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS (TABLE 2)

- Acute viral hepatitis
- Autoimmune hepatitis
- Drug-induced liver injury
- Other toxins and medications (i.e., acetaminophen toxicity)

WORKUP

- Diagnosed by laboratory parameters and the clinical context of a hospitalized patient.
- Workup is directed at identifying the predisposing cause.
- Liver biopsy is not required.
- Histology shows centrilobular (zone 3) necrosis with preservation of the hepatic architecture.
- Necrosis can extend to the midzonal hepatocytes in the setting of prolonged ischemia.

LABORATORY TESTS

- Extremely elevated aminotransferase levels, often exceeding 200 times the upper limit of normal.
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) rapidly rise after the ischemic insult.
- They peak within 1 to 3 days.
- They usually return to normal within 7 to 10 days if the initial ischemic insult is resolved.
- Lactate dehydrogenase (LDH) level is extremely elevated.
- ALT/LDH ratio of less than 1.5 is suggestive.
- Prothrombin time can be slightly prolonged.
- The serum bilirubin can be mildly increased.
- Serum bilirubin peaks after the aminotransferases peak.
- Increased blood urea nitrogen and creatinine levels from acute tubular necrosis and renal dysfunction.

IMAGING STUDIES

Imaging is not required for the diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Management is directed at treating the underlying illness causing the systemic disturbance.

ACUTE GENERAL Rx

- Hemodynamic resuscitation
- Inotropic agents for cardiogenic shock
- Intravenous fluid resuscitation with or without vasoconstrictors for septic or hypovolemic shock
- Blood transfusions if hypovolemic shock from blood loss
- These measures optimize hepatic perfusion and resolve tissue hypoxia
- There is no role for *N*-acetylcysteine administration

TABLE 1 Causes of Ischemic Hepatitis

Cardiovascular disease (most common): Cardiogenic shock
Respiratory failure
Sepsis/septic shock
Hypovolemic shock: Hemorrhage, volume depletion
Hypotension

TABLE 2 Common Differentials of Ischemic Hepatitis

Acute viral hepatitis (e.g., hepatitis A, hepatitis B)
Autoimmune hepatitis
Toxins (e.g., herbal supplements)
Medications (e.g., acetaminophen)

CHRONIC Rx

- Ensure stability of underlying illness
- No specific liver-directed therapy

DISPOSITION

- Most commonly a self-limited and benign condition if promptly managed.
- Occasionally associated with significant mortality.
- Prognosis is determined by the severity of the underlying illness. In-hospital mortality associated with ischemic hepatitis is roughly 50%.
- Patients with underlying chronic heart failure or cirrhosis have worse outcomes.
- Other poor prognostic factors include persistently elevated aminotransferase and multiorgan failure.

REFERRAL

- Referral to a hepatologist is not required once illness is resolved.
- Referral is appropriate if patient has underlying cirrhosis.

PEARLS & CONSIDERATIONS

COMMENTS

- Have a high index of suspicion for this diagnosis in a hospitalized patient with severe systemic illness and significantly elevated AST and ALT.
- Use ALT/LDH ratio to aid in the diagnosis.
- Do not be alarmed if bilirubin continues to rise after AST and ALT peak.
- Hypotension is often not documented or not present at all.
- Patients with significantly elevated liver enzymes should be evaluated for occult heart failure.

PREVENTION

Ensure stability of comorbidities (e.g., cardiac disease)

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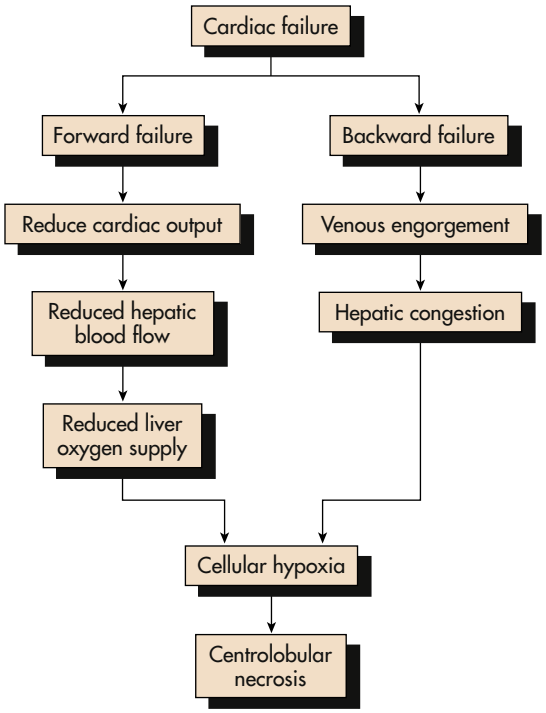

FIG. E1 The most common cause of hypoxic hepatitis is a combination of liver congestion due to chronic cardiac failure and an acute drop in cardiac output causing liver ischemia. (From Parrillo JE, Dellinger RP: *Critical care medicine: Principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Saunders.)

Ischemic Optic Neuropathy

BASIC INFORMATION

DEFINITION

Ischemic optic neuropathy (ION) is a general term for dysfunction of the optic nerve due to decreased blood supply and subsequent neuronal death.

Subclassifications:

- Arteritic anterior ischemic optic neuropathy (AAION)
- Nonarteritic anterior ischemic optic neuropathy (NAION)
- Posterior ischemic optic neuropathy (PION)

SYNONYMS

ION
AAION
NAION
PION

ICD-10CM CODE
H47.01 Ischemic optic neuropathy

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- 2.3 to 10 cases of anterior ischemic optic neuropathy per 100,000 per yr (15% AAION, 85% NAION).
- PION is much less common than anterior ischemic optic neuropathy (AION).

PREDOMINANT AGE, RACE, AND SEX:

- Age >50, though may occur at any age.
- White women are at particular risk of AAION due to giant cell arteritis (GCA).
- 95% of NAION patients are white.

RISK FACTORS:

- NAION: Diabetes mellitus, hypertension, episodic hypotension, obstructive sleep apnea, hypercholesterolemia. Emboli can be refractile yellow-white cholesterol (Hollenhorst) plaques (Fig. E1, *A*), grayish elongated fibrin-platelet aggregates (Fig. E1, *B*), or nonscintillating white calcific particles (Fig. E1, *C*)
- PION: Surgery (hemodilution, prolonged hypotension, orbital edema, and orbital compression), or factors associated with AAION and NAION

CLINICAL PRESENTATION

- AAION: Sudden, unilateral, often painless vision loss. Will commonly have systemic symptoms of GCA including headache, jaw claudication, scalp tenderness, fever, and weight loss, but vision loss may be the only presenting sign/symptom
- NAION: Sudden, unilateral, painless vision loss, often upon awakening
- PION: Sudden, painless loss of vision that is either unilateral or bilateral. Typically bilateral if following surgery or unilateral in its arteritic or nonarteritic form with symptoms similar to AAION and NAION, respectively

PHYSICAL FINDINGS

- All types of ION may result in a relative afferent pupillary defect and/or dyschromatopsia in the affected eye.
- AAION: Severe vision loss with visual acuity worse than 20/200 in a majority of patients. Fundoscopic view of the optic nerve head in the affected eye will show pallid edema ("chalky white" disc).
- NAION: Blurring/cloudiness of vision with relatively preserved central visual acuity (>20/64 in 31% to 52% of patients). Fundoscopic view of the optic nerve head during the acute phase will show edema and surface capillary dilation with peripapillary splinter hemorrhages. The unaffected eye will likely reveal a small cup-to-disc ratio.
- PION: Vision loss is worst in surgical PION, otherwise similar to AAION and NAION. Fundoscopic exam typically normal in acute setting, but may show pallor weeks later.

ETIOLOGY

- AAION: Sudden occlusion of the short posterior ciliary arteries that supply the optic nerve head as a result of vasculitis. The most common vasculitis is GCA, but others include

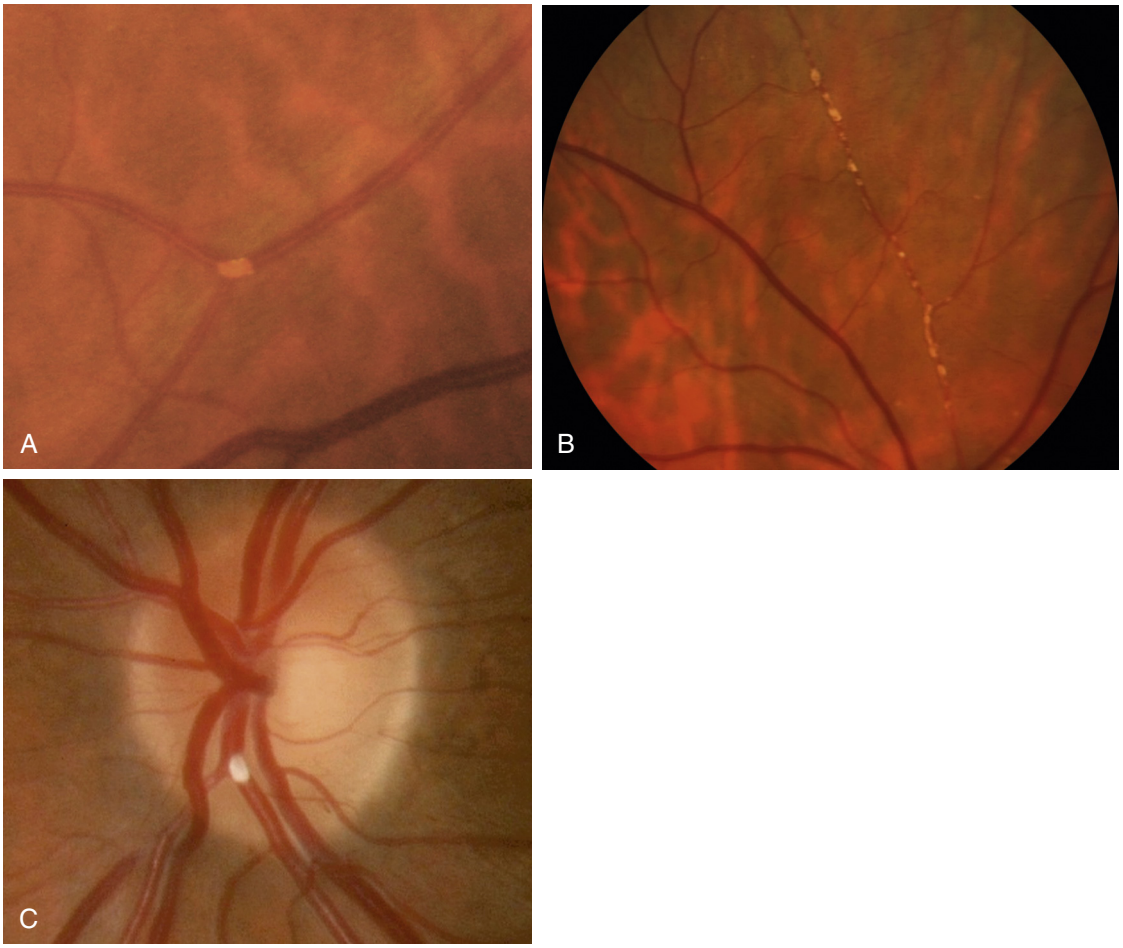

FIG. E1 Retinal emboli. A, Hollenhorst plaque; **B,** fibrin-platelet emboli; **C,** calcific embolus at the disc. (From Bowling B: *Kanski's clinical ophthalmology: a systematic approach,* ed 8, Edinburgh, 2016, Elsevier.)

eosinophilic granulomatosis with angiitis (previously Churg-Strauss syndrome), polyarteritis nodosa, or rheumatoid arthritis.
- NAION: It is hypothesized that hypoxia of the optic nerve head results in slight edema of the axons of the optic nerve. As the edema increases, a compartment syndrome develops resulting in the occlusion of the short posterior ciliary arteries in the optic nerve head.
- PION: Ischemia in the retrobulbar optic nerve due to hypoperfusion of the pial plexus. This may be secondary to either surgery or arteritic/nonarteritic causes as discussed previously.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Optic neuritis: Typically associated with painful vision loss and may be the presenting sign of multiple sclerosis or neuromyelitis optica
- Toxic/nutritional optic neuropathy: Typically bilateral, symmetric, painless, and slowly progressive, although may be acute (such as with methanol or ethylene glycol poisoning)
- Radiation-induced optic neuropathy: Typically develops within 3 yr of radiation to structures near the optic nerve. Progresses within weeks with no recovery of vision
- Infectious optic neuropathy: Optic neuropathy can develop as a result of a number of infections including bacterial (*B. henselae, M. tuberculosis*), spirochetes (*B. burgdorferi, T. pallidum*), fungi (*Cryptococcus* sp., *Aspergillus* sp.), or viruses (cytomegalovirus, Epstein-Barr virus, or varicella-zoster virus in immunocompromised patients)
- Compressive optic neuropathy (e.g., from tumor): Typically progressive vision loss but may present acutely

WORKUP

- Complete history focused on pertinent symptoms and risk factors.
- Workup should focus on excluding GCA (headache, jaw claudication, scalp tenderness, fever), as treatment delay may result in permanent vision loss in both eyes.
- Careful examination of optic disc, look for "chalky white" pallor suggestive of AAION or edema and peripapillary hemorrhages suggestive of NAION.
- The unaffected eye should also be examined and compared.

LABORATORY TESTS

- Complete blood count with C-reactive protein (level above 2.45 mg/dl highly suggestive of GCA) and erythrocyte sedimentation rate
- Tests to rule out infectious optic neuropathy as appropriate

IMAGING STUDIES

- Visual field testing: May detect any visual field defects associated with optic nerve injury (including altitudinal, arcuate, and central visual field defects). PION in particular is associated with central visual field defects.
- Optical coherence tomography: May show swelling of the optic disc.
- Fluorescein angiography: May show generalized choroidal filling delay (AAION) or delayed filling in the optic disc prelaminar layers (NAION). PION will show no abnormalities.

WORKUP

Temporal artery biopsy if high suspicion for GCA.

Rx TREATMENT

- AAION: Treatment should begin as soon as GCA is suspected. Corticosteroids are the mainstay of treatment. Recommendations include either oral prednisone (80-120 mg daily) or intravenous methylprednisolone (1 g daily) for 3 to 5 days followed by 1 to 2 mg/kg/day oral prednisone for 4 to 6 weeks and tapered gradually to 10 to 15 mg/day and maintained for 12 or more months.
- NAION: There is currently no effective treatment for NAION. Proposed treatments that have not been shown to be efficacious include corticosteroids, intravitreal anti-VEGF injections, aspirin, hyperbaric oxygen, and surgical decompression.
- PION: Arteritic and nonarteritic forms of PION should be treated as for AAION, and there is currently not an effective treatment for surgical PION.

DISPOSITION

- AAION: If not treated, the second eye is similarly affected in 50% to 95% of patients. With treatment, contralateral eye involvement is generally prevented and some patients have slight improvement in affected eye.
- NAION: Approximately 20% to 25% will spontaneously recover some vision, and the same amount may have some worsening. Although recurrent NAION in the same eye is not likely (3% to 8%), up to 30% to 40% of patients experience contralateral eye involvement in their lifetime.
- PION: Arteritic/nonarteritic forms as mentioned previously, patients with surgical PION generally have little change following vision loss.

REFERRAL

Recommend referral to an ophthalmologist or neuroophthalmologist for evaluation and workup. Again, if GCA is suspected, begin treatment immediately.

! PEARLS & CONSIDERATIONS

- Ischemic optic neuropathy can be classified as either anterior or posterior, and may be due to arteritic, nonarteritic, or surgical causes.
- Correct identification of the underlying etiology is key to preventing further vision loss, especially in patients with GCA.
- Patients suspected of having GCA should be treated with corticosteroids immediately and undergo temporal artery biopsy within a week of starting corticosteroid treatment.

AUTHORS: **Paul D. Chamberlain, MD,** and **Joseph S. Kass, MD, JD, FAAN**

SUGGESTED READINGS

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Peeler C, Cestari DM: Non-arteritic anterior ischemic optic neuropathy (NAION): a review and update on animal models, *Semin Ophthalmol* 31(-2):99-106, 2016.

BASIC INFORMATION

DEFINITION

Jaundice is a yellowish discoloration of the sclera, skin, and mucous membranes caused by an excessive amount of bilirubin in the bloodstream. Clinically detectable jaundice in adults is a serum bilirubin of 2.5 to 3 mg/dl.

SYNONYM

Icterus

ICD-10CM CODE
R17 Unspecified jaundice

EPIDEMIOLOGY & DEMOGRAPHICS

The prevalent causes of jaundice by age and sex:

- Young adulthood (for either sex): Viral hepatitis, Gilbert disease
- Middle adulthood (for either sex): Drug-induced hepatitis and cirrhosis
- Middle-aged and older men: Alcoholic liver disease, pancreatic cancer, hepatoma, primary hemochromatosis
- Women: Primary biliary cirrhosis, chronic active hepatitis, choledocholithiasis, carcinoma of the gallbladder

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Presentation can vary from an incidental finding to acute and life threatening. History and physical examination give important clues to the underlying condition.

Key history of present illness findings:

- Duration of jaundice
- Associated symptoms: Abdominal pain, fever, nausea, malaise, pruritus, chills, changes in urine and stool color, anorexia and/or weight loss

Key social history/exposure findings:

- Alcohol use, injection of illicit drugs, use of hepatotoxic medication or herbal products, blood transfusions, unprotected sex, ingestion of shellfish, travel, occupational exposure to toxins

Key medical history findings:

- Prior abdominal/biliary surgery, prior episodes of jaundice, prior diagnosis of hepatitis B or C, inflammatory bowel disease

Key physical findings:

- Vital sign abnormalities: Fever, hypotension, tachycardia
- Signs of acute disease: Abdominal tenderness, splenomegaly, abdominal mass, encephalopathy, Murphy sign
- Signs of chronic liver disease: Palmar erythema, spider angiomas, bruising, gynecomastia, testicular atrophy, ascites, weight loss, Kayser-Fleischer rings (Wilson), caput medusa, internal hemorrhoids, scleral icterus

ETIOLOGY

Disruption in any of the three phases of bilirubin metabolism can lead to jaundice:

- Prehepatic phase: An increase in heme degradation products from red blood cell catabolism, ineffective erythropoiesis, or breakdown of muscle myoglobin and cytochromes; leads to indirect (unconjugated) hyperbilirubinemia
- Intrahepatic phase: Destruction of the hepatocytes or disruption of either of the two separate biochemical processes that conjugate bilirubin in the hepatocyte; may lead to indirect (unconjugated) or direct (conjugated) hyperbilirubinemia
- Posthepatic phase: Blockage of the release of water-soluble bilirubin from the hepatobiliary system, preventing excretion into the stool or urine or recycling within the gut flora; leads to direct (conjugated) hyperbilirubinemia

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Prehepatic causes:

- Hemolytic processes (e.g., sickle cell disease, spherocytosis, thalassemia, G6PD, immune hemolysis, HUS), ineffective erythropoiesis (e.g., thalassemia, folate, severe iron deficiency), or large hematoma reabsorption

Intrahepatic causes:

- If unconjugated hyperbilirubinemia: Enzyme metabolism disorders (Gilbert disease, Crigler-Najjar syndrome), drugs that alter the enzymatic pathways such as rifampin, isoniazid, and probenecid
- If conjugated hyperbilirubinemia: Intrahepatic cholestasis caused by:
  1. Viruses: Hepatitis A, B, and C; Epstein-Barr, hemorrhagic viruses (yellow fever, Ebola)
  2. Other infections: Bacteria (leptospirosis, MAI), parasites (schistosomiasis, malaria, amebiasis), fungal *(Blastomyces, Histoplasma)*
  3. Alcohol: Alcoholic hepatitis, alcoholic cirrhosis
  4. Autoimmune: Primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis
  5. Hepatotoxic drug-induced: Acetaminophen (most common), penicillins (most commonly Augmentin), chlorpromazine, steroids (estrogenic or anabolic), NSAIDs, valproic acid, some herbals such as kava, ma huang, and off-market weight-loss supplements
  6. Hereditary/metabolic: Sickle cell disease and other RBC dyscrasias, hemochromatosis, Wilson disease, Dubin-Johnson and Rotor syndromes, α-antitrypsin deficiency, glycogen storage disease, NASH (nonalcoholic steatohepatitis), porphyria, benign recurrent intrahepatic cholestasis
  7. Systemic disease: Invading liver: Sarcoidosis, amyloidosis, hemochromatosis, tuberculosis, *Mycobacterium avium intracellulare*
  8. Other: Cirrhosis, sepsis, total parenteral nutrition, intrahepatic cholestasis of pregnancy, graft-versus-host disease, environmental toxins, benign postoperative state

Posthepatic causes:

- Intrinsic or extrinsic obstruction of the biliary system:
  1. Blockage within hepatobiliary tree: Strictures, cholangiocarcinoma, gallbladder cancer, carcinoma of ampulla of Vater, infection (e.g., cytomegalovirus, *Cryptosporidium* in patients with AIDS, parasites), choledocholithiasis
  2. Blockage outside of hepatobiliary tree: Pancreatitis, pancreatic carcinoma, pancreatic pseudocyst, lymphoma
- Pseudojaundice: Not related to bilirubin but rather resulting from excessive ingestion of foods containing beta carotene (e.g., carrots, melons, squash)

WORKUP

- History, physical examination, and first-line lab tests can often clarify diagnosis. Fig. 1 describes a clinical approach to jaundice.
- Table 1 summarizes the differential diagnosis of critical and emergent diagnoses in patients with jaundice.

LABORATORY TESTS

- First-line tests:
  1. Serum total and direct bilirubin
  2. Urinalysis
  3. Liver function tests (AST, ALT, GGTP, alkaline phosphatase), CBC, liver synthetic function (albumin, PT, PTT), pancreatic function (amylase, lipase)
- If serum total bilirubin and direct bilirubin are elevated and urine is positive for bilirubin, consider intrahepatic or posthepatic process. If serum total bilirubin is elevated but direct bilirubin is normal (unconjugated hyperbilirubinemia) and urine is negative for bilirubin, consider prehepatic or intrahepatic processes

Additional tests if diagnosis unclear:

- Screen for hepatitis A, B, and C; if still unclear, then consider following options based on H&P
- Other viruses: EBV, CMV
- Autoimmune disorders: Antimitochondrial antibody (elevated in primary biliary cirrhosis); anti-smooth muscle antibody, ANA (elevated in autoimmune hepatitis); antinuclear cytoplasmic antibody (elevated in primary sclerosing cholangitis)
- Ceruloplasmin (elevated in Wilson disease)
- Alpha-1 antitrypsin deficiency (elevated in cirrhosis and emphysema)
- Ferritin, Fe saturation (elevated in hemochromatosis)
- Blood smear (RBC dyscrasias)
- Diagnosis of exclusion: Gilbert syndrome
- Liver biopsy: Essential in diagnosis of chronic hepatitis. Can be used for diagnosis of liver masses but carries a substantial risk

IMAGING STUDIES

- Abdominal ultrasound: First-line study (Figs. E2 and E3) may be completed bedside, most sensitive for proximal biliary tract disease; presence of dilated ducts hints at an extrahepatic process.

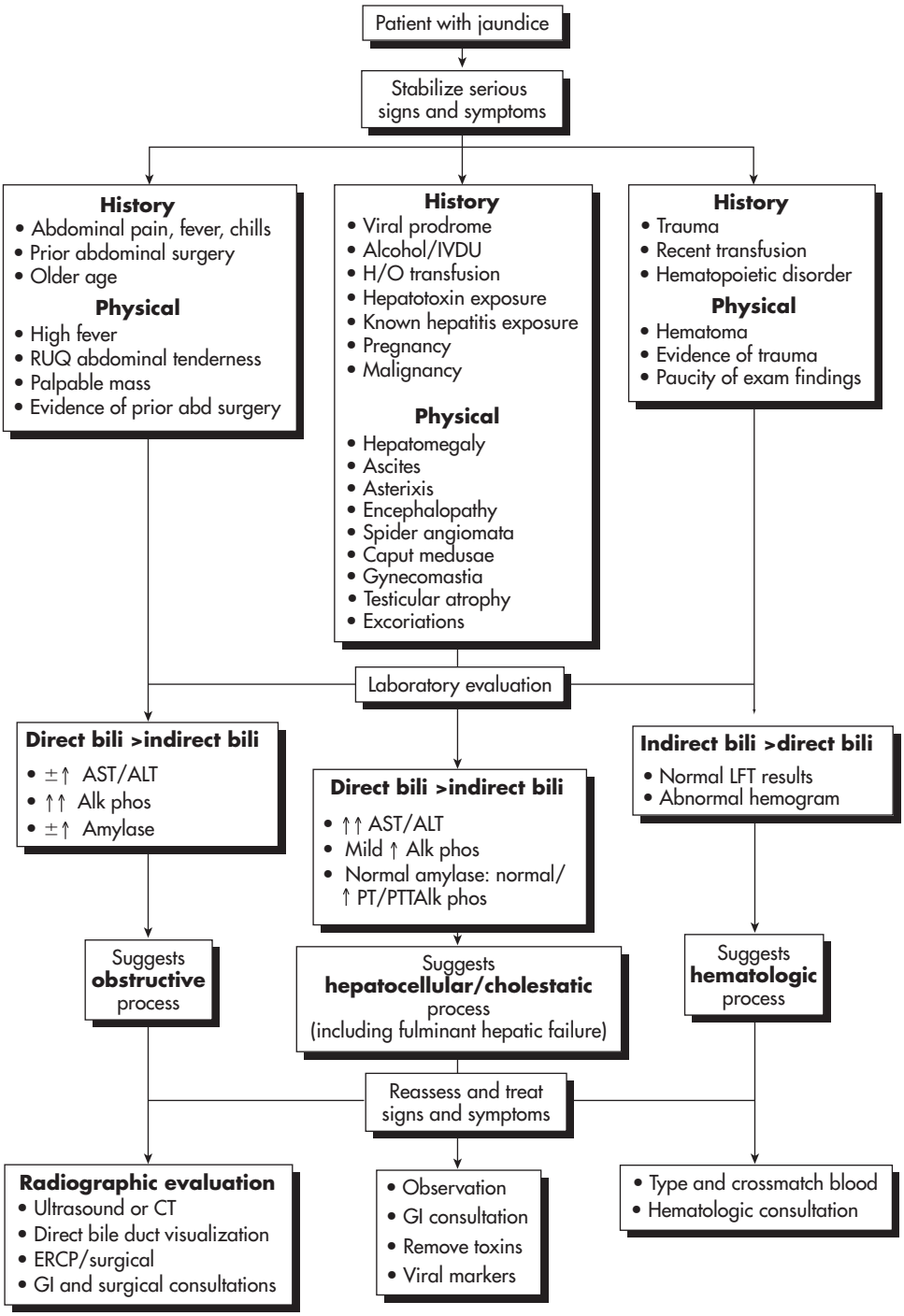


FIG. 1 Management of the patient with jaundice. *Alk phos,* Alkaline phosphatase; *ALT,* alanine aminotransferase; *AST,* aspartate aminotransferase; *bili,* bilirubin; *CT,* computed tomography; *ERCP,* endoscopic retrograde cholangiopancreatography; *GI,* gastrointestinal; *H/O,* history of; *IVDU,* intravenous drug use; *LFT,* liver function test; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *RUQ,* right upper quadrant. (From Marx AJ et al: *Rosen's emergency medicine: concepts and clinical practice,* ed 7, Philadelphia, 2010, Elsevier.)

- Abdominal CT: Often necessary to elucidate more information on liver, pancreas, and distal biliary system.
- Endoscopic retrograde cholangiopancreatography: Rarely necessary for diagnostics. Refer to GI consultant.
- Percutaneous transhepatic cholangiography: Rarely necessary for diagnostics. Refer to GI or surgical consultant.
- Magnetic resonance cholangiopancreatography: Noninvasive visualization of bile and pancreatic ducts. Refer to GI consultant.
- Endoscopic ultrasound: Used for characterization and, if needed, biopsy of any focal lesions found within biliary tree and/or pancreas. Refer to GI consultant.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Depends on underlying cause of the jaundice and clinical stability of the patient. Generally, obstructive causes require surgical treatment, while nonobstructive causes require medical treatment.

TABLE 1 Jaundice: Differential Diagnosis of Critical and Emergent Diagnoses

System	Critical	Emergent	Nonemergent
Hepatic	Fulminant hepatic failure	Hepatitis of any cause with confusion, bleeding, or coagulopathy	Hepatitis with normal mental status, normal vital signs, and no active bleeding
	Toxin	Wilson disease	
	Virus	Primary biliary cirrhosis	
	Alcohol	Autoimmune hepatitis	
	Ischemic insult	Liver transplant rejection	
	Reye syndrome	Infiltrative liver disease	
		Drug induced (isoniazid, phenytoin, acetaminophen, ritonavir, halothane, sulfonamides)	
		Toxin ingestion or exposure	
Biliary	Cholangitis	Bile duct obstruction (stone, inflammation, stricture, neoplasm)	
Systemic	Sepsis	Sarcoidosis	Posttraumatic hematoma resorption
	Heatstroke	Amyloidosis	Total parenteral nutrition
		Graft-versus-host disease	
Cardiovascular	Obstructing AAA	Right-sided congestive heart failure	
	Budd-Chiari syndrome	Veno-occlusive disease	
	Severe congestive heart failure		
Hematologic-oncologic	Transfusion reaction	Hemolytic anemia	Gilbert syndrome
		Massive malignant infiltration	Physiologic neonatal jaundice
		Inborn error of metabolism	
		Pancreatic head tumor	
		Metastatic disease	
Reproductive	Preeclampsia or HELLP syndrome	Hyperemesis gravidarum	
	Acute fatty liver of pregnancy		Cholestasis of pregnancy

AAA, Abdominal aortic aneurysm; *HELLP,* hemolysis, elevated liver enzymes, low platelets.
From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Saunders.

ACUTE GENERAL Rx

Acute, life-threatening illness (e.g., cholecystitis or ascending cholangitis) requires prompt diagnosis with basic labs and bedside diagnostics, with early surgical and GI consultation in conjunction. Suspicious medications should be stopped. Initiate medical management of symptoms with analgesia, IV fluids, correction of coagulopathies, and consideration of antibiotics. *N*-Acetylcysteine can be given for acetaminophen overdose.

CHRONIC Rx

Reversible causes must be ruled out first—suspicious medications and EtOH must be discontinued. Consider GI consult for management of many intrahepatic diseases, such as treatment of hepatitis B or C, Wilson disease with penicillamine, hemochromatosis with phlebotomy, or for stent insertion with ERCP for posthepatic obstruction. Consider surgical consult for resection of pancreatic masses, cholecystectomy, etc.

Symptomatic pruritus may be treated with cholestyramine for bilirubin binding or with antihistamines to decrease the itch reflex. Ursodiol may be used to treat primary biliary cirrhosis and for gallstone prevention/dissolution.

PEARLS & CONSIDERATIONS

COMMENTS

- Heed the warning signs of unstable vital signs to diagnose life-threatening illness; early collaboration with surgical and gastroenterology colleagues is helpful in complex patient care scenarios.
- Careful history and physical examination, basic labs, and prompt bedside imaging frequently lead to accurate diagnosis.
- Very high serum bilirubin (>15 mg/dl) is most likely to be seen in cirrhosis. Watch for hepatorenal syndrome in these patients.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Jaundice (Patient Information)

AUTHORS: **Alla Goldburt, MD,** and **Paolo G. Pace, MASc, MD**

SUGGESTED READINGS

Nguyen KD et al: Atypical causes of cholestasis, *World J Gastroenterol* 20(28):9418, 2014.

Privette TW et al: Emergencies of liver, gallbladder, and pancreas, *Emerg Med Clin North Am* 29(2):293-317, 2011.

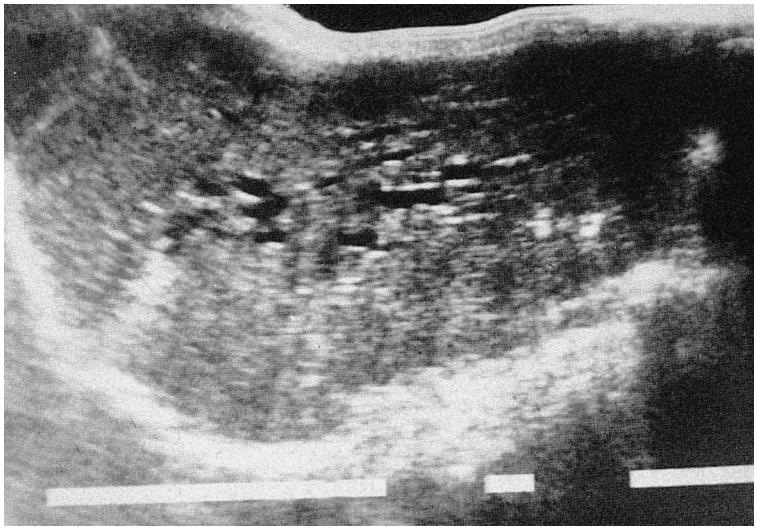


FIG. E2 Ultrasound showing a large calculus in the extrahepatic biliary tree. Dilated bile ducts can be seen to the left. (Courtesy Dr. M.C. Collins. Forbes A et al [eds]: *Atlas of clinical gastroenterology,* ed 3, St Louis, 2005, Mosby.)

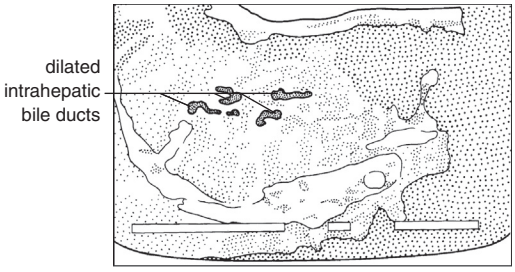


FIG. E3 Schematic representation of ultrasound abnormality seen in Fig. E2. (From Forbes A et al [eds]: *Atlas of clinical gastroenterology,* ed 3, St Louis, 2005, Mosby.)

Junctional Rhythm

BASIC INFORMATION

DEFINITION

Junctional rhythm is an abnormal cardiac rhythm originating in the His bundle or atrioventricular (AV) node. This diagnosis includes three distinct entities based on rate:

1. A junctional escape rhythm has a rate of 40-60 bpm.
2. Accelerated junctional rhythm has a rate of 60-100 bpm.
3. Junctional ectopic tachycardia (JET) has a rate of >100 bpm.

SYNONYMS

Junctional escape rhythm
Accelerated junctional rhythm
Junctional ectopic tachycardia (JET)
Nodal rhythm disorder
Ectopic rhythm disorder
Junctional premature depolarization

ICD-10CM CODE
I49.2 Junctional premature depolarization

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Junctional rhythm occurs more commonly in children due to higher vagal tone (13% of 10- to 13-yr-old boys, 45% of 7- to 10-yr-old children, and 19% of infants have junctional rhythm during sleep).[1] Endurance athletes have a 20% incidence of junctional rhythm, for a similar reason.

PREVALENCE: Junctional tachycardia is a rare cause of supraventricular tachycardia. It is rare in the pediatric population and even less common in adults. On the contrary, junctional rhythm is common although the prevalence is not well defined.

GENETICS: There is no known hereditary component.

RISK FACTORS: Conduction system disease, heart block, digitalis intoxication, heart surgery, endocarditis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

ESSENTIAL HISTORY:

- Previous history of syncope, presyncope, lightheadedness.
- Drugs, especially digoxin. Amount taken, time of ingestion. The digestion time is especially important because the serum digoxin level ideally should be measured at least 6 hours after ingestion to ensure accuracy. Obtain a thorough medication history to determine if any recent additions or dosing changes were made.

SYMPTOMS:

- Lightheadedness
- Syncope
- Palpitations
- Symptoms associated with digitalis intoxication: Gastrointestinal symptoms such as anorexia, nausea, vomiting, and abdominal pain. Neurologic manifestation such as lethargy, fatigue, delirium, confusion, weakness. Visual changes: Alteration in color vision, diplopia, photophobia, decreased visual acuity

PHYSICAL EXAMINATION:

- Vital signs
- Look for evidence of hypoperfusion and end organ dysfunction
- Cannon A-waves on examination of the jugular pulse

ETIOLOGY

Junctional tachycardia can occur as a primary arrhythmia (usually in children-JET), secondary to digitalis intoxication or catecholamine intoxication, or in the setting of injury to the His bundle (e.g., after valve surgery, abscess, sarcoidosis, myocarditis, ischemia, etc.).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- AVNRT (atrioventricular nodal reentrant tachycardia)
- AVRT (atrioventricular reentrant tachycardia)
- Accelerated idioventricular rhythm–in the case of junctional rhythm with aberrant conduction
- Fig. 1 illustrates arrhythmias originating in the atrioventricular node

WORKUP

- Vital signs
- 12-lead ECG (Figs. 2 and 3). The rhythm is almost perfectly regular and the QRS complex is generally narrow and similar to the complex seen during sinus rhythm. Retrograde P waves with a very short interval from QRS to P wave can be seen
- History of cardiac surgery, fevers, drug ingestion

LABORATORY TESTS

- Serum digoxin concentration
- Serum potassium concentration
- Creatinine and blood urea nitrogen (BUN) to assess renal function
- Troponin

IMAGING STUDIES

Echocardiogram

TREATMENT

Junctional tachycardia may be a marker for a serious underlying condition such as digitalis toxicity, postcardiac surgery, endocarditis, hypokalemia, or myocardial ischemia. Underlying conditions should be sought and corrected accordingly.

NONPHARMACOLOGIC THERAPY

- Junctional escape rhythm in the setting of sinus arrest or complete heart block without reversible cause necessitates permanent pacemaker implantation.
- Junctional ectopic tachycardia can be treated with antiarrhythmics or radiofrequency ablation.

ELECTROPHYSIOLOGY STUDY: The origin of this tachycardia is within the His bundle or AV node, and it can be diagnosed definitively by intracardiac recordings. Junctional rhythm most frequently takes the form of escape rhythms in the presence of sinus node dysfunction or AV nodal block, which can be diagnosed on electrophysiology (EP) study. These escape rhythms usually have a QRS morphology identical to that seen during sinus rhythm. In such cases, there is no P wave before the QRS complexes. The P waves can occur simultaneously with the QRS complexes; more commonly, they are retrograde. When the junctional rhythm is faster than 100 beats/min, it is called junctional tachycardia.

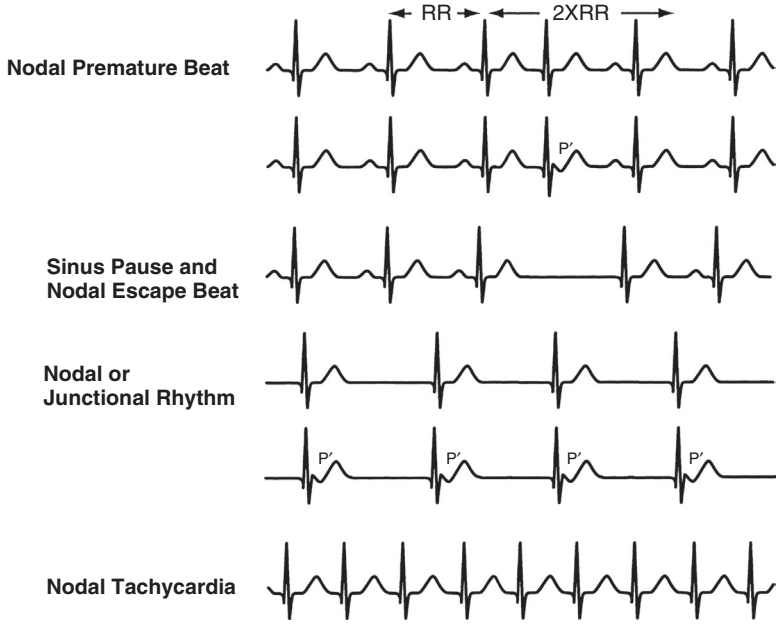


FIG. 1 Arrhythmias originating in the atrioventricular node. (From Park MK: *Park's pediatric cardiology for practitioners,* ed 6, Philadelphia, 2014, Elsevier.)

[1]Drago F et al: Neonatal and pediatric arrhythmias: clinical and electrocardiographic aspects, *Card Electrophysiol Clin* 10(2):397-412, 2018.

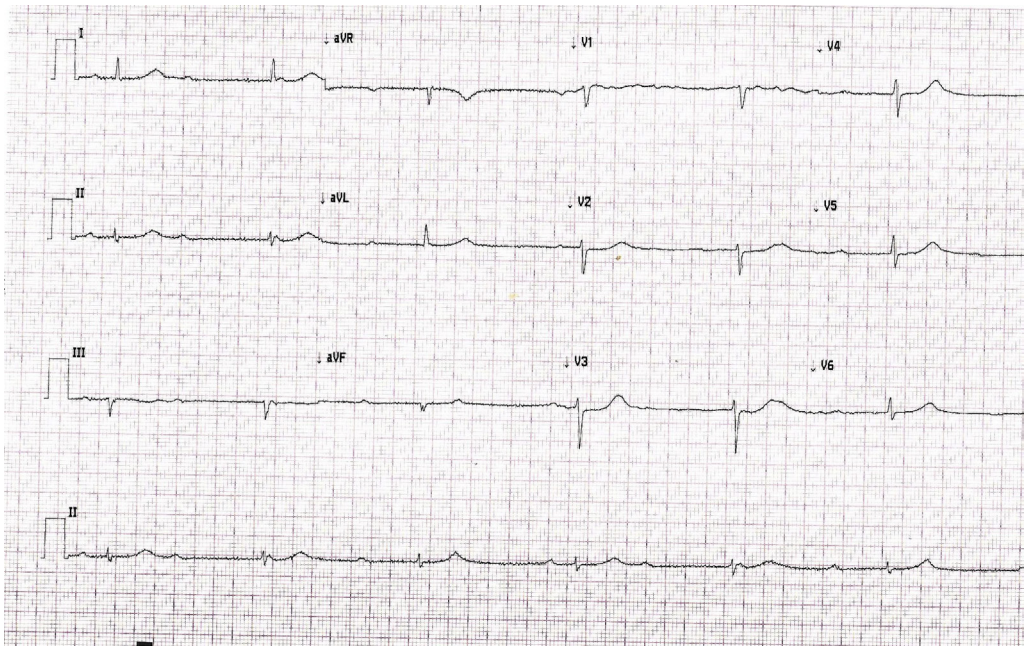


FIG. 2 Electrocardiogram of a patient with junctional rhythm and complete heart block. Note the narrow QRS complex and dissociated P waves. *aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right.

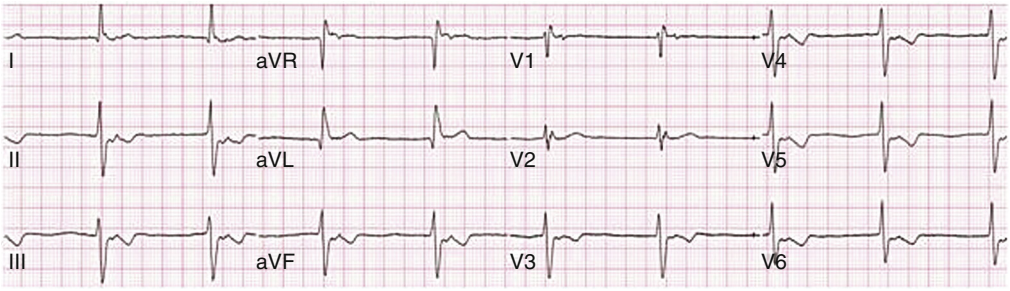


FIG. 3 Junctional rhythm with retrograde P waves that are negative in the inferior leads. *aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right. (From Parrillo JE, Dellinger RP: *Critical care medicine: principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Elsevier.)

ACUTE GENERAL Rx

The mainstay of managing nonparoxysmal junctional tachycardia is to correct the underlying abnormality. Withholding digitalis when junctional tachycardia is the only clinical manifestation of toxicity is usually adequate. If, however, ventricular arrhythmias or high-grade heart block are observed, then treatment with digitalis-binding agents may be indicated.

COMPLEMENTARY & ALTERNATIVE MEDICINE

N/A

DISPOSITION

Admit to cardiac telemetry if symptomatic. Consider specialty referral to cardiac electrophysiology.

REFERRAL

Refer to cardiologist.

PEARLS & CONSIDERATIONS

COMMENTS

- Junctional rhythm often is observed in patients with AV dissociation, which can lead to atrial contraction against closed atrioventricular valves, resulting in cannon A waves. This wave will cause pulsation in the neck and abdomen, headache, cough, jaw pain and possible hypotension.
- The presence of a perfectly regular rhythm in a patient with atrial fibrillation often indicates junctional rhythm with complete heart block.

PREVENTION

N/A

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Digoxin Overdose (Related Key Topic)
Sick Sinus Syndrome (Related Key Topic)
Heart Block, Complete (Related Key Topic)
Heart Block, Second-Degree (Related Key Topic)

AUTHOR: **John Wylie, MD, FACC**

SUGGESTED READING

2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia, 2016 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society, *J Amer Col Card* 13:e27-e115, 2016.

Juvenile Idiopathic Arthritis ALG PTG

BASIC INFORMATION

DEFINITION

Juvenile idiopathic arthritis (JIA), previously referred to as juvenile rheumatoid arthritis (JRA), is a diverse spectrum of chronic arthritides, involving ≥1 joints for ≥6 wk in a patient ≤16 yr of age. Other causes of arthritis must be excluded.

SYNONYMS

JIA
JRA
Juvenile rheumatoid arthritis (JRA)
Still disease (specifically systemic JIA)

ICD-10CM CODES

M08.00	Unspecified juvenile rheumatoid arthritis of unspecified site
M08.09	Unspecified juvenile rheumatoid arthritis, multiple sites
M08.20	Juvenile rheumatoid arthritis with systemic onset, unspecified site
M08.29	Juvenile rheumatoid arthritis with systemic onset, multiple sites
M08.40	Pauciarticular juvenile rheumatoid arthritis, unspecified site

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 1 per 1000 children in the U.S.; more common in children of European ancestry

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- JIA is subdivided into seven categories based on the International League of Associations for Rheumatology (ILAR) classification criteria (summarized in Table 1). Characteristics of the various categories of JIA are summarized in Table 2.
  1. Systemic onset JIA (sJIA) (4% to 17%)
     a. Arthritis in ≥1 joints with or preceded by fever (Fig. E1) of at least 2-wk duration that is quotidian (once daily) for at least 3 days and associated with at least one of the following: (1) evanescent erythematous rash (Fig. E2); (2) generalized lymphadenopathy; (3) hepatomegaly, splenomegaly, or both; and (4) serositis.
- Oligoarticular JIA (Fig. E3) (27% to 56%)
  1. Arthritis in <4 joints in the first 6 mo of disease. There are two subtypes:
     a. Persistent: ≤4 joints throughout the disease course.
     b. Extended: ≤4 joints during the first 6 mo extending to >4 joints after 6 mo.
- Polyarthritis, rheumatoid factor (RF) negative (11% to 28%)
  1. Arthritis in >5 joints during first 6 mo of the disease with negative RF.
- Polyarthritis, RF positive (2% to 7%)
  1. Arthritis involves ≥5 joints during first 6 mo of the disease with positive RF on >2 tests run 3 mo apart.
  2. Anticyclic citrullinated (CCP) antibodies may also be present.
  3. Most similar to adult rheumatoid arthritis; most likely to progress.
- Psoriatic arthritis (2% to 11%)
  1. Psoriasis and arthritis or psoriasis and ≥2 of the following:
     a. Dactylitis, nail pitting, onycholysis, and psoriasis in a first-degree relative.
- Enthesitis-related arthritis (3% to 11%)
  1. Arthritis or enthesitis and ≥2 of the following:
     a. Sacroiliac tenderness, positive HLA-B27, male age >6 yr, acute anterior uveitis, or first-degree relative with HLA-B27-associated disease.
- Undifferentiated arthritis (11% to 21%)
  1. Fulfills criteria in ≥2 categories above, or none of them

ETIOLOGY

Genetically susceptible individuals may develop an inappropriate immune response toward a self-antigen after exposure to an environmental trigger. Variants in HLA, PTPN22, and STAT4 loci may be associated with disease.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infection: Viral (parvovirus, toxic synovitis) or bacterial (Lyme, osteomyelitis, septic joints)
- Inflammation: Lupus, serum sickness, inflammatory bowel disease
- Reactive: Poststreptococcal, rheumatic fever
- Malignancy: Leukemia, bone tumors
- Table 3 summarizes conditions with arthralgia or arthritis that might be confused with JIA

TABLE 1 Overview of the Main Features of the Subtypes of Juvenile Idiopathic Arthritis

ILAR Subtype	Peak Age of Onset (yr)	Female:Male; % of All JIA	Arthritis Pattern	Extraarticular Features	Investigations	Notes on Therapy
Systemic arthritis	2-4	1:1; ~10% of JIA cases	Polyarticular, often knees, wrists, and ankles; also fingers, neck, and hips	Daily fever; evanescent rash; pericarditis; pleuritis	Anemia; WBC↑↑; ESR↑↑; CRP↑↑; ferritin;↑ platelets↑↑ (normal or ↑ in MAS)	Less responsive to standard treatment with MTX and anti-TNF agents; consider IL-1Ra in resistant cases
Oligoarthritis	>6	4:1; 50%-60% of JIA (but ethnic variation)	Knees ++; ankles, fingers +	Uveitis in ~30%	ANA positive in 60%; other tests usually normal; may have mildly ↑ ESR/CRP	NSAIDs and intraarticular steroids; occasionally require MTX
Polyarthritis, RF negative	6-7	3:1; 30% of JIA cases	Symmetric or asymmetric; small and large joints; cervical spine; TMJ	Uveitis in ~10%	ANA positive in 40%; RF negative; ESR ↑ or; ↑↑ CRP↑/normal; mild anemia	Standard therapy with MTX and NSAIDs, then if nonresponsive, anti-TNF agents or other biologics
Polyarthritis, RF positive	9-12	9:1; >10% of JIA cases	Aggressive symmetric polyarthritis	Rheumatoid nodules in 10%; low-grade fever	RF positive; ESR ↑↑; CRP ↑/normal; mild anemia	Long-term remission unlikely; early aggressive therapy is warranted
Psoriatic arthritis	7-10	2:1; >10% of JIA cases	Asymmetric arthritis of small or medium sized joints	Uveitis in 10%; psoriasis in 50%	ANA positive in 50%; ESR ↑; CRP ↑/normal; mild anemia	NSAIDs and intraarticular steroids; second-line agents less commonly
Enthesitis-related arthritis	9-12	1:7; 10% of JIA cases	Predominantly lower limb joints affected; sometimes axial skeleton (but less than adult AS)	Acute anterior uveitis; association with reactive arthritis and IBD	80% HLA-B27	NSAIDs and intraarticular steroids; consider sulfasalazine as alternative to MTX

ANA, Antinuclear antibody; *AS,* ankylosing spondylitis; *CRP,* C-reactive protein; *ESR,* erythrocyte sedimentation rate; *IBD,* inflammatory bowel disease; *ILAR,* International League of Associations for Rheumatology; *IL-1Ra,* interleukin-1 receptor antagonist; *JIA,* juvenile idiopathic arthritis; *MAS,* macrophage activation syndrome; *MTX,* methotrexate; *NSAID,* nonsteroidal antiinflammatory drug; *RF,* rheumatoid factor; *TMJ,* temporomandibular joint; *TNF,* tumor necrosis factor; *WBC,* white blood cell count.
From Firestein G et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, WB Saunders.

TABLE 2 Characteristics of the Various Categories of Juvenile Idiopathic Arthritis

Category	Age at Onset	Affected Joints	Systemic Features	Major Complications
Oligoarticular persistent	Early childhood	Large joints, asymmetric (knee, ankle, wrist, elbow, temporomandibular, cervical spine)	No	Chronic uveitis Local growth disturbances
Oligoarticular extended	Early childhood	Same as above, but more than four joints involved after the first 6 mo of disease	No	Chronic uveitis Local growth disturbances
Polyarticular RF negative	Throughout childhood	Any, often symmetric, often small joints	Malaise (subfebrile)	Chronic uveitis Local growth disturbances
Polyarticular RF positive	Teenage years	Any, usually symmetric and involving small joints	Malaise (subfebrile)	Local growth disturbances and articular damage
Systemic	Throughout childhood	Any (not necessarily at disease onset)	High fever, rash, polyserositis, marked acute-phase response	Acute: Macrophage activation syndrome Chronic: General growth disturbance, amyloidosis
Psoriatic	Late childhood	Spine, lower extremities, distal interphalangeal joints, dactylitis		Psoriasis Local growth disturbances
Enthesitis related	Late childhood	Spine, sacroiliac, lower extremities, thoracic cage joints	Inflammatory bowel disease	Acute symptomatic uveitis

RF, Rheumatoid factor.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE 3 Conditions with Arthralgia or Arthritis that Might Be Confused with Juvenile Idiopathic Arthritis

Type of Condition	Examples
Infections	Bacterial arthritis and osteomyelitis
	Borreliosis (Lyme disease)
	Viral and mycoplasmal arthritis
	Tuberculosis
Postinfectious conditions	Rheumatic fever
	Poststreptococcal arthritis
	Postenteritis and other reactive arthritis *(Salmonella, Campylobacter, Chlamydia)*
Noninflammatory conditions	Hypermobility and Ehlers-Danlos syndrome
	Growing pains, trauma, patellofemoral and other overuse syndromes
	Osgood-Schlatter disease and other juvenile osteochondroses
	Legg-Calvé-Perthes disease
	Slipped capital femoral epiphysis
	Foreign body synovitis
	Other congenital and genetic disorders of supportive tissue
Hematologic disorders	Sickle cell anemia
	Hemophilia
	von Willebrand disease
Systemic inflammatory disorders	Juvenile systemic lupus erythematosus
	Juvenile dermatomyositis
	Mixed connective tissue disease
	Scleroderma
	Vasculitis (e.g., Henoch-Schönlein purpura, Kawasaki disease, Behçet disease)
Autoinflammatory disorders	Cryopyrin-associated periodic syndrome
	Familial Mediterranean fever
	Other monogenic diseases (e.g., mevalonate kinase deficiency [hyperimmunoglobulinemia D], Blau syndrome, tumor necrosis factor receptor–associated periodic syndrome)
	Chronic recurrent multifocal osteomyelitis
	Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA syndrome)
Malignancies	Leukemia
	Neuroblastoma
	Localized bone tumors
Pain	Complex regional pain syndrome
	Pain amplification syndromes and fibromyalgia
	Nonspecific musculoskeletal pain
Miscellaneous conditions	Primary immunodeficiencies
	Sarcoidosis

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

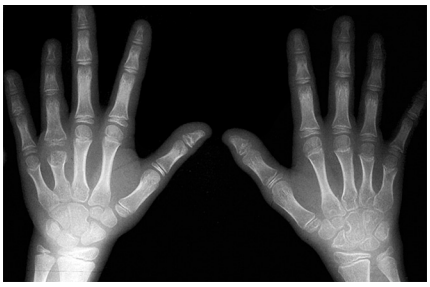


FIG. 4 Juvenile idiopathic arthritis (JIA). Oligoarticular-onset JIA in an 8-year-old. Epiphyseal destruction and undergrowth of the third metacarpophalangeal joint of the left hand are seen, as well as overgrowth of the carpal bones of the right wrist compared with the left wrist. Also note the widened appearance of the third phalanges caused by periosteal new bone formation. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

FIG. 5 Severe hip disease in a 13-year-old boy with active, systemic-onset juvenile idiopathic arthritis. Radiograph shows destruction of the femoral head and acetabula, joint space narrowing, and subluxation of left hip. The patient had received corticosteroids systemically for 9 years. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, WB Saunders.)

LABORATORY TESTS

- No single diagnostic test. Must rule out other causes of arthritis
- Elevated sedimentation rate and C-reactive protein; high ferritin
- Mild anemia, leukocytosis (WBC can be very high)
- Rheumatoid factor
- Antinuclear antibodies: Elevation associated with ocular complications
- Pancytopenia, a consumptive coagulopathy, elevated ferritin, and elevated liver enzymes are concerning for macrophage activation syndrome (MAS) in sJIA

IMAGING STUDIES

- Radiographs show soft tissue swelling and periarticular osteopenia early in the disease (Fig. 4).
- Joint destruction (Fig. 5) is less frequent, but bony erosion and cyst formation may be present.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Collaboration among the patient's pediatrician, rheumatologist, orthopedist, and physical therapist, along with education regarding weight management, is essential.

CHRONIC GENERAL RX

- NSAIDs: Used as monotherapy or in conjunction with intraarticular steroids
- DMARDs: Methotrexate, leflunomide, sulfasalazine
  1. Required by two thirds of children
  2. Axial involvement is less responsive to methotrexate
- Biologics: Improve morbidity associated with JIA. Individual subtypes show different responses to therapy.
  1. Tumor necrosis factor antagonists such as etanercept and adalimumab
  2. T-cell modulator, abatacept
  3. IL-1 (anakinra) and IL-6 antagonists (tocilizumab) useful in sJIA

Meta-analysis of randomized controlled trials did not show statistically significant differences in the efficacy or safety profile of these agents.

- Systemic corticosteroids should be limited when possible.
- Major medications and indications for treatment of JIA are summarized in Table 4. Fig. 6 illustrates an algorithm for medical treatment of oligoarticular-onset JIA. Treatment of polyarticular-onset JIA is illustrated in Fig. 7, and treatment of systemic onset JIA in Fig. 8.

DISPOSITION

- More than 50% continue to have active disease into adulthood.
- Patients with persistent oligoarticular disease are most likely to achieve remission, while those who are RF positive are least likely to achieve remission.
- Macrophage activation syndrome is a life-threatening complication of sJIA.
- Asymmetric joint involvement can lead to growth failure and limb length discrepancies.

REFERRAL

- Early rheumatology consultation
- Ophthalmology consultation at diagnosis and at least annually
- Children <7 yr old, with + ANA are at the highest risk for ocular inflammation (uveitis) and require screening every 3 to 4 mo

PEARLS & CONSIDERATIONS

COMMENTS

JIA is an autoinflammatory disease with a strong genetic component. Genomics is increasingly used to identify susceptibility loci. Immunomodulators have improved therapy in refractory disease. Normalization of the immune response early in the disease can limit disease progression. Children with JIA have an increased rate of malignancy compared with the general population.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Juvenile Rheumatoid Arthritis (Patient Information)

AUTHOR: **Michelle C. Maciag, MD**

TABLE 4 Major Medications and Indications for Treatment of Juvenile Idiopathic Arthritis

Medication	Arthritis Subtype	Indication
NSAIDs	All types	Symptomatic: pain, stiffness, serositis, antiinflammatory in mild cases
Intraarticular corticosteroids	All types, mainly oligoarthritis	Injection of few active joints
Systemic corticosteroids	Systemic, polyarthritis	Fever, serositis, bridging medication, MAS
Methotrexate	All types; less effective for systemic and enthesitis-related axial disease	Disease modifying
Leflunomide	Polyarthritis	Disease modifying
Sulfasalazine	Oligoarthritis, polyarthritis, enthesitis-related peripheral disease	Disease modifying
Cyclosporine	Systemic	MAS
Thalidomide	Systemic	Biologic modifier
Anti-TNF (etanercept infliximab, adalimumab, golimumab, certolizumab)	Polyarthritis, enthesitis-related, uveitis (infliximab, adalimumab), less effective for systemic disease	Biologic modifier
Abatacept	Polyarthritis	Biologic modifier
Anti–IL-1 (anakinra, canakinumab, rilonacept)	Systemic	Biologic modifier, MAS
Anti–IL-6 (tocilizumab)	Systemic, polyarthritis	Biologic modifier
IVIG	Systemic	Steroid sparing, MAS

IL-1, interleukin-1; *IVIG,* intravenous immune globulin; *MAS,* macrophage activation syndrome; *NSAID,* nonsteroidal antiinflammatory drug; *TNF,* tumor necrosis factor.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

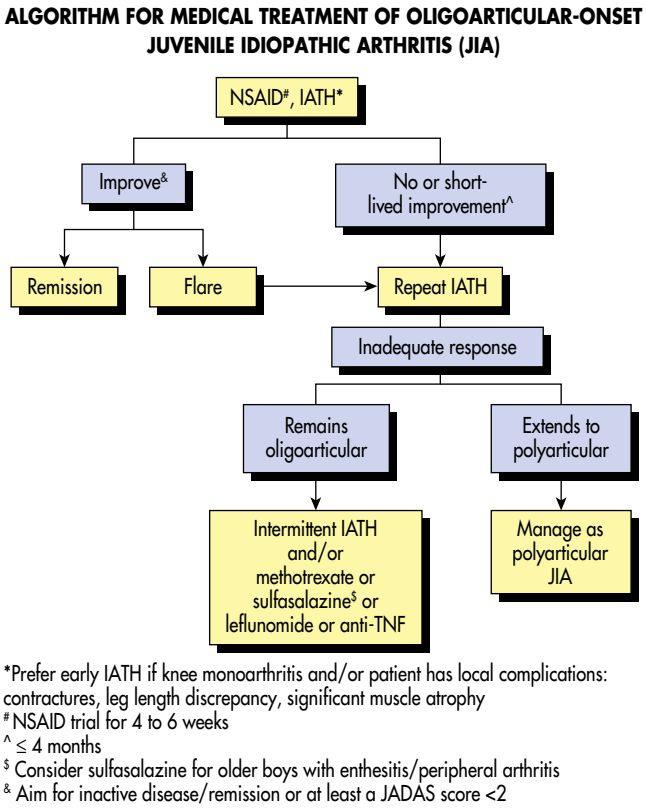
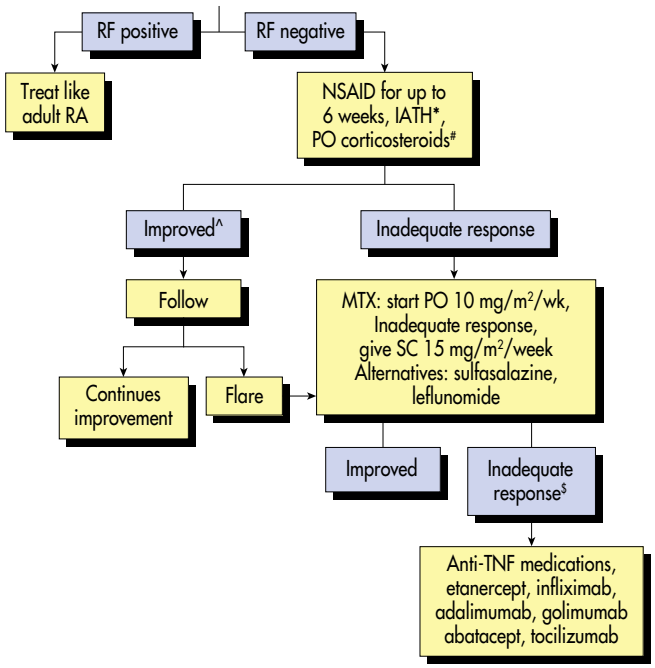


FIG. 6 Medical treatment of the oligoarticular type of juvenile idiopathic arthritis (JIA). *IATH,* Intraarticular triamcinolone hexacetonide; *JADAS,* Juvenile Arthritis Disease Activity Score; *NSAID,* nonsteroidal antiinflammatory drug; *TNF,* tumor necrosis factor. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

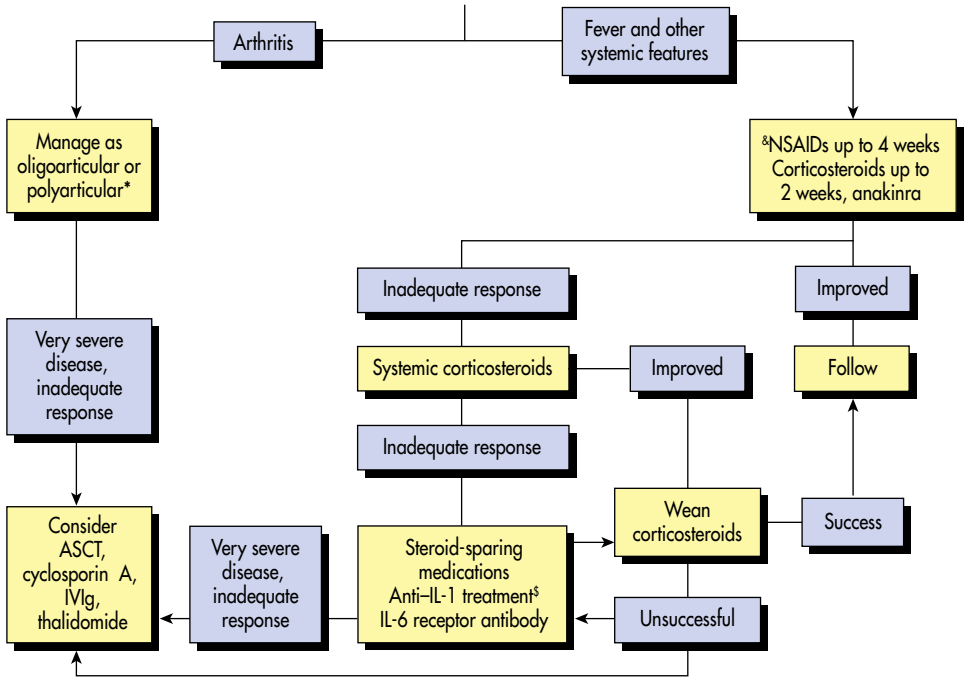
ALGORITHM FOR MEDICAL TREATMENT OF POLYARTICULAR-ONSET JUVENILE IDIOPATHIC ARTHRITIS (JIA)



* IATH for selected joints
# PO steroids can be considered as bridging medicine or during significant flares
$ If fails to respond to one anti-TNF agent, consider changing to another or to abatacept
^ Improved: pediatric ACR 70 response (or JADAS score <3.8)

FIG. 7 Medical treatment of the polyarticular type of juvenile idiopathic arthritis (JIA). *ACR70,* American College of Rheumatology 70% improvement; *IATH,* intraarticular triamcinolone hexacetonide; *JADAS,* Juvenile Arthritis Disease Activity Score; *MTX,* methotrexate; *NSAID,* nonsteroidal antiinflammatory drug; *PO,* oral; *SC,* subcutaneous; *RA,* rheumatoid arthritis; *RF,* rheumatoid factor; *TNF,* tumor necrosis factor. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

ALGORITHM FOR MEDICAL TREATMENT OF SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS (JIA)



* Methotrexate, intraarticular corticosteroids, anti-tumor necrosis factor drugs are less effective in systemic-onset JIA; anti-IL-1 and IL-6 receptor antibody may be more effective
$ Anti IL-1 treatments include anakinra, rilonacept, canakinumab
& Depends on physician global assessment and number of active joints

FIG. 8 Medical treatment of systemic juvenile idiopathic arthritis (JIA). *ASCT,* Autologous stem cell transplantation; *IL,* interleukin; *IVIG,* intravenous immunoglobulin; *NSAID,* nonsteroidal antiinflammatory drug; *TNF,* tumor necrosis factor. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

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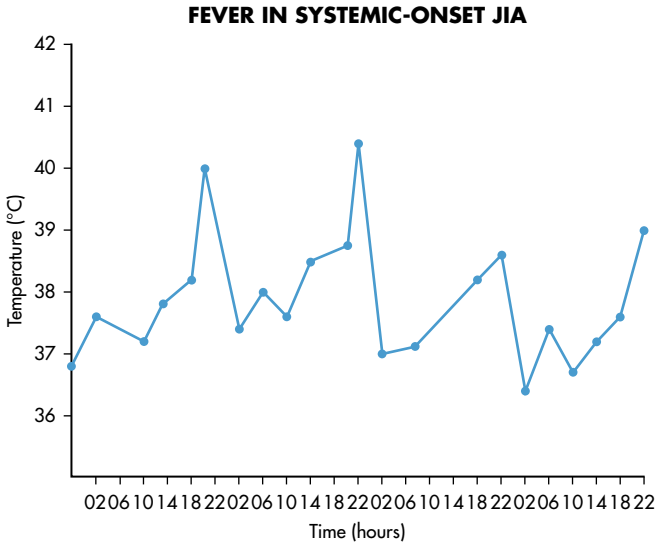

FIG. E1 An example of the typical fever curve seen in systemic juvenile idiopathic arthritis *(JIA)*.
(From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

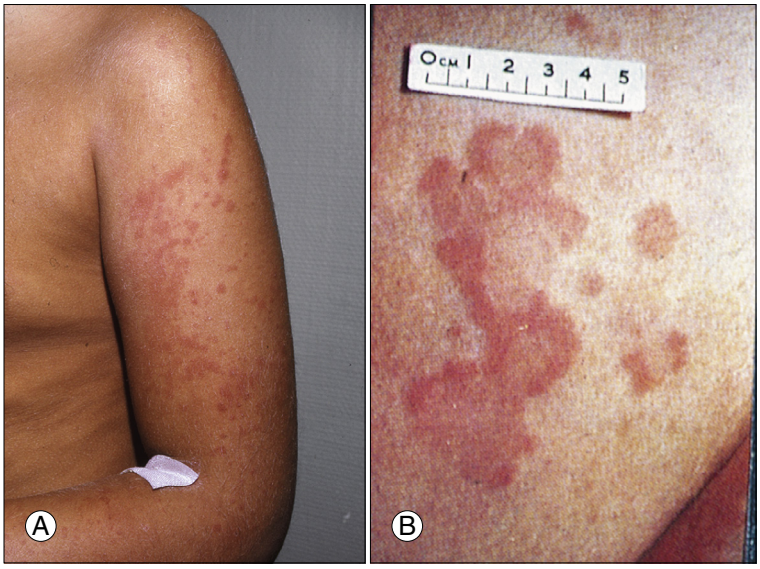

FIG. E2 The rash of systemic juvenile idiopathic arthritis. Larger lesions are becoming confluent **(A).** This must be differentiated from erythema marginatum **(B),** characteristic of the rash seen in rheumatic fever. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

FIG. E3 Oligoarticular juvenile idiopathic arthritis in a 2-year-old girl with arthritis in her left knee. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Kaposi sarcoma (KS) is a low-grade vascular tumor associated with Kaposi sarcoma herpes virus (KSHV) infection and is an AIDS-defining illness. Kaposi sarcoma lesions present predominantly at mucocutaneous sites but may involve all organs and anatomic locations.

SYNONYM

KS

ICD-10CM CODES

C46.0	Kaposi sarcoma of skin
C46.1	Kaposi sarcoma of soft tissue
C46.2	Kaposi sarcoma of palate
C46.3	Kaposi sarcoma of lymph nodes
C46.4	Kaposi sarcoma of gastrointestinal sites
C46.50	Kaposi sarcoma of unspecified lung
C46.51	Kaposi sarcoma of right lung
C46.52	Kaposi sarcoma of left lung
C46.7	Kaposi sarcoma of other sites
C46.9	Kaposi sarcoma, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- AIDS-related KS affects >35% of AIDS cases.
- Highest incidence is in homosexual men.

ETIOLOGY & CLASSIFICATION

KSHV has been isolated from patients with most forms of KS and is thought to be the causative agent. It can be transmitted sexually (homosexual or heterosexual activities) and by other forms of nonsexual contact such as maternal-infant transmission (common in African countries). KSHV establishes lifelong infection in the host, and its DNA is found in all KS lesions. KS prevalence follows KSHV seroprevalence, and in most cases fulminant KS is accompanied and preceded by a rise in KSHV viral load in the blood. KS is primarily the consequence of systemic viral reactivation from a latent reservoir, most likely a lymph node resident B cell. It appears that KS develops in response to severe T-cell depletion or inactivation. Infant immunodeficiency or aging-, chemical-, or HIV-induced immune deficiency is an essential cofactor for the development of KS.

It can be divided into the following four subsets:

1. Classic KS: Occurs mostly in elderly Eastern European and Mediterranean males. It consists initially of violaceous macules and papules with subsequent development of plaques and red-purple nodules. Growth is slow, and most patients die of unrelated causes.
2. Epidemic (AIDS-related) KS: Most frequently occurs in homosexual men. Lesions are generally multifocal and widespread (Fig. E1). Lymphadenopathy may be associated.
3. Endemic KS: Usually affects sub-Saharan African children and adults. An aggressive lymphadenopathic form affects African children in particular.
4. Immunosuppression-associated, or transplantation-associated, KS: Usually associated with immunosuppressive therapy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- KS lesions evolve from early (patch stage) macules into plaques (plaque stage) that may subsequently develop into larger nodules (tumor stage). These tumors may ulcerate, cause marked lymphedema, present as exophytic growths (e.g., cutaneous horns), or invade subjacent tissues (e.g., underlying bone). Different stages can coexist in the same individual at the same time.
- Although KS commonly presents at mucocutaneous sites, tumors may involve lymph nodes as well as visceral organs, most notably the respiratory and gastrointestinal tracts.
- Extracutaneous KS has also been described in unusual anatomic locations, including the musculoskeletal system, nervous system, heart, wounds, within pemphigus lesions, and in blood clots.
- AIDS-related KS: Multifocal and widespread red-purple (Fig. E1) or dark plaques and/or nodules on cutaneous or mucosal surfaces. This is a more aggressive illness with early dissemination.
- Generalized lymphadenopathy at the time of diagnosis is present in >50% of patients with AIDS-related KS; the initial lesions have a rust-colored appearance; subsequent progression to red or purple nodules or plaques occurs (Fig. E2).
- Most frequently affected areas are the face, trunk, oral cavity, and upper and lower extremities.
- The GI tract is the most frequent site of internal involvement in classic KS.
- In AIDS-associated KS, 25% of patients have cutaneous involvement alone, whereas 29% have visceral lesions only (lymph nodes 50%, GI tract 50%, lungs 37%).
- In most patients with HIV-associated KS who initiate HAART, the KS lesions stabilize with decreasing HIV plasma viremia and immune reconstitution, or even resolve completely without any specific treatment.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Stasis dermatitis
- Pyogenic granuloma
- Capillary hemangiomas
- Granulation tissue
- Postinflammatory hyperpigmentation
- Cutaneous lymphoma
- Melanoma
- Dermatofibroma
- Hematoma
- Prurigo nodularis

WORKUP

Diagnosis can generally be made on clinical appearance in a patient with one of the earlier clinical categories; a tissue biopsy is required to confirm the diagnosis.

LABORATORY TESTS

HIV in patients suspected of AIDS

TREATMENT

NONPHARMACOLOGIC THERAPY

Observation is a reasonable option in patients with slowly progressive disease. At present, there is no cure for KS.

GENERAL Rx

- Treatment goals of KS include symptom palliation, prevention of progression and organ compromise, improvement of cosmesis, and relieving psychologic stress. An algorithm for management of AIDS-associated Kaposi sarcoma is illustrated in Fig. E3.
- A significant proportion of HIV-related KS cases can regress following the start of ART alone, indicating the role of immune reconstitution in the management of this disease.
- All types of KS are radiosensitive. Radiation therapy is effective in non-AIDS KS and for large tumor masses that interfere with normal function.
- Surgical excision is restricted for cosmetically disturbing KS lesions, to alleviate discomfort, or to control local tumor growth. It often provides adequate treatment for single lesions and resected recurrences in classic KS.
- Liquid nitrogen cryotherapy can result in complete response in 80% of lesions.
- Interlesional chemotherapy with vinblastine is useful for nodular lesions >1 cm in diameter. Intralesional injection of interferon alfa-2b has also been reported as effective and well tolerated.
- Other local therapies used include laser therapy, cryotherapy, photodynamic therapy, and topical alitretinoin gel.
- Indications for systemic chemotherapy include widespread skin involvement, extensive oral KS, rapidly progressive disease, symptomatic visceral disease, and disease flare.
- Liposomal anthracyclines and paclitaxel are FDA-approved as first-line and second-line monotherapy for advanced KS. Interferon-α has been used with responses dependent upon the underlying immune status of the patient; the best responses are seen in patients with CD4 counts >400/μL.

- Current trials have shown encouraging initial responses in patients with relapsed KS with the use of thalidomide and immune checkpoint inhibitor therapy.
- Sirolimus is effective in inhibiting the progression of dermal KS in kidney transplant recipients.

PEARLS & CONSIDERATIONS

COMMENTS

- Immunosuppression-associated KS usually regresses with the cessation, reduction, or modification of immunosuppression therapy in most patients. Similarly, in HIV patients KS responds concurrently with the decrease in serum HIV RNA and increase in the CD4 count.
- Kaposi sarcoma is associated with an increased risk of developing secondary malignancies (lymphomas, leukemia, myeloma).

RELATED CONTENT

Kaposi Sarcoma (Patient Information)
Acquired Immunodeficiency Syndrome (Related Key Topic)

AUTHOR: **Ritesh Rathore, MD**

FIG. E1 Kaposi sarcoma: epidemic human immunodeficiency virus associated. A and **B,** Plaque lesions. **C,** Violaceous lesion affecting the lateral lower eyelid. **D,** Confluent plaque on the hard palate. **E,** Nodular lesion on the gingiva and nose. (Swartz MH: *Textbook of physical diagnosis, history and examination,* ed 7, Philadelphia, 2014, WB Saunders.)

FIG. E2 Classic Kaposi sarcoma with involvement of the lower extremities. Violaceous patches become plaques **(A, B)** and may develop a nodular component **(C, E)** or verrucous appearance **(D, E).** (B, Courtesy Frank Samarin, MD. C, Courtesy Kalman Watsky, MD.) (From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

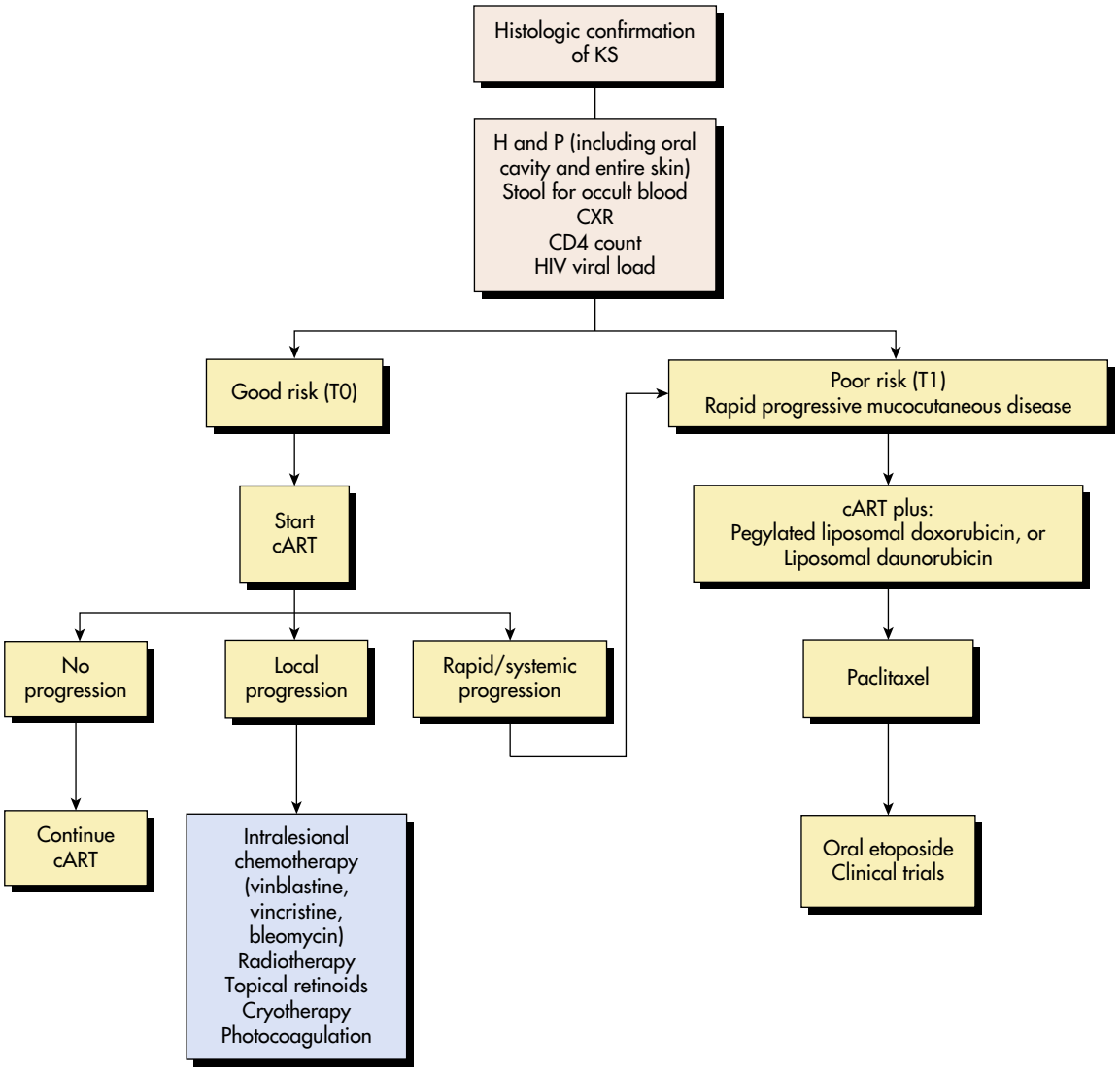

FIG. E3 Algorithms for management of AIDS-associated Kaposi sarcoma *(KS).* *cART,* Combination antiretroviral therapy; *CXR,* chest radiograph. (Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

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BASIC INFORMATION

DEFINITION

Kawasaki disease (KD) is an acute, febrile illness of unknown etiology that predominantly affects children younger than 5 yr old. It is the most common cause of acquired heart disease in children in developed countries. The pathology demonstrates a vasculitis of small- and medium-size blood vessels, with a predilection for the coronary arteries, which can result in coronary artery aneurysms. It is usually a self-limiting condition lasting an average of 12 days if not treated. Box E1 summarizes diagnostic criteria for classic or typical Kawasaki disease.

SYNONYMS

Kawasaki syndrome
Mucocutaneous lymph node syndrome
Infantile polyarteritis
KD

ICD-10CM CODE

M30.3 Mucocutaneous lymph node syndrome [Kawasaki]

EPIDEMIOLOGY & DEMOGRAPHICS

- KD is the leading cause of acquired heart disease in children in developed countries, including the U.S. and Japan. Rheumatic disease is still more common in underdeveloped countries.
- Commonly occurs in children <5 yr (80%); peak incidence is in infants ages 6 to 11 mo. Although occurrence is rare after late childhood, the disease can occur in adolescence.
- The highest incidence is found in Japan (~265 cases/100,000 children younger than 5).

BOX E1 Diagnostic Criteria for Classic or Typical Kawasaki Disease

- Fever for at least 5 days *plus* four of the following features:
  1. Bilateral conjunctival injection
  2. Polymorphous exanthem
  3. Changes in the lips and oral cavity (erythema, cracking of lips, oropharyngeal erythema, strawberry tongue)
  4. Peripheral extremity changes (erythema and swelling of hands and feet; later periungual desquamation, Beau lines)
  5. Cervical lymphadenopathy (≥1.5 cm in diameter)
- Exclusion of other diseases with similar features

The finding of fever plus three criteria in the presence of coronary abnormalities qualifies. In the presence of classic features, experienced clinicians may be able to establish a diagnosis before the fifth day of illness.

(From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.)

- Incidence of KD in the U.S. is estimated to be 25 cases/100,000 children <5 yr of age
- Children of Asian or Pacific Islander descent have a higher incidence of KD compared with those of European or African descent.
- More prevalent in males than females (1.5:1).
- Temporal clustering with winter and early spring predominance has been observed in KD in North America.
- 1% of patients with KD in Japan have a positive family history of KD.
- In Japan, the relative risk of KD in a sibling is 10-fold higher; half of these cases occur within 10 days of the initial case.
- Single-nucleotide polymorphisms in six genes or gene regions have been implicated in susceptibility to KD.
- Variants in transforming growth factor (TGF-β) signaling pathway genes have been associated with aneurysm risk in Europeans.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The clinical presentation is characterized by a systemic inflammation of small- and medium-sized blood vessels.
- There is no specific test that is diagnostic for KD. Confirmation of the diagnosis is based on clinical criteria.
- To meet the case definition of classic or typical KD, a child will have had fever persisting for ≥5 days and the presence of ≥4 of the following five principal features, which need not be present at the same time. The diagnosis may be made with only 4 days of fever in the presence of all 5 principal clinical criteria.
  1. Bilateral, bulbar conjunctival injection with limbic sparing and without exudate.
  2. Oral mucosal changes (Fig. E1): Erythema and fissured/cracking lips, strawberry tongue, diffuse injection of the oropharyngeal mucosa.
  3. Polymorphous exanthem (Fig. E2).
  4. Extremity changes: (a) Acute: Erythema and edema of hands and feet; (b) convalescent: Membranous desquamation of fingertips.
  5. Cervical lymph node enlargement (at least one lymph node ≥1.5 cm in diameter).
- Patients with unexplained fever ≥5 days and 4 criteria are categorized as "incomplete" or "atypical KD," but with evidence of coronary artery aneurysms these individuals are classified as complete KD. These patients are more likely to be infants and older children and consequently are at higher risk for coronary aneurysms.
- The fever of KD is mildly responsive to antipyretics and is usually >102.2 °F (39 °C) and often >104.0 °F (40 °C). If untreated, it lasts for an average of 12 days.
- The rash of KD can be maculopapular, diffuse erythroderma, or erythema multiforme-like; however, vesicles, bullae, purpura, and petechiae are never observed.
- The pericardium, myocardium, endocardium, valves, and coronary arteries may be inflamed during acute illness. Cardiac abnormalities in Kawasaki disease are summarized in Box E2.
- Valvular dysfunction occurs in about 25% of patients regardless of coronary artery involvement and most often involves the mitral valve.
- Approximately 5% of children with KD in the U.S. have cardiovascular collapse and shock at clinical presentation. Often, a diagnosis of bacterial sepsis is suspected at the outset, frequently with negative cultures and persistent fevers, in which case the diagnosis of KD should be suspected.
- Coronary artery aneurysms can develop in as many as 25% of untreated children between 1 to 4 weeks of illness. This subset of patients can develop myocardial infarction (MI) and congestive heart failure over time, which may lead to death.
- New aneurysms seldom form after 6 weeks. Half of the aneurysms show angiographic regression in 1 to 2 yr.
- Coronary z-scores are the preferred method for describing internal diameter of the coronary artery normalized by body surface area and should be used to describe the left anterior descending artery and right coronary arteries over time.
- Morbidity and mortality rates are highest if the aneurysm has both a z-score ≥10 and an absolute dimension ≥8 mm ("giant aneurysms").
- Children with KD who are <1 yr or >6 yr are more likely to develop the cardiac sequelae and are least likely to respond to treatment.

FIG. E1 Cheilitis and oral mucosal involvement observed in a child with Kawasaki disease. (Courtesy Joseph F. Merola. From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

FIG. E2 Polymorphous, exanthematous eruption seen in a patient with Kawasaki disease. (Courtesy Joseph F. Merola. From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

BOX E2 Cardiac Abnormalities in Kawasaki Disease

Acute Stage
- Pericardial effusion
- Decreased myocardial function
- Mitral regurgitation
- Enlargement (ectasia) of coronary arteries
- Arrhythmia (rare)

Subacute Stage
- Coronary aneurysms, irregularity, ectasia
- Significant mitral or aortic regurgitation, or both (rare)
- Coronary aneurysm rupture (very rare)
- Myocardial infarction (rare)

Convalescent Stage
- Persistent coronary aneurysms
- Regressed coronary aneurysms (residual fibrosis)
- Coronary artery stenosis
- Coronary aneurysm rupture (very rare)
- Myocardial infarction (rare)

From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

- Cervical lymphadenopathy is the most commonly absent physical manifestation in atypical KD, followed by exanthem and then extremity changes.
- Oral mucosal changes are the most common manifestations of KD, affecting approximately 90% of cases (either typical or atypical).
- Sensitivity to light, uveitis, as well as nonexudative conjunctivitis may develop.

BOX E3 Associated Noncardiac Features of Kawasaki Disease

Musculoskeletal System
- Arthritis or arthralgia

Central Nervous System
- Aseptic meningitis
- Facial nerve palsy
- Marked irritability
- Sensorineural hearing loss

Gastrointestinal System
- Hydrops of gallbladder
- Abdominal pain, diarrhea
- Hepatic dysfunction, obstructive jaundice
- Pancreatitis

Genitourinary System
- Urethritis, meatitis

Respiratory System
- Perihilar infiltrates or pulmonary nodules
- Preceding respiratory illness

Other
- Erythema and induration of bacille Calmette-Guérin vaccine site
- Anterior uveitis (mild)
- Desquamating groin rash
- Flare of atopic dermatitis or psoriasis
- Peripheral gangrene (young infants)

From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

- Redness and induration can be seen at the site of prior bacille Calmette-Guérin (BCG) inoculation.
- Beau lines (transverse lines across the nails), diarrhea, acute myocarditis, cough, rhinorrhea, dyspnea, arthralgia, and myalgia may also be seen.
- Aseptic meningitis can develop in 40% of cases.
- Interstitial nephritis, acute renal failure in rare cases, KD shock syndrome, and macrophage activation syndrome can also occur.
- Self-limiting arthritis involving large joints including knees, ankles, and hips was reported in 7.5% to 25% of patients, commonly in the second to third week of illness.
- Associated noncardiac features of Kawasaki disease are summarized in Box E3.

ETIOLOGY

- The cause of KD is still unknown despite decades of research.
- Evidence suggests an infectious etiology precipitating an immune-mediated reaction in genetically susceptible individuals.
- One hypothesis is that tropospheric winds from northeastern China carry the etiologic agent of Kawasaki disease from its source to Japan.

Dx DIAGNOSIS

Diagnosis of KD is made on the basis of clinical features (see "Physical Findings & Clinical Presentation"). The hallmark of KD is fever lasting >5 days. Typically, the clinical signs appear over the course of several days. Laboratory evaluation may be helpful in making the diagnosis in atypical KD. The timely diagnosis and treatment of KD are important in preventing complications, especially cardiac complications.

BOX E4 Laboratory Features of Kawasaki Disease

- Leukocytosis with neutrophilia
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein (and other acute-phase reactants)
- Anemia
- Thrombocytosis after week 1
- Sterile pyuria
- Hypoalbuminemia
- Hyponatremia
- Elevated serum levels of aminotransferases and γ-glutamyltransferase
- Plasma lipid abnormalities
- Cerebrospinal fluid pleocytosis
- Synovial fluid pleocytosis

From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

DIFFERENTIAL DIAGNOSIS

- Scarlet fever
- Stevens-Johnson syndrome
- Drug eruption
- Henoch-Schönlein purpura
- Toxic shock syndrome
- Measles
- Rocky Mountain spotted fever
- Epstein-Barr virus, adenovirus, echovirus, and enterovirus
- Juvenile rheumatoid arthritis
- Mercury hypersensitivity (acrodynia)
- Leptospirosis

WORKUP

Clinical findings in addition to laboratory and imaging studies are useful in searching for multiorgan system involvement and complications (e.g., cardiac, lung, liver).

LABORATORY TESTS

The diagnostic criteria do not include any laboratory tests for KD. However, systemic inflammation is characteristic of KD and evidence of systemic inflammation is helpful for the diagnosis of cases suspicious for atypical KD. Laboratory features of Kawasaki disease are summarized in Box E4.

- Complete blood count commonly shows leukocytosis with neutrophil predominance, normochromic normocytic anemia, and thrombocytosis, which usually rises by the second week.
- Abnormal liver function tests are found: Elevated transaminases (hepatic congestion), elevated bilirubin (gallbladder hydrops), and low albumin.
- Inflammatory markers will be increased in KD. If erythrocyte sedimentation (ESR), C-reactive protein (CRP), and platelet count are normal after 7 days of illness, KD is an

unlikely diagnosis. Ongoing inflammation is manifested by:

1. Elevated ESR often ≥40 mm/hr and not uncommonly elevated to levels of >100 mm/hr.
2. Elevated CRP ≥3 mg/dl.

- Thrombocytosis is a characteristic feature of KD but generally does not occur until the second week and peaks in the third week.
- Thrombocytopenia can be seen in the first or second weeks of illness; however, it can be a sign of consumptive coagulopathy (disseminated intravascular coagulation) and a risk factor for development of coronary artery abnormalities.
- Hyponatremia is associated with increased risk of coronary aneurysms.
- Urinalysis may show sterile pyuria.
- Impaired serum lipid profiles with decreased high-density lipoproteins (HDL) and elevated triglycerides and low-density lipoproteins (LDL) can occur.
- Cerebrospinal fluid (CSF) with increased white cell count and a mononuclear cell predominance without elevated CSF protein or glucose is found.
- Arthrocentesis of joints usually demonstrates purulent-appearing fluid with 125,000 to 300,000 white cells/mm^3, normal glucose level, and negative gram stain and cultures.
- The discovery of a 13-transcript gene expression signature distinguished patients with KD from others with bacterial, viral, and inflammatory illnesses and provides hope for development of a diagnostic test that will allow earlier detection of KD.

IMAGING STUDIES

- ECG changes including arrhythmias, abnormal Q waves, prolonged PR and/or QT intervals, occasionally low voltage, and ST-T wave changes can be seen.
- Chest radiograph may reveal pulmonary infiltrates. Cardiomegaly may also be present.
- Echocardiogram is the mainstay of diagnosis of KD. It is recommended at the time of illness and repeated in 1 to 2 weeks and then again 4 to 6 weeks after treatment (Class IB indication) for uncomplicated KD. Echocardiogram should include careful assessment of the coronary arteries for size and aneurysms, mural or intraluminal thrombi, effusions, valve function, and myocardial function.
- Patients with complicated KD or evolving coronary artery abnormalities (Z score >2.5) detected during acute illness should have echocardiographic evaluation repeated at least twice per week until luminal dimensions have stopped progressing, to determine risk for and presence of thrombosis (Class IB).
- A monthly echocardiogram until the third month after illness onset is recommended because failure to escalate thromboprophylaxis in time with the rapid expansion of aneurysms is the primary cause of morbidity and mortality (Class IIa).
- With respect to cardiovascular testing during long-term follow-up, echocardiographic measurements of the coronary artery become less reliable as patients grow. For that reason, advanced imaging techniques, such as computerized tomographic angiography (CTA) and magnetic resonance angiography (MRA), are becoming more popular.
- Intravascular ultrasound can assess for luminal irregularities of the coronary arteries.
- Exercise testing with myocardial perfusion studies can be done to assess for coronary blood flow and the presence of myocardial ischemia.

BOX E5 Treatment of Kawasaki Disease

Acute and Subacute Stages

- IVIG 2 g/kg infusion over 10 to 12 hours *plus* aspirin 80 to 100 mg/kg per day in four divided doses (until patient is afebrile at least 3 to 4 days; some recommend until 14th day of illness); then 3 to 5 mg/kg once daily for 6 to 8 weeks.
- IVIG may be repeated if fever persists or recurs together with at least one classic sign of disease and/or elevated C-reactive protein level.
- For patients thought to be at particularly high risk of coronary complications, an adjunctive course of corticosteroid may be considered, although optimal dosing and duration are unclear.

Convalescent Stage

- No coronary abnormalities: No therapy
- Transient coronary abnormalities: Aspirin 3 to 5 mg/kg once daily at least until resolution of coronary abnormalities
- Persistent, small to medium coronary aneurysms: Aspirin 3 to 5 mg/kg once daily
- Giant or multiple small coronary aneurysms: Aspirin 3 to 5 mg/kg once daily, with or without clopidogrel 1 mg/kg/day, with warfarin or low-molecular-weight heparin for most patients
- Coronary obstruction: Thrombolytic therapy, surgical or interventional procedures

IVIG, intravenous immunoglobulin
From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

TREATMENT

The goal of treatment of KD in the acute phase is directed at reducing clinical symptoms and reducing inflammation in the systemic and coronary arteries and preventing arterial thrombosis. Standard treatment, including IVIG and aspirin, is usually effective. The disease may recur. Coronary artery abnormalities are serious sequelae of Kawasaki disease. Long-term therapy in individuals who develop coronary aneurysms is aimed at preventing myocardial ischemia or infarction. Box E5 summarizes treatment of Kawasaki disease.

BOX E6 Rescue Therapy for Patients Not Responding to Standard Therapy

- Persistent or recurrent fever and/or elevated serum CRP levels 36 to 48 hours after primary therapy
  1. Repeat 2 g/kg IVIG
  2. Failure of two doses of IVIG: Therapeutic options
     a. Third dose of IVIG (2 g/kg) with or without tapering course of prednisone starting at 2 mg/kg
     b. IV methylprednisolone (usually 30 mg/kg daily in three doses) with or without subsequent oral steroid, tapered over 1 to 3 weeks
     c. Infliximab (5 mg/kg) single dose
     d. Cyclosporine (4 to 8 mg/kg daily for 14 to 21 days), usually IV, with monitoring of serum levels and dosing adjustments
     e. Methotrexate orally (10 mg/m^2) × 1 or 2 doses

CRP, C-reactive protein; *IV,* intravenous; *IVIG,* intravenous immunoglobulin
From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

Box E6 describes rescue therapy for patients not responding to standard therapy.

ACUTE GENERAL Rx

- IV immunoglobulin (IVIG) with high-dose aspirin is the treatment of choice in children diagnosed with complete KD or suspected KD, and ideally should be given within the first 10 days of the illness.
- IVIG is given as 2 g/kg over 10 to 12 hr as a single infusion with high-dose ASA of 80 to 100 mg/kg/day (antiinflammatory dosing) divided into four doses.
- High-dose ASA is given until the patient is afebrile for 48 to 72 hours. Low-dose ASA of 3 to 5 mg/kg/day (antithrombotic dosing) in a single daily dose is given until the followup echocardiogram at 6 to 8 weeks is normal, or it is continued indefinitely if coronary artery abnormalities exist.
- IVIG should not be administered beyond the tenth day of illness in absence of fever, significant elevation of inflammatory markers, or coronary artery abnormalities.
- IVIG infusion results in ESR elevation. CRP is not affected by IVIG and can be used to follow disease activity.
- NSAIDs (e.g., ibuprofen) are not effective in the treatment of KD and may be harmful due to their involvement in the cyclooxygenase pathway.
- Single-dose methylprednisolone should not be administered with IVIG as routine primary therapy for patients with KD (Class IIIB).
- Approximately 10% to 20% of patients develop recrudescent or persistent fever. If fever persists beyond 36 hours after completion of IVIG, patients are considered IVIG resistant.
- A second dose of IVIG 2 g/kg IV over 8 to 12 hr should be considered at least 36 hr after

the end of the first IVIG infusion (Class IIB) in IVIG-resistant patients. Most experts recommend withholding glucocorticoids unless fever persists after at least two courses of IVIG. Administration of pulse dose methylprednisolone 20 to 30 mg/kg intravenously for 3 days with or without subsequent course and taper of oral prednisone may be considered as an alternative to a second IVIG infusion for retreatment in patients with recurrent or recrudescent fever.
- Administration of a longer course of tapered corticosteroids (2 to 3 weeks), together with IVIG and ASA, may be considered for treatment in IVIG-resistant patients (Class IIB).
- Other therapies including urinary trypsin inhibitor (ulinastatin), pentoxifylline, infliximab (monoclonal antibody against tumor necrosis factor-α), etanercept, plasma exchange, abciximab (platelet glycoprotein IIb/IIIa receptor inhibitor), and immunosuppressive agents such as cyclosporine A have been used, but data are limited.
- Infliximab may be considered as an alternative to a second IVIG infusion or corticosteroid infusion in IVIG-resistant patients.
- Cyclosporine may be considered for patients in whom a second IVIG infusion, infliximab, or steroids have failed.
- Immunomodulatory monoclonal antibody therapy (except TNF-α blockers), cytotoxic agents and plasma exchange may be considered in those who are highly refractory.
- Patients with giant coronary artery aneurysms (>8 mm diameter) have a higher risk of coronary artery thrombosis. Aggressive systemic anticoagulation with either low-molecular-weight heparin or warfarin for an international normalized ratio (INR) target of 2.0 to 3.0 and antiplatelet therapy with ASA is needed to improve outcomes and prevent thrombosis within the aneurysm and MI.
- Most patients with moderate to large aneurysms should be maintained on a second antiplatelet agent.
- Acute coronary thrombosis should be managed with thrombolytic agents under cardiology supervision.

CHRONIC Rx

- All patients with a history of coronary artery aneurysm require lifelong surveillance to prevent coronary thrombosis and to treat myocardial ischemia and associated complications.
- Based upon the size of the aneurysm and the age of the patient, other anticoagulation and antiplatelet therapy may be added.
- Coronary revascularization (surgical or percutaneous) is performed for symptoms of angina or evidence of a significant territory of inducible ischemia on stress testing.

NONPHARMACOLOGIC THERAPY

- Emollient creams for peeling skin and balms for fissured lips
- Salt restriction in patients with congestive heart failure
- Oxygen in selected patients

DISPOSITION

- Mortality rate of children with KD is 0.5% to 2.8%, usually from coronary aneurysm thrombosis and MI.
- Death usually occurs in the third to fourth week of the illness.
- Before the use of IVIG, 25% of all patients with KD developed coronary artery aneurysms; this has fallen to 3% to 5% with the use of IVIG.
- Despite treatment with IVIG, 20% of children develop transient coronary artery dilation in the proximal LAD or proximal RCA, 5% develop coronary artery aneurysms, and 1% develop giant aneurysms.
- 50% of coronary artery aneurysms return to normal lumen diameter by 1 to 2 yr after onset of illness.
- Aspirin in high dose decreases the coronary artery involvement to <5% from 25%.
- IVIG has also been shown to improve left ventricular function during the acute stages of the disease.
- Risk factors for the development of coronary aneurysms or giant coronary aneurysms 8 mm or greater are:
  1. Fever lasting >10 days.
  2. Age <1 yr or >6 yr.
  3. Male.
  4. Recurrence of fever.
- A subset of genetically susceptible children (<25%) will suffer irreversible damage to the coronary arterial wall.
- Recurrence is in about 1% to 3% of cases most commonly within 1 yr of the initial occurrence.
- Aspirin should be discontinued upon exposure to varicella or influenza to decrease the risk of developing Reye syndrome.
- Measles, mumps, and varicella immunizations should be deferred for 11 mo after receiving high-dose IVIG.

REFERRAL

Multiple specialists may be consulted to assist in the diagnosis of KD, including dermatology, rheumatology, and infectious disease. Cardiology consultation is recommended in any patient with cardiac involvement and in the long-term follow-up of patients with KD. For patients who are pregnant or considering pregnancy, referral should be made to a high-risk obstetric service.

PEARLS & CONSIDERATIONS

COMMENTS

- The mechanism of action of IVIG therapy for KD remains unknown. Mechanism of action includes modulation of cytokine production, neutralization of toxins or other pathogenic agents, augmentation of regulatory T-cell activity, antibody synthesis suppression, and antiidiotypic antibody provision.
- Failure of corticosteroids suggests that the inflammatory response is different compared with other vasculitic conditions.
- Live vaccine (varicella, measles) administration is suggested to be postponed for 11 mo in children treated with IVIG because it interferes with vaccine immunogenicity.

PREVENTION

- Without a known etiologic agent for KD, primary prevention is not possible.
- Thrombosis leading to MI in a stenotic or aneurysmal coronary artery is the leading cause of death in these children and occurs most often in the first yr after illness onset. Therefore, serial imaging and occasionally stress testing are necessary in patients with significant coronary artery abnormalities (by echocardiography when possible, occasionally by CT coronary angiography or invasive angiography if other imaging is inadequate).

RELATED CONTENT

Kawasaki Disease (Patient Information)

AUTHORS: **Ailin Barseghian, MD,** and **Pranav M. Patel, MD, FACC, FAHA, FSCAI**

SUGGESTED READINGS

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BASIC INFORMATION

DESCRIPTION

Keloid may be defined as a benign growth of dense fibrous tissue developing from an abnormal healing response to cutaneous injury, extending beyond the original borders of the wound or inflammatory response (Fig. E1).

In 1806, Alibert used the term *cheloide,* derived from the Greek *chele,* meaning crab's claw, to describe lateral growth of tissue into unaffected skin.

ICD-10CM CODE
L91.0 Hypertrophic scar

EPIDEMIOLOGY & DEMOGRAPHICS

- Keloid is seen 5 to 15 times more often in pigmented ethnic groups than in whites.
- Its prevalence is 16% in blacks and Hispanics.
- The highest incidence is seen in the second decade of life.
- It affects both sexes equally.
- Combined incidence of keloid and hypertrophic scar ranges from 40% to 70% after surgery to up to 91% after burns.

ETIOLOGY

- Wounds from trauma, surgery, or body piercing (Fig. E2)
- Burns
- Other injuries such as insect bites, vaccination, folliculitis, or acne
- Rarely can be spontaneous without obvious injury
- Familial predisposition seen in some patients

RISK FACTORS:

- Family history of keloids
- Personal history of keloids
- Blacks, Hispanics, and Asians
- Pregnancy
- Puberty
- Patients with blood group A
- Injury over bones

PATHOGENESIS:

- Pathophysiology of keloid is not completely understood.
- Caused by benign dermal fibroproliferation because of disorder in the regulation of cellularity during the wound healing process.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Keloids usually appear within a few months of the injury, in contrast to hypertrophic scars, which develop within a few weeks. At times, it could take up to 1 yr to appear because the growth is slow.
- Keloids are often symptomatic in the early stages. Common complaints are pruritus, burning, pain, and tenderness.
- Keloids are commonly seen on the shoulders, sternum, upper back, nape of neck, ear lobes, mandibular border, and cheek. Hands and feet are often spared.
- Skin lesions vary from papules to nodules to large tuberous lesions (Fig. E3). They have the normal skin color most of the time with well-defined borders. Early on they can appear erythematous; older lesions may be hypopigmented or hyperpigmented. They can be firm to hard in consistency with smooth surface and are tender to touch. Hair follicles are absent in keloids.
- Unlike with hypertrophic scar, in keloids, the scar extends beyond the margin of the initial wound.

FIG. E1 Keloids. An abnormal reparative reaction to skin injury, keloids are characterized by proliferation of fibroblasts and collagen that extends beyond the margins of the original wound. (From Zitelli BJ, Davis HW: *Atlas of pediatric physical diagnosis,* ed 5, Philadelphia, 2007, Mosby.)

DIAGNOSIS

Workup is usually not necessary because it is a clinical diagnosis.

Biopsy is usually avoided because it may increase the keloid size. When biopsy is done, the histology shows randomly organized large collagen fibers in a dense connective tissue matrix. In fact, both major components of extracellular matrix, collagen and glycosaminoglycans, are increased.

DIFFERENTIAL DIAGNOSIS

- Hypertrophic scar
- Dermatofibroma
- Dermatofibrosarcoma protuberance
- Desmoid tumor
- Foreign body granuloma
- Scar with sarcoidosis
- Lobomycosis

TREATMENT

- There is no universally accepted treatment protocol. Prevention is the best strategy.
- Combination treatment is most effective.
- Surgical excision using cold knife followed by intralesional steroids is the preferred method.
- Treatment outcome is the best when it is initiated shortly after the keloid formation.
- Different treatment options include:
  1. Unlike with hypertrophic scars, surgery alone is associated with a 55% to 100% recurrence rate in patients with keloids. Results are significantly better when it is followed by intralesional steroids, radiotherapy, pressure therapy, or silicone application. Both complete and near-total excision has been advocated. Few recommend core extirpation. Use of Z-plasties or any wound-lengthening techniques is strongly discouraged.
  2. Intralesional steroid every 2 to 4 wk is administered either alone or following surgery. Duration of treatment depends on the treatment response. Triamcinolone is the most studied steroid and is used at a concentration of 10 to 40 mg/ml. Higher concentration is used for denser, more recalcitrant lesions, and those located in trunks or extremities. It could be used in combination with lidocaine to reduce the discomfort. A 27- to 30-gauge needle is used for its administration. To distribute the suspension evenly, it should be injected while continuously advancing the needle. No more than 20 to 30 mg of the drug is used during each treatment. Liquid nitrogen is applied to the injection briefly for 2 to 4 seconds about 10 to 15 min before steroid injection for better dispersal of the steroid and to minimize deposition into surrounding

FIG. E2 Keloid of ear lobe after piercing. (From Kliegman RM et al: *Nelson textbook of pediatrics,* Philadelphia, 2011, Saunders.)

FIG. E3 Extensive keloids. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Saunders.)

normal tissue. Hypopigmentation, skin atrophy, ulceration, and telangiectasia are the side effects associated with this treatment.

3. Cryotherapy has been used for smaller lesions. When this treatment is chosen, the entire lesion is treated with two to three freeze-thaw cycles of 30 seconds' duration each. Most lesions need 2 to 10 treatment sessions at 4-wk intervals. Pain and hypopigmentation are the main adverse events.
4. Silicone gel sheeting or cushioning can prevent keloids from recurring after surgery. These are applied as soon as reepithelialization is achieved and are worn for at least 12 hr/day for 2 to 4 mo.
5. Application of pressure by compression devices has been advocated in the treatment of keloids. These compression treatments include button compression, pressure earrings, pressure gradient garments, ACE bandages, elastic adhesive bandages, compression wraps, Spandex or Elastane bandages, and support bandages. About 24 to 40 mm Hg of pressure must be maintained. It must be instituted for long periods (>23 hr/day for 6-12 mo) before significant effect can be achieved. Unfortunately, many parts of the body are not amenable to this pressure. Patient discomfort frequently reduces compliance.
6. Radiation after surgery can also reduce the recurrence rate. X-rays of 700 to 1500 cGy in fractions over five to six treatments are the most frequently used treatment. Radiation is usually initiated within 10 days, preferably within 24 hr of surgery. It is avoided in pediatric and pregnant patients. At times, brachytherapy with interstitial iridium 192 is used. Most physicians use radiation only for keloids over the extremities. The reported risk of radiation-induced malignancy is theoretical.
7. 5-Fluorouracil can be used as an individual agent, after surgery, or in combination with intralesional steroids. Weekly injection of 0.5 to 2 ml at a 50 mg/ml concentration of 5-fluorouracil for 12 wk is the recommended dose.
8. Superiority of laser use to simple excision currently has not been demonstrated.
9. Topical 5% imiquimod cream has some role when used following surgery locally every night for a minimum of 2 mo.
10. Other treatments include Cordran tape, bleomycin, interferon, vitamin A, nitrogen mustard, antihistamines, zinc, tacrolimus, sirolimus, allantoin, botulinum toxin, colchicine, salicylic acid, calcipotriol, NSAIDs, d-penicillamine, relaxin, quercetin, dinoprostone, doxorubicin, ACE inhibitors, hyaluronidase, pentoxifylline, tranilast, mitomycin-C, tamoxifen, silver sulfadiazine, onion extract, vitamin E, intralesional verapamil.

FOLLOW-UP

Because of the high risk of recurrence, a follow-up of at least 12 mo is necessary to fully evaluate the effectiveness of therapy.

PREVENTION

- Avoid nonessential surgery such as body piercing, which carries a high risk for keloid formation.
- LASIK eye surgery and CO_2 laser resurfacing should be avoided in patients with a tendency for keloids.
- Use a laparoscopic approach when surgery is needed.
- Avoid making incisions over joint spaces or over midchest and ensure that they follow skin creases.
- Handle tissue gently during surgery.
- Ensure good hemostasis intraoperatively.
- Use tension-free primary wound closure.
- Use monofilament, synthetic permanent sutures.
- Use adhesives instead of sutures when possible for closure of wounds.
- Compressive pressure dressing is preferred in high-risk patients following surgery.
- Avoid wound infection.
- Avoid tattoos.
- Aggressively treat inflammatory acne.

COMPLICATIONS

- Psychological effects secondary to disfigurement.
- Contracture from keloids may result in loss of function if overlying a joint.

PROGNOSIS

- Unlike hypertrophic scars, keloids do not regress with time. However, they may continue to expand in size for decades.
- Regardless of the type of treatment, there is a high recurrence rate.
- Keloids never become malignant.

RELATED CONTENT

Keloids (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

BASIC INFORMATION

DEFINITION

Klinefelter syndrome is a congenital disorder in which a 47,XXY chromosome complement is associated with hypogonadism and infertility.

SYNONYM

47,XXY Hypogonadism

ICD-10CM CODE
Q98.4 Klinefelter syndrome, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1 in 500 men (most common sex chromosome disorder)
GENETICS: The most common mosaic complement is 46,XY/47,XXY. 47,XXY karyotypes 48,XXYY, 48,XXXY, and 49,XXXXY have been reported. The manifestations vary in severity by patient (Table E1). This sex chromosome mosaicism is believed to account for the variable presentation. Fertility, although very rare, has been reported in men with Klinefelter syndrome.

TABLE E1 Clinical Features of Klinefelter Syndrome

Karyotype	47,XXY
Inheritance	Sporadic; associated with advanced maternal age; nondisjunction during first or second meiotic division in either parent (67% maternal, 33% paternal); mitotic nondisjunction
Genitalia	Male
Wolffian duct derivatives	Normal
Müllerian duct derivatives	Absent
Gonads	Small, firm testes; seminiferous tubule dysgenesis; azoospermia; Leydig cell hyperplasia
Habitus	Poor to normal virilization at puberty: Gynecomastia; disproportionately long legs
Hormone profile	Testosterone levels variable but usually decreased; increased levels of plasma LH and FSH postpubertally

FSH, Follicle-stimulating hormone; *LH*, luteinizing hormone.
From Larsen PR et al: *Williams textbook of endocrinology*, ed 10, Philadelphia, 2003, Saunders.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Classic triad: Small firm testes, azoospermia, and gynecomastia.
- Prepubertal: Small testes; gonadal volume <1.5 ml is a result of loss of germ cells before puberty.
- Postpubertal: Gynecomastia (periductal fat growth) with small, firm testes. Exaggerated growth of the lower extremities results in a decreased crown-to-pubis/pubis-to-floor ratio. There are diminished strength, diminished ability to grow a full beard or mustache, and infertility. Decreased intellectual development and antisocial behavior are believed to occur with high frequency.

ETIOLOGY

- Several postulated mechanisms: Nondisjunction during meiosis and mitosis and anaphase lag during mitosis or meiosis
- Reason: Maternal age
  1. The incidence of Klinefelter syndrome rises from 0.6% when the maternal age is ≤35 yr to 5.4% when the maternal age is >45 yr.
  2. Of note, the extra X chromosome has a paternal origin as often as a maternal origin.

DIAGNOSIS

- Markedly elevated follicle-stimulating hormone levels.
- Total plasma testosterone levels are decreased in 50% to 60% of patients.
- Free testosterone levels are decreased.
- Plasma estradiol is increased, stimulating the increase in levels of testosterone-binding globulin with resultant decrease in the testosterone/estradiol ratio, which is thought to be the cause of gynecomastia.

LABORATORY TESTS

- Normal to low serum testosterone
- Increased sex hormone–binding globulin (acts to further suppress any available free testosterone)
- Normal to increased estradiol (a result of augmented peripheral conversion of testosterone to estradiol)
- Testis biopsy shows azoospermia, Leydig cell hyperplasia, hyalinization, and fibrosis of the seminiferous tubules. Mosaics may have focal areas of spermatogenesis and, on rare occasions, sperm may appear in the ejaculate. The extra X chromosome is the pivotal factor controlling spermatogenesis and also affects neuronal function directly, leading to the behavioral abnormalities related to decreased IQ
- Buccal smear: One sex chromatin body
- Prepubertal males: Gonadotropin levels are normal
- Postpubertal males: Gonadotropin levels are elevated even when the testosterone level is normal
- Disease associations:
  1. Malignancies: Breast cancer (20 times >XY men and 20% the rate of occurrence in women), nonlymphocytic leukemia, lymphomas, marrow dysplastic syndromes, extragonadal germ cell neoplasms
  2. Autoimmune disorders: Chronic lymphocytic thyroiditis, Takayasu arteritis, taurodontism (enlarged molar teeth), mitral valve prolapse, varicose veins, asthma, bronchitis, osteoporosis, abnormal glucose tolerance testing, diabetes, varicose veins

TREATMENT

- Revolves around three facets of Klinefelter syndrome:
  1. Hypogonadism: Androgen replacement in the form of testosterone
  2. Gynecomastia: Cosmetic surgery
  3. Psychosocial problems: Androgen therapy and educational support
- After extensive genetic counseling, intracytoplasmic sperm insertion has been used to treat infertility with limited success in mosaic men

PEARLS & CONSIDERATIONS

COMMENTS

- Androgen therapy should not be used in the case of severe mental retardation
- Rule out breast and prostate cancer before initiating or continuing androgen therapy
- Androgen therapy will not improve fertility; it may suppress any spermatogenesis that is taking place within the testes
- Other causes of primary hypogonadism:
  1. Myotonic muscular dystrophy
  2. Sertoli cell–only syndrome
  3. Kartagener syndrome
  4. Anorchia
  5. Acquired hypogonadism

RELATED CONTENT

Klinefelter Syndrome (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

Korsakoff Psychosis

BASIC INFORMATION

DEFINITION

Korsakoff psychosis (KP) is a disorder of declarative learning and memory that results from thiamine deficiency, largely (90%) secondary to chronic alcohol abuse in industrialized nations. It is classically, but not always, seen following the presentation of Wernicke encephalopathy (see "Wernicke Syndrome").

SYNONYMS

Korsakoff syndrome
Wernicke-Korsakoff syndrome
Alcoholic polyneuritic psychosis
KPF

ICD-10CM CODE

F10.96 Alcohol use, unspecified with alcohol-induced persisting amnestic disorder

EPIDEMIOLOGY & DEMOGRAPHICS

- The incidence of KP is declining as a result of improved patient nutrition and awareness by health professionals
- More common in males
- Age of onset evenly distributed between ages 30 and 70 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Impaired anterograde memory as a core feature, and commonly retrograde memory is impaired to a varying extent as well.
- Remote memory is relatively less impaired on neuropsychiatric testing.
- Confabulation (the fabrication of false memories to fill memory gaps) is common.
- Severe declarative amnesia and concomitant deficits in executive function result in compromised autonomy.

ETIOLOGY

KP is the result of thiamine deficiency. Thiamine deficiency is commonly seen in chronic alcoholism and other malnourished populations (anorexia, bariatric surgery, malignancy). It may also occur from prolonged infusion of dextrose-containing fluids without thiamine repletion.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Stroke, trauma, or tumor affecting the temporal lobes or hippocampi
- Cerebral anoxia
- Transient global amnesia
- Dementia of multiple causes

WORKUP

A high index of suspicion should be maintained in chronic alcoholism and malnourished states.

LABORATORY TESTS

- CBC
- Serum chemistries
- Erythrocyte thiamine transketolase concentration before and after replacement with thiamine pyrophosphate

IMAGING STUDIES

MRI brain may show nonspecific T_2 hyperintensities in the diencephalon and mesencephalon but is not pathognomonic. However, MRI/CT may be helpful in ruling out other diagnoses.

TREATMENT

NONPHARMACOLOGIC THERAPY

A supervised environment may be required.

- Acute: Treatment should be initiated in all patients with clinical suspicion of Wernicke encephalopathy (WE). Thiamine supplementation should precede glucose administration in all patients at risk for WE lest they develop Korsakoff syndrome.
- Alcoholics with WE: Treat with 500 mg of thiamine hydrochloride (dissolved in 100 ml of normal saline) infused intravenously over 30 minutes three times daily for 2 to 3 days.
- If a response is observed, continue with 250 mg of thiamine hydrochloride intravenously or intramuscularly daily until clinical improvement ceases.
- Nonalcoholics with WE: Treat with 200 mg of thiamine hydrochloride (dissolved in 100 ml of normal saline) infused intravenously over 30 minutes three times daily for 2 to 3 days.
- Parenteral magnesium must be infused concurrently with thiamine.
- Side effects of parenteral thiamine hydrochloride may include generalized pruritus, transient local irritation or, rarely, anaphylactic or anaphylactoid reactions.

CHRONIC Rx

Recommended oral dose after completed parenteral treatment for WE: Thiamine 30 to 100 mg twice daily for long-term thiamine replacement.

- Individuals with KP rarely recover; therefore, one must consider the need for additional support and supervision within the home versus placement in a long-term care facility.

REFERRAL

- Neurology to confirm the diagnosis and rule out other causes
- Neuropsychiatric testing to assess baseline functioning and further deterioration

PEARLS & CONSIDERATIONS

COMMENTS

- KP is frequently misdiagnosed or underdiagnosed!
- Memory problems may persist even in "recovered" patients.
- Replace thiamine in patients at risk even if clinical symptoms are not evident.
- Prolonged use of dextrose-containing IV fluids without supplemental thiamine may precipitate KP.
- Strengthening of procedural memory and encouragement of procedural learning can help restore some of the patient's autonomy.

RELATED CONTENT

Alcohol Use Disorder (Related Key Topic)
Delirium (Related Key Topic)
Vitamin Deficiency (Hypovitaminosis) (Related Key Topic)
Wernicke Syndrome (Related Key Topic)

AUTHORS: **Angad Jolly, PhD, Joseph S. Kass, MD, JD, FAAN,** and **Alexandra Boske, MD**

SUGGESTED READING

Oudman E et al: Procedural learning and memory rehabilitation in Korsakoff's syndrome: a review of the literature, *Neuropsychol Rev* 25:134-148, 2015.

BASIC INFORMATION

DEFINITION

Labyrinthitis is a peripheral vestibulopathy characterized by acute onset of vertigo usually associated with nausea and vomiting. It can be associated with hearing loss and gait abnormalities and may be either serous or purulent.

SYNONYMS

Acute labyrinthitis
Acute vestibular neuronopathy
Vestibular neuronitis
Viral neurolabyrinthitis

ICD-10CM CODES

H81.23	Vestibular neuronitis, bilateral
H83.09	Labyrinthitis, unspecified ear
H83.01	Labyrinthitis, right ear
H83.02	Labyrinthitis, left ear
H83.03	Labyrinthitis, bilateral

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Most common cause of prolonged spontaneous vertigo associated with nausea at any age
PREDOMINANT AGE: Any

PHYSICAL FINDINGS & CLINICAL PRESENTATION

CLINICAL PRESENTATION:

- Vertigo, nausea, and vomiting with onset over several hours.
- Symptoms usually peak within 24 hours, then resolve gradually over several weeks.
- During the first day, the patient usually has difficulty focusing the eyes because of spontaneous nystagmus.
- Usually has benign course with complete recovery within 1 to 3 mo, although older patients may have intractable dizziness that persists for many months.

PHYSICAL FINDINGS

- Nystagmus
- Nausea
- Vomiting
- Vertigo worsening with head movement
- Abnormal caloric ENG tests
- May have hearing loss in the affected ear or ears
- Normal otoscopic exam typically
- Normal neurologic exam; may have signs of vestibular loss, such as a positive head thrust test

ETIOLOGY

Symptoms often preceded for 1 to 2 wk by a viral-like illness. Labyrinthitis may be either bacterial or viral and may be either tympanogenic (i.e., resulting from spread of infection into the inner ear from the middle ear, antrum, or petrous apex), meningogenic, or hematogenic from encephalitis or brain abscess. The round window membrane is considered the most likely pathway of inflammatory mediators from the middle to the inner ear that subsequently give rise to labyrinthitis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute labyrinthine ischemia (ischemic stroke of the labyrinthine artery)
- Labyrinthine fistula
- Benign paroxysmal positional vertigo
- Ménière disease
- Cholesteatoma
- Drug-induced vestibulocochlear nerve damage
- Vestibulocochlear nerve (cranial nerve VIII) tumor
- Head trauma
- Vertebrobasilar stroke
- Dehiscence of the superior semicircular canal

WORKUP

- Otoscopic examination
- Neurologic examination, with close attention to cranial nerves
- Bedside test of vestibular function, specifically head thrust or head heave test
- Audiogram if symptoms accompanied by hearing loss
- Caloric test if presentation is atypical

LABORATORY TESTS

- Routine laboratory tests are generally not helpful.
- If there is a history of significant emesis, check electrolytes, BUN, and creatinine.

IMAGING STUDIES

- Imaging studies are usually not necessary.
- Gadolinium-enhanced MRI may show enhancement of bony labyrinth. MRI of the brain with and without contrast with fine cuts through the internal auditory canal is indicated if there is an abnormal cranial nerve exam, headache, concern for stroke, or suspicion of cranial nerve VIII nerve tumor.
- Head CT with fine cuts through temporal bones is indicated if there is a history of trauma or suspicion of cholesteatoma.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Reassurance
- Initial bed rest, then encourage increase in activity as tolerated

ACUTE GENERAL Rx

- Treatment is with antiemetics such as promethazine or ondansetron; vestibular suppressants such as the antihistamines meclizine or diphenhydramine; the anticholinergic scopolamine; and the benzodiazepines diazepam or lorazepam. These medications should only be continued for a few days during the acute phase. Some of these medications, especially scopolamine, should be used with caution in the elderly. Methylprednisolone 100 mg per day for 3 days, with slow taper over 3 wk.
- Valacyclovir has not been shown to be helpful.

CHRONIC Rx

- No specific pharmacologic chronic therapy.
- Vestibular rehabilitation is useful for patients with persistent symptoms.

DISPOSITION

Usually does not require hospital admission unless the patient is unable to tolerate oral intake of liquids

REFERRAL

- Refer if symptoms persist or neurologic abnormalities are present.
- Consider vestibular rehabilitation, particularly in the elderly.

PEARLS & CONSIDERATIONS

COMMENTS

Labyrinthitis is a term that usually implies peripheral vestibulopathy associated with hearing loss. The term *vestibular neuronitis* is typically used when hearing is not affected. Despite this technical distinction, many physicians use these terms interchangeably.

RELATED CONTENT

Labyrinthitis (Patient Information)
Benign Paroxysmal Positional Vertigo (Related Key Topic)
Vestibular Neuronitis (Related Key Topic)

AUTHORS: **Michael Pohlen, MD, Joseph S. Kass, MD, JD, FAAN,** and **Sharon S. Hartman Polensek, MD, PhD**

BASIC INFORMATION

DEFINITION

Lactic acidosis (LA) is a life-threatening condition characterized by accumulation of lactate, especially L-lactate, in the body. It represents an imbalance of lactate overproduction or underutilization usually resulting from tissue hypoperfusion and hypoxia (type A LA), or caused by toxins or medication-induced cellular toxicity (type B LA).

SYNONYMS

Lactic acidosis
Hyperlactatemia
LA

ICD-10CM CODE
E87.2 Acidosis

EPIDEMIOLOGY & DEMOGRAPHICS

RISK FACTORS:

- Sepsis
- Liver disease
- Severe anemia
- Severe trauma
- Advanced heart failure
- Cardiogenic shock
- Hypovolemic shock
- Diabetes mellitus
- Seizures
- Vigorous exercise
- Cocaine
- Medications (metformin, salicylates, beta 2 agonists, propofol, nucleoside reverse-transcriptase inhibitors)
- Thiamine deficiency
- Pheochromocytoma

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Shock, dehydration (tachycardia, decreased skin turgor, decreased urine output, hypotension, dry mucous membranes)
- Possible clues or precipitating factors (sepsis, bleeding, intoxication)
- Altered mental status
- Nausea, vomiting, abdominal pain
- Weakness, lethargy
- Tachypnea, rapid shallow breathing caused by acidosis (Kussmaul breathing)

ETIOLOGY

- Table E1 summarizes medication-induced lactic acidosis. Table E2 describes other pathologies associated with lactic acidosis.
- Type A: Related to tissue hypoperfusion or hypoxia, is probably the most common cause of LA.
  1. Sepsis leading to systemic hypotension and microcirculation dysfunction leading to decreased extraction of oxygen and lactate clearance by the peripheral tissues
  2. Shock: Cardiogenic, hemorrhagic and obstructive shock; LA in those conditions is thought to be related to decreased clearance
  3. Regional ischemia, such as acute mesenteric ischemia
  4. Burns
- Type B: Related to toxins, medications and liver dysfunction, alcoholism, malignancy.
  1. Metformin: Patients who are at increased risk of LA are those who are taking metformin and have renal or hepatic dysfunction, cardiac dysfunction, or those who overdose on the medication
  2. Cyanide poisoning, beta 2 agonist excessive use, thiamine deficiency
  3. Seizure

D-lactic acidosis is a rare type of LA that is associated with short bowel syndrome and bacterial overgrowth.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Alcoholic ketoacidosis
- Uremic acidosis
- Diabetic ketoacidosis
- Fulminant hepatic failure

WORKUP

- Laboratory measurement of lactic acid to confirm diagnosis and assess for precipitating factors
- Identification of triggering conditions such as infections (blood cultures, urine cultures, chest radiographs), blood drug and toxins level (alcohol, metformin, cyanide); liver and kidney function tests (hepatitis, acute kidney insufficiency)

LABORATORY TESTS

- Normal lactate level is 2.0 to 2.5 mEq/L.
- LA is defined by serum lactate concentration >4 mEq/L. An elevated blood lactate level is essential for confirmation of the diagnosis.
- Arterial blood gas analysis demonstrates metabolic acidosis usually with PH <7.3 and pCO_2 <40.
- Serum chemistries:
  1. Low serum bicarbonate <15 mEq/L
  2. Large anion gap (AG) metabolic acidosis: AG >12 usually caused by lactate accumulation. A normal AG does not rule out lactic acidosis. Correction of the AG for the effect of serum albumin can improve its sensitivity
  3. Calculate AG: $AG = NA^+ - (Cl^- + HCO_3^-)$
  4. Mixed metabolic disturbances might demonstrate more than only AG acidosis, especially in patients with vomiting, diarrhea, and acute kidney injury

IMAGING STUDIES

- Chest radiography is helpful if chest infection is suspected as a cause of sepsis or cardiogenic or obstructive shock is suspected.
- Abdominal CT scan or ultrasound might aid in the diagnosis if abdominal pain, regional ischemia, or liver failure is suspected as a cause of the lactic acidosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- The cornerstone of LA treatment is reversing the causative condition.
- Continuous monitoring for patients with LA is warranted, including monitoring of mental status, urine output, and vital signs.
- Lactate levels should be checked every 2 to 6 hr.
- Surgery in the case of regional tissue ischemia or trauma with shock.
- Cardiac assist devices in the case of cardiogenic shock.
- Hemodialysis for drugs or toxins removal (i.e., metformin-induced LA).

ACUTE GENERAL Rx

Pharmacologic treatment consists of:

- Resuscitating the intravascular component with IV crystalloid or colloid solution fluids in cases of shock.
- Sodium bicarbonate IV infusion should be considered only if pH <7.1 and serum bicarbonate level is less than 6 mEq/L. Infusion of 1-2 mEq/L of sodium bicarbonate in a bolus form repeated every 30 to 60 min if the pH is less than 7.1.
- Vasopressor therapy is cases of shock might be required; increasing doses of vasopressor might be needed as the acidosis can blunt the effect of catecholamines. Norepinephrine is generally preferred over dopamine as the initial vasopressor in most types of shock.
- Optimize oxygen delivery: When an inotrope is indicated to improve cardiac output, dobutamine is usually the preferred agent.

DISPOSITION

- Septic shock and lactic acid level >4 mEq/L are associated with a 28% mortality rate.
- There is a clear correlation with increasing lactate level and increased mortality.

REFERRAL

In general, patients with LA should be admitted to the intensive care unit for close monitoring, frequent lactate, chemistries, and arterial blood gas analysis.

PREVENTION

- Aggressive treatment of shock
- Avoidance of metformin in high-risk populations such as patients older than 85 yr and patients with kidney or liver impairment
- Early use of antibiotics in patients with sepsis

PEARLS & CONSIDERATIONS

COMMENTS

Hemodialysis is not an effective way of clearing lactate or reversing LA, especially in cases of overproduction and tissue hypoxemia; it could be of value in cases of drug- and toxin-induced LA for removal of the offending agent.

RELATED CONTENT

Diabetic Ketoacidosis (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

TABLE E1 Medication-Induced Lactic Acidosis

Condition	Source and/or Mechanism	Associated Clinical Manifestations/Important Clinical Information	Comments
Metformin	Metformin can bind to complex 1 of the mitochondrial electron transport chain. Alternatively, it has been postulated that it blocks gluconeogenesis, decreasing conversion of lactate to glucose.	A mortality of 30% of patients with lactate concentrations >5 mmol/L in the presence of metformin was reported in one study, in comparison with 11% in patients with <5 mmol/L.	Occurs in about 4.3 patients per 100,000 patient-yr. Metformin plasma concentration correlates with plasma lactate levels, pH, and creatinine.
Alcohols			
Ethanol	Metabolized in the liver to acetaldehyde, which can potentially inhibit the ETC. Usually, however, it is not associated with hyperlactatemia unless other causes are present, such as thiamine deficiency or salicylates.	Treatment includes administration of folic acid and thiamine to avoid Wernicke-Korsakoff syndrome.	
Methanol	Methanol is metabolized by hepatic alcohol dehydrogenase to formaldehyde and then rapidly oxidized to formic acid by the cytochrome P450 system. Formic acid is a potent inhibitor of OXPHOS.	Treatment options include: 1. Extracorporeal treatment (modality of choice—intermittent hemodialysis or HD) 2. The administration of an antidote—a competitive inhibitor of alcohol dehydrogenase in the form of ethanol or fomepizole. Methanol is eliminated by renal and nonrenal (presumed respiratory clearance) routes. In the absence of antidote therapy, methanol elimination half-life is 2.3-13.7 hours. HD can be terminated when the methanol concentration is <200 mg/L of 6.2 mmol/L and clinical improvement is observed.	The use of antidotes significantly increases the elimination half-life of methanol to a mean of 54 hours and thus extracorporeal removal may be beneficial to shorten ICU stay. Extracorporeal therapy has been recommended in the following circumstances with grade 1D evidence (level 1 = strong recommendation by experts, D = very low level of evidence): 1. Severe poisoning characterized by coma, seizures, new vision deficits, persistent metabolic acidosis despite adequate supportive measures, serum AG >24 mmol/L. 2. High methanol concentration (>700 mg/L with fomepizole treatment; >600 mg/L with ethanol treatment; >500 mg/L in the absence of antidote); in the setting of altered osmolar gap when methanol level is absent. 3. In the context of impaired renal function.
Ethylene glycol	Similar mechanism as methanol. However, ethylene glycol is metabolized to glycolate. In addition, can cause spurious hyperlactatemia because glycolate can cross-react with lactate in certain blood chemistry analyzers.	Fomepizole can be used in the treatment of ethylene glycol intoxication. The elimination (renal) half-life of ethylene glycol is approximately 16 hours during fomepizole treatment. A ≥50 mg/dl of ethylene glycol concentration has been used to determine the use of HD.	
Propylene glycol	Hyperlactatemia has been reported in patients receiving medications that use propylene glycol as a vehicle (lorazepam, diazepam, diphenylhydantoin, trimethoprim-sulfamethoxazole).	Hyperlactatemia is more frequent in patients with renal or hepatic dysfunction because propylene glycol is metabolized in the liver and kidney. Monitoring serum osmolarity has been recommended to detect potentially toxic levels of propylene glycol.	Commercial preparations of propylene glycol come in a 50:50 mixture of D and L isomers. The D isomer is metabolized to D^- lactate, which is cleared more slowly than L^+ lactate. Accumulation of D^- lactate in the brain has been implicated as the cause of the central nervous system manifestations of propylene glycol toxicity.
β_2-adrenergic receptor agonists	Stimulation of Na^+/K^+-ATPase in skeletal muscle.	Described initially in pregnant women undergoing tocolytic treatment with terbutaline, and in patients with asthma undergoing treatment with β_2-adrenergic receptor agonists.	
Salicylates	Salicylates induce hyperlactatemia by uncoupling OXPHOS and inhibiting the enzymes of the Krebs cycle.	Acidosis decreases renal elimination of salicylates and increases the nonionized fraction, which augments passage through the blood-brain barrier, thus increasing the potential for toxicity.	

Cyanide and nitroprusside	Cyanide combines with cytochrome c and inhibits OXPHOS, thus inducing hyperlactatemia. Nitroprusside infusion can cause cyanide toxicity.	Cyanide poisoning usually occurs as a result of smoke inhalation or in the context of a suicide attempt. Cyanide levels offer little help because of prolonged sample processing time. Cyanide poisoning should be suspected in patients exhibiting hyperlactatemia with neurologic and/or cardiovascular manifestations (i.e., confusion, seizures, coma, hypotension). Cyanide toxicity derived from nitroprusside treatment occurs particularly with prolonged infusions (i.e., >72 hours) and with high doses (>2 mg/kg/min). This also can occur with short infusions of very high doses that deplete thiosulfate stores. The best evaluation for possible toxicity in this setting is clinical (i.e., tachycardia, agitation, seizures) and measurement of blood lactate concentrations. Lactic acidosis can be eliminated by routine addition of sodium thiosulfate in the infusion bag.	
Carbon monoxide	Multiple mechanisms: Carboxyhemoglobinemia alters oxygen transport to the tissues and induces a leftward shift of the oxyhemoglobin curve, thus causing tissue dysoxia. More importantly, however, carbon monoxide binds to cytochromes in the electron transport chain, impairing OXPHOS and contributing to ROS production.	Leading cause of unintentional poisoning worldwide. It occurs most commonly in males, during winter, and often involves heating or cooking appliances. Burn victims are at risk of CO poisoning. CO levels usually do not correlate with symptoms.	Signs of CO poisoning: Neuro: Headache, dizziness, confusion, blurry vision, syncope, seizures, incontinence, coma (neuronal excitability $K_{v2.1}$ and Trek-1 channels, activation of soluble guanylyl cyclase and vasodilatation) Cardiovascular: Hypotension, palpitations, chest pain, myocardial ischemia Lung: Noncardiogenic pulmonary edema (epithelial sodium channel compromise [ENaC] and ROS generation) Abdominal: Nausea, vomiting, abdominal pain (ENaC, ROS generation, increased NO production), LFT elevation Muscle: Rhabdomyolysis (myoglobin binding), rigors (peripheral neuronal hyperexcitability from $Na_{v1.5}$ and $K_{v2.1}$ channels)
Antiretroviral agents	Thought to be caused by mitochondrial toxicity secondary to inhibition of DNA polymerase-γ, which uncouples OXPHOS.	Mild-moderate hyperlactatemia (i.e., 2.5-5 mmol/L) occurs in 25% of patients with human immunodeficiency virus under treatment with nucleoside reverse transcriptase inhibitors (particularly stavudine).	
Propofol	Lactic acidosis occurs secondary to uncoupling of OXPHOS and impaired oxidation of fatty acids.	Hyperlactatemia occurs in the setting of the "propofol infusion syndrome," or PIS, which consists of lactic acidosis, heart failure, rhabdomyolysis, and acute kidney injury.	Usually occurs in patients receiving infusions of propofol exceeding 5 mg/kg/hr for more than 48 hours.

AG, Anion gap; *ATPase,* adenosine triphosphatase; *CO,* carbon monoxide; *ETC,* electron transport chain; *HD,* hemodialysis; *ICU,* intensive care unit; *LFT,* liver function test; *NO,* nitric oxide; *OXPHOS,* oxidative phosphorylation; *ROS,* reactive oxygen species.
From Ronco C et al: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.

TABLE E2 Other Pathologies Associated with Lactic Acidosis

Condition	Source and/or Mechanism	Associated Clinical Manifestations/Important Clinical Information	Comments
Asthma	Increased lactate production from respiratory muscles. However, the peak of hyperlactatemia occurs while the patient is recovering and thus it is more likely that the mechanism relates to stimulatory effect of β_2 agonists on glycolytic flux.	Initial or delayed hyperlactatemia during status asthmaticus has little prognostic value.	Lactic acidosis develops only in some patients after β_2 agonist treatment. The reason for this selectivity is unknown but may be related to polymorphisms in the β_2 receptor gene.
Acute liver failure	Increase in lactate production from Kupffer cells and the lung. Impaired lactate clearance by hepatocytes. Increased hepatic lactate production from accelerated glycolytic rate.	Common in acute liver failure, consequent to an associated systemic inflammatory response resulting from hepatocellular necrosis.	Hyperlactatemia is unusual if there is no increased lactate production during chronic liver dysfunction. Hyperlactatemia has prognostic importance in this patient population.
Malignancy	Cytokine-mediated stimulation of glycolytic flux in neoplastic cells.	Hypoglycemia results from increased glucose utilization by neoplastic cells or may represent a paraneoplastic syndrome.	More frequent in leukemia or lymphomas but also in solid tumors with liver or bone marrow metastases. Lactic acidosis persists even after correction of hypoglycemia.
Thiamine deficiency	Impairment of PDH because thiamine pyrophosphate is an essential co-factor of PDH. Impairs OXPHOS of pyruvate in the Krebs cycle, which stimulates the glycolytic flux.		Can develop rapidly (days) in critically ill patients because of decreased intake or increased urinary or GI losses.
Cardiopulmonary bypass	Hyperglycemia and the administration of epinephrine, norepinephrine, and dobutamine are associated with hyperlactatemia in this setting. The contribution of tissue hypoperfusion to hyperlactatemia has been challenged: Microdialysis measurements during CPB have shown no association between tissue and plasma lactate. Hyperlactatemia has been shown to occur in patients with no evidence of tissue hypoperfusion. Local lung production after CPB has been found to be a significant contributor to hyperlactatemia. Cytokine-mediated and systemic inflammation resulting from exposure of blood to the extracorporeal circuit.	Patients with polymorphisms in the TNF-β or IL-10 genes experienced postoperative lactic acidosis in one study.	Hyperlactatemia during cardiac surgery is associated strongly with mortality.
Severe hypophosphatemia	Depletion of intracellular ATP and decreased 2,3-diphosphoglyceric acid. Nonanion gap acidosis secondary to impaired tubular reabsorption of bicarbonate.	Severe hypophosphatemia (i.e., phosphate <1.5 mg/dl) can be a cause of hyperlactatemia.	
Congenital	Mutations or deletions in respiratory chain genes or in the pyruvate dehydrogenase complex.	Manifests as episodes of lactic acidosis with neurologic and developmental abnormalities. Suspect a mitochondrial cause if in the absence of hypoxia or sepsis, the patient has muscle weakness, or it is difficult to wean from mechanical ventilation. Other neurologic manifestations include stroke, seizures, dementia, migraines, and ophthalmoplegia.	Usually appears during infancy or early childhood, but some may manifest until adulthood.
D-lactic acidosis	In patients with short bowel syndrome, ingested carbohydrates are malabsorbed and reach the colon undigested, where they are fermented by bacteria into organic acids. This acidifies the colonic milieu promoting overgrowth of gut flora with acid-tolerant mechanisms that produce D-lactate.	Occurs in patients with short bowel syndrome secondary to resection or bypass surgery or with chronic pancreatic insufficiency. Associated with neurologic manifestations—slurred speech, confusion, ataxia, triggered by ingestion of large amounts of carbohydrates lasting hours to days.	Suggestive laboratory findings include anion gap acidosis, increased strong ion gap, normal serum lactate level (analyzers only detect L-lactate). Confirmation is done by the finding of serum D-lactate level >3 mmol/L.
Hypoglycemia	Hypoglycemia is a potent stimulant of the sympathetic nervous system, releasing epinephrine, which increases glycolytic flux in muscle and thus the release of lactate. In addition, in hepatic dysfunction, a minimal amount of glucose is required as an energy source for effective conversion of lactate into glucose through gluconeogenesis.	Patients with chronic renal or hepatic disease.	Hypoglycemia-associated lactic acidosis responds promptly to administration of glucose, in contrast with hypoglycemia resulting from malignancy that does not respond to glucose administration.

ATP, Adenosine triphosphate; *CPB,* cardiopulmonary bypass; *GI,* gastrointestinal; *IL-10,* interleukin-10; *OXPHOS,* oxidative phosphorylation; *PDH,* pyruvate dehydrogenase; *TNF-β,* tumor necrosis factor-beta.
From Ronco C et al: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.

SUGGESTED READINGS

Andersen LW et al: Etiology and therapeutic approach to elevated lactate, *Mayo Clin Proc* 88(10):1127-1140, 2013.

Kraut JA, Madias NE: Lactic acidosis, *N Engl J Med* 371:2309–2319, 2014.

Reddy AJ et al: Lactic acidosis: clinical implications and management strategies, *Clev Clin J Med* 82:615-622, 2015.

Lactose Intolerance PTG

BASIC INFORMATION

DEFINITION

Lactose intolerance is the insufficient concentration of lactase enzyme, leading to fermentation of malabsorbed lactose by intestinal bacteria with subsequent production of intestinal gas and various organic acids, manifesting clinically with diarrhea, abdominal pain, flatulence, or bloating after lactose intake. *Lactose malabsorption* occurs when a substantial amount of lactose is not absorbed in the intestine. *Lactase deficiency* is defined as brush-border lactase activity that is markedly reduced relative to the activity observed in infants.

SYNONYM

Lactose malabsorption
Lactase deficiency
Milk intolerance
Carbohydrate malabsorption

ICD-10CM CODES
E73.9 Lactose intolerance, unspecified
E73.8 Other lactose intolerance

EPIDEMIOLOGY & DEMOGRAPHICS

- Nearly 50 million people in the U.S. have partial or complete lactose intolerance. There are racial differences, with <25% of white adults being lactose intolerant but >85% of Asian Americans and >60% of African Americans having some form of lactose intolerance.
- There are geographic variations: highest in Asians (up to 90%), lowest in northern Europeans (approximately 10%), intermediate in southern Europeans and Middle Eastern populations (up to 40%).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abdominal tenderness and cramping, bloating, flatulence.
- Diarrhea.
- Symptoms are directly related to the osmotic pressure of substrate in the colon and occur approximately 2 hr after ingestion of lactose.
- Physical examination: May be entirely within normal limits.

ETIOLOGY

- Before it can be absorbed, lactose is cleared to glucose and galactose by the enzyme lactase in the brush border of the small intestine. If the amount of lactase is marginal or its expression is left, lactose intolerance will result.
- Congenital lactase deficiency: Common in premature infants; rare in term infants and generally inherited as a chromosomal recessive trait.
- Secondary lactose intolerance: Usually a result of injury of the intestinal mucosa (Crohn disease, viral gastroenteritis, AIDS enteropathy, cryptosporidiosis, Whipple disease, sprue).
- Acquired primary lactase deficiency (adult-type hypolactasia OMIM # 223100) is the most common form of lactase deficiency worldwide. The decline in lactase activity is a multifactorial process that is regulated at the gene transcription level and leads to decreased biosynthesis, retardation of intracellular transport, or maturation of the enzyme lactase-phlorizin hydrolase.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Inflammatory bowel disease
- Irritable bowel syndrome
- Pancreatic insufficiency
- Nontropical and tropical sprue
- Cystic fibrosis
- Diverticular disease
- Bowel neoplasm
- Laxative abuse
- Celiac disease
- Parasitic disease (e.g., giardiasis)
- Viral or bacterial infections

WORKUP

- A detailed dietary history is essential in the evaluation of patients with suspected carbohydrate malabsorption.
- The diagnosis can usually be made on the basis of the history and improvement with dietary manipulation.
- Diagnostic workup may include confirming the diagnosis with hydrogen breath test and excluding other conditions listed in the differential diagnosis that may also coexist with lactase deficiency.

LABORATORY TESTS

- Laboratory evaluation may not be necessary in patients with significant history.
- Lactose breath hydrogen test: A rise in breath hydrogen >20 ppm within 90 min of ingestion of 50 g of lactose is positive for lactase deficiency. This test is positive in 90% of patients with lactose malabsorption. Common causes of false-negative results are recent use of oral antibiotics or recent high colonic enema. Fig. E1 illustrates the role of symptoms in determining the clinical importance of lactose malabsorption.
- The lactose tolerance test is an older and less accurate testing modality (20% rate of false-positive and false-negative results). The patient is administered an oral dose of 1 to 1.5 g of lactose/kg body weight. Serial measurement of blood glucose level on an hourly basis for 3 hr is then performed. The test is considered positive if the patient develops intestinal symptoms and the blood glucose level rises <20 mg/dl above the fasting baseline level.
- Diarrhea associated with lactase deficiency is osmotic in nature with an osmotic gap and a pH <6.5.

IMAGING STUDIES

Imaging studies are generally not indicated. A small bowel series may be useful in patients with significant malabsorption.

TREATMENT

NONPHARMACOLOGIC THERAPY

Management consists of reducing lactose exposure by avoiding milk and milk-containing products or using milk in which the lactose has been prehydrolyzed with lactase. A lactose-free diet generally results in prompt resolution of symptoms. Lactose is primarily found in dairy products but may be present as an ingredient or component of common foods and beverages. Possible sources of lactose include breads, candies, cold cuts, dessert mixes, cream soups, bologna, commercial sauces and gravies, chocolate, drink mixes, salad dressings, and medications. Labels should be read carefully to identify sources of lactose.

ACUTE GENERAL Rx

- Addition of lactase enzyme supplement (Lactaid tablets, Dairy Ease) before the ingestion of milk products may prevent symptoms in some patients. However, it is not effective for all lactose-intolerant patients.
- Lactose-intolerant patients must ensure adequate calcium intake. Calcium supplementation is recommended to prevent osteoporosis.

CHRONIC Rx

Patient education regarding foods high in lactose, such as milk, cottage cheese, or ice cream, is recommended.

DISPOSITION

Clinical improvement with restriction or elimination of milk products

REFERRAL

GI referral for endoscopic procedures if concomitant GI disorders are suspected

PEARLS & CONSIDERATIONS

COMMENTS

- There is great variability in signs and symptoms in patients with lactose intolerance depending on the degree of lactase

deficiency. Most individuals with presumed lactose malabsorption can tolerate 12 to 15 g of lactose or up to 12 oz of milk daily without symptoms.
- Nondairy synthetic drinks (e.g., Coffee-Mate) and use of rice milk are generally well tolerated.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Lactose Intolerance (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Shaukat A et al: Systematic review: effective management strategies for lactose intolerance, *Ann Intern Med* 152:797-803, 2010.

Suchy FA et al: NIH consensus development conference: lactose intolerance and health. http://consensus.nih.gov/2010/lactosestatement.htm.

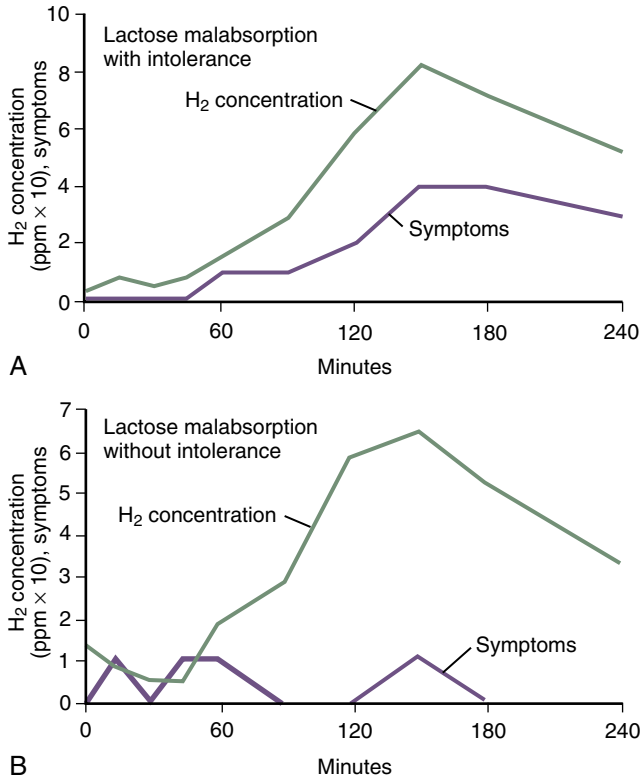

FIG. E1 Graphs illustrating the role of symptoms in determining the clinical importance of lactose malabsorption. Assessment of the clinical relevance of an abnormal lactose hydrogen breath test is made by monitoring abdominal symptoms (bloating, cramps, pain) during the test. Breath hydrogen concentration in parts per million (ppm) and GI symptoms using an arbitrary scoring system for two different patients are plotted on the graphs. **A,** The patient has symptoms associated with an increase in breath hydrogen concentration and therefore can be considered to have lactose intolerance. **B,** The patient has no increase in symptoms, although the breath hydrogen concentration increases considerably, so the patient has lactose malabsorption without lactose intolerance. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

Lambert-Eaton Myasthenic Syndrome

BASIC INFORMATION

DEFINITION

Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune disorder of neuromuscular transmission caused by antibodies directed against presynaptic voltage-gated P/Q calcium channels on motor and autonomic nerve terminals. There are two forms: Paraneoplastic (most common) and nonparaneoplastic (autoimmune).

SYNONYMS

Eaton-Lambert syndrome
LEMS

ICD-10CM CODES

G70.80	Lambert-Eaton syndrome, unspecified
G70.81	Lambert-Eaton syndrome in disease classified elsewhere
G73.1	Lambert-Eaton syndrome in neoplastic disease

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Uncertain; estimated at five cases per 1 million persons annually (in U.S.)
PEAK INCIDENCE: Sixth decade
PREVALENCE: Uncertain; estimated at one per 100,000 (in U.S.). Up to 3% of small cell lung cancer (SCLC) patients are estimated to develop LEMS.
PREDOMINANT SEX: Male:female ratio of 2:1

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Weakness with diminished or absent muscle stretch reflexes
- Proximal lower-extremity muscles affected most
- Ocular and bulbar muscles less commonly affected
- Transient strength improvement with brief exercise
- Reflexes may be facilitated by repeatedly tapping the tendon or after brief exercise
- Autonomic dysfunction common (dry mouth [75%], sexual dysfunction, blurred vision, constipation, orthostasis, etc.)

ETIOLOGY

- Antibodies directed against presynaptic voltage-gated P/Q calcium channels are present in most patients. The reduction in calcium influx causes a reduction in presynaptic acetylcholine release at motor and autonomic nerve terminals.
- Paraneoplastic forms, usually associated with SCLC, account for 50% to 70% of patients.
- Autoimmune forms, usually in patients with other autoimmune diseases, occur in 10% to 30% of patients.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Myasthenia gravis: The clinical presentation of Lambert-Eaton myasthenic syndrome is similar to that of myasthenia gravis except that in LEMS, weakness improves with exercise, and hyporeflexia and dysautonomia are present
- Polymyositis
- Primary myopathies
- Carcinomatous myopathies
- Polymyalgia rheumatica
- Botulism
- Guillain-Barré syndrome

WORKUP

Diagnosis is confirmed on basis of characteristic electrodiagnostic (electromyography [EMG]/nerve conduction study [NCS]) findings and detection of serum anti-voltage-gated calcium channel antibodies (90%). EMG reveals: Reduced motor amplitudes with normal sensory studies; >10% decrement in motor amplitudes on slow repetitive nerve stimulation (RNS) at 2 to 5 Hz, with >100% increment on fast RNS (20 to 50 Hz) or immediately after 10 sec of maximum exercise (post-exercise facilitation).

LABORATORY TESTS

Check P/Q calcium channel antibody titers (commercially available).

IMAGING STUDIES

Screen for an underlying malignancy. Presentation with LEMS may precede diagnosis of SCLC by up to 5 yr; hence, CT of the chest or positron emission tomography (PET) scan may be required every 6 to 12 mo to evaluate for SCLC.

TREATMENT

Treatment consists of treating any underlying malignancy or immunosuppression, intravenous immunoglobulin (IVIG), or plasmapheresis when dealing with a purely autoimmune disease.

Amifampridine is the only FDA-approved treatment for symptomatic treatment of LEMS. Amifampridine works by blocking presynaptic potassium channels, thereby increasing presynaptic calcium concentrations and enhancing acetylcholine release.

NONPHARMACOLOGIC THERAPY

Symptomatic treatment for autonomic dysfunction

ACUTE GENERAL Rx

- Amifampridine: Start 15 to 30 mg/day PO divided tid to qid and then increase by 5 mg/day every 3 to 4 days for a maximum of 20 mg per dose and 80 mg/day.
- Plasma exchange (200 to 250 ml/kg over 10 to 14 days) or IVIGs (2 g/kg divided over 2 to 5 days) often produces significant, temporary improvement.
- Prednisone 1.0 to 1.5 mg/kg/day can be gradually tapered over months to minimal effective dose.
- Azathioprine can be given alone or in combination with prednisone. Give up to 2.5 mg/kg/day. If patient is intolerant, can administer cyclosporine up to 3 mg/kg/day instead.

CHRONIC Rx

Treat underlying malignancy if present
Amifampridine for symptoms of weakness

DISPOSITION

- Gradually progressive weakness leading to impaired mobility if untreated
- Clinical remission may occur with chronic immunosuppressive therapy in 43% of cases
- Possible substantial improvement with successful treatment of underlying malignancy

REFERRAL

- Referral to a neurologist is highly recommended because this is a rare disease requiring highly specialized treatment in the context of weighing risk vs. benefit of the different therapeutic options.
- Surgical referral for tumor debulking in paraneoplastic forms necessary.

PEARLS & CONSIDERATIONS

COMMENTS

- Prominent autonomic symptoms (dry eyes, dry mouth, impotence, orthostasis) are often clues to the diagnosis in the appropriate clinical context.
- Many drugs may worsen weakness and should be used only if absolutely necessary. Included are succinylcholine, d-tubocurarine, quinine, quinidine, procainamide, aminoglycoside antibiotics, β-blockers, and calcium channel blockers.

PATIENT INFORMATION

Document link available through http://www.lems.com/resources.

AUTHORS: **Divya Singhal, MD,** and **Joseph S. Kass, MD, JD, FAAN**

SUGGESTED READINGS

Titulaer MJ et al: Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies, *Lancet Neurol* 10(12):1098-1107, 2011.
U.S. National Library of Medicine. PubChem compound summary: 3,4-Diaminopyridine. https://pubchem.ncbi.nlm.nih.gov/compound/3_4-diaminopyridine

Large Bowel Obstruction

BASIC INFORMATION

DEFINITION

A mechanical or functional interruption of normal intraluminal flow through the colon

SYNONYM

Colorectal obstruction

ICD-10CM CODES
K56.609 Unspecified intestinal obstruction
K56.699 Other intestinal obstruction

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: 73 yr of age, higher in the elderly due to increased rates of colorectal cancer
PREVALENCE: 25% of intestinal obstructions
PREDOMINANT SEX AND AGE: Affects males and females equally, more common in the elderly
RISK FACTORS: Colorectal cancer, prior abdominal surgery, prior colorectal resection, chronic constipation, radiation, diverticulitis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History:
  1. Patients commonly present with abdominal pain, abdominal distension, and obstipation.
  2. Patients may have nausea and vomiting, but these are very late-presenting symptoms.
  3. Patients may report a history of bloating or constipation prior to the onset of more severe symptoms.
  4. Inquiries should be made concerning recent weight loss or gain, bowel habits, narcotic use, prior surgery, and malignancy.
- Physical exam:
  1. Patient may be tachycardic or febrile from perforation, strangulation, or ischemia.
  2. Exam should include palpation of the abdomen, investigation for umbilical, inguinal and femoral hernias, as well as a rectal exam.
  3. Physical exam findings may include:
     a. Distended, tympanitic abdomen
     b. Nonspecific tenderness to palpation of the lower abdomen
     c. A palpable hernia
     d. Rectal mass or frank blood on rectal exam
  4. If possible, proctoscopy should be performed in the office to evaluate for volvulus or sigmoid mass.

ETIOLOGY

- Colorectal cancer, volvulus, diverticulitis, abscess, adhesions, anastomotic strictures, hernia, fecal impaction, inflammatory bowel disease, ischemic colitis, intussusception, colonic pseudoobstruction, narcotic associated adynamic ileus, sepsis or *C. difficile* infection.
- Box 1 summarizes causes of adult large bowel obstruction.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Colorectal cancer
- Volvulus
- Diverticulitis
- Abdominal abscess
- Abdominal adhesions
- Anastomotic stricture
- Hernia
- Fecal impaction
- Crohn disease
- Ischemic colitis
- Intussusception
- Pseudoobstruction (Ogilvie syndrome)
- Constipation
- Toxic megacolon

WORKUP

- Establish IV access with two large-bore IVs.
- Make the patient NPO.
- Flexible sigmoidoscopy or colonoscopy in stable patients.

LABORATORY TESTS

- Complete blood count with differential
- Basic metabolic panel

IMAGING STUDIES

- Acute abdominal series should demonstrate dilation of the colon (Fig. E1):
  1. Sensitivity 84%
  2. Specificity 72%
- CT abdomen and pelvis imaging is useful to pinpoint the obstruction and possibly identify the etiology (Fig. E2):
  1. Sensitivity 83%
  2. Specificity 93%
- Water contrast enema is useful for evaluating volvulus or distal obstruction cancer:
  1. Sensitivity 96%
  2. Specificity 98%
  3. Occasionally therapeutic

BOX 1 Causes of Adult Large Bowel Obstruction

Mechanical
- Neoplasm
- Volvulus (sigmoid, cecal, transverse colon)
- Diverticulitis
- Cecal bascule
- Intussusception
- Inflammatory bowel disease
- Incarcerated hernia
- Infection (abscess, inflammation)
- Fecal impaction
- Adhesion-related obstruction
- Foreign body

Functional
- Acute toxic or chronic megacolon
- Colonic pseudoobstruction (Ogilvie syndrome)

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

TREATMENT

- IV fluid resuscitation:
  1. Consider placing Foley catheter to monitor UOP
- Correction of electrolyte abnormalities
- Nasogastric tube to decompress the GI tract
- Cessation of narcotics and antihistamines

NONPHARMACOLOGIC THERAPY

- Emergent laparotomy for perforation, closed loop obstruction, peritonitis, or ischemia
  1. Placement of loop colostomy
- Rectal cancer: Loop colostomy for cancer, then neoadjuvant chemoradiation
- Colon cancer: Depends on location; Hartmann for sigmoid colon cancer, partial or total colectomy for other colon cancers
- Flexible sigmoidoscopy for colonic decompression of volvulus
- Endoscopic stenting for palliation or as a bridge to surgery

ACUTE GENERAL Rx

Neostigmine for pseudoobstruction

CHRONIC Rx

Not indicated

DISPOSITION

Immediate referral to general surgery and hospital admission

REFERRAL

General surgery

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Acute Colonic Pseudo-Obstruction (Ogilvie Syndrome) (Related Key Topic)
Constipation (Related Key Topic)
Colorectal Cancer (Related Key Topic)

AUTHORS: **Justin Pinkston, MD,** and **Mark F. Brady, MD, MPH, MMSc**

SUGGESTED READINGS

Fabrizio AC, Wick EC: The management of large bowel obstructions. In Cameron JL, Cameron AM, editors: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.

Mahmoud NN et al: Large bowel obstruction and pseudo-obstruction. In Townsend CM et al., editor: *Sabiston textbook of surgery*, Philadelphia, 2017, Elsevier.

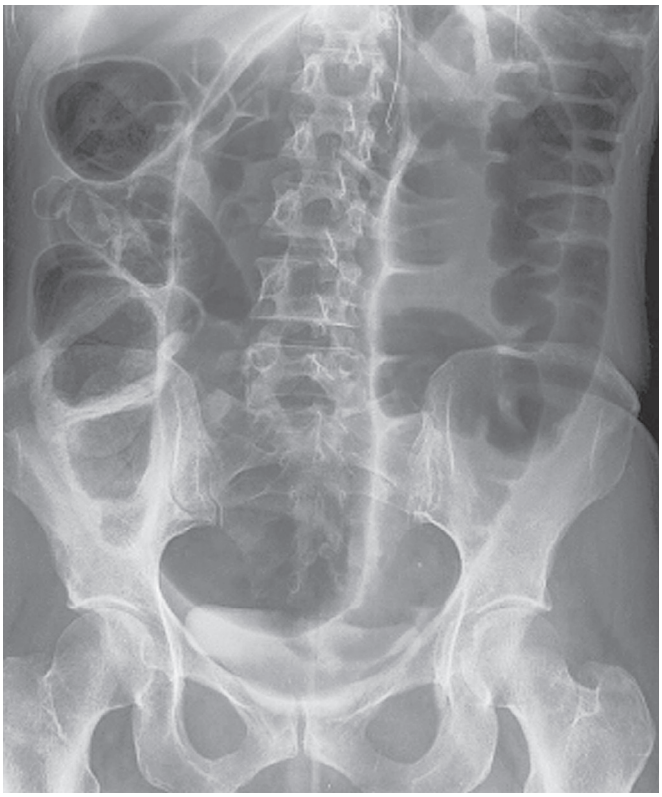

FIG. E1 Sigmoid volvulus. (Courtesy Harisinghani Mukesh, MD, MGH Radiology. In Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

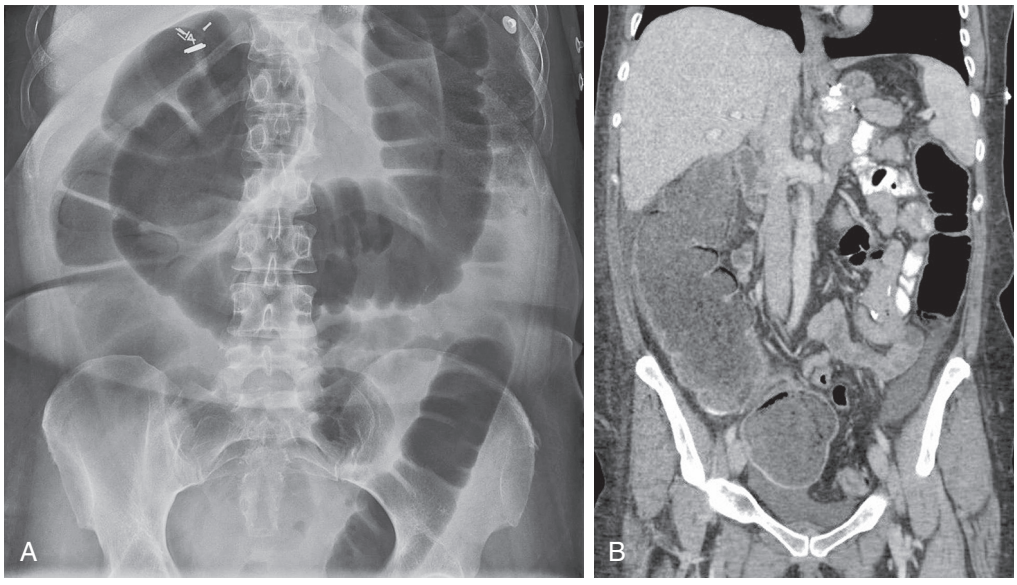

FIG. E2 A and **B,** Obstructing sigmoid colon cancer. (Courtesy Harisinghani Mukesh, MD, MGH Radiology. In Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

Laryngeal Carcinoma (PTG)

BASIC INFORMATION

DEFINITION

Laryngeal carcinoma is cancer of the larynx, including the vocal cords (glottis), supraglottis, and subglottis.

SYNONYMS

Laryngeal cancer
Head and neck cancer (subsite)

ICD-10CM CODES

D02.0	Carcinoma in situ of larynx
C32.8	Malignant neoplasm of overlapping sites of larynx
C32.9	Malignant neoplasm of larynx, unspecified
D14.1	Benign neoplasm of larynx
D38.0	Neoplasm of uncertain behavior of larynx

EPIDEMIOLOGY & DEMOGRAPHICS

It is estimated that there were 12,410 new cases and 3,760 deaths in 2019 in the U.S. The peak incidence is in the sixth decade, with 80% of cases detected in males. Approximately 60% of cases present as advanced disease (stages III to IV). Compared with Caucasians, African Americans develop laryngeal cancer at a younger age and have a higher incidence and mortality.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Glottis: Early diagnosis possible because of voice change (hoarseness). Any voice change of more than 2 wks' duration should prompt a laryngeal examination.
- Supraglottis:
  1. No early symptoms
  2. Cervical lymphadenopathy
  3. Neck or ear pain
  4. Discomfort and/or pain during swallowing
  5. Later: Hoarseness, dysphagia, airway obstruction
- Subglottis: Even more subtle than supraglottic lesion; the same signs occur, only later in the course.

ETIOLOGY

The following factors are implicated in the development of laryngeal cancer:

- Smoking
- Alcohol intake/abuse
- Diet (red meat)
- Gastroesophageal and laryngopharyngeal reflux
- Chronic laryngitis
- Exposure to textile dust, asbestos, polycyclic aromatic hydrocarbons
- Exposure to radiation
- Human papillomavirus is detected in 20% to 30% cases, but the causative aspects are yet to be determined

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Laryngitis
- Allergic and nonallergic rhinosinusitis
- Gastroesophageal reflux
- Voice abuse leading to hoarseness
- Laryngeal papilloma

TNM STAGING (AJCC EIGHTH EDITION): Primary Tumor:

- T_X: Primary tumor cannot be assessed
- T_{is}: Carcinoma *in situ*

Supraglottic cancers:

- T_1: Tumor limited to one subsite with normal cord mobility
- T_2: Tumor invades mucosa of more than one adjacent subsite (e.g., base of tongue, vallecula, pyriform sinus) without fixation of larynx
- T_3: Tumor is limited to larynx with vocal cord fixation and/or invasion of postcricoid area, pre-epiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
- T_{4a}: Moderately advanced local disease; tumor invades thyroid cartilage or extends into tissues beyond larynx (trachea, soft tissue of the neck, strap muscles, thyroid, or esophagus)
- T_{4b}: Very advanced local disease; tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottic cancers:

- T_1: Tumor limited to vocal cord with normal mobility
- T_{1a}: Tumor limited to one vocal cord
- T_{1b}: Tumor involves both vocal cords
- T_2: Tumor extends to supraglottis and/or subglottis and/or impairs cord mobility
- T_3: Tumor limited to larynx with cord fixation and/or invasion of paraglottic space and/or inner cortex of thyroid cartilage
- T_4: T_{4a} and T_{4b}—same as supraglottic staging

Subglottic cancers:

- T_1: Tumor limited to subglottis
- T_2: Tumor extends to vocal cord(s), with normal or impaired mobility
- T_3: Tumor limited to larynx with vocal cord fixation and/or inner cortex of thyroid cartilage
- T_4: T_{4a} and T_{4b}—same as supraglottic staging

Nodal status:

- N_X: Nodes cannot be assessed
- N_0: No regional node metastases
- N_1: Metastasis in a single ipsilateral node <3 cm in size
- N_{2a}: Metastasis in a single ipsilateral node >3 cm but <6 cm
- N_{2b}: Metastasis in multiple ipsilateral nodes none >6 cm in size
- N_{2c}: Metastasis in bilateral nodes none >6 cm in size
- N_{3a}: Metastasis in one or more nodes >6 cm in size
- N_{3b}: Metastasis in any lymph node with clinically overt extranodal extension

Distant metastases:

- M_0: No distant metastases
- M_1: Distant metastases present

Stage grouping:

- Stage I: T_1, N_0, M_0
- Stage II: T_2, N_0, M_0
- Stage III: T_3, N_0, M_0; or T_{1-3}, N_1, M_0
- Stage IVA: T_{1-3}, N_2, M_0
- Stage IVB: Any T, N_3, M_0; T_{4b}, any N, M_0
- Stage IVC: Any T, any N, M_1

WORKUP

- Primary workup includes either biopsy or fine-needle aspiration (FNA) of the presenting lesion or suspected neck lymph node for histopathologic analysis. HPV assessment with p16 immunohistochemical staining and confirmatory in situ hybridization (ISH) testing is not usually indicated unless extension of a primary pharyngeal tumor is suspected.
- Detailed examination of the oral cavity, pharynx, larynx, neck, ears, nose, and cranial nerves should be performed.
- Laryngoscopy and examination under anesthesia are commonly performed.
- Pretreatment evaluation of tumor size, the extent of invasion, and the presence or absence of regional lymph node metastases is critical for planning treatment.
- Laboratory workup can include complete blood count, complete chemistry panel, and thyroid function.
- Staging workup includes CT or MRI imaging (Fig. E1) of the head and neck and a chest x-ray. If locoregional or advanced disease is a consideration, a PET scan is typically completed.

HISTOLOGIC CLASSIFICATION

Epithelial cancers:

- Squamous cell carcinoma
- Superficially invasive cancer
- Verrucous carcinoma
- Pseudosarcoma
- Anaplastic cancer
- Transitional cell carcinoma
- Lymphoepithelial cancer
- Adenocarcinoma
- Neuroendocrine tumors, including small cell and carcinoid

Sarcomas:

- Metastatic or primary

TREATMENT

GENERAL Rx

The guiding treatment principles are focused on definitive cancer-directed therapy, larynx preservation, and voice rehabilitation in all patients.

- Early-stage (T_1 to T_2) patients can be treated with conservative surgery with or without neck dissection. Surgical options include transoral laser microscopic surgery or open conservation laryngeal surgery. Alternatively, definitive radiotherapy is also a curative option.

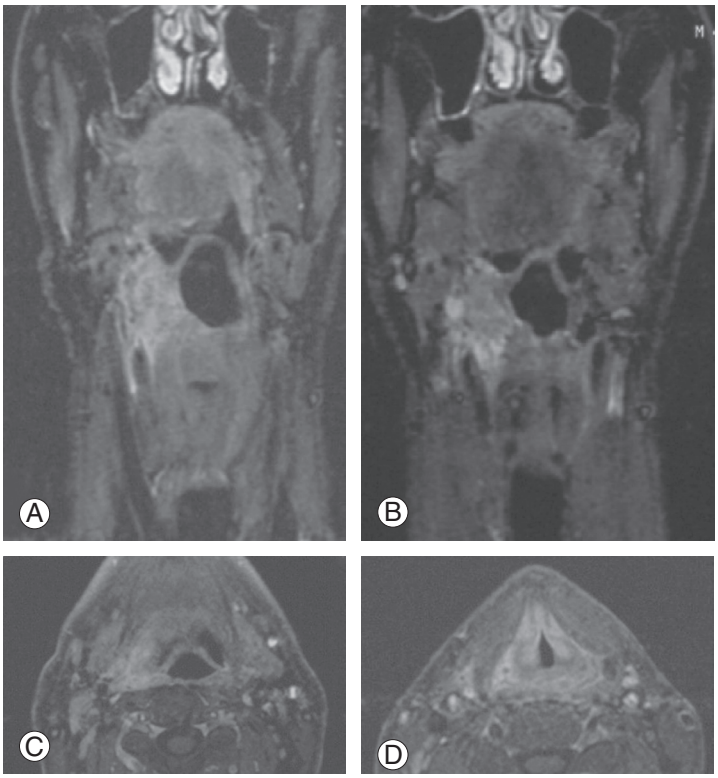

FIG. E1 Carcinoma of the larynx. (A,B) Coronal STIR and **(C,D)** axial T1WI + Gad FS. The coronal images demonstrate the superior and inferior extents while the axial images define the extent more accurately. (From Grant, LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.)

- Intermediate-stage patients can be treated with definitive radiotherapy, supraglottic laryngectomy with neck dissection with or without radiotherapy, or concurrent chemotherapy and radiotherapy.
- Advanced-stage patients are treated with concurrent chemotherapy and radiotherapy as initial therapy; salvage laryngectomy is reserved for cases of treatment failure.

In glottic cancers, early-stage and intermediate-stage cases are treated similarly as above. For advanced cases (T_4), total laryngectomy and neck dissection followed by postoperative radiation with or without chemotherapy in high-risk situations is a standard approach. Concurrent chemotherapy and radiotherapy can be considered for medically inoperable candidates.

Subglottic cancers require a total laryngectomy and neck surgery followed by radiotherapy with or without chemotherapy.

In case of unresectable cancers, the treatment consists of definitive chemotherapy and radiotherapy followed by neck dissection. If hypopharyngeal involvement exists, then laryngopharyngectomy with neck dissection and postoperative radiotherapy with or without chemotherapy is required.

Metastatic cancers:

- Patients who have metastatic cancers or unresectable locoregional recurrences are usually treated with systemic chemotherapy.
- Standard doublet chemotherapy regimens (platinum plus either 5-fluorouracil or a taxane) can be combined with the epidermal growth factor receptor (EGFR)–targeting antibody cetuximab. A recent study has demonstrated the superiority of frontline therapy with platinum plus 5-flurouracil chemotherapy in combination with the checkpoint inhibitor, pembrolizumab.
- In patients who have not received checkpoint inhibitor therapy previously, the use of nivolumab and pembrolizumab has been shown to improve survival outcomes after failure of first-line chemotherapy.

DISPOSITION

- Survival depends upon location of the tumor, with supraglottic cancers typically having better stage-for-stage 5-yr survival rates compared with glottic cancers.
- Voice rehabilitation, including the use of tracheoesophageal prosthesis, is associated with improved quality of life in patients receiving treatment for laryngeal cancers.
- Patients with metastatic cancers have improved outcomes with introduction of targeted therapies and immunotherapy drugs.
- Multiple molecular targets, including tyrosine kinase receptors (such as epidermal growth factor receptor [EGFR], fibroblast growth factor receptor 1 [FGFR1], and Erb-B2 receptor tyrosine kinase 2 [ERBB2]), oncogenes (cyclin-D1 [CCND1], Harvey rat sarcoma viral oncogene homolog [HRAS]), tumor suppressor genes (tumor protein 53 [TP53], neurofibromin 1 [NF1]), and the phosphoinositide 3-kinase (PI3-K) pathway have been identified, which can potentially be utilized as therapeutic targets.

REFERRAL

To multidisciplinary team consisting of an ENT or head and neck physician, radiation oncologist, and medical oncologist

RELATED CONTENT

Laryngeal Cancer (Patient Information)
Head and Neck Squamous Cell Carcinoma (Related Key Topic)

AUTHOR: **Ritesh Rathore, MD**

SUGGESTED READINGS

Bar-Ad V, et al.: Current management of locally advanced head and neck cancer: the combination of chemotherapy with locoregional treatments, *Semin Oncol* 41(6):798–806, 2014.

Burtness B, et al.: Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019, pii: S0140-6736(19)32591-32597. doi: 10.1016/S0140-6736(19)32591-7. [Epub ahead of print]

Forastiere AA, et al.: Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer, *N Engl J Med* 349(22):2091–2098, 2013.

Siegel RL, et al.: Cancer statistics, *CA Cancer J Clin* 69(1):7–34, 2019.

Steuer CE, et al.: An update on larynx cancer, *CA Cancer J Clin* 67(1):31–50, 2017.

BASIC INFORMATION

DEFINITION

Laryngitis is an acute or chronic inflammation of the laryngeal mucous membranes.

SYNONYM

Lower respiratory tract infection

ICD-10CM CODES
J04.0 Acute laryngitis
J37.0 Chronic laryngitis

EPIDEMIOLOGY & DEMOGRAPHICS

It is a common illness worldwide in both genders and all age groups, but the diagnosis is imprecise and, therefore, statistics are not readily available with respect to incidence and prevalence.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

ACUTE LARYNGITIS:

- Clinical syndrome characterized by the onset of hoarseness, voice breaks, or episodes of aphonia; may also have accompanying sore throat, cough, nasal congestion, and rhinorrhea
- Usually associated with viral upper respiratory infection
- Larynx with diffuse erythema, edema, and vascular engorgement of the vocal folds, and occasionally mucosal ulceration
- In young children subglottis is often affected, resulting in airway narrowing with marked hoarseness, inspiratory stridor, dyspnea, and restlessness
- Respiratory compromise rare in adults

CHRONIC LARYNGITIS: Characterized by hoarseness or dysphonia persisting for longer than 2 wk.

ETIOLOGY

ACUTE LARYNGITIS:

- Most often caused by viruses so treatment consists of supportive measures as outlined in "Nonpharmacologic Therapy" section.
- Studies evaluating the use of antibiotics (erythromycin, penicillin) in acute laryngitis failed to show objective clinical benefit over placebo so they are not routinely recommended. Antibiotics and other antimicrobials may be indicated in cases in which specific treatable pathogens are identified.
- Avoid decongestants because of their drying effect.
- Guaifenesin may be a useful adjunct as a mucolytic agent.
- In gastroesophageal reflux disease (GERD)-associated laryngitis use acid-suppressive therapy (H_2 blockers, proton pump inhibitors) and nocturnal antireflux precautions.

CHRONIC LARYNGITIS:

- Results from any of the following: Tuberculosis, usually through bronchogenic spread; leprosy, from nasopharyngeal or oropharyngeal spread; syphilis, in secondary and tertiary stages; rhinoscleroma, extending from the nose and nasopharynx; actinomycosis; cryptococcosis; histoplasmosis; blastomycosis; paracoccidioidomycosis; coccidiosis; candidiasis; aspergillosis; sporotrichosis; rhinosporidiosis; parasitic infections including leishmaniasis and Clinostomum infection following raw fresh-water fish ingestion.
- Noninfectious causes of both acute and chronic laryngitis include malignancy, voice abuse (singers), GERD, and chemical or environmental irritants such as cigarettes and allergens. Other causes of inflammatory or granulomatous lesions of the larynx include relapsing polychondritis, Wegener granulomatosis, and sarcoidosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Young children with signs of airway obstruction:
  1. Supraglottitis (epiglottitis)
  2. Laryngotracheobronchitis
  3. Tracheitis
  4. Foreign body aspiration
- In adults with persistent hoarseness, consider noninfectious causes of laryngitis as listed previously
- Table E1 summarizes the classification and definition of infectious illnesses involving the larynx and supraglottic and infraglottic regions

WORKUP

- History and physical examination: Diagnosis is usually apparent.
- Laryngoscopy for severe or persistent cases.
- Laryngeal cultures should be performed if a cause other than acute viral infection is suspected.
- Imaging not indicated unless there is evidence of airway compromise. Obtain plain radiographs of neck, anteroposterior and lateral views, to differentiate laryngitis from acute laryngotracheobronchitis or supraglottitis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Rest the voice.
- Use an air humidifier.
- Ensure adequate hydration. Avoid alcohol and caffeine because of diuretic effect.

ACUTE GENERAL Rx

- Antibiotics and other antimicrobials should generally not be used. They are indicated only when a specific pathogen is isolated; commonly employed antibacterial agents are macrolides; clarithromycin 500 mg by mouth bid for 5 to 7 days or azithromycin 500 mg followed by 250 mg once daily for 4 to 5 days if the cause of laryngitis is found to be *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae* (the new name for what was formerly known as *Chlamydia pneumoniae*).
- Avoid decongestants because of their drying effect.
- Guaifenesin may be a useful adjunct as a mucolytic agent.
- In GERD-associated laryngitis use acid-suppressive therapy (H_2 blockers, proton pump inhibitors) and nocturnal antireflux precautions.

DISPOSITION

Uncomplicated laryngitis is usually benign, with gradual resolution of symptoms.

REFERRAL

- If symptoms persist for >2 wk, refer to otolaryngologist for laryngoscopy.
- Consider referral to gastroenterologist if GERD is suspected.

PEARLS & CONSIDERATIONS

- Most cases of uncomplicated acute laryngitis are viral in origin, and antibacterial agents should not be routinely administered.
- A recent Cochrane analysis in 2013 found no evidence for the use of empiric antibiotics in adults with laryngitis.
- The most difficult clinical challenge is often convincing patients with acute laryngitis that they do not need and will not benefit from antibacterial agents.

SUGGESTED READING

Available at Expertconsult.com

RELATED CONTENT

Laryngitis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READING

Reveiz L, Cardona AF: Antibiotics for acute laryngitis in adults, *Cochrane Database Syst Rev Mar* 28(3):CD004783, 2013.

TABLE E1 Classification and Definition of Infectious Illnesses Involving the Larynx and Supraglottic and Infraglottic Regions

Category	Other Terms	Definitions
Supraglottitis	Epiglottitis	Infection of the epiglottis and/or arytena-epiglottic folds and ventricular bands of the base of the epiglottis, resulting in swelling and upper airway obstruction
Laryngitis		Inflammation of larynx resulting in hoarseness; usually occurs in older children and adults in association with common upper respiratory viral infections
Laryngeal diphtheria	Membranous croup, true croup, diphtheritic croup	Infection involving larynx and other areas of upper and lower airway due to *Corynebacterium diphtheriae,* resulting in gradually progressive obstruction of airway and associated inspiratory stridor
Laryngotracheitis	False croup, virus croup, acute obstructive subglottic laryngitis	Inflammation of larynx and trachea most often caused by infection with parainfluenza and influenza viruses
Laryngotracheobronchitis and laryngo-tracheobronchopneumonitis	Membranous laryngotracheobronchitis, pseudomembranous croup	Inflammation of larynx, trachea, and of bronchi or lung or all three; usually similar in onset to laryngotracheitis, but a more severe illness; bacterial infection frequently has causative role
Bacterial croup	Bacterial tracheitis, membranous croup, membranous tracheitis, membranous laryngotracheobronchitis, pseudomembranous croup	Severe form of laryngotracheitis, laryngotracheobronchitis, or laryngotracheobronchopneumonitis due to bacterial infection
Spasmodic croup	Spasmodic laryngitis, catarrhal spasm of the larynx, subglottic allergic edema	Illness characterized by sudden nighttime onset of inspiratory stridor; associated with mild upper respiratory infection without inflammation or fever but with edema in subglottic region

From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

Lead Poisoning PTG

BASIC INFORMATION

DEFINITION

Lead is a potent, pervasive neurotoxicant. Lead poisoning refers to multisystem abnormalities resulting from excessive lead exposure.

SYNONYM

Plumbism

ICD-10CM CODES

T56.0X1A	Toxic effect of lead and its compounds, accidental (unintentional), initial encounter
T56.0X1D	Toxic effect of lead and its compounds, accidental (unintentional), subsequent encounter
T56.0X1S	Toxic effect of lead and its compounds, accidental (unintentional), sequela
T56.0X2A	Toxic effect of lead and its compounds, intentional self-harm, initial encounter
T56.0X2D	Toxic effect of lead and its compounds, intentional self-harm, subsequent encounter
T56.0X2S	Toxic effect of lead and its compounds, intentional self-harm, sequela
T56.0X3A	Toxic effect of lead and its compounds, assault, initial encounter
T56.0X3D	Toxic effect of lead and its compounds, assault, subsequent encounter
T56.0X3S	Toxic effect of lead and its compounds, assault, sequela
T56.0X4A	Toxic effect of lead and its compounds, undetermined, initial encounter
T56.0X4D	Toxic effect of lead and its compounds, undetermined, subsequent encounter
T56.0X4S	Toxic effect of lead and its compounds, undetermined, sequela

EPIDEMIOLOGY & DEMOGRAPHICS

- Lead poisoning is most common in children ages 1 to 5 yr (17,000 cases/100,000 persons). The highest rates are among blacks, those with low income, and urban children.
- In 1991 the Centers for Disease Control and Prevention (CDC) lowered the definition of a safe blood lead level to <10 mcg/dl of whole blood (a blood lead level of 25 mcg/dl was considered acceptable before 1991).
- It is estimated that >15% of preschoolers in the U.S. have a blood lead level >15 mcg/dl.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Findings vary with the degree of toxicity (Table 1). Examination may be normal in patients with mild toxicity.
- Myalgias, irritability, headache, and general fatigue may be present initially.
- Abdominal cramping, constipation, weight loss, tremor, paresthesias and peripheral neuritis, seizures, and coma may occur with severe toxicity.
- Motor neuropathy is common in children with lead poisoning; learning disorders are also frequent.

ETIOLOGY

Chronic, repeated exposure to paint containing lead, plumbing, storage of batteries, pottery, or lead soldering. Concentration of lead is generally highest in lead-based paint on exterior surfaces. Among interior surfaces, windows are most likely to have the highest lead content. Table 2 summarizes common sources of lead.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Polyneuropathies from other sources
- Anxiety disorder, attention deficit disorder
- Malabsorption, acute abdomen
- Iron-deficiency anemia

WORKUP

Laboratory screening: All U.S. children should be considered to be at risk for lead poisoning and should be screened routinely starting at age 1 yr for low-risk children and age 6 mo for high-risk children.

LABORATORY TESTS

- Venous blood lead level: Normal level, <5 mcg/dl; levels of 50 to 70 mcg/dl, indicative of moderate toxicity; levels >70 mcg/dl, associated with severe poisoning
- Mild anemia with basophilic stippling on peripheral smear
- Elevated zinc protoporphyrin levels or free erythrocyte protoporphyrin level
- An increased body burden of lead with previous high-level exposure in patients with occupational lead poisoning can be demonstrated by measuring the excretion of lead in urine after premedication with calcium ethylenediamine tetraacetic acid (EDTA) or another chelating agent

IMAGING STUDIES

- Imaging studies are generally not necessary.
- A plain abdominal film can visualize lead particles in the gut.
- "Lead lines" may be noted on x-ray films of long bones.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Provide adequate amounts of calcium, iron, zinc, and protein in patient's diet.
- Family education on sources of lead exposure and potential adverse health effects.

ACUTE GENERAL Rx

- The use of chelation in cases of acute lead poisoning is guided by the patient's clinical status and the blood lead level (BLL). For children with blood levels of 10 to 19 mcg/dl, the CDC recommends nonpharmacologic interventions (see "Nonpharmacologic Therapy").
- For children with blood levels between 20 and 44 mcg/dl, the CDC recommendations include case management by a qualified social worker, clinical management, environmental assessment, and lead hazard control. Chelation therapy should be considered in children with refractory blood lead levels. Chelation therapy (Table 3) is indicated in children with blood lead levels >45 mcg/dl.
- Succimer (DMSA) 10 mg/kg PO q8h for 5 days then q12h for 2 wk can be used in patients with levels between 45 and 70 mcg/dl.

TABLE 1 Serum Lead Levels and Symptoms

	Symptoms	
Level (μg/dl)	**Adults**	**Children**
10	None	Decreased IQ
		Decreased hearing
		Decreased growth
20	Increased protoporphyrin	Decreased nerve conduction velocity
	No symptoms	Increased protoporphyrin
30	Increased blood pressure	Decreased vitamin D metabolism
	Decreased hearing	
40	Peripheral neuropathies	Decreased hemoglobin synthesis
	Nephropathy	
	Infertility (men)	
50	Decreased hemoglobin synthesis	Lead colic
70	Anemia	Anemia
		Encephalopathy
		Nephropathy
100	Encephalopathy	Death

IQ, Intelligence quotient.
From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.

- Edetate calcium disodium (EDTA) and dimercaprol (BAL) are effective in patients with severe toxicity.
- Use of both EDTA and DMSA is indicated in children with blood levels >70 mcg/dl.
- d-Penicillamine (Cuprimine) can also be used for lead poisoning, but it is not FDA approved for this condition.

TABLE 2 Sources of Lead

Paint chips
Dust
Soil
Parent's or older child's occupational exposure (auto repair, smelting, construction, remodeling, plumbing, gun/bullet exposure, painting, e-scrap)
Glazed ceramics
Herbal remedies (e.g., Ayurvedic medications)
Home remedies including antiperspirants, deodorants (litargirio)
Jewelry (toys or parents')
Stored battery casings (or living near a battery smelter)
Lead-based gasoline
Moonshine alcohol
Mexican candies; Ecuadorian chocolates
Indoor firing ranges
Retained bullet fragments
Imported spices (*svanuri marili, zafron, kuzhambu*)
Lead-based cosmetics (kohl, surma)
Lead plumbing (water)
Imported foods in lead-containing cans
Imported toys
Home renovations
Antique toys or furniture

From Kliegman RM: *Nelson's textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

CHRONIC Rx

- Reduce exposure, remove any potential lead sources.
- Correct iron deficiency and any other nutritional deficiencies.
- Recheck blood lead level 7 to 21 days after chelation therapy.

DISPOSITION

Patients with mild to moderate toxicity generally improve without any residual deficits. The presence of encephalopathy at diagnosis is a poor prognostic sign. Residual neurologic deficits may persist in these patients. Chelation therapy seems to slow the progression of renal insufficiency in patients with mildly elevated body lead burden.

REFERRAL

If exposure to lead is work related, it should be reported to the Office of the United States Occupational Safety and Health Administration (OSHA). Follow-up testing is mandatory in all patients after an abnormal screening blood lead level.

PEARLS & CONSIDERATIONS

COMMENTS

- Even blood lead concentrations as low as 5 to 10 mcg/dl are inversely associated with children's IQ scores at age 3 and 5 yr. A recent study evaluating long-term ramifications of childhood lead exposure revealed that childhood lead exposure was associated with lower cognitive function and socioeconomic status at age 38 yr, with declines in IQ, and downward social mobility.[1]
- Screening of household members of affected individuals is recommended.
- In children with blood lead levels of >45 mg/dl, treatment with succimer does not improve scores on tests of cognition, behavior, or neuropsychological function.
- Lead toxicity may delay growth and pubertal development in girls.
- Low-level environmental lead exposure may accelerate progressive renal insufficiency in patients without diabetes who have chronic renal disease. Repeated chelation therapy may improve renal function and slow the progression of renal failure.

RELATED CONTENT

Lead Poisoning (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

[1]Reuben A et al: Association of childhood blood lead levels with cognitive function and socioeconomic status at age 38 and with IQ change and socioeconomic mobility between childhood and adulthood, *JAMA* 317(12):1244–1251, 2017.

TABLE 3 Chelators*

Chelator	Dose	Indications	Contraindications
Deferoxamine	15 mg/kg/hr up to 24 hr (titrate up slowly because of hypotension)	Iron level >500 g/dl or systemic symptoms	
Dimercaprol (British anti-Lewisite [BAL])	Lead encephalopathy: 75 mg/m^2 deep IM injection every 4 hr for 5 days in children or 4 mg/kg every 4 hr for adults Arsenic (severe): No established regimen; consider 3 mg/kg IM every 4 hr for 48 hr; then twice daily for 7-10 days Mercury: 5 mg/kg IM first; then 2.5 mg/kg every 12-24 hr	Lead level >70 g/dl or encephalopathy Arsenic: Symptomatic patient with known exposure Mercury: Inorganic	Peanut allergy Organic mercury poisoning
$CaNa_2EDTA$	1500 mg/m^2/day continuous IV infusion 50 mg/kg/day or 1000 mg/m^2/day in 2-4 divided doses for up to 5 days if less severe symptoms	Lead: Given after first dose of BAL for blood lead level above 70 g/dl or encephalopathy	
Succimer (DMSA)	10 mg/kg q8h × 5 days; then q12h for 14 days	Lead level of 45-69 g/dl Arsenic: If tolerated orally for subacute and chronic toxicity Mercury: Acute and chronic	
D-Penicillamine	25 mg/kg q6h × 5 days	Lead level of 45-69 g/dl, succimer not tolerated Arsenic: Only if BAL and DMSA are unavailable Mercury: If BAL and DMSA are unavailable or not tolerated	Penicillin allergy
DMPS (investigational)	5 mg/kg/dose IM q6-8h day 1, q8-12h day 2, q12-24h day 3 and until 24-hr urine is <50 μg/L	Lead (chronic) Arsenic Mercury	

*Indications for chelation and dosing regimens may change. Consult with a toxicologist or poison control center for the most up-to-date recommendations.
BAL, Dimercaprol; *DMPS*, 2,3-Dimercapto-1-propanesulfonic acid; *DMSA*, dimercaptosuccinic acid; *EDTA*, edetate calcium disodium; *IM*, intramuscular; *IV*, intravenous.
From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.

BASIC INFORMATION

DEFINITION

Legg-Calvé-Perthes disease (LCPD) is a childhood condition characterized by disruption of the blood supply to the capital femoral epiphysis, leading to avascular necrosis of the femoral head(Fig. E1). The disease is self-limited; the blood supply to the femoral head recovers spontaneously after progressing through phases of infarction, fragmentation, reossification, and remodeling. The classification of LCPD is outlined in Fig. E2.

SYNONYMS

LCPD
Perthes disease
Coxa plana
Capital femoral osteochondrosis
Osteonecrosis of the proximal femoral epiphysis

ICD-10CM CODE
M91.10 Juvenile osteochondrosis of head of femur [Legg-Calvé-Perthes], unspecified leg

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Four to thirty-two cases per 100,000 children. Varies by country. More common in Caucasians, lower socioeconomic status, less densely populated areas, and people living farther from the equator.
PREDOMINANT SEX: Male:female ratio of 5:1
PREDOMINANT AGE: 4 to 8 yr old

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Initial symptom: A limp that can be painful or painless.
- Pain referred down the anterior hip and medial thigh.
- Positive roll test: With the patient in the supine position, rolling of the affected extremity into internal and external rotation elicits guarding.
- Limited abduction and internal rotation of the hip. Flexion and extension of the hip are usually spared.
- No history of trauma.
- Condition is bilateral in 10% to 20% of patients.

ETIOLOGY

Unknown, but suspected to be multifactorial. Likely a combination of genetic factors that confer susceptibility to vascular compromise and environmental factors (like subclinical trauma) that trigger the disease.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS (TABLE E1)

Unilateral disease:
- Transient synovitis
- Sickle cell disease
- Septic arthritis
- Neoplastic process
- Spondyloepiphyseal dysplasia tarda

Slipped capital femoral epiphysis

BILATERAL DISEASE

- Multiple epiphyseal dysplasia
- Sickle cell disease
- Juvenile idiopathic arthritis

WORKUP

Diagnosis is usually based on physical examination findings and radiographic evaluation.

IMAGING STUDIES

- Plain x-ray (AP and frog-leg lateral views) can be used to diagnose and follow disease progression.
- Contrast-enhanced MRI is the most sensitive for early LCPD.
- Technetium bone scan (Fig. E3) can help confirm the diagnosis in early cases. There is a correlation between size of the uptake defect and prognosis.
- Dynamic pneumoarthrography shows the relationship between the femoral head and the acetabulum, which can aid surgical planning.

TREATMENT

ACUTE GENERAL Rx

- The ultimate goal of treatment is to contain the femoral head inside the acetabulum to protect the vulnerable segment of bone from deforming forces.
- Nonoperative management includes non–weight-bearing status, bracing, range-of-motion exercises, and NSAIDs for pain control.
- Surgical intervention may be required in refractory cases, usually femoral or pelvic osteotomies.

DISPOSITION

- One of the most important prognostic factors is femoral head shape. Excursion of the femoral head is linked to future degenerative arthritis.
- Factors that portend a favorable outcome include younger age of onset, less extensive epiphyseal involvement, and male gender.
- Factors associated with a poor prognosis include obesity, stiffness with progressive loss of hip range of motion, adduction contracture, and a longer duration of disease.

REFERRAL

Refer to a pediatric orthopedist when the diagnosis is suspected

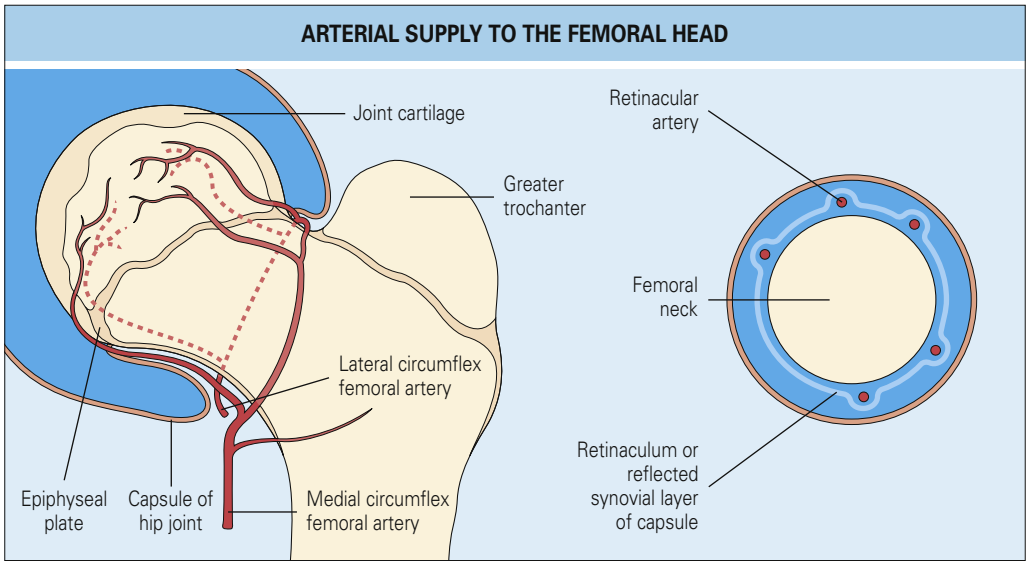

FIG. E1 Normal blood supply to the femoral head in a 4-yr-old child. A blockage of this blood supply, which is yet not fully understood, leads to Legg-Calvé-Perthes disease. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

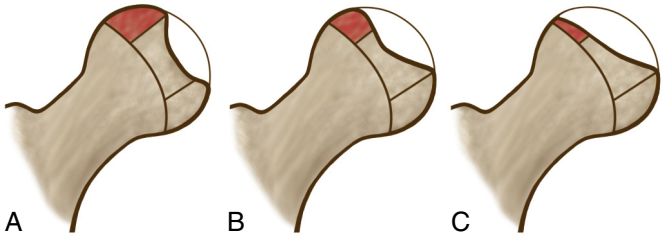

FIG. E2 Lateral pillar classification for Legg-Calvé-Perthes disease. A, There is no involvement of the lateral pillar. **B,** More than 50% of the lateral pillar height is maintained. **C,** Less than 50% of the lateral pillar height is maintained. (From Kliegman, RM: *Nelson Textbook of Pediatrics*, ed 21, Philadelphia, 2020, Elsevier.)

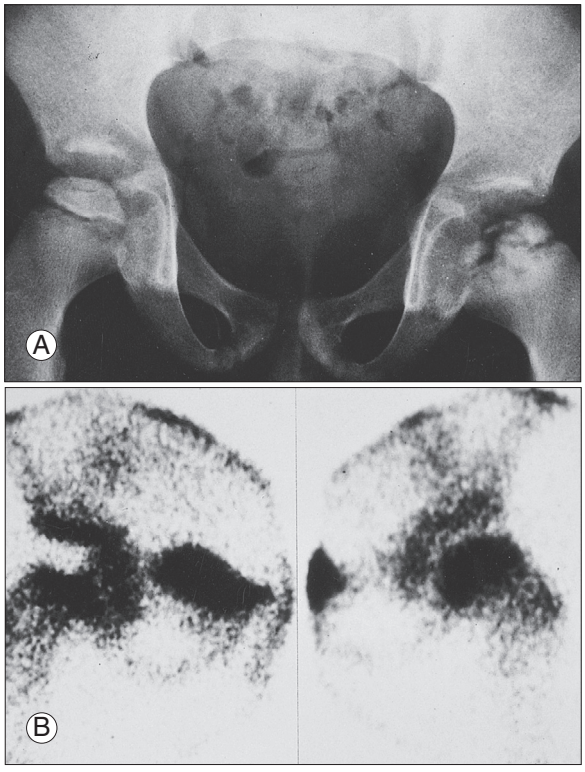

FIG. E3 Pelvic radiograph and technetium bone scintiscan for an 8-yr-old with Legg-Calvé-Perthes (LCP) disease. (A) The child has early involvement of the right hip, with relatively subtle changes apparent on the radiograph. **(B)** The bone scintiscan, however, shows complete blood loss in the right femoral head, consistent with osteonecrosis. The left hip shows classic, more advanced stages of LCP disease (in the revascularization phase), with return of normal blood flow visible on the scintiscan. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

TABLE E1 Differential Diagnosis of Legg-Calvé-Perthes Disease

Other Causes of Avascular Necrosis

- Sickle cell disease
- Other hemoglobinopathies (e.g., thalassemia)
- Chronic myelogenous leukemia
- Steroid medication
- Sequela of traumatic hip dislocation
- Treatment of developmental dysplasia of the hip
- Septic arthritis

Epiphyseal Dysplasias

- Multiple epiphyseal dysplasia
- Spondyloepiphyseal dysplasia
- Mucopolysaccharidoses
- Hypothyroidism

Other Syndromes

- Osteochondromatosis
- Metachondromatosis
- Schwartz-Jampel syndrome
- Trichorhinophalangeal syndrome
- Maroteaux-Lamy syndrome
- Martsolf syndrome

From Kim HKW, Herring JA: Legg-Calvé-Perthes disease. In Herring JA, editor: *Tachdjian's pediatric orthopaedics*, ed 5. Philadelphia, 2014, WB Saunders, Box 17.6, p. 613. In Kliegman, RM: *Nelson Textbook of Pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

PEARLS & CONSIDERATIONS

LCPD is an idiopathic, self-limited condition characterized by avascular necrosis of the skeletally immature femoral head. The etiology of LCPD remains controversial. Treatment recommendations vary widely and continue to evolve. A subset of patients will require surgical intervention; therefore, prompt referral to a pediatric orthopedist is warranted.

RELATED CONTENT

Legg-Calvé-Perthes Disease (Patient Information)

AUTHORS: **Sebastian Orman, MD,** and **Andrew P. Thome, Jr., MD**

SUGGESTED READINGS

Chou DTS, Ramachandran M: Legg-Calvé-Perthes' disease. *paediatric orthopaedics clinical practice*, London, 2016, Springer, pp 91-105.

Ibrahim T, Little DG: The pathogenesis and treatment of Legg-Calvé-Perthes' disease, *JBJS Reviews* 4(7), 2016.

Kachooei AR: Evolution in diagnosis and treatment of Legg-Calve-Perthes disease, *Arch Bone Jt Surg* 2(2):86-92, 2014.

Karimi MT, McGarry T: A comparison of the effectiveness of surgical and nonsurgical treatment of Legg-Calve-Perthes disease: a review of the literature, *Adv Orthop* 490806, 2012.

Laine JC et al: Role of advanced imaging in the diagnosis and management of active Legg-Calvé-Perthes disease, *J Am Acad Orthop Surg* 26(15):526-536, 2018.

Pavone V et al: Aetiology of Legg-Calvé-Perthes disease: a systematic review, *World J Orthop* 10(3):145-165, 2019.

Legionnaires Disease

BASIC INFORMATION

DEFINITION

Pneumonia caused by *Legionella pneumophila*

SYNONYM

Legionella pneumonia

ICD-10CM CODE

A48.1 Legionnaires' disease

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Rough estimates of 18 to 36 cases per 100,000, mostly sporadic cases, occasional community outbreaks due to contaminated fresh water sources. Nosocomial outbreaks have been reported.
PREDOMINANT SEX AND AGE: Male gender with twofold increased risk, age >50
RISK FACTORS: Chronic heart disease, smoking, end-stage renal disease, immunosuppression, cancer. No person-to-person transmission

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute respiratory illness similar to other forms of community-acquired pneumonia.
- Hypoxia, cough, physical exam with localizing chest findings.
- A febrile prodrome with myalgia, anorexia, and headaches can occur, which may be confused with influenza.
- Gastrointestinal symptoms such as diarrhea and abdominal pain are common.

ETIOLOGY

Legionella pneumophila, atypical agent. Grows in warm water sources and can cause outbreaks

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Clinically indistinguishable from other typical and atypical pneumonias

WORKUP

Similar to other pneumonias. CURB 65 or PSI may be used to stratify patients according to severity.

LABORATORY TESTS

- Legionella urinary antigen highly sensitive for Legionella serotype 1 (80% of Legionella strains).
- Additional lab abnormalities such as liver function tests, hyponatremia, elevated creatine kinase, coagulopathy are commonly seen.

IMAGING STUDIES

CXR (Fig. E1) with focal or diffuse consolidation, indistinguishable from other pneumonias

TREATMENT

NONPHARMACOLOGIC THERAPY

Supportive therapy: Oxygen, may require intubation for severe hypoxia, fluid management in case of diarrhea

ACUTE GENERAL Rx

- Antibiotic coverage for atypical pneumonia. Azithromycin or levofloxacin are recommended. Treatment duration similar to other forms of community-acquired pneumonia, with the exception of severely immunosuppressed patients who are treated for up to 21 days.
- Table 1 summarizes preferred therapy for Legionnaire disease.

DISPOSITION

- Mild cases managed as outpatient are likely under-diagnosed due to lack of specific testing.
- Recognized as cause of severe pneumonia with high rates of ICU admission.

REFERRAL

- Pulmonologist/infectious disease specialist in severe cases.
- Identified cases should be reported to public health authorities for prompt recognition of outbreaks.

PEARLS & CONSIDERATIONS

COMMENTS

Pontiac fever is an acute systemic illness caused by Legionella without specific pneumonia features. Local outbreaks have been reported.

PREVENTION

Prompt recognition of clusters to identify water source is pivotal to contain an outbreak.

PATIENT & FAMILY EDUCATION

To be recognized as potential public health problem. No risk for transmission to other family members.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pneumonia, Bacterial (Related Key Topic)

AUTHOR: **Sebastian G. Kurz, MD**

TABLE 1 Preferred Therapy for Legionnaires Disease

Clinical Condition	First Choices	Dosage*,†	Second Choices	Dosage*,†
Mild pneumonia inpatient or outpatient, not immunocompromised	Azithromycin *or*	500 mg 1×/day for 3-5 days	Doxycycline	200 mg load, then 100 mg 2×/day for 10-14 days
	Levofloxacin *or*	500 mg 1×/day for 7-10 days	Erythromycin	500 mg 4×/day for 10-14 days
	Ciprofloxacin *or*	500 mg 2×/days for 7-10 days		
	Moxifloxacin *or*	400 mg 1×/day for 7-10 days		
	Clarithromycin	500 mg 2×/day for 10-14 days		
Moderate to severe pneumonia or immunocompromised‡	Azithromycin *or*	500 mg 1×/day for 5-7 days	Ciprofloxacin *or*	750 mg 2×/day for 14 days
			Moxifloxacin *or*	400 mg 1×/day for 14 days
	Levofloxacin	500 mg 1×/day for 7-10 days 750 mg 1×/day for 5-7 days	Erythromycin *or*	750-1000 mg IV 4×/day for 3-7 days, then 500 mg 4×/day for a total course of 21 days
			Clarithromycin	500 mg IV 2×/day for 3-7 days, and then 500 mg 2×/day for a total course of 21 days

*Dosage adjustments have to be made for renal insufficiency for some of these drugs. Patients with mild disease may be treated entirely with oral therapy, whereas for severely ill patients parenteral therapy is advised until improvement is seen and oral absorption is sufficient.
†Therapy duration may need to be considerably longer for patients with lung abscesses, empyema, endocarditis, or extrathoracic infection.
‡Severely immunocompromised patients may require courses of therapy at the high end of the duration ranges given, or even longer. Close clinical follow-up is required to detect possible relapse after antibiotics have been discontinued.
IV, Intravenous.
From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.

SUGGESTED READINGS

Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 8, Philadelphia, 2015, Elsevier, pp 2633-2644.

Chahin A, Opal SM: Severe pneumonia caused by *Legionella pneumophila*: differential diagnosis and therapeutic considerations, *Infect Dis Clin N Am* 31:111-121, 2017.

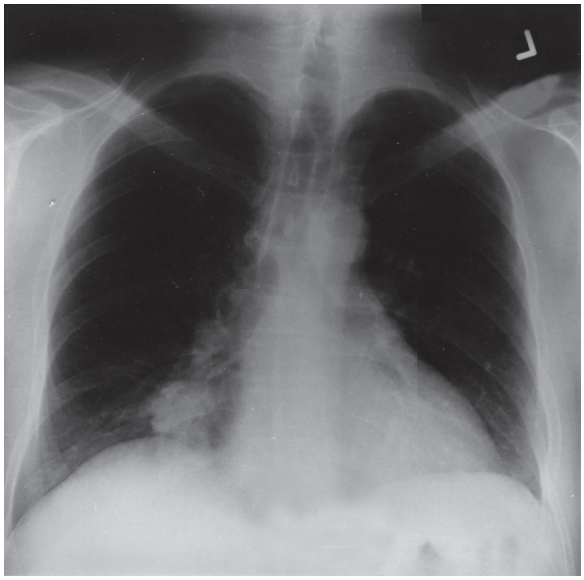

FIG. E1 Posteroanterior chest radiograph of a patient with community-acquired Legionnaires disease *(L. pneumophila)* manifesting as a right lower lobe nodular opacity. (From Goldman L, Schafer AI: *Goldman-Cecil medicine,* ed 24, Philadelphia, 2014, Elsevier.)

BASIC INFORMATION

DEFINITION

Leishmaniasis is a vector-borne infectious disease caused by a heterogeneous group of obligate intracellular protozoan parasites belonging to the genus *Leishmania* and resulting in a variety of different clinical syndromes. Leishmaniasis parasites mostly are transmitted to humans through sand fly bites.

SYNONYMS

Kala-azar
Old World leishmaniasis
New World leishmaniasis

ICD-10CM CODES

B55.9	Leishmaniasis, unspecified
B55.0	Visceral leishmaniasis
B55.1	Cutaneous leishmaniasis
B55.2	Mucocutaneous leishmaniasis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: ~2 million total new cases and 500,000 visceral cases occur each yr with almost 400 million people at risk for the disease. It is endemic in nearly 100 countries.

- Can be classified geographically into New World versus Old World disease (Fig. E1).
- Infection can be divided into cutaneous, mucocutaneous, visceral disease.
- Different *Leishmania* species are associated with different patterns of disease.
- Incubation period: From 1 wk to many mo for cutaneous and mucosal leishmaniasis; 2 to 6 mo (range is 10 days to yrs) for visceral leishmaniasis.
- Mode of transmission: By the female sand fly vector (mainly of the genera *Phlebotomus* in the Old World and *Lutzomyia* in the New World) in the majority of cases, but it also can be spread via shared needles, blood transfusions, organ transplants, vertically from the mother to fetus, or sexually.
- The reservoir for the parasite consists of canines, rodents, and humans.
- Cutaneous leishmaniasis had been reported in U.S. military personnel in Iraq (more than 2000 cases from 2001 to 2015).
- Travelers to endemic areas have become infected after <1 wk of exposure.
- Untreated visceral leishmaniasis is almost always fatal.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Cutaneous syndrome:

- Localized cutaneous leishmaniasis: Usually presents as an ulcerative skin lesion at the site of the sand fly bite (Fig. E2), which resolves within several wk or mo, often leaving a residual scar
- Mucosal leishmaniasis–usually caused by *L. braziliensis;* also known as "espundia"
- Leishmaniasis recidivans
- Diffuse cutaneous leishmaniasis visceral syndrome
- Viscerotrophic leishmaniasis: Fever, chronic fatigue, malaise, cough, intermittent diarrhea, and abdominal pain. Signs include adenopathy, hepatosplenomegaly, hyperpigmentation of skin, petechiae, jaundice, edema, and ascites
- Post–kala-azar dermal leishmaniasis: Generalized cutaneous rash that is often papular or nodular; severe forms with desquamation of skin and mucosa

ETIOLOGY

- Old World parasite: *Leishmania tropica, L. major, L. aethiopica, L. donovani, L. infantum.*
- New World parasite: *L. braziliensis and L. mexicana complex, L. chagasi, L. b. guyanensis, L. b. panamensis.*
- *L. chagasi* has recently been found to be identical to *L. infantum.*
- More than 20 distinct species of *Leishmania* have been described.
- After the host has been inoculated by the bite of the sand fly, the parasites in promastigote stage are phagocytized by macrophages in the dermis and transform into amastigotes,

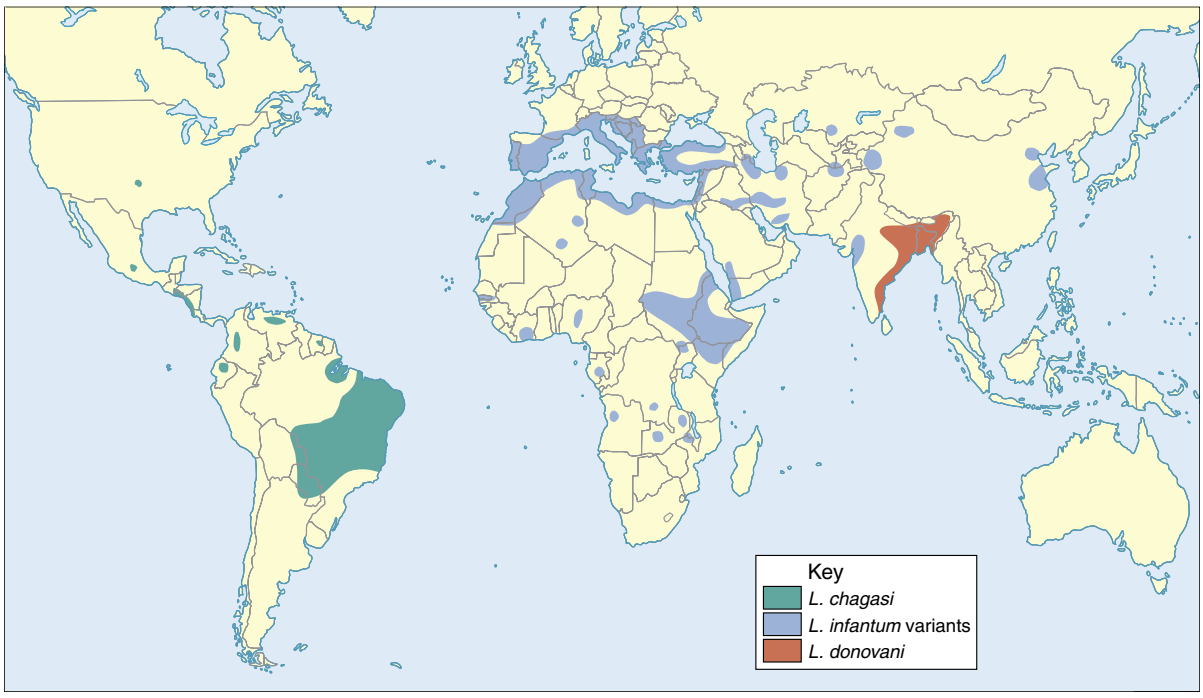

FIG. E1 Epidemiology of visceral leishmaniases (VL). VL caused by parasites of the *Leishmania donovani–Leishmania infantum* complex occurs in the Mediterranean littorals, the Middle East, adjacent parts of the former Soviet Union, the Sudan, East Africa, the Indian subcontinent, China, and South America *(Leishmania chagasi).* An arid, warm environment provides ideal ecologic conditions for the breeding of many species of sand fly. Zoonotic kala-azar due to *L. infantum* and *L. chagasi* is commonly associated with dry, rocky hill country, where cases typically are scattered. In India, *L. donovani* is essentially an anthroponosis. This type of kala-azar may occur in severe epidemic fashion, as can kala-azar in the Sudan. (From Hoffman R: *Hematology, basic principles and practice*, ed 6, Philadelphia, 2013, Saunders.)

FIG. E2 Cutaneous leishmaniasis. An erythematous, crusted plaque in a 4-yr-old child. (Courtesy William Burrows, M.D. In Paller AS, Mancini, AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

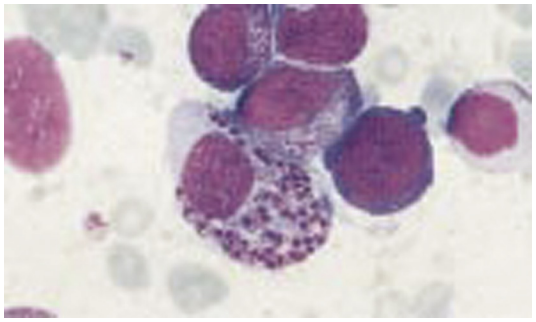

FIG. E3 *Leishmania infantum* in macrophage from bone marrow. Although typically found in macrophages as shown here, isolated extracellular amastigotes from disrupted host cells are commonly seen in such preparations. (From Hoffman R: *Hematology, basic principles and practice*, ed 6, Philadelphia, 2013, Saunders.)

which replicate by simple binary division, rupture the cell and invade other reticuloendothelial cells.

DX DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Malaria
- African trypanosomiasis
- Brucellosis
- Enteric fever
- Bacterial endocarditis
- Generalized histoplasmosis
- Chronic myelocytic leukemia
- Hodgkin disease and other lymphomas
- Sarcoidosis
- Hepatic cirrhosis
- Tuberculosis

WORKUP

- Full thickness punch biopsy of a skin lesion
- On biopsy specimen can perform culture and histology
- PCR: SMART Leish PCR, RT-PCR
- Bone marrow bx for visceral disease
- Splenic aspirate often done in resource-poor settings

LABORATORY TESTS

- CBC: Anemia, neutropenia, thrombocytopenia, and eosinopenia
- LFTs: Hypergammaglobulinemia, hypoalbuminemia, and hyperbilirubinemia
- Elevated BUN and creatinine
- Specific diagnosis confirmed by intracellular amastigote (Fig. E3) in Giemsa-stained impression smears or sectioned tissue or culture performed in NMN (Novy, MacNeal, Nicolle) or Schneider drosophila medium
- Serologic diagnosis: ELISA, direct agglutination tests, and K39 ELISA are limited by the fact they cannot detect past from present infection, and there may be cross-reaction between visceral and cutaneous leishmaniasis.
  1. Serology is not effective for diagnosis of cutaneous leishmaniasis.
- Montenegro skin test: Not in use in the U.S.
- PCR is one of the most sensitive diagnostic tests for cutaneous leishmaniasis. Examples include SMART Leish PCR and RT-PCR. These tests are also excellent for species detection.

RX TREATMENT

NONSPECIFIC OR SUPPORTIVE CARE

- Nutritional diet
- Antimicrobial agents for concurrent infections
- Blood transfusions
- Iron and vitamins

SPECIFIC ANTILEISHMANIAL THERAPY:

Visceral leishmaniasis

- Liposomal amphotericin B (AmBisome) in various regimens is the preferred drug for visceral leishmaniasis
- Pentavalent antimonials: Sodium stibogluconate (Pentostam) IV/IM and meglumine antimoniate IV/IM (Glucantime) may be used, but they can have significant cardiotoxicity and cause a clinical pancreatitis, and in some geographic areas (e.g., in Asia, northern India, and Nepal) a resistance has emerged.
- Miltefosine (2.5 mg/kg/day orally in two divided doses for 28 days, but patient must weigh at least 30 kg) is an effective oral choice for cutaneous, mucosal, and visceral disease. Teratogenic in animals, so cannot be used in pregnancy.

Extraintestinal leishmaniasis

- Pentavalent antimony or liposomal amphotericin B
- Miltefosine

Cutaneous leishmaniasis (mild disease)

- Paromomycin ointment BID × 10 days, rest 10 days, then 10 more days
- Paromomycin cream (15%)
- Cryotherapy with liquid nitrogen or laser therapy
- Intralesional antimony with Pentostam or Glucantime

Cutaneous leishmaniasis (moderate disease)

- Miltefosine
- Sodium stibogluconate (Pentostam)
- Meglumine antimonate (Glucantime)
- Fluconazole 200 mg PO qd × 6 wk
- Ketoconazole 600 mg PO qd × 30 days
- Amphotericin B

DISPOSITION

Follow-up examination is important for early detection and treatment relapse.

REFERRAL

To infectious disease experts for accurate diagnosis and management

PEARLS & CONSIDERATIONS

COMMENTS

- Prevention by reservoir control: Destruction of animal reservoir hosts, mass treatment of humans in kala-azar–prevalent areas.
- Prevention by vector control: Includes use of bed nets and screens, insecticide spraying in domestic and peridomestic areas.
- Vaccines are in various stages of development and clinical trials. None are licensed or commercially available at this time.
- Co-infection with HIV can lead to more severe disease and/or atypical presentations and requires more intense therapy as well as antiretroviral therapy.

AUTHOR: **Glenn G. Fort, MD, MPH**

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BASIC INFORMATION

DEFINITION

Lemierre syndrome refers to a jugular vein suppurative thrombophlebitis preceded by a pharyngitis and is often associated with a bacteremia with organisms of the oral flora and subsequent septic emboli. The most common pathogen is *Fusobacterium necrophorum*.

SYNONYMS

Postanginal sepsis
Necrobacillosis

ICD-10CM CODE
I80.8 Phlebitis and thrombophlebitis of other sites

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.6 to 3.6 cases per million overall but increases to 14.4 cases per million in ages 15 to 24 yr, and cases seem to be increasing.
PEAK INCIDENCE: In one study of 114 patients with Lemierre syndrome, the median age was 22 yr.
RISK FACTORS: Cases appear to be more common in the 15 to 24 yr age group due to involution of tonsillar tissue predisposing this age group to infections in tonsillar crypts.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- A diagnosis of Lemierre syndrome can be made with the following criteria:
  1. Recent pharyngeal infection followed 4 to 5 days later by high fever
  2. Complication of septic emboli: Lung (most frequent: Over 90%), joint, muscle
  3. Thrombosis of the internal jugular vein or findings of positive blood cultures with *F. necrophorum*
- Pharyngeal infection can be tonsillitis, pharyngitis, or common sore throat. Rarer presentations include neck swelling, odontogenic infections, central nervous system (CNS) infections.

ETIOLOGY

The infection begins as a localized oropharyngeal infection, which then spreads to involve the lateral pharyngeal space and then the structures of the carotid sheath, eventually causing an ipsilateral septic thrombophlebitis of the internal jugular vein and then septic emboli from the thrombus (Fig. E1).

MICROBIOLOGY

- Fusobacterium: *Fusobacterium necrophorum* is the most common isolated organism and is an anaerobic gram-negative rod that is part of the oral flora and causes up to 10% of cases of throat infection. Its detection in blood culture should prompt consideration of this syndrome. Other possible Fusobacteria include *F. nucleatum*
- Streptococcus: Includes *Streptococcus pyogenes*
- Others: *Eikenella corrodens, Porphyromonas asaccharolytica*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Viral pharyngitis
- Epstein-Barr virus
- Group A Streptococcal pharyngitis
- Peritonsillar abscess
- Retropharyngeal abscess

WORKUP

Consists of a clinical suspicion of a patient worsening after a pharyngitis, cultures, and appropriate imaging studies

LABORATORY TESTS

- Complete blood count with differential
- Blood cultures, as patients usually have high fever; Fusobacteria may take 2 to 7 days to grow
- C-reactive protein

IMAGING STUDIES

- High-resolution CT scans with contrast are best to detect the thrombophlebitis of the internal jugular vein and by extension the septic emboli to the lung.
- Ultrasound and MRI can also be used to demonstrate the thrombus in internal jugular vein.

TREATMENT

Antibiotics are the mainstay of treatment, with anticoagulation still a controversial issue.

ACUTE GENERAL Rx

- Fusobacteria can be resistant to penicillin and may produce beta-lactamase enzymes.
- Beta-lactamase resistant beta-lactam antibiotics are considered antibiotics of choice:
  1. Ampicillin-sulbactam: 3 g IV q6h for adults
  2. Piperacillin-tazobactam: 4.5 g IV q6h for adults
- Other effective antibiotics: Carbapenems antibiotics: Meropenem or imipenem.
- Metronidazole offers excellent coverage for *Fusobacterium* but not *Streptococci*.
- Length of therapy in studies ranges from 10 days to 8 wk. Mean duration is 4 wk.
- Anticoagulation is controversial but has been used only with evidence of extension of the clot.

DISPOSITION

Surgery: Accessible abscesses should be drained. Ligation of the affected vein is rarely needed.

PEARLS & CONSIDERATIONS

COMMENTS

- *Fusobacterium necrophorum* produces hemagglutinin, which promotes platelet aggregation that could then yield to thrombus formation.
- Lemierre syndrome is also known as the "forgotten disease" because the antibiotic era dramatically reduced cases, but cases may be rising again due to emphasis on avoiding excess antibiotics.
- Mortality rate is approximately 2%.

RELATED TOPICS

Pharyngitis/Tonsillitis (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

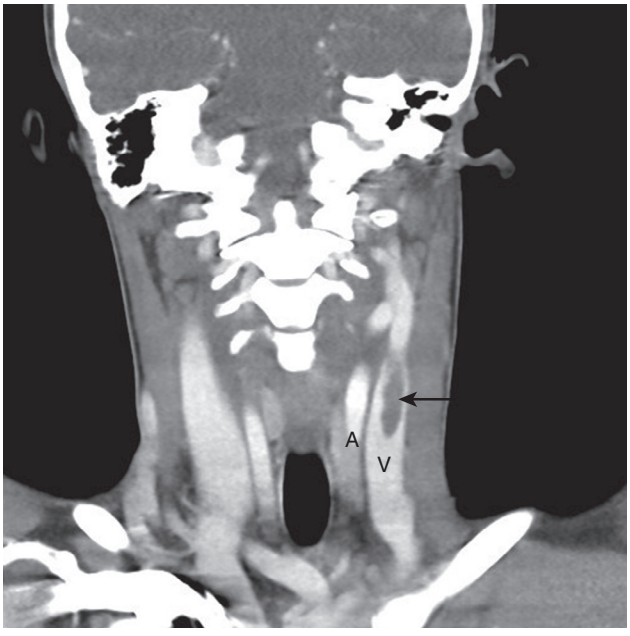

FIG. E1 Coronal computed tomography of the neck with contrast reveals a soft tissue attenuation filling defect in the left internal jugular vein (*black arrow*). The left common carotid artery (*A*) and internal jugular vein (*V*) are indicated. (Reproduced with permission, Ochsner Clinic Foundation, 2017. From Harper LK et al: Lemierre syndrome: the forgotten disease, *Ochsner J* 16(1):7-9, 2016.)

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BASIC INFORMATION

DEFINITION

Leprosy is a chronic granulomatous infectious disease of humans that primarily affects the skin and peripheral nerves.

SYNONYM

Hansen disease

ICD-10CM CODES

A30.0	Indeterminate leprosy
A30.1	Tuberculoid leprosy
A30.2	Borderline tuberculoid leprosy
A30.3	Borderline leprosy
A30.4	Borderline lepromatous leprosy
A30.5	Lepromatous leprosy
A30.8	Other forms of leprosy
A30.9	Leprosy, unspecified
B92	Sequelae of leprosy

EPIDEMIOLOGY & DEMOGRAPHICS

- The number of cases worldwide has fallen from >5.4 million cases in 1985 to about 211,000 cases in 2017 in 154 different countries, according to the World Health Organization (WHO).
- Nearly 75% of the cases of leprosy are found in India, Brazil, Nepal, Mozambique, Madagascar, and Myanmar (see Fig. E1).
- More than 85% of the cases diagnosed in the United States are found among immigrants.
- Annual incidence in the United States is between 50 and 100 new cases per yr (Fig. E2). In 2014 there were 175 new cases in the U.S., 75% of them from 7 states: Arkansas, California, Florida, Hawaii, Louisiana, New York, and Texas.
- Leprosy is more common in men than women (2:1).
- Leprosy can occur at any age but usually is found in young children.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- A skin lesion: Most common initial presentation
- Sensory loss
- Anhidrosis
- Neuritic pain
- Palpable peripheral nerves
- Nerve damage (most commonly affected nerves are ulnar, median, common peroneal, posterior tibial, radial cutaneous nerve of the wrist, facial, and posterior auricular)
- Muscle atrophy and weakness
- Foot drop
- Claw hand and claw toes
- Lagophthalmos, nasal septal perforation, collapse of bridge of nose, loss of eyebrows resulting in "leonine" facies
- Leprosy can present along a spectrum from simple cutaneous skin lesions (Fig. E3, Fig. E4) with minimal sensory loss to severe extensive skin involvement (Fig. E5), painful neuritis, muscle wasting and contractures, and multiple peripheral nerve damage. Erythema nodosum leprosum (ENL) occurs in half of patients with borderline lepromatous or lepromatous leprosy, 90% of the time within yrs of institution of antibiotic treatment for Hansen disease or during pregnancy. ENL is a circulating immune complex–mediated disease. Skin lesions are erythematous, subcutaneous, and dermal nodules that are

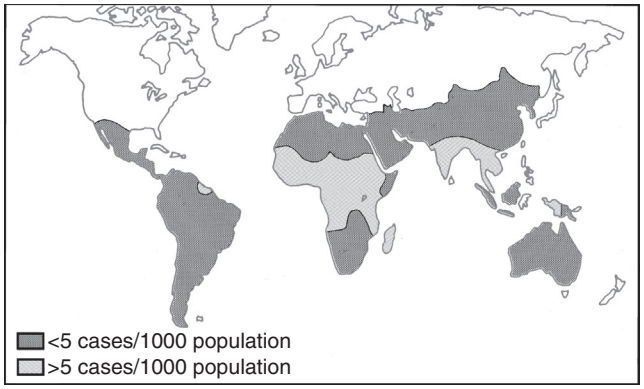

FIG. E1 Geographic distribution of leprosy. (From Souhami RL, Moxham J: *Textbook of medicine,* ed 4, London, 2002, Churchill Livingstone.)

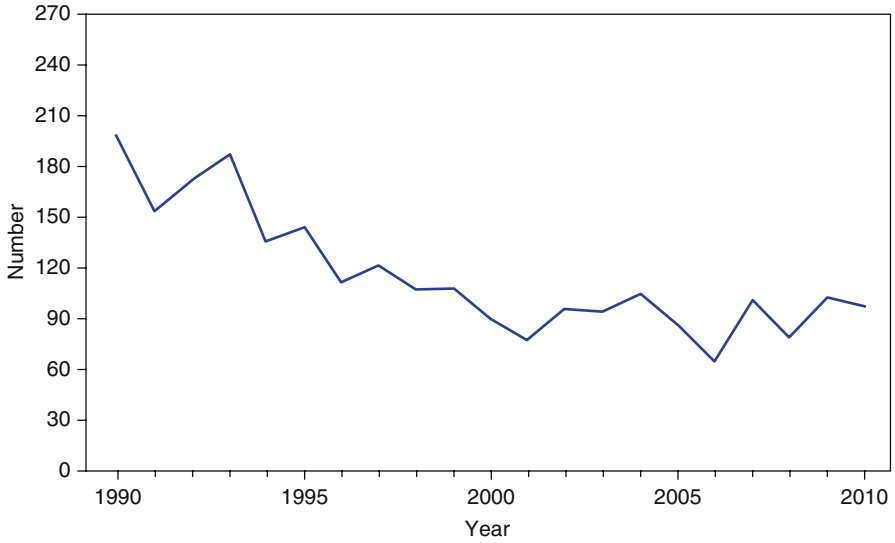

FIG. E2 Hansen disease (leprosy). Number of reported cases by yr—United States, 1990-2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59:1-111, 2012.)

FIG. E3 Lepromatous leprosy, ear involvement. (From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

FIG. E4 Histoid leprosy. (From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

FIG. E5 Type 1 reaction in Hansen disease. (Courtesy Curt Samlaska, MD, from James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

FIG. E6 Erythema nodosum leprosum. (From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

widely distributed (Fig. E6). They do not occur at sites of existing skin lesions
- Lucio phenomenon is an uncommon and unusual reaction that occurs in patients with diffuse lepromatous leprosy (DLL) of the "la bonita" type, most often found in western Mexico, and is often the reason for the initial presentation in affected patients. Purpuric macules evolve to bullous lesions that rapidly ulcerate, especially below the knees (Fig. E7)

ETIOLOGY

- Leprosy is caused by *Mycobacterium leprae,* an obligate intracellular acid-fast rod.
- The mode of transmission is thought to be through nasal secretions. Spread in humans is thought to occur via the respiratory route or entry through broken skin in patients with multibacillary disease or extensive paucibacillary disease.

FIG. E7 Lucio phenomenon, early bullous lesions. (From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

- Zoonotic transmission from armadillos has been shown in a few case reports. More common in the southern region of the United States such as Louisiana and Texas.
- The majority of people exposed to patients with leprosy do not develop the disease because of their natural immunity. Variants of genes in the *NOD2*-mediated signaling pathway (which regulates the innate immune response) are associated with susceptibility to infection with *M. leprae.*

Dx DIAGNOSIS

- The diagnosis of leprosy (Table E1) relies on a detailed history and physical examination and is established by the demonstration of acid-fast bacilli in skin smears or skin biopsies of the affected sites.
- Leprosy has been classified according to the WHO system into:
  1. Paucibacillary leprosy is defined as <5 skin lesions with no bacilli on skin smear.
  2. Multibacillary leprosy is defined as >5 skin lesions and may be skin-smear positive. This system of classification is designed for ease of use by paraprofessionals.
- Hansen disease may present with a broad spectrum of clinical disease. The Ridley-Jopling system classifies cases based on clinical, bacteriologic, immunologic, and histopathologic features (Table E2) as follows:
  1. Indeterminate leprosy
  2. Tuberculoid leprosy (paucibacillary [few organisms], intense inflammatory reaction (Fig. E8); few, well-demarcated skin lesions)

TABLE E1 Criteria for Classification of Leprosy

Group	Clinical Features	Histologic Features	Lepromin Reaction (Mitsuda)	Bacillary Density
Tuberculoid	• Single or few anesthetic macules or plaques • Borders well defined • Peripheral nerve involvement common	• Epithelioid-lymphocyte granulomas, with or without giant cells, in skin and nerves • No subepidermal clear zone • Bacilli in nerves, but rare	Strongly positive	Rare
Borderline tuberculoid	• Lesions similar to those of tuberculoid, but more numerous • Borders of lesions less distinct • Satellite lesions sometimes present around larger lesions • Peripheral nerve involvement common	• Granulomas similar to those in tuberculoid • Nerves are infiltrated • Bacilli frequently found in nerves	Positive	Scanty
Borderline	• More lesions than in borderline tuberculoid • Borders more vague • Satellite lesions often seen • Peripheral nerve involvement common	• Epithelioid cells and histiocytic infiltrations focalized by lymphocytes • Nerves show increased cellularity • Bacilli readily found in nerves	Negative or weakly positive	Moderate
Borderline lepromatous	• Lesions are numerous and similar to those of borderline • Some nerve damage	• Histiocytic infiltrations show a tendency to evolve toward epithelioid cells and foamy cells • Lymphocytes present • Nerves have less cellular infiltration • Bacilli plentiful in nerves	Negative	Heavy
Lepromatous	• Multiple, nonanesthetic, macular or papular, symmetrically distributed lesions • No neural lesions until late • Late complications of madarosis, leonine facies, testicular damage	• Foamy histiocytes containing large numbers of bacilli • Few or no lymphocytes • Subepidermal clear zone • Numerous bacilli in nerves and perineurium without significant intraneural cellular infiltration	Negative	Very heavy
Indeterminate	Vaguely defined hypopigmented or erythematous macule	• Often indistinguishable from mild nonspecific dermatitis • Lymphocytes and histiocytes around skin appendages and nerves	Weakly positive or negative	Negative or scanty

From Cherry JD et al.: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

TABLE E2 Spectrum of Host-Parasite Relationship in Hansen Disease

1. Indeterminate leprosy
2. Tuberculoid leprosy (paucibacillary [few organisms], intense inflammatory reaction (Fig. E8); few, well-demarcated skin lesions)
3. Borderline tuberculoid leprosy (Fig. E9)
4. Borderline lepromatous leprosy (Fig. E10)
5. Lepromatous leprosy (multibacillary [numerous organisms], inadequate host response; diffuse, poorly organized skin lesions [Fig. E11])
6. This system of classification is more accurate and is used by physicians

Modified from Dr. J. H. Petit, from James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.

FIG. E8 Tuberculoid leprosy. (From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

3. Borderline tuberculoid leprosy (Fig. E9)
4. Borderline lepromatous leprosy (Fig. E10)
5. Lepromatous leprosy (multibacillary [numerous organisms], inadequate host response; diffuse, poorly organized skin lesions [Fig. E11])
6. This system of classification is more accurate and used by physicians

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of leprosy includes sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, lymphomatoid granulomatosis, carpal tunnel syndrome, cutaneous leishmaniasis, fungal infections and other causes of hypopigmented, hyperpigmented, and erythematous skin lesions.

WORKUP

Any patient who presents with skin lesions and a sensory or muscle deficit should have a workup for leprosy.

FIG. E9 Borderline tuberculoid leprosy. (From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

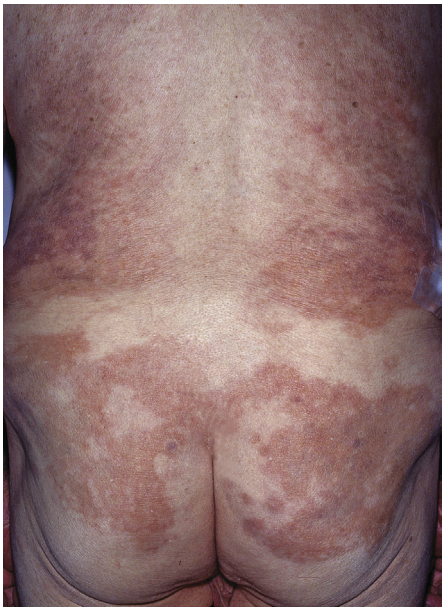

FIG. E10 Borderline lepromatous leprosy. (From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

LABORATORY TESTS

- *Mycobacterium leprae* cannot be cultured on artificial media. The bacteria proliferate when injected into the footpads of mice or armadillos and can be used for drug-sensitivity testing.
- Serologic tests, including the antibody to phenolic glycolipid 1 (PGL-1) and bacilli detection in tissue using PCR, are available and used for diagnostic confirmation and research epidemiologic studies.
- Lepromin intradermal skin test is not diagnostic and not for commercial use.
- Skin biopsies of active sites are stained for acid-fast bacilli.
- Peripheral nerve biopsy can be done in patients with sensory loss and no skin lesions. Common nerves biopsied are the radial cutaneous nerve of the wrist and the sural nerve of the ankle.

FIG. E11 Lepromatous leprosy. (From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

IMAGING STUDIES

Radiograph studies are usually of no benefit in the diagnosis or treatment of leprosy.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical therapy for patients with upper and lower extremity deformities.
- Proper foot care and footwear to prevent ulcer formation.

ACUTE GENERAL Rx (TABLE E3)

CURRENT STANDARD U.S. REGIMENS (FOR ADULTS): For paucibacillary leprosy:

- Dapsone 100 mg PO q day plus rifampin 600 mg PO q day for 6 mo (World Health Organization regimen). The National Hansen's Disease Program (NHDP) recommends dapsone 100 mg/day plus rifampin 600 mg/day PO for 12 mo.
- For multibacillary leprosy:
- Dapsone 100 mg PO q day plus clofazimine 50 mg/day plus rifampin 600 mg PO q day for 2 yr, (NHPD; WHO recommends 1 yr of therapy).
- An alternative regimen consists of dapsone 100 mg/day plus rifampin 600 mg/day plus minocycline 100 mg/day for 24 mo if clofazimine is refused or unavailable.

CHRONIC Rx

- If relapse occurs, the patient is treated with the same medical regimen; drug resistance is low.
- If relapse is from paucibacillary to multibacillary, the medical regimen for multibacillary should be used for therapy.

DISPOSITION

- Relapse is <1% for multibacillary and just over 1% in paucibacillary cases.
- Patients are initially followed up monthly and, when treatment is completed, every 3 to 6 mo for the next 5 to 10 yr.
- Some patients develop reactions known as erythema nodosum leprosum and reversal reaction, usually during treatment.
  1. Erythema nodosum leprosum results in tender nodules and is treated with thalidomide 100 mg qid, then tapered with response. Cases not responsive to thalidomide are treated with prednisone 60 to 80 mg qday.
  2. Reactive reaction results in the development of new skin lesions with swelling and erythema of existing lesions. Treatment is with prednisone 60 to 80 mg a day then a taper dose. Clofazimine and dapsone are options. Do not use thalidomide.
  3. Other agents used in the treatment of leprosy include ofloxacin, moxifloxacin, minocycline, and clarithromycin.

REFERRAL

- National Hansen's Disease Programs (NHDP) Center in Baton Rouge, Louisiana, and 15 outpatient clinics in the United States offer consultations and treatment. Telephone: 1-800-642-2477.
- Directly observed therapy (DOT), much like DOT for tuberculosis, is highly desirable and should be used if feasible, at least in the first 6 to 12 mo of therapy.
- Any suspected case of leprosy merits an infectious disease consultation. Consultation with orthopedics, podiatry, ophthalmology, physical therapy, plastic surgery, and psychology are all in order for any of the potential sequelae of the disease.

PEARLS & CONSIDERATIONS

COMMENTS

- The risk of transmission is low in patients with leprosy, and therefore no infection control precautions of hospitalized patients are needed.
- Family members and close contacts need to be examined frequently for the development of lesions.
- Dapsone or rifampin prophylaxis is not recommended in the prevention of leprosy.
- BCG vaccination has a 50% efficacy in the prevention of leprosy and may be considered.

RELATED CONTENT

Leprosy (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

TABLE E3 Suggested Dosing Regimens for Leprosy from the World Health Organization[1,2] and National Hansen's Disease Program[3]

Leprosy Classification	Drug	DOSE[d]			Duration
		Age <10 yr	Age 10-14 yr	Age ≥15 yr	
Paucibacillary[a]	Dapsone	1-2 mg/kg/day	1-2 mg/kg/day	100 mg daily	WHO: 6 mo NHDP: 12 mo
	Rifampin	10-20 mg/kg/day	10-20 mg/kg/day	600 mg daily (NHDP) 600 mg monthly (WHO)	
Multibacillary[b]	Dapsone	1-2 mg/kg/day	1-2 mg/kg/day	100 mg daily	WHO: 12 mo NHDP: 24 mo
	Rifampin	10 mg/kg/day	10 mg/kg/day	600 mg monthly (WHO) 600 mg daily (NHDP)	
	Clofazimine[c]	50 mg biweekly + 100 mg monthly (WHO) 1 mg/kg/day (NHDP)	50 mg every other day + 150 mg monthly (WHO) 1 mg/kg/day (NHDP)	50 mg daily (NHDP, WHO) ± 300 mg load monthly (WHO)	
	Minocycline (second line for dapsone or clofazimine)	25 mg monthly if <15 kg; 50 mg monthly if 15-30 kg (WHO) ND (NHDP)	50 mg monthly (WHO) ND (NHDP)	100 mg monthly (WHO) 100 mg daily (NHDP)	Extend multidrug therapy to 2 yr[4]
	Ethionamide (second line for clofazimine)	50-75 mg daily if <15 kg, 150-175 mg daily if 15-30 kg (WHO) ND (NHDP)	275-375 mg daily (WHO) ND (NHDP)	275-375 mg daily	
	Ofloxacin (second line for clofazimine or rifampin)	100 mg monthly if <15 kg, 200 mg monthly if 15-30 kg (WHO) Not recommended (NHDP)	200 mg monthly (WHO) Not recommended (NHDP)	400 mg monthly (WHO) 400 mg daily (NHDP)	

Because the National Hansen's Disease Program may change its recommendations for patient management, clinicians in the United States are advised to seek consultation prior to treating any patient with leprosy (800-642-2477, 225-756-3709). *ND,* No dosing information available; *NHDP,* National Hansen's Disease Program; *WHO,* World Health Organization.

[a]Tuberculoid leprosy, borderline-tuberculoid, and indeterminate

[b]Lepromatous, borderline, and borderline-lepromatous

[c]Higher doses may be used for patients with erythema nodosum leprosum.

[d]Pediatric dosing never should exceed adult maximum. Approximate pediatric dosing,[5] as a percentage of adult dosing, can be estimated at 25% for children <15 kg, 50% if 15 to 30 kg, 75% if 30 to 45 kg, and 100% if >45 kg.

From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

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BASIC INFORMATION

DEFINITION

Leptospirosis is a zoonosis caused by the spirochete *Leptospira interrogans.*

SYNONYM

Weil disease

ICD-10CM CODES

A27.9	Leptospirosis, unspecified
A27.0	Leptospirosis icterohemorrhagica
A27.81	Aseptic meningitis in leptospirosis
A27.89	Other forms of leptospirosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- 0.05 cases/100,000 persons
- Significant underestimation because of underreporting
- Hawaii consistently has the highest reported annual incidence rate in the U.S., but outbreaks also have occurred in Puerto Rico

PEAK INCIDENCE: Summer months, into the fall

PREDOMINANT SEX: Male (4:1)

PREDOMINANT AGE: Teenagers and young adults

GENETICS: Neonatal infection can occur.

PHYSICAL FINDINGS & CLINICAL PRESENTATION (SEE TABLE E1, FIG. E1, AND BOX E1)

ANICTERIC FORM:

- Milder and more common presentation of disease
- A self-limited systemic illness with two stages:
  1. Septicemic stage: Presents abruptly with fevers, headache, severe myalgias, rigors, prostration, and sometimes circulatory collapse; conjunctival suffusion is common; skin rash, pharyngitis, lymphadenopathy, hepatomegaly, splenomegaly
  2. Immune stage: Heralded by the production of antibodies, occurs a few days after first stage with similar symptoms and may include kidney disease, jaundice, pneumonitis, hemorrhage, cardiac arrhythmias, headache, and lethargy; hallmark is aseptic meningitis

ICTERIC LEPTOSPIROSIS (WEIL SYNDROME):

- Denotes severe cases, with symptoms of hepatic, renal, and vascular dysfunction
- Biphasic course: Persistence of fever, jaundice, and azotemia
- Complications: Oliguria or anuria, hemorrhage, hypotension, vascular collapse

ETIOLOGY

Caused by a spirochete, *L. interrogans*

- Infects a variety of animals, including most mammals.
- Specific serotypes associated with different hosts—*L. pomona* in livestock, *L. canicola* in dogs, and *L. icterohaemorrhagiae* in rodents.
- Organism penetrates skin or mucous membranes through exposure to animal urine or infected water.
- The most important reservoir for the bacteria is rats.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bacterial meningitis
- Viral hepatitis
- Malaria
- Dengue fever
- Hanta virus
- Influenza
- Legionnaires' disease

WORKUP

Culture of blood, CSF, and urine:

- Organism can be isolated from blood or CSF during first 10 days of illness.
- Urine should be cultured after first wk and for up to 30 days after onset of illness.
- Serology: MAT (microscopic agglutination test) is considered the gold standard but only available in reference labs. An ELISA is also available as a screening test and a PCR is available in reference labs.

LABORATORY TESTS

- Normal or elevated WBCs, at times with leukemoid reactions up to 70,000/mm^3
- Elevated transaminases or bilirubin
- Anemia, azotemia, hypoprothrombinemia in those with icteric illness
- Elevated CK in first phase
- Meningitis in both phases, but aseptic in second phase

IMAGING STUDIES

Chest x-ray may reveal interstitial nonlobar infiltrates.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive
- Observation for dehydration, hypotension, renal failure, hemorrhage

ACUTE GENERAL Rx

- Severe illness: IV penicillin G 1.5 million units IV q6h (children: 250,000 to 400,000 units/kg IV qd in four to six divided doses) or ceftriaxone 1 to 2 g q24h (children: 80 to 100 mg/kg IV once a day) or doxycycline 100 mg IV q12h (children ≥8: 2 mg/kg per day in two equally divided doses). Treatment should last 7 days.

TABLE E1 Signs and Symptoms of Admission in Patients with Leptospirosis in Large Case Series

	Puerto Rico, 1963 *n* = 208	China, 1965 *n* = 168	Vietnam, 1973 *n* = 150	Korea, 1987 *n* = 93	Barbados, 1990 *n* = 88	Seychelles, 1998 *n* = 75	Brazil, 1999 *n* = 193	Hawaii, 2001 *n* = 353	India, 2002 *n* = 74
Percent with:									
Jaundice	49	0	1.5	16	95	27	93	39	34
Anorexia	—	46	—	80	85	—	—	82	—
Headache	91	90	98	70	76	80	75	89	92
Conjunctival suffusion	99	57	42	58	54	—	28.5	28	35
Vomiting	69	18	33	32	50	40	—	73	—
Myalgia	97	64	79	40	49	63	94	91	68
Arthralgia	—	36	—	—	—	31	—	59	12
Abdominal pain	—	26	28	40	43	41	—	51	—
Nausea	75	29	41	46	37	—	—	77	—
Dehydration	—	—	—	—	37	—	—	—	—
Cough	24	57	20	45	32	39	—	—	—
Hemoptysis	9	51	—	40	—	13	20	—	35
Hepatomegaly	69	28	15	17	27	—	—	16	—
Lymphadenopathy	24	49	21	—	21	—	—	—	15
Diarrhea	27	20	29	36	14	11	—	53	—
Rash	6	—	7	—	2	—	—	8	12

From Mandell GL et al: *Principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Churchill Livingstone.

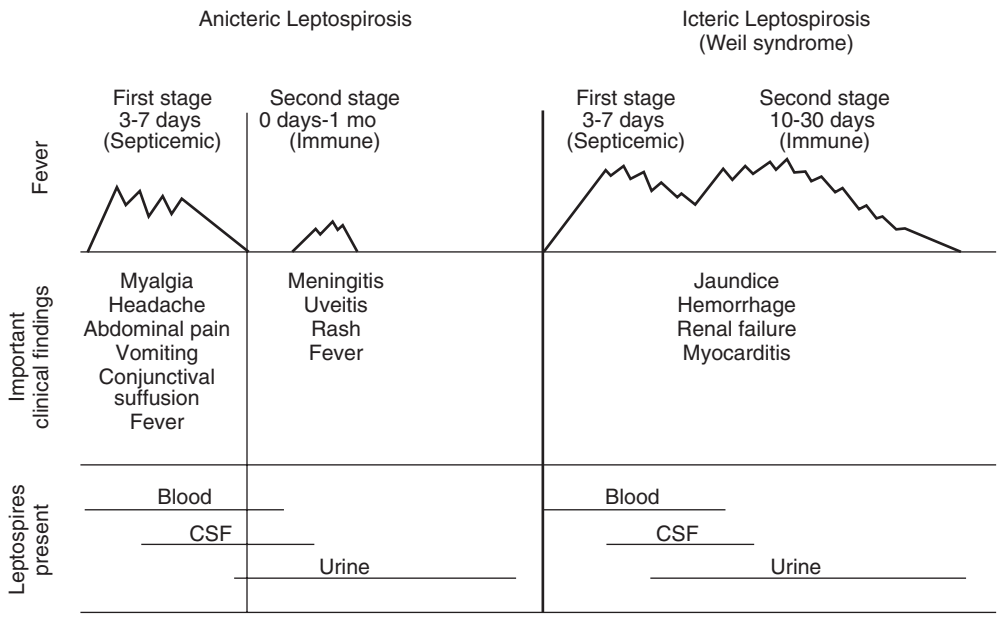

FIG. E1 Clinical course of leptospirosis: Anicteric and icteric disease. *CSF*, Cerebrospinal fluid. (From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.)

BOX E1 Pathophysiology of Specific Clinical Findings in Leptospirosis

Hemolytic Anemia, Jaundice, and Hepatic Injury
- Presence of a hemolysin in the supernate of leptospiral cultures
- Cloned hemolysin of *L. interrogans* serovar Lai demonstrated cell membrane pore-forming activity in vitro
- Thrombocytopenia, depletion of serum prothrombin, depletion of host vitamin K
- Capillary injury, perhaps by toxin
- Hemorrhage of skin or mucosal surfaces and, rarely, gastrointestinal or into a vital organ
- Hepatic manifestations, including jaundice, most likely are the result of hepatocellular injury
- Hemolysis possibly contributing to jaundice
- One or more toxins by leptospires or release of various products after lysis possibly injuring hepatocytes

Renal Injury
- Tubular epithelial cell necrosis, acute vasculitis, segmental thickening of basement membrane, and interstitial edema
- Infiltrates of lymphocytes, monocytes, plasma cells, and neutrophils
- Cells lining the lumen of the renal tubules distended, disorganized, and containing hyaline, granular, epithelial, and bile casts
- Glomeruli showing mesangial hyperplasia, focal fusion of foot processes, swelling of the epithelium in Bowman capsule, and thickening of the basement membrane
- Renal potassium wasting by increased secretion of aldosterone and cortisol
- Tubulointerstitial nephritis, the most common lesion associated with chronic infection
- Leptospires demonstrated in the liver, renal tubules, and interstices of the renal cortex
- Leptospires evading the renal immune system, including absence of complement, downregulation of antigens, delayed lymphocyte infiltration, and delayed colonization of renal tubules
- Impaired renal blood flow leading to nephropathy
- Host response to infection possibly inducing damage as B cells and T cells induce inflammation in the liver and kidneys via a TLR-independent pathway

Pulmonary Involvement
- Pulmonary lesions generally the result of hemorrhage rather than acute inflammation
- Leptospires visualized directly in lung parenchyma
- Alveolar septal deposition of immunoglobulin and complement

Cardiovascular Findings
- Hypovolemia or hypotension from dehydration, bleeding, or third spacing
- Vascular collapse seen with adrenal insufficiency secondary to hemorrhage
- Hypoperfusion, focal hemorrhagic myocarditis, acute coronary arteritis, pericarditis, aortitis, cardiac arrhythmias, congestive heart failure, hypertension, hypovolemia, electrolyte imbalance, or uremia
- Epicardium, endocardium, and myocardium all possibly involved

Ocular Involvement
- Possibly direct *Leptospira*-mediated injury to eye structures, but suggestion that cross-reacting antibodies play a role in *Leptospira*-associated recurrent uveitis

Nervous System Findings
- Meningeal reaction occurs only after the development of antibody; leptospiral meningitis suggested to be a reflection of an antigen-antibody reaction
- Uncommon features of leptospirosis include encephalitis, myelitis, radiculitis, and peripheral neuritis
- Neurologic manifestations attributed to subarachnoid, peripapillary, and subdural hemorrhages

Musculoskeletal Findings
- Myalgia an early clinical feature concurrent with leptospirosis septicemic stage, correlating with the timing of the histologic changes in muscle that often quickly resolve
- Muscle pain that subsides after leptospiral agglutinin titers develop
- Bone involvement in leptospirosis not a significant feature

Other
- No characteristic lesions noted in the adrenal glands, lymph nodes, spleen, gastrointestinal tract, pancreas, ureter, or bladder
- Interstitial edema with monocytic and lymphocytic infiltrates found in testicular tissue associated with impaired spermatogenesis

TLR, Toll-like receptor.
From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

- Mild illness: Doxycycline 100 mg PO bid for 7 days or amoxicillin 25 to 50 mg/kg in three equally divided doses for 7 days or azithromycin 500 mg PO qd for 3 days (children: 10 mg/kg orally on day one then 5 mg/kg per day for 2 days).
- For children ≦8 and pregnant females: Azithromycin or amoxicillin preferred.
- Vitamin K administration if hypoprothrombinemia present.
- Possible Jarisch-Herxheimer reaction when treated with penicillin.

DISPOSITION

- In anicteric leptospirosis, antibiotics can decrease severity and duration of symptoms.
- Icteric leptospirosis, even with supportive therapy, may have a mortality as high as 10%.

REFERRAL

- If more than mild disease
- If no response to treatment

PROPHYLAXIS

- Travelers at increased risk for infection may be given weekly chemoprophylaxis with doxycycline 200 mg once/wk, beginning 1 to 2 days before and continuing throughout the period of exposure.

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Haake DA, Levett PN: Leptospirosis in humans, *Curr Top Microbiol Immunol* 387:65-97, 2015.

Jimenez JIS: Leptospirosis: report from the Task Force on Tropical Diseases by the World Federation of Societies of Intensive and Critical Care Medicine, *J Crit Care* 43:361-365, 2018.

Lau C et al: Leptospirosis: an emerging disease in travelers, *Travel Med Infect Dis* 8(1):33-39, 2010.

Toyokawa T et al: Diagnosis of acute leptospirosis, *Expert Rev Anti Infect Ther* 9(1):111-121, 2011.

BASIC INFORMATION

DEFINITION

Rectal pain, described as a dull ache or pressure high in the rectum, typically worse when sitting

SYNONYMS

Levator spasm
Puborectalis syndrome
Chronic proctalgia
Pelvic tension myalgia
Levator syndrome
Proctodynia

ICD-10CM CODE
K59.4 Anal Spasm

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown
PREVALENCE: 6.6%, by survey
PREDOMINANT SEX AND AGE: Unknown
PEAK INCIDENCE: Unknown
RISK FACTORS: Middle age (30 to 60), Women
GENETICS: Unknown

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Diagnostic Criteria for Levator Ani Syndrome:

1. Chronic or recurrent rectal pain or aching
2. Episodes last 30 min or longer
3. Tenderness during traction on the puborectalis
4. Exclusion of other causes of rectal pain, such as inflammatory bowel disease, intramuscular abscess and fissure, thrombosed hemorrhoids, prostatitis, coccygodynia, and major structural alterations of the pelvic floor
5. Criteria fulfilled for the last 3 mo with symptom onset at least 6 mo before diagnosis

ETIOLOGY

Unclear, but hypothesized to be secondary to spasm of the pelvic floor muscles and elevated anal resting pressures. Alternative hypothesis of dyssynergic defecation as the cause

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Proctalgia fugax
- Unspecified anorectal pain
- Inflammatory bowel disease
- Intramuscular abscess and fissure
- Thrombosed hemorrhoids
- Prostatitis
- Coccygodynia and major structural alterations of the pelvic floor

Differentiation among the three anorectal pain disorders (levator ani syndrome, proctalgia fugax, and unspecified) can be confusing. There is a great deal of overlap in the conditions, which are distinguished by the duration of pain and presence of rectal tenderness.

- Levator ani syndrome: Episodes last more than 30 min; presence of rectal tenderness between episodes
- Proctalgia fugax: Episodes last less than 30 min; no rectal tenderness between episodes
- Unspecified: Does not fit into the above categories

WORKUP

Often can be diagnosed by history and presenting symptoms. Consider additional testing (e.g., stool studies, sigmoidoscopy, ultrasonography, and MRI) to exclude alternative diagnosis.

LABORATORY TEST

Stool studies if concerned about alternative diagnosis

IMAGING STUDIES

- Sigmoidoscopy
- Ultrasonography
- MRI if concerned about alternative diagnosis

TREATMENT

NONPHARMACOLOGIC THERAPY

- Combination of digital massage of the levator ani muscles, sitz baths, and biofeedback
- Massage consists of teaching patients twice a day, after sitz bath, to insert a finger into the anal sphincter and rotate the finger back and forth with as much force as tolerable.
- Biofeedback consists of teaching patients proper straining methods followed by effective pelvic floor relaxation while being monitored by an intra-anal electromyography probe. This is followed by counseling sessions to help patients identify possible triggers for the pain and effective strategies to avoid or cope with these triggers.

ACUTE GENERAL Rx

Muscle relaxants (methocarbamol, diazepam, cyclobenzaprine); best used in combination with massage, sitz baths, and biofeedback

CHRONIC Rx

Same as acute treatment

COMPLEMENTARY AND ALTERNATIVE MEDICINE

- Electrogalvanic stimulation: Found inferior to the above combination treatment
- Botulinum toxin injections into the levator ani muscles: Results similar to placebo injections

DISPOSITION

Outpatient treatment

REFERRAL

- Biofeedback therapy
- Behavioral counseling

PEARLS & CONSIDERATIONS

COMMENTS

Given the nature of the syndrome and pain, patients may be hesitant to discuss their concerns. Furthermore, the nature of treatment therapies may discourage compliance.

PREVENTION

None known

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Nicholas J. Inman, MD,** and **Brian Hawkins, MD**

SUGGESTED READINGS

Bharucha AE, Trabuco E: Functional and chronic anorectal and pelvic pain disorders, *Gastroenterol Clin N Am* 37:685-696, 2008.

Chiarioni G, et al.: Biofeedback is superior to electrogalvanic stimulation and massage for treatment of levator ani syndrome, *Gastroenterology* 138: 1321-1329, 2010.

Rao SSC et al: Anorectal disorders, *Gastroenterology* 150:1430-1442, 2016.

Lichen Planus PTG

BASIC INFORMATION

DEFINITION

Lichen planus (LP) refers to an idiopathic inflammatory disease manifesting with a papular skin eruption characteristically found over the flexor surfaces of the extremities, genitalia, and mucous membranes.

SYNONYMS

Lichen
Lichen planus et atrophicus
LP

ICD-10CM CODES

L43	Lichen planus
L43.0	Hypertrophic lichen planus
L43.1	Bullous lichen planus
L43.9	Lichen planus, unspecified
L43.8	Other lichen planus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: One in every 100 new patients seen in dermatology clinics in the United States is diagnosed with LP.
PREVALENCE: 440 cases/100,000 persons
PREDOMINANT SEX: Found equally between males and females (1:1)
PREDOMINANT AGE: Usually found in people between the ages of 30 and 60 yr
PREDISPOSING FACTORS:

- Associated with other autoimmune disorders (e.g., primary biliary cirrhosis, myasthenia gravis, ulcerative colitis, diabetes)
- Associated with hepatitis C infection
- Drug-induced form affects any area of the body surface (e.g., beta-blocker, methyldopa, penicillamine, quinidine, nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors, sulfonylurea agents)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Lichen planus often manifests with pruritic, flat-topped violaceous papules but the clinical presentation varies depending on the area involved.

History:

- Usually starts on an extremity and may remain localized or spread to involve other areas over a 1- to 4-mo period
- Pruritic

Physical findings:

- Anatomic distribution:
  1. Flexor surface of wrists, forearms, shins, and upper thighs
  2. Neck and back area
  3. Nails (5% to 10% of patients)
  4. Scalp (lichen planopilaris)
  5. Oral mucosa, buccal mucosa, tongue, gingiva, and lips; oral lichen planus can cause extensive desquamative gingivitis
  6. Vulva (Fig. E1), penis (Fig. E2)

Genital mucosa:

- Lesion configuration:
  1. Linear
  2. Annular (more common)
  3. Reticular pattern noted on oral mucosa and genital area
- Lesion morphology:
  1. Papules most common presentation (flat, smooth, shiny) (Fig. E3)
  2. Hypertrophic
  3. Follicular
  4. Vesicular
- Color:
  1. Dark red, bluish red, purplish-violaceous color is noted in cutaneous LP (Fig. E4).
  2. Individual lesions characteristically have white lines visible (Wickham striae) (Fig. E5).
  3. Oral and genital LP has a reticular network of white lines that may be raised or annular in appearance (Fig. E6).

- Scalp lesions may result in alopecia.
- The plaques of lichen planus may be hypertrophic but show the characteristic violaceous coloration and intense hyperpigmentation (Fig. E7).

ETIOLOGY

Lichen planus is characterized by an immunologic reaction mediated by CD8+ T cells. These cells induce keratinocytes to undergo apoptosis. Although the inflammatory reaction is believed to be autoimmune, the antigen targeted by these effector T lymphocytes is unknown.

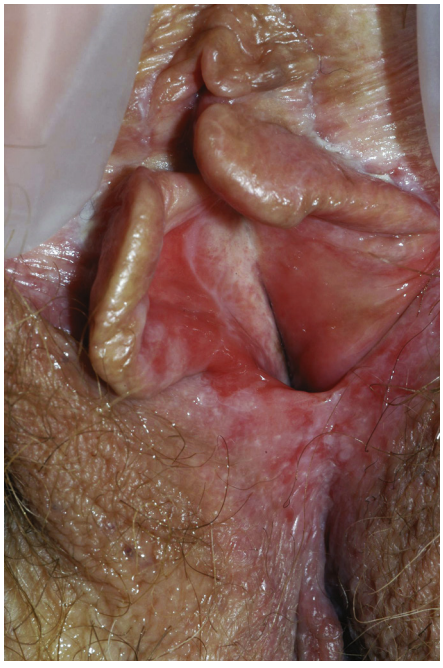

FIG. E1 Lichen planus of the vulva with a white, lacelike pattern and erythema. (From Crum CP et al: *Diagnostic gynecologic and obstetric pathology*, ed 3, Philadelphia, 2018, Elsevier.)

FIG. E2 Lichen planus of the penis. (From Swartz MH: *Textbook of physical diagnosis, history and examination,* ed 7, Philadelphia, 2014, Saunders.)

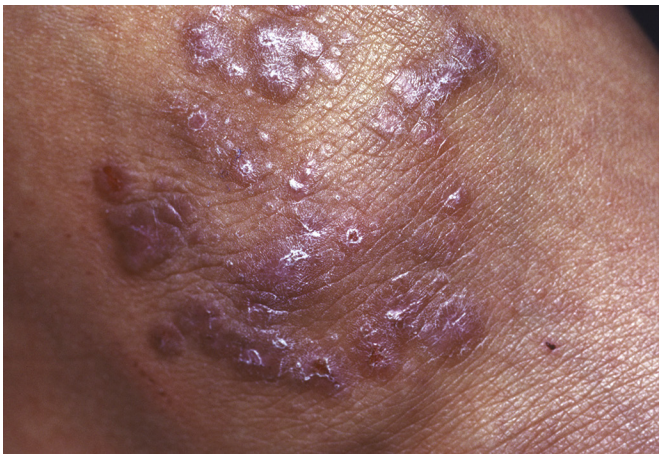

FIG. E3 Flat-topped, purple, polygonal papules of lichen planus. (From Morelli JG: Diseases of the epidermis. In Kliegman RM et al [eds]: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

FIG. E4 Shiny, flat-topped, polygonal, violaceous papules of lichen planus. Note the Wickham striae (linear, whitish-gray streaks) on the surface. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, 2016, Elsevier.)

Dx DIAGNOSIS

- Clinical history and physical findings usually establish the diagnosis of LP.
- Skin biopsy (deep shave or punch biopsy of the most developed lesion) can be performed to confirm the diagnosis.

DIFFERENTIAL DIAGNOSIS

- Drug eruption, psoriasis, Bowen disease, leukoplakia, candidiasis, lupus rash, secondary syphilis, seborrheic dermatitis, chronic graft-versus-host disease
- Table E1 summarizes variants of lichen planus

WORKUP

If the diagnosis is questionable, a skin biopsy is performed.

LABORATORY TESTS

Laboratory tests are not specific for the diagnosis of LP. Lipid panels screening is useful since increases in serum triglycerides and decreases in HDL cholesterol are common in patients with LP.

IMAGING STUDIES

Imaging studies are not helpful in diagnosing LP.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid scratching.
- Use mild soaps and emollients after bathing to prevent dryness.

GENERAL Rx

FOR CUTANEOUS LP:

- Topical steroids (e.g., triamcinolone acetonide 0.1%, fluocinonide 0.05%, clobetasol propionate 0.05% cream or ointment) with occlusion used twice daily
- Acitretin 30 mg/day PO for 8 wk
- Systemic prednisone 30 to 60 mg/day as a starting dose and tapered to 15 to 20 mg/day maintenance for 6 wk can be used for widespread lesions
- Intradermal steroid triamcinolone acetonide 5 mg/ml can be tried for thick hyperkeratotic lesions
- Hydroxyzine 25 mg PO q6h can be used for pruritus
- Phototherapy: PUVA or narrow-band ultraviolet B therapy: 2 or 3 times per wk, for a total of 12 sessions (i.e., one cycle)

FOR ORAL LP:

- Topical steroid fluocinonide in an adhesive base used six times/day for 9 wk
- Topical calcineurin in steroid-unresponsive cases
- Topical or systemic retinoids 0.1% retinoic acid in an adhesive base or gel
- Etretinate 75 mg/day for 2 mo

DISPOSITION

- Spontaneous remissions of cutaneous LP occur in >65% of cases within the first year.
- Spontaneous remission of oral LP usually occurs by 5 yr.
- Approximately 10% to 20% of patients will have recurrence.

REFERRAL

To dermatologist if diagnosis is unclear

! PEARLS & CONSIDERATIONS

COMMENTS

- LP can be remembered as purple, planar, pruritic, polygonal, papules, and plaques (six Ps).
- Lesions can develop at the site of prior skin injury (Koebner phenomenon).
- Although there is an increased risk of squamous cell carcinoma in chronic lesions of mucosal LP, transformation to skin cancer is uncommon.

RELATED CONTENT

Lichen Planus (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

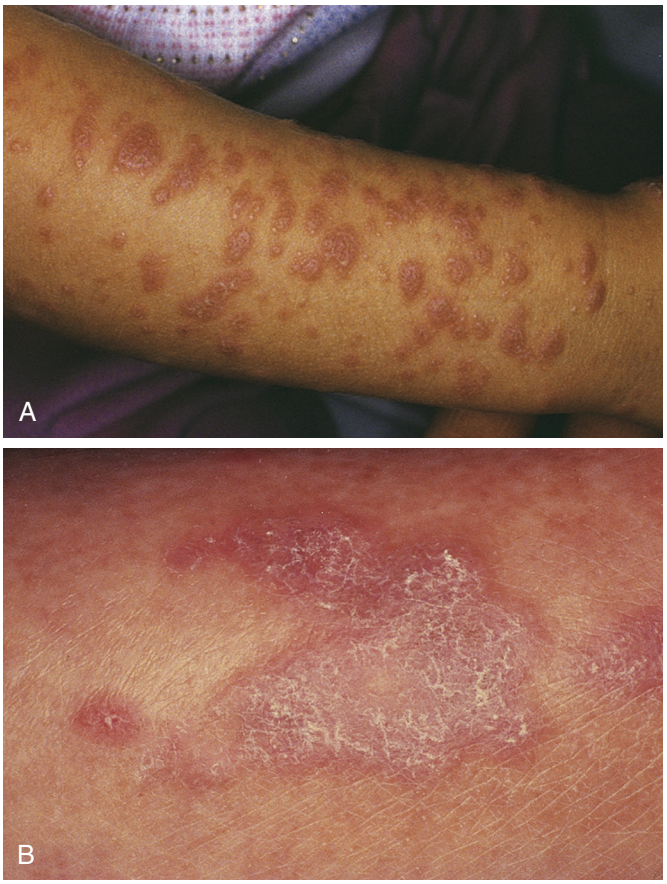

FIG. E5 A and **B,** Lichen planus. Note the fine, reticulated white scales. (Swartz MH: *Textbook of physical diagnosis, history and examination,* ed 7, Philadelphia, 2014, Saunders.)

FIG. E6 Oral lichen planus. Wickham striae on the buccal mucosa. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, 2016, Elsevier.)

FIG. E7 Lichen planus. The plaques of lichen planus may be hypertrophic but show the characteristic violaceous coloration and intense hyperpigmentation. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, 2016, Elsevier.)

TABLE E1 Variants of Lichen Planus

Variant Type	Characteristics
Bullous	Bullae develop on existent LP lesions
LP pemphigoides	LP + bullous pemphigoid with autoimmune reactivity, usually against type XVII collagen (bullous pemphigoid 180 antigen)
Actinic	Onset during spring, summer; primarily sun-exposed surfaces (face, neck, dorsum of arms and hands); often annular configuration; most common in children and young adults
Annular	Occur in 10% of patients, often scattered amid typical lesions of LP
Hypertrophic	Thick, pruritic, hyperkeratotic plaques, especially on the legs and dorsal regions of the feet; persistent
Atrophic	May represent a resolving phase in which larger plaques become centrally depressed with residual hyperpigmentation
Hemorrhagic/purpuric	Shows nonblanching component on diascopy
Linear	LP occurring spontaneously along the lines of Blaschko; presumably reflects somatic mosaicism
Erosive/ulcerative	Intensely painful ulcerations on the palms and soles; chronic lesions may evolve into squamous cell carcinoma; erosive lesions may occur on mucosal surfaces
LP/lupus erythematosus	Overlapping features of lupus and LP; lesions are usually acral and patients may show high titers of ANA
Lichen planopilaris	Follicular LP; keratotic plugs surrounded by violaceous erythema, especially on scalp but can affect any hair-bearing area; usually results in cicatricial alopecia

ANA, Anti-nuclear antibodies; *LP,* lichen planus.
From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, 2016, Elsevier.

SUGGESTED READINGS

Arias-Santiago S et al: Cardiovascular risk factors in patients with lichen planus, *Am J Med* 124:543–548, 2011.
Le Cleach L, Chosidow O: Lichen planus, *N Engl J Med* 366:723-732, 2012.

Lichen Sclerosus PTG

BASIC INFORMATION

DEFINITION

Lichen sclerosus (LS) is a chronic inflammatory condition of the skin usually affecting the vulva, penis, perianal area, and groin.

SYNONYMS

Lichen sclerosus et atrophicus
Kraurosis vulvae
Balanitis xerotica obliterans
LS

ICD-10CM CODE
L90.0 Lichen sclerosus et atrophicus

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common in postmenopausal women and men between ages 40 and 60 yr.
- More common in females (female:male ratio of 5:1). It affects 1.7% of the general adult female population.
- Can occur in children (usually prepubertal girls with involvement of the vulva and perineum).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Erythema may be the only initial sign. A characteristic finding is the presence of ivory-white atrophic lesions on the involved area.
- Close inspection of the affected area will reveal the presence of white-to-brown follicular plugs on the surface (dells).
- When the genitals are involved, the white, parchment-like skin assumes an hourglass configuration around the introital and perianal area ("keyhole" distribution; Fig. E1, Fig. E2). Inflammation, subepithelial hemorrhages, and chronic ulceration may develop.
- In males, lesions are atrophic and may be hypopigmented or depigmented, resembling vitiligo. Phimosis and paraphimosis are common complications in uncircumcised males with LS.
- Lesions may be surrounded by an erythematous to violaceous halo.
- Dyspareunia, genital bleeding, and anal bleeding are common.
- Pruritus may be a prominent symptom.

ETIOLOGY

Unknown. There may be an autoimmune association and a genetic familial component.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Localized scleroderma (morphea)
- Cutaneous discoid lupus erythematosus
- Atrophic lichen planus
- Psoriasis
- Lichen simplex chronicus
- Vulvar intraepithelial neoplasm
- Extramammary Paget disease
- Table E1 summarizes the differential diagnosis of common vulvar mucocutaneous disorders

WORKUP

Diagnosis is based on close examination of the lesions for the presence of ivory-white atrophic lesions and typical location.

LABORATORY TESTS

- Punch or deep shave biopsy can be used to confirm the diagnosis.
- Autoantibodies to extracellular matrix protein 1 (ECM-1) are present in 80% of LS patients and the ECM-1 titer correlates with disease activity.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Attention to hygiene and elimination of irritants or excessive bathing with harsh soaps.
- Cryotherapy and photodynamic therapy can be used in refractory cases.

GENERAL Rx

- Application of clobetasol propionate 0.05% topically bid for up to 4 wk is usually effective. Repeat courses of corticosteroids may be necessary because of the chronic nature of this disorder. Continual application of topical steroids may lead to atrophy of the vulva.
- There is no substantial evidence that use of topical sex hormones (e.g., topical testosterone [2%]) is effective in genital lichen sclerosus.
- Lubricants (e.g., Nutraplus cream) are useful to soothe dry tissues.
- Hydroxyzine 25 mg at bedtime is effective in decreasing nocturnal itching.
- Use of intralesional steroids, etretinate, and surgical management is usually reserved for refractory cases.

DISPOSITION

- The disease persists in approximately one third of patients.
- Most prepubertal girls improve spontaneously at menarche.
- Squamous cell carcinoma can develop within the lesions in 3% to 10% of older patients; therefore periodic examination and biopsy of suspicious areas are indicated.

PEARLS & CONSIDERATIONS

COMMENTS

- Prepubertal lichen sclerosus may be confused with sexual abuse in prepubertal girls and may lead to false accusations and investigations.
- Pregnancy leads to improvement and often complete resolution of lesions, suggesting a hormonal component to etiology of lesions.

FIG. E1 Lichen sclerosus with stenosis of the introitus, fissuring in the posterior fourchette, and perianal involvement producing the "keyhole appearance." (Fishe BK and Margesson LJ: Genital skin disorders: Diagnosis and treatment. In Disaia PJ et al: *Clinical gynecologic oncology*, ed 9, Philadelphia, 2017, Elsevier.)

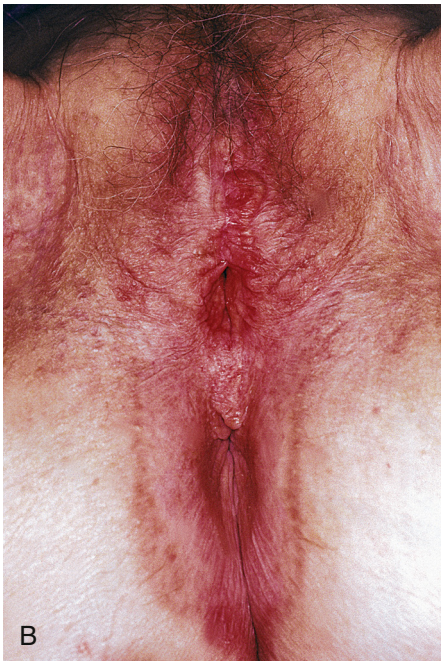

FIG. E2 A, Clinical appearance of lichen sclerosus. Note the atrophy of the labium minus. **B,** Lichen sclerosus with a prominent hourglass appearance. (From Crum CP et al: *Diagnostic gynecologic and obstetric pathology*, ed 3, Philadelphia, 2018, Elsevier.)

- Lichen sclerosus of the vulva (kraurosis vulvae) usually occurs after menopause and is generally chronic. It can be painful and interfere with sexual activity.
- Lichen sclerosus of the penis (balanitis xerotica obliterans) is seen more commonly in uncircumcised males. It affects the glans and prepuce and may lead to stricture if it encroaches into the urinary meatus.

RELATED CONTENT

Lichen Sclerosus (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

TABLE E1 Differential Diagnosis of Common Vulvar Mucocutaneous Disorders

Diagnosis	Acan	PK	Spong	HK	LI	ID	IEN	Sclerosis	Atroph	TTR	Exclude
Lichen simplex chronicus (LSC)	+		±	+						±	*Candida*
Lichen sclerosus (LS)	±			±	±	±		+	±		dVIN
Eczema	±		+	±							Seborrheic dermatitis
Lichen planus	±			±	+	+					Early LS
LSC + LS	+			+	+			+			dVIN
Eczema + LSC	+		+	+							*Candida*
Zoon			±		+				±		Syphilis
Psoriasis	+	+								±	LSC, *Candida*

Acan, Acanthosis; *Atroph,* atrophy; *dVIN,* differentiated vulvar intraepithelial neoplasia; *HK,* hyperkeratosis; *ID,* interface dermatitis; *IEN,* intraepithelial neutrophils; *LI,* lichenoid infiltrate; *PK,* parakeratosis; *Spong,* spongiosis; *TTR,* test tube rete; ±, may be present.
From Crum CP et al: *Diagnostic gynecologic and obstetric pathology*, ed 3, Philadelphia, 2018, Elsevier.

SUGGESTED READING

Chi CC et al: Topical interventions for genital lichen sclerosus, *Cochrane Database Syst Rev* 12:CD008240, 2011.

Lichen Simplex Chronicus

BASIC INFORMATION

DEFINITION

Lichen simplex chronicus (LSC) is neurodermatitis manifesting with localized areas of thickened, hyperplastic scaly skin due to prolonged and severe scratching in patients with no underlying dermatologic condition.

SYNONYMS

LCS
Neurodermatitis from rubbing
Circumscribed neurodermatitis

ICD-10CM CODE
L28.0 Lichen simplex chronicus

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Between 35 and 50 yr old
PREVALENCE: Increased in patients with underlying anxiety disorders
PREDOMINANT SEX AND AGE:
- Sex: Females > males (2:1)
- Age: Adults over 60

RISK FACTORS: Anxiety disorders, dry skin, insect bites

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients present with profound pruritus and localized scaly plaques with accentuated skin markings said to resemble tree bark.
- Lichenified circumscribed plaques. Trauma from rubbing and scratching accounts for persistence of the plaque.
- Commonly involved areas include hands and wrists, back and sides of neck (Fig. E1), anterior tibias, anogenital areas (Fig. E2), the scalp, the upper eyelid, the orifices of both ears, and ankles.

ETIOLOGY

- Neurodermatitis due to long-term chronic rubbing and scratching more vigorously than a normal pain threshold would allow, resulting in thickened and leathery skin.
- Common triggers are excess dryness of skin, heat, sweat, and psychological stress. It can also accompany other conditions such as obsessive-compulsive disorder, the fungal infections candidiasis or tinea cruris, or psoriasis, lichen sclerosus, and neoplasia, leading to squamous cell hyperplasia.
- Other causes include atrophic dermatitis and insect bites. Rare cases have shown links to lithium use, hair dye containing PPD, and long-term exposure to vehicle pollution.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Lichen planus
- Psoriasis
- Atopic dermatitis
- Insect bite
- Nummular eczema
- Contact dermatitis
- Stasis dermatitis

WORKUP

Patient history and skin examination. Skin biopsy when diagnosis is unclear or persistent symptoms.

LABORATORY TESTS

- Not generally necessary.
- Biopsy reveals hyperkeratosis, acanthosis, and mild to moderate lymphohistiocytic inflammatory infiltrate with prominent lichenification.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient education is essential to break the itch-scratch cycle and facilitate treatment of any underlying dermatitis.
- Psychotherapy.

ACUTE GENERAL Rx

- Cessation of pruritus is the goal. Antihistamine hydroxyzine 25 mg at bedtime is effective in decreasing nocturnal itching. Moisturizers are also helpful
- High-potency topical corticosteroids can be used initially but not indefinitely because of potential for steroid-induced atrophy
- Steroid-containing tape may be effective in providing both occlusion and antiinflammatory effect
- Intralesional corticosteroids
- Anxiolytics, SSRIs
- Oral doxepin (an antidepressant and anxiolytic)
- Mirtazapine
- Tropical calcineurin inhibitor for vulvar lichenification
- Cyclosporin A
- Topical tacrolimus, 0.1% ointment, can be used for sensitive skin, face
- Botulinum intradermal injections
- Alitretinoin, 30 mg daily for 3 mo, has shown some clinical improvement in case studies but needs further investigation as a potential Rx

CHRONIC Rx

Constant irritation of the skin must be avoided. Keeping skin moisturized, covering to prevent scratching, or filing nails may be necessary.

DISPOSITION

Psychological intervention improves recovery. Regular follow-up visits facilitate long-term management.

REFERRAL

Refer to a psychologist for psychological evaluation and consultation, and a dermatologist in resistant cases.

PEARLS & CONSIDERATIONS

- Significant scratching may occur during nocturnal hours.
- The involved area is always at a site that is easily reached for scratching.
- Chronic scratching can also cause keratinocyte necrosis and the development of amyloid in the papillary dermis, called lichen amyloidosis.

COMMENTS

Patients may be at increased risk for scarring of the skin, changes in skin pigmentation, and bacterial and fungal infections of the involved skin.

PREVENTION

Prevent future incidences by continued therapy, stress management, and avoidance of common triggers and accompanying conditions.

AUTHORS: **Fred F. Ferri, MD,** and **Heather Ferri, DO**

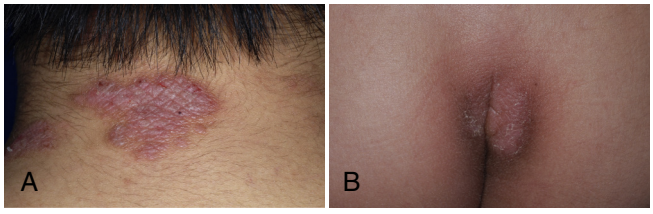

FIG. E1 (**A** and **B**) Lichen simplex chronicus. Localized plaques of dermatitis that result from repeated scratching and rubbing of the involved area. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, 2016, Elsevier.)

FIG. E2 A, Lichen simplex chronicus is characterized clinically by thickening of the mucosa, lending a leathery appearance that often is discolored (as in this case). **B,** Lichen simplex chronicus with pronounced changes associated with itch-scratch cycle. (From Crum CP et al: *Diagnostic gynecologic and obstetric pathology*, ed 3, Philadelphia, 2018, Elsevier.)

BASIC INFORMATION

DEFINITION

Listeriosis is a systemic infection caused by the gram-positive aerobic bacterium *Listeria monocytogenes.* The range of clinical syndromes varies from gastroenteritis to life-threatening meningitis and tends to be more severe in immunocompromised patients and in patients who are pregnant.

SYNONYMS

Listerial infection
Granulomatosis infantisepticum

ICD-10CM CODES

A32	Listeriosis
A32.0	Cutaneous listeriosis
A32.11	Listeria meningitis
A32.81	Oculoglandular listeriosis
A32.89	Other forms of listeriosis
P37.2	Neonatal (disseminated) listeriosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- *Listeria* meningitis: About 0.7 cases/100,000 persons (fourth most common cause of community-acquired bacterial meningitis in adults)
- In pregnant women: 3.0 cases per 100,000 population
- In general population: 0.29 confirmed cases per 100,000 persons in 2009 to 2011 in the United States, but 1.3 per 100,000 cases in persons over the age of 65
- Approximately 800 lab-confirmed cases are reported in the U.S. annually

PREDOMINANT SEX: Pregnant women are more susceptible to *Listeria* bacteremia, accounting for up to one third of reported cases.

PREDOMINANT AGE:

- Pregnant women
- Immunocompromised patients of any age
- Elderly patients are susceptible even in the absence of recognized immunocompromised states

GENETICS: Congenital infection:

- With transplacental transmission, syndrome termed *granulomatosis infantisepticum* in neonate
- Characterized by disseminated abscesses in multiple organs, skin lesions, and conjunctivitis
- Mortality: 33% to 100%

Neonatal infection:

- Infant becoming ill after 3 days of age; mother invariably asymptomatic
- Clinical picture is of sepsis of unknown origin

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Infections in pregnancy
  1. More common in third trimester
  2. Usually present with fever and chills without localizing symptoms or signs of infection
- Meningoencephalitis
  1. More common in neonates and immunocompromised patients, but up to 30% of adults have no underlying condition
  2. In neonates: Poor appetite with or without fever possibly the only presenting signs
  3. In adults: Presentation often subacute, with low-grade fever and personality change as only signs
  4. Focal neurologic signs seen without demonstrable brain abscess on CT scan
- Cerebritis/rhombencephalitis
  1. Headache and fever may be only presenting complaints
  2. Progressive cranial nerve palsies, hemiparesis, seizures, depressed level of consciousness, cerebellar signs, respiratory insufficiency may also be seen
- Focal infections
  1. Ocular infections (purulent conjunctivitis) and skin lesions (granulomatosis infantisepticum) as a result of inadvertent inoculation by laboratory and veterinary personnel
  2. Others: Arthritis, prosthetic joint infections, peritonitis, osteomyelitis, organ abscesses, cholecystitis

ETIOLOGY

- Listeria is a gram-positive rod that acts as a facultative intracellular parasite that helps protect the cell from host innate and adaptive immune responses. The primary habitat for the bacterium is soil and decaying vegetable matter.
- Listeria is a hardy organism that can withstand a wide range of conditions including refrigeration (can grow at standard refrigerated temperature of 40 degrees Fahrenheit), freezing, heat, and relatively high levels of acid, salinity and alcohol.
- Incubation period is between 11 and 70 days, with a mean of 31 days.
- Direct invasion of skin and eye has been documented, but most cases involve GI tract at the level of the intestine, with Listeria crossing the mucosal barrier by active endocytosis of the bacteria by endothelial cells. Once in the bloodstream, the organism can disseminate to any site, with a predilection for CNS and placenta.
- Organism's intracellular life cycle explanatory of:
  1. Importance of cell-mediated immunity in host defense
  2. Increased infection in neonates, pregnant women, and immunocompromised hosts

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Meningitis caused by other bacteria, mycobacteria, or fungi
- CNS sarcoidosis
- Brain neoplasm or abscess
- Tuberculous and fungal (especially cryptococcal) meningitis
- Cerebral toxoplasmosis
- Lyme disease
- Sarcoidosis

LABORATORY TESTS

- Cultures of blood and other appropriate body fluids
- Variable CSF findings, but neutrophils usually predominate
- Organisms uncommonly seen on Gram stain and may be difficult to identify morphologically
- Monoclonal antibodies, polymerase chain reaction, and DNA probe techniques to detect *Listeria* in foods

IMAGING STUDIES

- If focal cerebral involvement suspected: CT scan or MRI
- MRI most sensitive for evaluation of brainstem and cerebellum

TREATMENT

Empiric therapy should be administered when diagnosis is suspected because overall mortality is 23%.

ACUTE GENERAL Rx

- Drugs of choice: Meningitis, meningoencephalitis and bacteremia
  1. IV ampicillin 2 g IV q 4 hr for adults. Children: 300 mg/kg per day IV in 4 to 6 divided doses. Infants 8 days to 1 mo: 150 to 200 mg/kg per day divided in four doses. For infants ≤7 days: 100 mg/kg per day divided in two doses for infants weighing <2000 g and 150 mg/kg per day divided in three doses for infants weighing more than 2000 g.
  2. IV penicillin 12 to 24 million U/day in divided doses in adults.
- Continuation of therapy for 2 wk for bacteremia; 2 to 4 wk for meningitis.
- Alternative (if penicillin allergic): Trimethoprim/sulfamethoxazole (10 to 20 mg/kg based on trimethoprim component) IV per day divided every 6 to 12 hr or meropenem: 1 gram IV q 8 hrs if PCN allergy not IgE mediated.
- Gentamicin IV added to provide synergy in meningitis or endocarditis patients of any age (adults: 3 mg/kg per day IV in three divided doses and for children and infants will depend on age and weight).
- For febrile gastroenteritis: In immunocompetent hosts, spontaneous resolution occurs in less than 2 days, so no treatment is required. In immunocompromised, elderly, or pregnant patients: Amoxicillin 500 mg po TID x3 to 5 days or Bactrim DS: 1 tablet po BID x3 to 5 days

CHRONIC Rx

Relapses reported, especially in immunocompromised hosts, after 2 wk of therapy.

REFERRAL

Infectious disease consultation for all patients

PEARLS & CONSIDERATIONS

COMMENTS

- Foodborne cases have been linked to various products in recent years: Coleslaw, soft cheeses, unpasteurized milk and milk products, vegetables, undercooked chicken, hot dogs, luncheon meats, refrigerated smoked seafood, caramel apples, cantaloupes, and so on.
- Complete decontamination of food products is difficult because *Listeria* is resistant to pasteurization and refrigeration.
- Immunocompromised states include glucocorticoid use, anti-TNF therapies, malignancies (hematologic and solid), AIDS, end-stage renal disease, iron overload, collagen vascular diseases, liver disease, and alcoholism.

RELATED CONTENT

Listeriosis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Allerberger F, Wagner M: Listeriosis: a resurgent foodborne illness, *Clin Microbiol Infect* 16(1):6-23, 2010.

Gottlieb SL et al: Multistate outbreak of listeriosis linked to turkey deli meat and subsequent changes in U.S. regulatory policy, *Clin Infect Dis* 42(1):29, 2006.

Lamont RF et al: Listeriosis in human pregnancy: a systematic review, *J Perinat Med* 39(3):227-236, 2011.

de Noordhout CM et al: The global burden of listeriosis: a systematic review and meta-analysis, *Lancet Infect Dis* 14:1073-1082, 2014.

BASIC INFORMATION

DEFINITION

Liver abscess is a necrotic infection of the liver usually classified as pyogenic or amebic.

SYNONYMS

Pyogenic hepatic abscess
Amebic hepatic abscess

ICD-10CM CODE
K75.0 Abscess of liver

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Incidence of pyogenic liver abscess is 2.3 cases per 100,000 population.
PREVALENCE (WORLDWIDE): Amebic liver abscess is more common than pyogenic liver abscess.
PREVALENCE (IN U.S.): Pyogenic liver abscess is more common than amebic liver abscess.
PREDOMINANT SEX AND AGE: More common in men than women; male/female ratio of 2:1; most common in fourth to sixth decades of life.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever, chills, and sweats
- Weakness/malaise
- Anorexia with weight loss
- Nausea, vomiting, and diarrhea
- Cough with pleuritic chest pain
- Right upper quadrant abdominal pain
- Hepatomegaly
- Splenomegaly
- Jaundice
- Pleural effusions, rales, and friction rubs may be present
- Most abscesses occur on the right lobe of the liver

ETIOLOGY

- Pyogenic liver abscess is usually polymicrobial (*Klebsiella pneumoniae* [43%], *Escherichia coli* [33%], *Streptococcus* spp. [37%], *Pseudomonas aeruginosa, Proteus* spp., *Bacteroides* spp. [24%], *Fusobacterium* spp., *Actinomyces* spp., gram-positive anaerobes, and *Staphylococcus aureus*).
- Pyogenic liver abscess occurs from:
  1. Biliary disease with cholangitis (accounts for approximately 40% to 60%).
  2. Gallbladder disease with contiguous spread to the liver.
  3. Diverticulitis or appendicitis with spread via the portal circulation.
  4. Hematogenous spread via the hepatic artery, though uncommon; if a solitary organism is isolated, a distant source of hematogenous seeding should be sought.
  5. Penetrating wounds.
  6. Cryptogenic.
  7. Infection by way of portal system (portal pyemia).
  8. No causes found in approximately half of cases.
  9. Incidence increased in patients with diabetes and metastatic cancer.
  10. Table 1 summarizes underlying etiology and bacteriology of liver abscesses.
- Amebic hepatic abscess is caused by the parasite *Entamoeba histolytica*. Amebiasis is usually due to fecal-oral contamination and invades the intestinal mucosa, gaining entry into the portal system to reach the liver. Amebic abscess occurs in 3% to 7% of patients with amebiasis.
- A comparison of pyogenic and amebic liver abscess is summarized in Table 2.

Box 1 describes pearls for amebic liver abscesses. The abscess is usually solitary (85%) and in the right lobe (72%).

DIAGNOSIS

The diagnosis of liver abscess requires a high index of suspicion after a detailed history and physical examination. Imaging studies and microbiologic, serologic, and percutaneous techniques (e.g., aspiration) confirm the presence of a liver abscess.

TABLE 1 Underlying Etiology and Bacteriology

Etiology	Bacteriology
Biliary, benign	*Escherichia coli* *Klebsiella* spp. *Enterococcus*
Biliary, malignant	*Pseudomonas* spp. Multiply resistant GN aerobes VRE Yeast
Diverticulitis/appendicitis	GN aerobes *Bacteroides fragilis*
Severe cholecystitis	See Biliary, benign *Clostridium perfringens* *Bacteroides* spp.
Subcutaneous abscess	*Staphylococcus* spp. MRSA
Endocarditis	*Enterococcus* spp. *Staphylococcus* spp.
Cryptogenic	Anaerobes

GN, Gram-negative; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *VRE*, Vancomycin-resistant *Enterococcus*.
From Cameron, JL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, Saunders.

DIFFERENTIAL DIAGNOSIS

- Cholangitis
- Cholecystitis
- Diverticulitis
- Appendicitis
- Perforated viscus
- Mesentery ischemia
- Pulmonary embolism
- Pancreatitis

WORKUP

- The workup of a liver abscess should focus on differentiating between amebic and pyogenic causes.
- Features suggesting an amebic cause include travel to an endemic area, single abscess rather than multiple abscesses, subacute onset of symptoms, and absence of conditions predisposing to pyogenic liver abscess, as highlighted under "Etiology."
- Laboratory studies are not specific but are useful as adjunctive tests.
- Imaging studies cannot differentiate between the two, and bacteriologic cultures may be sterile in 50% of the cases.

LABORATORY TESTS

- Complete blood count: Leukocytosis
- Liver function tests: Alkaline phosphatase is most commonly elevated (95% to 100%); aspartate transaminase (AST) and alanine transaminase (ALT) elevated in 50% of cases; elevated bilirubin (28% to 30%); decreased albumin
- Prothrombin time (INR): Prolonged (70%)
- Blood cultures: Positive in 50% of cases
- Aspiration (50% sterile)
- Stool samples for *E. histolytica* trophozoites (positive in 10% to 15% of amebic liver abscess cases)
- Serologic testing for *E. histolytica* should be done on all patients, but it is important to remember that it does not differentiate acute from old infections

IMAGING STUDIES

- Ultrasound (80% to 100% sensitivity in detecting abscesses) shows round or oval hypoechogenic mass (Fig. E1, *A*).

TABLE 2 Comparisons of Pyogenic and Amebic Liver Abscess

Parameter	Pyogenic Liver Abscess	Amebic Liver Abscess
Number	Often multiple	Usually single
Location	Either lobe of liver	Usually right hepatic lobe, near the diaphragm
Presentation	Subacute	Acute
Jaundice	Mild	Moderate
Diagnosis	US or CT ± aspiration	US or CT and serology
Treatment	Drainage (if technically feasible) + IV antibiotics (see text)	Metronidazole, 750 mg 3 times daily for 7-10 days orally or IV; or tinidazole, 2 g orally for 3 days, followed by iodoquinol, 650 mg orally 3 times daily for 20 days; diloxanide furoate, 500 mg orally 3 times daily for 10 days; or aminosidine (paromomycin) 25-35 mg/kg/day orally in 3 divided doses for 7-10 days

CT, Computed tomography; *IV*, intravenous; *US*, ultrasonography.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

BOX 1 Pearls for Amebic Liver Abscesses

- Only 10%-20% of patients with amebic liver abscess have a history of diarrhea.
- Treat the intestinal infection to prevent relapse of amebic liver abscess. Failure to use luminal amebicidal agents after metronidazole in cases of amebic abscess results in a 10% relapse rate.
- Failure to show response to antiamebic medication requires evaluation for polymicrobial infection with bacteria.
- Amebic abscess usually responds clinically to antimicrobial therapy in 3 to 7 days, although imaging takes several mo to show resolution.
- Percutaneous drainage is rarely required.

From Cameron, JL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, Saunders.

- CT scan is more sensitive in detecting hepatic abscesses and contiguous organ extension and is the imaging study of choice (Fig. E1, *B,* and Fig. E2).
- Chest x-ray: Abnormal in 50% of the cases, may reveal elevated right hemidiaphragm, subdiaphragmatic air-fluid levels, pleural effusions, and consolidating infiltrates.
- Most liver abscesses are single; however, multiple liver abscesses can occur with systemic bacteremia.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- The management of pyogenic liver abscess differs from that of amebic liver abscess.
- Medical management is the cornerstone of therapy in amebic liver abscess, whereas early intervention in the form of surgical therapy or catheter drainage and parenteral antibiotics is the rule in pyogenic liver abscess greater than 3 cm. Smaller abscesses (<3 cm) can generally be treated with broad-spectrum antibiotics.

ACUTE GENERAL Rx

- Percutaneous drainage under CT or ultrasound guidance is essential in the treatment of pyogenic liver abscesses.
- Aspiration of hepatic amebic abscesses is not required unless there is no response to treatment or a pyogenic cause is being considered.
- Empiric broad-spectrum antibiotics are recommended initially until culture results are available. Common choices include:
  1. Metronidazole (500 mg IV q8h) plus ceftriaxone or levofloxacin.
  2. Monotherapy with a beta-lactam/beta-lactamase inhibitor, such as piperacillin/tazobactam (4.5 g q6h), ticarcillin-clavulanate (3.1 g q4h), or ampicillin-sulbactam (3 g q6h).
  3. Monotherapy with a carbapenem, such as imipenem (500 mg IV q6h), meropenem (1 g q8h), or ertapenem (1 g daily).
  4. Duration of antibiotic treatment is usually 4 to 6 wk with IV antibiotics used for the first 1 to 2 wk or until a favorable clinical response, followed thereafter with oral antibiotics (e.g., metronidazole 500 mg PO q8h plus ciprofloxacin 500 mg PO q12h).
  5. Third-generation cephalosporins should not be used as single agents for empiric therapy because of risk of the emergence of beta-lactamase-producing bacteria.
- Antibiotic coverage for amebic liver abscesses includes:
  1. Metronidazole 750 mg PO tid for 10 days or tinidazole.
  2. Eradication of the coexistent intestinal infection with paromomycin for 10 days.

CHRONIC Rx

- If fever persists for 2 wk despite percutaneous drainage and antibiotic therapy as outlined under "Acute General Rx," or if there is failure of aspiration or failure of percutaneous drainage, surgery is indicated.
- In patients not responding to intravenous antibiotics and percutaneous drainage, hepatic artery antibiotic infusion can be considered.
- In patients with evidence of metastatic disease that is causing biliary obstruction, a gastroenterology consultation for endoscopic retrograde cholangiopancreatography and stenting should be considered.

DISPOSITION

- Most patients with pyogenic liver abscesses defervesce within 2 wk of treatment with antibiotics and drainage.
- No randomized controlled studies have evaluated the optimal duration of antibiotic therapy for pyogenic liver abscess. Typical duration of antibiotic therapy is at least 4 to 6 wk.
- Pyogenic liver abscess cure rates using percutaneous drainage and antibiotics have been reported to be between 88% and 100%.
- Mortality rate of untreated pyogenic liver abscess is nearly 100%.
- Most patients with amebic liver abscesses defervesce within 4 to 5 days of treatment.
- Amebic liver abscess mortality rate is <1% unless complications occur (see "Comments").
- Follow-up imaging should be used to monitor response to therapy; continue treatment until CT scan shows complete or near-complete resolution of cavity.

REFERRAL

Infectious disease, gastroenterology, interventional radiology, and general surgical consultations are recommended in any patient with hepatic abscess.

PEARLS AND CONSIDERATIONS

COMMENTS

- Complications of pyogenic and amebic liver abscesses include:
  1. Pleuropulmonary extension, resulting in empyema, abscess, and fistula formation
  2. Peritonitis
  3. Purulent pericarditis
  4. Sepsis
- Amebic liver abscesses complicate amebic colitis in nearly 10% of cases.

RELATED CONTENT

Liver Abscess (Patient Information)
Amebiasis (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

FIG. E1 **A**, Amebic abscess. Sonogram demonstrates a hypoechogenic mass in the right lobe of the liver with a more hypoechoic surrounding rim. **B**, Computed tomography scan demonstrates a low-attenuation mass in the right lobe of the liver with a prominent halo. (From Kuhn JP et al: *Caffrey's pediatric diagnostic imaging*, vol 2, ed 10, Philadelphia, 2004, Mosby.)

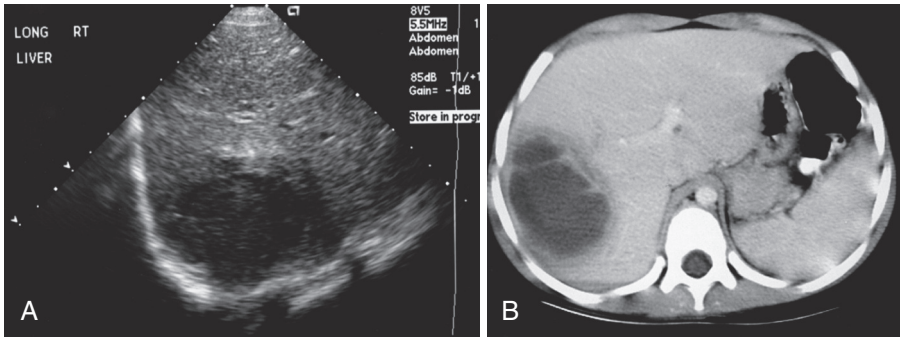

FIG. E2 **Pyogenic liver abscess.** A liver abscess containing *Escherichia coli* has irregular septations and contains a few bubbles of air (*arrows*). Because of the multiple loculations, this abscess did not respond to a percutaneous catheter for drainage and required surgical debridement. (From Webb WR, Brant WE, Major NM: *Fundamentals of body CT*, ed 4, Philadelphia, 2015, Saunders.)

Liver Transplantation

BASIC INFORMATION

DEFINITION

Liver transplantation is surgery to remove a diseased liver and replace it with a donated whole or partial healthy liver. Liver transplantation is a treatment option for acute liver failure, end-stage liver disease, and primary hepatic malignancy. Box E1 summarizes indications for liver transplantation.

ICD-10CM CODE
Z94.4 Liver transplant status

EPIDEMIOLOGY & DEMOGRAPHICS

- Cirrhosis remains the twelfth-leading cause of death for adults in the U.S., with a death rate of 9.2 cases per 100,000 people.
- Accounts for 1.1% of total deaths in the U.S.
- Hepatocellular carcinoma is a primary cancer originating in the liver. Hepatocellular carcinoma is responsible for more than 12,000 deaths a yr in the U.S. and is the highest rising malignancy in the U.S. It is more common in men than women and in those of African descent than whites.

INCIDENCE: Number of patients on liver transplant list exceeds 15,000
PREVALENCE: 6000 liver transplants are performed annually in the U.S.
GENETICS: Genetic factors that may induce end-stage liver failure include hemachromatosis, Wilson disease, alpha-1 antitrypsin deficiency, glycogen storage disease, tyrosinemia

RISK FACTORS

- Viral hepatitis (hepatitis B and C)
- Alcoholic liver disease or Laennec cirrhosis (most common cause of liver transplantation in 2017)
- Nonalcoholic steatohepatitis (NASH)
- Autoimmune liver disease (autoimmune hepatitis, cholestatic liver disease, primary biliary cholangitis, primary sclerosing cholangitis, neonatal sclerosing cholangitis, biliary atresia, Caroli disease, TPN-induced cholestasis)
- Genetics (hemachromatosis, Wilson disease, alpha-1 antitrypsin deficiency, glycogen storage disease, tyrosinemia)
- Vascular liver disease (Budd-Chiari syndrome)
- Hepatocellular carcinoma
- Acute liver failure (drug-induced liver failure [paracetamol/acetaminophen or APAP, non-APAP acute viral hepatitis [acute hepatitis B], Epstein-Barr virus, cytomegalovirus, herpes simplex virus, human immunodeficiency virus) (Box E2)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Cirrhosis alone does not warrant transplantation. Transplantation is considered when a patient presents with manifestations of compromised hepatic function such as portal hypertension or a manifestation of compromised hepatic function. Complications of portal hypertension include esophageal varices, hepatic encephalopathy, ascites, spontaneous bacterial peritonitis, hepatopulmonary syndrome.
- Physical findings and clinical presentation that warrant liver transplantation in patients with end-stage liver disease are recurrent variceal hemorrhage, intractable ascites, spontaneous bacterial peritonitis, refractory encephalopathy, severe jaundice, portal venous thrombosis, worsening hepatic synthetic dysfunction, sudden deterioration, and fulminant hepatic failure.

ETIOLOGY

The etiology of a liver transplant is from end-stage liver disease that has resulted in cirrhosis scarring. The most common are chronic hepatitis C virus (30%), alcoholic cirrhosis (18%), fatty liver disease including NASH, primary liver cancer, acute or chronic hepatitis B virus, bile duct disease, genetic disease, and autoimmune liver disease.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of acute liver decompensation in patients diagnosed with end-stage liver disease include eclampsia, preeclampsia, and sepsis with multiorgan failure.

WORKUP

- Patients with end-stage liver disease requiring a transplant are accessed by using the MELD-Na score (Model for End-Stage Liver Disease-Na). The MELD-Na score measures the severity of chronic liver disease and can predict mortality within 3 mo of surgery in patients who received a transjugular intrahepatic portosystemic shunt (TIPS) procedure. The score prioritizes who is in need of a transplant as soon as possible.
- MELD-Na score testing includes: Serum bilirubin, serum creatinine, international normalization ratio for prothrombin time, and serum sodium
- MELD-Na = [[3.78 × ln [serum bilirubin (mg/dl)] + 11.2 × ln [INR] + 9.57 × ln [serum creatinine (mg/dl)] + 6.43]] + 1.59 (135-Na)
  1. Maximum and minimum Na of 135 and 120 mmol/L, respectively
- 40 or more: 71.3% mortality
- 30 to 39: 52.6% mortality
- 20 to 29: 19.6% mortality
- 10 to 19: 6.0% mortality (MELD ≥15 warrants liver transplantation workup for waitlist)
- <9: 1.9% mortality

LABORATORY TESTS

MELD score testing: Serum bilirubin, serum creatinine, serum sodium, and the international normalization ratio for prothrombin time.

IMAGING STUDIES

- Abdominal US, CT, or MRI to screen for hepatocellular carcinoma.
- Patients with underlying cirrhosis should be screened for hepatocellular carcinoma with abdominal US every 6 to 12 mo.

TREATMENT

Patients with decompensated liver disease, end-stage liver disease, hepatocellular carcinoma

BOX E1 Indications for Liver Transplantation

- Acute liver failure
- Complications of cirrhosis
  - Ascites
  - Chronic GI blood loss due to portal hypertensive gastropathy
  - Encephalopathy
  - Liver cancer
  - Refractory variceal hemorrhage
  - Synthetic dysfunction
- Liver-based metabolic conditions with systemic manifestations
  - α_1-Antitrypsin deficiency
  - Familial amyloidosis
  - Glycogen storage disease
  - Primary oxaluria
  - Tyrosinemia
  - Urea cycle enzyme deficiencies
  - Wilson disease
- Systemic complications of chronic liver disease
  - Hepatopulmonary syndrome
  - Portopulmonary hypertension

GI, Gastrointestinal.
From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, WB Saunders.

BOX E2 Absolute Contraindications to Liver Transplantation

- AIDS
- Active alcoholism or substance abuse
- Advanced cardiac or pulmonary disease
- Anatomic abnormality that precludes liver transplantation
- Cholangiocarcinoma
- Extrahepatic malignancy
- Fulminant hepatic failure with sustained ICP >50 mm Hg or CPP <40 mm Hg
- Hemangiosarcoma
- Persistent nonadherence
- Uncontrolled sepsis

AIDS, Acquired immune deficiency syndrome; *ICP,* intracranial pressure; *CPP,* cerebral perfusion pressure (CPP = mean arterial pressure minus ICP).
From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, WB Saunders.

within Barcelona with a MELD >15 warrant evaluation at a liver transplant center for further workup and possible registration for the liver transplant waitlist. Allocation for liver transplantation is prioritized by a patient's acuity of illness determined by a patient's MELD-Na score.

LIVING DONOR OR DECEASED DONOR LIVER TRANSPLANTATION

Living donor:

- The scarcity of cadaveric organs has prompted some centers to use living donors, which guarantees transplantation but entails a risk to the donor. Donor compatibility is based on candidates who are family members or close friends of the recipient. The donor must be aged 18 to 60, have compatible blood type with the recipient, be the same physical size or larger, and in excellent health with no history of uncontrolled high blood pressure, liver disease, diabetes, or heart disease. Donor risk includes wound infections, hernia, abdominal bleeding, bile leakage, narrowing of the bile duct, intestinal problems including blockages and tears, organ impairment or failure that leads to the need for transplantation, and death.

Deceased donor:

- Orthotopic liver transplantation is effective for nonresectable early hepatocellular carcinoma, acute liver failure, and end-stage liver disease.

HEPATOCELLULAR CARCINOMA PATIENTS EVALUATED BY THE MILAN AND UCSF CRITERIA

- UCSF criteria: Criteria for liver transplant are as follows: single tumor <6.5 cm, maximum of 3 total tumors with none >4.5 cm, and cumulative tumor size <8 cm, or exceeded UCSF criteria.
- Acute liver failure:
  1. In the case of acute liver failure, the patient is evaluated for liver transplantation based on the "Kings College Criteria," which is based on:
     a. pH <7.3
        OR, in a 24-hour period, all 3 of:
     b. INR >6 (PT >100s) + Cr >300 mmol/L + grade III or IV encephalopathy
  2. Patients who fulfill these criteria and do not have underlying chronic liver disease should be referred to liver transplant centers for urgent evaluation.
- Pretransplant care: Pretransplantation treatment is focused on testing the patients' ability to handle stress of the surgery, immunosuppression, and posttransplantation care. This is achieved by extensive cardiopulmonary evaluation, screening for occult infection or cancer, and psychosocial evaluation. Additional testing includes ABO-Rh blood typing; liver biochemical and function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, international normalized ratio [INR]); complete blood count with differential; creatinine clearance; serum alpha-fetoprotein; calcium and vitamin D levels; serologies for cytomegalovirus, Epstein-Barr virus, varicella, HIV, hepatitis A, hepatitis B, hepatitis C, rapid plasma regain; urinalysis; and urine drug screen.
- Posttransplant care: The primary goal is to prevent posttransplant rejection of the donated liver. This is accomplished with immunosuppression of the immune system with corticosteroids, calcineurin inhibitors such as tacrolimus (FK-506, Prograf), mycophenolate mofetil (CellCept, Myfortic), mTOR inhibitors (Sirolimus; everolimus), antibodies that remove T cells from the circulation (Thymoglobulin, OKT-3).

REFERRAL

Gastroenterologist and liver transplant team

PROGNOSIS

Average survival rate is 92% after 1 yr and 75% to 85% after 5 yr.

PEARLS & CONSIDERATIONS

COMMENTS

- Cirrhosis alone does not warrant transplantation. Liver transplantation is considered when a patient has suffered either an end-stage liver disease or a manifestation of compromised hepatic function.
- Liver transplantation is always a last option, as the overall determining factor is the number of donor livers available at any time.

PREVENTION

Nongenetic factors such as lifestyle modification and hepatitis B vaccination to avoid developing end-stage liver disease.

PATIENT & FAMILY EDUCATION

Patients who have a genetic predisposition to developing end-stage liver disease from having hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency, glycogen storage disease, and tyrosinemia would be advised to have genetic screening of immediate family members.

RELATED CONTENT

Acute Liver Failure (Related Key Topic)
Cirrhosis (Related Key Topic)

AUTHORS: **Eddie L. Copelin II, MD, MHA, Rosann Cholankeril, MD,** and **George Cholankeril, MD**

SUGGESTED READINGS

Acute liver failure: Available at: http://emedicine.medscape.com/article/177354-overview.

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BASIC INFORMATION

DEFINITION

Long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by a prolongation of the QT interval on the ECG associated with an increased risk of developing life-threatening ventricular arrhythmias, most commonly torsades de pointes (a specific type of polymorphic ventricular tachycardia), which may lead to ventricular fibrillation and sudden cardiac death (SCD). This syndrome may be either genetic or acquired.

SYNONYMS

LQTS
Congenital forms:
Jervell and Lange-Nielsen syndrome (associated with deafness)
Romano-Ward syndrome (associated with normal hearing)

ICD-10CM CODE
I45.81 Long QT syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- Congenital LQTS is thought to account for >3000 deaths in childhood per yr in the United States.
- Prevalence is felt to be 1:2000 of apparently healthy white young births. It may be higher because this is based on genetic testing of infants in whom the QTc was in excess of 470 and 460 milliseconds, respectively (Schwartz, 2009).
- Presence of LQTS has been shown in all racial groups. Review of data from the US portion of the international LQTS registry found a lower incidence but higher severity of QT prolongation among African Americans.
- Incidence of LQTS is thought to be between 1:2500 and 1:10,000 in the general population, although it has been difficult to estimate due to incomplete penetrance. Congenital form associated with deafness is autosomal recessive (Jervell and Lange Nielsen syndrome) and is less common than the autosomal dominant form as well as more severe.
- Congenital form associated with normal hearing (Romano-Ward syndrome) is autosomal dominant. Although inheritance of LQTS is autosomal dominant, female predominance has often been observed and has been attributed to an increased susceptibility to cardiac arrhythmias in women. LQTS is more likely to express itself before puberty in males and after puberty in females.
- At least 17 different LQTS genes have been identified to date.
- Mortality rate is estimated to be about 1% per yr.
- Multiple mutations causing congenital LQTS have been described. The most common types of LQTS are described in Table 1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Many episodes are stress mediated.
- Palpitations, presyncope.
- Syncope caused by ventricular tachycardia.
- SCD.
- Seizure.
- Family history of LQTS, but a family history of SCD has not been proved to be a risk factor for SCD in patients with LQTS.
- Abnormal ECG (prolonged QT) in asymptomatic relatives of known case.
- Prolonged QTc interval on ECG (QTc should be >460 ms in women and >440 ms in men). Notably, 20% to 25% genotype positive LQTS may have normal QTc on resting ECG.
- In case of congenital LQTS, the presentation of syncope or SCD is typically triggered by exercise and swimming in LQT1 patients, in LQT2 patients by emotion, pregnancy, or noise, and patients with LQT3 are at highest risk of events when at rest or asleep.

ETIOLOGY

- Cardiac repolarization abnormality
- Congenital cause (hundreds of mutations on more than 10 genes have been identified)
- Most of the gene mutations affect function of ion channels leading to prolonged repolarization (i.e., sodium and potassium channels resulting in either increased Na^+ influx or decreased K^+ efflux). These mutations prolong depolarization and predispose the patient to torsades de pointes
- Acquired causes:
  1. Drugs: Dofetilide, ibutilide, bepridil, quinidine, procainamide, sotalol, amiodarone, ranolazine, disopyramide, phenothiazines and antiemetic agents (droperidol, domperidone), tricyclic antidepressants, antipsychotics (quetiapine, ziprasidone, iloperidone), citalopram, antihistamines, quinolones, azithromycin, astemizole or cisapride given with ketoconazole or erythromycin, clarithromycin, and antimalarials, particularly among patients with asthma or those using potassium-lowering medications; also common in patients receiving methadone
  2. Hypokalemia, hypomagnesemia, hypocalcemia (especially in patients with malabsorption syndrome)
  3. Liquid protein diet
  4. Central nervous system lesions
  5. Ischemia
  6. Hypothyroidism

DIAGNOSIS

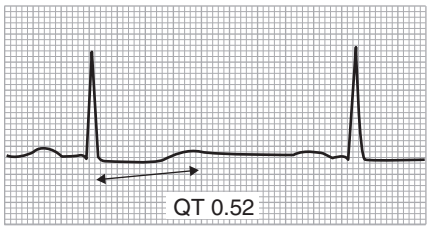
DIFFERENTIAL DIAGNOSIS

- See "Syncope."
- Brugada syndrome, arrhythmogenic right ventricular dysplasia, and LQTS are major causes of genetic sudden death syndromes (Fig. 1).

TABLE 1 Common Types of Long QT (LQT) Syndrome

	LQT1	LQT2	LQT3
Pathophysiology			
Gene	*KCNQ1 (KvLQT1)*	*KCNH2 (HERG)*	*SCN5A*
Protein	$K_v7.1$	$K_v11.1$	$Na_v1.5$
Ionic current	Decreased I_{Ks}	Decreased I_{Kr}	Increased late I_{Na}
Clinical Presentation			
Incidence of cardiac events	63%	46%	18%
Incidence of SCD	4%	4%	4%
Arrhythmia triggers	Emotional/physical stress (swimming, diving)	Emotional stress, arousal (alarm clock, telephone), rest, postpartum period	Sleep/rest
ECG	Broad-based T wave	Low-amplitude, bifid T wave	Long isoelectric ST segment
QT response to exercise	Attenuated QTc shortening and an exaggerated QTc prolongation during early and peak exercise	Normal QT during exercise but with exaggerated QT hysteresis	Supernormal QT shortening
Management			
Exercise restriction	+++	++	?
Response to beta blockers	+++	+++	?
Potassium supplement	+	++	+
Left cervicothoracic sympathectomy	++	++	++
Response to mexiletine	+	+	++

From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, Saunders.



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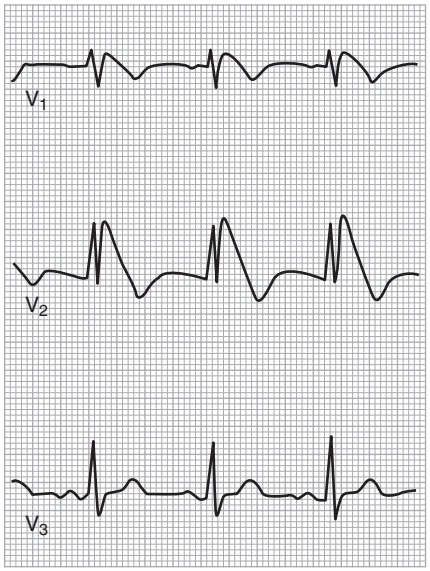

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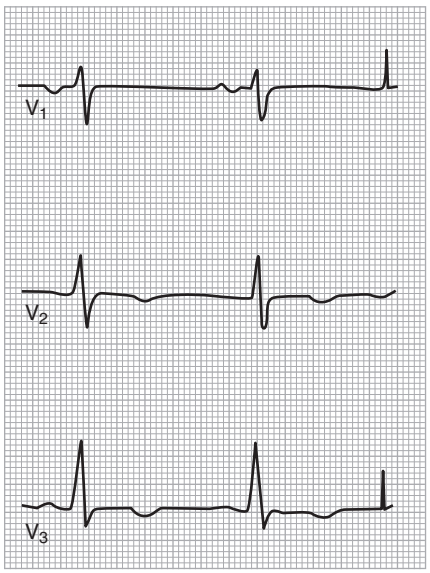

C

FIG. 1 Sinus rhythm electrocardiogram findings in three genetic sudden death syndromes. A, QT prolongation during sinus rhythm in a patient with long QT syndrome. **B,** ST elevation in V_1 and V_2 in a patient with Brugada syndrome. **C,** T wave inversion in V_1-V_3 in a patient with arrhythmogenic right ventricular dysplasia. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

Diagnostic criteria for the congenital LQTS as per 2013 HRS Guidelines:

LQTS is diagnosed:

- In the presence of an LQTS risk score ≥3.5 in the absence of a secondary cause for QT prolongation and/or
- In the presence of an unequivocally pathogenic mutation in one of the LQTS genes or
- In the presence of a QT interval corrected for heart rate using Bazett formula (QTc) ≥500 ms in repeated 12-lead electrocardiogram (ECG) and in the absence of a secondary cause for QT prolongation
- LQTS can be diagnosed in the presence of a QTc between 480 and 499 ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation

LQTS Risk Score (Schwartz 2011):

ECG Criteria	
QTc >480 ms	3 points
QTc 460-480 ms	2 points
QTc 450-460 ms (males)	1 point
QTc 4th minute of recovery from exercise stress test >480 ms	1 point
Torsade de pointes	2 points
T-wave alternans	1 point
Notched T wave in three leads	1 point
Bradycardia	0.5 point
History	
Syncope with stress	2 points
Syncope without stress	1 point
Congenital deafness	0.5 point
Definite family history of long QT	1 point
Unexplained cardiac death in first-degree relative <30 yr	0.5 point

Total score: 1 point: Low probability of LQTS. 1.5 to 3 points: Intermediate probability of LQTS. ≥ 3.5 points high probability.

WORKUP

Cardiology referral is recommended for all cases.

Genetic analysis is an essential step for risk stratification of patients with congenital prolonged QT and is important for identification of potential mutation carriers within the proband family. There is evidence for gene-specific triggers of events and therapeutic efficacy. Molecular screening should become part of the routine clinical management of LQTS.

In relatives of known patients with LQTS or in young patients with syncope:

- Stress test may prolong the QT interval or cause T-wave alternans.
- Valsalva maneuver: May prolong the QT interval or cause T-wave alternans.
- Prolonged ECG monitoring with various stimulations aimed at increasing catecholamines and assess for QT prolongation (perform in a setting that can provide resuscitation with α- and β-antagonists readily available).
- Epinephrine-induced prolongation of the QT interval (epinephrine infusion QT stress test).
- Genetic analysis:
  1. *LQT1* locus of *KCNQ1* potassium channel gene.
  2. *LQT2* locus of *KCNH2* potassium channel gene.
  3. *LQT3* locus of *SCN5A* sodium channel gene.
  4. These three variants account for >90% of all genotyped LQTS patients, whereas the remaining genes are responsible for a minority of cases.
- Risk stratification for each genetic variant on the basis of gender and QTc: Groups are defined on the basis of the probability of the first cardiac event (syncope, cardiac arrest, or sudden death) before the age of 40 yr or before therapy. Specific mutations, depending on type, location, and degree, may confer a high risk even if the ECG abnormalities are mild. Clinically, QT interval duration was the strongest predictor of risk for cardiac events; a QTc exceeding 500 ms identifies patients with the highest risk.
  1. High risk (>50% of cardiac event): QTc ≥500 ms and LQT1 or LQT2, or male with LQT3.
  2. Moderate risk (30% to 50%): QTc <500 ms in male with LQT3 or in female with LQT2 or LQT3, and female with LQT3 with QTc ≥500 ms.
  3. Low risk (<30%): QTc <500 ms and LQT1 or male LQT2 with QTc <500 ms.
  4. Prophylactic treatment should be considered in all patients with moderate or high risk for cardiac events based on the above risk stratification scheme (Table 2).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Focuses on exclusion of triggers of life-threatening arrhythmia—there are gene-specific triggers for symptoms:
  1. *LQT1* patients experience 90% of lethal events under physical and emotional stress. Swimming and diving should be avoided or performed under supervision.
  2. *LQT2* patients are at highest risk during arousal or emotions, also during sleep and at rest but not at all during exercise; avoid sudden or excessive acoustic stimuli, especially during sleep (e.g., avoid telephone and/or alarm clock in the proximity)—as opposed to *LQT3* patients, in whom 80% of the events occur at rest or while asleep.
- Previously, all patients with LQTS have been instructed to avoid competitive sports. More recently, low-risk, genetically confirmed LQTS with borderline QTc prolongation, without prior cardiac symptoms and no familial history of SCD are thought to be safe to participate in competitive sports where AED and BLS personnel is available. ICD implantation solely for the purpose of participating in sports is deemed inappropriate. For athletes with ICD implanted for another indication, returning to a low level of exertion is deemed reasonable, and a higher level of exertion may be considered after extensive discussion of potential risks.

TABLE 2 Cardiac Event Risk Stratification Scheme Based on Genes, Gender, and QTc

	QTc <500 ms		QTc ≥550 ms	
Genetic Subtype	**Male**	**Female**	**Male**	**Female**
LQT1	Low	Low	High	High
LQT2	Low	Intermediate	High	High
LQT3	Intermediate	Intermediate	High	Intermediate

Probability of the first cardiac event (syncope, cardiac arrest, or sudden death) before the age of 40 yr or before therapy. High = >50%, Intermediate = 30%-50%, Low = <30%.

TABLE 3 Management of Patients with Long QT Syndrome

Type of Syndrome	Management	Indication
Congenital	Beta-blockers	Asymptomatic patients, symptomatic patients (who do not have bronchospasm)
	Cervicothoracic sympathectomy	Refractory symptoms, especially in pediatric patients
	Cardiac pacing	Refractory symptoms associated with bradycardia, pauses
	Implantable cardioverter-defibrillator	Cardiac arrest, refractory syncope, prophylaxis for moderate- to high-risk patients for cardiac events
Acquired	Elimination of causative drug or condition	All patients
	Magnesium sulfate	Nonsustained ventricular tachycardia, torsades de pointes (even with a normal serum magnesium concentration)
	Administration of potassium (to keep serum K^+ >4.5 mEq/L)	Serum K^+ <4.5 mEq/L
	Maneuvers to increase heart rate (cardiac pacing, isoproterenol)	Bradycardia, arrhythmias refractory to magnesium sulfate

K^+, Potassium.
Adapted from Crawford MH et al [eds]: *Cardiology*, ed 2, St Louis, 2004, Mosby.

- Implantation of an implantable cardioverter-defibrillator (ICD) is recommended according to the ACC/AHA guidelines for patients with a good functional status for more than 1 yr and the following conditions (Table 3):
  1. Survivors of cardiac arrest (class 1).
  2. Patients with syncope or ventricular tachycardia while receiving β-blockers (class IIa).
  3. Prophylaxis of SCD with use of β-blocker in patients with characteristics that suggest high risk (such as *LQT2* and *LQT3, QTc >500 ms*) (class IIb).

PHARMACOLOGIC

- With few exceptions (mostly borderline QTc and LQT1 males aged >25 to 30 yr), all mutation carriers should be treated because of the risk of SCD during first cardiac event. All symptomatic patients should be treated as well.
- Beta-blockers, chiefly propranolol and nadolol, are an initial therapy of choice—there are differential responses to β-blocker therapy among different genetic variants; especially effective among LQT1 patients. Studies showed the efficacy of β-blockers with an overall mortality <2% over a mean follow-up exceeding 5 yr.
- In patients with LQT3, mexiletine shortens the QTc and can be given with a β-blocker for recurrent arrhythmias.
- In the 20% to 30% of patients who continue to have symptoms on a β-blocker, the main options are either left cardiac sympathetic denervation (LCSD) or the prophylactic implantation of an ICD.
- In patients with frequent ICD shocks or in those with high risk for SCD where ICD placement cannot be performed, cardiac pacing and/or LCSD may be indicated.
- In patients with recurrent syncope and/or aborted cardiac arrest despite combined ICD and β-blocker, LCSD as adjunctive therapy can be performed.
- Correctable factors including electrolyte disorder—hypokalemia and hypomagnesemia—and avoidance of precipitating drugs that may further prolong the QT interval is mandatory. A complete list of drugs that can potentially prolong QT may be found at www.crediblemeds.org.
- For patients with acquired form and torsades de pointes, IV magnesium and atrial or ventricular pacing are initial choices.
- Table 3 summarizes management of patients with LQTS.

PROGNOSIS

- In carefully treated patients, mortality is around 0.5% to 1% over 20 yr.
- The timing and frequency of syncope, QTc prolongation, and gender are predictive of risk for aborted cardiac arrest and SCD during adolescence. Higher risk is present in those with one or two or more episodes of syncope in the last 10 yr compared with those with no syncopal episodes, those with QTc >530 ms, and males aged 10 to 12 yr.

PEARLS & CONSIDERATIONS

COMMENTS

- Family history should be assessed for a history of sudden death and other deaths that may have occurred as manifestations of LQTS (e.g., sudden infant death, drowning, and loss of consciousness while driving).
- Propranolol and nadolol are considered superior to metoprolol for prevention of arrhythmias in LQTS.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Long QT Syndrome (Patient Information)
Torsade de Pointes (Related Key Topic)

AUTHOR: **John Wylie, MD, FACC,** and **Simon Gringut, MD**

SUGGESTED READINGS

Al-Khatib SM: *2017* AHA/ACC/HRS Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a REPORT of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society, *Heart Rhythm*, 2017.

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Lumbar Disk Syndrome

BASIC INFORMATION

DEFINITION

- Lumbar disk syndrome is an all-encompassing term that describes a spectrum of degenerative disk diseases ranging from isolated axial disk pain to disk protrusion and extrusion. Causes are usually secondary to degenerative changes (spondylosis), which can lead to a tear in the annulus fibrosis of a intervertebral disk and allow for the nucleus pulposis (the disk's contents) to herniate. Acute disk herniation (often due to a traumatic event) or gradual arthritic changes of the lumbar spine may lead to nerve root compression that results in lower-extremity pain, sensory changes, or weakness. Massive disk protrusion can sometimes lead to paralysis in the lower extremity, as well as to bowel and bladder dysfunction, a condition termed *cauda equina syndrome.* Cauda equina syndrome is considered a surgical emergency, and the patient must undergo emergent discectomy to relieve the pressure on the nerves.
- Low back pain can also be classified on the basis of symptom duration. Acute back pain is defined as lasting <4 wk, subacute back pain 4 to 12 wk, and chronic back pain lasts >12 wk.

SYNONYMS

Lumbago
Sciatica
Low back pain (LBP)
Radiating leg pain

ICD-10CM CODES	
M51.26	Other intervertebral disc displacement, lumbar region
M48.06	Spinal stenosis, lumbar region
G83.4	Cauda equina syndrome
M47.817	Spondylosis without myelopathy or radiculopathy, lumbosacral region

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- Low back pain is a leading cause of disability worldwide.
- At least one episode in 80% of adults during their lifetime.
- LBP is responsible for more than 3.5 million visits to U.S. emergency departments annually.

PREDOMINANT SEX: Male:female ratio is roughly 2:1

PREDOMINANT AGE: Herniation: 30 to 50 yr

RISK FACTORS: Smoking, obesity, weight-bearing sports (weightlifting, hammer throw), male, family history, and certain work activities that involve repeated lifting. Common degenerative causes of low back pain are summarized in Table E1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Overlapping clinical syndromes that may result:
  1. Mild herniation without nerve root compression and no leg symptoms
  2. Herniation with nerve root compression and radicular-type leg symptoms
  3. Cauda equina syndrome
  4. Diskitis
  5. Epidural abscess
  6. Chronic degenerative disease with or without leg symptoms
  7. Spinal stenosis
- Presentation and Symptoms:
  1. Low back pain, often worsened by activity or coughing and sneezing
  2. Local lumbar or lumbosacral tenderness
  3. Paresthesias, usually unilateral in the affected nerve's distribution (Fig. E1)
  4. Restricted low back motion
  5. Increased pain on bending toward affected side or flexion
  6. Weakness and reflex changes (L4—knee jerk and quadriceps, L5—extensor hallucis longus, S1—ankle jerk and toe walking) (Table E2)
  7. Sensory examination usually not helpful
  8. Lumbar stenosis can produce symptoms that are often misinterpreted as being vascular (pseudoclaudication). Pseudoclaudication usually recovers quickly with sitting or spine flexion (vascular disease is unaffected by spine position and is typically associated with atrophic skin changes and diminished pulses)
  9. Positive straight leg raising test if nerve root compression is present

ETIOLOGY

Multifactorial: Most commonly trauma and degenerative changes

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Soft tissue strain or sprain
- Tumor
- Stenosis
- Vascular claudication
- Degenerative arthritis of hip
- Insufficiency fracture of hip or pelvis

Section II describes the differential diagnosis of common low back pain syndromes. Red flags for potentially serious underlying causes of low back pain are described in Table E3.

WORKUP

In most cases the diagnosis can be established on a clinical basis alone.

IMAGING STUDIES

- Imaging is not warranted for most patients with acute low back pain. The American College of Physicians guideline for imaging in patients with low back pain recommends initial imaging in patients with major risk factors for cancer, patients with suspected spinal infection, patients with signs of cauda equina syndrome, and patients with severe neurologic deficits.
- Plain roentgenograms may be indicated within the first few weeks for persistent pain; they are usually normal in soft disk herniation, but with chronic degenerative disk disease loss of height of the disk space and osteophyte formation can occur.
- MRI (Fig. E2) may be indicated in patients whose symptoms do not resolve or when other spinal pathology may be suspected.
- Electrodiagnostic studies may confirm the diagnosis or rule out peripheral nerve disorders.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Short course (3 to 5 days) of limited physical activity for acute disk herniation with leg pain.
- Physical therapy for modalities plus a careful gradual exercise program. Physical

TABLE E1 Common Degenerative Causes of Low Back Pain*

	Muscle Strain	Spondylolisthesis	Herniated Disk	Osteoarthritis	Spinal Stenosis
Age (yr)	20-60	20-40	20-60	>40	>50
Pain pattern					
Initial location	Back	Back	Leg > back	Back > leg	Leg > back
Onset	Acute	Insidious	Acute	Insidious	Insidious
Standing	+	+	–	+	+
Sitting	–	–	+	–	–
Flexion	+	–	+	–	–
Extension	–	+	–	+	+
Straight-leg raise	–	–	+	–	–
Plain radiograph	–	+	–	+	+

*+ denotes presence of finding or pain with movement; – denotes absence of finding or pain with movement.
From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

therapists generally use the McKenzie method.
- Lumbosacral corset brace during rehabilitation process in conjunction with exercise program is beneficial in only a minority of cases.

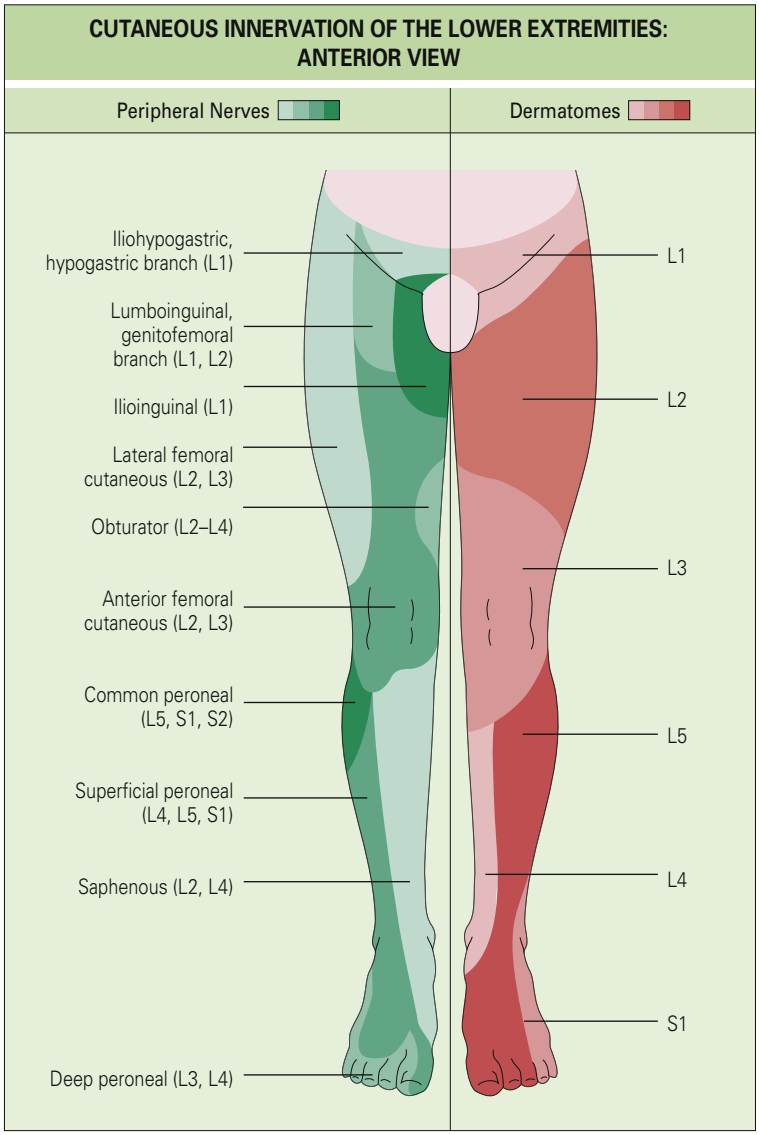

FIG. E1 Cutaneous sensory innervation. Anterior view of the lower extremities illustrating skin areas supplied by nerve roots (*right*) and peripheral nerves (*left*). (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

- Percutaneous electrical nerve stimulation may be beneficial in selected patients with chronic back pain.
- Acupuncture is modestly effective.
- A recent trial of spinal manipulation therapy (SMT) and home exercise with advice (HEA) for subacute and chronic back-related leg pain revealed that SMT plus HEA was more effective than HEA alone after 12 wk, but at 52 wk the benefit was sustained only for global improvement, satisfaction, and medication use and not for self-reported low-back pain, disability, and general health status.

ACUTE GENERAL Rx

- NSAIDs.
- Muscle relaxants for sedative effect are commonly used; however, trials have shown that among patients with acute, nontraumatic, nonradicular LBP presenting to the emergency department, adding cyclobenzaprine or oxycodone/acetaminophen to naproxen alone did not improve functional outcomes or pain at 1-wk follow-up. These findings do not support use of these additional medications in this setting.
- Analgesics provide only modest benefit.
- Injection therapy for low back pain and sciatica has limited clinical benefit and is generally not recommended. Epidural steroid injection for leg symptoms only in selected patients.
- Surgical management can be considered if the symptoms do not improve after conservative treatment. Patients with predominantly radiating leg pain or leg symptoms tend to benefit more from surgery than those with isolated low back pain.

DISPOSITION

- Almost all lumbar disk syndromes improve with time.
- Recurrent episodes usually respond to medical management.
- Recovery from the rare paralytic event is often incomplete.

REFERRAL

- For orthopedic or neurosurgical consultation for intractable pain or significant neurologic deficit
- Emergency referral for cauda equina syndrome
- Table E4 summarizes indications for surgical referral

TABLE E2 Symptoms and Signs of Common Root Compression Syndromes Produced by Lumbar Disk Prolapse

Root Lesion	Pain	Sensory Loss	Motor Weakness	Reflex Lost	Other Signs
S1	From buttock down back of thigh and leg to ankle and foot	Sole of foot and posterior calf	Plantar flexion of ankle and toes	Ankle jerk	Diminished straight leg raising
L5	From buttock to lateral aspect of leg and dorsum of foot	Dorsum of foot and anterolateral aspect of lower leg	Dorsiflexion of foot and toes	None	As above
L4	Lateral aspect of thigh to medial side of calf	Medial aspect of calf and shin	Dorsiflexion and inversion of ankle; extension of knee	Knee jerk	Positive femoral stretch test

From Ballinger A: *Kumar & Clark's essentials of clinical medicine*, ed 6, Edinburgh, 2012, Saunders.

TABLE E3 Red Flags for Potentially Serious Underlying Causes of Low Back Pain

Spinal Fracture
- Significant trauma
- Prolonged glucocorticoid use
- Age >50 yr

Infection or Cancer
- History of cancer
- Unexplained weight loss
- Immunosuppression
- Injection drug use
- Nocturnal pain
- Age >50 yr

Cauda Equina Syndrome
- Urinary retention
- Overflow incontinence
- Fecal incontinence
- Bilateral or progressive motor deficit
- Saddle anesthesia

Spondyloarthritis
- Severe morning stiffness
- Pain improves with exercise, not rest
- Pain during second half of night
- Alternating buttock pain
- Age <40 yr

From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.

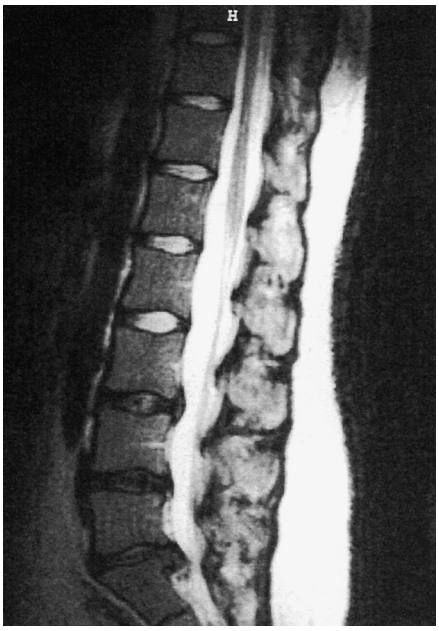

FIG. E2 MRI showing a prolapsed L5/S1 disk. (From Carr A, Hamilton W: *Orthopedics in primary care,* ed 2, Philadelphia, 2005, Saunders.)

TABLE E4 Indications for Surgical Referral

Disk Herniation
- Cauda equina syndrome (emergency)
- Serious neurologic deficit
- Progressive neurologic deficit
- Greater than 6 wk of disabling radiculopathy (elective)

Spinal Stenosis
- Serious neurologic deficit
- Progressive neurologic deficit
- Persistent and disabling pseudoclaudication (elective)

Spondylolisthesis
- Serious or progressive neurologic deficit

From Firestein GS et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.

PEARLS & CONSIDERATIONS

Red flags suggesting a more serious condition as a cause of the back pain include:
- Fever
- History of malignancy
- Pain at rest
- Incontinence
- Sudden worsening in level of pain
- Weight loss
- Significant motor loss, especially if associated with saddle anesthesia

COMMENTS

- Surgery is most consistently helpful when leg pain (not back pain) predominates.
- No substantial benefit has been shown with oral steroids, traction, epidural corticosteroid injections, or lumbar support.
- Clinicians should only consider opioids in patients who have failed other treatments and only if potential benefits outweigh the risks for individual patients.

RELATED CONTENT

Lumbar Disk Syndrome (Patient Information)
Pain Management in Chronic Pain (Related Key Topic)

AUTHORS: **Shyam A. Patel, MD,** and **Kalpit N. Shah, MD**

SUGGESTED READINGS

Deyo RA, Mirza SK: Herniated lumbar intervertebral disk, *N Engl J Med* 374:1763-1772, 2016.

Hooten WM, Cohen SP: Evaluation and treatment of low back pain: a clinically focused review for primary care specialists, *Mayo Clin Proc* 90(12):1699-1718, 2015.

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Lurie JD et al: Surgical versus nonoperative treatment for lumbar disc herniation: eight-year results for the spine patient outcomes research trial, *Spine* 39(1):3-16, 2014.

Qaseem A et al: Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians, *Ann Int Med* 166:514-530, 2017.

BASIC INFORMATION

DEFINITION

A lung abscess is an infection of the lung parenchyma resulting in a necrotic cavity containing pus.

SYNONYM

Pulmonary abscess

ICD-10CM CODES

J85.1	Abscess of lung with pneumonia
J85.2	Abscess of lung without pneumonia
A06.5	Amebic lung abscess

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Has decreased over the last 30 yr as a result of antibiotic therapy.

- Lung abscess in patients age 50 and over is associated with primary lung neoplasia in 30% of the cases.
- Lung abscesses commonly coexist with empyemas (pus in the pleural space).

RISK FACTORS (SEE TABLE 1):

- Alcohol-related problems
- Seizure disorders
- Cerebrovascular disorders with dysphagia
- Drug abuse
- Esophageal disorders (e.g., scleroderma, esophageal carcinoma)
- Poor oral hygiene
- Obstructive malignant lung disease
- Bronchiectasis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms are generally insidious and prolonged, occurring for weeks to months
- Fever, chills, and sweats
- Cough
- Sputum production (purulent with foul odor)
- Pleuritic chest pain
- Hemoptysis
- Dyspnea
- Malaise, fatigue, and weakness
- Tachycardia and tachypnea
- Dullness to percussion, whispered pectoriloquy, and bronchophony
- Amphoric breath sounds (low-pitched sound of air moving across a large open cavity)

ETIOLOGY

- The most important factor predisposing to lung abscess is aspiration.
- Following aspiration as a major predisposing factor is periodontal disease.
- Lung abscess is rare in an edentulous person.
- Approximately 90% of lung abscesses are caused by anaerobic microorganisms (peptostreptococci, microaerophilic streptococci such as *Streptococcus milleri, Bacteroides* species, *Fusobacterium nucleatum, Prevotella*). Pulmonary actinomycosis will also generate lung abscess.
- In most cases anaerobic infection is mixed with aerobic or facultative anaerobic organisms *(S. aureus, E. coli, K. pneumoniae, P. aeruginosa).*
- Parasitic organisms including *Paragonimus westermani* and *Entamoeba histolytica.*
- Fungi including *Aspergillus, Cryptococcus, Histoplasma, Blastomyces,* and *Coccidioides* spp.
- Immunocompromised hosts may become infected with *Aspergillus,* mycobacteria, *Nocardia, Legionella micdadei,* and *Rhodococcus equi.*
- Lung necrosis caused by community strains of Methicillin-resistant *Staphylococcus aureus* (MRSA) (USA 300 strain) in young adults or adolescents after acute influenza was initially reported in 2002 and can be quite fulminant.

DIAGNOSIS

Lung abscess may be primary or secondary.

- *Primary lung abscess* refers to infection from normal host organisms within the lung (e.g., aspiration, pneumonia).
- Secondary lung abscess results from other preexisting conditions (e.g., endocarditis, underlying lung cancer, pulmonary emboli).

Lung abscess may be acute or chronic.

- Acute lung abscess is present if symptoms are of less than 4 to 6 wk.
- Chronic lung abscess is present if symptoms last longer than 6 wk.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is similar to that for cavitary lung lesions:

- Bacterial (anaerobic, aerobic, infected bulla, empyema, actinomycosis, tuberculosis)
- Fungal (histoplasmosis, coccidioidomycosis, blastomycosis, aspergillosis, cryptococcosis, Zygomycetes)
- Parasitic (amebiasis, echinococcosis)
- Malignancy (primary lung carcinoma, metastatic lung disease, lymphoma, Hodgkin disease)
- Granulomatosis with polyangiitis, sarcoidosis, endocarditis, and septic pulmonary emboli

WORKUP

- The workup of a patient with lung abscess attempts to elicit a primary or a secondary cause.
- Blood tests are not specific in diagnosing lung abscesses.
- Most diagnoses are made from imaging studies; however, to diagnose a specific cause bacteriologic studies are needed.

LABORATORY TESTS

- CBC with leukocytosis
- Bacteriologic studies:
  1. Sputum Gram stain and culture (commonly contaminated by oral flora)
  2. Percutaneous transtracheal aspiration
  3. Percutaneous transthoracic aspiration
  4. Fiberoptic bronchoscopy using bronchial brushings or bronchoalveolar lavage is the most widely used intervention when trying to obtain diagnostic bacteriologic cultures
- Blood cultures on some occasions (<30%) may be positive
- If an empyema is present, obtaining empyema fluid via thoracentesis may isolate the organism

IMAGING STUDIES

- Chest x-ray makes the diagnosis of lung abscess showing the cavitary lesion with an air-fluid level.
- Lung abscesses are most commonly found in the posterior segment of the right upper lobe.
- Chest CT scan can localize and size the lesion and assist in differentiating lung abscesses from other pathologic processes (e.g., tumor, empyema, infected bulla) (Fig. 1).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Oxygen therapy
- Postural drainage
- Respiratory therapy maneuvers

ACUTE GENERAL Rx

- Piperacillin/tazobactam 3.375 g IV q6h in aspiration pneumonia with lung abscess.
- Ceftriaxone 1 to 2 g IV q24h plus metronidazole: 500 mg IV q8h.
- Clindamycin is more effective for anaerobic lung abscess than penicillin alone. Dose: 900 mg IV q8h until improved, then 300 to 600 mg PO q6h.
- Penicillin 1 to 2 million units IV q4h until improvement (afebrile, decreased phlegm production, followed by penicillin VK 500 mg

TABLE 1 Risk Factors for Aspiration Pneumonia and Lung Abscess

Increased bacterial inoculum	Periodontal disease, gingivitis, tonsillar or dental abscess, drugs that decrease gastric acidity
Impairment of consciousness	Drugs, alcohol, general anesthesia, metabolic encephalopathy, coma, shock, cerebrovascular accident, cardiopulmonary arrest, seizures, surgery, trauma
Impairment of cough and gag reflexes	Vocal cord paralysis, intratracheal anesthesia, endotracheal tube, tracheostomy, myopathy, myelopathy, other neurologic disorders
Impairment of esophageal function	Diverticula, achalasia, strictures, disorders of gastrointestinal motility, neoplasm, tracheoesophageal fistula, pseudobulbar palsy
Emesis	Nasogastric tube, gastric dilation, ileus, intestinal obstruction

From Cohen J, Powderly WG: *Infectious diseases*, ed 2, St Louis, 2004, Mosby.

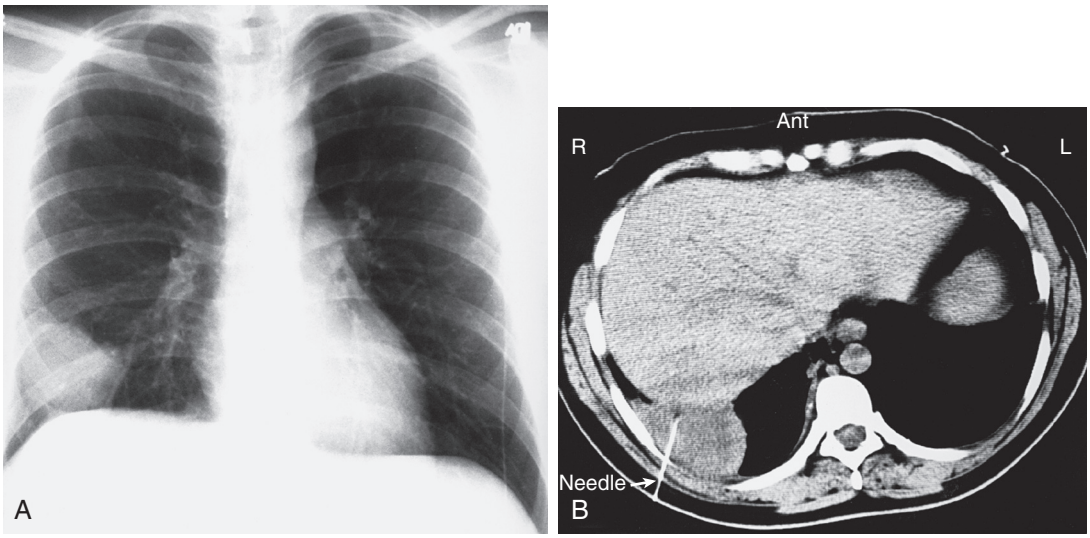

FIG. 1 Lung abscess. On a chest radiograph, a lung abscess may look to be a solid rounded lesion **(A),** or, if it has a connection with the bronchus, there may be an air-fluid level in a thick-walled cavitary lesion. CT scanning **(B)** can be used to localize the lesion and to place a needle for drainage and aspiration of contents for culture. (From Mettler FA [ed]: *Primary care radiology,* Philadelphia, 2000, Saunders.)

PO q6h for 2 to 3 wk but often up to 6 to 8 wk) can be given with metronidazole doses of 7.5 mg/kg IV q6h followed by PO 500 mg bid to qid dosing as an alternative to clindamycin.
- Penicillin should not be used alone because many mouth flora anaerobes now produce penicillinase enzymes. Metronidazole should not be used alone because it is not active against microaerophilic streptococci and some anaerobic cocci.
- Other alternatives are ampicillin/sulbactam and carbapenems such as ertapenem and meropenem.

CHRONIC Rx

- Bronchoscopy to assist with drainage and/or diagnosis is indicated in patients who fail to respond to antibiotics or if there is suspected underlying malignancy.
- Surgery is indicated on rare occasions (<10%) in patients with complications of lung abscess (see "Comments").

DISPOSITION

- More than 95% of patients are cured with the use of antibiotics alone
- Complications of lung abscesses include:
  1. Empyema
  2. Massive hemoptysis
  3. Pneumothorax
  4. Bronchopleural fistula
  5. Hepatobronchial fistula
  6. Brain abscess
  7. Bronchiectasis
- Mortality is low in community-acquired lung abscess (2.5%)
- Hospital-acquired lung abscess carries a high mortality rate (65%)

REFERRAL

If lung abscess is present, consultation with pulmonary and infectious disease specialist is recommended. An interventional radiologist also may be able to perform drainage and obtain cultures.

PEARLS & CONSIDERATIONS

COMMENTS

- Refractory cases are usually the result of:
  1. Large cavity size (>6 cm)
  2. Recurrent aspiration
  3. Thick-walled cavities
  4. Underlying lung carcinoma
  5. Empyema formation
- Necrotizing pneumonia is similar to a lung abscess but differs in size (<2 cm in diameter) and number (usually multiple suppurative cavitary lesions)

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Lung Abscess (Patient Information)
Aspiration Pneumonia (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Desai H, Agrawal A: Pulmonary emergencies: pneumonia, acute respiratory distress syndrome, lung abscess, and empyema, *Med Clin North Am* 96:1127-1148, 2012.

Kuhajda I et al: Lung abscess-etiology, diagnostic and treatment options, *Ann Transl Med* 3(13):183, 2015.

BASIC INFORMATION

DEFINITION

A primary lung neoplasm is a malignancy arising from lung tissue. The different types are non–small cell lung cancer (NSCLC, 85% of all lung cancers; squamous cell carcinoma, adenocarcinoma, and large cell carcinoma) and small cell lung cancer (SCLC, 15% of all lung cancers).

ADENOCARCINOMA: Represents 35% to 40% of lung carcinomas; frequently located in midlung and periphery; initial metastases are to lymphatics; frequently associated with peripheral scars; adenocarcinoma is described as preinvasive, minimally invasive, or invasive.

SQUAMOUS CELL: Represents 20% to 30% of lung cancers; central location; metastasis by local invasion; frequent cavitation and obstructive phenomena.

SMALL CELL: Represents 15% of lung carcinomas; central location; metastasis through lymphatics; associated with lesion of the short arm of chromosome 3; high cavitation rate.

LARGE CELL: Represents 10% to 15% of lung carcinomas; frequently located in the periphery; metastasis to central nervous system and mediastinum; rapid growth rate with early metastasis.

LEPIDIC-PREDOMINANT PATTERN (BRONCHOALVEOLAR): Represents 5% of lung carcinomas; frequently located in the periphery; may be bilateral; initial metastasis through lymphatic, hematogenous, and local invasion; no correlation with cigarette smoking; cavitation rare.

SYNONYM

Lung cancer

ICD-10CM CODES

C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung

EPIDEMIOLOGY & DEMOGRAPHICS

- Lung cancer is responsible for >30% of cancer deaths in males and >25% of cancer deaths in females. It has been the most common cancer in the world since 1985 and is the leading cause of cancer-related death in both sexes.
- Tobacco smoke is implicated in 90% of cases; of these, secondhand smoke is responsible for approximately 20% of cases.
- In the U.S., there were an estimated 228,150 new cases of lung cancer and 142,670 deaths from lung cancer in 2019. Worldwide 1.6 million tumor-related deaths are attributed annually to lung cancer.
- From 1990 through 2013 the percentage of patients with non–small cell lung cancer who never smoked rose from 8% to 16%, raising concerns about environmental carcinogens.
- Coincident with the decrease in smoking rates, the incidence of new cases and the rate lung cancer deaths in the U.S. continue to decrease. However, death rates among African Americans continue to be disproportionately higher.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Weight loss, fatigue, fever, anorexia, dysphagia
- Cough, hemoptysis, dyspnea, wheezing
- Chest, shoulder, and bone pain
- Paraneoplastic syndromes (see Table 1):
  1. Lambert-Eaton myasthenic syndrome: Myopathy involving proximal muscle groups
  2. Endocrine manifestations: Hypercalcemia, ectopic adrenocorticotropic hormone secretion, syndrome of inappropriate excretion of adrenocorticotropic hormone (SIADH)
  3. Neurologic: Subacute cerebellar degeneration, peripheral neuropathy, cortical degeneration
  4. Musculoskeletal: Polymyositis, clubbing, hypertrophic pulmonary osteoarthropathy
  5. Hematologic or vascular: Migratory thrombophlebitis, marantic thrombosis, anemia, thrombocytosis, or thrombocytopenia
  6. Cutaneous: Acanthosis nigricans, dermatomyositis
- Pleural effusion (10% of patients), recurrent pneumonias (from obstruction), localized wheezing
- *Superior vena cava syndrome:*
  1. Obstruction of venous return of the superior vena cava is most commonly caused by bronchogenic carcinoma or metastasis to paratracheal nodes
  2. The patient usually reports headache, nausea, dizziness, visual changes, syncope, and respiratory distress
  3. Physical examination reveals distention of thoracic and neck veins, edema of face and upper extremities, facial plethora, and cyanosis
- *Horner syndrome:* Constricted pupil, ptosis, facial anhidrosis caused by spinal cord damage between C8 and T1 as a result of a superior sulcus tumor (bronchogenic carcinoma of the extreme lung apex)
- *Pancoast tumor:* A superior sulcus tumor (Fig. 1) associated with ipsilateral Horner syndrome and shoulder pain

ETIOLOGY

- Tobacco abuse: The molecular pathology of smoking-related lung cancer is illustrated in Fig. E2. The chance of developing lung cancer for a 40-pack-yr persistent smoker is 20 times that of someone who never smoked.
- Environmental agents (e.g., radon) and industrial agents (e.g., ionizing radiation, asbestos, nickel, uranium, vinyl chloride, chromium, arsenic, coal dust).
- Lung cancer susceptibility and risk increased in inherited cancer syndromes caused by germline mutations in p53, retinoblastoma, and epidermal growth factor receptor *(EGFR)* genes.
- Fig. E3 illustrates the multistep cellular carcinogenesis in lung cancer.

TABLE 1 Paraneoplastic Syndromes Associated with Bronchogenic Carcinoma

Syndrome	Cell Type	Mechanism
Hypertrophic pulmonary osteoarthropathy and clubbing	All types	Unknown
Hyponatremia	SCLC most common; may be any type	SIADH, ectopic antidiuretic hormone production by tumor
Hypercalcemia	Usually squamous cell	Bone metastases, osteoclast-activating factor, parathyroid hormone–like hormone, prostaglandins
Cushing syndrome	Usually SCLC	Ectopic ACTH production
Lambert-Eaton myasthenic syndrome	Usually SCLC	Voltage-sensitive calcium channel antibodies in >75%; affects presynaptic neuronal calcium channel activity
Other neuromyopathic disorders	SCLC most common; may be any type	Antineuronal nuclear antibodies, also known as anti-Hu; others unknown
Thrombophlebitis	All types	Unknown

ACTH, Adrenocorticotropic hormone; *SCLC,* small cell lung cancer; *SIADH,* syndrome of inappropriate secretion of antidiuretic hormone.

Adapted from Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

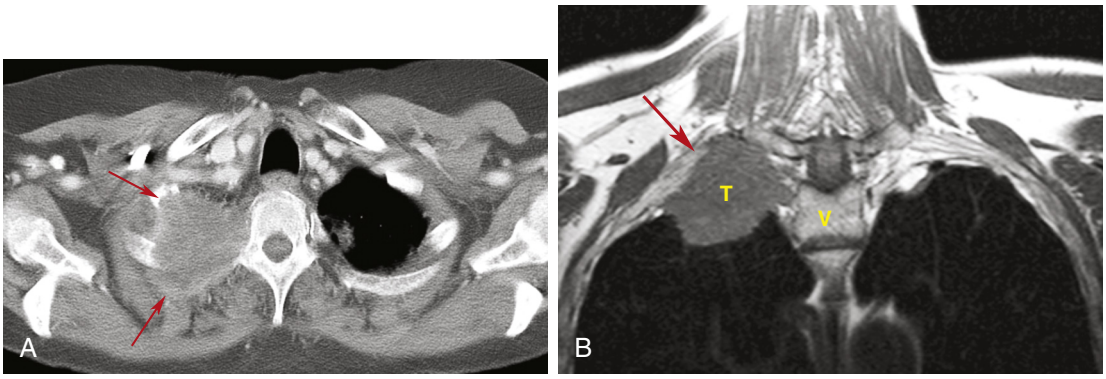

FIG. 1 Pancoast tumor with chest wall invasion. A, On computed tomography, a right apical mass is associated with invasion of the chest wall and rib destruction *(arrows)* . Although the tumor appears to contact the vertebral body, it appears intact. **B,** Coronal magnetic resonance imaging shows the relationship of the tumor (*T*) to the vertebral body (*V*) and the brachial plexus (*arrow*), which appears to be involved. (From Webb WR et al: *Fundamentals of body CT*, ed 4, Philadelphia, 2015, Elsevier.)

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pneumonia
- Tuberculosis (TB)
- Metastatic carcinoma to the lung
- Lung abscess
- Granulomatous disease
- Carcinoid tumor
- Sarcoidosis
- Benign lesions that simulate thoracic malignancy:
  1. Lobar atelectasis: Pneumonia, chronic inflammatory disease, allergic bronchopulmonary aspergillosis
  2. Multiple pulmonary nodules: Septic emboli, Wegener granulomatosis, sarcoidosis, rheumatoid nodules, fungal disease, multiple pulmonary atrioventricular fistulas
  3. Mediastinal adenopathy: Sarcoidosis, lymphoma, primary TB, fungal disease, silicosis, pneumoconiosis, drug-induced (e.g., phenytoin, trimethadione)
  4. Pleural effusion: Congestive heart failure, pneumonia with parapneumonic effusion, TB, viral pneumonitis, ascites, pancreatitis, collagen-vascular disease

WORKUP

- The workup generally includes chest CT, positron-emission tomographic (PET) scan, and tissue biopsy. Molecular testing for treatable oncogenic alterations should be performed to further classify NSCLC. This includes testing for mutations in the gene encoding epidermal growth factor receptor (eGFR) and in BRAF v600e, searching for translocations in the genes encoding anaplastic lymphoma kinase (ALK) and rat osteosarcoma (ROS1), and assessing expression of programmed death-ligand-1 (PD-L1).[1] Common immunohistochemical markers used in the diagnosis of lung tumors are summarized in Table 2. Table 3 describes common molecular alterations in lung tumors.
- Additional lab tests include CBC, serum chemistry studies.
- Diagnosis and staging of lung cancer should be performed simultaneously to minimize invasive testing.

LABORATORY TESTS

Various modalities are available to obtain a tissue diagnosis:

- Biopsy of any suspicious lymph nodes (e.g., supraclavicular or mediastinal node)
- Flexible fiberoptic bronchoscopy: Brush and biopsy specimens are obtained from any visualized endobronchial lesions. The use of a gene-expression classifier has a high sensitivity across different lesion sizes, locations, stages, and cell type of lung cancer. The combination of the classifier plus bronchoscopy has a sensitivity of >85%. In intermediate-risk patients with a nondiagnostic bronchoscopic examination, a negative classifier score provides support for a more conservative diagnostic approach[2]
- Transbronchial needle aspiration: Done with a special needle passed through the bronchoscope; this technique is useful to sample mediastinal masses or paratracheal lymph nodes
- Transthoracic fine-needle aspiration biopsy with fluoroscopic or CT scan guidance to evaluate peripheral pulmonary nodules
- Endobronchial ultrasound (EBUS) guided biopsy and staging is now routinely used to evaluate suspected mediastinal and hilar nodes
- Mediastinoscopy and anteromedial sternotomy in suspected tumor involvement of the mediastinum
- Pleural biopsy in patients with pleural effusion
- Thoracentesis of pleural effusion and cytologic evaluation of the obtained fluid may confirm diagnosis

IMAGING STUDIES

- Chest x-ray (Fig. 4): The radiographic presentation often varies with the cell type. Presence of pleural effusion, lobar atelectasis, and mediastinal adenopathy can occur in any cell type.
- CT scan of the chest (Fig. 5) can evaluate mediastinal and pleural extension. The chest CT should include liver and adrenal glands (common sites of metastases). CT or MRI of brain should be considered in a patient presenting with neurologic symptoms (e.g., headaches, vision disturbances).
- PET with ^{18}F-fluorodeoxyglucose (^{18}FDG-PET) (Fig. E6) is superior to CT in detecting mediastinal and distant metastases in NSCLC. It is useful for preoperative staging of NSCLC.
- The use of PET-CT (Fig. E7) for preoperative staging of NSCLC reduces both the total number of thoracotomies and the number of futile thoracotomies.

STAGING

After confirmation of diagnosis, patients should undergo staging:

- In NSCLC, the TNM staging system is used. Table 4 summarizes TNM stage groups. Both stage I (no lymph node involvement) and stage II (ipsilateral bronchopulmonary/ hilar lymph nodes or T_3 tumor) include localized tumors for which surgical resection is the preferred treatment. Stage III is subdivided into III_A (potentially resectable) and II_B/III_C (unresectable). Stage IV indicates metastatic disease with stage IV_A referring to intrathoracic metastases or pleural involvement or single extra-thoracic metastasis. stage IV_B includes tumors with multiple extra-thoracic metastases
- In SCLC, the staging system developed by the Veterans Administration Lung Cancer Study Group is used. It contains two stages:
  1. Limited-stage disease: Confined to the regional lymph nodes and to one hemithorax (excluding pleural surfaces), which can be included in a single radiation portal

[1]Silvestri GA et al: A bronchial genomic classifier for the diagnostic evaluation of lung cancer, *N Engl J Med* 373:243–251, 2015.

[2]Silvestri GA et al: A bronchial genomic classifier for the diagnostic evaluation of lung cancer, *N Engl J Med* 373:243–251, 2015.

TABLE 2 Common Immunohistochemical Markers Used in the Diagnosis of Lung Tumors

Diagnosis	Positive Immunohistochemical Markers
Squamous cell carcinoma	Cytokeratin (CK) cocktail (e.g., AE1/AE3)
	p63
	p40
	CK5/6
	CK7 in up to 30%
Adenocarcinoma including adenocarcinoma in situ or minimally invasive adenocarcinoma, nonmucinous	CK cocktail
	CK7
	TTF-1
	Napsin A
In situ and invasive mucinous adenocarcinoma	CK cocktail
	CK7
	CK20
	cdx-2
	TTF-1 rare
Large cell neuroendocrine carcinoma	CK cocktail
	TTF-1
	CD56
	Chromogranin A
	Synaptophysin
Carcinoid tumor	CK cocktail
	TTF-1 (weaker than in high-grade neuroendocrine tumors)
	CD56
	Chromogranin A
	Synaptophysin
Atypical carcinoid tumor	CK cocktail (tends to be patchy)
	TTF-1 (weaker than in high-grade neuroendocrine tumors)
	CD56
	Chromogranin A
	Synaptophysin
Common differential diagnoses:	
• Colonic adenocarcinoma	CK20+/CK7–
• Lung, breast, pancreatobiliary, upper gastrointestinal adenocarcinoma	CK7+/CK20–
• Urothelial carcinoma	CK7+/CK20+
• Prostatic adenocarcinoma	CK7–/CK20–
• Mesothelioma	Calretinin, WT1, CK5/6
• Malignant melanoma	S-100, HMB-45, Melan-A

From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

2. Extensive-stage disease: Spread beyond the confines of limited-stage disease

- Pretreatment staging procedures for lung cancer patients, in addition to complete history and physical examination, generally include the following tests:
  1. Chest radiograph (posteroanterior and lateral), ECG
  2. Laboratory evaluation: Complete blood count, complete metabolic panel; arterial blood gases and pulse oximetry in selected cases
  3. Pulmonary function studies
  4. CT scan of chest and PET scan: Trials have shown a reduction in futile thoracotomies for patients with suspected NSCLC who undergo preoperative assessment with PET in addition to conventional workup
  5. Mediastinoscopy or anterior mediastinotomy in patients being considered for possible curative lung resection
  6. Biopsy of any accessible suspect lesions
  7. CT scan to include liver and brain
  8. Bone marrow aspiration and biopsy only in selected patients with small cell carcinoma of the lung. In the absence of an increased lactate dehydrogenase or cytopenias, routine bone marrow examination is not recommended
  9. Newer technologies in preoperative staging include endoscopic bronchial ultrasonography and esophageal ultrasonography to guide biopsies; however, cervical mediastinoscopy is standard criterion in preoperative nodal staging (sensitivity >93%, specificity >95%)

TABLE 3 Examples of Common Molecular Alterations in Lung Tumors

Diagnosis	Common Molecular Alterations
Squamous preneoplasia	LOH—3p, 9p21, 8p21–23, aneuploidy, methylation
Atypical adenomatous hyperplasia	LOH—3p, 9p, aneuploidy
	K-ras codon 12 mutation
Adenocarcinoma	p53 mutation
	p16 mutation/inactivation
	K-Ras (42%); smokers more common
	EGFR overexpression (40%)
	EGFR mutation
	Her2/neu, COX-2 overexpression
Squamous cell carcinoma	p53 mutation
	p16 inactivation
	Allelic loss 3p
	EGFR overexpression (80%)
Large cell carcinoma	K-Ras, p53, loss p16
Large cell neuroendocrine carcinoma	p53
	bcl-2 overexpression
	Rb mutation
	3p21, FHIT, 3p22–24, 5q21,9p21
Small cell carcinoma	Rb mutation (80+%)
	p53 mutation 50%–80%
	BCL-2 expression
	3p21, FHIT, 3p22–24, 5q21,9p21

COX-2, Cyclooxygenase 2; *EGFR,* epidermal growth factor receptor; *LOH,* loss of heterozygosity.
From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Nutritional support
- Avoidance of tobacco and other substances toxic to the lungs
- Supplemental oxygen

ACUTE GENERAL Rx

NON–SMALL CELL CARCINOMA:

- Surgical resection is standard in patients with operable NSCLC (stage I or II) who are surgical candidates. Lobectomy is the best standard surgical approach. Lesser resections may be necessary in patients with marginal pulmonary reserve. Video-assisted thoracic surgery (VATS) decreases morbidity and shortens the hospital stay.
  1. Surgical resection is indicated in patients with limited disease (not involving mediastinal nodes, ribs, pleura, or distant sites). This represents approximately 15% to 30% of diagnosed cases. Stereotactic ablative radiotherapy is a

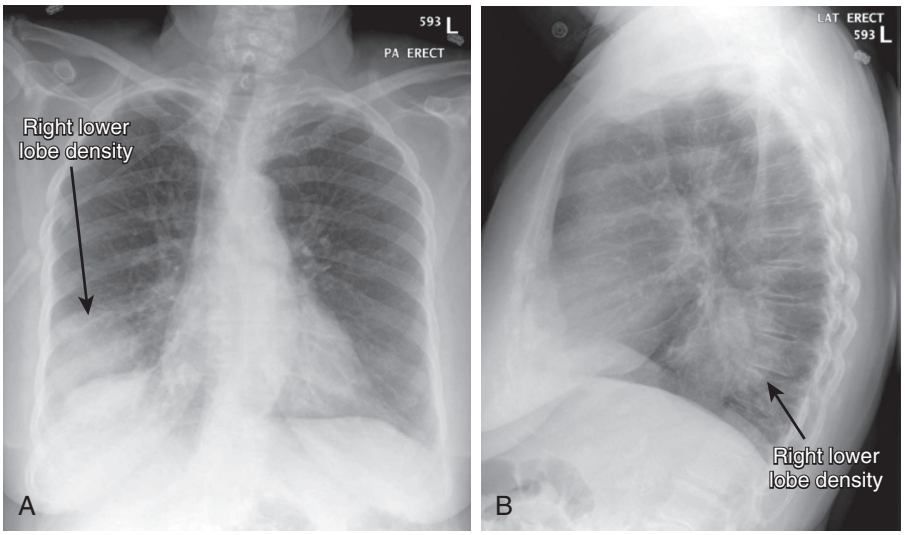

FIG. 4 Lung neoplasm, primary. Lung mass presenting with hemoptysis. **A,** Posterior-anterior (PA) chest x-ray. **B,** Lateral chest x-ray. This 83-yr-old female presented with hemoptysis of a quarter-sized clot. Her posterior-anterior chest x-ray shows a rounded right lower lobe density. On the lateral view, this is visible in the retrocardiac space. This density measures 7.6 cm in diameter. Pneumonia, neoplasm, or abscess could have this appearance on chest x-ray. Computed tomography was performed to further delineate the pathology (see Fig. 5). (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

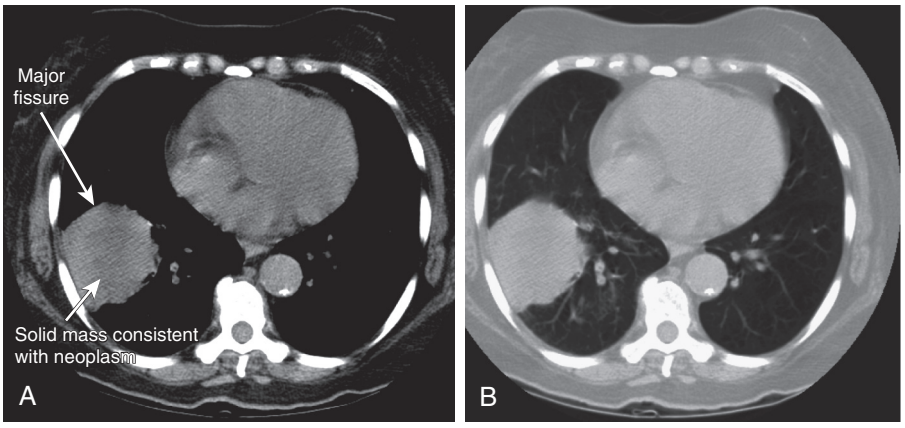

FIG. 5 Lung neoplasm, primary. Lung mass presenting with hemoptysis. Same patient as in Fig. 4. Noncontrast computed tomography was performed (contrast was withheld as a consequence of the patient's renal dysfunction) and shows a 6 by 6 cm round lesion abutting the oblique fissure (also called the major fissure) and lateral chest wall. **A,** Soft tissue windows. **B,** Lung windows. On soft tissue windows, the center appears slightly darker, indicating lower density that may represent central necrosis. If IV contrast had been given, an area of necrosis would have failed to enhance. Infection or infarction is technically possible, but a pulmonary neoplasm is the most likely explanation for this lesion. Biopsy showed this to be a moderately differentiated squamous cell carcinoma. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

reasonable option for patients with localized NSCLC who are not surgical candidates. Multimodality treatment guidelines are summarized in Table 5.

2. Preoperative evaluation includes cardiac status and pulmonary function assessment. Pneumonectomy is possible if the patient has a preoperative FEV_1 = 2 L or if the maximal voluntary ventilation is >50% of predicted capacity. Individuals with FEV_1 >1.5 L are suitable for lobectomy without further evaluation unless there is evidence of interstitial lung disease or undue dyspnea on exertion. In that case, carbon dioxide diffusion in the lung (DLCO) should be measured. If the DLCO is <80% predicted normal, the individual may not be clearly operable.
3. Conventional radiotherapy fails to durably control the primary lung tumor in nearly 70% of patients and 2-yr survival is less than 40%. Stereotactic body radiation (SBRT) uses several highly focused radiation beams to deliver total higher doses of radiotherapy (in high doses in 3 to 5 fractions) and is more effective than conventional radiotherapy, with a local control rate equivalent to that with surgery in inoperable early stage lung cancer.
4. Preoperative chemotherapy should be considered in patients with more advanced disease (stage IIIA) who are being considered for surgery because it increases the median survival time in patients with NSCLC compared with surgery alone.
5. Postoperative adjuvant chemotherapy with doublet regimens significantly increases 5-yr survival (69% vs. 54%) in patients with completely resected stage II-IIIA NSCLC. For stage I NSCLC there may be some patients who benefit from adjuvant chemotherapy. An algorithm for selecting patients with stage I NSCLC for postoperative adjuvant chemotherapy is outlined in Fig. 8.

- Treatment of unresectable NSCLC:
  1. Radiotherapy alone is used primarily for treatment of central nervous system and skeletal metastases, superior vena cava syndrome. Thoracic radiotherapy in combination with chemotherapy is standard therapy for unresectable stage 3 disease.
  2. Chemotherapy, targeted therapy, and immune checkpoint therapy are the mainstays of treatment for advanced stage IV or metastatic NSCLC. Initial stratification is done based on pathology (squamous vs. nonsquamous cancers), presence of driver mutations (e.g., *EGFR, ALK, ROS1,* and *BRAF* mutations in adenocarcinomas), and expression of programmed death receptor ligand-1 (PDL-1). Table 6 summarizes selected NSCLC oncogenes and targeted therapy.
  3. A platinum-based chemotherapy doublet regimen is recommended for fit patients, and single agents are offered to elderly patients and those with poor performance status. Various combination regimens are available with platinum plus pemetrexed preferred for nonsquamous cancers while other for squamous cancers other doublets such as paclitaxel plus carboplatin, cisplatin plus vinorelbine, gemcitabine plus cisplatin, and cisplatin plus docetaxel are utilized with none being clearly superior to the others. The addition of bevacizumab to paclitaxel plus carboplatin results in significant survival benefit in nonsquamous cancers.
  4. Upfront therapy with pembrolizumab, a PD-1 immune-checkpoint inhibitor antibody that disrupts PD-1 mediated signaling and restores antitumor immunity, is superior to chemotherapy in patients with >50% PD-L1 expression. When pembrolizumab is combined with chemotherapy in patients with 1-50% PD-L1 expression, there is an improvement in overall survival. In addition, atezolizumab and nivolumab (other checkpoint inhibitors) have been shown to have superior survival benefit versus docetaxel in advanced NSCLC that had previously received chemotherapy.

5. Tyrosine kinase inhibitors targeting activating mutations are of use in patients whose adenocarcinomas harbor the EGFR mutations, which are more commonly detected in patients who never smoked or are light smokers and in Asian patients. Gefitinib, erlotinib, afatinib, osimertinib, and dacomitinib are oral EGFR inhibitors that have showed impressive responses and improvements in median overall survival to the range of 30 mo. Currently, first-line therapy with the oral inhibitor osimertinib is the preferred option based on updated data demonstrating median overall survival of 36 mo.
6. Oncogenic fusion genes consisting of *EML4* and anaplastic lymphoma kinase (ALK) are present in 4% to 5% of adenocarcinomas and can be treated with inhibitors crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib. Approximately 2% of adenocarcinomas have genetic rearrangements involving the ROS1 proto-oncogenic receptor tyrosine kinase (ROS1), and these patients can be treated with the oral inhibitors crizotinib and ceritinib. Also, approximately 2% of adenocarcinomas harbor the BRAF V600E mutation, and these patients can be treated with the combination of BRAF inhibitor and MEK inhibitor therapy.
7. The addition of chemotherapy to radiotherapy (CRT) improves survival in patients with locally advanced, unresectable stages III NSCLC. The addition of the checkpoint inhibitor durvalumab has recently shown improvement in overall survival in this population when administered sequentially after CRT.
8. Early initiation of palliative care focusing on management of symptoms, psychosocial support, and assistance with decision making in patients with metastatic NSCLC leads to improved quality of life, longer survival, and less use of aggressive end-of-life care.

TABLE 4 TNM Stage Groups for Non–Small Cell Lung Cancer

Stage	T	N	M
Stage 0	T_{is}	N_0	M_0
Stage I_{A1}	T_{mi} or T_{1a}	N_0	M_0
Stage I_{A2}	T_{1b}	N_0	M_0
Stage I_{A3}	T_{1c}	N_0	M_0
Stage I_B	T_{2a}	N_0	M_0
Stage II_A	T_{2b}	N_0	M_0
Stage II_B	T_{1a-c}	N_1	M_0
	T_{2a-b}	N_1	M_0
	T_3	N_0	M_0
Stage III_A	T_{1a-c}	N_2	M_0
	T_{2a-b}	N_2	M_0
	T_3	N_1	M_0
	T_4	N_{0-1}	M_0
Stage III_B	T_{1a-c}	N_3	M_0
	T_{2a-b}	N_3	M_0
	T_{3-4}	N_2	M_0
Stage III_C	T_{3-4}	N_3	M_0
Stage IV_A	Any T	Any N	M_{1a-1b}
Stage IV_B	Any T	Any N	M_{1c}

TNM, Tumor, node, metastases.

SMALL CELL LUNG CANCER:

- Limited-stage disease: Standard treatments include thoracic radiotherapy and chemotherapy (cisplatin and etoposide).
- Extensive-stage disease: Standard treatments include combination chemotherapy (platinum plus etoposide or platinum plus irinotecan). The addition of the PD-1 antibody atezolizumab to standard first-line therapy has now been proven to improve overall survival and is considered the standard of care approach.
- Prophylactic cranial irradiation for patients in complete remission to decrease the risk of central nervous system metastasis.
- Despite high initial response rates, most patients eventually relapse. Topotecan or irinotecan may be an option for these patients. The anti-PD-1 antibody, nivolumab, has demonstrated survival benefit in SCLC patients who have failed standard therapies.

DISPOSITION

- The 5-yr survival of patients with NSCLC when the disease is resectable is approximately 30%. The 5-yr survival for stage 4 patients is now increasing, with long-term survivors seen after immunotherapy use and survival rates >20% reported in current trials.
- Median survival time in patients with limited-stage disease SCLC is 15 mo; in patients with extensive-stage SCLC, it is 9 mo.
- Among patients with metastatic NSCLC, early palliative care results in longer survival and significant improvements in both quality of life and mood.

PEARLS & CONSIDERATIONS

CT screening with use of low-dose computed tomography (LDCT) for detection of lung cancer among persons with a heavy history of smoking increases the percentage of lung cancer cases that are diagnosed in stage 1 and reduces mortality from lung cancer. The National Lung Screening Trial (NLST) showed that lung cancer screening with LDCT resulted in a 20% reduction in lung cancer mortality. New guidelines recommend annual LDCT for those who are current or former smokers aged 55 to 74. Screening should be discontinued once a person has not smoked for 15 yr or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Lung Cancer (Patient Information)
Lung Cancer Screening (Patient Information)
Horner Syndrome (Related Key Topic)
Lambert-Eaton Myasthenic Syndrome (Related Key Topic)
Paraneoplastic Syndromes (Related Key Topic)
Superior Vena Cava Syndrome (Related Key Topic)

AUTHOR: **Ritesh Rathore, MD**

TABLE 5 Summary of Multimodality Guidelines

Stage	Surgery	Adjuvant Therapy	Radiation	Chemotherapy	Level of Evidence
I	Yes	No	No	No	1B—Surgical resection 1B—Against postoperative chemotherapy 1A—Against postoperative radiation therapy
II	Yes	Yes	No	Yes	1B—Surgical resection 1A—Postoperative chemotherapy 2A—Against postoperative radiation therapy
IIIA					
(N2-occult)	Yes	Yes	May be considered	Yes	1A—Adjuvant chemo 2C—Adjuvant radiation
(N2-discrete)	Yes	No	Yes	Yes	1A—Definite or induction followed by surgery
			(Definitive or induction recommended)		1C—Against primary resection followed by adjuvant therapy
IIIB	No	No	Yes	Yes	1A—Definitive concurrent
(N2, N3)			(Definitive concurrent)		1A—Against induction followed by surgery

From Sellke FW, et al.: *Sabiston & Spencer surgery of the chest*, ed 9, 2016, Elsevier.

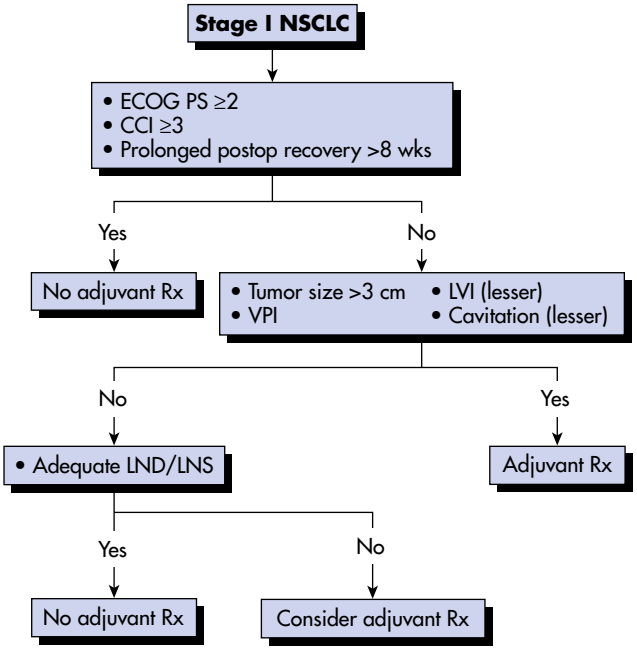

FIG. 8 Algorithm for selecting patients with stage I non–small cell lung cancer (NSCLC) for postoperative adjuvant chemotherapy. *CCI,* Charlson Comorbidity Index; *ECOG PS,* Eastern Cooperative Oncology Group Performance Status; *LND,* mediastinal lymph node dissection; *LNS,* systematic mediastinal lymph node sampling; *LVI,* lymphovascular invasion; *Rx,* treatment; *VPI,* visceral pleural invasion. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

TABLE 6 Selected Non–Small Cell Lung Cancer Oncogenes and Targeted Therapy

Oncogene Alteration	Incidence (%)	Clinical Relevance	Treatment
BRAF			
Mutation	1-3	V600E mutation: Most common, equal association with smokers and nonsmokers May be mechanism of acquired EGFR TKI resistance	dabrafenib plus trametinib
EGFR (ErbB1, HER1)			
Mutation	13-50	Exon 19 deletion and Exon 21 point mutation are the most common Predominantly adenocarcinoma and nonsmokers; up to 50% frequency in Asians	TKI: Gefitinib, erlotinib, afatinib, osimertinib
EML4-ALK			
Fusion	3-7	Most frequent in adenocarcinomas, nonsmokers, men, and younger patients	Nonspecific TKI: Crizotinib, ceritinib, alectinib, brigatinib
Her2/neu (ErbB2)			No approved therapy
Mutation	2-6	Mostly adenocarcinomas and nonsmokers	
Amplification	23	Mechanism of resistance to EGFR TKI	
KRAS			
Mutation	5-30	Mostly adenocarcinomas and smokers May contribute to resistance to ALF, BRAF, and PI3K inhibitors	No approved therapy
MET			No approved therapy
Mutation	<5		
Amplification	21	Mechanism of resistance to EGFR TKI	
PIK3CA			No approved therapy
Mutation	<10	Frequently occurs in association with other mutations; more common in squamous cell	
Amplification	5-43	Mechanism of resistance to EGFR TKI	
PTEN			
Mutation	1.7-10	Associated with PI3K activation, resistance to EGFR TKI, and sensitivity to PI3K inhibitors More frequent in squamous cell	
Loss of function	4-21	Associated with PI3K activation, resistance to EGFR TKI, and sensitivity to PI3K inhibitors More frequent in squamous cell	
RET fusion gene	1-2	Mostly adenocarcinomas and nonsmokers	No approved therapy
ROS1 fusion gene	2	Mostly adenocarcinomas, nonsmokers, and younger patients	TKI: Crizotinib
VEGF			Monoclonal antibodies: Bevacizumab VEGFR TKI

BRAF, v-raf murine sarcoma viral oncogene homolog B1; *EGFR,* epidermal growth factor receptor; *EML4-ALK,* echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase; *ERBB,* avian erythroblastosis oncogene B; *Her2,* human epidermal growth factor receptor 2; *KRAS,* Kirsten Rat sarcoma viral oncogene homolog; *MET,* mesenchymal-epithelial transition; *PIK3CA,* phosphoinositide-3-kinase catalytic alpha polypeptide; *PTEN,* phosphatase and tensin homolog; *RET,* rearranged during transfection; *ROS1,* reactive oxygen species 1; *TKI,* tyrosine kinase inhibitor; *VEGF,* vascular endothelial growth factor; *VEGFR,* vascular endothelial growth factor receptor.
From Sellke FW et al: *Sabiston & Spencer surgery of the chest*, ed 9, 2016, Elsevier.

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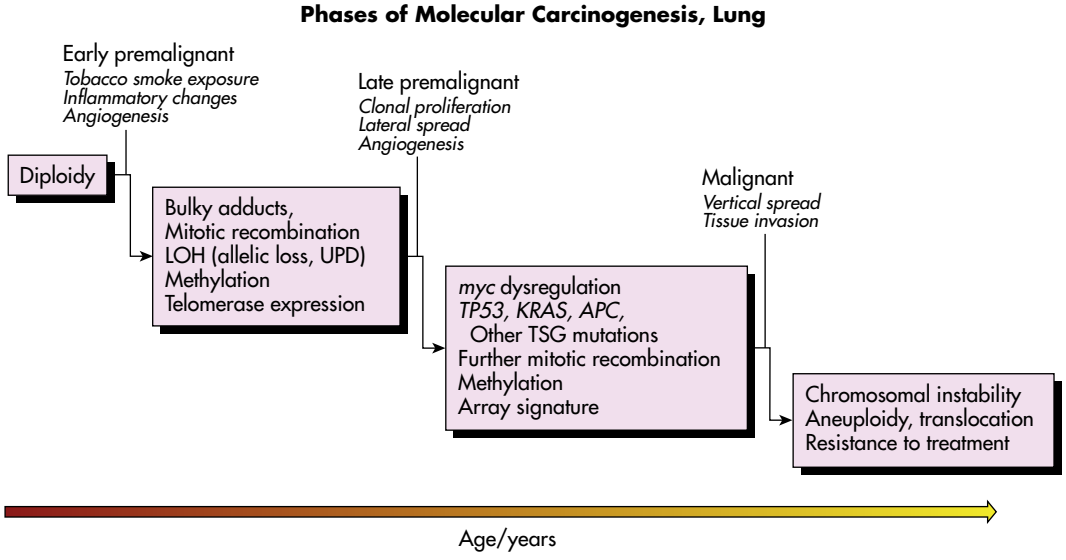

FIG. E2 The molecular pathology of smoking-related lung cancer begins with the direct interaction between metabolites of carcinogenic polyaromatic hydrocarbons in cigarette smoke with host DNA. This creates bulky adducts that affect DNA repair and create transcription errors. The result is a wide range of genomic losses, gains, translocations, and point mutations that account for the high degree of molecular heterogeneity in lung tumors with diverse physiologic effects. *LOH,* Loss of heterozygosity; *UPD,* uniparental disomy; *TSG,* tumor suppressor gene. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

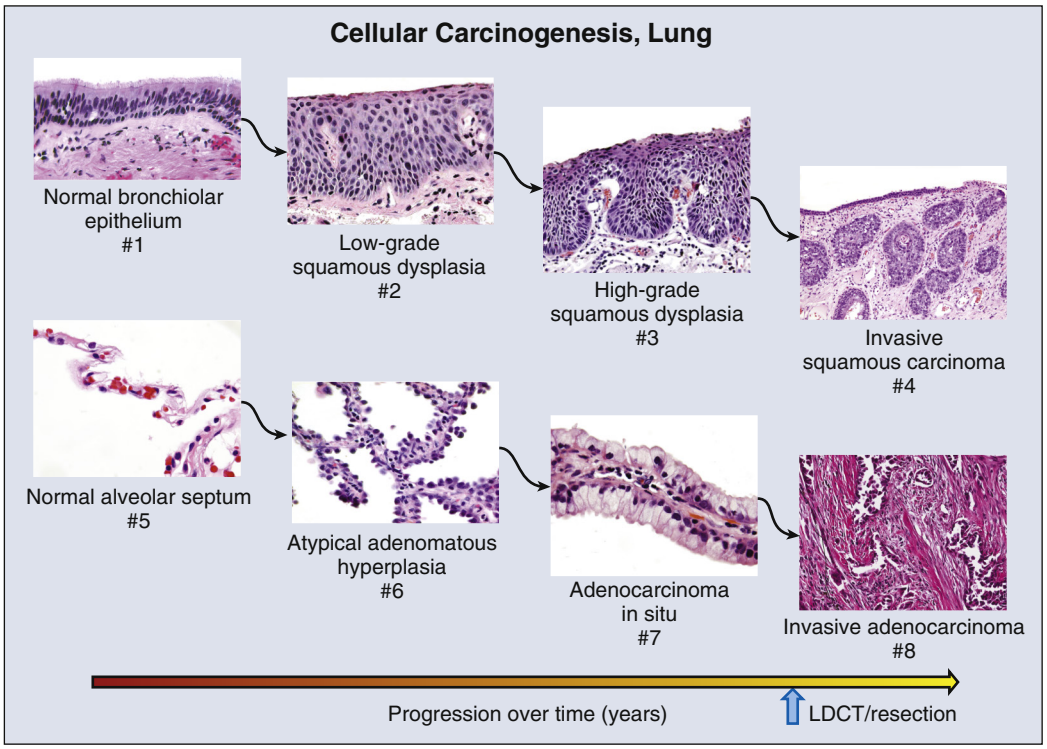

FIG. E3 Multistep carcinogenesis in the lung is complicated by the heterogeneity of tumor types that arise in separate locations in the respiratory tract. Squamous tumors typically form in the central airways, where they are thought to arise from *1,* the respiratory mucosa. The earliest premalignant lesion, *2,* low-grade squamous dysplasia, exhibits a polarity in which dark basaloid cells mature into large cells that flatten along the surface as seen in the cervix. *3,* High-grade squamous dysplasia exhibits less distinct maturation and a higher level of cytologic diversity. *4,* Invasive squamous cell carcinoma occurs when tumor cells extend in the underlying stroma, sometimes forming a mass visible on low–radiation dose computed tomography (LDCT). Adenocarcinomas typically arise peripherally in *5,* the alveoli and terminal bronchioles. The best-defined precursor lesion of adenocarcinoma is *6,* atypical adenomatous hyperplasia (AHH). These are small lesions (<5 mm) in which the alveolar architecture is preserved. *7,* Adenocarcinoma in situ (AIS) is a further progression of peripheral airway epithelium toward malignancy. This category represents a redefinition of the low-grade adenocarcinoma previously known as *bronchioloalveolar carcinoma.* These lesions are solitary small (≤3 cm) lesions consisting of a single cell layer that spreads in a nondestructive pattern of growth along the alveolar septae that is referred to as *lepidic* and is detectable as a ground-glass nodule by LDCT. *8,* Invasive adenocarcinoma spreads beyond the alveolar surface, forming a mass that appears solid on LDCT. The presence of a mass visible with LDCT suggests tumor. However, by the time this occurs, tumor is often invasive and must be treated aggressively. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

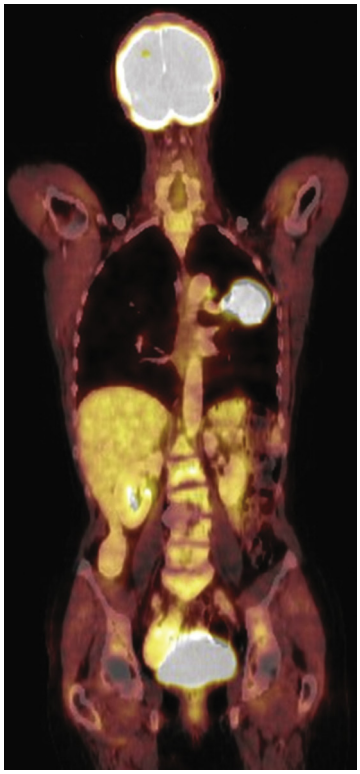

FIG. E6 Whole-body coronal [^{18}F]fluoro-2-deoxy-d-glucose positron emission tomography computed tomography (^{18}FDG-PET-CT) shows intense left upper lobe tracer accumulation in a patient with bronchogenic carcinoma. Note normal high tracer activity within the brain. (From Mason RJ: *Murray & Nadel's textbook of respiratory medicine*, ed 5, Philadelphia, 2010, Saunders.)

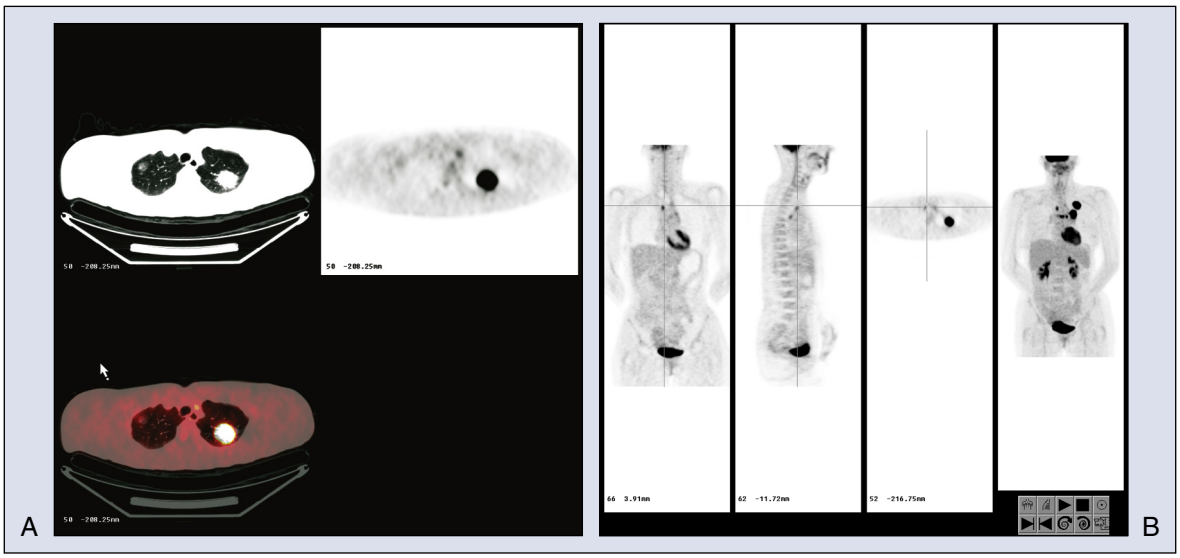

FIG. E7 A, Images obtained with positron emission tomography (PET) and computed tomography (CT). The upper left image is CT, the upper right image is PET, and the lower left image is a fusion of PET and CT data. The CT scan shows a smaller right apical nodule and a large left upper lung nodule. PET shows increased uptake of fluorine-18 fluorodeoxyglucose (^{18}F-FDG) in the left apical nodule, consistent with cancer, whereas only minimal uptake is seen in the right apical lesion, consistent with benign disease or a very low grade malignancy. Fused PET and CT images confirm the location of increased apical FDG uptake, as in the left lung nodule. **B,** Whole-body images from PET scans of the patient shown in **A**. The images include coronal, sagittal, transverse, and "projection" whole-body views, from left to right. They show cancer in the left upper lung, mediastinal involvement, and a right paratracheal tumor focus. Normal uptake is seen in the heart, brain, and excretory system (bladder). (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

BASIC INFORMATION

DEFINITION

Lyme disease is a multisystem inflammatory disorder caused by the transmission of a spirochete, *Borrelia burgdorferi,* via the bite of infected *Ixodes* ticks, taking 36 to 48 hr for a tick to take a blood meal and transmit the infecting organism to the host.

SYNONYMS

Bannwarth syndrome (Europe)
Acrodermatitis chronica atrophicans

ICD-10CM CODES

A69.20	Lyme disease, unspecified
A69.21	Meningitis due to Lyme disease
A69.22	Other neurologic disorders in Lyme disease
A69.23	Arthritis due to Lyme disease
A69.29	Other conditions associated with Lyme disease

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): In the U.S., 4.4 cases/100,000 persons; it is the most common vector-borne infection in the U.S., with more than 30,000 new cases reported each yr. 90% of cases are found in Massachusetts, Connecticut, Rhode Island, New York, New Jersey, Pennsylvania, Minnesota, Wisconsin, and California. The area of transmission in the U.S. is expanding farther into the South and upper Northeast (Fig. E1). The disease also occurs in Europe and Asia with a different *Ixodes* tick vector. Table E1 summarizes principal vector ticks and spirochetes associated with Lyme borreliosis.
PEAK INCIDENCE: May to November
PREDOMINANT SEX: Male = female
PREDOMINANT AGE: Median age of 28 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Lyme disease may present in the following stages:

- *Early localized stage (incubation period 3-30 days):* Early Lyme disease, erythema migrans (EM); skin rash, often at site of tick bite (the CDC has defined EM rash as an expanding red macule or papule that must reach at least 5 cm in size, with or without central clearing); target lesions from ECM can be found in 60% to 80% of localized infections; possible fever, myalgias 3 to 32 days after tick bite
- *Early disseminated stage (incubation period 3 to 6 wk):* Days to wk later; multiorgan system involvement, including CNS with aseptic meningitis–type picture or Bell palsy, joints (arthritis or arthralgias), cardiac including varying degrees of heart block; related to dissemination of spirochete
- *Late stage (incubation period months to years):* Months to years after tick exposure; affects central and peripheral nervous system, cardiac, joints

Common presenting signs and symptoms include:

- EM (Fig. E2). Most patients with EM (about 80%) have a single lesion but the bacteria can disseminate hematogenously to other sites in the skin and result in often smaller erythema migrans lesions.
- Lymphadenopathy, neck pains, pharyngeal erythema, myalgias, hepatosplenomegaly.
- Patients will complain of malaise, fatigue, lethargy, headache, fever/chills, neck pain, myalgias, back pain.

ETIOLOGY

B. burgdorferi transmitted from bite of an *Ixodes* tick (mostly in the nymph stage, but can also be from adult ticks). Human infection occurs through inoculation of spirochetes in infected saliva and usually requires tick attachment for more than 36 hours.

DIAGNOSIS

Clinical presentation, exposure to ticks in endemic area, and diagnostic testing for antibody response to *B. burgdorferi.* Serologic testing at early stages is usually negative; therefore, in early stage, documentation of erythema migrans lesion with a compatible epidemiologic history is sufficient for diagnosis, and laboratory testing is not indicated.

DIFFERENTIAL DIAGNOSIS

- Chronic fatigue/fibromyalgia
- Acute viral illnesses
- Babesiosis
- Human granulocytic anaplasmosis

WORKUP

Serologic testing is the principal means of laboratory diagnosis of Lyme disease. Current recommendations include using a sensitive enzyme immunoassay (EIA) or immunofluorescence assay, followed by a Western immunoblot assay for specimens yielding positive or equivocal results.

LABORATORY TESTS

- ELISA testing and if positive or equivocal then followed by a Western blot IgM and IgG (Table E2). A Western blot IgM assay is positive if 2 of 3 bands present. The Western blot IgG is positive if 5 of 10 bands present.
- An alternative serologic test is the VlsE C6 ELISA (C6 peptide), which detects an IgG response earlier and may be more sensitive than the ELISA, but its specificity is lower than the two-tier testing method.
- Early disease often is difficult to diagnose serologically, secondary to slow immune response.
- Culturing of skin lesions (EM) and polymerase chain reaction (PCR) of synovial fluid or CSF can also give the diagnosis of active infection.
- Fig. 3 is an algorithm for the diagnosis and treatment of arthritis associated with Lyme disease.

IMAGING STUDIES

- ECG
- Echocardiogram if conduction abnormalities are present with cardiac involvement
- CT scan, MRI of brain in patients with CNS involvement

TREATMENT

Early localized Lyme disease:

- Doxycycline 100 mg bid in adults (children: 2 mg/kg twice daily if ≥8 yr) [doxycycline offers the advantage of treating possible coinfection with the bacterial agents of ehrlichiosis] for 10 to 14 days or amoxicillin 500 mg tid for adults (children: 50 mg/kg per day in three divided doses) for 14 to 21 days.
- Alternative treatments for pregnancy and children ≦8 yr: Cefuroxime axetil 500 mg bid for 14 to 21 days (children: 30 mg/kg per day in two divided doses), azithromycin 500 mg PO for 7 to 10 days but should **not** be used as a first-line agent, as it is less effective than doxycycline and amoxicillin.
- A single dose of 200 mg doxycycline given within 72 hr of removing an engorged *Ixodes* tick can significantly reduce the risk of developing of Lyme disease in endemic areas and is reasonable prophylaxis in nonpregnant adults and children ≥8 yr old.

Early disseminated and late persistent infection:

- 28 days of treatment is often prescribed, although recent evidence supports treating patients with a 14-day course of oral doxycycline for early neurologic Lyme disease in ambulatory patients. Doxycycline and ceftriaxone appear equally effective for acute disseminated Lyme disease.[1]
- Arthritis: 28 days of doxycycline or amoxicillin plus probenecid.
- Neurologic involvement requires parenteral antibiotics. Those who fail to respond should be treated with IV ceftriaxone or cefotaxime.
- Ceftriaxone 2 g/day IV for 21 to 28 days; alternative: Cefotaxime 2 g q8h IV; alternative: Penicillin G 5 million U qid.
- Cardiac involvement: IV ceftriaxone or cefotaxime plus cardiac monitoring.
- Prolonged treatment with IV or PO antibiotic therapy for up to 90 days did not improve symptoms more than placebo.

Post–Lyme disease syndrome:

- Presence of disabling symptoms such as fatigue, malaise, diffuse pains, and poor concentration, which may be due to an exuberant host inflammatory response even in patients who have received proper antibiotic treatment
- Antibiotics are not indicated. Antibiotic treatment of patients with persistent unexplained symptoms despite previous antibiotic treatment of Lyme disease provides little, if any, benefit and carries significant risk
- Supportive care

[1]Sanchez E et al: Diagnosis, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: a review, *JAMA* 315(16):1767-1777, 2016.

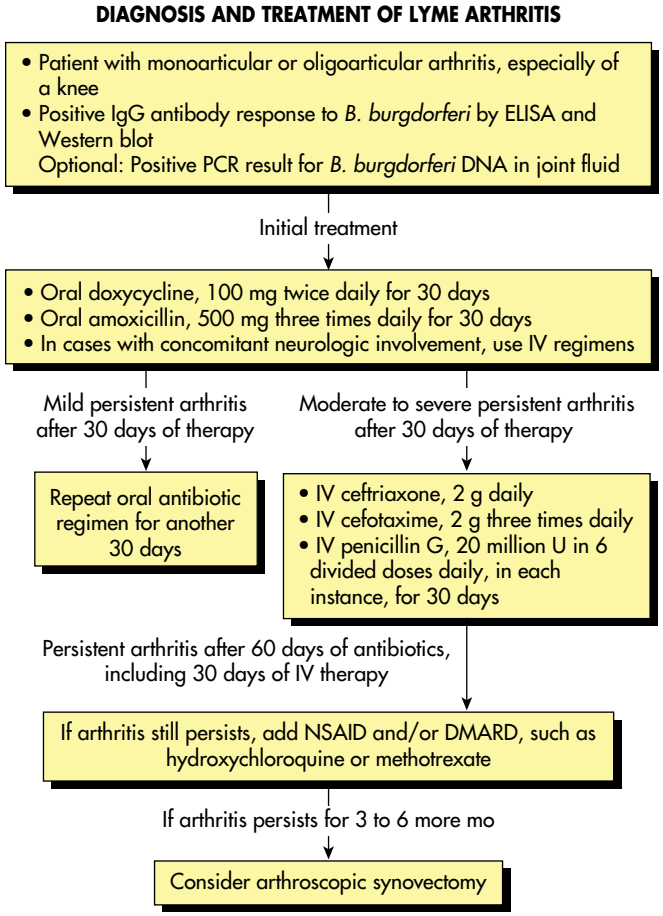

FIG. 3 Algorithm for the diagnosis and treatment of arthritis associated with Lyme disease. *DMARD,* Disease-modifying antirheumatic drug; *ELISA,* enzyme-linked immunosorbent assay; *Ig,* immunoglobulin; *IV,* intravenous; *NSAID,* nonsteroidal antiinflammatory drug; *PCR,* polymerase chain reaction. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

DISPOSITION

- The patient often needs careful follow-up and supportive care for the arthralgia-neuritis symptoms.
- 10% to 20% of treated patients may have lingering symptoms of fatigue, disrupted sleep, and musculoskeletal complaints. Repeat episodes of EM in appropriately treated patients are due to reinfection and not to relapse.

REFERRAL

- To a neurologist if significant neurologic complications (meningitis, myelitis, ophthalmoplegia, Bell palsy)
- To a cardiologist if the patient develops evidence of cardiac conduction disturbances or pericarditis

PEARLS & CONSIDERATIONS

- A physician diagnosis of classic EM in an endemic region of Lyme disease is sufficient to make a definitive diagnosis.
- In some patients with Lyme disease, nonspecific complaints such as headache, fatigue, and arthralgia may persist for months after appropriate (and ultimately successful) antibiotic treatment. Long-term antibiotic treatment does not provide additional beneficial effects.
- There is no evidence of current or previous *Borrelia burgdorferi* infection in most patients evaluated at university-based Lyme disease referral centers. Psychiatric comorbidity and other psychological factors are prominent in the presentation and outcome of some patients who inaccurately ascribe longstanding symptoms to "chronic Lyme disease."
- It is important to realize that one tick bite can transmit Lyme disease *and* the bacterial agents of either ehrlichiosis or babesiosis (protozoan parasite), or even both, and these latter agents require separate serologic testing and possibly therapy. *Ehrlichiosis* is treated with doxycycline, but *Babesia* would require a different therapy. Powassan virus can also be transmitted by the *Ixodes* tick bite and causes an encephalitis seen in eastern Canada and northcentral, northeastern, and upper midwestern United States. Cases have been increasing.
- Tick bite protection: EPA-registered insect repellents containing DEET, picaridin, IR3535, oil of lemon eucalyptus (OLE), para-menthane-3,8-diol (PMD), or 2-undecanone can prevent ticks from attaching when applied, and can last for several hours. OLE and PMD products cannot be used on children under 3 yr of age.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Lyme Disease (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

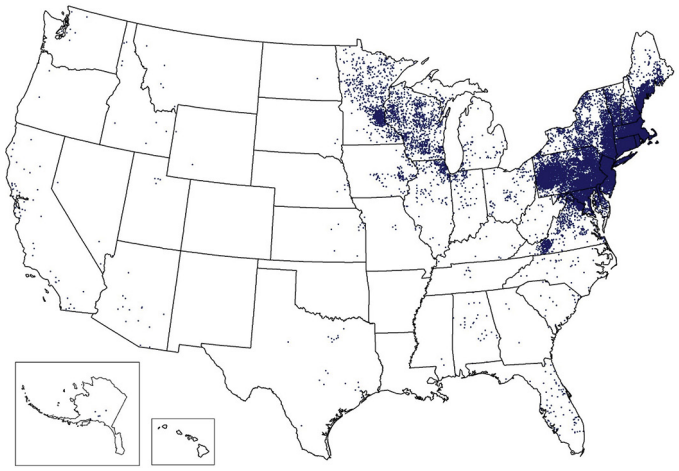

FIG. E1 Reported cases of Lyme disease–U.S., 2015. Each dot represents one case of Lyme disease and is placed randomly in the patient's county of residence. The presence of a dot in a state does not necessarily mean that Lyme disease was acquired in that state. The place of residence is sometimes different from the location where the patient became infected. (From Centers for Disease Control and Prevention. National Center for Emerging and Zoonotic Infectious Diseases, Division of Vector-Borne Diseases. In Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.)

TABLE E1 Principal Vector Ticks and Spirochetes Associated with Lyme Borreliosis

Tick Species	Distribution	Genotype of *Borrelia burgdorferi*
Ixodes scapularis	Eastern North America	*B. burgdorferi* sensu stricto
Ixodes pacificus	Western North America	*B. burgdorferi* sensu stricto
Ixodes ricinus	Western and central Europe	*B. garinii*, *B. afzelii*, *B. burgdorferi* sensu stricto
Ixodes persulcatus	Central Europe and Asia	*B. garinii*, *B. afzelii*

From Piesman J, Humair P-F: The spirochetes and vector ticks of Lyme borreliosis in nature. In Sood SK (ed): *Lyme Borreliosis in Europe and North America,* Hoboken, NJ, 2011, John Wiley & Sons.

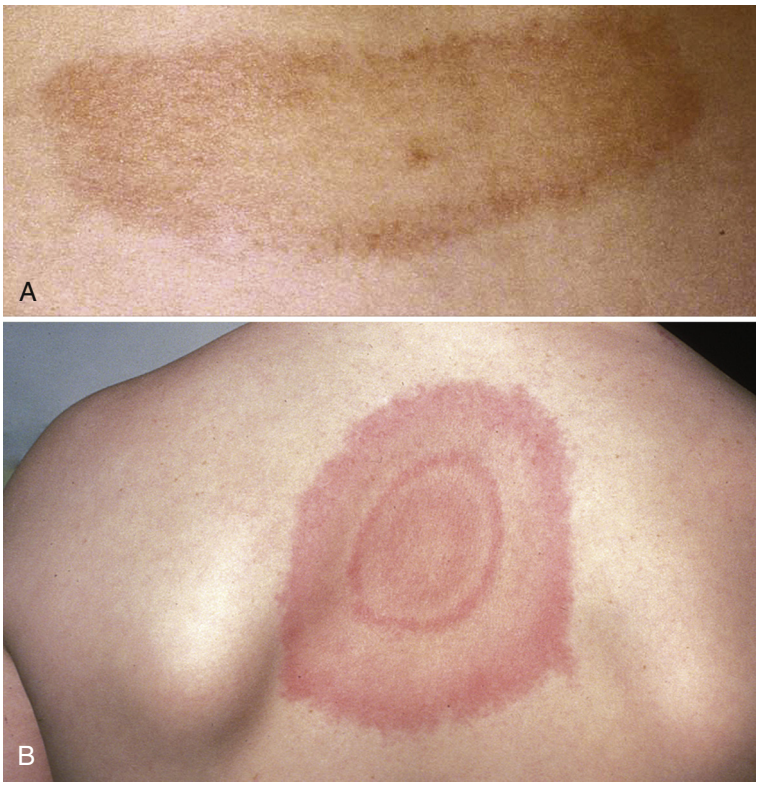

FIG. E2 Erythema migrans. (A) The site of the tick bite is visible near the center of the lesion. **(B)** Typical bull's-eye lesion. (From Huppert H-I, Dressler F. Lyme disease. In: Cassidy J et al [eds]: *Textbook of pediatric rheumatology,* ed 6, Philadelphia, 2011, WB Saunders. In Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

TABLE E2 Criteria for Western Blot Interpretation in the Serologic Confirmation of Lyme Disease

Duration of Disease	Isotype Tested	Criteria for Positive Test
First mo of infection	IgM	2 of the following 3 bands are present: 23 kD (OspC), 39 kD (BmpA), and 41 kD (Fla)
After first mo of infection	IgG	5 of 10 bands are present: 18 kD, 21 kD, 28 kD, 30 kD, 39 kD, 41 kD, 45 kD, 58 kD (not GroEL), 66 kD, and 93 kD

Ig, Immunoglobulin.
Modified from Centers for Disease Control and Prevention: Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease, *MMWR Morb Mortal Wkly Rep* 44:590-591, 1995.

SUGGESTED READINGS

Berende A et al: Randomized trial of longer-term therapy for symptoms attributed to Lyme disease, *N Engl J Med* 374:1209-1220, 2016.
Halperin JJ: Chronic Lyme disease: misconceptions and challenges for patient management, *Infect Drug Resist* 15:119-128, 2015.
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Nadelman RB et al: Differentiation of reinfection from relapse in recurrent Lyme disease, *N Engl J Med* 367:1883-1890, 2012.
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Shapiro ED: Lyme disease, *N Engl J Med* 370:1724-1731, 2014.
Yeung C, Baranchuk A: Diagnosis and treatment of Lyme carditis: JACC review topic of the week, *J Am Coll Cardiol* 73:717-726, 2019.

BASIC INFORMATION

DEFINITION

Lymphangitis refers to the inflammation of lymphatic vessels due to infectious or noninfectious causes. Infectious causes include bacteria, mycobacteria, viruses, fungi, and parasites.

SYNONYMS

Nodular lymphangitis
Sporotrichoid lymphangitis

ICD-10CM CODE
I89.1 Lymphangitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Several hundred cases/yr of sporotrichoid lymphangitis, which is a fungal infection; bacterial lymphangitis more common but not reported.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

ACUTE LYMPHANGITIS:

- Commonly associated with a bacterial cellulitis
- Usually develops after cutaneous inoculation of microorganisms into the lymphatic vessels through disrupted skin or as a result of spread from a distal infection
- May or may not recognize a site of skin trauma (i.e., laceration, puncture, ulcer)
- In hours to days, distal appearance of erythema, edema, and tenderness, with linear erythematous streaks extending proximally to regional lymph nodes
- Possible lymphadenitis and fever
- Predisposition to group A streptococcal infection of the skin in those with uncontrolled diabetes mellitus, chronic lymphedema, and superficial fungal infections (e.g., tinea pedis)

SPOROTRICHOID OR NODULAR LYMPHANGITIS:

- Includes subcutaneous nodules that develop along the path of involved lymphatics
- Usually preceded by an episode of cutaneous inoculation or trauma to the hand
- Lesions apparent from one to several weeks after inoculation
- Initially, nodular or papular lesion; may ulcerate
- Pain is organism-dependent
- May have frank pus or a serosanguineous discharge
- Systemic complaints uncommon, but infection with certain microorganisms associated with fever, chills, myalgias, and headache

ETIOLOGY

- Acute lymphangitis: Usually associated with *Streptococcus pyogenes* (group A streptococcus), and to a lesser extent staphylococcus species, including community-acquired methicillin-resistant *S. aureus* (CA-MRSA)
- Nodular lymphangitis caused by one of several organisms:
  1. *Sporothrix schenckii* ("Rose gardener's disease," corn cultivation)
     a. Most common recognized cause in the U.S., usually in the Midwest
     b. Fungus found in soil and plant debris
  2. *Nocardia brasiliensis:* Gram-positive rod-shaped bacteria found in soil
  3. *Mycobacterium marinum:* Associated with trauma related to water (e.g., aquariums, swimming pools, fish)
  4. *Leishmania brasiliensis:*
     a. Protozoal parasite transmitted to humans by sand flies, mostly to travelers in endemic areas (Texas, rural Central and South America, Africa, subtropical Asia)
  5. *Francisella tularensis:* Gram-negative bacteria. Also causes lymphadenitis:
     a. Most often in Southern/Midwestern states (Arkansas, Missouri, Oklahoma)
     b. Associated with contact with infected mammals (e.g., rabbits, squirrels, cats), tick bites, and (rarely) water exposure

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Nodular lymphangitis
  1. Blastomyces or Coccidioides, Histoplasma, *Bacillus anthracis*, Mycetoma
- Insect or snake bites
- Filariasis

WORKUP

- Acute lymphangitis: Blood cultures
- Nodular lymphangitis: Various stains and cultures of drainage or biopsy specimens of inoculation sites

LABORATORY TESTS

- WBCs possibly elevated with cellulitis
- Eosinophilia common with helminthic infections
- Skin biopsy and microbiologic cultures may be necessary to confirm diagnosis in nodular lymphangitis

TREATMENT

NONPHARMACOLOGIC THERAPY

Limb elevation

ACUTE GENERAL Rx

- Penicillin possibly sufficient, but 1 wk of dicloxacillin or cephalexin 500 mg PO qid commonly used to ensure antistaphylococcal coverage; if CA-MRSA suspected, then use oral Bactrim DS one PO bid or clindamycin 300 mg PO q6H. Reserve vancomycin 1 g IV every 12 hr for patients requiring IV therapy
- If allergic to penicillin:
  1. Clindamycin 300 mg PO qid for 7 days *or*
  2. Erythromycin 500 mg PO qid for 7 days
  3. Levofloxacin 500 mg PO daily or moxifloxacin 400 mg PO daily for 7 days
- Nodular lymphangitis: Specific therapy directed at etiologic agent
- For superficial fungal infections: Treatment may prevent recurrence of acute lymphangitis

DISPOSITION

- Acute lymphangitis: Usually resolves with therapy
- Recurrent attacks: May lead to chronic lymphedema of limb, rarely resulting in elephantiasis nostras (nonfilarial elephantiasis)
- Nodular lymphangitis: Usually responds to appropriate therapy

REFERRAL

- If acute lymphangitis is more than a mild disease or if it involves the face
- If nodular lymphangitis or filariasis is suspected

PEARLS & CONSIDERATIONS

COMMENTS

- Outside of the U.S., initial episodes of filariasis caused by Brugia malayi resemble acute lymphangitis.
- Chronic lymphedema or elephantiasis results from recurrent episodes.
- For chronic lymphedema, adherence to limb elevation, compression/support stockings, and adequate glycemic control (for patients with diabetes) all can reduce risk of acute lymphangitis.

SUGGESTED READINGS

Available at www.ExpertConsult.com

RELATED CONTENT

Lymphangitis (Patient Information)

AUTHOR: **Russell J. McCulloh, MD**

SUGGESTED READINGS

Cohen BE et al: Nonbacterial causes of lymphangitis with streaking, *J Am Board Fam Med* 29:808-812, 2016.

Takashima S, Ota M: Creeping lymphangitis, *BMJ* 351:h5416, 2015.

Tirado-Sanchez A, Bonifaz A: Nodular lymphangitis (sporotrichoid lymphocutaneous infections). Clues to differential diagnosis, *J Fungi (Basel)* 4(2), 2018, https://doi.org/10.3390/jof4020056.

BASIC INFORMATION

DEFINITION

A primary role of the lymphatic system is to transport proteins from the interstitium to the heart. When the transport capacity of the lymphatic system is reduced, proteins accumulate in the interstitium. Accumulated proteins attract water, which creates a high protein swelling in the subcutaneous tissues called lymphedema.

SYNONYM

Elephantiasis

ICD-10CM CODES

I89.0	Lymphedema, not elsewhere classified
I97.2	Postmastectomy lymphedema syndrome
Q82.0	Hereditary lymphedema

EPIDEMIOLOGY & DEMOGRAPHICS

PRIMARY LYMPHEDEMA:

- Found in 1.1/100,000 people aged <20 yr
- Females outnumber males 3.5:1
- Incidence peaks between ages 12 and 16 (puberty)

SECONDARY LYMPHEDEMA: See specific etiology in the following.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Lymphedema is a slow-onset, progressive disease characterized by an asymmetrical, inflammatory swelling, traveling distal to proximal, that can affect any body part including limbs, trunk, head/neck, and genitals (Fig. 1). Box 1 summarizes lymphedema staging from the International Society of Lymphology.

STAGE 0: LATENCY:

- Decreased lymphatic system transport capacity due to primary or secondary etiology
- Subjective complaints of affected body part feeling heavy or achy
- No objective findings, no apparent swelling

STAGE I: REVERSIBLE:

- Edema is observable, soft, pitting and reversible with elevation.
- No secondary skin changes are present.

STAGE II: SPONTANEOUSLY IRREVERSIBLE:

- Skin becomes more firm/fibrotic, therefore less pitting.
- Edema does not reverse to normal with elevation.
- Possibility of infections (cellulitis), wounds, or weeping (lymphorrhea).

STAGE III: ELEPHANTIASIS:

- Skin becomes very firm/fibrotic, therefore nonpitting.
- Evidence of substantial skin changes (e.g., papillomas, lobules, "peau d' orange").

ETIOLOGY: Lymphedema is caused by a reduction in lymphatic system transport and is classified into primary and secondary forms.

PRIMARY LYMPHEDEMA:

- Occurs when the lymphatic system does not mature properly during fetal development
  1. Aplasia
  2. Hypoplasia
  3. Hyperplasia
- Can be familial, genetic, or hereditary
- Lymphedema congenital: Symptoms present at birth
- Lymphedema praecox: Symptoms onset before the age of 35 (commonly during puberty)
- Lymphedema tardum: Symptoms onset at the age of 35 or after

SECONDARY LYMPHEDEMA:

- Occurs secondary to a disruption or obstruction of the lymphatic system caused by:
  1. Filariasis (number one cause worldwide)
  2. Lymph node surgery/radiation due to cancer (number one cause in the U.S.)
  3. Other: Chronic venous insufficiency (CVI), deep vein thrombosis (DVT), infection, surgery/trauma, lipedema, and obesity

FIG. 1 Lymphedema before treatment.

BOX 1 Lymphedema Staging

Stage 0: Latent
- Impaired lymphatic function
- No evident edema; subclinical
- May last months or years before progression

Stage I: Spontaneously Reversible
- Early accumulation of protein-rich fluid
- Pitting edema
- Subsides with elevation

Stage II: Spontaneously Irreversible
- Accumulation of protein-rich fluid
- Pitting edema progresses to fibrosis
- Does not resolve with elevation alone

Stage III: Lymphostatic Elephantiasis
- Nonpitting
- Significant fibrosis
- Trophic skin changes

From International Society of Lymphology: The diagnosis and treatment of peripheral edema: 2009 consensus document of the International Society of Lymphology, *Lymphology* 42(2):51-60, 2009.

DIAGNOSIS

- Lymphedema is primarily a clinical diagnosis made on the basis of past medical history and objective findings that distinguish it from other causes of chronic edema.
- A Stemmer sign is often used to identify lymphedema (inability to pick up or pinch a fold of skin at the base of the second toe or finger).
- When physical examination is inconclusive, other available imaging tests can help make the diagnosis (see "Imaging Studies").

DIFFERENTIAL DIAGNOSIS

Other causes of edema that should be ruled out before treatment for lymphedema include cardiac, renal, hepatic, and thyroid dysfunction.

WORKUP

A detailed history and physical examination should help exclude most of the differential diagnoses.

LABORATORY TESTS

- Blood urea nitrogen, creatinine, liver function tests, albumin, urine analysis, and thyroid function tests are obtained to exclude possible systemic causes of edema.
- Genetic testing may be practical in defining a specific hereditary syndrome with a discrete gene mutation such as lymphedema distichiasis (*FOXC2*), Milroy disease (*VEGFR-3*), Meige disease, or Klippel-Trenaunay-Weber syndrome.

IMAGING STUDIES

- Lymphoscintigraphy: Diagnostic image of choice for lymphedema (if needed)
- Indocyanine green (ICG) fluorescent lymphography: Can now be used to identify sentinel nodes, to demonstrate superficial lymph channels and functional lymphatics, to indicate treatment pathways, and to confirm the effectiveness of therapeutic techniques
- Magnetic resonance imaging (MRI): Primarily used in tumor diagnosis
- Duplex ultrasound: Determines venous involvement in the edema
- Computed axial tomography (CAT): Distinguishes between fatty tissue and accumulations of protein-rich fluids
- Lymphography: Phased out in favor of less invasive techniques

TREATMENT

NONPHARMACOLOGIC THERAPY

- Complete decongestive therapy (CDT) is backed by longstanding research and experience as the primary treatment of choice for lymphedema in both children and adults (Fig. 2). It should be delivered by a certified

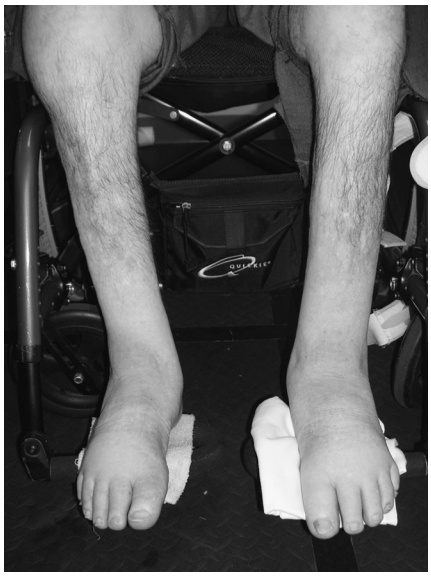

FIG. 2 Lymphedema after treatment.

lymphedema therapist (CLT). CDT involves a two-phase treatment program:

1. Phase 1—Reduce tissue congestion of affected body part with daily treatments:
   a. Manual lymph drainage.
   b. Skin care.
   c. Compression wrapping of limb.
   d. Decongestive exercises.
2. Phase 2—Maintain decongestion with home maintenance program:
   a. Daily use of elastic and inelastic compression garments that are properly fitted according to circumference and length to prevent lymphedema from returning.
   b. Compression is graduated; most of the compression is distal with decreasing compression in the stocking proximally.
   c. Different knits and compression classes are available for different stages of lymphedema.
   d. Choices of garments include below-the-knee stockings, thigh-high stockings, pantyhose, sleeves, bras, and truncal garments.

- Massage (or any modality that increases blood flow) can have negative effects on lymphedema by increasing vasodilation. Therefore it is contraindicated on the lymphedematous quadrants.
- Compression pumps have not been found to be effective in removing proteins from lymphedematous quadrants.
- Nutritional therapy (reducing the amount of proteins ingested) is ineffective in the treatment of lymphedema.

PHARMACOLOGIC THERAPY

No drugs have been shown to be beneficial in the treatment of lymphedema. Diuretics in particular have not been found to be effective in removing proteins from lymphedematous quadrants and may promote the development of volume depletion.

SURGERY

Surgery for lymphedema has been proven largely unsuccessful and should not be considered before CDT. Surgical procedures are divided into two types:

- Physiologic procedures: Those performed to improve lymph node drainage (e.g., anastomoses of the lymph system with the venous system, lymph node transplant).
- Excisional or debulking procedures: Those performed to excise the subcutaneous tissue (e.g., Charles procedure, Thompson procedure, the modified Homans procedure, and liposuction). Liposuction-circumferential suction-assisted lipectomy represents a newly proposed method to reduce morbidity involved in the traditional excisional techniques.

PEARLS & CONSIDERATIONS

- Lymphedema is a chronic, generally incurable but very manageable condition that requires lifelong care and attention along with psychosocial support.
- Children and adolescents (along with parents and adults) should be encouraged to pursue a normal life, participating in school activities and sports (preferably noncontact, such as swimming).
- Infections such as cellulitis should be treated promptly.
- If the etiology is filariasis caused by the parasites *Wuchereria bancrofti* or *Brugia malayi*, treatment is diethylcarbamazine citrate 5 mg/kg in divided doses for 3 wk.
- Patients with lymphedema commonly manifest psychiatric comorbidities as a result of their disease, such as anxiety, depression, adjustment problems, and difficulty in vocational, domestic, or social domains.
- Lymphedema can be complicated in rare cases by development of lymphangiosarcomata or other cutaneous malignancies.
- Gene therapy to develop new lymphangiosis in the affected body parts is a potential clinical remedy in the future.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Lymphedema (Patient Information)

AUTHORS: **Frank G. Fort, MD, FACS, RPHS,** and **Kathryn Taylor Anilowski, MS, PT, CLT-LANA**

SUGGESTED READINGS

Murdaca G et al: Current views on diagnostic approach and treatment of lymphedema, *Am J Med* 125, 2012.

Rockson SG: Lymphedema after breast cancer treatment, *N Engl J Med* 379:1937-1944, 2018.

Lymphogranuloma Venereum

BASIC INFORMATION

DEFINITION

Lymphogranuloma venereum (LGV) is a sexually transmitted, systemic disease caused by *Chlamydia trachomatis,* serovars L_1, L_2, or L_3.

SYNONYMS

Tropical bubo
Poradenitis inguinalis
LGV

ICD-10CM CODE
A55 Chlamydial lymphogranuloma (venereum)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Rare; <300 cases/yr
PREVALENCE: Endemic in Africa, India, parts of Southeast Asia, South America, and the Caribbean
PREDOMINANT SEX: Male:female ratio is 5:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Primary stage:
- Primary lesion caused by multiplication of organism at site of infection
- Papule, shallow ulcer
- Herpetiform lesion at site of inoculation (most common)
- Incubation period of 3 to 21 days
- Most common site of lesion in women: Posterior wall, fourchette, or vulva
- Spontaneous healing without scarring

Second stage:
- Inguinal syndrome: Characteristic inguinal adenopathy (Fig. E1)
- Begins 1 to 4 wk after primary lesion
- Syndrome is the most frequent clinical sign of the disease
- Unilateral inguinal adenopathy in 70% of cases
- Symptoms: Painful, extensive adenitis (bubo) and suppuration may occur with numerous sinus tracts
- "Groove sign" signaling femoral and inguinal node involvement (20%); most often seen in men
- Involvement of deep iliac and retroperitoneal lymph nodes in women may present as a pelvic mass

Third stage (anogenital syndrome):
- Subacute: Proctocolitis
- Late: Tissue destruction or scarring, sinuses, abscesses, fistulas, strictures of perineum, elephantiasis

ETIOLOGY

Chlamydia trachomatis is the causative agent. There are three serotypes: L1, L2, and L3.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Inguinal adenitis, suppurative adenitis, retroperitoneal adenitis, proctitis, schistosomiasis.

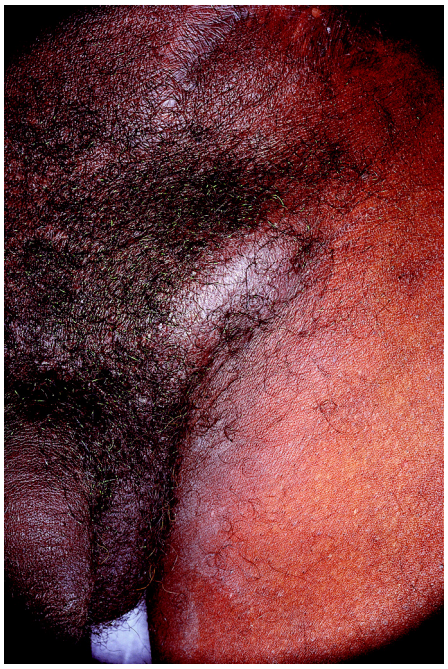

FIG. E1 Lymphogranuloma venereum. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Elsevier.)

- Recall exposure in women or men who have sex with men (MSM) can result in proctocolitis mimicking inflammatory bowel disease, and clinical findings may include mucoid and/or hemorrhagic rectal discharge, anal pain, constipation, fever, and/or tenesmus.
- Section II describes the differential diagnosis of genital sores.

WORKUP

- Diagnosis is based on clinical suspicion and serology, epidemiologic information, and the exclusion of other etiologies for proctocolitis, inguinal lymphadenopathy, or genital or rectal ulcers. Biopsy is contraindicated because sinus tracts develop.
- Screening for other sexually transmitted diseases.
- A clinical algorithm for evaluation of genital ulcer disease is described in Section III, "Evaluation of Patients with Genital Lesions or Ulcers."

LABORATORY TESTS

- Genital and lymph node specimens (i.e., lesion swab or bubo aspirate) can be tested for *C. trachomatis* by culture or direct immunofluorescence, using nucleic acid amplification techniques, including real-time polymerase chain reaction (PCR).
- Additional molecular procedures (e.g., PCR-based genotyping) can be used to differentiate LGV from non-LGV *C. trachomatis* in rectal specimen; however, they are not widely available and results are not available in a timeframe that would influence clinical management.
- Complement fixation test:
  1. Titer >1:64 in active infection, lower titers may be nonspecific.
  2. Convalescent titers no difference.
- Microimmunofluorescence titers >1:256 might support the diagnosis of LGV in the appropriate clinical context.
- Cell culture of *Chlamydia* aspiration of fluctuant node yields highest rates of recovery.
- Complete blood count: Mild leukocytosis with lymphocytosis or monocytosis.
- Elevated sedimentation rate.
- Venereal Disease Research Laboratories (VDRL) and HIV screening to rule out other sexually transmitted diseases.

IMAGING STUDIES

Computed tomography scan for suspected retroperitoneal adenitis

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid milk and milk products while taking medication.
- Practice sexual abstinence.
- Treat sexual partners. Persons who have had sexual contact with a patient who has LGV within 60 days before onset of the patient's symptoms should be examined, tested for urethral or cervical chlamydial infection, and treated with a chlamydia regimen (azithromycin 1 g orally single dose or doxycycline 100 mg orally twice a day for 7 days).

ACUTE GENERAL Rx

- Doxycycline 100 mg PO bid ×21 days
- Erythromycin base 500 mg PO qid ×21 days
- Surgical:
  1. Aspirate fluctuant nodes
  2. Incise and drain abscesses
- Combination of medical and surgical treatment may be necessary

CHRONIC Rx

- Longer course of therapy will be needed for chronic or relapsing cases, which may be caused by reinfection and/or inadequate treatment.
- A rectal stricture requires a colostomy.
- Surgery should be considered only after antibiotic treatment.

DISPOSITION

Good prognosis with early treatment, usually resulting in complete resolution of symptoms.

REFERRAL

Surgical consultation if patient develops obstruction, fistula, or rectal stricture. May need referral to plastic surgeon if patient has lymphatic obstruction.

PEARLS & CONSIDERATIONS

COMMENTS

- The most common clinical manifestation of LGV among heterosexuals is tender inguinal and/or femoral lymphadenopathy that is typically unilateral.

- Rectal exposure in women or MSM can result in proctocolitis mimicking inflammatory bowel disease.
- Pregnant and lactating women should be treated with erythromycin regimen (doxycycline contraindicated in pregnancy).
- Congenital transmission does not occur, but infection may be acquired through an infected birth canal.
- Persons with both LGV and HIV infection should receive the same regimens as those who are HIV negative. Prolonged therapy may be required, and delay in resolution of symptoms may occur.
- Patient education materials may be obtained through local and state health clinics.

SUGGESTED READING

CDC: *MMWR* 64(No.3), June 5, 2015.

RELATED CONTENT

Lymphogranuloma Venereum (Patient Information)

AUTHOR: **Emily Rosenfeld, MD, MPH**

BASIC INFORMATION

DEFINITION

Lynch syndrome is a hereditary predisposition to malignancy of the colon that is explained by a germline mutation in a DNA mismatch repair gene. The Lynch syndrome phenotype is characterized by a predominance of cancers on the right side of the colon and a propensity for synchronous and metachronous colorectal cancers.

SYNONYMS

Hereditary nonpolyposis colorectal cancer
HPNCC
Hereditary site-specific colon cancer

ICD-10 CM CODE

C18.9 Malignant neoplasm of colon, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

The lifetime risk for developing colon cancer in the U.S. is approximately 6%. Up to 30% of colon cancer is inherited and 3% may be attributable to Lynch syndrome. The incidence of Lynch syndrome is estimated to be between 1:660 and 1:2000. Lynch syndrome is the most common form of hereditary colon cancer. The average age of diagnosis for Lynch syndrome is 45 yr, although diagnosis can occur as early as the 20s or as late as the 70s.

RISK FACTORS: Family history of colon cancer or other hereditary nonpolyposis colorectal cancer (HNPCC)-related cancers such as endometrial (up to 40% of women with Lynch syndrome may develop endometrial cancer), biliary tract, ovarian, stomach, upper urinary tract, or brain. Table 1 summarizes the risk of Lynch syndrome.

GENETICS: Autosomal-dominant inheritance pattern.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Changes in bowel habits (prolonged constipation)
- Melena
- Hematochezia
- Abdominal pain
- Unexplained weight loss
- Decreased appetite
- Right sided colon cancer (70% to 85% of cases)

TABLE 1 Risk of Lynch Syndrome

Condition	Risk (%)
Endometrial cancer at any age	1.8
Endometrial cancer diagnosed before 50 yr of age	9
Endometrial and colon cancer at any age	18
Endometrial and colon cancer before 50 yr of age	43
Endometrial and ovarian cancer	7

From Disaia PJ et al: *Clinical gynecologic oncology*, ed 9, Philadelphia, 2017, Elsevier.

ETIOLOGY

Lynch syndrome is thought to be secondary to germline mutations in DNA mismatch repair genes. The predominant genes involved are *MSH2* and *MLH1,* which are tumor suppressor genes, although other genes have documented involvement (*PMS1, PMS2, MSH6,* and *EpCAM*). Mutations in these genes prevent repair of DNA mismatches during DNA replication. This is most prevalent in regions of DNA called microsatellites, causing DNA microsatellite instability and leading to an increased risk for malignancy, especially colon cancer. *MSH6* mutations are associated with a markedly lower cancer risk than *MLH1* or *MSH2* mutations.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Familial adenomatosis polyposis
- Peutz-Jeghers syndrome
- Juvenile polyposis
- Nonhereditary colorectal cancer. Table 2 compares Lynch syndrome and sporadic colorectal cancer
- Gardner syndrome

WORKUP

If an individual presents with numerous adenomatous polyps or has multiple relatives with cancer at a young age, a family history complete with pedigree must be obtained. Clinical diagnosis of the Lynch syndrome can be made with the Amsterdam or Bethesda criteria (Box 1) as well as newer models such as prediction model for gene mutations 5 (PREMM5).

- Revised Amsterdam (II) criteria (must meet all criteria):
  1. HNPCC-associated carrier diagnosis in at least three individuals in the family
  2. One of the patients is a first-degree family member of two other patients
  3. Involved patients occur in at least two successive generations with diagnosis of HNPCC
  4. At least one diagnosis in family of HNPCC was made before age 50
  5. The diagnoses are histologically confirmed
  6. Familial adenomatous polyposis is excluded.
- Bethesda criteria (must meet all criteria):
  1. Colorectal cancer before age 50
  2. Multiple colorectal cancers or other HNPCC-related cancers such as biliary tract, endometrial, stomach, or ovary
  3. Colorectal cancer with microsatellite instability histology <60 yr of age
  4. Colorectal cancer or HNPCC-related cancer in first-degree relative <50 yr of age
  5. Colorectal cancer or HNPCC-related cancer in at least two first- or second-degree relatives, any age
- If criteria for the Lynch syndrome are not met, no further analysis is necessary (although a genetic syndrome cannot be definitively excluded and genetic referral may be warranted)

LABORATORY TESTS

- If a patient meets criteria for Lynch syndrome, immunohistochemistry can be performed for the presence or absence of mismatch repair genes MLH1, MSH2, MSH6, and PMS2. Rarely, MLH3 is identified.
- Microsatellite instability analysis should also be performed if criteria for Lynch syndrome are met.

TREATMENT

- If the mutation has been identified in a family member, screening for this mutation can be performed via genetic testing. Informed consent must be obtained after a thorough explanation has been provided to each individual. Criteria for referral to a genetic counselor for suspected Lynch syndrome is summarized in Table 3.
- Surveillance using colonoscopy can be performed in individuals who screen positive, while those who screen negative can be discharged. The mismatch repair gene that is mutated guides screening.

TABLE 2 Comparison of Clinical Features in Lynch Syndrome and Sporadic Colorectal Cancer

Clinical Feature	Lynch Syndrome	Sporadic Colorectal Cancer
Mean age at diagnosis (yr)	45	67
Multiple colon cancers	35%	4%-11%
Synchronous colon cancers	18%	3%-6%
Metachronous colon cancers	24%	1%-5%
Proximal location of the initial cancer*	72%	35%
Increased risk of malignant tumors at other sites	Yes	No
Mucinous and poorly differentiated colon cancers	Common	Infrequent
Prognosis	Favorable†	Variable

*Proximal to the splenic flexure.
†Patients whose tumors demonstrate microsatellite instability have a more favorable prognosis than those with microsatellite-stable tumors.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

BOX 1 Amsterdam II Criteria for Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome)

Criteria defined by the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer
At least three relatives with CRC (one must be a first-degree relative of the other two) or a Lynch syndrome–associated cancer*
- CRC involving at least two successive generations
- One or more cancer cases before age 50 yr
- Familial adenomatous polyposis should be excluded
- Tumors should be verified by histologic examination

*Endometrium, ovary, stomach, ureter/renal pelvis, pancreas, brain, hepatobiliary tract, small intestine, and multiple sebaceous adenomas and carcinomas and keratoacanthomas in the Muir-Torre variant of Lynch syndrome.
CRC, Colorectal cancer.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE 3 Criteria for Referral to a Genetic Counselor for Suspected Lynch Syndrome

Bethesda guidelines
Amsterdam Criteria fulfilled
Persons with two relatives with Lynch syndrome
Colorectal cancer and first-degree relative with a Lynch cancer before 45 yr or a first-degree relative with an adenoma before 40 yr of age
Colorectal cancer or endometrial cancer before 45 yr of age
Right-sided, undifferentiated colon cancer before 45 yr of age
Signet ring colon cancer before 45 yr of age
Adenoma before 40 yr of age

From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

- According to the Netherlands Surveillance Protocol, for example, individuals with mutations in *MLH1, MSH2,* or *MSH6* should have colonoscopies every 1 to 2 yr starting at age 20 to 25 yr; urine cytology every 1 to 2 yr starting at age 30 to 35 yr; esophagogastroduodenoscopy every 1 to 2 yr starting at age 30 to 35 yr; and, in females, ultrasound of endometrium and CA-125 every 1 to 2 yr starting at age 30 to 35 yr.
- *Helicobacter pylori* testing is also indicated in patients with Lynch syndrome or at high risk for it.
- Aspirin may be protective against colorectal cancer in Lynch syndrome patients.

REFERRALS

- To gastroenterology for surveillance colonoscopies
- To genetic counselor if patient satisfies Bethesda criteria
- To psychologist as necessary for psychological support

PEARLS & CONSIDERATIONS

- Before genetic testing is instituted, informed consent must be obtained because consequences of this testing include the necessity of lifelong screenings such as colonoscopies.
- The risk of pancreatic cancer is increased in families with Lynch syndrome compared with the U.S. population.
- **Familial Colorectal Cancer Type X** refers to patients who meet the Amsterdam criteria for HPNCC but have no molecular evidence of a mismatch repair (MMR) deficiency. These patients have a lower risk of colon cancer and no increased risk of extracolonic cancer compared to those with Lynch syndrome.

PATIENT & FAMILY EDUCATION

For information on local genetic counselors, visit the National Society of Genetic Counselors website at www.nsgc.org.
For information on Lynch syndrome, visit www.mayoclinic.com/health/lynch-syndrome/DS00669.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Colorectal Cancer (Related Key Topic)
Familial Adenomatous Polyposis and Gardner Syndrome (Related Key Topic)
Peutz-Jeghers Syndrome and Other Polyposis Syndromes (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Bonadona V et al: Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome, *JAMA* 305(22):2304-2310, 2011.

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Moreira L: Identification of Lynch syndrome among patients with colorectal cancer, *JAMA* 328(15):1515-1516, 2012.

Power DG et al: Clinical genetics of hereditary colorectal cancer, *Hematol Oncol Clin N Am* 24:837-859, 2010.

Sinicrope FA: Lynch syndrome-associated colorectal cancer, 379(8):764-773, 2018.

BASIC INFORMATION

DEFINITION

Macular degeneration, usually referred to as *age-related macular degeneration* (AMD), is an acquired degeneration of the retinal pigment epithelium and subsequently the neurosensory retina and choroid resulting in loss of central vision. The etiology is not known but a combination of genetic predisposition to immune- and complement-mediated inflammation and certain risk factors plays an important role. Nonexudative (or "dry") AMD is the most common, but exudative (or "wet") AMD is the most visually devastating.

SYNONYMS

AMD
ARMD

ICD-10CM CODES

H35.31	Nonexudative age-related macular degeneration
H35.32	Exudative age-related macular degeneration

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Leading cause of irreversible blindness in people ≥50 yr in the developed world.
- Increases with age.
- In 2010, 2.1 million Americans over the age of 40 had advanced AMD. The number is expected to more than double to 5.4 million by 2050.
- About 10% of patients with AMD have the neovascular form manifested by an often rapid decrease in central visual acuity caused by bleeding and scarring secondary to choroidal neovascularization.

PEAK INCIDENCE:

- Ages 75 to 80 yr
- Risk increases threefold in patients over the age of 75 as compared with younger age groups

PREVALENCE (IN U.S.):

- Varies, but 6.5% of people >40 yr have some signs of macular degeneration, and 0.8% have late AMD.
- In the U.S., approximately 30% of people over the age of 75 have some form of macular degeneration.

PREDOMINANT SEX: Males and females are affected equally (15% of white women >80 yr have severe AMD)

PREDOMINANT AGE: >50 yr

RISK FACTORS:

- Advancing age, especially over 70
- Genetic factors
- History of smoking within past 20 yr
- Dietary factors (low intake of antioxidants, zinc, and omega-3 fatty acids; high fat intake)
- Obesity
- White race

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Decreased central vision, distortion of vision (metamorphopsia), poor night vision
- Drusen, atrophy, macular hemorrhage, pigmentation, macular edema, subretinal fluid
- The most common abnormality seen in AMD is the presence of drusen, or yellowish deposits deep to the retina
- Choroidal neovascular membrane (CNVM) develops with rapid change in vision due to leakage of exudative fluid and hemorrhage.

ETIOLOGY

- Oxidative and inflammatory changes in the retinal pigment epithelium due to a combination of environmental factors and genetic predisposition
- Genetics: 19 genes with mutations have been identified—dysregulation of the alternate complement system among other biochemical pathways
- Pigmentary and vascular changes with exudate, edema, and ultimately scar tissue development in exudative AMD
- Dry-type atrophy of the macula retinal pigment epithelium in nonexudative AMD
- The main mediator of neovascularization in wet AMD is vascular endothelial growth factor (VEGF). It induces angiogenesis and increases inflammation and vascular permeability

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Polypoidal choroidal vasculopathy (PCV)
- Central serous chorioretinopathy
- Pattern dystrophy of the retinal pigment epithelium
- Drug toxicity (hydroxychloroquine, deferoxamine)
- Multifocal choroiditis (inflammatory disease of the choroid and retinal pigment epithilium (RPE))
- Histoplasmosis and high myopia (less common causes of CNVM)
- Angioid streaks
- Trauma with macular scar

WORKUP

- Careful history including family history of ocular disease
- Complete eye examination including slit lamp biomicroscopy
- Optical coherence tomography (OCT) is essential

IMAGING STUDIES

- High-resolution OCT
- OCT angiography
- Fluorescein angiography
- Fundus autofluorescence
- Possibly indocyanine green angiography if other diseases are being considered

TREATMENT

NONPHARMACOLOGIC THERAPY

- There is no laser treatment for dry AMD.
- Photodynamic treatment with verteporfin can be used in the rare case of exudative AMD that does not respond to intravitreal pharmacotherapy.
- Thermal laser (argon) for certain classic membranes (CNVM) is rarely used in the era of biologics.

ACUTE GENERAL Rx

- The introduction of therapies blocking VEGF has dramatically changed the management of AMD and is now the standard of care in the management of neovascular AMD. Intravitreal injections of anti-VEGF agents (ranibizumab, bevacizumab, and aflibercept) are first-line treatments for neovascular AMD. Intravitreal administration of ranibizumab, a humanized antibody fragment that neutralizes all active forms of VEGF A, was shown to stabilize or improve vision in 95% of patients compared to 65% of patients treated with verteporfin photodynamic therapy (PDT). Aflibercept is a soluble protein that acts as a VEGF receptor decoy and is the most recently FDA-approved intravitreal therapy. Randomized controlled trials showed it to be noninferior to ranibizumab. Bevacizumab, a full-length monoclonal antibody to VEGF, is used off-label as intravitreal therapy. Its cost per intravitreal dose is significantly lower than that of ranibizumab and aflibercept. However, several comparative effectiveness trials have shown bevacizumab to be non-inferior to ranibizumab.
- A major concern regarding anti-VEGF treatment is the potential increased risk of stroke and cardiovascular disease but no study to date has shown an increased incidence due to intravitreal therapy.
- Laser photocoagulation therapy may be useful in patients with extrafoveal lesions but is no longer routinely recommended for wet AMD.

CHRONIC Rx

- Age Related Eye Disease Study 1 and 2 (AREDS): A large randomized controlled trial showed that supplementation with the antioxidant vitamins C (500 mg) and E (400 IU), beta carotene (15 mg), and the micronutrient zinc (80 mg zinc oxide and 2 mg cupric oxide to prevent zinc-induced anemia) in patients with intermediate nonexudative AMD resulted in a 25% risk reduction of progression to advanced AMD at 5 yr.
- AREDS 2 formula eliminates beta carotene and replaces it with 10 mg lutein and 2 mg zeaxanthin, thus avoiding the risk of lung cancer in former smokers.

DISPOSITION

- Follow closely by ophthalmologist, retinal specialist
- Frequency of follow-up determined by severity of disease
- Patients should self-monitor with Amsler grid daily and report changes immediately
- Smoking cessation, sunglasses with UVA and UVB protection, diet high in green leafy vegetables and fish
- Most anti-VEGF treatment failures are due to missed follow-up visits. Patients should be reminded repeatedly to call if their vision worsens

PEARLS & CONSIDERATIONS

COMMENTS

- Recent trials with embryonic stem cell transplants have shown promise in macular degeneration. Although stem cells represent new therapeutic strategies to repair and regenerate tissues damaged by disease or injury, much remains to be learned about how stem cells and their derivatives can be manufactured and delivered safely. Recent reports show success with autologous-induced stem-cell–derived retinal cells for macular degeneration,[1] whereas others performed outside of clinical trial settings have resulted in vision loss after intravitreal injection of autologous "stem cells" for AMD.[2] The International Society for Stem Cell Research has recently released guidelines for clinical translation of stem cells.[3,4]
- Statistically, the vision of only 1 of 10 affected persons can be saved, but the disease is so devastating that vigorous therapy should be considered in all patients.
- Vitamins with zinc and antioxidants may slow progression of AMD.
- Quitting smoking significantly reduces the risk of developing AMD.

[1] Daley GQ: Polar extremes in the clinical use of stem cells, *N Engl J Med* 376:1075-1077, 2017.

[2] Mandai M et al: Autologous induced stem-cell–derived retinal cells for macular degeneration, *N Engl J Med* 376:1038-1046, 2017.

[3] Kuriyan AE et al: Vision loss after intravitreal injection of autologous "stem cells" for AMD, *N Engl J Med* 376:1047-1053, 2017.

[4] Daley QC et al: Setting global standards for stem cell research and clinical translation: the 2016 ISSCR guidelines, *Stem Cell Reports* 6(6):787-797, 2016.

SUGGESTED READINGS

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Mitchell P et al: Macular Degeneration, *The Lancet* 392:1147-1159, 2018.

RELATED CONTENT

Macular Degeneration (Patient Information)

AUTHOR: **Robert H. Janigian, Jr., MD**

Malabsorption

BASIC INFORMATION

DEFINITION

Malabsorption is the diminished intestinal absorption of dietary nutrients. The majority of malabsorption is due to either congenital or acquired defects in the membrane transport system, absorption, and brush border processing in the intestinal epithelium.

SYNONYM

Maldigestion

ICD-10CM CODES

K90.4	Malabsorption due to intolerance, not elsewhere classified
K90.89	Other intestinal malabsorption
K90.9	Intestinal malabsorption, unspecified
K91.2	Postsurgical malabsorption, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX AND AGE: More common in females, with a mean age of 40
GENETICS: HLA-DQ2 present in 95% of celiac disease

RISK FACTORS:
- Excessive alcohol consumption
- History of celiac disease
- History of irritable bowel disease (IBD)
- Intestinal surgery

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most commonly nonspecific symptoms such as abdominal flatulence and distention are seen.
- Due to the osmotic load from maldigestion/malabsorption, watery diarrhea may be present. In the case of fat digestive disorder, steatorrhea ensues.
- Weight loss is very common but many patients are able to compensate by increased caloric load. Diffuse disease often has much more pronounced weight loss.
- Chronic protein malabsorption can cause hypoalbuminemia, leading to edema and ascites.
- Both microcytic and macrocytic anemia can result from micronutrient deficiency (iron/B_{12}). These patients can be pale and present with fatigue.
- Bleeding disorders from vitamin K deficiency can lead to ecchymosis, melena, and hematuria.
- Vitamin D deficiency can lead to bone disorders. Secondary hyperparathyroidism can be a presenting feature.
- Electrolyte and vitamin deficiency can lead to neurologic disorders such as ataxia, weakness, and neuropathy, and may have positive Chvostek or Trousseau sign.
- Autoimmune disease-specific dermatologic findings such as alopecia, pellagra, erythema nodosum, pyoderma gangrenosum, cheilosis, glossitis, and aphthous ulcers may be present.
- Cardinal clinical features of specific malabsorptive disorders are summarized in Table 1.

ETIOLOGY

- Can be congenital or acquired.
- Disease-specific etiology. Mechanisms of malabsorption, malabsorbed substrates, and representative causes are summarized in Table 2.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Crohn disease
- Celiac disease
- Hartnup disease
- Chronic pancreatitis
- Pancreatic insufficiency
- Cystic fibrosis
- Short bowel syndrome

TABLE 1 Cardinal Clinical Features of Specific Malabsorptive Disorders

Disorder	Cardinal Clinical Features
Adrenal insufficiency	Skin darkening, hyponatremia, hyperkalemia
Amyloidosis	Renal disease, nephrotic syndrome, cardiomyopathy, neuropathy, carpal tunnel syndrome, macroglossia, hepatosplenomegaly
Bile acid deficiency	Ileal resection or disease, liver disease
Carcinoid syndrome	Flushing, cardiac murmur
Celiac disease	Variable symptoms: Dermatitis herpetiformis, alopecia, aphthous mouth ulcers, arthropathy, neurologic symptoms, and (life-threatening) malnutrition; elevated liver biochemical test levels, mild iron deficiency
Crohn disease	Arthritis, aphthous mouth ulcers, episcleritis, uveitis, pyoderma gangrenosum, erythema nodosum, abdominal mass, fistulas, perianal fistulae, primary sclerosing cholangitis (PSC), laboratory signs of inflammation
CF	Chronic sinopulmonary disease, meconium ileus, distal intestinal obstruction syndrome (DIOS), elevated sweat chloride
Cystinuria, Hartnup disease	Kidney stones, dermatosis
Diabetes mellitus	Long history of diabetes and diabetic complications
Disaccharidase deficiency	Bloating and cramping, intermittent diarrhea
GI fistulas	Previous intestinal surgery or trauma, Crohn disease
Glucagonoma	Migratory necrolytic erythema, enlarged gallbladder
Hyperthyroidism, hypothyroidism	Symptoms and signs of thyroid disease
Hypogammaglobulinemia	Recurrent infections
Intestinal ischemia	Other ischemic organ manifestations; abdominal pain with eating (chronic mesenteric ischemia)
Lymphoma	Enlarged mesenteric or retroperitoneal lymph nodes, abdominal mass, abdominal pain, fever
Mastocytosis	Urticaria pigmentosum, peptic ulcer
Mycobacterium avium complex infection	AIDS
Pancreatic insufficiency	History of pancreatitis, abdominal pain, or alcoholism; large-volume fatty, oily stools; passage of orange oil
Parasitic infection	History of travel to endemic areas
PBC	Jaundice, itching
Scleroderma	Dysphagia, inability to open the mouth widely, Raynaud phenomenon, skin tightening
SIBO	Previous intestinal surgery, motility disorder (scleroderma, pseudo-obstruction), small intestinal diverticula, strictures
Tropical sprue	History of travel to endemic area
Tuberculosis	Specific history of exposure, living in or travel to endemic area, immunosuppression, abdominal mass or intestinal obstruction, ascites
Whipple disease	Lymphadenopathy, fever, arthritis, cerebral symptoms, heart murmur (pulmonary valve), oculomasticatory myorhythmia
ZES	Peptic ulcers, diarrhea

AIDS, Acquired immunodeficiency syndrome; *CF,* cystic fibrosis; *GI,* gastrointestinal; *PBC,* primary biliary cholangitis; *SIBO,* small intestinal bacterial overgrowth; *ZES,* Zollinger-Ellison syndrome.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE 2 Mechanisms of Malabsorption, Malabsorbed Substrates, and Representative Causes

Pathophysiologic Mechanism	Malabsorbed Substrate(s)	Representative Causes
Maldigestion		
Conjugated bile acid deficiency	Fat Fat-soluble vitamins Calcium Magnesium	Hepatic parenchymal disease Biliary obstruction SIBO with bile acid deconjugation Ileal bile acid malabsorption CCK deficiency
Pancreatic insufficiency	Fat Protein Carbohydrate Fat-soluble vitamins Vitamin B_{12} (cobalamin)	Congenital defects Chronic pancreatitis Pancreatic tumors Inactivation of pancreatic enzymes (e.g., ZES)
Reduced mucosal digestion	Carbohydrate	Congenital defects Acquired lactase deficiency
	Protein	Generalized mucosal disease (e.g., celiac disease, Crohn disease)
Intraluminal consumption of nutrients	Vitamin B_{12} (cobalamin)	SIBO Helminthic infections (e.g., *Diphyllobothrium latum* infection)
Malabsorption		
Reduced mucosal absorption	Fat Protein Carbohydrate Vitamins Minerals	Congenital transport defects Generalized mucosal diseases (e.g., celiac disease, Crohn disease) Previous intestinal resection or bypass Infections Intestinal lymphoma
Decreased transport from the intestine	Fat Protein	Intestinal lymphangiectasia Primary Secondary (e.g., solid tumors, Whipple disease, lymphomas) Venous stasis (e.g., from heart failure)
Other Mechanisms		
Decreased gastric acid and/or intrinsic factor secretion	Vitamin B_{12}	Pernicious anemia Atrophic gastritis Previous gastric resection
Decreased gastric mixing and/or rapid gastric emptying	Fat Calcium Protein	Previous gastric resection Autonomic neuropathy
Rapid intestinal transit	Fat	Autonomic neuropathy Hyperthyroidism

CCK, Cholecystokinin; *SIBO,* small intestinal bacterial overgrowth; *ZES,* Zollinger-Ellison syndrome.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

- Neoplasm
- Abetalipoproteinemia
- Lactose intolerance
- Small intestine bacterial overgrowth
- Chronic atrophic gastritis
- Zollinger-Ellison syndrome
- Chronic cholestasis
- Cirrhosis

WORKUP

- A detailed history including alcohol consumption and surgical history as well as autoimmune disease can help diagnose the underlying disease. It is important to screen for anemia and electrolyte abnormalities due to malabsorption.
- Table 3 summarizes malabsorptive diseases or conditions in which noninvasive tests can establish malabsorption or provide a diagnosis.

LABORATORY TESTS

- CBC, serum iron, Vitamin B_{12}, and folate to detect for anemia.
- **Prothrombin time:** Elevated PT can suggest vitamin K deficiency.
- **Fat malabsorption:** The gold standard is the 72-hour stool elastase or fat collection. More than 6/g day in the stool is pathologic. This test can be cumbersome so other options are available. Sudan III stain and acid steatocrit tests are qualitative measures of steatorrhea. Serologic testing for celiac disease should be considered as well.
- **Carbohydrate malabsorption:** Carbohydrate malabsorption leads to fermentation of the undigested carbohydrates by intestinal bacteria.
- The urinary D-xylose test for carbohydrate absorption in the small intestine. After loading with D-xylose, urinary D-xylose levels are measured. Low levels suggest intestinal malabsorption.
- Lactose intolerance can be tested by the lactose tolerance test or the breath test. The lactose tolerance test measures blood glucose after lactose administration. Development of symptoms or inadequate increase in blood sugar is indicative of lactose intolerance. H_2/CO_2 breath tests using specific forms of carbohydrates can detect malabsorption as well.
- **Protein malabsorption:** Protein malabsorption is likely due to small intestinal bacterial overgrowth or protein gastroenteropathies. Alpha-1 antitrypsin clearance or 99mTc-albumin gamma camera scintigraphy may aid in this diagnosis.
- **Pancreatic insufficiency:** Fecal elastase and chymotrypsin levels can distinguish from pancreatic and intestinal causes.
- **Vitamin deficiency:** It is important to assess serum vitamin B_{12} and methylmalonic acid levels. Schilling test is rarely used but can be useful in some cases.
- **Bile acid malabsorption:** Quantitative stool bile acid measurement is the preferred method of diagnosis. SeHCAT test (selenium homocholic acid taurine test) is another option but less likely used.
- **Bacterial overgrowth:** This can be detected with endoscopic jejunal aspirate culture or a less invasive hydrogen breath test.
- Table 4 summarizes useful laboratory tests for evaluating patients with suspected malabsorption and for establishing possible nutrient deficiencies.

IMAGING STUDIES

- Abdominal ultrasound can identify thickened small bowel wall
- Endoscopy for visualization and biopsy
- Small bowel follow through
- Abdominal CT/MRI
- Endoscopic retrograde cholangiopancreatography/magnetic resonance cholangiopancreatography/endoscopic ultrasound for identification of pancreatic abnormalities
- Capsule endoscopy

Rx TREATMENT

Involves identification and treatment of the underlying illness, treatment of diarrhea, and nutritional repletion

NONPHARMACOLOGIC THERAPY

- A gluten-free diet in patients with celiac disease. Avoidance of lactose-containing product in lactose intolerance.
- Avoidance of caffeine and high sugar containing compounds has been found to decrease diarrhea in some cases.

ACUTE GENERAL Rx

- Control of the underlying disease should be primary goal.
- It is also essential to control any volume and electrolyte abnormalities that might exist.

CHRONIC Rx

- Control of chronic diarrhea with loperamide should be one of the goals in a chronic malabsorptive state.
- Correction of volume and electrolyte disturbance with oral rehydration therapy should be made a priority.
- Bile acid conjugates can decrease steatorrhea in some cases.

TABLE 3 Malabsorptive Diseases or Conditions in Which Noninvasive Tests Can Establish Malabsorption or Provide a Diagnosis

Disease or Condition	Diagnostic Test(s)	Comment(s)
Lactose malabsorption	Lactose hydrogen breath test Lactose tolerance test	Tests do not differentiate between primary and secondary lactose malabsorption.
Incomplete fructose absorption	Fructose hydrogen breath test	
SIBO	^{14}C-D-xylose breath test Glucose hydrogen breath test Schilling test with and without antibiotics	A predisposing factor should be sought if the result of any of the tests is positive.
Bile acid malabsorption	SeHCAT test, ^{14}C-TCA test	Does not differentiate between primary and secondary causes.
Exocrine pancreatic insufficiency	Quantitative fecal fat determination	Used to establish malabsorption in chronic pancreatitis.
	Fecal elastase or chymotrypsin, tubeless tests	Variable sensitivity and specificity, depending on the type of test and stage of the disease.
Vitamin B_{12} malabsorption	Schilling test	The test is performed without intrinsic factor and, depending on the result with intrinsic factor, with antibiotics or pancreatic enzymes. Further tests are necessary if SIBO, terminal ileal disease, or pancreatic disease is suspected.

SeHCAT, Selenium-75-homotaurocholic acid test; *SIBO,* small intestinal bacterial overgrowth; *TCA,* taurocholic acid.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE 4 Useful Laboratory Tests for Patients with Suspected Malabsorption and for Establishing Possible Nutrient Deficiencies

Test	Comment(s)
Blood Cell Count	
Hematocrit, hemoglobin	Decreased in iron, vitamin B_{12}, and folate malabsorption or with blood loss
Mean corpuscular hemoglobin or mean corpuscular volume	Decreased in iron malabsorption; increased in folate and vitamin B_{12} malabsorption
White blood cells, differential	Decreased in vitamin B_{12} and folate malabsorption; low lymphocyte count in lymphangiectasia
Biochemical Tests (Serum)	
TGs	Decreased in severe fat malabsorption
Cholesterol	Decreased in bile acid malabsorption or severe fat malabsorption
Albumin	Decreased in severe malnutrition, lymphangiectasia, protein-losing enteropathy
Alkaline phosphatase	Increased in calcium and vitamin D malabsorption (severe steatorrhea); decreased in zinc deficiency
Calcium, phosphorus, magnesium	Decreased in extensive small intestinal mucosal disease, after extensive intestinal resection, or in vitamin D deficiency
Zinc	Decreased in extensive small intestinal mucosal disease or intestinal resection
Iron, ferritin	Decreased in celiac disease, in other extensive small intestinal mucosal diseases, and with chronic blood loss
Other Serum Tests	
Prothrombin time	Prolonged in vitamin K malabsorption
β-Carotene	Decreased in fat malabsorption from hepatobiliary or intestinal diseases
Immunoglobulins	Decreased in lymphangiectasia, diffuse lymphoma
Folic acid	Decreased in extensive small intestinal mucosal diseases, with anticonvulsant use, in pregnancy; may be increased in SIBO
Vitamin B_{12}	Decreased after gastrectomy, in pernicious anemia, terminal ileal disease, SIBO, and infection with *Diphyllobothrium latum*
Methylmalonic acid	Markedly elevated in vitamin B_{12} deficiency
Homocysteine	Markedly elevated in vitamin B_{12} or folate deficiency
Citrulline	May be decreased in destructive small intestinal mucosal disease or intestinal resection
Stool Tests	
Fat	Qualitative or quantitative increase in fat malabsorption
Elastase, chymotrypsin	Decreased concentrations and output in exocrine pancreatic insufficiency
pH	Less than 5.5 in carbohydrate malabsorption

SIBO, Small intestinal bacterial overgrowth; *TGs,* thyroglobulins.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

- Pancreatic insufficiency is typically treated with a low-fat diet and exogenous pancreatic enzymes.
- Teduglutide-homolog of GLP-2 has been shown to increase absorptive surface area in short bowel syndrome.
- Periodic DEXA scans are indicated in chronic malabsorption in the setting of vitamin D deficiency.
- Oral supplementation with vitamins and minerals is important, sometimes requiring parenteral therapy.

REFERRAL

- Gastroenterology consultation can help in diagnosis when initial laboratory testing is unclear.
- Nutrition consultation can help patients with diet modification to alleviate symptoms.

PEARLS & CONSIDERATIONS

COMMENTS

- Malabsorption should be considered a sign of an underlying disease.
- Treatment should focus on treating the underlying disorder.
- Nutrient and volume repletion should be priority in any treatment plan of malabsorption.

RELATED CONTENT

Celiac Disease (Related Key Topic)
Crohn Disease (Related Key Topic)
Cystic Fibrosis (Related Key Topic)
Irritable Bowel Syndrome (Related Key Topic)
Lactose Intolerance (Related Key Topic)
Chronic Pancreatitis (Related Key Topic)
Short Bowel Syndrome (Related Key Topic)
Small Bowel Intestinal Bacterial Overgrowth (Related Key Topic)
Ulcerative Colitis (Related Key Topic)

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BASIC INFORMATION

DEFINITION

Malaria is a protozoan disease caused by intraerythrocytic protozoa of the genus *Plasmodium* and transmitted by female *Anopheles* spp. mosquitoes. It is endemic throughout most of the tropics and is characterized by hectic fever and often presents with classic malarial paroxysm. Five species of genus *Plasmodium* usually infect humans (Table 1):

- *P. falciparum*
- *P. vivax*
- *P. malariae*
- *P. ovale*
- *P. knowlesi*

SYNONYMS

Periodic fever
Tertian malaria
Quartan malaria
Tropical splenomegaly

ICD-10CM CODES

B50.9	*Plasmodium falciparum* malaria, unspecified
B51.9	*Plasmodium vivax* malaria without complications
B52.9	*Plasmodium malariae* malaria without complications
B53.0	*Plasmodium ovale* malaria
B53.8	Other parasitologically confirmed malaria, not elsewhere classified
B54	Unspecified malaria

EPIDEMIOLOGY & DEMOGRAPHICS

Global:

- ~217 million cases in 2017 in more than 100 countries
- Approximately 435,000 deaths in 2017, with more than 80% of the deaths occurring in children of sub-Saharan Africa
- Three billion people live in malaria-endemic areas

U.S.:

- ~2078 cases reported to the CDC in the U.S. in 2017 (Fig. E1). In the majority of reported cases, U.S. civilians who acquired infection abroad had not adhered to a chemoprophylaxis regimen that was appropriate for the country in which they acquired malaria

More than 50% of the reported cases in the U.S. are *P. falciparum.* On average, there are six deaths per yr in the U.S.

- Most infections limited to:
  1. Immigrant population
  2. Returned travelers or troops from endemic area
- Occasionally, transmission through exposure to infected blood product or shared intravenous needles by users of injection drugs
- Congenital transmission possible
- Local mosquito-borne transmission reported
- Competent mosquito vectors present
  1. *A. albimanus* in Eastern U.S.
  2. *A. freeborni* in Western U.S.

Geographic distribution:

- *P. falciparum:* Sub-Saharan Africa, Papua New Guinea, Solomon Islands, Haiti, Indian subcontinent
- *P. vivax:* Central America, South America, North Africa, Middle East, Indian subcontinent
- *P. ovale:* West Africa
- *P. malariae:* Worldwide
- *P. knowlesi:* Southeast Asia

Parasite life cycle (Fig. E2):

- Human infection begins when a female anopheline mosquito bites (only female anopheline mosquito takes blood meal) and inoculates plasmodial sporozoites into bloodstream. The bite usually occurs between dusk and dawn.
- The sporozoites then travel to liver and invade to hepatocytes.
- In the hepatocytes, the sporozoites mature to tissue schizonts or become dormant hypnozoites.
- The tissue schizonts amplify the infection by producing a large number of merozoites (10,000 to 30,000).
- Each merozoite is capable of invading a RBC and can establish the asexual cycle of replication in RBCs.
- Asexual cycles produce and release 24 to 32 merozoites at the end of 48- or 72-hr *(P. malariae)* cycles.
- The hypnozoites are only found in relapsing malaria P. vivax or P. ovale and may remain dormant for up to 5 yr.
- Eventually some intraerythrocytic parasites develop into gametocytes. Male and female gametocytes are taken up by a female anopheline mosquito with a blood meal where they fertilize in the mosquito gut to produce a diploid zygote that matures to an ookinete; haploid sporozoites are generated that migrate to the salivary gland of the mosquito to infect another human.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever is the hallmark of malaria, known as malarial paroxysm, initially daily until synchronization of infection after several wk, when fever may occur every other day (tertian) in *P. vivax, P. ovale,* or *P. falciparum* malaria or every third day (quartan) in *P. malariae* malaria. Table 2 describes the WHO criteria for severe malaria.
- Classic malarial paroxysm characterized by:
  1. Cold stage: Abrupt onset of cold feeling associated with rigors, shakes
  2. Hot stage: High fever (~40° C; 104° F) associated with restlessness
  3. Sweating stage: Patient defervesces
- Nonspecific symptoms are:
  1. Headache
  2. Cough
  3. Myalgia
  4. Vomiting
  5. Diarrhea
  6. Jaundice
- *P. falciparum:*
  1. Most pathogenic of the four species.
  2. Rapidly progresses to high-level parasitemia.
  3. Important cause of the fatal malaria.

TABLE 1 Characteristics of the *Plasmodium* Species Responsible for Human Malaria

Characteristic	Species				
	P. falciparum	***P. vivax***	***P. ovale***	***P. malariae***	***P. knowlesi***
Incubation period in days (range)	12 (8-25)	14 (8-27)	17 (15 to ≥18)	28 (15 to ≥40)	11 (9 to >12)
Periodicity of febrile attacks (hours)	None	48	48	72	24
Earliest appearance of gametocytes (days)	10	3	?	?	?
Relapse	No	Yes	Yes	No	No
Duration of untreated infection (yrs)	1-2	1.5-4	1.5-4	3-50	?
RBC preference	Younger cells (but can invade cells of all ages)	Reticulocytes	Reticulocytes	Older cells	?
Characteristic morphology	Ring forms	Schüffner dots	Schüffner dots	Normal-sized cells	Ring forms
	Multiply infected cells	Enlarged RBCs	Enlarged RBCs	Band or rectangular forms of trophozoites	Occasional multiply infected cells
	Banana-shaped gametocytes				Band forms

RBC, Red blood cell.
From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

TABLE 2 World Health Organization Criteria for Severe Malaria, 2000

Impaired consciousness
Prostration
Respiratory distress
Multiple seizures
Jaundice
Hemoglobinuria
Abnormal bleeding
Severe anemia
Circulatory collapse
Pulmonary edema

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, WB Saunders.

4. Classic malarial paroxysm is usually absent.
5. Incubation period after exposure is 12 days (range: 9 to 60 days).
6. Cytoadherence and resetting of RBCs play central role in pathogenesis.
7. The sequestration of RBCs in vital organs leads to fatal complications.
8. Cerebral malaria is a feared complication.
9. Invades erythrocytes of all ages.
10. Lacks hypnozoites (intrahepatic stage), does not relapse.
11. Blood smear usually shows ring form only.
12. Pigment color is black.
13. Banana-shaped gametocytes; if seen in blood, smear is diagnostic.
14. Chloroquine resistance is widely present.

- *P. vivax:*
  1. Known as tertian malaria: Fever occurs every other day.
  2. Duffy blood-group antigen FYA- or FYB-related receptor is needed for attachment to RBC.
  3. FyFy phenotype (most West African) individuals are resistant to *P. vivax* malaria.
  4. Incubation period after exposure is 14 days (range: 8 to 27 days).
  5. Hypnozoites may cause relapse of infection after yrs.
  6. Infects mainly reticulocytes.
  7. Irregularly shaped large rings and trophozoites, enlarged RBCs, and Schüffner dots are seen in peripheral blood smear.
  8. Pigment color is yellow-brown.
  9. *P. vivax* from Papua New Guinea has reduced sensitivity to chloroquine.
  10. Primaquine is needed to eradicate the hypnozoites.
- *P. ovale:*
  1. Also known as tertian malaria; fever occurs every other day.
  2. Occurs mainly in tropical Africa.
  3. Incubation period after exposure is 14 days (range: 8 to 27 days).
  4. Hypnozoites may cause relapse of infection.
  5. Infects mainly reticulocytes.
  6. Infected RBC is seen as enlarged, oval shape containing large ring or trophozoites with Schüffner dots.
  7. Pigment color is dark brown.
  8. Primaquine needed to eradicate the hypnozoites.
  9. No chloroquine resistance has been encountered.
- *P. malariae:*
  1. Known as quartan malaria; fever occurs every third day.
  2. Common cause of chronic malarial infection.
  3. May persist for 20 to 30 yr after leaving the endemic area.
  4. Worldwide distribution.
  5. Incubation period after exposure is 30 days (range: 16 to 60 days).
  6. Lacks hypnozoites (intrahepatic stage).
  7. May persist in blood for many yrs if treated inadequately.
  8. Chronic infection may cause soluble immune-complex, resulting in nephritic syndrome.
  9. Infects mainly mature RBCs.
  10. Band or rectangular forms of trophozoites are commonly seen in peripheral blood smear.
  11. Pigment color is brown-black.
- Cerebral malaria:
  1. Feared complication of *P. falciparum* infection.
  2. Mortality is ~20%.
  3. Pathogenesis is poorly understood.
  4. Ischemia as a result of sequestration of parasites or cytokines induced by parasite toxin(s) is the key debate.
  5. Seizure and altered mental status leading to coma are cardinal manifestation.
  6. Hypoglycemia, lactic acidosis, and elevated circulating tumor necrosis factor alpha (TNF-a) may be present.
  7. CSF studies: No increase of WBC count or protein, raised lactate concentrate, and increased opening pressure, especially in children, may be present.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Typhoid fever
- Dengue fever
- Yellow fever
- Viral hepatitis
- Influenza
- Brucellosis
- Urinary tract infection
- Leishmaniasis
- Trypanosomiasis
- Rickettsial diseases
- Leptospirosis

WORKUP

- Clinical diagnosis is notoriously inaccurate.
- Demonstration of malarial parasites in blood smear is essential.
- Newer molecular diagnostic techniques (polymerase chain reaction, rapid diagnostic tests) are promising (Table 3).

LABORATORY TESTS

- The thick and thin blood film is required to identify malarial parasites (Fig. E3). A Giemsa-stained film of the patient's peripheral blood should be examined for parasites as soon as possible.
- The thick smears are more sensitive and primarily used to detect the presence of parasites.
- The thin smears are used for species differentiation and parasite density estimation.
- A patient who is suspected of having malaria but who has no parasite seen in blood smears should have blood smears repeated every 12 to 24 hr for 3 consecutive days.

PREPARATION OF BLOOD SMEAR:

- Must be prepared from fresh blood obtained by pricking the finger.
- The thin smear is fixed in methanol before staining.
- The thick smear is stained unfixed.
- The smear should be stained with a 3% Giemsa solution (pH of 7.2) for 30 to 45 min.
- The parasite density should be estimated by counting the percentage of RBCs infected, not the number of parasites, under an oil immersion lens on thin film.

COMMON ERRORS IN READING MALARIAL SMEARS:

- Platelets overlying an RBC
- Misreading artifacts as parasites
- Concern about missing a positive slide

MOLECULAR DIAGNOSIS OF MALARIA:

- Rapid diagnostic tests (RDT):
  1. Employ immunochromatographic lateral flow technology for antigen detection.
  2. Thus far only one RDT has been FDA approved: BinaxNOW Malaria test kit.
  3. This kit is based on antigens histidine-rich protein-2 (HRP-2) and aldolase.
  4. For *P. falciparum:* Sensitivity 95% and specificity 94%.
  5. For *P. vivax:* Sensitivity 69% and specificity 100%.
- Limitations of the BinaxNOW Malaria test:
  1. Not approved for mixed infections.
  2. Should not be used for *P. malariae* and *P. ovale* as data are limited.
  3. Positive test must be confirmed by microscopy.
  4. Negative results require confirmation by thick and thin smears.
  5. This test cannot be used to monitor therapy as antigen persists after the elimination of the parasite, causing false positives.
- Other diagnostic tests available include:
  1. Tagged monoclonal antibodies for malaria antigen detection.
  2. Nucleic acid amplification and detection: polymerase chain reaction (PCR) can detect parasites down to a level of one to five parasites per microliter of blood. PCR can detect mixed species infection and is now considered the gold standard for diagnosis.
  3. Fluorescence microscopy with acridine orange or other staining.
  4. Dark field microscopy.

TABLE 3 Malaria Rapid Diagnostic Tests Available in the U.S.[a]

RDT Name	Malaria Antigen Target	Malaria Species Detected	Sensitivity	Comment
BinaxNOW	HRP-2 and aldolase	*P. falciparum, P. vivax, P. malariae,* and *P. ovale*	94% for *P. falciparum* 84% for non-*P. falciparum* 87% for pure *P. vivax* infections 62% for pure *P. ovale* and *P. malariae* infections	Sensitivity increased to 96% for pure *P. falciparum* infection Overall specificity of 99% FDA-approved for use in the U.S.
ParaSight F	HRP-2	*P. falciparum*	96.5-100 in Kenya when >60 parasites/μL, lower with less parasitemia 40% in travelers when <50 parasites/μL, >93% when >100 parasites/μL	Antigen persists for 6-7 days 6 in 11.9%-20% of subjects whose blood smears had cleared Not FDA approved for use in the U.S.
ICT Malaria Pf/Pv	HRP-2 and aldolase	*P. falciparum* and *P. vivax*	97% for *P. falciparum* 44% for *P. vivax*	Specificity of 90% for *P. falciparum* Specificity of 100% for *P. vivax* Not FDA-approved for use in the U.S.
OptiMAL-IT	LDH	*P. falciparum, P. vivax, P. malariae,* and *P. ovale*	85-95%; decreased with lower parasite density	Specificity of 100% *P. falciparum*, 75%-85% for *P. vivax* Not FDA approved for use in the U.S.
Clearview	LDH	*P. falciparum, P. vivax, P. malariae,* and *P. ovale*	93% specificity of 100%, with sensitivities of 99%, 90.0%, 86%, and 60%, respectively, for *P. falciparum, P. vivax, P. malariae,* and *P. ovale*	Specificity of 100% for *P. falciparum*, 99% for *P. vivax*, 90% for *P. malariae*, and 60% for *P. ovale* Not FDA-approved for use in the U.S.

FDA, Food and Drug Administration; *HRP-2,* histidine-rich protein-2; *ICT,* immunochromatographic diagnostic test; *LDT,* laboratory developed test; *RDT,* rapid diagnostic test.
[a]Direct microscopy should be performed where available with a negative RDT, given higher false-negative rates with low parasitemia, and when severe malaria is suspected.
From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

ANTIMOSQUITO MEASURES:

- Eradication of mosquito breeding places by chemical spray
- Use of mosquito nets properly in the endemic areas
- Use of protective clothing
- Use of insect spray (permethrin), mosquito coils, or repellents such as diethyltoluamide (DEET). For adults, DEET (30% to 50%) is generally protective for at least 4 hr. For smaller children, use DEET at ≤20% concentration

ACUTE GENERAL Rx

A definitive diagnosis of malaria is essential for specific antimalarial chemotherapy.

UNCOMPLICATED CHLOROQUINE-SENSITIVE PLASMODIUM VIVAX, PLASMODIUM OVALE, OR PLASMODIUM MALARIAE (NON-FALCIPARUM MALARIA):

- Chloroquine:
  1. Adults: 600 mg base (= 1000 mg salt) orally immediately, followed by 300 mg base (= 500 mg salt) orally at 6, 24, and 48 hrs.
  2. Children: 10 mg base/kg orally immediately, followed by 5 mg base/kg orally at 6, 24, and 48 hrs.
  3. Maximum total dose: 1500 mg base (= 2500 mg salt).
  4. An alternative agent is hydroxychloroquine (Plaquenil): 620 mg base (= 800 mg salt) orally immediately, followed by 310 mg base (= 400 mg salt) orally at 6, 24, and 48 hrs.
- In the case of *P. vivax* and *P. ovale,* treatment with primaquine 15 mg daily for 14 days is needed to eradicate the exoerythrocytic forms, especially the hypnozoites responsible for relapses.
- G6PD should be measured before primaquine is given. Primaquine is not recommended for those who are glucose-6-phosphate dehydrogenase deficient, because primaquine can cause hemolysis and even death in G6PD-deficient persons. Normal G6PD levels must be documented before using primaquine for either chemoprophylaxis or treatment.
- Chloroquine-resistant *P. vivax* has been documented; in that case use quinine sulfate (10 mg/kg) plus either tetracycline or doxycycline or clindamycin for 7 days.

UNCOMPLICATED FALCIPARUM MALARIA OR SPECIES NOT IDENTIFIED:

- Chloroquine can be used cautiously for falciparum malaria acquired in chloroquine-sensitive areas (chloroquine is more rapidly effective than quinine).
- For uncomplicated *P. falciparum,* an oral artemisinin combination therapy (ACT), is recommended by the CDC as the first-line agent. While there are numerous ACT combinations, the only ACT approved in the U.S. is artemether-lumefantrine (Coartem), which is not widely available. Do not delay therapy in trying to obtain it; use another first-line agent. Dosage for adults: 4 tablets artemether-lumefantrine (20/120 mg) as a single dose, then 4 tablets again after 8 hr, then 4 tablets q12h for 2 days (take with food). Can cause prolongation of QT interval. Not recommended in infants <5 kg. Dose dependent on weight in children:
  1. 5 to 15 kg: 1 tablet (20/120 mg) as a single dose, then 1 tablet again after 8 hr, then 1 tablet q12h for 2 days
  2. 16 to 25 kg: 2 tablets (40/240 mg) as a single dose, then 2 tablets again after 8 hr, then 2 tablets q12h for 2 days
  3. 26 to 35 kg: 3 tablets (60/360 mg) as a single dose, then 3 tablets again after 8 hr, then 3 tablets q12h for 2 days
  4. >35 kg: Treat as adult
- Atovaquone-proguanil (Malarone): 250 mg atovaquone/100 mg proguanil): 4 adult tabs PO once a day for 3 days with food. Pediatric dosage: Pediatric tablets (62.5 mg atovaquone/25 mg proguanil) are used based on weight:
  1. 5 to 8 kg: 2 pediatric tabs PO once daily for 3 days
  2. 9 to 10 kg: 3 pediatric tabs PO once daily for 3 days
  3. 11 to 20 kg: 1 adult tab PO once daily for 3 days
  4. 21 to 30 kg: 2 adult tabs PO once daily for 3 days
  5. 31 to 40 kg: 3 adult tabs PO once daily for 3 days
  6. >40 kg: 4 adult tabs PO once daily for 3 days
- Another first-line option for treatment in adults is oral quinine sulfate 10 mg (salt)/kg (usually 650 mg) q8h for 3 to 7 days plus doxycycline 100 mg PO bid, both for 7 days. Pediatric dosage: Quinine sulfate 10 mg/kg PO tid plus clindamycin 20 mg/kg per day divided tid, both for 7 days.
- Table 4 summarizes some treatment guidelines for severe *Plasmodium falciparum* malaria.

ALTERNATIVES:

- Quinine sulfate plus clindamycin 900 mg tid for 7 days in adults
- Mefloquine 750 mg PO, then 500 mg PO 6 to 12 hr later in adults

TABLE 4 Treatment Guidelines for Severe *Plasmodium falciparum* Malaria

Drug	Dose	Comments
Artemisinin compounds		
Artesunate Artemether	2.4 mg/kg IV bolus at 0, 12, 24 hours, then daily until patient is able to transition to the following oral regimen: 1. Artemether + lumefantrine: Tablets containing 20 + 120 mg, 40 + 240 mg of artemether and lumefantrine, respectively • Adults ≥35 kg: 80 + 480 mg twice daily for 3 days • Children: • 5 to <15 kg: 20 + 120 mg twice daily for 3 days • 15 to <25 kg: 40 + 240 mg twice daily for 3 days • 25 to <35 kg: 60 + 360 mg twice daily for 3 days 2. Artesunate + amodiaquine: A fixed-dose combination tablet containing 25 + 67.5 mg, 50 + 135 mg, 100 + 270 mg of artesunate and amodiaquine, respectively • Adults ≥36 kg, 200 + 540 mg daily for 3 days • Children: • 4.5 to <9 kg: 25 + 67.5 mg daily for 3 days • 9 to <18 kg: 50 + 135 mg daily for 3 days • 18 to <36 kg: 100 + 270 mg daily for 3 days 3. Dihydroartemisinin (DHA) + piperaquine (PPQ): Tablets containing 20 + 160 mg, 40 + 320 mg of DHA and PPQ, respectively • Adults: • 36 to <75 kg: 120 + 960 mg daily for 3 days • ≥75 kg: 160 + 1280 mg daily for 3 days (no data on dose recommendation >100 kg) • Children • 5 to <7 kg: 10 + 80 mg daily for 3 days • 7 to <13 kg: 20 + 160 mg daily for 3 days • 13 to <24 kg: 40 + 320 mg daily for 3 days • 24 to <36 kg: 80 + 640 mg daily for 3 days 4. Artesunate or quinine PO to complete 7 days plus doxycycline, 100 mg PO bid × 7 days 5. Artesunate or quinine PO to complete 7 days plus clindamycin, 20 mg base/kg/d PO, tid × 7 days Initial dose: 3.2 mg/kg IM (anterior tight); maintenance dose: 1.6 mg/kg IM daily until patient is able to transition to oral regimen as described earlier for artesunate	Artesunate has "investigational new drug" status in the U.S. and is available only on request to the CDC (770-488-7788). Eligibility requirements include inability to take oral medications, high levels of parasitemia, clinical evidence of severe malaria, intolerance of or contraindication to quinidine, failure of quinidine therapy, and lack of rapid access to quinidine. Where available, artesunate rectal suppositories (10 mg/kg) may be used in children <5 yr of age if IV or IM administration is not possible. Doxycycline is contraindicated in children <8 yr of age and in pregnancy. Atovaquone/proguanil is packaged in the U.S. in fixed-dose combination tablets of 250 mg atovaquone/100 mg proguanil for adults and 62.5 mg atovaquone/25 mg proguanil for children. Safety of atovaquone/proguanil in pregnancy has not been established.
Cinchona Alkaloid Regimens		
Quinine dihydrochloride	20 mg salt/kg IV or IM on admission, then 10 mg/kg q8h. Can be given IM if IV administration is not possible. One of the following drugs should also be given concurrently: 1. ACT as listed earlier. 2. Doxycycline as listed earlier. If patient unable to take PO, give 100 mg IV q12h and switch to PO when possible. Avoid rapid IV administration. 3. Clindamycin as listed earlier. If patient unable to take PO, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV q8h and switch to PO when possible. Avoid rapid IV administration.	The infusion rate of IV quinine should be rate controlled and not exceed 5 mg salt/kg per hour. The drug is usually diluted in 5% dextrose and infused over 4 hours. IV quinine is not available in the U.S. When administering IM, the dose should be split and diluted to a concentration of 60-100 mg/kg and delivered to each thigh. Reduce the quinine dose by one third (to 10 mg salt/kg q12h) after 48 hours in patients with severe renal and/or hepatic dysfunction. Doxycycline is contraindicated in children <8 yr old and in pregnancy.
Quinidine gluconate	6.25 mg base/kg (= 10 mg salt/kg) IV on admission over 1-2 hours, then 0.0125 mg base/kg minute (= 0.02 mg salt/kg per minute) continuous infusion. An alternative regimen is 15 mg base/kg (= 24 mg salt/kg) loading dose IV infused over 4 hours, followed by 7.5 mg base/kg (= 12 mg salt/kg) infused over 4 hours q8h, starting 8 hours after the loading dose. A second drug should be given concurrently as listed earlier for quinine.	The loading dose should be omitted if the patient received >40 mg/kg quinine in the preceding 48 hours or mefloquine in the previous 12 hours. Reduce the dose by one third after 48 hours in patients with severe renal and/or hepatic dysfunction.

ACT, Artemisinin combination therapy; *bid,* twice a day; *CDC,* Centers for Disease Control and Prevention; *IM,* intramuscular; *IV,* intravenous; *PO,* by mouth; *q8h,* every 8 hours; *tid,* thrice a day.
(From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.)

- Atovaquone-proguanil (Malarone) or quinine sulfate plus doxycycline can be used when species is unknown. Artemether-lumefantrine is also recommended the World Health Organization (WHO) for treatment of unknown species, but in U.S. is only approved for *P.* falciparum
- Other ACT combinations not yet available in the U.S.: Artesunate-amodiaquine, artesunate-mefloquine, artesunate-sulfadoxine-pyrimethamine, dihydroartemisinin-piperaquine, artesunate-pyronaridine tetraphosphate.

NOTE: Parasitemia may paradoxically rise in the first 24 to 36 hr and is not an indication of treatment failure.

SEVERE FALCIPARUM MALARIA:

- It is a medical emergency; intensive care is preferred.
- Measurement of blood glucose, lactate, ABG is important.
- IV quinidine gluconate 10 mg salt/kg loading dose (maximum 600 mg) in normal saline (NS); infuse slowly over 1 to 2 hr, followed by continuous infusion of 0.02 mg/kg/min until patient can swallow.
- Need to monitor ECG for observation of QT interval as can prolong. Also need to monitor blood pressure and glucose to avoid hypoglycemia.
- Alternatively, IV artesunate: 2.4 mg/kg IV at hour 0, then at 12 and 24 hr followed by 2.4 mg/kg once daily. If <20 kg use 3.0 mg/kg per dose. This medication is not FDA approved but is available through the CDC. One recent study showed the superiority of parenteral artesunate over parenteral quinine in adults and children who could not take an oral medication.

TABLE 5 Drug Regimens Used for Prevention of Malaria

Drug	Adult Dosage	Pediatric Dosage	Comments
Chloroquine-Sensitive Areas			
Chloroquine phosphate (drug of choice)	500 mg salt (300 mg base) orally once/wk	8.3 mg/kg salt (5 mg/kg base) once/wk, up to adult dose of 300 mg base	Begin 1-2 wk before exposure, continue during exposure, and continue for 4 wk after exposure May be used in pregnant women
Hydroxychloroquine sulfate	400 mg salt (310 mg base) orally once/wk	6.5 mg/kg salt (5 mg/kg base) orally once/wk	Begin 1-2 wk before exposure, continue during exposure, and continue for 4 wk after exposure An alternative to chloroquine for use only in areas with chloroquine-sensitive malaria
Chloroquine-Resistant Areas			
Atovaquone-proguanil	250 mg/100 mg (1 tablet) daily	5-8 kg: Pediatric tablet daily 9-10 kg: Pediatric tablet daily 11-20 kg: 1 Pediatric tablet daily 21-30 kg: 2 Pediatric tablets daily 31-40 kg: 3 Pediatric tablets daily >40 kg: 1 Adult tablet daily	Begin 1-2 days before exposure, continue during exposure, and continue for 7 days after exposure Pediatric tablets contain 62.5 mg atovaquone and 25 mg proguanil hydrochloride See text for contraindications
Mefloquine	250 mg salt (228 mg base) orally once/wk	≤9 kg: 5 mg/kg salt (4.6 mg/kg base) orally once/wk 10-19 kg: Tablet orally once/wk 20-30 kg: Tablet orally once/wk 31-45 kg: Tablet orally once/wk >45 kg: 1 Tablet orally once/wk	Begin 1-2 wk before exposure, continue during exposure, and continue for 4 wk after exposure
Or			
Doxycycline	100 mg daily	2.2 mg/kg/day up to 100 mg/day	Begin 1-2 days before exposure, continue during exposure, and for 4 wk after exposure; not to be used in children >8 yr or pregnant women
Or			
Alternative			
Primaquine	52.6 mg salt (30 mg base) orally daily	0.8 mg/kg salt (0.5 mg/kg base) up to adult dose orally daily	Begin 1-2 days before exposure, continue during exposure, and continue for 7 days after exposure Contraindicated in people with G6PD deficiency, in pregnancy, and during lactation Prophylaxis to areas principally with *P. vivax*
Tafenoquine (Krintafel)	300 mg tab once		Prevention of relapse of *P. vivax* 300 mg once

(From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.)

- Plasmapheresis is an option for parasitemia >30% or in pregnant women and in elderly with severe malaria.

NOTE: WHO recommends IV artesunate as the treatment of choice for severe malaria in adults and children in area of low transmission. Data on children in high-transmission regions are limited, and WHO recommends treatment with artesunate, artemether, or quinine.

MULTIDRUG-RESISTANT MALARIA:

- Mefloquine 1250 mg as a single dose, *or*
- Halofantrine 500 mg every 6 hr for 3 doses, repeat same course after 1 wk
- Combination therapy usually preferred

DISPOSITION

RISK FACTORS FOR FATAL MALARIA:

- Failure to take chemoprophylaxis
- Delay in seeking medical care
- Misdiagnosis

COMPLICATIONS OF MALARIA:

- Anemia
- Acidosis
- Hypoglycemia
- Respiratory distress
- Disseminated intravascular coagulation
- Blackwater fever
- Renal failure
- Shock

REFERRAL

- To an infectious disease specialist or travel medicine expert for severe malaria complications
- To an intensive care specialist if severe cerebral malaria or other major organ failure develops
- All malaria cases are mandated to be reported to local and state health departments by health care providers or laboratory staff

PEARLS & CONSIDERATIONS

HOST RESPONSE

- The specific immune response to malaria confers protection from high-level parasitemia and disease, but not from infection.
- Asymptomatic parasitemia without illness (premunition) is common among adults in endemic areas.
- Immunity is specific for both the species and the strain of infecting malarial parasites.
- Immunity to all strains is never achieved.
- Normal spleen function is an important host factor because of immunologic as well as filtering functions of the spleen.
- Both humoral and cellular immunity is necessary for protection.
- Polyclonal increase in serum level of immunoglobulin G (IgG), IgM, and IgA occurs in immune individuals.
- Antibody to antigenically variant protein PfEMP1 is important for protection in case of *P. falciparum* malaria.
- Passively transferred IgG from immune individuals has been shown to be protective.
- Maternal antibody confers relative protection of infants from severe disease.
- Genetic disorders (sickle cell disease, thalassemia, and G6PD deficiency) confer protection from death because parasites are unable to grow efficiently in low-oxygen tensions, thus preventing high-level parasitemias.
- Individuals deficient of Duffy factor in RBCs are resistant to infection by *P. vivax.*
- Nonspecific defense mechanisms, such as cytokines (TNF-α, IL-1, -6, -8), also play an important role in protection, causing fever (temperatures of 40° C damage mature parasites) and other pathologic effects.

PREVENTION OF MALARIA: Medications are available for the prophylaxis of malaria and will vary depending on level of chloroquine resistance in a given area (Table 5).

Areas free of chloroquine-resistant Falciparum malaria

Chloroquine 300 mg base (500 mg chloroquine phosphate) PO/wk. Start 1 wk prior to

TABLE 6 Sources for Malaria Prophylaxis, Diagnosis, and Treatment Recommendations

Type of Information	Source	Availability	Telephone Number, Internet Address, or Electronic Mail Address
Prophylaxis	CDC's Traveler's Health Internet site (includes online access to Health Information for International Travel)	24 hours/day	wwwnc.cdc.gov/travel
	(The Yellow Book)	Order from Oxford University Press, Inc. Order Fulfillment 198 Madison Avenue, New York, NY 10016-4314	800-451-7556 or www.oup.com/us/
	CDC's Malaria Branch Internet site with Malaria Information and Prophylaxis, By Country (Red Pages)	24 hours/day	www.cdc.gov/malaria/travelers/country_table/a.html
	CDC Malaria Map Application	24 hours/day	www.cdc.gov/malaria/map
Diagnosis	CDC's Division of Parasitic Diseases and Malaria diagnostic internet site (DPDx)	24 hours/day	www.cdc.gov/dpdx/index.html
	CDC's Division of Parasitic Diseases and Malaria diagnostic CD-ROM (DPDx)	Order by electronic mail from CDC Division of Parasitic Diseases and Malaria	dpdx@cdc.gov
Treatment	CDC Malaria Branch	9:00 A.M.–5:00 P.M. Eastern time, Monday–Friday	770-488-7788 or toll-free 855-856-4713*
	CDC Malaria Branch	5:00 P.M.–9:00 A.M. Eastern time on weekdays and all day weekends and holidays	770-488-7100* (This number is for the CDC's Emergency Operations Center. Ask a staff member to page the person on call for the Malaria Branch.) www.cdc.gov/malaria/diagnosis_treatment/treatment.html

CDC, Centers for Disease Control & Prevention.
*These numbers are intended for health care professionals only.
From Cullen KA et al: Malaria surveillance—United States, 2013, *MMWR Surveill Summ* 65:1-22, 2016.

arrival in malaria area, then weekly while there and for 4 wk on leaving malaria area. Pediatric dose: 8.3 mg/kg (5 mg/kg base). Alternatives for adults include atovaquone-proguanil (Malarone): 1 adult tablet per day starting 1 to 2 days prior to arriving in malaria area, then daily while there and then for 7 days daily on leaving malaria area. For children, atovaquone-proguanil pediatric tablets based on weight:

- 11 to 20 kg: 1 pediatric tablet
- 21 to 30 kg: 2 pediatric tablets
- 31 to 40 kg: 3 pediatric tablets
- 40 kg: 1 adult tablet

Areas with chloroquine-resistant Falciparum malaria

- Atovaquone-proguanil (Malarone): Dosing as previously
- Mefloquine 250 mg (228 mg base) PO/wk, starting 1 wk before arriving in malaria area, weekly while there and then weekly for 4 wk on return. In children, mefloquine dose is based on weight:
  1. <15 kg: 5 mg/kg
  2. 16 to 19 kg: ¼ adult dose
  3. 20 to 30 kg: ½ adult dose
  4. 31 to 45 kg: ¾ adult dose
  5. >45 kg: Adult dose
- Doxycycline 100 mg PO/day for adults and children aged >8. Start 1 to 2 days before travel, daily while in malaria area, and then daily for 4 wk on return.
- Tafenoquine (Arakoda, Krintafel) is a long-acting primaquine analog FDA approved in two different strengths for antiretroviral therapy (Krintafel) for P. vivax infection (300 mg single dose) and for chemoprophylaxis (Arakoda): Loading dose is 200 mg once/day for 3 days. Maintenance dose is 200 mg once/wk starting 7 days after last loading dose, terminal dose is 200 mg once (7 days after last maintenance dose).

SPECIAL CONSIDERATIONS:

- Long-term visitors or travelers
- Children aged <12 yr
- Immunocompromised host
- Pregnant women: Chloroquine and mefloquine are safe in pregnancy but not atovaquone-proguanil. A recent trial revealed that the burden of malaria in pregnancy was significantly lower among adolescent girls or women who received intermittent preventive treatment with dihydroartemisinin-piperaquine than among those who received sulfadoxine-pyrimethamine, and monthly treatment with dihydroartemisinin-piperaquine was superior to three-dose dihydroartemisinin-piperaquine with regards to several outcomes.[1] Avoid doxycycline and primaquine.
- An increasing number of areas in southeast Asia have mefloquine-resistant malaria, including Cambodia, Thailand, and Vietnam. Therefore, in specific regions of these countries, mefloquine cannot be used for prophylaxis or treatment.

PREVENTION OF RELAPSE[2]:

- Treatment of *P. vivax* requires the clearing of asexual parasites, but relapse can be prevented only if dormant hypnozoites are cleared from the liver (a treatment termed "radical cure")
- Tafenoquine, slowly eliminated, single dose 8-aminoquinoline is effective in significantly lowering the risk of *P. vivax* recurrence in patients with phenotypically normal GG PD activity

VACCINATION:

- In 2015, Mosquirix (RTS,S), a recombinant protein-based vaccine, was approved in Europe to prevent malaria in babies in Africa. It showed an efficacy of about 30% in babies 6 to 12 wk old and about 46% in babies 5 to 17 mo old.
- New DNA-based vaccines are in development.

MALARIA INFORMATION:

- CDC Travelers' Health Hotline (877) 394-8747; CDC Travelers' Health Fax (888) 232-3299
- CDC Malaria Epidemiology (770) 488-7788; internet: www.cdc.gov
- Table 6 summarizes sources for malaria prophylaxis, diagnosis, and treatment recommendations.

[1] Kakuru A et al: Dihydroartemisinin-piperaquine for the prevention of malaria in pregnancy, *N Engl J Med* 374:928-939, 2016.
[2] Lacerda MVG et al: Single-dose tafenoquine to prevent relapse of Plasmodium vivax malaria, *N Engl J Med* 380:215–218, 2019.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Malaria (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Cohee LM, Laufer MK: Malaria in children, *Pediatr Clin North Am* 64:851-866, 2017.

Daily JP: Malaria 2017: update on the clinical literature and management, *Pediatr Clin North Am* 19(28), 2017.

Freedman DO et al: Medical considerations before international travel, *N Engl J Med* 375:247-260, 2016.

Haston JC et al: Guidance for using tafenoquine for prevention and antirelapse therapy for malaria - United States, 2019, *MMWR* 68(46):1062-1068, 2019.

Johnson BA, Kalra MG: Prevention of malaria in travelers, *Am Fam Physician* 85(10):973-977, 2012.

Lacerda MVG et al: Single-dose tafenoquine to prevent relapse of *Plasmodium vivax* malaria, *N Engl J Med* 380:215-218, 2019.

Plewes K et al: Malaria: what's new in the management of malaria, *Infect Dis Clin North Am* 33:39-60, 2019.

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White NJ et al: *Malaria, Lancet* 383:723-735, 2014.

Wilson MK: Malaria rapid diagnostic tests, *Clin Infect Dis* 54(11):1637-1641, 2012.

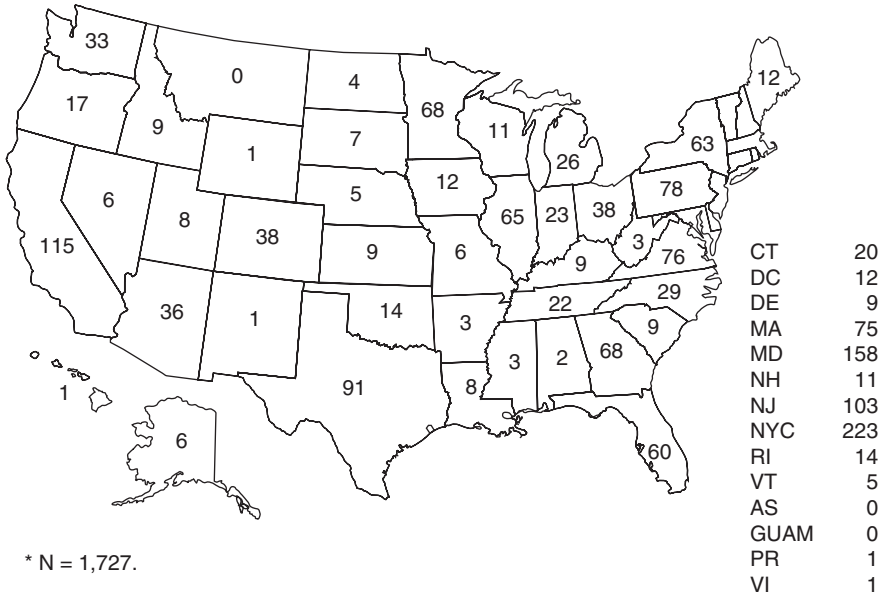

FIG. E1 Number of malaria cases, by state in which the disease was diagnosed—U.S., 2013. (Cullen KA et al: Malaria surveillance—United States, 2013, *MMWR Surveill Summ* 65:1-22, 2016.)

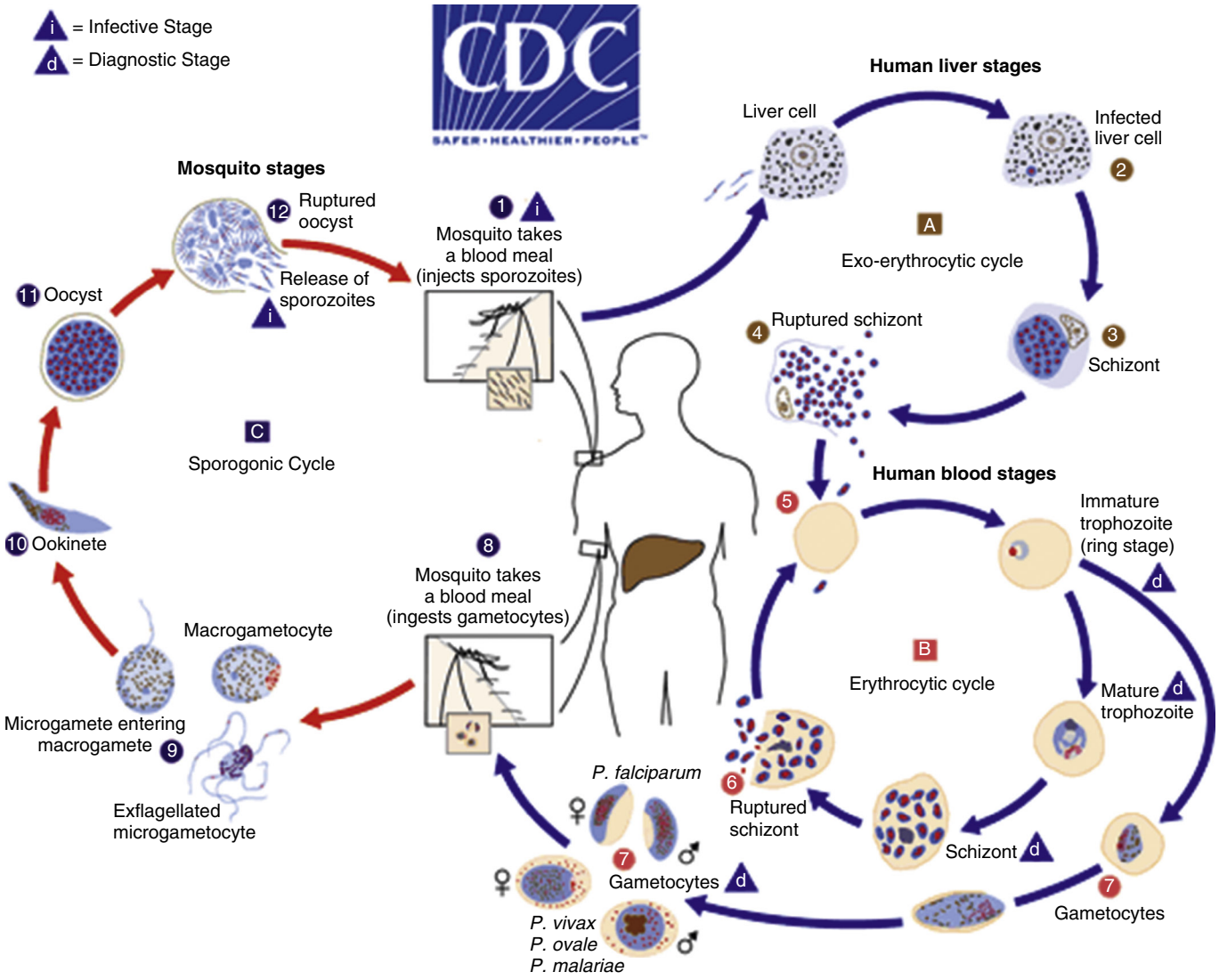

FIG. E2 Life cycle of human malaria parasites. The malaria parasite life cycle involves two hosts. During a blood meal, a malaria-infected female *Anopheles* mosquito inoculates sporozoites into the human host *(1).* Sporozoites infect liver cells *(2)* and mature into schizonts *(3),* which rupture and release merozoites *(4).* (Of note, in *P. vivax* and *P. ovale* a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream weeks, or even years, later.) After this initial replication in the liver (exo-erythrocytic schizogony *[A]*), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony *[B]*). Merozoites infect red blood cells *(5).* Ring stage trophozoites mature into schizonts, which rupture, releasing merozoites *(6).* Some parasites differentiate into sexual erythrocytic stages (gametocytes) *(7).* Blood stage parasites are responsible for clinical manifestations of the disease. The gametocytes, male (microgametocytes) and female (macrogametocytes), are ingested by an *Anopheles* mosquito during a blood meal *(8).* The parasites' multiplication in the mosquito is known as the sporogonic cycle *(C).* While in the mosquito's stomach, the microgametes penetrate the macrogametes, generating zygotes *(9).* The zygotes in turn become motile and elongated (ookinetes) *(10)* and invade the midgut wall of the mosquito, where they develop into oocysts *(11).* The oocysts grow, rupture, and release sporozoites *(12),* which make their way to the mosquito's salivary glands. Inoculation of the sporozoites *(1)* into a new human host perpetuates the malaria life cycle. (From Centers for Disease Control and Prevention. About Malaria: Biology; www.cdc.gov/malaria/about/biology/ in Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.)

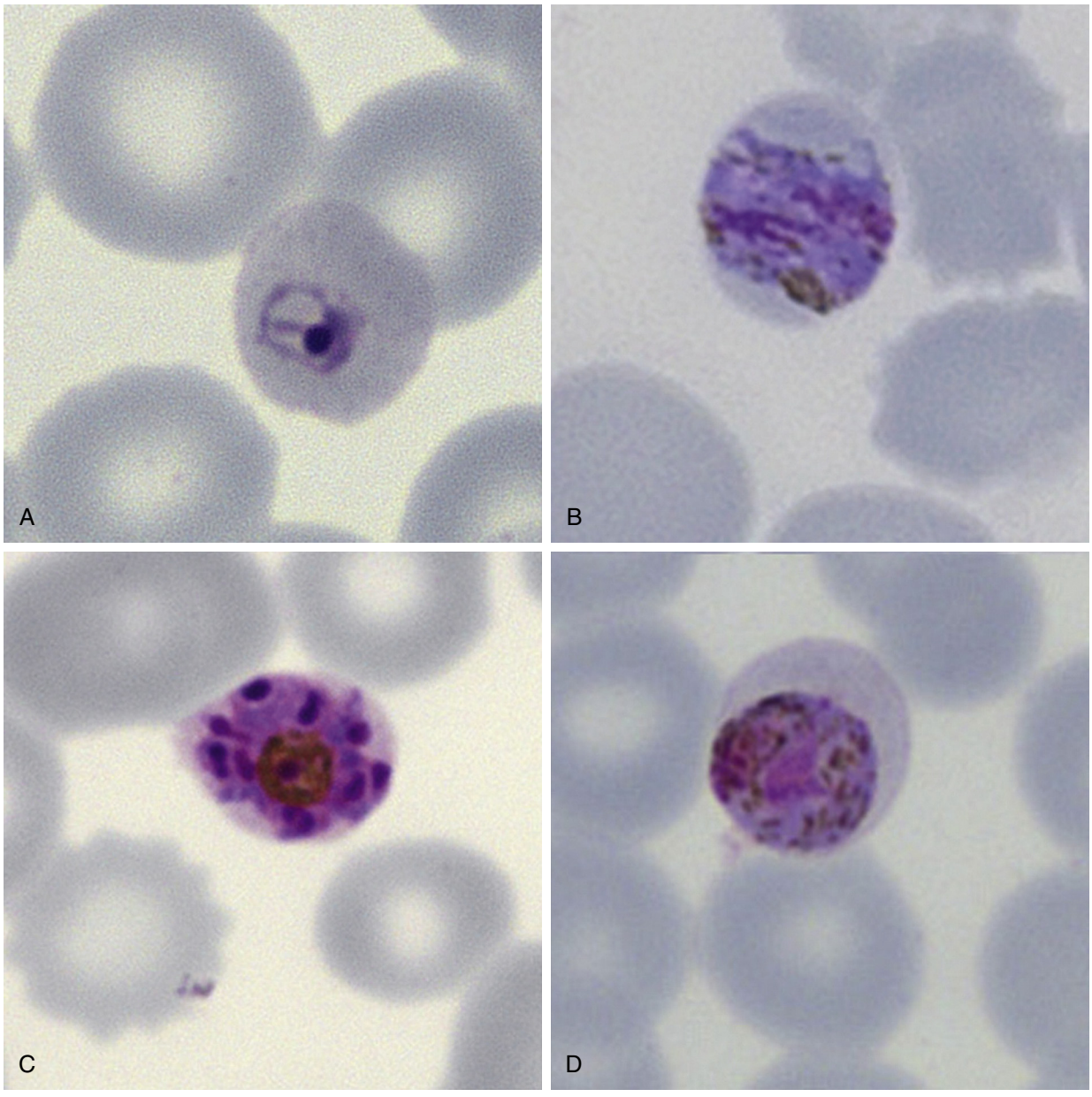

FIG. E3 Morphology of *P. malariae.* Early trophozoites **(A)** are small but less fine than those of *P. falciparum;* in this case the ring is irregular and the chromatin dot is within the main parasite cytoplasm. A late trophozoite **(B)** spans the erythrocyte as a thick "band form." A characteristic "daisy head" schizont **(C)** has eight merozoites arrayed around the central pigment. Finally, the gametocyte **(D)** is typically small and does not fill the normal-sized erythrocyte. (From Bain BJ et al: *Dacie and Lewis practical haematology*, ed 12, Philadelphia, 2017.)

BASIC INFORMATION

DEFINITION

Malignant hyperthermia (MH) is a rare life-threatening subclinical myopathy that can manifest clinical symptoms in MH-susceptible (MHS) individuals after exposure to triggering medications. These drugs include halogenated anesthetic gases, such as halothane, isoflurane, sevoflurane, and desflurane, as well as the depolarizing agent succinylcholine. When given to genetically susceptible individuals, these agents may cause excessive skeletal muscle contraction. Initial signs include rising end-tidal carbon dioxide ($ETCO_2$) levels and tachycardia, with subsequent hyperthermia, acidemia, and skeletal muscle rigidity. Symptomology may be variable, especially during surgery and general anesthesia. Mortality has recently been reported to be 1.4% to 5%, down from 70% in the past, likely due to the prevalence of intraoperative temperature and $ETCO_2$ monitoring and the use of dantrolene for treatment.

SYNONYMS

Anesthesia related hyperthermia
Hyperpyrexia, Malignant
Hyperthermia, Malignant
Malignant Hyperpyrexia
MHS
MH

ICD-10CM CODES	
T88.3	Malignant hyperthermia due to anesthesia
T88.3XXA	initial encounter
T88.3XXD	subsequent encounter
T88.3XXS	sequelae

EPIDEMIOLOGY & DEMOGRAPHICS

Malignant hyperthermia results from excess calcium accumulation in the skeletal muscle tissue of MHS individuals following exposure to one or more "triggering" medications, including halogenated volatile anesthetics and the skeletal muscle relaxant, succinylcholine. This is due to excessive release of sarcoplasmic calcium, which occurs because of a genetic anomaly. The result is a hypermetabolic and prolonged contractile state, with subsequent serious morbidity and possible mortality, especially when untreated. A recent study comparing human muscle fiber mitochondria from non-MHS patients to those from MHS patients found that mitochondria from MHS patients displayed anatomic and physiologic differences when exposed to halothane, while the non-MHS fibers did not.

All ethnic groups are at risk. MH susceptibility is associated with, although distinct from, two other diseases, central core and multiminicore disease.

PREVALENCE: In the general population, between 1:2000 to 1:3000 are thought to carry a defective gene for the ryanodine receptor. However, the prevalence of MHS is estimated to be 1:2000. In family cohorts of patients who are susceptible, the prevalence of susceptibility ranges from 1:200 to 1:5000 due to incomplete penetrance and variable expressivity. The majority of these MHS individuals are never exposed to a triggering agent such that a MH clinical event following exposure occurs with a frequency between 1:15,000 to 1:75,000.

PREDOMINANT SEX AND AGE: MH male to female ratio is 2:1. Children account for up to half of cases.

PEAK INCIDENCE: Among patients undergoing general anesthesia, the incidence is approximately 1:100,000. It is widely believed that unrecognized events occur and that half of afflicted patients have had a prior uneventful exposure to a triggering agent.

RISK FACTORS:

- Preoperatively, the patient and family history is used to evaluate the risk of MH and other myopathies. Patients with other *RYR1* abnormalities, such as central core myopathy or multiminicore disease (*RYR1* or *SELENON*), though not true MHS, should not receive succinylcholine or volatile anesthetics.
- Patients with dystrophinopathies such as Duchenne and Becker muscular dystrophy, enzymopathies of skeletal muscle such as McArdle disease, or exercise- and heat-induced rhabdomyolysis, may develop rhabdomyolysis when exposed to these agents, especially succinylcholine.
  1. This pathophysiology, though different from that of MH, may result in similar signs such as hyperkalemia-induced peaked T waves on the ECG, along with acidosis.
  2. However, it is important to understand that dantrolene is unlikely to be of value in treating these causes of rhabdomyolysis.
  3. Osteogenesis imperfecta, myotonia, and neuroleptic malignant syndrome are no longer believed to be associated with MHS.
- Increased muscle mass, especially in bodybuilders, appears to be an independent predictor of increased susceptibility to, recurrence of, and death from MH episodes. This finding is independent of the increased incidence in males noted above. Advanced age, muscularity, comorbidities, and disseminated intravascular coagulation (DIC) increase the risk of death.

GENETICS: Susceptibility to MH is due to at least six known genetic variations of MH, all of which are inherited in an autosomal dominant pattern. The most common is a mutation of the ryanodine receptor *RYR1,* causing MHS1. A *CACNA1S* mutation causes another form, *MHS5*. Other types are much less common, and in some cases (a *CACNA2D* mutation and *RYR1*) may interact (*MHS3*). Of note, patients with genetic susceptibility to MH may have an uneventful anesthesia while receiving known triggering agents; previous exposure does not exclude the possibility of a future MH crisis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Within minutes to hours after a triggering agent is administered, the patient may develop muscle rigidity, with resulting tachypnea and tachycardia. In the operating room, MH is often difficult to recognize, and rigidity may be attributed to inadequate sedation or absent due to general anesthesia and muscle paralysis. Vital sign perturbations may be missed due to ongoing surgery.
- Masseter muscle rigidity is rare now that succinylcholine is used rarely for muscle relaxation and is not related to MHS.
- Manifestations of increased skeletal muscle metabolism include increased CO_2 production, leading to elevated mixed venous and arterial pCO_2, and an elevated $ETCO_2$; tachycardia is common.
- Hyperthermia or a rapidly increasing temperature from an anesthesia-induced hypothermic state, also a result of hypermetabolism, is present in more than 50% of MH events.
  1. Hyperthermia is not always present early in MH crisis, eliminating increasing core body temperature as a definitive inclusion factor in diagnosing MH at an early stage.
  2. Higher core body temperature correlates with increased morbidity.
- Muscle injury with an elevated creatine kinase (CK) may lead to rhabdomyolysis, observed myoglobinuria (if a urinary catheter is present), and subsequent acute renal failure. DIC may develop.
- The skin may be erythematous initially, progressing to a mottled, cyanotic appearance.
- Box 1 summarizes the findings consistent with MH.

ETIOLOGY: Approximately 50% of cases of MH susceptibility (MHS) are inherited (primarily MH1 and MH5); the remainder are presumed to be the result of a new mutations. The majority of the mutations, either inherited or de novo, are on chromosome 19 (19q13.2, with at least 35 variants), but other mutations may be found at 1q32.1 (*CACNA1S* with at least five variants), 17q11.2-q24, 7q21.2, 3q13.1, or 5p. The result is the abnormality of skeletal muscle calcium homeostasis and susceptibility to MH, with significant clinical variability due to incomplete penetrance and variable expressivity.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Exertional heatstroke
- MH symptomology following excessive heat exposure to a MHS patient who did not receive a triggering agent
- Neuroleptic malignant syndrome
- Fever
- Thyrotoxicosis
- Pheochromocytoma
- Central nervous system infection or space-occupying lesion
- MDMA (Ecstasy), cocaine, alcohol withdrawal, or amphetamine use
- Serotonin syndrome
- Adverse reaction to monoamine oxidase inhibitors or anticholinergic drug
- Strychnine poisoning
- Sepsis

BOX 1 Positive Findings Consistent with Malignant Hyperthermia (MH)

History of recent exposure to trigger agent, including volatile anesthetic agents or succinylcholine
Family or personal history of MH susceptibility
Total body rigidity
Inappropriately elevated (38.8° C; 101.8° F) or rapidly increasing temperature (>1.5° C over 5 min)
Inappropriate tachypnea
Profuse sweating
Mottled, cyanotic skin
Dark urine, urine dipstick testing shows a positive result from blood without red cells in the sediment and no hemolysis
Unexplained, excessive bleeding
Unexplained ventricular tachycardia or fibrillation
Inappropriate hypercarbia (venous $Paco_2$ >65 mm Hg, arterial $Paco_2$ >55 mm Hg) if the patient is receiving positive-pressure ventilation or is spontaneously breathing with greater than normal minute ventilation
Arterial base excess more negative than –8 mEq/L
Arterial pH <7.25
Potassium concentration >6 mEq/L
Creatine kinase >10,000 IU/L

From Fuhrman BP et al: *Pediatric critical care*, ed 4, Philadelphia, 2011, Saunders.

- Drug withdrawal
- Rhabdomyolysis
- Transfusion reactions

WORKUP

- MH can often be distinguished from other causes of hyperthermia based on a history of exposure to a triggering agent.
- A rapid rise in $ETCO_2$ with no change in minute ventilation, especially in the setting of tachycardia, should prompt consideration of MH until proven otherwise.

LABORATORY TESTS

Considerations for laboratory testing fall into three scenarios:

- In the acute setting, electrolytes, arterial blood gas, and urine myoglobin to help confirm the diagnosis.
- Once the diagnosis is presumptive, it is important to monitor serial lab data including
  1. Blood gases
  2. Electrolytes, especially potassium and creatinine
  3. Creatine kinase
  4. Urine myoglobin
  5. Coagulation studies to evaluate for DIC
- If hyperthermia is less acute or the presentation atypical, thyroid function studies, CBC, toxicology screen, and urine vanillylmandelic acid (VMA) may be useful. Treatment should not be delayed while these labs are pending.

IMAGING STUDIES

A CT scan of the head may be obtained to evaluate for space-occupying lesion if clinically indicated. Imaging should never delay prompt treatment of strongly suspected MH.

SUSCEPTIBILITY TESTING:

- Testing for MH susceptibility involves genetic evaluation or the *in vitro* muscle contracture test.
  1. The *in vitro* muscle contracture test involves placing a muscle biopsy specimen in a bath of caffeine or halothane. Significant muscle contraction is 97% to 99% sensitive for MH susceptibility, with a specificity of 78% to 94% and a cost of $6 to $10,000. It is performed in only a few sites in the U.S.
  2. Genetic testing, while noninvasive, has a sensitivity of <50% and a cost of $1000 to $4000.
  3. Generally, a positive contracture test leads to genetic testing, unless there is a positive family history, in which case the patient may choose genetic testing directly.
- Testing for MHS can be performed preoperatively in patients deemed to be at risk or those with a personal or family history of anesthesia-induced complications suggestive of MH.
  1. Depending on the wishes of the patient and/or family following a thorough history and counseling, a decision to proceed with anesthesia and surgery without prior testing may be reasonable, with the avoidance of volatile agents or succinylcholine.
  2. In such a case, the patient should be counseled that forgoing testing may place them at risk if an intubation is required in an emergency setting, succinylcholine is used unknowingly, and the patient is truly MHS.
- After an acute event, the patient should undergo susceptibility testing to confirm the diagnosis and the need for testing other immediate family members at risk. If positive, the patient should be given a letter and wear a medical alert bracelet.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- The patient should be cooled to 38° C. This can be accomplished with ice packs to the axillae and groin, a cooling blanket, a fan with cool mist, or chilled IV fluids. In extreme situations, partial extracorporeal bypass or iced peritoneal lavage have proven helpful.
- Frequent evaluation of core temperature, hemodynamics, and gas exchange are imperative.

ACUTE GENERAL Rx (SEE BOX 2)

- Notify the surgeon to stop surgery immediately. Discontinue all triggering agents and switch to nontriggering agents if surgery must be continued.
- Get dantrolene and your hospital's MH cart; call for help.
- Hyperventilate with 100% oxygen at flows of 10 L/min to flush volatile anesthetics and decrease $ETCO_2$. Insert charcoal filters, if available, into the inspiratory and expiratory limb of the breathing circuit to further absorb agent.
- Administer dantrolene as a rapid IV bolus at a dose of 2.5 mg/kg through a large bore catheter. Repeat every five minutes until an observable decrease is seen in muscle rigidity, tachycardia, or $ETCO_2$; a total dose greater than 10mg/kg may be required, especially in patients with greater muscle mass.
- Up to 25% of patients will have recrudescence of their symptoms, on average 13 hours after the initiation of MH. Dantrolene, 1mg/kg IV every 4 to 6 hours or by continuous infusion at 0.1 to 0.3 mg/kg/hr IV, is recommended for at least 24 to 48 hours. Additional boluses may be needed for breakthrough signs.
- Recently, one study suggested that in at least one MH model involving the RyR receptor, dantrolene treatment may be ineffective in the setting of insufficient levels of cytoplasmic Mg^{++}. MgATP hydrolysis, a process that normally increases Mg^{++} during contraction, by itself may be insufficient to raise the Mg^{++} concentration in the setting of low resting Mg^{++} levels, thereby preventing dantrolene from being effective.
- Aggressive hydration with forced diuresis and alkalization of the urine should be instituted for rhabdomyolysis. Observe closely for the development of compartment syndrome, renal failure, and DIC. Beta-blockers and lidocaine may be useful for dysrhythmias. Use of calcium channel blockers should be avoided, as the combination with dantrolene may produce profound hyperkalemia and significantly depress cardiac function.

CHRONIC Rx

- MH is an acute disease, resolving in 24 to 48 hours with appropriate treatment.
- The MHS patient should be aware that exercise in excessive heat and/or humidity could trigger an episode of MH without exposure to a pharmacologic triggering agent.
- The patient as well as immediate family members should be advised to undergo susceptibility testing.
- The patient should be given a letter by his/her anesthesiologist and wear a medical alert bracelet.

BOX 2 Management of an Acute Malignant Hyperthermia Episode in the Intensive Care Unit

1. Administer high-flow 100% oxygen via a nonrebreathing mask and consider endotracheal intubation.
2. For ventilated patients, administer an FiO_2 of 1.0 and increase minute ventilation to control $PaCO_2$.
3. Administer dantrolene (2.5 mg/kg intravenously) over 10 min, and repeat until acidosis and muscle rigidity have resolved. Repeat dantrolene (1 mg/kg) every 6 hr.
4. Initiate cooling with ice packs in the axillae and groin; decrease room temperature; use hypothermia blankets, iced intravenous saline solution (10 ml/kg over 10 min, repeated as needed), and lavage body cavities with cold saline solution if temperature is greater than 39° C. Stop cooling when core temperature falls to 38° C.
5. Correct metabolic acidosis with sodium bicarbonate (1 to 2 mEq/kg initially), and give subsequent doses based on base excess and body weight.
6. Administer calcium chloride (10 mg/kg) or calcium gluconate (100 to 200 mg/kg) for cardiotoxicity associated with hyperkalemia.
7. Give regular insulin (0.1 U/kg) and glucose (0.3 to 0.5 g/kg) to correct hyperkalemia.
8. Administer lidocaine (1 mg/kg) to treat ventricular arrhythmias. Consider amiodarone (5 mg/kg IV) for refractory, stable ventricular tachycardia. Do not delay defibrillation or cardiopulmonary resuscitation if indicated by cardiovascular instability.
9. Maintain urine output of 2 ml/kg/hr with aggressive cold fluid administration, furosemide (0.5 to1 mg/kg), and additional mannitol (0.25 to 0.3 g/kg) if needed.
10. Consider quantitative end-tidal CO_2 monitoring.
11. Monitor core temperature (pulmonary artery, esophageal temperature probe, rectal probe).
12. Place arterial catheter for invasive blood pressure monitoring and frequent blood sampling. Consider central venous catheter and/or pulmonary artery catheter if indicated by cardiovascular instability.
13. Repeat venous blood gas and electrolytes until these normalize. Repeat CK at least every 6 hr while the patient is in ICU and then daily until CK returns to normal. Assess glucose, clotting function, and hepatic and renal functions, and treat symptomatically. Repeat lactic acid measurement after each dantrolene administration.
14. Consider hemodialysis if indicated.
15. Consider intensive care monitoring for at least 24 hr after MH episode or after recrudescence of MH.
16. Refer the patient for muscle caffeine-halothane contracture testing and consider genetic testing. Pursue a pathologic diagnosis for other occult myopathies.

CK, Creatine kinase; *ICU,* intensive care unit; *MH,* malignant hyperthermia.
From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

BOX 3 Anesthetics Associated with the Development of Malignant Hyperthermia and Neuroleptic Malignant Syndrome

Malignant Hyperthermia
Volatile Anesthetics
Desflurane, isoflurane, sevoflurane

Muscle Relaxants
Succinylcholine

Neuroleptic Malignant Syndrome
Phenothiazines
Fluphenazine, chlorpromazine, levomepromazine, thioridazine, trimeprazine, trifluoperazine, prochlorperazine

Butyrophenones
Haloperidol, bromperidol, droperidol
Dibenzoxazepine
Loxapine

Dopamine-Depleting Drugs
Alpha-methyltyrosine, tetrabenazine

Dopaminergic Agent Withdrawal
Levodopa-carbidopa, amantadine

Modified from Parrillo JE, Dellinger RP: *Critical care medicine: Principles of diagnosis and management in the adult*, ed 4, Philadelphia, 2014, Saunders.

COMPLEMENTARY & ALTERNATIVE MEDICINE

None

DISPOSITION

After MH crisis, patients should be admitted to the intensive care unit for at least 24 hrs where close monitoring and supportive care can be maximized.

REFERRAL

Anesthesiology, cardiology, nephrology, and hematology consultation as appropriate. After the acute event, a genetics consult may be warranted to facilitate testing

PEARLS & CONSIDERATIONS

COMMENTS

- MH is a life-threatening condition that requires prompt recognition to minimize illness, end-organ damage, and/or death.
- Family or personal history of problems with general anesthesia in the past are clues to susceptibility and should prompt careful preoperative evaluation.
- Prophylactic dantrolene is no longer recommended for known MHS patients undergoing general anesthesia with nontriggering agents.
- Box 3 summarizes anesthetics associated with the development of malignant hyperthermia and neuroleptic malignant syndrome.

PATIENT & FAMILY EDUCATION

- The patient and his/her family should be made aware of the diagnosis so that they can provide information to the anesthesiologist and other intraoperative caregivers when undergoing any type of surgery or procedure under sedation.
- The patient should be given a letter that can be shown to future care givers.
- A medical alert bracelet should be recommended.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Eveline Mordehai, MD,** and **Richard Gillerman, MD, PhD**

SUGGESTED READINGS

Butala B et al: Muscular body build and male sex are independently associated with malignant hyperthermia susceptibility, *Can J Anesthesia* 64:396, 2017.

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Riazi S et al: Updated guide for the management of malignant hyperthermia, *Can J Anesth* 65(6):709-721, 2018.

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Mallory-Weiss Tear PTG ALG

BASIC INFORMATION

DEFINITION

A Mallory-Weiss tear (MWT) is a longitudinal mucosal laceration in the region of the gastroesophageal junction and gastric cardia typically occurring after repeated episodes of severe vomiting or retching.

SYNONYMS

Mallory-Weiss syndrome
MWT

ICD-10CM CODE
K22.6 Mallory-Weiss syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- Accounts for 5% to 15% of cases of upper gastrointestinal (GI) bleeding
- Reported from early childhood to old age; the majority of patients are age 40 to 60 yr
- More common in males
- Alcohol use is present in 30% to 60%

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Vomiting, retching, or vigorous coughing will often, but not always, precede hematemesis.
- Patients may be clinically stable or present with tachycardia, hypotension, melena, hematochezia, epigastric pain, back pain, syncope, or hemorrhagic shock.
- Bleeding may be self-limited or severe. Rebleeding is more common in patients with advanced alcoholic liver disease.
- Tears may be seen in association with other upper GI tract lesions, including hiatal hernia (present in as many as 90% of patients), ulcers, and esophageal varices, particularly in alcoholics.

ETIOLOGY

- An acute increase in intragastric and intraabdominal pressure is transmitted to the gastroesophageal junction and esophagus, resulting in mucosal laceration.
- Vomiting may be associated with alcohol use, cannabinoid use, ketoacidosis, ulcer disease, uremia, pancreatitis, chemotherapy, cholecystitis, pregnancy (in particular associated with hyperemesis gravidarum), bulimia, myocardial infarction, or the postoperative period.
- Infrequently reported causes include chest wall trauma (including CPR), hiccups, coughing, seizures, lifting/straining, blunt abdominal trauma, acute severe asthma, labor and delivery, and even primal scream therapy.
- Tears may be iatrogenic, related to routine endoscopy (especially in struggling, retching, or older patients, or in association with hiatal hernias or distal gastrectomy), enteroscopy with or without overtubes, esophageal dilation, lower esophageal pneumatic disruption therapy for achalasia, endoscopic submucosal dissection, transesophageal echocardiography, or in association with polyethylene glycol electrolyte colonic lavage preparation.
- Tears are frequently found on the right lateral wall of the esophagus.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Esophageal or gastric varices
- Esophagitis or esophageal ulcers (peptic or pill-induced)
- Gastric erosions
- Gastric or duodenal ulcer
- Dieulafoy lesion
- Arteriovenous malformations
- Neoplasms (usually gastric)
- Boerhaave syndrome

WORKUP

Endoscopy is the diagnostic method of choice.

LABORATORY TESTS

- Complete blood count, prothrombin time, partial thromboplastin time
- Electrolytes, blood urea nitrogen, creatinine, liver function tests, pregnancy test, tests to evaluate for predisposing conditions

IMAGING STUDIES

- Upper GI series is usually not sensitive.
- Patients with concurrent chest pain, dyspnea, shock, or physical examination findings of crepitus or pleural effusion should have a chest radiograph or CT to exclude Boerhaave syndrome.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive care
- Avoidance of aspirin, nonsteroidal antiinflammatory drugs, and anticoagulants

ACUTE GENERAL Rx

- Patients with active bleeding or hemodynamic instability require large-bore IVs, fluid resuscitation, transfusion of blood products (red blood cells, fresh frozen plasma, platelets) and holding or reversal of anticoagulation as appropriate.
- Nasogastric decompression and antiemetics may be considered.
- Endoscopic therapy for patients with active or ongoing hemorrhage (Fig. E1). Therapeutic modalities include electrocoagulation, argon plasma photocoagulation, heater probe coagulation, injection (e.g., 1:10,000 epinephrine, polidocanol), sclerotherapy (for bleeding associated with esophageal varices), band ligation, endoscopic hemoclips (Fig. E2), over-the-scope clips, and hemostatic sprays (therapies may be used alone or in combination) (Fig. E3). Hemoclips combined with a nylon snare ("tulip-bundle" technique) have been successfully used for refractory bleeding.
- Arterial embolization in patients with active bleeding who are poor surgical candidates.
- Laparotomy, with gastrotomy and oversewing of the tear, is required in a small percentage of patients with uncontrolled bleeding.

CHRONIC Rx

- Healing will usually occur without specific therapy.
- H_2 blockers or proton pump inhibitors may be given to help facilitate healing but should not be used long term unless appropriate indications are present.

DISPOSITION

- Prognosis is good, with spontaneous cessation of bleeding in upward of 90% of patients. Endoscopic features can guide treatment. Blatchford score <6 suggests no need for transfusion or endoscopic intervention.
  1. Blatchford score is calculated by certain indices (sex, blood urea nitrogen, hemoglobin, systolic blood pressure, pulse, and the presence of melena, syncope, hepatic disease, or cardiac failure) and is used to determine which patients need clinical intervention for acute upper gastrointestinal bleeding.
- Delayed rebleeding is described in patients with high-risk stigmata (shock at initial presentation, spurting, or oozing at initial endoscopy).
- Death has been reported in 3% to 12%, often in association with severe bleeding and underlying comorbid conditions such as advanced age, coagulopathy, elevated transaminases, thrombocytopenia, alcohol use, presentation with a very low hemoglobin level or melena, and multi-system organ failure. Over the past decade, associated mortality appears to be significantly declining.

REFERRAL

- Gastrointestinal referral for endoscopy
- Surgical referral for bleeding unresponsive to endoscopic treatment or in the setting of coexistent perforation

PEARLS & CONSIDERATIONS

Conditions predisposing to retching or vomiting should be identified and treated at presentation.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Mallory-Weiss Tear (Patient Information)

AUTHOR: **Harlan G. Rich, MD, FACP, AGAF**

SUGGESTED READINGS

Kim HS: Endoscopic management of Mallory-Weiss tearing, *Clin Endosc* 48: 102-105, 2015.

Ljubičić N et al: Mortality in high-risk patients with bleeding Mallory-Weiss syndrome is similar to that of peptic ulcer bleeding. Results of a prospective database study, *Scand J Gastroenterol* 49(458), 2014.

Na S et al: Risk factors for an iatrogenic Mallory-Weiss tear requiring bleeding control during a screening upper endoscopy, *Gastroenterol Res Pract* 1-6, 2017.

Nojkov B, Cappell MS: Distinctive aspects of peptic ulcer disease, Dieulafoy's lesion, and Mallory-Weiss syndrome in patients with advanced alcoholic liver disease or cirrhosis, *World J Gastroenterol* 22:446-466, 2016.

Wuerth BA, Rockey DC: Changing epidemiology of upper gastrointestinal hemorrhage in the last decade: a nationwide analysis, *Dig Dis Sci* 63:1286-1293, 2018.

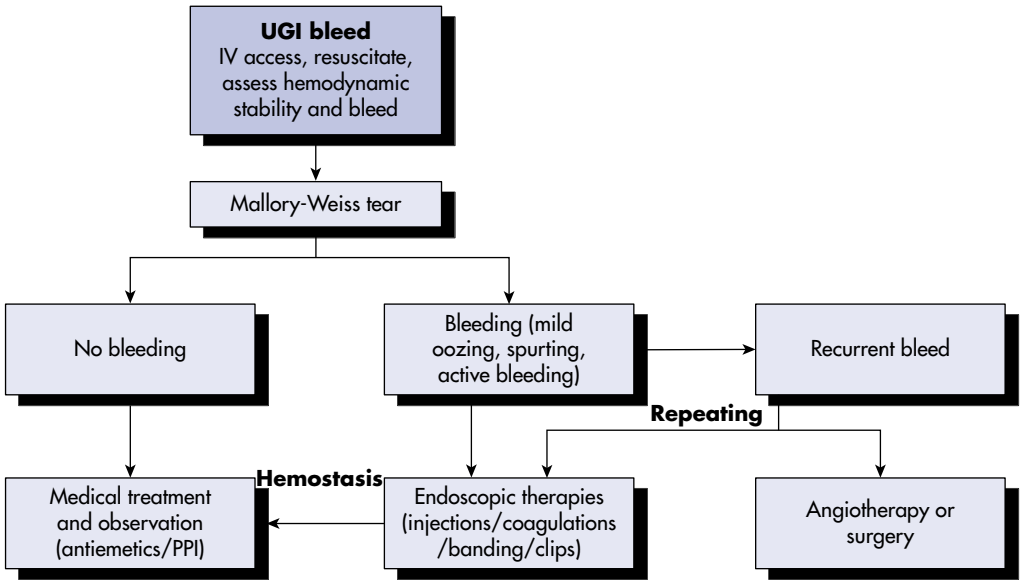

FIG. E1 Treatment algorithm for Mallory-Weiss syndrome. *IV,* Intravenous; *PPI,* proton-pump inhibitor; *UGI,* upper gastrointestinal. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

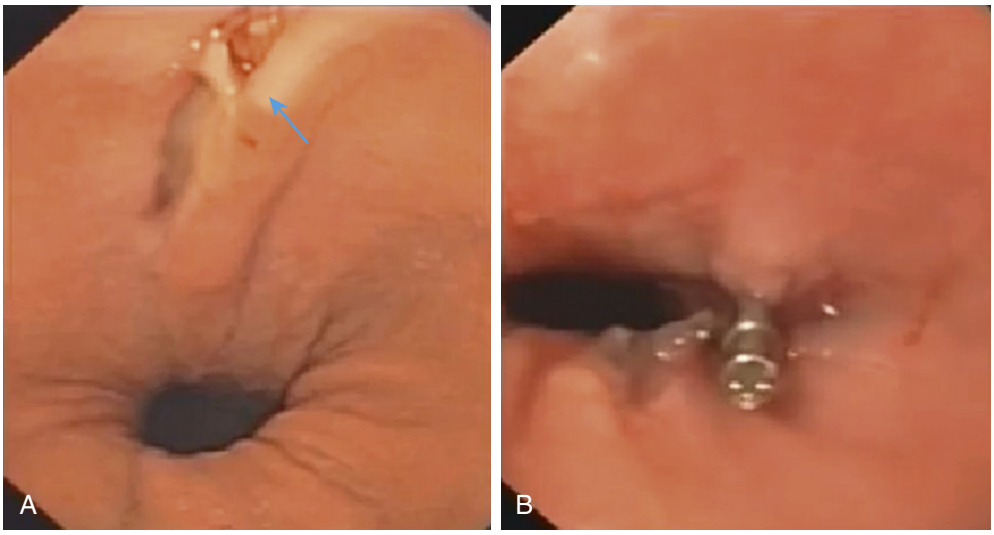

FIG. E2 A, Endoscopic view of a Mallory-Weiss tear (*blue arrow*) at the gastroesophageal junction. **B,** After hemoclip deployed at the lesion with good hemostasis. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

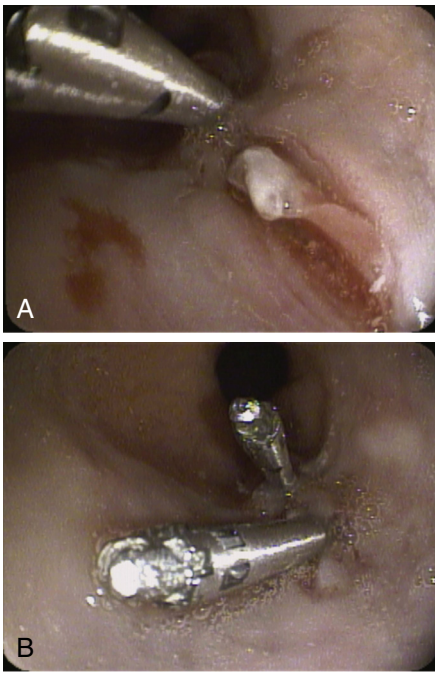

FIG. E3 Mallory-Weiss tear. A and **B,** Endoscopic views of Mallory-Weiss tear being treated with hemoclips. (Courtesy Isaac Raijman, MD, Associate Professor, Baylor College of Medicine. From Cameron JL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, WB Saunders.)

BASIC INFORMATION

DEFINITION

Marfan syndrome (MFS) is an inherited disorder of connective tissue involving the skeleton, cardiovascular system, eyes, lungs, and central nervous system.

SYNONYM

MFS

ICD-10CM CODES

Q87.40	Marfan syndrome, unspecified
Q87.410	Marfan syndrome with aortic dilation
Q87.418	Marfan syndrome with other cardiovascular manifestations
Q87.42	Marfan syndrome with ocular manifestations
Q87.43	Marfan syndrome with skeletal manifestation

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- One case per 10,000 persons.
- Both sexes are affected equally by this autosomal-dominant syndrome.
- Approximately 30% of cases are a new mutation.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Diagnostic criteria for MFS (Table E1):

- Skeleton: Joint hypermobility (Fig. E1), tall stature (Fig. E2A), pectus excavatum, reduced thoracic kyphosis, scoliosis, arachnodactyly (Fig. E2B), dolichostenomelia, pectus carinatum, and erosion of the lumbosacral vertebrae from dural ectasia
- Eye: Myopia, retinal detachment, elongated globe, ectopia lentis
- Cardiovascular: Mitral valve prolapse, endocarditis, arrhythmia, dilated mitral annulus, mitral regurgitation, tricuspid valve prolapse, aortic regurgitation, aortic dissection, dilation of the aortic root
- Pulmonary: Apical blebs, spontaneous pneumothorax
- Skin and integument: Inguinal hernias, incisional hernias, striae atrophicae
- Central nervous system: Attention deficit disorder, hyperactivity, verbal-performance discrepancy, dural ectasia, anterior pelvic meningocele

If the family history is positive for a close relative clearly affected by MFS, manifestations should be present in the skeleton and one of the other organ systems and the diagnosis confirmed by linkage analysis or mutation detection.

If the family history is negative or unknown, the patient should have manifestations in the skeleton, the cardiovascular system, and one other system and at least one of the manifestations indicated by an asterisk in the previous lists.

Manifestations are listed within each organ system in increasing specificity for MFS; although none is completely specific, those indicated by an asterisk are the most specific.

ETIOLOGY

Mutations in the gene that encodes fibrillin-1 (FBN_1), the major constituent of microfibrils, which form the frame for elastic fibers. All the manifestations of MFS can be explained by the defective microfibrils.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Each of the clinical manifestations of the syndrome may have other causes; however, if the diagnostic criteria are met, the diagnosis is made. Table E2 summarizes the differential diagnosis of Marfan syndrome.

WORKUP

- MFS diagnosis is made clinically, with genetic consultation if necessary
- Echocardiography to establish:
  1. Mitral valve prolapse
  2. Mitral regurgitation
  3. Tricuspid valve prolapse
  4. Aortic regurgitation
  5. Dilation of the aortic root
- Echocardiography should be repeated 6 mo after initial diagnosis to evaluate for rate of aortic diameter enlargement

TABLE E1 Diagnostic Criteria for Marfan Syndrome

In the absence of a family history of MFS, a diagnosis can be reached in one of four scenarios:
1. Aortic diameter at Sinuses of Valsalva Z-score ≥2 AND Ectopia Lentis = MFS*
2. Aortic diameter at Sinuses of Valsalva Z-score ≥2 AND *FBN1* mutation = MFS
3. Aortic diameter at Sinuses of Valsalva Z-score ≥2 AND Systemic Score ≥7 = MFS*
4. Ectopia Lentis AND *FBN1* mutation known to associate with aortic aneurysm = MFS

In the absence of a family history of MFS, alternative diagnoses include:
1. Ectopia lentis, 6 Systemic Score, AND *FBN1* mutation not known to associate with aortic aneurysm or no *FBN1* mutation = Ectopia lentis syndrome
2. Aortic diameter at sinuses of Valsalva Z-score >2 AND systemic score 2:5 (with at least one skeletal feature) without ectopia lentis = MASS phenotype
3. Mitral valve prolapse AND aortic diameter at sinuses of Valsalva Z-score <2 AND Systemic Score <5 without ectopia lentis = mitral valve prolapse syndrome

In the presence of a family history of MFS, a diagnosis can be reached in one of three scenarios:
1. Ectopia lentis AND family history of MFS = MFS
2. Systemic Score ≥7 AND family history of MFS = MFS*
3. Aortic diameter at sinuses of Valsalva Z-score ≥2 if older than 20 yr or ≥3 if younger than 20 yr AND family history of MFS = MFS*

Scoring of Systemic Features (in points)†

Wrist AND thumb sign = 3 (wrist OR thumb sign = 1)

Pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = 1)

Hindfoot deformity = 2 (plain pes planus = 1)

Pneumothorax = 2

Dural ectasia = 2

Protrusio acetabuli = 2

Reduced US/LS AND increased arm/height AND no severe scoliosis = 1

Scoliosis or thoracolumbar kyphosis = 1

Reduced elbow extension = 1

Facial features (3/5) = 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)

Skin striae = 1

Myopia >3 diopters = 1

Mitral valve prolapse (all types) = 1

Criteria for causal *FBN1* mutation

Mutation previously shown to segregate in a Marfan family

Any one of the following *de novo* mutations (with proven paternity and absence of disease in parents):

Nonsense mutation

In-frame and out-of-frame deletion/insertion

Splice site mutations affecting canonical splice sequence or shown to alter splicing on mRNA/cDNA level

Missense mutation affecting/creating cysteine residues

Missense mutation affecting conserved residues of the EGF consensus sequence [(D/N)X(D/N)(E/Q)Xm(D/N)Xn(Y/F), with m and n representing variable number of residues; D, aspartic acid; N, asparagine; E, glutamic acid; Q, glutamine; Y, tyrosine; F, phenylalanine]

Other missense mutations: Segregation in family, if possible, + absence in 400 ethnically matched control chromosomes; if no family history, absence in 400 ethnically matched control chromosomes

Linkage of haplotype for n≥6 meioses to the *FBN1* locus

*Without discriminating features of Shprintzen-Goldberg syndrome, Loeys-Dietz syndrome, or Ehlers-Danlos syndrome *and* after TGFBR1/2, collagen biochemistry, COL3A1 testing if indicated. Other conditions/genes will emerge with time.
†Maximum total: 20 points; score ≥7 indicates systemic involvement.
MASS, Mitral valve, myopia, aorta, skin and skeletal features; *MFS,* Marfan syndrome; *US/LS,* upper segment/lower segment ratio.
From Loeys BL et al: The revised Ghent nosology for the Marfan syndrome, *J Med Genet* 47(7):476–485, 2009.

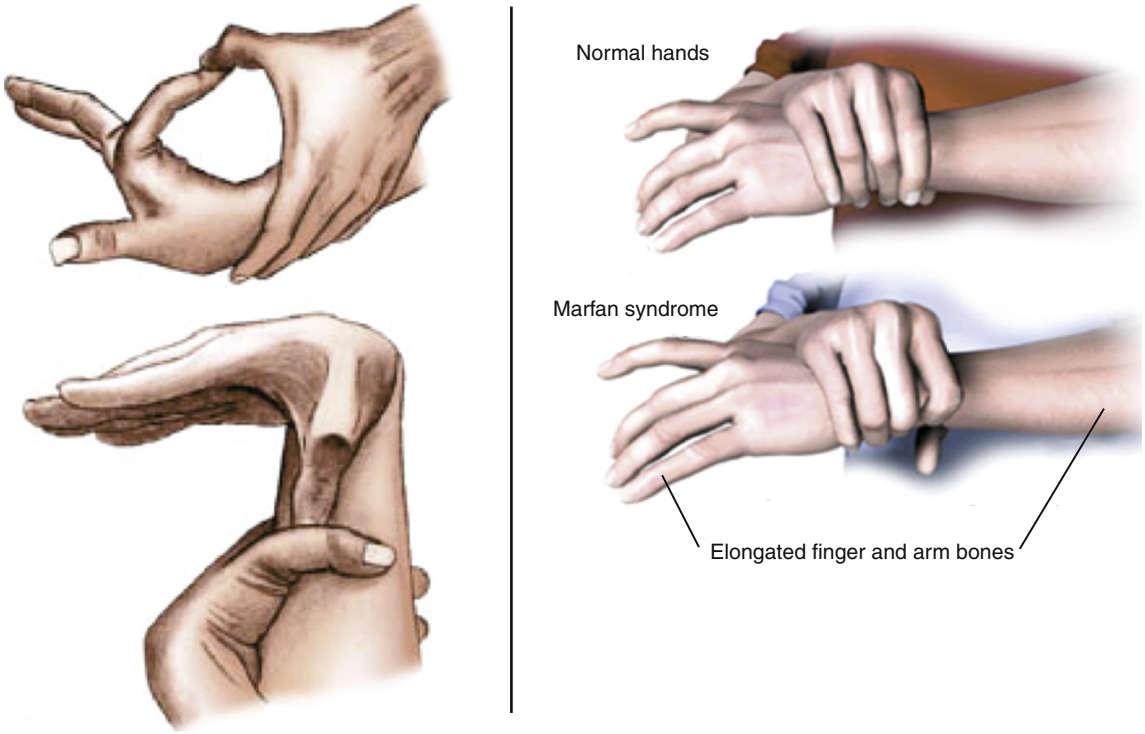

FIG. E1 Marfan syndrome. The Steinberg test (thumb) and the Walker-Murdoch test (wrist) show arachnodactyly. (From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, WB Saunders, Elsevier.)

- Chest radiograph
- Transesophageal echocardiography, chest CT scan, chest MRI, or aortography for suspected aortic dissection
- Chest radiograph for pulmonary apical bullae
- Ophthalmologic examination by ophthalmologist
- Testing for FBN_1 mutations is available

Rx TREATMENT

- Regular cardiac and aorta monitoring by physical examination and echocardiography. Surgical repair of the dilated aortic root/ascending aorta is generally performed when external diameter is ≥5 cm. Surgical repair may be performed earlier (at >4.0 cm diameter) in women contemplating pregnancy.
- Endocarditis prophylaxis.
- Restriction of contact sports, weight lifting, and overexertion.
- Beta-blockers are commonly prescribed to slow the rate of aortic root dilation. Patients with MFS and associated aneurysm should be receiving beta-blockers unless there is a contraindication to their use. Recent reports indicate that use of angiotensin receptor blockers also significantly slowed the rate of progressive aortic root dilation independent of hemodynamic effects. A recent trial among children and young adults with MFS who were randomly assigned to losartan or atenolol found no significant difference in the rate of aortic root dilation between the two treatment groups over a 3-yr period.[1]
- Genetic counseling.
- Monitor aorta during pregnancy because of the increased risk of dissection.

RELATED CONTENT

Marfan Syndrome (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

[1] Lacro RV, Sleeper LA et al: Atenolol versus losartan in children and young adults with Marfan's syndrome, *N Engl J Med* 371(21):2061-2071, 2014.

FIG. E2 **A**, Long limbs compared with the trunk. **B**, Arachnodactyly. (From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, WB Saunders.)

TABLE E2 Diagnostic Criteria for Marfan Syndrome

In the absence of a family history of MFS, a diagnosis can be established in four distinct scenarios:

1. Aortic root Z score ≥2 AND ectopia Lentis*
2. Aortic root Z score ≥2 AND a bona fide *FBN1* mutation
3. Aortic root Z score ≥2 AND a systemic score ≥7*
4. Ectopia lentis AND a bona fide *FBN1* mutation known to cause aortic disease

In the presence of a family history of MFS, a diagnosis can be established in the presence of:

1. Ectopia lentis
2. A systemic score ≥7*
3. Aortic root Z score ≥2 if older than 20 yr or ≥3 if younger than 20 yr*

In the absence of a family history of MFS, alternative diagnoses include:

1. Ectopia lentis ± systemic score AND *FBN1* mutation not known to associate with aortic aneurysm or no *FBN1* mutation = Ectopia lentis syndrome
2. Aortic root Z score <2 AND a systemic score ≥5 (with at least 1 skeletal feature) without ectopia lentis = MASS phenotype
3. Mitral valve prolapse AND Aortic root Z score <2 AND a systemic score <5 without ectopia lentis = Mitral valve prolapse syndrome

*Denotes caveat that features suggestive of an alternative diagnosis must be excluded and appropriate alternative molecular testing should be performed.

MASS, Mitral valve, myopia, aorta, skin, and skeletal features; *MFS,* Marfan syndrome.

From Kliegman, RM: *Nelson Textbook of Pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

BASIC INFORMATION

DEFINITION

Mastitis is local painful inflammation of the breast that may or may not be accompanied by infection, flulike symptoms, and abscess formation.

ICD-10CM CODES

N61	Inflammatory disorders of breast
O91.12	Abscess of breast associated with the puerperium
O91.22	Nonpurulent mastitis associated with the puerperium

EPIDEMIOLOGY & DEMOGRAPHICS

- Mastitis is the most common cause of inflammatory breast disease, and most cases are related to lactation.
  1. Nonpuerperal cases of mastitis can affect either the periareolar (periductal) region or peripheral breast tissue.
  2. Periductal mastitis is most common in younger, reproductive-age women. The majority of those affected are active smokers.
- In lactating mothers, mastitis typically occurs in the first 3 mo of the postpartum period (74% to 95% of cases).
- When severe, mastitis can lead to a breast abscess (5% to 11%) or septicemia.
- Delayed diagnosis and treatment of lactational mastitis can lead to discontinuation of breastfeeding, breast tissue damage, or recurrence.
- In younger, nonlactating women, infection often presents as periductal mastitis (PM) and is caused by inflamed milk ducts near the nipple.
- Granulomatous mastitis (GM) is a rarer form of benign inflammation of the breast and also most commonly occurs in reproductive-age women. It generally affects the breast peripherally.
- Mastitis also can occur in infancy when there is breast hypertrophy from maternal hormone.

PREVALENCE: Lactational mastitis occurs in up to 33% of mothers.

PREDOMINANT SEX: Females

RISK FACTORS:

- Previous mastitis
- Milk stasis and missed feedings
- Cracked, fissured, or sore nipples
- Primiparity and infant attachment difficulties
- Cleft lip or palate or short frenulum in infant
- Use of manual breast pump
- Diabetes
- Breast implants
- Nipple piercings
- Rapid weaning
- Smoking (periductal mastitis)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Warmth, redness, tenderness in breast
- Unilateral or bilateral
- Malaise, myalgias, fevers, chills
- Decreased milk output
- Breast is hard and swollen in a wedge-shaped area
- In PM, breast mass near nipple with retraction or discharge
- In GM, enlarged axillary lymph nodes or sinus tract formation

ETIOLOGY

- In lactational mastitis, infection occurs as a result of milk stasis and irritation of the milk ducts due to local immune response to milk proteins.
  1. Bacterial infection of subcutaneous tissue due to breaks in skin.
- Most commonly, *S. aureus;* less common, *S. epidermidis,* group A beta-hemolytic streptococci, *S. pneumoniae, E. coli, Candida albicans, M. tuberculosis.* GM results from inflammation with epithelioid histiocytes and multinucleated giant cells and can be caused by etiologies like tuberculosis, sarcoidosis, foreign body reaction, parasitic and mycotic infections, or idiopathic.
- Periductal mastitis occurs following inflammation around nondilated subareolar ducts and often can progress to abscess formation. Peripheral abscesses can result from trauma, usually in the setting of comorbid conditions impairing immunity such as diabetes or use of immunosuppressive medications.
- Neonatal mastitis caused by *S. aureus* or gram-negative enteric bacteria.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Engorgement, plugged duct (see Table 1)
- Breast abscess
- Inflammatory or other breast cancer (3% of women diagnosed with breast cancer are lactating)
- Mastitis as a symptom of hyperprolactinemia or galactorrhea
- GM can be manifestation of systemic disease (sarcoidosis, Wegener granulomatosis, giant cell arteritis (GCA), polyarteritis nodosa, tuberculosis (TB), syphilis)

WORKUP

- History and clinical exam with thorough breast exam and assessment of axillary nodes and nipple discharge are sufficient for diagnosis.
- Recurrent mastitis should include workup for underlying breast disease.

LABORATORY TESTS

- Simple lactational mastitis requires no milk culture or laboratory studies.
- Obtain midstream sample of milk for culture and sensitivities in refractory mastitis or in methicillin-resistant *Staphylococcus aureus*-suspected cases.
- CBC and blood cultures in toxic patients.
- In abscess formation, culture of drainage or aspirate fluid.
- Gram stain and culture indicated in infant mastitis.

IMAGING STUDIES

- Not necessary unless refractory mastitis or abscess suspected
- Consider ultrasound (US) (Fig. E1) to evaluate for abscess or mammogram when appropriate to exclude carcinoma
- In GM, mammogram and US-guided fine needle aspiration (FNA) are standard

TREATMENT

NONPHARMACOLOGIC THERAPY

- Mainstay of therapy is effective milk removal through continued breastfeeding or pumping.
- Consider referral to a certified lactation consultant to improve breastfeeding technique.
- Warm compresses, increased fluid intake, good nutrition, and rest.
- In abscess formation (10% of women who are treated for bacterial mastitis), surgical drainage or needle aspiration is necessary, followed by antibiotic therapy based on sensitivities of culture.

ACUTE GENERAL Rx

- NSAIDs and analgesics (e.g., acetaminophen, ibuprofen). There is insufficient evidence to support or refute the effectiveness of antibiotic therapy. Common regimens include:
- No history of MRSA:
  1. Dicloxacillin 250 mg 4×/day for 7 days
  2. Cephalexin 500 mg 4×/day for 10 to 14 days
  3. Inpatient: Nafcillin or oxacillin 2 g IV q4h
  4. Erythromycin may be used in patients allergic to penicillin
- Suspected MRSA or high-risk penicillin allergy:
  1. Trimethoprim/sulfamethoxazole 160 mg/800 mg 2×/day for 10 to 14 days; should not be used when breastfeeding healthy infants <2 mo or compromised infants
  2. Clindamycin 300 mg 4×/day for 10 to 14 days
  3. Inpatient: Vancomycin 1 g IV q12h
- Oxytocin nasal spray if letdown reflex disturbed

TABLE 1 Comparison of Findings of Engorgement, Plugged Duct, and Mastitis

Characteristics	Engorgement	Plugged Duct	Mastitis
Onset	Gradual, immediately	Gradual, after feedings	Sudden, after 10 days postpartum
Site	Bilateral	Unilateral	Usually unilateral
Swelling and heat	Generalized	May shift/little or no heat	Localized red, hot, and swollen
Body temperature	<38.4° C; 101.1° F	<38.4° C; 101.1° F	>38.4° C; 101.1° F
Systemic symptoms	Feels well	Feels well	Flulike symptoms

From Lawrence RA, Lawrence RM: *Breastfeeding: a guide for the medical profession,* ed 5, St Louis, 1999, Mosby.

- Consider treatment for candidal infection if bilateral symptoms and infant with thrush
  1. Topical clotrimazole for mother and oral nystatin for infant, with careful washing of all pacifiers and nipples
  2. If resistant to topical treatment, can consider oral fluconazole; however, data in breastfeeding are limited
- Infant mastitis typically is treated in an inpatient setting with parenteral antibiotics based on results of Gram stain.
- Most PM cases are treated adequately with a combination of antibiotics, needle aspiration/incision, and drainage. In recurrent cases, surgical removal of diseased ducts may be needed.
- If antibiotic and NSAID treatment for GM fails, immunosuppressive drugs (steroids, methotrexate) can be used. Surgical management is not recommended due to associated slow wound healing.

CHRONIC Rx

- No evidence proving benefit of prophylactic antibiotics to prevent lactational mastitis
- In GM, systemic corticosteroids or wide surgical resection

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Complementary therapies not assessed in prospective studies: *Belladonna, Phytolacca, Chamomilla,* sulfur, *Bellis perennis.*
- Several strains of lactobacilli have shown promise as probiotic agents that might be useful in treating mastitis, including *L. fermentum* and *L. salivarius.* These results should be replicated before this approach is adopted widely.

REFERRAL

Refer to surgeon for severe PM or significant lactational abscess that does not resolve with conservative measures

PEARLS & CONSIDERATIONS

COMMENTS

- 25% of breastfeeding mothers with one episode of mastitis stop breastfeeding.
- Increasing incidence of MRSA mastitis.
- Lactational mastitis is a risk factor for vertical transmission of infections (i.e., HIV-1, cytomegalovirus, measles, hepatitis B and C).
- When reassessing refractory nonlactational mastitis, the most important consideration is the possibility of cancer.
- Nonlactational mastitis can be a manifestation of systemic disease.
- GM mimics breast cancer both clinically and radiologically (>50% of reported cases are initially mistaken for carcinoma). This includes fine needle aspiration, which is sometimes interpreted as malignant.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Lactational Mastitis (Patient Information)
Mastitis (Patient Information)
Breast Abscess (Related Key Topic)
Fibrocystic Breast Disease (Related Key Topic)

AUTHOR: **Jhenette Lauder, MD**

SUGGESTED READINGS

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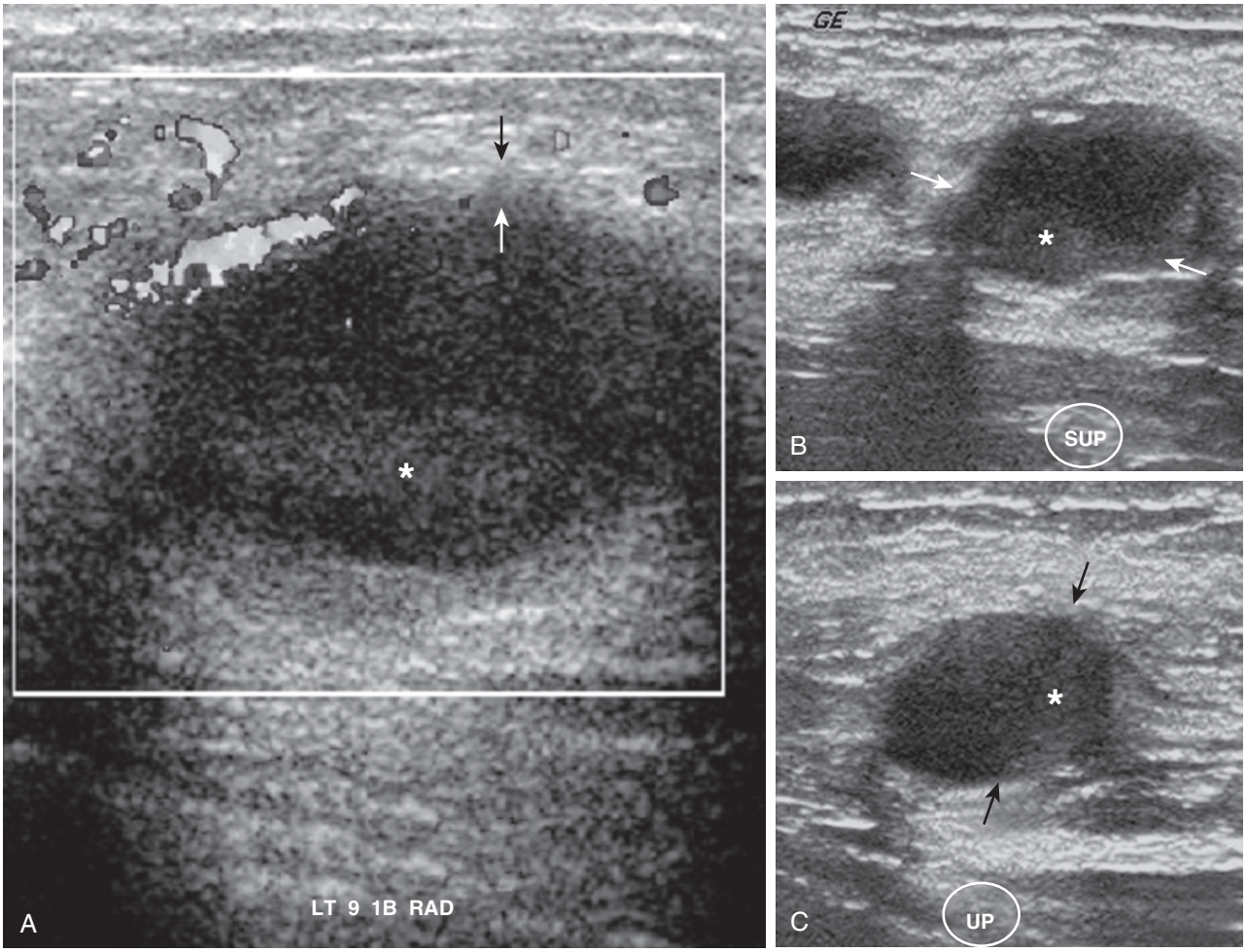

FIG. E1 Inflamed or infected cyst. A, Acutely inflamed or infected cysts demonstrate three findings: (1) Abnormal uniform isoechoic wall thickening *(between arrows),* (2) dependent debris *(asterisk)*, and (3) hyperemia of the thickened wall. **B,** Supine and **C,** upright images show the debris *(asterisk),* resembling sludge within a gallbladder, shifting to the dependent part of the cyst when the position of the patient is changed from supine to upright or lateral decubitus positions. Note the change in the position of the interface between the nondependent fluid and the dependent debris or pus *(between arrows).* (From Rumack CM et al: *Diagnostic ultrasound*, ed 4, Philadelphia, 2011, Mosby.)

BASIC INFORMATION

DEFINITION

Mastocytosis is a rare clonal hematopoietic disorder caused by the accumulation of abnormal mast cell population primarily in skin and bone marrow, and less commonly in liver and other tissues. Children usually have disease confined to the skin (urticaria pigmentosa) that resolves with adolescence. Adults typically have systemic disease of varying severity that is chronic. Indolent disease is typically defined by mast cell mediator related symptoms; advanced disease is associated with tissue injury from mast cell infiltrates and is less common.

SYNONYMS

Systemic mastocytosis
Urticaria pigmentosa (refers to skin disease only)
"Mastocytosis in the skin" (MIS, refers to skin disease only)

ICD-10CM CODES

Q82.2	Mastocytosis
D47.0	Indolent systemic
C96.2	Aggressive systemic
C96.2	Malignant
D47.0	Systemic, with an associated hematologic neoplasm (SM-AHM)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (SYSTEMIC MASTOCYTOSIS [SM], EXCLUDING URTICARIA PIGMENTOSA [UP]):

- 0.4 per 1,000,000 persons per yr (U.S.).
- Male:female approximately equal.
- Age at diagnosis typically 50 to 70 yr.
- Approximately two thirds of cases are indolent (excluding UP and systemic mastocytosis-aggressive systemic mastocytosis [SM-ASM]).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Most symptoms are related to release of mast cell mediators, mainly histamine but also serotonin, heparin, several proteases (most important tryptase, which is a diagnostic marker), leukotrienes and numerous cytokines (e.g. IL-6).

SYMPTOMS

- Mast cell mediator symptoms:
  1. Cutaneous: Flushing, pruritus, urticaria, angioedema
  2. Extra-cutaneous: Lightheadedness, sometimes with syncope; palpitations; wheezing
- Gastrointestinal symptoms: Nausea/vomiting, diarrhea, constipation, bloating
- Musculoskeletal symptoms due to mastocytosis related osteopenia/osteoporosis or direct bone involvement with mast cells lesions: Bone pain, less commonly myalgia/arthralgia
- Severe anaphylactoid reactions, especially to Hymenoptera (bees, wasps, ants) venom

PHYSICAL EXAM

- Urticaria pigmentosa is the hallmark lesion of systemic mastocytosis. In adults, the lesions are small, brown/red (Fig. E1), generally flat (maculopapular). Pediatric lesions are commonly larger and may be more nodular or plaque like. In adults, skin lesions are usually seen in indolent mast cell disease, less common in advanced disease.
- *Darier sign*: Wheal and reddening of lesions with stroking, persisting minutes to hours.
- Hepatomegaly and/or splenomegaly are common in advanced disease.
- Lymphadenopathy, by exam or imaging, is detected in about 20% of cases.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Mastocytosis is a rare disorder with a wide spectrum of symptoms and presentations. It should be considered in the evaluation of severe urticarial reactions to Hymenoptera venom exposures (i.e., bee stings mainly), unexplained angioedema, episodic hypotension and unexplained nausea or diarrhea. It should also be considered in premature osteopenia/osteoporosis, especially in males.
- Elevated tryptase levels may be seen with many myeloid hematologic malignancies, transiently with allergic reactions and helminth infections.
- *Mast cell activation syndrome (MCAS)* is a disorder with mast cell mediator symptoms, possibly from hyperresponsive mast cells, but who lack pathologic findings of systemic mast cell disease.

WORKUP

- The World Health Organization (WHO) diagnostic criteria for various forms of mastocytosis are outlined in Tables E1, E2, and E3. Smoldering systemic mastocytosis (SSM) is the 2016 classification now defined by two or more "B" findings (Table E4).
- Serum tryptase: Approximately 20% of cases have serum tryptase less than the WHO cutoff of 20 ng/ml. Elevated levels have

FIG. E1 Urticaria pigmentosa lesions in a patient with cutaneous mastocytosis. (From Hoffman R [ed]: *Hematology: Basic principles and practice,* ed 6, Philadelphia, 2013, Elsevier/Churchill Livingstone.)

TABLE E1 World Health Organization Diagnostic Criteria for Systemic Mastocytosis[a]

Major Criterion

Multifocal, dense infiltrates of mast cells (>15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s)

Minor Criteria

a. In biopsy sections of bone marrow or other extracutaneous organs, >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology; or of all mast cells in bone marrow aspirate smears, >25% are immature or atypical.
b. Detection of an activating point mutation at codon 816 in *KIT* in bone marrow, blood, or another extracutaneous organ.
c. Mast cells in bone marrow, blood, or other extracutaneous organs express CD2 and/or CD25 in addition to normal mast cell markers.
d. Serum total tryptase persistently exceeds 20 ng/ml (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid).

[a]Requires at least one major + one minor criterion or three minor criteria.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE E2 2016 World Health Organization Variants of Mastocytosis

1. Cutaneous mastocytosis (CM)
   a. Maculopapular CM
   b. Diffuse CM
   c. Mastocytoma of skin
2. Indolent systemic mastocytosis (ISM)
   a. Isolated bone marrow mastocytosis
3. Smoldering systemic mastocytosis (SSM)
4. Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN)*
   a. SM-MDS
   b. SM-MPN (e.g., PV, ET, MF, CML)
   c. SM-MDS/MPN (e.g., CMML, MDS/MPN-unclassified)
   d. SM-CEL
   e. SM-AML
   f. SM-lymphoid neoplasm (e.g., NHL, CLL, multiple myeloma)
5. Aggressive systemic mastocytosis (ASM)
6. Mast cell leukemia (MCL)
   a. Aleukemic MCL
7. Mast cell sarcoma (MCS)

*SM-AHN is a new term that may be used in lieu of the previous term, SM-AHNMD (systemic mastocytosis with an associated non-mast cell lineage disease).
AML, Acute myeloid leukemia; *CEL,* chronic eosinophilic leukemia; *CLL,* chronic lymphocytic leukemia; *CML,* chronic myeloid leukemia; *CMML,* chronic myelomonocytic leukemia; *ET,* essential thrombocythemia; *MDS,* myelodysplastic syndrome; *MF,* myelofibrosis; *MPN,* myeloproliferative neoplasm; *NHL,* non–Hodgkin lymphoma; *PV,* polycythemia vera.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE E3 2016 World Health Organization Diagnostic Criteria for Variants of (Systemic) Mastocytosis

1. **Indolent systemic mastocytosis (ISM):** Meets criteria for SM. No "B" or "C" findings. No evidence of associated clonal hematologic malignancy/disorder. In this variant, the mast cell burden is usually low; skin lesions are almost invariably present.
   - *Bone marrow mastocytosis:* As above, with bone marrow involvement, but no skin lesions.
2. **Smoldering systemic mastocytosis (SSM):** Meets criteria for SM. Two or more "B" findings and no "C" findings.
3. **Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN)*:** Meets criteria for SM and an associated hematologic neoplasm (MDS, MPN, MDS/MPN, CEL, AML, lymphoma, or other hematologic neoplasm that meets the criteria for a distinct entity in the WHO classification).
4. **Aggressive systemic mastocytosis (ASM):** Meets criteria for SM. One or more "C" findings. No associated clonal hematologic neoplasm. No evidence of mast cell leukemia.
5. **Mast cell leukemia (MCL):** Meets criteria for SM. Bone marrow biopsy shows diffuse infiltration, usually in an interstitial pattern, by atypical, immature mast cells. Bone marrow aspirate smears show 20% or more mast cells. Cases in which <10% of circulating WBCs are mast cells are referred to as 'aleukemic mast cell leukemia.'
6. **Mast cell sarcoma (MCS):** Unifocal mast cell tumor. No evidence of SM. No skin lesions. Destructive growth pattern. High-grade cytology.

*SM-AHN is a new term that may be used in lieu of the previous term, SM-AHNMD (systemic mastocytosis with an associated non-mast cell lineage disease.)
AML, Acute myeloid leukemia; *CEL,* chronic eosinophilic leukemia; *MDS,* myelodysplastic syndrome; *MPN,* myeloproliferative neoplasm; *SM,* systemic mastocytosis; *WBC,* white blood cell; *WHO,* World Health Organization.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

high specificity (98%). May be elevated after urticarial reactions; should not be elevated at baseline.
- Skin biopsy (Fig. E2) for urticarial pigmentosa/mastocytosis in the skin (MIS).
- Bone marrow examination (Fig. E3) in adults with MIS or elevated tryptase. In adult patients with cutaneous MC lesions, the large majority ultimately will be found to have SM according to WHO diagnostic criteria. A bone marrow biopsy usually is recommended in these patients to establish a diagnosis of SM (Fig. E4).
- Flow cytometry/immune histochemistry for aberrant CD25 and/or CD2 expression, in addition to normal mast cell markers.
- Molecular studies (polymerase chain reaction, PCR) for *KIT* D816V mutation, preferably on tissue (marrow/skin); peripheral blood studies are less sensitive. If *KIT* D816V negative, consider evaluation for other *KIT* mutations.
- CBC and liver function studies; imaging of liver/spleen if appropriate.
- Bone density study for early osteoporosis in all patients; skeletal imaging if symptomatic (bone scan, plain x-rays).

Rx TREATMENT

Therapy is primarily directed to blockade of histamine release symptoms along with cytoreductive therapy for organ injury or refractory histamine release symptoms. Fig. E5 provides a treatment algorithm for indolent versus advanced stages of SM.
- Due to high incidence of anaphylaxis, epinephrine injectors are often recommended for mastocytosis patients.
- Triggers (e.g., alcohol, abrupt temperature changes) should be identified and avoided.
- Pruritus/flushing:
  1. H_1 blockade: Cetirizine, fexofenadine, others. Doses sometimes adjusted upwards with caution. Use with caution in glaucoma, BPH; may cause dry mouth

TABLE E4 "B" Findings: Indication of High Mast Cell Burden

1. Infiltration grade (mast cells) greater than 30% in bone marrow in histology and serum total tryptase levels greater than 200 ng/ml
2. Hypercellular marrow with loss of fat cells, discrete signs of dysmyelopoiesis without substantial cytopenias, and without WHO criteria for an MDS or MPN
3. Organomegaly: Palpable hepatomegaly, splenomegaly, or lymphadenopathy (on CT or ultrasound) greater than 2 cm without impaired organ function

CT, Computed tomography; *MDS,* myelodysplastic syndrome; *MPN,* myeloproliferative neoplasm; *WHO,* World Health Organization.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

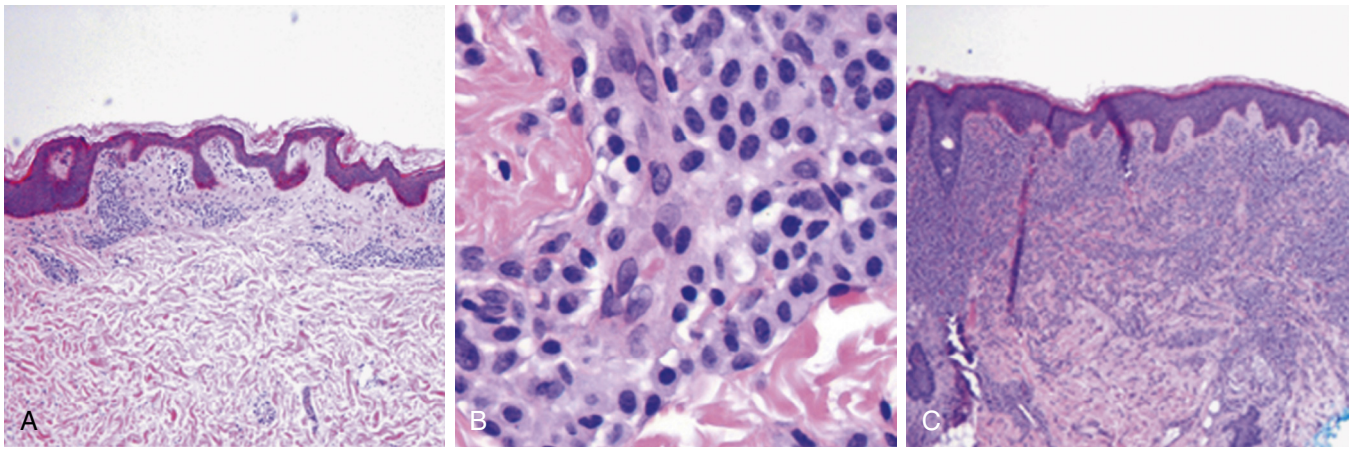

FIG. E2 Cutaneous mastocytosis. A skin biopsy of urticaria pigmentosa or maculopapular mastocytosis shows multiple focal aggregates of mast cells around blood vessels or skin appendages in the papillary dermis **(A).** The mast cells are plump with abundant cytoplasm and typically accumulate around vessels **(B,** *center***)**. In solitary mastocytoma of the skin or in diffuse cutaneous mastocytosis, the mast cell infiltrate is more extensive as it infiltrates the papillary and reticular dermis and even may extend into the subcutaneous tissues **(C).** The mast cells are bland and without cytologic atypia. In these disorders, there should be no evidence of systemic involvement. Evidence of systemic disease would indicate systemic mastocytosis. (From Hoffman R [ed]: *Hematology, basic principles and practice,* ed 6, Philadelphia, 2013, Elsevier/Churchill Livingstone.)

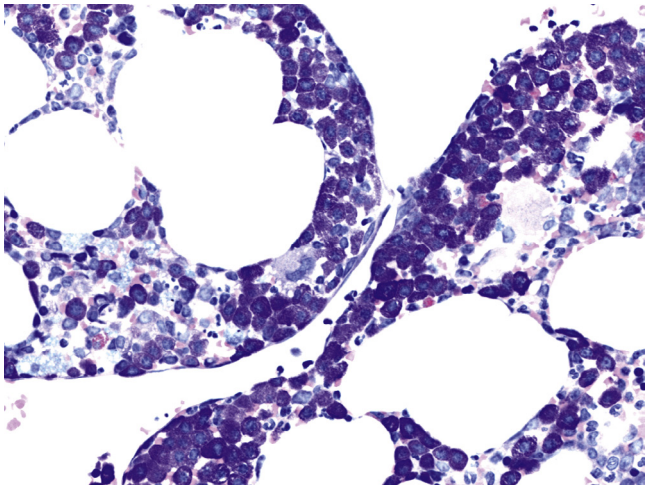

FIG. E3 Well-differentiated systemic mastocytosis. Core biopsy, Giemsa stain. Bone marrow shows aggregates of exclusively round mast cells with an abundance of metachromatic granules. This is the typical phenotypical appearance of a well-differentiated systemic mastocytosis. The disease otherwise was subtyped as indolent systemic mastocytosis with skin involvement but missing the *KIT* D816V mutation. There also was a lack of CD25 expression by the mast cells (not depicted). (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

2. Leukotriene antagonist (second line): Montelukast or zafirlukast
3. Aspirin (third line): Low doses sometimes helpful
4. Psoralen and ultraviolet A light (PUVA) (third/fourth line)

- Abdominal pain/nausea/diarrhea/bloating:
  1. H_2 blockade: Ranitidine or famotidine
  2. Proton pump inhibitors (second line): Omeprazole, others
  3. Cromolyn sulfate (mast cell stabilizer, third line) before meals and HS. This agent is expensive; availability may vary
  4. Corticosteroids for short courses (fourth line)
- Recurrent hypotension:
  1. Epinephrine injector ("Epi-Pen")
  2. H_1/H_2 receptor blockade
  3. Specific therapy for defined allergies (e.g., bee stings)
- Osteoporosis:
  1. Bisphosphonates: Alendronate, others
  2. Optimize vitamin D/calcium replacement
- Cytoreductive therapy:
  1. Midostaurin, an oral multikinase inhibitor, is FDA-approved for treatment of ASM, SM-AHN, and mast cell leukemia (MCL). The response rate in ASM was 75%, and progression-free survival (PFS) was 28.7 mo; lower for SM-AHN and MCL
  2. Cladribine: A recent study found response rates of 72%, more durable in indolent disease (3.71 yr for indolent, 2.47 for advanced)
  3. Interferon alpha, given TIW, adjusted to response and tolerance
  4. Tyrosine kinase inhibitors such as imatinib mesylate have limited efficacy in *KIT* D816V mutated disease, but have use with other *KIT* mutations

DISPOSITION

- Indolent mastocytosis patients had survivals that roughly parallel age-matched controls in a study 159 patients seen between 1976 and 2007 at Mayo Clinic.
- Advanced mastocytosis patients had median survival of 41 mo. It is not known what impact changes in treatment standards in the current treatment era will have on survival.

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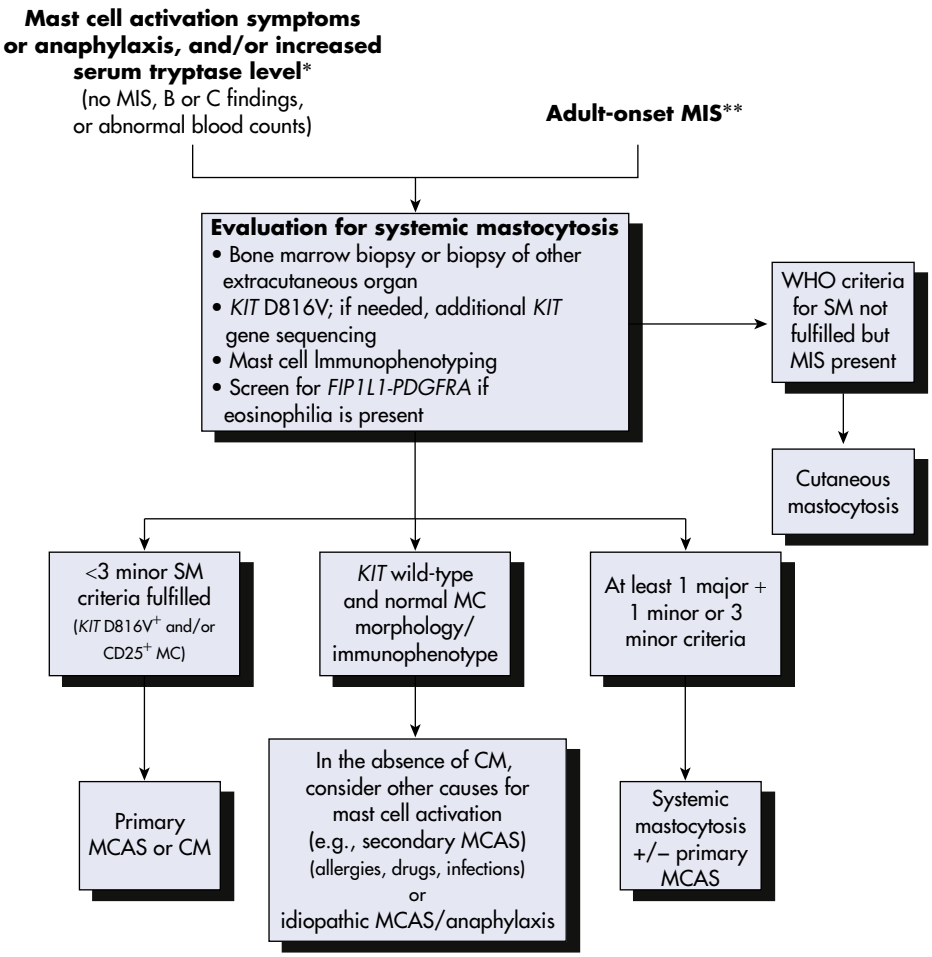

FIG. E4 Diagnostic decision pathways for patients with mast cell activation symptoms or adult-onset mastocytosis in the skin. For patients with mast cell activation symptoms or anaphylaxis (and/or increased serum tryptase level), or adult-onset MIS, screening to assess whether diagnostic criteria for SM are met should be the first diagnostic checkpoint. In patients not meeting the criteria for SM, evaluation for MCAS (primary vs. secondary vs. idiopathic) and idiopathic anaphylaxis is the next phase. Patients with MIS in whom no signs of SM can be found may be categorized as having cutaneous mastocytosis. *The serum tryptase level may be below the 20 ng/ml threshold, or only transiently elevated. **Although an evaluation for systemic mastocytosis generally is recommended in adults with MIS who have no blood count abnormalities or organ dysfunction and a normal or mildly increased serum tryptase level, the value of performing a bone marrow biopsy should be discussed with the patient. *CM,* Cutaneous mastocytosis; *MC,* mast cell; *MCAS,* mast cell activation syndrome; *MIS,* mastocytosis in the skin; *SM,* systemic mastocytosis; *PDGFRA,* platelet-derived growth factor receptor A; *WHO,* World Health Organization. (Adapted from: Pardanani A: How I treat patients with indolent and smoldering mastocytosis [rare conditions but difficult to manage], *Blood* 2013;121:3085, 2013; Valent P et al: Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus protocol, *Int Arch Allergy Immunol* 157:215, 2012. In Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

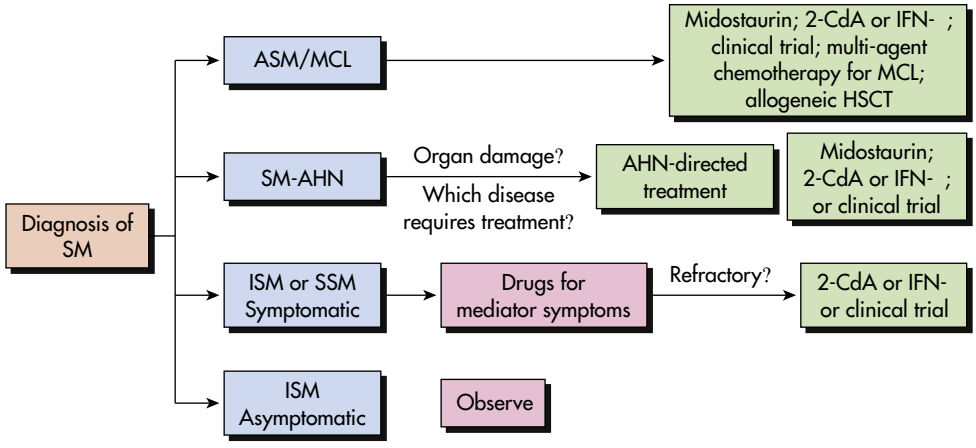

FIG. E5 Treatment options based on subtype of systemic mastocytosis. Treatment options are listed based on subvariant of SM (indolent vs. advanced forms of disease), whether organ damage is considered related to SM or the associated myeloid neoplasm in patients with SM-AHN, and whether cytoreductive therapy may need to be considered in patients with ISM and refractory mediator symptoms. *2-CdA,* 2-Chlorodeoxyadenosine; *ASM,* aggressive systemic mastocytosis; *HSCT,* hematopoietic stem cell transplantation; *ISM,* indolent systemic mastocytosis; *IFN-α,* interferon-α; *MCL,* mast cell leukemia; *SM,* systemic mastocytosis; *SM-AHN,* systemic mastocytosis with an associated hematologic neoplasm; *SSM,* smoldering systemic mastocytosis. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

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BASIC INFORMATION

DEFINITION

- Pain in the breast
- Usually cyclic but may be noncyclic or extramammary

SYNONYM

Mastalgia

ICD-10CM CODE
N64.4 Mastodynia

EPIDEMIOLOGY & DEMOGRAPHICS

- Mastodynia affects up to 70% of women at some time in their reproductive lives.
- Severe cyclic mastodynia lasting more than 5 days/mo and of sufficient intensity to interfere with sexual, physical, social, and work-related activities is reported among 30% of premenopausal women.
- Underlying fear of breast cancer is the reason most of these women seek medical consultation.
- One tenth of women with mastodynia require pain-relieving therapy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usually the breasts are normal bilaterally.
- Generalized breast nodularity without discrete lumps.
- Chest wall tenderness: Extramammary breast pain, unilateral, aggravated by activity.
- Distinguishing mammary from extramammary pain can be difficult.
- With the patient lying on her side so that the breast tissue falls away from the chest wall, tenderness can then be reproduced by direct pressure over the offending site.
- Cyclic mastodynia presents in the luteal phase of the menstrual cycle one wk prior to onset of menses and resolves with menstruation.
- Women with cyclic mastodynia tend to have abdominal bloating, leg swelling, and other symptoms of premenstrual syndrome.
- Noncyclic mastodynia is unrelated to the menstrual cycle.
- Extramammary breast pain simulates noncyclic mastodynia.

ETIOLOGY

- Hormonal imbalance: Theories include increased estrogen, decreased progesterone, and increased prolactin
- Abnormal lipid metabolism, increased saturated fatty acids
- Premenstrual syndrome (20%)
- Fibrocystic breast disease, breast cysts
- Emotional abuse and anxiety
- Excessive caffeine intake has not been proven
- Breast cancer (10%)
- Mastitis
- Tietze syndrome (idiopathic costochondritis)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- See "Etiology."
- The majority of women with mastodynia have no underlying abnormality.
- Breast fullness and tenderness associated with hormonal changes fluctuate with the menstrual cycle.
- Similarly, breast nodularity, which may or may not be the result of fibrocystic breast disease, also fluctuates with the menstrual cycle.
- Discrete breast lumps need full evaluation to rule out malignancy.
- Tietze syndrome is usually unilateral and may be associated with chest wall swelling.

LABORATORY TESTS

Although hormonal imbalance and abnormal lipid metabolism have been implicated in the etiopathogenesis of mastodynia, there is no good evidence to support any consistent pattern of serum hormonal or lipid profile in women with mastodynia. These tests are therefore not recommended.

IMAGING STUDIES

- Cyclical, bilateral, nonfocal: Usually does not require imaging.
- Ultrasound is helpful in the assessment of cystic breast lesions.
- Unilateral, noncylical, focal: Imaging based on age
- Consideration of family history for breast disease is important.
- There are no radiologic features associated with mastodynia: Rather, radiologic investigations are performed to exclude the rare presence of a subclinical carcinoma.

TREATMENT

NONPHARMACOLOGIC THERAPY

- 78% to 85% of women with mastodynia can be reassured after full clinical evaluation. In fact, reassurance can be considered first-line therapy for mastodynia since many women who present are concerned about significant pathology, especially cancer.
- A firm, supportive brassiere designed for postpartum use is particularly helpful if mastodynia is associated with breast swelling.
- Follow a low-fat, high-carbohydrate diet.
- Reducing caffeine intake has not been proven effective but may help some women.

ACUTE GENERAL Rx

- There is limited evidence supporting the use of evening primrose oil, which contains gamma-linolenic acid, but this may be offered to patients as it is generally benign.
- Topical NSAID preparations (diclofenac, salicylate) may confer some benefit and can be prescribed for these women.
- Hormonal therapy is the mainstay of treatment and may include progesterone-only oral contraceptives or cyclic Provera.
- Danazol is the only drug approved by the FDA for the treatment of mastodynia. Danazol has some androgenic and peripheral antiestrogenic effects. Its efficacy is well established, with significant relief of mastodynia in 70% to 93% of cases.
  1. Widespread use of danazol is limited because of its adverse side effects. These include menstrual irregularities, depression, acne, hirsutism, and, in severe cases, voice deepening. Women should be advised to use effective nonhormonal contraception because of the drug's potential adverse effects on the fetus. It is imperative to rule out pregnancy prior to drug initiation.
  2. The side effects of danazol can be significantly reduced by using a low dose (100 mg daily) and confining treatment to 2 wk preceding menstruation. However, alternatives should be explored.
- Tamoxifen, a synthetic antiestrogen, has also been shown to be effective in the treatment of mastodynia. Although effective in relieving symptoms, its use is extremely limited because of side effects, although it has fewer than Danazol. When used, it should be at a low dosage of 10 mg/day and duration should be limited to 6 mo at a time. In the U.S. this agent is not approved for use in women with mastodynia.
- Bromocriptine is a dopamine-receptor agonist whose primary action is inhibition of prolactin release. It has been used extensively in the treatment of severe cyclic mastodynia and is effective. Again, side effects such as headache and lightheadedness have limited its use and it is less effective than Danazol.
- Lisuride maleate was recently found to be effective by one study.
- Other hormonal agents that have been reported to be effective in small studies cannot be recommended. Either they have unacceptable side effect profiles or their efficacy is not established. These agents include gestrinone, gonadotropin-releasing hormone analogues, progesterone, and hormone replacement therapy.
- Investigational treatments: Phytoestrogens, agnus cactus, chamomile.

CHRONIC Rx

- Longstanding cases of mastodynia can be managed with intermittent low-dose danazol therapy to limit side effects. In between these courses of hormone, nonpharmacologic and nonhormonal therapy can be used.
- Severe, unremitting mastodynia that does not respond to medical treatment may require mastectomy; this is rare.

DISPOSITION

- Cyclic mastodynia resolves spontaneously in 20% to 30% of women.
- Noncyclic mastodynia responds poorly to treatment but may resolve spontaneously in up to 50% of women.

RELATED CONTENT

Breast Pain (Patient Information)
Fibrocystic Breast Disease (Related Key Topic)

AUTHOR: **Gina Ranieri, DO**

BASIC INFORMATION

DEFINITION

Mastoiditis is inflammation of the mastoid process and air cells, a complication of otitis media.

SYNONYM

Mastoid abscess

ICD-10CM CODES

H40.1 Chronic mastoiditis
H70.0 Acute mastoiditis
H70.8 Other mastoiditis and related conditions
H70.9 Mastoiditis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Since the introduction of antibiotic therapy and use of broad-spectrum antibiotics, there has been a marked decline in the incidence of acute mastoiditis.
PREDOMINANT SEX: More common in males
PREDOMINANT AGE: 2 mo to 18 yr
PEAK INCIDENCE: Early childhood

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute mastoiditis is usually a complication of acute otitis media.
- Most common presenting symptom is pain and tenderness in the postauricular region.
- Other signs or symptoms include:
  1. Fever
  2. Postauricular erythema and edema
  3. Protrusion of the pinna inferiorly and anteriorly
  4. Tympanic membrane usually intact with signs of acute otitis media
- Complications of acute mastoiditis include:
  1. Subperiosteal abscess (most common complication)
  2. Hearing loss
  3. Facial nerve palsy
  4. Labyrinthitis
  5. Intracranial complications such as hydrocephalus, meningitis, encephalitis, intracranial abscess, and lateral sinus thrombosis
- Chronic mastoiditis is characterized by chronic otorrhea and chronic tympanic membrane perforation.

ETIOLOGY

- Continuity exists between the middle air space and the mastoid cavity.
- Initial hyperemia and edema of the mucosal lining of the air cells result in accumulation of purulent exudate.
- Dissolution of calcium from bony septa and osteoclastic activity in the inflamed periosteum lead to bone necrosis and coalescence of air cells.
- Most common bacterial isolates (Table E1) are:
  1. *Streptococcus pneumoniae*
  2. *Streptococcus pyogenes*
  3. *Haemophilus influenzae*
  4. *Moraxella catarrhalis*
  5. *Staphylococcus aureus*
- Often, there are multiple organisms in chronic mastoiditis, with predominance of anaerobes and gram-negative bacteria.
- *Mycobacterium tuberculosis,* nontuberculous mycobacteria, *Aspergillus,* and *Rhodococcus equi* have been reported in cases of mastoiditis in severely immunocompromised individuals.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Children:
  1. Rhabdomyosarcoma
  2. Histiocytosis X
  3. Leukemia
  4. Kawasaki syndrome
- Adults:
  1. Fulminant otitis externa
  2. Histiocytosis X
  3. Metastatic disease
- Table E2 differentiates postauricular involvement of acute mastoiditis with periostitis/abscess.

WORKUP

A thorough history and physical examination are important in establishing diagnosis.

TABLE E1 Etiology of Acute Mastoiditis

Bacteria	Frequency
Streptococcus pneumoniae	10-51%
Streptococcus pyogenes	0-12%
Staphylococcus aureus	2-10%
Pseudomonas aeruginosa	10%
Haemophilus influenzae	2-3%
No growth	20-40%

From Kliegman RM: *Nelson Textbook of Pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

LABORATORY TESTS

- Fluid for Gram stain and culture may be obtained by myringotomy.
- If there is a perforation in the tympanic membrane with drainage, cultures of this may be taken after carefully cleaning the external canal.

IMAGING STUDIES

- Plain x-rays of the mastoid region may demonstrate clouding or opacification in areas of pneumatization.
- CT scan (Fig. E1) can demonstrate early involvement of bone (mastoiditis with bone destruction).
- MRI is more sensitive than CT scan in evaluating soft-tissue involvement and is useful in conjunction with CT scan to investigate other complications of mastoiditis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Myringotomy, if the ear is not already draining

ACUTE GENERAL Rx

- Initiated with IV antibiotics directed against the common organisms *S. pneumoniae* and *H. influenzae.* Useful agents are amoxicillin/clavulanate, ceftriaxone, and cefotaxime. If the disease in the mastoid has had a prolonged course, coverage for *S. aureus* with gram-negative enteric bacilli may be considered for initial therapy until results of cultures become available. Add vancomycin if methicillin-resistant *Staphylococcus aureus* (MRSA) suspected or nafcillin/oxacillin if culture is positive for *S. aureus*, methicillin susceptible.
- Antibiotics continued until all signs of mastoiditis have resolved

TABLE E2 Differential Diagnosis of Postauricular Involvement of Acute Mastoiditis With Periostitis/Abscess

	Postauricular Signs and Symptoms				External Canal Infection	Middle-Ear Effusion
Disease	Crease*	Erythema	Mass	Tenderness		
Acute mastoiditis with periostitis	May be absent	Yes	No	Usually	No	Usually
Acute mastoiditis with subperiosteal abscess	Absent	Maybe	Yes	Yes	No	Usually
Periostitis of pinna with postauricular extension	Intact	Yes	No	Usually	No	No
External otitis with postauricular extension	Intact	Yes	No	Usually	Yes	No
Postauricular lymphadenitis	Intact	No	Yes†	Maybe	No	No

*Postauricular crease (fold) between pinna and postauricular area.
†Circumscribed.
From Bluestone CD, Klein JO, eds: *Otitis media in infants and children*, ed 3, Philadelphia, 2001, WB Saunders, p 333. In Kliegman RM: *Nelson Textbook of Pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

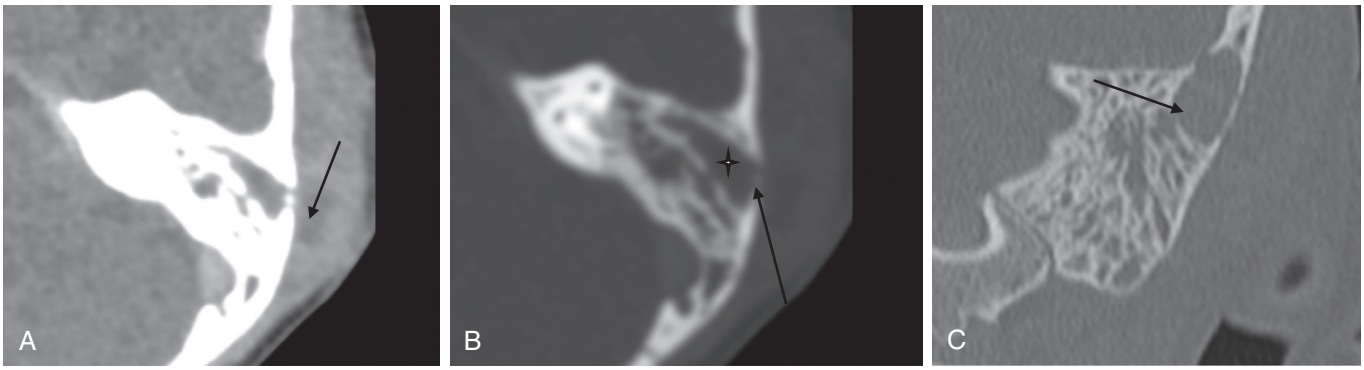

FIG. E1 This contrasted CT scan shows coalescent mastoiditis with subperiosteal abscess formation. Panels **A** and **B** contain axial images with soft tissue windows and bone windows, respectively. In panel **A**, the *arrow* points to the subperiosteal abscess. The *star* in panel **B** shows the loss of bony septations in the mastoid cavity and the *arrow* points to the erosion of the bony cortex. Panel **C** is a coronal image showing demineralization of the mastoid tegmen abutting the middle cranial fossa. The image in panel **C** is a precursor to epidural abscess formation. (From Kliegman RM: *Nelson Textbook of Pediatrics*, ed 21, Philadelphia, 2020, Elsevier.)

- Directed against enteric gram-negative organisms and anaerobes in chronic mastoiditis
- Indications for mastoidectomy:
  1. Failure to improve after 72 hr of therapy
  2. Persistent fever
  3. Imminent or overt signs of intracranial complications
  4. Evidence of a subperiosteal abscess in the mastoid bone

DISPOSITION

Proceed with mastoidectomy when medical therapy fails.

REFERRAL

- To otorhinolaryngologist:
  1. If diagnosis is in doubt
  2. If aural complications present
  3. To evaluate for surgical intervention
- To neurosurgeon if intratemporal or intracranial extension of infection suspected:
  1. Aural complications: Bone destruction, subperiosteal abscess, petrositis, facial paralysis, labyrinthitis
  2. Intracranial complications: Extradural abscess, lateral sinus thrombophlebitis or thrombosis, subdural abscess, meningitis, brain abscess, otitic hydrocephalus

PEARLS & CONSIDERATIONS

Mastoiditis is particularly difficult to eradicate because the mastoid air cells are poorly vascularized and difficult to drain.

RELATED CONTENT

Mastoiditis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Bunik M: Mastoiditis, *Pediatr Rev* 35:94-95, 2014.

Chesney J et al: What is the best practice for acute mastoiditis in children? *Laryngoscope* 124(5):1057-1058, 2014.

Lin HW et al: Clinical strategies for the management of acute mastoiditis in the pediatric population, *Clin Pediatr* 49(2):110-115, 2010.

Loh R et al: Management of pediatric acute mastoiditis: systematic review, *J Laryngol Otol* 132:96-104, 2018.

BASIC INFORMATION

DEFINITION

Measles is a childhood exanthem caused by an RNA virus called *Morbillivirus,* belonging to the family Paramyxoviridae.

SYNONYM

Rubeola

ICD-10CM CODES

B05.0	Measles complicated by encephalitis
B05.1	Measles complicated by meningitis
B05.2	Measles complicated by pneumonia
B05.3	Measles complicated by otitis media
B05.4	Measles with intestinal complications
B05.81	Measles keratitis and keratoconjunctivitis
B05.89	Other measles complications
B05.9	Measles without complication
Z23	Encounter for immunization

EPIDEMIOLOGY & DEMOGRAPHICS

- Before the introduction of an effective vaccine in 1963, measles was one of the most common childhood illnesses. In developing countries, where it mostly strikes children <5 yr, it remains a leading cause of childhood death.
- Although measles was eliminated in the United States in 2000 (Fig. E1), vaccine hesitancy and importation of the virus from other countries continues to cause outbreaks.
- In developed countries, measles outbreaks occasionally occur in adolescents and young adults who have not been immunized (incidence up to 10 per 100,000 person/yr).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation: 10 to 14 days (up to 3 wk in adults)
- Prodrome: 2 to 4 days; malaise, fever, rhinorrhea, conjunctivitis, cough
- Exanthem phase: 7 to 10 days
- The fever increases and peaks at 104° to 105° F together with the rash; it persists for 5 or 6 days. The patient's fever decreases over 24 hr
- Rash: Erythematous maculopapular eruption begins behind the ears, progresses to the forehead and neck, then spreads to face, trunk (Fig. E2, Fig. E3), upper extremities, buttocks, and lower extremities, in that order. After 3 days the rash fades in the same sequence by becoming copper brown and then desquamating
- Enanthem: *Koplik spots* are white papules 1 to 2 mm in diameter on an erythematous base. They first appear on the buccal mucosa opposite the lower molar 2 days before the rash and spread over 24 hr to involve most of the buccal and lower labial mucosa (Fig. E4). They fade after 3 days
- Other symptoms and signs: Malaise, anorexia, vomiting, diarrhea, abdominal pain, pharyngitis, lymphadenopathy, and occasional splenomegaly

Atypical measles (in vaccinated persons):

- Incubation: 10 to 14 days
- Prodrome: 1 to 3 days; high fever and headache
- Rash: Maculopapular, urticarial, or petechial rash that begins peripherally and progresses centrally
- Modified measles applies to patients who have received immune serum globulin and develop a milder illness
- Complications (30% of all cases):
  1. Otitis media
  2. Laryngitis, tracheitis
  3. Pneumonia (accounts for 90% of measles deaths)
  4. Encephalitis with lethargy, irritability, and seizures; 60% recover completely, 25% have neurologic sequelae (mental retardation, hemiplegia, paraplegia, epilepsy, deafness), and 15% die
  5. Myocarditis, pericarditis, hepatitis
  6. Complications more common in immunocompromised hosts and persons with AIDS

ETIOLOGY & PATHOGENESIS

- The measles virus is transmitted through the respiratory tract by airborne droplets. Patients shed measles virus from 7 days after exposure to 4 to 6 days after the onset of rash.
- Measles is one of the most contagious human pathogens. A single case of human measles results in 12 to 18 secondary cases in a susceptible population.
- It initially infects the respiratory epithelium; the patient becomes viremic during the prodromal phase, and the virus is disseminated to the skin, respiratory tract, and other organs.
- Generally patients with measles are infectious from 4 days before to 4 days after the onset of a rash.
- Viral clearance is achieved by cellular immunity.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other viral infections by enteroviruses, adenoviruses, human parvovirus B-19, rubella (Table E1)
- Scarlet fever
- Allergic reaction
- Kawasaki disease

WORKUP

Knowledge of outbreak, history, and physical findings (Koplik spots are diagnostic), laboratory tests

LABORATORY TESTS

- Enzyme-linked immunosorbent assay for measles antibodies, which appear shortly after the onset of the rash and peak 3 to 4 wk later
- Complete blood count: Leukopenia
- Cerebrospinal fluid analysis in encephalitis may reveal pleocytosis (lymphocytes) and an elevated protein

IMAGING STUDIES

Chest radiograph if pneumonia is suspected

TREATMENT

- Supportive (hydration, antipyretics for comfort and fever control, airway humidification in patients with respiratory tract involvement). Antiviral therapy is not effective.

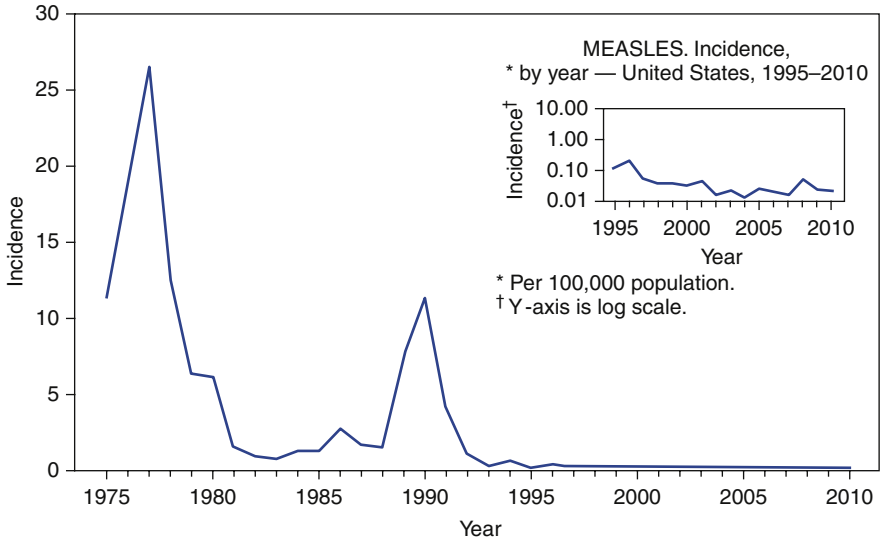

FIG. E1 Incidence by yr—U.S., 1975 to 2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, *MMWR Morb Mortal Wkly Rep* 59(53):1-111, 2012.)

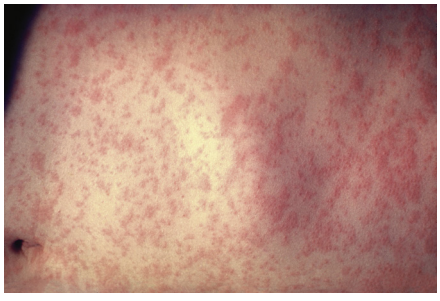

FIG. E2 Maculopapular rash of measles or rubeola showing coalescence of lesions. (Courtesy CDC/Dr. Heinz F. Eichenwald. From Gabbe SG: *Obstetrics,* ed 6, Philadelphia, 2012, WB Saunders.)

FIG. E3 Rubeola (measles). Intensely erythematous patches of the face with cephalocaudad spread onto the trunk and extremities. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

FIG. E4 Koplik spots on the buccal mucosa during the third day of rash. (From Centers for Disease Control and Prevention: Public Health Image Library, Image #4500, available at http://phil.cdc.gov/phil/details.asp.)

TABLE E1 A Guide to the Differential Diagnosis of Measles

	Conjunctivitis	Rhinitis	Sore throat	Exanthem	Leukocytosis	Specific Laboratory Tests
Measles	++	++	0	+	0	+
Rubella	0	±	±	0	0	+
Exanthem subitum	0	±	0	0	0	+
Enterovirus infection	0	±	±	0	0	+
Adenovirus infection	+	+	+	0	0	+
Scarlet fever	±	±	++	0	+	+
Infectious mononucleosis	0	0	++	±	±	
Drug rash	0	0	0	0	0	0

From Gabbe SG: *Obstetrics,* ed 6, Philadelphia, 2012, WB Saunders.

- Vitamin A therapy is beneficial in children >6 mo of age with measles who are hospitalized with measles and its complications or have any of the following risk factors: immunodeficiency, clinical evidence of vitamin A deficiency, impaired intestinal absorption, moderate to severe malnutrition, and recent immigration from areas where high mortality rates attributed to measles have been observed. Treatment regimen consists of a single dose of 200,000 IU orally for children >1 yr of age, 100,000 IU for children 6 mo to 1 yr of age and 50,000 IU for infants younger than 6 mo.
- Ribavirin is at times used for severe measles pneumonitis; however, it is not licensed in the U.S. for treatment of measles.
- Post-exposure prophylaxis: Measles vaccine given within 3 days after measles exposure, or human immune globulin given up to 6 days after exposure, can prevent or attenuate disease in susceptible persons.

PEARLS & CONSIDERATIONS

PREVENTION

- Passive immunization: Human immunoglobulin 0.5 ml/kg of body weight IM for persons weighing up to 30 kg and a dose of 400 mg/kg IU for persons of body weight OVER 30 kg
- Active immunization (see Section V).

RELATED CONTENT

Measles (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READING

Gastañaduy PA et al: A measles outbreak in an underimmunized Amish community in Ohio, *N Engl J Med* 375:1343-1354, 2016.

Strebel PM, Orenstein WA: Measles, *N Engl J Med* 381(4):349-357, 2019.

BASIC INFORMATION

DEFINITION

Meckel diverticulum is an ileal diverticulum located 100 cm proximal to the cecum. It results from failure of the omphalomesenteric duct to obliterate completely (as it should by the eighth wk of gestation).

SYNONYM

MD

ICD-10CM CODES

Q43.0	Meckel diverticulum (displaced) (hypertrophic)
C17.3	Meckel diverticulum, malignant

EPIDEMIOLOGY & DEMOGRAPHICS

- Meckel diverticulum, based on autopsy studies and intraoperative evidence, occurs in 0.3% to 4% of the population and is the most prevalent congenital anomaly of the gastrointestinal (GI) tract. Complications occur more frequently in males.
- Most patients who develop symptoms are <10 yr.
- The lifetime risk of complications developing in a case of Meckel diverticulum is 4%.
- In adults, complications (small bowel obstruction [25% to 40%], diverticulitis [20%]) are usually attributable to factors other than heterotopic mucosa.
- Tumors have rarely been reported in symptomatic Meckel diverticulum, with carcinoid being the most common type.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Painless lower GI bleeding (4%)
- Intestinal obstruction caused by intussusception, volvulus, herniation, or entrapment of a loop of bowel through a defect in the diverticular mesentery (6%)
- Meckel diverticulitis mimics acute appendicitis (5%)
- Rare primary tumor arising from diverticulum (carcinoid, sarcoma, leiomyoma, adenocarcinoma)
- Asymptomatic (80% to 95%)

ETIOLOGY & PATHOGENESIS

- As a remnant of the omphalomesenteric duct, Meckel diverticulum contains all layers of the intestinal wall and has its own mesentery and blood supply (branch of the superior mesenteric artery) (Fig. E1).
- The majority of complicated cases of Meckel diverticulum contain ectopic mucosa (75% gastric, 15% pancreatic). It causes ulceration and bleeding of ileal mucosa adjacent to the acidic ectopic gastric secretions. Alkaline secretions of ectopic pancreatic tissue can also cause ulcerations.

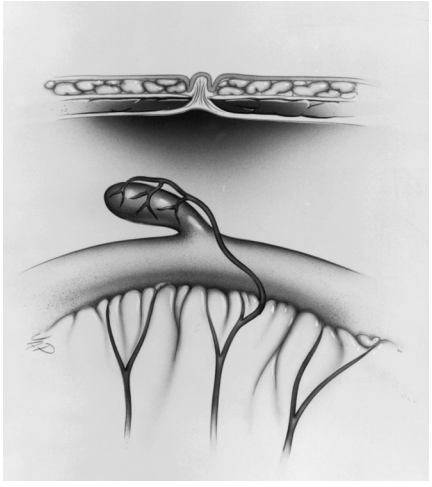

FIG. E1 Typical Meckel diverticulum located on the antimesenteric border. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, WB Saunders.)

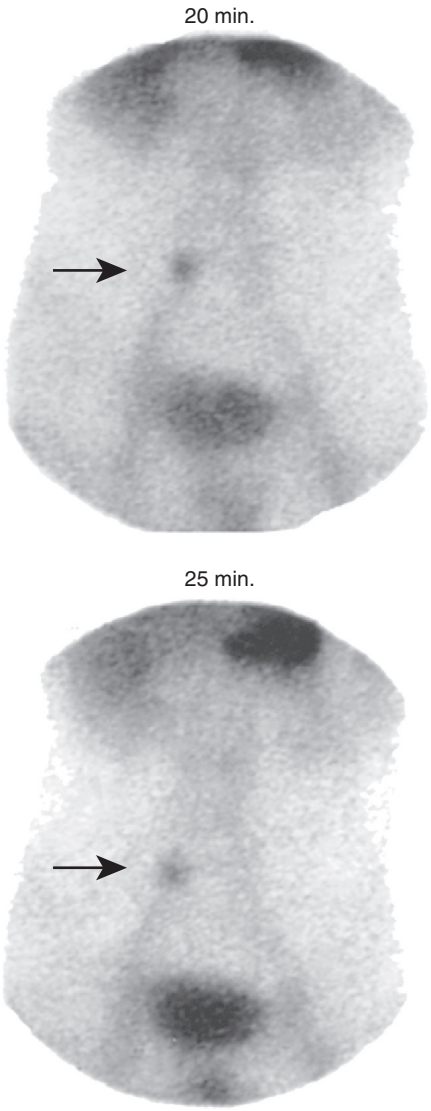

FIG. E2 Meckel scan demonstrating accumulation in the stomach superior bladder (inferior) and in the acid-secreting mucosa of a Meckel diverticulum. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, WB Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Appendicitis
- Crohn disease
- All causes of lower GI bleeding (polyp, colon cancer, arteriovenous malformation, diverticulosis, hemorrhoids)

WORKUP

- Diagnosis is often made intraoperatively when the preoperative diagnosis is appendicitis.
- Preoperative detection of symptomatic Meckel diverticulum requires a high index of suspicion.
- Meckel scan: In the case of GI bleeding of unknown source, a technetium scan will identify Meckel diverticulum (sensitivity: 85% in children, 62% in adults; specificity: 95% in children, 9% in adults) (Fig. E2).
- In patients with suspected small-bowel obstruction, intussusception, or diverticulitis, a CT scan of the abdomen and pelvis is helpful.

TREATMENT

- Surgical resection in symptomatic patients.
- There is controversy regarding the need to remove an incidentally found diverticulum, with most surgeons arguing in favor of resection.

RELATED CONTENT

Meckel Diverticulum (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

BASIC INFORMATION

DEFINITION

Mediastinitis is an infection involving the connective mediastinal tissue that fills the interpleural spaces and surrounds the mediastinal organs. It can be acute or chronic.

SYNONYMS

Fibrosing mediastinitis
Sclerosing mediastinitis
Granulomatous mediastinitis

ICD-10CM CODE
J98.5 Mediastinitis

EPIDEMIOLOGY

Acute mediastinitis (Box 1) occurs most frequently as a postoperative infection after a median sternotomy and can be a life-threatening infection. Most infections are bacterial in nature.

Chronic mediastinitis is a chronic form of infection in the mediastinum characterized by an invasive and compressive inflammatory infiltrate. It is mostly caused by fungi and some bacteria.

INCIDENCE: Incidence of postoperative mediastinitis ranges from 0.4% to 5%.

RISK FACTORS: Mediastinal infections have four possible sources:

- Direct contamination as seen in trauma or surgery (e.g., open heart, esophageal)
- Hematogenous or lymphatic spread
- Extension of infection from the neck or retroperitoneum
- Extension from the lung, pleura, or chest wall

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with acute mediastinitis present with acute onset of fever, tachycardia, chest pain, dysphagia, or respiratory distress. There may be signs of sternal wound infection or cellulitis and/or crepitus and edema of the chest wall.
- Patients with chronic mediastinitis are mostly asymptomatic until symptoms develop related to invasion or obstructions of structures within the mediastinum or adjacent to the mediastinum, such as cough, dyspnea, wheezing, chest pain, dysphagia, or hemoptysis. Complications of chronic or sclerosing mediastinitis include:
  1. Superior vena cava syndrome. Histoplasma is the most common nonmalignant cause of this syndrome, marked by edema of face, neck and torso; neck vein distention; and headache
  2. Pulmonary venous or arterial obstruction
  3. Esophageal obstruction, cor pulmonale, constructive pericarditis
  4. Thoracic duct obstruction

BOX 1 Classification of Mediastinitis

Acute Mediastinitis
- A. Due to traumatic perforation of the esophagus
  1. Spontaneous or postemetic
  2. Foreign body–associated
  3. Instrumentation or surgery
- B. Due to extension of infection from adjacent structures
  1. Infection of the head and neck
  2. Infections of lungs, pleura, lymph nodes, or pericardium
  3. Subphrenic infection
  4. Vertebral osteomyelitis
  5. Hematogenous dissemination
- C. Postoperative

Chronic Mediastinitis

From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

ETIOLOGY (TABLE 1)

Acute mediastinitis:

- Related to head and neck infections or esophageal perforation
  1. Anaerobic bacteria: *Peptostreptococci, Veillonella, Fusobacterium, Actinomyces, Prevotella, Eubacterium, Bacteroides*
  2. Aerobic bacteria: *Streptococcus, Staphylococcus, Corynebacterium, Moraxella*, enteric gram-negative rods
  3. Fungi: *Candida albicans*
- Related to cardiothoracic surgery
  1. Gram-positive bacteria: *Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus, Streptococcus*
  2. Gram-negative bacteria: *Escherichia coli, Enterobacter, Klebsiella, Proteus, Pseudomonas*, other Enterobacteriaceae
  3. Fungi: *Candida albicans*

Chronic mediastinitis:

- *Histoplasma capsulatum,* a dimorphic fungus, is the most common and can cause mediastinal granuloma or fibrosing mediastinitis. A leakage of fungal antigens from lymph nodes into the mediastinal space is believed to cause a hypersensitivity reaction and subsequent exuberant fibrotic response.
- Other: *Mycobacterium tuberculosis, Nocardia,* actinomycosis, aspergillosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

For chronic mediastinitis:

- Tumors that can also cause superior vena cava syndrome (e.g., Hodgkin and non-Hodgkin lymphomas, mesothelioma)
- Sarcoidosis
- Behçet syndrome
- Mediastinal fibrosis associated with radiation
- Silicosis

LABORATORY TESTS

- CBC with differential, C-reactive protein, and procalcitonin can point to bacterial infection
- Obtain cultures: Aerobic and anaerobic bacteria and fungi, intraoperatively or of any purulent drainage
- Pathologic examination: Distinguish between cancer and infection for chronic mediastinitis and allow for specific fungal stains on tissues

IMAGING STUDIES

- Chest x-ray: Can show diffuse mediastinal widening or evidence of mediastinal abscess, including gas bubbles or fluid level. Pneumomediastinum (Fig. E1) or pneumothorax can be seen with esophageal perforation (Table 2).

TABLE 1 Microbiology of Mediastinitis

Organisms Frequently Recovered in Mediastinitis Secondary to Infection of the Head and Neck or Esophageal Perforation

Anaerobic

Gram-positive cocci—*Peptostreptococcus* spp.
Gram-positive bacilli—*Actinomyces, Eubacterium, Lactobacillus*
Gram-negative cocci—*Veillonella*
Gram-negative bacilli—*Bacteroides* spp., *Fusobacterium* spp., *Prevotella* spp., *Porphyromonas* spp.

Aerobic or Facultative

Gram-positive cocci—*Streptococcus* spp., *Staphylococcus* spp.
Gram-positive bacilli—*Corynebacterium*
Gram-negative cocci—*Moraxella*
Gram-negative bacilli—Enterobacteriaceae, *Pseudomonas* spp., *Eikenella corrodens*
Fungi—*Candida albicans*

Representative Organisms Recovered in Mediastinitis Secondary to Cardiothoracic Surgery, with Representative Rate and Range

Gram-Positive Cocci

Staphylococcus aureus, 25% (7.1%-66.7%)
Staphylococcus epidermidis, 30% (6%-45.5%)
Enterococcus spp., 10% (8%-18.8%)
Streptococcus spp., 2% (0%-18.2%)

Gram-Negative Bacilli

Escherichia coli, 5% (0%-12.5%)
Enterobacter spp., 10% (4%-21.4%)
Klebsiella spp., 3% (0%-21.1%)
Proteus spp., 2% (0%-7.1%)
Other Enterobacteriaceae, 2% (0%-20%)
Pseudomonas spp., 2% (0%-54%)

Fungi

C. albicans, <2 (0%-20.5%)
Polymicrobial, 10% (0%-40%)

Others Occasionally Reported

Acinetobacter, Salmonella spp., *Legionella* spp., *Bacteroides fragilis, Corynebacterium* spp., *Burkholderia cepacia, Mycoplasma hominis, Candida tropicalis, Aspergillus* spp., *Nocardia* spp., *Kluyvera, Gordonia sputi, Mycobacterium fortuitum, Mycobacterium chelonae, Rhodococcus bronchialis*

Other Unusual Causes of Mediastinitis

Anthrax, brucellosis, actinomycosis, paragonimiasis, *Streptococcus pneumonia*

From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

TABLE 2 Risk Factors for Surgical Site Infection/Mediastinitis Post–Cardiac Surgery

Preoperative Risk Factors	Operative Risk Factors	Postoperative Risk Factors
Increasing age	Emergent surgery	Need for reexploration
Diabetes	Heart transplant	Prolonged ICU stay
Staphylococcus aureus nasal colonization	Increasing complexity of surgery	Need for mechanical ventilation >48 hr
Previous sternotomy	Use of internal thoracic arteries in CABG	Lack of perioperative glucose control
COPD	Prolonged operative time	Placement of tracheostomy
Peripheral vascular disease	Hair removal by razor, not clippers	Postoperative myocardial infarction
Class 3-4 angina	Inappropriate timing of antibiotics	Receipt of multiple blood products
Renal failure requiring hemodialysis	Prolonged time on cardiopulmonary bypass	Postoperative low cardiac output state
History of endocarditis	High core temperature during bypass (>38° C; 100.4° F)	
Cigarette smoking		
Low cardiac output		
Concurrent infection		
Prolonged preoperative hospitalization		
Preoperative use of a ventricular assist device		

CABG, Coronary artery bypass grafting; *COPD,* chronic obstructive pulmonary disease; *ICU,* intensive care unit.
From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

- Chest CT (Fig. E2): Can show the same as x-ray but is more sensitive in determining degree of mediastinal involvement and may guide drainage procedures for treatment or diagnosis.
- MRI may be superior to CT for sclerosing mediastinitis.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Surgery remains the gold standard treatment of mediastinitis for optimal drainage and debridement.

- Open techniques: Debridement of infected tissue and open packing of the wound with delayed closure or use of vacuum-assisted closure for acute mediastinitis
- Closed techniques: Debridement of infected tissues, closure of the sternum, and postoperative irrigation through drainage tubes for acute mediastinitis

ACUTE GENERAL Rx

- Intravenous antibiotics: Also a cornerstone of therapy but without surgery may fail. Broad-spectrum antibiotics should be used until cultures are finalized. Combination of piperacillin-tazobactam or meropenem plus vancomycin offers good initial coverage for acute mediastinitis. Other options include ciprofloxacin or cefepime for gram-negative rods, linezolid for gram-positive bacteria, metronidazole for anaerobic bacteria.
- Therapy is 2 to 3 wk, but some cases may require 4 to 6 wk.

CHRONIC Rx

There is no definitive cure for chronic fibrosing or sclerosing mediastinitis. Antifungal agents and steroids generally do not work. The goal of therapy is to palliate symptoms by relieving airway, vascular, or esophageal obstruction. Surgery in patients with extensive fibrosis has high morbidity and mortality.

DISPOSITION

Patients may need extensive wound care and possible vacuum-assisted closure and prolonged intravenous antibiotics.

REFERRAL

- Thoracic surgeon and/or head and neck surgeon for surgery and debridement
- Infectious diseases consultant for antibiotic selection and long-term management

PEARLS & CONSIDERATIONS

COMMENTS

Histoplasma capsulatum is a dimorphic fungus found commonly in bird and bat fecal material and is most prevalent in the Ohio and Mississippi river valleys of the United States.

PREVENTION

Antibiotic prophylaxis should be given within 60 min before incision for surgeries requiring sternotomy. Options include cefazolin 1 g IV if <80 kg and 2 g if >80 kg, or cefuroxime 1.5 g IV. If the patient is penicillin allergic or has a history of methicillin-resistant *S. aureus* (MRSA) infection or surgery is to be done in a hospital where MRSA infection is common, use vancomycin 1 g IV.

SUGGESTED READINGS

Available online at ExpertConsult.com

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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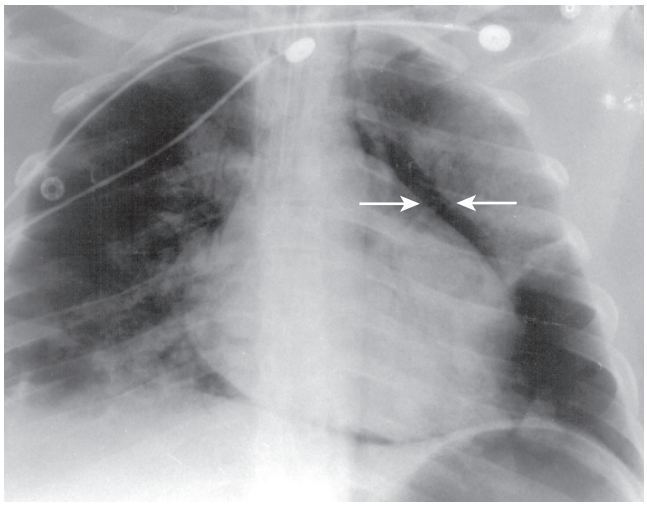

FIG. E1 Mediastinitis. Chest radiograph shows large pneumomediastinum and pneumopericardium *(arrows)* in a patient with mediastinitis. (From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.)

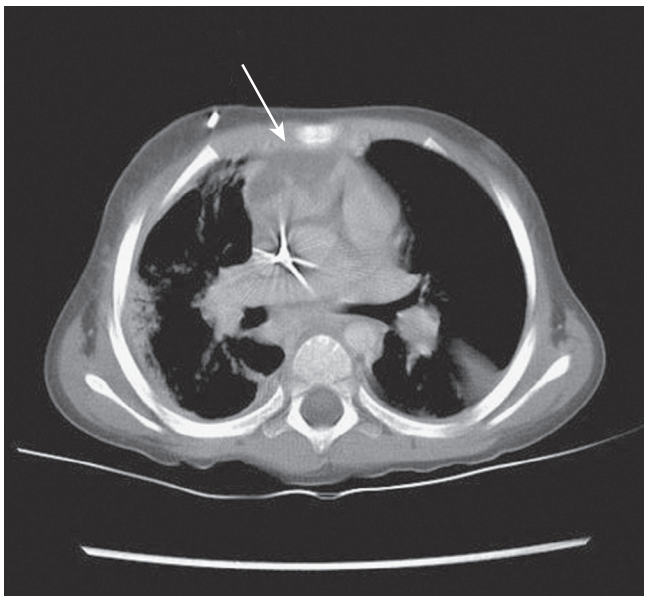

FIG. E2 Contrast-enhanced computed tomography scan shows a 3 cm × 3 cm heterogeneous enhancing abscess *(arrow)* in the anterior mediastinum of a child acutely ill with *Streptococcus pneumoniae* bacteremia and pneumonia with empyema. Cultures from the mediastinal abscess at the time of surgical drainage were sterile. (From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.)

Medical Marijuana

BASIC INFORMATION

DEFINITION

Medical cannabis refers to the use of the unprocessed marijuana plant or part of the plant or extracts from the marijuana plant as medical therapy to treat disease or alleviate symptoms.

SYNONYMS

Medical cannabis
Cannabinoids—are biologically active compounds that have affinity or activity to the cannabinoid receptors. They may be derived from the plant or be synthetic.
CBD—cannabinol
THC—Δ^9 -tetrahydrocannabinol

ICD-10CM CODES

F12.9	Cannabis use, unspecified
Z02.79	Encounter for issue of other medical certificate
Z79.899	Other long term (current) drug therapy

BACKGROUND

- First medical marijuana law (MML) was enacted in California in 1996, allowing for use of medical cannabis despite lack of Food and Drug Administration (FDA) testing for safety and efficacy.
- In 2014, 0.8% of the U.S. population used medical marijuana exclusively, and 0.5% used medical and recreational marijuana.
- Of 2014 marijuana smokers, 6.2% used medical marijuana only and 3.6% used medical and recreational marijuana.
- In 2015, 1.57% U.S. population used medical marijuana; highest increase in prevalence noted to be in 2015.
- Residents of medical marijuana states were 1.3 times more likely to use medical marijuana in 2015 compared to 2013.
- As of July 2019, state-level referendum and legislation resulted in 33 U.S. states, DC, Guam, and Puerto Rico with policies that legalized marijuana use for medical purposes.

MECHANISM OF ACTION

- Cannabinoids elicit their effects by interacting with cannabinoid receptors in various central nervous system (CNS) locations, eliciting diverse CNS and peripheral nervous system (PNS) effects.
- Primarily bind to CB1 G-protein-coupled receptors in the basal ganglia, hippocampus, cortex, and cerebellum, eliciting antinociception, locomotor, and psychoactive effects.
- Marijuana contains roughly 60 plant-derived cannabinoid compounds, with the major phytocannabinoids being cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC).

FORMULATIONS

Research has demonstrated a wide range of THC and CBD concentrations in various formulations, with frequent inaccurate labelling.

- Cigarettes
- Tinctures
- Capsules
- Vaporization cartridges
- Purified cannabinoids butane hash oil
- Supercritical fluid extracts (SFEs or "dabs")
- Buccal sprays
- Edibles
- Lozenges
- Transdermal patches

INDICATIONS

- Variable evidence for treatment of:
  1. Chronic pain
  2. Chemotherapy-induced nausea/vomiting
  3. HIV-related anorexia
  4. Glaucoma
  5. Anxiety
  6. Multiple sclerosis (MS)
  7. Seizures
- Marijuana has not been FDA approved as safe and effective for any indication and remains a Schedule I drug.
- However, there are phytocannabinoids and synthetic phytocannabinoid analogs that are FDA approved.
  1. Dronabinol and Nabilone (synthetic THC analogs) are schedule II FDA approved medications for AIDS associated anorexia and chemotherapy induced nausea, respectively.
  2. Purified cannabidiol oral solution (Epidiolex) is FDA approved for seizures associated with Dravet or Lennox-Gastaut syndrome.
- Qualifying diagnoses for certification for prescription medical marijuana vary by state, but typically include:
  1. Cancer
  2. Glaucoma
  3. HIV/AIDS
  4. Hepatitis C
  5. Cachexia
  6. Severe, debilitating, chronic pain
  7. Severe nausea
  8. Seizures
  9. Severe muscle spasms
  10. Crohn disease
  11. Alzheimer disease
  12. PTSD
  13. Sickle cell disease

EFFICACY

- There is evidence in the medical literature demonstrating that marijuana improves non–cancer-related pain, chemotherapy-induced nausea and vomiting, and spasticity in multiple sclerosis.
  1. A 2011 systematic review of randomized controlled trials (RCTs) demonstrated statistically significant improvement in pain scores for non–cancer-related chronic pain in 15 of 18 trials with no serious adverse effects.
  2. A 2015 systematic review and meta-analysis showed improved response in nausea and vomiting compared to placebo (OR 3.82).
  3. A 2018 systematic review demonstrated a decrease in nausea and vomiting following chemotherapy (RR 3.60 compared to placebo), improved spasticity with MS (RR 1.45 compared to placebo), and a modest benefit with primarily neuropathic pain (RR 1.37 compared to placebo) with frequent adverse effects including psychosis, "feeling high," and somnolence (number needed to harm = 5 to 8).
     a. No statistically significant improvement was noted in acute pain.
  4. A Cochrane review in 2013 found no statistically significant weight gain with dronabinol in HIV/AIDS patients, and multiple RCTs have identified megestrol acetate as superior to dronabinol for weight gain in cancer patients.

RISKS OF USE

- Marijuana use has been demonstrated to impair short-term memory consolidation, reaction time, and concept formation, and to increase incidence of road traffic accidents, ataxia, euphoria, disorientation, dry mouth, somnolence, and, at high doses, psychosis, panic, and paranoia.
- Meta-analyses demonstrate increased respiratory symptoms of cough, sputum production, and wheeze with smoking marijuana; however, there was no statistical difference in pulmonary function.
- Concomitant use of other medications such as opiates and benzodiazepines should be avoided as it could lead to somnolence and respiratory suppression.
- Acute marijuana intoxication is associated with reversible changes in P and T waves and ST segments (pseudo-Wellens syndrome).[1]
- Medical marijuana should be stored away from children given the risk of toxic ingestion.

PRESCRIBING

- Marijuana remains classified as a schedule I drug under the Controlled Substance Act of 1970.
- However, the Justice Department declared it would not prosecute any physician who recommends medical marijuana for a legitimate medical indication in a state where it has been legalized.
- Medical marijuana card (MMC)
  1. MMC allows a patient to possess a certain amount of marijuana for medical use and not be prosecuted for possession of marijuana.
  2. In order to obtain an MMC, a patient must obtain physician certification confirming a clinical indication for medical marijuana.
  3. With an MMC, the patient can go to a licensed medical marijuana compassion center (dispensary), which will dispense a dose and formulation of medical marijuana appropriate for the patient's medical condition.
  4. Physicians do not prescribe the dose or formulation of medical marijuana.
- To certify a patient for a medical marijuana card, physicians must

[1]Co MLF et al: Pseudo-Wellens syndrome after heavy marijuana use, *Cleve Clin J Med* 84(8):590-591, 2017.

1. Complete a Department of Health certification form.
   a. Forms vary by state, but typically consist of a single-page form indicating a qualifying diagnosis that is to be signed by the physician.
2. Complete and document a full medical history and physical exam.
3. Explain the risks, benefits, and side effects of medical marijuana.
4. Continue an ongoing role on the patient's health care team.
5. Maintain accurate medical records and documentation of the patient's clinical indication for medical marijuana.

- Some states require additional physician training and registration with the state medical marijuana program prior to being able to certify patients.
- Physicians are under no obligation to issue medical marijuana certifications.

PEARLS & CONSIDERATIONS

- Medical marijuana has been shown to improve non–cancer-related pain, chemotherapy-induced nausea and vomiting, and spasticity in multiple sclerosis.
  1. However, qualifying diagnoses for a medical marijuana card include cancer, glaucoma, HIV/AIDS, hepatitis C, cachexia, debilitating chronic pain, severe nausea, seizures, severe muscle spasms, Crohn disease, Alzheimer disease, PTSD, and sickle cell disease. Qualifying diagnoses may vary from state to state.
  2. Adverse effects include increased incidence of road traffic accidents and pulmonary and cognitive side effects. At high doses, psychosis, panic, and paranoia can occur.
  3. Hospitals may also have specific restrictions and policies regarding medical marijuana for inpatient stays.
- Medical marijuana laws and regulations permit patients to use medical marijuana if certified by a physician but vary by state.
  1. Physician certification involves documentation that a patient has a qualifying clinical condition.
  2. A medical marijuana card entitles a patient or designated caregiver to possess a given amount of marijuana and therefore will not be prosecuted for possession of marijuana.
  3. Medical marijuana can be obtained at state regulated medical marijuana compassion centers (dispensaries). Compassion centers obtain marijuana from licensed cultivators and offer a variety of formulations that are regulated by the state.
  4. There is no FDA oversight of the compassion centers.
- Physicians do not prescribe the dose or formulation of medical marijuana.
- Physicians are under no obligation to issue medical marijuana certifications.
- Emergency department (ED) visits attributable to inhaled cannabis are more frequent than those attributable to edible cannabis, although the latter is associated with more acute psychiatric visits and more ED visits than expected.[2]

PATIENT & FAMILY EDUCATION

- Patients must possess a valid state-issued ID and apply for a state medical marijuana card.
- Patients can obtain medical marijuana from compassion centers without a medical marijuana card but could then be prosecuted for possession of marijuana.
- Patients should be aware that concomitant use of other medications such as opiates and benzodiazepines should be avoided as it could lead to somnolence and respiratory suppression.
- Patients should store medical marijuana away from children given the risk of toxic ingestions.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pain Management in Chronic Pain (Related Key Topic)

Chemotherapy-Induced Nausea and Vomiting (Related Key Topic)

AUTHORS: **Anjulika Chawla, MD,** and **Seth Clark, MD, MPH**

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Medication-Related Osteonecrosis of the Jaw

BASIC INFORMATION

DEFINITION

The American Association of Oral and Maxillofacial Surgeons (AAOMS) defines bisphosphonate-related osteonecrosis of the jaw (BRONJ) as an exposure of bone in the maxillofacial region that does not heal within 8 wk, in patients receiving therapeutic doses of bisphosphonates (BPs) who have not undergone radiation therapy to the craniofacial region and who do not have evidence of metastatic disease in the jaw. Osteoclast apoptosis may occur due to the antiresorptive effects of BPs, preventing the release of bone-regenerative proteins and thus preventing bone renewal and remodeling. This results in tissue loss and exposed bone. BRONJ primarily involves the jawbone due to its higher risk for complications from minor injury and infection when the healing potential or vascular supply is compromised.

Cases of ONJ have also been reported in patients receiving denosumab as well as chemotherapeutic and immunosuppressive agents, such as bevacizumab, sirolimus, sorafenib, and sunitinib. The AAOMS therefore uses the term medication-related osteonecrosis of the jaw (MRONJ).

SYNONYMS

Bisphosphonate-induced osteonecrosis of the jaw (BIONJ)
Medication-related osteonecrosis of the jaw (MRONJ)
Antiresorptive agent-related osteonecrosis of the jaw (ARONJ)
Denosumab-related osteonecrosis of the jaw (DRONJ)

ICD-10CM CODE
M87.180 Osteonecrosis due to drugs, jaw

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- A 2015 systematic review and consensus of 14 national and international societies describe the incidence of BRONJ in patients receiving oral BPs for the treatment of osteoporosis as 1.04 to 69 per 100,000 patient-yrs. The incidence of BRONJ in patients receiving intravenous (IV) BPs ranged from 0 to 90 per 100,000 patient-yrs.
- BRONJ has been estimated at 3.9% with oral BPs and at 14.8% with IV BPs at 42 mo after tooth extraction.
- DRONJ has been estimated at 0.68% in patients with postmenopausal osteoporosis who underwent invasive oral procedures vs. 0.05% for those who did not. The overall exposure-adjusted rate of DRONJ was 5.2 per 10,000 patient-yrs.

PEAK INCIDENCE:

- BRONJ has been identified as early as 7 mo after the use of IV BPs in patients with malignancy and as early as 13 mo in patients with osteoporosis. Incidence may depend on when dentoalveolar surgery occurs during BP treatment.
- A 2017 retrospective secondary analysis of 349 patients made the following estimates of median time to onset for 50% of patients to develop BRONJ: (1) 6 yr for those treated with oral alendronate, (2) 2.2 yr for those treated with IV zoledronate, (3) 5.3 yr for patients with osteoporosis, and (4) 2.2 yr for those with malignancy.
- A 2016 case series of 13 patients with malignancy receiving denosumab and with no history of BP treatment reported that DRONJ occurred after 5 to 36 doses of denosumab 120 mg subcutaneous every 4 to 6 wk.

PREVALENCE:

- Prevalence in 2008: estimated 13.3% of patients with malignancy receiving an IV BP.
- Most prevalent in patients with multiple myeloma or breast cancer versus other cancers or osteoporosis.

PREDOMINANT SEX AND AGE:

- Sex not statistically associated with MRONJ.
- Age as a risk factor for adults is variably reported in the literature.

GENETICS:

- Single nucleotide polymorphisms have been identified in the *CYP2C8* gene among patients with multiple myeloma and exposure to IV BPs.
- Polymorphisms in the *RBMS3* gene in white patients of European descent have been associated with a nearly six fold increase in the risk of developing BRONJ.
- A 2014 study of patients in Taiwan who received alendronate estimated an incidence rate of 283 per 100,000 person-yrs, suggesting a higher incidence in this ethnic group.

RISK FACTORS:

- Patients with malignancy who are exposed to IV BPs and undergo dentoalveolar surgery have an estimated five- to twenty-one fold increased risk for BRONJ compared with similar patients who do not undergo this surgery
- The 2014 AAOMS position paper estimates that the risk of MRONJ is about 100 times greater for patients with malignancy who receive antiresorptive agents versus patients with osteoporosis
- With IV formulations such as zoledronic acid, the risk ratio for developing BRONJ is 14.6 with IV versus oral products
- Longer duration of antiresorptive therapy
- Concomitant antiangiogenic agents and corticosteroids
- History of periodontal and dental abscesses
- Trauma due to invasive oral procedures such as tooth extractions
- Bacterial infection
- Chronic inflammation
- Poor oral hygiene
- Smoking
- Concomitant diabetes
- Ill-fitting dentures, resulting in mechanical injury
- Renal impairment and advanced age may be associated with increased MRONJ severity
- Rheumatoid arthritis (RA):
  1. Compain et al (2018) found that BRONJ seems to occur earlier in patients with RA than with osteoporosis (46.8 vs. 63.6 mo); likely due to age at initiation of BP, cumulative dose, immunosuppression, chronic vasculitis, dental health status, and concomitant disease-modifying treatments.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Exposed areas of necrotic bone in the mandible or maxilla, with 65% of cases involving the mandible. Multifocal or bilateral involvement is possible but uncommon. Pathologic fracture of the jaw may occur.
- Pain in the maxillofacial region, although one third of lesions may be painless.
- Paresthesia of the chin is an early sign.
- Tooth mobility or spontaneous tooth loss.
- Mucosal swelling, erythema, ulceration, altered sensation.
- Infection.
- BRONJ due to IV BPs may produce larger and more frequent buccolingual cortical bone perforations than oral BPs.
- DRONJ may produce large sequestrum and periosteal reaction.

ETIOLOGY

Exposure to BPs as well as other antiresorptive and antiangiogenic agents

DIAGNOSIS

The AAOMS considers a diagnosis of MRONJ if the following three characteristics are present:

1. Current or previous treatment with a BP, denosumab, or antiangiogenic agent
2. Exposed bone or bone that can be probed through intraoral or extraoral fistulae in the maxillofacial region persisting for more than 8 wk
3. No history of radiation therapy to the maxillofacial region or evident metastatic disease to the jaw

DIFFERENTIAL DIAGNOSIS

- Suppurative osteomyelitis of the jaw (SOJ)
- Osteoradionecrosis of the jaw (ORNJ)
- Alveolar osteitis, gingivitis, sinusitis, fibro-osseous lesion, sarcoma, sclerosing osteomyelitis, periodontitis, dental caries, and temporomandibular joint disorders

WORKUP

- Treatment history, including medications and radiation therapy
- Past medical history, including osteoporosis and malignancy

LABORATORY TESTS

A validated diagnostic test is not available to identify patients at an increased risk of BRONJ. Tissue biopsy should only be performed if metastatic disease is strongly suspected and its detection would change the management of BRONJ. Histopathology of BRONJ shows empty osteocytic lacunae, empty Haversian and Volkmann canals, an absence of inflammatory cells or blood vessels in the marrow space, and absence of extracellular collagenase.

IMAGING STUDIES

Panoramic and periapical radiographs

Rx TREATMENT

Goals of treatment for MRONJ include:
- Control or reduce pain.
- Control secondary infection.
- Minimize progression or occurrence of bone necrosis, as well as extension of lesion(s).

NONPHARMACOLOGIC THERAPY

The AAOMS recommends the following surgical strategies based on MRONJ staging:
- Stage 0 (no clinical evidence of necrotic bone, nonexposed bone variant): No surgery
- Stage 1 (exposed and necrotic bone, or fistulae that probe to bone, asymptomatic, no infection): No surgery
- Stage 2 (exposed and necrotic bone, or fistulae that probe to bone, with pain or infection): Superficial debridement
- Stage 3 (exposed and necrotic bone with pain, infection, *and* one of the following features: necrosis extending beyond alveolar bone, pathologic fracture, extraoral fistula, oral antral or nasal communication, osteolysis extending to mandible of sinus floor): Surgical debridement or resection for palliation of infection and pain

Literature suggests that success rates with surgical management are higher and less variable than with conservative management. The AAOMS recommends surgery for patients with stage 3 MRONJ. However, a surgical margin with viable bone can be difficult to obtain. The entire jawbone likely has been exposed to accumulation of the drug (especially BPs), and therefore successful eradication of necrotic bone is often not possible. Those areas of necrosis that consistently irritate soft tissues should undergo debridement as necessary because dead tissue will interfere with wound healing and will be prone to infection. Another consideration is that some patients may not be surgical candidates if their overall health is poor and/or if chemotherapy is incomplete.

Limited evidence supports the use of hyperbaric oxygen as adjunct to surgery and antibiotics to slow progression and improve pain. Small case reports have documented the use of platelet-rich plasma, low-level laser irradiation, parathyroid hormone, and bone morphogenic protein; however, the efficacy of these methods has not been established through controlled studies.

With regards to surgery for stages 2 and 3, Kagami et al (2015) found that curettage under local anesthesia had a higher risk of relapse than sequestrectomy, saucerization, or mandibulectomy. Shibahara et al (2018) observed that the majority of patients with stage 2 BRONJ who underwent surgery (N = 936) achieved remission (46.3%) or improvement in BRONJ (30.6%). Stage 2 surgery may also be reasonable for older patients or those with limited life expectancy, rather than lengthy debridement that may significantly decrease quality of life.

ACUTE GENERAL Rx

Both chlorhexidine mouth rinse and antibiotics for 1 to 3 wk have been found useful for stage reduction. Most microbes are sensitive to penicillin antibiotics.
- Chlorhexidine 0.12% antibacterial mouth rinse daily for stages 1 to 3
- Oral antibiotics for symptomatic stage 2 and oral or IV antibiotics for stage 3
- Analgesics for stages 2 or 3

CHRONIC Rx

- Determine whether discontinuation of antiresorptive agent is appropriate. A multicenter retrospective chart review by Hayashida et al (2019) evaluated 427 cases in patients with osteoporosis or malignancy. Discontinuation of antiresorptive therapy significantly increased cure rate in those with osteoporosis who underwent nonsurgical treatment and did not impact any patients who underwent surgical treatment.
  1. Evaluate potential benefit of continuing antiresorptive agent, such as relief of bone pain in malignancy or prevention of fractures with high morbidity and mortality.
  2. BPs have a prolonged half-life, so return to normal osteoclast function and bone turnover may be too gradual.
  3. Consider other risks of antiresorptive agents, such as atypical femoral fractures.
- If discontinuing antiresorptive agents, consider alternative treatments for osteoporosis or bone pain.
- Anecdotal case reports exist for using teriparatide (unless the patient has bone metastases or is at risk for osteosarcoma) or pentoxifylline plus tocopherol to heal BRONJ.
- Patients with malignancy and any stage of MRONJ: Dental specialist should re-evaluate lesions every 8 wk and communicate condition to oncologist.

DISPOSITION

A retrospective cohort study in Japan by Shibahara et al (2018) showed that lack of risk factors for BRONJ, performing surgical removal/reduction/resection in stage 2 BRONJ, a completely closed wound, and discontinuing BPs were all associated with a positive prognosis.
- Patients with involvement of the maxilla appear to have a greater likelihood of repeat surgery.
- Patients taking oral rather than IV BPs may have less severe complications and may have a better response.
- Treatment with antibiotics and chlorhexidine mouth rinse, withdrawal of BPs, and surgical removal of loose sequestra may possibly reduce pain and lesions of osteonecrosis.

Concomitant diabetes, lower serum albumin, malignancy as indication for antiresorptive agent, and nonsurgical treatment of MRONJ were associated with worse outcomes, including poor healing rate, in the chart review by Hayashida et al (2019).

REFERRAL

Oral and maxillofacial surgeon

PEARLS & CONSIDERATIONS

COMMENTS

- Patients may be asymptomatic for wk to yrs before BRONJ is apparent.
- Radiographic changes may not be observed until significant disease has developed.
- Tooth extraction may be difficult to avoid in patients at high risk of BRONJ if an underlying bacterial infection is present.
- Patients with malignancy are at highest risk because the dosages of BPs are much higher than for osteoporosis.
- Use of BPs in pediatric patients has increased without identified cases of BRONJ to date. Further evaluation of long-term use of BPs in these patients is warranted.

PREVENTION

- Regular dental hygiene and routine (every 3 mo for patients with malignancy) dental examinations.
  1. Results from Coello-Suanzes et al (2018) for 255 patients with malignancy showed that patients who received dental procedures prior to initiation of zoledronic acid had a statistically significant lower incidence of BRONJ (7.3% vs. 36.5%).
- Appropriate fitting of dentures with periodic mucosal examination.
- Assessment of patients for other risk factors of MRONJ.
- Completion of any anticipated dental procedures before beginning antiresorptive therapy.
- Asymptomatic patients receiving IV BPs: Limit dental surgery to removal of nonrestorable teeth and avoid dental implants in patients who also have cancer.
- The 2014 AAOMS position paper supports a 2-mo drug holiday before oral surgery for patients who have received BPs for greater than 4 yr or for patients exposed to less than 4 yr of BPs and taking concomitant corticosteroids or antiangiogenics. Allow osseous healing to complete before restarting BPs. A 2017 retrospective study did not find a difference in ONJ incidence due to preextraction drug holidays of 2 or 3 mo. In terms of long-term BP drug holidays:
  1. Results from the FLEX trial suggest that women with postmenopausal osteoporosis who have taken alendronate for 5 yr and are at low risk of vertebral fractures may discontinue the drug for up to 5 yr.
  2. Results from the HORIZON-PFT extension trial suggest that women with postmenopausal osteoporosis who have taken IV zoledronic acid for 3 yr and are at low risk of vertebral fractures may discontinue for up to 3 yr.
- Careful monitoring of patients after dentoalveolar surgery and delayed initiation of BPs by at least 2 to 3 wk to allow for osseous healing.
- Evidence suggests a threefold reduction in the incidence of ONJ when preventive measures are practiced.

PATIENT & FAMILY EDUCATION

- All health care providers should be aware of past and current use of antiresorptive agents.
- Contact a health care provider if any of the following are observed:
  1. Presence of exposed bone in the maxillofacial area
  2. Persisting pain in the maxillofacial area

3. Signs of infection such as fever, pus, and swelling

- Practice good dental hygiene and keep regular dental appointments.
- Patients needing assistance with access to dental care may contact the AAOMS, the Centers for Medicare & Medicaid Services, the United Way, nearby dental schools, or their local health department.

AUTHORS: **Christine Eisenhower, PharmD,** and **Connie Wang, PharmD**

SUGGESTED READINGS

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Meigs Syndrome

BASIC INFORMATION

DEFINITIONS

- **Classic Meigs syndrome:** A triad characterized by the presence of ascites and pleural effusion (usually right-sided) in association with a benign fibroma or fibroma-like ovarian tumor (thecoma, granulosa cell tumor, or Brenner tumor).
- **Nonclassic Meigs syndrome:** Characterized by ascites and pleural effusion in conjunction with a benign ovarian, fallopian tube, or broad ligament tumor that is not included in the definition of classic Meigs syndrome.
- **Pseudo-Meigs syndrome:** Characterized by both ascites and pleural effusion but caused by a pelvic or abdominal tumor, either benign or malignant, not included in either classic Meigs or nonclassic Meigs syndrome, such as leiomyomas, struma ovarii, mucinous cystadenoma, teratoma, and malignancies that are metastatic to the ovary (particularly colorectal cancer).
- **Pseudo-pseudo Meigs (Tjalma) syndrome:** Characterized by the triad of ascites, pleural effusion, and an elevated CA-125 (Cancer antigen 125) in a patient with systemic lupus erythematosus.

ICD-10CM CODES

C56.9	Malignant neoplasm of unspecified ovary
D27.9	Benign neoplasm of unspecified ovary
D28.2	Benign neoplasm of uterine tubes and ligaments
D28.7	Benign neoplasm of other specified female genital organs
J91.8	Pleural effusion in other conditions classified elsewhere
R18.0	Malignant ascites
R18.8	Other ascites

EPIDEMIOLOGY & DEMOGRAPHICS

- Occurs in 1% to 2% of ovarian fibromas (associated with approximately 0.004% of ovarian tumors)
- <1% progress to malignancy
- Incidence begins to increase in the 30s. Most frequently encountered in postmenopausal women (average age 50 yr)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abdominal bloating/increased girth
- Intermittent pelvic pain (intermittent torsion)
- Weight gain or loss
- Pelvic mass on bimanual examination
- Acute pelvic/abdominal tenderness
- Fluid wave
- Shifting dullness
- "Puddle sign" (physical exam maneuver)
- Hyperresonance or flatness to chest percussion, absence of tactile and vocal fremitus
- Absent or loud bronchial breath sounds, rales, mediastinal displacement, tracheal shift

ETIOLOGY

- Unknown
- Hypothesized to be due to "edematous" fibromas (or other benign ovarian solid tumors) in excess of 10 cm that may stimulate the peritoneal lining to produce peritoneal fluid
- Alternative theory of large fibroma with narrow stalk has inadequate lymphatic drainage; when coupled with intermittent torsion, results in backflow transudation into the peritoneal cavity
- Pleural effusion likely arises from passage of accumulated peritoneal ascites to the right pleural cavity via lymphatics (overloaded thoracic duct) or abdominal pleural commutation (i.e., foramen of Bochdalek)
  1. Fluid accumulation may be due to substances like vascular endothelial growth factor (VEGF) that raise capillary permeability

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ovarian malignancy
- Various gynecologic disorders:
  1. Uterus: Endometrial tumor, sarcoma, leiomyoma ("pseudo-Meigs syndrome")
  2. Fallopian tube: Hydrosalpinx, granulomatous salpingitis, fallopian tube malignancy
  3. Ovary: Benign, serous, mucinous, endometrioid, clear cell, Brenner tumor, granulosa, stromal, dysgerminoma, fibroma, metastatic tumor
- Nongynecologic causes of abdominopelvic ascites:
  1. Portal vein obstruction
  2. Inferior vena cava obstruction
  3. Hypoproteinemia
  4. Thoracic duct obstruction
  5. Tuberculosis
  6. Amyloidosis
  7. Pancreatitis
  8. Gastrointestinal/genitourinary neoplasm
  9. Ovarian hyperstimulation
  10. Pleural effusion
  11. Congestive heart failure
  12. Collagen-vascular disease
  13. Cirrhosis

WORKUP

- Clinical condition characterized by ovarian mass, ascites, and predominantly right-sided pleural effusion
- History of early satiety, weight loss with increased abdominal girth, bloating, intermittent abdominal pain, dyspnea, and nonproductive cough

LABORATORY TESTS

- Complete blood count to rule out inflammatory process
- Tumor markers (CA-125, human chorionic gonadotropin, alpha-fetoprotein, carcinoembryonic antigen, lactic dehydrogenase) to evaluate gynecologic malignancy
- Chemical and liver function testing profile to evaluate metabolic or hepatic involvement
- Arterial blood gases if respiratory compromise

IMAGING STUDIES

- Pelvic sonography (color-flow Doppler evaluation of adnexal mass) initially to evaluate pelvic pathology (CT scan or MRI to further delineate neoplastic lesions)
- Chest x-ray to confirm pleural effusion

Procedures:

- Paracentesis/thoracentesis will usually show a transudate

TREATMENT

NONPHARMACOLOGIC THERAPY

- Informed consent and proper preparation of patient for possible staging laparotomy (total abdominal hysterectomy and bilateral salpingo-oophorectomy, possible omentectomy, possible bowel resection, and possible pelvic/periaortic lymphadenectomy)
  1. Can consider unilateral salpingo-oophorectomy in reproductive-age women, whereas total hysterectomy is preferred in postmenopausal women
- Bowel prep if considering pelvic malignancy

ACUTE GENERAL TREATMENT

Depending on clinical presentation, size of pelvic mass, amount of ascites, and pleural effusion:

- If pelvic mass <10 cm with minimal ascites/pleural effusion: Consider diagnostic laparoscopy (possible exploratory laparotomy) and salpingo-oophorectomy with removal of ovarian fibroma (tumor).
- If pelvic mass >10 cm with moderate/large amount ascites/pleural effusion: Consider pleurocentesis if respiratory compromise (cytology: acid fast bacillus) and exploratory laparotomy with salpingo-oophorectomy and removal of ovarian tumor.
- Treat pelvic malignancy, gastrointestinal, or genitourinary tumor as indicated.

CHRONIC TREATMENT

- Resolution of ascites and pleural effusion after removal of ovarian tumor
- Routine gynecologic follow-up for benign ovarian tumor

DISPOSITION

Dramatic resolution of ascites and effusion within wks of resection of pelvic mass is seen. Excellent progress and complete survival are expected. Recurrence rate is low.

REFERRAL

- To gynecologic oncologist for evaluation and treatment, especially if malignancy considered or encountered
- To pulmonologist for management of pleural effusion

SUGGESTED READING

Available at ExpertConsult.com

AUTHORS: **Nima R. Patel, MD, MS,** and **Terri Q. Huynh, MD, MSCR**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Melanoma is a skin neoplasm arising from the malignant degeneration of melanocytes. It is classically subdivided in four types (Table 1):

1. Superficial spreading melanoma (70%)
2. Nodular melanoma (15%)
3. Lentigo maligna melanoma (4% to 10%) (Fig. E1)
4. Acral lentiginous melanoma (5% to 10%)

SYNONYMS

Malignant melanoma
Cutaneous malignant melanoma

ICD-10CM CODES

C43.30	Malignant melanoma of unspecified part of face
C43.31	Malignant melanoma of nose
C43.4	Malignant melanoma of scalp and neck
C43.51	Malignant melanoma of anal skin
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant melanoma of other part of trunk
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified
D03.8	Melanoma in situ of other sites
D03.9	Melanoma in situ, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- In 2019, there were an estimated 96,480 new cases and 7,230 deaths in the U.S.; the estimated lifetime risk of development of melanoma is 1 in 50.
- Melanoma is much more common in whites (17.2 per 100,000 white men) than in African Americans (1 per 100,000 African American men). Increased risk of developing melanomas is found in patients with fair skin, red hair, light eyes, abundance of freckles, atypical moles or large amount of moles (>50). A personal history of any skin cancer or a family history of melanoma also increases the risk.
- Melanoma is the leading cause of death from skin cancer. Although it represents <10% of all skin-cancers, it accounts for at least 70% of deaths related to skin cancer.
- The median age at diagnosis is 53 yr.
- Superficial spreading melanoma occurs most often in young adults on sun-exposed areas.
- Acral lentiginous melanoma is most often found in Asian Americans and African Americans and is unrelated to sun exposure.
- Eight percent to 10% of melanomas arise in people with a family history of the disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Variable depending on the subtype of melanoma:

- Superficial spreading melanoma is most often found on the lower legs, arms, and upper back. It may have a combination of many colors or may be uniformly brown or black.
- Nodular melanoma can be found anywhere on the body, but it most frequently occurs on the trunk on sun-exposed areas. It has a dark-brown or red-brown appearance and can be dome shaped (Fig. E2) or pedunculated. Lesions are frequently misdiagnosed because they may resemble a blood blister or hemangioma and may also be amelanotic.
- Lentigo maligna melanoma is generally found in older adults in areas continually exposed to the sun and frequently arising from lentigo maligna (Hutchinson freckle) or melanoma in situ. It might have a complex pattern and variable shape; color is more uniform than in superficial spreading melanoma.
- Acral lentiginous melanoma frequently occurs on soles, subungual mucous membranes, and palms (sole of the foot is the most prevalent site). Unlike other types of melanoma, it has a similar incidence in all ethnic groups.
- The warning signs that the lesion may be a melanoma can be summarized with the ABCDE mnemonic (Table 2):
  - **A:** Asymmetry (e.g., lesion is bisected and halves are not identical)
  - **B:** Border irregularity (uneven, ragged border) (Fig. E3)
  - **C:** Color variegation (presence of various shades of pigmentation)
  - **D:** Diameter enlargement (>6 mm)
  - **E:** Evolving (mole changing in size, shape, or color, or mole that differs visibly from surrounding moles ["ugly duckling" sign])

ETIOLOGY

- Ultraviolet light is the most important cause of malignant melanoma.
- There is a modest increase in melanoma risk in patients with small nondysplastic nevi and a much greater risk in those with dysplastic lesions.
- The *CDKN2A* gene, residing at the 9p21 locus, is often deleted in patients with familial melanoma.
- A mutated signal transduction molecule, v-raf murine sarcoma viral oncogene homolog B *(BRAF),* has been identified in 40% to 60% of patients with melanoma.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Dysplastic nevi
- Solar lentigo
- Vascular lesions
- Blue nevus
- Basal cell carcinoma
- Seborrheic keratosis

WORKUP

- Dermoscopy (use of an instrument that shines polarized light on skin surfaces and magnifies skin lesions) can increase the accuracy in diagnosing melanoma by 10% to 27%.

TABLE 1 Four Histologic Subtypes of Cutaneous Melanoma

SUPERFICIAL SPREADING MELANOMA

- Incidence: Accounts for 70% of all melanomas, tends to occur in younger patients (median age, 50)
- Anatomic site: Any; predominantly trunk and extremities, anatomic sites associated with intermittent sun exposure
- Clinical appearance: Change in the appearance of a large mole, asymmetry, irregular border, variegated color (brown, black, pink, white, gray, and blue), often arising in a precursor mole
- Can be associated with mutation in *BRAF*

LENTIGO MALIGNA MELANOMA

- Incidence: Accounts for 4% to 10% of all melanoma; tends to occur more commonly in older patients
- Anatomic site: Areas with chronic exposure to the sun, head and neck regions, and distal extremities
- Clinical appearance: Macular (flat) lesion; arising in a lentigo maligna, which often appears as a flat, light brown skin lesion
- Can be associated with mutation in *KIT*

NODULAR MELANOMA

- Incidence: Accounts for 15% of melanomas
- Anatomic site: Any
- Clinical appearance: Rapidly enlarging, elevated, or polypoid lesion; often arising in normal skin; often blue, black, or pink and can be amelanotic

ACRAL LENTIGINOUS MELANOMA

- Incidence: 5%-10%
- Anatomic site: Most commonly on the palms or soles or subungual (under the nail bed)
- Clinical appearance: Darkly pigmented, flat to nodular lesion, highly irregular borders
- Can be associated with mutation in *KIT*

From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE 2 Clinical Features (ABCDE Signs) of Malignant Melanoma

	Clinical Feature	Comment
A	Asymmetry	The two halves of the lesion are not alike
B	Border irregularity	Borders notched, scalloped, irregular
C	Color changes	Especially blue, red, black, white
D	Diameter >6 mm	Size of a pencil eraser; not applicable to congenital nevi, which are often >6 mm early in their evolution
E	Enlargement	Evolutionary change in the lesion

From Paller AS, Mancini *AJ: Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.

- Any suspicious lesion (Fig. E4) should be biopsied. Perform excisional biopsy with elliptical excision that includes 1 to 2 mm of normal skin surrounding the lesion and extends to the subcutaneous tissue; incisional punch biopsy is sometimes necessary in surgically sensitive areas (e.g., digits, nose). It is essential that the size of the specimen be adequate to determine the histologic depth of penetration, which is known as the Breslow depth.
- Sentinel lymph node excision (SLNE) is the most important staging and potentially therapeutic procedure for patients with melanoma. It should be considered in patients with intermediate (1 to 4 mm) melanomas or high-risk skin tumors to obtain information regarding a patient's subclinical lymph node status with minimal morbidity. The National Comprehensive Cancer Network (NCCN) recommends that SLNE be discussed with and offered to patients classified as stage IB or II, and should be considered for patients with stage IA melanoma and "adverse" features that might portend a higher risk of sentinel node involvement (e.g., Clark level IV or V, tumor thickness of 0.75 mm or more, lymphovascular invasion, positive deep margins). SLNE involves the use of radiologic lymphoscintigraphy to map lymphatic drainage from the site of the primary melanoma to the first sentinel lymph node in the region. When properly performed, if the sentinel node is negative the remaining lymph nodes in the region will not have metastases in more than 98% of cases. If the sentinel nodes are negative, no additional regional surgery is recommended. The staging of intermediate thickness (1.2 to 3.5 mm) primary melanomas, according to the results of sentinel node biopsy, provides important prognostic information and identifies patients with nodal metastases whose survival can be prolonged by immediate lymphadenectomy.
- The staging system for melanoma adapted by the American Joint Committee on Cancer (AJCC) can be found in Table 3.

LABORATORY TESTS

The pathology report should indicate the following:

- Tumor thickness (Breslow microstage).
- Tumor depth: The depth of invasion is the most important histologic prognostic parameter in evaluating the primary tumor.
- Mitotic rate: Tabulated as mitoses per square millimeter in the dermal part of the tumor in which most mitoses are identified.
- Radial growth rates versus vertical growth rate: Radial growth phase describes the growth of melanoma within the epidermis and along the dermal-epidermal junction.
- Tumor infiltrating lymphocytes have a strong predictive value in vertical growth phase melanomas and are defined as brisk, nonbrisk, or absent.
- Histologic regression: Characterized by the absence of melanoma in the epidermis and dermis flanked on one or both sides by melanoma.
- Reverse-transcription polymerase chain reaction assay for tyrosine messenger RNA is a useful marker for the presence of melanoma cells. It is performed on sentinel lymph node biopsy and is useful for detection of submicroscopic metastases.

Rx TREATMENT

- Initial excision of the melanoma
- Re-excision of the involved area after histologic diagnosis:
  1. The margins of re-excision depend on the Breslow depth. For melanoma in situ with Breslow depth ≤2.0 mm, recommended surgical margin is 1 cm. If Breslow depth is ≤2.0 mm, margin should be 2 cm. For melanoma in situ, margin should be 5 mm.
  2. Low-risk or intermediate-risk tumors require excision of 1 to 3 cm.
  3. Melanomas of moderate thickness (0.9 to 2.0 mm) can be excised safely with 2-cm margins.
  4. A 1-cm margin of excision for melanoma with a poor prognosis (as defined by a tumor thickness ≥2 mm) is associated with a significantly greater risk of regional recurrence than is a 3-cm margin, but with a similar overall survival rate. Randomized clinical trials have also shown that radical surgery with 2-cm excision margins did not differ from that with 4-cm margins for survival in patients with cutaneous melanoma >2 mm thick.
- Lymph node dissection: Recommended in all patients with enlarged lymph nodes. Lymph node evaluation is important in patients with melanoma 1 mm in depth because it determines the overall prognosis and need for therapeutic lymph node dissection or adjuvant treatment.
  1. Elective lymph node dissection remains controversial.
  2. It is indicated with positive sentinel node. It may be considered in those with a primary melanoma between 1 and 4 mm thick (especially in patients >60 yr).
- Adjuvant therapy:
  1. Interferon alfa-2b and Peginterferon alfa-2b have been previously used for the adjuvant treatment resected stage III melanoma despite modest benefits.
  2. Ipilimumab, an antibody that blocks cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), improves survival in stage III high-risk resected melanoma but is associated with significant immune adverse events.
  3. Immune checkpoint PD-1 (programmed death receptor-1) antibodies nivolumab and pembrolizumab have demonstrated superiority to ipilimumab in patients with resected high-risk stage III melanoma; currently only nivolumab is approved in this setting.
  4. The combination regimen of BRAF inhibitor and MEK inhibitor (dabrafenib plus trametinib) has shown improved relapse-free survival in cases of resected BRAF V600-mutant stage III melanoma and is another option for these patients.
- Advanced disease:
  1. The use of immune checkpoint inhibitors has improved overall survival in patients with previously treated or untreated metastatic melanoma irrespective of BRAF mutation status. Monotherapy with the PD-1 inhibitors nivolumab or pembrolizumab has been approved for the treatment of metastatic melanoma in treatment-naïve patients and also in cases of progression after initial therapy with ipilimumab.
  2. Combination immunotherapy with the use of nivolumab and ipilimumab in previously untreated patients with unresectable or metastatic melanoma has been shown to be more effective than ipilimumab alone as first-line treatment in high-risk patients though severe immune toxicity is seen in the majority of patients.
  3. In patients who carry the V600E *BRAF* mutation, the combination of oral BRAF inhibitors and oral MEK inhibitors improves overall survival in patients with previously untreated melanoma. Three such combination regimens (vemurafenib plus cobimetinib; dabrafenib plus trametinib; and encorafenib plus binimetinib) are approved by the FDA for use in this setting. Targeted therapy is useful in patients with rapidly growing melanoma with *BRAF* mutations, but resistance appears in almost all patients, and median progression-free survival is 15 to 18 mo. Interestingly, the

TABLE 3 The TNM Classification for Melanoma Adapted by the American Joint Committee on Cancer (AJCC, 8th edition)

T classification	Thickness	Ulceration status/mitoses
T_{is} (in situ)	n/a	n/a
T_1	<1.0 mm	Unknown or unspecified
T_{1a}	<0.8 mm	Without ulceration
T_{1b}	0.8 mm-1.0 mm	With/without ulceration
T_2	>1.0-2.0 mm	Unknown or unspecified
T_{2a}	>1.0-2.0 mm	Without ulceration
T_{2b}	>1.0-2.0 mm	With ulceration
T_3	>2.0-4.0 mm	Unknown or unspecified
T_{3a}	>2.0-4.0 mm	Without ulceration
T_{3b}	>2.0-4.0 mm	With ulceration
T_4	>4.0 mm	Unknown or unspecified
T_{4a}	>4.0 mm	Without ulceration
T_{4b}	>4.0 mm	With ulceration
Regional nodes (N)	**Number of nodes**	**Presence of in-transit, satellite and/or microsatellite metastases**
N_0	0	None
N_1	One tumor-involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N_{1a}	One clinically occult (sentinel biopsy detected)	No
N_{1b}	One clinically detected	No
N_{1c}	No regional node	Yes
N_2	Two or three tumor-involved nodes or any number of in-transit, satellite, and/or micro-satellite metastases with one tumor-involved node	
N_{2a}	Two or three clinically occult (sentinel biopsy detected)	No
N_{2b}	Two or three, at least one clinically detected	No
N_{2c}	One clinically occult or clinically detected	yes
N_3	Four or more tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N_{3a}	Four or more clinically occult (sentinel biopsy detected)	No
N_{3b}	Four or more, at least one of which was clinically detected, or the presence of any number of matted nodes	No
N_{3c}	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes
M category	**Anatomic site**	**LDH level**
M_0	No distant metastases	n/a
M_1	Evidence of distant metastases	
M_{1a}	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	M_{1a}(0): Normal M_{1a}(1): Elevated
M_{1b}	Distant metastasis to lung with or without M_{1a} sites of disease	M_{1b}(0): Normal M_{1b}(1): Elevated
M_{1c}	Distant metastasis to non-CNS visceral sites with or without M_{1a} or M_{1b} sites of disease	M_{1c}(0): Normal M_{1c}(1): Elevated
M_{1d}	Distant metastasis to CNS with or without M_{1a}, M_{1b}, or M_{1c} sites of disease	M_{1d}(0): Normal M_{1d}(1): Elevated

CNS, Central nervous system; *LDH,* lactic dehydrogenase; *TNM,* tumor, nodes, metastases.

majority of patients with melanoma CNS metastases in this setting have similar response rates in the CNS as systemically.

4. The combination of atezolizumab (PD-L1 checkpoint inhibitor), cobimetinib (MEK inhibitor), and vemurafenib (BRAF inhibitor) has been shown to improve progression-free survival compared with placebo in patients with *BRAF* mutated advanced melanoma and is likely to be another option in this setting.

- Patients with a history of melanoma should be followed up with skin examinations every 6 mo or sooner if patient detects any new lesions; the assessments usually consist of medical history, physical examination, laboratory values, and chest radiograph.

DISPOSITION

- Prognosis varies with the stage of the melanoma. The 5-yr survival related to thickness is as follows: <0.76 mm, 99% survival; 0.6 to 1.49 mm, 85%; 1.5 to 2.49 mm, 84%; 2.5 to 3.9 mm, 70%; >4 mm, 44%.
- The 5-yr survival in patients with distant metastasis was historically <10% but is improving with current therapeutic options and is now >20%.
- Treatment of advanced disease consists (in addition to surgical excision and lymph node dissection) of chemotherapy, immunotherapy, and radiation therapy. Nivolumab combined with ipilimumab has shown clinically meaningful activity in melanoma metastatic to the brain (see Tawbi HA et al in Suggested Readings).

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Melanoma (Patient Information)

AUTHOR: **Bharti Rathore, MD**

SUGGESTED READINGS

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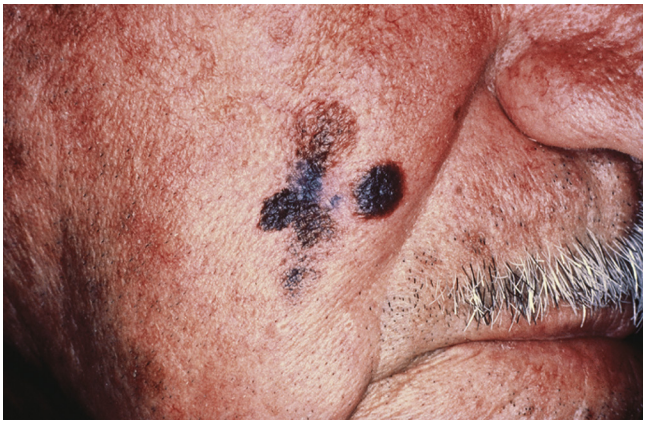

FIG. E1 Lentigo maligna melanoma. (From James WD et al: *Andrews' diseases of the skin: clinical dermatology,* ed 12, Philadelphia, 2016, Elsevier.)

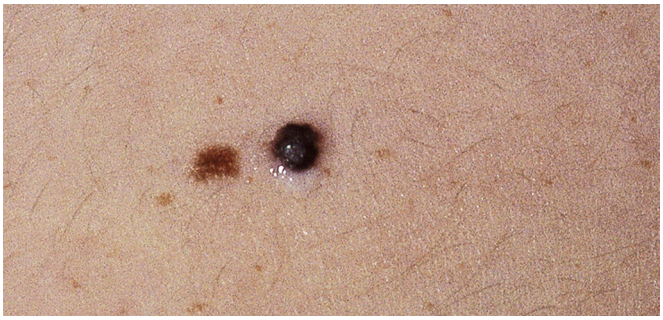

FIG. E2 Malignant melanoma (MM). (This small, black papule was noted on this 10-year-old male with fair skin and red hair; excision confirmed a nodular MM. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E3 Subungual melanoma with Hutchinson sign (pigment spreading from under the nail to involve the adjacent skin, usually of the proximal or lateral nail fold). (These lesions are thought to emanate from the nail matrix. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

FIG. E4 Melanoma of the vulva. (enign nevi, vulva melanosis, and melanoma may occur in the vulvar region. Any suspicious pigmented lesion should be biopsied. The patient here is 75 yrs old. (Courtesy Paul Koonings, MD; From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

Ménière Disease PTG

BASIC INFORMATION

DEFINITION

Ménière disease is a syndrome characterized by recurrent vertigo with fluctuating hearing loss, tinnitus, and fullness in the ear.

SYNONYMS

Endolymphatic hydrops
Lermoyez syndrome
Idiopathic endolymphatic hydrops

ICD-10CM CODES

H81.01 Ménière disease, right ear
H81.02 Ménière disease, left ear
H81.03 Ménière disease, bilateral
H81.09 Ménière disease, unspecified ear

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Approximately 190/100,000 persons
PREDOMINANT SEX: Female:male ratio of 1.3:1
PEAK INCIDENCE: Fourth to sixth decade of life

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hearing may be unilaterally decreased.
- Pallor, sweating, and nausea may occur during a severe attack.
- Usually the patient develops a sensation of fullness and pressure along with decreased hearing and tinnitus in a single ear.
- The patient typically experiences severe vertigo, which peaks within minutes, then slowly subsides over hours.
- May see spontaneous nystagmus on examination.
- Persistent sense of disequilibrium for days is typical after an acute episode.
- May have vestibulopathy demonstrable with a positive head thrust test.

ETIOLOGY

- Unknown; viral, autoimmune, and genetic causes have been suggested.
- Endolymphatic hydrops is the postmortem histologic hallmark. Endolymphatic hydrops may create cytochemical changes that disturb endolymphatic fluid homeostasis, leading to spiral ganglion cell death.

DIAGNOSIS

Proposed guidelines by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) for diagnosis of Ménière disease:

DIFFERENTIAL DIAGNOSIS

- Acoustic neuroma
- Migrainous vertigo
- Multiple sclerosis
- Autoimmune inner ear syndrome
- Otitis media
- Vertebrobasilar disease
- Labyrinthitis

WORKUP

- Diagnosis is primarily made by history, although further diagnostic tests may help support the diagnosis. Guidelines to define Ménière disease are described in Table 1.
- Audiogram may show sensorineural hearing loss with lower frequencies primarily affected. Hearing loss may recover either partially or completely after an attack. Recurrent attacks may lead to a persistent and progressive sensorineural hearing loss.
- Electronystagmography may show peripheral vestibular deficit.
- Both vestibular-evoked myogenic potential (VEMP) studies and electrocochleography (ECoG) have low sensitivity and specificity for Ménière disease and are not clinically useful.

LABORATORY TESTS

No laboratory serologic test is specific for Ménière disease. A thyroid panel, glucose, hemoglobin A1C, antinuclear antibodies, urinalysis, chemistry panel, rapid plasma reagin, Lyme disease antibodies, and allergy testing can be ordered to screen for other disorders such as thyroid or autoimmune diseases, diabetes, otorenal syndrome, syphilis, Lyme disease, and allergy-mediated Ménière disease.

IMAGING STUDIES

- MRI to rule out acoustic neuroma or other retrocochlear lesion, especially if cerebellar or CNS dysfunction is present.
- Recent efforts have shown a role for MRI with intratympanic gadolinium.

TREATMENT

NONPHARMACOLOGIC THERAPY

Limit activity during attacks.

ACUTE GENERAL Rx

- Prochlorperazine 5 to 10 mg PO q6h or 25 mg PO bid
- Promethazine 12.5 to 25 mg PO q4 to 6h
- Diazepam 5 to 10 mg IV/PO for acute attack
- Meclizine 25 mg q6h
- Scopolamine patch

CHRONIC Rx

- Diuretics such as furosemide, hydrochlorothiazide, or acetazolamide.
- Lifestyle modification recommendations include salt restriction and avoidance of caffeine.
- For refractory cases, intratympanic gentamicin injections to the affected ear; endolymphatic sac surgery.

DISPOSITION

- Patients are usually followed by an otoneurologist or ENT specialist.
- Usual course of disease consists of alternating attacks and remissions.
- Majority of patients can be managed medically. Of all patients, 10% to 30% will undergo surgical intervention for persistent incapacitating vertigo.

REFERRAL

To an otolaryngologist for surgical intervention if attacks persist despite medical therapy

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Ménière Disease (Patient Information)

AUTHORS: **Katherine Kostroun, MD, Joseph S. Kass, MD, JD, FAAN,** and **Sharon S. Hartman Polensek, MD, PhD**

TABLE 1 Guidelines to Define Ménière Disease

Definition	Symptoms
Certain Ménière disease	Histopathologic confirmation
Definite Ménière disease	≥2 definitive spontaneous episodes of vertigo 20 min to 12 hr Audiometrically documented low- to medium-frequency sensorineural hearing loss in one ear, defining the affected ear on at least one occasion before, during, or after one of the episodes of vertigo Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear Not better accounted for by another vestibular diagnosis
Probable Ménière disease	One definite episode of vertigo Audiometrically documented hearing loss on at least one occasion Tinnitus or aural fullness in the treated ear Other causes excluded
Possible Ménière disease	Episodic vertigo without documented hearing loss, or sensorineural hearing loss (SNHL) fluctuating or fixed, with disequilibrium but nonepisodic Other causes excluded

SUGGESTED READINGS

Harris JP, Alexander TH: Current-day prevalence of Ménière's syndrome, *Audiol Neurootol* 15(318), 2010.

Le CH et al: Novel techniques for the diagnosis of Ménière's disease, *Curr Opin Otolaryngol Head Neck Surg* 21:492-496, 2013.

Lopez-Escamez JA et al: Diagnostic criteria for Menière's disease, *J Vestib Res* 25(1), 2015.

Semaan MT, Megerian CA et al: Contemporary perspectives on the pathophysiology of Ménière's disease: implications for treatment, *Curr Opin Otolaryngol Head Neck Surg* 18:392-398, 2010.

BASIC INFORMATION

DEFINITION

Meningiomas are generally slow-growing tumors arising from arachnoid cells of the arachnoid villi; 90% are benign.

ICD-10CM CODE

D32.0 Benign neoplasm of cerebral meninges

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 7.92/100,000 persons/yr, but increases with age. Most common primary type of central nervous system tumor, and most common nonmalignant primary central nervous system tumor.

PREDOMINANT SEX AND AGE: Female:male ratio of almost 3:1 (in ages 35 to 54) in the brain and up to 6:1 in the spinal cord; 1:1 in childhood

PEAK INCIDENCE: Males: Sixth decade, females: Seventh decade, incidence increases with age, dramatic increase in incidence after age 65; rare in childhood

RISK FACTORS: Ionizing radiation results in increased incidence and a shorter latency period. Neurofibromatosis type 2 (NF2) is an autosomal dominant genetic disorder that predisposes to multiple intracranial tumors. Approximately half of all individuals with NF2 have meningiomas, most of which are intracranial. Studies have suggested a link between hormonal factors and development of meningioma, specifically estrogen exposure. Multiple prospective cohorts studies have also found an association between higher body mass index and meningioma, possibly relating to increased levels of circulating estrogen through increased adipose tissue. At present, there is no conclusive evidence to support a causal relationship with cell phone usage and subsequent development of meningioma.

GENETICS: Meningiomas may be isolated or found in association with other genetic diseases, such as NF2 and familial meningioma. Other genetic conditions associated with increased incidence of meningioma include BAP1 tumor predisposition syndrome, Rubinstein-Taybi syndrome, multiple endocrine neoplasia, type 1, Gorlin syndrome, Cowden syndrome 1, Werner syndrome, and familial meningiomatosis. Approximately half of meningiomas have allelic losses involving the *NF2* and *DAL-1* genes. Allelic losses of chromosomes 1p, 2p, 6q, 9q, 10q, 14q, 17p, and 18q may be associated with histologic progression. Genome-wide association studies (GWAS) have discovered two genomic variants associated with increased meningioma risk in genes for *MLLT10* and possibly *RIC8A*. Further, GWAS analysis also demonstrates an association between longer telomere length and increased risk of meningiomas.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Neurologic symptoms vary with location and size (see Table 1); meningiomas can arise from the dura at any site, although they most commonly occur within the skull and at sites of dural reflection (i.e., the cerebral convexities and the falx). Other less common locations include the sphenoid wing, olfactory groove, and optic nerve sheath.
- The presence of focal symptoms such as vision loss, hearing loss, or mental status change depend on the site of origin and the time course of growth.
- Most common presentation is with a focal or generalized seizure or gradually worsening neurologic deficit. Seizures are present preoperatively in 30% to 40%.
- Typically are slow growing and asymptomatic; many meningiomas are asymptomatic and/or discovered incidentally on a neuroimaging study or at autopsy.

ETIOLOGY

- Meningiomas are thought to arise from a multistep progression of genetic changes.
- Mutations of the *NF2* gene on chromosome 22 are found in patients with neurofibromatosis type 2 and >50% of sporadic meningiomas. This gene is thought to act as a tumor suppressor gene; the protein product, merlin, is also involved in cytoskeletal organization.
- *DAL-1*, located on chromosome 18p, is another tumor suppressor gene that has been identified in a subset of the approximately 40% of sporadic meningiomas with neither the *NF2* gene mutations nor allelic loss of chromosome 22q.
- Cranial radiation may be responsible for some cases following an appropriate latency period from 10 to 20 yr. Meningiomas that result from radiation are generally more aggressive.
- The link with steroid hormones and their receptors is suggested by the increase in growth rate and/or development of meningiomas during pregnancy, increased incidence in women who use postmenopausal hormones, and in association with breast carcinomas.

TABLE 1 Locations and Presentations of Meningiomas

Location	Presenting Manifestation
Parasagittal	Urinary incontinence, dementia, gradual paraparesis, seizures
Lateral convexity	Variable depending on structures compressed, including slow hemiparesis, speech abnormalities
Olfactory groove	Anosmia, visual disturbance, dementia, Foster-Kennedy syndrome
Suprasellar	Hormonal failure, bitemporal hemianopsia, optic atrophy
Sphenoid ridge	Extraocular nerve paresis, exostoses, proptosis, seizures

From Goetz CG, Pappert EJ: *Textbook of clinical neurology,* Philadelphia, 1999, WB Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other well-circumscribed intracranial tumors that involve the dura or subdural space:

- Acoustic schwannoma (typically at the pontocerebellar junction)
- Ependymoma, lipoma, and metastases within spinal cord
- Metastatic disease from lymphoma/adenocarcinoma
- Inflammatory disease such as sarcoidosis and Wegener granulomatosis
- Infections such as tuberculosis

WORKUP

Imaging studies with CT or MRI, followed by surgical removal with histologic confirmation

LABORATORY TESTS

According to the World Health Organization (WHO) classification, there are nine benign histologic variants (account for 90% of all meningiomas) and four variants associated with increased recurrence and rates of metastasis. 80% of meningiomas are classified as benign meningiomas or WHO grade I.

IMAGING STUDIES

- Cranial CT scanning or MRI can detect and determine the extent of meningiomas (Fig. 1). CT can show hyperostosis and/or intratumoral calcifications. MRI with contrast (Fig. 2) is the imaging modality of choice to demonstrate the dural origin of the tumor in most cases, with the characteristic "tail" sign that tracks along the dura outside brain parenchyma.
- On nonenhanced scans, meningiomas are typically isodense or slightly hyperdense to

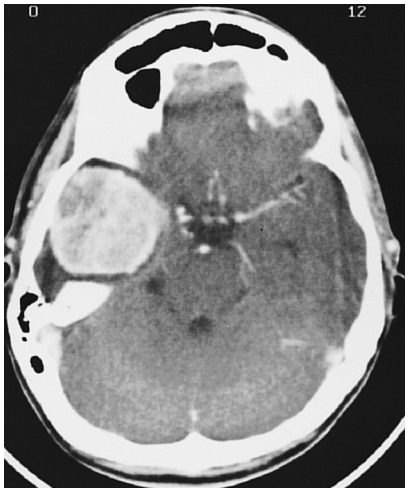

FIG. 1 Contrast-enhanced computed tomography scan demonstrates a large contrast-enhancing right sphenoid wing meningioma. (From Specht N [ed]: *Practical guide to diagnostic imaging,* St Louis, 1998, Mosby.)

FIG. 2 Magnetic resonance imaging picture of a posterior fossa meningioma, demonstrated an extra-axial homogeneously contrast-enhanced mass arising from the tentorium and compressing the cerebellar hemisphere. (From Goetz CG, Pappert EJ: *Textbook of clinical neurology,* Philadelphia, 1999, WB Saunders.)

brain and are homogeneous in appearance. They show homogeneous contrast enhancement; gadolinium can facilitate imaging of smaller additional lesions that are missed on unenhanced images.
- Indistinct margins, marked edema, mushroom-like projections from tumor, brain parenchymal infiltration, and heterogeneous enhancement are suggestive of more aggressive behavior.
- Positron emission tomography (PET) scan may help in predicting the aggressiveness of the tumor and the potential for recurrence, but it is not used routinely.

Rx TREATMENT

Primary management depends on signs or symptoms, age of patient, and location and size of tumor. Observation may be appropriate if tumors are discovered incidentally and/or if growth is indolent and unlikely to cause symptoms.

PHARMACOLOGIC THERAPY

- Although a variety of chemotherapeutic agents have been studied, such as hydroxyurea, there is no established effective systemic therapy.
- Inhibition of hormone receptors, such as progesterone, estrogen, and androgen, has failed to demonstrate clinical benefit.
- Treatment with molecularly targeted approaches, such as angiogenesis inhibition, is currently under way.

NONPHARMACOLOGIC THERAPY

- The mainstay of treatment for meningiomas remains surgical removal. Complete resection is usually attempted, when feasible. After total excision, recurrence rates of 0% to 20% have been observed, while 20% to 50% of patients recur within 5 yr of a subtotal resection.
- Active surveillance to monitor for tumor recurrence is important.
- Radiation therapy is the only validated form of adjuvant therapy and may be beneficial in patients with incomplete resections or inoperable tumors. Stereotactic radiosurgery can provide local control with more limited toxicity.

ACUTE GENERAL Rx

- For lesions that cause significant mass effect, steroids are sometimes used to decrease brain edema.
- Anticonvulsants are used if the patient presents with seizures.

CHRONIC Rx

- Prophylactic use of anticonvulsants is not recommended in patients without a history of seizures.
- There is limited data on the efficacy of traditional chemotherapy, and the evidence is largely anecdotal. The most extensively evaluated agents are hydroxyurea, mifepristone (RU486), and interferon alfa-2b. Recently, somatostatin analogs have been evaluated in multicenter clinical trials, primarily in malignant meningiomas.

DISPOSITION

- Estimated surgical mortality is 7%. Significant morbidity and mortality can be observed in meningiomas with otherwise favorable pathology secondary to unfavorable location (e.g., skull base). 10-yr relative survival is 80.4% in the cerebral meninges vs. 93.2% in spinal meninges.
- Long-term outcome varies based on pathology, tumor grade, location, and completeness of resection. 10-yr relative survival for nonmalignant meningioma is 81.5%, with highest survivability in the youngest age group. 10-yr relative survival for malignant meningioma is 53.5%, with similar age-based effects.
- Most incidentally discovered meningiomas remain asymptomatic and have a slow rate of growth. Calcified tumors may be less likely to progress than noncalcified ones.
- Meningiomas may recur after surgical resection or progress to a higher grade. Risk factors for recurrence include multiple allelic chromosomal losses, local brain invasion, high rate of mitosis, and highly anaplastic features.

REFERRAL

- Neurosurgical consultation for all cases
- Neurology, radiation oncology, and oncology consults depending on presence of other sequelae or in the setting of recurrence

PEARLS & CONSIDERATIONS

COMMENTS

- Many meningiomas are discovered incidentally; most are benign and remain asymptomatic. A first follow-up MRI should be performed 3 to 6 mo after the tumor is identified to rule out an atypical meningioma with rapid growth.
- "Dural tail," which is the thickening of the dura adjacent to the mass, is a classic finding on neuroimaging studies.
- Individuals with neurofibromatosis type 2 are at high risk to develop meningiomas.

PATIENT & FAMILY EDUCATION

- Meningioma Mommas: meningiomamommas.org
- Meningioma Support and Patient Information Group
- National Brain Tumor Society
- Meningioma Online Support Group: brainstrust.org/meningioma.htm

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Meningioma (Patient Information)

AUTHOR: **Lily Pham, MD**

SUGGESTED READINGS

Braganza MZ et al: Lonizing radiation and the risk of brain and central nervous system tumors: a systematic review, *Neuro Oncol* 14:1316, 2012.

Ostrom QT et al: "CBTRUS Statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011–2015, *Neuro-Oncology* 20(Suppl 4):1-86, iv, 2018, https://doi.org/10.1093/neuonc/noy131.

Ostrom QT et al: "Risk factors for childhood and adult primary brain tumors," *Neuro-Oncology* 21(11):1357-1375, 2019, https://doi.org/10.1093/neuonc/noz123.

Wiemels J et al: Epidemiology and etiology of meningioma, *J Neurooncol* 99:307, 2010.

BASIC INFORMATION

DEFINITION

Bacterial meningitis is an inflammation of meninges with increased intracranial pressure, and pleocytosis or increased WBCs in cerebrospinal fluid (CSF) secondary to bacteria in the pia-subarachnoid space and ventricles, leading to neurologic sequelae and abnormalities.

SYNONYMS

Spinal meningitis
Bacterial meningitis

ICD-10CM CODES

G00.9	Bacterial meningitis, unspecified
G00.8	Other bacterial meningitis
G01	Meningitis in bacterial diseases classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 1.3 to 2.0 cases/100,000 persons; 1.2 million cases per yr in the world; 135,000 deaths annually worldwide. The rate of bacterial meningitis declined dramatically in the U.S. starting in the early 1990s with the introduction of the *Haemophilus influenzae* type b (Hib) vaccine and in 2000 with the introduction of the conjugate pneumococcal vaccine.
PREDOMINANT SEX: Male = female
PREDOMINANT AGE: All ages, neonate to geriatric

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever
- Headache
- Neck stiffness, nuchal rigidity, meningismus
- Altered mental state, lethargy
- Vomiting, nausea
- Photophobia
- Seizures
- Coma; lethargy, stupor
- Rash: Petechial and purpuric lesions (Fig. E1) associated with meningococcal infection, purpura fulminans
- Myalgia
- Cranial nerve abnormality (unilateral)
- Papilledema
- Dilated, nonreactive pupil(s)
- Posturing: Decorticate/decerebrate
- Physical examination findings of Kernig sign and Brudzinski sign (Fig. E2) in adults with meningitis are often seen later in the course of disease and may not be helpful in determining early meningeal inflammation

ETIOLOGY

The bacterial etiology of meningitis depends on the age of the patient. *Neisseria meningitidis* is now more common than *Haemophilus influenzae* as a cause of bacterial meningitis in children as well as adults, and streptococci (*Streptococcus pneumoniae*) are still common causes of community-acquired bacterial meningitis. *H. influenzae* is the cause of >30% of cases of meningitis (usually in infants and children <6 yr of age). It is associated with sinusitis, otitis media.

- Neonates: Group B streptococcus, gram-negative rods such as *E. coli, Listeria monocytogenes*
- Infants ≥1 mo and <3 mo: Group B streptococci (40%), gram-negative rods (30%), *Streptococcus pneumoniae* (14%), and *Neisseria meningitidis* (12%)
- Infants ≥3 mo and <3 yr:
  1. *S. pneumoniae* (45%)
  2. *N. meningitidis* (34%)
  3. *S. agalactiae* (group B streptococci) (11%)
  4. *H. influenzae*
  5. *E. coli*
- Ages ≥3 yr and <10 yr:
  1. *S. pneumoniae* (47%)
  2. *N. meningitidis* (32%)
- Ages ≥10 yr and <19 yr
  1. *N. meningitidis* (55%)
  2. *S. pneumoniae*
- Adults: *S. pneumoniae, N. meningitidis,* and *Streptococcus agalactiae* (third most common cause in adults).
- *Listeria monocytogenes* is uncommon in the general population but is often seen in older adults and in those with cell-mediated immune deficiencies.
- People with HIV/AIDS are at increased risk for invasive meningococcal disease (IMD).

DIAGNOSIS

Diagnostic approach is based on patient presentation and physical examination (Fig. 3). Lumbar puncture should be performed as soon as possible. Key elements to diagnosis are CSF evaluation and CT scan or MRI if the patient is in a coma or has focal neurologic deficits, pupillary abnormalities, or papilledema. Table 1 describes tests of CSF in patients with suspected CNS infection.

DIFFERENTIAL DIAGNOSIS (BOX E1)

- Endocarditis, bacteremia
- Intracranial tumor
- Lyme disease
- Brain abscess
- Partially treated bacterial meningitis
- Medications
- SLE
- Seizures
- Acute mononucleosis
- Other infectious meningitides
- Neuroleptic malignant syndrome
- Subdural empyema
- Subarachnoid hemorrhage (Table 2)
- Rocky Mountain spotted fever

WORKUP

CSF examination (Table 3):

- Opening pressure >100 to 200 mm Hg
- WBC usually >1000/mm^3
- Neutrophilic predominance: >80%
- Gram stain of CSF: Positive in 60% to 90% of patients
- CSF protein: >50 mg/dl
- CSF glucose: <40 mg/dl
- Culture: Positive in 65% to 90% of cases
- Multiplex PCR assay for detection of *S. pneumoniae, H. influenza, N. meningitidis,* and *L. monocytogenes* offer 100% sensitivity and 98% specificity.

LABORATORY TESTS

Blood culturing, WBC with differential, and CSF examination (see "Workup")

IMAGING STUDIES

- Guidelines from the Infectious Society of America recommend CT of brain before lumbar puncture in patients presenting with:
  1. A high clinical suspicion for subarachnoid hemorrhage
  2. New focal neurologic deficit
  3. Papilledema
  4. Seizures within a wk
  5. Altered mental status
  6. History of central nervous system disease (e.g., tumor, stroke)
  7. Immunodeficiency
  8. Age 60 or older

TREATMENT

Empiric therapy (Table 4) is necessary with IV antibiotic treatment if patient has purulent CSF fluid at time of lumbar puncture, is asplenic, or has signs of DIC/sepsis pending gram stain and culture results. Try to obtain blood and CSF cultures before starting antimicrobial therapy, but do not delay therapy if obtaining them is not possible. If CT scan is indicated (see "Imaging Studies" for indications) it should not delay empiric antibiotic therapy. Therapy after gram stain pending cultures is recommended for the following:

- Neonates: Ampicillin: 200 to 400 mg/kg per day divided q6 to 8 hr plus gentamicin: 7.5 mg/kg IV in three divided doses plus a third-generation cephalosporin: cefotaxime or ceftriaxone
- 1 to 23 mo: Vancomycin: 60 mg/kg per day IV (maximum up to 4 g/day) divided in four doses plus third-generation cephalosporin: Ceftriaxone: 100 mg/kg (maximum dose 4 g/day) in one or two divided doses or cefotaxime: 300 mg/kg per day IV (maximum dose of 12 g/day) in three or four divided doses
- Children: Vancomycin: 60 mg/kg per day IV (maximum dose 4 g/day) in four divided doses plus third-generation cephalosporin: Ceftriaxone 100 mg/kg per day IV (maximum 4 g/day) or cefotaxime: 300 mg/kg IV (maximum dose of 12 g/day) in three or four divided doses
- Adults: Vancomycin: 15 to 20 mg/kg IV every 8 to 12 hours plus third-generation cephalosporin: Ceftriaxone: 2 g IV q12h or cefotaxime: 2 g IV q4 to 6 hr. For adults over 50 yr of age also add ampicillin 2 g IV every 4 hr to cover *Listeria*
- Immunocompromised patients: Vancomycin *plus* ampicillin *plus* either cefepime 2 g IV

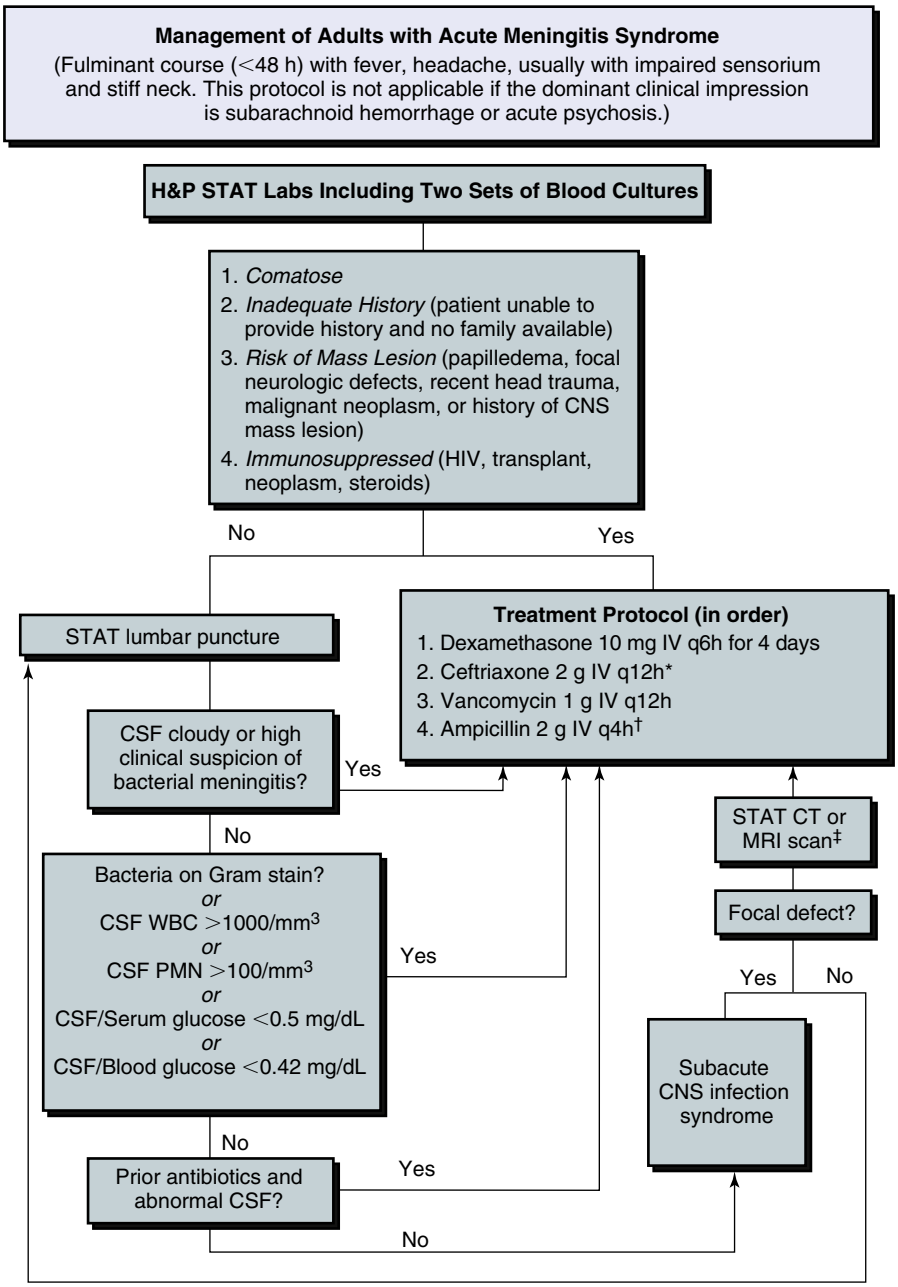

FIG. 3 Algorithm for management of adult patients with acute meningitis syndrome. *For severe cephalosporin allergy, consider meropenem or moxifloxacin. †Ampicillin is indicated if there is a history of alcoholism, organ transplant, malignancy, pregnancy, or age older than 50 yr. For penicillin-allergic patients, an alternative is trimethoprim-sulfamethoxazole. ‡Consider magnetic resonance imaging *(MRI)* if the patient is known or suspected to have human immunodeficiency virus *(HIV),* if it can be obtained rapidly. *CNS,* Central nervous system; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *H&P,* history and physical examination; *PMN,* polymorphonuclear leukocyte; *WBC,* white blood cell. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

every 8 hr to cover *Pseudomonas* or meropenem 2 g IV q8h for adults, which also covers *Pseudomonas*

Use of corticosteroids in adults:

- Dexamethasone 0.15 mg/kg q6h for first 4 days of therapy should be used for adults in developed countries with known or suspected bacterial meningitis. Decreased mortality and neurologic sequelae (hearing loss , etc.) are seen with adjunct therapy in patients with pneumococcal meningitis but not other pathogens. The benefit of dexamethasone is less clear in developing countries with high HIV prevalence and malnutrition or with delayed clinical presentations.
- Dexamethasone also benefits children with Hib meningitis if given at the same time or before the first dose of the antibiotic: 0.15 mg/kg per dose q6h for 2 to 4 d. The use and benefit of corticosteroids in children with suspected or pneumococcal or meningococcal meningitis to prevent neurologic sequelae is not as clear and should be individualized after analysis of risk and benefits.

TABLE 1 Tests of Cerebrospinal Fluid in Patients with Suspected Central Nervous System Infection

Routine Tests
White blood cell count with differential
Red blood cell count[a]
Glucose concentration[b]
Protein concentration
Gram stain
Bacterial culture
Selected Specific Tests Based on Clinical Suspicion
Viral culture[c]
Smears and culture for acid-fast bacilli
Venereal Disease Research Laboratory (VDRL)
India ink preparation
Cryptococcal polysaccharide antigen
Fungal culture
Antibody tests (IgM or IgG, or both)[d]
Nucleic acid amplification tests (e.g., polymerase chain reaction)[e]
Cytology[f]
Flow cytometry

[a]Should be checked in the first and last tubes; in patients with a traumatic tap, there should be a decrease in the number of red blood cells with continued flow of cerebrospinal fluid (CSF). See text for the formula for determining whether the numbers of CSF red blood cells and white blood cells are consistent with a traumatic tap.
[b]Compare with serum glucose drawn just before lumbar puncture.
[c]Yield of viral culture may be low.
[d]May be useful for specific causes of meningitis and encephalitis.
[e]Most useful for specific viral causes of encephalitis and causes of chronic meningitis.
[f]In patients with suspected malignancy.
From Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.

TABLE 2 Acute Bacterial Meningitis and Subarachnoid Hemorrhage

Finding	Frequency (%)
Acute Bacterial Meningitis	
Neck stiffness	84
Fever	66-97
Altered mental status	55-95
Kernig or Brudzinski sign	61
Focal neurologic signs	9-37
Seizures	5-28
Petechial rash	3-52
Subarachnoid Hemorrhage	
Neck stiffness	21-86
Seizures	7-32
Altered mental status	29-64
Focal neurologic findings	10-36
Fever	6
Preretinal hemorrhage	4

Diagnostic standard: For *meningitis,* cerebrospinal fluid pleocytosis and microbiologic or postmortem data supporting bacterial meningitis; for *subarachnoid hemorrhage,* computed tomography or lumbar puncture.
From McGee, S: *Evidence-based physical diagnosis,* ed 4, Philadelphia, 2018, Elsevier.

DISPOSITION

Bacterial meningitis is a reportable disease that needs to be reported to local health authorities. Droplet precautions should be used for first 24 hr of therapy for suspected or confirmed *N. meningitidis* infection.

REFERRAL

- To a neurologist if persistent neurologic sequelae develop after bacterial meningitis
- To an infectious disease consultant if a patient has recurrent bacterial meningitis; such patients deserve a workup for an anatomic (CSF dural leak) or immunologic defect (complement defect, hyposplenism, immunoglobulin deficiency)

TABLE 3 Typical Cerebrospinal Fluid Findings in Patients with Selected Infectious Causes of Meningitis

Cause of Meningitis	White Blood Cell Count (cells/mm^3)	Primary Cell Type	Glucose (mg/dl)	Protein (mg/dl)
Viral	50-1000	Mononuclear[a]	>45	<200
Bacterial	1000-5000[b]	Neutrophilic[c]	<40[d]	100-500
Tuberculous	50-300	Mononuclear[e]	<45	50-300
Cryptococcal	20-500[f]	Mononuclear	<40	>45

[a]May be neutrophilic early in presentation.
[b]Range from <100 to >10,000 cells/mm^3.
[c]About 10% of patients have cerebrospinal fluid lymphocyte predominance.
[d]Should always be compared with a simultaneous serum glucose; ratio of CSF to serum glucose is ≤0.4 in most cases.
[e]May see a "therapeutic paradox," in which a mononuclear predominance becomes neutrophilic during antituberculous therapy.
[f]More than 75% of patients with acquired immunodeficiency syndrome have <20 cells/mm^3.
From Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases, ed 8, Philadelphia,* 2015, Saunders.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients with bacterial meningitis often require ICU care either to manage complications evident on presentation or for monitoring for any complications that may subsequently develop during their course. Criteria for admission to an ICU are summarized in Table 5.
- Nosocomial bacterial meningitis may result from invasive procedures (e.g., placement of ventricular catheters, lumbar puncture, craniotomy, spinal anesthesia). Treatment of this different spectrum of microorganisms requires empirical antimicrobial therapy with vancomycin plus either cefepime, ceftazidime, or meropenem. In cases of basilar skull fracture, effective empirical antimicrobial therapy consists of vancomycin plus a third-generation cephalosporin.
- False-positive elevations of CSF where blood cell counts can be found after traumatic lumbar puncture or in patients with intracerebral or subarachnoid hemorrhage in which RBCs and WBCs are introduced into the

TABLE 4 Empiric Treatment of Suspected Bacterial Meningitis in Adults[a,1,2,3,4]

Host Factors to Consider

Age >50 yr? Risk for *Listeria monocytogenes* and aerobic gram-negative rods

Immune suppression? Includes host defects (e.g., HIV, alcoholism, lymphoma) and treatment-related (e.g., posttransplant, corticosteroids)

Health care–associated? Includes trauma, postneurosurgical, shunt- or ventriculostomy-related

Life-threatening penicillin/β-lactam allergy? Aztreonam or fluoroquinolone alternatives for gram-negative rods; trimethoprim-sulfamethoxazole an alternative for *L. monocytogenes*

Host	Likely Pathogens	Empiric Therapy	Additional Considerations
Age 15-50 yr Without Immune Suppression	*Streptococcus pneumoniae, Neisseria meningitidis*, group B β-hemolytic streptococci	Vancomycin + third-generation cephalosporin[b]	Adjuvant dexamethasone Consider rifampin if high rates of cephalosporin-resistant *S. pneumoniae*
Age ≥50 yr Without Immune Suppression	*S. pneumoniae, N. meningitidis,* group B β-hemolytic streptococci, *L. monocytogenes,* aerobic gram-negative rods	Vancomycin + ampicillin + third-generation cephalosporin[b]	Adjuvant dexamethasone Consider rifampin if high rates of cephalosporin-resistant *S. pneumoniae*
Immune Suppression	*S. pneumoniae, N. meningitidis,* group B β-hemolytic streptococci, *L. monocytogenes*, *Staphylococcus aureus*, aerobic gram-negative rods including *Pseudomonas aeruginosa*	Vancomycin + ampicillin + cefepime or meropenum[c]	Adjuvant dexamethasone Consider rifampin if high rates of cephalosporin-resistant *S. pneumoniae*
Health Care–Associated: Trauma, Postneurosurgical, or Shunt-Associated[c]	*S. aureus*, coagulase-negative staphylococci, aerobic gram-negative rods including *P. aeruginosa*	Vancomycin + ceftazidime or cefepime or meropenem[c]	Dexamethasone not indicated Consider rifampin for staphylococci Consider intrathecal therapy for shunt-/ventriculostomy-associated infection
Health Care–Associated: Basilar Skull Fracture	*S. pneumoniae*, *Haemophilus influenzae,* group A β-hemolytic streptococci	Vancomycin + third-generation cephalosporin[b]	Adjuvant dexamethasone Consider rifampin if high rates of cephalosporin-resistant *S. pneumoniae*

[a]Age older than 15 yr.
[b]Third-generation cephalosporin: ceftriaxone 2 g q12h or cefotaxime 2 g q4-6h.
[c]Dosing of other agents (modified for renal insufficiency): vancomycin targeted to vancomycin trough levels of 15-20 μg/ml; ampicillin 2 g q4h; ceftazidime 2 g q8h; cefepime 2 g q8h; meropenem 2 g q8h.
HIV, Human immunodeficiency virus.
(1)van de Beek D et al: Community-acquired bacterial meningitis, *Nat Rev Dis Primers* 2, 16074, 1-20, 2016.
(2)Thigpen MC et al: for the Emerging Infections Programs Network: Bacterial meningitis in the United States, 1998–2007, *N Engl J Med* 364(21):2016-2025, 2011.
(3)Tunkel AR et al: Practice guidelines for the management of bacterial meningitis, *Clin Infect Dis* 39(9):1267-1284, 2004.
(4)Tunkel AR et al: 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for healthcare-associated ventriculitis and meningitis, *Clin Infect Dis* 64(6):e34-e65, 2017.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

TABLE 5 Major Complications of Bacterial Meningitis Requiring ICU Level of Care for Monitoring and Management[1,2,3,4,5]

Type of Complication	Etiologies, Prevalence	Management Strategies
Neurologic Complications		
Increasing intracranial pressure	Brain edema, 6%-10%	Strategies: osmotic diuresis, intracranial pressure monitoring, head of bed elevation, prophylactic lumbar drain Glycerol and hypothermia not beneficial and may result in higher mortality
Hydrocephalus	Communicating hydrocephalus, 3%-8% Obstructive hydrocephalus uncommon	Repeated lumbar puncture, lumbar drain, ventriculostomy
Focal neurologic deficits	Arterial infarct or vasculitis, 10%-15% Venous infarction, 3%-5% Hearing loss, 14%-30% Cranial nerve deficits, especially eighth nerve, 15%-30% Hemorrhage, <1% Brain abscess, subdural empyema <1%	Radiographic studies to look for focal intracranial complications Administer dexamethasone for suspected pneumococcal meningitis to decreases risk of hearing loss
Seizures	Multiple etiologies, 14%-33%	Continuous EEG monitoring, antiepileptic agents Prophylactic antiepileptic agents not routinely recommended
Agitation	Common	Careful sedation
Other Complications		
Hyponatremia	Up to 25%-30%	? Hypertonic saline solution Presence of hyponatremia did not affect outcome
Sepsis and cardiorespiratory failure	38%	Hemodynamic support, mechanical ventilation
Pneumonia	17%, most often with *Streptococcus pneumoniae*	Ventilatory support

EEG, Electroencephalographic.
[1]van de Beek D et al: Community-acquired bacterial meningitis, *Nat Rev Dis Primers* 2(16074):1-20, 2016.
[2]Bijlsma MW et al: Community-acquired bacterial meningitis in adults in the Netherlands, 2006–2014: a prospective cohort study, *Lancet Infect Dis* 16(3):339-347, 2016.
[3]Durand ML et al: Acute bacterial meningitis in adults: review of 493 episodes, *N Engl J Med* 328(1):21-28, 1993.
[4]Tunkel AR et al: Practice guidelines for the management of bacterial meningitis, *Clin Infect Dis* 39(9):1267-1284, 2004.
[5]Brouwer MC et al: What's new in bacterial meningitis, *Intensive Care Med* 42(3):415-417, 2016.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

subarachnoid space. In those instances, the following formula should be used as a correction factor for the true WBC count in the presence of CSF RBCs:

$$\text{Adjusted WBC in CSF} = \text{Actual WBC in CSF} - \frac{\text{WBC in blood} \times \text{RBC in CSF blood}}{\text{RBC in blood}}$$

In the previous equation, the amount being subtracted is the predicted CSF WBC that would occur if all the CSF WBCs were the result of blood contamination.[1]

[1]Bennett JE et al: *Mandell, Douglas and Bennett's principles and practice of infectious diseases, ed 8,* Philadelphia, 2015, Saunders, p 1093.

- Prevention of meningitis can be achieved through chemoprophylaxis of close contacts (household members and anyone exposed to oral secretions).
- Effective medications are rifampin 10 mg/kg PO bid for 2 days or ceftriaxone 250 mg IM single dose in patients older than age 12; 125 mg IM if age 12 or younger.
- Ciprofloxacin 500 mg for prevention of *Neisseria* meningitis can be given to patients older than 18 yr who cannot tolerate rifampin to eradicate pharyngeal colonization.
- Menactra: A protein-conjugate vaccine against serogroup A, C, Y, W-135 capsular polysaccharides is available for adults (up to 55 yr) and children older than 2 yr.
- Two new vaccines for *Neisseria* meningitis serogroup B (MenB) are now available: Bexsero and Trumenba.
- Children with cochlear implants are at increased risk of developing bacterial meningitis.
- Patients on eculizumab (Soliris) are at high risk for invasive meningococcal disease and should receive Menactra and a MenB vaccine and may need lifelong antibiotic prophylaxis as well.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Meningitis (Patient Information)
Meningitis, Viral (Related Key Topic)
Meningitis, Fungal (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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McGill F et al: Acute bacterial meningitis in adults, *Lancet* 388:3036-3047, 2016.

Miller L et al: Elevated risk for invasive meningococcal disease among persons with HIV, *Ann Intern Med* 160:30-37, 2014.

van de Beek D et al: Nosocomial bacterial meningitis, *N Engl J Med* 362:146-154, 2010.

FIG. E1 Purpuric lesions are seen on the trunk and extremities of a young child with meningococcemia. (From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases, ed 8,* Philadelphia, 2019, Elsevier.)

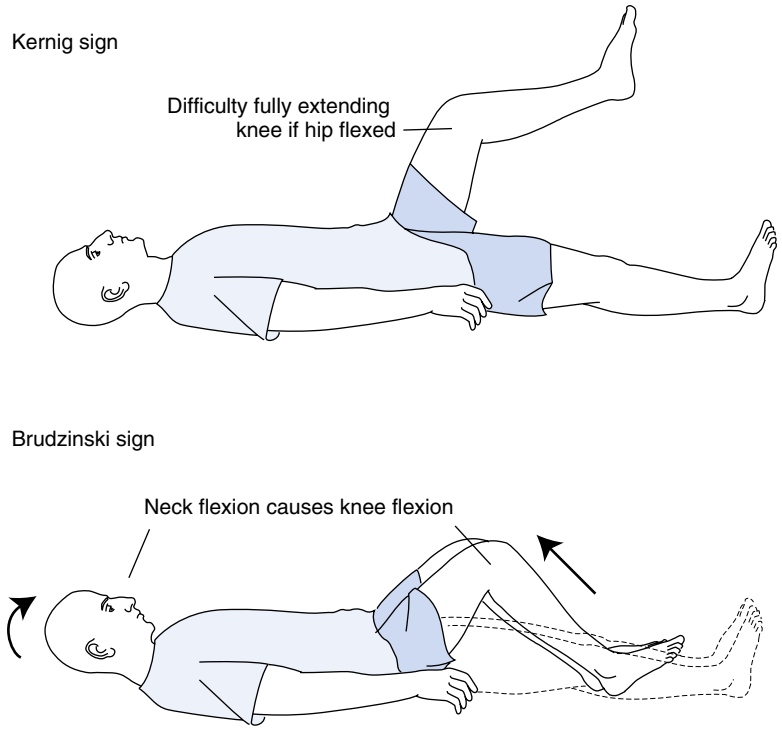

FIG. E2 Kernig sign and Brudzinski sign. In Kernig sign *(top),* the patient resists full extension of the knee when the knee and hip are first flexed (patient's left leg), although the knee extends normally if the hip is extended (patient's right leg). In Brudzinski sign *(bottom),* flexion of the patient's neck causes the hips and knees to flex, pulling both legs up toward the chest. (From McGee S: *Evidence-based physical diagnosis,* ed 4, Philadelphia, 2018, Elsevier.)

BOX E1 Differential Diagnosis Meningococcemia

Infectious

- Rocky Mountain spotted fever
- Ehrlichiosis
- Streptococcal *pneumoniae* sepsis
- *Haemophilus influenzae* type b sepsis
- Group A streptococcus sepsis
- *Staphylococcus aureus* sepsis
- Other bacterial sepsis with disseminated intravascular coagulation (i.e., enteric gram-negative organisms)
- Infective endocarditis
- Gonococcemia
- Rat bite fever
- Typhus
- Secondary syphilis

Noninfectious

- Henoch-Schönlein purpura
- Acute hemorrhagic edema of infancy
- Idiopathic thrombocytopenic purpura
- Collagen vascular disease
- Neoplastic processes

(From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.)

Meningitis, Fungal

BASIC INFORMATION

DEFINITION

Fungal meningitis is an infection of the meninges and/or central nervous system that is usually more subacute than acute and caused by a variety of different fungi or molds. The most common causes in the U.S. are *Cryptococcus neoformans* and *Coccidioides immitis* meningitis, but there was a recent multistate outbreak in the U.S. of fungal central nervous system infections and septic arthritis mostly caused by *Exserohilum rostratum* transmitted via epidural or paraspinal injections of methylprednisolone produced at a single compounding pharmacy. See Table E1. This chapter covers this outbreak. Also see chapters on Cryptococcosis and Coccidioidomycosis.

SYNONYMS

Fungal central nervous system infections
Fungal meningitis

ICD-10CM CODES

B37.5+	Candidal meningitis
B38.4+	Coccidioidomycosis meningitis
B39.3	Disseminated histoplasmosis capsulati
B40.7	Disseminated blastomycosis
B45.1	Cerebral cryptococcosis
B46.1	Rhinocerebral mucormycosis
B47.7	Disseminated sporotrichosis
B49	Unspecified mycosis

EPIDEMIOLOGY & DEMOGRAPHICS

- Outbreak started in September 2012.
- As of October 2013 there were 751 cases, including 64 deaths. No new cases were anticipated.
- Cases have been reported in 20 states, but Michigan, Tennessee, and Indiana have had the most cases.
- Some 14,000 patients had been injected with vials of methylprednisolone that were potentially contaminated with the mold.

INCIDENCE: Overall attack rate is calculated at 4.4 cases per 100 persons potentially exposed.

PREDOMINANT AGE AND SEX:

- Median age of affected patient is 64 yr (range 16 to 92).
- Females represent 60% of the cases.

PEAK INCIDENCE: Occurs within 6 wk of receiving an epidural or paraspinal injection of methylprednisolone contaminated with the mold, but cases have been detected after 3 mo.

RISK FACTORS: The source of this outbreak was traced to a single compounding pharmacy (New England Compounding Center). *E. rostratum* has been detected in two of three implicated lots of unopened vials of preservative-free methylprednisolone.

- 17,000 vials were potentially contaminated.
- 75 health care facilities (hospital and outpatient treatment centers) in 23 states received vials with lots that were subsequently recalled.
- Infection is only acquired via injection of the steroid and *not* transmitted person to person.

TABLE E1 Mycoses as a Cause of Fungal Meningitis

Cryptococcus neoformans and *Cryptococcus gattii*
Coccidioides immitis
Histoplasma capsulatum
Candida albicans and other *Candida* species
Sporothrix schenckii
Blastomyces dermatitidis
Molds: *Scedosporium, Aspergillus*
Molds with dark cell walls containing melanin: Many species including:
Cladophialophora
Exophiala species
Exserohilum rostratum

- Eventually all products manufactured at that facility were recalled and the facility closed.
- Contamination was felt to have occurred due to lack of sterility controls in manufacturing.
- Green-black material was visibly seen in 83 of 321 vials from one of the recalled lots.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Most patients present 1 to 4 wk after injection.

- Meningitis, stroke, and injection site infections.
  1. Meningitis: New or worsening headache, neck stiffness, photophobia.
  2. Stroke: Neurologic deficit with weakness, slurred speech, vertigo, ataxia, or diplopia. Stroke usually involves posterior circulation causing a basilar stroke.
  3. Injection site infections: Epidural abscess, arachnoiditis, discitis, vertebral osteomyelitis, or persistent back pain.
  4. Peripheral joint infections: 35 patients have developed only a peripheral joint infection due to an injection into that joint with a steroid from a contaminated lot.
- Pathogenesis: The steroid itself may impair local host defenses and facilitate the fungal infection into the central nervous system. The fungus accesses the cerebrospinal fluid (CSF) and spreads upward to the basal cisterns and then invades the basilar arteries.
- Fever has not been a consistent symptom.
- Some patients were found to have injection site infections on screening MRI but had no clinical symptoms yet.

ETIOLOGY

- Only about a third of the clinical cases have a proven culture result.
- *Exserohilum rostratum* is the documented cause in about 30% of clinical cases.
  1. Part of the Dematiaceae fungi group (darkly pigmented due to melanin)
  2. Found in soil and part of living or dead plant material
  3. Sensitive to voriconazole and amphotericin B but resistant to fluconazole
- Thirteen other mold species have been isolated in patients including *Aspergillus* species, *Alternaria* species, *Cladosporium* species, *Penicillium* species, and other species.
- Four different types of molds were isolated from the contaminated vials.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Meningitis: Bacterial, viral, or mycobacterial pathogens
- Stroke: Cardioembolic stroke, hemorrhagic stroke
- Tumors of the central nervous system
- Epidural abscess by bacterial pathogens
- Osteomyelitis of bacterial etiology

WORKUP

- A negative culture from a clinical specimen does not rule out the infection.
- Local health department should be contacted if case suspected.

LABORATORY TESTS

- CSF: If meningitis suspected perform lumbar puncture (LP). Obtain at least 10 to 20 ml of CSF.
  1. Obtain routine tests: Gram stain, culture, cell count, protein, glucose.
  2. At least 10 cc for fungal culture and hold for a minimum of 2 wk.
  3. Send unspun CSF to CDC for a polymerase chain reaction (PCR) for *E. rostratum.*
  4. Fungal CSF characteristics are summarized in Table E2.
- Other tests: Routine CBC with differential, blood urea nitrogen/creatinine (BUN/CR), liver function tests.

IMAGING STUDIES

Neuroimaging via MRI or MRI/MRA or CT can detect:

- Infarcts/strokes
- Large vessel involvement of the posterior circulation
- Dural and leptomeningeal enhancement
- Arachnoiditis
- Osteomyelitis/discitis of the spine
- Epidural abscess

TREATMENT

There are four cornerstones of the management of mold infections of the CNS: early diagnosis, administration of antifungal chemotherapy, neurosurgical assessment and intervention, and management of immunologic impairment.

ACUTE GENERAL Rx

Will depend on site of infection and severity:

- Meningitis: Voriconazole with or without liposomal amphotericin B.
  1. Voriconazole: 6 mg/kg q12h IV for severe cases or oral for mild cases has good penetration into CSF; side effects include changes in color vision or hallucinations.
  2. Liposomal amphotericin B (AmBisome): 7.5 mg/kg IV q24h can be added to voriconazole for the most severe cases or for patients who are not responding to

TABLE E2 Fungal Cerebrospinal Fluid Characteristics

Organism	WBCs	Protein	Glucose	Smears	Serology	Cultures
Blastomyces	Variable up to 15,000 cells/mm^3 with PMNs or lymphocytes	Elevated up to 300 mg/dl	Normal or low	Rare on smear	No good serology	CSF cultures rarely positive; increased yield with ventricular taps
Candida	Mean 600 cells/mm^3 up to 1900 cells/mm^3 with lymphocytes or PMNs	Elevated	Low or normal	40% positive on smears	Serology not helpful	CSF cultures useful
Coccidioides	100-750 WBCs, mostly lymphocytes	150-2000 mg/dl	21%-62% serum	Rare on smear	CSF CF antibody positive in 75%-95%	CSF cultures positive in 33%-60%
Cryptococcus	40-400 WBCs, mostly lymphocytes	High	Low	India ink positive in 25%-50%	CSF and serum cryptococcal antigen positive in 85%-90%	CSF cultures positive in 75%
Histoplasma	0-300 WBCs, lymphocytes, or PMNs; most 11-101/mm^3	Usually elevated, but can be normal	Usually low (<40 mg/dl) to normal	Rare on smear	Polysaccharide antigen in urine, blood, CSF positive in 61%	CSF cultures positive in 27%-65%

CF, Complement fixation; *CSF,* cerebrospinal fluid; *PMN,* polymorphonuclear leukocyte; *WBC,* white blood cells.
From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

voriconazole alone or relapse. Can cause nephrotoxicity that can be ameliorated by giving 1 L of IV normal saline prior to dose.

- Injection site infections: Epidural abscess, discitis, vertebral osteomyelitis, etc.
  1. Voriconazole: 6 mg/kg q12h IV or oral depending on presentation and can consider adding liposomal amphotericin B at 5 to 6 mg/kg IV q24h.

CHRONIC Rx

- Meningitis: Meningitis therapy should last at least 3 mo, but stroke or severe CNS disease may require 6 mo to 1 yr. Monitor liver function tests, and obtain a voriconazole trough concentration on day 5 of treatment that should be between >2 mcg/ml and <5 mcg/ml. Monitor for neurologic side effects of voriconazole. For patients on liposomal amphotericin B, kidney function and electrolytes (K+) need to be monitored frequently.
- Injection site infections: Therapy should last at least 3 to 6 mo.

DISPOSITION

Mortality has been about 8.8%, and highest risk factor is development of a stroke.

REFERRAL

- Infectious diseases physician for guidance on initial and long-term antifungal therapy
- Neurologist for evaluation and diagnosis
- Neuroradiologist for MRI/MRA interpretation

PEARLS & CONSIDERATIONS

PATIENT & FAMILY EDUCATION

This fungal disease is transmitted by the contaminated steroid injection and is not transmitted person to person and thus not contagious.

RELATED CONTENT

Candidiasis, Invasive (Related Key Topic)
Cryptococcosis (Related Key Topic)
Coccidioidomycosis (Related Key Topic)
Meningitis, Bacterial (Related Key Topic)
Meningitis, Viral (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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Ritter JM et al: Exserohilum infections associated with contaminated steroid injections: a clinicopathologic review of 40 cases, *Am J Pathol* 183(3):881-892, 2013.

Smith RM et al: Fungal infections associated with contaminated methylprednisolone injections, *N Engl J Med* 369:1598-1609, 2013.

BASIC INFORMATION

DEFINITION

Viral meningitis is an acute febrile illness with signs and symptoms of meningeal irritation, usually with a lymphocytic pleocytosis of the cerebrospinal fluid (CSF) and negative CSF bacterial stains and cultures.

SYNONYMS

Aseptic meningitis
Viral meningitis

ICD-10CM CODES

A87.8 Other viral meningitis
A87.9 Viral meningitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS (TABLE 1)

INCIDENCE (IN U.S.): 11 cases/100,000 persons; leads to 26,000 to 42,000 hospitalizations per yr
PREDOMINANT SEX: Male = female
GENETICS: Those with abnormal humoral immunity and agammaglobulinemia have associated difficulty with viral clearance.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever
- Headache
- Nuchal rigidity
- Photophobia
- Myalgias
- Vomiting
- Rash

ETIOLOGY

- Enterovirus: 85% to 95% of all cases. Most common are coxsackie viruses and echoviruses
- Parechoviruses
- Mumps virus
- Measles
- Arboviruses from mosquitoes: Eastern equine encephalitis (EEE), West Nile, St. Louis
- Herpes: HSV-1, HSV-2, VZV, HHV-6, and HHV-7
- Acute HIV
- Lymphocytic choriomeningitis virus
- Adenovirus
- Cytomegalovirus (CMV) and Epstein-Barr virus (EBV)
- Other arthropod-borne viruses: Powassan virus
- Influenza A and B virus
- Box E1 summarizes etiologic agents, factors, and diseases associated with aseptic meningitis

DIAGNOSIS

The diagnostic approach is similar to that for bacterial meningitis (see "Meningitis, Bacterial"); the foremost need is to rule out bacterial meningitis with CSF evaluation. Presentation may be similar to that of meningitis with bacterial involvement.

DIFFERENTIAL DIAGNOSIS

- Bacterial meningitis
- Meningitis secondary to Lyme disease, tuberculosis (TB), syphilis, amebiasis, leptospirosis
- Rickettsial illnesses: Rocky Mountain spotted fever
- Migraine headache
- Medications
- Systemic lupus erythematosus (SLE)
- Acute mononucleosis/Epstein-Barr virus
- Seizures
- Carcinomatous meningitis

WORKUP

CSF examination:
- Usually shows pleocytosis
- Lymphocytic predominance (neutrophils in early stages)
- Opening pressure: 200 to 250 mm Hg H_2O ($\leq$250 mm/H_2O)
- WBC: 100 to 1000 mm^3
- Increased CSF protein (<200 mg/dl)
- Slightly decreased or normal CSF glucose (>45 mg/dl)
- Negative gram stain, cultures, CIE, latex agglutination
- Viral cultures or serologic testing may be diagnostic
- Polymerase chain reaction (PCR) for HSV or enterovirus (which could shorten duration of antibiotic treatment and hospitalization if bacterial meningitis was suspected); Multiplex or panel-based PCR tests that test for multiple viruses and bacteria at the same time in a single CSF sample are available
- Antibody detection in CSF for diagnosis of West Nile virus meningitis

LABORATORY TESTS

CBC with differential, blood culturing, and CSF examination (see "Workup")

IMAGING STUDIES

CT scan or MRI: If cerebral edema, focal neurologic findings develop.

TREATMENT

- No specific antiviral therapy for most viruses. Treatment is supportive unless herpes simplex virus (HSV) is detected, which would be treated with IV acyclovir: 10 mg/kg q8h in adults for 14 to 21 days. Up to 20 mg/kg q8h in children >12 yr.
- Empiric antibiotics may be given until CSF cultures exclude bacterial meningitis.

DISPOSITION

Viral meningitis is almost always an uncomplicated illness that will resolve; however, relapsing headache, myalgia, and weakness may occur for 2 to 3 wk after onset of symptoms.

PEARLS & CONSIDERATIONS

- Enteroviruses are the most common cause of viral meningitis and are transmitted by fecal-oral route and less commonly by the respiratory route. They are more common in summer and fall mos. From 2000 to 2005, the most common serotypes were coxsackie viruses A9, B5, and B1 and echoviruses 6, 9, 13, 18, and 30.
- Herpes simplex type 2 (HSV-2) can be a cause of a primary episode of meningitis and also be a cause of recurrent episodes of lymphocytic meningitis. HSV-2 meningitis presents most often without a history of genital herpes or genital symptoms. Recurrent aseptic meningitis, also known as Mollaret disease, is predominantly caused by HSV-2 infection.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Meningitis (Patient Information)
Meningitis, Bacterial (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

TABLE 1 Epidemiology of Acute Viral Meningitis

Epidemiologic Factors*				
Season	**Patient's Age (yr)**	**Patient's Sex**	**Risk Factor**	**Suggested Viral Agent**
Summer-fall	Infant	—	Infected mother	Coxsackievirus B
	1-15	—	Swimming pools, closed communities	Enteroviruses
			Geographic area: California, southeastern U.S.	California serogroup virus
Winter	1-15	—	School exposure	Varicella virus, measles virus
		Male:female		Mumps virus
		3:1		
	16-21	—	College exposure	Measles virus
		Male:female		Mumps virus
		3:1		Epstein-Barr virus (mononucleosis)
	Any	—	Mice, rats, hamsters	Lymphocytic choriomeningitis virus
	Adults	—	Varicella-zoster	Varicella-zoster virus
Any	Any	—	Immunocompromise	Adenovirus
		—	Acquired immunodeficiency syndrome	Human immunodeficiency virus

*Epidemiologic factors are suggestive but should not be used to exclude diagnoses in individual cases.
From Gorbach SI: *Infectious diseases,* ed 2, Philadelphia, 1998, WB Saunders.

SUGGESTED READINGS

McGill F et al: Viral meningitis: current issues in diagnosis and treatment, *Curr Opin Infect Dis* 30:248-256, 2017.

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Swanson PA 2nd, McGavern DB: Viral diseases of the central nervous system, *Curr Opin Virol* 11:44-54, 2015.

Tuppeny M: Viral meningitis and encephalitis, *Crit Care Nurs Clin North Am* 25(3):363-380, 2013.

BOX E1 Etiologic Agents, Factors, and Diseases Associated with Aseptic Meningitis

Viruses
- Adenoviruses (1, 2, 3, 5, 6, 7, 12, 14, 32)
- Arboviruses (in the U.S.: West Nile, St. Louis, California, Colorado tick fever, eastern equine, western equine, Venezuelan equine, and Powassan)[a]
- Coronaviruses
- Cytomegalovirus
- Encephalomyocarditis
- Enteroviruses (echoviruses, coxsackieviruses A and B, polioviruses, enteroviruses)
- Epstein-Barr
- Hendra and Nipah
- Herpes simplex type 1
- Herpes simplex type 2
- Human herpesvirus–6
- Human herpesvirus–7
- Human immunodeficiency virus (HIV-1)
- Human parechoviruses
- Human T-cell lymphotrophic virus (HTLV-1)
- Influenza A and B
- Lymphocytic choriomeningitis
- Measles
- Mumps
- Parainfluenza
- Parechoviruses
- Parvovirus B19
- Rhinoviruses
- Rotaviruses
- Rubella
- Varicella zoster
- Variola

Bacteria

Atypical Mycobacteria
- *Bartonella henselae*
- *Borrelia* spp. (relapsing fever)
- *Borrelia burgdorferi* (Lyme disease)
- *Brucella* spp.
- *Leptospira* spp. (leptospirosis)
- *Mycobacterium tuberculosis*
- *Nocardia* spp. (nocardiosis)

Pyogenic: Partially Treated
- *Treponema pallidum* (syphilis)

Rickettsia
- *Anaplasma phagocytophila*
- *Coxiella burnetii*
- *Ehrlichia chaffeensis*
- *Rickettsia rickettsii* (Rocky Mountain spotted fever)
- *Rickettsia prowazekii* (typhus)

Mycoplasma
- *Mycoplasma hominis*
- *Mycoplasma pneumoniae*

Chlamydia
- *Chlamydia pneumoniae*
- *Chlamydia psittaci*

Ureaplasma
- *Ureaplasma urealyticum*

Fungi
- *Blastomyces dermatitidis*
- *Candida* spp.
- *Coccidioides immitis*
- *Cryptococcus neoformans*
- *Histoplasma capsulatum*
- Other: *Acremonium* spp., *Alternaria* spp., *Aspergillus* spp., *Blastoschizomyces capitatus*, *Cephalosporium* spp., *Cladosporium trichoides, Drechslera hawaiiensis, Fusarium* spp., *Paecilomyces* spp., *Paracoccidioides brasiliensis, Penicillium marneffei, Phaeohyphomycosis, Pseudallescheria boydii, Sporothrix schenckii, Trichosporon beigelii, Ustilago* spp., *Zygomycetes* spp.

Parasites (Eosinophilic Meningitis)
- Flukes: *Paragonimus westermani,* schistosomiasis, fascioliasis
- Roundworms: *Angiostrongylus cantonensis, Gnathostoma spinigerum, Baylisascaris procyonis, Strongyloides stercoralis, Trichinella spiralis, Toxocara canis*
- Tapeworms: *Cysticercosis*
- Protozoa and free-living amoebae (noneosinophilic meningitis)
- *Acanthamoeba*
- *Naegleria fowleri*
- *Toxoplasma gondii* (toxoplasmosis)

Vaccine Associated
- Measles
- Mumps
- Polio
- Rabies
- Vaccinia

Parameningeal Infection

Malignancy
- Central nervous system tumor
- Leukemia

Immune Diseases
- Behçet syndrome
- Lupus erythematosus
- Sarcoidosis

Medications
- Antimicrobial agents (e.g., trimethoprim-sulfamethoxazole)
- Intrathecal injections (e.g., contrast media, antibiotics)
- Nonsteroidal antiinflammatory drugs
- Other drugs

Miscellaneous
- Epidermoid, dermoid, other cysts
- Foreign bodies (shunt, reservoir)
- Heavy metal poisoning
- Kawasaki disease

[a]In other areas of the world, many other arboviruses are important.

From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

Meningomyelocele

BASIC INFORMATION

DEFINITION

Meningomyelocele is the most common type of open neural tube defect and is characterized by herniation of the spinal cord, nerves, or both through a bony defect of the spine covered only by a thin membrane or not covered.

SYNONYMS

Myelomeningocele
Spina bifida cystica

ICD-10CM CODES

Q05.2	Lumbar spina bifida with hydrocephalus
Q05.4	Unspecified spina bifida with hydrocephalus
Q05.7	Lumbar spina bifida without hydrocephalus
Q05.8	Sacral spina bifida without hydrocephalus
Q05.9	Spina bifida, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 4.6/10,000 births
PREDOMINANT SEX: Male = female
PEAK INCIDENCE: Newborn
GENETICS: Environmental and genetic factors have a joint role.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Evident at birth: A sac protruding in the lumbar region (Fig. E1, *A*)
- Severity of neurologic deficits depends on the location of the lesion along the neuraxis, and newborns may remain asymptomatic up to 6 wk
- Motor dysfunction in the legs below the level of the lesion
- Lack of bladder or bowel control in 97%
- Often associated with Chiari II malformation and resulting obstructive hydrocephalus

ETIOLOGY

- Failure of neural tube to close completely at about 4 wk gestation
- Associated with maternal valproate use, maternal diabetes, and prepregnancy obesity
- Growing recognition of role of environmental chemicals, including organic pollutants
- In the U.S., higher rates of neural tube defects reported among Hispanic women
- A small proportion of cases are associated with chromosomal or single-gene disorders

DIAGNOSIS

- Prenatal diagnosis through ultrasound and MRI is being made more frequently.
- Coexisting hydrocephalus detected by measurement of head size, ultrasonography, CT, or MRI.

DIFFERENTIAL DIAGNOSIS

- Teratoma
- Meningocele

WORKUP

- Evaluate for hydrocephalus.
- Evaluate for other congenital abnormalities, such as congenital heart disease, hydronephrosis, intestinal malformation, club foot, and skeletal deformities.

LABORATORY TESTS

Prenatal testing often reveals elevated alpha-fetoprotein in amniotic fluid or maternal serum.

IMAGING STUDIES

- MRI of spine (Fig. E1, *B* and *C*)
- X-ray studies of skull exhibit craniolacunia, a honeycombed pattern associated with hydrocephalus (not routinely performed)
- CT or MRI of head: May reveal hydrocephalus

TREATMENT

- Surgical closure of myelomeningocele is performed soon after birth
- Control of hydrocephalus (shunt)
- Management of urinary incontinence (bladder catheterization)

ACUTE GENERAL Rx

- Immediate goal after delivery is to close defect and prevent infection; surgery usually performed within 24 hours of birth
- Shunt placement for obstructive hydrocephalus
- Treatment of seizures, if present

CHRONIC Rx

- Follow closely for development of hydrocephalus
- Bladder catheterization
- Long-term management of neurologic sequelae
- Avoid use of latex-containing products to prevent development of latex allergy

DISPOSITION

Followed by a team of specialists including neurosurgeons, urologists, orthopedists, nurses, and physical therapists. Table E1 summarizes prognosis based on motor level spinal cord segment.

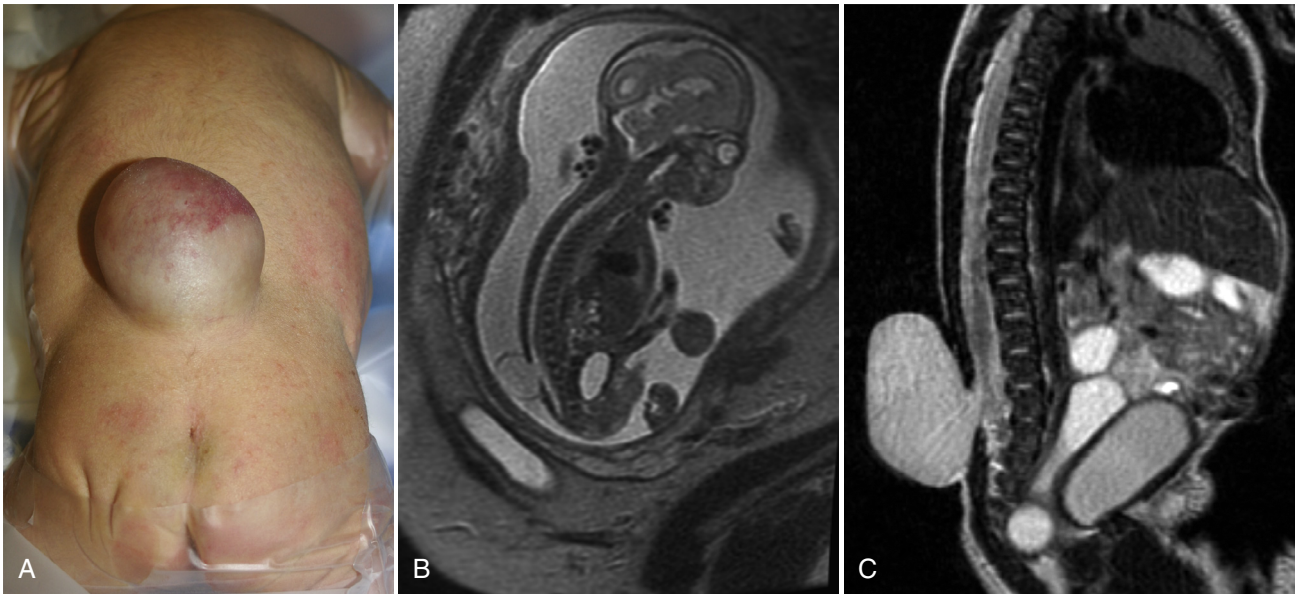

FIG. E1 Lumbar meningocele in a newborn. A, External appearance of the skin. **B,** Midline sagittal view from a fetal T2-weighted magnetic resonance image (MRI) study depicts a fluid-filled cystic lesion. Note homogeneous water signal within the lesion, suggesting the diagnosis of meningocele, rather than meningomyelocele. **C,** Midline sagittal T2-weighted image from the postnatal MRI showing the fluid-filled sac and the spinal cord within the spinal canal. (From Swaiman KF et al: *Swaiman's pediatric neurology, principles and practice,* ed 6, Philadelphia, 2017, Elsevier.)

TABLE E1 Prognosticating in Myelomeningocele

Motor Level Spinal Cord Segment	Critical Motor Function Present	Mobility: School Age	Range: Adult	Activity: Adolescent
T12	Totally paralyzed lower limbs	Standing brace, wheelchair	Wheelchair	Wheelchair, no ambulation
L1-L2	Hip flexor muscles	Crutches, braces, wheelchair	Wheelchair, household ambulation	Wheelchair, nonfunctional ambulation
L3-L4	Quadriceps muscles	Crutches, braces, household ambulation, wheelchair	Crutches, household ambulation, wheelchair	50% Wheelchair, household ambulation with crutches
L5	Medical hamstrings, anterior tibial muscles	Crutches, braces, community ambulation	Crutches, community ambulation	Community ambulation with crutches
S1	Lateral hamstring and peroneal muscles	Community ambulation	Community ambulation	Community ambulation 50% crutch or cane
S2-S3	Mild loss of intrinsic foot muscles possible	Normal	Normal	Limited endurance because of late foot deformities

From Braddon RL (ed): *Physical medicine & rehabilitation,* ed 4, Philadelphia, 2011, WB Saunders, Table 54.1, p. 1284.

PEARLS & CONSIDERATIONS

All mothers of children with neural tube defects should be instructed on nutritional supplementation with folate for future pregnancies.

COMMENTS

- Intrauterine repair of meningomyelocele decreases the incidence of hindbrain herniation and shunt-dependent hydrocephalus in infants, but increases the incidence of premature delivery and is associated with maternal and fetal risks.
- U.S. Public Health Service recommends 400 mg of folate intake per day for all women capable of becoming pregnant for primary prevention of neural tube defects.

AUTHORS: **Corey Goldsmith, MD,** and **Maitreyi Mazumdar, MD, MPH, MSc**

SUGGESTED READINGS

Adzick NS et al: A randomized trial of prenatal versus postnatal repair of myelomeningocele, *N Engl J Med* 364:993-1004, 2011.

Meniscal Tear

BASIC INFORMATION

DEFINITION

Damage or tear of semicircular cartilage located between the femur and tibia in the knee joint. Each knee joint contains two menisci (medial and lateral). Classically, injury results from forceful twisting or rotation of the knee.

SYNONYMS

Knee cartilage tear
Tear of semilunar or semicircular cartilage

ICD-10CM CODES

S83.202	(A,D,S) Bucket-handle tear of unspecified meniscus, current injury, unspecified knee
S83.209	(A,D,S) Unspecified tear of unspecified meniscus, current injury, unspecified knee
S83.219	(A,D,S) Bucket-handle tear of medial meniscus, current injury, unspecified knee
S83.229	(A,D,S) Peripheral tear of medial meniscus, current injury, unspecified knee
S83.239	(A,D,S) Complex tear of medial meniscus, current injury, unspecified knee
S83.259	(A,D,S) Bucket-handle tear of lateral meniscus, current injury, unspecified knee
S83.269	(A,D,S) Peripheral tear of lateral meniscus, current injury, unspecified knee
S83.279	(A,D,S) Complex tear of lateral meniscus, current injury, unspecified knee

A, Initial encounter; *D,* subsequent encounter; *S,* sequela.

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Estimated >200,000 cases per yr in the U.S.

PEAK INCIDENCE:

- Males: Peak incidence 21 to 30 yr.
- Females: Peak incidence 11 to 20 yr.
- In patients older than 65 yr, 60% of meniscal tears are degenerative.

PREVALENCE (IN U.S.):

- May be the most common knee injury.
- Estimated prevalence of acute meniscal tears: 61 cases per 100,000 persons.

PREDOMINANT AGE AND SEX

- Overall male:female incidence: Approximately 2.5 to 1.
- Rare in children younger than 10 yr.
- Degenerative tears are common in patients older than 65 yr.

RISK FACTORS: Trauma, age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Key historical points:
  1. Mechanism of injury (e.g., twisting, squatting, or cutting maneuver on a weight-bearing knee)
  2. Pain (commonly intermittent and localized to the joint line)
  3. Mechanical complaints (clicking, popping, or painful locking of the joint on either flexion or extension of the knee)
  4. Swelling (often delayed, sometimes absent; degenerative tears may manifest with recurrent effusions)
- Physical examination findings suggestive of a potential meniscal injury include:
  1. Joint line tenderness
  2. Presence of knee effusion
  3. Impaired range of motion (locking of knee joint may occur with severely displaced tears)
- Several provocative examination maneuvers have been developed to aid in diagnosing ligamentous and meniscal injuries. Common stability tests include:
  1. **McMurray test:** Patient lies supine with the knee hyperflexed. The foot is grasped by examiner with one hand and the knee with the other. The examiner then flexes and extends the knee while simultaneously internally and externally rotating the tibia on the femur and providing slight varus and valgus stress. Positive test result is the presence of "clicking" palpable along the joint line or locking of the knee.
  2. **Apley grinding test:** With patient prone, knee is flexed 90 degrees, and the leg is internally and externally rotated with downward pressure applied to the heel. Presence of popping and/or pain localized to the joint line indicates a positive test. The pain should be relieved with distraction of the knee and rotation of the leg back to a neutral position.
  3. **Thessaly test:** Hold patient's outstretched hands while he or she stands flat-footed on one leg, internally and externally rotating three times with the knee flexed 20 degrees. Presence of pain or "clicking" indicates a positive test. Test first with the uninjured knee for comparison.
- Above-mentioned maneuvers are variably accurate, at best, when compared with magnetic resonance imaging (MRI) or arthroscopy findings.

ETIOLOGY

- May arise from a single traumatic event, a degenerative process, or a combination.
- Force required can be minimal, such as rising from a chair while turning.
- Intermittent locking of the knee results from a meniscal fragment blocking joint movement.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Patellofemoral pain syndrome
- Popliteal tendinitis
- Loose bodies
- Osteochondrotic lesions
- Tibial spine fractures
- Plica syndromes
- Inflammatory arthritis

WORKUP

- Rule out fracture or vascular injury.
- Identify potential infections and inflammatory conditions hidden by a history of minor trauma.

LABORATORY TESTS

None needed

IMAGING STUDIES

- MRI: Criterion standard for imaging meniscus pathology and associated intraarticular disorders. Fig. E1 illustrates a normal meniscus. Tears can be horizontal/oblique (Figs. E2 and E3), vertical (Figs. E4 and E5), bucket handle (Figs. E6 and E7), radial (Figs. E8 and E9), and parrot beak (Figs. E10 and E11).
- Arthroscopy: Perhaps the best tool for diagnosing meniscal tear. Both therapeutic and diagnostic and offers the option of immediate treatment of most meniscal disorders.
- Plain radiographs of the knee are not helpful in establishing diagnosis of meniscal tear.

TREATMENT

- Recommendations must take into consideration the patient's age, activity level, duration of symptoms, type of meniscus tear, and associated injuries, such as ligamentous pathology.

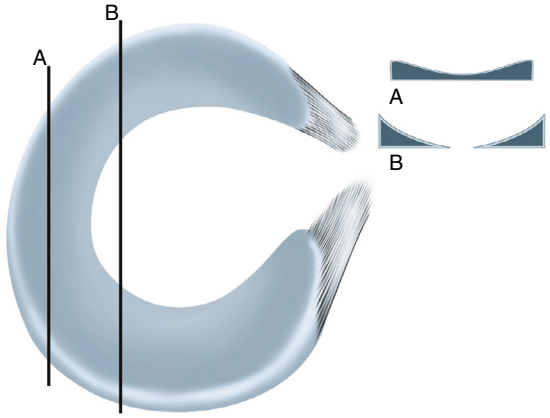

FIG. E1 Normal meniscus. This schematic shows the normal "bow tie" configuration at the periphery of the meniscus **(A)** and triangular configuration of the anterior and posterior horns of the menisci more centrally **(B)** on sagittal images. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, Elsevier.)

- Trial of conservative treatment should be attempted in all but the most severe cases, such as a locked knee secondary to a displaced tear.
- Unfortunately, most tears do not heal without operative intervention.

NONPHARMACOLOGIC THERAPY

- Home physical therapy (PT) program: Goals are to minimize effusion, normalize gait and pain-free range of motion, prevent muscle atrophy, maintain proprioception, and maintain cardiovascular fitness.
- Ice, rest, and activity modification.
- Surgical intervention may be considered for patients with persistent symptoms that limit activity.
- Untreated tears may increase in size and may abrade articular cartilage, resulting in arthritis.
- Surgical options (arthroscopic or open) include the following:

1. Partial meniscectomy: Treatment of choice for tears in the avascular portion of the meniscus or complex tears that are not amenable to repair.
2. Meniscus repair: Recommended for tears located in the vascular region, those longer than 1 cm, root tears, those involving greater than 50% of the meniscal thickness, and tears that are unstable to arthroscopic probing.
3. Meniscus transplantation: A relatively new procedure for which specific indications and long-term results have not yet been clearly established.

ACUTE GENERAL Rx

Nonsteroidal antiinflammatory drugs

CHRONIC Rx

- Natural history of a short (<1 cm), vascular, longitudinal tear is often one of healing or resolution of symptoms with conservative treatment.
- Likewise, stable tears with minimal displacement, degenerative tears, or partial-thickness tears may become asymptomatic with nonoperative treatment.

DISPOSITION

Outpatient management

REFERRAL

- Referral to an orthopaedic surgeon is warranted if conservative treatment does not lead to resolution of symptoms.
- Urgent orthopaedic consultation is required for a knee that is locked and cannot be extended or flexed secondary to a displaced bucket handle meniscal tear.

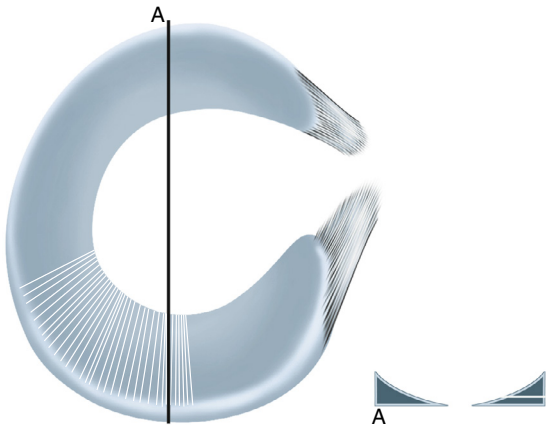

FIG. E2 Horizontal/oblique tear. This schematic shows the appearance of a horizontal meniscal tear *(A)* seen on a sagittal image through the meniscus. The tear can extend to the articular surfaces or the free apical edge of the meniscus. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, Elsevier.)

PEARLS & CONSIDERATIONS

COMMENTS

- Meniscal tears commonly accompany ligamentous injuries, especially ACL tears.
- Most meniscal tears might not require surgery. A recent 2-yr follow-up study showed no benefit of partial meniscectomy compared to sham procedure in patients with knee pain and nontraumatic meniscal tears without osteoarthritis.[1]

PREVENTION

Avoiding high-impact maneuvers that are higher risk for meniscal tears

RELATED CONTENT

Patellofemoral Pain Syndrome (Related Key Topic)

AUTHORS: **Nora Rader, MD,** and **Alan Taylor, MD**

[1]Sihuonen R et al: Arthroscopic partial meniscectomy versus placebo surgery for a degenerative meniscus tear: a 2-year follow-up of the randomized controlled trial, *Ann Rheum Dis* 77:188, 2018.

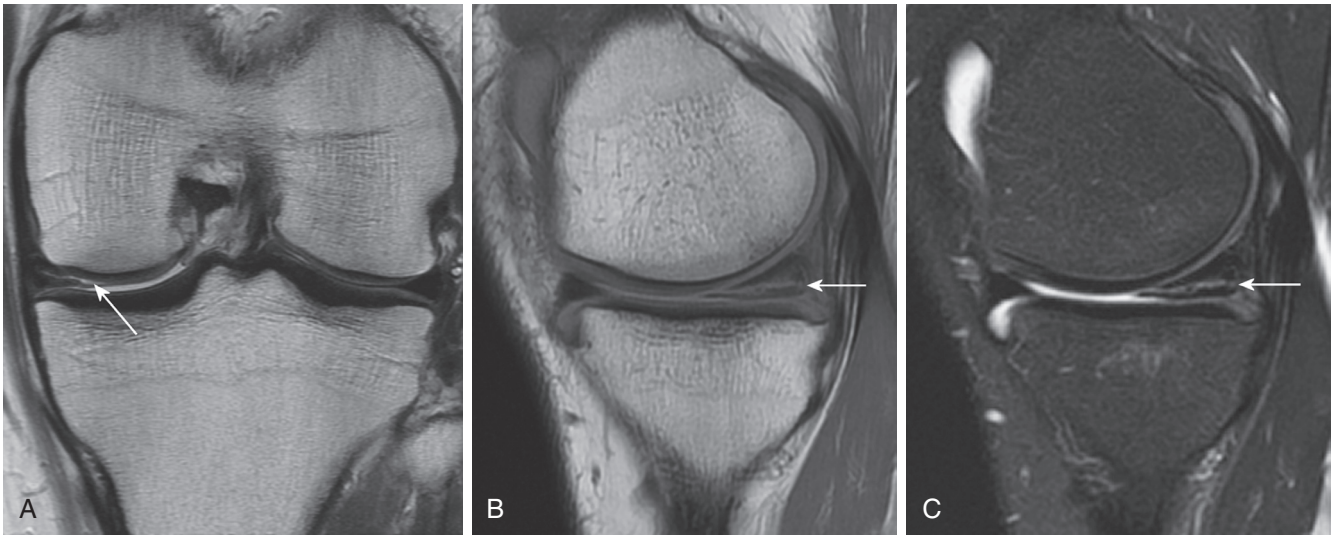

FIG. E3 Horizontal tear. Coronal and sagittal fast spin-echo, proton density-weighted (TR/TE 2200/15) **(A, B)** and sagittal T2-weighted, fat-suppressed, fast spin-echo (TR/TE 2800/63) **(C)** MR images through the knee. A medial meniscal tear is present *(arrows)* with extension to the free apical margin of the body and posterior horn of the meniscus. *MR,* Magnetic resonance; *TE,* echo time; *TR,* repetition time. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, Elsevier.)

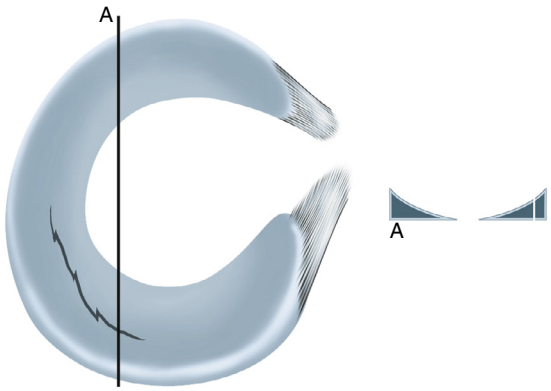

FIG. E4 Vertical tear. This schematic shows the appearance of a vertical meniscal tear *(A)* seen on a sagittal image through the meniscus. The tear can extend to both the superior and inferior articular surfaces of the meniscus. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, Elsevier.)

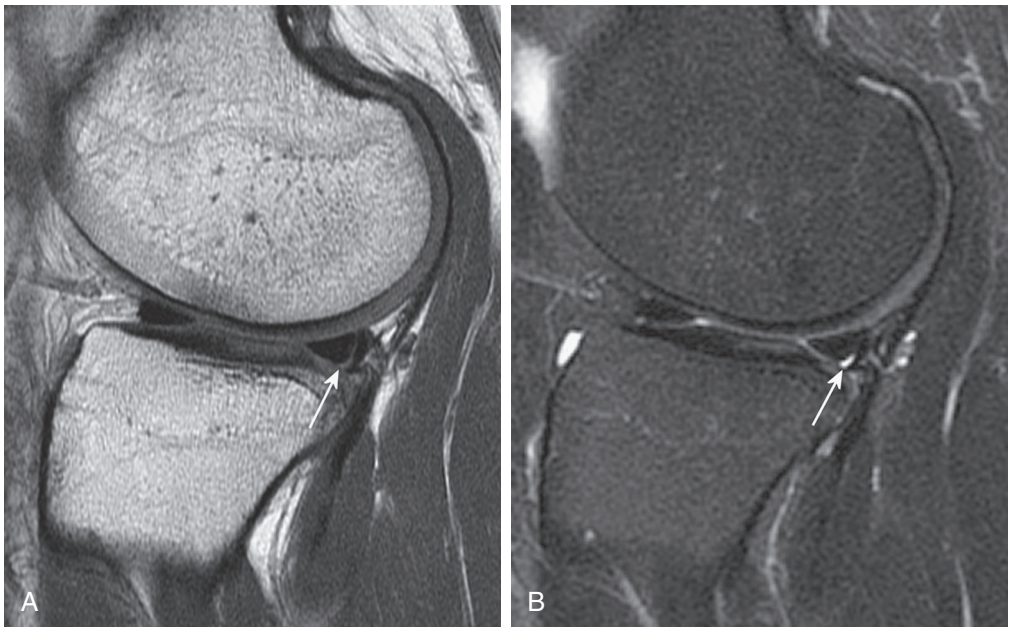

FIG. E5 Vertical tear. Sagittal fast spin-echo, proton density-weighted (TR/TE 2200/15) **(A)** and sagittal T2-weighted, fat-suppressed, fast spin-echo (TR/TE 2800/63) **(B)** images through the knee. A vertical tear is seen in the posterior horn of the lateral meniscus *(arrows). TE,* Echo time; *TR,* repetition time. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, Elsevier.)

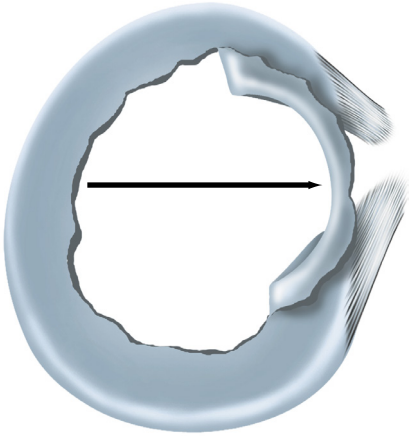

FIG. E6 Bucket handle tear. This schematic shows a centrally displaced fragment of meniscal tissue due to an extensive vertical longitudinal tear. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, Elsevier.)

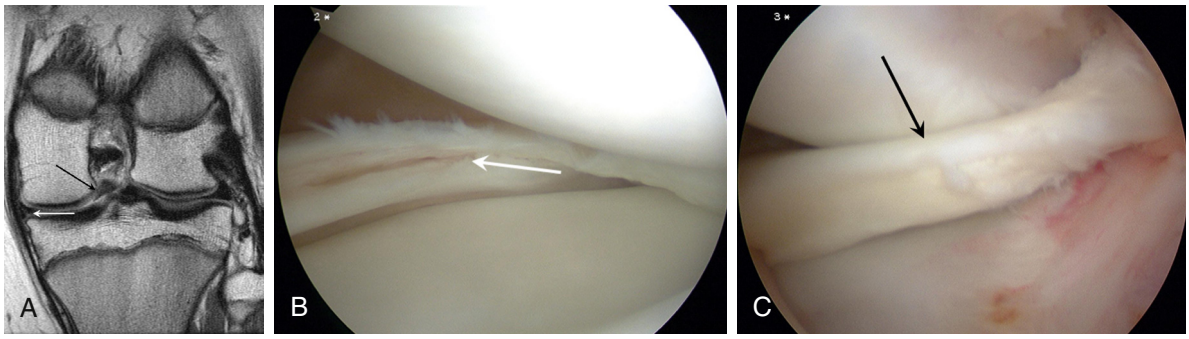

FIG. E7 Bucket handle tear with tear of the meniscal remnant and arthrographic correlation. A, Coronal fast spin-echo, proton density-weighted (TR/TE 2200/15) through the knee with a bucket handle tear and displaced meniscal tissue centrally in the intercondylar notch *(black arrow).* Oblique horizontal tear is in the remnant meniscal body *(white arrow).* **B,** Arthroscopic correlation demonstrating an oblique horizontal tear in the remnant meniscal body. **C,** Centrally displaced meniscal tissue. *TE,* Echo time; *TR,* repetition time. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, Elsevier.)

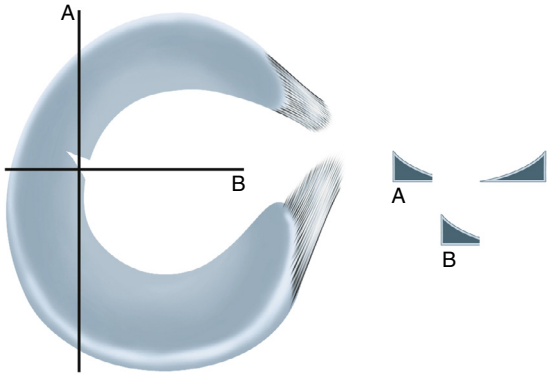

FIG. E8 Radial tear. This schematic shows a radial tear along the free edge of the meniscal body. This causes a blunted appearance on the sagittal **(A)** and coronal **(B)** images. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, Elsevier.)

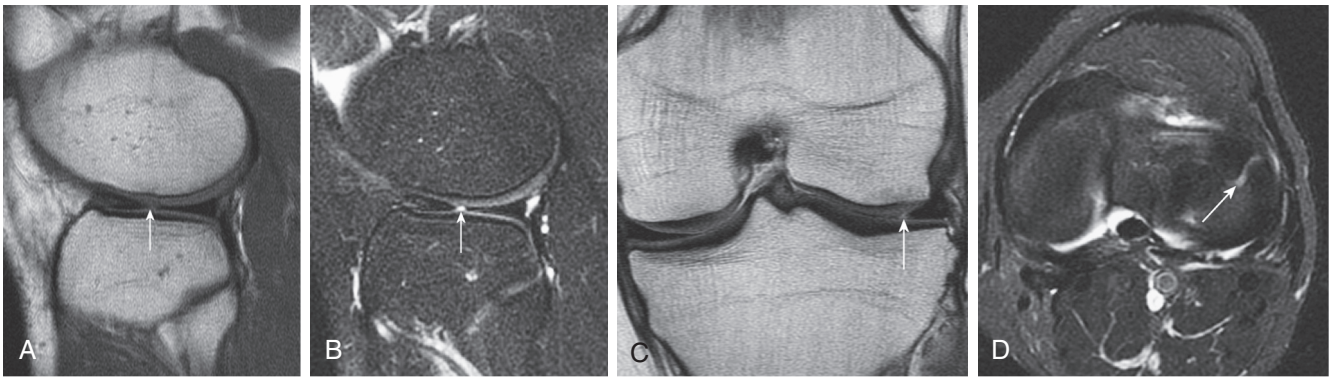

FIG. E9 Radial tear. Sagittal and coronal fast spin-echo, proton density-weighted (TR/TE 2200/15) **(A, C)** and sagittal and axial T2-weighted, fat-suppressed, fast spin-echo (2800/63) **(B, D)** MR images through the knee. A defect is seen in the normal bow tie configuration of the meniscus on the sagittal images, and there is a blunted appearance to the normal triangular configuration at the free apical margin of the meniscal body on the coronal image, consistent with a radial tear. This is confirmed on the axial image, which shows a radially oriented tear cleft through the body of the meniscus *(arrows). MR,* Magnetic resonance; *TE,* echo time; *TR,* repetition time. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, Elsevier.)

FIG. E10 Parrot beak tear. This schematic shows a radial tear configuration along the free apical margin of the meniscal body with a small, contiguous portion that extends along the longitudinal orientation of the meniscus, giving the appearance of a parrot beak. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, Elsevier.)

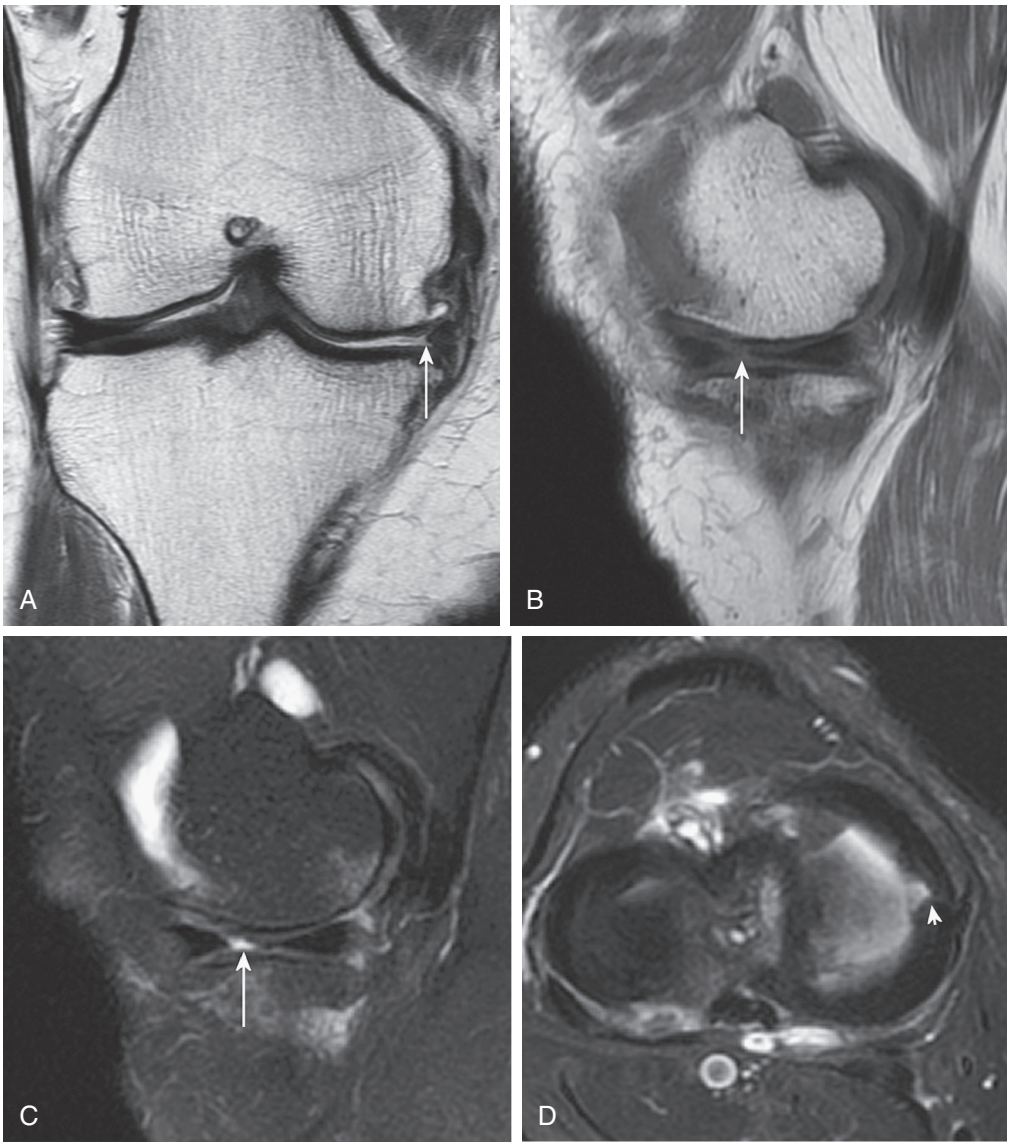

FIG. E11 Parrot beak tear. Coronal and sagittal fast spin-echo, proton density-weighted (TR/TE 2200/15) **(A, B)** and sagittal and axial T2-weighted, fat-suppressed, fast spin-echo (2800/63) **(C, D)** MR images through the knee. The coronal and sagittal images demonstrate a radial-type tear with blunting of the free apical margin of the meniscal body (*long arrow*, **A** through **C**). This also can be seen on the axial image, which has a small portion of the tear that begins to course along the longitudinal orientation of the meniscus, forming a parrot beak configuration (*short arrow*, **D**). *MR,* Magnetic resonance; *TE,* echo time; *TR,* repetition time. (From Pope TL et al: *Musculoskeletal imaging*, ed 2, Philadelphia, 2015, Elsevier.)

BASIC INFORMATION

DEFINITION

Menopause is the permanent cessation of menstrual periods for 1 yr after age 40 or permanent cessation of ovulation after lost ovarian activity without any other obvious pathologic or physiologic cause. It is the reproductive stage of life marked by waxing and waning estrogen levels followed by decreasing ovarian function. Primary ovarian insufficiency (previously also referred to as premature ovarian failure) and no menstrual periods may also occur because of depletion of ovarian follicles before the age of 40 yr.

SYNONYMS

Change of life
Climacteric ovarian failure

ICD-10CM CODES	
E28.310	Symptomatic premature menopause
E28.319	Asymptomatic premature menopause
N95.1	Menopausal and female climacteric states
N95.8	Other specified menopausal and perimenopausal disorders
Z78.0	Asymptomatic menopausal state

EPIDEMIOLOGY & DEMOGRAPHICS

- Average age of menopause in the U.S. is 51 yr.
- Age at which menopause occurs is primarily genetically determined.
- Smokers experience menopause an average of 1.5 yr earlier than nonsmokers.
- The menopausal transition, or perimenopause, begins on average 4 yr before the last menstrual period.
- Onset of perimenopause is usually in a woman's mid- to late-40s.
- Approximately 4000 women begin menopause each day.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Menopausal vasomotor symptoms: (VMS, hot flashes, flushes), night sweats, cardiovascular disease, coronary artery disease, atherosclerosis, headaches, tiredness, and lethargy; the median duration of hot flashes is 7.4 yr, but that the length of hot flashes was largely dictated by how early they began in the perimenopause
- Either complete cessation of menses or a period of irregular cycles and diminished or heavier bleeding
- Atrophic vaginitis, which can cause burning, itching, bleeding, dyspareunia
- Osteoporosis
- Osteopenia
- Psychological dysfunction:
  1. Anxiety
  2. Depression
  3. Insomnia
  4. Nervousness
  5. Irritability
  6. Inability to concentrate
- Sexual changes, decreased libido, dyspareunia
- Urinary incontinence

ETIOLOGY

- The most common etiology: Physiologic, caused by depleted granulosa and theca cells that fail to react to endogenous gonadotropins, producing less estrogen; decreased negative feedback in the hypothalamic pituitary access, increased follicle-stimulating hormone (FSH), and increased luteinizing hormone (LH), which leads to stromal cells that continue to produce androgens as a result of the LH stimulation
- Surgical castration
- Other factors that contribute to menopause can be family history of early menopause, cigarette smoking, blindness, abnormal chromosomal karyotype (Turner syndrome, gonadal dysgenesis), precocious puberty, and left-handedness

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary ovarian insufficiency
- Asherman syndrome
- Hypothalamic dysfunction
- Hypothyroidism
- Pituitary tumors
- Adrenal abnormalities
- Ovarian abnormalities
- Polycystic ovarian syndrome
- Pregnancy
- Ovarian neoplasm
- Tuberculosis of the endometrium

WORKUP

- Physical examination, height, weight, blood pressure, breast examination, and pelvic examination are needed.
- If the clinical picture is highly suggestive of menopause, reassurance or hormone replacement therapy such as estrogen can be prescribed to help with menopausal symptoms (after appropriate counseling). If all symptoms resolve, then a diagnosis essentially has been made. Before estrogen is prescribed, however, a complete history and physical examination are needed. If a patient has an estrogen-dependent malignancy, unexplained abnormal uterine bleeding, a history of thrombophlebitis, or acute liver disease, estrogen therapy is contraindicated.
- Progesterone challenge test: Medroxy progesterone 10 to 20 mg PO or progesterone 100 mg IM to induce withdrawal bleeding. If no withdrawal bleeding is obtained, a hypoestrogenic state is assumed to be present. This test is increasingly controversial, even if very commonly performed.
- Assess risk for coronary artery disease, osteoporosis, cigarette smoking, personal history, history of breast cancer, liver disease, active coagulation disorder, or any unexplained vaginal bleeding.

LABORATORY TESTS

- FSH, LH, and estrogen levels: Markedly elevated FSH and markedly depressed estrogen level constitute laboratory diagnosis of ovarian failure; LH only if polycystic ovarian disease is to be ruled out in a younger patient. It is not necessary to obtain an FSH if the patient fulfills the clinical criteria for menopause. Similarly, since estradiol levels vary during the menstrual cycle, estradiol levels are rarely necessary or informative.
- Anti-Müllerian hormone (produced by the granulosa cells) will demonstrate a decrease.
- TSH to rule out thyroid dysfunction and prolactin level if patient has symptoms of galactorrhea and if suspicion of pituitary adenoma exists.
- A general chemistry profile to check for any systemic diseases.
- Pap smear per standard guidelines, endometrial biopsy, or dilation and curettage in patients who have had irregular periods or intermenstrual or postmenopausal bleeding.
- Mammogram as recommended by American Congress of Obstetricians and Gynecologists for preventative care.

IMAGING STUDIES

- Per standard protocols, CT scan or MRI of sella if pituitary tumor is suspected
- Bone density studies if high-risk condition for osteoporosis exists
- Pelvic ultrasound to check endometrial stripe as determined by clinical history (i.e., in the setting of postmenopausal bleeding)

TREATMENT

NONPHARMACOLOGIC THERAPY

- A balanced diet: Low in fat, with total fat intake being <30% of calories; total calories sufficient to maintain body weight or produce weight loss if that is desired
- Avoidance of smoking and excessive alcohol or caffeine intake
- Exercise: Weight-bearing exercise for osteoporosis prevention
- Kegel exercises for strengthening the pelvic floor
- Adequate calcium intake: 1500 mg elemental calcium daily is necessary to maintain zero calcium balance in postmenopausal women
- Change in the ambient temperature (may ameliorate hot flashes and reduce night sweats)
- Vitamin E
- Avoidance of caffeine, alcohol, and spicy foods if they trigger hot flashes
- Vaginal lubricants to help with the dyspareunia attributable to vaginal dryness (e.g., Replens, K-Y Jelly, or Gyne-Moistrin cream)

ACUTE GENERAL Rx

Vasomotor symptoms are best managed with systemic hormone therapy given in the lowest dose and for the shortest period possible. Estrogen replacement in symptomatic patients can be administered in a variety of forms, including oral estrogen and transdermal estrogen patch. The lowest effective dose should be prescribed.

- Examples of oral estrogen include:
  1. Conjugated estrogens: Start with 0.3 mg daily and increase to 1.25 mg daily depending on symptoms.
  2. Estradiol: Start with 0.5 mg daily and increase up to 2 mg daily.
  3. Esterified estrogens: Start with 0.3 to 1.25 mg daily.
  4. Estropipate: Start with 0.75 to 3.0 mg daily.
  5. Esterified estrogen/testosterone combination: Give 1.25 mg and methyltestosterone 2.5 mg (Estratest) and esterified estrogen 0.625 mg and methyltestosterone 1.25 mg (Estratest HS [half-strength]). May improve sexual enjoyment and libido.
- If the patient has had a hysterectomy for benign disease, estrogen alone is sufficient. In patients who have an intact uterus, progestin is critical to prevent endometrial hyperplasia associated with unopposed estrogen, which is protective against endometrial cancer. Progestins can be prescribed as continual daily dose or cyclic fashion. Most commonly prescribed progestins include medroxyprogesterone acetate 2.5 mg, 5 mg, and 10 mg; Prometrium 100 mg, 200 mg, and 400 mg; and Aygestin 5 mg. Continuous hormone replacement therapy is preferred because after time the patient should be amenorrhoeic. Patients should be counseled that they may experience some irregular spotting for the first 6 to 9 mo after starting hormone replacement therapy. Cyclic therapy will cause withdrawal bleeding.
- Combination oral preparations Femhrt, Prefest, Prempro, Activella, Premphase are commonly used. However, the U.S. Preventive Services Task Force recommends against the use of combined estrogen and progestin for the prevention of chronic conditions such as cardiovascular disease in postmenopausal women.
- The combination of conjugated estrogen and bazedoxifene is approved for the treatment of moderate to severe vasomotor symptoms associated with menopause and also for prevention of postmenopausal osteoporosis in women with an intact uterus.
- Transdermal patches can be either estradiol (Estraderm, Vivelle, FemPatch) 0.025 to 0.1 mg applied twice weekly or Climara 0.025 to 0.1 mg used once a wk. With these preparations, progesterone should be used in a similar fashion. Apply CombiPatch twice weekly (combination estrogen and progesterone) or Climara Pro once per wk (one patch).
- Vaginal creams can be used; these should be reserved for local therapy of atrophic vaginitis. Minimal systemic absorption does occur; however, blood levels are unpredictable. Usual dose 0.5 to 2 g intravaginally daily, cyclically 3 wk on 1 wk off. When symptoms improve, once to twice weekly is adequate maintenance.
- Vagifem estradiol vaginal tablets. Initial dosage: One Vagifem tablet, inserted vaginally, daily for 2 wk. Maintenance dose: One Vagifem tablet, inserted vaginally, twice weekly.
- Femring vaginal ring delivering the equivalent of 0.5 mg/day inserted every 3 mo or Estring 0.0075 mg/day.
- EstroGel 0.06% (estradiol gel) One Pump (1.25 g/day) applied to one arm from wrist to shoulder.
- The FDA contraindications to menopause hormone therapy include the following diseases and disorders: Active liver disease; current, past, or suspected breast cancer; active or recent anterior thromboembolic disease (angina, myocardial infarction); known or suspected estrogen-sensitive malignant conditions; known hypersensitivity to the active substance of the therapy or to any of the excipients; porphyria cutanea tarda; previous idiopathic or current venous thromboembolism; undiagnosed genital bleeding; untreated hypertension; untreated endometrial hyperplasia.
- For women in whom estrogen is contraindicated or for those who do not wish to take estrogen, the following regimens can be used:
  1. Serotonin reuptake inhibitors, especially in women with menopausal mood disorders
  2. Depo-Provera 150 mg IM every mo (may be helpful in alleviating hot flashes)
  3. Clonidine 0.05 to 0.15 mg PO daily (questionable efficacy) or transdermal clonidine patch
  4. Bellergal-S (questionable efficacy)
- Tibolone significantly improves vasomotor symptoms, libido, and vaginal lubrication. Not available in the U.S.

CHRONIC Rx

Hormone replacement therapy should be used only for the short term unless benefits outweigh the risks of long-term use. As a result of the results of the Women's Health Initiative (WHI), the FDA has instituted a "black box" warning on postmenopausal hormone replacement products suggesting that the lowest dose should be used for the shortest period of time. This necessitates a considered counseling session with patients contemplating hormone replacement prior to the initiation of therapy and then on a periodic basis after that, usually at least on a yearly basis.

DISPOSITION

If treated, the patient should have resolution of her symptoms and reduced incidence of osteoporosis. Lifelong medical supervision is necessary to monitor adequacy of treatment and prevention of complications. This should include regular Pap smears in accordance with American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines until the age of 65, pelvic examinations, breast examinations, mammography, and endometrial sampling of any type of abnormal bleeding. If untreated, the vasomotor symptoms will eventually dissipate; however, this may take several years in a small percentage of women. Some women who are in their 80s have experienced hot flashes. Urogenital atrophy will continue to worsen. Osteoporosis and coronary artery disease risks will increase with every passing yr.

REFERRAL

Most menopausal women are managed by their gynecologists. However, this condition can be managed adequately by the patient's primary care physician who has an interest in treating menopausal women.

PEARLS & CONSIDERATIONS

COMMENTS

- Short-term risks of hormone replacement therapy (HT) include an eighteenfold increased rise for cholecystitis, three-and-a-halffold risk of a thrombo-cardiac event in the first yr, and possible increased risk of stroke and myocardial infarction.
- Results of the WHI study found that for every 10,000 women taking HT (combination of both estrogen and progesterone) for 1 yr (10,000 person-yr), seven more would have coronary events, eight would have more strokes, eight would have more pulmonary emboli, and eight would have earlier breast cancer than would 10,000 women taking placebo. Benefits of HT were six fewer cases of colorectal cancer and five fewer hip fractures per 10,000 women.
- HT should not be initiated or continued for the primary or secondary prevention of coronary heart disease.
- Estrogen-replacement therapy should only be prescribed for patients with sufficient menopausal symptoms that impact the patient's quality of life.
- Interestingly, women who start hormone therapy early in menopause may have cardiac and other benefits. A recent trial showed that oral estradiol therapy was associated with less progression of subclinical atherosclerosis (measured as change in carotid-artery intima media thickness [CIMT]) than with placebo when therapy was initiated within 6 yr after menopause but not when it was initiated 10 or more yr after menopause. Estradiol had no significant effect on cardiac CT measures of atherosclerosis in either postmenopause stratum.[1]

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Menopause (Patient Information)
Hot Flashes (Related Key Topic)
Osteoporosis (Related Key Topic)

AUTHOR: **Ghamar Bitar, MD**

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SUGGESTED READINGS

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Pinkerton JV: Hormone therapy for postmenopausal women, *N Engl J Med* 382(5):446-455, 2020.

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Meralgia Paresthetica

BASIC INFORMATION

DEFINITION

Meralgia paresthetica is a condition that presents with pain and/or dysesthesia in the anterolateral thigh due to compression of the lateral femoral cutaneous nerve.

SYNONYMS

Lateral femoral cutaneous nerve entrapment
Bernhardt-Roth syndrome
Skinny pants syndrome: Named due to a rise in teenagers wearing skin-tight pants

ICD-10CM CODE
G57.1 Meralgia paresthetica

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The incidence rate for males and females is similar, and it is one of the most common mononeuropathies of the lower limb.
PEAK INCIDENCE: The mean age at diagnosis is 50 yr old.
RISK FACTORS: Obesity, diabetes mellitus, and older age are the most commonly associated conditions. Other risk factors include large abdomens, tight belts and garments around the waist, pregnancy, and scar tissue near the inguinal ligament. During surgery, iatrogenic injury or compression due to improper positioning is also an important cause of meralgia paresthetica. Motor vehicle accidents with seat belt injury are a less common but recognized cause. Long periods of leg exercise that increases tension on the inguinal ligament, such as from long distance biking or walking for an extensive period of time, may also cause pressure on the nerve. Leg-length discrepancy can also cause hip hyperextension, leading to symptoms. Alternatively, weight loss or aging may remove protective overlying fat layers so the nerve can squeeze against underwear, belts, or other clothing. Rare risk factors include ascites, endometriosis, and pelvic masses (neoplasms, hemorrhages, or abscesses), which can cause compression of the nerve.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The patient can have numbness and tingling, burning pain, or decreased sensation over the region of the outer upper thigh, which usually presents in a gradual fashion. Sometimes the patient will rub the affected area when discussing the discomfort. There is no motor involvement, as the lateral femoral cutaneous nerve only has sensory fibers. Change in patient position may abate the pain, with walking or standing often aggravating symptoms. However, if the cause is extrinsic compression, such as from a tight belt, sitting may exacerbate symptoms. Pain spreading across the buttocks or aching in the groin area can sometimes be present. Pain may radiate into the rib cage, groin, thigh, and knee. Often the affected region is more sensitive to light touch than to firm pressure. Hypersensitivity to heat can be present. Usually the symptoms are unilateral but can be bilateral in up to 20% of cases. Deep palpation below the anterior superior iliac spine (pelvic compression testing) can often reproduce symptoms.

ETIOLOGY

Meralgia paresthetica mainly results from entrapment of the lateral femoral cutaneous nerve (Fig. E1) as it passes under the inguinal ligament (Fig. E2). However, it can also be compressed within the lumbosacral plexus, abdominal cavity, or in the subcutaneous tissue of the thigh.

DIAGNOSIS

The diagnosis is based mainly on the unique description of pain and the typical location; the sensory abnormalities present on exam in the affected area without neurologic abnormalities on the lower half of the affected leg. Loss of sensation often can be clearly demarcated over the anterior thigh.

While the diagnosis should largely be a clinical one, studies have shown the success for ultrasound-guided diagnosis which reveals a hypoechoic and swollen lateral femoral cutaneous nerve.

DIFFERENTIAL DIAGNOSIS

Lumbar radiculopathy, vasculitic neuropathy

WORKUP

Usually the diagnosis requires no testing other than a thorough neurologic examination. The entire lower extremity should be examined. Light touch and pinprick examination are usually abnormal in an oval-shaped area on the anterolateral thigh. There should be no abnormality in the straight leg test, and there should be no findings suggesting hip, back, or sacroiliac joint involvement. Motor strength and deep tendon reflexes should be normal. On occasion, precise diagnosis may require an abdominal and/or pelvic examination to exclude problems in those areas.

IMAGING & OTHER STUDIES

- X-rays of the hip/pelvis are usually unnecessary in patients with typical findings of meralgia paresthetica. Lumbar spine imaging can be considered if the patient has findings suggesting spinal stenosis, disk issues, or spondylolisthesis. More advanced imaging such as CT or MRI scans can be done to exclude soft tissue causes such as a tumor.
- Nerve conduction and electromyography (EMG) are rarely necessary. These studies are mainly utilized to exclude radiculopathy or lumbar plexus problems.
- Ultrasound imaging has recently been offered as an alternate diagnostic method, which reveals a swollen and hypoechoic nerve would be visualized. Additionally, it offers the benefit of serving as a means of immediate therapeutic intervention through guided injection.
- Rarely, an anesthetic nerve block injection, with or without ultrasound guidance, can be performed into the lateral femoral cutaneous nerve. Relief of the pain is confirmatory of the diagnosis of meralgia paresthetica.

TREATMENT

NONPHARMACOLOGIC THERAPY

Many patients experience sudden spontaneous resolution of their symptoms.

ACUTE GENERAL Rx

- Reassurance of the patient is vital.
- Methods to reduce compression or pressure on the nerve include avoidance of tight garments, undergarments, and belts around the waist. Wearing suspenders rather than belts can be suggested. Weight loss in obese patients, especially in the abdominal region, is also important. Correction of any leg-length discrepancy with shoe lifts can also be therapeutic.

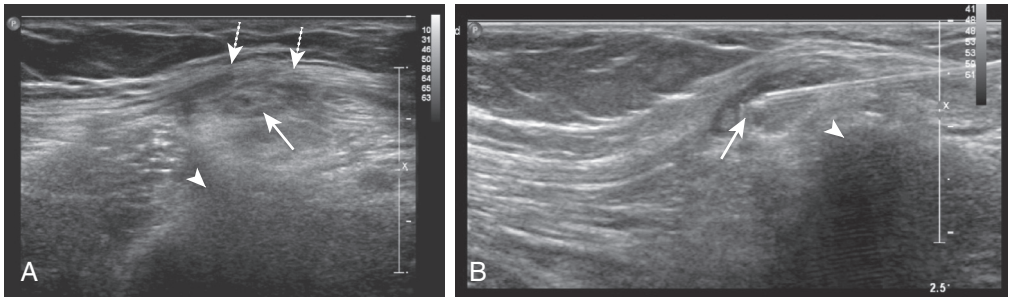

FIG. E1 Scarring of the lateral femoral cutaneous nerve causing meralgia paresthetica. A, Ultrasound image at the level of the anterior superior iliac spine *(arrowhead)* shows the lateral femoral cutaneous nerve *(dashed arrows)* surrounded by scar tissue *(solid arrow).* **B,** Ultrasound image shows steroid and anesthetic injection with the needle tip inside the scar *(solid arrow).* (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2014, WB Saunders.)

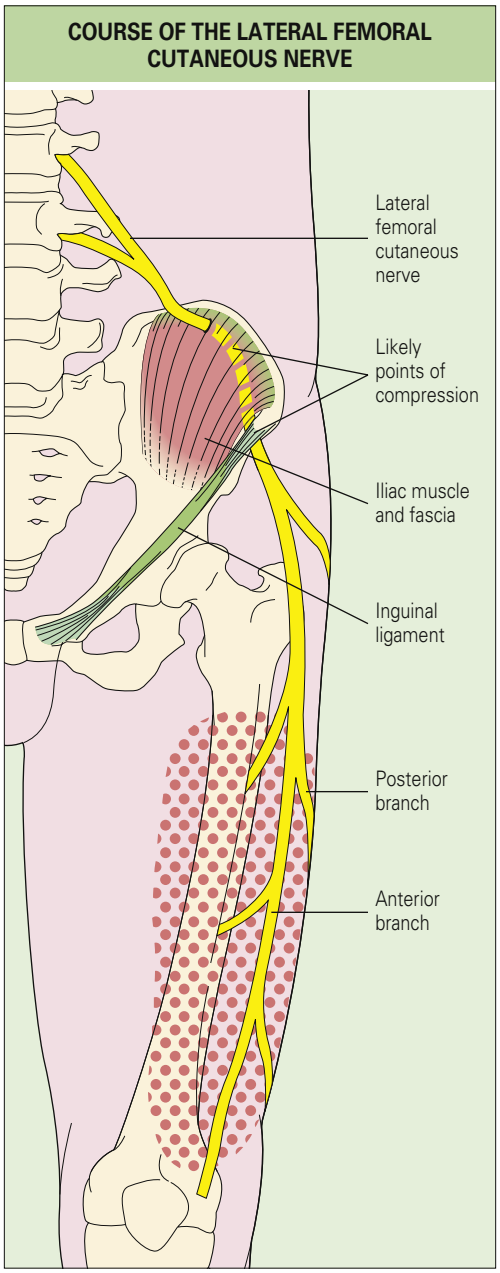

FIG. E2 The potential for entrapment of the lateral femoral cutaneous nerve can be seen by its course just under the inguinal ligament and medial to the anterior superior iliac spine. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

SUGGESTED READINGS

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CHRONIC Rx

- Persistent symptoms after 1 to 2 mo despite conservative approach may warrant verification of diagnosis through reexamination of affected area, repeat questioning, and possibly other studies.
- Gabapentin, amitriptyline, phenytoin, and carbamazepine may prove beneficial in reducing the associated neuropathic pain. However, in the majority of patients they are not beneficial.
- Lidocaine patches and titanium dioxide patches can be utilized as additional modes of treatment for more refractory cases.
- Physical therapy including stretching and massage, moist heat, and low-intensity phonophoresis can play a large role in the management of pain.
- Consultation with an anesthesia specialist or interventional radiologist for local nerve blockade can be done. Glucocorticoid or local anesthetic, or a mixture of both, can be injected into the appropriate region for temporary relief.
- A recent small case series showed that ultrasound-guided neurolysis with 50% alcohol can be used for refractory meralgia paresthetica to provide pain relief and can help avoid surgical treatment.
- Surgical treatment—either decompression, removal of the nerve, or cutting of the nerve—have provided benefit to patients in refractory cases. Predictors of good surgical results include presence of an abnormal electromyographic (EMG) study before surgery and immediate relief of symptoms after the blocking of the lateral femoral cutaneous nerve.
- A few reports have mentioned the utility of radiofrequency nerve ablation in treating the condition, but this has not been studied adequately.

DISPOSITION

This is a self-limited, nonthreatening condition in most patients. Conservative measures are enough for >90% of patients, but recurrence of symptoms is common.

REFERRAL

- Patients with meralgia paresthetica can often be easily managed by the primary care physician.
- Referral to anesthesiologist, interventional radiologist, or neurosurgeon may be indicated in refractory cases.

AUTHOR: **Jacob Modest, MD**

Mesenteric Adenitis

BASIC INFORMATION

DEFINITION

Acute mesenteric lymphadenitis is a syndrome of acute right lower quadrant abdominal pain associated with mesenteric lymph node enlargement and a normal appendix.

SYNONYMS

Acute mesenteric lymphadenitis
Mesenteric lymphadenitis

ICD-10CM CODE
I88.0 Nonspecific mesenteric lymphadenitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence unknown
- Affects mostly children (<18 yr) with no sex preference
- When *Yersinia* enterocolitis is the cause, boys are more frequently involved

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abdominal pain of variable severity (mild ache to severe colic) beginning in upper abdomen or right lower quadrant; eventually localizes in the right side but not in a precise location (unlike appendicitis)
- In *Yersinia* infection outbreaks (see Table E1), symptoms include abdominal pain (84%), diarrhea (78%), fever (43%), anorexia (22%), nausea (13%), and vomiting (8%)
- Physical findings:
  1. Other lymphadenopathy (20% of cases)
  2. Right lower quadrant tenderness (site of maximal tenderness may vary from one examination to the next)
  3. Guarding (rare)
  4. Mild fever

ETIOLOGY & PATHOGENESIS

- Reactive hyperplasia of lymph nodes that drain the ileocecal region, similar to that seen in inflammatory or allergic conditions. One study reported that approximately two thirds of cases are secondary (reactive) and one third are primary (no demonstrable associated inflammatory process).
- *Yersinia enterocolitica, Y. pseudotuberculosis, Salmonella* species, *Escherichia coli,* and streptococci have been implicated in mesenteric adenitis. Clinical manifestations of yersiniosis are described in Table E2.

DIAGNOSIS

In general, the diagnosis is made on exploration of the abdomen of a patient suspected of having acute appendicitis. On examination the appendix appears normal, and enlarged mesenteric lymph nodes are noted. Excision of an enlarged lymph node with culture and nodal histology may provide information regarding the etiology but is not routinely used.

DIFFERENTIAL DIAGNOSIS

- Acute appendicitis (5% to 10% of patients admitted to hospitals with a diagnosis of appendicitis are discharged with a diagnosis of mesenteric adenitis)
- Crohn disease

Section II describes the differential diagnosis of right lower quadrant abdominal pain.

LABORATORY TESTS

- Complete blood count may show leukocytosis.
- Abdominal sonography and CT scan with IV and oral contrast (Fig. E1) may be useful.
- Laparotomy if appendicitis is suspected.

PROGNOSIS

Recurrent bouts are common; therefore if laparotomy is performed and a normal appendix is found, it should be removed.

AUTHOR: **Fred F. Ferri, MD**

TABLE E1 Symptoms in Four Outbreaks of Mesenteric Adenitis Caused by *Yersinia* Enterocolitis

Location	Japan (110)	Japan (111)	Japan (111)	U.S. (112)
Serotype	03	03	03	08
Number ill	198	188	544	38
Percentage with				
Abdominal pain	76	86	64	97
Fever	61	76	50	100
Diarrhea	36	60	32	74
Vomiting	12	4	11	—
Percentage undergoing appendectomy	2	—	—	42

From Mandell GL et al: *Principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, WB Saunders.

TABLE E2 Clinical Manifestations of Yersiniosis

Yersinia enterocolitica	Yersinia pseudotuberculosis
Gastroenteritis	Mesenteric lymphadenitis
Mesenteric lymphadenitis	Ulcerative ileitis
Ulcerative ileitis	Septicemia
Septicemia	Erythema nodosum
Hepatic or splenic abscesses	
Reactive polyarthritis (HLA-B27)	
Reiter syndrome	
Erythema nodosum	
Meningitis	
Exudative pharyngitis	

HLA, Human leukocyte antigen.
From Cohen J, Powderly WG: *Infectious diseases,* ed 2, St Louis, 2004, Mosby.

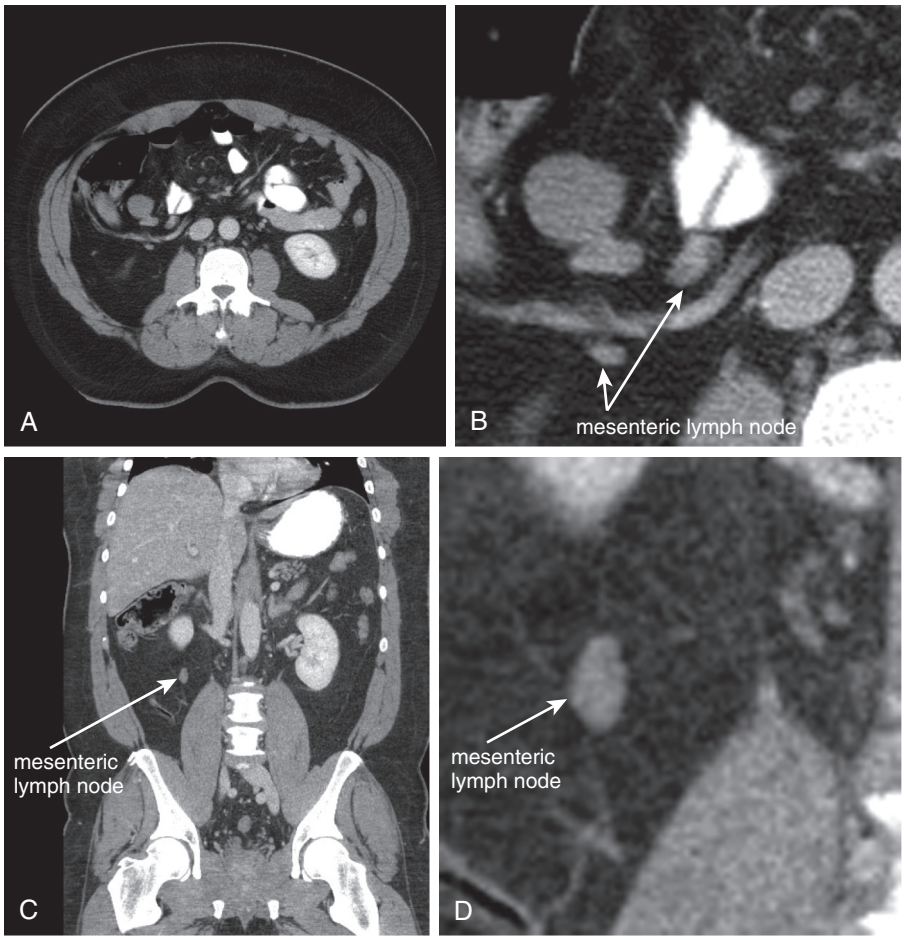

FIG. E1 Mesenteric adenitis, computed tomography (CT) with intravenous and oral contrast, soft-tissue window. Mesenteric adenitis can mimic appendicitis in its clinical presentation. Enlarged lymph nodes are visible on CT. Lymph nodes have soft-tissue density and appear as discrete, rounded structures. On a single image they may appear similar to blood vessels or to the appendix, but on inspection of adjacent images it becomes clear that lymph nodes are rounded, not tubular like a blood vessel or the appendix. **A,** Axial image. **B,** Close-up from **A. C,** Coronal reconstruction. **D,** Close-up from **C.** (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, WB Saunders.)

Mesenteric Venous Thrombosis

BASIC INFORMATION

DEFINITION

Mesenteric venous thrombosis (MVT) is a thrombotic occlusion of the mesenteric venous system involving major trunks or smaller branches and can lead to intestinal infarction in its acute form.

SYNONYM

MVT

ICD-10CM CODES

K55.0 Acute vascular disorders of intestine
K55.1 Chronic vascular disorders of intestine

EPIDEMIOLOGY & DEMOGRAPHICS

Between 5% and 15% of patients with acute mesenteric ischemia has MVT. MVT is slightly more common in men than women. The typical age of occurrence is 50 to 60 yr. Table E1 summarizes the incidence of ischemic bowel disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

ACUTE MVT:

- Symptoms: Abdominal pain in 90% of patients, typically out of proportion to the physical findings. Nausea and vomiting occur in 50% and gastrointestinal (GI) bleeding occurs in 50% (occult) and 15% (gross).
- Physical findings:
  1. Early: Abdominal tenderness, decreased bowel sounds, abdominal distention
  2. Later: Guarding and rebound tenderness, fever, septic shock

SUBACUTE MVT:

- Symptoms: Nonspecific abdominal pain for wk or mo
- Physical findings: None

CHRONIC MVT:

- Symptoms: Typically asymptomatic, tends to present with complications of portal hypertension (hemorrhage from bleeding varices, ascites) due to concomitant portal vein or splenic vein thrombosis.
- Physical findings: None other than signs of portal hypertension if the portal/splenic veins are also involved.

ETIOLOGY & PATHOGENESIS

HYPERCOAGULABLE STATES:

- Personal or family history of thrombophilia or personal history of thromboembolism
- Neoplasms
- Antithrombin III, protein C, protein S deficiencies or activated protein C resistance
- Lupus anticoagulant (antiphospholipid antibody syndrome)
- Factor V Leiden or prothrombin G20210A mutations
- Oral contraceptive use, pregnancy
- Myeloproliferative disorders (polycythemia vera, essential thrombocytosis)
- Paroxysmal nocturnal hemoglobinuria

TABLE E1 Incidence of Ischemic Bowel Diseases

Disease	Incidence (%)*
Superior mesenteric artery (SMA) embolism: • The SMA is susceptible to embolism because of large vessel caliber and a narrow angle of departure from the aorta. • The proximal SMA is most commonly obstructed within 6-8 cm of the aorta	50
Nonocclusive ischemia	25
SMA thrombosis	20
Mesenteric venous thrombosis	5

*Percentage of all cases of acute mesenteric ischemia.
From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

BOX E1 Factors Associated with Mesenteric Venous Thrombosis

Hypercoagulable states
  Polycythemia vera
  Sickle cell disease
  Antithrombin III deficiency
  Protein C or S deficiency
  Malignancy
  Myeloproliferative disorders
  Estrogen therapy, oral contraceptive pills
  Pregnancy
Inflammatory conditions
  Pancreatitis
  Diverticulitis
  Appendicitis
  Cholangitis
Trauma
  Operative venous injury
  Postsplenectomy
  Blunt or abdominal trauma
  Miscellaneous
  Congestive heart failure
  Renal failure
  Decompression sickness
Portal hypertension

From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, WB Saunders.

PORTAL HYPERTENSION:

- Cirrhosis

INFLAMMATION:

- Pancreatitis
- Peritonitis (e.g., appendicitis, diverticulitis, perforated viscus)
- Inflammatory bowel disease
- Pelvic or intraabdominal abscess
- Intraabdominal cancer

POSTOPERATIVE STATE OR TRAUMA:

- Blunt abdominal trauma
- Postoperative states (abdominal surgery)
- Box E1 summarizes factors associated with mesenteric venous thrombosis

Thrombosis may begin in small mesenteric branches (e.g., in hypercoagulable states) and propagate to the major venous mesenteric trunks or begin in large veins (e.g., in cirrhosis, intraabdominal cancer, surgery) and extend distally. If collateral drainage is inadequate, the intestine becomes congested, edematous, cyanotic, and hemorrhagic and eventually may infarct.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

All other causes of abdominal pain (e.g., peritonitis, intestinal obstruction, pancreatitis, peptic ulcer disease, gastritis, inflammatory bowel disease, perforated viscus) are also to be considered in the differential diagnosis.

WORKUP

Laboratory tests and imaging studies

LABORATORY TESTS

- Complete blood count: Leukocytosis
- Electrolytes: Metabolic acidosis (lactic) indicates bowel infarction
- Tests for hypercoagulable states

IMAGING STUDIES

- Computed tomography (CT) with and without oral and IV contrast (Fig. E1) is a good initial screening study due to widespread availability and the ability to detect sequelae of MVT (such as intestinal ischemia or infarction).
- If CT with and without oral and IV contrast does not demonstrate MVT and the clinical suspicion is high, computed tomographic angiography (CTA) is another imaging modality with higher sensitivity but more use of contrast material. Use of two-phase imaging improves sensitivity for venous thrombosis.
- Magnetic resonance angiography/venography (MRA/MRV) can also be used; it avoids the risk of radiation and contrast material but takes longer and may be limited due to motion artifact.

TREATMENT

- Acute and subacute MVT: Anticoagulation with unfractionated heparin or low-molecular-weight heparin with eventual transition to a vitamin K antagonist or novel oral anticoagulant for 3 to 6 mo, or longer if a hypercoagulable state has been identified. When medical treatment is unsuccessful, options include transhepatic and percutaneous mechanical thrombectomy, intravascular catheter-directed thrombolysis, and open intraarterial thrombolysis.

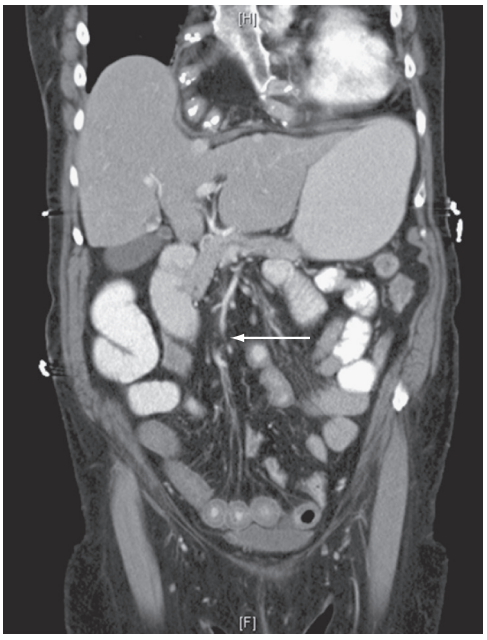

FIG. E1 Computed tomography after administration of oral and intravenous contrast in a patient with an embolism to the superior mesenteric artery and ischemia of the small bowel and right colon. The arrow points to the embolus in the superior mesenteric artery. (From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.)

- Intravenous fluid administration (due to relative hypovolemia from bowel wall edema), bowel rest and decompression if ileus forms.
- Consider prophylactic antibiotics to reduce the incidence of bacterial translocation.
- Laparotomy if intestinal infarction is suspected.

CHRONIC MVT

- Anticoagulation should be considered but is a decision specific to each individual patient.
- If anticoagulation is pursued, ensure potential bleeding complications (esophageal varices) have been identified and treated.
- If varices are present, initiate beta blockade, similar to cirrhosis-related portal hypertension.

PROGNOSIS

- Mortality rate of acute MVT: With prompt diagnosis and anticoagulation, 10% to 20%. The presence of intestinal infarction is a poor prognostic sign for overall mortality.
- Recurrence rate: 15% to 25%.

RELATED CONTENT

Acute Mesenteric Ischemia (Related Key Topic)

AUTHOR: **David J. Lucier, Jr., MD, MBA, MPH**

SUGGESTED READING

Clair DG: Beach JM: mesenteric ischemia, *N Engl J Med* 374:959-968, 2016.

Mesothelioma, Malignant PTG

BASIC INFORMATION

DEFINITION

Malignant mesothelioma is a neoplasm originating from the mesothelial surfaces of the pleural (80%) or peritoneal cavities (20%). The three major histologic subtypes are epithelial (most common), sarcomatous, and mixed (epithelial/sarcomatous).

SYNONYM

Malignant mesothelioma

ICD-10CM CODES

C45.0 Mesothelioma of pleura
C45.1 Mesothelioma of peritoneum
C45.2 Mesothelioma of pericardium
C45.7 Mesothelioma of other sites
C45.9 Mesothelioma, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Associated with asbestos exposure (all fiber types) and has a latency of 20 to 40 yr.
- About 3000 new cases are diagnosed in the U.S. annually.
- More common in men (5:1) as a result of workplace asbestos exposure; however, even family members of workers exposed to asbestos have a higher risk due to cleaning of contaminated clothes.
- Incidence in the U.S. has leveled off due to lack of asbestos use and mining.
- Incidence of mesothelioma increases with age; median age at presentation is >70 yr.
- More than 8 million persons in the U.S. are currently at risk for mesothelioma because of prior asbestos exposure.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Dyspnea
- Nonpleuritic chest pain
- Fever, weight loss, sweats, fatigue, loss of appetite
- Dysphagia, superior vena cava syndrome, Horner syndrome in advanced stages
- Auscultation may reveal unilateral loss of breath sounds
- Dullness on percussion may be present

ETIOLOGY

- Asbestos exposure (>70% of patients).
- Other reported potentially causal factors include prior radiation therapy and extravasated thorotrast, zeolite, and erionite fibers.
- Mutations of BRCA1-associated protein 1 (BAP1) cyclin-dependent kinase inhibitor 2A gene *(CDKN2A)* have been causally linked to development of mesothelioma.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Metastatic adenocarcinomas (from lung, breast, ovary, kidney, stomach, prostate)

WORKUP

- Staging evaluation (Box 1) includes complete history (including occupational history), physical examination, and testing to determine potential operability (CT, bone scan, pulmonary function tests [PFTs]).
- Thoracoscopy, pleuroscopy, and open-lung biopsy are useful in obtaining adequate tissue samples for diagnosis.
- Pulmonary function tests.
- PET-CT scan (Figs. E1 and E2) is performed only in patients considered candidates for surgery to determine resectability.
- Staging: The TNM system categorizes mesothelioma in stages I to IV similar to that used for non–small cell lung cancer.

LABORATORY TESTS

- Diagnostic thoracentesis is generally insufficient for diagnosis because pleural effusions may only reveal atypical mesothelial cells.
- Immunohistochemistry is useful to distinguish adenocarcinoma from epithelial malignant mesothelioma (mesotheliomas are generally carcinoembryonic antigen negative and cytokeratin positive).
- Thrombocytosis and anemia may be found on initial laboratory evaluation.
- Serum osteopontin levels (when available) can also be used to distinguish persons with exposure to asbestos who do not have cancer from those with exposure to asbestos who have pleural mesothelioma.

BOX 1 International Mesothelioma Interest Group (IMIG) Staging System

T: Primary Tumor and Extent

T_1:
a. Tumor limited to ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura; no involvement of the visceral pleura
b. Tumor involving the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura; scattered foci or tumor also involving the visceral pleura

T_2 Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic pleura); scattered foci or tumor also involving the visceral pleura:
a. Involvement of diaphragmatic muscle
b. Confluent visceral pleura (including the fissures) or extension of tumor from visceral pleura into the underlying pulmonary parenchyma

T_3 Locally advanced but potentially resectable tumor; tumor involving all the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:
a. Involvement of the endothoracic fascia
b. Extension into mediastinal fat
c. Solitary, complete resectable focus or tumor extending into the soft tissues of the chest wall
d. Nontransmural involvement of the pericardium

T_4 Locally advanced, technically nonresectable tumor; tumor involving all the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:
a. Diffuse extension or multifocal mass of tumor in the chest wall, with or without associated rib destruction
b. Direct transdiaphragmatic extension of the tumor to the peritoneum
c. Direct extension of tumor to the contralateral pleura
d. Direct extension of tumor to one or more mediastinal organs
e. Direct extension of tumor into the spine
f. Tumor extending through the internal surface of the pericardium with or without a pericardial effusion or tumor involving the myocardium

N: Lymph Nodes

N_x Regional lymph nodes cannot be assessed
N_0 No regional lymph node metastases
N_1 Metastases in ipsilateral bronchopulmonary or hilar lymph nodes
N_2 Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary nodes
N_3 Metastases in contralateral mediastinal, contralateral internal mammary, ipsilateral, or contralateral supraclavicular scalene lymph nodes

M: Metastases

M_x Presence of distant metastases cannot be assessed
M_0 No (known) metastasis
M_1 Distant metastasis present

Stage Grouping

I.
a. $T_{1a}N_0M_0$
b. $T_{1b}N_0M_0$
II. $T_2N_0M_0$
III. Any T_3M_0, any N_1M_0, any N_2M_0
IV. Any T_4, any N_3, any M_1

From Sellke FW et al: *Sabiston & Spencer surgery of the chest,* ed 9, Philadelphia, 2016, Elsevier.

BOX 2 Therapeutic Options for Malignant Pleural Mesothelioma

Single-Modality Therapy
- Debulking surgery (pleurectomy/decortication or extrapleural pneumonectomy)
- Radiation (external beam, brachytherapy)
- Chemotherapy (single- or double-agent approach: Doxorubicin, cyclophosphamide, cisplatinum; gemcitabine, pemetrexed, and cisplatin)

Multimodality Therapy
- Surgery and adjuvant radiation
- Surgery and adjuvant chemotherapy
- Surgery and adjuvant chemoradiotherapy

Innovative Therapies under Investigation
- Intracavitary lavage with hyperthermic chemotherapy
- Photodynamic therapy
- Gene therapy
- Angiogenesis
- Immunogenic therapy

From Sellke FW et al: *Sabiston & Spencer surgery of the chest,* ed 9, Philadelphia, 2016, Elsevier.

IMAGING STUDIES

- Chest radiographs may reveal pleural plaques (Fig. E3) or calcifications in the diaphragm.
- CT scans of the chest and abdomen, bone scan, and PET scan are used to assess the stage of disease.

Rx TREATMENT

GENERAL Rx

- Box 2 summarizes therapeutic options for malignant pleural mesothelioma.
- Operable patient (epithelial type, no positive nodes, confined to pleura, adequate PFTs): The two surgical techniques for therapeutic intervention are decortication (pleurectomy) and extrapleural pneumonectomy. Postoperative chemotherapy with cisplatin and pemetrexed and subsequent external-beam radiation are used with limited success.
- Inoperable patient (elderly patient, extensive disease, sarcomatous or mixed histology type, poor PFTs): Chemotherapy is administered to improve survival; supportive care is a standard option. Combined modality therapies (radiation therapy, chemotherapy, and biologics) have also been used to reduce both local and distant recurrences. First-line chemotherapy options include the combination of cisplatin and pemetrexed with or without additional bevacizumab (antiangiogenic agent).
- Patients with progressive cancer after initial chemotherapy can often be treated with single-agent chemotherapy such as gemcitabine or vinorelbine.
- Recent data have shown improvement in survival with use of immune checkpoint inhibitors targeting the programmed death-1 (PD-1) pathway such as pembrolizumab and nivolumab with or without ipilimumab.
- Intrapleural instillation of cisplatin or biologics (e.g., interferons, interleukin-2) is generally limited to very early disease because it can only penetrate a very limited depth of the tumor and there is a propensity of the pleural space to become progressively obliterated with advancing disease.
- Radiation therapy is often used for palliation of local chest pain.
- Obliteration of the pleural space (pleurodesis) with instillation of talc or tetracycline into the pleural cavity is done in the treatment of recurrent symptomatic pleural effusions.
- Several biomarkers have been evaluated extensively in mesothelioma management. Serum mesothelin is not sensitive or specific for diagnostic purposes, but serial measurements during chemotherapy can be useful as a monitoring tool. Recent data reveal that plasma fibulin-3 levels can distinguish healthy persons with exposure to asbestos from patients with mesothelioma. In conjunction with effusion fibulin-3 levels, plasma fibulin-3 levels can further differentiate mesothelioma effusions from other malignant and benign effusions.

DISPOSITION

The overall prognosis of malignant mesothelioma is dismal, with a median survival of 6 to 8 mo. Survival is better for patients with the epithelial form, although overall median survival is approximately still 1 yr.

PEARLS & CONSIDERATIONS

- Patients with early disease should be referred to treatment centers specializing in multidisciplinary therapy before attempts are made to obliterate the pleural space with pleurodesis.
- Patients with advanced or resected disease should be treated with appropriate combination chemotherapy as listed previously.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Mesothelioma (Patient Information)
Asbestosis (Related Key Topic)

AUTHOR: **Bharti Rathore, MD**

SUGGESTED READINGS

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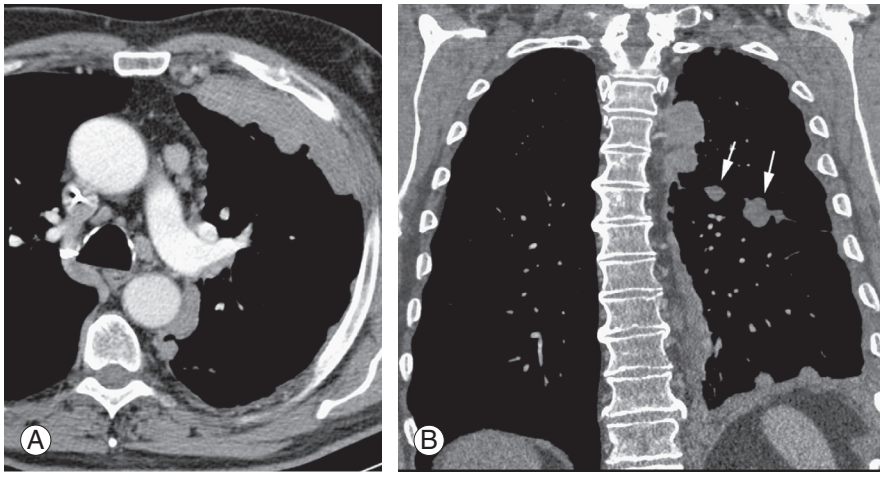

FIG. E1 Malignant mesothelioma. A and **B,** Axial and coronal CT. Diffuse lobulated and nodular thickening of the pleura with tumor extension into the lobar fissure *(arrows).* Note the metastatic hilar and mediastinal adenopathy. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

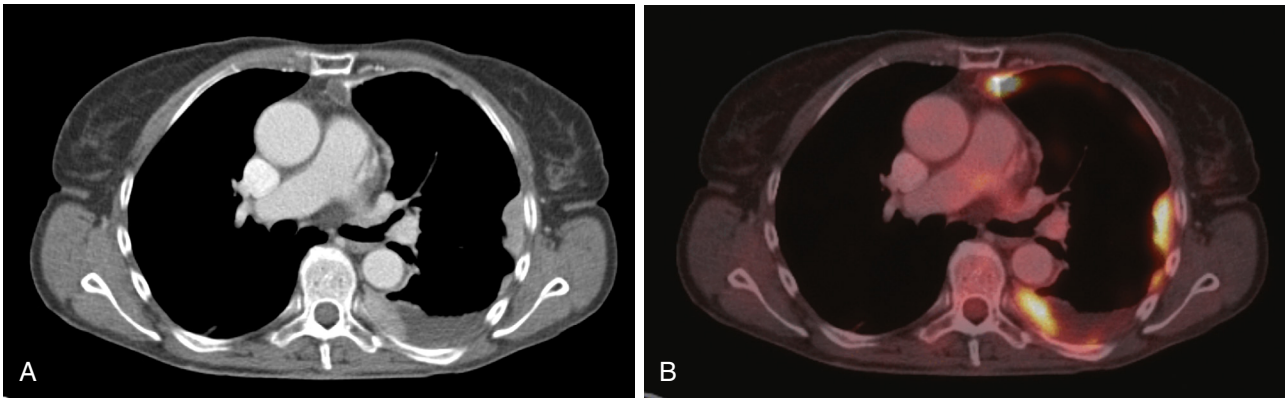

FIG. E2 Malignant mesothelioma. CT and PET-CT fusion image showing tumor extent. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

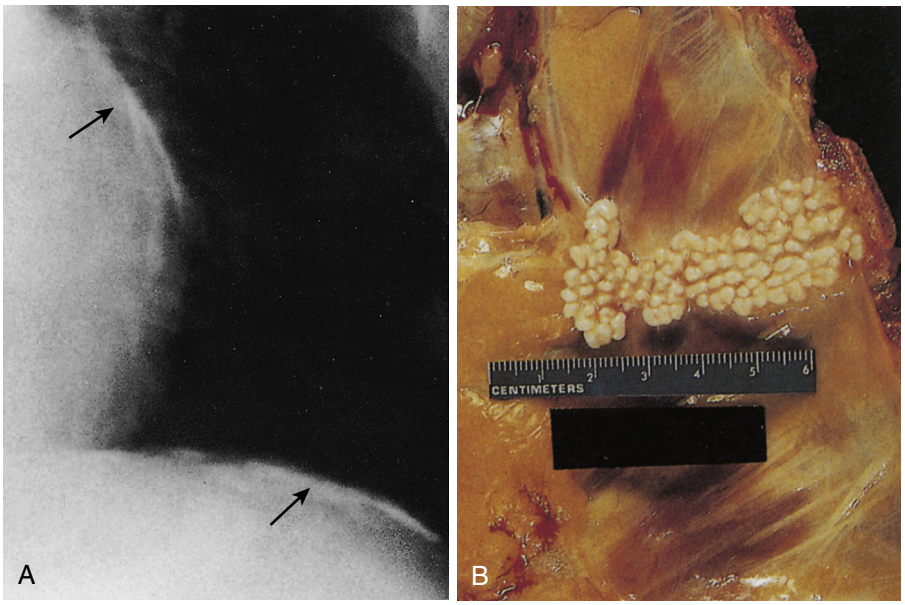

FIG. E3 A, Chest radiograph showing the left lower lung of a 57-yr-old man demonstrates pericardial and pleural plaques *(arrows)* representing fibrous thickening. These features are common findings indicating pulmonary asbestosis. **B,** Autopsy features of calcified pleural plaques are quite striking. This specimen from a patient with mesothelioma shows focal calcifications on the lateral pleural surface. (Courtesy Pathology Department, Brigham and Women's Hospital, Boston, MA. From Skarin AT: *Atlas of diagnostic oncology,* ed 4, St Louis, 2010, Mosby.)

BASIC INFORMATION

DEFINITION

Metabolic syndrome refers to a constellation of risk factors for development of cardiovascular disease and type 2 diabetes mellitus. Hyperglycemia, dyslipidemia, abdominal obesity, and hypertension are critical components of metabolic syndrome. Over the yrs, many definitions of the syndrome have been proposed and debated (see Table E1). In 2009, a consensus statement defined "metabolic syndrome" as the presence of any three of the following criteria[1]:

- Abdominal waist circumference >94 cm (37 in) in men and >80 cm (31 in) in women (the use of population- and country-specific definitions is suggested; However, until better data are available, The International Diabetes Federation [IDF] recommends using these cutoffs)
- Serum hypertriglyceridemia ≥150 mg/dl (1.7 mmol/L) or drug treatment for elevated triglycerides
- Serum high-density lipoprotein (HDL) cholesterol <40 mg/dl (1 mmol/L) in men and <50 mg/dl (1.3 mmol/L) in women or drug treatment for low HDL-C
- Blood pressure ≥130/85 mm Hg or drug treatment for elevated blood pressure
- Fasting glucose ≥100 mg/dl (5.6 mmol/L) or drug treatment for elevated blood glucose

SYNONYMS

Syndrome X
Insulin resistance syndrome
Obesity dyslipidemia syndrome

ICD-10CM CODE
E88.81 Metabolic syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- Affects close to 25% of U.S. adults.
- Prevalence increases with age, affecting more than 40% of individuals >60 yr.
- Increasing prevalence among women, especially in the African American and Mexican American populations.
- Prevalence increases with weight. Metabolic syndrome is noted in 5% of normal weight, 22% of overweight, and 60% of obese individuals.
- Other risk factors include low socioeconomic status, lack of physical activity, high-carbohydrate diet, alcohol intake, smoking, genetic predisposition, use of atypical antipsychotics, and postmenopausal status.

CLINICAL PRESENTATION

- Obesity, hypertension, dyslipidemia, and hyperglycemia as defined.
  1. Blood pressure: ≥130/85 mm Hg
  2. Abdominal obesity with waist circumference: >94 cm (37 in) in men and >80 cm (31 in) in women
  3. Triglycerides: ≥150 mg/dl (1.7 mmol/L)
  4. HDL: <40 mg/dl (1 mmol/L) in men and <50 mg/dl (1.3 mmol/L) in women
  5. High fasting glucose: ≥100 mg/dl (5.6 mmol/L)
- Patients with metabolic syndrome are at twice the risk of developing cardiovascular disease and have a sevenfold increase in risk for type 2 diabetes and a one-point-fivefold increase in all-cause mortality compared to patients without the syndrome. Other complications include cognitive decline in the elderly, fatty liver disease, polycystic ovary syndrome, obstructive sleep apnea, gout, and chronic kidney disease.
- Focus history on symptoms of diabetes and its complications, obesity and its complications, coronary artery disease (angina), and polycystic ovary syndrome.
- Complete physical examination, including height, weight, waist circumference, and blood pressure.

ETIOLOGY

- Genetic and environmental factors associated with obesity increase the risk of developing metabolic syndrome.
- Abdominal obesity is associated with insulin resistance and hyperinsulinemia.
- Insulin resistance results in ineffective glucose utilization, eventually leading to type 2 diabetes mellitus.
- Hyperinsulinemia and inflammatory markers/cytokines play an important role in development of abnormal lipid profile, hypertension, and vascular endothelial dysfunction, which can lead to the development of atherosclerotic cardiovascular disease.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other causes of weight gain or obesity (Cushing syndrome, hypothyroidism)
- Other causes of hyperlipidemia (familial hyperlipidemia, hypothyroidism)
- Other causes of hypertension (Cushing syndrome, hyperaldosteronism)
- Other forms of diabetes (type 1)

LABORATORY TESTS

- Fasting lipid profile (total cholesterol, low-density lipoprotein [LDL] cholesterol, HDL cholesterol, and triglycerides)
- Fasting glucose

TREATMENT

NONPHARMACOLOGIC THERAPY

- Lifestyle modification:
  1. Dietary modifications aimed at weight loss. The American Heart Association (AHA) recommendations include:
     a. Consuming vegetables and fruits
     b. Eating whole grains and high-fiber foods (≥30 g/day)
     c. Eating fish twice weekly
     d. Consuming lean animal and vegetable proteins
     e. Reducing intake of sugary beverages
     f. Minimizing sugar and sodium intake
     g. Maintaining moderate to no alcohol intake
     h. Consuming 50% to 55% of calories from carbohydrates, 15% to 20% of calories from protein, and 30% to 35% of calories from fat
     i. Limiting saturated fat to less than 7% of energy, trans fat to less than 1% of energy, and cholesterol to less than 300 mg/day
  2. Physical activity of moderate intensity (i.e., brisk walking): 30 min daily
  3. Smoking cessation
- Consider bariatric surgery in the management of obesity:
  1. Body mass index (BMI) ≥40 kg/m^2 in patients who have not responded to diet and exercise (with or without drug therapy).
  2. Individuals with BMI >35 kg/m^2 and comorbidities (hypertension, impaired glucose tolerance, diabetes mellitus, dyslipidemia, sleep apnea) are also potential surgical candidates.

TABLE E1 Common Definitions for Metabolic Syndrome

Criterion	NCEP ATP III (3 or more criteria)
Abdominal obesity	Waist circumference
Men	>40 inches (>102 cm)
Women	>35 inches (>88 cm)
Hypertriglyceridemia	>150 mg/dl (≥1.7 mmol/L)
Low HDL	
Men	<40 mg/dl (<1.03 mmol/L)
Women	<50 mg/dl (<1.30 mmol/L)
Hypertension	≥130/85 mm Hg or on antihypertensive medication
Impaired fasting glucose or diabetes	>100 mg/dl (5.6 mmol/L) or taking insulin or hypoglycemic medication

ATP, Adult Treatment Panel; *HDL,* high-density lipoprotein; *NCEP,* National Cholesterol Education Program. From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, WB Saunders.

[1]Alberti KG et al: Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity,. *Circulation* 120:1640-5, 2009.

ACUTE GENERAL Rx

- Treat obesity (see "Obesity"): Pharmacologic treatment: Consider orlistat and other approved agents (e.g., liraglutide, topiramate/phentermine, bupropion/naltrexone, lorcaserin) in patients who have not responded to diet and exercise if BMI >30 kg/m^2 or a BMI of 27 to 30 kg/m^2 with comorbid conditions. Drug therapy still needs to be in conjunction with diet and exercise.
- Treat hypertension (see "Hypertension"): Systolic blood pressures >130/85 mm Hg: Consider angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker as first-line therapy.
- Treat hyperlipidemia: The 2018 Guideline on the Management of Blood Cholesterol from the American College of Cardiology and American Heart Association (ACC/AHA) specifies four groups that may require statin therapy[2] (potential statin side effects will need to be discussed with the patient prior to any initiation):
  1. Patients with atherosclerotic cardiovascular disease (ASCVD) should be started on high-intensity statin therapy.
  2. Patients with LDL-C levels of ≥190 mg/dl should be started on high-intensity statin therapy.
  3. Patients with diabetes, age 40 to 75, with LDL-C >70 mg/dl should be started on moderate-intensity statin therapy.
  4. Patients without diabetes, age 40 to 75 with LDL-C levels of 70 to 190 mg/dl, and a 10-yr ASCVD risk of 7.5% or higher as determined by the ACC/AHA Pooled Cohort Equations.
- Treat diabetes:
  1. Goal HbA1c determined in an individualized fashion based on age and comorbidities; ACP recommends target of 7.0 to 8.0% for most patients
  2. Metformin as first-line therapy to improve insulin sensitivity provided no contraindications
- Treat cardiovascular risk factors:
  1. Consider aspirin. Aspirin should be started in patients with metabolic syndrome and an intermediate or elevated Framingham cardiovascular risk, if there are no contraindications.
  2. Risk can be lowered with weight loss, exercise, smoking cessation, blood pressure control, diabetes management, and treatment of hyperlipidemia.

CHRONIC Rx

- Encourage lifestyle modification as discussed previously.
- Pharmacologic and surgical management to maintain therapeutic goals described previously.

DISPOSITION

Weight loss can prevent disease progression. Appropriate treatment of obesity, hypertension, hyperlipidemia, and diabetes can improve morbidity and mortality rates.

REFERRAL

- To nutritionist for dietary counseling
- To weight loss and exercise programs
- To endocrinologist if difficulty reaching therapeutic goal and also to consider weight loss pharmacotherapy
- To bariatric surgeon if patient meets surgical criteria (as noted previously)

PEARLS & CONSIDERATIONS

PREVENTION

- Weight loss is essential for the prevention and treatment of metabolic syndrome.
- Recommend dietary modifications and moderate physical activity.
- Consider pharmacologic and surgical options in select individuals (as noted previously).
- Participating in resistance exercise, even less than 1 hour per wk, is associated with lower risk of developing metabolic syndrome, independent of aerobic exercise. Health professionals should recommend that patients perform resistance exercise along with aerobic exercise to reduce risk of metabolic syndrome.[3]

PATIENT & FAMILY EDUCATION

- Weight reduction programs, including Weight Watchers, Curves, etc.
- American Diabetes Association: http://www.diabetes.org.
- Polycystic Ovarian Syndrome Association: http://www.pcosaa.org/.
- The Hormone Foundation: http://www.hormone.org/.

RELATED CONTENT

Metabolic Syndrome (Patient Information)
Obesity (Related Key Topic)

AUTHORS: **Harikrashna B. Bhatt, MD, Shivang U. Danak, MD,** and **Russell E. Bratman, MD**

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BASIC INFORMATION

DEFINITION

A symptom of various pathologies causing localized pain to the forefoot, specifically beneath metatarsal heads 2, 3, and 4.

ICD-10CM CODES

M77.40 Metatarsalgia, unspecified foot
M77.41 Metatarsalgia, right foot
M77.42 Metatarsalgia, left foot

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain beneath metatarsals 2, 3, and/or 4
- Callus formation to plantar metatarsal head(s) (Fig. E1)
- Hallux rigidus/bunion deformity
- Pain during midstance or heel strike phases of gait
- Fat pad atrophy
- Obesity, recent weight gain, or increase/change in type of activity

ETIOLOGY

Primary metatarsalgia: Anatomic abnormalities/variants that alter the weight-bearing metatarsal parabola

- Long or plantar-flexed metatarsal, most commonly number 2
- Cavus foot type
- Equinus/pseudoequinus
- Fractures/surgery

Secondary metatarsalgia: Changes in the lesser metatarsals and/or adjacent first and fifth rays that lead to acquired changes in the anatomic and biomechanical function of the foot.

- Hallux limitus/rigidus, which tends to transfer pressure to the lesser metatarsal heads
- Hammertoe deformity, which is theorized to allow distal shifting of the plantar fat pad
- Inflammatory arthropathy
- Lesser metatarsophalangeal joint instability
- Lesser metatarsophalangeal joint synovitis
- Fat pad atrophy
- Increased forefoot pressures as seen with equinus and neuropathy
- Referred pain due to interdigital neuroma, tarsal tunnel syndrome, spinal lesions

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Morton neuroma, most commonly of the third interspace
- Foreign body
- Metatarsal fracture, stress or traumatic in nature
- Freiberg infarction, most commonly of second metatarsal
- Plantar plate rupture
- Metatarsophalangeal joint capsulitis
- Arthritis
- Limb length discrepancy leading to unilateral forefoot overload
- Equinus deformity, which leads to forefoot overloading
- Neuropathy or peripheral vascular disease

WORKUP

- It is important to remember that metatarsalgia is a symptom of one or more anatomic and/or functional abnormalities. It is important to find the underlying etiology of the pain and to treat it directly.
- Start with a general evaluation of foot type and location of pain.
- Callus patterns are a window into the mechanical function of the foot and should be noted (see Fig. E1).
- Evaluate for equinus and be sure to make note of any first ray pathology including bunion and hallux rigidus deformities.

LABORATORY TESTS

As indicated to evaluate for rheumatologic disease

IMAGING STUDIES

- X-rays (standing dorsoplantar view and lateral view): Evaluate position and length of metatarsals, rule out fracture, tumor, avascular necrosis, arthritic process/joint disease.
- MRI: Evaluate for any plantar plate injury, capsular injury, tendon rupture, or neuroma.
- Bone scan: If stress fracture suspected (may take 2 wk to show up on x-ray).

TREATMENT

Proper supportive shoe gear is essential for pedal health. Treatment of the underlying problem is paramount in the extended relief of metatarsalgia. Evaluation and treatment of any first ray pathology should not be overlooked. Relative rest and offloading should also be discussed.

Dynamic metatarsal cushioning consists of a Plastazote insert reinforced with a less compressible foam layer, which supports the entire arch and midfoot. This combination proves to provide a significant reduction in forefoot pressures and is an excellent option for a more sedentary adult. Functional orthosis aims to reestablish proper biomechanics leading to reduction of pressure points and an improved biomechanical gait. These custom devices are ideal for a more ambulatory patient.

Other treatments include:

- Silicone padding provides symptomatic relief and works well for fat pad atrophy.
- Moleskin or padding will reduce frictional forces without adding bulk for long-term use.
- Custom orthotics address functional or structural etiology.
- Heel lift or shoes with short heel or wedge are effective when equinus is etiology.
- Rocker-bottom shoes reduce pressure at metatarsal heads; they are indicated mostly for diabetics and for limited ankle motion.
- Nonsteroidal antiinflammatory drugs.
- Intraarticular injection in cases of primary arthritic process; however, these should be limited due to increased risk of plantar plate rupture.

DISPOSITION

Varies depending on etiology

REFERRAL

Referral to podiatric or foot/ankle orthopedic surgeon is highly recommended for this diagnosis due to complexity of differential diagnosis and necessity of early diagnosis. Specialized casting, orthotics, or surgical evaluations are frequently necessary.

RELATED CONTENT

Metatarsalgia (Patient Information)

AUTHOR: **Michael Bergen, MD**

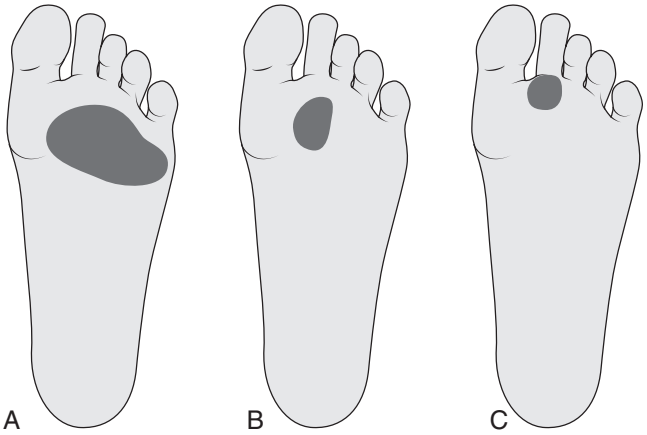

FIG. E1 Various callus patterns that may be associated with metatarsalgia. A, Callus under metatarsal heads 2 to 5 indicates pathology to the first ray that is transferring the weight-bearing surface to the lesser metatarsal heads. **B,** Callus directly plantar to the metatarsal indicates a plantarflexed or prominent metatarsal head seen with pathology during midstance phase of gait. **C,** Callus just distal to the metatarsal head indicates pathology during dynamic phase of gait such as toe off; it can be seen with a long metatarsal. (Courtesy Brian Hochman, DPM.)

SUGGESTED READINGS

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Methanol and Ethylene Glycol Poisoning PTG

BASIC INFORMATION

DEFINITION

An accidental or intentional ingestion of 1 g per kg methanol or ethylene glycol is considered lethal, although even small amounts can be toxic. Inhalational and dermal exposures rarely cause toxicity.

SYNONYMS

Toxic alcohols
Moonshine
Wood alcohol
Antifreeze

ICD-10CM CODES	
T51.8	Toxic effect of alcohols
T51.1X1	Toxic effect of methanol
T51.1X2	Toxic effect of methanol, intentional self-harm
T52.8X1	Ethylene glycol poisoning

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- In 2016, the American Association of Poison Control Centers reported 6,508 single-exposure cases of ethylene glycol poisoning and 1,853 of methanol poisoning.
- Most cases are reported in adults and predominantly in men.
- Accidental exposure is common in children, while alcoholism, polysubstance abuse, depression, and suicide are seen in adults.
- Suicide attempts involving toxic alcohols frequently involve the ingestion of multiple substances.
- Outbreaks or epidemic poisoning with methanol is frequently the result of bootleg distillation or counterfeit alcohol.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical manifestations depend on the quantity of ingestion, duration of time since ingestion, and whether co-ingestion of other substances occurs.
- Early ingestion of either substance causes CNS depression, nausea, and vomiting; inebriation can mimic ethanol ingestion. Late effects include progressive CNS dysfunction, including seizure and coma, as well as respiratory and cardiopulmonary failure.
- Visual symptoms ranging from blurry or snowy vision to complete visual loss and findings of papillary edema and, later, optic atrophy, fixed and dilated pupils, retinal hyperemia, and a Parkinson-like syndrome are indicative of methanol poisoning. Other CNS effects are hemorrhage and white matter lesions in the putamen, subcortical structures, brainstem, and cerebellum.
- Oliguria, hematuria, calcium oxalate crystalluria, tetany, cranial nerve palsy, and acute kidney injury suggest ethylene glycol toxicity.
- Abdominal pain may result from exposure to either substance, while methanol can cause acute pancreatitis.
- Kussmaul respirations (rapid, labored breathing) may be evident with severe acidosis.

PATHOPHYSIOLOGY

- Toxicity of these alcohols is related to their metabolites rather than the parent compound.
- Lethal dose for methanol is >15 to 30 ml and >1 to 1.5 ml/kg for ethylene glycol.
- Sequential metabolism by alcohol and aldehyde dehydrogenases converts methanol to formaldehyde and then formic acid, while ethylene glycol is converted to glycoaldehyde, glycolic acid, and then oxalate.
- Fig. E1 depicts the pathways involved in methanol metabolism.
- While methanol metabolites primarily cause retinal injury, ethylene glycol metabolites produce renal tubular injury and calcium oxalate stones.
  1. Formaldehyde binds to tissue proteins and is likely the major toxin in methanol poisoning involving necrosis of retinal and optic neurons and the basal ganglia (putamen). Formic acid, the acid produced in the largest quantity, inhibits cytochrome oxidase, preventing oxygen utilization by mitochondria and causing further organ dysfunction. Leukotriene has been implicated in the inflammation and neurotoxicity characteristic of acute methanol poisoning.
  2. Glycoaldehyde may be the major nephrotoxin, while glycolic acid is the acid produced in the largest quantity in ethylene glycol poisoning, with a small quantity converted to oxalic acid by lactate dehydrogenase. Oxalate then forms calcium oxalate crystals, which are deposited in the renal parenchyma, cerebral blood vessels, and meninges, causing hypocalcemic tetany.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other causes of a high anion gap metabolic acidosis include lactic acidosis, diabetic and alcoholic ketoacidosis, kidney failure (acute and chronic), early toluene toxicity, and salicylate intoxication. Of note, L-lactate may be elevated in methanol toxicity due to cytochrome oxidase inhibition by formic acid and an increase of the NADH:NAD^+ ratio that is driven by methanol metabolism.
- Elevated plasma osmolal gap may be encountered in ethyl alcohol or isopropyl alcohol ingestion.

EVALUATION AND WORKUP

- Diagnosis depends on history, clinical presentation, and laboratory abnormalities.
- High anion gap metabolic acidosis (AG >12 mEq/L) with elevated plasma osmolal gap (>10 mOsm/kg; usually >25 mOsm/Kg) in an appropriate clinical setting should raise the suspicion of methanol or ethylene glycol ingestion.
- In either intoxication, an osmolal gap will initially be positive, but as the parent compound is converted to its metabolites, the osmolal gap will normalize and the serum anion gap will increase.
- Serum methanol and ethylene glycol levels are elevated in their respective ingestions.
- Acute kidney injury, hypocalcemia with prolonged QT interval, and calcium oxalate crystalluria are seen with ethylene glycol toxicity.
- Metabolic acidosis in the absence of acute kidney injury suggests methanol toxicity; that is, ethylene glycol is more often associated with acute kidney injury.
- Wood's light uses ultraviolet light to detect urinary presence of fluorescein, which is contained in some ethylene glycol preparations. Fluorescence lacks sensitivity and specificity. Therefore, fluorescence is not considered a reliable clinical tool.

LABORATORY TESTS

- Calculation of the anion gap and serum osmolal gap
  1. Anion gap determination: Electrolytes and albumin
  2. Osmolal gap determination: Measured and calculated serum osmolalities (sodium, BUN, glucose, ± ethanol)
- Arterial blood gas analysis, lactate, calcium, and creatine kinase
- Creatinine and urinalysis to evaluate presence of tubular injury and calcium oxalate crystals
- ECG to evaluate QT interval
- Toxicology screen with quantification: Acetaminophen, salicylate, ethanol, methanol, ethylene glycol, and isopropyl alcohol

TREATMENT

High index of suspicion and immediate recognition with early treatment remain crucial to reduce mortality. Box 1 describes common commercial products that may contain ethylene glycol.

NONPHARMACOLOGIC THERAPY

- Cardiorespiratory support as required.
- Rapid (within 60 min) gastric decontamination (charcoal and/or gastric lavage). Later intervention is not beneficial due to rapid and complete invasion (methanol).
- Induction of vomiting is contraindicated even in conscious patients given the risks

BOX 1 Common Commercial Products That May Contain Ethylene Glycol

Paints and lacquers
Polishes and detergents
Inks
Cosmetics
Hydraulic brake fluids
Solar collector fluids
Car wash fluids

Data are from Kruse JA: Methanol, ethylene glycol, and related intoxications. In Carlson RW, Geheb MA (eds): *Principles and practice of medical intensive care,* Philadelphia, 1993, WB Saunders.

of development of central nervous system depression in these patients.

ACUTE GENERAL Rx

- Principles of therapy include prevention of formation of toxic metabolites, correction of acidosis, and toxin removal.
- Intravenous isotonic fluids can facilitate urinary excretion of volatile alcohol and its metabolites; when acidosis is present (pH <7.3), isotonic bicarbonate should be used because reversal of acidosis helps prevent end-organ damage from toxic metabolites (target pH: 7.35 to 7.45).
- Ethanol, a competitive substrate, and fomepizole (4-methylpyrazole or 4-MP), a competitive inhibitor of alcohol dehydrogenase, prevent formation of toxic metabolites of ethylene glycol and methanol.
- Fomepizole is preferred over ethanol given the increased incidence of GI and CNS adverse events with ethanol administration, greater inhibition of alcohol dehydrogenase, and easier administration. Cost and availability of fomepizole may influence the decision to administer this agent vs. ethanol.
- Ethanol: Dosing:
  1. Target ethanol concentration is 100 to 200 mg/dl and requires close monitoring.
  2. Loading dose: 800 mg/kg in a 10% solution of 5% dextrose in water will raise serum ethanol by 100 mg/dl.
  3. Maintenance dose: Infusion of 80 to 160 mg/kg/hr based on blood concentrations.
  4. Comment on dosing adjustment in patients receiving concomitant dialysis.
- Fomepizole: Indications for use:
  1. Plasma concentration of methanol or ethylene glycol >20 mg/dl OR
  2. Documented ingestion with an osmolal gap >10 mOsm/kg OR
  3. Suspected ingestion with at least two of the following criteria:
     a. Arterial pH <7.3
     b. Serum bicarbonate <20 mEq/L
     c. Osmolal gap >10 mOsm/L
     d. Urinary oxalate crystals in the case of ethylene glycol toxicity
- Fomepizole (4-methylpyrazole): Dosing:
  1. Loading dose: 15 mg/kg body weight
  2. Maintenance dose: 10 mg/kg body weight every 12 hr for 4 doses, then 15 mg/kg every 12 hr (if blood levels do not reach goal by 48 hr)
  3. During hemodialysis: Add 1 to 1.5 mg/kg/hr, or repeat loading dose every 4 hr
- The half-lives of ethylene glycol and methanol increase with ethanol or fomepizole.
- The half-life of methanol metabolism during treatment with fomepizole is as much as 87 hr. Treatment with fomepizole alone is not recommended, and hemodialysis should be considered to prevent a prolonged requirement for intensive care.
- In contrast, the observed half-life of ethylene glycol with use of fomepizole is only around 17 hours. Ethylene glycol poisoning (even with levels greater than 50 mg/dl) in patients without kidney injury or acidosis can be managed with fomepizole alone, and without hemodialysis.
- Hemodialysis is indicated for likely or confirmed methanol poisoning in the setting of any of the following: New vision or neurologic deficit (particularly seizure or coma); metabolic acidosis or acidemia with pH ≤7.15; elevated anion gap >24 mmol/L; methanol concentration >70 mg/dl (or 21.8 mmol/L) in the context of fomepizole, or >50 mg/dl (or 15.6 mmol/L) in the absence of an ADH blocker.
- Hemodialysis is indicated for likely or confirmed ethylene glycol poisoning in the setting of any of the following: Acute kidney injury; anion gap metabolic acidosis; EG level >50mg/dl (see earlier regarding use of fomepizole when elevated levels without acidosis or acute kidney injury are present).
- Hemodialysis also should be considered in patients with poisoning and electrolyte imbalances refractory to pharmacologic treatments, or hemodynamic instability.
- Average duration of dialysis in studies was 8.4 ± 3.2 hr.
  1. Treatment with medications and/or hemodialysis is continued until the methanol or ethylene glycol concentration is <20 mg/dl.
  2. Intermittent hemodialysis is the preferred modality of dialysis, as continuous renal replacement therapy (CRRT) alone is ineffective in achieving rapid clearance of methanol and ethylene glycol. In the treatment of a mass outbreak of methanol poisoning, acidemia correction was faster with intermittent hemodialysis than CRRT.
  3. CRRT is an acceptable alternative when intermittent hemodialysis is not available.
  4. If blood concentration levels are not available, start by conducting an 8-hr intermittent hemodialysis session followed by 18 hr of continuous renal replacement therapy; adjust therapy afterward as clinically indicated.
  5. Do not use heparin with dialysis, as heparin may increase the risk for cerebral hemorrhage.

ADJUNCTIVE Rx

- In ethylene glycol poisoning, thiamine (100 mg IV q6h) and pyridoxine (100 mg IV daily) may decrease oxalic acid formation and direct metabolism to less toxic metabolites.
- In methanol poisoning, folinic acid doses (50 mg IV every 6 hr) may increase formic acid metabolism to CO_2 and H_2O. Correct electrolyte abnormalities (hypocalcemia, etc.).
- Treat seizures.

DISPOSITION

Transfer to a hospital with an intensive care unit and hemodialysis capabilities should be carried out early in the course of intoxication.

REFERRAL

- Regional poison center (toxicologist) and nephrology recommended to avoid treatment delays
- Ophthalmology for patients with visual symptoms
- Psychiatry if depression and suicidal ideation are present
- Detoxification centers for patients with substance abuse

PROGNOSIS

- Coma or seizures at presentation and prolonged severe acidosis correlate with increased mortality
- High osmolal gap and high anion gap acidosis associated with high mortality
- Hyperglycemia may correlate with worse prognosis in methanol poisoning

PEARLS & CONSIDERATIONS

- Profound plasma osmolal gap or anion gap metabolic acidosis should raise suspicion for ethylene glycol and/or methanol ingestion. A high index of suspicion and early treatment are crucial to reducing mortality. The metabolites of methanol and ethylene glycol produce the clinical toxidrome.
- Complaints of visual blurring, central scotomata, and blindness are consistent with methanol poisoning.
- Calcium oxalate crystalluria, oliguria, hematuria, and acute kidney injury are consistent with ethylene glycol poisoning.
- Fomepizole is preferred to ethanol due to complications associated with ethanol use.
- Emergent hemodialysis is indicated with end organ damage and/or severe metabolic acidosis.
- Elevated osmolal gap and anion gap metabolic acidosis may occur rarely with other toxic alcohols such as diethylene glycol and propylene glycol.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Algorithm for the Management of Acute Poisoning (Algorithm, Section III)

AUTHOR: **Nikolas Harbord, MD**

SUGGESTED READINGS

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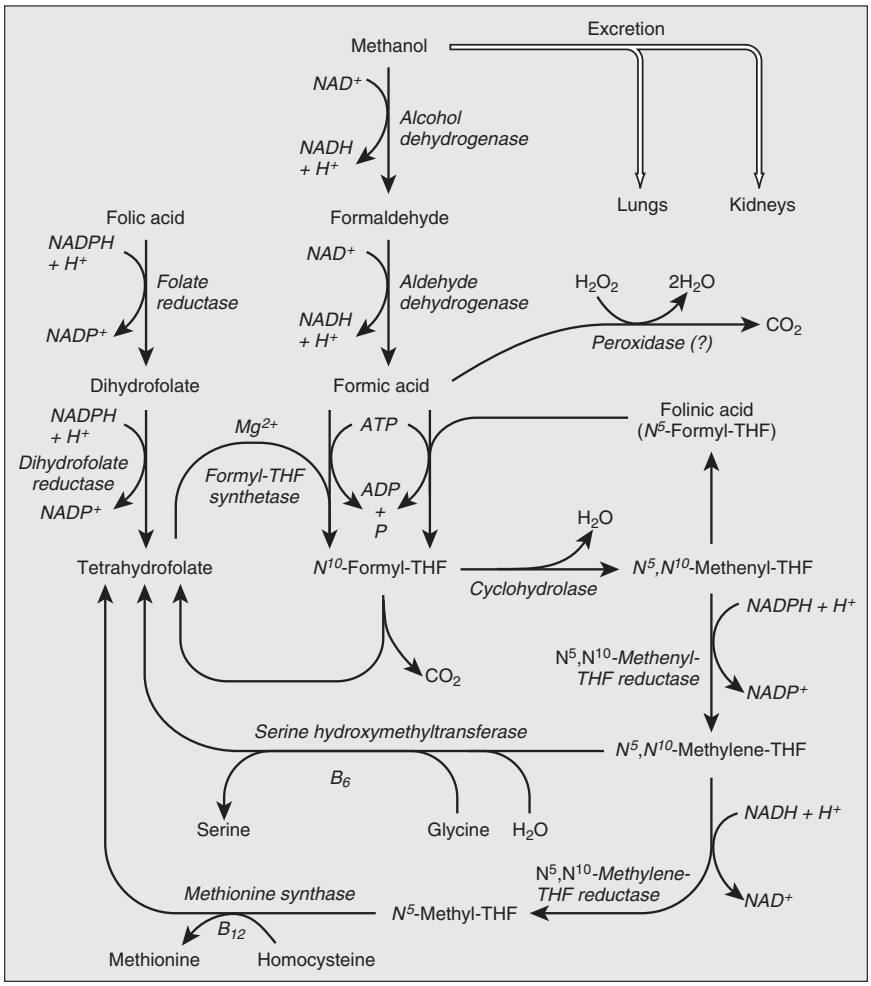

FIG. E1 Metabolic pathways involved in methanol metabolism, showing the role of folate derivatives as enzymatic cofactors operative in the elimination of formic acid. *ADP,* Adenosine diphosphate; *ATP,* adenosine triphosphate; *NAD^+* and *NADH,* oxidized and reduced forms of nicotinamide adenine dinucleotide, respectively; *$NADP^+$* and *NADPH,* oxidized and reduced forms of nicotinamide adenine dinucleotide phosphate, respectively; *THF,* tetrahydrofolate. (Adapted from Kruse JA: Methanol poisoning, *Intensive Care Med* 18:391-397, 1992, with permission. From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.)

Methicillin-Resistant *Staphylococcus aureus* (MRSA) PTG

BASIC INFORMATION

DEFINITION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common bacterial pathogen with resistance to many antibiotics. It is defined as an *S. aureus* that shows a minimum inhibitory concentration (MIC) of greater than or equal to 4 mcg/ml to oxacillin. There are two types of MRSA:

- HA-MRSA: Hospital-acquired MRSA, usually multidrug resistant
- CA-MRSA: Community-acquired MRSA; an emerging pathogen, usually acquired outside of the hospital setting; resistance may differ from HA-MRSA and is generally susceptible to more antibiotics than HA-MRSA

SYNONYMS

Multidrug-resistant *Staphylococcus aureus*
Oxacillin-resistant *Staphylococcus aureus*

ICD-10CM CODES

A41.02	Sepsis due to Methicillin resistant *Staphylococcus aureus*
A49.02	Methicillin resistant *Staphylococcus aureus* infection, unspecified site
B95.62	Methicillin resistant *Staphylococcus aureus* infection as the cause of diseases classified elsewhere
J15.212	Pneumonia due to Methicillin resistant *Staphylococcus aureus*
Z22.322	Carrier or suspected carrier of Methicillin resistant *Staphylococcus aureus*
Z86.14	Personal history of Methicillin resistant *Staphylococcus aureus* infection

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1:3000
PEAK INCIDENCE: Occurs yr-round; may peak during summer and fall mos for CA-MRSA.
PREVALENCE: The national rate of MRSA colonization or infection is 46.3 per 10,000 inpatients. Hospital prevalence rate of MRSA is as high as 60% in hospitals, which means that 60% of *S. aureus* strains in that hospital will be MRSA.
PREDOMINANT AGE AND SEX: All ages and both sexes
RISK FACTORS:

- HA-MRSA: Hospitalization, invasive medical device, residing in long-term nursing facility
- CA-MRSA: Initially seen in young men engaged in athletic activities and in gyms, prisons, military barracks, etc., but has now spread to the entire age spectrum including neonates and the elderly

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- CA-MRSA: Can present with skin infection, associated with opening in the skin; red bump, pustule, or boil; erythema, swelling; edema, often fluctuant and very painful
- HA-MRSA: Bacteremia; infection associated with intravenous device:
  1. Catheters: Pneumonia
  2. Skin: Cellulitis
  3. Bone: Osteomyelitis
  4. Endocarditis
  5. Abscesses: Skin or organ
  6. Pneumonia: Nosocomial

ETIOLOGY

- CA-MRSA: The most prevalent strain in the U.S. on pulse field electrophoresis (PFGE) is called USA 300.
  1. CA-MRSA: Common cause of skin and soft-tissue infections seen in the emergency room. It can, however, also cause necrotizing pneumonia, sepsis, osteomyelitis, etc.
  2. Virulence factors particular to CA-MRSA: Panton-Valentine leukocidin (PVL) toxin, alpha-hemolysin toxin, phenol-soluble modulins, etc., that enhance ability to cause infection.
- HA-MRSA: Most strains on PFGE are USA 100 or USA 200 and tend to have multidrug resistance. Patients with HA-MRSA infection have higher mortality and morbidity than patients with a methicillin-sensitive *S. aureus* (MSSA) infection.
- By definition, all MRSA strains carry the *mecA* gene, which confers resistance to all beta-lactam antibiotics, including cephalosporins and carbapenems.

DIAGNOSIS

LABORATORY TESTS

- Rapid detection methods for MRSA:
  1. Rapid culture methods: Chromogenic agar, which uses a culture media that changes color if *Staphylococcus aureus* is present and then has antibiotics incorporated into media that only allows MRSA strains to grow. This allows for early detection of MRSA in 24 to 48 hr.
  2. Molecular methods that target gene sequences of the bacteria: PCR and gene probe hybridization. Examples include IDI-MRSA, Genotype MRSA direct and Gene Expert MRSA assay. The sensitivity and specificity of these assays compared to traditional cultures range from 90% to 98% and from 91% to 99%, respectively.
- PFGE is usually done only for epidemiologic or outbreak purposes.

IMAGING STUDIES

- Radiographs or computed tomography scan of suspected organ
- Echocardiogram: All adult patients with *S. aureus* bacteremia should undergo echocardiography

TREATMENT

- CA-MRSA: Oral antibiotics that may be effective include trimethoprim-sulfamethoxazole, doxycycline, minocycline, or clindamycin; linezolid and tedizolid are other options but are very expensive
- HA-MRSA: Intravenous antibiotics, vancomycin, linezolid, tedizolid, daptomycin, tigecycline, and newer agent eravacycline

ACUTE GENERAL Rx

- Trimethoprim-sulfamethoxazole, one double-strength tablet PO bid, is useful in cases of CA-MRSA since 95% of community-acquired MRSA strains are susceptible to it in vitro. Other agents that can be used for CA-MRSA include:
  1. Clindamycin: 300 to 450 mg q6h to q8h also inhibits toxin production. If strain tests sensitive to clindamycin but resistant to erythromycin, then a D test must be done to ensure there will not be inducible resistance while on therapy with the clindamycin.
  2. Doxycycline: 100 mg PO q12h and minocycline also have some activity against MRSA.
  3. Rifampin: Never used alone but can be used with one of the other oral agents.
- Vancomycin 15 to 20 mg/kg IV q8 to 12h is the mainstay of parenteral therapy for MRSA infections. There is an increasing concern of MRSA strains developing tolerance to vancomycin, requiring higher doses to achieve eradication. True vancomycin-resistant strains (MIC ≥32 mg/L) remain rare. Vancomycin trough levels of at least 15 to 20 mcg/ml are recommended to treat MRSA infections.
- Linezolid 600 mg PO or IV bid is a synthetic oxazolidinone FDA-approved for MRSA skin and soft tissue infections and pneumonia. It has been shown to be more effective than vancomycin for MRSA pneumonia. A similar agent, tedizolid (200 mg IV or PO for 6 days), is approved for skin and soft tissue infections. These agents are much more expensive than vancomycin.
- Daptomycin: 4 mg/kg/day to 6 mg/kg/day IV is approved for skin and soft tissue infections, bacteremia, and right-sided endocarditis but should not be used for pneumonia as it is inactivated by pulmonary surfactant.
- Tigecycline: 100 mg IV load, then 50 mg IV q12h, is approved for MRSA skin and soft tissue infections and intraabdominal abscess.
- Eravacycline, a derivative of tetracycline, does cover MRSA, VRE, and resistant GNRs but currently is approved only for complicated intraabdominal infections.
- Ceftaroline is a fifth-generation cephalosporin, also effective against MRSA but only skin and soft-tissue infections, not pneumonia: 600 mg IV q12h.
- Newer glycopeptide agents: Dalbavancin (1000 mg IV followed by 500 mg IV a wk later for complicated skin and soft tissue infections) and telavancin (10 mg/kg IV daily for 7 to 14 days) to treat skin infections or pneumonia; these are expensive alternatives to vancomycin.

CHRONIC Rx

- Patients with MRSA colonization may have reexposure or may be unable to eradicate colonized state.
- Oral agents used to attempt eradication of nasal colonization of MRSA are rifampin, tetracycline, and minocycline.

- Topical agents used in an attempt to eradicate MRSA nares carriage include mupirocin nasal ointment 2% applied bid ×5 days. If mupirocin resistant, can use bacitracin or polymyxin.
- There are protocols for using an antiseptic on skin, such as chlorhexidine, along with mupirocin nasal ointment to eradicate MRSA carriage from the body. Postdischarge MRSA decolonization with chlorhexidine and mupirocin results in a 30% lower risk for MRSA infection than education alone.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Methicillin-Resistant *Staphylococcus aureus* (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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Microangiopathic Hemolytic Anemia

BASIC INFORMATION

DEFINITION

Microangiopathic hemolytic anemia (MAHA) is used to describe any nonautoimmune hemolytic anemia that results in red blood cell fragmentation associated with small vessel disease. Several diseases, including thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), hemolytic-uremic syndrome (HUS), atypical hemolytic-uremic syndrome (aHUS), hemolysis, elevated liver enzymes, and low platelets syndrome of pregnancy (HELLP), and malignant hypertension, are associated with MAHA.

SYNONYMS

MAHA
Thrombotic microangiopathy (TMA)
Mechanical hemolytic anemias
Nonautoimmune hemolytic anemias
Fragmentation hemolytic anemia

ICD-10CM CODE
D59.4 Other non-autoimmune hemolytic anemias

EPIDEMIOLOGY & DEMOGRAPHICS

- TTP: Increased incidence in women and African Americans
- Typical HUS:
  1. Associated with *E. coli* O157:H7 in 80% of cases.
  2. Person-person transmission is implicated.
  3. Children are more commonly affected than adults.
- Atypical HUS:
  1. Diarrhea is not a presenting feature.
  2. Adults are more commonly affected.
- DIC:
  1. Always secondary to underlying causes, including sepsis, trauma, malignancy, surgery, or obstetrical complications.
  2. DIC can occur in about 20% of acute leukemias.
- HELLP syndrome:
  1. Occurs in 10% to 20% of pregnancies with preeclampsia.
  2. Develops between 28 and 36 wks of gestation.
  3. Can also present after delivery of fetus in 30% cases.
- Malignant hypertension: MAHA complicates about 25% of malignant hypertension cases.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Mucosal pallor
- Fatigue
- Acute onset of generalized weakness
- Jaundiced skin
- Icteric sclera
- Dark-colored urine

ETIOLOGY

TTP	Idiopathic or familial deficiency of ADAMTS13 Acquired antibodies against ADAMTS13
Typical HUS	Shiga toxin–producing enterohemorrhagic *E. coli* O157:H7
Atypical HUS	Inherited disorders of complement regulation
DIC	Secondary to multiple causes resulting in subendothelial tissue factor exposure and subsequent activation of coagulation cascade
HELLP syndrome	Mechanism not clearly identified, but endothelial injury from hypertension associated with preeclampsia has been implicated
Malignant hypertension	Endothelial damage

DIAGNOSIS

Pathognomonic findings in MAHA include anemia consistent with an intravascular hemolytic picture, including schistocytes (Fig. 1) on peripheral blood smear, elevated lactate dehydrogenase (LDH), increased indirect bilirubin, decreased serum haptoglobin, increased urinary urobilinogen, along with an elevated reticulocyte count and negative Coombs test.

DIFFERENTIAL DIAGNOSIS

- Immune-mediated hemolysis (positive Coombs test):
  1. Autoimmune hemolytic anemia
  2. Paroxysmal nocturnal hemoglobinuria
  3. Cold agglutinin disease
- Infections affecting red blood count (RBC):
  1. Malaria
  2. Babesiosis
  3. Bartonellosis
- Hemolysis due to mechanical stress or oxidative injury:
  1. G6PD deficiency
  2. Runner's anemia or march hemoglobinuria
- Extravascular hemolysis:
  1. Intrinsic RBC defects
  2. Liver disease
  3. Hypersplenism

WORKUP

- Peripheral blood smear showing schistocytes.
- Laboratory workup including CBC, liver function tests, LDH, haptoglobin, reticulocyte count, Coombs test, and urine analysis.
- MAHA and thrombocytopenia are sufficient to make a diagnosis of TTP or HUS; the classic "pentad" of fever, neurologic abnormalities, and renal failure is no longer necessary.
- In DIC, activated partial thromboplastin time and prothrombin time are prolonged, along with decreased fibrinogen levels and increased fibrin degradation products (including D-dimer).
- Blood pressure is greater than 180/120 mm Hg in malignant hypertension and usually associated with acute kidney injury (including hematuria and proteinuria).
- Additional specific tests:
  1. ADAMTS13 activity assay: Decreased activity is associated with idiopathic TTP, and ADAMTS13-directed antibodies are associated with secondary TTP.
  2. Stool culture for shiga toxin–producing *E. coli* in typical HUS.
  3. Although gold standard, renal biopsy is often not required for diagnosis of malignant hypertension.

TREATMENT

If specific etiology of MAHA is not readily identified, plasma exchange therapy should be instituted immediately, in presence of thrombocytopenia and appropriate clinical picture.

- TTP:
  1. Emergent plasma exchange (PEX) to remove unusually large von Willebrand factor (vWF) multimers and autoantibodies directed against ADAMTS13.
  2. Platelet transfusions reserved only for bleeding patients.
  3. If needed, PEX can be increased from once a day to twice daily, along with concomitant use of corticosteroids.
  4. Patients nonresponsive to PEX can be treated with second-line rituximab with or without cyclophosphamide.
- Typical HUS: Supportive care, including hemodialysis, for severe acute kidney injury and hypertension management

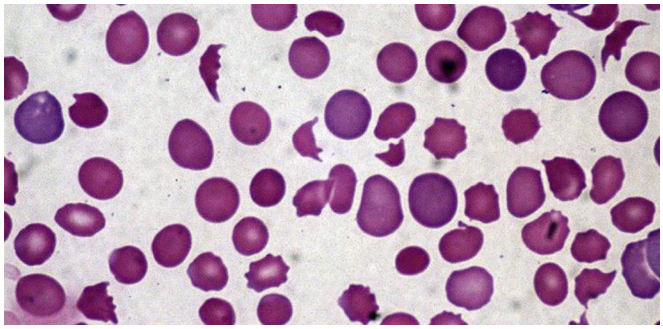

FIG. 1 Peripheral blood smear depicting schistocytes or fragmented red blood count.

- Atypical HUS: Eculizumab has been shown to be more effective than PEX. Eculizumab is an expensive drug, and current manufacturer recommendations include lifelong use, which can be cumbersome. Research is ongoing looking into shorter courses of treatments and outcomes.
- DIC:
  1. Treatment of underlying cause corrects the coagulopathy.
  2. Supportive care, including hemodynamic support and antimicrobial therapy, as indicated.
  3. Activated protein C (APC) is FDA approved for DIC complicated by sepsis.
- HELLP syndrome:
  1. Emergent delivery of fetus if more than 34 wk into gestation, preferably vaginal delivery.
  2. If less than 34 wks' gestation, corticosteroids are recommended for expediting fetal lung maturation and delivery, but not beneficial to the mother.
- Malignant hypertension:
  1. Control blood pressure with medical therapy as indicated.
  2. Care should be taken to avoid rapid lowering of systolic blood pressure, which can lead to ischemia or hyperperfusion syndrome.

MONITORING & FOLLOW-UP

Serial laboratory monitoring of CBC, LDH, and presence of schistocytes on peripheral smear is required to asses MAHA disease activity.

- TTP:
  1. Idiopathic TTP has a relapse rate of 18%, which can happen up to 10 yr from initial presentation.
  2. Serial measurements of ADAMTS13 activity may have predictive value in assessing risk of relapse.
- Typical HUS: Full recovery of renal function, baseline neurologic status, and resolution of diarrhea
- DIC: With adequate management of underlying cause, coagulopathy associated with DIC is reversible.
- HELLP syndrome:
  1. MAHA, thrombocytopenia, and liver injury are resolved within 48 hours after fetal delivery.
  2. Patients should be monitored for at least 2 days, with laboratory workup including CBC, LDH, and liver function.
- Malignant hypertension:
  1. Early adequate blood pressure control can reverse acute kidney injury.
  2. Patients can be discharged from the hospital after achieving adequate blood pressure control on an oral regimen.

PROGNOSIS

- TTP:
  1. If untreated, TTP has a high mortality rate of 90%.
  2. With PEX, mortality rate in idiopathic TTP is 15% and up to 59% in nonidiopathic TTP.
- Typical HUS:
  1. Typical HUS has a mortality rate of 5%, and younger children have better prognosis compared with adults.
  2. Central nervous system involvement or other extrarenal manifestations portend poor outcomes.
- Atypical HUS:
  1. Mortality ranges between 15% and 25%.
  2. Adults have poor prognosis compared with children.
  3. At 1-yr mark, about 25% of all patients have chronic renal failure.
- DIC:
  1. Prognosis of DIC depends on the severity of coagulopathy and underlying condition.
  2. DIC has been shown to be an independent predictor of mortality in sepsis and trauma, increasing the risk of death by a factor of 1.5 to 2.
- HELLP:
  1. Increased risk of preeclampsia in future pregnancies.
  2. Recurrence of HELLP with subsequent pregnancies is about 5%.
- Malignant hypertension:
  1. 10-yr overall survival is approximately 50%.
  2. MAHA in malignant hypertension predicts an increased likelihood of need for future hemodialysis.

REFERRAL

- Hematologist
- Nephrologist
- Neurologist
- Obstetrician

PEARLS & CONSIDERATIONS

- MAHA is not an individual clinical entity by itself, but rather includes many causes with different pathologic mechanisms, with a common phenomenon of small-vessel disease causing intravascular hemolysis.
- Presence of anemia with schistocytes and thrombocytopenia are key features in recognizing MAHA.
- If the etiology of MAHA is not readily apparent on initial evaluation, PEX must be immediately instituted for presumed TTP because it has a very high mortality rate of 90% if untreated.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Disseminated Intravascular Coagulation (Related Key Topic)
HELLP Syndrome (Related Key Topic)
Hemolytic-Uremic Syndrome (Related Key Topic)
Thrombotic Thrombocytopenic Purpura (Related Key Topic)

AUTHOR: **Shiva Kumar R. Mukkamalla, MD, MPH**

SUGGESTED READING

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Microscopic Colitis (Lymphocytic Colitis) ALG

BASIC INFORMATION

DEFINITION

Microscopic colitis (MC), also known as lymphocytic colitis, is an inflammatory condition of the colon that most often presents as chronic watery diarrhea. Although clinically similar, lymphocytic colitis and collagenous colitis represent two histopathologic subtypes of microscopic colitis.

SYNONYMS

Lymphocytic colitis
Collagenous colitis
MC

ICD-10CM CODES

K52.839	Microscopic colitis
K52.838	Other microscopic colitis
K52.832	Lymphocytic colitis
K52.831	Collagenous colitis
K52.9	Colitis, nonspecific

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Incidence of microscopic colitis is 24 to 103 in 100,000 person-yr.
PEAK INCIDENCE: Most cases of microscopic colitis are diagnosed in patients 60 to 70 yr of age.
PREVALENCE: Approximately 7.5% of patients who undergo workup for chronic watery diarrhea are diagnosed with MC.
PREDOMINANT AGE AND SEX: Microscopic colitis, more specifically the collagenous variant, is often diagnosed later in life (>65 yr) and most commonly affects females.
GENETICS: It is unclear how important specific genetic polymorphisms are in the pathophysiology of MC. However, a recent study described genetic similarities in human leukocyte antigen (HLA) genes for patients with microscopic colitis when compared with patients with Crohn disease.
RISK FACTORS:

- Increased age
- Smoking: One study demonstrated that patients who smoke are diagnosed with MC an average of 10 yr earlier than their nonsmoker counterparts
- Autoimmune disorders such as rheumatoid arthritis, thyroid disease, type 1 diabetes
- Celiac disease
- Medications: NSAIDs, proton pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), HMG-COA reductase inhibitors (statins)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most often presents with chronic watery diarrhea (>3 BM daily). Classically, patients with microscopic colitis will experience nocturnal bowel movements.
- Other symptoms include abdominal pain, fecal incontinence, urgency, and less commonly, weight loss.
- Melena and hematochezia are not hallmarks of this disease.

ETIOLOGY

- The pathophysiology of MC remains unclear. Some studies suggest that colonic inflammation promotes a breakdown in electrolyte transport, leading to a combined osmotic and secretory diarrhea. Luminal agents including dietary items, bacterial flora, and medications may influence inflammation.
- Serotonin signaling also may play an important role in the development of MC as patients with a specific polymorphism in a serotonin receptor show a higher incidence of the disease.
- Microbiome studies show dysregulation and decreased bacterial diversity in patients with microscopic colitis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Irritable bowel syndrome (IBS)
- Inflammatory bowel disease (IBD)
- Ischemic colitis
- Infectious colitis (*C. difficile, E. coli, Giardia, Cryptosporidium, Entamoeba histolytica)*
- Pancreatic insufficiency
- Celiac sprue
- Intestinal lymphoma
- Carcinoid tumor
- Diverticulitis
- Small intestine bacterial overgrowth

WORKUP

- Given the breadth of causes of watery diarrhea, the diagnostic workup is largely guided by history.
- Infectious causes of symptoms should be ruled out first, particularly if the patient has specific risk factors including recent travel, consumption of untreated water, or recent antibiotic use or hospitalization.
- A careful history may elucidate specific dietary triggers such as lactose intolerance.
- Celiac disease is often comorbid with MC and should be ruled out in all patients with chronic watery diarrhea.

LABORATORY TESTS

- CBC
- Hepatic function panel
- Electrolyte panel
- *C. difficile* stool PCR
- If the patient has been exposed to untreated drinking water, testing for giardia, cryptosporidium, and *E. histolytica* is indicated
- IgA tissue transglutaminase
- Consider fecal elastase if history is concerning for pancreatic insufficiency
- Fecal calprotectin: Unclear diagnostic benefit

IMAGING STUDIES

- MC is both a clinical and histopathologic diagnosis.
- Abdominal imaging is not helpful in diagnosing MC but may be warranted in patients with severe abdominal pain, evidence of obstruction, or a clinical history suggestive of infectious colitis or diverticulitis. Perforation is a rare complication of MC.
- Colonoscopy is a necessary part of MC diagnosis. On gross endoscopic examination, the colonic mucosa most often appears normal. Nonspecific findings such as erythema or mucosal cracking can be observed in a rare subset of patients.
- Obtaining multiple biopsies of each part of the large colon is foundational for endoscopic evaluation and maximizes diagnostic sensitivity. Lymphocytic colitis and collagenous colitis represent two histologic subtypes of MC. Lymphocytic colitis is marked by >20 intraepithelial lymphocytes to 100 surface epithelial cells in the presence of normal colonic mucosa. Collagenous colitis is characterized by increased intraepithelial lymphocytes and a thickened (>1 mm) subepithelial collagen band in the setting of normal colonic mucosa.

TREATMENT

There is no evidence to suggest that MC increases one's risk of colorectal cancer, nor is it believed to portend increased mortality. However, treatment is important to limit the significant burden on quality of life and healthcare costs. Both histopathologic subtypes of MC are clinically similar and managed using the same modalities. A treatment algorithm for collagenous and lymphocytic colitis is shown in Fig. 1.

NONPHARMACOLOGIC THERAPY

- The first step in management is to withdraw any medications that can provoke disease activity.
  1. NSAIDs are most notably associated with microscopic colitis and should be withheld.
  2. Other medications that may be associated with microscopic colitis include SSRIs, PPIs, statins, and bisphosphonates. Many of these medications are both common and effective, and a careful consideration of risk vs. benefit should occur before withdrawal.
- Smoking cessation.

ACUTE GENERAL Rx

- Antidiarrheal agents including loperamide can be used in patients with mild symptoms. Nighttime dosing of these meds may curb nocturnal diarrhea.
- Budesonide (see Table 1) Shown to be the most effective first-line induction therapy and is often given for up to 8 wk.
  1. Induction therapy dose: 9 mg once daily for 6 to 8 wk.
  2. Maintenance therapy dose: Administer in patients who relapse after completion of induction course. 6 mg daily tapered to lowest effective dose for duration of 6 to 12 mo OR alternating 3 mg and 6 mg daily dose for 12 mo.
- Mesalamine (see Table 1): Although several studies demonstrate that it is less effective than budesonide, mesalamine 3 mg PO once daily also can be used for induction therapy.
- Bismuth salicylate (see Table 1): For those with contraindications to budesonide and

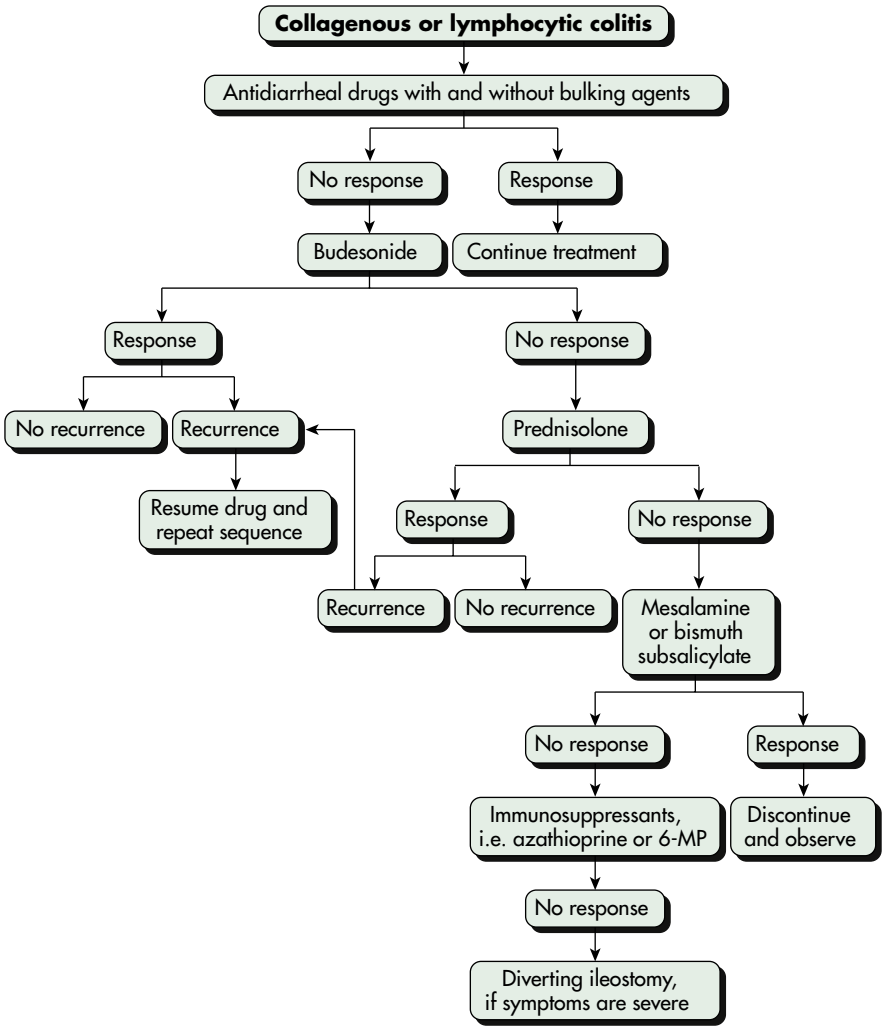

FIG. 1 Algorithm for the treatment of collagenous or lymphocytic colitis. *6-MP,* 6-Mercaptopurine. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

TABLE 1 Treatment Regimens for Lymphocytic Colitis

Medication	Induction	Maintenance
Budesonide	9 mg once daily for 6-8 wk	6 mg daily tapered to lowest effective dose for duration of 6-12 mo* OR Alternating 3 mg and 6 mg daily dose for 12 mo
Mesalamine	3 mg PO once daily†	Not studied as a maintenance therapy
Bismuth subsalicylate	Nine 262-mg tablets daily, divided into three doses	Not studied as a maintenance therapy

*Administer in patients who relapse after completion of induction course.
†Shown to be inferior to budesonide in head-to-head randomized clinical trials.

mesalamine, bismuth salicylate is another medication shown to be superior to watchful waiting in patients with mild symptomatic disease. The dose of bismuth salicylate is nine 262 mg tablets daily, divided into three doses.

- Bile acid sequestrants: There are limited data to suggest that bile acid sequestrants such as cholestyramine may be useful as single-agent or adjuvant induction therapy in patients with mild symptoms.
- Immune modulators: Although limited supporting evidence exists for their use, immune modulators such as azathioprine, vedolizumab, and anti-TNF-alpha inhibitors may also have a role for induction therapy in budesonide refractory disease.
- There is no role for systemic steroids such as prednisone in the treatment of microscopic colitis.
- Rarely, patients require surgical intervention with colonic diversion.

CHRONIC Rx

Approximately two thirds of patients with microscopic colitis experience relapsed disease and require maintenance therapy. Budesonide is the most studied maintenance agent that can be administered for up to 12 mo at doses lower than those used for induction. For less severe disease, patients also can continue using bismuth salicylate or cholestyramine.

COMPLEMENTARY & ALTERNATIVE MEDICINE

It is unclear whether probiotics provide benefit.

DISPOSITION

Symptoms associated with MC are often episodic. While induction therapy is highly effective, 66% of patients in remission will experience a subsequent disease flare.

REFERRAL

- Gastroenterology referral should be offered to patients with long standing chronic diarrhea whose workups have ruled out acute infectious causes.

- Nutrition referrals also may be helpful in patients with severe symptoms such as weight loss.

PEARLS & CONSIDERATIONS

COMMENTS

- MC poses a significant burden on patient quality of life and is often under-recognized.
- Chronic watery diarrhea in the older adult, particularly with nighttime symptoms, should prompt the provider to consider MC. Identification of MC through clinical history and endoscopic evaluation should not be delayed as induction therapy is highly effective at improving disease morbidity.
- Budesonide remains the most effective mainstay medication for both induction and maintenance therapy. Other medications such as bismuth salicylate and cholestyramine are well tolerated and suitable as adjunct or single-agent therapies. Refractory cases may require immunomodulator therapy such as azathioprine or anti-tumor necrosis factor biologic agents such as infliximab.

PREVENTION

As with many other chronic illnesses, smoking cessation is an important part of both management and prevention.

PATIENT & FAMILY EDUCATION

There is no known genetic abnormality, but presentation may trend in families.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Irritable Bowel Syndrome (Related Key Topic)
Crohn Disease (Related Key Topic)
Ulcerative Colitis (Related Key Topic)
Traveler's Diarrhea (Related Key Topic)

AUTHORS: **Breton Roussel, MD,** and **Sarah Hyder, MD**

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Microscopic Polyangiitis

BASIC INFORMATION

DEFINITION

Microscopic polyangiitis (MPA) is an ANCA (antineutrophil cytoplasmic autoantibody)-associated small to medium vessel systemic vasculitis. It is characterized by necrotizing, pauciimmune, small-vessel vasculitis in the absence of granulomatous inflammation. Most patients present with both renal and pulmonary involvement that may cause severe organ dysfunction leading to renal and respiratory failure. However, MPA may affect any organ or tissue, including the skin, nervous system, and gastrointestinal (GI) tract. MPA belongs to the family of ANCA-associated vasculitides that also includes granulomatosis with polyangiitis (GPA, previously known as Wegener granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg-Strauss syndrome) (Table E1).

TABLE E1 Classification Scheme of Vasculitides according to Size of Predominant Blood Vessels Involved

Predominantly Large-Vessel Vasculitides

Takayasu arteritis

Giant cell arteritis

Cogan syndrome

Behçet syndrome*

Predominantly Medium-Vessel Vasculitides

Classic polyarteritis nodosa

Cutaneous polyarteritis nodosa

Rheumatoid vasculitis†

Buerger disease (thromboangiitis obliterans)

Kawasaki disease

Primary angiitis of the central nervous system

Predominantly Small-Vessel Vasculitides

Immune Complex Mediated

- Cutaneous leukocytoclastic angiitis ("hypersensitivity" vasculitis)
- Henoch-Schönlein purpura
- Urticarial vasculitis
- Cryoglobulinemic vasculitis†
- Goodpasture syndrome (anti-glomerular basement membrane disease)

"ANCA-Associated" Disorders

- Granulomatosis with polyangiitis (previously, Wegener granulomatosis)†
- Microscopic polyangiitis†
- Eosinophilic granulomatosis with polyangiitis (previously known as Churg-Strauss syndrome)†

Miscellaneous Small-Vessel Vasculitides

Connective tissue disorders†

Paraneoplastic diseases

Infection

Inflammatory bowel disease

*May involve small, medium, and large blood vessels.

†Frequent overlap of involvement of small- and medium-size blood vessels.

ANCA, Antineutrophil cytoplasmic antibody.

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.

SYNONYMS

Microscopic polyarteritis

MPA

ICD-10CM CODE

M31.7 Microscopic polyangiitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence is 9.5 to 95 million/yr in Europe, lower elsewhere.
- Prevalence is 20 to 50 cases per 1,000,000.
- More common in Caucasians than in African Americans.
- The male:female ratio is 1.8 to 1.
- MPA occurs at all ages, even in young children. The incidence rises with increasing age, peaking in the sixth and especially seventh decades.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- In 60% to 80% of cases, there is a protracted and indolent course over many wk to mo with nonspecific symptoms such as fatigue, fever, "flu-like" symptoms, weight loss, and anorexia
- Many have migratory arthralgias with no or only mild signs of arthritis affecting a few joints at a time
- Macroscopic hematuria, proteinuria, edema, decreased urinary output
- Pulmonary symptoms, including hemoptysis, cough, dyspnea, pulmonary hemorrhage, pleuritic pain, and lung infiltrates
- Palpable purpura (41%) is the most common cutaneous manifestation. Livedo reticularis (12%), skin ulcers, digital gangrene may also be present
- Inflammation of visceral blood and gut vessels causes pain and bloody stools, and may lead to perforation
- Peripheral nervous system involvement manifesting as mononeuritis multiplex (57%), CNS involvement manifesting as seizures (11%)
- Kidney involvement up to 90%
- Weight loss >70%
- Myalgias 50%, arthralgias (10% to 50%), arthritis
- Chest pain, heart failure symptoms
- Mild ENT symptoms including nasal congestion, sinusitis, and epistaxis can occur in up to 30% of cases
- Severe or destructive disease of the upper airways is not compatible with MPA and suggests a diagnosis of GPA
- Ophthalmic involvement: Episcleritis and ulcerative keratitis are the most common clinical manifestations, occurring in 10% to 20% of cases. Uveitis, conjunctivitis, and necrotizing scleritis have also been described

ETIOLOGY

- Autoimmune process of unknown etiology. ANCA, most specifically those directed at cytoplasmic myeloperoxidase, are felt to contribute to the inflammatory process. Once bound to their cellular epitope, antimyeloperoxidase (MPO) antibodies likely contribute to degranulation of the neutrophil, which presumably contributes to endothelial injury. Most recently, investigators have demonstrated that anti-MPO antibodies alone can cause necrotizing and crescentic glomerulonephritis.
- In addition to antibodies directed against PR3 and MPO, it has been demonstrated that patients with ANCA-associated necrotizing glomerulonephritis tend to have IgG antibodies against human lysosomal membrane protein 2 (hLAMP-2).
- Many hypotheses involve microbial agents in the development of disease activity.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Polyarteritis nodosa
- Kawasaki disease
- Infective endocarditis
- Lymphoma
- Amyloidosis
- Hypercoagulable states
- Systemic lupus erythematosus
- Paraproteinemia
- Cryoglobulinemia

MPA is distinguished from GPA by the absence of granuloma formation (Table E2) and from EGPA by the absence of asthma and eosinophilia.

WORKUP

- Thorough medical history and physical examination to detect sites of organ involvement and to exclude other illnesses that may have a similar appearance, especially infections.
- Diagnosis is confirmed with kidney biopsy revealing nongranulomatous necrotizing pauciimmune vasculitis of small vessels or pauciimmune necrotizing crescentic glomerulonephritis.

LABORATORY TESTS

- May reveal elevated sedimentation rate (ESR), C-reactive protein, leukocytosis, thrombocytosis, and normocytic anemia
- Elevated serum blood urea nitrogen and creatinine suggest renal impairment
- Urinalysis to detect proteinuria, hematuria, erythrocyte casts, abnormal urine sediment
- ANCA positive 82% to 94%
- Perinuclear ANCA directed at myeloperoxidase (50% to 70%)
- Cytoplasmic ANCA directed at proteinase 3 (25% to 30%)
- Serum complement levels
- Aspartate aminotransferase, alanine aminotransferase, and creatine phosphokinase to evaluate for liver or muscle involvement
- Blood cultures to rule out bacterial endocarditis

IMAGING AND OTHER STUDIES

- Tissue for pathology diagnosis is usually required to confirm the diagnosis; characteristic histologic lesion in MPA is pauciimmune necrotizing small-vessel vasculitis.

TABLE E2 Names and Definitions of Vasculitis Adopted by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis

Name	Definition
Large-Vessel Vasculitis*	
Giant cell (temporal arteritis)	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. Usually occurs in patients older than 50 yr and often is associated with polymyalgia rheumatica.
Takayasu arteritis	Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50 yr.
Medium-Sized Vessel Vasculitis*	
Polyarteritis nodosa (classic polyarteritis nodosa)	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules. Kawasaki disease arteritis involving large, medium-sized, and small arteries and associated with mucocutaneous lymph node syndrome. Coronary arteries often are involved. Aorta and veins may be involved. Usually occurs in children.
Small-Vessel Vasculitis*	
Granulomatosis with polyangiitis‡	Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels, e.g., capillaries, venules, arterioles, and arteries. Necrotizing glomerulonephritis is common.
Churg-Strauss syndrome	Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels and associated with asthma and blood eosinophilia.
Microscopic polyangiitis (microscopic polyarteritis)	Necrotizing vasculitis with few or no immune deposits affecting small vessels, e.g., capillaries, venules, or arterioles. Necrotizing arteritis involving small- and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.
Henoch-Schönlein purpura‡	Vasculitis with immunoglobulin A–dominant immune deposits affecting small vessels, e.g., capillaries, venules, or arterioles. Typically involves the skin, gut, and glomeruli and is associated with arthralgias or arthritis.
Essential cryoglobulinemic vasculitis‡	Vasculitis with cryoglobulin immune deposits affecting small vessels, e.g., capillaries, venules, or arterioles, and associated with cryoglobulins in serum. Skin and glomeruli often are involved.
Cutaneous leukocytoclastic angiitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

*_Large artery_ refers to the aorta and the largest branches directed toward major body regions (e.g., to the extremities, head and neck); _medium-sized artery_ refers to the main visceral arteries (e.g., renal, hepatic, coronary, and mesenteric arteries); and _small artery_ refers to the distal arterial radicals that connect with arterioles (e.g., renal arcuate and interlobular arteries). Note that some small- and large-vessel vasculitides may involve medium-sized arteries, but large- and medium-sized vessel vasculitides do not involve vessels smaller than arteries.
†Strongly associated with antineutrophil cytoplasmic autoantibodies (ANCA).
‡May be accompanied by glomerulonephritis and can manifest as nephritis or pulmonary renal vasculitic syndrome.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.

- Biopsy of the skin reveals nonspecific leukocytoclastic vasculitis with little or no complement and immunoglobulin on immunofluorescence.
- Kidney biopsy usually reveals necrotizing crescentic glomerulonephritis that is usually pauciimmune on immunofluorescence and necrotizing vasculitis of microscopic vessels (small arteries, arterioles, capillaries, venules).
- Intestinal angina is often a result of mesenteric ischemia and can be assessed using mesenteric angiography when renal function permits.
- Chest radiograph would show diffuse parenchymal infiltrates secondary to pulmonary alveolar hemorrhages (Fig. E1).
- Computed tomographic (CT) scanning may disclose previously undetected nodules, unsuspected cavitation in nodules, alveolar opacities, large-airway inflammation or stenotic lesions, and pleural-based lesions.
- An EMG may reveal a sensorimotor peripheral neuropathy in patients with mononeuritis multiplex.
- Electrocardiography is indicated in those with cardiac symptoms.

Rx TREATMENT

ACUTE GENERAL Rx

- Induction: Depends on severity of disease and organ system involvement.
  1. Corticosteroids combined with cyclophosphamide, followed by maintenance therapy with methotrexate, azathioprine, or mycophenolate mofetil.
  2. Rituximab is an effective alternative to cyclophosphamide for initial induction therapy as well as for relapse.
  3. Plasmapheresis is an option for patients with severe bleeding in the lungs or rapidly progressive kidney failure leading to dialysis.

CHRONIC Rx

- Maintenance therapy: Mycophenolate mofetil, azathioprine, methotrexate, and rituximab can be used for maintenance therapy, although dosing intervals and duration of therapy are still being determined.
- Prophylaxis for opportunistic infections like *Pneumocystis jirovecii (carinii)* pneumonia (PCP) is with low-dose sulfamethoxazole/trimethoprim given as one double-strength tablet three times weekly or as a single-strength tablet once daily. Atovaquone is preferred in patients who are allergic to sulfonamides or who do not tolerate trimethoprim-sulfamethoxazole.
- Relapse therapy:
  1. Mild or non–life-threatening relapses while on maintenance therapy can be treated by increasing glucocorticoid dose and/or by adding azathioprine or methotrexate.
  2. In severe cases, treatment is the same as in remission induction; however, rituximab is often preferred over cyclophosphamide.

DISPOSITION

- Poor prognosis if untreated.
- Prompt diagnosis is important to permit initiation of therapy that may be life saving and organ sparing.
- Renal failure and pulmonary involvement are the major causes of morbidity and mortality.
- With treatment, 1- to 5-yr survival rates are 82% and 76%.

REFERRAL

- Nephrology consultation is needed for the diagnosis and management of renal disease.
- Multiple specialists may be consulted depending on other organ system involvement.

PEARLS & CONSIDERATIONS

- Relapse occurs in one third of the cases.
- PCP occurs in 6% of the patients as a complication of immunosuppressive therapy.

AUTHOR: **Daphne Scaramangas-Plumley, MD**

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FIG. E1 Pulmonary hemorrhage in microscopic polyangiitis. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

BASIC INFORMATION

DEFINITION

Microsporidiosis is an infection caused by single-celled intracellular spore-forming organisms previously classified as protozoan, but now classified as fungi. Infections occur more commonly in patients with HIV/AIDS, travelers, children, organ transplant recipients, contact lens wearers, and elderly adults.

SYNONYMS

Enterocytozoon bieneusi infection
Encephalitozoon species infection

ICD-10CM CODES

A07.8 Microsporidiosis, intestinal
B60.8 Microsporidiosis
H16.8 Keratitis, microsporidia

EPIDEMIOLOGY & DEMOGRAPHICS

Microsporidia are a phylum of ubiquitous protists that exist worldwide in the environment and can infect vertebrate and invertebrate hosts, entering via ingestion or inhalation of spores and by direct contact through broken skin or lesions in the eyes.

PREVALENCE: Prevalence in immunocompetent persons is unclear, with rates varying from 5% to 45% in recent studies of stool from healthy human subjects.

In the postantiretroviral therapy era, prevalence rates have decreased; however, in a study of asymptomatic HIV patients, 15% had evidence of microsporidia on small bowel biopsy.

RISK FACTORS: Infections such as a nonbloody watery diarrhea and keratoconjunctivitis in contact lens wearers can occur in normal hosts, but immunocompromised hosts such as AIDS patients, organ transplant recipients, and bone marrow graft recipients are at greater risk for more severe disease, other organ involvement, and disseminated infection. Patients living with AIDS who have CD4 counts <200 should be advised to avoid untreated water and undercooked meat or seafood.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Each species of microsporidia has different reported infections:

- *Enterocytozoon bieneusi* can cause diarrhea, wasting syndrome, cholangitis, rhinitis, or bronchitis.
- *Encephalitozoon intestinalis* can cause diarrhea, intestinal perforation, cholangitis, nephritis, keratoconjunctivitis, and disseminated infection.
- *Encephalitozoon cuniculi* can cause hepatitis, peritonitis, encephalitis, urethritis, prostatitis, nephritis, sinusitis, keratoconjunctivitis, cystitis, cellulitis, and disseminated infection.
- *Encephalitozoon hellem* can cause keratoconjunctivitis, sinusitis, pneumonitis, nephritis, prostatitis, urethritis, cystitis, and disseminated infection.

ETIOLOGY

- There are 1200 species of Microsporidia, but only 14 infect humans from seven different genera. The four most common species to cause human disease are:
  1. *Enterocytozoon bieneusi*
  2. *Encephalitozoon intestinalis*
  3. *Encephalitozoon cuniculi*
  4. *Encephalitozoon hellem*
- These genotypes that infect humans have been identified in domestic, farm, and wild animals and thus may be a form of zoonotic disease.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other causes of watery non-bloody diarrhea: *Norovirus, Giardia, Cryptosporidia, Cyclospora,* and *Isospora belli*
- Other causes of keratoconjunctivitis: Herpetic keratoconjunctivitis and acanthamoeba keratitis

WORKUP

Consists of the microscopic detection of microsporidia spores (1 to 2 μm in diameter) in stool, body fluids, or tissue samples.

LABORATORY TESTS

- Modified trichrome stain with light microscopy can be used on stool, urine, mucus, or tissues. Spores stain pink against a blue-green background
- Fluorescent techniques: Calcofluor white stain, Uvitex 2B, and Fungi-Fluor kit
- Indirect immunofluorescence
- Serology: Detects IgM and IgG antibodies
- For exact speciation: PCR

TREATMENT

ACUTE GENERAL Rx

Treatment will depend on organism and site involved.

- There is no available therapy currently for *E. bieneusi*; however, immune restoration through initiation of antiretroviral therapy (ART) has been shown to resolve symptoms in AIDS patients. ART should be offered as a part of initial management where applicable. Systemic fumagillin has shown some success.
- Intestinal or disseminated infection caused by microsporidia other than *E. bieneusi* and *V. corneae*: Albendazole 400 mg PO bid for 2 to 4 wk depending on level of immunosuppression. Children: 15 mg/kg/day PO in divided doses. For disseminated disease (especially *Trachipleistophora* or *Anncaliia* infections), consider the addition of itraconazole.
- Keratoconjunctivitis: Topical fumagillin 70 mcg/ml eye drops (2 drops every 2 hours for 4 days, then 2 drops 4 times a day). If associated with intestinal disease, add albendazole 400 mg PO bid for 2 to 4 wk depending on degree of immunosuppression.

CHRONIC Rx

- Antimotility agents are useful to control diarrhea.
- Recurrence or relapse may occur with ongoing immunosuppression; therefore, consider chronic maintenance therapy until CD4 counts remain >200 for 6 mo in those living with HIV.

REFERRAL

- Infectious diseases physician for antiretroviral therapy if positive for HIV/AIDS
- Ophthalmologist if keratoconjunctivitis is suspected

PEARLS & CONSIDERATIONS

COMMENTS

- Microsporidia infections occur particularly in HIV-positive patients with $CD4^+$ cell counts <50/ml.
- Microsporidia spores can remain active in the environment for prolonged periods of time (e.g., mos).

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Tara C. Bouton, MD, MPH, TM, Philip A. Chan, MD, MS,** and **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents: Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.

Middle East Respiratory Syndrome (MERS)

BASIC INFORMATION

DEFINITION

Middle East respiratory syndrome (MERS) is a viral respiratory disease caused by a novel coronavirus known as Middle East respiratory syndrome coronavirus (MERS-CoV) that was first identified in Saudi Arabia in 2012.

SYNONYMS

Human coronavirus-EMC (Erasmus Medical Center)
MERS

ICD-10CM CODE
B97.29 Other coronavirus as the cause of diseases classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

As of July 2018, there have been 2220 cases worldwide in 27 countries but mostly in the Middle East, with a total of 790 deaths. Outside the Middle East, cases have been travel related and traceable to the Arabian Peninsula.

INCIDENCE: In one study in Saudi Arabia of more than 10,000 people, the positive serology rate was only 0.15%, was higher in men than in women, and was higher among camel shepherds and slaughterhouse workers (3.1%) than the general population.

PREDOMINANT SEX AND AGE: More than 60% of cases are in men, and the median age is 48 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The spectrum of disease for MERS ranges from a mild viral respiratory disease to a rapidly fatal viral pneumonia associated with acute respiratory distress syndrome (ARDS) and acute renal failure.
- Patients will present with an influenza-like illness with fever, chills, headache, and a dry cough.
- MERS progresses rapidly to a viral pneumonia within a wk of onset of the infection with bilateral interstitial infiltrates and development of ARDS with severe hypoxemia.
- Other possible symptoms include myalgias, sore throat, vomiting, diarrhea, abdominal pain, and hemoptysis.

ETIOLOGY

- MERS-CoV is closely related to a coronavirus found in bats, which implies that bats may be a reservoir for MERS-CoV. The virus was then transmitted to dromedary camels sometime in the distant past. Camels likely serve as hosts for MERS-CoV for animal-to-human transmission.
- Human-to-human transmission has been documented in various cluster outbreaks and in household contacts.
- While MERS has a high case fatality rate (35% to 50%), its transmissibility appears to be modest.
- The median incubation period for human-to-human transmission is 5 days.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Severe acute respiratory syndrome (SARS), also caused by a novel coronavirus (SARS-CoV), emerged in 2002 in China. The virus also likely originated in bats, and the intermediate host for the virus was the palm civet cat. SARS has a high transmissibility rate but a low case fatality rate.
- Influenza, including pandemic H1N1 influenza and avian influenza H7N9.
- MERS has a high frequency of renal failure, and influenza does not.

WORKUP

MERS should be considered when there is a direct epidemiologic link with a person with MERS or when a patient resides in or has traveled to the Middle East and presents with a febrile acute respiratory illness.

LABORATORY TESTS

- Lower respiratory tract specimens such as sputum or BAL should be tested using a real-time reverse-transcriptase polymerase chain reaction test (rRT-PCR), and these test sites appear to be more sensitive than testing of upper respiratory tract secretions via combined nasopharyngeal and oropharyngeal swab with the same rRT-PCR.
- Serology: A serum sample within first 10 to 12 days of onset should be obtained for rRT-PCR and repeated 14 days later.
- Other serologic tests include ELISA screening followed by indirect immunofluorescence.
- Nonspecific laboratory tests with MERS: Leukopenia, relative lymphopenia, and thrombocytopenia.

IMAGING STUDIES

- Radiographic abnormalities include either unilateral or bilateral airspace opacities, patchy infiltrates, interstitial changes, nodular opacities, reticular opacities, pleural effusions, and even total segmental or lobar opacification.
- ARDS pattern is typically seen with severe cases.

TREATMENT

ACUTE GENERAL Rx

Currently there are no approved treatments for MERS. Experimental therapies include:

- Combination of interferon (IFN)-alpha-2a and ribavirin
- Monoclonal antibodies
- Convalescent serum
- Nitazoxanide: A broad-spectrum antiviral agent
- Steroids are not recommended for use in patients with MERS
- Ongoing placebo controlled trial in Saudi Arabia of oral lopinavir-ritonavir and SQ interferon-beta

NONPHARMACOLOGIC THERAPY

There is ongoing research in vaccine development, including camel vaccination, which may be a novel approach to preventing human infection.

REFERRAL

If a case is suspected, the local health department should be involved as well as an infectious diseases physician.

PEARLS & CONSIDERATIONS

COMMENTS

In South Korea, a single imported case created an outbreak of 185 cases and 36 deaths in 2015.

PREVENTION

- Health care workers are at risk of exposure to the disease and thus should use both contact and airborne precautions in the hospital setting if in close contact with symptomatic individuals or patients with MERS.
- In the Middle East, infection-control practices include prohibiting consumption of unpasteurized camel milk (virus can be found in milk and feces) and use of camel urine, which is believed to have medicinal purposes.
- With 10 million Hajj pilgrims visiting Saudi Arabia each yr from more than 180 countries, a high degree of suspicion of the clinical illness is important in persons returning to their home nations.

RELATED CONTENT

Influenza, Avian (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Migraine headaches are recurrent severe headaches that either are preceded by a focal neurologic symptom (migraine with aura), occur independently without preceding focal neurologic symptoms (migraine without aura), or have atypical presentations (migraine variants). The migraine aura (Box 1) typically is characterized by visual or sensory symptoms that develop over 5 to 60 min. If the aura includes unilateral motor weakness, the migraine is referred to as hemiplegic. In migraine with and without aura, the headache is typically moderate to severe, unilateral, pulsatile, made worse with head movement, and associated with nausea and vomiting, photophobia, and phonophobia. Migraines that occur ≥15 days every mo for ≥3 mo are known as chronic; otherwise, they are referred to as episodic. Table 1 summarizes criteria for migraine.

ICD-10CM CODES

G43.909	Migraine, unspecified, not intractable, without status migrainosus
G43.1	Migraine with aura (classical migraine)
G43.0	Migraine without aura (common migraine)
G43.2	Status migrainosus
G43.3	Complicated migraine

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Increases from infancy, peaks during the third decade of life, then decreases
PREVALENCE (IN U.S.): Migraine is very common, affecting 1 in 6 people in the U.S. It is the fourth or fifth most common reason for an emergency room visit and the seventh leading cause of time spent disabled worldwide.
AGE: Peak prevalence between ages of 18 and 49
PREDOMINANT SEX: Female:male ratio of 3:1
GENETICS: Familial predisposition: More than 50% of migraine sufferers have an affected family member.

BOX 1 Auras of Migraine

- Sensory phenomena
  - Special senses
    - Visual, olfactory, auditory, gustatory
  - Paresthesias, especially lips and hand
- Motor deficits
  - Hemiparesis, hemiplegia
- Neuropsychologic changes
- Aphasia
- Perceptual impairment, especially for size, shape, and time
- Emotional and behavioral
  - Anxiety, depression, irritability, (rarely) hyperactivity

From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists*, ed 8, Philadelphia, 2017, Elsevier.

- Autosomal-dominant transmission for some rare migraine variants (familial hemiplegic migraine, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]); familial hemiplegic migraines have been associated with calcium channelopathy, sodium channelopathy, and Na^+/K^+-ATPase dysfunction.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Normal between episodes
- Normal for migraine without aura
- Focal motor or sensory abnormalities possible for migraine with aura or migraine variants
- Common aura types include scintillating scotoma, bright zigzags (fortifications), and other visual distortions such as macropsia or micropsia (enlargement or shrinkage of objects) that often cross visual fields. Homonymous visual disturbance, sensory phenomena such as hemibody paresthesia, speech disturbances, or hemiparesis (familial or sporadic hemiplegic migraine) also can occur independently or associated with visual symptoms

ETIOLOGY

The pathophysiology of migraines is not clearly understood, although the primary neuronal event results in a trigeminovascular reflex causing neurogenic inflammation. Calcitonin-gene related peptide (CGRP) is released by the trigeminal ganglion and binds receptors around meningeal vessels leading to inflammation. Serotonin, substance P, and nitric oxide also play a role, but the exact mechanism is unknown. Cortical spreading depressions also likely are responsible for the aura.

DIAGNOSIS

Migraine without aura:
- Five attacks fulfilling criteria
- Headache attacks lasting 4 to 72 hr
- Headache has at least two of the following characteristics:
  1. Unilateral location
  2. Pulsating quality
  3. Moderate or severe pain intensity
  4. Aggravation or causing avoidance of routine physical activity
- At least one of the following during headache:
  1. Nausea and/or vomiting
  2. Photophobia and phonophobia

Migraine with typical aura:
- At least two attacks
- Aura consisting of at least one of the following, but no motor weakness:
  1. Fully reversible visual symptoms, including positive and/or negative features
  2. Fully reversible sensory symptoms, including positive and/or negative features
  3. Fully reversible dysphasic speech disturbance
- At least two of the following:
  1. Homonymous visual symptoms and/or unilateral sensory symptoms
  2. At least one aura symptom develops gradually over >5 min and/or different aura symptoms occur in succession over >5 min
  3. Each symptom lasts between 5 and 60 min
- A migraine occurring during or within 60 min of the aura

DIFFERENTIAL DIAGNOSIS

- A diagnosis of migraine is possible only after five recurrent episodes.
- The first or the worst headache should always be investigated, and the differential includes headaches from all secondary causes.
- Headache red flags can be remembered by the mnemonic SSNOOP5:
  1. S: Systemic symptoms of fever, weight loss
  2. S: Secondary risk factors of immunosuppression from any cause, cancer
  3. N: Neurologic deficits, altered consciousness
  4. O: Onset is sudden, abrupt, split second thunderclap
  5. O: Older, age >50 for new-onset headache should be worked up for giant cell arteritis
  6. P: Pattern: change in headache pattern
  7. P: Pregnancy
  8. P: Positional or postural
  9. P: Papilledema
  10. P: Precipitation with Valsalva maneuver or exertion
- Section II describes the differential diagnosis of headaches. Table 1 compares tension-type and migraine headaches.
- Useful mnemonic for migraine is POUND: Pulsatile, One day in duration, Unilateral, Nausea/vomiting, Disabling.

WORKUP

- In general, no additional investigation is needed with recurrent, typical attacks with usual age of onset, family history, and a normal physical examination.

TABLE 1 Comparison of Tension-Type and Migraine Headaches

	Tension-Type	Migraine
Location	Bilateral	Hemicranial*
Nature	Dull ache	Throbbing*
Severity	Slight–moderate	Moderate–severe
Associated symptoms	None	Nausea, hyperacusis, photophobia
Behavior	Continues working	Seeks seclusion
Effect of alcohol	Reduces headache	Worsens headache

*In approximately half of patients, at least at onset.
From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.

- If there is an unusual presentation, headache with red flags, and/or unexpected findings on examination, investigation for other causes is required.

LABORATORY TESTS

Lumbar puncture for history of abrupt-onset headaches and uncertain diagnosis of migraine

IMAGING STUDIES

- Imaging should be done in patients with any of the red flags for secondary headache such as described by the SSNOOP5 mnemonic (see "Differential Diagnosis" above).
- MRI brain with and without contrast is the imaging modality of choice for almost all headache types, although CT head without contrast may be used in the acute setting to evaluate for subarachnoid hemorrhage or other causes of acute intracranial hemorrhage.

Rx TREATMENT

Consider the use of a headache log/diary to identify triggers of headaches, record efficacy of treatments, and track history of headaches.

NONPHARMACOLOGIC THERAPY

- Avoid any identifiable provoking factors: Caffeine, tobacco, and alcohol may trigger attacks, as may dietary or other environmental precipitants (less common).
- Avoid emotional stressors and minimize variations in daily routine with regular sleep, meals, and exercise.
- Relaxation training, behavioral therapy, and biofeedback. Trials have shown that among young persons with chronic migraine, the use of cognitive-behavioral therapy (CBT) plus amitriptyline results in greater reductions in days with headaches and migraine-related disability compared with use of headache education plus amitriptyline.
- Trials in patients with migraine without aura have shown that acupuncture may be associated with long-term reduction in migraine recurrence.[1]

ACUTE ANALGESIC Rx

- Many oral agents are ineffective because of poor absorption from migraine-induced gastric stasis. Nonoral route of administration should be selected in patients with severe nausea or vomiting.
- NSAIDs such as ketorolac, ibuprofen, and naproxen, or combination analgesics, may be used first line for mild migraine headaches.
- Barbiturate-containing compounds should be avoided because they are potentially addictive and promote medication overuse headaches.
- Opioids are not effective for treating patients with migraine headaches and should not be used.

ACUTE ABORTIVE Rx

- Triptans (SC, PO, and intranasal) are the drug class of choice for abortive therapy. Metaanalysis suggests that 10 mg rizatriptan, 40 mg eletriptan, and 12.5 mg almotriptan are most effective. Sumatriptan may also be given, especially in combination with naproxen. Early administration improves effectiveness. Triptans are relatively contraindicated in heart disease and hemiplegic migraine.
- IV antiemetics (prochlorperazine, metoclopramide, chlorpromazine) may be used in addition to triptans. Acute dystonic reactions, QT prolongation, and akathisia are rare side effects. These are generally not used as monotherapy.
- Ergotamine, ergotamine combinations (PO/PR), and dihydroergotamine (DHE 45) (SC, IV, IM, intranasal) have well-documented efficacy against migraines. DHE is usually administered in combination with an antiemetic drug (Table 2) but cannot be given within 24 hr of a triptan.
- IV dexamethasone may be used to prevent recurrence but should not be used frequently due to risk for toxicity.
- Greater and lesser occipital nerve blocks may also be performed to alleviate pain in the acute setting. These injections may be combined with auriculotemporal, supraorbital, and supratrochlear nerve block to achieve anesthesia in the area of perceived pain.
- A recent phase 3 trial with rimegepant, an oral gene-related peptide receptor showed efficacy in acute treatment.[2]

PROPHYLAXIS Rx

- Prophylactic treatment is generally indicated when headaches are disabling more than 5 days of the mo or when symptomatic treatments are contraindicated or not effective. All prophylaxes should be maintained for at least 3 mo before deeming the medication a failure.
- Well-established options for prophylactic treatment include β-blockers (propranolol, timolol, atenolol, metoprolol), tricyclic antidepressants (amitriptyline, nortriptyline), and the antiepileptic drugs topiramate and sodium divalproate (valproic acid).
- CGRP monoclonal antibodies: A new class of injectable drugs that target the CGRP molecule or its receptor have been approved recently. There are currently three FDA-approved drugs in this class, erenumab (Aimovig), fremanezumab (Ajovy), and galcanezumab (Emgality), with more under study. These drugs can be used first line for episodic and chronic migraine.
- Less-established options include calcium channel blockers, selective norepinephrine serotonin reuptake inhibitors, memantine, and other antiepileptic medications.
- Supraorbital transcutaneous electrical stimulation has been approved by the FDA for prophylaxis of episodic migraine and is widely available with a prescription in Europe and North America.
- The FDA has approved injection of onabotulinum toxin A (Botox) for prevention of headaches in adult patients with chronic migraines only (≥15 headache days/mo for ≥3 mo).
- Surgical treatment for migraine using nerve decompression remains highly controversial, with poorly established results. This should be pursued only in collaboration with a headache specialist.

DISPOSITION

With advancing age, many patients will have sustained reduction in frequency of migraine headaches.

REFERRAL

To neurologist if uncertain about diagnosis or treatment not effective

PEARLS & CONSIDERATIONS

- Migraines that change in character or headaches that are different from the patient's typical ones need to be reevaluated.
- Long-term and frequent use of analgesic medications can result in medication overuse or rebound headaches. Early initiation of prophylactic medication is key.
- Avoid use of narcotics, barbiturates, and benzodiazepines because they are habit forming. Narcotics and barbiturates also promote medication overuse headaches.
- Migraine with aura is associated with excess stroke and thromboembolism risk, and is a relative contraindication to the use of combined oral contraceptives in women.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Migraine Headache (Patient Information)

AUTHORS: **Corey Goldsmith, MD,** and **Joseph S. Kass, MD, JD, FAAN**

[1]Zhao L et al: The long-term effect of acupuncture for migraine prophylaxis: a randomized clinical trial, *JAMA Intern Med* 177(4):508–515, 2017.

[2]Lipton RB et al: Rimegepant, an Oral Calcitonin Gene-Related Peptide Receptor Antagonist, for Migraine, *N Engl J Med* 381:142–149, 2019.

TABLE 2 Abortive and Analgesic Therapy for Migraine*

Drug	Route	Dose
Triptans (Serotonin Agonists)		
Sumatriptan	Subcutaneous	6 mg, repeat in 2 hr (max 2 doses/day)
Sumatriptan	Oral	25 mg, 50 mg, 100 mg, repeat in 2 hr (max 200 mg/day)
Sumatriptan	Nasal spray	5 mg, 20 mg, repeat in 2 hr (max 40 mg/day)
Zolmitriptan	Oral	1.25, 2.5 mg, 5 mg, repeat in 2 hr (max 10 mg/day)
Zolmitriptan	Nasal spray	5 mg, repeat in 2 hr (max 10 mg/day)
Zolmitriptan	Orally disintegrating tab	2.5, 5 mg, repeat in 2 hr (max 10 mg/day)
Naratriptan	Oral	1 mg, 2.5 mg, repeat in 4 hr (max 5 mg/day)
Rizatriptan	Oral	5 mg, 10 mg, repeat in 2 hr (max 30 mg/day)
Almotriptan	Oral	6.25 mg, 12.5 mg, may repeat in 2 hr (max 25 mg/day)
Eletriptan	Oral	20 mg, 40 mg, may repeat in 2 hr (max 80 mg/day)
Frovatriptan	Oral	2.5 mg, may repeat in 2 hr (max 7.5 mg/day); may also be used for mini prophylaxis
Ergotamine Preparations		
Ergotamine and caffeine	Oral	2 tablets, may repeat 1 tab q30 min (max 6/day)
Ergotamine and caffeine	Rectal	1 suppository, repeat in 1 hr (max 2/day)
Ergotamine	Sublingual	1 tablet, repeat in 1 hr (max 2/day)
Dihydroergotamine	Intramuscular	0.5-1.0 mg, repeat twice at 1-hr intervals (max 3 mg/attack)
	Subcutaneous	
	Intravenous	
	Nasal spray	
Isometheptene + dichloralphenazone + acetaminophen	Oral	1 to 2 capsules, repeat in 4 hr (max 8/day)
Nonsteroidal Antiinflammatory Drugs		
Acetaminophen + (should not be used alone)	Oral	2 tablets, repeat in 6 hr (max 8/day aspirin + caffeine)
Naproxen	Oral	550-750 mg, repeat in 1 hr (max 3 times/wk)
Meclofenamate	Oral	100-200 mg, repeat in 1 hr (max 3 times/wk)
Flurbiprofen	Oral	50-100 mg, repeat in 1 hr (max 3 times/wk)
Ibuprofen	Oral	200-300 mg, repeat in 1 hr (max 3 times/wk)
Antiemetics		
Promethazine	Oral	50-125 mg
	Intramuscular	No clear benefit in migraine, may be used
Prochlorperazine	Oral	1-25 mg
	Rectal	2.5-25 mg (suppository)
	Intramuscular/IV	5-10 mg, good evidence for strong benefit
Chlorpromazine	Oral	10-25 mg
	Rectal	50-100 mg (suppository)
	Intravenous	Up to 35 mg, use with monitoring, some evidence for good benefit
Trimethobenzamide	Oral	250 mg
	Rectal	200 mg
Metoclopramide	Oral	5-10 mg
	Intramuscular	10 mg
	Intravenous	5-10 mg
Dimenhydrinate	Oral	50 mg

*For side effects and contraindications, consult the manufacturer's drug insert before prescribing any of these drugs.
Modified from Wiederholt WC: *Neurology for non-neurologists,* ed 4, Philadelphia, 2000, WB Saunders.

SUGGESTED READINGS

Charles A: Migraine, *N Engl J Med* 377:553-561, 2017.

Gilmore B, Magdalena M: Treatment of acute migraine headache, *Am Fam Physician* 83(3):271-280, 2011.

Jackson JL et al: Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults, *J Am Med Assoc* 307(16):1736-1745, 2012.

MacGregor EA: In the clinic, migraine, *Ann Int Med* 159(9):ITC5-1, 2013.

BASIC INFORMATION

DEFINITION

Significant cognitive impairment in the absence of dementia with preserved activities of daily living (ADLs). Mild cognitive impairment (MCI) is an intermediate state between normal cognitive function and dementia. The main distinctions between MCI and mild dementia are that in the latter, more than one cognitive domain is invariably involved and substantial interference with daily life is evident.[1]

SYNONYMS

Mild neurocognitive disorder
MCI

ICD-10CM CODE
G31.84 Mild cognitive impairment, so stated

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:
- 12 to 15 cases per 1000 person/yr age ≥65
- 51 to 77 cases per 1000 person/yr age ≥75

PEAK INCIDENCE: In the elderly
PREVALENCE: 15% to 25% in those older than age 70
PREDOMINANT SEX AND AGE: Male, age ≥75
GENETICS: *APOE4* genotype
- Various pathways result in amyloid accumulation and deposition in pre-Alzheimer presenting as MCI.

RISK FACTORS: Male sex, age, lower socioeconomic status, lower educational level

CLINICAL PRESENTATION

- Subjective memory problems, preferably corroborated by another person.
- Preserved functional status (ADLs).
- Normal general thinking and reasoning skills.
- Subtypes of MCI include amnestic (mainly involves memory loss) vs. nonamnestic with involvement of other cognitive domains (single domain vs. multiple domains).
- Domains affected in MCI include memory, visuospatial skills, language, attention, and executive function.
- Olfactory dysfunction may be associated with amnestic MCI and progression to Alzheimer dementia.

ETIOLOGY

Neurodegenerative, vascular, traumatic, depression, or due to underlying medical condition

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Delirium
- Dementia
- Depression
- "Reversible" cognitive impairment:
  1. Medication related (anticholinergics)
  2. Hypothyroidism
  3. Vitamin B_{12} deficiency
- Reversible CNS conditions:
  1. Subdural hematoma
  2. Normal pressure hydrocephalus
  3. Metastatic disease

WORKUP

History:
- Focus on cognitive deficits and impairment.
- Review all medications that may impact cognition (i.e., anticholinergics).
- Rule out depression and delirium.
- Perform functional assessment.
- Additional history from family members or caregivers is important.

Physical exam:
- Check blood pressure
- Neurologic exam to rule out reversible CNS causes of cognitive impairment
- Gait and balance assessment

Cognitive function testing:
- Brief mental status testing using MOCA (Montreal Cognitive Assessment) or SLUMS (St. Louis University Mental Status) for office screening followed by neuropsychological testing if appropriate for specific deficits in cognitive domains. MOCA may be a better tool in identifying and following MCI with higher sensitivity to monitor cognitive decline in longitudinal monitoring.

LABORATORY TESTS

- Complete blood count
- Comprehensive metabolic profile
- TSH
- Vitamin B_{12}

IMAGING STUDIES

- CT imaging can detect most reversible CNS conditions leading to cognitive impairment.
- MRI further evaluates vascular, infectious, neoplastic, and inflammatory conditions.

TREATMENT

- There is insufficient evidence to recommend use of cholinesterase inhibitors for MCI. They are not approved for treating MCI, have shown little efficacy in altering progression to dementia, and can have significant side effects.
- Consider treatment with these medications only if memory complaints appear to be affecting day-to-day quality of life in individual patients or in amnestic subtypes of MCI after risk-versus-benefit discussion with patient and family.

NONPHARMACOLOGIC THERAPY

- Role of cognitive rehabilitation to target specific deficits
- Caregiver education and counseling
- Physical and mental exercises to maintain cognition should be recommended

COMPLEMENTARY & ALTERNATIVE MEDICINE

No clear indications for antioxidants, and studies in humans are inconclusive.

DISPOSITION

- Progression to Alzheimer at the rate of 5% to 15% per yr.
  1. Risk factors for progression to dementia include presence of vascular risk factors, significant cognitive impairment, depression, and presence of extrapyramidal signs.
- Mortality of those with MCI is twice that of those without MCI.
- Two- to threefold increase in risk of nursing home placement in those with MCI.

REFERRAL

Consider referral to a memory specialist if more than just memory is involved or for further evaluation of specific deficits.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients with MCI usually report short-term memory concerns such as misplacing things, not remembering names of people, word-finding difficulties, forgetting day-to-day tasks, not being able to read a book, or not being able to follow a conversation.
- MCI becomes clinically relevant when quality of life is affected such as problems making financial decisions and problems with personal day-to-day interactions.
- Depression should be ruled out prior to making a diagnosis of MCI since it is highly prevalent in the elderly.
- Anticholinergic medication use should be evaluated carefully prior to making a diagnosis of MCI.

PREVENTION

Patients with MCI should be counseled on strategies to prevent progression to dementia. They should remain physically and mentally active, have a well-balanced diet, continue activities that are socially engaging, reduce stress in their lives, and aggressively pursue treatment of vascular risk factors.

PATIENT & FAMILY EDUCATION

- Patients with MCI typically have poor retention and rapid loss of newly learned information.
- For additional information for patients, families, and clinicians: Alzheimer's Association (http://www.alzheimers.org).

AUTHORS: **Birju B. Patel, MD,** and **N. Wilson Holland, MD**

[1]Knopman DS, Petersen RC: Mild cognitive impairment and mild dementia: a clinical perspective, *Mayo Clin Proc* 89:1452, 2014.

Mitral Regurgitation PTG

BASIC INFORMATION

DEFINITION

Mitral regurgitation (MR) is retrograde blood flow into the left atrium resulting from any part of an incompetent mitral valve apparatus. This condition may cause left ventricular (LV) failure, as well as increased left atrial and pulmonary pressures leading to pulmonary hypertension and right-sided heart failure.

SYNONYMS

Mitral insufficiency
MR

ICD-10CM CODES

I34.0	Nonrheumatic mitral (valve) insufficiency
I05.1	Rheumatic mitral insufficiency
I05.9	Mitral valve disease, unspecified
I05.2	Rheumatic mitral stenosis with insufficiency
Q23.3	Congenital mitral insufficiency

EPIDEMIOLOGY & DEMOGRAPHICS

The incidence of MR has increased over the past 30 yr. However, this may be due to increasing availability of echocardiography leading to MR diagnosis rather than to an actual increase in the prevalence of this condition.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Heart sounds:
- Diminished S1 as valve leaflets fail to coapt properly
- Widely split S2 as A2 occurs earlier because of decreased LV ejection time
- Presence of an S3 as a result of increased flow into a dilated LV caused by severe MR with systolic impairment

Heart murmurs:
- Holosystolic, high-pitched, "blowing" murmur is most easily audible at apex with radiation to base, left axilla, or back. There is a poor correlation between the intensity of the systolic murmur and the degree of regurgitation. However, an early diastolic to middiastolic rumble (pseudomitral stenosis) suggests severe MR.
- The murmur of acute MR (e.g., from papillary muscle rupture) can be very soft or inaudible because of a large regurgitant volume entering a noncompliant left atrium. This causes an acute rise in left atrial pressure and a decline in LV filling pressure, and thus a lack of significant gradient for an audible murmur.
- Hyperdynamic apex, sometimes with palpable LV lift and apical thrill.
- Symptomatic patients with MR generally present with the following:
  1. Symptoms suggestive of heart failure (fatigue, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema)
  2. Hemoptysis (caused by pulmonary hypertension)
  3. Atrial fibrillation

ETIOLOGY

Primary MR:
- Idiopathic myxomatous degeneration of the mitral valve, mitral valve prolapse (most common cause of MR in industrialized countries)
- Papillary muscle dysfunction or rupture (typically as a result of an inferior wall myocardial infarction)
- Ruptured chordae tendineae
- Infective endocarditis
- Calcified mitral valve annulus
- Rheumatic valvulitis (may be combined with mitral stenosis; common in developing countries)
- Systemic lupus erythematosus (Libman-Sacks endocarditis)
- Drugs: Fenfluramine, dexfenfluramine, pergolide, cabergoline
- Congenital cleft valve
- Ischemic MR due to papillary muscle dysfunction from multivessel coronary artery disease (CAD)

Secondary MR:
- Hypertrophic cardiomyopathy
- LV dilation (e.g., secondary to dilated cardiomyopathy)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hypertrophic cardiomyopathy
- Tricuspid regurgitation
- Aortic stenosis
- Aortic sclerosis
- Ventricular septal defect
- Atrial septal defect

WORKUP

- Diagnostic workup consists of echocardiography, ECG, and chest radiograph; cardiac catheterization is sometimes needed to confirm severity of the disease.
- Tables 1 and 2 summarize stages of chronic primary and chronic secondary MR.
- Recent studies suggest that in patients with severe asymptomatic MR, normal LV function and elevations of brain natriuretic peptide (BNP) >105 pg/ml have an independent and additive prognostic value that may identify high-risk patients and aid in the selection of patients for early surgery.

IMAGING STUDIES

- Echocardiography (Fig. 1): Findings include dilated left atrium, hyperdynamic left ventricle, erratic motion of the leaflet in patients with ruptured chordae tendineae, and color flow Doppler with evidence of MR. The most important aspect of the echocardiographic examination is the quantification of the severity of MR (Table 3). A vena contracta width >0.7 cm, a regurgitant volume >60 ml, regurgitant orifice area >0.40 cm^2 by PISA (proximal isovelocity surface area), and systolic pulmonary vein flow reversal are all echocardiographic criteria of severe MR.
- Chest x-ray:
  1. Left atrial enlargement, LV enlargement
  2. Possible pulmonary congestion, although most often normal
- ECG:
  1. Left atrial enlargement
  2. LV hypertrophy
  3. Atrial fibrillation
- Cardiac catheterization: To confirm severity of MR, or to rule out presence of coronary artery disease in patients being evaluated for surgical replacement.
- Can consider cardiac MRI in cases where echocardiography is limited or LV function/dimensions are borderline, or when clinical condition and echocardiographic findings are discordant.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Salt restriction
- Surgical repair or replacement (see the following)

ACUTE GENERAL Rx

- Medical: Medical therapy is primarily directed toward treatment of the source or its complications (e.g., atrial fibrillation, ischemic heart disease, infective endocarditis, hypertension, and heart failure).
  1. The utility of afterload reduction to decrease the regurgitant fraction and increase cardiac output depends upon the etiology of MR. In acute MR, intravenous nitroprusside has shown some utility. Long-term use of oral afterload reducers (e.g., ACE inhibitors or angiotensin receptor blockers), while they do not slow the progression of MR, should be implemented when other indications such as hypertension and LV dysfunction are present.
  2. Control ventricular response in atrial fibrillation when rapid ventricular response is present. Use anticoagulants if atrial fibrillation occurs. Note that current guidelines do not consider AF in patients with MR "valvular," and non–vitamin K anticoagulation agents may be used for stroke prophylaxis.
  3. Diuresis and achieving a euvolemic state may significantly decrease the degree of functional MR caused by volume overload and heart failure.
- Surgery: Surgery is the only definitive treatment for MR. Although no randomized trial of mitral valve repair vs. replacement exists, repair is favored over replacement in degenerative mitral valve disease due to its lower perioperative risk, improved event-free survival, freedom from complications of prosthetic valves, and better postoperative LV function. It is a class I indication in patients with the following diagnoses (Fig. 2):
  1. Acute severe MR
  2. Symptomatic patients with severe primary MR despite optimal medical therapy and LVEF >30%, LV dilation, severe MR by echo criteria
  3. Asymptomatic patients with severe MR but with evidence of declining LV function (EF <60% but >30%) or progressive dilation (LV at end-systole >40 mm)

TABLE 1 Stages of Chronic Primary Mitral Regurgitation

Grade	Definition	Valve Anatomy	Valve Hemodynamics*	Hemodynamic Consequences	Symptoms
A	**At risk for MR**	Mild mitral valve prolapse with normal coaptation Mild valve thickening and leaflet restriction	No MR jet or small central jet area <20% LA on Doppler Small vena contracta <0.3 cm	None	None
B	**Progressive MR**	Severe mitral valve prolapse with normal coaptation Rheumatic valve changes with leaflet restriction and loss of central coaptation Previous IE	Central jet MR 20%-40% LA or late systolic eccentric jet MR Vena contracta <0.7 cm Regurgitant volume <60 ml Regurgitant fraction <50% ERO <0.40 cm^2 Angiographic grade 1-2+	Mild LA enlargement No LV enlargement Normal pulmonary pressure	None
C	**Asymptomatic severe MR**	Severe mitral valve prolapse with loss of coaptation or flail leaflet Rheumatic valve changes with leaflet restriction and loss of central coaptation Previous IE Thickening of leaflets with radiation heart disease	Central jet MR >40% LA or holosystolic eccentric jet MR Vena contracta ≥0.7 cm Regurgitant volume ≥60 ml Regurgitant fraction ≥50% ERO ≥0.40 cm^2 Angiographic grade 3-4+	Moderate or severe LA enlargement LV enlargement Pulmonary hypertension may be present at rest or with exercise C1: LVEF >60% and LVESD <40 mm C2: LVEF ≤60% and LVESD ≥40 mm	None
D	**Symptomatic severe MR**	Severe mitral valve prolapse with loss of coaptation or flail leaflet Rheumatic valve changes with leaflet restriction and loss of central coaptation Previous IE Thickening of leaflets with radiation heart disease	Central jet MR >40% LA or holosystolic eccentric jet MR Vena contracta ≥0.7 cm Regurgitant volume ≥60 ml Regurgitant fraction ≥50% ERO ≥0.40 cm^2 Angiographic grade 3-4+	Moderate or severe LA enlargement LV enlargement Pulmonary hypertension present	Decreased exercise tolerance Exertional dyspnea

ERO, Effective regurgitant orifice; *IE,* infective endocarditis; *LA,* left atrium; *LV,* left ventricle; *LVEF,* left ventricular ejection fraction; *LVESD,* left ventricular end-systolic dimension; *MR,* mitral regurgitation.

*Several valve hemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient. Classification of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

From Nishimura RA et al: 2014 AHA/ACCF guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 63:e57, 2014.

TABLE 2 Stages of Chronic Secondary Mitral Regurgitation

Grade	Definition	Valve Anatomy	Valve Hemodynamics*	Associated Cardiac Findings	Symptoms
A	At risk of MR	Normal valve leaflets, chords, and annulus in a patient with coronary disease or a cardiomyopathy	No MR jet or small central jet area <20% LA on Doppler Small vena contracta <0.30 cm	Normal or mildly dilated LV size with fixed (infarction) or inducible (ischemia) regional wall motion abnormalities Primary myocardial disease with LV dilation and systolic dysfunction	Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
B	Progressive MR	Regional wall motion abnormalities with mild tethering of mitral leaflet Annular dilation with mild loss of central coaptation of the mitral leaflets	ERO <0.20 cm^2† Regurgitant volume <30 ml Regurgitant fraction <50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction due to primary myocardial disease	Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
C	Asymptomatic severe MR	Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet Annular dilation with severe loss of central coaptation of the mitral leaflets	ERO ≥0.20 cm^2† Regurgitant volume ≥30 ml Regurgitant fraction ≥50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction due to primary myocardial disease	Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
D	Symptomatic severe MR	Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet Annular dilation with severe loss of central coaptation of the mitral leaflets	ERO ≥0.20 cm^2† Regurgitant volume ≥30 ml Regurgitant fraction ≥50%	Regional wall motion abnormalities with reduced LV systolic function LV dilation and systolic dysfunction due to primary myocardial disease	HF symptoms due to MR persist even after revascularization and optimization of medical therapy Decreased exercise tolerance Exertional dyspnea

ERO, Effective regurgitant orifice; *HF,* heart failure; *LA,* left atrium; *LV,* left ventricle; *MR,* mitral regurgitation.

*Several valve hemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

†The measurement of the proximal isovelocity surface area by two-dimensional transthoracic echocardiogram (TTE) in patients with secondary MR underestimates the true ERO because of the crescentic shape of the proximal convergence.

From Nishimura RA et al: 2014 AHA/ACCF guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 63:e57, 2014.

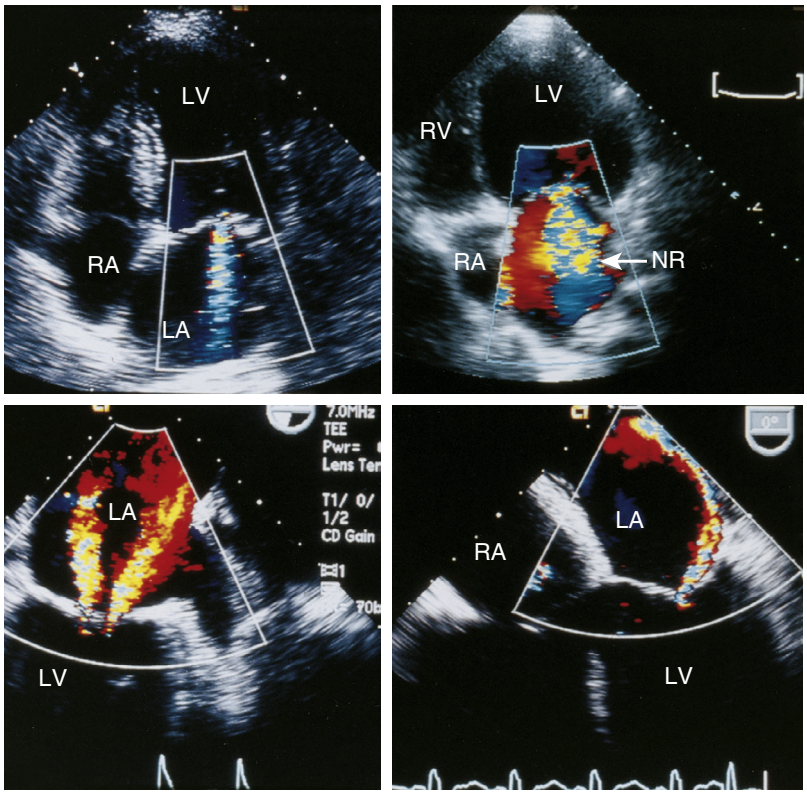

FIG. 1 Mitral regurgitation. Four panels depicting varying degrees of mitral regurgitation; the two top panels are apical four-chamber transthoracic views showing, on the left, mild mitral regurgitation and, on the right, moderate to severe mitral regurgitation. On the left, note the relatively narrow jet directed from the tips of the mitral valve toward the posterior left atrial wall. On the right, note the larger jet, filling approximately 40% of the left atrial cavity. The two bottom panels are transesophageal echocardiograms. On the left, note the mitral regurgitation occurring in two discrete jets and, on the right, the highly eccentric jet, which courses along the extreme lateral wall of the left atrium. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (From Zipes DP et al [eds]: *Braunwald's heart disease,* ed 7, Philadelphia, 2005, WB Saunders.)

TABLE 3 Mitral Regurgitation Severity*

	I (Mild)	II (Moderate)	III (Moderate)	IV (Severe)
MR = jet (%LA)	<15	15-30	35-50	>50
Spectral Doppler	Faint	—	—	Dense
Vena contracta	<3 mm	—	—	≥7 mm
Pulmonary vein flow	S > D	Normal to systolic blunting	Systolic blunting	Systolic reversal
RV (ml)	<30	30-44	45-59	≥60
ERO (cm2)	<0.2	0.2-0.29	0.3-0.39	≥0.40
PISA	Small	—	—	Large

D, Antegrade flow in diastole; *ERO,* effective regurgitant orifice; %*LA,* percentage of left atrial area encompassed by the MR jet with color flow Doppler; *MR,* mitral regurgitation; *PISA,* proximal isovelocity surface area; *RV,* regurgitant volume; *S,* antegrade flow in systole.

*For some parameters, the observation is valid at the extremes of MR severity and there may be marked overlap in intermediate (grades II, III) MR. In these instances, no value is presented.

From Zipes DP et al (eds): *Braunwald's heart disease,* ed 7, Philadelphia, 2005, WB Saunders; and the 2017 American Society of Echocardiography Guidelines.

4. Concomitant mitral valve repair or MVR is indicated in patients with chronic severe primary MR undergoing cardiac surgery for other indications

- Surgery is a class IIa (reasonable) recommendation in:
  1. Severe MR with new-onset atrial fibrillation, even if asymptomatic.
  2. Asymptomatic severe MR with pulmonary hypertension (≥50 mm Hg at rest or ≥60 mm Hg during exercise).
  3. Asymptomatic severe MR secondary to flail leaflet.
  4. A recent study of early surgical intervention for severe MR secondary to a flail leaflet in patients with asymptomatic disease shows greater long-term survival and reduced rates of heart failure when compared with medical therapy alone.
     a. Asymptomatic severe MR with preserved LVEF (>60%) and size (<40 mm in end-systole) in whom the likelihood of successful repair without residual MR is >95% and operative mortality is <1%.
- Surgery is a class IIb recommendation in symptomatic patients (New York Heart Association [NYHA] class III to IV) with severe MR with severe LV dysfunction or dilatation (LVEF <30% or LV at end-systole >55 mm, respectively) in whom LV dysfunction is not the primary cause for the MR as well as functional MR where it is secondary to LV dysfunction.
- Quantitative grading of MR is a powerful predictor of the clinical outcome of asymptomatic MR. In general, patients with regurgitant orifice areas of ≥40 mm^2 should be considered for prompt surgery, whereas those with orifices between 20 and 39 mm^2 can be followed closely.
- Percutaneous mitral valve repair methods are currently being investigated. The MitraClip device is FDA approved for use in patients with significant symptomatic degenerative MR (>3+) who are too high risk for surgery. The device is a catheter-delivered clip that grasps and approximates the edges of the mitral leaflets at the origin of the regurgitant jet. Early data are limited and had not demonstrated a significant efficacy in MR reduction compared with surgical replacement; however, in a recent trial, investigators compared guideline-directed medical therapy (GDMT) alone vs. transcatheter mitral repair with MitraClip plus GDMT in patients with severe MR who were not surgical candidates. After 24 mo, heart failure hospitalizations were 36% in the MitraClip group versus 68% in the medical therapy group. Device therapy also improved symptoms and quality of life, and decreased all-cause mortality (29% in device vs. 46% in the GDMT-only group).[1]
- Ischemic MR has been a source of controversy as to whether moderate or greater MR should be fixed at the time of revascularization with coronary artery bypass graft surgery (CABG). Mitral valve repair can be considered at the time of CABG in moderate MR, and mitral valve repair is reasonable for severe MR (class IIa) in the presence of a basal aneurysm or dyskinesis, significant leaflet tethering due to wall motion abnormalities, and moderate-to-severe LV remodeling (LV end-diastolic diameter >65 mm).
- American College of Cardiology/American Heart Association (ACC/AHA) guidelines for intervention for chronic primary MR are summarized in Table 4. Interventions for chronic secondary MR are described in Table 5.

DISPOSITION

Prognosis is generally good unless there is significant impairment of LV function or significantly elevated pulmonary artery pressures. Most patients remain asymptomatic for many yr (average interval from diagnosis to onset of symptoms is 16 yr). In patients with chronic severe MR, MR is commonly progressive, with onset of other symptoms or LV dysfunction

[1] Stone GW et al: Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 379:2307-18, 2018.

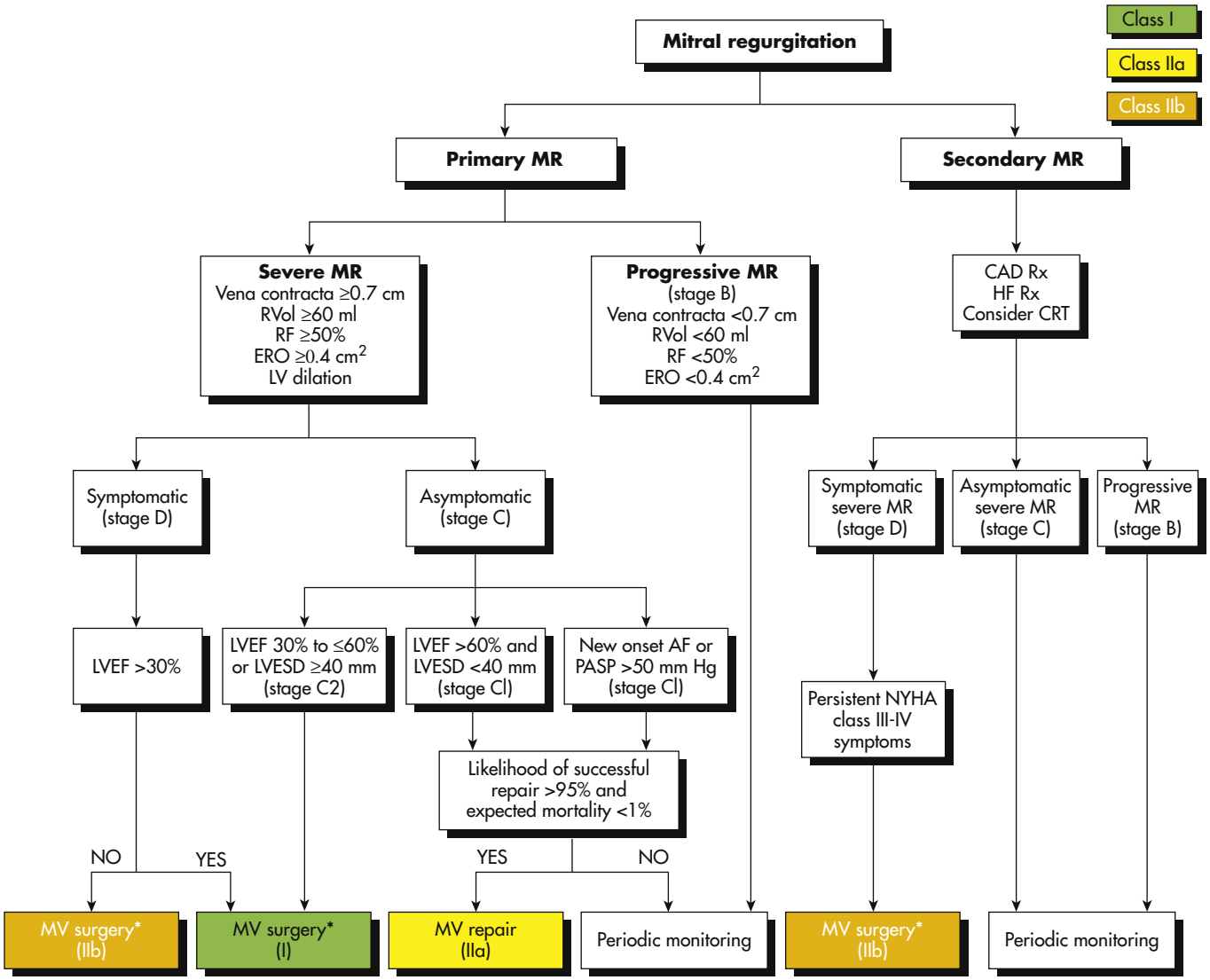

FIG. 2 Indications for surgery for MR. *Mitral valve repair is preferred over MVR when possible. *AF,* Atrial fibrillation; *CAD,* coronary artery disease; *CRT,* cardiac resynchronization therapy; *ERO,* effective regurgitant orifice; *HF,* heart failure; *LV,* left ventricle; *LVEF,* left ventricular ejection fraction; *LVESD,* left ventricle end-systolic dimension; *MR,* mitral regurgitation; *MV,* mitral valve; *MVR,* mitral valve replacement; *NYHA,* New York Heart Association; *PASP,* pulmonary artery systolic pressure; *RF,* regurgitant fraction; *RVol,* regurgitant volume; *Rx,* therapy. (From Nishimura RA et al: ACC/AHA focused update of valvular heart disease guideline, *J Am Coll Cardiol* 70:254-289, 2017.)

within 6 to 10 yr. However surgery should be advised well before the onset of symptoms in case of worsening LVEF and LV systolic dimensions and presence of pulmonary hypertension or atrial fibrillation, all of which are poor prognostic signs.

REFERRAL

- Surgical referral in selected patients (see "Acute General Rx"). Emergency surgery is usually necessary in patients with acute MR caused by ruptured papillary muscle or chordae tendineae after myocardial infarction.
- Mitral valve repair can also be accomplished with percutaneous implantation of a MitraClip device in patients who are too high risk for surgery, although exact indications for this procedure are still evolving.

PEARLS & CONSIDERATIONS

COMMENTS

- Although vasodilators and other agents should be used to treat hypertension in patients with severe MR, there is no evidence that they will delay the need for eventual valve surgery, which is the definitive treatment for severe MR.
- In 2007, the AHA guidelines for prevention of infectious endocarditis were revised and routine antibiotic prophylaxis to undergo dental or other invasive procedures is no longer recommended, unless the patient has had prior endocarditis.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Mitral Regurgitation (Patient Information)

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TABLE 4 Updated ACC/AHA Guidelines for Intervention for Chronic Primary Mitral Regurgitation (MR)[1]

Class	Indication	LOE
I	MV surgery for symptomatic patients with severe primary MR (stage D) and LVEF greater than 30%.	B
	MV surgery for asymptomatic patients with severe primary MR and LV dysfunction (LVEF 30% to 60% and/or LVESD ≥40 mm, stage C2).	B
	MV repair in preference to MVR when surgical treatment for patients with severe primary MR limited to the posterior leaflet.	B
	MV repair in preference to MVR when surgical treatment for patients with severe primary MR involving the anterior leaflet or both leaflets when a successful and durable repair can be accomplished.	B
	Concomitant MV repair or replacement in patients with severe primary MR undergoing cardiac surgery for other indications.	B
IIa	MV repair is reasonable in asymptomatic patients with severe primary MR (stage C1) with preserved LV function (LVEF >60% and LVESD <40 mm) in whom the likelihood of a successful and durable repair without residual MR is greater than 95% with an expected mortality less than 1% when performed at a Heart Valve Center of Excellence.	B
	MV surgery is reasonable for asymptomatic patients with severe primary MR and preserved LV function (LVEF >60% and LVESD <40 mm) with a progressive increase in LV size or decrease in LVEF on serial imaging studies. *(New 2017)*	C
	MV repair is reasonable for asymptomatic patients with severe nonrheumatic primary MR (stage C1) and preserved LV function in whom there is a high likelihood of a successful and durable repair with (1) new onset of AF or (2) resting pulmonary hypertension (PA systolic pressure >50 mm Hg).	B
	Concomitant MV repair is reasonable in patients with moderate primary MR (stage B) undergoing cardiac surgery for other indications.	C
IIb	MV surgery may be considered in symptomatic patients with severe primary MR and LVEF of 30% or less (stage D).	C
	Transcatheter MV repair may be considered for severely symptomatic patients (NYHA class III/IV) with severe primary MR (stage D) who have a reasonable life expectancy, but a prohibitive surgical risk because of severe comorbidities.	B
III	MVR should not be performed for the treatment of isolated severe primary MR limited to less than one half of the posterior leaflet unless MV repair has been attempted and was unsuccessful.	B

[1]Kapadia S, Stewart WJ, Anderson WN et al: Outcomes of inoperable symptomatic aortic stenosis patients not undergoing aortic valve replacement: insight into the impact of balloon aortic valvuloplasty from the PARTNER Trial (Placement of AoRtic TraNscathetER Valve Trial), *JACC Cardiovasc Interv* 8:324-333, 2015.

ACC/AHA, American College of Cardiology/American Heart Association;*AF,* atrial fibrillation; *LOE,* level of evidence; *LV,* left ventricular; *LVEF,* LV ejection fraction; *LVESD,* LV end-systolic dimension; *MR,* mitral regurgitation; *MV,* mitral valve; *MVR,* mitral valve replacement; *NYHA,* New York Heart Association; *PA,* pulmonary artery.

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 5 Updated ACC/AHA Guidelines for Intervention for Chronic Secondary Mitral Regurgitation (MR)[1]

Class	Indication	LOE
IIa	MV surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR.	C
	It is reasonable to choose chordal-sparing MVR over downsized annuloplasty repair if operation is considered for severely symptomatic patients (NYHA class III/IV) with chronic severe ischemic MR (stage D) and persistent symptoms despite GDMT for heart failure. (*New 2017*)	B
IIb	MV surgery may be considered for severely symptomatic patients (NYHA class III-IV) with chronic severe secondary MR (stage D).	B
	In patients with chronic, moderate, or ischemic MR (stage B) undergoing CABG, the usefulness of mitral valve repair is uncertain. (*Modified 2017*)	B

[1]Kapadia S, Stewart WJ, Anderson WN et al: Outcomes of inoperable symptomatic aortic stenosis patients not undergoing aortic valve replacement: insight into the impact of balloon aortic valvuloplasty from the PARTNER Trial (Placement of AoRtic TraNscathetER Valve Trial). JACC Cardiovasc Interv 8:324-333, 2015.

ACC/AHA, American College of Cardiology/American Heart Association; *AVR,* aortic valve replacement; *CABG,* coronary artery bypass graft surgery; *GDMT,* guideline-directed medical therapy; *LOE,* level of evidence; *MV,* mitral valve; *NYHA,* New York Heart Association.

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

SUGGESTED READINGS

Acker MA et al: Mitral-valve repair versus replacement for severe ischemic mitral regurgitation, *N Engl J Med* 370:23-32, 2014.

Feldman T et al: Percutaneous repair of surgery for mitral regurgitation, *N Engl J Med* 364:1395-1406, 2011.

Foster E: Mitral regurgitation due to degenerative mitral valve disease, *N Engl J Med* 363:156-165, 2010.

Nishimura RA et al: ACC/AHA focused update of valvular heart disease guideline, *J Am Coll Cardiol* 70(2):254-289, 2017.

Nishimura RA et al: ACC/AHA guidelines for the management of patients with valvular heart disease, *J Am Coll Cardiol* 63(22):e57-e185, 2014.

Suri RM et al: Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets, *J Am Med Assoc* 310(6):609-16, 2013.

BASIC INFORMATION

DEFINITION

Mitral stenosis is a narrowing of the mitral valve orifice that prevents proper opening during diastole and obstruction of blood flow from the left atrium to the left ventricle. Due to thickening of the leaflets there is restricted movement. The obstruction leads to increased pressure in the left atrium, pulmonary vasculature, and the right side of the heart. The cross section of a normal orifice measures 4 to 6 cm^2. Symptoms usually develop with exercise when the orifice measures <2.5 cm^2, and symptoms may develop at rest when the orifice is <1.5 cm^2.

SYNONYM

MS

ICD-10CM CODES

I05.0	Rheumatic mitral stenosis
I05.2	Rheumatic mitral stenosis with insufficiency
I34.2	Nonrheumatic mitral (valve) stenosis
Q23.2	Congenital mitral stenosis

EPIDEMIOLOGY & DEMOGRAPHICS

- The predominant cause of mitral stenosis is rheumatic heart disease; however, the occurrence of mitral valve stenosis has decreased worldwide over the past 30 yr (particularly in developed countries) as a result of declining incidence of rheumatic fever due to appropriate antibiotic use.
- Rheumatic heart disease has a predilection for the mitral valve, aortic valve, and to some extent the tricuspid valve.
- The incidence of MS is higher in women (2:1 female-to-male ratio).
- There is high prevalence of rheumatic heart disease in developing countries.
- Outbreaks of rheumatic fever in the U.S. are due to increased virulence of a streptococcal strain or enhanced immigration from where rheumatic heart disease is prevalent.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Dyspnea is the most common symptom, along with fatigue and decreased exercise capacity. These symptoms occur due to an inability to increase cardiac output, especially with exercise, and elevated pulmonary capillary wedge pressures, with resultant increase in pulmonary artery pressures. Stages of mitral stenosis are summarized in Table 1.
- "Mitral facies" which are pinkish-purple patches on the cheek due to low cardiac output and vasoconstriction, usually indicate severe MS.
- Paroxysmal nocturnal dyspnea (PND) and orthopnea secondary to elevated left atrial pressure may occur.
- Acute pulmonary edema may occur after an increase in flow across the mitral valve secondary to an increase in cardiac output or heart rate (exertion, tachyarrhythmias, fever, anemia, etc.).
- Pulmonary hypertension that results from chronically elevated pulmonary capillary wedge pressures can lead to right ventricular (RV) dysfunction and signs and symptoms of right heart failure (hepatomegaly, pulsatile liver, peripheral edema, ascites).
- The left ventricle is typically "protected" in mitral stenosis and exists in a low-pressure state; however, MS often coexists with mitral regurgitation and occasionally with aortic valve dysfunction, both of which can cause left ventricular dysfunction.
- Hemoptysis can be present secondary to rupture of thin-walled dilated bronchial veins due to an abrupt increase in left atrial pressure.
- Systemic embolic events are caused by left atrial thrombi. These are associated with atrial fibrillation 80% of the time, since mitral stenosis leads to left atrial enlargement, which is a predisposing factor for atrial arrhythmias.
- Atrial fibrillation is more prevalent in patients with more severe MS, increasing age, and other valvular abnormalities.
- Chest pain can be caused by RV pressure overload and/or concomitant coronary artery disease in up to 15% of patients.
- Loud first heart sound (S1) caused by delayed valve closure preceded by an opening snap and rapid rising left ventricular (LV) pressure.
- A low-pitched rumbling diastolic murmur is heard best at the apex. The intensity of the murmur is not related to the severity of the stenosis, but the duration is holodiastolic in severe MS.
- An opening snap (OS) caused by tensing of the valve leaflets after the cusps have opened completely. The OS follows S2 by 0.03 to 0.14 sec, and the shorter the S2 to OS interval, the more severe the MS, due to the increasing left atrial pressures.
- Prominent A wave on the pulmonary capillary wedge pressure tracing. This is analogous to the prominent A wave seen in systemic venous pressure tracings with tricuspid stenosis.
- A diastolic thrill may be palpable at the apex, especially with the patient in the left lateral recumbent position.
- A left parasternal heave secondary to RV hypertrophy and pulmonary hypertension.
- An accentuated P2 and/or a soft, early diastolic decrescendo murmur (Graham Steell murmur) caused by pulmonary regurgitation may be present in patients with pulmonary hypertension (not specific for mitral stenosis).
- Hoarseness due to the enlargement of the left atrium compressing the recurrent laryngeal nerve.

TABLE 1 Stages of Mitral Stenosis

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	**At risk for MS**	Mild valve doming during diastole	Normal transmitral flow velocity	None	None
B	**Progressive MS**	Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered MVA >1.5 cm^2	Increased transmitral flow velocities MVA >1.5 cm^2 Diastolic pressure half-time <150 msec	Mild to moderate LA enlargement Normal pulmonary pressure at rest	None
C	**Asymptomatic severe MS**	Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered MVA ≤1.5 cm^2 (MVA ≤1 cm^2 with very severe MS)	MVA ≤1.5 cm^2 (MVA ≤1 cm^2 with very severe MS) Diastolic pressure half-time ≥150 msec (Diastolic pressure half-time ≥220 msec with very severe MS)	Severe LA enlargement Elevated PASP >30 mm Hg	None
D	**Symptomatic severe MS**	Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered MVA ≤1.5 cm^2	MVA ≤1.5 cm^2 (MVA ≤1 cm^2 with very severe MS) Diastolic pressure half-time ≥150 msec (Diastolic pressure half-time ≥220 msec with very severe MS)	Severe LA enlargement Elevated PASP >30 mm Hg	Decreased exercise tolerance Exertional dyspnea

The transmitral mean pressure gradient should be obtained to determine the full hemodynamic effect of the MS and usually is >5 to 10 mm Hg in severe MS; however, because of the variability of the mean pressure gradient with heart rate and forward flow, it has not been included in the criteria for severity.

LA, Left atrium; *MS,* mitral stenosis; *MVA,* mitral valve area; *PASP,* pulmonary artery systolic pressure.

From Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.

- Straightening of the left heart border seen on chest radiography indicative of left atrial enlargement.
- Fig. 1 shows schematic representations of LV, aortic, and left atrial (LA) pressures, showing normal relationships and alterations with mild and severe MS.

ETIOLOGY

- Rheumatic fever (RF) is the predominant cause of MS. RF causes thickening of the leaflet tips, commissure fusion, and chordal shortening and fusion. This leads to the classic doming of the leaflets in diastole due to fusion of the leaflet tips at the commissures. Rheumatic fever involves the leaflet tips first with progression toward the annulus. This is opposite of mitral annular calcification, which typically starts in the annulus and proceeds out to the leaflet tips, leading to mitral stenosis in severe cases.
- Congenital defect (parachute valve) has the usual two mitral leaflets, but the chordae, instead of diverging to insert into two papillary muscles, converge into one major papillary muscle, which allows little mobility of the leaflets, as in cor triatriatum (heart with three atria), in which there is a thin membrane that obstructs the pulmonary vein flow and simulates mitral stenosis.
- Rare causes are severe mitral annular calcification usually seen in end-stage renal disease patients, endomyocardial fibroelastosis, malignant carcinoid syndrome, systemic lupus erythematosus, Whipple disease, Fabry disease, rheumatoid arthritis, and 3,4-methylenedioxy-methamphetamine (MDMA) use.
- Atrial septal defect in association with rheumatic mitral stenosis is termed Lutembacher syndrome.
- Medications: Ergot alkaloids (methysergide and ergotamine).

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Left atrial myxoma
- Ball valve thrombus
- Other valvular abnormalities (e.g., tricuspid stenosis, mitral regurgitation)
- Atrial septal defect

IMAGING STUDIES

- Echocardiography (Fig. 2):
  1. Two-dimensional echocardiogram can measure valve area by direct planimetry or calculate it by the Doppler pressure half-time method (this may be inaccurate in patients with concomitant diastolic dysfunction, atrial septal defects, or aortic insufficiency, and those who recently have undergone mitral valvuloplasty), or the continuity equation can be used to calculate the valve area. It also can be measured using the proximal isovelocity surface area method. A valve area ≤1.5 cm^2 is consistent with severe MS (and ≤1.0 cm^2 with very severe MS). The transmitral gradient can also be calculated. A mean gradient of >10 mm Hg indicates severe MS, a gradient of 5 to 10 mm Hg is consistent with moderate MS, and 0 to 5 mm Hg is consistent with mild MS or no MS.
  2. M-Mode echocardiography will also show a markedly diminished E-to-F slope of the anterior mitral valve leaflet during diastole. There can be loss of the "A-wave" due to increased left atrial pressure or the

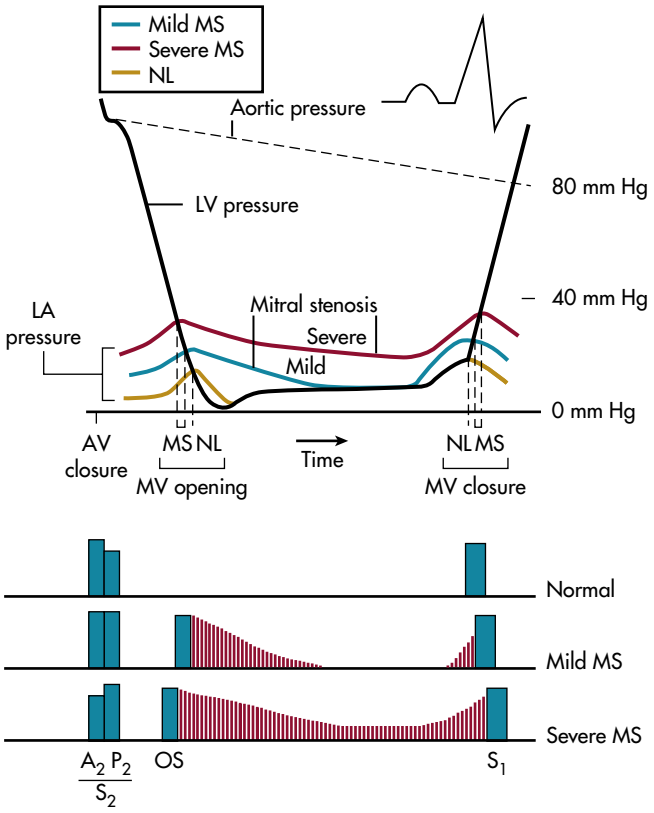

FIG. 1 Schematic representation of left ventricular *(LV)*, aortic, and left atrial *(LA)* pressures, showing normal relationships and alterations with mild and severe mitral stenosis *(MS)*. Corresponding classic auscultatory signs of MS are shown at the bottom. The higher left atrial V wave of severe MS causes earlier pressure crossover and earlier mitral valve *(MV)* opening, leading to a shorter time interval between aortic valve *(AV)* closure and the opening snap *(OS)*. The higher left atrial end-diastolic pressure with severe MS also results in later closure of the mitral valve. With severe MS, the diastolic rumble becomes longer and there is accentuation of the pulmonic component *(P_2)* of the second heart sound *(S_2)* in relation to the aortic component *(A_2)*. *NL*, Normal limits. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

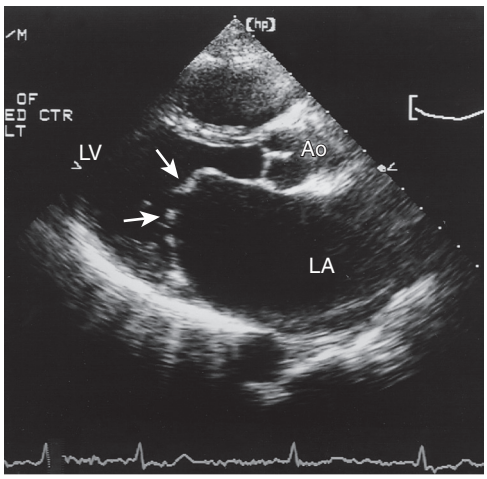

FIG. 2 Mitral stenosis. Parasternal long-axis view of a patient with mitral stenosis and a pliable noncalcified mitral valve leaflet. Note the "doming" motion of the mitral valve leaflets *(arrows)*. Valves with these morphologic features are excellent candidates for percutaneous balloon valvotomy. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle. (From Zipes DP et al [eds]: *Braunwald's heart disease,* ed 7, Philadelphia, 2005, WB Saunders.)

presence of associated atrial fibrillation. There is also fusion of the commissures, resulting in "doming" of the leaflets during diastole.

3. Grading of leaflet thickness, mobility, calcification, and subvalvular thickening (Wilkins score) with a score of 0 to 4 for each characteristic can predict hemodynamic results and outcome of balloon mitral valvuloplasty (a low score of less than 8 is favorable for balloon valvuloplasty and a high score is unfavorable). A score above 8 would favor a surgical approach. In addition, mitral regurgitation that is greater than mild would preclude a balloon mitral valvuloplasty procedure.
4. Doppler echocardiography can be used to assess for pulmonary hypertension and to give an estimate of the pulmonary artery systolic pressure at rest and with exercise.
5. Patients with known mitral stenosis: A follow-up echocardiography is recommended to assess for pulmonary artery pressures and valve gradient, and to determine the optimal timing of surgical or percutaneous intervention. According to the 2014 American Heart Association/American College of Cardiology (AHA/ACC) valve guideline, echocardiogram is recommended every yr for very severe MS with mitral valve area <1.0 cm^2, every 1 to 2 yr with severe MS with mitral valve area ≤1.5 cm^2, and every 3 to 5 yr with progressive MS with mitral valve area >1.5 cm^2.

- Chest radiograph:
  1. Straightening of the left cardiac border caused by enlarged left atrium
  2. Left atrial enlargement on lateral chest radiograph
  3. Prominence of pulmonary arteries that indicates pulmonary hypertension
  4. Possible pulmonary congestion and edema (Kerley B lines)
- ECG:
  1. RV hypertrophy; right axis deviation caused by pulmonary hypertension
  2. Left atrial enlargement (broad, biphasic P waves in lead V1 and duration of P-waves >0.11 sec in lead II); this is termed "P-mitrale"
  3. Atrial fibrillation
- Cardiac catheterization:
  1. Allows the measurement of pulmonary artery pressure and transmitral pressure gradients at rest or with exercise (supine biking or raising weights with arms while lying supine).
  2. Allows the measurement of transmitral flow and calculation of the valve area.
  3. Is not routinely recommended for the evaluation of MS but is useful when the echocardiographic findings are nondiagnostic or discrepant with the clinical scenario.
  4. Cardiac catheterization in addition to echocardiography can be used to monitor the hemodynamics during a balloon mitral valvuloplasty procedure.

TABLE 2 Approaches to Mechanical Relief of Mitral Stenosis

Approach	Advantages	Disadvantages
Closed surgical valvotomy	Inexpensive Relatively simple Good hemodynamic results in selected patients Good long-term outcome	No direct visualization of valve Only feasible with flexible, noncalcified valves Contraindicated with MR grade higher than 2+ Surgical procedure with general anesthesia
Open surgical valvotomy	Visualization of valve allows directed valvotomy. Concurrent annuloplasty for MR is feasible.	Best results with flexible, noncalcified valves Surgical procedure with general anesthesia
Valve replacement	Feasible in all patients regardless of extent of valve calcification or severity of MR	Surgical procedure with general anesthesia Effect of loss of annular-papillary muscle continuity on LV function Prosthetic valve Chronic anticoagulation
Balloon mitral valvotomy	Percutaneous approach Local anesthesia Good hemodynamic results in selected patients Good long-term outcome	No direct visualization of valve Only feasible with flexible noncalcified valves Contraindicated with MR grade higher than 2+

LV, Left ventricular; *MR,* mitral regurgitation.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Decrease level of activity in symptomatic patients, and salt restriction if pulmonary congestion is present.

ACUTE GENERAL Rx

- Medical:
  1. Anticoagulation for the prevention of systemic embolic events in patients with MS and:
     a. Atrial fibrillation: In patients with atrial fibrillation and rheumatic mitral stenosis, anticoagulation with a vitamin K antagonist with a goal international normalized ratio (INR) of 2.5 is indicated. Further study is needed to establish the efficacy of direct oral anticoagulants (DOACs) in this setting
     b. Prior embolic event
     c. Documented left atrial thrombus or left atrial appendage thrombus
  2. Ventricular rate control (to increase diastolic filling period) with beta-blockers, non dihydropyridine calcium channel blockers, or digitalis and aggressive treatment of tachyarrhythmias.
  3. Treat congestive heart failure with loop diuretics and sodium restriction.
  4. Antibiotic prophylaxis to prevent recurrent rheumatic fever is usually not indicated unless presence of high-risk features such as prior endocarditis, prosthetic heart valves, valvulopathy of the transplanted heart, and certain cases of cyanotic congenital heart disease.
  5. Physical activity and exercise. Patients with mild MS in sinus rhythm with a peak pulmonary artery pressure <50 mm Hg can participate in all competitive sports. Patients with moderate MS and in sinus rhythm or atrial fibrillation with a peak pulmonary artery pressure of <50 mm Hg can participate in low to moderate static and dynamic sports. Patients in sinus rhythm with severe MS should not participate in any competitive sports. Patients in atrial fibrillation with any degree of MS and on anticoagulation should avoid all competitive sports.
  6. Pregnancy in females with advanced MS may be poorly tolerated due to the hemodynamic changes such as increased cardiac output occurring in pregnancy. Mild to moderate MS may be tolerated in pregnancy with medical therapy alone.
- Table 2 summarizes approaches to mechanical relief of mitral stenosis.
- Percutaneous mitral balloon commissurotomy (PMBC) is the therapy of choice for symptomatic patients with severe MS (valve area ≤1.5 cm^2) with a favorable valvuloplasty score, minimal or no mitral regurgitation, and no left atrial thrombus. PMBC is reasonable for asymptomatic patients with very severe MS (mitral valve area ≤1.0 cm^2) and favorable valve morphology in the absence of left atrial thrombus or moderate to severe MR (class IIa indication). PMBC is also considered the procedure of choice in pregnant women with rheumatic MS and in New York Heart Association (NYHA) class III to IV heart failure and/or unresponsive to adequate medical treatment. In addition, it may be considered for severely symptomatic (NYHA class III/IV) patients with very severe MS (mitral valve area ≤1.5 cm^2) who are not candidates for surgery or are at high risk for surgery, even if they have suboptimal valve anatomy (class IIb indication). Regular follow-up is needed

TABLE 3 ACC/AHA Guidelines for Intervention for Mitral Stenosis (MS)[1]

Class	Indication	LOE
I	PMBC for symptomatic patients with severe MS (MVA ≤1.5 cm^2, stage D) and favorable valve morphology in the absence of contraindications.	A
	Mitral valve surgery in severely symptomatic patients (NYHA Class III/IV) with severe MS (MVA ≤1.5 cm^2, stage D) who are not high risk for surgery and who are not candidates for or failed previous PMBC.	B
	Concomitant mitral valve surgery for patients with severe MS (MVA ≤1.5 cm^2, stages C or D) undergoing other cardiac surgery.	C
IIa	PMBC is reasonable for asymptomatic patients with very severe MS (MVA ≤1 cm^2, stage C) and favorable valve morphology in the absence of contraindications.	C
	Mitral valve surgery is reasonable for severely symptomatic patients (NYHA class III/IV) with severe MS (MVA ≤1.5 cm^2, stage D) provided there are other operative indications.	C
IIb	PMBC may be considered for asymptomatic patients with severe MS (MVA ≤1.5 cm^2, stage C) and favorable valve morphology who have new onset of AF in the absence of contraindications.	C
	PMBC may be considered for symptomatic patients with MVA greater than 1.5 cm^2 if there is evidence of hemodynamically significant MS during exercise.	C
	PMBC may be considered for severely symptomatic patients (NYHA class III/IV) with severe MS (MVA ≤1.5 cm^2, stage D) who have suboptimal valve anatomy and are not candidates for surgery or at high risk for surgery.	C
	Concomitant mitral valve surgery may be considered for patients with moderate MS (MVA, 1.6 to 2.0 cm^2) undergoing other cardiac surgery.	C
	Mitral valve surgery and excision of the left atrial appendage may be considered for patients with severe MS (MVA ≤1.5 cm^2, stages C and D) who have had recurrent embolic events while receiving adequate anticoagulation.	C

[1]Nishimura R et al: 2013 AHA/ACCF guideline for valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 63:e57-e185, 2014.

New York Heart Association (NYHA) *LOE,* level of evidence; *MVA,* mitral valve area; *NYHA,* New York Heart Association; *PMBC,* percutaneous mitral balloon commissurotomy.

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

after PMBC because restenosis may reoccur. Repeat intervention can be performed as long as valve anatomy remains favorable; however, there is usually more fibrosis and deformation of the valve with subsequent procedures. The approximate frequency of repeat intervention is 10% at 7 yr.

- Mitral valve surgery is indicated for patients with moderate to severe symptomatic MS when PMBC is not available or is contraindicated (valvuloplasty score greater than or equal to 8) or the valve is calcified, when MR is more than mild, when left atrial thrombus is present, and when the surgical risk is acceptable. The surgical approaches include closed mitral valvotomy, open valvotomy and repair (preferred), and mitral valve replacement when repair is not possible.
- Table 3 summarizes guidelines for intervention for mitral stenosis.

DISPOSITION

- Prognosis is generally good except in patients with chronic pulmonary hypertension.
- Operative mortality rates for mitral valve replacement are 1% to 5% at most institutions.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Mitral Stenosis (Patient Information)

AUTHORS: **Vrinda Trivedi, MBBS,** and **Aravind Rao Kokkirala, MD, FACC**

SUGGESTED READING

Nishimura RA et al: AHA/ACC Guidelines for the management of patients with valvular heart disease, *Circulation* 129:e521–e643, 2014.

BASIC INFORMATION

DEFINITION

Mitral valve prolapse (MVP) is the bulging of one or both of the mitral valve leaflets ≥2 mm above the annular plane into the left atrium during systole. MVP syndrome refers to a constellation of MVP and associated symptoms (e.g., autonomic dysfunction, palpitations) or other physical abnormalities (e.g., pectus excavatum). Table 1 describes a classification of mitral valve prolapse.

SYNONYMS

MVP
Mitral click murmur syndrome
Barlow syndrome

ICD-10CM CODES
I34.1 Nonrheumatic mitral (valve) prolapse
I34.0 Nonrheumatic mitral (valve) insufficiency

EPIDEMIOLOGY & DEMOGRAPHICS

- MVP can be found by echocardiogram in 1% to 2.4% of the general population, with some studies suggesting that it is more common in women than in men.
- Increased incidence is seen with autoimmune thyroid disorders, Ehlers-Danlos syndrome, Marfan syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, pectus excavatum, anorexia nervosa, and bulimia.
- Compared to men, women with MVP have less posterior prolapse (22% vs. 31%), less flail (2% vs. 8%), more leaflet thickening (32% vs. 28%), and less frequent severe mitral regurgitation (MR) (10% vs. 23%).

TABLE 1 Classification of Mitral Valve Prolapse

Mitral Valve Prolapse Syndrome
Younger age (20-50 yr)
Predominantly female
Click or click-murmur on physical examination
Thin leaflets with systolic displacement on echocardiography
Associated with low blood pressure, orthostatic hypotension, palpitations
Benign long-term course
Myxomatous Mitral Valve Disease
Older age (40-70 yr)
Predominantly male
Thickened, redundant valve leaflets
Mitral regurgitation on physical exam and echocardiography
High likelihood of progressive disease requiring mitral valve surgery
Secondary Mitral Valve Prolapse
Marfan syndrome
Hypertrophic cardiomyopathy
Ehlers-Danlos syndrome
Other connective tissue diseases

Modified from Otto CM: *Valvular heart disease,* ed 2, Philadelphia, 2004, WB Saunders, p. 369.

- Although MVP is more common in women than men, men more often develop severe regurgitation requiring surgical intervention.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The most common auscultatory finding in cardiac examination is a nonejection mid to late systolic click, heard best at the apex. It is caused by degeneration of the valve resulting in an abnormal ratio between the length of the mitral apparatus and left ventricle (LV) during contraction. When the valve prolapses, it gets caught by the subvalvular structures, causing an abrupt halt that creates the click.
- If regurgitation is present, a crescendo mid to late systolic murmur may be heard that worsens with standing and Valsalva maneuver.
- Timing of click within the cardiac cycle varies with loading conditions within the left ventricle (i.e., may occur earlier with standing or Valsalva and later with squatting or expiration).
- May be associated with small anteroposterior chest diameter, scoliosis, pectus excavatum, or low BMI.
- Most patients with MVP are asymptomatic; symptoms if present consist primarily of chest pain, palpitations, fatigue, dyspnea, and anxiety.
- Neurologic abnormalities (e.g., transient ischemic attack [TIA] or stroke) are rare.
- A spectrum of arrhythmias, mainly paroxysmal supraventricular tachycardia and atrial and ventricular premature beats, etc. is also observed with mitral valve prolapse. There is also an increased association with Wolff-Parkinson-White syndrome and QT prolongation.

ETIOLOGY

- Myxomatous degeneration of connective tissue within mitral valve, usually involving multiple leaflet segments (e.g., Barlow disease). In contrast, fibroelastic deficiency of single leaflet segment develops in elderly patients.
- Congenital deformity of mitral valve and supportive structures.
- Secondary to other disorders of connective tissue such as Ehlers-Danlos, Marfan, or pseudoxanthoma elasticum; association with other connective tissue disorders suggests MVP result of defective embryogenesis in cells of mesenchymal origin.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other valvular abnormalities (especially mitral regurgitation [MR])
- Anxiety or panic disorders
- Pulmonary embolism
- Atypical chest pain

WORKUP

- Medical history and physical examination, with increased suspicion in patients with other findings of connective tissue disorder.
- Two- or three-dimensional echocardiography in patients with a systolic click or murmur on careful auscultation.
- Cardiac MRI is an emerging tool for the evaluation and diagnosis of MVP but has not yet been independently validated. However, MRI should be considered because it may be helpful in accurately quantifying the amount of mitral regurgitation when present. ECG is most often normal but may show nonspecific ST-T wave changes, prolonged QT interval, prominent Q waves, or early repolarization with J-point elevation in young patients.

IMAGING STUDIES

Echocardiography (Fig. 1) shows one or more leaflets prolapsing >2 mm into the left atrium during systole in a long axis view. Mitral leaflets may be thickened (>5 mm) with myxomatous degeneration. MR is typically present but may only occur during late systole or with exertion. If moderate or severe MR is present findings of dilated left atrium, LV dilation and/or dysfunction, and elevated estimated RV systolic pressures may also be present. There is an increased incidence of secundum-type atrial septal defects (ASDs) in patients with MVP, which may also be identified with echocardiography.

TREATMENT

NONPHARMACOLOGIC THERAPY

Avoidance of stimulants (e.g., caffeine, nicotine) in patients with palpitations. Sometimes

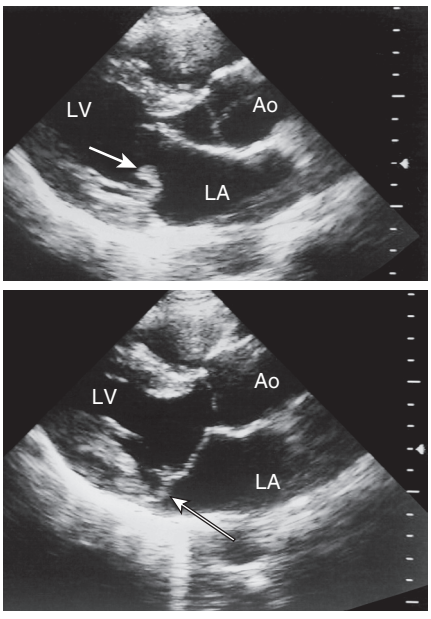

FIG. 1 Mitral valve prolapse. Parasternal long-axis view in diastole *(top)* and systole *(bottom)* in a patient with mitral valve prolapse and myxomatous changes. In the *upper panel,* note the open mitral valve and the diffuse thickening of the posterior mitral valve leaflet *(arrow).* The *lower panel* was recorded in systole. Note that both leaflets prolapse behind the plane of the mitral valve annulus. The prolapse of the posterior leaflet is somewhat more prominent *(arrow). Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle. (From Zipes DP et al [eds]: *Braunwald's heart disease,* ed 7, Philadelphia, 2005, WB Saunders.)

TABLE 2 Predictors of Clinical Outcome in Mitral Valve Prolapse

Predictor	Survival	Valve Surgery	Arrhythmias or Sudden Death	Endocarditis
Age	+++	+++	–	–
Gender	++	++	–	–
Leaflet thickness or redundancy	+++	+++	++++	++++
Severity of mitral regurgitation	++++	++++	++++	++++
Systolic click	+	–	–	–
Left ventricular dilation	+	++++	++	–
Left atrial dilation	–	++	+	–

Symbols indicate the relative predictive value of each variable for the listed clinical outcomes on a scale of no predictive value (–) to strongly predictive (++++).
From Bonow RO et al: *Braunwald's heart disease: a textbook of cardiovascular medicine,* Philadelphia, 2012, WB Saunders.

reassurance is sufficient to reduce the severity of symptoms in many patients.

ACUTE GENERAL Rx

β-blockers may be used in symptomatic patients (e.g., palpitations, chest pain) to decrease the heart rate and contractility, thus potentially decreasing the stretch on the prolapsing valve leaflets.

CHRONIC Rx

Monitoring for complications:

- Mitral regurgitation (most common complication); on rare occasion may occur acutely due to rupture of chordae tendineae.
- Routine echocardiographic monitoring is indicated at the following intervals with patients with evidence of mitral regurgitation:
  1. Stage B with mild regurgitation: Every 3 to 5 yr.
  2. Stage B with moderate regurgitation: Every 1 to 2 yr.
  3. Stage C1 (asymptomatic severe MR without LV dysfunction): Every 6 to 12 mo.
- Bacterial endocarditis (risk is three to eight times that of the general population); higher risk in patients with concomitant regurgitation. However, routine antibiotic prophylaxis is not recommended.
- TIA or stroke caused by embolic phenomena (from fibrin and platelet thrombi) in patients with thickened leaflets; risk in young patients is <0.05% per yr. If present, aspirin (75 to 325 mg) is indicated for secondary prevention.
- Cardiac arrhythmias with the vast majority being supraventricular and benign.
- Sudden death (rare); most often associated with acute flail leaflets or caused by ventricular arrhythmias associated with other structural heart disease.
- The incidence of complications of MVP is very low (<1% per yr). Mitral leaflet thickness is ≤0.5 mm, young patients <45 yr, and in the absence of mitral systolic murmur or MR on Doppler echocardiography. Table 2 lists variables that are predictors of favorable clinical outcome in mitral valve prolapse.
- Risk factors that predict higher risk of complications are presence of moderate to severe MR, LV ejection fraction <50%, LA dimension >40 mm, age >50 yr.

SURGICAL REFERRAL

Surgical referral may be necessary in patients who develop progressive MR with surgical indications as per guidelines for valvular heart disease (see topic on mitral regurgitation).

PEARLS & CONSIDERATIONS

COMMENTS

- Recent studies suggest that the prevalence of MVP and its propensity to cause symptoms and serious complications have been overestimated in the past.
- The relationship between MVP syndrome and sudden cardiac death is unclear. The best evidence suggests that there is only a slight risk in subsets of patients with MVP who have severe MR, severe valvular deformity, complex ventricular arrhythmias, QT prolongation, and a history of syncope.
- Asymptomatic patients with MVP and mild or no MR can be evaluated clinically every 3 to 5 yr. High-risk patients (those with symptoms, arrhythmias, or significant regurgitation) should undergo a follow-up examination once a year.
- In 2007, the AHA guidelines for prevention of infectious endocarditis were revised and prophylactic antibiotics are no longer recommended for patients with MVP without previous endocarditis.

PATIENT & FAMILY EDUCATION

www.themitralvalve.org

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Mitral Valve Prolapse (Patient Information)

AUTHORS: **Maad M. Alhudairy, MD, MAS,** and **Uyen T. Lam, MD**

SUGGESTED READING

Nishimura RA et al: 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 63:e57–e185, 2014.

Mixed Connective Tissue Disease

BASIC INFORMATION

DEFINITION

An overlap syndrome with clinical features of systemic lupus erythematosus (SLE), inflammatory myositis, and systemic sclerosis (SSc), requiring a high titer of anti U1-ribonucleoprotein (RNP) antibodies, especially to the 68- to 70-kDa epitope. Raynaud phenomenon is present in almost all mixed connective tissue disorder (MCTD) patients.

SYNONYMS

MCTD
Overlap syndrome
Sharp syndrome

ICD-10CM CODES

M35.1 Other overlap syndrome
M35.9 Systemic involvement of connective tissue, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Rare, with little data. From a 2011 Norwegian study, 3.8 per 100,000 adults.
PREDOMINANT SEX: Female predominant, ranging from 3:1 to 15:1
PREDOMINANT AGE: Average age at onset is 37 yr, with range between 40 and 80 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- **General:** Malaise, fatigue, low-grade fever.
- **Joints:** Arthralgias are an early symptom, often more severe than with classic lupus. 60% develop arthritis, including Jaccoud arthropathy. Erosions are less common.
- **Skin and mucosa:** Often the presenting feature. Raynaud phenomenon is present in 90%. Swollen hands and puffy fingers are characteristic (Fig. E1). May also see malar rash, discoid plaques, orogenital or buccal ulcerations, nasal septal perforation, sicca complex, sclerodermatous change, and abnormal nail fold capillaries.
- **Muscle:** Myalgias are common. Most patients have no demonstrable weakness, although persistent inflammatory myopathy can occur (similar to polymyositis).
- **Lung:** 75% have lung involvement, although most are asymptomatic. Manifestations may include pleural effusions, pleuritic pain, pulmonary artery hypertension (PAH), interstitial lung disease, thromboembolic disease, alveolar hemorrhage, diaphragmatic dysfunction, aspiration pneumonitis, obstructive airway disease, pulmonary infections, and pulmonary vasculitis. Need screening echocardiograph to evaluate for PAH.
- **Heart:** All three layers of the heart may be involved. Up to 20% of patients have an abnormal ECG with hemiblock, bundle branch block, and atrioventricular block. Echocardiogram findings include pericardial effusions and mitral valve prolapse. The most common cardiac clinic manifestation is pericarditis. Patients are at risk of accelerated atherosclerosis.
- **Hematopoietic:** Anemia of chronic disease, leukopenia (usually lymphopenia), hypergammaglobulinemia, Coombs positivity, thrombocytopenia.
- **Gastrointestinal tract:** Similar to those of SSc, with disordered motility, mostly esophageal dysfunction. Less commonly seen: Intestinal vasculitis, pancreatitis, autoimmune hepatitis, primary biliary cirrhosis, portal hypertension, and ascites.
- **Kidney:** Absence of renal involvement is characteristic but may have membranous nephropathy or nephrotic range proteinuria.
- **Nervous system:** Trigeminal neuropathy, headache, aseptic meningitis, sensorineural hearing loss. Rare to have severe central nervous system disease.

ETIOLOGY

Autoimmune disorder

FIG. E1 Sausage-shaped fingers in a patient with mixed connective tissue disease. An identical appearance may be found in patients with early scleroderma and eosinophilic fasciitis. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

TABLE E1 Diagnostic Criteria by Alarcon-Segovia and Kahn

Alarcon-Segovia Criteria	Kahn Criteria
Serologic Criteria	
Anti-RNP at hemagglutination titer of ≥1:1600	High-titer anti-RNP corresponding to a speckled ANA of ≥1:1200 titer
Clinical Criteria	
1. Swollen hands	1. Swollen fingers
2. Synovitis	2. Synovitis
3. Myositis	3. Myositis
4. Raynaud phenomenon	4. Raynaud phenomenon
5. Acrosclerosis	
MCTD is present if:	
Serologic criteria + ≥3 clinical criteria (must include synovitis or myositis)	Serologic criteria + Raynaud + ≥2 of other 3 clinical criteria

ANA, Antinuclear antigen; *MCTD,* mixed connective tissue disease; *RNP,* ribonucleoprotein.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other connective tissue disorders (SLE, SSc, rheumatoid arthritis [RA], myositis), infection, malignancy

WORKUP

- Table E1 summarizes diagnostic criteria.
- Alarcon-Segovia: Serologic criterion accompanied by ≥3 clinical criteria, one of which must be synovitis or myositis (sensitivity 63%, specificity 86%).
- Kahn: Serologic criterion accompanied by Raynaud phenomenon and at least two out of three remaining clinical criteria.
- Once diagnosis is made, must screen for PAH.

LABORATORY TESTS

- Positive antinuclear antibody (ANA), speckled, often high titer (>1:1280).
- High titer of U1-RNP antibodies, especially to the 68- to 70-kDa antigen.
- SLE-specific and SSc-specific autoantibodies are generally absent (possible overlap).
- Rheumatoid factor and anti-CCP are positive in 50% to 70% of patients.
- Antiphospholipid antibodies may be associated with pulmonary hypertension.

TREATMENT

- Generally therapy is targeted to the specific features present.
- Arthralgias, arthritis, fatigue, myalgias, pleurisy may respond to NSAIDs, antimalarials, and low-dose corticosteroids (<20 mg/day).

- Inflammatory myositis is treated with high doses of prednisone (60 mg/day).
- Methotrexate, cyclophosphamide, azathioprine, mycophenolate may be considered.
- Intravenous immunoglobulin (IVIG) can be used for steroid-resistant myositis or severe skin disease.
- Rituximab can be considered for steroid-resistant thrombocytopenia or autoimmune hemolytic anemia.
- For Raynaud phenomenon, keeping warm, avoiding beta-blockers, and smoking cessation are important. Can use dihydropyridine calcium channel blocker, if necessary.
- Most require acid-lowering therapies (proton pump inhibitors, antacids).
- For PAH and/or lung disease, therapy may include steroids, cyclophosphamide, low-dose aspirin. May also require anticoagulation, angiotensin-converting-enzyme inhibitors, endothelin receptor antagonist, IV prostacyclin, cyclic GMP phosphodiesterase type 5 inhibitors (sildenafil and tadalafil). Lung transplant may be necessary when severe.

DISPOSITION

- Patients with high titers of U1-RNP antibodies have low prevalence of serious renal disease and life-threatening neurologic disorders.
- Disease-related mortality is usually related to PAH and cardiac sequelae.

REFERRAL

Rheumatology consultation

PEARLS & CONSIDERATIONS

COMMENTS

Pulmonary arterial hypertension is definitively diagnosed by cardiac catheterization and is the main disease-related cause of death. Early detection of PAH and aggressive treatment may improve prognosis.

RELATED CONTENT

Scleroderma (Systemic Sclerosis) (Related Key Topic)

AUTHOR: **Daphne Scaramangas-Plumley, MD**

SUGGESTED READINGS

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Molar Pregnancy ALG

BASIC INFORMATION

DEFINITION

Molar pregnancy (hydatidiform mole) is a premalignant gestational disorder and is included in the spectrum of disorders characterized as gestational trophoblastic disease. Molar pregnancies are classified as complete or partial based on morphologic and pathologic examination. Both complete and partial molar pregnancies have an abnormal placenta with enlargement and swelling of the chorionic villi and hyperplasia of the villous trophoblastic cells. Most molar pregnancies are complete and are characterized by generalized hydropic villous changes with no fetal tissue. Partial moles are characterized by a mixture of large hydropic villi and normal placental tissue and often have fetal tissue present. Gestational trophoblastic disease (GTD) is composed of a spectrum of neoplastic conditions derived from the placenta. Whereas hydatidiform moles, gestational choriocarcinoma, and placental site trophoblastic tumor (PSTT) are histologic diagnoses, postmolar gestational trophoblastic neoplasia (GTN) is defined by clinical and laboratory criteria. The disease entities included in GTD have a wide variation in behavior, but GTN specifically refers to those with the potential for tissue invasion and metastases.

The risk of malignant sequelae (gestational trophoblastic neoplasia) for a complete mole is 6% to 32% and for a partial mole is less than 5%.

SYNONYM

Hydatidiform mole

ICD-10CM CODES	
O01.0	Classical hydatidiform mole
O01.1	Incomplete and partial hydatidiform mole
O01.9	Hydatidiform mole, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1/1500 pregnancies in the U.S.
PREDOMINANT SEX & AGE: Females of reproductive age, highest rates at extremes of reproductive ages
RISK FACTORS:

- Extremes of reproductive age (<21 and >40 yr)
- Previous molar pregnancy
- History of spontaneous abortion
- Use of combined oral contraceptives

PHYSICAL FINDINGS & CLINICAL PRESENTATION (TABLE E1)

Complete molar pregnancy:

- 80% to 90% present with vaginal bleeding at 6 to 16 wk gestational age
- 28% with uterine enlargement greater than expected for gestational age
- 8% with hyperemesis gravidarum
- 1% with pregnancy-induced hypertension in the first or second trimester
- 15% to 25% with bilateral theca lutein cysts
- 15% will have a beta hCG >100,000 mIU/ml
- <10% with anemia

Partial molar pregnancy:

- 90% present with an incomplete or missed abortion
- 75% present with vaginal bleeding
- <10% will have a beta hCG of >100,000 mIU/ml

ETIOLOGY

Complete molar pregnancy:

- Fertilization of an oocyte with absent or inactive maternal chromosomes (Fig. E1) and duplication of paternal chromosomes (85% to 90% are 46, XX) or fertilization of an empty oocyte with 2 sperm (46, XY or XX).
- Diffuse villous enlargement and trophoblastic proliferation (Fig. E2) with no development of a fetus.

Partial molar pregnancy:

- Fertilization of a normal oocyte with two sperm (usually 69, XXY or 69, XXX)
- Focal villous edema and trophoblastic proliferation with identifiable fetus

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Complete mole, partial mole (Table E2), ectopic pregnancy, abortion (incomplete or spontaneous), normal intrauterine pregnancy

WORKUP

- Pelvic exam to evaluate for uterine size and bleeding
- Blood pressure to assess for gestational hypertension or preeclampsia (systolic blood pressure >140 or diastolic blood pressure >90)
- Fig. E3 describes an algorithm for the diagnosis and management of molar pregnancy

LABORATORY TESTS

- Quantitative beta human chorionic growth hormone (beta hCG); significantly elevated levels >100,000 will raise suspicion for molar pregnancy
- Complete blood count (CBC) to assess for acute anemia from vaginal bleeding
- Comprehensive metabolic panel to evaluate for renal or liver disease
- Thyroid stimulating hormone to evaluate for hyperthyroidism
- Urinalysis for proteinuria to evaluate for preeclampsia
- Type and screen to evaluate Rh status and to prepare for surgery

IMAGING STUDIES

- Pelvic ultrasound (Figs. E4 and E5):
  1. Complete moles in the first trimester will demonstrate a complex, echogenic, intrauterine mass containing many small cystic spaces that are secondary to swollen chorionic villi and no identifiable fetus. This is the classic "snowstorm" appearance (Fig. E6).
  2. Partial mole will show a thickened, hydropic placenta with fetal parts.
  3. Baseline chest x-ray to use for comparison if malignant trophoblastic disease develops.
- Magnetic resonance image (Fig. E7)

TREATMENT

NONPHARMACOLOGIC THERAPY

Surgical uterine evacuation with dilatation and curettage (D&C) is the mainstay of management of a molar pregnancy, either partial or complete. Tables E3 and E4 summarize the management of hydatidiform moles.

ACUTE GENERAL Rx

D&C, Rh immune globulin if Rh negative

CHRONIC Rx & DISPOSITION

If pathology results are consistent with complete or partial mole, patients must be followed to evaluate for trophoblastic neoplasia. 15% to 20% of complete moles and 1% to 5% of partial moles can develop into trophoblastic neoplasia. Quantitative beta hCG should be followed weekly until three consecutive results show normal levels. After that, check quantitative beta hCG every month for a total of 6 mo. Patients should remain on reliable contraception during this time to prevent confusion from a rising beta hCG in the case of a new pregnancy.

TABLE E1 Classic Presenting Signs and Symptoms of Complete and Partial Hydatidiform Moles

Sign or Symptom	Complete Mole (%) (*n* = 306)	Partial Mole (%) (*n* = 81)
Vaginal bleeding	97	73
Excessive uterine size	51	4
Theca lutein cysts >6 cm	50	0
Preeclampsia	27	3
Hyperemesis	26	0
Hyperthyroidism	7	0
Trophoblastic emboli	2	0

From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

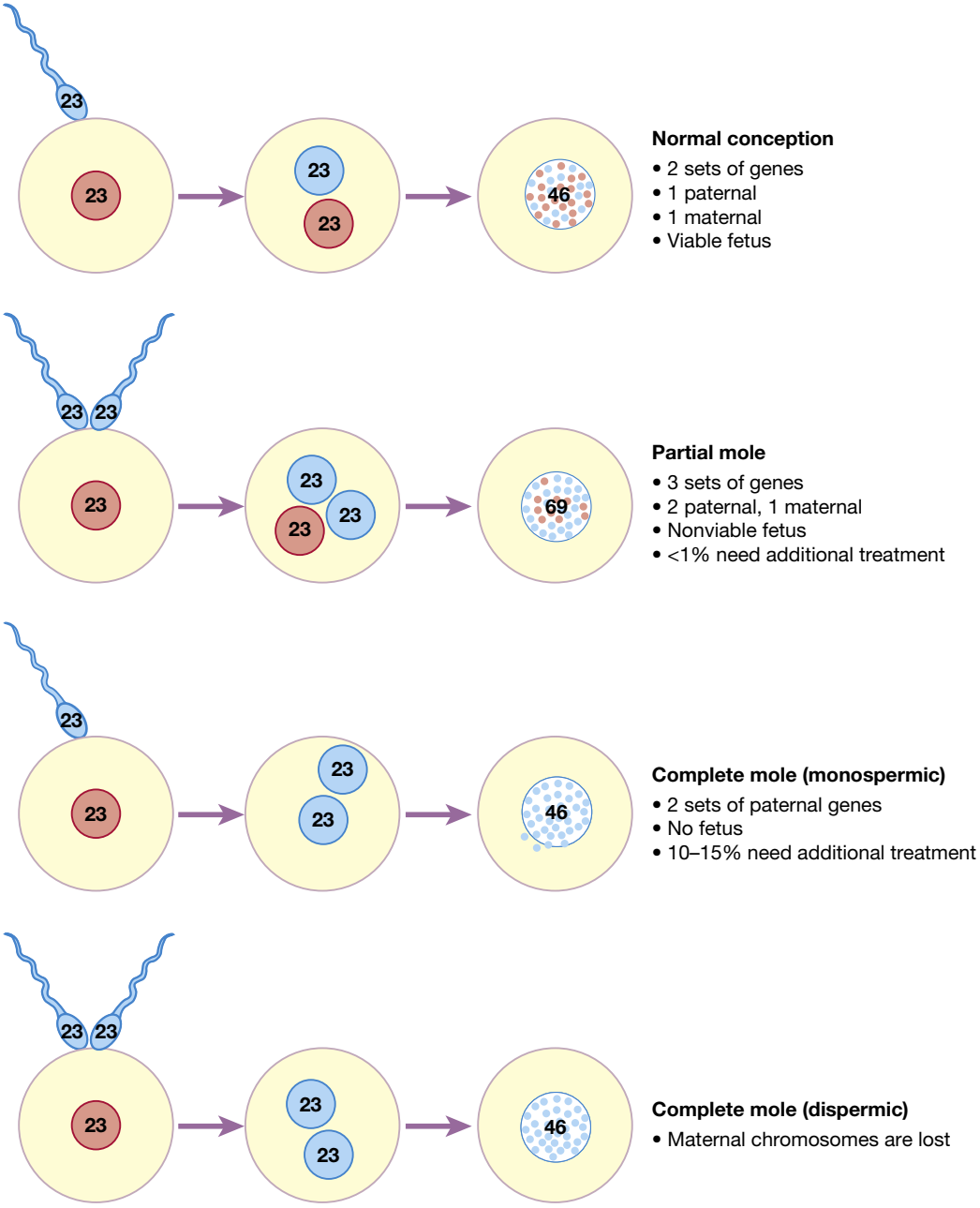

FIG. E1 Genetic makeup of normal pregnancy and partial and complete molar pregnancies. (From Magowan BA: *Clinical obstetrics & gynecology,* ed 4, 2019, Elsevier.)

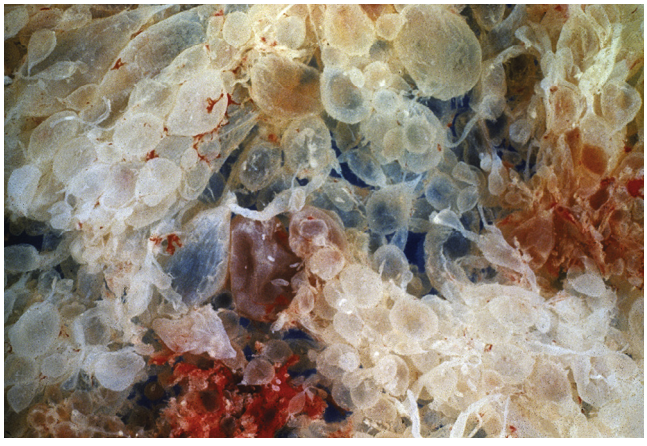

FIG. E2 Complete hydatidiform mole, gross specimen. Note the diffuse hydropic placental villi that make up almost the entire specimen. (Courtesy David Mutch, MD. From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2017, Elsevier.)

TABLE E2 Features of Partial and Complete Hydatidiform Moles

Feature	Partial Mole	Complete Mole
Karyotype	69, XXX or –, XXY	46, XX or –, XY
Pathology		
Fetus	Often present	Absent
Amnion, fetal RBC	Usually present	Absent
Villous edema	Variable, focal	Diffuse
Clinical Presentation		
Diagnosis	Missed abortion	Molar gestation
Uterine size	Small for dates	50% large for dates
Theca-lutein cysts	Rare	25%-30%
Postmolar GTN	2.5%-7.5%	6.8%-20%

GTN, Gestational trophoblastic neoplasia; *RBC,* red blood cell.
From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2017, Elsevier.

Specific criteria by beta hCG have been established by International Federation of Gynecology and Obstetrics (FIGO) for diagnosis of postmolar gestational trophoblastic disease (see Tables E5, E6, and E7).

REFERRAL

- If there is concern for a molar pregnancy, the patient should be managed by a gynecologist for uterine evacuation and follow-up.
- If there is a plateau or rise of the beta hCG during follow-up, the patient should be referred to a gynecologic oncologist for treatment with either further surgery or prophylactic chemotherapy.

RELATED CONTENT

Spontaneous Abortion (Related Key Topic)
Vaginal Bleeding During Pregnancy (Related Key Topic)

AUTHORS: **Matthew H. H. Young, MD, JD,** and **Helen B. Gomez, MD**

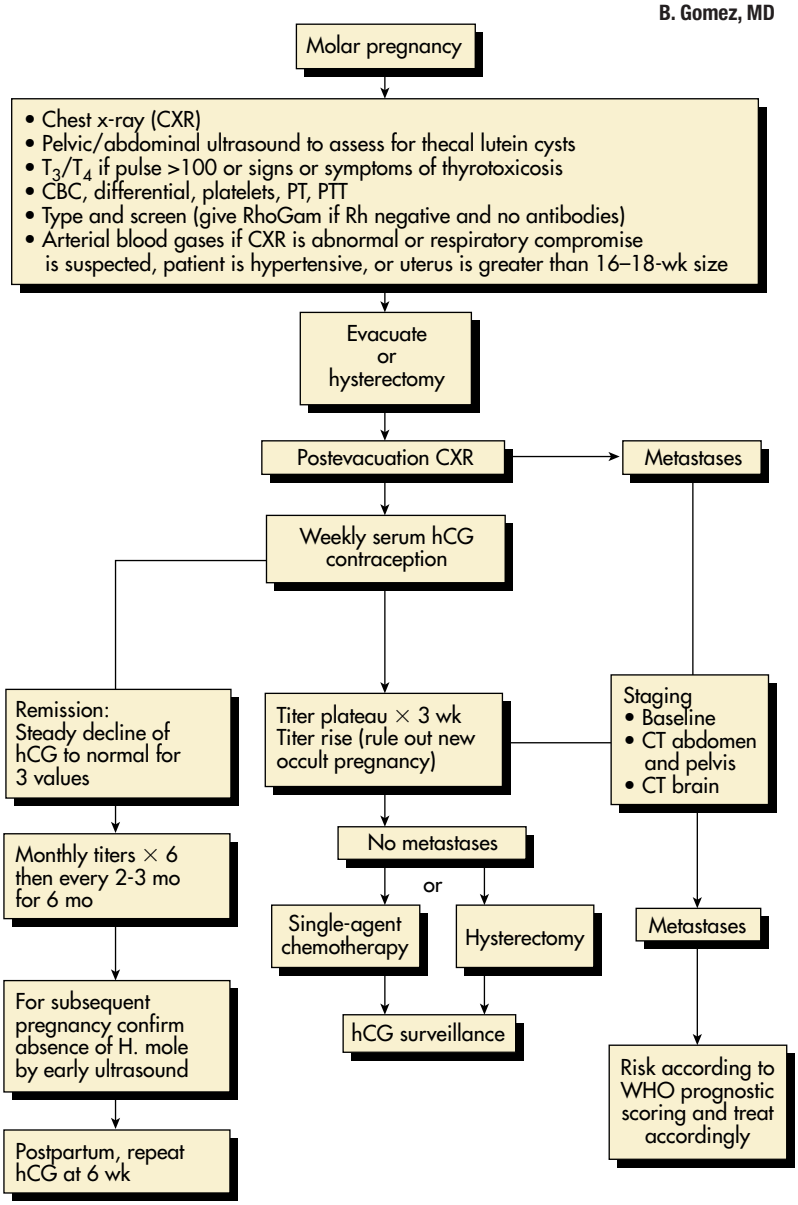

FIG. E3 Algorithm for the management of molar pregnancy. *CBC,* Complete blood count; *hCG,* human chorionic gonadotropin; *PT,* Prothrombin Time; *PTT,* partial thromboplastin time; *WHO,* World Health Organization. (From Gabbe SG: *Obstetrics,* ed 6, Philadelphia, 2012, WB Saunders.)

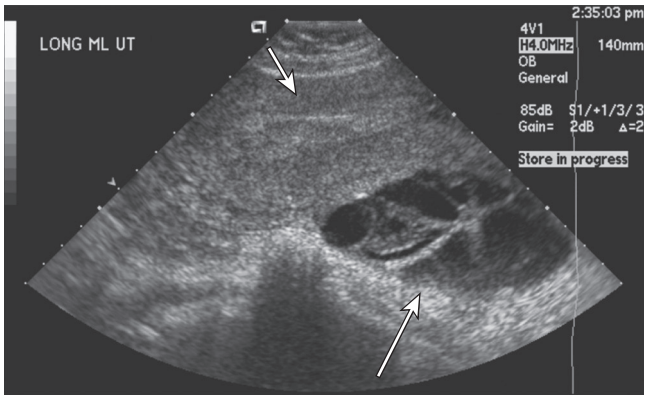

FIG. E4 Endovaginal ultrasound of the theca lutein cyst with early molar pregnancy. Note enlarged anechoic cystic spaces within the ovary *(arrows).* (From Fielding JR et al: *Gynecology imaging,* Philadelphia, 2011, WB Saunders.)

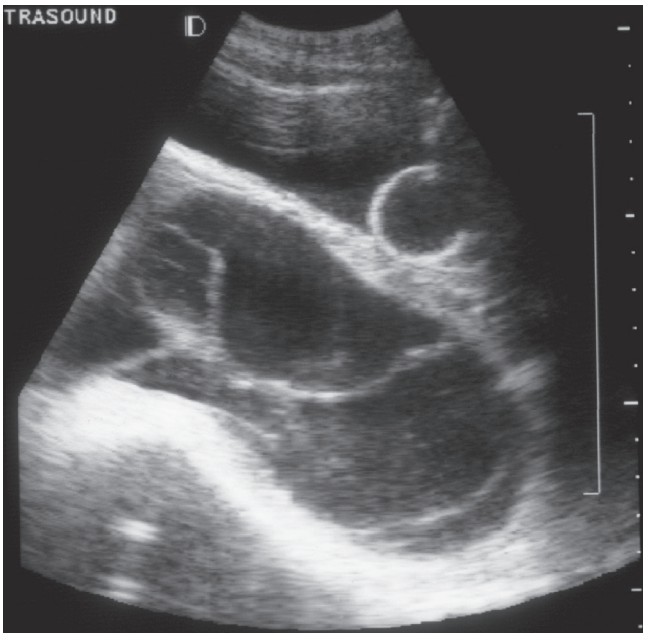

FIG. E5 Ultrasound image demonstrating a large theca-lutein ovarian cyst associated with a complete hydatidiform mole. These usually contain multiple thin septations and have an appearance similar to iatrogenic ovarian hyperstimulation during ovulation induction. Theca-lutein cysts regress spontaneously after evacuation of the molar pregnancy, but regression often lags behind human chorionic gonadotropin level decline. (Courtesy John Soper, MD. From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2017, Elsevier.)

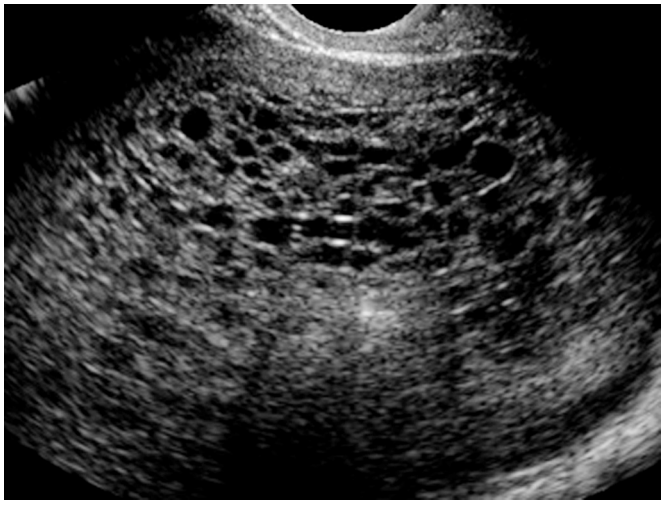

FIG. E6 Complete molar pregnancy: Classic appearance. Transabdominal scan shows a vesicular echogenic mass distending the endometrium. The mass is filled with innumerable uniformly distributed cystic spaces that corresponded to hydropic chorionic villi at pathology. (From Rumack CM et al: *Diagnostic ultrasound,* ed 4, Philadelphia, 2011, Mosby.)

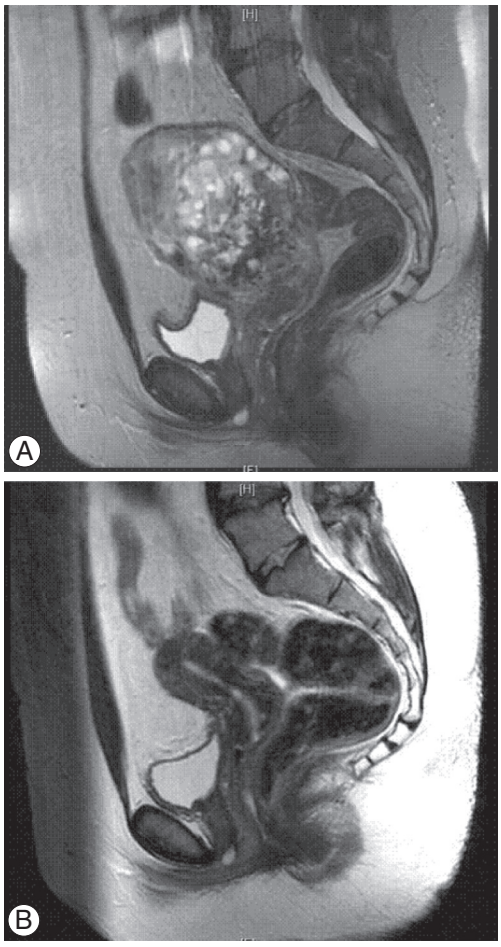

FIG. E7 Invasive complete molar pregnancy. A, Magnetic resonance imaging appearance prior to chemotherapy treatment. **B,** Follow-up scan performed 3 months after chemotherapy completion. (From Magowan BA: *Clinical obstetrics & gynecology,* ed 4, 2019, Elsevier.)

TABLE E3 Management of Hydatidiform Mole

Evacuation: Suction D&E (or hysterectomy in selected patients)

Postevacuation quantitative hCG level and chest radiography

Monitor quantitative hCG levels every 1-2 wk until three normal values or criteria for GTN

After hCG level is normal for three values, then monitor hCG levels every 1-3 mo for 6 mo

Initiate chemotherapy for GTN using indications listed in Table E4:
1. Plateaued or rising hCG values
2. Histologic diagnosis of choriocarcinoma, invasive mole, or placental site trophoblastic tumor
3. Persistent hCG >6 mo after evacuation
4. Metastatic disease

D&E, Suction dilation and evacuation; *GTN,* gestational trophoblastic neoplasia; *hCG,* human chorionic gonadotropin.
From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2017, Elsevier.

TABLE E4 Diagnosis and Evaluation of Gestational Trophoblastic Neoplasia

Diagnosis of GTN

After molar evacuation: Four values or more of plateaued hCG (±10%) over at least 3 wk: Days 1, 7, 14, and 21

After molar evacuation: A rise of hCG of 10% or greater for three values or more over at least 2 wk: Days 1, 7, and 14

After molar evacuation: Persistence of hCG beyond 6 mo

The histologic diagnosis of choriocarcinoma, invasive mole, or PSTT

Metastatic disease without established primary site with elevated hCG (pregnancy has been excluded)

Evaluation of GTN

Complete physical and pelvic examination; baseline hematologic, renal, and hepatic functions

Baseline quantitative hCG level

Chest radiograph or CT scan of chest

Brain MRI

CT or MRI scan of abdomen and pelvis

CT, Computed tomography; *GTN,* gestational trophoblastic neoplasia; *hCG,* human chorionic gonadotropin; *MRI,* magnetic resonance imaging; *PSTT,* placental site trophoblastic tumor.
From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2017, Elsevier.

TABLE E5 The 2002 Criteria for the Diagnosis of Post Hydatidiform Mole Trophoblastic Neoplasia

hCG-level plateau of 4 values ±10% recorded over a 3-wk duration (days 1, 7, 14, and 21)

An hCG-level increase of more than 10% of 3 values recorded over a 2-wk duration (days 1, 7, and 14)

Persistence of detectable hCG for more than 6 mo after molar evacuation

hCG, Human chorionic gonadotropin.

TABLE E6 International Federation of Gynecology and Obstetrics Staging of Gestational Trophoblastic Neoplasia

Stage I	Disease confined to the uterus
Stage II	GTN extends outside the uterus but is limited to the genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extends to the lungs with or without genital tract involvement
Stage IV	All other metastatic sites

GTN, Gestational trophoblastic neoplasia.
From Kohorn EI: The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and critical assessment, *Int J Gynecol Cancer* 11:73-77, 2001.

TABLE E7 The World Health Organization (WHO) Prognostic Scoring System Is Used for the Medical Management of Patients with Partial, Complete Moles, and Choriocarcinomas

FIGO Scoring	0	1	2	4
Age	<40	≥40	—	—
Antecedent pregnancy	Mole	Abortion	Term	—
Interval months from index pregnancy	<4	4-<7	7-<13	≥13
Pretreatment serum hCG (IU/L)	<103	103-<104	104-<105	≥105
Large tumor size (including uterus) cm	<3	3-<5	≥5	—
Site of metastases	Lung	Spleen, kidney	Gastrointestinal	Liver, brain
Previous failed chemotherapy	—	—	Single drug	2 or more drugs

FIGO, International Federation of Gynecology and Obstetrics; *hCG,* human chorionic gonadotropin.

SUGGESTED READINGS

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Lurain JR: Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole, *Am J Obstet Gynecol* 203(6):531-539, 2010.

BASIC INFORMATION

DEFINITION

Molluscum contagiosum is a poxvirus infection characterized by discrete skin lesions with central umbilication.

SYNONYM

MC

ICD-10CM CODE
B08.1 Molluscum contagiosum

EPIDEMIOLOGY & DEMOGRAPHICS

- Molluscum contagiosum spreads by autoinoculation, scratching, or touching a lesion.
- It usually occurs in young children. It is also common in sexually active adults and patients with HIV infection.
- Incubation period varies between 4 and 8 wk.
- Spontaneous resolution in immunocompetent patients can occur after several mo.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The individual lesion appears initially as a small (2 to 3 mm), flesh-colored, firm, smooth-surfaced papule with subsequent central umbilication. Lesions are frequently grouped (Fig. 1). The size of each lesion generally varies from 2 to 6 mm in diameter.
- Typical distribution in children involves the face, extremities, and trunk. Mucous membranes are spared.
- Distribution in adults generally involves pubic and genital areas (Fig. E2).
- Erythema and scaling at the periphery of the lesions may be present as a result of scratching or hypersensitivity reaction.
- Lesions are not present on the palms and soles.

ETIOLOGY

Viral infection of epithelial cells caused by a poxvirus, molluscum contagiosum

DIAGNOSIS

Diagnosis is usually established by the clinical appearance of the lesions (distribution and central umbilication). A magnifying lens can be used to observe the central umbilication. If necessary, the diagnosis can be confirmed by removing a typical lesion with a curette and examining the content on a slide after adding potassium hydroxide and gentle heating. Staining with toluidine blue will identify viral inclusions.

DIFFERENTIAL DIAGNOSIS

- Verruca plana (flat warts): No central umbilication, not dome shaped, irregular surface, can involve palms and soles
- Herpes simplex: Lesions become rapidly umbilicated
- Varicella: Blisters and vesicles are present
- Folliculitis: No central umbilication, presence of hair piercing the pustule or papule
- Cutaneous cryptococcosis in AIDS patients: Budding yeasts will be present on cytologic examination of the lesions
- Basal cell carcinoma: Multiple lesions are absent
- Cellulitis

WORKUP

Careful examination of the papules

LABORATORY TESTS

Generally not indicated in children. Screening for other sexually transmitted diseases is recommended in all cases of genital molluscum contagiosum.

TREATMENT

GENERAL Rx

- Therapy is individualized depending on number of lesions, immune status, and patient's age and preference.
- Observation for spontaneous resolution is reasonable in patients with few, small, nonirritated, and nonspreading lesions. Genital lesions should be treated in all sexually active patients.
- Liquid nitrogen cryotherapy.
- Carbon dioxide laser.
- Curettage after pretreatment of the area with combination prilocaine 2.5% with lidocaine 2.5% cream (EMLA) for anesthesia is useful for treatment of a few lesions. Curettage should be avoided in cosmetically sensitive areas because scarring may develop.
- Treatments with liquid nitrogen therapy in combination with curettage are effective in older patients who do not object to some discomfort.
- Application of cantharidin 0.7% to individual lesions covered with clear tape will result in blistering over 24 hr and possible clearing without scarring. This medication should be avoided on facial lesions.
- Other treatment measures include use of imiquimod cream or tretinoin 0.025% gel or 0.1% cream at bedtime, daily use of salicylic acid (Occlusal) at bedtime, and use of laser therapy.
- Trichloroacetic acid peel generally repeated every 2 wk for several wk is useful in immunocompromised patients with extensive lesions.

DISPOSITION

Most patients respond well to the therapeutic modalities listed previously. Spontaneous resolution can occur after 6 to 9 mo in some immunocompetent patients.

REFERRAL

To dermatology when diagnosis is in doubt or in patients with extensive lesions

PEARLS & CONSIDERATIONS

COMMENTS

Genital molluscum contagiosum in children may be indicative of sexual abuse.

RELATED CONTENT

Molluscum Contagiosum (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

FIG. 1 Grouped molluscum. (From Kliegman RM et al: *Nelson textbook of pediatrics*, ed 19, Philadelphia, 2011, WB Saunders.)

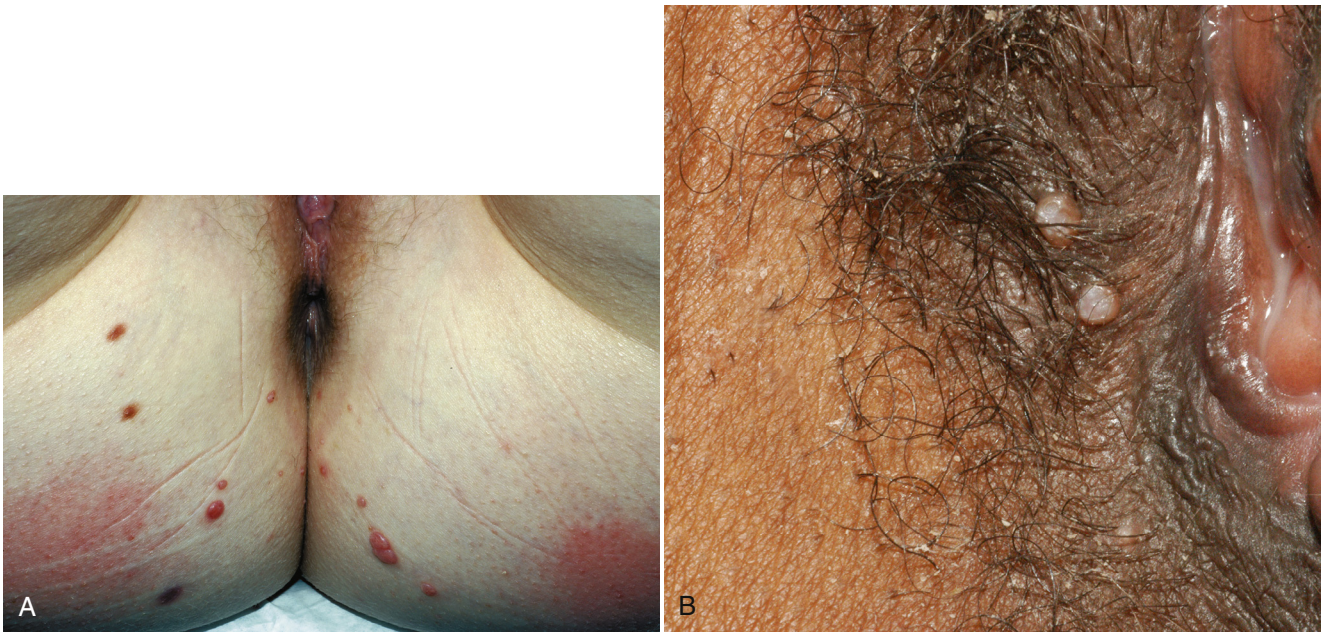

FIG. E2 **A,** Clinical presentation of molluscum contagiosum, with discrete, dome-shaped, pink papules. **B,** A depressed center (umbilicated papule), characteristic of the disease, allows for clinical diagnosis in most cases. (From Crum CP et al: *Diagnostic gynecologic and obstetric pathology*, ed 3, Philadelphia, 2018, Elsevier.)

BASIC INFORMATION

DEFINITION

Monoclonal gammopathy of renal significance (MGRS) describes a group of hemato-nephrologic disorders characterized by production of a serum nephrotoxic M protein, but they do not meet criteria for symptomatic multiple myeloma (MM) or lymphoma. The term *MGRS* was introduced to distinguish monoclonal gammopathies that result in the development of kidney disease from benign disorders. All forms of MGRS arise from B-cell clones. The monoclonal proteins may be of light chain, heavy chain, or intact immunoglobulin origin. The hematologic disorder is generally consistent with monoclonal gammopathy of undetermined significance (MGUS) in which the M protein is <3 g/dl, clonal plasma cells in the bone marrow are <10%, and there is no evidence of end-organ dysfunction.

SYNONYMS

Monoclonal immunoglobulin deposition disease (MIDD) with MGUS
Glomerulopathies with MGUS

ICD-10CM CODE
None currently exists for MGRS.

EPIDEMIOLOGY & DEMOGRAPHICS

MM and other malignant conditions with monoclonal gammopathy commonly lead to kidney disease, and the majority are associated dysproteinemia. Renal impairment is a defining criterion in MM. Although a growing number of kidney diseases associated with monoclonal gammopathies are being recognized, these gammopathies are typically characterized as MGUS and treatments are withheld. MGRS has been estimated to accompany 10% of MGUS cases, with prevalence rates of 0.32% and 0.53% in persons older than 50 and 70 yr, respectively. Although MGRS is considered a benign or premalignant condition, its effects on the kidney are not benign. Afflicted individuals may develop progressive kidney disease and/or end-stage renal disease (ESRD). The high rate of recurrence (60% to 90%) of MGRS-related kidney disease is associated with significant morbidity.

INCIDENCE: The exact frequency of MGRS is unclear. Many patients with MGRS are miscategorized as MGUS.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Kidney disease in patients with MGRS can present as a complication of a previously diagnosed, nonmalignant or premalignant hematologic disorder; MGUS; smoldering MM; or the initial clinical manifestation of a monoclonal gammopathy.
- Affected individuals may present with acute or subacute kidney injury, chronic kidney disease, proteinuria, and/or nephrotic syndrome.
- The most common presentation is renal impairment with proteinuria, with or without hematuria.
- Electrolyte abnormalities may be prominent when renal tubular lesions are present.

DIAGNOSIS

- MGRS should be suspected in the presence of nonmalignant or premalignant monoclonal gammopathy, i.e., MGUS, smoldering MM, Waldenström macroglobulinemia, or monoclonal B-cell lymphocytosis that presents with unexplained renal impairment and/or proteinuria.
- Individuals who manifest unexplained renal impairment and/or proteinuria with a monoclonal gammopathy (i.e., by serum or urine protein electrophoresis, serum or urine immunofixation electrophoresis, or serum free light chain assay) should be evaluated for MGRS.
- Percentage of proteinuria ratios to delineate the proportion of proteinuria that is albuminuria may be helpful. This urine ratio equals the albumin:creatinine ratio (mg/g) divided by the total protein:creatinine ratio (mg/g).
  1. In myeloma cast nephropathy, the bulk of protein is constituted by a Bence Jones protein (monoclonal light chain). In these cases, the albumin percentage is frequently <10% and typically <20%.
  2. For patients with MGRS, the albumin proportion may exceed 50% when there is principally glomerular pathology. In light chain proximal tubulopathy and crystal-storing histiocytosis, the glomeruli are relatively spared, and the albumin percentage can be low.
- A kidney biopsy is required for diagnosis, unless contraindicated. The presence of monoclonal immunoglobulin deposits in the kidney establishes the diagnosis of MGRS.
- Immunofluorescence reveals monoclonal proteins restricted to a single class of light and/or heavy chain.

CLASSIFICATION ACCORDING TO RENAL PATHOLOGY

The renal lesions on MGRS are classified based on the ultrastructure of deposits in the kidney (Table 1). Although glomerular and tubulointerstitial regions are most affected by MGRS, the renal vasculature may also be involved. Immunofluorescence and electron microscopy are essential to identification of MGRS lesions specifically. Identification of specific MGRS lesions is critical for assessing prognosis and to initiate proper therapy, MGRS renal lesions are broadly divided into those that are organized (with substructure) and those that are nonorganized (granular without substructure). Fig. 1 demonstrates the MGRS-associated lesions.

LABORATORY TESTS

- Kidney biopsy: It is the definitive means of demonstrating the nephrotoxicity of the monoclonal protein. The existence of a serum or urine monoclonal protein alone does not prove that a monoclonal protein is responsible for the kidney disease.

TABLE 1 Classification of Monoclonal Gammopathy of Renal Significance Lesions in the Kidney

Glomerulopathies (GN)	Tubular Disorders	Intrarenal Lesions
Renal amyloidosis (light chain, heavy chain, light and heavy chain)	Light chain Fanconi syndrome (LCFS)	Atypical hemolytic uremic syndrome (aHUS)
Fibrillary GN	Light chain proximal tubulopathy without crystals	
Immunotactoid GN	Crystal-storing histiocytosis	
Cryoglobulinemic glomerulonephritis (CG)		
Randall-type monoclonal immunoglobulin (Ig) deposition disease (MIDD) (light chain, heavy chain, light and heavy chain)		
Proliferative glomerulonephritis with monoclonal Ig deposits (PGNMID)		
Membranoproliferative glomerulonephritis (MPGN) associated with monoclonal Ig		
Membranous nephropathy (MN) secondary to monoclonal Ig		
C3 glomerulopathy (C3G) associated with monoclonal Ig		
C4 dense deposit disease (C4 DDD) associated with monoclonal Ig		

Adapted from Ciocchini M et al: Monoclonal gammopathy of renal significance (MGRS): the characteristics and significance of a new meta-entity, *Int Urol* Nephrol 49:2171-2175, 2017.

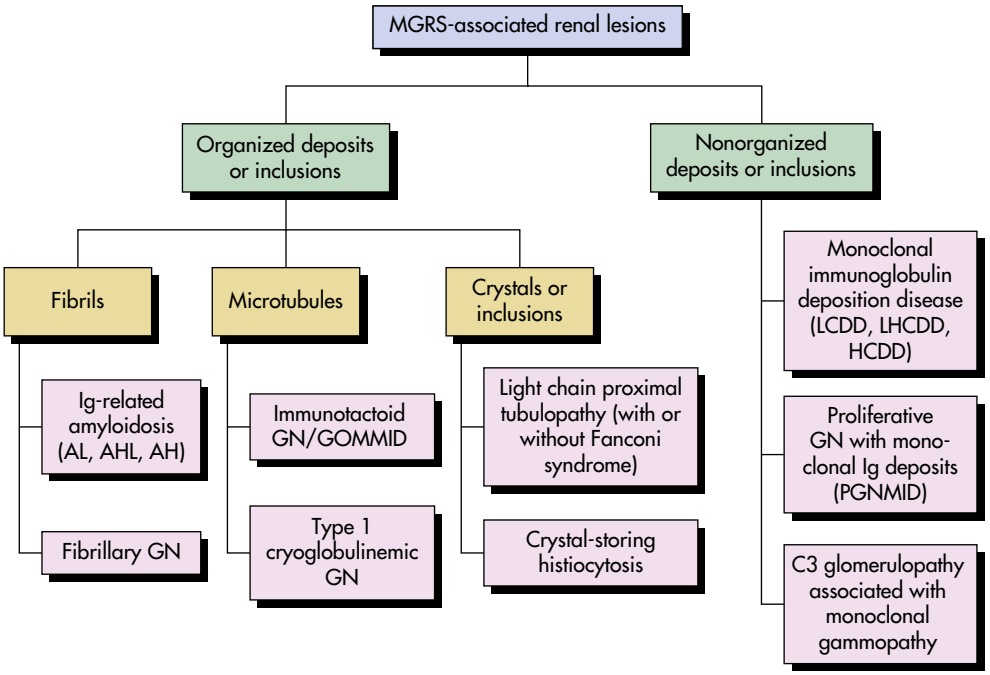

FIG. 1 Diagram of MGRS-associated renal lesions. *AH,* Immunoglobulin heavy chain amyloidosis; *AHL,* immunoglobulin heavy and light chain amyloidosis; *AL,* immunoglobulin light chain amyloidosis; *GN,* glomerulonephritis; *GOMMID,* glomerulonephritis with organized microtubular monoclonal immunoglobulin deposits; *HCDD,* heavy chain deposition disease; *Ig,* immunoglobulin; *LCDD,* light chain deposition disease; *LHCDD,* light and heavy chain deposition disease; *MGRS,* monoclonal gammopathy of renal significance; *PGNMID,* proliferative glomerulonephritis with monoclonal immunoglobulin G deposits. (From Bridoux F et al: Diagnosis of monoclonal gammopathy of renal significance, Kidney Int 87:698-711, 2015.)

- Monoclonal protein testing: The circulating monoclonal protein, if detected, must match the monoclonal protein within kidney deposits.
- Serum protein electrophoresis and immunofixation
- 24-hour urine protein electrophoresis and immunofixation
- Serum free light chain assay
- The value of urine free light chain evaluation is unknown and not required
- Bone marrow aspirate and biopsy: Analysis of the bone marrow should include immunohistochemistry and flow cytometry for surface and intracellular markers of plasma cells and B cells.
- Staining for kappa and lambda light chains should be performed to demonstrate that an identified clone exhibits the same light chain restriction as the monoclonal deposits in the kidney.

IMAGING STUDIES

Imaging studies (such as computed tomography of the chest, abdomen, and pelvis, combined with positive emission tomography, if available) may be required in patients who do not have a B-cell clone or have an IgM monoclonal protein.

Rx TREATMENT

- MGRS requires treatment to prevent progression of renal failure and not from a "tumoral" (proliferative rate and bulk) standpoint.
- Historically, reluctance in treatment was due to concerns of toxicity associated with chemotherapeutic agents.
- The treatment of MGRS-related kidney diseases should be tailored to the underlying clone responsible. Identification of a serum or urine monoclonal protein, if present, is also important in monitoring the response to therapy. No therapies are available to remove existing deposits.
- Hematologic response to chemotherapy is associated with improvement in kidney function and prevention of recurrence after kidney transplantation.
- Evidence suggests that once the specific renal lesion has been identified by kidney biopsy, chemotherapeutic agents directed against the pathologic clone are required.
- Agents such as monoclonal antibodies, cytotoxic agents, proteasome inhibitors, and immunomodulatory drugs have been proposed.
- Autologous hematopoietic cell transplantation may be considered in some patients with amyloidosis or MIDD. This disorder is defined by Congo red–negative deposits of monoclonal light or heavy chains, or both.

REFERRAL

The treatment of MGRS should be selected and administered in consultation with a hematologist or oncologist experienced in the use of antimyeloma and antilymphoma agents.

RELATED CONTENT

Monoclonal Gammopathy of Undetermined Significance (Related Key Topic)
Multiple Myeloma (Related Key Topic)

AUTHOR: **Snigdha T. Reddy MD**

SUGGESTED READINGS

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Leung N et al: Laboratory testing in monoclonal gammopathy of renal significance (MGRS), *Clin Chem Lab Med* 54(6):929-937, 2016.

Leung N et al: The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group, *Nat Rev Nephrol* 15(1):45-59, 2019.

Monoclonal Gammopathy of Undetermined Significance (MGUS)

BASIC INFORMATION

DEFINITION

MGUS is a premalignant disorder characterized by the clonal expansion of plasma cells or lymphoplasmacytic cells. It is typically detected incidentally when patients undergo testing with serum or urine protein electrophoresis. The term "monoclonal gammopathy of undetermined significance" (MGUS) is defined by the presence of a serum monoclonal (M) protein less than 3 g/dl and clonal plasma cells less than 10% in the bone marrow. In addition, there must be no evidence of end organ dysfunction such as renal insufficiency, anemia, hypercalcemia, or bony lesions on skeletal surveys (Table 1).

SYNONYMS

MGUS
Non-IgM MGUS
IgM MGUS
Light chain MGUS

ICD-10CM CODE

D47.2 Monoclonal gammopathy of undetermined significance (MGUS)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: In the U.S., the estimated age-adjusted incidence of MGUS is higher in men than in women. The annual incidence of MGUS in men is 120 per 100,000 at age 50 yr and increases to 530 per 100,000 at age 80 yr, whereas the incidence for women is 60 per 100,000 at age 50 yr and 370 per 100,000 at age 80 yr.

PREVALENCE: MGUS is associated with increasing age; approximately 1.5% of persons older than 50 yr and 3.0% of persons older than 70 yr have an elevated M protein level without end organ dysfunction. Studies have shown that at clinical diagnosis, MGUS is most likely to have been present undetected for a median duration of more than 10 yr. The prevalence of MGUS is also higher in African Americans. In one study, there was an almost threefold increase in prevalence among the African American population compared with the Caucasian population (8.6% vs. 3.6%).

PREDOMINANT SEX & AGE: The median age at diagnosis is about 70 yr. Prevalence is higher in men than in women at any given age.

RISK FACTORS: Race (African American), older age, male sex, or exposure to pesticides. Environmental and/or genetic defects play an important role, since the risk of MGUS in relatives of multiple myeloma or MGUS patients is increased twofold to threefold when compared to the general population. The cumulative risk of progression into multiple myeloma or related disorders is approximately 1% per yr. A variety of disorders (Table 2) are also associated with monoclonal gammopathy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- MGUS typically is detected after a routine blood test reveals an elevated total protein concentration and is a common finding in medical practice.
- Patients are asymptomatic.
- Physical exam is normal.

ETIOLOGY

- The mechanism is unknown, and most cases are sporadic. The causes of malignant transformation of MGUS into multiple myeloma is still not well understood. Genetic predisposition, cytokine release, and bone marrow angiogenesis may play a role in the progression of MGUS into multiple myeloma.
- Characterized by a rearrangement of immunoglobulin genes resulting in the production of a monoclonal protein.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Smoldering myeloma (Table E3)
- Multiple myeloma
- Waldenström agammaglobulinemia
- Secondary monoclonal gammopathies
  1. Chronic liver disease
  2. Rheumatologic diseases
  3. Chronic myelomonocytic leukemia
  4. Chronic neutrophilic leukemia
  5. Lichen myxedematosus
- Pyoderma gangrenosum
- AL amyloidosis
- Idiopathic Bence Jones proteinuria

LABORATORY TESTS

- Protein studies with serum free light chain assay
- Serum protein electrophoresis (Fig. E1): IgG most common, followed by IgM and IgA
- 24-hour urine protein excretion and urine electrophoresis
- Serum and urine immunofixation
- Determination of serum free light chain ratio (kappa and lambda free light chains)
- Hemoglobin
- Serum calcium and creatinine
- Examination of the bone marrow aspirate only when clinically indicated. It is not necessary in MGUS patients with low risk fractures (no end organ damage. Ig gammopathy less than 1.5 g/dl, normal serum free light chain ratio)

IMAGING STUDIES

- Skeletal survey
- Bone mineral density resting at baseline (MGUS is associated with increased risk of osteoporosis)

TREATMENT

- Risk stratification:
  1. Low risk: Serum M protein <1.5 g/dl, IgG subtype, normal genetics, free light chain ratio between 0.26 and 1.65. Absolute risk of progression (ARP) at 20 yr is 5%
  2. Low-intermediate risk: Any 1 factor abnormal. ARP at 20 yr is 21%
  3. High-intermediate risk: Any 2 factors abnormal. ARP at 20 yr is 37%
  4. High risk: More than 3 factors abnormal. ARP at 20 yr is 58%
- Follow-up by risk category: Patients with MGUS should be tested again within 4 to 6 mo from the time of first diagnosis to exclude evolving multiple myeloma. Those with low-risk MGUS can be followed up every 1 to 2 yr, whereas those with intermediate- or high-risk MGUS need to be followed up at least annually for life or until they develop a life-expectancy-threatening condition.
- Reevaluation consists of:
  1. Serum protein electrophoresis with immunofixation
  2. 24-hour urine protein excretion
  3. Serum free light chain assessment:
     a. Complete blood count
     b. Serum creatinine and calcium
     c. Careful history and physical examination to look for signs and symptoms known to evolve from MGUS

DISPOSITION

- Risk of myeloma at 25 yr is 30%
- Annual risk of transformation to myeloma depends on type of M protein:
  1. Immunoglobulin MGUS: 1% per yr
  2. Light-chain MGUS: 0.3% per yr
- IgM MGUS are more likely to progress to Waldenström macroglobulinemia, at a rate of 1.5% per yr
- Risk of infection (bacterial and viral) is twofold compared with healthy controls
- Increased risk of mortality from bacterial infections

REFERRAL

To hematologist/oncologist for evaluation

PEARLS & CONSIDERATIONS

- Approximately 55% of 70-yr-old patients diagnosed as having MGUS have had the condition for more than 10 yr.
- Most patients with MGUS should be monitored every 6 to 12 mo for signs and symptoms of progression.
- There is no indicated treatment, but some patients with MGUS can develop MGUS-related renal disease or neuropathy, and treatment sometimes is indicated in these cases.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Jorge J. Castillo, MD,** and **Irene M. Ghobrial, MD**

TABLE 1 Disease Definitions for the Monoclonal Gammopathies: MGUS and Related Disorders

Type of Monoclonal Gammopathy	Premalignancy with a Low Risk of Progression (1%-2% per yr)	Premalignancy with a High Risk of Progression (10% per yr)	Malignancy
IgG and IgA (non-IgM) monoclonal gammopathies*	**Non-IgM MGUS** All 3 criteria must be met: Serum monoclonal protein <3 g/dl Clonal bone marrow plasma cells <10%, and Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder	**Smoldering multiple myeloma** Both criteria must be met: Serum monoclonal protein (IgG or IgA) ≥3 g/dl and/or clonal bone marrow plasma cells ≥10%, and Absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to a plasma cell proliferative disorder	**Multiple myeloma** All 3 criteria must be met except as noted: Clonal bone marrow plasma cells ≥10% Presence of serum and/or urinary monoclonal protein (except in patients with true nonsecretory multiple myeloma), and Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically Hypercalcemia: Serum calcium >11.5 mg/dl or renal insufficiency: Serum creatinine >2 mg/dl or estimated creatinine clearance <40 ml/min Anemia: Normochromic, normocytic with a hemoglobin value of >2 g/dl below the lower limit of normal or a hemoglobin value <10 g/dl Bone lesions: Lytic lesions or severe osteopenia attributed to a plasma cell proliferative disorder or pathologic fractures
IgM monoclonal gammopathies	**IgM MGUS†** All 3 criteria must be met: Serum IgM monoclonal protein of any level Normal bone marrow and absence of end-organ damage such as anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder	**Smoldering Waldenström macroglobulinemia** Both criteria must be met: Serum IgM monoclonal protein of any level and/or bone marrow lymphoplasmacytic infiltration of any level, and No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder	**Waldenström macroglobulinemia** All criteria must be met: IgM monoclonal gammopathy of any level, and any level of bone marrow lymphoplasmacytic infiltration (usually intratrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (e.g., surface IgM^{+}, CD5$^{+/-}$, CD10^{-}, CD19^{+}, CD20^{+}, CD23^{-}) that satisfactorily excludes other lymphoproliferative disorders including chronic lymphocytic leukemia and mantle cell lymphoma Evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder. Presence of the *MYD88* L265P mutation **IgM myeloma** All criteria must be met: Symptomatic monoclonal plasma cell proliferative disorder characterized by a serum IgM monoclonal protein regardless of size Presence of 10% plasma cells on bone marrow biopsy Presence of lytic bone lesions related to the underlying plasma cell disorder and/or translocation t(11;14) on fluorescence in situ hybridization
Light-chain monoclonal gammopathies	**Light-chain MGUS** All criteria must be met: Abnormal FLC ratio (<0.26 or >1.65) Increased level of the appropriate involved light-chain (increased kappa FLC in patients with ratio >1.65 and increased lambda FLC in patients with ratio <0.26) No immunoglobulin heavy-chain expression on immunofixation Clonal bone marrow plasma cells <10%, and Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder	**Idiopathic Bence Jones proteinuria** All criteria must be met: Urinary monoclonal protein on urine protein electrophoresis ≥500 mg/24 h and/or clonal bone marrow plasma cells ≥10% No immunoglobulin heavy-chain expression on immunofixation Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder	**Light-chain multiple myeloma†** Same as multiple myeloma except no evidence of immunoglobulin heavy-chain expression

CRAB, hypercalcemia, renal failure, anemia, and bone disease; *FLC,* free light chain; *Ig,* immunoglobulin; *MGUS,* monoclonal gammopathy of undetermined significance.

*Occasionally patients with IgD and IgE monoclonal gammopathies have been described and will be considered to be part of this category as well.

†Note that conventionally IgM MGUS is considered a subtype of MGUS, and similarly light-chain multiple myeloma is considered as a subtype of multiple myeloma. Unless specifically distinguished, when the terms MGUS and multiple myeloma are used in general, they include IgM MGUS and light-chain multiple myeloma, respectively.

Modified from Rajkumar SV et al: Advances in the diagnosis, classification, risk stratification, and management of monoclonal gammopathy of undetermined significance: implications for recategorizing disease entities in the presence of evolving scientific evidence, *Mayo Clin Proc* 85:945-948, 2010.

TABLE 2 Diseases Associated with Monoclonal Gammopathy

Plasma cell and related disorders	MGUS Solitary plasmacytoma: Bone Soft tissue Multiple myeloma Waldenström macroglobulinemia Primary amyloidosis	
Lymphoid disorders	Non-Hodgkin lymphoma	Monoclonal protein observed in CLL (>20% of cases with IgM, ≈50% with IgG, light chains also observed), extranodal marginal zone lymphomas (>30% of cases and correlated with BM involvement), follicular, mantle cell, and diffuse large B-cell lymphomas also reported with serum M proteins as has AITL
	Hodgkin lymphoma	Rare but reported
	Castleman disease	<2% with monoclonal gammopathy
Other hematologic disorders	Acquired von Willebrand disease	IVIG more effective than factor concentrate in increasing factor VIII coagulant and VWF levels
	Gaucher disease	Observed in 25% in one study; M protein declined after splenectomy
	Pernicious anemia, pure RBC aplasia, hereditary spherocytosis, MPD, MDS	
Connective tissue disorders	SLE	IgG, IgM, and IgA have been observed, no difference in disease activity or outcome
	Inclusion body myositis	80% with IgG M protein
	Polymyositis, RA, scleroderma	
Neurologic disorders	POEMS syndrome	Most have M-protein of λ light chain
	Peripheral neuropathy	Most common is IgM followed by IgG and IgA In half, IgM protein binds to myelin-associated glycoprotein Size of M protein not correlated with severity of neuropathy Some benefit from plasma exchange for those with IgG and IgA Fludarabine and rituximab with some benefit for IgM
	Myasthenia gravis, ALS, Alzheimer disease	
Dermatologic disorders	Schnitzler syndrome	Neutrophilic urticarial dermatitis, monoclonal IgM protein, and two of: Lymphadenopathy, fever, hepatosplenomegaly, joint pain, increased ESR, increased neutrophils, or abnormal bone imaging
	Scleredema	
	Pyoderma gangrenosum	Frequently an IgA protein
Infections	HIV	Both IgG and IgM M proteins observed
	HCV	M protein present in up to 10% of patients
Immunosuppression	Renal transplant	In children CMV infection associated with M protein
	Liver and heart transplant	Most patients with posttransplant lymphoproliferative disorders have M proteins
	BM transplant	Observed in both autologous and allogeneic transplants Appearance of M protein correlated with GVHD

AITL, Angioimmunoblastic T-cell lymphoma; *ALS,* amyotrophic lateral sclerosis; *BM,* bone marrow; *CLL,* chronic lymphocytic leukemia; *CMV,* cytomegalovirus; *ESR,* erythrocyte sedimentation rate; *GVHD,* graft-versus-host disease; *HCV,* hepatitis C virus; *HIV,* human immunodeficiency virus; *Ig,* immunoglobulin; *IVIG,* intravenous immunoglobulin; *MDS,* myelodysplastic syndrome; *MGUS,* monoclonal gammopathy of uncertain significance; *MPD,* myeloproliferative disorder; *POEMS,* polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; *RA,* rheumatoid arthritis; *RBC,* red blood cell; *SLE,* systemic lupus erythematosus; *VWF,* von Willebrand factor.

From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE E3 Diagnostic Criteria for MGUS, Multiple Myeloma, and Other Conditions*

Variable	MGUS	Smoldering Multiple Myeloma	Multiple Myeloma	Waldenström Macroglobulinemia	Primary Amyloidosis
Bone marrow plasma cells (%)	<10	≥10	≥10	Any lymphoplasmacytic infiltrate	<10
	and	and/or	and/or	and	and
Circulating monoclonal protein (g/dl)	<3	≥3	≥3	Any amount of IgM paraprotein	<3
Clinical manifestations	Absent	Absent	Present‡	Present§	Present¶

Ig, Immunoglobulin; *MGUS,* monoclonal gammopathy of undetermined significance.
*Data are from the International Myeloma Working Group.
‡Clinical features may include increased serum calcium concentrations, renal failure, anemia, skeletal involvement (lytic lesions), recurrent bacterial infections, and extramedullary plasmacytomas.
§Clinical features included anemia, hyperviscosity, neuropathy, and lymphadenopathy.
¶Clinical features include fatigue, weight loss, purpura, nephritic syndrome, congestive heart failure, peripheral neuropathy, orthostatic hypotension, and massive hepatomegaly.
From Bladé J: Clinical practice. Monoclonal gammopathy of undetermined significance, *N Engl J Med* 355:2765-2770, 2006.

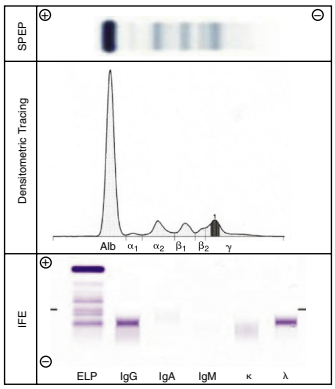

FIG. E1 Serum electrophoresis from a 73-yr-old man with monoclonal gammopathy of undetermined significance. The patient has no clinical, hematologic, or imaging evidence of a plasma cell dyscrasia, except for a persistent, modest (0.4 g/dl), single M protein peak on the densitometric tracing *(shaded area, middle panel)* of the serum protein electrophoresis pattern *(SPEP).* The M protein was identified by immunofixation electrophoresis *(IFE)* as IgGλ, located in the β_2 region of the electrophoresis *(ELP)* pattern. *Alb,* Albumin; *Ig,* immunoglobulin. (Courtesy Drs. Frank H. Wians Jr. and Dennis C. Wooten, Department of Pathology, University of Texas Southwestern Medical Center, Dallas. From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.)

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BASIC INFORMATION

DEFINITION

Infectious mononucleosis (IM) is a symptomatic infection most commonly caused by Epstein-Barr virus (EBV) and characterized by a classic triad of fever, tonsillar pharyngitis, and lymphadenopathy (predominantly cervical). Fatigue is also a very common finding. IM was first coined in 1920 to describe a syndrome characterized as an acute infectious process accompanied by atypical large peripheral blood lymphocytes.

SYNONYMS

Mononucleosis
EBV
Kissing disease

ICD-10CM CODES

B27 Infectious mononucleosis
B27.0 Gamma herpesviral mononucleosis
B27.1 Cytomegaloviral mononucleosis
B27.8 Other infectious mononucleosis
B27.9 Infectious mononucleosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 500 cases/100,000 persons/yr; worldwide, approximately 90% lifetime prevalence by age 30 yr

PREDOMINANT SEX: Incidence is the same, but occurs earlier in females.

PREDOMINANT AGE: Symptomatic infection most common between the ages of 15 and 24 yr. The age at which primary EBV infection is acquired is potentially increasing in developed countries.

Young children rarely develop clinical signs of IM. Infection during childhood is more common in lower socioeconomic groups and may vary by geographic location or social factors, such as crowding, sharing a bedroom, maternal education, daycare attendance, and school catchment area.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Following an incubation period of 4 to 7 wk, there are two common presentations. The first presentation represents the prodromal period with gradual onset of fever, chills, malaise, and anorexia for several days. This is followed by the second presentation of the classic triad of pharyngitis, fever, and lymphadenopathy. These patients often report the worst sore throat of their life. Pharyngitis (Fig. E1) is typically the most severe symptom and is characterized by white tonsillar exudates that may spread to the tongue. Up to half of patients may have palatal petechiae.
- Lymphadenopathy (nonnecrotic) can be diffuse, but most commonly occurs in both the anterior and posterior triangles of the neck.
- Splenomegaly may be palpable, most commonly during the second wk of illness. Most patients have some degree of splenomegaly on ultrasound assessment. Hepatomegaly with some degree of hepatitis is also common. In 75% of cases there is some increase in alanine aminotransferase (ALT).
- Rash (Fig. E2) is uncommon but will occur in nearly all patients who receive ampicillin or amoxicillin due to a transient penicillin hypersensitivity.
- IM is usually a self-limited illness (2 to 4 wk), but symptoms of malaise and fatigue may last mos before resolving.
- At times, IM can present as fever and adenopathy without pharyngitis.
- Although acute complications may be severe, they are uncommon and tend to resolve completely. Reported complications include cholestatic liver disease, chronic hepatitis, or even liver failure; hemolytic anemia; splenic rupture; or airway compromise.
- Splenic rupture is rare, with an incidence rate <1%, but it is the most feared. It should be suspected in anyone with confirmed or suspected IM who presents with acute abdominal or chest pain. Most cases occur in the first 3 wk of symptoms.
- Airway compromise, as evidenced by stridor, cyanosis, and/or tachypnea, is reported in 1% to 3% of cases and is an indication for hospitalization.
- Systemic corticosteroids are indicated for treating those at risk or with impending airway obstruction, and usually leads to improvement in 12 to 36 hr. Acute tonsillectomy may be pursued if steroids are not sufficient to mitigate the risk for obstruction.
- Late complications may include lymphoproliferative cancers (Burkitt lymphoma and Hodgkin lymphoma), multiple sclerosis, rheumatoid arthritis, and chronic active EBV infection (CAEBV).
- EBV may also cause hemophagocytic disease, alternatively referred to as EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH), characterized by fever, splenomegaly, and cytopenias with high ferritin and soluble CD25.
- Box 1 and Table 1 summarize the features of IM in immunocompetent patients.

ETIOLOGY

The most common cause of IM (90%) is primary infection with EBV. Cytomegalovirus (CMV) is the most common cause of the other 10% of IM, but CMV infection often occurs in infancy or early childhood and is minimally symptomatic. Other causes include human herpes virus-6, herpes simplex virus-1, and HIV. Primary EBV infection during childhood also often causes few or no symptoms; persistent fatigue and recurrent/persistent fevers are the most common reasons parents bring symptomatic children to medical care.

BOX 1 Summary of Features of Infectious Mononucleosis (IM) in Immunocompetent Patients

Epstein-Barr Virus (Human Herpesvirus-4)

Pathophysiology
- Virus enters through oropharyngeal epithelial and lymphoid cells.
- Virus attaches to CD21 on B cells.
- Viral antigens—viral capsid antigen (VCA), early antigen (EA), Epstein-Barr nuclear antigen (EBNA)—are produced and elicit antibody production.

Humoral Immune Response
- Immunoglobulin (Ig)M against VCA rises during incubation and prodrome, falls over few wks to mos.
- IgG against VCA rises during incubation, decreases during convalescence, remains detectable for life.
- Antibodies to EA rise 2-3 wk after onset of illness, then fall.
- Antibodies to EBNA rise during convalescence, detectable for life.

Cellular Immune Response
- T cells activated during second wk of illness.
- CD8-positive cytotoxic T cells kill infected B cells.
- Natural killer cells kill infected B cells.
- Some resting memory B cells remain latently infected.

Clinical Features
- 4- to 7-wk incubation period
- Vague onset of symptoms
- Fever, sore throat, lymphadenopathy
- Adolescents, young adults more often symptomatic than younger children

Laboratory Features
- Leukocytosis with absolute lymphocytosis and atypical lymphocytes
- Transient monocytosis
- Relative and absolute neutropenia early on
- Mild thrombocytopenia in half of cases
- Hemolytic anemia in 1% to 3% of cases, often with anti-I specificity
- Elevated transaminases in 85% to 100% of cases, but clinical jaundice rare
- Spot test is simple, rapid, specific, based on agglutination of horse red blood cells (RBCs)
- Heterophil antibody (HA) test is based on differential absorption of IM-specific HA by beef RBC stroma and guinea pig kidney

From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, Philadelphia, 2017, Elsevier.

EBV infects epithelial cells and resting B cells of the oropharynx. It is then found in saliva, making it transmittable through coughing, sharing drink/food, and kissing; thus the pseudonym "kissing disease." IM is more prevalent during adolescence when these types of close contact increase. How it is transmitted in younger children is less clear.

EBV levels peak during the active phase of infection but can persist in the oropharynx for up to 18 mo. Transmission may also occur sexually because EBV can be isolated in cervical epithelial cells and male seminal fluid. It has also been shown to be transmitted by blood transfusion, solid organ transplantation, or hematopoietic cell transplantation.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Heterophile-negative IM caused by CMV
- Bacterial and viral causes of pharyngitis
- Toxoplasmosis
- Acute retroviral syndrome of HIV, lymphoma

WORKUP

Initial testing consists of heterophile antibody (monospot) and CBC with differential. Fig. 3 illustrates the serologic evaluation of patients with clinical symptoms of acute IM and atypical lymphocytosis.

LABORATORY TESTS

- About 85% of patients with EBV-related IM will have a positive heterophile antibody test, making it the best initial test for diagnosis of EBV infection (sensitivity of 71% to 90% for diagnosing IM). However, the test has a 25% false-negative rate in the first wk of illness because the amount of heterophile antibody may not be above the limit for detection early in the disease. A negative test should be repeated if clinical suspicion is high; negative results are common in patients symptomatic for <2 wk and children <4 yr. False-positive heterophile antibody tests have been reported in other acute infections, autoimmune diseases, and cancer.
- About 10% of patients will have a persistently negative heterophile antibody test. In this event, further testing may be pursued with EBV viral capsid antigen (VCA) IgG and IgM antibody testing, as well as EBV nuclear antigen (EBNA) antibodies for staging of infection. Early diagnosis in monospot-negative cases may be made by isolating IgM to the VCA, which is usually positive during the acute illness and disappears after 4 to 6 wk. If the monospot test remains negative (without evidence of acute infection with antibody testing) for 8 wk, alternative diagnoses should be considered. The monospot usually remains positive for 3 to 6 mo but can last >1 yr.
- Increased white blood count (WBC) is common, with a relative lymphocytosis and neutropenia. Atypical lymphocytes (Fig. E4) are the hallmark of IM but are not pathognomonic. Mild thrombocytopenia is common. A falling hematocrit may signal splenic rupture or severe immune-mediated hemolytic anemia. Elevated hepatocellular enzymes and cryoglobulins occur in many cases.

IMAGING STUDIES

Chest x-ray may rarely show infiltrates. An elevated left hemidiaphragm may occur in cases of splenic rupture.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- No specific treatment exists; focus is on supportive care and symptomatic relief with analgesics, antipyretics, and hydration. Supportive rest is advocated by some, but the effect on outcome is not clear. Prolonged rest may result in deconditioning, which may contribute to further fatigue.
- Splenectomy if rupture occurs; transfusions for severe anemia or thrombocytopenia.

GENERAL Rx

- Pharmacologic therapy, including corticosteroids, is not indicated in mild illness or for symptomatic relief. Use of corticosteroids is controversial because they may impair clearance of the viral load.
- The use of steroids, however (Fig. E5), should be considered in patients who have severe acute complications, such as thrombocytopenia, hemolytic anemia, or impending airway obstruction.
- There is no role for antiviral agents such as acyclovir in the management of IM.

CHRONIC Rx

CAEBV is treated with hematopoietic cell transplantation.

DISPOSITION

Eventual resolution of all symptoms is the rule.

PEARLS & CONSIDERATIONS

COMMENTS

- Contact sports should be avoided during the first mo of illness because splenic rupture can occur during this time, even in the absence of clinically detectable splenomegaly.
- Between 30% and 75% of college freshmen are seronegative for EBV. Each yr nearly 20% of susceptible persons become infected and up to 50% of these persons develop IM.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Mononucleosis (Patient Information)
Epstein-Barr Virus Infection (Related Key Topic)

AUTHORS: **Lauren J. Maskin, MD,** and **Russell J. McCulloh, MD**

TABLE 1 Clinical Manifestations of Infectious Mononucleosis in Children and Adults

	FREQUENCY (%)		
Sign or Symptom	**Age <4 yr**	**Age 4-16 yr**	**Adults (Range)**
Lymphadenopathy	94	95	93-100
Fever	92	100	63-100
Sore throat or tonsillopharyngitis	67	75	70-91
Exudative tonsillopharyngitis	45	59	40-74
Splenomegaly	82	53	32-51
Hepatomegaly	63	30	6-24
Cough or rhinitis	51	15	5-31
Rash	34	17	0-15
Abdominal pain or discomfort	17	0	2-14
Eyelid edema	14	14	5-34

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

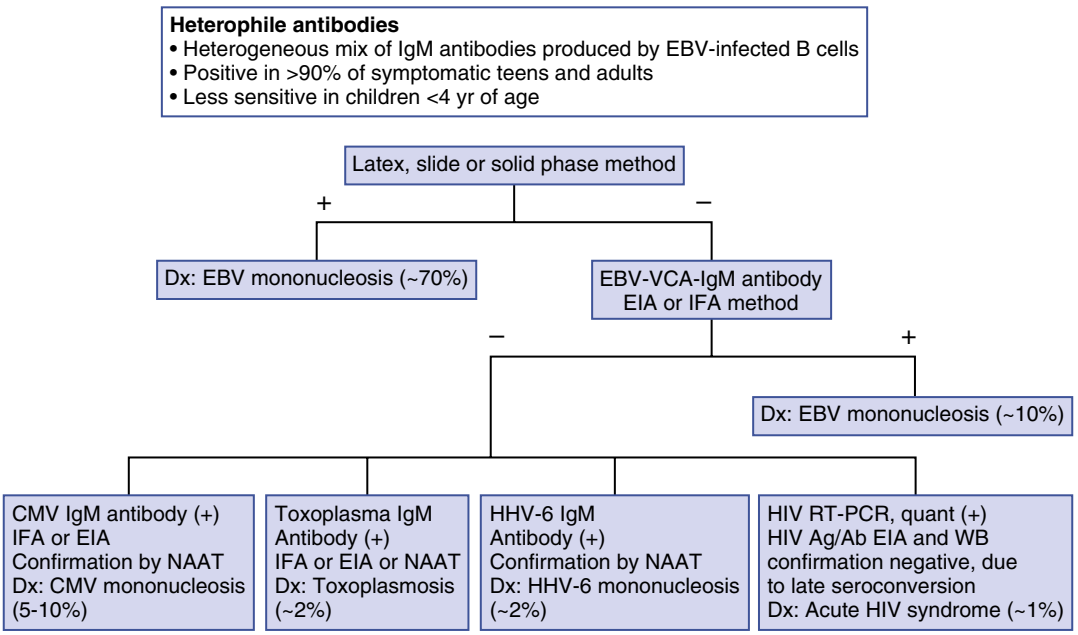

FIG. 3 Serologic evaluation of patients with clinical symptoms of acute infectious mononucleosis and atypical lymphocytosis. *Ab,* Antibody; *Ag,* antigen; *CMV,* cytomegalovirus; *Dx,* diagnosis; *EBV,* Epstein-Barr virus; *EIA,* enzyme immunoassay; *HHV-6,* human herpesvirus 6; *HIV,* human immunodeficiency virus; *IFA,* immunofluorescent assay; *IgM,* immunoglobulin M; *NAAT,* nucleic acid amplification testing; *quant,* quantitative; *RT-PCR,* reverse transcriptase polymerase chain reaction; *VCA,* viral capsid antigen; *WB,* Western blot. (From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, Philadelphia, 2017, Elsevier.)

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FIG. E1 Exudative pharyngitis with palatal petechiae in a young adult patient with infectious mononucleosis. (Courtesy Dr. Lauren Kjolhede, Baylor College of Medicine, Children's Hospital of San Antonio, San Antonio, TX. In Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

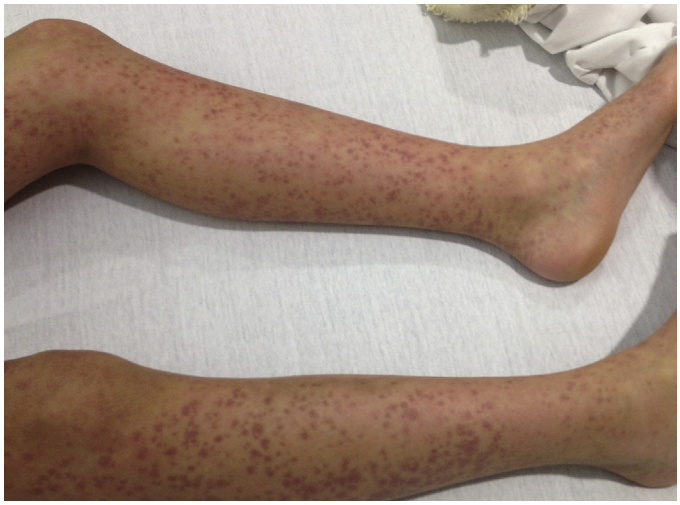

FIG. E2 Generalized exanthem on a 10-yr-old boy with infectious mononucleosis. (Courtesy Dr. Luis A. Castagnini, Baylor College of Medicine, Children's Hospital of San Antonio, San Antonio, TX. In Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

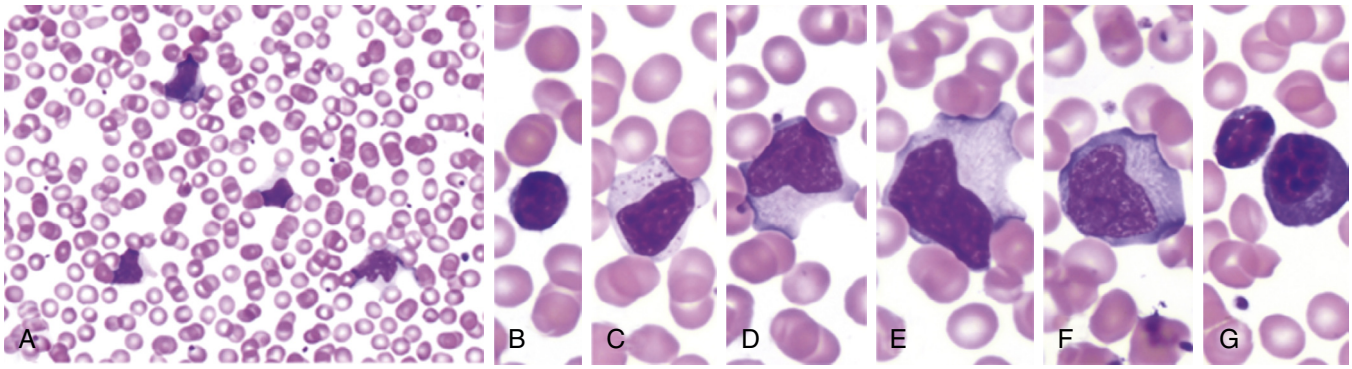

FIG. E4 Mononucleosis. Peripheral blood smear in infectious mononucleosis. Low power **(A)** shows moderately high white blood cell count and high number of reactive, or "atypical" lymphocytes. Higher power **(B** through **G)** illustrates spectrum of lymphoid morphology, including small resting lymphocyte **(B)** for comparison, large granular lymphocyte **(C),** atypical forms **(D** through **F),** also referred to as "reactive" lymphs, and circulating plasma cell **(G).** (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

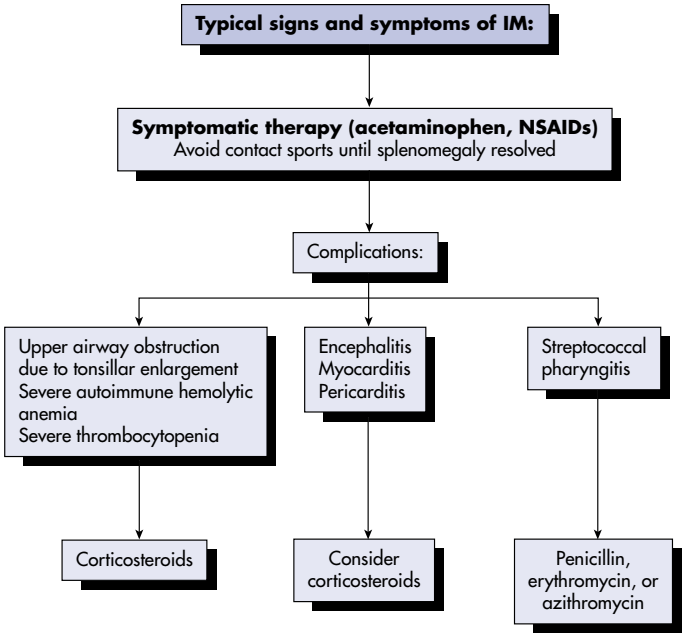

FIG. E5 Algorithm for management of infectious mononucleosis. *IM,* Infectious mononucleosis; *NSAID,* nonsteroidal antiinflammatory drug. (From Young NS et al [eds]: *Clinical hematology,* St Louis, 2006, Mosby.)

BASIC INFORMATION

DEFINITION

Morton neuroma is a compressive neuropathy of the interdigital nerve that results in forefoot pain. Morton neuroma manifests as pain or burning in the forefoot, often localized between the metatarsal heads.

SYNONYMS

Morton metatarsalgia
Interdigital neuroma
Interdigital neuritis
Plantar neuroma
Metatarsal neuralgia

ICD-10CM CODES

G57.6 Lesion of plantar nerve
G57.8 Other mononeuropathies of lower limb
G57.9 Mononeuropathy of lower limb, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Morton neuroma affects one of the common plantar digital nerves located at any of the four interspaces of the foot.
  1. The term "Morton neuroma" refers to a neuroma specifically in the second or third intermetatarsal space, whereas the term "neuroma" may be used to describe a nerve lesion in any interspace.
- Morton neuroma is usually unilateral.
- The condition occurs more frequently in women and usually presents between the fourth and sixth decade of life.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with Morton neuroma will present complaining of pain and burning in the forefoot, typically localized between the metatarsal heads of the affected interspace.
- The pain may be described as stabbing, burning, or tingling and may radiate to the digits.
- The pain is exacerbated by the use of tight-fitting shoes. Patients often feel as though they are walking on a marble.
- The pain can often be recreated by applying pressure at the plantar aspect of the interspace, starting just proximal to the metatarsal heads and proceeding distally.
- Mulder sign: Compression of the forefoot at the level of the metatarsophalangeal joints combined with plantar pressure at the affected interspace elicits a palpable "click."

ETIOLOGY

- While the exact etiology of Morton neuroma is uncertain, most histologic studies show evidence of hyperplasia within the nerve.
- The neuroma is further considered to be an entrapment neuropathy of the affected common digital plantar nerve (Fig. E1) between adjacent metatarsal heads or by the transverse metatarsal ligament.
- The common plantar digital nerves are branches of the medial and lateral plantar nerve that course distally to supply the digits of the foot, passing just beneath the deep transverse intermetatarsal ligament. Within the third intermetatarsal space, a communicating branch of the medial plantar nerve often joins with a communicating branch of the lateral plantar nerve to supply the third and fourth digits. This anatomic variation results in a thicker nerve that is more prone to trauma between the constrictive metatarsal heads, a reason often cited to explain the prevalence of Morton neuroma specifically within the third interspace.
- The deep transverse intermetatarsal ligament may also be implicated in the cause of a neuroma. If it is thickened or has aberrant bands, it may cause compression of the affected nerve.
- Soft tissue masses such as a plantar lipoma may also cause compression of the nerve against the ligament, leading to the formation of a neuroma.
- Histologic examination of resected Morton neuroma exhibits increased neural width, demyelination, intraneural fibrosis, and thickened endoneural capillaries.

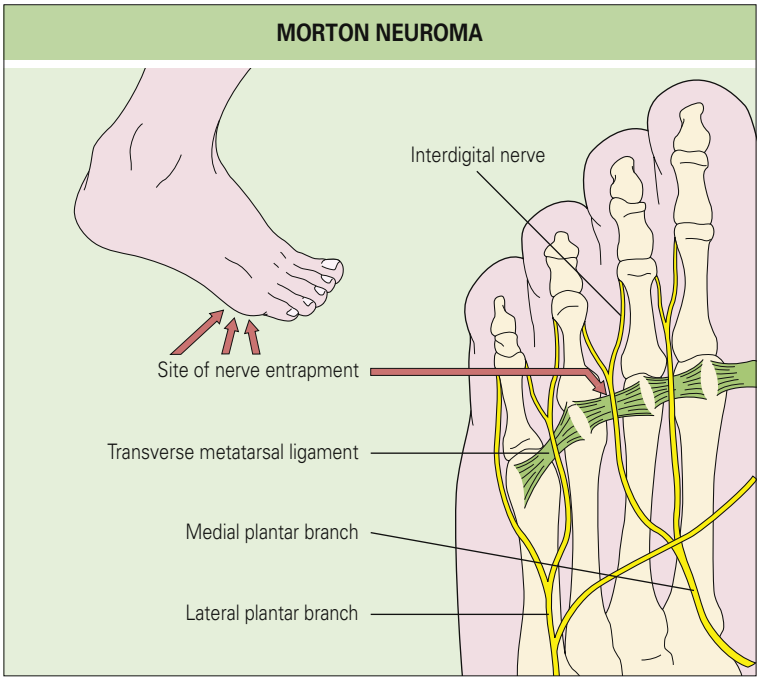

FIG. E1 On the plantar surface of the foot, the interdigital nerve is compressed below the transverse metatarsal ligament and not between the metatarsal heads (plantar view). (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

DIAGNOSIS

The diagnosis of Morton neuroma is primarily clinical. Laboratory tests and imaging modalities are generally not necessary.

DIFFERENTIAL DIAGNOSIS

- Peripheral neuropathy
- Tarsal tunnel syndrome
- Metatarsal stress fracture
- Freiberg infraction
- Metatarsophalangeal joint capsulitis or bursal swelling
- Osteoarthritis
- Rheumatoid nodule
- Plantar lipoma

WORKUP

- Exclude other causes mentioned in "Differential Diagnosis."
- A common digital nerve block with a small amount of local anesthetic into the interspace has significant diagnostic value if temporary pain relief is achieved.

IMAGING STUDIES

As Morton neuroma is a clinical diagnosis, imaging is not an absolute requirement; however, it can be useful when clinical assessment is unclear or when more than one interspace is affected.

- Weight-bearing radiographs may be performed to exclude other pathology.
- MRI may be indicated when evaluating patients with recurrent neuromas or atypical symptoms.
- Ultrasound imaging (Fig. E2) can be used to visualize a larger neuroma, which will typically present as a hypoechoic mass. Smaller lesions may be missed by imaging but are still able to cause symptoms.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Altering footwear is the first line of treatment.
- Wide shoes with a low heel are recommended.

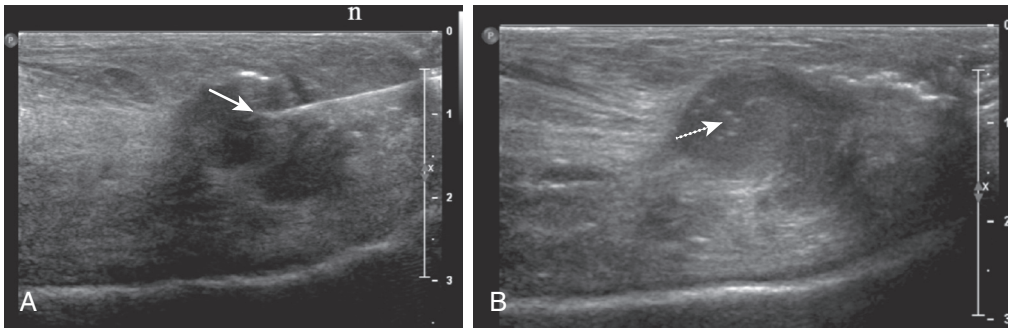

FIG. E2 Ultrasound-guided injection of a Morton neuroma in the third intermetatarsal space with steroid and anesthetic. Ultrasound image **(A)** shows the needle tip inside the Morton neuroma *(solid arrow).* Ultrasound image **(B),** immediately following the injection, shows multiple punctate echogenic foci within the Morton neuroma *(dashed arrow),* indicating successful injection of the steroid and anesthetic into the lesion. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2014, WB Saunders.)

FIG. E3 Injection for interdigital (Morton) neuroma. The area is injected most easily from the dorsal aspect, usually between the metatarsal heads of the third and fourth toes. The area of tenderness is marked, the needle is inserted to 1 inch, and steroid with anesthetic is injected. (From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, WB Saunders.)

- A metatarsal pad may also provide relief as it splays the metatarsal heads thereby decreasing the pressure on the neuroma.
- If adequate relief is noted with the previous steps, then orthotics may also be considered.
- Physical therapy treatment and evaluation may be beneficial and includes cryotherapy, ultrasonography, deep-tissue massage, and stretching exercises.

ACUTE GENERAL Rx

- If conservative measures are unsuccessful, other treatment options include serial injections (Fig. E3) with corticosteroids or a sclerosing agent. A recent level one randomized controlled trial with 41 patients demonstrated good short-term outcomes for patients with corticosteroid injections. Despite this, 48% opted for surgical excision of the neuroma at the conclusion of the trial.
- Nonsteroidal antiinflammatory agents may also provide relief.

CHRONIC RX

- Recent small-scale studies support use of new conservative modalities, including radio frequency ablation, extracorporeal shockwave therapy, and laser therapy.
- If conservative treatment fails to provide a resolution to symptoms, then surgical intervention (neurectomy) should be considered.
- Possible complications of surgery include hematoma formation, numbness, infection, and recurrent "stump" neuroma.

DISPOSITION

- Following surgery, patients are often placed on a partial weight-bearing status. Sutures are removed 2 to 3 wk following the initial surgery. Patients generally return to their previous activity level in 4 to 6 wk.
- Should a neuroma recur, a second surgical procedure may be performed.

REFERRAL

If surgery is being considered, a consultation with either a podiatrist or a foot and ankle specialized orthopedic surgeon is indicated.

PEARLS & CONSIDERATIONS

COMMENTS

- Dr. Thomas G. Morton is given credit for describing this disorder in 1876.
- Morton neuroma may occur in any of the four interspaces of the foot but most commonly affects the third interspace.
- If conservative treatment and serial injections fail, surgery should be considered for the excision of the neuroma.

RELATED CONTENT

Morton Neuroma (Patient Information)

AUTHOR: **Andrew P. Thome, Jr., MD**

SUGGESTED READINGS

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Motion Sickness (PTG)

BASIC INFORMATION

DEFINITION

Motion sickness is a clinical syndrome associated with motion or perception of motion. Patients with motion sickness suffer perspiration, nausea, vomiting, increased salivation, and generalized malaise in response to movement.

SYNONYM

Physiologic vertigo

ICD-10CM CODE
T75.3 Motion sickness

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Common
PREVALENCE (IN U.S.): Common
PREDOMINANT SEX: Male = female
PREDOMINANT AGE: Any age
PEAK INCIDENCE: Any age
GENETICS: Not known to be genetic

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Vomiting
- Sweating
- Pallor

ETIOLOGY

- Motion (e.g., amusement rides, rides in automobiles or planes)
- Exacerbated by anxiety, fumes (e.g., industrial pollutants), visual stimuli
- Fig. E1 describes a proposed neural pathway resulting in motion sickness

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute labyrinthitis
- Gastroenteritis
- Metabolic disorders
- Viral syndrome

WORKUP

None necessary in routine case

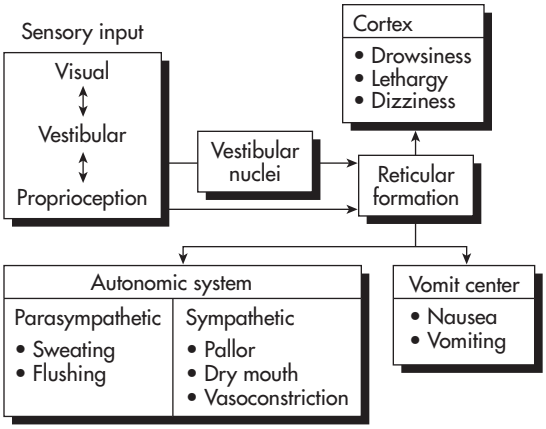

FIG. E1 Proposed neural pathway resulting in motion sickness. (From Kuhn SM: Motion sickness. In Keystone JS et al: *Travel medicine,* ed 2, Philadelphia, 2008, Elsevier, pp. 435-440.)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Fixate on far object
- Cease motion
- Avoid reading
- Avoid alcohol

ACUTE GENERAL Rx

- Scopolamine patch is most effective. It should be applied to a hairless area behind the ear every 3 days prn. It should be applied >4 hr before antiemetic effect is required.
- Oral promethazine is effective but highly sedating.
- Over-the-counter oral preparations (e.g., Dramamine) are less effective.
- Meclizine 12.5 to 25 mg q6h may be effective but is very sedating.

CHRONIC Rx

- Rarely chronic
- Symptoms generally resolve completely with cessation of motion exposure

DISPOSITION

Follow-up is not needed.

REFERRAL

If another diagnosis is suspected (e.g., purulent ear, fever, cranial nerve abnormalities)

PEARLS & CONSIDERATIONS

COMMENTS

- Many patients with migraine report having had severe motion sickness as a child.
- Improved ventilation, avoidance of large meals before travel, semirecumbent sitting, and avoidance of reading while in motion will minimize the risk of motion sickness.

RELATED CONTENT

Motion Sickness (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

BASIC INFORMATION

DEFINITION

Mucormycosis is a fungal infection by Zygomycetes fungi and includes species in the order Mucorales (*Rhizopus* sp., *Rhizomucor, Cunninghamella, Apophysomyces, Saksenaea, Absidia, Syncephalastrum, Cokeromyces, Mortierella*) and in the order Entomophthorales (*Conidiobolus* and *Basidiobolus*).

SYNONYM

Zygomycosis

ICD-10CM CODES

B46.0 Pulmonary mucormycosis
B46.1 Rhinocerebral mucormycosis
B46.3 Cutaneous mucormycosis
B46.4 Disseminated mucormycosis
B46.5 Mucormycosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Mucormycosis is the third most frequent cause of invasive fungal infections in immunocompromised hosts. These fungi are ubiquitous in nature and can be found in soil and decaying vegetation. Infection is seen in association with underlying conditions, including diabetes mellitus especially with ketoacidosis, hematologic malignancies, stem cell or solid organ transplants, severe burns or trauma, treatment with deferoxamine or iron overload states, steroid treatment, immunodeficiency states (e.g., AIDS), injection drug use, and malnutrition. Immunocompetent hosts may become infected in tropical climates.
- The fungus gains entry to the body most commonly through the respiratory tract. The spores are deposited in the nasal turbinates and may be inhaled into the pulmonary alveoli. In cases of cutaneous mucormycosis, the spores are introduced directly into the skin lesion.
- After a tornado with winds >200 mph struck Joplin, Missouri, in May 2011, there were 13 confirmed cases of mucormycosis *(Apophysomyces trapeziformis),* including five deaths. While two patients had diabetes, none were immunocompromised. It was felt that the fungus entered through wounds sustained during the tornado. Wooden splinters were found in four patients.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Rhinocerebral-rhinoorbital-paranasal syndrome (Fig. E1) is the most common presentation, which presents with fever, facial and orbital pain, headache, diplopia, loss of vision, facial or orbital cellulitis, facial anesthesia, cranial nerve dysfunction, black nasal discharge, epistaxis, and seizure. Physical findings in this situation include proptosis; chemosis; nasal, palatal, or pharyngeal necrotic ulcerations; and retinal infarction. Thrombosis of the cavernous sinus or internal carotid artery may occur. This form of mucormycosis is found most commonly in diabetics, primarily in the presence of acidosis, and in patients with leukemia and neutropenia. Isolated CNS mucormycosis may result from hematogenous spread (can occur with injection drug users).
- Pulmonary mucormycosis can present with pneumonia, lung abscess, pulmonary infarction, pleurisy, pleural effusion, hemoptysis, chills, and fever. This form of mucormycosis is found most commonly in immunocompromised neutropenic hosts after chemotherapy for hematologic malignancies.
- Gastrointestinal zygomycosis presents with abdominal pain, diarrhea, gastrointestinal hemorrhage, ulcers, peritonitis, and bowel infarction. This form of mucormycosis is found most commonly in patients with extreme malnutrition and is believed to arise from ingestion of spores of the fungi.
- Cutaneous zygomycosis presents as nodular lesions (hematogenous seeding) or a wound infection. It primarily involves the epidermis and dermis after use of occlusive dressings that have not been properly sterilized.
- Cardiac mucormycosis is a form of endocarditis.
- Septic arthritis and osteomyelitis.
- Brain abscess occurs most often from extension of the fungus from the nose or paranasal sinuses through adjacent bones in severely debilitated patients.
- Disseminated zygomycosis (rare but uniformly fatal).
- Physical findings depend on the location of the infection.

ETIOLOGY & PATHOGENESIS

The cause of mucormycosis is infection by a fungus of the Zygomycetes class (see "Definition"). Rhizopus and mucor species are the most common causes. Normal host defenses include leukocytes and pulmonary macrophages. Quantitative (e.g., neutropenia) or qualitative (e.g., diabetes mellitus or steroid treatment) disruption in the host defenses predisposes the patient to infection. Patients treated with deferoxamine for iron-overload states are also at risk.

DIAGNOSIS

A high index of suspicion is critical since mucormycosis infection is acute and rapidly faster if untreated. The hallmark of mucormycosis is infarction and necrosis of host tissues that result from invasion of the vasculature by the fungal elements. Black eschars and discharges should be closely evaluated. Diagnosis depends on the demonstration of the organism in the tissue of a biopsy specimen.

DIFFERENTIAL DIAGNOSIS

- Infection of the sites described previously by other organisms (bacterial [including tuberculosis and leprosy], viral, fungal, or protozoan)
- Noninfectious tissue necrosis (e.g., neoplasia, vasculitis, degenerative) of the sites described previously

WORKUP

- Biopsy of infected tissue with direct-light microscopy examination establishes the diagnosis within minutes of the biopsy in the case of nasopharyngeal infection. Fungal hyphae are broad (5- to 15-micron diameter) and irregularly branched and have rare septations, in contrast to molds such as *Aspergillus,* which are narrower, have regular branching, and have many septations.
- Bronchoalveolar lavage or bronchoscopy with biopsy for smear, culture, and histologic examination.
- Radiographs and other imaging studies such as CT of symptomatic sites may be required before infection is suspected and tissue specimens are obtained.
- It should be noted that serum tests that measure fungal cell wall components, such as the 1, 3-beta D glucan assay and the Aspergillus galactomannan assay used to diagnosis other invasive fungal diseases, will be negative in mucormycosis, as mucormycosis agents lack these cell wall components.

TREATMENT

- Aggressive correction of underlying disease (e.g., hyperglycemia, high steroid doses, use of immunosuppressive drugs) should be undertaken.
- Standard therapy consists of aggressive surgical debridement of involved tissues and antifungal therapy. For invasive mucormycosis recommended treatment is with a lipid formulation of amphotericin B that allows higher doses with less nephrotoxicity. The start dose is 5 mg/kg of liposomal amphotericin B or amphotericin B lipid complex. Doses as high as 10 mg/kg have also been used. Weeks of therapy are usually required.
- Traditional amphotericin B given IV at a daily dose of 1.0 to 1.5 mg/kg infused over 2 to 4 hr daily for a total of 1 to 4 g can also still be used, but is associated with significant nephrotoxicity and adverse reactions such as fever, chills, myalgias, vomiting, and electrolyte disturbances.
  1. Other antifungals do not appear to be effective except posaconazole, which may serve as an oral step-down therapy after amphotericin B at a dose of 400 mg bid with a fatty meal. Isavuconazole is another agent with efficacy in mucormycosis that, like posaconazole, comes in IV and oral formulation and can serve to transition patient from IV to PO.
  2. Some studies suggest that caspofungin with amphotericin B may be synergistic for *Rhizopus oryzae* infections only.
  3. The role of colony-stimulating factors remains unclear, beyond that of increas-

ing the neutrophil count in patients with neutropenia.
4. Hyperbaric oxygen has been used in some patients but its utility in therapy is still not clear.

PROGNOSIS

- Sinus infection with no underlying disease: 75% survival
- Sinus infection with diabetes: 60% survival
- Sinus infection with renal disease: 25% survival

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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Zahoor B et al: Cutaneous mucormycosis secondary to penetrative trauma, *Injury* 47:1383-1387, 2016.

FIG. E1 Extensive central necrosis and associated swelling and erythema in a patient with mucormycosis. (From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

BASIC INFORMATION

DEFINITION

These are gram-negative bacteria that are resistant to at least one antimicrobial in three or more antimicrobial classes (antipseudomonal penicillins, third-generation cephalosporins, fluoroquinolones, carbapenems, and aminoglycosides).

SYNONYMS

Carbapenem-resistant Enterobacteriaceae (CRE)
Extended-spectrum beta-lactamases (ESBL)
Multidrug-resistant gram-negative bacilli (MDR-GNB)
Multidrug-resistant organisms (MDRO)
New Delhi metallo-beta-lactamase-1 (NDM-1)

ICD-10CM CODES

Z16.10	Resistance to unspecified beta lactam antibiotics
Z16.30	Resistance to unspecified antimicrobial drugs

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: There is an increasing incidence of these bacteria in hospitals and long-term care facilities in the U.S. and around the world. ESBL bacteria were first discovered in Europe in 1984 and in the U.S. in 1988. CRE bacteria were first described in the late 1990s in the U.S. The NDM-1 bacteria were first noted in 2009 in Sweden in a patient from India.

PREDOMINANT SEX & AGE: These bacteria can be seen in any age group. They may be more frequent in women due to increased risk of urinary tract sepsis.

RISK FACTORS: In general, these bacteria are more common in hospitals and long-term care facilities, but they are spread nosocomially through patient care and thus are now entering the community, where the incidence is also increasing. Specific risk factors include:

- Length of stay in the hospital
- Length of ICU stay
- Use of central line catheters
- Abdominal surgery
- Presence of gastrostomy or jejunostomy tube
- Prior administration of any antibiotic
- Prior residence in a long-term care facility
- Presence of indwelling urinary catheter

PHYSICAL FINDINGS & CLINICAL PRESENTATION

All these resistant bacteria have the capability of causing diverse infections, including:

- Pneumonia
- Bacteremia
- Urinary tract sepsis
- Central line–associated infections
- Ventilator-associated pneumonia (VAP)
- Surgical site infections
- VAP from *A. baumannii* now accounts for 8.4% of GNR pneumonias in the ICU

ETIOLOGY

- Several different classes of MDR-GNRs exist based on their resistance mechanism.
  1. ESBL: These bacteria contain enzymes that break open the beta-lactam ring of penicillins, cephalosporins, and aztreonam and thus inactivate antibiotics from those classes. Enzymes conferring resistance include:
     a. TEM beta-lactamases
     b. SHV beta-lactamases
     c. CTX-M beta lactamases
     d. OXA beta-lactamases
     e. These enzymes are plasmid-mediated and thus can spread from one gram-negative bacteria to another, causing outbreaks in a single institution
  2. CRE: Enzymes conferring resistance include:
     a. Class A beta-lactamases: Encoded on chromosomes or plasmids (e.g., *Klebsiella pneumoniae* carbapenemase [KPC], which has caused outbreaks in hospitals around the world)
     b. Class B: Metallo-beta-lactamases (e.g., NDM-1). Encoded on a mobile plasmid that can spread to other gram-negative bacteria
     c. Class C and class D beta-lactamases
  3. *MCR-1* gene: In May 2016, the *MCR-1* gene was reported for the first time in *E. coli* from a patient (urine culture) in the U.S. This gene makes bacteria resistant to the antibiotic colistin, which is used to treat other MDR-GNR organisms. This raises the concern that this plasma-encoded gene could be spread to CRE bacteria.
- *Stenotrophomonas maltophilia:* MDR-GNR that acts as an opportunistic pathogen among mostly hospitalized patients with high morbidity and mortality. It has intrinsic or acquired resistance mechanisms to multiple antibiotic classes and has the ability to adhere to foreign materials and form a biofilm, which escapes host defenses.
- *Acinetobacter* sp. (e.g., *Acinetobacter baumannii*): Strains have emerged that are resistant to all commercially available antibiotics. These bacteria have the capability to acquire diverse mechanisms of resistance including:
  1. AmpC beta-lactamases
  2. Beta-lactamases: Serine and metallo-beta-lactamases

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other gram-negative rods such as:

- *Pseudomonas aeruginosa*
- *Klebsiella pneumoniae* that are not ESBL or CRE by resistance pattern
- *Morganella morganii*
- *Providencia, Proteus* sp., *Serratia*

WORKUP

- Detection of ESBL and CRE bacteria can pose problems for the clinical microbiology laboratory:
  1. To detect ESBL bacteria: Automated systems such as Vitek use disk diffusion or broth dilution techniques, or double disk test or E-test strip with clavulanate.
  2. To detect CRE: Modified Hodge test to detect carbapenemase-producing bacteria. Polymerase chain reaction testing, pulsed-field gel electrophoresis, and whole genome sequencing are useful for detecting CRE.
  3. In 2010, testing guidelines with respect to susceptibility involving several beta-lactam antibiotics were changed to better identify these bacteria via automated systems.

LABORATORY TESTS

Clinical testing is the same in infections from these resistant organisms as with nonresistant organisms:

- Cultures of any wounds, blood, sputum, urine, catheter tips
- CBC, liver function tests, urinalysis

TREATMENT

- Because of multidrug resistance, only a few reliable antibiotics are available to treat these infections.
  1. ESBL bacteria: Carbapenem antibiotics such as imipenem, meropenem, ertapenem, or the cephalosporin cefoxitin or tigecycline.
  2. CRE bacteria: Selection of antibiotic will depend on testing but tigecycline may be used clinically. Other alternatives include:
     a. IV colistin.
     b. *Stenotrophomonas maltophilia*: Only available agents are Bactrim (drug of choice), Levaquin, and minocycline.
     c. *A. baumannii*: Will depend on susceptibility testing, but ampicillin-sulbactam, imipenem or meropenem, or tigecycline can be used for MDR strains. For pan-resistant strains, IV colistin ± rifampin can be used. Inhaled colistin can be used for pneumonia patients.
     d. Newer antibiotics such as ceftolozane/tazobactam and ceftazidime/avibactam offer coverage for some of the resistant enzymes, but not all, and thus they require susceptibility testing to confirm.
     e. A next generation aminoglycoside plazomicin (Zemdri) was approved in 2018 for complicated urinary tract infections and has efficacy against CRE.

DISPOSITION

- Morbidity and mortality can be quite high with infections from these MDR bacteria.
  1. Nosocomial *Acinetobacter* pneumonia carries a mortality rate of 35% to 70%.
  2. *Stenotrophomonas* infections carry a mortality rate of 21% to 69%.
  3. ESBL infections carry a mortality rate of 3.7% despite therapy with carbapenem antibiotics.

AUTHOR: **Glenn G. Fort, MD, MPH**

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Multifocal Atrial Tachycardia

BASIC INFORMATION

DEFINITION

Multifocal atrial tachycardia (MAT) is a supraventricular tachyarrhythmia (rate greater than 100 beats/min) with P waves having at least three or more different morphologies and irregular P-P, P-R, and R-R intervals. MAT is differentiated from atrial fibrillation by discrete P wave depolarizations and an isoelectric baseline between P waves.

SYNONYMS

MAT
Chaotic atrial rhythm
Chronic atrial tachycardia
Repetitive multifocal paroxysmal atrial tachycardia
Multifocal ectopic atrial tachycardia
The term *wandering pacemaker* is used for a similar arrhythmia associated with a normal or slow heart rate (<100 beats/min)

ICD-10CM CODE

I47.1 Supraventricular tachycardia

EPIDEMIOLOGY & DEMOGRAPHICS

Estimated prevalence in hospitalized patients of 0.05% to 0.32%. Average age is 70s. Usually associated with underlying pulmonary disease with right atrial electromechanical delay. Chronic obstructive pulmonary disease (COPD) is present in approximately 55% of patients with MAT. It may also be seen in patients with valvular heart disease, pulmonary hypertension, and hypomagnesemia.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms:
- Palpitation
- Lightheadedness
- Syncope
- Symptoms of the underlying pulmonary disease
- Physical findings associated with the underlying pulmonary disease

ETIOLOGY

- Exact mechanism unknown
- Potentially caused by right atrial distention such as in pulmonary hypertension due to underlying lung disease
- Exacerbated by underlying pulmonary disease (COPD, hypoxia, pulmonary embolism, pneumonia), cardiac disease, hypercarbia, acidosis, electrolyte disturbances

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Atrial fibrillation (up to 55% of patients with MAT will develop atrial fibrillation)
- Atrial flutter with variable AV conduction
- Sinus tachycardia
- Paroxysmal atrial tachycardia
- Sinus tachycardia with premature atrial or ventricular contractions

WORKUP

- ECG (Fig. 1)
- Chest x-ray
- Pulmonary function tests
- Electrolytes
- Arterial blood gases

TREATMENT

- Correction and/or improvement in the underlying pulmonary or metabolic dysfunction if possible.
- Avoid drugs such as theophylline, isoproterenol, etc.
- Electrolyte repletion, especially magnesium and potassium, to normal levels.
- Intravenous magnesium infusion may occasionally be helpful in patients with normal magnesium levels.
- Calcium channel blockers: Verapamil may be effective acutely and chronically and is often used as first line in patients with preserved LV function.
- β-blockers are typically contraindicated by obstructive lung disease or acute heart failure.
- If the arrhythmia is asymptomatic, it can be left untreated.
- Direct current cardioversion is ineffective.
- No significant role for antiarrhythmics or catheter ablation.
- Anticoagulation is not indicated, although some recent studies have linked frequent atrial ectopy on ambulatory monitoring with stroke risk.
- In extreme cases of refractory MAT in symptomatic patients who cannot tolerate medical therapy or in MAT resistant to medical therapy, AV nodal ablation with pacemaker implantation has been performed.
- Table E1 summarizes the treatment of multifocal atrial tachycardia.

SUGGESTED READINGS

Available at ExpertConsult.com

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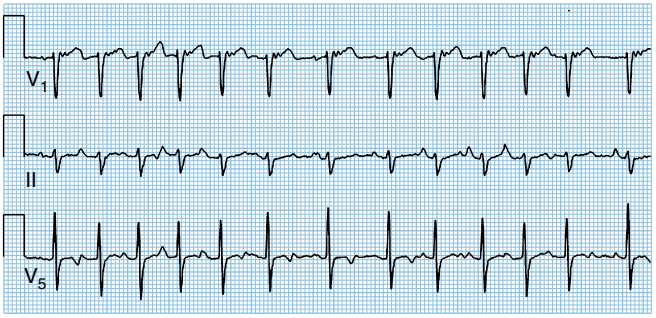

FIG. 1 Multifocal atrial tachycardia. This three-lead rhythm strip (leads V_1, II, and V_5) shows an irregularly irregular narrow QRS complex rhythm. However, unlike atrial fibrilation (AF), each QRS complex is preceded by discrete P waves. There are at least three different P wave morphologies and PR intervals, consistent with MAT. (From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

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TABLE E1 Multifocal Atrial Tachycardia Therapy

Acute therapy, stable and unstable	• Treat underlying condition. Aggressive treatment of COPD exacerbation usually treats arrhythmia, but MAT may persist for hours to days after management of the underlying condition is effective. Treatment of the MAT itself does not affect the course or prognosis of the medical illness. Avoid digoxin, as AV block and slowing of ventricular rate is unlikely to occur. DCC is ineffective in terminating the rhythm. • Cardioversion is of no benefit for MAT. However, AF may be confused with MAT; if the diagnosis is uncertain and the patient is hemodynamically unstable, cardioversion can be considered in selected cases. Hemodynamic instability generally results from the underlying medical condition and not from the rhythm or rapid rate per se. • Lower the dose of sympathomimetics and methylxanthines, as tolerated, if applicable. • Maintain K^+ and Mg^{2+} within normal limits. • Drugs to control ventricular rate (data on effectiveness are inconclusive): Preferred: Calcium blocker (IV or oral diltiazem). Verapamil can cause substantial hypotension in patients with COPD but may be effective. Ventricular rate control is difficult due to excess catecholamines for most of these patients. β-adrenergic blockers rarely can be given due to concurrent bronchospastic pulmonary disease. • IV magnesium 2- to 4-g bolus of magnesium sulfate may terminate the episodes and help control the ventricular rate, but success is limited and unpredictable. • Digoxin may worsen MAT and is unlikely to control the ventricular response. • Amiodarone can be considered to control ventricular rate and suppress the arrhythmia, but there are no data to support its use.
Chronic prevention	• Options include calcium channel blockers (e.g., oral diltiazem) for ventricular rate control or possibly amiodarone to prevent recurrences; drug therapy without aggressive treatment of the underlying condition is often futile. • Treat pulmonary disease; maintain K^+ >4.0 and Mg^{2+} >2.0, if possible.
MI	• Rapid rate and ineffective atrial kick (PR interval <0.14 s) can worsen ischemia and CHF. Rate control is often required. A calcium channel blocker such as diltiazem is the first-line therapy, unless β-adrenergic blockers can be tolerated.

AF, Atrial fibrillation; *AV,* atrioventricular; *CHF,* congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *DCC,* direct current cardioversion; *IV,* intravenous; *MAT,* multifocal atrial tachycardia; *MI,* myocardial infarction.

From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.

BASIC INFORMATION

DEFINITION

Multiple endocrine neoplasia (MEN) refers to a group of heritable genetic syndromes characterized by the development of specific groups of tumors of the endocrine glands.

SYNONYMS

MEN I: Wermer syndrome
MEN IIA: Sipple syndrome

ICD-10CM CODES

E31.2	Multiple endocrine neoplasia [MEN] syndromes
E31.20	Multiple endocrine neoplasia [MEN] syndrome, unspecified
E31.21	Multiple endocrine neoplasia [MEN] syndrome type I
E31.22	Multiple endocrine neoplasia [MEN] syndrome type IIA
E31.23	Multiple endocrine neoplasia [MEN] syndrome type IIB

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- MEN I: 25 in 10,000
- MEN II: 1 in 30,000

PREVALENCE:

- MEN I: 1/30,000
- MEN II: 1/35,000 (predominantly MEN IIA)

GENETICS:

- MEN I: Autosomal-dominant mutation in MEN1 tumor-suppressor gene
- MEN IIA and MEN IIB: Autosomal-dominant mutations in RET proto-oncogene

RISK FACTORS: Family history of MEN syndrome, although it can also occur sporadically

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients may present due to screening or may present with a MEN-associated tumor. Tumors are found incidentally due to biochemical abnormalities or to symptoms.
- MEN I (PPP [pituitary, pancreas, parathyroid])
  1. Diagnostic criteria generally include two MEN-associated tumors, one tumor in a patient with a family history, or positive genetic testing.
  2. Primary hyperparathyroidism (parathyroid adenoma or hyperplasia) is the most common manifestation and can cause hypercalcemia (urolithiasis, GI disturbance, bone pain, neuropsychiatric disturbances).
  3. Pancreatic neuroendocrine tumors cause symptoms related to their secretory properties or metastases.
     a. Gastrinoma: Peptic ulcers, diarrhea, esophageal symptoms (see "Gastrinoma")
     b. Insulinoma: Hypoglycemic symptoms upon fasting and after exercise (see "Insulinoma")
     c. Glucagonoma: Necrolytic migratory erythema (a blistering skin lesion), diabetes/glucose intolerance, weight loss
     d. VIPoma: Diarrhea, hypokalemia, decreased gastric acid
     e. Nonfunctioning tumors can metastasize (frequently to the liver), a frequent cause of death in MEN I
  4. Pituitary tumors may cause compressive symptoms, such as visual field defects or hypopituitarism (see "Pituitary Adenoma"). Hormonal secretion may also cause symptoms.
     a. Prolactinoma (most common pituitary tumor in MEN I): Menstrual irregularities, sexual dysfunction, gynecomastia, and/or galactorrhea (see "Prolactinoma").
     b. Somatotroph adenomas (producing growth hormone): Gigantism or acromegaly (frontal bossing, increased shoe/hat size, hyperglycemia, hyperhidrosis) depending on patient age (see "Acromegaly").
     c. Corticotroph adenomas (producing adrenocorticotropic hormone): Cushingoid features such as weight gain, moon facies, hyperglycemia, bone loss, proximal muscle weakness, hypertension, hypokalemia (see "Cushing Disease and Syndrome").
     d. Nonfunctioning (nonsecretory) tumors.
  5. Other manifestations: Carcinoid tumors, collagenomas, angiofibromas, meningiomas, lipomas.
- MEN IIA:
  1. Medullary thyroid carcinoma (MTC) is a tumor of the thyroid's calcitonin-secreting C cells. It can present with a neck mass, as well as flushing and diarrhea due to elevated calcitonin levels.
  2. Primary hyperparathyroidism: See MEN I. Less aggressive in MEN IIA.
  3. Pheochromocytoma is an adrenal tumor producing catecholamines, which can lead to life-threatening hypertensive crises.
- MEN IIB:
  1. Medullary thyroid carcinoma (MTC)
  2. Pheochromocytoma
  3. Oral mucosal neuromas

ETIOLOGY

Tumor development facilitated by the previously described genetic mutations (Table E1).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Tumors associated with MEN may occur sporadically.

WORKUP

- MEN I: Note that opinions vary regarding the aggressiveness and frequency of screening for MEN-associated tumors.
  1. Genetic testing: Offered to patients meeting MEN I clinical criteria or to patients in whom there is high suspicion, as well as to first-degree relatives of MEN I patients.
  2. Hyperparathyroidism screening: Parathyroid hormone (PTH) and calcium annually.
  3. Pancreatic tumor screening: Annual pancreas imaging (endoscopic ultrasonography, CT, or MRI) and annual biochemical testing (glucose, gastrin, vasoactive intestinal peptide [VIP], glucagon, insulin, pancreatic polypeptide, chromogranin A). Notably, Gallium-68 DOTATATE PET-CT is an exciting new tool for neuroendocrine tumor localization, though it is not typically utilized in screening at this time.
  4. Pituitary tumor screening: Insulin-like growth factor 1 (IGF-1) and prolactin annually and pituitary MRI every 3 to 5 yr.
  5. Carcinoid tumor screening: Chest CT or MRI every 2 yr.
- MEN IIA:
  1. Genetic testing: At-risk members of families with known RET mutations should undergo screening for the specific mutation. Patients with MTC should have genetic testing of the tumor and genetic testing based on results. Cutaneous lichen amyloidosis (a skin finding) should prompt testing; Hirschsprung disease may also prompt testing.
  2. Hyperparathyroidism screening: PTH and calcium annually.
  3. Pheochromocytoma: Plasma catecholamines and metanephrines annually for screening, age to begin depending on specific mutation; CT and MRI may localize; I-123 and PET (possibly including Gallium-68 DOTATATE PET-CT) also helpful for localization.
  4. MTC screening: Depends on risk category; physical exam, neck ultrasound, and calcitonin level yearly; carcinoembryonic antigen may also be indicated.
- MEN IIB:
  1. Genetic testing: See MEN IIA
  2. Pheochromocytoma: See MEN IIA
  3. MTC screening: Although there may be a role for monitoring, prophylactic thyroidectomy is typically performed early

LABORATORY TESTS

See "Workup."

IMAGING STUDIES

See "Workup."

TREATMENT

No therapy to reverse the underlying cause. Treatment (both medical and surgical) focuses on tumor prevention and management.

NONPHARMACOLOGIC THERAPY

- MEN I:
  1. For hyperparathyroidism, surgical parathyroidectomy is indicated in patients with significant hypercalcemia, osteoporosis, renal disease, or nephrolithiasis or found to be at high risk for nephrolithiasis. Hyperparathyroidism may be treated surgically with subtotal or total

parathyroidectomy, which may include gland reimplantation at an alternate site.
2. Pituitary tumors may be surgically excised via transsphenoidal approach; notably, medical therapy is first line for prolactinoma.
3. Pancreatic tumor treatment is extremely variable. Gastrinoma is frequently complicated by duodenal metastases, which are difficult to treat surgically. Ulcers caused by gastrinoma may require endoscopic or surgical management. Surgery is preferred for insulinoma, VIPoma, and glucagonoma. Nonfunctioning tumors may be treated surgically depending on tumor size and location. Conservative management for insulinoma may involve frequent carbohydrate intake.

- MEN IIA:
  1. MTC is generally treated surgically. Prophylactic thyroidectomy is considered based on genetic mutation. Almost all children with MEN IIA will require thyroidectomy (screening as previously described). Patients should undergo ultrasound and total thyroidectomy with cervical lymph node dissection. Extent of further neck dissection depends on metastases and may be guided by calcitonin levels. A more palliative surgical approach is considered in the setting of advanced disease.
  2. Hyperparathyroidism: Resection of only enlarged glands with intraoperative PTH monitoring is preferred.
  3. Pheochromocytoma is treated surgically. Unilateral adrenalectomy is preferred, although many patients will develop a contralateral pheochromocytoma. Preoperative blood pressure control with alpha blockade is key. If present, pheochromocytoma must be removed before thyroidectomy.
- MEN IIB:
  1. MTC: Prophylactic thyroidectomy offered in childhood.
  2. Pheochromocytoma: See MEN IIA.

ACUTE GENERAL Rx

- MEN I:
  1. Hyperparathyroidism causes hypercalcemia that may be treated with IV hydration, diuretics, and bisphosphonates. Early vitamin D repletion prevents bone destruction postoperatively.
  2. Gastrinoma may lead to peptic ulcers requiring IV proton-pump inhibitor (PPI).
  3. Supportive care (glucose for hypoglycemia caused by insulinoma; fluids and electrolytes for hypovolemia caused by diarrhea from VIPoma or gastrinoma) is required.
- MEN IIA:
  1. Hyperparathyroidism: See "MEN I."
  2. Pheochromocytoma: Preoperative blood pressure control is key; alpha blockers are first line. Phenoxybenzamine irreversibly blocks alpha adrenergic receptors; doxazosin is also first line. Calcium channel blockers and then beta-blockers can be added if needed.
- MEN IIB:
  1. Pheochromocytoma: See "MEN IIA."

CHRONIC Rx

- MEN I:
  1. Hyperparathyroidism may be amenable to agonists of the calcium-sensing receptor (cinacalcet), although surgery is preferred in patients who meet surgical criteria and are operative candidates.
  2. Pancreatic tumors may benefit from medical therapy.
     a. Gastrinoma: PPI or H2 antagonists
     b. Insulinoma: Diazoxide or somatostatin agonists (such as octreotide)
     c. Glucagonoma and VIPoma: Somatostatin agonists
  3. Pituitary tumors may be treated medically although surgical treatment is first-line with the exception of prolactinoma (for which medical therapy is first line). Radiation therapy and/or medical therapy are considered in cases of incomplete resection or regrowth.
     a. Prolactinoma: Dopamine agonists (bromocriptine or cabergoline)
     b. Somatotroph adenoma: Somatostatin or dopamine agonists, growth hormone receptor antagonists
     c. Corticotroph adenoma: Antiadrenal agents, adrenal enzyme blocker (such as ketoconazole), somatostatin or dopamine agonists, glucocorticoid receptor blockers
  4. MEN II A:
     a. Hyperparathyroidism: See "MEN I."
     b. MTC: Tyrosine kinase inhibitors and chemotherapy may help treat metastatic disease. After thyroidectomy, levothyroxine is indicated (TSH suppression not required).

COMPLEMENTARY & ALTERNATIVE MEDICINE

MEN is unlikely to be amenable to this.

DISPOSITION

Most workup can be done as an outpatient (multidisciplinary team); inpatient stays may be required due to acute complications or for surgical procedures.

REFERRAL

Patients with MEN should be followed by a multispecialty team, including endocrinologists, endocrine surgeons, and genetic counselors.

PEARLS & CONSIDERATIONS

COMMENTS

MEN is a group of genetic syndromes that requires close monitoring and intervention to prevent and treat tumor development, as well as genetic counseling of patients and family members.

PREVENTION

Prevention focuses on screening for MEN in persons at risk and early identification of MEN-associated tumors.

PATIENT & FAMILY EDUCATION

- American Multiple Endocrine Neoplasia Support: http://www.amensupport.org/
- Association for Multiple Endocrine Neoplasia Disorders: http://www.amend.org.uk/

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Acromegaly (Related Key Topic)
Cushing Disease and Syndrome (Related Key Topic)
Gastrinoma (Related Key Topic)
Hyperparathyroidism (Related Key Topic)
Insulinoma (Related Key Topic)
Pheochromocytoma (Related Key Topic)
Pituitary Adenoma (Related Key Topic)
Prolactinoma (Related Key Topic)
Thyroid Carcinoma (Related Key Topic)

AUTHORS: **Harikrashna B. Bhatt, MD,** and **Russell E. Bratman, MD**

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TABLE E1 Tumors in Multiple Endocrine Neoplasia Syndromes

Type (Chromosomal Location)	Tumors (Estimated Penetrance)
MEN 1 (11q13)	Parathyroid adenoma (90%)
	Enteropancreatic tumor (30%-70%) Gastrinoma (40%) Insulinoma (10%) Nonfunctioning and PPoma (20%-55%) Glucagonoma (<1%) VIPoma (<1%)
	Pituitary adenoma (30%-40%) Prolactinoma (20%) Somatotropinoma (10%) Corticotropinoma (<5%) Nonfunctioning (<5%)
	Associated Tumors Adrenal cortical tumor (40%) Pheochromocytoma (<1%) Bronchopulmonary NET (2%) Thymic NET (2%) Gastric NET (10%) Lipomas (30%) Angiofibromas (85%) Collagenomas (70%) Meningiomas (8%)
MEN 2 (10 cen- 10q11.2)	
MEN 2A	MTC (90%) Pheochromocytoma (50%) Parathyroid adenoma (20%-30%)
MTC only	MTC (100%)
MEN 2B (also known as MEN 3)	MTC (>90%) Pheochromocytoma Associated abnormalities (40%-50%) Mucosal neuromas Marfanoid habitus Medullated cornel nerve fibers Megacolon

MEN, Multiple endocrine neoplasia; *MTC,* medullary thyroid carcinoma; *NET,* neuroendocrine tumor; *PPoma,* pancreatic polypeptidoma; *VIPoma,* vasoactive intestinal peptidoma.

Modified from Thakker RV: Multiple endocrine neoplasia type 1. In Jameson JL et al (eds): *Endocrinology: adult and pediatric,* Philadelphia, 2016, WB Saunders.

BASIC INFORMATION

DEFINITION

Multiple myeloma (MM) is a plasma cell neoplasm characterized by clonal proliferation of malignant plasma cells in the bone marrow, monoclonal protein in the blood or urine, and associated end-organ dysfunction. The transition from normal cells to genomic instability is not well understood, but current evidence suggests that antigenic stimulation may be a key factor (Fig. E1). Diagnostic criteria for the diagnosis of MM was revised by the International Myeloma Working Group (IMWG) in 2014 and now requires the following:

- Presence of ≥10% plasma cells on examination of the bone marrow (or biopsy of a tissue with monoclonal plasma cells) and any one or more of the following myeloma-defining events:
  1. Evidence of end-organ damage (calcium elevation, renal insufficiency, anemia, or bone lesions [CRAB criteria])
  2. Clonal bone marrow plasma cell percentage ≥60%
  3. Involved: Uninvolved serum free light ratio ≥100
  4. >1 focal lesion on MRI studies

SYNONYM

MM

ICD-10CM CODES

C90.00	Multiple myeloma not having achieved remission
C90.01	Multiple myeloma in remission
C90.02	Multiple myeloma in relapse

EPIDEMIOLOGY & DEMOGRAPHICS

ANNUAL INCIDENCE:

- Five cases/100,000 persons (African Americans affected twice as frequently as whites, males more than females).
- MM accounts for 10% of all hematologic cancers and is the most common primary bone malignancy.
- More than 30,770 new cases and 12,770 deaths occurred in 2018 in the U.S.

PREDOMINANT AGE: The peak incidence is in the seventh decade at a median age of 70 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The patient usually comes to medical attention because of one or more of the following:

- Bone pain (58%) commonly in the back and thorax or pathologic fractures (30%) caused by osteolytic lesions
- Anemia from bone marrow infiltration by plasma cells
- Recurrent infections as a result of impaired neutrophil function and deficiency of normal immunoglobulins (humoral deficiency)
- Nausea and vomiting caused by constipation and uremia
- Delirium resulting from hypercalcemia
- Neurologic complications, such as spinal cord or nerve root compression, blurred vision from hyperviscosity
- Purpura, epistaxis from thrombocytopenia
- Paresthesias, weight loss, generalized weakness

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Metastatic carcinoma to bone marrow
- Lymphoma, non-Hodgkin
- Bone neoplasms (e.g., sarcoma)
- Monoclonal gammopathy of undetermined significance
- Primary amyloidosis
- Waldenström macroglobulinemia
- Table 1 compares diagnostic criteria for multiple myeloma, myeloma variants, and monoclonal gammopathy of unknown significance (MGUS)

LABORATORY TESTS

- The evaluation of patients with multiple myeloma is summarized in Table 2.
- Normochromic, normocytic anemia; rouleaux formation on peripheral smear (Fig. 2).

TABLE 1 Diagnostic Criteria for Multiple Myeloma, Myeloma Variants, and Monoclonal Gammopathy of Unknown Significance

Monoclonal Gammopathy of Undetermined Significance (MGUS) or Monoclonal Gammopathy, Unattributed/Unassociated (MG[u])

M protein in serum <30 g/L
Bone marrow clonal plasma cells <10%
No evidence of other B-cell proliferative disorders
No myeloma-related organ or tissue impairment (no end-organ damage, including bone lesions)

Asymptomatic Myeloma (Smoldering Myeloma)

M protein in serum >30 g/L and/or
Bone marrow clonal plasma cell ≥10%-60%
No related organ or tissue impairment (no end-organ damage, including bone lesions) or symptoms

Symptomatic Multiple Myeloma (MM)

M protein in serum and/or urine[a]
Bone marrow (clonal) plasma cells[a] or plasmacytoma
Related organ or tissue impairment (end-organ damage, including bone lesions)
Clonal bone marrow plasma cell percentage ≥60%
Involved: Uninvolved serum free light ratio ≥100
>1 focal lesion on MRI studies

Solitary Plasmacytoma of Bone

No M protein in serum and/or urine[b]
Single area of bone destruction caused by clonal plasma cells
Bone marrow not consistent with MM
Normal skeletal survey (and MRI of spine and pelvis if done)
No related organ or tissue impairment (no end-organ damage other than solitary bone lesion)[b]

Nonsecretory Myeloma

No M protein in serum and/or urine with immunofixation
Bone marrow clonal plasmacytosis ≥10% or plasmacytoma
Related organ or tissue impairment (end-organ damage, including bone lesions)

Extramedullary Plasmacytoma

No M protein in serum and/or urine[c]
Extramedullary tumor of clonal plasma cells
Normal bone marrow
Normal skeletal survey
No related organ or tissue impairment (end-organ damage including bone lesions)

Multiple Solitary Plasmacytomas (Recurrent or Not)

No M protein in serum and/or urine[d]
More than one localized area of bone destruction or extramedullary tumor of clonal plasma cells that may be recurrent
Normal bone marrow
Normal skeletal survey and MRI of spine and pelvis if done
No related organ or tissue impairment (no end-organ damage other than the localized bone lesions)

Myeloma-Related Organ or Tissue Impairment (End-Organ Damage)

Calcium levels increased: Serum calcium >0-25 mmol/L above the upper limit of normal or >2-75 mmol/L
Renal insufficiency: Creatinine >173 mmol/L
Anemia: Hemoglobin 2 g/dl below the lower limit of normal or hemoglobin <10 g/dl
Bone lesions: Lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)
Other: Symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (more than two episodes in 12 mo)

[a]If flow cytometry is performed, most plasma cells (>90%) will show a neoplastic phenotype.
[b]A small M component may sometimes be present.
[c]A small M component may sometimes be present.
[d]A small M component may sometimes be present.
CT, Computed tomography; *MRI,* magnetic resonance image.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 2 Evaluation of Patients with Multiple Myeloma

Evaluation for Diagnosis

Evaluation for Monoclonal Protein

Serum protein electrophoresis, immunofixation
Quantitative immunoglobulin by nephelometric method
24-hour urine collection for electrophoresis and Bence Jones protein assessment and immunofixation
Serum free light chain and ratio

Evaluation for Clonal Plasma Cells

Bone marrow aspirate and biopsy for
Histology
Clonality by immunostaining or flow cytometry by κ/λ staining
Fine-needle aspiration of plasmacytoma if indicated

Evaluation for End-Organ Damage

Hemogram to detect anemia
Chemistry panel for renal function and calcium
Radiologic evaluation: Skeletal survey
PET-CT or MRI as indicated for bone lesions or extramedullary disease

Evaluation for Risk Stratification

β_2-Microglobulin and serum albumin for ISS stage
Cytogenetics and fluorescence in situ hybridization on bone marrow sample
LDH
C-reactive protein

Other Investigations for Selected Patients

Abdominal fat pad or rectal biopsy for amyloid
Solitary lytic lesion biopsy
Serum viscosity if IgM component or high IgA levels or serum M component >7 g/dl
Immunofixation for IgD or IgE in select cases

CT, Computed tomography; *Ig,* immunoglobulin; *ISS,* International Staging System; *LDH,* lactate dehydrogenase; *MRI,* magnetic resonance imaging; *PET,* positron emission tomography.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

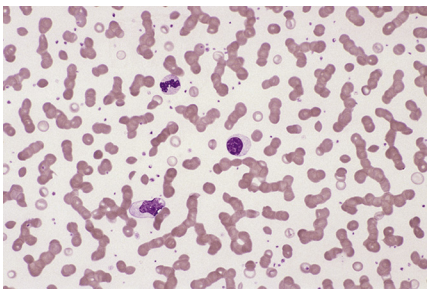

FIG. 2 Increased rouleaux formation is seen in this blood smear from a patient with a large M protein. Marked rouleaux formation is often a clue to the diagnosis of a plasma cell neoplasm but may also be observed in other conditions (Wright-Giemsa stain). (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.)

- Hypercalcemia is present in 15% of patients at diagnosis.
- Elevated blood urea nitrogen, creatinine, uric acid, and total protein.
- Urine protein immunoelectrophoresis: Proteinuria from overproduction and secretion of free monoclonal kappa or lambda chains (Bence Jones protein).
- Serum protein immunoelectrophoresis: Monoclonal spike (M spike) on protein immunoelectrophoresis in approximately 75% of patients (Fig. 3); decreased levels of normal immunoglobulins (Ig).
  1. The increased immunoglobulins are generally IgG (70%) and IgA (20%).
  2. Approximately 5% to 10% of patients have only increased light chains in the urine by electrophoresis (light chain MM).
  3. A small percentage (<2%) of patients have nonsecretory MM (no increase in immunoglobulins and no light chains in the urine) but have other evidence of the disease (e.g., positive bone marrow examination).
- Elevated serum free light chains (kappa or lambda types) with abnormally elevated or decreased kappa:lambda ratios suggestive of the presence of monoclonal light chain proteins.
- Hyponatremia, increased serum viscosity (more common with production of IgM).
- Bone marrow examination demonstrates nests or sheets of plasma cells, which comprise >10% of the bone marrow.
- Serum beta 2-microglobulin is useful for prognosis, and elevated levels indicate high tumor mass and advanced stage disease.
- Elevated serum lactate dehydrogenase at diagnosis defines a subgroup of myeloma patients with very poor prognosis.
- Nearly all patients with MM present with abnormal chromosomes (Table 3) identified by fluorescence in situ hybridization (FISH). High-risk patients (<25% of patients at diagnosis) are those with any of the following: Deletion 17p, translocation 4:14, translocation 14:16, translocation 14;20, and gain of chromosome 1q21.

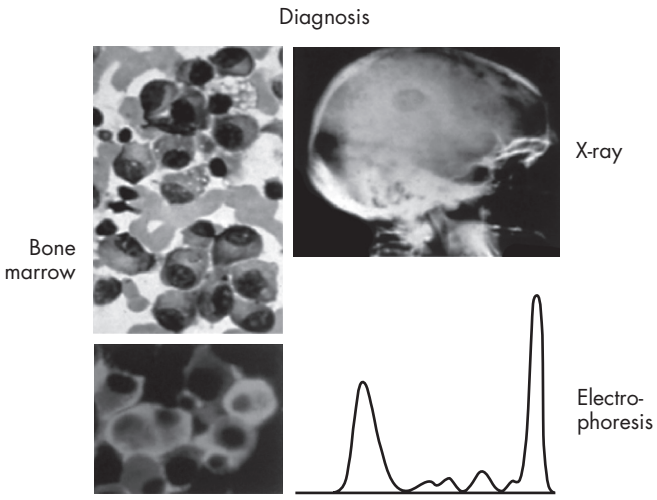

FIG. 3 Common diagnostic features in multiple myeloma. Light chain–restricted plasma cells in a bone marrow aspirate; multiple lytic lesions in a skull radiograph; large monoclonal spike in the g-globulin area in serum electrophoresis. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

IMAGING STUDIES

Imaging modalities for disease assessment in myeloma are summarized in Table 4. Radiograph films of painful areas often demonstrate punched-out lytic lesions or osteoporosis (Figs. 3, E4, E5, and E6). CT can identify rib involvement not evident on plain films and differentiate it from osteoporotic and traumatic fractures (Fig. E7). MRI is the preferred technique for suspected spinal compression or soft tissue plasmacytomas. Bone scans may not be useful because MM lesions are not blastic. Positron emission tomography scans are increasingly used for detection of osseous and extraosseous disease.

STAGING

Table 5 describes the Revised International Staging System (R-ISS) for multiple myeloma that incorporates traditional laboratory parameters alongside high-risk chromosomal abnormalities detected by FISH techniques on bone marrow samples. This system provides important prognostic assessment and classifies patients into three risk groups (high, intermediate, and standard). Risk stratification in multiple myeloma is summarized in Tables 6 and 7.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Prevention of renal failure with adequate hydration and avoidance of nephrotoxic agents and dye contrast studies.

ACUTE GENERAL Rx

- Treatment strategy is initially related to the determination of transplant-eligible patients.
- All transplant-eligible patients should be considered for approximately 12 wk of induction chemotherapy with triplet regimens such as the VRD regimen (bortezomib, lenalidomide, and dexamethasone) or the CyBorD regimen (cyclophosphamide, bortezomib, and dexamethasone). Upon demonstration of at least a very good partial response, these patients can undergo stem cell mobilization and collection.

- All patients with high-risk features (high R-ISS stage, poor cytogenetics) should be offered autologous stem cell transplant (ASCT) subsequently, provided they have adequate cardiac, pulmonary, and hepatic function. Currently, ASCT can be safely performed in most centers in fit patients up to age 75 yr. Although recent data do not clearly demonstrate superior survival with upfront transplantation in the current era, ASCT is associated with significantly longer progression-free survival.
- Patients should be offered maintenance chemotherapy with either lenalidomide and/or bortezomib after recovery from ASCT for at least 2 yr or until disease progression. The choice of maintenance therapy depends on risk category.
- Induction chemotherapy in patients ineligible for transplantation (age >75 yr, high comorbidity index, poor performance status) can be identical to that offered transplant-eligible patients but is dose modified to allow for better tolerability. Daratumumab is a monoclonal antibody targeting CD38, which has recently been approved in combination with lenalidomide and dexamethasone in transplant-ineligible myeloma. Alternatively, less aggressive regimens (doublet regimens or single agents) can be recommended, including the following:
  1. Lenalidomide and dexamethasone (RD)
  2. Bortezomib and dexamethasone (VD)
- Therapy for relapsed and refractory myeloma can include second- or third-generation proteasome inhibitors (carfilzomib and ixazomib), immunomodulatory drugs (thalidomide, pomalidomide), and monoclonal antibodies elotuzumab (targeting signaling lymphocytic activation molecule F7 [SLAMF7]) and daratumumab. All of these agents have shown improved progression-free survival in relapsed or refractory multiple myeloma in various combinations and are useful options in this setting. The histone deacetylase inhibitor panobinostat is also approved in this setting, along with recent drug approval of nuclear protein transport inhibitor selinexor.
- If the relapse occurs more than 6 mo after conventional therapy is stopped, the initial chemotherapy regimen can be reinstituted.
- ASCT can be considered as salvage therapy in patients who had stem cells cryopreserved early in the course of the disease.
- Approximately 15% of patients with newly diagnosed MM are recognized incidentally and present without significant symptoms (asymptomatic MM, formerly known as smoldering myeloma). The rate of progression of smoldering MM to symptomatic disease is 10% per yr for the initial 5 yr, decreasing to 5% for the next 5 yr, and decreasing further to 1.5% per yr thereafter. Observation alone is reasonable in these patients because no survival advantage has been demonstrated by treating them.
- An exception to this may be in high-risk smoldering myeloma patients. Two phase III trials have shown that early treatment with lenalidomide with or without dexamethasone in patients with high-risk smoldering myeloma delays progression to active disease.

TABLE 3 Recurrent Cytogenetic Changes in Myeloma

Chromosomal Abnormality	Patients (%)	Genes Involved
Common Cytogenetic Alterations		
Hyperdiploidy	50-60	Unclear
Hypodiploid	20	Unclear
Pseudodiploid	15	Unclear
del(17p)	8	p53
t(4:14)	15	*FGFR3*, *MMSET*
t(11;14)	20	Cyclin D1
t(14;16)	3	*c-MAF*
t(14;20)	1	*MAFB*
t(6p25 or 6p21;14)	1	*IRF4* or *CCND3*
t(8;14)	5	*c-Myc*
t(9;14)	<1%	*PAX5*
del(13 or 13q)	50%	Unclear
Recently Identified Alterations		
1q+	35%	
1p–	30%	
5q+	50%	
12p–	10%	

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

CHRONIC Rx

- Promptly diagnose and treat infections. Common bacterial agents are *Streptococcus pneumoniae* and *Haemophilus influenzae.* Prophylactic therapy against *Pneumocystis jiroveci* with trimethoprim-sulfamethoxazole must be considered in patients receiving chemotherapy and high-dose corticosteroid regimens. Vaccinate against *S. pneumoniae,* influenza, and *H. influenzae.*

TABLE 4 Imaging Modalities for Disease Assessment in Myeloma

	Use	Sensitivity/Specificity	False-Negatives	False-Positives
Bone scan	• For diagnostic screening, except for multiple myeloma	Varies	• Pure osteolytic lesions	• Trauma • Inflammation • Benign tumor • Healing
X-ray	• Can clarify nonspecific findings on bone scan • Assesses risk of fracture • Possible follow-up of tumor response, but evidence of response takes considerable time to appear	Low sensitivity	• Low disease burden • Osteopenia	• Trauma • Inflammation • Benign tumor • Healing
CT	• For anatomic detail in axial skeleton • Possible follow-up of tumor response, but role is still undefined	High sensitivity	• Low disease burden	• Trauma • Inflammation • Benign tumor • Healing
MRI	• Detection of spinal cord compression • Can help distinguish benign from malignant vertebral compression fracture • Possible follow-up of tumor response, but role is still undefined	High sensitivity and specificity	• Lesion only in cortex	• Edema
PET scan	• May eventually become first-line screening test for bone metastases • Possible follow-up of tumor response, but role is still undefined	High specificity	• Lesion only in cortex	• After chemotherapy
Bone density	• Measure osteoporosis • Response to bisphosphonates	High specificity and sensitivity		• Age-related osteoporosis

CT, Computed tomography; *MRI,* magnetic resonance imaging; *PET,* positron emission tomography.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 5 Revised International Staging System (R-ISS) for Multiple Myeloma Staging System

Stage	Criteria
I	ALL of the following: • Serum β-2 microglobulin <3.5 mg/L • Serum albumin >3.5 mg/dl • no high-risk chromosomal abnormalities by FISH • Normal LDH level
II	• Fitting neither stage I nor III
III	• Serum β-2 microglobulin >5.5 mg/L *AND* either elevated LDH *OR* high-risk chromosomal abnormalities by FISH [(del 17(p) and/or translocation t(14;16) and/or translocation t(4;14)]

FISH, Fluorescence in situ hybridization; *LDH,* lactate dehydrogenase.

TABLE 6 Risk Stratification in Multiple Myeloma

Investigations Recommended for Risk Stratification
Serum albumin and β_2-microglobulin to determine ISS stage
Bone marrow examination for t(4;14), t(14;16), and del(17p) on identified PCs by FISH
LDH
Immunoglobulin type: IgA
Histology: Plasmablastic disease or plasma cell leukemia
Additional Investigations for Risk Stratification
Cytogenetics
Gene expression profiling
Labeling index
MRI/PET scan
DNA copy number alteration by CGH/SNP array

CGH/SNP, Comparative genomic hybridization/single-nucleotide polymorphism; *DNA,* deoxyribonucleic acid; *FISH,* fluorescence in situ hybridization; *IgA,* immunoglobulin A; *ISS,* International Staging System; *LDH,* lactate dehydrogenase; *MRI,* magnetic resonance imaging; *PC,* plasma cell; *PET,* positron emission tomography.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 7 Standard Risk Factors for Multiple Myeloma and the Revised International Staging System

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin <3.5 mg/L, serum albumin ≥3.5 g/dl
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH below the upper limit of normal
High	Serum LDH above the upper limit of normal
A New Model for Risk Stratification for MM R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

CA, Chromosomal abnormalities; *iFISH,* interphase fluorescence in situ hybridization; *ISS,* International Staging System; *LDH,* lactate dehydrogenase; *MM,* multiple myeloma; *R-ISS,* Revised International Staging System.
From Greipp PR et al: International staging system for multiple myeloma, *J Clin Oncol* 23:3412, 2005. In Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

- Hypercalcemia is aggressively treated with IV fluids, bisphosphonates, and corticosteroids. Monthly infusions of the bisphosphonate pamidronate or zoledronate provide significant protection against skeletal complications and improve the quality of life of patients with advanced MM. The receptor activator of nuclear factor kappa B (RANK)-ligand inhibitor denosumab is effective in the treatment of hypercalcemia in this setting and in cases in which bisphosphonates are contraindicated (e.g., renal failure). Denosumab has also been studied in a large phase III study and has been shown to be noninferior to zoledronicacid.
- Control pain with analgesics; radiation therapy to treat painful bone lesions or cord compression. Perform surgical stabilization of pathologic fractures. Consider vertebroplasty or kyphoplasty for selected vertebral lesions.
- Anemia is treated with erythropoietin.

DISPOSITION

- In patients presenting at an age <60 yr, the 10-yr survival is approximately 30%. The median length of survival after diagnosis is now 7 to 8 yr and is rapidly increasing due to novel agents. Prognosis is better in asymptomatic patients with indolent or smoldering myeloma. Median survival time is approximately 10 yr in persons with no lytic bone lesions and a serum myeloma protein concentration <3 g/dl. Adverse outcome is associated with increased levels of beta-2 microglobulin, low levels of serum albumin, circulating plasma cells, plasmablastic features in bone marrow, increased plasma cell labeling index, poor cytogenetics (t (4;14) or t (14;16) translocation, deletion 17p).
- Tandem transplantation (two successive ASCT) improves survival among patients with MM who do not have a very good partial response after undergoing a single transplantation.
- Recent trials reveal that among patients with newly diagnosed myeloma, survival in recipients of a hematopoietic stem cell autograft followed by a stem cell allograft from an human leukocyte antigen (HLA)-identical sibling is superior to that in recipients of tandem stem cell autografts.

REFERRAL

To hematologist for management of disease, and bone marrow transplant specialist for transplantation options and management.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Multiple Myeloma (Patient Information)

AUTHORS: **Omar Nadeem, MD,** and **Bharti Rathore, MD**

SUGGESTED READINGS

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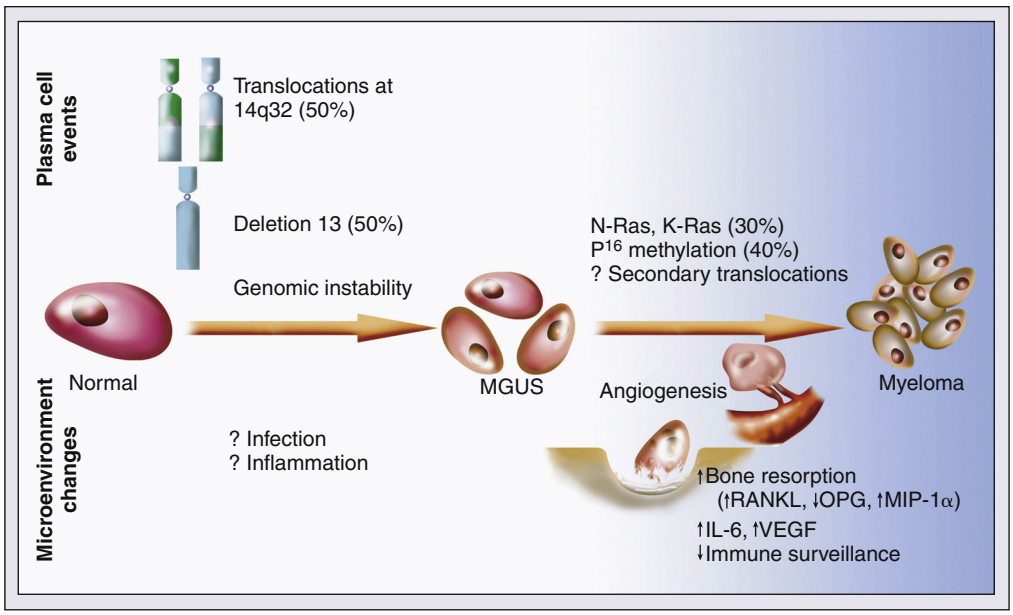

FIG. E1 Pathogenesis of myeloma. *IL-6,* Interleukin-6; *MGUS,* monoclonal gammopathy of undetermined significance; *MIP-1α,* macrophage inflammatory protein-1α; *OPG,* osteoprotegerin; *RANKL,* receptor activator of nuclear factor-κB ligand; *VEGF,* vascular endothelial growth factor. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

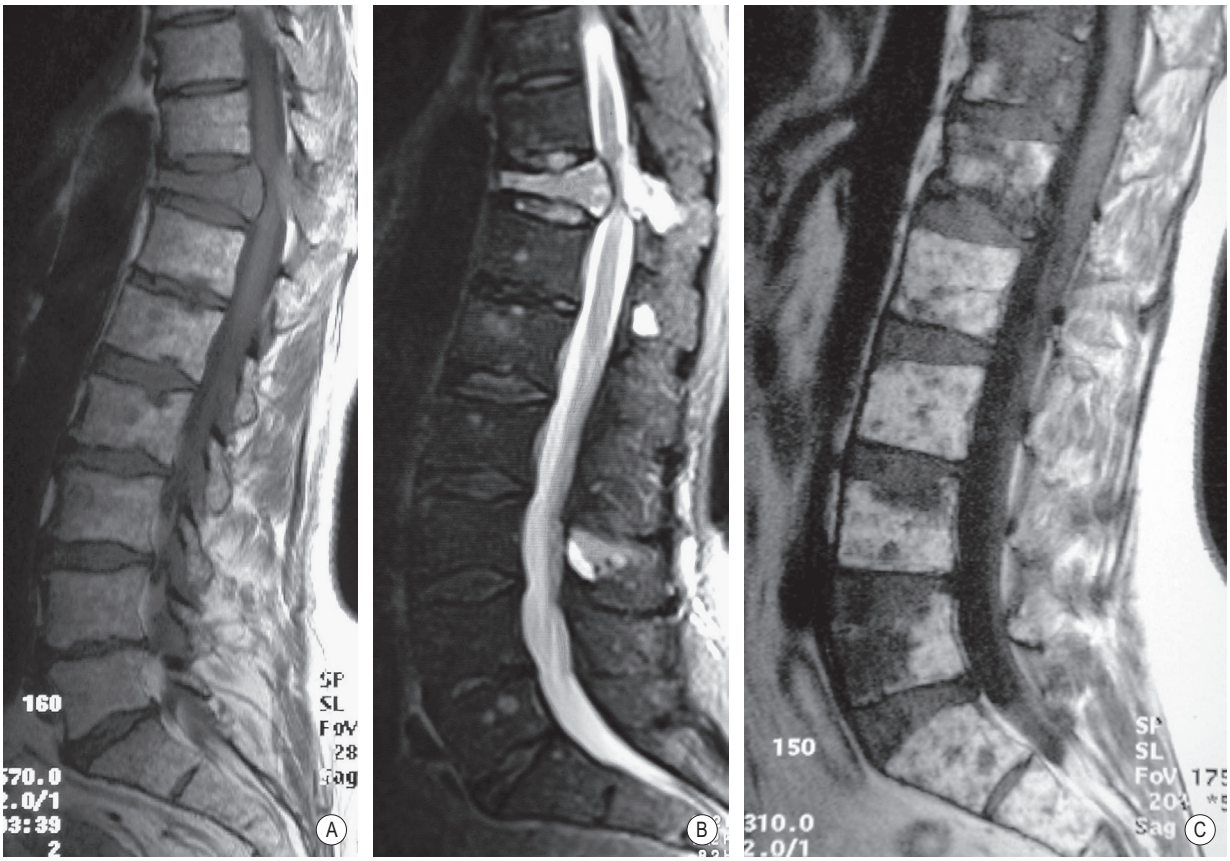

FIG. E4 Multiple myeloma. (A) Sagittal T1-weighted imaging (T1WI) and **(B)** fat-suppressed T2WI showing pathologic collapse of T11 with cord compression and multiple smaller areas of focal marrow involvement. **(C)** Sagittal T1WI showing the variegated pattern of marrow involvement. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

FIG. E5 Myeloma. Typical localized lesions that are sharply defined, rounded defects with endosteal erosion of the cortex. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

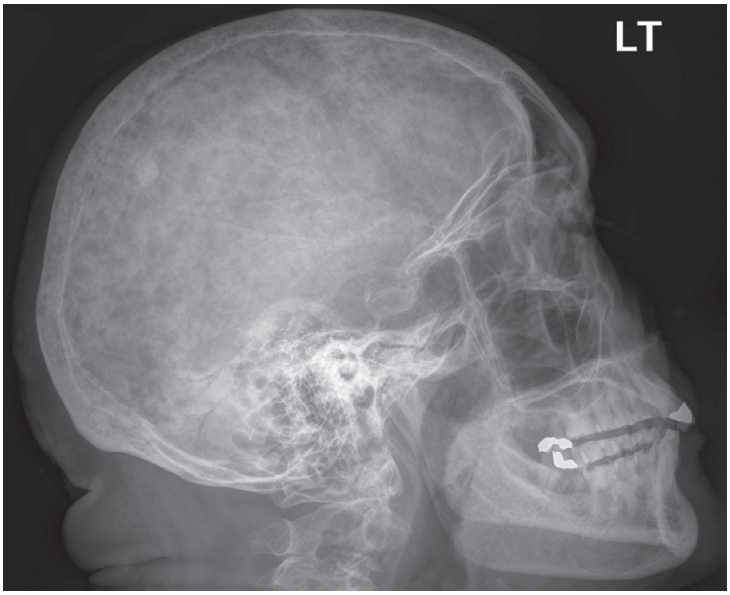

FIG. E6 Myeloma. Lateral skull XR showing the classic "pepper-pot" appearance of the skull. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

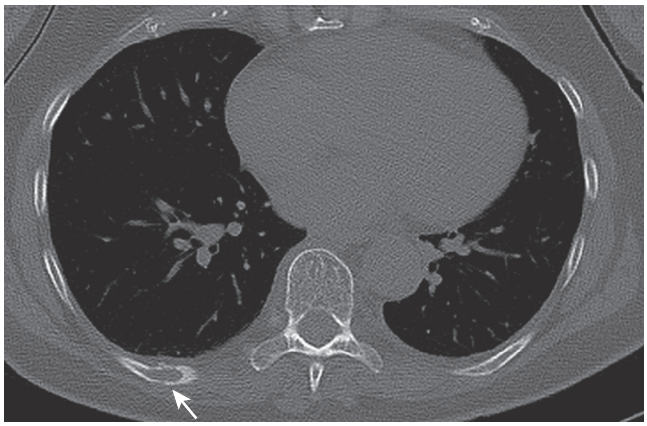

FIG. E7 Rib involvement in multiple myeloma *(arrow).* There is thinning of the cortex and enlargement of a circumscribed area of the rib. Soft tissue Hounsfield units are noted within the lesion. In contrast with osteoporotic or traumatic fractures of the rib, no callous formation is seen. In a whole-body examination, every single rib must be screened by scrolling through it posteriorly to anteriorly. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, WB Saunders.)

BASIC INFORMATION

DEFINITION

Multiple sclerosis (MS) is a chronic predominantly autoimmune demyelinating disease of the central nervous system (CNS) characterized by subacute neurologic deficits correlating with CNS lesions separated in time and space, excluding other possible disease.

Subtypes include:

- **Relapsing-remitting MS (RRMS)** (82%): Relapses followed by complete or near-complete recovery, 50% to 85% of which later transition to SPMS
- **Secondary progressive MS (SPMS):** Progression of disability with few or no relapses
- **Primary progressive MS (PPMS)** (18%): Progression from the onset, rare relapses
- Progressive relapsing or relapsing progressive courses can be incorporated into PPMS or SPMS, respectively
- Relapses are defined as a subacute onset of neurologic dysfunction that lasts for at least 24 hr due to inflammatory demyelination

Classic rare MS variants include:

- **Marburg variant:** MRI reveals a tumor-like lesion with notable edema in one cerebral hemisphere. Pathology shows severe inflammation with necrosis: Typically acute onset with a fulminant, often malignant, course. May also involve peripheral nerves.
- **Balo concentric sclerosis:** Neuroimaging and pathology show alternating rings of myelination and demyelination resembling an onion bulb macroscopically and microscopically.
- **Schilder diffuse sclerosis:** Childhood onset with one to two large confluent lesions. Some cases were later found to be due to metabolic defects, and many have thus abandoned this disorder.

Neuromyelitis optica spectrum disorder (NMOSD): NMOSD is a distinct demyelinating disease with unique pathophysiology, treatment, and prognosis. Unlike MS, NMOSD usually involves extensive portions of the optic nerves and spinal cord (typically three or more spinal segments). Other areas of the CNS may also be involved, including the area postrema (presenting with intractable hiccups or nausea/vomiting), the brainstem, or the cerebral cortex. Additionally, patients may present with symptomatic narcolepsy. The lesions look very different on MRI than typical MS demyelinating lesions. The majority of patients are aquaporin-4 receptor Ab positive (NMO immunoglobulin G [IgG] positive) while some are antibody negative or are myelin oligodendrocyte glycoprotein Ab positive (MOG-IgG positive), which has a better prognosis. The actual diagnostic criteria for NMOSD vary depending on the patient's aquaporin-4 receptor antibody status. Prognosis is typically worse than MS, and this condition does not respond to MS-specific therapies. Steroids, plasma exchange, rituximab, mycophenolate mofetil, and azathioprine are among the treatments that may be used.

SYNONYMS

MS
Disseminated sclerosis

ICD-10CM CODE
G35 Multiple sclerosis

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: 20 to 40 yr in two thirds of patients; it is the most common permanently disabling disorder of the central nervous system in young adults; mean age of onset is 30 yr, range is infancy to 70 yr.

PREVALENCE: More common in people raised in northern latitudes and in certain genetic clusters. Prevalence per 10,000 varies from 20 in southern Europe to 150 to 180 in Canada, northern United States, and northern Europe; and <10 in Asia, Central America, and most of Africa.

PREDOMINANT SEX & AGE: Female/male ratio is 2 to 3:1.

GENETICS: Frequency of MS in dizygotic twins and siblings is 3% to 5%, and 20% to 40% in monozygotic twins. Most common associations include human leukocyte antigen classes I and II *(DRB1*1501, DQA1*0102, DQB1*0602),* (*DRB1*0405-DQA1*0301-DQB1*0302* in Mediterranean population). A notable epigenetic interaction between vitamin D and the main MS-linked HLA-DRB1*1501 allele has been elucidated.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Findings depend on the location of the CNS lesion(s) and may include the following:

- Common: Nonspecific complaints such as fatigue, blurred vision, diplopia, vertigo, falls, hemiparesis, paraparesis, monoparesis, numbness, paresthesias, ataxia, cognitive deficits, depression, sexual dysfunction, and urinary dysfunction
- Visual abnormalities: Horizontal nystagmus, visual field defects, ***Marcus Gunn pupil*** (i.e., relative afferent papillary defect—normal direct and consensual light reflexes; however, when swinging flashlight from one eye to the other, direct light causes dilatation of pupil of affected eye), ***internuclear ophthalmoplegia*** (paresis of the adducting eye on conjugate lateral gaze with horizontal nystagmus of the abducting eye) (Fig. 1)
- Corticospinal tract(s) involvement: Leads to upper motor neuron signs such as spasticity, hyperreflexia, clonus, extensor plantar responses, and upper motor neuron pattern of weakness
- Sensory loss: May include partial or full dermatomal loss of pain and temperature, loss of vibration (common) and position sense, or a thoracic band of sensory loss
- Ataxia: Intention tremor, dysmetria, dysdiadochokinesis, titubation, inability to tandem gait
- Bladder dysfunction: Detrusor hyperreflexia (urge incontinence), flaccidity (neurogenic bladder), and dyssynergia (bladder contracts against a closed sphincter)
- ***Lhermitte* sign:** Flexion of the neck elicits an electrical sensation extending down the spine and occasionally into the extremities
- ***Uhthoff* phenomenon:** Transient worsening of preexisting symptoms with small elevations in body temperature (e.g., during exercise or warm bathing)

ETIOLOGY

Remains unknown but multifactorial with evidence for autoimmunity (autoreactive T and B cells), environmental factors, and genetics (Mendelian and epigenetic). Environmental risk factors during childhood include certain viruses (e.g., Epstein-Barr virus and human herpes virus 6), low UV exposure, and month of birth (higher in spring). Other risk factors include low vitamin D level and smoking.

DIAGNOSIS

- MS: Based on revised 2017 McDonald criteria (Table 1)
- RRMS: See Table 1
- PPMS: Insidious progression of disability for at least 1 yr with a positive CSF and MRI evidence of >1 brain or >2 spinal cord MS-like lesions

DIFFERENTIAL DIAGNOSIS (TABLE 2)

- Autoimmune: Acute disseminated encephalomyelitis (ADEM), postvaccination encephalomyelitis, neuromyelitis optica spectrum disorder
- Degenerative: Subacute combined degeneration of the cord (vitamin B_{12} deficiency), amyotrophic lateral sclerosis, primary lateral sclerosis
- Infections: Lyme disease, neurosyphilis, HIV, tropical spastic paraparesis, progressive multifocal leukoencephalopathy, Whipple disease, acute flaccid myelitis, CNS tuberculosis, or fungal disease

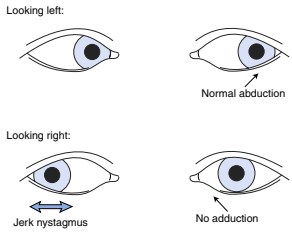

FIG. 1 Internuclear ophthalmoplegia. When the patient in the figure looks to the left (*top* row), both eyes move normally, but when the patient looks to the right (*bottom* row), the left eye fails to adduct ("weak" medial rectus) and the contralateral eye develops a jerk nystagmus. The finding is named for the side with weak adduction (i.e., in this example, a *left* internuclear ophthalmoplegia), and the lesion is in the *ipsilateral* medial longitudinal fasciculus (i.e., *left* medial longitudinal fasciculus in this example). See the text. (From McGee S: *Evidence-based physical diagnosis,* ed 4, Philadelphia, 2018, Elsevier.)

TABLE 1 Summary of Revised 2017 McDonald Criteria for Diagnosis of Multiple Sclerosis

RRMS/Clinical Attacks	Clinical Lesions	Paraclinical Testing Needed
2	2	None
2	1	MRI dissemination in space *or* a second clinical attack at a different CNS site
1	2	MRI dissemination in time *or* CSF-specific oligoclonal bands
1	1	1. Additional clinical attack at a different CNS site or MRI dissemination in space 2. MRI dissemination in time or CSF-specific oligoclonal bands

Evidence of clinical lesions by physical examination or evoked potentials.
CNS, Central nervous system; *CSF,* cerebrospinal fluid; *MRI dissemination in space,* ≥1 T2 lesions in 2 of the 4 typical areas for MS lesions—periventricular, juxtacortical, infratentorial, or spinal cord; *MRI dissemination in time,* a new lesion at follow-up MRI at any time, or presence of both an enhancing and nonenhancing lesion at any time; *RRMS,* relapsing-remitting multiple sclerosis.

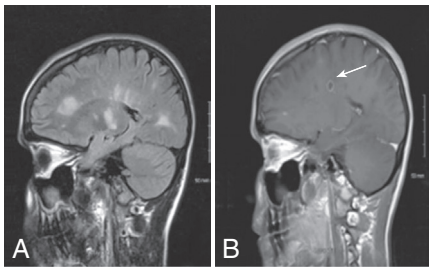

FIG. 2 Multiple sclerosis. A, Sagittal fluid-attenuated inversion recovery (FLAIR) image magnetic resonance scan shows multiple lesions in corpus callosum, "Dawson fingers" (periventricular finger-like lesions oriented toward the ventricles), along with ovoid and punctuate lesions in the deep white matter. **B,** Gadolinium-enhanced scan shows an enhancing lesion *(arrow).*

TABLE 2 Conditions that Can Be Mistaken for Multiple Sclerosis and Other Diseases of Myelin

Vascular Disease
Small-vessel cerebrovascular disease
Vasculitis
CADASIL
Antiphospholipid antibody syndrome

Structural Lesions
Craniocervical junction, posterior fossa, or spinal tumors
Cervical spondylosis or disc herniation
Chiari malformation or syrinx

Degenerative Diseases
Hereditary myelopathy
Spinocerebellar degeneration

Infections
HTLV-1 infection
HIV myelopathy or HIV-related cerebritis
Neuroborreliosis (e.g., Lyme disease)
John Cunningham (JC) JC virus/progressive multifocal leukoencephalopathy
Neurosyphilis

Other Inflammatory Conditions
Systemic lupus erythematosus
Sjögren syndrome
Sarcoidosis
Monofocal or Monophasic Demyelinating Syndromes
Neuromyelitis optica spectrum disorder
Acute disseminated encephalomyelitis

Other Conditions
Hashimoto thyroiditis with or without encephalopathy
Nonspecific MRI abnormalities related to migraine, aging, or trauma

CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; *HTLV,* human T-cell lymphotropic virus.
From Goldman L, Schafer AI: *Goldman's cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

- Inflammatory: Systemic lupus erythematosus, vasculitis, sarcoidosis, Sjögren disease, Behçet disease, celiac disease
- Inherited metabolic disorders: Leukodystrophies
- Mitochondrial: Leber hereditary optic neuropathy, mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS)
- Neoplasms: CNS lymphoma, metastases
- Vascular: Subcortical infarcts, Binswanger disease

WORKUP

- Lumbar puncture for cases that are atypical and to evaluate for mimics of MS. Typical CSF abnormalities may include increased protein (less than 100 mg/dl), mild elevation of mononuclear white blood cells, and increased IgG synthesis rate. 70% of clinically definite MS (CDMS) have elevated CSF IgG index, and 90% have CSF oligoclonal bands. (Serum for a serum protein electrophoresis needs to be sent to lab simultaneously with CSF for both tests.) False-positive results with IgG index and rarely with positive OCBs can be seen in CNS infections, parainfections, vasculitis, and CNS lymphoma.
- Serum: Complete blood count (CBC), chemistry panel, liver function tests, vitamin B_{12}, 25-OH vitamin D_3.
- Consider in the proper clinical setting: Aquaporin-4 IgG, MOG-IgG, antinuclear antibody (ANA), ACE (a test with low specificity and sensitivity for sarcoidosis) thyroid stimulating hormone (TSH), free T_4, very-long-chain fatty acids, arylsulfatase A.
- Consider optical coherence tomography or evoked potentials (visual, somatosensory, and brain stem auditory evoked response).

IMAGING STUDIES

Brain MRI with and without gadolinium is recommended in all cases. Fig. 2 illustrates imaging features of MS. MRI with and without contrast of the cervical (Fig. E3) and thoracic spine can be helpful. MRI assesses acute and chronic lesions as well as atrophy. A normal MRI of the brain does not conclusively exclude early MS but makes it extremely unlikely.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Patient education regarding disease characteristics, treatment options, risks and benefits of treatment, and prognosis. Often patients need intermittent rest periods on a daily basis and when physically active, and avoid exposure to heat, which typically worsens symptoms (not the disease).

Recommend physical therapy for new or worsening weakness, incoordination, or spasticity.

ACUTE GENERAL Rx

Relapses: High-dose IV methylprednisolone (3-5 days of 1 g/day), often followed by a 7- to 10-day prednisone or methylprednisolone taper. High-dose corticosteroids do not alter the long-term course of disease. May consider plasmapheresis for refractory cases.

CHRONIC Rx

- The vast majority of FDA-approved therapies are only for relapsing MS; the FDA-approved ocrelizumab is the first medication for primary progressive MS.
- Disease-modifying injection therapy includes interferon beta-1a (intramuscular injection [IM Avonex, IM] Plegridy, subcutaneous [SC] Rebif), interferon beta-1b (SC Betaseron, SC Extavia), and glatiramer acetate (SC Copaxone, SC Glatopa). These medications have a low risk of side effects but are not as efficacious in preventing future relapses. Common side effects for interferons include flulike symptoms, depression, liver toxicity, and leukopenia; CBC and Liver function tests (LFTs) (initially q1mo, then q3mo). Common side effects for glatiramer acetate include injection site reactions and benign chest tightness; no serum studies are needed.
- Disease-modifying oral therapy: These medications are newer and more efficacious in preventing multiple sclerosis relapses; however, they have a higher risk of serious side effects and infections. Consider baseline pregnancy test and infectious tests for all oral therapies, although not required by the FDA, such as VZV Ab, Lyme Ab, tuberculosis (TB) test, JC virus Ab, hepatitis Ab panel. Also review general risk of infections (hx UTIs, kidney stones, smoking, diabetes, bronchitis, disability, pulmonary function, and age). Typically monthly CBC and liver function tests for 6 mo then q3mo; pregnancy test.

1. Fingolimod (Gilenya), a sphingosine-1-phosphate receptor modulator and lymphocyte sequester. Possible side effects: Liver toxicity, bradycardia with first dose (requiring cardiac monitoring and ECG for at least 8 hr after administration of first dose), arrhythmia, pancytopenia, macular edema (ophthalmologic exam at baseline, at 3 mo, and thereafter for those with hx DM or uveitis), and reduced pulmonary function. Obtain varicella-zoster virus (VZV) serology.
2. Teriflunomide (Aubagio), reversible inhibitor of pyrimidine synthesis (enzyme dihydroorotate dehydrogenase). Possible side effects: Diarrhea, abnormal liver function tests, nausea, and hair loss; pregnancy category X. Men should not impregnate their partners while on teriflunomide. Serum levels can be measured, and drug can be eliminated by charcoal or cholestyramine. Obtain TB test.
3. Dimethyl fumarate (Tecfidera), mechanism includes inhibition of transcription of Nuclear factor-κB NF-κB. Frequent side effects include nausea, abdominal discomfort, and flushing—especially during the first month—and rarely leukopenia.
4. Siponimod (Mayzent): A selective sphingosine-1-phosphate receptor modulator and lymphocyte sequester. This is the only drug approved not only for relapsing forms of MS but also for secondary progressive MS. Possible side effects: Liver toxicity but does not cause first-dose bradycardia and requires observation. Obtain VZV serology.
5. Cladribine (mavenclad) is a purine antimetabolite recently FDA approved for oral treatment of adults with relapsing form of MS who cannot tolerate or have had an inadequate response to other MS treatments.

- Disease-modifying IV therapy: These medications are newer and more efficacious in preventing multiple sclerosis relapses; however, they have a higher risk of serious side effects and infections.
  1. Natalizumab (Tysabri) is a monoclonal humanized Ab that binds integrin-α4 interfering with binding to VCAM-1. It has been associated with a *higher* risk of progressive multifocal leukoencephalopathy (JC virus) than other immunomodulatory therapies. Test for JC virus Ab at least annually because conversion to a positive antibody occurs at increased frequency while on this drug. If positive, progressive multifocal leukoencephalopathy (PML) is still rare, but risk increases with increased length of therapy (>2 yr), history of chemotherapy, and concomitant immunosuppressants.
  2. Alemtuzumab (Lemtrada): An anti-CD52 humanized monoclonal antibody and second-line therapy for patients who have failed at least two FDA-approved MS therapies. The medication is delivered in two treatment courses. After an initial series of five daily infusions, the medication is administered 1 yr later for 3 days. Serious side effects include the development of autoimmune conditions (34% developed autoimmune thyroid disorders), infusion reactions, and certain cancers. The medication is only available through a restricted access program.
  3. Ocrelizumab (Ocrevus): A first-line therapy that is a humanized monoclonal antibody to CD20+ B cells. This is the only drug approved not only for relapsing forms of MS but also for primary progressive MS. Infections are the most common side effects.
- Symptomatic therapy:
  1. Dalfampridine (Ampyra) is a potassium channel blocker recently approved to improve walking speed in patients with MS. This medication is contraindicated in patients with epilepsy.
  2. Treat spasticity with baclofen or tizanidine. Onabotulinum toxin type A injection for focal intractable spasticity. Intrathecal baclofen pump for generalized intractable spasticity. Acute worsening may be due to infections such as urinary tract infection (UTI), injury, recent surgery, or colder temperatures.
  3. Treat urge incontinence with anticholinergic/muscarinic therapy such as oxybutynin, tolterodine, or solifenacin. Treat urinary retention with tamsulosin. In both cases, rule out a bladder infection.
  4. Treat dysesthesias with gabapentin or pregabalin.
  5. Fatigue: Consider amantadine 100 mg bid, modafinil, or a stimulant.
  6. Tremor: Clonazepam, propranolol, or gabapentin.
  7. Depression and anxiety are common. Consider referring to both a counselor and psychiatrist.

DISPOSITION

Most patients have complete or near-complete recovery weeks to months after a relapse. Typically, two relapses occur in RRMS patient per yr (75% will have >1 relapse). Although the rate of disease progression is highly variable, there is higher risk of greater long-term disability with higher relapse rate during the first 2 to 5 yr, poor recovery from initial relapses, older age of onset, involvement of multiple systems, male sex, African American, and primary progressive disease.

Disease-modifying treatment has improved, and the current treatment goal is no relapses and no disease progression on imaging.

REFERRAL

- Referral to neurologist is highly recommended. Referral to MS specialist should be considered in cases of poor response to therapy and/or if there is concern about complications of therapies.
- Consider referrals for physical, speech, and occupational therapy.
- Consider referral to urology if bladder-sphincter dyssynergia is possible or if not responsive to treatment.

PEARLS & CONSIDERATIONS

- Clinically isolated syndrome (CIS): Isolated demyelinating event and assessing risk of CDMS 1) in optic neuritis, if brain MRI is completely normal, there is 20% to 25% chance of CDMS over 15 yr. 2) In CIS, if there are >1 T2 hyperintensity on brain MRI, there is 84% risk, and if there are >2 Gd + lesions there is a 96% risk of CDMS over 18 mo.
- Pseudorelapses may occur with heat, fever, or infections (urinary tract infections common in patients with MS).
- Headache, fever, altered mental status, elevated CSF WBCs, or recurrent relapses over days to weeks raises concern for CNS infection or ADEM.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Multiple Sclerosis (Patient Information)

AUTHORS: **Corey Goldsmith, MD,** and **Alexandra Degenhardt, MD, MMSc**

SUGGESTED READINGS

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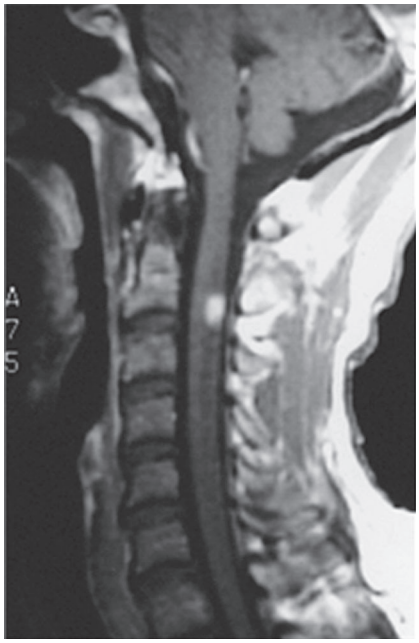

FIG. E3 This magnetic resonance image of a patient with multiple sclerosis reveals a plaque—the hyperintense lesion—in the high cervical spinal cord. (From Kaufman DM, Geyer HL, Milstein MJ: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.)

Multiple System Atrophy

BASIC INFORMATION

DEFINITION

Multiple system atrophy (MSA) is an adult-onset (>30 yr) fatal neurodegenerative disorder characterized by autonomic failure associated with parkinsonism and/or cerebellar symptoms.

MSA is further subdivided into two main types:

- MSA-P (parkinsonism subtype), previously *striatonigral degeneration*
- MSA-C (cerebellar subtype), previously *olivopontocerebellar atrophy*

SYNONYMS

MSA
Atypical parkinsonism
Synucleinopathy
Shy-Drager syndrome
Olivopontocerebellar atrophy
Striatonigral degeneration

ICD-10CM CODES
G23.2 Striatonigral degeneration
G23.8 Olivopontocerebellar degeneration

EPIDEMIOLOGY & INCIDENCE

INCIDENCE: Estimated mean incidence is 0.6 to 0.7 cases per 100,000 persons per yr, with a range of 0.1 to 2.4 cases.

PREVALANCE:

- Estimated point prevalence is 4.4 cases per 100,000 patients
- Rises to about 7.8 cases per 100,000 for age >40 yr
- Subtype distribution:
  1. MSA-P: 68% of cases
  2. MSA-C: 32% of cases

PREDOMINANT SEX & AGE:

- Male:female ratio is 1.3:1
- Mean age of onset is 57.8 yr
- In Japan, the predominant subtype is MSA-C and mean survival is short

RISK FACTORS: People with MSA perform some activities more often than the general population, such as drinking alcohol and tea, eating seafood, taking aspirin, and working in plant and machine operations. However, it is not clear if these behaviors are risk factors or coincidence.

GENETICS: A large, genome-wide association study found no significant loci, including no association with the *SNCA* and *COQ2* gene variants that previously had been suggested.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Parkinsonism (see "Parkinson Disease"):
  1. Tremor: Resting tremor in MSA is more likely to be a jerky tremor or myoclonic tremor. It is usually faster and symmetrical.
  2. Rigidity: Usually symmetric.
  3. Postural instability: Seen early in the disease, usually within 1 to 3 yr of onset, and is rapidly progressive, with patients being wheelchair dependent within 5 yr. Falls are common early in MSA (within 3 yr) and are more common in MSA-C.
- Dysautonomia:
  1. Hallmark of MSA, present in both subtypes (99% of patients).
  2. Orthostatic hypotension is symptomatic in 75% of the patients with lightheadedness or dizziness, especially in early morning and when quickly getting up after prolonged sitting. Drop in blood pressure of 30/15 mm Hg within in 3 min of standing is required for diagnosis.
  3. Erectile dysfunction is seen in 84% of males with MSA.
  4. Cold hands or feet with red hand sign due to Raynaud phenomenon.
  5. Respiratory dysfunction with inspiratory stridor or sighs.
- Sleep-related breathing disorders: More commonly obstructive sleep apnea and stridor. This results from airway obstruction and vocal cord restriction (in >50%). Nocturnal stridor and snoring and later daytime stridor are common.
- Urine incontinence (73% of patients).

ETIOLOGY

- Etiology of MSA is unclear. It is generally considered a sporadic disease. Many different factors have been proposed, including environmental toxins such as formaldehyde, malathion, diazinon, benzene, hexane, ketone, and pesticides.
- MSA is a synucleinopathy similar to Parkinson disease (PD) and Lewy body disease. Deposition of alpha-synuclein is seen in cerebellar subcortical white matter and early on in cerebellar brain stem projections with gradual spread.

DIAGNOSIS

- Definitive diagnosis of MSA requires pathologic confirmation on autopsy.
- Possible and probable diagnoses of MSA are based on clinical findings (Table E1).

DIFFERENTIAL DIAGNOSIS

- Progressive supranuclear palsy: Atypical parkinsonism that presents with early falls and postural instability and can be differentiated by lack of tremors, supranuclear ocular palsy, lack of myoclonus, and, most important, less frequent dysautonomia.
- PD: PD can develop mild dysautonomia and postural instability. Key in differentiation is timing of onset of these symptoms (much later for PD), levodopa responsiveness, asymmetry of PD, and much slower progression of PD.
- Corticobasal syndrome: Atypical parkinsonism that can present with early falls and postural instability and can have myoclonus. Differentiated due to marked asymmetry of the disease, early cognitive involvement, and presence of apraxia.
- Secondary parkinsonism: Usually lacks the presence of dysautonomia and may be more slowly progressive.
- Main differential diagnosis of MSA-C includes sporadic late-onset ataxias and autosomal dominant spinocerebellar ataxias (SCA).
- Fragile X associated tremor ataxia syndrome (FXTAS) must be distinguished from MSA and can be present in up to 5% of adult-onset progressive cerebral ataxia.

WORKUP

Autonomic failure early in disease can differentiate MSA and can be determined with:

- Thermoregulatory testing
- Thermal skin sweat test
- Tilt table test
- Ambulatory 24-hour blood pressure monitoring

LABORATORY TESTS

- No routine laboratory tests are indicated.
- It is important to work up for secondary causes of parkinsonism and dysautonomia as appropriate.

TABLE E1 Diagnostic Criteria for Multiple System Atrophy (MSA)

Possible MSA	A sporadic, progressive, **adult (>30 yr)** onset disease characterized by • Parkinsonism or cerebellar syndrome • At least one feature of autonomic or urogenital dysfunction • At least one of the additional features	Additional Features: • Stridor • Babinski sign • Rapidly progressive parkinsonism • Poor response to levodopa • Postural instability within 3 yr • Cerebellar ataxia • Dysphagia within 5 yr • MRI changes suggestive of MSA
Probable MSA	A sporadic, progressive, **adult (>30 yr)** onset disease characterized by • Autonomic failure involving urinary dysfunction • Poorly levodopa-responsive parkinsonism or cerebellar dysfunction	
Definitive MSA	A sporadic, progressive, **adult (>30 yr)** onset disease pathologically confirmed by presence of high-density glial cell inclusions in association with degenerative changes in striatonigral and olivopontocerebellar pathways	

MRI, Magnetic resonance image.

IMAGING STUDIES

Some changes have been described on MRI of the brain in MSA, although they are not common or exclusive.

- Hot cross bun sign or T2 hyperintensity in a crosslike fashion in the *basis pontis.*
- T2 linear hyperintensities on the outer margin of the putamen.
- Middle cerebellar peduncle atrophy and infratentorial atrophy.
- Changes in diffusion tensor imaging in putamen and middle cerebellar peduncle.
- Ancillary neuroimaging tests include FDG-PET, transcranial ultrasonography, F-DOPA PET, ^{18}F-fluorodopamine PET, and ^{123}I-IBZM SPECT.

Rx TREATMENT

- Parkinsonism in MSA may respond to levodopa in 60% patients; however, <10% have an excellent response and the best response is usually seen at higher doses. This improvement is transient in >90% patients, usually 2 to 3 yr on average.
- Parkinsonism in MSA does NOT respond to deep brain stimulation (DBS) surgery and is a diagnosis of exclusion for DBS surgery. Currently, there is no surgical treatment for parkinsonism in MSA.
- Antiaggregation and truncation of alpha-synuclein is under investigation as a treatment strategy.

NONPHARMACOLOGIC THERAPY

Most often, the initial treatment for orthostatic hypotension includes physical and supportive countermeasures to raise blood pressure, such as:

- Crossed leg stance with leaning against the wall
- Elastic stockings
- Correcting volume depletion and anemia
- Avoiding dehydration
- Liberal salt use

ACUTE GENERAL Rx

ORTHOSTATIC HYPOTENSION:

- Second FDA-approved medication for neurogenic orthostatic hypotension is *Droxidopa* (with midodrine being the only other medication).
- Recently approved droxidopa is a synthetic amino acid prodrug of norepinephrine that is orally bioavailable and has limited crossover through the blood-brain barrier and increases norepinephrine levels in brain.
- Other medications are used frequently to treat orthostatic hypotension (generally before droxidopa), including pyridostigmine, fludrocortisone, midodrine, and octreotide (Table E2).

CHRONIC Rx

- Bladder dysfunction: Medication used includes oxybutynin, tolterodine, solifenacin, darifenacin, tamsulosin, prazosin, and moxisylyte (specific antagonist of bladder α-adrenergic receptors), and use of botulinum toxin for bladder spasticity and urgency.
- Erectile dysfunction: Medication used includes sildenafil and tadalafil.
- Constipation: Medications include polyethylene glycol, bisacodyl, magnesium sulphate, macrogol, lubiprostone, and botulinum toxin. Long-term use of polyethylene glycol is safe in parkinsonian patients and is the recommended treatment of choice in PD.
- Sleep apnea: Usually treated with continuous positive airway pressure or bilevel positive airway pressure.
- Stridor: Continuous positive airway pressure is first-line therapy, but tracheostomy may be required for persistent and severe stridor.

COMPLEMENTARY & ALTERNATIVE MEDICINE

No evidence-based therapy. Patients with parkinsonism use *Mucuna pruriens* powder and fava beans. Both of them have levodopa in varying concentration and are not known to be any superior to *carbidopa/levodopa.*

DISPOSITION

MSA is a relentlessly and rapidly progressive disabling disease. Mean survival in both subtypes is 7 to 9 yr; sudden death and pneumonia are the two most common causes of death. Older age of onset and early autonomic dysfunction are predictive factors for rapid progression with shorter disease survival.

REFERRAL

- Neurology consultation is important to make the distinction between MSA and other causes of parkinsonism. Yearly evaluation for diagnosis may be needed. Reliability of diagnosis by a movement disorders expert is superior to that from a general neurologist (95% vs. 70%).
- Due to high incidence of nonmotor complications, a close coordination by different care providers is needed.

TABLE E2 Medications for Orthostatic Hypotension in Parkinsonism

Medication	Mechanism of Action	Suggested Dosage	Common/Serious Side Effects
Fludrocortisone*,† (9 alpha-fluoro-17-hydroxy-corticosterone)	A synthetic corticosteroid with mineralocorticoid effect on the kidney (inducing permease), enhancing Na+ reabsorption and increasing K+ excretion	0.1-0.5 mg per day	Acute withdrawal adrenal insufficiency, edema, hypokalemia, interaction with lithium and through CYP450.
Midodrine*,† (2-amino-N-[dimethoxyphenyl-hydroxyethyl]-acetamide)	Midodrine is converted to active metabolite desglymidodrine by that selectively binds to and activates alpha-1-adrenergic receptors of vasculature	5-10 mg per day	Contraindicated in patients with severe organic heart disease, acute renal disease, urinary retention, pheochromocytoma, or thyrotoxicosis.
Droxidopa*,† (D,L Threo 3,4-Dihydroxy-phenylserine)	An orally active synthetic precursor of epinephrine that crosses blood-brain barrier and increases brain epinephrine levels	200-2000 mg per day	Headache, dizziness, and nausea. No significant known toxicity.
Mestinon† (hydroxymethyl-pyridinium bromide dimethyl-carbamate)	Binds reversibly to acetyl-cholinesterase in PNS and increases ACH, leading to muscarinic effects of contraction of bronchial and intestinal smooth muscles, exocrine gland secretions, and nicotinic effect of skeletal muscle contraction	120 to 660 mg per day in divided doses (usually QID)	Toxicity with confusion, ataxia, seizures; generalized weakness, fatigue and twitching, nausea, vomiting and cramps. Coma and death can occur. Antidote is atropine.
Octreotide‡ (pentaoxo-dithia-pentazacycloicosane-4-carboxamide)	A synthetic somatostatin analogue; even more potent inhibitor of growth hormone, glucagon, and insulin	100-1500 μg per day subcutaneously	Abdominal pain, decreased appetite, diarrhea

ACH, Acetylcholine; *CYP450,* cytochrome P450; *PNS,* peripheral nervous system; *QID,* four times daily.
*Drug warning: Potentially serious side effect of marked elevation of supine blood pressure.
†FDA Pregnancy Risk Category C.
‡FDA Pregnancy Risk Category B.

PEARLS & CONSIDERATIONS

Red flags for MSA in patient presenting with parkinsonism:

- Early postural instability, especially if wheelchair bound within 5 yr
- Rapid progression
- Abnormal postures, such as Pisa syndrome
- Severe bulbar dysfunction
- Respiratory dysfunction: Inspiratory stridor or inspiratory signs
- Emotional lability

PATIENT & FAMILY EDUCATION

The Multiple System Atrophy Coalition supporting patients and caregivers: https://www.multiplesystematrophy.org

RELATED CONTENT

Parkinson Disease (Related Key Topic)

AUTHOR: **Danish Bhatti, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Mumps is an acute generalized viral infection that is usually characterized by nonsuppurative swelling and tenderness of one or both parotid glands. It is caused by mumps virus, a single-stranded RNA paramyxovirus, of which humans are the only natural host.

SYNONYMS

Viral parotitis
Parotitis

ICD-10CM CODES

B26.0	Mumps orchitis
B26.1	Mumps meningitis
B26.2	Mumps encephalitis
B26.3	Mumps pancreatitis
B26.81	Mumps hepatitis
B26.82	Mumps myocarditis
B26.83	Mumps nephritis
B26.84	Mumps polyneuropathy
B26.85	Mumps arthritis
B26.89	Other mumps complications
B26.9	Mumps without complication

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- In 2016 there were 6369 cases in the U.S., and in 2017 there were 5629 cases in the U.S., which was the highest in a decade. Sporadic outbreaks still occur in schools, colleges, military posts, or summer camps started by an unvaccinated person.
- Recent mumps outbreaks in the U.S.: At an Ohio university in 2014 (386 cases), at a California university in 2011 (29 cases).
- More than 150,000 cases/yr before licensure of mumps vaccine in 1967.

PREDOMINANT SEX: Males = females
PREDOMINANT AGE: 75% of disease in teenage years
PEAK INCIDENCE: Late winter and early spring months
GENETICS:

- Congenital infection:
  1. First-trimester infection is associated with excessive fetal deaths.
  2. Second- and third-trimester infection is not associated with increased fetal mortality.
- Neonatal infection:
  1. Uncommon
  2. Uncommon in infants <1 yr because of passive immunity conferred by placental transfer of maternal antibody

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Prodromal period: Includes low-grade fever, malaise, anorexia, and headache
- Parotid swelling and tenderness; often the first signs of infection:
  1. Progresses over 2 to 3 days, then opposite side may become involved
  2. Unilateral parotitis in 25% of cases
  3. Considerable pain with parotid swelling, causing trismus and difficulty with mastication and pronunciation
  4. Pain exacerbated by eating or drinking citrus and other acidic foods
  5. Possible fever with parotid swelling, ranging up to 40° C (104° F)
  6. Parotid swelling, usually resolving within 1 wk
- Central nervous system involvement:
  1. May occur from 1 wk before to 2 wk after the onset of parotitis or even in its absence
  2. Meningitis:
     a. Occurs in 1% to 10% of patients with mumps parotitis
     b. Occurs three times more often in males than females
     c. Symptoms: Headache, fever, nuchal rigidity, and vomiting
     d. Full recovery with no sequelae
  3. Encephalitis:
     a. May develop early, as a result of direct viral invasion of neurons, or late, around the second wk after onset of parotitis, and is a postinfectious demyelinating process.
     b. Mumps accounted for only 0.5% of viral meningitis.
     c. Symptoms: Fever, alterations in the level of consciousness, possible seizures, paresis or paralysis, and aphasia. Fever can be quite high (40° to 41° C; 104 to 105.8° F).
     d. Cerebellitis and hydrocephalus are serious complications of mumps encephalitis.
     e. May result in permanent sequelae or death.
  4. Other rare neurologic complications include cerebellar ataxia, transverse myelitis, Guillain-Barré syndrome, and facial palsy.
- Epididymoorchitis:
  1. Most common extrasalivary gland complication of mumps in adult men
  2. Occurs in 38% of postpubertal males who have mumps
  3. Most often unilateral but is bilateral in 30% of males who develop this complication
  4. May precede development of parotitis and may be only manifestation of mumps
  5. Two thirds of cases develop during first week of parotitis
  6. Symptoms:
     a. Severe pain, swelling, and tenderness of the testes and scrotal erythema
     b. Fever and chills
  7. Some degree of testicular atrophy in 50% of cases, mo to yr later
  8. Sterility from bilateral orchitis is rare
- Involvement of pancreas and ovaries:
  1. Pancreas: Abdominal pain, fever, and vomiting
  2. Ovaries: Oophoritis
     a. Occurs in 5% of postpubertal women with mumps
     b. Symptoms include fever, nausea, vomiting, and lower abdominal pain
     c. May rarely result in decreased fertility and premature menopause
- Transient renal impairment: Common and manifested by hematuria and polyuria
- Joint involvement:
  1. Migratory polyarthritis is most frequent
  2. Infrequently affects adults with mumps
  3. Occurs rarely in children
  4. Self-limited, with complete resolution
- Deafness:
  1. Most often unilateral, involving high frequencies; may rarely cause bilateral involvement
  2. Most patients recover
  3. Permanent unilateral deafness reported in 1 in 20,000 cases
  4. Labyrinthitis and end lymphatic hydrops also reported
- Myocardial involvement:
  1. Uncommon
  2. Rarely causes progressive and fulminant fatal myocarditis with dilated cardiomyopathy
  3. Refractory arrhythmia and congestive heart failure
  4. Coronary artery involvement
- Eye involvement:
  1. Corneal endotheliitis following mumps parotitis

ETIOLOGY

- Virus is spread via direct contact, droplet nuclei, fomites, or oral or nasal secretions.
- Patients are contagious from 48 hr before to 9 days after parotid swelling.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other viruses that may cause acute parotitis:
  1. Parainfluenza types 1 and 3
  2. Coxsackie viruses
  3. Influenza A
  4. Cytomegalovirus
- Suppurative parotitis:
  1. Most often caused by *Staphylococcus aureus*
  2. May be differentiated from mumps
     a. Extreme indurations, tenderness and erythema overlying the gland
     b. Ability to express pus from Stensen duct or massage of parotid
- Other conditions that may occur with parotid enlargement or swelling:
  1. Sjögren syndrome
  2. Leukemia
  3. Diabetes mellitus
  4. Uremia
  5. Malnutrition
  6. Cirrhosis
- Drugs that cause parotid swelling:
  1. Phenothiazines
  2. Phenylbutazone
  3. Thiouracil
  4. Iodides

- Conditions that cause unilateral swelling:
  1. Tumors
  2. Cysts
  3. Stones causing obstruction
  4. Strictures causing obstruction

WORKUP

- Diagnosis based on history of exposure and physical finding of parotid tenderness with mild to moderate constitutional symptoms.
- Diagnosis is confirmed by a variety of serologic tests or isolation of the virus.

LABORATORY TESTS

- Diagnosis is confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) performed on serum or on buccal or oral swab with the same specimen also being used to perform viral culture, or by a positive IgM mumps antibody that generally stays elevated for 4 wk. However, serologic mumps testing is particularly unhelpful in some vaccinated individuals who can have mumps without having the usual immunoglobulin M (IgM) spike. Serologic tests cannot distinguish between vaccination and prior true mumps exposure.
- Virus can be isolated from the saliva, usually from 2 to 3 days before to 4 to 5 days after the onset of parotitis. Researchers have shown that many cases labeled as "parotitis" are actually caused by other viruses (EB virus, human herpesvirus 6B, human herpesvirus 6B, human parainfluenza virus).[1]
- Virus can be cultured from cerebrospinal fluid (CSF) in patients with meningitis during the first 3 days of meningeal findings. More rapid confirmation of mumps in the CSF is done through the RT-PCR.
- Virus can be detected in urine during the first 2 wk of infection.
- White blood count (WBC):
  1. May be normal or possible mild leukopenia with a relative lymphocytosis
  2. Leukocytosis with left shift with extrasalivary gland involvement, such as meningitis, orchitis, or pancreatitis
- Serum amylase:
  1. Elevated in the presence of parotitis
  2. May remain elevated for 2 to 3 wk
  3. May be differentiated from mumps and parotids by isoenzyme analysis or serum pancreatic lipase
- Mumps meningitis:
  1. CSF WBCs from 10 to 2000 WBC/mm^3 with a predominance of lymphocytes
  2. In 20% to 25% of patients, predominance of polymorphonuclear cells
  3. CSF protein normal or mildly elevated
  4. CSF glucose low, <40 mg/dl, in 6% to 30% of patients

[1] Barshey AE et al: Viruses detected among sporadic cases of parotitis, United States 2009-2011, *J Infect Dis* 208:1979, 2013.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive treatment
- Adequate hydration and nutrition

ACUTE GENERAL Rx

- Analgesics and antipyretics to relieve pain and fever
- Narcotic analgesics, along with bed rest, ice packs, and a testicular bridge, to relieve pain associated with mumps orchitis
- IV fluids for patients with frequent vomiting associated with mumps pancreatitis or meningitis

DISPOSITION

Most patients recover without incident.

REFERRAL

- To a neurologist if significant neurologic complications develop during or following mumps (myelitis, encephalitis, cranial nerve involvement, cerebellar ataxia, etc.)
- To a cardiologist if viral perimyocarditis develops
- To a urologist if orchitis develops

PEARLS & CONSIDERATIONS

COMMENTS

Prevention:

- Attenuated live mumps virus vaccine has been available since 1967.
  1. Usually given in combination with measles and rubella vaccines (MMR) or as a measles-mumps-rubella-varicella vaccine (MMRV). A monovalent mumps vaccine is no longer available.
  2. Either vaccine should be given at 12 to 15 mo of age and again at 4 to 6 yr of age.
  3. Seroconversion in about 100% of infants given the vaccine.
  4. Contraindicated in pregnant women and immunocompromised patients.
  5. Patients with asymptomatic HIV infection and patients with symptomatic HIV infection, in the absence of severe immunosuppression, can safely receive the MMR vaccine.
  6. Adverse events of vaccination include local pain, indurations, thrombocytopenic purpura, Guillain-Barré syndrome, and cerebellar ataxia.
  7. Adults born before 1957 are considered immune. Those born after 1957 who lack documentation of immunization are considered susceptible. Adults can receive two doses 1 mo apart.
- The CDC and American Academy of Pediatrics (AAP) recommend that patients with mumps stay home from work or school for 5 days after onset of clinical symptoms.
- Because virus may be shed before the onset of parotid swelling, isolation possibly not of great value in limiting spread of infection. Use droplet precautions as per CDC and AAP.
- Mumps is a notifiable disease in all U.S. states.

RELATED CONTENT

Mumps (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Bockelman C et al: Mumps: an emergency medicine-focused update, *J Emerg Med* 54:207-214, 2018.

Marin M et al: Use of combination measles, mumps, rubella, and varicella vaccine: recommendation of the Advisory Committee on Immunization Practices (ACIP), *MMWR Recomm Rep* 59(RR-3):1-12, 2010.

Marin M et al: Recommendation of the Advisory Committee on Immunization Practices for the use of a third dose of mumps virus-containing vaccine in persons at increased risk for mumps during an outbreak, *MMWR Morb Mortal Wkly Rep* 67:33-38, 2018.

Principi N, Esposito S: Mumps outbreaks: a problem in need of solutions, *J Infect* 76:503-506, 2018.

BASIC INFORMATION

DEFINITION

Muscular dystrophy (MD) refers to a heterogeneous group of inherited disorders resulting in characteristic patterns of muscle weakness, some with cardiac involvement. Only disorders with childhood or adult onset are considered here (i.e., excluding congenital myopathies).

SYNONYM

MD

ICD-10CM CODE
G71.0 Muscular dystrophy

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Most common childhood MD is Duchenne muscular dystrophy (DMD) with an incidence of 1/3500 male births.
- Most common adult MD is myotonic dystrophy with an incidence as high as 1/8000.

GENETICS:

- **Dystrophinopathies:** X-linked recessive defect in dystrophin gene resulting in either absence (DMD) or reduced/defective (Becker MD [BMD]) dystrophin
- **MD:** Autosomal dominant (AD) CTG trinucleotide repeat (see "Myotonia")
- **Limb-girdle muscular dystrophy (LGMD):** The majority are autosomal recessive, also autosomal dominant forms. Associated with deficiencies identified in multiple proteins (sarcoglycan, calpain, dystroglycan, and dysferlin may be most common; also may involve telethonin, lamin A/C, myotilin, and caveolin-3)
- **Emery-Dreifuss MD:** X-linked recessive defect in nuclear protein emerin or AR/AD defect in inner nuclear lamina proteins lamin A/C
- **Facioscapulohumeral MD:** AD; genetic mutation causes deletion of 3.3 kb repeat
- **Oculopharyngeal DM:** AD GCG trinucleotide repeat resulting in deficient mRNA transfer from nucleus

PHYSICAL FINDINGS & CLINICAL PRESENTATION

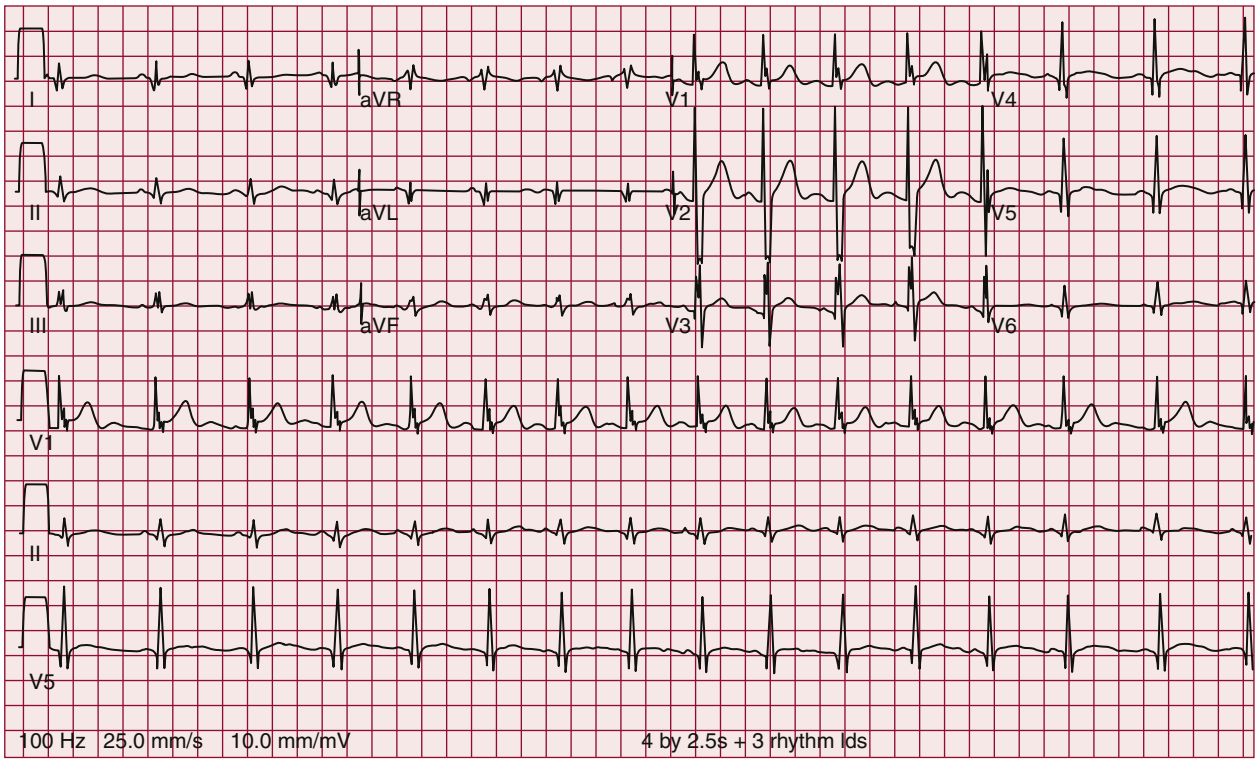
- **Dystrophinopathies:** Proximal arm and leg weakness with hypertrophic calf muscles (Fig. E1), delayed motor milestones, cognitive impairment, cardiac involvement (Fig. E2), progressive course resulting in respiratory complications and respiratory failure.
  1. DMD onset at 2 to 3 yr old, typically wheelchair-bound by 12 yr
  2. BMD onset at 5 to 15 yr old, ambulatory beyond age 15 yr
- **Myotonic dystrophy:** Variable age of onset and severity manifesting as predominantly distal weakness with long face, percussion and grip myotonia, temporalis and masseter wasting, ptosis, hypersomnolence, cognitive impairment, and cardiac conduction defects. May be associated with frontal balding, cataracts, impaired glucose tolerance, and male infertility.
- **LGMD:** Phenotypically and genetically heterogenous characterized by proximal hip and shoulder girdle weakness, some genotypes featuring cardiac involvement. Extraocular muscles are spared, and usually facial muscles and intellect are spared. With LGMD, less severe forms can emerge during the first three decades, leading to loss of ambulation after 30 yr of age. The most severe forms start at 3 to 5 yr of age and progress rapidly.
- **Emery-Dreifuss MD:** Early adulthood onset with predominantly humeroperoneal weakness, early contractures, and cardiac dysfunction
- **Facioscapulohumeral MD:** Onset typically in late childhood or adolescence with weakness mostly in face and shoulder girdle musculature (Fig. E3) and possible later, mild involvement of lower extremities
- **Oculopharyngeal MD:** Symptom onset typically in mid-adult life with ptosis, ophthalmoparesis usually without diplopia, dysphagia, dysarthria, and proximal muscle weakness
- Table E1 shows a classification of muscular dystrophies. Fig. E4 illustrates the Gower maneuver in a patient with Becker muscular dystrophy.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Spinal muscular atrophy, myasthenia gravis, inflammatory myopathy, metabolic myopathy,

FIG. E1 A, Calf pseudohypertrophy in an 8-year-old male with Duchenne muscular dystrophy. **B,** Becker muscular dystrophy in a 24-year-old male. Dystrophy of the shoulder girdle and calf pseudohypertrophy is evident. (**A,** Courtesy Dr. Laurence E. Walsh; **B,** courtesy Dr. Robert M. Pascuzzi. In Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.)



A

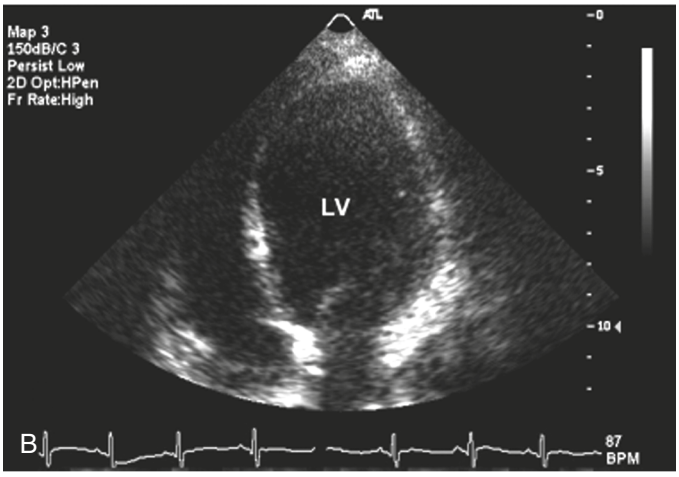


FIG. E2 Dilated cardiomyopathy in a 19-year-old man with Duchenne muscular dystrophy. A, Electrocardiogram showing a QRS complex that is typical of Duchenne dystrophy, with tall R waves in lead V1 and deep narrow Q waves in leads I and aVL. **B,** Two-dimensional echocardiogram (parasternal four-chamber view) showing a dilated, thinned left ventricle *(LV). aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right. (From Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.)

endocrine myopathy, toxic myopathy, mitochondrial myopathy

WORKUP

- Creatine kinase
- ECG, Holter monitor, echocardiography
- Electromyography
- Muscle biopsy with immunohistochemistry useful for diagnosis of dystrophinopathies and LGMD
- DNA testing: Single gene or panel depending on suspicion
- Assessment of respiratory parameters, including forced vital capacity (FVC)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Genetic counseling
- Physical, occupational, respiratory, speech therapy as symptoms dictate
- Screening for sleep-disordered breathing with overnight polysomnogram (PSG) if clinically indicated
- Pacemaker placement may be necessary if cardiac conduction defect present

ACUTE GENERAL Rx

- Prednisone may modestly prolong ambulation in DMD. A dose of 0.75 mg/kg/day may improve muscle strength and function over 6 mo to 2 yr. These short-term benefits must be weighed against the side effects of long-term steroid therapy. Deflazacort could be an alternative treatment.
- Eteplirsen has recently been approved for treatment of DMD specifically caused by mutations in the dystrophin gene amenable to exon 51 skipping. Other specific gene therapy drugs are also in development.

FIG. E3 Clinical photograph showing bilateral winging of the scapulae in a patient with facioscapulohumeral muscular dystrophy. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

CHRONIC Rx

Vigilance to avoid cardiac and respiratory complications, joint contractures

DISPOSITION

Variable course, because severity of phenotype is contingent upon both diagnosis and genotype

REFERRAL

- Surgical referral for correction of scoliosis or contractures may be necessary
- Assessment and follow-up in an MD specialty clinic

PEARLS & CONSIDERATIONS

Formal evaluation by anesthetist is recommended before any operation with general anesthesia in patients with dystrophinopathy.

RELATED CONTENT

Muscular Dystrophy (Patient Information)

AUTHORS: **Taylor Harrison, MD,** and **Corey Goldsmith, MD**

TABLE E1 Classification of Muscular Dystrophies

Disease	Genetic Locus	Inheritance	Protein	Outcome/Distinguishing Characteristics
Duchenne/Becker		XR	Dystrophin	Lethal
Emery-Dreifuss		XR	Emerin, lamins A and C	40% lethality
Limb-Girdle Muscular Dystrophies				
LGMD 1A	5q31	AD	Myotilin	
LGMD 1B	1q11-q21	AD	Laminin A/C	Most common AD LGMD Common cardiac involvement requiring pacemaker
LGMD 1C	3p35	AD	Caveolin	Associated with rippling muscle disease
LGMD 1D	6q23	AD	DNAJB6	
LGMD 1E	7q	AD	Desmin	Cardiac
LGMD 1F	7q32	AD	Transportin 3	
LGMD 1G	4p21	AD	HNRNPDL	
LGMD 1H	3p25.1-p23	AD	—	
LGMD 2A	15q15.1-q21.1	AR	Calpain 3	Most common LGMD (15%-40%). Scapular winging, abdominal laxity
LGMD 2B	2p13	AR	Dysferlin	Second most common LGMD (5%-35%) Common distal involvement
LGMD 2C	13q12	AR	γ-Sarcoglycan	
LGMD 2D	17q12-q21.33	AR	α-Sarcoglycan	
LGMD 2E	4q12	AR	β-Sarcoglycan	
LGMD 2F	5q33-q34	AR	δ-Sarcoglycan	
LGMD 2G	17q11-q12	AR	Telethonin	
LGMD 2H	9q31-q34.1	AR	E3-Ubiquitin ligase (TRIM32)	
LGMD 2I	19q13.3	AR	Fukutin-related protein	More frequent Cardiomyopathy, may look like Duchenne
LGMD 2J	2q24.3	AR	Titin	
LGMD 2K	9q34	AR	Protein O-mannosyltransferase	Cognitive involvement
LGMD 2L		AR	Anoctamin 5	Adult onset 20-50 years old 25% wheelchair
LGMD 2M		AR	Fukutin	
CMDs with CNS Involvement				
Fukuyama CMD	9q31	AR	Fukutin	LE, 11-16 yr
Walker-Warburg CMD	1p32	AR	O-Mannosyltransferase	LE, <3 yr
Muscle-eye-brain CMD	1p32-34	AR	O-MNAGAT	LE, 10-30 yr
CMDs without CNS Involvement				
Merosin-deficient classic type	6q2	AR	Merosin (laminin A_2)	Many patients never walk; others have an LGMD pattern
Merosin-positive classic type	4p16.3	AR	Selenoprotein N1, collagen VI α_2	Course stabilizes in late childhood; many continue to walk into adulthood
Integrin-deficient CMD	12q13	AR	Integrin α7	Presents early in infancy with hypotonia and delayed milestones
Other Dystrophies				
Facioscapulohumeral	4q35	AD	DUX4	20% wheelchair bound
Oculopharyngeal	14q11.2-q13	AD/AR	Polyadenylate binding protein nuclear 1	Onset: ≈48 yr, 100% symptomatic by age 70
Myotonic dystrophy	19q13.3	AD	DMPK, CCHC-type zinc finger and CNBP	Onset: 50% show signs by age 20; variable severity

AD, Autosomal dominant; *AR,* autosomal recessive; *CCHC,* cysteine and histidine amino acid sequence in this class of zinc finger; *CMD,* congenital muscular dystrophy; *CNBP,* cellular nucleic acid–binding protein; *CNS,* central nervous system; *DMPK,* dystrophia myotonica-protein kinase; *DUX4,* double homeobox protein 4; *LE,* life expectancy; *LGMD,* limb-girdle muscular dystrophy; *O-MNAGAT,* O-mannose β-1,2-*N*-acetylglucosaminyl transferase; *XR,* X chromosome related.

Adapted from Firestein GS: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, WB Saunders.

FIG. E4 Patient with Becker muscular dystrophy caused by an in-frame deletion of exons 45 to 47 in the dystrophin gene. The patient is using the Gower maneuver to rise from sitting to standing position: while sitting **(A)**, he uses the force of his hands to stand **(B through D)**. **E,** Using his thighs, he pushed himself upright, leading to the characteristic hyperlordosis posture. (Courtesy Dr. Meir H. Kryger. In Kryger M et al: *Principles and practice of sleep medicine,* ed 6, 2017, Elsevier.)

Mushroom Poisoning PTG

BASIC INFORMATION

DEFINITION

Mushroom poisoning is intoxication resulting from ingestion of poisonous mushrooms.

ICD-10CM CODE

T62.0X1A Toxic effect of ingested mushrooms, accidental (unintentional), initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

- 5% of all mushrooms are poisonous. Distinction between poisonous and edible mushrooms may be difficult even by experienced persons.
- Common poisonous species include *Amanita, Russula, Gyromitra,* and *Omphalotus* (see Table E1). *Amanita phalloides,* colloquially known as the "death cap," belongs to the *Phalloideae* section of the *Amanita* family of mushrooms and is responsible for most deaths following ingestion of foraged mushrooms worldwide.
- Identification of syndromes is more important than knowing the associated species (Table 2).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- *Russula* causes confusion, delirium, visual disturbance, tachycardia, and diarrhea within a few hours of ingestion. Prognosis: Spontaneous recovery (mortality rate >1%).
- *Amanita* and *Gyromitra* intoxication begins with symptoms of gastroenteritis (nausea, vomiting, diarrhea, and abdominal cramps) approximately 10 hr after ingestion. *Amanita* then causes cardiomyopathy and hepatic and renal failure. *Gyromitra* produces jaundice and seizures. Both mushrooms are associated with a 50% mortality rate.
- *Omphalotus* causes symptoms of gastroenteritis that subside spontaneously within 24 hr.

ETIOLOGY

- *Amanita* contains cytotoxic substances and isoxazoles that are gamma-aminobutyric acid neurotransmitter analogs. Amatoxins, consisting of alpha-, beta-, and gamma-amanitin, account for >90% of deaths related to mushroom poisoning. The amanitas are heat stable and not inactivated by cooking.
- *Gyromitra* contains a pyridoxine antagonist that disrupts the gastrointestinal mucosa and causes hemolysis.
- *Russula* contains a cholinergic substance.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Food poisoning
- Overdose of prescription or illegal drug
- Other intoxications
- See topic on specific organ failure (e.g., renal or hepatic failure) for differential diagnosis of those conditions

WORKUP

- History
- Inspection and identification of suspected mushrooms
- Mushroom or gastric content analysis (by thin-layer chromatography or radioimmunoassay)

TREATMENT

- Gastric lavage.
- Repeated administration of activated charcoal.
- Penicillin G or silibinin can be used for *Amanita* mushroom intoxication. Silibinin interferes with hepatic uptake of alpha-amanitin. IV silibinin is not currently available in the U.S. Where available, it is given at a rate of 5 mg/kg IV over 1 hr, followed by 20 mg/kg/day. An oral form of silibinin is available in health food stores as an extract from milk thistle called silymarin. Dose is 1 g PO qid. IV benzyl penicillin reduces hepatocyte uptake of amatoxin.
- Supportive care as needed (may require respiratory assistance, hemodialysis, or emergency liver transplantation) in the event of irreversible fulminant liver failure.
- In patients with severe *Amanita* poisoning, early contact with the nearest liver transplant center is recommended.
- Box E1 summarizes the general management of mushroom poisoning.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Mushroom Poisoning (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

TABLE 2 Summary Common Mushroom-Associated Syndromes

Syndrome	Clinical Course	Toxin(s)	Typical Causative Mushroom(s)
Delayed gastroenteritis followed by hepatorenal syndrome	Stage 1: 24 hr after ingestion: onset of nausea, vomiting, profuse cholera-like diarrhea, abdominal pain, hematuria Stage 2: 12-48 hr after ingestion: apparent recovery; levels of hepatic enzymes are rising during this stage Stage 3: 24-72 hr after ingestion: progressive hepatic and renal failure, coagulopathy, cardiomyopathy, encephalopathy, convulsions, coma, death	Cyclopeptides, principally amatoxins	"Deadly *Amanitas*," *Galerina* species
Hyperactivity, delirium, coma	30 min to 2 hr after ingestion: delirium, hallucinations, and coma	Muscimol, ibotenic acid	*Amanita muscaria, Amanita pantherina*
Delayed gastroenteritis with central nervous system abnormalities	6-24 hr after ingestion: nausea, vomiting, diarrhea, abdominal pain, muscle cramps, delirium, convulsions, coma; hemolysis and methemoglobinemia may occur	Gyromitrin	*Gyromitra esculenta* ("false morel")
Cholinergic syndrome	30 min to 2 hr after ingestion: bradycardia, bronchorrhea, bronchospasm, salivation, perspiration, lacrimation, convulsions, coma	Muscarine	*Boletus* species, *Clitocybe* species, *Inocybe* species, *Amanita* species
Disulfiram-like reaction with ethanol	30 min after drinking ethanol (may occur up to 1 wk after eating coprine-containing mushrooms): flushing of skin of face and trunk, hypotension, tachycardia, chest pain, dyspnea, nausea, vomiting, extreme apprehension	Coprine	*Coprinus atramentarius*
Hallucinations	30 min to 3 hr after ingestion: hallucinations, euphoria, drowsiness, compulsive behavior, agitation	Psilocybin and psilocin	*Psilocybe* species
Delayed gastritis and renal failure	Abdominal pain, anorexia, vomiting starting over 30 hr after ingestion, followed by progressive renal failure 3-14 days later	Orelline, orellanine	*Cortinarius* species
Immune-mediated hemolytic anemia	Syncope, gastroenteritis, oliguria, hemoglobinuria, back pain, hemolysis	Immunoglobulin mediated	*Paxillus involutus*
General gastrointestinal irritants	30 min to 2 hr after ingestion: nausea, vomiting, abdominal cramping, diarrhea; may recover without treatment	Unidentified, probably multiple	*Chlorophyllum molybdites,* backyard mushrooms ("little brown mushrooms"), many others

From Brent J et al (eds): *Haddad and Winchester's clinical management of poisoning and drug overdose,* ed 4, Philadelphia, 2007, WB Saunders, Table 23-1.

BOX E1 General Management of Mushroom Ingestion

1. Determine history of ingestion: How many types of mushrooms ingested, what time, if anyone else ate them, and what symptoms are present.
2. Attempt to determine which of the possible syndromes (see Table 2) the patient may have. For example, gastrointestinal symptoms occurring more than 6 hr after ingestion strongly suggest cyclopeptide, gyromitrin, or *Cortinarius* poisoning.
3. Administer activated charcoal. If the patient has diarrhea, do not give a cathartic. If a cathartic is used, give it only with the first dose of activated charcoal. Use repeated doses of activated charcoal for suspected amatoxin poisonings.
4. If feasible and when indicated, send gastric aspirate or emesis, along with any remaining mushrooms, to a mycologist for identification.
5. Try to perform a preliminary identification of mushroom and spores. Start to develop a spore print as soon as possible.
6. Maintain supportive measures, including airway support, intravenous fluids, and vasopressors (if needed). Monitor volume status.
7. Avoid antispasmodics for gastrointestinal symptoms.
8. Anticipate the clinical course.

From Brent J et al (eds): *Haddad and Winchester's clinical management of poisoning and drug overdose,* ed 4, Philadelphia, 2007, WB Saunders, Box 23.1.

TABLE E1 Mushroom Groups

Group/Toxin	Representative Example	Clinical Effects
Early Onset of Symptoms		
Coprine	*Coprinus atramentarius*	Disulfiram reaction with alcohol
GI toxin	Many species	Nausea, vomiting, diarrhea, abdominal pain
Ibotenic acid and muscimol	*Amanita muscaria*	Diverse CNS effects, including hallucinations, seizures, delirium, coma, agitation
Muscarine	*Clitocybe dealbata*	Peripheral cholinergic toxidrome
Psilocybin	*Psilocybe cubensis*	CNS effects, including hallucinations and euphoria
Late Onset of Symptoms		
Cyclopeptides	*Amanita phalloides*	GI effects followed by hepatotoxicity
Gyromitrin	*Gyromitra esculenta*	GI effects followed by seizures
Orellanine	*Cortinarius orellanus*	GI effects followed by renal toxicity

CNS, Central nervous system; *GI,* gastrointestinal.
From Marx J: *Rosen's emergency medicine: concepts and clinical practice,* ed 7, Philadelphia, 2010, Elsevier.

SUGGESTED READING

Vo KT et al: *Amanita phalloides* mushroom poisonings—Northern California, December 2016, *MMWR* 66(21):549-553, 2017.

BASIC INFORMATION

DEFINITION

Myasthenia gravis (MG) is an autoimmune disorder affecting postsynaptic neuromuscular transmission, most commonly mediated by antibodies directed against the nicotinic acetylcholine receptor (AChR) of the neuromuscular junction. Anti-AChR antibodies cause a decrease in functional postsynaptic ACh receptors, resulting in fatigable weakness. A small percentage of MG patients lack AChR antibodies, and a subset of these patients possess antibodies against muscle-specific tyrosine kinase (MuSK), impacting both pre- and postsynaptic function of the neuromuscular junction. A classification of MG is described in Table 1.

SYNONYM

MG

ICD-10CM CODES

G70.00	Myasthenia gravis without (acute) exacerbation
G70.01	Myasthenia gravis with (acute) exacerbation
P94.0	Transient neonatal myasthenia gravis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 8 to 10 cases annually per 1 million persons. It is the most common disorder of neuromuscular junction transmission.
PREVALANCE (IN U.S.): 150 to 250 cases per 1 million
PREDOMINANT SEX: Females are affected more often than males (3:2) in adults; they are equally affected in the elderly.
PEAK INCIDENCE: Female, second to third decades; male, sixth to eighth decades
GENETICS: Increased frequency of HLA-B8, DR3

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The hallmark of MG is weakness worsened with exercise and improved with rest.
- Generalized weakness involving proximal muscles, diaphragm, and neck extensors is common.
- Weakness is confined to eyelids and extraocular muscles in approximately 15% of patients (Fig. 1).
- Bulbar symptoms of ptosis, diplopia, dysarthria, and dysphagia are common.
- Reflexes, sensation, and coordination are normal.

ETIOLOGY

Antibody-mediated decrease in nicotinic AChR in the postsynaptic neuromuscular junction resulting in defective neuromuscular transmission and subsequent muscle weakness and fatigue. Early-onset MG is associated with *HLA-DR3, HLA-B8,* and non-*HLA* genes. Late-onset MG is associated with *HLA-DR2, HLA-B27,* and *HLA-DRB1*. MuSK antibodies have been recognized since 2001 and present with a similar syndrome to AChR MG although they may have more bulbar weakness, proximal muscle atrophy, and either lack of or paradoxical response to pyridostigmine. Serologic and clinical presentation of myasthenia gravis subgroups are summarized in Table 2.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Lambert-Eaton myasthenic syndrome, botulism, medication-induced myasthenia, chronic progressive external ophthalmoplegia, congenital myasthenic syndromes, thyroid disease, basilar meningitis, intracranial mass lesion with cranial neuropathy, Miller-Fisher variant of Guillain-Barré syndrome

WORKUP

- Edrophonium (Tensilon) test (Fig. 2): Useful in MG patients with ocular symptoms, although uncommonly used now. Cardiac monitoring and atropine ready at the bedside are essential. Patients with MG may also have a positive ice pack test (Fig. E3).
- Repetitive nerve stimulation: Successive stimulation shows decrement of muscle action potential in clinically weak muscle; may be negative in up to 50%.
- Single-fiber electromyography: Highly sensitive; abnormal in up to 95% of patients.
- Serum AChR antibodies found in up to 90% of patients.
- A subset of patients with seronegative MG may have MuSK antibodies.

LABORATORY TESTS

- Forced vital capacity (FVC) is the most useful test for assessing neuromuscular respiratory status. Patients with an FVC of <20 ml/kg are at high risk of respiratory failure and should be monitored in an ICU setting. Although the decision of when to intubate is a clinical one, FVC falling below 10 to 15 ml/kg generally requires intubation.
- CT scan with contrast of anterior chest to look for thymoma or residual thymic tissue. 10% of patients with MG have a thymoma and the prevalence increases with age.
- Thyroid-stimulating hormone, free T_4 to rule out thyroid disease.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient education to facilitate recognition of worsening symptoms and impress need for medical evaluation at onset of clinical deterioration
- Avoidance of selected drugs (Table 3) known to provoke exacerbations of MG (beta-blockers, aminoglycoside and quinolone antibiotics, penicillamine, interferons, class I antiarrhythmics [procainamide, quinidine, etc.])

TABLE 1 Osserman Classification Used by the Myasthenia Gravis Foundation of America to Standardize Clinical Symptoms[1]

Class I	Any ocular muscle weakness
Class II	Ocular muscle weakness of any severity, MILD limb weakness
Class IIa	Predominantly limb and/or axial muscle weakness
Class IIb	Predominantly bulbar and/or respiratory muscle weakness
Class III	Ocular muscle weakness of any severity, MODERATE weakness of other muscles
Class IIIa	Predominantly limb and/or axial muscle weakness
Class IIIb	Predominantly bulbar and/or respiratory muscle weakness
Class IV	Ocular muscle weakness of any severity, SEVERE weakness of other muscles
Class IVa	Predominantly limb and/or axial muscle weakness
Class IVb	Predominantly bulbar and/or respiratory muscle weakness
Class V	Intubation with or without mechanical ventilation

[1]Jaretzki A et al: Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America, *Neurology* 55:16-23, 2000.
From Parrillo JE, Dellinger RP: *Critical care medicine: principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

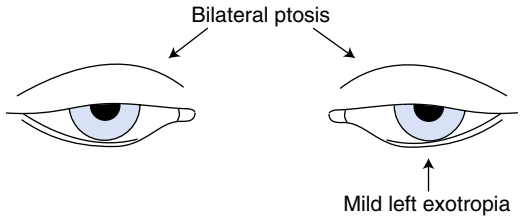


FIG. 1 Myasthenia gravis. Myasthenia gravis may mimic any ocular disorder causing diplopia, although most often it mimics weakness of the superior rectus muscle or medial rectus muscle (i.e., difficulty with sustained elevation or adduction of the eye, respectively). Clues to the diagnosis of myasthenia gravis are associated ptosis, fluctuating course, and normal pupils. (From McGee S: *Evidence-based physical diagnosis,* ed 4, Philadelphia, 2018, Elsevier.)

TABLE 2 Serologic and Clinical Presentation of Myasthenia Gravis Subgroups[1-7]

	AChR Antibody	MuSK Antibody	Striated Muscle Antigens Titin Antibody RyR Antibody	Age at Onset Sex	Clinical Findings	Response to Therapy	Response to Thymectomy	Prognosis
Ocular MG	50%-75%	None	None	Older Male	Ocular	Good	Good	Good (but 50% can develop generalized MG in 2 yr)
Early-onset generalized MG	80%-85% (high titer)	None	None-rare	<50 yr	General	Rarely needs immunosuppression	Good	Less severe Low mortality
Late-onset generalized MG	None-rare	None	50% 54% titin 33% RyR	≥50 yr	General	Often requires immunosuppression	Poor	Severe
Thymomatous-associated MG	Positive, nearly 100% (low titer)	None	95% 50% titin 47% RyR	Ranges: Older but <40 yr if RyR	General If RyR: Ocular, bulbar, respiratory weakness	Often requires immunosuppression	Fair	RyR: Invasive, malignant thymoma Severe Higher mortality
Generalized MG MuSK positive	None	100%	None	Younger Female	Facial, bulbar, neck, respiratory weakness paraspinal, esophageal muscles	Poor response to AChE inhibitors	Poor (no thymic changes)	Severe, progressive course
MG with thymic hyperplasia	89%	None	None	Younger Female	General	Good	Good	Good
ACh antibody negative	Negative	Negative	Present	Younger Female	General	Poor		Fair

AChE, Acetylcholinesterase; *AChR,* acetylcholine receptor; *MG,* myasthenia gravis; *MuSK,* muscle-specific tyrosine kinase; *RyR,* ryanodine receptor.
[1]Romi F, Aarli JA, Gilhus NE: Myasthenia gravis patients with ryanodine receptor antibodies have distinctive clinical features, *Eur J Neurol* 14:617-620, 2007.
[2]Romi F, Gilhus NE, Aarli JA. Myasthenia gravis: clinical, immunological, and therapeutic advances, *Acta Neurol Scand* 111:134-141, 2005.
[3]Akaishi T et al: Response to treatment of myasthenia gravis according to clinical subtype, *BMC Neurol* 16:225, 2016.
[4]Gilhus NE, Verschuuren JJ: Myasthenia gravis: subgroup classification and therapeutic strategies, *Lancet Neurol* 14:1023-1036, 2015.
[5]Hong Y et al: Autoantibody profile and clinical characteristics in a cohort of Chinese adult myasthenia gravis patients, *J Neuroimmunol* 298:51-57, 2016.
[6]Gilhus NE et al: Myasthenia gravis-autoantibody characteristics and their implications for therapy, *Nat Rev Neurol* 12:259-268, 2016.
[7]Roberts PF et al: Thymectomy in the treatment of ocular myasthenia gravis, *J Thorac Cardiovasc Surg* 122:562-568, 2001.
From Parrillo JE, Dellinger RP: *Critical care medicine: principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

FIG. 2 Positive edrophonium test in myasthenia gravis. A, Asymmetric ptosis in the primary position. **B,** Defective upgaze. **C,** Following injection of edrophonium, there is marked bilateral improvement of ptosis and modest improvement of left upgaze. (From Kanski JJ et al: *Clinical ophthalmology: a systematic approach,* ed 7, Philadelphia, 2010, WB Saunders.)

TABLE 3 Medications to Avoid in Myasthenia Gravis[1]

Medications to Avoid	Examples	Recommendation for Avoidance	Mechanism of Weakness
Antibiotics			
Aminoglycosides	Gentamycin Streptomycin	Contraindicated	Blocks ACh receptor, prevents release of ACh
	Tobramycin Amikacin	Less likely problematic	
Antimalarials	Quinine Chloroquine	Contraindicated	Presynaptic blockage of voltage-dependent sodium channels and postsynaptic potentiation of depolarization
Macrolides	Erythromycin, Tetracycline Azithromycin	Relative	Affects presynaptic transmission
Fluoroquinolones	Moxifloxacin Ciprofloxacin Levofloxacin Ofloxacin	FDA black box warning	Unknown
Ketolide	Telithromycin	FDA black box warning	Unknown
	Polymyxins	Contraindicated	Presynaptic and postsynaptic effects
Cardiovascular			
Antiarrhythmics	Procainamide Propafenone	Contraindicated	Decreases the release of ACh Sodium influx blocker
β-Blockers	Propranolol Atenolol Ophthalmic timolol	Relative	Unclear—may be at the neuromuscular junction or muscle membrane
Calcium channel blocker	Verapamil Amlodipine	Relative	Presynaptic and postsynaptic blockade of L-type calcium channels
Anticonvulsants			
	Phenytoin	Relative	Depressed postsynaptic response to ACh; inhibition of calcium channel; increase in muscle membrane threshold
	Carbamazepine	Relative	Triggers immune response
	Gabapentin	Relative	Binds voltage-gated calcium channel
Chemotherapeutic Agents			
	Doxorubicin Etoposide Cisplatin	Relative	Unknown
Others			
	Interferon	Relative	Autoantibody production
Neuromuscular blocking agents	Atracurium Cisatracurium Vecuronium	Relative	Blocks ACh receptors
Statins		Relative	Unknown
Corticosteroids		Relative	Direct blocking of ACh receptor through ionic channels
Botulinum toxin		Contraindicated	Impairs synaptic transmission
Magnesium		Relative	Impairs synaptic transmission
Penicillamine		Contraindicated	Binds the ACh receptor; induces antibodies to receptor

[1]Ahmed A, Simmons Z: Drugs which may exacerbate or induce myasthenia gravis: a clinician's guide, *Internet J Neurol* 10:1-8, 2008.
ACh, Acetylcholine; *FDA,* Food and Drug Administration.
From Parrillo JE, Dellinger RP: *Critical care medicine: principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

- Prompt treatment of infections, diet modification, and speech evaluation with dysphagia

ACUTE GENERAL Rx

- Symptomatic treatment with acetylcholinesterase inhibitors:
  1. Pyridostigmine 30 to 60 mg PO q4 to 6h initially; onset of effects is 30 min, duration 4 hr. May be titrated up to 120 mg every 4 hr. GI upset is not uncommon with higher doses and may respond to hyoscyamine.
- Immunosuppressive treatment with corticosteroids and azathioprine is first-line treatment:
  1. Prednisone initiated at 10 to 20 mg qd titrated by 5-mg increments to effect or dose of 1 mg/kg/day with improvement in 2 to 4 wk and maximal response by 3 to 6 mo.
  2. Azathioprine initiated at 50 mg qd titrated to 2 to 3 mg/kg/day with clinical effect in 6 to 12 mo. Azathioprine is not recommended in patients with no thiopurine methyltransferase activity.
- Alternative secondary agents:
  1. Eculizumab, a first-in-class compliment inhibitor, is FDA-approved for adult patients who are acetylcholine-antibody positive and continue to suffer from severe symptoms despite current immunotherapy use.
  2. Cyclosporine initiated at 5 mg/kg/day with clinical effect within 1 to 2 mo.
  3. Mycophenolate mofetil 500 mg twice a day titrated to 2 g/day with clinical effect in 3 to 6 mo, but can be up to 12 mo.
  4. Rituximab.
- Plasmapheresis and IV immunoglobulin are short-term options for immunotherapy during an exacerbation. There is no significant difference in efficacy between intravenous immunoglobulin (IVIG) and plasmapheresis.
- Mechanical ventilation is lifesaving in setting of a myasthenic crisis. Consider elective intubation if forced vital capacity <10 to 15 ml/kg.

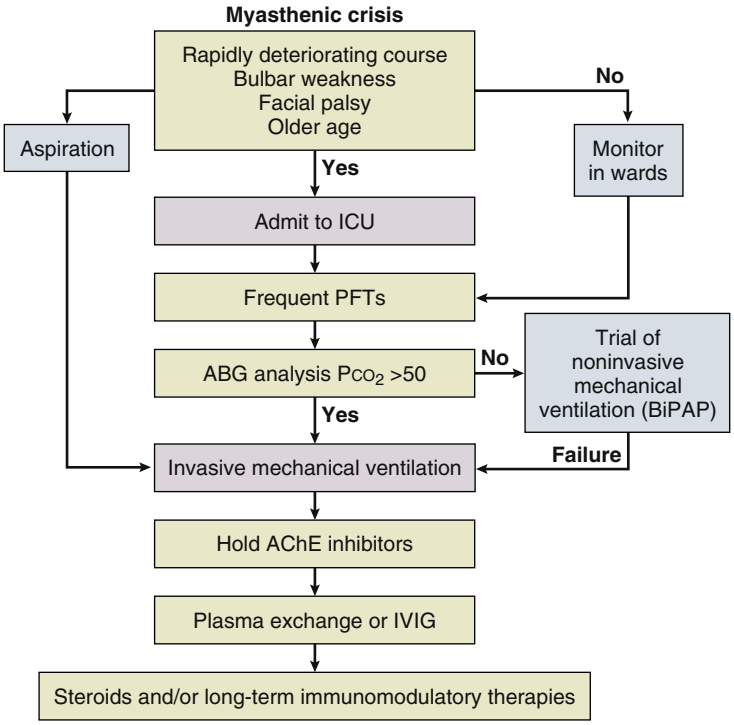


FIG. 4 Clinical flowchart for the management of myasthenic crisis. *ABG,* Arterial blood gas; *AChE,* acetyl cholinesterase; *BiPAP,* bilevel positive airway pressure; *ICU,* intensive care unit; *IVIG,* intravenous immunoglobulin; *PFT,* pulmonary function test. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Elsevier.)

- Fig. 4 illustrates a flowchart for the management of myasthenic crisis.

SURGICAL Rx

- In thymomatous MG, thymectomy is indicated in all patients. If the tumor cannot be surgically resected, chemotherapy can be considered for prevention of local invasion and symptom relief.
- For nonthymomatous autoimmune MG, thymectomy improves clinical outcomes and reduces the need for steroids sustained over at least a 5-yr period. Surgical referral should be considered in patients <60 yr old without significant medical comorbidities even if no frank thymic tissue seen on imaging, especially if they are refractory to therapy.
- MuSK myasthenia is not associated with thymic pathology.

DISPOSITION

Course of disease is highly variable. Mortality rate has decreased from 75% to 4.5% over the past four decades.

REFERRAL

- Referral to a general neurologist or neuromuscular specialist is appropriate.
- Surgical referral for thymectomy in selected cases (see "Surgical Rx").

PEARLS & CONSIDERATIONS

- Sustained upward or lateral gaze and arm abduction for 120 sec may be necessary to elicit subtle signs on examination.
- Myasthenic patients can worsen rapidly and warrant careful observation during an exacerbation or when ill.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Myasthenia Gravis (Patient Information)

AUTHORS: **Radhika Sampat, DO, Corey Goldsmith, MD,** and **Taylor Harrison, MD**

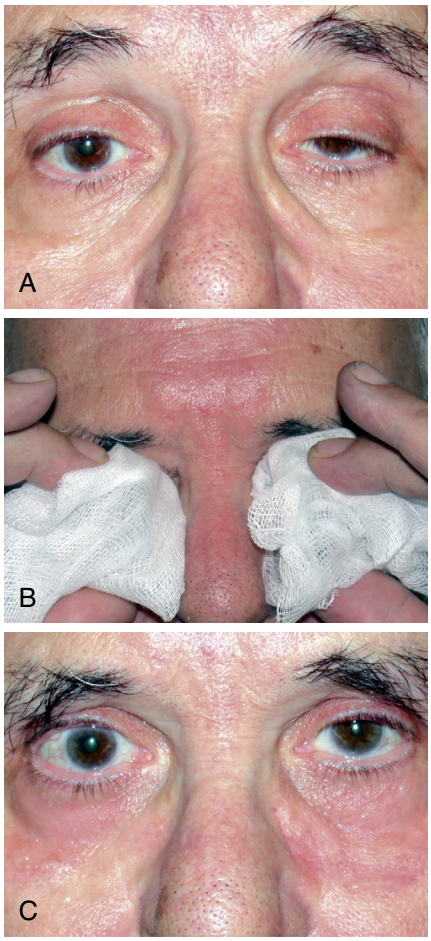


FIG. E3 Positive ice test in myasthenia gravis. A, Asymmetric ptosis. **B,** Application of ice. **C,** Improvement of ptosis. (Courtesy J. Yanguela. From Kanski JJ et al: *Clinical ophthalmology: a systematic approach,* ed 7, Philadelphia, 2010, WB Saunders.)

SUGGESTED READINGS

Barth D et al: Comparison of IVIg and PLEX in patients with myasthenia gravis, *Neurology* 76:2017-2023, 2011.

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Wolfe GI et al: Randomized trial of thymectomy in myasthenia gravis, *N Engl J Med* 375(6):511-522, 2016.

Mycosis Fungoides ALG

BASIC INFORMATION

DEFINITION

Mycosis fungoides is an epidermotropic cutaneous T-cell lymphoma characterized by a proliferation of small- to medium-size T lymphocytes with cerebriform nuclei with skin as their primary site.

SYNONYMS

Cutaneous T-cell lymphoma
MF

ICD-10CM CODES

C84.00	Mycosis fungoides, unspecified site
C84.01	Mycosis fungoides, lymph nodes of head, face, and neck
C84.02	Mycosis fungoides, intrathoracic lymph nodes
C84.03	Mycosis fungoides, intra-abdominal lymph nodes
C84.04	Mycosis fungoides, lymph nodes of axilla and upper limb
C84.05	Mycosis fungoides, lymph nodes of inguinal region and lower limb
C84.06	Mycosis fungoides, intrapelvic lymph nodes
C84.07	Mycosis fungoides, spleen
C84.08	Mycosis fungoides, lymph nodes of multiple sites
C84.09	Mycosis fungoides, extranodal and solid organ sites

EPIDEMIOLOGY & DEMOGRAPHICS

- The annual incidence of cutaneous lymphomas in the U.S. is about 0.6 to 1.0 per 100,000, and mycosis fungoides constitutes about 50% of the cutaneous lymphomas.
- More commonly affects males than females (2:1).
- The majority of patients are Caucasian (70%).
- Median age of diagnosis is 55 to 60 yr but it can also be seen in young adults and children.

CLINICAL PRESENTATION

Mycosis fungoides usually presents in the skin with erythematous patches, plaques, and, less frequently, tumors. Scaling is often found on patch and plaque lesions. The lesions are usually pruritic and patients may have alopecia. Rarely, lesions are atrophied and dyspigmented. Some patients of mycosis fungoides develop erythroderma later in the course of the disease.

Mycosis fungoides usually has an indolent clinical course with slow progression over years and sometimes over decades from patches to more infiltrative plaques and eventually to tumors. The initial skin lesions have predilection for the buttocks and other sun-protected areas ("bathing suit" areas). Patients with tumor-stage MF characteristically show a combination of patches, plaques, and tumors, which often show ulceration. If only tumors are present, without preceding or concurrent patches or plaques, a diagnosis of MF is highly unlikely and another type of cutaneous T-cell lymphoma should be considered.

Sézary syndrome (SS) is considered in patients with erythroderma, circulating T cells, and with or without associated lymphadenopathy.

STAGING

Staging patients with mycosis fungoides (Table E1) is helpful in guiding therapy and it has prognostic value too. The lesions of mycosis fungoides are classified into four tumor (T) groups, T_1-patches and plaques affecting less than 10% of body surface area, T_2-patches and plaques affecting more than 10% of body surface area, T_3-presence of tumors (i.e., raised, dome-shaped lesions >1 cm in diameter), and T_4-erythroderma affecting more than 80% of body surface area.

Because patients with extensive mycosis fungoides lesions (T_2 or T_3 disease) can have substantial blood involvement in the absence of erythroderma, blood assessment is needed in these patients.

- Stage I_A disease is defined as a patch or plaque skin disease involving <10% of the skin surface area and with absence of blood involvement or with low blood tumor burden (<5% of atypical T cells [Sézary cells] in the peripheral blood).
- Stage I_B disease is defined as a patch or plaque skin disease involving ≥10% of the skin surface area (Fig. E1) with absence of blood involvement or low blood tumor burden (<5% Sézary cells).
- Stage II_A and stage II_B diseases are defined by the presence of tumors with or without clinically abnormal peripheral lymph nodes with absence of blood involvement or low blood tumor burden. In approximately 5% of cases of mycosis fungoides, the presentation may be a diffuse, painful, pruritic erythroderma with Sézary cells (Fig. E2) in the peripheral blood (known as Sézary syndrome) (Fig. E3).
- Stage III disease is defined by the presence of generalized erythroderma from the spread of cancer cells through the skin but not yet to the lymph nodes.
- Stage IV_A disease is defined by a lymph node biopsy showing large clusters of atypical cells, more than six cells, or total effacement by atypical cells.
- Stage IV_B disease is defined by the presence of visceral involvement.

ETIOLOGY

Several etiologies have been postulated for mycosis fungoides. There is a supporting role of the skin microenvironment in the pathogenesis, as MF is thought to arise in the background of chronic inflammation. Extravasation and migration of malignant T cells are facilitated by chemokines, cytokines, and adhesion molecules. Th1 and Th2 cytokines are both involved in different stages of the course of MF.

DIAGNOSIS

The diagnosis of mycosis fungoides is established by skin biopsy. This may be difficult to differentiate from other skin lesions in the early phases of the disease (e.g., premycotic patch or early plaque lesions); therefore the diagnosis can only be suspected.

The biopsy of the skin lesions in mycosis fungoides usually shows superficial band like or lichenoid infiltrate, mainly consisting of lymphocytes and histocytes. Atypical T cells of small to regular size with irregular (cerebriform) nuclei are frequently present on or within the epidermis (epidermotropism). The presence of intraepidermal collection of atypical cells (Pautrier microabscesses) is sometimes present and they are a fairly specific but insensitive histologic marker for mycosis fungoides. Because histologic findings are often nondiagnostic, especially in patch stage disease, serial biopsies are frequently needed for the confirmation of diagnosis.

Immunohistochemical staining generally shows atypical CD4+ T cells along with demonstration of aberrant T-cell phenotype (e.g., loss of T-cell antigens). Clonal T-cell gene rearrangements are detected in most cases of mycosis fungoides. These findings help in the diagnosis of mycosis fungoides but they are not very specific.

The diagnosis of early mycosis fungoides often needs integration of clinical, histologic, and molecular features since it can be confused with benign eczematous skin disease.

DIFFERENTIAL DIAGNOSIS

- Contact dermatitis
- Atopic dermatitis
- Nummular dermatitis
- Parapsoriases
- Superficial fungal infections
- Drug eruptions
- Psoriasis
- Photodermatitis
- Alopecia mucinosa
- Lymphomatoid papulosis

WORKUP

Any patient who is suspected of having mycosis fungoides should have a staging workup. Prognosis in patients with mycosis fungoides depends on the type of skin lesions and the extent of disease. The workup should focus on:

- Complete physical examination:
  1. The type of skin lesion and the extent of skin involvement of the body (e.g., skin involvement is >10% or <10% of the skin surface)
  2. Identification of palpable lymph node (especially those >1.5 cm in largest diameter)
  3. Identification of organomegaly (e.g., lungs, liver)
- Skin biopsy:
  1. Biopsy of the most indurated area
  2. Immunophenotyping
  3. Evaluation for clonality
- Blood test:
  1. Complete blood count with differential, liver function tests, lactate dehydrogenase, chemistry
  2. T-cell receptor gene rearrangement

TABLE E1 TNMB Classification and Staging for Patients with Mycosis Fungoides/Sézary Syndrome

T (Skin)	
T_1	Limited patch or plaque (<10% of BSA)
T_2	Generalized patch or plaque (>10% of BSA) T_{2a} = patch only
T_3	One or more tumors (>1 cm)
T_4	Generalized erythroderma (>80% of BSA)
N (Nodes)	
N_0	No clinically abnormal peripheral lymph nodes
N_1	Clinically abnormal peripheral lymph nodes Dutch grade 1, NCI grade LN_0-LN_2
N_{1a}	Clone negative
N_{1b}	Clone positive
N_2	Clinically abnormal peripheral lymph nodes Dutch grade 2, NCI grade LN_3
N_{2a}	Clone negative
N_{2b}	Clone positive
N_3	Clinically abnormal peripheral lymph nodes Dutch grade 3, NCI grade LN_4, clone positive or negative
N_x	Clinically abnormal peripheral lymph nodes No histologic confirmation
M (Viscera)	
M_0	No visceral organ involvement
M_1	Visceral organ involvement (pathology confirmation required)
B (Blood)	
B_0	Atypical circulating cells not present (<5%)
B_{0a}	Clone negative
B_{0b}	Clone positive
B_1	Atypical circulating cells present (>5%)
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	≥1000/μL Sézary cells, clone positive

Stage	T	N	M	B
I_A	1	0	0	0, 1
I_B	2	0	0	0, 1
II_A	1, 2	1, 2	0	0, 1
II_B	3	0-2	0	0, 1
III_A	4	0-2	0	0
III_B	4	0-2	0	1
IV_{A1}	1-4	0-2	0	2
IV_{A2}	1-4	3	0	0-2
IV_B	1-4	0-3	1	0-2

BSA, Body surface area; *NCI,* National Cancer Institute; *TNMB,* tumor, node, metastasis, blood.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

3. Determination of Sézary cell count and/or flow cytometry
- Radiologic tests: Depending on the stage of the disease, chest radiograph; ultrasound; and CT scan of the chest, abdomen, and pelvis alone, with or without fluorodeoxyglucose positron emission tomography scan
- Lymph node biopsy:
  1. Excisional biopsy
  2. Biopsy of the largest lymph node
  3. If multiple nodes enlarged, order of preference is cervical, axillary, and inguinal areas
  4. Histopathology, flow cytometry, T-cell receptor gene rearrangement

Rx TREATMENT

Treatment is guided according to the stage of disease (Box E1) and involves a multidisciplinary team consisting of dermatopathologists, dermatologists, radiation oncologists, and medical oncologists. Therapeutic options are summarized in Table E2, and a treatment algorithm is described in Fig. E4.

NONPHARMACOLOGIC THERAPY

- For dry, cracking skin, emollients (e.g., lanolin and petrolatum) are applied bid.
- Moisturizing lotion (e.g., ammonium lactate) applied bid.
- Topical antibiotics (e.g., bacitracin) are used on ulcerative tumors.

ACUTE GENERAL Rx

- Treatment of patients with stage I_A limited patch or plaque phase includes skin-directed therapies: Topical corticosteroids, topical chemotherapy (nitrogen mustard or carmustine), topical retinoid, phototherapy, and local radiation. There are no well-designed prospective randomized controlled trials comparing the efficacy of these treatment modalities. Most of the patients respond to one or another modality of therapy.
- Treatment of patients with stage I_B to II_A disease is similar to stage I_A. Skin-directed therapies alone or in combination are used with good results:
  1. Topical chemotherapy (nitrogen mustard, carmustine)
  2. Topical retinoids
  3. Phototherapy includes ultraviolet A light with oral methoxypsoralen (PUVA)
  4. Total skin electron beam therapy
  5. Combination of PUVA phototherapy with systemic interferon has been studied in patients with stage I_B to II_A and complete response rates of about 80% have been reported. Similarly, a randomized trial comparing PUVA with systemic interferon and systemic interferon with retinoids has shown superior response rate and less time to response with PUVA phototherapy and systemic interferon compared to interferon with retinoids
- Treatment of patients with stage II_B disease with generalized tumor and plaque disease:
  1. Total skin electron beam therapy has shown effectiveness in patients with II_B disease. The 5-yr disease-free survival is about 50%. Patients with <10% BSA involvement do better than patients with extensive involvement. Phototherapy in combination with interferon have shown a response rate of about 50%.
  2. Patients who do not respond to local therapies need treatment with systemic therapy.
- Topical therapies can be considered in stage III disease but the response and duration of response are less. Hence systemic therapies (biologic therapy or systemic chemotherapy) are considered in stage III and stage IV disease.

Biologic therapies used in these advanced diseases are interferon alfa, photopheresis, systemic retinoid, histone deacetylase inhibitors (vorinostat, romidepsin, belinostat, and panobinostat), denileukin diftitox (recombinant DNA derived cytotoxic protein), and monoclonal antibodies (alemtuzumab, brentuximab, mogamulizumab). The combination of biological agents has shown improved response rate.

FIG. E1 Mycosis fungoides. A, Plaques of mycosis fungoides often have a polycyclic appearance. **B,** Tumors are more elevated above the skin surface. By the time tumors supervene, sun-exposed skin, such as the face, is often involved. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.)

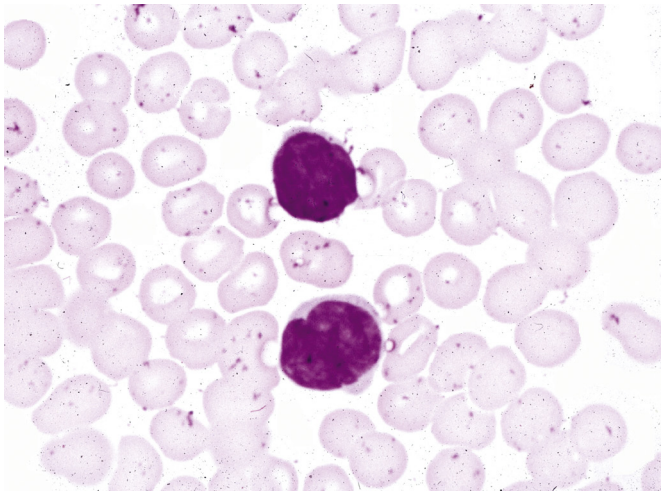

FIG. E2 Sézary cells in a peripheral blood smear. Recognition of these cells is no longer critical for the diagnosis since the advent of clonality studies and flow cytometry. (From Jaffe ES et al: *Hematopathology,* ed 1, Philadelphia, 2011, WB Saunders.)

FIG. E3 Sézary syndrome presents with erythroderma-diffuse red skin. The term *erythroderma* is overused by clinicians; it should refer to confluent erythema, not just widespread erythematous lesions. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.)

BOX E1 Summary of Treatment Approaches for Patients with Mycosis Fungoides and Sézary Syndrome

Early-Stage Mycosis Fungoides
Topical
- Corticosteroids
- Phototherapy
- Nitrogen mustard
- Bexarotene
- Radiation or TSEBT

Refractory Early-Stage Mycosis Fungoides
Combined therapy
- PUVA or NB-UVB and INF-α
- PUVA or NB-UVB and bexarotene (low dose)

Advanced Mycosis Fungoides/Sézary Syndrome
Biologic therapy
- Interferons (INF-α, IFN-γ)
- Retinoid or rexinoid (bexarotene)
- Extracorporeal photopheresis
- Alemtuzumab
- HDACIs (romidepsin, vorinostat)
- Bortezomib
- Antifolates (methotrexate, pralatrexate)
- Mogamulizumab (anti-CCR4)
- Denileukin diftitox (Ontak)
- Brentuximab vedotin

Combined therapy
- INF-α and phototherapy
- INF-α and retinoid or rexinoid
- Retinoid and phototherapy
- ECP and INF-α
- ECP and retinoid or rexinoid

Systemic chemotherapy
Single agent
- Pegylated doxorubicin
- Purine or pyrimidine analogues
  - Pentostatin
  - Gemcitabine
- Temozolomide

Multiagent
- CHOP and CHOP-like, CMED, CHOEP

Stem cell transplant
- Autologous
- Allogeneic
- Nonmyeloablative allogeneic

Investigational therapy
- Lenalidomide

CHOP, Cyclophosphamide, doxorubicin, vincristine, and prednisone; *CHOEP,* cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone; *CMED,* cyclophosphamide, methotrexate, etoposide, dexamethasone; *ECP,* extracorporeal photopheresis; *HDACI,* histone deacetylase inhibitor; *INF,* interferon; *NB-UVB,* narrow-band ultraviolet-B light therapy; *PUVA,* psoralens and ultraviolet-A light therapy; *TSEBT,* total-skin electron-beam therapy.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE E2 Therapeutic Options for Mycosis Fungoides

Topical Therapy

Ultraviolet A with psoralen
Ultraviolet B
External beam radiation therapy
Total-skin electron beam radiation
Topical chemotherapy
Topical retinoids

Systemic Therapy

Photophoresis
Interferon-α
Oral retinoids
Targeted therapies
Single-agent chemotherapy
Combination chemotherapy
Stem cell transplantation
Investigational agents

From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

Unfortunately, most of these patients relapse and develop disease that is refractory to treatment.

Cytotoxic combination chemotherapy regimens have demonstrated activity in advanced-stage cutaneous T-cell lymphoma. Even though they produce higher responses, these are not durable and there are significant toxicities. Hence, single-agent systemic chemotherapy is preferred over combination chemotherapy unless patients are refractory or immediate palliation is needed for extensive tumor burden. Allogenic stem cell transplant has been shown to induce complete and durable remissions in a small number but carries a risk of transplant-related mortality. Hence, reduced intensity allogenic stem cell transplantation is currently being investigated.

DISPOSITION

The 10-yr rates of overall survival are as follows:

- Stage I disease: 65% to 90%
- Stage II disease: 35% to 50%
- Stage III disease: 25% to 35%
- Stage IV disease: 15% to 20%

REFERRAL

Any patient with suspected mycosis fungoides should be referred to a dermatologist with expertise in this entity for definitive diagnosis and initiating therapy. Oncology consultation is indicated in patients with more advanced disease.

PEARLS & CONSIDERATIONS

- The International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC) recommended revisions to the TNM classification and staging system

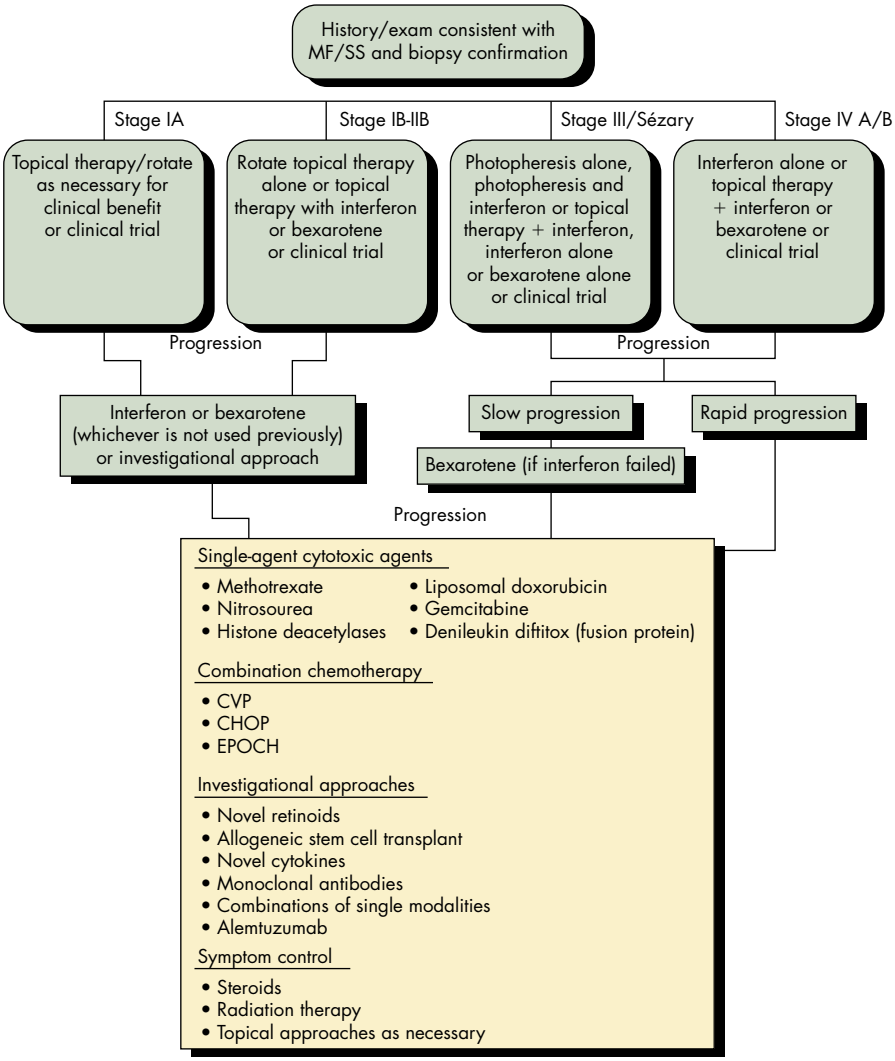

FIG. E4 Algorithm for the care of patients with mycosis fungoides or Sézary syndrome. *CHOP,* Cyclophosphamide, doxorubicin (hydroxorubicin), Oncovin (vincristine), prednisone; *CVP,* central venous pressure; *EPOCH,* etoposide-prednisone-Oncovin-cyclophosphamide-hydroxydaunorubicin; *MF,* mycosis fungoides; *SS,* Sézary syndrome. (Modified from Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

TABLE E3 Comparison of EORTC and WHO Classifications of Primary Cutaneous Lymphoma

EORTC Classification	WHO Classification
Cutaneous T-Cell Lymphoma	
Indolent clinical behavior	Mycosis fungoides
Mycosis fungoides variants	Mycosis fungoides variants
Follicular mycosis fungoides	Follicular mycosis fungoides
Pagetoid reticulosis	Pagetoid reticulosis
CTCL, large cell, CD30+	Primary cutaneous CD30+ ALCL (CD30+ lymphoproliferative disease, including lymphomatoid papulosis)
Lymphomatoid papulosis	
Aggressive clinical behavior	
Sézary syndrome	Sézary syndrome
CTCL, large cell, CD30–	Peripheral T-cell lymphoma, unspecified (most); extranodal NK/T-cell lymphoma, nasal type
Provisional Entities	
CTCL, pleomorphic, small/medium sized	
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
Cutaneous B-Cell Lymphoma	
Indolent clinical behavior	Extranodal marginal zone B-cell lymphoma
Primary cutaneous immunocytoma (marginal zone B-cell lymphoma)	
Follicle center cell lymphoma (any grade)	
Intermediate clinical behavior	
Primary cutaneous large B-cell lymphoma of the leg	
Provisional Entities	
Primary cutaneous plasmacytoma	Plasmacytoma
Intravascular large B-cell lymphoma	Diffuse large B-cell lymphoma (intravascular)

ALCL, Anaplastic large-cell lymphoma; *CTCL,* cutaneous T-cell lymphoma; *EORTC,* European Organization for Research and Treatment of Cancer; *MF,* mycosis fungoides; *NK,* natural killer; *SS,* Sézary syndrome; *WHO,* World Health Organization.
From Hoffman R: *Hematology: basic principles and practice,* ed 7, 2018, Elsevier.

of cutaneous T-cell lymphoma in 2007. Table E3 compares EORTC and WHO classifications of primary cutaneous lymphoma. The ISCL/EORTC revision to the classification of MF and SS (adaptation) is described in Table E4.

- Diagnostic workup always includes assessment of skin, blood, nodes, and the viscera.
- The prognosis of mycosis fungoides in most patients with limited patch/plaque disease is favorable and similar to that of an age-, sex-, and race-matched control population.
- Important quality-of-life considerations include pruritus, xerosis, and the prevention of skin infections.

AUTHOR: **Bharti Rathore, MD**

TABLE E4 ISCL/EORTC Revision to the Classification of MF and SS (Adaptation)

TNMB Stages	
Skin	
T_1	Limited patches, papules, and/or plaques covering <10% of the skin surface. May stratify into T_{1a} (patch only) vs T_{1b} (plaque ± patch).
T_2	Patches, papules or plaques covering ≥10% of skin surface. May stratify into T_{2a} (patch only) vs T_{2b} (plaque ± patch).
T_3	One or more tumors (≥1-cm diameter)
T_4	Confluence of erythema covering ≥80% body surface area
Node	
N_0	No clinically abnormal peripheral lymph nodes; biopsy not required
N_1	Abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_2	Abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN_3
N_3	Abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN_4
N_x	Abnormal peripheral lymph nodes; no histologic confirmation
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and involved organ should be specified)
Blood	
B_0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sézary) cells
B_1	Low blood tumor burden: >5% of peripheral blood lymphocytes are atypical (Sézary) but does not meet the criteria for B_2
B_2	High blood tumor burden: ≥1000/μL Sézary cells with positive clones
Clinical Staging	
I_A	T_1, N_0, M_0, $B_{0,1}$
I_B	T_2, N_0, M_0, $B_{0,1}$
II_A	$T_{1,2}$, $N_{1,2}$, M_0, $B_{0,1}$
II_B	T_3, N_{0-2}, M_0, B0,1
III_A	T_4, N_{0-2}, M_0, B_0
III_B	T_4, N_{0-2}, M_0, B_1
IV_{A1}	T_{1-4}, N_{0-2}, M_0, B_2
IV_{A2}	T_{1-4}, N_3, M_0, B_{0-2}
IV_B	T_{1-4}, N_{0-3}, M_1, B_{0-2}

CTCL, Cutaneous T-cell lymphoma; *EORTC,* European Organization of Research and Treatment of Cancer; *ISCL,* International Society for Cutaneous Lymphomas; *MF,* mycosis fungoides; *NCI LN,* National Cancer Institute lymph node grading system; *SS,* Sézary syndrome; *TNMB,* tumor-node-metastasis-blood.
From Hoffman R: *Hematology: basic principles and practice,* ed 7, 2018, Elsevier.

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Myelodysplastic syndromes (MDS) are a group of acquired clonal disorders affecting hematopoietic stem cells and are characterized by altered differentiation and proliferation. Patients present with peripheral blood cytopenias and morphologic abnormalities but have a hypercellular bone marrow upon examination. The increased marrow cellularity reflects ineffective hematopoiesis with inadequate maturation resulting in cytopenias.

CLASSIFICATION

- In 1982, the French-American-British (FAB) classification included refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), chronic myelomonocytic leukemia (CMML), and refractory anemia with excess blasts in transformation (RAEB-T).
- In 1999, the World Health Organization (WHO) modified the FAB by incorporating newer morphologic insights and cytogenetic findings. It reduced the blast percentage for the diagnosis of acute myeloid leukemia (AML) to 20%, added refractory cytopenia with multilineage dysplasia (RCMD), refined refractory anemia with excessive blasts into types 1 and 2 (RAEB-1, RAEB-2), and added unclassified MDS, and MDS associated with isolated del(5q).
- In 2008, the WHO further modified the classification by subcategorizing MDS into six different categories (Table 1).

SYNONYMS

MDS
Preleukemia

ICD-10CM CODES

D46.9	Myelodysplastic syndrome, unspecified
D46.C	Myelodysplastic syndrome with isolated del(5q) chromosomal abnormality
D46.Z	Other myelodysplastic syndromes

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Approximately five new cases/100,000 persons per yr. An estimated 30,000 new cases are diagnosed annually in the U.S.

PREDOMINANT AGE: More common in elderly patients; median age >65 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients often present with fatigue due to anemia and also with thrombocytopenia and leukopenia.
- Skin pallor, mucosal bleeding, and ecchymosis may be present.
- Fever, infection, and dyspnea are common.

ETIOLOGY

Exposure to radiation, chemotherapeutic agents, benzene, or other organic compounds is associated with myelodysplasia. Table 2 describes predisposing factors and epidemiologic associations of patients with MDS. Up to 40 genes that affect specific functional pathways are mutated in MDS, with 90% of patients having at least one mutation and a median of two to three mutations detected per patient. The most common mutations occur in genes involved in RNA splicing *(SF3B1, SRSF2, U2AF1,* and *ZRSR2),* epigenetic modification *(TET2, ASXL1,* and *DNMT3A),* regulators of signal transduction *(NRAS* and *JAK2),* and transcription factors *(RUNX1* and *TP53).*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hereditary dysplasias (e.g., Fanconi anemia, Diamond-Blackfan syndrome)

TABLE 1 2008 World Health Organization Classification of the Adult Myelodysplastic Syndromes

Refractory Cytopenia with Unilineage Dysplasia	
Dysplasia	≥10% of cells from a single lineage
Blasts	<5% in marrow; <1% in peripheral blood; no Auer rods
Notes	Includes refractory anemia (RA), refractory neutropenia, refractory thrombocytopenia; RA is by far the most common subtype
Refractory Anemia with Ring Sideroblasts	
Dysplasia	Isolated erythroid dysplasia
Blasts	<5% in marrow; <1% in peripheral blood; no Auer rods
Notes	≥15% of erythroid precursors are ring sideroblasts Frequently associated with SF3B1 mutations
MDS with Isolated del(5q)	
Dysplasia	Normal or increased megakaryocytes with hypolobated nuclei
Blasts	<20% (though usually much less)
Notes	del(5q31) must be sole chromosomal abnormality
Refractory Cytopenia with Multilineage Dysplasia	
Dysplasia	≥10% of cells from two or more myeloid lineages
Blasts	<5% in marrow; <1% in peripheral blood; no Auer rods
Notes	Peripheral monocyte count must be $<1 \times 10^9$/L; ring sideroblasts may be present
Refractory Anemia with Excess Blasts	
Dysplasia	No specific requirement
Blasts	RAEB-1: 5%-9% in marrow, <5% in peripheral blood, AND no Auer rods RAEB-2: 10%-19% in marrow, 5%-19% in peripheral blood, OR Auer rods
Notes	Old designation of RAEB-t (20%-30% blasts) now considered AML
Unclassifiable MDS	
Dysplasia	Minimal, or not meeting criteria for another subtype
Blasts	<5% in marrow; <1% in peripheral blood; no Auer rods
Notes	In presence of *clonal cytogenetic finding* considered diagnostic of MDS

Excludes refractory cytopenias of childhood. MDS/myeloproliferative neoplasms such as chronic myelomonocytic leukemia and RARS with thrombocytosis are classified separately.
AML, Acute myeloid leukemia; *MDS,* myelodysplastic syndrome; *RAEB,* refractory anemia with excess blast.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 2 Predisposing Factors and Epidemiologic Associations of Patients with Myelodysplastic Syndrome

Heritable

Constitutional Genetic Disorders

Trisomy 8 mosaicism
Familial monosomy 7
Down syndrome (trisomy 21)
Neurofibromatosis 1
Germ cell tumors [embryonal dysgenesis del(12p)]

Congenital Neutropenia

Kostmann syndrome
Shwachman-Diamond syndrome

DNA Repair Deficiencies

Fanconi anemia
Ataxia-telangiectasia
Bloom syndrome
Xeroderma pigmentosum
Pharmacogenomic polymorphisms (GSTq1-null)

Acquired

Senescence

Mutagen Exposure

Alkylator therapy (chlorambucil, cyclophosphamide, melphalan, N-mustards)
Topoisomerase II inhibitors (anthracyclines)
β Emitters (32p)
Autologous stem cell transplantation
Environmental/occupational (benzene)
Tobacco
Aplastic anemia
Paroxysmal nocturnal hemoglobinuria

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Churchill Livingstone.

- Vitamin B_{12}/folate deficiency
- Exposure to toxins (drugs, alcohol, chemotherapy)
- Renal failure
- Irradiation
- Autoimmune disease
- Paroxysmal nocturnal hemoglobinuria

WORKUP

Diagnostic workup includes laboratory evaluation and bone marrow examination (Fig. E1). Cytogenetic analysis (Box E1) by conventional metaphase karyotyping or by MDS FISH assessment should be performed in patients with MDS. Genes recurrently mutated in myelodysplastic syndrome are summarized in Table 3. Physical examination, medical history, and laboratory tests aiding in diagnosis of MDS are described in Table 4. Key features of the major myelodysplastic syndromes are summarized in Table 5.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Packed red blood cell transfusions in patients with severe symptomatic anemia
- Platelet transfusions in patients with severe thrombocytopenia or those with bleeding episodes

ACUTE GENERAL Rx

- The initial focus of MDS therapy involves stratification of patients into low-, intermediate-, and high-risk states using well-defined and validated risk stratification systems. The original International Prognostic Scoring System (IPSS), which incorporated cytopenias, cytogenetics, and blast percentage, is still clinically used. The revised IPSS (IPSS-R) has been created from an evaluation of more than 7000 patients and utilizes a five-tier risk grouping that accounts for the degree of cytopenias and bone marrow blast percentage and has 15 cytogenetic subtypes.
- Fig. 2 and Table 6 summarize a treatment approach for MDS.
- Low-risk patients are treated with supportive care or growth factors.
- Intermediate- and high-risk patients are offered treatment with hypomethylating agents along with supportive care.
- Appropriate patients are offered allogeneic donor stem cell transplantation as a potentially curative option, with high-volume centers treating patients <80 yr old.
- Erythropoietin (10,000 to 40,000 units/week) or pegylated erythropoietin (200-500 mg every 1 to 3 wk) is used in patients

TABLE 3 Genes Recurrently Mutated in Myelodysplastic Syndrome

Gene	Frequency (%)	Notes
Splicing Factors		
SF3B1	20-30	Strong association with RARS
SRSF2	10-15 (MDS) 40 (CMML)	Enriched in CMML
U2AF1	5-12	Association with del(20q)
Epigenetic Modifiers		
TET2	20-30 (MDS) 40-50 (CMML)	Enriched in CMML Mutually exclusive with IDH
DNMT3A	8-13	
ASXL1	10-20 (MDS) 30-40 (CMML)	Enriched in CMML
EZH2	5-10 (MDS) 20-30 (CMML)	Enriched in CMML May be functionally involved in 7q–
IDH1/2	<5	More frequent in AML
ATRX	Rare	Associated with acquired thalassemia
Transcription Factors		
RUNX1	10-15	Can be somatic or germline
GATA2	Rare	Mostly germline
ETV6	<5	Can be somatic or germline
TP53	10-12	Association with complex karyotype, therapy-related disease
Kinases and Receptors		
JAK2	<5	Enriched in RARS-T
NRAS	5-10	Seen in progression to AML
CBL	<5	Enriched in JMML
PTPN11	<5	More common in JMML
BRAF	Rare	Also seen in hairy cell leukemia
Cohesin Complex		
STAG2	5-10	Cohesin class mutations enriched in high-risk MDS and secondary AML.
RAD21	<5	
SMC3	<2	
SMC1A	<2	
GCPR Complex		
GNAS	Rare	Mutations recently described in wide range of hematologic malignancies, including MDS.
GNB1	Rare	

AML, Acute myeloid leukemia; *CMML,* chronic myelomonocytic leukemia; *GCPR,* G-coupled protein receptor; *IDH,* isocitrate dehydrogenase; *JMML,* juvenile myelomonocytic leukemia; *MDS,* myelodysplastic syndrome; *RARS,* refractory anemia with ring sideroblasts; *RARS-T,* RARS with thrombocytosis.

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 4 Physical Examination, Medical History, and Laboratory Tests Aiding in Diagnosis of Myelodysplastic Syndrome

Medical History

- Duration of symptoms
- History of blood disease
- History of exposure to occupational toxins or cytotoxic agents
- Medication history
- Alcohol intake
- Comorbid conditions

Physical Examination

- Pallor
- Petechiae
- Purpura
- Bruising
- Tachypnea
- Signs of infection
- Splenomegaly

Laboratory Testing

- Complete blood count with a manual differential
- Reticulocyte count
- Vitamin B_{12} and folate levels
- Consider methylmalonic acid and red blood cell folate levels
- Iron, total iron-binding capacity, and ferritin level
- Thyroid-stimulating hormone level
- Lactate dehydrogenase
- Antinuclear antibody
- Coombs test and haptoglobin
- Serum erythropoietin level
- Human leukocyte antigen (histocompatibility antigens) typing in appropriate patients
- Paroxysmal nocturnal hemoglobinuria screen

Bone Marrow Testing

- Hematopathology
- Percentage of blasts on 200 cell aspirate differential
- Presence or absence of Auer rods
- Percentage of cellularity of bone marrow biopsy
- Iron stain on aspirate (ringed sideroblasts)
- Iron stain on biopsy (storage)
- Dysplastic features (% and number of dysplastic lineages)
- Cytogenetics (karyotype of 20 metaphase cells)
- Fluorescent in situ hybridization
- Flow cytometry (not useful for quantitation)

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Churchill Livingstone.

TABLE 5 Diagnostic Criteria for Myelodysplastic Syndrome

A. Presence of at Least One Unexplained Cytopenia for at Least 6 Mo[a]

Hemoglobin <11 g/dl, *or*

Absolute neutrophil count $<1.5 \times 10^9$/L, *or*

Platelet count $<100 \times 10^9$/L

***plus* B. Presence of One or More MDS-Qualifying Criteria:**

>10% dysplasia in one or more hematopoietic lineage, *or*

5%–19% blasts in bone marrow, *or*

MDS-defining cytogenetic abnormality, such as:

t(1;3)(p36.3;q21.1)	t(2;11)(p21;q23)	inv(3)(q21;q26.2)
t(3;21)(q26.2;q22.1)	–5 or del(5q)	t(6;9)(p23;q34)
–7 or del(7q)		del(9q)
del(11q)	t(11;16)(q23;p13.3)	del(12p) or t(12p)
–13 or del(13q)	i(17q) or del(17p)	idic(X)(q13)

***plus* C. Exclusion of Alternative Diagnoses**

AML (i.e., <20% blasts, and no t(8;21), inv(16), t(16;16), t(15;17), or erythroleukemia) or *ALL*

Other hematologic diseases (aplastic anemia, PNH, LGL, lymphoma, myelofibrosis and other MPN)

Viral infections (HIV, EBV, parvovirus)

Nutritional deficiencies (iron, copper, B_{12}, folate)

Medications (methotrexate, azathioprine, isoniazid, cytotoxic chemotherapy)

Alcohol or other toxins

Autoimmune diseases (SLE, Felty syndrome, ITP, autoimmune hemolytic anemia)

Congenital disorders (Diamond-Blackfan anemia, Shwachman-Diamond syndrome, Fanconi anemia, and others)

[a]Diagnosis can be made earlier than 6 mo if no other cause is apparent for cytopenias, or there are excess blasts or an MDS-defining cytogenetic abnormality.

ALL, Acute lymphoblastic leukemia; *AML,* acute myeloid leukemia; *EBV,* Epstein-Barr virus; *ITP,* immune thrombocytopenic purpura; *LGL,* large granular lymphocyte leukemia; *MDS,* myelodysplastic syndrome; *MPN,* myeloproliferative neoplasm; *PNH,* paroxysmal nocturnal hemoglobinuria; *SLE,* systemic lupus erythematosus.

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

with symptomatic anemia. Responses with increase in hemoglobin and decreased transfusion requirements are achieved typically in patients who have serum erythropoietin levels <500 U/L and adequate iron stores.

- DNA methyltransferase inhibitors: Azacitidine, a pyrimidine nucleoside analogue of cytidine, has been shown to improve the quality of life for patients and to prolong overall survival. Decitabine, another nucleoside analogue, has also been FDA approved for patients with MDS. These agents may also be useful in preventing the transition of MDS to AML.
- Immunomodulators: Lenalidomide, a novel analogue of thalidomide, has demonstrated hematologic activity in patients with low-risk MDS who have no response to erythropoietin or who are unlikely to benefit from conventional therapy. Lenalidomide can also reduce transfusion requirements and reverse cytologic and cytogenetic abnormalities in patients who have MDS with the 5q31 deletion.
- Glasdegib, a Hedgehog pathway inhibitor, has shown promising initial activity and a favorable benefit-risk profile when used in combination with low-dose chemotherapy in high-risk MDS patients who are unsuitable for intensive chemotherapy.
- Results of chemotherapy are generally disappointing. Combination chemotherapy regimens (e.g., cytarabine plus doxorubicin) that are used to treat AMLs generally induce a complete response in only a minority of patients, and the average duration of response is <1 yr.
- The use of myeloid growth factors (granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]) is reserved for patients with severe neutropenias and high infection risk. Additionally, these provide a synergistic effect when used in combination with erythropoietin in terms of improvement in the hemoglobin levels.

CHRONIC Rx

Monitor for infections, bleeding, and complications of anemia. Supportive measures include packed red blood cell (PRBC) transfusions and erythropoietin for anemia and antimicrobials to treat opportunistic infections. Iron overload from frequent transfusions (>100 PRBC units) requires iron chelation therapy.

DISPOSITION

- The 5-yr overall survival is approximately 30%. Median overall survival rates are best for patients with refractory anemia (56 mo), refractory anemia with ring sideroblasts (48 mo), and deletion 5q subtype (32 mo). The International Prognostic Scoring System (IPSS) for MDS is summarized in Tables 7 and 8. Table 9 describes survival based on IPSS.
- Long-term remission rates in young patients with allogeneic stem cell transplantation approach 40% to 50%.
- The risk of transformation to AML varies with the percentage of blasts in the bone marrow.

REFERRAL

- Hematology referral for all patients
- Bone marrow transplant evaluation for stem cell transplant eligibility as a potentially curative modality

PEARLS & CONSIDERATIONS

COMMENTS

- Somatic point mutations in *TP53, EZH2, ETV6, RUNX1,* and *ASXL1* are predictors of poor overall survival in patients with MDS independent of established risk factors. Patients with cytogenetic abnormalities associated with poor prognosis should be considered for upfront allogeneic stem cell transplantation.
- Many younger patients who respond to immunosuppressive therapy with drugs such as antithymocyte globulin and cyclosporine have clonal expansions of cytotoxic $CD8^+$ T cells that suppress normal hematopoiesis, as well as expansion of $CD4^+$ helper T cell subsets that promote and sustain autoimmunity.
- Nearly 50% of the deaths that result from MDS are the result of cytopenias associated with bone marrow failure.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Myelodysplastic Syndrome (Patient Information)

AUTHOR: **Ritesh Rathore, MD**

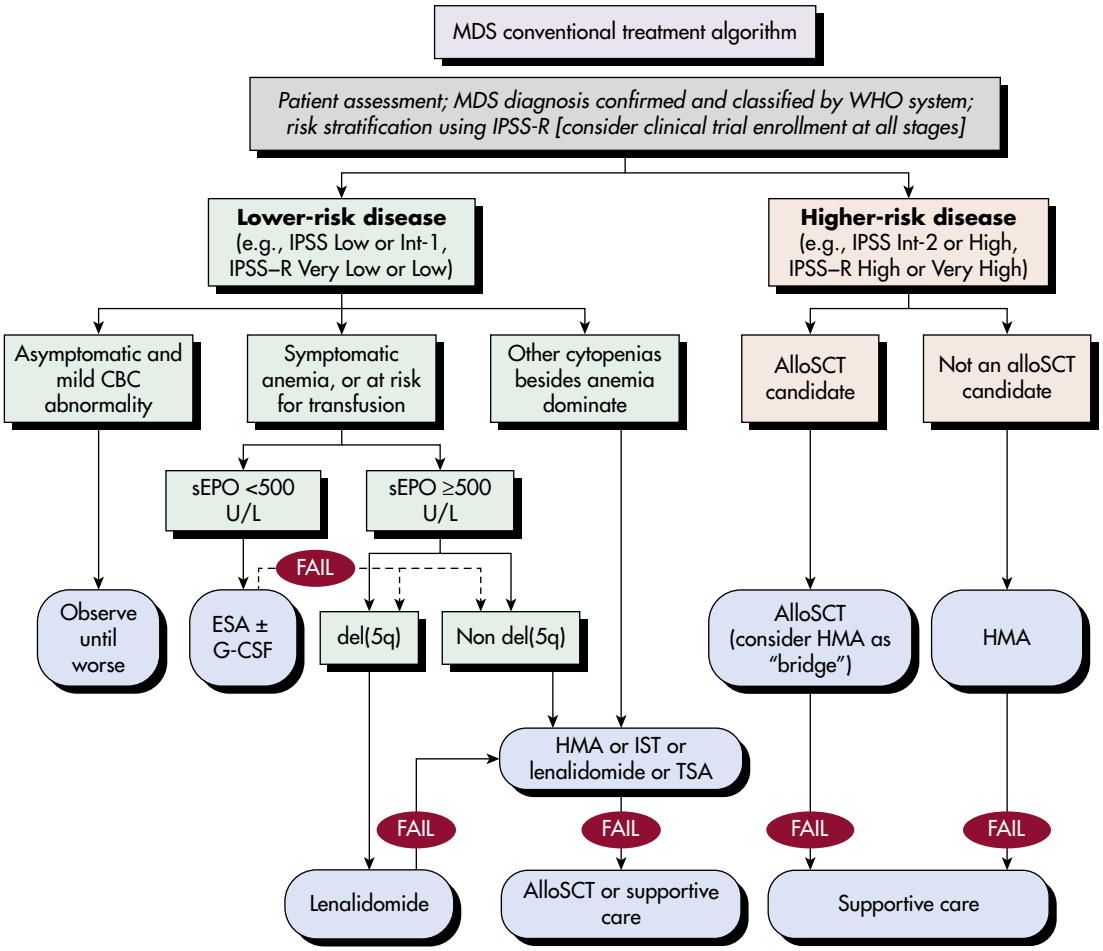

FIG. 2 A suggested treatment algorithm for myelodysplastic syndrome (MDS), described further in the text and in Table 6. Risk assessment has traditionally been based on the International Prognostic Scoring System *(IPSS)* (and more recently the IPSS-R), but that is likely to change with the advent of new prognostic scoring systems and molecular markers. IPSS-R intermediate-risk disease may follow the track for lower- or higher-risk disease. Disease classification should use the 2016 World Health Organization *(WHO)* system. Clinical trial enrollment should be considered at each step. Some clinicians would proceed to lenalidomide without a trial of an ESA if del(5q) is present, even if the serum erythropoietin level is less than 500 U/L. *CBC,* Complete blood count; ESA, erythropoiesis-stimulating agent (epoetin or darbepoetin—off-label uses); *G-CSF,* granulocyte colony-stimulating factor (e.g., filgrastim or tbo-filgrastim); *HMA,* hypomethylating agent (azacitidine or decitabine); *IPSS-R,* revised International Prognostic Scoring System; *IST,* immunosuppressive therapy (antithymocyte globulin with cyclosporine A or tacrolimus—off-label uses); *SCT,* stem cell transplantation; *sEPO,* serum erythropoietin level; *TSA,* thrombopoiesis-stimulating agent (e.g., eltrombopag, romiplostim—off-label uses). (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

TABLE 6 Available Therapies for Myelodysplastic Syndromes in the United States and Preferred Dosage Regimen[a]

1. Erythropoiesis-stimulating agents (should hold if hemoglobin ≫10 g/dl)
   a. Epoetin alfa 20-60,000 mIU/wk subcutaneously; dose can be adjusted every 1-2 mo depending on response; or
   b. Darbepoetin alfa 200–300 μg subcutaneously every 1-2 wk or 500 μg subcutaneously every 3 wk; or
   c. Epoetin alfa as per (a) plus G-CSF (filgrastim) 0.5 μg /kg subcutaneously 1-3 times per wk (pegfilgrastim is commonly substituted in the United States, but data are absent, and splenic rupture and leukemoid reactions are risks); epoetin beta and other ESAs (e.g., Mircera) are available outside the United States
2. Iron chelation therapy
   a. Deferoxamine (starting dose ~20 mg/kg/day; a typical effective dose for an adult is 6 g/day subcutaneously or intravenously, administered by infusion pump over 8-16 h daily); or
   b. Deferasirox, tablet for oral suspension 20–30 mg/kg/day orally once daily oral tablet, 14-28 mg/kg/day, adjust as tolerated and according to efficacy.
   c. Deferiprone (L1) is available outside the United States, but is only approved for thalassemia in the United States and is a weaker chelator than the other two and cytopenias can be problematic
3. Lenalidomide: 10 mg orally once daily for 21-28 days per 28-day cycle (dose reduction due to cytopenias is commonly required)
4. Azacitidine: 75 mg/m^2/day subcutaneously or intravenously for 7 days, repeat every 28 days; "weekend-sparing" schedules may also be effective
5. Decitabine: 15 mg/m^2/dose over 3-4 h intravenously every 8 h × 9 doses (=3 days); or 20 mg/m^2/day intravenously over 1-2 h daily × 5 consecutive days; repeat every 4-6 wk
6. Immunosuppression: equine ATG per aplastic anemia regimens (e.g., 40 mg/kg/day × 4 days intravenously, after test dose), with corticosteroids to prevent serum sickness, with or without cyclosporine A or tacrolimus
7. Miscellaneous therapies such as antifibrinolytics (aminocaproic acid, tranexamic acid), androgens (danazol), or romiplostim can be useful in some cases.

[a]Consult the package insert in each case. Only azacitidine, lenalidomide, and decitabine are approved by the U.S. Food and Drug Administration for myelodysplastic syndrome–related indications in the United States.

ATG, Antithymocyte globulin; *ESA,* erythropoiesis-stimulating agent; *G-CSF,* granulocyte colony-stimulating factor.

From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE 7 1997 International Prognostic Scoring System for Myelodysplastic Syndromes (IPSS)

	Score			
Variable	**0**	**0.5**	**1**	**1.5**
Marrow blasts (%)	<5	5-10	–	11-20
Karyotype	Good	Intermediate	Poor	–
Cytopenias	0-1	2-3	–	–

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 8 2012 Revised International Prognostic Scoring System for Myelodysplastic Syndrome (IPSS-R)

Cytogenetic Risk	**Included Karyotypic Abnormalities**
Very good	del(11q), –Y
Good	Normal, del(20q), del(5q) alone or +1 other abnormality, del(12p)
Intermediate	+8, del(7q), i(17q), +19, +21 Any other single or double abnormality Two or more independent clones
Poor	der(3q), –7, double with del(7q), complex with exactly 3 abnormalities
Very poor	Complex with >3 abnormalities

Scoring Table

Parameter	**Category/Score**				
	Very good	**Good**	**Intermediate**	**Poor**	**Very poor**
Cytogenetic risk	**0**	**1**	**2**	**3**	**4**
Marrow blasts (%)	≤2 0	3-4 1	5–10 2	>10 3	
Hemoglobin (g/dl)	≥10 0	8-9.9 1	<8 1.5		
Platelet count ($\times 10^9$/L)	≥100 0	50-99 0.5	<50 1		
Neutrophil count ($\times 10^9$/L)	≥0.8 0	<0.8 0.5			

IPSS-R Risk Group	**Total Score**	**% of Patients**	**Median Survival (Years)**	**25% With AML (Years)**
Very low	≤1.5	19	8.8	NR
Low	2-3	38	5.3	10.8
Intermediate	3.5-4.5	20	3	3.2
High	5-6	13	1.6	1.4
Very high	>6	10	0.8	0.73

AML, Acute myeloid leukemia; *NR,* not reached.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 9 Survival Based on International Prognostic Scoring System for Myelodysplastic Syndromes (Percent)

IPSS Risk Group	**# Patients**	**2 Years**	**5 Years**	**10 Years**	**15 Years**
Low	267 (33%)	85	55	28	20
Intermediate-1	314 (38%	70	35	17	12
Intermediate-2	179 (22%)	30	8	0	–
High	56 (7%)	5	0	–	–

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

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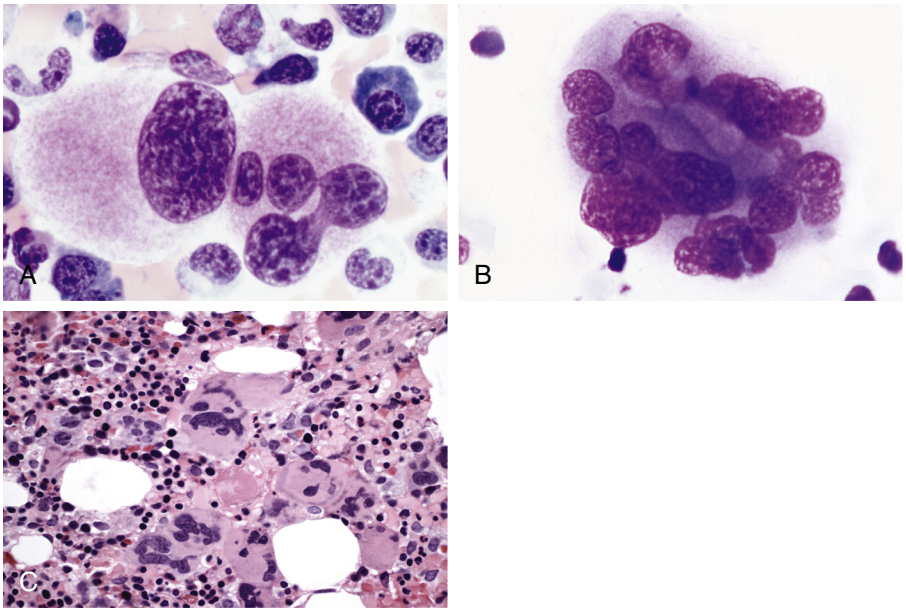

FIG. E1 Megakaryocytic dysplasia in bone marrow aspirate smears and biopsies in myelodysplastic syndrome. A, Abnormal nuclear features in bone marrow aspirate smears include monolobate and multiple separate small nuclei. **B,** Hyperlobation of megakaryocytic nuclei. **C,** Clustered dysplastic megakaryocytes in a bone marrow biopsy. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2001, WB Saunders.)

BOX E1 Cytogenetic Abnormalities in Myelodysplastic Syndrome

Gain or loss of chromosomal material

- –7, 7q–
- 5q–, –5
- +8
- +21, –21
- 17p–, –17
- –20, 20q–
- 11q–, +11
- –Y
- 9q–
- +6
- 12p–
- 13q–

Uncommon translocations and inversions

- t(3;3)(q21;q26), inv3(q21q26), t(3;21)(q26;q22) and other 3q21 and 3q26 translocations
- t(1;7)(p11;p11)
- t(2;11)(p21;q23)
- t(11;16)(q23;p13)
- i(17)q, unbalanced and dicentric translocations at 17p

Any acquired clonal cytogenetic abnormality in hematopoietic cells, except characteristic *de novo* acute myeloid leukemia (AML) translocations[1]

Complex abnormalities (multiple cytogenetic abnormalities, excluding those characteristic of *de novo* AML)

From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.

[1]Common *de novo* AML translocations: t(15;17), t(8;21), inv(16) or t(16;16), t(9;11), t(11;19), t(11;17), t(8;16), t(1:22).

BASIC INFORMATION

DEFINITION

Myocardial infarction (MI) is a clinical syndrome characterized by symptoms of myocardial ischemia, persistent electrocardiographic (ECG) changes, and release of biomarkers of myocardial necrosis resulting from an insufficient supply of oxygenated blood to an area of the heart. MI may be classified as ST-segment elevation MI (STEMI) and non–ST-segment elevation MI (NSTEMI) depending on the ECG findings on MI presentation. Acute coronary syndrome (ACS) refers to acute myocardial ischemia without myocardial necrosis (unstable angina) or myocardial infarction (NSTEMI or STEMI). According to the European Society of Cardiology/American College of Cardiology guidelines, the following criteria for acute evolving or recent MI (NSTEMI and STEMI) satisfies the diagnosis:

- Detection of the rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit and with at least one of the following:
  1. Symptoms of ischemia
  2. Development of pathologic Q waves in the ECG
  3. Imaging evidence of new loss of viable myocardium or a new regional wall motion abnormality
  4. Identification of an intracoronary thrombus by angiography or autopsy pathologic findings of acute MI
  5. Electrocardiogram criteria:
     a. STEMI:
        (1) New, or presumed new, significant ST-T changes or new left bundle branch block (LBBB)
        (2) New ST elevation at the J-point in at least 2 contiguous leads of ≥2 mm (0.2 mV) in men or ≥1.5 mm (0.15 mV) in women in leads V2 to V3 and/or of ≥1 mm (0.1 mV) in another contiguous chest leads or the upper limb leads
     b. NSTEMI:
        (1) New ST-segment depression ≥0.5 mV (0.5 mm) and T-wave abnormalities

New generation troponin assays are extremely sensitive to small changes in serum troponin levels at the cost of diagnostic specificity for MI related to plaque rupture or erosion.

Universal classification of acute MI:

- Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection.
- Type 2: MI secondary to ischemia, other than coronary artery disease, due to either increased oxygen demand or decreased supply (e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, anemia, arrhythmias, respiratory failure, hypertension with/without left ventricular hypertrophy (LVH), or hypotension). Also in critically ill patients or in patients undergoing major noncardiac surgery, elevated values of cardiac biomarkers may appear due to the direct toxic effects of endogenous or exogenous high circulating catecholamine levels.
- Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumed new ST elevation, new left bundle branch block, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, or death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood.
- Type 4a: MI associated with percutaneous coronary intervention. Elevation of cTn >5× percentile of upper reference limit (URL) in patients with normal baseline value, or a rise of cTn >20% if the baseline values are stable and are stable or falling. In addition to either symptoms of ischemia, new ischemic ECG changes or new LBBB, or angiographic loss of a patent coronary artery, persistent slow or no-flow, or embolization, or imaging of new wall motion abnormality.
- Type 4b: MI associated with stent thrombosis as documented by angiography or at autopsy in the setting of myocardial ischemia and with a rise/fall of cardiac biomarker values.
- Type 5: MI associated with coronary artery bypass grafting. Elevation of cardiac biomarker values >10× 99% URL in patients with normal baseline cTn values, in addition to either new pathological Q waves or new LBBB, or new native coronary artery occlusion or imaging of new abnormal wall motion abnormality.
- Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA): It is defined as acute myocardial infarction in the absence of obstructive coronary artery disease. Conditions like takotsubo cardiomyopathy, spontaneous coronary artery dissection, coronary artery spasm, microvascular dysfunction, and pulmonary embolism come under this novel category.

SYNONYMS

MI
Myocardial infarction
ST-elevation MI
Heart attack
Acute myocardial infarction
AMI
Coronary thrombosis
Coronary occlusion

ICD-10CM CODES

I21.01	ST elevation (STEMI) myocardial infarction involving left main coronary artery
I21.02	ST elevation (STEMI) myocardial infarction involving left anterior descending coronary artery
I21.09	ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall
I21.11	ST elevation (STEMI) myocardial infarction involving right coronary artery
I21.19	ST elevation (STEMI) myocardial infarction involving another coronary artery of inferior wall
I21.21	ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery
I21.29	ST elevation (STEMI) myocardial infarction involving other sites
I21.3	ST elevation (STEMI) myocardial infarction of unspecified site
I21.4	Non-ST elevation (NSTEMI) myocardial infarction
I22.0	Subsequent ST elevation (STEMI) myocardial infarction of anterior wall
I22.1	Subsequent ST elevation (STEMI) myocardial infarction of inferior wall
I22.2	Subsequent non-ST elevation (NSTEMI) myocardial infarction
I22.8	Subsequent ST elevation (STEMI) myocardial infarction of other sites
I22.9	Subsequent ST elevation (STEMI) myocardial infarction of unspecified site

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE (IN U.S.):

- According to data from National Health and Nutrition Examination Survey (NHANES) 2009 to 2012 (National Heart, Lung, and Blood Institute [NHLBI] tabulation), the overall prevalence for MI is 2.8% in U.S. adults ≥20 years of age. MI prevalence is 4.0% for men and 1.8% for women.
- In 2013 in the U.S., coronary heart disease alone caused ≈1 of every 7 deaths. In 2013, 370,213 Americans died of coronary heart disease. Each year, an estimated 660,000 Americans have a new coronary attack (defined as first hospitalized myocardial infarction or coronary heart disease death), and 305,000 have a recurrent attack. It is estimated that an additional 160,000 silent myocardial infarctions occur each year. Approximately every 34 seconds, one American has a coronary event, and approximately every 1 minute 24 seconds, an American will die of one.
- Community incidence rates as well as mortality rates from STEMI have declined over the past decade, whereas those for NSTEMI have increased. At present, STEMI comprises approximately 30% to 40% of MI presentations. In-hospital mortality (approximately 5% to 6%) and 1-yr mortality (approximately 7% to 18%). The most common cause of death in adults over the age of 40 is myocardial infarction. A heart attack takes the life of >1,500,000 people each yr in the U.S.
- Modifiable risk factors such as hypertension, diabetes, and cigarette smoking have recently declined, although hyperlipidemia has shown no significant change, and obesity has steadily increased.
- Tobacco use remains the second-leading cause of total deaths and disability. The percentage of adults who reported current cigarette use declined from 24.1% in 1998 to 15.5% in 2016. Still, almost one third of coronary heart disease deaths are attributable to smoking and exposure to secondhand smoke. Patients with first acute MI were

found to have an almost threefold increase in cigarette smoking from 2002 to 2009. Cigarette smoking is associated with endothelial dysfunction, prothrombotic defects, and increased oxidative stress.
- It is more prevalent in males between the ages of 45 and 65 yr old; there is no predominant sex differential after the age of 65.
- Women comprised 30% of STEMI patients. They experience more lethal and severe first acute MIs than men regardless of comorbidity, previous angina, or age. Studies have suggested that women are less likely to receive reperfusion therapy, have longer reperfusion times, are often given the standard of care treatment within 24 hours of presentation, and have higher risk of bleeding with antithrombotic therapy.
- At least one fourth of all MIs are clinically unrecognized. Approximately 23% of patients with STEMI in the U.S. have diabetes mellitus, and three quarters of all deaths among patients with diabetes mellitus are related to coronary artery disease. Diabetes mellitus is associated with higher short- and long-term mortality after STEMI. In the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) trial, 7% of eligible patients did not receive reperfusion therapy. The most important factor for not providing reperfusion therapy in eligible patients was increasing age.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The clinical presentation of myocardial infarction is usually based on a history of substernal pressure type chest pain radiated to the neck, lower jaw, left arm, or mid-back lasting 20 min or more that is not completely relieved by sublingual nitroglycerin. The pain may not be severe. Some patients may present with atypical symptoms such as nausea/vomiting, shortness of breath, fatigue, palpitations, and diaphoresis. The elderly in particular may present with dizziness, or syncope. The patients who tend to present with atypical symptoms are more likely to be women, diabetic patients, or elderly patients and less frequently receive reperfusion therapy and other evidence-based therapies than patients with a typical chest pain presentation. Records show that up to 30% of patients with STEMI present with atypical symptoms.

Physical findings:
- Skin may be diaphoretic and exhibit pallor (because of decreased oxygen).
- Rales may be present at the bases of lungs (indicative of heart failure [HF]).
- Cardiac auscultation may reveal an apical systolic murmur caused by mitral regurgitation from papillary muscle dysfunction; S_3 or S_4 may also be present.
- Up to 10% of patients may present with acute pulmonary edema and/or cardiogenic shock.
- Physical examination may be completely normal.

ETIOLOGY

- Coronary atherosclerosis and plaque rupture
- Coronary artery spasm
- Coronary embolism (caused by infective endocarditis, rheumatic heart disease, intracavitary thrombus, atrial fibrillation)
- Periarteritis and other coronary artery inflammatory diseases
- Dissection into coronary arteries (aneurysmal or iatrogenic or spontaneous)
- Anomalous origin of coronary artery, especially interarterial (aorta and pulmonary artery) course of coronary artery
- MI with normal coronaries: More frequent in younger patients and cocaine addicts. The risk of acute MI is increased by a factor of 24 during the 60 min after the use of cocaine in persons who are otherwise at relatively low risk. Most patients with cocaine-related MI are young, nonwhite, male cigarette smokers without other risk factors for coronary heart disease and who have a history of repeated cocaine use. Blood and urine toxicology screen for cocaine is recommended in all young patients who present with acute MI.
- Hypercoagulable states, increased blood viscosity (polycythemia vera and autoimmune diseases such as systemic lupus, antiphospholipid syndrome)

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The various causes of myocardial ischemia are described along with the differential diagnosis of chest pain.

LABORATORY TESTS

- Electrocardiogram (Fig. 1): A 12-lead ECG should be performed and shown to an experienced emergency physician within 10 min of emergency department (ED) arrival for all patients with chest discomfort (or anginal equivalent) or other symptoms suggestive of MI. Table 1 and Table E2 describe ECG findings in myocardial infarction. If the initial ECG is not diagnostic for MI but the patient remains symptomatic and

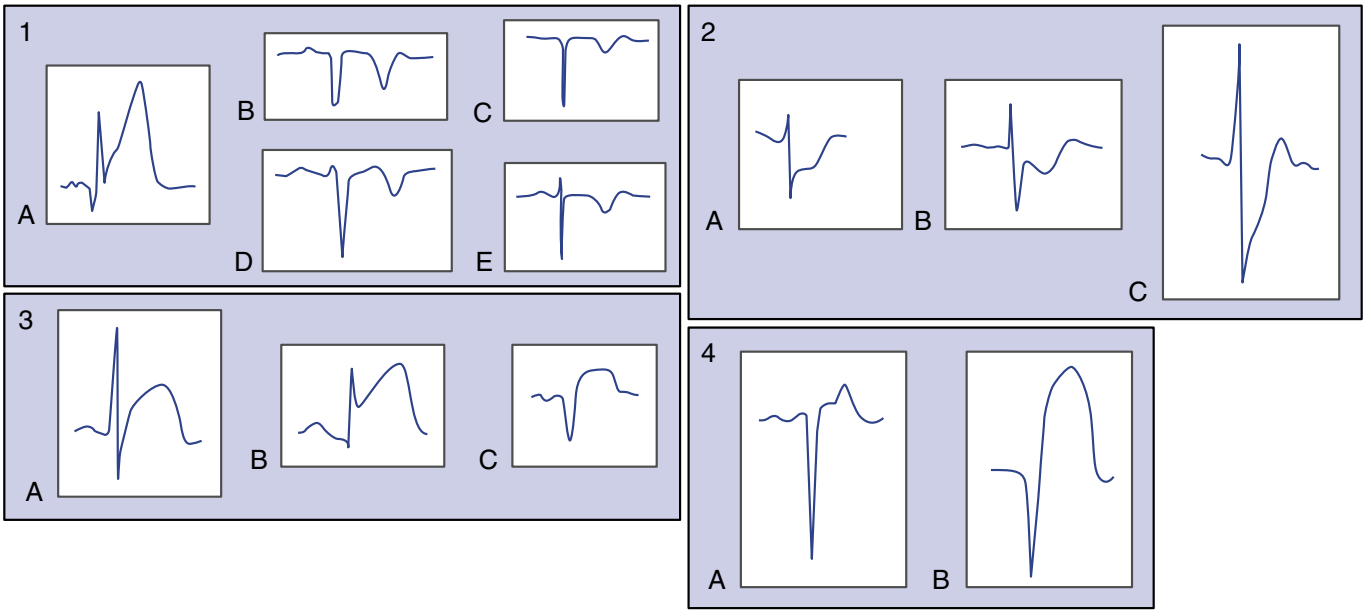

FIG. 1 Electrocardiographic findings of acute myocardial infarction (AMI). 1, T-wave abnormalities of AMI. *A,* Prominent "hyperacute" T wave. *B* through *E,* T-wave inversions of non–ST-segment elevation MI (NSTEMI). **2,** ST-segment depression. *A,* Flat. *B,* Downsloping. *C,* Upsloping. **3,** ST-segment elevation. *A,* Convex ST-segment elevation. *B,* Obliquely straight ST-segment elevation. *C,* Convex ST-segment elevation. **4,** Pathologic Q waves. *A,* Pathologic Q wave of completed myocardial infarction. *B,* Simultaneous ST-segment elevation with pathologic Q wave 2 hours into the course of ST-segment elevation MI (STEMI). (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.)

there is a high clinical suspicion for MI, serial ECGs at 5- to 10-min intervals or continuous 12-lead ST-segment monitoring should be performed to detect the potential development of ST deviation. In patients with inferior STEMI, right-sided ECG leads should be obtained to look for ST elevation suggestive of right ventricular (RV) infarction. The joint ESC/ACCF/AHA committee for the definition of MI established the definition for the diagnosis of ST-elevation MI, which is considered to be present when there is an ST-segment elevation in two contiguous leads, ≥2 mm for men and ≥1.5 mm for women in precordial leads and/or ≥1 mm in limb leads. ST-segment elevation is measured at 0.08 sec after the J point (the junction between the end of the QRS and the beginning of the ST segment). In addition, ST depression in >2 precordial leads (V1 to V4) may indicate transmural posterior injury; multilead ST depression with coexistent ST elevation in lead aVR has been described in patients with left main or proximal left anterior descending artery involvement.

- New or presumably new LBBB at presentation occurs infrequently, may interfere with ST-elevation analysis, and should not be considered diagnostic of acute myocardial infarction (MI) in isolation.
- Diagnosing new STEMI in patients with old left bundle branch block could be challenging. Sgarbossa and colleagues emphasized that concordant 1 mm ST-segment elevation in any lead with a positive QRS deflection or discordant ST-segment elevation >5 mm in any lead with negative QRS deflection suggest STEMI.
- New ST-segment depression ≥0.5 mV (0.5 mm) and T-wave abnormalities suggest NSTEMI. ECG findings alone, without laboratory results, are sufficient to diagnose STEMI; therefore, treatment should not be delayed until biomarkers are available.
- Cardiac troponin levels: Cardiac-specific troponin T (cTnT) and cardiac-specific troponin I (cTnI) are generally indicative of myocardial injury with increases in serum levels of >99th percentile of a normal reference population. Detection of a rise and fall pattern of the measurements is essential to the diagnosis of AMI. The rise may occur relatively early after muscle damage (3 to 6 hours), peak at 12 to 16 hours, and may be present for several days after MI (up to 7 days for cTnI and more than 14 days for cTnT). Earlier peaking and rapid decline of cardiac enzymes may present in light of successful revascularization (Fig. 2). cTnT or cTnI tests can be falsely positive for myocardial infarction in patients with renal failure, heart failure, myocarditis, aortic dissection, and pulmonary embolism. Recently, highly sensitive troponin assays (hs-cTnI, hs-cTnT) have also been developed to facilitate an early diagnosis of AMI. Most patients can be diagnosed with AMI within the first 2 to 3 hours of presentation. However, an initial negative high-sensitivity troponin at the time of presentation is not sensitive enough to completely rule out AMI. MI can be excluded in most patients by 6 hours of presentation, and guidelines suggest serial samples be obtained every 3 to 6 hours after an initial sample if there is a high degree of suspicion for AMI.
- Troponin is the preferred marker for the diagnosis of myocardial necrosis. A single high-sensitivity assay for cardiac troponin (hs-cTnT) concentration below the limit of detection in combination with a nonischemic ECG may successfully rule out an MI in patients presenting to EDs with possible emergency acute coronary syndrome.[1] Because troponins need 7 to 14 days to be cleared by the kidneys, they are not sensitive enough to detect a recurrent MI within days from the initial MI. CK-MB isoenzyme can be useful in such circumstances (Fig. 2).

TABLE 1 Leads Showing Abnormal Electrocardiographic Findings in Myocardial Infarction

	Limb Leads	Precordial Leads
Lateral	I, aVL	V5, V6
Anterior		V1, V2, V3
Anterolateral	I, aVL	V2-V6
Diaphragmatic	II, III, aVF	
Posterior		V1-V3*

*None of the leads is oriented toward the posterior surface of the heart. Therefore, in posterior infarction, changes that would have been present in the posterior surface leads will be seen in the anterior leads as a mirror image (e.g., tall and slightly wide R waves in V1 and V2, comparable to abnormal Q waves, and tall and wide, symmetric T waves in V1 and V2).

aVF, Augmented vector foot; *aVL,* augmented vector left.

From Park MK: *Park's pediatric cardiology for practitioners,* ed 6, Philadelphia, 2014, Elsevier.

[1]Pickering JW et al: Rapid rule-out of acute myocardial infarction with a single high-sensitivity cardiac troponin T measurement below the limit of detection: a collaborative meta-analysis, *Ann Intern Med* 166:715-724, 2017.

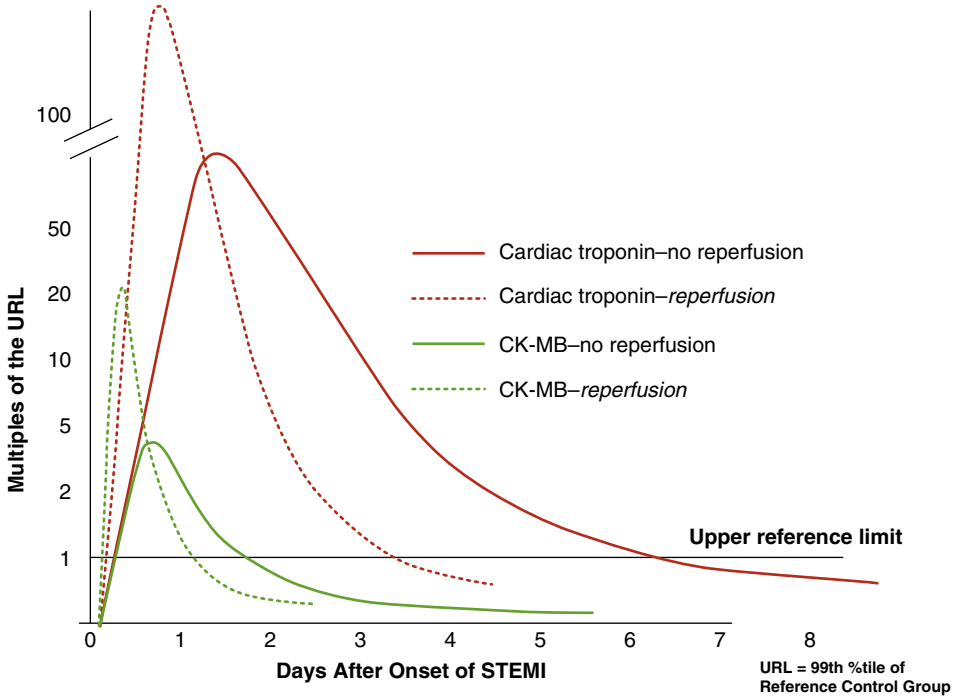

FIG. 2 Trends of Troponin and CK-MB following revascularization in MI. *CK-MB,* Creatine kinase-MB; *STEMI,* ST-segment elevation myocardial infarction; *URL,* upper reference limit. (Modified from Shapiro BP, Jaffe AS: Cardio biomarkers. In: Murphy JG, Lloyd MA [eds]: *Mayo Clinic cardiology: concise textbook,* ed 3, Rochester, MN, 2007, Mayo Clinic Scientific Press, and New York, 2007, Informa Healthcare USA. Used with permission of Mayo Foundation for Medical Education and Research.)

- CK-MB isoenzyme is also a useful marker for MI if troponin levels are not available. It is released in the circulation in amounts that correlate with the size of the infarct. An increased CK-MB value for the diagnosis of MI is defined as a measurement above the 99th percentile of the upper reference limit. CK-MB can be detected within 3 to 8 hours of the onset of chest pain, peak at 12 to 24 hours, and return to baseline levels within 24 to 48 hours.

IMAGING STUDIES

Imaging studies such as a high-quality portable chest x-ray, transthoracic echocardiography, and a contrast chest CT scan should be used to differentiate MI from aortic dissection, pulmonary embolism, and other intrathoracic causes of chest pain (i.e., pneumonia and pneumothorax) in patients for whom this distinction is initially unclear, or to assess for complications of AMI such as pulmonary edema. Transthoracic echocardiography may provide evidence of focal wall motion abnormalities and facilitate triage in patients with ECG findings that are difficult to interpret.

RISK ASSESSMENT

For STEMI patients, TIMI (Thrombolysis in Myocardial Infarction) risk index, TIMI risk score (30-day outcomes), and GRACE (Global Registry of Acute Coronary Events) risk score (6-mo outcomes) are commonly available risk assessment models. In the TIMI risk score for STEMI, the mean 30-day mortality was 6.7%. It is composed of eight baseline variables. The risk score showed a >40-fold graded increase in mortality, with scores ranging from 0 to >8 ($P < 0.0001$); 30-day mortality was 0.1% among patients with a score of 0, 2.25 with a score of 5, and >8.8% among patients with a score of 8 or greater. The higher the score, the higher the 30-day mortality rate. The variables are divided between historic, exam, and presentation:

Historic:
- Age 65 to 74 (2 points), >75 (3 points)
- Diabetes/HTN or angina (1 point)

Exam:
- SBP <100 mm Hg (3 points)
- Heart rate >100 bpm (2 points)
- Killip 2 to 4 (2 points)
- Weight <67 kg (1 point)

Presentation:
- Anterior ST elevation or LBBB (1 point)
- Time to reperfusion >4 hours (1 point)

For NSTEMI patients, TIMI risk score (14-day outcomes) and GRACE (Global Registry of Acute Coronary Events) risk score (in hospital outcomes) are available.
- Age ≥65 yr
- Presence of ≥3 risk factors for CAD
- Known CAD (coronary artery stenosis ≥50%)
- Aspirin use in the past 7 days
- ≥2 episodes of angina within 24 hours
- ST changes ≥0.05 mV
- Positive cardiac enzymes

In TIMI score for the NSTEMI patients, each variable scores one point. The risk score of 6 to 7 carries estimated major acute coronary event (MACE) rate of 41% during 14 days of post-MI. Risk assessment is a continuous process that should be repeated throughout hospitalization and at time of discharge.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Limit patient's activity: Bed rest with bedside commode for the initial 12 to 24 hours. If the patient remains stable, gradually increase.1
- Diet: Nothing by mouth until stable, then clear liquids as tolerated to advance gradually to a diet tailored to the patient's comorbidities (i.e., diabetes, hypertension, heart failure, hyperlipidemia, renal failure, chronic obstructive pulmonary disease [COPD], etc.).
- Patient education to decrease the risk of subsequent cardiac events, counseling on smoking cessation, dietary restrictions, regular exercise, and medication compliance should be initiated when the patient is medically stable.

ACUTE GENERAL Rx

- Fig. 3 shows a treatment algorithm for STEMI. Assessment and treatment algorithm for non–ST-segment MI is described in Fig. 4. Rationale of the treatment of a patient with STEMI is based on "time is muscle." Therefore, all communities should create and maintain a regional system of STEMI care that includes assessment and continuous quality improvement of EMS and hospital-based activities. A 12-lead ECG must be done by EMS personnel at the site of first medical contact (FMC).
- Reperfusion therapy should be administered to all eligible patients with STEMI with symptom onset within 12 hours. Indications for primary angioplasty and comparison with fibrinolytic therapy are described in Table 3. Primary PCI (Fig. E5) is the recommended method of reperfusion when it can be performed in a timely fashion by experienced operators with an ideal FMC-to-device time system goal of 90 min or less.
- In the absence of contraindications, fibrinolytic therapy (Table 4) should be administered to patients with STEMI at non–PCI-capable hospitals when the anticipated FMC-to-device time at a PCI-capable hospital exceeds 120 min because of unavoidable delays. Door-in door-out time (DIDO) for fibrinolytic therapy should be less than 30 min. If more than 30 min delay, transfer the patient to a PCI-capable hospital.
- Among STEMI patients who were treated with fibrinolytics, patients with >50% ST-segment resolution on EKG were at much lower risk for cardiac-related mortality compared with those with <50% resolution at 30 days.
- PCI is superior to thrombolytic therapy and is the standard of care. It is effective and generally results in more favorable outcomes than thrombolytic therapy.
- Primary PCI should be performed in patients with STEMI and persistent ischemic symptoms and who have contraindications to fibrinolytic therapy, irrespective of the time delay from FMC, or in patients with cardiogenic shock or acute severe HF irrespective of time delay from myocardial infarction (MI) onset, first medical contact to balloon time is <90 minutes or door to balloon/door to needle time is <1 hour, symptoms onset was >3 hours ago and when diagnosis of STEMI in doubt. Coronary stents (drug-eluting or bare-metal) are useful in patients with STEMI.
- The question of culprit vessel vs. complete revascularization during PCI has been brought up since the stent technology was applied to the management of STEMI. The most recent clinical trials (CuLPRIT, PRAMI and DANAMI3-PRIMULTI [FFR-driven revascularization]) appear to favor complete revascularization in the setting of STEMI. However, CULPRIT-SHOCK trial showed culprit vessel only PCI associated with 9.5% absolute reduction in the rate of death or renal replacement therapy at 30 days compared to multivessel PCI in acute MI patients with cardiogenic shock. One-yr outcomes did not show significant difference in mortality between two groups. Korea Acute Myocardial Infarction-National Institutes of Health (KAMIR-NIH) Registry data showed better outcomes with multivessel PCI in cardiogenic shock patients compared to culprit vessel-only PCI. Thus, multivessel PCI should be reserved for few selective patients.
- For patients presenting to a non–PCI-capable hospital, rapid assessment should be done of (1) the time from onset of symptoms, (2) the risk of complications related to STEMI, (3) the risk of bleeding with fibrinolysis, (4) the presence of shock or severe HF, and (5) the time required for transfer to a PCI-capable hospital and a decision about administration of fibrinolytic therapy reached. Because the effectiveness of thrombolytics is time dependent, these agents should ideally be administered either in the field or within 30 min of the patient's arrival to the emergency department (door-to-needle time).
- Fibrinolytic therapy: If tissue plasminogen activator (t PA) or reteplase is used, anticoagulants, such as heparin, are given to increase the likelihood of patency in the infarct-related artery for 48 hr and preferably for the duration of the index hospitalization, up to 8 days. In patients receiving fibrinolysis for STEMI, treatment with enoxaparin is superior to treatment with unfractionated heparin for 48 hr but is associated with an increase in major bleeding episodes. In patients receiving streptokinase or APSAC, heparin after thrombolysis is not indicated because it does not offer any additional benefit and can result in increased bleeding complications. Tenecteplase and reteplase are comparable with accelerated infusion recombinant t-PA in terms of efficacy and safety but are more convenient because they are administered by bolus injection. Lanoplase and heparin bolus plus infusion are as effective as tPA with regard to mortality rate, but the rate of intracranial hemorrhage is significantly higher.

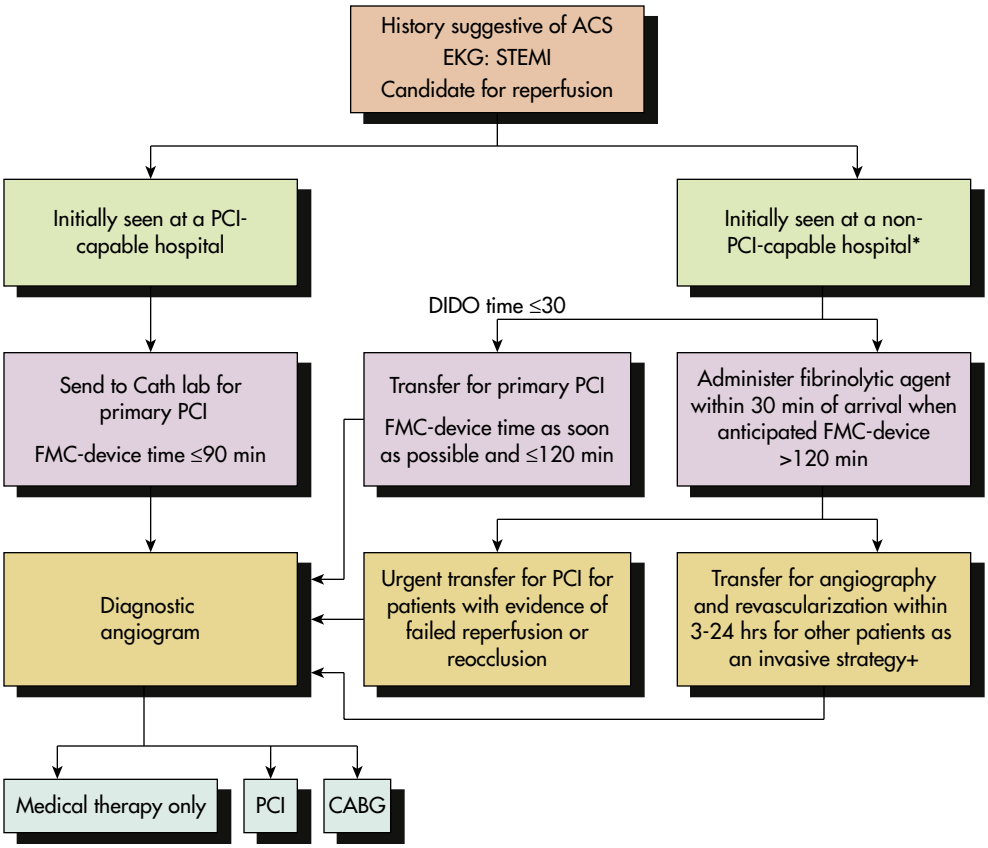

FIG. 3 Reperfusion therapy for patients with STEMI. *Patients with cardiogenic shock or severe heart failure initially seen at a non–PCI-capable hospital should be transferred for cardiac catheterization and revascularization as soon as possible, irrespective of time delay from MI onset. +Angiography and revascularization should not be performed within the first 2 to 3 hours after administration of fibrinolytic therapy. *ACS,* Acute coronary syndrome; *CABG,* coronary artery bypass graft; *Cath,* catheterization; *DIDO,* door-in to door-out; *EKG,* electrocardiogram; *FMC,* first medical contact; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention; *STEMI,* ST-elevation myocardial infarction. (Modified from O'Gara PT et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, *JACC* 61(4): e78-e140, 2013.)

- Absolute contraindications to thrombolytic therapy (Table 5) include history of intracranial hemorrhage, known intracranial malignant neoplasm or arteriovenous malformation, ischemic stroke within 3 mo (except acute ischemic stroke within 4.5 hours), suspected aortic dissection, active bleeding or bleeding diathesis (except menses), significant closed head or facial trauma within 3 mo, intracranial or intraspinal surgery within 2 mo, or severe uncontrolled hypertension (unresponsive to therapy). For streptokinase, this applies to prior treatment within 6 mo.
- Relative contraindications: History of chronic severe, poorly controlled hypertension, SBP >180 mm Hg, DBP >110 mm Hg, history of prior ischemic stroke more than 3 mo, dementia, known intracranial pathology, traumatic or prolonged CPR (>10 min), major surgery <3 wk, recent internal bleeding within 2 to 4 wk, noncompressible vascular punctures, pregnancy, active peptic ulcer, oral anticoagulant therapy. After the administration of thrombolytics, immediate transfer to a PCI-capable facility is advisable without waiting for lytic results.
- Transfer to a PCI-capable hospital: Immediate transfer for STEMI patients who develop cardiogenic shock or acute severe HF, irrespective of the time delay from MI onset. Urgent transfer if the patient demonstrates evidence of failed reperfusion or reocclusion after fibrinolytic therapy.
- Coronary angiography should not be performed within the first 2 to 3 hours after administration of fibrinolytic therapy.
- Coronary artery bypass graft (CABG): Urgent CABG is indicated in patients with STEMI and coronary anatomy not amenable to PCI who have ongoing or recurrent ischemia, cardiogenic shock, severe HF, or other high-risk features. CABG is recommended in patients with STEMI at time of operative repair of mechanical defects. Box 1 summarizes CABG in patients with MI.
- Therapeutic hypothermia should be started as soon as possible in comatose patients with STEMI and out-of-hospital cardiac arrest caused by ventricular fibrillation (VF) or pulseless ventricular tachycardia, including patients who undergo primary PCI.
- Immediate angiography and PCI when indicated should be performed in resuscitated out-of-hospital patients.
- The use of mechanical circulatory support is reasonable in patients with STEMI who are hemodynamically unstable and require urgent CABG.
- For NSTEMI patients, immediate invasive strategy (within 2 hours) recommended in patients with refractory angina, signs or symptoms of congestive heart failure or new or worsening ischemic mitral regurgitation, hemodynamic instability, recurrent angina or ischemia at rest or with low level activities despite intensive medical therapy and sustained ventricular tachycardia or ventricular fibrillation.
- Early invasive strategy (<24 hours) for NSTEMI patients recommended if GRACE risk for more than 140, dynamic ST changes on EKG and temporal change in troponin levels.
- NSTEMI patient with low-risk TIMI score (0 or 1) and/or low GRACE score (<109) and/or troponin-negative female patients can benefit from ischemia-guided strategy. Fibrinolytic therapy is contraindicated in NSTEMI patients.

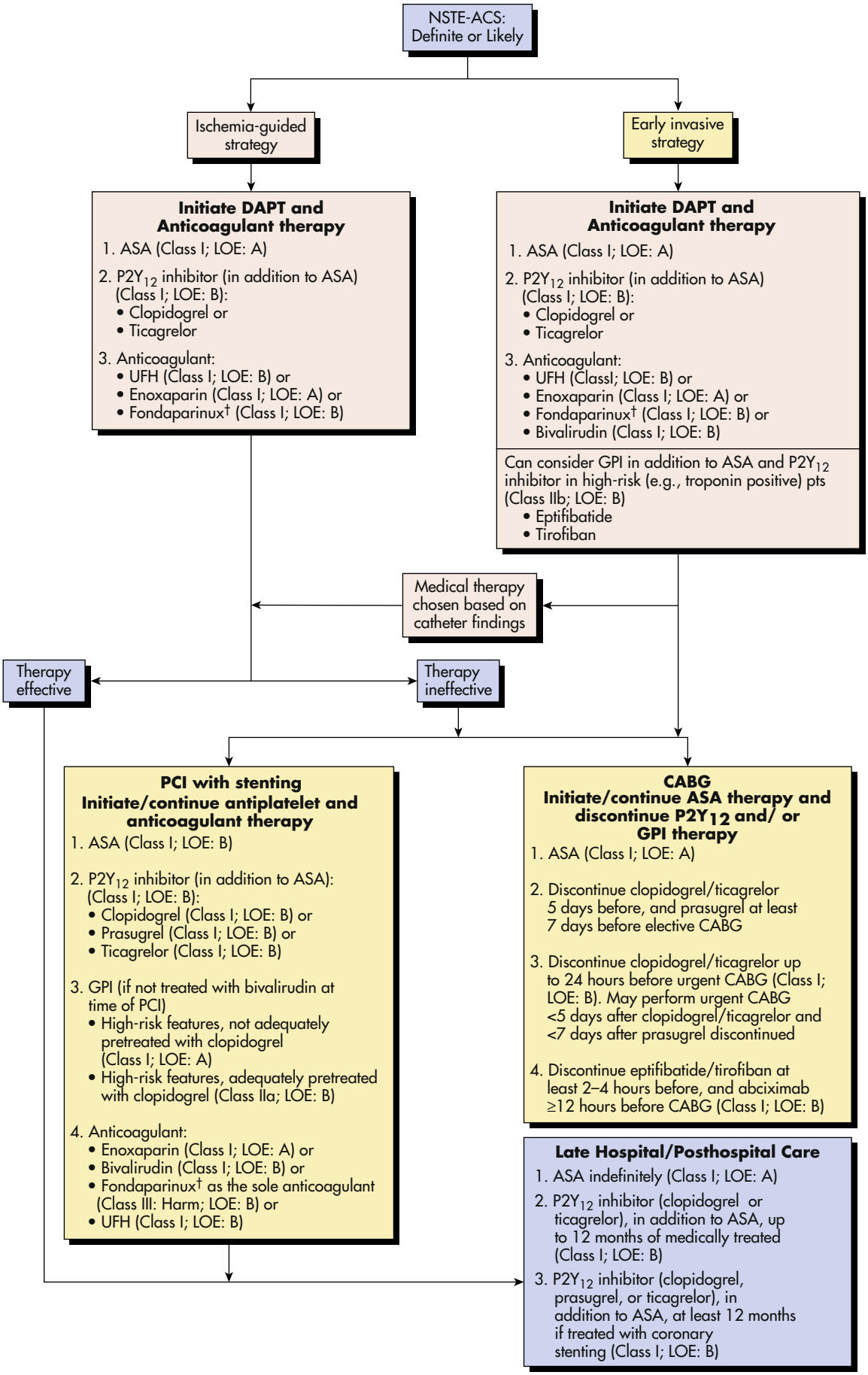

FIG. 4 Algorithm for management of patients with definite of likely non–ST-elevation acute coronary syndromes *(NSTE-ACS).* †In patients who have been treated with fondaparinux (as upfront therapy) who undergo percutaneous coronary intervention (PCI), an additional anticoagulant with anti-IIa activity should be administered at the time of PCI because of the risk of catheter thrombosis. *ASA,* Acetylsalicylic acid (aspirin); *CABG,* coronary artery bypass grafting; *DAPT,* dual-antiplatelet therapy; *GPI,* glycoprotein inhibitor; *LOE,* level of evidence; *UFH,* unfractionated heparin. (From Amsterdam EA et al: 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 2014;64:e139-228. In Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

TABLE 3 Indications for Primary Angioplasty and Comparison with Fibrinolytic Therapy

Indications
Alternative recanalization strategy for ST segment elevation or LBBB acute MI within 12 hours of symptom onset (or >12 hours if symptoms persist)
Cardiogenic shock developing within 36 hours of ST segment elevation/Q wave acute MI or LBBB acute MI in patients >75 yr old who can be revascularized within 18 hours of shock onset
Recommended only at centers performing >200 PCI/yr with backup cardiac surgery and for operators performing <75 PCI/yr
Advantages of Primary PCI
Higher initial recanalization rates
Reduced risk of intracerebral hemorrhage
Less residual stenosis; less recurrent ischemia or infarction
Usefulness when fibrinolysis contraindicated
Improvement in outcomes with cardiogenic shock
Disadvantages of Primary PCI (Compared with Fibrinolytic Therapy)
Access, advantages restricted to high-volume centers, operators
Longer average time to treatment
Greater dependence on operators for results
Higher system complexity, costs

LBBB, Left bundle branch block; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention (includes balloon angioplasty, stenting).
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.

TABLE 4 Dosing Regimens of Commonly Used Thrombolytic Agents

Thrombolytic Agents	Dosing Regimen
t-PA (alteplase)	15 mg bolus IV, followed by 0.75 mg/kg body weight (not to exceed 50 mg) over 30 min, followed by 0.5 mg/kg (not to exceed 35 mg) over 60 min
r-PA (reteplase)	Two 10-U IV boluses, given 30 min apart
TNK–t-PA (tenecteplase)	Single bolus IV 0.5 mg/kg (dose rounded to the nearest 5 mg, ranging from 30 to 50 mg)
Streptokinase	1.5 million U IV over 60 min

IV, Intravenous; *PA,* plasminogen activator; *r-PA,* recombinant plasminogen activator; *TNK–t-PA,* tenecteplase tissue plasminogen activator; *t-PA,* tissue plasminogen activator; *U,* units.
From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, WB Saunders.

- Medical therapy should be initiated immediately in the emergency department for all MI patients. This includes:
  1. Routine measures
     a. Oxygen: Supplemental oxygen should be administered to patients with arterial oxygen desaturation (SaO_2 less than 90%). No benefit has been demonstrated to supplemental oxygen in patients with normal SaO_2.
     b. Nitroglycerin: Increase oxygen supply by reducing coronary vasospasm and decrease oxygen consumption by reducing ventricular preload. Patients with ongoing ischemic discomfort should receive sublingual nitroglycerin every 5 min for a total of three doses, after which an assessment should be made about the need for intravenous nitroglycerin. Intravenous nitroglycerin is indicated for relief of ongoing ischemic discomfort, control of hypertension, or management of pulmonary congestion. Nitrates should not be administered to patients whose systolic blood pressure is <90 mm Hg or ≥30 mm Hg below baseline or severe bradycardia (<50 beats/min), tachycardia (>100 beats/min), or suspected RV infarction. Nitrates should not be administered to patients who have received a phosphodiesterase inhibitor for erectile dysfunction within the last 24 hours (48 hours for tadalafil).
     c. Adequate analgesia: Morphine sulfate 2 to 4 mg IV initially with increments of 2 to 8 mg IV at 5- to 10-min intervals can be given for severe pain unrelieved by nitroglycerin. Morphine can reduce the catecholamine surge caused by anxiety and pain, particularly in patients with anterior myocardial infarctions, which in turn can reduce heart rate and pulmonary capillary wedge pressure (PCWP), the increased cardiac workload and oxygen demand, leading to decreased ischemia and pulmonary congestion. Hypotension from morphine can be treated with careful IV hydration with saline solution. If sinus bradycardia accompanies hypotension, use atropine (0.5 to 1.0 mg IV q5min prn to a total dose of 2.5 mg). Respiratory depression caused by morphine can be reversed with naloxone 0.8 mg. Morphine sulfate and nitroglycerine should be avoided in patients with RV involvement who usually present with bradycardia and hypotension. Pain management in these cases should be provided preferentially with meperidine 25 to 50 mg intravenously q 4h, in combination with Phenergan 12.5 mg to prevent nausea and/or vomiting. Blood pressure support with normal saline solution is of critical importance to maintain adequate hemodynamics until optimal revascularization is accomplished.
     d. Aspirin 162 to 325 mg PO should be crushed and chewed to enhance drug absorption and delivery. It should be given as soon as possible and continued indefinitely, at 81 mg daily. Depending on the clinical and ECG findings, if the patient is suspected to have a coronary anatomy that needs CABG rather than PCI, aspirin should be continued. P2Y12 receptor antagonists should be avoided (except Cangrelor) because they increase the perioperative bleeding risk; on-pump surgery should be deferred for at least 24 hours after clopidogrel and ticagrelor. Off-pump surgery might be considered within 24 hours of clopidogrel or ticagrelor if the benefits of revascularization outweigh the risk of bleeding. However, if the coronary artery disease is likely to benefit from PCI alone, then a loading dose of clopidogrel 600 or 300 mg or ticagrelor 180 mg PO or prasugrel 60 mg should be given as early as possible and no later than 1 hour after PCI. P2Y12 receptor antagonist should be continued for at least 1 yr after acute coronary syndrome or after primary PCI. Prasugrel showed significant net clinical benefit (MACE vs. bleeding complications) only in patients with MI who underwent revascularization. It shouldn't be given for nonrevascularized patients. Ticagrelor or Clopidogrel can be given in patients with MI with or without catheter-based revascularization. Cangrelor is the newest direct-acting P2Y12 platelet receptor inhibitor. It has a similar chemical structure to ATP, with a half-life of 3 to 6 min. It is given IV as a bolus plus 120 min of infusion at the time of primary PCI in patients who are naïve to P2Y12 receptor antagonists. It was approved by the FDA in 2015 after the CHAMPION PHOENIX trial. Clopidogrel and prasugrel should be started after its infusion is finished. The ticagrelor loading dose can be given during the infusion. Considering rapid onset action and

TABLE 5 Contraindications to and Cautions in the Use of Fibrinolytics for Treating ST-Elevation Myocardial Infarction*

Absolute Contraindications

Any previous intracranial hemorrhage
Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
Known malignant intracranial neoplasm (primary or metastatic)
Ischemic stroke within 3 mo *except* acute ischemic stroke within 4.5 hours
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed-head or facial trauma within 3 mo
Intracranial or intraspinal surgery within 2 mo
Severe uncontrolled hypertension (unresponsive to emergency therapy)
For streptokinase, previous treatment within the previous 6 mo

Relative Contraindications

History of chronic, severe, poorly controlled hypertension
Significant hypertension at initial evaluation (SBP >180 mm Hg or DBP >110 mm Hg)†
History of previous ischemic stroke >3 mo
Dementia
Known intracranial pathology not covered in Absolute Contraindications
Traumatic or prolonged (>10 min) cardiopulmonary resuscitation
Major surgery (<3 wk)
Recent (within 2 to 4 wk) internal bleeding
Noncompressible vascular punctures
Pregnancy
Active peptic ulcer
Oral anticoagulant therapy

*Viewed as advisory for clinical decision making and may not be all-inclusive or definitive.
†Could be an absolute contraindication in low-risk patients with MI.
DBP, Diastolic blood pressure; *SBP,* systolic blood pressure.
From O'Gara PT et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 2013;61:e78. In Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

BOX 1 CABG in Patients With Acute MI

Class I

1. Emergency CABG is recommended in patients with acute MI in whom (1) primary PCI has failed or cannot be performed, (2) coronary anatomy is suitable for CABG, and (3) persistent ischemia of a significant area of myocardium at rest or hemodynamic instability refractory to nonsurgical therapy is present.
2. Emergency CABG is recommended in patients undergoing surgical repair of a postinfarction mechanical complication of MI, such as ventricular septal rupture, mitral valve insufficiency because of papillary muscle infarction or rupture, or free wall rupture.
3. Emergency CABG is recommended in patients with cardiogenic shock and who are suitable for CABG irrespective of the time interval from MI to onset of shock and time from MI to CABG.
4. Emergency CABG is recommended in patients with life-threatening ventricular arrhythmias (believed ischemic in origin) in the presence of left main stenosis greater than or equal to 50% or three-vessel CAD.

Class IIa

1. The use of CABG is reasonable as a revascularization strategy in patients with multivessel CAD with recurrent angina or MI within the first 48 hours of STEMI presentation as an alternative to a more delayed strategy.
2. Early revascularization with PCI or CABG is reasonable for selected patients older than 75 yr of age with ST-segment elevation or left bundle branch block who are suitable for revascularization irrespective of the time interval from MI to onset of shock.

Class III

1. Emergency CABG should not be performed in patients with persistent angina and a small area of viable myocardium who are stable hemodynamically.
2. Emergency CABG should not be performed in patients with no reflow (successful epicardial reperfusion with unsuccessful microvascular reperfusion).

CABG, Coronary artery bypass graft; *CAD,* coronary artery disease; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention; *STEMI,* ST-segment elevation myocardial infarction.
From Hillis LD et al: 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol.* 2011;58:e123-e210. In Parrillo JE et al: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

clearance, Cangrelor can be started in the emergency room at the time of high-risk acute myocardial infarction diagnosis irrespective surgical or catheter-based revascularization.

2. In patients receiving fibrinolytics only or balloon angioplasty without stent, P2Y12 antagonists can be given for as little as 14 days. Clopidogrel is recommended for post-fibrinolytic patients.
3. Unfractionated heparin (UFH) is recommended in all patients with NSTEMI and STEMI (fibrinolysis or invasive revascularization). UFH infusion should not exceed more than 48 hours after PCI or fibrinolysis in the absence of an ongoing indication due to risk of heparin-induced thrombocytopenia. NSTEMI patients who underwent ischemia-guided therapy, low molecular weight heparin (LMWH) showed better MACE outcomes compared with UFH. The benefit was not significant in revascularized patients. Bivalirudin was associated with lower MACE and bleeding events in STEMI patients compared with UFH. However, it increased the risk of stent thrombosis. In NSTEMI patients who are undergoing PCI, LMWH, Bivalirudin, and UFH are acceptable.
4. Beta-adrenergic blocking agents should generally be given to all patients who do not exhibit evidence of shock. Table 6 summarizes recommendations for beta-blocker therapy for STEMI. Beta-blockers are useful to reduce myocardial oxygen consumption and prevent tachyarrhythmias. Early IV beta blockage (in the initial 24 hr) followed by institution of an oral maintenance regimen is also effective in reducing recurrent infarction and ischemia. Oral beta-blockers should be initiated in the first 24 hours in patients with MI who do not have any of the following: signs of HF, evidence of a low-output state, sinus tachycardia, increased risk for cardiogenic shock, or other contraindications for its use (bradycardia, PR interval more than 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airways disease).
5. They should be continued during and after hospitalization for all patients with MI and with no contraindications to their use for at least 2 yr. Patients with initial contraindications to the use of beta-blockers in the first 24 hours after MI should be reevaluated to determine their subsequent eligibility. It is reasonable to administer intravenous beta-blockers at the time of presentation to patients with MI and no contraindications to their use who are hypertensive or have ongoing ischemia.
6. In patients with acute MI, treatment with drug-eluting stents is associated with decreased mortality rates and a reduction in the need for repeated revascularization

TABLE 6 Recommendations for Beta-Blocker Therapy for ST-Elevation Myocardial Infarction (STEMI)

Recommendation	COR	LOE
Oral beta blockers should be initiated in the first 24 hours in patients with STEMI who do not have any of the following: Signs of heart failure or evidence of a low-output state Increased risk for cardiogenic shock*: • Age >70 yr • Systolic blood pressure <120 mm Hg • Sinus tachycardia >110 beats/min or heart rate <60 beats/min • Increased time since the onset of symptoms of STEMI Other relative contraindications to use of oral beta blockers: • PR interval longer than 0.24 second • Second- or third-degree heart block • Active asthma or reactive airways disease	I	B
Beta blockers should be continued during and after hospitalization for all patients with STEMI and no contraindications to their use.	I	B
Patients with initial contraindications to the use of beta blockers in the first 24 hours after STEMI should be reevaluated to determine their subsequent eligibility.	I	C
It is reasonable to administer IV beta blockers at initial encounter to patients with STEMI and no contraindications to their use who are hypertensive or have ongoing ischemia.	IIa	B

*The greater the number of risk factors present, the higher the risk for development of cardiogenic shock.
COR, Class of recommendation; *IV,* intravenous; *LOE,* level of evidence.
Modified from O'Gara PT et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 2013;61:e78. In Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

procedures compared with treatment including bare-metal stents.

7. Gp IIb/IIIa inhibitors in the era of DAPT therapy and primary PCI have failed to show benefit with "upstream" treatment. Abciximab might be useful in the presence of large thrombus burden during primary PCI. For patients receiving bivalirudin as the primary anticoagulant, routine adjunctive use of GP IIb/IIIa inhibitors is not recommended but may be considered as adjunctive or "bail-out" therapy in selected cases. In patients with acute coronary syndrome with high-risk features and not adequately pretreated with P2Y12 inhibitors, it is useful to administer GP IIb/IIIa inhibitors at the time of PCI.

CHRONIC Rx

- Discharge medications in all patients with MI (unless contraindicated) should include anti-ischemic medications (e.g., nitroglycerin, beta-blocker), lipid-lowering agents, and antiplatelet therapy (aspirin and/or P2Y12 antagonists).
- Aspirin, 81 mg PO daily, but should be continued indefinitely unless not tolerated (e.g., GI bleed). In MI patients, Clopidogrel 75 mg PO daily; ticagrelor, 90 mg bid, or prasugrel, 10 mg PO daily, can be combined with aspirin and should be continued without interruption for a minimum of 12 mo after drug-eluting stent placement; however, aspirin should be continued indefinitely. In cases of high bleeding risk or significant overt bleeding, consider discontinuation of P2Y12 inhibitor after 6 mo (Fig. 6). Combining P2Y12 antagonists with aspirin reduces risk for repeat myocardial infarction and stent thrombosis. If there is an elective surgical intervention pending, it is recommended to defer the surgery until completion of the full course of the P2Y12 antagonist treatment.
- Angiotensin-converting enzyme inhibitors (ACEIs) should be started within the first 24 hours of MI to all patients having MI with anterior infarction, pulmonary congestion, or LV EF <40%, in the absence of hypotension. They reduce LV dysfunction and dilation and slow the progression to HF during and after acute MI. Angiotensin receptor blockers (ARBs) should be given to patients who have indication but are intolerant of ACEIs. IV formulations of ACEIs should not be given within the first 24 hours of STEMI due to risk of hypotension. ARBs offer no advantage over ACEIs and should be considered only in patients who are intolerant to ACEIs.
  1. Commonly used ACEIs are ramipril 2.5 mg PO bid, captopril 12.5 mg PO bid, enalapril 2.5 mg PO bid, and lisinopril 2.5 to 5 mg PO qd initially, with subsequent titration as needed. Ramipril is associated with a lower mortality rate than most ACEIs.
  2. ACEIs may be stopped in patients without complications and no evidence of LV dysfunction after 6 to 8 wk.
  3. ACEIs should be continued indefinitely in patients with impaired LV function (EF <40%) or clinical HF.
- Long-term aldosterone antagonist therapy should be prescribed for post-MI patients without significant renal dysfunction (creatinine ≤2.5 mg/dl in men and ≤2.0 mg/dl in women) or hyperkalemia who are already taking an ACEI, a beta-blocker, and have LV EF <40% with symptomatic HF or diabetes.
- In late 2018, American College of Cardiology (ACC) recommended LDL goal of <70 mg/dL for secondary prevention of atherosclerotic cardiovascular disease. High-intensity statins (atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg) should be started as early as possible in all patients with MI regardless of lipid panel, not only for their lipid-lowering effects, but also their antiinflammatory properties (JUPITER trial), which can stabilize the ruptured plaque. Atorvastatin 80 mg can be used (PROVE IT-TIMI 22 and MIRACL trials). IMPROVE-IT trial showed adding ezetimibe to statin treatment could decrease recurrent MI and ischemic stroke in MI patients. FDA also approved two PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (alirocumab and evolocumab) for heterozygous familial hypercholesterolemia patients who are receiving maximally tolerated statins or patients with clinical atherosclerotic cardiovascular disease who require lowering LDL levels. Newer 2018 lipid guidelines suggested starting PCSK9 inhibitor in very high risk atherosclerotic cardiovascular disease patients who did not meet the LDL goal on high intensity statin and ezetimibe. One should always consider adding ezetimibe to high intensity statin prior to initiation of PCSK9 inhibitor due to cost issues. A fasting lipid panel should be checked during the first 24 hours of hospital course, and the intensive therapy can be stepped down if appropriate.
- In diabetic patients, HbA1c goal should be aimed at below or around 7.0% to reduce micro- and macrovascular complications. Oral hypoglycemic agents GLP1 (glucagon like peptide) agonist (liraglutide) and SGLT2 (sodium-glucose cotransporter) inhibitor (empagliflozin) showed significant mortality benefit in type 2 diabetic patients with history of CAD.
- ACC/AHA 2017 hypertension guidelines recommend initiation of blood pressure (BP)-lowering medications in patients with clinical CVD and an average SBP ≥130 mm Hg or a DBP ≥80 mm Hg for goal BP of <130/80.

COMPLICATIONS OF MI

- Cardiogenic shock: Emergent revascularization with either PCI or CABG is the recommended treatment.
- Sustained ventricular tachycardia: Implantable cardioverter-defibrillator therapy (ICD) is indicated before discharge in patients who develop sustained ventricular tachycardia/ventricular fibrillation more than 48 hours after STEMI, provided the arrhythmia is not due to transient or reversible ischemia, reinfarction, or metabolic abnormalities.
- Pacing in MI: Temporary pacing is indicated for symptomatic bradyarrhythmias

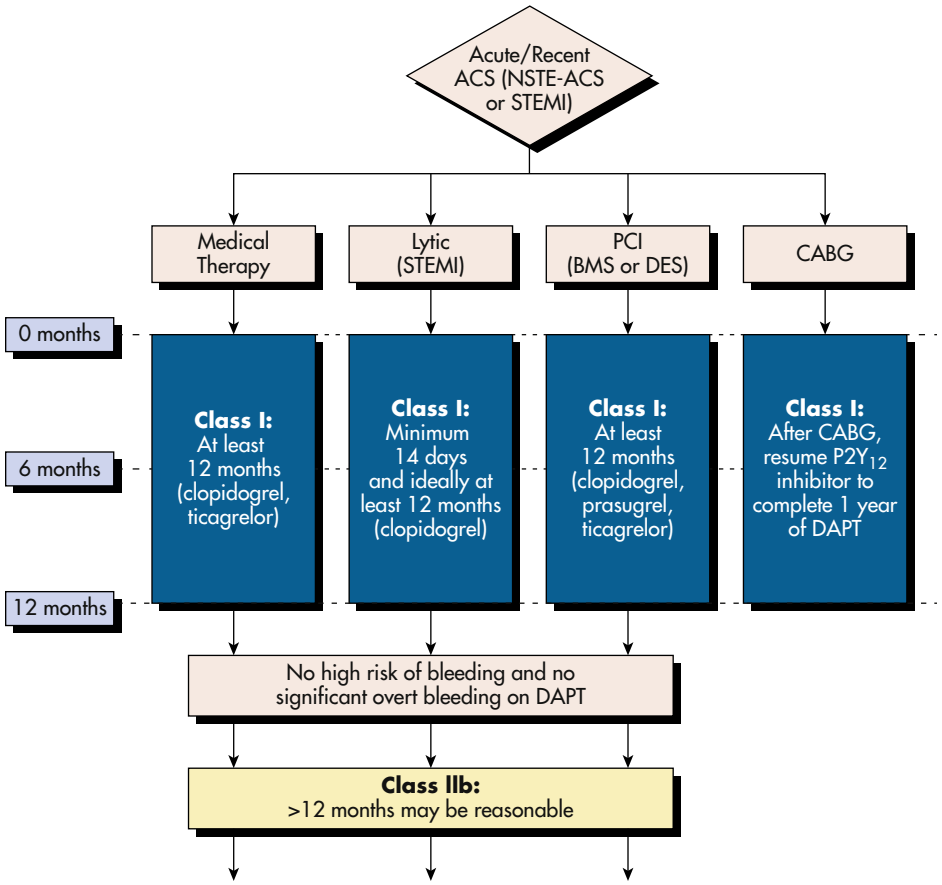

FIG. 6 ACC/AHA guideline recommendation for duration and choice of antiplatelet agent in patients with recent acute coronary syndrome (ACS), including STEMI. Aspirin therapy is generally continued indefinitely post-ACS. In patients treated with dual-antiplatelet therapy (DAPT) after DES implantation who have a high risk of bleeding (e.g. use of oral anticoagulant therapy, major intracranial surgery) or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 6 mo for ACS may be reasonable. The optimal duration of prolonged DAPT is not established. *BMS,* Bare-metal stent; *CABG,* coronary artery bypass grafting; *CAD,* coronary artery disease; *DES,* drug-eluting stent; *Hx,* history; *lytic,* fibrinolytic therapy; *NSTE-ACS,* non–ST-elevation acute coronary syndrome; *PCI,* percutaneous coronary intervention; *STEMI,* ST-elevation myocardial infarction. (Modified from Levine GN et al: 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease, J Am Coll Cardiol 2016;68(10):1082-115. In Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

unresponsive to medical treatment and after revascularization. AV block and bradyarrhythmias in the setting of inferior wall MI are usually transient, will not require long-term pacing, and usually resolve within 2 to 4 wk of the event. On the contrary, AV block and bradyarrhythmias or new LBBB in the presence of an anterior wall MI is usually a sign of severe disruption of the bundle of His and often requires a permanent pacemaker.

- Pericarditis after MI: Post-MI pericarditis can occur early after MI. Dressler syndrome is an autoimmune inflammatory reaction to myocardial antigen after myocardial infarction. Symptoms of pericarditis usually occur 2 to 3 wk after myocardial infarction. Aspirin is recommended for treatment of pericarditis after MI. Glucocorticoids and nonsteroidal antiinflammatory drugs are potentially harmful for treatment of pericarditis after STEMI.
- Severe mitral regurgitation from papillary muscle rupture (1%), interventricular septum rupture (0.2%), and free wall rupture (1% to 3%) are the three major mechanical complications that can occur after acute myocardial infarction. Echocardiogram is helpful in diagnosing papillary muscle rupture, ventricular septal rupture, and free wall rupture. Right heart catheterization is needed to show "step-up" in oxygen saturation at the level of right ventricle. Emergent surgical repair is the treatment of choice for ventricular free wall rupture, intraventricular septum rupture, and papillary muscle rupture.

EVALUATION OF POST-MI PATIENTS

- Noninvasive testing for ischemia should be performed before discharge to assess the presence and extent of inducible ischemia in patients with STEMI who have not had coronary angiography and do not have high-risk clinical features for which coronary angiography would be warranted. It might be considered before discharge to evaluate the functional significance of a noninfarct artery stenosis previously identified at angiography and/or before discharge to guide the postdischarge exercise prescription.
- Assessment of LV function: LV ejection fraction should be measured in all patients with STEMI. Echocardiography to rule out presence of mural thrombi in patients suspected of having an extensive infarction (more common with anterior wall MI); contrast echocardiography is added if mural thrombus is suspected.
  1. Assessment of risk for sudden cardiac death: Patients with an initially reduced LV ejection fraction, <40%, who are possible candidates for implantable cardioverter-defibrillator therapy should undergo reevaluation of LV ejection fraction at 90 days (or 42 days if no revascularization was performed). ICD is recommended when LVEF remains <35% in the presence of NYHA class II or III heart failure, or in patients with LVEF <30% regardless of symptoms, if the life expectancy is >1 yr.

- Cardiac rehabilitation/secondary prevention programs are recommended for patients with STEMI.

DISPOSITION

The prognosis after MI depends on multiple factors:

- New bundle branch block, Mobitz II second-degree block, and third-degree heart block adversely affect outcome.
- Size of infarct: The larger it is, the higher the post-MI mortality rate. Significant myocardial stunning with subsequent improvement of ventricular function occurs in most patients after anterior MI. A lower level of creatine kinase, an estimate of the extent of necrosis, is independently predictive of recovery of function.
- Site of infarct: Inferior wall MI carries a better prognosis than anterior wall MI; however, patients with inferior wall MI and right ventricular involvement have a high risk for arrhythmic complications and cardiogenic shock.
- Ejection fraction after MI: The lower the LV ejection fraction, the higher the mortality rate after MI. The risk of death is higher in the first 30 days after MI among patients with LV dysfunction, HF, or both.
- Presence of post-MI angina indicates a high mortality rate.
- Performance on low-level exercise test: The presence of ST-segment changes during the test is a predictor of high mortality rate during the first yr.
- Presence of pericarditis during the acute phase of MI increases mortality rate at 1 yr.
- Type A behavior (competitive drive, ambitiousness, hostility) is associated with a lower mortality rate after symptomatic MI.
- The Killip classification is an independent predictor of all-cause 30-day mortality:
  1. Killip class I includes individuals with no clinical signs of HF. Mortality rate is 6%.
  2. Killip class II includes individuals with rales or crackles in the lungs, S_3 gallop, and elevated jugular venous pressure. Mortality rate is 17%.
  3. Killip class III describes individuals with frank acute pulmonary edema. Mortality rate is 38%.
  4. Killip class IV describes individuals in cardiogenic shock or hypotension (measured as systolic blood pressure <90 mm Hg) and evidence of peripheral vasoconstriction (oliguria, cyanosis, or sweating). Mortality rate is 67%.
- Self-reported moderate alcohol consumption in the yr before acute MI is associated with reduced 1-yr mortality rate.
- Discharge medication in patients with MI should include lipid-lowering agents. Statins may also lower vascular inflammation and damage by mechanisms other than reduction of low-density lipoprotein cholesterol. Early initiation of statin treatment in patients with acute MI is associated with reduced 1-yr mortality rate.
- Additional poor prognostic factors include cigarette smoking, history of hypertension or prior MI, presence of ST-segment depression in acute MI, older age, diabetes mellitus, and female sex (especially women >50 yr). Lammintausta and Fonarow reported that single men and women who live alone have a 60% to 70% greater risk of a heart attack. Furthermore, the study showed >160% increase in the risk of sudden death in these groups when compared to people who are married or live with family.
- Renal disease, even mild, as assessed by the estimated glomerular filtration rate, is a major risk factor for cardiovascular complications after MI.
- Although black patients with MI have worse outcomes than their white counterparts, these differences did not persist after adjustment for patient factors and site of care.

PEARLS & CONSIDERATIONS

COMMENTS

- Approximately 1.5 million patients undergo PCI in the U.S. each yr. Depending on local practices and the diagnostic criteria used, 5% to 30% of these patients have evidence of a periprocedural MI.
- The 12-lead ECG has low sensitivity for the detection of MI if the culprit lesion is in the left circumflex artery (LCX). If the initial 12-lead ECG is not diagnostic and high clinical suspicion for acute coronary syndrome exists, it is reasonable to obtain additional posterior chest leads (V_7 to V_9) to detect LCX occlusion.
- Triad of hypotension, elevated jugular venous pressure, and clear lungs are suggestive of RV infarction in patients with inferior AMI. Administration of nitroglycerin is contraindicated due to hypotension. IV fluids, inotropic support, and early reperfusion are the mainstays of treatment.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Heart Attack (Patient Information)
Acute Coronary Syndrome (Related Key Topic)
Angina Pectoris (Related Key Topic)
Coronary Artery Disease (Related Key Topic)

AUTHOR: **Maheswara Satya Gangadhara Rao Golla, MD**

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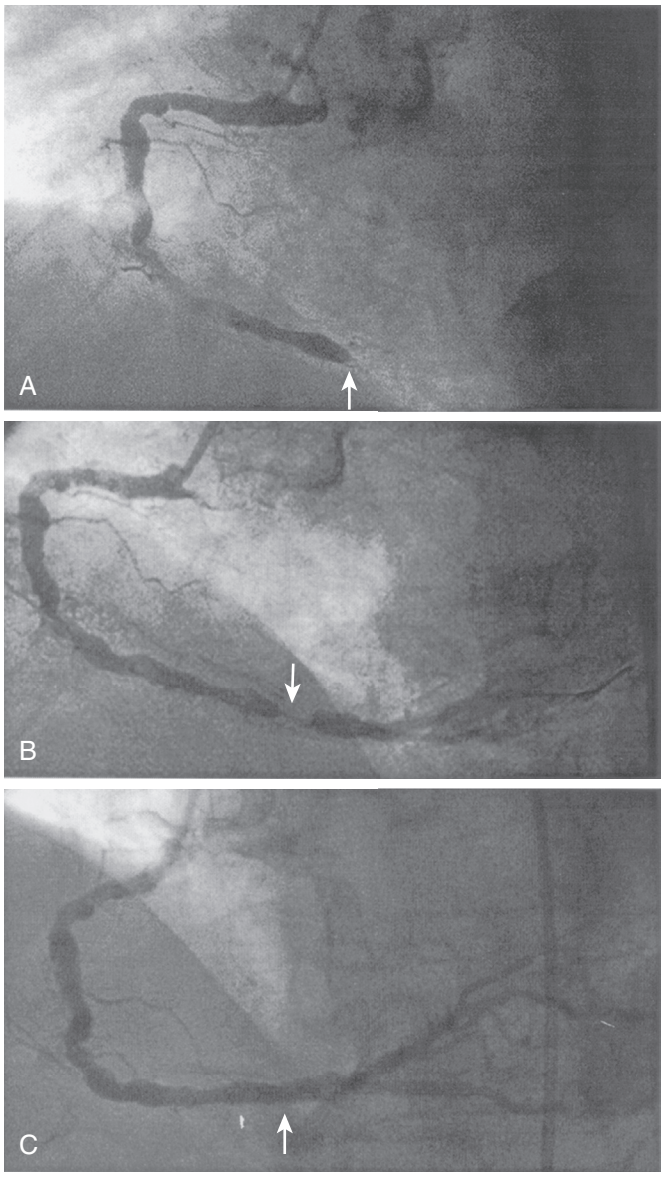

FIG. E5 Primary coronary angioplasty for acute myocardial infarction. This 50-year-old man presented at midnight with 70 min of crushing substernal chest pressure accompanied by inferior ST segment elevation. Emergency angiography performed 45 min after arrival found 100% occlusion of the right coronary artery (**A,** *arrow*). Within 10 min, a guidewire was negotiated through the obstruction (presumably caused by fresh thrombus), allowing perfusion into the distal vessel and uncovering a high-grade stenotic lesion (**B,** *arrow*). After deployment of a coronary stent (**C,** *arrow*), the stenosis was abolished and significant myocardial damage aborted. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.)

TABLE E2 Electrocardiographic Manifestations of Myocardial Infarction

Electrocardiographic Manifestations of Acute Myocardial Ischemia (In the Absence of Left Bundle Branch Block)

ST Elevation

New ST elevation at the J point in two contiguous leads with the following cut points:

- ≥0.1 mV in all leads (except V2-V3)
- In leads V2-V3 the following cut points apply:
  1. ≥0.2 mV in men ≥40 yr
  2. ≥0.25 mV in men <40 yr
  3. ≥0.15 mV in women

ST Depression and T Wave Changes

New horizontal or downsloping ST depression ≥0.05 mV in two contiguous leads

T-wave inversion ≥0.1 mV in two contiguous leads with a prominent R wave or R/S ratio >1

Electrocardiographic Manifestations of Ischemia In the Setting of Left Bundle Branch Block

Electrocardiographic Criterion	Points
ST-segment elevation ≥1 mm and concordant with the QRS complex	5
ST-segment depression ≥1 mm in lead V1, V2, or V3	3
ST-segment elevation ≥5 mm and discordant with the QRS complex	2

A score of ≥3 had a specificity of 98% for acute MI

Electrocardiographic Changes Associated with Previous Myocardial Infarction (In the Absence of Left Ventricular Hypertrophy and Left Bundle Block)

Any Q wave in leads V2-V3 ≥0.02 sec or a QS complex in leads V2 and V3

Q wave ≥0.03 sec and ≥0.1-mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any 2 leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, aVF)

R wave ≥0.04 sec in V1-V2 and R/S ≥1 with a concordant positive T wave in absence of a conductions defect

aVF, Augmented vector foot; *aVL,* augmented vector left; *MI,* myocardial infarction.

Based on criteria from O'Gara PT et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 2013;61:e78. In Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,*, ed 11, Philadelphia, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Myocarditis broadly refers to inflammation of the heart muscle (myocardium). Disease severity may range from benign and self-limiting illness to severe, acute decompensation requiring intensive care. Myocarditis may result from exposure to external antigens such as viruses, bacteria, parasites, and drugs, or from autoimmune conditions.

ICD-10CM CODES

I40.0	Infective myocarditis
I40.1	Isolated myocarditis
I40.8	Other acute myocarditis
I40.9	Acute myocarditis, unspecified
A39.52	Meningococcal myocarditis
B26.82	Mumps myocarditis
B33.22	Viral myocarditis
B58.81	Toxoplasma myocarditis
D86.85	Sarcoid myocarditis
I01.2	Acute rheumatic myocarditis
I09.0	Rheumatic myocarditis
I41	Myocarditis in diseases classified elsewhere
I51.4	Myocarditis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Myocarditis is often underdiagnosed.
- The incidence of focal myocarditis reported at autopsy is 1% to 9% in asymptomatic patients and 50% in patients infected with HIV.
- Myocarditis is the third leading cause of sudden unexpected death (as high as 8% to 9%) in young adults <40 yr of age, especially in cases of idiopathic dilated cardiomyopathy, where myocarditis may account for 10% to 40% of the cases overall.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The most common presentations in patients are new onset heart failure (<6 months), chest pain, and arrhythmias, which include sinus tachycardia as well as atrial and ventricular premature contractions.
- Chest pain, especially pleuritic and positional, presents when the pericardium is involved.
- Persistent tachycardia out of proportion to fever.
- Bradyarrhythmia and new-onset unexplained heart block may also occur both in infectious (e.g., Lyme disease) and in immune-mediated forms of myocarditis.
- Faint S_1, S_3, and S_4 gallops on auscultation are important signs of impaired ventricular function.
- Murmur of functional mitral regurgitation and functional tricuspid regurgitation caused by severe left ventricular and right ventricular dilation.
- Pericardial friction rub if associated with pericarditis as in the clinical syndrome of myopericarditis.
- Patients may present with a history of a recent flulike syndrome or nonspecific viral prodrome (fever, arthralgias, malaise, fatigue); children often have a more fulminant presentation than adults. Difficulty breathing is the most common presentation of pediatric myocarditis.
- Congestive heart failure (CHF) symptoms that usually manifest with fatigue and decreased exercise capacity.
- If myocarditis is severe and diffuse and rapid in evolution, it can present with acute CHF symptoms leading to cardiogenic shock and death.
- Signs of biventricular failure (hypotension, hepatomegaly, peripheral edema, distention of neck veins, S_3 sounds, and pulmonary edema).
- Presyncope or syncope secondary to ventricular arrhythmias.
- Sudden cardiac death from ventricular tachycardia/ventricular fibrillation mediated by inflammation and/or a scar, which sets up a reentry-mediated pathway for ventricular arrhythmias.
- Acute coronary syndrome, which can occur due to local coronary spasm and inflammation and can present on ECG as acute injury pattern or ischemic changes.

ETIOLOGY

- Infection:
  1. Viral (adenovirus, parvovirus B19, hepatitis C virus [HCV], Coxsackie B virus, cytomegalovirus, enterovirus, poliovirus, mumps, HIV, and Epstein-Barr virus, etc.). Viruses are the most common cause of myocarditis in developed countries. In the 1980s and 1990s, enteroviruses were frequently associated with myocarditis and dilated cardiomyopathy. In the past 10 yr, however, other viruses such as adenovirus, HCV, parvovirus B19, and herpesvirus 6 (HH6) have emerged as the significant pathogens (Box E1)
  2. Bacterial (*Staphylococcus aureus, Clostridium perfringens,* diphtheria, mycoplasma, and any severe bacterial infection)
  3. Mycotic (*Candida, Mucor, Aspergillus, Blastomyces, Histoplasma*)
  4. Parasitic (*Trypanosoma cruzi*—most common worldwide, *Trichinella, Echinococcus, Amoeba*, *Toxoplasma*)
  5. *Rickettsia rickettsii*
  6. Spirochetal *(Borrelia burgdorferi*–Lyme carditis)
- Rheumatic fever
- Systemic lupus erythematosus
- Granulomatosis with polyangiitis (Wegener granulomatosis)
- Giant cell arteritis and Takayasu arteritis
- Drugs (e.g., cocaine, emetine, doxorubicin, sulfonamides, isoniazid, methyldopa, amphotericin B, tetracycline, phenylbutazone, lithium, 5-fluorouracil, phenothiazines, interferon-alfa, nivolumab, ipilimumab, tricyclic antidepressants, cyclophosphamides, smallpox vaccination)
- Toxins (carbon monoxide, ethanol, diphtheria toxin, lead, arsenicals)
- Systemic and collagen-vascular disease (scleroderma, sarcoidosis, celiac disease, Sjögren's syndrome, Kawasaki syndrome, etc.)
- Celiac disease: Two reports from Italy suggest that celiac disease, which is often clinically unsuspected, accounts for as many as 5% of patients with autoimmune myocarditis or idiopathic DCM
- Radiation
- Postpartum status
- Post–stem cell transplantation
- Hypersensitivity reactions from insect bites, such as bee and wasp bites; from snake bites; and from tetanus toxoid

DIAGNOSIS (TABLE 1)

DIFFERENTIAL DIAGNOSIS

- Ischemic cardiomyopathy and other, nonischemic cardiomyopathies
- Acute coronary syndromes
- Valvulopathies
- Infiltrative diseases of the myocardium, such as sarcoidosis, amyloidosis, hemochromatosis, and Chagas disease

The differential diagnosis of chest pain is described in Section II.

WORKUP

- Medical history: The clinical presentation of myocarditis is nonspecific and can consist of fatigue, palpitations, dyspnea, precordial discomfort, and myalgias.
- Diagnostic workup includes chest x-ray examination, ECG, laboratory evaluation, echocardiogram, cardiac catheterization, cardiac MRI with late gadolinium enhancement, and endomyocardial biopsy (in selected patients on the basis of the likelihood of finding specific treatable disorders such as giant cell myocarditis). Of note, endomyocardial biopsy has a sensitivity of only 10% to 35% using standard histologic criteria. This is due to variability in interpretation and sampling error.

LABORATORY TESTS

- Elevated cardiac troponin is suggestive of myocarditis in patients with clinically suspected myocarditis. Troponin I specificity is 89%; sensitivity is 34% to 53%. Elevated troponin aids in diagnosis but does not confer a prognostic value. A normal level does not rule out the diagnosis
- Increased creatine kinase (CK) (with elevated MB fraction, lactate dehydrogenase), and aspartate aminotransferase from myocardial necrosis
- Elevation of cardiac troponin I or T is more common than CK-MB elevation in patients with biopsy-proven myocarditis
- The elevations of cardiac troponin I were correlated with a short duration (typically less than 1 mo) of CHF symptoms, indicating that

TABLE 1 Expanded Criteria for Diagnosis of Myocarditis

Suggestive of myocarditis:	2 positive categories
Compatible with myocarditis:	3 positive categories
High probability of being myocarditis:	all 4 categories positive

(Any matching feature in category = positive for category)

Category I: Clinical Symptoms

- Clinical heart failure
- Fever
- Viral prodrome
- Fatigue
- Dyspnea on exertion
- Chest pain
- Palpitations
- Presyncope or syncope

Category II: Evidence of Cardiac Structural or Functional Perturbation *in the Absence* of Regional Coronary Ischemia

- Echocardiography evidence
- Regional wall motion abnormalities
- Cardiac dilation
- Regional cardiac hypertrophy
- Troponin release
- High sensitivity (>0.1 ng/ml)
- Positive indium In 111 antimyosin scintigraphy
- Normal coronary angiography *or*
- Absence of reversible ischemia by coronary distribution on perfusion scan

Category III: Cardiac Magnetic Resonance Imaging

- Increased myocardial T2 signal on inversion recovery sequence
- Delayed contrast enhancement after gadolinium-DTPA infusion

Category IV: Myocardial Biopsy—Pathologic or Molecular Analysis

- Pathology findings compatible with Dallas criteria
- Presence of viral genome by polymerase chain reaction or in situ hybridization

DTPA, Diethylenetriamine penta-acetic acid.
From Bonow RO et al: *Heart disease,* 9th ed, Philadelphia, 2012, Saunders.

the majority of myocardial necrosis occurs early in the disease course
- Persistent elevations of cardiac biomarkers are indicative of ongoing myocardial necrosis
- BNP or NT-proBNP is recommended if patient has heart failure symptoms
- Increased erythrocyte sedimentation rate (nonspecific but may be of value in following the progress of the disease and the response to therapy)
- Increased white blood cell count, again, nonspecific (increased eosinophils if parasitic infection)
- Viral titers (acute and convalescent)
- Cold agglutinin titer, antistreptolysin O titer, blood cultures
- Lyme disease antibody titer
- RPR, VDRL
- Histology on endomyocardial biopsy may reveal histiocytic and mononuclear cellular infiltrates, fulfilling the Dallas criteria, which were developed by a panel of cardiac pathologists as a working standard to define the disease; active myocarditis is defined as "an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease"
- Based on the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, immunohistochemical criteria of myocarditis are abnormal inflammatory infiltrates defined as >14 leukocytes/mm^2 including up to 4 monocytes/mm^2 with the presence of >7 CD^3 positive T lymphocytes/mm^2

IMAGING STUDIES

- Chest x-ray: Enlargement of cardiac silhouette with or without pulmonary congestion may be present.
- ECG: May be normal or show nonspecific findings. Sinus tachycardia with nonspecific ST-T wave changes unless there is concomitant pericarditis in which the ECG changes are more specific; intraventricular conduction defects and bundle branch blocks are uncommon in typical viral myocarditis but are common manifestations in cardiac sarcoid and idiopathic giant cell myocarditis. The presence of Q waves or left bundle branch block was associated with higher rates of death or transplantation in some patients.
  1. Lyme disease and diphtheria can cause varying degrees of heart block.
  2. Changes mimicking acute myocardial infarction (regional ST elevations and Q waves) can occur with focal necrosis from myocarditis.
- Echocardiogram:
  1. The most useful test in detecting decreased ventricular function in suspected myocarditis even when subclinical.
  2. Acute severe myocarditis is associated with systolic dysfunction with decreased ejection fraction.
  3. Dilated and hypokinetic chambers.
  4. The systolic dysfunction is generally global but may be regional or segmental as in the case of focal myocarditis.
  5. Exercise-induced wall motion abnormalities may also be seen. This is usually due to microvascular dysfunction.
  6. Abnormal tissue Doppler signal can provide additional evidence for the presence of myocarditis.
  7. The echocardiogram can also be helpful with diagnosing coexisting pericardial involvement.
  8. The spheroid dysfunctional ventricle in acute myocarditis tends to remodel to the more normal elliptical shape over several months.
- Cardiac catheterization and angiography:
  1. To rule out coronary artery disease and valvular disease. Coronary angiography is most commonly normal with evidence of minimal or no coronary artery disease.
  2. A right ventricular endomyocardial biopsy can confirm the diagnosis, although a negative biopsy result does not exclude myocarditis owing to the low sensitivity of this test. Recent studies have shown that myocardial biopsy may be unnecessary because immunosuppression therapy based on biopsy results is generally ineffective. However, if idiopathic giant cell myocarditis is suspected, biopsy can confirm this diagnosis, and immunosuppression therapy is often helpful in this patient cohort.
- Cardiac MRI (Fig. E1):
  1. Can be used to detect myocardial edema and myocyte injury in myocarditis.
  2. Increased focal or global signal intensity can be used to calculate an edema ratio. Edema in the absence of necrosis or scar represents reversible injury and thus can predict functional recovery.
  3. Late gadolinium enhancement (LGE) and the presence of increased focal and global myocardial contrast enhancement relative to skeletal muscle.
  4. Any combination of two of the above has a sensitivity and specificity of 76% and 96%, with 85% diagnostic accuracy, and is probably the gold standard for diagnosis of myocarditis, as opposed to routine biopsy.
  5. Cardiac MRI has demonstrated that myocarditis tends to start as a focal process and becomes a more global process over time, with the extent of myocardial enhancement correlating with clinical status and left ventricular function.
  6. The pattern of LGE is different from that in ischemic cardiomyopathy. LGE in myocarditis tends to involve the epicardium with variable extension into the midmyocardium and sparing of the endocardium. This is in contrast to ischemic injury, which involves endocardium first with extension outward.
- Indium-111-labeled antimyosin antibody scintigraphy is positive in myocarditis with a sensitivity of up to 65%.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive care is the first line of therapy for patients with myocarditis.
- Restrict physical activity (to decrease cardiac work). Bed rest is advisable during viremia.
- Avoid heavy use of alcohol.
- Nonsteroidal antiinflammatory drugs (NSAIDs) should be avoided in patients with HF generally, given the risk of HF exacerbation and possible risk of increased mortality. NSAIDs in the lowest required dose are reserved for patients with perimyocarditis in whom LV function is clearly normal and who have prominent chest pain from pericarditis.

ACUTE GENERAL Rx

- Treat underlying cause (e.g., use specific antibiotics for bacterial infection).
- Treat congestive heart failure (CHF) with diuretics, angiotensin-converting enzyme inhibitors (ACE inhibitors), and salt restriction. A beta-blocker may be added once clinical stability has been achieved. Digoxin should be used with caution and only at low doses.
- In patients with myocarditis associated with severe left ventricular dysfunction, major treatment decisions such as referral for heart transplant, left ventricular assist device, and with implantable cardioverter-defibrillator (ICD) implantation should be deferred for 3 to 6 months when feasible to allow for improvement with optimal medical therapy.
- Patients who are left with an LVEF ≤35% despite optimal medical therapy for 3 to 6 mo, and who have good functional status with prognosis >1 yr, will benefit from primary prevention therapy with ICD implantation as in patients with ischemic cardiomyopathy and other nonischemic cardiomyopathies.
- Antiarrhythmics if needed for ventricular arrhythmias. When antiarrhythmic therapy is necessary, options include amiodarone, dofetilide, and, in patients without class IV HF, cautious use of beta-blockers or calcium channel blockers. ICD implantation for secondary prevention in patients who have life-threatening ventricular arrhythmias and have good functional status with prognosis >1 yr.
- Complete heart block and/or symptomatic bradycardia are indications for pacing during the acute phase of myocarditis but are usually transient, so temporary pacing is sufficient.
- In patients with chronic CHF from myocarditis, only ACE inhibitors, beta-blockers, and possibly aldosterone receptor antagonists will decrease their mortality in the long term (as with all CHF etiologies).
- Anticoagulation is indicated in patients with evidence of systemic embolism or presence of acute left ventricular thrombus. Standard criteria for anticoagulation for atrial fibrillation should also be applied. Heart failure and/or low EF with normal sinus rhythm are generally not indications for anticoagulation.
- Inotropes or mechanical assist devices such as intraaortic balloon pumps, Impella device, and left ventricular assist device (LVAD) if severe heart failure or if cardiogenic shock persists despite medical therapy.
- Cardiac transplantation in patients with chronic or acute fulminant myocarditis with intractable cardiomyopathy and persistent CHF.
- Corticosteroid use is contraindicated in early infectious myocarditis; it may be justified in only selected patients with intractable CHF, severe systemic toxicity, and severe life-threatening arrhythmias.
- Immunosuppressive drugs (prednisone with cyclosporine/Cytoxan or azathioprine) do not have any significant effect on the prognosis of myocarditis and should not be used in the routine treatment of patients with myocarditis. Immunosuppression may have a role in the treatment of myocarditis from systemic autoimmune disease (e.g., lupus, scleroderma); in idiopathic giant cell myocarditis, sarcoidosis, or myocarditis caused by hypersensitivity reactions; or in severe hemodynamic compromise.
- Observational data suggest that patients with giant cell myocarditis treated with certain immunosuppressive regimes have improved survival compared with patients who do not receive immunosuppressive treatment.
- In patients with ongoing viral genomic expression, preliminary data suggest that treatment with interferons may improve both symptoms and left ventricular function when compared with standard heart failure therapy.
- IV immunoglobulins have been studied, but because of lack of efficacy data, at present there is no indication for their use except in some pediatric cases or those refractory to immunosuppressive therapy.
- Improved cardiac function and arrhythmias have been reported in patients with celiac disease and myocarditis or DCM following a gluten-free diet with or without immunosuppressive therapy, but controlled data are lacking.
- A treatment algorithm for patients with myocarditis is described in Fig. E2.

DISPOSITION

- Most patients with acute myocarditis and mild cardiac involvement have a partial or a full clinical recovery. In some cases, however, the process may continue subclinically with eventual progression to a cardiomyopathy. Therefore all patients with myocarditis should be followed up at least initially at intervals of 1 to 3 mo, depending on their initial severity of illness. Of those with advanced cardiac dysfunction, one third will have residual cardiac dysfunction, and 25% may progress to cardiac transplantation or death.
- Prognosis is best for patients with fulminant lymphocytic myocarditis (severe hemodynamic compromise, rapid onset of symptoms, or high fever). These patients tend to have complete recovery with total resolution of myocarditis on repeat biopsy.
- In contrast, patients with giant cell myocarditis have an extremely poor prognosis with a median survival of <6 mo, and most require cardiac transplantation.
- The American Heart Association recommends 3 to 6 mo abstinence from competitive sports after myocarditis.

REFERRAL

Consider heart transplant if intractable CHF develops.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Myocarditis (Patient Information)

AUTHORS: **Vrinda Trivedi, MBBS,** and **Aravind Rao Kokkirala, MD, FACC**

SUGGESTED READINGS

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BOX E1 Causes of Myocarditis

Viruses
Coxsackieviruses A and B
Echoviruses
Polioviruses
Rubella
Measles
Adenoviruses
Vaccinia
Mumps
Herpes simplex
Epstein-Barr
Cytomegalovirus
Rhinoviruses
Hepatitis viruses
Arboviruses
Influenza viruses
Varicella

Rickettsia
Rickettsia rickettsii
Rickettsia tsutsugamushi

Bacteria
Meningococcus
Klebsiella
Leptospira
Staphylococcus
Treponema pallidum
Haemophilus influenzae
Hemolytic streptococci
Mycobacterium tuberculosis
Salmonella enterica subsp. enterica serovar Typhi (typhoid)

Mycoplasma
Mycoplasma pneumoniae
Chlamydia psittaci

Protozoa
Trypanosoma cruzi
African trypanosomiasis
Toxoplasma
Amebiasis

Other Parasites
Toxocara canis
Trichinella spiralis

Fungi and Yeasts
Actinomyces
Coccidioides
Histoplasma
Candida

Toxin
Diphtheria
Scorpion

Drugs
Sulfonamides
Phenylbutazone
Cyclophosphamide
Neo-mercazole

Hypersensitivity/Autoimmunity
Rheumatoid arthritis
Rheumatic fever
Ulcerative colitis
Systemic lupus erythematosus

Other
Sarcoidosis
Scleroderma
Idiopathic
Cornstarch

From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

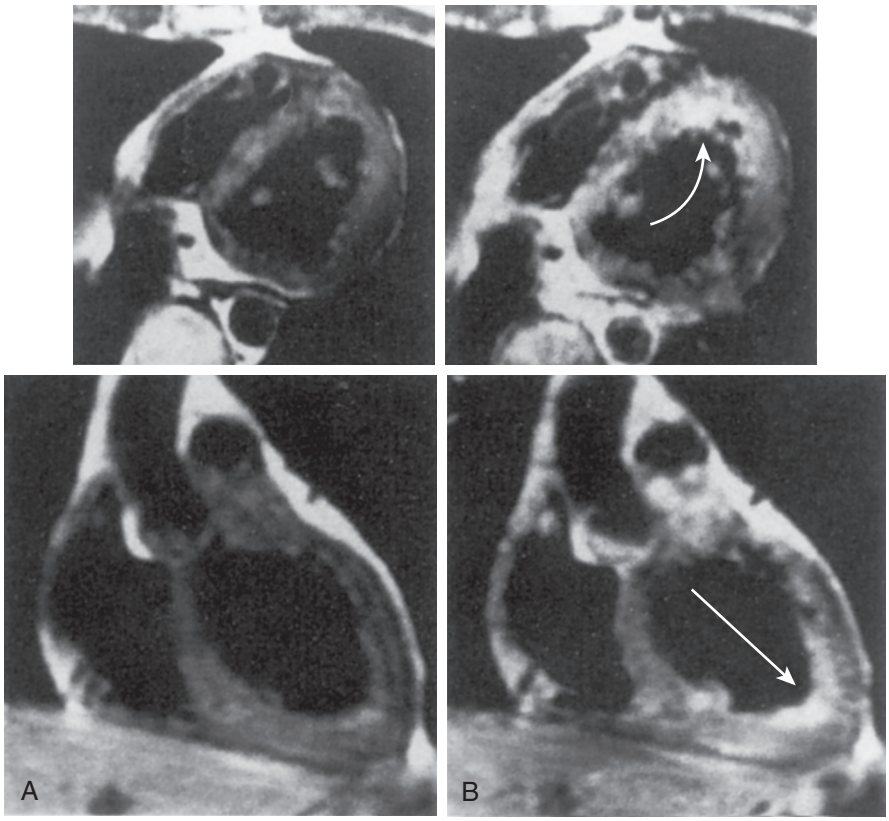

FIG. E1 A, Precontrast T1-weighted transaxial *(upper)* and coronal *(lower)* magnetic resonance images through the left ventricle in a patient with myocarditis. **B,** Postcontrast magnetic resonance images at the same levels after contrast injection. Note enhancement of the myocardial signal in the septum and apical region *(arrows)*. (From Zipes DP et al [eds]: *Braunwald's heart disease,* ed 7, Philadelphia, 2005, Saunders.)

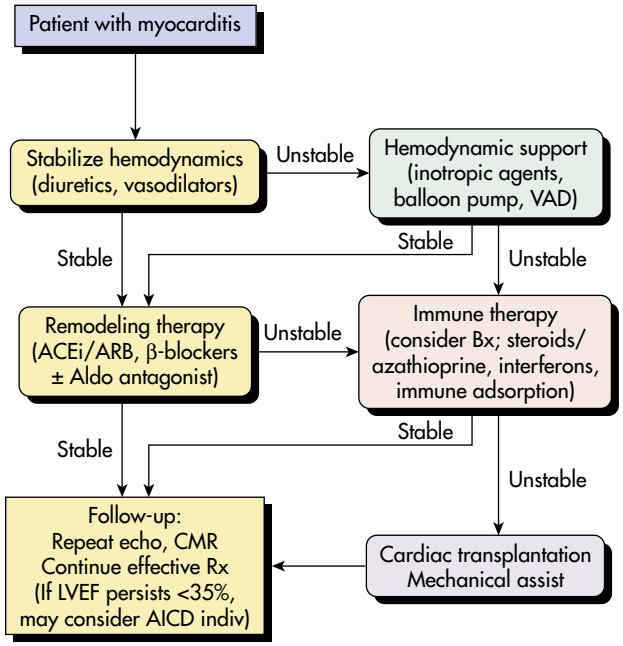

FIG. E2 Treatment algorithms for patients with myocarditis, depending on hemodynamic stability and response to general supportive and remodeling treatment regimen at each step. All patients require aggressive support and appropriate follow-up. Immune therapy at present is still indicated mainly to support those who have failed to improve spontaneously. *ACEi,* angiotensin-converting enzyme inhibitor; *AICD,* automatic implantable cardioverter-defibrillator; *Aldo,* aldosterone; *ARB,* angiotensin receptor blocker; *Bx,* biopsy; *CMR,* cardiac magnetic resonance; *echo,* echocardiography; *indiv,* based on individual assessment of risk versus benefit; *LVEF,* left ventricular ejection fraction; *VAD,* ventricular assist device. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Myoclonus is defined as a sudden, brief (<500 ms), involuntary movement of the extremities, face, or trunk. Positive myoclonus is caused by excessive muscle contraction, whereas negative myoclonus, asterixis, is due to a transient loss of postural tone. Myoclonus can be seen in a wide variety of neurologic and systemic disorders.

ICD-10CM CODE
G25.3 Myoclonus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1.3/100,000 persons
PREVALENCE: 8.6/100,000 persons
PREDOMINANT SEX & AGE: No gender preference; age at onset varies by the etiology of the myoclonus
GENETICS: Varies by etiology, can be hereditary or sporadic

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinically, myoclonus can be classified by its distribution: focal (only one body part involved), multifocal, segmental (spread to adjacent body parts), axial (muscles innervated by one or several spinal levels), or generalized. It can occur at rest, with maintenance of a posture, with action, or in response to an external stimulus (reflex myoclonus).
- Myoclonus can originate from the cerebral cortex, brain stem, spinal cord, or peripheral nerve. The causal location may not always influence the characteristics of the myoclonus.
- Negative myoclonus is typically seen in postural muscles of the limbs, causing a bobbing appearance. Asterixis is a form of negative myoclonus.

ETIOLOGY

- The causes of myoclonus are numerous and can be grouped into the categories of physiologic, essential, epileptic, and symptomatic.
- Physiologic myoclonus is a normal phenomenon and includes sleep (hypnic) jerks, hiccups (singultus), and exercise-induced myoclonus.
- Essential myoclonus occurs in the absence of other neurologic symptoms and is usually autosomal dominant. When dystonia is present, it is called myoclonus-dystonia. The myoclonus is often responsive to alcohol in this condition.
- In epileptic myoclonus, seizures dominate the clinical picture. Syndromes include infantile spasms and juvenile myoclonic epilepsy. Progressive myoclonic epilepsies are symptomatic myoclonus associated with some combination of seizures, ataxia, and dementia.
- Symptomatic or secondary myoclonus comprises myoclonus in the setting of an underlying neurologic or systemic disorder. The number of secondary causes prevents giving a full list, but common etiologies include neurodegenerative diseases (Alzheimer, atypical forms of parkinsonism), CNS infections (Creutzfeldt-Jakob disease, viral encephalitis), metabolic derangements (uremia, hepatic failure), as well as drug-induced (selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants [TCAs], lithium, stimulants, opioids, gabapentin), autoimmune, paraneoplastic, and post-hypoxic etiologies (myoclonic status epilepticus, Lance-Adams syndrome).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Tremor: A rhythmic oscillation around a point; slower than myoclonus
- Tic: A rapid, patterned movement that, unlike myoclonus, may be briefly suppressed voluntarily or may be accompanied by a premonitory urge
- Dystonia: Patterned contractions of agonist/antagonist muscles causing twisting or pulling; slower than myoclonus
- Chorea: Typically slower, more complex writhing, patterned movements
- Psychogenic myoclonus: Variable in duration and location, distractible, or entrainable

LABORATORY TESTS

- Evaluate for metabolic precipitants (renal and hepatic function, Mg, Ca, thyroid studies, ammonia)
- Toxicology screen (amphetamines, cocaine, opiates/opioids)
- Lumbar puncture if an infectious, inflammatory (including autoimmune), or paraneoplastic CNS process is suspected. Paraneoplastic antibody testing if clinically indicated (i.e., opsoclonus-myoclonus syndrome, limbic encephalitis)
- Electroencephalogram to evaluate for epileptic/cortical myoclonus
- Electromyography (EMG) may be useful in patients with psychogenic or mixed movement disorders, particularly to characterize subtle myoclonus from a coexistent tremor if there is clinical uncertainty

IMAGING STUDIES

MRI of the brain with and without gadolinium can evaluate for a structural lesion if the myoclonus is cortical. Creutzfeldt-Jakob disease can show diffusion weighted abnormalities in the striatum and/or cortical gray matter.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Treatment should be directed toward correcting the underlying cause if it is reversible (e.g., hepatic or renal failure).
- Carefully remove or decrease potentially causative medications.

ACUTE Rx

Following evaluation for systemic infections and metabolic derangements, myoclonus that is epileptic; interferes with respiration, swallowing, or walking; or causes other severe distress to the patient may be managed acutely with IV formulation antiepileptic drugs such as valproic acid, levetiracetam, or benzodiazepines (lorazepam or midazolam).

CHRONIC Rx

- Clonazepam (preferred over other benzodiazepines for its long half-life), valproic acid, and levetiracetam are typically used for all forms of myoclonus, and often combinations of these medications are more effective.
- If dystonia is present (myoclonus-dystonia), a trial of levodopa is worthwhile although only rarely effective. Anticholinergics may also help dystonia. Botulinum toxin is used for focal dystonia.
- Peripheral focal myoclonus (e.g., hemifacial spasm) can also be helped by botulinum toxin.

DISPOSITION

The ultimate prognosis depends on the etiology of the myoclonus.

REFERRAL

Referral to a general neurologist or movement disorders center is appropriate.

PEARLS & CONSIDERATIONS

COMMENTS

- When myoclonus is seen with parkinsonism, atypical forms of parkinsonism should be high on the differential, such as dementia with Lewy bodies, corticobasal syndrome, and multiple system atrophy. Myoclonus is only rarely seen in idiopathic Parkinson disease.
- Symptomatic palatal myoclonus is a specific syndrome that is often associated with a focal brain-stem lesion. In essential palatal myoclonus (no lesion), ear "clicking" is an additional symptom that is not seen in the symptomatic form.

AUTHORS: **Jennifer E. Vaughan, MD,** and **Andrew P. Duker, MD**

SUGGESTED READING

Lozsadi D: Myoclonus: a pragmatic approach, *Pract Neurol* 12:215-224, 2012.

Myofascial Pain Syndrome

BASIC INFORMATION

DEFINITION

- Myofascial pain syndrome is myalgia characterized by trigger point.
- Trigger point: Trigger points are discrete, focal, hyperirritable spots located in a taut band of skeletal muscle. They produce pain locally and in a referred pattern. Muscle involvement is asymmetric and focal.

SYNONYMS

Chronic myofascial pain
CMP

ICD-10CM CODE
M79.1 Myalgia, myofascial pain syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

Myofascial pain syndrome is a common painful muscle disorder which can affect any sex at any age. About 85% of the general population at some point suffers from it during their lifetime. It also coexists with other chronic pain conditions.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Regional body pain and stiffness; often muscles responsible for body posture are affected. Neck, upper back, and lower back muscles are commonly involved. The most commonly affected muscles are trapezius, scalene, infraspinatus, subscapularis, levator scapulae, piriformis, tensor fasciae latae, iliopsoas, gluteus, and quadratus lumborum. Pain is present at rest and with muscle movement
- Table E1 lists some distinguishing features of myofascial pain and fibromyalgia
- Limited range of motion and pain-related weakness of affected muscle
- Twitch response: Brisk contraction of a taut band of skeletal muscle fibers elicited by snapping palpation of a trigger point in that band producing a taut band
- One or more trigger points asymmetrical location
- Referred pain from a trigger point to a zone of reference, but not following dermatomal distribution
- Resolution of the symptoms with lidocaine injection of the trigger point

ETIOLOGY

- Etiology is unknown. There are several proposed histopathologic mechanisms to account for the development of trigger points, but they are lacking scientific evidence. Most researchers agree that acute trauma or repetitive microtrauma may lead to the development of a trigger point.
- Fig. E1 lists causes of myofascial pain and dysfunction.
- Lack of exercise, prolonged poor posture, vitamin deficiencies, sleep disturbances, and joint problems may all predispose to the development of microtrauma.

TABLE E1 Distinguishing Features of Myofascial Pain and Fibromyalgia

	Myofascial Pain	Fibromyalgia
Age distribution	20-40 yr	20-50 yr
Gender distribution	Mainly women	Mainly women
Distribution of pain	Localized; usually unilateral	Generalized; bilaterally symmetric
Tender points	Few	Multiple
Trigger points	Uncommon	Common
Fatigue	Localized muscle fatigue	Generalized fatigue
Sleep disturbance	Common	Common

From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, WB Saunders.

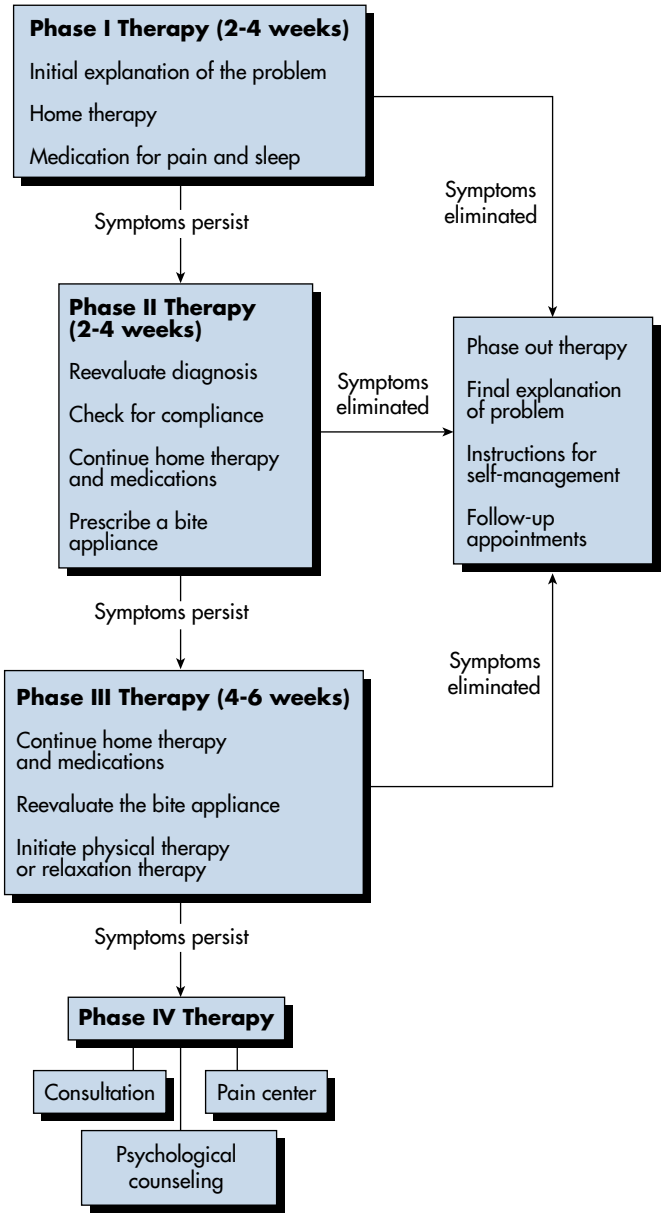

FIG. E1 Management of myofascial pain and dysfunction. Treatments are divided into four phases. If the symptoms are eliminated in any of the first three phases, the ongoing therapy is gradually phased out, and the patient is instructed in continued self-management of the condition. (Modified from Laskin DM, Block S: Diagnosis and treatment of myofascial pain-dysfunction [MPD] syndrome, *J Prosthet Dent* 56:75-84, 1986.)

DIAGNOSIS

A detailed physical examination and clinical presentation usually make the diagnosis of myofascial pain syndrome.

DIFFERENTIAL DIAGNOSIS

- Fibromyalgia
- Polymyositis
- Migraine
- Tension headache
- Muscle strain
- Bursitis and tendinitis
- Radiculopathies

WORKUP

Not indicated usually, treatment can be started on clinical grounds alone.

LABORATORY TESTS

Generally not indicated, except to exclude other causes of myalgia.

IMAGING STUDIES

Generally not indicated in clear-cut cases of myofascial pain syndrome. Indicated only to exclude other causes of pain (e.g., referred pain).

TREATMENT

- Spray and stretch therapy: Involves passive stretching of the affected muscle. Position patient for maximum decrease in muscle tension, identify trigger points, and mark them. Apply vapocoolant spray over entire length of the affected muscle. Passively stretch muscle by applying gentle pressure.
- Physical therapy: TENS unit, ultrasound, massage therapy, myofascial release technique.
- Invasive technique: Trigger point injection with 1% lidocaine is the most commonly used technique.
- NSAIDs and muscle relaxants: Short-term use.
- Fig. E2 shows the management of myofascial pain and dysfunction.

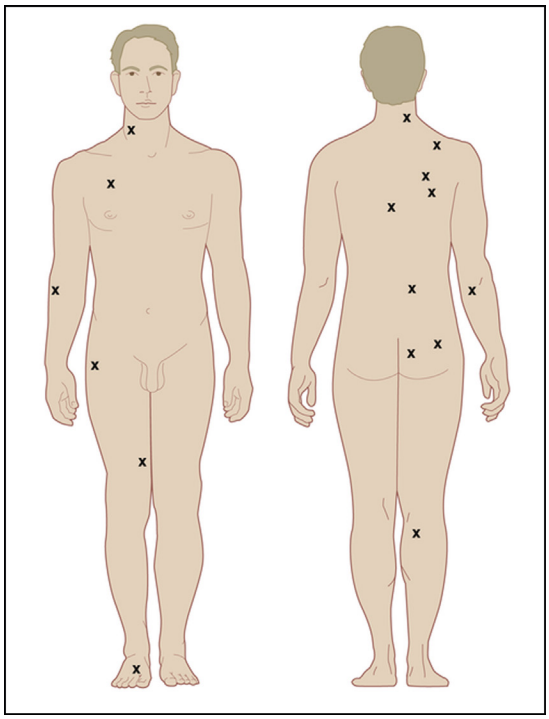

FIG. E2 Most frequent locations of myofascial trigger points. (Adapted from Rachlin E, Rachlin I: *Myofascial pain and fibromyalgia: trigger point management,* ed 2, St Louis, 2002, Mosby.)

REFERRAL

An interventional pain management referral is made if trigger point injection is indicated. To physical therapist for increasing range of motion and massage therapy.

PEARLS & CONSIDERATIONS

- Trigger point is commonly misdiagnosed as tender point, which is characteristic finding of fibromyalgia.
- Tender point: Characterized as non-palpable nodule with symmetric and multiple locations. Tender points are located close to muscle attachment, usually not associated with specific muscle activity. Lacking twitch response and relief of symptoms with localized lidocaine injection.

AUTHORS: **Uzma Nasir, MD,** and **Syeda M. Sayeed, MD**

SUGGESTED READINGS

Karadaş Ö et al: Lidocaine injection of pericranial myofascial trigger points in the treatment of frequent episodic tension-type headache, *J Headache Pain* 14(44), 2013.

Tsai CT et al: Remote effects of dry needling on the irritability of the myofascial trigger point in the upper trapezius muscle, *Am J Phys Med Rehabil* 89(2):133-140, 2010.

Myotonia

BASIC INFORMATION

DEFINITION

Myotonia is a type of muscular dystrophy in which relaxation of a muscle after contraction is delayed or prolonged. The most common type of muscular dystrophy with myotonia is myotonic dystrophy. The nondystrophic myotonias (NDMs) are rare disorders (prevalence 1:100,000) caused by mutations in skeletal muscle chloride and sodium channels with the common clinical feature of myotonia without muscle wasting.

SYNONYM

Myotonic dystrophy

ICD-10CM CODES	
G71.1	Myotonic disorders
M62.89	Other specified disorders of muscle
M62.40	Contracture of muscle, unspecified site
G71.12	Myotonia congenita
G71.14	Drug induced myotonia

EPIDEMIOLOGY & DEMOGRAPHICS

- Three to five cases/100,000 persons
- Genetic disorder inherited as an autosomal-dominant illness
- Symptoms usually manifest during adolescence or early adulthood. Cases of infantile myotonic dystrophy have been described

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usual first symptom is distal extremity weakness sometimes associated with muscle stiffness, cramps, or difficulty relaxing grasp (Fig. E1).
- Weakness spreads to eventually involve all muscle groups. Flexor neck muscle weakness and masseter and temporal wasting are often prominent features, as is dysarthria.
- Percussion of a muscle produces a slow contraction followed by prolonged relaxation. The myotonic reflex is best tested by percussing the thenar muscles and observing a slow flexion followed by slow relaxation of the thumb.
- As the disease progresses, generalized weakness becomes more pronounced, and myotonia becomes less evident.
- Extramuscular involvement:
  1. Mental retardation of variable severity (may be absent)
  2. Frontal baldness (Fig. E2, Fig. E3)
  3. Cataracts
  4. Diabetes mellitus
  5. Hypogonadism
  6. Adrenal failure
  7. Cardiomyopathy
- Infantile myotonic dystrophy presents as neonatal extreme hypotonia with "shark mouth" deformity (upper lip forming an inverted V).

FIG. E1 Grip myotonia in myotonic dystrophy. The patient is unable to fully open the hand **(A)** after exerting a grip **(B).** (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

FIG. E2 Myotonic muscular dystrophy (DM1). Findings in a patient with myotonic muscular dystrophy include wasting of the temporal muscles (shown) and male-pattern baldness that began at an early age. These patients may also have weakness of other facial muscles and micrognathia. (Courtesy Dr. Meir H. Kryger. From Kryger M et al: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.)

ETIOLOGY & PATHOGENESIS

Genetic disorder encoded on chromosome 19 leading to sustained firing of the muscle membrane, causing prolonged muscle contraction. Myotonic dystrophy 1 (the more common form) is caused by an expanded CTG repeat within the noncoding 3′ untranslated region of the myotonic dystrophy protein kinase *(DMPK)* gene. The less common form (myotonic dystrophy 2) is caused by an expanded CCTG repeat in the first intron of the zinc finger protein 9 *(ZNF9)* gene.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The disease is limited to muscles and causes hypertrophy and stiffness after rest. Muscle function normalizes with exercise. There is no weakness. Symptoms are exacerbated by exposure to cold.

- Myotonia congenita (Thomsen disease)
- May be autosomal dominant or recessive (two distinct varieties)
- Paramyotonia congenita (autosomal-dominant disease): Weakness and stiffness of facial muscles and distal upper extremities, especially or exclusively on cold exposure
- Muscular dystrophies
- Inflammatory myopathies (polymyositis)
- Metabolic muscle diseases
- Myasthenic syndromes
- Motor neuron disease

WORKUP

- History and physical examination usually sufficient

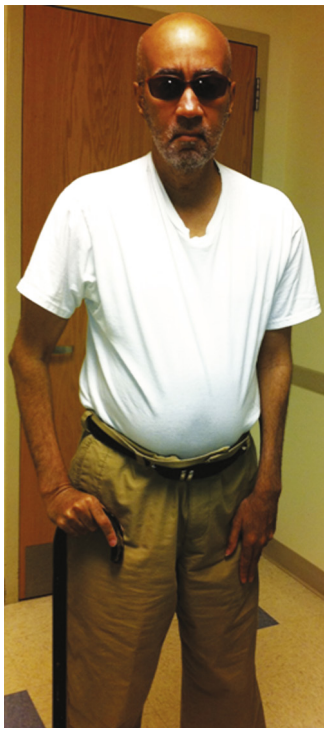

FIG. E3 The patient is a 54-year-old man with myotonic dystrophy type 1. Typical characteristics of balding, thin face, and distal muscle atrophy are evident. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

- Muscle enzymes usually abnormal (creatine phosphokinase, aldolase, aspartate aminotransferase)
- Electromyography: Typical myotonic "dive bomber" bursts
- Muscle biopsy: Type I fiber atrophy, ring fibers, increased central nucleation

Rx TREATMENT

- Phenytoin
- Quinine
- Quinidine
- Procainamide
- Acetazolamide
- Genetic counseling
- Assistive devices, orthotics
- The use of mexiletine resulted in improvement of patient-reported stiffness in patients with nondystrophic myotonias[1]

[1]Statland JM et al: Mexiletine for symptoms and signs of myotonia in nondystrophic myotonia, *JAMA* 308(13): 1357-1365, 2012.

DISPOSITION

- In myotonic dystrophy, death is usually caused by the wasting of skeletal muscle and defects in cardiac function.
- Among patients with myotonic dystrophy type 1, an invasive strategy based on systemic electrophysiological studies and prophylactic permanent pacing is associated with longer survival than a noninvasive strategy.[2]

REFERRAL

- To neurologist
- To physical therapy

AUTHOR: **Fred F. Ferri, MD**

[2]Wahbi K et al: Electrophysiological study with prophylactic pacing and survival in adults with myotonic dystrophy and conduction system disease, *JAMA* 307(12):1292-1301, 2012.

Myxedema Coma (PTG)

BASIC INFORMATION

DEFINITION

Myxedema coma is a rare life-threatening complication of hypothyroidism characterized by profound lethargy or coma and usually accompanied by hypothermia.

ICD-10CM CODES

E03.5 Myxedema coma
E03.8 Other specified hypothyroidism
E03.9 Hypothyroidism, unspecified

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Mental obtundation, profound lethargy or coma
- Hypothermia (rectal temperature <35° C [95° F]); often missed by using ordinary thermometers graduated only to 34.5° C (94.1° F) or because the mercury is not shaken below 36° C (96.8° F)
- Bradycardia, hypotension (attributable to circulatory collapse)
- Delayed relaxation phase of deep tendon reflexes, areflexia
- Myxedema facies (Fig. E1)
- Alopecia, macroglossia, ptosis, periorbital edema, nonpitting edema, doughy skin
- Bladder dystonia and distention
- Pleural, pericardial, and peritoneal effusions

ETIOLOGY

Decompensation of hypothyroidism from:

- Sepsis
- Exposure to cold weather
- Central nervous system depressants (sedatives, narcotics, antidepressants)
- Trauma, surgery
- Stroke, congestive heart failure, burns
- Intravascular volume contraction (GI blood loss, diuretic use)
- Myocardial infarction
- Metabolic derangements

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Severe depression, primary psychosis
- Drug overdose
- Cerebrovascular accident, liver failure, renal failure
- Hypoglycemia, CO_2 narcosis, encephalitis

WORKUP

Diagnosis of hypothyroidism and exclusion of contributing factors (e.g., sepsis, cerebrovascular accident) with laboratory and radiographic studies (see "Laboratory Tests")

LABORATORY TESTS

- Serum thyroid stimulating hormone and T_4 levels should be tested immediately. Results reveal markedly increased thyroid-stimulating hormone (if primary hypothyroidism), decreased serum free T_4
- Complete blood count with differential, urine and blood cultures to rule out infectious process
- Electrolytes, blood urea nitrogen, creatinine, liver function tests, calcium, glucose
- Arterial blood gases to rule out hypoxemia and carbon dioxide retention
- Stat cortisol level to rule out concomitant adrenal insufficiency prior to initiation of thyroid hormone replacement
- Elevated creatine phosphokinase may be present
- Hyperlipidemia is common

IMAGING STUDIES

- CT scan of head in suspected cerebrovascular accident
- Chest x-ray to rule out infectious process

TREATMENT

NONPHARMACOLOGIC THERAPY

- Prevent further heat loss; cover the patient but avoid external rewarming because it may produce vascular collapse. Consider warmed IV fluids.
- Support respiratory function; intubation and mechanical ventilation may be required.
- Monitor patient in the intensive care unit.

ACUTE GENERAL Rx

- Give levothyroxine 5 to 8 mcg/kg (200 to 500 mcg) IV infused over 15 min, then 50 to 100 mcg IV q24h until transition to an oral formulation is possible. Oral daily dose following IV administration is 1.6 mcg/kg. Lower doses may be indicated in patients with cardiac disease or advanced age.
- Glucocorticoids should also be empirically administered until coexistent adrenal insufficiency can be ruled out. Hydrocortisone hemisuccinate 100 mg IV bolus is initially given, followed by 100 mg IV q8h until initial plasma cortisol level is confirmed normal.
- IV hydration with D_5NS is used to correct hypotension and hypoglycemia (if present); avoid overhydration and possible water intoxication because clearance of free water is impaired in these patients.
- Rule out and treat precipitating factors (e.g., antibiotics in suspected sepsis).

CHRONIC Rx

Refer to "Hypothyroidism" in Section I.

DISPOSITION

Mortality rate in myxedema coma is high, up to 40% despite aggressive therapy.

REFERRAL

Endocrinology consultation

PEARLS & CONSIDERATIONS

COMMENTS

If the diagnosis is suspected, initiate treatment immediately without waiting for confirming laboratory results.

RELATED CONTENT

Hypothyroidism (Patient Information)
Hypothyroidism (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

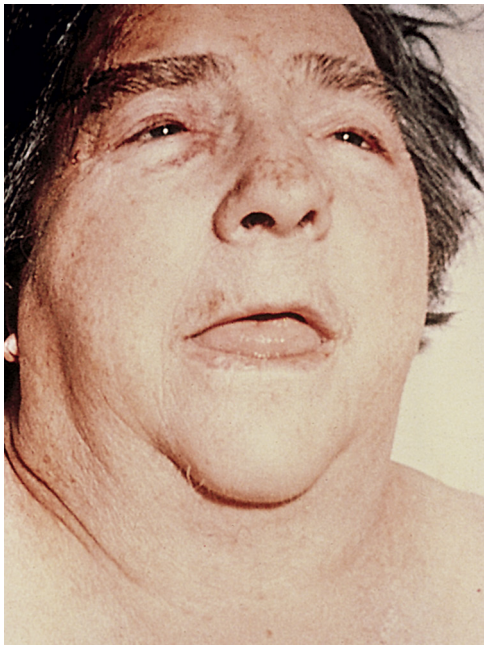

FIG. E1 Myxedema facies. Note dull, puffy, yellowed skin; coarse, sparse hair; temporal loss of eyebrows; periorbital edema; and prominent tongue. (Courtesy Paul W. Ladenson, MD, The Johns Hopkins University and Hospital, Baltimore, MD. In Seidel HM [ed]: *Mosby's guide to physical examination,* ed 5, St Louis, 2004, Mosby.)

BASIC INFORMATION

DEFINITION

Narcissistic personality disorder (NPD) is characterized by a pattern of grandiosity, need for admiration, and lack of empathy that begins by early adulthood and causes significant distress or impairment in multiple domains of functioning. The individual must meet five or more of the following criteria, each of which should be enduring and pervasive across contexts:

- Grandiose sense of self-importance. For example, the person may exaggerate achievements and talents or expect recognition as superior without commensurate achievements.
- Preoccupied with fantasies of unlimited success, power, brilliance, beauty, or ideal love.
- Views self as "special" and unique and should only associate with other special or highly regarded people and institutions.
- Requires excessive admiration.
- Sense of entitlement. For example, unreasonable expectations of especially favorable treatment or automatic compliance with his or her expectations.
- Interpersonally exploitative.
- Lacks empathy: Unwilling to recognize or identify with the feelings or needs of others.
- Often envious of others or believes others envious of him or her.
- Shows arrogant or haughty behaviors.

SYNONYM

NPD

ICD-10CM CODE
F60.81 Narcissistic personality disorder
DSM-5 CODE
301.81 Narcissistic personality disorder

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Less than 1% of the general population; estimates range from 2% to 6% in the clinical population
PREDOMINANT SEX: More commonly diagnosed in males (up to 3:1)
PREDOMINANT AGE: 20s and 30s

CLINICAL PRESENTATION

- Patients have an underlying sense of inferiority and inadequacy, despite outward behavior that suggests high self-regard.
- To avoid these beliefs and their associated painful effects, patients seek to convince self and others that they are special, the best, or unusually talented.
- They are astutely aware of status and "pecking order."
- Vulnerability in self-esteem makes these patients exquisitely sensitive to criticism, defeat, or perceived weakness, which in turn can lead to feeling humiliated, degraded, and empty.
- These patients react to perceived slights either with more intense grandiosity and admiration-seeking or with disdain and rage. Either approach seeks to bolster their sense of self, often by devaluing or criticizing the other person.
- Experiences of self-deflation can lead to social withdrawal, depressed mood, or feigned humility that can obscure the grandiosity.
- Interpersonal relationships are typically shallow and limited.
- Although ambition and confidence may lead to high achievement, vocational functioning may be disrupted by intolerance for criticism.

ETIOLOGY

- Twin studies suggest high heritability—up to 80%.
- Classic hypotheses focus on impaired development of self as "worthy" because of insufficient affirmation and warmth from parents.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Mania and hypomania
- Dysthymia and major depressive episode
- Substance-induced euphoria, especially cocaine abuse
- Histrionic, borderline, antisocial, and paranoid personality disorders share common features and are often comorbid
- Personality changes from a general medical condition, including central nervous system processes in the frontal-temporal regions of the brain

WORKUP

- History: Collateral information essential to establishing presence of long-standing interpersonal pattern in multiple domains of the patient's life
- Physical examination
- Mental status examination

LABORATORY TESTS

Tests necessary to rule out medical causes of personality changes

IMAGING STUDIES

Those necessary to rule out medical causes of personality changes

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral therapy to help patients control rage, manage perceived criticism, and develop social skills
- Psychodynamic psychotherapy to help develop improved self-concept, affect tolerance, and interpersonal functioning
- Guidelines for general management of the patient with NPD:
  1. Be respectful and nonconfrontational.
  2. Help patient use self-perceived talents in the service of treatment.
  3. Do not take the patient's criticism personally, but understand it as the patient attempting to manage his or her own intense insecurity.
  4. Appeal to the patient's narcissism strategically. For example, agree with the patient that he or she is "entitled" to appropriate care and cite "top authorities" to support evidence-based care.

ACUTE GENERAL Rx

Benzodiazepines or low-dose antipsychotics for acute aggressive behavior, which is higher risk in NPD comorbid with impulsive disorders such as borderline or antisocial personality disorder

CHRONIC Rx

There is no evidence for specific pharmacologic treatment for NPD, so any medications used should target comorbid symptoms, such as selective serotonin reuptake inhibitors for depression.

COMPLEMENTARY & ALTERNATIVE MEDICINE

No evidence of efficacy in NPD

DISPOSITION

- Severity is variable, and course is chronic. The majority of patients obtain greater functioning in fifth decade and beyond when pessimism replaces grandiosity. Often lifelong difficulty maintaining intimate relationships.
- At increased risk for major depressive disorder and substance abuse or dependence (especially cocaine).

REFERRAL

If pharmacotherapy or psychotherapy is indicated

PEARLS & CONSIDERATIONS

COMMENTS

- Medical illness threatens these patients' image of superiority.
- To defend against this threat, patients may minimize symptoms or deny presence of illness.
- Patients will commonly demand special treatment from senior and well-known physicians.
- Patients may devalue, criticize, or question the behavior or credentials of the treating physician.

RELATED CONTENT

Narcissistic Personality Disorder (Patient Information)

AUTHORS: **Timothy R. Kreider, MD, PhD,** and **John Q. Young, MD, MPP, PhD**

SUGGESTED READINGS

American Psychiatric Association: *Diagnostic and statistical manual of mental disorders*, ed 5, Arlington, VA, 2013, American Psychiatric Publishing.

Angstman KB, Rasmussen NH: Personality disorders: review and clinical application in daily practice, *Am Fam Phys* 84(11):1253-1260, 2011.

Roepke S, Vater A: Narcissistic personality disorder: an integrative review of recent empirical data and current definitions, *Curr Psychiatry Rep* 6(5):445, 2014.

BASIC INFORMATION

DEFINITION

Narcolepsy is a chronic neurologic sleep disorder characterized by excessive daytime sleepiness and dysregulation of rapid eye movement (REM) sleep. It is the second most common cause of disabling daytime sleepiness after obstructive sleep apnea. Symptoms of REM sleep dysregulation include cataplexy, sleep paralysis, and hallucinations during transition between wake and sleep. Difficulty sleeping with either frequent awakenings or disrupted sleep may also occur. An international classification of sleep disorders is summarized in Table 1.

SYNONYMS

Hypersomnia of central origin
Narcolepsy with cataplexy
Narcolepsy-cataplexy syndrome
Narcolepsy with hypocretin deficiency
Gélineau syndrome

ICD-10CM CODES

G47.411 Narcolepsy with cataplexy
G47.419 Narcolepsy without cataplexy

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.74/100,000 persons/yr
PREVALENCE: 1 in 2000 people
PREDOMINANT SEX: Males and females equally affected
AGE OF ONSET: Peak 15 to 30 yr (range, 10 to 55 yr)
GENETICS:

- Associated with human leukocyte antigen (HLA) subtypes, specifically, *DQB1*0602,* which is present in 95% of patients with cataplexy and 96% of patients with hypocretin deficiency.
- Risk of narcolepsy increases 20 to 40 times if a family member is affected.
- Monozygotic twin concordance rate is 17% to 36%, thus indicating an incomplete penetrance and suggesting an environmental factor in the disease process.

RISK FACTORS: Anesthesia, head injury, history of meningitis or encephalitis, family history of narcolepsy, tumor, vascular malformations, stroke, and obesity.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Overwhelming urge to sleep with chronic hypersomnia may occur during the day.
- Cataplexy occurs in 60% to 100% of patients with narcolepsy and is reported as a partial or complete loss of voluntary muscle control with preserved consciousness that is precipitated by a strong emotion, more commonly with laughter. This is the most specific symptom and is considered pathognomonic for narcolepsy.
- Hypnagogic (wake to sleep) or hypnopompic (sleep to wake) hallucinations have been reported in 60% to 80% of patients with narcolepsy.
- Sleep paralysis, defined as loss of muscle tone during the transition between sleep and wakefulness, occurs in 60% to 80% of patients with narcolepsy. It may occur with hallucinations and can be interrupted by sensory stimuli.
- Only about one third of patients will have all four symptoms of narcolepsy: Chronic daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis.
- Fragmented sleep is seen in 60% to 80% of narcolepsy patients and can often be mistaken for insomnia or other intrinsic sleep disorder.
- Other symptoms that have been reported in narcolepsy include automatic behavior or semipurposeful movements in 40% of patients and memory disturbance in 50% of patients.

ETIOLOGY

The loss of hypocretin/orexin signaling, genetic factors, and brain lesions are presently identified factors in the development of narcolepsy. May be a manifestation of neuromyelitis optica spectrum disorder.

TABLE 1 International Classification of Sleep Disorders: Definitions and Pathophysiology

Condition	Diagnostic Criteria*	Pathophysiology
Type 1 narcolepsy	Presence of two or more of the following: Cataplexy, positive MSLT, and low CSF hypocretin-1	Hypocretin deficiency 98% HLA-DQB1*06:02
Type 2 narcolepsy	Positive MSLT; most often with no or unclear cataplexy	Unknown, heterogenous ~16% Hypocretin deficiency ~40% HLA-DQB1*0602
Secondary narcolepsy	As above, but due to neurologic conditions	With or without hypocretin deficiency, various disorders
Idiopathic hypersomnia	No cataplexy, no SOREMPs during the MSLT	Unknown, likely heterogeneous

*Abnormal Multiple Sleep Latency Test (MSLT): Sleep latency ≤8 min, ≥2 sleep-onset REM periods (SOREMPs), including a nocturnal SOREMP. For details, see *International Classification of Sleep Disorders*, third edition. (American Academy of Sleep Medicine: *International classification of sleep disorders*, ed 3, Darien, IL, 2014, American Academy of Sleep Medicine.)
CSF, Cerebrospinal fluid.
From Kryger M, Roth T, Dement WC et al: *Principles and practice of sleep medicine*, ed 6, Philadelphia, 2017, Elsevier.

HYPOCRETIN/OREXIN:

- Loss of hypocretin-1 and hypocretin-2 (also known as orexin-A and orexin-B) producing neurons in the lateral hypothalamus.
- Human cerebrospinal fluid (CSF) levels of hypocretin-1 are low to undetectable in narcoleptics with cataplexy.
- Narcolepsy without cataplexy may have a different cause because CSF hypocretin levels are usually normal in these patients, so there may be a completely separate mechanism in these patients, or it may result from less extensive loss of hypocretin neurons or impaired signaling.

SECONDARY ETIOLOGIES:

- Central nervous system lesions including tumors, vascular malformations, and strokes have all been reported to cause secondary narcolepsy.
- Direct injury to the hypocretin neurons or their projections is the most likely cause of secondary narcolepsy due to central nervous system lesions.
- Narcolepsy has been reported in genetic syndromes, including Prader-Willi syndrome and Niemann-Pick disease type C, as well as neuromyelitis optica spectrum disorder and paraneoplastic syndromes.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Excessive daytime somnolence:

- Autism
- Autosomal dominant cerebellar ataxia, deafness, and narcolepsy
- Behaviorally induced insufficient sleep syndrome
- Central or obstructive sleep apnea (sleep-disordered breathing)
- Circadian rhythm disorder
- Depression
- Diencephalic lesions
- Drug or alcohol abuse
- Hypothyroidism
- Idiopathic hypersomnia with long or short sleep time
- Inadequate sleep hygiene
- Insufficient sleep
- Increased intracranial pressure

Insomnia:

- Kleine-Levin syndrome
- Medication effect
- Menstrual-related hypersomnia
- Posttraumatic narcolepsy
- Seizures
- Sleep fragmentation (multiple causes)

Cataplexy:

- Seizures
- Periodic paralysis
- Cardiovascular insufficiency
- Psychogenic (multiple causes)
- Lesions of the hypothalamus or brain stem

WORKUP

- Because persistent sleepiness can occur with many conditions, it is important to rule out other sleep disorders.

- Narcolepsy is often diagnosed by clinical history. The Epworth Sleepiness Scale is very useful in determining the degree of excessive daytime sleepiness (Table 2).
- The diagnosis of narcolepsy can be made without the need for further testing if there is a clear history of cataplexy in the setting of excessive daytime somnolence. Sleep laboratory testing is otherwise necessary if cataplexy does not exist, if a diagnosis needs to be confirmed, or if concerns exist for another sleep disorder.
- The medical history should include questions regarding severity of daytime hypersomnia while also evaluating for sleep-disordered breathing, transient muscle weakness triggered by emotion, hallucinations while falling asleep or upon awakening, and inability to move after awakening. The clinical evaluation should also address symptoms of seizures and paraneoplastic disorders while also asking about previous stroke or genetic disorders. A detailed family history is imperative. Hypothalamic dysfunction such as unexplained weight gain, endocrine abnormalities, circadian dysrhythmias, and autonomic nervous system problems may provide useful insight.
- A thorough examination including a detailed neurologic examination should be performed.
- Nocturnal polysomnography followed by a multiple sleep latency test (MSLT) remains the gold standard for the diagnosis of narcolepsy. A drug screen should also be performed to rule out pharmacologic modulations of sleep.

LABORATORY TESTS

None

Rx TREATMENT

Narcolepsy can be treated with a combination of behavioral and pharmacologic approaches. Examples of initial treatment packages for adults are summarized in Table 3.

NONPHARMACOLOGIC THERAPY

Avoidance of over-the-counter drugs and illicit drugs, optimal sleep hygiene and scheduled daily naps, and psychosocial support can be used for symptoms of excessive daytime somnolence. However, nonpharmacologic therapy is typically not sufficient for treatment of narcolepsy alone but is often used as adjunct therapy with medications.

PHARMACOLOGIC THERAPY (TABLE 4)

For excessive daytime somnolence:

- Sodium oxybate: A central nervous system depressant that can be used for the treatment of cataplexy and REM-related symptoms
- Modafinil 200 to 600 mg PO every morning or divided bid
- Armodafinil 150 or 250 mg PO as a single dose in the morning
- Methylphenidate 5 to 15 mg PO bid to tid

TABLE 2 Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent time. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation.

0 = Would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

Situation	Chance of Dozing
Sitting and reading	
Watching TV	
Sitting and inactive in a public place (theater or meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch (without alcohol)	
In a car, while stopped for a few minutes in traffic	
Total	

From Johns MW: A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale, *Sleep* 14:540-545, 1991.

TABLE 3 Examples of Initial Treatment Packages for Adults

General Measures

Avoid shifts in sleep schedule
Avoid heavy meals and alcohol intake
Regular timing of nocturnal sleep: 10:30 P. M. to 7 A. M.
Naps: Strategically timed naps if possible (e.g., 15 min at lunchtime, 15 min at 5:30 P. M.)

Medications for Sleepiness

The effects of stimulant medications vary widely among patients. The dosing and timing of medications should be individualized to optimize performance. Additional doses, as needed, may be suggested for periods of anticipated sleepiness.

Modafinil* 100-200 mg (taken when waking up in the morning) and 100-200 mg at lunchtime *or*
Sodium oxybate† at bedtime: Dosage must start low at 2.25 g taken twice while in bed (at bedtime and 2.5-4 hr after bedtime); increase to total dosage of 5-6 g within 2-4 wk. This initial dose is usually ineffective, so increase to 3 g at bedtime and 3 g approximately 2.5-4 hr after bedtime if tolerated. Depending on response, dosage can be increased to as high as 9 g total nightly dose. Do not increase above 9 g because of risk of serious side effects during sleep. It may take more than 2 mo for daytime symptoms to improve, and cataplexy ma improve faster than excessive daytime sleepiness. If the patient is already taking a daytime stimulant, it may be possible to reduce the stimulant dose or to discontinue it once a therapeutic dosage of sodium oxybate has been reached.
Methylphenidate 5 mg (three or four tablets; 10 mg when waking up; 5 mg 30 min before lunch; 5 mg near 3 P. M.; better action is always obtained if the drug is taken on an empty stomach) or 20 mg SR in the morning (on an empty stomach)

If Persistent Difficulties

Modafinil 200 mg in the morning and 200 mg at lunch (total daily dosage, 400 mg) *or*
Add sodium oxybate (GHB) at bedtime: Dosage must start low as indicated above.
Methylphenidate (SR): 20 mg in the morning; 5 mg after noon nap; 5 mg at 4 P. M. *or*
Possibly (more in teenagers) atomoxetine: Start at 0.5 mg/kg within 1 wk to appropriate dosage of 1-1.2 mg/kg taken in the morning

If No Response

Dextroamphetamine sulfate: 15 mg on awakening; 5 mg after noon nap; 5 mg at 3:30 or 4 P. M. (or 15 mg at awakening and 15 mg after noon nap)

Medications for Cataplexy‡

Sodium oxybate (see above)
Venlafaxine 150-300 mg
Fluoxetine 20-60 mg
Duloxetine 60 mg

If No Response

Clomipramine 75-125 mg, *or*
Viloxazine 150-200 mg, *or*
Imipramine 75-125 mg

SR, Sustained-release tablet.
*Modafinil works best in naive subjects. It should be the drug of first choice in children and adults.
†Response to sodium oxybate is slow.
‡Medications may be taken in the evening near bedtime (sodium oxybate, clomipramine, imipramine), only in the morning (fluoxetine), or in the morning and at lunchtime (viloxazine, venlafaxine). The only medications specifically approved for use in narcolepsy by the Food and Drug Administration are modafinil and sodium oxybate.
From Kryger M et al: *Principles and practice of sleep medicine*, ed 6, Philadelphia, 2017, Elsevier.

TABLE 4 Narcolepsy Drugs Currently Available

Drug	Usual Dosage* (All Drugs Administered Orally)
Treatment of EDS	
Stimulants†	
Modafinil	100-400 mg/day
Sodium oxybate	6-9 g/day (divided in two doses)
Methylphenidate	10-60 mg/day
Atomoxetine	10-25 mg/day
Dextroamphetamine	5-60 mg/day
Methamphetamine	20-25 mg/day
Treatment of Auxiliary Effects (e.g., Cataplexy)	
Sodium oxybate (gamma-hydroxybutyrate)	6-9 g/day (divided in two doses)
Antidepressants	
Without Atropinic Side Effects	
Venlafaxine XR	75-300 mg/day
Fluoxetine	20-60 mg/day
Viloxazine	50-200 mg/day
Duloxetine	60 mg/day
With Atropinic Side Effects	
Protriptyline	2.5-20 mg/day
Imipramine	25-200 mg/day
Clomipramine	25-200 mg/day
Desipramine	25-200 mg/day

*On occasion, depending on clinical response, the dose may be outside the usual dosage range.

†Most stimulants should be administered in divided doses, commonly in the morning and at lunchtime. This is recommended for amphetamines and modafinil. Methylphenidate has a fast elimination rate, so the slow-release (SR) formula may be helpful in the morning (e.g., 20 mg SR). If it is administered by 5-mg increments, the usual timing of methylphenidate administration is every 3 to 4 hr until 3 p.m.

EDS, Excessive daytime somnolence. From Kryger M, Roth T, Dement WC: *Principles and practice of sleep medicine*, ed 6, Philadelphia, 2017, Elsevier.

- Methylphenidate SR 18 to 54 mg PO every morning or divided bid
- Dextroamphetamine 10 to 60 mg PO qd
- Eldepryl 5 mg PO bid

For cataplexy:

- Sodium oxybate: A central nervous system depressant that can be used for the treatment of cataplexy and rapid eye movement (REM) related symptoms
- Fluoxetine 20 mg PO qd initially
- Sertraline 25 mg PO qd initially
- Venlafaxine 25 mg PO qd initially
- Clomipramine 25 mg/day initially
- Protriptyline 5 mg tid initially
- Imipramine 25 to 50 mg/day initially
- Desipramine 10 mg bid initially

DISPOSITION

This is a chronic sleep disorder that may worsen for the first few years and then persist for life.

REFERRAL

Because of the complexity of this disorder and its ever-changing management and treatment, patients should be referred to centers or programs with highly trained sleep specialists with expertise caring for these patients, especially if sodium oxybate (Xyrem) therapy is needed.

PEARLS & CONSIDERATIONS

Many narcoleptics report the onset of symptoms beginning in childhood to early adulthood, with a long delay of actual diagnosis on the order of 10 to 15 yr. Typically, excessive daytime sleepiness is the initial symptom, followed by REM dysregulation (e.g., cataplexy, sleep paralysis, hypnagogic hallucinations). Patients with narcolepsy also have higher than expected incidence of other sleep disorders, including obstructive sleep apnea, periodic limb movements of sleep, and REM sleep behavior disorder.

COMMENTS

Narcolepsy is a rare disorder that is underdiagnosed. The average time from onset of symptoms to diagnosis is 5 to 15 yr. Cataplexy is specific for narcolepsy, but other symptoms of REM dysregulation, including sleep paralysis and hypnagogic or hypnopompic hallucinations, can occur even in normal patients. Sleep-onset REM or REM periods on an MSLT may occur as a result of sleep deprivation or withdrawal from REM-suppressing drugs.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Narcolepsy (Patient Information)

AUTHOR: **Don Hayes, Jr., MD, MS, MEd**

SUGGESTED READINGS

Alshaikh MK et al: Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis, *J Clin Sleep Med* 8(4):451-458, 2012.

Branch AF et al: Progressive loss of the orexin neurons reveals dual effects on wakefulness, *Sleep* 39(2):369-377, 2016.

Cipolli C et al: Overnight distribution and motor characteristics of REM sleep behaviour disorder episodes in patients with narcolepsy-cataplexy, *Sleep Med* 12(7):635-640, 2011.

España RA et al: Sleep neurobiology from a clinical perspective, *Sleep* 34(7):845-858, 2011.

Flores NM et al: The humanistic and economic burden of narcolepsy, *J Clin Sleep Med* 12(3):401-407, 2016.

Mignot EJ: A practical guide to the therapy of narcolepsy and hypersomnia syndromes, *Neurotherapeutics* 9(4):739-752, 2012.

Ohayon MM: Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population, *Sleep Med* 14(6):488-492, 2013.

Poli F et al: High prevalence of precocious puberty and obesity in childhood narcolepsy with cataplexy, *Sleep* 36(2):175-181, 2013.

Scammell TE: *Narcolepsy, N Engl J Med* 373:2654-2662, 2015.

Nasal Polyps

BASIC INFORMATION

DEFINITION

Nasal polyps are benign inflammatory masses arising from the mucosa of the nose and paranasal sinuses. They are a manifestation of chronic rhinosinusitis. Chronic inflammation of the lining of the nasal and sinus cavities results in reactive hyperplasia of the mucosal epithelium in the form of nasal polyps.

SYNONYMS

Nasal polyps
NP
Chronic rhinosinusitis with nasal polyps

ICD-10CM CODE
J33.0 Polyp of nasal cavity

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:
- Affects 0.2% to 4.3% of the population.
- Approximately 10% of patients with nasal polyposis have asthma.

PREDOMINANT SEX & AGE:
- Greater than 2:1 male:female ratio.
- Childhood presentation (age <20) is rare and should prompt evaluation for cystic fibrosis or other pathology.

PEAK INCIDENCE: Mean age of onset is 42 yr

GENETICS: Some literature suggests there is a genetic component to the disease with an association between HLA-A74 and nasal polyposis.

RISK FACTORS:
- 10% of cases of nasal polyposis are associated with Samter Triad (asthma, aspirin sensitivity, nasal polyposis).
- Conditions associated with nasal polyps include asthma, bronchiectasis, cystic fibrosis, ciliary dyskinesia syndromes, Churg-Strauss syndrome, allergic fungal sinusitis, and bacterial rhinosinusitis.

CLASSIFICATION: Box E1 describes a classification of nasal polyps.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients usually present with nasal obstruction, anosmia/hyposmia, watery rhinorrhea, and/or post nasal drip.
- Physical exam:
  1. Smooth, round, mucosal-lined masses within the nasal cavity, often arising from the middle meatus
  2. Most often bilateral

ETIOLOGY

- The exact etiology is unclear but is thought to be multifactorial.
- Cytokine and cellular inflammatory markers found to be largely involved include T-helper 2 (Th-2) cells, eosinophils, IL-5 cytokines, and decreased T-regulatory function.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Possible alternative diagnoses include encephalocele, glioma, inverted papilloma, antrochoanal polyp, and neoplasm.

WORKUP

- Diagnosis can most often be made with history and physical exam.
- Anterior rhinoscopy.
- Nasal endoscopy (Figs. E1 and E2).

LABORATORY TESTS

Allergy testing may be considered based on symptoms and clinical presentation.

IMAGING STUDIES

CT sinus (Fig. E3): Not essential, but recommended for surgical planning if surgery is being considered. It is also important to help exclude other diagnoses in the case of unilateral polyps. Findings suggestive of nasal polyps include lobulated cysts or masses in the nasal cavity and partial or complete sinus or nasal cavity opacification.

TREATMENT

ACUTE GENERAL Rx

- Medical management is generally the first consideration in treatment. Goals of treatment are reduction in size of nasal polyps resulting in improvement of symptoms.
  1. Nasal corticosteroid sprays are a mainstay of treatment acutely and over the long term.
  2. Short courses of oral corticosteroids are reserved for advanced or refractory cases.
  3. Antihistamines may be helpful in controlling allergic symptoms but have little effect on nasal polyps.
- Surgical management may be considered for those who have failed medical therapy. Provides symptomatic relief but is rarely curative.
  1. High recurrence rate.
  2. Nasal polypectomy or more extensive functional endoscopy sinus surgery (FESS) performed by an otolaryngologist.
  3. Nasal saline irrigation is important postoperatively and can be continued by the patient as desired.

COMPLEMENTARY & ALTERNATIVE MEDICINE

There is some evidence that suggests topical intranasal capsaicin may be beneficial in treating nasal polyps.

DISPOSITION

Patients often require long-term intranasal corticosteroid therapy to reduce nasal inflammation. Recurrence after surgery is common, and the goals of treatment are to reduce symptoms.

BOX E1 Classification of Nasal Polyps

1. The antrochoanal polyp, mostly arising from the maxillary sinus and prolapsing into the choana; a commonly large, isolated, unilateral cyst-like noneosinophilic formation
2. Idiopathic unilateral or bilateral; mostly eosinophilic polyps without involvement of the lower airways
3. Bilateral eosinophilic polyposis with concomitant asthma and/or aspirin sensitivity
4. Polyposis with underlying systemic disease such as cystic fibrosis, primary ciliary dyskinesia, Churg-Strauss syndrome, or Kartagener syndrome

From Adkinson NF et al: *Middleton's allergy principles and practice,* ed 8, Philadelphia, 2014, WB Saunders.

FIG. E1 Nasal polyps. (From Swartz MH: *Textbook of physical diagnosis, history and examination*, ed 7, Philadelphia, 2014, Elsevier.)

REFERRAL

Referral to an otolaryngologist should be made in cases in which the diagnosis is unclear or the disease is not responsive to standard medical treatments.

PEARLS & CONSIDERATIONS

COMMENTS

- The inferior or middle turbinates are often mistaken for nasal polyps by inexperienced observers.
- When unilateral polyps are identified, histologic evaluation should be undertaken to exclude malignancy or other pathology as described previously.

PREVENTION

Avoidance of aspirin in sensitive patients

AUTHOR: **Louis Insalaco, MD**

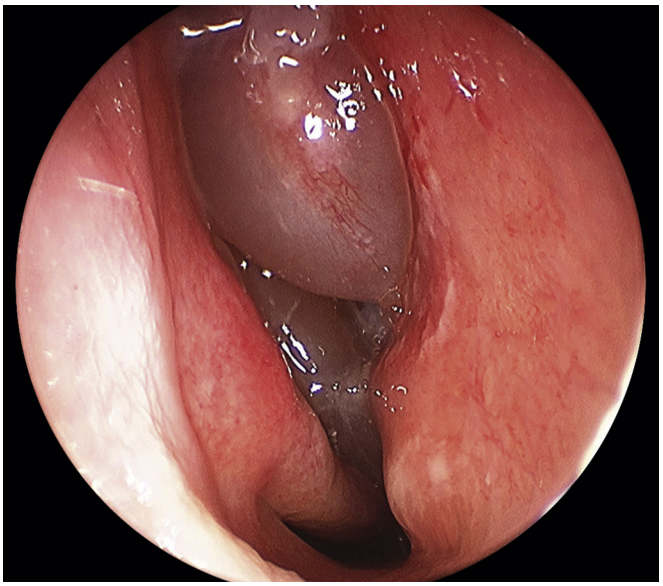

FIG. E2 Nasal polyposis in a patient with aspirin-exacerbated respiratory disease. (From Manning SC: *Cummings otolaryngology head and neck surgery,* ed 5, Philadelphia, 2010, Mosby/Elsevier.)

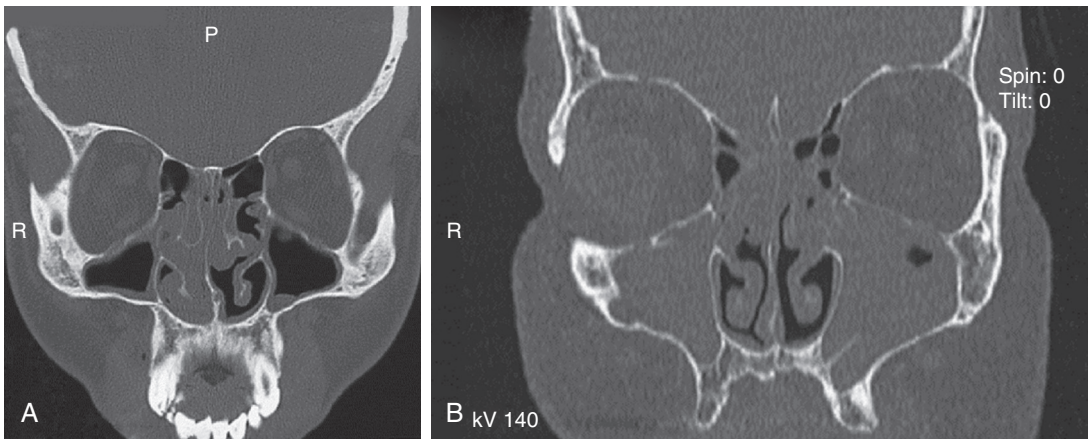

FIG. E3 Computed tomography scans obtained in patients with nasal polyposis. A, Central disease, representing an early stage of polyposis. **B,** Near-total "white-out," which is a late-stage manifestation. (From Adkinson NF et al: *Middleton's allergy principles and practice,* ed 8, Philadelphia, 2014, WB Saunders.)

SUGGESTED READINGS

Chaaban MR et al: Epidemiology and differential diagnosis of nasal polyps, *Am J Rhinol Allergy* 27(6):473-478, 2013.

Hopkins C: Chronic rhinosinusitis with nasal polyps, *N Engl J Med* 381(1):55-63, 2019.

Settipane RA et al: Chapter 6: nasal polyps, *Am J Rhinol Allergy* 27(Suppl 1):S20-S25, 2013.

BASIC INFORMATION

DEFINITION

Nasopharyngeal carcinoma (NPC) is an epithelial carcinoma originating in the nasopharynx that is clinically distinct from other head and neck carcinomas.

SYNONYM

Nasopharynx cancer

ICD-10CM CODE

C11.9 Malignant neoplasm of nasopharynx, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- NPC is an uncommon cancer that is endemic to east and southeast Asia (70% of cases).
- Incidence rate of 3 per 100,000 population in China and 0.4 per 100,000 in Caucasian population.
- Incidence is higher in males (2.5 times than females).
- Incidence is decreasing steadily in the endemic regions in Asia.

GENETICS:

- HLA genes residing at the MHC region on chromosome 6p21 have been widely recognized as major risk loci conferring nasopharyngeal carcinoma risk.
- Genomic changes involved in the development of NPC include: multiple loss-of-function mutations in the NFkB–negative regulators, recurrent genetic lesions such as loss of the *CDKN2A/CDKN2B* locus, *CCND1* amplification, *TP53* mutation, and mutations in the PI3K/MAPK signaling pathways.

RISK FACTORS:

- Epstein-Barr virus (EBV) infection
- Tobacco smoking
- Alcohol consumption
- Family history
- Consumption of preserved foods
- Poor oral hygiene

ETIOLOGY

- Pathological subtypes of squamous NPC are: keratinising, non-keratinising, and basaloid type. The keratinising subtype accounts for less than 20% of cases worldwide and is seen in non-endemic areas. The non-keratinising subtype constitutes most cases in endemic areas (>95%) and is predominantly associated with Epstein-Barr virus (EBV) infection.
- Persistent EBV infection in genetically mutated epithelial cells and the proliferation of infected cells lead to tumorigenic transformation. Chronic exposure of the nasopharyngeal mucosa to environmental carcinogens increases DNA damage and leads to somatic genetic changes in the nasopharyngeal epithelial cells. EBV infection in turn facilitates inactivation of a variety of cancer-related genes. During tumor development, acquired mutations of regulatory factors in the NF-κB signaling pathway alter the activity of additional cancer-related genes. Mutations in the MHC class I genes, PI3K/MAPK pathways as well as somatic mutations of *TP53* and *RAS* genes may be at play in the development of tumor recurrence and metastasis.

CLINICAL PRESENTATION

- Chronically blocked or stuffy nose
- Recurrent epistaxis and bloody rhinorrhea
- Hearing impairment and tinnitus
- Headache
- Ear pain
- Palpable neck adenopathy
- Cranial nerve palsies

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Nasal polyps
- Nasopharyngeal lymphoma
- Nasopharyngeal sarcoma

WORKUP

- Direct nasopharyngoscopy by ENT physician followed by biopsy (Fig. E1) and imaging studies (Figs. E2 and E3)

LABORATORY TESTS

- Complete blood count
- Comprehensive chemistry panel
- Circulating cell-free EBV DNA is a biomarker for nasopharyngeal carcinoma. Pretreatment plasma EBV-DNA levels may add to the prognostic value of conventional TNM staging systems (Table 1)

IMAGING STUDIES

- CT or MRI of the head and neck; MRI is better than CT for soft-tissue extent assessment and retropharyngeal nodal detection
- PET/CT is used to assess for detection of distant metastasis and for detection of residual cancer after completion of therapy

TREATMENT

The mainstay of therapy is concurrent chemotherapy and radiation therapy. Both adjuvant chemotherapy and to a lesser extent neoadjuvant chemotherapy are routinely utilized after and before chemoradiotherapy in the clinical setting.

NONPHARMACOLOGIC THERAPY

- Surgery is utilized for diagnostic biopsies and for neck dissection in the setting of residual neck lymphadenopathy after completion of definitive chemoradiotherapy.
- Supportive care with gastrostomy tube nutrition is often required to maintain nutritional and hydration status during treatment.

ACUTE GENERAL Rx

- Intensity modulated radiotherapy (IMRT) with concurrent every 3-wk cycles of cisplatin and 5-fluorouracil chemotherapy over a period of 6 to 7 wk is the standard approach. Adjuvant chemotherapy with cisplatin and gemcitabine is routinely administered with benefits seen in reduction of distant metastases and improvement in overall survival. Neoadjuvant chemotherapy with the same regimen prior to definitive chemoradiotherapy was shown to improve survival in a recent report.
- Significant supportive care with nutrition, hydration, and mucositis management (especially pain control) is required.
- Post-therapy rehabilitation with swallowing therapy, dental care, endocrinology care, and lymphedema care are often required.

DISPOSITION

Patients with early stage disease typically have a good outcome (5-yr survival is 60% to 75%), whereas patients with stage IV disease have a poor outcome (5-yr survival is <40%).

REFERRAL

Diagnosis is usually confirmed by biopsy performed by otorhinolaryngology physician. Referrals include to medical oncology, radiation oncology, dietitian, and gastroenterology.

PEARLS & CONSIDERATIONS

- Analysis of EBV DNA in plasma samples has been found to be useful in screening for early asymptomatic cases. NPC was detected significantly earlier and outcomes were better in participants who were identified by screening compared to those in a historical cohort.
- Higher pre-treatment, mid-treatment, and post-treatment EBV DNA levels have been significantly correlated with poor outcomes for patients afflicted with NPC.

RELATED TOPIC

Head and Neck Squamous Cell Carcinoma (Related Key Topic)

AUTHOR: **Ritesh Rathore, MD**

TABLE 1 Current TNM Staging Systems for Nasopharyngeal Carcinoma

Comparison of the seventh and eighth editions of the UICC/AJCC staging system for nasopharyngeal carcinoma.

Seventh edition		Eighth edition
Primary tumor (T)		
T_X	Primary tumor cannot be assessed	Primary tumor cannot be assessed
T_0		No tumor identified, but there is EBV-positive cervical node(s) involvement
T_1	Nasopharynx, oropharynx, or nasal cavity without parapharyngeal extension	Nasopharynx, oropharynx, or nasal cavity without parapharyngeal extension
T_2	Parapharyngeal extension	Parapharyngeal extension, adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)
T_3	Bony structures of skull base and/or paranasal sinuses	Bony structures (skull base, cervical vertebra) and/or paranasal sinuses
T_4	Intracranial, cranial nerves, hypopharynx, orbit, infratemporal fossa or masticator space	Intracranial extension, cranial nerve, hypopharynx, orbit, extensive soft tissue involvement (beyond the lateral surface of the lateral pterygoid muscle, parotid gland)
Regional lymph nodes (N)		
N_X	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis	No regional lymph node metastasis
N_1	Unilateral cervical, unilateral, or bilateral retropharyngeal lymph nodes, above the supraclavicular fossa; ≤6 cm	Unilateral cervical, unilateral, or bilateral retropharyngeal lymph nodes, above the caudal border of cricoid cartilage; ≤6 cm
N_2	Bilateral metastasis in lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa	Bilateral metastasis in lymph node(s), ≤6 cm in greatest dimension, above the caudal border of cricoid cartilage
N_{3a}	>6 cm in dimension	>6 cm and/or below caudal border of cricoid cartilage (regardless of laterality)
N_{3b}	Supraclavicular fossa	
Distant metastasis (M)		
M_0	No distant metastasis	No distant metastasis
M_1	Distant metastasis	Distant metastasis
Stage group		
I	T_1 N_0 M_0	T_1 N_0 M_0
II	T_2 N_0-$_1$ M_0, T_1 N_1 M_0,	T_2 N_0-$_1$ M_0, T_0-$_1$ N_1 M_0
III	T_1-$_3$ N_2 M_0, T3 N_0-$_1$ M_0	T_3 N_0-$_2$ M_0, T_0-$_2$ N_2 M_0
IVA	T_4 N_0-$_2$ M0	T_4 or N_3 M_0
IVB	Any T, N_3 M_0	Any T, any N, M_1
IVC	Any T, any N, M_1	

EBV, Epstein-Barr virus; *UICC/AJCC,* International Union Against Cancer/American Joint Committee on Cancer. T category: T_0 is added for EBV-positive cervical node(s) involvement despite unidentified primary tumor. Involvement of medial pterygoid, lateral pterygoid, and prevertebral muscles is now staged as T_2. In T_4, the original "infratemporal fossa or masticator space" has been replaced by specific description of soft tissue involvement to avoid potential ambiguity. N category: the previous N_{3b} criterion of "supraclavicular fossa" has been changed to "below caudal border of cricoid cartilage." N_{3a} and N_{3b} have been merged into a single N_3. Stage group: the previous stages IVA and IVB have been merged into IVA. The previous IVC has been upstaged to IVB.

From Chen YP et al: Nasopharyngeal carcinoma, *Lancet* 394(10192):64-80, 2019.

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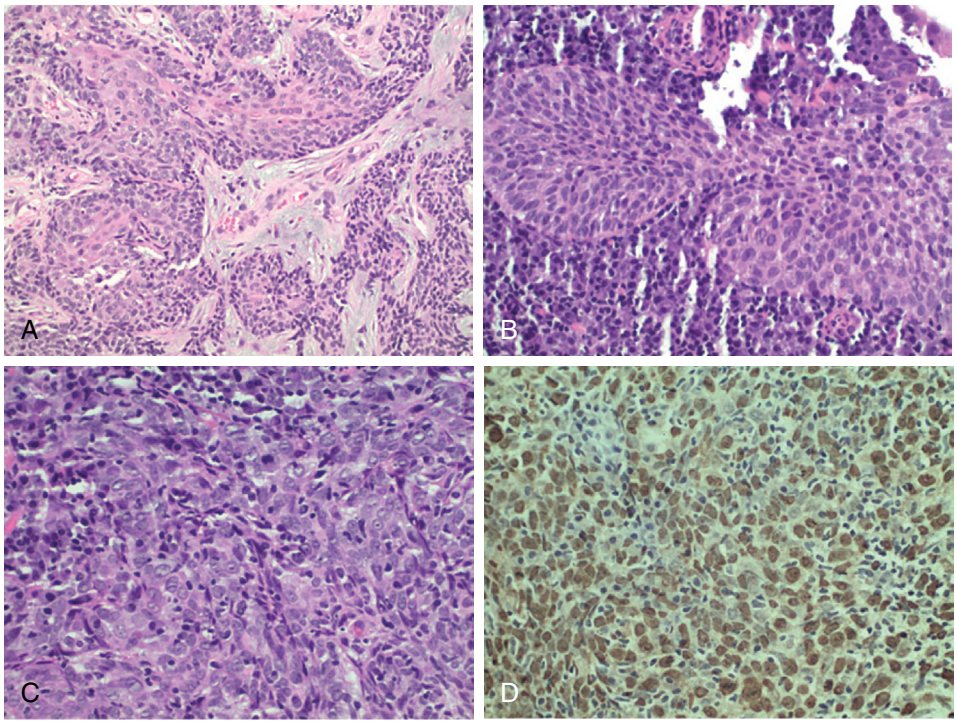

FIG. E1 Light microscopic appearance of nasopharyngeal carcinoma. (A) Keratinising squamous cell carcinoma; haematoxylin and eosin (H&E) stain, magnification 200×. **(B)** Non-keratinising carcinoma, differentiated subtype; H&E stain, magnification 400×. **(C)** Non-keratinising carcinoma, undifferentiated subtype; H&E stain, magnification 400×. **(D)** Detection of Epstein-Barr virus-encoded small RNA by in-situ hybridisation. (From Chua MLK et al: Nasopharyngeal carcinoma, *Lancet* 387(10022):1012-1024, 2016.)

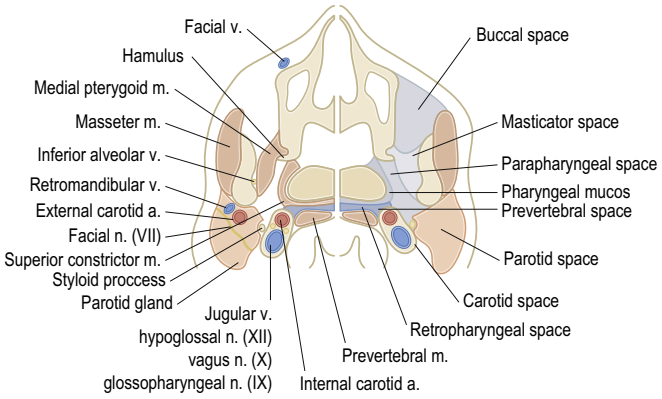

FIG. E2 Anatomy of the parotid and parapharyngeal spaces. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

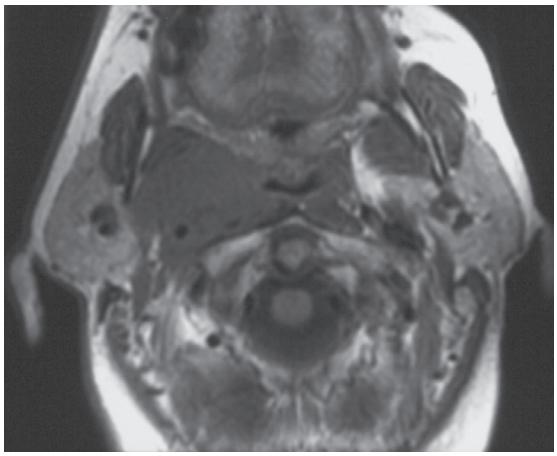

FIG. E3 Nasopharyngeal carcinoma. Axial T1WI shows a large parapharyngeal mass in contact with the deep lobe of the parotid laterally and partially encasing the carotid. (From Grant, LA: Grainger & Allison's diagnostic radiology essentials, ed 2, Philadelphia, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Necrotizing autoimmune myopathy (NAM) is a subgroup of idiopathic inflammatory myopathies (IIM) that presents with myalgias, weakness, and markedly elevated CPK levels (up to 50 times upper limit of normal). Most cases of NAM are seen in patients who have a history of statin use, the average duration of which is about 3 yr. Unlike typical statin-induced myopathy, the symptoms of NAM may present long after statins are initiated and can persist long after statins have been discontinued. In contrast with IIM, there is necrosis but sparse inflammation seen on muscle biopsy. Two specific autoantibodies associated with NAM are anti–signal recognition particle (SRP) and anti–3-hydroxy-3-methylglutaryl-coenzyme-A reductase (HMGCR). Statins have been associated with developing anti-HMGCR in all populations; however, these autoantibodies can be present without statin exposure. Rarely, an individual with NAM can have both antibodies.

SYNONYMS

Immune-mediated necrotizing myopathy
NAM
Necrotizing autoimmune myositis

ICD-10CM CODE
G72.49 Other inflammatory and immune myopathies, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Incidence of IIM in a homogenous population is 2.2 to 7.7 per million, and NAM, which is a rare disorder, accounts for 20% of IIM. Anti-SRP–associated NAM accounts for 3% to 6% of IIM, while anti-HMGCR accounts for 5% to 7% of IIM.

PREDOMINANT SEX & AGE: Primarily affects adults >18 yr, with mean age at onset around 50 to 60 yr, while younger ages of 47 to 49 have been reported in European studies. Also, statin- and cancer-related NAM patients are found to be older (60s). Anti-SRP–positive patients tend to be younger. There is a female predominance.

GENETICS: *HLADRB1*11:01* is associated with an increased risk of developing anti-HMGCR NAM in whites and African Americans when exposed to statins. *HLADRB1*08:03* may be associated with increased risk of anti-SRP NAM in Japanese. DQA1 and DQB6 may be protective against anti-HMGCR NAM.

RISK FACTORS:

- Statin exposure: Atorvastatin and simvastatin more than others (although this may reflect prescribing patterns)
- Cancer: GI origin most common as well as lung, thymoma, ovarian, etc.
- CTD: Scleroderma, Sjögren, and less with systemic lupus erythematosus
- Infections: Rarely HIV
- Can occur in association with the antisynthetase syndrome

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Acute (<4 wk) or subacute (<6 mo) onset of severe symmetrical proximal muscle weakness and atrophy that can involve both shoulder and pelvic girdle. Distal weakness may be present, along with myalgias and arthralgias. May be associated with interstitial lung disease, cardiac conduction abnormalities, mechanic hands, dysphagia or dyspnea, weight loss, and Raynaud. Case reports of isolated involvement of neck extensors have been reported.

ETIOLOGY

The exact pathogenesis of NAM is not clear, but studies suggest that statin exposure upregulates HMGCR in muscle in genetically susceptible individuals. Variable durations of statin exposure suggest environmental triggers may initiate autoimmunity. Increased TH1 responses and increased INF-gamma production by macrophages have been described. The presence of an autoantibody to HMGCR suggests that statins may be pathogenic, and that the aberrant immune response is sustained due to high levels of HMGCR expression by regenerating muscle fibers. However, elevated levels of HMGCR are often seen after full remission, suggesting that HMGCR antibodies may have a less direct role in pathogenesis.

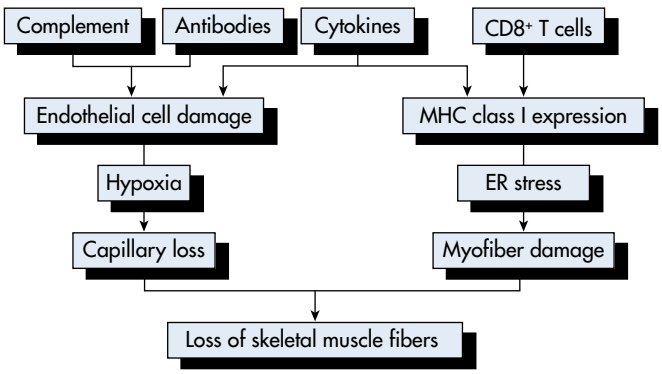

FIG. E1 Mechanisms of muscle fiber damage in myositis. *ER,* Endoplasmic reticulum; *MHC,* major histocompatibility complex. (From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, WB Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other conditions that cause muscle weakness and/or elevated muscle enzymes, such as muscular dystrophy, polymyositis, dermatomyositis, inclusion body myopathy, drug-induced myopathy, and thyroid myopathy.

WORKUP

- MRI of affected muscle: Muscle and/or fascial edema, muscle atrophy, fatty replacement
- Electromyography: Commonly shows an irritable myopathy
- Muscle biopsy:Histopathologic findings on muscle biopsy include muscle fiber necrosis with prominent regeneration and minimal or no inflammatory infiltrate. Specific findings with immunofluorescence staining include upregulation of major histocompatibility complex class I and membrane attack complex C5b-9 on small blood vessels (Fig. E1).

LABORATORY TESTS

- Complete blood count
- Creatine kinase
- Aldolase
- Comprehensive metabolic panel (renal function, aspartate transaminase/alanine aminotransferase)
- Anti-HMGCR antibody (anti 200/100)
- Anti-signal recognition particle antibody
- Connective tissue disease antibody testing (antinuclear antibodies, extractable nuclear antigen antibodies, anti-Scl70, etc.)
- HIV, hepatitis testing
- Thyroid function tests

IMAGING STUDIES

- MRI of involved muscles
- CT chest/abdomen/pelvis and other age-appropriate cancer screening
- Echocardiogram, ECG
- Pulmonary function tests

TREATMENT

No guidelines yet exist, and therapy has to be individualized. Stop statins immediately if they are suspected to be the causative agent. Treatment of underlying malignancy can also ameliorate disease. Steroids are the mainstay of therapy; however, steroid monotherapy seldom is effective long term, so the addition of an immunosuppressant agent should be considered. Aggressive therapy from the beginning is preferred. Options include intravenous immunoglobulin, methotrexate, azathioprine, mycophenolate mofetil, rituximab, cyclosporine, cyclophosphamide, and plasmapheresis. Relapse can occur.

REFERRAL

- Rheumatology
- Neurology

PEARLS & CONSIDERATIONS

- NAM must be considered in patients who have persistent myalgias and weakness after discontinuation of statins.
- Not all cases of NAM have a history of statin use. Individuals with NAM without prior statin exposure can be more treatment resistant.
- Muscle biopsy is essential for diagnosis.

PREVENTION

Avoid statin rechallenge.

PATIENT & FAMILY EDUCATION

Report to your doctor immediately any symptoms of muscle pains and/or weakness at any time after starting statin therapy.

RELATED CONTENT

Inclusion Body Myositis (Related Key Topic)
Inflammatory Myopathies (Related Key Topic)
Statin-Induced Muscle Syndrome (Related Key Topic)

AUTHOR: **Danielle Wang, MD**

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van de Vlekkert J: Long-term follow-up of 62 patients with myositis, *J Neurol* 261(5):992-998, 2014.

BASIC INFORMATION

DEFINITION

Necrotizing fasciitis (NF) is a rapidly spreading bacterial infection of the deep fascia, with associated inflammation, leading to necrosis of subcutaneous tissue planes. This infection can occur in wounds from trauma or surgical wounds or can be spontaneous or idiopathic. There are two clinical types, both of which carry a high rate of morbidity and mortality.

SYNONYMS

NF
Soft tissue gangrene
Flesh-eating bacteria
Fournier gangrene
Hemolytic streptococcal gangrene

ICD-10CM CODE
M72.6 Necrotizing fasciitis

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: Male > female
PREDOMINANT AGE: 6 to 50 yr; less common in children
INCIDENCE: Invasive group A *Streptococcus* infection occurs at a rate of 3.5 cases per 100,000 persons, with a case fatality rate of around 24%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

CLINICAL TYPES OF NECROTIZING FASCIITIS:

- Type I: Necrotizing fasciitis: At least one anaerobic species is isolated in conjunction with one or more facultative anaerobic species, such as streptococci (not group A), *and* members of the Enterobacteriaceae (gram-negative rods).
- Anaerobic bacteria, most commonly *Bacteroides* or *Peptostreptococcus* spp.
- Enterobacteriaceae: *Escherichia coli, Klebsiella* spp., *Proteus* spp., *Enterobacter* spp.
- Usually associated with diabetes or peripheral vascular disease.
- Example of type I: Fournier gangrene of the perineum.
- Type II: Necrotizing fasciitis: Group A *Streptococcus* is isolated alone or in combination with other bacteria, most likely *Staphylococcus aureus.* Also known as hemolytic streptococcal gangrene.
  1. Example of type II: Invasive group A *Streptococcus*, associated with virulence factors type 1 and type 3 M protein

EXAMPLES OF NECROTIZING FASCIITIS:

- Fournier gangrene: Aggressive type I infection of the perineum usually caused by penetration of the gastrointestinal or urethral mucosa by enteric organisms. It can rapidly spread to involve the scrotum, penis, and abdominal wall or gluteal muscles, causing gangrene. Use of sodium-glucose cotransporter-2 (SGLT2) inhibitors in diabetics has been associated with Fournier gangrene.
- Clostridial cellulitis: Caused by *Clostridium perfringens* associated with local trauma or surgery and crepitus caused by gas production; generally noted in the skin, with deeper tissues generally spared.

PHYSICAL FINDINGS

Minor skin trauma, toxic-appearing patient:

- Open skin wound
- Severe pain at injury or surgical site
- Fever, confusion, weakness, diarrhea
- Early skin erythema, quickly spreading in hours to days
- Skin redness changes to purple discoloration
- Gangrenous skin changes may develop
- Loosening of skin and subcutaneous skin in association with deep fascial necrosis (Fig. E1). "Woody" induration and crepitus of involved area are characteristics
- Muscle involvement, thrombosis of blood vessels, and myonecrosis may develop
- Bullae and gas formation at site

ETIOLOGY

- NF usually arises from skin damage or trauma. Risk is increased with presence of comorbidities (diabetes mellitus, cancer, liver disease, immunosuppression, use of SGLT2 inhibitors)
- Polymicrobial: Mixture of anaerobes and aerobic enteric gram-negative rods
- Group A streptococci *(S. pyogenes)*
- *S. aureus*
- *C. perfringens*
- *Bacteroides fragilis*
- *Vibrio vulnificus*
- Methicillin-resistant *S. aureus* (MRSA), especially community-acquired MRSA

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cellulitis
- Pyomyositis
- Gas gangrene
- A classification of necrotizing skin, soft-tissue, and muscle infections is described in Table 1

WORKUP

- Diagnosis of necrotizing fasciitis generally requires incision and probing. In patients with necrotizing fasciitis, there is no resistance to probing subcutaneously, and there is fascial plane involvement.
- Laboratory tests:
  1. The laboratory risk indicator for necrotizing fasciitis (LRINEC) consists of the following 6 variables. When present, the reported positive predictive value is 92%: Complete blood cell count (CBC) with differential (leukocytosis [white blood count >15,000], anemia [Hb <13.5]), elevated C-reactive protein (≥15 mg/dl), hyponatremia (sodium <135 mEq/L), elevated creatinine (>1.6 mg/dl), hyperglycemia (glucose >180 mg/dl).
  2. Cultures of skin, soft tissue, or debrided tissue, aerobically and anaerobically. Blood cultures are positive in 60% of patients with type II infections and 20% with type I infections.
- Imaging:
  1. Radiographs may show subcutaneous gas in fascial planes (Fig. 2).
  2. Computed tomography (CT) or magnetic resonance imaging (MRI) may be helpful because they can detect gas in the tissues. MRI with contrast is more sensitive than CT.

TREATMENT

- Aggressive surgical debridement of involved necrotic tissues is essential *as soon as possible* to reduce mortality.
- Fasciotomies of extremities may be necessary.
- Immediate start of empiric antibiotics:
  1. Type I: Vancomycin, daptomycin, or linezolid plus piperacillin/tazobactam; a carbapenem (such as imipenem, meropenem, or doripenem); and third-generation cephalosporin + metronidazole or a fluoroquinolone plus metronidazole (ceftriaxone) are reasonable choices pending cultures. Empiric clindamycin may also be added to suppress toxin production by staphylococci and streptococci. It is important to always have anaerobic coverage. Use the highest dosages possible for age and CrCl.
  2. Type II: For group A *Streptococcus*, give intravenous (IV) penicillin G, 4 million U q4h in patients who weigh >60 kg with clindamycin, 600 to 900 mg IV q8h.
     a. Clindamycin has the added effect of suppressing toxin production. If MRSA is suspected, add vancomycin, daptomycin, or linezolid.
- Intravenous gammaglobulin (IVIG): 1 g/kg on day 1 and 0.5 g/kg on days 2 and 3 neutralizes circulating streptococcal toxins and has been shown beneficial in severe forms of invasive group A streptococcal infections, although data are not definitive.
- For *Vibrio vulnificus* use doxycycline plus ceftazidime; for *Aeromonas hydrophila* use doxycycline plus ciprofloxacin.
- Hyperbaric oxygen evaluation as an adjunct to surgery and IV antibiotics.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Glenn G. Fort, MD, MPH**

TABLE 1 Classification of Necrotizing Skin, Soft-Tissue, and Muscle Infections

Disease	Bacteriology	Comments
Necrotizing Cellulitis		
Clostridial cellulitis	*Clostridium perfringens*	Local trauma, recent surgery; fascial/deep muscle spared
Nonclostridial cellulitis	Mixed: *Escherichia coli, Enterobacter, Peptostreptococcus* spp., *Bacteroides fragilis*	Diabetes mellitus predisposes; produces foul odor
Meleney synergistic gangrene	*Staphylococcus aureus,* microaerophilic streptococci	Rare infection; postoperative; slowly expanding, indolent, ulceration in superficial fascia
Synergistic necrotizing cellulitis	Mixed aerobic and anaerobic, including *B. fragilis, Peptostreptococcus* spp.	Diabetes mellitus predisposes; variant of necrotizing fasciitis type I; involves skin, muscle, fat, and fascia
Necrotizing Fasciitis		
Type I	Mixed aerobic and anaerobic; staphylococci, *B. fragilis, E. coli,* group A streptococci, *Peptostreptococcus* spp., *Prevotella, Porphyromonas* spp., *Clostridium* spp.	Usually requires a breach in the mucous membrane layer either through surgery or penetrating injuries or from chronic medical conditions such as diabetes, peripheral vascular disease, malignancy, and anal fissures
Type II	Group A streptococci	Increasing in frequency and severity since 1985; very high mortality; often begins at site of nonpenetrating minor trauma such as a bruise or muscle strain but often no identified precursor Predisposing factors: Blunt/penetrating trauma, varicella (chickenpox), intravenous drug abuse, surgical procedures, childbirth, nonsteroidal antiinflammatory drug use
Myonecrosis		
Clostridial myonecrosis	*Clostridium* spp.	Predisposing factors: Deep/penetrating injury, bowel and biliary tract surgery, improperly performed abortion and retained placenta, prolonged rupture of the membranes, and intrauterine fetal demise or missed abortion in postpartum patients. Recurrent gas gangrene occurs at sites of previous gas gangrene.
Streptococcal myonecrosis	Streptococci	
Special Type of Necrotizing Soft-Tissue Infection		
Fournier gangrene	Polymicrobial, with *E. coli* the predominant aerobe and *Bacteroides* the predominant anaerobe. Other microflora: *Proteus, Staphylococcus, Enterococcus,* aerobic and anaerobic *Streptococcus, Pseudomonas, Klebsiella,* and *Clostridium*	Necrosis of the scrotum or perineum that starts with scrotal pain and erythema and rapidly spreads onto anterior abdominal wall and gluteal muscle. It is more often seen in diabetics and can be associated with trauma.

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.

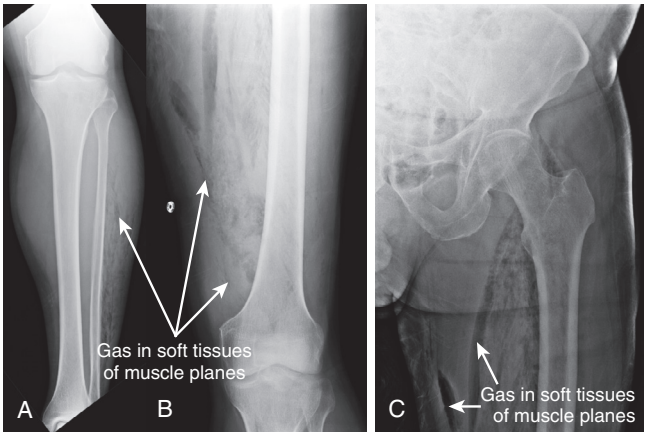

FIG. 2 Necrotizing fasciitis. This 71-yr-old man with aplastic anemia presented with fevers to 38.9° C (102.02° F), leg weakness, and extreme leg pain. Initially, the patient was thought to have neuropathic pain and weakness, possibly indicating spinal disease such as epidural abscess. He rapidly developed crepitus of his legs. Radiographs of the patient's legs were obtained, followed by noncontrast computed tomography. **A,** Anterior-posterior (AP) tibia and fibula. **B,** AP femur. **C,** AP hip. Air is seen dissecting in muscle planes of the legs. On radiograph, air appears black. Given the wide distribution of air, a focal abscess is unlikely, and necrotizing fasciitis with gas-producing organisms should be suspected. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, WB Saunders.)

FIG. E1 Necrotizing fasciitis. The so-called flesh-eating bacteria, group A β-hemolytic Streptococcus, can cause significant tissue destruction rapidly. This 32-yr-old woman had pain, erythema, and swelling of the foot followed by necrotic ulceration over a week. There was no history of trauma. (Courtesy Roger Bitar, MD. From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

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Nephroblastoma

BASIC INFORMATION

DEFINITION

Nephroblastoma is an embryonal malignant renal tumor of childhood that accounts for 95% of childhood kidney tumors. Most tumors are unicentric, but some are multifocal in one or both kidneys.

SYNONYM

Wilms tumor

ICD-10CM CODE
C64 Malignant neoplasm of kidney

EPIDEMIOLOGY & DEMOGRAPHICS

- It represents 6% of all pediatric malignancies and 75% of all renal cancers in children
- Slightly more frequent in girls
- 75% of cases occur in patients at age <5 yr with most cases at age 2 to 3 yr
- Incidence is approximately 8 cases per yr per 1 million white children <15 yr (approximately 650 new cases annually in the U.S.); the incidence is double in black children
- Associated syndromes (Table E1):
  1. Cryptorchidism
  2. Hypospadias
  3. Hemihypertrophy with or without the Beckwith-Wiedemann syndrome, aniridia
  4. Denys-Drash syndrome (nephroblastoma, pseudohermaphroditism, glomerulonephritis)
  5. WAGR syndrome (***W***ilms tumor, ***a***niridia, ***g***enitourinary malformations, and mental ***r***etardation)
- Familial nephroblastoma occurs in 1.5% (with younger age at diagnosis and more frequent multifocal tumors)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Nephroblastoma often is discovered when a parent notices a mass while bathing or dressing a child, most commonly a child who is approximately age 3 yr, or during a routine physical examination. The mass is unilateral, firm, and nontender and below the costal margin
- Abdominal swelling and/or pain
- Nausea
- Vomiting
- Constipation
- Loss of appetite
- Fever of unknown origin
- Night sweats
- Hematuria (less common than in adult renal malignancies)
- Malaise
- High blood pressure that is triggered when the tumor obstructs the renal artery
- Varicocele
- Signs of associated syndromes

ETIOLOGY & PATHOGENESIS

- Three cell types: Blastomal, stromal, and epithelial may be present. Structural diversity is characteristic.
- Anaplasia is evidenced by the presence of gigantic polyploid nuclei. The term *focal anaplasia* is used to describe such findings when it is confined within the primary tumor in the kidney.
- Abnormalities in the Wilms tumor gene *(WT1)* on locus 11p13 are present in the syndromes associated with this disease. These include deletions or point mutation in the WT1 locus. The *WT1* gene is a transcriptional regulator with a role in metanephric stem cell differentiation. Multiple studies in North America and Europe have suggested that LOH at 1p and/or 16q is associated with relapse and overall poor prognosis and is included in risk stratification of these patients.
- Gene mutations in Wilms tumors are summarized in Table E2.
- Staging: The staging system of the Children's Oncology Group is summarized in Table E3.

TABLE E1 Syndromes Associated with Development of Wilms Tumor

Syndrome	Genes	Locus	Wilms Tumor Risk
WAGR	*WT1*	11p13	50%
Denys-Drash	*WT1*	11p13	50%
Frasier	*WT1*	11p13	5%-10%
Beckwith-Wiedemann	*WT2*	IGF2, H19, p57, Klp2	5%-10%
Familial Wilms tumor	*FWT1*	17q21	30%
	FWT2	19q13	
Perlman	Unknown		>20%
Mosaic variegated aneuploidy	*BUB1B*	15q15	>20%
Fanconi anemia D1	*BRCA2*	13q12.3	>20%
Simpson-Golabi-Behmel	*GPC3*	Xq26	10% (in males)
Li-Fraumeni	*P53*	17p13	Low
Neurofibromatosis	*NF1*	17q11	Low
Sotos	*NSD1*	5q35	Low
Trisomy 18	Unknown	18	Low
Bloom	*BLM*	15q26	Low

WAGR, Wilms tumor, aniridia, genital anomalies, mental retardation.
From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other renal malignancies:
  1. Hypernephroma
  2. Transitional cell carcinoma
  3. Lymphoma
  4. Clear cell sarcoma
  5. Rhabdoid tumor of the kidney
- Renal cyst
- Other intraabdominal or retroperitoneal tumors

LABORATORY TESTS

- Complete blood count
- Comprehensive chemistry panel
- Urinalysis

IMAGING STUDIES

- Renal ultrasound to confirm existence of a solid mass in a kidney
- Abdomen and pelvis MRI or CT scan with contrast (Fig. E1)
- Chest CT scan

TREATMENT

- Accurate staging and risk stratification are both required for appropriate treatment planning. Risk stratification is based upon age at diagnosis, local and overall stage, tumor weight, and loss of heterozygosity (LOH) of chromosomes 1p and 16q.
- Upfront surgical resection of unilateral nephroblastoma is recommended. This also provides the necessary biologic information for risk stratification and selection of appropriate therapy.
- Surgical resection and surgical staging: Radical nephroureterectomy with lymph node sampling is preferred, although some centers are performing nephron-sparing surgery after neoadjuvant chemotherapy use. The sequence of chemotherapy and surgery in localized disease is not definitively established; in Europe preoperative chemotherapy is preferred, whereas in the U.S. upfront surgery is standard.
  1. Stages I and II: Surgery followed by chemotherapy.
  2. Stages III and IV: Surgery followed by radiation and chemotherapy.
  3. Stage V: Preoperative chemotherapy for 6 to 12 wk followed by nephron-sparing surgery.
- Chemotherapeutic agents used in the treatment of nephroblastoma traditionally include vincristine, dactinomycin, and doxorubicin. Modern intensive regimens in high-risk disease can also include cyclophosphamide, etoposide, and carboplatin.

PROGNOSIS

- Stage I: 95% survival
- Stage II: 91% survival
- Stage III: 91% survival
- Stage IV: 81% survival
- Prognosis is better for patients <2 yr age

AUTHOR: **Bharti Rathore, MD**

TABLE E2 Gene Mutations in Wilms Tumors

Gene	Type of Mutation	Frequency (%)	Somatic or Germline
11p15	H19 epimutation Paternal uniparental disomy	74	Both
WTX	Deletion or insertion Nonsense	33	Somatic only
WT1	Deletion or insertion Missense and nonsense	21	Both
CTNNB1	In-frame deletions Missense	20	Somatic only
TP53	Missense	4	Both

From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

TABLE E3 Staging System of the Children's Oncology Group

Stage	
I	Tumor confined to the kidney and completely resected. The renal capsule is intact and the tumor was not ruptured before removal. No renal sinus extension. There is no residual tumor.
II	Extracapsular penetration, but tumor is completely resected. Renal sinus extension or extrarenal vessels may contain tumor thrombus or be infiltrated by tumor.
III	Residual nonhematogenous tumor confined to the abdomen: Lymph node involvement, any tumor spillage, peritoneal implants, tumor beyond surgical margin either grossly or microscopically, or tumor not completely removed.
IV	Hematogenous metastases to lung, liver, bone, brain, and so on.
V	Bilateral renal involvement at diagnosis.

From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

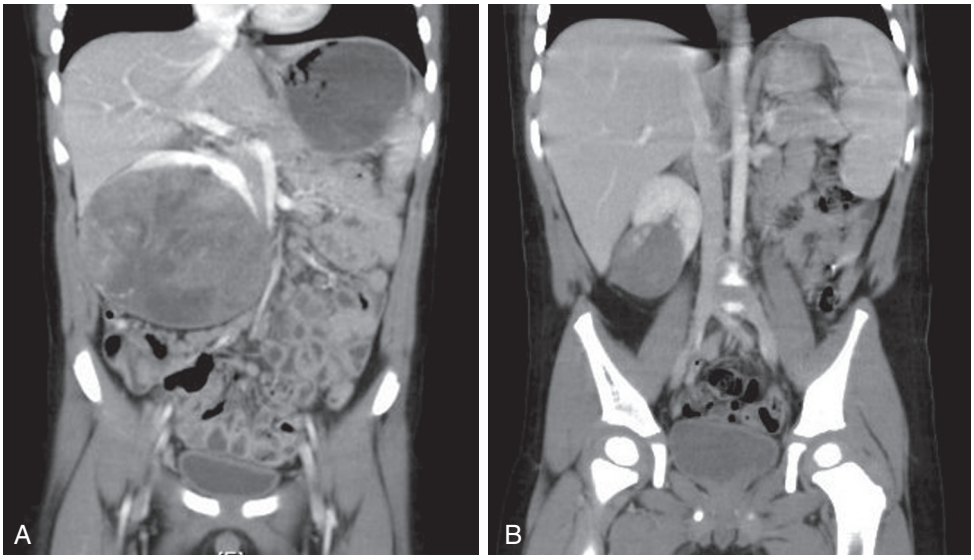

FIG. E1 A, Computed tomography scan of a Wilms tumor that was pretreated with chemotherapy. **B,** After 6 weeks of chemotherapy, the tumor is much smaller. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

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Nephrogenic Systemic Fibrosis

BASIC INFORMATION

DEFINITION

Nephrogenic systemic fibrosis (NSF) is a systemic sclerosis-like condition with induration of skin and contractures of joints seen in patients with acute or chronic kidney injury and end-stage renal disease. The adjective *nephrogenic* is a misnomer though, because gadolinium within gadolinium-based contrast agents (GBCAs) is considered the inciting factor. Patients may have a history of GBCA exposure; however, an exposure to nuclear magnetic resonance contrast is not required for diagnosis. Rarely, GBCA-induced systemic fibrosis has been reported with normal renal function. (Note that joint contractures, skin gadolinium deposition, and abnormal skin immunoreactivity have been described in a single patient with *normal renal function* and multiple exposures to gadolinium-based contrast.)

SYNONYMS

NSF
Nephrogenic fibrosing dermopathy
Nephrogenic systemic fibrosis
Gadolinium-associated systemic fibrosis

ICD-10CM CODES	
L90.8	Other atrophic disorders of skin
M34	Diseases of the musculoskeletal system and connective tissue
M34.0	Progressive systemic sclerosis
M34.2	Systemic sclerosis induced by drug and chemical
M34.9	Systemic sclerosis, unspecified
M35.5	Multifocal fibrosclerosis
T50.8X5	Adverse effect of diagnostic agents
T50.891A	Toxic effect of unspecified metal, accidental (unintentional)
T56.94XA	Toxic effect of unspecified metal, undetermined, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Annually, the incidence is 0.0043 cases per dialysis-dependent patient. In one retrospective study of patients referred to an academic nephrology subspecialty group, 18% were diagnosed with the disorder.

PREDOMINANT SEX AND AGE: The male:female ratio is 1:1. Ages have ranged from 8 to 87 yrs. Nationally, reported cases are U.S. > Europe > Asia, Australia, Canada, and South America.

RISK FACTORS:

- Renal insufficiency
- Exposure to gadolinium-based contrast
- Hepatorenal syndrome
- Infection
- Inflammatory condition
- Acidemia
- Erythropoietin-stimulating agents
- Hypercoagulability

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Onset of systemic fibrosis is variable, ranging from 24 hours to yrs after contrast exposure. Patients may complain of skin pain, paresthesia, or pruritus. The major clinicopathological criteria are patterned plaques, "cobblestoning," hardened/tethered/indurated skin, *peau d'orange* texturing, and joint contractures. Minor clinicopathologic criteria include puckered skin, linear banding, superficial plaques or patches, dermal papules, and scleral plaques. Patients have also presented with edema, hyperpigmentation, papules, and subcutaneous nodules. There can be fibrosis of several organs—skeletal muscle or visceral. *Gadolinium exposure is not requisite for the diagnosis.*

ETIOLOGY

- Gadolinium retention in the tissues may be the trigger; this element has been found in some skin lesions. Bone marrow–derived circulating fibrocytes constitute a large degree of cellularity in affected organs. Bone marrow retains a "memory" of prior gadolinium exposure that may explain why repeated exposures correlate with more severe forms of the disease.
- Brands with low reported numbers of contrast-induced fibrosis (e.g., "high thermodynamic stability" agent, gadoteridol) still demonstrate gadolinium deposition in the skin with a concomitant expression of profibrotic cytokines, such as transforming growth factor-β. Table E1 summarizes gadolinium agents and risk of NSF.
- The length of time on the market for any GBCA correlates with the respective number of NSF cases reported to the U.S. Food & Drug Administration Adverse Event Reporting System.
- Gadolinium tissue retention may lead to the liberation of substances that recruit circulating fibrocytes to affected areas. There is usually involvement of the limbs, with sparing of the upper trunk, neck, and face. In an experimental model, skin concentrations of monocyte chemoattractant protein-1 and C-C ligand 19 are elevated. Coadministration with an antagonist of monocyte chemoattractant protein-1 receptor reduced gross lesions, dermal cellularity, and extracellular matrix accumulation.
- See Fig. E1.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Amyloidosis
- β_2-microglobulin amyloidosis
- Borreliosis
- Calciphylaxis
- Carcinoid syndrome
- Chronic graft vs. host disease
- Dermatofibrosarcoma protuberans
- Environmental sclerotic disease (silica, polyvinyl chloride, toxic "Spanish" oil, eosinophilia-myalgia syndrome, bleomycin)
- Fibroblastic rheumatism
- Lipodermatosclerosis
- Melorheostosis
- Early cellulitis
- Early panniculitis
- Eosinophilic fasciitis
- Phenylketonuria
- Porphyria cutanea tarda
- Pretibial myxedema
- Progeria
- Scleroderma
- Systemic sclerosis/morphea

WORKUP

Skin biopsy

LABORATORY TESTS

Antibodies for nuclei, Scl 70, centromeres, phospholipids, and cardiolipin are negative. Skin biopsy demonstrates hypercellular fibrosis ± mucin, and immunostaining for CD34, procollagen type I, CD68, and Factor XIIIa may be positive. Important clinicopathologic findings on histologic examination are increased dermal cellularity, CD34-positive cells ("tram-tracked" around elastic fibers), thick and thin collagen bundles, preserved elastic fibers, septal involvement, and osseous metaplasia (Fig. E2).

TABLE E1 Gadolinium Agents and NSF

HIGHEST RISK OF NSF	Gadodiamide (Omniscan); Gadopentetate dimeglumine (Magnevist); Gadoversetamide (OptiMARK)
Contraindicated: CKD 4 and 5 (GFR <30 ml/min) – including if on dialysis; acute renal insufficiency; pregnancy; neonates	
Used with caution: CKD 3 (GFR = 30-60 ml/min) – at least 7 days between injections; children <1 yr	
Lactating women: Stop breastfeeding for 24 hrs and discard milk	
eGFR and clinical assessment mandatory before administration; never given in doses >0.1 mmol/kg	
INTERMEDIATE RISK OF NSF	Gadobenate dimeglumine (MultiHance); Gadofosveset trisodium (Vasovist); Gadoxetate disodium (Primovist)
LOWEST RISK OF NSF	Gadobutrol (Gadovist); Gadoterate meglumine (Dotarem); Gadoteridol (ProHance)
Used with caution: CKD 4 and 5 (GFR <30 ml/min) – at least 7 days between injections	
Pregnant women: Can be used to give essential information	
Lactating women: Discussion required whether to discard breast milk for 24 hours after injection	
eGFR testing not mandatory	

CKD, Chronic kidney disease; *eGFR,* estimated glomerular filtration rate; *GFR,* glomerular filtration rate. From Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.

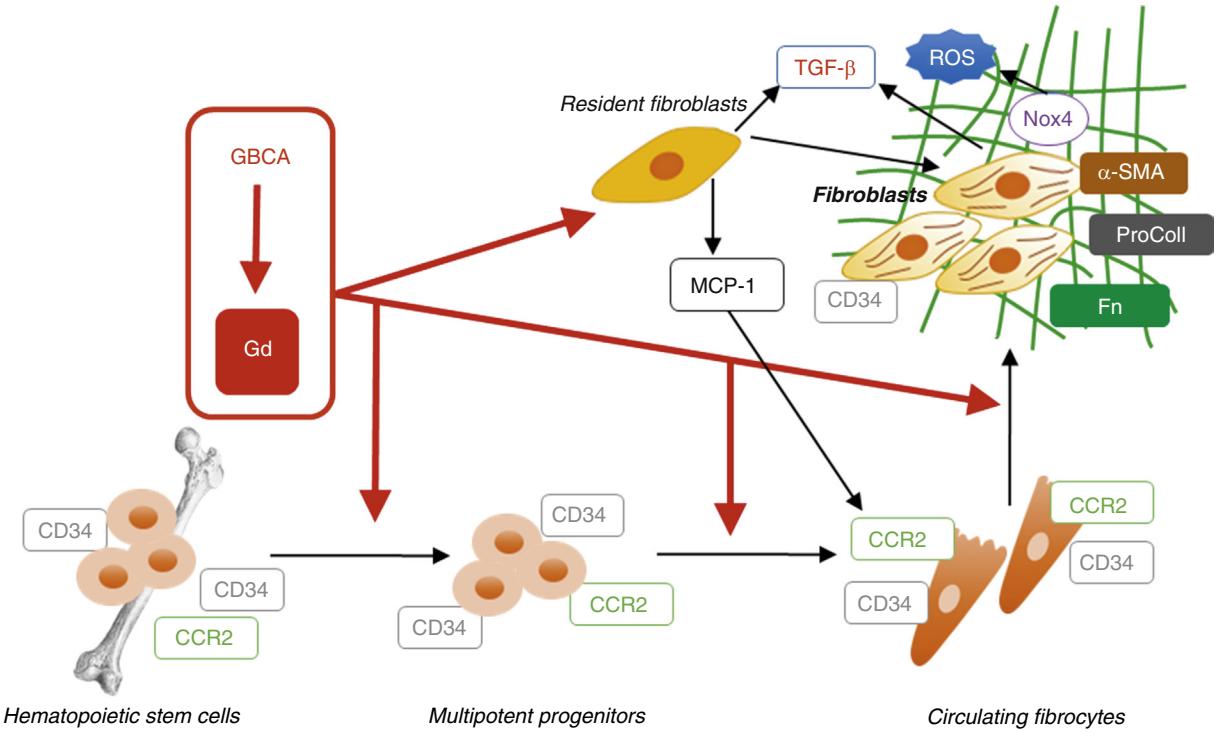

FIG. E1 The molecular mechanisms of gadolinium-based contrast agent-induced fibrosis. Gadolinium-based contrast agents (GBCA) may liberate gadolinium (Gd) as part of the initial disease process—this has yet to be experimentally confirmed. Bone marrow-derived cells are now known to infiltrate skin lesions. These myeloid cells express the C-C chemokine receptor 2 (CCR2) and migrate into affected areas in response to monocyte chemoattractant protein-1 (MCP-1). NADPH oxidase 4- (Nox4-) derived reactive oxygen species (ROS) generation is part of the disease process. Transforming growth factor-β (TGF-β) has been detected in patients and in preclinical models. Activated fibroblasts express α-smooth muscle actin (α-SMA). Other markers of myeloid-derived fibrocytes are procollagen I (ProColl) and CD34. The process culminates in the deposition of extracellular matrix. Fibronectin (Fn) is a marker of this scarring.

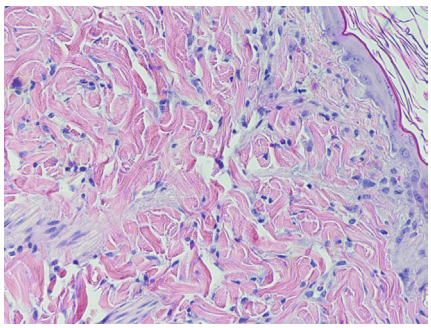

FIG. E2 Skin from a rodent model of gadolinium-induced systemic fibrosis. In addition to many of the protein markers of fibrosis, this model replicates the human condition in terms of increased cellularity of the dermis, thick and thin collagen bundles surrounded by clefts, and epidermal changes. Hematoxylin and eosin stain 20×.

IMAGING STUDIES

None

Rx TREATMENT

No single treatment has yet been found that is universally effective.

REFERRAL

Dermatology, physical therapy

PEARLS & CONSIDERATIONS

COMMENTS

In December 2013, Tomonori Kanda, MD, PhD, and colleagues reported that gadolinium-based contrast agent exposure correlated with high signal intensities in the dentate nucleus and globus pallidus even in the setting of normal renal function. Robert McDonald, MD, PhD, confirmed that these regions of the brain contained gadolinium (using mass spectroscopy with autopsy specimens). By July 2017, the European Medicines Agency restricted the use of a class of gadolinium-based contrast agents (i.e., those with a linear polyaminocarboxylate structure). Later, the U.S. Food & Drug Administration mandated a new class warning (i.e., *for all classes*) for all gadolinium-based contrast agents warning providers and consumers of long-term retention of the metal in various tissues. Provided the dire consequences of nephrogenic systemic fibrosis, and the lack of understanding of its pathophysiology, there is concern that adverse reactions reported in those with normal renal function may be a continuum with the well-established disease that occurs in renal impairment.

PREVENTION

Minimize patient exposure to GBCAs where feasible. Gadolinium contrast used in MRI must be avoided in patients with eGFRs <30 ml/min/1.73m^2. The severity of the disorder correlates with the total quantity of contrast an individual has been exposed to in a lifetime. Hence, the type and quantity of GBCAs should be clearly documented for all exposed individuals, particularly in the presence of liver and/or kidney disease. *There is no evidence that immediate hemodialysis can prevent contrast-induced systemic fibrosis.* Regular chronic dialysis three times weekly in end-stage renal disease has not been shown to prevent MRI contrast-induced systemic fibrosis. It has been well-documented that GBCAs rapidly disseminate into nondialyzable compartments, and the thresholds where disease is triggered remains unknown. Once in such a dialysis-protected space, the back diffusion of gadolinium is either absent or slow.

GBCAs are nephrotoxic. Acute kidney injury is a recognized adverse reaction listed in the respective prescribing information sheet of each GBCA. Preclinical models have shown that GBCAs are far from inert and may precipitate into gadolinium-rich nanostructures in kidney and skin.

PATIENT & FAMILY EDUCATION

Information on gadolinium-based contrast agents: www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142882.htm

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BASIC INFORMATION

DEFINITION

Nephrotic syndrome is characterized by heavy proteinuria (usually defined as >3.5 g/24 hr), hypoalbuminemia, hyperlipidemia, lipiduria, and edema. Nephrotic-range proteinuria involves urine protein excretion of >3.5 g/24 hours without other features of the nephrotic syndrome. Proteinuria, primarily in the form of albuminuria, can have many causes that share a common mechanism of glomerular injury , the most common being diabetes, focal segmental glomerulosclerosis, membranous nephropathy, minimal change disease, and amyloidosis. Though less common, disorders that are classically categorized under the nephritic syndrome also may lead to nephrotic-range proteinuria.

ICD-10CM CODES

N04.9	Nephrotic syndrome with unspecified morphologic changes
N04.0	Nephrotic syndrome with minor glomerular abnormality
N04.1	Nephrotic syndrome with focal and segmental glomerular lesions
N04.2	Nephrotic syndrome with diffuse membranous glomerulonephritis
N04.3	Nephrotic syndrome with diffuse mesangial proliferative glomerulonephritis
N04.4	Nephrotic syndrome with diffuse endocapillary proliferative glomerulonephritis
N04.5	Nephrotic syndrome with diffuse mesangiocapillary glomerulonephritis
N04.6	Nephrotic syndrome with dense deposit disease
N04.7	Nephrotic syndrome with diffuse crescentic glomerulonephritis
N04.8	Nephrotic syndrome with other morphologic changes

EPIDEMIOLOGY & DEMOGRAPHICS

- Among children (especially <6 yr of age), the most common causes of nephrotic syndrome are:
  1. Minimal change disease (MCD) (75% of pediatric cases)
  2. Focal and segmental glomerulosclerosis (FSGS) (7% to 20% of cases)
- Among adults, diabetes is the most common cause of nephrotic syndrome. FSGS is the most common *primary* (nonsystemic) cause of nephrotic-range proteinuria. Membranous nephropathy is the second most common primary cause of nephrotic syndrome. FSGS is more common in persons of African ancestry, while membranous nephropathy is seen more commonly in Caucasians.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients usually present with severe lower extremity, periorbital edema, and weight gain.
- Ascites and anasarca may occur.
- Hypercoagulability is a potential clinical manifestation.
- Patients are at higher risk for infections due to urinary immunoglobulin loss.

ETIOLOGY

Glomerular diseases can be thought of as diseases affecting one of five elements that comprise the renal corpuscle: endothelium, basement membrane, podocyte, mesangium, or parietal epithelium. In general, disorders that involve the endothelium and/or mesangial compartment activate inflammatory mediators. Disorders that exclusively affect the basement membrane or podocyte generally have a noninflammatory pathology. Compromised structural integrity of the glomerulus leads to a breach of the normal mechanisms that prevent abnormal filtration, leading to proteinuria as primarily albuminuria, the hallmark of glomerular disease.

Traditionally, the clinical correlate to this pathological schema has been a subdivision of patients into those with a nephrotic versus nephritic presentation. Disorders that are considered "nephritic" have subnephrotic proteinuria and low glomerular filtration rates. "Nephrotic" disorders have greater proteinuria and more robust glomerular filtration rates. While generally true, this schema may cause diagnostic confusion because nephritic disease may present with nephrotic-range proteinuria, *especially earlier in the disease course before glomerular filtration is substantially reduced*. It is better to categorize these diseases with a noninflammatory urine sediment (proteinuria alone with no casts or cellular elements) versus an inflammatory sediment (i.e., RBC casts and/or dysmorphic RBCs in conjunction with proteinuria).

Fig. 1 details this breakdown. In this chapter, we focus on primary diseases that present with a noninflammatory sediment (namely, minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, and amyloidosis) and on primary disorders with inflammatory sediment often with nephrotic-range proteinuria, membranoproliferative glomerulonephritis (MPGN). The evaluation of "nephritic syndrome" is noted by worsening GFR in the setting of proteinuria and hematuria as detailed elsewhere. Important points regarding the most common etiologies of nephrotic syndrome are detailed in the following text (Table 1).

- MCD has a bland urine sediment with abrupt onset of disease and abrupt remission. Proteinuria may exceed 20 grams daily. Nonsteroidal antiinflammatory drug (NSAID) use, lithium use, viral infections, and lymphomas are associated with secondary forms of MCD.
- FSGS, primary or secondary: Primary FSGS denotes an idiopathic cause that typically manifests with heavy proteinuria and nephrotic syndrome and requires immunosuppressive therapy. FSGS is more prevalent

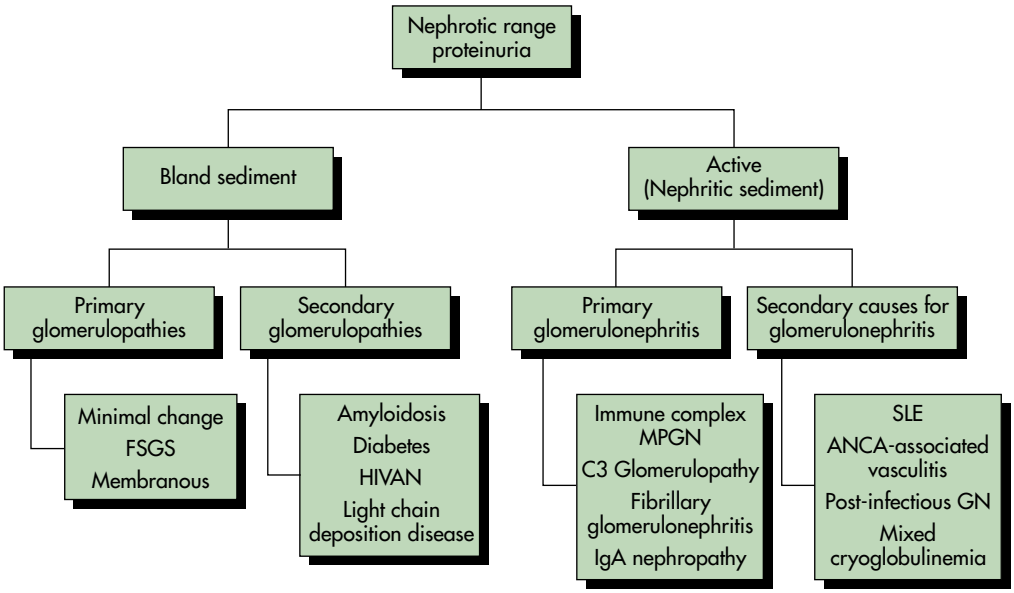

FIG. 1 An approach to nephrotic-range proteinuria. *ANCA,* Antineutrophil cytoplasmic antibody; *C3,* complement component 3; *FSGS,* focal and segmental glomerulosclerosis; *GN,* glomerulonephritis; *IgA,* immunoglobulin A; *HIVAN,* HIV-associated nephropathy; *MPGN,* membranoproliferative glomerulonephritis; *SLE,* systemic lupus erythematosus.

TABLE 1 Important Clinical, Serological, and Pathological Features of Selected Diseases Causing Nephrotic Syndrome

Disease	Important Clinical Features	Serological Features	Pathological Features
Minimal change disease	Rapid onset with heavy proteinuria and rapid remission with therapy. True steroid resistance is rare and should prompt repeat biopsy to rule out FSGS.	Complements are normal.	Light microscopy (LM) shows completely normal kidney architecture. Immunofluorescence microscopy: Normal. Electron microscopy (EM): Diffuse podocyte effacement.
Primary FSGS	Often heavier proteinuria and low serum albumin and edema. Tip lesion subtype and collapsing FSGS often have more explosive onset. Sediment usually bland, but RBCs can be seen. Usually no cellular casts.	Complements are normal.	LM: Only one glomerulus need show features of FSGS to make diagnosis. Immunofluorescence microscopy: Often devoid of immunoglobulin, although IgM can be seen. EM: Often has diffuse podocyte effacement.
Secondary FSGS	Proteinuria is often subnephrotic, or if nephrotic, serum albumin levels are maintained. Minimal edema.	HIV and parvovirus infection can cause phenotype identical to idiopathic collapsing FSGS.	LM: Often shows evidence of glomerulomegaly. EM: Foot process effacement is less diffuse.
Primary membranous nephropathy	Often seen in older Caucasian patients. More likely than other forms of nephrotic syndrome to be associated with thrombotic complications Sediment: Bland. RBCs can be found, although RBC casts are usually found.	Serum antiphospholipase A2 receptor antibodies are found in 70% of patients with idiopathic primary membranous nephropathy. Antineutral endopeptidase antibodies are found in a minority of others.	LM: Characterized by thickening of the GBM; "spikes" can be seen on silver stain. Immunofluorescence microscopy: C3 and IgG noted in granular pattern. Newer techniques stain for antiphospholipase A2 receptor antibody in situ. EM: Associated with subepithelial deposits.
Secondary membranous nephropathy	Associated with **malignancy,** lupus, syphilis, hepatitis B and C, medications (gold, captopril, penicillamine, etc.).	Notable for the absence of antiphospholipase A2 antibodies. ANA, hepatitis B, HCV serologies are helpful. RPR can be sent in context of appropriate history.	Morphology is exactly the same except when examined by EM. On high power, one sees both subendothelial and mesangial deposits in addition to classic subepithelial deposits.
Amyloidosis	Often found with massive proteinuria. Kidney size is enlarged. Bland sediment.	UPEP, SPEP, serum free light chains may be positive. The UPEP will show glomerular proteinuria, which can help differentiate from myeloma kidney.	LM: Often notable for nodular pattern. Diagnosis can be made by staining using Congo red or thioflavin T. Immunofluorescence microscopy: Antibody use can differentiate AA from AL amyloid. EM: Shows characteristic random 10-nm fibrils.
Diabetes	Often associated with nephrotic-range proteinuria in the setting of retinopathy. Kidney sizes are preserved.	No specific serologic tests are positive.	LM: Nodular pattern often seen, thickened GBM.
MPGN	Often associated with nephrotic-range proteinuria with a "nephritic" sediment. RBC casts often seen along with dysmorphic RBC.	C3 and C4 are often low in immune complex MPGN. Immune complex GN warrants checking SPEP and UPEP, as gammopathy is associated with MPGN. Hepatitis B, HCV, ANA, and cryoglobulins are also warranted. C3 alone is low in dense deposit disease and C3 glomerulonephritis, which may prompt specific tests for complement dysregulation.	The key point here is to look at the IF. If immunofluorescence shows both immunoglobulin and complement deposition, the diagnosis is immune complex MGPN. If only complement, the diagnosis is most likely C3 glomerulopathy (either dense deposit disease or C3 glomerulonephritis).

ANA, Anti-nuclear antibody; *C3,* complement component 3; *FSGS,* focal and segmental glomerulosclerosis; *GBM,* glomerular basement membrane; *GN,* glomerulonephritis; *HCV,* hepatitis C virus; *Ig,* immunoglobulin; *MPGN,* membranoproliferative glomerulonephritis; *RBC,* red blood cell; *RPR,* rapid plasma reagin; *SPEP,* serum protein electrophoresis; *UPEP,* urine protein electrophoresis.

in persons of African ancestry. Secondary FSGS is caused by a known etiology, including heroin use, sickle cell disease, scarring of any kind from prior injury, obesity, low nephron mass, HIV, etc. Most cases of secondary FSGS are associated with lower levels of proteinuria (often subnephrotic), higher albumin levels, and less significant edema (e.g., HIV-associated nephropathy is an important exception in that it is associated with heavy proteinuria and rapid progression when untreated). Distinguishing between primary and secondary FSGS is important for therapy (see following text). It should be noted that prior kidney injury can produce morphological features of FSGS over time. Essentially, proteinuric disease attributable to secondary FSGS can be seen in any progressive kidney disease and generally portends worse outcomes.

- Membranous nephropathy may be primary or secondary. Primary membranous nephropathy is due to in situ deposition of antibodies directed against a glomerular antigen. In 70% or more cases, the epitope is identified as phospholipase A2 receptor. A second, less-common epitope is thrombospondin type-1 domain-containing 7A (THSD7A). Proteinuria in membranous nephropathy may be massive. Secondary membranous nephropathy is often due to infection (e.g., hepatitis B, malaria, schistosomiasis, syphilis), autoimmune disease (e.g., systemic lupus erythematosus [SLE]), medications (e.g., D-penicillamine, gold), and malignancies. Distinguishing between the two subtypes is important for management (see following text).
- Amyloidosis is frequently due to overproduction of immunoglobulin light chains (AL amyloid) or a chronic inflammatory state (AA amyloid). Kidney size is often enlarged, and proteinuria may be massive. Congo red staining of amyloid often establishes the diagnosis.
- Diabetic nephropathy is often characterized by slowly progressive proteinuria with retinopathy and preserved kidney size. The correlation between retinopathy, proteinuria, and diabetic nephropathy is very strong in type 1 diabetic patients, and kidney biopsies

are usually not done. The relationship is less strong in type 2 diabetes, and absence of retinopathy does not preclude a diagnosis of diabetic nephropathy.

- Membranoproliferative glomerulonephritis (MPGN) is usually from immune complex deposition with complement, or activation of the alternate complement system without immune complex formation (e.g., C3 glomerulopathy). Prior classification schema involving types 1, 2, and 3 MGPN are now deemed obsolete after better understanding of the pathophysiology of this morphology. Common immune complex causes are from infections (e.g., hepatitis C), autoimmune disorders (e.g., SLE), disorders of the alternative complement pathway (C3 glomerulopathy), or dysproteinemias (e.g., monoclonal gammopathies). Distinguishing between these possibilities guides therapy. The urine is associated with heavy proteinuria. Urinary sediment often contains dysmorphic erythrocytes and erythrocyte casts, and is also associated with heavy proteinuria.

TABLE 2 Important Definitions in Dealing with Treatment of Primary Nephrotic Syndrome

	Adults	Children
Definition		
Complete Remission	Reduction in proteinuria to <0.3 g/24 hours	<4 mg/m^2/hr on at least 3 occasions within 7 days and serum albumin >3.5 g/dl
Partial Remission	Reduction in proteinuria between 0.3 g/24 hours and 3.5 g daily with ≥50% decrease in proteinuria from baseline	Disappearance of edema, increase in serum albumin >3.5 g/dl, and persistent proteinuria >4 mg mg/m^2/hr or >100 mg mg/m^2/hr
Relapse*	Increase in proteinuria to >3.5 g daily after one mo of complete or partial remission	Urine dipstick 3+ or proteinuria >40 mg/m^2/hr occurring on 3 days within 1 wk
Steroid Dependent*	Two consecutive relapses occurring during therapy or within 14 days of completing therapy	Two relapses of proteinuria within 14 days after stopping or during alternate-day steroid therapy
Steroid Resistant*	Persistence of proteinuria without significant reduction despite prednisone therapy at 1 mg/kg for 16 wk	Persistence of proteinuria despite prednisone therapy at 60 mg/m^2 for 4 wk

*These definitions only truly apply to diseases such as minimal change disease and FSGS.
(Adapted from Cattran DC et al: Cyclosporine in idiopathic glomerular disease associated with the nephrotic syndrome: workshop recommendations, *Kidney Int* 72(12):1429-1447, 2007, and *KDIGO clinical practice guidelines for glomerulonephritis*.)

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other states that present with edema (CHF, cirrhosis, protein-losing enteropathy, severe malnutrition)
- Glomerulonephritis from disorders commonly associated with inflammatory urinary sediment and glomerular inflammation
- Mimickers of glomerulonephritis (thrombotic microangiopathy due to malignant HTN, preeclampsia, or antiphospholipid syndrome)

WORKUP

- Evaluation includes determining the rate of change of serum creatinine, quantification of proteinuria by 24-hr collection, and urinary sediment examination.
- Abnormalities in any of the above tests should prompt nephrology consultation.
- Serologic testing may include urine and serum electrophoresis, HIV, hepatitis B surface antigen, hepatitis C virus (HCV) antibody, and antinuclear antibody (ANA). As urinary sediment examination is not 100% sensitive in ruling out an inflammatory process, C3 and C4 can be checked, as complement levels are often low in many inflammatory glomerulonephritides and often low in MPGN. Low complement levels may change the nature of the differential diagnosis before kidney biopsy. Depending on practice patterns, these tests are used selectively before or (in some cases) after biopsy to better define an etiology.
- A newer serological test available to clinicians commercially is an antiphospholipase A2 receptor antibody (anti-PLA2r) titer. Positive titers are seen in primary membranous nephropathy but less commonly in secondary membranous nephropathy. With treatment, patients may go into an immunologic remission (decreasing titers) prior to a clinical remission based on urine proteinuria. Thus, monitoring titers during the course of treatment may help guide treatment duration and limit toxic side effects of therapy.
- Patients should have a kidney ultrasound to document organ size and the presence of two kidneys prior to biopsy.

Rx TREATMENT

NON-IMMUNOSUPPRESSIVE THERAPY

- Control of proteinuria is key to mitigating risk of progression. Almost all trials of non-diabetic chronic kidney disease demonstrate that reducing proteinuria improves renal survival. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers should be used at maximally tolerated doses, except in MCD, where proteinuria reduction is often seen rapidly with treatment. Dual angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker therapy is generally not recommended due to increased risks of hyperkalemia and elevating the serum creatinine. Non-dihydropyridine calcium channel blockers (verapamil and diltiazem) can be used to in lieu of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers when the latter are contraindicated.
- For proteinuria >1 gram per day, target blood pressure is <125/75 mm Hg.
- With the exception of MCD, patients with nephrotic-range proteinuria and hyperlipidemia should be treated with HMG CoA synthetase inhibitors (statins).
- Although some patients with nephrotic syndrome are hypercoagulable (particularly patients with membranous nephropathy), the role of prophylactic anticoagulation is not well-defined and controversial. For patients with membranous nephropathy and serum albumin levels <2.0 g/dl, anticoagulation should be considered if bleeding risk is low.
- Low sodium diet (<2 gram per day) with diuretics.
- Diuretic resistance is common due to gut wall edema and hypoalbuminemia. More bioavailable diuretics (bumetanide, torsemide) may increase urine output better than furosemide, along with thiazide diuretics.
- To prevent "diuretic braking," most loop diuretics should be dosed at least on a twice-daily basis.

IMMUNOSUPPRESSIVE THERAPY

Important terms in dealing with the management of nephrotic-range proteinuria due to primary glomerular diseases are listed in Table 2. First-line therapies for each disease are highlighted in the following.

- MCD: First-line therapy in adults is prednisone (1 mg/kg per day to a maximum of 80 mg per day) for a minimum of 4 wk and maximum of 16 wk. Steroids are tapered over 6 mo for favorable responses. Second-line options include cyclophosphamide and/or calcineurin inhibitors. Newer, randomized, controlled trial data from children (not adults) have suggested an impressive record for rituximab in steroid-dependent patients unable to be weaned off steroids without inducing relapse and frequently relapsing MCD. Consequently, rituximab may become a reasonable option for patients who do not respond to conventional therapy.
- FSGS: Primary FSGS is often treated with high-dose prednisone (maximum, 80 mg daily in adults) that is tapered over 6 mo. Alternative regimens include low-dose prednisone with cyclosporine. Mycophenolate mofetil (MMF) has also been used with success in primary FSGS. A new, randomized, controlled trial

aims to examine whether a novel agent that blocks endothelin-1 and angiotensin II receptors (RE-021) has efficacy in treatment of primary FSGS. Treatment of secondary FSGS is based on arresting the underlying cause and nonspecific therapy with blockade of the renin-angiotensin-aldosterone system, BP control, weight loss, and dietary protein restriction. Immunosuppression is avoided.

- Membranous nephropathy: Acceptable treatment options include alternating months of cyclophosphamide and steroids, calcineurin inhibitors with low dose steroids or without steroids, and rituximab. Given conflicting reports from the U.S. and Europe, exogenous ACTH can be viewed as a last-line resort when all other options have failed, but it is not the standard of care. Therapy for secondary membranous nephropathy is directed at treating the underlying cause (malignancy, SLE, etc.).
- Treatment of amyloidosis, diabetes, and immune complex MPGN is directed at the underlying disorder. In rapidly progressive HCV-related MPGN, immunosuppressive therapy with rituximab or glucocorticoids and cyclophosphamide can be administered during HCV therapy.
- More recently, reclassification of MPGN has shown that some forms of MPGN are caused by alternative complement cascade activation (C3 glomerulonephritis). There is renewed interest in using medications (e.g., eculizumab) that target the end product of this pathway (membrane attack complex). Prior non-targeted approaches (e.g., steroids) for MPGN have been largely unsuccessful except in selected pediatric cases.

REFERRAL

Nephrology consultation is recommended for all cases of nephrotic syndrome.

PEARLS & CONSIDERATIONS

- Albuminuria generally implies glomerular disease is present. The urine protein electrophoresis defines the type(s) of proteins excreted: albumin, immunoglobulins, and tubular.
- Massive proteinuria (>20 g per day) is rarely seen with inflammatory diseases and generally indicates MCD, FSGS, membranous nephropathy, or amyloidosis.
- Partial remissions and steroid resistance are rarely seen in primary minimal change disease. These circumstances mandate reexamination of the cause of nephrotic syndrome because repeat biopsy in these cases often demonstrates FSGS.
- Quantification of proteinuria should be done with a 24-hr urine collection with evaluation of urinary creatinine excretion to document validity of the collection. Spot collections have not been validated for heavy proteinuria or patients with rapidly changing creatinine values. A "spot" urine protein-to-creatinine ratio taken from the 24-hr collection defines the relationship between spot and "true" collections to monitor response to therapy.
- Most noninflammatory processes progress slowly. If a sediment without red blood cell casts is detected with a rapidly increasing serum creatinine and heavy proteinuria, the differential is relatively narrow:
  1. MCD with acute tubular necrosis or acute interstitial nephritis, as occurs with nonsteroidal anti-inflammatory drug administration
  2. Any form of nephrotic syndrome associated with acute tubular necrosis from hypovolemia
  3. Bilateral renal vein thrombosis superimposed on nephrotic syndrome
  4. Myeloma cast nephropathy
  5. Collapsing FSGS

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Nephrotic Syndrome (Patient Information)

AUTHOR: **Rupali Avasare, MD**

SUGGESTED READINGS

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Kidney Disease Improving Global Outcomes: KDIGO Clinical Practice Guideline for Glomerulonephritis. A summary of take-home points for each major disorder is available in bullet form for the busy clinician. The data behind guideline recommendations is also available for the more interested reader. http://kdigo.org/home/glomerulonephritis-gn/.

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BASIC INFORMATION

DEFINITION

Neuroblastomas are tumors of postganglionic sympathetic neurons that typically originate in the adrenal medulla or the sympathetic chain/ganglion. They are often present at birth, but not diagnosed until later, when the child shows symptoms of the disease. They are almost exclusively a disease of childhood.

ICD-10CM CODE

C74.90 Malignant neoplasm of unspecified part of unspecified adrenal gland

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 8% to 10% of all solid tumors of childhood (third most common childhood cancer, after leukemia and brain tumors); 10.54 cases per 1 million per yr in children younger than 15 yr.

PREDOMINANT SEX: Male/female ratio of 1:1.3

PEAK AGE: Early childhood. Mean age of onset is 18 mo; 33% onset by 1 yr; 75% onset by 5 yr; 97% by 10 yr. In rare cases, neuroblastoma can be discovered by fetal ultrasound.

GENETICS: Although the majority of neuroblastomas are sporadic, in 1% to 2% of cases, there are exceptions associated with familial neuroblastoma. Germline deletion at the 1p36 or 11q14-23 locus is associated with familial neuroblastoma, and the same deletions are found somatically in sporadic neuroblastomas. Amplification of *N-MYC* gene (2p23), which encodes a nuclear transcription factor in the basic helix-loop-helix leucine zipper family, is present. The prevalence of N-myc amplification is about 22% in neuroblastoma and is associated with advanced-stage disease and poor prognosis. ALK germline mutation is also seen in familial neuroblastoma (14% in the high-risk group, 6% in the intermediate-risk group, and 8% in the low-risk group). The ATRX mutation is seen almost exclusively in older children with high-risk neuroblastoma and is associated with telomere lengthening (alternative lengthening of telomeres).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The most common presentation of neuroblastoma is an abdominal mass. Neuroblastomas can arise anywhere along the sympathetic nervous system. The most common primary site is the adrenal gland (40%), followed by a mass in the abdomen (25%), thorax (15%), neck (5%), and pelvis (5%). In approximately 1% of cases a primary site cannot be identified. Metastatic neuroblastoma are seen in 70% to 80% of children. The most common site for metastasis are regional lymph node involvement, bone marrow, cortical bone, orbits, liver, and skin at time of presentation
- Spinal cord/paraspinal: Can present with localized back pain, signs of cord compression—paraplegia or stool/urine retention, abdominal mass, pain, or constipation
- Horner syndrome (ptosis, miosis, anhidrosis) if it involves the stellate ganglion
- Thoracic: Difficulty breathing, dysphagia, infections, chronic cough
- Secondary symptoms referable to metastatic disease: Fatigue, chronic pain (typically bony pain), pancytopenia, periorbital ecchymosis, proptosis, anorexia, weight loss, unexplained fever, multiple subcutaneous bluish nodules, irritability
- Progressive cerebellar ataxia
- Paraneoplastic syndromes: Opsoclonus-myoclonus syndrome (OMS) is described as "dancing eyes, dancing feet," which manifest as myoclonic jerks and chaotic eye movements in all directions. This may be initial presentation before tumor diagnosis; present in 1% to 3% of patients with neuroblastoma; of all patients with opsoclonus-myoclonus, approximately 50% have an underlying neuroblastoma. Patients who present with this syndrome must be evaluated for neuroblastoma; when present, the neuroblastoma often has more favorable biologic features. The tumors may secrete a vasoactive intestinal peptide that, on rare occasions, causes a watery diarrhea. Another cause of diarrhea is protein-losing enteropathy secondary to intestinal lymphangiectasia

DIAGNOSIS

WORKUP

- Careful general physical examination to look for mass
- Biopsy and resection of tumor when possible

LABORATORY TESTS

- Complete blood count, coagulation studies, erythrocyte sedimentation rate
- 24-hour urine for catecholamines: Homovanillic acid (HVA) and vanillylmandelic acid (VMA) are secreted by up to 90% of tumors
- Nonspecific serum markers such as neuron-specific enolase, lactate dehydrogenase (marker for increased cell turnover), and ferritin
- Bone marrow biopsy and aspirate: Karyotype, DNA index, *N-MYC* copy number
- Minimum criteria for diagnosis are based on international consensus panel and require one of the following: (1) unequivocal pathologic diagnosis made from tumor tissue or (2) combination of bone marrow aspirate with unequivocal tumor cells and increased levels of serum or urinary catecholamine metabolites, as described above
- Genetic/biologic variables have been studied in children with neuroblastoma, in particular the histology, aneuploidy of tumor DNA, and amplification of the *N-MYC* oncogene within tumor tissue, because treatment decisions may be based on these factors
  1. Hyperdiploid DNA is associated with favorable prognosis, especially in infants.
  2. *N-MYC* amplification is associated with poor prognosis, regardless of patient age, likely due to association with deletion of chromosome 1p and gain of chromosome 17q.
  3. Other biologic factors studied include profile of GABAergic receptors, expression of neurotrophin receptors, level of telomerase RNA and serum ferritin and lactate dehydrogenase.

IMAGING STUDIES

- Chest x-ray, abdominal plain film, skeletal survey, abdominal and renal/bladder ultrasound
- CT scan or MRI of the chest and abdomen (Figs. E1, E2, E3) to provide information about regional lymph nodes, vessel invasion, and distant metastases
- Body scan with ^{131}I-MIBG (meta-iodobenzylguanidine), which is taken up by neuroblasts and is sensitive to metastases in the bone and soft tissue (64% of patients will develop thyroid dysfunction)
- Bone scan with Tc-99 MDP to visualize lytic bone lesions and metastases

Staging (staged according to the International Neuroblastoma Staging System [INSS])

I	Localized tumor with complete gross excision with or without microscopic residual disease
II_A	Localized tumor with incomplete gross resection; ipsilateral lymph nodes negative
II_B	Localized tumor with or without incomplete gross resection; ipsilateral lymph nodes positive
III	Unresectable unilateral tumor infiltrating across midline, with or without lymph node involvement
IV	Metastases to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs, except as defined for stage IVs.
IV_S	Localized primary tumor with dissemination limited to skin, liver, or bone marrow; limited to infants <18 mo of age

DIFFERENTIAL DIAGNOSIS

- Other small, round, blue-cell childhood tumors, such as lymphoma, rhabdomyosarcoma, soft tissue sarcoma, and primitive neuroectodermal tumors (PNETs).
- Wilms tumor. Table E1 describes features distinguishing between Wilms tumor and neuroblastoma. Opsoclonus myoclonus may occur with other tumors such as hepatoblastoma, infections (e.g., Coxsackie virus, Lyme disease, rickettsia, HIV), ingestions (phenytoin, amitriptyline, diazepam, lithium), toxic exposures, and metabolic derangements (biotin-responsive multiple carboxylase deficiency).

TREATMENT

- Overall, treatment will be determined by several factors, including age at diagnosis,

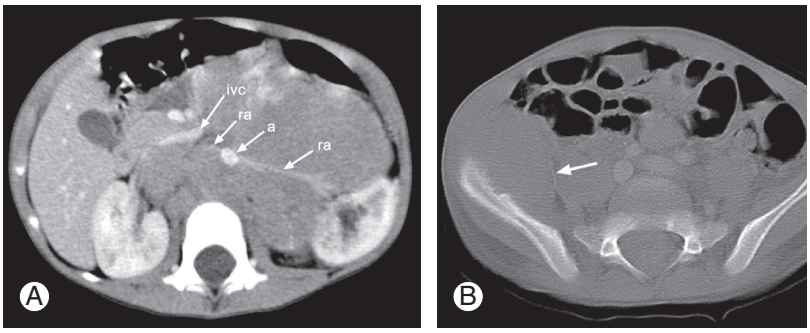

FIG. E1 Abdominal neuroblastoma: CECT. (A) A prevertebral tumor extends across the midline in the retroperitoneum, displaces and encases the aorta (a) anteriorly and encases the renal arteries (ra). The inferior vena cava (ivc), partially encased, is displaced anterolaterally and compressed by the tumor and nodes. The mass extends to both the renal hili. **(B)** Infiltrative lesion to the right iliac bone with a large soft tissue component *(arrow)* that projects inwards as a space-occupying mass. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.)

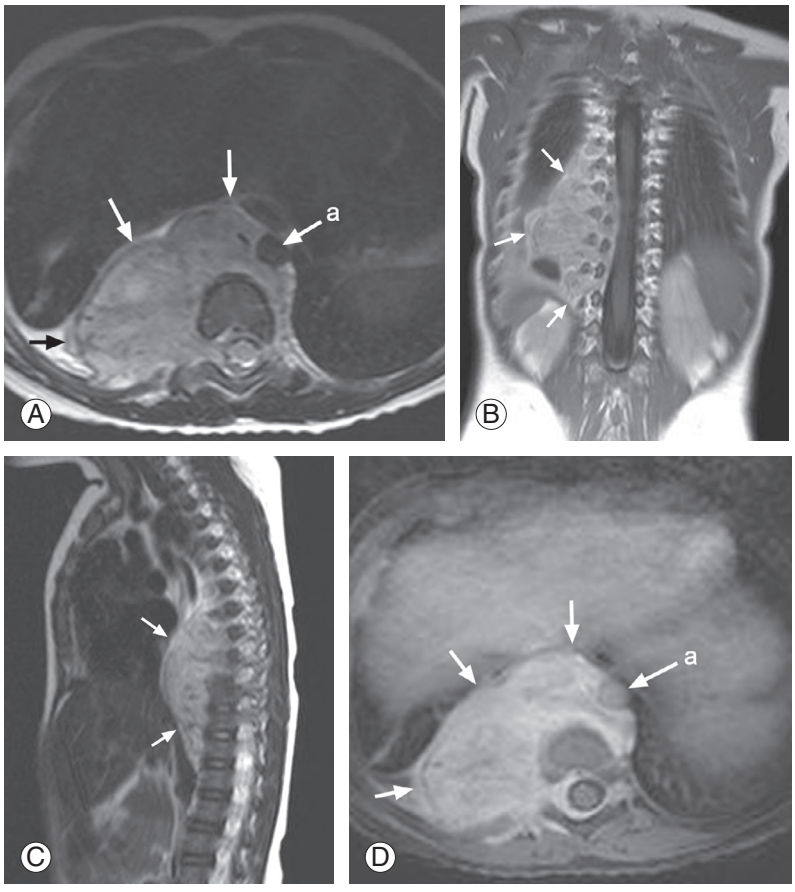

FIG. E2 Thoracic neuroblastoma with intraspinal extension: MRI. (A, B) Axial and coronal T1WI + Gad. **(C)** Sagittal T1WI + Gad. **(D)** Axial T2WI. Large posterior mediastinal mass *(arrows)* with anterior and lateral displacement of the aorta (a), which is encased. There is massive tumor extension into the canal through the right neural foramina to displace the spinal cord to the left. Extension into the right paraspinal soft tissues is evident. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

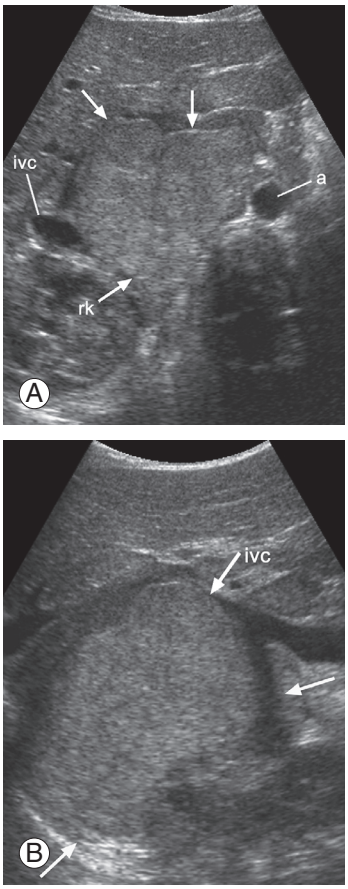

FIG. E3 Abdominal neuroblastoma. (A) Transverse US through the right abdomen shows a solid paraspinal mass *(arrows)* anterior to the right kidney *(rk).* The aorta *(a)* and inferior vena cava *(ivc)* are displaced by the mass. **(B)** Longitudinal image through the right flank shows the mass *(lower arrows)* and the stretched inferior vena cava *(ivc).* (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

stage of disease, site of primary tumor and metastases, tumor histology, and quantitative DNA content of the tumor.
- Surgery: Particularly for low-risk tumors.
- Radiation therapy may be tried for unresectable tumors or tumors that are not responsive to chemotherapy.
- Multiagent chemotherapy is mainstay of treatment (e.g., cisplatinum, etoposide, doxorubicin, cyclophosphamide).
- Autologous bone marrow transplantation following aggressive chemotherapy for stage IV disease or patients who are at highest risk based on presence of disseminated disease or unfavorable markers such as *N-MYC* amplification.
- Novel therapies include immunotherapy using monoclonal antibodies and vaccines that attempt to initiate an immune reaction against the disease and targeting of tumor cells with drugs that induce apoptosis or have antiangiogenic effect. Immunotherapy with ch14.18, a monoclonal antibody against the tumor-associated disialoganglioside (GD2), has activity against neuroblastoma. Recent trials have shown that immunotherapy with ch14.18, GM-CSF, and interleukin-2 is associated with a significantly improved outcome as compared with standard therapy in patients with high-risk neuroblastoma. Children with opsoclonus/myoclonus syndrome may benefit from immunologic treatment (e.g., prednisone, pulse dexamethasone, IVIG, plasma exchange, cyclophosphamide, or mycophenolate).

DISPOSITION

- Overall survival is >40%. Children under the age of 1 yr have a cure rate as high as 90%.
- Approximately 70% of patients with neuroblastoma have metastases at diagnoses.
- Prognosis is related to age at time of diagnosis, clinical stage, and regional lymph node involvement. Children with localized disease and infants <1 yr at diagnosis and favorable disease characteristics have better

TABLE E1 Features Distinguishing Between Wilms Tumor and Neuroblastoma

Feature	Wilms Tumor	Neuroblastoma
Age	2-3 yr	<2 yr
Origin	Kidney	Retroperitoneal neural crest
Renal mass effect	Intrinsic mass effect	External compression
Laterality	10% bilateral	Almost always
Calcification	<15%	85%-95%
Vessel involvement	Renal vein invasion in 5%-10%	Frequent encasement

From Weissleder R et al: *Primer of diagnostic imaging,* ed 5, St Louis, 2011, Mosby.

prognosis, whereas poorer prognosis is noted in older children with stage IV disease (20% survival compared with >95% in stage I), age >1 yr at diagnosis, increased number of *N-MYC* copies, adrenal tumor, and chronic 1p deletion.

- Children treated for neuroblastoma may be at risk for second malignancies, including renal cell carcinoma, myelodysplastic syndrome, and leukemia, especially after treatment of high-risk neuroblastoma with chemotherapy. Other long-term effects include thyroid dysfunction (^{131}I-MIBG), cardiac toxicity (doxorubicin), and hearing loss (cisplatin).

REFERRAL

To multidisciplinary oncology team with experience in treating cancers of childhood and adolescence

PEARLS & CONSIDERATIONS

- Neuroblastoma is predominantly a tumor of early childhood that originates in the sites where the sympathetic nervous system tissue is present.
- Symptoms occur due to tumor mass or bone pain from metastases.
- Children can present with classic paraneoplastic neurologic symptoms, including cerebellar ataxia and opsoclonus myoclonus.
- Recent trials have shown a very high rate of survival among patients with intermediate-risk neuroblastoma with biologically based treatment assignment involving a substantially reduced duration of chemotherapy and reduced doses of chemotherapeutic agents as compared with regimens used in earlier trials. These data provide support for further reduction in chemotherapy with more refined risk stratifications.
- Despite recent advances, 50% to 60% of patients with high-risk neuroblastoma have a relapse, and currently no salvage treatment regimens are known to be curative.

RELATED CONTENT

Neuroblastoma (Patient Information)

AUTHORS: **Hussain Mohammad H. Naseri, MD,** and **Donny V. Huynh, MD**

SUGGESTED READINGS

Baker DL et al: Outcome after reduced chemotherapy for intermediate-risk neuroblastoma, *N Engl J Med* 363:1313-1323, 2010.

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Yu AL et al: Anti-GD2 antibody with GM-CSF, interleukin-2 and isotretinoin for neuroblastoma, *N Engl J Med* 363:1324-1334, 2010.

BASIC INFORMATION

DEFINITION

The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition (DSM-5), includes delirium and major and mild neurocognitive disorders, as well as their subtypes, under the grouping *neurocognitive disorders*.

The core features of neurocognitive disorders (NCDs) are deficits in cognitive function. The cognitive dysfunction is acquired rather than developmental and thus represents a decline from a previously attained level of functioning. The NCDs are subtyped according to known or presumed etiologic/pathologic entities underlying the decline. The subtypes may be distinguished by clinical characteristics such as time course, physical examination, and cognitive domains affected. It is possible for more than one NCD to be identified in a given patient at a given time.

In major and mild NCDs, the cognitive deficits are present in one or more cognitive domains. The initial evidence is based on concern brought forth by the patient, a knowledgeable informant, or the clinician and is often supported by performance on objective standardized assessments such as neuropsychological testing. In major NCDs, the deficits interfere with independence in everyday activity, whereas in minor NCDs, the impairment is more modest and does not interfere with capacity for independence in everyday activity.

In the DSM-5, *delirium* (acute encephalopathy) is subsumed under the category *neurocognitive disorders*. Although it shares the core feature of acquired deficit in cognitive function, it is discussed as a distinct entity from major and minor neurocognitive disorders and is discussed separately in this text. The DSM-IV term *dementia* (chronic encephalopathy) is subsumed under the entity *major neurocognitive disorder* in the DSM-5, and the DSM-IV term *amnestic disorder* and its subtypes are subsumed under the category *major neurocognitive disorder due to another medical condition* in the DSM-5.

Some of the more commonly seen NCDs include major or mild NCD due to Alzheimer disease, major or mild vascular NCD, and major or mild NCD due to Lewy body disease.

ICD-10CM CODES	
F02.80	Major or mild neurocognitive disorder, without behavior disturbance
F02.81	Major or mild neurocognitive disorder, with behavior disturbance
DSM-5 CODES	
294.10	Major or mild neurocognitive disorder, without behavior disturbance
294.11	Major or mild neurocognitive disorder, with behavior disturbance

EPIDEMIOLOGY & DEMOGRAPHICS

The prevalence varies depending on the etiology of the neurocognitive disorder and age of the patient. Among patients >60 yr, the prevalence tends to increase sharply for the most common neurocognitive disorders. Overall prevalence estimates for major NCDs are approximately 1% to 2% at 65 yr old and as high as 30% at 85 yr. Mild NCD prevalence is variable, ranging from 2% to 10% at age 65 and 5% to 25% at age 85. The strongest risk factor for major and mild NCD is age. Female gender is associated with a higher prevalence in major and mild NCD due to Alzheimer disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Neurocognitive domains that are affected in NCDs include:

- Complex attention, including sustained attention, divided attention, selective attention, and processing speed
- Executive functioning, such as planning, decision making, working memory, and mental flexibility
- Learning and memory, including immediate memory, recent memory
- Language expression and reception, including word recall, grammar, and syntax
- Perceptual motor skills, including visual construction, praxis, and gnosis
- Social cognition, including recognition of emotions

Associated physical findings, time course of illness, and response to treatment depend on etiology of the NCD. Mood disturbance, psychosis, and behavior disturbances are recognized as common neuropsychiatric symptoms associated with NCDs. Mood symptoms are common early in the course of NCDs due to Alzheimer disease, NCD with Lewy bodies, and vascular NCD. Psychoses, including delusions and paranoia, may present across the spectrum of illness but are more common in mild to moderate stages of NCD with Lewy bodies and in moderate to severe stages of NCD due to Alzheimer disease. Psychosis, agitation, and other behavioral disturbances lead to increased rate of hospitalization, early admission to assisted living environments or nursing homes, and increased level of caregiver depression and distress. Apathy manifests early in the course of NCDs and is the most common neuropsychiatric symptom of NCD due to Alzheimer disease across the spectrum of the disease.

ASSOCIATED SIGNS AND SYMPTOMS BY ETIOLOGY

(For each etiology, the criteria are met for major or mild neurocognitive disorder.)

- **Major or mild neurocognitive disorder due to Alzheimer disease:** Insidious onset and gradual progression, occasionally with brief plateaus. Impairment in memory, learning, and executive function are prominent early in the disease. In moderate to severe disease, language deficits manifest and problematic behaviors, including agitation, combativeness, and psychosis, may arise. Apathy, agitation, and psychosis are often more distressing to caregivers than the cognitive deficits.
- **Major or mild frontotemporal neurocognitive disorder:** Behavior and language variants are characterized by progressive development of personality changes, behavior changes including disinhibition, and/or language impairment. Patients with behavior variant may present with impaired insight, socially inappropriate behaviors, apathy, hyperorality, or compulsive behaviors. Learning and memory dysfunction may be spared in the early stages. It now is recognized that the *C9orf72* gene can lead to hereditary frontotemporal degeneration (FTD) with amyotrophic lateral sclerosis. Symptoms of FTD usually come before motor symptoms.
- **Major or mild neurocognitive disorder with Lewy bodies:** Cognitive decline occurs prior to or within 1 yr of the onset of parkinsonism motor symptoms. Recurrent, well-formed, and detailed visual hallucinations and fluctuating cognition that can resemble delirium are core features. Mood disturbances, autonomic dysfunction, and REM sleep disorder are suggestive of this diagnosis. Patients with major or mild neurocognitive disorder with Lewy bodies are sensitive to neuroleptics, which can often worsen symptoms and should be used with caution. Individuals with major or mild neurocognitive disorder with Lewy bodies are typically functionally more impaired than would be expected for their cognitive deficits because of the motor and autonomic impairments. They can present with multifocal myoclonus and visual hallucinations.
- **Major or mild neurocognitive disorder due to Parkinson disease:** Parkinson disease onset precedes the onset of major neurocognitive decline by at least 1 yr. Apathy, depression, hallucinations, and REM sleep disorder are suggestive of this diagnosis. The atypical parkinsonian syndrome progressive supranuclear palsy presents with early postural instability and retropulsion, supranuclear gaze palsy, and early cognitive impairment with depression, apathy, and anxiety. Corticobasal degeneration is a progressive asymmetric movement disorder with attentional deficits, slow processing speed, extreme rigidity, aphasia, apraxia, and alien-limb syndrome.
- **Major or mild vascular neurocognitive disorder:** The onset of cognitive decline is temporally related to one or more cerebrovascular events. The diagnosis is supported by neuroimaging evidence of parenchymal injury, including large vessel infarcts or hemorrhages, two or more lacunar infarcts outside the brainstem, or confluent white matter lesions attributed to cerebrovascular disease. Patients typically present with decline in processing speed, complex attention, and executive dysfunction. Stepwise and/or fluctuating decline is described. Prominent depression, apathy, and personality changes are common.
- **Major or mild neurocognitive disorder due to traumatic brain injury (TBI):** This NCD presents immediately after the occurrence of or can be attributed to a traumatic brain injury that causes loss of consciousness, posttraumatic amnesia, disorientation, or neurologic signs such as seizure or hemiparesis. Cognitive presentation may be variable but may include difficulty with complex attention, executive dysfunction, or deficits in learning and memory. Associated findings include disturbances in emotional function and personality change. The features of major or mild NCD due to TBI vary by age of patient and specifics

of the injury as well as other factors, such as premorbid functioning of the patient. Chronic traumatic encephalopathy can be seen in individuals susceptible to multiple concussive episodes of the kind that may occur playing certain sports or working in a dangerous job.

- **Substance/medication-induced major or mild neurocognitive disorder:** An NCD that persists beyond the duration of intoxication and acute withdrawal from a substance. NCD due to alcohol frequently manifests with memory, learning, and executive impairments. Wernicke syndrome is an acute neurologic disorder caused by thiamine deficiency manifesting with a clinic triad of encephalopathy, oculomotor dysfunction, and gait ataxia. Korsakoff syndrome is a late manifestation of Wernicke syndrome manifesting with dense anterograde amnesia and confabulation. MRI may show mammillary body or medial dorsal thalamic nucleus atrophy. Major or mild NCD may be induced by medication or combinations of medications, including those with sedating and pain-ameliorating properties and those with anticholinergic properties. Particular attention should be paid to review of medications in any patient with major or mild NCD, especially those in the geriatric population.
- **Major or mild neurocognitive disorder due to HIV infection:** Neurocognitive deficits may show a subcortical pattern with prominent impairment of executive function with slowed processing speed and difficulty with learning new information.
- **Major or mild neurocognitive disorder due to Prion disease:** Neurocognitive deficits occur rapidly, typically over 6 mo as occurs in Creutzfeldt-Jakob disease. In some variants, prominent psychiatric symptoms such as depression and anxiety may occur prior to neurocognitive deficits. Ataxia, myoclonus, chorea, and a prominent startle reflex are typically present.
- **Major or mild neurocognitive disorder due to Huntington disease:** Early prominent changes in processing speed, organization, and planning rather than learning and memory are common. Behavior changes, changes in mood, anxiety, obsessive-compulsive symptoms, irritability, and apathy often precede motor symptoms.
- **Major or mild neurocognitive disorder due to another medical condition:** Many medical conditions can cause NCDs. Examples include structural brain lesions such as primary or secondary brain tumors, subdural hematomas or those seen in normal pressure hydrocephalus, hypoxia, infectious causes, endocrine conditions, immune disorders, and metabolic conditions. The temporal association between the onset or exacerbation of the medical condition and the development of the cognitive deficit supports the diagnosis.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Etiology is assessed by a detailed history from the patient, family members, or other informants, complete physical examination, and ancillary tests, including neuropsychological testing and imaging studies.

LABORATORY TESTS & IMAGING STUDIES

- Detailed physical examination and neuropsychological testing and neuroimaging are indicated. In some cases, serology and lab testing, including B12 and thyroid-stimulating hormone (TSH) levels, are useful or diagnostic. Biomarkers and genetic screening tests are diagnostic in some cases. Particular attention should be paid to rule out underlying medical causes of the major or mild NCD.
- Alzheimer disease: Detailed history and physical examination including neuropsychological testing often points to the diagnosis. MRI may show hippocampal and temporoparietal cortical atrophy. PET scan may reveal hypometabolism in temporoparietal regions. Cerebrospinal fluid biomarkers include elevated total tau and phosphorylated tau levels with reduced amyloid beta-42. Amyloid PET scanning may have diagnostic value. *APOE* testing may detect APOE4, a risk factor for development of Alzheimer disease. For early onset, autosomal dominant inheritance mutation in *APP, PSEN1,* or *PSEN2* may be detected.
- Frontotemporal disorder: In cases with early-onset behavior or language disorders, an MRI or CT scan may show atrophy in frontal lobes and/or corresponding parts of anterior or inferior temporal lobes either bilaterally or asymmetrically. Functional imaging may show hypoperfusion in the corresponding regions. In familial cases, genetic mutations in genes encoding the microtubule-associated protein tau and the granulin gene may confirm the diagnosis.
- Lewy body disease: Sleep study may help to confirm a diagnosis of REM sleep behavior disorder. Nuclear medicine testing including single photon emission computed tomography (SPECT) or PET may show low striatal dopamine transporter uptake.
- Parkinson disease: Abnormal dopamine transporter scans are supportive of the diagnosis.
- Vascular disorder: Neurologic assessment often reveals a history of stroke or transient ischemic attack (TIA). MRI or CT scan may show significant parenchymal injury attributed to cerebrovascular disease.
- TBI: May be associated with abnormal CT or MRI scan showing petechial hemorrhages, diffuse axonal injury, subdural or subarachnoid hemorrhage, or evidence of contusion.
- Prion disease: May be suspected in patients with appropriate clinical presentation, including rapidly progressive course. MRI may show gray matter hyperintensities in the subcortical region, particularly in the putamen and head of caudate nuclei. Electroencephalogram (EEG) reveals periodic synchronous biphasic or triphasic sharp waves complexes. Cerebrospinal fluid (CSF) biomarkers including 14-3-3, tau, S100 protein, or neuron-specific enolase are suggestive, though not diagnostic.
- Huntington disease: Genetic testing for trinucleotide cytosine-adenine-guanine (CAG) repeat expansion in the gene that encodes Huntington protein on chromosome 4 is diagnostic.

Rx TREATMENT

- Initial treatment is directed to the underlying etiology.
- Treatment of memory disturbance may be indicated in some causes of major or mild NCDs, such as those caused by Alzheimer disease.
- Treatment both acutely and chronically is often supportive and aimed at ameliorating behavior and other neuropsychiatric disturbances that may be present.
- Behavioral treatments should be considered first line for most behavior manifestations, although management of agitation in dementia is notoriously difficult. Acetylcholinesterase inhibitors and memantine can be prescribed for cognitive enhancement, and nighttime agitation can be treated with trazodone. If agitation persists, citalopram can be tried with attention paid to potential prolongation of the QTc, or another selective serotonin reuptake inhibitor (SSRI) can be tried. Treatment with low doses of atypical antipsychotics such as quetiapine can be effective if Lewy body dementia has been ruled out after appropriate consideration of and disclosure of potential adverse effects including QTc prolongation, torsade des pointes, extrapyramidal symptoms/neuroleptic malignant syndrome (NMS) and stroke, and risk vs. benefit has been calculated. Recently, Nuedexta (dextromethorphan/quinidine) has been tried with preliminary benefit for agitation as well as pathological affect. Pharmacologic treatments for behavior disturbance have a limited role in improving overall quality of life for most causes of major or minor NCD, although they may have short-term efficacy in acute circumstances.
- Pharmacologic and cognitive behavior treatment may be helpful for associated psychiatric symptoms such as mood disorders, psychosis, and anxiety.
- Patient safety, including risks associated with driving, wandering, and cooking, should be addressed early in the course of the illness.
- Family education and support may help reduce the need for a skilled nursing facility and reduce caregiver stress and burnout.
- Cognitive rehabilitation to promote recovery may be helpful.
- Supervised living may ensure appropriate long-term care in late stages of progressive illness.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Alzheimer Disease (Related Key Topic)
Delirium (Related Key Topic)
Human Immunodeficiency Virus (Related Key Topic)
Huntington Disease (Related Key Topic)
Parkinson Disease (Related Key Topic)
Progressive Supranuclear Palsy (Related Key Topic)
Traumatic Brain Injury (Related Key Topic)
Wernicke Syndrome (Related Key Topic)

AUTHOR: **Michael Friedman, MD**

SUGGESTED READINGS

American Psychiatric Association: *Diagnostic and statistical manual of mental disorders*, ed 5, Arlington, VA, 2013, American Psychiatric Association.

Blazer DG, Wallace RB: Cognitive aging: what every geriatric psychiatrist should know, *Am J Geriatr Psychiatry* 24(9):776-781, 2016.

Borsje P et al: The course of neuropsychiatric symptoms in community-dwelling patients with dementia: a systematic review, *Int Psychogeriatr* 1-21, 2016.

Luck T et al: Prevalence of DSM-5 mild neurocognitive disorder in dementia-free older adults: results of the population-based LIFE-Adult-Study, *Am J Geriatr Psychiatry* 25(4):340-341, 2016.

BASIC INFORMATION

DEFINITION

Neurofibromatosis (NF) is an autosomal-dominant disorder affecting bone, the nervous system, soft tissue, and skin. There are three major subtypes of NF disorders: NF type 1 (NF1), NF type 2 (NF2), and schwannomatosis (SWN). SWN has only recently been recognized as a distinct disorder; currently very little is known about it.

SYNONYMS

NF1: von Recklinghausen disease, peripheral NF
NF2: Bilateral acoustic neurofibromatosis, central NF

ICD-10CM CODES

Q85.00 Neurofibromatosis, unspecified
Q85.01 Neurofibromatosis, type 1
Q85.02 Neurofibromatosis, type 2

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence of NF1 (one case/3000 live births), NF2 (one case/25,000 live births).
- Prevalence of NF1 (one case/5000 persons), NF2 (one case/210,000 persons).
- NF1 and NF2 are autosomal dominant; approximately 50% of cases have no family history.
- The two disorders affect approximately 100,000 people in the U.S.
- Affects males and females equally.
- NF1 may be associated with optic gliomas, astrocytomas, spinal neurofibromas, pheochromocytomas, and chronic myeloid leukemia.
- NF2 may be associated with meningiomas, spinal schwannomas, and cataracts.
- For SWN, the incidence is one per 30,000 persons, and the disease is mostly sporadic in nature.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Common features of NF1 include:
  1. Café-au-lait macules (100% of children by age 2 yr)
     a. Hyperpigmented skin lesions (Fig. 1) occurring anywhere on the body except the face, palms, and soles
     b. Appear early in life and increase in size and number during puberty
     c. Are focal or diffuse
  2. Axillary and inguinal freckling (70%)
  3. Multiple neurofibromas (Fig. 2) can be soft or firm; three subtypes:
     a. Cutaneous: Circumscribed, not specific for NF1
     b. Subcutaneous: Circumscribed, not specific for NF1
     c. Plexiform: Noncircumscribed, thick and irregular; can cause disfigurement of supportive structures and specific for NF1
  4. Lisch nodule (small hamartoma of the iris) found in >90% of adult cases
  5. Visual defects possibly related to optic gliomas (2% to 5%)
  6. Neurodevelopment problems such as learning disability and mental retardation (30% to 40%)
  7. Skeletal disorders, including long bone dysplasia, pseudoarthrosis, scoliosis, short stature, and decreased bone mineral density
- Common features of NF2 include:
  1. Hearing loss and tinnitus related to bilateral acoustic neuromas (>90% of adults)
  2. Cataracts (81%)
  3. Headache (may be due to intracranial meningiomas, which are present in 80% of patients)
  4. Unsteady gait
  5. Cutaneous and subcutaneous neurofibromas but fewer than in NF1
  6. Café-au-lait macules (1%) (Fig. 3)
- Common features of SWN include painful multiple schwannomas of the spinal (74%), peripheral (89%), or cranial nerves *except* the vestibular nerve (9%)

ETIOLOGY

- NF1 is caused by DNA mutations located on the long arm of chromosome 17 responsible for encoding the protein neurofibromin.
- NF2 is caused by DNA mutations located in the middle of the long arm of chromosome 22 responsible for encoding the protein merlin, which is a potent inhibitor of glioma growth.
- Both proteins are speculated to act as tumor suppressors.
- The etiology of SWN remains unclear; however, most cases are attributed to mutations on chromosome 22, which inactivate two distinct tumor-suppressor genes.

DIAGNOSIS

- NF1 is diagnosed if the person has two or more of the following features:
  1. Six or more café-au-lait macules >5 mm in prepubertal patients and >15 mm in postpubertal patients
  2. Two or more neurofibromas of any type or one plexiform neurofibroma
  3. Axillary or inguinal freckling
  4. Optic glioma
  5. Two or more Lisch nodules (iris hamartomas)
  6. Sphenoid wing dysplasia or cortical thinning of long bones, with or without pseudoarthrosis
  7. A first-degree relative (parent, sibling, or child) with NF1 based on the previous criteria
- NF2 is diagnosed if the person has either of the following two criteria:
  1. Bilateral eighth nerve masses seen by appropriate imaging studies (e.g., CT, MRI)
  2. A first-degree relative with NF2 and either a unilateral eighth nerve mass or two of the following: Neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacity

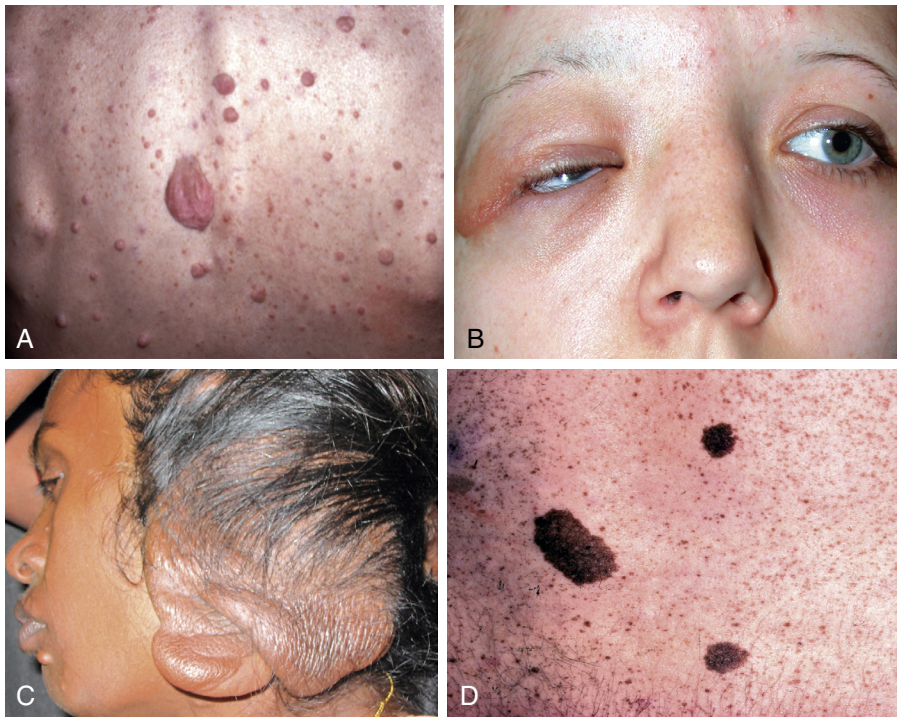

FIG. 1 Systemic features of Neurofibromatosis type 1. A, Discrete neurofibromas. **B,** Nodular plexiform neurofibroma of the eyelid. **C,** Elephantiasis nervosa. **D,** Cafe-au-lait spots. (Courtesy S. Kumar Puri; From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, WB Saunders.)

FIG. 2 Multiple neurofibromas are present in this individual. (From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

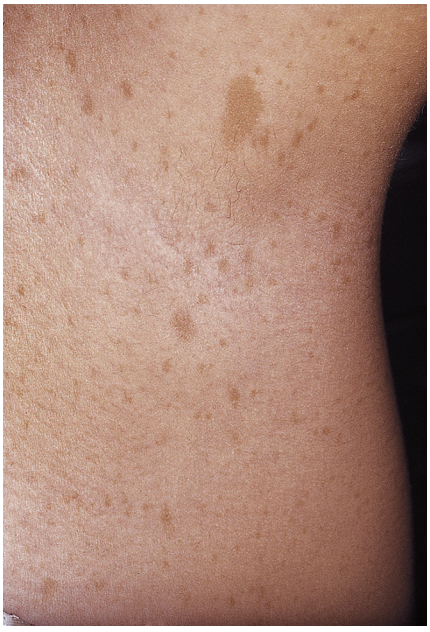

FIG. 3 A café-au-lait spot and multiple freckles (Crowe sign) in the axillary vault is seen in this patient with neurofibromatosis. (From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

- SWN is diagnosed in an individual >30 yr having either of the following two criteria:
  1. Two nonintradermal schwannomas, no vestibular tumor found on MRI scan, no NF2 mutation
  2. One nonvestibular schwannoma and a first-degree relative fitting the above criteria

DIFFERENTIAL DIAGNOSIS

- Abdominal NF
- Myxoid lipoma
- Nodular fasciitis
- Fibrous histiocytoma
- Segmental NF

WORKUP

The diagnosis of NF is usually self-evident. Workup is dictated by clinical symptoms in NF1 and usually includes MRI evaluation of the head and spine in NF2 and SWN. In fact, if NF2 is suspected but no vestibular nerve schwannomas are found, the diagnosis points to SWN.

LABORATORY TESTS

- Genetic testing is possible in individuals who desire prenatal diagnosis for NF1. There is no single standard test and multiple tests are required. Results can only tell if an individual is affected but cannot predict the severity of the disease due to variable expression.
- In NF2, linkage analysis testing provides a >99% certainty the individual has NF2.

IMAGING STUDIES

- MRI with gadolinium is the imaging study of choice in both NF1 and NF2 patients. MRI increases detection of optic gliomas, tumors of the spine, acoustic neuromas, and "bright spots" believed to represent hamartomas.
- MRI of the spine is recommended in all patients diagnosed with NF2 to exclude intramedullary tumors.

OTHER TESTS

- Wood's lamp examination may be useful in patients with very pale skin for visualizing café-au-lait spots.
- Slit-lamp examination is recommended for children >6 yr to confirm the presence of Lisch nodules and subcapsular opacity.

Rx TREATMENT

Treatment is directed primarily at symptoms and complications of NF1 and NF2. As for SWN, resection should be reserved for tumors that are symptomatic or threaten to cause spinal cord compression.

NONPHARMACOLOGIC THERAPY

- Counseling addressing prognosis and genetic, psychological, and social issues.
- Hearing testing and speech pathology evaluation.

ACUTE GENERAL Rx

- Surgery is usually not done on skin tumors unless cosmetically requested or if suspicion of malignant transformation exists.
- Surgery may be indicated for spinal or cranial neurofibromas, gliomas, or meningiomas.
- Acoustic neuromas can be treated by surgical excision.

CHRONIC Rx

- Radiation may be indicated in optic nerve gliomas and patients whose central nervous system tumors show radiographic progression.
- Stereotactic radiosurgery with a gamma knife may be an alternative approach to surgery for acoustic neuromas.
- Bevacizumab continues to be studied as a treatment option for NF2 meningiomas (which express vascular endothelial growth factor [VEGF]).

DISPOSITION

- Prognosis varies according to the severity of involvement.
- There is no cure for NF.

REFERRAL

A multidisciplinary team of consultants is needed in patients with NF, including neurosurgeon, otolaryngologist, dermatologist, neurologist, audiologist, speech pathologist, geneticist, and neuropsychologist.

PEARLS & CONSIDERATIONS

- Friedrich Daniel von Recklinghausen first reported his cases in 1882, although there had been similar accounts dating back to the 1600s.
- A high SPRED1 mutation detection rate has been identified in NF1 mutation-negative families with an autosomal dominant phenotype of café-au-lait macules with or without freckling and no other NF1 features.

COMMENTS

For additional information and patient resources, refer to the Neurofibromatosis Network or Neurofibromatosis Inc. (www.nfnetwork.org).

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Neurofibromatosis Type 1 (Patient Information)
Neurofibromatosis Type 2 (Patient Information)

AUTHOR: **Craig Blakeney, MD**

SUGGESTED READINGS

Blakeley JO, Plotkin SR: Therapeutic advances for the tumors associated with neurofibromatosis type 1, type 2, and schwannomatosis, *Neuro Oncol* 18(5):624-638, 2016.

Shah KN: The diagnostic and clinical significance of café-au-lait macules, *Pediatr Clin North Am* 57(5):1131-1153, 2010.

Neuroleptic Malignant Syndrome

BASIC INFORMATION

DEFINITION

Neuroleptic malignant syndrome (NMS) is a disorder characterized by hyperthermia, muscular rigidity, autonomic dysfunction, and depressed/fluctuating levels of arousal that evolve over 24 to 72 hr. This occurs as an idiosyncratic adverse reaction to medications that affect the central dopaminergic system, usually D2 receptors blockade.

SYNONYM

NMS

ICD-10CM CODE
G21.0 Malignant neuroleptic syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 0.02% to 0.2% annual incidence in psychiatric population
PREDOMINANT SEX: More than two thirds of patients are male.
PREDOMINANT AGE: Young and middle-aged adults
PREDISPOSING FACTORS: History of intake of dopamine antagonists, e.g., antipsychotics

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Syndrome typically begins abruptly while the patient is taking therapeutic (not toxic) dosages of neuroleptics and reaches maximum severity within 72 hr
- Severe muscle rigidity (hypertonia, cogwheeling, or "lead pipe" rigidity)
- Hyperthermia (38.6° to 42.3° C [101.48° to 108.14° F], usually <40° C [104° F])
- Autonomic symptoms: Diaphoresis, dysphagia, sialorrhea, skin pallor, urinary incontinence
- Tachycardia, tachypnea
- Labile blood pressure (hypertension or postural hypotension)
- Agitation, catatonia, fluctuating consciousness, obtundation

ETIOLOGY

- Exact etiology is unknown, but it has been suggested that sudden and marked dopamine receptor blockade in nigrostriatal, hypothalamic, mesolimbic, and mesocortical pathways leads to clinical manifestations seen in NMS.
- Neuroleptic drugs have different potencies for inducing NMS:
  1. Typical neuroleptics:
     a. High potency: Haloperidol
     b. Medium potency: Chlorpromazine, fluphenazine
     c. Low potency: Levomepromazine, loxapine
  2. Atypical neuroleptics:
     a. Low potency: Risperidone, olanzapine, clozapine, quetiapine

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infectious: Encephalitis, meningitis, brain abscess, rabies, tetanus, sepsis
- Endocrine: Pheochromocytoma, thyrotoxicosis
- Toxic: Substances of abuse (ecstasy, phencyclidine), heavy metals (lead, arsenic), lithium, salicylates
- Pharmacologic: Serotonin syndrome, malignant hyperthermia, drug withdrawal, or overdose
- Environmental: Heatstroke, spider envenomation
- Neuropsychiatric: Catatonia, acute psychosis with agitation, status epilepticus
- Table E1 summarizes the differential diagnosis of neuroleptic malignant syndrome

WORKUP

A careful and thorough drug history should be obtained. There is a significant overlap in

TABLE E1 Differential Diagnosis of Neuroleptic Malignant Syndrome

Disease*	Pathologic Mechanism	Differentiating Factor	Time Course	Treatment
Neuroleptic malignant syndrome	Impaired thermoregulation in hypothalamus and basal ganglia due to relative lack of dopamine activity	Antipsychotic medication use, muscle rigidity	Gradual, progresses over several days	Stop offending medication Hydration Active cooling Intravenous benzodiazepines to relax muscles and control agitation Neuromuscular blockade (nondepolarizing agents) Controversial Bromocriptine or amantadine Dantrolene
Serotonin syndrome	Excess serotonin and dopamine levels in central nervous system	Medications (usually a combination) that increase serotonin levels (e.g., SSRIs, MAOIs, dextromethorphan, lithium, meperidine, tramadol, tryptophan); muscle rigidity	Usually rapid after introduction of new medication or increase in dose; can be gradual	Stop offending medication Hydration Active cooling Cyproheptadine
Heat stroke	Environmental heat stress	Environmental exposure history; muscle rigidity rare	Rapid or gradual	Hydration Active cooling
Malignant hyperthermia	Genetic instability of sarcoplasmic reticulum, causing massive calcium release after administration of triggering medication	Occurs after administration of inhalational anesthetic or succinylcholine; muscle rigidity	Sudden, provoked by administration of anesthetic	Stop anesthetic Hydration Active cooling Dantrolene

*Other clinical entities to consider in the diagnosis of these conditions include Addison syndrome, central nervous system infection, delirium tremens, hypocalcemia, hypoglycemia, hyponatremia, intracranial hemorrhage, lethal catatonia, poisoning (e.g., amphetamines, anticholinergics, cocaine, nicotine, salicylates, sympathomimetics, strychnine, theophylline), sedative-hypnotic drug withdrawal, sepsis, status epilepticus (including nonconvulsive status), tetanus, thalamic infarct, thyroid storm, and psychotic agitation.
MAOIs, Monoamine oxidase inhibitors; *SSRIs,* selective serotonin reuptake inhibitors.
From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, WB Saunders.

the features of NMS and serotonin syndrome. The major difference is the presence of hyperreflexia and myoclonus with serotonin syndrome.

LABORATORY TESTS

- Elevated creatine phosphokinase (CPK) (sensitivity 0.71)
- Urinary myoglobin
- Leukocytosis, usually 10,000 to 40,000/mm3
- Electrolytes and renal function
- Blood gases
- Drug levels

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Stop all neuroleptic drugs and reinstitute any recently discontinued dopaminergic agonists.
- Remember that metoclopramide is also an antidopaminergic drug that must be discontinued and avoided.
- Respiratory and nutritional support as required.
- Careful fluid balance monitoring with adequate hydration (intravenous in severe cases).
- Active cooling (cooling blanket and antipyretics).
- Skilled nursing care is necessary to prevent decubitus ulcers in bed-confined patients.

ACUTE GENERAL Rx

- Bromocriptine, a dopamine receptor agonist, is the mainstay of therapy for patients with NMS. Initial doses of 2.5 to 10 mg are given IV q8h and are increased by 5 mg/day until clinical improvement is seen. The drug should be continued for at least 10 days after the syndrome has been controlled and then tapered slowly.
- Dantrolene, which blocks calcium efflux from the sarcoplasmic reticulum of skeletal muscles, inhibits the excessive muscle contractions that generate myoglobinemia. Initially, patients can be given 0.25 mg/kg IV q6 to 12h, followed by a maintenance dose up to 3 mg/kg/day. After 2 to 3 days, patients may be given the drug orally (25 to 600 mg/day in divided doses). Oral dantrolene therapy (50 to 600 mg/day) may be continued for several days afterward.
- Amantadine, an N-Methyl-D-aspartate (NMDA) receptor antagonist with possible dopaminergic properties, can be administered orally at doses of 100 to 200 mg PO bid for moderate to severe cases. As an adjunctive treatment, it has been shown to reduce mortality in comparison to supportive therapy alone.
- IV benzodiazepines (e.g., diazepam 2 to 10 mg, with total daily dose of 10 to 60 mg) to relax muscles and control agitation.
- Electroconvulsive therapy with neuromuscular blockage may be beneficial in pharmacologically refractory cases. Succinylcholine should not be used because it may cause hyperkalemia and cardiac arrhythmias in patients with rhabdomyolysis or dysautonomia.

CHRONIC Rx

- Respiratory care, nutritional support, and physical therapy may be required in more severe cases.
- Appropriate therapy would be required in patients with persistent neuropsychiatric sequelae of NMS (e.g., antidepressants for depression, cognitive behavioral therapy for cognitive deficits, rehabilitation for contractures).

DISPOSITION

- Mortality rate is currently 5% to 10% despite therapeutic measures. Serious sequelae may occur in a further 20%. Complete recovery occurs in >70% of patients.
- Rhabdomyolysis is the most common complication. Other complications include acute kidney injury, respiratory failure, pneumonia, and sepsis.
- Causes of death include cardiac arrhythmias, myocardial infarction, renal failure secondary to rhabdomyolysis, seizures, pulmonary edema, and bronchopneumonia.
- Factors adversely affecting mortality are increased age, acute respiratory failure, renal failure, and core temperature >104° F (40° C).
- Patients should be monitored closely for future complications of pharmacologic therapy.

REFERRAL

If the patient's condition is critical, it is preferable to treat the patient in a medical/neurologic ICU.

PEARLS & CONSIDERATIONS

COMMENTS

- Early detection and diagnosis lead to a more favorable outcome. Refer to recent consensus diagnostic criteria as a guide. Treatment is a medical emergency.
- Sudden withdrawal from dopaminergic agents (such as those used in Parkinson disease) may lead to "levodopa withdrawal syndrome" that presents with similar clinical manifestations.
- Patients with dementia with Lewy bodies have increased susceptibility to neuroleptic malignant syndrome.

SUGGESTED READING

Available at ExpertConsult.com

AUTHORS: **Chloe Mander Nunneley, MD, Joseph S. Kass, MD, JD, FAAN,** and **Fariha Jamal, MD**

SUGGESTED READING

Gurrera RJ et al: An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method, *J Clin Psychiatry* 72:1222-1228, 2011.

BASIC INFORMATION

DEFINITION

Neuropathic pain is not itself a disease but rather a symptom that is associated with multiple different diseases. Thus, it is not enough to define its presence without searching for a cause. It is defined as the sensation derived from the abnormal discharges of impaired or injured neural structures in either the peripheral or central nervous system. Descriptors include:

- Hyperesthesia: Heightened sensitivity to nonpainful stimuli (e.g., light touch)
- Hyperalgesia: Heightened sensitivity to painful stimuli (e.g., pinprick), or reduced threshold to feel pain
- Allodynia: Pain provoked by a stimulus that is not normally painful

SYNONYM

Neuralgia

ICD-10CM CODES

B02.29	Postherpetic neuralgia
G50.0	Trigeminal neuralgia
G58.0	Intercostal neuropathy
G58.7	Mononeuritis multiplex
G58.8	Other specified mononeuropathies
G58.9	Mononeuropathy, unspecified
G61.9	Inflammatory polyneuropathy, unspecified
G62.0	Drug-induced polyneuropathy
G62.1	Alcoholic polyneuropathy
G62.9	Polyneuropathy, unspecified
G63.2	Diabetic polyneuropathy
G63.5	Polyneuropathy in systemic connective tissue disease
G63.8	Polyneuropathy in other diseases classified elsewhere
M79.2	Neuralgia and neuritis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Estimates of the prevalence of neuropathic pain in the general population range from 1.6% to 8.2%
- Demographics vary widely depending on etiology, for example:
  1. Postherpetic neuralgia: Affects elderly, pain seen in almost 100% of cases
  2. AIDS: 30% of patients affected
  3. Diabetes mellitus: 20% to 24% affected (prevalence rates vary, increasing with longer disease duration)
  4. Fabry disease: Affects mostly children, pain in 81% to 90% of patients

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History: Localize the disease with questions
  1. Quality (description) of neuropathic pain: Burning, hot or cold, "icy hot," "pins and needles," stinging, lancinating, sharp, shooting
  2. Distribution of symptoms may aid in localization (i.e., "stocking-glove" symptoms in generalized neuropathy, numbness in a peripheral nerve territory in focal neuropathy)
  3. Generalized small fiber neuropathy: Dysesthesias without numbness common, but many etiologies (e.g., diabetes) cause both small and large fiber dysfunction
  4. Large fiber neuropathy (LFPN): Coexisting numbness, hyporeflexia, or weakness may be seen, usually worse distally
  5. Nerve root: Coexisting neck or low back pain that radiates along a specific dermatome; most common cause is structural compression
  6. Spinal cord symptoms: Coexisting spasticity, bowel or bladder involvement, sensory level
  7. Prior history of thalamic stroke in central thalamic pain syndrome (Dejerine-Roussy syndrome)
  8. Family history may suggest a genetic cause
- Examination: See Table 1. Table 2 describes joint involvement in neuropathic arthropathy. Fig. 1 illustrates a diagnostic approach to neuropathic pain. Fig. 2 shows a neuropathic ankle

ETIOLOGY & LABORATORY EVALUATION (Table 3)

- Metabolic: Diabetes mellitus; malnutrition and alcoholism; vitamin B_{12} deficiency; thiamine deficiency; porphyria; Fabry disease
- Inflammatory: Autoimmune diseases (systemic vasculitides, systemic lupus erythematosus, Sjögren syndrome, etc.), acute inflammatory demyelinating polyneuropathy (classically presents with ascending weakness and numbness, although pain is also a common feature), chronic inflammatory demyelinating polyneuropathy, sarcoidosis, multiple sclerosis
- Infiltrative: Amyloidosis, paraproteinemias (e.g., monoclonal gammopathy of uncertain significance [MGUS] associated neuropathy)
- Infectious: Postviral (brachial neuritis), HIV/AIDS, HSV, varicella-zoster virus (VZV; postherpetic neuralgia), Lyme disease, leprosy (thickened nerves and skin lesions), syphilis
- Neoplastic and paraneoplastic-carcinomatous infiltration of nerve/nerve root, anti-Hu
- Drugs/toxins: History of exposure to alcohol, chemotherapeutic agents (paclitaxel, vincristine), isoniazid, metronidazole, or heavy metals (thallium, arsenic)

DIAGNOSIS

LABORATORY TESTS

- Fasting blood glucose (FBG)
- 2-hour oral glucose tolerance test (OGTT)
- Vitamin B_{12} level
- If B_{12} level normal: Serum methylmalonic acid and homocysteine levels
- Serum erythrocyte sedimentation rate (ESR), ANA, SS-A and SS-B, c-ANCA, p-ANCA
- RPR or FTA-ABS
- Serum ACE level (sarcoid)
- HIV antibody
- SPEP, UPEP, immunofixation
- Urine and stool protoporphyrins, if porphyria is suspected clinically

TABLE 1 Examination

Exam Finding	Localization
Pinprick/temperature loss alone	Small fibers only
Pinprick/temperature loss + vibratory/proprioceptive loss	Small and large fibers
Sensory loss and motor dysfunction worse distally than proximal	Large fiber neuropathy
Sensory loss and motor dysfunction along single nerve distribution	Single nerve
Sensory loss and motor dysfunction along multiple single nerves	Multiple mononeuropathies (i.e., mononeuropathy multiplex)
Motor and sensory loss involving multiple nerves belonging to specific region of brachial or lumbar plexus	Plexopathy
Sensory loss along dermatome with multiple myotomal muscles affected	Nerve root lesion
Asymmetric sensory loss without weakness and pseudoathetosis	Dorsal root ganglion
Vibratory/proprioceptive loss without pinprick/temperature loss	Dorsal column dysfunction (from compressive lesion, B_{12} deficiency, or tabes dorsalis from neurosyphilis)
Sensory level with weakness below the level of lesion and long tract signs (spasticity/Babinski sign)	Spinal cord lesion
Hemisensory hyperalgesia	Contralateral thalamus

TABLE 2 Joint Involvement in Neuropathic Arthropathy

Disease	Site of Involvement
Diabetes mellitus	Midtarsal, metatarsophalangeal, tarsometatarsal
Syringomyelia	Shoulder, elbow, wrist
Amyloidosis	Knee, ankle
Congenital sensory neuropathy	Knee, ankle, intertarsal, metatarsophalangeal
Tabes dorsalis	Knee, hip, ankle
Leprosy	Tarsal, tarsometatarsal

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

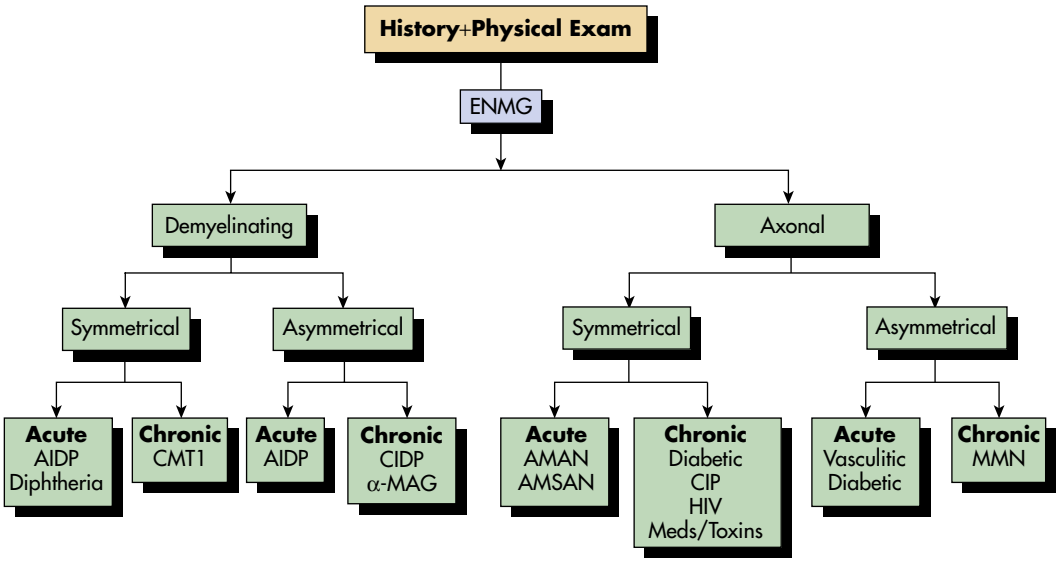

FIG. 1 A systematic approach to evaluate neuropathy. The diseases listed are examples of neuropathies associated with specific neurophysiologic and clinical findings. Diabetic distal, predominantly sensory neuropathies are manifested as chronic axonal neuropathies; acute asymmetric neuropathies can also occur with diabetes. Most neuropathies caused by toxins or by side effects of medication are chronic, symmetric axonal neuropathies. AIDP, AMAN, and AMSAN are subtypes of Guillain-Barré syndrome. These and other examples are discussed in more detail in the text. *AIDP,* Acute inflammatory demyelinating polyradiculoneuropathy; *AMAN,* acute motor axonal neuropathy; *AMSAN,* acute motor and sensory axonal neuropathy; *CIDP,* chronic inflammatory polyradiculoneuropathy; *CIP,* chronic illness polyneuropathy; *CMT1,* Charcot-Marie-Tooth disease type 1, a genetic disorder; *ENMG,* electroneuromyography; *HIV,* human immunodeficiency virus–related neuropathy; *α-MAG,* alpha-myelin-associated glycoprotein; *MMN,* multifocal motor neuropathy. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.)

FIG. 2 Neuropathic ankle. Marked instability of the subtalar and midtarsal joints is seen with collapse on weight bearing. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

- Hu antibody: Can be seen in both small cell and non–small cell lung cancers, may be positive without evidence of lung cancer
- Lumbar puncture: Protein elevation, oligoclonal bands, CSF/serum IgG index

ELECTROPHYSIOLOGY STUDIES

- Electrophysiologic testing (electromyography with nerve conduction studies): May be normal in small fiber neuropathies or CNS lesion, but is often abnormal in large fiber neuropathies
- Quantitative sensory testing: Abnormal in small and large fiber neuropathy
- Evoked potentials (only if suspicion for spinal cord lesion)

PATHOLOGY STUDIES

- Nerve biopsy is occasionally useful in selected cases, particularly when vasculitis, sarcoidosis, or amyloid neuropathy are in the differential.
- Skin biopsy for intraepidermal nerve fiber (IENF) density may be useful for small fiber neuropathy when other studies are normal.
- Rectal or abdominal fat pad biopsy may show amyloid deposition in systemic amyloidosis.

IMAGING STUDIES

Based on localization:

- MRI (with and without contrast):
  1. Of the brain to exclude thalamic pathology if symptoms and signs are consistent with thalamic lesion (hemibody pain)
  2. Of the spinal cord and nerve roots to exclude structural, inflammatory, neoplastic, or infectious causes
  3. Of the lumbar spine to evaluate for arachnoiditis
- If MRI cannot be performed, consider:
  1. CT of the brain for thalamic pathology
  2. CT myelography of the spinal cord to evaluate for structural/neoplastic disease, but only if clinical signs of spinal or nerve root compromise are present

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Counseling should be initiated at the beginning of therapy to address psychological issues exacerbating physiologic pain.
- Physical therapy: Especially in cases of chronic neck and low back pain.
- Cognitive behavioral therapy

ACUTE GENERAL Rx

- Treatment of the underlying cause if possible will help slow or prevent worsening.
- Medications may reduce or alleviate pain but do not affect numbness.
- Antidepressants:
  1. Tricyclic antidepressants (TCAs): Nortriptyline preferred over amitriptyline (fewer anticholinergic side effects with nortriptyline). Begin 25 mg PO qd in adults, or 10 mg qd in elderly. Increase dose by 25 mg every wk as tolerated until usual maximal effective dose of 150 mg/day.
  2. Duloxetine: Begin 30 mg daily, increase to 60 to 120 mg daily. Duloxetine is effective in diabetic neuropathy, post-herpetic neuropathy, and chemotherapy-induced painful peripheral neuropathy.
  3. Venlafaxine.
- Antiepileptics:
  1. Gabapentin: Begin 300 mg PO qd, advance to 300 mg PO tid by the end of the first wk. Effective dose: Higher than 1600 mg/day. Max dose: 1200 mg PO tid.
  2. Carbamazepine: For trigeminal neuralgia. Begin 400 mg PO bid, increase to tid if necessary. Side effects and drug levels help to determine optimal dosing. Risk of aplastic anemia and hyponatremia (monitor CBC and chemistries). Risk of Stevens-Johnson syndrome, especially in Asian population (check HLA before starting).

TABLE 3 Clinical Presentation and Laboratory Findings

Neuropathy Type	Predisposition	Examination Findings	EMG/NCS	Laboratory Analysis
Idiopathic small fiber PN	Age >50	Strength: Normal Reflexes: Normal Pos/vib: Normal Pain/temp: Decreased distally	Normal	Serum studies: Normal skin biopsy: Abnormal sudomotor studies: Abnormal
Diabetic PN	Long-standing disease Family history	Strength normal to reduced, sensation reduced distally	Abnormal	Abnormal glucose tolerance: High fasting glucose
Inherited PN	Family history	Pes cavus, hammer toes, reduced reflexes, sensation reduced distally	Abnormal	Genetic studies may be abnormal, other studies normal
Familial amyloid PN	Family history	Pain/temp loss, reduced reflexes, orthostasis	Abnormal if large fibers affected; also carpal tunnel syndrome	Transthyretin genetic study
Acquired amyloid PN	Monoclonal gammopathy	Pain/temp loss, reduced reflexes, orthostasis	Abnormal if large fibers affected; also carpal tunnel syndrome	SPEP, UPEP, immunofixation abnormal
Fabry disease	Age, renal failure, strokes	Normal; possible reduced pain/temp sensation	Normal	α-Galactosidase levels in cultured fibroblasts
PN + mixed connective tissue disease	History of lupus, rheumatoid arthritis, Sjögren syndrome	Reduced reflexes and distal sensation	Abnormal	ANA, RF, SS-A/SS-B may be abnormal
Peripheral nerve vasculitis	Asymmetric disease	Multiple peripheral nerves involved	Abnormal	ANA, RF, SS-A/SS-B, ANCA, cryoglobulins may be abnormal
Paraneoplastic neuropathy	Lung cancer risk factors, chemical exposures	Asymmetric sensory loss, pseudoathetosis, relatively preserved strength	Abnormal	Anti-Hu
Sarcoidosis	Pulmonary sarcoid	Multiple mononeuropathies	Abnormal	Abnormal biopsy, elevated serum ACE, CXR abnormal
Arsenic	Pesticides, copper smelting	Reduced reflexes and distal sensation	Abnormal	Elevated arsenic in plasma, urine, and hair
HIV	Promiscuity, unprotected sex, IV drug abuse, blood transfusion	Variable, but most often reduced reflexes and distal sensation	Abnormal if large fibers involved	HIV antibody

ACE, Angiotensin-converting enzyme; *ANA,* antibody to nuclear antigens; *ANCA,* antineutrophil cytoplasmic antibodies; *CXR,* chest x-ray; *EMG,* electromyography; *HIV,* human immunodeficiency virus; *IV,* intravenous; *NCS,* nerve conduction studies; *PN,* polyneuropathy; *Pos,* position sensation; *RF,* rheumatoid factor; *SPEP,* serum protein electrophoresis; *SS-A,* Sjögren syndrome A; *SS-B,* Sjögren syndrome B; *Temp,* temperature sensation; *UPEP,* urine protein electrophoresis; *Vib,* vibration sensation.
Adapted from Mendell JR, Sahenk Z: Painful sensory neuropathy, *N Engl J Med* 348(13):1243, 2003.

3. Oxcarbazepine: Better tolerated than carbamazepine. Start 150 mg PO bid and gradually increase to a dose of 600 mg bid. Maximum dose is 1200 mg bid.
4. Pregabalin: Begin 50 mg PO tid, increase slowly to 100 to 200 mg PO tid.

- Analgesics: When first-line agents are ineffective. While effective, the use of opioids is associated with substantial adverse effects as well as novel pain syndromes. Chronic use of opioids leads to tolerance and escalation of dose:
  1. Tramadol: 150 mg/day (50 mg tid), increase by 50 mg/wk, max 200 to 400 mg/day.
  2. Morphine (oral): 15 to 30 mg q8h, max 90 to 360 mg/day.
  3. Oxycodone: 20 mg q12h, increase by 10 mg/wk, max 40 to 160 mg/day.
  4. Fentanyl patch: 25 to 100 mcg transdermally q3 days.
- Topical anesthetics:
  1. 5% lidocaine patch, apply to area of pain, max three patches every 12 hr.
  2. Capsaicin cream and patches are inconsistent in their ability to relieve pain and may exacerbate it. A capsaicin 8% patch is approved specifically for post-herpetic neuralgia and is applied for 60 min under medical supervision.
- Procedural/surgical: This option is considered mostly when the patient suffers from pain secondary to spinal cord or cauda equina injury. Studies are limited and benefit is not completely established. Procedures should be considered only when all other therapeutic modalities have failed. In addition, the patient should be cautioned that surgical procedures may not result in pain relief and may be associated with significant morbidity and even mortality.
  1. Dorsal root rhizotomy.
  2. Nerve blocks.
  3. Spinal cord stimulator.

DISPOSITION

Prognosis depends on multiple factors, including:
- Etiology of pain
- Treatment of any underlying condition
- Initiation of appropriate (often multiple) therapeutic modalities
- Patient compliance with prescribed regimen

Most care is accomplished in the outpatient setting, except when surgery is required.

REFERRAL

- Pain clinic
- Neurology
- Psychiatry
- Psychology
- Physiatry
- Anesthesiology (nerve blocks)
- Neurosurgery if considering surgical management

PEARLS & CONSIDERATIONS

- Factitious disorder and malingering frequently manifest with pain complaints. These are diagnoses of exclusion and require negative evaluation for organic etiologies before diagnosis is made.
- Peripheral neuropathy in diabetics increases the risk of foot ulceration by sevenfold. Abnormal results in monofilament testing and vibratory perception (alone or in combination with the appearance of the feet, ulceration, and ankle reflexes) are the most helpful sign for the detection of LFPN.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Joseph S. Kass, MD, JD, FAAN, Gavin Brown, MD,** and **Corey Goldsmith, MD**

SUGGESTED READINGS

Callaghan BC et al: Distal symmetric polyneuropathy: a review, *JAMA* 314(20):2172-2181, 2015.

Kanji JN et al: Does this patient with diabetes have large-fiber peripheral neuropathy? *JAMA* 303(15):1526-1532, 2010.

Smith EM et al: Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial, *JAMA* 309(13):1359-1367, 2013.

Neuropathy, Hereditary

BASIC INFORMATION

DEFINITION

Any disorder affecting the peripheral nervous system, including nerve roots, plexuses, and individual peripheral nerves, that has a genetic basis of inheritance and has been or is capable of being transmitted along generations.

There are many different types of hereditary peripheral neuropathies, including Dejerine-Sottas disease, inherited metabolic neuropathies, hereditary sensory and autonomic neuropathies (HSANs), and hereditary motor neuropathies. Most disorders are diagnosed in infancy or childhood; as such, adult clinicians rarely see these patients. For this reason, this chapter discusses only the hereditary motor and sensory neuropathies that an adult clinician might encounter.

SYNONYMS

Charcot-Marie-Tooth (CMT) disease
Hereditary motor-sensory neuropathy (HMSN)
Hereditary neuropathy with liability to pressure-sensitive palsies (HNPP)

ICD-10CM CODES

G60.0	Hereditary motor and sensory neuropathy
G60.8	Other hereditary and idiopathic neuropathies
G60.9	Hereditary and idiopathic neuropathy, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

All CMT: Approximately 30 per 100,000
- CMT type 1 (demyelinating pathophysiology): 1 in 2500
- CMT type 2 (axonal pathophysiology): 7 in 1000
- CMT type 4 and CMT-X: Rare (either axonal or demyelinating pathophysiology)

HNPP: 2 to 5 per 100,000

PHYSICAL FINDINGS & CLINICAL PRESENTATION

CMT: Highly variable
- Age at onset earlier for CMT-1 than CMT-2, but both may present from childhood to old age.
- Severely affected patients have severe distal weakness and muscle atrophy with hand (prominently affecting interossei) and foot deformities (pes cavus, high arched feet, hammer toes).
- Mildly affected patients may have only foot deformity (pes cavus) with little or no weakness/sensory loss.
- Legs can be affected greater than arms, and patients will complain of gait abnormalities (steppage), which cause them to trip and fall.
- Sensory complaints (paresthesias, numbness, dysesthesia) are uncommon despite physical findings of impaired sensation.
- Decreased or absent reflexes.
- Some patients may have postural tremor of the upper limbs.

HNPP (a.k.a. tomaculous neuropathy):
- Age at onset is commonly adolescence.
- Disorder is characterized by recurrent entrapment of peripheral nerves with accompanying signs and symptoms (paresthesias and/or weakness in anatomic distributions). Most common are:
  1. Median nerve at the wrist (carpal tunnel syndrome)
  2. Ulnar nerve at the elbow (cubital tunnel syndrome)
  3. Painless brachial plexopathies
  4. Lateral femoral cutaneous nerve (meralgia paresthetica)
  5. Peroneal nerve at the fibular head
- May be associated with a generalized polyneuropathy.

ETIOLOGY

CMT: More than 30 subgroups have been identified and have various chromosomal abnormalities.
- Most common mutation is PMP-22 duplication, giving rise to CMT 1A demyelinating phenotype.
- Other mutations include P0 (demyelinating) and neurofilament light chain mutations (demyelinating or axonal phenotype)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

CMT: Other genetic, metabolic, and multisystem disorders including:
- Spinocerebellar ataxias
- Friedreich ataxia
- Leukodystrophies
- Refsum disease (elevated serum phytanic acid)
- Distal spinal muscular atrophies and distal myopathies, which can present with pes cavus and other foot deformities
- Chronic inflammatory demyelinating polyneuropathy (CIDP)

HNPP:
- Hereditary neuralgic amyotrophy (HNA), which typically is painful rather than painless. In addition, in HNA, there is no evidence of generalized polyneuropathy
- Multifocal motor neuropathy with conduction block (MMNCB)—autoimmune-mediated pure motor neuropathy
- Neuropathy associated with renal failure
- Lead neuropathy
- Neuropathy relating to paraproteinemia (demyelinating pathophysiology)

EVALUATION

CMT:
- History of gradual onset symptoms is important to distinguish CMT from other forms of neuropathy.
- Detailed family history with pedigree is essential. Consider examination of multiple family members.
- History should evaluate for potential heavy metal exposure.
- History of dysesthesias is uncommon and should prompt search for acquired neuropathy or other inherited neuropathies (e.g., Fabry disease).

HNPP: Genetic testing after identification of multiple entrapment neuropathies on electromyography (EMG) and nerve conduction studies

LABORATORY TESTS

- Neurophysiology: EMG and nerve conduction studies (NCSs) must be done first to determine type of pathophysiology: demyelinating or axonal. This will guide genetic testing.
- NCSs in CMT-1 will reveal demyelinating physiology characterized by very slow conduction velocities (around 15 to 30 m/s) with prolonged distal latencies. Inherited demyelinating disorders can be distinguished from acquired demyelinating disorders (e.g., chronic inflammatory demyelinating polyneuropathy or CIDP) by the presence of conduction block in the latter.
- In HNPP, diffusely prolonged distal latencies with superimposed entrapment neuropathies at common sites will be seen on NCSs.
- EMG will reveal reinnervation characterized by long-duration, large-amplitude, polyphasic motor unit potentials (MUPs) with decreased MUP recruitment.
- Genetic tests are available for some CMT subtypes:
  1. CMT-1A: Chromosome 17p11-PMP-22 duplication
  2. CMT-1B: Chromosome 1q22-P0 mutation
  3. CMT-2E: Chromosome 8p21-neurofilament light chain (NF-L) point mutation
  4. CMT-X: Connexin 32 mutations
  5. HNPP: Chromosome 17p11 deletion, which includes the *PMP-22* gene
- Serum and 24-hour urine levels of heavy metals (arsenic, lead, etc.).
- Serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), immunofixation (for paraprotein).
- Anti-GM1 antibody (positive in ~50% of patients with MMNCB).
- Lumbar puncture may reveal elevated CSF protein in CIDP.
- Peripheral nerve biopsy:
  1. Demyelination with "onion bulb formation." Tomaculae, or focal thickening of myelin sheaths, is seen in HNPP.
  2. Generally not indicated unless diagnosis is uncertain.

IMAGING STUDIES

- Spine plain films: For evaluation of scoliosis.
- MRI: Indicated if dissociative sensory loss (dorsal column dysfunction with intact spinothalamic tract function) or if upper motor neuron findings (spasticity, Babinski sign, clonus, increased tendon reflexes) are present.
- Exclusion of involvement of brain or spinal cord compressive lesions causing arm or leg weakness.
- Some inherited peripheral demyelinating disorders (i.e., CMT-X) are associated with intracerebral white matter abnormalities on MRI.
- Exclusion of structural, infectious, or inflammatory nerve root pathology.

TREATMENT

There is no known cure for any of these disorders. Management is supportive.

NONPHARMACOLOGIC THERAPY

- Physical therapy (PT) and occupational therapy (OT) to provide assistance with gait and coordination
- PT and OT might provide walking aid such as ankle foot orthosis (AFO), cane, walker, or wheelchair depending on the severity of the neuropathy
- Wrist splints for superimposed carpal tunnel syndrome
- Elbow pads (Heelbo Pads) to cushion the ulnar nerve at the elbow
- Heel-cord strengthening
- Stretching exercises
- Analgesics for pain associated with foot deformity
- Surgical correction of foot deformities by orthopedic surgeons if indicated

Vincristine may worsen existing neuropathy (important for oncologist to know if patient develops cancer requiring chemotherapy).

SURGICAL TREATMENT

- Patients with HNPP should probably not undergo surgical decompression of the median nerve at the wrist or the ulnar nerve at the elbow; these nerves are sensitive to manipulation. Poor results have been reported with ulnar nerve transposition.
- Anesthesiologists should be aware of HNPP diagnosis in patients undergoing surgery to prevent compression neuropathies from occurring during surgical procedures.

GENETIC COUNSELING

Must be routinely done for patient and family when diagnosis is established. Many aspects of the patient and family's life are affected, including:

- Future progeny of patient and/or patient's parents or children
- Psychosocial aspects including social functioning, marriage, employment
- Financial needs
- Medical and life insurability

PROGNOSIS

- CMT: Slowly progressive, and patients often remain ambulatory until late in life. Life expectancy is normal. Patients with respiratory involvement (i.e., phrenic nerve involvement with diaphragm paresis) may have shorter life expectancy.
- HNPP: Benign prognosis.

DISPOSITION

Outpatient care. Routine follow-up appointments should be done initially every 6 mo, and then every 1 to 2 yr.

REFERRAL

- Neurology and/or neuromuscular disease specialist
- Podiatry for recurrent foot problems, including appropriate arches

PEARLS & CONSIDERATIONS

PATIENT & FAMILY EDUCATION

Patients can benefit from use of Muscular Dystrophy Association (MDA) resources.

RELATED CONTENT

Charcot-Marie-Tooth Disease (Related Key Topic)
Neuropathic Pain (Related Key Topic)

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New Onset Seizures ALG

BASIC INFORMATION

DEFINITION

An unprovoked seizure is a seizure that occurs without triggers or precipitating factors. In contrast, an acute symptomatic seizure occurs in the setting of an insult to the brain (infectious, toxic, etc.). The presentation of a new seizure can vary greatly depending on the type (focal or generalized), progression, and severity.

SYNONYM

Convulsions

ICD-10CM CODES

G40.001	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, not intractable, with status epilepticus
G40.009	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, not intractable, without status epilepticus
G40.10	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable
G40.101	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, with status epilepticus
G40.109	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, without status epilepticus
G40.201	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, not intractable, with status epilepticus
G40.209	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, not intractable, without status epilepticus
G40.301	Generalized idiopathic epilepsy and epileptic syndromes, not intractable, with status epilepticus
G40.309	Generalized idiopathic epilepsy and epileptic syndromes, not intractable, without status epilepticus
G40.A01	Absence epileptic syndrome, not intractable, with status epilepticus
G40.A09	Absence epileptic syndrome, not intractable, without status epilepticus
G40.4	Other generalized epilepsy and epileptic syndromes
G40.401	Other generalized epilepsy and epileptic syndromes, not intractable, with status epilepticus
G40.409	Other generalized epilepsy and epileptic syndromes, not intractable, without status epilepticus
G40.501	Epileptic seizures related to external causes, not intractable, with status epilepticus
G40.509	Epileptic seizures related to external causes, not intractable, without status epilepticus
G40.909	Epilepsy, unspecified, not intractable, without status epilepticus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 29 to 39 per 100,000 per yr for acute symptomatic seizures. 23 to 61 per 100,000 person-yr for unprovoked seizures. Approximately 8% to 10% of the population will experience a seizure during their lifetime; however, less than 3% go on to develop epilepsy.
PREVALENCE: 5 to 8.4 cases per 1000 persons
PREDOMINANT SEX AND AGE: Males younger than 12 mo and older than 65 yr
RISK FACTORS:

- Age of onset
- Family history of epilepsy
- Excessive sleep deprivation, use of alcohol, or illicit drugs
- History of head trauma, diseases of the brain, brain surgeries, and strokes
- History of congenital cerebral anomalies or developmental delay

GENETICS

Although some new onset seizures are related to specific genes, most are not.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with generalized seizures will typically have normal physical exams. Patients with focal seizures due to persistent structural CNS damage may have exam findings consistent with the location of the lesion.
- A generalized seizure may start without warning and can typically last from 30 to 120 seconds, during which the patient will be unconscious and may have increased rigidity and/or jerking of the whole body, or staring spells. Cyanosis (especially of the lips and face) can result from temporary airway compromise due to muscle spasms. Tonic-clonic seizures can cause injuries, tongue biting, and bladder incontinence. Patients are usually unaware of the seizure afterwards. A postictal state characterized by confusion, lethargy, headaches, or drowsiness may result and can last from min to hours depending on the severity of the seizure.
- During a focal seizure, a patient may be aware (focal aware seizure) or have impaired consciousness (focal impaired awareness seizures). A focal impaired awareness seizure may be associated with an aura (itself a focal aware seizure) and lasts between 30 and 120 seconds. Motor or nonmotor symptoms may predominate in focal seizures, including jerking of one limb, automatisms, head turning, auditory hallucinations, or feelings of derealization. A focal seizure may progress to a generalized seizure, which usually involves the head and eye turning to one side. Postictal weakness may result after focal seizures and can last for hours but usually resolves within 1 day. Persistent neurological deficits beyond this time may indicate other causes and should be investigated.

ETIOLOGY

- New, unprovoked seizures are often idiopathic.
- Acute symptomatic seizures can be due to cerebral abnormalities (e.g., infections/abscesses, subarachnoid hemorrhages, ischemic strokes, tumors, arteriovenous malformations, venous malformations) or systemic causes (e.g., electrolyte abnormalities, hypoglycemia, hyperthyroidism, drug intoxication or withdrawal).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Syncope
- Transient ischemic attacks
- Migraines
- Sleep disorders
- Paroxysmal movement disorders
- Panic attacks, hallucinations, and other psychiatric disorders

WORKUP

- Ambulatory 30-min EEG if patient fully recovers after seizure within 30 to 60 min. May be delayed if treatment does not depend on EEG result.
- Consider inpatient continuous EEG if patient does not fully recover within 60 min or for recurrent seizures.
- ECG.
- Fig. 1 illustrates an algorithm for the approach to the child with a suspected convulsive disorder.

LABORATORY TESTS

Comprehensive metabolic panel and urine drug screen

IMAGING STUDIES

- Acutely, CT of the head with and without contrast to evaluate for hemorrhage and space-occupying lesions
- Brain MRI with and without contrast with epilepsy protocol in patients with recurrent seizures, in consultation with a neurologist

TREATMENT

- Provoked seizures do not need long-term treatment.
- The choice of treatment depends largely on seizure type and etiology. Antiepileptics may be thought of as narrow- or wide-spectrum drugs. Treatment with wide-spectrum antiepileptics is advisable in generalized seizures or those of unknown type, whereas partial seizures are better controlled with narrow-spectrum antiepileptics.
- Narrow-spectrum drugs include carbamazepine, oxcarbazepine, gabapentin, pregabalin, lacosamide, and phenytoin. Wide-spectrum drugs include valproate, topiramate, zonisamide, lamotrigine, and levetiracetam.

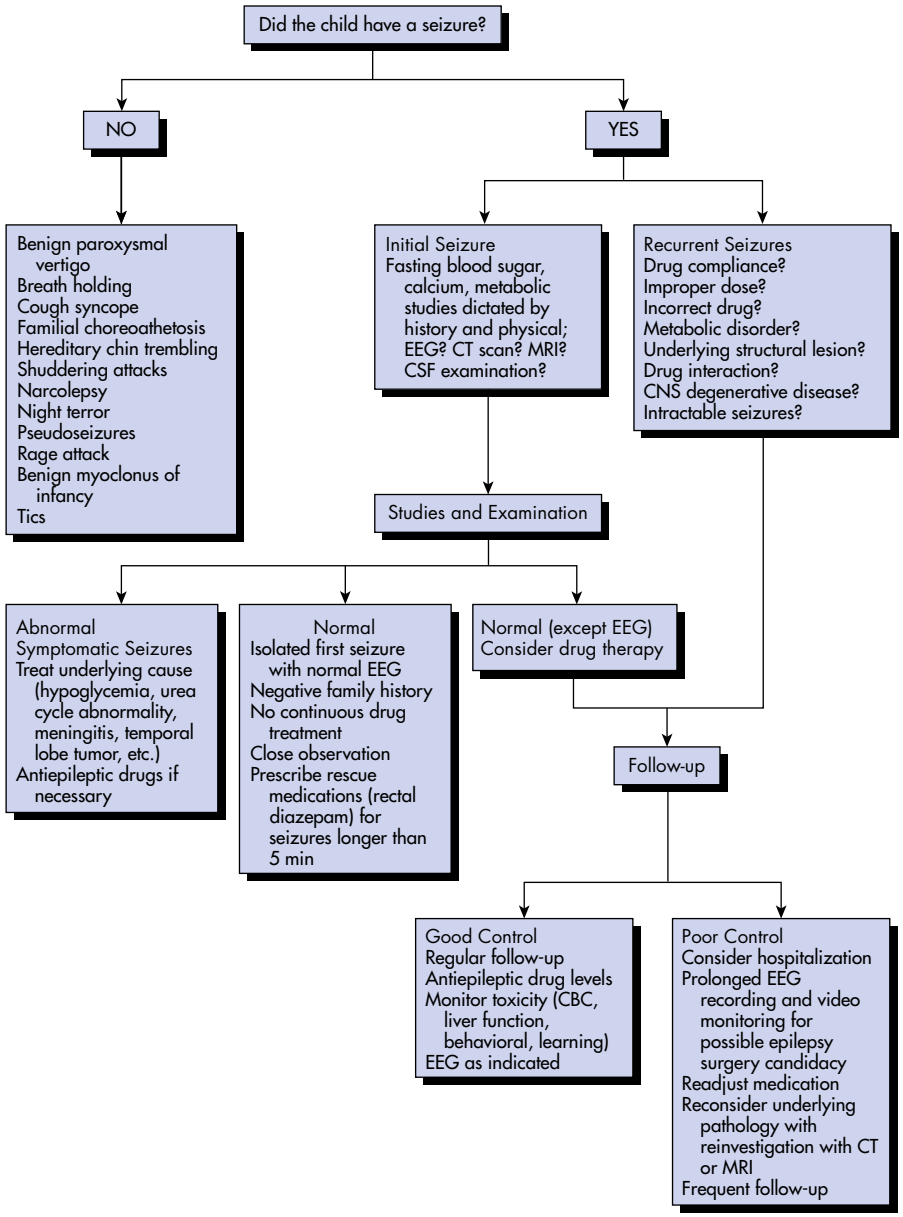

FIG. 1 Algorithm for the approach to the child with a suspected convulsive disorder. *CBC,* Complete blood count; *CT,* computed tomography; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *EEG,* electroencephalogram; *MRI,* magnetic resonance imaging. (From Kliegman RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.)

- In patients with significant comorbidities, the use of antiepileptics with limited drug interactions is advised (lamotrigine, levetiracetam, lacosamide).
- Older patients may benefit from lamotrigine, levetiracetam, or gabapentin due to a lower risk of adverse events.

NONPHARMACOLOGIC THERAPY

None

ACUTE GENERAL Rx

- Patients with a first unprovoked seizure who have a normal EEG, imaging, lab values, and physical exam do not require treatment with antiepileptic drugs but may be offered therapy because the use of an antiepileptic drug after a first unprovoked seizure in an adult reduces the absolute risk of seizure recurrence at 2 yr by 35%. However, there is no difference at 3 yr.
- For generalized seizures: **Levetiracetam** initial dose of 500 mg bid. If recurrent seizures, increase by 500 mg every 1 to 2 wk until maximum dose of 1500 mg bid is reached.
- For partial seizures: **Oxcarbazepine** initial dose 300 mg bid, increase by 300mg/day every 3 days to 600 mg bid. If recurrent seizures, continue to titrate by 300 mg/day every 3 days to 1200 mg bid.

CHRONIC Rx

Patients with two or more unprovoked seizures, or those with one seizure and an abnormal workup consistent with epilepsy findings, should be continued on antiepileptic drugs. Patients electing antiepileptic therapy after first unprovoked seizure with negative workup may be weaned off antiepileptic drug if seizure-free after 2 yr.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Not applicable

DISPOSITION

- Patients should avoid swimming unobserved, bathing alone, working at heights, using heavy machinery, or other activities that may be high-risk in the event of a seizure.
- Discontinue driving until seizures are well controlled and in accordance with state laws.

REFERRAL

Patients may be referred to a neurologist.

PEARLS & CONSIDERATIONS

COMMENTS

- Driving: Physicians should be aware of the law in their jurisdiction about driving after a seizure. Although a few U.S. states require physicians to notify the state government authority that issues driver's licenses, most do not impose such an obligation on physicians. However, states do require patients to self-report and abstain from driving until seizure-free for a specified period of time, depending on the state.
- Recurrence risk: Greatest recurrence risk in an adult with a first unprovoked seizure is within the first 2 yr and is between 21% and 45%. The recurrence risk is lower in patients treated with an antiepileptic drug and higher in patients with a brain MRI abnormality causing the seizure or an EEG showing epileptiform activity.

PREVENTION

Patients with recurrent seizures should be extensively counseled on avoiding seizure triggers such as sleep deprivation, alcohol or drug use, stress, and exposure to excessive flashing lights. Such patients may need dose titration of antiepileptic drug and referral to a neurologist.

PATIENT & FAMILY EDUCATION

- Physicians should inform patients with first-time seizures that they are subject to state law restrictions on driving after a seizure. Physicians should also counsel patients with epilepsy about not swimming unattended, not climbing heights, and taking showers rather than baths (because of the risk of drowning in a bathtub during a generalized seizure). Physicians should counsel women of childbearing potential about effects of antiepileptic drugs on both oral contraceptive efficacy and on a developing fetus. They should recommend supplemental folic acid for such women if they are taking antiepileptic drugs. They should also recommend that women plan pregnancy if they are on antiepileptic drugs to minimize adverse effects on the pregnancy. All such counseling should be documented in the medical record.
- A diagnosis of epilepsy has significant medical, social, and emotional consequences. Patient information on seizures and locating support groups can be found at the Epilepsy Foundation website: http://www.epilepsy.com.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Absence Seizures (Related Key Topic)
Febrile Seizures (Related Key Topic)
Seizures, Generalized Tonic-Clinic (Related Key Topic)
Focal Seizures (Related Key Topic)
Status Epilepticus (Related Key Topic)

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SUGGESTED READINGS

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Nocardiosis PTG

BASIC INFORMATION

DEFINITION

Nocardiosis is an infection caused by aerobic actinomycetes found in soil and characterized by lung, soft tissue, or central nervous system (CNS) involvement.

SYNONYMS

Mycetoma
Nocardia

ICD-10CM CODES
A42.9 Actinomycosis, unspecified
A43.0 Pulmonary nocardiosis
A43.1 Cutaneous nocardiosis
A43.8 Other forms of nocardiosis
A43.9 Nocardiosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- *Nocardia* species are found worldwide in the soil.
- Nocardiosis is found most commonly in patients who are immunocompromised (e.g., chronic corticosteroid or immunosuppressive therapy, lymphoma, leukemia, AIDS, lung cancer, transplant recipients, chronic pulmonary infections).
- Other underlying conditions associated with nocardiosis are pemphigus vulgaris, Whipple disease, Goodpasture syndrome, Cushing disease, liver cirrhosis, ulcerative colitis, rheumatoid arthritis, and pulmonary alveolar proteinosis.
- Use of steroids is an independent risk factor for developing nocardiosis.
- Between 500 and 1000 new cases are diagnosed each yr in the U.S. Approximately 2% of patients with AIDS develop nocardiosis.
- Occurs more commonly in men than in women (2:1).
- Adults are affected more often than children.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Inhalation of *Nocardia* organisms is the most common mode of entry, and pneumonia is the most common presentation, with 75% manifesting with fever, chills, dyspnea, and a productive cough (Fig. E1).
  1. Presentation can be acute, subacute, or chronic.
  2. Nocardiosis should be suspected if soft tissue abscesses or CNS tumors or abscesses form in conjunction with the pulmonary infection.
  3. Pulmonary infection may spread into the pericardium, mediastinum, and superior vena cava.
- Cutaneous disease usually occurs by direct inoculation of the organism as a result of skin puncture by a thorn or splinter, surgery, IV catheter use, or animal scratches or bites manifesting in:
  1. Cellulitis.
  2. Lymphocutaneous nodules appearing along lymphatic sites draining the infected puncture wound.
  3. Mycetoma (Madura foot), a chronic deep nodular infection usually involving the hands or feet that can cause skin breakdown or fistula formation and that spreads along the fascial planes to infect surrounding skin, subcutaneous tissue, and bone.
- The CNS is infected in approximately one third of all cases. Brain abscess is the most common pathologic finding.
- Dissemination of nocardiosis may infect other tissues and organs, including the kidney, heart, skin, and bone.

ETIOLOGY

- The most common *Nocardia* species leading to infection in human beings are:
  1. *N. asteroides* (causing more than 80% of the cases of pulmonary nocardiosis)
  2. *N. brasiliensis* (most common cause of mycetoma)
  3. *N. otitidiscaviarum*
- *N. asteroides* has two subgroups:
  1. *N. farcinica*
  2. *N. nova*

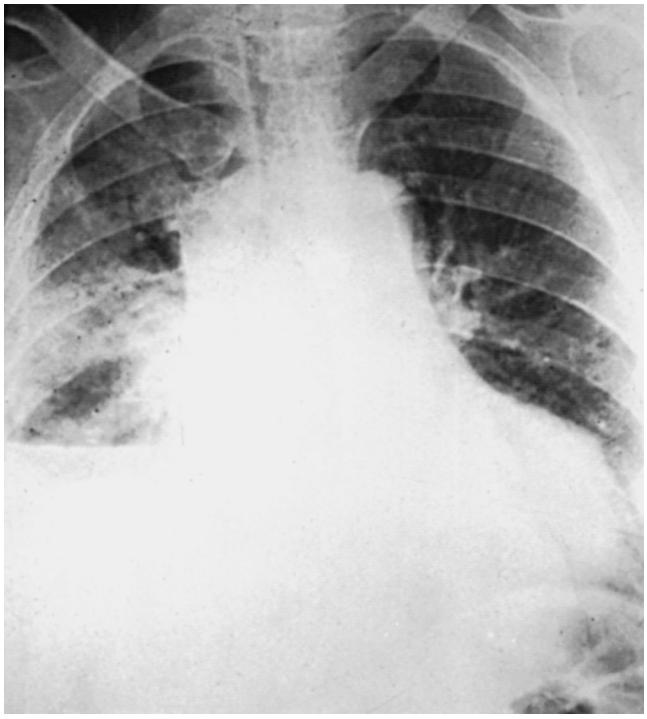

FIG. E1 Right lower lobe *Nocardia* pneumonia in a kidney transplant recipient. (From Gorbach SL: *Infectious diseases,* ed 2, Philadelphia, 1998, WB Saunders.)

DIAGNOSIS

The diagnosis of nocardiosis requires a high index of clinical suspicion in the proper clinical setting and is confirmed by bacteriologic staining and growth of the organism in culture.

DIFFERENTIAL DIAGNOSIS

There are no pathognomonic findings separating nocardiosis pneumonia from other infectious etiologies of the lung. Diagnoses presenting in a similar manner and often confused for nocardiosis include:

- Tuberculosis
- Lung abscess
- Lung tumor
- Other causes of pneumonia
- Actinomycosis
- Mycosis
- Cellulitis
- Coccidioidomycosis
- Histoplasmosis
- Aspergillosis
- Kaposi sarcoma

WORKUP

All patients with suspected nocardiosis need laboratory identification of the microorganism by obtaining sputum in the case of pneumonia, cultures of the infected skin lesions in mycetoma or lymphocutaneous disease, or the sampling of any purulent material (e.g., brain abscess, lung abscess, or pleural effusion).

LABORATORY TESTS

- Blood tests are not very sensitive in the diagnosis of nocardiosis.
- Gram stain shows gram-positive beaded filaments with multiple branches (Fig. E2). Gomori methenamine silver staining may detect the organism.
- *Nocardia* species are acid-fast on a modified Ziehl-Neelsen stain.
- *Nocardia* are slow-growing organisms; colony growth in cultures may take up to 2 to 3 wk.

IMAGING STUDIES

- Chest radiograph or CT of chest (Fig. E3) may demonstrate infiltrates, densities, nodules, cavitary masses, or multiple abscesses.
- CT scan of the brain is indicated in the appropriate clinical setting to exclude CNS brain abscesses.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive therapy with oxygen in patients with pneumonia
- Chest physiotherapy
- For any abscess formation, surgical drainage is indicated (e.g., skin, lung, or brain)

ACUTE GENERAL Rx

- There are no prospective, randomized trials to date highlighting the most effective treatment of nocardiosis. Culture and sensitivity should always be done on the specimen
- For cutaneous infection, trimethoprim-sulfamethoxazole (TMX-SMX) 5 mg/kg of the trimethoprim component divided in 2 doses
- *Nocardia* infection that does not involve CNS: TMX-SMX (15 mg/kg/day of TMP component IV in 2 to 4 divided doses) *plus* (amikacin 7.5 mg/kg q12h). An alternate regimen consists of imipenem 500 mg IV q6h *plus* amikacin 7.5 mg/kg IV q12h
- In patients with CNS disease, TMX-SMX 15 mg/kg/day of TMP component IV divided in 2 to 4 doses *plus* imipenem 500 mg q6h IV. If multiorgan involvement, add amikacin 7.5 mg/kg q12h. Measure peak sulfonamide levels; target is 100 to 150 mcg/ml 2 hr post dose. An alternative regimen consists of linezolid 600 mg IV or PO q12h *plus* meropenem 2 g q8h. For infections without involvement of the CNS the patient can be switched to oral therapy after the initial IV therapy for 3 to 6 wk or until clinical improvement. For infections involving CNS the initial IV therapy should be continued for minimum of 6 wk and clear evidence of clinical improvement before switching to combination oral therapy. The combination oral antibiotics that can be used following initial IV therapy include:
  1. TMP/SMX (10 mg/kg per day of the trimethoprim component in two to three divided doses) and/or
  2. Minocycline (100 mg twice daily) and/or
  3. Amoxicillin/clavulanic acid (875 mg) twice daily
- Alternative drug treatment includes:
  1. Third-generation cephalosporin
  2. Minocycline 100 to 200 mg bid
  3. Extended-spectrum fluoroquinolones (moxifloxacin)
  4. Linezolid (use of linezolid >4 wk is associated with hematologic toxicity)
  5. Tigecycline
  6. Dapsone

CHRONIC Rx

- Although the optimal duration of therapy has not been determined, long-term therapy is generally recommended for all infections caused by *Nocardia.*
- Patients with cellulitis and lymphocutaneous syndrome are treated for 2 to 4 mo depending on whether there is bone involvement.
- Mycetomas are best treated with antibiotics for 6 to 12 mo but may require surgical drainage.
- Pulmonary and systemic nocardiosis excluding the CNS is treated for at least 6 mo in immunocompromised hosts.
- CNS involvement is treated with drainage and antibiotics for 12 mo.
- All immunosuppressed patients should receive 12 mo of antibiotic therapy.

DISPOSITION

- Patients with pulmonary nocardiosis have a mortality rate of 15% to 30%.

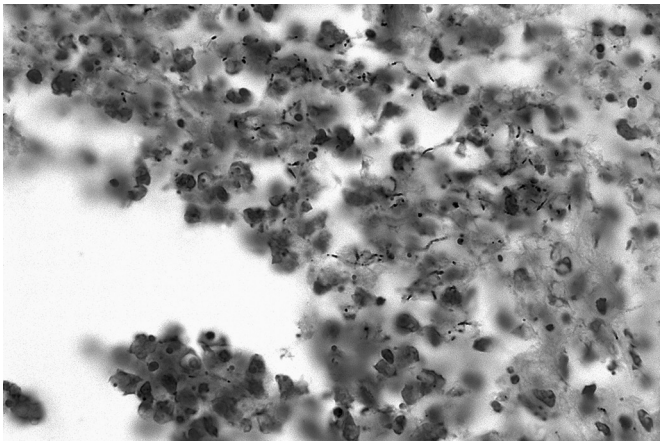

FIG. E2 *Nocardia* pneumonia. Thin, branching, irregularly staining gram-positive bacilli course through necrotic pulmonary tissue (Brown-Hopps Gram, ×1000). (From Silverberg SG et al [eds]: *Silverberg's principles and practice of surgical pathology and cytopathology,* ed 4, Philadelphia, 2006, Churchill Livingstone.)

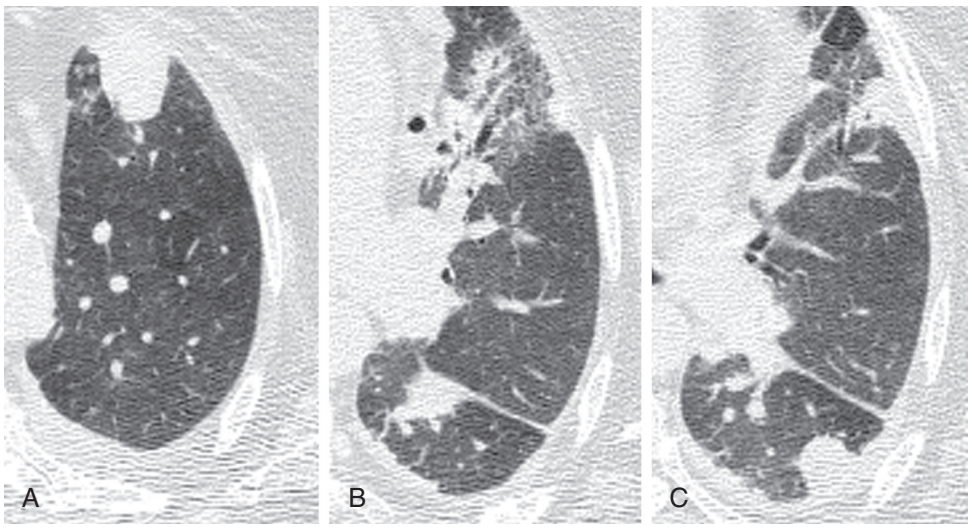

FIG. E3 Nocardiosis with multiple nodules. A to **C,** Multiple ill-defined nodules reflect nocardia pneumonia in an immunosuppressed patient. (From Webb WR et al: *Fundamentals of body CT,* ed 4, Philadelphia, 2015, WB Saunders.)

- CNS involvement carries a >40% mortality rate.
- Isolated skin lesions have a low mortality rate.

REFERRAL

Whenever the diagnosis of nocardiosis is suspected, consultation with infectious disease is indicated. Pulmonary evaluation and assistance may be needed in pulmonary nocardiosis. Neurosurgery consultation is indicated in patients with single or multiple brain abscesses.

PEARLS & CONSIDERATIONS

- Nocardiosis does not spread from animal to animal.
- Nocardiosis is not transmitted from person to person.
- Nocardiosis is distinguished by its ability to disseminate to any organ and its tendency to relapse despite appropriate antibiotic therapy.

COMMENTS

Tuberculosis and nocardiosis may coexist in the same patient.

RELATED CONTENT

Nocardiosis (Patient Information)

AUTHOR: **Maher Tabba, MD, FACP, FCCP**

BASIC INFORMATION

DEFINITION

- *Nonalcoholic fatty liver disease* (NAFLD) is a spectrum of diseases based on histopathologic findings and representing a morphologic rather than a clinical diagnosis. It is liver disease occurring in patients who do not abuse alcohol and manifesting histologically by mononuclear cells and/or polymorphonuclear cells, hepatocyte ballooning, and spotty necrosis. Nonalcoholic steatohepatitis (NASH) is a subset of NAFLD. Patients with NASH have progressive disease that can result in fibrosis and cirrhosis. A diagnosis of NAFLD is contingent on the following factors:
  1. Alcohol consumption in amounts less than those considered hepatotoxic.
  2. Absence of serologic evidence of other hepatic diseases or disorders.
  3. Liver biopsy showing predominant macrovesicular steatosis or steatohepatitis.
- NAFL is defined as ≥5% hepatic steatosis without evidence of hepatocellular injury or fibrosis.
- NASH is ≥5% hepatic fibrosis with inflammation and hepatocellular injury with or without fibrosis.
- *NASH cirrhosis* is the presence of cirrhosis with current or past evidence of steatosis.

SYNONYMS

Nonalcoholic steatohepatitis (NASH)
NAFLD
Fatty liver hepatitis
Diabetes hepatitis
Alcohol-like liver disease
Laënnec disease

ICD-10CM CODE
K76.0 Fatty (change of) liver, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

- NAFLD affects 30% to 40% of the adult general population in the U.S.
- Increased prevalence in obese persons (57% to 74%), type 2 diabetes mellitus, and hyperlipidemia (primarily hypertriglyceridemia).
- Most common cause of abnormal liver test results in adults in the United States (accounts for up to 90% of cases of asymptomatic ALT elevations).
- NAFLD is more prevalent in men than women.
- NAFLD is more prevalent in the Hispanic population.
- Approximately 20% of patients with NAFLD have NASH, and 10% to 30% of patients with NASH have NASH cirrhosis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most patients are asymptomatic.
- Patients may report a sensation of fullness or discomfort on the right side of the upper abdomen.
- Nonspecific complaints of fatigue or malaise may be reported.
- Hepatomegaly (Table 1) is generally the only positive finding on physical examination.
- Acanthosis nigricans may be found in children.

ETIOLOGY

- Metabolic syndrome and insulin resistance are the most reproducible factors in the development of NAFLD and accumulation of triglycerides within the liver. High baseline and continuously increasing fasting insulin levels are independent determinants for future development of NAFLD. The transition from NAFLD to NASH is poorly understood; there may be a genetic component. The presence of the I48M variant of PNPLA3 increases risk for and severity of NAFLD.

TABLE 1 Symptoms, Signs, and Laboratory Features of Nonalcoholic Fatty Liver Disease

Symptoms	Signs	Laboratory Features
Common		
None (48%-100% of patients)	Hepatomegaly	2- to 4-fold elevation of serum ALT and AST levels AST/ALT ratio <1 in most patients Serum alkaline phosphatase level slightly elevated in one third of patients Normal serum bilirubin, serum albumin, and prothrombin time Elevated serum ferritin level
Uncommon		
Vague right upper quadrant pain Fatigue Malaise	Splenomegaly Spider telangiectasias Palmar erythema Ascites	Low-titer (<1:320) antinuclear antibodies

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

BOX 1 Causes of Fatty Liver Disease

Acquired Metabolic Disorders
Diabetes mellitus
Dyslipidemia
Kwashiorkor and marasmus
Obesity
Rapid weight loss
Starvation

Cytotoxic and Cytostatic Drugs
L-Asparaginase
Azacitidine
Bleomycin
Cisplatin
5-Fluorouracil
Methotrexate
Tetracyclines (inhibit mitochondrial beta oxidation)

Other Drugs and Toxins
Amiodarone
Camphor
Chloroform
Cocaine
Ethanol
Ethyl bromide
Estrogens
Glucocorticoids
Griseofulvin
HAART (zidovudine, stavudine, didanosine)
Lycopodium serratum (Jin Bu Huan, an herbal supplement)
Nifedipine
Nitrofurantoin
NSAIDs (piroxicam, ibuprofen, indomethacin, sulindac)
Tamoxifen
Valproic acid

Metals
Antimony
Barium salts
Chromates
Mercury
Phosphorus
Rare earth metals of low atomic number
Thallium compounds
Uranium compounds

Inborn Errors of Metabolism
Abetalipoproteinemia
Familial hepatosteatosis
Galactosemia
Glycogen storage disease
Hereditary fructose intolerance
Homocystinuria
Systemic carnitine deficiency
Tyrosinemia
Weber-Christian syndrome
Wilson disease

Surgical Procedures
Biliopancreatic diversion
Extensive small bowel resection
Jejunoileal bypass

Miscellaneous Conditions
Industrial exposure to petrochemicals
IBD
Jejunal diverticulosis with bacterial overgrowth
Partial lipodystrophy
TPN

HAART, Highly active antiretroviral therapy; *IBD,* inflammatory bowel disease; *NSAIDs,* nonsteroidal antiinflammatory drugs; *TPN,* total parenteral nutrition.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

TABLE 2 NAFLD Activity Score on a Liver Biopsy Specimen

Steatosis	
5%	1
5%-33%	2
33%-66%	3
Ballooning	
None	0
Few	1
Many	2
Lobular Inflammation	
Mild	1
Moderate	2
Severe	3
Total Score	
0-2	Likely not NASH
3-4	Intermediate
5-8	Likely NASH

NAFLD, Nonalcoholic fatty liver disease; *NASH,* nonalcoholic steatohepatitis.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

Genetic polymorphism (TM6SF2) also increases NAFLD risk.
- Risk factors are obesity (especially truncal obesity), diabetes mellitus, hyperlipidemia.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Alcohol-induced liver disease (a daily alcohol intake of 20 g in females and 30 g in males [three 12-oz beers or 12 oz of wine] may be enough to cause alcohol-induced liver disease)
- Viral hepatitis
- Autoimmune hepatitis
- Toxin- or drug-induced liver disease
- Box 1 summarizes the various causes of fatty liver disease

WORKUP

Diagnosis is usually suspected on the basis of hepatomegaly, asymptomatic elevations of transaminases, or "fatty liver" on sonogram of abdomen in obese patients with little or no alcohol use. Fig. E1 describes an algorithm for the diagnostic approach to NAFLD. Transient elastography is a noninvasive imaging modality that can be used to screen for the development of hepatic fibrosis. In obese patients newer "XL" FibroScan machines are more accurate. Liver biopsy can confirm diagnosis and provide prognostic information. It should be considered in patients with suspected advanced liver fibrosis (presence of obesity or type 2 diabetes, AST/ALT ratio 1, age 45 yr). NAFLD activity score on liver biopsy is described in Table 2.

LABORATORY TESTS

- Elevated ALT, AST: AST/ALT ratio is usually <1, but can increase as fibrosis advances. In advanced fibrosis AST to ALT ratio is >1 and platelet count is low.
- Negative serology for infectious hepatitis; generally normal GGTP and serum alkaline phosphatase.
- Hyperlipidemia (primarily hypertriglyceridemia) may be present.
- Elevated glucose levels may be present.
- Prolonged prothrombin time, hypoalbuminemia, and elevated bilirubin may be present in advanced stages.
- Elevated serum ferritin and increased transferrin saturation may be found in up to 10% of patients; however, hepatic iron index and hepatic iron level are normal.
- Antismooth muscle antibodies and antinuclear antibodies at low titer are not uncommon.

IMAGING STUDIES

- Ultrasound generally reveals diffuse increase in echogenicity as compared with that of the kidneys; CT scan reveals diffuse low-density hepatic parenchyma. The sensitivity of ultrasound and CT scan for detection of fat in liver is over 90% if hepatic steatosis exceeds 33%.
- Occasionally patients may have focal rather than diffuse steatosis, which may be misinterpreted as a liver mass on ultrasound or CT (Fig. E2); use of MRI in these cases will identify focal fatty infiltration.
- Ultrasound elastography (FibroScan) can also be used to evaluate hepatic fibrosis and to further stratify patients.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Weight reduction in all obese patients. The American Gastroenterological Association recommends that the initial target weight loss be 10% of baseline weight at a rate of 1 to 2 lb (0.45 to 0.90 kg) per week.
- Increase physical activity. Vigorous and moderate exercise are equally effective in reducing intrahepatic triglyceride content, the effect being largely mediated by weight loss.
- Alcohol has a deleterious effect on NAFLD and should be avoided.

ACUTE GENERAL Rx

- There are no drugs currently approved by FDA for NAFLD. Medications to control hyperlipidemia (e.g., fenofibrates for elevated triglycerides) and hyperglycemia (e.g., pioglitazone, insulin, metformin) can lead to improvement in abnormal liver test results.
- A 3-yr trial with pioglitazone (30 mg/day), an insulin-sensitizing thiazolidinedione, revealed that pioglitazone treatment was associated with long-term metabolic and histologic improvement in patients with prediabetes or type 2 diabetes mellitus and NASH. These results suggest that that NASH progression may be halted and the natural history of the disease may be modified with the use of pioglitazone in patients with prediabetes or type 2 diabetes mellitus.[1]

DISPOSITION

- Patients with pure steatosis on liver biopsy generally have a relatively benign course.
- The presence of steatohepatitis or advanced fibrosis on liver biopsy is associated with a worse prognosis.

REFERRAL

Liver transplantation should be considered in patients with decompensated, end-stage disease; however, in these patients there may be a recurrence of NAFLD posttransplantation.

PEARLS & CONSIDERATIONS

COMMENTS

- NAFLD is closely associated with metabolic disorders, even in nonobese, nondiabetic subjects. It can be considered an early predictor of metabolic disorders, particularly in the normal-weight population. The presence of metabolic syndrome is a strong predictor of NAFLD.
- NAFLD is associated with an increased risk of incident cardiovascular disease that is independent of the risk conferred by traditional risk factors and components of the metabolic syndrome.
- 10% of patients with NASH have progression to advanced fibrosis. Most common in patients older than 50, ALT > twice normal, BMI >28, triglycerides >150 mg/dl.
- Statins are not contraindicated in patients with NASH and should be considered in hypercholesterolemic patients.
- A recent trial has shown that daily aspirin use is associated with reduced risk for fibrosis progression in patients with NAFLD.[2]

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Fatty Liver (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

[1]Cusi K et al: Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial, *Ann Intern Med* 165:305-315, 2016.
[2]Simon TG et al: Daily aspirin use associated with reduced risk for fibrosis progression in patients With nonalcoholic fatty liver disease, *Clin Gastroenterol Hepatol* 17(13):2776-2784.e4, 2019.

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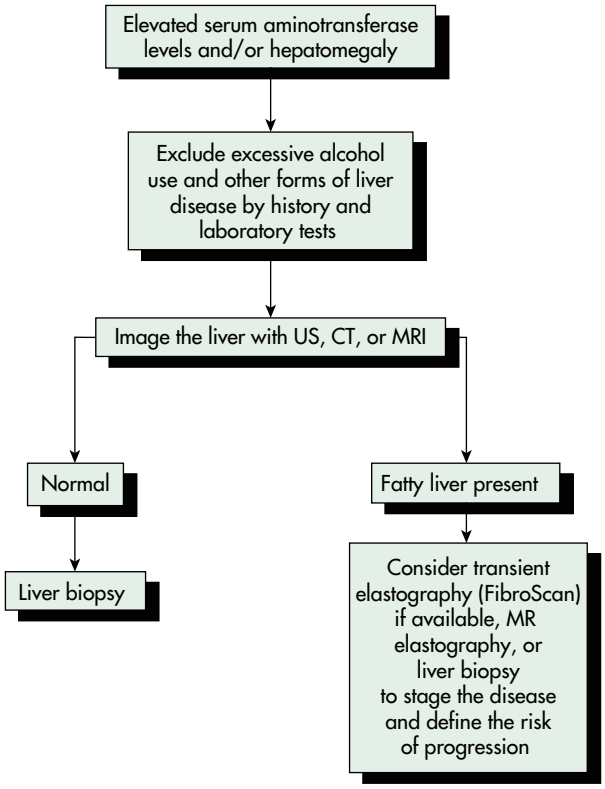

FIG. E1 Algorithm for a diagnostic approach to the patient with suspected nonalcoholic fatty liver disease (NAFLD). The diagnosis of NAFLD is based on clinical and histologic criteria. Most patients are evaluated because of elevated serum aminotransferase levels and/or hepatomegaly. The diagnosis of NAFLD should be considered when excessive alcohol use is absent and laboratory test results exclude other causes of liver disease. Imaging studies may demonstrate fatty liver. Liver biopsy is the standard means of diagnosis and the only test that can reliably differentiate simple steatosis from NASH, although noninvasive methods for assessing fibrosis, such as transient elastography, are being used increasingly to identify hepatic fibrosis. *CT,* Computed tomography; *MR,* magnetic resonance; *MRI,* magnetic resonance imaging; *NASH,* nonalcoholic steatohepatitis; *US,* ultrasound. (Modified from Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

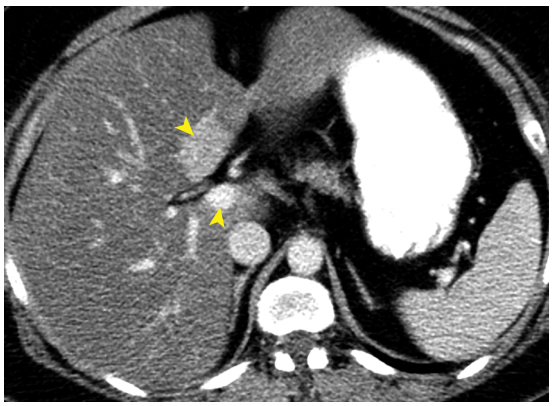

FIG. E2 Focal sparing. Two islands of normal parenchyma (*arrowheads*) in segment IVb and the caudate lobe (segment 1) simulate mass lesions in a liver with extensive fatty infiltration. Most of the liver parenchyma shows fatty infiltration, making these islands of normal parenchyma appear of high attenuation by comparison. (Webb WR et al: *Fundamentals of body CT,* ed 4, Philadelphia, 2015, WB Saunders.)

BASIC INFORMATION

DEFINITION

Nonallergic rhinitis (NAR) is characterized by chronic episodic or perennial symptoms of rhinitis (congestion, rhinorrhea, and postnasal drainage) that are not the result of IgE-mediated events. It is a heterogeneous group of diseases classified as inflammatory (infectious rhinosinusitis, nonallergic rhinitis with eosinophilia syndrome) or noninflammatory (including but not limited to gustatory rhinitis, atrophic rhinitis, rhinitis medicamentosa, hormone-induced rhinitis, rhinitis in the elderly, rhinitis associated with systemic disease). Vasomotor rhinitis has previously been used interchangeably with NAR but is being phased out, as the term is too narrow with regard to the multiple mechanisms of action associated with NAR.

SYNONYMS

Chronic nonallergic rhinitis
Idiopathic rhinitis
Intrinsic rhinitis
NAR
Nonallergic-noninfectious chronic rhinitis
Vasomotor rhinitis

ICD-10CM CODES	
J30.0	Vasomotor rhinitis
J31.0	Chronic rhinitis NOS (atrophic, granulomatous, hypertrophic, obstructive rhinitis)

EPIDEMIOLOGY & DEMOGRAPHICS

- Nonallergic rhinitis affects approximately 17 to 22 million individuals in the U.S.
- Approximately 50% of patients presenting with rhinitis may have NAR alone or a "mixed form" that includes both allergic and nonallergic components.
- Nonallergic rhinitis usually presents in adulthood with 70% of patients presenting after 20 yr of age. Onset of allergic rhinitis typically occurs in childhood.
- Risk factors for nonallergic rhinitis include female sex and age of >40 yr.
- May have genetic component in those individuals whose parents have allergic rhinitis.
- Medications that can cause chronic nasal symptoms are summarized in Table 1.
- Table 2 describes occupations with increased prevalence of work-related rhinitis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients tend to present with a specific set of symptoms, predominantly rhinorrhea, postnasal drip, and throat clearing. Conversely, allergic symptoms such as nasal pruritus, sneezing, and conjunctival irritation are traditionally absent but can be variably present in mixed disease.
- Physical exam can be completely unremarkable, but it can present with the following features:
  1. Clear nasal secretions
  2. Nasal crusting
  3. Anosmia can be consistent with some forms (e.g., atrophic rhinitis)
  4. Inspection of turbinates may be erythematous or pale

ETIOLOGY

- NAR is composed of a heterogeneous group of diseases without a clear unifying theory of pathogenesis. In general, inflammatory NAR involves elevated numbers of immune cells (eosinophils, mast cells, neutrophils) leading to mediator release and inflammatory changes. For noninflammatory NAR, it is postulated that an abnormality in the autonomic nervous system is present with increased concentrations of intranasal neuropeptides. These are often triggered by perfumes, strong odors, changes in climate, and smoke. Specific subtypes likely have unique pathophysiologies:
  1. Infectious rhinosinusitis: Viral, bacterial, or fungal infections. Typically occurs following an acute viral infection.
  2. Nonallergic rhinitis with eosinophilia syndrome (NARES): Unknown etiology.
  3. Gustatory rhinitis: Abnormal vagally mediated rhinitis after ingestion of any food.
  4. Atrophic rhinitis: Unknown etiology but bacterial infection is thought to be involved.
  5. Rhinitis medicamentosa: Rebound nasal congestion from prolonged use of decongestant/vasoconstrictor agents (phenylephrine, oxymetazoline). Can also occur from cocaine, α-receptor antagonist, or phosphodiesterase-5-selective inhibitors.
  6. Hormone-induced rhinitis: Pregnancy-associated, menstrual cycle–associated, and oral contraceptive–related hormonal changes.
  7. Rhinitis associated with systemic disease: Severe hypothyroidism, diabetes mellitus.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Allergic rhinitis (sensitivity to pollens, indoor allergens, occupational allergens)
- Systemic diseases with nasal manifestations (e.g., systemic lupus erythematosus, granulomatous disease, GERD)
- Mechanical obstruction (e.g., deviated septum, nasal polyps, nasal neoplasms, foreign bodies)
- Cerebral spinal fluid (CSF) leak from head trauma as it may represent a skull base fracture, postoperative complication from sinus surgery, or spontaneous leak
- Local allergic rhinitis
- Chronic rhinosinusitis
- Box 1 summarizes the differential diagnosis in chronic rhinitis

WORKUP

- A detailed history and physical examination can be helpful to determine if diagnostic testing is necessary.
- Distinguishing NAR from allergic rhinitis or other forms of rhinitis can be difficult, but a detailed history (lack of allergic symptoms such as sneezing, nasal pruritus) can be helpful. Questionnaires, including the Cincinnati Irritant Index Scale, have proven useful in differentiating NAR from allergic rhinitis.
  1. Because allergic rhinitis cannot be definitively ruled out with history alone, skin testing or assessment for serum-specific IgE should be considered. Adding to the diagnostic complexity, many individuals have a "mixed form" of rhinitis including both allergic and nonallergic types.
  2. Given the common overlap between NAR and AR, it may be reasonable to revisit diagnostic testing if patients do not respond to therapy as expected.
- Although not typically performed routinely in a clinical setting, examination of nasal smears for the presence of neutrophils and eosinophils may be helpful.

TABLE 1 Medications Associated with Chronic Nasal Symptoms

Category	Example(s)
Antihypertensives	Angiotensin-converting enzyme inhibitors
	β-Adrenergic blockers
	Amiloride
	Prazocin
	Hydralazine
Psychotropics	Risperidone
	Chlorpromazine
	Amitriptyline
Phosphodiesterase-5 inhibitors	Sildenafil
	Tadalafil
	Vardenafil
Nonsteroidal antiinflammatory drugs	Ibuprofen
Others	Gabapentin

From Adkinson NF et al: *Middleton's allergy principles and practice,* ed 8, Philadelphia, 2014, Elsevier.

TABLE 2 Occupations with Increased Prevalence of Work-Related Rhinitis

Category	Occupation	Likely Trigger
Irritant	Drywall installer	Gypsum dust
	Makeup artist	Cosmetic powder, perfume
Corrosive	Janitor	Ammonia
	Chemistry technician	Hydrochloric acid
Immunologic		
Immunoglobulin E	Baker	Grain flour
	Furrier	Animal dander
	Livestock breeder	Animal dander
	Veterinarian	Animal dander
	Food-processing worker	Foodstuffs
	Pharmacist	Medication powders
Low-molecular-weight substances	Boat builder	Anhydrides

From Adkinson NF et al: *Middleton's allergy principles and practice,* ed 8, Philadelphia, 2014, Elsevier.

- Anterior rhinoscopy or nasal endoscopy may be necessary to rule out nasal polyps or anatomic deformity, which may contribute to chronic rhinorrhea.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Identification and avoidance of specific triggers (e.g., smoke/smog, specific foods, perfumes, strong odors, occupational irritants) may provide relief.
- Discontinuing any medication/drugs that could be contributing, including topical decongestants/vasoconstrictors, oral contraceptives (OCPs), cocaine, and alcohol (Table 1).
- Daily nasal lavage (distilled water mixed with saline packets) and over-the-counter nasal saline sprays have been shown to improve symptoms.
- Surgical intervention (turbinectomy, vidian nerve resection, turbinoplasty) may be considered if medical measures fail, but such surgeries are not commonly performed in the U.S. There is limited data showing the efficacy of turbinoplasty with regard to symptom reduction, although there is a risk of empty nose syndrome (ENS).

ACUTE AND CHRONIC Rx

- Second-generation antihistamines have not been shown to be beneficial in nonallergic rhinitis. Although first-generation antihistamines may improve rhinorrhea due to their anticholinergic properties, topical therapies including intranasal steroids (fluticasone propionate, triamcinolone, mometasone), intranasal antihistamines (azelastine, olopatadine), and intranasal anticholinergics (ipratropium bromide) have been shown to be most efficacious.
- Treatments should be individualized to the underlying pathophysiology.
  1. *Vasomotor rhinitis:* Initial therapy typically involves intranasal steroids with the addition of an intranasal antihistamine or intranasal ipratropium bromide if symptoms are not well controlled. A combination intranasal steroid and intranasal antihistamine is now available that may be more convenient.
  2. *Infectious rhinosinusitis:* Supportive care and intranasal saline spray. May take up to 6 to 8 wk to improve after resolution of acute infection.
  3. *Nonallergic rhinitis with eosinophilia syndrome (NARES):* Topical nasal corticosteroids.
  4. *Gustatory rhinitis*: Preprandial intranasal ipratropium bromide and/or dietary modification also may be useful in patients with specific triggers.
  5. *Atrophic rhinitis:* Frequent irrigation with nasal saline, antibiotics to treat potential underlying bacterial infection; debridement and possible surgical intervention to reduce nasal cavity size can be considered.
  6. *Rhinitis medicamentosa:* Discontinuation of offending agent (topical decongestant/vasoconstrictor agent, cocaine, α-receptor antagonist or phosphodiesterase-5-selective inhibitors). Patient may require short course of nasal or oral corticosteroids during withdrawal process.
  7. *Hormone-induced rhinitis:* Typically resolves with delivery if during pregnancy. Consider discontinuing OCP if offending agent. Nasal saline spray alone can be efficacious.
  8. *Rhinitis associated with systemic disease:* Optimally managing the underlying condition.
  9. *Rhinitis in the elderly:* Intranasal ipratropium bromide.
- Several studies have shown that repeated administration of topical capsaicin has a long-term beneficial effect on symptoms in patients with idiopathic rhinitis. Comparative studies on NAR with capsaicin vs. steroids demonstrate the superiority of capsaicin; however, the exact dose and frequency have not been determined.
- Alternative treatments: Silver nitrate, acupuncture.

DISPOSITION

Most patients experience mild to moderate symptomatic relief with avoidance of triggers and appropriate use of medications. Up to 52% of patients with NAR report worsening symptoms at 3- to 7-yr follow-ups. Periodic reevaluations should be performed, as there is evidence supporting increase in comorbidities (asthma, allergic rhinitis, conjunctivitis) with length of NAR diagnosis.

Furthermore, diagnostic testing is not precise for NAR versus AR. In a systematic review published in 2017, Nasal Allergen Provocation Testing (NAPT) was shown to better separate patients with NAR versus AR. Approximately 26% of patients presumed to have NAR had positive testing with NAPT despite negative skin-prick and/or serum IgE testing. It would be reasonable to revisit the diagnosis periodically and adjust management.

BOX 1 Differential Diagnosis in Chronic Rhinitis

- Concha bullosa
- Nasal septal deviation
- Adenoidal enlargement
- Nasal polyps
- Nasal cancer
- Nasal foreign body
- Basilar skull fracture
- Allergic rhinitis
- Cholinergic toxidromes
- Relapsing polychondritis
- Hypertrophic turbinates without rhinitis
- Choanal atresia
- Sarcoidosis
- Primary ciliary dyskinesia

Adapted from Adkinson NF et al: *Middleton's allergy principles and practice,* ed 8, Philadelphia, 2014, Elsevier.

REFERRAL

Referral to allergist and/or ENT may be appropriate when severe symptoms are unresponsive to standard therapy and/or diagnosis is uncertain.

PEARLS & CONSIDERATIONS

COMMENTS

- Nonallergic rhinitis symptoms are nonspecific, and a specific trigger is often never identified. Compared to allergic rhinitis, patients typically lack symptoms of sneezing, nasal pruritus, and conjunctival symptoms.
- Second-generation oral antihistamines are typically not efficacious, and the treatment of nonallergic rhinitis should be individualized based on its underlying pathophysiology.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Allergic Rhinitis (Patient Information)
Allergic Rhinitis (Related Key Topic)

AUTHORS: **Shyam Joshi, MD,** and **Charles Fox Sherrod IV, MD**

SUGGESTED READINGS

Gevorgyan A et al: Capsaicin for non-allergic rhinitis, *Cochrane Database Syst Rev* 7:CD010591, 2015.

Hamizan AW et al: Positive allergen reaction in allergic and non-allergic rhinitis: a systematic review, *Int Forum Allergy Rhinol* 9:868-877, 2017.

Hellings PW et al: Non-allergic rhinitis: position paper of the European academy of allergy and clinical immunology, *Allergy* 72:1657-1665, 2017.

Lieberman P, Smith P: Nonallergic rhinitis—treatment, *Immunol Allergy Clin North Am* 36:305-319, 2016.

Seidman MD et al: Clinical practice guideline: allergic rhinitis, *Otolaryngol Head Neck Surg* 152:S1-S43, 2015.

Settipane RA, Kaliner MA: Nonallergic rhinitis, *Am J Rhinol Allergy* 27(3):48-51, 2013.

BASIC INFORMATION

DEFINITION

Non-celiac gluten sensitivity (NCGS) is an intestinal and/or extraintestinal reaction to ingested gluten or wheat that improves once gluten-containing foods have been eliminated from the diet. Gluten is a group of proteins found in grains (wheat, rye, barley, and oats). The two main protein components of gluten are gliadin and glutenin. Celiac disease and wheat allergy must be excluded before the diagnosis of NCGS can be made.

SYNONYMS

Non-celiac wheat sensitivity (NCWS)
NCGS

ICD-10CM CODE
K90.41 Non-celiac gluten sensitivity

EPIDEMIOLOGY & DEMOGRAPHICS

- Prevalence of NCGS ranges from 0.6% to 13% in the general population. Its actual prevalence is not well established due to the absence of diagnostic markers and is based primarily on self-reported questionnaires for gluten sensitivity.
- Reported prevalence has increased significantly over the past decade, directly correlating to the increase in sales of gluten-free foods, which have doubled since 2011.
- NCGS is reported more often in women than in men.
- It is more commonly reported in urban areas.
- The median age of diagnosis is in the fourth decade of life.

PHYSICAL FINDINGS AND CLINICAL PRESENTATION

- Intestinal symptoms include abdominal pain, bloating, diarrhea (with or without alternating constipation), and flatulence.
- Extraintestinal findings may include constitutional symptoms such as fatigue and weight loss as well as neurological changes (headache, brain fog, numbness) and psychological changes (anxiety). Less commonly, anemia and dermatological findings such as eczema may be seen.
- Symptoms of NCGS greatly overlap with IBS and therefore may be difficult to distinguish.

ETIOLOGY

- There is no known biomarker or diagnostic test for NCGS, making the pathogenesis unclear.
- It has been suggested that in patients with NCGS, ingestion of gluten may lead to increased intestinal permeability by increasing serum concentration of zonulin, a protein that increases permeability through changes in epithelial tight junctions. The rise in zonulin leads to breaks and leakage through the intestinal epithelial wall.
- Several studies have found changes in the intestinal microbiome of patients with NCGS compared with those in healthy controls. These changes revert to normal following initiation of a gluten-free diet (GFD).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Celiac disease
- Wheat allergy
- Irritable bowel syndrome (IBS)

WORKUP

- There are no strict diagnostic criteria; therefore, there is a great deal of dependence on the patient's perception of symptoms and nocebo effect.
- Salerno Experts' Criteria is the most widely used method for diagnosing NCGS.
  1. Patient must be on a normal gluten-containing diet for at least 6 weeks. During this time, the patient is assessed by a diagnostic questionnaire (Table E1) at week –2, –1, and 0 to establish baseline symptoms.
  2. At time 0, patient begins a strict GFD as instructed by a dietician. Patient will remain on GFD for 6 weeks with weekly data recording via the questionnaire.
  3. Response is assessed, with a positive result defined as a decrease of ≥30% in the baseline score in 1 to 3 categories for ≥50% of the observation time.
  4. The diagnosis of NCGS is excluded in subjects failing to show symptomatic improvement after six weeks. These patients should be worked up for other causes of IBS-like symptoms, including intolerance to fermentable oligo-, di- and monosaccharides and polyols (FODMAPS) or small bowel bacterial overgrowth.
  5. This 6-wk test study is followed by a double-blind placebo-controlled challenge of ≥8 g/day of gluten (or placebo) for a week of each. Gluten is given in a "vehicle" such as a bar, bread, or muffin. Gluten and placebo must be indistinguishable in look, texture, and taste.
  6. Again, a positive result is defined as a variation of ≥30% between gluten and placebo.
  7. While the Salerno Expert Criteria is the proposed method for diagnosis of NCGS, it is often impractical to perform in the primary care setting. Therefore, simply asking the patient to adopt a GFD will achieve the same desired clinical outcome.

LABORATORY TESTS

- Mainly a clinical diagnosis as there are no diagnostic tests or biomarkers for NCGS
- Celiac disease and wheat allergy must be excluded through their respective laboratory tests prior to the diagnosis of NCGS

TREATMENT

NONPHARMACOLOGIC THERAPY

Treatment of NCGS is strict elimination of gluten from the diet. A low-FODMAPS diet may be indicated if symptoms are not responding to a GFD.

ACUTE GENERAL Rx

- Correct nutritional deficiencies
- Lifelong elimination of gluten or wheat

DISPOSITION

Unlike celiac disease, which requires a strict, lifelong gluten-free diet, it is unclear whether NCGS is a permanent condition. Some authors have suggested reintroduction of gluten after 1 to 2 yr.

REFERRAL

A multidisciplinary team approach is recommended for patients with NCGS, with involvement of the primary doctor, gastroenterologist, and nutritionist.

PEARLS AND CONSIDERATIONS

COMMENTS

- The gluten-free market is rising, likely due to the perceived health benefits of a GFD. This, however, is debatable, as grains should be the main energy source in the human diet. A GFD is poor in trace elements and vitamins such as zinc, iron, magnesium, calcium, vitamin D, vitamin B_{12}, folate, and fiber. It is also high in calories, fat, sugar, and salt.
- Studies show that intake of gluten through whole grains is associated with a lower risk of elevated triglycerides and lower risk of cardiovascular disease.

RELATED CONTENT

Celiac Disease (Related Key Topic)
Irritable Bowel Syndrome (Related Key Topic)

AUTHOR: **Christina M. Bortz, MD**

SUGGESTED READINGS

Khan A et al: Nonceliac gluten and wheat sensitivity, *Clinical Gastroenterology and Hepatology* 17:5, 2019.

Roszkowska A et al: Non-celiac gluten sensitivity: a review, *Medicina (Kaunas, Lithuania)* 55:222, 2019.

TABLE E1 Diagnostic Questionnaire

During each week of gluten-free diet, rate symptoms on a scale from 1-10. (Score of 1 = minimal symptoms / 10 = severe symptoms)

	Wk 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6
Abdominal pain							
Acid reflux							
Nausea/vomiting							
Borborygmus							
Abdominal distention							
Belching							
Flatulence							
Decreased stool frequency							
Increased stool frequency							
Diarrhea							
Constipation							
Fecal urgency							
Feeling of incomplete evacuation							
Dermatitis							
Headache							
Foggy mind							
Fatigue							
Limb numbness							
Joint/muscle pain							
Fainting							
Oral/tongue lesions							

Non-Hodgkin Lymphoma ALG PTG

BASIC INFORMATION

DEFINITION

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies of the lymphoreticular system. There are approximately 60 different NHL subtypes. The WHO classification of lymphomas is summarized in Table 1 and Fig. 1.

SYNONYM

NHL

ICD-10CM CODES

C85.90 Non-Hodgkin lymphoma, unspecified, unspecified site
C85.91 Non-Hodgkin lymphoma, unspecified, lymph nodes of head, face, and neck
C85.92 Non-Hodgkin lymphoma, unspecified, intrathoracic lymph nodes
C85.93 Non-Hodgkin lymphoma, unspecified, intra-abdominal lymph nodes
C85.94 Non-Hodgkin lymphoma, unspecified, lymph nodes of axilla and upper limb
C85.95 Non-Hodgkin lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C85.96 Non-Hodgkin lymphoma, unspecified, intrapelvic lymph nodes
C85.97 Non-Hodgkin lymphoma, unspecified, spleen
C85.98 Non-Hodgkin lymphoma, unspecified, lymph nodes of multiple sites
C85.99 Non-Hodgkin lymphoma, unspecified, extranodal and solid organ sites

EPIDEMIOLOGY

- Sixth most common neoplasm in the U.S. (>70,000 new cases annually). Incidence increases with age; majority of patients are above 60 yr of age.
- In the U.S. and Europe, diffuse large B-cell lymphoma (DLBCL) is the most common subtype (30% of the cases), and follicular lymphoma (FL) is the second most common subtype (25% of the cases).
- In patients with HIV, NHL is the most common tumor (followed by Kaposi sarcoma). DLBCL accounts for 80% to 90% of the cases of HIV-associated NHL.
- Factors associated with an increased risk of non-Hodgkin lymphoma are summarized in Box 1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients often present with lymphadenopathy.
- Approximately one third of the NHL involve extranodal sites, which can result in

TABLE 1 World Health Organization Classification of Lymphomas[a]

Mature B-Cell Neoplasms

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

- B-cell prolymphocytic leukemia
- Splenic B-cell marginal zone lymphoma
- Hairy cell leukemia
- *Splenic B-cell lymphoma/leukemia, unclassifiable*
- *Splenic diffuse red pulp small B-cell lymphoma*
- *Hairy cell leukemia-variant*
- Lymphoplasmacytic lymphoma
- Waldenström macroglobulinemia
- Heavy chain diseases
- Alpha heavy chain disease
- Gamma heavy chain disease
- Mu heavy chain disease

Plasma Cell Myeloma

- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma

Extranodal Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT Lymphoma)

- Nodal marginal zone lymphoma
- *Pediatric nodal marginal zone lymphoma*

Follicular Lymphoma

- *Pediatric-type follicular lymphoma*
- Primary cutaneous follicle center lymphoma

Mantle Cell Lymphoma

Diffuse Large B-Cell Lymphoma (DLBCL), NOS

- T-cell/histiocyte–rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV-positive DLBCL
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- HHV8-positive diffuse large B-cell lymphoma and primary effusion lymphoma
- Burkitt lymphoma
- High grade B-cell lymphomas, with *MYC* and *BCL2* and/or *BCL6* rearrangements
- B-cell lymphoma unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classic Hodgkin lymphoma

Mature T-Cell and NK-Cell Neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK-cells*
- Aggressive NK leukemia
- Systemic EBV-positive T-cell lymphoma of childhood
- Hydroa vacciniforme-like lymphoma
- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma

Mycosis Fungoides

- Sézary syndrome
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorders
- Lymphoid papulosis
- Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
- Primary cutaneous CD4-positive small/medium T-cell lymphoproliferative disease

Peripheral T-Cell Lymphoma, NOS

Angioimmunoblastic T-Cell Lymphoma

Anaplastic Large Cell Lymphoma, ALK-Positive

- Anaplastic large cell lymphoma, ALK-negative

Hodgkin Lymphoma

Nodular Lymphocyte Predominant Hodgkin Lymphoma

Classic Hodgkin Lymphoma

Nodular Sclerosis Hodgkin Lymphoma

- Lymphocyte-rich classic Hodgkin lymphoma
- Mixed cellularity classic Hodgkin lymphoma
- Lymphocyte-depleted classic Hodgkin lymphoma

[a]Most common entities are underlined. Provisional entities are in italics. Some rare entities or variants are omitted.
ALK, Anaplastic lymphoma kinase; *CNS,* central nervous system; *EBV,* Epstein-Barr virus; *HHV-8,* human herpesvirus-8; *NK,* natural killer; *NOS,* not otherwise specified.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

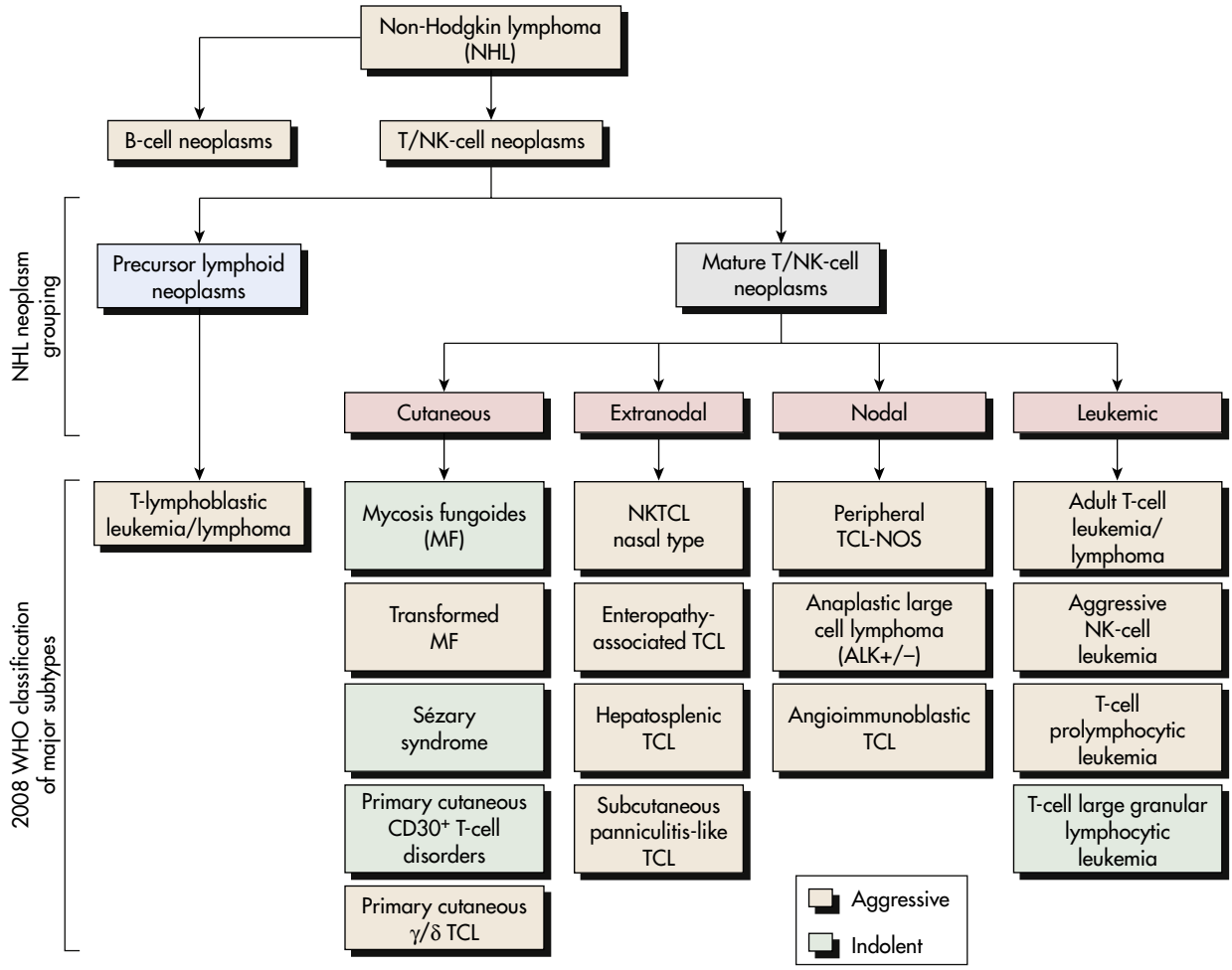

FIG. 1 World Health Organization *(WHO)* classification of the mature T-cell neoplasms. *NK,* Natural killer; *NKTCL,* nasal NK/T-cell lymphoma; *NOS,* not otherwise specified; *TCL,* T-cell lymphoma; *WHO,* World Health Organization. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

BOX 1 Factors Associated with an Increased Risk of Non-Hodgkin Lymphoma

- Immunosuppression, acquired
  - After solid-organ or hematopoietic stem cell transplantation
  - HIV/AIDS
- Congenital immunodeficiency syndromes
- Increasing age (waning immunity)
- Previous history of HL or NHL
- Family history of NHL
- Drugs
  - Methotrexate
  - TNF-α inhibitors
- Occupational exposures
  - Herbicides, pesticides, wood dust, epoxy glue, organic solvents
  - Farming, forestry, painting, carpentry, tanning

AIDS, Acquired immunodeficiency syndrome; *HIV,* human immunodeficiency virus; *HL,* Hodgkin lymphoma; *NHL,* non-Hodgkin lymphoma; *TNF,* Tumor necrosis factor.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

unusual presentations (e.g., gastrointestinal tract involvement can simulate peptic ulcer disease).
- Presence of B symptoms like unexplained weight loss, fever, fatigue, and night sweats are seen typically in aggressive or highly aggressive lymphomas.
- Aggressive lymphomas have acute or subacute presentation with increasing size of the mass and B symptoms.
- Indolent lymphomas have a more chronic course, with asymptomatic lymphadenopathy and/or slowly progressive cytopenias.
- Hepatomegaly and splenomegaly may be present.
- Cough, dyspnea with bulky mediastinal involvement.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hodgkin lymphoma
- Viral infections
- Metastatic carcinoma
- Autoimmune conditions
- Sarcoidosis

WORKUP

Initial laboratory evaluation may be entirely normal. Elevated LDH may be seen in aggressive lymphoma or in indolent lymphoma with high disease bulk. In cases of highly aggressive NHL (e.g., Burkitt lymphoma), spontaneous tumor lysis syndrome (TLS) may be seen, but rarely; it is characterized by hyperkalemia, hyperuricemia, hypocalcemia, hyperphosphatemia, and acidosis. TLS can be life threatening and is considered a medical emergency. Acute management includes aggressive IV fluid repletion and rasburicase. Proper staging of NHL includes the following:
- A thorough history and physical examination.
- Excisional or incisional surgical biopsy is preferred. Image-guided core needle biopsies may be acceptable in patients without peripheral adenopathy. Fine needle aspirates are not adequate for precise lymphoma subclassification. Laparoscopic lymph node biopsy or mediastinoscopy can be used on an outpatient basis for most patients with intraabdominal or mediastinal lymphoma, respectively.
- Tissue biopsy with histologic, immunophenotypic, and genetic studies interpretation.

TABLE 2 Major Molecular Alterations in Non-Hodgkin Lymphomas

NHL Histologic Type	Alteration	Cases Affected (%)	Proto-Oncogene Involved	Mechanism of Proto-Oncogene Activation	Proto-Oncogene Function
Lymphoplasmacytic lymphoma	*MYD88* L265P mutation	95	*MYD88*	Activation	B-cell signaling
Follicular lymphoma	t(14;18)(q32;q21)	90	*BCL-2*	Transcription deregulation	Negative regulator of apoptosis
Mantle cell lymphoma	t(11;14)(q13;q32)	70	*BCL-1/cyclin D1*	Transcription deregulation	Cell cycle regulator
MALT lymphoma	t(11;18)(q21;q21)	50	*API_2/MLT*	Fusion protein	*API_2* has antiapoptotic activity
	t(1;14)(p22;q32)		*BCL-10*	Transcription deregulation	Antiapoptosis
Diffuse large B-cell lymphoma	der(3)(q27)	35	*BCL-6*	Transcription deregulation	Transcriptional repressor required for GC formation
	t(14;18)(q32;q21)	15	*BCL-2*	Transcription deregulation	Negative regulator of apoptosis
	t(8;14)(q24;q32)	10	MYC	Transcription deregulation	Transcription factor regulating cell proliferation and growth
Burkitt lymphoma	t(8;14)(q24;q32)	80	MYC	Transcription deregulation	Transcription factor regulating cell proliferation and growth
	t(2;8)(p11;q24)	15	MYC		
	t(8;22)(q24;q11)	5	MYC		
Anaplastic large T-cell lymphoma	t(2;5)(p23;q35)	60	NPM/ALK	Fusion protein	*ALK* is a tyrosine kinase

GC, Gastric cancer; *MALT,* mucosa-associated lymphoid tissue; *NHL,* non-Hodgkin lymphoma.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

Major molecular alterations in non-Hodgkin lymphomas are summarized in Table 2.

- Routine laboratory evaluation (complete blood count, flow cytometry in selected circumstances, ESR, urinalysis, LDH, blood urea nitrogen, creatinine, serum calcium, uric acid, liver function tests, serum protein electrophoresis).
- HIV and hepatitis B testing.
- Bone marrow evaluation (aspirate and biopsy) (Fig. E2).
- CT scan of chest, abdomen, and pelvis with IV contrast, if possible.
- Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) integrated with CT (Fig. E3) has emerged as a powerful tool for staging, response evaluation, and posttreatment surveillance in patients with aggressive subtypes of NHL.
- Depending on the histopathology, the results of the previous studies, and the planned therapy, some other tests may be performed.
- Lumbar puncture is needed in some patients with aggressive NHL, and most patients with HIV-associated NHL, to evaluate for CNS involvement by lymphoma.
- The evaluation of a new patient with non-Hodgkin lymphoma is summarized in Table 3.

CLASSIFICATION: For clinical approach, NHL is subdivided lymphomas into indolent, aggressive, and highly aggressive disease.

STAGING: The Ann Arbor staging system that was initially developed for Hodgkin lymphoma (HL) was revised as the Lugano criteria and remains the current standard; but unlike HL, NHL does not spread predictably via lymphatic channels to contiguous nodal regions, so stage is only one of multiple contributors to prognosis (Table 4). Histopathology has greater therapeutic implications in NHL than in Hodgkin lymphoma.

TABLE 3 Evaluation of a New Patient with Non-Hodgkin Lymphoma

Evaluation	Mandatory	As Indicated
Confirm diagnosis	Adequate biopsy reviewed by experienced hematopathologists	Immunophenotyping with immunohistochemistry +/– flow cytometry Cytogenetics/molecular studies
General overview and risks of therapy	History and physical examination Complete blood cell count Chemistry screen (including liver and renal function studies) HIV serology Hepatitis B serologies	Blood coagulation studies EBV serology and PCR assay Hepatitis C serology Serum electrolytes, uric acid Assessment of cardiac ejection fraction Pregnancy testing in women Discussion of fertility issues
Prognostic categorization	Serum lactate dehydrogenase Serum albumin	Erythrocyte sedimentation rate Serum β_2-microglobulin
Anatomic disease	Chest, abdominal, and pelvic CT with contrast enhancement	Ultrasonography FDG-PET/CT MRI
Occult sites of involvement		Unilateral bone marrow biopsy with aspirate Lumbar puncture with flow cytometry of CSF Biopsy of suspicious sites Blood flow cytometry

CSF, Cerebrospinal fluid; *CT,* computed tomography; *EBV,* Epstein-Barr virus; *FDG-PET,* fluorodeoxyglucose-18–labeled positron emission tomography; *HIV,* human immunodeficiency virus; *MRI,* magnetic resonance imaging; *PCR,* polymerase chain reaction.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE 4 Non-Hodgkin Lymphoma: Lugano Staging Classification

Stage	Features
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer ring), or a single extranodal location without nodal involvement (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm or limited nodal disease with limited contiguous extranodal involvement (IIE)
III	Involvement of lymph node regions or structures on both sides of the diaphragm
IV	Involvement of diffuse or noncontiguous extranodal site(s)

From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

Fig. 4 illustrates a diagnostic algorithm outlining the steps in classification of B-cell lymphomas composed of cells of small to intermediate size.

Rx TREATMENT

ACUTE GENERAL Rx

The therapeutic regimen varies with specific lymphoma subtype and pathologic stage. Following are the commonly used therapeutic modalities:

INDOLENT NHL:

- Deferment of therapy and careful observation in asymptomatic patients with low volume disease.
- Local radiotherapy for stage I disease.
- Rituximab, an anti-CD20 monoclonal antibody, with or without chemotherapy is used in patients with symptomatic or progressive disease.
- The addition of rituximab to chemotherapy is generally well tolerated and has increased response and survival rates in NHL patients. Patients who received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) had higher response rates (96% vs. 90%) with a better 2-yr overall survival rate (95% vs. 90%) than patients who received CHOP without rituximab. Similarly, patients who received rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) had higher response rates (81% vs. 57%) and better overall survival at 4 yr (83% vs. 77%) than patients who were treated with CVP without rituximab.
- In a recent phase III noninferiority study, the combination of bendamustine and rituximab was associated with better progression-free survival rates than R-CHOP (70 vs. 31 mo) with fewer toxic effects. Subset analyses showed better progression-free survival in patients with follicular lymphoma, mantle cell lymphoma, and lymphoplasmacytic lymphoma.
- Maintenance rituximab after rituximab-containing regimens has been associated with a better progression-free survival at 3 yr (75% vs. 58%) than observation alone without a difference in overall survival.
- The combination of obinutuzumab and chemotherapy followed by obinutuzumab maintenance was approved by the FDA in previously untreated patients with follicular lymphoma based on a randomized study, in which obinutuzumab and chemotherapy were associated with longer median progression-free survival than rituximab and chemotherapy.

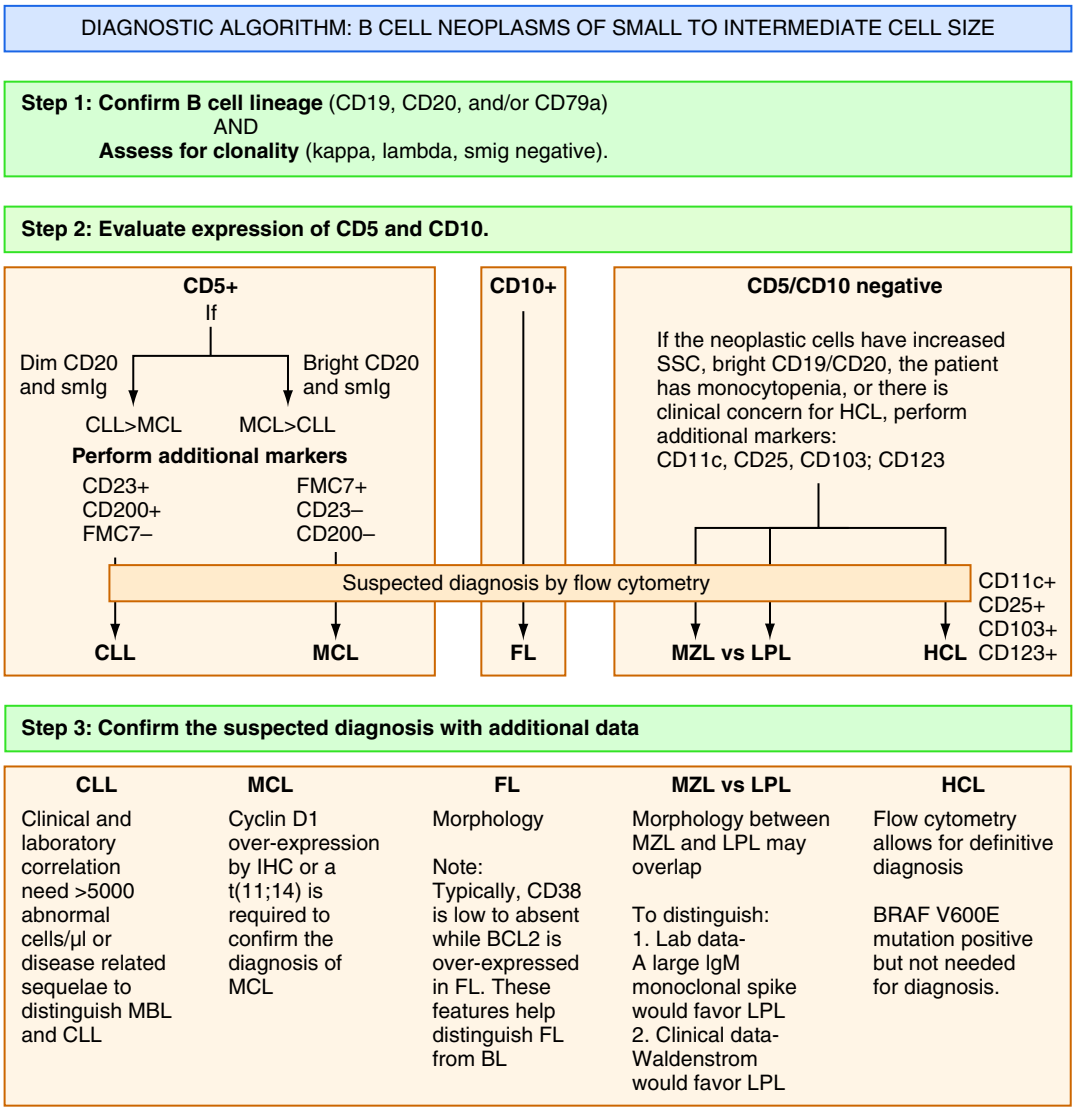

FIG. 4 This diagnostic algorithm outlines the steps in classification of B-cell lymphomas composed of cells of small to intermediate size. *BL,* Burkitt lymphoma; *CLL,* chronic lymphocytic leukemia; *FL,* follicular lymphoma; *HCL,* hairy cell leukemia; *IgM,* immunoglobulin M; *IHC,* immunohistochemistry; *LPL,* lymphoplasmacytic lymphoma; *MBL,* monoclonal B-cell lymphocytosis; *MCL,* mantle cell lymphoma; *MZL,* marginal zone lymphoma; *SmIg,* surface immunoglobulin; *SSC,* scleroderma and systemic sclerosis. (From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, Philadelphia, 2017, Elsevier.)

- The combination of obinutuzumab and bendamustine followed by obinutuzumab maintenance was approved by the FDA for the treatment of patients with rituximab-refractory follicular lymphoma.
- The oral BTK inhibitor ibrutinib is FDA-approved for the treatment of patients with relapsed mantle cell lymphoma, lymphoplasmacytic lymphoma, and marginal zone lymphoma. Acalabrutinib, a second-generation BTK inhibitor, has also been approved for relapsed mantle cell lymphoma.
- The oral PI3K inhibitors idelalisib and copanlisib, as well as the novel anti-CD20 monoclonal antibody obinutuzumab, have been FDA-approved for the treatment of relapsed follicular lymphoma.
- The proteasome inhibitor bortezomib and the immunomodulating agent lenalidomide are FDA-approved for the treatment of relapsed mantle cell lymphoma.
- *H. pylori*-associated gastric marginal zone lymphoma can be treated with a course of antibiotics. For persistent cases after eradication or *H. pylori*-negative cases, radiotherapy is highly effective.
- Splenic marginal zone lymphoma is typically treated with rituximab or splenectomy. Chemoimmunotherapy or ibrutinib may be appropriate in relapsed disease.
- Stem cell transplantation (autologous or allogeneic) may confer long-term disease control in multiple relapsed or refractory disease.
- Table 5 summarizes chemotherapy regimens in indolent lymphomas.

AGGRESSIVE NHL: The most common aggressive NHL is DLBCL. The addition of rituximab against CD20 B-cell lymphoma to the CHOP regimen (R-CHOP) increased the complete response rate and prolonged overall survival in patients with DLBCL, based on randomized controlled trials, without clinically significant increase in toxicity. R-CHOP has shown to be safe and effective in patients with HIV-associated NHL with CD4+ counts >50 cells/mm^3.

Most common regimens used in DLBCL include:

- Three cycles of R-CHOP followed by involved-field radiotherapy or 6 cycles of R-CHOP alone are appropriate approaches in patients with localized DLBCL.
- 6 cycles of R-CHOP with or without radiotherapy are appropriate in patients with advanced-stage DLBCL.
- For patients with double-hit lymphomas (defined as harboring rearrangement of MYC, BCL-2, and/or BCL-6), who have poorer outcomes to R-CHOP than regular DLBCL, the use of R-EPOCH (infusional etoposide, doxorubicin, and vincristine, along with cyclophosphamide, prednisone, and rituximab) might also be effective.
- Granulocyte-colony stimulating factor (e.g., filgrastim, MYC) may be effective in reducing the risk of febrile neutropenia in patients over 65 yr with aggressive lymphoma undergoing chemotherapy.
- Treatment with high-dose chemotherapy and autologous bone marrow transplant: Compared with conventional chemotherapy, increases overall survival in patients with chemotherapy-sensitive relapsed DLBCL.
- Chimeric antigen receptor T-cell therapy was recently approved for patients with relapsed or refractory diffuse large B-cell lymphoma after two prior lines of chemotherapy.
- Combination chemotherapy regimens for NHL are described in Table 6.

HIGHLY AGGRESSIVE NHL: The most common high-grade NHL subtype is Burkitt lymphoma (BL). BL affects younger patients than DLBCL and is common in HIV-infected individuals. Regimens more intensive than R-CHOP are needed to cure patients with high-grade NHL. The most commonly used multi-agent regimens include hyper-CVAD, CODOX-M/IVAC, and dose-adjusted EPOCH, usually in combination with rituximab. The 5-yr survival approximates 75%.

DISPOSITION

- Patients with indolent NHL in the rituximab era experience long survival despite the

TABLE 5 Chemotherapy Regimens in Indolent Lymphomas

BR (Every 28 Days)
- Bendamustine 120 mg/m^2 days 1 and 2
- Rituximab 375 mg/m^2 IV day 1

CVP-R (Every 21 Days)
- Cyclophosphamide 750 mg/m^2 IV on day 1
- Vincristine 1.4 mg/m^2, up to a maximal dose of 2 mg IV, on day 1
- Prednisone 40 mg/m^2 daily PO days 1-5
- Rituximab 375 mg/m^2 IV day 1[32]

R-CHOP (Every 21 Days)
- Cyclophosphamide 750 mg/m^2 IV on day 1
- Doxorubicin 50 mg/m^2 IV on day 1
- Vincristine 1.4 mg/m^2, up to a maximal dose of 2 mg IV, on day 1
- Prednisone 100 mg daily orally on days 1-5
- Rituximab 375 mg/m^2 IV on day 1 of each therapy cycle[33] or by alternate schedule[34]

CNOP (Every 21 Days)
- Cyclophosphamide 750 mg/m^2 IV on day 1
- Mitoxantrone 10 mg/m^2 IV on day 1
- Vincristine 1.4 mg/m^2, up to a maximal dose of 2 mg IV, on day 1
- Prednisone 50 mg/m^2 daily orally on days 1-5

R-CHVP-IFN (Every 28 Days for 6 Mo, Then Every 2 Mo for 6 Mo). [35]
- Cyclophosphamide 600 mg/m^2
- Doxorubicin 25 mg/m^2
- Etoposide 100 mg/m^2 on day 1 (replaces original teniposide 60 mg/m^2 on day 1)
- Prednisolone 40 mg/m^2 on days 1-5
- Interferon-α 5-3 times a wk
- Patients being treated with R-CHVP also received 375 mg/m^2 of rituximab IV on day 1 of each therapy cycle for 6 cycles

FMD (Every 28 Days)
- Fludarabine 25 mg/m^2 IV on day 1-3
- Mitoxantrone 10 mg/m^2 IV on day 1
- Dexamethasone 20 mg/day PO days 1-5
- Patients being treated with R-FMD also received 375 mg/m^2 of rituximab IV on day 1 of each therapy cycle

ProMACE-MOPP
- Cycles repeated every 28 days

Day 1
- Cyclophosphamide 650 mg/m^2 IV
- Doxorubicin 25 mg/m^2 IV
- Etoposide 120 mg/m^2 IV
- Prednisone 60 mg/m^2 orally daily days 1-14

Day 8
- Mechlorethamine 6 mg/m^2 IV
- Vincristine 1.4 mg/m^2 (maximum 2 mg) IV on day 8
- Procarbazine 100 mg/m^2 orally daily days 8-14

Day 15
- Methotrexate 500 mg/m^2 IV on day 15 with leucovorin 50 mg/m^2 orally every 6 hours for four doses beginning 24 hours after methotrexate

R-Hyper-CVAD (Every 21 Days)[36]

Cycles 1, 3, 5, and 7
- Rituximab 375 mg/m^2 IV on day 1
- Cyclophosphamide (with mesna) 300 mg/m^2 IV over 3 hours every 12 hours on days 2-4 (total 6 doses)
- Vincristine 1.4 mg/m^2 (maximum 2 mg) IV on days 5 and 12
- Doxorubicin 16.6 mg/m^2 IV by continuous infusion on days 5-7
- Dexamethasone 40 mg/day PO/IV on days 2–5 and days 12-15

Cycles 2, 4, 6, and 8
- Rituximab 375 mg/m^2 IV on day 1
- Methotrexate 200 mg/m^2 IV over 2 hours, followed by 800 mg/m^2 IV continuous infusion over 22 hours on day 2
- Leucovorin 50 mg PO starting 12 hours after completion of methotrexate infusion, followed by 15 mg PO every 6 hours for 8 dosed until the methotrexate level is less than 0.1 μM/L
- Cytarabine 3000 mg/m^2 IV over 2 hours every 12 hours on days 3 and 4 (4 doses total)

Rituximab Monotherapy

Rituximab 375 mg/m^2 weekly for 4 wk

NOTE: Reference endnotes retained from the source. *IV,* Intravenous; *PO,* by mouth.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 6 Combination Chemotherapy Regimens for Non-Hodgkin Lymphoma

Regimen	Dose	Days of Administration	Frequency
R-Bendamustine			**Every 28 days**
Bendamustine	90 mg/m$_2$ IV	1-2	
Rituximab	375 mg/m$_2$ IV	1	
R-CHOP			**Every 21 days**
Cyclophosphamide	750 mg/m$_2$ IV	1	
Doxorubicin	50 mg/m$_2$ IV	1	
Vincristine	1.4 mg/m$_2$ IV	1	
Prednisone, fixed dose	100 mg PO	1-5	
Rituximab	375 mg/m$_2$ IV	1	
R-CVP			**Every 21 days**
Cyclophosphamide	1000 mg/m$_2$ IV	1	
Vincristine	1.4 mg/m$_2$ IV	1	
Prednisone, fixed dose	100 mg PO	1-5	
Rituximab	375 mg/m$_2$ IV	1	

IV, Intravenous; *PO,* by mouth.
Adapted from Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.

TABLE 7 Clinical Prognostic Indexes

International Prognostic Index (IPI) for Aggressive Lymphomas[1]

Risk Group	IPI Score[a]	CR Rate (%)	5-Yr OS Rate (%)
Low	0, 1	87	73
Low intermediate	2	67	51
High intermediate	3	55	43
High	4,5	44	26

Follicular International Prognostic Index (FLIPI)[2]

Risk Group	FLIPI Score[b]	Distribution (%)	5-Yr OS Rate (%)
Low	0-1	36	90.6
Intermediate	1-2	37	77.6
Poor	≥3	27	52.5

Mantle Cell International Prognostic Index (MIPI)[3]

Risk Group	MIPI Score[c]	Distribution (%)	Median Survival Rate
Low	0-3	44	Not reached
Intermediate	4-5	35	51 mo
High	6-11	21	29 mo

CR, Complete response; *OS,* overall survival.
[a]One point is given for the presence of each of the following characteristics: age older than 60 yr, elevated serum lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group performance status ≥2, Ann Arbor stage III or IV, and more than two extranodal sites.
[b]One point is given for the presence of each of the following characteristics: age older than 60 yr, elevated serum LDH level, hemoglobin level <12 g/dl, Ann Arbor stage III or IV, and number of nodal sites ≥5.
[c]Points are based on age, ECOG performance status, white blood cell count, and serum LDH level.
(1)The International Non-Hodgkin's Lymphoma Prognostic Factors Project: A predictive model for aggressive non-Hodgkin's lymphoma, *N Engl J Med* 329:987-994, 1993.
(2)Solal-Celigny P et al: Follicular lymphoma international prognostic index, *Blood* 104:1258-1265, 2004.
(3)Hoster E et al: A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma, *Blood* 111:558-565, 2008.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

lack of curative potential of chemoimmunotherapy. Patients with aggressive NHL may achieve a cure with chemoimmunotherapy.

- Complete remission occurs in 50% to 60% of patients with aggressive NHL. Prognostic factors include the lymphoma subtype, age of patient, and extent of disease. Table 7 describes the International Prognostic Index (IPI) for aggressive lymphomas. More recently, studies of the IPI in the modern era incorporating the anti-CD20 monoclonal antibody rituximab show an overall improved prognosis with 33% of the highest-risk patients alive 5 yr from diagnosis and 96% in the lowest risk.
- Patients who present with HIV-related NHL and low CD4+ cell count have a poor prognosis (median duration of survival is 15 to 34 mo). Despite therapeutic advances, the management of HIV-associated lymphomas is challenging due to potential pharmacologic interactions and increased risk of infectious complications. It is important to optimize the CD4 cell count during treatment. Referral to an HIV oncologist is recommended.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Non-Hodgkin Lymphoma (Patient Information)

AUTHORS: **Jorge J. Castillo, MD,** and **Ann S. LaCasce, MD, MMSc**

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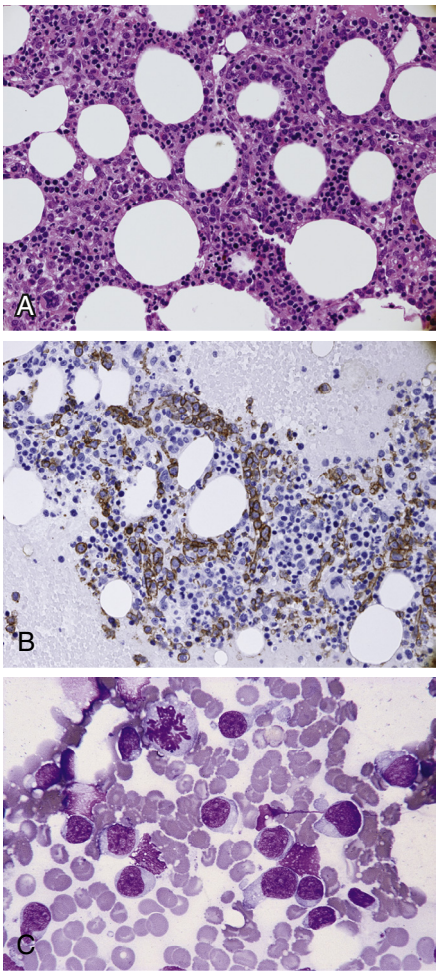

FIG. E2 Intravascular large B-cell lymphoma in a bone marrow trephine biopsy and bone marrow aspirate. A, Collections of lymphoma cells are present within the sinuses of the hematoxylin-eosin stained section. The infiltrate is subtle and could easily be missed. **B,** CD20 immunostain highlights the intrasinusoidal lymphoma cells. **C,** Lymphoma cells in the bone marrow aspirate are large, with blue-gray cytoplasm; many contain visible nucleoli. (Courtesy Dr. Robert Pooley, Department of Pathology, Little Company of Mary Hospital, Evergreen Park, Ill. From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, WB Saunders.)

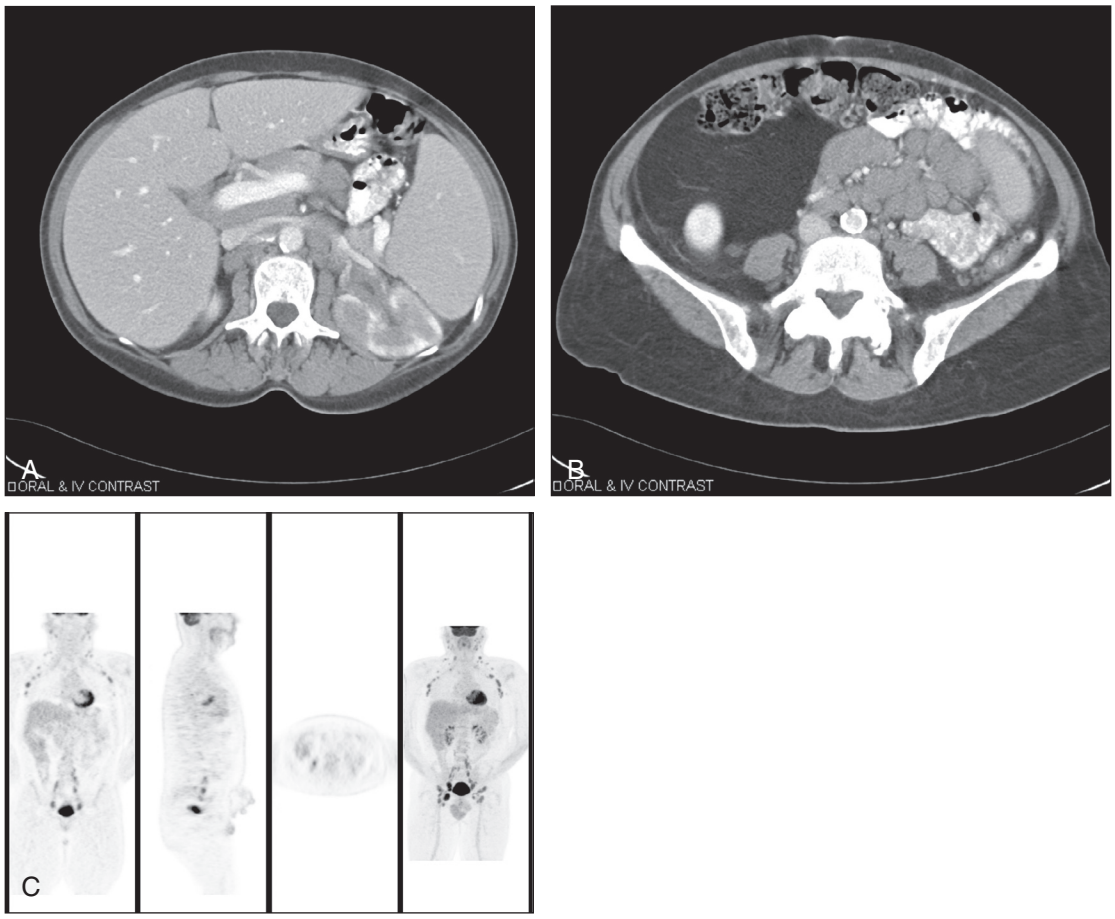

FIG. E3 (A) Axial computed tomography image with oral and intravenous contrast agent shows paraaortic adenopathy and infiltration of the left kidney by lymphoma. **(B)** Image of the lower abdomen in the same patient shows enlarged mesenteric nodes. **(C)** Positron emission tomography–only images (*left to right:* coronal, sagittal, transverse, and anterior projections) show focal areas of increased fluorine-18–fluorodeoxyglucose uptake in multiple lymph node groups, including the axillary, inguinal, and iliac regions, consistent with disseminated lymphoma. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

BASIC INFORMATION

DEFINITION

Obesity refers to having an excess amount of body fat in relation to lean body mass, or a body mass index (BMI) of ≥30 kg/m^2. Overweight is defined as BMI of 25 to 29.9 kg/m^2, and morbid obesity refers to adults with a BMI ≥40 kg/m^2. BMI is used as a surrogate measure of obesity. Abdominal obesity is defined as waist circumference >102 cm (40 inches) in men and >88 cm (35 inches) in women.

ICD-10CM CODES

E66.01	Morbid (severe) obesity due to excess calories
E66.09	Other obesity due to excess calories
E66.1	Drug-induced obesity
E66.2	Morbid (severe) obesity with alveolar hypoventilation
E66.8	Other obesity
E66.9	Obesity, unspecified
O99.210	Obesity complicating pregnancy, unspecified trimester
O99.211	Obesity complicating pregnancy, first trimester
O99.212	Obesity complicating pregnancy, second trimester
O99.213	Obesity complicating pregnancy, third trimester
O99.214	Obesity complicating childbirth
O99.215	Obesity complicating the puerperium

EPIDEMIOLOGY & DEMOGRAPHICS

- The World Health Organization first recognized obesity as a worldwide epidemic in 1997. As of 2005, 1.6 billion adults worldwide were classified as overweight, 400 million of whom were obese. It is predicted that the combination of overweight and obesity will soon eclipse public health issues such as malnutrition and infectious diseases as the most significant cause of poor health.
- Worldwide, data from the Global Burden of Disease Study from 1980 to 2013 indicate the prevalence of adult obesity has increased from 28.8% to 36.9% in men and 29.8% to 38% in women. The prevalence of childhood and adolescent obesity has also substantially increased.
- Based on U.S. NHANES data from 2011 to 2012, the prevalence of abdominal obesity was 54%. It is estimated that by 2020, 2 in every 5 adults and 1 in every 4 children in the U.S. will be categorized as obese.
- The present cost of obesity in the U.S. population is estimated at $100 billion annually. Approximately two thirds of people living in the United States are overweight, which is the highest percentage in the world (Marie Ng, 2014).
- For persons with a BMI ≥30 kg/m^2, all-cause mortality is increased by 50% to 100% above that of persons with BMI in the range of 20 to 25 kg/m^2.
- Obesity is an independent risk factor for cardiovascular disease (CVD), type 2 diabetes, hypertension, cancer (particularly colon, prostate, breast, and gynecologic malignancies), sleep apnea, degenerative joint disease, thromboembolic disorders, digestive tract diseases (gallstones), and dermatologic disorders.
- Significant morbidity and risk of death are projected to begin in young adulthood, resulting in >100,000 excess cases of CHD by 2035, even with the most modest projection of future obesity.
- When children enter kindergarten, 12.4% are obese, and another 14.9% are overweight. Data show that incident obesity between the ages of 5 and 14 yr is more likely to have occurred at younger ages.[1]
- Obesity in adolescence is significantly associated with increased risk of incident severe obesity in adulthood, with variations by sex and race/ethnicity. Overweight or obese adults who were obese as children have increased risk of type 2 DM, dyslipidemia, hypertension, and carotid artery atherosclerosis.
- Obesity is a major preventable cause of death and disability in the U.S. (the other is tobacco).
- Extensive data indicate that weight loss can reverse or arrest the harmful effects of obesity.
- In 2013 nearly 180,000 bariatric surgery procedures were performed in the U.S. Of these procedures 42% were laparoscopic sleeve gastrectomy, 34% were Roux-en-Y gastric bypass, and 15% were laparoscopic adjustable gastric banding.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination should assess the degree and distribution of body fat, signs of secondary causes of obesity, and obesity-related comorbidities.
- Increased waist circumference is apparent. Excess abdominal fat is clinically defined as a waist circumference >40 inches (>102 cm) in men and >35 inches (>88 cm) in women (in Asian men and women, >36 inches and >33 inches, respectively). Central obesity is a risk factor for mortality even among individuals with normal BMIs.
- Symptoms associated with hypertension, coronary artery disease (CAD), and diabetes (e.g., polyuria, polydipsia, acanthosis nigricans, retinopathy, and neuropathy) may be present.
- Obesity is associated with cardiac hypertrophy, diastolic dysfunction, and decreased aortic compliance, which are independent predictors of cardiovascular risk.
- Joint pain and swelling are associated with degenerative joint disease secondary to obesity.
- The physical exam and ECG often underestimate the presence and extent of cardiac dysfunction in obese patients. Jugular venous distention and hepatojugular reflux may not be seen and heart sounds are frequently distant.
- A large quantity of fluid is present in the interstitial space of adipose tissue, as the interstitial space is ~10% of the tissue wet weight. This excess fluid in this compartment, if redistributed into the circulation, can have negative repercussions in obese individuals with heart failure. Obese individuals have higher cardiac output and a lower total peripheral resistance than do lean individuals, and obesity is associated with persistence of elevated cardiac filling pressure during exercise.
- Obesity predisposes to heart failure through several different mechanisms: increased total blood volume, increased cardiac output, LVH, left ventricular diastolic dysfunction, and adipositas cordis (excessive epicardial fat and fatty infiltration of the myocardium).

ETIOLOGY

- The pathophysiology of obesity is complex and poorly understood, but includes social, nutritional, physiologic, psychological, and genetic factors.
- Environmental factors such as a sedentary lifestyle and chronic ingestion of excess calories can cause obesity.
- Obesity may be related to genetic factors, which are thought to be polygenic. Genetic studies with adopted children have demonstrated that they have similar BMIs to their biologic parents but not their adoptive parents. Twin studies also demonstrate a genetic influence on BMI.
- Secondary causes of obesity can result from medications (antipsychotics, steroids, and protease inhibitors being common ones) and neuroendocrine disorders (like Cushing syndrome and hypothyroidism).

DIAGNOSIS

- BMI will establish the diagnosis of obesity. BMI is defined as the adult's weight in kilograms divided by the square of his or her height—and is closely correlated with total body fat content.
- BMI values can categorize patients into three classes of obesity:
  1. Class I (mild): BMI of 30.0 to 34.9 kg/m^2
  2. Class II (moderate): BMI of 35.0 to 39.9 kg/m^2
  3. Class III (severe): BMI of ≥40 kg/m^2
- Although BMI is commonly used to define obesity, it is not a highly accurate indicator of body fat composition in children, who are undergoing rapid changes in height, or in bodybuilders or athletes who have large amounts of muscle tissue.
- Waist circumference or waist-hip ratio is indicative of visceral adipose tissue/intraabdominal fat, which may be more deleterious than overall overweight or obesity.

[1]Cunningham SA et al: Incidence of childhood obesity in the United States, *N Engl J Med,* 370:403-411, 2014.

DIFFERENTIAL DIAGNOSIS

It is important to evaluate obese patients for secondary medical causes of obesity. Hypothalamic disorders, hypothyroidism, Cushing syndrome, insulinoma, depression, and drugs (corticosteroids, antidepressants, second-generation antipsychotics, sulfonylureas, and HIV protease inhibitors) can cause obesity. In children, certain genetic conditions, such as Prader-Willi syndrome, are associated with obesity.

WORKUP

History should be obtained regarding weight change, family history of obesity, and eating and exercise behavior. Assessment for eating disorders and depression should be made. Attention should be directed to the use of nutritional supplements, over-the-counter medications, hormones, diuretics, and laxatives. The workup of an obese patient typically requires laboratory work to assess for risks and complications as well as to rule out underlying causative medical conditions. Fig. E1 describes the evaluation of patients with suspected endocrine cause of obesity.

LABORATORY TESTS

- Obese patients should be assessed for medical consequences of their obesity by screening for metabolic syndrome. This includes measurement of fasting lipid profile, blood pressure, and waist circumference and screening for diabetes or prediabetes (oral glucose tolerance test, fasting glucose, or hemoglobin A1C).
- Polycythemia might warrant screening for sleep apnea. Liver function tests should be obtained to screen for hepatic steatosis.
- In the proper clinical setting, thyroid function studies and dexamethasone suppression testing will exclude hypothyroidism and Cushing syndrome as underlying causes of obesity. If insulinoma is suspected, the patient will need to undergo a 72-hr fast to confirm hypoglycemia with inappropriate insulin secretion.
- Obesity is associated with changes in the ECG, including a reduction in voltage and nonspecific ST-T changes that may interfere with diagnosis of left ventricular hypertrophy (LVH) or CAD.

IMAGING STUDIES

- Several methods are available for determining or calculating total body fat but offer no significant advantage over the BMI. These include measurement of total body water, total body potassium, bioelectrical impedance, and dual-energy x-ray absorptiometry.
- Buoyancy testing is an accurate method for determining total body fat composition.

OTHER STUDIES

Obesity increases the risk of obstructive sleep apnea, which, in turn, increases the risks of hypertension, cardiac arrhythmias, CVD, stroke, and heart failure. Therefore, one should have a low threshold to screen obese patients for obstructive sleep apnea via sleep study/polysomnography.

TABLE 1 Weight-Loss Treatment Guidelines from the National Heart, Lung, and Blood Institute*

	BMI				
Treatment	**25.0-26.9**	**27.0-29.9**	**30.0-34.9**	**35.0-39.9**	**>40.0**
Diet, physical activity, behavioral therapy, or all three	Yes	Yes	Yes	Yes	Yes
Pharmacotherapy†		In patients with obesity-related diseases	Yes	Yes	Yes
Surgery‡				In patients with obesity-related diseases	Yes

*Data are from www.nhlbi.nih.gov/science/obesity-nutrition-and-physical-activity. These guidelines are generally consistent with those from the American Heart Association, the American Medical Association, the American Diabetic Association, the Obesity Society (Practical Guide), the American Diabetes Association, the American Academy of Family Physicians, the American College of Sports Medicine, and the American Cancer Society. *BMI* denotes body mass index, calculated as the weight in kilograms divided by the square of the height in meters.

†Pharmacotherapy should be considered only in patients who are not able to achieve adequate weight loss with available conventional lifestyle modifications and who have no absolute contraindications for drug therapy.

‡Bariatric surgery should be considered only in patients who are unable to lose weight with available conventional therapy and who have no absolute contraindications for surgery.

Rx TREATMENT

The National Heart, Lung, and Blood Institute (NHLBI) developed guidelines for selecting treatment strategies for overweight and obese patients based on BMI and comorbidities. They recommend a combination of dietary management, physical activity management, and behavior therapy for anyone with a BMI ≥25 or with a high-risk waist circumference and two or more obesity-associated comorbidities. Pharmacotherapy should be considered for patients with a BMI ≥30 or ≥27 with comorbidities.

Bariatric surgery is indicated for patients with a BMI ≥35 with comorbidities and for any patient with a BMI ≥40 (Table 1).

NONPHARMACOLOGIC THERAPY

- The cornerstones for weight management and reduction are calorie restriction, exercise, and behavioral modification. Assessment of patient's willingness to make changes must be evaluated, as treatment is more likely to succeed in motivated patients.
- The NHLBI guidelines recommend an initial diet to produce a calorie deficit of 500 to 1000 kcal/day. This has been shown to reduce total body weight by an average of 8% over 3 to 12 mo.
- These guidelines recommend the use of a food diary to focus on dietary substitutes.
- Thirty min of moderate-intensity activity on 5 or more days of the wk results in health benefits for obese individuals. Moreover, several studies indicate that 60 to 80 min of moderate to vigorous physical activity may provide additional benefit.
- Increased physical activity without caloric restriction (minimal or no weight loss) can reduce abdominal (visceral) adipose tissue and improve insulin resistance.
- The key features of the standard behavioral modification program include goal setting, self-monitoring, stimulus control (modification of one's environment to enhance behaviors that will support weight management), cognitive restructuring (increased awareness of perceptions of oneself and one's weight), and prevention of relapse (weight regain).
- Mammalian sleep is closely integrated with the regulation of energy balance. Trials have shown that the amount of human sleep contributes to the maintenance of fat-free body mass at times of decreased energy intake. Lack of sufficient sleep may compromise the efficacy of typical dietary interventions for weight loss and related metabolic risk reduction.

ACUTE GENERAL Rx

- According to the NHLBI *Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* and the U.S. Food and Drug Administration (FDA), pharmacotherapy is indicated for:
  1. Obese patients with a BMI ≥30
  2. Overweight patients with a BMI of ≥27 and concomitant obesity-related risk factors or diseases, such as hypertension, diabetes, or dyslipidemia
- Pharmacologic treatment options include:
  1. Gastrointestinal lipase inhibitors: Orlistat is the only drug available for long-term treatment of obesity. It blocks the digestion and absorption of ingested dietary fat. It is a reversible inhibitor of pancreatic, gastric, and carboxyl ester lipases and phospholipase A2, which are required for the hydrolysis of dietary fat in the gastrointestinal tract. Side effects include flatulence, fecal incontinence, cramps, and oily spotting. There can also be impairment of absorption of fat-soluble vitamins (A, D, E, K) and beta-carotene.

Oxalate-associated acute kidney injury and rare severe liver injury have also been reported.

2. C serotonin agonists: Lorcaserin is a selective serotonin agonist that acts centrally to reduce appetite, aiding weight loss. Adverse effects include headache, upper respiratory infections, dizziness, and nausea. While there is little evidence of serotonin-associated cardiac valvular disease or pulmonary hypertension (as seen with nonselective serotonergic agonists fenfluramine and dexfenfluramine), long-term data is currently limited.
3. Sympathomimetic medications: Phentermine and diethylpropion are currently approved for short-term treatment of obesity. They reduce food intake by causing early satiety. Side effects include increased blood pressure and increased pulse. They are Schedule IV drugs with a potential for abuse. Other sympathomimetic drugs that have been removed from the market due to concerns about cardiovascular safety are sibutramine, phenylpropanolamine, and ephedrine.
4. Antidepressants: While not FDA-approved for treatment of obesity alone, bupropion and fluoxetine are antidepressants that have been associated with modest weight loss. The FDA has recently approved a fixed-dose combination of bupropion with the opioid receptor antagonist naltrexone. It is called Contrave and approved for use as an adjunct to diet and exercise in patients with BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 and one or more weight-related comorbidities (e.g., diabetes, hypertension, dyslipidemia).
5. Antiepileptic drugs: Zonisamide and topiramate (also used in migraine therapy) have been associated with weight loss in clinical trials but are not currently FDA-approved for treatment of obesity alone.
6. Diabetes drugs: While not FDA-approved for treatment of obesity alone, metformin, pramlintide (synthetic human amylin), and glucagon-like polypeptide-1 agonists (GLP-1) (exenatide) have been associated with weight loss in the treatment of individuals with diabetes. The GLP-1 receptor agonist liraglutide (Victoza) is now FDA approved at a higher dose as Saxenda for chronic weight management in adults with BMI ≥30 or a BMI ≥27 with a weight-related comorbidity such as hypertension, dyslipidemia, or diabetes.

CHRONIC Rx

- According to the NHLBI guidelines, surgical intervention is an option for selected patients with clinically severe obesity (a BMI ≥40 or a BMI ≥35 with comorbid conditions), when patients are at high risk for obesity-associated morbidity or death, and when less invasive methods of weight loss have failed. Box 1 summarizes patient requirements for bariatric surgery.

BOX 1 Patient Requirements for Bariatric Surgery

1. Patients with a BMI of 40 kg/m^2 or greater are potential candidates for bariatric surgery.
2. Patients with a BMI of 35 to 40 kg/m^2 with significant obesity-related comorbidity are also potential candidates for bariatric surgery.
3. Patients with a history of dieting.
4. Patients with no recent substance abuse.
5. Patients should be evaluated by a multidisciplinary team that includes a dietician and psychologic evaluation before surgery.

BMI, Body mass index.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

- Eligible patients should also be at an acceptable risk for surgery, well informed, and motivated.
- Restrictive surgeries limit the amount of food the stomach can hold and slow the rate of gastric emptying. These include vertical banded gastroplasty and laparoscopic adjustable silicone gastric banding (LAGB). Band slippage is the most common LAGB complication. Other potential complications include port or tubing malfunction, stomal obstruction, band erosion, pouch dilatation, and port infection. Gastric necrosis of the stomach wall is a rarer late complication that results from ischemia caused by a combination of gastric prolapse—the part of the stomach below the band herniates up through the device —and pressure from the band. Complications of bariatric surgery are summarized in Box 2.
- Gastric bypass has better outcomes than gastric band procedures for long-term weight loss, type 2 diabetes control and remission, hypertension, and hyperlipidemia. These procedures have benefits that include lower perioperative mortality rate, a quicker recovery period, and no malabsorption issues. However, they are not as effective as gastric bypass for weight reduction and comorbidity improvement.
  1. Malabsorptive surgeries reduce nutrient absorption by shortening the length of small intestine. These include jejunoileal bypass and the duodenal switch operation (DS).
  2. Restrictive malabsorptive bypass procedures combine the elements of gastric restriction and selective malabsorption. These include Roux-en-Y gastric bypass (considered the gold standard because of its high level of effectiveness and durability) and biliopancreatic diversion. These procedures have higher rates of comorbidity improvement than restrictive surgeries, but can be complicated by malabsorption and nutritional deficiencies.
- Compared with usual care, bariatric surgery is associated with reduced number of cardiovascular deaths and lower incidence of cardiovascular events in obese adults. A study on bariatric surgery patients demonstrated a significant reduction in long-term cardiovascular events. Ten-yr follow-up estimated relative risk reductions ranging from 18% to 79% according to the Framingham risk score, and 8% to 62% with the PROCAM risk score.
- A long-term observational study of obese patients with type 2 diabetes showed that bariatric surgery was associated with higher diabetes remission rates and fewer complications than usual care (Sjöström et al., 2014). Remission of type 2 DM occurs in 60% to 80% of patients 2 yr after surgery

BOX 2 Complications of Bariatric Surgery

Complications Common to All Bariatric Procedures
Early (Up to 30 Days After Surgery)
Venous thromboembolic disease
Bleeding
Anastomotic leaks
Wound infections
Persistent nausea/vomiting, dehydration
Regional abdominal organ trauma
Incisional and internal hernias
Bowel obstruction
Atelectasis
Pneumonia
Cardiac dysrhythmias
Urinary tract infection
Death

Late (Beyond 30 Days After Surgery)
Incisional and internal hernias
Bowel obstruction from adhesions
Nutritional deficiencies
Anastomotic strictures and marginal ulcers or erosions
Cholelithiasis
Anemia
Persistence or recurrence of obstructive sleep apnea
Need for body contouring
Regaining weight

Procedure-Unique Complications/ Adverse Effects
Roux-en-Y Gastric Bypass
Dumping syndrome

Laparoscopic Adjustable Gastric Banding
Band slippage or erosion
Port or device malfunction

Vertical Sleeve Gastrectomy
Refractory reflux

Biliopancreatic Diversion
Loose, foul-smelling stools
Protein-calorie malnutrition

From Kryger M et al: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier

and persists in about 30% of patients 15 yr after Roux-en-Y gastric bypass.
- Liposuction is removal of fat by aspiration after injection of physiologic saline. This technique reduces the subcutaneous fat but has failed to improve insulin sensitivity or risk factors for CHD.
- The Maestro Rechargeable System is a subcutaneously implanted device recently FDA approved for weight loss in adults with a BMI of 40 to 45 or with a BMI of ≥35 and at least one obesity-related comorbidity. It utilizes high-frequency electrical pulses to block vagus nerve signals between the brain and stomach. It is less effective than bariatric surgery for weight loss. The list price for the Maestro system exceeds $15,000.
- The AspireAssist device is FDA approved for weight loss in adults ≥22 yr old with a BMI of 35 to 55. It requires the insertion of a PEG tube endoscopically and pulled through a percutaneous incision. Thirty min after a meal, the patient attaches a connector to it and drains a portion of their stomach content into a toilet. The tube is then flushed with potable water. The connector stops working after 115 cycles (6 wk) and is replaced at a follow-up appointment. Estimated cost for procedure and follow-ups are $13,000 for the first yr.

DISPOSITION

- The incidence of venous thromboembolism in the upper tertile of BMI was 2.42 times that of the lowest BMI tertile. Obese patients have a higher incidence of postoperative thromboembolic events when undergoing noncardiac surgery.
- Obesity may be associated with higher rates of postoperative pulmonary complications and poor wound healing.
- Weight-stable obese subjects have an increased risk of arrhythmias and sudden death even in the absence of cardiac dysfunction.
- Obesity and the cardiac autonomic nervous system are intrinsically related. A 10% increase in body weight is associated with a decline in parasympathetic tone accompanied by a rise in mean heart rate. Conversely, a 10% weight loss in severely obese patients is associated with significant improvement in autonomic nervous system cardiac modulation, including decreased heart rate and increased heart rate variability.
- Postmortem Determinants of Atherosclerosis in Youth (PDAY) study data provided convincing evidence that obesity in adolescents and young adults accelerates the progression of atherosclerosis decades before the appearance of clinical manifestations.
- Obesity accelerates the progression of native coronary atherosclerosis and after coronary artery bypass grafting.
- In older adults, obesity is associated with protection against hip fracture, but this protective effect on bone status does not offset the extensive array of potential adverse effects on conditions common in the older population.

REFERRAL

Obesity is commonly seen in the primary care setting. If pharmacologic therapy is considered, consultation with physicians specializing in obesity and experienced with the use of the drug is recommended. In addition, consultation with nutritionists and behavioral therapists is helpful. A consultation with general surgery is indicated in patients being considered for surgical intervention.

PEARLS & CONSIDERATIONS

COMMENTS

- Enhanced weight-loss counseling helps about one third of obese patients achieve long-term, clinically meaningful weight loss. Adults can lose 1 to 2 lb (0.45 to 0.9 kg per wk) by consuming 500 to 1000 fewer calories per day.
- The NHLBI launched the Obesity Education Initiative in January 1991. The overall purpose of the initiative is to help reduce the prevalence of overweight along with the prevalence of physical inactivity to reduce the risk of CHD and overall morbidity and mortality rates from CHD.
- A recent study on BMI and all-cause mortality in a large prospective study suggests that optimal BMI range is between 20 and 24.9 (Patel AV, 2014).
- Recent research indicates that brown adipose tissue represents a natural target for the modulation of energy expenditure. The presence of brown adipose tissue in humans may be quantified with the use of ^{18}F-FDG PET-CT. The amount of brown adipose tissue is inversely correlated with BMI, suggesting a potential role of brown adipose tissue in adult human metabolism.
- Obesity, glucose intolerance, and hypertension in childhood are strongly associated with increased rates of premature death from endogenous causes in this population.
- Recent trials have shown that among persons living in a controlled setting, calories alone account for the increase in fat. Protein affected energy expenditure and storage of lean body mass, but not body fat storage.
- There have been no evidence-based studies supporting combination medical therapy for weight loss.
- Data are lacking for the role of pharmacotherapy and bariatric surgery in the elderly population.

PREVENTION

- Prevention of overweight and obesity involves both increasing physical activity and dietary modification to reduce caloric intake.
- There is compelling evidence that prevention of weight regain in formerly obese individuals requires 60 to 90 min of moderate-intensity activity or lesser amounts of vigorous intensity activity.
- Moderate-intensity activity of approximately 45 to 60 min per day, or 1.7 physical activity level (PAL), is required to prevent the transition to overweight or obesity. For children, even more activity time is recommended.
- Clinicians can help guide patients to develop personalized eating plans and help them recognize the contributions of fat, concentrated carbohydrates, and large portion sizes.
- Clinicians must work with patients to modify other risk factors such as tobacco use, high glycemic intake, and elevated blood pressure to prevent the long-term chronic disease sequelae of obesity. Generally lower carbohydrate, moderate fat intake, with stable protein and energy intake results in higher energy expenditure during weight-loss maintenance.[3]
- Regular screening of body weight and BMI measurements at routine office visits can help identify early weight gain.
- Among obese adolescents, the most rapid weight gain occurs between 2 and 6 yr of age. Most children who are obese at that age are obese in adolescence.[2]

PATIENT & FAMILY EDUCATION

Information can be obtained on the American Obesity Association website (www.obesity.org) and the American Medical Association website (www.ama-assn.org).

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Obesity, Female (Patient Information)
Obesity, Male (Patient Information)
Obesity, Child (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

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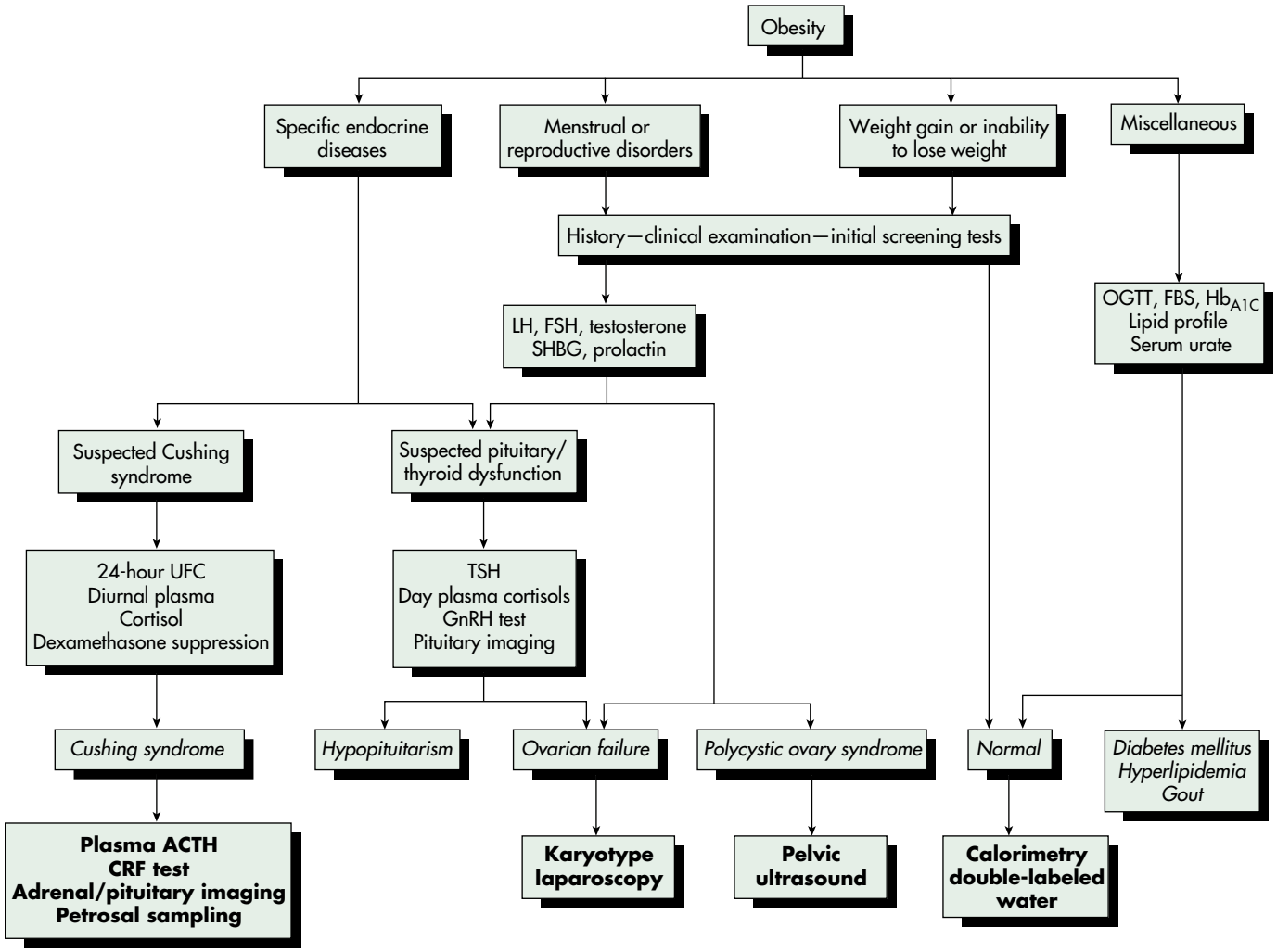

FIG. E1 Endocrine evaluation of obesity. *ACTH,* Adrenocorticotropic hormone; *CRF,* corticotropin-releasing factor; *FBS,* fasting blood sugar; *FSH,* follicle-stimulating hormone; *GnRH,* gonadotropin-releasing hormone; Hb_{A1C}, glycohemoglobin; *LH,* luteinizing hormone; *OGTT,* oral glucose tolerance test; *SHBG,* sex hormone-binding globulin; *TSH,* thyroid-stimulating hormone; *UFC,* urinary free cortisol. (Modified and updated from Besser CM, Thorner MO: *Comprehensive clinical endocrinology,* ed 3, St Louis, 2002, Mosby.)

Obesity-Hypoventilation Syndrome ALG

BASIC INFORMATION

DEFINITION

The obesity-hypoventilation syndrome (OHS), also known as Pickwickian syndrome, is conventionally defined as a combination of obesity (body mass index [BMI] ≥30 kg/m^2) and daytime hypercapnia ($PaCO_2$ ≥45 mm Hg in arterial blood gas analysis) in the absence of other causes for hypoventilation. This syndrome is often accompanied by obstructive sleep apnea (apnea-hypopnea index [AHI] ≥5 events/hour) or nonobstructive sleep hypoventilation (AHI <5, $PaCO_2$ >55 mm of Hg for more than 10 min or an increase in the $PaCO_2$ >10 mm of Hg compared with daytime $PaCO_2$, to a value >50 mm of Hg for >10 min during sleep). The hypercapnia stems from low tidal volumes and from inappropriate central respiratory response to hypoxemia and elevated PCO_2 levels.

SYNONYMS

Pickwickian syndrome
OHS
Extreme obesity with alveolar hypoventilation
Obesity alveolar hypoventilation syndrome

ICD-10CM CODE

E66.2	Obesity hypoventilation syndrome (OHS)

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: The worldwide prevalence of obesity more than doubled in the last 30 yr and has become a global epidemic. In 2014, the World Health Organization estimated that more than 600 million adults were obese. A Centers for Disease Control report in 2015 estimated the prevalence of obesity among U.S. adults during 2011 to 2014 at 36.5%. The obesity epidemic is likely to increase the prevalence of myriad complications such as OHS. The prevalence of OHS in the general population is estimated to be 0.6%, and 8% to 20% in patients evaluated for sleep breathing disorders at sleep clinic centers.
PREDOMINANT SEX & AGE: Male gender and 50 to 60 yr of age
RISK FACTORS:

- Male gender
- 50 to 60 yr of age
- Morbidly obese (BMI ≥40 kg/m^2)
- Severe OSA (≥30 obstructive respiratory events/hour of sleep)
- Increased waist-hip ratio
- Neck circumference >45 cm

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Most of the OHS symptoms are similar to OSA:

- Excessive daytime somnolence
- Fatigue
- Disorientation
- Loss of concentration
- Change in mood
- Amnesia
- Morning headache

Symptoms and signs most common in OHS compared with OSA:

- Injected sclera (probably related to high PCO2 leading to cerebral vasodilation)
- Anasarca, dyspnea on exertion, signs of circulatory congestion, and cor pulmonale on cardiac and hepatic exam

ETIOLOGY

- Etiology of hypoventilation in obese patients depends on many factors.
- Three hypotheses for chronic hypoventilation are widely accepted (Fig. E1): the increase in mechanical load on respiratory muscles from obesity; leptin resistance inhibiting central respiratory drive causing worsening hypoventilation; and decreased response to elevated PCO_2 levels in OSA.
- Often subclinical OHS becomes clinical with external triggers such as sedative medications, overdiuresis, and other systemic disease.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Anemia
- Heart failure with excessive diuresis
- Liver failure
- Stroke
- Central sleep apnea
- OSA
- Circadian rhythm disorder
- Drug or alcohol abuse
- Depression
- Hypothyroidism
- Sedative medication
- Metabolic abnormalities (e.g., hypo- or hypernatremia, hypercalcemia)
- Neuromuscular disease
- Pulmonary and lung disease
- Restless legs syndrome

WORKUP

- Detailed history and physical examination are helpful to identify patients who are at high risk for OHS. Fig. 2 illustrates a decision tree to screen for obesity-hypoventilation syndrome. Diagnostic features of obesity-hypoventilation syndrome are summarized in Box E1. Physiologic differences between eucapnic morbidly obese patients and those with obesity-hypoventilation syndrome are summarized in Box 2.
- Screen for OHS in men or women with BMI ≥30 or with sleep breathing disorder.
- The Epworth Sleepiness Scale (ESS) and the Stanford Sleepiness Scale (SSS) are the most commonly used scales for daytime sleepiness.
- If OSA is suspected, screen with STOP-BANG questionnaire (***s***noring, ***t***iredness, ***o***bserved apnea, blood ***p***ressure, ***B***MI, ***a***ge >50, ***n***eck circumference >16 inches, and ***g***ender).
- Overnight polysomnography to confirm whether AHI >5.
- Assess daytime oxygen saturation (SpO_2) levels to assess blood oxygenation level and serum bicarbonate level to assess carbon dioxide retention.
- If SpO_2 <90% on room air, serum bicarbonate >27 mEq/L, and BMI >30 with underlying sleep breathing disorder, consider obtaining an arterial blood gas to diagnose OHS.
- Consider forced vital capacity (FVC) and negative inspiratory force (NIF) if any suspicion of neuromuscular disease.
- ECG and echocardiogram are helpful to assess structural changes of the heart and pulmonary hypertension.

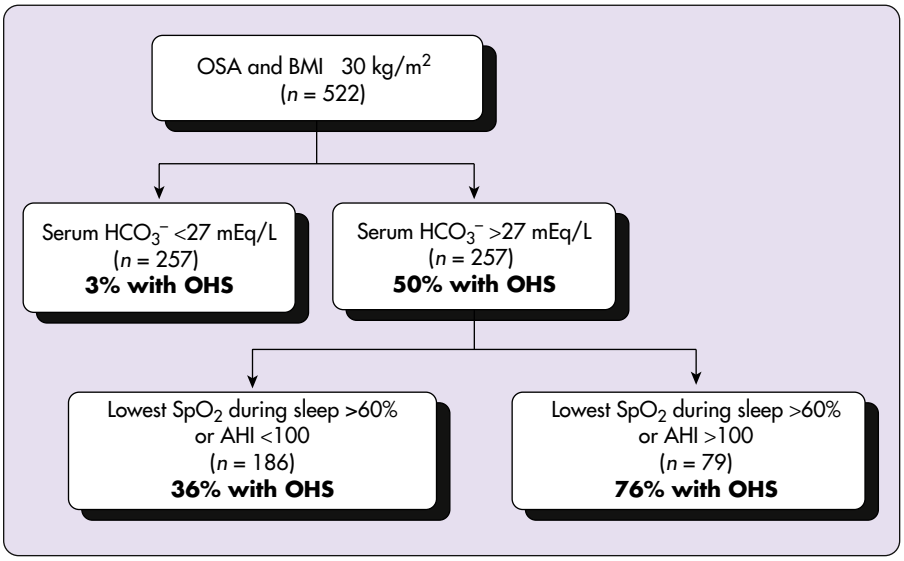

FIG. 2 Decision tree to screen for obesity-hypoventilation syndrome *(OHS)* based on observation in 522 obese patients with OSA (BMI ≥30 kg/m^2 and AHI ≥5). Among those with a venous serum bicarbonate level above 27 mEq/L, OHS was present in 50% of patients. Very severe OSA (AHI >100 events/hour or SpO_2 nadir during sleep <60%) increased the prevalence of OHS to 76%. *AHI,* Apnea-hypopnea index; *BMI,* body mass index; *OSA,* obstructive sleep apnea; *SpO_2,* the saturation of arterial blood with oxygen as measured by pulse oximetry. (From Kryger M et al: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.)

BOX 2 Physiologic Differences Between Eucapnic Morbidly Obese Patients and Those with Obesity-Hypoventilation Syndrome

	Eucapnic Morbid Obesity	Obesity-Hypoventilation Syndrome
Waist:hip ratio	↑	↑↑
FEV_1 /FVC	Normal	Normal/↓
Total lung capacity	Normal	Slight ↓
Functional residual capacity	↓	↓
Vital capacity	Normal or ↓	↓↓
Expiratory reserve volume	↓	↓↓
Work of breathing	↑	↑↑
Hypercapnic/hypoxic ventilatory drive	Normal	↓
Inspiratory muscle strength	Normal	↓

FEV1, Forced expiratory volume in first second; *FVC,* forced vital capacity.
From Kryger M et al: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.

- Polysomnography with continuous positive airway pressure (CPAP) titration can guide the physician to choose appropriate settings for positive airway pressure.
- Avoid medications that decrease respiratory drive and worsen ventilation.

LABORATORY TESTS

- Arterial blood gas (ABG) analysis on room air is the gold standard test to diagnose OHS in appropriate clinical setting.
- Venous blood gases (VBG), end-tidal carbon dioxide, arterialized capillary blood gases, and transcutaneous carbon dioxide monitoring can be used as alternatives to ABG to assess hypoventilation and carbon dioxide retention.
- Serum bicarbonate (>27 mEq/L) can be used as a great screening tool for OHS in an appropriate clinical setting. In a patient with normal kidney function, respiratory acidosis from OHS is usually compensated by retaining serum bicarbonate.
- Several studies showed serum bicarbonate level <27 mEq/L carries 97% negative predictive value for excluding a diagnosis of OHS in patients diagnosed as obese with OSA and normal renal function.
- Sleep hypoventilation can be measured by continuous end-tidal or transcutaneous carbon dioxide level measurement.

IMAGING STUDIES

- Echocardiogram will be helpful to assesses structural changes of the heart and pulmonary hypertension.
- Consider chest x-ray if any suspicion of pneumonia, COPD, or any lung disease.
- Consider CT chest or bronchoscopy if clinical condition warrants.

Rx TREATMENT

Four types of therapies available for both acute and chronic therapies for OHS: Positive airway (PAP) therapy, supplemental nasal oxygen, bariatric surgery, and oral respiratory stimulants.

NONPHARMACOLOGIC THERAPY

Positive airway therapy:

- Two types of PAP therapy available: CPAP and bilevel PAP (BiPAP). PAP therapy is considered first line for OHS.
- Short-term (≤3 weeks of PAP use) benefits of PAP: Improvement in $PaCO_2$ and PaO_2 levels and sleep breathing disorder.
- Long-term benefits of PAP (≥4 weeks of PAP use): Improvement in $PaCO_2$ and PaO_2 levels, lung volumes, central respiratory drive to carbon dioxide, and possible lowering of mortality.
- BiPAP recommend in patients who failed CPAP therapy (AHI ≥5 or a mean nocturnal oxygen saturation <90% on CPAP therapy) or who are intolerant to high PAP.

Oxygen therapy:

- Approximately 40% of patients with OHS on PAP therapy were at risk of hypoxemia during sleep. It can be controlled with supplemental oxygen as low as possible. However, inadvertent administration of excess oxygen might decrease minute ventilation significantly, which results in hypercapnia and respiratory acidosis.

Bariatric surgery:

- Bariatric surgery is indicated in all patients with a BMI ≥40 or with BMI ≥35 with obesity-related comorbid conditions. Recent studies showed significant improvement in PaO_2, $PaCO_2$, FEV_1, and FVC after bariatric surgery. After successful surgery, 14% of OHS patients may need PAP.

Tracheostomy:

- Reserved for patients who are not tolerant to PAP therapy

ACUTE GENERAL Rx

- Two respiratory stimulants currently available: Medroxyprogesterone acetate and acetazolamide.
- Medroxyprogesterone acetate stimulates respiratory center in hypothalamus. Clinical data showed neutral effect on $PaCO_2$ level.
- Acetazolamide increases bicarbonate excretion by the kidneys and causes metabolic acidosis, which increases respiratory drive. Acetazolamide has been shown to improve respiratory drive and decrease $PaCO_2$ level. However, clinical data are limited.

REFERRAL

Sleep specialist referral in case of diagnostic uncertainty and/or for patients not responding to positive airway therapy.

PEARLS & CONSIDERATIONS

- It is impossible to differentiate OHS from OSA based on clinical presentation alone.
- If SpO_2 <90% on room air, serum bicarbonate (>27 mEq/L), and BMI of >30 with underlying SBD, get an ABG to diagnose OHS.
- Positive airway therapy is a very effective treatment of choice for OHS.

PREVENTION

- Avoid sedative medications.
- Avoid overdiuresis in heart failure patients.
- Avoid alcohol intake.

PATIENT/FAMILY EDUCATION

- Weight loss
- Avoid sedative medication
- Avoid alcohol intake and recreational drug use
- Daily use of positive airway therapy for sleep

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Sleep Apnea (Related Key Topic)
Obesity (Related Key Topic)

AUTHOR: **Maheswara Satya Gangadhara Rao Golla, MD**

SUGGESTED READING

Chau EH et al: Obesity hypoventilation syndrome: a review of epidemiology, pathophysiology, and perioperative considerations, *Anesthesiology* 117(1):188-205, 2012.

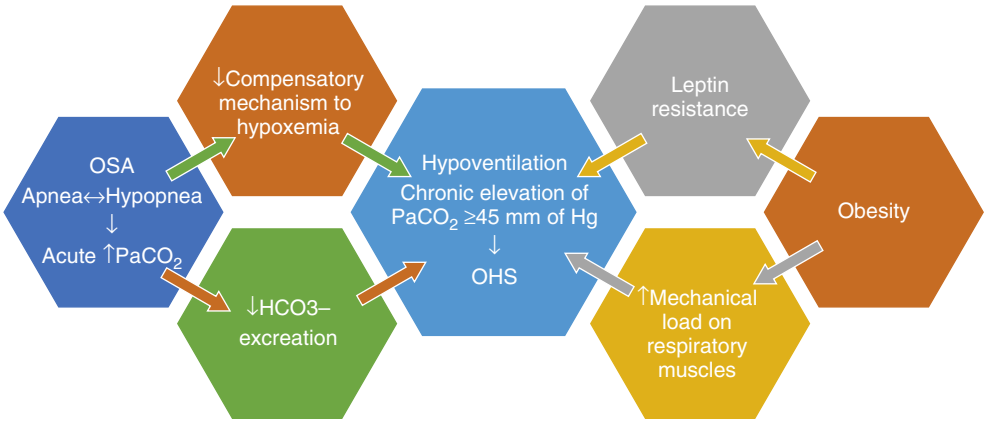

FIG. E1 Mechanism of obesity hypoventilation syndrome *(OHS).* *OSA,* Obstructive sleep apnea.

BOX E1 Diagnostic Features of Obesity-Hypoventilation Syndrome

Obesity
Body mass index ≥30 kg/m^2

Chronic Hypoventilation
Awake daytime hypercapnia (sea-level arterial PCO_2 ≥45 mm Hg)
Possible role of serum venous bicarbonate or calculated bicarbonate >27 mEq/L from capillary blood gas

Sleep Breathing Disorder
Obstructive sleep apnea (apnea-hypopnea index [AHI] ≥5 events/hour)
Nonobstructive sleep hypoventilation (AHI <5 events/hour, $PaCO_2$ above 55 mm Hg for more than 10 min, or an increase in the $PaCO_2$ [or surrogate] above 10 mm Hg [compared with awake supine $PaCO_2$] to a value >50 mm Hg for >10 min during sleep, or sustained hypoxemia with oxygen saturation ≤88% without obstructive respiratory events)

Exclusion of Other Causes of Hypoventilation
Severe obstructive airways disease (e.g., chronic obstructive pulmonary disease)
Severe interstitial lung disease
Severe chest wall disorders (e.g., kyphoscoliosis)
Severe hypothyroidism
Neuromuscular disease
Congenital hypoventilation syndromes

$PaCO_2$, Partial pressure of carbon dioxide in arterial blood; PCO_2, partial pressure of carbon dioxide.
From Kryger M et al: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.

Obsessive-Compulsive Disorder (OCD) PTG

BASIC INFORMATION

DEFINITION

Obsessive-compulsive disorder (OCD) is characterized by obsessions (recurrent and persistent thoughts, urges, or images experienced as intrusive and unwanted) and/or compulsions (repetitive behaviors or mental acts performed in response to obsessions, or according to rules that must be applied rigidly) that are time-consuming (e.g., >1 hr/day) or cause marked impairment or distress. The symptoms are usually, but not always, perceived as excessive and unreasonable.

SYNONYM

OCD

ICD-10CM CODES

F42 Obsessive-compulsive disorder
F60.5 Obsessive-compulsive personality disorder

DSM-5 CODES

300.3 Obsessive-compulsive disorder
301.4 Obsessive-compulsive personality disorder

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Mean age at onset is 19.5 yr.
12-MO PREVALENCE: 1.2% of adults in the U.S., international prevalence estimates are similar (1.1% to 1.8%).
PREDOMINANT SEX: Slightly more common among females than males in adulthood, although males are more commonly affected in childhood.
PREDOMINANT AGE:

- Modal age of onset for females is between 20 and 29 yr.
- Modal age of onset for males is between 6 and 15 yr.

DISEASE COURSE:

- Condition is chronic with waxing and waning pattern.
- Symptoms typically worsen with stress.
- 15% show progressive deterioration, whereas 5% show an episodic course with little impairment between episodes.

GENETICS:

- OCD is a multifactorial familial condition that involves both polygenic and environmental risk factors.
- Rate of concordance is higher in monozygotic (57%) compared with dizygotic (27%) twins.
- Rate of disorder is also much higher in first-degree relatives of individuals with OCD and Tourette disorder (8.2%) than in the general population (2%).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Persistent and recurrent intrusive and ego-dystonic obsessive ideas, thoughts, urges, or images that are perceived as alien and beyond one's control.
- Frequent experiencing of obsessions related to contamination (e.g., when using the telephone), excessive doubt (e.g., was the door locked?), organization (the need for a particular order), violent impulses (e.g., to yell obscenities in church), or intrusive sexual imagery.
- Compulsive behaviors (e.g., repeated hand washing, checking, rearranging) or mental rituals (e.g., counting, repeating phrases) meant to temporarily ameliorate anxiety caused by obsessions.
- Obsessions and compulsions are almost always accompanied by high anxiety and subjective distress. Both are usually, but not always, seen as excessive and unreasonable.

ETIOLOGY

- Strong evidence of cortico-striato-thalamo-cortical circuit dysfunction.
- OCD onset may be temporally associated with infectious illness of CNS (e.g., Von Economo encephalitis, Sydenham chorea).
- A condition called Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) usually involves children under age 12. It is diagnosed when OCD and/or tic disorders suddenly appear following a streptococcal infection (e.g., strep throat or scarlet fever) or symptoms of OCD or tic symptoms worsen after a strep infection.
- OCD may follow head trauma or other premorbid neurologic condition, including birth hypoxia and Tourette syndrome.
- Intrusive, obsessive thinking may be part of the picture in patients with complex partial seizures.
- Serotonergic, dopaminergic, and glutamatergic systems believed important in some ritualistic instinctual behaviors, with dysfunction of these pathways possibly giving rise to OCD.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Obsessive-compulsive personality disorder (OCPD) is a maladaptive personality style defined by excessive rigidity, need for order and control, preoccupation with details, and excessive perfectionism. Unlike OCD, OCPD is ego-syntonic.
- Other psychiatric disorders in which obsessive or intrusive thoughts occur (e.g., body dysmorphic disorder, eating disorders, hypochondriasis, phobias, posttraumatic stress disorder).
- Impulse control disorders (e.g., trichotillomania [hair-pulling disorder], excoriation [skin-picking] disorder, pathologic gambling disorder, compulsive shopping, kleptomania, paraphilias/sexual compulsions).
- Neurologic disorders with repetitive behaviors (e.g., Tourette syndrome, Sydenham chorea, torticollis, autism).
- Delusions or psychosis, which may be mistaken for obsessive thoughts; unlike OCD, these individuals do not believe their obsessions are unreal and may likely meet criteria for another psychotic spectrum disorder that fully accounts for the obsessions (e.g., schizophrenia).

WORKUP

- Careful history leading to diagnosis
- In adolescents and children: Psychological testing to reveal learning disabilities
- Screen for presence of past or current tic disorder, and ascertain degree of insight (good or fair, poor, absent/delusional) into OCD beliefs

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral therapy (CBT), comprising exposure/response prevention with or without cognitive reappraisal, is successful in up to 70% of patients. Best results are found for contamination obsessions and washing compulsions.
- Barriers to CBT include lack of availability/access, intense time requirements, and patient motivation to engage in treatment (e.g., anxiety resulting from exposure exercises).

ACUTE GENERAL Rx

- Antidepressants with serotonin reuptake blockade, including clomipramine, fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram, and escitalopram; optimal dosages are typically at the high end of the prescription range. Risk/benefit/alternatives discussion is crucial (e.g., dose-related risk of QT interval prolongation with serotonin reuptake inhibitors in general and clomipramine, citalopram, and escitalopram in particular).
- Benzodiazepines (e.g., clonazepam) have limited efficacy in OCD.
- Most experience some symptom relief with treatment, but even after adequate treatment trials, 40% to 60% of patients endorse significant residual symptoms.
- Likely indefinite treatment. Relapse is common if medications are discontinued.
- Recent studies suggest that combination CBT and pharmacotherapy yields superior outcomes. More severe symptoms warrant combination therapy.
- Patients who do not respond to first-line treatments and those with comorbid psychosis and/or tic disorders may benefit from augmentation with a first- or second-generation antipsychotic medication (e.g., haloperidol, olanzapine, risperidone).
- Neurosurgical intervention (e.g., cingulotomy, deep brain stimulation) is reserved for the most severely symptomatic and treatment-resistant cases.

DISPOSITION

- Most mild to moderate cases can be managed on a regular outpatient basis. Treatment should typically start with SSRI monotherapy with regular follow-up to assess treatment response and side-effect management. Dose should be increased to maximum tolerated.
- Patient and family education may help improve medical adherence and support.

PEARLS & CONSIDERATIONS

Patients with OCD typically have insight regarding the irrationality of their obsessions and compulsions but lack the ability to control them. This may cause intense shame and avoidance of medical care unless patient education and support are provided. Screen for OCD, especially among patients who present with "depression" or "anxiety."

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Obsessive-Compulsive Disorder (OCD) (Patient Information)

AUTHOR: **Agustin G. Yip, MD, PhD**

SUGGESTED READINGS

Gillan CM et al: A trans-diagnostic perspective on obsessive-compulsive disorder, *Psychol Med* 47:1528, 2017.

Hirschtritt ME et al: Obsessive-compulsive disorder: advances in diagnosis and treatment, *JAMA* 317:1538, 2017.

Skapinakis P et al: Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis, *Lancet Psychiatry* 3:730, 2016.

Ocular Foreign Body (PTG)

BASIC INFORMATION

DEFINITION

The term *ocular foreign body* refers to a foreign body on the surface of the corneal or conjunctival epithelium.

ICD-10CM CODES

T15	Foreign body on external eye
T15.0	Foreign body in cornea
T15.1	Foreign body in conjunctival sac
T15.8	Foreign body in other and multiple parts of external eye
T15.9	Foreign body on external eye, part unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Universal, with a predominance in active people. Common with industrial jobs and activities such as metal work, landscaping, and woodworking.

PREDOMINANT SEX: Perhaps slightly more common in men

PREDOMINANT AGE: Childhood through active adult yrs

PEAK INCIDENCE: Childhood through active adult yrs

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain with foreign body sensation is the most common symptom.
- Sudden onset: Patient may pinpoint the exact moment it occurred.
- Causes of most common foreign bodies:
  1. Grinding
  2. Drilling
  3. Auto repair
  4. Airborne particles, such as blown by fans
- Fig. E1 illustrates various ocular foreign bodies.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- History of corneal foreign body seen (small, white, superficial ring scars on cornea)
- Hemorrhage, loss of vision (with perforation of the globe)
- Distorted anterior chamber, soft eye
- Corneal abrasion
- Corneal ulceration (infection, bacterial or viral keratitis) or laceration
- Other keratitis
- Intraocular foreign body

WORKUP

- Fluorescein stain, slit-lamp examination if no foreign body is found
- Ultrasound examination
- Plain radiographs

LABORATORY TESTS

Intraocular pressure to make certain that eye has not been penetrated

IMAGING STUDIES

Occasionally, MRI of the orbits to identify foreign bodies not found by other means. Do not perform MRI if suspect metallic foreign body. Plain radiographs and ultrasound are sufficient.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Remove foreign body
- Treat infection
- Repair eye if ruptured
- Treat corneal abrasion or injury

ACUTE GENERAL Rx

- Saline irrigation
- Removal of foreign body with moist cotton-tipped applicator after instillation of topical anesthetic drops
- Use burr or more aggressive treatment if needed (often needed for deeper "rust ring" after metallic foreign body)
- Cycloplegics, antibiotics, and pressure dressing after removal of foreign body
- Repair corneal laceration or perforated eye (refer urgently to ophthalmologist)

DISPOSITION

If symptoms persist 24 hr after examination, refer to an ophthalmologist.

REFERRAL

To ophthalmology within 24 hr if patient not completely comfortable

PEARLS & CONSIDERATIONS

COMMENTS

- Make sure foreign body is not intraocular (inside eye).
- Alkaline or acidic chemical foreign bodies can be dangerous; pH test must be performed if either of these is suspected (for all chemical foreign bodies).

RELATED CONTENT

Corneal Foreign Body (Patient Information)

AUTHOR: **R. Scott Hoffman, MD**

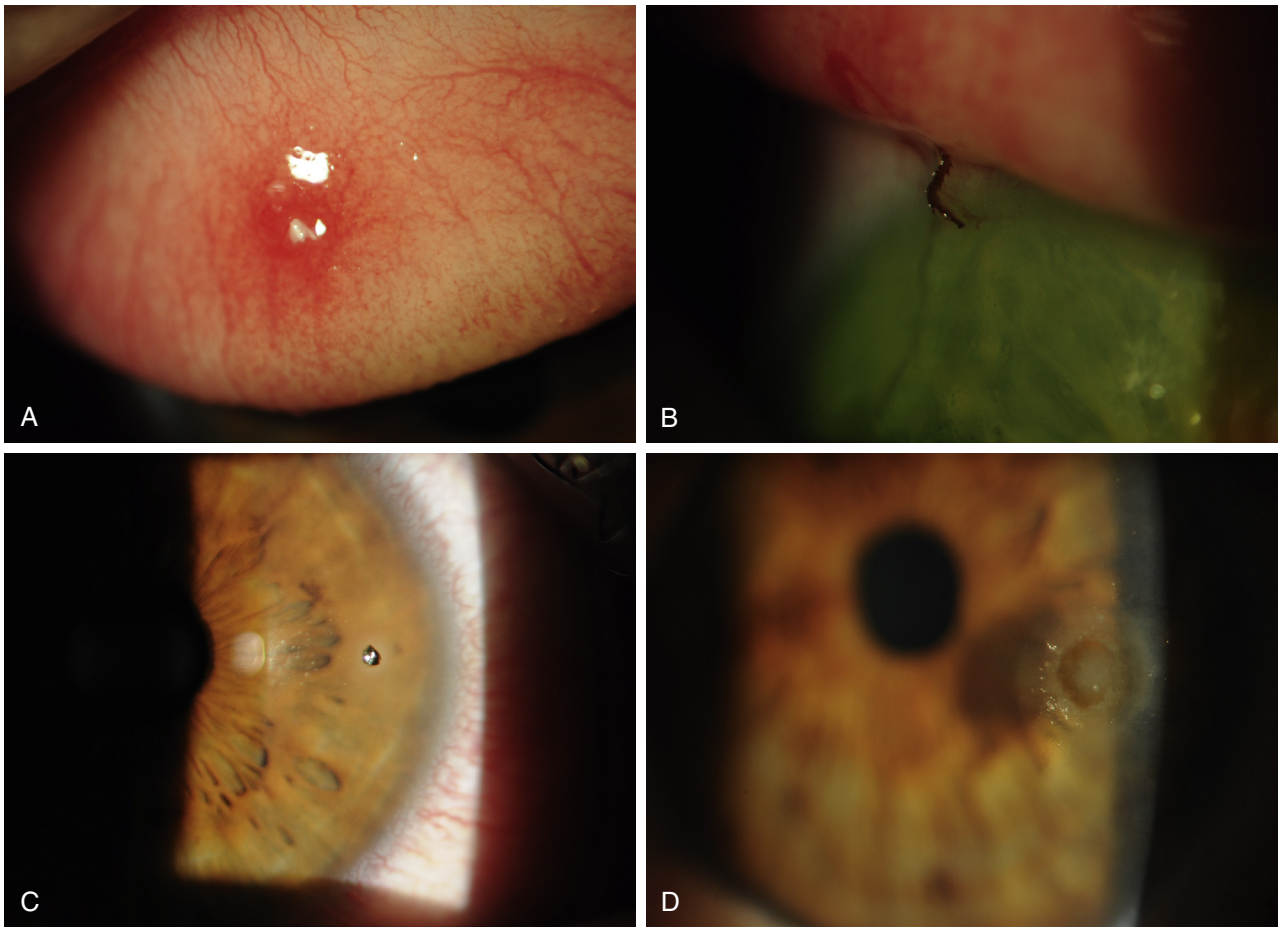

FIG. E1 Superficial foreign bodies. A, Retained subtarsal foreign body**. B,** Barbed insect leg embedded in the subtarsal conjunctiva. **C,** Recently embedded foreign body with mild surrounding cellular infiltration. **D,** Rust ring after removal of metallic foreign body. (From Bowling B: *Kanski's clinical ophthalmology, a systemic approach,* ed 8, Philadelphia, 2016, Elsevier.)

Opioid Overdose

BASIC INFORMATION

DEFINITION

Excessive use of an opioid, either derived from the opium poppy or semi- or fully synthetic, resulting in respiratory depression, central nervous system depression, and/or death

SYNONYMS

Opiate overdose
Heroin overdose
Narcotic overdose
Opioid poisoning

ICD-10CM CODES

T40.0X1	Poisoning by opium, accidental (unintentional)
T40.0X2	Poisoning by opium, intentional self-harm
T40.0X3	Poisoning by opium, assault
T40.0X4	Poisoning by opium, undetermined
T40.0X5	Adverse effect of opium
T40.1X	Poisoning by heroin
T40.4	Poisoning by other synthetic narcotics

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Drug overdose deaths and opioid-involved deaths continue to increase in the U.S. The majority of drug overdose deaths (more than six out of ten) involve an opioid. 91 Americans die every day from an opioid overdose.

PREVALENCE: From 1999 to 2017 more than 700,000 U.S. residents died from drug overdoses. From 2013 to 2017, the number of opioid-involved overdose deaths (opioid deaths) in the U.S. increased 90% from 25,052 to 47,600. This increase was primarily driven by substantial increases in deaths involving illicitly manufactured fentanyl (IMF) or fentanyl analogs mixed with heroin, sold as heroin, or pressed into counterfeit prescription pills.

PREDOMINANT SEX AND AGE: The "typical" heroin death involves experienced users in their 20s to 30s using coingestants, with a male predilection.

RISK FACTORS: The majority of drug-overdose deaths are unintentional or accidental (74%). The following increase risk for opioid overdose:

- Opioid dependence, in particular following reduced tolerance (following detoxification, release from incarceration, cessation of treatment)
- Injecting opioids
- Using prescription opioids, in particular taking higher doses
- Using opioids in combination with other sedating substances
- Using opioids and having comorbidities such as HIV, liver or lung disease, or suffering from depression
- Household members of people in possession of opioids (including prescription opioids)

The highest drug-induced mortality is associated with the following factors: 40 to 49 yr of age, male gender, non-Hispanic whites, and living in the South, all of which account for approximately 38.2% of drug-induced deaths in the U.S.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients with opioid overdose classically present with the triad of altered mental status, pinpoint pupils, and respiratory depression. Patients may be apneic or with low respiratory rate and tidal volumes. Respiratory depression becomes profound enough to cause anoxia, leading to death. Little to no response will be elicited from painful stimuli. Look for clinical clues, such as "track marks" or darkening along the length of veins from injection drug use that may suggest opioid overdose. The use of coingestants, which is exceedingly common in opioid overdose, can alter the classic exam findings one may expect. For example, use of sympathomimetics like cocaine can cause pupillary dilation. Respiratory rate <12 breaths/min is most sensitive for predicting response to naloxone. Once the patient is hemodynamically stable, examine for other sequelae of drug use, including pulmonary rales suggestive of aspiration pneumonia or murmurs and skin lesions associated with endocarditis in IV drug abusers.

ETIOLOGY

N/A

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hypoglycemia
- Alcohol or sedative overdose
- Postictal state
- Infectious or metabolic encephalopathy
- Clonidine overdose
- Phenothiazine overdose
- Organophosphate exposure

WORKUP

Opioid overdose requires little workup if the patient's altered mental status can be completely attributed to the overdose (i.e., by full recovery with naloxone). However, if the patient remains altered or with significant respiratory compromise after adequate treatment, continue appropriate workup. Obtain an ECG in the following scenarios: use of methadone, oxycodone, loperamide or a coingestant tricyclic antidepressant to screen for QTc prolongation; coingestion of a sympathomimetic to rule out arrhythmias.

LABORATORY TESTS

- Serum glucose should be quickly obtained as with any resuscitation.
- Urine drug screen is not routinely required unless the history or physical exam raises suspicion for coingestants that would alter management.
- Tylenol and aspirin levels in intentional overdoses or when used in a combination formulation with an opioid.

IMAGING STUDIES

Not required unless guided by your physical exam and/or response to therapy:

- Computed tomography of the head and cervical spine for suspected trauma
- Chest x-ray if signs of aspiration
- Echocardiogram if concerned for endocarditis

TREATMENT

The principal goals of treatment for opioid overdose are support of ventilation and reversal of the drug.

NONPHARMACOLOGIC THERAPY

Support the airway and breathing. For apneic or bradypneic patients, use bag-valve-mask ventilation.

ACUTE GENERAL Rx

Administer naloxone, a short-acting opioid antagonist, as soon as possible. Intravenous is the preferred route; however, in November 2015, Narcan Nasal Spray became the first FDA-approved non-injectable naloxone product for the treatment of opioid overdose. Higher concentration intranasal naloxone 2 mg/ml seems to have efficacy similar to IM naloxone for reversal of opioid overdose. Via the IV route, onset of action is within 1 to 2 min. Dosing is as follows:

- For most adult patients, 0.4 to 1.2 mg should yield recovery of consciousness.
- For patients in cardiac arrest, 2 mg is the starting dose.
- Younger than 5 yr or body weight 20 kg or less: 0.1 mg/kg administered by IV push, intraosseous (IO) push, or by endotracheal tube (ETT).
- 5 yr and older or body weight more than 20 kg: 2 mg administered by IV push, IO, or ETT.

Prepare for adverse effects of acute withdrawal, including agitation, nausea, vomiting, piloerection, diarrhea, lacrimation, yawning, and rhinorrhea after naloxone administration to chronic opioid users, especially with higher doses. Naloxone continues to block binding of additional opioids to the receptor for 20 to 90 min.

CHRONIC Rx

- Naloxone autoinjectors and nasal sprays are available in some states and intended for buddy administration. Patients can buy these formulations over-the-counter in some states, whereas others require a prescription. Check your state's legislature for continual updates on this matter.
- A 2016 nonrandomized study demonstrated that patients prescribed opioids plus naloxone had 47% fewer opioid-related emergency department visits within 6 mo than those not prescribed naloxone.

REFERRAL

Patients can be offered referral to drug rehabilitation services. Otherwise, follow up with the primary care physician is appropriate.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Drug Use Disorder (Related Key Topic)
Opioid Use Disorder (Related Key Topic)

AUTHORS: **Amanda Box, MD, MS,** and **Mark F. Brady, MD, MPH, MMSc**

SUGGESTED READINGS

Babu KM et al: Prevention of opioid overdose, *N Engl J Med* 380(23):2246-2255, 2019.

Centers for Disease Control and Prevention: Opioid overdose guidelines. www.cdc.gov/drugoverdose/prescribing/resources.html

Centers for Disease Control and Prevention: Understanding the epidemic. www.cdc.gov/drugoverdose/epidemic/index.html

Chou R: Management of suspected opioid overdose with naloxone in out-of-hospital settings, *Ann Int Med* 167:867-875, 2017.

Fink DS et al: Association between prescription drug monitoring programs and nonfatal and fatal drug overdoses, *Ann Int Med* 168:783-790, 2018.

O'Coffin P et al: Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain, *Ann Int Med* 165(4):245-252, 2016.

United States Food and Drug Administration: Insys Development Company, 2016. Naloxone for treatment of opioid overdose.

World Health Organization: Information sheet on opioid overdose. www.who.int/substance_abuse/information-sheet/en/.

BASIC INFORMATION

DEFINITION

- Opioid use disorder is defined as a cluster of cognitive, behavioral, and physiologic symptoms in which the individual continues use of opiates despite significant opiate-induced problems. Opiate use disorder is a chronic, relapsing disorder characterized by repeated self-administration that usually results in opiate tolerance, withdrawal, and compulsive drug use. Tolerance is the need to increase dose to achieve the same effect. Dependence may occur with or without the physiologic symptoms of tolerance and withdrawal.
- There are four stages of addiction:
  1. Stage I, acute drug effects: Rewarding effects of drug result from neurobiologic changes in response to the acute drug use. Duration varies from hours to days.
  2. Stage II, transformation to addiction: Associated with changes in neuronal function that accumulate with repeated administration and diminish over days or weeks after discontinuation of drug use.
  3. Stage III, relapse after extended periods of abstinence: Precipitated by an incubation of cue-induced craving (people, places, and things as triggers) and priming (relapse precipitated by drug exposure).
  4. Stage IV, end-stage addiction: Vulnerability to relapse endures for yr and results from prolonged changes at the cellular level.
- Pseudoaddiction: Undertreatment of pain resulting in "opiate-seeking" behaviors such as "doctor shopping" and multiple emergency department visits. These behaviors disappear with adequate treatment of pain.

SYNONYMS

Opioid dependence
OUD (opioid use disorder)
Opiate addiction
Opiate abuse
Narcotic addiction
Narcotic abuse
Substance use disorder

ICD-10CM CODES

F11.10	Opioid abuse, uncomplicated
F11.120	Opioid abuse with intoxication, uncomplicated
F11.121	Opioid abuse with intoxication delirium
F11.122	Opioid abuse with intoxication with perceptual disturbance
F11.129	Opioid abuse with intoxication, unspecified
F11.14	Opioid abuse with opioid-induced mood disorder
F11.150	Opioid abuse with opioid-induced psychotic disorder with delusions
F11.151	Opioid abuse with opioid-induced psychotic disorder with hallucinations
F11.159	Opioid abuse with opioid-induced psychotic disorder, unspecified
F11.181	Opioid abuse with opioid-induced sexual dysfunction
F11.182	Opioid abuse with opioid-induced sleep disorder
F11.188	Opioid abuse with other opioid-induced disorder
F11.19	Opioid abuse with unspecified opioid-induced disorder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: It is estimated that more than 2.5 million Americans have an opioid use disorder.

PREVALENCE:

- In 2014, U.S. retail pharmacies dispensed 245 million prescriptions for opioid pain relievers.
- In 2014, 10.3 million persons reported using prescription opioids nonmedically.
- In the U.S., 400,000 persons have used heroin in the past mo, and 4 million have reported nonmedical use of prescription pain relievers.
- Emergency department visits involving misuse or abuse of prescription opioids increased 153% between 2004 and 2011.
- Admissions to substance-abuse treatment programs linked to prescription opioids more than quadrupled between 2002 and 2012.
- The percentage of eighth-, tenth-, and twelfth-graders who have used heroin has more than doubled since the late 1990s. This increase has largely been attributed to decreased price and increased purity in the last decade.
- In 2015, 33,000 Americans died of opioid-related overdose—quadrupling the rates from 1999.
- In March and October 2015, the Drug Enforcement Administration and Centers for Disease Control and Prevention issued nationwide alerts identifying fentanyl, particularly illicitly manufactured fentanyl, as a threat to public health and safety. Illicitly manufactured fentanyl is pharmacologically similar to pharmaceutical fentanyl but is unlawfully produced in clandestine laboratories and obtained via illicit drug markets; it also includes fentanyl analogs. Fentanyl is a synthetic opioid 50 to 100 times more potent than morphine and approved for the management of surgical/postoperative pain, severe chronic pain, and breakthrough cancer pain.
- In the U.S., approximately 10 million adults are prescribed long-term opioid therapy (LTOT) for chronic pain despite inadequate evidence of long-term benefit and growing evidence of harm.

PREDOMINANT SEX: Males abuse opioids more commonly than females, with a male:female ratio of 3:1 for heroin and 1.5:1 for prescription opiates.

PEAK INCIDENCE: The majority of new abusers of opiates are <26 yr.

RISK FACTORS:

- Family history
- Prior history of addiction
- Psychiatric disorders

GENETICS:

- Genetic epidemiologic studies suggest a high degree of heritable vulnerability for opioid dependence.
- Gene polymorphism for dopamine receptor/transporters, opioid receptors, serotonin receptors/transporters, proenkephalin, and catechol-*O*-methyltransferase all appear to be associated with vulnerability to opioid dependence. Future interventions for opiate dependence may include medications identified through genetic research.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination is often noncontributory.
- Small-sized pupils may be the only observable sign of use because only mild tolerance develops for miosis.
- Scars or tracks from chronic IV use may be visible over the veins of the arms, hands, ankles, neck, and breasts.
- Inflamed nasal mucosa or respiratory wheezing may be apparent in patients who are snorting heroin or OxyContin.
- Patients in withdrawal may have more dramatic findings such as tachycardia, hypertension, fever, piloerection (goose flesh), mydriasis, lacrimation, central nervous system (CNS) arousal, irritability, and repeated yawning. In patients with sympathetic overactivity and panic attacks, use of CNS stimulants, such as amphetamines or cocaine, should also be ruled out.
- Although gastrointestinal symptoms of nausea, vomiting, and abdominal pain are common in opioid withdrawal, other causes such as gastroenteritis, pancreatitis, peptic ulcer disease, and intestinal obstruction need to be ruled out.
- The history may provide relevant information in making the diagnosis. Significant findings may include:
  1. A long history of opioid self-administration, typically by the IV or intranasal route but sometimes through smoking as well.
  2. Polysubstance use. Intoxication by drugs other than narcotics (e.g., benzodiazepines, barbiturates) should be ruled out in unconscious patients.
  3. A high incidence of nonopioid-related psychiatric disorders (>80%).
  4. History of problems at work, school, or relationships associated with drug use.
  5. History of legal problems associated with drug use, such as arrest for possession, robbery, or prostitution.
  6. History of interpersonal violence (as perpetrator or victim).
  7. History of physical problems such as skin infections, phlebitis, endocarditis, or liver diseases attributable to acetaminophen toxicity (Vicodin/Percocet) or viral hepatitis. Hepatitis C is the most prevalent bloodborne pathogen. It is present in approximately 90% of opiate-dependent people and is often spread by sharing IV drug paraphernalia or snorting devices. There is also a higher incidence of HIV infection.

ETIOLOGY

Opioid use disorder is a biopsychosocial disorder. Pharmacologic, social, genetic, and psychodynamic factors interact to influence abusive

TABLE 1 CAGE-AID

1. Have you ever tried to **C**ut down on your alcohol or drug use?
2. Do you get **A**nnoyed when people comment about your drinking or drug use?
3. Do you feel **G**uilty about things you have done while drinking or using drugs?
4. Do you need an **E**ye-opener to get started in the morning?

Two or more questions answered in the affirmative require further assessment.
AID, adapted to include drugs.
From Bowman S et al: Reducing the health consequences of opioid addiction in primary care, *Am J Med* 126, 565-571, 2013.

TABLE 2 Drug Abuse Screening Test (DAST-10)

1. Have you used drugs other than those required for medical reasons?
2. Do you abuse more than one drug at a time?
3. Are you unable to stop using drugs when you want to?
4. Have you ever had blackouts or flashbacks as a result of drug use?
5. Do you ever feel bad or guilty about your drug use?
6. Does your spouse (or parents) ever complain about your involvement with drugs?
7. Have you neglected your family because of your use of drugs?
8. Have you engaged in illegal activities in order to obtain drugs?
9. Have you ever experienced withdrawal symptoms (felt sick) when you stopped taking drugs?
10. Have you had medical problems as a result of your drug use (e.g., memory loss, hepatitis, convulsions, bleeding)?

Two or more questions answered in the affirmative require further assessment.
From Bowman S et al: Reducing the health consequences of opioid addiction in primary care, *Am J Med* 126, 565-571, 2013.

behaviors. Pharmacologic factors are especially prominent in opiate addiction because these drugs are strong reinforcing agents due to their euphoric effects and their ability to reduce anxiety and increase self-esteem and the patient's subjective feelings of improved ability to cope with daily challenges.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Psychiatric disorders (e.g., anxiety, depression, bipolar disorder).
- Acute medical illness (e.g., hypoglycemia, seizure disorder, sepsis, renal or hepatic insufficiency) may mimic opiate withdrawal symptoms.

WORKUP

The history is the most important part of the workup. Useful screening tools are the CAGE-AID (Table 1), the DAST-10 (Table 2), and the CRAFFT (Table 3). The CAGE-AID has a sensitivity of 70% and a specificity of 85% when two questions are answered in the affirmative. The DAST-10 can discriminate between current users versus former users. The CRAFFT is a useful screening tool for adolescents. A CRAFFT score of 2 or higher is optimal for identifying any problem (sensitivity 76%, specificity 94%), any disorder (sensitivity 80%, specificity 86%), and drug dependence (sensitivity 92%, specificity 80%).

TABLE 3 CRAFFT Screening Tool for Adolescents

1. Have you ever ridden in a **C**ar driven by someone (including yourself) who was high or had been using alcohol or drugs?
2. Do you ever use alcohol or drugs to **R**elax, feel better about yourself, or fit in?
3. Do you ever use alcohol or drugs while you are by yourself **A**lone?
4. Do you ever **F**orget things you did while using alcohol or drugs?
5. Do your **F**amily or Friends ever tell you that you should cut down on your drinking or drug use?
6. Have you ever gotten into **T**rouble while you were using alcohol or drugs?

Two or more questions answered in the affirmative require further assessment.
From Bowman S et al: Reducing the health consequences of opioid addiction in primary care, *Am J Med* 126, 565-571, 2013.

- Observation of opioid withdrawal is indicative of opioid addiction.
- Observation of purposeful behaviors such as complaints and manipulations directed at getting more drugs and anxiety during withdrawal is suggestive of opioid addiction.
- Screen blood and urine for opioid metabolites.
- Screen for communicable diseases: HIV, hepatitis B and hepatitis C, tuberculosis.
- Screen for endocarditis in patients with newly diagnosed murmurs.

LABORATORY TESTS

- Urine and serum toxicology screen
- Complete blood count
- Chemistries (alanine aminotransferase, aspartate aminotransferase, serum creatinine): Elevated liver function test (LFT) results may be from viral hepatitis or acetaminophen toxicity
- Hepatitis screen: If hepatitis C antibody positive, follow up with hepatitis C polymerase chain reaction (viral load) even in patients with normal LFTs
- HIV
- PPD

IMAGING STUDIES

Generally not helpful in routine diagnosis and treatment. Consider echocardiography in patients with heart murmurs and liver sonography or CT scan in patients with elevated LFTs or who are positive for hepatitis C or B (increased risk of hepatocellular carcinoma).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Brief counseling interventions during a visit with their primary care physician or OB/GYN have proved efficacious in motivating patients for treatment.
- Therapeutic communities (residential).
- 12-step or other self-help groups (e.g., Alcoholics Anonymous, Narcotics Anonymous).
- Relapse prevention (counseling).
- Opioid prevention education (Table 4).

TABLE 4 Basic Components of Opioid Overdose Prevention Education Curriculum

1. Know the signs of an opioid overdose (e.g., unresponsive, limp, slow, shallow breathing, pale or clammy, finger nails or lips turning blue, gurgling).
2. Call 911.
3. Administer rescue breathing.
4. Administer naloxone if no response and Emergency Medical Services have not yet arrived
5. Stay with the person until help arrives.

From Bowman S et al: Reducing the health consequences of opioid addiction in primary care, *Am J Med* 126, 565-571, 2013.

ACUTE GENERAL Rx

- Medical withdrawal (not overdosed). Opioid withdrawal alone is not recommended for treatment of opioid use disorder in most patients because of increased risk of overdose death and infectious disease (e.g., HIV through IV drug use) following detoxification.
- Short- (30 days) or long-term (30 to 180 days) protocols.
- Buprenorphine (opioid partial agonist) or methadone (opioid agonist) is initiated in tapering doses.
- Clonidine 0.1 mg bid to tid can be used to minimize autonomic symptoms (sweating) and craving.
- Nonsteroidal antiinflammatory drugs for body and muscle aches.
- The anticholinergic dicyclomine can be used to minimize gastrointestinal hyperactivity.
- Nonbenzodiazepine hypnotics, low-dose atypical antipsychotics (e.g., quetiapine), or low-dose tricyclic antidepressants are effective for promoting adequate sleep.
- Psychosocial supports tailored to patient needs should be offered as an adjunct to medical treatment.

CHRONIC Rx

Opioid antagonist treatment:

- Buprenorphine/naloxone is the preferred first-line treatment. Methadone is an alternative in certain populations.
- Naltrexone: Does not stabilize neuronal circuitry like partial or full opioid agonists and generally results in poor outcomes, much like Antabuse for alcohol.
- Opioid partial agonist therapy: Buprenorphine (Suboxone, Bunavail).
- Opioid agonist therapy: Methadone.

NOTE: Buprenorphine and methadone are both metabolized by the cytochrome P450 3a4 and 2d6 I isoenzyme pathways. Prescribers should be aware of multiple possible drug interactions.

Methadone and buprenorphine produce similar improvements during opioid withdrawal, although buprenorphine is associated with less sedation and respiratory depression. To avoid precipitating more intense withdrawal, buprenorphine should be initiated 12 to 18 hours after the last administration of opioids in patients who misuse shorter-acting opioids (48 hours in patients who are receiving long-acting drugs such as methadone), with initial doses of 4 to 8 mg.[1]

PATIENT SELECTION FOR BUPRENORPHINE OR METHADONE

- Appropriate patients for buprenorphine office-based treatment:
  1. Patients interested (highly motivated) in treatment
  2. Have no major contraindications (see following)
  3. Can be expected to be reasonably compliant with treatment
  4. Understand the benefits and risks of buprenorphine treatment
  5. Willing to follow safety precautions
- Less likely to be appropriate for office-based treatment:
  1. Have comorbid dependence on benzodiazepines or other CNS depressants (including ethylene alcohol)
  2. Have significant untreated psychiatric comorbidities
  3. Have active or chronic suicidal or homicidal ideation or attempts
  4. Have multiple previous treatments with frequent relapses
  5. Have poor response to previous treatment with buprenorphine
  6. Have significant medical complications (e.g., hepatic insufficiency, bacterial endocarditis, active tuberculosis)
- Methadone maintenance: Narcotic treatment program (clinic setting) indications:
  1. Evidence of opiate addiction >1 yr
  2. Two failed previous treatment attempts
  3. Patients not appropriate for office-based treatment
  4. Eligible without active "use" if prior methadone maintenance patient within previous 2 mo
  5. Pregnancy

DISPOSITION

- Opioid addiction is a chronic, relapsing disease
- High rate of relapse after "detox."
- Relapse potential after medically supervised withdrawal from methadone:
  1. 90% after 1 yr stable in treatment
  2. 80% after 3 yr stable in treatment
  3. 70% after 5 yr stable in treatment
- Postmarketing surveillance indicates that the diversion and abuse of prescription opioid medications increased between 2002 and 2010 and plateaued or decreased between 2011 and 2013. These findings suggest that the U.S. may be making some progress in controlling the abuse of opioid analgesics[2]

[1]Schuckit MA: Treatment of opioid-use disorders, *N Engl J Med* 375:357-368, 2016.

TABLE 5 Organizations Providing Referral Information for Patients

Organization	Resources/Website
Substance Abuse and Mental Health Services Administration (SAMHSA)	Opioid treatment program directory: dpt2.samhsa.gov/treatment/
Physicians who provide buprenorphine	Buprenorphine physician and treatment program locator: https://www.samhsa.gov/medication-assisted-treatment/treatment/buprenorphine
Pain Action	Chronic pain management materials for patients: www.painaction.com/
Substance abuse treatment facilities	Substance Abuse treatment facility locator: http://dasis3.samhsa.gov/
Harm Reduction Coalition	Local risk reduction resources and programs, overdose prevention education, and naloxone prescribing information: www.harmreduction.org/
Narcotics Anonymous (NA)	General information and meeting information for NA, a 12-step program modeled after Alcoholics Anonymous: www.na.org

From Bowman S et al: Reducing the health consequences of opioid addiction in primary care, *Am J Med* 126, 565-571, 2013.

REFERRAL

Refer to addiction medicine specialist or narcotic treatment program when the neurobiologic disease of opioid addiction is identified.

PEARLS & CONSIDERATIONS

COMMENTS

- Methadone maintenance is the gold standard for the pregnant opioid-addicted patient regardless of the duration of the addiction or prior treatment attempts. Detoxification is contraindicated during pregnancy.
- Breastfeeding is encouraged in mothers on methadone maintenance. The American Academy of Pediatrics statement regarding "Transfer of Drugs and Other Chemicals into Human Milk" has placed methadone into the "usually compatible with breastfeeding" group based on the assumption that maternal urine is monitored to detect use of illicit drugs. The U.S. Department of Health and Human Services also recommends that mothers on methadone be encouraged to breastfeed.
- When a physician identifies a patient as a "drug seeker," it is imperative that the physician avoid abruptly stopping the opioid prescription because this will often result in the patient's buying the drugs illegally. These patients should be counseled and referred for treatment.
- Patients on methadone or buprenorphine who have pain resulting from an acute injury will need pain medication in addition to their daily dose of methadone or buprenorphine. They will require higher than usual doses of pain medications because of opioid receptor blockade attributable to their methadone or buprenorphine use.
- Opioid-dependent patients have a lower pain threshold resulting from hyperalgesia caused by the long-term use of opioids.

[2]Dart RC et al: Trends in opioid analgesic abuse and mortality in the United States, *N Engl J Med* 372:241-248, 2015.

PREVENTION

Education is the hallmark of prevention:

- School drug prevention education programs.
- Educate children about their family medical history, including diseases of addiction.
- Address childhood psychiatric disorders to prevent self-medicating.

Opioid overdose:

- Naloxone (Narcan) is a competitive mu-opioid receptor antagonist in the brain and is effective for opioid overdose. It is available for IM/IV and intranasal administration. It begins to reverse respiratory depression, sedation, and hypotension 2 to 5 min after IM administration and 1 to 2 min after IV administration.

PATIENT & FAMILY EDUCATION

- Stigma of addictions and treatment often interferes with good treatment.
- Family needs to be educated so they can support the patient's efforts.
- Encourage family meeting with addiction specialist, counselor.
- Recommend support groups for family members. Table 5 identifies organizations providing referral information for patients. Recommendations for integrating risk reduction strategies for addressing opioid misuse in the primary care setting are summarized in Table E6.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Drug Use Disorder (Patient Information)
Opioid Overdose (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Babu KM et al: Prevention of opioid overdose, *N Engl J Med* 380(23):2246-2255, 2019.

Ballantyne JC et al: Opioid dependence vs addiction: a distinction without a difference? *Arch Intern Med* 172:1342-1343, 2012.

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Compton WM: Relationship between nonmedical prescription-opioid use and heroin use, *N Engl J Med* 374:154-163, 2016.

Dunlap B, Cifu AS: Clinical management of opioid use disorder, *JAMA* 316(3):338-339, 2016.

Frank JW et al: Patient outcomes in dose reduction or discontinuation of long-term opioid therapy, *Ann Intern Med* 167:181-191, 2017.

Gladden RM: Fentanyl law enforcement submissions and increases in synthetic opioid-involved overdose deaths—27 states, 2013-2014, *MMWR Morb Mortal Wkly Rep* 65:837-843, 2016.

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Krupitsky E: Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicenter randomized trial, *Lancet* 377:1506-1513, 2011.

Larochelle MR: Medications for opioid use disorder after nonfatal opioid overdose and association with mortality, *Ann Int Med* 169:137-145, 2018.

Martin SA: The next stage of buprenorphine care for opioid use disorder, *Ann Intern Med* 169:628–635, 2018.

Murphy SM: Cost-effectiveness of buprenorphine-naloxone versus extended-release naltrexone to prevent opioid relapse, *Ann Int Med* 170:90-98, 2019.

Pace CA: Samet JH: In the clinic: substance use disorders, *Ann Intern Med* 164(7):ITC49-ITC64, 2016.

Shapiro B: A primary care approach to substance misuse, *Am Fam Physician* 88(2):113-121, 2013.

Volkow ND: Neurobiologic advances from the brain disease model of addiction, *N Engl J Med* 374:363-371, 2016.

Volkow ND, McLellan AT: Opioid abuse in chronic pain misconceptions and mitigation strategies, *N Engl J Med* 374:1253-1263, 2016.

Von Korff M, et al: Long-term opioid therapy reconsidered, *Ann Intern Med* 155:325-328, 2011.

TABLE E6 Recommendations for Integrating Risk Reduction Strategies for Addressing Opioid Misuse in the Primary Care Setting

Risk Reduction Tools	Type of Client	Delivery Recommendations
Brief substance abuse screening	All clients, particularly those individuals prescribed opioid medications or with a history of substance abuse problems	Administer CAGE-AID* or similar screening tool as part of routine treatment.
Motivational interviewing	Clients who have identified opioid use or abuse	Standard procedure may be delivered by primary care provider or other clinic staff.
Comprehensive tools for safer injections, including safer injection education	Clients who have reported or are suspected of injection drug use; tools should be available to all patients, not just those identified as drug users.	Resources including educational materials, syringes, alcohol wipes, etc. distributed and discussed by the primary care provider or other clinic staff.
Naloxone prescription and distribution	Targeting individuals using illicit or prescribed opioids, including individuals prescribed opioids	Discussion, prescription of naloxone by the primary care provider; additional education may be delivered by other clinic staff.
Buprenorphine prescription	Targeting individuals using illicit or prescribed opioids, seeking medication assisted treatment	Discussion and prescription by the primary care provider

*For a full definition of CAGE-AID, see Table 1.

From Bowman S et al: Reducing the health consequences of opioid addiction in primary care, *Am J Med* 126, 565-571, 2013.

Oppositional Defiant Disorder (ODD) PTG

BASIC INFORMATION

DEFINITION

Oppositional defiant disorder (ODD) is an ongoing pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness, that is not developmentally appropriate, lasts more than 6 mo, and leads to impairment in social, academic, or occupational functioning for a child or adolescent.

SYNONYM

ODD

ICD-10CM CODE
F91.3 Oppositional defiant disorder
DSM-5 CODE
313.81 Oppositional defiant disorder

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Usually diagnosed in school-aged children (roughly ages 6-12)
PREVALENCE: Ranges from 1% to 16% based on source (community prevalence)
PREDOMINANT SEX AND AGE:
- Males more than females
- Highest diagnosis in prepubertal children
- Usually present by age 8

GENETICS: Some evidence for genetic factors, but studies are not usually specific to ODD (e.g., studies also include conduct disorder or more generally refer to aggressive or delinquent behaviors) and include potential confounding factors (e.g., difficult to distinguish between genetic and environmental contribution)
RISK FACTORS:
- Male gender, low socioeconomic status
- The following risk factors have been identified more generally for development of disruptive behavior disorders or aggression:
  1. Family history (especially parental) of aggressive or criminal behaviors
  2. Parental substance abuse (e.g., fetal alcohol syndrome)
  3. Prenatal or early childhood exposure to toxins (e.g., lead)
  4. Perinatal complications
  5. Head injuries
  6. Cognitive impairment
  7. Learning disabilities
  8. History of abuse or witnessed domestic violence
  9. Overall family instability

PHYSICAL FINDINGS & CLINICAL PRESENTATION

DSM-5 criteria are met when there is a pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness for at least 6 mo, and four or more symptoms from any category are present
- Angry/irritable mood:
  1. Often loses temper
  2. Is touchy or easily annoyed
  3. Is often angry and resentful
- Argumentative/defiant behavior:
  1. Often argues with adults
  2. Often actively defies or refuses to comply with requests from authority figures or with rules
  3. Often deliberately annoys others
  4. Often blames others for his or her mistakes/misbehavior
- Vindictiveness:
  1. Has been spiteful/vindictive at least twice within the past 6 mo

Symptoms are associated with distress in the individual or others, or they negatively impact social, educational, occupational, or other important areas of functioning. Symptoms may not occur only during the course of a psychotic, mood, or substance use disorder. Also, criterion must not be met for disruptive mood dysregulation disorder and, if 18 yr or older, for antisocial personality disorder. Symptoms are classified in terms of severity based on whether they are confined to only one setting, e.g., at home or at school (mild), to at least two settings (moderate), and three or more settings (severe). Finally, the DSM-5 specifies that symptoms may not occur only in the context of a sibling relationship.

ETIOLOGY

Multiple hypothetical models have been developed for disruptive behavior disorders and antisocial behaviors in general, including a few focused specifically on ODD that address the complex interaction between various predisposing and protective factors. These models identify some biologic factors (including genetic, structural, toxin exposure, etc.), some child functional factors (including cognitive, social, and neuropsychological deficits), and broad psychosocial factors that focus on parenting styles (including history of physical abuse), peer involvement, and other environmental factors.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Child abuse or neglect
- Learning disorder or other deficits in executive functioning
- Intellectual disability (intellectual developmental disorder)
- Communication disorders (including language disorder, speech sound disorder, childhood-onset fluency disorder, and social communication disorder)
- Attention deficit hyperactivity disorder
- Intermittent explosive disorder
- Conduct disorder
- Antisocial personality disorder
- Mood disorder (bipolar disorder or depression)
- Psychotic disorders
- Substance use disorders
- Parent-child relational problem

WORKUP

Diagnosis is made based on history, including individual and family interviews as well as collateral data from additional sources (parents, teachers, other medical providers, therapist, etc).

LABORATORY TESTS

None indicated

IMAGING STUDIES

None indicated

TREATMENT

Initial treatment of ODD should include psychosocial interventions aimed at changing the maladaptive patterns of interaction between the child or adolescent and his or her family and environment.

If the interventions listed here are not effective, or if serious concerns exist regarding safety or impairment in functioning, pharmacologic interventions targeting specific symptoms (such as aggression) or comorbid disorders (such as ADHD, anxiety disorders, or mood disorders) may help.

There are currently no medications approved by the FDA for the treatment of ODD.

NONPHARMACOLOGIC THERAPY

- Parent management training
- Cognitive problem-solving skills training
- Social skills training
- Individual psychotherapy
- Family psychotherapy

ACUTE GENERAL Rx

- Medication may be considered as an adjunct to behavioral treatment or in cases where comorbidity is a factor. There is some evidence for symptom improvement with trials of stimulants, mood stabilizers, or atypical antipsychotics, but medication should never be used alone or as first-line treatment for ODD.
- Higher levels of care such as a hospital or acute residential setting may be required for stabilization if acute safety concerns develop in the context of ODD, such as severe aggression.

COMPLEMENTARY & ALTERNATIVE MEDICINE

No evidence-based treatments are available.

DISPOSITION

- Most patients with ODD can be managed in an outpatient setting with either standard or intensive, home-based support; treatment should always be provided in the least restrictive setting possible.
- Hospitalization is sometimes necessary for crisis management only; consideration of different levels of care, including day treatment, therapeutic school settings, or residential facilities, may be appropriate for more severe cases or in situations where the family is not willing or able to participate adequately in the outpatient regimen.

REFERRAL

Consider referral to a mental health provider specializing in the treatment of children, adolescents, and families (including potentially a

child and adolescent psychiatrist) if the patient and family are not responding to basic parenting interventions or are demonstrating significant safety concerns or other evidence of impairment in functioning at home, in school, or in the community.

PEARLS & CONSIDERATIONS

COMMENTS

- Involvement of the family and school is crucial in the management of patients with this disorder.
- Polypharmacy (the prescribing of multiple medications simultaneously) to target the more complicated symptoms of this disorder should be implemented with great caution and only after discrete trials of therapeutic interventions and single medication agents have failed.
- Standardized assessment tools used to identify ADHD, disruptive behavior disorders, and general child and adolescent psychopathology may be helpful in confirming the diagnosis of ODD and/or monitoring progress throughout treatment.
- ODD symptoms are independently associated with increased externalizing symptoms, internalizing symptoms, delinquent behaviors, and social and academic functioning.
- One-time, intensive interventions are not considered effective treatment options (including boot camps, shock incarceration) and may carry additional risks.
- When ODD coexists with attention deficit hyperactivity disorder, stimulant therapy can reduce the symptoms of both disorders.

PREVENTION

Most effective prevention strategies include both individualized treatment and universal interventions that incorporate a parent-directed component as one of the primary elements. They also may incorporate social-cognitive skills training, academic skills training, proactive classroom management and teacher training, and group therapy. These may take place in schools, clinics, and other community-based settings in addition to targeted clinical work.

PATIENT & FAMILY EDUCATION

ODD: A Guide for Families by the American Academy of Child and Adolescent Psychiatry (www.aacap.org/AACAP/Families_and_Youth/Resource_Centers/Oppositional_Defiant_Disorder_Resource_Center/home.aspx)

American Academy of Pediatrics: HealthyChildren.org (www.healthychildren.org/English/health-issues/conditions/emotional-problems/Pages/Disruptive-Behavior-Disorders.aspx)

RELATED CONTENT

Attention Deficit Hyperactivity Disorder (Related Key Topic)

Conduct Disorder (Related Key Topic)

AUTHORS: **Hassan M. Minhas, MD,** and **Elizabeth A. Lowenhaupt, MD**

SUGGESTED READINGS

Carliner H et al: Trauma exposure and externalizing disorders in adolescents: results from the National Comorbidity Survey Adolescent Supplement, *J Am Acad Child Adolesc Psychiatry* 56(9):755-764, 2017.

Noordermeer SD et al: A systematic review and meta-analysis of neuroimaging in oppositional defiant disorder (ODD) and conduct disorder (CD) taking attention-deficit hyperactivity disorder (ADHD) into account, *Neuropsychol Rev* 26:44, 2016.

Ghosh A et al: Oppositional defiant disorder: current insight, *Psychol Res Behav Manag* 10:353-367, 2017.

Leadbeater BJ et al: The longitudinal effects of oppositional defiant disorder symptoms on academic and occupational functioning in the transition to young adulthood, *J Abnorm Child Psychol* 45(4):749-763, 2017.

Optic Atrophy

BASIC INFORMATION

DEFINITION

- *Optic atrophy* refers to the degeneration of axons of the optic nerve.
- It is a sign indicative of optic nerve insult rather than a distinct disease entity.

SYNONYM

Unilateral/bilateral optic atrophy

ICD-10CM CODE
H47.2 Optic atrophy

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: Depends on etiology
PREDOMINANT AGE: Variable
PEAK INCIDENCE: Varies depending on cause

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Optic atrophy is identified weeks to months after an initial insult such as optic neuritis, trauma, or ischemia. Frequently, it is noted by the physician during a routine eye exam.
- Asymmetry of disc color is often first subtle finding.
- Temporal part of optic disc is pale initially; later, the entire disc becomes pale/white.
- Optic disc pallor (Fig. E1) occurs 4 to 6 wk after optic nerve insult.
- Unilateral lesion produces a relative afferent pupillary defect (RAPD): Swing flashlight eye to eye; abnormal pupil dilates to direct light.
- Decreased visual acuity, blurred vision, visual field deficits (e.g., central scotoma), abnormal color vision (e.g., red desaturation).

ETIOLOGY

- Inflammatory optic neuritis: MS, sarcoidosis, neuromyelitis spectrum disorder, infections (syphilis, CMV, HIV, Lyme disease, cat-scratch disease)
- Vascular: Ischemic optic neuropathy, central retinal artery occlusion, temporal arteritis
- Compression: Pituitary tumor, meningioma, thyroid eye disease
- Hereditary: Leber hereditary optic neuropathy, dominant optic atrophy
- Nutritional, toxic, and metabolic: Amiodarone, isoniazid, B_{12} deficiency, tobacco, alcohol
- Trauma
- Glaucoma (end-stage disease)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Optic disc anomalies such as myelinated nerve fibers, "blonde" fundus

WORKUP

- A detailed history to identify onset and course, exposure to risk factors such as toxic/nutritional factors, detailed family history, and associated findings such as headache, eye pain, proptosis, or neurologic deficits.
- Ophthalmic examination to document deficits of visual acuity, color vision, contrast sensitivity, and visual fields must be performed. Relative afferent pupillary defect (RAPD) on swinging flashlight examination is sine qua non for unilateral optic nerve disease and must be documented. Absence indicates retinal disease or bilateral lesions.
- General examination and neurologic examination can provide clues to an underlying cause.
- Pertinent laboratory testing as noted below; genetic studies with a genetic consultation can be obtained in cases with a suggestive history.
- In the absence of an obvious cause, contrasted MRI of brain and orbits should be obtained to evaluate for demyelinating lesions and compressive lesions of the anterior visual pathways. Lumbar puncture should be obtained in patients with unexplained optic atrophy, especially with neurologic deficits.

LABORATORY TESTS

- Depends on suspected cause: None for trauma, tumor, or MS
- Serum B_{12}, RPR, HIV
- Autoimmune diseases: ESR, ANA, ACE, aquaporin-4 antibodies (NMO IgG)

IMAGING STUDIES

- MRI of the brain and orbits with contrast , fat suppression, and special (thin) cuts through orbits is necessary to identify compressive lesions in all patients with unexplained optic atrophy; especially important in patients with positive predictive factors for abnormal imaging (e.g., young age, progression, bilateral findings).
- If sarcoid is suspected, order chest x-ray and/or chest CT.

TREATMENT

ACUTE GENERAL Rx

Treat the underlying cause—discontinue identifiable toxins, use B_{12} replacement, neurosurgical intervention is necessary if tumor is found; consider IV steroids if there is evidence for active demyelinating disease.

CHRONIC Rx

The optic nerve does not regenerate, although symptoms often improve.

DISPOSITION

- Visual loss usually occurs over weeks to months
- Appointment with neurologist or ophthalmologist

REFERRAL

Depends on the underlying disease process

PEARLS & CONSIDERATIONS

COMMENTS

- An experienced clinician should be able to identify pale optic discs and a RAPD.
- Pupillary dilation with mydriatic agents (e.g., tropicamide) may be necessary to optimize funduscopic examination.
- Patient education material can be obtained from the National Eye Institute, Department of Health and Human Services, 9000 Rockville Pike, Bethesda, MD 20814.

AUTHOR: **Sachin Kedar, MBBS, MD**

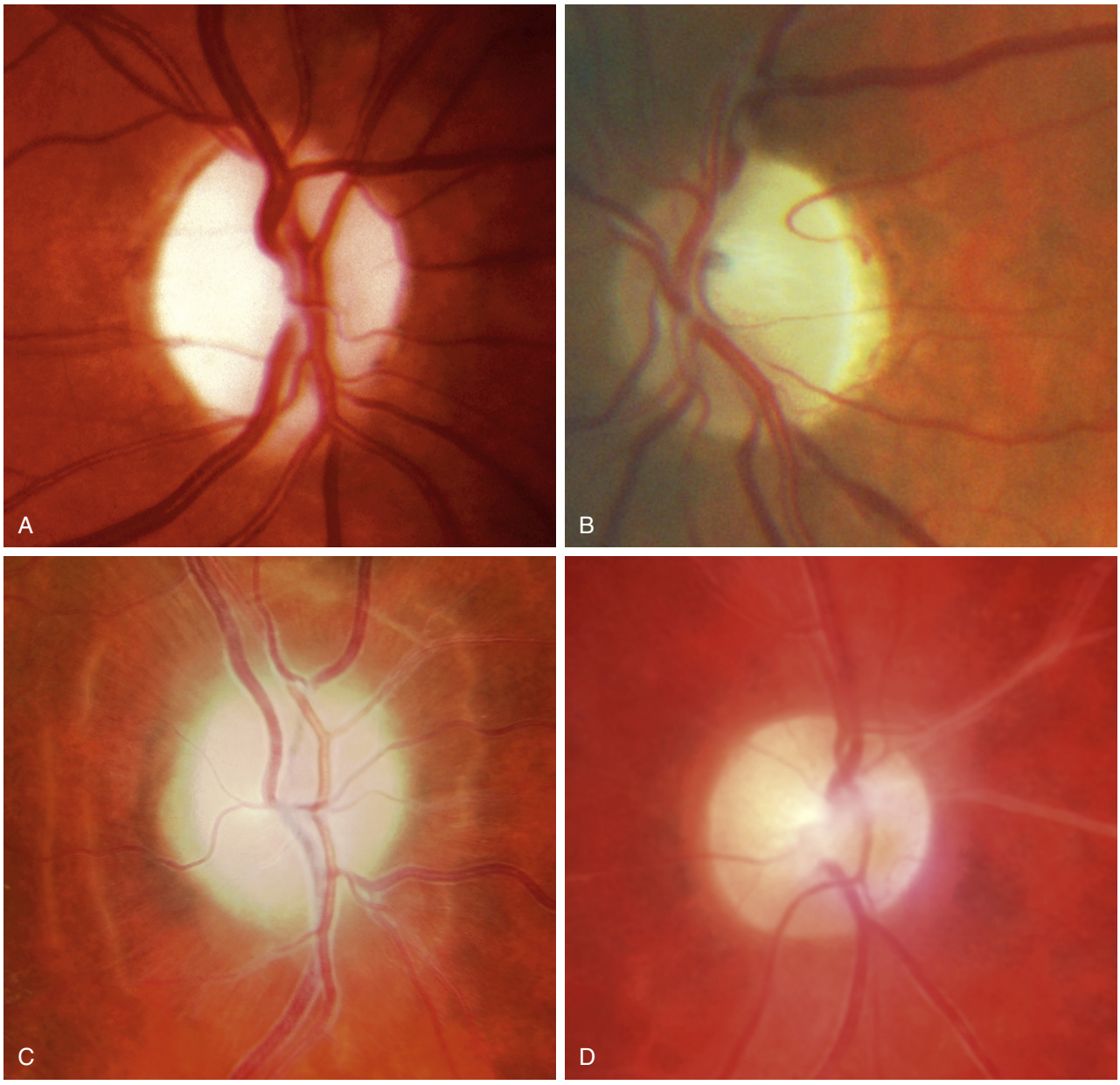

FIG. E1 Optic atrophy. A, Primary due to compression. **B,** Primary due to nutritional neuropathy—note predominantly temporal pallor. **C**, Secondary due to chronic papilloedema—note prominent Paton lines (see text). **D,** Consecutive due to vasculitis. (Courtesy P. Gili, Fig. C. From Bowling B: *Kanski's clinical ophthalmology: a systemic approach,* ed 8, Philadelphia, 2016, Elsevier.)

Optic Neuritis

BASIC INFORMATION

DEFINITION

Optic neuritis is an inflammation of the optic nerve resulting in impaired visual function.

SYNONYMS

Optic papillitis
Retrobulbar neuritis

ICD-10CM CODES
H46.8 Other optic neuritis
H46.9 Unspecified optic neuritis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 1 to 5/100,000 person(s) per yr; rates vary according to incidence of multiple sclerosis (MS). Optic neuritis affects 1% to 5% of patients with neurosarcoid.
PREVALENCE (IN U.S.): Common in patients with MS
PREDOMINANT SEX: Female:male ratio: 1.8:1
PEAK INCIDENCE: 20 to 49 yr, mean 30
GENETICS: Unknown. If due to MS, it is more common in patients with certain human lymphocyte antigen (HLA) blood types and in monozygotic twins of affected siblings.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presentation with acute or subacute (days) visual loss, often accompanied by periocular tenderness that worsens with eye movements.
- **Marcus Gunn pupil** (relative afferent pupillary defect [RAPD]): Direct and consensual response is normal; however, when flashlight is swung from eye to eye, the affected eye's pupil dilates to direct light.
- Decreased visual acuity.
- Unilateral visual field abnormalities—often a central scotoma (Fig. E1).
- Color desaturation; red is most often affected.
- Normal fundus examination in 66% cases; disc edema is noted in 33%. Other abnormalities include uveitis or periphlebitis. In neurosarcoid, the optic nerve head may exhibit a lumpy appearance suggestive of granulomatous infiltration, and there may be associated vitritis (Fig. E2).
- May have movement or light-induced phosphenes (flashes of light lasting 1 to 2 sec).
- Uhthoff phenomenon (benign exercise- or heat-induced deterioration of vision) is seen in some. Vision may also worsen in bright sunlight.
- Over time the optic disc may atrophy and become pale.

ETIOLOGY

An inflammatory response associated with an infection or autoimmune disease (such as collagen vascular disease, granulomatous disease, MS, or neuromyelitis optica).

DIAGNOSIS

Diagnosis is clinically established in a young patient with acute onset of monocular vision loss associated with retroorbital pain associated with eye movements and presence of RAPD lasting more than 24 hr. Absence of other orbital or ocular pathology is based on clinical examination.

DIFFERENTIAL DIAGNOSIS

For optic neuritis:
- Inflammatory: MS, neuromyelitis optica spectrum disorder (NMOSD), sarcoidosis, lupus, Sjögren, Behçet, postinfectious, postvaccination, neuroretinitis, acute disseminated encephalomyelitis, paraneoplastic, autoimmune optic neuropathy
- Infectious: Syphilis, TB, Lyme disease, *Bartonella,* HIV, cytomegalovirus (CMV), herpes, helminths, chickenpox, Q fever, periorbital infections, *Toxocara* sp.
- Ischemic: Anterior and posterior ischemic optic neuropathies, diabetic papillopathy, branch or central retinal artery or vein occlusion
- Drugs and toxins: Arsenic, methanol, ethambutol, cyclosporine, etc.
- Mitochondrial: Leber hereditary optic neuropathy, other mitochondrial

WORKUP

A thorough neurologic examination; dilated ophthalmoscopy

LABORATORY TESTS

Acute optic neuritis is a clinical diagnosis based on presentation with classical features: acute, painful unilateral loss of vision associated with RAPD in a young person with no other apparent causes such as trauma. In atypical cases additional studies may be considered.
- CBC, antinuclear antibody (ANA), ACE, erythrocyte sedimentation rate (ESR)
- Consider HIV Ab, Lyme titer, rapid plasma reagin (RPR), other autoimmune or infectious causes
- Bilateral or recurrent optic neuritis (ON): neuromyelitis optica (NMO) immunoglobulin (IgG), myelin oligodendrocyte glycoprotein (MOG IgG), paraneoplastic CRMP-5-IgG

IMAGING STUDIES

- Contrast-enhanced MRI of the brain is performed to assess the risk of developing MS. Often enhancement of the optic nerve is seen. MRI orbits with thin sections of fat suppressed sequences may be needed if the patient demonstrates atypical features (Fig. E3).
- Consider using optical coherence tomography to follow optic nerve atrophy objectively longitudinally.

TREATMENT

NONPHARMACOLOGIC THERAPY

Assure patient that in most cases of typical optic neuritis, there is near complete recovery of vision.

ACUTE Rx

Treat if the visual loss is significant, atypical features, or if there is an abnormal MRI (higher risk of MS). Treatment is with methylprednisolone (MP) 250 mg IV every 6 hr (or 1 g IV daily) for 3 days followed by an oral prednisone taper of 11 days. Optic neuritis from NMOSD is often more severe and has a worse prognosis; therefore plasma exchange can be considered.

CHRONIC Rx

Depends on underlying cause. Disease-modifying treatment when increased risk of developing MS or neuromyelitis optica spectrum disorder. See topic "Multiple Sclerosis."

DISPOSITION

Most often vision is worst at the end of wk 1, followed by recovery over months. In the Optic Neuritis Treatment Trial (ONTT), 90% had 20/40 or better vision at 1 yr and 3% had 20/200 or worse. Of initial 20/200 or worse cases, only 5% remained in that group at 6 mo.

REFERRAL

- To neurologist for other neurologic signs and to assess risk of developing MS. In ONTT (Optic Neuritis Treatment Trial), risk of MS >15 yr was 72% with ≥1 lesion(s) on MRI, and 25% with a normal MRI.
- To ophthalmologist when atypical features or slowly progressive; urgently when other ocular pathology is present or if vision worsens or does not improve after several wk, or pain is severe.

PEARLS & CONSIDERATIONS

- Bilateral optic neuritis suggests a systemic inflammatory disorder, infection, NMOSD, or paraneoplastic, but can also occur in MS.
- Acute bilateral loss of vision with a severe headache or diplopia should raise concern for pituitary apoplexy and/or giant cell arteritis.

RELATED CONTENT

Idiopathic Intracranial Hypertension (Related Key Topic)
Multiple Sclerosis (Related Key Topic)

AUTHORS: **Sachin Kedar, MBBS, MD,** and **Corey Goldsmith, MD**

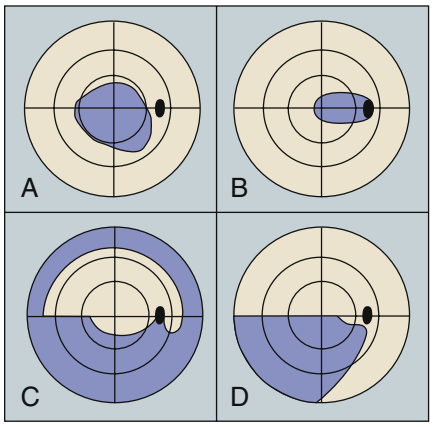

FIG. E1 Visual field defects in optic neuritis. A, Central scotoma. **B,** Centrocecal scotoma. **C,** Nerve fiber bundle. **D,** Altitudinal. (From Kanski JJ, Bowling B: *Clinical ophthalmology: a systematic approach,* ed 7, Philadelphia, 2010, WB Saunders.)

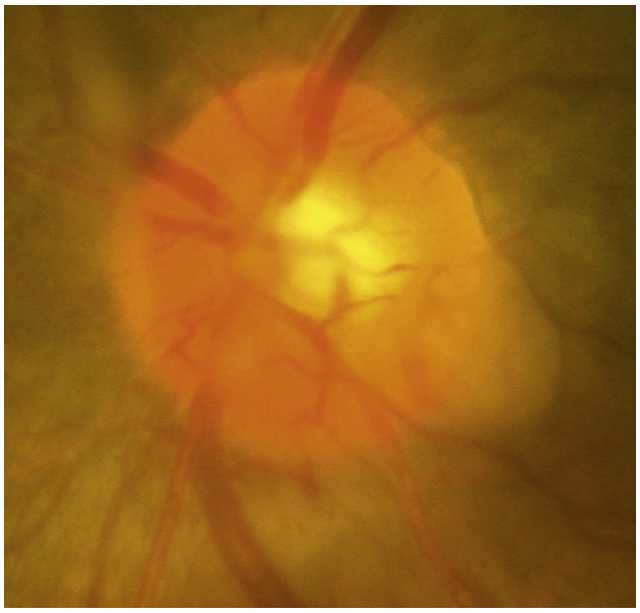

FIG. E2 Sarcoid granuloma of the optic nerve head with overlying vitreous haze. (From Bowling B: *Kanski's clinical ophthalmology, a systemic approach,* ed 8, Philadelphia, 2016, Elsevier.)

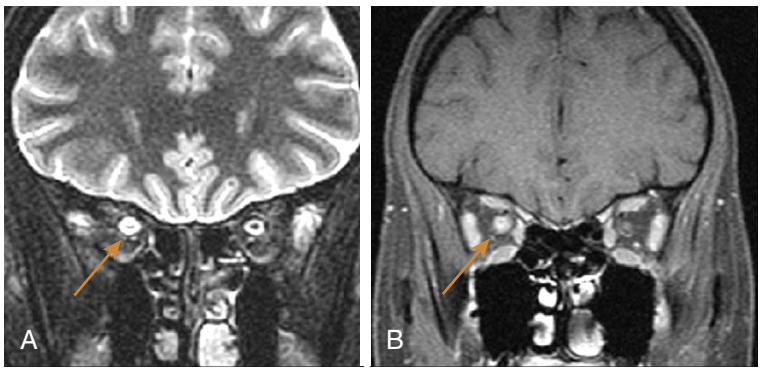

FIG. E3 Right optic neuritis. Coronal fat-suppressed T2-weighted fast spin-echo **(A)** and fat-suppressed contrast-enhanced T1-weighted MR images. There is hyperintensity of the right optic nerve, with diffuse enhancement *(arrows)* **(B).** (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Oral cancers refer to malignant transformation of the oral tissues usually preceded by a process of sequential dysplastic changes leading to the development of squamous carcinoma. Oral squamous cell cancers (OSCC) include oral cavity cancers (lip, floor of mouth, buccal mucosa, anterior tongue, gingivae, hard palate, retromolar trigone), oropharynx cancers (base of tongue, tonsils, soft palate, pharyngeal walls), and hypopharynx cancers (pyriform sinus, postcricoid area, posterior pharyngeal wall).

SYNONYMS

Head and neck cancer
Oral malignant neoplasm
OSCC

ICD-10CM CODES

C01	Malignant neoplasm of base of tongue
C03	Malignant neoplasm of gum
C04	Malignant neoplasm of floor of mouth
C05	Malignant neoplasm of palate
C06	Malignant neoplasm of other and unspecified parts of mouth
C09	Malignant neoplasm of tonsil
C10	Malignant neoplasm of oropharynx
C11	Malignant neoplasm of nasopharynx
C12	Malignant neoplasm of piriform sinus
C13	Malignant neoplasm of hypopharynx
C14	Malignant neoplasm of other and ill-defined sites of lip, oral cavity and larynx
C14.0	Malignant neoplasm of pharynx, unspecified
C14.2	Malignant neoplasm of Waldeyer ring
C14.8	Malignant neoplasm of overlapping sites of lip, oral cavity and pharynx

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE & PREVALENCE: OSCC comprise the sixth most common cancer in the world. An estimated 530,000 cases are diagnosed annually around the globe, and the rates have been rising, particularly in young people and among minorities. It was estimated that in 2019, approximately 53,000 new cases and 10,860 deaths would occur in the U.S. The incidence of oral cancers linked to alcohol and tobacco use has been declining in the U.S., whereas those linked to human papillomavirus (HPV), primarily HPV type 16, are on the rise, especially for cancers located in the tonsils and base of tongue. In developed countries across the world, HPV is increasingly implicated in the growing incidence of oral cancer. In Asian countries where chewing betel nut is customary, oral cancer accounts for up to 40% of cancers in some regions. Squamous cell carcinoma is the most common malignancy that occurs in the oral cavity.

PREDOMINANT SEX & AGE: The ratio of oral cancer in males: females is 2.5:1 in the U.S. Black males have a higher early incidence in the 50- to 60-yr age group, but with increasing age, white men predominate.

GENETICS: The genes that are critically altered in OSCC include *TP53,* the retinoblastoma family, *p16* and cyclin *D1*. The *TP53, CCND1,* and *CDKN2A* genes are established cancer genes in HPV-negative cancers. *TP53* and the genes encoding the Rb family are established cancer genes in HPV-positive cancers. Signaling pathways that are involved in the pathogenesis of oral cancers include that of the human epidermal receptor (HER) family, vascular endothelial growth factor (VEGF) receptor, and signal transducer and activator of transcription 3 (STAT 3). The tumor suppressor gene *TP53* is frequently mutated in HPV-negative tumors.

RISK FACTORS (Fig. 1): The following factors are implicated in the development of oral cancer:

- Tobacco use
- HPV infection (primarily types 16 and 18)
- Alcohol
- Immune deficiency
- Radiation
- Betel nut consumption
- Solar radiation

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Specific patient complaints may include the following: oral ulcers or mass, choking, difficulty breathing, dysphagia, odynophagia, voice hoarseness, globus sensation, otalgia, ear or nose stuffiness, hemoptysis, trismus, neck mass, and pain in the head/neck region.
- Generalized symptoms and signs may include weight loss, fatigue, anorexia, altered mood, and sleep.

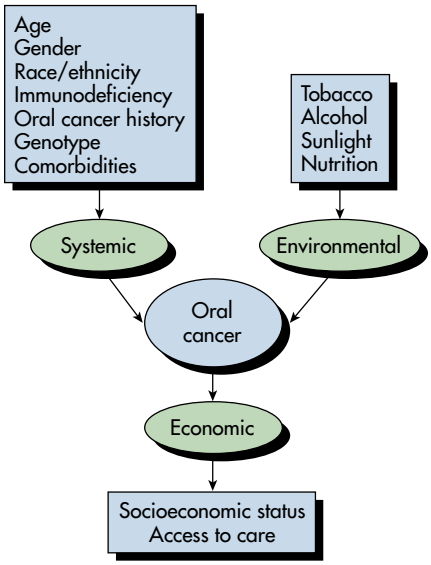

FIG. 1 Risk model for oral cancer. Oral cancer is a multifactorial disease process that includes systemic, environmental, and economic effects. The interplay of these variables ultimately leads to the incidence of this disease. The multifactorial nature of oral cancer should be addressed in the assessment of a patient's risk. (From Jones DL, Rankin KV: Oral cancer and associated risk factors. In Cappelli D, Mobley C [eds]: *Prevention in clinical oral health care,* St Louis, 2008, Elsevier, pp 68-77.)

- Clinically, oral cancers can present as:
  1. Erythroplakia (flat red patch); can mimic inflammatory or traumatic lesions
  2. Leukoplakia (white patch; Fig. E2)
  3. Raised lesion
  4. Ulcerated lesion
  5. Warty lesion or growth

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Oral leukoplakia
- Invasive fungal infections
- Chancre of early syphilis and gumma of tertiary syphilis
- Chronic ulcer
- Metastatic or locally invading cancers from sinuses or other sites of the body

PATIENT WORKUP

- Primary workup includes either biopsy or fine-needle aspiration (FNA) of the presenting lesion or suspected neck lymph node for histopathologic analysis. HPV assessment with p16 immunohistochemical staining and confirmatory in situ hybridization (ISH) testing is performed when indicated for oropharynx primary tumors.
- Detailed examination of the oral cavity, pharynx, larynx, neck, ears, nose, and cranial nerves should be performed.
- Laryngoscopy and examination under anesthesia are commonly performed.
- Pretreatment evaluation of tumor size, the extent of invasion, and the presence or absence of regional lymph node metastases is critical for planning treatment.
- Laboratory workup can include complete blood count, complete chemistry panel, and thyroid function.
- Staging workup includes CT or MRI imaging of the head and neck and a chest x-ray. If locoregional or advanced disease is a consideration, a PET scan is typically completed.
- The TNM system is used for staging of OSCC and is subdivided according to primary tumor sites: (1) lip and oral cavity, (2) pharynx.

TREATMENT

- Surgery, radiation therapy, and chemotherapy are treatment modalities involved in the treatment plan for OSCC.
- The use of supportive and special therapeutic modalities such as nutritional therapy including feeding gastrostomy, speech and swallowing therapy, reconstructive surgery, and speech prosthesis is required often.
- For treatment purposes OSCC are classified as early (T1 or T2 lesions), locoregional (T3-4 or any N), or metastatic (M1) stages. Site-specific TNM staging is done as per the primary tumor site (e.g., oral cavity, oropharynx, hypopharynx, etc.).
- After staging completion, the initial treatment considerations include:
  1. Determination of primary tumor resectability (resectable vs. unresectable)
  2. Management of neck nodes

3. Intent of radiation therapy (curative vs. palliative)
4. Need for organ preservation
5. Need for reconstructive surgery
6. Need for chemotherapy
7. HPV status of tumor

- Localized tumors (stage I or II) can be approached by initial surgical resection or definitive radiotherapy. Loco-regionally advanced tumors (stage III and localized IV) that are resectable are typically approached by upfront surgery followed by adjuvant radiation and/or chemotherapy. Unresectable patients are typically treated with definitive chemotherapy and radiotherapy. Patients with distant metastatic disease are treated with systemic chemotherapy, while locally recurrent tumors can be approached with either surgery or chemotherapy or both.
- Surgery is typically associated with less long-term morbidity than radiation therapy. Surgical therapy traditionally involved wide-exposure approaches (mandibulotomy, transpharyngeal access). Newer surgical techniques allow tumor resection through the mouth. Recently, transoral robotic surgery (TORS) has been developed to improve access to oropharyngeal squamous cell carcinomas with excellent oncologic outcomes.
  1. Acute surgical complications can include infection, bleeding, aspiration, wound breakdown, fistula, and flap loss.
  2. Surgical procedures can cause functional deficits in speech and swallowing, but these adverse effects can be minimized by appropriate reconstruction and prostheses.
- Definitive radiation therapy is reserved for patients who cannot tolerate surgery or for whom surgical resection would result in particularly severe functional impairment.
  1. Radiation therapy can include external beam radiation and brachytherapy.
  2. Radiation therapy side effects include mucositis, radiation dermatitis, loss of taste, dysphagia, dental caries and decay, and xerostomia.
  3. Late complications can include skin/soft tissue atrophy and fibrosis, osteoradionecrosis, and trismus.
- Systemic chemotherapy can be administered alone or in combination with radiotherapy, depending on the disease stage. Agents typically used include cisplatin, carboplatin, 5-fluorouracil, taxanes, and the epidermal growth factor receptor (EGFR) antibody cetuximab.
- For locally advanced OSCC, the combination of cisplatin and radiotherapy is the regimen of choice. In selected patients with large primary tumors or bulky nodal disease, neoadjuvant chemotherapy may be utilized prior to chemoradiotherapy administration.
- Patients who have metastatic cancers or unresectable locoregional recurrences usually are treated with systemic chemotherapy.
- Standard doublet chemotherapy regimens (platinum plus either 5-fluorouracil or a taxane) can be combined with the epidermal growth factor receptor (EGFR)–targeting antibody cetuximab. A recent study has demonstrated the superiority of frontline therapy with platinum plus 5-fluorouracil chemotherapy in combination with the checkpoint inhibitor pembrolizumab.
- In patients who have not received checkpoint inhibitor therapy previously, nivolumab and pembrolizumab have been shown to improve survival outcomes after failure of first-line chemotherapy.
- The negative predictive value of post-treatment PET imaging in patients with locally advanced cancer who have been treated with chemoradiotherapy is 98% to 99%.

DISPOSITION

- Prognosis depends on the staging and resectability of the primary tumor as well as on patient performance status.
- Tumor HPV status is a strong and independent prognostic factor for survival among patients with base of tongue and oropharyngeal cancer.

REFERRAL

Referral to multidisciplinary head and neck cancer team consisting of ENT or head/neck surgeon, radiation oncologist, and medical oncologist

PEARLS & CONSIDERATIONS

COMMENTS

- Oral and pharyngeal cancer is the sixth most common cancer globally.
- Biopsy with HPV-status assessment is the key for accurate diagnosis.
- Posttreatment rehabilitation and surveillance is important.

PREVENTION

- Encourage patients to stop using any type of tobacco and drinking alcohol.
- Examine oral cavities at annual checkups and work up suspicious lesions.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Mouth Cancer (Patient Information)

AUTHOR: **Ritesh Rathore, MD**

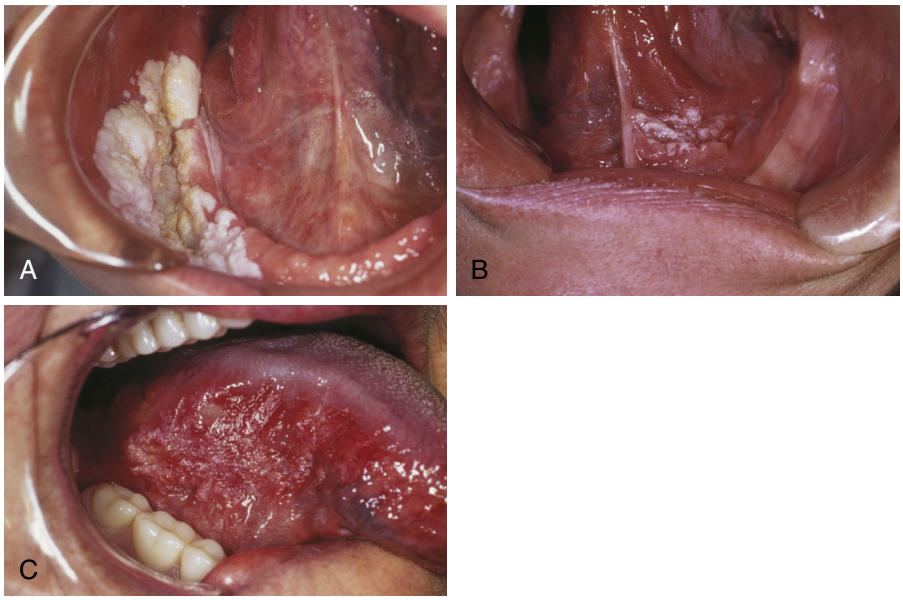

FIG. E2 Squamous cell carcinoma of the oral mucosa. A, Leukoplakia. **B,** Invasive carcinoma of the floor of the mouth. **C,** Invasive carcinoma of the tongue. (Courtesy G. Putnam. In White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

SUGGESTED READINGS

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Siegel RL et al: Cancer statistics, *CA Cancer J Clin* 69(1):7-34, 2019.

BASIC INFORMATION

DEFINITION

Oral hairy leukoplakia (OHL) is a painless, white, nonremovable, plaquelike lesion typically located on the lateral aspect of the tongue.

SYNONYMS

Oral hairy leukoplakia
OHL

ICD-10CM CODE
K13.3 Hairy leukoplakia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE AND PREVALENCE: Epstein-Barr virus (EBV) is implicated in the etiology of OHL, and the incidence of EBV seroprevalence is high in individuals who are HIV seropositive. However, OHL occurs in only 25% of these cases but may also occur in other immunosuppressed individuals, for example, organ transplant recipients.
RISK FACTORS: OHL is usually found in HIV-seropositive individuals (median CD4 count is 468/ml) but may also be identified in smokers and other immunocompromised patients such as transplant recipients (particularly renal) and patients taking steroids. Diagnosing OHL is an indication to institute a workup to evaluate and manage HIV disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Varying morphology and appearance, which may change daily.
- May be unilateral or bilateral.
- White plaques can be small with fine, vertical corrugations on the lateral margin of the tongue (Fig. 1). The plaques from OHL are adherent to the tongue surface (in contrast to candidal plaques, which may be easily scraped off).
- Irregular surface; may have prominent folds or projection, occasionally markedly resembling hairs.
- May spread to cover the entire dorsal surface or spread onto the ventral surface of the tongue where the lesions usually appear flat.
- Rarely, lesions can manifest on the soft palate, buccal mucosa, or posterior oropharynx.
- Usually asymptomatic, but some patients have mouth pain, soreness, or a burning sensation; impaired taste, or difficulty eating; others complain of its unsightly appearance.
- OHL may rarely progress to oral squamous cell carcinoma, particularly in smokers, which has a poor prognosis.

ETIOLOGY

EBV is implicated in its etiology, and OHL is a result of unchecked lytic replication of EBV in the epithelium of keratinized cells. OHL differs from most EBV-related diseases in that infection is predominantly lytic rather than latent, with abundant virus production resulting in cell lysis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Oral homogenous/non-homogenous leukoplakia
- *Candida albicans*
- Lichen planus
- Idiopathic leukoplakia
- White sponge nevus
- Dysplasia
- Squamous cell carcinoma

WORKUP

Requires physical examination and evaluation of HIV disease

LABORATORY TESTS

The *provisional* diagnosis is clinical and based on:
- Visual inspection
- Inability to scrape the lesion off the tongue with a blade
- Failure to respond to antifungal therapy

The *presumptive* diagnosis requires biopsy and histologic demonstration of:
- Epithelial hyperplasia with hairs
- Absence of inflammatory cell infiltrate

The *definitive* diagnosis requires:
- In situ hybridization of histologic or cytologic specimens revealing EBV DNA *or*
- Electron microscopy of specimens revealing herpes-like particles
- Measurement of the DNA content in cells of oral leukoplakia may be used to predict the risk of oral carcinoma

NOTE: Specimens obtained from lesions may demonstrate hyphae of *Candida albicans,* which may coexist and potentiate EBV-induced OHL.

TREATMENT

NONPHARMACOLOGIC THERAPY

OHL is usually asymptomatic and requires no specific therapy. It may resolve spontaneously and is generally benign in HIV-seropositive patients.

ACUTE GENERAL Rx

- Antiretroviral therapy (ART) has considerably changed the frequency of oral lesions caused by opportunistic infections in HIV-seropositive individuals.
- Topical retinoids (0.1% vitamin A) may improve the appearance of OHL-affected oral surfaces through their dekeratinizing and immunomodulation effects; however, they are expensive, and prolonged use may result in a burning sensation over the treated area.
- Topical podophyllin resin 25% solution has been reported to induce resolution.
- Surgical excision and cryotherapy may help, but the lesions may recur.
- High-dose acyclovir 800 mg five times per day, valacyclovir 1000 mg tid, famciclovir 500 mg tid, ganciclovir 1000 mg tid, or foscarnet 40 mg/kg IV tid will cause lesions to resolve but only temporarily.

REFERRAL

Referral to ENT or oral surgeon for biopsy of tongue to confirm diagnosis

PEARLS & CONSIDERATIONS

- OHL may be the presenting sign of patients infected with HIV who are unaware of their status.
- The incidence has decreased significantly in the era of antiretroviral therapy.

RELATED CONTENT

Acquired Immunodeficiency Syndrome (Related Key Topic)
Oral Hairy Leukoplakia (Patient Information)
Epstein-Barr Virus Infection (Related Key Topic)
Human Immunodeficiency Virus (Related Key Topic)

AUTHOR: **Sajeev Handa, MD, SFHM**

FIG. 1 Oral hairy leukoplakia. (From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

BASIC INFORMATION

DEFINITION

Orchitis is an inflammatory process (usually infectious) involving the testicles. Infection may be viral or bacterial and can be associated with infection of other male sex organs (prostate, epididymis, or bladder) or lower urogenital tract or sexually transmitted diseases often via hematogenous spread. Common causes are:

- Viral: Mumps—20% postpubertal; Coxsackie B virus
- Bacterial: Pyogenic via spread from involving epididymis; bacteria include *Escherichia coli, Klebsiella pneumoniae, P. aeruginosa, Staphylococcus, Streptococcus* or *Rickettsia, Brucella* spp.
- Other:
  1. Viral—HIV-associated, CMV
  2. Fungi
     a. Cryptococcosis
     b. Histoplasmosis
     c. *Candida*
     d. Blastomycosis
     e. Syphilis
  3. *Mycobacterium tuberculosis* and *M. leprae*
  4. Parasitic causes: Toxoplasmosis, filariasis, schistosomiasis
- Table 1 describes a classification of epididymitis and orchitis based on etiology.

SYNONYMS

Epididymo-orchitis
Testicular infection
Testicular inflammation

ICD-10CM CODES

N45.9	Orchitis, epididymitis, and epididymo-orchitis without abscess
A54.1	Gonococcal orchitis
A56.1	Chlamydial orchitis
N51.1	Mumps orchitis

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: Male
PREDOMINANT ORGANISM: The leading cause of viral orchitis is mumps. The mumps virus rarely causes orchitis in prepubertal males but involves one or both testicles in nearly 30% of postpubertal males.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Testicular pain, unilateral or bilateral swelling
- May have associated epididymitis, prostatitis, fever, scrotal edema, erythema, cellulitis
- Inguinal lymphadenopathy
- Acute hydrocele (bacterial)
- Rare development: Abscess formation, pyocele of scrotum, testicular infarction
- Spermatic cord tenderness may be present
- Granulomatous

DIAGNOSIS

Clinical presentation as described previously with possible history of acute viral illness or concomitant epididymitis

DIFFERENTIAL DIAGNOSIS

- Epididymo-orchitis-gonococcal
- Autoimmune disease
- Vasculitis
- Epididymitis
- Mumps, with or without parotitis
- Neoplasm
- Hematoma
- Spermatic cord torsion

LABORATORY TESTS

- CBC with differential
- Urinalysis
- Viral titer—mumps. Mumps IgM will be detectable after 5 days of onset of clinical mumps and remain positive for up to 4 wk. A reverse-transcriptase PCR (RT-PCR) on serum or buccal or oral swab is another option.
- Urine culture for mumps virus
- Ultrasound of testicle to rule out abscess

IMAGING STUDIES

Ultrasound if abscess suspected

TREATMENT

- Dependent on cause
- Viral (mumps): Observation; bed rest, ice packs, analgesics, and a scrotal sling for support may provide some relief of discomfort that accompanies mumps orchitis
- Bacterial: Empiric antibiotic treatment with parenteral antibiotic treatment until pathogen identified: Ceftriaxone (250 mg IM once) plus doxycycline (100 mg PO bid for 10 days), in men <35 yr old to cover *Neisseria gonorrhoeae* and *Chlamydia trachomatis.* In men who have sex with men or men >35 yr old: Levofloxacin 500 to 750 mg IV/PO qd for 10 to 14 days *or* ampicillin-sulbactam *or* third-generation cephalosporin or piperacillin/tazobactam
- Surgery for abscess, pyogenic process

DISPOSITION

Follow-up for evidence of recurrence, hypogonadism, and infertility may be needed with bilateral orchitis.

REFERRAL

- To a urologist if surgical drainage is needed
- To an endocrinologist if hypogonadism develops
- To a fertility specialist if infertility develops

PEARLS & CONSIDERATIONS

Consider tuberculous orchitis if symptoms fail to respond to standard antibacterial therapy, even in the absence of chest radiographic evidence of pulmonary tuberculosis.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Orchitis (Patient Information)
Epididymitis (Related Key Topic)
Mumps (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

TABLE 1 Classification of Epididymitis and Orchitis

Acute Epididymitis or Epididymo-orchitis	Granulomatous Epididymitis or Orchitis	Viral Orchitis
Neisseria gonorrhoeae	*Mycobacterium tuberculosis*	Mumps
Chlamydia trachomatis	*Treponema pallidum*	Enteroviruses
Escherichia coli		
Streptococcus pneumoniae	*Brucella* spp.	
Klebsiella spp.	Sarcoid	
Salmonella spp.	Fungal	
Other urinary tract pathogens	Parasitic	
Idiopathic	Idiopathic	

From Cohen J, Powderly WG: *Infectious diseases,* ed 2, St Louis, 2004, Mosby.

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Orthostatic hypotension (OH) is defined as the presence of at least one of the following:

- Decrease in systolic blood pressure by ≥20 mm Hg or
- Decrease in diastolic blood pressure by ≥10 mm Hg, within 3 min of standing.

It is a physical sign that requires further investigation to discern its underlying etiology.

Recent studies have shown that blood pressure measurements within 1 min might be more useful in predicting fractures, falls, and other adverse events and for most patients, assessment within 1 min of standing rather than waiting for 3 min may be sufficient.[1]

SYNONYMS

Postural hypotension
OH

ICD-10CM CODE
I95.1 Orthostatic hypotension

EPIDEMIOLOGY & DEMOGRAPHICS

- The incidence of OH is increased in older people. Surveys have shown OH to be present in approximately 20% of adults over 65 yr of age.
- Also, higher incidence noted in those with diseases associated with autonomic dysfunction (e.g., Parkinson disease, diabetes mellitus).
- OH may cause up to 30% of all syncopal events in the elderly, and OH is associated with an increased risk of heart failure among those aged 45 to 55 yr and an increased risk of cardiovascular disease and all-cause mortality among those aged 55 yr and older.
- There is an association between orthostatic hypotension and cognitive dysfunction among older adults.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms may include dizziness, lightheadedness, syncope, visual and auditory disturbances, weakness, diaphoresis, pallor, and nausea.
- OH may be asymptomatic, especially in older hypertensive patients with autonomic dysfunction. These patients tend to have systolic hypertension when seated or supine.
- Associated with increased autonomic activity during meals (from increased splanchnic blood flow), exercise, prolonged standing, and hot weather.
- Supine and nocturnal hypertension in patients with OH may indicate an underlying autonomic dysfunction.

[1]Juraschek SP et al: Associated of history of dizziness and long-term adverse outcomes with early vs. later orthostatic hypotension assessment times in middle-aged adults, *JAMA Intern Med* 2017.

ETIOLOGY

- There are two main mechanisms for OH: autonomic dysfunction and volume depletion.
- Normal response: Assumption of an upright posture results in the pooling of approximately 500 ml of blood in the lower extremities due to gravity and decreased venous return, decreased cardiac output, and decreased arterial pressure. The consequent increase in sympathetic tone due to increased carotid baroreceptor activity causes arterial and venous constriction as well as positive inotropic and chronotropic effects, thereby limiting the fall in upright blood pressure. Peripheral vasoconstriction is also mediated by increased activity of the renin-angiotensin system and decreased activity of atrial natriuretic factor.
- Autonomic Dysfunction: Impairment of the baroreceptor reflex, as in central (such as Parkinson disease) or peripheral autonomic dysfunction (such as diabetes) and aging, may cause OH because decreased blood pressure cannot be counteracted by the aforementioned regulatory mechanisms.
- Volume depletion: May be caused by diuretics, vomiting, hemorrhage, and hyperglycemia. Mechanism of OH in these patients is similar to what is described earlier, with failure of the regulatory mechanisms kicking in.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Common:

- Medications: Antihypertensives, antidepressants (tricyclics), antipsychotics (phenothiazines), alcohol, narcotics, barbiturates, insulin, nitrates, PDE-5 inhibitors, alpha-adrenergic antagonists
- Reduced intravascular volume (hemorrhage, dehydration, hyperglycemia, hypoalbuminemia)
- Postprandial effect (especially in the elderly)
- Vasovagal syncope
- Deconditioning
- Central autonomic dysfunction (Parkinson disease)
- Peripheral autonomic dysfunction (diabetes mellitus, Guillain-Barré syndrome)

Uncommon:

- Central autonomic dysfunction (Shy-Drager syndrome)
- Postganglionic autonomic dysfunction: Impaired norepinephrine release
- Autoimmune autonomic dysfunction: Nicotinic acetylcholine receptor autoantibodies
- Paraneoplastic autonomic dysfunction: Anti-Hu antibodies (in small-cell lung cancer)
- Postural tachycardia syndrome (POTS): Usually occurs in young women; an abnormally large increase in heart rate is observed in the upright position, caused by increased venous pooling from autonomic dysfunction of the lower extremities, but blood pressure is not affected because of an excess of plasma norepinephrine
- Impaired cardiac output (myocardial infarction, aortic stenosis, arrhythmias)
- Cerebrovascular accident
- Adrenal insufficiency
- Deconditioning
- Carotid sinus hypersensitivity
- Anxiety, panic attacks
- Seizures
- Sepsis
- Idiopathic

WORKUP

- Obtain a detailed history including medication list, recent history of potential volume loss, medical history of congestive heart failure, malignancy, diabetes and alcoholism, evidence on history and physical examination of parkinsonism, ataxia, peripheral neuropathy, or dysautonomia.
- Measure supine blood pressure after the patient has been resting comfortably. The duration of time that the patient should spend supine and standing when measuring orthostatic hypotension is controversial. Limited evidence supports having the patient remain supine for 5 to 10 min before obtaining the supine blood pressure, followed by blood pressure measurement within 1 min of standing and again after 3 min of standing. The blood pressure cuff must be held at the level of the right atrium; holding the cuff below this level will result in a 5 to 10 mm Hg underestimation of blood pressure.
- Thorough neurologic examination should be performed.

LABORATORY TESTS

- Hemoglobin and hematocrit
- Consider BUN/Creatinine if suspecting dehydration as the cause
- EKG if suspecting underlying cardiac cause
- Consider when treatable causes of OH have been ruled out:
  1. Blood pressure and heart rate monitoring with a tilt table test
  2. Plasma norepinephrine measurements (to distinguish postganglionic from preganglionic autonomic dysfunction)
  3. Other methods, which use the Valsalva maneuver or measure sweating as indirect means of evaluating the autonomic nervous system

IMAGING STUDIES

None

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient education (leg crossing, prolonged sitting before first standing in the morning, avoid excessive straining and hot baths)
- High-salt diet (e.g., bouillon cubes); caution if history of heart failure
- Liberal fluid intake
- Take needed antihypertensive medications at different times of the day
- Raise the head of the bed at night

TABLE 1 Management of Orthostatic Hypotension in Older Adults

Identify and treat correctable causes.

Reduce or eliminate drugs causing orthostatic hypotension.

Avoid situations that may exacerbate orthostatic hypotension.

- Standing motionless
- Prolonged recumbency
- Large meals
- Hot weather
- Hot showers
- Straining at stool or with voiding
- Isometric exercise
- Ingesting alcohol
- Hyperventilation
- Dehydration

Raise the head of the bed to a 5- to 20-degree angle.

Wear waist-high, custom-fitted, elastic stockings and an abdominal binder.

Participate in physical conditioning exercises.

Participate in controlled postural exercises using the tilt table.

Avoid diuretics and eat salt-containing fluids (unless congestive heart failure is present).

Drug therapy:

- Caffeine
- Fludrocortisone
- Midodrine
- Desmopressin
- Erythropoietin

From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

- Compression stockings (to include splanchnic circulation)
- Multiple low-carbohydrate meals to avoid postprandial OH
- Avoid large carbohydrate loads and excess alcohol consumption

ACUTE GENERAL Rx

- Correction of volume status and impairment of cerebral perfusion.
- Review medication list and attempt to eliminate those potentially contributing to OH.

CHRONIC Rx

- Fludrocortisone: 0.1 mg/day (may combine with an alpha-1 agonist to lower the dose of each); monitor for electrolyte disturbances and supine hypertension
- Midodrine (alpha-1 agonist): 10 mg three times a day; monitor for supine hypertension
- Erythropoietin (consider if anemic)
- Caffeine (for postprandial hypotension)

Table 1 summarizes management of orthostatic hypotension in older adults.

OTHER TREATMENTS

- Pyridostigmine (enhances renal sodium reabsorption): 0.2 to 0.6 mg/day (not FDA-approved for this indication)
- Octreotide: 300 to 600 mg/day (not FDA-approved for this indication)
- Indomethacin (prostaglandin inhibitor)
- DDAVP (experimental)
- Droxidopa (used for patients with autonomic dysfunction to increase the availability of norepinephrine) has been FDA approved for treatment of adults with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure or nondiabetic autonomic neuropathy

PEARLS & CONSIDERATIONS

COMMENTS

- The presence of OH should always trigger a search for an underlying etiology.
- OH is diagnosed by observing changes in blood pressure, not heart rate.
- Volume depletion should cause an increased heart rate on standing; a lack of heart rate response in this setting suggests autonomic dysfunction.
- Pharmacotherapy with mineralocorticoids may require concomitant potassium replenishment and monitoring for hypertension.
- Evidence to support the efficacy of pharmacologic interventions to treat OH, including midodrine, is limited.
- The etiology of OH is often multifactorial in older patients, but increased susceptibility to volume depletion due to decreased baroreceptor reflexes frequently contributes. Chronic vitamin D deficiency is associated with the development of OH.
- Intensive blood pressure control did not increase injurious falls compared with controls among community-dwelling older adults participating in the Systolic Blood Pressure Intervention Trial (SPRINT).
- The physical examination of patients with dizziness, gait disturbance, and/or falls should include an assessment for OH. OH is an independent predictor of unexplained falls in older adults.
- Because OH may be asymptomatic, physical examination of those at risk must include assessment of blood pressure in both the supine and upright positions.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Timothy W. Farrell, MD, AGSF,** and **Hussain R. Khawaja, MD**

SUGGESTED READINGS

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Osgood-Schlatter Disease (PTG)

BASIC INFORMATION

DEFINITION

Osgood-Schlatter disease is painful swelling of the growing tibial tuberosity in adolescents.

SYNONYMS

Juvenile osteochondrosis
Tibial tubercle apophysitis

ICD-10CM CODE

M92.40 Juvenile osteochondrosis of patella, unspecified knee

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 4 cases/100 adolescents.
PREDOMINANT SEX: Male:female ratio of 3:1.
PREDOMINANT AGE: Males: Ages 13 to 15 yr, females: Ages 11 to 13 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Gradual onset of pain and swelling of the tibial tubercle
- Worsening of pain with athletic activity
- Dull ache exacerbated by jumping or climbing stairs
- Tenderness to touch over tibial tubercle, particularly with resisted knee extension

ETIOLOGY

- Repetitive microtrauma and avulsion of the developing ossification center of the tibial tuberosity
- Anatomic variants such as patella alta
- Baseline muscle tightness (quadriceps, gastrocnemius, soleus)
- Lower strain in the patellar tendon leads to faster force transmission

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Stress fracture of the proximal tibia
- Hoffa disease
- Sinding-Larsen-Johansson syndrome
- Patellar tendinitis

WORKUP

- The diagnosis of Osgood-Schlatter disease is made with history and physical examination.
- Imaging may be indicated to exclude fracture or bony tumors.

IMAGING STUDIES

- Lateral x-rays may show separation and fragmentation of the upper tibial epiphysis (Fig. E1).
- Musculoskeletal ultrasound (Fig. E2) can also be used and may show shorter patellar tendon excursion per force applied compared with normal tendons.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Activity modification with increased periods of rest
- Physical therapy

ACUTE GENERAL Rx

- Ice, especially after exercise
- Nonsteroidal antiinflammatory drugs
- Quadriceps stretching exercises and cross-training with low-impact sports
- Injections of local anesthetic mixed with dextrose have shown efficacy in randomized controlled trials
- Surgical (open or arthroscopic) debridement indicated in refractory cases, although this is controversial
- Newer arthroscopic techniques have been developed in order to minimize patient morbidity

DISPOSITION

- Condition usually heals when the epiphysis closes.
- 90% of patients respond to conservative treatment.
- Recent studies have shown promising results with the use of hyperosmolar dextrose injections in recalcitrant disease.
- Surgery is rarely needed in the treatment of Osgood-Schlatter disease but can be used for relief of persistent symptoms in patients that have separated ossicles or an abnormally ossified tibial tuberosity.

REFERRAL

Orthopedic consultation is recommended when symptoms persist >6 to 8 wk. with conservative treatment.

PEARLS & CONSIDERATIONS

COMMENTS

Larsen-Johansson disease is a similar disorder. While the diagnosis of Osgood-Schlatter disease is clinical, imaging may be needed to rule out infection, fracture, and malignancy.

RELATED CONTENT

Osgood-Schlatter Disease (Patient Information)

AUTHOR: **Steven L. Bokshan, MD**

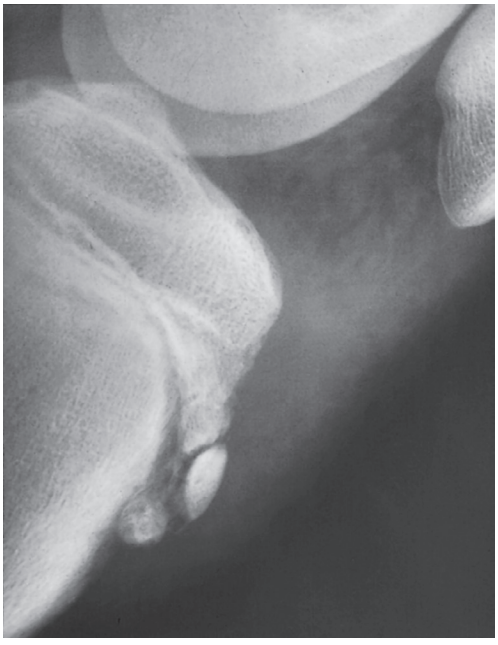

FIG. E1 Osgood-Schlatter disease. Fragmentation may be seen and a portion of the tibial tubercle ossification center is elevated. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.)

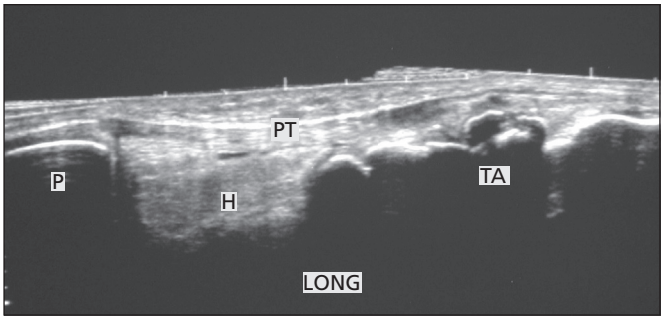

FIG. E2 Extended field of view (EFOV) of a patient with Osgood-Schlatter disease in the long axis with a knee in extension showing irregularity and fragmentation of the distal tibial apophysis. *H*, Hoffa fat; *P*, Patella; *PT*, patella tendon; *TA*, tibial apophysis. (From McNally E: *Practical musculoskeletal ultrasound*, ed 1, New York, 2005, Churchill Livingstone, p. 146.)

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BASIC INFORMATION

DEFINITION

Osteoarthritis (OA) is a progressive disease of the joint representing failed repair of joint damage. It is a complex disorder involving the articular cartilage, the subchondral bone, ligaments, menisci, periarticular muscles, peripheral nerves, and synovium. The process often starts with "micro-cracks" in the articular cartilage with resultant inflammatory cascade perpetuated by the cartilage, synovium, and other joint structures. It results in pain, stiffness, and functional disability often leading to reduced health-related quality of life. It also has a significant economic burden (up to 2.5% of the GDP in the U.S.) and is the leading cause of analgesic consumption and joint replacement surgeries. The American College of Rheumatology Classification criteria for osteoarthritis is described in Table 1.

SYNONYMS

Degenerative joint disease (DJD)
DJD
Arthrosis
OA

ICD-10CM CODES

M15.1	Heberden nodes (with arthropathy)
M15.2	Bouchard nodes (with arthropathy)
M15.3	Secondary multiple arthritis
M15.4	Erosive OA
M15.8	Other polyosteoarthritis
M15.9	Polyarthrosis, unspecified
M17	Gonarthrosis (arthrosis of knee)
M18	Arthrosis of first metacarpal joint
M19	Other arthrosis
M19.8	Other specified arthrosis
M19.9	Arthrosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Affects more than 30 million individuals in the U.S. Approximately 10% of men and 18% of women over the age of 60 yr are affected.

PREDOMINANT SEX: Prior to age 50, there is almost no gender discrepancy. After age 50, there is increased incidence of OA in females compared to males.

PREDOMINANT AGE: Occurs more frequently after 50 yr of age, but it is increasingly being recognized that OA may occur as early as 30 yr of age.

GENETICS: 39% to 65% heritability rate in twin studies of women who have generalized OA, concordance rate of 0.64 in monozygotic twins. In genome-wide association studies, 11 candidate loci have been identified, but all with a very small effect size.

RISK FACTORS: Osteoarthritis is considered predominantly a mechanical noninflammatory form of arthritis (Fig. 1). OA is thought to be the result of hostile biomechanics on an already susceptible joint (Fig. E2). Risk factors may be classified as either local or systemic. Local or biomechanical factors include obesity leading to increased load on the articular cartilage, mechanical environment of the joint (includes deformities like pes planus, genu varus and valgus, proprioception at the joint), local joint activity/occupation (textile worker leading to hand OA, high-impact runners leading to knee OA), and muscle weakness (quadriceps weakness leading to knee OA). Other deformities, such as femoro-acetabular impingement and limb length inequality, can confer significant risk of developing end-stage OA Systemic risk factors include nutritional factors such as antioxidant and vitamin D deficiency, hormonal status, high bone mineral density, and genetics (candidate genes being evaluated include IGF-1 gene, cartilage oligomeric protein gene, vitamin D receptor gene). That said, there is no concrete evidence showing that preventing the disease or reducing disease progression can be achieved by supplemental vitamin D, antioxidants, or estrogen. Obesity also increases the susceptibility of developing osteoarthritis via systemic adipokines.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Similar symptoms in most forms: Pain generally with activity, stiffness, or gelling (generally short-lived and morning stiffness lasting less than 30 min), crepitus

TABLE 1 American College of Rheumatology Classification Criteria for Osteoarthritis

Hip	Knee (Clinical Criteria)	Hand
Pain in the hip and two of the following: ESR <20 mm/hr Radiographic joint space narrowing Radiographic osteophytes	Pain in the knee and five of the following: Age >50 <30 min morning stiffness Crepitus Bony enlargement Bony tenderness No synovial warmth	Pain, aching, and stiffness in the hand and three of the following: Fewer than three MCP joints swollen Hard tissue enlargement of two or more DIP joints Hard tissue enlargement of two or more of the following joints: Second and third DIP, second and third PIP, both CMC joints Deformity of at least one of the following joints: Second and third DIP, second and third PIP, both CMC joints

CMC, Carpometacarpal; *DIP,* distal interphalangeal; *ESR,* erythrocyte sedimentation rate; *MCP,* metacarpophalangeal joint; *PIP,* proximal interphalangeal.

Modified from (1) Altman R et al: The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand, *Arthritis Rheum* 33:1601-1610, 1990; (2) Altman R et al: The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip, *Arthritis Rheum* 34:505-514, 1991; (3) Altman R et al: Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee, *Arthritis Rheum* 29:1039-1049, 1986. In: Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

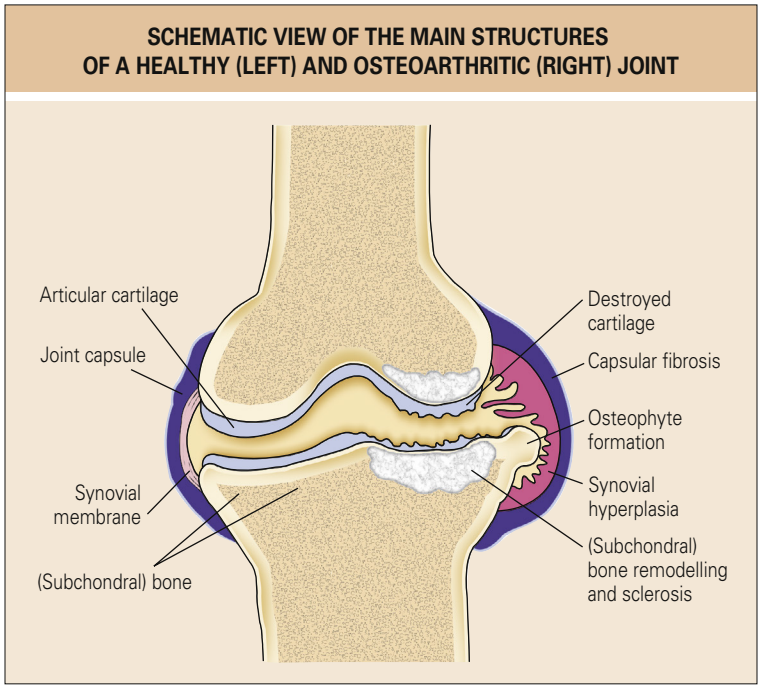

FIG. 1 In osteoarthritis (OA), the articular cartilage is lost or severely thinned, the subchondral bone is sclerotic, the joint capsule is thickened, and the synovial membrane is activated. (Courtesy of E. Bartnik, Frankfurt, Germany. In Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

TABLE 2 Risk Factors for Osteoarthritis

Host Factors		Environmental Factors	
Genetic factors	Familial clustering has also been found at the hip and knee	Biomechanics	Repetitive ergonomic and biomechanical demands may create joint stresses leading to OA Hemiparesis associated with reduction of expression of OA in the affected limb and overexpression in the remaining functional limb Chopstick use associated with OA of the IP joint of the thumb, second and third MCP, and PIP joints
Age	The strongest identifiable risk factor	Trauma	Injuries to the joint, such as dislocations, fractures, ligament ruptures, and meniscal tears
Gender	The age association is strongest in women: Possibly a hormonal influence Hand OA has a peak incidence in menopausal women		
Hormones	Controversial Hand OA has a peak in menopausal women; however, the Chingford and Framingham studies suggested estrogen has protective effect		
Bone mineral density	Negative relationship between bone mineral density and OA at some sites		
BMI	Obesity is strongly associated with the incidence of knee OA Hand OA likely to be related to biomechanical factors		
Joint alignment	Varus deformity of the knee is associated with progressive OA, as is varus/valgus ligamentous instability at the knee joint Developmental problems leading to altered joint biomechanics such as congenital dysplasias		

BMI, Body mass index; *IP,* interphalangeal; *MCP,* metacarpophalangeal joint; *OA,* osteoarthritis; *PIP,* proximal interphalangeal.
Modified from Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

- Loss of function in joints (e.g., loss of dexterity in patients with hand osteoarthritis, with or without significant pain)
- Joint tenderness (Fig. E3), swelling
- Crepitus with motion, pain with range of motion
- Bouchard and Heberden nodes (bony enlargement of the proximal interphalangeal [PIP] and distal interphalangeal [DIP] joints of the hand, respectively) (Fig. E4)

ETIOLOGY

Osteoarthritis is most often primary or idiopathic and can be monoarticular, oligoarticular, or polyarticular. Secondary OA is due to an identifiable condition such as trauma, mechanical abnormalities, or congenital disorders. Risk factors for osteoarthritis are summarized in Table 2. Inflammatory arthritis, crystal deposition diseases, metabolic disorders, Paget disease of bone, and osteonecrosis may also contribute to the development of secondary OA.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bursitis, tendinitis
- Crystal arthropathies like calcium pyrophosphate arthropathy
- Inflammatory arthritis such as rheumatoid arthritis (Fig. E5), seronegative arthritis

WORKUP

- No specific laboratory test exists for osteoarthritis, and investigations are not always needed for the diagnosis of osteoarthritis.
- Rheumatoid factor, ESR, CBC, and antinuclear antibody tests may be required if inflammatory component is suggested by history and are normal in patients with OA.
- Arthrocentesis of swollen joints: Synovial fluid examination is noninflammatory (clear, viscous fluid with normal white cell count).

IMAGING STUDIES

- Plain x-ray of the involved joints is the first step and usually of high diagnostic value
- Radiographic evaluation (Fig. E6) reveals:
  1. Joint space narrowing (Fig. E7)
  2. Subchondral sclerosis
  3. New bone formation in the form of osteophytes
- MRI (Fig. E8) can detect early OA changes and other sources of pain such as synovial thickening, effusions, bone marrow edema, bony attrition, and periarticular lesions
- Musculoskeletal ultrasound (MSKUS) is emerging as an alternative modality to identify joint damage, osteophytes, effusions, and synovial proliferation

Rx TREATMENT

- Optimal use of both pharmacologic and nonpharmacologic measures (Fig. 9) yields best outcome
- Education and reassurance

NONPHARMACOLOGIC THERAPY

HAND OA:

- Joint protection techniques
- Assistive devices
- Thermal modalities
- Trapeziometacarpal splints

HIP AND KNEE OA:

- Weight loss for overweight patients is probably the most crucial recommendation
- Pedometer step-count of more than 10,000 steps per day has been shown to prevent osteoarthritis; a dose-response curve has been noted for this modality with benefits seen at step counts as low as 6000 per day
- Physical therapy includes closed-chain quadriceps strengthening, aerobics, aquatics, and resistance exercises
- Medial wedge insoles for knee valgus, subtalar strapped lateral insoles for varus knees
- Patellar taping
- Hinged and unhinged knee braces, off-loader knee braces
- Assistive devices such as canes or walkers
- Thermal agents
- Tai chi

ACUTE GENERAL Rx/ PHARMACOLOGIC Rx

- Hot or cold fomentation.
- Topical applications of capsaicin or topical application of NSAIDs (diclofenac gel).
- Oral acetaminophen is no longer recommended by American College of Rheumatology or European League against Rheumatism as a first-line analgesic. However, it can be tried for low-grade pain given its relative safety.
- Oral NSAIDs are the first-line analgesics for OA pain. One must consider side effects of NSAIDs, including GI bleeding, cardiovascular toxicity, and renal toxicity. All NSAIDs can increase myocardial infarction risk. Topical NSAIDs are safer than oral NSAIDs.
- Duloxetine if previous initial treatment fails.
- Opioid analgesics including tramadol are recommended only for severe pain that is unresponsive to other treatment modalities.
- Arthrocentesis of the involved joint, followed by intraarticular steroid injection, has

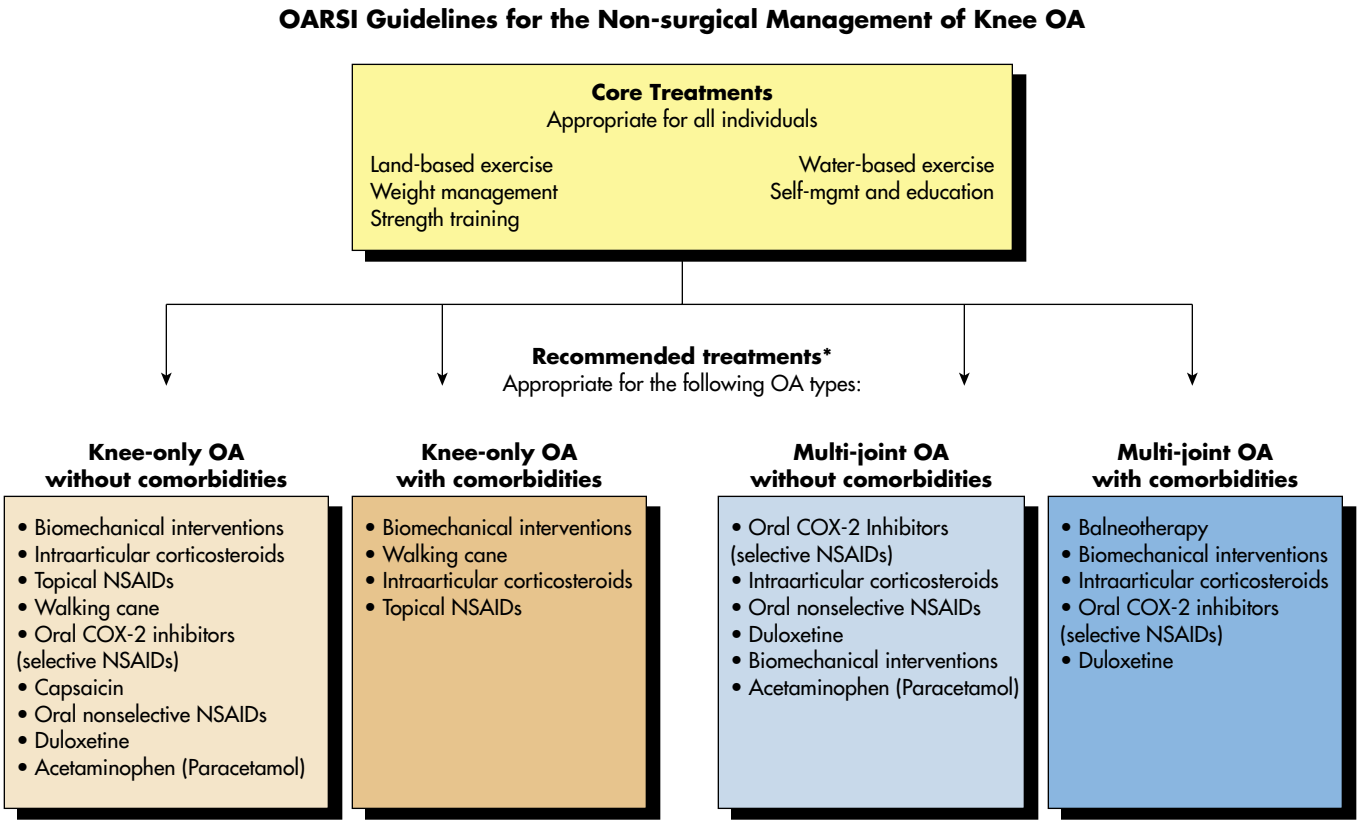

FIG. 9 Appropriate treatments summary. *COX-2,* Cyclooxygenase-2; *NSAID,* nonsteroidal antiinflammatory drug; *OA,* osteoarthritis; *OARSI,* Osteoarthritis Research Society International. (From McAlindon TE et al: OARSI guidelines for the non-surgical management of knee osteoarthritis, *Osteoarthritis Cartilage* 22:363-388, 2014.)

been shown to provide short-term relief of symptoms.

- Nutritional supplements such as glucosamine and chondroitin are unproven. Most trials indicate that neither glucosamine sulfate nor glucosamine hydrochloride reduces pain compared with placebo in knee or hip osteoarthritis. A recent trial did however show modest long-term benefit for physical function with glucosamine sulfate.[1]
- Use of intraarticular hyaluronan injection is controversial. Most trials have shown that hyaluronic acid injections are only minimally better than sham injections in improving pain and function in patients with knee DJD. Positive trials could possibly be influenced by the pharmaceutical industry.

[1]Gregori D et al: Association of pharmacological treatments with long-term pain control in patients with knee osteoarthritis: a systematic review and meta-analysis, *JAMA* 320:2564-2579, 2018.

DISPOSITION

Progression of OA is not always inevitable, and the prognosis is variable depending on the site and extent of disease. Research is currently very active to find other targets to treat OA pain.

REFERRAL

Orthopedic surgical consultation for patients not responding to nonpharmacologic and pharmacologic management. Rheumatology referral could be sought for local injections.

PEARLS & CONSIDERATIONS

COMMENTS

Surgical intervention is generally helpful in degenerative joint disease. Arthroplasty, arthrodesis, and realignment osteotomy are the most common procedures performed. Arthroscopic debridement of the knee appears to be of questionable value. In patients needing hip arthroplasty, resurfacing hip arthroplasty (in which the femoral head is resurfaced with a cap and the neck is preserved) is increasingly popular among younger patients because it results in more hip movement and allows total hip arthroplasty later in the patient's life if necessary.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Osteoarthritis (Patient Information)
Osteoarthritis of the Knee (Patient Information)

AUTHOR: **Deepan S. Dalal, MD, MPH**

SUGGESTED READINGS

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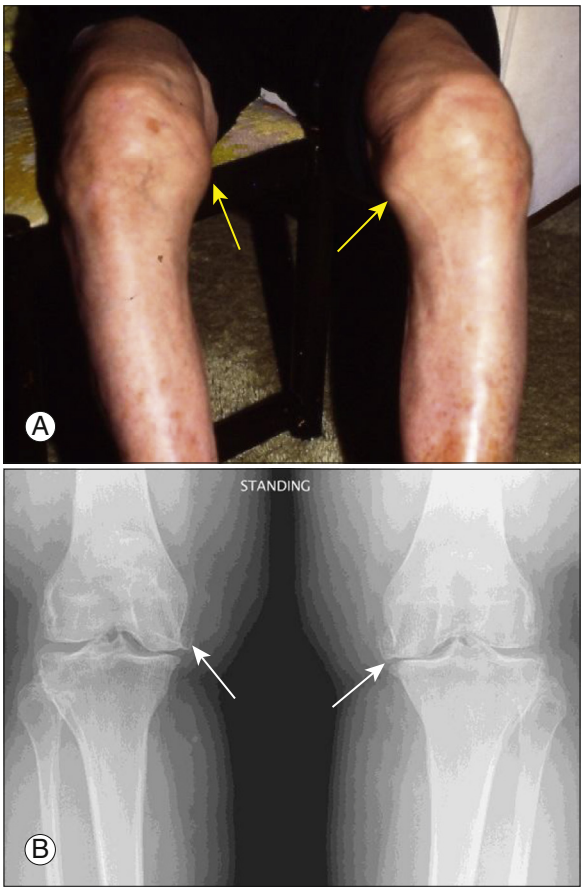

FIG. E2 Osteoarthritis (OA) of the knees. A, Bony prominences caused by osteophytes at the medial joint margins are visible to inspection *(arrows).* **B,** Radiographic appearance of medial osteophytes *(arrows).* Also, characteristic of OA, there is asymmetric narrowing of the joint space; in this case, the medial compartments (adjacent to the *arrows*) are more narrowed than the lateral compartments. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

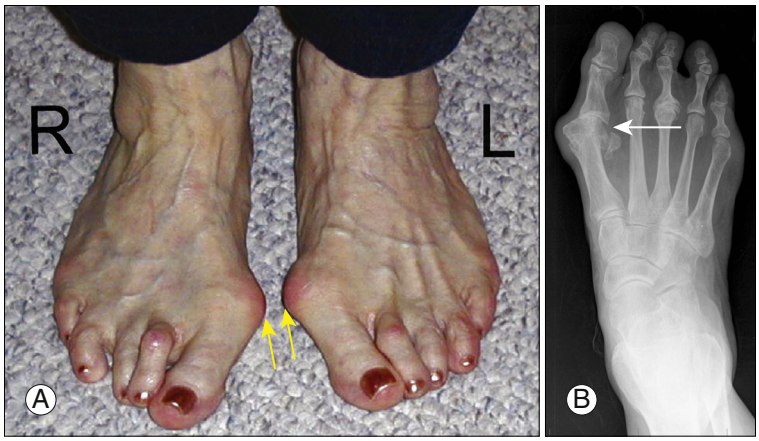

FIG. E3 A, Metatarsophalangeal (MTP) and interphalangeal osteoarthritis (OA) of the feet. There is bilateral enlargement of the first MTP joint *(arrows)*, with medial subluxation of the phalanx (bunion), as well as relaxation of the transtarsal ligament, with medial subluxation of the MTP and bony enlargement of the fifth MTP joints (tailor bunion, bunionette). **B,** Radiographic appearance of first MTP OA with bunion *(arrow).* (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

FIG. E4 The fingers of a patient with primary nodal osteoarthritis of the hands demonstrating Heberden and Bouchard nodes. (Heberden nodes: Posterior lateral swelling of the distal interphalangeal joints. Bouchard nodes: Posterior lateral swelling of the proximal interphalangeal joints.) (From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.)

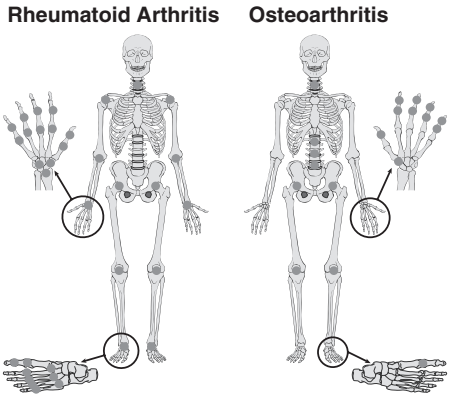

FIG. E5 Distribution of involved joints in the two most common forms of arthritis: Rheumatoid arthritis and osteoarthritis. *Shaded circles* are shown over the involved joint areas. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.)

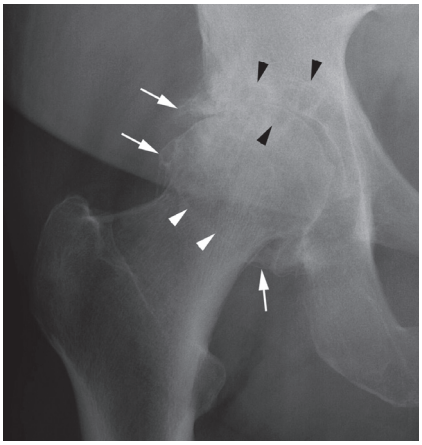

FIG. E7 Severe osteoarthritis of the hip. There is joint space narrowing that has occurred asymmetrically within the joint, in this case affecting the superior joint (the most common pattern of hip involvement). Note also subchondral cyst formation *(black arrowheads)* and osteophytosis *(arrows).* The osteophytes form a rim around the femoral head/neck junction and are superimposed over the neck, visible as a sclerotic line *(white arrowheads),* which should not be mistaken for a fracture. (From Adam A et al: *Grainger and Allison's diagnostic radiology,* ed 6, 2015, Elsevier. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

FIG. E6 Osteoarthritis (degenerative joint disease). A, Primary osteoarthritis of the fingers with characteristic cartilage loss, deviations, and spurs of the proximal (Bouchard nodes) and distal (Heberden nodes) interphalangeal joints. **B,** Primary osteoarthritis of the carpus showing characteristic involvement of the radial side with cartilage loss, subchondral sclerosis, and small spur formation from the base of the first metacarpal to the distal articular surface of the scaphoid. (From Grainger RG, Allison D: *Grainger & Allison's diagnostic radiology: A textbook of medical imaging,* ed 4, London, 2001, Churchill Livingstone.)

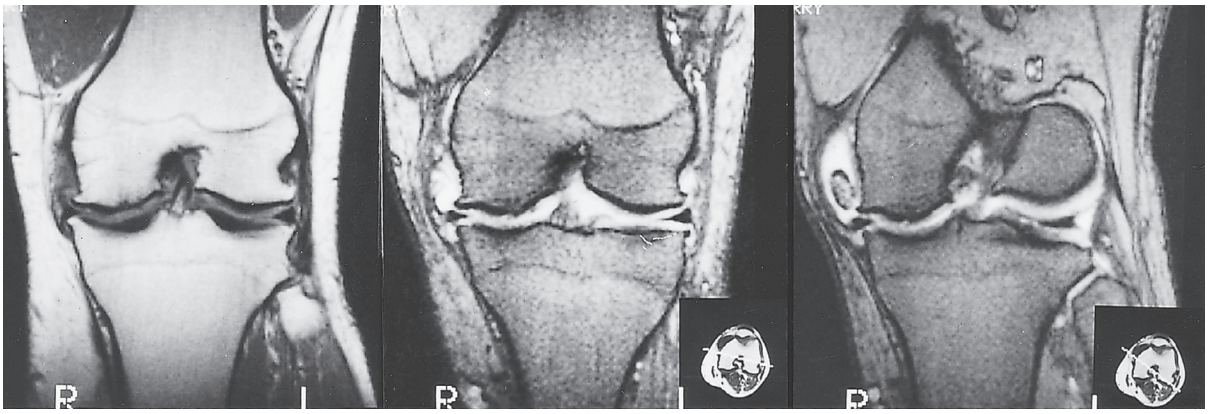

FIG. E8 Osteoarthritis. Magnetic resonance image demonstrates degenerative changes of the knee with an effusion, loss of the medial meniscus, marginal osteophytosis, and a large loose body lying medially within the joint. (From Sutton D: *Textbook of radiology and imaging,* ed 7, 1998, Churchill Livingstone. In Grant, LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Osteochondritis dissecans (OCD) is a relatively common cause of joint pain and dysfunction in the pediatric and young adult population. This pathology results from a localized area of subchondral bone destruction with resultant risk for disruption of the overlying cartilage. OCD is subclassified further into the juvenile form (skeletally immature) and the adult form (skeletally mature). If left untreated, OCD may lead to loose bodies in the joint space and predispose the patient to the early development of osteoarthritis.

SYNONYM

Osteochondrosis

ICD-10CM CODES

M93.20	Osteochondritis dissecans of unspecified site
M93.211	Osteochondritis dissecans, right shoulder
M93.212	Osteochondritis dissecans, left shoulder
M93.219	Osteochondritis dissecans, unspecified shoulder
M93.221	Osteochondritis dissecans, right elbow
M93.222	Osteochondritis dissecans, left elbow
M93.229	Osteochondritis dissecans, unspecified elbow
M93.231	Osteochondritis dissecans, right wrist
M93.232	Osteochondritis dissecans, left wrist
M93.239	Osteochondritis dissecans, unspecified wrist
M93.241	Osteochondritis dissecans, joints of right hand
M93.242	Osteochondritis dissecans, joints of left hand
M93.249	Osteochondritis dissecans, joints of unspecified hand
M93.251	Osteochondritis dissecans, right hip
M93.252	Osteochondritis dissecans, left hip
M93.259	Osteochondritis dissecans, unspecified hip
M93.261	Osteochondritis dissecans, right knee
M93.262	Osteochondritis dissecans, left knee
M93.269	Osteochondritis dissecans, unspecified knee
M93.271	Osteochondritis dissecans, right ankle and joints of right foot
M93.272	Osteochondritis dissecans, left ankle and joints of left foot
M93.279	Osteochondritis dissecans, unspecified ankle and joints of foot
M93.28	Osteochondritis dissecans other site
M93.29	Osteochondritis dissecans multiple sites

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Adolescent Age Group
PREVALENCE: 15 to 29/100,000 persons
PREDOMINANT SEX: Male/female ratio of 2-4:1
PREDOMINANT AGE: Typically between 10 and 20 years of age
GENETICS: While there is emerging evidence that OCD has a genetic component, the genetic basis is still largely unknown.
RISK FACTORS: Repetitive microtrauma, young athletes

CLINICAL PRESENTATION & PHYSICAL FINDINGS

- OCD most commonly affects the knee (75%) followed by the elbow (6%) and the ankle (4%); other joints are affected in 15% of cases.
- Common lesion locations are the medial femoral condyle (see Fig. E2), capitellum of the humerus, and talus.
- Clinical symptoms are variable and nonspecific; early lesions cause poorly localized pain with activity.
- As the disease progresses, stiffness and intermittent swelling may occur.
- In the knees, range of motion typically remains intact.
- If a loose fragment becomes detached, it can cause locking or catching.
- Physical exam reveals tenderness at the site of the lesion; crepitus may also be present.
- When the knee is involved, a positive Wilson sign can sometimes be elicited (pain with knee extension and internal rotation). Antalgic gait and limp can occur in chronic cases.
- Rarely, cases may be asymptomatic.

ETIOLOGY & PATHOPHYSIOLOGY

- While the exact cause of OCD remains unknown, proposed etiologies include mechanical, inflammatory, genetic, and vascular causes. Repetitive microtrauma has gained attention as a leading theory of the most common cause of OCD. The disease process is thought to start with bony injury resulting in hypovascularization, with subsequent defective repair causing necrosis of the bone with structural collapse and detachment of the overlying subchondral bone and cartilage. Given the various proposed theories, the likely etiology of OCD is multifactorial.
- OCD is seen more frequently in children and adolescents and is more commonly associated with repetitive trauma and athletic participation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Knee: Meniscal tear, patellofemoral syndrome, medial plica syndrome, stress fracture
- Elbow: Panner disease, Little League elbow, epicondyle avulsion fracture, epicondylitis
- Ankle: Ankle sprain, os trigonum, tarsal coalition

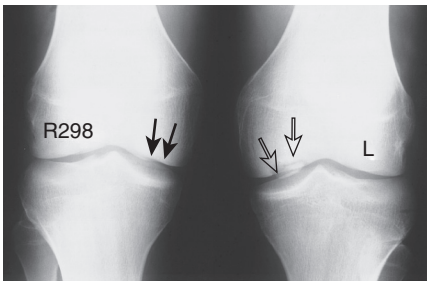

FIG. E1 Bilateral, asymmetrical osteochondritis dissecans with a healed right lesion *(black arrows)* and an unhealed, unstable left lesion (*open arrows*) in a 17-yr-old tennis player. (From DeLee D, Drez D [eds]: *DeLee and Drez's orthopaedic sports medicine,* ed 2, Philadelphia, 2003, Saunders.)

FIG. E2 Osteochondritis dissecans (OCD). A coronal MRI of an OCD lesion of the medial femoral condyle. (From Frontera WR: *Clinical sports medicine: medical management and rehabilitation,* Philadelphia, 2006, Saunders.)

IMAGING STUDIES

- X-rays including weight-bearing films and "tunnel views," where the knee is flexed between 30 and 50 degrees, are the initial test of choice.
- Early small lesions can look normal or can demonstrate subtle increased subchondral bone density.
- The defining lesion of OCD is seen on x-ray as a subchondral bone fragment surrounded by a radiolucent, crescent-shaped line (Fig. E1). Sclerosis on plain radiographs is a sign of a poor prognosis.
- MRI (Fig. E2) is the most sensitive test (91% to 96%) and is useful to identify OCD in symptomatic patients with normal x-rays.
- Contrast is used to evaluate blood supply to the affected fragment and to evaluate stability of the lesion.

TREATMENT

ACUTE GENERAL Rx

- Conservative management: Typically indicated in juvenile OCD without an intraarticular foreign body and in adult patients who have a small, stable fragment or asymptomatic lesion.

- Non–weight-bearing and immobilization for 4 to 6 wk; physical therapy may be initiated once healing starts.
- Surgery: Indicated for juvenile OCD with a loose body and in cases that fail to improve after 4 to 6 mo of conservative management; also indicated in adults with symptomatic OCD.

DISPOSITION & PROGNOSIS

- Office follow-ups are initially frequent, every 2 wk.
- X-ray changes should be monitored every 6 wk while immobilized.
- Return to activity can be attempted once the patient is pain-free and has full, active range of motion; this usually takes 3 to 6 mo.
- Once complete healing occurs, joint function typically returns to normal.
- Complete healing is frequent in skeletally immature children with small lesions (95%), but in adults with larger lesions, complete healing is less common (50%).

REFERRAL

- Orthopedic consultation for most symptomatic children and adults with OCD for staging and management options.
- Surgical options include arthroscopic subchondral drilling, fixation of the unstable fragment with Kirschner wires, osteochondral allograft resurfacing, autologous chondrocyte implantation, or in severe cases, arthroplasty.

PEARLS & CONSIDERATIONS

COMMENTS

- Although inflammation is suggested by the name, ischemia and subchondral bony trauma rather than inflammation have been implicated as the most likely causes of OCD. *Osteochondral lesion* or *osteochondrosis dissecans* may be more appropriate terms to describe these disorders.
- The condition is often bilateral, especially in the knee, which could suggest the possibility of an endocrine or genetic cause.
- The prognosis of OCD in younger patients is better, and an open physis is a predictor of success with nonoperative management.
- This condition should always be considered in the patient whose "sprained" ankle does not improve over the usual course of treatment.

RELATED CONTENT

Osteochondritis Dissecans (Patient Information)

AUTHORS: **Edward J. Testa, MD,** and **Andrew P. Thome, Jr., MD**

SUGGESTED READINGS

Masquijo J, Kothari A: Juvenile osteochondritis dissecans (JOCD) of the knee: Current concepts review, *EFFORT Open Rev* 4(5):201-212, 2019, https://doi.org/10.1302/2058-5241.4180079.

Andriolo L et al: Osteochondritis dissecans of the knee: etiology and pathogenetic mechanisms, *A systematic review, Cartilage* 1:19, 2018.

Edmonds EW, Polousky J: A review of knowledge in osteochondritis dissecans: 123 years of minimal evolution from König to the ROCK Study Group, *Clin Orthop Rel Res* 471:1118-1126, 2012.

Harris SS et al: *Care of the young athlete*, Elk Grove Village, IL, 2017, American Academy of Orthopaedic Surgeons.

Heyworth BE, Kocher MS: Osteochondritis dissecans of the knee, *JBJS Reviews* 3(7), 2015.

BASIC INFORMATION

DEFINITION

Rickets is a result of deficient mineralization of osteoid matrix before closure of the epiphyseal plate causing softening and weakening of bones in infants and children. The mineralization impairment may be secondary to abnormal calcium, phosphorus, or vitamin D metabolism leading to accumulation of osteoid before epiphyseal closure, compromising bone stability at sites of rapid bone growth. When this occurs in adulthood after epiphyseal closure, it is referred to as osteomalacia. Renal osteodystrophy is a term used to describe a similar condition in patients with chronic kidney disease. Certain forms of the disorder may respond only to high doses of vitamin D and are referred to as vitamin D–resistant rickets (VDRR).

ICD-10CM CODES	
E55.0	Rickets, active
E83.30	Disorder of phosphorus metabolism, unspecified
M83.9	Adult osteomalacia, unspecified
N25.0	Renal osteodystrophy

RISK FACTORS

- Children ages 6 to 24 mo
- Premature infants
- Residents of northern latitudes with inadequate sunlight exposure
- Solely breastfed infants
- Darker skin pigmentation
- Use of anticonvulsants

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The classic clinical presentation of children with rickets includes the following:

- Apathy, muscle weakness, muscle cramps, delayed growth, short stature
- Skeletal pain and swollen joints (Figs. E1 and E2)
- Protuberant abdomen due to muscle hypotonia
- Widened sutures, delayed closure of fontanelles, and frontal bossing of head
- Craniotabes (softening of skull bones)
- Delayed eruption of teeth and poorly mineralized teeth
- Bowing deformity of lower extremities, specifically femur and tibia (Fig. E3)
- Table E1 summarizes clinical features of rickets
- Rachitic rosary (enlargement and prominence of the rib head at the costochondral junctions)
- Harrison groove (indentation of the lower ribs)
- Breastbone that is pushed forward (pigeon chest)
- Pathologic fractures
- Scoliosis or kyphosis

The less pronounced clinical presentation of adults with osteomalacia includes the following:

- Skeletal pain and bone tenderness
- Muscle hypotonia and proximal muscle weakness
- Pathologic fractures and decreased bone density
- Gait disturbances

ETIOLOGY

The most common cause of rickets and osteomalacia is vitamin D deficiency. Not having enough calcium and phosphorus intake can also lead to rickets. Vitamin D and PTH play an important role in calcium homeostasis. Vitamin D is required for adequate calcium absorption in the gastrointestinal tract. Low vitamin D leads to a reduced intestinal absorption of calcium, causing a compensatory increase in PTH and resorption of bone, leading to increased alkaline phosphatase levels. This may arise from various conditions, including inadequate dietary intake, malabsorption, chronic parenteral nutrition, and the additional risk factors listed previously. Malabsorption that causes inefficient mineral-

FIG. E1 Rachitic "rosary" in a child with rickets. (Courtesy of Dr. Thomas D. Thacher, Rochester, MN. In Kliegman, RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.)

FIG. E2 Hands and forearms of a young child with rickets show prominence above the wrist, resulting from flaring and poor mineralization of the lower end of the radius and ulna. (From Bullough PG: *Orthopaedic pathology,* ed 5, St Louis, 2010, Mosby, Fig 8-31. In Kliegman, RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.)

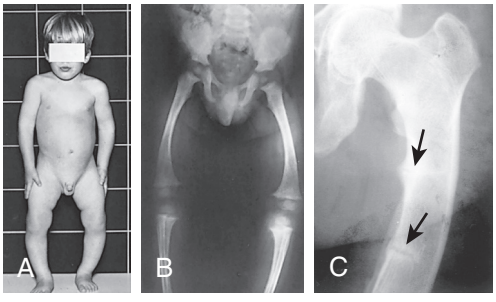

FIG. E3 A, A typical example of rickets. Note the bowing of the femurs and tibiae, which may result from vitamin D deficiency, phosphate deficiency, or other causes. **B,** A skeletal radiograph of a child with rickets. Note that the weight-bearing bones of the lower extremities are bowed and that the epiphyses are open, mottled, and overgrown. **C,** Looser zones or pseudofractures that are characteristic of osteomalacia or rickets. Because the epiphyses are closed, the patient is an adult. This radiograph is diagnostic of osteomalacia. (From Stewart A: Metabolic bone diseases. In Andreoli TE et al [eds]: *Cecil essentials of medicine,* ed 8, Philadelphia, 2010, WB Saunders.)

TABLE E1 Clinical Features of Rickets

General
Failure to thrive (malnutrition)
Listlessness
Protruding abdomen
Muscle weakness (especially proximal)
Hypocalcemic dilated cardiomyopathy
Fractures (pathologic, minimal trauma)
Increased intracranial pressure

Head
Craniotabes
Frontal bossing
Delayed fontanel closure (usually closed by 2 yr)
Delayed dentition
No incisors by age 10 mo
No molars by age 18 mo
Caries
Craniosynostosis

Chest
Rachitic rosary
Harrison groove
Respiratory infections and atelectasis*

Back
Scoliosis
Kyphosis
Lordosis

Extremities
Enlargement of wrists and ankles
Valgus or varus deformities
Windswept deformity (valgus deformity of one leg with varus deformity of other leg)
Anterior bowing of tibia and femur
Coxa vara
Leg pain

Hypocalcemic Symptoms†
Tetany
Seizures
Stridor caused by laryngeal spasm

*These features are associated most frequently with vitamin D deficiency disorders.
†These symptoms develop only in children with disorders that produce hypocalcemia (see Table E3).
From Kliegman RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

ization is observed in diseases such as cystic fibrosis, in intestinal disorders such as celiac disease, and in many chronic illnesses, including severe liver disease. The biochemistry of osteomalacia and rickets is summarized in Table E2. Chronic renal failure can produce bone mineralization deficiency due to electrolyte abnormalities causing hypocalcemia and renal osteodystrophy (renal rickets). This results in decreased excretion of phosphate, therefore elevating serum phosphorus, along with elevated parathyroid hormone (PTH) and low levels of 1,25-OH vitamin D.

Other causes specifically include vitamin D–dependent rickets (VDDR - type I & II) and VDRR, also known as hereditary hypophosphatemic rickets.

- VDDR type I (VDDR-1) results from abnormalities in the vitamin D 1-alpha hydroxylase enzyme that converts to the active metabolite of $1,25(OH)_2D$.
- VDDR type II (VDDR-II), also known as hereditary vitamin-D resistant rickets (HVDRR), results from defective vitamin D receptors due to a mutation in the gene that encodes the vitamin D receptor.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Osteoporosis
- Hyperparathyroidism
- Hyperthyroidism
- Hypophosphatasia
- Skeletal dysplasia

WORKUP

- Rickets is a clinical diagnosis. It is often challenging to determine the exact etiology; however, clinical, biochemical, and radiologic findings can be useful.
- A thorough dietary and medication history for children is important. Bone biopsy is generally not performed; however, it is the diagnostic gold standard.

LABORATORY TESTS

Blood testing should include serum calcium, inorganic phosphorus (Pi), alkaline phosphate, PTH, 25-OH vitamin D, creatinine, and liver enzymes. Table E3 summarizes laboratory findings in various disorders that cause rickets. Children may present solely with an elevated alkaline phosphatase level and characteristic physical findings.

IMAGING STUDIES

- In rickets, characteristic radiologic findings include irregular epiphyseal-metaphyseal junctions with widening and flaring of the epiphyses of long bones, causing bowing.
- Pseudofractures (Looser zones) and narrow radiolucent lines may be seen as a result of microfractures at high stress points or at the location of entry of blood vessels into the bone and are observed in severe rickets and osteomalacia.

Rx TREATMENT

- Treatment is dependent on the underlying etiology; however, high doses of vitamin D resolve most deficiencies. Nutritional deficiency of vitamin D is rare with the amount of vitamin D currently present in milk and dairy products; however, if a deficiency is detected, initial treatment with 2000 IU vitamin D_2 or D_3 daily is recommended, with periodic monitoring of vitamin D levels and dose adjustment as needed to maintain normal levels.
- VDDR type I is treated with both vitamin D and phosphate replacement. The earliest biochemical change after initiation of treatment is an increase in the level of phosphorus followed by a rise in calcium level. Serum calcium, phosphorus, alkaline phosphatase, calcidiol levels, and urine calcium and phosphorus levels should be obtained within 2 wk of initiation of therapy and at periodic intervals thereafter. The treatment of type II VDDR is more complex and requires the expertise of an endocrinologist and/or nephrologist.
- Familial hypophosphatemic rickets is treated with calcitriol and oral phosphorus.
- Oral phosphorus alone is the treatment of choice for hereditary hypophosphatemic rickets with hypercalciuria.

REFERRAL

- Because of the complex nature of many of these disorders, a qualified endocrinologist and nephrologist should be consulted for treatment.
- Orthopedic consultation may be required for some cases of bowlegs or spinal deformities, which may require specific bracing for long-term growth of the bones. Corrective surgery may be necessary if the deformity is very severe.
- Surgical care is also indicated for slipped capital femoral epiphysis, which is fairly common in renal rickets.

RELATED CONTENT

Vitamin D Deficiency (Patient Information)

AUTHOR: **Shefali Majmudar, DO**

SUGGESTED READINGS

Allgrove J, Shaw NJ: A practical approach to vitamin D deficiency and rickets, *Endocr Dev* 28:119-133, 2015.
Munns CF et al: Global consensus recommendations on prevention and management of nutritional rickets, *J Clin Endocrinol Metab* 101(2):394-415, 2016.
Vahed LK et al: The frequency of clinical manifestations of hypophosphatemic rickets in patients with therapeutic strategies, *Clin Pract* 8(2):1072, 2018.

TABLE E2 Biochemistry of Osteomalacia and Rickets

	Ca	PO_4	25(OH)D	1,25(OH)D	PTH	Other
Deficiencies						
Vitamin D deficiency	≈↓ or N	≈↓ or N	↓↓	↑ or N	↑	
Calcium-deficient diet	↓	↓ or N	↓ or N	↑ or N	↑	↑ ALP
Kidney disease	↓	↑	N or ↓	↓ or N	↑ or N	
1α-Hydroxylase deficiency, "vitamin D–dependent rickets" type 1	↓	↓	N	↓↓	↑	↑ ALP
Vitamin D resistance, "vitamin D–dependent rickets type 2"	↓	↓	N	↑↑↑	↑	↑ ALP
Hypophosphatemia						
X-linked hypophosphatemic rickets	N	↓↓	N	↓ or low N	N	↑ FGF-23/phosphatonins ↑ Urine phosphate
Autosomal dominant hypophosphatemic rickets	N	↓↓	N	↓ or low N	N	↑ FGF-23/phosphatonins ↑ Urine phosphate
Autosomal recessive hypophosphatemic rickets	N	↓↓	N	↓ or low N	N	↑ FGF-23/phosphatonins ↑ Urine phosphate
Oncogenic osteomalacia with FGF-23 secretion	N	↓↓	N	↓ or low N	N	↑ FGF-23/phosphatonins ↑ Urine phosphate
"Hereditary hypophosphatemic rickets with hypercalciuria," NaPi2c mutation	N	↓↓	N	↑ or N	N	↑ Urine calcium ↑ Urine phosphate
Renal phosphate loss (including Fanconi syndrome, Dent disease, cadmium toxicity, heavy metal poisoning)	N	↓↓	N	N or low N	N	↑ Urine phosphate ↑ Urine amino acids ↑ Urine bicarbonate ↑ ALP
Toxicities						
Fluoride	N	N	N	N	N	↑ Fluoride in bone biopsy specimens
Etidronate	N or low N	N	N	N	N	
Parenteral aluminum	N	N	N	N or ↓	N or ↑↓	Aluminum-staining bone biopsy specimen
Hypophosphatasia	N	N	N	N	N	↓↓ ALP
Acidosis	N	N	N	N or low N	Low N	↓ Bicarbonate in urine

ALP, Alkaline phosphate; *FGF-23,* fibroblast growth factor 23; *N,* normal; *PTH,* parathyroid hormone.
From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

TABLE E3 Laboratory Findings in Various Disorders Causing Rickets

Disorder	Ca	Pi	PTH	25-(OH)D	1,25-$(OH)_2$D	ALP	Urine Ca	Urine Pi
Vitamin D deficiency	N, ↓	↓	↑	↓	↓, N, ↑	↑	↓	↑
VDDR, type 1A	N, ↓	↓	↑	N	↓	↑	↓	↑
VDDR, type 1B	N, ↓	↓	↑	↓	N	↑	↓	↑
VDDR, type 2A	N, ↓	↓	↑	N	↑↑	↑	↓	↑
VDDR, type 2B	N, ↓	↓	↑	N	↑↑	↑	↓	↑
Chronic kidney disease	N, ↓	↑	↑	N	↓	↑	N, ↓	↓
Dietary Pi deficiency	N	↓	N, ↓	N	↑	↑	↑	↓
XLH*	N	↓	N, ↑	N	RD	↑	↓	↑
ADHR*	N	↓	N	N	RD	↑	↓	↑
HHRH	N	↓	N, ↓	N	↑	↑	↑	↑
ARHR, type 1 or type 2*	N	↓	N	N	RD	↑	↓	↑
Tumor-induced rickets†	N	↓	N	N	RD	↑	↓	↑
Fanconi syndrome	N	↓	N	N	RD or ↑	↑	↓ or ↑	↑
Dent disease	N	↓	N	N	N	↑	↑	↑
Dietary Ca deficiency	N, ↓	↓	↑	N	↑	↑	↓	↑

1,25-$(OH)_2$D, 1,25-dihydroxyvitamin D; *25-OHD*, 25-hydroxyvitamin D; ↓, decreased; ↑, increased; ↑↑, extremely increased; *ADHR*, autosomal dominant hypophosphatemic rickets; *ALP*, alkaline phosphatase; *ARHR*, autosomal recessive hypophosphatemic rickets; *Ca*, calcium; *HHRH*, hereditary hypophosphatemic rickets with hypercalciuria; *N*, normal; *Pi*, inorganic phosphorus; *PTH*, parathyroid hormone; *RD*, relatively decreased (because it should be increased given the concurrent hypophosphatemia); *VDDR*, vitamin D–dependent rickets; *XLH*, X-linked hypophosphatemic rickets.
*Elevated fibroblast growth factor-23 (FGF-23).
†FGF-23 elevated in some patients.
From Kliegman RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

BASIC INFORMATION

DEFINITION

Osteomyelitis is an acute or chronic infection of the bone secondary to the hematogenous or contiguous source of infection or direct traumatic inoculation, which is usually bacterial.

SYNONYM

Bone infection

ICD-10CM CODES

M86	Osteomyelitis
M86.0	Acute hematogenous osteomyelitis
M86.1	Other acute osteomyelitis
M86.2	Subacute osteomyelitis
M86.3	Chronic multifocal osteomyelitis
M86.6	Other chronic osteomyelitis
M86.9	Osteomyelitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: Male > female
PREDOMINANT AGE: All ages

PHYSICAL FINDINGS & CLINICAL PRESENTATION

HEMATOGENOUS OSTEOMYELITIS:

- Usually occurs in tibia/fibula (children)
- Localized inflammation: Often secondary to trauma with accompanying hematoma or cellulitis
- Abrupt fever
- Lethargy
- Irritability
- Pain in involved bone

VERTEBRAL OSTEOMYELITIS:

- Usually hematogenous
- Fever: 50%
- Localized pain/tenderness. Back pain is the most common initial symptom (86% of cases)
- Neurologic defects: Motor/sensory (sensory loss, weakness, radiculopathy)

CONTIGUOUS OSTEOMYELITIS:

- Direct inoculation
- Associated with trauma, fractures, surgical fixation
- Chronic infection of skin/soft tissue
- Fever, drainage from surgical site

CHRONIC OSTEOMYELITIS:

- Bone pain
- Sinus tract drainage, nonhealing ulcer
- Chronic low-grade fever
- Chronic localized pain

ETIOLOGY

- *Staphylococcus aureus*
- MRSA: Methicillin-resistant S. *aureus*
- *Pseudomonas aeruginosa*
- Enterobacteriaceae
- *Streptococcus pyogenes*
- Enterococcus
- Mycobacteria
- Fungi
- Coagulase-negative staphylococci
- *Salmonella* (in sickle cell disease)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gaucher disease
- Bone infarction
- Charcot joint
- Fracture

WORKUP

- ESR, C-reactive protein: Nondiagnostic but if significantly elevated they increase the pretest probability of osteomyelitis and can be useful in monitoring therapeutic response
- Blood culturing, CRC with differential
- Bone culture. A culture of a biopsy specimen has a significantly higher overall diagnostic yield than does a blood culture. Bone samples should be cultured for aerobic and anaerobic bacteria and for fungi
- Pathologic evaluation of bone biopsy for acute/chronic changes consistent with necrosis or acute inflammation
- PCR analysis of specimens obtained by means of biopsy or puncture may be useful for organisms that are difficult to identify (anaerobic bacteria, *Bartonella* sp., *Kingella kingae*); however, broad-range PCR has suboptimal sensitivity and specificity due to contamination and may not provide sufficient information on the susceptibility of the microorganisms to antibiotics

IMAGING STUDIES

- Bone radiograph examination (Fig. E1): Initial study but not sensitive in early osteomyelitis as may not show changes for as much as 2 wks
- MRI with and without contrast (Fig. E2): Most accurate imaging study. CT only if patient has contraindication to MRI
- Triple-phase technetium-99m bone scan (Fig. E3) when MRI is unavailable or contraindicated. Typically positive within a few days after onset of symptoms but accuracy is lower than that of MRI
- Gallium scan (Ga-67) scintigraphy with single-photon emission CT (SPECT) has higher accuracy than bone scan but is less sensitive for detection of epidural abscess in vertebral osteomyelitis
- Indium-111–labeled leukocyte scintigraphy scan; low sensitivity (<20%) for vertebral osteomyelitis
- Positron emission tomography (PET) scanning with ^{18}F-fluorodeoxyglucose has high accuracy (similar to MRI) and is useful in patients with metallic implants
- Table 1 summarizes imaging findings in osteomyelitis

TREATMENT

- Surgical debridement in biopsy-positive cases will guide direction for antibiotic therapy. This will vary with type of osteomyelitis. Duration of therapy is usually 4 to 6 wk for acute osteomyelitis; chronic osteomyelitis may need a longer course of medication
- Orthopedic hardware should be removed if possible
- *S. aureus:* Cefazolin IV, nafcillin IV, vancomycin IV (in patient allergic to penicillin)
- *S. aureus* (methicillin resistant): Vancomycin IV, linezolid, daptomycin
- *Streptococcus* spp.: Ceftriaxone, IV penicillin G in sensitive species
- *P. aeruginosa:* Cefepime, imipenem/cilastatin, or meropenem
- Enterobacteriaceae: Ceftriaxone or ertapenem
- Anaerobes: Clindamycin, ticarcillin clavulanate, cefotetan, or metronidazole
- Table 2 summarizes antimicrobial therapy for selected microorganisms in osteomyelitis
- Hyperbaric oxygen therapy: May be useful in chronic osteomyelitis
- Wound-assisted vacuum device may help closure of wound
- Surgical debridement of all devitalized bone and tissue
- Immobilization of affected bone (plaster, traction) if bone is unstable

DISPOSITION

Acute hematogenous osteomyelitis usually resolves without recurrence or long-term complications, but contiguous focus osteomyelitis, bone infections from open fractures, or osteomyelitis frequently recurs.

REFERRAL

- To an orthopedic surgeon if chronic osteomyelitis with need for bone debridement, bone grafting, or stabilization of infected tissue adjacent to a bone fracture
- To an infectious disease specialist for appropriate treatment for difficult-to-treat or recalcitrant infections
- To a hyperbaric oxygen chamber service for nonhealing, chronic osteomyelitis

PEARLS & CONSIDERATIONS

- Chronic osteomyelitis is one of the most challenging infections to treat; the high failure rate is a consequence of poor vascular supply, nondistensible bone tissue, and limited penetration of bone tissue.
- Parenteral antibiotics are usually chosen initially, but oral fluoroquinolones have good bone penetration and may be used in stable patients. A recent trial comparing oral versus IV antibiotics for bone and joint infections found that oral antibiotic therapy is not inferior to IV antibiotic therapy when used during the first 6 wk for complex orthopedic infections.[1]

[1]Li HK, et al: Oral versus intravenous antibiotics for bone and joint infection, *N Engl J Med* 380(5): 425-436, 2019.

TABLE 1 Imaging Findings in Osteomyelitis

	Plain Radiograph	CT	MRI	NM
Acute	Minimal findings Soft-tissue swelling may be seen	Not useful	Bone marrow edema can occur as early as 24-48 h, seen as low T1, and high T2 signal	May show increased uptake, but takes a few days
Subacute	Lucent or sclerotic lesion, periosteal reaction, soft-tissue swelling	Cortical and marrow abnormalities including abscess, periosteal reaction, soft-tissue edema, and abscess	Bone marrow changes, cortical abnormalities seen as thickening, bone abscess, periosteal reaction, increased T2 signal in soft tissues, abscess formation. Postgadolinium T1W sequences outline abscess cavities clearly	Three-phase bone scintigram, indium-111 WBC scan and combined studies are useful, especially to assess multifocal involvement. PET-CT generally not used in this context, but may be useful in exceptional circumstances
Chronic	Bone sclerosis, cortical thickening, sequestrum and cloaca, bone destruction, resorption, and deformities	Much better than plain radiographs to demonstrate cloaca and sequestrum, periosteal new bone formation, and abscess	Better soft-tissue and bone marrow resolution to demonstrate medullary and cortical changes, sequestra and cloaca well demonstrated, useful to outline soft-tissue abscess, and sinus tracts	Generally useful if there is a problem with diagnosis. Combined WBC and bone marrow scintigram is useful. May highlight multiple sites of involvement

CT, Computed tomography; *MRI,* magnetic resonance imaging; *NM,* nuclear medicine; *PET,* positron emission tomography; *WBC,* white blood cell.
From Grant, LA: *Grainger & Allison's Diagnostic Radiology Essentials*, ed 2, 2019, Elsevier.

TABLE 2 Antimicrobial Therapy for Selected Microorganisms in Chronic Osteomyelitis in Adults

Microorganism	First Choice*	Alternative Choice
Methicillin/oxacillin/nafcillin-sensitive staphylococci	Nafcillin sodium or oxacillin sodium 1.5-2 g IV q4- for 4-6 wk *or* cefazolin 1-2 g IV q8h for 4-6 wk	Vancomycin 15 mg/kg IV q12h for 4-6 wk
Methicillin/oxacillin/nafcillin-resistant staphylococci (MRSA)	Vancomycin† 15 mg/kg IV q12h for 4-6 wk *or* daptomycin 6 mg/kg IV q24h	Linezolid 600 mg PO/IV q12h *or* levofloxacin† 500-750 mg PO/IV daily, plus rifampin 600-900 mg PO for 6 wk if susceptible to both drugs
Penicillin-sensitive streptococci	Aqueous penicillin G 20 × 10^6 U/24 hr IV either continuously or in six equally divided daily doses *or* ceftriaxone 1-2 g IV q24h *or* cefazolin 1-2 g IV q8h for 4-6 wk	Vancomycin 15 mg/kg IV q12h for 4-6 wk
Enterococci	Aqueous crystalline penicillin G 20 × 10^6 U/24 hr IV either continuously or in six equally divided daily doses *or* ampicillin sodium 12 g/24 hr IV either continuously or in six equally divided daily doses; the addition of gentamicin sulfate 1 mg/kg IV or IM q8h for 1-2 wk is *optional*	Vancomycin† 15 mg/kg IV q12h; the addition of gentamicin sulfate 1 mg/kg IV or IM q8h for 1-2 wk is *optional*
Enterobacteriaceae	Ceftriaxone 1-2 g IV q24h for 4-6 wk or ertapenem 1 g IV q24h	Ciprofloxacin 500-750 mg PO q12h for 4-6 wk or levofloxacin 500-750 mg PO q24h
Pseudomonas aeruginosa	Cefepime 2 g IV q12h, meropenem 1 g IV q8h, or imipenem 500 mg IV q6h for 4-6 wk	Ciprofloxacin 750 mg PO q12h for 4-6 wk or ceftazidime 2 g IV q8h

IM, Intramuscular; *IV,* intravenous; *MRSA*, methicillin-resistant *Staphylococcus aureus; PO,* by mouth.
*Antimicrobial selection should be based on in vitro sensitivity data, as well as allergies, intolerances, and drug interactions in individual patients.
†Doses shown are based on normal renal and hepatic function and may need to be adjusted or serum levels monitored (vancomycin).

- The optimal duration of therapy for vertebral osteomyelitis is unclear. Trials comparing 6 wk to 12 wk of antibiotic treatment in pyogenic vertebral osteomyelitis showed similar cure rates (91%) in both groups.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Osteomyelitis (Patient Information)

AUTHORS: **Glenn G. Fort, MD, MPH,** and **Tanya Ali, MD**

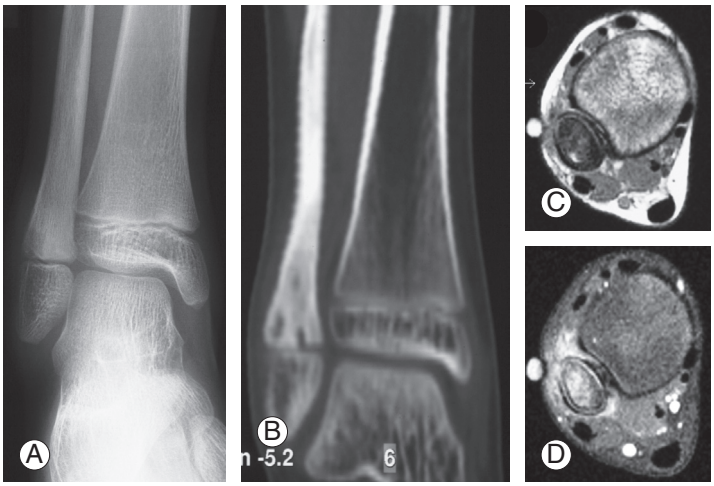

FIG. E1 Acute osteomyelitis. A, Plain radiograph of a child showing ill-defined lucency adjacent to the growth plate of the distal fibula with surrounding sclerosis. **B,** Coronal CT reconstruction demonstrating the lucent areas adjacent to the growth plate with prominent surrounding sclerosis. Axial T1WI **(C)** and T1WI (FS), gadolinium-enhanced **(D)** MR images. The abnormal, infected marrow is of low signal intensity on the T1-weighted pulse sequence. After administration of the gadolinium chelate, osteomyelitis is demonstrated by the high signal-enhancing area adjacent to the growth plate in the distal fibula associated with periosteal new bone formation. (In Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, 2019, Elsevier.)

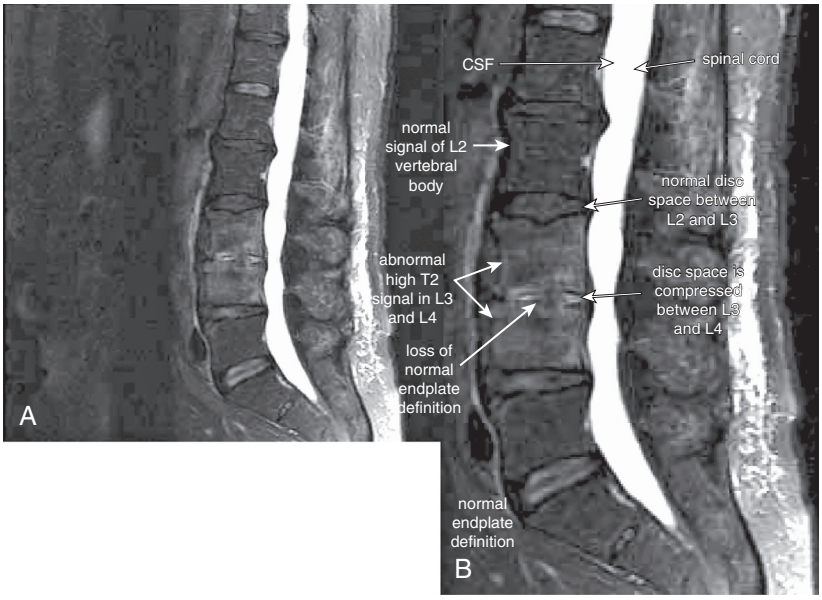

FIG. E2 Osteomyelitis and discitis of L3 and L4. A, T2-weighted fast spin–echo magnetic resonance imaging without contrast demonstrates typical findings of vertebral osteomyelitis and discitis. **B,** Close-up. The inferior endplate of L3 and the superior endplate of L4 are abnormal and ill-defined. The L3 and L4 vertebral bodies show a high T2 signal, indicating an abnormally high fluid content. In comparison, L2 shows a normal marrow signal and appears dark gray due to a normal fat signal. *CSF,* Cerebrospinal fluid. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

FIG. E3 Osteomyelitis. Intense accumulation of Tc-99m white blood cells in proximal phalanx of fifth digit of left foot at 4 hours after injection.

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Osteonecrosis, also known as avascular necrosis (AVN), is ischemic death of bone due to insufficient blood supply. It is not a specific disease entity but a final common pathway to several disorders that impair blood supply to the femoral head and other locations.

SYNONYMS

AVN
Avascular necrosis
Aseptic necrosis

ICD-10CM CODES

M87	Idiopathic aseptic necrosis of bone
M87.1	Osteonecrosis due to drugs
M87.2	Osteonecrosis due to previous trauma
M87.3	Other secondary osteonecrosis
M87.9	Osteonecrosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- 15,000 new cases per yr in the U.S. It is most commonly associated with the hip and accounts for 10% of total hip replacements in the U.S.
- Usually occurs in middle age and is more frequent in males than females
- Associated conditions:
  1. Corticosteroid treatment: 35%
  2. Alcohol abuse: 22%
  3. Idiopathic and other: 43%
  4. Hemoglobinopathies, pancreatitis, chronic renal failure, SLE, chemotherapy, decompression sickness
- Common sites involved
  1. Femoral head
  2. Femoral condyle
  3. Humeral head
  4. Navicular and lunate wrist bones
  5. Talus

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- May be asymptomatic in early stages
- Pain in the involved area exacerbated by movement or weight bearing in later stages
- Decreased range of motion as the disease progresses
- Functional limitation

ETIOLOGY

Final common pathway of conditions that lead to impairment of the blood supply to the involved bone. Trauma disrupting the blood supply is the most common cause of osteonecrosis. Arterial factors are considered the most common cause of osteonecrosis. Table 1 describes proposed mechanism of disease of common conditions associated with osteonecrosis.

STAGING

Tables 2 and 3 and Box 1 illustrate various staging systems for osteonecrosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- None in late stages
- Early: Any condition causing focal musculoskeletal pain, including arthritis, bursitis, tendinitis, myopathy, neoplastic bone and joint diseases, traumatic injuries, pathologic fractures

WORKUP

Fig. 1 describes a diagnostic algorithm for osteonecrosis.

IMAGING STUDIES (FIG. 2)

- MRI: The most sensitive technology to diagnose early aseptic necrosis. The first sign is a margin of low signal. An inner border of high signal associated with a low-signal line is specific for aseptic necrosis ("double line sign"). Sensitivity is 75% to 100%.
- Radiography: Insensitive early in the course. The earliest changes include diffuse osteopenia, areas of radiolucency with sclerotic border, and linear sclerosis. Later, a subchondral lucency (crescent sign) indicates subchondral fracture. More advanced cases reveal flattening, collapsed bone, and abnormal bone contour. In late disease, osteoarthritic changes are seen.
- Bone scan:
  1. Early: "Cold" area
  2. Later: Increased radionuclide uptake as a result of remodeling
  3. Sensitivity in early disease is only 70% and specificity is poor
- CT scan: May reveal central necrosis and area of collapse before those are visible on radiographs.

TREATMENT

PREVENTION

- Manage etiologic conditions
- Minimize corticosteroid use

NONPHARMACOLOGIC THERAPY

- Core decompression: Effectiveness 35% to 95% in early phases
- Bone grafting
- Osteotomies
- Joint replacement

ACUTE GENERAL Rx

- Decrease weight bearing of affected area.
- Pulsing electromagnetic fields applied externally (still experimental).
- Peripheral vasodilators (e.g., dihydroergotamine) (unproven).
- Late-stage AVN is most often treated by total joint arthroplasty.

PROGNOSIS

- When diagnosed at an early stage treatment is appropriate in all cases because 85% to 90% can be expected to progress to a more advanced stage.
- Contralateral joint involvement is common (30% to 70%).

RELATED CONTENT

Avascular Necrosis (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

TABLE 1 Proposed Mechanism of Disease of Common Conditions Associated with Osteonecrosis

	Mechanism of Osteonecrosis							
Associated Condition	**Apoptosis**	**Osteoblast/ Osteoclast Homeostasis**	**Lipid Abnormalities**	**Coagulation Abnormalities**	**Oxidative Stress**	**Parathyroid/ Calcium Imbalance**	**Vascular Plugging**	**Vasoactive Substances**
Corticosteroids	X	X	X	X	X			X
Bisphosphonates	X	X	X					
Alcohol abuse	X	X	X	X	X			
Trauma	X	X						X
Renal transplantation	X	X		X		X		
Dialysis						X		
Sickle cell disease							X	

From Firestein GS et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.

TABLE 2 Ficat Staging System

Stage	Description
I	Normal radiographic findings
II	Sclerotic or cystic lesions
III	Subchondral collapse
IV	Osteoarthritis with articular collapse

From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

TABLE 3 Steinberg Staging System

Stage	Description
I	Normal radiographic findings; abnormal bone scan and/or magnetic resonance imaging findings • Mild (<15% of head affected) • Moderate (15%-30% of head affected) • Severe (>30% of head affected)
II	Lucent and sclerotic changes in the femoral head • Mild (<15% of head affected) • Moderate (15%-30% of head affected) • Severe (>30% of head affected)
III	Subchondral collapse without flattening • Mild (<15% of head affected) • Moderate (15%-30% of head affected) • Severe (>30% of head affected)
IV	Flattening of the femoral head • Mild (<15% of head affected) • Moderate (15%-30% of head affected) • Severe (>30% of head affected)
V	Joint narrowing and/or acetabular changes • Mild • Moderate • Severe
VI	Advanced degenerative changes

From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

BOX 1 International Classification of Osteonecrosis of the Femoral Head (Association Research Circulation Osseous)

- Stage 0: Bone biopsy results consistent with osteonecrosis; other test results normal
- Stage I: Positive findings on bone scan, magnetic resonance imaging (MRI), or both
  - A: <15% involvement of the femoral head (MRI)
  - B: 15% to 30% involvement
  - C: >30% involvement
- Stage II: Mottled appearance of femoral head, osteosclerosis, cyst formation, and osteopenia on radiographs; no signs of collapse of femoral head on radiographic or computed tomographic study; positive findings on bone scan and MRI; no changes in acetabulum
  - A: <15% involvement of the femoral head (MRI)
  - B: 15% to 30% involvement
  - C: >30% involvement
- Stage III: Presence of crescent sign lesions classified on basis of appearance on anteroposterior and lateral radiographs
  - A: <15% crescent sign or <2-mm depression of femoral head
  - B: 15% to 30% crescent sign or 2- to 4-mm depression
  - C: >30% crescent sign or >4-mm depression
- Stage IV: Articular surface flattened; joint space shows narrowing; changes in acetabulum with evidence of osteosclerosis, cyst formation, and marginal osteophytes

From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

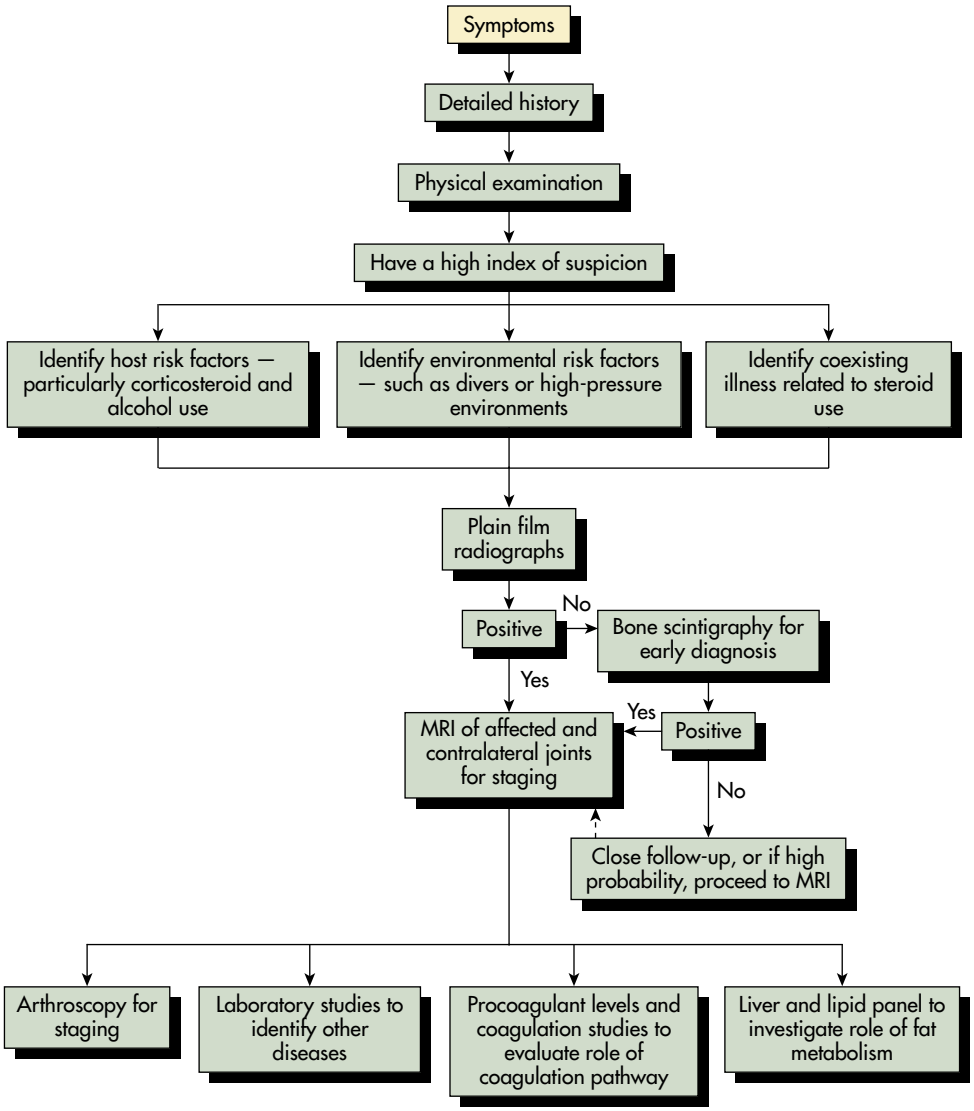


FIG. 1 Diagnostic algorithm for osteonecrosis. *MRI*, Magnetic resonance image. (From Firestein GS et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.)

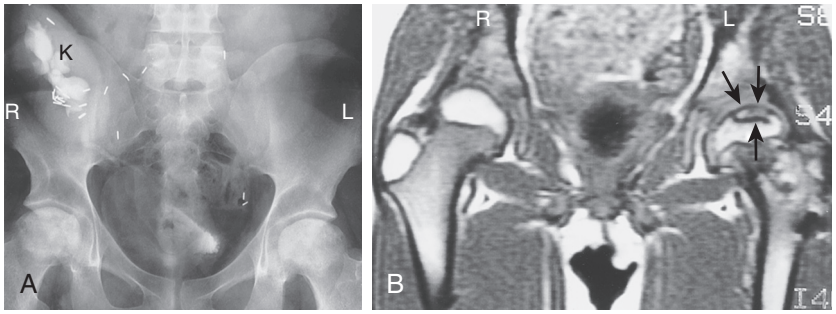


FIG. 2 Aseptic necrosis of the hips. A, Aseptic necrosis can occur from a number of causes, including trauma and steroid use. In this patient, an anteroposterior view of the pelvis shows a transplanted kidney *(K)* in the right iliac fossa. Use of steroids has caused this patient to have bilateral aseptic necrosis. The femoral heads are somewhat flattened, irregular, and increased in density. **B,** Aseptic necrosis in a different patient is demonstrated on an MRI scan as an area of decreased signal *(arrows)* in the left femoral head. This is the most sensitive method for detection of early aseptic necrosis. (From Mettler FA [ed]: *Primary care radiology,* Philadelphia, 2000, Saunders.)

BASIC INFORMATION

DEFINITION

Osteoporosis is a skeletal disorder characterized by a progressive loss of bone mass and a decline in bone quality that results in increased bone fragility and a higher fracture risk. Poor bone mass acquisition during adolescence and bone loss during the sixth decade of life are the main processes responsible for osteoporosis. The various types are as follows:

PRIMARY OSTEOPOROSIS: Primary osteoporosis is the loss of bone mass due to aging and decreased gonadal function, not to any other chronic illness.

- Idiopathic osteoporosis: Unknown pathogenesis; may occur in children and young adults.
- Type I osteoporosis (postmenopausal women): Occurs after menopause due to an abrupt decline in estrogen production. It is characterized by accelerated and disproportionate trabecular bone loss and is associated with fractures of the spine, hip, and wrist.
- Type II osteoporosis (involutional): Occurs in both men and women aged >70 yr due to the progressively negative balance between bone formation and resorption. It is characterized by both trabecular and cortical bone loss and associated with fractures of the spine, long bones, and hip.

SECONDARY OSTEOPOROSIS: Secondary osteoporosis is bone loss due to another chronic condition such as thyroxine excess, hyperparathyroidism, malignancies, gastrointestinal disease, medications, renal failure, and connective tissue diseases (see "Differential Diagnosis").

ICD-10CM CODES

M81.0	Age-related osteoporosis without current pathological fracture
M81.4	Drug-induced osteoporosis
M81.5	Idiopathic osteoporosis
M81.6	Localized osteoporosis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.):

- Affects more than 10 million people in the U.S.
- Annual incidence of osteoporotic fractures exceeds 1.5 million in the U.S. (70% women)
- Twice as common in women
- Results: Institutionalization, death, and costs in excess of $17 billion annually

RISK FACTORS:

- Female sex
- Postmenopausal state
- Advanced age
- Petite body frame, low body weight (<58 kg)
- White or Asian ancestry
- Sedentary lifestyle
- Nulliparity
- Calcium deficiency
- Previous low-trauma fracture
- Parental history of hip fracture
- Tobacco use
- Excess alcohol or caffeine use
- Long-term glucocorticoid use
- Chronic disease states; e.g., primary ovarian insufficiency, diabetes mellitus, androgen deficiency, inflammatory bowel disease, hyperthyroidism, hypercortisolism

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most commonly silent with no signs and symptoms.
- Insidious and progressive development of dorsal kyphosis ***(dowager's hump),*** loss of height, and skeletal pain typically associated with fracture; reduced gait speed or grip strength; other physical findings related to other conditions with associated increased risk for osteoporosis such as nodular thyroid, hepatic enlargement, jaundice, cushingoid features (see "Risk Factors" and Boxes 1 and 2).

ETIOLOGY

Normal bone turnover involves balance between process of bone resorption and bone formation. Osteoclasts resorb bone, and osteoblasts secrete bone matrix for building bone. In postmenopausal women, rate of bone turnover increases after loss of ovarian function, leading to progressive bone loss.

Several fracture risk calculation tools have been developed. FRAX is the leading tool among them. Clinical risk factors used in the World Health Organization Fracture Risk Assessment Tool (WHO FRAX) 10-yr fracture risk calculator are summarized in Box 3.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Malignancy (multiple myeloma, lymphoma, leukemia, metastatic carcinoma)
- Primary hyperparathyroidism
- Osteomalacia
- Paget's disease
- Osteogenesis imperfecta: Types I, III, and IV

WORKUP

- History and physical examination, with appropriate evaluation for identified risk factors and secondary causes. Medications associated with osteoporosis are summarized in

BOX 1 Major Clinical Risk Factors for Osteoporotic Fracture

- Age
- Gender
- Previous fragility fracture
- Glucocorticoid therapy
- History of falls
- Family history of hip fracture
- Other causes of secondary osteoporosis
- Low body mass index
- Smoking
- High alcohol intake

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

BOX 2 Causes of Secondary Osteoporosis

- Endocrine
  1. Hypogonadism in either sex, including untreated, premature menopause and treatment with aromatase inhibitors or androgen deprivation therapy
  2. Hyperthyroidism
  3. Hyperprolactinemia
  4. Cushing disease
  5. Diabetes
- Gastrointestinal
  1. Celiac disease
  2. Inflammatory bowel disease
  3. Chronic liver disease
  4. Chronic pancreatitis
  5. Other causes of malabsorption
- Rheumatologic
  1. Rheumatoid arthritis
  2. Other inflammatory arthropathies
- Hematologic
  1. Multiple myeloma
  2. Hemoglobinopathies
  3. Systemic mastocytosis
  4. Chronic heparin treatment
- Respiratory
  1. Cystic fibrosis
  2. Chronic obstructive pulmonary disease
- Metabolic
  1. Homocystinuria
- Chronic renal disease
- Immobility

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

BOX 3 Clinical Risk Factors Included in the FRAX Case-Finding Algorithm

- Age (50 to 90 yr)
- Sex
- Weight (in kilograms) and height (in centimeters). Body mass index is automatically computed from height and weight
- Previous fragility fracture (yes/no)
- Parental history of hip fracture (yes/no)
- Current tobacco smoking (yes/no)
- Long-term use of oral glucocorticoids (over 3 mo) (yes/no)
- Rheumatoid arthritis (yes/no)
- Alcohol consumption of 3 or more units daily (yes/no)
- Other causes of secondary osteoporosis (yes/no): Includes type I diabetes, osteogenesis imperfecta, longstanding untreated hyperthyroidism, hypogonadism or premature menopause (<45 yr), chronic malnutrition, malabsorption, chronic liver disease.

From World Health Organization. WHO risk fracture assessment tool. www.shef.ac.uk/FRAX.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE 1 Medications Associated with Osteoporosis

System	Medication
Endocrine	Aromatase inhibitors (e.g., anastrozole) Excess thyroxine replacement Glucocorticoids Gonadotropin-releasing hormone agonists Ovarian-suppressing drugs (e.g., medroxyprogesterone acetate) Thiazolidinediones SGLT2 inhibitors
Gastrointestinal	Proton pump inhibitors
Hematologic	Heparin Warfarin
Infectious disease	Antiretroviral therapy
Immunosuppressant	Cyclosporine Cytotoxic drugs Tacrolimus
Neurologic	Anticonvulsants—phenytoin, phenobarbital, carbamazepine
Psychiatric	Selective serotonin reuptake inhibitors
Renal	Loop diuretics (e.g., furosemide)

SGLT2, Sodium-glucose transport protein 2.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

Table 1. Investigations for secondary osteoporosis are summarized in Box E4.

- WHO guidelines for the diagnosis of osteoporosis are based on bone mineral density (BMD) measurements of the hip or spine in g/cm^2 and are reported as a T score.
  1. Dual-energy x-ray absorptiometry (DEXA) is the gold standard for screening and monitoring changes in BMD due to excellent precision, widespread availability, low cost, and minimal radiation exposure.
  2. DEXA (Fig. 1) is indicated in all women 65 yr and older and in postmenopausal women younger than 65 yr of age who are at risk for fracture (e.g., weight <127 lbs, parental history of hip fracture, use of medications that cause bone loss, current smoking, excessive alcohol use (>2 drinks per day), rheumatoid arthritis, or presence of diseases that cause bone loss). Causes of erroneous bone mineral density measures by DEXA in the lumbar spine are summarized in Table 2.
  3. FRAX questionnaire (Fig. 2): Use of FRAX calculator (https://shelf.ac.uk/FRAX/) is proposed by the U.S. Preventive Services Task Force (USPSTF) to determine the need for screening in women between the ages of 50 and 64. If the FRAX 10-yr major osteoporotic risk is greater than or equal to 9.3%, the USPSTF recommends screening with DEXA scan.
  4. Currently, routine testing in men for osteoporosis is not recommended unless there are clinical manifestations of low bone mass.
  5. Quantitative ultrasound can be used as an adjunctive tool to predict risk of fracture in both men and women. It is cheaper than DEXA and has no radiation. However, at this point, additional research and trials are needed to establish its utility in diagnosis and management of osteoporosis.
- Recommendations as to when to repeat bone density testing should be based on initial T scores (Fig. 3). Data from the Study of Osteoporotic Fractures indicates that in women with normal bone density or mild osteopenia, repeat testing might not be necessary for another 10 to 15 yr. For women with moderate osteopenia, a screening interval of 3 to 5 yr may be appropriate. For women with advanced bone loss/osteoporosis, testing every 1-2 yr is recommended.

LABORATORY TESTS (BOX 5)

- Biochemical profile to evaluate renal and hepatic function, primary hyperparathyroidism, and malnutrition.
- CBC: For nutritional status and myeloma.
- TSH to rule out the presence of hyperthyroidism.
- 24-hour urinary calcium levels and 26-hydroxyvitamin D level may be helpful in evaluating for secondary causes of osteoporosis.
- May consider celiac panel and serum protein electrophoresis. Biochemical markers of bone remodeling may be useful to predict rate of bone loss and/or follow therapy response. Specific biochemical markers are followed (e.g., 3-mo interval) to document normalization as a response to therapy.
  1. High-turnover osteoporosis: High levels of resorption markers (lysyl pyridinoline, deoxy lysyl pyridinoline, n-telopeptide of collagen cross-links, C-telopeptide of collagen cross-links) and formation markers (osteocalcin and bone-specific alkaline phosphatase); accelerated bone loss responding best to antiresorptive therapy.
  2. Low-normal-turnover osteoporosis: Normal or low levels of the markers of resorption and formation (see "high-turnover osteoporosis" listed previously); no accelerated bone loss; responds best to drugs that enhance bone formation.

IMAGING STUDIES

- BMD determination (see "Workup") should be performed on all women with determined risk factors and/or associated secondary causes; criteria for diagnosis of osteoporosis based on measurement of bone density and T score equivalent cut points are summarized in Table 3.
  1. Normal: BMD <1 SD of the young adult reference mean
  2. Osteopenia: BMD 1 to 2.5 SD below the young adult reference mean
  3. Osteoporosis: BMD >2.5 SD below the young adult reference mean
- For patient undergoing treatment: The frequency of BMD monitoring is controversial and many experts recommend that clinicians should not monitor BMD during the initial 5-yr drug treatment period because no studies have proven that such monitoring improves fracture outcomes.
- X-ray exam of appropriate part of skeleton (Figs. E4 and E5) to evaluate clinical osteoporotic fracture only.

Rx TREATMENT

When to treat:

- Osteoporosis based on DEXA measurements of BMD
- History of hip and vertebral fracture
- Osteopenia on DEXA + 10-yr FRAX score of greater than or equal to 3% at hip or greater than or equal to 20% of major osteoporotic fracture

NONPHARMACOLOGIC THERAPY

Prevention:

- Identification and minimization of risk factors
- Appropriate diagnosis and treatment of secondary causes
- Behavioral modification: Proper nutrition, physical activity, fracture prevention strategies

ACUTE GENERAL Rx

- Vitamin D supplement: 600 IU/day for persons 19 to 70 yr of age and 800 IU/day for persons 71 yr and older. Recommended supplementation of calcium and vitamin D is summarized in Table 4.
- Calcium supplement: The recommended dietary intake of calcium for women 19 to 50 yr of age and men 19 to 70 yr of age is 1000 mg/day; women older than age 50 and men older than age 70 require 1200 mg/day. Calcium intake above 2500 mg/day (2000 mg/day in persons >50 yr of age) should be avoided. Consumption of calcium-rich foods and beverages is the preferred approach to ensuring adequate calcium intake.[1]
- Oral bisphosphonates (alendronate, risedronate): Decrease bone resorption by attenuating osteoclast activity. They are first-line therapy for the treatment of most patients with osteoporosis, with proven efficacy to reduce fracture risk. The bisphosphonates

[1]Bauer DC: Calcium supplements and fracture prevention, *N Engl J Med* 369:1537-1543, 2013.

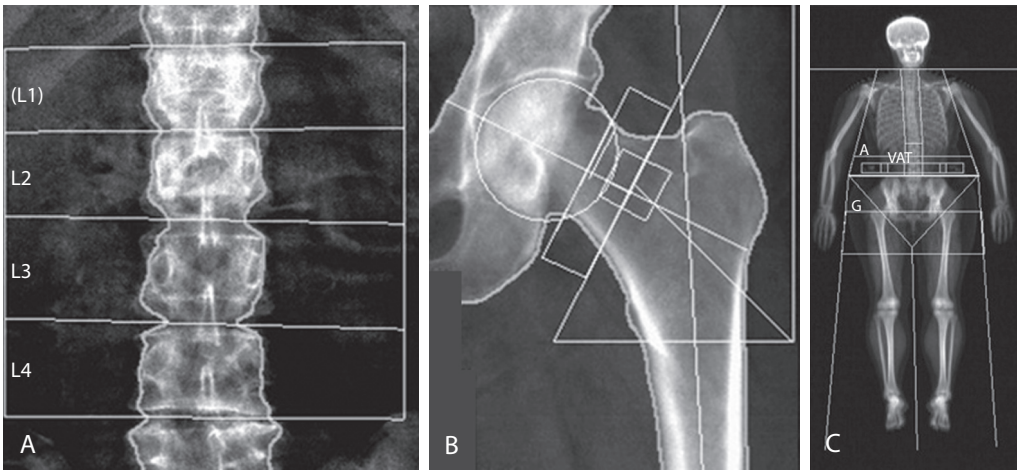


FIG. 1 Dual-energy x-ray absorptiometry (DEXA) provides "areal" bone mineral density (BMD) (g/cm^2) and is currently the gold standard for diagnosis of osteoporosis by bone densitometry (World Health Organization definition T score –2.5 or below) in **(A)** posteroanterior lumbar spine *(L1 through L4)* or **(B)** hip (femoral neck or total). **C,** DEXA of the whole body can provide information on total and regional BMD and body composition (fat and muscle mass). Recent additional parameters measured are android *A*/gynoid *G* ratio and visceral adipose tissue *(VAT).* (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2014, WB Saunders.)

TABLE 2 Causes of Erroneous Bone Mineral Density Measures by DEXA in the Lumbar Spine

Overestimation of Bone Mineral Density
Extraneous calcification (lymph nodes, aorta)
Degenerative disk and spine disease (osteophytes)
Ankylosing spondylitis
Vertebral fracture
Sclerotic metastases
Vertebral hemangioma
Overlying metal artifacts (navel rings)
Surgical interventions (metallic rods, spinal fusion)
Vertebroplasty
Paget disease
Treatment with strontium ranelate
Underestimation of Bone Mineral Density
Laminectomy

DEXA, Dual-energy x-ray absorptiometry.
From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2014, WB Saunders.

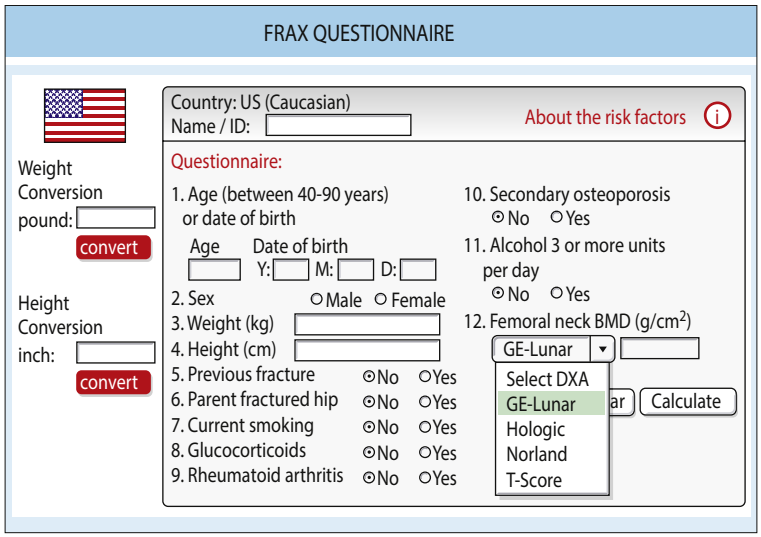
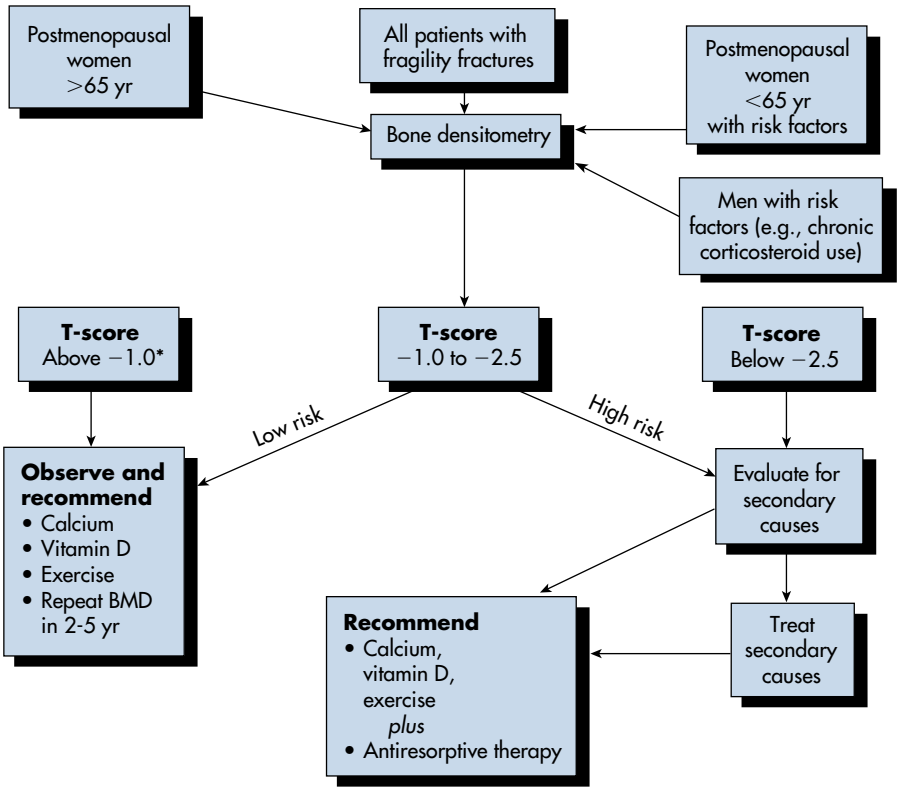


FIG. 2 FRAX questionnaire. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

differ in binding affinity, dose frequency, and route of administration. To facilitate absorption, most oral bisphosphonates are taken on an empty stomach with a full glass of water. Patients are instructed to remain in a sitting or standing position for 30 to 60 min. Contraindications include esophageal disorders, inability to remain standing for 30 to 60 min after taking the medication, chronic kidney disease, and Roux-en-Y gastric bypass procedures. Adverse side effects include gastroesophageal reflux disease, esophagitis, transient hypocalcemia, musculoskeletal pain, renal impairment, ocular side effects, jaw necrosis, and atypical femur fracture. Zoledronic acid: A bisphosphonate given by IV infusion over at least 15 min, 5 mg once/yr may be used in patients who are unable to tolerate oral bisphosphonates. It is contraindicated in patients with acute renal failure.

- Biologic agents: Denosumab is a human monoclonal antibody that inhibits osteoclast formation and prevents resorption for treatment of postmenopausal osteoporosis. Dosage is 60 mg subcutaneously every 6 mo. Romosozumab is a monoclonal antibody that increases bone formation and decreases bone resorption by binding to sclerostin. It may be considered for patients who are at high risk for fracture and cannot tolerate any other osteoporotic therapies. Dosage is two consecutive subcutaneous injections (105 mg each) for a total dose of 210 mg once monthly. It should not be used in patients who have had a myocardial infarction or stroke in the past yr.
- Teriparatide is a recombinant human parathyroid hormone used for postmenopausal women with osteoporosis who are at high risk for fracture, especially vertebral fractures. It is also used in men with primary or hypogonadal osteoporosis who are at high risk of fracture. It is administered by injection 20 mcg qd SC into the thigh or abdominal wall. Use for >2 yr is not recommended. It stimulates bone formation and reduces the risk of fracture but may increase the risk of stroke in older women with osteoporosis. Common side effects include headaches,



*Patients with fragility fractures and a T-score above −1.0 should be evaluated for other causes of pathologic fracture.

FIG. 3 Diagnosis and management of osteoporosis.

BOX 5 Recommended Laboratory Investigations for Individuals with Osteoporosis

Recommended screening in all patients
Serum calcium, albumin, phosphorus*,†,‡,§
Serum creatinine*,†,‡,§
Liver function tests*
Bicarbonate*
Complete blood count*
24-hour urinary calcium level*,†,‡,§
25-hydroxyvitamin D level*,†,‡,§
Thyroid-stimulating hormone level*,†,‡,§

Other testing, if appropriate
Biochemical markers of bone turnover*,†,‡,§
Cortisol levels*,‡
Protein electrophoresis*,†,§
Parathyroid hormone level*,§

*American Association of Clinical Endocrinologists guidelines.
†National Osteoporosis Foundation Physician's Guide.
‡U.S. Surgeon General's report.
§American College of Obstetricians and Gynecologists.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE 3 Diagnostic Categories for Osteoporosis Based on World Health Organization Criteria

Category	Definition
Normal	BMD not more than 1 SD below the young adult mean value
Low bone mass (osteopenia)	BMD lying between 1 and 2.5 SD below the young adult mean value
Osteoporosis	BMD more than 2.5 SD below the young adult mean value

BMD, Bone mineral density; *SD,* standard deviation.
From World Health Organization data, 1994. In Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE 4 Recommended Supplementation of Calcium and Vitamin D

Individual Age Categories	Elemental Calcium	Vitamin D*
Birth-6 mo	400 mg	200 IU
6-12 mo	600 mg	200 IU
1-10 yr	800 mg	200 IU
11-24 yr	1200-1500 mg/day	400 IU
Women and men 25-65 yr: Premenopausal or postmenopausal women taking estrogen	1000 mg/day	400-600 IU
Postmenopausal women, no estrogen	1500 mg/day	400-600 IU for men and women >65 yr
Pregnant and lactating women	1200-1500 mg/day	400 IU
National Osteoporosis Foundation guidelines	1200 mg	800-1000 IU

*These recommendations are guidelines and may be sufficient for healthy individuals with normal 25-hydroxyvitamin D levels. In many circumstances, however, they are insufficient.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

myalgia, hypercalcemia, and hypercalciuria. Trials involving abaloparatide, a selective activator of the parathyroid hormone type 1 receptor have also shown reduced risk of new vertebral and nonvertebral fractures in postmenopausal women with osteoporosis.
- Estrogen prescription drugs or raloxifene should not be prescribed to treat women with osteoporosis.

CHRONIC Rx

- Lifelong attention to behavior modification issues (nutrition, physical activity, fracture prevention strategies) and compliance with pharmacologic intervention. Recommendations include weight-bearing and muscle-strengthening exercises, smoking cessation, reduced alcohol intake, and adoption of fall prevention strategies.
- There is little evidence to guide physicians about long-term bisphosphonate therapy. The decision to continue drug therapy beyond 5 yr should reflect reassessment of risk and benefit. The risk of atypical fracture of the femur increases after 5 yr of bisphosphonate use. It is reasonable to consider a drug holiday in postmenopausal women who are not at high fracture risk after 3 yr (IV) to 5 yr (oral) of bisphosphonate therapy. Continued treatment may be advisable in those at highest risk.
- Continuing need to eliminate high-risk factors when possible and to optimally manage secondary causes of osteoporosis.

DISPOSITION

Goals for diagnosis and treatment include identification of women at risk; initiation of preventive measures for all women lifelong; institution of treatment modalities that will result in a decrease in fracture risk; and reduction of morbidity, mortality, and unnecessary institutionalization, thereby improving quality of independent life and productivity. Table E5 summarizes the effect of major treatment options on the risk of vertebral, nonvertebral, and hip fractures.

REFERRAL

- To reproductive endocrinologist, medical endocrinologist, gynecologist, or rheumatologist if unfamiliar with diagnosis and management of osteoporosis
- If multidisciplinary management is required, to other specialties depending on presence of acute fracture and/or secondary associated disorders

PEARLS & CONSIDERATIONS

COMMENTS

- Osteonecrosis of the jaw is a known complication of high-dose IV bisphosphonate therapy for cancer; however, there is considerable debate on whether low-dose bisphosphonates used for osteoporosis can also cause this disorder. Evidence for this is inconclusive.
- Long-term use (>10 yr) of bisphosphonates has been reported to increase risk of atypical subtrochanteric or femoral shaft fractures in several uncontrolled case series. Prodromal symptoms of thigh pain, lack of trauma prior to the procedure, and specific radiologic characteristics (cortical thickening) have been reported. The evidence remains inconclusive. Patients can be reassured that short or intermediate use of bisphosphonates does not increase the risk of atypical femoral fractures. Current strategies should include considering a 12-mo interruption in therapy after 5 yr in patients who are clinically stable and considering teriparatide treatment in individuals who experience an atypical fracture while receiving bisphosphonate therapy.
- Increased risk of esophageal cancer and atrial fibrillation have been reported as possible adverse effects of bisphosphonate therapy.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Osteoporosis (Patient Information)
Medication-Related Osteonecrosis of the Jaw (Related Key Topic)
Vertebral Compression Fractures (Related Key Topic)

AUTHORS: **Emily E. Nuss, MD,** and **Rachel Wright Heinle, MD, FACOG**

SUGGESTED READINGS

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BOX E4 Investigations for Secondary Osteoporosis in Older People with Low Trauma Fractures or Low Bone Mineral Density

- Full blood count
- ESR or CRP
- Biochemical profile: Including renal function, adjusted serum calcium, and alkaline phosphatase
- Thyroid function tests
- Consider serum testosterone, sex hormone–binding globulin, LH, FSH (men)
- Serum and urine electrophoresis (vertebral fractures)
- Serum 25OHD and PTH

CRP, C-reactive protein; *ESR,* erythrocyte sedimentation rate; *FSH,* follicle-stimulating hormone; *LH*, luteinizing hormone; *PTH,* parathyroid hormone; *25OHD,* 25 hydroxyvitamin.
From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

FIG. E4 Regional osteoporosis. Hand radiograph in early rheumatoid arthritis (RA) shows periarticular osteopenia at the metacarpophalangeal and interphalangeal joints, with joint space narrowing and juxta-articular erosions. The periarticular osteopenia is the earliest radiographic feature of RA and is related to hyperemia, synovial inflammation, and local cytokines that stimulate osteoclastic bone resorption. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, WB Saunders.)

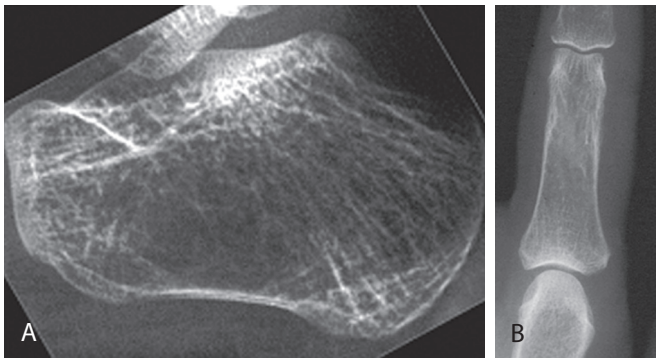

FIG. E5 General osteoporosis. Radiographic features include reduced radiographic density (osteopenia) with reduction in the number of trabeculae, which may be destroyed completely, and the bone cortex becomes thinned as evident in the lateral radiograph of the calcaneus **(A)** and radiograph of the phalanx **(B).** When these features are present, bone densitometry using dual-energy x-ray absorptiometry (DEXA) should be suggested. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, WB Saunders.)

TABLE E5 Effect of Major Treatment Options on the Risk of Vertebral, Nonvertebral, and Hip Fractures

	Vertebral Fractures	Nonvertebral Fractures	Hip Fractures
Alendronate	A	A	A
Etidronate	A	ND	ND
Risedronate	A	A	A
Raloxifene	A	ND	ND
Strontium ranelate	A	A	(A)
Teriparatide	A	A	ND
Denosumab	A	A	A
Zoledronate*	A	A	A
Ibandronate*	A	(A)	ND
Calcium and vitamin D*	ND	A	A

A indicates evidence from randomized, controlled trials and/or meta-analysis; (A) reflects that a beneficial effect on fracture risk was found only in post hoc subgroup analysis; ND indicates that fracture reduction has not been demonstrated.
*Not included in current National Institute for Health and Clinical Excellence (NICE) guidance.
From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, 2017, Elsevier.

BASIC INFORMATION

DEFINITION

Otitis externa refers to a variety of conditions causing inflammation and/or infection of the external auditory canal (and/or auricle and tympanic membrane). There are six subgroups of otitis externa:

1. Acute localized otitis externa (furunculosis)
2. Acute diffuse bacterial otitis externa (i.e., "swimmer ear")
3. Chronic otitis externa
4. Eczematous otitis externa
5. Fungal otitis externa (otomycosis)
6. Invasive or necrotizing (malignant) otitis externa

SYNONYMS

See "Definition."

ICD-10CM CODES

H60.90	Unspecified otitis externa, unspecified ear
H60.2	Malignant otitis externa
H60.3	Other infective otitis externa
H60.5	Acute otitis externa, non-infective
H60.8	Other otitis externa

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Among the most common disorders
- An estimated 10% of people develop external otitis during their lifetime
- Affects 3% to 10% of patients seeking otologic care

PREVALENCE (IN U.S.):

- Diffuse otitis externa is most often seen in swimmers and in hot, humid climates, conditions that lead to water retention in the ear canal. In the U.S., 44% of AOE-related healthcare visits occur June to August.
- Necrotizing otitis externa is more common in elderly, diabetics, and immunocompromised patients.

PREDOMINANT SEX: None

PREDOMINANT AGE:

- Occurs at all ages, however incidence is highest during childhood and decreases with age
- Necrotizing otitis externa: Typically occurs in elderly: Mean age >65 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The two most common symptoms are otalgia, ranging from pruritus to severe pain exacerbated by motion (e.g., chewing), and otorrhea. Patients may also experience aural fullness and hearing loss as a result of swelling with occlusion of the canal. More intense symptoms may occur with bacterial otitis externa, with or without fever, and lymphadenopathy (anterior to tragus). Findings unique to specific forms of the infection include:

- Acute localized otitis externa (furunculosis):
  1. Occurs from infected hair follicles, usually in the outer third of the ear canal, forming pustules and furuncles
  2. Furuncles are superficial and pointing or deep and diffuse
- Impetigo:
  1. In contrast to furunculosis, this is a superficial spreading infection of the ear canal that may also involve the concha and the auricle
  2. Begins as a small blister that ruptures, releasing straw-colored fluid that dries as a golden crust
- Erysipelas:
  1. Caused by group A streptococcus (*Streptococcus pyogenes*, GAS)
  2. May involve the concha and canal
  3. May involve the dermis and deeper tissues
  4. Area of cellulitis, often with severe pain
  5. Fever, chills, malaise
  6. Regional adenopathy
- Eczematous or seborrheic otitis externa:
  1. Stems from a variety of dermatologic problems that can involve the external auditory canal
  2. Severe itching, erythema, scaling, crusting (Fig.E1), and fissuring possible
- Acute diffuse otitis externa (swimmer ear):
  1. Begins with itching and a feeling of pressure and fullness in the ear that becomes increasingly tender and painful
  2. Mild erythema and edema of the external auditory canal, which may cause narrowing and occlusion of the canal (Fig.E2), leading to hearing loss
  3. Minimal serous secretions, which may become profuse and purulent
  4. Tympanic membrane may appear dull and infected
  5. Usually absence of systemic symptoms such as fever, chills
- Otomycosis:
  1. Chronic superficial infection of the ear canal and tympanic membrane
  2. In primary fungal infection, major symptom is intense itching
  3. In secondary infection (fungal infection superimposed on bacterial infection), major symptom is pain
  4. Fungal growth of variety of colors
- Chronic otitis externa:
  1. Dry and atrophic canal
  2. Typically lack of cerumen
  3. Itching, often severe, and mild discomfort rather than pain
  4. Occasionally mucopurulent discharge
  5. With time, thickening of the walls of the canal, causing narrowing of the lumen
- Necrotizing otitis externa (also known as malignant otitis externa). Typically seen in older patients with diabetes or in patients who are immunocompromised
  1. Redness, swelling, and tenderness of the ear canal
  2. Classic finding of granulation tissue on the floor of the canal and the bone–cartilage junction
  3. Small ulceration of necrotic soft tissue at bone–cartilage junction
  4. Most common symptoms: Pain (often severe) and otorrhea
  5. Lessening of purulent drainage as infection advances
  6. As the infection advances, osteomyelitis of the base of the skull and temporomandibular joint osteomyelitis can develop
  7. Facial nerve palsy often the first and only cranial nerve defect
  8. Possible involvement of other cranial nerves

ETIOLOGY

- Box 1 summarizes common pathogens in otitis externa
- Acute localized otitis externa: *Staphylococcus aureus*
- Impetigo:
  1. *S. aureus* including MRSA
  2. *Streptococcus pyogenes* (GAS)
- Erysipelas: GAS
- Eczematous otitis externa:
  1. Seborrheic dermatitis
  2. Atopic dermatitis
  3. Psoriasis
  4. Neurodermatitis
  5. Lupus erythematosus
- Acute diffuse otitis externa:
  1. Swimming
  2. Hot, humid climates
  3. Tightly fitting hearing aids
  4. Use of ear plugs
  5. *Pseudomonas aeruginosa*
  6. *S. aureus* including MRSA
- Otomycosis:
  1. Prolonged use of topical antibiotics and steroid preparations
  2. Uncontrolled diabetes mellitus can contribute to risk
  3. *Aspergillus* (80% to 90%)
  4. *Candida*
- Chronic otitis externa: Persistent low-grade infection and inflammation
- Necrotizing otitis externa (NOE):

BOX 1 Common Pathogens in Otitis Externa

Gram-negative Organisms
Pseudomonas aeruginosa
Pseudomonas spp. Nov. "otitidis"
Proteus mirabilis
Serratia marcescens

Gram-positive Organisms
Staphylococcus aureus
Staphylococcus epidermidis
Corynebacterium auris
Enterococcus faecalis

Fungi and Yeasts
Aspergillus fumigatus
Candida albicans
Candida parapsilosis

From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.

1. Complication of persistent otitis externa
2. Extends through Santorini fissures, small apertures at the bone-cartilage junction of the canal, into the mastoid and along the base of the skull
3. *P. aeruginosa*

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute otitis media
- Bullous myringitis
- Mastoiditis
- Foreign bodies
- Neoplasms
- Contact dermatitis
- Eczema
- Ramsey-Hunt syndrome
- Seborrhea
- Otomycosis
- Referred pain
- Table 1 describes the differential diagnosis of painful external ear and auditory canal disorders.

WORKUP

Thorough history and physical examination

LABORATORY TESTS

- Cultures from the canal are usually not necessary unless the condition does not respond to treatment.
- Leukocyte count normal or mildly elevated.
- Erythrocyte sedimentation rate is often quite elevated in malignant otitis externa.

IMAGING STUDIES

- CT scan is the best technique for defining bone involvement and extent of disease in malignant otitis externa.
- MRI is slightly more sensitive in evaluation of soft tissue changes and intracranial extension of infection.
- Gallium scans are more specific than bone scans in diagnosing NOE.
- Follow-up scans are helpful in determining efficacy of treatment. NOTE: Expert opinion supports history and physical examination as the best means of diagnosis. Persistent pain that is constant and severe should raise the question of NOE (particularly in the elderly, diabetics, and immunocompromised patients).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Cleansing and debridement of the ear canal with cotton swabs and hydrogen peroxide or other antiseptic solution allows a more thorough examination of the ear.
- If the canal lumen is edematous and too narrow to allow adequate cleansing, a cotton wick or gauze strip inserted into the canal serves as a conduit for topical medications to be drawn into the canal. Usually remove wick after 2 days.
- Local heat is useful in treating deep furunculosis.
- Incision and drainage is indicated in treatment of superficial pointing furunculosis.

ACUTE GENERAL Rx

Topical medications:

- An acidifying agent such as 2% acetic acid (Vosol) inhibits growth of bacteria and fungi
- Topical antibiotics (in the form of otic or ophthalmic solutions) or antifungals, often in combination with an acidifying agent and a steroid preparation. Direct application of topical agents to the infected site is a key element in the treatment of external otitis regardless of severity. Proper installation of eardrops entails tilting the head toward the opposite shoulder, pulling the superior aspect of the auricle upward, and filling the ear canal with drops. In young children, the earlobe should be pulled downward to fill the canal
- The ideal antibiotic regimen should have coverage against the most common pathogens, *S. aureus* and *P. aeruginosa*
- Side effect profile can also influence choice of treatment. Ototoxicity is the most important concern with aminoglycoside drugs, including neomycin, tobramycin, and gentamicin. Aminoglycosides are a significant potential source for iatrogenic hearing loss and balance dysfunction, particularly in the presence of tympanic membrane perforation. Allergic contact dermatitis is commonly associated with neomycin when used for prolonged courses. Topical fluoroquinolones can cause local irritation
- The following are some of the available preparations:
  1. Neomycin otic solutions and suspensions:
     a. With polymyxin-B-hydrocortisone (Cortisporin)
     b. With hydrocortisone-thonzonium (Coly-Mycin S)
  2. Polymyxin-B-hydrocortisone (Otobiotic)
  3. Quinolone otic solutions:
     a. Ofloxacin 0.3% solution (Floxin Otic)
     b. Ciprofloxacin 0.3% with hydrocortisone (Cipro HC)
  4. Quinolone ophthalmic solutions:
     a. Ofloxacin 0.3% (Ocuflox)
     b. Ciprofloxacin 0.3% (Ciloxan)
  5. Aminoglycoside ophthalmic solutions:
     a. Gentamicin sulfate 0.3% (Garamycin)
     b. Tobramycin sulfate 0.3% (Tobrex)
     c. Tobramycin 0.3% and dexamethasone 0.1% (TobraDex)
  6. Chloramphenicol 0.5% otic solution or 0.25% ophthalmic solution (Chloromycetin)
  7. Gentian violet (methylrosaniline chloride 1%, 2%)
  8. Antifungals:
     a. Amphotericin B 3% (Fungizone lotion)
     b. Clotrimazole 1% solution (Lotrimin)
     c. Tolnaftate 1% (Tinactin)
- Topical preparations should be applied qid (bid for quinolones, antifungals), generally for 3 days after cessation of symptoms (average 10-14 days total)

TABLE 1 Differential Diagnosis of Painful External Ear and Auditory Canal Disorders

Disorder	Clinical Features
Acute otitis externa	Diffuse redness, swelling, and pain of the canal with greenish to whitish exudate; often very tender pinna
Malignant otitis externa	Rapidly progressive, severe swelling and redness of pinna, which may be laterally displaced
Dermatitis	
Eczema	History of atopy, presence of lesions elsewhere; lesions are scaly, red, pruritic, and weeping
Contact	History of cosmetic use or irritant exposure; lesions are scaly, red, pruritic, and weeping
Seborrhea	Scaly, red, papular dermatitis; scalp may have thick, yellow scales
Psoriasis	History or presence of psoriasis elsewhere; erythematous papules that coalesce into thick, white plaques
Cellulitis	Diffuse redness, tenderness, and swelling of the pinna
Furuncles	Red, tender papules in areas with hair follicles (distal third of the ear canal)
Infected periauricular cyst	Discrete, palpable lesions; history of previous swelling at same site; cellulitis may develop, obscuring cystic structure
Insect bites	History of exposure; lesions are red, tender papules
Herpes zoster	Painful, vesicular lesions in the ear canal and tympanic membrane in the distribution of cranial nerves V and VII
Perichondritis	Inflammation of the cartilage, usually secondary to cellulitis
Tumors	Palpable mass, destruction of surrounding structures
Foreign body	Foreign body may cause secondary trauma to the ear canal or become a nidus for an infection of the ear canal
Trauma	Bruising and swelling of external ear; there may be signs of basilar skull fracture (cerebrospinal fluid otorrhea, hemotympanum)

From Kliegman RM, Lye PS, Bordini BJ, et al, editors: *Nelson pediatric symptom-based diagnosis*, Philadelphia, 2018, Elsevier, table 4.1, p. 62, in Kliegman, RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

Systemic antibiotics:
- Reserved for when the infection has spread beyond the ear canal.
- Treatment usually for 10 days with ciprofloxacin 750 mg q12h or ofloxacin 400 mg q12h, or with antistaphylococcal agent (e.g., dicloxacillin or cephalexin 500 mg q6h). Use Bactrim or clindamycin when MRSA suspected or cultured at one DS twice a day instead of cephalexin or dicloxacillin. For malignant otitis externa (due to Pseudomonas aeruginosa in >90% of cases), effective agents are meropenem 1 g IV q8h or ciprofloxacin 400 mg IV q12h or 750 mg PO q12h or cefepime 2 g q12h.

Treatment for NOE:
- Requires prolonged therapy up to 3 mo; whether to use oral parenteral therapy is based on clinical judgment
- Oral quinolones, ciprofloxacin 750 mg q12h or ofloxacin 400 mg q12h may be appropriate initial therapy or used to shorten the course of IV therapy
- Intravenous antipseudomonals with or without aminoglycosides are also appropriate
- Local debridement

Pain control:
- May require NSAIDs or opioids
- Topical corticosteroids to reduce swelling and inflammation

CHRONIC Rx
- Patients prone to recurrent infections should try to identify and avoid precipitants to infection.
- Swimmers should try tight-fitting ear plugs or tight-fitting bathing caps and remove all excess water from the ears after swimming.
- Treat underlying systemic diseases and dermatologic conditions that predispose to infection.
- Hearing aids should be removed nightly and regularly cleaned.

DISPOSITION
Inadequate treatment of otitis externa may lead to NOE and mastoiditis.

REFERRAL
To an otolaryngologist:
- NOE
- Treatment failure
- Severe pain

PEARLS & CONSIDERATIONS
Otitis externa varies in severity from a mild irritation of the external acoustic canal (swimmer ear) that resolves spontaneously by simply removing the offending agent (stay out of freshwater or wear ear plugs when swimming) to a life-threatening infection with the risk of intracranial extension, gram-negative bacterial meningitis, and severe neurologic impairment with multiple cranial neuropathy. Do not miss severe malignant otitis externa in patients who are diabetic or immunocompromised.

SUGGESTED READINGS
Available at ExpertConsult.com

RELATED CONTENT
Otitis Externa (Patient Information)

AUTHOR: **Russell J. McCulloh, MD**

SUGGESTED READINGS

Kausnik V et al: Interventions for acute otitis externa, *Cochrane Database Syst Rev* 1:CD004740, 2010.
Long M: Otitis externa, *Pediatr Rev* 34(3):143-144, 2013.
Rosenfeld RM et al: Clinical practice guideline: acute otitis externa, *Otolaryngol Head Neck Surg* 150(1):S1-S24, 2014.

FIG. E1 Patient with acute otitis externa, with purulent drainage from the ear canal and mild edema and erythema of the pinna. (From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.)

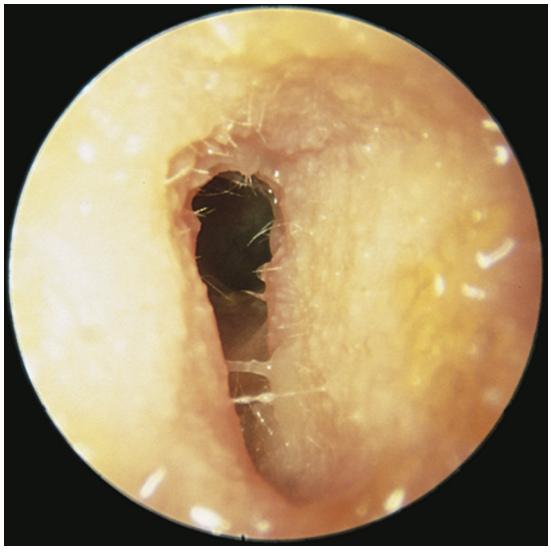

FIG. E2 Acute otitis externa. (From Swartz MH: *Textbook of physical diagnosis, history and examination,* ed 7, Philadelphia, 2014, Elsevier.)

BASIC INFORMATION

DEFINITION

Acute otitis media (AOM) is defined by infected middle ear fluid resulting in moderate to severe bulging of the tympanic membrane (TM) or new onset of otorrhea not due to acute otitis externa. Care should be taken to differentiate AOM from serous otitis media, which involves noninfected middle ear fluid that does not result in bulging of the TM. Serous otitis media does not require antibiotic treatment.

SYNONYMS

Acute suppurative otitis media
Purulent otitis media
Acute otitis media
AOM

ICD-10CM CODES

H65.3	Chronic mucoid otitis media
H66.0	Acute suppurative otitis media
H66.4	Suppurative otitis media, unspecified
H66.9	Otitis media, unspecified
H66.1	Chronic tubotympanic suppurative otitis media
H66.2	Chronic atticoantral suppurative otitis media

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Affects patients of all ages but is largely a disease of infants and young children.
- Affects approximately 80% of all children by age 5 yr.
- Occurs three or more times in one third of all children by age 3 yr.
- Costs associated with otitis media exceed $5 billion, with 40% of the costs occurring from patients ages 1 to 3.
- One of the most common indications for antibiotic prescription among children.

PEAK INCIDENCE:

- AOM occurs at all ages but is most prevalent between 6 and 24 mo of age.
- A second peak in incidence occurs between 4 and 6 yr of age.
- AOM is most frequent in the fall, winter, and early spring (coincident with peak respiratory virus prevalence in the community).
- Incidence of infection declines with age; AOM is seen infrequently in adults.

RISK FACTORS:

- Daycare attendance
- Limited or no breastfeeding
- Tobacco smoke exposure
- Pacifier use
- Craniofacial anomalies
- Immune globulin G (IgG) or subclass deficiencies

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Moderate to severe bulging of the TM.
- Fluid in the middle ear along with signs and symptoms of local inflammation.
  1. Erythema with diminished light reflex (Fig. E1)
- As infection progresses, middle ear exudation occurs (exudative phase); the exudate rapidly changes from serous to purulent (suppurative phase).
- Retraction and poor mobility of the TM ensue, and the TM begins to bulge.
- At any time during the suppurative phase, the TM may rupture, releasing the middle ear contents (otorrhea).
- Erythema of the TM without other abnormalities is not a diagnostic criterion for acute otitis media (AOM) because it may occur with any inflammation of the upper respiratory tract, crying, or nose blowing.
- Symptoms:
  1. Rapid- or recent-onset otalgia, ranging from slight discomfort to severe, is the most common presenting symptom.
  2. Hearing loss while middle ear fluid is present.
  3. Otorrhea (if TM has ruptured).
  4. Systemic symptoms such as fever, listlessness, irritability, decreased appetite, vomiting, and diarrhea are common. Vertigo, facial swelling, nystagmus, tinnitus, lethargy, and facial nerve palsies can occur as complications of AOM.
  5. Table 1 summarizes symptom scoring systems designed to aid in diagnosis.
- After an episode of AOM:
  1. Persistence of effusion for wks or mos (called secretory, serous, or nonsuppurative otitis media).
  2. Fever and otalgia usually absent.
  3. Hearing loss possible (10 to 50 dB, with predominant involvement of the low frequencies).
  4. Manifestations of the sequelae and complications of otitis media are summarized in Table E2.

ETIOLOGY

- Most common etiology is a viral upper respiratory tract infection, which causes inflammation and dysfunction of the eustachian tube and transient aspiration of nasopharyngeal secretions into the middle ear (Fig. 2). Bacterial colonization from the nasopharynx in conjunction with eustachian tube dysfunction leads to infection.
- May occasionally develop as a result of hematogenous spread or by direct invasion from the nasopharynx.
- Conjugated pneumococcal vaccination of children has resulted in decreases in *Streptococcus pneumoniae* causing AOM.
- Most common bacterial pathogens:
  1. *S. pneumoniae* causes up to half of cases and is the least likely of the major pathogens to resolve without treatment.
  2. *Haemophilus influenzae.*
  3. *Moraxella catarrhalis.*
  4. Of increasing importance, infection caused by penicillin-nonsusceptible *S. pneumoniae* (MIC >0.1 mg/ml), ranging from 8% to 34%. About 50% of PNSSP isolates are penicillin-intermediate (MIC 0.1 to 2.0 mg/ml).
  5. Group A streptococci is associated with higher rates of TM perforation than AOM caused by other pathogens.
- Viral pathogens:
  1. Respiratory syncytial virus (RSV)
  2. Rhinovirus
  3. Adenovirus
  4. Influenza
- Others:
  1. *Mycoplasma pneumoniae*
  2. *Chlamydia trachomatis*
  3. *Streptococcus pyogenes* (Latin America)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Otitis externa
- Otitis media with effusion (OME): An algorithm for distinguishing between acute otitis media and otitis media with effusion is illustrated in Fig. 3
- Referred pain from mouth, nasopharynx, or throat
- Section II describes the differential diagnosis of earache

WORKUP

Thorough otoscopic examination. AOM is a visual diagnosis based on viewing the tympanic membrane. Adequate visualization of the tympanic membrane may require removal of cerumen and debris.

- Tympanometry
  1. Measures compliance of the tympanic membrane and middle ear pressure
  2. Detects the presence of fluid, but cannot determine whether the fluid is infected
- Acoustic reflectometry
  1. Measures sound waves reflected from the middle ear
  2. Is useful in infants >3 mo
  3. Increased reflected sound correlated with the presence of effusion, but cannot determine whether the fluid is infected

LABORATORY TESTS

- Tympanocentesis.
  1. Not necessary in most cases because the microbiology of middle ear effusions has been shown to be extremely consistent
  2. May be indicated in:
     a. Patients who do not respond to treatment in 72 hours or those who experience multiple treatment failures
     b. Immunocompromised patients
- Cultures of the nasopharynx are not helpful.
- Blood counts (generally unnecessary)usually reveal leukocytosis with polymorphonuclear elevation.
- Plain mastoid radiographs (generally unnecessary) reveal haziness in the periantral cells that may extend to entire mastoid.
- CT or MRI may be indicated if serious complications are suspected (meningitis, brain abscess, severe mastoiditis).

TABLE 1 Acute Otitis Media Symptom Scoring Systems Designed to Aid in Diagnosis

3-Item Otitis Media Score (OM-3)	Ear Treatment Group Symptom Questionnaire (ETG-5)	Acute Otitis Media Faces Scale (AOM-FS)	Otoscopic Severity Scale (OS-8)	Acute Otitis Media Severity of Symptom Scale (AOM-SOS)	Otitis Media Clinical Severity Index (OM-CSI) 30-Point Scale[a]	Otitis Media Clinical Severity Index (OM-CSI) 10-Point Scale[a]
Physical suffering	Ear pain	Seven facial expressions ranging from no problem to extreme problem	Eight categories of TM inflammation[b]	Ear pain	Ear pain	Ear pain
Emotional distress	Fever			Ear tugging	Fever	Fever
Limitation of activities	Irritability			Irritability	Irritability	Irritability
	Appetite			Decreased play	Fever at examination	Fever at examination
	Sleep quality			Decreased appetite	TM erythema	TM erythema
				Difficulty sleeping	TM mobility	TM mobility
				Fever	TM position	TM position
					Effusion color	Effusion color
					Otorrhea	Otorrhea

TM, Tympanic membrane.
[a]The 30-point scale used a 2- to 5-point Likert scale and the 10-point scale used a 2- to 3-point Likert scale.
[b]0 = normal; 1 = erythema only; 2 = erythema, air-fluid level, clear fluid; 3 = erythema, complete effusion, no opacification; 4 = erythema, opacification with air-fluid level or air bubbles, no bulging; 5 = erythema, complete effusion, opacification, no bulging; 6 = erythema, bulging rounded doughnut appearance of the tympanic membrane; 7 = erythema, bulging, complete effusion and opacification with bulla formation.
From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.

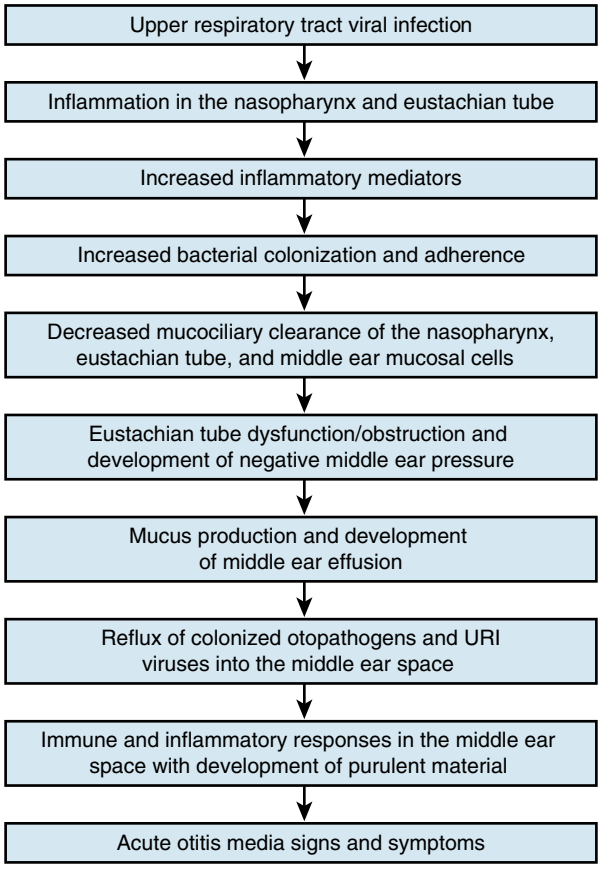

FIG. 2 Pathogenesis of virus-induced acute otitis media. *URI,* Upper respiratory infection. (From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.)

Rx TREATMENT

ACUTE GENERAL Rx

Hydration, avoidance of irritants (e.g., tobacco smoke), nasal decongestants, cool mist humidifier, and oral ibuprofen or acetaminophen. Topical procaine or lidocaine preparations (if available) are an alternative to oral analgesics for children ≥2 yr but should not be used in children with tympanic membrane perforation.

Antimicrobials:

NOTE: Most uncomplicated cases of AOM resolve spontaneously, without complications. Studies have demonstrated limited therapeutic benefit from antibiotic therapy. Watchful waiting is appropriate for children who look well, can be comforted with supportive care, and are old enough to easily evaluate. Children <24 mo with bilateral AOM should receive antibiotic therapy. Children with severe signs or symptoms (moderate or severe otalgia or otalgia for ≥48 hr or temperature ≥39°C) should also receive antibiotic therapy. Fig. E4 illustrates an algorithm for management of acute otitis media in pediatric populations.

When opting to use antibiotic therapy:

- Amoxicillin remains the drug of choice for first-line treatment of uncomplicated AOM despite increasing prevalence of drug-resistant *S. pneumoniae.*
- Treatment failure is defined by lack of clinical improvement of signs or symptoms after 3 days of therapy.
- With treatment failure, in the absence of an identified etiologic pathogen, therapy should be redirected to cover:
  1. Drug-resistant *S. pneumoniae*
  2. β-lactamase–producing strains of *H. influenzae* and *M. catarrhalis*
- Agents fulfilling these criteria include amoxicillin/clavulanate, second-generation (e.g., cefuroxime axetil, cefaclor) or third-generation (e.g., oral cefdinir or cefpodoxime or IM ceftriaxone) cephalosporins. Cefaclor, cefixime, loracarbef, and ceftibuten should be avoided given their limited activity against pneumococci.
- Cross-resistance between TMP/SX and macrolides and the β-lactams exists; therefore patients who do not respond to amoxicillin are more likely to have infections resistant to TMP/SMX and macrolides.
- Fluoroquinolones are not indicated as first- or second-line therapy for AOM and should be avoided in young children due to risks of musculoskeletal effects and limited dosing guidance.

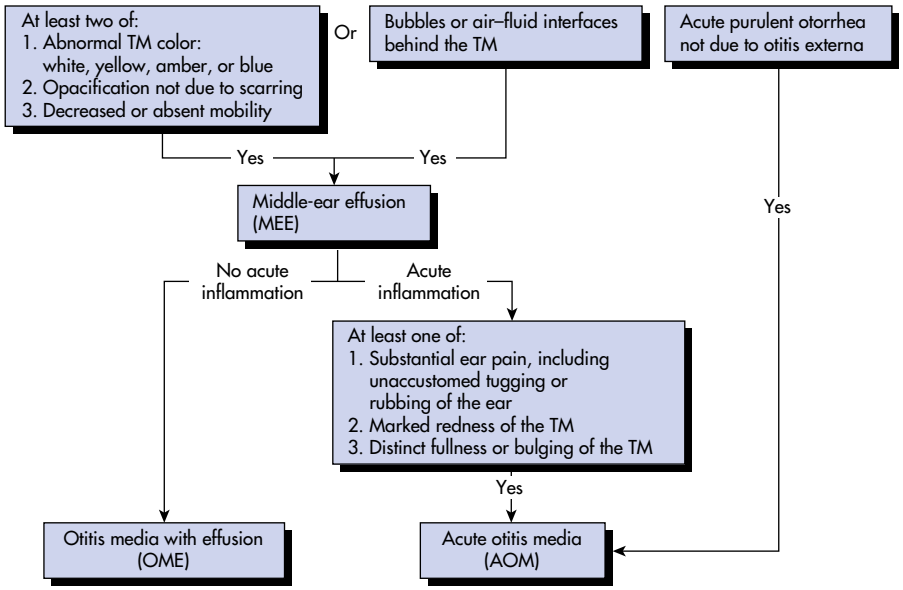

FIG. 3 Algorithm for distinguishing between acute otitis media and otitis media with effusion. *TM,* tympanic membrane. (From Kliegman RM: *Nelson Textbook of Pediatrics*, ed 21, Philadelphia, 2020, Elsevier.)

- Treatment should be modified according to cultures and sensitivities when available.
- Treatment course is 10 days for children <2 yr and those with severe symptoms, 7 days for children age 2 to 5 yr, and 5 to 7 days for children ≥6 yr.
- Follow-up should be tailored to clinical improvement and concern for neurocognitive developmental delays in at-risk children. Standard follow-up of all cases is no longer recommended.
- Antibiotic prophylaxis to reduce the frequency of AOM episodes in children with recurrent AOM is not recommended.
- Table E3 summarizes suggested antibiotics for treatment of otitis media and for patients who have failed first-line antibiotic treatment.

NOTE: Effusions may persist for 8 wk or longer in many cases of adequately treated otitis media.

SURGICAL Rx

- There is no evidence to support the routine use of myringotomy, but in severe cases it provides prompt pain relief and accelerates resolution of infection.
- Purulent secretions retained in the middle ear can lead to increased pressure that may lead to spread of infection to contiguous areas. Myringotomy to decompress the middle ear is sometimes necessary to avoid complications such as mastoiditis, facial nerve paralysis, labyrinthitis, meningitis, and brain abscess.

CHRONIC Rx

- Myringotomy and tympanostomy tube placement for persistent or recurrent middle ear effusion unresponsive to medical therapy can be considered if fluid has persisted for ≥3 mo if bilateral or ≥6 mo if unilateral.
- Adenoidectomy, with or without tonsillectomy, often is advocated for treatment of recurrent otitis media, although evidence for this procedure is controversial.
- Long-term complications include tympanic membrane perforations, cholesteatoma, tympanosclerosis, ossicular necrosis, toxic or suppurative labyrinthitis, hearing loss, and intracranial suppuration.

DISPOSITION

Patients can be treated at home as outpatients with the rare exception of patients with evidence of local suppurative complications (e.g., meningitis, acute mastoiditis, brain abscess, cavernous sinus, or lateral vein thrombosis).

REFERRAL

- To otorhinolaryngologist in cases of:
  1. Medical treatment failure
  2. An uncertain diagnosis; adults with one or more episodes of AOM should be referred for evaluation to rule out an underlying process (e.g., malignancy)
  3. Any of the above-mentioned acute and chronic complications

PEARLS & CONSIDERATIONS

COMMENTS

- Otoscopic findings are critical for accurate AOM diagnosis.
- AOM microbiology has changed with use of pneumococcal conjugate vaccine (PCV13).
- Antibiotics are modestly more effective than no treatment but cause adverse effects in 4% to 10% of children.
- Most antibiotics have comparable clinical success.

Prevention:

- Vaccinate against common pathogens.
- Breastfeed and bottle-feed infants in an upright position.
- Avoid irritants (e.g., tobacco smoke).

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Stephen Dolter, MD,** and **Russell J. McCulloh, MD**

SUGGESTED READINGS

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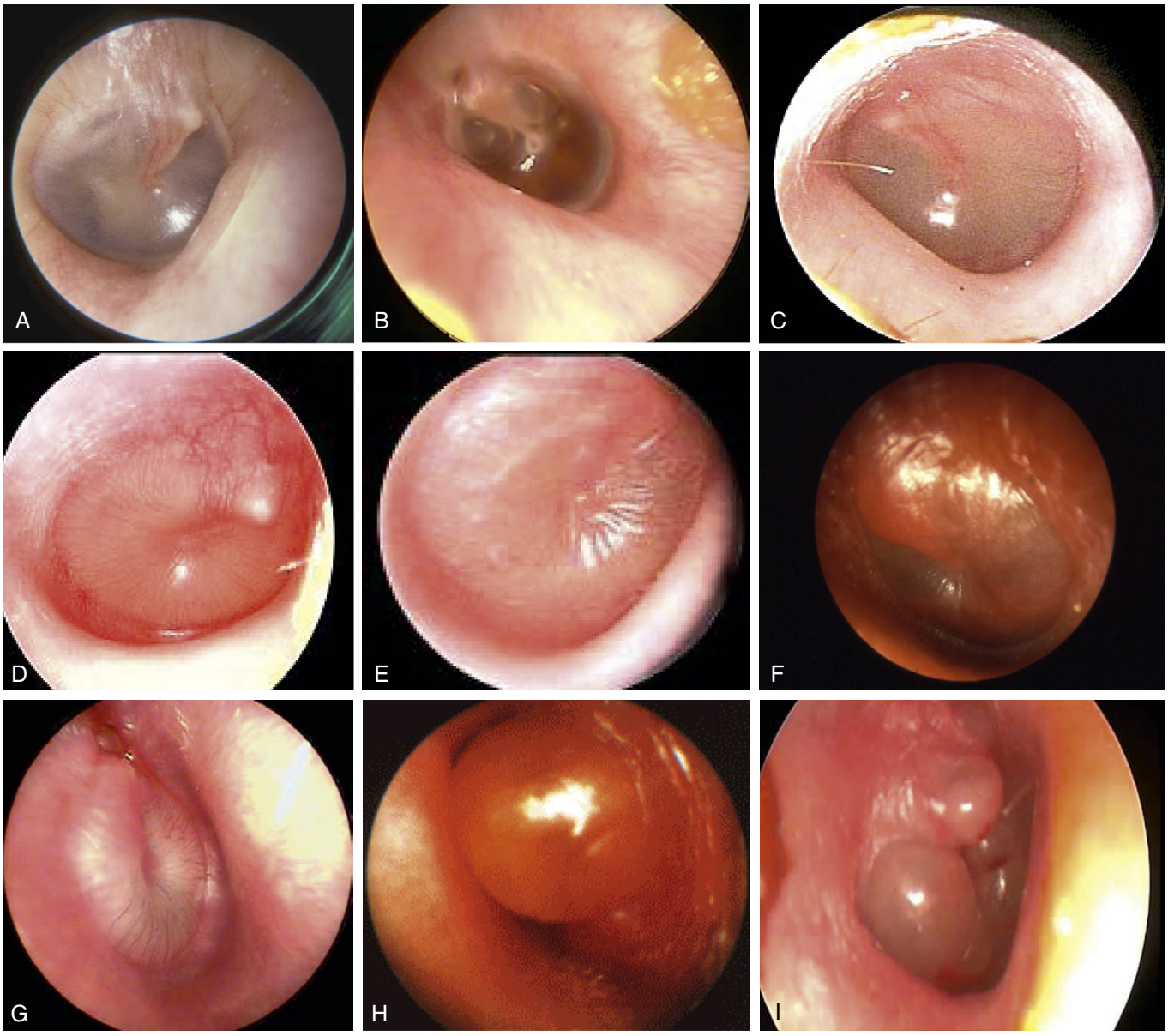

FIG. E1 Transition from normal to otitis media with effusion (OME) to acute otitis media. A, Normal tympanic membrane with pearly gray, translucent appearance. **B,** OME with air bubbles. **C-D,** OME fully filled with effusion; note retracted and translucent tympanic membrane with prominent head of the malleus. **E,** Slight bulging with semiopaque white tympanic membrane. **F,** Bulging semiopaque tympanic membrane. **G,** Markedly bulging, donut appearance, opaque, white tympanic membrane. **H-I,** Severe bulging with bullae formation. (Courtesy Dr. Hoberman, University of Pittsburgh. In Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.)

TABLE E2 Manifestations of the Sequelae and Complications of Otitis Media

Complication	Clinical Features
Acute	
Perforation with otorrhea	Immobile tympanic membrane secondary to visible perforation, exudate in ear canal
Acute mastoiditis with periostitis	Tenderness and erythema over mastoid process, no destruction of bony trabeculae
Acute mastoid osteitis	Destruction of bony trabeculae; tenderness and erythema over mastoid process coupled with outward displacement of pinna
Petrositis	Infection of perilabyrinthine cells; may present with otitis, paralysis of lateral rectus, and ipsilateral orbital or facial pain (Gradenigo syndrome)
Facial nerve palsy	Peripheral cranial nerve VII paralysis
Labyrinthitis	Vertigo, fever, ear pain, nystagmus, hearing loss, tinnitus, nausea and vomiting
Lateral sinus thrombosis	Headache, fever, seizures, altered states of consciousness, septic emboli
Meningitis	Fever, headache, nuchal rigidity, seizures, altered states of consciousness
Extradural empyema	Fever, headache, seizures, altered states of consciousness
Subdural empyema	Fever, headache, seizures, altered states of consciousness
Brain abscess	Fever, headache, seizures, altered states of consciousness, focal neurologic examination findings
Nonacute	
Chronic perforation	Immobile tympanic membrane secondary to perforation
Otitis media with effusion (OME)	Immobile, opaque tympanic membrane
Adhesive otitis	Irreversible conductive hearing loss secondary to chronic OME
Tympanosclerosis	Thickened white plaques may cause conductive hearing loss
Chronic suppurative otitis media	Following acute otitis media with perforation, secondary infection with *Staphylococcus aureus, Pseudomonas aeruginosa*, or anaerobes develops, causing chronic otorrhea
Cholesteatoma	White, pearl-like, destructive tumor with otorrhea arising near or within tympanic membrane; may be secondary to chronic negative middle ear pressure
Otitic hydrocephalus	Increased intracranial pressure secondary to AOM; signs and symptoms include severe headaches, blurred vision, nausea, vomiting, papilledema, diplopia (abducens paralysis)

AOM, Acute otitis media.

From Kliegman RM, Lye PS, Bordini BJ, Toth H, Basel D, editors: *Nelson pediatric symptom-based diagnosis*, Philadelphia, 2018, Elsevier, Table 4.6, p 67. In Kliegman, RM: *Nelson Textbook of Pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

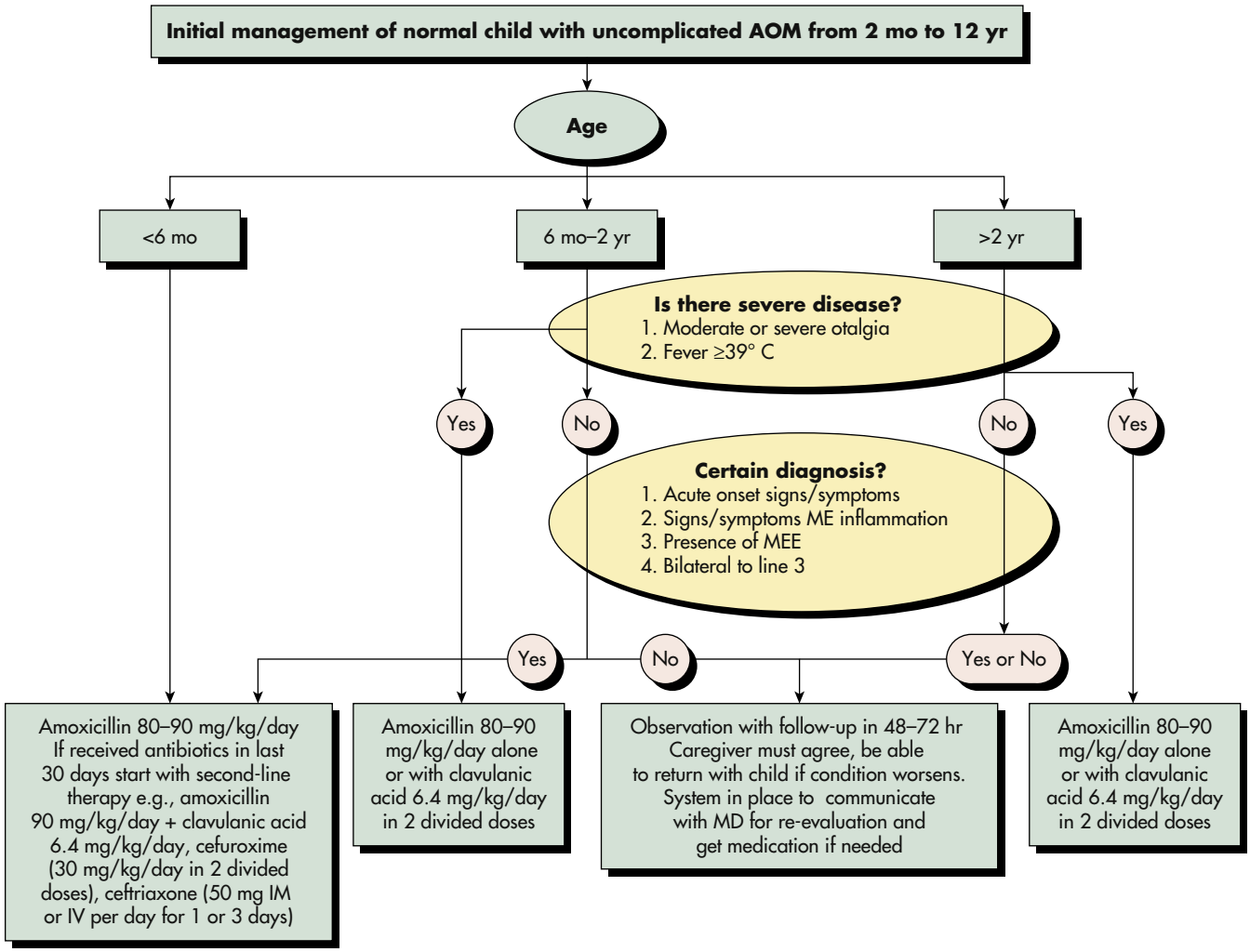

FIG. E4 Congenital chronic otitis media with cholesteatoma. (From Chole RA, Sudhoff HH: *Chronic otitis media, mastoiditis, and petrositis*. In Flint PW, Haughey BH, Lund VJ et al (eds): *Cummings otolaryngology—head and neck surgery*, ed 5, Philadelphia, 2010, Elsevier, Fig 139-6. In Kliegman RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.)

TABLE E3 Suggested Antibiotics for Treatment of Otitis Media and for Patients Who Have Failed First-Line Antibiotic Treatment

Initial Immediate or Delayed Antibiotic Treatment		Antibiotic Treatment After 48-72 hr of Failure of Initial Antibiotic Treatment	
Recommended First-Line Treatment	**Alternative Treatment (If Penicillin Allergy or Suspicion of Beta Lactamase-Producing Organisms)**	**Recommended Treatment**	**Alternative Treatment**
Amoxicillin (Pathogens include *Pneumococcus*, *H. influenzae* non-type B, *Moraxella)*	Cefdinir	Amoxicillin-clavulanate	Ceftriaxone
or	*or*	*or*	Failure of second antibiotic
Amoxicillin-clavulanate Ceftriaxone IM/IV for 1-3 days	Cefpodoxime Ceftriaxone Levofloxacin	Ceftriaxone	Azithromycin Tympanocentesis*

Antibiotic Dosage

- Amoxicillin 90 mg/kg/day bid for 10 days
- Amoxicillin-clavulanate (ratio 14:1) 90 mg/kg/day of amoxicillin component bid for 10 days
- Ceftriaxone 50 mg/kg/day qd IM, IV for 1-3 days
- Cefdinir 14 mg/kg/day qd for 10 days
- Cefpodoxime 10 mg/kg/day bid for 10 days
- Levofloxacin 20 mg/kg/day bid if ≤5 yr for 10 days; 10 mg/kg/day bid if >5 yr for 10 days
- Azithromycin 10 mg/kg/day on day 1 QD then 5 mg/kg/day days 2-5 qd or 10 mg/kg/day for 3 days QD or 20 mg/kg once

IM, Intramuscular; *IV*, intravenous; *bid*, twice daily; *qd*, once daily.
*Tympanocentesis for those who fail second-line therapy.
From Kliegman RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

Otosclerosis (Otospongiosis)

BASIC INFORMATION

DEFINITION

Otosclerosis is conductive hearing loss caused by fixation of the stapes, resulting in gradual hearing loss. Most commonly, it affects both ears, with approximately 15% of cases affecting only one ear.

ICD-10CM CODES

H80	Otosclerosis
H80.0	Otosclerosis involving oval window, non-obliterating
H80.1	Otosclerosis involving oval window, obliterating
H80.2	Cochlear otosclerosis
H80.8	Other otosclerosis
H80.9	Otosclerosis, unspecified
H80.93	Unspecified otosclerosis, bilateral

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Most common cause of hearing loss in young adults

PEAK INCIDENCE: Onset of hearing impairment usually occurs between third and fifth decade of life.

PREVALENCE (IN U.S.):

- Clinically apparent in approximately five cases per 1000 persons, although subclinical histologically confirmed disease prevalence is higher.
- More common in northern white populations.
- Rare among Africans and Asians.
- Pregnancy is associated with acceleration of the disease.

PREDOMINANT SEX: Female:male ratio of 2:1

PREDOMINANT AGE: Symptoms start between ages 20 and 40 yr, with slowly progressive conductive hearing loss.

GENETICS: Autosomal dominant inheritance with incomplete penetrance in about 40% to 45% of patients

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients present with slowly progressive hearing loss, tinnitus (80%), family history of otosclerosis, sensorineural hearing loss, and vestibular symptoms (vertigo/dizziness).
- Tympanic membrane is normal in most cases. Tested with pneumatic otoscopy to rule out middle ear effusion, tympanic membrane perforation, or other cause of conductive hearing loss.
- Rinne test with 512-Hz tuning fork abnormal with bone conduction greater than air conduction (this suggests at least 15- to 20-dB conductive hearing loss).
- Weber test with 512-Hz tuning fork lateralizes to affected ear.

ETIOLOGY

- The disease is characterized by abnormal resorption and deposition of bone forming the otic capsule, resulting in disorganized fibrotic bone rich in blood vessels.
- The process involves an early stage of bone remodeling (otospongiosis), a transitional phase, and a late phase of sclerotic bone formation (otosclerosis).
- There is some evidence to suggest a relationship between the measles virus and the development of otosclerosis.
- Exact etiology is unknown.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hearing loss from any cause: Cochlear otosclerosis, aural polyps, granulomas, tumors, osteogenesis imperfecta, chronic ear infections, trauma, Paget disease.
- Table E1 describes common types of conductive and sensorineural hearing loss.

WORKUP

- The diagnosis is based mainly on clinical history and audiometry findings.
- Audiometry will show a conductive hearing loss and may show the characteristic Carhart notch, which is a depressed bone conduction threshold at 2000 Hz. Stapedial reflex may be absent.

LABORATORY TESTS

None, unless infection suspected

IMAGING STUDIES

High-resolution CT scan with fine cuts through the temporal bone is not essential but may be helpful in confirming the diagnosis or in ruling out other causes of hearing loss, such as mass or other anatomic abnormalities. Diffuse sclerosis may be seen in advanced disease, but findings may be subtle or absent, and a negative CT scan does not rule out the diagnosis. However, recent studies suggest that the CT scan's sensitivity in identifying otosclerosis may be as high as 95% (Fig. E1).

TREATMENT

NONPHARMACOLOGIC THERAPY

- All patients with otosclerosis may use hearing aids as an alternative to surgery.
- Oral fluoride therapy has been shown to be beneficial in patients with sensorineural hearing loss as a result of otosclerosis.

CHRONIC Rx

- Surgical treatment with stapedectomy or stapedotomy is the treatment of choice.

TABLE E1 Common Types of Conductive and Sensorineural Hearing Loss

Conductive Hearing Loss	Sensorineural Hearing Loss
Otitis media with effusion	Presbycusis (hearing loss with aging)
TM perforation	Ototoxicity
Tympanosclerosis	Ménière disease
Retracted TM (eustachian tube dysfunction)	Idiopathic loss
Ossicular problems	Noise-induced loss
Otosclerosis	Perilymphatic fistula
Foreign body in ear canal	Hereditary (congenital) loss
Cerumen impaction	Multiple sclerosis
Tumor of the ear canal or middle ear	Diabetes
Cholesteatoma	Syphilis, acoustic neuroma

TM, Tympanic membrane.
From Rakel RE [ed]: *Principles of family practice,* ed 6, Philadelphia, 2002, WB Saunders.

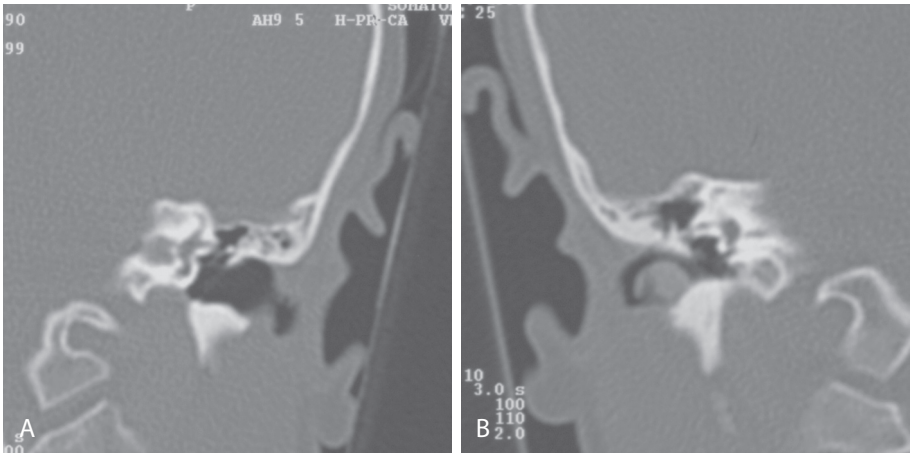

FIG. E1 A patient with conductive hearing loss. By comparing the normal **(A)** and abnormal **(B)** sides on a computed tomography scan, the practitioner clearly can appreciate the narrowing of the oval window. This results in fixation of the stapes footplate and conductive hearing loss. (From Grainger RG et al [eds]: *Grainger & Allison's diagnostic radiology,* ed 4, Philadelphia, 2001, Churchill Livingstone.)

1. Carried out in the worse-hearing ear first; the better-hearing ear may be addressed 6 to 12 mo later.
2. Results in improved hearing in approximately 90% of patients.
3. 2% of patients may develop persistent profound sensorineural hearing loss as a result of surgery.

- If left untreated, the disease will progress to a maximal conductive hearing loss of up to 60 dB. Rarely does the disease cause sensorineural hearing loss or lead to complete deafness.

REFERRAL

To ENT specialist for surgery if moderate hearing loss suspected

PEARLS & CONSIDERATIONS

COMMENTS

A full ENT evaluation in a young or middle-aged person with hearing loss is mandatory unless the cause is obvious (such as trauma or repeated infection).

PATIENT & FAMILY EDUCATION

http://american-hearing.org/disorders/otosclerosis/

AUTHOR: **Louis Insalaco, MD**

BASIC INFORMATION

DEFINITION

Ovarian cancer is not one disease but a constellation of distinct cancer subtypes classified according to their tissue of origin. About 90% of tumors are epithelial ovarian cancers, 5% are gram cell tumors, and 5% are sex cord-stromal tumors. A classification of ovarian epithelial tumors is summarized in Table 1.

SYNONYMS

Epithelial ovarian cancer
Germ cell tumor
Sex cord stromal tumor
Ovarian tumor of low malignant potential

ICD-10CM CODES

C56.9	Malignant neoplasm of unspecified ovary
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 12.9 to 15.1 cases/100,000 persons; ~25,000 new cases annually. Lifetime risk for developing ovarian cancer is 1.3%. It is the leading cause of gynecologic cancer-related deaths.

PREVALENCE: It is most commonly diagnosed in those 55 to 64 yr of age.

RISK FACTORS:

- Low parity
- Delayed childbearing
- Smoking
- Polycystic ovary syndrome
- Endometriosis
- High-fat diet
- Lynch II syndrome (nonpolyposis colon cancer, endometrial cancer, breast cancer, and ovarian cancer clusters in first- and second-degree relatives)
- Breast-ovarian familial cancer syndrome
- Site-specific familial ovarian cancer
- The **strongest** risk factors are advancing age and family history of ovarian and breast cancer
- Factors that **decrease** the risk of ovarian cancer include previous pregnancy, oral contraceptive pill use, hysterectomy, tubal ligation, or salpingectomy
- Table 2 summarizes risk and protective factors for ovarian cancer

GENETICS: The greatest risk factors of ovarian cancer are a family history and associated genetic syndromes. More than 90% of inherited ovarian malignancies are associated with *BRCA1 and BRCA2* mutations. *BRCA* mutations interact with and affect DNA repair proteins. The estimated lifetime risk of ovarian cancer for patients with either of these mutations is 65% to 74%.

Genetic counseling is recommended for certain patients, including those with:

- Epithelial ovarian cancer at any age
- Breast cancer diagnosed at age 45 yr or younger
- Breast cancer with two distinct and sequential primaries, the first one diagnosed at age 50 yr or younger
- Breast cancer that is triple-negative and diagnosed at age 60 yr or younger
- Breast cancer at any age, with at least one close relative diagnosed at age 50 yr or younger
- Breast cancer diagnosed at any age, with two or more close relatives with breast cancer; one close relative with epithelial ovarian cancer; or two close relatives with pancreatic cancer or aggressive prostate cancer
- Breast cancer, with a close male relative at any age who has breast cancer
- Breast cancer and Ashkenazi Jewish ancestry
- A family with a known deleterious *BRCA1* or *BRCA2* mutation

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- 60% present with advanced disease
- Abdominal fullness, early satiety, dyspepsia
- Pelvic pain, back pain, constipation
- Pelvic or abdominal mass
- Lymphadenopathy (inguinal)
- Sister Mary Joseph nodule (umbilical mass)

ETIOLOGY

- Can be inherited as site-specific familial ovarian cancer (two or more first-degree relatives have ovarian cancer)
- Breast-ovarian cancer syndrome (clusters of breast and ovarian cancer among first- and second-degree relatives)
- Lynch syndrome
- No family history and unknown etiology in the majority of ovarian cancer cases

TABLE 1 Classification of Ovarian Epithelial Tumors

Terminology	Notes
Serous Tumors	Most common epithelial tumor group
Adenocarcinoma	More than 85% involve the ovarian surface or adjacent structures
	Includes low (~10%) and high (~90%) grade carcinomas
Noninvasive low-grade serous carcinoma (LGSC)	Grade 1, synonymous with micropapillary/cribriform borderline
Borderline	Can be intracystic or involve the ovarian surface
Benign	Includes adenofibroma
Mucinous Tumors	Include intestinal (common) and müllerian (less common) types
Adenocarcinoma	Includes borderline tumors with "intraepithelial carcinoma"
Borderline	
Benign	
With mural nodules	
Endometrioid Tumors	
Adenocarcinoma	High-grade carcinomas overlap with high-grade serous carcinomas (HGSCs)
Carcinosarcoma	
Adenosarcoma	
Borderline	Also known as *proliferative cystadenoma/adenofibroma;* including squamous morules
Benign	
Clear Cell Tumors	
Adenocarcinoma	Papillary and adenofibromatous types
Borderline	Occur in adenofibromas
Benign	Very rare
Transitional Cell Tumors	
Malignant	Includes malignant Brenner tumors and the rare transitional cell carcinoma
Borderline	Typically proliferating Brenner tumors
Benign	Usually Brenner tumors
Squamous Cell Tumors	
Malignant	Rare squamous carcinomas with or without a coexisting teratoma
Benign	Epidermoid cysts
Mixed Epithelial Tumors	
Malignant	Commonly a mixture of high-grade serous and endometrioid (high-grade müllerian)
Borderline and benign	Overlap with serous and müllerian mucinous tumors, also called "seromucinous borderline tumors"
Benign	
Undifferentiated or Unclassified	

Modified from the World Health Organization in Crum CP et al: *Diagnostic gynecologic and obstetric pathology*, ed 3, Philadelphia, 2018, Elsevier.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary peritoneal cancer mesothelioma
- Benign ovarian tumor
- Functional ovarian cyst
- Endometriosis
- Ovarian torsion
- Pelvic kidney
- Pedunculated uterine fibroid
- Primary cancer from breast, gastrointestinal tract, or other pelvic organ metastasized to the ovary

TABLE 2 Risk and Protective Factors for Ovarian Cancer

Increased Risk	Protective
Lifestyle and diet factors	Lifestyle and diet factors
Aging	Soy intake
Obesity	Flavonoids
Tall stature	High-calcium
Animal fat intake	Sun exposure
α-linolenic acid	Long sleep
Dairy foods	Metformin
Lactose product	
Cigarette use	
Diabetes mellitus	
Reproductive factors	Reproductive factors
Menopausal hormone therapy	Oral contraceptive
Menopausal age	Breastfeeding
Infertility	Tubal sterilization
Polycystic ovarian syndrome	Salpingectomy
Endometriosis	Hysterectomy
Pelvic inflammatory disease	Parity
Genetic factors	

From Niederhuber JE: *Abeloff's Clinical Oncology*, ed 6, Philadelphia, 2020, Elsevier.

WORKUP

- Definitive diagnosis made at laparotomy; epithelial ovarian cancer most common type of ovarian cancer (90% of ovarian cancer)
- Careful physical and history, including family history
- Exclusion of nongynecologic etiologies
- Observation of small cystic masses in premenopausal women for regression for 2 mo
- FIGO classification of ovarian carcinoma is described in Table 3
- Referral to specialists who have extensive training and experience in treating ovarian cancer significantly increases survival after an ovarian cancer diagnosis

LABORATORY TESTS

- Complete blood count.
- Chemistry profile including liver tests and calcium (to evaluate for paraneoplastic syndrome).
- CA-125 or lysophosphatidic acid level. Use of these tests for annual screening is controversial, and most experts warn against universal screening with this marker. Only about 50% of early-stage ovarian cancers will be associated with elevated CA-125. Additionally, false elevations may occur with uterine leiomyoma, endometriosis, pregnancy, and intraabdominal infections. The PLCO cancer screening trial revealed that annual screening based on CA-125 and vaginal ultrasound is ineffective, and diagnostic follow-up of false positives resulted in 15% serious complication rate.
- Consider: Human chorionic gonadotropin, inhibin, alpha-fetoprotein, neuron-specific enolase, and lactate dehydrogenase in patients at risk for germ cell tumors.
- A panel of three serum biomarkers (apolipoprotein A-1 [ApoA-1], transthyretin [TTR], and transferrin [TF]) has been reported useful in distinguishing normal samples from early-stage ovarian cancer with a sensitivity of 84% and normal samples from late-stage ovarian cancer with a sensitivity of 97%.
- *BRCA1/2* testing is recommended for all women with ovarian cancer.

IMAGING STUDIES

- Ultrasound
- Chest x-ray
- CT or MRI of abdomen and pelvis help evaluate extent of disease (Fig. E1)
- Mammogram

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Virtually all cases of ovarian cancer involve surgical exploration. This includes:

- Abdominal cytology
- Total abdominal hysterectomy and bilateral salpingo-oophorectomy (except in early stages in which fertility preservation is an issue)
- Omentectomy
- Diaphragm sampling
- Selective lymphadenectomy (pelvic and paraaortic nodes)
- Primary cytoreduction with a goal of residual tumor diameter <2 cm
- Bowel surgery, splenectomy if needed to obtain optimal (<2 cm) cytoreduction
- Conventional treatment includes surgical debulking (cytoreduction) followed by chemotherapy. However, patients with low-grade, well-differentiated stage I ovarian cancer do not benefit from adjuvant chemotherapy

ACUTE GENERAL Rx

- Optimal cytoreduction (debulking) is generally followed by chemotherapy (except in some early-stage disease [stage I without high-risk features is treated with surgery alone]).
- Cisplatin-based combination chemotherapy is used for stage II or greater, 6-mo treatment. Compared with IV paclitaxel plus cisplatin, IV paclitaxel plus intraperitoneal cisplatin and paclitaxel improves survival rates in patients with optimally debulked stage III ovarian cancer.
- Chemotherapy regimens continue to change as research continues. Bevacizumab, a humanized antivascular endothelial growth factor monoclonal antibody, has been shown to be effective in improving progression-free survival in women

TABLE 3 International Federation of Gynecology and Obstetrics (FIGO) Classification of Ovarian Carcinoma

Stage I	Growth limited to the ovaries:
	Stage I_A: Growth limited to one ovary, no ascites and no tumor present on the external surface; capsule intact
	Stage I_B: Growth limited to both ovaries, no ascites and no tumor present on the external surface; capsule intact
	Stage I_C: Stage 1_A or 1_B where there is tumor on the surface of either ovary; or with ruptured capsules or with ascites containing malignant cells or positive peritoneal washings. Surgical spillage of a malignant cyst upgrades the patient to I_C, although it is unlikely that this event affects prognosis.
Stage II	Growth involving one or both ovaries with pelvic extension:
	Stage II_A: Extension and/or metastases to the uterus and tubes
	Stage II_B: Extension to other pelvic tissues
	Stage II_C: Stage II_A or II_B with tumor on the surface of either ovary or positive peritoneal washings or malignant ascites
Stage III	Growth involving one or both ovaries with peritoneal implants outside the pelvis or positive retroperitoneal or inguinal lymph nodes:
	Stage III_A: Microscopic seeding of abdominal peritoneal surfaces
	Stage III_B: Macroscopic disease outside the pelvis less than 2 cm in diameter
	Stage III_C: Abdominal implants greater than 2 cm and/or positive nodes
Stage IV	Growth involving one or both ovaries with distant metastases including parenchymal (but not superficial) liver metastases and pleural effusions containing malignant cells

From Symonds EM, Symonds IM: *Essential obstetrics and gynaecology*, ed 4, London, 2004, Churchill Livingstone.

with ovarian cancer. Trials using bevacizumab during and up to 10 mo after carboplatin and paclitaxel chemotherapy have shown prolongation of the median progression-free survival by about 4 mo in patients with advanced epithelial ovarian cancer.

- PARP inhibitors are up-and-coming chemotherapeutic agents that have been used for maintenance therapy and have been shown to improve progression-free survival among patients with platinum-sensitive high-grade serous cancers. PARP inhibitors work by pharmacologically inhibiting the enzyme poly (ADP-ribose) polymerase. Three PARP inhibitors are currently FDA approved for different indications. Olaparib, an oral polymerase inhibitor, was approved in 2014 and has shown antitumor activity in patients with high-grade serous ovarian cancer with or without *BRCA1* and *BRCA2* germline mutations. Rucaparib was approved in 2016 to treat high-grade serous cancers with *BRCA1* and *BRCA2* germline or somatic mutations. Lastly, Niraparib was approved in 2017 for use in high-grade serous cancers with or without *BRCA1* and *BRCA2* mutations.
- Second-look surgery when chemotherapy is complete generally is no longer recommended because this has not been shown to improve survival.
- In most cases, neoadjuvant (presurgical) chemotherapy has no advantage over postsurgical initiation of chemotherapy. However, some trials have shown that neoadjuvant chemotherapy followed by interval debulking surgery is not inferior to debulking surgery followed by chemotherapy as a treatment option for patients with bulky stage IIIC or IV ovarian carcinoma. Complete resection of all macroscopic disease, whether performed as primary treatment or after neoadjuvant chemotherapy, remains the objective whenever cytoreductive surgery is performed.

CHRONIC Rx

- If CA-125 elevated, may have recurrent disease
- Physical and pelvic examinations every 3 mo for 2 yr, every 4 mo during third yr, then every 6 mo
- Routine monitoring of CA-125 at every visit does not improve survival and should be reserved for addressing specific clinical concerns
- Yearly Pap smear
- A treatment approach algorithm for recurrent ovarian cancer is illustrated in Fig. 2

DISPOSITION

- Overall 5-yr survival rates remain low because of the preponderance of late-stage disease:
  1. Stage I and II: 80% to 100%
  2. Stage III: 15% to 20%
  3. Stage IV: 5%
- Younger patients (<50 yr) in all stages have a considerably better 5-yr survival than older patients (40% vs. 15%)
- Among women with high-grade serous ovarian cancer, *BRCA2* mutation, but not *BRCA1* deficiency, is associated with improved survival, improved chemotherapy response, and genome instability compared with *BRCA* wild-type
- Among patients with invasive epithelial ovarian cancer (EOC), having a germline mutation in *BRCA1* or *BRCA2* is associated with improved 5-yr overall survival. *BRCA2* carriers have the best prognosis

COMMENTS

- The U.S. Preventive Services Task Force has concluded that current evidence does not show any mortality benefit to routine screening for ovarian cancer with transvaginal ultrasonography or single-threshold serum CA-125 testing and that the harms of such screening are at least moderate. This recommendation applies to asymptomatic women who are not known to have a high-risk hereditary cancer syndrome.
- Oral contraceptives reduce the risk of ovarian cancer by 40% to 50%. The greatest risk reduction is present after ≥15 yr of oral contraceptive use.
- Patients at high risk for developing ovarian cancer (*BRCA1/BRCA2* gene mutation, hereditary nonpolyposis colorectal cancer syndrome) should consider prophylactic salpingo-oophorectomy after childbearing is complete. Prophylactic bilateral salpingo- oophorectomy reduces ovarian cancer by 80%. It is recommended by age 35 to 40 yr for *BRCA1* carriers and by age 45 for *BRCA2* carriers. If surgery is declined, the National Comprehensive Cancer Network guidelines recommend intensive surveillance with pelvic and abdominal sonogram and serum CA-125 every 6 mo starting at age 35 or 10 yr earlier than cancer diagnosis in family member.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Ovarian Cancer (Patient Information)
Ovarian Neoplasm, Benign (Related Key Topic)

AUTHORS: **Anthony Sciscione, DO,** and **Helen Toma, MD, MSPH**

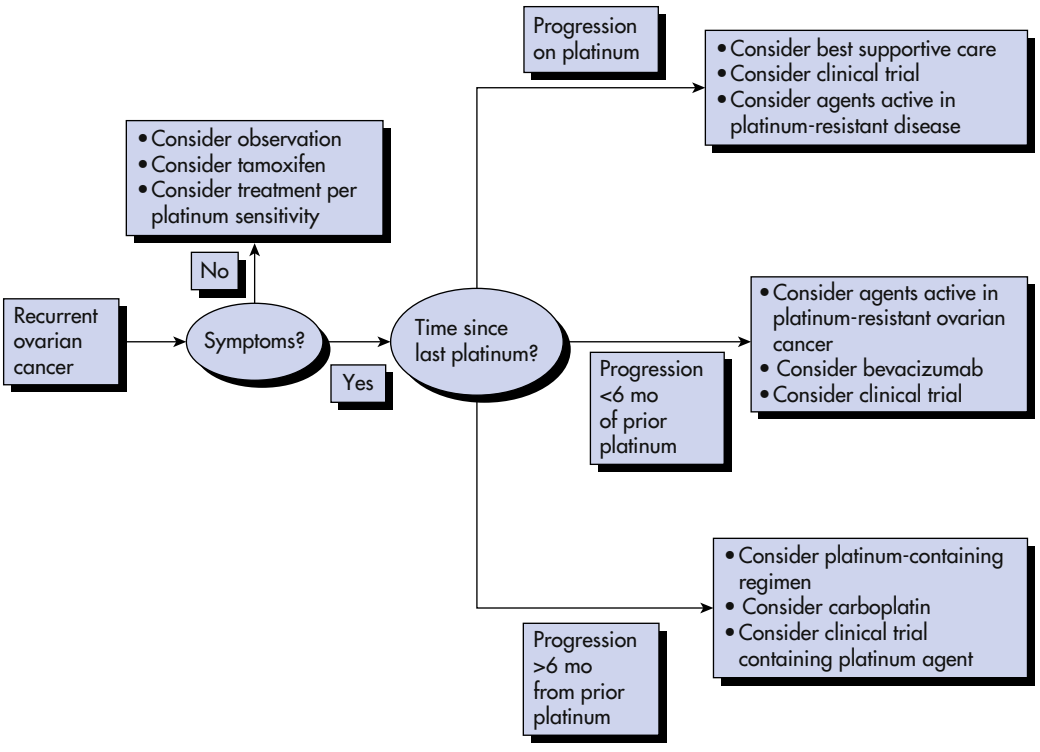

FIG. 2 Treatment approach algorithm for recurrent ovarian cancer. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

SUGGESTED READINGS

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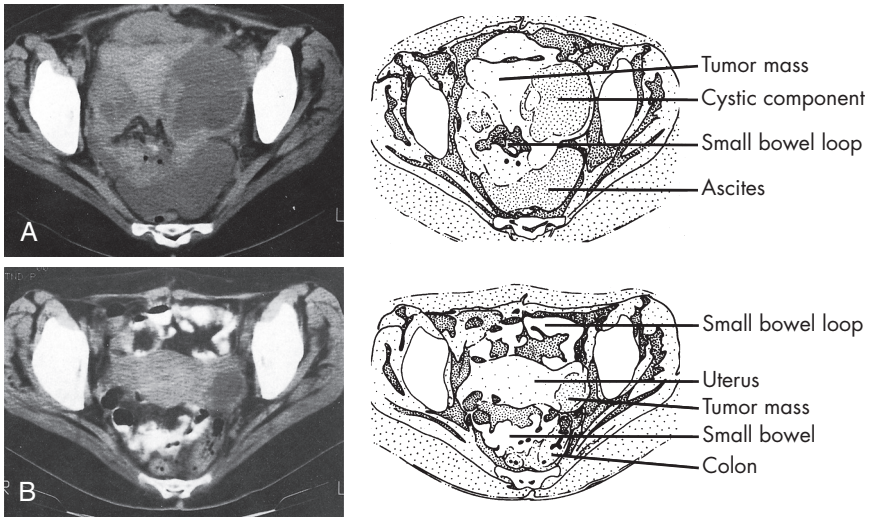

FIG. E1 Response to chemotherapy. A 51-yr-old woman presented with a rapid increase in abdominal girth. **A,** On computed tomography (CT) scan, she was found to have a 12 x 8 cm ovarian mass with a cystic component; peritoneal involvement was extensive, and 6 L of ascites was removed. Pathologic examination showed a poorly differentiated tumor. It was not resectable, and she was treated with combination chemotherapy. After one cycle of therapy, her abdomen returned to normal size. **B,** A CT scan reveals only a small residual ovarian mass. Surgery after four cycles of chemotherapy showed no gross or microscopic tumor. She received four more cycles of chemotherapy but relapsed 1 yr later with abdominal metastases. (From Skarin AT: *Atlas of diagnostic oncology,* ed 3, St Louis, 2003, Mosby.)

BASIC INFORMATION

DEFINITION

Benign ovarian neoplasms are often clinically indistinguishable from their malignant counterparts. Therefore, all persistent adnexal masses must be considered malignant until proven otherwise. Nonneoplastic tumors include:

- Germinal inclusion cyst
- Follicle cyst
- Corpus luteum cyst
- Pregnancy luteoma
- Theca lutein cysts
- Sclerocystic ovaries
- Endometrioma

Neoplastic tumors derived from coelomic epithelium include:

- Cystic tumors: Serous cystadenoma, mucinous cystadenoma, mixed forms
- Tumors with stromal overgrowth: Fibroma, adenofibroma, Brenner tumor

Tumors derived from germ cells are dermoids (benign cystic teratomas)

ICD-10CM CODES

D27.0	Benign neoplasm of right ovary
D27.1	Benign neoplasm of left ovary
D27.9	Benign neoplasm of unspecified ovary

EPIDEMIOLOGY & DEMOGRAPHICS

- **Reproductive years:**
  1. Most common benign ovarian neoplasms: Serous cystadenoma and benign cystic teratoma
  2. Most common adnexal mass: Functional cyst
  3. Risk of malignancy increases after age 40 yr
- **Infants:** Adnexal masses are usually follicular cysts attributable to maternal hormone stimulation that regress during first few mos of life.
- **Childhood:**
  1. Adnexal masses are rare.
  2. 9% to 11% malignant.
  3. Almost always dysgerminomas or teratomas (germ cell origin).
  4. Frequency of malignancy is inversely correlated with age.
- **Adolescence:**
  1. Most common adnexal mass is a functional cyst.
  2. Most common neoplastic ovarian tumor is a benign cystic teratoma.
  3. Solid/cystic adnexal tumors are rare and almost always dysgerminomas or malignant teratomas.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usually asymptomatic
- Pelvic pain or pressure
- Dyspareunia
- Abdominal pain ranging from mild to severe peritoneal irritation
- Increasing abdominal girth or distention
- Adnexal mass of pelvic examination
- Children: Abdominal or rectal mass, early-onset puberty

ETIOLOGY

- Physiologic
- Endometriosis
- Unknown

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ovarian torsion
- Endometrioma
- Uterine fibroid
- Ectopic pregnancy
- Tubo-ovarian abscess
- Paratubal or paraovarian cyst
- Hydrosalpinx
- Malignancy: Ovary, fallopian tube, colon
- Diverticular abscess, diverticulitis
- Appendiceal abscess, appendicitis (especially in children)
- Urethral diverticulum
- Nerve sheath tumors
- Distended bladder
- Pelvic kidney
- Retroperitoneal cyst or neoplasm

WORKUP

- Complete history and physical examination
- Pelvic or rectovaginal examination to reveal firm, irregular, mobile mass
- Pelvic ultrasound
- Laparoscopy or laparotomy to establish diagnosis

LABORATORY TESTS

- Pregnancy test
- Serum tumor markers:
  1. Cancer antigen 125 (CA-125)
  2. Alpha-fetoprotein (endodermal sinus tumor, immature teratoma)
  3. Beta-human chorionic gonadotropin
  4. Lactate dehydrogenase (dysgerminoma)

IMAGING STUDIES

Ultrasound (Fig. 1):

- May differentiate adnexal mass from other pelvic masses

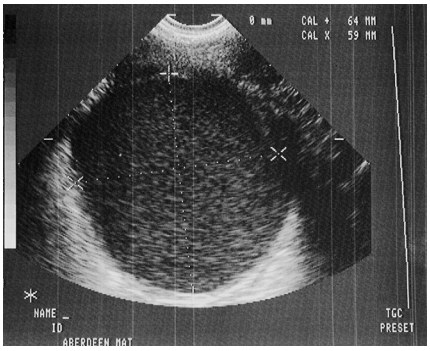

FIG. 1 Ultrasonogram reveals a cyst 6.5 cm across, which was found at laparotomy to be an endometrioma full of altered blood, the so-called chocolate cyst. This may cause cyclical or chronic pelvic pain. (From Greer IA et al: *Mosby's color atlas and text of obstetrics and gynecology,* London, 2000, Harcourt.)

- Features that increase risk of malignancy include solid component, papillae, multiple septations or solitary thick septa, ascites, matted bowel, bilaterality, irregular borders
- CT scan with contrast
- Colonoscopy or barium enema, if symptomatic

TREATMENT

NONPHARMACOLOGIC THERAPY

Repeat pelvic examination, typically with transvaginal pelvic ultrasound, for premenopausal women in 4 to 6 wk to rule out persistent cyst.

ACUTE GENERAL Rx

Indications for surgery:

- Postmenopausal or premenarchal palpable adnexal mass
- Adnexal mass with suspicious ultrasound features
- Adnexal mass greater than 10 cm
- Suspected torsion or rupture

CHRONIC Rx

- Depends on diagnosis
- Possible suppression of formation of new cysts by oral contraceptives

DISPOSITION

- Depends on diagnosis.
- One study showed that all malignant masses demonstrated growth within 7 mo. Expert opinion recommends limiting observation of stable masses without solid components to 1 yr and with solid components to 2 yr.

REFERRAL

- If malignancy suspected
- If surgery required

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Ovarian Cysts (Patient Information)
Ovarian Cancer (Related Key Topic)

AUTHORS: **Anthony Sciscione, DO, and Helen Toma, MD, MSPH**

SUGGESTED READING

Stukan M: Usefulness of diagnostic indices comprising clinical, sonographic and biomarker data for discriminating benign from malignant ovarian masses, *J Ultrasound Med* 34(2):207-217, 2015.

Over-the-Counter Medication in Pregnancy

BASIC INFORMATION

DEFINITION

Over-the-counter (OTC) medications are pharmacologic agents that patients can buy without a physician's prescription. They come in different forms, such as pills, creams, ointments, patches, or drops.

SYNONYM

Medications without a prescription

ICD-10CM CODE

V22.1 Supervision of otherwise normal pregnancy

EPIDEMIOLOGY AND DEMOGRAPHICS

INCIDENCE: More than 90% of women take some form of OTC medications in pregnancy.
PEAK INCIDENCE: Majority of use occurs in winter and spring due to common respiratory illnesses.

DIAGNOSIS

WORKUP

At the initial prenatal visit, a full history and physical should be performed. Patients should be asked regarding all prescription and OTC medication use, along with herbals and supplements in order to ensure that no harmful or dangerous substances are being used.

COUNSELING

Despite their availability, certain OTC medications can have significant side effects, interact with other medications, and can be toxic when exceeding recommended doses. Patients should therefore be cautious and aware of these issues when taking OTC medications.

PEARLS AND CONSIDERATIONS

COMMENTS

- OTC medications are most commonly used for treatment of cough/cold, allergies, gastrointestinal issues, skin rashes/lesions, and pain relief.
- In general, pregnant women are excluded from clinical trials to determine drug safety, and the majority of information regarding fetal effects results from animal studies. Due to this lack of information, many OTC medications are not rated as category A according to the FDA risk classification system (Table E1).
- Certain medications are considered to be safe in pregnancy due to widespread use with no well-known association with teratogenicity (Table E2), whereas others have been known to have a causal relationship with adverse effects in pregnancy (Table E3).

TABLE E1 Food and Drug Administration Pregnancy Risk Classification System

Category	Definition
Category A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in any trimester of pregnancy.
Category B	Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Category C	Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans. However, potential benefits may warrant use of the drug in pregnant women despite potential risks.
Category D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans. However, potential benefits may warrant use of the drug in pregnant women despite potential risks.
Category X	Studies in animals or humans have demonstrated fetal abnormalities, and there is positive evidence of human fetal risk based on available data. Risks involved in use of this drug by pregnant women clearly outweigh potential benefits.

TABLE E2 Over-the-Counter Medications Considered to Be Relatively Safe in Pregnancy*

Drug Name	Drug Class	FDA Risk Classification
Folic acid	Dietary supplement	A
Pseudoephedrine	Decongestant	B
Cetirizine	Antihistamine	B
Diphenhydramine	Antihistamine	B
Ranitidine	Antihistamine	B
Dimenhydrinate	Antiemetic	B
Loperamide	Anti-diarrheal	C
Hydrocortisone (topical)	Corticosteroid	C
Dextromethorphan	Antitussive	C
Docusate sodium	Stool softener	C
Omeprazole	Proton pump inhibitor	C
Calcium carbonate	Antacid	C
Simethicone	Antiflatulent	C

FDA, Food and Drug Administration.
*Despite claims regarding the relative safety of these products, questions remain about their risks in pregnancy. For example, pseudoephedrine was considered low risk based on older cohort studies, but newer data show some association with birth defects such as hemifacial microsomia, small intestinal atresia, and gastroschisis.

TABLE E3 OTC Medications to Use with Caution in Pregnancy

Drug Name	Drug Class	FDA Risk Classification	Safety Concerns
Aspirin	Salicylate	B	Associated with neonatal hemorrhage and increased perinatal mortality. Can be used in specific situations, such as maternal clotting disorders or history of pre-eclampsia
Guaifenesin	Expectorant	C	Possible increased risk of neural tube defects if used in the first trimester, but otherwise considered safe in pregnancy
Caffeine	Stimulant	C	Associated with spontaneous abortion in high doses; use with caution
Ibuprofen, Naproxen	NSAID	D	Associated with oligohydramnios, premature closure of ductus arteriosus in third trimester, and fetal nephrotoxicity
Nicotine	Stimulant	D	Associated with intrauterine growth restriction and preterm birth; however, nicotine replacement is preferable to smoking in pregnancy

FDA, Food and Drug Administration; *NSAID,* nonsteroidal anti-inflammatory drug; *OTC,* over-the-counter.

- The most sensitive period during a pregnancy is the first trimester due to organogenesis. Therefore, any medications that are not absolutely essential should be avoided during this time.

PATIENT & FAMILY EDUCATION

Patients should be referred to the CDC website (cdc.gov/pregnancy/meds) for information regarding the use of specific medications.

AUTHOR: **Ghamar Bitar, MD**

SUGGESTED READING

Servey J, Chang J: Over-the-counter medications in pregnancy, *Am Fam Phys* 90(8):548-555, 2014.

Paget Disease of Bone PTG

BASIC INFORMATION

DEFINITION

Paget disease of bone is a focal disorder of chaotic bone remodeling with increased osteoblastic and osteoclastic activity that results in disorganized woven and lamellar bone (Fig. E1) in one or more skeletal sites. The end result is bone of poor quality that is enlarged, hypervascular, and susceptible to deformation and fracture.

SYNONYM

Osteitis deformans

ICD-10CM CODES

M88.9	Osteitis deformans of unspecified bone
M88.0	Osteitis deformans of skull
M88.1	Osteitis deformans of vertebrae
M88.869	Osteitis deformans of unspecified lower leg
M88.89	Osteitis deformans of multiple sites
M90.60	Osteitis deformans in neoplastic diseases, unspecified site
M90.679	Osteitis deformans in neoplastic diseases, unspecified ankle and foot
M90.68	Osteitis deformans in neoplastic diseases, other site
M90.69	Osteitis deformans in neoplastic diseases, multiple sites

EPIDEMIOLOGY & DEMOGRAPHICS

Epidemiologic data suggest an origin of Paget disease in Great Britain spreading to other areas by English colonists beginning in the seventeenth century. Highest prevalence occurs in Eastern and Western Europe and in those who have emigrated to New Zealand, Australia, South Africa, and North America. Paget is rarely seen in Japanese, Chinese, Asian Indians, sub-Saharan Africans, and Middle Eastern Arabs.

- Most commonly diagnosed in those aged >50 yr and rare before 40 yr.
- Prevalence estimates of up to 3% of population aged >50 yr and up to 10% in those aged >90 yr.

PREDOMINANT SEX: Variable preponderance of males
PREDOMINANT AGE: Middle or advanced yr
FAMILIAL INCIDENCE: Common, family history positive in up to 40% of cases

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most common sites of involvement: Pelvis (70%), lumbar spine (53%), sacrum, femur (55%), skull (42%), tibia (30%) (Fig. E2), humerus, scapula
- Uncommon: Hand, foot, fibula
- Lesions in one (monostotic) or more bones (polyostotic)
- Gradual progression of disease in affected bone(s) with rare appearance at new site(s)
- Many patients are asymptomatic, but up to 40% of patients who come to medical attention present with bone pain
- Symptoms and signs include bone and articular pain often related to secondary arthritis, bone deformities and enlargement, increased warmth over pagetic bone, skull enlargement, nerve entrapment or compression syndromes, cranial nerve deficits especially deafness (Fig. E3), spinal cord compression and vascular steal syndromes, fissure fractures, fractures, and neoplastic degeneration

ETIOLOGY

Fig. E4 illustrates the pathophysiology of Paget disease. Extensive epidemiologic and laboratory data are in keeping with potential role of paramyxoviral infection of osteoclasts in a genetically susceptible individual with or without documented genetic mutations.

DIAGNOSIS

Diagnosis is often suspected in asymptomatic patients with isolated elevation of alkaline phosphatase without evidence of liver disease.

DIFFERENTIAL DIAGNOSIS

- Osteosclerosis
- Hyperphosphatasia
- Familial expansile osteolysis
- Fibrous dysplasia
- Skeletal neoplasm (primary or metastatic)
- Osteomalacia with secondary hyperparathyroidism

LABORATORY TESTS

- Increase in serum alkaline phosphatase or bone-specific alkaline phosphatase
- Increase in urine NTx/creatinine ratio or plasma CTx
- Bone biopsy is rarely needed but may be necessary in selected cases to rule out sarcomatous degeneration or metastatic disease

IMAGING STUDIES

Bone scintigraphy (Fig. E5) is the most sensitive test for delineating the extent and site of pagetic lesions but nonspecific in that areas of uptake may be related to arthritis or metastatic lesions. Radiographs (Fig. E6) will further delineate characteristic pagetic changes (thickening of cortical bone, coarsened trabecular markings, distortion and expansion of involved bone).

TREATMENT

Indications for therapy include extensive or symptomatic disease; neurologic complications; involvement of weight-bearing bones, skull, vertebrae, and other areas of critical involvement (e.g. in proximity to joints); prevention of excess bleeding from an orthopedic procedure on pagetic bone; and if serum alkaline phosphatase is more than 4 times the upper limit of normal.

NONPHARMACOLOGIC THERAPY

- Optimization of calcium and vitamin D intake and appropriate guidance regarding ambulatory needs.
- Orthopedic stabilization may be required for patients with pseudofractures.

SPECIFIC THERAPY

Bisphosphonates are the mainstay of therapy and include oral alendronate or risedronate and intravenous pamidronate or zoledronic acid. A one-time dose of zoledronic acid (5mg IV) may be effective in controlling symptoms for over 3 yr.

- SC salmon calcitonin when bisphosphonates are not tolerated or are contraindicated as in those with GFR of <35 ml/min
- Acetaminophen, aspirin, and nonsteroidal drugs for relief of pain

DISPOSITION

- Without treatment, progression of disease is common.
- With treatment, remissions of varying duration in most patients. Bisphosphonates can normalize bone turnover in a high proportion of patients, but evidence that long-term suppression of bone turnover prevents complications or improves the clinical outcome is currently inconclusive.
- Careful and regular clinical and biochemical follow-up at 3 to 6-mo intervals with necessity of retreatment in patients with continued pagetic activity or reactivation.
- With first-ever intravenous dose of pamidronate or zoledronic acid, patients may experience a flulike syndrome that may be prevented with acetaminophen.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Paget Disease of Bone (Patient Information)

AUTHOR: **Joseph R. Tucci, MD, FACP, FACE**

SUGGESTED READINGS

Cundy T et al: Durability of response to zoledronate treatment and competing mortality in Paget's disease of bone, *J Bone Miner Res* 32(4):753-756, 2017.

Michou L, Orcel P: The changing countenance of Paget's disease of bone, *Joint Bone Spine* 83:650-655, 2016.

Ralston SH: Paget's disease of bone, *N Engl J Med* 368:644-650, 2013.

Ralston SH et al: Diagnosis and management of Paget's disease of bone in adults: a clinical guideline, *J Bone Miner Res* 34(4):579-604, 2019.

Singer FR: Paget disease of bone-genetic and environmental factors, *Nat Rev Endocrinol* 11:662-671, 2015.

Tucci JR: Preoperative management of Paget disease. In Aaron RK, editor: *Diagnosis and management of hip disease*, Cham, Switzerland, 2015, Springer International Publishing, pp. 159-174.

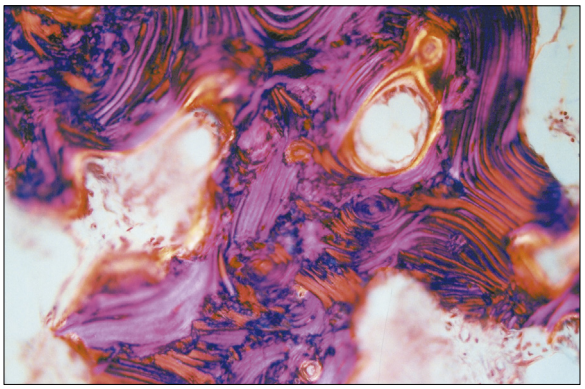

FIG. E1 Characteristic Pattern Of "Mosaic" Bone In Paget Disease Of Bone. Lamellar bone is interspersed with woven bone. An 8-μm-thick section of nondecalcified bone is viewed under polarized light. Solochrome Cyanin R staining. Magnification ×200. (Courtesy of Dr. Louis-Georges Ste-Marie and Dr. Natalie Dion, Laboratoire des maladies osseuses métaboliques at Centre de recherche du CHUM, Université de Montréal, Montréal, Canada. In Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

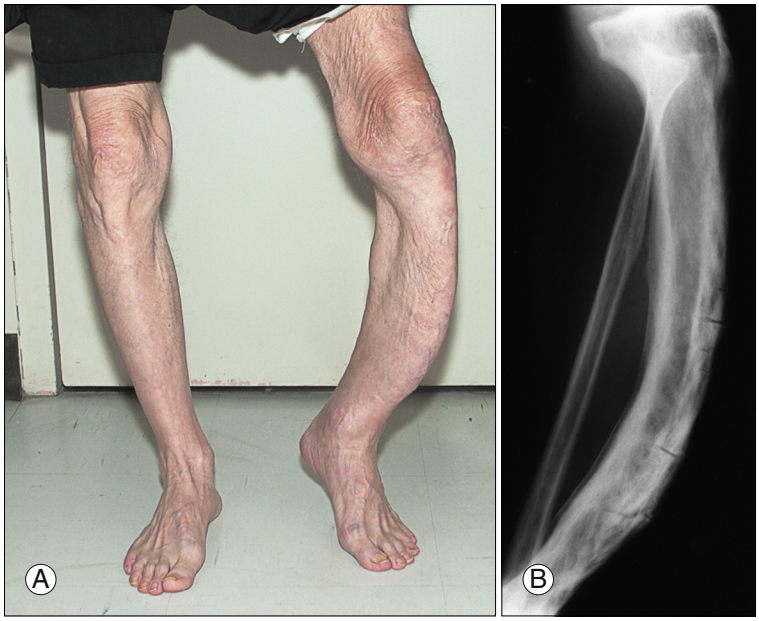

FIG. E2 Paget disease of the left tibia. A, Important deformity with anterolateral bowing. **B,** Several fissure fractures can be seen on the anterior part of the tibial shaft. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

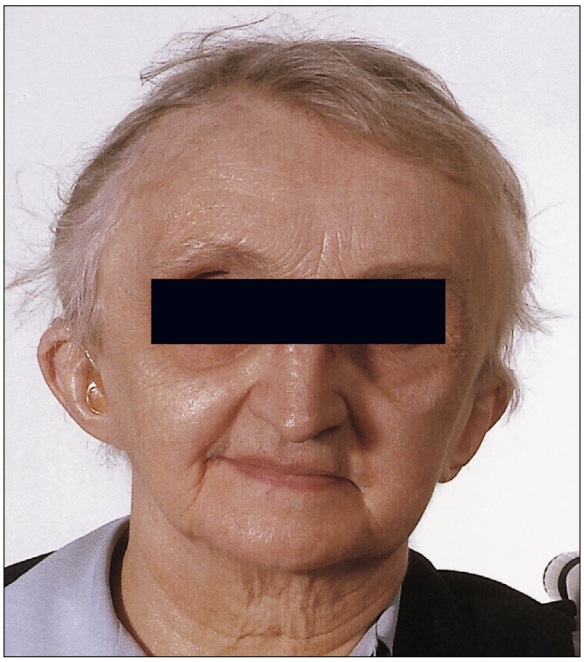

FIG. E3 Paget disease producing a right deformity of the skull, deafness (see the hearing amplifier device in the right ear), and apathy as a result of vascular steal syndrome. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

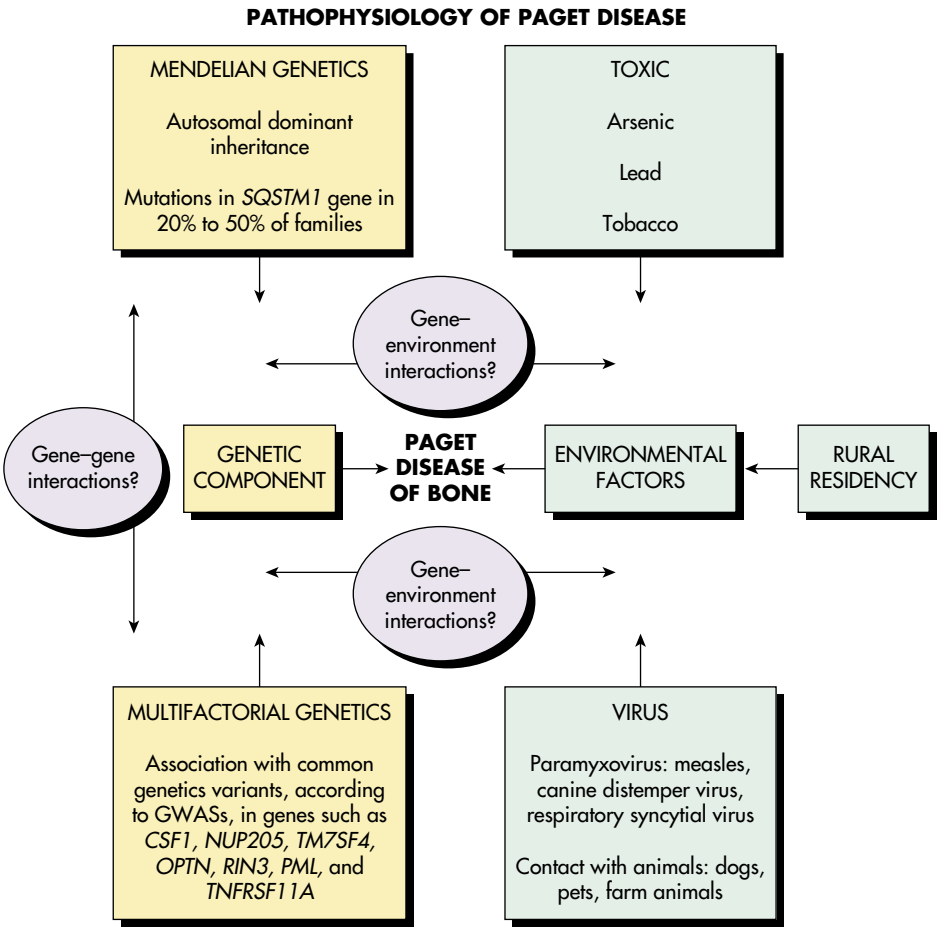

FIG. E4 Pathophysiology of Paget disease of bone. *GWAS*, Genome-wide association study. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

FIG. E5 A technetium-99m MDP (methylene diphosphonate) bone scan shows polyostotic Paget disease involving the sternum, right scapula, two lumbar vertebral bodies, and right hemipelvis. Early pagetic disease may be involving the right side of the skull as well. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

FIG. E6 Paget disease of the bone. Frontal radiograph of the pelvis shows marked prominence of the trabeculae in the right ilium, ischium, and pubic bones, with small lytic areas identified as compatible with the later stages of Paget disease. (From Specht N [ed]: *Practical guide to diagnostic imaging,* St Louis, 1998, Mosby.)

BASIC INFORMATION

DEFINITION

Paget disease of the breast is a malignant disease that presents itself as a scaly, sore, eroding, bleeding ulcer of the nipple. It represents an extension of a ductal adenocarcinoma of the breast. Microscopically, typical large clear cells (Paget cells) with pale and abundant cytoplasm and hyperchromatic nuclei with prominent nucleoli are found in the epidermal layer. Paget disease is more often associated with primary invasive or in situ carcinoma of the breast.

ICD-10CM CODES

C50.0	Malignant neoplasm of nipple and areola
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.029	Malignant neoplasm of nipple and areola, unspecified male breast

EPIDEMIOLOGY & DEMOGRAPHICS

- 1% to 3% of new female breast cancer cases
- Peak incidence ages 50s through 60s

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Variable; most often reveals an erythematous, irregularly bordered plaque that starts on the nipple and spreads to the areola.
- Itching or burning nipple and/or reported lump. Itching/burning may occur before lesion.
- Very minimal scaly lesion that may bleed when scales are lifted.
- Typical ulcer located on nipple with serous fluid weeping or small amount of bleeding coming from it (Fig. E1) Bloody discharge may also occasionally occur.
- Palpable carcinoma in the breast of some patients.
- 20% with no palpable mass will have suspicious finding on mammogram.

ETIOLOGY

- Exact origin unknown
- Possibly migration of either in situ or invasive carcinoma cells in breast to nipple skin to produce Paget disease

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Chronic dermatitis
- Florid papillomatosis of the nipple or nipple adenoma
- Eczema
- Skin cancer

WORKUP

- Clinically apparent
- Careful breast examination with diagnosis in mind
- Palpable mass or mammographic lesions in 50% of patients

LABORATORY TESTS

Biopsy of nipple lesion

IMAGING STUDIES

Mammograms to search for possible primary carcinoma

TREATMENT

NONPHARMACOLOGIC THERAPY

- Paget disease without palpable mass and negative mammogram:
  1. Consideration of wide excision of nipple with radiation
  2. Mastectomy is also an option
- Paget disease with palpable mass or abnormal mammogram findings:
  1. Mastectomy
  2. Breast conservation surgery and whole breast radiation

Presence of underlying in situ or invasive carcinoma in mastectomy specimen of majority of patients.

Evaluation of axilla is the same for other breast cancers and depends on underlying type.

ACUTE GENERAL Rx

Systemic adjuvant therapy depending on extent of invasive carcinoma found

DISPOSITION

- Parallel prognosis to that of breast cancer patient without Paget disease
- Prognosis is better in those without palpable mass
- Regular follow-up as in other invasive or in situ carcinoma patients

REFERRAL

At outset, all suspicious nipple lesions should be referred for evaluation and treatment.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Paget Disease of the Breast (Patient Information)
Breast Cancer (Related Key Topic)

AUTHORS: **Gina Ranieri, DO,** and **Anthony Sciscione, DO**

SUGGESTED READING

Helme S et al: Breast conserving surgery in patients with Paget's disease, *Br J Surg* 102(10):1167-1174, 2015.

Caliskan M et al: Paget's disease of the breast: the experience of the European Institute of Oncology and review of the literature, *Breast Cancer Res Treat* 112:513, 2008.

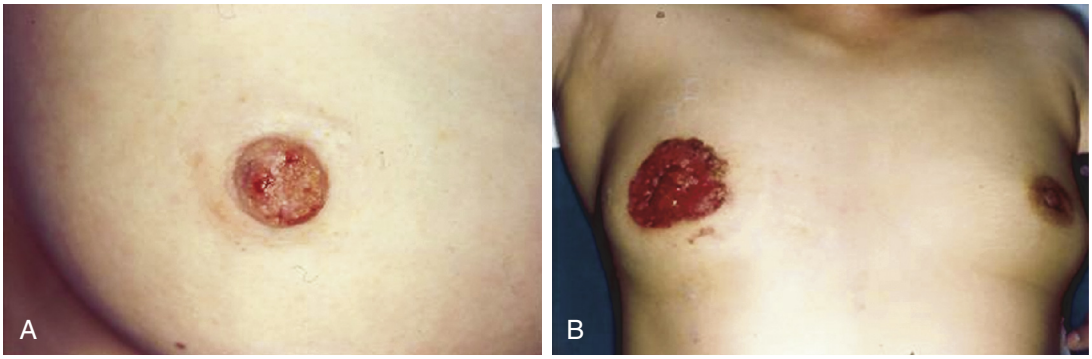

FIG. E1 **A** and **B,** Paget disease of the nipple. (Courtesy Sehwan Han, MD)

BASIC INFORMATION

DEFINITION

Chronic pain is pain that persists for longer than the expected time frame (typically >3 mo) or that is associated with progressive, nonmalignant disease. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. The perception of pain is influenced by physiologic, psychological, and social factors. Chronic pain may be the direct result of an underlying disease process, or it may be a separate condition in its own right.

SYNONYMS

Chronic pain management
Nonmalignant chronic pain
Pain management

ICD-10CM CODES

G89.21	Chronic pain due to trauma
G89.22	Chronic post-thoracotomy pain
G89.3	Neoplasm-related pain (acute) (chronic)
G89.4	Chronic pain syndrome
G89.28	Other chronic post-procedural pain
G89.29	Other chronic pain

EPIDEMIOLOGY & DEMOGRAPHICS

Estimates of the prevalence of chronic pain in the U.S. vary widely. A 2011 report from the Institute of Medicine, *Relieving Pain in America*, estimates that 116 million adults live with chronic pain at a cost of almost $635 billion per yr. Chronic pain is the third leading cause of physical impairment in the U.S. and the leading cause of disease burden and disability globally. Patients with chronic pain may also experience mood changes, depression, sleep disturbances, fatigue, and decreased overall physical functioning.

CLINICAL PRESENTATION

- History: Comprehensive patient assessment, including history of present illness (cause of pain, location, timing, characteristics, exacerbating/relieving factors, triggers), past therapies (pharmacologic and nonpharmacologic and outcomes of these therapies), medical history, family and social history, psychiatric history (including history of depression, anxiety, abuse, and/or other psychological disorders), substance use history, allergies, sleep patterns and disturbances, and current medications. Social supports, coping mechanisms, and spirituality can also help guide development of a treatment plan.
- Pain assessment should be performed at each visit; includes pain intensity (1 to 10), response to medication, and attributes of pain. Standardized templates for both initial and follow-up pain assessment have been developed by various organizations. The Brief Pain Inventory is an example of a widely used assessment tool. In addition, a functional assessment should be performed. Tools such as the Functional Ability Questionnaire (FAQ5) can guide the clinician in determining a patient's functional status. Lastly, consider assessment of a patient's risk for substance abuse.
- Physical examination: Directed at systems affected by pain (often musculoskeletal) and neurologic examination.
- Look for contributing factors (e.g., comorbidities, lifestyle factors) and barriers to effective care (e.g., behavioral, social, insurance). Increasing evidence points to a relation between obesity and chronic pain.
- Components of a comprehensive assessment of cancer pain are summarized in Box 1.

ETIOLOGY

Mechanisms of chronic pain can be divided into three broad categories:

- Nociceptive—pain arising from damage to peripheral tissue from injury or inflammatory, mechanical, or metabolic causes
- Neuropathic—peripheral nerve impairment
- Central—central disturbance in pain processing

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Depends on etiology:
  1. Nociceptive—osteoarthritis, rheumatoid arthritis, postsurgical pain, posttraumatic, cancer pain
  2. Neuropathic—postherpetic neuralgia, diabetic neuropathy, nerve root compression
  3. Central—fibromyalgia, irritable bowel syndrome, chronic headache, phantom limb
- Many chronic pain syndromes may involve one or more of the previously named mechanisms. The etiology of pain in cancer patients is summarized in Box 2.
- Depression and anxiety disorders can be both a cause and a result of chronic pain, so temporal association of these disorders is important.
- Coping mechanisms also can contribute to the risk of developing chronic pain. For example,

BOX 1 Components of A Comprehensive Assessment of Cancer Pain

I. Detailed history of current pain problem
  A. Catalog of pain (number and locations)
  B. Information for each type of pain
    1. Intensity (0-10)
    2. Locations and radiation
    3. Onset and changes over time
    4. Temporal pattern (e.g., constant or intermittent) and quality (e.g., burning)
    5. Exacerbating and relieving factors
    6. Associated neurologic or vasomotor abnormalities
    7. Other associated factors
    8. Interference with the patient's life
    9. Current therapeutic modalities (e.g., schedule, efficacy, and adverse effects)
    10. Prior therapeutic modalities (e.g., schedule, efficacy, and adverse effects)
II. Oncologic history
  A. Histologic type
  B. Presentation: Date, stage, and sites of involvement
  C. Antineoplastic therapies: Dates, types, doses, toxicities, and response to each therapy
  D. Current sites of disease: Stable, responding, or progressive
  E. Patient expectations and goals
III. Medical history—may be affected by pain therapies
  A. Coexisting diseases
  B. Medications and allergies
  C. Substance abuse history
  D. Other constitutional symptoms such as anorexia, fatigue, sedation and other changes in mental status, nausea, vomiting, dysphagia, dyspnea, constipation, urinary and sexual dysfunction, depression, dry mouth; also, the ability to take medications by mouth and the presence of a central venous catheter
IV. Personal and social history
  A. Background: Age, education, employment, marital status, place of residence, religious affiliation, and cultural and ethnic background
  B. Current status: Functional status, caregivers and their health and availability, support system
V. Physical examination
VI. Review of additional information
  A. Medical records, radiologic and laboratory studies
  B. Family members, physicians and/or nurses who know the patient and his or her illness
VII. Differential diagnosis
VIII. Recommendations regarding workup and therapy
IX. Reassessment

From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

anxiety and fear about pain is associated with an increased likelihood of developing chronic pain. Patients with a passive attitude toward treating pain (e.g., rest, medication use) also are associated with higher rates of chronic pain than those with active attitudes.
- Genetic factors play a role. There are at least 150 genes that contribute to chronic pain. It has been shown to be a heritable phenotype, although no one set of genes has been identified as the culprit.
- Factors such as socioeconomic background, employment status, physical activity, sleep disorders, and weight can have a bidirectional effect on chronic pain.

WORKUP

- Workup should be directed at identifying the source of pain. Identification of the mechanism of pain will guide the development of an appropriate treatment plan.
- Laboratory testing, imaging studies, and/or electromyographic (EMG) studies should be used when etiology of chronic pain is unknown or unclear, when comorbidities are suspected, and as the history and physical examination direct.
- Consider use of random urine drug screens or other tests to screen for presence of illegal drugs, unreported prescribed medications, or alcohol use.

Rx TREATMENT

- Studies increasingly support the application of a multidisciplinary, biopsychosocial approach that addresses the multiple facets of pain and includes the patient's perspective and goals
- Therapeutic goal is the reduction of pain (elimination of chronic pain is generally unlikely and providers need to discuss these limitations with patients at outset)
- A written care plan that includes methods to address the patient's personal goals, improve sleep, increase physical activity, manage stress, and reduce pain

NONPHARMACOLOGIC THERAPY

- Exercise (recommended for all patients and tailored to individual abilities and needs). Recent studies demonstrate the benefit of tai chi for patients with osteoarthritis and therapeutic exercise for those with all forms of chronic pain
- Modalities: Heat therapy, cold therapy, transcutaneous electrical nerve stimulation (TENS) units, manipulative therapy, cognitive behavioral therapy, psychological counseling and physical therapy
- Electrostimulation therapy: TENS units
- Behavioral therapies: Cognitive behavioral therapy, hypnosis, biofeedback, relaxation therapy, mindfulness
- Music therapy (in conjunction with other types of therapy)
- Surgery (rarely considered a first-line therapy for chronic pain)

GENERAL PHARMACOLOGIC Rx

- Short-acting antiinflammatory and analgesic medications (e.g., acetaminophen/NSAIDs/opioids). Avoid use of NSAIDs in patients with hypertension, congestive heart failure (CHF), or any type of chronic kidney disease (CKD). These medications should be considered first-line therapy for all patients without contraindications
- Topical analgesics (lidocaine, NSAIDs, capsaicin)
- Trigger-point or joint injections (immediate anesthetic plus long-acting corticosteroids)
- Epidural steroid injections
- Nerve blocks (Table 1)
- Antidepressants (tricyclic and selective serotonin reuptake inhibitors)
- Anticonvulsant medications (e.g., carbamazepine, valproic acid, gabapentin, pregabalin); particularly helpful for neuropathic conditions
- Ketamine (N-methyl-d-aspartate [NMDA] receptor antagonist). Recent studies have been done on its use in patients with opioid tolerance and hyperalgesia. The efficacy of ketamine is moderate to weak, and it only should be considered as third-line

BOX 2 Etiology of Pain in Patients with Cancer

A. Direct tumor involvement (70%)
   1. Invasion of bone
   2. Invasion or compression of neural structures
   3. Obstruction of hollow viscus or ductal system of solid viscus
   4. Vascular obstruction or invasion
   5. Mucous membrane ulceration or involvement
B. Cancer-induced syndromes (<10%)
   1. Paraneoplastic syndromes
   2. Pain associated with debility (e.g., bedsores, constipation, rectal or bladder spasms)
   3. Other (e.g., postherpetic neuralgia)
C. Diagnostic or therapeutic procedures (20%)
   1. Procedure-related pain (e.g., bone marrow aspiration or biopsy and lumbar puncture)
   2. Acute postoperative pain or postsurgical syndromes (e.g., postmastectomy, postthoracotomy, and postamputation syndromes)
   3. After radiation (e.g., injury to plexus or spinal cord, mucositis, and enteritis)
   4. After chemotherapy (e.g., mucositis, peripheral neuropathy, and aseptic necrosis)
D. Pain unrelated to the malignancy or its treatment (<10%)

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TABLE 1 Regional Anesthetic Techniques

	Types of Blocks	Examples	Indications	Comments
Local anesthetic blocks	Diagnostic	Intercostal nerve block	Determine etiology of pain and the response and adverse effects following local therapies	Analgesic effect will last only hours
	Treatment of sympathetically maintained pain	Stellate ganglion block	Sympathetically maintained pain	Repeated blocks might be needed
	Trigger point injections	Trigger point injection	Myofascial pain syndrome	Repeated blocks might be needed
Neurolytic (alcohol or phenol) blocks	Peripheral	Intercostal nerve blocks	Chest wall tumor	Pain relief usually lasts several mo
	Visceral	Celiac plexus block Superior hypogastric block Ganglionic impar block	Pancreatic cancer Gastrointestinal or genitourinary cancers	Pain relief usually lasts several mo
	Neuraxial	Epidural	Pain localized to two or three dermatomes	Pain relief usually lasts several mo
		Intrathecal neurolysis Spinal cord stimulator		

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TABLE 2 Commonly Used Adjuvant Analgesics for Cancer Pain

Drug Category	Indications	Drugs	Common Toxicities	Comments
Antidepressants	Neuropathic pain	Amitriptyline Nortriptyline Desipramine Duloxetine Venlafaxine	Sedation, dry mouth, constipation, postural hypotension, urinary retention	Begin with low doses and increase the dose every few days
Anticonvulsants	Neuropathic pain	Carbamazepine Pregabalin Clonazepam Gabapentin	Drowsiness, dizziness, nausea, rash, bone marrow depression	Monitor platelets with carbamazepine
Corticosteroids	Spinal cord compression, increased intracranial pressure, visceral distention	Dexamethasone Methylprednisolone Prednisone	Gastritis, insomnia, fluid retention, hyperglycemia, myopathy, increased appetite	
Muscle relaxants	Muscle spasm	Diazepam Baclofen Methocarbamol Cyclobenzaprine	Sedation, dizziness, nausea, weakness, confusion	
Benzodiazepines	Muscle spasm, myoclonus, anxiety, insomnia	Diazepam Lorazepam Alprazolam Midazolam Temazepam	Sedation, delirium, hypotension, headache, respiratory depression	Not analgesics; synergistic effect with opioids can cause respiratory depression
Antispasmodics	Gastrointestinal or bladder spasm	Diphenoxylate and atropine Loperamide Scopolamine patch Dicyclomine	Sedation, dry mouth, constipation	
Neuroleptics	Delirium, agitation, nausea and vomiting, hiccups	Olanzapine Risperidone Quetiapine Haloperidol Prochlorperazine	Sedation, orthostatic hypotension, confusion, extrapyramidal reactions	Useful for symptoms other than pain
Bisphosphonates	Bone pain	Pamidronate Zoledronic acid Alendronate Risedronate Ibandronate Etidronate Denosumab	Hypocalcemia, fever, gastrointestinal disturbances, anemia	Delays time to painful skeletal events; also used with analgesics for bone pain

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treatment. Ketamine also requires regular infusion, and its efficacy is limited by side effects (mainly psychological).
- Implantable methods, epidural and intrathecal drug delivery systems, dorsal column stimulators
- Treatment of insomnia and sleep disorders to reduce pain with standard sleep-inducing agents (trazodone, antihistamines)
- Many patients may require combination drug therapy (CDT) for adequate control of pain, with appropriate attention given to interactions and side effects. Commonly used adjuvant analgesics for cancer pain are summarized in Table 2

OPIOID THERAPY

- Although a mainstay of treatment over the past two decades, limited evidence is available demonstrating the efficacy of both immediate- and long-acting opioid preparations. Some patients with severe chronic pain syndromes may still benefit from this form of treatment. Full opioid agonists are generally the drug of choice for severe chronic cancer pain. Tenets of opioid prescribing are summarized in Box 3.
- Opioids are rarely beneficial in the treatment of inflammatory or mechanical pain and are not indicated for treatment of headaches. Recent studies also have demonstrated the development of hyperalgesia with long-term opioid use.
- The Centers for Disease Control and Prevention has published detailed guidelines for prescribing opioids for chronic pain in light of rising rates of opioid addiction and overdose. The guidelines include when and with whom to use opioid therapy, opioid selection, dosing, duration, and follow-up, along with assessment of the risks, benefits, and discontinuation of therapy.
- Current recommendations include aiming for daily opioid doses of <50 MME/day to limit the risk of overdose and side effects, prescribing naloxone to patients receiving daily doses >50 MME/day due to risk of overdose, avoiding concomitant use with benzodiazepines, and avoiding doses >90 MME/day, or referral to a pain management specialist for close monitoring.
- Sustained-release opioids (used for moderate to severe pain that has failed other therapeutic interventions): Oxycodone, morphine sustained release(SR), methadone (use with caution), or fentanyl patch; short-acting opioids can be used in conjunction with these agents for management of breakthrough pain. Conversion to a long-acting opioid should be based on an equi-analgesic conversion. Table E3 compares morphine milligram equivalent doses for commonly prescribed opioids.

Table 4 provides guidelines for opioid dose selection, conservative initial starting doses for opioid-naïve individuals, and conversion ratios for opioid rotation in patients on chronic opioids. Titration of these medications should not exceed the equivalent of 100 mg morphine/Day to avoid risk of overdose. Box E4 summarizes CDC recommendations for prescribing opioids for chronic pain outside of active cancer and palliative and end-of-life care. Box E5 summarizes the interpretation of recommendation categories and evidence types.

MEDICAL MARIJUANA

- Limited studies on efficacy, side effects, or outcomes for use in CNCP
- Some small randomized controlled trials (RCTs) show benefit of low-dose cannabinoids for chronic neuropathic pain

BOX 3 Management Approach: Tenets of Opioid Prescribing

- Order opioids on a scheduled "around-the-clock" basis to optimize relief.
- Order an as-needed opioid to treat breakthrough or incidental pain.
- Initiate a prophylactic bowel regimen at the same time opioids are prescribed. Patients usually require a combination of stool softeners and stimulant laxatives to treat opioid-induced constipation.
- Treat opioid-induced nausea and vomiting with aggressive antiemetic management, which includes giving patients antiemetics on an around-the-clock basis. Patients often become tolerant to this adverse effect several days after beginning opioids.
- Once baseline opioid requirements are determined, sustained-release opioid preparations can be used to reduce the number of pills taken each day.
- Teach the patient and family about the purpose and benefits of opioids to allay their fears about adverse effects and addiction. This instruction will improve patient compliance.
- Frequent assessment of pain relief is paramount during the opioid titration period. Titrate doses based on the patient's report of pain relief and/or the amount of as-needed opioid that has been required for patient comfort.
- Maximize the doses of one opioid before changing to another agent or route. Changes should be made primarily because of toxicities. For example, a patient taking 200 mg of controlled-release morphine every 12 hr and 200 mg of immediate-release morphine daily for breakthrough pain should have the dose of controlled-release morphine increased to 300 mg every 12 hr if he or she is not experiencing significant opioid adverse effects. This approach is more likely to be beneficial than beginning titration with subcutaneous or intravenous morphine or oral hydromorphone.
- Refer to equianalgesic tables when initiating or changing a patient's analgesic regimen.
- Avoid chronic administration of intramuscular or rectal opioids.
- Avoid chronic administration of meperidine, which can be associated with the accumulation of normeperidine, a neurotoxic metabolite.

From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Acupuncture and massage (evidence-based for some indications). Acupuncture is most likely to benefit patients with low back pain, neck pain, chronic idiopathic or tension headache, migraine, and knee osteoarthritis. Recent evidence has demonstrated the benefit of modalities such as yoga, tai chi, and music therapies. Supplements, although popular, do not have substantial evidence to recommend for or against their use.

REFERRAL

- Pain medicine specialist or multidisciplinary pain clinic: Useful when primary therapies fail, in patients with complex pain conditions, in patients requiring a high daily morphine milligram equivalent (MME), or for invasive therapies
- Consider referral to an addiction specialist if patient has a history of substance abuse or addiction
- Psychiatry/psychological services for counseling, if needed

PEARLS & CONSIDERATIONS

- Patient consent should be obtained in the form of a written treatment agreement before initiating treatment. This agreement should outline the goals of therapy, use of a single provider or treatment team and a single pharmacy, limitations on dose and number of prescribed medications, prohibition on use with alcohol or sedating medications, keeping medication safe and secure, prohibition on selling or sharing medication, limitations on refills, compliance with all components of the treatment plan, the role of drug screening, and consequences of non-adherence.
- Follow-up assessment should occur every 1 to 6 mo and include a complete pain assessment (see earlier), review of the type of long-acting analgesic used and dosage, use of breakthrough analgesics, side effects and their management, use of nonpharmacologic therapies, and adjunct medication use.

COMMENTS

- Medication dependence and addiction should not be confused. Most patients receiving chronic opioid therapy can become dependent on these medications for pain relief but opioid addiction does not occur. Patients exhibiting signs of addiction often will seek escalating doses of medication, request refills of prescriptions earlier than planned, and engage in drug-seeking activities (e.g., emergency department visits between prescriptions, seeking multiple prescriptions).
- Side effects need not preclude use of opioid medications and should be anticipated. Antiemetics can aid in controlling nausea. Constipation can be managed with stool softeners and laxatives.
- The emphasis of comprehensive pain management for non–cancer-related chronic pain has led to a fourfold increase in prescribing of opioid medications in the U.S. This increase in opiate use has also led to a rise in the misuse and abuse of these medications. Providers should proceed with caution before initiating pain management with opiate medications and should familiarize themselves with processes and tools for pain assessment and medication management. Forty-two states have developed prescription drug monitoring programs (PDMPs) to assist providers in identifying issues of abuse, polypharmacy, and misuse of controlled substances.

PATIENT & FAMILY EDUCATION

- National Pain Foundation (www.painconnection.org)
- American Pain Foundation (www.painfoundation.org)
- National Institutes of Health (www.nih.gov)

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pain Medications (Patient Information)

AUTHOR: **Anngene Anthony, MD, MPH, FAAFP**

TABLE 4 Guidelines for Opioid Dose Selection, Conservative Initial Starting Doses for Opioid-Naïve Individuals, and Conversion Ratios for Opioid Rotation in Patients on Chronic Opioids

Opioid Naïve	Morphine SR	Codeine	Oxycodone	Hydrocodone	Hydromorphone	Methadone	Fentanyl	Oxymorphone
Initial dose and range in opioid-naive patient (starting dose range for repeated dosing)*	15 mg (15-30 mg q8-12h)	30 mg (15-60 mg q4-6h)	5 mg (5-15 mg q4-6h)	5 mg (5-10 mg q4-6h)	2 mg (2-4 mg q4-6h)	2.5 mg q6-12h	NA	5 mg q4-6h
Opioid Tolerant Converting from:	Morphine PO	Codeine	Oxycodone	Hydrocodone	Hydromorphone	Methadone	Fentanyl	Oxymorphone
Morphine IM 10 mg (the gold standard for opioid comparisons)	20-30 mg	60-90 mg†	5 mg	5-10 mg q4-6h	2 mg	2.5 mg	25-μg patch/72 hr	5 mg (the gold standard for opioid comparisons)
Morphine SR 30 mg PO q8-12h, 60-90 mg/24h		30-90 mg q4h	3-45 mg/24 hr oxycodone, approx. 50% of morphine dose	30-45 mg/24 hr	12-18 mg/24 hr	24-hr dose morphine 30-90 mg 4:1 conversion 90-300 mg 8:1 conversion >300 mg 12:1	25-mcg patch/72 hr	5 mg q12h ER
Codeine 30-60 mg q4h	15-30 mg q3-4h		5-7.5 mg q4h	5-10 mg q4h	12 mg/24 hr	2.5 mg q8-12h	12.5-μg patch/72 hr	2.5-5 mg q4-6h IR
Oxycodone 5 mg q3-4h	10 mg	30-60 mg q3-4h		5-10 mg q4h	12 mg/24 hr	2.5 mg q8-12h	25-μg patch/72 hr	5 mg q4-6h IR
Hydrocodone 10 mg q3-4h	15 mg	30-60 mg q3-4h	5 mg q3-4h		12 mg/24 hr		12.5-μg patch/72 hr	2.5-5 mg q4-6h IR
Hydromorphone 2 mg q4h	10 mg		5 mg	5-10 mg q4h		2.5 mg q8-12h	25-μg patch/72 hr	5 mg q4-6h IR
Methadone 5 mg q8h	20 mg SR q8h		10 mg q3-4h		4 mg q4-6h		25-μg patch/72 hr	5 mg q12h ER
Fentanyl 25 μg/hr patch	90 mg morphine per 24 hr (1 μg to 4 mg morphine)					5 mg q8-12h		5 mg q12h ER
Oxymorphone ER 5 mg q12h	15 mg SR q12h		5 mg q8-12h	10 mg q4-6h	12 mg/24 hr	5 mg q8-12h	25-μg patch/72 hr	

NOTE: Recommended starting doses are low and should be titrated upward slowly to minimize adverse effects. Limitations of equianalgesic tables exist because they are based on single-dose studies in opioid-naïve individuals. Convert opioid 1 to morphine equivalents and calculate dose of opioid 2 according to conversion ratio, then reduce the calculated dose for opioid 2 by one third to one half to ensure safety of the 24-hr total daily dose. Rescue dose is 10% to 20% of daily opioid dose given every 3 to 4 hr as needed. Titration upward for unrelieved pain should be by 25% to 30% of the current 24-hr dose, adjusted by daily amount of rescue medications needed over a several-wk period. Equivalent or equianalgesic doses for the different opioid preparations vary in different publications.

ER, Extended release; *IM*, intramuscular; *IR*, immediate release; *PO*, by mouth; *SR*, Sustained release.

*Conservative low equianalgesic starting doses for opioid-naïve individuals adapted from published recommendations.

†Doses above 1.5 mg/kg not recommended because of increase in side effects.

From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.

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TABLE E3 Morphine Milligram Equivalent Doses for Commonly Prescribed Opioids

Opioid	Conversion Factor*
Codeine	0.15
Fentanyl transdermal (in μg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1-20 mg/day	4
21-40 mg/day	8
41-60 mg/day	10
≥61-80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3
Tapentadol	0.4

MME, Morphine milligram equivalent.

*Multiply the dose for each opioid by the conversion factor to determine the dose in MMEs.

Adapted from Von Korff M et al: De facto long-term opioid therapy for noncancer pain, *Clin J Pain* 24:521-527, 2008; and Washington State Interagency Guideline on Prescribing Opioids for Pain www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf.

From Dowell D et al: CDC guideline for prescribing opioids for chronic pain—United States, 2016, JAMA 315(15):1624-1645, 2016.

BOX E4 CDC Recommendations for Prescribing Opioids for Chronic Pain Outside Active Cancer, Palliative, and End-of-Life Care

Determining When to Initiate or Continue Opioids for Chronic Pain

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic expectations for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and the patient's and clinician's responsibilities for managing therapy.

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dose. Clinicians should use caution when prescribing opioids at any level. They should reassess carefully the evidence of individual benefits and risks when increasing the dose to ≥50 morphine milligram equivalents (MME)/day, and they should avoid increasing it to ≥90 MME/day or should carefully justify a decision to titrate it to ≥90 MME/day.
6. Long-term opioid use often begins with treatment of acute pain. When they are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or fewer often is sufficient; more than 7 days will rarely be needed.
7. Clinicians should evaluate risks and benefits in patients within 1 to 4 wk of starting opioid therapy for chronic pain or 1 to 4 wk of dose escalation. Clinicians should discuss risks and benefits of continued therapy with patients every 3 mo or more frequently. If benefits do not outweigh risks of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or discontinue them.

Assessing Risk and Addressing Harms of Opioid Use

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including offering naloxone when factors that increase risk for opioid overdose are present. These include history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), and concurrent benzodiazepine use.
9. Clinicians should review the patient's history of controlled substance prescriptions and use state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, at time intervals ranging from every prescription refill to every 3 mo.
10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider retesting at least annually to assess for prescribed medications, other controlled prescription drugs, and illicit drugs.
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

All recommendations are category A (apply to all patients outside active cancer treatment, palliative care, and end-of-life care) except recommendation 10 (designated category B, with individual decisionmaking required).
CDC, Centers for Disease Control and Prevention. From Dowell D et al: CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016, *JAMA* 315(15):1624-1645, 2016.

BOX E5 Interpretation of Recommendation Categories and Evidence Types

Recommendation Categories

Based on evidence type, balance between desirable and undesirable effects, values and preferences, and resource allocation (cost)
Category A recommendation: Applies to all persons; most patients should receive the recommended course of action
Category B recommendation: Individual decisionmaking needed; different choices will be appropriate for different patients. Clinicians help patients arrive at a decision consistent with patient values and preferences and specific clinical situations

Evidence Type

Based on study design and a function of limitations in study design or implementation, imprecision of estimates, variability in findings, indirectness of evidence, publication bias, magnitude of treatment effects, dose-response gradient, and constellation of plausible biases that could change effects
Type 1 evidence: Randomized clinical trials or overwhelming evidence from observational studies
Type 2 evidence: Randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies
Type 3 evidence: Observational studies or randomized clinical trials with notable limitations
Type 4 evidence: Clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations

From Dowell D et al: CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016, *JAMA* 315(15):1624-1645, 2016.

BASIC INFORMATION

DEFINITION

The Diabetes Control and Complications Trial (DCCT) demonstrated in patients with type 1 diabetes mellitus (T1DM) that intensive insulin therapy may slow the rate of secondary complications of diabetes at the expense of causing life-threatening, iatrogenic hypoglycemia. Pancreas transplantation (PTX) is the most effective treatment for glycemic control and forestalling microvascular end-organ damage in T1DM. Compared to insulin-based treatment of T1DM, functional pancreata result in euglycemia; do not cause hypoglycemia; and lead to improvements of retinopathy, peripheral neuropathy, and progression of native diabetic nephropathy (DN) or recurrence of diabetic nephropathy (DN) in the transplanted kidney.

Currently, PTX is not only the first choice for organ replacement in T1DM but also in patients with type 2 diabetes mellitus (T2DM) with BMI ≤28 mg/kg/m^2 and patients undergoing pancreatectomy for malignancy localized to the pancreas or chronic pancreatitis with irreversible damage.

SYNONYMS

Simultaneous kidney-pancreas transplant (SPK)
Pancreas after Kidney transplant (PAK)
Pancreas transplant alone (PTA)

ICD-10CM CODES

Z76.82	Pancreas transplant candidate
Z94.3	Pancreas transplant status (CMS-HCC)

EPIDEMIOLOGY & DEMOGRAPHICS

Since the first SPK transplant in 1966 the outcomes, surgical technique, immunosuppression, and complications of pancreas transplant modalities have evolved and improved. In the past 30 yr more than 31,000 PTX procedures have been performed in the United States. The success in survival of PTX and recipients is the result of better procurement techniques, changes in pancreas exocrine drainage from the urinary bladder to the small intestine (Figs. 1 and 2), and advances in immunosuppression.

The introduction in the 1980s of OKT3 and calcineurin inhibitors such as cyclosporine was pivotal in improving PTX outcomes. With the introduction of rabbit antithymocyte globulin in the late 1990s (replacing OKT3) and tacrolimus (replacing cyclosporine), there has been an additional reduction in PTX loss in the first 90 days posttransplant and in PTX rejection. Similarly, the survival of the kidney (native or transplant) has improved due to reduction of nephrotoxicity and chronic immune injury.

INCIDENCE: Despite an increasing prevalence of DM, the number of PTX in the United States decreased from 2006 through 2012 but reversed in 2014. Since then, the PTX overall numbers have remained relatively stable. The preferred modality of PTX is the SPK, representing more than 70% of all PTX in 2017. The SPK recipient is usually a patient with T1DM with end-stage kidney disease or advanced CKD stage 4 with an eGFR of ≤20 ml/min per 1.73 m^2. SPK transplants are most commonly performed when recipients are already obligated to immunosuppressive therapy by the kidney graft. Thus the added surgical risk of a PTX is minimized. SPK grafts have the lowest rate of kidney transplant failure at 4.9%, 16.6%, and 34.9% at 1, 5, and 10 yr posttransplantation, respectively.

With respect to organ survival, accurate rates of pancreas graft loss are more difficult to ascertain given the lack of a precise definition of pancreas graft failure and that pancreas graft losses are not usually reported. The remaining 30% are solitary PTX performed after kidney transplantation (PAK) or in nonuremic patients with or without DN with brittle (or labile) diabetes (including recurrent episodes of hypoglycemia and/or hypoglycemic unawareness; PTA).

The PAK has a kidney graft failure of 2.9%, 16.1%, and 47.1% after 1, 5 and 10 yr, respectively. The slightly poorer long-term outcomes of PAK likely reflects kidney graft age and cumulative injury before PTX. Of all PTX modali-

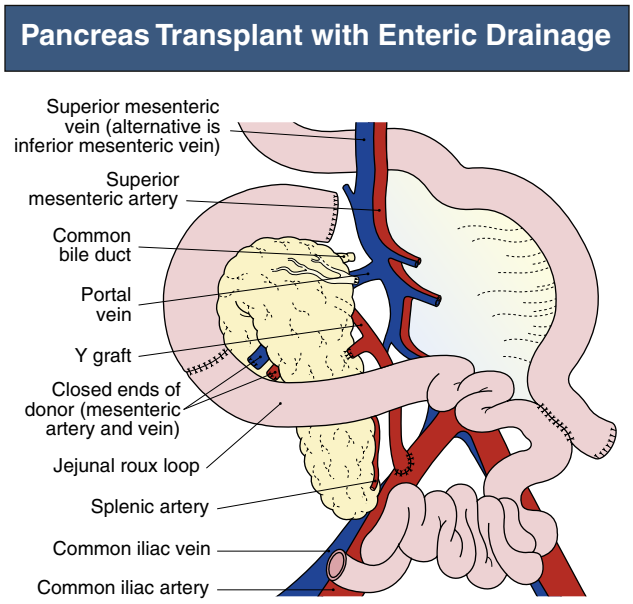

FIG. 1 Pancreas transplant with enteric (portal) drainage. (From Feehally J et al: *Comprehensive clinical nephrology,* ed 6, Philadelphia, 2019, Elsevier.)

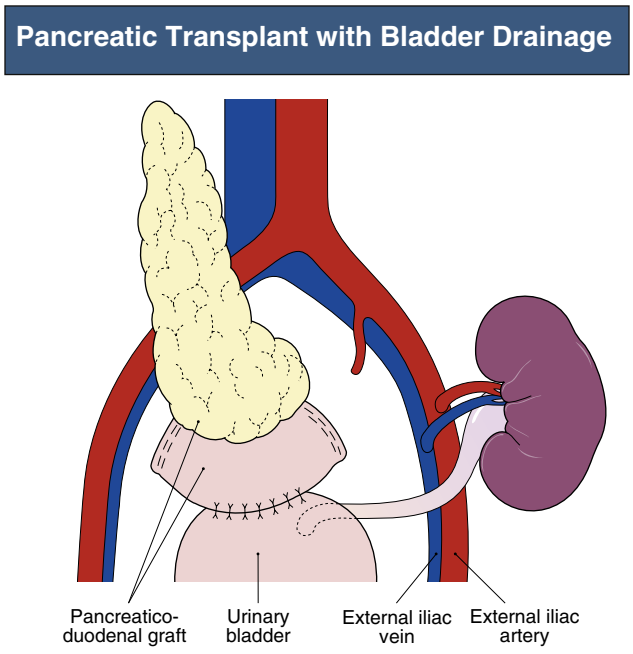

FIG. 2 Pancreas transplant with bladder drainage. The pancreas may be placed in either the intraperitoneal or extraperitoneal position. (From Feehally J et al: *Comprehensive clinical nephrology,* ed 6, Philadelphia, 2019, Elsevier.)

ties, PTA is the least-favored modality due to poor pancreas survival. Concerning the kidney benefits of PTA, however, reversal of DN has been demonstrated by clinical measurements and histology after 5 or more yr of euglycemia.

Regarding active PTX waiting list (WL) candidates in 2014, 55.2% of SPK, 50.6% of PTA, and 39.7% of PAK were transplanted within 3 yr. The median waiting time to transplant in 2016 to 2017 decreased to 12.9 and 22.8 mo for SPK and PTA, respectively.

PREVALENCE: There are 24,557 functional SPK and 8,885 solitary PTX (i.e., PKA and PTA), respectively, in the United States. There are only 48 SPK and 24 PTA from living donors. The most recent SPK and PTA from living donors were performed in 2013 and 2008, respectively. Currently all PTX donors are deceased. African American and Hispanic donors of PTX account for 33.1% of all PTX performed by 2017, and no donors were ≥65 yr old.

PREDOMINANT SEX AND AGE: The typical SPK candidate has T1DM (80%), is 35 to 49 yr old, 55.4% are male, and 40% have a BMI of 18.5 to 25 kg/m^2. Although the majority of pancreas wait-listed patients are Caucasian, there has been an increase in PTX candidates who are African American, Hispanic, and Asian. In addition there is an increase in the proportion of candidates aged ≥50 yr reflecting the changes in organ allocation allowing for PTX of T2DM.

RISK FACTORS: The risk factors for PTX loss are similar to other transplanted organs: African American race, recipients of two or more transplants, high titers of antidonor antibody, and long waiting time. The most common causes of graft failure are death with a functional graft due to cardiovascular disease, infections, malignancies, surgical complications, and rejection. PTXs are particularly susceptible to graft rejection, with an incidence of 15% to 21% at 1 yr and 27% to 30% at 5 yr posttransplant. These frequencies greatly exceed those of kidney transplant rejection.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The exam of PTX recipients is no different than that of other organ recipients. PTX is surgically placed in the right lower quadrant of the abdomen. Abdominal pain is a common sign of rejection, graft thrombosis (complicating 5% to 10% of PTX), and pancreatitis (complicating 3% of PTX). Fever is a common finding in viral infections of the PTX (e.g., cytomegalovirus, adenovirus) or intrabdominal bacterial infections. An anastomotic leak is a rare and serious complication, contributing to 4% of graft failures. The diagnosis is suggested by peritonitis, fever, leukocytosis, and confirmed by imaging studies.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute rejection
- Surgical complications
- Transplant pancreatitis
- Viral infections: CMV, adenovirus, Coxsackie virus, and mumps virus
- Posttransplant lymphoproliferative lymphoma occurs more commonly in pancreatic transplants compared to kidney transplants

In bladder-drained PTX, urological complications include urethral stenosis and hemorrhagic cystitis, recurrent urinary tract infections, severe metabolic acidosis, and volume depletion from exocrine sodium bicarbonate loss in urine. These complications often require surgical conversion from bladder drainage to enteric drainage.

WORKUP

Laboratory tests:

- Graft monitoring:
  1. Amylase and lipase levels (lipase being more specific)
  2. Fasting blood glucose level
  3. Fasting C-peptide level
  4. Hemoglobin A1c
  5. Bladder-drained PTX: Urinary amylase may be helpful
- Specific tests:
  1. Viral polymerase chain reaction: Cytomegalovirus, adenovirus, BK virus, mumps rubulavirus
  2. PTX biopsy
  3. Bacterial cultures as indicated: Blood, urine, peritransplant collections
- Elevated fasting glucose or hemoglobin A1c levels or a low fasting C-peptide level predict poor graft survival. In these circumstances, the risks associated with treatment of graft rejection may outweigh its benefits.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Surgical conversion of pancreatic graft bladder drainage to enteric drainage
- Acute rejection: Acute immunosuppression with antithymocyte globulin, IV pulse glucocorticoids, antiproliferative agents (mycophenolate-based drugs or mTOR inhibitors—everolimus or rapamycin), and calcineurin inhibitor (i.e., tacrolimus)
- Chronic or maintenance immunosuppression: Generally comprised of calcineurin inhibitor (i.e., tacrolimus), antiproliferative agent (Mycophenolate based drugs or mTOR inhibitors—everolimus or rapamycin, and calcineurin inhibitor) and glucocorticoids

DISPOSITION

Admission to intensive care or transplant floor depending on severity of clinical presentation. Management may require consultations to infectious diseases and urology where appropriate.

PEARLS & CONSIDERATIONS

- Weekly monitoring of PTX function for the first mo, twice monthly during the first 6 mo, and monthly afterward.
- PTX recipients must always be maintained on glucocorticoid steroids.
- Immunosuppressant medication changes must always be done in collaboration with a transplant specialist.
- Coronary artery disease (CAD) is the most common cause of death in PTX recipients regardless of age.
- PTX recipients should be on statin and low-dose ASA.
- PTX recipients should undergo screening for CAD yearly in prevalent patients and every 2 yr in patients without a history of documented CAD.
- PTX recipients have a greater risk of stroke and peripheral vascular disease than the general population.

SUGGESTED READINGS

Available at ExpertConsult.com

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SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Pancreatic cancer is an adenocarcinoma derived from pancreatic duct epithelium. Microscopic premalignant pancreatic lesions in the pancreatic ducts are referred to as pancreatic intraepithelial neoplasia (PIN) in which there is a stepwise progression from low grade to high grade associated with accumulating genetic alterations. Intraductal papillary mucinous neoplasms (IPMN) are a second type of precursor to pancreatic cancer that are associated with an overall risk of invasive cancer of approximately 25%, especially in those arising from the main pancreatic duct.

ICD-10CM CODES

C25.9	Malignant neoplasm of pancreas, unspecified
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: In the U.S., it is estimated that there were 56,770 new cases and 45,750 deaths in 2019. It is the fourth leading cause of cancer-related death in the U.S. The majority of patients present with advanced disease, and less than 20% of patients present with potentially resectable tumors.
PREDOMINANT SEX: Male:female ratio of 2:1
PREDOMINANT AGE: Median age at diagnosis is 71 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Presenting symptoms are generally related to location:

- Jaundice (60% to 70% of pancreatic cancers are located in the head of the pancreas)
- Abdominal pain: Generally dull upper abdominal pain or vague abdominal discomfort
- Weight loss
- Anorexia/change in taste, asthenia
- Nausea
- Uncommonly: Depression, gastrointestinal bleeding, acute pancreatitis (from obstruction of the pancreatic duct), back pain
- Trousseau syndrome (hypercoagulability in the setting of malignancy) may be initial presentation in some patients
- Table 1 summarizes demographic features and presenting symptoms in pancreatic cancer patients

Physical findings:

- Icterus
- Cachexia, temporal wasting
- Ascites, peripheral lymphadenopathy, hepatomegaly
- Excoriations from scratching pruritic skin

ETIOLOGY

Unknown, but several conditions have been associated with pancreatic cancer:

- Smoking
- Alcoholism
- Genetics: up to 20% of patients have a family history of the disease
- Genetic syndromes and associated genes: Hereditary pancreatitis (*PRSS1, SPINK1*), Peutz-Jeghers syndrome (*STK11[LKB1]*), familial atypical multiple mole and melanoma syndrome (*p16*), hereditary breast and ovarian cancer syndromes (*BRCA1, BRCA2, PALB2*), ataxia telangiectasia (*ATM*), Li-Fraumeni syndrome (*P53*)
- Gallstones
- Diabetes mellitus (present in at least 50% of patients with pancreatic cancer)
- Chronic pancreatitis
- Diet rich in animal fat
- Occupational exposure: Oil refining, paper manufacturing, chemical industry
- Overweight or obesity during early adulthood is associated with a greater risk of pancreatic cancer and a younger age of disease onset. Obesity at an older age is associated with a lower overall survival in patients with pancreatic cancer
- There are four major driver genes for pancreatic cancer: *KRAS*, *CDKN2A*, *TP53*, and *SMAD4. KRAS* mutation and alterations in *CDKN2A* are early events in pancreatic cancer tumorigenesis
- Table 2 summarizes nongenetic and genetic risk factors for pancreatic cancer

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Common duct cholelithiasis
- Cholangiocarcinoma
- Common duct stricture
- Sclerosing cholangitis
- Primary biliary cirrhosis
- Autoimmune pancreatitis
- Drug-induced cholestasis (e.g., phenothiazines)
- Other pancreatic tumors (islet cell tumor, cystadenocarcinoma, epidermoid carcinoma, sarcomas, lymphomas)

WORKUP

Initial laboratory testing includes complete blood count, serum chemistries. The bile duct antigen CA 19-9 is not used as a screening test but can be utilized as a modality for detecting recurrence and for therapeutic monitoring in patients undergoing therapy.

As per updated consensus guidelines, all patients diagnosed with pancreatic cancer should undergo assessment of risk for hereditary syndromes known to be associated with an increased risk of cancer. Germline genetic testing for cancer susceptibility should be considered even if family history is unremarkable.

Routine Laboratory Tests	% Abnormal
Alkaline phosphatase	80
Bilirubin	55
Total protein	15
Amylase	15
Hemoglobin	60

IMAGING STUDIES

- Multidetector helical CT (Fig. E1) with IV administration of contrast is the imaging procedure of choice for initial evaluation.
- Endoscopic ultrasonography (Fig. E2) is useful when the diagnosis is strongly suspected and tissue is required for diagnostic purposes. Fine-needle aspiration biopsy combined with endoscopic ultrasonography is the preferred modality for evaluation of cystic or mass lesions to determine malignancy.
- Endoscopic retrograde cholangiopancreatography (ERCP, Fig. E3) is useful in patients with jaundice needing an endoscopic stent to relieve obstruction.
- PET scans are of limited value in pancreatic cancer and are not part of standard management.

TABLE 1 Demographic Features and Presenting Symptoms and Signs in Patients with Unresectable (Palliated) and Resectable (Resected) Pancreatic Cancer

	Palliated (*N* = 256)	Resected (*N* = 512)
Demographic Features		
Age, average (yr)	64.0	65.8
Men/women	57%/43%	55%/45%
Race	91% white	91% white
Symptoms and Signs (%)		
Abdominal pain	64	36*
Jaundice	57	72*
Weight loss	48	43
Nausea/vomiting	30	18*
Back pain	26	2*

*P = 0.001 vs. palliated group.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE 2 Nongenetic and Genetic Risk Factors for Pancreatic Cancer

Variable	Risk Increase
Nongenetic Risk Factors	
Chronic pancreatitis	13.3
New onset type 2 diabetes	7.9
Long-standing diabetes mellitus	2.0
Obesity	2.0
Smoking	1.8
Alcohol abuse	1.2
Non-O blood group	1.3
Genetic Syndrome And Associated Genes	
Familial pancreatic cancer (unknown gene)	
One first-degree relative	9
Three first-degree relatives	32
Familial adenomatous polyposis *(APC)*	4.5-6
Breast and ovarian cancer syndrome *(BRCA1, BRCA2, PALB2)*	2-3.5
Peutz-Jeghers syndrome *(STK11/LKB1)*	132
Hereditary pancreatitis *(PRSS1, SPINK1)*	69
Familial atypical multiple mole melanoma pancreatic carcinoma syndrome *(P16INK4A/CDKN2A)*	47
Lynch syndrome *(MLH1, MSH2, MSH6, PMS2, EPCAM)*	8.6
Cystic fibrosis *(CFTR)*	3.5
Ataxia-telangiectasia *(ATM)*	Unknown
Genetic Polymorphisms	
ABO	1.3
NR5A2	1.3
TERT	1.2
PDX1	1.2
BCAR1, CTRB1, CTRB2	1.5
ZNRF3	1.2
LINC00673	1.3
ETAA1	1.1
TP63	1.1
SUGCT	1.1

From Niederhuber JE: *Abeloff's Clinical Oncology*, ed 6, Philadelphia, 2020, Elsevier.

Noninvasive Imaging	% Abnormal
Abdominal ultrasonography	60
Abdominal CT scan (with contrast) (Fig. E4)	90
Abdominal MRI scan	90

Invasive Imaging	% Abnormal
ERCP	90
CT scan or ultrasonography-guided needle aspiration cytology	90-95

STAGING

2018 AJCC eight edition staging system for Pancreatic Cancer

PRIMARY TUMOR (T):

T_X	Primary tumor cannot be assessed
T_0	No evidence of primary tumor
T_1	Tumor <2 cm
T_2	Tumor >2 cm and <4 cm
T_3	Tumor >4 cm
T_4	Tumor involves celiac axis or superior mesenteric artery (unresectable primary)

LYMPH NODES (N):

N_0	No regional lymph nodes
N_1	metastasis in 1-3 regional lymph nodes
N_2	metastasis in >4 regional lymph nodes

DISTANT METASTASES (M):

M_X	Presence of distant metastasis cannot be assessed
M_0	No distant metastasis
M_1	Distant metastasis

STAGING GROUPS:

I_A	T_1, N_0, M_0
I_B	T_2, N_0, M_0
II_A	T_3, N_0, M_0
II_B	T_{1-3}, N_1, M_0
III	T_{1-3}, N_2, M_0 T_4, any N, M_0
IV	Any T, any N, M_1

Rx TREATMENT

Treatment sequencing strategies are summarized in Fig. 5 and Table 3.

SURGERY FOR RESECTABLE DISEASE

- Classification of resectability of pancreatic cancer per the National Comprehensive Cancer Network and Surgical Oncology Expert Consensus Statement is summarized in Table 4.
- Curative cephalic pancreaticoduodenectomy (Whipple procedure) for tumors in the head and neck of the pancreas is appropriate for only 10% to 20% of patients whose lesion is <5 cm, solitary, and without locoregional invasion. Surgical mortality rate can be up to 5%. Tumors in the body or tail of the pancreas are removed by means of a distal pancreatectomy, which often includes a splenectomy. Due to the complexity of surgery and risk for significant morbidity and mortality, current guidelines recommend that pancreatic resections be carried out in centers that perform at least 15 to 20 cases annually. In addition, a recent review concluded that high-volume institutions are associated with higher negative-margin status and higher 5-yr survival rates, and that patients are more likely to receive multimodality therapy at these centers.

ADJUVANT THERAPY

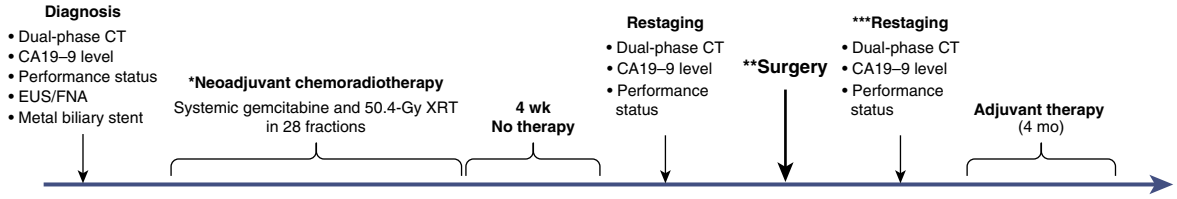
Adjuvant chemotherapy has been demonstrated to improve postoperative survival in multiple randomized trials and is considered the standard of care in patients with resected cancers.

- The use of single agent 5-fluorouracil (5-FU) or gemcitabine is associated with median survival in the 20 to 24-mo range and reserved for patients with older age or borderline status.
- The combination of gemcitabine and capecitabine is superior to gemcitabine alone in the adjuvant setting, with median overall survival in the 28-mo range.
- Most recently, the use of a triplet chemotherapy combination regimen (FOLFIRNOX; 5-FU, oxaliplatin, and irinotecan) in this setting strikingly improves outcomes with median overall survival reported at 54 mo.

The use of adjuvant radiotherapy in this setting is controversial and is best limited to patients with poor risk features, margin-positive surgery, or with multiple nodal or extranodal tumor involvement. An emerging strategy is the use of neoadjuvant preoperative chemotherapy combined with radiotherapy in patients with resectable pancreatic cancer. Palliative therapeutic ERCP with metal or plastic stents is performed for biliary decompression.

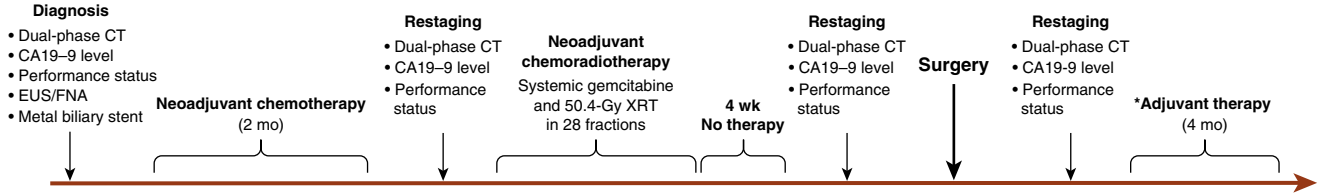
RECURRENT/METASTATIC DISEASE

In patients with metastatic disease, accepted upfront chemotherapy treatment approaches have demonstrated improvement in survival outcomes. Acceptable chemotherapy regimens for locally advanced and metastatic disease are summarized in Table 5.



*Systemic therapy alone (FOLFIRINOX, gem-nab) is being considered by many clinicians because of the efficacy of these regimens in advanced disease and the challenges of delivering FOLFIRINOX in the adjuvant setting after such a large operation.
**Surgery is typically performed in the fifth week after the completion of XRT.
***Patients are restaged during postop week six if their recovery has been uncomplicated; however, there is no need to restage if recovery is complicated and the patient is not a suitable candidate to receive further systemic therapy.

A



*The benefit of further postoperative/adjuvant systemic therapy after a more prolonged induction phase is being questioned, especially in those patients of advanced age or when postoperative recovery is slow.

B

FIG. 5 Schematic representation of treatment sequencing in **(A)** resectable and **(B)** borderline resectable pancreatic cancer (PC). *CA19-9*, Cancer antigen 19-9; *CT*, computed tomography; *EUS*, endoscopic ultrasound scan; *FNA*, fine-needle aspiration; *FOLFIRINOX*, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; *gem-nab*, gemcitabine/nab-paclitaxel; *XRT,* external radiotherapy. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

TABLE 3 Comparison of Treatment Sequencing Strategies for Patients with Pancreatic Cancer (outside of a clinical trial)

Stage	NCCN	MCW
Resectable	• Surgery • Restaging • Adjuvant therapy (+/– chemoradiotherapy; 6 mo)	• Neoadjuvant chemoradiotherapy (5.5 wk)* • Restaging • Surgery • Restaging • Adjuvant therapy (4 mo)
Borderline resectable	• Neoadjuvant therapy (regimen not specified) • Restaging • Surgery • Restaging • Consider adjuvant therapy	• Neoadjuvant chemotherapy (2 mo) • Restaging • Neoadjuvant chemoradiotherapy (5.5 wk) • Restaging • Surgery • Restaging • Adjuvant therapy (4 mo)
Locally advanced	• Chemotherapy • Restaging • Chemoradiotherapy in selected patients	• Chemotherapy (minimum 4 mo) • Restaging • Chemoradiotherapy • Restaging • Surgery in highly selected patients
Metastatic	• Systemic therapy • Clinical trial	• Systemic therapy • Clinical trial

NOTE: Clinical trials are preferred in all patients with pancreatic cancer (regardless of stage of disease) who have a performance status acceptable for treatment.
FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; *gem-nab*, gemcitabine/nab-paclitaxel; *MCW*, Medical College of Wisconsin; *NCCN*, National Comprehensive Cancer Network.
*Systemic therapy alone (FOLFIRINOX, gem-nab) is being considered by many clinicians because of the efficacy of these regimens in advanced disease and the challenges of delivering FOLFIRINOX in the adjuvant setting after such a large operation.
From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.

- Treatment options can include the administration of gemcitabine alone, combination regimen consisting of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX), or the combination of nab-paclitaxel plus gemcitabine. Multiagent regimens have an improved survival outcome compared with single-agent therapy. Liposomal irinotecan in combination with infusional 5-fluorouracil is now also approved in the setting of progressive cases.
- The use of maintenance olaparib (after systemic chemotherapy) among patients with a germline *BRCA* mutation in metastatic pancreatic cancer has demonstrated improvement in progression-free survival compared with placebo.
- Poor survival outcomes are seen in patients with poor performance status, significant weight loss, and with liver metastases.
- Combined chemotherapy and radiotherapy can be utilized in the case of patients with locally advanced but unresectable cases and confers a modest improvement in median overall survival.

DISPOSITION

- Adjuvant postoperative chemotherapy has a significant survival benefit in patients with resected pancreatic cancer.
- Adjuvant chemotherapy with FOLFIRINOX regimen significantly delays the development of recurrent disease after complete resection of pancreatic cancer. Median survival in this setting is approximately 54 mo.
- Pancreatic cancer is usually diagnosed at an advanced stage and is resistant to therapy. Median survival for locally unresectable disease is about 14 to 16 mo, while the median survival for metastatic disease is 10 to 12 mo.

PEARLS & CONSIDERATIONS

COMMENTS

- Risk factors for pancreatic cancer and recommendations for screening of individuals at risk are summarized in Tables 6 and 7.
- The U.S. Preventive Services Task Force (USPSTF) recommends against routine screening for pancreatic cancer in

TABLE 4 Classification of Resectability of Pancreatic Cancer per the National Comprehensive Cancer Network and Surgical Oncology Expert Consensus Statement

Resectability Status	Criteria
Resectable	• No distant metastases • No radiographic evidence of SMV and portal vein abutment, distortion, tumor thrombus, or venous encasement • Clear fat planes around the celiac axis, hepatic artery, and SMA

Borderline resectable	• For tumors of the head or uncinate process:
	  • Solid tumor contact with the SMV or portal vein of >180 degrees with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement, allowing for safe and complete resection and vein reconstruction
	  • Solid tumor contact with the IVC
	  • Solid tumor contact with the common hepatic artery without extension to the celiac axis or hepatic artery bifurcation, allowing for safe and complete resection and reconstruction
	  • Solid tumor contact with the SMA ≤180 degrees
	  • Solid tumor contact with variable anatomy (e.g., accessory right hepatic artery, replaced right hepatic artery, replaced common hepatic artery, and the origin of replaced or accessory artery), and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning
	• For tumors of the body or tail:
	  • Solid tumor contact with the celiac axis of ≤180 degrees
	  • Solid tumor contact with the celiac axis >180 degrees without involvement of the aorta and with an intact and uninvolved gastroduodenal artery, thereby permitting a modified Appleby procedure (although some members of the consensus committee preferred this criterion to be in the unresectable category)

Unresectable/locally advanced	• Head of pancreas or uncinate lesions:
	  • Solid tumor contact with the SMA >180 degrees
	  • Solid tumor contact with the celiac axis >180 degrees
	  • Solid tumor contact with the first jejunal SMA branch
	  • Unreconstructable SMV or portal vein because of tumor involvement or occlusion (can be because of tumor or bland thrombus)
	  • Contact with the most proximal draining jejunal branch into the SMV
	• Body and tail lesions:
	  • Solid tumor contact of >180 degrees with the SMA or celiac axis
	  • Solid tumor contact with the celiac axis and aortic involvement
	  • Unreconstructable SMV or portal vein because of tumor involvement or occlusion (can be because of tumor or bland thrombus)
	• For all sites:
	  • Distant metastases
	  • Metastases to lymph nodes beyond the field of resection

Metastatic	• Any presence of distant metastases

From Niederhuber JE: *Abeloff's Clinical Oncology*, ed 6, Philadelphia, 2020, Elsevier.

asymptomatic adults by abdominal palpation, ultrasonography, or serologic markers. The USPSTF found no evidence that screening for pancreatic cancer is effective in reducing mortality rates. There is potential for significant harm because of the low prevalence of pancreatic cancer, limited accuracy of available screening tests, invasive nature of diagnostic tests, and poor outcome of treatment. Alcohol consumption, specifically liquor consumption of three or more drinks per day, increases pancreatic cancer mortality independent of smoking.

- Patients should be referred for pancreatic cancer surgery to high-volume medical centers that perform at least 15 to 20 cases a yr.
- Adjuvant chemotherapy with either a single-agent or doublet regimen for 6 mo has been shown to improve survival and should be recommended in all patients with a maintained performance status after surgical resection. The role of radiotherapy in the adjuvant setting is best restricted to patients who have a high risk for locoregional recurrence.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pancreatic Cancer (Patient Information)

AUTHOR: **Ritesh Rathore, MD**

TABLE 5 Acceptable Chemotherapy Regimens for Locally Advanced and Metastatic Disease[a]

Locally Advanced or Unresectable	Metastatic Disease
Options for patients with good performance status: • FOLFIRINOX • Gemcitabine + albumin bound-paclitaxel • Gemcitabine + erlotinib • Gemcitabine + capecitabine • Gemcitabine + cisplatin (especially for in patients with *BRCA1/2* mutation and/or family history) • Capecitabine single agent • CI 5-FU • Fixed-dose gemcitabine/docetaxel/capecitabine (GTX regimen) • Fluoropyrimidine + oxaliplatin • Chemotherapy (any of above) followed by chemoradiation or SBRT • Chemoradiation or SBRT	Options for patients with good performance status: • FOLFIRINOX (category 1) • Gemcitabine + albumin bound-paclitaxel (category 1) • Gemcitabine + erlotinib (category 1) • Gemcitabine (category 1) • Gemcitabine + capecitabine • Gemcitabine + cisplatin (especially for in patients with *BRCA1/2* mutation and/or family history) • Fixed-dose gemcitabine/docetaxel/capecitabine (GTX regimen) (category 2B) • Fluoropyrimidine + oxaliplatin (category 2B)
Options for patients with poor performance status: • Gemcitabine • Capecitabine • CI 5-FU	Options for patients with poor performance status: • Gemcitabine (category 1) • Capecitabine (category 2B) • CI 5-FU (category 2B)

[a]Level of Recommendation is based on National Comprehensive Cancer Network (NCCN) Guidelines. Category 1 is based on high-level evidence with uniform NCCN consensus that the intervention is appropriate. Category 2B is based on lower level evidence with NCCN consensus that the intervention is appropriate.
CI, Continuous infusion; *5-FU,* 5-fluoroacil; *FOLFIRINOX,* 5-FU, irinotecan, oxaliplatin; *GTX,* gemcitabine, docetaxel, capecitabine; *SBRT,* stereotactic body radiation therapy.
From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

TABLE 6 Risk Factors for Pancreatic Cancer

Risk Factor	Relative Increase in Risk
High Risk (>10-fold)	
FAMMM	13- to 47-fold
Hereditary pancreatitis	50- to 83-fold
Peutz-Jeghers syndrome	132-fold
Three or more first-degree relatives with PC	14- to 32-fold
Moderate Risk (5- To 10-fold)	
Two first-degree relatives with PC	4- to 6.4-fold
Cystic fibrosis	5.3-fold
Chronic pancreatitis	2- to 19-fold
BRCA2 mutation carrier	3.5- to 10-fold
PALB2 mutation carrier	6-fold
Low Risk (<5-fold)	
Cigarette smoking	1.5- to 3-fold
Alcohol consumption	None to 1.2-fold
Obesity	None to 1.7-fold
Diabetes mellitus	1.3- to 2.6-fold
One first-degree relative with PC	3-fold
BRCA1 mutation carrier	None to 2-fold
Familial adenomatous polyposis	4-fold
Li-Fraumeni syndrome	2-fold
Lynch syndrome	2- to 8-fold

FAMMM, Familial atypical multiple-mole melanoma; *PC,* pancreatic cancer.
From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

TABLE 7 Recommendations for Screening

HRIs To Consider For Screening
FAMMM patients with *CDKN2A*
Patients with hereditary pancreatitis
Patients with hereditary PJS
Three or more first-, second-, or third-degree relatives with PC with at least one being a first-degree relative
Two or more first-degree relatives with PC
BRCA1, BRCA2, or *PALB2* mutation carriers with at least one first- or second-degree relative with PC
Age To Start Screening
Age 45-50 yr *or*
15 yr before age of earliest occurrence of PC in the family (whichever is earliest)
Consider age 30 yr for patients with PJS

FAMMM, Familial atypical multiple-mole melanoma; *HRI,* high-risk individual; *PC,* pancreatic cancer; *PJS,* Peutz-Jeghers syndrome.
From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

SUGGESTED READINGS

American Cancer Society: *Global Cancer: Facts & figures*, ed 3, www.cancer.org/acs/groups/content/@research/documents/document/acspc-044738.pdf.

Azoulay L et al: Incretin-based drugs and the risk of pancreatic cancer: international multicentre cohort study, *BMJ* 352:i581, 2016.

Ballehanina UK et al: The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: an evidence based appraisal, *J Gastrointest Oncol* 3(2):105-119, 2012.

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La Torre M et al: Hospital volume, margin status, and long-term survival after pancreaticoduodenectomy for pancreatic adenocarcinoma, *Am J Surg* 78(2):225-229, 2012.

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Siegel RL et al: Cancer statistics, *CA Cancer J Clin* 69(1):7-34, 2019.

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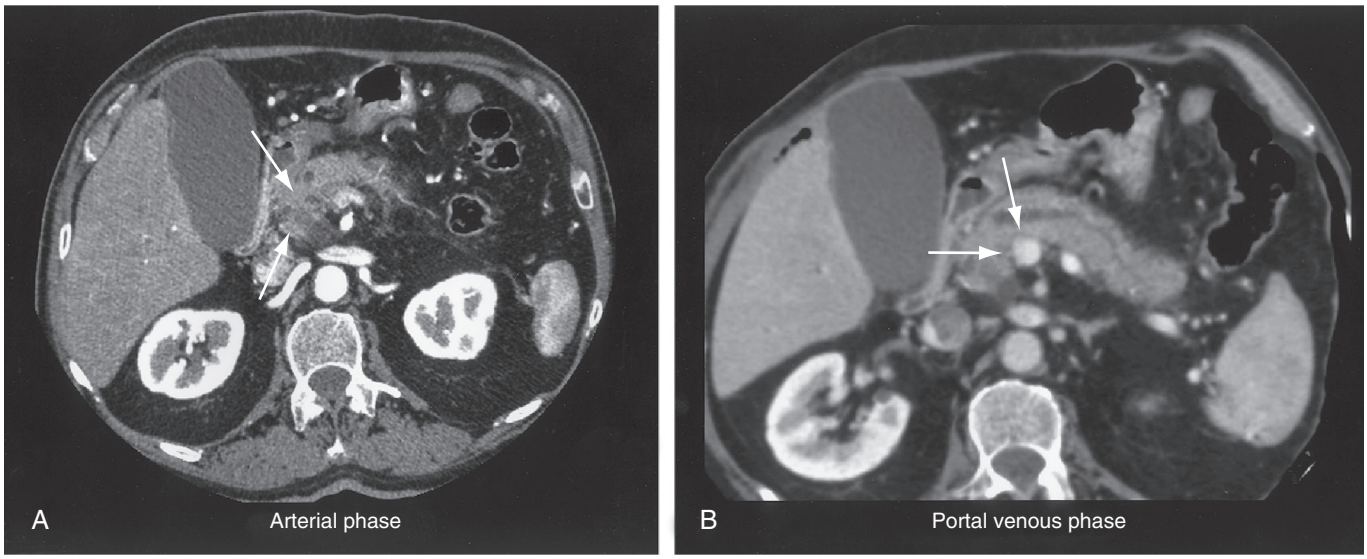

FIG. E1 Pancreatic computed tomography protocol in a patient with pancreatic cancer. A, Arterial phase showing a nonenhancing lesion in the head of the pancreas *(arrows)*. **B,** Venous phase showing a non-involved fat plane around the portal vein *(arrows)*. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

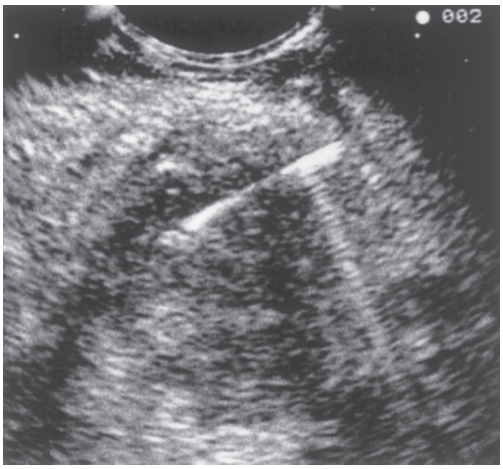

FIG. E2 EUS image of pancreatic cancer showing the needle during biopsy of the tumor. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

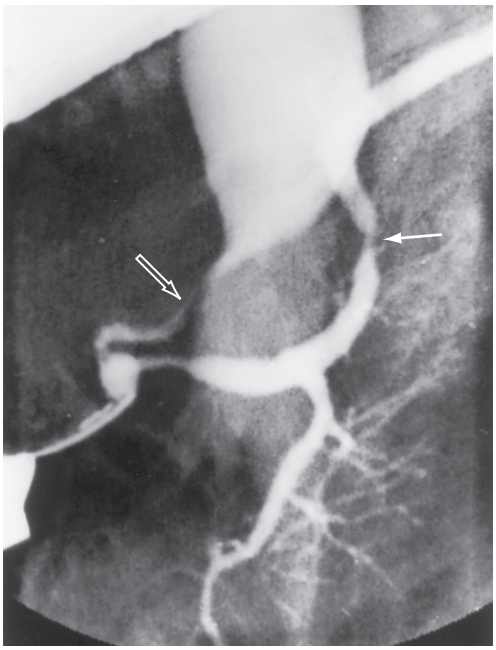

FIG. E3 Endoscopic retrograde cholangiopancreatography showing strictures of the bile duct *(open arrow)* and pancreatic duct *(closed arrow)* in a patient with pancreatic cancer. The bile duct is markedly dilated proximal to the bile duct stricture. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

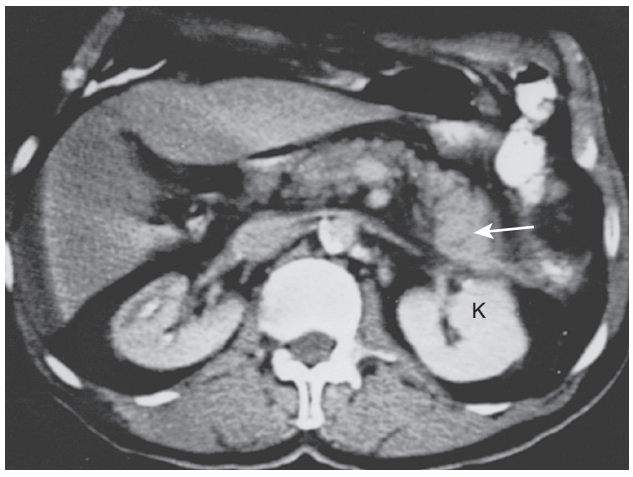

FIG. E4 Computed tomography scan of a patient with adenocarcinoma of the body and tail of the pancreas. The tumor *(arrow)* is seen anterior and adjacent to the left kidney *(K).* At operation, the tumor was invading Gerota fascia. (From Sabiston D: *Textbook of surgery,* ed 17, Philadelphia, 2005, Saunders.)

BASIC INFORMATION

DEFINITION

- Acute pancreatitis is an inflammatory process of the pancreas with intrapancreatic activation of enzymes that may also involve peripancreatic tissue and/or remote organ systems. The diagnosis of acute pancreatitis requires at least two of the following criteria: serum amylase or lipase ≥3 times normal, abdominal pain consistent with pancreatitis, and radiographic findings (CT or MRI) of acute pancreatitis.
- Commonly used scoring systems for acute pancreatitis are described in Table 1.
- The **Revised Atlanta Criteria**[1] use early prognostic signs, organ failure, and local complications to define disease severity:
  1. **Mild pancreatitis:** No organ failure, no local or systemic complications, pancreatitis typically resolves in first wk
  2. **Moderate pancreatitis:** Transient organ failure (≤48 hours) *or* local complications (e.g., pancreatic necrosis, peripancreatic fluid collections, peripancreatic necrosis) *or* exacerbation of comorbid disease
  3. **Severe pancreatitis:** Persistent organ failure (>48 hours)
- The **BALI Score**[2] evaluates only four variables:
  1. BUN ≥25 mg/dl
  2. Age ≥65 yr
  3. LDH ≥300 U/L
  4. Interleukin-6 level ≥300 pg/ml
- These measurements are taken at admission and at 48 hours. Mortality is >25% for a score of 3 and exceeds 50% with a score of 4.
- **Severe acute pancreatitis (SAP)** is diagnosed by the presence of any of the following four criteria:
  1. Organ failure with one or more of the following: Shock (systolic blood pressure <90 mm Hg), pulmonary insufficiency (Pa_{O_2} ≤60 mm Hg), renal failure (serum creatinine >2 mg/dl after rehydration), and gastrointestinal bleeding (>500 ml/24 hr)
  2. Local complications such as necrosis, pseudocyst, or abscess
  3. At least three of Ranson criteria (see tables) *or*
  4. At least eight of the Acute Physiology and Chronic Health Evaluation II (APACHE II) criteria

ICD-10CM CODES

K85.0	Idiopathic acute pancreatitis
K85.1	Biliary acute pancreatitis
K85.2	Alcohol induced acute pancreatitis
K 85.3	Drug induced pancreatitis
K85.6	Other acute pancreatitis
K85.9	Acute pancreatitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- The incidence of pancreatitis is increasing in the U.S. Admissions for acute pancreatitis have increased dramatically, and acute pancreatitis was the number-one GI-related cause for admission across U.S. hospitals in 2012. There are >270,000 cases of acute pancreatitis reported annually in the U.S., with 40%+ due to gallstone disease (most common cause) and 30% due to alcohol.
- Incidence in urban areas is twice that of rural areas (20/100,000 persons in urban areas).
- 20% of patients have necrotizing pancreatitis; the remainder have interstitial, or edematous, pancreatitis.
- Drugs are responsible for less than 5% of all cases of acute pancreatitis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Epigastric tenderness and guarding, often radiating to the back; pain usually developing suddenly, reaching peak intensity within 10 to 30 min, severe and lasting several hours without relief. Rarely, some patients can have painless severe pancreatitis
- Nausea and vomiting (up to 90% of cases)
- Hypoactive bowel sounds (from ileus)
- Tachycardia, shock (from decreased intravascular volume)
- Confusion (from metabolic disturbances)
- Fever (SIRS response or infection when pancreatic necrosis is present)
- Decreased breath sounds (pleural effusions) or rales (atelectasis, acute respiratory distress syndrome [ARDS])
- Jaundice (from obstruction or compression of biliary tract)
- Ascites (from tear in pancreatic duct, leaking pseudocyst)
- Palpable abdominal mass (pseudocyst, phlegmon, abscess, carcinoma)
- Evidence of hypocalcemia (Chvostek sign, Trousseau sign)
- Evidence of retroperitoneal bleeding (hemorrhagic pancreatitis):
  1. Ecchymosis around the umbilicus **(Cullen sign)**
  2. Ecchymosis involving the flanks **(Grey Turner sign)**
- Tender subcutaneous nodules (caused by subcutaneous fat necrosis)

TABLE 1 Commonly Used Scoring Systems: Advantages and Disadvantages

System	Scoring	Advantages	Disadvantages
Ranson criteria on admission: 1. Age >55 yr 2. WBC >16 × 10^9/L 3. LDH >350 U/L 4. AST >250 U/L 5. Glucose >200 mg/dl During initial 48 hr: 1. Hgb falls below 10 mg/dl 2. BUN rises by >5 mg/dl 3. Ca <8 mg/dl 4. Pa_{O_2} <60 mm Hg 5. Base deficit >4 mEq/L 6. Fluid sequestration >6 L	One point for each factor listed; score >3 indicates SAP	Well known, relatively easy to calculate	Requires 48 hr to complete evaluation
APACHE II*	Score >8 predicts SAP	Can be calculated within 24 hr of admission	Requires large dataset for processing
BISAP 1. BUN >25 mg/dl 2. Altered mental status 3. Presence of SIRS 4. Age >60 yr 5. Pleural effusions	One point for each factor listed; score >3 indicates SAP	Ease of use, available within 24 hr of admission	Significantly lower sensitivity than either Ranson or APACHE II; results in greater likelihood of missing severe AP
CTSI	Based on radiographic data	Excellent predictor of local complications; can show infected pancreatic necrosis	Requires 72 to 96 hr, making it a poor test for guiding decisions at admission

AP, Acute pancreatitis; *APACHE,* Acute Physiology and Chronic Health Evaluation; *AST,* aspartate aminotransferase; *BISAP,* Bedside Index for Severity in Acute Pancreatitis; *BUN,* blood urea nitrogen; *Ca,* serum calcium; *CTSI,* Computed Tomography Severity Index; *Hgb,* hemoglobin; *LDH,* lactate dehydrogenase; *SAP,* severe acute pancreatitis; *SIRS,* systemic inflammatory response syndrome; *WBC,* white blood cell count.

*Based on diverse variables, including age, physiology, and long-term health; equation available at www.sfar.org/scores2/apache22.html#calcul. Adding body mass index (BMI) to APACHE II (the APACHE 0 score) increases discrimination (1 point added for BMI 26-30; 2 points for BMI >30).

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

[1] Banks PA, et al: Acute Pancreatitis Classification Working Group: classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus, *Gut* 62(1):102-111, 2013.

[2] Spitzer AL, et al: Applying Ockham's razor to pancreatitis prognostication: a four-variable predictive model, *Ann Surg* 243(3):380-388, 2006.

ETIOLOGY

- In >90% of cases: Biliary tract disease (calculi or sludge) or alcohol, most common after 5 to 10 yr of heavy drinking
- Hypertriglyceridemia (usually >1000 mg/dl) from any cause
- Drugs (e.g., thiazides, furosemide, corticosteroids, tetracycline, estrogens, valproic acid, metronidazole, azathioprine, methyldopa, pentamidine, ethacrynic acid, procainamide, amiodarone, sulindac, nitrofurantoin, angiotensin-converting enzyme inhibitors, danazol, cimetidine, piroxicam, gold, ranitidine, sulfasalazine, isoniazid, acetaminophen, cisplatin, didanosine, opiates, erythromycin, metformin, GLP-1 receptor agonists, incretin mimetics)
- Abdominal trauma
- Surgery
- Endoscopic retrograde cholangiopancreatography (ERCP), especially with manipulation of the pancreatic duct
- Infections (predominantly viral)
- Peptic ulcer (penetrating duodenal ulcer)
- Pancreas divisum (congenital failure to fuse of dorsal or ventral pancreas)
- Idiopathic
- Pregnancy
- Vascular (vasculitis, ischemic)
- Hypercalcemia
- Pancreatic carcinoma (primary or metastatic)
- Renal failure
- Hereditary pancreatitis, such as in patients with cystic fibrosis
- IgG4 disease
- Occupational exposure to chemicals: Methanol, cobalt, zinc, mercuric chloride, creosol, lead, organophosphates, chlorinated naphthalenes
- Others: Scorpion venom, obstruction at ampulla region (neoplasm, duodenal diverticula, Crohn disease, rarely celiac disease), hypotensive shock, autoimmune pancreatitis

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- PUD
- Acute cholangitis, biliary colic
- High intestinal obstruction
- Early acute appendicitis
- DKA
- Pneumonia (basilar)
- Myocardial infarction (inferior wall)
- Renal colic
- Ruptured or dissecting aortic aneurysm
- Mesenteric ischemia

LABORATORY TESTS

Pancreatic enzymes:

Amylase is increased, usually elevated in the initial 3 to 5 days of acute pancreatitis. Isoamylase determinations (separation of pancreatic cell isoenzyme components of amylase) are useful in excluding occasional cases of salivary hyperamylasemia. The use of isoamylase rather than total serum amylase reduces the risk of erroneously diagnosing pancreatitis and is preferred by some as initial biochemical test in patients suspected of having acute pancreatitis.

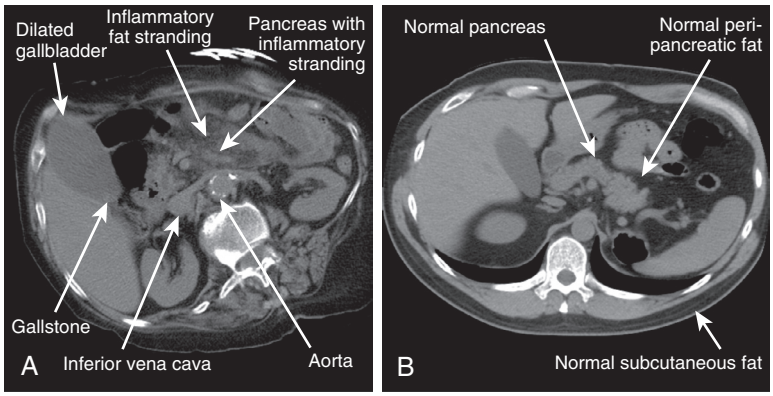

FIG. 1 Gallstone pancreatitis and normal pancreas for comparison, axial computed tomography without contrast. A, Gallstone pancreatitis CT. A dilated gallbladder is visible with a hyperdense dependent lesion consistent with a gallstone. The region of the pancreas shows significant inflammatory stranding. In this patient, the pancreas lies just anterior to the left renal vein, which can be seen crossing anterior to the aorta and entering the inferior vena cava. **B,** A normal pancreas is visible. This pancreas is surrounded by uninflamed fat, which is dark (nearly black). Compare this normal fat with normal subcutaneous fat. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

Urinary amylase determinations are useful to diagnose acute pancreatitis in patients with lipemic serum, to rule out elevated serum amylase caused by macroamylasemia, and to diagnose acute pancreatitis in patients whose serum amylase is normal.

Serum lipase levels are elevated in acute pancreatitis; the elevation is less transient than serum amylase and more sensitive in patients with alcoholic pancreatitis. Concomitant evaluation of serum amylase and lipase increases diagnostic accuracy of acute pancreatitis. Elevated serum trypsin levels are diagnostic of pancreatitis (in absence of renal failure).

Serum C-reactive protein is an excellent laboratory marker of severity; a level >150 mg/dl at 48 hours is associated with severe pancreatitis.

Rapid measurement of urinary trypsinogen-2 (if available) is useful in the emergency department as a screening test for acute pancreatitis in patients with abdominal pain; a negative dipstick test for urinary trypsinogen-2 rules out acute pancreatitis with a high degree of probability, whereas a positive test indicates need for further evaluation.

Interleukin-6 level: Worse prognosis with level ≥300 pg/ml.

ADDITIONAL TESTS

- Complete blood count: Reveals leukocytosis; hematocrit (Hct) may be initially increased as a result of hemoconcentration; decreased Hct may indicate hemorrhage or hemolysis.
- Blood urea nitrogen (BUN) is increased because of dehydration. Serial BUN measurements are the most valuable lab test for predicting mortality during the initial 48 hr.
- Elevation of serum glucose in a previously normal patient correlates with the degree of pancreatic malfunction and may be related to increased release of glycogen, catecholamines, and glucocorticoid release and decreased insulin release.
- Liver profile: Aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) are increased as a result of tissue necrosis; bilirubin and alkaline phosphatase may be increased from common bile duct obstruction. A threefold or greater rise in serum alanine aminotransferase concentrations is an excellent indicator (95% probability) of biliary pancreatitis.
- Serum calcium is decreased as a result of saponification, precipitation, and decreased parathyroid hormone response.
- Arterial blood gases: Pa_{O_2} may be decreased as a result of ARDS, pleural effusion(s); pH may be decreased as a result of lactic acidosis, respiratory acidosis, and renal insufficiency.
- Serum electrolytes: Potassium may be increased from acidosis or renal insufficiency; sodium may be increased from dehydration.

IMAGING STUDIES

- Abdominal plain films are useful initially to distinguish other conditions that may mimic pancreatitis (perforated viscus). They may reveal localized ileus (sentinel loop), pancreatic calcifications (chronic pancreatitis), blurring of left psoas shadow, dilation of transverse colon, calcified gallstones.
- Chest x-ray may reveal elevation of one or both diaphragms, pleural effusions, basilar infiltrates, or platelike atelectasis.
- Abdominal ultrasonography is useful in detecting gallstones (sensitivity of 60% to 70% for detecting stones associated with pancreatitis). Its availability and noninvasive nature make it the initial imaging study of choice; its major limitation is the presence of distended bowel loops overlying the pancreas.
- CT scan (Fig. 1) is less sensitive than ultrasound in identifying gallstones and exposes the patient to risk of contrast-induced nephropathy. It is, however, superior to ultrasonography in identifying pancreatitis and defining its extent, and it also plays a role in diagnosing pseudocysts (they appear as

TABLE 2 Computed Tomography (CT) Severity Index Score for Pancreatitis*

Grade†	CT Findings	Score
A	Normal pancreas	0
B	Focal or diffuse enlargement of the pancreas, contour irregularities, heterogeneous attenuation, no peripancreatic inflammation	1
C	Grade B plus peripancreatic inflammation	2
D	Grade C plus a single fluid collection	3
E	Grade C plus multiple fluid collections or gas	4
Percent Necrosis Present on CT		
0		
<33		
33-50		
>50		

*Severity Index Score = Grade score + Percent necrosis score. Maximum score = 10; severe disease = 6 or higher.
†Severity of the acute inflammatory process.
From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

a well-defined area surrounded by a high-density capsule); gastrointestinal fistulization or infection of a pseudocyst can also be identified by the presence of gas within the pseudocyst. Sequential contrast-enhanced CT is useful for detection of pancreatic necrosis. The severity of pancreatitis can also be graded by CT scan (Table 2). (A = normal pancreas, B = enlarged pancreas [1 point], C = pancreatic and/or peripancreatic inflammation [2 points], D = single peripancreatic collection [3 points], E = at least two peripancreatic collections and/or retroperitoneal air [4 points]. Percentage of pancreatic necrosis <30% [2 points], 30% to 50% [4 points], >50% [6 points]. The CT severity index is calculated by adding grade points to points assigned for percentage of necrosis.)

- Magnetic resonance cholangiopancreatography (MRCP) has >90% sensitivity for choledocholithiasis and can identify other anatomic abnormalities.
- Endoscopic ultrasonography (EUS) is a minimally invasive test that provides high-resolution imaging of the pancreas. It is useful to identify anatomic abnormalities of the pancreas and has good sensitivity and specificity for small gallstones (≤5 mm).
- ERCP indications: Useful to perform biliary sphincterotomy and stone removal in the presence of a retained bile duct stone seen on imaging. The role and timing of ERCP in patients with acute biliary pancreatitis has been controversial. Guidelines from the American College of Gastroenterology suggest that urgent ERCP (within 24 hr of admission) is indicated in patients with biliary pancreatitis who have concurrent acute cholangitis, but it is not needed in most patients who do not have evidence of ongoing biliary obstruction.[3,4,5]

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Bowel rest with avoidance of liquids or solids during the acute illness. Limited data suggest that early feeding in patients with acute pancreatitis does not seem to increase adverse events and, for patients with mild to moderate pancreatitis, may reduce length of hospital stay.[6]
- Avoidance of alcohol and any drugs associated with pancreatitis.

ACUTE GENERAL Rx

GENERAL MEASURES:

- Assess severity of pancreatitis (see Table 1).
- An algorithm for the management of acute pancreatitis is described in Fig. 2.
- Maintain adequate intravascular volume with vigorous IV hydration. Aggressive fluid resuscitation (250 to 500 ml/hr) with isotonic crystalloids is critical in managing acute pancreatitis, unless cardiac or renal disease precludes it.
- Patient should remain NPO until clinically improved, stable, and hungry. Enteral feedings are preferred over total parenteral nutrition if supplemental nutrition is necessary. Enteral nutrition reduces mortality, multiple organ failure, systemic infections, and operative interventions more than total parenteral nutrition does in patients with acute pancreatitis. Parenteral nutrition may be necessary in patients who do not tolerate enteral feeding or in whom an adequate infusion rate cannot be reached within 2 to 4 days. Early (within 24 to 48 hr of admission) enteral feeding through a nasogastric (NG) feeding tube has limited evidence to support this strategy. A recent trial did not show superiority of early NG tube feeding, as compared with oral diet after 72 hours, in reducing the rate of infection or death in patients with acute pancreatitis at high risk for complications.
- Nasogastric suction is useful only in severe pancreatitis to decompress the abdomen in patients with ileus.
- Control pain: IV hydromorphone or fentanyl. Meperidine and morphine are also commonly used narcotics for pain control, although morphine has been shown to increase sphincter of Oddi pressure and has delayed metabolite clearance in patients with concomitant renal failure.
- Correct metabolic abnormalities (e.g., replace calcium and magnesium as necessary).
- Prophylactic antibiotics are not recommended, regardless of the severity or presence of pancreatic necrosis.
- An algorithm for the management of acute pancreatitis at various stages is described in Fig. 2.

SPECIFIC MEASURES:

- Pancreatic or peripancreatic infection develops in 30% of patients with pancreatic necrosis. The use of antibiotics is justified if the patient has evidence of septicemia, pancreatic abscess, or pancreatitis caused by biliary calculi with concomitant cholangitis. Their use should generally be limited to 5 to 7 days to prevent development of fungal superinfection. Appropriate empiric antibiotic therapy should penetrate pancreatic necrosis. Options include a carbapenem alone (due to anaerobic coverage) or a quinolone, ceftazidime, or cefepime, combined with an enteric anaerobic agent such as metronidazole. CT-guided fine-needle aspiration (FNA) can be performed to culture the infected necrosis and tailor antibiotic therapy. If sampling of infected necrosis occurs and is sterile, antibiotics should be discontinued
- Surgical therapy has a limited role in acute pancreatitis; it is indicated in the following:
  1. Gallstone-induced pancreatitis: Cholecystectomy when acute pancreatitis subsides. However, randomized trials have shown that patients with mild gallstone pancreatitis can undergo cholecystectomy safely during the first 48 hr of hospitalization
  2. Perforated peptic ulcer
  3. Necrotizing pancreatitis with infected necrotic tissue is associated with an elevated rate of complications and increased risk of death. Traditional treatment has been open necrosectomy; surgical necrosectomy induces a proinflammatory response and is associated with a high complication rate. Recent trials have shown that a step-up approach consisting of percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy may have a lower rate of complications and death. Endoscopic transgastric necrosectomy, a form of natural orifice transluminal endoscopic surgery, has been shown in recent trials to be effective in reducing the proinflammatory response as well as reducing complications
- Identification and treatment of complications:
  1. **Pseudocyst:** Round or spheroid collection of fluid, tissue, pancreatic enzymes, and blood

[3] Fogel EL, Sherman S: ERCP for gallstone pancreatitis, *N Engl J Med* 370:150-157, 2014..
[4] Tenner S, et al: American College of Gastroenterology guidelines: management of acute pancreatitis, *Am J Gastroenterol* 108:1400-1415, 2013.
[5] Bakker OJ, et al: Early versus on-demand nasogastric tube feeding in acute pancreatitis, *N Engl J Med* 371:1983-1993, 2014.
[6] Vaughn VM, et al: Early versus delayed feeding in patients with acute pancreatitis, a systematic review, *Ann Intern Med* 66:883-892, 2017.

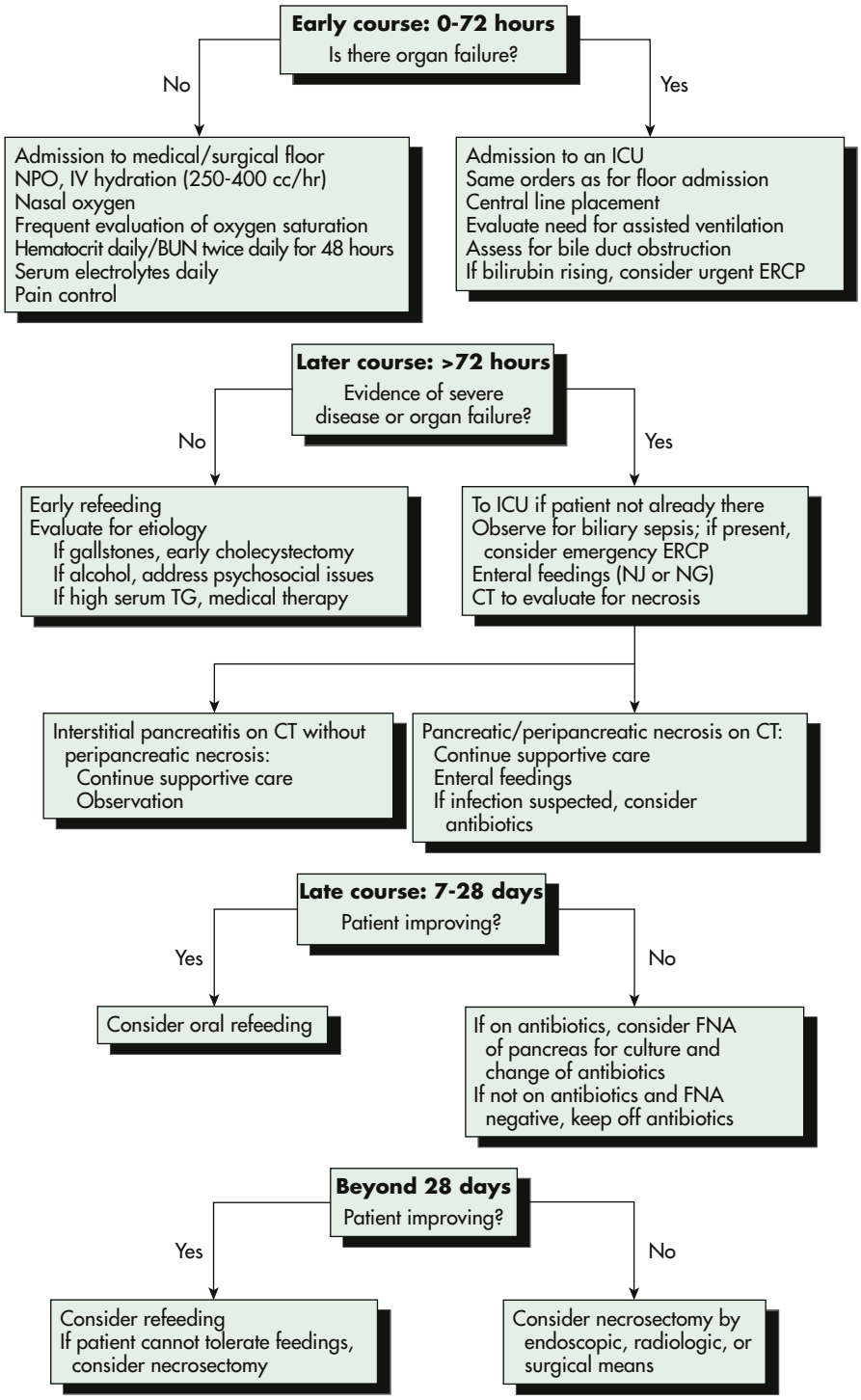

FIG. 2 Algorithm for the management of acute pancreatitis at various stages in its course. *NJ*, Nasojejunal. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

a. Diagnosed by CT scan or sonography.
b. Treatment: Pancreatic pseudocysts can be drained surgically or endoscopically. The endoscopic approach is preferable when the patient's anatomy is suitable and an experienced endoscopist is available. CT scan or ultrasound-guided percutaneous drainage (with a pigtail catheter left in place for continuous drainage) can be used, but the recurrence rate is high; the conservative approach is to reevaluate the pseudocyst (with CT scan or sonography) after 6 to 7 wk and surgically drain it if the pseudocyst has not decreased in size.
c. Generally, pseudocysts <5 cm in diameter are reabsorbed without intervention, whereas those >5 cm require surgical intervention after the wall has matured.

2. **Phlegmon:** Represents pancreatic edema. It can be diagnosed by CT scan or sonography. Treatment is supportive as it usually resolves spontaneously
3. **Pancreatic abscess:** Diagnosed by CT scan (presence of air in the retroperitoneum); Gram staining and cultures of fluid obtained from guided percutaneous aspiration usually identify bacterial organism. Therapy is surgical (or catheter) drainage and IV antibiotics (carbapenem is the drug of choice)
4. **Pancreatic ascites:** Usually caused by leaking of pseudocyst or tear in pancreatic duct. Paracentesis reveals very high amylase and lipase levels in the pancreatic fluid; ERCP may demonstrate the lesion. Treatment is surgical correction if exudative ascites from severe pancreatitis does not resolve spontaneously
5. **Abdominal compartment syndrome:** Caused by intraabdominal leakage of fluids from volume resuscitation or ascites. Diagnosed with sustained intraabdominal pressure >20 mm Hg with new-onset organ failure
6. **Gastrointestinal bleeding:** Caused by alcoholic gastritis, bleeding varices, stress ulceration, or disseminated intravascular coagulation (DIC)
7. **Renal failure:** Caused by hypovolemia, resulting in oliguria or anuria, cortical or tubular necrosis (shock, DIC), or thrombosis of renal artery or vein
8. **Hypoxia:** Caused by ARDS, pleural effusion, or atelectasis
9. **Vascular:** Splenic, portal, or superior mesenteric vein thrombosis; pseudoaneurysm

THERAPY OF UNCOMMON FORMS OF PANCREATITIS

- **Autoimmune pancreatitis (AIP):** Fibroinflammatory disease characterized by an IgG4 lymphoplasmacytic infiltrate. It is a variant of chronic pancreatitis and has been associated with other autoimmune disorders (e.g., primary sclerosing cholangitis, Sjögren syndrome). The inflammatory process is generally responsive to corticosteroid therapy. Older men aged 60 to 70 yr are primarily affected. Patients present with abdominal pain, weight loss, anorexia, and obstructive jaundice. Immunoglobulin G_4 levels are elevated. Radiographically on CT, the pancreas is diffusely enlarged, with a characteristic smooth, capsulelike rim ("sausage pancreas"). Features of type 1 and type 2 autoimmune pancreatitis are summarized in Table 3. Type II autoimmune hepatitis (idiopathic duct-centric chronic pancreatitis) is associated with inflammatory bowel disease and not related to IgG4 cell deposition.
- **Hypertriglyceridemic pancreatitis (HTGP):** IV insulin therapy is the cornerstone of immediate treatment, with supplemental IV

TABLE 3 Features of Type 1 and Type 2 Autoimmune Pancreatitis

Feature	Type 1	Type 2
Histology	Lymphoplasmacytic infiltration Dense periductal infiltrate without damage to ductal epithelium Storiform fibrosis Obliterative phlebitis Abundant (>10 cells/HPF) IgG4-positive cells Fibroinflammatory process may extend to peripancreatic region	Periductal lymphoplasmacytic and neutrophilic infiltration Destruction of the duct epithelium by neutrophils (granulocytic epithelial lesion, or GEL) Obliterative phlebitis is rare No IgG4-positive cells
Average age at presentation	60-70 yr	40-50, but may present in young adults and even children
Gender predominance	Male	Equal
Usual clinical presentations	Obstructive jaundice (75%) Acute pancreatitis (15%)	Obstructive jaundice (50%) Acute pancreatitis (33%)
Pancreatic imaging	Diffuse pancreatic enlargement (40%) Focal pancreatic enlargement (60%)	Diffuse pancreatic enlargement (15%) Focal pancreatic enlargement (85%)
IgG4	Level elevated in serum (~2/3 of patients) Positive in staining of involved tissues	Not associated
Other organ involvement	Biliary strictures Pseudotumors Kidney Lung Others Retroperitoneal fibrosis Sialoadenitis	Not associated
Associated diseases	See above (other organ involvement)	IBD
Long-term outcome	Frequent relapses	Rare or no relapse

HPF, High power field; *IBD,* inflammatory bowel disease; *IgG4,* Immunoglobulin G, subclass 4.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE 4 Prognostic Criteria for Acute Pancreatitis

Ranson Criteria*	Simplified Glasgow Criteria†	Computed Tomography Criteria‡
On admission: Age >55 yr WBC >16,000/μL AST >250 U/L LDH >350 U/L Glucose >200 mg/dl *48 hr after admission:* Hematocrit decrease by >10 BUN increase by >5 mg/dl Ca^{2+} <8 mg/dl Arterial Po_2 <60 mm Hg Base deficit >4 mEq/L Fluid sequestration >6 L	*Within 48 hr of admission:* Age >55 yr WBC >15,000/μL LDH >600 U/L Glucose >180 mg/dl Albumin <3.2 g/dl Ca^{2+} <8 mg/dl Arterial Po_2 <60 mm Hg BUN >45 mg/dl	Normal Enlargement Pancreatic inflammation Single fluid collection Multiple fluid collection

AST, Aspartate aminotransferase; *BUN,* blood urea nitrogen; *LDH,* lactate dehydrogenase; *WBC,* white blood cells.
*Three or more Ranson criteria predict a complicated clinical course. Data from Ranson JH et al: Prognostic signs and nonoperative peritoneal lavage in acute pancreatitis, *Surg Gynecol Obstet,* 143:209-219, 1976.
†Data from Blamey SL et al: Prognostic factors in acute pancreatitis, *Gut* 25:1340, 1984.
‡Grades A and B represent mild disease with no risk of infection or death. Grade C represents moderately severe disease with a minimal likelihood of infection and essentially no risk of mortality. Grades D and E represent severe pancreatitis with an infection rate of 30% to 50% and mortality rate of 15%. Data from Balthazar EJ et al: Acute pancreatitis value of CT in establishing prognosis, *Radiology,* 174:331, 1990.
From Goldman L, Ausiello D (eds): *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.

glucose infusion if the serum glucose levels are not elevated. IV heparin was previously used as well, but its effectiveness has come into question. Antihyperlipidemic agents (fibrates) should be initiated as adjuvant therapy as soon as possible for long-term control. Beneficial results have been reported with early (within 48 hr) initiation of apheresis with therapeutic plasma exchange when there is concomitant hypocalcemia, lactic acidosis, or other signs of organ dysfunction.

DISPOSITION

Prognosis varies with the severity of pancreatitis; overall mortality rate in acute pancreatitis is 5% to 10%. Prognostic criteria for acute pancreatitis are described in Table 4.

REFERRAL

- Hospitalization is indicated in moderate to severe cases of pancreatitis.
- Surgical consultation is needed in suspected gallstone pancreatitis, perforated peptic ulcer, or presence of necrotic or infected foci. Acute pancreatitis can generally be attributed to gallstones when patients have both abnormal liver enzymes and gallstones (or sludge) on imaging. Such patients should consider cholecystectomy prior to discharge to prevent recurrent pancreatitis.
- Gastroenterology consultation in severe or recurrent pancreatitis, when ERCP is needed for gallstone pancreatitis, or when the cause of pancreatitis is unclear.
- Consider intensive care unit transfer for patients who require aggressive fluid resuscitation and are at risk of volume overload from cardiac or renal causes. Similarly, consider transfer for patients with developing ARDS, patients with abdominal compartment syndrome (with surgical consultation), and those who require apheresis.

PEARLS & CONSIDERATIONS

- Acute pancreatitis is the most common major complication of ERCP. NSAIDs are potent inhibitors of phospholipase A_2, cyclooxygenase, and neutrophil-endothelial interactions, which play an important role in the pathogenesis of acute pancreatitis. Preliminary trials show that among patients at high risk for post-ERCP pancreatitis, rectal indomethacin (given as two 50-mg indomethacin suppositories administered immediately after ERCP) significantly reduced the incidence of post-ERCP pancreatitis.
- Pancreatic stent placement decreases the risk of post-ERCP pancreatitis.
- Statins reduce risk for pancreatitis in adults. Fibrates do not affect risk for pancreatitis other than in patients with hypertriglyceridemia-induced pancreatitis.
- Diabetes mellitus may develop from extensive pancreatic necrosis.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Acute Pancreatitis (Patient Information)

AUTHOR: **David J. Lucier, Jr., MD, MBA, MPH**

SUGGESTED READINGS

Al-Omran M et al: Enteral versus parenteral nutrition for acute pancreatitis, *Cochrane Database Syst Rev* 1:CD002837, 2010.

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BASIC INFORMATION

DEFINITION

- A **panic attack** is a relatively brief, sudden episode of intense fear or apprehension, often associated with a sense of impending doom and various uncomfortable and disquieting physical symptoms. Panic attacks may be uncued ("out of the blue") or cued (i.e., triggered by a particular object or situation). Panic attacks may be present in a variety of different anxiety-related disorders (e.g., phobias, social anxiety, obsessive-compulsive disorder). Table 1 describes criteria for diagnosis of panic attack.
- **Panic disorder** is diagnosed after at least two uncued panic attacks have occurred followed by at least 1 mo (or more) of significant concern about future attacks, worry about their implications, or a major change in behavior related to these attacks. The criteria for diagnosis of panic disorder are summarized in Table 2. **Agoraphobia** is anxiety about, and avoidance of, places or situations in which the ability to escape is perceived to be limited or embarrassing or in which help might not be available in the event of having a panic attack.

SYNONYMS

Anxiety attacks
Fear attacks
Ataque de nervios

ICD-10CM CODES
F41.0 Panic disorder
F40.0 Agoraphobia
DSM-5 CODES
300.01 Panic disorder
300.22 Agoraphobia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 1% 1-mo incidence of panic attacks.

TABLE 1 Criteria for Diagnosis of a Panic Attack

A discrete period of intense fear or discomfort, in which ≥4 of the following symptoms developed abruptly and reached a peak within 10 min:
- Palpitations, pounding heart, or accelerated heart rate
- Sweating
- Trembling or shaking
- Sensations of shortness of breath or being smothered
- Feeling of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy, unsteady, light-headed, or faint
- Derealization (feelings of unreality) or depersonalization (being detached from oneself)
- Fear of losing control or going crazy
- Paresthesias (numbness or tingling sensations)
- Chills or hot flashes

From Kliegman RM et al: *Nelson essentials of pediatrics,* ed 5, Philadelphia, 2006, Saunders.

PREVALENCE (IN U.S.):
- 15% to 20% lifetime prevalence of one or more panic attacks.
- Panic disorder is much more uncommon, with a lifetime prevalence of 1.5% to 3.5%; chronicity of condition reflected by a similar 1-yr prevalence rate of 1% to 2%.
- Agoraphobia is relatively rare; 0.3% to 1% lifetime prevalence; 30% to 50% of patients diagnosed with panic disorder also have agoraphobia.
- Lower rates of panic disorder are reported among Latinos, African Americans, Caribbean blacks, and Asian Americans (DSM-5).
- Lower estimates for Asian, African, and Latin American countries (0.1% to 0.8%) (DSM-5).

PEAK INCIDENCE:
- Chronic condition with a waxing and waning course.
- Bimodal incidence peaks noted, with the first peak between ages 15 and 24 yr and second peak between ages 35 and 44 yr.

PREDOMINANT SEX:
- Women more commonly affected (>85% of clinical population).
- Panic disorder twice as common in women.
- Panic disorder with agoraphobia three times as common in women.

PREDOMINANT AGE:
- Age of onset is typically late adolescence to mid-30s. Onset earlier in males (24 yr) than females (28 yr).
- Onset after age 45 yr is rare and should raise suspicion of different etiology.

GENETICS:
- Risk of developing panic disorder in first-degree relatives of individuals with panic disorder is four to seven times that of general population.
- Findings in twin studies: Approximately 60% of contributing factors to panic are genetic.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Panic disorder:
- Present either with a panic attack or with fear and anxiety related to anticipation of a future panic attack or its implications.
- Typical presentation: Unexpected, untriggered periods of intense anxiety and fear with associated physiologic changes (e.g., palpitations, sweating, tremulousness, shortness of breath, chest pain, gastrointestinal distress, faintness, derealization, paresthesia). This is accompanied by associated fears of dying, heart attack, stroke, passing out, losing control, or losing one's mind. Panic attacks are often described as "the most terrifying" episode an individual has experienced.

TABLE 2 Criteria for Diagnosis of Panic Disorder

1. Recurrent unexpected panic attacks with associated worry or behavior change
2. Not due to effects of a drug, medication, or medical condition

- Emergency or physician visits often occasioned by physical symptoms such as chest pain, dizziness, or difficulty breathing. Thirty percent of patients presenting with chest pain have panic disorder.
- In a recent study of 1327 patients reporting noncardiac chest pain, 77.1% had visited the emergency department.
- Patients reporting a fear of dying from a panic attack tend to have more symptomatic panic attacks and agoraphobia.

Agoraphobia:
- Rare complaints to physician. May manifest in missed office visits or tardiness. Patients may request home visits or telephone care.
- Activities usually self-limited by avoiding public situations where the patient believes he or she might experience a panic attack and would be unable to exit readily, such as the following:
  1. Crowded public areas (stores, public transportation, flying, church)
  2. Individual interactions (hairdresser, dentist, neighborhood meetings)
  3. Driving (especially if alone, far from home, over bridges, through tunnels, on highways, or on isolated roads)
- On exposure to or anticipation of exposure to feared situations, significant anxiety occurs. Anxiety may generate somatic symptoms that trigger a full-blown panic attack. Patients believe that escape from these situations reduces the alarming symptoms, thus reinforcing future avoidance. In actuality, symptom relief stems from adrenaline breaking down in the body after approximately 20 minutes.

ETIOLOGY

Hypotheses (NOTE: There are sufficient data to support each model. Models are not mutually exclusive.):
- Central dyscontrol of autonomic arousal (typically localized to the locus ceruleus); similar symptoms may be chemically induced with yohimbine, caffeine, or cholecystokinin.
- Cognitive overreaction (i.e., "catastrophic misinterpretation") to relatively mild or benign physiologic cues that then triggers a genuine autonomic cascade and further misinterpretations.
- Dysfunction of a central suffocation alarm mechanism; some signs of compensated respiratory alkalosis. Can be experimentally induced with sodium lactate or carbon dioxide.

RISK FACTORS

- Temperamental: Negative affect and anxiety sensitivity are risk factors for the onset of panic attacks. Severe separation anxiety in childhood may precede the panic disorder.
- Environmental: Sexual and physical abuse in childhood is common in panic disorder. Most panic sufferers are able to identify a coalescence of stressors preceding their first panic attack.
- Genetic and physiological: Although the exact genes are unknown, it is believed that multiple genes contribute to the vulnerability to panic attacks.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Medical conditions:

- Endocrinopathies:
  1. Hyperthyroidism
  2. Hyperparathyroidism
  3. Pheochromocytoma
  4. Carcinoid tumor
- Cardiac and respiratory diseases:
  1. Arrhythmias
  2. Myocardial infarction
  3. Chronic obstructive pulmonary disease
  4. Asthma
  5. Mitral valve prolapse
- Metabolic:
  1. Hypoglycemia
  2. Electrolyte imbalances
  3. Porphyria
- Seizure disorders: Complex partial seizures can present with ictal panic attacks.
- Psychiatric disorders (NOTE: Panic attacks are common in a variety of psychiatric disorders. Panic disorder could be conceptualized as a phobia of the somatic sensations or situations that have become paired with panic attacks.)
  1. Phobias (e.g., specific phobia or social phobia). Note that fear of going on a plane because of crashing would be a specific phobia, whereas fear of going on a plane because one is then trapped and worries about panic is more suggestive of panic disorder with agoraphobia
  2. Obsessive-compulsive disorder (cued by exposure to the object of the obsession)
  3. Posttraumatic stress disorder (cued by recall of a stressor)
  4. Generalized anxiety disorder (cued by excessive worry)
- Therapeutic (theophylline, steroids) and recreational (cocaine, amphetamine, caffeine, diet pills) drugs and drug withdrawal (alcohol, cannabis, barbiturates, benzodiazepines)

WORKUP

- Emergency presentation: Cardiac, respiratory, or neurologic symptoms
- History and physical examination to rule out a concomitant medical or substance-related condition

NOTE: Panic disorder and agoraphobia are not diagnoses of exclusion, but exclusion of other conditions is usually required.

LABORATORY TESTS

- Thyroid profile
- Electrolyte measures, including calcium
- Toxicology screen
- ECG
- Acute cases: Possible monitoring and cardiac enzymes to rule out arrhythmia or ischemia

IMAGING STUDIES

- For temporal lobe dysfunction (e.g., temporal lesions or as ictal or interictal manifestation of temporal lobe complex partial seizures): Brain CT scan or MRI or an electroencephalogram in some patients
- Holter monitor to rule out occult or episodic arrhythmias
- Chest x-ray, arterial blood gases, or pulmonary function tests if respiratory compromise suspected

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral therapy (CBT), in particular Panic Controlled Treatment, is generally very effective, with strongest results for cognitive restructuring (i.e., challenging catastrophic misinterpretations of somatic symptoms), in vivo or imaginal exposures (i.e., exposure to panic triggers in a controlled graded hierarchical fashion from least to most difficult with the goal of habituation and extinction of the fear response), and interoceptive exposures (i.e., repeated recreation and management of feared somatic sensations via activities such as chair spinning, straw breathing, and hyperventilation).
- CBT effect sizes are equal to or larger than for pharmacotherapy, attrition rates are lower, and relapse rates are lower. Treatment may take several sessions spread over weeks and may require referral to a behavioral specialist. CBT has been shown to be the most effective intervention for panic disorder with or without agoraphobia across treatment sites.
- A recent dismantling study of cognitive-behavioral therapy components for panic disorder suggests that interoceptive exposure and a face-to-face setting were associated with better treatment efficacy whereas muscle relaxation and virtual reality exposure were associated with significantly lower efficacy.

ACUTE GENERAL Rx

- Benzodiazepines, particularly clonazepam and alprazolam: Highly effective in the acute setting, although long-term use is contraindicated for effective outcome and due to addictive potential.
- Low-dose clonazepam for patients with rare panic attacks and asymptomatic periods (0.25-0.5 mg PO or sublingually prn).
- Start patient on selective serotonin reuptake inhibitor (SSRI) or similar agent and taper patient off benzodiazepine by wk 2 to 3.

CHRONIC Rx

- Preferred pharmacologic agents: Antidepressants with a significant serotonin reuptake inhibitory action. Generally, start at low dose and titrate upward. Minimum treatment duration is 6 to 8 mo, but many patients need to take medications indefinitely. These medications should not be discontinued abruptly; they should be tapered due to withdrawal effects including rebound anxiety.
  1. SSRIs: Sertraline (50-200 mg/day), citalopram (20-60 mg/day), escitalopram (5-30 mg/day), and fluoxetine (5-60 mg/day)
  2. Imipramine (100-300 mg/day)
  3. SNRIs: Venlafaxine (75-225 mg/day)
- Combination CBT plus SSRI has shown good long-term effects and is somewhat better than antidepressants or CBT alone. Combination CBT plus benzodiazepine does not provide any added benefit and may undermine CBT (interoceptive and in vivo exposures may be less effective if the benzodiazepine is completely controlling the anxiety).

DISPOSITION

- Typical course is chronic but with significant waxing and waning (common to have long periods of remission).
- Presence of agoraphobia associated with a more chronic course.
- Findings with long-term follow-up studies: 6 to 10 yr after treatment some 30% are in remission, 40% to 50% have improved with residual symptoms, and the remainder are either unchanged or worse.

REFERRAL

- If patients do not respond to an SSRI.
- Cognitive-behavioral therapy is the preferred treatment.

PEARLS & CONSIDERATIONS

- Patient and family education is an important first step in the management of panic disorder. Education provides more adaptive explanations for the benign somatic sensations paired with panic. Presentation of genetic information and explanation of the benign nature of the physiology of each of the symptoms the patient experiences serve as a good start to allay fears and reduce stigma.
- Resumption of avoided activities or situations is a positive prognostic sign and may promote further therapeutic gains.
- The therapist's adherence to the treatment protocol and the therapeutic alliance established during the first session predict a better outcome for the long-term success of CBT for panic disorder with or without agoraphobia.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Panic Disorder (Patient Information)

AUTHOR: **Jeffrey P. Wincze, PhD**

SUGGESTED READINGS

Barlow DH et al: The unified protocol for transdiagnostic treatment of emotional disorders compared with diagnosis-specific protocols for anxiety disorders, *JAMA Psychiatry* 74(9):875-884, 2017.

Boettcher J et al: Internet-based mindfulness treatment for anxiety disorders: a randomized controlled trial, *Behav Ther* 45(2):241-253, 2014.

Foldes-Busque G et al: A closer look at the relationships between panic attacks, emergency department visits and non-cardiac chest pain, *J Health Psychol*, 2017. 1359105316683785.

Lutz W et al: Patterns of early change and their relationship to outcome and early treatment termination in patients with panic disorder, *J Consult Clin Psychol* 82:287-297, 2014.

Pompoli A et al: Dismantling cognitive-behaviour therapy for panic disorder: a systematic review and component network meta-analysis, *Psycholog Med*, 2018, https://doi.org/10.1017/S0033291717003919.

Vervliet B et al: Fear extinction and relapse: state of the art, *Annu Rev Clin Psychol* 9:215-248, 2013.

BASIC INFORMATION

DEFINITION

Panniculitis refers to inflammation of subcutaneous fat. Most cases are found in association with a systemic disease. Panniculitis can be separated into groups based on histopathologic characteristics. Panniculitis is classified into lobular or septal panniculitis based on whether the inflammation is seen in the fat lobules or septae, respectively. It can be further classified based on whether the inflammation is found with or without vasculitis (Table 1) and by predominant cell type. A classification of the panniculitides is summarized in Box 1.

ICD-10CM CODES

M79.3	Unspecified panniculitis
M5400	Panniculitis affecting regions of neck and back, site unspecified
M5401	Panniculitis affecting regions of neck and back, occipito-atlanto-axial region
M5402	Panniculitis affecting regions of neck and back, cervical region
M54.03	Panniculitis affecting regions of neck and back, cervicothoracic region
M54.04	Panniculitis affecting regions of neck and back, thoracic region
M54.05	Panniculitis affecting regions of neck and back, thoracolumbar region
M54.06	Panniculitis affecting regions of neck and back, lumbar region
M54.07	Panniculitis affecting regions of neck and back, lumbosacral region
M54.08	Panniculitis affecting regions of neck and back, sacral and sacrococcygeal region
M54.09	Panniculitis affecting regions, neck and back, multiple sites in spine

EPIDEMIOLOGY & DEMOGRAPHICS

The epidemiology of the various panniculitides varies with each disease process. The most common panniculitis is erythema nodosum (refer to topic "Erythema Nodosum"). Another common panniculitis seen in the clinical setting is lipodermatosclerosis (LDS), which is usually seen in young, overweight females with associated venous insufficiency.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Skin lesions can appear as nonspecific areas of erythema or erythematous nodules and/or plaques. The nodules can be palpated beneath the dermis. Ulceration, atrophy, and sclerosis can be associated clinical features of these lesions.
- The lesions are frequently painful and tender to palpation.
- Associated constitutional symptoms such as low-grade fevers, malaise, fatigue, myalgias, and arthralgias may be present.
- These skin findings usually are found on the lower limbs; however, the location of these lesions can vary with each specific panniculitis, that is, erythema nodosum is found on the pretibial areas of the lower extremities (Fig. E1), erythema induratum occurs on the calf, and lupus panniculitis occurs on the upper arms, shoulders, and face.
- Skin findings tend to evolve as the types of inflammatory cells change over the course of a few days.

ETIOLOGY

Panniculitis can be either primary/idiopathic or secondary. Common secondary etiologies can be classified into the following broad categories:

- Infections: Bacterial (streptococci), mycobacterial, fungal, parasitic, and viral
- Inflammatory/connective tissue disease: Erythema nodosum, erythema induratum, lipodermatosclerosis, lupus panniculitis, cutaneous polyarteritis nodosa, dermatomyositis-associated panniculitis
- Malignancy: Subcutaneous panniculitis-like type T-cell lymphoma
- Pancreatic disease: Pancreatic panniculitis, which is associated with pancreatitis or pancreatic carcinoma
- Immunodeficiency states: Alpha-1 antitrypsin deficiency panniculitis, which is associated with pulmonary and hepatic disease
- Trauma: Cold panniculitis (due to exposure to the cold), traumatic panniculitis, and factitial panniculitis (due to injection of medication or foreign substances into the subcutaneous fat)
- Deposition: Calciphylaxis, gout

Panniculitis can be a sign of an underlying systemic disease. Lupus panniculitis can occur alone or may present before or after the onset of either discoid lupus erythematosus or systemic lupus erythematosus.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- The skin lesions of panniculitis need to be distinguished from other skin lesions that may manifest similarly, such as insect bites, thrombophlebitis, and cellulitis.
- Disorders affecting the deep dermis or fascia (i.e., plaque morphea, eosinophilic fasciitis), benign or malignant tumors manifesting as subcutaneous nodules, and nodules with deep bruising may have similar clinical findings and be difficult to distinguish from panniculitis.

WORKUP

- Diagnosis of panniculitis depends on a thorough history and physical examination, evaluation of patient's risk factors, skin lesion appearance and distribution, as well as any associated clinical findings.
- If the diagnosis is unclear or needs to be confirmed, a deep skin biopsy should be performed. The preferred biopsy is an excisional biopsy, but a large 6- to 8-mm punch biopsy may be sufficient.

Although the above often establishes a diagnosis, there are times when it is difficult to accurately diagnose a specific panniculitis. Different forms of panniculitides have similar clinical findings while others are rare, complicating the presentation. Biopsy specimens may be too superficial to assess

TABLE 1 Classification of Panniculitis

I. Without prominent vasculitis
  A. Septal inflammation
    1. Lymphocytic and mixed: Erythema nodosum and variants
    2. Granulomatous: Palisaded granulomatous diseases, sarcoidosis, subcutaneous infection: Tuberculosis, syphilis
    3. Sclerotic: Scleroderma, eosinophilic fasciitis, lipodermatosclerosis, toxins
  B. Lobular inflammation
    1. Neutrophilic: Infection, ruptured folliculitis and cysts, pancreatic fat necrosis
    2. Lymphocytic: Lupus panniculitis, post-steroid panniculitis, lymphoma/leukemia
    3. Macrophagic: Histiocytic cytophagic panniculitis
    4. Granulomatous: Erythema induratum/nodular vasculitis, palisaded granulomatous diseases, sarcoidosis, Crohn disease
    5. Mixed inflammation with many foam cells: α1-antitrypsin deficiency, traumatic fat necrosis
    6. Eosinophilic: Eosinophilic panniculitis, arthropod bites, parasites
    7. Enzymatic fat necrosis: Pancreatic enzyme panniculitis
    8. Crystal deposits: Scleredema neonatorum, subcutaneous fat necrosis of the newborn, gout, oxalosis
    9. Embryonic fat pattern: Lipoatrophy, lipodystrophy
II. With prominent vasculitis (septal or lobular)
  A. Neutrophilic: Leukocytoclastic vasculitis, subcutaneous polyarteritis nodosa, thrombophlebitis, ENL
  B. Lymphocytic: Nodular vasculitis, perniosis, angiocentric lymphomas
  C. Granulomatous: Nodular vasculitis/erythema induratum, ENL, granulomatosis with polyangiitis, Churg-Strauss allergic granulomatosis
III. Mixed patterns

ENL, Erythema nodosum leprosum.

From Lee L, Werth V: The skin and rheumatic diseases: panniculitis, In Firestein G et al [eds]: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, Elsevier Saunders, p. 611.

BOX 1 Classification of the Panniculitides

Mostly septal panniculitis without vasculitis
- Erythema nodosum
- Vilanova disease: Subacute nodular migratory panniculitis

Mostly lobular panniculitis without vasculitis
- Idiopathic neutrophilic panniculitis
- Subcutaneous fat necrosis of the newborn
- Postcorticosteroid panniculitis
- Calcifying panniculitis
- Pancreatic panniculitis
- α_1-Antitrypsin deficiency
- Physical or factitial panniculitis
- Histiocytic cytophagic panniculitis
- Lipodystrophy syndromes
- Connective tissue panniculitis
- Subcutaneous panniculitis–like T-cell lymphoma
- Sclerosing panniculitis: Lipodermatosclerosis

Mixed panniculitis
- Lupus profundus: Lupus erythematosus panniculitis
- Erythema nodosum–like lesions of Behçet syndrome

Panniculitis with vasculitis
- Small-vessel vasculitis (postcapillary venule), also known as *leukocytoclastic vasculitis*
- Medium-sized-vessel vasculitis (arterioles or small arteries): Polyarteritis nodosa
- Erythema induratum, also known as *nodular vasculitis*

From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

for the involvement of the subcutaneous fat or to assess for the presence of vasculitis. Inflammation of the subcutaneous fat is a changing process, with varying histologic findings as well as physical characteristics of skin lesions based on the stage of evolution. Cellular infiltrates may not be confined to one location in the subcutaneous fat, and may overlap between septa and lobules (Fig. E2).

LABORATORY TESTS

Depending on the suspected underlying disorder, the following workup may be considered:
- Throat swab for rapid streptococcal screen, ASO titer, CBC, PPD, chest radiograph, tissue cultures, and histologic stains for organisms
- Amylase, lipase
- Serum alpha-1 antitrypsin level
- ESR, CRP
- Laboratory evaluation for possible connective tissue disease
- Further special studies of biopsy sample if malignancy is suspected

IMAGING STUDIES

- Chest radiography
- Ankle-brachial index for assessment of peripheral vascular disease
- Further imaging based on clinical suspicion (i.e., CT scan of abdomen for pancreatitis)

Rx TREATMENT

Treatment of panniculitis is toward treatment of the underlying etiology. Any suspected medications should be discontinued. Appropriate antibiotics to treat underlying infections should be prescribed.

NONPHARMACOLOGIC THERAPY

- Leg elevation, bed rest
- Support stockings

ACUTE GENERAL Rx

- Nonsteroidal antiinflammatory medications (NSAIDs)
- Oral corticosteroids

CHRONIC Rx

- Oral potassium iodide (300 to 900 mg per day)
- Oral corticosteroids
- Colchicine
- Hydroxychloroquine
- Immunosuppressive medications

REFERRAL

- Dermatology for biopsy of skin lesions
- Specific specialists based on underlying etiology

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Erythema Nodosum (Related Key Topic)

AUTHOR: **Joanne Szczygiel Cunha, MD**

SUGGESTED READINGS

Tomasini C: Panniculitides in rheumatoid syndromes: the role of histopathology, *Dermatopathology (Basel)* 5(1):10-13, 2018.

Wick M: Panniculitis: a summary, *Semin Diagn Pathol* 34(3):261-272, 2017.

Zundler S: Pancreatic panniculitis and polyarthritis, *Curr Rheumatol Rep* 19(10):62, 2017.

FIG. E1 Erythema nodosum secondary to acute sarcoidosis. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

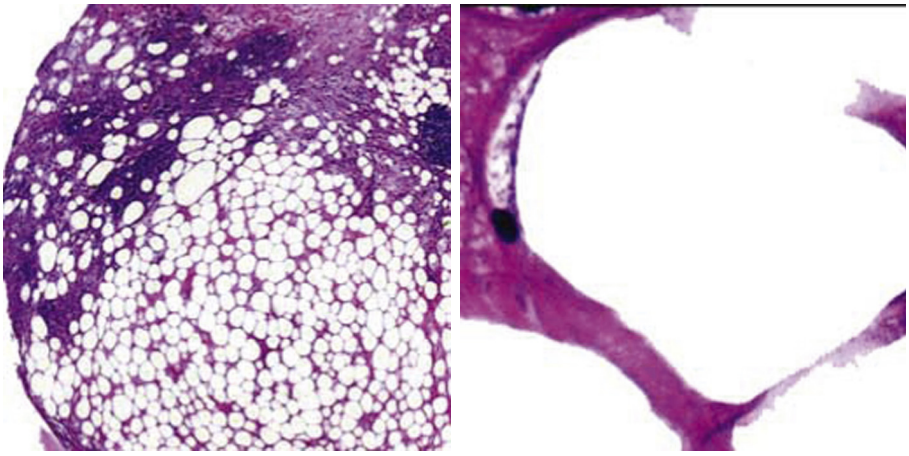

FIG. E2 Mixed lobular and septal panniculitis. (From Callen JP, Requena L: Cutaneous vasculitis and panniculitis, In Hochberg MC et al [eds]: *Rheumatology,* ed 6, Philadelphia, 2015, Elsevier Mosby, p 1350.)

BASIC INFORMATION

DEFINITION

Paralytic shellfish poisoning (PSP) is caused by the consumption of molluscan shellfish contaminated with a marine toxin produced by dinoflagellates (algae) that has a rapid onset of neurological symptoms and can be severe and even life-threatening.

SYNONYMS

Neurotoxic Shellfish Poisoning
PSP

ICD-10CM CODE
T61.78 Other shellfish poisoning

EPIDEMIOLOGY & DEMOGRAPHICS

- In the U.S., there are about 30 cases a yr reported.
- About 1 person dies every 4 yr from this toxic seafood poisoning.

INCIDENCE: Toxin-containing shellfish are generally found in the cold-water regions of the coast of northwestern and northeastern U.S., southern Chile, Japan and the North Sea.

PEAK INCIDENCE: PSP has been associated with algal blooms known as "red tides," but cases can occur even without red tides. Cases are more common in the summer as dinoflagellates grow better in warmer seasons.

RISK FACTORS: Shellfish including mussels; scallops; clams; and, at times, crustaceans (Dungeness crabs, shrimp, or lobsters), gastropod mollusks (e.g., whelk, moon snails or abalone), and fish that ingest zooplankton (Atlantic salmon, herring, mackerel). Most common are mussels or clams.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms usually occur within 30 minutes (few minutes to 4 hours) after exposure. Symptoms include:
  1. Tingling and numbness periorally spreading to neck and face
  2. Headache, nausea, vomiting, and diarrhea
  3. Ataxia, difficulty swallowing
  4. Weakness to paralysis and respiratory failure
- Death can occur within 2 to 12 hours of ingestion of contaminated seafood. Case fatality rate: 12%
- Neurotoxic symptoms improve after 12 hours and resolve completely within a few days

ETIOLOGY

- The illness is caused by marine toxins: Saxitoxin produced by algae, especially dinoflagellates and possibly other algae and bacteria. The toxin is not destroyed by heat or freezing, and the contaminated fish will smell and look normal.
- Saxitoxin blocks voltage-gated sodium channels in nerve and muscle cell membranes thus blocking nerve signal transmission.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ciguatera fish poisoning: Caused by ingesting tropical reef fish such as barracuda, grouper, sea bass, and snapper containing ciguatoxin, which is produced by dinoflagellates. Presents with a clinical picture of nausea/vomiting, diarrhea, cramps, muscle aches, itching, and dizziness.
- Pufferfish poisoning (tetrodotoxin): Pufferfish, porcupine, and sun fish may become highly poisonous at certain times of the yr. The toxin tetrodotoxin derives from Pseudomonas bacteria and is cardio- and neurotoxic and can cause death in 2 to 6 hours of ingestion by blocking voltage-gated sodium ion channels.
- Scombroid fish poisoning (histamine fish poisoning): Caused by improper fish storage and bacterial overgrowth that converts high levels of histidine in the fish flesh to histamine. Patients will present with rash and facial and upper body flushing, vomiting, burning, or metallic taste in the mouth.
- Botulism.

WORKUP

Should be considered when a history is elicited of consumption of a known seafood that can serve as a vector for PSP followed by onset of neurological symptoms including paralysis

LABORATORY TESTS

Assay for the detection of saxitoxin in urine of affected patients through health departments and assays on samples of food

TREATMENT

Supportive treatment including mechanical ventilation, may be necessary.

PEARLS & CONSIDERATIONS

COMMENTS

Saxitoxin is a potent neurotoxin three orders of magnitude more toxic than sodium cyanide

PREVENTION

Monitoring of shellfish beds by health departments and avoidance of shellfish that have been harvested from areas deemed contaminated

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Scombroid Poisoning (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READING

Warrell DA: Venomous bites, stings and poisoning: an update, *Infect Dis Clin N Am* 33:17-38, 2019.

BASIC INFORMATION

DEFINITION

Paraneoplastic syndromes are a large group of disorders caused by either an abnormal immune response to a malignancy or as a result of hormonal or other soluble factors produced by these malignancies. They often affect areas of the body away from the site of the original tumor or metastases, which is in contrast to syndromes that are direct complications of tumor invasion, compression, or metastasis (e.g., superior vena cava syndrome). Findings and symptoms are specific to each syndrome. Paraneoplastic syndromes affect multiple organ systems and remain a challenging diagnostic entity.

ICD-10CM CODES

E22.2	Syndrome of inappropriate secretion of antidiuretic hormone
E83.5	Disorders of calcium metabolism
G13.0	Paraneoplastic neuromyopathy and neuropathy
G13.1	Other systemic atrophy primarily affecting central nervous system in neoplastic disease
G73.1	Lambert-Eaton syndrome in neoplastic disease
G73.3	Myasthenic syndromes in other diseases classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

- Paraneoplastic syndromes may affect as many as 8% of cancer patients.
- See Table 1 for epidemiology of each syndrome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Hypercalcemia of malignancy:
- Nausea/vomiting
- Constipation
- Abdominal pain
- Anorexia
- Hypertension
- Fatigue
- Altered mental status (from confusion to coma)
- Depression/anxiety
- Polyuria
- Acute kidney injury
- Bone pain

Syndrome of inappropriate antidiuretic hormone (SIADH):
- Headache
- Weakness
- Anorexia
- Nausea, vomiting
- Memory impairment, irritability, restlessness, seizures
- Obtundation or coma may be seen with hyponatremia <125 mEq/L

Cushing syndrome:
- Muscle weakness
- Rapid weight gain
- Centripetal fat distribution, progressing to obesity; limbs are often spared or wasted
- Characteristic "moon facies" due to accumulation of fat deposition in the cheeks
- Skin atrophy, easy bruising, and purple abdominal striae due to skin fragility
- Hyperpigmentation, notably in sun-exposed areas
- Menstrual irregularity, mild hirsutism in women
- Hypertension
- Depression, anxiety, irritability

Paraneoplastic thrombocytosis:
- Thrombosis
- Nausea, vomiting
- Paresthesias, visual disturbances, head ache

Paraneoplastic erythrocytosis:
- Erythroderma
- Post-shower (aquagenic) pruritus
- Plethora

Paraneoplastic glomerulonephritis:
- Renal failure: Oliguric or anuric
- Malaise
- Nausea, vomiting

Paraneoplastic Neurological Syndromes: (Table 2 and Table 3)

Paraneoplastic cerebellar degeneration (PCD):
- May develop prodrome of dizziness, nausea, vomiting
- Ataxia
- Diplopia
- Dysphagia, dysarthria

Lambert-Eaton myasthenic syndrome (LEMS):
- Gradual onset of symmetric proximal muscle weakness and fatiguability; lower extremity involvement is more common
- Hyporeflexia
- Mild bulbar dysfunction, although respiratory failure can occur late in the disease process
- Dysautonomia, especially erectile dysfunction

Myasthenia gravis (MG):
- Ocular symptoms: Ptosis and diplopia
- Weakness of facial muscles, notably with fatigable chewing
- Weakness of neck extensor and flexor muscles; proximal and distal extremities may also be involved
- May progress to involve muscles of respiration and respiratory crisis

Opsoclonus myoclonus syndrome (OMS):
- Truncal ataxia and unsteady gait
- Involuntary and conjugate gaze rapid eye movements (opsoclonus)
- Muscle twitching (myoclonus)
- Other symptoms: Irritability, sleep disturbance, dysarthria or mutism

Limbic encephalitis (LE):
- Insidious mood or psychiatric changes; hallucinations
- Short-term memory loss
- Hyperthermia or somnolence if hypothalamic involvement
- Seizures occur in up to half of patients

Paraneoplastic dermatologic and rheumatologic syndromes:
- Acanthosis nigricans
- Dermatomyositis (DM)
- Necrolytic migratory erythema
- Hypertrophic osteoarthropathy

TABLE 1 Epidemiology of Each Paraneoplastic Syndrome

Condition	Prevalence	Risk Factors
Hypercalcemia of malignancy	Up to 20% of all cancer patients	Squamous cell cancers (lung, head, and neck), breast, kidney, bladder, and ovarian cancers, lymphoma
Syndrome of inappropriate antidiuretic hormone (SIADH)	Up to 2% of all cancer patients Found in 10%-45% of SCLC patients	SCLC
Cushing syndrome	Approximately 2% of all cancer patients (50% of these are SCLC)	SCLC Pituitary adenoma, benign and malignant adrenal tumors, carcinoid tumors
Limbic encephalitis (LE)	Less than 1%	SCLC Testicular germ cell tumor Breast cancer Ovarian teratoma
Paraneoplastic cerebellar degeneration	Less than 1%	SCLC Hodgkin lymphoma Breast cancer
Lambert-Eaton myasthenic syndrome (LEMS)	3% of SCLC patients	SCLC, prostate cancer, lymphoma
Paraneoplastic thrombocytosis	5%-20% of patients with solid tumors	Lung, colorectal, mesothelioma
Paraneoplastic erythrocytosis	4% of patients	Renal cell carcinoma, hepatocellular carcinoma
Paraneoplastic glomerulonephritis	2%-4% of patients	Hodgkin lymphoma, thymoma, prostate cancer
Myasthenia gravis (MG)	15% of thymoma patients	Thymoma
Opsoclonus myoclonus syndrome (OMS)	Less than 1%	SCLC, breast cancer, ovarian teratoma in adults; neuroblastoma in children

SCLC, Small cell lung cancer.

TABLE 2 Paraneoplastic Syndromes

Syndrome	Tumor	Associated Antibodies
Cerebellar degeneration	SCLC Gynecologic Breast Lymphoma Thymoma	Anti-Hu Anti-Yo Anti-Ri Anti-CV2 Anti-TR
Limbic encephalitis	SCLC Testes Breast Ovarian teratoma Thymoma	Anti-Hu Anti-Ma Anti-Amphiphysin Anti-NMDA receptor Anti-VGKC Anti-GAD
Lambert–Eaton myasthenic syndrome	SCLC	Anti-VGCC
Sensory neuronopathy	SCLC	Anti-Hu
Stiff-person syndrome	SCLC Breast Thymoma	Anti-GAD Anti-Amphiphysin
Opsoclonus-myoclonus	Neuroblastoma SCLC Gynecologic Breast	Anti-Ri
Dermatomyositis/ polymyositis	Ovary Pancreas Stomach Colorectal Non-Hodgkin lymphoma	Variety of antibodies have been associated, including anti-TIF1

GAD, Glutamic acid decarboxylase*; NMDA,* N-methyl-D-aspartate*; SCLC*, small cell lung cancer*; VGCC,* voltage-gated calcium channel*; VGKC,* voltage-gated potassium channel.
Adapted from Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists*, ed 8, Philadelphia, 2017, Elsevier.

TABLE 3 Paraneoplastic Syndromes of the Nervous System

Classical

Limbic encephalitis
Encephalomyelitis
Cerebellar degeneration
Opsoclonus-myoclonus
Sensory neuronopathy
Gastrointestinal pseudoobstruction/autonomic neuropathy
Lambert–Eaton myasthenic syndrome
Inflammatory myopathy

Nonclassical

Brainstem encephalitis
Stiff-person syndrome
Motor neuron disease
Necrotizing myelopathy
Optic neuropathy/retinopathy
Acute sensorimotor neuropathy
Chronic sensorimotor neuropathy
Myasthenia gravis

Autoimmune Encephalitides

NMDAR encephalitis
AMPAR encephalitis

AMPAR, Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; *NMDAR,* anti-*N*-methyl-D-aspartate receptor.
From Swaiman KF: *Swaiman's Pediatric Neurology, Principles and Practice*, ed 6, 2017, Elsevier.

- Leukocytoclastic vasculitis
- Paraneoplastic pemphigus (PNP)
- Polymyalgia rheumatica (PMR)
- Sweet syndrome (acute febrile neutrophilic dermatosis)
- Sign of Leser-Trélat (explosive onset of multiple seborrheic keratoses)

ETIOLOGY

Paraneoplastic endocrine syndromes (PES) are due to ectopic production of bioactive substances (e.g., hormones or peptides) that lead to metabolic derangements:

- **Hypercalcemia of malignancy:**
  1. *Humoral hypercalcemia of malignancy (HHM):* Due to production of parathyroid hormone-related peptide (PTHrP). Accounts for 80% of hypercalcemia of malignancy cases. Most common in lung (Table 4) and breast cancer (also seen in renal, bladder, and ovarian cancer).
  2. *Other etiologies of hypercalcemia of malignancy:* 1,25-dihydroxyvitamin D production from increased 1α-hydroxylase activity causes hypercalcemia in most Hodgkin and some non-Hodgkin lymphomas. Tumors can also produce ectopic parathyroid hormone (PTH).
  3. *Osteolytic activity:* 20% of hypercalcemia of malignancy cases. Tumor cells produce local factors that stimulate osteoclast activation, resulting in increased bone resorption.
- **SIADH:** Ectopic production of antidiuretic hormone (ADH) (arginine vasopressin, atrial natriuretic peptide) by tumor cells leads to inappropriately concentrated urine and natriuresis.
- **Cushing syndrome:** Ectopic ACTH promotes excess production of cortisol and other glucocorticoids from the adrenal glands, which do not respond to normal HPA feedback.
- **Paraneoplastic erythrocytosis**: Mediated by inappropriate production of erythropoietin (EPO) and is associated most commonly with renal cell carcinoma and hepatocellular carcinoma.
- **Paraneoplastic thrombocytosis**: Overproduction of inflammatory cytokines, especially IL-6, which induces thrombopoietin (TPO) mRNA expression and protein synthesis in the liver. Unlike secondary (reactive) thrombocytosis, TPO levels are not elevated.
- **Paraneoplastic glomerulonephritis**: Acute renal failure in the setting of newly diagnosed malignancy that is not explained by direct tumor involvement of the kidneys or genitourinary system. Diseases include minimal change disease, rapidly progressive glomerulonephritis, focal segmental glomerulonephritis, IgA nephropathy, and membranous nephropathy.
- **Paraneoplastic neurologic syndromes (PNS):** Due to immune cross-reactivity between tumor cells and components of the nervous system. Tumor-directed antibodies (onconeural antibodies) are produced by the patient in response to a developing cancer. These onconeural antibodies and associated onconeural antigen-specific T lymphocytes attack components of the nervous system because of antigenic similarity (molecular mimicry). Diagnostic criteria for paraneoplastic neurologic syndromes is summarized in Table 5.

TABLE 4 Hypercalcemia of Malignancy

Cancer	Frequency (%)	Mechanism
Lung	35	PTHrP Local osteolysis
Breast	25	PTHrP Local osteolysis
Head and neck	6	PTHrP
Renal	3	PTHrP Local osteolysis
Multiple myeloma	15	PTHrP (rare) Local osteolysis 1,25-Dihydroxyvitamin D
Prostate	7	Local osteolysis
Lymphoma	15	1,25-Dihydroxyvitamin D PTHrP

PTHrP, Parathyroid hormone-related protein.
From Skorecki K et al: *Brenner and Rector's the kidney*, ed 10, Philadelphia, 2016, Elsevier.

TABLE 5 Diagnostic Criteria for Paraneoplastic Neurologic Syndromes

Definite Paraneoplastic Neurologic Syndromes

- A classical syndrome and cancer that develops within 5 yr of the diagnosis of the neurologic disorder
- A nonclassical syndrome that resolves significantly after cancer treatment without concomitant immunotherapy provided that the syndrome is not susceptible to spontaneous remission
- A nonclassical syndrome with onconeural antibodies (well characterized or not) and cancer that develops within 5 yr of the diagnosis of the neurologic disorder
- A neurologic syndrome (classical or not) with well-characterized onconeural antibodies (anti-Hu, Yo, CV2, Ri, Ma2, or amphiphysin) and no cancer

Possible Paraneoplastic Neurologic Syndromes

- A classical syndrome, no onconeural antibodies, no cancer, but at high risk to have an underlying tumor
- A neurologic syndrome (classical or not) with partially characterized onconeural antibodies and no cancer
- A nonclassical syndrome, no onconeural antibodies, and cancer present within 2 yr of diagnosis

From Swaiman KF et al: *Swaiman's pediatric neurology: principles and practice*, ed 6, Philadelphia, 2017, Elsevier.

BOX 1 Evaluation and Diagnosis of Paraneoplastic Syndromes

- Characterize abnormality; obtain laboratory studies, imaging, and biopsy as necessary.
- Carefully elicit any additional symptoms and signs.
- Eliminate common causes.
- If there is no obvious etiology, consider a paraneoplastic syndrome.
- If signs and symptoms are consistent with a paraneoplastic syndrome, undertake a search for an unknown primary cancer or recurrence or progression of a known primary tumor.
- Screening should include a careful physical examination with breast, gynecologic, and prostate evaluations; basic hematology, chemistry, and urine studies; chest radiograph; and mammography.
- Computed tomography (CT) of the chest, abdomen and pelvis, or positron emission tomography/CT is indicated if there are any suspicious symptoms, signs, or laboratory abnormalities. Antibody testing for paraneoplastic neurologic syndromes and/or skin biopsy should be performed as indicated.
- Consider treatment of cancer and/or appropriate palliative treatment, including immunosuppressive therapy for paraneoplastic symptoms when possible.

- **LE, PCD, LEMS, MG, OMS:** Cross-reactive autoantibodies against various components of the central and peripheral nervous system.

DX DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- **Hypercalcemia of malignancy:** Primary hyperparathyroidism, familial hypocalciuric hypercalcemia, excess calcium intake, vitamin D toxicity, chronic granulomatous disorders, thiazide diuretics. It is important to differentiate between HHM and osteolytic causes of malignancy-associated hypercalcemia because prognosis and response to treatment differ
- **SIADH:** Hypovolemic hyponatremia, volume overload, reset osmostat, adrenal insufficiency, hypothyroidism, psychogenic polydipsia
- **Cushing syndrome:** Excess glucocorticoid administration, pituitary adenoma, benign or malignant adrenal tumors
- **Paraneoplastic thrombocytosis**: Reactive thrombocytosis from iron deficiency anemia, infection, inflammation, essential thrombocythemia
- **Paraneoplastic erythrocytosis**: Polycythemia vera, secondary polycythemia from smoking, high-affinity hemoglobinopathies, or chronic hypoxia (e.g., obstructive sleep apnea)
- **Paraneoplastic glomerulonephritis**: Renal failure from intrinsic injury from nephrotoxic agents (e.g., chemotherapy), postrenal failure from bladder obstruction, or rarely direct metastatic invasion from a primary tumor
- **LE, PCD, LEMS, MG, OMS:** Multiple sclerosis, stroke, meningitis, encephalitis, neurodegenerative diseases, myelitis, mixed connective tissue disease

WORKUP

- History and physical examination. Box 1 summarizes the evaluation and diagnosis of paraneoplastic syndromes.
- Age-appropriate cancer screening
- Chest-abdomen-pelvis CT
- Paraneoplastic neurologic syndromes: Lumbar puncture, PET, EEG, EMG

LABORATORY TESTS

Hypercalcemia of malignancy

- Serum calcium and albumin levels to measure corrected calcium (HHM more common when serum Ca^{2+} >13 mg/dl)
- Ionized serum calcium
- PTH (low to normal)
- PTHrP (elevated)
- $1,25(OH)_2D$ levels (if the above values are inconclusive)

SIADH

- Serum (corrected for glucose) and urine sodium (serum sodium <135 mEq/L or urine sodium >40 mEq/L)
- Serum and urine osmolality (serum osm <280 mOsm/kg of water and/or urine osm >100 mOsm/kg of water)

Cushing syndrome

- Initial testing: Low-dose dexamethasone suppression test, late-night salivary cortisol, 24-hour urinary free cortisol excretion.
- Once diagnosis is confirmed: High-dose dexamethasone suppression tests can help to distinguish Cushing syndrome (pituitary hypersecretion of ACTH) from patients with ectopic ACTH production.
- Potassium and glucose should be monitored closely due to increased risk of hypokalemia and hyperglycemia.

LE: Anti-Hu, Anti-Ma2, Anti-CRMP5, Anti-LGI1, Anti-AMPAR, Anti-mGluR5, CSF analysis, Anti-NMDAR, Anti-GABA-AR, Anti-GABA-BR

PCD: Anti-Yo, Anti-Tr Anti-Hu, Anti-Ma, Anti-Ri, Anti-CV2, Anti-VGCC, Anti-mGluR1, CSF analysis

LEMS: Anti-VGCC (P/Q), CSF analysis

MG: Anti-AChR, Anti-MuSK, CSF analysis

Paraneoplastic thrombocytosis: CBC, liver panel, iron panel, *JAK2* mutation, *CALR* mutation, *MPL* mutation

Paraneoplastic erythrocytosis: CBC, EPO level, *JAK2* mutation, peripheral blood smear

Paraneoplastic glomerulonephritis: BMP, urinalysis, urine protein to creatinine ratio, 24-hour urine protein collection, urine sediment analysis

IMAGING STUDIES

- **Hypercalcemia of malignancy:** CT imaging to evaluate for breast lesion, lung mass, or lymphadenopathy
- **SIADH:** CT imaging to evaluate for brain or lung mass
- **Cushing syndrome:** CT scan, MRI, or octreotide scan
- **LE, PCD, LEMS, MG:** CT chest, FDG-PET scan, MRI
- **Paraneoplastic erythrocytosis**: CT renal mass protocol or renal ultrasound to evaluate for renal cell carcinoma

RX TREATMENT

NONPHARMACOLOGIC THERAPY

Hypercalcemia of malignancy

- Treatment of underlying malignancy, either surgical resection or chemotherapy/radiation of identified tumors
- Fluid resuscitation, typically with initial 1 L bolus of isotonic saline followed by 200 to 300 ml/hr to achieve euvolemia, followed by maintenance hydration

SIADH

- Surgical resection of identified tumors
- Fluid restriction

- Maintain adequate dietary protein and salt intake

Cushing syndrome: Surgical resection of identified tumors

LE, PCD, LEMS, MG

- IVIG
- Plasma exchange

ACUTE GENERAL Rx

Hypercalcemia of malignancy

- Aggressive fluid hydration with normal saline (0.9%) to promote renal calcium excretion
- Bisphosphonates, either pamidronate or zoledronic acid intravenous infusions (treatment side effects are renal dysfunction and osteonecrosis of the jaw)
- Calcitonin weight-based dosing, although tachyphylaxis occurs after 48 hours of administration
- Loop diuretics if concurrent heart failure or renal failure
- Corticosteroids in cases of myeloma and lymphoma
- Hemodialysis in severe cases

SIADH

- If patient develops seizure or obtundation in cases of severe hyponatremia, then sodium replacement with hypertonic saline (3%) is indicated
- Sodium should not be corrected at a rate faster than 8 mEq/L in any 24-hour period to decrease chances of osmotic demyelination syndrome. Desmopressin, free water, and/or nephrology consultation may be required for an overly rapid correction.

Cushing syndrome

- Diuretics and antihypertensive agents for blood pressure and volume status management

CHRONIC Rx

- Chronic treatment is centered on treatment of the underlying malignancy
- **Hypercalcemia of malignancy**
  1. Bisphosphonate therapy every 4 wk in cases of bone metastasis
  2. Chronic calcitonin use can be considered
  3. Denosumab, a monoclonal antibody that inhibits osteoclastic bone resorption by blocking RANKL from binding to osteoclastic RANK receptors, can be used in patients refractory to bisphosphonate therapy
- **SIADH**
  1. Demeclocycline and vasopressin receptor antagonists (vaptans: Conivaptan and tolvaptan, although tolvaptan should not be used for longer than 30 days and should be avoided in patients with liver disease)
  2. Cessation of any possible causative medications
  3. Oral salt tablets if dietary salt intake insufficient
- **Cushing syndrome:** If surgery contraindicated, consider inhibition of adrenal enzymes with ketoconazole, mitotane, metyrapone
- **LE/PCD:** Glucocorticoids, cyclophosphamide, rituximab
- **LEMS:** Pyridostigmine, azathioprine, glucocorticoids
- **MG:** Pyridostigmine, azathioprine, cyclosporine, mycophenolate, rituximab
- **Paraneoplastic thrombocytosis**: Consider prophylactic low-molecular-weight heparin or aspirin if no contraindications exist, siltuximab (antibody against IL-6)

DISPOSITION

Specific to each condition; however, humoral hypercalcemia of malignancy carries a poor overall prognosis with 30-day mortality of 50%.

REFERRAL

Oncology, endocrinology, neurology, nephrology

PEARLS & CONSIDERATIONS

COMMENTS

- Signs or symptoms of a paraneoplastic syndrome may manifest prior to the identification of a malignancy.
- If paraneoplastic syndrome is suspected, a thorough workup for a tumor is indicated.
- With treatment of the primary tumor, the clinical effects of hypercalcemia of malignancy, SIADH, and Cushing syndrome may improve or resolve.
- Neurologic paraneoplastic syndromes can have long-term effects due to permanent CNS or PNS damage. Tumor detection can also be difficult as these immune-mediated syndromes may also be keeping the tumor in check.
- New neurologic deficits after starting a checkpoint inhibitor (e.g., PD-1 inhibitor) may indicate drug-induced autoimmunity rather than a paraneoplastic syndrome.

PREVENTION

- Smoking cessation
- Age-appropriate cancer screening

PATIENT & FAMILY EDUCATION

In conditions with autoimmune etiology (LE, PCD, LEMS, MG, OMS), symptoms may not improve even if the tumor is identified and treated, as damage to the nervous system may be sustained or permanent.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Hetal D. Mistry, MD,** and **John L. Reagan, MD**

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Paranoid Personality Disorder (PTG)

BASIC INFORMATION

DEFINITION

Paranoid personality disorder (PPD) is characterized by a pattern of pervasive distrust and suspiciousness that leads the person to assign malevolence to the motives of others. PPD begins by early adulthood and causes significant distress or impairment in multiple domains of functioning. Individuals must meet four or more of the following criteria, each of which should be enduring and inflexible across contexts:

- Suspect, without justification, that others are exploiting, harming, or deceiving them.
- Preoccupied with unwarranted doubts about the loyalty or trustworthiness of friends or associates.
- Reluctant to confide in others because of unjustified fear that the information will be used against them in a malicious fashion.
- Infer demeaning or threatening statements from benign remarks or events.
- Bear grudges for extended periods. For example, PPD patients are unforgiving of perceived or real insults and slights.
- Perceive attacks on their character that are not apparent to others. Quick to react angrily or to counterattack.
- Recurrent suspicions, without justification, regarding fidelity of spouse or partner.

SYNONYM

PPD

ICD-10CM CODE
F60.0 Paranoid personality disorder
DSM-5 CODE
301.0 Paranoid personality disorder

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Epidemiologic studies report a prevalence of 2.3% to 4.4% in the general U.S. population.
PREDOMINANT SEX: More commonly diagnosed in males in clinical samples.
GENETICS: Increased prevalence of PPD in relatives of patients with schizophrenia and delusional disorder, paranoid type.

CLINICAL PRESENTATION

- These patients are highly suspicious and hypervigilant to interpersonal threats.
- They may present as cold, guarded, and resistant, as if the clinical interviewer were inappropriately prying.
- Alternatively, they may be oppositional and argumentative, defending against perceived attacks, and they may threaten litigation.
- They may be rigid and controlling in relationships, constantly questioning and criticizing the behavior and motives of others, including romantic partners (pathologic jealousy).
- Because they do not easily trust in other people, patients with PPD seek to be self-sufficient and autonomous, and therefore any vulnerability (such as medical illness) can feel dangerous to them.
- In response to stress, they may experience very brief psychotic episodes (minutes to hours). However, they do not have persistent, bizarre delusions.

ETIOLOGY

- Genetic influence is suggested by increased prevalence of PPD in families with schizophrenia and delusional disorder, paranoid type.
- Childhood maltreatment, bullying, and trauma are associated with the development of paranoid traits.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Schizophrenia or delusional disorder, paranoid type, each of which requires the presence of persistent positive psychotic symptoms such as delusions or hallucinations
- Substance-induced paranoia, especially in the context of cocaine, PCP, or methamphetamine use disorder
- Personality changes caused by a general medical condition that affects the central nervous system
- Paranoid traits associated with a sensory disability (e.g., hearing impairment)
- Other personality disorders:
  1. Schizotypal personality disorder includes magical thinking and unusual perceptual experiences.
  2. Schizoid and borderline personality disorders do not have prominent paranoid ideation.
  3. Avoidant personality disorder includes fear of embarrassment.
  4. Narcissistic personality disorder includes the fear that hidden "flaws" or "inferiority" may be revealed.
- Common comorbid disorders include major depressive disorder, obsessive-compulsive disorder, agoraphobia, and substance use disorders
- The most common co-occurring personality disorders are schizotypal, schizoid, narcissistic, avoidant, and borderline
- Consider whether the behaviors and attitudes are not pathologic but instead adaptive responses to a particular sociocultural context, such as chronic stress due to minority or immigrant status that results in a cycle of anger and mistrust. For a diagnosis of PPD, the traits should be inflexible, maladaptive, and persistent

WORKUP

- History: Collateral information is essential to establishing the presence of longstanding interpersonal pattern in multiple domains of the patient's life.
- Physical examination
- Mental status examination

LABORATORY TESTS

Those necessary to rule out medical causes of personality changes

IMAGING STUDIES

Those necessary to rule out medical causes of personality changes

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral therapy to help patients control rage, manage perceived criticism, and develop social skills
- Psychodynamic psychotherapy to help patient develop capacity to trust and improve interpersonal functioning.
- Guidelines for general management of the patient with PPD:
  1. Convey your intent to "do no harm."
  2. Address the patient's fears and concerns, no matter how irrational, in a clear, direct, and detailed manner.
  3. Remember that behind the patient's hostility lies fears that are real to him or her.
  4. Maintain a professional and neutral stance.
  5. Avoid responding with too much warmth and friendliness, which can intensify paranoia.
  6. Give the patient detailed and factual information about the treatment plan.
  7. Give the patient as much control as possible over the treatment plan.
  8. Do not take the patient's hostility or suspicion personally, but understand it as an attempt to manage intense fear.
  9. Validate the patient's concerns about the diagnosis or treatment plan.

ACUTE GENERAL Rx

Benzodiazepines or low-dose antipsychotics to control hostility and paranoia

CHRONIC Rx

- Low-dose antipsychotic medication may have small benefit in treating suspiciousness. Increase dose in small increments to minimize risk of side effects.
- Treat comorbid symptoms, such as by using selective serotonin inhibitors for depression or agoraphobia.

COMPLEMENTARY & ALTERNATIVE MEDICINE

No evidence of efficacy in PPD.

DISPOSITION

- Severity is variable and course is chronic. Often patients have lifelong difficulty maintaining intimate relationships.
- In some cases, PPD is an antecedent of delusional disorder, paranoid type.

REFERRAL

- For pharmacotherapy or psychotherapy, if acceptable to patient

- If patient has acute worsening of functioning due to a stressor

PEARLS & CONSIDERATIONS

COMMENTS

- Medical illness exacerbates these patients' sense of vulnerability, which increases their fear and therefore their oppositional behaviors.
- Communicating personal information to the physician challenges the guarded, self-protective approach to others and will often heighten PPD patients' fear that the physician will harm them.
- The encounter with the physician intensifies hypervigilance. As a result, innocuous or even overtly helpful behaviors by the physician may be perceived as manipulating or threatening.
- With the perceived threat, these patients will often confront and challenge the physician on their motives and their rationale for diagnosis and treatment. Conflict and argument are common.
- Thus, establishing an alliance with the patient can be challenging.
- Faced with such a patient, physicians may understandably react defensively to unfounded suspicion or distance and not respond to the patient's concerns. Both responses increase the patient's anxiety and paranoia.

RELATED CONTENT

Paranoid Personality Disorder (Patient Information)

AUTHORS: **Timothy R. Kreider, MD, PhD,** and **John Q. Young, MD, MPP, PhD**

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Paraphilic Disorders

BASIC INFORMATION

DEFINITION

It is important to distinguish between paraphilia and paraphilic disorders.

- The term *paraphilia* applies to sexual arousal that is repeatedly and intensely stimulated by thoughts and/or behavior elicited by stimuli other than that which is associated with consensual mature human partners. For example, sexual arousal that is repeatedly and intensely stimulated by **activity** such as rubbing up against an unsuspecting person or by a **target preference** such as shoes or diapers would be identified as paraphilia.
- To meet the DSM-5 criteria for a **paraphilic disorder,** there must be the presence of a paraphilia over at least a 6-mo period that is causing distress or impairment to an individual or harm or risk of harm to others. In addition, the intensity of the paraphilia sexual arousal must equal or exceed the intensity of an individual's normophiliac sexual arousal.
- Paraphilia that does not meet DSM-5 criteria is not considered a mental illness, but individuals with paraphilic thoughts and behavior may still present for treatment.
- It is not unusual for a person to express more than one paraphilic interest. Recent research has also identified the "wish to experience" and the "actual occurrence" of at least one lifetime paraphiliac act to be common in both men and women.

SYNONYMS

Atypical sexual behavior
Hypersexuality
Sexual impulsivity disorder

ICD-10CM CODES

F65	Paraphilias
F65.0	Fetishism
F65.1	Transvestic fetishism
F65.2	Exhibitionism
F65.3	Voyeurism
F65.4	Pedophilia
F65.5	Sadomasochism
F65.50	Unspecified
F65.51	Sexual masochism
F65.52	Sexual sadism
F65.8	Other paraphilias
F65.81	Frotteurism
F65.89	Other paraphilias
F65.9	Paraphilia, unspecified

DSM-5 CODE

Depends on specific diagnosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown due to: (1) the secretive nature of the behavior; (2) changes in criterion over time; and (3) differences between cultural definitions of abnormality. It is estimated, however, that only about 1% to 2% of men presenting with paraphilia behavior are distressed by their behavior and meet the criteria of paraphilic disorder.

PEAK INCIDENCE: Although prepubescent individuals can be diagnosed with a paraphilic disorder, diagnosis is usually made postpubescence during late adolescence and early adulthood.

PREVALENCE: Prevalence rates for paraphilia and paraphilic disorders are extremely difficult to report with any certainty. While the seemingly unlimited variety of sexually arousing material available on the Internet suggests a wide range of potentially sexually arousing stimulation that human males and females may be interested in, there are no data to accurately describe whether or not such interests are reflective of paraphilia prevalence rates.

PREDOMINANT SEX AND AGE:

- Males are at a much higher risk than females to experience paraphilias and paraphilic disorders. Although lacking in convincing research, studies estimate the male-to-female ratio to be 20:1 or greater.
- Paraphilia behavior can begin in early childhood but is manifested most commonly in late adolescence and early adulthood and may be expressed throughout the life cycle. Paraphilia behavior and paraphilic disorders tend to become less intense and less frequent in older age.

GENETICS: Although the literature points to some possible genetic influences on sexual interest in males and females, it is inconclusive that any genetic influences exist regarding the development of paraphilias or paraphilic disorders.

RISK FACTORS: Possible risk factors associated with paraphilia and paraphilic disorders include:

- Male gender
- Low self-esteem in childhood and adolescence
- Perceived lack of availability of consensual sexual partners
- Inhibition of normative sexual outlets often related to extreme religiosity or negative sexual messages from parents or caretakers
- Early exposure to paraphilia stimulation and opportunity for repeated exposure

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usually diagnosed in late adolescence or early adulthood
- May be diagnosed in males as erectile dysfunction or delayed ejaculation during consensual sexual relations when paraphilic stimuli are absent
- May be identified as a result of illegal offenses in some cases such as pedophilia, voyeurism, exhibitionism, or stealing of clothing
- Paraphilic behavior may be so time consuming or obsessive compulsive that it interferes with work, education, relationships, and/or productivity
- Certain paraphilic behaviors may put an individual at risk for disease and/or physical harm (self-inflicted or from others)

ETIOLOGY

There are no conclusive theories that satisfactorily explain the etiology of paraphilias and paraphilic disorders. It is quite possible, however, that the combination of biologic vulnerability and a conditioned learning process lead to paraphilic interests. Males are more at risk for developing paraphilic behavior, perhaps because males are more easily aroused sexually and are more aware of their arousal because of their erectile response. A repeated association of an erection response with certain visual, auditory, olfactory, imagined, or tactile stimuli may condition paraphilia behavior.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Medical: Dementia, substance intoxication, seizures, dissociative fugue state, frontal parietal traumatic brain injury, sexsomnia
- Psychiatric: Manic episode, schizophrenia, dissociative disorder, posttraumatic stress disorder, erotomania delusion, nonparaphilic hypersexuality disorder (i.e., compulsive masturbation, protracted promiscuity, cybersex dependence, pornography dependence), obsessive compulsive disorder, adjustment disorder, impulse control disorder

WORKUP

- A very detailed psychosexual developmental history is necessary and must include a review of sexual experiences with others as well as fantasies and stimuli that accompany masturbation. Paraphilic interests are typically first manifested in childhood or adolescence and persist to a greater or lesser degree throughout life. Such interests are often essential for sexual arousal and must be intense and persistent to meet DSM-5 criteria.
- A detailed psychiatric assessment is necessary to make a differential diagnosis and to identify common comorbid conditions that often accompany paraphilic interests such as low self-esteem and deficits in social skills.
- A physical examination should be performed in cases in which possible physical injury may have resulted from paraphilic behavior such as in cases of masochism or unusual genital, breast, or anal stimulation.
- Information from sexual partners (if available) is helpful for diagnosis and treatment.
- Information regarding the impact of paraphilic behavior on relationships, finances, work productivity, and legal problems is necessary to determine the diagnosis of paraphilic disorder.

TREATMENT

Pharmacologic agents may be used to suppress sexual fantasies, sexual desire, sexual urges, and obsessive compulsive behavior associated with paraphilia. Pharmacologic therapy is used as an adjunct therapy to psychotherapy and not a monotherapy.

PHARMACOLOGIC THERAPY

- Long-acting gonadotropin-releasing hormones (used for dangerous sex offenders where there is a risk of harm to self or others):
  1. Triptorelin (Trelstar)
  2. Leuprolide (Lupron)

3. Goserelin (Zoladex)

- Antiandrogens: (used for dangerous sex offenders where there is a risk of harm to self or others):
  1. Medroxyprogesterone acetate (Depo-Provera)
  2. Spironolactone (Aldactone)
- Selective serotonin reuptake inhibitors (SSRIs): (used for treatment of less serious paraphilia behavior that has obsessive compulsive features)
  1. Fluvoxamine (Luvox)
  2. Fluoxetine (Prozac)

NONPHARMACOLOGIC THERAPY

Individually tailored therapy that addresses patient needs and comorbid mental health problems combined with a strong alliance with the therapist are important ingredients for successful treatment outcome with paraphilia and paraphilic disorders. Common psychotherapeutic interventions include the following:

- Cognitive behavior therapy
- Social skills training
- Relapse prevention

ACUTE GENERAL Rx

Acute therapy begins with a comprehensive assessment of the intensity, frequency, duration, and topography of the paraphilia and assessment of comorbid mental health problems. Paraphilic disorders will be determined by the distress level and risk of harm to self and to others. If it is determined that there is a risk of harm, then therapy should begin with a consideration of pharmacotherapy in conjunction with psychotherapy.

Psychotherapy involves building an alliance with the patient to increase motivation and encourage full disclosure of all aspects of the paraphilia thoughts and behaviors. Individual therapy tailored for each patient's needs and mental health issues is most effective. Punishment or shaming of a patient only serves to inhibit therapeutic progress and goals.

Therapy typically includes techniques and strategies to suppress and manage paraphilia thoughts and behaviors along with strategies to increase positive social skills, constructive use of time, challenging distortions in thinking, and managing comorbid mental health problems.

CHRONIC Rx

It is unlikely that paraphilia thoughts and desires will remit completely and, therefore, strategies for long-term management should be implemented. In cases of paraphilic disorders, lifetime management involves awareness of all personal risk factors for relapse, plans for managing risks of relapse, building positive support systems, building constructive competing behaviors that interfere with opportunities for expressing and acting on paraphilic behavior and commitment to long-term therapy.

Full remission of a paraphilic disorder is established if there is a 5-yr period without stress or impairment or harm to self or others related to paraphilic behavior.

REFERRAL

- Diagnosis complicated by untreated or poorly managed comorbid psychiatric conditions or active substance abuse.
- Consultation for individuals presenting with autism spectrum disorder, intellectual disability, or other cognitive impairments should be considered.

PEARLS & CONSIDERATIONS

- Since there is often a great deal of shame associated with paraphilic disorders, health care professionals must be especially sensitive, nonjudgmental, and supportive of patients presenting with problems in this area.
- Treatment of paraphilic disorders should focus on how the paraphilic behavior is impacting relationships, productivity, employment, education, and finances.
- If a significant other is available, he or she should be included in the assessment process in order to add to a comprehensive understanding of the problem and in order to correct any misunderstandings.

AUTHOR: **John P. Wincze, PhD**

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BASIC INFORMATION

DEFINITION

Idiopathic Parkinson disease (PD) is a progressive neurodegenerative disorder characterized clinically by rigidity, tremor, postural instability, and slowness of movement (bradykinesia).

SYNONYMS

PD
Paralysis agitans

ICD-10CM CODES

G20	Parkinson disease
G21.1	Other drug-induced secondary parkinsonism
G21.11	Neuroleptic induced parkinsonism
G21.2	Secondary parkinsonism due to other external agents
G21.3	Postencephalitic parkinsonism
G21.4	Vascular parkinsonism
G21.8	Other secondary parkinsonism
G21.9	Secondary parkinsonism, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- It is the second most common neurodegenerative disease worldwide and is found in every country.
- Affects more than 1 million people in North America at 0.3% of the population and 1% of people over the age of 60. Prevalence increases with age.
- In those aged >70 yr, 700/100,000 are affected.
- Lifetime risk of Parkinson disease is 2% in men and 1.3% in women.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Tremor (Fig. E1)—typically a resting tremor with a frequency of 4 to 6 Hz that is often first noted in the hand as a pill-rolling tremor (thumb and forefinger). Can also involve the leg and lip. Tremor improves with purposeful movement. Usually starts asymmetrically.
- Rigidity—increased muscle tone that persists throughout the range of passive movement of a joint. Rigidity, like resting tremor, is usually asymmetric at onset.
- Akinesia/bradykinesia—slowness in initiating movement and decrement with repeated movements.
- Postural instability—tested by "pull test." Ask patient to stand in place with back to examiner. Examiner pulls patient back by the shoulders, and proper response would be to take no steps back or very few steps back without falling. Retropulsion is a positive test, as is falling straight back. Postural instability is not usually severe early on. If falls and postural reflexes are greatly impaired early on, then consider other disorders, such as progressive supranuclear palsy.
- Masked facies (hypomimia)—face seems expressionless, giving the appearance of depression. Decreased blink; often there is excess drooling.
- Gait disturbance.
- Stooped posture, decreased arm swing.
- Difficulty initiating the first step; small shuffling steps that increase in speed (festinating gait). Steps become progressively faster and shorter while the trunk inclines further forward.
- Other complaints and findings early on include handwriting becoming smaller (micrographia), and voice becoming softer and often "gruffer" (hypophonia).
- Nonmotor symptoms in Parkinson disease include neuropsychiatric (depression, apathy, impulse control disorders, hallucinations), cognitive, dysautonomia (especially orthostatic hypotension, sexual dysfunction, and anosmia), and sensory abnormalities. These symptoms also may be subject to fluctuations during "on" versus "off" states.
- Common premotor symptoms of Parkinson disease include constipation, anosmia, depression, and REM sleep behavior disorder.

ETIOLOGY

- Most cases are sporadic. Age is the most common risk factor, although a combination of both environmental and genetic factors likely contributes to disease expression.
- Approximately 5% to 10% have a genetic etiology. Several different genes have been identified; these include the parkin gene, a significant cause of early-onset autosomal recessive PD, and *LRRK2*, the most common cause of familial and sporadic parkinsonism.

DIAGNOSIS

- A clinical diagnosis can be made based on a comprehensive history and physical examination. The four cardinal signs used to diagnose PD are (mnemonic = TRAP):
  1. **T**remor (resting, typically 4-6 Hz)
  2. **R**igidity, of the cogwheel type
  3. **A**kinesia/bradykinesia—slowing and decrement of movement
  4. **P**ostural instability—failure of postural "righting" reflexes leading to poor balance and falls
- Bradykinesia plus at least one other sign are necessary, but all four cardinal signs do not need to be present to make a presumptive diagnosis of PD and begin treatment.

DIFFERENTIAL DIAGNOSIS

- Multiple system atrophy—distinguishing features include early autonomic dysfunction (including urinary incontinence, orthostatic hypotension, and erectile dysfunction), parkinsonism, cerebellar signs, and normal cognition
- Dementia with Lewy bodies—parkinsonism with concomitant dementia: Patients often have early hallucinations and fluctuations in level of alertness and mental status
- Corticobasal syndrome—often begins asymmetrically with apraxia, cortical sensory loss in one limb, and sometimes, alien limb phenomenon
- Progressive supranuclear palsy—tends to have axial rigidity greater than appendicular (limb) rigidity. These patients have early and severe postural instability. Hallmark is supranuclear gaze palsy that usually involves vertical gaze (especially downward) before horizontal
- Essential tremor—bilateral postural and action tremor
- Secondary (acquired) parkinsonism (Box 1):
  1. Iatrogenic—any of the neuroleptics and antipsychotics. The high-potency D_2-blocker neuroleptics are most likely to cause parkinsonism. Quetiapine is an atypical antipsychotic with lower risk of parkinsonism. Metoclopramide can also cause parkinsonism. Abuse of methamphetamine has been recently linked to risk of PD
  2. Postinfectious parkinsonism—von Economo encephalitis
  3. Dementia pugilistica—parkinsonism and dementia after repeated head trauma
  4. Toxins (e.g., MPTP, manganese, carbon monoxide)
  5. Cerebrovascular disease "vascular parkinsonism" (basal ganglia infarcts); often lower limbs (especially gait) affected more than upper extremities

WORKUP

- Identification of clinical signs and symptoms associated with PD (see "Physical Findings"), and elimination of conditions that may mimic it with a comprehensive history and physical examination.
- Routine genetic testing is not recommended.

IMAGING STUDIES

Computed tomographic (CT) scan has almost no role in investigations. Magnetic resonance imaging (MRI) of the head may sometimes distinguish between idiopathic PD and other conditions that present with signs of parkinsonism (see "Differential Diagnosis").

Dopamine transporter imaging (DaTscan with [^{123}I]β-CIT SPECT) evaluates the level of dopamine in the striatum and can be used to confirm parkinsonism in atypical cases. DaTscan is approved to distinguish essential tremor from parkinsonism but cannot distinguish between different causes of parkinsonism. Interpretation can be tricky, and routine use is not recommended at this time.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical therapy, patient education and reassurance, treatment of associated conditions (e.g., depression) are important. A safe, practical, and reasonable exercise regimen must be encouraged.
- Avoidance of drugs that can induce or worsen parkinsonism: neuroleptics (especially high potency), certain antiemetics (prochlorperazine, trimethobenzamide), metoclopramide, nonselective MAO inhibitors (may induce hypertensive crisis), reserpine, methyldopa.

BOX 1 Causes of Parkinsonism

Primary Parkinsonism
- Parkinson disease (idiopathic/sporadic parkinsonism)

Secondary Parkinsonism
- Drug-induced parkinsonism
  - Neuroleptic drugs
  - Calcium blocker cinnarizine
- Vascular parkinsonism (pseudoparkinsonism)
  - Multi-infarct states
  - Single basal ganglia/thalamic infarct
  - Binswanger disease
- Multisystem degenerative diseases
  - Progressive supranuclear palsy
  - Multiple system atrophy (striatonigral type)
  - Corticobasal degeneration
  - Alzheimer disease
  - Wilson disease (young-onset parkinsonism)
  - Dementia with Lewy bodies
  - Neurofibrillary tangle parkinsonism
- Toxins
  - MPTP
  - Manganese
- Familial parkinsonism
- Postinfectious parkinsonism
  - Creutzfeldt-Jakob disease
  - AIDS
  - Postencephalitis (encephalitis lethargica)
- Miscellaneous causes
  - Hydrocephalus
  - Posttraumatic
  - Tumors
- Metabolic causes (postanoxic)

AIDS, Acquired immunodeficiency syndrome; *MPTP,* 1-methyl-4-phenyl-1,2,2,6-tetrahydropyridine.
From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

ACUTE GENERAL Rx

- There continues to be controversy whether levodopa or dopamine agonists should be the initial treatment. In younger patients, agonists may be favored; in patients >65 yr, levodopa is typically the preferred initial therapy.
- It is appropriate to initiate pharmacotherapy when required by symptoms; prior practice of waiting for limitation of ADLs is now outdated. Fig. 2 describes an approach to patients with parkinsonism.
- Motor complications do develop during the course of the disease and likely reflect the combination of disease progression together with the side effects of dopaminergic medications.

CHRONIC Rx

- Levodopa therapy:
  1. The most efficacious treatment and cornerstone of symptomatic therapy—should be used with a peripheral dopa decarboxylase inhibitor (carbidopa) to minimize side effects (nausea, lightheadedness, postural hypotension). The combination of the two drugs is marketed under the trade name Sinemet. Levodopa therapy has been found to reduce morbidity and mortality in PD patients.
  2. Usual starting dose is 25/100 mg (carbidopa/levodopa) tid 1 hr before (or after) meals.

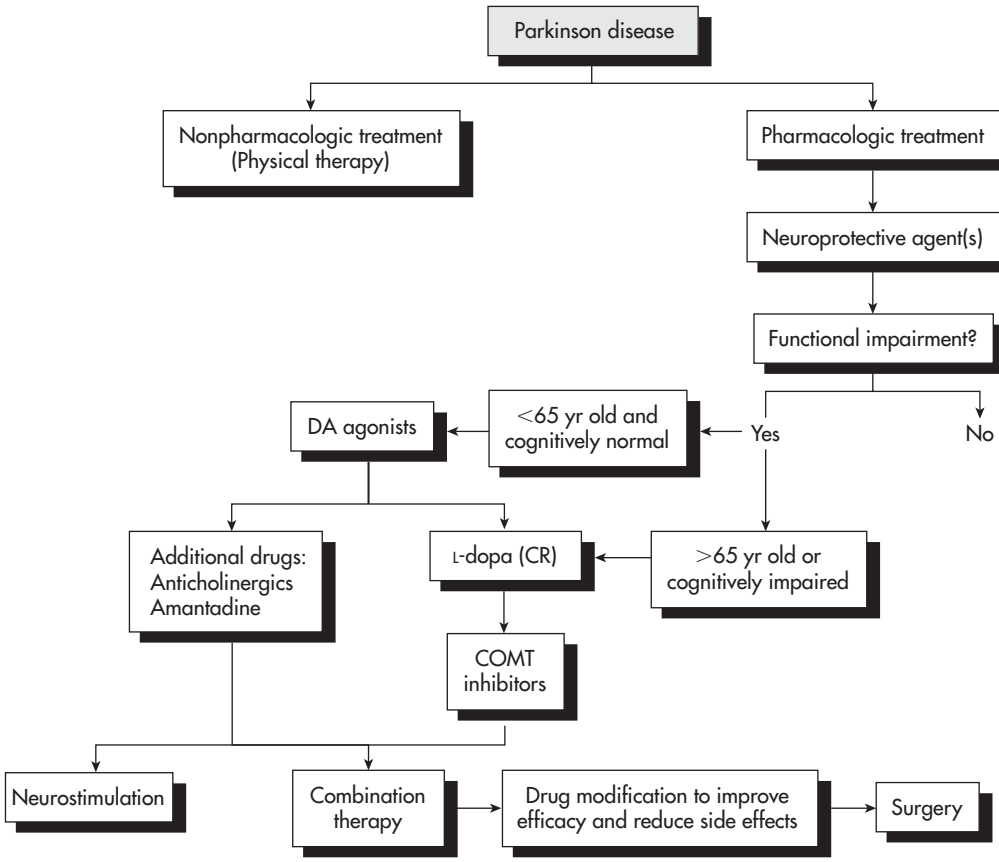

FIG. 2 Diagrammatic representation of a therapeutic approach to patients with parkinsonism. *COMT,* Catechol-O-methyl transferase; *CR,* controlled release; *DA,* dopamine. (Modified from Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, WB Saunders.)

3. Controlled-release (Sinemet CR) and extended-release (Rytary) preparations are also available, but their use should be supervised by a neurologist.
4. Stalevo (combination Sinemet and entacapone, a COMT inhibitor). Useful for patients with motor fluctuations (wearing off); has no role in treating early patients with PD.
5. Duopa (carbidopa/levodopa), administered via a 16-hour infusion to the jejunum through either a nasojejunal tube (short-term) or PEG-J tube (long-term), is used for treating motor fluctuations in patients with advanced PD.

- Dopamine receptor agonists (ropinirole, pramipexole, rotigotine) are not as potent as levodopa, but they are often used as initial treatment in younger patients to attempt to delay the onset of complications (dyskinesias, motor fluctuations) associated with levodopa therapy. These medications are more expensive than levodopa. In general, they cause more side effects than levodopa, including nausea, vomiting, light-headedness, peripheral edema, confusion, and somnolence. They can also cause impulse control behaviors such as hypersexuality, binge eating, and compulsive shopping and gambling. Presence of these must be assessed at each visit as the appearance of these side effects is often under-reported and their consequences can be severe. Dopamine agonists also can be associated with a prolonged withdrawal syndrome.
  1. Ropinirole: Initial dose is 0.25 mg tid but must be titrated over the course of 4 weeks to 1 mg tid and then may be increased by 1.5 mg/week to a maximum of 24 mg/day. An extended-release formulation is also available.
  2. Pramipexole: Initial dose is 0.125 mg tid but must be titrated over the course of weeks to 1.5 to 4.5 mg/day in three doses. An extended-release formulation is also available.
  3. Rotigotine: 2 mg to 6 mg/24 hour transdermal patch.
  4. Apomorphine: A dopamine agonist used for acute, intermittent treatment of unpredictable "off" episodes with advanced Parkinson disease.
- COMT inhibitors (entacapone and tolcapone) are used as adjunct to levodopa therapy to treat end-of-dose wearing off.
- MAO-B inhibitors can be used as monotherapy early in the disease or as adjunctive therapy in later stages; they have been shown to have milder symptomatic benefit than dopamine agonists or levodopa. They are well tolerated and easy to titrate. Concurrent use of stimulants and sympathomimetics should be avoided. Certain food restrictions may apply.
  1. Rasagiline: Initial dose is 0.5 mg qd, then 1 mg daily. The ADAGIO study suggests that 1 mg rasagiline may have disease-modifying benefits, but results must be interpreted with caution.
  2. Selegiline: Usual dose, 5 mg bid with breakfast and lunch. Has amphetamine byproduct so has mild stimulant-like effects, which can be beneficial in some patients.
  3. Safinamide: FDA approved as add-on therapy for carbidopa-levodopa that reduces "off time" and increases "on time" with fewer dyskinesias. Starting dose is 50 mg daily for 2 weeks, which can be increased if needed to 100 mg daily.
  4. Istradefylline is the first FDA-approved adenosine A 2A receptor agonist for use as an adjunct to carbidopa/levodopa in adults with Parkinson disease experiencing "off" episodes.
- Amantadine (unclear mechanism of action, but reported to modulate the dopamine and glutamate systems in the CNS) can be used alone early in the disease. Later in the disease, it is especially useful in the treatment of dyskinesias. Dosage is 100 mg tid (titrate q week from 100 mg qd). Must adjust for elderly and renal impairment. The most notable side effect, especially in the elderly, is confusion. An extended-release version is now FDA approved for the treatment of dyskinesia.
- Anticholinergic agents are only helpful in treating tremor but may be more effective than levodopa for tremor in some circumstances. They can also be used to treat drooling in patients with PD. Potential side effects include constipation, urinary retention, memory impairment, and hallucinations. They should be avoided in the elderly.
  1. Trihexyphenidyl: Initial dose, 1 mg PO tid.
  2. Benztropine: Usual dose, 0.5 to 1 mg qd or bid.
- Treatment of nonmotor symptoms: Nonmotor symptoms such as depression, anxiety, irritability, dementia, psychosis, urinary and sexual dysfunction, sleep disturbances such as REM behavior disorder, decreased sense of smell, and impulsive behavior among others often cause a great deal of distress for patients and caretakers alike. Treatable symptoms should be addressed pharmacologically using medications appropriate for elderly patients sensitive to antidopaminergic medications. In addition, two medications are specifically indicated for nonmotor symptoms associated with PD.
- Psychosis: Pimavanserin (Nuplazid) is FDA approved for the treatment of Parkinson disease psychosis and has been shown effective for the treatment of hallucinations and delusions associated with Parkinson disease psychosis. The medication is an inverse agonist of 5-HT2A and 5-HT2C receptors without any evidence of dopamine blockade.
- Parkinson disease dementia: Rivastigmine (Exelon), a cholinesterase inhibitor available both orally and transdermally as a patch (with few GI side effects), is approved to treat not only Alzheimer disease but also Parkinson disease dementia.

SURGICAL OPTIONS

- Pallidal (globus pallidus interna) and subthalamic deep-brain stimulation (subthalamic nucleus) are currently the surgical options of choice for patients with advanced PD; similar improvement in motor function and adverse effects have been reported after either procedure. Compared with ablative procedures, DBS has the advantage of being reversible and adjustable. Thalamic DBS may be useful for refractory tremor. It improves the cardinal motor symptoms, extends medication "on" time, and reduces motor fluctuations during the day. In general, patients are likely to benefit from this therapy if they show a clear response to levodopa. Therefore, when considering DBS, patients should be evaluated for motor response to levodopa by stopping levodopa overnight and evaluating motor response before and after a dose of levodopa.
- Surgery is often limited to patients with disabling, medically refractory problems, and patients must still have a good response to L-dopa to undergo surgery. Yet for many patients, earlier stimulation might provide an improved motor benefit before disability from other symptoms has occurred and should be considered at an earlier stage of PD. DBS results in decreased dyskinesias, fluctuations, rigidity, and tremor.

DISPOSITION

PD usually follows a slowly progressive course leading to disability over the course of several yr. However, every patient will progress individually, and patients should be reassured that this diagnosis does not, by definition, result in being either wheelchair- or bed-bound.

REFERRAL

- Neurology consultation is recommended at initial diagnosis of PD.
- Exercise is important for all patients with PD.
- Participation in outpatient physical therapy program is recommended for patients with moderate to advanced disease.

PEARLS & CONSIDERATIONS

- Asymmetry of symptoms at onset is typical of PD and therefore very useful in distinguishing PD from other causes of parkinsonism.
- Although resting tremor is a common presenting symptom, up to 25% of patients with idiopathic PD do not have classic resting tremor.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Parkinson Disease (Patient Information)

AUTHORS: **Corey Goldsmith, MD,** and **U. Shivraj Sohur, MD, PhD**

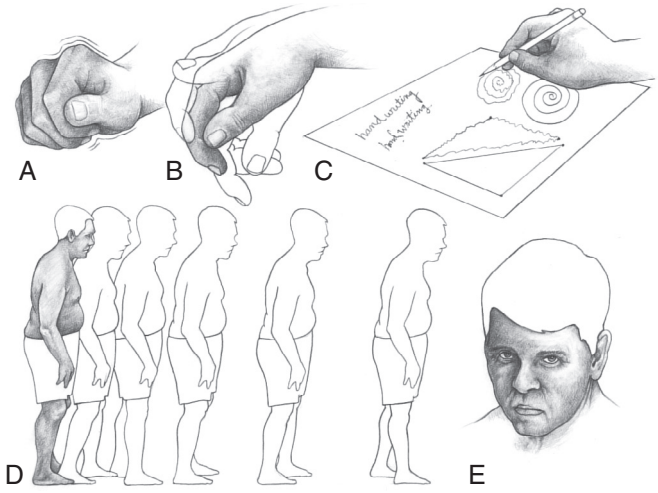

FIG. E1 The parkinsonian syndrome. A, The "pill-rolling" tremor. **B,** Tremor that can worsen with emotional stress. **C,** Handwriting abnormalities, including micrographia. **D,** Typical posture and gait, which becomes faster (festination). **E,** Lack of facial expression as well as "stare" from decreased blinking.

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Paronychia

BASIC INFORMATION

DEFINITION

Paronychia is a localized superficial infection or abscess of the lateral and proximal nail fold. Paronychia may be acute or chronic.

SYNONYMS

Nail bed infection
Nail bed abscess

ICD-10CM CODES

B37.2	Candidiasis of skin and nail
L03.019	Cellulitis of unspecified finger

EPIDEMIOLOGY & DEMOGRAPHICS

- Acute paronychia affects males and females equally.
- Chronic paronychia is more common in females than males (9:1).
- Acute paronychia most often occurs in children.
- Chronic paronychia usually presents in the fifth or sixth decade of life.
- Paronychia is the most common infection of the hand.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute paronychia usually presents with the sudden onset of redness, swelling, and pain with abscess or cellulitis formation in the nail fold. Fluid with purulence is often present (Fig. E1).
- Chronic paronychia is insidious, presenting with mild swelling and erythema of the nail folds.
- Acute paronychia usually involves only one finger.
- Chronic paronychia may involve more than one finger.
- Acute paronychia usually involves the thumb.
- Chronic paronychia commonly involves the middle finger.

ETIOLOGY

- Any disruption of the seal between the proximal nail fold and the nail plate can cause paronychial infections.
- Acute paronychia is almost always bacterial in origin (e.g., methicillin-sensitive *Staphylococcus aureus* [most common, but also consider MRSA], *Streptococcus pyogenes, Enterococcus faecalis, Proteus* and *Pseudomonas* species, and anaerobes).
- Paronychia can also be associated with use of lamivudine and indinavir, which are used in HIV therapy.
- Chronic paronychia is commonly caused by *Candida albicans* (70%), with bacterial organisms accounting for the remaining 30%.
- Trauma, nail biting, hangnails, diabetes, and long-term exposure to water are common predisposing features of paronychia.

DIAGNOSIS

The diagnosis of paronychia is self-evident on physical examination.

DIFFERENTIAL DIAGNOSIS

- Herpetic whitlow caused by herpes simplex
- Pyogenic granuloma
- Viral warts
- Ganglions
- Squamous cell carcinoma

WORKUP

A workup is usually not pursued unless there is treatment failure.

LABORATORY TESTS

- Gram stain and culture any purulent drainage.
- Potassium hydroxide (KOH) mount may show pseudohyphae.

IMAGING STUDIES

Radiographs of the digit if concerned about osteomyelitis

TREATMENT

NONPHARMACOLOGIC THERAPY

- For acute paronychia without purulent drainage, warm soaks tid or qid are helpful. If pus is present, surgical drainage is required (Fig. E2).
- For chronic paronychia, avoid frequent immersion in water or exposure to moisture.

ACUTE GENERAL Rx

- Trimethoprim-sulfamethoxazole DS 1 PO bid for 7 days is usually the antibiotic of choice for acute paronychia as it covers methicillin-susceptible *Staphylococcus aureus* strains (MSSA) and methicillin-resistant *S. aureus* (MRSA) strains.
- Alternative antibiotic choices include dicloxacillin 500 mg qid, cephalexin 500 mg qid, clindamycin, and amoxicillin-clavulanate.
- Surgical drainage is indicated if purulent discharge is noted.
- Use local anesthesia such as digital block or ethyl chloride spray.
- A No. 11 blade scalpel is used to lift the lateral perionychium and proximal eponychium off the nail, facilitating drainage.
- If the pus is located beneath the nail, the lateral edge of the nail can be lifted off the nail bed and excised.

FIG. E1 Paronychia with pus visible at the paronychial fold and a collection extending below the eponychial fold. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

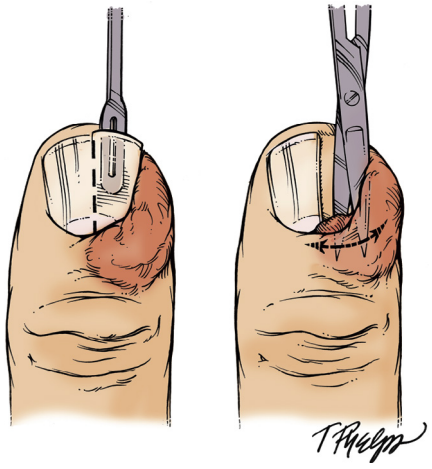

FIG. E2 Surgical drainage of acute paronychia. The lateral nail on the affected side is elevated gently from the nail bed, and a longitudinal strip of nail is removed. If this does not decompress the infection adequately, the margins of the nail fold are opened gently to drain the adjacent soft tissues. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

CHRONIC Rx

- If no fungal organism is found, tincture of iodine (2 drops bid) helps keep the nail and skin dry.
- Chronic paronychia caused by *Candida albicans* is treated with topical antifungal agents (e.g., miconazole or ketoconazole applied tid).
- Unresponsive cases may be treated with oral itraconazole, fluconazole, or terbinafine, but this should be done in consultation with dermatology and/or infectious disease as it requires prolonged therapy and has significant drug-to-drug interactions.
- One study suggested that topical steroids such as methylprednisolone aceponate were more effective than antifungals, implying that the origin is chronic dermatitis, not fungus. Topical tacrolimus ointment 0.1% has also been found effective.
- Surgery may be needed in refractory cases.

DISPOSITION

- Most acute paronychias with appropriate treatment resolve within 7 to 10 days.
- Osteomyelitis is a potential complication of paronychia.
- Untreated chronic paronychia leads to thickening and discoloration with eventual nail loss.

REFERRAL

Chronic paronychia refractory to topical medical therapy is best referred to dermatology and/or infectious disease. A hand surgeon is consulted if abscess drainage or surgery is being considered.

PEARLS & CONSIDERATIONS

COMMENTS

The gastrointestinal tract, including the mouth and bowel, and the genitourinary tract in women are the usual sources of *C. albicans* in chronic paronychia.

RELATED CONTENT

Paronychia (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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Paroxysmal Cold Hemoglobinuria

BASIC INFORMATION

DEFINITION

Paroxysmal cold hemoglobinuria (PCH) was the first, albeit rarest, autoimmune hemolytic anemia to be identified. It is characterized by transient or episodic massive intravascular hemolysis after exposure to cold temperatures and was first described in patients with secondary or tertiary syphilis. In modern times, chronic PCH is very rare, usually occurs in the elderly, and is associated with malignancy. Most cases are of the acute transient type, which is usually idiopathic in adults and secondary to a viral syndrome or immunization in children.

SYNONYMS

PCH
Donath-Landsteiner hemoglobinuria

ICD-10CM CODE

D59.6	Hemoglobinuria due to hemolysis from other external causes

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Estimated at 0.4 cases per 100,000 people
PREVALENCE: Accounts for up to 5% of all adult hemolytic anemias and 30% to 40% of childhood cases
PREDOMINANT SEX AND AGE: Mild male sex predilection with reported male-to-female ratio of 2:1 to 5:1. PCH affects both young children (acute form) and the elderly (chronic form).
GENETICS: None
RISK FACTORS: Age (most common in young population), infections, and neoplasms have been associated with the development of Donath-Landsteiner antibody.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Within min to a few hours after cold exposure, there is a sudden onset of fever, rigors, and chills followed by red to brown urination.
- Associated symptoms include back, leg, and abdominal pain.
- Headaches, nausea, vomiting, diarrhea, and esophageal spasm are common.
- Oliguria and anuria can develop following renal dysfunction.
- May be associated with Raynaud phenomenon.
- Associated with cold urticaria.
- Transient splenomegaly and hepatomegaly with jaundice may occur.
- Symptoms and gross hemoglobinuria usually resolve within hours.
- Symptoms believed to be mediated by smooth muscle dysfunction as a result of nitric oxide deficiency associated with hemoglobinemia.

ETIOLOGY

- The Donath-Landsteiner antibody is a biphasic, usually polyclonal, immunoglobulin G (IgG). It is known to bind to various antigens such as I-, i-, p-, Pr-, which are normally present on the red blood cell (RBC) surface, yet the glycosphingolipid P antigen is considered its primary target. The antibody in PCH also has thermal properties. It sensitizes RBCs in peripheral circulation (where typical thermal range for RBC binding is <20° C [<68° F]). As blood warms to 37° C [98.6° F] in the central circulation, the antibodies dissociate upon rewarming, but complement remains attached to the RBCs and ensures hemolysis.
- In children, the appearance of the antibody usually follows the onset of a viral respiratory illness by 1 to 3 wk. Symptoms may persist for several wks.
- PCH has been associated with multiple infectious pathogens, including syphilis, *Haemophilus influenzae,* Epstein-Barr virus (EBV), cytomegalovirus (CMV), influenza A, varicella, measles, mumps, adenovirus, parvovirus B19, coxsackie A9, *Mycoplasma pneumoniae,* and *Klebsiella pneumoniae.*
- Chronic PCH has also been associated with hematologic and solid organ malignancy such as small cell lung cancer, Hodgkin and non-Hodgkin lymphoma, primary myelofibrosis, myelodysplastic syndrome, and chronic lymphocytic lymphoma.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cold agglutinin disease, paroxysmal nocturnal hemoglobinuria, malaria, drug-induced hemolytic anemia, and hemolytic transfusion reaction
- Other causes of acute massive intravascular hemolysis and myoglobinuria secondary to rhabdomyolysis
- Table E1 differentiates various types of autoimmune hemolytic anemias

WORKUP

CBC, U/A, peripheral blood smear, hemolysis labs (LDH, total bilirubin, haptoglobin, reticulocyte count), iron studies, indirect and direct Coombs, complement levels, flow cytometry for PNH testing for CD55 or CD59 on the RBC membrane if clinically indicated, viral studies (if clinically warranted with thick and thin smear to rule out malaria)

LABORATORY TESTS

- The presence of IgG that reacts with the RBC at reduced temperatures but not at body temperature. In the Donath-Landsteiner test, a patient's serum is incubated with papainized pooled donated RBCs and complement at 4° C (39.2° F), and then warmed to 37° C (98.6° F). Lysis is observed in a positive test.
- A more sensitive test involves using radiolabeled monoclonal anti-IgG. This is incubated at 4° C (39.2° F) with the patient's serum and donor RBCs. The degree of radioactivity on the separated RBCs will be elevated in PCH compared with a control run at 37° C (98.6° F).
- Elevated bilirubin and lactate dehydrogenase, free plasma hemoglobin, low haptoglobin, low complement (C2, C3, C4).
- Abnormal RBC forms on the peripheral blood smear such as poikilocytosis, spherocytosis, anisocytosis, and nucleated RBCs.
- Erythrophagocytosis by neutrophils and monocytes may be seen.

IMAGING STUDIES

If chronic PCH, imaging could be considered to rule out underlying malignancy as the etiology when clinically warranted.

TREATMENT

NONPHARMACOLOGIC THERAPY

The mainstay of treatment is the avoidance of exposure to cold and presence of supportive care.

ACUTE GENERAL Rx

- In children in particular, warmed, packed RBC transfusion may be necessary because the anemia may become life threatening and hemolysis may be ongoing for several wk.
- Testing and treatment for underlying secondary condition.
- Hydration and alkalinization of the urine may be necessary to prevent renal failure.
- Plasma exchange therapy with 5% albumin fluid replacement has been successfully employed.
- Treatment with rituximab has resulted in termination of hemolysis in a case report.
- Azathioprine and cyclophosphamide have also been suggested in case reports.
- Steroids, although commonly used, have not been shown to be beneficial.
- Splenectomy is not indicated, as it plays no role in the pathogenesis of the hemolysis in PCH.
- Folic acid supplementation to prevent consumptive folate deficiency.

CHRONIC Rx

Several case reports suggest that rituximab and immunosuppressants such as azathioprine may be effective. Treatment of the underlying cause such as infection or malignancy may also help in chronic disease. In addition, cold avoidance is appropriate for all patients.

COMPLEMENTARY & ALTERNATIVE MEDICINE

None

DISPOSITION

- Postinfectious varieties are self-limited.
- Adult idiopathic form is generally manageable by avoiding cold exposure.

REFERRAL

To hematologist to aid in diagnosis and management

TABLE E1 Characteristics of Autoimmune Hemolytic Anemia

Characteristic	Type of Autoimmune Hemolytic Anemia		
	Warm Autoimmune Hemolytic Anemia	Cold Agglutinin Disease	Paroxysmal Cold Hemoglobinuria
Antibody isotope	IgG, rare IgA, IgM	IgM	IgG
Direct antiglobulin test (DAT) result	IgG and/or C3	C3	C3
Antigen specificity	Multiple, primarily Rh	i/I, Pr	P
Hemolysis	Primarily extravascular	Primarily extravascular	Intravascular
Common disease associations	B-cell neoplasia/ lymphoproliferative, collagen-vascular	Viral, neoplasia	Syphilis, viral

From Hoffman R et al: *Hematology: Basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

SUGGESTED READINGS

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Zeller MP et al: Paroxysmal cold hemoglobinuria: a difficult diagnosis in adult patients, *Transfusion* 57(1):137-143, 2016.

PEARLS & CONSIDERATIONS

COMMENTS

- PCH is associated with brown or red discoloration of urine after cold exposure in adults or after a viral infection in children.
- PCH can be associated with viral or bacterial infections, including syphilis, *H. influenzae*, EBV, CMV, influenza A, varicella, measles, mumps, and adenovirus, or malignancy, especially in adults.
- PCH can cause life-threatening hemolysis in children.

PREVENTION

None

AUTHORS: **Hussain Mohammad H. Naseri, MD,** and **Donny V. Huynh, MD**

Paroxysmal Nocturnal Hemoglobinuria

BASIC INFORMATION

DEFINITION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem disorder characterized by episodes of bone marrow failure, hemolytic anemia, and recurrent venous thrombosis.

SYNONYM

PNH

ICD-10CM CODE

D59.5 Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence: 2 to 5 per million in the U.S.
- Affects patients of any age (reported spectrum 6 to 82 yr) but most common in patients aged 30 to 50 yr
- Affects both sexes (slight female predominance) and all races

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The initial manifestations in PNH are as follows:

- Hemoglobinuria: Typically the first morning void reveals dark urine, with progressive clearing during the day. Hemolysis occurs at night as the P_{CO_2} level rises during sleep, lowering pH levels and facilitating complement-mediated lysis.
- Hemolysis: In addition to the circadian hemolysis and resulting hemoglobinuria, episodes of hemolytic exacerbations can accompany infections, menstruation, transfusion, surgery, iron therapy, and vaccinations. Symptoms of severe hemolysis include chest, back, or abdominal pain, headache, fever, malaise, and fatigue.
- Aplastic anemia: This may be the presenting manifestation of PNH (therefore PNH must be in the differential diagnosis of aplastic anemia) or may develop as a later complication of PNH.
- Thrombosis: This is a leading cause of death in PNH and occurs in 40% of patients. It can occur as deep vein thrombosis in the lower extremities, subclavian vein, portal or mesenteric vein, hepatic vein (Budd-Chiari syndrome), or cerebrovascular thromboses.
- Renal failure: Acute renal failure associated with massive hemoglobinuria (acute tubular necrosis) or progressive renal failure associated with thrombosis within renal small veins.
- Dysphagia.
- Infections (associated with leukopenia or immunosuppressive therapy).
- Physical findings include:
  1. Pallor (anemia)
  2. Jaundice (hemolysis)
  3. Splenomegaly
  4. Unilateral extremity swelling (DVT)
  5. Ascites (Budd-Chiari syndrome)

ETIOLOGY & PATHOGENESIS

- Hemolysis in PNH is complement mediated and is a direct result of PNH cells acquiring a deficiency of complement regulatory proteins; the erythrocytes are abnormally sensitive to acidified serum.
- Patients have two populations of red blood cells (RBCs): Some sensitive to hemolysis (PNH III cells) and others not (PNH I cells), in variable proportions (10% to 75% PNH III cells). Approximately 20% PNH III are required for hemoglobinuria to be detectable.
- The RBC defects in PNH are in the membrane proteins as follows:
  1. Decay-accelerating factor deficiency
  2. Membrane inhibitor of reactive lysis deficiency
  3. C-8 binding protein deficiency
- Protein deficiencies are the result of an acquired mutation located in the X chromosome, which regulates glycosyl phosphatidyl inositol (GPI). GPI anchors the above-mentioned proteins in the RBC membrane; GPI-deficient RBCs proliferate as an abnormal clone. Hemolysis is caused by the absence of decay-accelerating factor (CD55) and the membrane inhibitor of reactive lysis (CD59), which are glycosylphosphatidylinositol-dependent complement regulatory proteins.
- Hemolysis in PNH is chronic because of a continuous state of complement activation, but paroxysms resulting in brisk hemolysis coincide with increases in complement activation triggered by surgery, infection, or inflammation.
- The pathophysiology of the relation of PNH and aplastic anemia is unknown. The leading hypothesis is that PNH stem cells have a conditional survival advantage in the setting of an autoimmune attack (e.g., aplastic anemia) that targets the bone marrow.

DIAGNOSIS

It is useful to classify PNH patients as either "classical" or "hypoplastic." This can usually be accomplished by ordering a complete blood count, reticulocyte count, LDH level, peripheral blood flow cytometry for PNH, and BM aspirate, biopsy, and cytogenetics. Most, but not all, patients can be readily subdivided into classical or hypoplastic PNH, a distinction that aids with therapeutic decisions.

Patients with classical PNH tend to have mild to moderate cytopenias, a normocellular to hypercellular BM, an elevated reticulocyte count, a markedly elevated LDH level, and a relatively large PNH granulocyte population (>30%).

In contrast, hypoplastic PNH patients present with manifestations similar to that of aplastic anemia or hypoplastic MDS. These patients typically present with moderate to severe cytopenias, a hypocellular BM (<25% cellularity), a decreased corrected reticulocyte count, a normal or mildly elevated LDH level, and a relatively small (<20%) PNH granulocyte population.

Clinical situations:

- Intravascular hemolysis
- Hemoglobinuria
- Pancytopenia associated with hemolysis
- Iron deficiency associated with hemolysis
- Recurrent venous thrombosis
- Recurrent episodes of abdominal pain, headache, or back pain associated with hemolysis

DIFFERENTIAL DIAGNOSIS

- See "Anemia, Autoimmune Hemolytic" in Section I.
- See "Anemia, Aplastic" in Section I.
- See "Anemia" algorithm in Section III.

LABORATORY TESTS

- Complete blood count: Anemia, leukopenia, thrombocytopenia
- Bone marrow aspiration and biopsy
- RBC smear: Reticulocytosis, spherocytosis (Fig. E1)
- Negative Coombs test
- Elevated lactate dehydrogenase
- Low serum haptoglobin
- Low serum iron saturation, low ferritin
- Elevated urine hemoglobin, urine urobilinogen, urine hemosiderin
- Positive Ham test (acidified serum RBC lysis)
- Assaying granulocytes is the most reliable method of diagnosing PNH because they are not affected by blood transfusions. Identification of GPI-anchored protein deficiency on hematopoietic cells by using monoclonal antibodies or flow cytometry; flow cytometric analysis of granulocytes is the best way to diagnose PNH. Most hematologists prefer to use FLAER over monoclonal antibodies on granulocytes and monocytes because of improved sensitivity and specificity; anti-CD59 is the most reliable marker on erythrocytes
- Cytogenetic studies are not diagnostic

TREATMENT

- Eculizumab, a humanized antibody that inhibits the activation of terminal complement components, is an effective approved therapy for PNH; it reduces intravascular hemolysis, hemoglobinuria, and need for transfusion in patients with PNH. It is very expensive and requires lifelong administration. Vaccination against meningococcus is mandatory before eculizumab administration due to increased susceptibility to neisserial infection.
- Prednisone (0.5 to 1.0 mg/day) for 6 to 8 wk is helpful to reduce complement activation if eculizumab is unavailable.
- Danazol 400 mg/day can also decrease hemolysis.

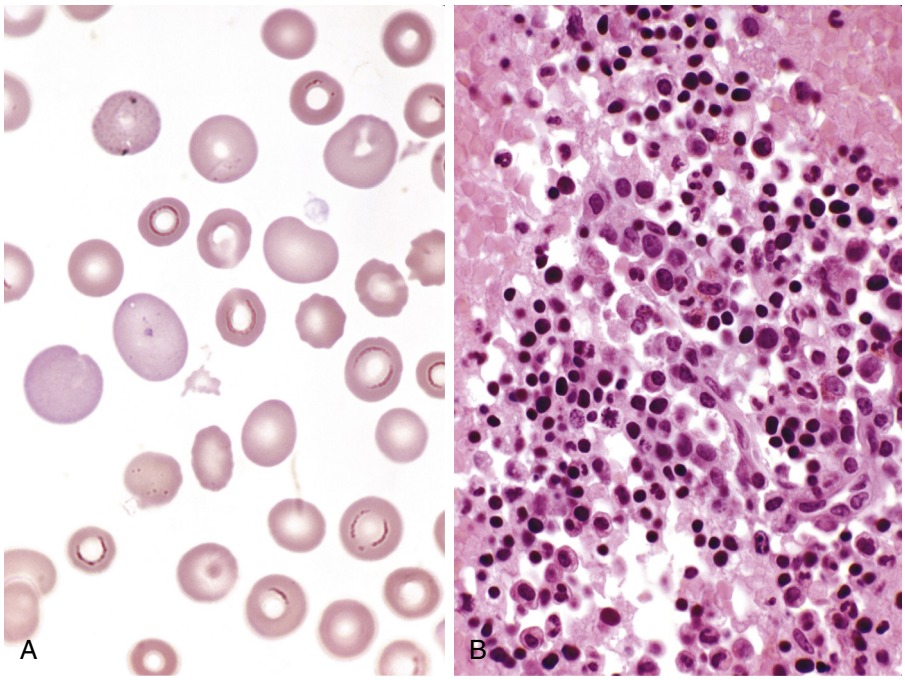

FIG. E1 Paroxysmal nocturnal hemoglobinuria. A, Large polychromatophilic red cells (shift cells) are seen following an episode of hemolysis. **B,** The bone marrow biopsy shows marked erythroid hyperplasia. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

- Iron replacement, folic acid supplementation: All patients with classical PNH should be prescribed folic acid (1 to 2 mg/day). Iron supplementation is recommended in those with absent iron stores.
- Packed red blood cell transfusions.
- Treatment and prevention of thrombosis (heparin, warfarin).
- Avoidance of oral contraceptives.
- Allogeneic bone marrow transplantation is a therapeutic option that is offered in cases of eculizumab failure.

REFERRAL

To hematologist

PROGNOSIS

- Median survival is 10 to 15 yr.
- 25% survive up to 25 yr.
- With thrombosis at presentation, only 40% survival to 4 yr.
- 1% incidence of leukemia.
- 5% incidence of myelodysplastic syndrome.
- Death often results from thrombosis or progressive pancytopenia.

AUTHOR: **Bharti Rathore, MD**

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Patellofemoral Pain Syndrome PTG ALG

BASIC INFORMATION

DEFINITION

Patellofemoral pain syndrome is overuse or overload of the patellofemoral region leading to anterior knee pain.

SYNONYMS

PFPS
Retropatellar pain syndrome
Runner's knee
Lateral facet compression syndrome
Idiopathic anterior knee pain

ICD-10CM CODES

M22.2	Patellofemoral disorders
M25.569	Pain in unspecified knee

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Estimated >20% of adolescents. Patellofemoral pain syndrome (PFPS) is the most common diagnosis in outpatients presenting with knee pain. PFPS also constitutes 16% to 25% of all injuries to runners.
PREDOMINANT SEX AND AGE: Nearly 2:1 female predominance; disproportionately affects active adolescents and adults in the second and third decades of life.
RISK FACTORS: Increase in physical activity intensity or duration, overuse, joint overload, trauma, anatomic abnormalities, malalignment, patellar hypermobility, quadriceps weakness.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Gradual or acute onset of anterior knee pain
- Sometimes localized under or around the patella
- Also described as a catching sensation under the patella
- Worsened pain with squatting, running, prolonged sitting, or ascending or descending steps
- Effusion implies intraarticular pathology not explained by PFPS
- Pain may be elicited by compression of the patella into the trochlear groove while the leg is extended

ETIOLOGY

No clear consensus; likely multifactorial, including muscle overuse or joint overload with malalignment and/or trauma potentially contributing, resulting in imbalances in the forces controlling patellar tracking during knee flexion and extension.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Patellofemoral arthritis
- Patellar instability
- Patellar stress fracture
- Osgood-Schlatter disease (osteochondritis of the tibial tubercle)
- Articular cartilage injury
- Prepatellar bursitis
- Pes anserine bursitis
- Iliotibial band syndrome
- Plica synovitis (also called plica syndrome)
- Chondromalacia
- Bony abnormalities
- Bone tumors
- Patellar tendinopathy
- Other: Referred pain from lumbar spine or hip joint pathology, osteochondritis dissecans, Sinding-Larsen-Johansson syndrome (patellar apophysitis), symptomatic bipartite patella

WORKUP

- PFPS is a clinical diagnosis of exclusion; evaluate and rule out other possibilities on the differential.
- Physical exam should include:
  1. Dynamic patellar tracking
     a. Can be assessed by having the patient perform a single leg squat and stand.
     b. Positive "J" sign—lateral tracking of the patella when knee is moved from flexion to extension.
  2. Patellar mobility testing
     a. Displace patella medially; displacement >3 quadrants is considered hypermobile.
  3. Patellar grind (or inhibition) test
     a. With knee extended, push patella inferiorly into the trochlear groove.
     b. Ask patient to contract quadriceps muscle while maintaining gentle pressure on the patella to prevent movement of the patella superiorly.
     c. Positive test if pain is produced.
  4. Patellar tilt test
     a. Assesses for tightness of the lateral structures, which predisposes to PFPS.
     b. Extend knee and grasp patella between thumb and forefinger.
     c. Compress medial aspect of patella posteriorly while elevating lateral aspect.
     d. Positive test if lateral aspect is fixed and cannot be raised to a horizontal position (0 degrees).

IMAGING STUDIES

- No imaging is necessary in the initial workup.
- Consider plain films if symptoms do not improve after 1 to 2 mo of therapy.

TREATMENT

There is a general lack of consensus. Management should focus on the implementation of a comprehensive rehabilitation program.

NONPHARMACOLOGIC THERAPY

- Physical therapy
  1. Quadriceps, hamstring, iliotibial band, and calf-stretching exercises
  2. Quadriceps and hip abductor strengthening
  3. Core muscle strengthening might improve pain and dynamic balance

ACUTE GENERAL Rx

- Short-term (2 to 3 wk) nonsteroidal anti-inflammatory drugs or acetaminophen for pain relief
- Activity modification
- Ice for 10 to 20 min after activity

CHRONIC Rx

- Physical therapy: Strengthening and flexibility exercises.
- Consider arch supports or evaluation for custom orthotics.
- Spontaneous resolution may occur in some cases, although 50% of individuals with PFPS will have long-term symptoms (>5 yr after diagnosis).

DISPOSITION

Outpatient management

REFERRAL

Consider referral to orthopedics for surgical evaluation as a last resort if conservative therapies fail. Surgical options include release of the lateral retinaculum, articular cartilage procedures, and proximal realignment, usually with anteromedialization of the tibial tubercle.

PEARLS & CONSIDERATIONS

PATIENT & FAMILY EDUCATION

The American Academy of Family Practice website www.familydoctor.org contains frequently asked questions, patient information, and example stretching and strengthening exercises. Information is available in English and Spanish.

RELATED CONTENT

Knee Pain (Patient Information)
Patellofemoral Pain Syndrome (Patient Information)

AUTHOR: **Kate Cahill, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

The ductus arteriosus (DA) is a fetal vascular communication between the proximal descending aorta and main pulmonary artery. It derives from the left sixth aortic arch. During development, this connection allows right ventricular blood to bypass the increased pulmonary vascular resistance of the nonfunctional fetal lungs into the low resistance system of aortic and placental circulation. Closure typically occurs first functionally within hours of delivery, then anatomically within the first few days, though this may take longer in premature infants. If a ductus fails to close within 72 hours of birth in a full-term infant, diagnosis of a patent ductus arteriosus (PDA) can be made. Postnatal DA closure and obliteration are driven by multiple mechanisms, including increased oxygen saturation, decreased levels of endogenous prostaglandins and nitric oxide, and intimal proliferation and fibrosis. Failure of complete closure results in PDA, which may have hemodynamic consequences, the severity of which depends on the size and length of the defect.

SYNONYM

PDA

ICD-10CM CODE
Q25.0 Patent ductus arteriosus

EPIDEMIOLOGY & DEMOGRAPHICS

- PDA is the third most common congenital abnormality.
- Prevalence is 2.9 per 10,000 live births. Incidence has increased due to improved survival of premature infants (especially those born <30 wk gestation).
- Female predominance 2:1.
- Genetics play a role in PDA, with sibling recurrence risk of approximately 5%.
- Risk factors include first trimester rubella infection, high altitude birth, chromosomal abnormalities such as Down syndrome, and associated cyanotic congenital heart disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Continuous, "machinery-like" murmur, appreciated over the left scapula and in the left infraclavicular area in patients with left-to-right shunting (Fig. E1). The murmur intensity increases during systole and peaks at the second heart sound. Oftentimes, the increase in flow through the aortic valve produces a flow murmur at the right upper sternal border.
- The apical impulse may be hyperdynamic if there is significant left-to-right shunting.
- Widened pulse pressure.
- S1 is normal, but S2 may be split with an accentuated P2 component if there is pulmonary hypertension. An S3 may be appreciated if shunt volume is significant.
- Increased jugular venous pressure (with RV failure):
  1. When the defect has resulted in irreversible pulmonary hypertension, no murmur may be present due to minimal shunt. However, cyanosis and clubbing, particularly of the feet (differential cyanosis), may develop.
- Exertional dyspnea, fatigue, and signs of volume overload or congestive heart failure.
- Atrial fibrillation due to progressive left atrial enlargement.
- Small defects are generally asymptomatic and may be diagnosed later in life.
- Fig. E2 shows the anatomy of patent ductus arteriosus.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rule out other causes of continuous murmurs such as aortopulmonary shunts or window, coronary fistula, ruptured sinus of Valsalva aneurysm, aortic-cameral fistula, and mixed aortic stenosis and regurgitation.
- Coarctation of the aorta also will have a murmur over the scapula, but has an arm-leg blood pressure gradient and hypertension.
  1. In patients with Eisenmenger syndrome, consider ASD and VSD in the differential diagnosis.

WORKUP

- ECG:
  1. When the defect is large enough to cause left-sided volume overload, there may be LA enlargement, LV hypertrophy.
  2. When pulmonary hypertension has occurred, right-axis deviation, RVH and P pulmonale may be present.
- Chest x-ray
- Echocardiography (Fig. E3)
- Cardiac magnetic resonance imaging (MRI) or CT
- Cardiac catheterization
- Adults with PDA should have oxygen saturation measured in feet and hands to rule out right-to-left shunting

IMAGING STUDIES

- Chest x-ray may be normal. In moderate to large shunts, cardiomegaly, left heart enlargement, and increased pulmonary vascular markings may be present.
- Echocardiography with Doppler flow studies is generally diagnostic. The parasternal short-axis and suprasternal views can show the presence of the PDA, the size of the defect, and the direction of shunting. Color flow Doppler may be useful to view even tiny ductus flow. Echocardiography can also estimate the degree of shunt by the effects of the PDA on left heart chamber sizes and may be used to determine the pulmonary: Systemic shunt ratio (Qp:Qs), which describes shunt size. Lastly, echocardiography can measure pulmonary artery pressures to determine if pulmonary hypertension has developed.

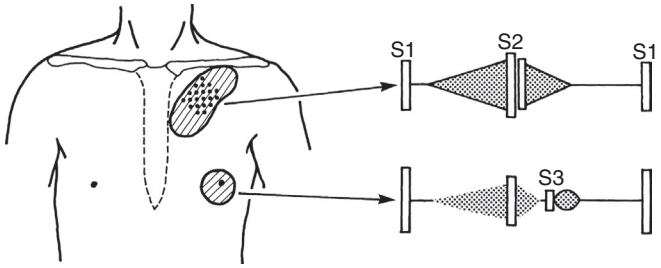

FIG. E1 Cardiac findings of patent ductus arteriosus. A systolic thrill may be present in the area shown by dots. (From Park MK: *Park's pediatric cardiology for practitioners,* ed 6, Philadelphia, 2014, WB Saunders.)

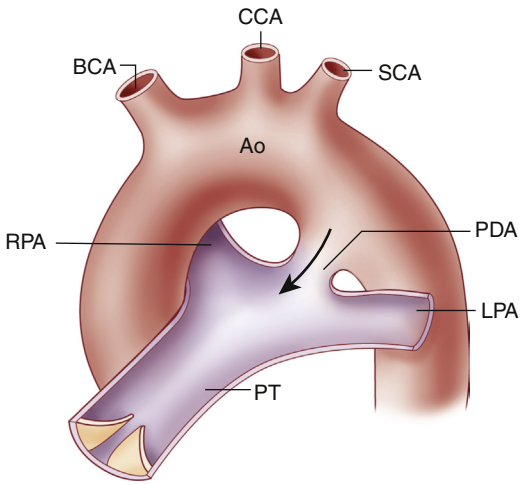

FIG. E2 Anatomy of a patent ductus arteriosus. Note the relationships among the position of the ductus, left subclavian artery, and pulmonary artery bifurcation. *Ao,* Aorta; *BCA,* brachiocephalic; *CCA,* common carotid artery; *LPA,* left pulmonary artery; *PDA,* patent ductus arteriosus; *PT,* pulmonary trunk; *RPA,* right pulmonary artery; *SCA,* subclavian artery. (From Perloff JK [ed]: *Clinical recognition of congenital heart disease,* ed 4, Philadelphia, 1994, WB Saunders.)

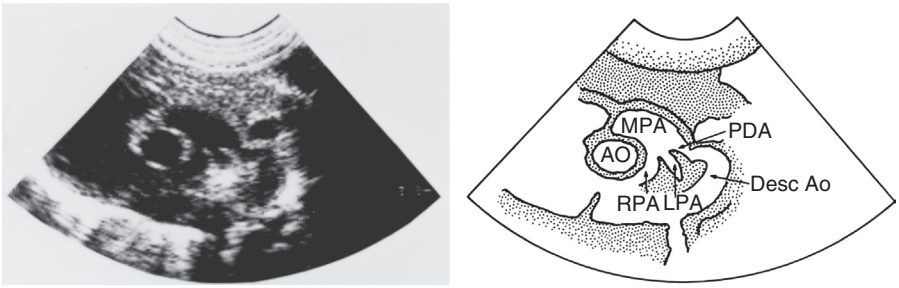

FIG. E3 Parasternal short-axis view demonstrating patent ductus arteriosus *(PDA)* that connects the main pulmonary artery *(MPA)* and the descending aorta *(Desc Ao).* *AO*, Aorta; *LPA*, left pulmonary artery; *RPA*, right pulmonary artery. (From Park MK: *Park's pediatric cardiology for practitioners,* ed 6, Philadelphia, 2014, WB Saunders.)

- Transesophageal echocardiography is modestly helpful, especially when patients have poor acoustic windows.
- Cardiac MRI and CT: May be useful if echo is not diagnostic; the PDA may be directly visualized and its morphology described with either technique. MRI is gold standard for assessing LV size and function. It can determine whether the left-sided chambers are enlarged and establish the degree of shunting using phase contrast imaging to determine the Qp:Qs noninvasively. MRI is also useful to assess for associated lesions; cardiac CT can offer similar information at the price of radiation exposure.
- Cardiac catheterization: Left- and right-heart catheterization can be used when the diagnosis remains unclear. It can also help to estimate the degree of left-to-right shunting, demonstrate PDA morphology, establish right-sided pressures and, if elevated, assess the response to vasodilators, and attempt closure where technically feasible.
- PDAs are classified based on the ratio of left-to-right shunting:
  1. Small: Qp:Qs <1.5:1
  2. Moderate: Qp:Qs 1.5 to 2.2:1
  3. Large: Qp:Qs >2.2:1
- "Silent" PDA refers to a very small PDA with minimal shunt and no audible murmur, discovered incidentally by imaging studies.

Rx TREATMENT

PHARMACOLOGIC THERAPY

- Cyclooxygenase inhibitors (e.g., indomethacin, ibuprofen) are useful agents for PDA closure in the premature infant. These inhibit local prostaglandin synthesis, which is often necessary for the duct to remain open. These are ineffective in term infants and older patients.
- Antibiotic prophylaxis is recommended only in patients with a history of endocarditis, or within 6 mo of closure device placement.
- In patients with signs and symptoms of volume overload, diuretics and digoxin may be used until formal device or surgical closure can be performed.
- In older patients with secondary pulmonary hypertension, pulmonary vasodilators can be extremely helpful in improving symptoms and mortality, as well as potentially allowing safe closure of the defect.
- In the absence of indications for closure, timing and treatment for PDA vary among physicians and are not well standardized.

SURGICAL Rx

- Device closure is the preferred PDA closure method when technically suitable. Closure of a PDA is considered if the following are present:
  1. Signs of left ventricular volume overload.
  2. Patients with pulmonary arterial hypertension and pulmonary arterial pressure <2/3 of systemic pressure, or pulmonary vascular resistance <2/3 of systemic vascular resistance.
  3. Either pulmonary arterial hypertension and pulmonary artery pressure >2/3 of systemic pressure or pulmonary vascular resistance >2/3 of systemic vascular resistance when one of the following is present:
     a. Net left to right shunt (Qp:Qs >1.5)
     b. Pulmonary vascular reactivity to testing (preferred with nitric oxide)
  4. Consider closure in patients with small PDAs with continuous murmur.
- Avoid PDA closure in patients with Eisenmenger syndrome or exercise-induced lower limb desaturation.
- Closure of PDA should not be performed in patients with a very small PDA without murmur.
- More than 95% of PDAs can successfully be closed percutaneously with a low rate of complications. Various occlusion devices may be used, depending on the underlying morphology.
- In patients with pulmonary hypertension, treatment with pulmonary vasodilators should be considered prior to closure.
- Surgical closure may be performed when a patient is undergoing cardiac surgery for other reasons or when the PDA is not suitable for device closure, such as in the case of very large defects, distorted ductal anatomy (e.g., aneurysm, endarteritis), or when the child is too small (<6 kg).
- Patients with severe, irreversible pulmonary hypertension are not recommended for PDA repair as they may require right-to-left shunting to maintain cardiac output.

DISPOSITION

- Long-term outcome depends on the size of the lesion and the associated degree of left-to-right shunting. Defects with a small shunt generally have good outcomes, except in rare instances of endarteritis (<0.25% annually). Patients with moderate shunts may develop left atrial and left ventricular volume overload and shortness of breath or arrhythmias. Very large shunts may lead to early heart failure, with subsequent Eisenmenger syndrome (fixed pulmonary hypertension with reversal of shunt causing cyanosis) if unrepaired.
- Infective endarteritis is uncommon and can generally be treated medically. Vegetations usually develop at the site where the high-velocity jet lesion enters the PA, and there are rare cases of septic embolization to the lung. Staphylococcal and streptococcal species are commonly implicated.
- Aneurysm of the DA has an unclear incidence and often spontaneously resolves. Rarely, these aneurysms may clinically manifest as thoracic masses, causing compression of adjacent structures with subsequent hoarseness or left bronchial obstruction, prompting surgical resection.
- Basic preoperative assessment for patients with adult congenital heart disease (ACHD) should include systemic arterial oximetry, an ECG, chest radiograph, TTE, and blood tests for full blood count and coagulation screen.
- Intracardiac shunts are considered moderate risk in preoperative evaluation for noncardiac procedures. High-risk features include severe systolic dysfunction (EF <35%), severe pulmonary hypertension (either primary or secondary), cyanotic heart disease, or severe left-side outlet obstruction.
- Clinical follow-up is recommended for adult patients to exclude residual deficits, pulmonary hypertension and LV dilation and dysfunction, and atrial arrhythmias.
- Patients with small, hemodynamically insignificant PDA should be reexamined every 3 to 5 yr to assess for cardiopulmonary decompensation.
- Infective endocarditis prophylaxis for dental procedures:
  1. Prophylaxis is not indicated for an unrepaired PDA or for a repaired PDA with no residual shunt after 6 mo.
- Prophylaxis is indicated for a repaired PDA in the first 6 mo following the repair, or where prosthetic material is present and there is a residual defect.
- The estrogen-containing oral contraceptive pill is not recommended in ACHD patients at risk of thromboembolism, such as those with cyanosis related to an intracardiac shunt, atrial fibrillation, severe PAH, or Fontan repair.
- Women with a repaired PDA generally can undergo pregnancy and delivery normally. Those with an unrepaired defect of a size that would ordinarily be repaired are recommended to undergo repair before becoming pregnant.

AUTHORS: **Craig L. Basman, MD,** and **Adam J. Prince, MD**

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Patent Foramen Ovale

BASIC INFORMATION

DEFINITION

- Patent foramen ovale (PFO) is a vestige of the fetal circulation, and results from failure of the primum and secundum septa to fuse postnatally. Persistence of the one-way flap valve overlying this foramen ovale allows right to left blood flow when right atrial pressure exceeds that of the left.
- Foramen ovale remains open during intrauterine life, in a valve-like manner, to allow highly oxygenated blood to reach the left atrium from the inferior vena cava. High right atrial pressure in the fetus keeps it open.
- Soon after birth, as the pulmonary circulation fills, the left atrial pressure rises higher than that of the right atrium. This pushes the septum primum against the septum secundum, closing the right-to-left pathway through the foramen ovale.

SYNONYM

PFO

ICD-10CM CODE

Q21.1 Atrial septal defect

EPIDEMIOLOGY & DEMOGRAPHICS

- PFO fails to close in as much as one fourth of the population.
- PFO has similar frequency among males and females.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most patients with isolated PFO are asymptomatic.
- It cannot be detected on clinical examination.

COMPLICATIONS:

- Cryptogenic stroke (particularly <55 yr)
- The proposed mechanism of stroke with PFO includes paradoxical embolization, in situ thrombosis within the canal of the PFO, associated atrial arrhythmia, and concomitant hypercoagulable state
- Migraine with aura
- Decompression sickness and air embolism
- Increases risk of hypoxemia during sleep in patients with obstructive sleep apnea
- Platypnea-orthodeoxia syndrome (characterized by both dyspnea and arterial desaturation in the upright position with improvement in supine position)
- Increased risk of postoperative atrial fibrillation and hypoxemia, in off-pump coronary artery bypass surgery

ETIOLOGY

Unknown

DIAGNOSIS

- Testing for PFO is primarily performed in patients with a cerebral ischemic event of uncertain origin.
- A variety of echocardiography modalities have been used to diagnose PFO. These include:
  1. Transthoracic echocardiography (TTE)
  2. Transesophageal echocardiogram (TEE) (Fig. E1)
  3. Transmitral Doppler (TMD)
  4. Transcranial Doppler (TCD) of middle cerebral artery after injection of agitated saline peripherally
- TEE, especially when performed with contrast injected during a cough or Valsalva, is the most sensitive and preferred test for diagnosing PFO.
- Essentially, a PFO is suggested by the presence of echo dropout in the atrial septum visualized in more than one plane during echocardiography. The appearance of microbubbles in the left atrium within three to five cardiac cycles after injection of agitated saline peripherally is considered diagnostic of PFO with associated right-to-left shunt (RLS).
- The diagnosis of PFO is enhanced with multiple intravenous contrast injections with maneuvers that cause transient elevations of right atrial pressure (cough or Valsalva) to enhance RLS.
- TCD has the advantage of being noninvasive and easy to perform at bedside. But it can only detect a right-to-left shunt, not the location of the shunt or other cardiac structural anomalies.

TREATMENT

- Management guidelines from professional societies are shown in Table E1.
- Most patients with a PFO as an isolated finding receive no special treatment. This is because the yearly risk of cryptogenic stroke in healthy persons with PFO may be as low as 0.1%.
- As it is not associated with increased risk for endocarditis, antibiotic prophylaxis is not indicated.

PHARMACOLOGIC TREATMENT

When PFO is associated with an otherwise unexplained neurologic event, traditional treatment has been antiplatelet treatment (e.g., aspirin) therapy alone in low-risk patients and combined with therapeutic anticoagulants (e.g., warfarin) in high-risk patients.

Risk factors associated with a higher risk of complications, particularly stroke, include:

- Coexisting atrial septal aneurysm
- Large PFO
- Spontaneous right-to-left shunting
- Major shunt (>50 bubbles)
- Valsalva-provoking activity preceding the onset of stroke
- Presence of Chiari network (a congenital remnant of the right valve of the sinus venosus)
- Eustachian valves
- Younger age (<55 yr)
- Multiple clinical events or infarcts
- Pulmonary hypertension
- Failure or contraindications to anticoagulants
- High risk for recurrent deep venous thrombosis
- Pulmonary embolism at time of initial event
- Hypercoagulable state

PERCUTANEOUS TRANSCATHETER CLOSURE OF PFO

Percutaneous method of closure is usually preferred over open surgical closure because of invasiveness, procedure time, and patient convenience.

- Indications:
  1. Recurrent cryptogenic stroke due to presumed paradoxical embolism through PFO while on adequate medical treatment with antiplatelets or anticoagulants.

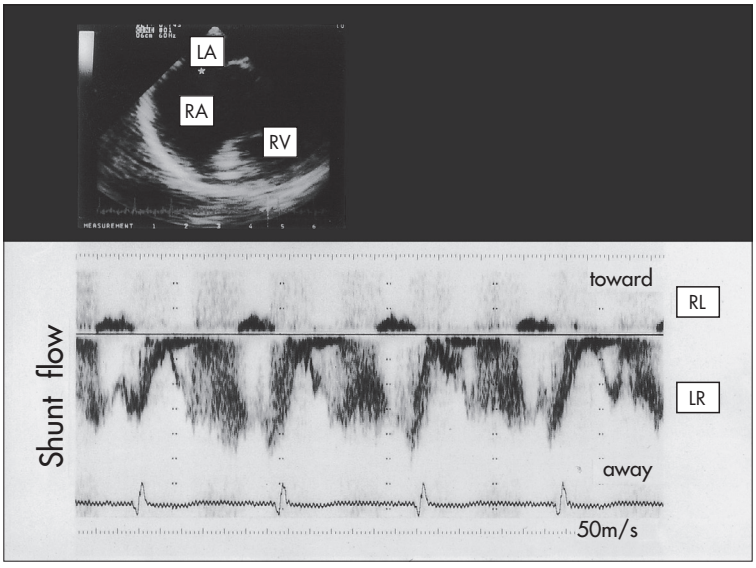

FIG. E1 Transesophageal echocardiography of an internal defect and pulsed Doppler flow signal. Pulsed Doppler echocardiographic signal is consistent with left-to-right level. *LA,* Left atrium; *LR,* left-to-right shunt signal; *RA,* right atrium; *RL,* right-to-left shunt signal; *RV,* right ventricle. (From Crawford MH et al [eds]: *Cardiology,* ed 2, St Louis, 2004, Mosby.)

TABLE E1 Management Guidelines from Professional Societies

	American Academy of Neurology	American College of Chest Physicians
PFO	Evidence is insufficient to determine whether warfarin or aspirin is superior in preventing recurrent strokes or death, but minor bleeding is more frequent with warfarin. There is insufficient evidence to evaluate the efficacy of surgical or endovascular closure.	
PFO alone		Antiplatelet therapy recommended over no therapy. Antiplatelet therapy suggested over warfarin
PFO with other risk factors		Inadequate data available to allow recommendation of optimal medical therapy vs. endovascular or surgical closure
PFO with concomitant deep vein thrombosis or pulmonary embolism	At least 3 mo of anticoagulation	Anticoagulation recommended

PFO, Patent foramen ovale.

The American Heart Association and American College of Cardiology have discouraged the use of devices to close a PFO as a means of preventing recurrent stroke. A recent trial (CLOSURE I) revealed that in patients with cryptogenic stroke or TIA who had a PFO, closure with a device did not offer a greater benefit than medical therapy alone for the prevention of recurrent stroke or TIA. More recent trials have shown that current guidelines may be too restrictive and it may be reasonable to consider a first embolic stroke and no other demonstrable cause as reason enough to close PFO.[1] Among adults who had a cryptogenic ischemic stroke, a recent multicenter trial found that closure of a PFO was associated with a lower rate of recurrent ischemic strokes than medical therapy alone during extended follow-up.[2]

2. In presence of contraindications to anticoagulants

- Contraindications:
  1. Presence of thrombus on the implant site or in the venous system used for access
  2. Active endocarditis or bacteremia
  3. Inadequate size of femoral vein for access
  4. Atrial septal anatomy without an adequate rim to hold the device
  5. Atrial septal anatomy that may result in the occluder obstructing an intracardiac structure
  6. Known hypercoagulable state
  7. Presence of an intracardiac mass or vegetation
- The CardioSEAL Septal Occlusion System and Amplatzer PFO Occluder devices are FDA approved.
- Requires SBE prophylaxis and antiplatelets (aspirin and clopidogrel for first 3 mo, followed by aspirin for another 3 mo) for 6 mo postprocedure. During this period of endothelialization, the risk of recurrent stroke is highest.
- The 1-yr rate of recurrent neurologic events ranged from 0% to 5% with percutaneous closure group vs. 4% to 12% with medical therapy group.
- MRI or metal detectors do not affect these implants, as they are not metallic.

SURGICAL CLOSURE (OPEN THORACOTOMY)

Indications:

- PFO >25 mm in size
- Inadequate rim of tissue around the defect
- Percutaneous device failure
- In presence of other indication for open heart surgery

PEARLS & CONSIDERATIONS

COMMENTS

- PFO is found on transesophageal echocardiography in about 50% of young survivors of stroke without clear cause for their stroke. In these patients, it is unclear whether the PFO was the cause of the stroke or whether it was an incidental finding.
- The frequency of ischemic stroke in patients in with symptomatic pulmonary embolism is higher in patients with PFO than in those without PFO. This finding supports the hypothesis that paradoxical embolism is a significant mechanism of ischemic stroke in patients with PFO.

AUTHOR: **Fred F. Ferri, MD**

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[2]Saver JL et al: Long-term outcomes of patent foramen ovale closure or medical therapy after stroke, *N Engl J Med* 377:1022-1032, 2017.

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Pediatric Medication Errors

BASIC INFORMATION

DEFINITION

A medication error is a preventable event that represents failure of intended prescription, dispensation, or administration of desired drug therapy. Medication errors may result in inappropriate medication use or an adverse drug event (ADE) (i.e., direct harm or injury to the patient).

SYNONYMS

Dosing errors or mistakes. Medication errors are not synonymous with ADEs because not all cause harm (a requirement of ADEs).

- Types of medication errors from the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Index for Categorizing Medication:
  1. Category A: Circumstances or events that have the capacity to cause error.
  2. Category B: An error occurred that did not reach the patient.
  3. Category C: An error occurred that reached the patient but did not cause harm.
  4. Category D: An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm.
  5. Category E: An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.
  6. Category F: An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.
  7. Category G: An error occurred that may have contributed to or resulted in permanent patient harm.
  8. Category H: An error occurred that required intervention necessary to sustain life.
  9. Category I: An error occurred that may have contributed to or resulted in the patient's death.

ICD-10CM CODE
NEC T50.9 Wrong drug (given in error)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- 15% of pediatric outpatient prescriptions are either underdosed (7%) or overdosed (8%).
- Nearly 6% of medication orders for a hospitalized child contain an error. One percent of pediatric medication orders will result in a potential ADE. Less than 1% of medication orders for a child will contain an error that ultimately results in harm or injury.
- Potential for medication errors is three times higher in the pediatric inpatient population and eight times higher in the neonatal inpatient population than in hospitalized adult patients.
- A recent randomized controlled experiment found that 84.4% of parents made one or more dosing errors over nine attempts, especially when using medicine cups.

PEAK INCIDENCE: Among outpatient prescriptions, medication errors occur more frequently in children <4 yr compared with older children (20% vs. 13%).
PREVALENCE: Not applicable
PREDOMINANT SEX AND AGE: Children <4 yr
GENETICS: Not applicable
RISK FACTORS:

- Patient aged <4 yr
- Medications requiring calculation of individual doses based on weight (mg/kg), body surface area (mg/m^2), or age
- Off-label (non-FDA approved) medication use or lack of published information regarding dosing, pharmacokinetics, safety, efficacy, and clinical use
- Wide range of correct drug doses depending on indication
- Different and changing pharmacokinetic parameters between patients of various ages and stages of development
- Lack of computerized prescriber order entry (CPOE), standardized order sets, or alert systems
- Infants or children with multiple health care needs or those in intensive care or emergency department
- Limited ability of child to communicate to prevent error or signal that error has occurred
- Limited parental health literacy, the use of kitchen teaspoons or tablespoons for medication administration, and the use of medication dosing cups (instead of medication oral syringes)
- Limited reserve to withstand errors
- Errors of hospital medication administration and dispensing may be more common during evening, nighttime, and weekend shifts
- Most medications are prepared in concentrations and dosages intended for adult patients and requiring manipulation for administration to children

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Signs and symptoms of toxicity specific to the current drug regimen
- Lack of clinical efficacy of the current drug regimen

ETIOLOGY

Common sources of pediatric medication errors include:

- Prescribing errors: Lack of knowledge of medication; lack of recognition of the age-specific pharmacokinetics of a particular agent; use of medical abbreviations within the prescription or medication order; "look alike, sound alike" substitution errors; doses of liquid medications written as teaspoonfuls or tablespoonfuls
- Calculation errors: mg/kg/*dose* versus mg/kg/*day* dosing recommendations; "tenfold" decimal mistakes such as the use of trailing zeros (1 vs. 1.0) and naked decimals (0.1 vs. 1); patient weight in pounds versus kilograms
- Administration errors: Lack of patient or caregiver understanding; inappropriate medication administration tools; deviation from the "five rights" (i.e., the *right* drug at the *right* dose for the *right* patient by the *right* route at the *right* time)
- Dispensing errors: Inappropriate formulation recommended, prepared, or dispensed; nonstandardized intravenous and extemporaneous oral liquid concentrations; use of adult formulations for children

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Iatrogenic adverse drug reaction (unpreventable ADEs)
- Patient nonadherence

WORKUP

Alert from CPOE systems, deviation from standardized order set, or detection on review of prescription or medication order by pharmacist or nurse:

- Immediately discontinue medication order or prescription
- Determine if suspected error has reached the patient
- Assess harm to patient and intervene if necessary
- Determine source of error if possible
- Resume correct drug therapy with appropriate monitoring of efficacy and toxicity
- Report error to institution or facility for tracking and quality improvement purposes
- Report sentinel events to the Joint Commission

LABORATORY TESTS

Supratherapeutic or subtherapeutic serum drug concentrations (if applicable)

TREATMENT

Management of an ADE may include acute treatment of a toxic reaction or long-term management of a suboptimally treated condition. It should always include the workup described above.

ACUTE GENERAL Rx

If the medication error has reached the patient and resulted in an ADE, immediate intervention may be required. Disclosure to the patient or caregiver of an error resulting in harm to the patient is necessary.

CHRONIC Rx

Long-term management of injury or harm resulting from a medication error may be necessary.

DISPOSITION

- Reestablishing trust with the patient or caregiver after an error that resulted in harm to ensure optimal care in the future may be needed.
- The reporting of medication errors should be nonpunitive in nature and intent on individual education and correction of health systems–related flaws.

REFERRAL

Consultation with a pharmacist trained in pediatric pharmacotherapy may improve individual drug therapy and ensure age-specific drug dosing. Interpreters may be necessary to ensure drug information is accurately relayed to non–English-speaking patients or caregivers. Institutional bioethicists or legal counsel may be needed for significant or sentinel events.

PEARLS & CONSIDERATIONS

COMMENTS

- 20% of ADEs occurring in hospitalized children are preventable.
- The most common tenfold dosing errors in the home involve histamine H_2 antagonist medications and metoclopramide (in children ≤12 mo) and antibiotics or antihistamine-decongestant combination products (in children >12 mo). The top 5 drug classes with tenfold pediatric dosing errors in a university-affiliated hospital setting included opioid analgesics, antimicrobials, anticoagulants, gastrointestinal drugs, and intravenous nutrition.
- Careful attention must always be focused on the impact growth and development has on the pharmacokinetic characteristics of drugs used in children. A child's dose should not exceed that of an adult. Equations that calculate proportionate doses based on body weight or body surface area do not take into consideration these age-related changes.

PREVENTION

- Health systems management: Medication reconciliation at a transition in care (i.e., admission, discharge, or transfer); independent verification of medication orders by pharmacists and administration by nurses; elimination of medical abbreviations within medication orders and prescriptions; use of milliliters as the standard unit of measure; use of oral syringes that only display the metric scale to measure accurate doses; storing pediatric medications separately from adult preparations; use of patient-specific, ready-to-administer or unit doses dispensed by pharmacy; ensuring concentration always appears on the label. Automated clinical decision supports can provide prompts or use of forced functions at the time of prescribing or ordering. Computerized provider order entry can provide standardized order sets and alerts if necessary information is missing. Development and maintenance of order sets, templates, and dose alerts should include a pediatric pharmacist. Medication orders should include a dose calculation requiring prescribers to double-check weight-based dosing. Hospitals should consider use of smart infusion pumps with medication libraries including standard concentrations and dose limits. Institutions should devise event reporting systems to track trends and use a systematic analysis (e.g., root cause analysis) to evaluate medication errors when they occur in practice.
- Communication: Interdisciplinary cooperation can prevent medication errors. Limit interruptions or use distraction-free zones during medication preparation. Ensure appropriate pediatric representation on committees responsible for medication management. Drug information must be presented and reinforced at a level and in a language understandable to patients or caregivers.
- Education: Health care professionals must remain knowledgeable of current standards of care and new drug therapy options. Integrate pharmacists into interdisciplinary rounds. Provide competency and training to all staff. Incorporate bar coding, smart infusion pump technology, standardized intravenous and extemporaneous oral liquid concentrations, and error tracking. Educate parents and caregivers to use oral metric syringes to draw up liquid medications in milliliters.
- Review of drug therapy: Reassess prescriptions for accurate age-appropriate dosing and the indication for drug therapy, monitor for efficacy and toxicity, and reconfirm a patient or caregiver's understanding of the drug regimen.

PATIENT & FAMILY EDUCATION

- Caregivers should always remind a child's doctor of any drug allergies or side effects the child has had in the past.
- Caregivers should be instructed on the correct method of measuring liquid medication doses in milliliters using appropriately gradated oral medication syringes or droppers and to not use common kitchen utensils.
- Do not use over-the-counter cough and cold medicines for children less than 4 yr.
- An up-to-date list of all the medicines, including over-the-counter products and herbal and dietary supplements, a child uses should be kept and shared with each provider the child sees.
- Parents or caregivers should ask questions about medications and voice any concerns. If medication is required during school hours, a registered nurse should administer it whenever possible. Emergency medications such as epinephrine auto-injectors and inhalers should be made available to school staff.
- Counsel child and caregivers, verifying understanding of drug name, purpose, route of administration, dose, dose frequency, potential adverse effects, and management of adverse effects if they occur.

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BASIC INFORMATION

DEFINITION

Pediculosis is lice infestation. Human beings can be infested with three kinds of lice: *Pediculus capitis* (head louse, Fig. 1), *Pediculus corporis* (body louse), and *Phthirus pubis* (pubic, or crab, louse). Lice feed on human blood and deposit their eggs (nits) on the hair shafts (head lice and pubic lice) and along the seams of clothing (body lice). Nits generally hatch within 7 to 10 days. Lice are obligate human parasites and cannot survive away from their hosts for longer than 7 to 10 days. Fig. 2 illustrates the life cycle of the head louse.

SYNONYM

Lice

ICD-10CM CODES

B85.0	Pediculosis due to *Pediculus humanus capitis*
B85.1	Pediculosis due to *Pediculus humanus corporis*
B85.2	Pediculosis, unspecified
B85.4	Mixed pediculosis and phthiriasis
Z20.7	Contact with and (suspected) exposure to pediculosis, acariasis and other infestations

EPIDEMIOLOGY & DEMOGRAPHICS

- There are 6 to 12 million cases of head lice in the United States yearly. The estimated annual direct and indirect cost of head lice infestation in the United States is $1 billion.
- Lice infestation of the scalp is most common in children (girls affected more often than boys).
- Infestation of the eyelashes is most frequently seen in children and may indicate sexual abuse.
- The chance of acquiring pubic lice from one sexual exposure with an infested partner is >90% (most contagious sexually transmitted infection [STI] known).
- Body lice are most common in conditions of poor hygiene.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pruritus with excoriation may be caused by hypersensitivity reaction, inflammation from saliva, and fecal material from the lice.
- Nits can be identified by examining hair shafts (Fig.E3).
- The presence of nits on clothes is indicative of body lice.
- Lymphadenopathy may be present (cervical adenopathy with head lice, inguinal lymphadenopathy with pubic lice).
- Head lice are most frequently found in the back of the head and neck, behind the ears.
- Scratching can result in pustules and crusting.
- Pubic lice may affect the hair around the anus.

ETIOLOGY

Lice are transmitted by close personal contact or use of contaminated objects (e.g., combs, clothing, bed linen, hats).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Seborrheic dermatitis
- Scabies
- Eczema
- Other: Pilar casts, trichonodosis (knotted hair), monilethrix
- Table 1 describes the differential diagnosis of nits

WORKUP

Diagnosis is made by seeing the lice (Fig. 4) or their nits. Combing hair with a fine-toothed comb is recommended because visual inspection of the hair and scalp may miss more than 50% of infestations.

LABORATORY TESTS

Wood's light examination is useful to screen a large number of children: Live nits fluoresce, empty nits have a gray fluorescence, and nits with unborn lice reveal white fluorescence.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patients with body lice should discard infested clothes and improve their hygiene. Items that cannot be washed can be sealed in a plastic bag for 48 hours.
- Combing out nits is a widely recommended but unproven adjunctive therapy.
- Personal items such as combs and brushes should be soaked in hot water for 15 to 30 min. Clothing and bed linens should be washed in hot water (>130 °F; 54.4 °C) and then dried for at least 10 min at the hottest setting.
- Close contacts and household members should also be examined for the presence of lice.

ACUTE GENERAL Rx

The following products are available for treatment of lice:

- Permethrin: Available over the counter (1% permethrin [Nix]) or by prescription (5% permethrin [Elimite]); should be applied to the hair and scalp and rinsed out after 10 min. A repeat application 7 days later is generally not necessary in patients with head lice. It can be applied to clean, dry hair and left on overnight (8-14 hours) under a shower cap. Resistance to permethrin is now widespread.
- Malathion, an organophosphate, is effective in head lice. It is available by prescription. Use should be avoided in children ≤2 yr. It is not commonly used because of its objectionable odor, fear of flammability, and prolonged application time (8-12 hours).
- Spinosad (Natroba) is a newer FDA-approved product for head lice. It is a topical suspension applied to dry hair for 10 min, then rinsed. It may be repeated 7 days later if necessary. It is more effective than permethrin but also much more expensive. It is safe in pregnancy (category B—no evidence of risk in humans).
- Benzyl alcohol lotion, 5% (Ulesfia) can be used for treatment of head lice in patients >6 mo old. The lotion is applied to dry hair and left on for 10 min. Treatment must be repeated after 7 days because the drug is not ovicidal.
- Eyelash infestation can be treated with the application of petroleum jelly rubbed into the eyelashes three times a day for 5 to 7 days. The application of baby shampoo to

FIG. 1 Head louse family. From left to right: Female, male, and nymph. (With permission from Taplin D, Meinking TL: Infestations. In Schachner LA, Hansen RC [eds]: *Pediatric dermatology*, ed 4, Edinburgh, 2011, Mosby, pp 1141–80; Bolognia JL et al: *Dermatology*, ed 4, Philadelphia, 2018, Elsevier.)

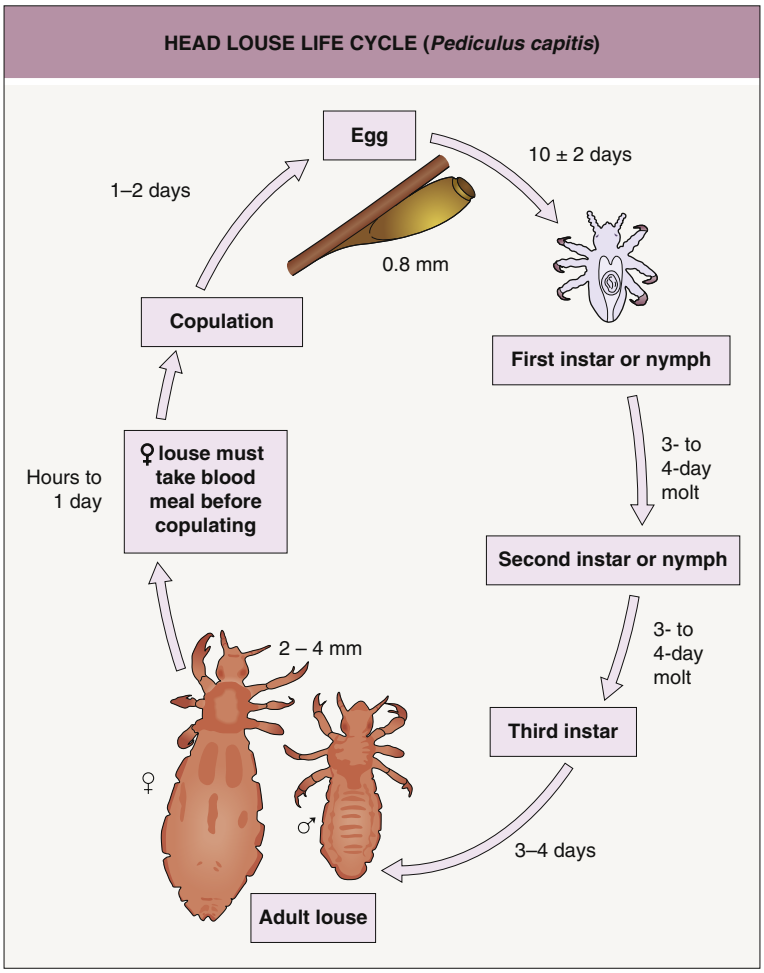

FIG. 2 Head louse life cycle (*Pediculus capitis*). (From Bolognia JL et al: *Dermatology*, ed 4, Philadelphia, 2018, Elsevier.)

the eyelashes and brows three or four times a day for 5 days is also effective. The use of fluorescein drops applied to the lids and eyelashes is also toxic to lice.

- In patients who have previously not responded to treatment or in whom resistance with 1% permethrin cream rinse occurs, a 10-day course of trimethoprim-sulfamethoxazole (TMP-SMX) 8 mg/kg/day in divided doses is an effective treatment for head lice infestation, especially for eyelash infestations with *Phthirus pubis.*
- Ivermectin, an antiparasitic drug, given as an oral dose of 400 mcg/kg of body weight on days 1 and 8, is effective for head lice resistant to other treatments (currently not FDA approved for pediculosis). Ivermectin 0.5% lotion is FDA approved as a single-use topical treatment for head lice in patients 6 mo or older. Cost is more than $200 for 4 oz.
- Fig. 5 summarizes treatments for head lice.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients with pubic lice should notify their sexual contacts. Sex partners within the last month should be treated.

TABLE 1 Differential Diagnosis of Nits

Diagnosis	Comment
Nits	Firmly adherent to hair shaft; not easily removed with fingers
Seborrheic dermatitis (dandruff)	Diffuse scalp scaling; scales occasionally adhere to hair but easy to remove; scalp erythema may be present
Hair casts	Keratin protein that encircles hair shaft; easily removed
Piedra	Fungal infection of hair; firm nodules attached to hair shafts, white or black in color
Psoriasis	Thick silvery scales, often present overlying red plaques on the scalp
Hair products	Hairspray, mousse, gel

From Paller AS, Mancini, AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.

FIG. 4 Body louse, *Pediculus humanus* var. *corporis,* as it was obtaining a blood meal from human host. (Courtesy Public Health Image Library, Centers for Disease Control and Prevention. From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

- Parents of patients should also be educated that head lice infestation (unlike body lice) does not indicate poor hygiene.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Lice (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

TREATMENTS FOR HEAD LICE				
Treatment	**Group**	**Administration on days 1 and 8**	**Concerns**	**Efficacy & resistance**
Pyrethrins (0.33%) synergized with piperonyl butoxide (4%), various formulations*	Natural botanicals	Topical application for 10 minutes to dry hair	Allergic reactions in individuals with sensitivity to chrysanthemums, ragweed, and related plants	Poor–fair; resistance common
Permethrin cream rinse or lotion (1%)*	Synthetic pyrethroid	Topical application for 10 minutes to clean, dry hair	None	Poor–fair; resistance common
Permethrin cream (5%)†	Synthetic pyrethroid	Topical overnight application to clean, dry hair	Allergic contact dermatitis in individuals with sensitivity to formaldehyde	Poor–fair; resistance common
Lindane shampoo (1%)	Organochlorine	Topical application for 4 minutes to clean, dry hair, then add water to lather and rinse	Potential CNS toxicity; not recommended for infants, children, breastfeeding mothers or pregnant women (category C)	Poor; resistance common
Carbaryl shampoo (0.5%)	Carbamate cholinesterase inhibitor	Topical application for 8–12 hours	Possible carcinogen	Poor–fair; resistance common (not approved in the U.S.)
Benzyl alcohol lotion (5%)§	Alcohol	Topical application for 10 minutes to dry hair	Potential skin irritation	Good; no resistance noted to date
Dimethicone (4%)	Silicone oil	Topical application for 15 minutes or overnight	None	Good
Spinosad cream rinse (0.9%)§	Bacterial fermentation product	Topical application for 10 minutes to dry hair	None	Good; no resistance noted to date
Malathion lotion or gel (0.5%)‡	Organophosphate cholinesterase inhibitor	Topical application for 8–12 hours to dry hair (Ovide® and gel products with isopropyl alcohol base are effective at 20 minutes)	Flammable isopropyl alcohol base; burning or stinging at sites of eroded skin	Excellent (in U.S.); resistance noted in Europe and Australia, but to date not in U.S.
Ivermectin solution (0.5%)§	Avermectin	Topical application for 10 minutes to dry hair	Potential skin and eye irritation	Excellent; no resistance noted to date
Oral ivermectin (available as 3 mg tablets)		Oral dose of 200–400 mcg/kg	Potential CNS toxicity; not recommended for children weighing <33 pounds (15 kg), breastfeeding mothers or pregnant women (category C)	

*Over-the-counter products.
†Approved for individuals ≥2 mo of age; pregnancy category B.
‡Approved for individuals ≥6 yr of age; pregnancy category B.
§Approved for individuals ≥6 mo of age; pregnancy category B.

FIG. 5 Treatments for head lice. In general, treatments should be given on two separate occasions, 1 wk apart. However, the FDA-approved regimen for treatment of head lice with 0.5% ivermectin solution is a single application. AirAllé ® is an FDA-cleared medical device that uses hot air to treat head lice via dehydration of their eggs and, to a lesser degree, hatched lice. Abametapir 0.74% lotion, an ovicidal metalloprotease inhibitor, has been shown in phase 3 clinical trials to have efficacy in the treatment of head lice. *CNS,* Central nervous system; *FDA,* U.S. Food and Drug Administration. (Bolognia JL et al: *Dermatology*, ed 4, Philadelphia, 2018, Elsevier.)

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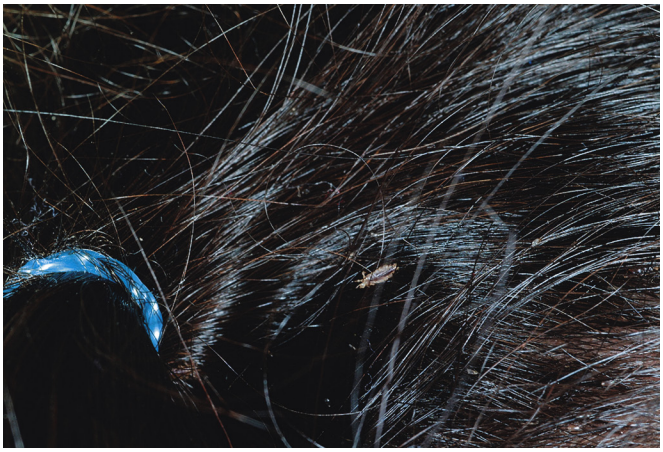

FIG. E3 Pediculosis capitis. Note the live head louse, easily seen with the naked eye. (From Paller AS, Mancini, AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

Pedophilic Disorder

BASIC INFORMATION

DEFINITION

According to the DSM-5, pedophilic disorder (PD) is one of eight identified paraphilic disorders. A paraphilic disorder is described as "any intense and persistent sexual interest other than sexual interest in genital stimulation or preparatory fondling with phenotypically normal, physically mature, consenting human partners," that either causes distress or functional impairment to the individual or entails personal harm or risk of harm to others.

Diagnostic criteria for PD include the presence of recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving sexual activity with a prepubescent child or children (generally age 13 yr or younger) that occur over a period of at least 6 mo. The individual has acted on these urges or the urges have caused significant distress or interpersonal difficulty. The individual must be at least 16 yr and at least 5 yr older than the object of the sexual interest. DSM-5 subtypes pedophilic disorder into categories based on his/her victim gender preference (males, females, or both), on the exclusivity of the sexual urges (attracted only to children or not), and on his/her relationship with the victim ("limited to incest"). Individuals in late adolescence involved in ongoing sexual relationships with 12- or 13-yr-old children are not included for this disorder in DSM-5.

SYNONYM

Pedophilia

ICD-10CM CODE
F65.4 Pedophilia
DSM-5 CODE
302.2 Pedophilic disorder

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Unknown, with likely maximum of 5% in the male population and much smaller in the female population.
ONSET: Around the time of puberty, as adolescents begin to develop sexual interest.
PREDOMINANT SEX: The significant majority of pedophiles are men (females commit roughly 1%-6% of child sexual assault).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Diagnosis is made by clinical interview and is often complicated by reluctance to disclose symptoms unless the behaviors have already been identified.
- Legal involvement is common and may be the reason for presentation for care.
- Sex offenders have higher rates of *general* crime recidivism than *sexual* crime recidivism. When known child molesters are rearrested, ~40% of their rearrests are for sexual offenses.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Antisocial personality disorder
- Conduct disorder
- Substance use disorder or intoxication
- Obsessive-compulsive disorder

WORKUP

Requires comprehensive data from multiple sources, including self-report, past sexual offense convictions, past and present partner report, psychophysiologic assessments, forensic computer analysis, and/or assessment tools. Deviant sexual preferences and lifestyle instability/criminality are strongly associated with general sexual recidivism. Therefore, clinical interview should explore sexual preferences (sex drive, paraphilic interests, victim characteristics), past sexual behaviors (including inquiry into the use of child pornography), and a history of rule violation, substance abuse, and risk taking. It is also important to explore opportunities that the individual has to be around children as well as exploring an individual's strengths and protective factors.

SCALES AND LABORATORY TESTS

- Penile plethysmography: The penile volume or circumference is measured in response to a variety of sexual materials. The result may be a predictor of sexual recidivism for individuals who have committed sexual offenses. However, ~20% to 30% of individuals tested are considered low or nonresponders. Further, in the U.S., possession of the viewing material (child pornography) presents a legal dilemma for researchers. Other limitations include its lack of applicability to females, lack of applicability to males with impotence, and ability of individuals to try to suppress sexual feelings via distraction. This form of testing is not currently admissible in court for the purpose of determining guilt.
- Viewing time: Viewing time is correlated with self-reported sexual interest and phallometric sexual arousal to children. No studies report that this measure predicts recidivism.
- Both of the above tests require the provider to show visual stimuli that may violate U.S. laws around possession of child pornography.
- Scales: For the prediction of general sexual recidivism, the most accurate approach appears to be the use of certain actuarial and mechanical measures. Some of the measures include the Static 99, MNSOST-3, Risk Matrix-2000, and the SVR 20 for adults, or the J-SOAP-II, ERASOR, and J-SORRAT-II for juveniles+. An individual's likelihood to recidivate is estimated based on the average risk of a group of individuals with similar characteristics.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Treatment for sexually aggressive behaviors in general typically incorporates multiple modalities, including individual, group, family, social skill, behavioral, and educational therapies.
- Key elements of treatment include taking responsibility for behaviors, developing empathy for victims, developing skills to prevent re-offending.
- General goals of treatment include improved control of deviant behaviors, impulse control, and coping; enhanced conflict resolution, anger management, and social skills; enhanced sense of empathy; understanding of cycle of thoughts, feelings, and events leading to inappropriate behaviors; respect within male-female relationships; and sexual education promoting healthy sexual behaviors (especially when working with juveniles).
- Community interventions might include the education of parents (re: high-risk situations, neighborhood sex offenders) and the education of children (re: assertiveness training, etc.).

PHARMACOLOGIC THERAPY

- *All used off-label in adults, adolescents, and children*
- Goals of treatment include suppression and elimination of deviant sexual fantasies, elimination of deviant sexual urges and behaviors, and reduction of risk for recidivism
- Selective serotonin reuptake inhibitors (SSRIs)
- Primary choice in adolescents, since few side effects (especially on adolescent physiological development)
- Case reports and small studies supporting use of fluoxetine, sertraline
- Antiandrogens and hormonal agents
- Medroxyprogesterone acetate (MPA):
  1. Most common hormonal agent in the U.S.
  2. Evidence mostly based on open trials
  3. Reduces sex drive, sexual fantasy, sexual activity
  4. Side effects include nausea, vomiting, feminization, weight gain, decreased sperm production, diabetes mellitus, headaches, deep vein thrombosis, hot flashes
  5. Induces testosterone-reductase in the liver, increasing metabolic clearance of testosterone and decreasing plasma testosterone
  6. Also has progestinic effect, leading to reduction of gonadotropin secretion
- Cyproterone acetate (CPA):
  1. Most common in Canada
  2. Antiandrogenic, antigonadotropic, progestinic effects

3. Principal effect at androgen receptors—blocks intracellular testosterone uptake and metabolism of androgen
4. Similar effects to MPA
5. Effects are dose dependent
6. Research indicates decrease in posttreatment recidivism rates for paraphilias
7. Side effects include decreased erections, masturbation, and sexual intercourse; liver dysfunction; adrenal suppression; osteoporosis; osteopenia

- Should be used only rarely by psychiatrists with experience in conjunction with pediatric endocrinologist for severe behaviors (short-term use)
- Luteinizing hormone-releasing hormone (LHRH) agonists
  - Leuprolide acetate most common in the United States
  - Goserelin acetate available, triptorelin acetate likely available soon
  - Specifically target paraphilias
  - Pharmacologic castration effect
  - Not recommended in children <18 yr, only indicated for severe symptoms in adults
  - Overstimulation of hypothalamic-pituitary axis leading to inhibition of gonadotropin secretion
  - Reduction or elimination of testosterone makes them useful in treating prostate cancer

REFERRAL

Refer to specialty mental health.

PEARLS & CONSIDERATIONS

- Individuals with pedophilia who have had no known risk of prior sexual contacts with children are at unknown risk to offend.
- Physicians must be aware of reporting requirements in their jurisdiction.

RELATED CONTENT

Pedophilia (Patient Information)

AUTHORS: **Hassan M. Minhas, MD,** and **Elizabeth A. Lowenhaupt, MD**

SUGGESTED READINGS

Fazio RL: Toward a neurodevelopmental understanding of pedophilia, *J Sex Med* 2018.

Lett TA et al: Multimodal neuroimaging measures and intelligence influence pedophile child sexual offense behavior, *Eur Neuropsychopharmacol* 2018.

Nassau C et al: Executive functioning in pedophilia and child sexual offending, *J Int Neuropsychol Soc* 23(6):460-470, 2017.

Pelvic Abscess PTG

BASIC INFORMATION

DEFINITION

Pelvic abscess is an acute or chronic infection, most commonly involving the pelvic viscera. Treatment requires directed therapy including broad-spectrum antimicrobials and, if medical therapy fails, surgical intervention. There are four categories based on etiologic factors:

- Ascending infection, spreading from cervix through endometrial cavity to adnexa, forming a tuboovarian complex
- Infection occurring in the puerperium, which spreads to the adnexa from the endometrium or myometrium by a hematogenous or lymphatic route
- Abscess complicating pelvic surgery
- Involvement of the pelvic viscera as a result of spread from contiguous organs, such as appendicitis or diverticulitis

SYNONYMS

Tuboovarian abscess (TOA)
Vaginal cuff abscess

ICD-10CM CODES	
K63.0	Abscess of intestine
K65.1	Peritoneal abscess
K68.11	Postprocedural retroperitoneal abscess
K68.12	Psoas muscle abscess
K68.19	Other retroperitoneal abscess
N70.93	Salpingitis and oophoritis, unspecified
N70.0	Acute salpingitis and oophoritis
N70.1	Chronic salpingitis and oophoritis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- 34% of hospitalized patients with pelvic inflammatory disease
- 1% to 2% of patients undergoing hysterectomy, most frequently with vaginal approach
- Peak incidence third to fourth decade

RISK FACTORS: Same risk factors as for pelvic inflammatory disease, although in 30% to 50% of patients there is no prior history of salpingitis before abscess forms.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abdominal or pelvic pain (90%)
- Fever or chills (50%)
- Abnormal bleeding (21%)
- Vaginal discharge (28%)
- Nausea (26%)
- Up to 60% to 80% present without fever or leukocytosis; absence of these findings should not exclude diagnosis

ETIOLOGY

- Mixed flora of anaerobes, aerobes, and facultative anaerobes, such as *Escherichia coli, Bacteroides fragilis, Prevotella* spp., aerobic streptococci, and *Peptococcus* and *Peptostreptococcus* spp.
- *Neisseria gonorrhoeae* and *Chlamydia* are the major etiologic bacteria in cervicitis and salpingitis but are rarely found in abscess cavity cultures.
- In elderly patients consider diverticular disease.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pelvic neoplasms, such as ovarian tumors and leiomyomas.
- Ovarian torsion.
- Inflammatory masses involving adjacent bowel or omentum, such as ruptured appendicitis or diverticulitis.
- Pelvic hematomas, as may occur after cesarean section or hysterectomy.

LABORATORY TESTS

- CBC with differential
- Aerobic as well as anaerobic cultures of cervix, blood, urine, sputum, peritoneal cavity (if entered), and abscess cavity before starting antibiotics
- Pregnancy test in patients of reproductive age

IMAGING STUDIES

- Sonogram: Noninvasive, inexpensive study to confirm diagnosis, estimate size of abscess, and monitor response to therapy; sensitivity >90%
- CT scan: Used for both diagnosis and therapy (CT-guided drainage) (Fig. E1)
  1. Useful where sonogram provides insufficient information, as with intraabdominal abscesses
  2. Success rate with CT-guided abscess drainage: Unilocular, 90%; multilocular, 40%

TREATMENT

Major concerns:

- Desire for future fertility
- Likelihood of rupture of abscess, with resulting peritonitis, septic shock, and morbid sequelae

ACUTE GENERAL Rx

- Clinical quandary is whether patient requires immediate laparoscopic surgery (uncertain diagnosis or suspicion of rupture) or management with IV antibiotics, reserving surgery for those with inadequate clinical response (e.g., 48 to 72 hr of therapy, with persistent fever or leukocytosis, increasing size of mass, or suspicion of rupture).
- Surgery indicated in poor response to medical therapy. Early surgery may be needed in those with large adnexal masses (>8 cm), or in immunocompromised patients.
- Antibiotic combinations:
  1. Clindamycin 900 mg IV q8h or metronidazole 500 mg IV q6 to 8h plus gentamicin either 5 to 7 mg/kg q24h or 1.5 mg/kg q8h
  2. Alternatives: Ampicillin-sulbactam 3 g IV q6h or cefoxitin 2 g IV q6h or cefotetan 2 g IV q12h plus doxycycline 100 mg IV q12h
- During medical management, high index of suspicion for acute rupture, such as acute worsening of abdominal pain or new-onset tachycardia and hypotension, mandating immediate surgical intervention after patient stabilization.
- Surgical options:
  1. Laparoscopy with drainage and irrigation
  2. CT-guided drainage (interventional radiology)
  3. Transvaginal colpotomy (abscess must be midline, dissect rectovaginal septum, and be adherent to vaginal fornix)
  4. Laparotomy, including total abdominal hysterectomy with bilateral salpingo-oophorectomy or unilateral salpingo-oophorectomy
  5. Evidence of ruptured tuboovarian abscess is a surgical emergency

DISPOSITION

- Of patients treated with medical therapy, response in 75%, with a 50% pregnancy rate. Pregnancy rate decreases with recurrent episodes.
- No response in 30% to 40%; can be treated with either CT-guided drainage or surgical intervention, keeping in mind that unilateral adnexectomy may give equal chance of cure versus hysterectomy, yet preserve reproductive potential.

REFERRAL

If patient has a tuboovarian abscess, refer to gynecologist.

PEARLS & CONSIDERATIONS

COMMENTS

- If *Actinomyces* species is isolated from culture, treatment with penicillin is required for an extended period (6 wk to 3 mo).
- Most common cause of preventable death: Physician delay in diagnosis.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Pelvic Abscess (Patient Information)
Pelvic Inflammatory Disease (Related Key Topic)

AUTHORS: **Anthony Sciscione, DO,** and **Ella Stern, MD**

SUGGESTED READING

To J et al: Image-guided drainage versus antibiotic-only treatment of pelvic abscesses: short-term and long-term outcomes, *Fertil Steril* 102(4):1155-1159, 2014.

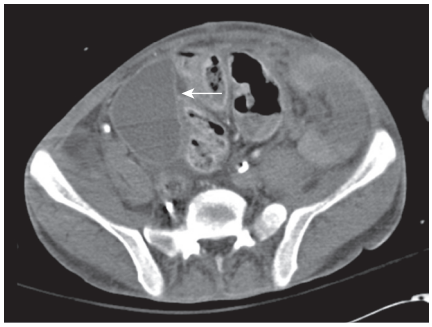

FIG. E1 Computed tomography with oral and intravenous contrast material in patient with large pelvic abscess. Abscess cavity demonstrates classic rim enhancement of abscess wall. Percutaneous drainage should be performed under image guidance. (From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, WB Saunders.)

Pelvic Congestion Syndrome

BASIC INFORMATION

DEFINITION

Pelvic congestion syndrome (PCS) is a poorly understood association between varicose or dilated pelvic veins and chronic pelvic pain (CPP).

SYNONYMS

PCS
Pelvic venous syndrome
Pelvic venous insufficiency
Pelvic varices
Pelvic vascular dysfunction

ICD-10CM CODE

N94.89 Other specified conditions associated with female genital organs and menstrual cycle

EPIDEMIOLOGY & DEMOGRAPHICS

- Reported in reproductive-age women. Incidence and prevalence are unclear. Pelvic varices are reported in 10% to 30% of CPP patients.
- Proposed risk factors include pregnancy, obesity, increased abdominal pressure, pelvic surgery, estrogen exposure, valvular insufficiency, and presence of other varicose veins (especially vulvar or perineal). Similar pain and dilation have also been reported in patients with mechanical compression in the setting of nutcracker syndrome, May-Thurner syndrome, thrombosis, or pelvic masses.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- There are no universally accepted or well-defined clinical criteria for the diagnosis of PCS. It is generally described as an association between CPP (at least 3 to 6 mo duration) and evidence of pelvic vascular insufficiency on imaging in the absence of other causes of pain.
- Common presenting features include sensation of a dull ache or heaviness, dysmenorrhea, dyspareunia, ovarian point tenderness on examination, and pain exacerbation with increases in abdominal pressure (such as pregnancy or standing position). Left-sided pathology is described more commonly, likely due to the anatomic course of the left ovarian vein into the renal vein as opposed to the inferior vena cava on the right side.

ETIOLOGY

Postulated mechanisms include the activation of pain receptors or release of nociceptive factors from local stasis and stretch of the venous walls.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for CPP is broad and includes gynecologic, urologic, gastrointestinal, musculoskeletal, neurologic, and psychologic disorders. Common causes of CPP include endometriosis, interstitial cystitis, irritable bowel syndrome, pelvic floor myalgia, and myofascial pain.

WORKUP

- Detailed history and physical examination, imaging, and evaluation for other causes of CPP are part of the workup. Evaluation often requires a multidisciplinary approach and may include trials of medical management for other common pain conditions.
- There are no specific laboratory tests for PCS.

IMAGING STUDIES

- Pelvic varices are seen in 10% to 38% of asymptomatic women and thus have low specificity for pelvic congestion syndrome. Similarly, there are no agreed-upon criteria for imaging findings. Pelvic ultrasound, mitral regurgitation (MR), CT, and catheter venography are all reasonable considerations for imaging workup.
- Pelvic ultrasound (Fig. E1) is considered first line for CPP, as it can be used to assess both pelvic anatomy and vasculature by evaluating Doppler flow. Common findings include:
  1. Slow (<3 cm/s), reversed, or retrograde blood flow
  2. Ovarian vein diameter >4 mm or >6 mm
  3. Pelvic congestion, tortuous venous plexuses, dilated arcuate pelvic veins
  4. Evidence of venous valvular incompetence
  5. Worsening findings with standing or Valsalva
- MR and CT venography have low specificity, are expensive, and may require radiation (CT), although they are less invasive than catheter venography.
  1. Suggested criteria include four or more tortuous parauterine veins, parauterine vein diameter >4 mm, and ovarian vein diameter >8 mm.
- Catheter venography is often reserved for cases in which intervention is planned. Findings suggestive of PCS include:
  1. Ovarian vein diameter >6 mm
  2. Pelvic vein diameter >5 to 10 mm
  3. Contrast retention >20, >40, or >60 sec or subjectively slow
  4. Tortuosity (absent/moderate/severe)
  5. Congestion of pelvic venous plexus, opacification of internal iliac vein, or filling of vulvovaginal/thigh varices
- Laparoscopy has been considered for the diagnosis and treatment of PCS, although this may be more beneficial for other causes of pelvic pain, such as endometriosis, ovarian cysts, or adhesive disease.

TREATMENT

- Referral to multidisciplinary teams, including gynecology, GI, pain specialists, physical therapy, and interventional radiology, may be indicated when the diagnosis is suspected to evaluate for other causes of pelvic pain.
- Clinical trials of oral medroxyprogesterone acetate, subcutaneous etonogestrel, and

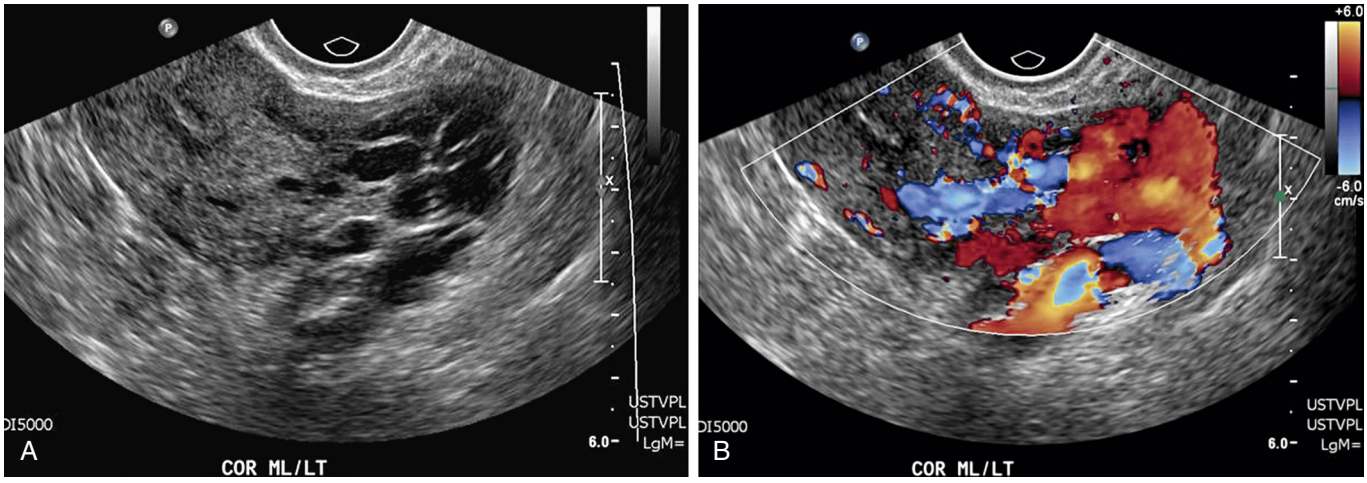

FIG. E1 Pelvic congestion syndrome. Transvaginal ultrasound without **(A)** and with **(B)** color Doppler imaging showing tortuous tubular anechoic structures in the adnexa that fill with color Doppler signal, compatible with dilated pelvic venous plexuses seen in pelvic congestion. (From Fielding JR et al: *Gynecologic imaging*, Philadelphia, 2011, WB Saunders.)

gonadotropin-releasing hormone agonists have shown a statistically significant decrease in pain for PCS patients. Other oral progesterones, danazol, and combined estrogen/progesterone contraceptives have also been suggested for medical treatment of PCS.

- Percutaneous endovascular embolization and sclerotherapy are the most common therapies studied with PCS. Symptomatic improvement is reported in 50% to 80% of patients and may increase with time. Complications were noted in approximately 2% of patients, including coil misplacement, coil migration, vein perforation, and phlebitis. Statistically significant decreases in pain scores are reported in most studies examining percutaneous treatment, although evidence is low quality and pooled from multiple small studies with inconsistent criteria for diagnosis and outcomes. Data on menses, fertility, and pregnancy are limited with no known complications.
- Laparoscopic ligation or excision of ovarian veins, hysterectomy, and salpingo-oophorectomy have been studied but have increased complications and similar efficacy to endovascular treatment.

PEARLS & CONSIDERATIONS

COMMENTS

- Pelvic congestion syndrome is a controversial condition describing the association between chronic pelvic pain and pelvic varices without clear diagnostic criteria.
- The differential diagnosis for CPP is broad, and medical treatment for PCS overlaps with methods that are effective for other common causes of CPP.
- Some low-quality evidence suggests symptom improvement with embolization or sclerotherapy.

AUTHOR: **Rachel Wright Heinle, MD, FACOG,** and **Allison Dillon, MD**

SUGGESTED READINGS

Borghi C, Dell'Atti L: Pelvic congestion syndrome: the current state of the literature, *Arch Gynecol Obstet* 293:291-301, 2016.

Daniels JP et al: Effectiveness of embolization or sclerotherapy of pelvic veins for reducing chronic pelvic pain: a systematic review, *J Vasc Interv Radiol* 27:1478-1486, 2016.

Glovicczki P et al: The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum, *J Vasc Surg* 53:16S, 2011.

Phillips D et al: Pelvic congestion syndrome: etiology of pain, diagnosis, and clinical management, *J Vasc Interv Radiol* 25:725-733, 2014.

Tu FF et al: Pelvic congestion syndrome-associated pelvic pain: a systematic review of diagnosis and management, *Obstet Gynecol* 65(5), 2010.

BASIC INFORMATION

DEFINITION

Pelvic inflammatory disease (PID) is infection and inflammation of the upper female genital tract (including uterus, fallopian tubes, ovaries, and/or pelvic peritoneum) unrelated to pregnancy or surgical intervention. PID can be classified as acute (≤30 days duration), subclinical, or chronic (>30 days duration).

SYNONYMS

PID
Salpingitis
Oophoritis
Adnexitis
Pyosalpinx
Tubo-ovarian abscess
TOA

ICD-10CM CODES

A18.17	Tuberculous female pelvic inflammatory disease
A52.76	Syphilitic pelvic inflammatory disease
A54.2*	Gonococcal pelviperitonitis and other gonococcal genitourinary infections
A54.24	Gonococcal female pelvic inflammatory disease
A56.1*	Chlamydial infection of pelviperitoneum and other genitourinary organs
A56.11	Chlamydial female pelvic inflammatory disease
A56.19	Other chlamydial genitourinary infection
N70*	Salpingitis and oophoritis
N70.0*	Acute salpingitis and oophoritis
N70.01	Acute salpingitis
N70.02	Acute oophoritis
N70.03	Acute salpingitis and oophoritis
N70.1*	Chronic salpingitis and oophoritis
N70.11	Chronic salpingitis
N70.12	Chronic oophoritis
N70.13	Chronic salpingitis and oophoritis
N70.9*	Salpingitis and oophoritis, unspecified
N70.91	Salpingitis, unspecified
N70.92	Oophoritis, unspecified
N70.93	Salpingitis and oophoritis, unspecified
N71*	Inflammatory disease of uterus, except cervix
N71.0	Acute inflammatory disease of uterus
N71.1	Chronic inflammatory disease of uterus
N71.9	Inflammatory disease of uterus, unspecified
N72	Inflammatory disease of cervix uteri
N73*	Other female pelvic inflammatory diseases
N73.0	Acute parametritis and pelvic cellulitis
N73.1	Chronic parametritis and pelvic cellulitis
N73.2	Unspecified parametritis and pelvic cellulitis
N73.3	Female acute pelvic peritonitis
N73.4	Female chronic pelvic peritonitis
N73.5	Female pelvic peritonitis, unspecified
N73.6	Female pelvic peritoneal adhesions (postinfective)
N73.8	Other specified female pelvic inflammatory diseases
N73.9	Female pelvic inflammatory disease, unspecified
N74	Female pelvic inflammatory disorders in diseases classified elsewhere

*Indicates nonbillable codes

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE: Pelvic inflammatory disease is most often diagnosed in young, sexually active women. The incidence of PID is difficult to ascertain given its broad diagnostic criteria, its propensity to be missed as a diagnosis, and the challenges with follow-up due to patients seeking urgent or emergent care for this condition. The Centers for Disease Control and Prevention estimates 1 million new cases of PID are diagnosed yearly. The incidence may be rising given recent sharp increases in STDs associated with PID in the United States. PID has long-term health risks for women, including recurrent infection, chronic pelvic pain, pelvic adhesive disease, and tubal disease resulting in ectopic pregnancy and infertility.

RISK FACTORS:

- Sexually active adolescent and young women
- Previous episode of PID
- Prior chlamydial infection
- Multiple or new sexual partners within past 12 mo
- Sexual partner diagnosed with sexually transmitted infection (STI)
- Nonuse of barrier contraception

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Lower abdominal pain
- Abnormal vaginal discharge
- Abnormal uterine bleeding
- Postcoital bleeding
- Dysuria
- Dyspareunia
- Fever
- Nausea and vomiting (suggestive of peritonitis)

PHYSICAL FINDINGS

- Fever
- Abdominal tenderness
- Abnormal vaginal discharge
- Cervical friability
- Cervical motion tenderness
- Adnexal tenderness
- Adnexal mass
- Right upper quadrant tenderness (perihepatitis): 5% of PID cases

NOTE: Women with PID may be asymptomatic and/or have a benign physical examination.

ETIOLOGY

Pelvic inflammatory disease occurs as a result of ascending infection from the lower genital tract. Infections are often polymicrobial, and although gonorrheal and chlamydial infections are commonly implicated in the development of PID, fewer than 50% of women test positive for these organisms. This is likely due in part to increased STI screening efforts. PID may also arise in the setting of organisms associated with normal vaginal flora such as:

- *Bacteroides fragilis*
- *Escherichia coli* and other enteric gram-negative rods
- *Gardnerella vaginalis*
- *Haemophilus influenzae*

Rarer infectious causes include the following: *Mycoplasma hominis, Ureaplasma urealyticum, Mycoplasma genitalium* (a concern due to antibiotic resistance), *Mycobacterium tuberculosis* (an important cause in developing countries), and cytomegalovirus (CMV).

DIAGNOSIS

Diagnosis of PID is made when a patient has clinical or pathologic evidence of upper genital tract infection and inflammation. Although no single test or measure reliably diagnoses the spectrum of disorders that comprise PID:

- Providers should maintain a low threshold for diagnosis and treatment of PID given significant long-term health risks associated with the disease, especially if untreated
- Definitive criteria for diagnosis of PID include:
  1. Laparoscopic abnormalities consistent with PID
  2. Histopathologic evidence of endometritis in women with clinical suspicion for PID
  3. Transvaginal sonography or other imaging techniques showing thickened, fluid-filled tubes, with or without free pelvic fluid or tubo-ovarian complex
- The CDC suggests that women with risk factors, abdominal or pelvic pain, and any pelvic tenderness (cervical, uterine, and/or adnexal) be treated for PID

DIFFERENTIAL DIAGNOSIS

- Appendicitis
- Ectopic pregnancy
- Intrauterine/other pregnancy
- Ovarian cyst
- Adnexal torsion
- Endometriosis
- Urinary tract infection (cystitis or pyelonephritis)

WORKUP

- History—as in risk factors and clinical presentation, previously
- Physical examination—as in physical findings, previously

LABORATORY TESTS

- Wet mount: Clue cells, increased white cells
- Gram stain of endocervical exudate: >30 polymorphonuclear cells per high-power field correlates with chlamydial or gonococcal infection
- Endocervical cultures for *N. gonorrhoeae* and *C. trachomatis*
- Fallopian tube aspirate or peritoneal exudate culture if laparoscopy performed
- WBC: Leukocytosis
- Elevated acute phase reactants: ESR >15 mm/hr, C-reactive protein
- HCG to rule out intrauterine or ectopic pregnancy
- HIV, with consideration for other STI screening such as RPR, HBsAg, Hep C Ab (HIV increases incidence of TOA)

IMAGING STUDIES

Ultrasonography is commonly used to assess for PID and can be used to determine inpatient vs. outpatient treatment by presence or absence of TOA. Findings include:

- Thick-walled adnexal mass with heterogenous or cystic contents suggestive of abscess
- Dilated fallopian tubes (note that normal fallopian tubes are rarely identified on ultrasonography)
- "Cogwheel sign" indicating thickened fallopian tube walls
- Heterogenous fluid within the endometrium

CT scan or MRI may be useful to better characterize adnexal masses and/or rule out other pathology such as appendicitis or renal calculus. Choice of imaging modality will depend on clinical suspicion, logistical access, and associated cost.

PROCEDURES

Endometrial biopsy that reveals endometritis may support a diagnosis of PID. Laparoscopy has been utilized as a gold standard for diagnosing PID, but due to the invasive nature of this procedure and the risks, and costs associated, it is rarely indicated as a diagnostic tool.

Rx TREATMENT

Primary management of PID is medical, with broad-spectrum antibiotics administered in an outpatient setting. Inpatient treatment should be initiated when:

- Surgical emergency is not excluded
- Tubo-ovarian abscess is present
- Patient is unable or unwilling to complete outpatient treatment (including medication regimen and clinical follow-up)
- Outpatient treatment fails to improve symptoms in 48 to 72 hours
- Pregnancy, immunodeficiency, or other complicating medical condition exists

Evidence-based guidelines recommended by the CDC for acute PID are as follows:

INPATIENT REGIMENS

Recommended parenteral regimens

- Cefotetan 2 g IV q12h *PLUS* doxycycline 100 mg PO or IV q12h OR
- Cefoxitin 2 g IV q6h *PLUS* doxycycline 100 mg PO or IV q12hOR
- Clindamycin 900 mg IV q8h *PLUS* gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) q8h. Single daily dosing (3-5 mg/kg) can be substituted.

Alternative parenteral regimen

- Ampicillin/sulbactam 3 g IV q6h *PLUS* doxycycline 100 mg PO or IV q12h

When clinical improvement is apparent based on symptoms, physical exam, and laboratory criteria, antibiotics may be transitioned from IV to PO with doxycycline PO or clindamycin PO (depending on the regimen selected) administered to complete 14 days of total antibiotic therapy. If a patient does not improve despite use of a recommended antibiotic regimen, further workup and potential procedural intervention are warranted.

OUTPATIENT REGIMENS

Recommended intramuscular/oral regimens

- Ceftriaxone 250 mg IM in a single dose *PLUS* doxycycline 100 mg PO bid for 14 days
  WITH or WITHOUT metronidazole 500 mg PO bid for 14 days
  OR
- Cefoxitin 2 g IM in a single dose and probenecid, 1 g PO administered concurrently in a single dose *PLUS* doxycycline 100 mg PO bid for 14 days
  WITH or WITHOUT metronidazole 500 mg PO bid for 14 days
  OR
- Other third-generation cephalosporin (ceftizoxime or cefotaxime) *PLUS* doxycycline 100 mg orally bid for 14 days
  WITH or WITHOUT metronidazole 500 mg orally twice a day for 14 days

Alternative intramuscular/oral regimen

- Azithromycin 1 g PO once weekly for 2 wk PLUS ceftriaxone 250 mg IM in a single dose

TREATMENT CONSIDERATIONS

- Antimicrobials should include coverage against *N. gonorrhoeae* and *C. trachomatis* even if these organisms are not identified on culture.
- Due to increasing antibiotic resistance of *N. gonorrhoeae*, fluoroquinolones should be avoided in the treatment of PID. If gonorrhea is isolated in a woman with PID, addition of azithromycin 1 g orally one time should be considered in treatment.
- Women should avoid sexual activity until they and their sexual partners have been adequately treated and symptoms have resolved.
- TOA may require drainage, which may be accomplished by interventional radiology via aspiration or placement of a drain, or by a gynecologist via vaginal or laparoscopic means. Recurrent/persistent TOAs may be managed by total abdominal hysterectomy with bilateral salpingo-oophorectomy after acute treatment of infection.
- Treatment of PID in women with intrauterine devices (IUDs) does not include/require removal of the device unless there is no clinical improvement after 48 to 72 hours of treatment with an approved regimen. IUDs rarely serve as a source for PID, especially greater than 3 wk after insertion.
- Sexual partners of patients diagnosed with PID or other STIs should be evaluated and treated appropriately. In the setting of PID, treat all sexual partners within 60 days of onset of symptoms. Some states allow for expedited partner therapy (EPT), such that a woman's provider is able to supply her with enough medication to treat herself and her partner(s).
- Treatment of chronic PID may be aimed at a different spectrum of microbes and should be tailored appropriately.

DISPOSITION

- Given the risk of reinfection, all women should be retested for gonorrhea and chlamydia 3 to 6 mo after treatment.
- Follow-up includes confirmation of partner treatment, education on use of barrier contraception, and risks of PID and long-term sequelae, including:
  1. Recurrent PID.
  2. Chronic pelvic pain.
  3. Fallopian tubal damage that leads to infertility and/or ectopic pregnancy.
  4. Fitz-Hugh-Curtis syndrome.
  5. Potential risk for cancer: Limited studies have suggested a small association between PID and ovarian, endometrial, and colon cancer.

PEARLS & CONSIDERATIONS

COMMENTS

- Maintain a low threshold for the diagnosis and treatment of PID given the risks for progression to severe infection and to significant and chronic medical and reproductive complications.
- Most patients are candidates for outpatient therapy, but inpatient hospitalization is recommended in select cases.
- Use only CDC-recommended treatment regimens unless contraindicated due to severe patient allergy; in such cases, check local susceptibilities of suspected pathogen.
- Offer HIV and other STI screening to all women with suspected or diagnosed PID.
- IUDs may be retained unless women have failed to improve with 48 to 72 hours of treatment.
- Treat sexual partners of women with PID, with EPT if possible.
- Counsel patients on abstinence until they and their partners have completed treatment.
- Test for reinfection with gonorrhea and chlamydia 3 to 6 mo after treatment.

PREVENTION

Women aged <25 yr and/or participating in high-risk sexual behavior should be screened annually for chlamydia; studies have shown such screening to reduce cases of PID by >50%. The importance of minimizing partner exposures and using barrier contraception (either alone or in conjunction with another method) should also be emphasized.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pelvic Inflammatory Disease (Patient Information)
Chlamydia Genital Infections (Related Key Topic)
Gonorrhea (Related Key Topic)
Pelvic Abscess (Related Key Topic)

AUTHOR: **Gretchen Makai, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Pelvic organ prolapse (POP) refers to descent of vaginal tissue and/or the uterus into the vaginal canal. It results from injury to or weakness in the connective tissue and muscles of the pelvic floor. Modern definitions of POP describe anterior and posterior vaginal wall defects, as well as apical defects in pelvic floor connective tissue. Synonyms for POP include cystocele (Fig. E1), rectocele, uterine prolapse (Fig. E2), enterocele (Fig. E3), and vaginal vault prolapse. Descriptions of this condition as a "dropped bladder," "dropped uterus," or defect in other pelvic organs should be avoided. These types of descriptions do not accurately reflect the pathophysiology of POP and often create confusion and unnecessary stress for patients. Table 1 describes the various types of POP affecting each vaginal compartment with corresponding ICD-10 codes.

SYNONYMS

Vaginal prolapse
Uterine prolapse
Genital prolapse
Uterine descensus
POP
Pelvic floor disorder
PFD

ICD-10CM CODES

N81.I8	Other female genital prolapse
N81.2	Incomplete uterovaginal prolapse
N81.4	Uterovaginal prolapse, unspecified
N81.5	Vaginal enterocele
N81.6	Rectocele
N81.82	Incompetence or weakening of pubocervical tissue

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE AND PREVALENCE: Exact prevalence estimates are difficult to determine due to varying definitions of POP and various diagnostic criteria. Based on self-reported symptoms in the National Health and Nutrition Examination Survey, the prevalence of POP is 3% to 4%. However, based on physical examination, the prevalence of POP is much higher. The incidence of POP surgery is 1.5 to 1.8 surgeries per 1000 women yrs. Annual direct health care costs are high, and repeat operations are common.

GENETICS: Data suggest a heritable component to POP; however, no specific genes or genetic factors outside of specific connective tissue diseases have been identified. Connective tissue disorders associated with an increased risk include Marfan syndrome and Ehlers-Danlos syndrome. In general, a genetic susceptibility exists in certain families, which is then affected by external factors to increase an individual woman's risk of POP.

RISK FACTORS: POP has a long latency and is multifactorial. Multiple risk factors have been identified. Some are modifiable, suggesting POP may be preventable; however, many risk factors are not. Some of the most common risk factors include:

- Pregnancy, labor, and vaginal childbirth
- Parity
- Age
- Chronic obstructive pulmonary disease (COPD) and chronic coughing
- Smoking
- Chronic constipation
- Chronic heavy lifting
- Chronic steroid use
- Connective tissue diseases (Marfan syndrome, Ehlers-Danlos syndrome)
- Pelvic surgery
- Menopause
- Family history
- Caucasian and Hispanic race

ETIOLOGY

- The cause of pelvic organ prolapse is usually multifactorial, but pregnancy is the most commonly associated risk factor.
- Muscle injury (levator ani) and connective tissue damage (pubocervical fascia) cause failure of pelvic floor support.
- Increased intraabdominal pressure results in strain on pelvic floor support structures.
- Injury to pelvic floor muscles or connective tissue supports results in uncompensated forces on pelvic floor, resulting in further injury to pelvic floor support structures.
  1. Acute (traumatic) injury to pelvic floor support can result from vaginal delivery, labor, or surgery.
  2. Chronic injury or strain on pelvic floor connective tissue and muscle can result from conditions such as COPD with chronic coughing or chronic constipation.
  3. Neurologic injury from acute or chronic strain on pelvic floor can result in denervation and subsequent muscular atrophy.
  4. Diseases or medications that weaken connective tissue (Marfan syndrome, corticosteroids) can predispose to injury.
  5. Hypoestrogenism may weaken pelvic floor tissue and impair ability to heal from injury.
- With injury to pelvic floor support structures, vaginal tissue becomes subjected to the forces from intraabdominal pressure and will stretch, allowing the bladder, uterus, or intestines to be displaced downward into the vaginal canal, resulting in clinical symptoms.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Bulge symptoms
  1. Vaginal pressure
  2. Protrusion from vagina (Fig. E4)
- Urinary symptoms
  1. Urinary hesitancy
  2. Urinary frequency or urgency
  3. Manual reduction of prolapse to complete urination
  4. Incomplete emptying
  5. Weak urinary stream
- Bowel symptoms
  1. Incomplete defecation
  2. Altered rectal sensation (urgency, lack of sensation)
  3. Splinting of vagina/perineum to defecate
- Sexual symptoms
  1. Dyspareunia
  2. Difficulty with vaginal penetration
- Other
  1. Vaginal bleeding from excoriated vaginal epithelium from chronic exteriorization
  2. Incarcerated prolapse with inability to be manually reduced

DIAGNOSIS

WORKUP

- Elicit specific symptoms. Determine the degree of bother with symptoms.
- Perform detailed pelvic exam. Examine anterior, posterior, and apical segments of vagina independently. Assess pelvic floor muscle tone.
  1. Exam is done in standard lithotomy position, and POP is assessed with Valsalva during exam.
  2. If symptoms are out of proportion to findings, repeat exam in standing position.
- Describe exam findings objectively (Boxes 1, 2, and 3).
  1. Quantitatively with POP-Q
  2. Descriptively with Baden-Walker halfway systems
- Urinary symptoms should be evaluated separately.
  1. POP is associated with urinary incontinence but *does not cause* urinary incontinence.

TABLE 1 Types of Genital Prolapse

Original Position of Organs	Prolapse	Symptoms (in addition to the general symptoms of discomfort, dragging, the feeling of a "lump," and, rarely, coital problems)
Anterior	Urethrocele Cystocele	Urinary symptoms (stress incontinence, urinary frequency)
Central	Cervix/uterus: 1st, 2nd, and 3rd degree Procidentia	Bleeding and/or discharge from ulceration in association with procidentia
Posterior	Rectocele Enterocele	Bowel symptoms, particularly the feeling of incomplete evacuation and sometimes having to press the posterior wall backward to pass stool

BOX 1 Points of Reference for POP-Q

Point	Description	Range of Values
Aa	3 cm above the hymen on anterior vaginal wall roughly corresponds with the urethrovesical junction.	–3 cm to +3 cm
Ba	The lowest extent of the segment of vagina between point Aa and the apex of the vagina. Unlike point Aa, it is not fixed but will be the same as Aa if point Aa is the most protruding point. In maximal prolapse, it will be the same as point C.	–3 cm to + TVL
C	Most distal edge of cervix (vaginal cuff if uterus/cervix absent).	
D	Posterior fornix (n/a if hysterectomy).	
Ap	3 cm above the hymen on posterior vaginal wall.	–3 cm to +3 cm
Bp	The lowest extent of the segment of vagina between point Ap and the apex of the vagina. Unlike point Ap, it is not fixed but will be the same as Ap if point Ap is the most protruding point. In maximal prolapse it will be the same as point D.	–3 cm to + TVL
GH (Genital Hiatus)	From urethral meatus to inferior hymenal ring.	
PB (Perineal Body)	From inferior hymenal ring to middle of anal orifice.	
TVL (Total Vaginal Length)	Without stretch or Valsalva.	

Key Points: Measure position of six points with respect to the position of the hymen. Points above the hymen (inside) are negative, points below the hymen are positive, and points at the hymen are 0.
Modified from Pemberton J (ed): *The pelvic floor,* Philadelphia, 2002, WB Saunders; and Bump RC et al: *Am J Obstet Gynecol* 175(1):13, 1996.

BOX 2 POP-Q Examination and Staging

Stage 0	No prolapse
Stage I	Leading edge ≥1 cm above hymenal ring
Stage II	Leading edge ≤1 cm above hymenal ring but ≤1 cm below hymenal ring
Stage III	Most distal point is >1 cm but < (TVL-2) cm below the hymenal ring
Stage IV	Leading edge ≥ (TVL-2) cm below hymenal ring

BOX 3 Baden Walker Halfway System

Grade 0	Normal position for each respective site
Grade 1	Descent halfway to the hymen
Grade 2	Descent to the hymen
Grade 3	Descent halfway past the hymen
Grade 4	Maximum possible descent for each site

- Evaluate postvoid residual urine volume in advanced POP (stage 3 and stage 4).
  1. Bladder ultrasound or catheterization at time of exam

LABORATORY TESTS

- Not indicated for routine evaluation of POP. Urine testing may be indicated based on presence or absence of urinary tract symptoms. Urodynamic testing may be performed for additional information and surgical planning.

IMAGING STUDIES

- Not indicated for routine evaluation of POP. Imaging studies for other gynecologic or urologic conditions may be indicated.
- Pelvic ultrasound may be considered in the *absence of POP* in patients with specific symptoms (i.e., pelvic pressure) (Fig. E5).

Rx TREATMENT

PRIMARY PREVENTION:

- Diagnosis and treatment of chronic cough
- Correction of constipation
- Weight control, nutrition, and smoking cessation counseling
- Pelvic muscle exercises
- Proper management of vaginal apex at time of hysterectomy in patients without POP
- McCall culdoplasty to prevent vaginal vault prolapse
- Cesarean delivery NOT indicated for prevention of POP
- Untreated urinary retention, even if asymptomatic, can cause bladder infection, reflux, and renal damage

POP TREATMENT OPTIONS:

- Expectant management: Can be appropriate, except in cases of incomplete bladder emptying.
- Pessaries (Fig. E6):
  1. Support device
  2. Silicone, not latex
  3. Exists in various shapes and sizes
     a. Use the simplest and smallest pessary that works
  4. 85% of women can be fitted successfully with a pessary (Fig. E7)
     a. Includes sexually active womena.
  5. Self-care can be learned by the majority of women
     a. Usually remove and clean once per mo; otherwise, office visit every 3 mo for cleaning and exam.
  6. Side effects/complications:
     a. Risk of UTI.
     b. Small vaginal erosions and very mild bleeding or spotting are common
        1) First episode of vaginal bleeding needs evaluation in postmenopausal patients
     c. Neglected pessaries can cause vaginitis, odor, severe vaginal erosion/bleeding, and fistula
     d. Vaginal estrogen may prevent or treat erosions and minimize risk of vaginitis and UTI
- Surgery:
  1. Indicated for bothersome POP and when patients fail or decline nonsurgical treatments.
  2. Goals of surgery are to eliminate vaginal bulge and improve associated symptoms.
     a. Most reliable symptom resolution is elimination of bulge/protrusion.
     b. Resolution of bladder and bowel symptoms is not routinely associated with surgical correction of POP.
     c. Choice of operation should be tailored to patient's presenting problems, lifestyle, and goals for the surgery.
  3. Evaluate and treat all defects present on exam.
     a. Combination defects are the most common presentation. Seen in 60% of patients.
     b. Anterior and apical combination is most common.
  4. There are multiple ways to classify operations for POP (Table 2).
     a. Obliterative:
        1) Narrow, shorten, or completely close off the vagina.
        2) High success rates with low morbidity.
        3) First-line treatment for women with significant medical comorbidities

TABLE 2 Surgical Approach to Pelvic Organ Prolapse

POP-Q Site	Vaginal	Abdominal
Aa	Anterior repair	Retropubic urethropexy
Urethra	Bladder neck suspension sling	
Ba	Anterior repair	Wedge colpectomy
Bladder	Paravaginal repair	Paravaginal repair
	Colpocleisis	Abdominal sacrocolpopexy
C	Uterosacral ligament suspension	Abdominal hysterectomy
Cervix/cuff	Iliococcygeus suspension	Uterosacral ligament suspension
	Sacrospinous fixation	Abdominal sacral colpopexy
	Manchester operation	Uterine suspension
	Hysteropexy	
	Vaginal hysterectomy	
	Colpocleisis	
D	McCall culdoplasty	Halban culdoplasty
Cul-de-sac		Moschcowitz culdoplasty
Ap	Rectovaginal plication (posterior repair)	Colpoperineopexy
	Site-specific repairs	

POP-Q, Pelvic Organ Prolapse Quantification System.
From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

TABLE 3 Procedures for POP

Classification		Procedure	Compartment(s)
Obliterative		Le Fort colpocleisis	All
		Total colpocleisis	All
Reconstructive	Restorative	Uterosacral ligament suspension	Apex
		Hysteropexy	Apex
		Paravaginal defect repair	Anterior
		Anterior colporrhaphy	Anterior
		Posterior colporrhaphy	Posterior
		Defect-directed posterior repair	Posterior
		Perineorrhaphy	Posterior
	Compensatory		
	Mesh	Sacral colpopexy	All
		Sacral hysteropexy	Apex
		Transvaginal mesh	All
	Nonmesh	Sacrospinous ligament suspension	Apex
		Ileococcygeus suspension	Apex
		Enterocele repair	Posterior

who do not desire future vaginal intercourse.
4) Associated with high rates of postoperative incontinence; most surgeons offer antiincontinence procedure at the same setting.

b. Reconstructive:
1) Restorative procedures use normal anatomic relationships and structures.
2) Compensatory procedures utilize nonanatomic relationships and may or may not use synthetic meshes and graphs.

5. Table 3 categorizes various common procedures for POP.
6. Hysterectomy alone does not treat POP.
a. Often performed concomitantly with POP repair as necessary step to expose critical anatomy.
7. For symptomatic women who desire childbearing: Management with pessaries or pelvic muscle exercises is recommended; if surgical correction is required, uterosacral ligament hysteropexy is the preferred method.
a. Patients should be counseled that repair will likely break down with subsequent pregnancy.
8. Women without stress incontinence undergoing vaginal surgery for POP are at risk for postoperative urinary incontinence.
a. Use of a prophylactic midurethral sling inserted during vaginal prolapse surgery has been shown to result in a lower rate of urinary incontinence at 3 and 12 mo, but also in a higher rate of adverse events (UTIs, major bleeding complications, incomplete bladder emptying).
9. Abdominal mesh-based repairs and anterior vaginal mesh repairs have superior durability but higher risk and potential for unique complications.
a. Use of mesh with posterior repairs does not improve outcomes and is associated with increased complications.
10. Mesh erosion rates have been reported up to 10%, with similar incidence between biologic and synthetic graft. However, synthetic graft erosion often requires surgical revision.

DISPOSITION

- Surgical success rates range between 70% and 95%.
- Up to 30% of patients may require a second operation for POP.
- Untreated POP does not necessarily worsen.

REFERRAL

- To a urogynecologist/gynecologist if surgical intervention is needed or for complex cases involving bladder dysfunction.
- Treating physicians should have special training with synthetic mesh products, if they are used.

PEARLS & CONSIDERATIONS

- POP rarely, if ever, causes pain.
- Stage of POP does not dictate treatment or prognosis.
- Treatment for POP is based on symptoms and patient bother.
- Options for most patients are no treatment, pessary, or surgery.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pelvic Organ Prolapse (Patient Information)
Uterine Prolapse (Patient Information)
Incontinence, Urinary (Related Key Topic)

AUTHORS: **Shivani Shah, MD,** and **Matthew J. Fagan, MD, FACOC**

SUGGESTED READINGS

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Iglesia C, Smithling KR: Pelvic organ prolapse, *Am Fam Phys* 96(3):179-186, 2017.

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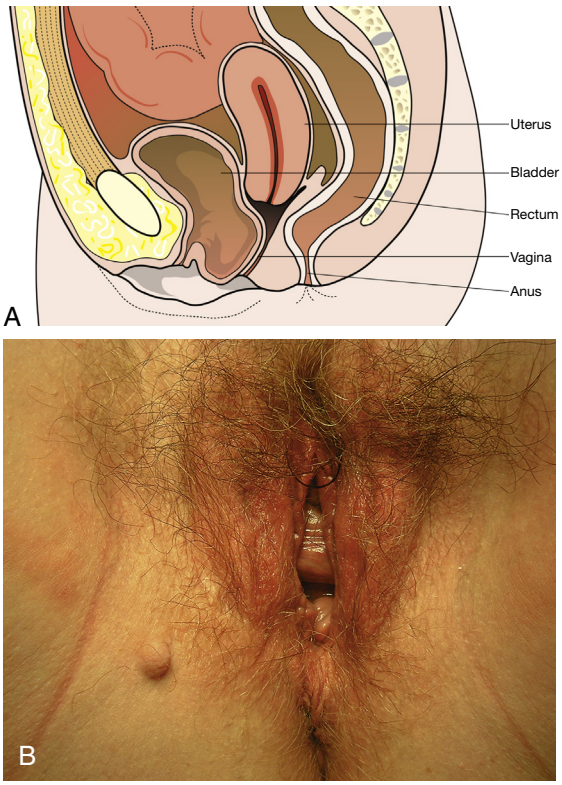

FIG. E1 (A,B) Cystocele. (From Magowan BA: *Clinical Obstetrics & Gynecology*, ed 4, 2019, Elsevier.)

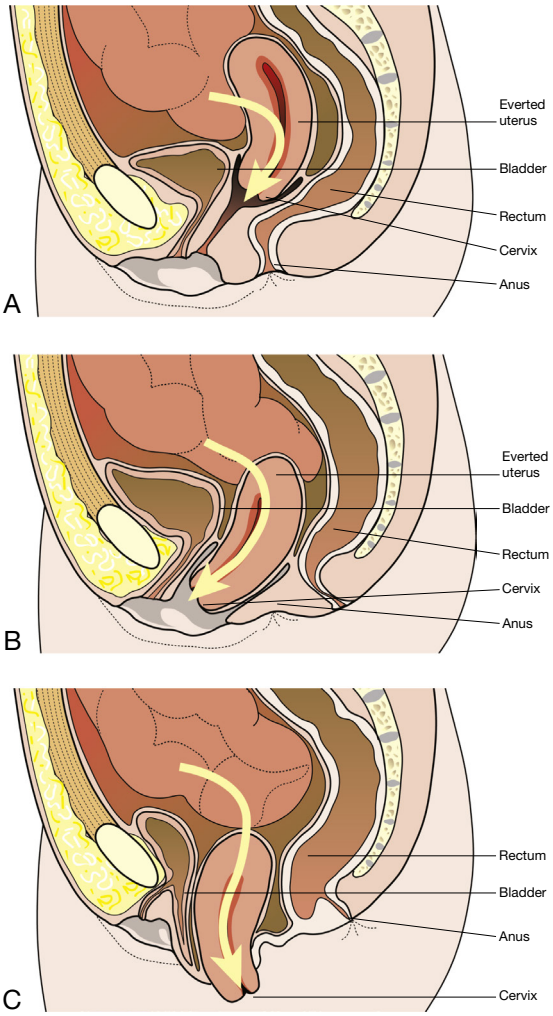

FIG. E2 Uterine prolapse. (A) Stage I; **(B)** stage II, and **(C)** stage III. (From Magowan BA: *Clinical Obstetrics & Gynecology*, ed 4, 2019, Elsevier.)

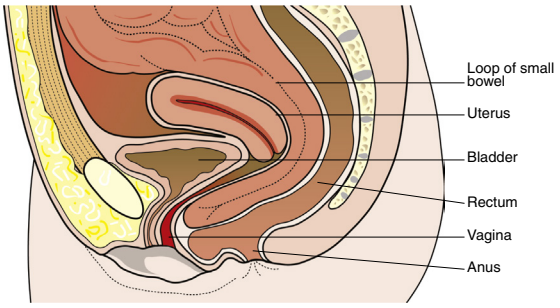

FIG. E3 Enterocele. (From Magowan BA: *Clinical Obstetrics & Gynecology*, ed 4, 2019, Elsevier.)

FIG. E4 Vaginal prolapse, resulting in edema of the vagina. (From Crum, CP et al: *Diagnostic gynecologic and obstetric pathology,* ed 3, Philadelphia, 2018, Elsevier.)

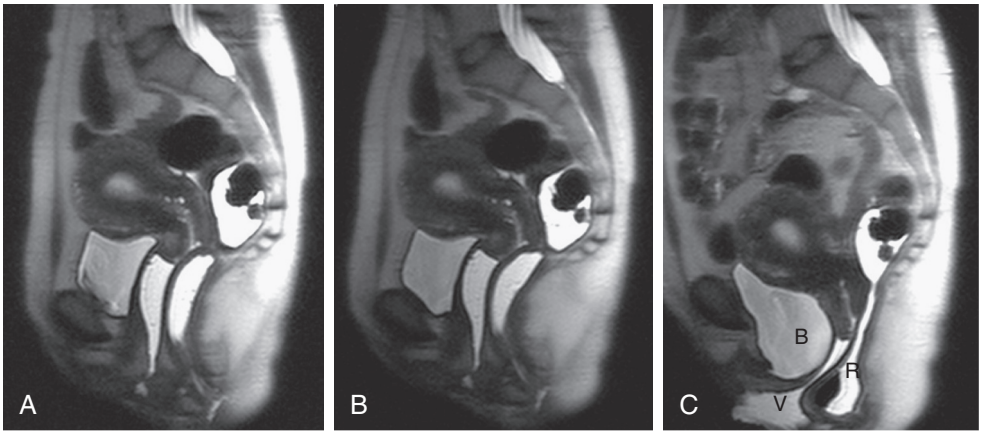

FIG. E5 A, Moderate global pelvic prolapse in a woman with stress urinary incontinence, pelvic heaviness, and constipation after three vaginal deliveries. At rest, all viscera are normally situated in the pelvis. **B,** With Kegel contraction, note that all viscera remain normally situated in the pelvis. **C,** With maximal strain, bladder *(B)*, vagina *(V),* and rectum *(R)* are well below the pelvic floor. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, WB Saunders.)

FIG. E6 A selection of the commonly used vaginal pessaries. (From Magowan BA: *Clinical Obstetrics & Gynecology*, ed 4, 2019, Elsevier.)

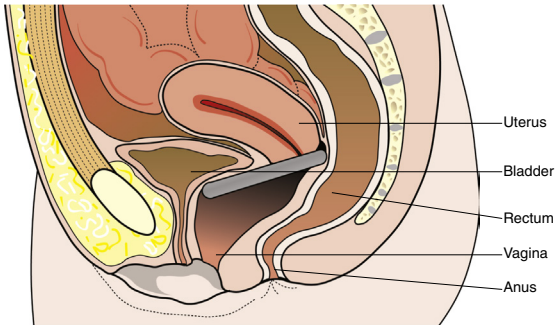

FIG. E7 Ring pessary in situ. Note that the anterior vaginal wall is elevated to reduce the cystocele and the uterine prolapse has been corrected. (From Magowan BA: *Clinical Obstetrics & Gynecology*, ed 4, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

The word "pemphigus" is derived from the Greek word *pemphix,* meaning blister. The pemphigus dermatoses encompass a group of rare, potentially fatal, chronic, autoimmune bullous diseases that are characterized by intraepidermal blisters of the skin and mucous membranes.

Pemphigus has four main subtypes:

- Pemphigus vulgaris (PV) (Fig. E1): The most common of the pemphigus diseases
  1. Pemphigus vegetans of Neumann, a rare clinical variant of PV in which healing is accompanied by vegetative proliferation of the epidermis
  2. Pemphigus vegetans of Hallopeau, a milder clinical variant of PV in which bullae do not precede vegetating plaques. Most common on intertriginous areas
- Pemphigus foliaceus (PF): A superficial form of pemphigus without oral mucosa involvement and a more favorable prognosis than that of PV.
  1. Pemphigus seborrhoicus, a rare clinical variety of PF in which lesions occur in a seborrheic distribution
  2. Pemphigus erythematosus, a localized variant of PF that mainly affects the elderly and can resemble cutaneous lupus erythematosus; the majority of cases will have positive antinuclear antibody (ANA) and negative anti–double-stranded DNA antibody (anti-dsDNA)
  3. Endemic pemphigus foliaceus (fogo selvagem), an endemic variant of PF that is seen mainly in endemic regions of Brazil and North Africa. The black fly (*Simulium nigrimanum)* may serve as a vector
  4. Pemphigus herpetiformis, pemphigus vulgaris or pemphigus foliaceus with urticarial plaques and vesicles in a herpetiform pattern
- Paraneoplastic pemphigus: Presents with hemorrhagic stomatitis and mucous membrane erosions; associated with malignancy (most commonly non-Hodgkin lymphoma and chronic lymphocytic leukemia [CLL]); complete neoplastic workup is required when diagnosis is suspected
- Immunoglobulin (Ig) A pemphigus: Fluid-filled blisters that progress to pustules and have a tendency to coalesce; mucosal involvement is rare
  1. Subcorneal pustular dermatosis-type IgA pemphigus
  2. Intraepidermal neutrophilic IgA dermatosis

SYNONYMS

Pemphigus
PV
Fogo selvagem: Endemic pemphigus foliaceus
Senear-Usher syndrome: Pemphigus erythematosus

ICD-10CM CODE
L10.0 Pemphigus vulgaris

EPIDEMIOLOGY & DEMOGRAPHICS

- Pemphigus vulgaris makes up 80% of all pemphigus cases
- Incidence is estimated at 1 to 5 cases per 1 million person-yr, but it is substantially higher in geographic regions with large populations of Ashkenazi Jewish or Mediterranean descent
- Typically occurs in the fourth to sixth decades of life, although range of ages affected is broad and may occur in the very young or the elderly
- Slight female predilection (1.5:1)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History:
  1. Multiple oropharyngeal ulcerations (Fig. E2) and erosions typically occur first (50% to 70% of cases), which can then be followed by a more generalized bullous eruption involving the skin within several weeks or months:
     a. Blisters are flaccid and rupture easily, leaving painful nonhealing erosions and ulcerations that may be the predominant clinical finding.
     b. Pain associated with oral mucosal blistering often results in dysphagia and hoarseness; nasal cavity involvement can lead to nasal congestion and mucus discharge.
     c. Skin bullae may occasionally be the initial manifestation of PV; most commonly involves the scalp (Fig. E3), upper chest, and back.
     d. Not commonly pruritic.

Physical findings:

1. Anatomic distribution:
   a. Oral mucosa: Most common sites are buccal, labial, and palatal mucosa, along with the tongue
   b. Can also involve the pharynx, larynx, vagina, penis, anus, and conjunctival mucosa; a recent study reported that 39% of patients with PV had pharyngoesophageal involvement as determined by upper gastrointestinal endoscopy
   c. Generalized cutaneous involvement (Fig. E4)
2. Other clinical findings:
   a. Nail dystrophy, paronychia, and subungual hematomas
   b. Ocular symptoms, though rare, may include conjunctival injection, pain, tearing, photophobia, and irritation; visual acuity is not affected; associated conjunctival papillomas and inflammatory masses have recently been reported

FIG. E1 Pemphigus vulgaris. (Courtesy Dr. Lawrence Lieblich. From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Elsevier.)

FIG. E2 Oral pemphigus vulgaris. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Elsevier.)

FIG. E3 Chronic pemphigus vulgaris of the scalp. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Elsevier.)

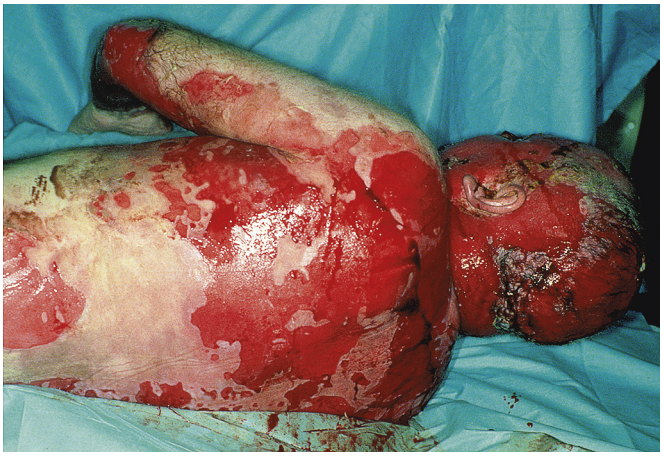

FIG. E4 Pemphigus vulgaris. (From James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, Elsevier.)

3. Lesion configuration:
   a. Mucosal membranes
   b. No preferential distribution
4. Lesion morphology:
   a. Flaccid bullae and vesicles progressing to ulcerations and erosions with a collarette of loose epidermis.
   b. Positive Nikolsky sign: When the clinician applies lateral pressure to normal-appearing skin at the periphery of active lesions, separation of the superficial epidermis occurs.
   c. Positive Asboe-Hansen sign: When gentle pressure is applied on intact bulla, the fluid spreads under the adjacent skin, thereby enlarging the blister.
   d. In the absence of treatment, healing with crusting followed by re-epithelialization may occur; scarring is rare, but some patients experience hyperpigmentation.
   e. Possibility for large areas of denuded skin with resulting bacterial superinfection.

ETIOLOGY

Autoimmune disease caused by autoantibodies against the cell surface of keratinocytes leading to separation of adjacent keratinocytes (called *acantholysis*). The predominant antibody in PV is directed against desmoglein 3 (Dsg-3) or both Dsg-3 and desmoglein 1 (Dsg-1; in PF it is directed against desmoglein 1. Desmoglein 1 is concentrated mainly in superficial epidermal layers, whereas desmoglein 3 is present mainly in the deeper epidermis layers, thus accounting for the differences in the sites of blister formation in PV versus PF.

Additional antibodies directed toward keratinocyte acetylcholine receptors have also been identified. Circulating antibodies are detected in approximately 80% of patients with active disease, and levels generally correlate with disease severity. Immunoglobulin (Ig) G, and rarely IgM, IgA, or complement protein C3, deposition occurs in lesional and healthy perilesional skin in 90% of patients.

Several drugs, including captopril, penicillamine, aspirin, calcium channel blockers, and rifampin, have been identified as potential triggers in the development of PV. Cessation of use generally leads to rapid resolution. Ultraviolet radiation, including phototherapy, may also exacerbate pemphigus vulgaris and foliaceus.

Dx DIAGNOSIS

The diagnosis of pemphigus vulgaris should be suspected in patients with painful oral erosions and flaccid bullae or erosions on the skin. The diagnosis is confirmed by histology, direct immunofluorescence (DIF) pattern of perilesional skin, indirect immunofluorescence (IIF) testing of serum, or ELISA testing for anti-desmoglein 1 and anti-desmoglein 3 autoantibodies.

DIFFERENTIAL DIAGNOSIS

- Herpetic stomatitis
- Aphthous stomatitis
- Erythema multiforme
- Stevens-Johnson syndrome
- Drug eruptions
- Lichen planus
- Systemic or bullous lupus erythematosus
- Mucous membrane or cicatricial pemphigoid
- Paraneoplastic pemphigus
- Pemphigus foliaceus
- Linear IgA bullous dermatosis
- Hailey-Hailey disease
- Grover disease
- Bullous pemphigoid (Table E1)
- Behçet syndrome
- Dermatitis herpetiformis
- Epidermolysis bullosa acquisita
- IgA pemphigus

WORKUP

Skin biopsy is diagnostic; specimens should be sent for routine histochemical staining and direct immunofluorescence. An upper endoscopy should be considered in patients with dysphagia to determine degree of esophageal involvement and check for esophageal Nikolsky sign. Airway evaluation is indicated for patients with any evidence of airway obstruction. DIF is positive in all patients with PV or PF. Alternative diagnosis should be considered if DIF is negative. DIF is negative in some patients with drug-induced pemphigus.

LABORATORY TESTS

- Light microscopy: Intraepithelial blisters with acantholysis; basal layer with single layer of intact cells (known as "tombstoning")
- DIF: Intercellular IgG and C3 deposition in "chicken-wire" lattice pattern
- IIF: Tests for presence and titer of antibodies; should be used in conjunction with clinical, histopathological, and DIF evaluation; estimated 90% positive predictive value and low negative predictive value; titers may correlate with disease state and can potentially be used for tracking progression and treatment response
- ELISA: Similar sensitivity but inferior specificity compared to IIF; antidesmoglein antibodies titers correlate with disease activity (however, there is a subset of patients with high anti-Dsg-3 antibodies but low disease activity)

Rx TREATMENT

A rating scale, such as the Pemphigus Disease Area Index (PDAI), can be used to assess disease severity. This scale correlates well with

TABLE E1 Differentiation of Pemphigus Vulgaris and Bullous Pemphigoid

Characteristics	Pemphigus Vulgaris	Bullous Pemphigoid
Age	Usually occurs in middle-aged persons	Usually occurs in elderly persons
Site	Oral mucosa, face, chest, groin	Flexural areas, groin, axilla; less often involving mucosal surfaces
Findings	Flaccid bullae and erosions, intraepidermal blisters, IgG autoantibodies against keratinocyte surfaces	Intact tense bullae, subepidermal blisters, IgG autoantibodies against hemidesmosomal antigens
Treatment	Prednisone 0.5-1.5 mg/kg/day with adjuvant immunosuppressant agents; refractory disease may require rituximab, intravenous immunoglobulin, immunoadsorption, plasmapheresis, or extracorporeal photochemotherapy	Prednisone 0.5-1 mg/kg/day with adjuvant immunosuppressant therapy as needed for refractory cases; localized disease may be controlled with topical steroids
Prognosis	>90% respond; steroid side effects significant; mortality rate under 5%	>90% respond; remissions and recurrences common; mortality rate up to 23%

IgG, Immunoglobulin G.

physician's assessment of disease severity and can be used for patients with even mild disease. Briefly, it requires quantitative measurement of the number and size of total skin and mucosal lesions and incorporates disease activity and damage. Similar to severe burns, PV can be fatal without adequate treatment due to secondary infections and metabolic disturbances. The mainstay of therapy is systemic corticosteroids with the goal of complete absence of, or only occasional, blistering.

NONPHARMACOLOGIC THERAPY

- Mild soaps and emollients to skin.
- Burow solution may be useful for weeping erosions.
- Avoid trauma to the skin.
- When there are extensive raw surfaces, daily baths are helpful in removing the thickened crusts and reducing foul odor; can be followed with nonstick bandaging (e.g., petrolatum gauzes).
- Soft diet and viscous lidocaine can be used in patients with oral lesions; flossing should be avoided in the presence of symptomatic lesions.
- A mixture of equal parts of simethicone (Maalox), elixir of diphenhydramine, and viscous lidocaine is also effective.

ACUTE GENERAL Rx

- For localized disease, topical steroids may be effective.
- For generalized disease, oral glucocorticoids are the mainstay of therapy and often work rapidly to halt blistering.
  1. Optimum dosing guidelines have not yet been established.
  2. Initial dose of prednisone is usually 0.5 to 1.5 mg/kg/day; if new lesions continue to form, the dose can be increased up to 2 mg/kg/day. Pulsed dosing may also be used.
  3. Adjuvant therapy with rituximab administered with prednisone as initial therapy may lead to improve mortality rates compared to prednisone alone.
  4. Alternative adjuvant therapies can also be initiated simultaneously with prednisone include azathioprine, mycophenolate mofetil (MMF), cyclophosphamide, cyclosporine, dapsone, infliximab, intravenous immunoglobulin, and plasma exchange. These agents help reduce the risk of relapse.
  5. Tumor necrosis factor (TNF)-α blockers should be avoided, given conflicting data regarding their efficacy in the treatment of PV.
  6. For patients with severe disease requiring initial prednisone dosing greater than 100 mg daily, treatment with pulse oral or intravenous (IV) steroids can be very effective; a common regimen is IV dexamethasone 100 mg for 3 days and repeated every 2 to 3 wk.
  7. Steroid tapering should begin once no new lesions have developed for at least 2 wk and approximately 80% of the existing lesions have healed. The steroid dose should be decreased by 25% at biweekly intervals, with slower reductions once a dose of 20 mg per day is reached. If fewer than three new lesions form during taper, increase steroid dose to last effective dose. If three or more new lesions form during taper, increase steroid dose back to prior doses.
  8. Ocular involvement in PV generally responds to prednisone and/or immunosuppressant therapy; lubricating artificial tears or topical ophthalmic corticosteroids can provide further symptomatic relief.

CHRONIC Rx

- Adjuvant therapy such as immunosuppressants, antiinflammatories, chemotherapeutic agents, and biologics are useful for disease control and to shorten the length of treatment with oral steroids. Azathioprine, MMF, dapsone, methotrexate, cyclophosphamide, and cyclosporine can also be used as monotherapy for patients with contraindications to corticosteroids. Treatment duration and dosing are determined by clinical response:
  1. Azathioprine: First-line adjuvant immunosuppressant. 1 to 3 mg/kg/day based on thiopurine methyltransferase (TPMT) activity; an initial dose of 50 mg daily can be started and increased after a week in the absence of adverse effects.
  2. Mycophenolate mofetil (MMF): Steroid-sparing agent. 2 g daily for average patient of 75 kg, or 1 g daily for elderly patients.
  3. Cyclophosphamide: Second-line immunosuppressant adjuvant agent. 500 mg IV infusion or 2 mg/kg/day PO. Use limited by potential long-term side effects, including infertility, infections, increased risk of cancers, and genitourinary complications.
  4. Methotrexate: Steroid-sparing agent. 10 to 20 mg/wk.
  5. Dapsone 100 mg daily or up to ≤1.5 mg/kg/day; serum G6PD activity should be checked prior to beginning therapy.
  6. Rituximab (anti-CD20 monoclonal antibody): Typical regimen is 1000 mg IV at baseline and 2 wk, then 500 mg every 6 mo.

Refractory disease:

- A relapse or flare is defined as the appearance of three or more lesions in a month without spontaneous resolution, or the extension of established lesions in a patient who has previously attained control of disease activity. A variety of treatment modalities are available:
  1. Intravenous immunoglobulin (IVIG): Refractory disease or for patients with contraindications to immunosuppressants. Dosing is 2 g/kg per cycle administered over 2 to 5 consecutive days each month. Contraindicated in IgA deficiency; can lead to aseptic meningitis in patients with history of chronic migraines.
  2. Immunoadsorption: Rapid removal of circulating antibodies. Indicated in PV patients who have failed corticosteroid therapy combined with azathioprine or MMF. Recommended schedule is four treatments on 4 consecutive days (2.5-fold plasma volume/day) repeated monthly. Can be combined with rituximab or cyclophosphamide therapy.
  3. Plasmapheresis: No standardized protocol. Four to five plasma exchanges of 1 to 1.5 plasma volumes over a period of 7 to 10 days is sufficient to remove 90% of total body initial immunoglobulin burden.

Should be used with caution in patients with cardiac dysfunction.

4. Extracorporeal photochemotherapy: Collection and reinfusion of mononuclear cells after extracorporeal irradiation with ultraviolet-A light in the presence of 8-metoxypsoralen. Case series have reported excellent clinical response with no adverse effects.

DISPOSITION

- Medication is continued until clinical disease is suppressed.
- Age of onset ≥65 yr, presence of coronary heart disease and/or cardiac arrhythmias at time of diagnosis, and level of anti-Dsg-1 autoantibodies ≥100 U/ml at diagnosis to be associated with greater mortality in PV patients.
- Before the use of oral corticosteroids, PV was usually a fatal disease with a mortality rate of greater than 73% and survival measured in months after diagnosis.
- Combined corticosteroids and adjuvant therapy have decreased mortality rates to less than 5%. However, patients with PV continue to have significantly increased mortality risks compared with the general population.
- The risk of all-cause mortality in PV patients is two to three times greater than expected for the general population. Death generally occurs from systemic and respiratory tract infections or complications related to medical therapy.

REFERRAL

- Dentistry
- Dermatology
- Ophthalmology
- Otolaryngology

PEARLS & CONSIDERATIONS

COMMENTS

- PV, unlike bullous pemphigoid, is generally a disease of middle-aged persons.
- Prednisone is the mainstay of treatment.
- Monitoring anti-Dsg-1 antibodies during treatment course may be helpful, as persistently high levels are a positive predictive marker for cutaneous relapse. In contrast, high levels of anti-Dsg-3 do not always correlate with a mucosal relapse.
- Because PV is mediated by IgG autoantibodies that can cross the placenta, neonates born to mothers with active PV can present with transient disease that self-resolves as the antibody is degraded.

RELATED CONTENT

Pemphigus Vulgaris (Patient Information)

AUTHORS: **Sara Moradi Tuchayi, MD,** and **Kachiu C. Lee, MD, MPH**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Peptic ulcer disease (PUD) is an ulceration in the stomach or duodenum resulting from an imbalance between mucosal protective factors and various mucosal damaging mechanisms (see "Etiology").

SYNONYMS

PUD
Duodenal ulcer (DU)
Gastric ulcer (GU)

ICD-10CM CODES

K25.3	Acute gastric ulcer without hemorrhage or perforation
K25.7	Chronic gastric ulcer without hemorrhage or perforation
K26.3	Acute duodenal ulcer without hemorrhage or perforation
K26.7	Chronic duodenal ulcer without hemorrhage or perforation
K27.0	Acute peptic ulcer, site unspecified, with hemorrhage
K27.1	Acute peptic ulcer, site unspecified, with perforation
K27.2	Acute peptic ulcer, site unspecified, with both hemorrhage and perforation
K27.3	Acute peptic ulcer, site unspecified, without hemorrhage or perforation
K27.4	Chronic or unspecified peptic ulcer, site unspecified, with hemorrhage
K27.5	Chronic or unspecified peptic ulcer, site unspecified, with perforation
K27.6	Chronic or unspecified peptic ulcer, site unspecified, with both hemorrhage and perforation
K27.7	Chronic peptic ulcer, site unspecified, without hemorrhage or perforation
K27.9	Peptic ulcer, site unspecified, unspecified as acute or chronic, without hemorrhage or perforation
P78.82	Peptic ulcer of newborn
Z87.11	Personal history of peptic ulcer disease

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence: 250,000 to 500,000 (200,000 to 400,000 duodenal; 50,000 to 100,000 gastric) annually; duodenal ulcer/gastric ulcer ratio is 4:1.
- Anatomic location: <90% of duodenal ulcers occur in the first portion of the duodenum; gastric ulcers occur most frequently in the lesser curvature near the incisura angularis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Epigastric pain is the most frequently reported symptom of PUD. The pain is typically improved with food or antacids and worsened by fasting.
- Physical examination is often unremarkable.
- Patient may have epigastric tenderness, tachycardia, pallor, hypotension (from acute or chronic blood loss), nausea and vomiting (if pyloric channel is obstructed), board-like abdomen and rebound tenderness (if perforated), and hematemesis or melena (with a bleeding ulcer). Box 1 describes key symptoms and signs of peptic ulcer.

ETIOLOGY

Often multifactorial. The following are common mucosal damaging factors:

- *Helicobacter pylori* infection. *H. pylori* is the major cause of PUD. It is found in more than 70% of patients with duodenal ulcers and gastric ulcers in the U.S. Rates are much higher (>90%) in other parts of the world. Eradication of *H. pylori* markedly reduces peptic ulcer recurrence
- Medications (NSAIDs, glucocorticoids). Risk factors for development of NSAID-related ulcers are described in Table 1
- Incompetent pylorus or lower esophageal sphincter
- Bile acids
- Impaired proximal duodenal bicarbonate secretion
- Decreased blood flow to gastric mucosa
- Acid secreted by parietal cells and pepsin secreted as pepsinogen by chief cells
- Cigarette smoking
- Alcohol

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gastroesophageal reflux disease
- Cholelithiasis syndrome
- Pancreatitis
- Gastritis
- Nonulcer dyspepsia
- Neoplasm (gastric carcinoma, lymphoma, pancreatic carcinoma)
- Angina pectoris, myocardial infarction, pericarditis
- Dissecting aneurysm
- Other: High small-bowel obstruction, pneumonia, subphrenic abscess, early appendicitis

WORKUP

Comprehensive history and physical exam to exclude other diagnoses. Diagnostic modalities include endoscopy or upper GI series. Endoscopy is preferred and remains the gold standard for diagnosis of PUD. The presence of a mucosal break ≥5 mm in the stomach or duodenum confirms the diagnosis.

BOX 1 Key Symptoms and Signs of Peptic Ulcer

Uncomplicated Ulcer
No symptoms ("silent ulcer" in up to 40% of cases)
Epigastric pain
Pain may radiate to the back, thorax, other parts of abdomen (cephalad most likely, caudad least likely)
Pain may be nocturnal (most specific), "painful hunger" relieved by food, or continuous (least specific)
Nausea
Vomiting
Heartburn (mimics or associated with gastroesophageal reflux)

Complicated Ulcer
Acute perforation
Severe abdominal pain
Shock
Abdominal boardlike rigidity (and rebound and other signs of peritoneal irritation)
Free intraperitoneal air
Hemorrhage
Hematemesis and/or melena
Hemodynamic changes, anemia
Previous history of ulcer symptoms (80%)
Gastric outlet obstruction
Satiation, inability to ingest food, eructation
Nausea, vomiting (and related disturbances)
Weight loss

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

TABLE 1 Risk Factors for Development of NSAID-Related Ulcers

Definite	Possible
Advanced age	Concomitant infection with *Helicobacter pylori*
History of ulcer	Cigarette smoking
Concomitant corticosteroid therapy	Consumption of alcohol
Concomitant anticoagulation therapy	
High doses of NSAIDs	
Serious systemic disorders	

NSAID, Nonsteroidal antiinflammatory drug.
From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

LABORATORY TESTS

- Routine laboratory evaluation is usually unremarkable.
- Anemia may be present in patients with significant GI bleeding.
- *H. pylori* testing by endoscopic biopsy, urea breath test or stool antigen test (*H. pylori* stool antigen) is recommended:
  1. The urea breath test documents active infection (sensitivity and specificity >90%). The patient ingests a small amount of urea labeled with carbon 13 or carbon 14. If urease is present (produced by the organism), the urea is hydrolyzed and the patient exhales labeled carbon dioxide that is then collected and measured. Use of proton pump inhibitors (PPI) within 2 wk of the urea breath test may interfere with test results.
  2. Stool antigen test is an ELISA that identifies *H. pylori* antigen in a stool specimen through a polyclonal anti–*H. pylori* antibody. It is as accurate as the urea breath test for diagnosis of active infection and follow-up evaluation of patients treated for *H. pylori.* A negative result on the stool antigen test 6 wk after completion of therapy identifies patients in whom eradication of *H. pylori* was successful.
  3. Serologic testing for antibodies to *H. pylori* is easy and inexpensive; however, the presence of antibodies demonstrates previous but not necessarily current infection. Antibodies to *H. pylori* can remain elevated for mos to yrs after infection has cleared; therefore antibody levels must be interpreted in light of the patient's symptoms and other test results (e.g., PUD seen on upper GI series).
  4. Histologic evaluation of endoscopic biopsy samples is considered by many the gold standard for accurate diagnosis of *H. pylori* infection. However, detection of *H. pylori* depends on the site and number of biopsy samples, the method of staining, and experience of the pathologist.
- Additional laboratory evaluation is indicated only in specific cases (e.g., amylase level in suspected pancreatitis, serum gastrin level in suspected Zollinger-Ellison [ZE] syndrome).

IMAGING STUDIES

- Conventional upper GI barium studies identify approximately 70% to 80% of PUD; accuracy can be increased to approximately 90% by using double contrast.
- Abdominal CT is helpful when suspecting perforating peptic ulcer disease (sensitivity >95%).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Stop smoking; smoking increases the risk of PUD, decreases the healing rate, and increases the frequency of recurrence.
- Avoid NSAIDs and alcohol.
- Special diets have been proved unrelated to ulcer development and healing; however, avoid foods that cause symptoms.

ACUTE GENERAL Rx

Eradication of *H. pylori,* when present, can be accomplished with various regimens (see "*Helicobacter pylori* Infection")

PUD patients testing negative for *H. pylori* should be treated with antisecretory agents:

- H_2 receptor antagonists (H_2RAs): Ranitidine, famotidine, and nizatidine are all effective; they are usually given in split dose or at nighttime.
- PPIs: Can also induce rapid healing; they are usually given 30 min before meals.

Antacids and sucralfate are also effective agents for the treatment and prevention of PUD.

CHRONIC Rx

Maintenance therapy in peptic ulcer patients is indicated in the following situations:

- Persistent smokers
- Recurrent ulcerations
- Long-term treatment with NSAIDs, glucocorticoids
- Elderly or debilitated patients
- Aggressive or complicated ulcer disease (e.g., perforation, hemorrhage)
- Asymptomatic bleeders

DISPOSITION

- The recurrence rate for untreated PUD is ~60% (>70% in smokers). Treatment decreases the recurrence rate by nearly 30%.
- Patients with recurrent ulcers should be re-treated for an additional 8 wk and then placed on maintenance therapy with H_2RAs, PPIs, sucralfate, or antacids.
- An ulcer is considered refractory to treatment if healing is not evident after 8 wk for duodenal ulcers and 12 wk for gastric ulcers. In these patients, maximum acid inhibition (e.g., esomeprazole 40 mg bid) is preferred over continued therapy with standard antiulcer therapy.
- Eradication of *H. pylori* (when present) is indicated in all patients. A negative stool antigen test for *H. pylori* 6 wk after treatment accurately confirms cure of *H. pylori* infection with reasonable sensitivity in initially seropositive healthy subjects.
- Screening for ZE syndrome should also be considered in patients with multiple recurrent ulcers; in patients with ZE, the serum gastrin level is >1000 pg/ml and the basal acid output is usually >15 mEq/hr.
- Surgery for refractory ulcers is now only rarely performed; it consists of highly selective vagotomy for duodenal ulcers or ulcer removal with antrectomy or hemigastrectomy without vagotomy for gastric ulcers.

REFERRAL

- GI referral for patients requiring endoscopy
- Surgical referral for patients with nonhealing ulcers despite appropriate medical therapy

PEARLS & CONSIDERATIONS

COMMENTS

- Patients with gastric ulcers should generally have repeat endoscopy after 8 to 12 wk of antisecretory therapy to document healing and test exfoliative cytology for gastric carcinoma. Patients with duodenal ulcers and those with low risk gastric ulcers, such as young patients on NSAIDs, generally do not require endoscopic surveillance.
- After endoscopic treatment of bleeding peptic ulcers, bleeding recurs in up to 20% of patients. PPI administration intravenously by continuous infusion substantially reduces the risk of recurrent bleeding. High-dose IV esomeprazole (80 mg IV bolus followed by 8 mg/hr infusion over 72 hr) given after successful endoscopic therapy to patients with high-risk peptic ulcer bleeding has been reported to reduce recurrent bleeding at 72 hr and to maintain sustained clinical benefits for up to 30 days.
- Among low-dose aspirin recipients who had peptic ulcer bleeding, continuous aspirin therapy may increase the risk for recurrent bleeding.

RELATED CONTENT

Peptic Ulcer (Patient Information)
Helicobacter pylori Infection (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

BASIC INFORMATION

DEFINITION

Acute pericarditis is the inflammation (or infiltration) of the pericardium. It is characterized by at least two of the following four criteria: (1) chest pain, (2) specific electrocardiographic changes, (3) pericardial friction rub, or (4) pathognomonic pericardial friction rub.

ICD-10CM CODES

I30.0	Acute nonspecific idiopathic pericarditis
I30.1	Infectious pericarditis
I30.8	Other forms of acute pericarditis
I30.9	Acute pericarditis, unspecified
I301.0	Chronic adhesive pericarditis
I31.1	Chronic constrictive pericarditis
I31.3	Pericardial effusion (non-inflammatory)
I31.9	Diseases of pericardium, unspecified (tamponade)
I31.2	Hemopericardium

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common form of pericardial disease worldwide
- It is diagnosed in 0.1% to 0.2% of hospitalized patients and is responsible for 5% of patients admitted for nonischemic chest pain.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Chest pain: Characteristically sharp, pleuritic, positional (improved by sitting up and leaning forward).
- Pericardial rub: A triphasic (ventricular systole, early diastole, atrial contraction), scratchy sound best heard at the lower left sternal border is pathognomonic. Unlike pleural friction rub, the rub of pericarditis is not affected by respiration.
- Pericardial effusion: Beck triad (hypotension, elevated jugular venous pressure, and muffled heart sounds) suggests pericardial tamponade.

ETIOLOGY

- Etiology is dichotomized into infectious and noninfectious causes.
- In developed countries, viral and idiopathic etiologies are the most common causes of pericarditis. Tuberculosis accounts for 80% to 90% of pericarditis in developing countries.
- Other infectious agents include HIV, fungus, parasites, and bacteria.
- Noninfectious causes include neoplasm (7% to 13%), autoimmune syndromes (3% to 4%), and perimyocardial infarction (Dressler syndrome, typically 2 wk after MI).
- Drug-induced: Procainamide, hydralazine, phenytoin, isoniazid, rifampin, doxorubicin, mesalamine, adalimumab.
- Metabolic: Uremia, myxedema, anorexia nervosa.
- Posttraumatic: Postpericardiotomy, postpacemaker lead placement, postcatheter ablation, post-CPR.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Angina pectoris and acute coronary syndrome
- Myopericarditis/perimyocarditis
- Dissecting aortic aneurysm
- Pulmonary causes: Embolism, infarction, pneumothorax, pneumonia with pleurisy
- Gastrointestinal causes: Hepatitis, cholecystitis, GERD, esophageal spasm or rupture
- Costochondritis
- Box 1 summarizes the differential diagnosis of pericardial effusion by etiology

WORKUP (TABLE 1)

Table 2 summarizes an initial approach to acute pericarditis. Diagnosis of pericarditis requires at least two of the four following clinical criteria:

- Typical pleuritic chest pain
- Pericardial friction rub
- Suggestive ECG changes (diffuse concave ST segment elevation, PR depression in all leads except for AVR where there is elevation)
- New or worsening pericardial effusion

LABORATORY TESTS

Laboratory tests may help elucidate the underlying cause and are adjunctive to the clinical criteria.

- Inflammatory markers: Erythrocyte sedimentation rate, (high-sensitivity) C-reactive protein (CRP), and complete blood count with differential are elevated in pericarditis.
- Basic metabolic profile.
- Cardiac biomarkers (troponin I and T) when elevated indicate involvement of the myocardium (i.e., myopericarditis).

The following tests may be useful when specific etiologies of pericarditis are suspected:

- HIV
- PPD
- Antinuclear antibody, rheumatoid factor
- Routine viral studies are not indicated since they are low yield

PERICARDIAL SAMPLING

Indications for echocardiogram or pericardiocentesis are:

- Tamponade physiology
- Moderate to large pericardial effusion with symptoms, or refractory to medical therapy
- Suspicion of a neoplastic, bacterial, or tuberculous process
- Evidence of constrictive or effusive-constrictive pericarditis
- Pericardiocentesis is for diagnostic and therapeutic purposes. The pericardial fluid should be analyzed for RBC, WBC, Gram stain, culture, cytology, glucose, pH, LDH, and protein. In select cases, consider checking triglyceride for chylopericardium, ADA or PCR for tuberculosis
- Pericardial biopsy may be helpful in recurrent pericardial effusion with an elusive diagnosis and when malignancy or tuberculosis is suspected

IMAGING STUDIES

- ECG (Fig. 1): Changes in the ECG reflect inflammation of the epicardium, since the parietal pericardium is electrically inert. The ECG changes are staged as follows:
  1. Stage I (Acute phase): Hours to few days. PR-segment depression in all leads except aVR (where PR elevation is seen) and diffuse concave ST-segment elevations
  2. Stage II (Intermediate phase): Seen in first wk with return of PR and ST segments to baseline
  3. Stage III (Intermediate): T-wave inversion in leads previously showing ST-segment elevation
  4. Stage IV (Late phase): Normalization of the ECG or indefinite persistence of T-wave inversions

BOX 1 Major Differential Diagnosis of Pericardial Effusion by Etiology

Noninfectious

- Malignancy (usually metastatic)
- Myocardial infarction associated (Dressler syndrome)
- Uremia
- Myxedema (rare cause of tamponade physiology)
- Trauma (penetrating or nonpenetrating)
- Chylopericardium
- Acute idiopathic
- Rheumatic fever
- Collagen vascular disease (systemic lupus erythematosus, rheumatoid arthritis, scleroderma, Wegener granulomatosis)
- Postsurgical (cardiac and intrathoracic)
- Drug induced (procainamide, hydralazine, phenytoin, doxorubicin, isoniazid)

Infectious

- Viral (coxsackievirus, echovirus, mumps, adenovirus, hepatitis, human immunodeficiency virus)
- Bacterial (pneumococcus, streptococcus, staphylococcus)
- Tuberculous
- Fungal (histoplasmosis, coccidiomycosis, *Candida*, particularly in immunosuppressed patients)

From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

TABLE 1 Diagnostic Pathway and Sequence of Performance in Acute Pericarditis

Diagnostic Measure	Characteristic Findings
Obligatory	
Auscultation	Pericardial rub (monophasic, biphasic, or triphasic)
ECG*	*Stage I:* Anterior and inferior concave ST segment elevation. PR segment deviations opposite to P wave polarity
	Early stage II: All ST junctions return to the baseline. PR segments deviated
	Late stage II: T waves progressively flatten and invert
	Stage III: Generalized T-wave inversions in most or all leads
	Stage IV: ECG returns to prepericarditis state
Echocardiography	Effusion types B to D (Horowitz)
	Signs of tamponade
Blood analyses	Erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, leukocytes (inflammation markers)
	Troponin I,† CK-MB (markers of myocardial involvement)
Chest radiograph	Ranging from normal to "water bottle" shape of the heart shadow
	Performed primarily to reveal pulmonary or mediastinal pathology
Mandatory in Tamponade, Optional in Large/Recurrent Effusions or if Previous Tests Inconclusive in Small Effusions	
Pericardiocentesis/drainage	Polymerase chain reaction and histochemistry for etiopathogenetic classification of infection or neoplasia
Optional or if Previous Tests Inconclusive	
CT	Effusions, pericardium, and epicardium
MRI	Effusions, pericardium, and epicardium
Pericardioscopy, pericardial/epicardial biopsy	Establishing the specific etiology

CK-MB, Creatine kinase-MB; *CT,* computed tomography; *ECG,* electrocardiogram; *MRI,* magnetic resonance imaging.

*Typical lead involvement: I, II, aVL, aVF, and V3-V6. The ST segment is always depressed in aVR, frequently in V1, and occasionally in V2. Stage IV may not occur, and there are permanent T-wave inversions and flattenings. If an ECG is first recorded in stage III, pericarditis cannot be differentiated by ECG from diffuse myocardial injury, "biventricular strain," or myocarditis. ECG in early repolarization is very similar to stage I. Unlike stage I, this ECG does not acutely evolve, and J-point elevations are usually accompanied by a slur, oscillation, or notch at the end of the QRS just before and including the J point (best seen with tall R and T waves—large in an early repolarization pattern). Pericarditis is likely if, in lead V6, the J point is greater than 25% of the height of the T-wave apex (using the PR segment as a baseline).

†A rise in cardiac muscle troponin I (cTnI) is detected in 32.2% of patients, more frequently in younger, male patients, with ST segment elevation and pericardial effusion at presentation. An increase beyond 1.5 ng/ml is uncommon (7.6%) and associated with CK-MB elevation. cTnI increase and is not a negative prognostic marker for the incidence of recurrences, constrictive pericarditis, cardiac tamponade, or residual left ventricular dysfunction.

From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.

TABLE 2 Initial Approach to the Patient with Definite or Suspected Acute Pericarditis

1. If the diagnosis is suspected but not certain, listen often for pericardial rub and obtain ECGs frequently to check for diagnostic findings.
2. If the diagnosis is suspected or certain, obtain the following tests to help confirm the diagnosis (if necessary) and determine whether a specific causative diagnosis and/or significant associated conditions and/or complications are present:
   - Hemogram
   - hsCRP
   - Troponin I
   - Chest radiograph
   - Echocardiogram
   - Consider additional testing on the basis of clinical suspicion of a specific etiology
3. If the diagnosis is likely or certain, initiate therapy with an NSAID plus colchicine.

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.

- Echocardiogram is used to evaluate for pericardial effusion (present in 50% to 60% of patients) (Fig. 2). Echocardiogram can help exclude STEMI (through absent wall motion abnormality) and make the diagnosis of constrictive pericarditis or tamponade.
- Chest x-ray: Done primarily to rule out abnormalities of the mediastinum or lung fields that may cause chest pain. Cardiac silhouette may appear enlarged in patients with pericardial effusion if ≥200 ml of fluid has accumulated (Fig. 3). Calcifications around the heart may be seen with chronic constrictive pericarditis.
- Computed tomography: Evaluation of associated pleuropulmonary and extra thoracic diseases and pericardial calcifications.
- MRI (Fig. 4) may be useful in patients with chronic constrictive pericarditis and when malignancy is suspected.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical activity restriction until pain abates and normalization of (high sensitivity) CRP, ECG, and echo
- Athletes should avoid competitive activity for 3 mo, whereas nonathletes can resume activities after remission (expert consensus)
- Patient education regarding potential complications: e.g., cardiac tamponade, recurrent pericarditis (which can occur in up to one third of patients), and chronic constrictive pericarditis

ACUTE GENERAL Rx

- High-dose aspirin (750 to 1000 mg tid) or NSAIDs (e.g., ibuprofen 600 to 800 mg tid, indomethacin 50 mg tid) for 1 to 2 wk. Proton pump inhibitor should be provided for gastric protection. NSAIDs should be avoided in patients with recent MI, CHF, acute renal failure, and upper GI bleed.
- Colchicine 0.5 to 0.6 mg once daily (<70 kg) or bid (>70 kg) for 3 mo. Current evidence (COPE, CORE, CORP, ICAP, CORP-2 trials) supports the effectiveness of colchicine in symptomatic relief and prevention of recurrent pericarditis.
- Corticosteroids should be used only as second-line treatment. They are associated with

severe adverse effects, more hospitalizations, and higher rates of recurrences.
- Low- to moderate-dose (0.25 to 0.5 mg/kg/day) systemic steroid therapy for 1 mo, followed by taper (6 to 12 wk), is restricted to patients with rheumatologic disease, renal failure, or contraindication to NSAID/colchicine.
- Azathioprine, intravenous immunoglobulins, anakinra can be considered for patients with refractory recurrent pericarditis.
- Pericardiectomy and pericardiotomy at specialized centers are reserved for recurrent cardiac tamponade or refractory pericarditis.
- Avoidance of anticoagulants (increased risk of hemopericardium).

TREATMENT OF UNDERLYING CAUSE:
- Bacterial pericarditis: Systemic antibiotics and drainage of pericardium
- Collagen vascular disease: Steroid (prednisone)
- Tuberculous pericarditis: Rifampicin, isoniazid, pyrazinamide, and ethambutol for 2 mo, then isoniazid and rifampicin for 6 mo
- Thyroid-related pericardial effusion: Thyroid replacement therapy
- Uremic: Dialysis
- Malignant pericardial effusion: Fig. 5

POTENTIAL COMPLICATIONS FROM PERICARDITIS:
- **Chronic constrictive pericarditis:** Occurs in <1% of patients with acute idiopathic pericarditis.
  1. Physical examination: Signs of right heart failure—hepatomegaly, splenomegaly, ascites, pedal edema, scrotal edema, possible anasarca, jugular venous pressure, Kussmaul sign (paradoxical increase in jugular venous pressure during inspiration), pericardial knock (early diastolic filling sound heard 0.06 to 0.1 sec after S2), and clear lungs.
  2. ECG: Low QRS voltage, nonspecific ST-segment changes, biatrial enlargement.
  3. Chest radiograph: Mild alveolar edema, pleural effusions, biatrial enlargement, pericardial calcification (seen in tuberculous pericarditis).
  4. Echocardiography: May show thickened pericardium (>4 mm), >25% mitral and >50% tricuspid valve inflow variation with respiration, interventricular septal bounce; and mitral annulus reversus (medial e' velocity > lateral e' velocity) suggests constrictive pericarditis.[1]
  5. Hemodynamics (Fig. 6): Elevation of right-sided filling pressures, equalization of diastolic pressures, as well as prominent "x" and rapid "y" descent in the atrial tracing are seen in constrictive pericarditis. Right ventricular pressure tracing typically shows a "dip and plateau" (square root sign) that is due to the unimpeded early filling of the RV with an abrupt halt to the late diastolic filling by the stiff pericardium. Discordance of right ventricular and left ventricular systolic pressures during respiration is also suggestive of constrictive pericarditis.
  6. Therapy: Complex surgical stripping or removal of both layers of the constricting pericardium improves the functional class in majority of late survivors, but has high operative mortality.[2]

[1]Welch TD, Ling LH, Espinosa RE et al: Echocardiographic diagnosis of constrictive pericarditis, *Circ Cardiovasc Imaging* 7(3):526–534, 2014.

[2]Vustarini N, Chen C, Mazine A et al: Pericardiectomy for constrictive pericarditis: 20 years of experience at the Montreal Heart Institute, *Ann Thorac Surg* 100(1):107–113, 2015.

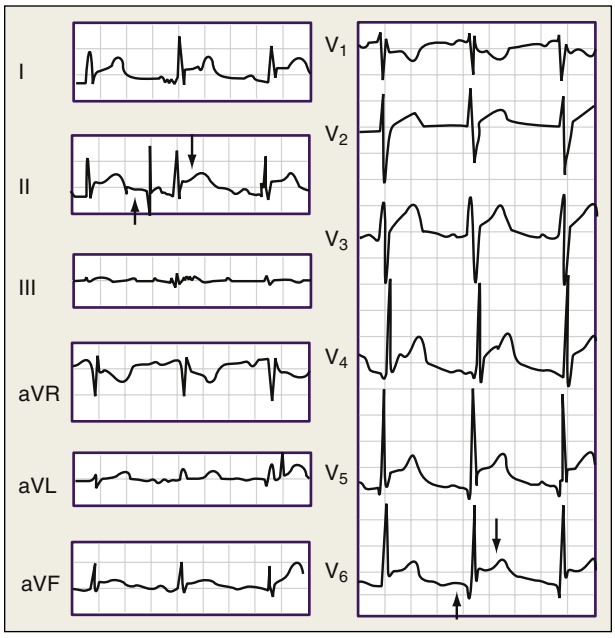


FIG. 1 Typical electrocardiographic changes in acute pericarditis: PR depression (*small arrow*) and concave ST-segment elevation (*large arrow*). *aVF,* Augmented vector foot; *aVL,* augmented vector left; *aVR,* augmented vector right. (From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.)

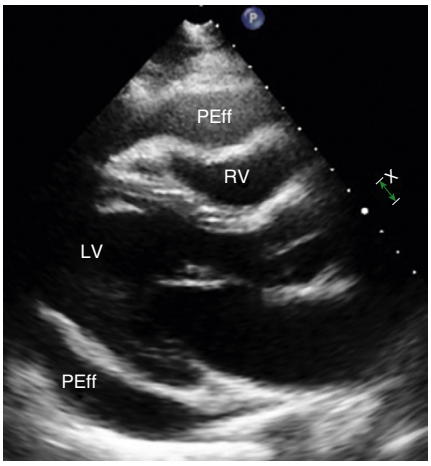


FIG. 2 Bedside echocardiogram showing pericardial effusion compressing the right ventricle during diastole, consistent with cardiac tamponade. *LV,* Left ventricle; *PEff,* pericardial effusion; *RV,* right ventricle.

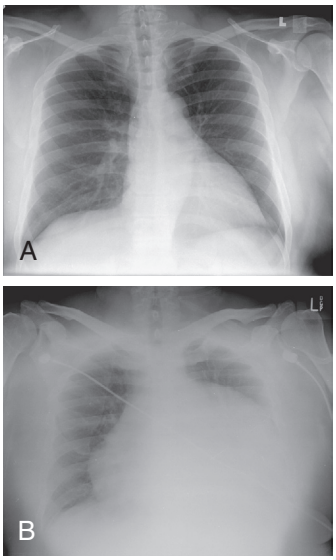


FIG. 3 Chest x-ray. A, Patient's chest radiograph 1 yr before presentation with cardiac tamponade. **B,** Same patient's chest radiograph on presentation to the emergency department with cardiac tamponade. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

- **Cardiac tamponade:** Occurs in 5% to 15% of patients with idiopathic pericarditis, but in up to 60% of those with neoplastic, tuberculous, or purulent pericarditis.
  1. Signs and symptoms: Dyspnea, orthopnea, chest pain, fatigue
  2. Physical examination: Beck triad (distended neck veins, distant heart sounds, hypotension), reduced apical impulse, diaphoresis, tachypnea, tachycardia, narrowed pulse pressure, or pulsus para-

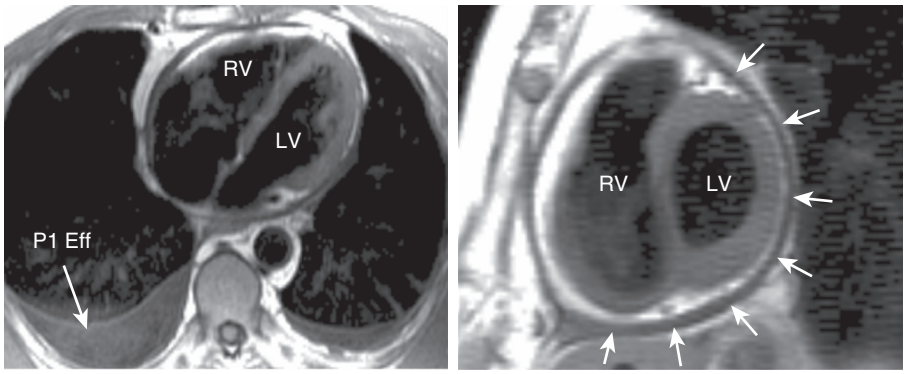


FIG. 4 Cardiovascular magnetic resonance in a patient with constrictive pericarditis. On the *right* is a basal short-axis view of the ventricles showing a thickened pericardium encasing the heart (*arrows*). On the *left* is a transaxial view, again showing the thickened pericardium, particularly over the right heart, but also a pleural effusion (*Pl Eff*). *LV,* Left ventricle; *RV,* right ventricle. (From Zipes DP et al [eds]: *Braunwald's heart disease,* ed 7, Philadelphia, 2005, Saunders.)

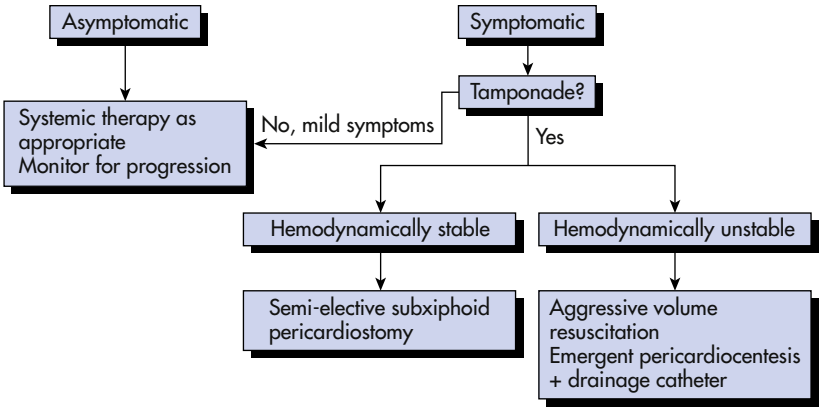


FIG. 5 Treatment approach algorithm to malignant pericardial effusions. (From Niederhuber JE*: Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

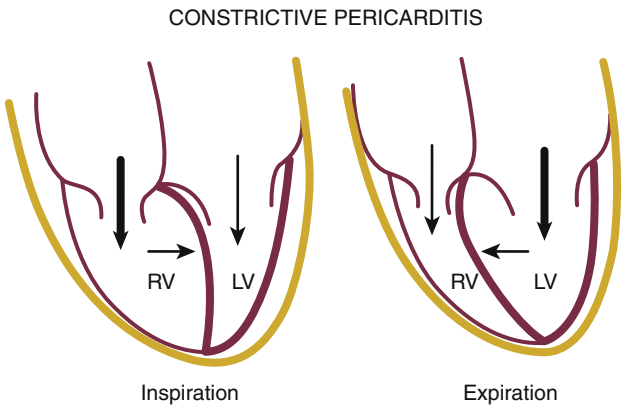


FIG. 6 Ventricular interdependence in constrictive pericarditis. *LV,* left ventricle; *RV,* right ventricle. (Courtesy Miguel Quinones, MD, Houston Methodist DeBakey Heart and Vascular Center. In Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.)

doxus (decrease in systolic blood pressure ≥10 mm Hg during inspiration; most specific sign)

3. ECG: Decreased amplitude of the QRS complex, electrical alternans (occurs more frequently with large neoplastic effusions)
4. Chest x-ray: Cardiomegaly ("water-bottle" configuration of the cardiac silhouette may be seen) with clear lungs
5. Echocardiography (Table 3): Pericardial effusion, >25% mitral and >50% tricuspid valve inflow variation with respiration, paradoxical motion of interventricular septum, diastolic right or left atrium collapse, diastolic right ventricular collapse (pathognomonic)
6. Hemodynamics: Equalization of diastolic pressures within chambers of the heart, elevation of right atrial pressure with a prominent "x" but blunted "y" descent. Table 4 summarizes hemodynamics in cardiac tamponade and constrictive pericarditis
7. Therapy: Cardiac tamponade is a life-threatening condition usually requiring emergent pericardiocentesis. Avoid drugs (diuretics, nitrates) or therapies (high PEEP) that reduce the preload, as volume repletion may be required. In patients with recurrent effusions (e.g., neoplasms), placement of a percutaneous drainage catheter or pericardial window may be necessary

- **Effusive-constrictive pericarditis:** Uncommon syndrome characterized by concomitant tamponade caused by tense pericardial effusion and constriction caused by the visceral pericardium.
  1. Signs and symptoms of both tamponade and or constriction. Pulsus paradoxus is present but Kussmaul sign and pericardial knock are typically absent.
  2. Echocardiography: Low sensitivity to distinguish effusive-constrictive pericarditis from other types.
  3. Cardiac catheterization: Before drainage, "y" descent is usually less prominent than expected, and right atrial "v" wave persists. After drainage, may continue to have elevated right atrial and pulmonary wedge pressures.
  4. Therapy: Extensive epicardiectomy (with disruption of the visceral layer of pericardium) is the procedure of choice in symptomatic patients.
- **Myopericarditis**: Myocarditis and pericarditis may coexist in 20% to 30% of patients presenting with pericarditis. The laboratory hallmark is the elevation of cardiac enzymes. Overall, myopericarditis has a good prognosis with very low rates of morbidity, mortality, and heart failure.

DISPOSITION

- Complete resolution of pain and other signs and symptoms during the initial 3 wk of therapy occurs in 70% to 90% of cases.
- Admission is highly recommended if any of the following poor prognostic features (high risk factors) is present: Fever >38° C (100.4° F), subacute onset, large pericardial effusion/tamponade, failure to respond to 1 wk of outpatient treatment.
- The following are considered moderate risk factors but should also prompt admission: myopericarditis, trauma, immunosuppression, oral anticoagulant therapy.
- Recurrent pericarditis occurs after 4 to 6 wk of a symptom-free interval after a first episode of pericarditis. Incidence is reported as 10% to 15% and increases to 50% in patients who are not on colchicine.

TABLE 3 Hemodynamic and Echocardiographic Features of Constrictive Pericarditis Compared with Restrictive Cardiomyopathy

	Constriction	Restriction
Prominent y descent in venous pressure	Present	Variable
Paradoxic pulse	~1/3 cases	Absent
Pericardial knock	Present	Absent
Equal right- and left-sided filling pressures	Present	Left at least 3-5 mm Hg higher than right
Filling pressures >25 mm Hg	Rare	Common
Pulmonary artery systolic pressure >60 mm Hg	No	Common
Square root sign	Present	Variable
Respiratory variation in left-sided and-right-sided pressures/flows	Exaggerated	Normal
Ventricular wall thickness	Normal	Usually increased
Pericardial thickness	Increased	Normal
Atrial size	Possible LA enlargement	Biatrial enlargement
Septal bounce	Present	Absent
Tissue Doppler E′ velocity	Increased	Reduced
Speckle tracking	Normal longitudinal, decreased circumferential restoration	Decreased longitudinal, normal circumferential restoration

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 4 Hemodynamics in Cardiac Tamponade and Constrictive Pericarditis

	Tamponade	Constriction
Paradoxical pulse	Usually present	Present in ~1/3
Equal left/right-sided filling pressure	Present	Present
Systemic venous wave morphology	Absent y descent	Prominent y descent (M or W shape)
Inspiratory change in systemic venous pressure	Decrease (normal)	Increase or no change (Kussmaul sign)
"Square root" sign in ventricular pressure	Absent	Present

From Mann DL, Zipes DP, Libby P, Bonow RO: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

- Incessant pericarditis is defined as pericarditis lasting for >4 to 6 wk but <3 mo without remission, while chronic pericarditis is pericarditis lasting for >3 mo.
- In patients with pericardial effusion after cardiac surgery, use of NSAIDs is not recommended because they have not been shown to reduce the size of the effusions or prevent late cardiac tamponade. The COPPS trial suggested that prophylactic colchicine may reduce the risk of developing a postpericardiotomy pericarditis.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pericarditis (Patient Information)
Cardiac Tamponade (Related Key Topic)

AUTHOR: **Maxwell Eyram Afari, MD**

SUGGESTED READINGS

Adler Y et al: 2015 ESC Guidelines for the diagnosis and management of pericardial diseases, *Eur Heart J* 36(42):2921-2964, 2015.

Brucato A et al: Management of idiopathic recurrent pericarditis in adults and in children: a role for IL-1 receptor antagonism, *Intern Emerg Med* 13(4):475-489, 2018.

Imazio M et al: Colchicine for recurrent pericarditis, *Ann Intern Med* 155:409-414, 2011.

Imazio M et al: A randomized trial of colchicine for acute pericarditis, *N Engl J Med* 369:1522-1528, 2013.

Imazio M et al: Evaluation and treatment of pericarditis, a systemic review, *J Am Med Assoc* 314(14):1498-1506, 2015.

Khandaker MH et al: Pericardiectomy vs medical management in patients with relapsing pericarditis, *Mayo Clin Proc* 87(11):1062-1070, 2012.

LeWinter MM: Clinical practice acute pericarditis, *N Engl J Med* 371:2410-2416, 2014.

Mevrin P et al: NSAID treatment for postoperative pericardial effusion, *Ann Intern Med* 152:137-143, 2010.

Mody P et al: Trends in acute pericarditis hospitalizations and outcomes among the elderly in the USA, 1999-2012, *Eur Heart J Qual Care Clin Outcomes* 4(2):98-105, 2018.

Søgaard KK et al: Pericarditis as a marker of occult cancer and a prognostic factor for cancer mortality, *Circulation* 136(11):996-1006, 2017.

BASIC INFORMATION

DEFINITION

A disorder characterized by periodic episodes of involuntary repetitive limb movements during sleep, causing sleep disturbances that are not due to a primary sleep disorder. They consist of triple flexion movements of the legs that repeat in 5- to 90-second cycles during sleep.

SYNONYMS

PLMD
Periodic leg movements of sleep (PLMS)
Nocturnal myoclonus

ICD-10CM CODE
G47.61 Periodic limb movement disorder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown
PEAK INCIDENCE: None
PREVALENCE: 5% to 8%
PREDOMINANT SEX AND AGE: Prevalence is higher in females and increases with age.
GENETICS: Unknown, but may share autosomal dominant inheritance pattern if concurrent with restless leg syndrome.
RISK FACTORS:

- Musculoskeletal disease, heart disease, obstructive sleep apnea, narcolepsy, psychiatric disorders, diabetes mellitus
- Shift work
- Snoring
- Stress
- Restless leg syndrome
- Parkinson disease, idiopathic REM sleep behavior disorder

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients may complain of excessive daytime sleepiness, fatigue, and unrestful sleep.
- During an episode of periodic limb movements, the patient may experience repetitive dorsiflexion of the ankle and extension of the big toe, but other movements may occur, such as kicking. These movements last up to 5 seconds and may recur every 5 to 90 seconds, with the total episode lasting minutes to an hour. The movements are typically involuntary, and the patient is unaware of their occurrence, in contrast to those of restless leg syndrome (RLS).
- Neurologic examination is usually normal but may reveal an associated neuropathy or myelopathy.
- Periodic leg movements of sleep are present in most patients with RLS but are not specific nor sensitive for RLS.

ETIOLOGY

The exact etiology is unknown. It is hypothesized that PLMD may share a common pathophysiology with restless leg syndrome, which involves iron metabolism and dopaminergic pathways in the brain.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Restless leg syndrome
- Neuroleptic-induced akathisia
- Positional discomfort
- Nocturnal leg cramps

WORKUP

In addition to a history of excessive daytime sleepiness or sleep disturbance, the diagnosis of PLMD requires a polysomnographic study to exclude other sleep disorders and to document the periodic limb movements resulting in sleep disturbances. During the study, the movements must occur in a series of at least four, recurring every 5 to 90 seconds, each with a duration of 0.5 to 5 seconds.

LABORATORY TESTS

- No laboratory tests are required to diagnose PLMD.
- A CBC, iron panel, and BMP may be ordered if RLS is suspected.

IMAGING STUDIES

Imaging studies are not required for diagnosis of PLMD.

TREATMENT

- Patients with periodic limb movements only, without sleep disturbances of insomnia or excessive daytime sleepiness, do not require treatment.
- The treatment of PLMD is the same as that for RLS.
- Calcium channel ligands such as gabapentin or pregabalin are effective and do not worsen symptoms with long-term use.
- Dopaminergic agonists such as pramipexole or ropinirole have been shown to decrease PLMS, but long-term use may be associated with worsening of symptoms (augmentation).
- Iron replacement should be started in case of iron deficiency, and the cause of iron-deficiency investigated.

NONPHARMACOLOGIC THERAPY

- Follow good sleep hygiene.
- Minimize shift work.
- Avoid caffeine, alcohol, nicotine.

ACUTE GENERAL Rx

- Treatment is indicated when PLMD is suspected and causing significant sleep fragmentation
- For calcium channel ligands: Gabapentin initial dose of 100 to 300 mg/day before bedtime, with therapeutic range of 300 to 2400 mg/day. Pregabalin initial dose of 50 to 75 mg/day, with therapeutic range of 75 to 450 mg/day
- For dopamine agonists: Pramipexole initial dose of 0.125 mg before bedtime, with a therapeutic range of 0.125 to 0.75 mg/day. Ropinirole initial dose of 0.25 mg/day, with a therapeutic range of 0.25 to 4 mg/day

CHRONIC Rx

For patients treated with dopamine agonists, close monitoring is recommended to screen for augmentation of symptoms.

COMPLEMENTARY & ALTERNATIVE MEDICINE

None

REFERRAL

Refer to neurologist if diagnosis is uncertain or an underlying disorder is suspected.

PEARLS & CONSIDERATIONS

COMMENTS

- Periodic limb movements disorder is a diagnosis of exclusion. PLMS occur during many sleep disorders and do not support a diagnosis of PLMD until all possible underlying causes are excluded.
- Certain medications such as antihistamines, dopamine receptor blockers, selective serotonin reuptake inhibitors, and stimulants may worsen PLMS and should be avoided if possible.

PREVENTION: As mentioned in "Nonpharmacologic Therapy."

PATIENT & FAMILY EDUCATION

Patient information on PLMD and other sleep disorders can be found at the National Sleep Foundation website: www.sleepfoundation.org

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Restless Legs Syndrome (Related Key Topic)

AUTHORS: **Sudad Kazzaz, MD,** and **Corey Goldsmith, MD**

SUGGESTED READINGS

Figorilli M et al: The clinical importance of periodic leg movements in sleep, *Curr Treat Options Neurol* 19:10, 2017.

Wijeemanne S et al: Restless legs syndrome: clinical features, diagnosis and a practical approach to management, *Pract Neurol* 17:444-452, 2017.

Winkelman JW et al: Practice guideline summary: treatment of restless legs syndrome in adults. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology, *Neurology* 87(1-9), 2016.

BASIC INFORMATION

DEFINITION

Peripheral artery disease (PAD) refers to atherosclerotic, inflammatory, occlusive, and aneurysmal diseases involving the abdominal aorta and its branch arteries. (This topic focuses on lower-extremity PAD.)

SYNONYMS

PAD
Peripheral vascular disease (PVD)
Arteriosclerosis obliterans
Atherosclerotic occlusive disease
Atherosclerosis of the extremities
Peripheral arterial stenosis
Vasoocclusive disease of the legs
Chronic critical limb ischemia

ICD-10CM CODES

I70	Atherosclerosis
I70.2	Atherosclerosis of native arteries of the extremities
I70.21	Atherosclerosis of native arteries of extremities with intermittent claudication
I70.22	Atherosclerosis of native arteries of extremities with rest pain
I70.3	Atherosclerosis of unspecified type of bypass graft(s) of the extremities
I73	Other specified peripheral vascular diseases
I73.8	Other specified peripheral vascular diseases
I73.9	Peripheral vascular disease, unspecified
I79	Disorders of arteries, arterioles, and capillaries in diseases classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

- There are >202 million patients afflicted with PAD globally; it affects approximately 8.5 million Americans above the age of 40.
- The prevalence is nearly equal in men and women. It increases with age, from 5.28% in those aged 40 to 49 yr to 18.83% in those aged 70 to 79 yr. However, symptoms of claudication are more likely to be present in males with PAD (50%) vs. women with PAD (25%).
- As per the PARTNERS study, the prevalence of PAD in patients >70 yr or 50 to 69 yr with history of smoking or diabetes was 29%.
- Risk factors that increase risk of PAD according to a 2013 meta-analysis of 112,027 studied patients include:
  1. Smoking (odds ratio 2.72).
  2. Diabetes (odds ratio 1.88).
  3. Hypertension (odds ratio 1.55).
  4. Hypercholesterolemia (odds ratio 1.19).
- Smoking is three times more likely to lead to PAD than CAD. Conversely, the association of HTN and hyperlipidemia with PAD is lower than that with CAD and cerebrovascular disease.
- Patients at increased risk of PAD include those aged greater than 65 yr, those aged 50 to 64 yr with risk factors of atherosclerosis, those aged less than 50 yr with diabetes and an additional risk factor, as well as those individuals with known atherosclerotic disease in another vascular bed.
- Black race/ethnicity has greater prevalence according to NHANES data (odds ratio 2.83).
- Patients with newly diagnosed PAD are six times more likely to die within the next 10 yr when compared with patients without PAD.
- The total annual costs associated with the hospitalization of patients with PAD in the U.S. exceed $21 billion, and account for ~13% of all Medicare Part A and B expenditures.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Peripheral artery disease may present in a variety of ways:
  1. 20% to 50%: Asymptomatic
  2. 10% to 35%: Intermittent claudication (IC), defined as aching pain, cramping, weakness, numbness, or heaviness of the leg induced by exercise, relieved by rest
  3. 1% to 2%: Critical limb ischemia (CLI), defined as chronic (>2 wk) rest pain, or tissue loss with nonhealing ulceration, necrosis, or gangrene (Fig. E1)
  4. 40% to 50%: Atypical symptoms involving the calf, thigh, or buttock
  5. Acute limb ischemia (ALI) will be present in 14 per 100,000 individuals in the general population. It is defined as acute (<2 wk) onset of symptoms due to severe poor perfusion of the extremities, and further categorized into the following:
     a. Viable: No sensory or muscle weakness with audible Doppler pulses
     b. Threatened: Mild to moderate sensory or motor loss; inaudible arterial Doppler
     c. Irreversible: Severe sensory loss and muscle weakness; inaudible arterial Doppler
- Physical findings include:
  1. Diminished pulses and/or cool skin temperature of lower extremities
  2. Bruits heard over the distal aorta, iliac, or femoral arteries
  3. Change in skin color:
     a. Dependent rubor in critical limb ischemia
     b. Livedo reticularis, or a mottled reticulated vascular pattern that appears lacelike
  4. Trophic changes of hair loss, brittle nails, and muscle atrophy

ETIOLOGY

PAD is primarily the result of atherosclerotic narrowing of the arterial lumen that results in impaired blood flow to the lower-extremity tissues. Fig. 2 illustrates the pathophysiology of intermittent claudication.

Symptoms initially manifest with exercise as metabolic demands increase. Critical limb ischemia (CLI) may develop gradually from progressive atherosclerosis or in a subacute fashion from multisegmental atherothrombosis or atheroembolization. In contrast, acute limb ischemia (ALI) is marked by a sudden onset of symptoms (<2 wk) due to poor perfusion of the extremities.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Vasculitis
- Musculoskeletal disorder
- Spinal stenosis or nerve root compression (neurogenic or pseudoclaudication)
- Peripheral neuropathy
- Reflex sympathetic dystrophy
- Raynaud phenomenon
- Compartment syndrome
- Deep venous thrombosis
- Popliteal entrapment syndrome
- Direct vascular injury

WORKUP

- Thorough history, including symptoms regarding walking impairment, claudication, ischemic rest pain, or nonhealing wounds in patients ≥70 yr or those ≥50 yr with a history of smoking and/or diabetes
- Careful physical examinations include:
  1. Measurement of blood pressure in both arms; pressure difference of >15 to 20 mm Hg is abnormal and suggestive of subclavian artery stenosis
  2. Palpation and recording of carotid pulses, upstroke, amplitude, and presence of bruits
  3. Auscultation and palpation of abdomen for bruits, aortic pulsation, and diameter
  4. Palpation of brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial pulses. Pulse intensity should be recorded as follows: 0, absent; 1+, diminished; 2+, normal; 3+, bounding
  5. Auscultation of femoral arteries for the presence of bruits
  6. Extremities should be inspected for color, temperature, integrity of the skin, hair loss, and hypertrophic nails
- Classification/staging system for PAD
  1. Fontaine staging system (Table 1):
     a. I: Asymptomatic
     b. IIa: Mild claudication
     c. IIb: Moderate-severe claudication
     d. III: Ischemic rest pain
     e. IV: Ulceration or gangrene
- Resting ankle-brachial index (ABI) is the first-line noninvasive test to establish a diagnosis of PAD in individuals with symptoms or signs suggestive of disease (individuals with one or more of the following exertional leg symptoms: Nonhealing wounds, age >65 yr, or age >50 yr with smoking or diabetes history)
- ABI of each leg is calculated by dividing the highest dorsalis pedis or posterior tibial systolic blood pressure by the highest systolic brachial pressure obtained from either the right or left arm
  1. Noncompressible/calcified: >1.40
  2. Normal: 1.00 to 1.40 at rest

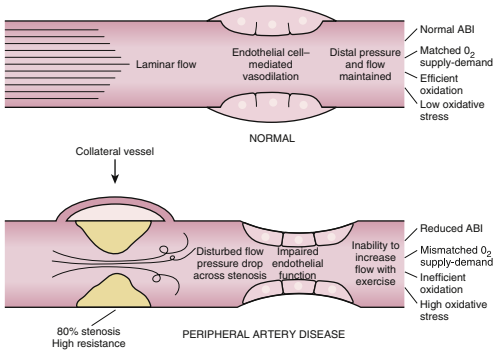


FIG. 2 Pathophysiology of intermittent claudication. In healthy arteries *(top),* flow is laminar and endothelial function is normal; therefore blood flow and oxygen delivery match muscle metabolic demand at rest and during exercise. Muscle metabolism is efficient and results in low oxidative stress. In contrast, in peripheral artery disease *(PAD) (bottom),* arterial stenosis results in disturbed flow, and the loss of kinetic energy results in a drop in pressure across the stenosis. Collateral vessels have high resistance and only partially compensate for the arterial stenosis. In addition, endothelial function is impaired, thereby resulting in further loss of vascular function. These changes limit the blood flow response to exercise and result in a mismatch of oxygen delivery to muscle metabolic demand. Changes in skeletal muscle metabolism further compromise the efficient generation of high-energy phosphates. Oxidant stress, the result of inefficient oxidation, further impairs endothelial function and muscle metabolism. *ABI,* Ankle-brachial index. (From the text *Anatomie, physiologie, pathologie des vaisseaux lymphatiques* by PC Sappey [1874], courtesy Harvard Medical Library, Francis A. Countway Library of Medicine, in Hiatt WR, Brass EP: Pathophysiology of intermittent claudication. In Creager MA et al [eds]: *Vascular medicine. A companion to Braunwald's heart disease*, ed 2, Philadelphia, 2013, Elsevier.)

TABLE 1 Fontaine Classification of Peripheral Artery Disease

Stage	Symptoms
I	Asymptomatic
II	Intermittent claudication
IIa	Pain free, claudication walking >200 m
IIb	Pain free, claudication walking <200 m
III	Rest and nocturnal pain
IV	Necrosis, gangrene

From Bonow RO et al: *Braunwald's heart disease: a textbook of cardiovascular medicine,* ed 9, Philadelphia, 2012, WB Saunders.

3. Borderline: 0.91 to 0.99 at rest
4. Abnormal: ≤0.90

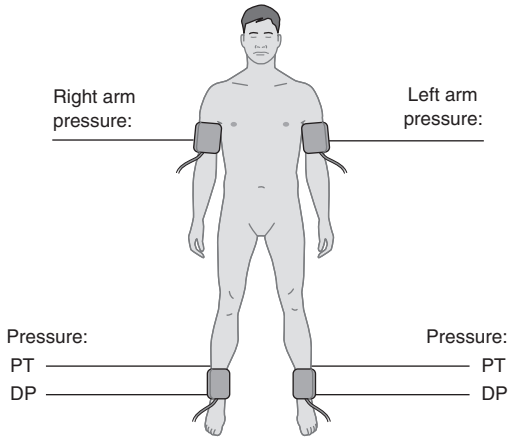
- ABI should be measured in both legs in all new patients (Fig. 3)
- Exercise ABI is recommended if resting ABI is borderline or normal (>0.9) and symptoms of claudication are suggestive
- Toe-brachial index should be used in patients suspected of PAD with ABI of >1.4. A TBI of <0.70 is abnormal and diagnostic of PAD. TBI may be used to assess perfusion in patients with suspected CLI
- Routine screening for lower-extremity PAD in the absence of risk factors, history, signs, or symptoms is not recommended
- PAD is recognized as a risk factor for abdominal aortic aneurysm (AAA), and in observational studies the prevalence of AAA was higher in patients with symptomatic PAD

LABORATORY TESTS

Laboratory tests can help identify risk factors or other potential causative etiologies. These include lipid profile, hemoglobin A_{1C}, d-dimer, and CRP/ESR.

How to Perform and Calculate the ABI

Partners Program ABI Interpretation
Above 0.90—Normal
0.71-0.90—Mild Obstruction
0.41-0.70—Moderate Obstruction
0.00-0.40—Severe Obstruction



RIGHT ABI **LEFT ABI**

$$\frac{\text{Higher right ankle pressure}}{\text{Higher arm pressure}} = \frac{\text{mm Hg}}{\text{mm Hg}} ____ = \frac{\text{Higher left ankle pressure}}{\text{Higher arm pressure}} = \frac{\text{mm Hg}}{\text{mm Hg}} = ____$$

EXAMPLE

$$\frac{\text{Higher ankle pressure}}{\text{Higher arm pressure}} = \frac{92 \text{ mm Hg}}{164 \text{ mm Hg}} = 0.56$$ See ABI Chart

FIG. 3 Performing pressure measurements and calculating the ankle-brachial index *(ABI).* To calculate the ABI, systolic pressures are determined in both arms and both ankles with the use of a handheld Doppler instrument. The highest readings for the dorsalis pedis (DP) and posterior tibial (PT) arteries are used to calculate the index. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.)

PHYSIOLOGIC TESTING AND IMAGING STUDIES

- Rest or exercise pulse volume recordings (PVRs) and segmental limb pressures are also useful. PVRs measure volume of limb flow per pulse in different segments of the limb (e.g., thigh, calf, ankle, metatarsal, and toes). They help to assess the location and severity of the lesion with alterations in the pulse volume contour and amplitude indicating proximal arterial obstruction.
- Duplex ultrasound (DUS) incorporates anatomic and physiologic evaluation by combining 2D ultrasound to visualize arterial segments and pulse wave Doppler to sample blood flow velocities at specific locations in the arterial lumen.
- Conventional contrast angiography remains the gold standard, but duplex ultrasonography, computed tomography angiography (CTA), and magnetic resonance angiography (MRA) have largely replaced catheter-based

angiography in anatomic assessment for revascularization. Contrast angiography (Fig. 4) is now reserved for patients with PAD who are being considered for endovascular revascularization. It allows assessment of translesional pressure gradients prior to percutaneous intervention.

- Carotid intima-media thickness and brachial artery flow-mediated dilation have shown promise but have not been widely applied.

Rx TREATMENT

The treatment goal in patients with PAD is to focus on cardiovascular risk factor reduction to decrease morbidity and mortality as well as to improve limb-related symptoms. There are also medical and surgical approaches to management of limb-related symptoms. Fig. 5 illustrates an approach to a patient with PAD. ACCF/AHA guidelines for medical management of patients with peripheral artery disease are summarized in Table 2.

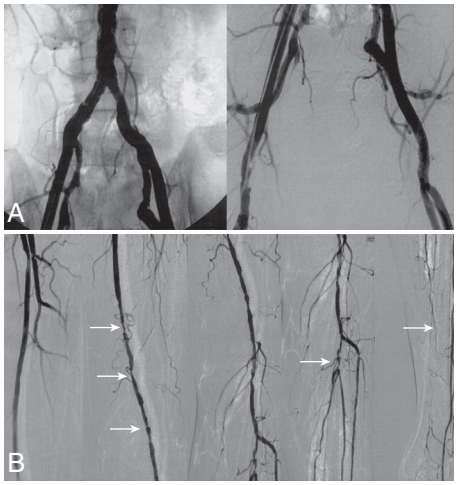


FIG. 4 Angiogram of a patient with disabling left calf claudication. A, The aorta and bilateral common iliac arteries are patent. **B,** The left superficial femoral artery has multiple stenotic lesions *(arrows).* There is a significant stenosis of the left tibioperoneal trunk and left posterior tibial artery *(arrows).* (From Zipes DP et al [eds]: *Braunwald's heart disease,* ed 7, Philadelphia, 2005, WB Saunders.)

MEDICAL THERAPY (TABLE 3)

LOWERING CARDIOVASCULAR RISK FACTORS, MORBIDITY, AND MORTALITY:

- Smoking cessation or avoidance of secondhand smoke should be emphasized in patients with PAD at each visit with assistance of behavioral and pharmacologic treatment (Class I).
- Proper foot care, including use of appropriate footwear, chiropody/podiatric medicine, daily foot inspection, skin cleansing, and use of topical moisturizing creams, should be encouraged, and skin lesions and ulcerations should be addressed urgently in all patients with diabetes and lower-extremity PAD (Class I).
- A foot infection should be suspected in patients presenting with local pain, peri-wound erythema, edema, or discharge; these patients should undergo prompt diagnosis and treatment with an interdisciplinary care team to avoid amputation.
- Antiplatelet therapy is indicated to reduce risk of myocardial infarction, stroke, and

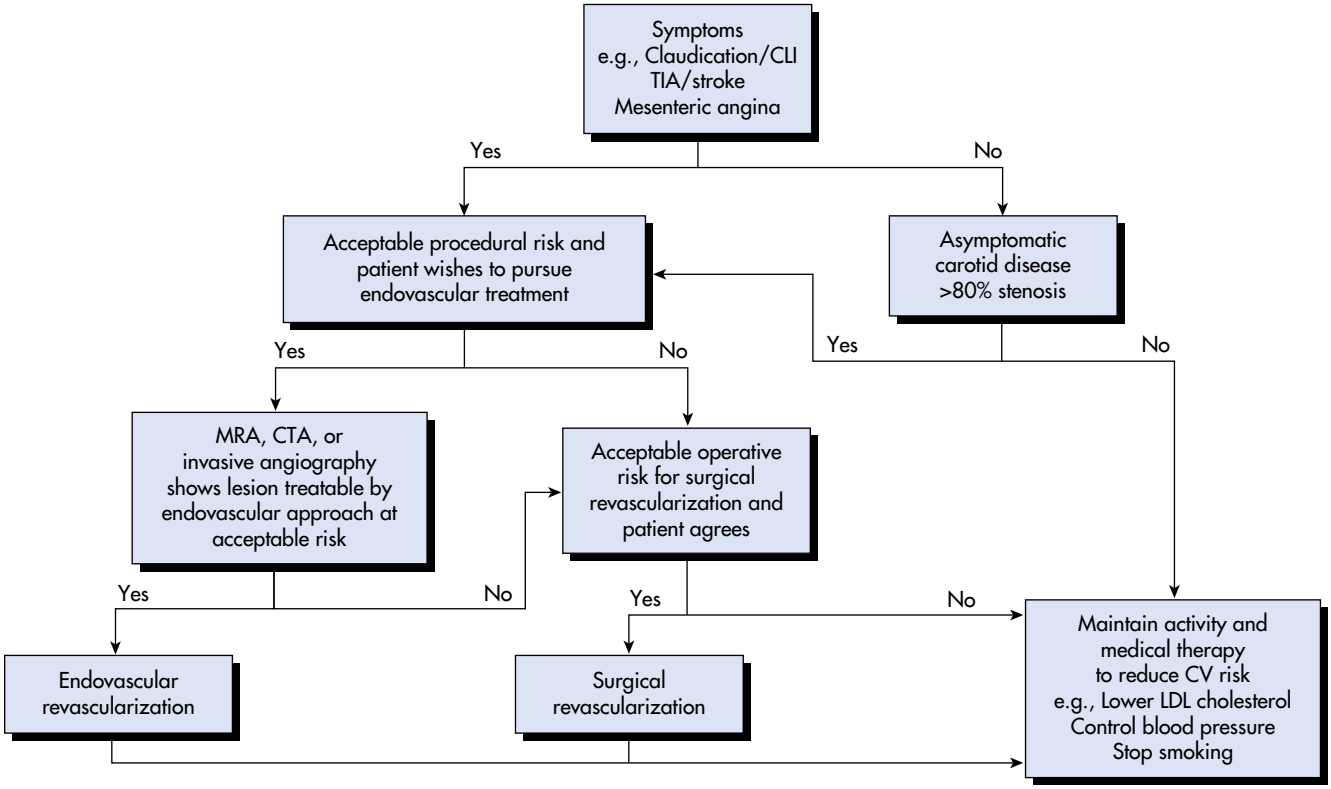


FIG. 5 Approach to a patient with peripheral artery disease. This strategy is based on assessment of the risk for adverse events with and without treatment by taking into consideration procedural or operative risks and the patient's informed decision to proceed with revascularization. *CLI,* Critical limb ischemia; *CTA,* computed tomographic angiography; *CV,* cardiovascular; *LDL,* low-density lipoprotein; *MRA,* magnetic resonance angiography; *TIA,* transient ischemic attack. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

TABLE 2 ACCF/AHA Guidelines for Medical Therapy for Patients with Peripheral Artery Disease

COR	Indication	LOE
I	1. Antiplatelet therapy with aspirin alone (range, 75 to 325 mg/day) or clopidogrel alone (75 mg/day) is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD.	A
	2. Treatment with a statin medication is indicated for all patients with PAD.	A
	3. Antihypertensive therapy should be administered to patients with hypertension and PAD to reduce the risk of MI, stroke, heart failure, and cardiovascular death.	A
	4. Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit.	A
	5. Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (varenicline, bupropion, and/or nicotine replacement therapy) and/or referral to a smoking cessation program.	A
	6. Patients with PAD should avoid exposure to environmental tobacco smoke at work, at home, and in public places.	B-NR
	7. Management of diabetes mellitus in the patient with PAD should be coordinated between members of the health care team.	C-EO
	8. Cilostazol is an effective therapy to improve symptoms and increase walking distance in patients with claudication.	A
	9. Patients with PAD should have an annual influenza vaccination.	C-EO
IIa	1. In asymptomatic patients with PAD (ABI ≤0.90), antiplatelet therapy is reasonable to reduce the risk of MI, stroke, or vascular death.	C-EO
	2. The use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD.	A
	3. Glycemic control can be beneficial for patients with CLI to reduce limb-related outcomes.	B-NR
IIb	1. In asymptomatic patients with borderline ABI (0.91-0.99), the usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death is uncertain.	B-R
	2. The effectiveness of dual-antiplatelet therapy (aspirin and clopidogrel) to reduce the risk of cardiovascular ischemic events in patients with symptomatic PAD is not well established.	B-R
	3. Dual-antiplatelet therapy (aspirin and clopidogrel) may be reasonable to reduce the risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization.	C-LD
	4. The overall clinical benefit of vorapaxar added to existing antiplatelet therapy in patients with symptomatic PAD is uncertain.	B-R
	5. The usefulness of anticoagulation to improve patency after lower extremity autogenous vein or prosthetic bypass is uncertain.	B-R
III	1. Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD.	A
	2. Pentoxifylline is not effective for treatment of claudication.	B-R
	3. Chelation therapy (e.g., ethylenediaminetetraacetic acid) is not beneficial for treatment of claudication.	B-R
	4. B-complex vitamin supplementation to lower homocysteine levels for prevention of cardiovascular events in patients with PAD is not recommended.	B-R

ABI, Ankle-brachial index; *ACCF,* American College of Cardiology Foundation; *AHA,* American Heart Association; *CLI,* critical limb ischemia; *COR,* class of recommendation; *LOE,* level of evidence; *MI,* myocardial infarction.

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

vascular death in individuals with symptomatic PAD with either aspirin (75 to 325 mg) or clopidogrel (75 mg) (Class I) and in asymptomatic patients (Class IIa). Uncertain benefit has been observed with combination aspirin and clopidogrel therapy (Class IIb). Limited data on use of newer P2Y12 receptor antagonists in PAD. In the EUCLID trial, ticagrelor was not shown to be superior to clopidogrel for the reduction of cardiovascular events, with major bleeding being similar in the two groups. Uncertain benefit with vorapaxar (Class IIb).

- Anticoagulation with low-dose (2.5 mg twice daily) rivaroxaban (Xarelto) plus aspirin daily showed significant reductions in both major cardiovascular and limb events, including amputations, in patients with peripheral arterial disease in the COMPASS trial.
- Warfarin is not indicated except in select postsurgical bypass conditions.
- Lipid-lowering therapy in patients with lower limb PAD has been shown to help slow disease progression, alleviate symptoms, and improve walking distance. The 2018 ACC/AHA Guideline on the Treatment of Blood Cholesterol recommends that patients with atherosclerotic PAD receive high-intensity statin therapy in order to lower risk of cardiovascular events regardless of baseline cholesterol values (Class I). In patients who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe (Class I). Prior guidelines have recommended goal LDL cholesterol of <100 mg/dl and possibly <70 mg/dl in high-risk patients.
- Management of hypertension should be in accordance with current HTN guidelines.
- Control of blood sugar in diabetic patients with PAD is recommended (hemoglobin A_{1C} goal <6.5), although studies have failed to demonstrate a beneficial effect on intensive insulin therapy in lowering risk of PAD. Annual influenza vaccination reduces CV event rates in patients with PAD (Class I).

TREATMENT OF CLAUDICATION:

- Exercise therapy: Supervised exercise-training may be as beneficial as stent revascularization in symptomatic improvement. Patients should be prescribed exercise for a minimum of 30 to 45 min, in sessions performed at least three times per wk for a minimum of 12 wk (Class I).
  1. Pharmacologic therapy:
     a. Cilostazol (100 mg bid) is indicated as effective therapy for enabling pain-free and maximal walking distance (Class 1). It is a phosphodiesterase (PDE-3) inhibitor that reduces platelet aggregation and causes vasodilatation. It may have an added benefit of reducing restenosis and repeat revascularization following endovascular therapy. Cilostazol is contraindicated in patients with systolic heart failure.
     b. Pentoxifylline is no longer considered effective in treatment of claudication (Class III).

REVASCULARIZATION

In general, there is no difference in clinical outcomes in percutaneous vs. surgical revascularization in iliac and femoropopliteal disease except for the higher morbidity with surgery and greater re-interventions in the percutaneous approach.

- The 2016 ACC/AHA guidelines on PAD have recommended revascularization as a reasonable treatment option for the patient with lifestyle-limiting claudication with inadequate response to guideline-directed medical therapy. The following approach is discussed:
  1. Considerations in percutaneous/endovascular treatment:
     a. In patients with a vocational- or lifestyle-limiting disability due to claudication or limb ischemia from either significant aortoiliac or femoropopliteal disease despite optimal medical therapy when clinical features

TABLE 3 Approved Medical Therapies for Patients with Peripheral Artery Disease (PAD)

			Indications			
Therapy	**Mechanism of Action**	**Key Clinical Trials**	**European Medicines Agency**	**European Society of Cardiology**	**FDA**	**ACC/AHA**
Statin (Class effect)	Cholesterol lowering HMG-CoA reductase inhibitor	Heart Protection Study 13% RRR with simvastatin 40 mg daily vs. placebo in all-cause mortality, 18% RRR in coronary heart death Approval for PAD based on subgroup of 6748 patients, 2700 had PAD and no CHD	Reduction in MACE and mortality	Class I for lipid lowering with LDL <2.5 mmol/L, optimally <1.8 mmol/L	Reduction in MACE and mortality	Class I, LOE A
ACEI or ARB (Class effect)	Blood pressure lowering and other vascular effects Renin-angiotensin system inhibition	HOPE 22% RRR with ramipril 10 mg daily vs. placebo for composite of MI, stroke, or CV death Approval for PAD based on subgroup of 4051 patients, 1725 with "clinical PAD"	Reduction in MACE	Class I for blood pressure lowering to ≤140/90 mm Hg	Reduction in MACE	Class I, LOE A for antihypertensive therapy Class IIa, LOE A for ACEI/ARB specifically
Clopidogrel	Antiplatelet $P2Y_{12}$ inhibitor	CAPRIE 8.7% RRR vs. aspirin for composite of ischemic stroke, MI, or vascular death Approval for PAD based on subgroup of 6452 patients	As monotherapy Reduction in MACE	Class I monotherapy for risk reduction Class I added to ASA after lower extremity stenting	As monotherapy Reduction in MACE	Class I, LOE A for monotherapy Class IIb, LOE B-R, C-LD, when added to aspirin as DAPT
Vorapaxar	Antiplatelet PAR-1 antagonist	TRA2P-TIMI 50 20% RRR vs. placebo for composite of MI, stroke, or CV death Approval for PAD based on subgroup of 3787 patients	Added to aspirin or clopidogrel Reduction in MACE, limb benefits mentioned	Approved after most recent guidelines	Added to aspirin and/or clopidogrel Reduction in MACE	Class IIb, LOE B-R added to aspirin and/or clopidogrel
Pentoxifylline	Decreases blood viscosity Mechanism not fully understood	Meta-analysis of six studies including 788 patients who showed minimal increase in maximal walking distance with (+59 m)	Improve function and symptoms in patients with intermittent claudication	Described but no clear recommendation	Improve function and symptoms in patients with intermittent claudication	Class III, LOE B-R
Cilostazol	Antiplatelet and vasodilator Mechanism not fully understood	50 mg bid (n = 303), 100 mg bid (n = 998), and placebo (n = 973) Improvement in maximal walking distance with 100 mg bid, expressed as the percent mean change from baseline, 28%-100% vs. placebo, which were −10%-41%	Reduction of symptoms of intermittent claudication, as indicated by an increased walking distance	Class I for symptoms	Reduction of symptoms of intermittent claudication, as indicated by an increased walking distance	Class I, LOE A

ACC/AHA, American College of Cardiology/American Heart Association; *ACEI,* angiotensin-converting enzyme inhibitor; *ARB,* angiotensin receptor blocker; *bid,* twice daily; *ASA,* acetylsalicylic acid; *CAPRIE,* Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; *CHD,* coronary heart disease; *CV,* cardiovascular; *DAPT,* dual-antiplatelet therapy; *FDA,* U.S. Food and Drug Administration; *HOPE,* Heart Outcomes Prevention Evaluation; *LDL,* low-density lipoprotein; *LOE,* level of evidence *(B-R,* moderate-quality evidence from one or more randomized clinical trials; *C-LD,* randomized or nonrandomized observational/registry studies or a meta-analysis); *MACE,* major adverse cardiovascular events; *MI,* myocardial infarction; *PAR-1,* protease-activated receptor 1; *RRR,* relative risk reduction; *TRA2P-TIMI 50,* Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

suggest a reasonable likelihood of symptomatic improvement with endovascular intervention.
   b. Endovascular intervention is not indicated as prophylactic therapy in an asymptomatic patient with lower-extremity PAD.
   c. Durability of endovascular intervention is greater in iliac artery than in the femoropopliteal segment.
2. Considerations in surgical revascularization:
   a. Individuals with claudication symptoms who have a significant functional disability that is vocational or lifestyle limiting. These patients need to also be unresponsive to exercise or pharmacotherapy and should have a reasonable likelihood of symptomatic improvement with an acceptable surgical risk and technical factors favoring surgical vs. endovascular approach.
   b. Autogenous vein graft is superior to prosthetic graft if surgical revascularization is performed (Class I).
   c. Iliac or femoropopliteal disease with long segments; multifocal segments; long segment occlusions; and eccentric, calcified stenosis, which are less amenable to percutaneous interventions.
   d. Surgical intervention is not indicated to prevent progression to limb-threatening ischemia in patients with intermittent claudication as generally claudication does not progress to severe ischemia.
3. Revascularization for acute limb ischemia (Table 4):
   a. Management approach is dependent on whether affected limb is viable, threatened, or irreversible. Initial management will depend on the absence of sensation and movement. If absent, then urgent surgery should be considered.
   b. Heparin should be given to all patients with ALI; direct thrombin inhibitor is used if patient has history of HIT.
   c. Catheter-based thrombolysis is effective in ALI with salvageable limb.
   d. Amputation should be performed in patients with irreversible damage.

DISPOSITION

Risk factors for atherosclerosis should be assessed, and appropriate modification instituted. Focus should be placed on smoking cessation, dietary adjustment, and pharmacotherapy for dyslipidemia, hyperglycemia, and hypertension. All patients with PAD should receive aspirin therapy unless contraindicated. Revascularization should be considered for refractory lifestyle-limiting symptoms.

TABLE 4 ACCF/AHA Guidelines for Management of Patients with Acute Limb Ischemia (ALI)

COR	Indication	LOE
I	1. Patients with ALI should be emergently evaluated by a clinician with sufficient experience to assess limb viability and implement appropriate therapy.	C-EO
	2. In patients with suspected ALI, initial clinical evaluation should rapidly assess limb viability and potential for salvage and does not require imaging.	C-LD
	3. In patients with ALI, systemic anticoagulation with heparin should be administered unless contraindicated.	C-EO
	4. In patients with ALI, the revascularization strategy should be determined by local resources and patient factors (e.g., etiology, degree of ischemia).	C-LD
	5. Catheter-based thrombolysis is effective for patients with ALI and a salvageable limb.	A
	6. Amputation should be performed as the first procedure in patients with a nonsalvageable limb.	C-LD
	7. Patients with ALI should be monitored and treated (e.g., fasciotomy) for compartment syndrome after revascularization.	C-LD
	8. In the patient with ALI, a comprehensive history should be obtained to determine the cause of thrombosis and/or embolization.	C-EO
IIa	1. In patients with ALI with a salvageable limb, percutaneous mechanical thrombectomy can be useful as adjunctive therapy to thrombolysis.	B-NR
	2. In patients with ALI due to embolism and with a salvageable limb, surgical thromboembolectomy can be effective.	C-LD
	3. In the patient with a history of ALI, testing for a cardiovascular cause of thromboembolism can be useful.	C-EO
IIb	The usefulness of ultrasound-accelerated catheter-based thrombolysis for patients with ALI with a salvageable limb is unknown.	C-LD

ACCF, American College of Cardiology Foundation; *AHA,* American Heart Association; *COR,* class of recommendation; *LOE,* level of evidence.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.

- More than 1 in 6 patients with peripheral arterial disease who undergo peripheral arterial revascularization have unplanned readmission within 30 days with high associated mortality risks and costs. Procedure- and patient-related factors were the primary reasons for readmission.[1]

REFERRAL

Consultation with vascular medicine, vascular surgery, interventional cardiology, or other physicians with expertise in PAD is recommended in patients with rest pain, functional disability from pain, ABI <0.90 at rest, or any physical signs of limb ischemia or gangrene.

PEARLS & CONSIDERATIONS

COMMENTS

- PAD is a highly prevalent disease process that remains underdiagnosed and undertreated.
- Patients with PAD are at markedly higher risk of future coronary, cerebrovascular, and other vascular events.
- Medical treatment is aimed mainly at cardiovascular risk factor modification, except for cilostazol.
- Studies of the natural history of claudication show the relative safety of initial conservative treatment of PAD in the absence of critical limb ischemia.
- When PAD limits a patient's ability to walk and exercise, revascularization should be considered.
- Exercise training is an important and often neglected treatment strategy that has proven beneficial in improving functional status, reducing symptoms, and improving quality of life. Exercise capacity alone is the strongest predictor of mortality in patients with PAD.
- Surgical intervention should be considered in patients who meet the criteria for intervention but have lesions that are not amenable to PTA/stenting or in older patients with a low surgical risk. Advances in endovascular therapy have broadened the range of revascularization options for refractory claudication and critical and acute limb ischemia in patients with multiple comorbidities.

PREVENTION

Cardiovascular disease is the major cause of death in patients with intermittent claudication. Therefore, the treatment of claudication is directed not only at improving walking distance but also at reducing cardiovascular risk.

PATIENT & FAMILY EDUCATION

The following organizations offer more information about PAD:

- American College of Cardiology (www.acc.org)
- Vascular Disease Foundation (www.vdf.org)

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Peripheral Arterial Disease (Patient Information)

AUTHORS: **Peter Nguyen, MD,** and **Pranav M. Patel, MD, FACC, FAHA, FSCAI**

[1]Secemsky EA et al: Readmissions after revascularization procedures for peripheral arterial disease, *Ann Int Med* 168:93-99, 2018.

FIG. E1 Ulceration and gangrene of the foot representative of critical limb ischemia in a patient with peripheral artery disease. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

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Perirectal Abscess PTG

BASIC INFORMATION

DEFINITION

A perirectal abscess is a localized inflammatory process that can be associated with infections of soft tissue and anal glands based on anatomic location. Perianal and perirectal abscesses may be simple or complex, causing suppuration. Infections in these spaces may be classified as superficial perianal or perirectal with involvement in the following anatomic spaces: Ischiorectal, intersphincteric, perianal, and supralevator. The Parks classification of anorectal abscess is subdivided into intersphincteric, transsphincteric, suprasphincteric, and extrasphincteric abscess (Fig. 1).

SYNONYMS

Rectal abscess
Perianal abscess
Anorectal abscess

ICD-10CM CODES
K61.0 Anal abscess
K61.1 Rectal abscess

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Commonly encountered
PREDOMINANT SEX: Male > female
PREDOMINANT AGE: All ages
PEAK INCIDENCE: Not seasonal; common
GENETICS: None known

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Localized perirectal or anal pain—often worsened with movement or straining
- Perirectal erythema or cellulitis
- Perirectal mass by inspection or palpation
- Fever and signs of sepsis with deep abscess
- Urinary retention

ETIOLOGY

- Polymicrobial aerobic and anaerobic bacteria involving one of the anatomic spaces (see "Definition"), often associated with localized trauma
- Microbiology: Most infections are polymicrobial, mixed enteric, and skin flora
- Predominant anaerobic bacteria:
  1. *Bacteroides fragilis*
  2. *Peptostreptococcus* spp.
  3. *Prevotella* spp.
  4. *Porphyromonas* spp.
  5. *Clostridium* spp.
  6. *Fusobacterium* spp.
- Predominant aerobic bacteria:
  1. *Staphylococcus aureus*
  2. *Streptococcus* spp.
  3. *Escherichia coli*
  4. *Enterococcus* spp.

Dx DIAGNOSIS

Many patients will have predisposing underlying conditions including:
- Malignancy or leukemia
- Immune deficiency
- Diabetes mellitus
- Recent surgery
- Steroid therapy

DIFFERENTIAL DIAGNOSIS

- Neutropenic enterocolitis
- Crohn disease (inflammatory bowel disease)
- Pilonidal disease
- Hidradenitis suppurativa
- Tuberculosis or actinomycosis; Chagas disease
- Cancerous lesions
- Chronic anal fistula
- Rectovaginal fistula
- Proctitis—often STD-associated, including syphilis, gonococcal, chlamydia, chancroid, condylomata acuminata
- AIDS-associated: Kaposi sarcoma, lymphoma, CMV

WORKUP

- Examination of rectal, perirectal/perineal areas
- Rule out necrotic process and crepitance suggesting deep tissue involvement
- Local aerobic and anaerobic culture
- Blood cultures if toxic, febrile, or compromised
- Possible sigmoidoscopy

IMAGING STUDIES

Usually not indicated unless extensive disease is suspected. CT has a sensitivity of 77% and is relatively poor in detecting a perirectal abscess in immunocompromised patients.

Rx TREATMENT

ACUTE GENERAL Rx

- Incision and drainage of abscess
- Debridement of necrotic tissue
- Rule out need for fistulectomy
- Local wound care—packing
- Sitz baths
- Antibiotic treatment: Directed toward coverage for mixed skin and enteric flora

OUTPATIENT—ORAL:
- Trimethoprim/sulfamethoxazole DS bid or ciprofloxacin 500 mg bid or levofloxacin 500 mg q24h plus metronidazole 500 mg q8h x 7 to 10 days
- Amoxicillin/clavulanic acid 875 to 1000 mg 1 tabs bid
- Clindamycin 150 to 300 mg PO q6 to 8h ± ciprofloxacin

INPATIENT—INTRAVENOUS:
- Piperacillin/tazobactam 3.375 g IV q6 to 8h
- Ampicillin/sulbactam 1.5 to 3 g IV q6h
- Cefotetan 1 to 2 g IV q8h
- Imipenem or meropenem 500 to 1000 mg IV q8h

DISPOSITION

Follow-up with a general surgeon or infectious disease physician is often warranted.

REFERRAL

- General surgeon or colorectal surgeon for drainage.
- AIDS specialist may be needed for perirectal complications of HIV infection.
- Gastroenterologist follow-up may be warranted in Crohn disease with perirectal fistula and other complications.
- Endoscopic ultrasound–guided perirectal abscess drainage is a recently described promising alternative treatment.

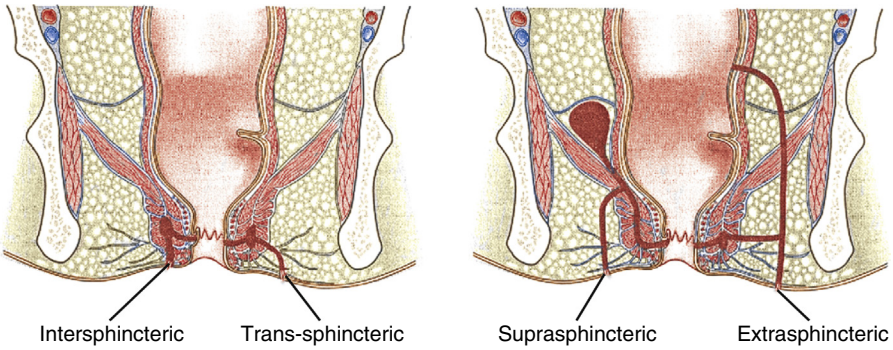

FIG. 1 Parks classification of anorectal abscess. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, WB Saunders.)

PEARLS & CONSIDERATIONS

Perirectal abscess may be a presenting manifestation of type 2 diabetes mellitus in older adults. Check the blood sugar in patients to exclude the possibility of undiagnosed diabetes mellitus.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Perirectal Abscess (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Caliste X et al: Sensitivity of computed tomography in detection of perirectal abscess, *Am Surg* 77(2):166-168, 2011.

Choi EK et al: Endoscopic ultrasound-guided perirectal abscess drainage without a drainage catheter: a case series, *Clin Endosc* 50:297-300, 2017.

Javed S, Ho S: Endoscopic ultrasound guided perirectal abscess drainage using a novel lumen-apposing covered metal stent, *Am J Gastroenterol* 111:1381, 2016.

Klein JW: Common anal problems, *Med Clin North Am* 98:609-623, 2014.

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BASIC INFORMATION

DEFINITION

Peritonitis refers to the acute onset of severe abdominal pain caused by peritoneal inflammation.

Secondary peritonitis is peritonitis stemming from another condition; commonly a defect in an abdominal viscus.

SYNONYMS

Acute abdomen
Surgical abdomen

ICD-10CM CODES

K65.0	Generalized (acute) peritonitis
K65.8	Other peritonitis
K65.9	Peritonitis, unspecified
A18.31	Tuberculous peritonitis
A54.85	Gonococcal peritonitis
A74.81	Chlamydial peritonitis
K35.2	Acute appendicitis with generalized peritonitis
K35.3	Acute appendicitis with localized peritonitis
K65.2	Spontaneous bacterial peritonitis
N73.3	Female acute pelvic peritonitis
N73.4	Female chronic pelvic peritonitis
N73.5	Female pelvic peritonitis, unspecified
P78.1	Other neonatal peritonitis

EPIDEMIOLOGY & DEMOGRAPHICS

Common presentation as a result of diverse etiologies; for example, 5% to 10% of the population has acute appendicitis at some point in their lives.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute abdominal pain
- Abdominal distention and ascites
- Abdominal rigidity, rebound, and guarding
- Altered mental status
- Fever, chills
- Exacerbation with movement
- Anorexia, nausea, and vomiting
- Constipation or diarrhea
- Decreased bowel sounds
- Hypotension and tachycardia
- Tachypnea, dyspnea

ETIOLOGY

- One of the early steps is disturbance in gut flora with overgrowth and extraintestinal organismal overtake. Most common are gram-negative bacteria (*Escherichia coli, Enterobacter, Klebsiella, Proteus*), gram-positive bacteria (enterococci, streptococci, staphylococci), anaerobic bacteria (*Bacteroides, Clostridium*), and fungi
- It can be acute perforation peritonitis: Gastrointestinal perforation, intestinal ischemia, pelvic peritonitis, and other forms
- Postoperative peritonitis: Anastomotic leak, accidental perforation, and devascularization
- Posttraumatic peritonitis: After blunt or penetrating abdominal trauma

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Postoperative: Abscess, sepsis, bowel obstruction, injury to internal organs
- Gastrointestinal: Perforated viscus, appendicitis, inflammatory bowel disease, infectious colitis, diverticulitis, acute cholecystitis, peptic ulcer perforation, pancreatitis, bowel obstruction
- Gynecologic: Ruptured ectopic pregnancy, pelvic inflammatory disease, ruptured hemorrhagic ovarian cyst, ovarian torsion, degenerating leiomyoma
- Urologic: Nephrolithiasis, interstitial cystitis
- Miscellaneous: Abdominal trauma, penetrating wounds, infections caused by intraperitoneal dialysis

WORKUP

- Acute peritonitis is mainly a clinical diagnosis based on patient history and physical examination.
- Laboratory and imaging studies assist in determining the need for and type of intervention.
- If patient is hemodynamically unstable, immediate diagnostic laparotomy should be performed in lieu of adjuvant diagnostic studies.

LABORATORY TESTS

- Ascitic fluid testing
  1. Anaerobic and aerobic cultures
  2. Cell count and differential
  3. Albumin, protein, amylase, bilirubin
  4. Glucose
  5. LDH
- Complete blood count: Leukocytosis, left shift, anemia
- SMA7: Electrolyte imbalances, kidney dysfunction
- Liver function tests: Indicative of cirrhosis as ascites from liver disease, cholelithiasis
- Amylase: Pancreatitis
- Blood cultures: Bacteremia, sepsis
- Blood gas: Respiratory versus metabolic acidosis
- Urinalysis and culture: Urinary tract infection
- Cervical cultures for gonorrhea and *Chlamydia*
- Urine/serum human chorionic gonadotropin

IMAGING STUDIES

- Abdominal series: Free air from perforation, small or large bowel dilation from obstruction, identification of fecalith
- Chest x-ray examination: Elevated diaphragm, pneumonia
- Pelvic/abdominal ultrasound: Abscess formation, abdominal mass, intrauterine versus ectopic pregnancy, identify free fluid suggestive of hemorrhage or ascites
- CT: Mass, ascites

TREATMENT

NONPHARMACOLOGIC THERAPY

- IV hydration to correct dehydration, hypovolemia
- Blood transfusion to correct anemia from hemorrhage
- Nasogastric decompression, especially if obstruction is present
- Oxygen: Intubation if necessary
- Bed rest

ACUTE GENERAL Rx

- Surgery to correct underlying pathology, such as controlling hemorrhage, correcting perforation, draining abscess
- Broad-spectrum antibiotics to cover both gram-negative aerobic and gram-negative anaerobic bacteria:
  1. Mild-moderate disease: Piperacillin-tazobactam 3.375 g IV q6h or 4.5 g IV q8h *or* ticarcillin-clavulanate 3.1 g IV q6h. Alternative agents are ciprofloxacin 400 mg IV q12h or levofloxacin 750 mg IV q24h *plus* metronidazole 1 g IV q12h.
  2. Severe life-threatening disease: Imipenem 500 mg IV q6h or meropenem 1 g IV q8h. Alternative agents are ampicillin *plus* metronidazole *plus* ciprofloxacin.
  3. Antibiotic therapy should be tailored to culture results and sensitivities.
- Pain control: Morphine or meperidine as needed (hold until diagnosis confirmed)

DISPOSITION

Depends on etiology of peritonitis, age of patient, coexisting medical disease, and duration of process before presentation.

REFERRAL

Surgical consultation is required in all cases of acute peritonitis.

PEARLS & CONSIDERATIONS

Computed tomographic scan guides therapeutic approach and should be considered as the primary imaging study if available. As with forms of sepsis, early administration of broad spectrum antibiotics, fluid resuscitation, and rapidly obtaining anatomic source control (when appropriate) will lead to improved outcomes.

AUTHOR: **Ghamar Bitar, MD**

BASIC INFORMATION

DEFINITION

Peritonsillar abscess is an acute infection located between the capsule of the palatine tonsil and the superior constrictor muscle of the pharynx.

SYNONYMS

Quinsy
PTA

ICD-10CM CODE
J36 Peritonsillar abscess

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 30:100,000/yr for ages 5 to 59. For adolescents, the incidence is 40:100,000/yr. It is the most common deep infection of the head and neck in children and adolescents, accounting for at least 50% of cases.
PREVALENCE: 45,000 cases/yr in the U.S.
PREDOMINANT SEX: Male > female
PREDOMINANT AGE: Highest incidence is adults aged 20 to 40 yr
PEAK INCIDENCE: Bimodal frequency during the yr, with highest occurrence from November to December and April to May
RISK FACTORS: Smoking, periodontal disease, oropharyngeal or dental infection, male gender

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- There is often a delay of 2 to 5 days between abscess formation and local and systemic symptoms
- Sore throat, which may be severe and unilateral (Table 1)
- Dysphagia and odynophagia
- Otalgia on the side of abscess
- Foul-smelling breath
- Facial swelling
- Drooling
- Headache
- Fever
- Trismus: The examination of the pharynx can be limited by trismus
- Hoarseness, muffled voice (also called "hot potato voice")
- Tender submandibular and anterior cervical lymph nodes
- Tonsillar hypertrophy with likely peritonsillar edema
- Contralateral deflection of the uvula: The distinguishing feature of peritonsillar abscess is inferior medial displacement of the infected tonsil with contralateral deviation of the uvula (Fig. E1)
- Stridor

ETIOLOGY

- Peritonsillar abscess is usually a complication of tonsillitis or acute bacterial pharyngitis caused by blockage of salivary ducts. Tonsillitis → peritonsillar cellulitis → peritonsillar abscess.
- Group A β-hemolytic *Streptococcus* is the most common bacterial cause, accounting for 15% to 30% of cases in children and 5% to 10% of cases in adults.
- Less common aerobic causes are *Staphylococcus aureus, Haemophilus influenzae, Neisseria* species.
- The most common anaerobic organism is *Fusobacterium.*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hypertrophic tonsillitis
- Infectious mononucleosis
- Peritonsillar cellulitis
- Retropharyngeal abscess
- Epiglottitis
- Dental abscess (retromolar)
- Lymphoma
- Ludwig angina
- Tubercular granuloma
- Cervical adenitis
- Diphtheria
- Foreign body
- Neoplasm

WORKUP

- Based on history and physical exam. Aspiration of pus established diagnosis of peritonsillar abscess.
- Consider additional testing if presentation is less clear.

LABORATORY TESTS

- Consider rapid strep antigen testing and/or pharyngeal culture and sensitivity.
- Aspiration of the abscess for culture and sensitivity (see "Treatment" for role of aspiration in Tx).
- Consider lab testing for mononucleosis (patients with peritonsillar abscess have a 20% incidence of mononucleosis).

IMAGING STUDIES

- Consider ultrasound, CT scan (Fig. 2), or MRI (Fig. 3) to help differentiate abscess from cellulitis or mass when diagnosis is unclear.
- Intraoral ultrasound may improve diagnosis and aspiration of PTA compared with visual inspection in adult patients.
- MRI provides better soft-tissue differentiation than CT.

TREATMENT

NONPHARMACOLOGIC THERAPY

Drainage of the abscess by needle aspiration or by surgical incision and drainage. Intraoral ultrasound-guided needle aspira-

TABLE 1 Clinical Differentiation of Common Conditions Arising as Sore Throat

Feature	Viral Pharyngitis	Bacterial Tonsillitis	Peritonsillar Abscess	Epiglottitis
Tonsillar Enlargement	Usual	Rare	None	None
Tonsillar Exudates	Occasional (mononucleosis)	Usual	Often	None
Tonsillar Asymmetry	None	None	Usual	None
Trismus (Inability to Open Jaw)	None	None	Usual	None
Cervical Adenopathy	Occasional	Usual (tender)	Usual (tender)	None
Tender Larynx	Rare	None	None	Usual

From Goldman L, Schafer AI: *Goldman's Cecil Medicine*, ed 24, Philadelphia, 2012, Saunders.

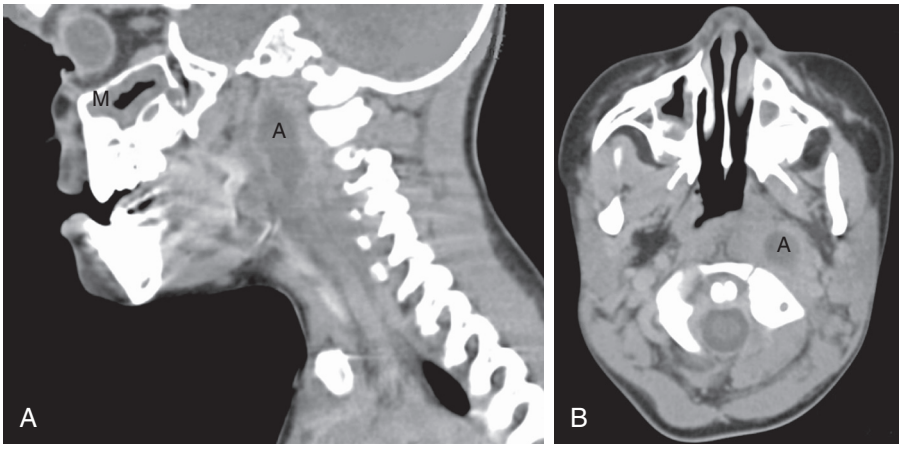

FIG. 2 Computed tomography of parapharyngeal abscess in a 3-yr-old child. A, Sagittal section demonstrating parapharyngeal abscess *(A)* and mucosal swelling *(M)* in the maxillary sinus. **B,** Coronal section of parapharyngeal abscess *(A).* (From Kliegman RM et al: *Nelson textbook of pediatrics*, ed 19, Philadelphia, 2011, Saunders.)

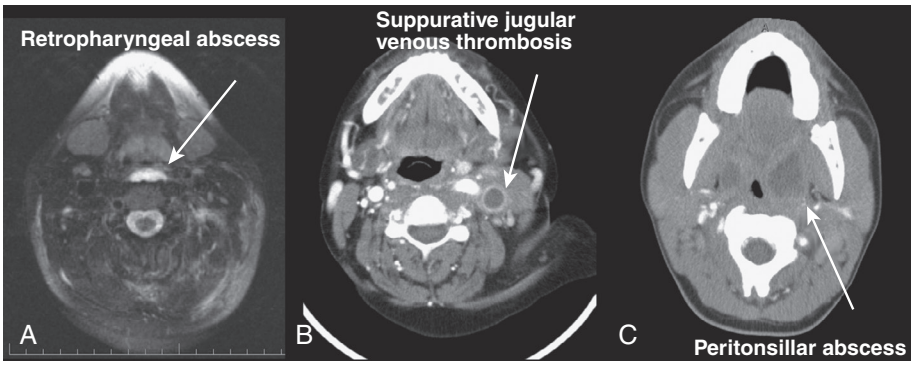

FIG. 3 Magnetic resonance imaging and computed tomography images showing a variety of life-threatening head and neck infections including retropharyngeal abscess **(A),** suppurative jugular venous thrombosis **(B),** and peritonsillar abscess **(C).** (Images provided by Dr. Joshua Brody, Department of Radiology, the Cooper Health System, Camden, NJ. In Parrillo JE, Dellinger RP: *Critical Care Medicine, Principles of Diagnosis and Management in the Adult*, ed 5, Philadelphia, 2019, Elsevier.)

tion is a useful adjunct in the presence of trismus.

ACUTE GENERAL Rx

- Aspiration or surgical drainage AND antibiotics for 10 to 14 days
- Initial antibiotics should cover group A *Streptococcus* and anaerobes
- Intravenous
  1. Piperacillin/tazobactam or ticarcillin/clavulanate. If penicillin allergic, use IV clindamycin (600 to 900 mg IV q8h)
  2. Ampicillin-sulbactam 3 g q6h
  3. Penicillin G 10 million units q6h AND metronidazole 500 mg q6h (may use clindamycin 900 mg q8h if penicillin allergic)
- OR oral
  1. Amoxicillin-clavulanic acid 875 mg twice daily
  2. Penicillin VK 500 mg 4 times daily AND metronidazole 500 mg 4 times daily
  3. Clindamycin 600 mg twice daily or 300 mg 4 times daily
- Selection of antibiotics should be guided by culture and sensitivity of the organism. Consulting local antimicrobial guidelines for resistance profiles is also advisable for empiric coverage before culture results are available

CHRONIC Rx

- Tonsillectomy can be considered 3 to 6 mo after diagnosis of peritonsillar abscess with or without the diagnosis of recurrent tonsillitis.
- Though rare, in adults and children with an acute case of peritonsillar abscess and a history of recurrent pharyngitis or previous peritonsillar abscess, a specialist may recommend a *quinsy or hot tonsillectomy,* an immediate removal of the tonsils after starting IV antibiotics.

DISPOSITION

- Successful treatment is defined by symptomatic improvement in sore throat, fever, and/or tonsillar swelling within 24 hr of intervention.
- Treatment failure is defined by lack of symptomatic improvement or worsening despite 24 hr of antimicrobial therapy (with or without surgical drainage).

REFERRAL

- Consider ENT or diagnostic radiology for drainage of abscess.
- Consider ENT for tonsillectomy if criteria are met.

PEARLS & CONSIDERATIONS

COMMENTS

- Risk for a recurrence is immediate (within 4 days) and long term (2 to 3 yr).
- Most recurrences occur shortly after the initial presentation, suggesting continued infection rather than recurrence.
- Overall recurrence rate is 10% to 15%.
- Supportive treatment for pain control and hydration. Newer reports suggest a single dose of dexamethasone (10 mg) administered following needle aspiration will reduce pain at 24 hours as compared with placebo (see "Suggested Readings").

PREVENTION

- Adequate treatment of peritonsillar abscess.
- Up to 30% of patients with peritonsillar abscess meet criteria for tonsillectomy.

PATIENT & FAMILY EDUCATION

Advise family members to call with any trouble breathing, swallowing, or talking.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Peter J. Sell, DO, Amity Rubeor, DO, CAQSM,** and **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Chau JKM et al: Corticosteroids in peritonsillar abscess treatment: a blinded placebo-controlled clinical trial, *Laryngoscope* 124:97-103, 2014.

Galioto NJ: Peritonsillar abscess, *Am Fam Physician* 95:501-506, 2017.

Hur K et al: Adjunct steroids in the treatment of peritonsillar abscess: a systematic review, *Laryngoscope* 128:72-77, 2018.

Powell EL et al: A review of the pathogenesis of adult peritonsillar abscess: time for a re-evaluation, *J Antimicrob Chemother* 68:1941-1950, 2013.

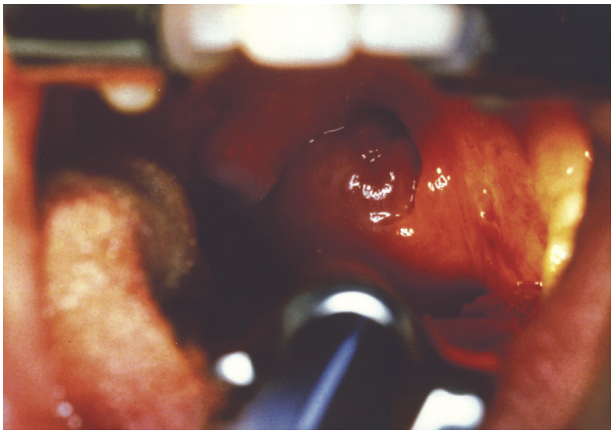

FIG. E1 Peritonsillar abscess with uvular displacement to the right. (From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, WB Saunders.)

BASIC INFORMATION

DEFINITION

Pertussis is a prolonged bacterial infection of the upper respiratory tract characterized by paroxysms of an intense cough.

SYNONYM

Whooping cough

ICD-10CM CODES

A37.00	Whooping cough due to Bordetella pertussis without pneumonia
A37.01	Whooping cough due to Bordetella pertussis with pneumonia
A37.10	Whooping cough due to Bordetella parapertussis without pneumonia
A37.11	Whooping cough due to Bordetella parapertussis with pneumonia
A37.80	Whooping cough due to other Bordetella species without pneumonia
A37.81	Whooping cough due to other Bordetella species with pneumonia
A37.90	Whooping cough, unspecified species without pneumonia
A37.91	Whooping cough, unspecified species with pneumonia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Case reports from 2016 were 15,737, including seven deaths. This represents a decrease in the number of case reports compared with each of the 3 previous yr. The reported rates were 20,762 and 32,971 in 2015 and 2014, respectively. In 2012, there were 48,277 cases reported, which is the highest rate reported since 1955. The highest incidence, in 2016, was among infants <6 mo (85.5/100,000), with a second peak in adolescents 11 to 19 yr of age (13.9/100,000).

PEAK INCIDENCE:

- Childhood
- Usually affects children aged <1 yr
- Increasing infections seen in adolescence

PREDOMINANT AGE:

- 50% in children aged <1 yr
- 20% in children aged >15 yr
- Classically an infection of infants and young children, pertussis is often overlooked as a cause of chronic cough in adults. However, a resurgence of pertussis has been observed in recent yr, with nearly 50% of all cases identified in adolescents and adults, likely due to waning immunity and decreased effectiveness of acellular vaccines in early childhood compared to older, whole-cell-derived vaccines

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Infection is characterized by three phases: Catarrhal, paroxysmal, and convalescent.
- Catarrhal phase: Usually begins with a 1- to 2-wk prodrome that resembles a common cold. This phase may be mild or absent in adolescents and adults given partial immunity from prior immunization.
- After this initial phase, increased production of mucus occurs. Excessive lacrimation and conjunctival infection should heighten the suspicion for pertussis.
- Paroxysmal phase: Increased mucus production is followed by an intense, paroxysmal cough, ending with gasps and an inspiratory whoop.
- In some children, apnea, cyanosis, and anoxia are noted; posttussive gagging and vomiting are characteristic of pertussis.
- Cases can be severe and life-threatening in young infants, particularly children <6 mo old.
- When prolonged, frank exhaustion and even apnea occur. The paroxysmal phase lasts from 2 wk to 2 mo.
- Convalescent phase: Lasts over 2 mo and is characterized by cough of decreasing severity.
- See Box 1 for complications of pertussis.

ETIOLOGY

Bordetella pertussis, a gram-negative rod that adheres to human cilia and respiratory epithelia

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Croup
- Epiglottitis
- Foreign body aspiration
- Bacterial pneumonia
- Viral pneumonia

WORKUP

Pertussis is often overlooked as a cause of chronic cough, especially in adolescents and adults. The presence of posttussive emesis and/or inspiratory whoop increases the likelihood of pertussis but only modestly. Therefore, clinicians must use their overall impression in pursuing the diagnosis.

- Enzyme-linked immunosorbent assay for detection of antibody to pertussis. Polymerase chain reaction (PCR) is the most sensitive method for rapid detection of pertussis. PCR testing should be used only to confirm a diagnosis in persons with signs and symptoms consistent with pertussis. PCR testing sensitivity declines and is unlikely to be positive after 1 mo of infection. PCR testing after 5 days of treatment with antibiotics can cause false-negative results and is generally not recommended
- Blood cultures in hospitalized patients
- Chest x-ray
- Culture of bacteria, usually from nasopharynx by aspiration or by swabbing the posterior nasopharynx with a polyester-tipped, rayon-tipped, or nylon-flocked swab
- Immunofluorescent staining of nasopharyngeal secretions
- Serologic tests for immunoglobulin G (IgG) or A (IgA) are available. A twofold increase between acute and convalescent sera is considered proof of seroconversion. A single elevated IgG or IgA titer is considered diagnostic when no acute serum is available. Can be useful for diagnosis later in illness

BOX 1 Pertussis Complications

- Periorbital edema
- Subconjunctival hemorrhage
- Petechiae
- Epistaxis
- Hemoptysis
- Subcutaneous emphysema
- Pneumothorax
- Pneumomediastinum
- Diaphragmatic rupture
- Umbilical and inguinal hernias
- Rectal prolapse

From Marx J et al: *Rosen's emergency medicine: Concepts and clinical practice*, ed 7, Philadelphia, 2010, Mosby.

LABORATORY TESTS

Complete blood count, which usually demonstrates marked lymphocytosis:

- Up to 18,000 white blood cells
- 70% to 80% lymphocytes

IMAGING STUDIES

Chest x-ray examination is of value if secondary bacterial pneumonia is suspected.

TREATMENT

ACUTE GENERAL Rx

- Intensive supportive care:
  1. Adequate hydration
  2. Control of secretions
  3. Maintenance of airway
- Antibiotics (Table 1) are indicated, even though their ability to alter the course of the disease is controversial
  1. Azithromycin 500 mg on day 1, followed by 250 mg for days 2 to 5. Erythromycin 50 mg/kg/day for 14 days. Recent literature reports indicate that a 7-day treatment regimen may be as effective as a 14-day course of erythromycin. TMP/SMX 320/1600 mg per day in divided doses can be used in patients with allergy or intolerance to macrolides
  2. Although unproved, dexamethasone 1 mg/kg/day in four doses for severe, life-threatening paroxysms
  3. Ceftriaxone 75 mg/kg/day in two doses for broad coverage of secondary bacterial pneumonias
  4. Close observation of infants <6 mo old as risk for apnea is high in this age group
- Vaccination is successful in preventing the disease: Universal vaccination is advised for all children and adults. Children are recommended to receive the five-dose DTaP series at months 2, 4, 6, and 15 to 18, and at 4 to 6 yr of age
- The Advisory Committee on Immunization Practices (ACIP) updated Tdap recommendations to include a single dose of Tdap vaccine in place of routine Td for adults age 19 to 64 yr and a single-dose Tdap for adults 65

TABLE 1 Recommended Antimicrobial Treatment and Postexposure Prophylaxis for Pertussis, by Age Group

	Primary Agents		Alternate Agent*	
Age Group	**Azithromycin**	**Erythromycin**	**Clarithromycin**	**TMP-SMZ**
<1 mo	Recommended agent. 10 mg/kg/day in a single dose for 5 days (only limited safety data available)	Not preferred. Erythromycin is substantially associated with infantile hypertrophic pyloric stenosis. Use if azithromycin is unavailable; 40-50 mg/kg/day in 4 divided doses for 14 days	Not recommended (safety data unavailable)	Contraindicated for infants aged <2 mo (risk for kernicterus)
1-5 mo	10 mg/kg/day in a single dose for 5 days	40-50 mg/kg/day in four divided doses for 14 days	15 mg/kg/day in two divided doses for 7 days	Contraindicated at age <2 mo. For infants aged ≥2 mo: TMP 8 mg/kg/day plus SMZ 40 mg/kg/day in two divided doses for 14 days
Infants aged ≥6 mo and children	10 mg/kg in a single dose on day 1 (maximum 500 mg), then 5 mg/kg/day (maximum 250 mg) on days 2-5	40 mg/kg/day (maximum 1-2 g/day) in four divided doses for 14 days	15 mg/kg/day in 2 divided doses (maximum 1 g/day) for 7 days	TMP 8 mg/kg/day plus SMZ 40 mg/kg/day in two divided doses for 14 days
Adolescents and adults	500 mg in a single dose on day 1 then 250 mg/day on days 2-5	2 g/day in four divided doses for 14 days	1 g/day in two divided doses for 7 days	TMP 320 mg/day, SMZ 1600 mg/day in two divided doses for 14 days

SMZ, Sulfamethoxazole; *TMP,* trimethoprim; *TMZ,* trimethoprim.

*Trimethoprim-sulfamethoxazole (TMP-SMZ) can be used as an alternative agent to macrolides in patients aged ≥2 mo who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare, macrolide-resistant strain of *Bordetella pertussis*.

From Centers for Disease Control and Prevention: Recommended antimicrobial agents for treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines, *MMWR Morbid Mortal Wkly Rep* 54:1-16, 2005.

yr and older who have or will have close contact with an infant (<12 mo). The ACIP also recommends that all pregnant women receive a dose of Tdap with every pregnancy, preferably during wk 27 to 36 of gestation

- Azithromycin, clarithromycin, or erythromycin is recommended for all household contacts and should be given to all persons at high risk of severe disease from pertussis and who were in contact with a pertussis case within 21 days of cough onset: TMP/SMX in two oral doses per day for those intolerant to macrolides

DISPOSITION

Close attention to accepted vaccination schedules is the best prevention.

REFERRAL

To intensive care setting for life-threatening infections:

- Pulmonologist
- Infectious disease specialist

PEARLS & CONSIDERATIONS

- The diagnosis of pertussis in a young child is easily recognized, but in adults pertussis can be a subtle diagnosis and is often missed. The tip-off is often a persistent, hacking, and productive cough with minor or no fever in a previously healthy person that lasts <2 wk.
- Approximately 11% of pertussis cases in the pediatric population are attributable to vaccine refusal, dispelling the myth that herd immunity protects children whose parents refuse pertussis vaccine.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pertussis (Patient Information)

AUTHOR: **Russell J. McCulloh, MD**

SUGGESTED READINGS

AAP Committee on Infectious Diseases: Pertussis (whooping cough). In Kimberlin DW et al: *Red book*, ed 30, Elk Grove Village, IL, 2015, American Academy of Pediatrics, 2015, Report of the Committee on Infectious Diseases, pp. 608-621.

Centers for Disease Control and Prevention: 2016 Provisional pertussis surveillance report, available at: www.cdc.gov/pertussis/downloads/pertuss-surv-report-2016-provisional.pdf. Accessed October 22, 2017.

Cornia PB et al: Does this coughing adolescent or adult patient have pertussis? *J Am Med Assoc* 304:890-896, 2010.

Kline JM et al: Pertussis: a re-emerging infection, *Am Fam Phys* 88:507-514, 2013.

Koepke R et al: Estimating the effectiveness of tetanus-diphtheria-acellular pertussis vaccine (Tdap) for preventing pertussis: evidence of rapidly waning immunity and difference in effectiveness by Tdap brand, *J Infect Dis* 10:942-953, 2014.

Paisley RD et al: Whooping cough in adults: an update on a reemerging infection, *Am J Med* 125:141-143, 2012.

Shapiro ED: Acellular vaccines and resurgence of pertussis, *J Am Med Assoc* 308:2149-2150, 2012.

Spector TB, Maziarz EK: *Pertussis, Med Clin North Am* 97:537-552, 2013.

BASIC INFORMATION

DEFINITION

- A hamartomatous polyp is a benign intestinal growth that may contain all components of the intestinal mucosa. In Peutz-Jeghers syndrome (PJS), hamartomas are found primarily in the small bowel but can also be present in the colon and stomach. In gastrointestinal polyposis, multiple such polyps coexist within the intestinal tract, and associated manifestations are usually also present.
- Juvenile polyps are benign polyps composed of cystic dilations of glandular structures within the fibroblastic stroma of the lamina propria. They may cause bleeding or intussusception.
- Commonly recognized syndromes are Peutz-Jeghers syndrome, juvenile polyposis syndrome, Cowden disease, Bannayan-Ruvalcaba-Riley syndrome, and Cronkhite-Canada syndrome. Other, lesser-known inherited hamartomatous polyposis syndromes are hereditary mixed polyposis syndrome, intestinal ganglioneuromatosis and neurofibromatosis (variant of von Recklinghausen syndrome), Devon family syndrome, basal cell nevus syndrome, and tuberous sclerosis (may involve gastrointestinal tract). Table 1 describes general features of some inherited colorectal cancer syndromes.

ICD-10CM CODE

D12.6 Colon, unspecified (adenomatosis of colon, hereditary polyposis)

EPIDEMIOLOGY

- The incidence of PJS is 1 in 200,000.
- Colonic adenomas, the precursors of nearly all colorectal cancers, are found in nearly 40% of patients by age 60 yr.
- 25% of men and 15% of women who undergo colonoscopy are found to have one or more adenomas.
- Detection of any adenoma in patients <60 yr confers an increased risk of colorectal cancer (by a factor of 2.6) in their first-degree relatives.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

PEUTZ-JEGHERS SYNDROME:

- Transmission: Autosomal dominant with incomplete penetrance. The syndrome is caused in the majority of patients by a germline mutation of the *STK11/LKB1* tumor suppression gene on chromosome 19P13.
- Disease expression:
  1. Stomach, small and large intestinal hamartomas with bands of smooth muscle in the lamina propria
  2. Pigmented lesions around mouth (lips and buccal mucosa [Fig. E2]), nose, hands, feet, genitals, and perineal areas
  3. Ovarian tumors
  4. Sertoli cell testicular tumors
  5. Airway polyps
  6. Pancreatic cancer
  7. Breast cancer
  8. Urinary tract polyps
- Cumulative lifetime cancer risk:
  1. Colon cancer: 39%
  2. Stomach cancer: 29%
  3. Small intestine cancer: 13%
  4. Pancreatic cancer: 36%
  5. Breast cancer: 54%
  6. Ovarian cancer: 10%
  7. Sertoli cell tumor: 9%
  8. Overall cancer risk: 93%
- Clinical manifestation:
  1. Gastrointestinal, small-bowel obstruction, intussusception, gastrointestinal bleeding
  2. See chapters on relevant malignancies for their signs and symptoms

DIAGNOSIS: The diagnosis of PJS is made with any of four major criteria:

1. Two or more histologically confirmed PJS polyps
2. Any number of PJS polyps and a family history of PJS
3. Characteristic mucocutaneous pigmentation and a family history of PJS, or
4. Any number of PJS polyps and characteristic mucocutaneous pigmentation

JUVENILE POLYPOSIS SYNDROME:

- Transmission: Autosomal dominant
- Disease expression:
  1. Solitary juvenile polyps numbering 10 or more in the rectum or throughout the gastrointestinal tract; the polyps are smooth and covered with normal epithelium
  2. Various congenital abnormalities coexist in 20%
- Cumulative cancer risk is increased (may be as high as 50%)
- Clinical manifestation:
  1. Intestinal obstruction
  2. Intussusception
  3. Gastrointestinal bleeding

COWDEN DISEASE:

- Transmission: Autosomal dominant, rare
- Disease expression:
  1. Juvenile intestinal polyposis
  2. Orocutaneous hamartomas
  3. Fibrocystic breast disease and breast cancer
  4. Goiter and thyroid cancer
  5. Facial tricholemmomas (papules) in 83%
- Cumulative cancer risk:
  1. Gastrointestinal: Same as general population
  2. Thyroid: 3% to 10%
  3. Breast: 25% to 50%

BANNAYAN-RUVALCABA-RILEY SYNDROME:

- Transmission: Autosomal dominant, rare
- Disease expression:
  1. Juvenile intestinal polyposis
  2. Macrocephaly
  3. Developmental delay
  4. Penile pigmented spots
  5. Cumulative cancer risk unknown

TABLE 1 General Features of Some Inherited Colorectal Cancer Syndromes

Syndrome	Polyp Histology	Polyp Distribution	Age of Onset	Risk of Colon Cancer	Genetic Lesion	Clinical Manifestations	Associated Lesions
Familial adenomatous polyposis (Fig. E1)	Adenoma	Large intestine, duodenum	16 yr (range, 8-34 yr)	100%	5q (*APC* gene)	Rectal bleeding, abdominal pain, bowel obstruction	Desmoids, CHRPE
Peutz-Jeghers syndrome	Hamartoma	Large and small intestine	First decade	Slightly above average	19p (*STK11* gene)	Possible rectal bleeding, abdominal pain, intussusception	Orocutaneous melanin pigment spots, other tumors
MUTYH-associated polyposis	Adenoma	Large intestine, duodenum	45-50 yr (range, 13-60 yr)	75% (range, 50%-100%)	1p (*MYH* gene)	Rectal bleeding, abdominal pain, bowel obstruction	CHRPE, osteomas
Juvenile polyposis	Hamartoma (rarely adenoma)	Large and small intestine	First decade	~9%	*PTEN, SMAD4, BMPR1*	Possible rectal bleeding, abdominal pain, intussusception	Pulmonary AVMs
Hereditary nonpolyposis colon cancer	Adenoma	Large intestine	40 yr (range, 18-65 yr)	30%	Mismatch repair genes+*	Rectal bleeding, abdominal pain, bowel obstruction	Other tumors (e.g., ovary, uterus, pancreas, stomach)

AVM, Arteriovenous malformation; *CHRPE,* congenital hypertrophy of the retinal pigment epithelium; *MUTYH,* mutY homolog (*Escherichia coli*).
*Including *hMSH2, hMSH3, hMSH6, hMLH1, hPMS1*, and *hPMS2*.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.

CRONKHITE-CANADA SYNDROME:
- Transmission: Acquired
- Age of onset: Midlife
- Disease expression:
  1. Diffuse gastrointestinal juvenile polyposis (50% to 95% of cases)
  2. Chronic diarrhea and protein-losing enteropathy (the entire intestinal mucosa may be inflamed), which leads to abdominal pain, weight loss, and various complications of malnutrition
  3. Dystrophic nails
  4. Alopecia
  5. Hyperpigmentation
- Cumulative cancer risk: Same as the average population

Dx DIAGNOSIS

Diagnosis is suggested in many cases by family history and confirmed by colonoscopy and physical findings described previously.

Rx TREATMENT

GENERAL Rx/SURVEILLANCE

Peutz-Jeghers syndrome:
- Colonoscopies with polypectomies and upper endoscopy every 2 to 3 yr beginning in teen yr
- MRI or endoscopic ultrasound of the pancreas every 1 to 2 yr beginning at age 30
- Screening for breast cancer, testicular cancer, possibly ovarian cancer
- Surveillance of small bowel with capsule endoscopy or CT or magnetic resonance enterography every 2 to 3 yr starting at age 8 to 10 yr

Juvenile polyposis syndrome:
- Colonoscopies with polypectomies and upper endoscopy every 2 to 3 yr beginning at age 15
- Total colectomy if numerous polyps
- Esophagogastroscopies and polypectomies

Cowden disease:
- Rigorous breast cancer screening or prophylactic simple bilateral mastectomy with reconstruction

Cronkhite-Canada syndrome:
- Progressive malabsorption syndrome is the hallmark of this syndrome, and no specific treatment exists. Enteral or parenteral feeding is the cornerstone of management and can result in remission.

Other syndromes:
- Serrated polyposis syndrome: Colonoscopy yearly
- PTEN hamartoma tumor syndrome: Colonoscopy every 5 yr beginning at age 35

DISPOSITION

- The screening of first-degree relatives of patients with colonic adenomas detected before 60 yr of age is controversial. Some recommend beginning colonoscopic screening at age 40 yr, or 10 yr younger than the age at diagnosis of the youngest person in the family with an adenoma.
- Recommended intervals between colonoscopies from the U.S. Consensus Guidelines for Colonoscopic Surveillance after Polypectomy are as follows:
  1. 10 yr for small, rectal hyperplastic polyps
  2. 5 to 10 yr for one to two low-risk adenomas (tubular adenomas <1 cm)
  3. 3 yr for low-risk adenomas or any high-risk adenoma (large [≥1 cm] or histologically advanced adenomas [tubulovillous or villous adenomas or villous adenomas and those with high-grade dysplasia])
  4. <3 yr for presence of >10 adenomas
  5. 2 to 6 mo for inadequately removed adenomas

RELATED CONTENT

Peutz-Jeghers Syndrome (Patient Information)
Colorectal Cancer (Related Key Topic)
Familial Adenomatous Polyposis and Gardner Syndrome (Related Key Topic)
Lynch Syndrome (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

FIG. E1 Familial adenomatous polyposis. This disorder is marked by the development of hundreds of large bowel adenomas, as seen in this segment of large bowel, which is covered with adenomas of various sizes. It usually arises in the second and third decades. (From Skarin AT: *Atlas of diagnostic oncology*, 4th ed, St Louis, 2010, Mosby.)

FIG. E2 Peutz-Jeghers syndrome, macular pigmentation of lower lip. (From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, WB Saunders.)

Peyronie Disease PTG ALG

BASIC INFORMATION

DEFINITION

Peyronie disease is an abnormal curvature and shortening of the penis during an erection. This is caused by scarring of the tunica albuginea of the corpora cavernosa.

SYNONYMS

Plastic induration of the penis
Penile fibromatosis

ICD-10CM CODE
N48.6 Induratio penis plastica

EPIDEMIOLOGY & DEMOGRAPHICS

- Peyronie disease occurs in approximately 1% of men.
- It is commonly seen between the ages of 45 and 60 yr.
- A genetic predisposition has been suggested.
- There are no incidence and prevalence data available in the literature.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Painful erections
- Tenderness over the scar tissue area
- Erectile dysfunction
- Curvature of the erected penis interfering with penetration
- Dupuytren contracture is a commonly associated finding in patients with Peyronie disease

ETIOLOGY

- Specific cause is unknown. It is believed that scar tissue forms on either the dorsal or ventral midline surface of the penile shaft. The scar restricts expansion at the involved site, causing the penis to bend or curve in one direction.
- The precipitating factor appears to be trauma from repetitive microvascular injury caused by vigorous sexual intercourse, accidents, or prior surgeries (e.g., transurethral or radical prostatectomy, cystoscopy).

DIAGNOSIS

Diagnosis is based on the clinical findings.

DIFFERENTIAL DIAGNOSIS

- The history differentiates congenital from acquired curvatures of the penis.
- Other causes of erectile dysfunction must be excluded, including metabolic, diabetic, thyroid, and renal causes, in addition to hypogonadism and hyperprolactinemia.

WORKUP

History and physical examination alone will usually establish the diagnosis of Peyronie disease. The curvature can be measured with goniometer (Fig. E1).

LABORATORY TESTS

There are no specific blood tests to diagnose Peyronie disease. Electrolytes, blood urea nitrogen, creatinine, glucose, thyroid function tests (thyroid-stimulating hormone, T_3U, T_4), testosterone, and prolactin levels are blood tests to exclude other medical causes of erectile dysfunction.

IMAGING STUDIES

Penile duplex ultrasonography (Fig. E2, Box E1)

TREATMENT

NONPHARMACOLOGIC THERAPY

A conservative approach of reassurance and observation is taken at first because the disease process may be self-limiting.

FIG. E1 Measurement of curvature with goniometer. (From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.)

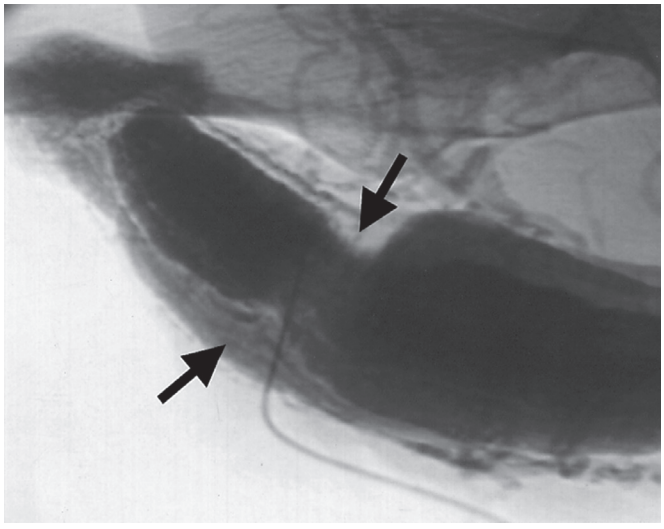

FIG. E2 Peyronie disease. Cavernosogram in a patient with erectile failure confined to the distal penis. There is a circumferential stricture *(arrows)* of the mid-shaft of both corpora cavernosa. (From Adam A et al: *Grainger & Allison's diagnostic radiology*, ed 5, 2007, Churchill Livingstone. In Grant LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, 2019, Elsevier.)

BOX E1 Value of Penile Duplex Ultrasonography for Peyronie Disease

- Identification and measurement of plaque calcification
- Identification of corporeal fibrosis
- Observation of erectile response to vasoactive intracavernosal injection
- Measurement of penile vascular parameters (peak systolic velocity, end-diastolic velocity, and resistive index)
- Optimum objective measurement of erect penile deformity (curvature, girth irregularities, hinge effect)

From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

ACUTE GENERAL Rx

Other medications that can be helpful include verapamil, tamoxifen, and interferon. Oral agents for Peyronie disease are summarized in Table E1. Although not substantiated by direct randomized, controlled clinical trials, the following treatment modalities have been tried:

- Vitamin E 400 mg bid
- Paraaminobenzoic acid 12 g/day
- Colchicine 0.6 mg bid for 2 to 3 wk
- Fexofenadine 60 mg bid for 3 mo
- Steroid injection into the scar tissue
- Collagenase injection into the scar tissue
- Table E2 summarizes intralesional agents for Peyronie disease
- Radiation to the scar tissue area
- Extracorporeal shockwave therapy (ESWT): Current evidence on the safety, but not the efficacy, of ESWT appears adequate. From comparative studies, the main benefits of ESWT were the alleviation of pain and reduction of angulation of the penis. In one comparative study, 10 of 20 patients receiving ESWT had a decrease in the curvature of at least 30%. Case series evidence also suggested some improvement of sexual performance
- Table E3 summarizes external force applications for treatment of Peyronie disease

CHRONIC Rx

In patients who have progressed to intractable pain with erection or erectile dysfunction, surgical treatment with excision of the plaque and skin grafting may be indicated. Boxes E2 and E3 summarize indications for surgery and preoperative consent. An algorithm for the surgical management of Peyronie disease is described in Fig. E3.

DISPOSITION

Peyronie disease evolves slowly and, in some cases, can resolve on its own. Waiting for 1 yr before proceeding with surgical attempts is recommended.

TABLE E1 Oral Agents for Peyronie Disease (PD)

Treatment	Mechanism of Action	Study Outcomes	Adverse Effects
Potaba	Decreases serotonin levels by increasing monoamine oxidase activity, resulting in enhancement of the antifibrotic properties of tissues	Decreased plaque size, no decrease in curvature	Anorexia, nausea, fever, skin rash, hypoglycemia, acute hepatitis
Vitamin E	Antioxidant, limits oxidative stress of reactive oxygen species shown to be increased in PD	No benefit	Possible cerebrovascular events, nausea, vomiting, diarrhea, headache, dizziness
Tamoxifen	Induces the production of TGF-β in an estrogen receptor–independent fashion, theoretically causing macrophage deactivation and T-lymphocyte suppression, thus preventing further fibrogenesis	No benefit	Alopecia, retinopathy, thromboembolism, pancytopenia
Colchicine	Microtubule depolymerization; inhibits cell mitosis, mobility, adhesion of leukocytes, and transcellular movement of collagen and stimulates the production of collagenase	No benefit	Myelosuppression, diarrhea, nausea, vomiting
Carnitine	Increases mitochondrial respiration; decreases free radical formation	No benefit	Seizures, diarrhea, nausea, stomach cramps, vomiting
Pentoxifylline	Blocks the TGF-β1–mediated pathway of inflammation; prevents deposition of collagen type I; is a nonspecific phosphodiesterase inhibitor; decreases platelet-activating factor	Decreased curvature in 33% of patients, mean 23 degrees	Nausea, vomiting, dyspepsia, malaise, flushing, dizziness, and headache

TGF, Transforming growth factor.
From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

TABLE E2 Intralesional Agents for Peyronie Disease (PD)

Treatment	Mechanism of Action	Study Outcomes	Adverse Effects
Verapamil	Calcium channel blocker inhibits fibroblast proliferation, extracellular matrix protein synthesis and secretion; increases collagenase activity	Reduction of curvature and plaque-associated penile narrowing, improvement in quality of erection	Nausea, light-headedness, penile pain, ecchymoses
Nicardipine	DHP type of calcium channel blocker. In vitro study demonstrated that it is more effective than a non-DHP type, verapamil, in reducing glycosaminoglycan biosynthesis and production of extracellular matrix, such as collagen	Reduction of pain, improvement in IIEF-5 score, and reduction of plaque size; no benefit in curvature	No severe side effects, such as hypotension or other cardiovascular events
Interferon alfa-2b	Decreases plaque fibroblast proliferation in dose-dependent fashion, decreases the production of extracellular collagen, and increases the production of collagenase	Decrease in curvature of 27% (13.5 degrees) vs. 9% (4.5 degrees) in the placebo group	Sinusitis, flulike symptoms (fever, chills, and arthralgia), and minor penile swelling with ecchymosis
Clostridial collagenase	Selectively degrades collagen types I and III in connective tissues despite the presence of TIMPs, which have been shown to be elevated in PD and to increase apoptosis of fibroblasts	Decrease in penile curvature by 34%, mean decrease of 17 degrees vs. 18%, mean decrease 9.3 degrees in placebo; PD symptom bothersomeness score significantly improved vs. placebo	Contusions, ecchymoses, corporeal rupture

DHP, Dihydropyridine; *IIEF,* International Index of Erectile Function; *TIMPs,* tissue inhibitors of metalloproteinases.
From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

TABLE E3 External Force Application for Peyronie Disease

Treatment	Mechanism of Action	Study Outcomes	Adverse Effects
Electromotive drug administration	Bypasses hepatic metabolism, increases concentration of drug to target tissues compared with topical application alone	Verapamil alone: No benefit Verapamil + dexamethasone: Decreases in plaque volume as well as penile curvature from 43 to 21 degrees	Temporary erythema at the electrode site
Extracorporeal shockwave therapy	Direct damage to the penile plaque; increases vascularity of the targeted area inducing an inflammatory reaction, resulting in lysis of the plaque and removal by macrophages	Improvements in pain, IIEF-5 score, and mean QoL score; no curvature reduction	Local petechiae and ecchymoses
Penile traction	Decreases α-smooth muscle actin, increases matrix metalloproteinases involved in collagen degradation	Length increased 0.5-2.0 cm; girth increased 0.5-1.0 cm; curvature mean decrease of 20 degrees; pain decreased; softening or shrinking of plaque; overall satisfaction 85%	Erythema in the balanopreputial sulcus, discomfort
Vacuum therapy	Unknown; mechanical effects similar to traction have been suggested	Reduction in the angle of curvature by 5-25 degrees in 21 of 31 patients	Development of PD, urethral bleeding, skin necrosis, and penile ecchymosis
Radiation therapy	Antiinflammatory effects via functional modulation of the adhesion of white blood cells to activated endothelial cells and modulation of the induction of nitric oxide synthase in activated macrophages	No clinical benefit	Possible malignant change, increased risk of ED in elderly

ED, Erectile dysfunction; *IIEF,* International Index of Erectile Function; *PD*, Peyronie disease; *QoL*, quality of life.
From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

BOX E2 Indications for Surgery

- Stable deformity for at least 6 mo from onset of symptoms
- Inability to engage in satisfactory penetrative sexual intercourse because of deformity and/or inadequate rigidity
- Failed conservative treatment
- Desire for most rapid and reliable result

From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

BOX E3 Preoperative Consent

Set expectations regarding outcome:
- Persistent or recurrent curvature: The goal is "functionally straight" (curvature <20 degrees)
- Change in length: The result is more likely shorter with plication than with grafting
- Diminished rigidity
  - ≥5% in all studies—grafting more than plication
  - ≥30% if suboptimal preoperative rigidity—dependent on preoperative erectile quality
- Decreased sexual sensation
  - Typically resolves in 1 to 6 mo
  - Rarely compromises orgasm or ejaculation

From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

REFERRAL

A urologic consultation is recommended in patients with progressive symptoms and erectile dysfunction.

PEARLS & CONSIDERATIONS

COMMENTS

- Peyronie disease is not commonly seen in younger patients because they are able to sustain intracorporeal pressures high enough to stretch the scar tissue, preventing it from deforming the penis during erection.
- Trauma from buckling of the erected penis is thought to be the precipitant cause of scar formation and Peyronie disease. It is found more often in men who are sexually very active and vigorous, having sexual intercourse daily or almost daily.
- Sexual positions with the woman being on top or thrusting the penis into the anterior vaginal wall are thought to increase the chances of developing Peyronie disease.

RELATED CONTENT

Peyronie Disease (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

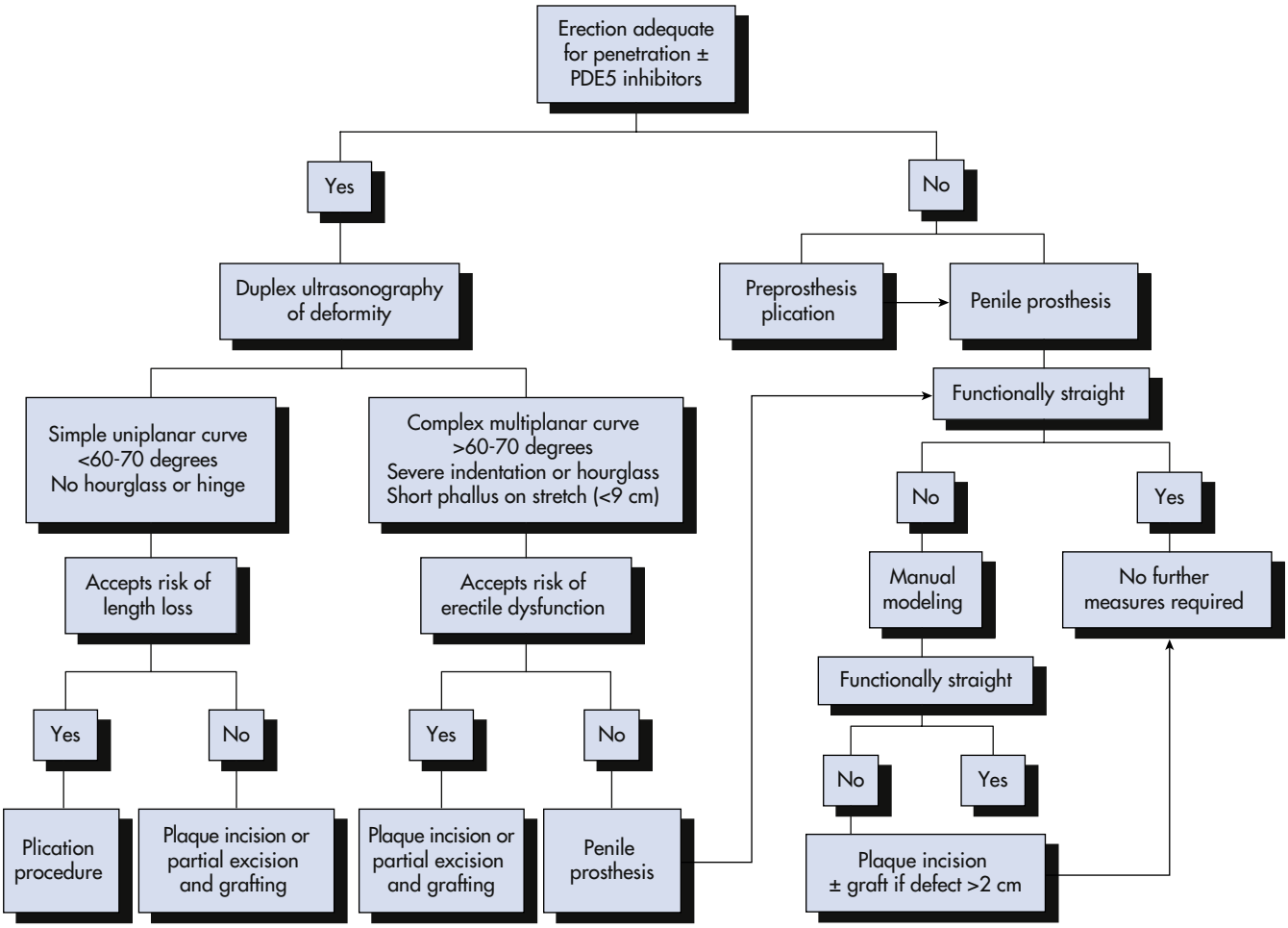

FIG. E3 Algorithm for the surgical management of Peyronie disease. *PDE5,* Phosphodiesterase type 5.
(From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Inflammation of the pharynx or tonsils

SYNONYMS

Sore throat
Group A streptococci (GAS)
Pharyngitis
Tonsillitis
GABHS

ICD-10CM CODES

J02.9	Acute pharyngitis, unspecified
J03.0	Acute tonsillitis
J03.9	Acute tonsillitis, unspecified
J04.0	Acute laryngitis

EPIDEMIOLOGY & DEMOGRAPHICS

Acute pharyngitis accounts for 1.3% of outpatient visits to health care providers in the U.S. and is diagnosed in 2 million persons in the outpatient setting each yr in the U.S.

PEAK INCIDENCE: Late winter/early spring (GAS infections)

PREDOMINANT SEX: Females = males

PREDOMINANT AGE:

- All ages affected
- Streptococcal pharyngitis most common among school-age children (5 to 15 yr of age). GAS are responsible for 5% to 15% of cases of pharyngitis in adults and 20% to 30% of cases in children (5 to 15 yr of age).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pharynx:
  1. May appear normal to severely erythematous (Fig. E1)
  2. Tonsillar hypertrophy and exudates commonly seen but do not indicate etiology
- Viral infection:
  1. Rhinorrhea
  2. Conjunctivitis
  3. Cough
- Bacterial infection, especially GAS:
  1. High fever
  2. Systemic signs of infection
- Herpes simplex or enterovirus infection: Vesicles
- Streptococcal infection:
  1. Rare complications:
     a. Scarlet fever
     b. Rheumatic fever
     c. Acute glomerulonephritis
  2. Extension of infection (Fig. E2): Tonsillar, parapharyngeal, or retropharyngeal abscess presenting with severe pain, high fever, trismus
- Streptococcal tonsillitis is manifested as acute onset of fever, headache, neck pain, odynophagia, sore throat, otalgia, red tongue with enlargement of papillae, sore throat, red swollen uvula, and tender anterior cervical adenitis.
- Peritonsillar abscess (accumulation of pus between the tonsil and its capsule) is the most common complication of acute tonsillitis. Clinical signs include deformed posterior pharynx, medial displacement of the uvula, trismus, and muffled voice (hot-potato voice).
- Lingual tonsillitis is a rarely diagnosed cause of pharyngitis that predominantly occurs in patients who have had palatine tonsils removed. The lingual tonsils are located below the inferior pole of the palatine tonsils and anterior to the vallecula at the base of the tongue. The lymphoid tissue may enlarge after tonsillectomy and repeated infections. Patients have a sore throat that worsens with movement of the tongue. Physical findings often include a normal-appearing pharynx and hyperemia. Lateral soft tissue neck films reveal a normal-appearing epiglottis and a scalloped appearance of the lingual tonsil (Fig. E3).
- Table 1 describes seven danger signs in patients with sore throat.

ETIOLOGY

- Viruses:
  1. Respiratory syncytial virus
  2. Influenza A and B
  3. Epstein-Barr virus
  4. Adenovirus
  5. Herpes simplex
- Bacteria:
  1. GAS: *Streptococcus pyogenes*. β-Hemolytic GAS are the most common cause of acute tonsillitis.
  2. *Neisseria gonorrhoeae*
  3. *Fusobacterium necrophorum* (10% of pharyngitis): Highest incidence in patients aged 15 to 30 yr
- Other organisms:
  1. *Mycoplasma pneumoniae*
  2. *Chlamydophila pneumoniae*
  3. *Arcanobacterium haemolyticum*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Sore throat associated with granulocytopenia, thyroiditis
- Tonsillar hypertrophy associated with lymphoma

TABLE 1 Seven Danger Signs in Patients with Sore Throat

1. Persistence of symptoms longer than 1 wk without improvement
2. Respiratory difficulty, particularly stridor
3. Difficulty in handling secretions
4. Difficulty in swallowing
5. Severe pain in the absence of erythema
6. A palpable mass
7. Blood, even in small amounts, in the pharynx or ear

From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, WB Saunders.

- Section II describes the differential diagnosis of sore throat

WORKUP

The Centor criteria (Boxes 1 and 2) to identify patients at risk for GAS consists of (1) fever subjective or measured >38.1° C (100.5° F), (2) absence of cough, (3) tonsillar exudates, (4) tender anterior cervical lymphadenopathy. Patients with ≤1 criteria are at low risk and do not need additional testing. The McIsaac criteria adds one point for ages 3 to 14 and subtracts one point for ages ≥45 yr.

- Rapid streptococcal antigen test (culture should be performed if rapid test negative)
- Throat swab for culture to exclude *S. pyogenes, N. gonorrhoeae* (requires specific transport medium) in selected cases

LABORATORY TESTS

- Bloodwork is only rarely necessary
- Complete blood count with differential
  1. May help support diagnosis of bacterial infection when diagnosis is unclear
  2. Streptococcal infection suggested by leukocytosis >15,000/mm^3
- Viral cultures, serologic studies rarely needed
- Monospot if diagnosis is unclear

IMAGING STUDIES

Seldom indicated. If necessary to distinguish between tonsillitis and peritonsillar abscess, CT or MRI of the neck can be done.

BOX 1 Centor Criteria for Determining Group A Beta-Hemolytic Streptococcal Pharyngitis

- Tonsillar exudates
- Tender anterior lymphadenopathy or lymphadenitis
- Absence of cough
- History of fever

From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Elsevier.

BOX 2 Centor Criteria Scoring for Determining Testing and Treatment for Group A Beta-Hemolytic Streptococcal Pharyngitis

Centor Score	Testing and Treatment
0-1	None
2-3	Treatment based on results of rapid streptococcal test results
4	Treat without testing

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Fluids
- Saltwater gargles

ACUTE GENERAL Rx

- Analgesics: Aspirin (adults) or acetaminophen or ibuprofen (adults and children). Clinical trials have shown that corticosteroids can hasten pain relief in patients with sore throat. Single dose oral dexamethasone (10 mg in adults, 0.6 ms/kg for children) was the most common intervention and resulted in pain resolution approximately 11 hours sooner than placebo.[1] Prescribing corticosteroids in all cases of sore throat is not indicated and should be considered only in cases of severe sore throat.
- If streptococcal infection proven or suspected:
  1. Amoxicillin 500 mg bid or penicillin V 500 mg PO bid for 10 days or benzathine penicillin 1.2 million U IM once (adults). Children: Penicillin V 250 mg bid or tid
  2. Azithromycin 500 mg on day 1, then 250 mg on days 2 through 5 or erythromycin 500 mg PO bid or 250 mg qid for 10 days if penicillin allergic
- If gonococcal infection proven or suspected: ceftriaxone 250 mg IM once.
- Treatment of peritonsillar abscess is drainage through needle or incision.
- Avoid quinolones, sulfonamides, and tetracyclines due to treatment failures.

CHRONIC Rx

- Recurrent streptococcal infections are common and may represent reinfection from other household members, including pets.
- There is no conclusive evidence from randomized clinical trials that tonsillectomy is superior to antibiotic therapy for recurrent tonsillitis in adults.
- Tonsillopharyngitis is generally managed in an outpatient setting with follow-up arranged in 1 to 2 wk. Admission to the hospital is indicated for local suppurative complications (peritonsillar abscess; lateral pharyngeal or posterior pharyngeal abscess; impending airway closure; or inability to swallow food, medications, or water).

REFERRAL

- To otolaryngologist:
  1. If peritonsillar or other abscess is suspected
  2. If tonsillar hypertrophy persists

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Sore Throat (Patient Information)
Strep Throat (Patient Information)
Tonsillitis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

[1]Sadehira B et al: Corticosteroids for treatment of sore throat: systematic review and meta-analysis of randomized trials, *BMJ* 358:3887, 2017.

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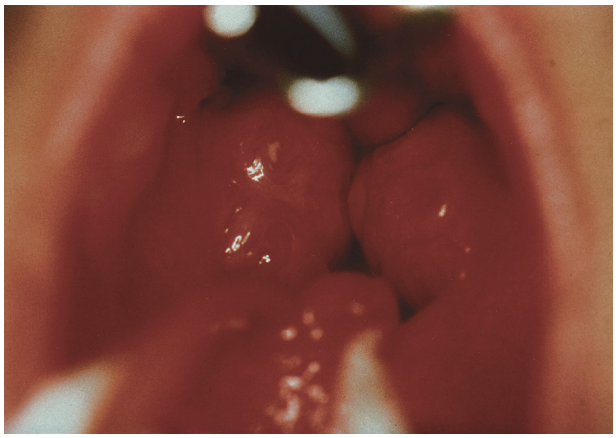

FIG. E1 Bilateral tonsillopharyngitis. (From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Elsevier.)

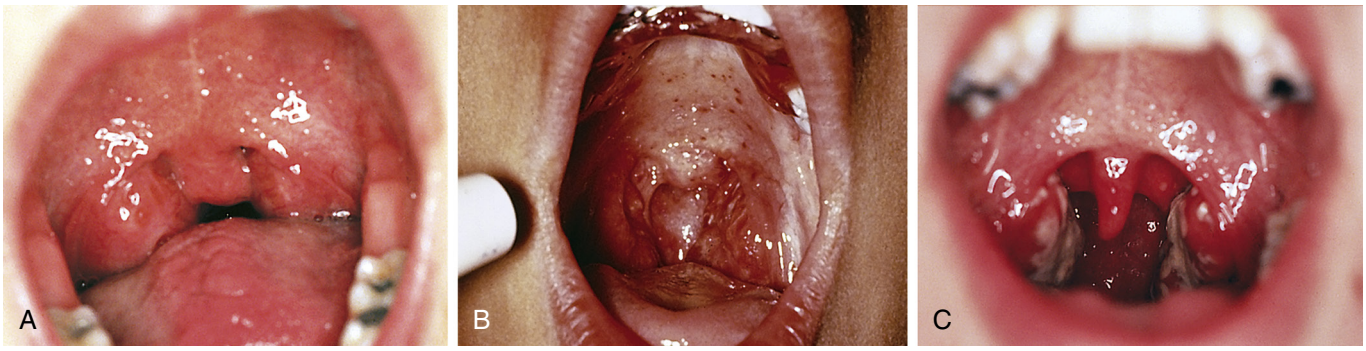

FIG. E2 Pharyngotonsillitis. This common syndrome has a number of causative pathogens and a wide spectrum of severity. **A,** The diffuse tonsillar and pharyngeal erythema seen here is a nonspecific finding that can be produced by a variety of pathogens. **B,** This intense erythema, seen in association with acute tonsillar enlargement and palatal petechiae, is highly suggestive of group A β-streptococcal infection, though other pathogens can produce these findings. **C,** This picture of exudative tonsillitis is most commonly seen with either group A streptococcal or Epstein-Barr virus infection. (**B,** Courtesy Michael Sherlock, MD, Lutherville, MD. From Yellon RF et al: Otolaryngology. In Zitelli BJ, Davis HW [eds]: *Atlas of pediatric physical diagnosis*, ed 4, Philadelphia, 2002, Mosby, p. 852; Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.)

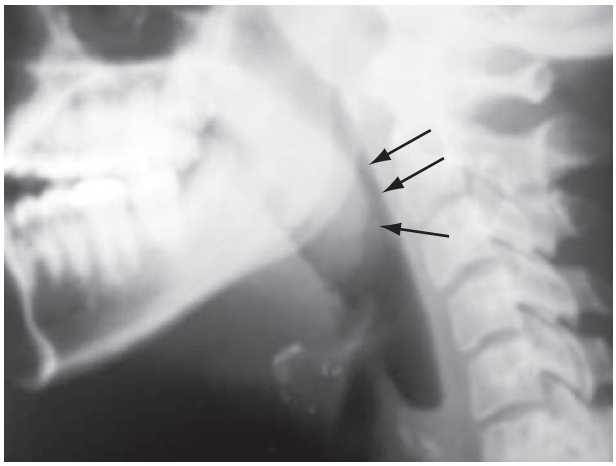

FIG. E3 Lingual tonsillitis. Notice the scalloped appearance of the lingual tonsil on the anterior surface of the vallecula (arrows) with a normal epiglottis and aryepiglottic fold. (From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Elsevier.)

BASIC INFORMATION

DEFINITION

Pheochromocytomas are catecholamine-producing tumors that originate from the chromaffin cells of the adrenergic system. While they generally secrete both norepinephrine and epinephrine, norepinephrine is usually the predominant amine.

SYNONYM

Paraganglioma

ICD-10CM CODES

C74.9 Malignant neoplasm of adrenal gland, unspecified
C75.9 Malignant neoplasm of endocrine gland, unspecified
E27.5 Adrenomedullary hyperfunction

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence: 0.05% of population; peak incidence in 30s and 40s.
- Approximately 25% of patients with apparently sporadic pheochromocytoma may be carriers of mutations.
- Approximately 25% of pheochromocytomas are familial and associated with genetic disorders (Table 1). Pheochromocytoma is a feature of two disorders with an autosomal-dominant pattern of inheritance:
  1. Multiple endocrine neoplasia (MEN) type 2
  2. von Hippel-Lindau disease: Angioma of the retina, hemangioblastoma of the central nervous system, renal cell carcinoma, pancreatic cysts, and epididymal cystoadenoma
- Pheochromocytomas occur in 5% of patients with neurofibromatosis type 1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hypertension: Can be sustained (55%) or paroxysmal (45%).
- Headache (80%): Usually paroxysmal in nature and described as "pounding" and severe.
- Palpitations (70%): Can be present with or without tachycardia.
- Hyperhidrosis (60%): Most evident during paroxysmal attacks of hypertension.
- Physical examination may be entirely normal if done in a symptom-free interval; during a paroxysm the patient may demonstrate marked increase in both systolic and diastolic pressure, profuse sweating, visual disturbances (caused by hypertensive retinopathy), dilated pupils (from catecholamine excess), paresthesias in the lower extremities (caused by severe vasoconstriction), tremor, and tachycardia.
- Orthostatic hypotension is common among patients with pheochromocytoma due to reduction of blood volume and desensitization of adrenergic receptors by the chronic excess of catecholamines.
- Table E2 summarizes features suggestive of pheochromocytoma.

ETIOLOGY

- Catecholamine-producing tumors that are usually located in the adrenal medulla.
- Specific mutations of the RET protooncogene cause familial predisposition to pheochromocytoma in MEN 2.
- Mutations in the von Hippel-Lindau tumor suppressor gene (VHL gene) cause familial disposition to pheochromocytoma in von Hippel-Lindau disease.
- Recently identified genes for succinate dehydrogenase subunit D *(SDHD)* and succinate dehydrogenase subunit B *(SDHB)* predispose carriers to pheochromocytoma and globus tumors.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Anxiety disorder
- Thyrotoxicosis
- Amphetamine or cocaine abuse
- Carcinoid
- Essential hypertension

WORKUP

Laboratory evaluation and imaging studies to locate the neoplasm (Fig. 1). Anatomic and functional imaging studies that can be used to localize pheochromocytomas are summarized in Table E3. Misdiagnosis of pheochromocytoma is common. Correct interpretation of biochemical tests and imaging is crucial to a correct diagnosis.

LABORATORY TESTS

- Although there is no consensus on the best test, plasma-free metanephrines have been suggested as the test of first choice for excluding the tumor. Elevated plasma concentrations of normetanephrine or metanephrine have a sensitivity of up to 100%, but the specificity is markedly lower (85%).
- 24-hr urine collection will also show increased metanephrines (90% sensitivity, 95% specificity); the accuracy of the 24-hr urinary levels for metanephrines can be improved by indexing urinary metanephrine levels by urine creatinine levels.

IMAGING STUDIES

- Abdominal CT scan (Fig. E2) with and without contrast (88% sensitivity) is useful in locating pheochromocytomas >0.5 inch in diameter (90% to 95% accurate).

TABLE 1 Autosomal Dominant Syndromes Associated with Pheochromocytoma and Paraganglioma

Syndrome	Gene	Gene Locus	Protein Product	Protein Function	Gene Mechanism	Typical Tumor Location
SDHD (familial paraganglioma type 1)*	*SDHD*	11q23	SDH D subunit	ATP production	Tumor suppressor	Skull base and neck; occasionally adrenal medulla, mediastinum, abdomen, pelvis
Familial paraganglioma type 2*	*SDHAF2*	11q13.1	Flavination cofactor	ATP production	Tumor suppressor	Skull base and neck; occasionally abdomen and pelvis
SDHC (familial paraganglioma type 3)	*SDHC*	1q21	SDH C subunit	ATP production	Tumor suppressor	Skull base and neck
SDHB (familial paraganglioma type 4)	*SDHB*	1p36.1-35	SDH B subunit	ATP production	Tumor suppressor	Abdomen, pelvis and mediastinum; rarely adrenal medulla, skull base, and neck
MEN1	*MEN1*	11q13	Menin	Transcription regulation	Tumor suppressor	Adrenal medulla
MEN2A and MEN2B	*RET*	10q11.2	RET	Tyrosine kinase receptor	Protooncogene	Adrenal medulla, bilaterally
Neurofibromatosis type 1	*NF1*	17q11.2	Neurofibromin	GTP hydrolysis	Tumor suppressor	Adrenal-periadrenal
von Hippel-Lindau disease	*VHL*	3p25-26	VHL	Transcription elongation suppression	Tumor suppressor	Adrenal medulla, bilaterally; occasionally paraganglioma
Familial pheochromocytoma	*FP/TMEM127*	2q11	Transmembrane protein	Regulation of the mTORC1 signaling complex	Tumor suppressor	Adrenal medulla

*Associated with maternal imprinting.
ATP, Adenosine triphosphate; *GTP,* guanosine triphosphate; *MEN,* multiple endocrine neoplasia; *mTORC1,* mammalian target of rapamycin complex 1; *RET,* "rearranged during transfection" protooncogene; *SDH,* succinate dehydrogenase; *VHL*, von Hippel–Lindau disease.
From Melmed S: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders, Elsevier.

- MRI with contrast: Pheochromocytomas demonstrate a distinctive MRI appearance (up to 100% sensitivity); MRI may become the diagnostic imaging modality of choice.
- Scintigraphy with 131 or 1-123 I-MIBG (up to 100% sensitivity) (Fig. E2): This norepinephrine analog localizes in adrenergic tissue; it is particularly useful in locating extraadrenal pheochromocytomas.
- 6-[18F]Fluorodopamine positron emission tomography is reserved for cases in which clinical symptoms and signs suggest pheochromocytoma, and results of biochemical tests are positive but conventional imaging studies cannot locate the tumor. It is also used for identification of metastatic disease.

Rx TREATMENT

GENERAL Rx

Laparoscopic adrenalectomy (surgical resection for both benign and malignant disease):

- Preoperative stabilization with combination of alpha-adrenergic blocking agents (phenoxybenzamine, prazosin, doxazosin, or terazosin), beta-blocker, and liberal fluid and salt intake starting 10 to 14 days before surgery. Beta-blockers should be avoided until patients receive adequate alpha-adrenergic blockade for several days to avoid hypertensive crisis due to unopposed alpha stimulation. Amlodipine or verapamil can be added to beta-blockers if blood pressure control is still inadequate. Table E4 describes orally administered drugs to treat pheochromocytoma.
- Hypertensive crisis preoperatively and intraoperatively can be controlled with nitroprusside. Table E5 summarizes intravenously administered drugs used to treat pheochromocytoma.

PEARLS & CONSIDERATIONS

COMMENTS

- Obtaining a detailed family history is important because 25% of pheochromocytomas are familial.
- Screening for pheochromocytoma should be considered in patients with any of the following:
  1. Malignant hypertension
  2. Poor response to antihypertensive therapy
  3. Paradoxical hypertensive response
  4. Hypertension during induction of anesthesia, parturition, surgery, or thyrotropin-releasing hormone testing
  5. Hypertension associated with imipramine or desipramine
  6. Neurofibromatosis (increased incidence of pheochromocytoma)
- All patients with pheochromocytoma should be screened for MEN-2 and von Hippel-Lindau disease with the pentagastrin test, serum parathyroid hormone, ophthalmoscopy, MRI of the brain, CT scan of the kidneys and pancreas, and ultrasonography of the testes.
- In patients with pheochromocytoma, routine analysis for mutations of *RET, VHL, SDHD,* and *SDHB* is indicated to identify pheochromocytoma-associated syndromes.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pheochromocytoma (Patient Information)
Hypertension (Related Key Topic)

AUTHORS: **Brett Patrick, MD, Mark F. Brady, MD, MPH, MMSc,** and **Fred F. Ferri, MD**

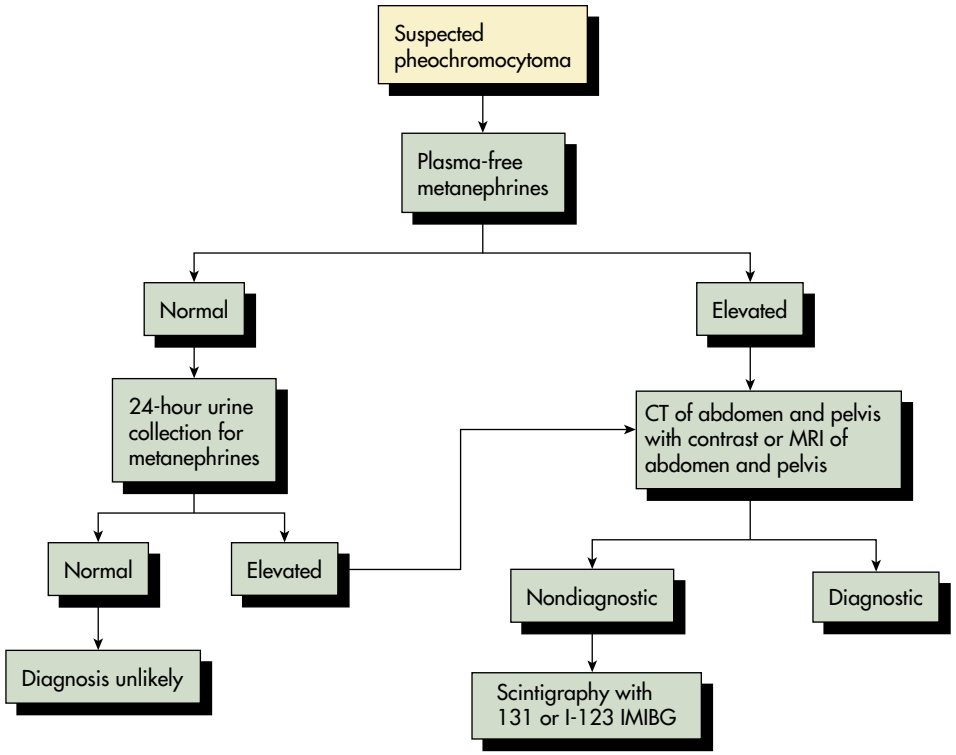

FIG. 1 Pheochromocytoma. *CT,* Computed tomography; *IMIBG,* iodine metaiodobenzylguanidine; *MRI,* magnetic resonance imaging.

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National Cancer Institute: Pheochromocytoma and paraganglioma treatment (PDQ®): health professional version. PDQ Adult Treatment Editorial Board, *PDQ Cancer Information Summaries*, Epub Jul 10, 2015.

Neumann HPH et al: Pheochromocytoma and paraganglioma, *N Engl J Med* 381 (6): 552–565, 2019.

TABLE E2 Features Suggestive of Pheochromocytoma

Hypertension, Persistent or Paroxysmal

Markedly variable blood pressures (± orthostatic hypotension)
Sudden paroxysms (± subsequent hypertension) in relation to:
- Stress: Anesthesia, angiography, parturition
- Pharmacologic provocation: Histamine, nicotine, caffeine, beta blockers, glucocorticoids, tricyclic antidepressants
- Manipulation of tumors: Abdominal palpation, urination

Rare patients persistently normotensive
Unusual settings
Childhood, pregnancy, familial
Multiple endocrine adenomas: Medullary carcinoma of the thyroid (MEN-2), mucosal neuromas (MEN-2B)
von Hippel-Lindau disease
Neurocutaneous lesions: Neurofibromatosis

Associated Symptoms

Sudden spells with headache, sweating, palpitations, nervousness, nausea, vomiting
Pain in chest or abdomen

Associated Signs

Sweating, tachycardia, arrhythmia, pallor, weight loss

From Zipes DP*: Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.

TABLE E3 Anatomic and Functional Imaging Studies That Can Be Used to Localize Pheochromocytomas and Paragangliomas

Imaging Modality	MRI	CT	^{18}F-FDG	^{68}Ga-DOTA Peptide	^{18}F-FDA	^{18}F-DOPA	MIBG
Advantages	Anatomic detail	Anatomic detail	Widely available, preferred functional imaging test	Most sensitive functional imaging study for all sites of disease, potential for therapy with avid disease	Sensitive functional imaging for primary tumor (except skull base and neck)	Most sensitive functional imaging study for skull base and neck paragangliomas	Potential for therapy if disease avid tumor is not resectable
Disadvantages	Lower specificity	Lower specificity	Lower sensitivity and higher false-positive rate as compared with other functional imaging studies	Not widely available	Not widely available	Not widely available	Lower sensitivity than other functioning imaging studies
Best clinical setting to use imaging studies	Initial localization of tumor	Initial localization of tumor	Rule out metastatic disease or multiple primary	Rule out metastatic disease or multiple primary; *SDHx* mutation carriers; when planning treatment with peptide receptor radionuclide therapy	Rule out metastatic disease or multiple primary	Patients with primary skull base and neck paragangliomas; multiple and metastatic disease	When planning treatment with ^{131}I-MIBG

CT, Computed tomography; *DOPA*, dihydroxyphenylalanine; *DOTA*, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; *FDA*, fluorodopamine; *FDG*, fluorodeoxyglucose; *MIBG*, metaiodobenzylguanidine; *MRI*, magnetic resonance imaging; *SDH*, succinate dehydrogenase.
From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.

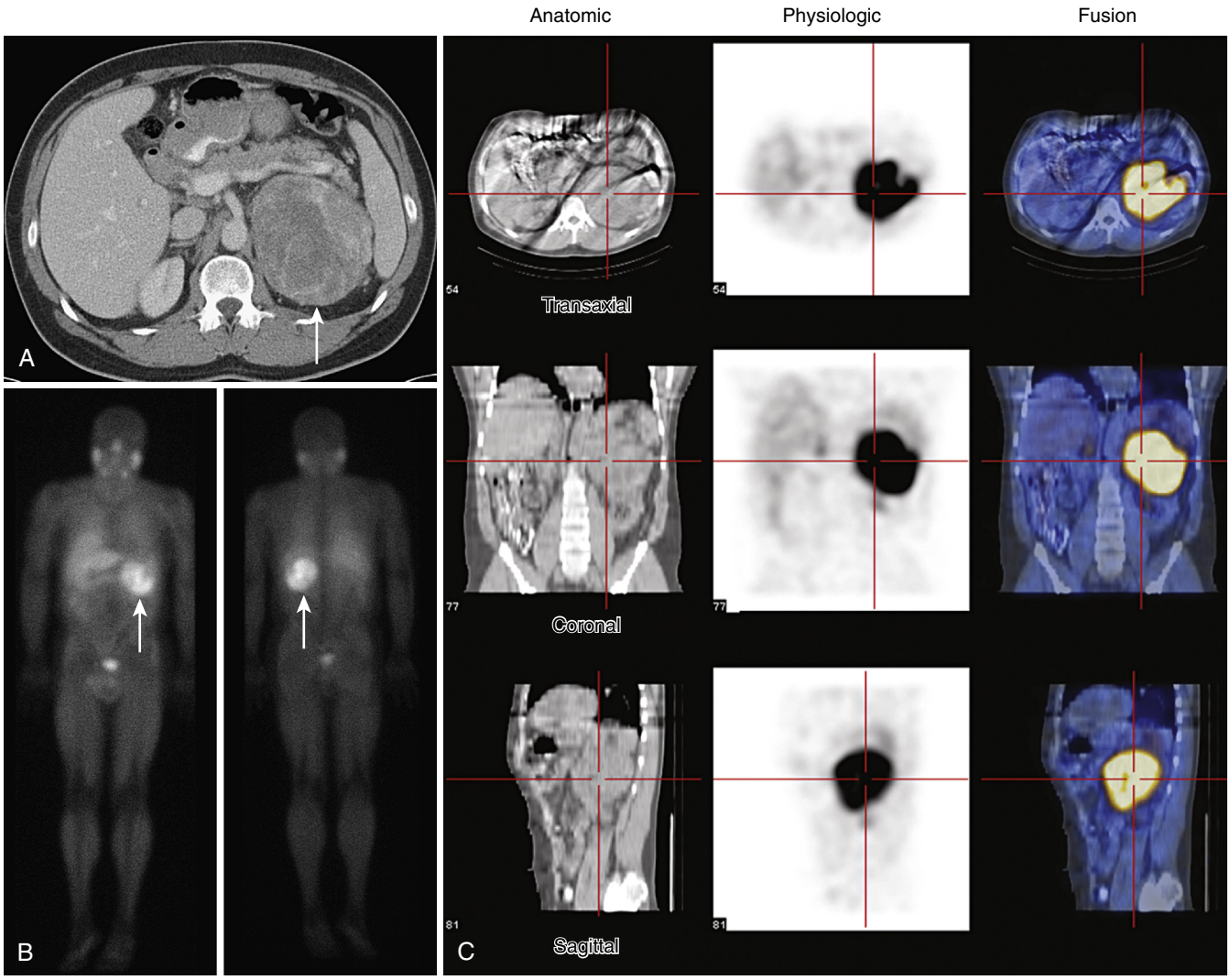

FIG. E2 Computed tomography (CT) and ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) imaging of a 44-yr-old man. He presented with a 9-yr history of hypertension and recent onset of head throbbing, chest pressure, and abdominal pain. The 24-hour urine studies were abnormal: Norepinephrine, 900 μg (normal, <170); epinephrine, 28 μg (normal, <35); dopamine, 468 μg (normal, <700); and total metanephrines, 17,958 μg (normal, <1000). **A,** Axial CT image with contrast shows a large, partially vascular, and partially necrotic left adrenal tumor *(arrow).* **B,** ^{123}I-MIBG whole-body scan shows a large focus of increased radiotracer uptake in the left upper abdomen *(arrow)* that corresponds to the mass seen on the CT image; no other abnormal uptake is seen. **C,** ^{123}I-MIBG and single-photon emission computed tomography (SPECT) fusion CT images correlate the images seen on CT (anatomic) with those seen on ^{123}I-MIBG (physiologic) in the axial, coronal, and sagittal planes. After α- and β-adrenergic blockade, a 13.5-cm × 12-cm × 9-cm, 680-g pheochromocytoma was removed. (From Melmed S: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders, Elsevier.)

TABLE E4 Orally Administered Drugs Used to Treat Pheochromocytoma

Drug	Initial Dosage, mg/day* (Maximum)	Side Effects
α-Adrenergic Blocking Agents		
Phenoxybenzamine	10† (100)†	Postural hypotension, tachycardia, meiosis, nasal congestion, diarrhea, inhibition of ejaculation, fatigue
Prazosin	1 (20)‡	First-dose effect, dizziness, drowsiness, headache, fatigue, palpitations, nausea
Terazosin	1 (20)†	First-dose effect, asthenia, blurred vision, dizziness, nasal congestion, nausea, peripheral edema, palpitations, somnolence
Doxazosin	1 (20)	First-dose effect, orthostasis, peripheral edema, fatigue, somnolence
Combined α- and β-Adrenergic Blocking Agent		
Labetalol	200† (1200)†	Dizziness, fatigue, nausea, nasal congestion, impotence
Calcium Channel Blocker		
Nicardipine sustained-release	30† (120)†	Edema, dizziness, headache, flushing, nausea, dyspepsia
Catecholamine Synthesis Inhibitor		
α-Methyl-ϱ-l tyrosine (metyrosine)	1000‡ (4000)‡	Sedation, diarrhea, anxiety, nightmares, crystalluria, galactorrhea, extrapyramidal symptoms

*Given once daily unless otherwise indicated.
†Given in two doses daily.
‡Given in three or four doses daily.
From Melmed S: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders, Elsevier.

TABLE E5 Intravenously Administered Drugs Used to Treat Pheochromocytoma

Agent	Dosage Range
For Hypertension	
Phentolamine	Administer a 1-mg IV test dose, then 2- to 5-mg IV boluses as needed or continuous infusion.
Nitroprusside	IV infusion rates of 2 μg/kg of body weight per min are suggested as safe. Rates >4 μg/kg per min may lead to cyanide toxicity within 3 hr. Doses >10 μg/kg per min are rarely required, and the maximal dose should not exceed 800 μg/min.
Nicardipine	Initiate therapy at 5.0 mg/hr; the IV infusion rate may be increased by 2.5 mg/hr q15 min up to a maximum of 15.0 mg/hr.
For Cardiac Arrhythmia	
Lidocaine	Initiate therapy with an IV bolus of 1-1.5 mg/kg (75-100 mg); additional boluses of 0.5-0.75 mg/kg (25-50 mg) can be given q5-10 min if needed up to a maximum of 3 mg/kg. Loading is followed by maintenance IV infusion of 2-4 mg/min (30-50 μg/kg per min) adjusted for effect and settings of altered metabolism (e.g., heart failure, liver congestion) and as guided by blood level monitoring.
Esmolol	An initial IV loading dose of 0.5 mg/kg is infused over 1 min, followed by a maintenance infusion of 0.05 mg/kg per min for the next 4 min. Depending on the desired ventricular response, the maintenance infusion may then be continued at 0.05 mg/kg per min or increased stepwise (e.g., by 0.1 mg/kg per min increments to a maximum of 0.2 mg/kg per min), with each step being maintained for ≥4 min.

IV, Intravenous.
From Melmed S: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders, Elsevier.

Phobias PTG ALG

BASIC INFORMATION

DEFINITION

Specific phobias are anxiety disorders characterized by an excessive, persistent fear elicited by a specific object or situation that is then avoided or tolerated with intense distress. The provoking stimulus may be a specific object, such as an animal or insect; natural environments, such as heights or water; or a specific situation, such as the sight of blood, the receipt of an injection, or being in a tunnel or on a bridge. Social anxiety disorder (formerly named social phobia) is a specific, separately diagnosed disorder characterized by a fear of being embarrassed, humiliated, or rejected in social or performance situations. Agoraphobia also is a separately diagnosed disorder, characterized by an intense anxiety about being in a place or situation from which they would not be able to escape in the event of a panic attack or panic-like symptoms. Such situations include being in enclosed/crowded spaces or being more than a certain distance from home while alone. If agoraphobia is present in individuals with panic disorder, both diagnoses are given.

SYNONYMS

Simple phobia (obsolete name for specific phobia)

Phobias named for the provoking stimulus, such as arachnophobia (fear of spiders) and acrophobia (fear of heights)

Specific phobias:
ICD-10CM CODES
F40.1 Social phobias
F40.2 Specific phobias
F40.8 Other phobic anxiety disorders
F40.9 Phobic anxiety disorder, unspecified
DSM-5 CODE
300.23 Social phobias
300.29 Other isolated specific phobias
Agoraphobia:
ICD-10CM CODES
F40.00 Agoraphobia, unspecified
DSM-5 CODE
300.22 Agoraphobia

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: The majority of cases of specific phobia tend to onset prior to age 10; median onset is from ages 7 to 10.

PREVALENCE (IN U.S.):

- Specific phobias are prevalent in 7% to 9% of the general population (12-mo prevalence rate); cross-national prevalence rates are 7.4% (lifetime) and 5.5% (12-mo).
- Agoraphobia is prevalent in approximately 1.7% of the general population per yr.

PREDOMINANT SEX AND AGE:

- Females with specific phobias outnumber males 2:1, though rates vary by phobia.
- Agoraphobia is more prevalent in women than men (2:1).
- Most specific phobias have childhood onset (median onset = 8 yr), although it is possible for them to develop at any age.
- Specific phobia often precedes the onset of other mental disorders.
- Situational phobias tend to have a later age of onset compared to natural environment, animal, or blood-injection phobias.
- Onset of agoraphobia typically occurs in late adolescence or early adulthood; two thirds of cases onset prior to age 35.

GENETICS: Specific phobia is more common in first-degree relatives.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- When approaching the phobic stimulus, the experience of extreme anxiety is often accompanied by autonomic symptoms such as tachycardia, tremor, and diaphoresis; depersonalization may occur. In blood or injection phobias, symptoms are often followed by a parasympathetic response that can cause vasovagal syncope.
- Specific phobias frequently occur with other anxiety disorders.

ETIOLOGY

There is no clear etiology and likely is a combination of factors including temperamental (e.g., behavioral inhibition, neuroticism), environmental (e.g., negative encounters with the feared stimulus, parental overprotection), and genetic.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Social anxiety disorder is distinguished from specific phobias in that what is feared is humiliation or embarrassment in social interaction or performance situations rather than fear of a specific object or environment.
- Panic attacks (with or without agoraphobia): Anxiety symptoms seen in specific phobia may resemble symptoms of panic attacks, but the stimulus in the specific or social situation is clear, whereas panic attacks do not have a clearly associated provoking stimulus (i.e., they occur unexpectedly in the absence of a trigger).
- Posttraumatic stress disorder (PTSD): Anxiety and physiologic arousal associated with specific cues from the traumatic event defining the PTSD may resemble the symptoms induced by a phobia.
- Psychotic disorders can present with a fear of being in public that arises from delusions.

WORKUP

- History: Usually diagnostic. This should include information about other medical disorders, medications, any history of past trauma, and substance abuse. Fig. E1 describes a diagnostic decision tree for specific phobias.
- Physical examination: To confirm absence of cardiovascular abnormalities such as arrhythmias or evidence of endocrinologic reasons for hyperarousal such as an enlarged or tender thyroid gland.

LABORATORY TESTS

No specific laboratory tests are indicated.

IMAGING STUDIES

No specific imaging studies are recommended.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral therapy (CBT) and exposure-based treatments have been effective for treating specific phobia in controlled trials and are considered an appropriate first-line treatment.
- Behavioral treatments sometimes involve relaxation training, often paired with visualization and progressive desensitization.
- Success rates in treating specific phobias are higher when the phobia is not complicated by other anxiety disorders.

ACUTE GENERAL Rx

Although benzodiazepines provide rapid relief of anxiety associated with exposure to provoking stimuli, they are associated with adverse effects including somnolence, accidents, abuse, and dependence, and thus are not recommended as a first-line treatment.

CHRONIC Rx

If the phobic stimulus is rarely encountered, benzodiazepines used on an as-needed basis can be an appropriate long-term treatment; however, there is a risk of abuse and dependence that makes them a less desirable choice for long-term treatment.

COMPLEMENTARY & ALTERNATIVE MEDICINE

No definitive evidence supports complementary or alternative medicines in the treatment of phobic disorders.

DISPOSITION

Phobic disorders are generally present for life, although outpatient-based treatment may effectively reduce symptoms.

REFERRAL

Recommended for confirmation of diagnosis and for evaluation for psychotherapy and other treatment modalities.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Phobias (Patient Information)
Panic Disorder, with or without Agoraphobia (Related Key Topic)
Posttraumatic Stress Disorder (Related Key Topic)
Social Anxiety Disorder (Related Key Topic)

AUTHOR: **Kristy L. Dalrymple, PhD**

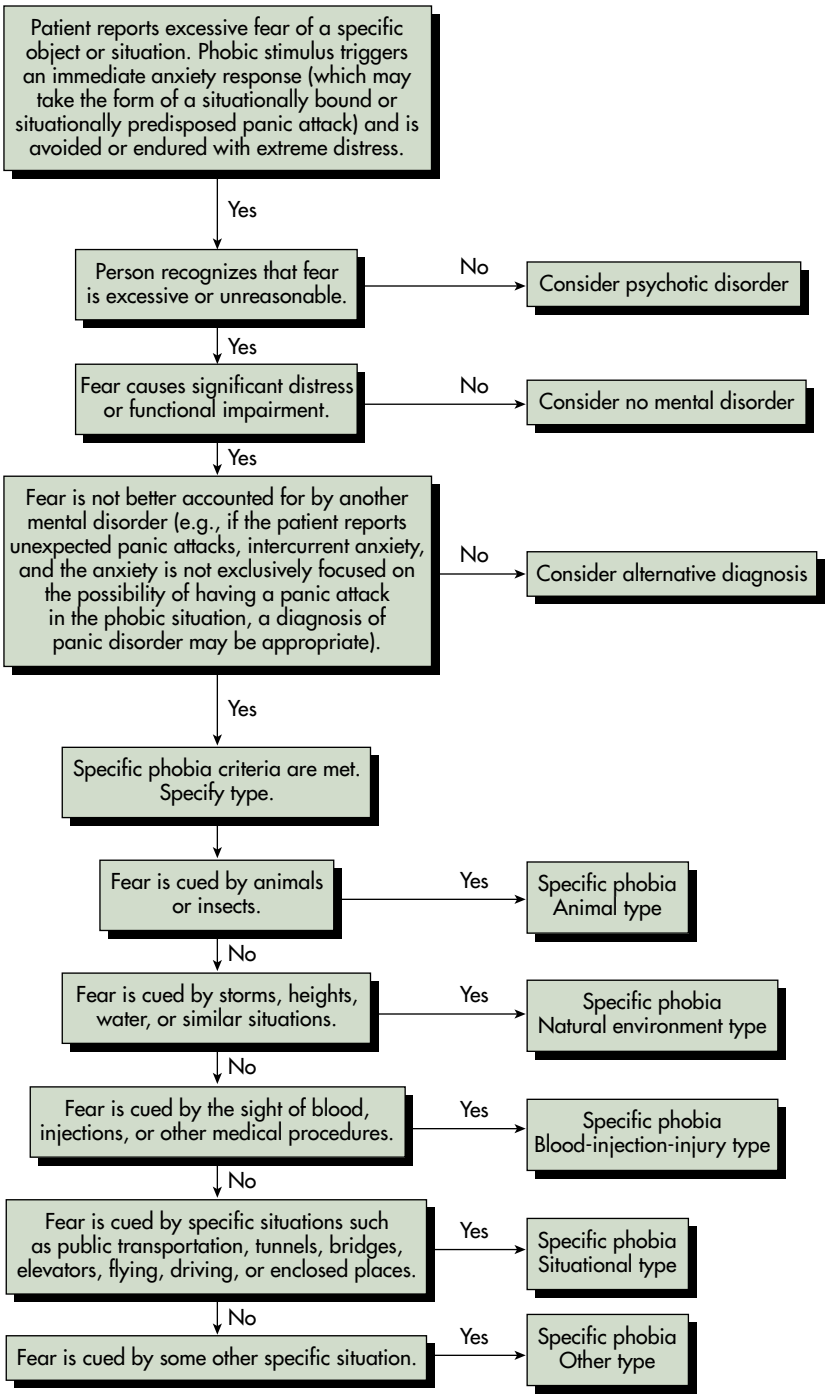

FIG. E1 Specific phobia: Diagnostic decision tree. (From Lieberman K: Social and specific phobias. In Lieberman K [ed]: *Psychiatry behavioral science and clinical essentials: a companion to Tasman,* Philadelphia, 2000, WB Saunders, pp. 368-378.)

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Sigström R et al: Nine-year follow-up of specific phobia in a population sample of older people, *Depress Anxiety* 33(4):339-346, 2016.

Wardenaar KJ et al: The cross-national epidemiology of specific phobia in the world mental health surveys, *Psychol Med* 47:1744-1760, 2017.

Pilonidal Disease PTG

BASIC INFORMATION

DEFINITION

From the Latin words *pilus,* meaning "hair," and *nidus,* meaning "nest."

A *pilonidal sinus* is a short tract extending from the skin surface that contains hair and skin debris. It is most commonly found in the intergluteal fold sacrococcygeal region, but it can also occur in the interdigital area, umbilicus, chest wall, and scalp. An *acute pilonidal abscess* consists of pus and a wall of edematous fat. A chronic *pilonidal cyst* develops from a chronic abscess of long duration as a thin and flat lining of epithelium grows into the cavity from the skin surface.

SYNONYMS

Jeep disease: During World War II, many soldiers developed pilonidal cysts thought to be caused by hours of riding on Jeeps
Pilonidal sinus
Pilonidal cyst

ICD-10CM CODES

L05	Pilonidal cyst
L05.0	Pilonidal cyst with abscess
L05.9	Pilonidal cysts without abscess

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 26 cases per 100,000 persons
PREDOMINANT SEX: Males are more commonly affected than females (2.2:1).
AVERAGE AGE OF PRESENTATION: 21 yr
RISK FACTORS:

- Male sex
- Local trauma or irritation
- Family predisposition
- Obesity
- Sedentary lifestyle
- Occupation requiring prolonged sitting or excessive exposure to hair (barbers)
- Local hirsutism
- Poor hygiene
- Increased sweat activity

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Asymptomatic pits or pores in the natal cleft (Fig. E1)
- Tenderness after physical activity or prolonged sitting
- Acute pilonidal abscess presents as a hot, tender, fluctuant swelling just lateral to the midline over the sacrum that may exude pus through the midline pit
- Acute pilonidal abscess in 20% of patients with pilonidal disease
- Chronic pilonidal may have recurrent pain and drainage
- Chronic pilonidal abscess in 80% of patients with pilonidal disease
- Infrequently, systemic reaction: Occasionally fever, leukocytosis, and malaise

ETIOLOGY

- Currently believed to be acquired rather than congenital.
- Drilling of hair shed from the perineum or the head into sebaceous or hair follicles in the natal cleft.
- Drilling is facilitated by the friction of the natal cleft.
- Subsequent infection by skin organisms leads to pilonidal abscess.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Perianal abscess arising from the posterior midline crypt
- Hidradenitis suppurativa
- Skin abscess: Furuncle or carbuncle
- Folliculitis
- Anorectal fistula
- Anal complication of Crohn disease
- Case report of squamous cell carcinoma arising from neglected chronic pilonidal sinuses

WORKUP

- Diagnosis is based on history and physical examination.
- Midline pits present behind the anus overlying the sacrum and coccyx.
- Broken hairs are often seen extruding from the midline pits.
- Insert probe in pilonidal sinus in path away from the anus.
- Complicated anal fistula may be angulating posteriorly before passing into a retrorectal abscess, but thorough examination of the anal cavity usually discloses point of origin.

TREATMENT

NONPHARMACOLOGIC THERAPY

Prevention of exacerbations:

- Local hygiene
- Avoidance of prolonged sitting position
- Weight reduction
- Early in the infection, sitz baths may decrease pain and decrease the chance that a cyst may develop into an abscess
- Treatment of an asymptomatic sinus is not indicated

Treatment of acute abscess:

- Procedure of choice for first-episode acute abscess: Simple incision and drainage in an outpatient setting. Box E1 describes surgical options for the treatment of pilonidal sinus.
- Cure rate of about 50% within 5 wk; recurrence rate 20% to 55%.
- Antibiotics: Generally not indicated, except for the treatment of cellulitis or in patients with immunosuppression, high risk of endocarditis, methicillin-resistant Staphylococcus aureus (MRSA), or underlying systemic disease.
- First-generation cephalosporin plus metronidazole is the antibiotic regimen of choice.

TREATMENT OF CHRONIC OR RECURRENT DISEASE

Elective treatment of pilonidal disease:

- Minimal surgery:
  1. Remove hair from midline pits and shave buttocks.
  2. May use a fine wire brush with local anesthesia to clear the pits and any lateral openings of granulation tissue and hair (Fig. E2).
  3. Keep area clean.
- Fistulotomy and curettage:
  1. Used when minimal surgery does not control episodes of suppuration.
  2. Pass probe to outline the pilonidal sinus and open tract surgically.
  3. Curette granulation tissue at the base of the sinus and excise edges of the skin.
  4. Keep open granulating wound meticulously clean and allow to heal.
  5. If complete healing does not take place, use a skin graft or advancement flap to close the defect.
- Marsupialization:
  1. This is the treatment of choice for chronic pilonidal disease.
  2. Wide excision of the pilonidal area is performed, including all affected skin and subcutaneous tissues down to the presacral fascia.
  3. Wound is left open, allowed to marsupialize, or closed as a primary procedure.
  4. Give antibiotics for 24 hr (particularly those directed against *Staphylococcus* and *Bacteroides* species).
- Other procedures:
  1. Excision and primary closure or closure with skin grafts or flaps: Z-plasty, V-Y advancement flap, rhomboid flap, gluteus maximus myocutaneous flap
  2. Bascom procedure (follicle removal and lateral drainage)
  3. Recurrence rate for excision (most definitive procedure): 1% to 6%
  4. Incidence of squamous cell carcinoma in a chronic, recurrent pilonidal sinus is rare (<1%)

REFERRAL

- Emergency department for incision and drainage for an acute abscess
- General surgeon for elective treatment or management of chronic or recurrent disease

PEARLS & CONSIDERATIONS

COMMENTS

Because of significant associated morbidity, the elective surgical procedures outlined are performed only after the potential risks versus benefits are carefully weighed by a general or colorectal surgeon.

RELATED CONTENT

Pilonidal Cyst (Patient Information)

AUTHOR: **Maria E. Soler, MD, MPH, MBA**

FIG. E1 Midline pits in the gluteal cleft represent a classic finding of pilonidal disease. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 19, Philadelphia, 2011, Saunders.)

BOX E1 Surgical Options for the Treatment of Pilonidal Sinus

Midline Approach
Sinus excision: open vs. marsupialization vs. closure

Unroofing and Curettage
- Asymmetric or oblique excision
- Karydakis procedure
- Bascom: open vs. closure
- Cleft
- Flaps
  1. Rhomboid
  2. V-Y advancement
  3. Z-plasty
  4. Gluteal myocutaneous

Others
- Phenolization
- Vacuum-assisted closure

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

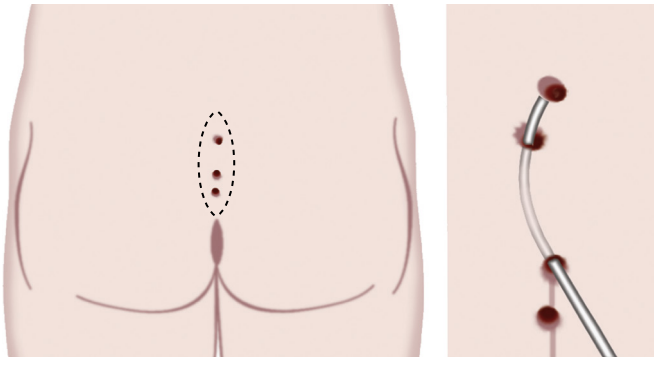

FIG. E2 Pilonidal disease. On examination, there may be multiple pits or external openings in the intergluteal cleft proximal to the anus **(A).** The openings often communicate with each other **(B).** A probe can be passed between the communicating network of tracts. Trapped loose hair is usually found in these tracts. One successful treatment option is to unroof all the tracts. (From Feldman M et al [eds]: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Saunders.)

BASIC INFORMATION

DEFINITION

Pinworms are a noninvasive infestation of the intestinal tract by *Enterobius vermicularis,* a helminth of the nematode family. It is a small (1 cm in length), white, thread-like roundworm that typically inhabits the cecum, appendix, and adjacent areas of the ileum and ascending colon.

SYNONYMS

Enterobiasis
Oxyuriasis

ICD-10CM CODE
B80 Enterobiasis

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common intestinal nematode; approximately 30,000 cases annually in the U.S.
- Worldwide distribution, but most common in temperate climates.
- The prevalence of pinworm infection is lowest in infants and reaches highest infection rate in school-age children (ages 5 to 14 yr).
- Eggs are infective within 6 hr of oviposition and may remain so for 20 days.
- Clusters are found in families, institutionalized persons, and homosexual men.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most infested persons are asymptomatic.
- Perianal itching is the most common reported symptom, with scratching leading to excoriation and sometimes secondary infection.
- The vagina may become infested with pinworms.
- Rarely insomnia, irritability, anorexia, and weight loss are described.
- Granulomas have been described in various organs resulting from worms wandering outside the intestines and dying there.

ETIOLOGY & PATHOGENESIS

- *E. vermicularis* is highly prevalent throughout the world, particularly in countries of the temperate zone. Human beings are the only host for this worm. Infestation is by fecal-oral route; ingested eggs hatch in the stomach and the larvae migrate to the colon, where they mature. Gravid female worms containing an average of 10,000 ova migrate to the perianal skin at night, lay their eggs there, and die. The eggs embryonate within 6 hr and cause itching; scratching causes egg deposition under fingernails, from which they can contaminate food or lead to autoreinfection. Ova may also be airborne and collect in dust that may be on the floor or on furniture.
- *E. vermicularis* may be transmitted between sexual partners, especially those engaging in oral-anal sex.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Perianal itching related to poor hygiene. Section II describes the causes of pruritus ani.
- Hemorrhoidal disease and anal fissures
- Perineal yeast/fungal infections

WORKUP

Identification of adult worms or eggs. *E. vermicularis* ova are ovoid but flattened on one side and measure approximately 56 × 27 micrometers (Fig. 1). The eggs can be identified on transparent tape (Fig. 2) placed on the perianal skin on awakening. (NOTE: Five consecutive negative tests rule out the diagnosis.) A single examination detects 50% of infections, three examinations detect 90%, and five examinations detect 99%.

TREATMENT

- Single dose of mebendazole (100 mg) with a repeat dose given after 2 wk results in cure rates of 90% to 100%.
- Single dose of albendazole (400 mg) with a second dose given 2 wk later is also highly effective.
- Pyrantel pamoate (11 mg/kg up to 1 g) can prevent against *E. vermicularis.* It is available as a suspension and has minimal toxicity (mild transient gastrointestinal symptoms, headache, drowsiness). A repeat dose after 2 wk is recommended because of the frequency of reinfection and autoinfection.
- Other infected family members, classmates, or residents of long-term care facilities should be treated at the same time as the index case.

FIG. 1 Adult male pinworm, *Enterobius vermicularis,* with curved posterior end; note prominent esophageal bulb (4x). (From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, Philadelphia, 2017, Elsevier.)

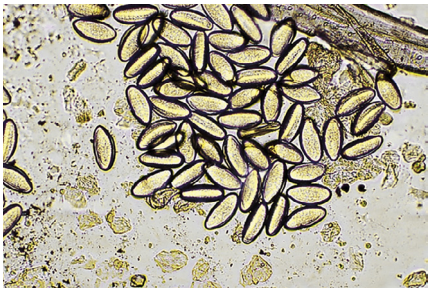

FIG. 2 Numerous eggs of *Enterobius vermicularis* as seen on a cellophane tape preparation (400x). (From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, Philadelphia, 2017, Elsevier.)

PEARLS & CONSIDERATIONS

- Eosinophilia is not observed in most cases because tissue invasion does not occur.
- Good hand hygiene is the most effective method of prevention.
- Frequent changing of underclothes, bed clothes, and bed sheets is helpful to decrease risk of autoinfection.
- Personal hygiene and cleanliness are crucial. Fingernails should be cut short and scrubbed frequently.

RELATED CONTENT

Pinworms (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

BASIC INFORMATION

DEFINITION

Piriformis syndrome is a form of low back pain caused by impingement of the sciatic nerve by prolonged or excessive contraction of the piriformis muscle and causing buttock pain, sciatica, or both. The pain is also present in the hip, groin, buttock, coccyx, and distal part of the lower extremity. Four main symptoms that constitute piriformis syndrome are:

1. Buttock pain
2. Pain aggravated on sitting
3. External tenderness near the greater sciatic notch
4. Pain with increased piriformis muscle tenderness

SYNONYMS

Deep gluteal syndrome
Pelvic outlet syndrome
Infrapiriform foramen syndrome
Wallet sciatica
Pocket sciatica

ICD-10CM CODE

S74.00 Injury of sciatic nerve at hip and thigh level

EPIDEMIOLOGY & DEMOGRAPHICS

- Women are affected more than men.
- Female-to-male incidence ratio is 6:1.
- It occurs in middle-aged patients (mean age of about 38).
- Incidence of piriformis syndrome has been estimated at 2.4 million/yr.
- About 0.3% to 6% of patients with sciatica have piriformis syndrome.

PHYSICAL FINDING & CLINICAL PRESENTATION

CLINICAL PRESENTATION: Patients with piriformis syndrome may present the following symptoms:

- Gluteal pain (97.9% of cases), which may:
  1. Be chronic
  2. Radiate to the distal part of the lower extremities
  3. Worsen with squatting or walking
- Rectal pain (worse during defecation)
- Hip movements (especially adduction and internal rotation) cause pain
- Labia majora or scrotal pain
- Dyspareunia in women
- Disturbances of potency in men
- Pain and discomfort on sitting (leading to the "wallet sign" in males who are unable to sit on their wallets without causing symptoms

PHYSICAL FINDINGS:

- Piriformis syndrome is a diagnosis of exclusion (after ruling out signs of lumbar radiculopathy via provocative tests).
- There are no neurologic deficits in patients with piriformis syndrome.
- There is tenderness over the gluteal area (the only sign that is predictive of the disease).
- Gluteal atrophy may be present.
- Sacroiliac tenderness.
- Shortening of the limb on the affected side.
- Other signs used in diagnosing piriformis syndrome include:
  1. *Lasègue sign*—Extension of the knee with the hip flexed to 90 degrees produces pain in the vicinity of the greater sciatic notch.
  2. *Pace sign*—Resisted abduction-external rotation of the thigh causes pain and weakness on the affected side.
  3. *Freiberg sign*—With the patient in the supine position, passive internal rotation of the extended thigh causes pain.
  4. Pain in the back when the patients lie down with the painful side up and involved leg flexed.

ETIOLOGY

- Trauma to the buttocks/gluteal region
- Spinal stenosis
- Anatomic variations of the division of the sciatic nerve
- As the sciatic nerve passes through the greater sciatic foramen, it is in close proximity to the piriformis muscle (Fig. E1). Pain results from compression of the sciatic nerve by the piriformis muscle
- Laminectomy
- Intragluteal injection
- Hypertrophy and spasm of the piriformis muscle
- Excessive exercise
- Leg length discrepancy (leading to altered biomechanics causing stretching and shortening of piriformis muscle)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Lumbosacral disk or spine injury (lumbar radiculopathy)
- Sacroiliac joint injury/inflammation (sacroiliitis)
- Hamstring injury
- Sciatic nerve entrapment
- Paraspinal muscle spasm
- Herniated intervertebral disk
- Unrecognized pelvic fracture
- Iliac vein thrombosis
- Postlaminectomy syndrome
- Undiagnosed nephrolithiasis
- Trochanteric bursitis

WORKUP

Usually involves imaging studies

- Computed tomography scan:
  1. Used to identify spinal stenosis
  2. May show a large mass anterior to the piriformis muscle
- Magnetic resonance imaging:
  1. May show an enlarged piriformis muscle on T1- or T2-weighted images
  2. Asymmetry in piriformis muscle size between symptomatic and asymptomatic sides (Fig. E2)
- Electromyogram (EMG):
  1. Normal EMG findings in the gluteus minimus, gluteus medius, and tensor fasciae latae muscles
  2. Abnormal EMG findings in the gluteus maximus and piriformis muscles

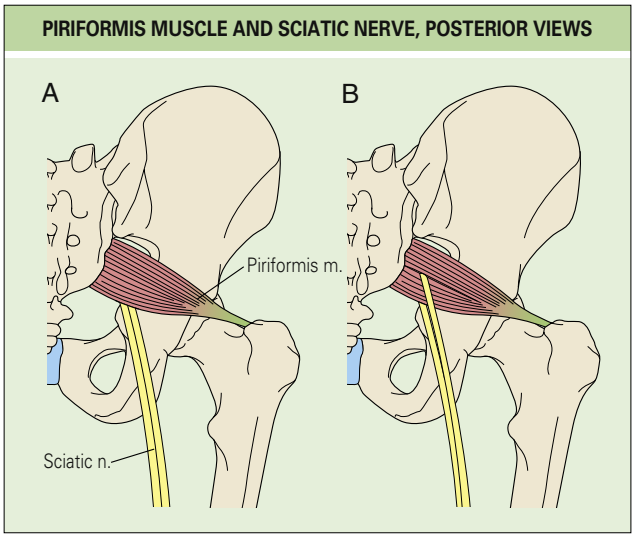

FIG. E1 Piriformis muscle and sciatic nerve, posterior views. The piriformis muscle arises from the anterior surface of the sacrum and the gluteal surface of the ilium and crosses the greater sciatic foramen to insert onto the superior border of the greater trochanter. **A,** In most instances, the sciatic nerve passes along the anterior surface of the piriformis muscle and exits the pelvis below the piriformis muscle, passing posteriorly along its inferior border. **B,** In some individuals, a portion of the sciatic nerve passes through the piriformis muscle. Other anatomic variants have been described. *m*, Muscle; *n*, nerve. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

TREATMENT

Sciatica due to piriformis syndrome is usually treated conservatively. Treatment modalities include physical therapy, lifestyle modalities, medications, and psychotherapy.

TREATMENT DURING ACUTE PHASE

- Stop offending activities
- Start physical therapy (PT) and occupational therapy treatment
- PT:
  1. The basic PT treatment is **stretching** and **manual therapy.**
  2. PT modalities are most beneficial when used in conjunction with stretching exercise.
  3. Ultrasound and/or moist heat is recommended before stretching.
  4. Massage of the lumbosacral and gluteal areas reduces muscle tightness and sciatic nerve irritation.
  5. Cold pack and/or electrical stimulation may be applied after exercise.
- Occupational therapy: Advise patients to:

1. Avoid sitting for prolonged periods.
   2. Make frequent stops when driving to get up and stretch.
- Surgical intervention: This is considered only when medical treatment fails and symptoms become intractable and/or disabling. Indications for surgical intervention include hematoma, abscess, neoplasm, compression of the nerve by gluteal vein varicosities. Response to surgical treatment is often disappointing. Promising results include:
  1. Piriformis tendon release (piriformis tenotomy)
  2. Sciatic neurolysis
- Other treatment modalities:
  1. Local injection of glucocorticoids or anesthetics into trigger points
  2. Botulinum toxin injection
  3. Nonsteroidal antiinflammatory drugs (NSAIDs)
  4. Consider brief course of opioids only in severe pain refractory to NSAIDs
  5. Transrectal massage

TREATMENT DURING RECOVERY PHASE

- Start gradual strengthening activities for the piriformis and gluteal muscles.
- Continue therapeutic modalities.
- Start light sport-specific activities and functional training if patient is asymptomatic.
- Some athletes may consider changing their footwear to avoid additional stress on the piriformis muscle.

TREATMENT DURING MAINTENANCE PHASE

- Continue performing a home exercise program for increasing flexibility and strength.
- Athletes may increase their training volume as tolerated.
- Compliance to a daily stretching program is crucial to avoid recurrence of this syndrome.

REFERRAL

- Physical therapist: To instruct patients about stretching and pain-relieving maneuvers
- Orthopedic: When diagnosis is in doubt, the patient failed conservative treatment, and surgical evaluation is needed
- Neurologist: For EMG studies

PEARLS & CONSIDERATIONS

COMMENTS

Athletes may return to play when:

- They are pain free with full range of motion
- They have full strength in the affected side

PREVENTION

To prevent the recurrence of pain:

- Avoid risk factors.
- Continue stretching exercises.
- Correction of biomechanical deficiencies.

AUTHOR: **Daniel K. Asiedu, MD, PhD, FACP**

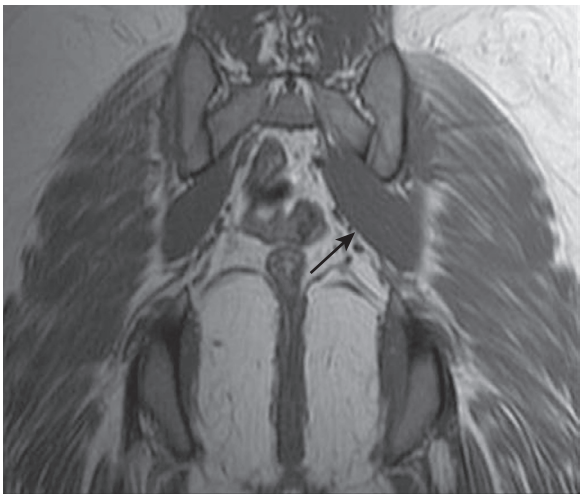

FIG. E2 Piriformis syndrome. Coronal T1-weighted MR image shows hypertrophy of the left piriformis muscle *(arrow).* (Pope TL et al: *Musculoskeletal imaging*, ed 2, Philadelphia, 2014, WB Saunders.)

SUGGESTED READING

Mitra SR et al: Piriformis syndrome: a review, *J Evolution Medi Dental Sciences* 3(14):3804-3814, 2014.

BASIC INFORMATION

DEFINITION

Pituitary adenoma is a benign neoplasm of the anterior lobe of the pituitary that causes symptoms, either by excess secretion of hormones or by a local mass effect as the tumor impinges on other, nearby structures (e.g., optic chiasm, hypothalamus, pituitary stalk). Pituitary adenomas are classified by their size, function, and features that characterize their appearance. Microadenomas are <10 mm in size, macroadenomas are ≥10 mm in size, and giant adenomas are ≥40 mm in size.

- *Nonsecretory pituitary adenomas* are those in which the neoplasm is a space-occupying lesion whose secretory products do not cause a specific disease state.
- *Secretory pituitary adenomas* can cause endocrine manifestations related to what they are secreting.

Endocrine manifestations of secretory adenomas include:

Acromegaly, a disease state characterized by a pituitary adenoma that secretes growth hormone (GH)

Galactorrhea, which is the result of a *prolactinoma* that secretes prolactin (PRL)

Cushing disease, a disease state of hypersecretion of adrenocorticotropic hormone (ACTH)

Hyperthyroidism due to a thyrotropin-secreting pituitary adenomas, which secrete primarily thyroid-stimulating hormone (TSH)

ICD-10CM CODE

D35.2 Benign neoplasm of pituitary gland

EPIDEMIOLOGY & DEMOGRAPHICS

CLASSIFICATION (BY HORMONE SECRETED):

- PRL only: 35%
- No hormone: 30%
- GH only: 20%
- PRL and GH: 7%
- ACTH: 7%
- Luteinizing hormone (LH), follicle-stimulating hormone (FSH), TSH: 1%

PREVALENCE/INCIDENCE:

- Pituitary adenomas: Up to 10% to 15% of all intracranial neoplasms; 3% to 27% at autopsy series. True prevalence is likely underestimated due to nonfunctioning pituitary adenomas going undiagnosed until they are large
- Prolactinomas: Up to 20% in women with unexplained primary or secondary amenorrhea
- GH-secreting pituitary adenoma: 50 to 60 cases per 1 million persons. They account for 8% to 16% of pituitary tumors and are most common in men over age 50
- Thyrotropin-secreting pituitary adenoma: 1% of pituitary adenomas with a slight female/male predominance of 1.7:1
- Corticotropin-secreting pituitary adenomas: Female/male predominance of 8:1 but overall uncommon diagnosis, accounting for 2% to 6% of adenomas

PHYSICAL FINDINGS & CLINICAL PRESENTATION

All sellar masses can cause visual defects by compression of the optic chiasm (bitemporal hemianopsia) or headaches.

PROLACTINOMAS:

- Females:
  1. Galactorrhea
  2. Amenorrhea
  3. Oligomenorrhea with anovulation
  4. Infertility
  5. Estrogen deficiency and associated osteopenia
  6. Decreased vaginal lubrication
- Males:
  1. Large tumors more common as a result of delayed diagnosis
  2. Possible impotence, decreased libido, or hypogonadism
  3. Galactorrhea rare because males lack the estrogen-dependent breast growth and differentiation

GH-SECRETING PITUITARY ADENOMA: ACROMEGALY:

- Coarse facial features
- Oily skin
- Prognathism
- Carpal tunnel syndrome
- Osteoarthritis
- History of increased hat, glove, or shoe size
- Decreased exercise capacity
- Visual field deficits
- Diabetes mellitus

CORTICOTROPIN-SECRETING PITUITARY ADENOMA: CUSHING DISEASE:

- Usually present when the tumor is small (1 to 2 mm)
- 50% of the tumors are <5 mm
- Other symptoms:
  1. Truncal obesity
  2. Round facies (moon face)
  3. Dorsocervical fat accumulation (buffalo hump)
  4. Hirsutism
  5. Acne
  6. Menstrual disorders
  7. Hypertension
  8. Striae
  9. Bruising
  10. Thin skin
  11. Hyperglycemia

THYROTROPIN-SECRETING PITUITARY ADENOMA:

- In males, larger, more invasive, and more rapidly growing tumors that present later in life
- Other symptoms: Thyrotoxicosis, goiter, visual impairment

NONSECRETORY PITUITARY ADENOMAS (ENDOCRINE INACTIVE PITUITARY ADENOMA):

- Usually large at the time of diagnosis
- Symptoms:
  1. Bitemporal hemianopsia as a result of compression of the optic chiasm
  2. Hypopituitarism from compression of the pituitary gland
  3. Hypogonadism in men and in premenopausal women
  4. Cranial nerve deficits caused by extension into the cavernous sinus
  5. Hydrocephalus from extension into the third ventricle, compressing the foramen of Monro
  6. Diabetes insipidus resulting from compression of the hypothalamus or pituitary stalk (a rare complication)

ETIOLOGY

Benign neoplasms of epithelial origin linked to genetic mutations of *MEN1, Gs-Alpha,* and *AIP*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

PROLACTINOMA:

- Pregnancy
- Postpartum puerperium
- Primary hypothyroidism
- Breast disease
- Breast stimulation
- Drug ingestion (especially phenothiazines, antidepressants, haloperidol, methyldopa, reserpine, opiates, amphetamines, and cimetidine)
- Chronic renal failure
- Liver disease
- Polycystic ovarian disease
- Chest wall disorders
- Spinal cord lesions
- Previous cranial irradiation

ACROMEGALY: Ectopic production of GH-releasing hormone from a carcinoid or other neuroendocrine tumor

CUSHING DISEASE:

- Diseases that cause ectopic sources of ACTH overproduction (including small-cell carcinoma of the lung, bronchial carcinoid, intestinal carcinoid, pancreatic islet cell tumor, medullary thyroid carcinoma, or pheochromocytoma)
- Adrenal adenomas, adrenal carcinoma
- Nelson syndrome

THYROTROPIN-SECRETING PITUITARY ADENOMAS: Primary hypothyroidism

NONSECRETORY PITUITARY ADENOMA: Nonneoplastic mass lesions of various etiologies (e.g., infectious, granulomatous)

WORKUP

Pituitary adenomas should be identified at an early stage so that effective treatment can be implemented.

Screening tests for functional pituitary adenomas are described in Table 1.

PROLACTINOMA: First step: Measurement of basal PRL levels (practitioners should be aware of discriminatory values in their own institutions).

- Elevated PRL levels are correlated with tumor size.
- Level >200 ng/ml indicates likely prolactinoma, with levels of 100 to 200 ng/ml being equivocal and possibly associated with medications or other sources.
- Basal PRL levels between 20 and 100 suggest a microadenoma but can be due to common medications (estrogen, antidepressants,

TABLE 1 Screening Tests for Functional Pituitary Adenomas

Disorder	Test	Comments
Acromegaly	IGF-1 OGTT with GH obtained at 0, 30, and 60 min	Interpret IGF-1 relative to age- and gender-matched controls. Normal subjects should suppress GH to <1 μg/L.
Prolactinoma	Serum PRL level	A level >500 μg/L is pathognomonic for macroprolactinoma. If >200 μg/L, prolactinoma is likely.*
Cushing disease	24-hr UFC Nighttime salivary cortisol dexamethasone (1 mg) at 11 P.M. and fasting plasma cortisol measured at 8 A.M. ACTH assay	Ensure that urine collection is total and accurate by measuring urinary creatinine. Free salivary cortisol reflects circadian rhythm, and elevated levels may indicate Cushing disease. Normal subjects suppress to <1.8 μg/dl. Distinguishes adrenal adenoma from ectopic ACTH or Cushing disease.
TSH-secreting tumor	TSH measurement free T_4 by dialysis total T_3	If T_4 or T_3 is elevated and TSH is measurable or elevated, a TSH-secreting tumor may be present.

*Risperidone may result in prolactin levels >200 μg/L.
ACTH, Adrenocorticotropic hormone; *GH*, growth hormone; *IGF-1*, insulin-like growth factor type 1; *OGTT*, oral glucose tolerance test; *PRL*, prolactin; T_3, triiodothyronine; T_4, thyroxine; *TSH*, thyroid-stimulating hormone; *UFC*, urinary free cortisol.
From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders.

metoclopramide, Aldomet, and others) or recent breast stimulation.
- Basal level <20 ng/ml is usually considered normal. Each laboratory should develop its own normative values, however, and practitioners should refer to these values.
- Threshold level for obtaining imaging such as MRI should be developed by individual providers depending on the level of specificity and sensitivity desired.

ACROMEGALY:
- First screening tests are the measurement of the serum insulin-like growth factor I level, postprandial serum GH, and thyrotropin-releasing hormone (TRH) stimulation test.
- Follow with an oral glucose tolerance test.
- Failure to suppress serum GH to <2 ng/ml with an oral load of 100 g glucose is considered conclusive.
- A GH-releasing hormone level >300 ng/ml is indicative of an ectopic source of GH.

CUSHING DISEASE:
- Measurement of late-night salivary cortisol level is the best screening test.
- Normal or slightly elevated corticotropin levels ranging from 20 to 200 pg/ml; normal is 10 to 50 pg/ml (normative data should be developed by each institution for its population).
- Level <10 pg/ml usually indicates an autonomously secreting adrenal tumor.
- Level >200 pg/ml suggests an ectopic corticotropin-secreting neoplasm.
- Cushing disease can be assessed by absence of cortisol suppression with the low-dose dexamethasone test but with the presence of cortisol suppression after the high-dose test. As a method to distinguish Cushing disease from an ectopic source of ACTH, this test is robust.
- 24-hr urine collection should demonstrate an increased level of cortisol excretion.

THYROTROPIN-SECRETING PITUITARY ADENOMA:
- Highly sensitive thyrotropin assays, which evaluate the presence of thyrotoxicosis, are one way to detect a thyrotropin-secreting tumor.
- Free alpha subunit is secreted by >80% of tumors, with the ratio of the alpha subunit to thyrotropin <1.
- With central resistance to thyroid hormone, ratio is <1, and the sella is normal.
- Laboratory tests show elevated serum levels of both T_3 and T_4.

NONSECRETORY PITUITARY ADENOMA:
- Visual field testing
- Assessment of the pituitary and organ function to determine if there is hypopituitarism or hypersecretion of hormones (even if the effects of hypersecretion are subclinical)
- TRH to provoke secretion of FSH, LH, and LH-beta-subunit; will not elicit response in normal persons
- Exclusion of Klinefelter syndrome in patient with longstanding primary hypogonadism, elevated gonadotropin levels, and enlargement of the sella

IMAGING STUDIES

Study of choice: MRI of the pituitary (Fig. E1) and hypothalamus. If an MRI shows the tumor impinging on the optic chiasm, then formal visual field testing is indicated.
- When evaluating Cushing disease, small size at the onset of symptoms noted.
- MRI, in this case, only 60% sensitive at best and may yield false-positive results.
- CT scan only when MRI is unavailable or is otherwise contraindicated.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

SURGERY:
- Selective transsphenoidal resection of the adenoma (Table 2) is the treatment of choice for acromegaly, Cushing disease, and thyrotropin-secreting pituitary adenomas, all of which tend to be microadenomas at the time of onset of symptoms.

TABLE 2 Transsphenoidal Pituitary Surgery

Primary Indications

General
Visual tract or central nervous system compression arising from within sella
Relief of compressive hypopituitarism by presenting, residual, or recurrent tumor tissue
Tumor recurrence after surgery or irradiation
Pituitary hemorrhage
Cerebrospinal fluid leak
Resistance to medical therapy
Intolerance of medical therapy
Personal choice
Desire for immediate pregnancy with macroadenoma
Requirement for diagnostic tissue histology

Specific
Acromegaly
Cushing disease
Clinically nonfunctioning macroadenoma
Prolactinoma
Nelson syndrome
TSH-secreting adenoma

Side Effects

Transient
Diabetes insipidus
Cerebrospinal fluid leak and rhinorrhea
Inappropriate ADH secretion
Arachnoiditis
Meningitis
Postoperative psychosis
Local hematoma
Arterial wall damage
Epistaxis
Local abscess
Pulmonary embolism
Narcolepsy

Permanent (up to 10%)
Diabetes insipidus
Total or partial hypopituitarism
Visual loss
Inappropriate ADH secretion
Vascular occlusion
CNS damage: oculomotor palsy, hemiparesis, encephalopathy
Nasal septum perforation

Surgery-Related Mortality (up to 1%)
Brain, hypothalamic
Vascular damage
Postoperative meningitis
Cerebrospinal fluid leak
Pneumocephalus
Acute cardiopulmonary disease
Anesthesia-related
Seizure

ADH, Antidiuretic hormone; *CNS,* central nervous system; *TSH,* thyroid-stimulating hormone.
From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders.

- Macroadenomas, such as the nonsecretory pituitary adenoma, may also be surgically removed, but risk of recurrence is greater with these tumors and adjunctive therapy such as irradiation may also be necessary.
- Bilateral adrenalectomy has been performed in patients with Cushing disease after failure of other therapies; complications requiring lifelong hormone replacement or Nelson

syndrome (rapid enlargement of pituitary tumor due to adrenal resection) may occur.

RADIOTHERAPY:

- Radiotherapy is used primarily as adjuvant treatment. It is reserved for patients who have not responded to surgical treatment and who still have symptoms of the adenoma.
- Used with varying degrees of success in all the different pituitary adenomas.
- Radiotherapy complications include long-term hypopituitarism (40% of patients) and secondary neoplasms (1.5% of patients).

ACUTE GENERAL Rx

PROLACTINOMA:

- For prolactinomas, initial therapy is generally dopamine agonists. Bromocriptine, a dopamine analogue, is generally given orally in divided doses of 1.5 to 10 mg. Cabergoline is given once or twice weekly. It is better tolerated and more effective than bromocriptine for tumor shrinkage but more expensive.
- Side effects include orthostatic hypotension, nausea, and dizziness; avoided by beginning with low-dose therapy.
- Other compounds include pergolide mesylate, a long-acting ergot derivative with dopaminergic properties, as well as other nonergot derivatives.

ACROMEGALY:

- Somatostatin analogues: Octreotide, lanreotide administered as monthly injections.
- Cabergoline or bromocriptine can also be used. They have modest activity but can be administered orally and are less expensive than somatostatin analogues.
- Pegvisomant can also be used to normalize IGF-1 levels.

CUSHING DISEASE:

- Ketoconazole, which inhibits the cytochrome P-450 enzymes involved in steroid biosynthesis, is effective in managing mild to moderate disease in daily oral doses of 600 to 1200 mg.
- Metyrapone and aminoglutethimide can be used to control hypersecretion of cortisol but are generally used when preparing a patient for surgery or while waiting for a response to radiotherapy.

THYROTROPIN-SECRETING PITUITARY ADENOMA:

- Ablative therapy with either radioactive iodide or surgery is indicated.
- Treatment directed to the thyroid alone may accelerate growth of the pituitary adenoma.
- Octreotide has been shown to be effective in doses similar to those used for acromegaly.

NONSECRETORY PITUITARY ADENOMA:

- There is no role for medical therapy at this time.

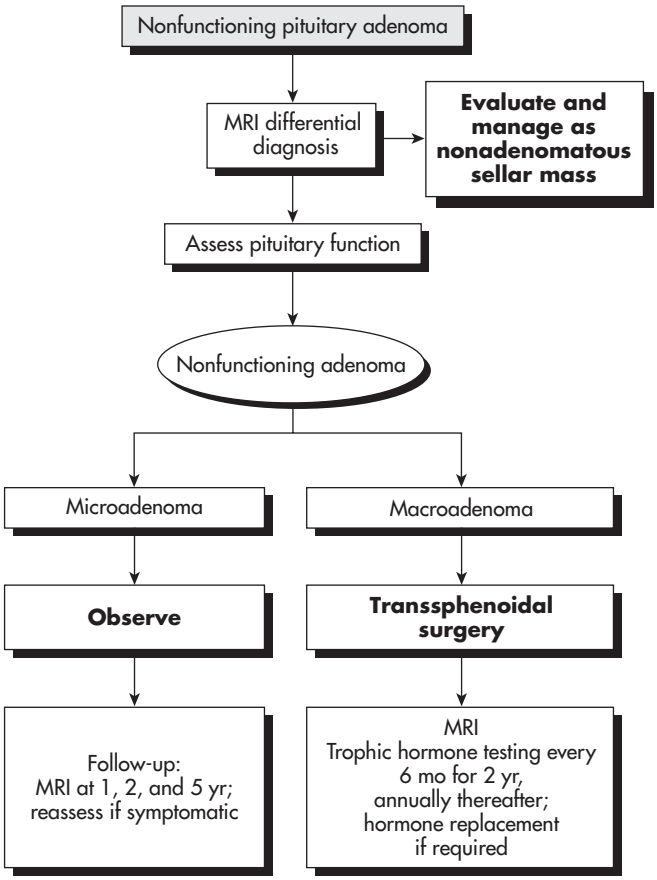

FIG. 2 Management of nonfunctioning pituitary adenomas. Skilled interpretation of magnetic resonance images is crucial to diagnosing a nonadenomatous mass such as a meningioma, aneurysm, or other sellar lesion. *MRI,* Magnetic resonance imaging. (From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, WB Saunders.)

- Surgery and radiotherapy may be indicated. An algorithm for the management of nonfunctioning pituitary adenomas is described in Fig. 2.

CHRONIC Rx

For all pituitary adenomas:

- Careful follow-up is important. Patients undergoing transsphenoidal microsurgical resection should be seen in 4 to 6 wk to ensure that the adenoma has been completely removed and that the endocrine hypersecretion is resolved.
- If there is good clinical response, patient should be monitored yearly for recurrence and to follow the level of the hypersecreted hormone.
- Patients who have undergone irradiation should have close follow-up with backup medical therapy because response to radiotherapy may be delayed; incidence of hypopituitarism also increases with time.
- Surgical resection is not indicated in pituitary incidentalomas that are microadenomas since only 10% will experience tumor growth.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pituitary Adenoma (Patient Information)
Acromegaly (Related Key Topic)
Amenorrhea (Related Key Topic)
Cushing Disease and Syndrome (Related Key Topic)
Galactorrhea (Related Key Topic)
Prolactinoma (Related Key Topic)

AUTHOR: **Ghamar Bitar, MD**

SUGGESTED READINGS

Molitch ME: Diagnosis and treatment of pituitary adenomas: a review, *JAMA* 317(5):516-524, 2016.

Trouillas J: In search of a prognostic classification of endocrine pituitary tumors, *Endocr Pathol* 25(2):124-132, 2014.

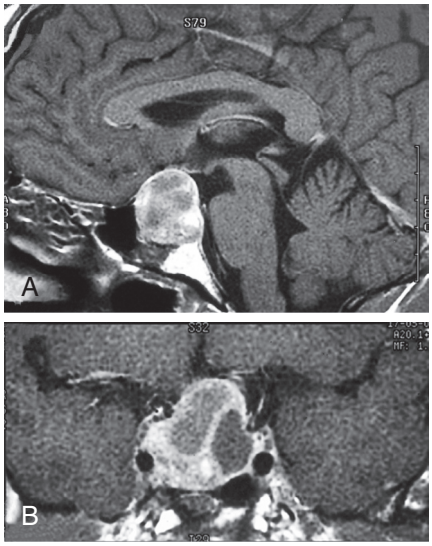

FIG. E1 Magnetic resonance T1-weighted gadolinium-enhanced image of a pituitary adenoma. A, Sagittal image. **B,** Coronal image. (Courtesy D. Thomas. From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, WB Saunders.)

Pityriasis Rosea PTG

BASIC INFORMATION

DEFINITION

Pityriasis is a common self-limiting skin eruption of unknown etiology.

ICD-10CM CODE
L42 Pityriasis rosea

EPIDEMIOLOGY & DEMOGRAPHICS

- Most cases of pityriasis rosea occur between ages 10 and 35 yr; mean age is 23 yr.
- The incidence of disease is highest in the fall and spring.
- Female:male ratio is 1.5:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Initial lesion (herald patch), an annular pink patch with trailing scale, precedes the eruption by approximately 1 to 2 wk; typically measures 3 to 6 cm; it is round to oval in appearance and most frequently located on the trunk (Fig. E1).
- Eruptive phase follows within 2 wk and peaks after 7 to 14 days.
- Lesions are most frequently located in the lower abdominal area. They have a salmon-pink appearance in whites and a hyperpigmented appearance in blacks.
- Most lesions are 4 to 5 mm in diameter; center has a "cigarette paper" appearance; border has a characteristic ring of scale (collarette) (Fig. E2). When stretched across the long axis, the scales tend to fold across the lines of stretch, the so-called "hanging curtain sign."
- Lesions occur in a symmetric distribution and follow the cleavage lines of the trunk (Christmas tree pattern).
- An inverse pattern showing distribution along skin lines may be present (Fig. E3). The axillary area is a good site to look for orientation along skin lines, facilitating the diagnosis (Fig. E4).
- The number of lesions varies from a few to hundreds. They generally disappear spontaneously after 3 to 8 wk.
- Most patients are asymptomatic; pruritus is the most common symptom.
- History of recent fatigue, headache, sore throat, and low-grade fever is present in approximately 25% of cases.

ETIOLOGY

Unknown, possibly viral exanthem. Active replication of human herpesvirus (HHV)-6 and HHV-7 has been demonstrated in mononuclear cells of lesional skin.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Tinea corporis (can be ruled out by potassium hydroxide examination)

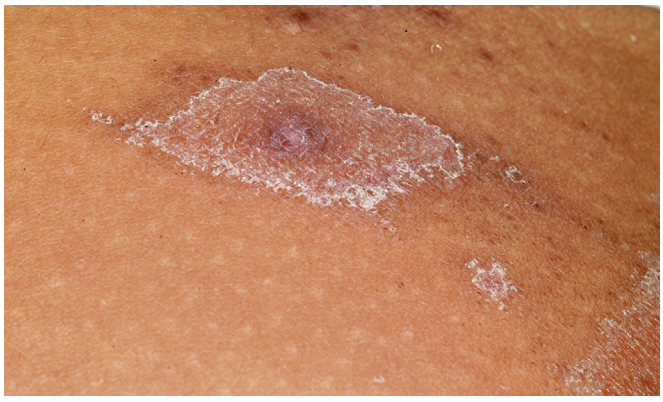

FIG. E1 Herald patch (pityriasis rosea). Oval lesion with finely scaled, elevated border, occasionally misdiagnosed as tinea corporis. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

FIG. E2 Pityriasis rosea. The collarette of scale can be subtle. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

FIG. E3 Pityriasis rosea. Inverse pattern showing the distribution along skin lines. Scaling may be more difficult to appreciate in intertriginous areas. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

FIG. E4 Pityriasis rosea. Truncal involvement with larger plaques and predominantly round papular lesions, most commonly seen in young children and African Americans. Note the peripheral scale and distribution along skin lines. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

- Secondary syphilis (absence of herald patch, positive serologic test for syphilis)
- Psoriasis
- Nummular eczema
- Drug eruption: Medications that may cause rashes similar to pityriasis rosea include clonidine, captopril, interferon, bismuth, barbiturates, gold, hepatitis B vaccine, and imatinib mesylate
- Other viral exanthem
- Seborrheic dermatitis
- Eczema
- Lichen planus
- Tinea versicolor (the lesions are more brown and the borders are not as ovoid)
- Erythema migrans

WORKUP

Presence of herald lesion and characteristic rash are diagnostic. Skin biopsy is generally reserved for atypical cases.

LABORATORY TESTS

Generally not necessary; serologic test for syphilis if clinically indicated

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

The disease is self-limited and generally does not require any therapeutic intervention.

ACUTE GENERAL Rx

- Use calamine lotion or oral antihistamines in patients with significant pruritus. Corticosteroid lotions or creams also provide some relief from itching.
- Use prednisone tapered over 2 wk in patients with severe pruritus.
- Direct sun exposure or use of ultraviolet light within the first wk of eruption is beneficial in decreasing the severity of disease.
- One small trial showed improvement of rash and pruritus with erythromycin 250 mg qid for 2 wk.

DISPOSITION

- Spontaneous complete resolution of the rash within 4 to 8 wk
- Recurrence rare (<2% of cases)

PEARLS & CONSIDERATIONS

COMMENTS

Reassure patient that the disease is not contagious, and its course is benign.

RELATED CONTENT

Pityriasis Rosea (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READING

Drago F: Evidence of human herpesvirus-6 and -7 reactivation in miscarrying women with pityriasis rosea, *J Am Acad Dermatol* 71:198-199, 2014.

BASIC INFORMATION

DEFINITION

The diagnosis of placenta previa is based on sonography and requires the identification of echogenic homogeneous placental tissue over the internal cervical os. When the placental edge is <2 cm from the internal os, the placenta is called "low-lying." The historic terms "marginal" and "partial" for characterizing a placenta previa are no longer used.

One hypothesis is that the lower uterine cavity contains more vascularized decidua, which promotes implantation of trophoblast toward the cervical os. Another hypothesis is that a particularly large placental surface area increases the probability that the placenta will implant over the cervical os.

ICD-10CM CODES

O44	Placenta previa
O44.0	Complete placenta previa NOS or without hemorrhage
O44.1	Complete placenta previa with hemorrhage
O44.2	Partial placenta previa without hemorrhage
O44.3	Partial placenta previa with hemorrhage
O44.4	Low-lying placenta NOS or without hemorrhage
O44.5	Low-lying placenta with hemorrhage

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The pooled prevalence of major placenta previa was 4.3 cases per 1000 pregnancies. Prevalence was highest among Asian studies (12.2 per 1000) and lower among studies from Europe (3.6 per 1000), North America (2.9 per 1000), and sub-Saharan Africa (2.7 per 1000).

RISK FACTORS:

- Previous placenta previa (recurs in 4% to 8% of subsequent pregnancies)
- Previous cesarean delivery (increases incidence by 47% to 60%)
- Multiparity
- Multiple gestation (increases prevalence by 40%)
- Smoking and cocaine use
- Previous intrauterine surgical procedure or Asherman syndrome
- Abnormal or large placenta

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The classic presentation of placenta previa is painless vaginal bleeding, usually in the second or third trimester. 10% to 20% of women present with uterine contractions, pain, and bleeding. On physical examination, the uterus is soft and pain free. The fetus is often in breech, transverse lie, or high. Fetal distress is usually not present.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Morbidly adherent placenta (accreta, increta, percreta)
- Vasa previa
- Abruptio placentae
- Vaginal or cervical trauma
- Labor
- Local malignancy

WORKUP

- Do *not* perform a digital vaginal examination.
- Perform a speculum examination in a hospital setting to exclude any local bleeding.
- Perform a transvaginal ultrasonography to assess for placental location.
- Exclude the presence of placenta previa-accreta in patients with a history of cesarean sections. In a prospective study, the frequency of placenta accreta increased with an increasing number of cesarean deliveries: 3% for first cesarean, 11% for second cesarean, 40% for third cesarean, 61% for fourth cesarean, and up to 67% for fifth or more cesarean sections.

LABORATORY TESTS

- A complete blood count can be used to monitor hemoglobin and hematocrit.
- A Kleihauer-Betke preparation of maternal blood in all Rh-negative women and Rh-immune globulin when indicated

IMAGING STUDIES

- The simplest and safest method of placental localization is transabdominal sonography with confirmatory imaging by transvaginal ultrasonography (TVUS). Transabdominal ultrasonography alone is inaccurate in the diagnosis of placenta previa and should be used only as a screening tool. TVUS (Fig. 1) has become the gold standard for the diagnosis of placenta previa. It is safe even in the presence of active bleeding.
- MRI has also been effective in detecting placenta previa, although sonography remains the preferred method due to lower cost, widespread availability, and well-established accuracy.

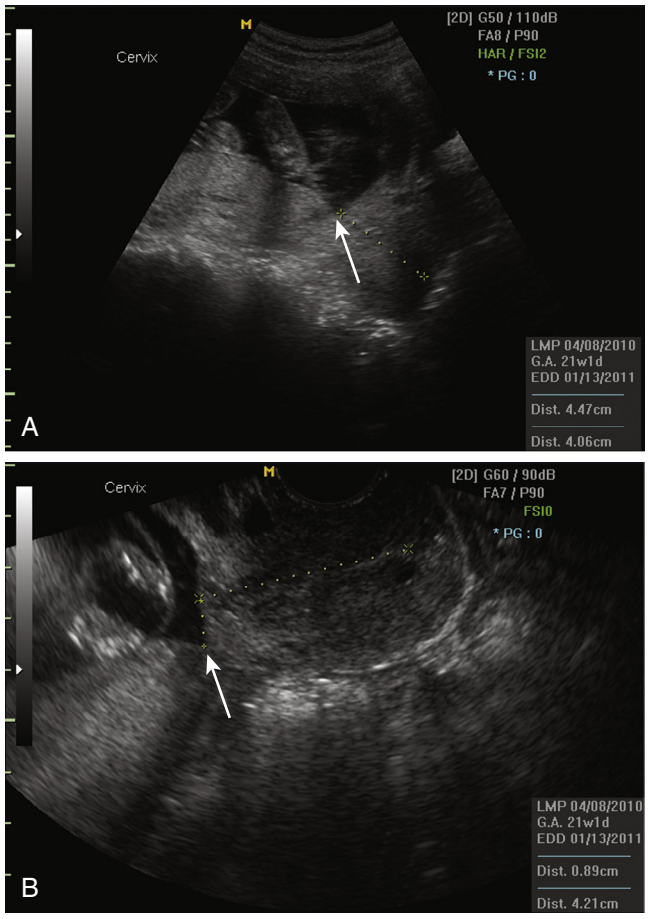

FIG. 1 Transabdominal ultrasonography and transvaginal ultrasonography of marginal placenta previa. *Arrows* identify placental edge. (Courtesy K. Francois. From Gabbe SG: *Obstetrics*, ed 6, Philadelphia, 2012, WB Saunders.)

Rx TREATMENT

MANAGEMENT OF ASYMPTOMATIC PLACENTA PREVIA

- Avoid sexual activity, digital exams, and extraneous exercise.
- Review bleeding precautions and anticipatory guidance, including the need for cesarean section and the risk for hysterectomy early in pregnancy.

Sequential assessment of placental location:

- At 32 wks, follow-up is indicated:
  1. If the placental edge is ≥2 cm from the internal os, placenta previa has resolved and no further assessment is required.
  2. If the placental edge is over or <2 cm from the internal os, placenta previa persists and repeat at 36 wks is indicated.
- At 36 wks:
  1. If the placental edge is ≥2 cm, the patient is consented for vaginal delivery.
  2. If the placental edge is over the internal os, cesarean delivery is scheduled.

Timing of delivery:

- Cesarean delivery at 36+0 to 37+6 wks in pregnancies with uncomplicated placenta previa

MANAGEMENT OF SYMPTOMATIC PLACENTA PREVIA

- Initial assessment for signs of maternal hemodynamic compromise or hemorrhagic shock; large-bore IV access with crystalloid fluid resuscitation.
- Assess fetal status and gestational age by sonogram and continuous fetal heart rate monitoring.
- Cross-matched blood should be made available during bleeding episodes.
- Tocolytic therapy should not be administered in an actively bleeding patients.
- Magnesium sulfate therapy for fetal neuroprotection should be considered in those with symptomatic preterm (less than 32 wks) placenta previa if the decision has been made to likely deliver the patient within 24 hours. Emergent delivery should not be delayed to administer magnesium.
- Cesarean delivery is indicated for active labor, nonreassuring fetal heart rate tracing, active bleeding with hemodynamic instability, and significant bleeding after 34 wks' gestation.

Expectant management after a resolved bleed:

- Antenatal corticosteroid should be administered to symptomatic women between 23+0 and 36+6 wks of gestation to enhance fetal pulmonary maturity.
- Correct anemia.
- Administer anti-D immune globulin to D-negative women.

DISPOSITION

Inpatient versus outpatient: Consider discharge for women whose bleeding has stopped for 24 hours and live in close proximity to the hospital, demonstrate compliance with medical management, can maintain bed rest, understand bleeding precautions, and have an adult companion available for transport 24 hours a day.

PEARLS & CONSIDERATIONS

COMMENTS

- Placenta previa is diagnosed by TVUS, with repeat assessment at 32 and 36 wks when indicated.
- Asymptomatic placenta previa can be managed expectantly with a planned cesarean delivery at 36+0 to 37+6 wks.
- Symptomatic placenta previa is managed by assessing hemodynamic stability, considering steroids for fetal lung maturity, magnesium sulfate for fetal neuroprotection when indicated, and cesarean delivery.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Placenta Previa (Patient Information)
Vaginal Bleeding During Pregnancy (Related Key Topic)

AUTHORS: **Helen B. Gomez, MD,** and **Anthony Sciscione, DO**

SUGGESTED READINGS

Fan D et al: Prevalence of antepartum hemorrhage in women with placenta previa: a systematic review and meta-analysis, *Sci Rep* 7:40320, 2017.

Gyamfi-Bannerman C: Society for maternal-fetal medicine (SMFM) Consult Series #44: management of bleeding in the late preterm period, *Am J Obstet Gynecol* 218(B2), 2018.

Weiner E et al: The effect of placenta previa on fetal growth and pregnancy outcome, in correlation with placental pathology, *J Perinatol* 36:1073, 2016.

BASIC INFORMATION

DEFINITION

Despite its name, plantar fasciitis is characterized by chronic degeneration of the plantar fascia without signs of inflammation. The plantar fascia consists of longitudinal collagen fibers that extend from the anteromedial calcaneus and divide distally into five digital bands that insert in the corresponding metatarsophalangeal joints. The function of the plantar fascia is to provide dynamic shock absorption, medial longitudinal arch support, and protection to underlying anatomic structures. Over time, repetitive microtrauma to the plantar fascia causes myxoid degeneration, microtears in the fascia, collagen necrosis, and angiofibroblastic hyperplasia culminating in the clinical presentation of plantar fasciitis.

Patients with plantar fasciitis have pain that is typically elicited along the medial calcaneal tuberosity on which the medial band of the plantar fascia inserts or along the coursing of the plantar fascia (Fig. E1).

SYNONYM

Heel spur syndrome

ICD-10CM CODES

M72.2	Plantar fascial fibromatosis
M77.30	Calcaneal spur, unspecified foot
M77.31	Calcaneal spur, right foot
M77.32	Calcaneal spur, left foot

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Plantar fasciitis is the most common cause of plantar heel pain and occurs bilaterally in up to 30% of cases. In the U.S., it is estimated that greater than two million people suffer from and are treated for plantar fasciitis on an annual basis. Most patients seek their primary care physicians for initial consultation. Studies have shown that plantar fasciitis resolves in 80% of patients who do not seek any medical treatment during a 12-mo period.

PREDOMINANT SEX: Predominance of plantar fasciitis varies according to studies.

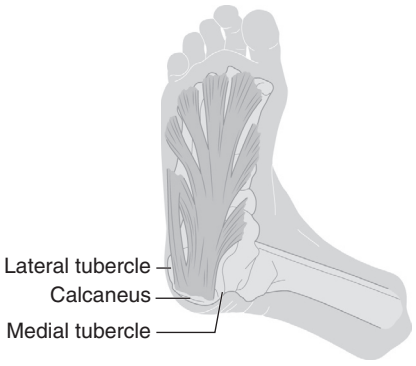

FIG. E1 Plantar view of origin and insertion of plantar fascia. (From Frontera WR: *Essentials of physical medicine and rehabilitation,* ed 2, Philadelphia, 2008, WB Saunders.)

PREDOMINANT AGE: Peak incidence ranges from ages 40 to 60 yr old but can occur at any age.

RISK FACTORS: Rapid increase in activity, weight gain, obesity, pes cavus or pes planus foot type, prolonged standing, excessive running, and abrupt change in activity, trauma, and ambulating on hard surfaces barefoot.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Pain is commonly localized to the medial tubercle of the calcaneus and may radiate along the course of the plantar fascia. Pain outside of the plantar heel should raise the suspicion of an alternative diagnosis. The pain is often described as sharp, deep, and achy. Nerve paresthesias are not common. Additionally, passive ankle dorsiflexion can cause discomfort in the proximal plantar fascia, and the plantar fascia may be thickened. Classically, patients experience poststatic dyskinesia–heel pain with the first few steps in the morning and upon standing after sitting for a prolonged period of time. Symptoms typically improve with ambulation secondary to the plantar fascia being in a relaxed position.

ETIOLOGY

- Repetitive, prolonged microtrauma to the plantar heel
- Calcaneal heel spurs may or may not be present, and are more likely an incidental finding rather than a factor related to the etiology
- Achilles tendon contracture (equinus, pseudoequinus)
- Intrinsic biomechanical factors: Forefoot varus, compensated rearfoot varus, rearfoot varus, flexible forefoot valgus, compensated forefoot valgus, tibial varum, excessive femoral anteversion
- Poor footwear
- Prolonged standing/walking occupations
- Heel pad atrophy
- Ambulating barefoot on hard surfaces
- Exercising on uneven terrain
- Overtraining
- Obesity

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Calcaneal fracture
- Tarsal tunnel syndrome
- Foreign body
- Bone cyst or bone tumor
- Bone contusion
- Posterior tibial tendon dysfunction
- Flexor hallucis longus tendonitis
- Plantar fascial fibromatosis
- Rheumatoid arthritis
- Seronegative arthropathies including reactive arthritis, psoriatic arthritis, and ankylosing spondylitis
- Plantar fascial rupture
- Bursitis of the plantar heel
- Baxter neuritis
- Piezogenic plantar papules
- L5 to S1 radiculopathy
- Disruption in the morphology of plantar fat pad

STUDIES

Additional studies play a limited role in diagnosing plantar fasciitis but may reveal alternative causes of heel pain.

- Weight-bearing x-rays—osseous abnormalities including tumors, fractures (lateral, oblique, anterior-posterior, calcaneal axial [Harris] views); however, these usually are not high yield in identifying plantar fasciitis
- MRI—soft tissue and osseous structures in greater anatomic detail without any exposure to radiation and is useful for ruling out other causes of heel pain
- CT—osseous structure abnormalities such as tarsal coalitions and osteocartilaginous lesions in greater anatomic detail
- Bone scan—stress fractures
- Ultrasound—soft tissue structure anomalies or abnormalities; therapeutic ultrasound is also an early, effective treatment modality
- Nerve conduction tests—nerve disorders such as tarsal tunnel syndrome

TREATMENT

Nonsurgical treatment is the mainstay of treatment for plantar fasciitis

- Supportive shoe gear with appropriate modifications (e.g., gel heel cup for comfort)
- Custom-molded orthotics (rearfoot posting to correct for rearfoot varus or valgus)
- Physical therapy: Ultrasound, iontophoresis, electrical stimulation (TENS unit); stretching, strengthening, and proprioception exercises
- Ice, NSAIDs, oral corticosteroids, activity reduction
- Weight reduction in those who are overweight
- Stretching before activities
- Corticosteroid injection (Caution: Can lead to plantar fascia rupture and is not routinely recommended)
- Botulin toxin injection: Inhibits the release of acetylcholine in overactive muscles
- Platelet-rich plasma injection
- Dorsiflexion night splint to maintain ankle joint at 90 degrees (stretches plantar fascia)
- Manual deep foot massage
- Heel lifts or heel cup if the etiology is Achilles equinus
- Severe cases may require a controlled ankle movement (CAM) boot or short leg cast for 4 to 6 wk of immobilization
- Recalcitrant cases may require surgical intervention
- Pulsed radiofrequency electromagnetic field therapy
- Extracorporeal shock-wave therapy (ESWT): Last option before surgical intervention in those who have failed all other conservative treatment modalities. Mechanism of action (MOA): Increases proliferation of growth factors; inhibits demyelinated plantar sensory nerves; reduces calcification within the plantar fascia; increases peripheral blood circulation, angiogenesis, and neovascularization in the degenerative tissue of the heel

DISPOSITION

Higher success rates for treating plantar fasciitis are associated with early recognition . It is imperative to recognize the biomechanical components when assessing plantar fasciitis. Pathology that is not recognized early typically involves a longer treatment course, and those cases that are recalcitrant to conservative treatment modalities tend to need surgical intervention.

REFERRAL

- For biomechanical exam, orthotics, or surgical consult (podiatric surgeon and/or foot and ankle orthopedic surgeon)
- Physical therapy can be used as an adjunct to conservative treatment measures

PEARLS & CONSIDERATIONS

COMMENTS

- Plantar fasciitis is commonly misdiagnosed. The cases that are recalcitrant to treatment need to be reevaluated to exclude other etiologies.
- A recent meta-analysis of 20 randomized trials comparing foot orthoses with sham orthoses, other treatments, or no treatment revealed that although some trials showed modest improvement with orthoses the overall results revealed no significant short- or long-term benefit for custom-made or prefabricated orthoses.[1]
- A recent systematic review and meta-analysis reveal that corticosteroid injection was no better than placebo for short-term treatment of plantar fasciitis.[2]

[1]Rasenberg N et al: Efficacy of foot orthoses for the treatment of plantar heel pain: a systemic review and meta-analysis, *Br J Sports Med* 52(16):1040-1046, 2018.

[2]Whittaker GA et al: Corticosteroid injection for plantar heel pain: a systematic review and meta-analysis, *BMC Musculoskelet Disord* 20(1):378, 2019.

PREVENTION

- Avoid sitting for prolonged periods of time without stretching.
- Avoid wearing unsupportive shoe gear.
- Avoid abrupt change and intensity in physical activity.
- Perform stretches before any exercises or strenuous activity.
- Seek early medical attention with onset of heel pain.

RELATED CONTENT

Plantar Fasciitis (Patient Information)

AUTHORS: **Michael Kutschke, MD,** and **Brad Blankenhorn, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Pleural effusion is the pathologic accumulation of fluid in the pleural space, with a wide range of etiologies.

SYNONYMS

Hydrothorax
Hemothorax
Chylothorax
Empyema

ICD-10CM CODES

J90	Pleural effusion
J91.8	Pleural effusion in other conditions classified elsewhere

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Subjective symptoms include dyspnea, cough, fatigue, fever, chest pain. Box 1 summarizes signs and symptoms of pleural effusion
- Physical examination findings include dullness to percussion, decreased tactile fremitus, and decreased breath sounds
- Bedside transthoracic ultrasound can be helpful to identify characteristics of pleural effusion, including:
  1. Size, location, and laterality
  2. Presence of loculations, pleural adhesions, or implants
  3. Safe site for thoracentesis
  4. Underlying lung parenchymal pathology (e.g., pulmonary edema, consolidation, pneumothorax)

ETIOLOGY

Caused by a number of factors, including increased capillary permeability, increased vascular hydrostatic pressure, decreased vascular oncotic pressure, inflammation of the pleurae, traumatic/iatrogenic causes, and/or obstruction of normal pleural fluid efflux. Box 2 summarizes causes of pleural effusion.

BOX 1 Signs and Symptoms of Effusion

Dyspnea
Cough (dry, nonproductive)
Chest pain (pleuritic or nonpleuritic)
Chest wall discomfort
Decreased breath sounds
Dullness to percussion
Egophony, tactile fremitus
Pleural friction rub
Disease-specific signs and symptoms may include:
Orthopnea
Paroxysmal nocturnal dyspnea
Fever
Night sweats

From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Transudate (pleural to serum LDH ratio <0.6 or total protein ratio <0.5)

- Congestive heart failure
- Cirrhosis (hepatic hydrothorax)
- Chronic renal insufficiency
- Hypoalbuminemia

BOX 2 Causes of Pleural Effusions

Transudates
Atelectasis (early)
Congestive heart failure
Cirrhosis
Glomerulonephritis
Hypoalbuminemia
Myxedema
Nephrotic syndrome
Peritoneal dialysis
Pulmonary embolism
Superior vena cava syndrome

Exudates
Infectious
Bacterial infection
Bronchiectasis
Fungal infection
Lung abscess
Parasitic infection
Traumatic hemothorax
Tuberculosis
Viral illness

Malignancies
Lymphoma
Mesothelioma
Primary lung cancer
Pulmonary metastasis

Connective Tissue Disease
Rheumatoid arthritis
Systemic lupus erythematosus

Abdominal/Gastrointestinal
Esophageal rupture
Pancreatic disorders
Subphrenic abscess

Other
Atelectasis (chronic)
Chylothorax
Drug reactions (amiodarone)
Postpartum state
Pulmonary infarction or embolism
Uremia

From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

- Constrictive pericarditis
- Superior vena cava obstruction
- Urinothorax

Exudate (defined as pleural to serum LDH ratio ≥0.6 or total protein ratio ≥0.5)

- Malignancy (secondary to metastatic cancer or primary; e.g., mesothelioma)
- Infection
  1. Uncomplicated parapneumonic effusion (pH >7.2)
  2. Complicated parapneumonic effusion (pH ≤7.2)
  3. Tuberculous effusion
  4. Viral pleurisy
- Pulmonary embolism
- Hemothorax
- Chylothorax
- Esophageal perforation
- Pleuropancreatic fistula
- Connective tissue disease

WORKUP

The Light criteria for classification of pleural effusions is summarized in Box 3. Fig. 1 illustrates a diagnostic algorithm for pleural effusions. Fig. E2 illustrates an approach to malignant pleural effusions.

LABORATORY TESTS

See Table 1.

IMAGING STUDIES

Chest radiography (Fig. 3)**:** Blunting of the costophrenic angle, ipsilateral atelectasis, contralateral shift of the mediastinum with large effusions, elevated hemidiaphragm with subpulmonic effusions, "spine sign" on lateral chest x-ray, may be free-flowing or fixed on lateral decubitus film depending on etiology.

Ultrasonography (Fig. E4): Can demonstrate size/location of effusion relative to chest wall, lung, and diaphragm. Can be used to assess for loculations, septations/adhesions, and parietal/visceral pleural implants.

Computed tomography (Fig. E5): Useful to identify loculated effusions and to assess underlying lung parenchyma to aid in establishing a diagnosis. In empyema, can demonstrate heterogeneity and gas bubbles.

TREATMENT

- Table 2 summarizes treatment options for pleural effusions.

BOX 3 Light Criteria for Classification of Pleural Effusions

In 1972, Light et al developed the currently accepted benchmark for classifying pleural fluid, as follows:
Pleural fluid protein to serum protein ratio >0.5:1
Pleural fluid lactate dehydrogenase (LDH) to serum LDH ratio >0.6:1
Pleural fluid LDH greater than two thirds the upper limit of normal for serum LDH (a cutoff value of 200 IU/L was used previously)
Pleural fluid is classified as an exudate if it meets any of the aforementioned criteria. Conversely, if all three characteristics are absent, the fluid is classified as a transudate. These researchers achieved a diagnostic sensitivity of 99% and a specificity of 98% for classification of an exudate.

From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

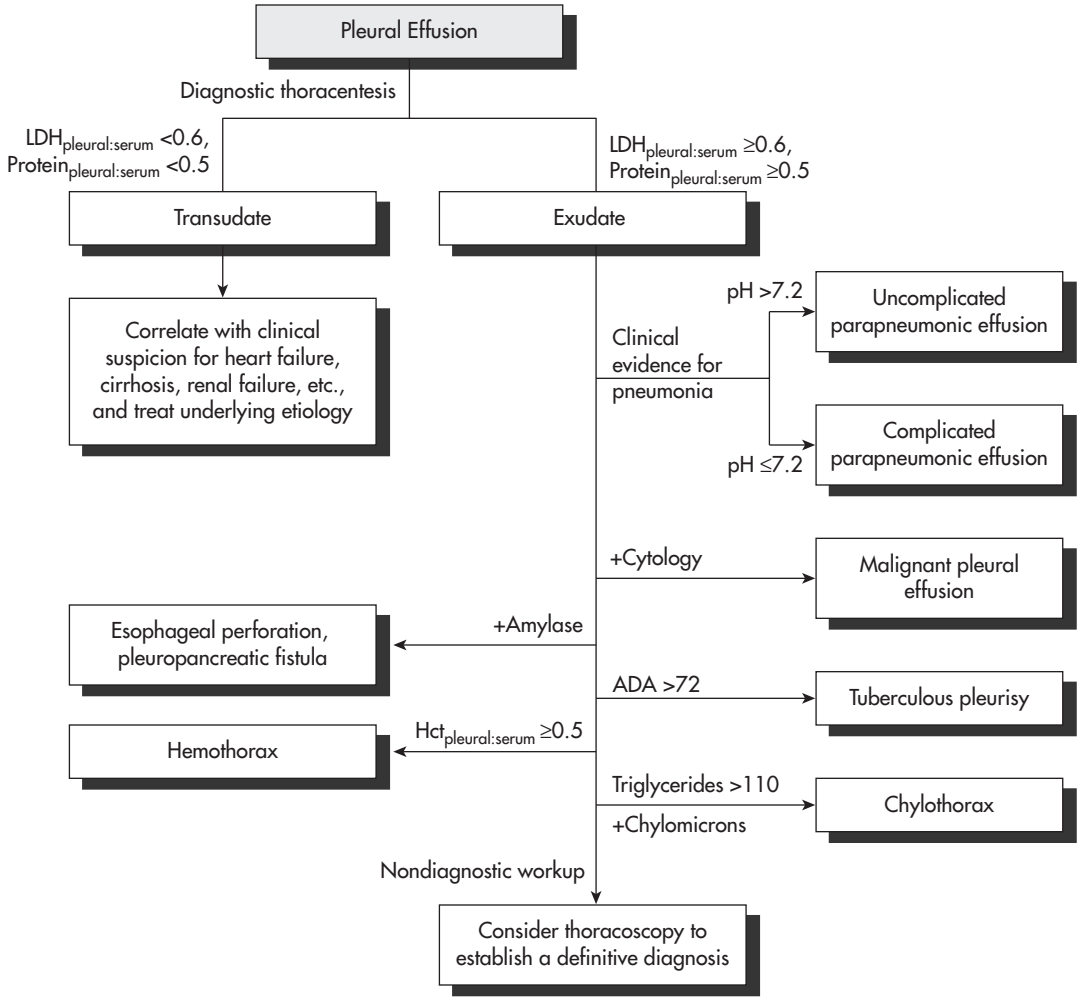

FIG. 1 Diagnostic algorithm. *ADA,* Adenosine deaminase; *Hct,* hematocrit; *LDH,* lactate dehydrogenase.

TABLE 1 Selected Laboratory Tests Used to Diagnose Pleural Effusion

Test	Diagnostic Utility	Comments
Adenosine deaminase (ADA)	>40 IU/L suggestive of tuberculous pleurisy	Values >72 IU/L highly specific for tuberculosis, with improved yield with pleural biopsy and PCR
Albumin	Pleural: serum albumin ratio <0.83 more consistent with transudate	Can be used to corroborate mixed findings from LDH and protein ratios
Amylase	Esophageal perforation, pancreatitis	
Cell count	**Lymphocyte** predominance suggestive of tuberculosis, lymphoma, other pleural malignancy, pulmonary embolism **Neutrophil** predominant effusions seen with bacterial infection, occasionally with malignancy (20%)	Helpful in distinguishing causes of exudative effusions
Chylomicrons	Positive finding adds to specificity of triglycerides for establishing chylothorax	Consider thoracic duct defect (due to malignancy, trauma or iatrogenic)
Creatinine	Pleural:serum creatinine >1 suggests urinothorax	
Culture	Positive findings used to narrow therapy	Should be sent from every suspected parapneumonic effusion to guide antimicrobial selection
Cytology	Sensitivity for malignancy of ~65%	Modest increment in diagnostic yield with up to three serial samples
Glucose	<60 mg/dl suggests complicated parapneumonic effusion, malignancy, tuberculous pleurisy or rheumatoid effusion	
Hematocrit	Pleural fluid hematocrit >50% peripheral blood hematocrit consistent with hemothorax	Pleural fluid with relatively low hematocrit can appear bloody on gross exam, does not necessarily represent hemothorax
Lactate dehydrogenase (LDH)	Pleural to serum LDH ratio >0.6 or pleural LDH >2/3 the upper limit of normal serum LDH suggests exudate	
NT-proBNP	>1500 pg/ml suggests heart failure even if effusion meets criteria for exudate	Chronic pleural effusions related to heart failure in patients on diuretic therapy may appear exudative
pH	≤7.2 with clinical suspicion highly suggestive of complicated parapneumonic effusion	Can also have low pH with malignant pleural effusions and esophageal perforation
Triglycerides	Triglycerides >110mg/dl seen with chylothorax	Absent triglycerides w/high suspicion for chylothorax can be confirmed with pleural chylomicrons

NT-proBNP, N-terminal pro b-type natriuretic peptide; *PCR,* polymerase chain reaction.

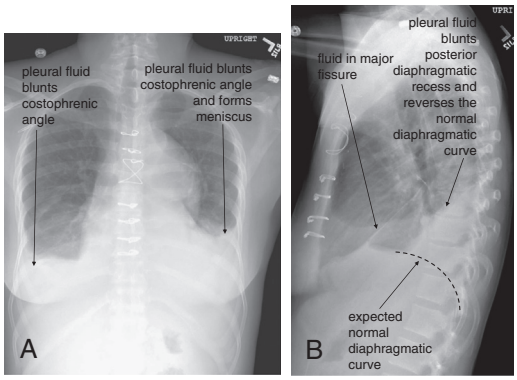

FIG. 3 Pleural effusions. A, Posterior-anterior upright view in which a pleural effusion is most evident on this patient's left side. Both costophrenic angles are blunted. The pleural effusion forms a meniscus against the left lateral chest wall. **B,** Lateral upright view shows two meniscus densities, suggesting bilateral pleural effusions. The posterior diaphragmatic recess is filled with pleural fluid, which forms a meniscus with the posterior chest wall. (From Broder JS: *Diagnostic imaging for the emergency physician*, Philadelphia, 2011, Saunders.)

TABLE 2 Treatment Options for Pleural Effusion

Thoracentesis	Site selection should be guided by ultrasonography whenever possible; evacuation of pleural fluid can be limited when the lung cannot fully re-expand, including central airway obstruction, chronic atelectasis, and the presence of extensive pleural adhesions; aspiration in these circumstances can lead to pneumothorax ex vacuo
Tube thoracostomy	Consider when ongoing drainage will be needed, especially for empyema or hemothorax
Indwelling tunneled pleural catheter	A cuffed pleural drainage catheter tunneled through subcutaneous tissue, drained regularly on an outpatient basis, most commonly used to manage malignant pleural effusions
Pleurodesis	Instillation of a chemical irritant under direct thoracoscopic visualization (e.g., talc poudrage) or via tube thoracostomy to adhere the visceral and parietal pleurae
Pharmacotherapy	Based on underlying etiology (e.g., diuretics, antimicrobials, chemotherapy)

- Fig. E6 describes a treatment approach to malignant pleural effusions.

REFERRAL

Negative diagnostic workup after initial pleural fluid sampling should be followed by referral to a pulmonologist for further evaluation (including consideration for thoracoscopy for pleural biopsy).

PEARLS & CONSIDERATIONS

- One-time drainage of pleural effusions alone is seldom a definitive therapy. Early identification of the underlying etiology of new effusions should be pursued.
- Managing patients with malignant pleural effusion can be challenging. A recent trial showed that, among patients with malignant pleural effusion, outpatient administration of talc via an indwelling tunneled pleural catheter resulted in a higher rate of pleurodesis than placement of a tunneled catheter alone.[1]
- In patients with malignant pleural effusion near the end of life, simple thoracentesis, repeated as needed, is a reasonable strategy.

[1]Bhatnagar R et al: Outpatient talc administration by indwelling pleural catheter for malignant effusion, *NEJM* 378:1313–1322, 2018.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Empyema (Related Key Topic)
Heart Failure (Related Key Topic)
Lung Neoplasms, Primary (Related Key Topic)

AUTHOR: **Vivek Murthy, MD**

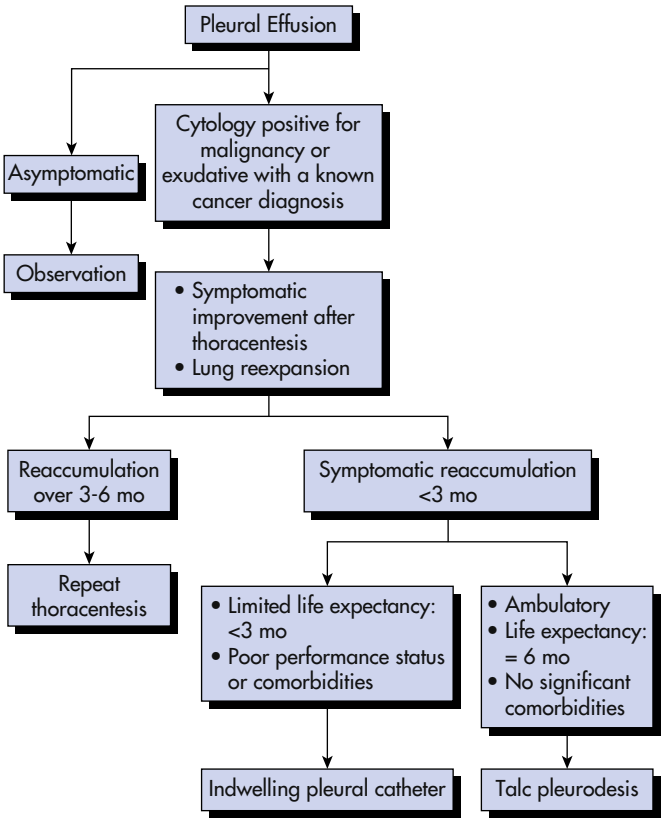

FIG. E2 Evaluation of suspected malignant pleural effusion. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

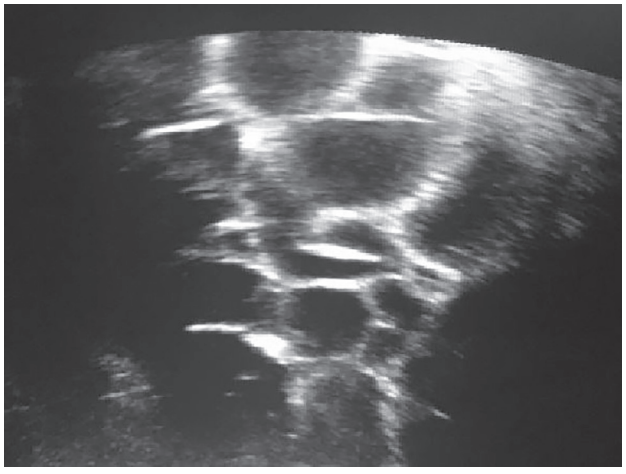

FIG. E4 Ultrasound examination of a multiloculated pleural effusion. Pleural fluid with a pH of less than 7.20 in such patients with multiple loculations should be treated with early chest tube drainage. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

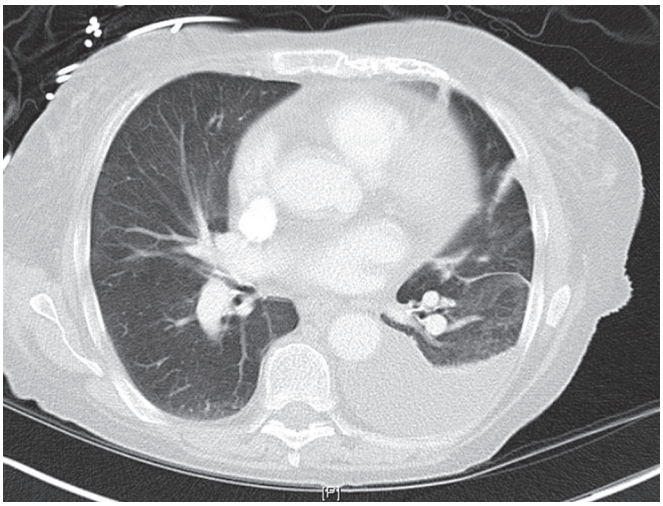

FIG. E5 Chest computed tomography scan showing a left pleural effusion. With the patient supine, the fluid lies posteriorly against the chest wall in the dependent portion of the left hemithorax. (From Weinberger SE*: Principles of pulmonary medicine*, ed 7, Philadelphia, 2019, Elsevier.)

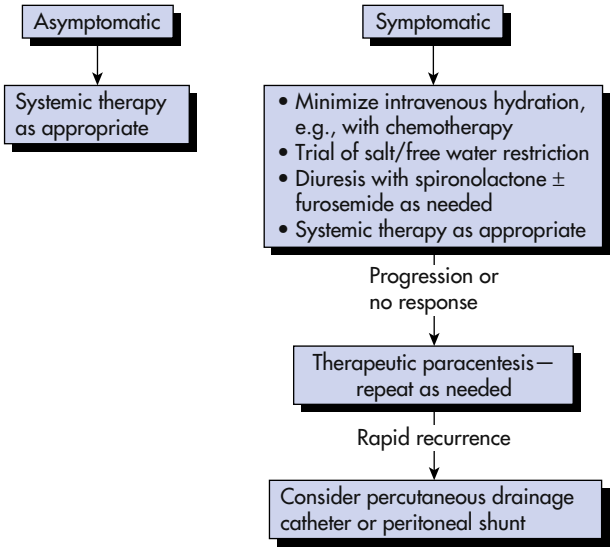

FIG. E6 Treatment approach algorithm to malignant pleural effusions. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

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Wahla AS: Managing malignant pleural effusion, *Cleve Clin J Med* 86:95-99, 2019.

BASIC INFORMATION

DEFINITION

Pleurisy refers to the inflammation of the parietal pleura. This inflammation results in pleuritic chest pain that is characteristically worsened with respiration or movement.

SYNONYM

Pleuritis

ICD-10CM CODE
R09.1 Pleurisy

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: One of the most common causes of pleuritic chest pain is viral pleurisy. However, there are a variety of disorders that may result in pleurisy. Infectious diseases, rheumatologic disorders, thromboembolic events, and trauma may all lead to pleural inflammation. Therefore, the incidence of pleurisy varies in accordance with the underlying etiology.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The defining characteristic of pleurisy is chest pain that worsens with respiration, coughing, or sneezing.
- Pleuritic chest pain is typically described as sharp or stabbing. However, pleuritic chest pain may also be described as dull pain, burning pain, or a "catch" while breathing.
- Movements of the trunk or chest wall may exacerbate pain. Patients with pleurisy may locate the position of minimal discomfort and remain still in that position.
- Dyspnea may be associated with pleurisy.
- Physical exam may be remarkable for a pleural friction rub.
- Decreased breath sounds, rales, or egophony may be appreciated if pneumonia is the underlying etiology of the patient's pleurisy.

ETIOLOGY

- Pleurisy is caused by inflammation of the parietal pleura. The visceral pleura is not innervated by nociceptors. However, injury or inflammation at the periphery of the lung parenchyma often results in inflammation of the overlying parietal pleura. The parietal pleura, which lines the rib cage and the lateral portion of each hemidiaphragm, is innervated by intercostal nerves; therefore pain is localized to the cutaneous distribution of those nerves (over the chest wall). The parietal pleura of the central diaphragm is innervated by fibers that travel with the phrenic nerve; therefore pain associated with inflammation in this area is referred to the ipsilateral shoulder or neck.
- Various underlying etiologies may result in pleurisy, including the following:
  1. Thromboembolism (pulmonary embolism)
  2. Viral infection (coxsackieviruses, respiratory syncytial virus [RSV], cytomegalovirus [CMV], adenovirus, Epstein-Barr virus [EBV], parainfluenza, influenza)
  3. Bacterial infection (pneumonia or tuberculous pleuritis)
  4. Fungal infection (coccidioidomycosis, histoplasmosis)
  5. Rheumatologic disease (rheumatoid arthritis, systemic lupus erythematosus [SLE])
  6. Medications
  7. Malignancy of the lung or pleura
  8. Trauma (rib fracture)
  9. Hereditary (familial Mediterranean fever, sickle cell disease)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cardiac: Myocardial infarction, ischemia, pericarditis
- Intraabdominal process: Pancreatitis, cholecystitis
- Thromboembolic: Pulmonary embolism, infarction of lung parenchyma
- Traumatic/mechanical: Rib fracture or pneumothorax
- Viral infection: Viral infections may lead to epidemic pleurodynia (also known as Bornholm disease). Implicated viruses include coxsackieviruses, RSV, CMV, adenovirus, EBV, parainfluenza, influenza. Of note, viral pleurisy is a diagnosis of exclusion
- Bacterial infection: Pneumonia or tuberculous pleurisy
- Fungal infection: Coccidioidomycosis, histoplasmosis
- Rheumatologic disease: Rheumatoid arthritis, SLE
- Medications: Drug-induced lupus
- Hereditary causes: Familial Mediterranean fever, sickle cell disease
- Malignancy: Malignancy affecting the lung or pleura
- Uremia

WORKUP

- A thorough history and physical exam of all patients presenting with pleuritic chest pain should be taken. The time course of the patient's symptoms can provide valuable diagnostic clues. Acute onset of symptoms is suggestive of traumatic injuries, spontaneous pneumothorax, pulmonary embolism, or myocardial infarction. Subacute onset of symptoms suggests a potential infectious, rheumatologic, or medication-induced cause. Viral pleurisy is often associated with prodromal symptoms of upper respiratory infection. Chronic or recurrent symptoms suggest a potential malignant, tuberculous, or hereditary cause.
- Chest x-ray to evaluate for pneumonia, pneumothorax, or pleural effusion.
- ECG to evaluate for infarction, ischemia, or pericarditis.
- Evaluation for pulmonary embolism should be undertaken if clinical suspicion exists.

LABORATORY TESTS

- Laboratory testing varies based on suspected underlying etiology. Consider CBC, Chem 7, and D-Dimer testing depending on clinical presentation.
- If a pleural effusion is present, diagnostic thoracentesis may provide valuable diagnostic clues to the underlying etiology.

IMAGING STUDIES

- Chest x-ray
- ECG
- CT chest in selected patients

TREATMENT

- Treatment of pleurisy consists of pain control as well as treating the underlying condition.
- NSAIDs are the preferred first-line agent to control pain associated with pleurisy. Human studies have been limited to trials using indomethacin for pain control, although an NSAID class effect is presumed.
- Indomethacin 50 mg orally up to three times a day has been found to be effective in relieving pain and is associated with an improvement in mechanical lung function.

AUTHOR: **Chakravarthy Reddy, MD**

BASIC INFORMATION

DEFINITION

Pneumonia is defined as inflammation of the pulmonary parenchyma caused by an infectious agent (in this case, bacteria). It can be further categorized as community-acquired or health care-associated. The definition of community-acquired pneumonia (CAP), traditionally referred to alveolar infection that develops in the outpatient setting or within 48 hours of admission, now includes patients previously categorized as having health care-associated pneumonia (HCAP) since the microbiology and treatment is similar. Hospital-acquired pneumonia (HAP) is pneumonia occurring ≥48 hours after hospital admission and not incubating at the time of admission.

SYNONYMS

Community-acquired pneumonia
CAP

ICD-10CM CODES

J15.9	Unspecified bacterial pneumonia
J13	Pneumonia due to *Streptococcus pneumoniae*
J15.1	Pneumonia due to *Pseudomonas*
J15.20	Pneumonia due to staphylococcus, unspecified
J15.0	Pneumonia due to *Klebsiella pneumoniae*
J14	Pneumonia due to *Haemophilus influenzae*
J15.211	Pneumonia due to methicillin-susceptible *Staphylococcus aureus*
J15.212	Pneumonia due to methicillin-resistant *Staphylococcus aureus*
J15.6	Pneumonia due to other aerobic gram-negative bacteria
J15.7	Pneumonia due to *Mycoplasma pneumoniae*

EPIDEMIOLOGY & DEMOGRAPHICS

- The annual incidence of pneumonia in the U.S. is 24.8 cases per 10,000 adults, with the highest rates among adults between 65 and 79 yr of age (63 cases per 10,000 adults) and those 80 yr or older (164.3 cases per 10,000 adults). Health care expenditures for CAP exceed $10 billion annually.
- Hospitalization rate for pneumonia is 15% to 20%. Incidence is highest among the oldest adults.
- In 2014, the eighth leading cause of mortality in the U.S. reported by the National Center for Health Statistics was influenza and pneumonia together.
- Globally, *Streptococcus pneumoniae* (pneumococcus) is the most common pathogen causing community-acquired pneumonia.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever, tachypnea, chills, tachycardia, cough; pleurisy in the case of pleural effusion.
- Presentation varies with the cause of pneumonia, the patient's age, and the clinical situation:
  1. Patients with streptococcal pneumonia usually present with high fever, chills, atypical chest pain, cough, and copious production of rusty-appearing purulent sputum. Pleurisy in the setting of parapneumonic effusions can also occur. Potential complications include bacteremia, empyema, and distant infections (e.g., meningitis).
  2. *Mycoplasma pneumoniae:* Insidious onset; headache; dry, paroxysmal cough that is worse at night; myalgias; malaise; sore throat; extrapulmonary manifestations (e.g., erythema multiforme, aseptic meningitis, urticaria, erythema nodosum) may be present.
  3. *Chlamydia pneumoniae:* Persistent, nonproductive cough, low-grade fever, headache, sore throat.
  4. *Legionella pneumophila:* High fever, mild cough, mental status change, myalgias, diarrhea, respiratory failure.
  5. MRSA pneumonia: Often preceded by influenza, may present with shock and respiratory failure.
  6. Elderly or immunocompromised hosts with pneumonia may initially present with only minimal symptoms (e.g., low-grade fever, confusion); respiratory and nonrespiratory symptoms are less commonly reported by older patients with pneumonia.
  7. In general, auscultation of patients with pneumonia reveals crackles and diminished breath sounds.
  8. Dullness on percussion may be an indication that pleural effusion is present.
  9. The clinical impression of pneumonia has an overall sensitivity of 70% to 90%; specificity ranges from 40% to 70%.

ETIOLOGY

- Table 1 summarizes common pathogens causing CAP
- *Streptococcus pneumoniae* (5% to 15% of hospitalized CAP cases): Incidence has been declining due to widespread use of pneumococcal vaccination and reduced rate of cigarette smoking
- *Haemophilus influenzae* (3% to 10% of CAP cases)
- *L. pneumophila* (1% to 5% of adult pneumonias) (2% to 8% of CAP cases)
- *Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli*
- *Staphylococcus aureus* (3% to 5% of CAP cases)
- Atypical organisms such as *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Legionella pneumophila* implicated in up to 40% of cases of CAP
- Influenza infection is one of the important predisposing factors to *S. pneumoniae* and *S. aureus* pneumonia; gram-negative organisms cause >80% of nosocomial pneumonias
- Predisposing factors (Table 2 and Table 3):
  1. Chronic obstructive pulmonary disease: *H. influenzae, S. pneumoniae, Legionella, Moraxella catarrhalis*
  2. Seizures: Aspiration pneumonia
  3. Compromised hosts: *Legionella*, gram-negative organisms
  4. Alcoholism: *K. pneumoniae, S. pneumoniae, H. influenzae*
  5. HIV: *S. pneumoniae*
  6. IV drug addicts with right-sided bacterial endocarditis: *S. aureus*
  7. Older patient with comorbid diseases: *C. pneumoniae*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Viral pneumonias: Viral pneumonias/pneumonitis are on the rise. Several viruses alone or in combination can cause pneumonias in adults. Influenza is the predominant virus, but respiratory syncytial virus (RSV), parainfluenza viruses, adenoviruses, rhinoviruses, coronaviruses, and human metapneumovirus are all possible etiologies. The diagnosis is based on clinical suspicion, negative bacterial workup, and/or respiratory cultures, serologies, or rapid PCR testing
- Exacerbation of chronic bronchitis
- Pulmonary embolism or infarction
- Lung neoplasm
- Bronchiolitis
- Sarcoidosis
- Hypersensitivity pneumonitis
- Pulmonary edema
- Drug-induced lung injury
- Fungal pneumonias
- Parasitic pneumonias
- Atypical pneumonia
- Tuberculosis

WORKUP

Diagnostic testing for CAP is summarized in Table 4. Useful tools for assessing severity of illness are the *CURB-65* (see "Disposition") and *Pneumonia Severity Index* (Fig. 1 and Box 1). Poor prognostic indicators are hypotension (SBP <90 or DBP <60), respiratory rate >30/min, fever (>40° C; 104° F), or hypothermia (<35° C; 95° F). None of these indices is as valuable as clinical judgment.

LABORATORY TESTS

- Complete blood count with differential; white blood cell count is elevated, usually with left shift or the presence of bandemia
- Blood cultures (hospitalized patients only): Positive in approximately 20% of cases of pneumococcal pneumonia
- Pneumococcal urinary antigen test can be used to detect the C-polysaccharide antigen of *S. pneumoniae* (70% sensitivity). It is a useful tool in the treatment of hospitalized adult patients with CAP
- When suspecting *Legionella,* a respiratory specimen culture on special media and/or a urinary antigen should be requested

TABLE 1 Common Pathogens Causing Community-Acquired Pneumonia

Inpatient, with No Cardiopulmonary Disease or Modifying Factors

Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydophila pneumoniae, mixed infection (bacteria plus atypical pathogen), viruses (including influenza), *Legionella* spp., and others (*Mycobacterium tuberculosis*, endemic fungi, *Pneumocystis jirovecii*)

Inpatient, with Cardiopulmonary Disease and/or Modifying Factors

All of the above, but drug-resistant *S. pneumoniae* (DRSP) and enteric gram-negative organisms are more of a concern

Severe Community-Acquired Pneumonia, with No Risks for *Pseudomonas Aeruginosa*

S. pneumoniae (including DRSP), *Legionella* spp., *H. influenzae*, enteric gram-negative bacilli, *Staphylococcus aureus* (including methicillin-resistant *S. aureus*), *M. pneumoniae*, respiratory viruses (including influenza), others (*C. pneumoniae, M. tuberculosis*, endemic fungi)

Severe CAP, with Risks for *P. Aeruginosa*

All of the pathogens above plus *P. aeruginosa*

From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

TABLE 2 Risk Factors for Developing Severe Community-Acquired Pneumonia

Advanced age
Comorbid illness (e.g., chronic respiratory illness, cardiovascular disease, diabetes mellitus, neurologic illness, renal insufficiency, malignancy)
Cigarette smoking
Alcohol abuse
Absence of antibiotic therapy before hospitalization
Failure to contain infection to its initial site of entry
Immune suppression
Genetic polymorphisms in the immune response

From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

TABLE 3 Clinical Associations with Specific Pathogens

Condition	Commonly Encountered Pathogens
Alcoholism	*Streptococcus pneumoniae* (including penicillin-resistant), anaerobes, gram-negative bacilli (possibly *Klebsiella pneumoniae)*, tuberculosis
Chronic obstructive pulmonary disease/current or former smoker	*S. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*
Residence in nursing home	*S. pneumoniae*, gram-negative bacilli, *H. influenzae, Staphylococcus aureus, Chlamydophila pneumoniae;* consider *M. tuberculosis.* Consider anaerobes, but these are less common
Poor dental hygiene	Anaerobes
Bat exposure	*Histoplasma capsulatum*
Bird exposure	*Chlamydophila psittaci, Cryptococcus neoformans, H. capsulatum*
Rabbit exposure	*Francisella tularensis*
Travel to southwestern United States	*Coccidioidomycosis;* hantavirus in selected areas
Exposure to farm animals or parturient cats	*Coxiella burnetii* (Q fever)
Postinfluenza pneumonia	*S. pneumoniae, S. aureus* (including the community-acquired strain of methicillin-resistant *S. aureus*), *H. influenzae*
Structural disease of the lung (e.g., bronchiectasis, cystic fibrosis)	*Pseudomonas aeruginosa, Pseudomonas cepacia,* or *S. aureus*
Sickle cell disease, asplenia	Pneumococcus, *H. influenzae*
Suspected bioterrorism	Anthrax, tularemia, plague
Travel to Asia	Severe acute respiratory syndrome, tuberculosis, melioidosis

From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

- Serologic testing for HIV in selected patients
- Serum electrolytes (hyponatremia in suspected *Legionella* pneumonia), BUN, creatinine
- Test for and treat influenza during flu season[1]

[3]Metlay JP et al: Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America, *Am J Respir Crit Care Med* 200:e45–e67, 2019 .

- Serum procalcitonin level: Often used to distinguish pneumonia from heart failure in patients presenting to the emergency department with acute dyspnea. The procalcitonin level is significantly higher in patients with pneumonia than in those without.[1] However, serum procalcitonin should not be used to determine initiation or duration of antibiotic therapy in patients with radiographically confirmed CAP unless antibiotic therapy is being extended beyond 5 to 7 days. Recent trials regarding procalcitonin-guided use of antibiotics for lower respiratory tract infections did not result in less use of antibiotics than did usual care among patients with suspected lower respiratory tract infection[2]
- Pulse oximetry or arterial blood gases: Hypoxemia with partial pressure of oxygen <60 mm Hg while the patient is breathing room air, a standard criterion for hospital admission
- Fig. 2 illustrates an algorithm for the diagnosis and treatment of nosocomial pneumonia

IMAGING STUDIES

Chest x-ray (PA and lateral) (Fig. 3): Findings vary with the stage and type of pneumonia and the hydration of the patient:

- Classically, pneumococcal pneumonia presents with a segmental lobe infiltrate.
- Diffuse infiltrates on chest x-ray can be seen with *L. pneumophila* (Fig. 4), *M. pneumoniae,* viral pneumonias, *P. jirovecii (carinii),* miliary tuberculosis, aspiration, aspergillosis.
- An initial chest x-ray is also useful to rule out the presence of any complications (pneumothorax, empyema, abscesses).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of tobacco use
- Oxygen to maintain partial oxygen pressure in arterial blood >60 mm Hg or oxygen saturation >88% in COPD patients and >92% in non-COPD patients
- IV hydration, correction of dehydration
- Assisted ventilation in patients with significant respiratory failure

ACUTE GENERAL Rx

- Antibiotic therapy should be based on clinical, radiographic, and laboratory evaluation. Empiric therapy regimens for severe community-acquired pneumonia are summarized in Table 5.
- Macrolides (azithromycin or clarithromycin) or doxycycline can be used for empiric outpatient treatment of CAP as long as the patient has not received antibiotics within the past 3 mo and does not reside in a community in which the prevalence of macrolide resistance is high. Updated guidelines from the American Thoracic Society and Infectious Diseases Society of America[3] have added amoxicillin as a first-line agent for heart adult outpatients

[1]Alba GA et al: Diagnostic and prognostic utility of procalcitonin in patients presenting to the emergency department with dyspnea, *Am J Med* 129:96, 2016.
[2]Huang DT et al: Procalcitonin-guided use of antibiotics for lower respiratory tract infection, *N Engl J Med* 379:236-49, 2018.

TABLE 4 Diagnostic Testing for Community-Acquired Pneumonia

Test	Sensitivity	Specificity	Comment
Chest radiograph	65%-85%	85%-95%	Computed tomography is more sensitive to infiltrates. Recommended for all patients.
Computed tomography	Gold standard	Not infection specific	Should not be performed routinely but helpful to identify cavitation and loculated pleural fluid. Recommended in the evaluation of nonresponding patients.
Blood cultures	10%-20%	High when positive	Usually shows pneumococcus (in 50%-80% of positive samples) and defines antibiotic susceptibility. Recommended in patients with severe CAP, particularly if not on antibiotic therapy at the time of testing.
Sputum Gram stain	40%-100% depending on criteria	0%-100% depending on criteria	Can correlate with sputum culture to define predominant organism and can be used to identify unsuspected pathogens. Recommended if sputum culture is obtained. May not be able to narrow empiric therapy choices.
Sputum culture			Use if suspect drug-resistant or unusual pathogen, but a positive result cannot differentiate colonization from infection. Obtain via tracheal aspirate in all intubated patients.
Oximetry or arterial blood gas			Define both severity of infection and need for oxygen; if hypercarbia is suspected, a blood gas sample is needed. Recommended in severe community-acquired pneumonia.
Serologic testing for *Legionella, Chlamydophila pneumoniae, Mycobacterium pneumoniae*, viruses			Accurate, but usually requires acute and convalescent titers collected 4 to 6 wk apart. Not routinely recommended.
Legionella urinary antigen	50%-80%		Specific to serogroup 1, but the best acute diagnostic test for *Legionella.*
Pneumococcal urinary antigen	70%-100%	80%	False positives if recent pneumococcal infection. Can increase sensitivity with concentrated urine.
Serum procalcitonin			Not a routine test, but if performed, should be measured with the highly sensitive Kryptor assay. May help guide duration of therapy and need for ICU admission.

From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

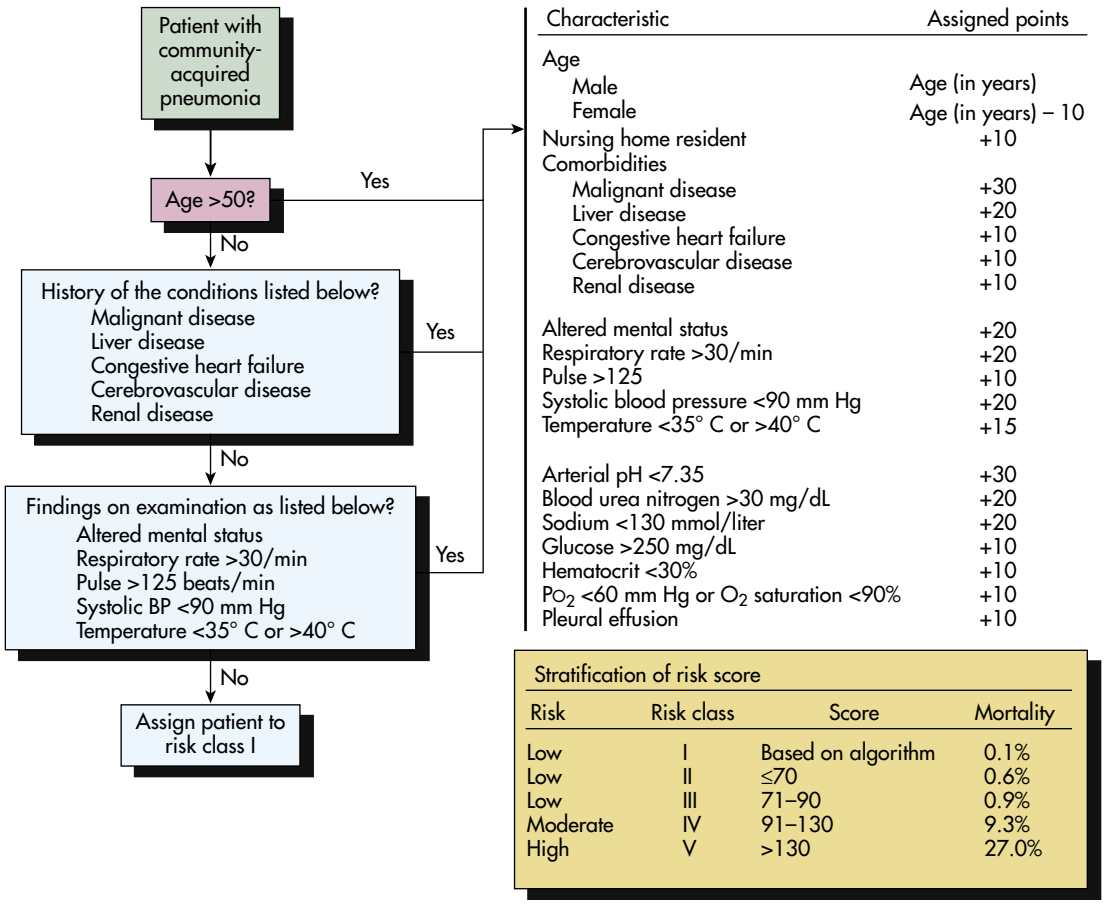

FIG. 1 The pneumonia severity index. *BP,* Blood pressure; *O_2,* oxygen; *P_{O_2},* partial pressure of oxygen. (From Sellke FW et al: *Sabiston & Spencer surgery of the chest,* ed 9, 2016, Elsevier.)

BOX 1 Severe Pneumonia: Diagnostic Criteria[1]

Major Criteria
Invasive mechanical ventilation
Use of vasopressors to maintain blood pressure

Minor Criteria
Respiratory rate ≥30 breaths/min
Multilobar infiltrates
New-onset confusion/disorientation
Uremia (BUN >20 mg/dl)
Leukopenia (WBC count <4000 cells/μL)
Pao_2/Fio_2 ratio ≥250
Thrombocytopenia (platelet count <100,000 cells/μL)
Hypothermia (core temperature <36°C; 96.8º F)
Hypotension requiring aggressive fluid resuscitation

ATS/IDSA, American Thoracic Society/Infectious Diseases Society of America; *BUN,* blood urea nitrogen; *WBC,* white blood cell.
[1]According to ATS/IDSA 2007 guidelines.
From Parrillo JE, Dellinger RP: *Critical care medicine: principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Saunders.

with CAP. Fig. 5 summarizes empiric therapy for CAP. The treatment of choice in suspected *Legionella* pneumonia is either a quinolone (e.g., moxifloxacin) or a macrolide (e.g., azithromycin) antibiotic. A beta-lactam antibiotic is usually added to macrolides.

- In the hospital setting, patients admitted to the general ward can be treated empirically with a second- or third-generation cephalosporin (ceftriaxone, cefotaxime, or cefuroxime) plus a macrolide (azithromycin or clarithromycin) or doxycycline. An antipseudomonal quinolone (levofloxacin or moxifloxacin) can be substituted in place of the macrolide or doxycycline.
- Empiric therapy in ICU patients: IV beta-lactam (ceftriaxone, cefotaxime, ampicillin-sulbactam) plus an IV quinolone (levofloxacin, moxifloxacin) or IV azithromycin.
- In hospitalized patients at risk for *P. aeruginosa* infection, empiric treatment should consist of an antipseudomonal beta-lactam (meropenem, doripenem, imipenem, or piperacillin-tazobactam) with or without a second antipseudomonal agent such as an aminoglycoside or an antipseudomonal quinolone.
- In patients with suspected methicillin-resistant *S. aureus,* vancomycin or linezolid is effective.
- Corticosteroids: Corticosteroids (i.e., methylprednisolone 0.5 mg/kg IV q12h for 5 days) are often administered in hospitalized adult patients presenting with severe CAP.
- Adjunctive treatment with corticosteroids improves initial clinical response and reduces length of hospital stay but does not offset mortality or clinical failure and increases readmission rate in hospitalized patients with CAP. Recent guidelines[4] do not recommend routine treatment with corticosteroids in CAP except in patients with concurrent refractory septic shock.
- Duration of treatment ranges from 5 to 14 days. Trials have shown that in adults hospitalized with CAP, stopping antibiotic treatment after 5 days in clinically stable patients is reasonable and noninferior to usual care. Hematogenous *Staphylococcus* infection, abscesses, and cavitary lesions might require prolonged antibiotic therapy, sometimes until radiological resolution is documented.

CHRONIC Rx

Parapneumonic effusion and empyema can be managed with chest tube placement for drainage. Instillation of fibrinolytic agents (streptokinase, urokinase, or, more commonly, tissue plasminogen activator [TP]) along with DNase (i.e., dornase alfa) twice a day via chest tube may facilitate the drainage of effusions not responding to chest tube drainage alone. A thoracoscopic debridement or a surgical decortication may be necessary in resistant cases.

DISPOSITION

Risk factors for a poor outcome from CAP are summarized in Table E6. Indications for hospital admission are:

- Hypoxemia (oxygen saturation <90% while patient is breathing room air)
- Hemodynamic instability
- Inability to tolerate medications
- Active coexisting condition requiring hospitalization. A criterion often used to determine hospital admission is known as the "CURB-65": **C**onfusion, B**U**N >19.6 mg/dl, **R**espiratory rate >30 breaths/min, systolic **B**P <90 mg Hg, and diastolic BP ≤60 mm Hg, age ≥**65.** Patients are generally admitted to the hospital if they fulfill 2 or more criteria and to the ICU if they have 3 or more criteria

PEARLS & CONSIDERATIONS

COMMENTS

- Use of gastric acid suppressive therapy (H_2 receptor antagonists, proton pump inhibitors [PPIs]) has been reported to increase the risk of CAP. It has been reported that PPI therapy started within the previous 30 days is associated with a risk for CAP, whereas longer-term current use is not. Recent studies have failed to confirm increased risk of CAP with PPI use and have shown that risk of CAP is higher during 30 days before PPI prescription than during the 30 days after PPI prescription.[4]
- Causes of slowly resolving or nonresolving pneumonia:
  1. Difficult to treat infections: Viral pneumonia, *Legionella,* pneumococci or staphylococci with impaired host response, tuberculosis, fungi
  2. Neoplasm: Lung, lymphoma, metastasis
  3. Congestive heart failure
  4. Pulmonary embolism
  5. Immunologic or idiopathic: Wegener granulomatosis, pulmonary eosinophilic syndromes, systemic lupus erythematosus
  6. Drug toxicity (e.g., amiodarone)
- If patients with pneumonia don't improve within a reasonable time frame, repeat films should be taken promptly. In those with complete clinical recovery, it is reasonable to wait 6 to 8 wk before repeating the imaging study to document clearing of the infiltrate. The benefit of routine radiography after pneumonia has been questioned due to the low 1-yr incidence of lung cancer. Opponents propose a selective approach limiting follow-up chest x-ray to middle-aged and older adults.
- Prevention: The 23-valent pneumococcal polysaccharides vaccine (PPSV23) and the pneumococcal conjugated vaccine (PCV13) are currently available for older adults. The ACIP recommends giving the PCV13 first to be followed after a yr by the PPSV23. This recommendation includes patients younger than 65 yr with some defined risk factors (end-stage renal disease, sickle cell disease, congenital or acquired asplenia, HIV infection, congenital or acquired immunodeficiency, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression, solid organ transplant, multiple myeloma, CSF leak, cochlear implant). The CDC no longer supports routine administration of PVC13 to older adults (≥65) and limits its administration to compromised older adults and those with cerebrospinal fluid leak or cochlear implants.
- Prevention: During the influenza season, patients should also receive influenza vaccination.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Bacterial Pneumonia (Patient Information)
Aspiration Pneumonia (Related Key Topic)
Pneumonia, Mycoplasma (Related Key Topic)

AUTHOR: **Jorge Mercado, MD**

[4]Othman F et al: Community acquired pneumonia incidence before and after proton pump inhibitor prescription, *BMJ* 355:i5813, 2016.

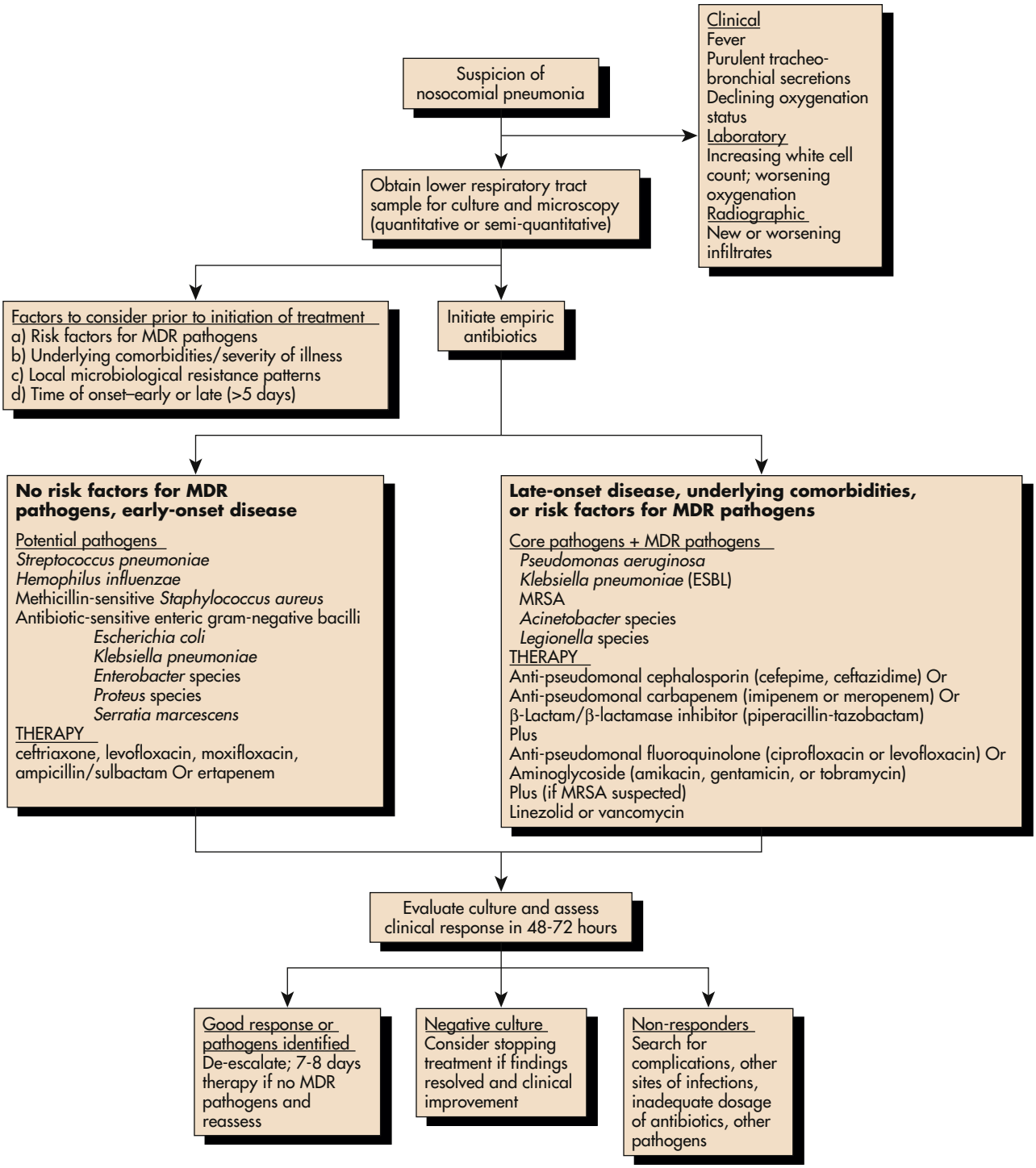

FIG. 2 A suggested algorithm for the diagnosis and treatment of nosocomial pneumonia. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Elsevier.)

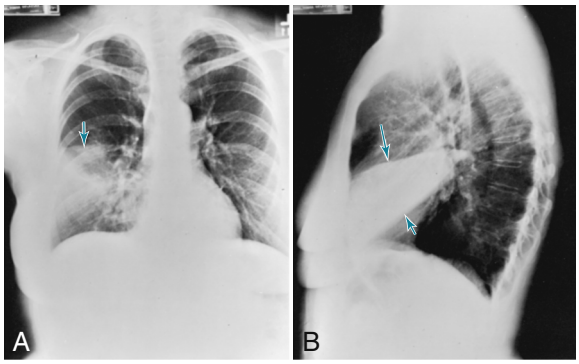

FIG. 3 Posteroanterior **(A)** and lateral **(B)** chest radiographs show lobar pneumonia (probably caused by *Streptococcus pneumoniae*) affecting the right middle lobe. In **A,** the arrow points to a minor fissure, which defines the upper border of the middle lobe. In **B,** the long arrow points to a minor fissure, and the short arrow points to a major fissure. (From Weinberger SE: *Principles of pulmonary medicine,* ed 7, Philadelphia, 2019, Elsevier.)

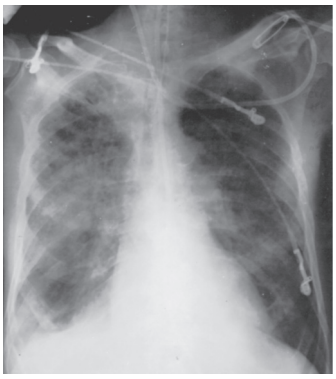

FIG. 4 Chest radiograph of a patient with extensive gram-negative pneumonia. Note the patchy infiltrates throughout both lungs, which are more prominent on the right. (From Weinberger SE: *Principles of pulmonary medicine,* ed 7, Philadelphia, 2019, Elsevier.)

TABLE 5 Empiric Therapy Regimens for Severe Community-Acquired Pneumonia

No Pseudomonal Risk Factors

Selected beta-lactam (cefotaxime, ceftriaxone)

plus

Intravenously administered macrolide *or* quinolone (moxifloxacin or levofloxacin*)

Pseudomonal Risk Factors Present

Selected antipseudomonal beta-lactam (cefepime, piperacillin/tazobactam, imipenem, meropenem)

plus

Ciprofloxacin

or

Selected antipseudomonal beta-lactam

plus

Aminoglycoside

plus

Intravenously administered macrolide or antipneumococcal quinolone (moxifloxacin or levofloxacin*)

NOTE: Although routine methicillin-resistant *Staphylococcus aureus* (MRSA) coverage is NOT recommended for all severe community-acquired pneumonia, consider community-acquired MRSA, especially after influenza and with bilateral necrotizing pneumonia, and if suspected, treat by adding either linezolid or the combination of vancomycin and clindamycin.

*For patients with normal renal function, the recommended dose of levofloxacin is 750 mg daily.

From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

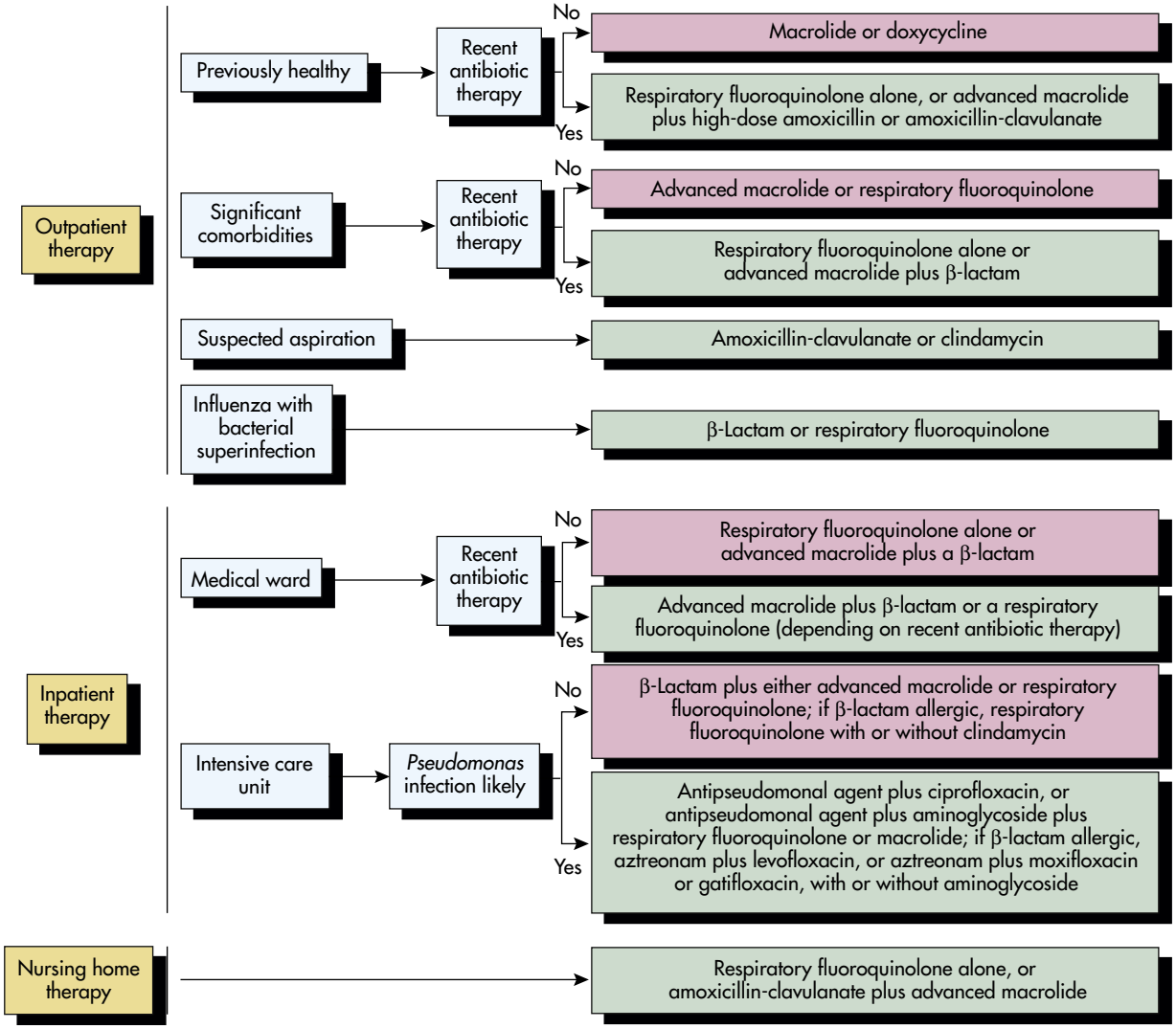

FIG. 5 Empiric therapy for community-acquired pneumonia. (From Sellke FW, del Nido PJ, Swanson SJ: *Sabiston & Spencer surgery of the chest,* ed 9, Philadelphia, 2016, Elsevier.)

TABLE E6 Risk Factors for a Poor Outcome from Community-Acquired Pneumonia

Patient-Related Factors

Male sex
Absence of pleuritic chest pain
Nonclassic clinical presentation
Neoplastic illness
Neurologic illness
Age >65 yr
Family history of severe pneumonia or death from sepsis

Abnormal Physical Findings

Respiratory rate >30 breaths/min on admission
Systolic (<90 mm Hg) or diastolic (<60 mm Hg) hypotension
Tachycardia (>125 beats/min)
High fever (>40° C; 104° F) or afebrile
Confusion

Laboratory Abnormalities

Blood urea nitrogen >19.6 mg/dl
Leukocytosis or leukopenia (<4000/mm^3)
Multilobar radiographic abnormalities
Rapidly progressive radiographic abnormalities during therapy
Bacteremia
Hyponatremia (<130 mmol/L)
Multiple organ failure
Respiratory failure
Hypoalbuminemia
Thrombocytopenia (<100,000/mm^3) or thrombocytosis (>400,000/mm^3)
Arterial pH <7.35
Pleural effusion

Pathogen-Related Factors

High-risk organisms
Type III pneumococcus, *Staphylococcus aureus*, gram-negative bacilli (including *Pseudomonas aeruginosa*), aspiration organisms, severe acute respiratory syndrome
Possibly high levels of penicillin resistance (minimal inhibitory concentration of at least 4 mg/L) in pneumococcus

Therapy-Related Factors

Delay in initial antibiotic therapy (more than 4 hours)
Initial therapy with inappropriate antibiotic therapy
Failure to have a clinical response to empiric therapy within 72 hours

From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Mycoplasma pneumonia is an infection of the lung parenchyma caused by a small rod-shaped bacterium, *Mycoplasma pneumoniae.*

SYNONYMS

Primary atypical pneumonia
Eaton pneumonia
Walking pneumonia

ICD-10CM CODE

J15.7 Pneumonia due to *Mycoplasma pneumoniae*

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- It is a frequent cause of community-acquired pneumonia (CAP), accounting for up to 37% of CAP in patients treated as outpatients and 10% of pneumonia in persons requiring hospitalization. The Centers for Disease Control (CDC) estimates 2 million cases a yr with 100,000 pneumonia-related hospitalizations.
- Many cases probably resolve without coming to medical attention.
- Incidence is estimated at one case per 1000 persons annually.
- Incidence is estimated to at least triple every (approximately) 5 yr during epidemics.

PREVALENCE (IN U.S.):

- Estimated to be present in one in every five patients hospitalized for pneumonia (generally a self-limited disease, so its true prevalence is unknown)
- Estimated to cause 7% of all cases of pneumonia and approximately half the cases in those aged 5 to 20 yr

PEAK INCIDENCE:

- Some increased incidence in fall to early winter
- Seems more prevalent in temperate climates

PREDOMINANT SEX: Equal distribution

PREDOMINANT AGE:

- Most commonly affected: School-age children and young adults (ages 5 to 20 yr)
- Occurs in older adults as well, especially with household exposure to a young child
- More severe infections in affected elderly patients

GENETICS: Familial disposition:

- None known
- May be more severe in patients with sickle cell anemia
- Neonatal infection: Severe respiratory distress, sometimes requiring intubation, attributed to this disease in infants

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Nonexudative pharyngitis (common)
- Headache, otalgia common
- Fever may be mild or not present
- Rhonchi or rales without evidence of consolidation (common) in lower lung zones
- Associated with bullous myringitis (nonspecific finding; perhaps no more frequently than in other pneumonias)
- Skin rashes in up to one fourth of patients:
  1. Morbilliform
  2. Urticaria
  3. Erythema nodosum (unusual)
  4. Erythema multiforme (unusual)
  5. Stevens-Johnson syndrome (rare)
- Muscle tenderness (<50% of the patients)
- On examination (and confirmed with testing)
  1. Mononeuritis or polyneuritis
  2. Transverse myelitis
  3. Cranial nerve palsies
  4. Meningoencephalitis
- Lymphadenopathy and splenomegaly
- Conjunctivitis
- Table 1 summarizes the clinical manifestations of *Mycoplasma pneumoniae*

ETIOLOGY

- Infection is spread person-to-person via respiratory droplets or secretions with an incubation period of 1 to 4 wk. Incubation period is generally 2 to 3 wk.
- Mycoplasma are the smallest free-living organisms and lack a cell wall and are not visible after Gram staining.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- *Chlamydia* (now known as *Chlamydophila) pneumoniae*
- *Chlamydophila psittaci*
- *Legionella* spp
- *Coxiella burnetii*
- Several viral agents
- Q fever
- *Streptococcus pneumoniae*
- Pulmonary embolism or infarction

WORKUP

- Chest x-ray (Fig. 1)
- Thorough history and physical examination
- Laboratory tests
- Evaluation guided by symptoms and findings

LABORATORY TESTS

- White blood cells (WBCs):
  1. WBC count >10,000/mm^3 in approximately one fourth of patients
  2. Differential count nonspecific
  3. Leukopenia rare
- Cold agglutinins:
  1. Detected in approximately 50% to 70% of all patients within 1 to 2 wk after infection; highest in children with yield decreasing with age. Since neither sensitive nor specific, the use of cold agglutinins has come into question
  2. Also may be found in:
     a. Lymphoproliferative diseases
     b. Influenza
     c. Mononucleosis
     d. Adenovirus infections
     e. Occasionally, Legionnaires' disease
  3. Titers typically >1:64:
     a. May be detectable with bedside testing
     b. Appear between days 5 and 10 of the illness (so may be demonstrable when patient is first examined) and disappear within 1 mo
- Complement fixation testing assay specific for mycoplasma antigens of paired sera (fourfold rise) or a single titer ≥1:32 in patients with pneumonia and a compatible history:
  1. Considered diagnostic in the appropriate clinical setting
  2. Other assays include enzyme-linked immunosorbent assay (ELISA), antigen capture-enzyme immunoassay, and polymerase chain reaction (PCR); if available, is considered diagnostic test of choice on nasopharyngeal samples
- Culture of the organism from specimens
  1. Only truly specific test for infection
  2. Technically difficult and done reliably by few laboratories
  3. May require weeks to get results
- Sputum:
  1. Often no sputum produced for laboratory testing
  2. When present, Gram-stained specimens show polymorphonuclear cells without organisms
- Infection occasionally complicated by pancreatitis or glomerulitis
- Disseminated intravascular coagulation is a rare complication
- Electrocardiographic evidence of pericarditis or myocarditis may be present

TABLE 1 Clinical Manifestations of *Mycoplasma pneumoniae* Infection

Respiratory tract	Pharyngitis, laryngitis, acute bronchitis, bronchopneumonia
Skin and mucosa	Maculopapular and vesicular exanthema, urticaria, purpura, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome
Central nervous system	Meningitis, meningoencephalitis, acute psychosis, cerebellitis, Guillain-Barré syndrome*
Parenchymatous organs	Pancreatitis, diabetes mellitus, nonspecific reactive hepatitis, subacute thyroiditis*
Miscellaneous	Hemorrhagic bullous myringitis, hemolytic anemia, pericarditis, thromboembolism*

*Some association remains uncertain.
From Cohen J, Powderly WG: *Infectious diseases,* ed 2, St Louis, 2004, Mosby.

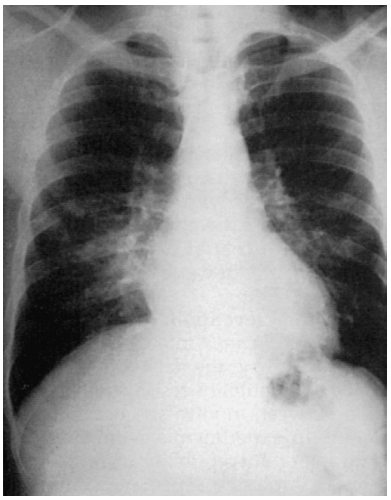

FIG. 1 Radiographic findings in *Mycoplasma pneumoniae* pneumonia are nonspecific. Bilateral bronchopneumonia occurred in this patient. (From Mason RJ et al: *Murray and Nadel's textbook of respiratory medicine*, ed 5, Philadelphia, 2010, WB Saunders.)

FIG. 2 Localized airspace opacification resulting from *Mycoplasma pneumoniae*. (From Specht N [ed]: *Practical guide to diagnostic imaging,* St Louis, 1998, Mosby.)

IMAGING STUDIES

- Predilection for lower lobe involvement (upper lobes involved in less than a fourth), with radiographic abnormalities frequently out of proportion to those on physical examination (Fig. 2)
- Small pleural effusions in approximately 30% of patients
- Large effusions: Rare
- Infiltrates: Patchy, unilateral, and with a segmental distribution, although multilobar involvement may be seen
- Evidence of hilar adenopathy on chest radiographs in 20% to 25%
- Rare cases reported:
  1. Associated lung abscess
  2. Residual pneumatoceles
  3. Lobar collapse
  4. Hyperlucent lung syndrome

Rx TREATMENT

ACUTE GENERAL Rx

- Therapy: Azithromycin 500 mg qd × 3 or 500 mg initially, then 250 mg daily for 4 days for adults. For children: 10 mg/kg in one dose on first day, then 5 mg/kg in one dose for 4 days or clarithromycin: 500 mg bid for 10 days in adults, 15 mg/kg per day in two divided doses for 10 days in children. Alternatives include erythromycin (500 mg qid) for adults or 30 to 40 mg/kg per day in four divided doses in children or doxycycline: 2 to 4 mg/kg per day in one or two divided doses for 10 days, maximum daily dose: 100 to 200 mg, but this agent cannot be used in young children or women of childbearing age. Respiratory fluoroquinolones such as Levaquin or moxifloxacin are alternative agents for treatment in adults but should not be used in young children.
- Therapy shortens the duration and severity of symptoms and may hasten radiographic clearing, but the disease is self-limiting.
- Macrolide resistance is becoming a concern, starting in Asia in 2000s and then spread to Europe and North America. One study showed resistance of 5% to 13% in France and U.S.

CHRONIC Rx

- Effective antimicrobial therapy does not eliminate the organism from the respiratory secretions, which may be positive for weeks.
- Serum antibody response does not necessarily provide lifelong immunity.
- Chronic symptoms do not occur, although clinical relapses may occur 7 to 10 days after the initial response and may be associated with new areas of infiltration.

DISPOSITION

- Clinical improvement is almost universal within 10 days.
- Infiltrates generally clear within 5 to 8 wk.
- Rare deaths are likely attributable to underlying medical diseases.
- Person-to-person spread can be minimized by avoiding open coughing, especially in enclosed areas. Azithromycin prophylaxis can prevent infection in close contacts of patients.

REFERRAL

- Not responding to treatment
- Severe infection
- Severe extrapulmonary manifestations
- Multilobe involvement accompanied by respiratory embarrassment (very rare)

PEARLS & CONSIDERATIONS

COMMENTS

- Outbreaks occur in military recruits, group homes, nursing homes, and in the community. Between 2006 and 2013, the CDC investigated 17 sporadic cases, clusters, and local outbreaks in the U.S.
- Infection control: In the hospital these patients should be on droplet precautions.
- X-ray resolution complete by 8 wk in approximately 90% of patients.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Mycoplasma Pneumonia (Patient Information)
Pneumonia, Bacterial (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Bajantri B et al: Mycoplasma pneumoniae: a potentially severe infection, *J Clin Med Res* 10:535-544, 2018.

Diaz MH et al: Investigations of Mycoplasma pneumoniae infections in the United States: trends in molecular typing and macrolide resistance from 2006 to 2013, *J Clin Microbiol* 53:124-130, 2015.

Waites KB et al: Mycoplasma pneumoniae from the respiratory tract and beyond, *Clin Microbiol Rev* 30:747-809, 2017.

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BASIC INFORMATION

DEFINITION

Pneumocystis jiroveci pneumonia (PJP) is a respiratory infection caused by the fungal pathogen *P. jiroveci* (formerly known as *P. carinii*).

SYNONYMS

Pneumocystis jiroveci pneumonia
PCP
PJP

ICD-10CM CODE
B59 Pneumocystosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):
- Approximately 95% of cases occur in HIV-infected individuals with CD4 counts <200/mm^3 who are not on prophylaxis.
- Also seen in other immunocompromised patients with severe cell-mediated immune deficiency (congenital T-cell deficiency, acute leukemia, lymphoma, bone marrow or organ transplant deficiency).
- May be associated with prednisone use (usually higher than 20 mg/day), usually in conjunction with a second immune-modulating agent.
- Rituximab use has been associated with PJP in HIV-negative patients, most of whom have hematologic cancers.

PREDOMINANT SEX: Equal incidence when adjusted for HIV status
PREDOMINANT AGE: 20 to 40 yr
PEAK INCIDENCE: Age 20 to 40 yr (parallel to AIDS epidemic)
GENETICS: Neonatal infection:
- Most frequent opportunistic infection among HIV-infected children
- Neonatal occurrence unusual

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever, cough, shortness of breath present in almost all cases. May be subacute or insidious in HIV patients; acute onset with rapid progression seen in non–HIV-immunocompromised patients
- Lungs frequently clear to auscultation, although rales occasionally present
- Cyanosis and pronounced tachypnea in severe cases
- Hemoptysis is unusual. Spontaneous pneumothorax is possible

ETIOLOGY

- *P. jiroveci* (formerly *P. carinii*) reclassified as a fungal organism (previously classified as a protozoan) (Fig. E1)
- Reactivation of dormant infection
- Extrapulmonary involvement rare but possible

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other opportunistic respiratory infections:
  1. Tuberculosis
  2. Histoplasmosis
  3. Cryptococcosis
  4. Mycobacterium avium complex (MAC)
- Nonopportunistic infections:
  1. Bacterial pneumonia
  2. Viral pneumonia
  3. Mycoplasma pneumonia
  4. *Legionella*
- Occurs almost exclusively in the setting of profound depression of cellular immunity

WORKUP

- Chest x-ray (Fig. 2) or chest CT (Fig. E3).
- Arterial blood gases.
- Because *Pneumocystis* cannot be cultured, diagnosis relies on detection of the organism by cytologic stains, direct immunofluorescent antibody test, or PCR.
- Sputum examination for cysts of PJP and to exclude other pathogens.
- Bronchoscopy with bronchoalveolar lavage or lung biopsy for diagnosis if sputum examination is negative or equivocal. PCR on lavage is very sensitive but less specific.
- Serum beta-D glucan has good negative predictive performance (very sensitive, less specific).
- Fig. 4 describes an algorithm for the diagnostic evaluation and management of patients with suspected *Pneumocystis* pneumonia.

LABORATORY TESTS

- Arterial blood gas monitoring
- Elevated lactate dehydrogenase in majority of cases
- HIV antibody test and CD4 cell count if cause of underlying immune deficiency state is unclear
- Beta-D-glucan testing may be positive (92% sensitivity, 86% specificity)

IMAGING STUDIES

PJP may appear as diffuse, unilateral, bilateral, or interstitial infiltrates on chest x-ray. CT with mixed alveolar-interstitial patterns, often with sparing of the periphery. Pneumatoceles, which may cause pneumothorax, are common.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Supplemental oxygen
- Ventilation support if needed
- Prompt chest tube placement if pneumothorax develops

ACUTE GENERAL Rx

For confirmed or suspected PJP:
- Trimethoprim-sulfamethoxazole (15 to 20 mg/kg trimethoprim and 75 to 100 mg/kg sulfamethoxazole qd) PO or IV per day divided and given q6 to 8h
- Pentamidine (4 mg/kg IV qd) (severe cases with a contraindication to trimethoprim/sulfamethoxazole). Careful monitoring is required, can cause nephrotoxicity, numerous electrolyte disturbances, and cardiac arrhythmias
- Either regimen with prednisone (40 mg PO bid):
  1. If arterial oxygen pressure <70 mm Hg
  2. If arterial-alveolar oxygen pressure difference >35 mm Hg
  3. Dose tapered to 20 mg bid after 5 days and 20 mg qd after 10 days
- Therapy continued for 3 wk
- Alternative therapies available for patients unable to tolerate conventional therapy:
  1. Dapsone/trimethoprim
  2. Clindamycin/primaquine
  3. Atovaquone
- Table 1 summarizes causes of deterioration in an HIV-infected patient receiving treatment for PJP

CHRONIC Rx

- After completion of therapy, prophylaxis should be maintained with trimethoprim-sulfamethoxazole (one single-strength tablet PO qd or double-strength three times weekly) until the CD4 cell count is >200 for 3 mo.

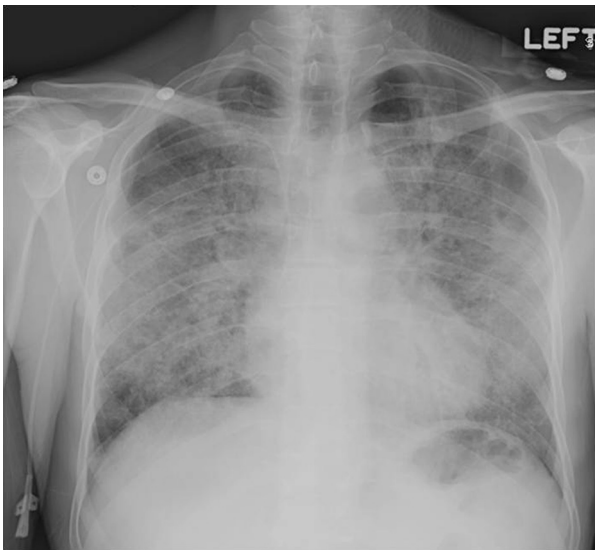

FIG. 2 Chest radiograph showing diffuse interstitial infiltrate in a patient with *Pneumocystis jiroveci* pneumonia. (From Firestein GS et al [eds]: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, WB Saunders.)

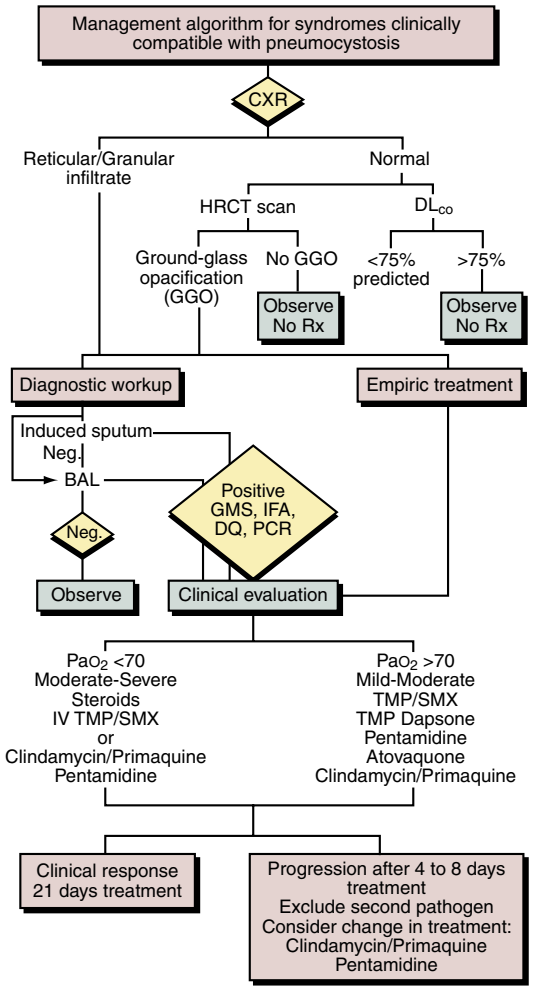

FIG. 4 Algorithm for the diagnostic evaluation and management of patients with suspected *Pneumocystis* pneumonia *BAL*, Bronchoalveolar lavage; *CXR*, chest x-ray; DL_{CO}, single-breath diffusing capacity for carbon monoxide; *DQ*, Diff-Quik (stain); *GGO*, ground-glass opacities; *GMS*, Gomori methenamine silver (stain); *HRCT*, high-resolution computed tomography; *IFA*, immunofluorescent antibody (stain); *IV*, intravenous; *Neg.,* negative; PaO_2, partial pressure of oxygen in arterial blood; *PCR*, polymerase chain reaction; *Rx*, treatment; *TMP/SMX*, trimethoprim-sulfamethoxazole. (Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 8, Philadelphia, 2015, WB Saunders.)

TABLE 1 Causes of Deterioration in an HIV-Infected Person Receiving Treatment for PJP

Etiology	Explanation
Severe Progressive PJP	
Iatrogenic	Pulmonary edema due to IV fluid overload when giving TMP-SMX IRIS following early initiation of ART
Side effects of therapy	Anemia (e.g., caused by TMP-SMX), methemoglobinemia (e.g., caused by dapsone, primaquine)
Inadequate therapy	Incorrect dosage or route of administration Adjuvant glucocorticoids not given for treatment of moderate or severe PJP
Postbronchoscopy	Sedation Pneumothorax
Pneumothorax	Spontaneous Associated with intubation and positive pressure ventilation
Copathology in lung	Bacterial infection Pulmonary Kaposi sarcoma Intercurrent pulmonary embolism
Wrong diagnosis	Empiric diagnosis of PJP, and correct diagnosis is another pathology (e.g., bacterial pneumonia)

ART, Antiretroviral therapy; *HIV*, human immunodeficiency virus; *IRIS*, immune reconstitution inflammatory syndrome; *IV*, intravenous; *PJP*, *Pneumocystis jiroveci* pneumonia; *TMP-SMX*, trimethoprim-sulfamethoxazole.
Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 8, Philadelphia, 2015, WB Saunders.

- Patients intolerant of this therapy should be treated with dapsone (100 mg PO qd) or atovaquone (1500 mg PO qd).
- Inhaled pentamidine (300 mg monthly by standardized nebulizer) is less effective and is reserved for patients intolerant to other forms of prophylaxis.

DISPOSITION

After completion of therapy, long-term ambulatory follow-up is mandatory to provide secondary prevention of PJP (see "Chronic Rx" previously) and management of the underlying immunodeficiency syndrome.

REFERRAL

- To pulmonologist for bronchoscopy if diagnosis cannot be confirmed by sputum examination
- To an infectious disease specialist if case is severe or difficult to manage and to evaluate underlying immune deficiency

PEARLS & CONSIDERATIONS

COMMENTS

- All patients, especially those with severe infection or intolerant of conventional therapy, should be followed by a physician experienced in the management of PJP and, if appropriate, in the long-term management of HIV infection or other underlying disease.
- Severe and life-threatening hypoglycemia may occur 1 or 2 wk after start of IV pentamidine. Monitor closely and advise the patient of symptoms of hypoglycemia.

RELATED CONTENT

Pneumocystis Pneumonia (Patient Information)
Acquired Immunodeficiency Syndrome (Related Key Topic)

AUTHOR: **Sebastian G. Kurz, MD**

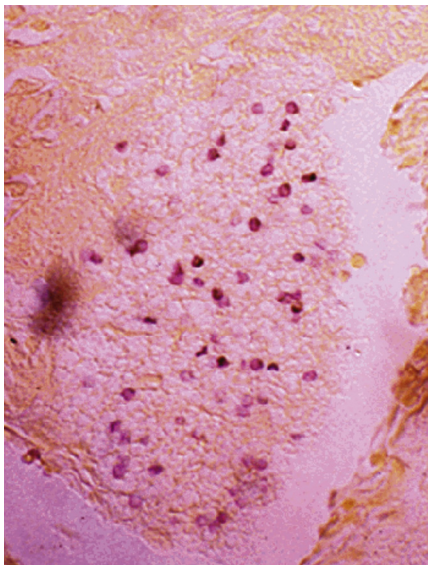

FIG. E1 Wright-Giemsa stain of *Pneumocystis jiroveci (carinii)* pneumonia. (From Gabbe SG: *Obstetrics*, ed 6, Philadelphia, 2012, WB Saunders.)

FIG. E3 Computed tomography scan of the chest demonstrating ground-glass opacity in a patient with *Pneumocystis jiroveci* pneumonia. (From Firestein GS et al [eds]: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, WB Saunders.)

BASIC INFORMATION

DEFINITION

Viral pneumonia is a lung infection caused by any of a large number of viral pathogens. The most important viruses are discussed in this chapter.

SYNONYMS

Viral pneumonia
Nonbacterial pneumonia

ICD-10CM CODES
J12.9 Viral pneumonia, unspecified
J12.89 Other viral pneumonia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Influenza virus:
  1. 10% to 20% of population in temperate zones infected during 1 to 2 mo epidemics occurring yearly during winter mos.
  2. Up to 50% infected during pandemics.
  3. Secondary bacterial pneumonia develops in a small percentage of infected persons.
- Incidence of other important viral pathogens that cause pneumonia can vary widely depending on setting, geography, and testing modalities. With the more widespread use of rapid molecular testing of respiratory secretions, an increase in the detection of viral pathogens has been observed. However, drawing conclusions as to causality of the identified virus to the actual pneumonia remains challenging because respiratory viruses remain detectable for several wks after initial infection, and the pneumonia may be due to secondary bacterial infection.

PREVALENCE (IN U.S.):

- Often related to immune status of the population or presence of an epidemic
- Normal hosts (estimates):
  1. 86% of cases of pneumonia resulting in hospitalization in American adults
  2. 16% of pediatric pneumonias managed as outpatients
  3. 49% of hospitalized infants with pneumonia
- Important problem in hosts with impaired immunity

PREDOMINANT SEX:

- Equal predominance.
- Male sex may predispose to more severe respiratory disease in RSV infection.

PREDOMINANT AGE:

- Influenza:
  1. Overall incidence greatest at age 5 yr
  2. Lower incidence with increasing age
  3. The most serious sequelae in those with chronic medical illnesses, especially cardiopulmonary disease
  4. Hospitalizations greatest in infants and adults aged >64 yr
- RSV and parainfluenza virus:
  1. Young children (as the major cause of pneumonia)
  2. Occurs throughout life
- Adenoviruses:
  1. Young children
  2. Adults, primarily military recruits
- Varicella:
  1. Approximately 16% of adults (not infected in childhood) who contract chickenpox
  2. Acute varicella during pregnancy more likely to be complicated by severe pneumonia
  3. 90% of reported varicella pneumonia cases are in adults (highest incidence ages 20 to 60 yr)
- Measles:
  1. Young adults and older children who received a single vaccination (5% failure rate)
  2. Measles during pregnancy more likely to be complicated by pneumonia
  3. Underlying cardiopulmonary diseases and immunosuppression predispose to serious pneumonia complicating measles
  4. Before availability of measles vaccine, 90% of pneumonias in those <10 yr
  5. Currently more than one third of patients >14 yr in the U.S.
  6. 3% to 50% of measles cases are complicated by pneumonia
- CMV:
  1. Neonatal through adult
  2. Immunosuppression is key predisposing factor
- Human metapneumovirus:
  1. Children: Peak incidence 11 mo
  2. Increasingly detected in adults (bronchitis, chronic obstructive pulmonary disease [COPD] exacerbation, pneumonia)
  3. Frequent cause of lower respiratory tract infection (LRTI) in lung transplant recipients

PEAK INCIDENCE:

- Influenza:
  1. Winter mos for influenza A
  2. Yr-round for influenza B
  3. Peak of pneumonia seen wks into the outbreak of infection
- Respiratory syncytial virus (RSV) and parainfluenza virus: Winter and spring
- Adenovirus: Endemic (military)
- Varicella: Spring in temperate zones
- Measles: Yr-round
- Cytomegalovirus (CMV): Yr-round
- Human metapneumovirus: Winter mos

GENETICS: Familial disposition:

- Close contact, not genetics, is important in acquisition
- Congenital anomalies and immunosuppression worsen course of RSV pneumonia

Congenital infection:

- CMV is the most common intrauterine infection in the U.S.
- Pneumonia occurs occasionally in infants with symptomatic congenital infection

Neonatal infection:

- Severe RSV pneumonia
- Adenovirus pneumonia
  1. 5% to 20% mortality rate
  2. Can lead to residual restrictive or obstructive functional abnormalities
- "Varicella neonatorum"
  1. Disseminated visceral disease including pneumonia
  2. May develop in neonates whose mothers develop peripartum chickenpox
- CMV pneumonia
  1. Generally fatal
  2. Associated with severe cerebral damage in this population

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Influenza:
  1. Fever, cough, or sore throat (referred to as influenza-like illness [ILI])
  2. Uncomfortable or lethargic appearance
  3. Prominent dry cough (rarely hemoptysis)
  4. Flushed integument and erythematous mucous membranes
  5. Rales or rhonchi
- RSV, parainfluenza, and human metapneumovirus:
  1. Fever
  2. Tachypnea
  3. Prolonged expiration
  4. Wheezes and rales
- Adenoviruses:
  1. Hoarseness
  2. Pharyngitis
  3. Tachypnea
  4. Cervical adenitis
- Measles:
  1. Conjunctivitis
  2. Rhinorrhea
  3. Koplik spots (white lesions on the buccal mucosa)
  4. Exanthem (maculopapular rash that starts on the head, then moves down to rest of body)
  5. Pneumonitis
     a. May occur as a complication in 3% to 4% of adolescents and young adults
     b. Coincident with rash
     c. May also develop after apparent recovery from measles
  6. Fever
  7. Dry cough
- Varicella:
  1. Fever
  2. Maculopapular or vesicular rash (all lesions at the same stage)
     a. Becomes encrusted
     b. Pneumonia typical 1 to 6 days after rash appears
     c. Pneumonia (Fig. 1) accompanied by cough and occasionally hemoptysis
  3. Few auscultatory abnormalities noted on examination of the lungs
- CMV:
  1. Fever
  2. Paroxysmal cough
  3. Occasional hemoptysis
  4. Diffuse adenopathy when pneumonia occurs after transfusion

ETIOLOGY

Viral infection can lead to pneumonia in both immunocompetent and immunocompromised hosts.

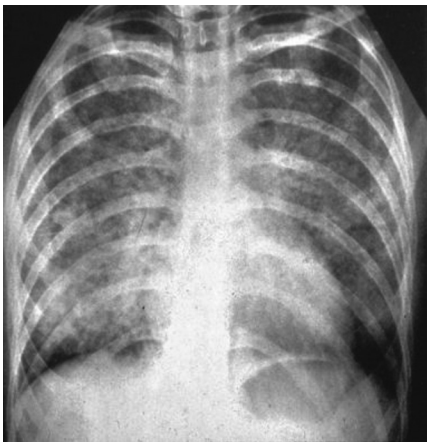

FIG. 1 This chest radiograph demonstrates bilateral nodular and interstitial pneumonia characteristic of varicella pneumonia. The patient, a 27-yr-old gravida 6, para 2, abortus 3, was exposed to varicella infection in her two children. Characteristic skin vesicles of varicella occurred several days before the development of pulmonary symptoms. She required endotracheal intubation and mechanical ventilation for 6 days. She was treated with intravenous acyclovir and ceftazidime for possible superimposed infection. The patient recovered fully and delivered a healthy infant at term. (From Gabbe SG: *Obstetrics*, ed 6, Philadelphia, 2012, WB Saunders.)

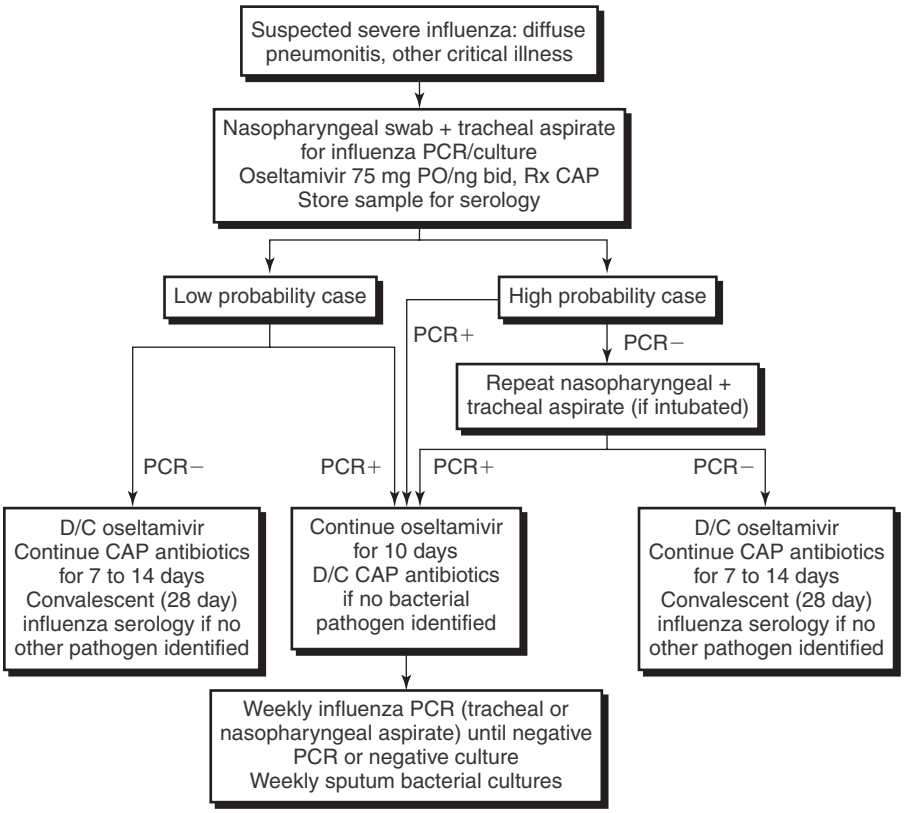

FIG. 2 Suggested algorithm in the workup and management of suspected severe influenza pneumonia in the critical care unit. *CAP,* Community-acquired pneumonia; *D/C,* discontinue; *PCR,* polymerase chain reaction; *PO,* by mouth; *Rx*, prescription. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.)

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bacterial pneumonia, which frequently complicates (i.e., can follow or be simultaneous with) viral pneumonia
- Other causes of atypical pneumonia:
  1. *Mycoplasma* spp.
  2. *Chlamydia* spp.
  3. *Coxiella* spp.
  4. Legionnaires' disease

  In certain patient populations (e.g., immunocompromised), consider fungal infections, tuberculosis, or atypical mycobacterium.
- Acute respiratory distress syndrome (ARDS)
- Physical findings and associated hypoxemia confused with pulmonary emboli

WORKUP

- Information about the current prevalent strain of influenza virus can be obtained from local health departments or from the Centers for Disease Control and Prevention.
- Influenza and other viruses may be cultured from respiratory secretions during the initial few days of the illness (special media and techniques necessary).
- Respiratory viral panels that use PCR-based assays to test for a variety of viruses are extremely sensitive and are becoming the test of choice.
- Rapid flu tests have a 50% sensitivity in diagnosing influenza (a negative test does not mean the patient does not have influenza).
- Measles and adenovirus pneumonia are usually diagnosed clinically and can be confirmed with serology.
- CMV may be grown in culture or PCR amplified from bronchoalveolar lavage samples. An algorithm for the workup and management of suspected severe influenza pneumonia in the critical care unit is described in Fig. 2. Open lung biopsy is required for a definite diagnosis of CMV pneumonia.

LABORATORY TESTS

- Sputum Gram stain (usually produced in scanty amounts) typically shows few polymorphonuclear leukocytes and few bacteria.
- White blood cell count may vary from leukopenic to modest elevation, usually without a leftward shift.
- Disseminated intravascular coagulation occasionally complicates adenovirus type 7 pneumonia.
- Multinucleated giant cells on Tzanck preparation of an unroofed vesicular lesion are useful in diagnosing varicella in a patient with an infiltrate (also found in herpes simplex).
- Severe immunosuppression is associated with symptomatic CMV pneumonia (usually reactivation of latent infection or in previously seronegative recipients from the donor).
- Hypoxemia may be profound.
- Cultures may be helpful in identifying superinfecting bacterial pathogens.
- When they occur, parapneumonic pleural effusions are exudative.

IMAGING STUDIES

- Chest radiographs may demonstrate a spectrum of findings from ill-defined, patchy, or generalized interstitial infiltrates, which can be associated with ARDS.
- A localized dense alveolar infiltrate suggests a superimposed bacterial pneumonia.
- Small calcified nodules may develop as a radiographic residual of varicella pneumonia.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

General:

- Measures to diminish person-to-person transmission
- Modified bed rest
- Maintenance of adequate hydration
- Possible ventilation support for severe pneumonia or ARDS

Influenza:

- Yearly prophylactic strain-specific influenza vaccination can be given to prevent infection.
- Live, attenuated influenza vaccines administered by nose drops as effective as injected inactivated viral vaccines.

RSV:

- Isolation techniques are important in limiting spread of RSV infections.

- Immunoglobulins with a high RSV-neutralizing antibody titer are beneficial in treatment.

Adenoviruses:
- Intestinal inoculation of respiratory adenoviruses has been used to successfully immunize military recruits.
- Although they produce no disease in recipients, the viruses may be shed chronically and may infect others at a later date.
- These vaccines are not available for civilian populations.

Varicella:
- Live, attenuated varicella vaccine has been successfully used in clinical trials.
- Varicella-zoster immune globulin should be administered within 4 days of exposure to prevent or modify the disease in susceptible persons.
- Nonimmunized persons exposed to varicella are potentially infectious between 10 and 21 days after exposure.

Measles:
- Effective measles vaccine is available.
  1. The vaccine should be administered at age 15 mo.
  2. A second dose should be administered at the time of school entry.
- Live, attenuated vaccine or gamma-globulin can prevent measles in unvaccinated persons if administered early after exposure.
- Vitamin A given PO for 2 days reduces morbidity and mortality rates from measles in exposed children.

ACUTE GENERAL Rx

- General: Administer appropriate antibiotics for bacterial superinfections.
- Influenza:
  1. Amantadine and rimantadine for influenza A (not active against influenza B). Early use can speed recovery from small airway dysfunction, but whether it influences the development or course of pneumonia is uncertain.
  2. The neuraminidase inhibitors oseltamivir and zanamivir are effective if given in the first 48 hours of symptoms of influenza; their efficacy in established influenza pneumonia is unclear.
  3. Aerosolized ribavirin or amantadine may have a role in treating severe influenza pneumonia, but they have not been approved for this indication.
- RSV and parainfluenza:
  1. Ribavirin aerosol may be effective for severe RSV pneumonia.
  2. There is no approved antiviral therapy for parainfluenza virus pneumonia.
- Adenoviruses: No effective agent; some case reports of cidofovir use but unproved.
- Varicella:
  1. Varicella pneumonia can be treated with IV acyclovir.
  2. Adults who develop chickenpox should be considered for acyclovir treatment, which may prevent the development of pneumonia.
- Measles: No effective antimeasles agent.
- CMV:
  1. Acyclovir can prevent CMV infection in renal transplant recipients.
  2. Ganciclovir and foscarnet, with or without CMV hyperimmune globulin, show promise in the treatment of serious CMV infection, including pneumonia, in compromised hosts.
- Human metapneumovirus: No specific treatment available

DISPOSITION

- Supportive therapy is useful.
- Death is possible during acute illness.
- Residual functional abnormalities may be persistent or develop into or predispose to chronic respiratory diseases in later life.
- Morbidity and mortality rates after most viral pneumonias are increased by bacterial superinfection.

REFERRAL

- Uncertainty about the diagnosis in a compromised host.
- Symptoms or findings are progressive.
- Severe respiratory compromise, diffuse infiltrates, or the development of ARDS.

PEARLS & CONSIDERATIONS

COMMENTS

- Influenza spreads by close contact and by small droplets transmitted by cough.
- RSV is effectively transmitted by fomites and by direct contact (little by aerosol).
- Varicella is transmitted by direct contact or by aerosol.
- Of the three major forms of parainfluenza viruses (types 1 to 3), type 3 is the most common cause of viral pneumonia; types 1 and 2 primarily cause laryngotracheitis.
- Human metapneumovirus is a recently identified common cause of upper respiratory infections and pneumonia.

RELATED CONTENT

Viral Pneumonia (Patient Information)
Cytomegalovirus Infection (Related Key Topic)
Influenza (Related Key Topic)
Varicella (Related Key Topic)

AUTHOR: **Sebastian G. Kurz, MD**

Pneumothorax, Spontaneous ALG PTG

BASIC INFORMATION

DEFINITION

A spontaneous pneumothorax (SP) is defined as air in the pleural space, collapsing the lung without a precipitating event. This can be primary SP (otherwise healthy people without any obvious underlying lung disease) or secondary SP (with underlying lung disease).

SYNONYMS

Primary spontaneous pneumothorax (PSP)
Secondary spontaneous pneumothorax (SSP)
SP
PSP
SSP

ICD-10CM CODES	
J93.0	Spontaneous tension pneumothorax
J93.11	Primary spontaneous pneumothorax
J93.12	Secondary spontaneous pneumothorax
J93.81	Chronic pneumothorax
J93.83	Other pneumothorax
J93.9	Pneumothorax, unspecified
J95.811	Postprocedural pneumothorax
P25.1	Pneumothorax originating in the perinatal period
S27.0XXA	Traumatic pneumothorax, initial encounter
S27.0XXD	Traumatic pneumothorax, subsequent encounter
S27.0XXS	Traumatic pneumothorax, sequela

EPIDEMIOLOGY & DEMOGRAPHICS

- Approximately 20,000 new cases of SP occur each yr in the U.S.
- SP is more common in men than women (6:1).
- Incidence of primary SP is 7.4 per 100,000 in men and 1.2 per 100,000 in women.
- Incidence of secondary SP is 6.3 per 100,000 in men and 2.0 per 100,000 in women.
- SP is commonly seen in tall, thin young men aged 20 to 40 yr.
- Risk factors include smoking, family history, Marfan syndrome, homocystinuria, and thoracic endometriosis.
- Anorexia nervosa is thought to be a risk factor due to pulmonary parenchymal consequences of malnutrition.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Sudden onset of pleuritic chest pain (90%), usually at rest and no relationship between the onset of pneumothorax and physical activity, which often becomes dull after a few hours
- Pain is usually unilateral and can be sharp and agonizing and associated with considerable apprehension
- Dyspnea (80%), which often resolves within 24 hr, despite persistence of pneumothorax
- Cough (10%)
- Asymptomatic (5%); may take up to 7 days to come to medical attention
- Tachycardia
- Hypoxemia
- Hypercapnia is rare because the alveolar ventilation is maintained by the contralateral lung
- Decreased chest excursion on the affected side (Fig. 1)
- Diminished breath sounds
- Subcutaneous emphysema may be present
- Hyperresonance on percussion

ETIOLOGY

- In primary SP, rupture of small blebs and bullae, usually located near the apex of the upper lobes, is a common cause.
- In secondary SP, chronic obstructive pulmonary disease is the most common cause, but it can also be associated with pneumonia, bronchogenic carcinoma, mesothelioma, sarcoidosis, tuberculosis, cystic fibrosis, and many other lung diseases. Causes of secondary spontaneous pneumothorax are summarized in Box 1.

DIAGNOSIS

Established by the chest x-ray (CXR) (Fig. 2)

DIFFERENTIAL DIAGNOSIS

- Pleurisy
- Pulmonary embolism
- Myocardial infarction
- Pericarditis
- Asthma
- Pneumonia

WORKUP

CXR

LABORATORY TESTS

Arterial blood gases may show hypoxemia and hypocapnia as a result of hyperventilation.

IMAGING STUDIES

- SP is usually confirmed by upright CXR:
  1. A white visceral pleural line. The absence of vessel markings peripheral to this line helps differentiate from mimicking conditions such as an overlying skin fold. A lateral width of 1 cm corresponds to 27% pneumothorax, and 2 cm occupies 49% of the hemithorax.
  2. The left lateral decubitus position is the most sensitive and the supine position the least sensitive. Inspiratory and expiratory films have equal sensitivities.
  3. As little as 50 ml of air can be detected on upright film.
- Tension pneumothorax (Fig. 3) is a medical emergency and should be suspected when the patient is hemodynamically unstable or with contralateral tracheal and mediastinal deviation and ipsilateral flattening or inversion of the diaphragm on the CXR (Fig. 4).
- CT scan is considered acceptable for a patient with recurrent pneumothorax or persistent air leak, and for planning surgery.
- Lung ultrasound has emerged as a rapid and accurate screening tool for pneumothorax.

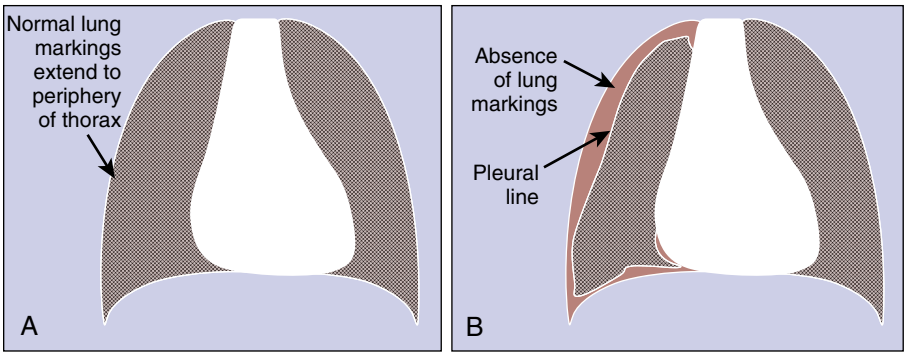

FIG. 1 Pneumothorax. A, Schematic of normal lung. **B,** Schematic of pneumothorax. Pneumothoraces can range in size from tiny to massive. Because of the variability in their size and location, pneumothoraces can be difficult to detect on chest x-ray. For example, a pneumothorax that is anterior or posterior rather than lateral may be hidden on frontal chest x-ray, particularly one taken in the supine position. An upright chest x-ray should be obtained if possible. An expiratory film is thought to be more sensitive, because the lung and thorax decrease in size during expiration, but air trapped in the pleural space remains the same size and thus appears relatively larger. Subtle pneumothoraces may not be visible on chest x-ray. In some cases, subcutaneous air may be the only visible clue to underlying lung injury. CT is extremely sensitive for pneumothorax, although controversy remains over the proper management of pneumothoraces seen only on CT. Ultrasound is also thought to be more sensitive than chest x-ray for detection of pneumothorax, although, again, the management of pneumothorax seen only on ultrasound is uncertain because this is a relatively newly described method of detection. The chest x-ray findings of pneumothorax include a lack of the normal lung markings, which should be visible to the periphery of the chest wall. Sometimes a line marking the boundary of the lung and visceral pleura is visible, although this can be confused with ribs and with the medial margin of the scapula. Depending on the degree of pneumothorax and lung collapse, the lung parenchyma may appear denser than the opposite side. In extreme cases of tension pneumothorax, the pressure exerted by the air in the pleural space may begin to displace other structures, including the diaphragm and mediastinum. In tension pneumothorax, the hyperinflated hemithorax may also have abnormally positioned ribs, with a position more horizontal than usual. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, WB Saunders.)

The lung point sign, a sonographic representation of the point of the chest wall where the pleural layers re-adhere, is 100% specific to confirm the diagnosis.

Rx TREATMENT

INITIAL MANAGEMENT

- 100% oxygen administration reduces the partial pressure of nitrogen in pleural capillaries, consequently quadrupling the rate of pneumothorax absorption, and should be administered to all patients with pneumothorax.
- Further treatment is based on the size of the pneumothorax.
  1. If the pneumothorax is small (<2 cm between lung and chest wall on CXR) and the patient is asymptomatic, the patient can be treated with observation alone. Repeat imaging should be performed to ensure stability/resorption of the pneumothorax. Some studies have shown that using a cutoff of 35 mm for deciding which patients can be managed with observation is reasonable in selected patients with nonoccult traumatic pneumothoraces after consultation with trauma consultants.
  2. If the pneumothorax is large (>2 cm), or if the patient is symptomatic with chest pain and dyspnea, initial management should focus on removing air from the pleural space. Needle aspiration is the treatment of choice in the clinically stable patient.
- Needle aspiration can be done at the bedside using a large-bore angiocatheter needle or commercially available catheter aspiration kit. The needle is introduced in the second intercostal space midclavicular line. The catheter is left in place and attached to a three-way stopcock and a large syringe. Air is aspirated until resistance is met or the patient experiences significant coughing. Repeat CXR is done immediately after aspiration and again in 4 to 24 hours to document reexpansion of the lung. If the pneumothorax fails to resolve with aspiration, repeated aspiration is reasonable for primary spontaneous pneumothorax.
- If there is improvement but not complete resolution of pneumothorax after the aspiration, the catheter can be attached to a Heimlich (one-way) valve to allow further lung expansion. Some stable patients can be discharged home with this device in place if close follow-up monitoring can be obtained. Chest tube insertion has been recommended for patients with primary SP who are unsuccessful in controlling symptoms by simple aspiration or catheter aspiration. Most patients can be managed with small chest tubes (<12 Fr). The chest tube can be connected to a water seal device, with or without suction, and left in position until the pneumothorax has resolved.
- An algorithmic approach to the treatment of primary spontaneous pneumothorax is outlined in Fig. 5.

PREVENTION

- Approximately 25% to 50% of patients with primary SP with have a recurrence within 5 yr. Recurrence rate is higher in patients with secondary spontaneous pneumothorax.
- Prevention of spontaneous pneumothorax is surgical intervention or instillation of sclerosing agents through a chest tube.
- Indication for the surgical intervention is second ipsilateral SP, first contralateral SP, simultaneous bilateral SP, persistent air leak (>5 to 7 days), failure of lung reexpansion by the chest tube, and professions at risk (e.g., pilots, divers).
- The current recommended surgical approach is the use of video-assisted thoracoscopy (VATS) with bullectomy and pleurodesis. Surgical chemical pleurodesis is best achieved with sterile talc. The overall recurrence rate is estimated at <5% after VATS.
- Instillation of a sclerosing agent through a chest tube: Doxycycline and talc slurry are the preferred agents; minocycline is considered to be an acceptable agent. The recurrence rates for the instillation of sclerosing agents (minocycline 5 mg/kg in 50 ml of normal saline or doxycycline 500 mg in 50 ml of normal saline) are higher than for VATS-guided therapy (<25%). Therefore this mode of therapy should be reserved for patients who are poor surgical candidates.

DISPOSITION

- Smoking cessation should be advised.
- Death from primary SP is uncommon. In patients with secondary SP and chronic obstructive pulmonary disease, mortality rates range from 1% to 16%.

REFERRAL

A pulmonary specialist and surgical consultation are recommended.

PEARLS & CONSIDERATIONS

- The rate of pleural air absorption is approximately 1.25% of the volume of the hemithorax per day. Therefore the interval for complete resolution of pneumothorax with observation can be estimated.

BOX 1 Causes of Secondary Spontaneous Pneumothorax

Airway Disease
- Chronic obstructive pulmonary disease
- Asthma
- Cystic fibrosis

Infections
- Necrotizing bacterial pneumonia, lung abscess
- *Pneumocystis jirovecii* pneumonia
- Tuberculosis

Interstitial Lung Disease
- Sarcoidosis
- Idiopathic pulmonary fibrosis
- Lymphangiomyomatosis
- Tuberous sclerosis
- Pneumoconioses

Neoplasms
- Primary lung cancers
- Pulmonary or pleural metastases

Miscellaneous
- Connective tissue diseases
- Pulmonary infarction
- Endometriosis, catamenial pneumothorax

From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Elsevier.

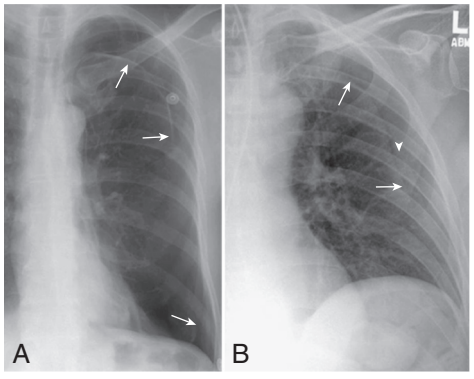

FIG. 2 A, Chest radiograph of a pneumothorax. The pleural line has lucency on either side, representing air in the pleural space on one side of the line and air in the lung on the other. The line is sharply demarcated and can be traced along its course *(lower arrow)*. No blood vessels can be seen beyond the superior *(upper arrow)* and lateral *(middle arrow)* extent of the line. **B,** Chest radiograph of a skinfold *(arrows)* that could be mistaken for a pneumothorax. The border is more of an edge, with lucency on only one side. The edge is poorly defined and cannot be followed continuously *(lower arrow)*. Blood vessels can be traced beyond the border of the fold *(arrowhead)*. (Courtesy Michael B. Gotway, MD, Scottsdale Medical Imaging, and the Department of Radiology, University of California, San Francisco. From Mason RJ et al: *Murray & Nadel's textbook of respiratory medicine*, ed 5, Philadelphia, 2010, WB Saunders.)

[1]Aspler A et al: Double-lung point sign in traumatic pneumothorax, *Am J Emerg Med* 32:819, 2014.

- Catamenial pneumothorax is a rare condition characterized by recurrent SP coinciding with the onset of menses. It usually affects the right lung and is believed to be caused by endometriosis with involvement of the diaphragm and/or pleura. It is believed to be hormonally related, and treatment is aimed at endometrial suppression.
- Air travel should be avoided until complete resolution of pneumothorax.
- Scuba diving is contraindicated. It may be considered on a case by case basis in patients who have had surgical pleurectomy.

COMMENTS

- A recent trial revealed that conservative management of spontaneous pneumothorax is safe and effective and noninferior to interventional management and it also has a lower risk of serious adverse events.[2]
- Patients with AIDS and *Pneumocystis jirovecii* infection have a high incidence of SP. Treatment typically requires chest tube placement and either thoracoscopy or open thoracotomy.

[2]Brown SGA et al: Conservative versus interventional treatment for spontaneous pneumothorax, *N Engl J Med* 382(5):405-415, 2020.

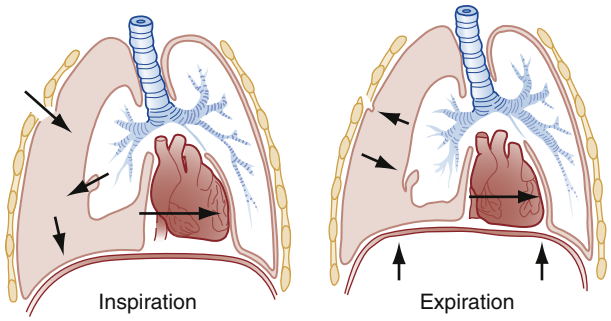

FIG. 3 Tension pneumothorax with total collapse of the right lung and shift of mediastinal structures to the left. Air is forced into the pleural space during inspiration and cannot escape during expiration. (From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Elsevier.)

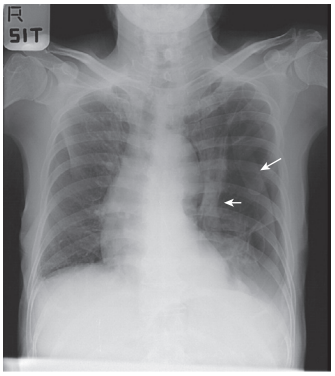

FIG. 4 Chest radiograph showing left pneumothorax with shift of the mediastinum and trachea to the right side *(white arrows).* The left lung is not completely collapsed, suggesting the presence of a loculated tension pneumothorax. (From Chan SSW: Tension pneumothorax managed without immediate needle decompression, *Am J Emerg Med* 36[3]:242-245, 2009.)

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pneumothorax (Patient Information)

AUTHOR: **Hisashi Tsukada, MD, PhD**

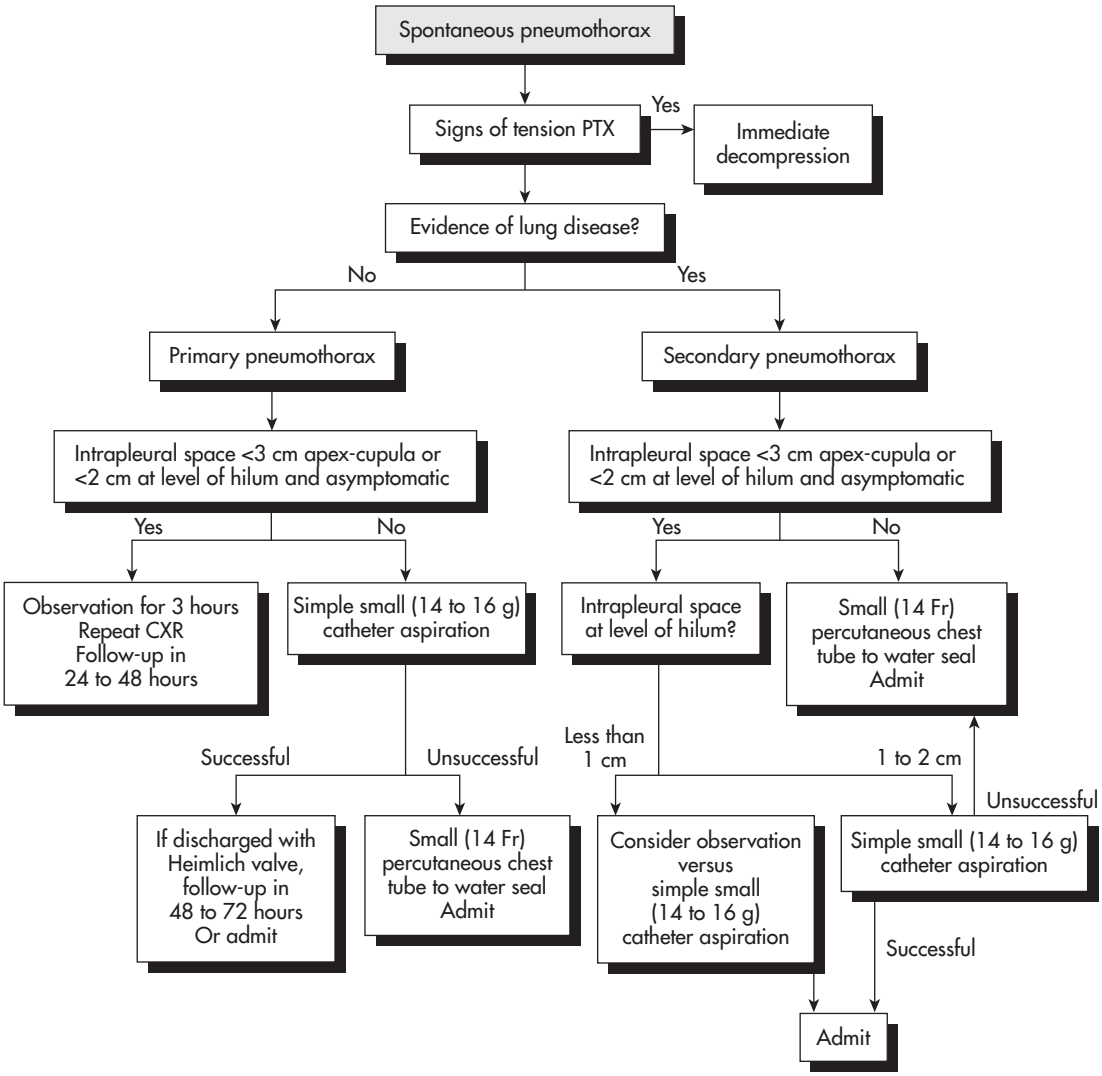

FIG. 5 Algorithmic approach to the treatment of primary spontaneous pneumothorax. *CXR*, Chest radiograph; *PTX*, pneumothorax. (From Adams JG et al: *Emergency medicine: clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

SUGGESTED READINGS

Bou Zein Eddine S et al: Observing pneumothoraces: the 35 mm rule is safe for blunt and penetrating chest trauma, *J Trauma Acute Care Surg* 86(4):557-564, 2019.

Morse JL, Sadafer B: Acute tension pneumothorax and tension pneumoperitoneum in a patient with anorexia nervosa, *J Emerg Med* 38:e13, 2010.

Biffl WL et al : The management of pneumothorax in patients with anorexia nervosa: a case report and review of the literature, *Patient Saf Surg* 4(1):1, 2010.

Poison Ivy Dermatitis PTG

BASIC INFORMATION

DEFINITION

Poison ivy dermatitis is a contact dermatitis caused by exposure to urushiol, the oil of plants of the genus *Toxicodendron,* which includes poison ivy, poison oak, and poison sumac.

SYNONYMS

Rhus dermatitis
Toxicodendron dermatitis

ICD-10CM CODE
L23.7 Allergic contact dermatitis due to plants, except food

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Affects 10 million to 40 million Americans annually.
PREVALENCE: From 50% to 75% of the adult population is clinically sensitive to these plants. Sensitivity rates are lower in urban areas. (Tolerance is found in 10% to 15% of the population.)
PREDOMINANT SEX AND AGE: Sensitization occurs most commonly between ages 8 and 14 yr. Sensitivity wanes with age, especially in individuals with limited exposure or prior mild reactions.
PEAK INCIDENCE: More frequent in mos when outdoor activity is more common.
GENETICS: There is thought to be a genetic susceptibility to sensitivity; however, the rash occurs in all ethnicities and skin types.
RISK FACTORS: Firefighters, forestry workers, farmers, and outdoor workers in general, as well as those who participate in outdoor recreation. These plants are indigenous to the U.S., Canada, and Mexico, and cases are most common in these areas.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients typically present with intense pruritus and rash. The patient may not be aware of exposure to the plant.
- Symptoms typically peak from 1 to 14 days after exposure, depending on the degree of exposure and thickness of affected skin.
- Dermatitis may initially present as erythema and may develop into papules, vesicles, and bullae.
- Lesions may be found in the classic linear configuration, typically in exposed areas likely to have been in contact with plants (Fig. E1). Atypical appearance or location of dermatitis is more common with secondary exposure, such as through pets or infected tools or clothing.
- Face and genital involvement may present with significant edema.
- Inhalation of urushiol aerosolized by fire can cause significant respiratory tract inflammation. This can be a particular occupational hazard of forest firefighters.
- Postinflammatory hyperpigmentation may occur, more commonly in dark skin types. This usually resolves with treatment.

FIG. E1 Allergic contact dermatitis to *Rhus*. A, The classic appearance of allergic contact dermatitis is illustrated in this patient, who came into contact with poison oak. The lesions are linear but not following Blaschko lines. The eruption is microvesicular and extremely pruritic. **B,** *Rhus* dermatitis. Linear bullae are characteristic of an allergic contact dermatitis. (Courtesy O. Dale Collins III. From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

ETIOLOGY

- Initial contact with oil of plants in this genus, which is released with damage to plant parts, causes a classic T-lymphocyte–mediated delayed-type allergic reaction.
- Contact with any part of the plant, including leaves, stems (vines), and roots, can cause dermatitis. Even minimal damage is enough to release the oil.
- Subsequent exposures cause a cell-mediated cytotoxic immune response.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Allergic contact dermatitis from other plants or nonplant substances
- Irritant contact dermatitis
- Nummular dermatitis
- Arthropod reactions, including scabies and bedbug bites

WORKUP

Typically not needed. Diagnosis is based on characteristic rash and possibly history of exposure.

TREATMENT

Prevention is the most effective treatment.

NONPHARMACOLOGIC THERAPY

- After known exposure, patients should remove contaminated clothing and wash the skin gently with soap and water. Washing after appearance of dermatitis does not prevent further lesions.
- Calamine lotion, cool compresses, baking soda, or colloidal oatmeal baths may provide symptomatic relief.
- Keep nails short and clean to help prevent secondary bacterial infection.
- Exposed clothing, as well as tools, pets, and equipment, should be washed with soap and water to prevent secondary exposure.

ACUTE GENERAL Rx

- Topical steroids are generally not helpful. They may be effective for symptom management in mild, early cases with erythema and pruritus but no vesiculation.
- Topical antibiotics should be avoided.
- Use of antihistamines for associated pruritus may be effective, but this has not been extensively studied.
- Systemic corticosteroids offer significant relief in moderate to severe *Rhus* dermatitis, including generalized rash or severe facial or genital involvement.
- Effective dosing of oral prednisone is 1 mg/kg/day over 7 to 10 days (maximum 60 mg initial dose), with tapering over an additional 7 to 10 days.
- Inadequate doses or too-rapid tapering of systemic steroids may cause symptom rebound.
- Intramuscular (IM) treatment with long-acting triamcinolone suspension may be considered for patients intolerant of oral therapy.

CHRONIC Rx

- Recurrence may be caused by repeated exposure to fomites, including contaminated clothing, equipment, or pets.
- Secondary bacterial infection of the skin is the most common complication of *Rhus* dermatitis. Staph and strep are the most common pathogens. Methicillin-resistant *Staphylococcus aureus* (MRSA) must be considered.

DISPOSITION

Untreated *Rhus* dermatitis will resolve in 1 to 3 wk.

REFERRAL

Refer to dermatology if there is diagnostic confusion.

PEARLS & CONSIDERATIONS

PREVENTION

- Patients should be educated regarding identification and avoidance as well as washing to remove the oil after known exposure.
- Total avoidance of the plants may not be practical.
- The use of barrier creams applied before exposure to prevent dermatitis may be of some benefit, particularly in potential occupational (therefore predictable) exposure. These need to be regularly reapplied.
- Products available for postexposure prophylaxis are effective; however, equal efficacy may be obtained from less expensive liquid dishwashing soap.

- Desensitization has not been found to be effective.

PATIENT & FAMILY EDUCATION

- "Leaves of three, let it be" is a helpful reminder for patients.
- Patient education material, including access to photographs of the leaves of these plants in a variety of seasons and conditions, may be useful.

SUGGESTED READING

Colbeck C et al: Poison ivy dermatitis, *Arch Dis Child* 98:1022, 2013.

RELATED CONTENT

Poison Ivy (Patient Information)
Contact Dermatitis (Related Key Topic)

AUTHOR: **Margaret Tryforos, MD**

Poliomyelitis (PTG)

BASIC INFORMATION

DEFINITION

Poliomyelitis is a symptomatic infection caused by poliovirus, which is transmitted by fecal-oral route, and which (on rare occasions) may result in paralysis.

SYNONYMS

Polio
Infantile paralysis

ICD-10CM CODES

A80.0	Acute paralytic poliomyelitis, vaccine-associated
A80.1	Acute paralytic poliomyelitis, wild virus, imported
A80.2	Acute paralytic poliomyelitis, wild virus, indigenous
A80.30	Acute paralytic poliomyelitis, unspecified
A80.39	Other acute paralytic poliomyelitis
A80.4	Acute nonparalytic poliomyelitis
A80.9	Acute poliomyelitis, unspecified
B91	Sequelae of poliomyelitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- All cases in the U.S. and Western Hemisphere are now vaccine associated (because of use of the live-attenuated oral polio vaccine [OPV]).
- Before 1997, there were 6 to 10 cases per yr in the U.S. caused by OPV. Since 2000, only inactivated polio vaccine (IPV) has been used in the U.S.

PREDOMINANT AGE: Almost always infants or young children

GENETICS

NEONATAL INFECTION: Most cases occur in otherwise healthy infants who receive OPV, or their contacts.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Exposure of a nonimmune host to poliovirus usually results in asymptomatic infection.
- A small percentage of individuals may have one of three presentations after an incubation period of 7 to 14 days:
  1. Abortive poliomyelitis: A flulike illness
     a. Fever
     b. Malaise
     c. Headache
     d. Sore throat
  2. Nonparalytic poliomyelitis: An aseptic meningitis that correlates with invasion of the central nervous system (CNS)
     a. Headache
     b. Neck stiffness
     c. Change in mental status
  3. Paralytic poliomyelitis
     a. Most commonly affects the lumbar or bulbar regions
     b. Following paralysis, a period of variable degrees of recovery, the majority of which occurs in 2 to 6 mo
     c. Paralysis from involvement of motor neurons in the spinal cord
     d. Flaccid paralysis without sensory defects
     e. Postpolio syndrome late sequelae, which may occur many yr after the acute illness
     f. Functional deterioration of muscle groups that had recovered from initial paralysis thought to result from failure of reinnervation, which initially was able to restore function to weakened or paralyzed areas

ETIOLOGY

- Virus of genus *Enterovirus* (three serotypes of polio virus [types 1 to 3]).
- Classic endemic and epidemic disease caused by wild-type poliovirus.
- Due to vaccination efforts, there have been no endemic polio cases in the Western Hemisphere since 1991. Only 33 cases occurred worldwide in 2018. India and Nigeria reported their last cases of polio in 2014.
- Only two nations remain with endemic polio: Pakistan and Afghanistan.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Guillain-Barré syndrome
- Cerebrovascular accident (CVA)
- Botulism food poisoning
- Spinal cord compression
- West Nile virus
- Other nonpolio enteroviruses such as Enterovirus A71 and Enterovirus D68: The cause of acute flaccid myelitis
  1. Aseptic meningitis
  2. Paralysis (rare)

WORKUP

- Isolation of virus:
  1. Stool or a rectal swab
  2. Throat swabs
  3. Rarely cerebrospinal fluid (CSF)
- Paired sera for antibody titer determinations for each of the three serotypes, but serologic tests cannot distinguish between wild-type virus and vaccine-virus infection.
- Gold standard is now a polymerase chain reaction (PCR) on CSF.

LABORATORY TESTS

CSF:

- Aseptic meningitis
- Elevated WBCs
- Elevated protein
- Normal glucose
- PCR for enterovirus

IMAGING STUDIES

MRI may show involvement of anterior horn of the spinal cord.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Maintenance of respiration and hydration
- Early mobilization and exercise once fever subsides

ACUTE GENERAL Rx

- Aimed at reduction of pain and muscle spasm
- No agent to alter the course of disease

CHRONIC Rx

Physical therapy

DISPOSITION

- In the abortive and nonparalytic forms, complete recovery
- Paralytic disease:
  1. Variable degrees of recovery
  2. 80% usually in the first 6 mo following illness

REFERRAL

Always refer to an infectious disease consultant. Cases should be reported to public health agencies.

PEARLS & CONSIDERATIONS

COMMENTS

- Risk of disease in recipients of OPV is approximately 1 in 2.5 million.
- Use of IPV is not associated with disease:
  1. Does not confer local (mucosal) immunity.
  2. Will not immunize nonvaccinated contacts.
  3. Requires boosters.
  4. Is given by injection.
- To decrease the incidence of vaccine-associated polio, the routine childhood vaccination schedule in the U.S. was changed to immunization with four doses of inactivated poliovirus vaccine at 2, 4, and 6 mo through 18 mo and 4 through 6 yr of age. Exclusive use of IPV is now recommended. OPV use is limited to unvaccinated persons with plans for imminent (<4 wk) travel to polio-endemic areas but is not available in the U.S.
- Postpolio syndrome (PPS): Consists of new or progressive muscle weakness and disability of unclear etiology decades after development of acute poliomyelitis.
- Acute flaccid myelitis (AFM): A polio-like illness was described in the U.S. in 2014 to 2015 and starts as a febrile or respiratory illness followed by limb weakness, variable cranial nerve abnormalities, and MRI evidence of gray matter involvement of spinal cord. AFM appears to be temporally related to an enterovirus D68 infection.

RELATED CONTENT

Poliomyelitis (Patient Information)
Postpoliomyelitis Syndrome (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

American Academy of Pediatrics Committee on Infectious Diseases: Poliovirus, *Pediatrics* 128(4):805, 2011.

Bitnun A, Yeh EA: Acute flaccid paralysis and enteroviral infections, *Curr Infect Dis Rep* 20:34, 2018.

Blake IM et al: Type 2 poliovirus detection after global withdrawal of trivalent oral vaccine, *N Engl J Med* 379:834-845, 2018.

Cochi SL et al: Global polio eradication initiative: lessons learned and legacy, *J Infect Dis* 210(Suppl 1):S540-S546, 2014.

Ghafoor S, Sheikh N: Eradication and current status of poliomyelitis in Pakistan: ground realities, *J Immunol Res* 2016: 6837824, 2016.

Lopalco PL: Wild and vaccine-derived poliovirus circulation, and implications for polio eradication, *Epidemiol Infect* 145:413-419, 2017.

Polyarteritis Nodosa

BASIC INFORMATION

DEFINITION

Polyarteritis nodosa (PAN) is a systemic vasculitic syndrome involving medium-sized to small arteries, characterized histologically by necrotizing inflammation of the arterial media and inflammatory cell infiltration. It is not associated with antineutrophil cytoplasmic antibodies (ANCA).

SYNONYMS

Periarteritis nodosa
PAN
Necrotizing arteritis

ICD-10CM CODE
M30.0 Polyarteritis nodosa

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence is 1/100,000 persons annually
- Increased incidence in patients with hepatitis B surface antigen or hepatitis C virus
- There is no gender predilection
- Commonly occurs between age 40 to the mid-60s
- Can also occur in children
- No racial predilection is observed
- Prevalence is 2 to 33/1,000,000
- Is also associated with hairy cell leukemia

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typical presentation is subacute in >90% of cases
- Weight loss
- Nausea, vomiting, headache
- Testicular pain or tenderness (more commonly seen in hepatitis B infection)
- Myalgias, weakness, or leg tenderness in 24% to 80% of cases
- Neuropathy (mononeuritis multiplex), foot drop
- Cutaneous manifestations like tender nodules, livedo reticularis, palpable purpura, ulceration of digits
- Abdominal pain after meals, hematemesis, hematochezia, occasionally with diarrhea and gastrointestinal bleeding in severe cases
- Liver function abnormalities
- Asymmetric polyarthritis (tending to involve large joints of lower extremities); true synovitis occurs only in a minority of patients
- Presence of lung vasculitis suggests other causes
- Fever (PAN is often a cause of fever of unknown origin) can range from intermittent, low-grade fevers to high fevers with chills
- Chest pain secondary to ischemic infarcts in the coronary arteries, pericarditis, cardiomyopathy, and arrhythmias are seen with cardiac involvement
- Tachycardia is common and often striking
- Hypertension secondary to renal ischemia, perirenal hematomas

ETIOLOGY

- Unknown.
- Hepatitis B virus (HBV)–associated PAN appears to be an immune complex–mediated disease.
- Hepatitis C, hairy cell leukemia, and human immunodeficiency virus are also associated in some cases.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cryoglobulinemia
- Systemic lupus erythematosus
- Infections (e.g., subacute bacterial endocarditis, trichinosis, *Rickettsia*)
- Blood dyscrasias (hyperviscosity syndrome)
- Henoch-Schönlein purpura (immunoglobulin A [IgA] vasculitis)
- Granulomatosis with polyangiitis (Wegener granulomatosis)
- Microscopic polyangiitis
- Kawasaki disease
- Eosinophilic granulomatosis with polyangiitis (EGPA)
- Giant cell arteritis
- Human immunodeficiency virus
- Drug-induced vasculitis
- Ergot toxicity
- Occupational hazards

WORKUP

Laboratory evaluation, arteriography, and biopsy of small or medium-sized arteries can confirm diagnosis. Clinical manifestations are variable and depend on the arteries involved and the organs affected (e.g., kidney involvement occurs in >80% of cases). Table E1 summarizes investigations for patients with suspected PAN.

The presence of any three of the following 10 items allows the diagnosis of PAN with a sensitivity of 82% and a specificity of 86%:

1. Weight loss >4 kg
2. Livedo reticularis
3. Testicular pain or tenderness

TABLE E1 Investigations for Patients with Suspected Polyarteritis Nodosa (PAN)

Test	Supports Diagnosis of PAN	Supports an Alternative Diagnosis	Comment
Elevated C-reactive protein	+		Supports the presence of systemic inflammation
Elevated sedimentation rate	+		Supports the presence of systemic inflammation
Elevated serum creatinine	+/–	+/–	Raised serum creatinine, typically without hematuria or proteinuria on urinalysis, may indicate renal ischemia or infarction. Significant proteinuria or hematuria (especially red cell casts) would suggest glomerular disease, which is *not* a feature of PAN
Abnormal liver function tests	+		May suggest hepatitis, either from HBV or as a result of ischemic hepatitis from PAN affecting the hepatic arteries
Positive HBV serology	+		Seen in HBV PAN
Anemia	+		Due to chronic inflammation or from gastrointestinal blood loss
Positive ANCA		+	A positive ANCA would suggest an alternative type of vasculitis such as granulomatosis with polyangiitis or MPA
Elevated creatine kinase	+/–	+/–	Normal or mildly elevated, despite any muscle involvement
Blood cultures		+	To exclude endocarditis or other infective mimic of vasculitis
Positive HCV serology and cryoglobulins		+	HCV associated with a skin limited manifestation of PAN, but typically it is associated with a small vessel vasculitis related to cryoglobulinemia
Positive rheumatoid factor and ACPA		+	To rule out rheumatoid arthritis, especially in the context of a patient presenting predominantly with arthritis
Positive ANA and anti-dsDNA		+	In patients with clinical features consistent with SLE or other connective tissue disease
HIV positive		+	

ACPA, Anticitrullinated protein antibody; *ANA,* antinuclear antibody; *ANCA,* antineutrophil cytoplasm antibody; *dsDNA,* double-stranded deoxyribonucleic acid; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HIV,* human immunodeficiency virus; *MPA,* microscopic polyangiitis; *SLE,* systemic lupus erythematosus.

4. Myalgias, weakness, or leg tenderness
5. Neuropathy
6. New-onset diastolic blood pressure >90 mm Hg
7. Elevated blood urea nitrogen (BUN) or creatinine
8. Positive test for hepatitis B virus
9. Arteriography revealing small or large aneurysms and focal constrictions between dilated segments
10. Biopsy of small or medium-sized artery containing necrotizing inflammatory infiltrate

LABORATORY TESTS

- Elevated BUN or creatinine, positive test for hepatitis B virus or hepatitis C.
- Elevated erythrocyte sedimentation rate and C-reactive protein, anemia, elevated platelets, eosinophilia, proteinuria, hematuria.
- Biopsy of small or medium-sized artery of symptomatic sites (muscle, nerve) is >90% specific. Biopsy of the gastrocnemius muscle and sural nerve is commonly performed.
- Circumferential or segmental vessel wall involvement with necrotizing mixed cell inflammation with fibrinoid necrosis is characteristic lesion of active PAN.
- Assays for antinuclear antibody and rheumatoid factor are negative; however, low, nonspecific titers may be detected.
- Serum and urine immunofixation electrophoresis for monoclonal gammopathy and human immunodeficiency virus should also be tested for alternative diagnoses.

IMAGING STUDIES

Arteriography can be done in patients with negative biopsies or if there are no symptomatic sites. Mesenteric angiography will reveal aneurysmal dilation of the renal, mesenteric (Fig. E1), or hepatic arteries. Less invasive techniques, such as computed tomography (CT) and MRI angiography, also help evaluate the extent and resolution of the disease.

Nerve conduction studies are useful in patients with neuropathy suggesting PAN, helping to evaluate nerves or muscles to biopsy.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Low-sodium diet in hypertensive patients

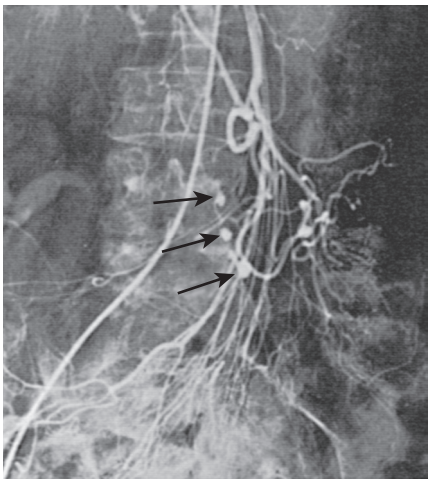

FIG. E1 Superior mesenteric arteriogram in patients with polyarteritis. Several small aneurysms *(arrows)* are present in branches of superior mesenteric artery. (Courtesy Dr. A.W. Stanson. From Harris ED et al: *Kelley's textbook of rheumatology,* ed 7, 2005, WB Saunders.)

ACUTE GENERAL Rx

- Prednisone 1mg/kg/day with higher doses initially, then tapering the doses slowly with overall course of average 9 mo or longer.
- Patients with isolated cutaneous involvement may be treated with steroids alone or in combination with methotrexate or azathioprine.
- Severe PAN with multi-organ involvement treated with a combination of cyclophosphamide 1.5 to 2 mg/kg per day and glucocorticoids has shown good disease outcomes. Once patient achieves stable remission, transition to a less toxic immunomodulatory therapy such as methotrexate or azathioprine, along with tapering doses of oral prednisone, is indicated for chronic therapy.
- In conditions where the disease is resistant to cyclophosphamide glucocorticoids, pulse steroids for few months then switching to alternate agents such as mycophenolate, azathioprine, or methotrexate is tried.
- If hepatitis B is identified, then appropriate antiviral treatment (interferon alpha-2b or lamivudine with or without plasma exchange) is initiated.
- Plasma exchange has been shown to have a limited role in treatment of severe forms of acute hepatitis B–associated PAN.

CHRONIC Rx

Monitoring for infections and potential complications such as thrombosis, infarction, or organ necrosis. Hypertension in patients with renal involvement in PAN is treated with angiotensin-converting enzyme inhibitor.

DISPOSITION

The 5-yr survival is <15% in untreated patients. Treatment with corticosteroids increases survival to approximately 50%. Use of both corticosteroids and immunosuppressive drugs may increase 5-yr survival to >80%. Poor prognostic signs are severe renal or gastrointestinal involvement. Prognosis is better in patients with cutaneous PAN without systemic involvement and in hepatitis B virus (HBV)–associated PAN than for non–HBV-associated disease. Patients on cyclophosphamide should have regular white cell count monitoring for leukopenia. Cyclophosphamide can cause increased risk of infertility, myelodysplasia, lymphoma, bladder malignancy, and when given in combination of high-dose corticosteroids can predispose patients to infection with *Pneumocystis jiroveci (carinii)* pneumonia. Therefore, close follow-up and PCP prophylaxis are recommended.

REFERRAL

Patients with suspected diagnosis of PAN should be immediately referred to a rheumatologist.

PEARLS & CONSIDERATIONS

- After treatment, patients should be followed up closely for relapse throughout their lifetime.
- Smoking cessation, exercise, and lifestyle modifications should be discussed to decrease vascular complications.

AUTHORS: **Sarah Aziz, DO Candidate,** and **Syeda M. Sayeed, MD**

BASIC INFORMATION

DEFINITION

Polycystic ovary syndrome (PCOS) is characterized by an accumulation of incompletely developed follicles in the ovaries due to anovulation and associated with ovarian androgen production. In its complete form, it is associated with polycystic ovaries, amenorrhea, hirsutism, and obesity. Criteria for PCOS according to published definitions are described in Table 1.

SYNONYMS

Polycystic ovarian syndrome
Stein-Leventhal syndrome
PCOS

ICD-10CM CODE
E28.2 Polycystic ovarian syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- 6% to 25% of reproductive-age women (most common endocrine disorder in this population).
- Symptoms usually begin around the time of menarche, and the diagnosis is often made during adolescence or young adulthood.
- Increased risk of endometrial and ovarian cancers.
- PCOS is the most common cause of anovulatory infertility.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Oligomenorrhea or amenorrhea
- Dysfunctional uterine bleeding
- Infertility
- Hirsutism
- Acne, alopecia, acanthosis nigricans (Fig. E1)
- Obesity (40% only), predominantly abdominal obesity
- Insulin resistance (type 2 diabetes mellitus)
- Hypertension

ETIOLOGY & PATHOGENESIS

Elevated serum luteinizing hormone (LH) concentrations and an increased serum LH/follicle-stimulating hormone (FSH) ratio result either from an increased gonadotropin-releasing hormone hypothalamic secretion or less likely from a primary pituitary abnormality. This results in dysregulation of androgen secretion and increased intraovarian androgen, the effect of which in the ovary is follicular atresia, maturation arrest, polycystic ovaries, and anovulation. Hyperinsulinemia is a contributing factor to ovarian hyperandrogenism, independent of LH excess. A role for insulin growth factor (IGF) receptors has been postulated for the association of PCOS and diabetes. Fig. E2 illustrates the pathologic mechanisms in PCOS.

DIAGNOSIS

The diagnosis of PCOS excludes secondary causes (androgen-producing neoplasm, hyperprolactinemia, adult-onset congenital adrenal hyperplasia).

Clinical:

- The symptoms, signs, and biochemical features of PCOS vary greatly among women and may change over time.
- PCOS is the most common cause of chronic anovulation with estrogen present. A positive progesterone withdrawal test establishes the presence of estrogen. Medroxyprogesterone (Provera) 10 mg qd is administered for 5 days and bleeding occurs if estrogen is present.
- The presence of oligomenorrhea, hirsutism, obesity, and documented polycystic ovaries establishes the diagnosis.

DIFFERENTIAL DIAGNOSIS

Causes of amenorrhea:

- Primary (unusual in PCOS):
  1. Genetic disorder (Turner syndrome)
  2. Anatomic abnormality (e.g., imperforate hymen)
- Secondary:
  1. Pregnancy
  2. Functional (cause unknown, anorexia nervosa, stress, excessive exercise, hyperthyroidism, less commonly hypothyroidism, adrenal dysfunction, pituitary dysfunction, severe systemic illness, drugs such as oral contraceptives, estrogens, or dopamine agonists)
  3. Abnormalities of the genital tract (uterine tumor, endometrial scarring, ovarian tumor)

LABORATORY TESTS

- Glucose tolerance test at the initial presentation and every 2 yr thereafter (rule out diabetes mellitus). Impaired glucose tolerance is very common, occurring in approximately 30% of women with PCOS
- Fasting lipid panel (rule out dyslipidemia), alanine aminotransferase, aspartate aminotransferase (rule out hepatic steatosis)
- Elevated LH/FSH ratio >2.5
- Prolactin level elevation in 25%
- Elevated androgens (testosterone [free and total levels], DHEA-S) (rule out androgen-secreting tumor)
- Other: Thyroid-stimulating hormone (rule out hypothyroidism), 17-hydroxyprogesterone (rule out congenital adrenal hyperplasia), 24-hr urine for cortisol and creatinine (rule out Cushing syndrome)
- TSH
- Table 2 summarizes laboratory testing to exclude other causes of ovulatory dysfunction and hyperandrogenism

IMAGING STUDIES

Pelvic ultrasound (Fig. E3) reveals the presence of twofold to fivefold ovarian enlargement with a thickened tunica albuginea, thecal hyperplasia, and 20 or more subcapsular follicles from 1 to 15 mm in diameter. It is important to note that having polycystic ovaries alone does not make the diagnosis of PCOS because 20% of women with polycystic ovaries have no symptoms.

TREATMENT

The goal is to interrupt the self-perpetuating abnormal hormone cycle:

- Reduction of ovarian androgen secretion by laparoscopic ovarian wedge resection. Laparoscopic ovarian surgery (laparoscopic ovarian drilling [LOD]) is a useful alternative that does not trigger ovarian hyperstimulation.

TABLE 1 Criteria for Polycystic Ovary Syndrome According to Published Definitions

	NICHD/NIH/1990	Rotterdam 2003	AE-PCOS/2009
Diagnostic criteria	Requires simultaneous presence of: • Clinical and/or biochemical hyperandrogenism • Menstrual dysfunction	Requires the presence of at least two criteria: • Clinical and/or biochemical hyperandrogenism • Ovulatory dysfunction • PCOM	Requires the presence of: • Hyperandrogenism and/or hyperandrogenemia • Ovarian dysfunction: Oligoovulation or anovulation and/or polycystic ovaries
Exclusion criteria	Congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome, and hyperprolactinemia	Congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing syndrome	21-hydroxylase-deficient nonclassic adrenal hyperplasia, androgen-secreting neoplasms, androgenic–anabolic drug use or abuse, the hyperandrogenic-insulin resistance-acanthosis nigricans syndrome, thyroid dysfunction, and hyperprolactinemia
Clinical traits	Hirsutism, acne, and alopecia	Hirsutism, acne, and androgenic alopecia	Hirsutism
PCOM	Not included	At least one ovary showing either: • Twelve or more follicles of 2-9 mm in diameter • Ovarian volume, 10 ml	At least one ovary showing either: • Twelve or more follicles of 2-9 mm in diameter • Ovarian volume, 10 ml

AE-PCOS, Androgen Excess and PCOS Society; *NICHD/NIH,* National Institute for Child Health and Human Development/National Institutes of Health; *PCOM,* polycystic ovarian morphology.
From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.

TABLE 2 Laboratory Testing to Exclude Other Causes of Ovulatory Dysfunction and Hyperandrogenism

Lab	Evaluation for:	Comment
Total and/or bioavailable testosterone	Androgen-secreting tumor	Measure if there are symptoms concerning for an androgen-secreting tumor or if biochemical evidence of hyperandrogenism is needed to make the diagnosis of polycystic ovary syndrome. Rapid progression or a total testosterone >200 ng/dl should prompt a workup for an androgen-secreting tumor.
Dehydroepiandrosterone sulfate	Androgen-secreting tumor	Measure if there are symptoms concerning for an androgen-secreting tumor. Although modest elevations in dehydroepiandrosterone sulfate can be seen in polycystic ovary syndrome, rapid progression or greater elevations should prompt a workup for an adrenal androgen-secreting tumor.
Morning 17-hydroxyprogesterone	Late-onset congenital adrenal hyperplasia	This disorder is caused by a partial adrenal enzyme defect that leads to impaired cortisol production, compensatory elevation in adrenocorticotropic hormone, and subsequent excess androgen production. Symptoms may mimic polycystic ovary syndrome. Normal values <200 ng/dl. If higher than this, adrenocorticotropic hormone stimulation test recommended.
24-hour urine for cortisol and creatinine; dexamethasone suppression test; salivary cortisol	Cushing syndrome	Consider ruling out Cushing syndrome in women with an abrupt change in menstrual pattern, later-onset hirsutism, or other evidence of cortisol excess such as hypertension, facial plethora, supraclavicular fullness, hyperpigmented striae, and fragile skin.
Prolactin	Hyperprolactinemia	May be accompanied by galactorrhea. Consider ruling this out in all women with irregular menstrual cycles.
Thyroid function studies	Hyperthyroidism or hypothyroidism	Consider ruling out thyroid dysfunction in all women with irregular menstrual cycles.

From Setji TL, Brown AJ: Polycystic ovary syndrome: update on diagnosis and treatment, *Am J Med* 127:912-919, 2014.

- Reduction of ovarian androgen secretion by using oral contraceptives or LH-releasing hormone (LHRH) analogs.
- Weight reduction for all obese women with PCOS. Loss of abdominal fat seems to be crucial to restore ovulation.
- FSH stimulation with clomiphene HMG or pulsatile LHRH.
- Urofollitropin (pure FSH) administration.
- Metformin improves ovulation, insulin sensitivity, and possibly hyperandrogenemia.

Choice of treatment:

- The management of hirsutism without risking pregnancy includes oral contraceptives, glucocorticoids, LHRH analogs, or spironolactone (an antiandrogen). Finasteride and flutamide may be similarly effective in reducing hirsutism as spironolactone.
- Pregnancy can be achieved with clomiphene (alone or with glucocorticoids, human chorionic gonadotropin, or bromocriptine), HMG, urofollitropin, pulsatile LHRH, or ovarian wedge resection. Metformin may also induce ovulation. Recent trials comparing the aromatase inhibitor letrozole to clomiphene for infertility have shown higher live-birth and ovulation among infertile women with PCOS treated with letrozole. When considering in vitro fertilization (IVF), the transfer of fresh embryos is generally preferred over the transfer of frozen embryos; however, a recent trial among infertile women with PCOS undergoing IVF revealed that frozen-embryo transfer is associated with a higher rate of live birth, a lower risk of the ovarian hyperstimulation syndrome, and a higher risk of preeclampsia after the first transfer than with fresh-embryo transfer.[1]
- Psychological screening for depression is recommended. Women with PCOS are fourfold more likely to have abnormal depression scores.
- Table 3 describes a mnemonic for assessment and management of PCOS.

[1] Chen ZJ et al: Fresh versus frozen embryos for infertility in the polycystic ovary syndrome, *N Engl J Med* 375:523-533, 2016.

DISPOSITION

Table 4 summarizes metabolic complications in PCOS.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Polycystic Ovarian Syndrome (Patient Information)
Amenorrhea (Related Key Topic)
Abnormal Uterine Bleeding (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

TABLE 3 MY PCOS: Mnemonic for Assessment and Management of Polycystic Ovary Syndrome (PCOS)

	Assessment	Management
Metabolic	2-hour glucose tolerance test with 75 grams oral glucose, measuring serum glucose at time 0 and 120 min. Lipid profile Liver function tests (if other risk factors for nonalcoholic fatty liver disease)	Lifestyle intervention: Diet, exercise, and weight loss (if overweight or obese) Metformin for abnormal glucose tolerance not controlled with lifestyle Statin therapy if patient meets criteria (Adult Treatment Panel-III or American College of Cardiology/American Heart Association guidelines)
Cycle control	Ask about menstrual pattern; normal cycle length is 28 days (range 21-35)	If amenorrhea for 3 months or more, induce withdrawal bleed with progesterone (after negative pregnancy test) Hormonal therapy Examples: • Estrogen-containing oral contraceptives (monthly cycling, seasonal cycling, continuous use) • Vaginal ring • Patch • Progestin-only pill (smokers, hypertension) • Progestin-eluting intrauterine device (Mirena) • Progesterone prn to induce withdrawal bleeding (medroxyprogesterone acetate 10 mg daily for 10-14 days, micronized progesterone 400 mg daily for 10-14 days) • Metformin (second-line therapy)
Psychosocial	Screen for depression, disordered eating Affirm that polycystic ovary syndrome is an important medical issue; provide nonjudgmental support Discuss stress management Reinforce self-care behaviors	Mental health referral and/or antidepressant therapy may be warranted if depression or disordered eating is identified
Cosmetic	Ferriman-Gallwey score as guide to assess hirsutism Evaluate for acne and male pattern hair loss Serum androgen levels if uncertain about degree of hirsutism or atypical symptoms	Estrogen-containing hormonal contraception Antiandrogens such as spironolactone or finasteride. Teratogenic; only use with contraception Cyproterone acetate (not available in the U.S.) Eflornithine hydrochloride 13.9% cream Laser or electrolysis Topical treatment for acne Minoxidil 2.5% or 5% for male pattern hair loss
Ovulation and fertility	Counsel that fertility is reduced in polycystic ovary syndrome, but patients typically not infertile Assess fertility goals	If subfertility is an issue, consider referral to Reproductive Endocrine for possible clomiphene citrate therapy Metformin has limited role
Sleep apnea	Screen for sleep apnea: Daytime somnolence, morning headache, reflux symptoms, snoring, observed interrupted breathing	Refer for sleep study Continuous positive airway pressure therapy recommended if sleep apnea diagnosed

PCOS, Polycystic ovary syndrome.
From Setji TL, Brown AJ: Polycystic ovary syndrome: Update on diagnosis and treatment, *Am J Med* 127:912-919, 2014.

TABLE 4 Metabolic Complications in Polycystic Ovary Syndrome

Abnormal glucose tolerance (impaired glucose tolerance or type 2 diabetes)	30% of obese polycystic ovary syndrome women have impaired glucose tolerance, and 10% have type 2 diabetes by age 40. In thin women with polycystic ovary syndrome, 10% have impaired glucose tolerance, and 1.5% have type 2 diabetes.
Obesity	Prevalence of obesity varies considerably in women with polycystic ovary syndrome. Previously, prevalence rates of obesity were estimated based on populations of women with polycystic ovary syndrome seeking care. A recent study comparing patients presenting for care in a polycystic ovary syndrome clinic with an unselected population evaluated during a preemployment physical suggests that obesity and overweight may not be more common in polycystic ovary syndrome. In that study, 63.7% of polycystic ovary syndrome clinic patients were obese, compared with 28% of unselected women with polycystic ovary syndrome identified during screening, and 28% of nonpolycystic ovary syndrome controls. Polycystic ovary syndrome symptoms, including hyperandrogenism and oligo-ovulation, are exacerbated by obesity.
Metabolic syndrome	33%-50% of U.S. women with polycystic ovary syndrome have metabolic syndrome compared to only 12% in a similarly aged National Health and Nutrition Examination Survey population. In contrast, only 8.2% of women with polycystic ovary syndrome in Italy met criteria for metabolic syndrome. Thus, metabolic syndrome varies by geographic location, a finding likely related to different body mass index, though other causes including genetics and diet could also be playing a part.
High blood pressure	Data have been conflicting, but a large Kaiser Permanente study demonstrated that hypertension or elevated blood pressure was more than twice as common in women with polycystic ovary syndrome (27% vs. 12%).
Dyslipidemia	Dyslipidemia is more prevalent in women with polycystic ovary syndrome compared to controls (15% vs. 6%). In a meta-analysis, triglyceride values were 26 mg/dl higher (95% CI 17-35), low-density lipoprotein cholesterol was 12 mg/dl higher (95% CI 10-16), and high-density lipoprotein-cholesterol was 6 mg/dl lower (95% CI 4-9) in women with polycystic ovary syndrome compared with controls. Women with polycystic ovary syndrome also have higher concentrations and proportions of small, dense low-density lipoprotein cholesterol.
Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis	Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis have recently been recognized as a potential complication in women with polycystic ovary syndrome. Prevalence of fatty liver disease in polycystic ovary syndrome women has been estimated to be 15%-55%, depending on the diagnostic parameter used (level of serum alanine aminotransferase or ultrasound). Individuals that may be at higher risk of nonalcoholic fatty liver disease including nonalcoholic steatohepatitis include those with metabolic syndrome, insulin resistance, and possibly hyperandrogenemia.
Cardiovascular disease	Many studies demonstrate abnormal surrogate markers of cardiovascular disease in women with polycystic ovary syndrome. However, data regarding cardiovascular disease risk are conflicting with some studies suggesting an increased risk in women with polycystic ovary syndrome, whereas other studies have not found this difference in cardiovascular risk. While it is important to recognize and treat cardiovascular risk factors in this population, further research of cardiovascular risk and complications is still needed to clarify the long-term risk.

CI, Confidence interval.
From Setji TL, Brown AJ: Polycystic ovary syndrome: update on diagnosis and treatment, *Am J Med* 127:912-919, 2014.

SUGGESTED READINGS

Dokras AS et al: Increased risk for abnormal depression scores in women with polycystic ovary syndrome: a systematic review and meta-analysis, *Obstet Gynecol* 117(1):145-152, 2011.

Legro RS et al: Letrozole versus clomiphene for infertility in the polycystic ovary syndrome, *N Engl J Med* 371:119-129, 2014.

McCartney CR, Marshall JC: Clinical practice: polycystic ovary syndrome, *N Engl J Med* 375:54-64, 2016.

Setji TL, Brown AJ: Polycystic ovary syndrome: update on diagnosis and treatment, *Am J Med* 127:912-919, 2014.

Wilson JF: In the clinic: the polycystic ovary syndrome, *Ann Intern Med* 154(3): ITC2-2–ITC2-15; quiz ITC2-16, 2011.

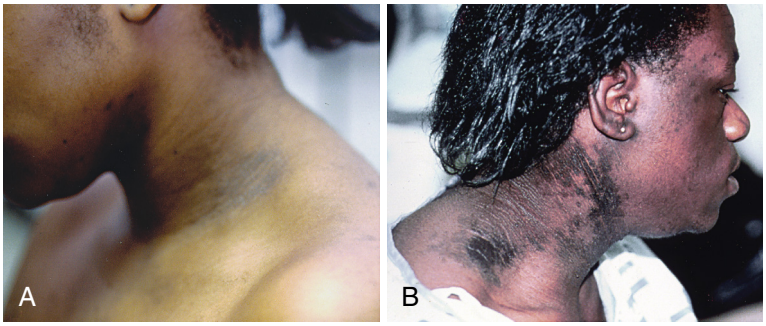

FIG. E1 Acanthosis nigricans. A, Moderate acanthosis nigricans (i.e., darkening and thickening of skin) at the lateral lower fold of the neck. Notice facial hirsutism (sideburns) in the same patient. **B,** Severe acanthosis nigricans in another patient with severe insulin resistance. (**B,** Courtesy Dr. R. Ann Word, Dallas, Texas. From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

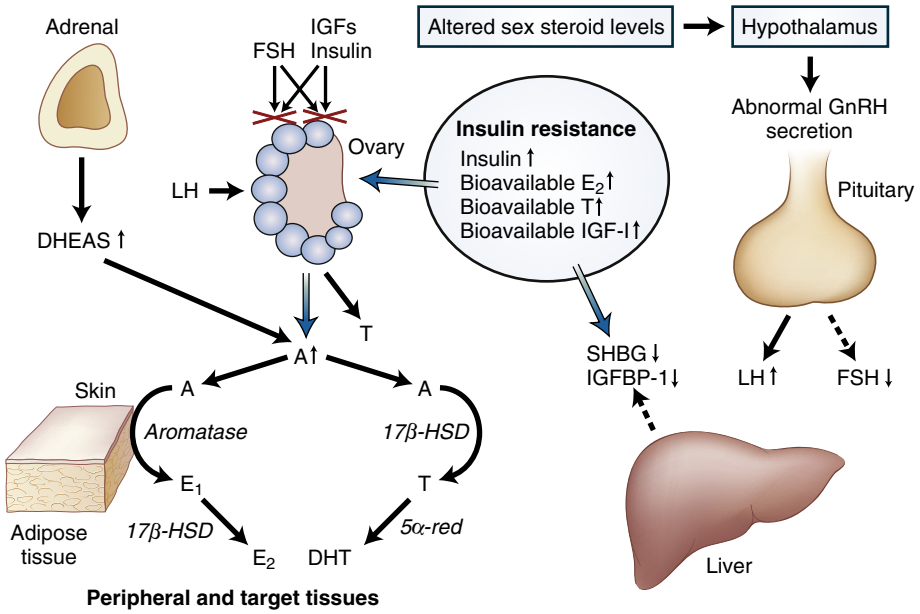

FIG. E2 Pathologic mechanisms in polycystic ovary syndrome (PCOS). A deficient in vivo response of the ovarian follicle to physiologic quantities of follicle-stimulating hormone *(FSH),* possibly because of an impaired interaction between signaling pathways associated with FSH and insulin-like growth factors *(IGFs)* or insulin, may be an important defect responsible for anovulation in PCOS. Insulin resistance associated with increased circulating and tissue levels of insulin and bioavailable estradiol *(E2),* testosterone *(T),* and IGF1 gives rise to abnormal hormone production in a number of tissues. Oversecretion of luteinizing hormone *(LH)* and decreased output of FSH by the pituitary, decreased production of sex hormone–binding globulin *(SHBG)* and IGF-binding protein 1 *(IGFBP-1)* in the liver, increased adrenal secretion of dehydroepiandrosterone sulfate *(DHEAS),* and increased ovarian secretion of androstenedione *(A)* all contribute to the feed-forward cycle that maintains anovulation and androgen excess in PCOS. Excessive amounts of E_2 and T arise primarily from the conversion of A in peripheral and target tissues. T is converted to the potent steroids estradiol or DHT (dihydrotestosterone). Reductive 17β-hydroxysteroid dehydrogenase (17β-HSD) enzyme activity may be conferred by protein products of several genes with overlapping functions; 5α-reductase (5α-red) is encoded by at least two genes, and aromatase is encoded by a single gene. *GnRH,* Gonadotropin-releasing hormone. (From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

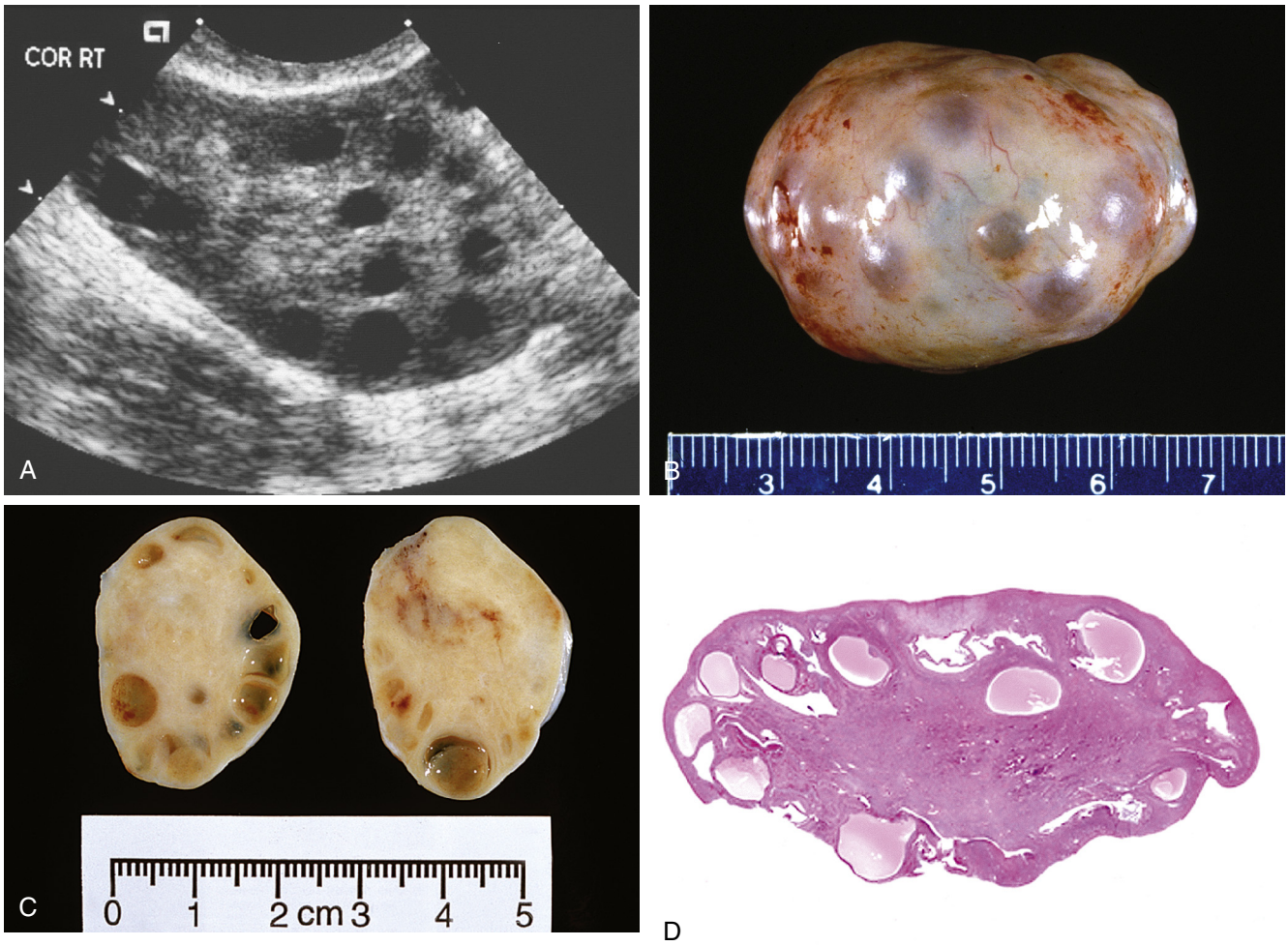

FIG. E3 **A,** Ultrasonography of polycystic ovaries depicting numerous cysts. **B,** Gross appearance of polycystic ovaries. Numerous follicles can be appreciated beneath the capsule. **C,** Cross section of **B** illustrates subcortical cystic follicles. **D,** Low-power microphotograph exhibits combination of cystic follicles and fibrotic ovarian cortex. (From Crum CP et al: *Diagnostic gynecologic and obstetric pathology,* ed 3, Philadelphia, 2018, Elsevier.)

BASIC INFORMATION

DEFINITION

Polycythemia vera is a clonal disorder of aberrant myeloid/erythroid stem cells resulting in erythropoietin-independent proliferation of erythrocytes.

SYNONYMS

PV
Primary polycythemia

ICD-10CM CODE
D45 Polycythemia vera

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- 1 case per 100,000 persons
- Occurs most commonly in patients ages 50 to 75 yr
- Mean age at onset is 60 yr; men are affected more often than are women

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Polycythemia vera has a latent, proliferative, and spent phase. The patient generally comes to medical attention because of symptoms associated with increased blood volume and viscosity or impaired platelet function:

- Impaired cerebral circulation resulting in headache, vertigo, blurred vision, dizziness, transient ischemic attack, cerebrovascular accident
- Fatigue, poor exercise tolerance
- Pruritus, particularly after bathing (caused by overproduction of histamine)
- Bleeding: Epistaxis, upper gastrointestinal bleeding (increased incidence of peptic ulcer disease)
- Abdominal discomfort from splenomegaly; hepatomegaly may be present
- Hyperuricemia may result in nephrolithiasis and gouty arthritis
- Up to 40% of patients experience arterial or venous thrombosis during the course of their disease. Cerebral and splanchnic thrombotic events occur commonly and can be presenting events.

The physical examination may reveal:

- Facial plethora, congestion of oral mucosa, ruddy complexion
- Enlargement and tortuosity of retinal veins
- Erythromelalgia—painful redness, swelling, and warmth of the skin of the hands and feet
- Splenomegaly (found in >75% of patients)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Smoking:

- Polycythemia is caused by increased carboxyhemoglobin, resulting in left shift in the hemoglobin (Hgb) dissociation curve.
- Laboratory evaluation shows increased hematocrit (Hct), RBC mass, erythropoietin level, and carboxyhemoglobin.
- Splenomegaly is not present on physical examination.

Hypoxemia (secondary polycythemia):

- Living for prolonged periods at high altitudes, pulmonary fibrosis, congenital cardiac lesions with right-to-left shunts.
- Laboratory evaluation shows decreased arterial oxygen saturation and elevated erythropoietin level.
- Splenomegaly is not present on physical examination.

Erythropoietin-producing states:

- Renal cell carcinoma, hepatoma, cerebral hemangioma, uterine fibroids, polycystic kidneys.
- The erythropoietin level is elevated in these patients, and the arterial oxygen saturation is normal.
- Splenomegaly may be present with metastatic neoplasms.

Stress polycythemia (Gaisböck syndrome, relative polycythemia):

- Laboratory evaluation demonstrates normal RBC mass, arterial oxygen saturation, and erythropoietin level; plasma volume is decreased.
- Splenomegaly is not present on physical examination.

Hemoglobinopathies associated with high oxygen affinity:

- An abnormal oxyhemoglobin-dissociation curve (P50) is present.

WORKUP

The revised 2016 WHO diagnostic criteria for PV use a hemoglobin/hematocrit level exceeding 16.5 g/dl/49% in men or 16 g/dl/48% in women after secondary causes have been excluded. Initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a biopsy, and this finding may predict a more rapid progression to overt post-polycythemia myelofibrosis.

Janus kinase 2 *(JAK2)* gene mutations are detected in approximately 99% of patients with polycythemia vera and can be used for diagnostic purposes. The exon 14 JAK2V617F mutation is seen in 97% cases and the remainder 3% of JAK2 mutations are spread across exons 12, 13, and 14. Testing for the *JAK2 V617F* mutation with polymerase chain reaction assay is routine. In patients with high hematocrit (>52% in men or >48% in women) and in the absence of coexisting secondary erythrocytosis, the presence of a *JAK2* mutation is sufficient for the diagnosis of polycythemia vera.

The World Health Organization diagnostic criteria for polycythemia vera are described in Table 1.

LABORATORY TESTS

- Elevated RBC count (>6 million/mm^3), elevated Hgb (>18.5 g/dl in men, >16.5 g/dl in women), elevated Hct (<54% in men, <49% in women)
- Increased white blood cell count (often with basophilia; basophilia is a strong predictor of PV instead of a reactive state); thrombocytosis is found in the majority of patients
- Elevated leukocyte alkaline phosphatase, serum vitamin B_{12}, and uric acid levels were used previously but have been supplanted by molecular testing
- Low serum erythropoietin level
- Peripheral blood smear: May reveal basophils or immature myeloid forms
- Bone marrow aspiration revealing RBC hyperplasia and absent iron stores

TREATMENT

NONPHARMACOLOGIC THERAPY

Phlebotomy to keep Hct >45% in men and >42% in women is the mainstay of therapy. Phlebotomy, however, has no effect on the development of myelofibrosis.

TABLE 1 World Health Organization 2016 Diagnostic Criteria for Polycythemia Vera

Major Criteria

- Hemoglobin (Hgb) >16.5 g/dl (men), >16.0 (women); *or* Hematocrit (Hct) >49% (men), >48% (women); *or* elevated red cell mass (>25% above mean normal predicted value)
- BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
- Presence of *JAK2 V617F* or similar mutation

Minor Criterion

- Subnormal serum erythropoietin level

1. Diagnosis of PV requires meeting either all three major criteria, or the first two major criteria and the minor criterion
2. BM biopsy may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dl in men (hematocrit, 55.5%) or >16.5 g/dl in women (hematocrit, 49.5%) if major criterion 3 and the minor criterion are present.

From Arber DA et al: *Blood,* 127(20):2391-2405, 2016.

BOX 1 Algorithm for Management of Patients with Polycythemia Vera

Low-Risk Young Patients (Age <60 Yr) and No History of Thrombosis, Platelet Count <1.5 × 106 mm–3

Phlebotomy + low-dose aspirin (81 mg/day) to maintain hematocrit lower than 45%. Aspirin should not be used in patients with histories of a hemorrhagic episode or with extreme thrombocytosis (>1.5 × 10^6 mm^{-3}) or acquired von Willebrand syndrome.

↓

Thrombosis or hemorrhage
Systemic symptoms
Severe pruritus refractory to histamine antagonists
Painful splenomegaly

↓

Hydroxyurea 15 to 20 mg/kg (unless age <40 yr, pregnant, intolerant to hydroxyurea; consider pegylated interferon [IFN])

↓

Pegylated IFN 45 to 180 μg/wk or IFN-α (3 × 10^6 units three times a week; alter dose depending on response and toxicity) or ruxolitinib 10 mg twice daily and titrate dose depending on the response. →

In a patient with a prior thrombosis or a history of bleeding due to acquired von Willebrand syndrome, normalization of platelet numbers is necessary. If platelet control is inadequate or the patient cannot tolerate interferon, one option is the use of anagrelide. In this case, supplemental phlebotomy is required to maintain hematocrit lower than 45%, and the use of hydroxyurea should be considered, especially if the patient continues to have thrombotic episodes.

↓

If the patient has increasing splenomegaly, systemic symptoms, or repeated thromboses despite adequate dose of hydroxyurea (2 to 3 g/day) or if unable to tolerate hydroxyurea, start ruxolitinib 10 mg twice daily and titrate up or down based on hematologic parameters.

For patients unable to tolerate ruxolitinib or resistant to it, start low doses of busulphan or melphalan, which should be administered until the blood counts are normalized. Therapy should be then discontinued because patients frequently enjoy drug-free prolonged remissions lasting months. Therapy should be reinstituted only at the time the blood counts begin to be elevated again. Such therapy with alkylating agents should be rarely used in young patients. It should be mentioned that the sequential use of hydroxyurea and alkylating agents may be associated with an increased risk of leukemia. Supplemental phlebotomy may be required.

Painful splenomegaly

↓

Patients should be treated with ruxolitinib
If unable to tolerate or insufficient response
Splenectomy + continued systemic therapy

↓

High-risk patients (age >60 yr), previous thrombosis, platelet count >1.5 × 10^6 mm^{-3}
Phlebotomy to hematocrit of 45%
Aspirin (81 mg/day) to be given only in patients with platelet counts <1.5 × 10^6 mm^{-2}
Myelosuppressive therapy with hydroxyurea 30 mg/kg orally for 1 week
Then 15 to 20 mg/kg

↓

If patient continues to have thrombotic episodes and has extreme thrombocytosis or cannot tolerate hydroxyurea

Consider pegylated IFN 45 to 180 μg/week, anagrelide, or ruxolitinib 10 mg twice daily, or add intermittent busulphan or melphalan (in older patients).

If on busulphan or melphalan, stop when blood counts are normalized or platelet count is lower than 300,000 mm^{-3}.

Occasional supplemental phlebotomy if hematocrit is >45%; when patient relapses (patient is symptomatic), initiate busulphan therapy again at same dose.

Patient Age >70 yr

Phlebotomy + low-dose aspirin + hydroxyurea

↓

No response or poor compliance
Ruxolitinib, melphalan, or busulfan.

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

ACUTE GENERAL Rx

- Add aspirin in patients younger than 60 yr without prior thromboembolic event.
- Hydroxyurea can be used in conjunction with phlebotomy in patients older than 60 yr to decrease the incidence of thrombotic events.
- Pegylated interferon-alpha-2b is effective in achieving non-inferior rates of complete hematologic remission compared to hydroxyurea without major side effects and is approved in Europe for initial therapy.
- Box 1 describes an algorithm for management of patients with polycythemia vera.
- Ruxolitinib, a Janus kinase (JAK) 1 and 2 inhibitor, is superior to standard therapy in controlling the hematocrit, reducing the spleen volume and improving symptoms associated with polycythemia vera.

CHRONIC Rx

- Patient education regarding need for lifelong monitoring and treatment.
- Adjunctive therapy: Treatment of pruritus with antihistamines, control of significant hyperuricemia with allopurinol, reduction of gastric hyperacidity with antacids of H_2 blockers, low-dose aspirin to treat vasomotor symptoms in patients without bleeding diathesis. Low-dose aspirin can safely prevent thrombotic complications in patients with polycythemia vera and should be given to all patients in absence of contraindications.

DISPOSITION

- The median survival time without treatment is 6 to 18 mo after diagnosis; phlebotomy extends the average survival time to 12 yr.
- Patients with polycythemia vera with a hematocrit <45% have a significantly lower rate of cardiovascular death and major thrombosis than those with hematocrit of 45% to 50%.
- Prognosis is worse in patients >60 yr and those with a history of thrombosis.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Polycythemia Vera (Patient Information)

AUTHOR: **Bharti Rathore, MD**

SUGGESTED READINGS

Arber DA et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, *Blood* 127(20):2391-2405, 2016.

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BASIC INFORMATION

DEFINITION

Polymyalgia rheumatica (PMR) is an inflammatory condition characterized by neck, shoulder, and pelvic girdle muscle pain and stiffness, which is worse in the morning, and primarily affects the elderly. PMR can occur alone or in conjunction with giant cell arteritis (GCA

SYNONYMS

Anarthritic rheumatoid syndrome
PMR

ICD-10CM CODE

M31.5 Polymyalgia rheumatica with giant cell arteritis
M35.3 Polymyalgia rheumatica

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE: In the U.S., incidence is 52.5 cases per 100,000; increases with advancing age. Prevalence is 0.5% to 0.7%. Scandinavian and Northern European populations have higher incidence.
PREDOMINANT SEX: Female:male ratio of 2:1.
PREDOMINANT AGE: Almost exclusively occurs above age 50, with peak incidence between seventh and eighth decades.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with PMR often have symptoms for 1 to 3 mo before a diagnosis is made.
- Onset of symmetric muscle aching and stiffness, worse in the morning. Stiffness recurs with periods of inactivity.
- Neck, shoulders, lower back, hips, thighs, and occasionally trunk and arms are involved. Shoulders are usually affected first. Pain distribution in PMR is illustrated in Fig. 1.
- Constitutional symptoms of fatigue, malaise, weight loss, loss of appetite, and low-grade fever may accompany pain and stiffness.
- Physical exam may reveal limited range of motion of shoulder (most common), cervical spine, and hips. May have subdeltoid and subacromial bursitis and peripheral joint synovitis. Motor exam is normal, although can be limited by pain.
- High-spiking fevers, night sweats, visual disturbances, headaches, or jaw claudication should raise suspicion of giant cell arteritis and be further evaluated promptly.

ETIOLOGY

The cause is unknown, but both PMR and GCA are associated with HLA-DR4 haplotype. With both conditions, also see elevated Th17 cells and decreased Treg cells.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

See Box 1.

WORKUP

- Initial laboratory evaluation: ESR, CRP, CBC, CPK.
- ESR >40 in majority of patients. CRP elevation may be more common than high ESR.
- CBC may show a normocytic anemia and thrombocytosis.
- CPK is normal. Antibodies (ANA, RF, CCP) are typically negative.
- An algorithm for diagnosing polymyalgia rheumatica without giant cell arteritis (GCA) is described in Fig. E2, and Tables 1 and 2 describe various classification criteria for PMR.
- Ultrasonography, MRI and PET may identify bursitis or tenosynovitis, (features of the 2012 PMR classification of criteria), which increase sensitivity and specificity.

TREATMENT

- Prednisone 15 to 20 mg/day, with dramatic improvement usually within 3 days; up to one third of patients may have incomplete response at 4 weeks.
- Dose adjustment may be necessary for weight, symptom severity, and comorbidities (e.g., diabetes mellitus, hypertension, or heart failure).
- If symptoms persist after 1 week, increase dose by 5 mg. Ongoing symptoms require consideration of alternative diagnosis.
- If nighttime symptoms are bothersome, can try divided dose of prednisone.
- Initial prednisone dose should be maintained for 4 to 8 weeks. Steroid dose is then tapered every 2 to 4 weeks as tolerated to minimum amount required to remain symptom free. When dose reaches 10 mg/day, taper slowly, usually by 1 mg/month.
- Flares are typical during tapering, can manage by increasing prednisone 10% to 20%. Most require treatment for 1 to 2 yr with steroids; others are unable to taper off fully.
- Monitor both clinical response and ESR and CRP intermittently.
- Gastroprotection should be considered, and attention should be paid to bone health, with calcium and vitamin D supplementation started early. Consider prophylactic bisphosphonates if indicated.
- Routine use of adjunctive therapy is not recommended, but certain cases (refractory disease, high-risk steroid use) can consider methotrexate. TNFi has not been shown to have benefit. It has been found more recently that tocilizumab (IL6i) may be beneficial in patients with contraindications to methotrexate use, and was recently approved to treat GCA.

PEARLS & CONSIDERATIONS

Patients with PMR should be monitored closely for the development of GCA. Patients who have incomplete response to prednisone or have an evolving pattern of pain and swelling should be re-evaluated for the possibility of a different diagnosis such as rheumatoid arthritis.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Polymyalgia Rheumatica (PMR) (Patient Information)
Giant Cell Arteritis (Related Key Topic)
Vasculitis, Systemic (Related Key Topic)

AUTHOR: **Daphne Scaramangas-Plumley, MD**

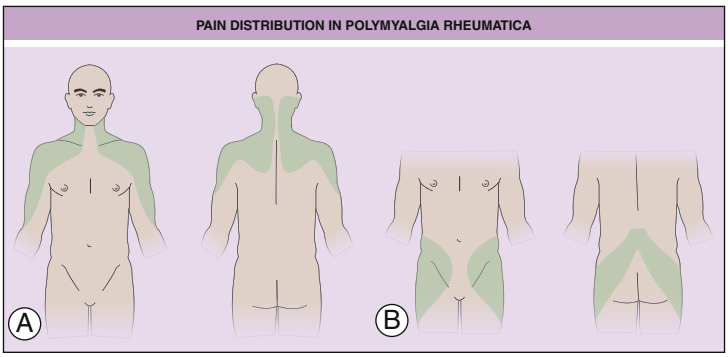

FIG. 1 Typical distribution of pain in patients with polymyalgia rheumatica (PMR). Shaded areas demonstrate typical sites of pain in individuals with PMR, including **(A)** shoulder girdle and neck pain distribution and **(B)** pelvic girdle pain distribution. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

BOX 1 Differential Diagnosis of Polymyalgia Rheumatica

- Rheumatoid arthritis
- Rotator cuff syndrome
- Osteoarthritis of shoulder and hip joints
- Fibromyalgia
- Polymyositis/dermatomyositis
- Spondyloarthritis
- Systemic lupus erythematosus
- Vasculitides
- Paraneoplastic myalgias
- Infection-associated myalgias
- RS3PE (remitting seronegative symmetric synovitis and pitting edema)
- Parkinson disease
- Hypothyroidism

TABLE 1 2012 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Polymyalgia Rheumatica*

Criteria	Points With Ultrasonography	Points Without Ultrasonography
1. Morning stiffness duration >45 min	2	2
2. Hip pain or limited range of movement	1	1
3. Absence of rheumatoid factor or anticitrullinated protein antibody	2	2
4. Absence of other joint involvement	1	1
5. ≥1 shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and ≥1 hip with synovitis and/or trochanteric bursitis	1	—
6. Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis	1	—

*Score ≥4 without ultrasonography or ≥5 with ultrasonography is categorized as polymyalgia rheumatica.

TABLE 2 Classification Criteria for Polymyalgia Rheumatica

Chuang Criteria

1. Patients aged 50 yr or older
2. Bilateral aching and stiffness persisting for 1 month or more involving two of the following areas: Neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs
3. ESR >40 mm/hr
4. Exclusion of other diagnoses except GCA; the presence of all these criteria defines diagnosis of PMR.

Healey Criteria (22)

1. Persistent pain (for at least 1 month) involving two of the following areas: Neck, shoulders, and pelvic girdle
2. Morning stiffness lasting >1 hr
3. Rapid response to prednisone (≤20 mg/day)
4. Absence of other diseases capable of causing the musculoskeletal symptoms
5. Age >50 yr
6. ESR >40 mm/hr

The diagnosis of PMR is made if all the above criteria are satisfied.

Bird Criteria (23)*

1. Bilateral shoulder pain and/or stiffness
2. Onset of illness within 2 wk
3. Initial ESR >40 mm/hr
4. Morning stiffness >1 hr
5. Age >65 yr
6. Depression or loss of weight
7. Bilateral upper arm tenderness

*A diagnosis of probable polymyalgia rheumatica (PMR) is made if any three or more of these criteria are fulfilled. The presence of any three or more criteria yields a sensitivity of 92% and a specificity of 80%.

ESR, Erythrocyte sedimentation rate; *GCA,* giant cell arteritis.

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

SUGGESTED READINGS

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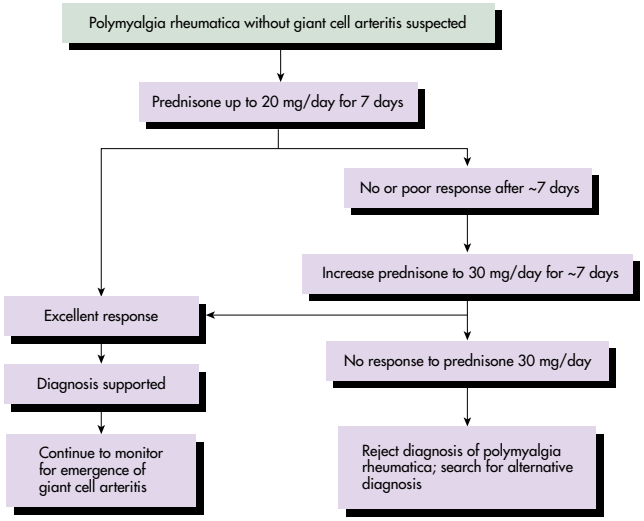

FIG. E2 Algorithm for diagnosing polymyalgia rheumatica without giant cell arteritis. (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

Polypharmacy

BASIC INFORMATION

DEFINITION

Polypharmacy is the concomitant use of many different medications, with the most common definition being the use of five or more medications for one patient. Polypharmacy is important when the medications are inappropriate without a clear benefit to the patient. Medication errors, adverse drug reactions, drug interactions, hospitalizations, nonadherence, functional decline, worse clinical outcomes, and/or increased costs have been associated with polypharmacy. A systematic review has found that polypharmacy was associated with increased mortality.

SYNONYM

Potentially inappropriate medications (PIMs)

ICD-10CM CODE
X71.9 Counseling, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Incidence increases with age and disease burden.
PREVALENCE: One in five Americans receives potentially inappropriate drug therapy, although prevalence may be substantially higher in specific clinical settings.
PREDOMINANT SEX, AGE, AND RACE:
- Adults aged 65 and older
- Women
- White

RISK FACTORS:
- Multiple chronic diseases, particularly hypertension and depression
- Poor health status
- Frequent hospitalizations
- Multiple providers and pharmacies
- Low educational level

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presence of one or more drugs without a clearly defined indication
- Presence of therapeutic duplications such as multiple NSAIDs
- Unexpected response to drug therapy
- Expanded list of new medications for a patient late in life or at the end of life
- Decreased patient adherence and limited patient understanding of their drug regimen
- Presence of a "geriatric syndrome" such as falling, excessive sedation and confusion, urinary retention or incontinence, reduced oral intake, and general failure to thrive
- Decreased self-perceived health status and lower quality of life

ETIOLOGY

- Inadequate communication & coordination between providers, pharmacists, and patients
- Prescriber adherence to single-disease guidelines
- Not recognizing a new problem as an adverse effect and prescribing a second drug to treat the problem
- Continuing medications without a review of risks and appropriateness of therapy
- Under-representation of elderly in studies, leading to inadequate knowledge about the benefits and harms of a drug

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Misuse, overuse, or underuse of drug therapy

WORKUP

- Obtain a thorough medication history including prescriptions, OTC drugs, supplements, and drugs "borrowed" from other individuals.
- "Brown bag" approach: Visually verify all medication bottles for actual ingredients.
- Risk assessment tools such as the Drug Burden Index (DBI) can help guide the medication review process. The DBI estimates the use of sedative and anticholinergic medications and their associated physical and cognitive impairments.
- Use standard tools to evaluate drug regimens:
  1. **Beers criteria:** Identifies potentially dangerous or ineffective drugs for older adults, such as ketorolac, muscle relaxants, and drugs with strong anticholinergic properties.
  2. **Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria:** Helps detect inappropriate prescribing and underprescribing of clinically indicated medications for older adults.
  3. **Medication Appropriateness Index (MAI):** Evaluates key elements of appropriate prescribing.
     a. Is there an indication for the drug?
     b. Is the medication effective for the condition?
     c. Is the dose appropriate for the patient and the condition?
     d. Are the directions practical and correct?
     e. Are there clinically significant drug-drug or drug-disease interactions?
     f. Is there unnecessary duplication with other drugs?
     g. Is the duration of therapy appropriate?
     h. Is this drug the least expensive of the equally effective alternatives?
- Utilize informatic software programs such as Micromedex, Epocrates, and Lexi-Interact.
- Pharmacogenomic tools may be used to identify how an individual reacts to different medications and can be used to assess current prescribing and promote deprescribing if necessary.

TREATMENT

NONPHARMACOLOGIC THERAPY

Consider nonpharmacologic alternatives to drug therapy.

ACUTE GENERAL Rx

If acute drug-related problems are identified, establish priorities for safely withdrawing/tapering the offending drugs.

CHRONIC Rx

- Always assess the potential risks and benefits from each specific medication, especially in patients with multiple comorbid conditions or limited life expectancy.
- Consideration should be given to the incremental benefit from each drug added to a complex drug regimen in the frail elderly.

DISPOSITION

- Prioritize medications for deprescribing based on those with the least benefit and greatest potential harm, on the patient's willingness to stop a medication, and on the medications easiest to discontinue or least likely to cause withdrawal reactions.
- Stop medications one at a time so a specific drug may be linked to reversal of adverse reactions, withdrawal symptoms, or worsening of disease state. The site http://medstopper.com/ may be useful when withdrawing medications.
- Evidence-based algorithms for deprescribing medications such as proton-pump inhibitors are available for use (http://www.open-pharmacy-research.ca/evidence-based-ppi-deprescribing-algorithm/).
- Closely monitor for withdrawal or return of original symptoms after discontinuation.
- Notify other members of the patient's health care team when a medication has been discontinued and document the reason for discontinuing the medication.
- Ensure EHR is always up to date.

REFERRAL

Referral to a clinical pharmacist for a comprehensive drug regimen review and potentially to a geriatrician, especially for frail older adults

PEARLS & CONSIDERATIONS

COMMENTS

- The prevention and/or identification of polypharmacy should focus on the appropriateness of the medications for the *individual* person and not simply the number of medications. In addition, clinical practice guidelines for chronic diseases rarely acknowledge the presence of concomitant conditions when recommending drug therapies. Deprescribing is a patient-centered process that considers a patient's preference concerning his/her drug treatment regimen, such as maintaining quality of life versus prolonging life. The decision regarding what is "appropriate" should consider the patient's own priorities, expected risk and benefit to that individual, and the patient's life expectancy.
- The EMPOWER study showed direct-to-consumer education may help start conversations regarding deprescribing. Prescribers and pharmacists should give a consistent message about the potential benefits of deprescribing.

PREVENTION

- Multiple systems are needed to prevent inappropriate polypharmacy.
- Adverse effects and adherence problems should be assessed at each encounter.
- Consider whether a drug is needed for a new symptom and whether the symptom is actually an unrecognized adverse effect.
- Confirm whether a drug is used for symptomatic relief or to prevent future events.
- Nonpharmacologic therapies should be encouraged whenever possible and appropriate.
- Update the drug list in the EHR at each visit and every care transition against what the patient is actually taking.
- Verify patient understanding about options such as tapering or discontinuing a drug.
- Counseling at hospital discharge during which the provider ensures patient and caregiver understanding of any medication change. Written and oral instructions should be provided in the patient's preferred language and at the appropriate literacy level.
- Effective communication between health care professionals is essential, with one prescriber taking overall responsibility for drug therapy.
- Regular evaluation of how frequently "as needed" medications are being used by the patient.

PATIENT & FAMILY EDUCATION

- An up-to-date list of all drugs taken on a regular or prn basis must be maintained. The list should include all prescription and OTC drugs including eye drops, inhalers, and skin creams. Dietary supplements should also be on the list. The National Transitions of Care Coalition's "My Medicine List" is an excellent tool for patients (https://static1.squarespace.com/static/5d48b6eb75823b00016db708/t/5d48ccd81475550001d26a77/1565052120781/My_Medicine_List.pdf)
- After hospital discharge, patients and/or caregivers should compare newly prescribed drugs to their existing drugs. They should ask which drugs should be stopped, which should be continued, and which should be continued but in a different dosage or frequency.
- Patients enrolled in Medicare Part D may be eligible for Medication Therapy Management (MTM) review programs.

AUTHORS: **Lauren Sittard, PharmD Candidate,** and **Anne L. Hume, PharmD**

SUGGESTED READINGS

2019 American Geriatrics Society Beers Criteria Update Expert Panel: American Geriatrics Society 2019 updated AGS Beers Criteria for potentially inappropriate medication use in older adults, *J Am Geriatr Soc* 67(4):674-694, 2019.

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BASIC INFORMATION

DEFINITION

Porphyrias are rare inherited (mostly autosomal dominant) disorders due to deficiencies of heme synthesis enzymes. Table E1 classifies the various types. They are named after the Greek word *porphurus* ("purple"), after the red fluorescence of phorphyrins exposed to ultraviolet light. Table E2 summarizes the various types of porphyrias.

SYNONYMS

Acute intermittent porphyria (AIP)
Porphyria cutanea tarda (PCT)
Variegate porphyria (VP)
Hereditary coproporphyria (HCP)
Congenital erythropoietic porphyria (CEP)
Hepatoerythropoietic porphyria
Erythropoietic protoporphyria
ALA-dehydrase porphyria

ICD-10CM CODE
E80.20 Unspecified porphyria

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.13 cases/million/yr (Europe) with a peak incidence in Sweden (0.51 cases/million/yr)
PREVALENCE: 1:75,000 population in Europe (1:1000 population in Sweden)
PREDOMINANT SEX AND AGE: Equal female-to-male ratio, except for AIP (female predominance). Pubertal onset is common.
GENETICS: Acute intermittent porphyria is more prevalent in northern Sweden (1:1,000); variegate porphyria is more common in descendants of Dutch settlers from South Africa (both due to founder effect).

RISK FACTORS: No risk factors are identified.
Triggers for acute crisis involve:
- Alcohol
- Barbiturates
- Sulfonamides
- Progesterone and other steroid hormones
- Emotional/physical stress
- Rapid weight loss

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Porphyrias can present as skin stigmata (porphyria cutanea), neurologic symptoms (acute intermittent porphyria), or both (variegata). Skin stigmata (Figs. E1, E2, and E3) are the result of absorption of solar radiation by porphyrin and consequent blistering skin findings. Porphyrins do not cross the blood-brain barrier and only affect the autonomic and peripheral nervous systems. However, vasospasm can cause CNS findings. Neurologic symptoms in acute attacks include abdominal pain, vomiting, constipation, and urinary retention. Pain in the back or extremities is common. There is no convincing evidence that delta-aminolevulinic acid is the cause of pain in acute porphyrias. Motor neuropathy affects proximal muscles of upper extremities and the sensory component affects the trunk. Seizures associated with severe hyponatremia may occur. Hallucination, insomnia, restlessness, and psychosis are described. Porphyrias can be acute or chronic. Precipitating factors in acute porphyria are summarized in Table E3.

These disorders are in the differential of acute abdomen; however, characteristically, rebound tenderness is not present.

ETIOLOGY

Porphyrin binds to iron to form heme, the core of the hemoglobin molecule. Porphyrins are synthesized in the cytosol and mitochondria, and mutations in any of the eight enzymes involved in heme synthesis can result in porphyrias. When the defect is physiologically significant, it results in overproduction of pathway precursors preceding the defective step that enter the circulation and are excreted into urine or bile.

This metabolic pathway is limited only by iron in the red blood cell and not by its end product, heme, which therefore is used in the treatment of hepatic porphyrias, where it inhibits the ALAS enzyme. Table E4 summarizes the distribution of porphyrins in red cells, urine, and feces in different forms of porphyria.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Lead toxicity
- Paroxysmal nocturnal hemoglobinuria
- Acute abdomen

WORKUP

Laboratory tests:
- Screening
- 24-hour urine for delta-aminolevulinic acid (markedly elevated in AIP attacks) and porphobilinogen

Confirmatory tests:
- Plasma porphobilinogen (increased in AIP, VP, and HCP)
- Erythrocyte zinc protoporphyrin, uroporphyrin, and coproporphyrin
- Stool (coproporphyrins)

IMAGING STUDIES

- Usually performed to rule out causes of acute abdomen if the porphyria is to be diagnosed
- Imaging if localized pain or rebound tenderness is present, when a primary surgical cause may be present

TABLE E1 Porphyrias: Clinical Involvement, Enzymatic Etiology, and Chromosomal Location

Porphyria (Synonym)	Acute Attack, Skin and Organ Involvement	Enzyme of Heme Biosynthesis Affected	Chromosome Location
=	=	Hepatic, 5-aminolevulinate synthase, nonspecific, mitochondrial (ALAS1)	3p21
X-linked sideroblastic anemia	Bone marrow	5-Aminolevulinate synthase, erythroid-specific, mitochondrial (ALAS2)	Xp11.21
X-linked dominant protoporphyria	Skin, red cells, liver	5-Aminolevulinate synthase, erythroid-specific, mitochondrial (ALAS2)	Xp11.21
ALA dehydratase deficiency porphyria (plumboporphyria)	Acute liver	ALA dehydratase (porphobilinogen synthase)	9q33.1
Acute intermittent porphyria (intermittent acute porphyria)	Acute liver	Porphobilinogen deaminase (hydroxymethylbilane synthase)	11q23.3
Congenital erythropoietic porphyria (Günther disease)	Skin, red cells, bone marrow	Uroporphyrinogen III synthase	10q25.2-q26.3
Porphyria cutanea tarda (symptomatic porphyria, cutaneous hepatic porphyria)	Skin, liver	Uroporphyrinogen decarboxylase	1p34
Hereditary coproporphyria	Acute skin, liver	Coproporphyrinogen oxidase	3q12
Variegate porphyria (porphyria variegata)	Acute skin, liver	Protoporphyrinogen oxidase	1q22
Erythropoietic protoporphyria (erythrohepatic protoporphyria)	Skin red cells, liver	Ferrochelatase (heme synthase)	18q21.3

ALA, 5-Aminolevulinate.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE E2 Classification of Porphyrias

Classification	Disease	Biochemistry	Clinical Features
Acute porphyria	Acute intermittent porphyria	Increased ALA and PBG	Acute attack
	Variegate porphyria	Increased ALA and PBG; increased porphyrin	Acute attack; photosensitivity
	Hereditary coproporphyria	Increased ALA and PBG; increased porphyrin	Acute attack; photosensitivity
	ALA dehydratase deficiency porphyria	Increased ALA; increased porphyrin	Acute and chronic neuropathy
Nonacute porphyria	Porphyria cutanea tarda	Increased porphyrin	Photosensitivity
	Erythropoietic protoporphyria	Increased porphyrin	Photosensitivity
	Congenital erythropoietic porphyria	Increased porphyrin	Photosensitivity
	X-linked dominant protoporphyria	Increased porphyrin	Photosensitivity
Porphyrinurias	Lead, alcohol, iron deficiency anemia, liver disease	Various biochemical manifestations	Various clinical presentations

ALA, 5-Aminolevulinate; *PBG,* porphobilinogen.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

FIG. E1 Porphyria cutanea tarda. Eroded blisters and crusts. (Courtesy the Yale Residents' Collection. From Skorecki K et al: *Brenner & Rector's the kidney,* ed 10, Philadelphia, 2016, Elsevier.)

FIG. E2 Congenital erythropoietic porphyria. Vesicles, bullae, and crusts on sun-exposed areas. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E3 Erythropoietic protoporphyria (EPP). Vesicular lesions are only occasionally seen in patients with EPP. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Curative: Liver transplantation
- Acute crisis: High carbohydrate intake: 2000 kcal/24 hr daily oral or 300 kcal/day administered intravenous 10% dextrose solution

ACUTE GENERAL Rx

- Opioids: Pain
- Phenothiazines: Nausea and psychiatric manifestations
- Propranolol: Tachycardia and hypertension
- Chloral hydrate or benzodiazepines: Insomnia
- Levetiracetam: Seizures
- Hematin: Given IV 1 to 4 mg/kg once daily for 3 to 14 days
- Givosiran is an investigational RNA interference therapeutic agent that inhibits hepatic ALAS synthesis. In patients who had recurrent porphyria attacks, givosiran resulted in reductions in induced ALAS mRNA levels, nearly normalized levels of the neurotoxic intermediates delta ALA and porphobilinogen, and a lower attack rate than that observed with placebo.

CHRONIC Rx

- It is advisable to carry a medical bracelet with the name of the porphyria and for specific avoidance of substances that may trigger porphyria in medical emergency or hospital admissions for other reasons.
- Consume sufficient carbohydrates.
- Avoid alcohol and other triggers, including rapid weight loss or emotional/physical stress.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Avoid herbs and toxins (alcohol) that may potentially interact with phenothiazines or cause hepatic interactions.

DISPOSITION

Admit all patients in acute attacks for hematin infusion.

TABLE E3 Changes in Porphyrins and Their Precursors in the Porphyrias, Porphyrinurias, and Hereditary Sideroblastic Anemia

Porphyrias and Other Conditions	ALA	PBG	Urine Uroporphyrin	Urine Coproporphyrin	Feces Coproporphyrin	Feces Protoporphyrin	Erythrocyte Protoporphyrin
Acute Porphyrias							
Acute intermittent porphyria	Raised, very high in attack	Raised, very high in attack	Usually raised[a]	Sometimes raised	Sometimes raised	Sometimes raised	Normal
Variegate porphyria	Raised in attack	Raised in attack	Usually raised in attack	Usually raised in attack	Raised	Raised	Normal
Hereditary coproporphyria	Raised in attack	Raised in attack	Sometimes raised in attack	Usually raised, always in attack	Raised	Usually normal	Normal
ALA dehydratase–deficiency porphyria	Raised in attack	Normal	Normal	Usually raised in attack	Normal	Normal	Occasionally raised
Nonacute Porphyrias							
Porphyria cutanea tarda	Normal	Normal	Raised (7-/8-carboxylate porphyrin levels very high in attack)	Slightly raised	Isocoproporphyrin raised in remission	Raised in remission	Normal
Erythropoietic protoporphyria	Normal	Normal	Normal	Normal	Normal	Usually raised	Raised, usually very high
Congenital erythropoietic porphyria	Usually normal	Usually normal	Raised, isomer I	Raised, isomer I	Normal	Usually raised	Usually raised
X-linked dominant protoporphyria	Normal	Normal	Normal	Normal	Normal	Usually raised	Raised, usually very high
Other Conditions							
Hereditary sideroblastic anemia	Normal	Normal	Normal	Normal	Normal	Normal	Occasionally raised
Lead poisoning	Raised	Normal	Normal	Sometimes raised	Normal	Normal	Raised when blood lead level >2 μM
Hereditary tyrosinemia	Raised	Normal	Normal	Normal	Normal	Normal	Normal
Iron deficiency anemia	Normal	Normal	Normal	Normal	Normal	Normal	Raised

ALA, 5-Aminolevulinate; *PBG,* porphobilinogen.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE E4 Precipitating Factors in Acute Porphyria

Drugs	Other stimuli
Alcohol	Fasting or dieting
Barbiturates	Hormones, stress
Angiotensin-converting enzyme (ACE) inhibitors	Smoking
Anticonvulsants	
Antidepressants	
Calcium channel blockers	
Cephalosporins	
Ergot derivatives	
Erythromycin	
Steroids or anabolic steroids	
Contraceptives, hormone replacement therapy	
Sulfonamides	
Sulfonylureas	

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

REFERRAL

- Centers that carry hematin
- Outpatient follow-up with hematologist for education on triggers, screening of hepatocellular carcinoma, genetic counseling

PEARLS & CONSIDERATIONS

COMMENTS

- The efficacy of hemin infusion is due to its inhibition of hepatic delta-aminolevulinic acid synthase-1, the enzyme that catalyzes delta-aminolevulic acid formation.
- The inability to diagnose porphyrias puts patients at risk of unnecessary surgeries.
- Attacks are triggered by prescribed drugs, alcohol, hormonal changes, fasting, or stress and may be prevented by avoiding triggers.
- Cancer (hepatocellular carcinoma) may be diagnosed in an early stage.
- Skin biopsies are not diagnostic and may cause harm.

PREVENTION

- Zinc oxide sunscreens.
- Attacks can be prevented by avoiding triggers (see earlier).
- Screen for hemachromatosis in PCT, as increasing liver iron triggers this disease.
- Monitor for hepatocellular carcinoma with limited ultrasound of the liver (alpha-fetoprotein is not usually increased).

PATIENT & FAMILY EDUCATION

Genetic counseling may be offered. Most porphyrias are autosomal dominant with incomplete penetrance (half of carriers manifest symptoms).

AUTHOR: **Bharti Rathore, MD**

SUGGESTED READINGS

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Stein P et al: British and Irish Porphyria Network. Best practice guidelines on clinical management of acute attacks of porphyria and their complications, *Ann Clin Biochem* 50(Pt 3):217-223, 2013.

Stein PE et al: Update review of the acute porphyrias, *Br J Haematol* 176(4):527-538, 2017.

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BASIC INFORMATION

DEFINITION

Clinically significant portal hypertension is defined as a portal vein pressure >10 mm Hg, most commonly attributable to liver disease.

ICD-10CM CODE
K76.6 Portal hypertension

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence of portal hypertension is not known.
- Cirrhosis is the most common cause of portal hypertension in the U.S.
- Portal hypertension is developed by >90% of patients with cirrhosis.
- Alcoholic and viral liver diseases are the most common causes of cirrhosis and portal hypertension in the U.S.
- Schistosomiasis is the main cause of portal hypertension outside the U.S.
- Esophageal varices may appear when portal vein pressure rises to >10 mm Hg.
- Variceal hemorrhage is the most serious complication of portal hypertension and may occur when portal pressures rise >12 mm Hg.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Jaundice
- Ascites (Fig. 1)
- Spider angiomata
- Testicular atrophy
- Gynecomastia
- Palmar erythema
- Dupuytren contracture
- Asterixis (with advanced liver failure)
- Irritability, encephalopathy
- Splenomegaly
- Dilated veins in the anterior abdominal wall
- Venous pattern on the flanks
- Caput medusae (tortuous collateral veins around the umbilicus)
- Hemorrhoids
- Hematemesis
- Melena
- Pruritus

ETIOLOGY

Pathophysiologically caused by:

- Conditions resulting in an increased resistance to flow:
  1. **Prehepatic** (e.g., portal vein thrombosis, splenic vein thrombosis, congenital stenosis)
  2. **Hepatic** (e.g., cirrhosis, alcoholic liver disease, primary biliary cirrhosis, schistosomiasis)
  3. **Posthepatic** (e.g., Budd-Chiari syndrome, constrictive pericarditis, inferior vena cava obstruction, cor pulmonale, tricuspid regurgitation)
- Conditions leading to increase in portal blood flow:
  1. Splanchnic arterial vasodilation accompanying portal hypertension, mediated by local release of nitric oxide
  2. Arterial-portal venous fistulae

Table 1 describes the pathophysiologic changes in portal hypertension and Table 2 summarizes the etiologies of portal hypertension.

DIAGNOSIS

- The diagnosis of portal hypertension is made on clinical grounds after a comprehensive history and physical examination.
- Noninvasive and invasive procedures confirm diagnosis and determine the severity of portal hypertension.

DIFFERENTIAL DIAGNOSIS

- Ascites from infection, neoplasm, or other inflammatory processes
- Obesity
- Abdominal organomegaly

WORKUP

The workup of portal hypertension includes blood tests and noninvasive imaging studies to determine if the cause of portal hypertension is prehepatic, hepatic, or posthepatic. Ascitic fluid analysis is a key part of the diagnosis.

LABORATORY TESTS

- Complete blood count with platelets
- Liver function tests with serum albumin
- Prothrombin and partial thromboplastin times
- Hepatitis B surface antigen and antibody
- Hepatitis C antibody
- In selected cases: Iron, total iron-binding capacity, and ferritin; antinuclear antibody, anti–smooth muscle antibodies, antimitochondrial antibody, ceruloplasmin, alpha-1 antitrypsin
- Ascitic fluid analysis: A serum-ascites albumin gradient ≥1.1 mg/dl suggests portal hypertension. Polymorphonuclear cells ≥250 cells/ml or positive Gram stain or culture suggest complicating spontaneous bacterial peritonitis (SBP)

IMAGING STUDIES

- Duplex-Doppler ultrasound is effective in screening for portal hypertension.
- Less commonly, CT/MRI/MRA scanning (Figs. E2 and E3) or liver-spleen nuclear medicine scanning can be used if the results from ultrasound are equivocal.
- Upper endoscopy is the most reliable test documenting the presence of esophageal varices.

TREATMENT

The treatment of portal hypertension is complex and involves measures to reduce the hypertension directly, minimize volume overload, correct underlying disorders, and prevent complications (most notably SBP and variceal bleeding).

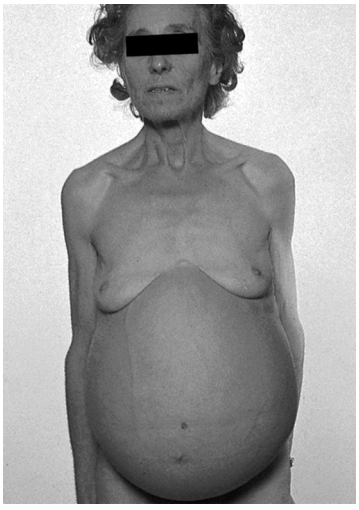

FIG. 1 Ascites secondary to portal hypertension. Note the dilated collateral vein running up the right side of the abdomen. (From Forbes A et al [eds]: *Atlas of clinical gastroenterology,* ed 3, Oxford, 2005, Mosby.)

TABLE 1 Pathophysiologic Changes in Portal Hypertension

Pathophysiologic Change	Specifics
Hepatic resistance	
	Passive, mechanical component: 60%-70%
	Active, dynamic component: 30%-40%
Portal hypertension	
Shunts	
Splanchnic vasodilation	
Increased portal inflow	
Decrease in effective circulating volume; redistribution total blood volume	
Increase in endogenous vasopressors (RAA, SNS, VP)	
	Increase in endothelin-1
	Angiotensin II
	Norepinephrine
	Vasopressin
	PGF-2 alpha
Decrease in NO, CO	

CO, Carbon monoxide; *NO,* nitrogen monoxide; *PGF,* prostaglandin; *RAA,* renin-angiotensin-aldosterone; *SNS,* sympathetic nervous system; *VP,* vasopressin.
From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

TABLE 2 Etiology of Portal Hypertension Grouped by Location of Insult

Site of Increased Resistance	Condition	FHVP	WHVP	HVGP	SPP
Presinusoidal (extrahepatic)	Extrahepatic portal, splenic, or mesenteric vein thrombosis	Normal	Normal	Normal	Increased
Presinusoidal (intrahepatic)	Early primary biliary cirrhosis	Normal	Normal/raised (?)	Normal/raised (?)	Increased
Presinusoidal (intrahepatic)	PSC	Normal	Normal/raised (?)	Normal/raised (?)	Increased
Presinusoidal (intrahepatic)	Sarcoid	Normal	Normal/raised (?)	Normal/raised (?)	Increased
Presinusoidal (intrahepatic)	Schistosomiasis	Normal	Normal/raised (?)	Normal/raised (?)	Increased
Presinusoidal (intrahepatic)	Congestive heart failure	Normal	Normal/raised (?)	Normal/raised (?)	Increased
Presinusoidal (intrahepatic)	Noncirrhotic portal fibrosis	Normal	Normal/raised (?)	Normal/raised (?)	Increased
Intrahepatic sinusoidal	Cirrhosis (any etiology)	Normal	Increased	Increased	Increased
Intrahepatic sinusoidal	Alcoholic hepatitis	Normal	Increased	Increased	Increased
Intrahepatic sinusoidal	Fulminant liver failure (any etiology)	Normal	Increased	Increased	Increased
Extrahepatic postsinusoidal hypertension	Budd-Chiari syndrome	Increased	Increased	Normal	Increased
Extrahepatic postsinusoidal hypertension	Constrictive pericarditis	Increased	Increased	Normal	Increased
Extrahepatic postsinusoidal hypertension	Inferior vena cava obstruction	Increased	Increased	Normal	Increased
Extrahepatic postsinusoidal hypertension	Congenital inferior vena cava web	Increased	Increased	Normal	Increased
Extrahepatic postsinusoidal hypertension	Right heart failure	Increased	Increased	Normal	Increased

FHVP, Free hepatic venous pressure; *HVPG,* hepatic venous pressure gradient; *PSC,* primary sclerosing cholangitis; *SPP,* systolic pulse pressure; *WHVP,* wedged hepatic venous pressure.
From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

TABLE 3 Indications, Contraindications, and Complications of the TIPS Procedure

Indications	Relative Contraindications	Contraindications	Acute Complications	Chronic Complications
Upper GI bleeding	Pulmonary hypertension	Right-sided heart failure	Neck hematoma	Congestive heart failure
Ascites	Severe liver failure	Biliary tract obstruction	Arrhythmia	Portal vein thrombosis
Hepatic hydrothorax	Portal vein thrombosis	Uncontrolled infection	Stent displacement	Progressive liver failure
	Multiple hepatic cysts	Chronic recurrent disabling hepatic encephalopathy	Hemolysis	Chronic recurrent encephalopathy
		Hepatocellular carcinoma involving hepatic veins	Bilhemia	Stent dysfunction
			Hepatic vein obstruction	TIPSitis
			Shunt thrombosis	
			Hemoperitoneum	
			Hemobilia	
			Liver ischemia	
			Cardiac failure	
			Sepsis	

GI, Gastrointestinal; *TIPS,* transjugular intrahepatic portosystemic shunt.
From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

NONPHARMACOLOGIC THERAPY

Dietary sodium restriction to generally 2000 mg/day forms the basis of therapy to limit fluid overload.

ACUTE GENERAL Rx

- For tense ascites, serial large-volume paracentesis (LVP) is generally recommended. The use of albumin infusion (8 to 10 g/L of ascites fluid removed) during LVP >5 L has been shown to reduce the incidence of postparacentesis circulatory dysfunction, although its use remains somewhat controversial.
- IV diuretics, typically furosemide and spironolactone, are used to achieve natriuresis and net negative salt and water balance. Renal function and serum electrolytes are monitored frequently, with transition to an oral regimen for long-term therapy.
- SBP is treated with IV antibiotics directed against enteric bacteria.
- Acute variceal hemorrhage is treated with crystalloid and blood product resuscitation, IV octreotide, terlipressin/vasopressin or somatostatin, and urgent upper endoscopy, often with sclerotherapy or band ligation. Patients with acute variceal hemorrhage should receive empiric antibiotic therapy for SBP.
- Traditionally, a transjugular intrahepatic portosystemic shunt (TIPS) or surgical shunt placement may be considered in patients not responding to above measures. However, recent data show *early* TIPS placement improved outcomes in acute variceal hemorrhage. Table 3 summarizes indications, contraindications, and complications of the TIPS procedure.
- Table 4 compares treatment modalities for portal hypertension.

CHRONIC Rx

- Dietary sodium restriction in combination with diuretics: The typical ratio of furosemide

TABLE 4 Comparison of Treatment Modalities

Treatment Modality	No (%), N = 77	Age, Yr (Mean)	Female %	Initial Meld (Mean, Range)	Child-Pugh Score (N = 74)	Ascites Size	Death (No, %) (N = 44)	Days from Presentation Until Death or End of Study
Medical management	64/77 (83%)	52	23/64 (36%)	16 (4-46)	A = 1 B = 31	None: 6 Small: 34 Moderate: 16 Large: 8	40/64 (63%)	321 ± 463
TIPS	8/77 (10%)	56	5/8 (63%)	12 (7-28)	A = 0 B = 5 C = 2	None: 1 Small: 3 Moderate: 3 Large: 1	4/8 (50%)	845 ± 407
Transplant	5/77 (7%)	54	0	21 (10-40)	A = 1 B = 1 C = 1	Large: 1	0	1896 ± 1752

TIPS, Transjugular intrahepatic portosystemic shunt.
From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

40 mg to spironolactone 100 mg retains normal serum potassium levels in most patients.
- Nonselective beta-blockers (propranolol and nadolol) in dosages sufficient to reduce the resting heart rate by 25% have been shown to be effective in primary prophylaxis for first-time variceal bleeding and for preventing recurrent variceal bleeding. Dosages are usually given bid and decreased if heart rate falls to <55 beats/min or systolic blood pressure drops to <90 mm Hg. The addition of a long-acting nitrate (e.g., isosorbide-5-mononitrate) has been shown to improve portal hemodynamics. Findings of a prospective trial of beta-blockers to prevent the formation of varices were negative. The combination of beta-blockade plus endoscopic esophageal variceal banding is superior to either intervention alone.
- Intermittent LVP may be needed in "diuretic-resistant" patients.
- Patients with prior SBP merit lifelong antibiotics for secondary prevention.
- Abstinence from alcohol or treatment for hepatitis B or hepatitis C. Vaccination for hepatitis A and B as appropriate.
- Hepatic transplantation is an option in selected patients.

DISPOSITION

- The most common complication associated with portal hypertension is variceal bleeding. The risk of bleeding from varices is approximately 15% at 1 yr.
- Development of the hepatorenal syndrome (HRS) is associated with high near-term mortality. In particular, HRS may complicate SBP, which emphasizes the importance of making the diagnosis of SBP and instituting appropriate prophylaxis.

REFERRAL

Consultation with a gastroenterologist is recommended in all patients with portal hypertension to screen for esophageal varices.

PEARLS & CONSIDERATIONS

Splanchnic arterial vasodilation is increasingly recognized as an important component of the pathophysiology of portal hypertension and ascites. There may be vasodilation in other capillary beds as well; of note, pulmonary arteriolar vasodilation can create a significant shunt fraction and resultant hypoxemia in the absence of chest radiograph or CT chest evidence of parenchymal disease. The diagnosis is suspected when otherwise unexplained hypoxia arises in a patient with cirrhosis, along with platypnea (dyspnea worse when sitting upright) and orthodeoxia (desaturation with upright posture). The diagnosis is confirmed by echocardiography with agitated saline, in which there is delayed appearance of bubbles in the left heart after injection into a peripheral vein.

COMMENTS

Portal hypertension and its complications carry significant morbidity and mortality rates. Emphasize ethanol abstinence, provide vaccinations and prophylactic therapy where indicated, and consider early referral to a specialist for assistance with management and consideration for hepatic transplantation.

SUGGESTED READING

Available at ExpertConsult.com

AUTHOR: **Fred F. Ferri, MD**

FIG. E2 Magnetic resonance angiography showing portal hypertension with collaterals. The shrunken liver and collateral are obvious. (From Forbes A et al [eds]: *Atlas of clinical gastroenterology,* ed 3, St Louis, 2005, Mosby.)

SUGGESTED READING

Ge PS, Runyon B: Treatment of patients with cirrhosis, *N Engl J Med* 375: 767-777, 2016.

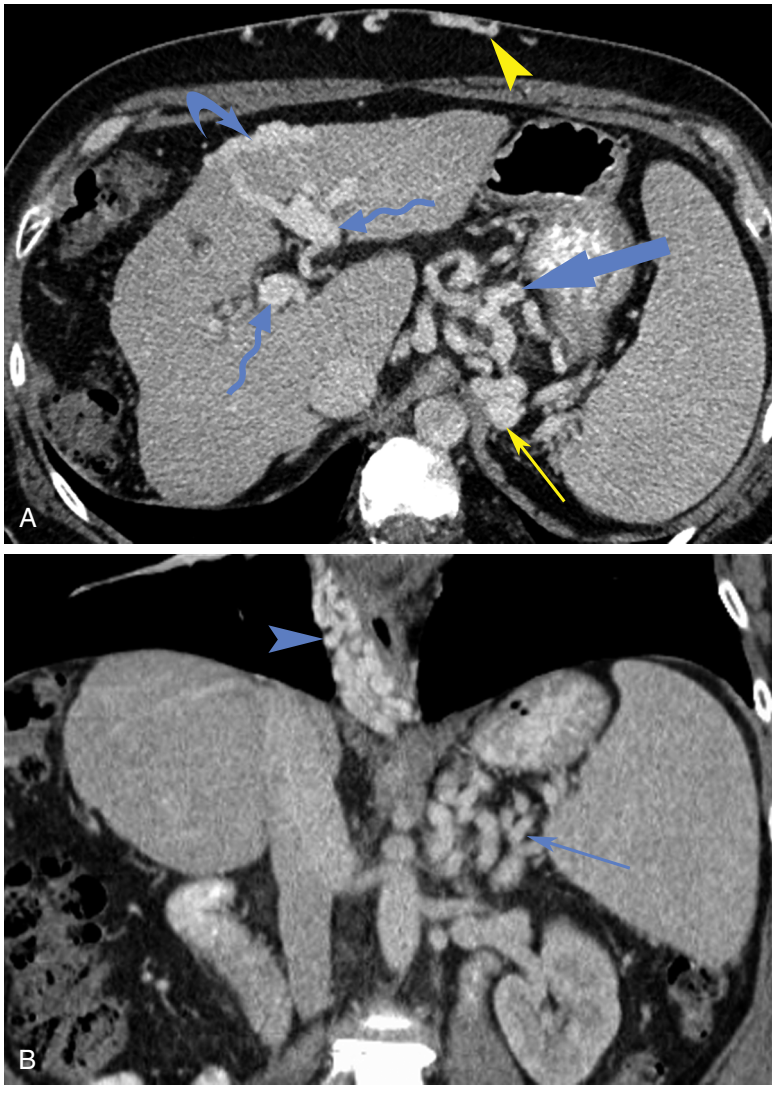

FIG. E3 Portal hypertension. A, Axial postcontrast computed tomography (CT) reveals signs of advanced portal hypertension. The right and left portal veins *(blue squiggly arrows)* are enlarged, measuring 15 mm. Dilated and tortuous cardinal veins *(fat straight blue arrow)* are seen in the gastrohepatic ligament and retroperitoneum *(skinny straight yellow arrow).* Paraumbilical collateral veins are patent and dilated, extending through the fissure of the ligamentum teres and falciform ligament *(blue curved arrow)* and as subcutaneous collaterals *(arrowhead).* Visualization of the patent paraumbilical collateral veins is the most specific CT sign of portal hypertension. **B,** Coronal CT image of the same patient reveals dramatic paraesophageal varices *(arrowhead)* and a tangle of retroperitoneal and perigastric collaterals *(arrow).* (From Webb WR et al: *Fundamentals of body CT,* ed 4, Philadelphia, 2015, WB Saunders.)

Portal Vein Thrombosis

BASIC INFORMATION

DEFINITION

Portal vein thrombosis (PVT) is thrombotic occlusion of the portal vein. The thrombus can also involve segments of the mesenteric veins and/or the splenic vein.

SYNONYMS

Pylethrombosis
PVT

ICD-10CM CODE
I81 Portal vein thrombosis

EPIDEMIOLOGY & DEMOGRAPHICS

- Occurs with equal frequency in children (peak age: 6 yr) and adults (peak age: 40 yr)
- Occurs in 8% to 25% of patients with decompensated cirrhosis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute PVT may present with sudden onset of fever and abdominal pain (when there is mesenteric extension).
- Upper gastrointestinal hemorrhage (hematemesis and/or melena) caused by esophageal varices.

ETIOLOGY & PATHOPHYSIOLOGY

In children: Umbilical sepsis (pathophysiology unknown). In adults:

- Hypercoagulable states:
  1. Antiphospholipid syndrome
  2. Neoplasm (common cause)
  3. Paroxysmal nocturnal hemoglobinuria
  4. Myeloproliferative diseases
  5. Oral contraceptives
  6. Polycythemia vera
  7. Pregnancy
  8. Protein S or C deficiency
  9. Sickle cell disease
  10. Thrombocytosis
- Inflammatory diseases:
  1. Crohn disease
  2. Pancreatitis
  3. Ulcerative colitis
- Complications of medical intervention:
  1. Ambulatory dialysis
  2. Chemoembolization
  3. Liver transplantation
  4. Partial hepatectomy
  5. Sclerotherapy
  6. Splenectomy
  7. Transjugular intrahepatic portosystemic shunt
- Infections:
  1. Appendicitis
  2. Diverticulitis
  3. Cholecystitis
- Miscellaneous:
  1. Cirrhosis (common cause)
  2. Bladder cancer

Pathophysiology: PVT results in portal hypertension, leading to esophageal and gastrointestinal varices. The liver sustained by the hepatic artery maintains normal function.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Causes of upper gastrointestinal hemorrhage and abdominal pain are described in Section II.

WORKUP

- Abdominal ultrasound with Doppler (Fig. 1) or MRI may show the PVT. Abdominal ultrasound color Doppler imaging has a 98% negative predictive value and is considered the imaging modality of choice in diagnosing PVT.
- Determination of underlying cirrhosis of the liver should be the foremost step. It is crucial to differentiate acute from chronic PVT because chronic PVT does not require treatment.
- Esophagogastroscopy typically shows esophageal varices.
- Laboratory evaluation for hypercoagulable state is not cost-effective in patients with cirrhosis.

TREATMENT

- Anticoagulation data on thrombolytic therapy are inconclusive and there is no formal recommendation for or against anticoagulation in acute PVT. However, anticoagulation is generally recommended for patients with extension of PVT into the superior mesenteric vein to prevent intestinal infarction. In patients with chronic PVT and concomitant cirrhosis, long-term anticoagulation is generally not recommended.
- Variceal sclerotherapy or banding.
- Surgical mesocaval or splenorenal shunt.
- The roles of thrombolysis and transjugular intrahepatic portosystemic shunt continue to evolve.

REFERRAL

- To surgeon to rule out intestinal infarction
- To gastroenterologist

SUGGESTED READING

Available at ExpertConsult.com

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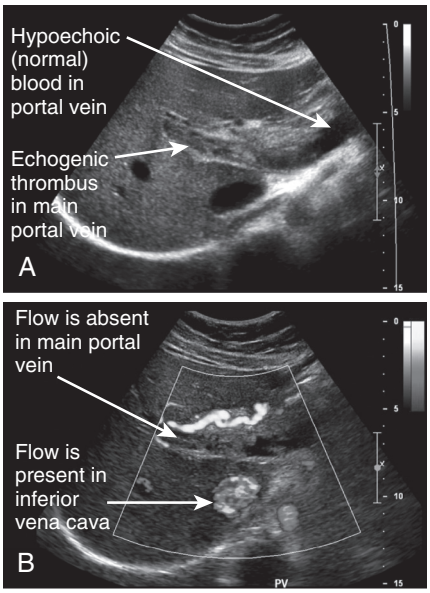

FIG. 1 Portal vein thrombosis: Ultrasound. This 22-yr-old female, 2 mo postpartum, presented with 1 wk of right upper quadrant pain. Ultrasound was performed to evaluate for suspected cholecystitis or symptomatic cholelithiasis. Instead, portal vein thrombosis was discovered. The postpartum state is a risk factor for this condition. Hypercoagulable states and inflammatory or neoplastic abdominal conditions, including pancreatitis and abdominal malignancies, also can result in portal vein thrombosis. **A,** Ultrasound gray scale image showing thrombus in the main portal vein. **B,** Doppler ultrasound showing no flow within the portal vein. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, WB Saunders.)

SUGGESTED READING

Parikh S et al: Portal vein thrombosis, *Am J Med* 123:111-119, 2010.

BASIC INFORMATION

DEFINITION

Postconcussion syndrome (PCS) refers to nonspecific neurologic, cognitive, and psychological symptoms that result from traumatic brain injury (TBI) and persist beyond the expected recovery period. There is no consensus regarding the duration of symptoms to make the diagnosis, but symptoms usually manifest or significantly worsen within a few days following head trauma and persist for wks to mos. PCS can also follow moderate and severe brain injury, although it is more commonly associated with mild brain injury or concussion. Concussion is an acute trauma-induced alteration of mental function lasting <24 hours, with or without preceding loss of consciousness.

SYNONYMS

PCS
Postconcussive syndrome
Posttraumatic nervous instability or brain injury
Postcontusion syndrome or encephalopathy
Status post commotio cerebri

ICD-10CM CODE
F07.81 Postconcussional syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence is approximately 27 cases per 100,000 persons/yr.
- From 30% to 80% of patients with mild to moderate brain injury will experience some symptoms of PCS.
- Usually reported in the young, ages 20 to 30 yr old.
- Risk factors include female sex, low socioeconomic status, anxiety sensitivity, previous TBI, severe bodily injury from TBI, headaches, and unsettled court cases.
- Acute post-injury symptoms such as headache, dizziness, photophobia, diplopia, or tinnitus are associated with development of persistent symptoms.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms start within a few days to wks after the head injury and usually persist after 3 mo. 15% of patients will have persistent symptoms 1 yr later.
- At least three of the following symptoms after TBI are required to meet ICD-10 criteria:
  1. Headache (usually of frontooccipital location and showing characteristics of tension or migraine headache). The International Headache Society suggests that coding and attribution of headaches with characteristics of primary headaches but in the setting of an inciting event should be attributed to the event, unless there was a known history of the headache and the inciting event was seen as aggravating/initiating the preexisting migraine/tension headache
  2. Fatigue
  3. Dizziness and/or vertigo
  4. Impaired memory
  5. Difficulty in concentrating
  6. Insomnia
  7. Irritability/frustration
  8. Lowered tolerance of stress, emotion, or alcohol
- Other associated symptoms: Noise sensitivity, neck pain, nondermatomal paresthesias, interference with social role functioning.
- Focal neurologic deficits are typically absent on examination.

ETIOLOGY

- The inciting TBI may occur as a result of events such as falls, motor vehicle accidents, military injuries, and contact sports.
- The primary injury triggers a slew of pathophysiological changes at the cellular level secondary to the axonal stretching and injury, leading to alterations in membrane and intracellular physiology, thereby affecting neurotransmission. These changes are believed to be a factor in determining whether the outcome will be an apparent normal recovery or persistent postconcussion symptoms.
- Postmortem findings reveal diffuse axonal injury as the primary pathologic finding, along with small petechial hemorrhages and local edema.
- Prior history of anxiety is a strong risk factor for occurrence of PCS.

DIAGNOSIS

A careful history, a nonfocal neurologic examination, and normal neurologic testing will usually establish the diagnosis.

DIFFERENTIAL DIAGNOSIS

- Headache (dissection of the vertebral artery, occipital neuralgia)
- Epidural hematoma
- Subdural hematoma
- Skull fracture
- Cervical spine disk disease
- Whiplash
- Cerebrovascular accident
- Depression
- Anxiety
- Posttraumatic stress disorder

WORKUP

To exclude other causes of neurologic symptoms after TBI:

- Normal results of electroencephalography
- Normal evoked potentials
- Neuropsychological testing, which often reveals difficulties in concentration, memory, language, and executive function

LABORATORY TESTS

Various biomarkers in blood and cerebrospinal fluid and genetic testing have been proposed and studied in patients with TBI, but these tests are not specific and are not routinely used.

IMAGING STUDIES

- There is no imaging modality to diagnose PCS. PCS is primarily a clinical diagnosis. The American College of Emergency Physicians' clinical policy regarding neuroimaging in adults with mild traumatic brain injury is summarized in Box 1.
- 10% of CT scans of the head following mild TBI are abnormal, showing mild subarachnoid hemorrhage, subdural hemorrhage, or contusions.

BOX 1 American College of Emergency Physicians' Clinical Policy Regarding Neuroimaging in Adults with Mild Traumatic Brain Injury

A noncontrast head CT is indicated (level one recommendation) in adults with LOC or posttraumatic amnesia only if at least one of the following is present:

- Headache
- Vomiting
- Age older than 60 yr
- Drug or alcohol intoxication
- Deficits in short-term memory
- Physical evidence of trauma above the clavicle
- Posttraumatic seizure
- GCS score below 15
- Focal neurologic deficit
- Coagulopathy

A noncontrast head CT should be considered (level two recommendation) in head trauma patients with no LOC or posttraumatic amnesia if any of the following is present:

- Focal neurologic deficit
- Vomiting
- Severe headache
- Age 65 yr or older
- Physical signs of a basilar skull fracture
- GCS score below 15
- Coagulopathy
- A dangerous mechanism (e.g., ejection from motor vehicle, pedestrian struck, fall of more than 3 feet or 5 stairs)

CT, Computed tomography; *GCS,* Glasgow Coma Scale; *LOC,* loss of consciousness.
From Marx J et al: *Rosen's emergency medicine: concepts and clinical practice*, ed 7, Philadelphia, 2010, Mosby.

- MRI of the head after a mild traumatic brain injury (mTBI) is abnormal in 30% of patients with normal CT scans and may show irregular brain contours or old cerebral contusions.
- Recent improvements in imaging modalities, including diffuse tensor imaging (DTI) and susceptibility weighted imaging (SWI) in MRI, functional MRI (fMRI), and metabolic imaging such as magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) imaging, appear to be promising in elucidating the underlying pathophysiology of TBI and PCS, although they have not found a major role in clinical practice yet.
- None of the imaging modalities have been able to predict the occurrence of PCS in patients with mild TBI.

Rx TREATMENT

PCS must be recognized as a physiologic and psychological problem and treated accordingly. Treatment should be individualized to target the patient's particular symptoms and is typically completed on an outpatient basis. Some symptoms may be refractory to treatment.

NONPHARMACOLOGIC Rx

- Early reassurance and patient education are major components of treatment. Explanation of symptoms and expectations, combined with early follow-up with reassurance, may hasten resolution of symptoms.
- Graduated physical activity is preferred over prolonged cognitive and physical rest. Light aerobic activity that avoids risk for reinjury has been shown beneficial in mitigating refractory concussion symptoms. Physical and occupational therapy may be beneficial.
- Cognitive behavioral therapy may be effective in treating symptoms.
- Avoidance of alcohol, narcotics, and sleep deprivation.

PHARMACOLOGIC THERAPY

- Supportive symptomatic care may include the use of nonnarcotic analgesics and antiemetics.
- Amitriptyline has been widely used for posttraumatic tension-type headaches as well as for nonspecific symptoms such as irritability, dizziness, insomnia, and depression. Amantadine is also a consideration.
- Posttraumatic migraine-type headaches can be treated with a trial of propranolol or amitriptyline alone or in combination.
- Depression can be treated with selective serotonin reuptake inhibitors but may not respond as well when compared with patients without PCS who have depression.

DISPOSITION

- Most patients improve after mild TBI without any residual deficits within 3 mo, though the cognitive and emotional symptoms resolve more slowly.
- Although good improvement is typically seen within the first 6 mo, patients can continue to show improvement for up to 12 to 18 mo.
- Patients with very severe brain injuries (low Glasgow Coma Scale [GCS] score) and prolonged anterograde amnesia are at increased risk of development of some degree of permanent cognitive and personality disturbance.
- Predictors for the development of persistent PCS include:
  1. Female sex
  2. Ongoing litigation (conflicting studies)
  3. Low socioeconomic status
  4. Prior headaches
  5. Prior TBI
  6. Prior psychiatric illnesses, particularly anxiety

REFERRAL

Early consultations with psychologists, psychiatrists, neurologists, and rehabilitation specialists in an outpatient setting may be beneficial.

PEARLS & CONSIDERATIONS

- PCS starts within a few days after the injury.
- Recognizing depression and treating pain symptoms early in the course may help prevent the development of persistent PCS (>1 yr).
- The severity of the trauma does not clearly predict the risk of PCS and symptoms do not cluster in a predictable manner.
- The severity of brain injury is usually documented by initial GCS score, duration of loss of consciousness, and duration of amnesia; however, there is a move toward tests of function, such as neuropsychological testing or fMRI.

COMMENTS

- Attempts to determine how much of a role psychological and/or neurologic factors play in the PCS are important but very difficult.
- No medication at hospital discharge has been proved to change the natural course of the disease.
- Engaging in physical activity within 7 days after concussion is associated with a lower rate of persistent postconcussive symptoms.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Post-concussion Syndrome (Patient Information)
Concussion (Related Key Topic)
Traumatic Brain Injury (Related Key Topic)

AUTHORS: **Chloe Mander Nunneley, MD, Corey Goldsmith, MD,** and **Prashanth Krishnamohan, MBBS, MD**

SUGGESTED READINGS

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Anderson EE et al: Mild traumatic brain injuries: a 10-yr follow-up, *J Rehabil Med* 43(4):323-329, 2011.

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Jotwani V, Harmon KG: Postconcussion syndrome in athletes, *Curr Sports Med Rep* 9(1):21-26, 2010.

Polinder S et al: A Multidimensional approach to post-concussion symptoms in mild traumatic brain injury, *Front Neurol* 9:1113, 2018.

BASIC INFORMATION

DEFINITION

Postherpetic neuralgia (PHN) is a pain syndrome that results as a complication of herpes zoster (HZ). HZ, also known as shingles, is a painful vesicular eruption in a dermatomal distribution. HZ is caused by the reactivation of varicella zoster virus (VZV) in someone with a known history of varicella. PHN is pain and/or dysesthesia that persist for 3 or more months at the site of resolved HZ.

ICD-10CM CODE

B02.29 Other postherpetic nervous system involvement

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: PHN occurs in approximately 9% to 34% of HZ patients. It is the most frequent chronic complication of herpes zoster and the most common neuropathic pain disorder resulting from infection. In one study, approximately 60% of patients with HZ developed PHN at age 60 yr, and 75% developed PHN at age 70 yr. In another study, the incidence of PHN at 9 yr post-HZ eruption was 21%.

PEAK INCIDENCE: Unknown

PREDOMINANT SEX AND AGE:

- PHN occurs equally in males and females.
- The likelihood of developing PHN significantly increases with advancing age.

GENETICS: Family history of HZ is considered a risk factor for HZ, with higher risk if multiple family members have had HZ.

RISK FACTORS:

- Advanced age
- Greater severity of HZ prodromal pain
- Greater severity of pain during acute HZ eruption
- Location—specifically ophthalmic (V1) location and brachial plexus
- Severe immunosuppression

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- HZ typically presents as a painful vesicular eruption in a dermatomal distribution. Rarely, HZ can occur subclinically with dermatomal pain in the absence of a rash.
- PHN is pain that continues for 3 months at the dermatomal site of the resolved HZ. The pain may be described as burning, stabbing, shooting, or shock-like.
- Patients may note an amplified response to stimuli at the site of PHN, with increased pain response (hyperalgesia), pain to typically nonnoxious stimuli (allodynia), or focal changes in autonomic function (e.g., increased sweating).
- Physical examination should include a comparison of sensory function in the affected dermatome with that on the contralateral side.

ETIOLOGY

PHN is associated with damage and scarring to the dorsal root ganglion secondary to inflammation related to active herpes zoster infection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Zoster sine herpete (subclinical HZ without skin eruption)

TREATMENT

ACUTE GENERAL Rx

- Administration of acyclovir or valacyclovir within 72 hours of HZ onset is thought to help reduce the likelihood of developing PNH. However, one Cochrane review paper found no difference with acyclovir administration.
- A single published study supports the use of amitriptyline (25 mg daily) as an adjunct to an antiviral agent in acute HZ to decrease the incidence of PHN and the pain associated with subsequent PHN.
- A suggestive noncontrolled study with coadministration of valacyclovir and gabapentin during acute HZ reduced the incidence of PHN as well.
- Corticosteroids do NOT prevent PHN.

CHRONIC Rx

TOPICAL TREATMENTS:

- Lidocaine 5% patches may be used for mild pain.
- Capsaicin 0.075% cream (although little reported efficacy) 5 times per day.
- Capsaicin 8% patch has greater efficacy, but overall analgesia may be minimal at best, with one third of patients unable to tolerate the agent due to burning, stinging, and erythema. However, a single 60-minute treatment with high concentration capsaicin patch was found in one study to reduce PHN for up to 12 weeks regardless of concomitant systemic neuropathic pain medication use.

ORAL TREATMENTS: First line:

- Gabapentinoids (gabapentin, pregabalin) are the only FDA-approved oral therapy for PHN and are some of the most commonly used first-line therapies for chronic PHN pain. Gabapentin may be administered in the immediate-release or extended-release formulation. Dosing includes gabapentin 300 mg 3 times a day (titrating up to max 3600 mg/day) and pregabalin 75 mg nightly (titrating up to 300 mg twice daily).
- Tricyclic antidepressants such as amitriptyline (25 mg/day, increased by 25 mg every night to a maximum of 75 mg/night), desipramine (10-25 mg/day, increased by 25 mg/day every 3 days as needed to a maximum of 150 mg/day), and nortriptyline (10-25 mg/day, increased by 25 mg/day weekly as needed to maximum of 75 mg day) are other first-line treatments. These medications have a delayed onset of action and may not work as well in patients with certain types of pain, such as burning pain or allodynia. They have a considerable side effect profile. Their use in elderly patients should be carefully considered. A recent study showed the combination of gabapentin and nortriptyline was more efficacious than either drug as monotherapy for neuropathic pain.

Second line:

- Opiates (e.g., controlled-release oxycodone): Side effects, the possibility of misuse, and the potential for abuse must be weighed.

Other modalities:

- Dorsal root entry zone (DREZ) lesions have been used with an improvement rate of 20% in long-term studies.
- For recalcitrant cases, epidural corticosteroids and nerve blocks, botulinum toxin, and cryotherapy.
- Fig. 1 describes a treatment algorithm for HZ and PHN.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Acupuncture:
  1. Studies on acupuncture and PHN pain have had varying results; however, the only randomized, controlled study showed no significant difference in pain reduction between control and treatment groups.

REFERRAL

For complicated cases, dermatology, neurology, and/or pain management input can be helpful.

PEARLS & CONSIDERATIONS

COMMENTS

- Careful consideration of treatment side effects and drug interactions is needed.
- The natural history of PHN is slow resolution, and most individuals respond to medical therapy. However, a subtype of patients may develop severe, long-lasting pain that is recalcitrant to medical therapy.
- In a questionnaire study of 385 adults age >65 yr with persistent acute pain, the mean duration of PHN was 3.3 yr.

PREVENTION

- Vaccination:
  1. A nonlive VZV vaccine (Shingrix®) is approved by the FDA for individuals age 50 and older. It is administered as two shots spaced 2 months apart and is 97% effective against shingles in people ages 50 to 69, and 91% effective against PHN in people 50 and older. It is more effective than the live attenuated VZV vaccine (zostvax).
  2. The CDC recommends that those who received Zostavax be revaccinated with Shingrix.
  3. Those who have had HZ should still receive the vaccine.

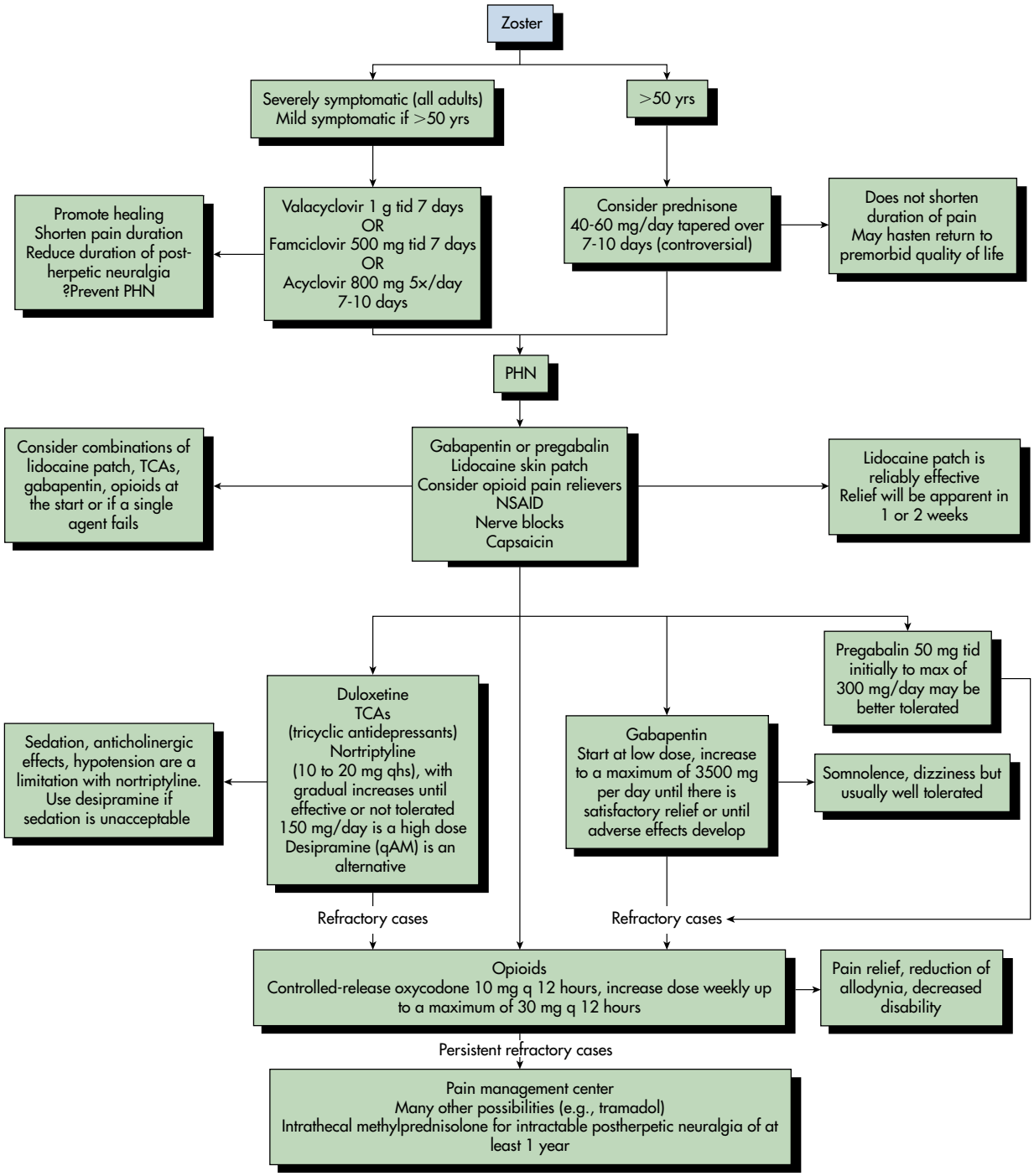

FIG. 1 Treatment of herpes zoster and postherpetic neuralgia. *NSAID,* Nonsteroidal antiinflammatory drug; *PHN,* postherpetic neuralgia. (Modified from Habif TA: *Clinical dermatology,* ed 6, St Louis, 2016, Elsevier.)

PATIENT & FAMILY EDUCATION

- The only well-documented means of preventing PHN is the prevention of herpes zoster through vaccination.
- Patients should understand both the benefits and the potential adverse effects of treatment.
  1. They should be informed that pain relief will likely not be immediate.
  2. Frequent reassessment may be needed, and drug doses should be increased as necessary.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Herpes Zoster (Related Key Topic)

AUTHOR: **Lisa Pappas-Taffer, MD**

SUGGESTED READING

Gan EY et al: Management of herpes zoster and post-herpetic neuralgia, *Am J Clin Dermatol* 14(2):77-85, 2013.

Johnson RW, Rice AS: Postherpetic neuralgia, *N Engl J Med* 371:1526-1533, 2014.

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Saguil A et al: Herpes zoster and postherpetic neuralgia: prevention and management, *Am Fam Physician* 96(10):656-663, 2017.

BASIC INFORMATION

DEFINITION

Major or minor depressive episodes that are severe enough to affect activities of daily living and occur most commonly within 1 to 3 wk after delivery but can also present up to 12 mo postpartum.

SYNONYMS

Spectrum of disease presentation
Postpartum blues
Postpartum depression
Postpartum psychosis

ICD-10CM CODES

F53	Includes postpartum depression and postpartum psychosis
090.6	Includes postpartum blues, postpartum dysphoria and sadness

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Approximately 800,000 women who deliver in the U.S. or 20% of all live births are affected by postpartum depression annually.
PREVALENCE: Perinatal depression affects approximately 10% to 15% of women.
RISK FACTORS: Risk factors include depression or anxiety during pregnancy, traumatic birth experiences, stressful life events during pregnancy or the postpartum period, infant NICU admission or preterm delivery, poor social support, history of depression, and problems with breastfeeding.
GENETICS: A family history of mood disorders is a risk factor for postpartum depression.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients present with depressed or irritable mood, decreased interest in activities, appetite and sleep changes, weight changes, decreased energy, excessive guilt or feelings of worthlessness, psychomotor agitation or retardation, and possibly suicidal/homicidal ideation. The diagnosis of major depressive episode requires that symptoms be present nearly every day for 2 wk and that the woman experiences a decline from a previous level of functioning.

ETIOLOGY

The decline in reproductive hormones following delivery is believed to contribute to the development of postpartum depression in some women. In addition, women with a history of depression, premenstrual syndrome or dysphoric disorder, stressful life events, and a family history of mood disorders have an increased risk of both depression and postpartum depression.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hyperthyroid
- Hypothyroid
- Postpartum blues: Syndrome involving symptoms of depression, anxiety, or anger that usually occurs 2 to 3 days after delivery and resolves within a few days to 1 to 2 wk postpartum without treatment
- Postpartum psychosis: Usually occurs between 1 to 2 wk post delivery and is characterized by extreme disorganization of thought, hallucinations, and bizarre behavior. It requires rapid intervention, as there is a real risk of suicide or infanticide
- Bipolar disorder

WORKUP

- History and physical examination
- Screening all postpartum women with a screening instrument such as the Edinburgh Postnatal Depression Scale (specific to the postpartum period and takes less than 5 min to complete) or the Patient Health Questionnaire-9
- In any patient with postpartum depression, screening for bipolar disorder

LABORATORY TESTS

Thyroid screening tests (if high suspicion for thyroid disorder)

TREATMENT

NONPHARMACOLOGIC THERAPY

Psychotherapy: Studies have shown psychotherapy to be equally effective to fluoxetine.

ACUTE GENERAL Rx

- Therapy with a selective serotonin reuptake inhibitor should be considered as first-line treatment because of low risk of toxic effects with overdose and ease of dosing. However, if the patient has had good success with another medication in the past, then it is appropriate to restart that medication. Start at half the recommended dose and increase after 4 days, with gradual up-titration until therapeutic effects are seen.
- A single medication is favored over multiple medications in order to decrease exposure to the fetus/neonate.
- Sertraline is the first-line selective serotonin reuptake inhibitor recommended for breastfeeding mothers secondary to existing evidence suggesting little risk for infants. There is, however, no evidence of adverse infant effects from mothers taking sertraline, paroxetine, or fluvoxamine. Fluoxetine may be present in higher levels in breast milk and breastfed infants.
- Tricyclic antidepressants do not appear to pass in significant amounts into breastfeeding infants and their use appears to be safe. Data regarding atypical antidepressants and breastfeeding are limited.
- The FDA recently approved an IV infusion of the drug brexanolone (Zulresso). It is administered as a single 60-hour IV drip and is currently only available to patients through a restricted distribution program at certified health care facilities.

CHRONIC Rx

- Medical therapy should be continued until at least 6 mo after remission.
- Long-term therapy should be considered for women with a history of three or more episodes of depression.

DISPOSITION

- Without treatment, the duration of postpartum depression averages 7 mo.
- 15% to 85% of women will experience at least one relapse after completing medical therapy.

REFERRAL

- Consider referral to psychiatrist if a patient demonstrates no improvement after 6 wk of drug therapy or experiences a relapse.
- Prompt or urgent referral to psychiatrist is indicated if a patient has signs/symptoms of postpartum psychosis, bipolar disorder, or expresses suicidal/homicidal ideation.

PEARLS & CONSIDERATIONS

COMMENTS

- Depression and anxiety both during and after pregnancy can have negative effects not only on the mother but also on her fetus, new baby, and family. Low birth weight, decreased fetal growth, increased NICU admission rates, increased neonate crying, and decreased developmental scores have been seen with these disorders when untreated. In addition, depression is associated with increased smoking, alcohol, and drug use, which can have negative effects on the infant and family. These factors should be taken into account when counseling women about medical therapy.
- Selective serotonin reuptake inhibitors do pass through breast milk but are present in very small quantities compared with the transplacental exposure infants receive in utero. Adverse infant effects are extremely rare; however, long-term data are lacking.

PREVENTION

In a patient with a history of postpartum depression, recurrence risk is approximately 25%. These patients should be screened for depression both during and after pregnancy. It is reasonable to initiate prophylactic therapy in patients with a history of depression, and they should have close postpartum follow-up for early identification of depressive episodes.

PATIENT & FAMILY EDUCATION

- National Women's Health Information Center: www.womenshealth.gov
- Postpartum Support International: www.postpartum.net
- Centers for Disease Control and Prevention: www.cdc.gov/reproductivehealth/depression/

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Depression, Major (Related Key Topic)

AUTHOR: **Jhenette Lauder, MD**

SUGGESTED READINGS

ACOG: *Screening for perinatal depression, committee opinion number 630*, American College of Obstetrics and Gynecologists, 2015.

Bobo WV, Yawn BP: Concise review for physicians and other clinicians: postpartum depression, *Mayo Clin Proc* 89(6):835-844, 2014.

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Stewart DE: Postpartum depression, *N Engl J Med* 375:2177-2186, 2016.

Werner E et al: Preventing postpartum depression: review and recommendations, *Arch Womens Mental Health* 18(1):41–60, 2015.

Postpartum Hemorrhage

BASIC INFORMATION

DEFINITION

Postpartum hemorrhage (PPH) is defined, for both vaginal and cesarean deliveries, as an estimated blood loss ≧1000 ml OR blood loss resulting in signs/symptoms of hypovolemia within 24 hr following delivery. PPH is further categorized into primary or secondary. Primary PPH occurs within the first 24 hr after delivery. Secondary PPH occurs >24 hr after delivery but within 12 wk following delivery.

SYNONYMS

Obstetric hemorrhage
Maternal hemorrhage
PPH

ICD-10CM CODES

O72.0 Third stage hemorrhage
O72.1 Other immediate postpartum hemorrhage
O72.2 Delayed and secondary postpartum hemorrhage
O72.3 Postpartum coagulation defects

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Depending on definitions used and scope considered, anywhere from 1% to 6% of obstetric patients will experience postpartum hemorrhage. Postpartum hemorrhage is the leading cause of maternal mortality worldwide and is implicated in >10% of maternal deaths in the U.S.
PREDOMINANT SEX AND AGE: Female of reproductive age
RISK FACTORS: Antepartum factors: History of PPH, primiparity or high parity, macrosomic infant, multiple gestation, polyhydramnios, uterine fibroids, prior uterine surgery, abnormal placentation, bleeding disorder

Intrapartum factors: prolonged labor, augmented labor, rapid labor, preeclampsia, chorioamnionitis, operative delivery, episiotomy, lacerations, retained products, placental abruption, fetal demise

PHYSICAL FINDINGS & CLINICAL PRESENTATION (TABLE 1)

- Bleeding is generally brisk at time of delivery.
- Examination findings include boggy uterus with continued passage of clot or blood with fundal pressure.
- Objective findings can also include hypotension, tachycardia, and oliguria with substantial blood loss.

ETIOLOGY

- Primary: Uterine atony (70% to 80%), retained placenta, lacerations and coagulopathies
- Secondary: Subinvolution of placental site, retained products (includes abnormal placentation), infection and coagulopathies

DIAGNOSIS

WORKUP

- Bladder should be emptied
- Bimanual examination to evaluate for atony; remove clots; massage if it is present
- Examination to verify that no lacerations are present, including cervical examination with necessary lighting and retractors
- Ensure adequate IV access
- Ultrasonography at bedside to evaluate for retained tissue or clot
- Examination to verify that placenta is intact

LABORATORY TESTS

Significant hemorrhage can lead to disseminated intravascular coagulation (DIC). If DIC is suspected, complete blood count and coagulation panels should be ordered. Similarly, if coagulopathy is suspected, evaluation of clotting factors should be ordered.

IMAGING STUDIES

Ultrasonography can be used to scan for retained products, including clot or placenta. It can be performed to assess the need for more invasive measures, such as instrumentation or a manual sweep.

TREATMENT

The most effective strategy for the prevention of postpartum hemorrhage is active management of the third stage of labor (AMTSL). Medical management with uterotonics is generally the first line of treatment:

- Oxytocin (IV, 10 to 40 units diluted into IV solution, or 10 units IM); often given prophylactically immediately after delivery to minimize EBL with delivery of placenta
- Methergine (IM, 0.2 mg)—contraindicated in hypertensive patient
- Hemabate (IM, 0.25 mcg)—contraindicated in patient with history of asthma
- Misoprostol (400 to 800 mcg sublingually, buccally, or rectally)

Other medical management:

- Tranexamic acid (IV, 1 g)

NONPHARMACOLOGIC THERAPY

- Active management of third stage of labor: controlled cord traction (Brandt-Andrews maneuver) and uterine massage after delivery of placenta
- Uterine tamponade (Fig. E1): Packing with gauze, Foley catheter, or tamponade balloon (Bakri)
- Uterine curettage for suspected retained products
- Uterine artery embolization
- Surgical management with laparotomy:
  1. Hypogastric artery ligation
  2. Bilateral uterine artery ligation (O'Leary sutures)
  3. B-lynch sutures
  4. Hysterectomy

ACUTE GENERAL Rx

- Uterotonics, surgical management, embolization, blood transfusion. Fig. 2 outlines the management of postpartum hemorrhage.
- Table 2 describes therapeutic response to initial fluid resuscitation. Dosing regimen for oxytocic drugs is summarized in Table 3. Blood product replacement is described in Box 1.

CHRONIC Rx

For anemia (Hb <10 g/dl) – Ferrous sulfate and ascorbic acid supplementation to support new red blood cell production

DISPOSITION

- The patient should be closely watched for at least 24 hr after a postpartum hemorrhage. Vital signs should be monitored for evidence of hemodynamic stability and appropriate response to anemia. Serial laboratory tests can be performed in the setting of concern for ongoing bleeding.
- Morbidity can include: shock, acute respiratory distress syndrome, Sheehan syndrome, thromboembolic disease, and loss of fertility.
- For cases with large blood loss (e.g., >2 L) and hemodynamic instability, intensive care unit admission may be warranted.

TABLE 1 Presentation of Symptoms in Postpartum Hemorrhage

% Blood loss (ml)	Systolic blood pressure (mm Hg)	Signs and symptoms
10-15 (500-1000)	Normal	Tachycardia, palpitations, dizziness
15-25 (1000-1500)	Low-normal	Tachycardia, weakness, diaphoresis
25-35 (1500-2000)	70-80	Restlessness, pallor, oliguria
35-45 (2000-3000)	50-70	Collapse, air hunger, anuria

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.

TABLE 2 Therapeutic Response to Initial Fluid Resuscitation

Response	Description	Follow-up treatment
Rapid response	<20% of blood volume lost	No additional fluids or blood are needed.
Transient response	20%-40% of blood volume lost; responds to initial fluid bolus but later has worsening vital signs	Continue fluids and consider blood transfusions.
Minimal or no response	Ongoing severe hemorrhage with >40% blood volume lost	Continue aggressive fluid and blood product replacements.

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.

TABLE 3 Dosing Regimens for Oxytocic Drugs

Drugs	Regimens
Oxytocin (Pitocin)	5-unit IV bolus
	Add 20-40 units oxytocin to 1 L of fluids for continuous infusion
	10 units intramyometrially
Methylergonovine (Methergine)	0.2 mg IM every 2-4 h
Ergonovine maleate (Ergotrate)	100-125 μg IM or intramyometrially every 2-4 h
	200-250 μg IM
	Total dose 1.25 mg
Carboprost (Hemabate)	250 μg IM or intramyometrially every 15-90 min
	Total dose 2 mg (8 doses maximum)
Misoprostol	800-1000 μg PR, oral, or sublingual

IM, intramuscular; *IV,* intravenous; *PR,* per rectum.
From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

BOX 1 Blood Product Replacement

Crossmatched blood.
Type-specific or "saline crossmatched" blood.
Compatible ABO and Rh blood types.
Rh-negative blood is preferable.
- Warm the blood, if possible, especially if the rate of infusion is >100 ml/min or if the total volume transfused is high; cold blood is associated with an increased incidence of arrhythmias and paradoxic hypotension.
- Administer calcium if blood is transfused rapidly at >100 ml/min because of binding of calcium by anticoagulants in banked blood.
- Give 6-10 units fresh frozen plasma (FFP) for every 10 units of packed red blood cell (PRBC) transfusions.

Give 10-12 units of platelets if the platelet count decreases to $<50 \times 10^9$/L.
Cryoprecipitate can be given to replace fibrinogen in addition to the FFP.
Consider 60-120 μg/kg intravenous bolus injection of recombinant activated factor VII (rFVIIa).

From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

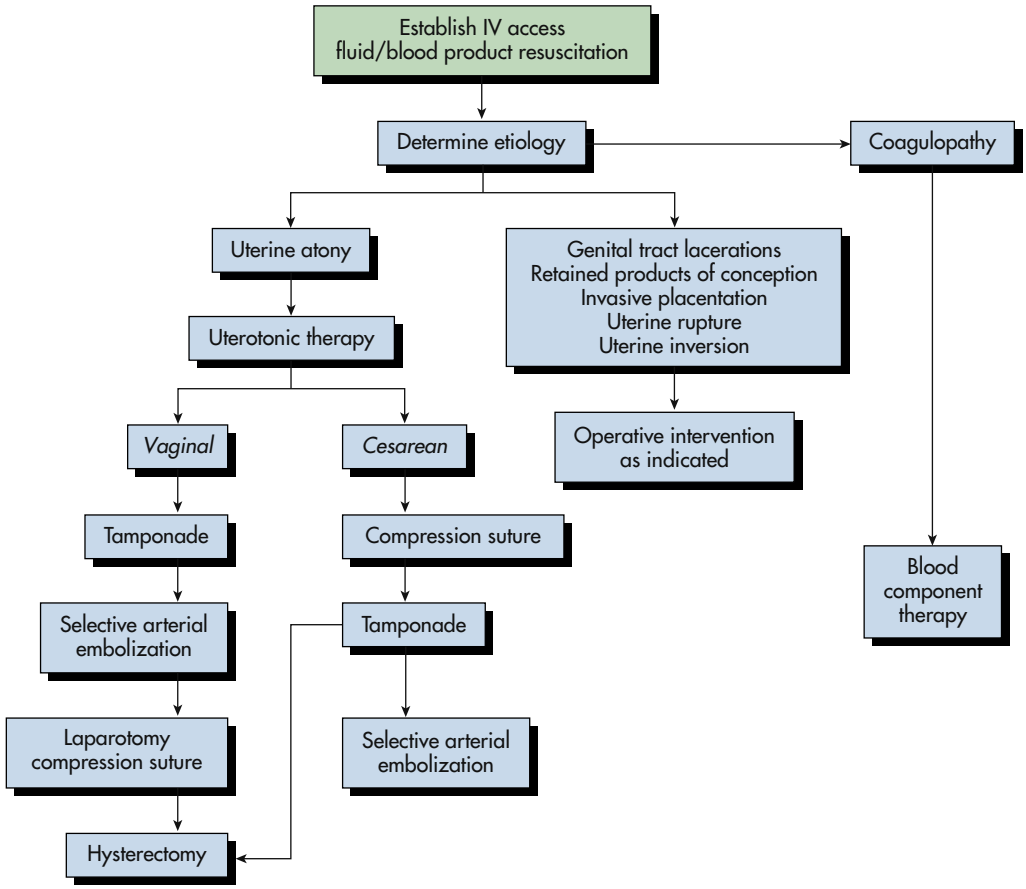

FIG. 2 Management of postpartum hemorrhage. (From Gabbe SG: *Obstetrics,* ed 6, Philadelphia, 2012, WB Saunders.)

REFERRAL

During the course of a postpartum hemorrhage, the anesthesiology department, blood bank, and OR staff should be notified, and adequate nursing should be available. Early considerations should be made to notify obstetricians. If bleeding is brisk or estimated blood loss is considerable, preparation should be made for transfusion of blood products, including drawing blood for typing and notifying the blood bank.

PEARLS & CONSIDERATIONS

PREVENTION

- Active management of third stage of labor
- Implementation of institution-specific PPH risk assessment tools effective for identifying patients at increased risk, though clinical suspicion should be maintained in all patients

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Anthony Sciscione, DO,** and **Scott J. Merrill, MD**

FIG. E1 An intrauterine balloon often provides effective uterine tamponade in atonic postpartum hemorrhage. (From Magowan BA: *Clinical obstetrics & gynecology,* ed 4, 2019, Elsevier.)

SUGGESTED READINGS

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Sentilhes L et al: Tranexamic acide for the prevention of blood loss after vaginal delivery, *N Engl J Med* 379:731-742, 2018.

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Postpoliomyelitis Syndrome

BASIC INFORMATION

DEFINITION

Postpoliomyelitis syndrome (PPS) is a disorder typically characterized by the gradual onset and slow progression of new weakness, fatigue, and pain in survivors of paralytic poliomyelitis after a period of partial or complete recovery and many years of neurologic stability. The symptoms are persistent and cannot be explained by the presence of other neurologic, medical, or orthopedic conditions.

SYNONYMS

PPS
Post polio syndrome
Progressive postpoliomyelitis muscular atrophy

ICD-10CM CODES
G14 Post polio myelitic syndrome
B91 Sequelae of poliomyelitis
Excludes 1: Sequelae of poliomyelitis (B91)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Estimates vary from 22% to 85% of individuals who survive acute poliomyelitis.
PEAK INCIDENCE: About 30 to 36 yr following acute poliomyelitis, although cases have been reported between 8 and 71 yr.
RISK FACTORS:
- Increasing age and greater length of time since the episode of acute poliomyelitis
- Acute poliomyelitis at an older age
- Greater severity of the acute poliomyelitis, especially with respiratory involvement or chronic deficits after recovery

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The most common clinical features are new weakness (20% to 60%), fatigue (59% to 89%), and pain (38% to 86%).
- The symptoms typically have an insidious onset with gradual progression.
- The new weakness is typically, but not exclusively, in muscles that were previously affected by the acute poliomyelitis.
- Fatigue may be described as either general or muscular in nature and is often the most disabling symptom.
- Pain is usually described as severe aching, cramping, or burning localized to the muscles or joints, particularly in areas previously affected by acute poliomyelitis.
- Respiratory weakness and sleep-disordered breathing with nocturnal hypoventilation occur less frequently.
- Other less common features include fasciculations, dysphagia, dysarthria, and cold intolerance.
- Neurologic examination reveals evidence of asymmetric, lower motor neuron weakness with or without musculoskeletal deformities secondary to longstanding polio such as asymmetric limb size, kyphoscoliosis, degenerative joint disease, and joint instability.

ETIOLOGY

The pathophysiologic basis of PPS remains unclear, although there are several proposed mechanisms. The most popular hypothesis is that the reduced population of enlarged motor units after acute poliomyelitis is subject to increased stress and overuse over the course of years. This leads to distal degeneration of the motor units and worsening denervation, causing clinical symptoms.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

PPS is a diagnosis of exclusion. A particular individual's symptoms will determine the differential, but some commonly considered entities are:
- Amyotrophic lateral sclerosis (ALS)
- Cervical or lumbosacral radiculopathy
- Acquired demyelinating polyneuropathies
- Myasthenia gravis
- Fibromyalgia
- Chronic fatigue syndrome
- Anemia
- Hypothyroidism
- Arthritis
- Depression
- Normal aging

WORKUP

- A detailed history should confirm a past history of acute poliomyelitis followed by a period of stability prior to emergence of the new symptoms.
- A neurologic exam confirms weakness of the lower motor neuron pattern.
- Nerve conduction studies and electromyography confirm the presence of denervation and help exclude other potential causes of weakness.
- A sleep study should be strongly considered to evaluate for the presence of sleep-disordered breathing.
- Pulmonary function tests should be strongly considered to evaluate for evidence of respiratory weakness.
- A swallow study should be performed in patients with difficulty swallowing.

LABORATORY TESTS

Complete blood count, electrolytes, and thyroid function tests are conducted to exclude other causes of fatigue. Erythrocyte sedimentation rate is typically normal, and an increase in creatine kinase levels (if any) is nonspecific.

IMAGING STUDIES

Magnetic resonance imaging of the brain and spine can be helpful in excluding other potential causes of weakness.

CRITERIA FOR DIAGNOSING POSTPOLIOMYELITIS SYNDROME

- Prior episode of poliomyelitis with evidence of residual lower motor neuron loss
- Duration of acute onset of polio and neurologic and functional stability of 15 or more yr
- Gradual onset of persistent new weakness and abnormal muscle fatigability (lasting 1 yr or longer)
- Exclusion of other conditions mentioned in the previous differential diagnosis section

TREATMENT

There is no specific therapy for PPS. However, a multidisciplinary management program tailored to the patient's presentation can be very helpful in the management of symptoms, resulting in improved functionality and quality of life.
- Most individuals will benefit from physical activity regimens (i.e., nonfatiguing exercise programs) designed by a physical therapist to focus on energy conservation and pacing.
- Orthoses and assistive devices may facilitate ambulation and other activities of daily living as well as reduce the risk of falls.
- Pain can often be controlled with conservative measures such as activity and lifestyle modifications, but analgesic medications may be necessary in some cases. Amitriptyline has been found to help with relief of pain and fatigue in anecdotal cases.
- Trials indicate that drugs such as intravenous immune globulin (IVIG) and lamotrigine as well as application of static magnetic fields over identified trigger points may be beneficial in treating muscle weakness and pain, but results have been conflicting and routine clinical use is not recommended.
- Several studies evaluating the use of pyridostigmine for the treatment of weakness and fatigue in PPS have had conflicting results.
- Studies evaluating amantadine, modafinil, prednisone, and human growth hormone have failed to show any definitive benefit.

DISPOSITION

- The symptoms of PPS tend to be slowly progressive and may stabilize over the course of years.
- The weakness, fatigue, and pain may result in disability.
- Rarely fatal, but individuals with respiratory weakness and dysphagia are at increased risk and may benefit from early use of noninvasive respiratory support.

REFERRAL

- Neuromuscular specialist can assist in diagnosis and management.
- Physiatry, physical therapy, and occupational therapy for rehabilitation and assistive devices.
- Speech therapy referral is useful in patients with dysarthria or dysphagia.
- Pulmonary consult should be obtained for patients with symptoms or signs of respiratory weakness.
- Orthopedic consult may be necessary for patients requiring surgical correction of joint deformities.

- A mental health professional can assist with management of depression and other psychosocial issues.

PEARLS & CONSIDERATIONS

COMMENTS

- A diagnosis of PPS should only be made after a thorough evaluation for other potential causes of the patient's symptoms has been completed.
- Due to the high incidence of PPS among the large number of poliomyelitis survivors, PPS is the most common motor neuron disease worldwide.
- For patients with PPS who need to undergo surgical procedures, shorter-acting anesthetic agents should be used due to these patients' impaired baseline respiratory status and their potentially increased sensitivity to anesthetic and nondepolarizing neuromuscular blocking agents.

SUGGESTED READINGS

Koopman FS et al: Treatment for post-polio syndrome (review), *Cochrane Database Syst Rev* 16(2):CD007818, 2011.

Lo JK et al: Post-polio syndrome and the late effects of poliomyelitis: part 2. treatment, management, and prognosis, *Muscle Nerve* 58(6):760-769, 2018.

PATIENT & FAMILY EDUCATION

Website: www.mayoclinic.com/health/post-polio-syndrome/DS00494

RELATED CONTENT

Poliomyelitis (Related Key Topic)

AUTHOR: **Divya Singhal, MD**

Postthrombotic Syndrome

BASIC INFORMATION

DEFINITION

Postthrombotic syndrome (PTS) is a delayed complication of deep vein thrombosis (DVT) that leads to signs and symptoms of venous insufficiency.

SYNONYMS

Postphlebitic syndrome
Chronic venous insufficiency
PTS

ICD-10CM CODES

I87.001	Postthrombotic syndrome without complications of right lower extremity
I87.002	Postthrombotic syndrome without complications of left lower extremity
I87.003	Postthrombotic syndrome without complications of bilateral lower extremities

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 23% to 60% of people with DVT will experience postthrombotic syndrome, often within 2 yr of onset of DVT.
PREVALENCE: Unknown
PREDOMINANT SEX: Slightly female predominance
RISK FACTORS: Symptomatic DVT, postoperative DVT, recurrent DVT, underlying primary venous insufficiency, younger age, obesity, presence of varicose veins, proximal DVT, residual thrombus after 6 months of treatment, and inadequate antithrombotic treatment

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms can be intermittent or constant and often appear weeks to months following DVT, but can occur up to years later. Symptoms are generally progressive over time and include pain in the extremity, heaviness of effected limb, itching, cramps, and paresthesia. Physical signs include edema of extremity, changes in skin pigmentation, venous dilation, telangiectasia, and ulceration (Fig. E1).

ETIOLOGY

Venous insufficiency results from chronic venous hypertension due to obstruction from thrombus and to reflux related to valvular incompetence. Inflammatory cytokines such as interleukin-6 are thought to play a role.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

DVT, primary venous insufficiency, Baker cyst, tumor, lymphedema, lipedema, and injury to extremity.

WORKUP

Clinical diagnosis based on history of DVT and signs and symptoms of chronic venous insufficiency. The Villalta scale can be used in cases when the diagnosis is uncertain. It is the most widely used scoring system for both diagnosing postthrombotic syndrome (PTS) and assessing its severity.

- Entails five patient symptoms (pain, leg cramps, heaviness in extremity, paresthesia, and pruritus) and six physical signs (pretibial edema, skin induration, hyperpigmentation, pain with calf compression, venous ectasia, and redness).
- Scored on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe).
- Total score ranges from 0 to 33; a score ≥5 is consistent with a diagnosis of PTS.
  1. PTS can also be diagnosed if a venous ulcer is present independent of total score.
- Severity is assessed based on score:
  1. Mild = score of 5 to 9
  2. Moderate = score of 10 to 14
  3. Severe = score of 15 to 33

LABORATORY TESTS

None presently used

IMAGING TESTS

Venous duplex ultrasonography or compression ultrasonography can be done to look for prior evidence of DVT but is not necessary to make the diagnosis.

TREATMENT

- First-line treatment includes compression stockings, regular exercise, and elevation of extremity.
- Lymphedema therapy and intermittent pneumatic compression devices can be used as well.
- Skin care is important, particularly in cases with eczematous changes. Moisturizing lotions can be used in conjunction with mild potency corticosteroids.
- Diuretics have a limited role but can decrease edema in some patients.
- Endovascular recanalization can be considered for cases that are refractory to treatment and where pain control is difficult. Two randomized controlled trials have been done to study the benefits.
- A 2007 randomized controlled trial, Catheter Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis, sought to answer the question of whether early endovascular recanalization would reduce long-term venous disease or improve quality of life. After 2 yr of follow up, there was no significant difference between groups with respect to either primary end point.
- A second trial, Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT), was a randomized multicenter trial conducted to assess whether catheter-directed thrombolysis (CDT) along with a device that aspirates and breaks down thrombus was superior to standard therapy at preventing postthrombotic syndrome. However, no significant difference was found between groups (47% in the treatment group vs 48% in the control group developed PTS; risk ratio, 0.96; 95% confidence interval, 0.82 to 1.1; P=0.56).
- The American College of Cardiology does not recommend routine use of CDT as first-line treatment but states it may be useful for patients at low risk of bleeding or for those with limb-threatening complications.
- Surgical repair is generally reserved for severe cases causing acute limb-threatening circulatory compromise and for those with nonhealing ulcers. Surgical options include angioplasty, venous bypass, or endophlebectomy.

DISPOSITION

- Chronic venous insufficiency can impair quality of life and is often a chronic condition.
- Early treatment with anticoagulation may decrease the risk of postthrombotic syndrome.
- Early use of compression stockings can reduce symptoms of venous insufficiency and halt progression.

REFERRAL

Lymphedema clinic, interventional radiology, and vascular surgery

PEARLS & CONSIDERATIONS

COMMENTS

Compression stockings have the most evidence both for preventing postthrombotic syndrome and for treatment once the syndrome has developed.

PREVENTION

There is evidence both for and against early treatment with thrombolytic drugs to prevent postthrombotic syndrome. Reducing the recurrence of DVT is the best way to prevent PTS. With each subsequent DVT the risk of PTS increases. Periodic leg elevation, weight loss, smoking cessation, and regular exercise are all thought to prevent PTS; however, no randomized controlled trial has been done to evaluate.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Deep Vein Thrombosis (Related Key Topic)
Venous Insufficiency, Chronic (Related Key Topic)

AUTHOR: **Lynn Dado, MD**

FIG. E1 Left medial malleolus venous ulcer due to postthrombotic syndrome in a 57-yr-old man with a history of left iliofemoral DVT and extensive tobacco use. Note the erythema and thickening of the skin of the left lower calf. (Courtesy Suresh Vedantham, MD. In Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

SUGGESTED READINGS

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Kahn SR, Shrier I et al: Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis, *Ann Intern Medicine* 149:698-707, 2008.

Vedantham S, Goldhaber SZ et al: Acute venous thrombosis: thrombus removal with adjunctive catheter-directed thrombolysis, *American Heart Journal* 165:523-530.e3, 2013.

BASIC INFORMATION

DEFINITION

Posttraumatic stress disorder (PTSD) develops in some people after witnessing or experiencing a traumatic event that involves actual or threatened injury to self or others. Symptoms continue longer than a mo after the event or may have delayed onset and include intrusive thoughts, nightmares, flashbacks, avoidance of things associated with the trauma, hypervigilance, sleep disturbance, and negative changes in mood and cognition. These symptoms cause distress and a decline in interpersonal, social, and occupational functioning. People with PTSD may feel numb or irritable, may be easily startled or frightened, and sometimes isolate themselves from others. They are at risk for comorbid psychiatric illness, substance abuse, and suicide.

SYNONYMS

PTSD
Soldier's heart
Effort syndrome
Shell shock
Concentration camp syndrome

ICD-10CM CODES	
F43.10	Post-traumatic stress disorder, unspecified
F43.11	Post-traumatic stress disorder, acute
F43.12	Post-traumatic stress disorder, chronic
DSM-5 CODES	
309.81	Posttraumatic stress disorder
309.89	Other specified trauma and related disorder
309.9	Unspecified trauma and stressor-related disorder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Fewer than 10% of individuals who have experienced a traumatic event will develop PTSD; however, there is considerable variability in prevalence rates associated with specific trauma types.

PREVALENCE (IN U.S.):

- 12-mo prevalence in the U.S. 3% to 6%. Estimated lifetime prevalence 7.8% to 12.3%.
- Prevalence among high-risk populations (e.g., combat veterans or victims of violent crimes) up to 58%.
- Comorbidity is common: depression, anxiety, substance use, personality disorders, and somatic symptom disorder.
- Factors most associated with development are previous traumatic experience and subsequent life stress and perceived lack of social support.

PREDOMINANT AGE AND SEX:

- No predisposing age factors.
- Twice as many women as men are affected (prevalence 10% to 14% for women and 5% to 6% for men). More than 50% of cases in women are related to sexual assault.

GENETICS: Several studies, including twin studies, have demonstrated genetic factors associated with increased risk of developing PTSD after trauma exposure.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Core symptom clusters include intrusion, avoidance, negative mood and cognition, hyperarousal, and sometimes dissociative symptoms. Individuals present with different variations of these symptoms.. Individuals who display these core symptom clusters within the first posttrauma mo are said to have acute stress disorder. In PTSD, these symptoms must be present >1 mo after the trauma and result in significant distress and functional impairment.

Key PTSD symptoms:

- Distressing memories or dreams of the event. NOTE: Children older than 6 yr may express this symptom in repetitive play
- Flashbacks
- Intense distress after reminders of the event
- Avoidance due to trauma-related thoughts or feelings
- Persistent negative trauma-related emotions
- Feeling detached
- Aggressive or reckless behavior
- Hypervigilance
- Problems with concentration or sleep
- Depersonalization

ETIOLOGY

- Common types of trauma: Violent personal assault, natural disaster, military combat, rape, motor vehicle accident, childhood abuse and neglect, critical illness or hospitalization in ICU, severe physical injury, diagnosis of life-threatening illness.
- Risk factors: Previous trauma, initial severity of reaction to event, psychiatric history, traumatic brain injury, childhood abuse or neglect, poor social support, gender, age.
- Interpersonal violence is more likely to cause PTSD than events such as motor vehicle accidents or natural disasters.
- Severity of physical injury is a weaker predictor of PTSD than the psychological distress; stress duration and social support are factors, among others.
- Proposed mechanisms include activation of the amygdala, disruption of prefrontal cortex modulation of the amygdala, and excessive stress-induced HPA and alpha-1 receptor activation.

DIAGNOSIS

Diagnosis is made when the stressor is consistent with DSM-5 definition, with symptoms of reexperiencing, avoidance, negative mood and cognition, and arousal and reactivity. The symptoms must be present for >1 mo, must cause impairment in functioning, and must not be attributable to substance use or other medical conditions. Subtypes include dissociative (PTSD criteria and depersonalization or derealization) and delayed onset (PTSD criteria starting at least 6 mo after the event).

Definition of stressor:

- Exposure to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence with directly experiencing the event, witnessing the event occur to others, or learning that a close relative or close friend was exposed to trauma. If the event involved actual or threatened death, it must have been violent or accidental.
- Repeated or extreme indirect exposure to aversive details of the event(s), usually in the course of professional duties (e.g., first responders collecting body parts; professionals repeatedly exposed to details of child abuse).

DIFFERENTIAL DIAGNOSIS

- Adjustment disorders: Precipitating stress is less catastrophic and psychological reaction is less specific
- Mood disorder: Depression or bipolar
- Anxiety disorders
- Somatic symptom or conversion disorder (functional neurological symptom disorder)
- Psychotic disorder
- Traumatic brain injury

WORKUP

- Validated self-report questionnaires and structured diagnostic instruments include the Posttraumatic Diagnostic Scale and Clinician Administered PTSD Scale (CAPS).
- Although numerous potential biomarkers have been identified and are under investigation, at this time evidence is not conclusive. To date, laboratory and imaging are not clinically useful.
- Primary care PTSD (PC-PTSD) screen recommended by the Veterans' Administration.
- "Yes" answer to three of four of the following questions is a positive screen. In your life, have you ever had any experience that was so frightening, horrible, or upsetting that, in the past mo, you:
  1. Have had nightmares about it or thought about it when you did not want to?
  2. Tried hard not to think about it or went out of your way to avoid situations that reminded you of it?
  3. Were constantly on guard, watchful, or easily startled?
  4. Felt numb or detached from others, activities, or your surroundings?

TREATMENT

- According to the most recent International Society for the Study of Traumatic Stress (ISTSS) treatment guidelines, cognitive-behavioral therapy approaches, including prolonged exposure (PE) and cognitive processing therapy (CPT), have the greatest empirical support to date among psychotherapy approaches.
- Prolonged exposure (PE) includes psychoeducation on the stress response, imaginal exposure focused on recounting trauma memories, and in vivo exposure focusing on reducing avoidance of anxiety-provoking situations associated with the trauma.

- CPT includes written exposure to the trauma memory combined with cognitive therapy.
- A recent clinical trial found that brief written exposure therapy intervention was noninferior to standard CPT and had fewer dropouts.
- Group therapy. Current standards recommend individual therapy as first-line. A growing number of studies have demonstrated efficacy of cognitive behavioral therapy (CBT) in a group format, although results are mixed, with some studies finding individual therapy to be superior.
- Eye movement desensitization reprocessing (EMDR) is considered an evidence-based treatment for PTSD in treatment guidelines, demonstrating comparable efficacy to traditional CBT approaches in clinical trials. However, to date it is unclear whether it offers advantages over, or operates through distinct mechanisms from, traditional CBT approaches. Evidence supporting the efficacy of the eye movements and parallel stimulation component is limited.
- A growing number of studies have demonstrated efficacy of CBT approaches for PTSD delivered through novel formats, including exposure therapy integrating virtual reality technology and Internet- and telephone-delivered CBT, although more research is needed to ascertain whether these approaches are comparable to traditional formats.
- Couples therapy when appropriate.

MEDICATIONS

There is no definitive cure for PTSD, and individuals have varying responses to different medications. Sertraline and paroxetine, both SSRIs, are the only FDA-approved medications for PTSD. Other medication use is off-label with differing levels of evidence to support use. Medications are used to target symptoms and the physiologic changes associated with PTSD and with psychiatric disorders that are frequently comorbid with PTSD. According to ISTSS treatment guidelines, SSRIs and SNRIs are currently considered the first-line pharmacologic treatments for PTSD, and it is recommended that they be prescribed for duration of at least 8 to 12 wk, with some studies demonstrating maximum benefit reached as late as 36 wk.

- SSRIs: Sertraline, paroxetine, fluoxetine.
- SNRIs: Venlafaxine, duloxetine.
- Other antidepressants: Mirtazapine has shown efficacy in small randomized trials.
- Alpha-adrenergic receptor blockers: Prazosin has demonstrated some efficacy in reducing nightmares. A meta-analysis of six RCTs comparing prazosin to placebo found a significant reduction in distress and/or frequency of nightmares, but a recent RCT in military veterans with PTSD did not show efficacy.
- Atypical antipsychotics (e.g., risperidone, quetiapine, olanzapine) have demonstrated efficacy as augmenting agents for individuals with partial response to SSRIs and may be particularly beneficial for individuals with paranoia, extreme anxiety, or angry outbursts.
- Transcranial magnetic stimulation (TMS) is being evaluated as a possible effective treatment modality.
- Ketamine: Recent clinical trials of intravenous ketamine infusion showed PTSD and depression symptom reduction, although more research is needed.
- *N*-methyl-D-aspartate (NMDA) agonists and partial agonists have shown some efficacy in early clinical trials, although more research is needed.
- Recent efforts are underway to examine the efficacy of pharmacologic interventions in preventing development of PTSD early after exposure to trauma, though more research is needed.

ACUTE GENERAL Rx

- Immediate post-incident debriefing may worsen outcome.
- Benzodiazepines are not currently recommended as monotherapy for the treatment of PTSD, as there is no evidence that they reduce reexperiencing and avoidance/numbing symptoms.
- Betaadrenergic blockers may be helpful if given within hours after the trauma to disrupt the physiologic stress response, although more research is needed.
- Sedating antidepressants or sleep aids may be helpful for initial insomnia.

DISPOSITION

- Recovery rates are highest in the first 12 mo after onset.
- Average duration of symptoms is 36 mo for those who undergo treatment and 64 mo for those never treated.
- 50% chance of remission at 2 yr; 50% have chronic symptoms.
- Predictors of chronic course include previous trauma, premorbid psychiatric function, panic reaction at time of event, prolonged terror, or dissociation at time of event.

REFERRAL

Because early intervention improves outcome, refer to a specialist as soon as diagnosis made.

PEARLS & CONSIDERATIONS

- PTSD is associated with increased occurrence of suicidal ideation and attempts.
- PTSD can be associated with aggressive and violent behavior.
- Traumatic medical experiences such as being in the ICU, myocardial infarction, or an emergent cesarean section can cause PTSD.
- Individuals with PTSD frequently present with comorbid psychiatric disorders, including substance abuse, major depression, anxiety disorders, and personality disorders.
- Among combat veterans of recent wars, there is a 41% cooccurrence with mild TBI.
- PTSD may vary culturally and present as culturally specific syndromes and idioms of distress.
- Treatment can be effective even if it begins yrs after the traumatic event occurred.
- Cannabis is available from medical dispensaries in many states for treating PTSD, yet its efficacy in treating PTSD symptoms remains uncertain. Current evidence is insufficient to draw conclusions about the benefits and harms of plant-based cannabis preparations in patients with PTSD, but several ongoing studies may soon provide answers.[1]

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Posttraumatic Stress Disorder (PTSD) (Patient Information)

AUTHOR: **Catherine D'Avanzato, PhD**

[1] O'Neil MF et al: Benefits and harms of plant-based cannabis for posttraumatic stress disorder, *Ann Int Med* 167:332-340, 2017.

SUGGESTED READINGS

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Sloan DM et al: A brief exposure-based treatment vs cognitive processing therapy for posttraumatic stress disorder: a randomized noninferiority clinical trial, *JAMA Psychiatry* 75:233-239, 2018.

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Postural Orthostatic Tachycardia Syndrome (POTS)

BASIC INFORMATION

DEFINITION

Postural orthostatic tachycardia syndrome (POTS) is an under-recognized autonomic disorder defined as a form of orthostatic intolerance in which an exaggerated increase in heart rate (HR >30 beats per min from baseline, or an increase to 120 beats per min within the first 10 min of standing or tilt table testing) occurs during postural change, without orthostatic hypotension. Symptoms occur while standing and are relieved by recumbency. The orthostatic intolerance should be chronic, lasting for at least 3 to 6 months. Symptoms may be profoundly exacerbated by simple activities, dehydration, or even eating; thus, POTS can be very disabling.

SYNONYMS

Orthostatic tachycardia
Orthostatic intolerance
POTS
Postural tachycardia syndrome
Chronic orthostatic intolerance
Neurocirculatory asthenia

ICD-10CM CODE

I49.8 Disorder of the autonomic nervous system, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown

PREVALENCE: Most prevalent form of orthostatic intolerance—estimated to be 5 to 10 times more common than orthostatic hypotension; ~3,000,000 patients in the United States (25% are disabled and unable to work)

PREDOMINANT SEX AND AGE: Female:male ratio of 5:1. Mean age is 30 yr old (most commonly between 15 to 50 yr old).

GENETICS: POTS is a heterogeneous entity, and thus, no single mutation is responsible for the syndrome. Mutations in a norepinephrine transporter have been identified in one case of familial POTS. They result in decreased norepinephrine clearance at the synaptic cleft, causing excessive sympathetic activation. Additionally, polymorphisms in genes encoding the beta-2 adrenoreceptor and nitric oxide synthase may also play a role in some patients.

RISK FACTORS:

- Female sex
- Family history
- Preceding viral infection or systemic illness (up to 50% of cases)
- Deconditioning and prolonged bed rest
- Medications (e.g., vasodilators, diuretics, antidepressants, anxiolytic agents)
- Predisposition to hypovolemia
- Autoimmune disorders (e.g., multiple sclerosis, mast cell activation syndrome)
- Excessive sympathetic states (e.g., sepsis, trauma, surgery)
- Underlying autonomic neuropathy such as in advanced diabetic states
- Chronic fatigue syndrome (40% have POTS)
- Mitral valve prolapse
- Joint hypermobility disorders (e.g., Ehlers-Danlos syndrome)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms vary and may be related to orthostasis (with cerebral hypoperfusion) or autonomic dysfunction. In some patients, symptoms manifest as non-orthostatic, generalized complaints. Common symptoms on presentation include:

- Palpitations, particularly with standing
- Anxiety, depression, or memory problems
- Tremulousness
- Dizziness, lightheadedness, blurred vision, presyncope, and syncope
- Intolerance to exercise or heat and constantly feeling cold
- Nausea, abdominal pain, and irritable bowel syndrome
- "Coat-hanger" headaches involving the upper trapezius muscle
- Cyclic nature (e.g., worsening with intravascular volume changes during menstrual cycle)
- Chronic fatigue and daytime sleepiness

Physical findings are key in raising clinical suspicion for POTS. Important physical findings include the orthostatic hemodynamic changes and a reduced pulse pressure with marked beat-to-beat variability of both pulse pressure and HR. Flack sign is the difficulty in palpating a radial pulse with continued standing or Valsalva maneuver. There may be venous prominence with continued standing resulting in acrocyanosis and swelling of the feet.

- 10% of dysautonomic POTS may progress to paroxysmal atrial fibrillation.
- Recent studies suggest a link between dysautonomia, POTS, and joint hypermobility syndrome.

ETIOLOGY

Heterogenous etiologies, which overlap in different types of POTS:

- Hypovolemic POTS: Decreased effective intravascular volume with peripheral and splanchnic venous pooling that worsens with standing. Studies have demonstrated a reduced plasma volume and red blood cell count in patients with POTS. These patients were also noted to have low renin and aldosterone levels despite their hypovolemic states, which suggests a renal involvement in the pathophysiology of POTS.
- Neuropathic or dysautonomic POTS: Patchy sympathetic denervation of lower extremities and kidneys resulting in orthostatic venous pooling and relative hypovolemia with failure of the peripheral vasculature to vasoconstrict properly upon standing.
- Hyperadrenergic or beta hypersensitivity POTS: High orthostatic plasma norepinephrine levels (≥600 pg/ml); prominent symptoms are of sympathetic over-activation. Patients may have significant orthostatic hypertension. An underlying genetic disorder may be a possible cause.
- Deconditioned POTS: Venous pooling in lower extremities due to weak leg "muscle pump"; fibromyalgia-type symptoms with anxiety, exercise intolerance, and fatigue.
- Immune-related POTS: Classically associated with mast cell activation syndrome (MCAS), though can occur in the setting of other autoimmune disorders. Patients will complain of episodic flushing with tachycardia. Hypertension with orthostatic tachycardia is common.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Orthostatic hypotension
- Inappropriate sinus tachycardia

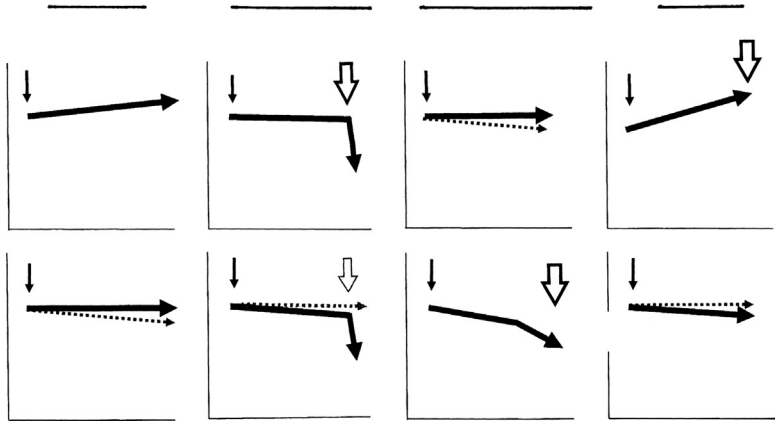

FIG. E1 Schematic drawing of changes in heart rate (HR) and blood pressure (BP) observed during the head-up tilt test. Thin arrows mark the start of orthostatic stress. Large unfilled arrows indicate the appearance of symptoms with changes seen in HR and BP. In normal individuals, the HR increases slightly with no change or a slight reduction in BP. In patients with vasovagal syncope, both the HR and BP drop precipitously with the appearance of symptoms. Postural hypotension is characterized by a drop in BP by 10 to 15 mm Hg as symptoms appear within 10 minutes of standing. Postural hypotension may not occur in the presence of good hydration. In POTS, the HR increases significantly by more than 30 beats/min (or the HR is 120 beats/min or higher) with development of symptoms within 10 minutes of standing. *POTS,* Postural orthostatic tachycardia syndrome. (Park MK: *Park's pediatric cardiology for practitioners,* ed 6, Philadelphia, 2014, WB Saunders.)

BOX E1 Pharmacologic Management of POTS

I β-adrenergic antagonists
- Atenolol 1-2 mg/kg per day
- Metoprolol 1-2 mg/kg per day
- Propranolol 0.5-4 mg/kg per day
- Nadolol

II α-adrenergic agonists
- Midodrine 2.5-10 mg tid
- Pseudoephedrine 60 mg bid
- Methylphenidate 5-10 mg tid

III Mineralocorticoids
- Fludrocortisone 0.1-0.3 mg/day

IV Pyridostigmine 30 mg bid

V Selective serotonin receptor reuptake inhibitors
- Fluoxetine 10-20 mg/day
- Sertraline 25-50 mg/day

POTS, Postural orthostatic tachycardia syndrome. From Swaiman KF et al: *Swaiman's pediatric neurology, principles and practice,* ed 6, Philadelphia, 2017, Elsevier.

- Dehydration or anemia
- Medication side effects
- Other forms of autonomic neuropathies
- Other forms of central dysautonomia
- Deconditioning
- Anxiety and panic attacks
- Vasovagal syncope
- Structural cardiac abnormalities (heart failure, valvulopathy, congenital heart disease)

WORKUP

- Full autonomic system review to evaluate for autonomic neuropathies
- Orthostatic vital signs
- 12-lead electrocardiogram
- Holter monitor in patients with syncope to rule out malignant tachyarrhythmias
- Head-up tilt table testing is diagnostic (Fig. E1). It should be considered in patients where clinical suspicion is high, but HR criteria have not been met after 10 min of standing. To improve diagnostic sensitivity, testing should take place in the morning. Findings during head-up tilt include:
  1. Increase in HR of ≥30 beats/min from baseline, or ≥120 beats/min within 10 min
  2. Absence of hypotension
  3. Orthostatic intolerance symptoms (see earlier)
  4. In select patients, plasma catecholamines can be measured during tilt-table, first while supine and again after standing for 15 min. In 50% of patients who are standing, norepinephrine level ≥600 pg/ml is found, signifying a hyperadrenergic response

LABORATORY TESTS

- Iron studies and complete blood count to evaluate for anemia
- Thyroid stimulating hormone to evaluate for thyroid disease
- 24-hr urine sodium; a level <100 mEq/L suggests a hypovolemic state
- Plasma and urine catecholamines in select patients to rule out pheochromocytoma in appropriate patients

IMAGING STUDIES

Transthoracic echocardiogram to rule out any underlying structural heart disease

Rx TREATMENT

Education about the pathophysiology of POTS and aggravating and alleviating factors can help patients better handle the condition. Suspected medications should be discontinued. ~40% to 90% of patients respond to a combination of non-pharmacotherapy and pharmacotherapy (Box E1). Nonpharmacologic therapies should be implemented first, with pharmacologic therapy reserved for patients with refractory symptoms. Additionally, proper management of underlying medical conditions that may be associated with the disorder can improve quality of life.

NONPHARMACOLOGIC THERAPY

Cornerstone of therapy is increasing vascular tone and effective intravascular volume with prevention of venous pooling. Treatment should take a graded approach, beginning with increasing water and salt intake, exercise and compression stockings.

- Aggravating factors such as alcohol intake, excessive caffeine, dehydration, and extreme heat should be avoided.
- Some measures, such as contracting muscles below the waist for 30 seconds and wearing abdominal binders or support hose, can reduce venous capacitance and increase total peripheral resistance.
- Drinking two 8-oz glasses of water sequentially can result in sympathetically mediated pressor response lasting for 1 to 2 hr.
- Patients, especially those with hypovolemic POTS, usually improve with increasing fluid (2 to 3 L/day) and sodium intake (10 to 20 g of salt). This should be avoided in patients with hyperadrenergic POTS.
- All patients (especially deconditioned ones) can benefit from an exercise-training program (aerobic with lower-extremity strengthening). Patients should work toward 20 to 30 min of aerobic exercise, three times weekly. Supine exercise, such as rowing and recumbent cycling, can be particularly beneficial. Regular supine exercise has been shown to improve symptoms to the point of remission in >70% of patients with POTS.
- Atrioventricular node ablation and pacemaker implantation can be considered for recurrent syncope refractory to all other therapies.

ACUTE GENERAL Rx

- Volume expansion with 1 L of normal saline over 1 to 3 hours
- Discontinuation of exacerbating factors

CHRONIC Rx

Appropriate pharmacologic treatment of POTS is dependent on the subtype. Treatments that are beneficial for one subtype may worsen other subtypes.

- Volume expanders such as fludrocortisone or desmopressin (DDAVP) can be useful for hypovolemic and neuropathic POTS.
- β-blockers (propranolol and atenolol) for neuropathic (allow for unopposed α-receptor-mediated vasoconstriction) and hyperadrenergic (block β1 receptors in heart) POTS. They may worsen symptoms in hypovolemic POTS by decreasing cardiac output.
- Ivabradine, which decreases HR but does not affect BP, improved symptoms in 60% of patients in one study. Especially helpful in hyperadrenergic POTS.
- SSRIs for neuropathic and hyperadrenergic POTS (decrease the central production of serotonin).
- Vasoconstrictors such as midodrine may be helpful for neuropathic POTS. Droxidopa should only be considered in refractory cases.
- Central sympatholytic agents (clonidine and methyldopa) for hyperadrenergic POTS.
- Erythropoietin for refractory neuropathic or hypovolemic POTS (increases sensitivity to angiotensin II).
- Pyridostigmine reduces tachycardia and may be an effective agent.
- Immunomodulatory agents such as IVIG and rituximab are being studied in the treatment of POTS to target immune dysautonomia but as of now are purely investigational.

DISPOSITION

Can usually be managed in an outpatient setting

REFERRAL

Cardiology and occasionally expertise in electrophysiology as needed

PEARLS & CONSIDERATIONS

COMMENTS

This syndrome remains poorly understood, and current therapies may not be effective. Because of its debilitating nature, young age of presentation, and recurrent symptoms, patients often feel discouraged and may need psychological support.

PREVENTION

None except therapies previously mentioned

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Orthostatic Hypotension (Related Key Topic)

AUTHORS: **Esseim Sharma, MD,** and **Aravind Rao Kokkirala, MD, FACC**

SUGGESTED READINGS

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Thanavaro JL et al: Postural orthostatic tachycardia syndrome: diagnosis and treatment, *Heart Lung* 40(6):554-560, 2011.

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BASIC INFORMATION

DEFINITION

Precocious puberty is defined as the development of secondary sexual characteristics before age 8 in females and age 9 in males.

SYNONYM

Pubertas praecox

ICD-10CM CODE
E30.1 Precocious puberty

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Estimated to be between 1 in 5000 to 1 in 10,000
PREDOMINANT SEX: Females are affected five times more often than males for the idiopathic variant; for other causes, it is dependent on the underlying etiology.
GENETICS: The genetics for some of the etiologies of precocious puberty is known. The most common genetic cause of central precocious puberty (CPP) in humans is a deficiency of *MKRN3* (makorin ring finger protein 3). Other reported genetic causes of CPP include a *MRF3* (MA3 domain-containing translation regulatory factor) loss of function mutation and a *KISS1* (KiSS-1 metastasis suppressor) gain of function mutation.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- In females: Breast development, pubic hair development, accelerated growth, menarche
- In males: Increase in testicular volume (>4 ml) and penile length, pubic hair development, accelerated growth, muscular development, acne, change in voice, penile erections

ETIOLOGY

- Central (Gonadotropin hormone-releasing hormone [GnRH]-dependent, "true precocious puberty"):
  1. Idiopathic (74%)—diagnosis of exclusion
  2. CNS problem (7%)
     a. Tumor, encephalitis, head trauma, hydrocephalus
- Peripheral (GnRH-independent, incomplete, pseudopuberty):
  1. Ovarian cyst or tumor (11%)
  2. McCune-Albright syndrome (5%)
  3. Adrenal feminizing or masculinizing (2%)
  4. Ectopic gonadotropin production (0.5%)
  5. Severe hypothyroidism (very rare)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Most common diagnoses to consider: Premature thelarche (breast tissue development in absence of other secondary sex characteristics or menarche) and premature adrenarche (axillary or pubic hair growth, acne, and/or body odor in absence of other secondary sex characteristics or menarche)
- Constitutional precocity—onset near 8 yr of age, familial
- GnRH-dependent precocious puberty: Idiopathic, CNS tumors, hypothalamic hamartomas, neurofibromatosis type I, tuberous sclerosis, hydrocephalus, status after acute head injury, ventricular cysts, status after CNS infection
- GnRH-independent precocious puberty: Congenital adrenal hyperplasia, adrenocortical tumors (males), McCune-Albright syndrome (females), gonadal tumors, ectopic human chorionic gonadotropin (hCG)-secreting tumors (chorioblastoma, hepatoblastoma), exposure to exogenous sex steroids, severe hypothyroidism
- Table E1 summarizes the differential diagnosis of sexual precocity

WORKUP

Priorities:
- Rule out life-threatening disease (neoplasm of central nervous system [CNS], gonad, adrenal). A classification of sexual precocity is summarized in Table E2.
- Establish velocity of process.
- A thorough history and physical examination are essential to determine if the patient has true precocious puberty. Particular attention should be paid to growth, development, order of appearance of the secondary sexual characteristics, pubertal development in family members, medications, neurologic symptoms, Tanner staging, abdominal and neurologic examination. Flowcharts for diagnosing sexual precocity in females and males are shown in Figs. 1 and 2.

LABORATORY TESTS

- GnRH stimulation testing will help determine if dependent or independent cause.
- Sex hormone studies: Luteinizing hormone, follicle-stimulating hormone, hCG, testosterone (males), estrogen (females). Levels of sex steroids should be determined in the morning, with use of assays that have detection limits adapted to pediatric values. In girls, serum estradiol levels are highly variable and have a rather low sensitivity for the diagnosis of precocious puberty.
- Free T_4, thyroid-stimulating hormone (TSH).

IMAGING STUDIES

- Bone age: Left hand/wrist x-ray establishes severity of process
- CT scan or MRI of the brain to evaluate for CNS pathology
- Consideration of pelvic ultrasound in female patients to evaluate for ovarian cysts or tumors
- Abdominal imaging with CT scan if intraabdominal pathology suspected

TREATMENT

NONPHARMACOLOGIC THERAPY

- Good communication with parents is essential to care.
- Psychological support for the child may be needed to address issues with self-image and peer acceptance.
- Given that sexual development occurs in advance of aging and maturity, social and emotional difficulties may occur. These children are also particularly vulnerable to sexual abuse.

ACUTE GENERAL Rx

There is no acute therapy for precocious puberty.

CHRONIC Rx

Therapy depends on the etiology of precocious puberty. For the treatment of central or gonadotropin-dependent precocious puberty depot GnRH agonists (leuprorelin, leuprolide, triptorelin, goserelin, histrelin, buserelin) are effective.
- Leuprolide is given 0.25 to 0.3 mg/kg with a 7.5 mg minimum IM every 4 wk. Local side effects include pain, erythema, and inflammatory reactions. Other side effects include headaches and menopausal-like symptoms (asthenia, hot flashes).
- For other CNS lesions and extragonadal tumors, therapy is dependent on the type of lesion, location of the lesion, and the overall prognosis of the underlying problem.
- For severe hypothyroidism, treatment with thyroid hormone will result in regression of the sexual development. The child will subsequently undergo appropriate pubertal development later in life.
- For familial male gonadotropin-independent precocious puberty, the androgen-synthesis inhibitor ketoconazole can be used at doses of 600 mg/day divided tid, or a combination of the aromatase inhibitors testolactone or anastrozole and spironolactone can be used.

DISPOSITION

- For true precocious puberty and some CNS lesions, long-term outcome is usually favorable. When pharmacological therapy is initiated, it is typically continued until the child is deemed to be of an appropriate age to progress through puberty.
- For other cases, long-term outcomes depend on the prognosis of the underlying cause.

REFERRAL

- Initial workup can be instituted by the primary care provider.
- Referral to an endocrinologist is indicated for most children for long-term management, monitoring, and treatment.
- Attention to the emotional well-being of the child is important.

RELATED CONTENT

Precocious Puberty (Patient Information)

AUTHORS: **Rachel Wright Heinle, MD FACOG,** and **Ashlie Sewdass Carter, MD**

TABLE E1 Differential Diagnosis of Sexual Precocity

Disorder	Plasma Gonadotropins	Lh Response to GnRH	Serum Sex Steroid Concentration	Gonadal Size	Miscellaneous
Gonadotropin Dependent					
True (central) precocious puberty	Prominent LH pulses (premature reactivation of GnRH pulse generator)	Pubertal LH response initially during sleep	Pubertal values of testosterone or estradiol	Normal pubertal testicular enlargement or ovarian and uterine enlargement	MRI of brain to rule out CNS tumor or other abnormality
Gonadotropin Independent					
Males					
Chorionic gonadotropin-secreting tumor in males	High hCG, low LH	Prepubertal LH response	Pubertal value of testosterone	Slight to moderate uniform enlargement of testes	Hepatomegaly suggests hepatoblastoma; MRI of brain if chorionic gonadotropin-secreting CNS tumor suspected
Leydig cell tumor in males	Suppressed	No LH response	High testosterone	Irregular, asymmetric enlargement of testes	
Familial, male-limited precocious puberty (FMPP, "testotoxicosis")	Suppressed	No LH response	Pubertal values of testosterone	Testes symmetric and >2.5 cm but smaller than expected for pubertal development; spermatogenesis occurs	Activating mutation of the LHCG receptor; autosomal dominant transmission
Virilizing congenital adrenal hyperplasia	Prepubertal	Prepubertal LH response	Elevated 17-OHP in CYP21 deficiency or elevated 11-deoxycortisol in CYP11B1 deficiency	Testes prepubertal	Autosomal recessive, variable severity/age of onset; may have salt loss in CYP21 deficiency or hypertension in CYP11B1 deficiency
Virilizing adrenal tumor	Prepubertal	Prepubertal LH response	High DHEAS, DHEA, and/or androstenedione values	Testes prepubertal	CT, MRI, or US of abdomen
Females					
Granulosa cell tumor (follicular cysts may present similarly)	Suppressed	Prepubertal LH response	Very high estradiol	Ovarian enlargement on physical examination, CT, MRI, or US	Tumor often palpable on physical examination
Follicular cyst	Suppressed	Prepubertal LH response	Prepubertal to very high estradiol	Ovarian enlargement on physical examination, CT, MRI, or US	Single or recurrent episodes of menses and/or breast development; exclude McCune-Albright syndrome
Feminizing adrenal tumor	Suppressed	Prepubertal LH response	High estradiol, variable DHEAS increase	Ovaries prepubertal	Unilateral adrenal mass
Nonclassical congenital adrenal hyperplasia	Prepubertal	Prepubertal LH response	Elevated 17-OHP in basal or corticotropin-stimulated state	Ovaries prepubertal	Autosomal recessive
In Both Sexes					
McCune-Albright syndrome	Suppressed	Suppressed	Sex steroid pubertal; estradiol may be quite high in girls	Ovarian enlargement (asymmetrical) on US; slight (usually symmetrical) testicular enlargement	Skeletal survey/bone scan for polyostotic fibrous dysplasia and skin examination for café au lait spots
Primary hypothyroidism	LH prepubertal; FSH may be slightly elevated	Prepubertal; FSH response flat	Estradiol may be pubertal	Testicular enlargement; ovaries cystic	TSH and prolactin elevated; T_4 low
Incomplete Precocity/Variations Of Puberty					
Premature thelarche	Prepubertal	Prepubertal LH	Prepubertal or early pubertal estradiol response	Ovaries prepubertal	Onset usually before 3 yr of age
Premature adrenarche (males)	Prepubertal	Prepubertal LH response	Prepubertal testosterone; DHEAS, or urinary 17-ketosteroid values appropriate for pubic hair stage 2	Testes prepubertal	Onset usually after 6 yr of age; more frequent in CNS-injured children
Premature adrenarche (females)	Prepubertal	Prepubertal LH response	Prepubertal estradiol; DHEAS or urinary 17-ketosteroid values appropriate for pubic hair stage 2	Ovaries prepubertal	Onset usually after 6 yr of age; more frequent in brain-injured children

CNS, Central nervous system; *CT,* computed tomography; *CYP,* P450 cytochrome isoenzyme; *DHEAS,* dehydroepiandrosterone sulfate; *FSH,* follicle-stimulating hormone; *GnRH,* gonadotropin-releasing hormone; *hCG,* human chorionic gonadotropin; *LH,* luteinizing hormone; *MRI,* magnetic resonance imaging; 17-*OHP,* 17-hydroxyprogesterone; T_4, thyroxine; *TSH,* thyrotropin; *US,* ultrasonography.
Modified from Styne DM, Grumbach MM: Physiology and disorders of puberty. In Melmed S et al (eds): *Williams textbook of endocrinology,* ed) 13, Philadelphia, 2016, Elsevier, Table 25.41, pp 1196-1197. In Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

TABLE E2 Classification of Sexual Precocity

True Precocious Puberty Or Complete Isosexual Precocity (GnRH-Dependent Sexual Precocity Or Premature Activation Of The Hypothalamic GnRH Pulse Generator)

Idiopathic true precocious puberty
CNS tumors
Optic glioma associated with neurofibromatosis type 1
  Hypothalamic astrocytoma
Other CNS disorders:
  Developmental abnormalities including hypothalamic hamartoma of the tuber cinereum
  Encephalitis
  Static encephalopathy
  Brain abscess
  Sarcoid or tubercular granuloma
  Head trauma
  Hydrocephalus
  Arachnoid cyst
  Myelomeningocele
  Vascular lesion
  Cranial irradiation
True precocious puberty after late treatment of congenital virilizing adrenal hyperplasia or other previous chronic exposure to sex steroids
True precocious puberty due to mutations:
  in *KISS1R/GRP54* gene
  in *KISS1 gene*
  MKRN3 gene

Incomplete Isosexual Precocity (Hypothalamic GnRH-Independent)

Males

Gonadotropin-secreting tumors:
  hCG-secreting CNS tumors (e.g., chorioepitheliomas, germinoma, teratoma)
  hCG-secreting tumors located outside the CNS (hepatoma, teratoma, choriocarcinoma)
Increased androgen secretion by adrenal or testis:
  Congenital adrenal hyperplasia (CYP21 and CYP11B1 deficiencies)
  Virilizing adrenal neoplasm
  Leydig cell adenoma
  Familial testotoxicosis (sex-limited autosomal dominant pituitary gonadotropin-independent precocious Leydig cell and germ cell maturation)
    Cortisol resistance syndrome

Females

Ovarian cyst
Estrogen-secreting ovarian or adrenal neoplasm
Peutz-Jeghers syndrome with SCTAT

Both Sexes

McCune-Albright syndrome
Hypothyroidism
Iatrogenic or exogenous sexual precocity (including inadvertent exposure to estrogens in food, drugs, or cosmetics)

Variations Of Pubertal Development

Premature thelarche
Premature isolated menarche
Premature adrenarche
Adolescent gynecomastia in boys
Macroorchidism

Contrasexual Precocity

Feminization in Males

Adrenal neoplasm
Chorioepithelioma
CYP11B1 deficiency
Testicular neoplasm (Peutz-Jeghers syndrome)
Increased extraglandular conversion of circulating adrenal androgens to estrogen
Iatrogenic (exposure to estrogens)

Virilization in Females

Congenital adrenal hyperplasia:
  CYP21 deficiency
  CYP11B1 deficiency
  3β-HSD deficiency
Virilizing adrenal neoplasm (Cushing syndrome)
Virilizing ovarian neoplasm (e.g., arrhenoblastoma)
Iatrogenic (exposure to androgens)
Cortisol resistance syndrome
Aromatase deficiency

CNS, Central nervous system; *CYP11B1,* 11-hydroxylase; *CYP21,* 21-hydroxylase; *GnRH,* gonadotropin-releasing hormone; *hCG,* human chorionic gonadotropin; *3β-HSD,* 3β-hydroxysteroid dehydrogenase 4,5-isomerase; *KISS1R/GPR54,* kisspeptin/G protein–coupled receptor 54; *SCTAT,* sex cord tumor with annular tubules.

Modified from Styne DM, Grumbach MM: Physiology and disorders of puberty. In Melmed S et al (eds): *Williams textbook of endocrinology,* ed 13, Philadelphia, 2016, Elsevier, Table 25.25, p 1163. In Kliegman RM: *nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

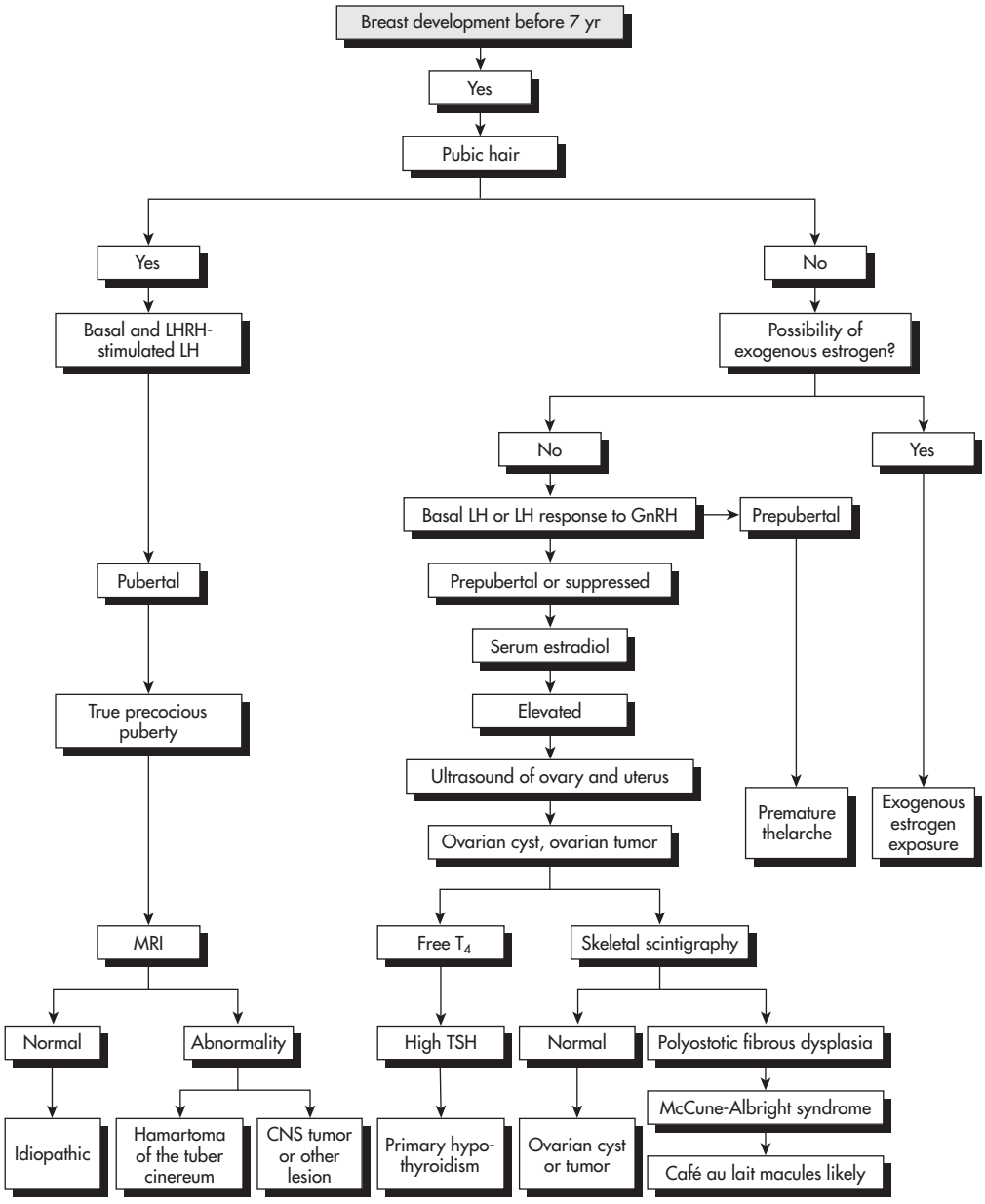

FIG. E1 Flowchart for diagnosing sexual precocity in girls. *CNS,* Central nervous system; *GnRH,* gonadotropin-releasing hormone; *LH,* luteinizing hormone; *LHRH,* luteinizing hormone-releasing hormone; *MRI,* magnetic resonance imaging; *T4,* thyroxine; *TSH,* thyroid-stimulating hormone. (From Melmed S et al: *Williams textbook of endocrinology,* ed 3, Philadelphia, 2011, WB Saunders.)

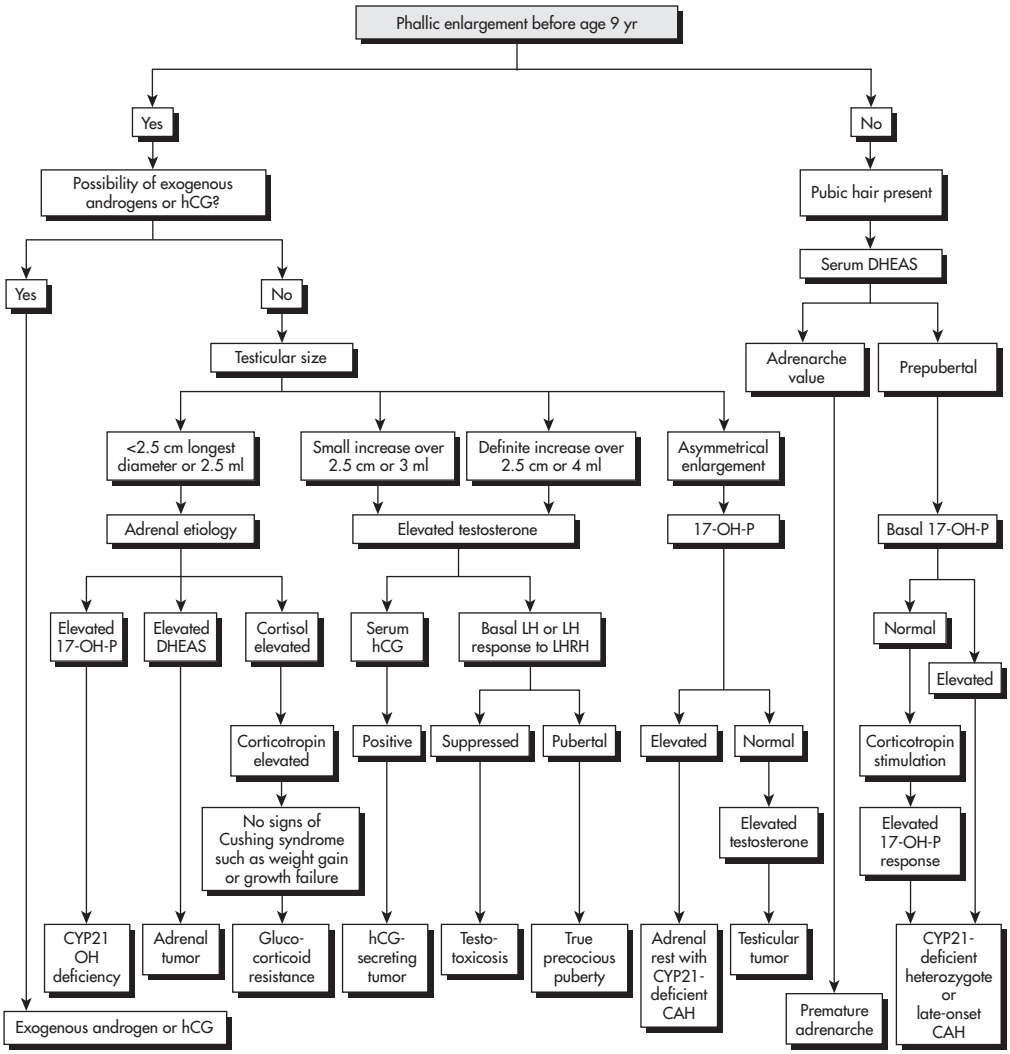

FIG. E2 Flowchart for diagnosing sexual precocity in a phenotypic male. *CAH,* Congenital adrenal hyperplasia; *CYP,* P450 cytochrome isoenzyme; *DHEAS,* dehydroepiandrosterone sulfate; *hCG,* human chorionic gonadotropin; *LH,* luteinizing hormone; *LHRH,* luteinizing hormone-releasing hormone; *17-OH-P,* 17-hydroxyprogesterone. (From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, WB Saunders.)

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Preeclampsia involves the presence of hypertension with other associated comorbidities in a pregnant woman. In 2013, the American College of Obstetrics and Gynecology (ACOG) Task Force on Hypertension in Pregnancy revised the criteria, making preeclampsia a hypertensive disorder and one where the presence of proteinuria was no longer needed to make the diagnosis. The task force reinforced the importance of hypertension as a necessary condition and deemphasized proteinuria. In the absence of proteinuria, thrombocytopenia, new development of renal insufficiency, impaired liver function, pulmonary edema, and new-onset cerebral or visual symptoms could substitute as criteria.

Additionally, the task force emphasized the categories employed in prior ACOG bulletins:

- Preeclampsia: Hypertension with or without proteinuria, but with the presence of one of the previously mentioned comorbidities
- Preeclampsia with severe features (Table 1)
- Chronic hypertension: Hypertension predating pregnancy or present at <20 wk gestation
- Gestational hypertension: Hypertension in pregnancy after 20 wk without proteinuria or any of the previously mentioned comorbidities
- Chronic hypertension with superimposed preeclampsia: The presence of chronic hypertension with sudden increase in blood pressure or escalation of medication when previously well controlled or with development of new onset of signs or symptoms meeting criteria for severe preeclampsia. Table 1 summarizes the criteria for the diagnosis of severe preeclampsia
- Atypical preeclampsia: Onset prior to 20 wk; onset after 48 hr postpartum; gestational proteinuria with symptoms of preeclampsia, hemolysis, thrombocytopenia, or elevated liver enzymes

SYNONYMS

Pregnancy-induced hypertension
Toxemia of pregnancy

ICD-10CM CODES

011.1	Pre-existing hypertension with pre-eclampsia, first trimester
011.2	Pre-existing hypertension with pre-eclampsia, second trimester
011.3	Pre-existing hypertension with pre-eclampsia, third trimester
011.9	Pre-existing hypertension with pre-eclampsia, unspecified trimester
014.00	Mild to moderate pre-eclampsia, unspecified trimester
014.02	Mild to moderate pre-eclampsia, second trimester
014.03	Mild to moderate pre-eclampsia, third trimester
014.10	Severe pre-eclampsia, unspecified trimester
014.12	Severe pre-eclampsia, second trimester
014.13	Severe pre-eclampsia, third trimester
014.90	Unspecified pre-eclampsia, unspecified trimester
014.92	Unspecified pre-eclampsia, second trimester
014.93	Unspecified pre-eclampsia, third trimester

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 2% to 7% in primigravidas, up to more than 50% in multigravidas with risk factors
RISK FACTORS: See Table 2.
GENETICS: Positive correlation with maternal and paternal family history

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Preeclampsia typically presents with hypertension and proteinuria, most commonly in the third trimester of pregnancy.
- May be asymptomatic.
- Generalized swelling or nondependent edema, possibly manifested by rapid weight gain (>4 lb/wk), even in the absence of edema, is common but is nonspecific and is seen in many normal pregnancies.
- Auscultation of pulmonary rales.
- Cerebral symptoms: headache, vision changes
- Right upper quadrant pain (HELLP syndrome [hemolysis, elevated liver enzymes, and low platelet count] or subcapsular liver hematoma).
- Hyperreflexia or clonus.
- Vaginal bleeding (placental abruption).
- Chronic fetal compromise manifested by intrauterine growth restriction or acute fetal compromise manifested by nonreassuring fetal testing.
- Wide range of symptoms attributable to multiorgan system dysfunction, involving hepatic, hematologic, renal, pulmonary, and central nervous systems.
- Possibility of severe disease despite "normal" blood pressure readings, so a high index of suspicion must be maintained in high-risk situations.

ETIOLOGY

- Exact etiology is unknown.
- Theories:
  1. Imbalance between thromboxane A_2 (vasoconstrictor and platelet aggregator) and prostacyclin (vasodilator)
  2. Abnormal trophoblastic invasion of spiral arteries
  3. Increased sensitivity to angiotensin II by the muscular walls of the arteries
  4. Excess circulating soluble FMS-like tyrosine kinase 1 (*sFlt1*), which binds placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), may have a pathogenic role
- Potential secondary effects of the metabolic, inflammatory endothelial alternatives in preeclampsia are described in Table 3.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute fatty liver of pregnancy
- Appendicitis
- Diabetic ketoacidosis
- Gallbladder disease
- Gastroenteritis
- Glomerulonephritis
- Hemolytic-uremic syndrome
- Hepatic encephalopathy
- Hyperemesis gravidarum
- Idiopathic thrombocytopenia
- Thrombotic thrombocytopenic purpura
- Nephrolithiasis
- Pyelonephritis
- Peptic ulcer disease
- Systemic lupus erythematosus

TABLE 1 Criteria for the Diagnosis of Preeclampsia with Severe Features

In patients with preeclampsia, **preeclampsia with severe features** can be diagnosed if any one of the following criteria is present:

Blood pressure ≥160 mm Hg systolic or ≥110 mm Hg diastolic on two separate occasions at least 4 hr apart

Serum creatinine >1.1 mg/dl or a doubling of the serum creatinine

New onset of cerebral or visual disturbances

Pulmonary edema

Hepatocellular injury (serum transaminases at least twice normal) or severe persistent right upper quadrant or epigastric pain

Thrombocytopenia <100,000

TABLE 2 Risk Factors for Preeclampsia

- Nulliparity
- Age >40 yr
- Pregnancy with assisted reproduction
- Interpregnancy interval >7 yr
- Family history of preeclampsia
- Woman born small for gestational age
- Obesity/gestational diabetes
- Multifetal gestation
- Preeclampsia in a previous pregnancy
- Poor outcome in a previous pregnancy
- Fetal growth restriction, placental abruption, fetal death
- Preexisting medical-genetic conditions
- Chronic hypertension
- Renal disease
- Type 1 (insulin-dependent) diabetes mellitus
- Antiphospholipid antibody syndrome

From Gabbe SG et al: *Obstetrics,* ed 7, 2016, Philadelphia, Elsevier.

- Viral hepatitis
- Medications or medication withdrawal

WORKUP

Hypertension:

- Two blood pressure measurements at least 4 hr apart, with the patient sitting or semi-reclining with the back supported, with an absolute pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic
- Blood pressure ≥160 mm Hg systolic or ≥110 mm Hg diastolic
- Hypertension can be confirmed in a brief period to allow for immediate treatment of severe range blood pressure.

Proteinuria:

- ≥300 mg per 24-hr urine collection
- Protein/creatinine ratio ≥0.3
- +1 on dipstick ONLY IF OTHER METHODS NOT AVAILABLE

TABLE 3 Potential Secondary Effects of the Metabolic, Inflammatory Endothelial Alternatives in Preeclampsia

CVS	Increased peripheral resistance leading to hypertension; increased vascular permeability and reduced maternal plasma volume.
Lungs	Laryngeal and pulmonary edema.
Renal	Glomerular damage leading to proteinuria, hypoproteinemia, and reduced oncotic pressure, which further exacerbates the hypovolemia. May develop acute renal failure ± cortical necrosis.
Clotting	Hypercoagulability, with increased fibrin formation and increased fibrinolysis (i.e., disseminated intravascular coagulation).
Liver	HELLP syndrome hepatic rupture.
CNS	Thrombosis and fibrinoid necrosis of the cerebral arterioles. Eclampsia (convulsions), cerebral hemorrhage, and cerebral edema.
Fetus	Impaired uteroplacental circulation, potentially leading to FGR, hypoxemia, and intrauterine death.

CVS, Cardiovascular system; *CNS,* central nervous system; *FGR,* fetal growth restriction; *HELLP,* hemolysis, elevated liver enzymes, low platelets.
From Drife J, Magowan B: *Clinical obstetrics and gynecology,* Philadelphia, 2004, WB Saunders.

- In the absence of proteinuria, preeclampsia may be diagnosed with new onset of hypertension and one of the following:
  1. Platelet count less than 100,000/ml
  2. New-onset, progressive renal insufficiency, serum creatinine concentrations greater than 1.1 mg/dl, or doubling of serum Cr levels in the absence of other renal disease
  3. Elevated serum liver transaminases to twice the normal concentration
  4. Pulmonary edema
  5. New-onset cerebral or visual symptoms
- Because of the insidious nature of the disease with potential for multiple organ involvement, as well as its prevalence, complete evaluation for preeclampsia in any pregnant patient presenting with central nervous system derangement or gastrointestinal symptoms after 20 wk of gestation
- Evaluation for associated conditions such as disseminated intravascular coagulation, hepatic dysfunction, or subcapsular hematoma
- Fig. 1 outlines a management plan for patients with severe preeclampsia

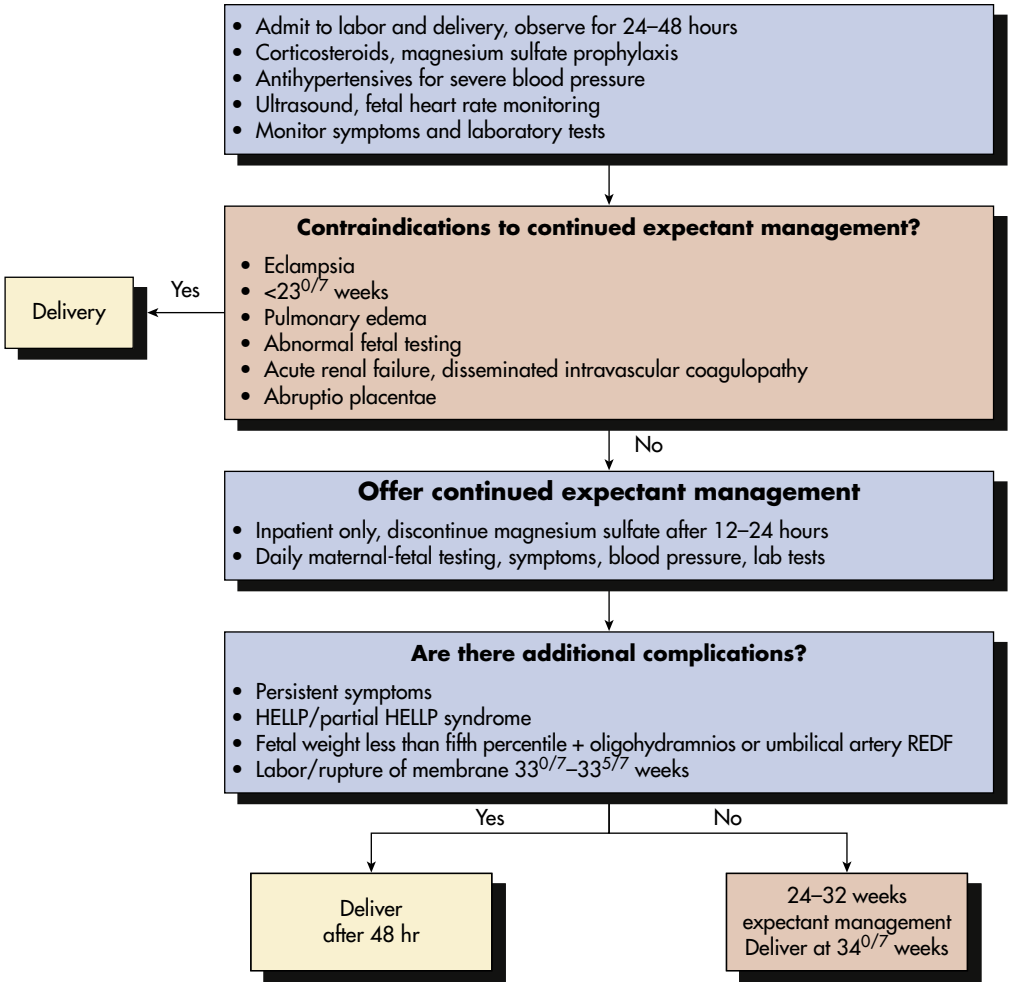

FIG. 1 Management plan for patients with preeclampsia with severe features before 34 wks' gestation. *HELLP,* hemolysis, elevated liver enzymes, and low platelets; *REDF,* reversed end-diastolic flow. (From Gabbe SG et al: *Obstetrics: Normal and problem pregnancies,* ed 7, Philadelphia, 2017, Elsevier.)

LABORATORY TESTS

- High-risk patients: Baseline assessment of renal function (24-hr urine collection for total protein and creatinine clearance or protein:creatinine ratio), complete blood count, serum creatinine, liver function tests (LFTs), and uric acid should be obtained at the first prenatal visit.
- Complete blood count (hemoglobin, hematocrit, platelets) may show signs of hemoconcentration or HELLP syndrome.
- LFTs (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase) are useful in evaluation for HELLP syndrome or to exclude important differentials.
- Hyperuricemia or increased creatinine may indicate decreasing renal function.
- Prothrombin time, partial thromboplastin time, and fibrinogen can be checked to rule out disseminated intravascular coagulation, if clinically appropriate.
- Peripheral smear may demonstrate microangiopathic hemolytic anemia.
- Complement levels can be used to differentiate from an acute exacerbation of a collagen-vascular disease.
- The ratio of soluble FMS-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PlGF) is elevated in pregnant women before the clinical onset of preeclampsia. Increased levels of sFlt1 and reduced levels of PlGF predict subsequent development of preeclampsia. An sFlt-1:PlGR ratio of 38 or lower can be used to predict the short-term absence of preeclampsia in women in whom the syndrome is suspected clinically.[1]

IMAGING STUDIES

- CT or MRI scan of head if atypical presentation of eclampsia or preeclampsia with atypical cerebral symptoms, possibility of intracerebral bleed, or prolonged postictal state
- Sonogram of fetus to evaluate for intrauterine growth restriction amniotic fluid, placenta
- Sonogram of maternal liver if subcapsular hematoma suspected

Rx TREATMENT

ACUTE GENERAL Rx

Delivery is the treatment of choice and the only cure for the disease. This must be taken in the context of the gestational age of the fetus, severity of the preeclampsia, and the likelihood of a successful induction and reliability of patient, if pursuing expectant management.

- For preeclampsia with severe features, administer magnesium sulfate 4 to 6 g IV loading dose, with 2 g/hr maintenance (adjust dosage for renal insufficiency). If there is a contraindication to magnesium sulfate, such as myasthenia gravis, then use phenytoin at 10 to 15 mg/kg loading dose, then 200 mg IV q8h starting 12 hr after loading dose.
- Treat blood pressure (BP) >160 mm Hg systolic or >110 mm Hg diastolic either with hydralazine 5 to 10 mg IV, then 10 mg, every 20 min to a max dose of 20 mg; or with labetalol hydrochloride 20, 40, 80, 80 mg IV, escalating dosage every 10 min to a max dose of 300 mg IV; or with nifedipine 10 to 20 mg orally every 20 min for acute blood pressure control, to a max dose of 180 mg/day. If maximum dose of one medication is reached, add an additional medication to reach goal of BP 140 to 150/90 to 100 mm Hg.
- Continuous fetal monitoring.
- Epidural is anesthesia of choice for pain management in labor or cesarean section.
- All patients undergoing induction of labor or cesarean section should receive antiseizure medications (magnesium sulfate) if disease with severe features, for delivery and 24 hr postpartum.

CHRONIC Rx

- Preeclampsia without severe features <37 wk: Close observation for worsening maternal or fetal condition, with delivery at 37 wk. If 24 to 36 wk, consider antenatal corticosteroids. If severe features develop or there is evidence of fetal compromise, earlier delivery is appropriate.
- Preeclampsia with severe features: Delivery in the presence of maternal or fetal compromise, labor, or 34 wk; at 24 to 34 wk consider steroids with very close monitoring, and at <24 wk consider termination of pregnancy. Risks of expectant management include severe worsening of disease, eclampsia, abruptio placenta, stillbirth, HELLP syndrome, ICU admission, and pulmonary edema.
- Contraindications to expectant management include eclampsia, HELLP syndrome, pulmonary edema, disseminated intravascular coagulation, abruptio placenta, uncontrollable severe hypertension, fetal demise, and nonreassuring fetal status.
- Labetalol, hydralazine, and nifedipine are the drugs of choice for long-term blood-pressure control during pregnancy.

DISPOSITION

Preeclampsia is a progressive and unpredictable disease process; a course of expectancy should be managed with caution. Up to 20% of patients who have seizures are normotensive.

The reoccurrence rate for preeclampsia in a subsequent pregnancy is approximately 20%, and higher in cases with a second trimester presentation or complications. This risk may be decreased with the use of low-dose aspirin.

REFERRAL

Obstetric management is indicated because of the insidious nature of the disease, with transfer of all cases <34 wk to a facility with appropriate maternal and neonatal care facilities.

PEARLS & CONSIDERATIONS

COMMENTS

- Low-dose aspirin, beginning as early as the second trimester, decreases the risk of preeclampsia, preterm birth, and intrauterine growth retardation in women who are at high risk of preeclampsia. The American College of Obstetricians and Gynecologists (ACOG) and the U.S. Preventive Services Task Force (USPSTF) recommend the use of low-dose aspirin as preventive medication starting after 12 wk of gestation (ideally before 16 wk) in women who are at high risk for preeclampsia (previous preeclampsia, multifetal gestation, chronic hypertension, type 1 or 2 diabetes, renal disease, or autoimmune disease).
- The use of low-dose aspirin, 150 mg/day started at 11 to 14 wk gestation, has been demonstrated to decrease the incidence of preterm preeclampsia in a selected high-risk population.[2] In the U.S., low-dose aspirin is available as an 81 mg tablet. U.S. clinicians who recommend aspirin for preeclampsia prevention could consider prescribing two 81 mg tablets daily.
- Although the absolute risk of end-stage renal disease (ESRD) in women who have had preeclampsia is low, preeclampsia is a marker for an increased risk of subsequent ESRD.
- The development of preeclampsia may be one of the earliest identifiable risk markers for potential future cardiovascular disease in women. It has been shown that women who develop preeclampsia have a higher incidence of cardiovascular risk factors including components of the metabolic syndrome within 1 yr of delivery. Women with a history of preeclampsia, particularly preterm or recurrent, are at increased risk for cardiovascular disease and appropriate follow-up should be encouraged.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Preeclampsia (Patient Information)
Eclampsia (Related Key Topic)
Hypertension (Related Key Topic)

AUTHOR: **Philip A. Shlossman, MD**

[1]Zeisler H et al: Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia, *N Engl J Med* 374:13-22, 2016.

[2]Rolnick DL et al: Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia, *N Engl J Med* 377:613-622, 2017.

SUGGESTED READINGS

American College of Obstetricians and Gynecologists: Low-dose aspirin use in pregnancy, ACOG Committee Opinion No. 743, *Obstet Gynecol* 132:e44-e52, 2018.

Committee on Obstetric Practice: Committee Opinion No.: 692: Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period, *Obstet Gynecol* 129(4):e90-e95, 2017.

Gestational hypertension and preeclampsia: ACOG Practice bulletin No. 202. American College of Obstetricians and Gynecologists, *Obstet Gynecol* 133:e1-e25, 2019.

Hypertension in pregnancy: Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy, *Obstet Gynecol* 122(5):1122-1131, 2013.

LeFevre ML: Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement, *Ann Intern Med* 161:819-826, 2014.

Rolnik DL et al: Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia, *N Engl J Med* 377(7):613-622, 2017.

Premature Rupture of Membranes

BASIC INFORMATION

DEFINITION

Premature rupture of membranes (PROM) is defined as rupture of membranes at term before the onset of labor.

SYNONYMS

Preterm premature rupture of membranes (prior to 37 weeks)
PROM

ICD-10CM CODES

042	Premature rupture of membranes
042.113	Preterm premature rupture of membranes

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Affects approximately 8% of all pregnancies

RISK FACTORS: Intraamniotic infection, low socioeconomic status, second- and third-trimester bleeding, low body mass index, nutritional deficiencies, connective tissue disorders, maternal cigarette use, cervical conization or cerclage, short cervix, pulmonary disease in pregnancy, uterine overdistention, amniocentesis, prior history of PROM, prior history of preterm delivery

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients will classically present complaining of leakage or gush of fluid from the vagina. Patients may also present with contractions and vaginal bleeding. Additional symptoms can include fever, chills, or abdominal pain if there is concurrent infection. Ultrasound will often demonstrate oligohydramnios.

ETIOLOGY

Premature rupture of membranes at term may occur due to physiologic changes in addition to uterine contractions causing shearing forces. Although there are many risk factors for PROM, it often occurs in the absence of any known risk factor.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes leakage of urine or vaginal discharge.

WORKUP

Sterile speculum examination demonstrating pooling of fluid in posterior fornix, visualization of fluid coming out of the cervix during Valsalva maneuver, basic vaginal pH, and characteristic fern pattern of vaginal fluid that is dried on a microscope. Table E1 summarizes bedside testing for premature rupture of membranes.

Care should be taken to avoid any procedure that may introduce infection, so digital examination should be avoided unless patient is in active labor or delivery is imminently planned. This is of particular importance in preterm PROM.

LABORATORY TESTS

- pH test: Sample vaginal fluid from posterior fornix. Normal vaginal pH is 4.5 to 6.0. pH of amniotic fluid is 7.1 to 7.3. False-positive test can occur in presence of blood or semen, antiseptic or bacterial vaginosis.
- Microscopy: Visualization of fern of vaginal fluid allowed to dry on the microscope slide. False-positive test can occur if cervical mucus is sampled.
- Commercially available tests: AmniSure and other tests such as free fetal fibronectin (FFN) are available and demonstrate good sensitivity and specificity; however, per the American College of Obstetrics and Gynecology, these should be considered ancillary to standard evaluation.

IMAGING STUDIES

- Abdominal ultrasound: Evaluation of amniotic fluid volume either by maximum vertical pocket or amniotic fluid index. Oligohydramnios or low fluid volume in itself should not be considered diagnostic of PROM.
- Amniotic fluid dye test: This is considered the gold standard in diagnosis of PROM, used in clinical scenario of suspected preterm PROM with equivocal testing. Indigo carmine dye is injected via ultrasound guidance into the amniotic sac, and diagnosis made if blue dye passes into vagina.

TREATMENT

NONPHARMACOLOGIC THERAPY

All patients with PROM should have prompt evaluation of gestational age, fetal well-being via NST monitoring, and fetal presentation. In a patient with evidence of intraamniotic infection or fetal distress, prompt delivery is recommended. Close monitoring and consideration of delivery is recommended if there is concern for placental abruption. Collect swab for evaluation of GBS status and gonorrhea/chlamydia.

ACUTE GENERAL Rx

Term PROM:

- At 37.0 weeks' gestation or more, delivery is recommended for all women with ruptured membranes. Induction of labor has been shown to decrease time to delivery, risk of chorioamnionitis, endometritis, and NICU admissions, with no increase in rate of operative delivery.
- A period of expectant management can be offered in select patients who decline induction and have been appropriately counseled.
- Routine induction agents may be used. The most researched agents for induction in setting of PROM include oxytocin and prostaglandins. Oxytocin has been shown to be associated with lower rates of chorioamnionitis. Infection is also a concern with mechanical methods of cervical ripening, such as Foley balloon, but decision for induction method should be made on a case-by-case basis.
- GBS prophylaxis should be provided in GBS-positive individuals or individuals with GBS-unknown status and concurrent risk factors.

Preterm PROM:

- 34 weeks or above: Clinician should proceed toward delivery as in term patients. Administration of betamethasone for fetal lung maturity as indicated by Antenatal Late Preterm Steroids trial. Steroids should not be administered if patient has already received a course
- 24 to 34 weeks:
  1. Administration of betamethasone for fetal lung maturity
  2. Administration of prophylactic antibiotics to prolong latency period, consisting of 7-day course of parenteral and oral therapy. Current guidelines recommend ampicillin or amoxicillin and erythromycin
  3. Expectant management until 34 weeks, unless fetal lung maturity is demonstrated between 32 to 34 weeks
  4. Magnesium sulfate administration if delivery is imminent and <32 weeks
- GBS prophylaxis in setting of GBS unknown/GBS positive if delivery is expected

CHRONIC Rx

Hospitalization with expectant management is recommended for all patients with preterm PROM. Ongoing maternal and fetal surveillance in a hospital setting allows for quick recognition of infection, labor, or fetal compromise secondary to cord compression.

DISPOSITION

- Most women with preterm PROM will proceed to deliver within one week despite medical interventions. Latency period is generally longer when PROM occurs at an earlier gestational age.

TABLE E1 Bedside Testing for Premature Rupture of Membranes

Method	Result
Nitrazine	Amniotic fluid (pH >6.5) will turn nitrazine paper blue; normal vaginal secretions (pH <5.5) will leave nitrazine paper yellow.
Ferning	Amniotic fluid crystallizes.
Smear combustion	Amniotic fluid, when flamed, turns white and crystallizes.
	Vaginal secretions caramelize and turn brown.

From Marx J et al: *Rosen's emergency medicine: concepts and clinical practice,* ed 7, Philadelphia, 2010, Mosby.

- Clinical chorioamnionitis develops in 13% to 16% of preterm PROM. This risk is increased with earlier PROM as well as with an increase in the number of digital vaginal examinations.
- Complications of preterm PROM are related mostly to complications of prematurity, and decrease with increasing gestational age at time of delivery. The most common complications include respiratory distress, neonatal infection, intraventricular hemorrhage, and necrotizing enterocolitis.
- There is a 1% to 2% risk of antenatal demise in the setting of preterm PROM.

REFERRAL

Consultation with an Ob-Gyn or maternal fetal medicine specialist is recommended in the setting of preterm PROM.

PEARLS & CONSIDERATIONS

PREVENTION

Patients with a history of preterm delivery (with or without PROM) may benefit from administration of progesterone supplementation in future singleton pregnancy starting at 16 to 24 weeks to prevent preterm delivery.

SUGGESTED READINGS

Peaceman AM et al: Length of latency with preterm premature rupture of membranes before 32 weeks' gestation, *Am J Perinatol* 32(1):57-62, 2015.

Prelabor Rupture of Membranes: ACOG Practice Bulletin: *Clinical management guidelines for obstetrician-gynecologists*. 188, 2016.

Wong LF et al: Outcomes of expectantly managed pregnancies with multiple gestations and preterm premature rupture of membranes prior to 26 weeks, *Am J Obstet Gynecol* 212(2):215.e1-215.e9, 2015.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Abruptio Placentae (Related Key Topic)
Preterm Labor (Related Key Topic)

AUTHOR: **Ghamar Bitar, MD**

Premenstrual Dysphoric Disorder

BASIC INFORMATION

DEFINITION

The *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition, requires as criteria for definition of premenstrual dysphoric disorder (PMDD) the presence of five or more of the following symptoms in most menstrual cycles for the past yr.

- The symptoms should be present most of the time during the last wk of the luteal phase, with remission beginning within a few days after the onset of the follicular phase, and absent during the wk after menses. One or more of the following symptoms must be present:
  1. Marked depressed mood, feeling of hopelessness, or self-deprecating thoughts
  2. Marked anxiety, tension, feeling of being "keyed up" or "on edge"
  3. Marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection)
  4. Persistent and marked anger or irritability or increased interpersonal conflicts
- One (or more) of the following symptoms must additionally be present to reach a total of five symptoms when combined with symptoms 1 through 4 noted previously:
  1. Decreased interest in usual activities (e.g., work, school, friends, hobbies)
  2. Subjective sense of difficulty in concentrating
  3. Lethargy, easy fatigability, or marked lack of energy
  4. Marked change in appetite, overeating, or specific food cravings
  5. Hypersomnia or insomnia
  6. A subjective sense of being overwhelmed or out of control
  7. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," or weight gain
- The disturbance markedly interferes with work or school or with usual social activities and relationships with others (e.g., avoidance of social activities, decreased production and efficiency at work or school).
- The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may be superimposed on any of these disorders).
- The first three criteria must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles (diagnosis may be made provisionally before such confirmation).
- The symptoms are not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition (e.g., hyperthyroidism).

NOTE: In menstruating women, the luteal phase corresponds to the period between ovulation and the onset of menses, and the follicular phase begins with menses. In nonmenstruating women (e.g., women who have had a hysterectomy), determination of the timing of the luteal and follicular phases may require measurement of circulating reproductive hormones.

ICD-10CM CODE
N94.3 Premenstrual tension syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- PMDD affects 3% to 5% of women of reproductive age.
- Genetic factors play a significant role (increased incidence in monozygotic twins and in women whose mothers had PMDD).
- 30% to 76% of women with PMDD have a lifetime history of depression.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination may be completely normal.
- Depressed mood, tachycardia, sweating from comorbid disorders (e.g., panic disorder, major depression) may be present.
- Symptoms occur during the last half of the menstrual cycle (the luteal phase) and are absent from the first day of menstruation until ovulation (follicular phase).

ETIOLOGY

- Unknown. Serotonin deficiency and altered sensitivity in serotoninergic system in response to phasic hormone fluctuations in the menstrual cycle are believed to play a role.
- Progesterone appears to be the main precipitating factor in PMDD symptoms, but estrogen may also provoke symptoms.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Premenstrual syndrome
- Dysthymic syndrome
- Personality disorder
- Panic disorder
- Major depressive disorder
- Hyperthyroidism
- Polycystic ovarian syndrome
- Drug or alcohol abuse
- Irritable bowel syndrome
- Endometriosis

WORKUP

- Diagnosis is based on obtaining a detailed history and ruling out the presence of physical or psychiatric disorders. No objective diagnostic tests exist.
- The diagnosis should be confirmed by using a symptom checklist prospectively for two consecutive menstrual cycles. Commonly used diagnostic instruments include the Calendar of Premenstrual Experiences, the Premenstrual Syndrome Diary, and the Daily Record of Severity of Problems (DRSP).

LABORATORY TESTS

- None are usually necessary.
- A serum thyroid-stimulating hormone test to exclude thyroid problems, complete blood count to rule out anemia, and a chemistry profile to assess electrolytes may be ordered if diagnosis is unclear.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Reduction in intake of caffeine, refined sugars, or sodium may be helpful in some patients.
- Increased aerobic exercise, smoking cessation, alcohol restriction, and regular sleep are often beneficial.
- Stress reduction and management will decrease severity of symptoms.
- Cognitive behavior therapy may also be helpful for reducing symptoms.

GENERAL Rx

- Selective serotonin reuptake inhibitors are useful for the treatment of PMDD. Commonly used agents and initial doses are fluoxetine 10 mg qd, sertraline 50 mg qd, paroxetine 10 mg qd, and citalopram 20 mg qd. Many patients will require titration to significantly higher doses to achieve therapeutic benefit. These medications can be administered continuously during the menstrual cycle or only when the patients experience symptoms. Luteal phase or intermittent administration involves initiating medication at the time of ovulation and stopping it at the beginning of menses. Serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine may also be effective in women with predominantly psychological symptoms.
- Other useful agents are benzodiazepines (alprazolam 0.25 mg tid prn) and the tricyclic antidepressant clomipramine (25 mg qd as starting dose).
- Gonadotropin-releasing hormone (GnRH) agonists are effective in treating patients with PMDD. The accelerated bone loss and vasomotor symptoms associated with long-term use of a GnRH agonist will require add-back therapy. Hormonal intervention with monthly intramuscular injections of leuprolide has been reported effective in some patients; however, it should be reserved only for patients unresponsive to first- and second-line agents.
- Nutritional supplementation (vitamin B_6 up to 100 mg/day, vitamin E up to 600 IU/day, calcium carbonate up to 1200 mg/day, and magnesium up to 500 mg/day) are also commonly used for symptom reduction in some patients with limited results.
- Ovariectomy may be considered in severe refractory cases.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Premenstrual Syndrome (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

American Psychiatric Association. *Desk reference to the diagnostic criteria from DSM-5.* American Psychiatric Association: Arlington, VA.

Biggs WS, DeMuth RH: Premenstrual syndrome and premenstrual dysphoric disorder, *Am Fam Physician* 84(8):918-924, 2011.

Hofmeister S, Bodden S: Premenstrual syndrome and premenstrual dysphoric disorder, *Am Fam Physician* 94(3):236-240, 2016.

BASIC INFORMATION

DEFINITION

Premenstrual syndrome (PMS) consists of various somatic and physical complaints that develop during the luteal phase of the menstrual cycle and that are of sufficient severity to interfere with daily functioning and/or interpersonal relationships. The symptoms resolve shortly after the onset of menses.

SYNONYM

PMS

ICD-10CM CODE
N94.3 Premenstrual tension syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- Premenstrual disorders affect about 12% of reproductive-age women, although as many as 80% of women will report at least one somatic or affective symptom during their luteal phase (Table 1).
- Severe cases of premenstrual dysphoric disorder (PMDD), which is more of a psychiatric diagnosis, occur in approximately 1.3% to 5.3% of women.
- The prevalence of PMS is not associated with age, race, or socioeconomic status.
- Those seeking treatment for PMS are usually in their 30s or 40s.
- Based on some identical twinning studies, a genetic component is thought to exist, but no genes have been identified.
- The natural history of PMS has not been clearly elucidated.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Diverse and potentially disabling symptoms. Table 1 summarizes common symptoms of PMS
- Associated with multiple psychological, physical, and behavioral symptoms
- Most frequent reason for seeking treatment: Emotional symptoms
- Most common emotional symptoms: Depression, irritability, anxiety, labile moods, anger, crying easily, sadness, extreme sensitivity, nervous tension
- Most common physical symptoms: Headache, bloating, cramps, breast tenderness, migraines, fatigue, weight gain, aches and pains, palpitations
- Most common behavior symptom: Food cravings
- Other behavioral symptoms: Increased appetite, increased alcohol intake, decreased motivation, decreased efficiency, avoidance of activities, staying home, sleep changes, libido changes, forgetfulness, decreased concentration

ETIOLOGY

- Etiology is poorly understood. The syndrome is thought to result from steroid hormone effects on serotonin, ϒ-aminobutyric acid, dopamine systems, and the renin-aldosterone system, thus causing some of the bloating symptoms.
- Because of the multifactorial, multiorgan nature of PMS, a single etiologic cause is unlikely.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- A diagnosis of exclusion, so other medical or psychological disorders should be ruled out
- Common disorders to rule out: Depression or anxiety, anemia, migraines, endometriosis, thyroid disease

WORKUP

- History.
- Physical examination.
- Laboratory studies to rule out alternative diagnosis.
- If no alternative diagnosis, confirm by either history of regular menses, basal body temperature charting, or elevated luteal progesterone that patient is ovulatory.
  1. If she is not ovulating, it is not PMS.
  2. A prospective questionnaire given over two menstrual cycles has been found to be the most accurate way to assess the presence of PMS or PMDD. If symptoms are not occurring only in the luteal phase, it is not PMS, and further investigation is needed.
     a. If symptoms occur in the follicular phase, patient has premenstrual exacerbation of another condition.
     b. If symptoms do not occur in the follicular phase, diagnosis of PMS is confirmed.

LABORATORY TESTS

- None available to specifically confirm the diagnosis of PMS
- Thyroid function tests to rule out thyroid disease

TREATMENT

NONPHARMACOLOGIC THERAPY

- Individualization of the treatment plan to maximize therapeutic response.
- Psychosocial intervention:
  1. Education
  2. Stress management
  3. Environmental changes
  4. Adequate rest and sleep
  5. Regular exercise
- Nutritional recommendations:
  1. Regularly eaten, well-balanced meals
  2. Adequate amounts of protein, fiber, and complex carbohydrates; low fat
  3. Avoidance of foods that are high in salt and simple sugars; may promote water retention, weight gain, and physical discomfort
  4. Avoidance of alcohol and illicit drugs; may worsen emotional lability
  5. Calcium supplementation (1000 mg/day for women 19 to 50 yr, 1300 mg/day for girls 14 to 18 yr) to reduce the physical and emotional symptoms
  6. The data are mixed regarding the benefits of vitamin D supplementation in reducing PMS symptoms, so more studies are needed
  7. Pyridoxine (vitamin B_6) 80 mg qd to improve depression, fatigue, and irritability has been suggested in small studies

ACUTE GENERAL Rx

Suppression of ovulation:

- Oral contraceptives: One pill per day; continuous use associated with better treatment effect
- Progestin-only oral contraceptive: One pill per day
- Oral micronized progesterone: 100 mg every morning and 200 mg every evening on days 17 through 28 of menstrual cycle
- Progestin suppository: 200 to 400 mg bid on days 17 through 28 of menstrual cycle
- Medroxyprogesterone: 150 mg IM q3mo
- Levonorgestrel implants: Surgical insertion every 5 yr

TABLE 1 Common Symptoms of Cyclic Premenstrual Syndrome

Somatic Symptoms	
Abdominal bloating	Constipation or diarrhea
Acne	Headache
Alcohol intolerance	Peripheral edema
Breast engorgement and tenderness	Weight gain
Clumsiness	
Emotional and Mental Symptoms	
Anxiety	Insomnia
Change in libido	Irritability
Depression	Lethargy
Fatigue	Mood swings
Food cravings (especially salt and sugar)	Panic attacks
Hostility	Paranoia
Inability to concentrate	Violence toward self and others
Increased appetite	Withdrawal from others

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, WB Saunders.

- Transdermal estradiol: One or two 100-μg patches every 3 days
- Danazol: 100 to 200 mg/day (ovulation not suppressed at this dose); has significant side-effect profile
- Gonadotropin-releasing hormone (GnRH) agonists: Daily by intranasal spray or monthly by depot injection; profound hypoestrogenism, concerns for osteoporosis and vasomotor symptoms

Suppression of physical symptoms:

- Spironolactone: 25 to 50 mg bid on days 14 through 28 of menstrual cycle—need a reliable form of birth control
- Mefenamic acid
  1. For fluid retention: 250 mg tid on days 24 through 28 of cycle
  2. For pain: 500 mg tid on days 19 through 28 of cycle
- Bromocriptine: 5 mg/day on days 10 through 26 of cycle
- Naproxen: 550 mg bid on days 17 through 28 of cycle, Naprosyn-500 mg bid on days 17 through 28 of cycle

Suppression of psychological symptoms:

- SSRI, or serotonergic antidepressants, are first-line treatment for PMS/PMDD, treating mostly the psychological aspects but also some physical aspects
- Sertraline, paroxetine, fluoxetine, citalopram, escitalopram
- In 2013 the *Cochrane Reviews* reported a statistically significant benefit over placebo when taken either continuously or in the luteal phase
- Serotonin-norepinephrine reuptake inhibitors (SNRI) such as venlafaxine; use is off-label, but onset of action is quick and has been found to be helpful
- Seroquel: Smaller studies
- Wellbutrin: Not as effective as the other options

CHRONIC Rx

- Therapy is largely trial and error, with the goal of providing effective treatment with the safest therapy. Provider should initially attempt to ameliorate the most pronounced symptom(s).
- Limited evidence exists that acupuncture and/or acupressure may ameliorate some symptoms associated with PMS and improve quality of life. More studies are needed to determine if this option is as good as or better than conventional therapies such as treatment with an SSRI.
- For severe intractable PMS: Bilateral oophorectomy; give trial of GnRH therapy or danazol before surgery (bilateral oophorectomy should be exceedingly rare).
- Estrogen replacement therapy recommended postoperatively to reduce the risk of osteoporosis, heart disease, and genitourinary atrophy.

DISPOSITION

Improved symptoms in 90% of women over time

REFERRAL

- For counseling with a psychologist or psychiatrist if underlying psychiatric disorder is discovered (cognitive-behavioral therapy)
- To a gynecologist if surgical therapy is contemplated

RELATED CONTENT

Premenstrual Syndrome (Patient Information)
Dysmenorrhea (Related Key Topic)
Premenstrual Dysphoric Disorder (Related Key Topic)

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Adrienne B. Neithardt, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

The 2016 National Pressure Ulcer Advisory Panel (NPUAP) defines pressure injury (previously pressure ulcer) as a localized area of damage to the skin and/or underlying soft tissue over a bony prominence or related to a medical or other device. This occurs as a result of intense or prolonged pressure or pressure in combination with shear and friction. The tolerance of soft tissue for pressure and shear may also be affected by other factors such as microclimate, nutrition, perfusion, comorbidities, and condition of the soft tissue. Common sites include the sacrum, heels, elbows, lateral malleoli, occiput, scapula, ischium, and calcaneus among others. It can present as an intact skin or an open ulcer that could be painful. This revised nomenclature allows for the recognition of lesser degrees of skin damage that are not necessarily associated with pressure injuries.

SYNONYMS

Decubitus ulcers
Pressure sores
Bed sores
Pressure ulcers
Pressure-induced skin injury
Pressure-induced soft tissue injury

ICD-10CM CODES

L89 Pressure ulcers

Subcategories of codes determined by stage and location of ulcer

L89.153 Example: Stage 3 ulcer of sacral area

New codes for Deep Tissue Injury [DTI]: introduced 10/1/19 for all patient encounters and discharges. Determined by location:

L89.016 Example: Pressure-induced deep tissue damage of the right elbow

EPIDEMIOLOGY & DEMOGRAPHICS

- An estimated 2.5 million cases of pressure injuries are treated each yr in acute care facilities across the U.S.
- Worldwide, the prevalence of pressure injury in the acute care setting ranges from 6% to 18%.
- Pressure injuries resulted in 28,500 documented deaths globally in 2013, more than double from 13,700 deaths in 1990.
- Development of pressure injury results in increased hospital length of stay by 7 to 10 days. These patients are three times more likely to be discharged to long-term care facilities.
- In the U.S., the Centers for Medicare and Medicaid (CMS) does not provide any reimbursement to hospitals for treatment of stage 3 and 4 pressure injuries acquired during hospitalization.
- In 2016, the national cost for pressure injury management was $22 billion. Hospital-acquired pressure injuries added $8200 to the cost of the surgical stay, which conferred an additional 44% increase in surgical stay costs.
- Patients who develop pressure injuries tend to be older patients (mean age of 71 yrs), debilitated, immobile, and have multiple medical problems such as dementia, lung disease, diabetes mellitus, urinary or fecal incontinence, and nutritional deficiencies to include a few. A cohort study observed that pressure injuries occurred in 36% of older patients with hip fracture.
- Occur in all health care settings including hospitals, nursing homes, and residential homes. The reported rates upon admission to a nursing home range from 10% to 35%. The incidence rate is highest in institutions with lower staffing levels of registered nurses and certified nursing assistants, reflecting the importance of health care resources rather than medical decision-making.
- Associated with impaired quality of life and significant morbidity and mortality. 1-yr mortality rate approaches 40%, and if complicated by bacteremia may exceed 55%. Emotional and psychological trauma often accompany pressure injury, leading to more significant reduction in overall well-being and quality of life.
- Significant pain occurs in two thirds of patients with stage 2 or greater pressure injury.

CLINICAL PRESENTATION

There are a number of staging systems that have been developed and utilized to describe the stages of pressure injury. The most commonly used system is from the National Pressure Ulcer Advisory Panel (NPUAP). The European Pressure Ulcer Advisory Panel (EPUAP) recommends similar staging except for the presence of suspected deep tissue injury and unstageable ulcers. The staging of the wound should be based according to the extent or depth of injury. Common locations of pressure injury have been demonstrated in the following settings: supine position, prone position, lying in bed with head elevated, and sitting position. In order of prevalence, sites most commonly involved are those over the sacrum, calcaneus, ischium, and greater trochanter. In general, up to 75% of all pressure injuries are located around the pelvic girdle. Heel is the second most common site after the sacrum and the most common site in the case of suspected deep tissue injuries.

The NPUAP 2016 guidelines (Fig. 1) described the staging system as follows:

- **Stage 1 pressure injury: Nonblanchable erythema of intact skin.** Skin is intact with a localized area of nonblanchable erythema, which may appear differently in patients with darkly pigmented skin color. The presence of blanchable erythema or changes in sensation, temperature, or firmness may precede visual changes. Color changes do not include purple or maroon discoloration; these may indicate deep tissue pressure injury.
- **Stage 2 pressure injury: Partial-thickness skin loss with exposed dermis.** The wound bed is viable, pink or red, moist, and may also present as an intact or ruptured serum-filled blister. Adipose tissue (fat) is not visible, and deeper tissues are not visible. Granulation tissue, slough, and eschar are not present. These injuries commonly result from adverse microclimate and shear in the skin over the pelvis and shear in the heel. This stage should not be used to describe moisture-associated skin damage, including

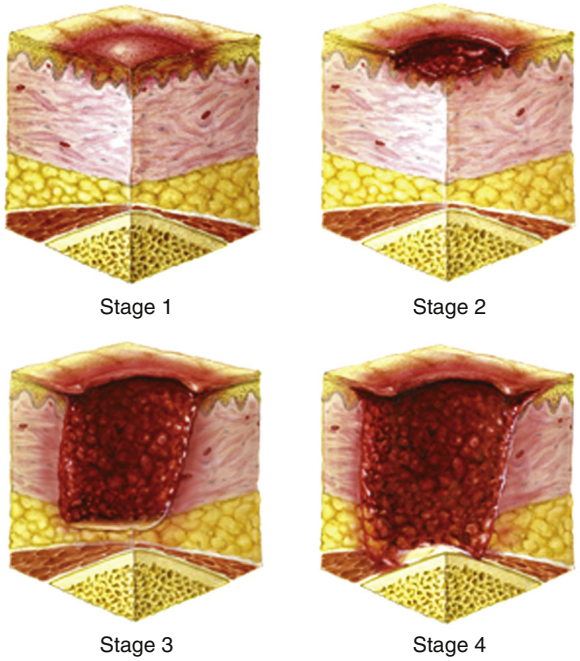

FIG. 1 Staging of pressure ulcers. Used with permission of the National Pressure Ulcer Advisory Panel. (From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Elsevier.)

incontinence-associated dermatitis, intertriginous dermatitis, medical adhesive–related skin injury, or traumatic wounds (skin tears, burns, abrasions).

- **Stage 3 pressure injury: Full-thickness skin loss.** At this stage there is full-thickness loss of skin with adipose tissue visible in the ulcer; granulation tissue and epibole (rolled wound edges) are often present. Slough and/or eschar may be visible. The depth of tissue damage varies by anatomical location; areas of significant adiposity can develop deep wounds. Undermining and tunneling may occur. Fascia, muscle, tendon, ligament, cartilage, and/or bone are not exposed. If slough or eschar obscures the extent of tissue loss, this is an unstageable pressure injury. The depth of a stage 3 pressure injury varies by anatomic location.
- **Stage 4 pressure injury: Full-thickness skin and tissue loss.** At this stage there is full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage, or bone in the ulcer. Slough and/or eschar may be visible. Epibole (rolled edges), undermining, and/or tunneling often occur. Depth varies by anatomical location. If slough or eschar obscures the extent of tissue loss, this is an unstageable pressure injury. The extent of stage 4 ulcers is often underestimated due to undermining and fistula formation. A relatively small superficial defect may mask extensive tissue necrosis.
- **Unstageable pressure injury: Obscured full-thickness skin and tissue loss.** Unstageable pressure injury is full-thickness skin and tissue loss in which the extent of tissue damage within the ulcer cannot be confirmed because it is obscured by slough or eschar. If slough or eschar is removed, a stage 3 or stage 4 pressure injury will be revealed. Stable eschar (i.e., dry, adherent, intact without erythema or fluctuance) on the heel or ischemic limb should not be softened or removed.
- **Deep tissue pressure injury: Persistent nonblanchable deep red, maroon, or purple discoloration:** New ICD-10 subcategory for DTPI: separates this category of pressure injury from unstageable wounds.
  1. Deep tissue pressure injury consists of intact or nonintact skin with a localized area of persistent nonblanchable deep red, maroon, or purple discoloration, or with epidermal separation revealing a dark wound bed or blood-filled blister. Pain and temperature changes often precede skin color changes. Discoloration may appear differently in darkly pigmented skin. This injury results from intense and/or prolonged pressure and shear forces at the bone-muscle interface. Early stage deep tissue pressure injuries do not have an outer layer of slough or eschar and are not debrided. The wound may evolve rapidly to reveal the actual extent of tissue injury, or it may resolve without tissue loss. If necrotic tissue, subcutaneous tissue, granulation tissue, fascia, muscle, or other underlying structures are visible, a full-thickness pressure injury is present (unstageable, stage 3 or stage 4). Deep tissue pressure injury should not be used to describe vascular, traumatic, neuropathic, or dermatologic conditions.
  2. Deep tissue injury (DTI) prevalence is highest in the ICU. It accounts for about 14% of all ulcers. Common areas affected include coccyx, sacrum, buttocks, and heels.
- **Medical device–related pressure injury:** Medical device–related pressure injuries (MDR PIs) result from the use of devices designed and applied for diagnostic or therapeutic purposes. The resultant pressure injury generally conforms to the pattern or shape of the device. The most commonly implicated medical devices include splints, braces, tubing, and respiratory devices. Prevention is an indicator of quality care. The nature of the devices used, anatomical site involved, and condition of the patient often present a challenge to prevention and treatment. A meta-analysis of 29 studies with a mean age of 39 in adults and 5.9 in children showed a pooled 12% incidence and 10% prevalence rate in hospitalized patients. Analysis of the 2016 International Pressure Ulcer Prevalence Data in Canada and the US included acute care, long-term care, subacute care, long-term acute care hospitals, and hospice. This large database identified a prevalence rate of 0.6% MDR PIs, including mucosal and nonmucosal MDRs. 75% of these were facility-acquired. Over half (>50%) were stage 1 to 2, 22% stage 3 to 4, and 15% deep tissue PI. These injuries tend to form up to 3 days faster than non-MDR pressure injuries. The most common site is the ears, associated with respiratory cannulas, tubings and masks. Another common site is the feet, associated with casts and splints. The resultant pressure injury generally conforms to the pattern or shape of the device. The injury should be classified using the staging system.
- **Mucosal membrane pressure injury:** Mucosal membrane pressure injury is found on mucous membranes with a history of a medical device use at the location of the injury. Due to the anatomy of the tissue, these ulcers cannot be staged. Unique characteristics of mucosa include difficulty to detect non-blanchable erythema and absence of scar formation that in turn lead to an underappreciation of the severity of the injuries.
- **Incontinence-associated dermatitis (IAD):**There is intense and diffuse erythema of specific sites such as perineum, buttocks, and inner thighs. Associated symptoms include itching, burning sensation, pain, and concomitant fungal infections. The presentation can be varied. This includes ulcers with diffuse and irregular edges, papules, scaling, and weeping lesions. These are not classified as pressure injuries, however serve as a significant risk factor for the evolution to pressure injury.

PATHOGENESIS

The development of a pressure injury is a complex interaction of external forces and host-specific (intrinsic) factors. These forces include pressure, friction, shear, and moisture. Pressure applied to the skin in excess of the arteriolar pressure of 32 mm Hg prevents the delivery of oxygen and nutrients to tissues, leading to tissue hypoxia, accumulation of metabolic waste products, and free radical generation. The tolerance of soft tissue for pressure and shear may also be affected by immobility, microclimate factors, nutrition, perfusion, incontinence, comorbidities (including sensory perception disorders), and the condition of the soft tissue. The 2016 NPUAP consensus statement identified risk factors in specific situations that may lead to the development of unavoidable pressure injuries. These include the following: impaired tissue oxygenation, cardiovascular instability, hypovolemia, sepsis, anasarca, peripheral vascular disease, sensory impairment, immobility, end-of-life skin failure, and multi-organ failure. Body mass index (BMI) has an important role in the risk for pressure injury. Underweight (BMI <19 kg/m^2) and morbidly obese (BMI >40 kg/m^2) patients are at high risk for pressure injury formation. Other contributing mechanisms for the development of pressure injury include reperfusion injury, increased capillary permeability, soft tissue edema, lymphatic impairment, direct mechanical cellular injury, up-regulated autophagy, and accelerated cell senescence. Diseases that affect tissue perfusion such as peripheral vascular disease, diabetes mellitus, and heart failure pose a heightened risk for pressure injury development. However, it is important to note that patients with poor hemodynamics in addition to liver failure, sepsis, and acute respiratory distress syndrome may present with acute skin failure (ASF) rather than pressure injury. This is most commonly observed in the ICU setting.

Unlike other wounds, pressure injuries do not often follow the normal phases of healing (i.e. initial inflammatory phase, proliferative phase, and final remodeling and maturation phase). Instead, they become arrested in the inflammatory phase.

Complications of untreated pressure injuries include cellulitis, abscess formation, sinus tract formation, heterotopic calcification, systemic amyloidosis from chronic inflammation, rhabdomyolysis, and malignant transformation such as squamous cell cancer, particularly in a non-healing pressure injury.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Venous insufficiency ulcers
- Arterioocclusive ulcers
- Diabetic foot ulcers
- Neuropathic ulcers
- Skin cancer
- Cellulitis and erysipelas
- Skin abscess
- Kennedy terminal ulcers (KTU)
- Acute skin failure (ASF)
- Incontinence-associated dermatitis (IAD)
- Perineal dermatitis
- Device-related pressure injury

WORKUP

- A comprehensive assessment targeting source identification, contributing factors, underlying comorbidities, and other elements affecting wound healing should be implemented.
- A proper documentation of wound history is a must. This includes onset, duration, prior treatments, and procedures.
- A thorough physical examination of the identified areas of skin damage and of a minimum of 4 cm of periwound tissue should be performed.
- These areas should be evaluated for their length, width, and depth and for the presence of sinus tracts, undermining, tunneling, fistulas, exudate, and necrotic tissue as well as any evidence for healing such as the formation of granulation tissue.
- Adequate documentation such as the use of photographs for comparison can be extremely helpful to track changes over time.
- It is essential to rule out infection, as this would impair wound healing. The presence of cellulitis, abscess, and osteomyelitis should be explored.

LABORATORY TESTS

- Directed at identifying causes, risk factors, and/or any complications arising from the pressure injury (e.g., abscess or osteomyelitis).
- Cultures of wound bed are not believed to be helpful and should be avoided. Deep tissue biopsy is the gold standard to rule out osteomyelitis.
- Potentially useful markers for nutritional status include prealbumin, albumin, transferrin, lymphocyte count, and total cholesterol level.
- Complete blood count may be obtained if systemic infection is suspected.

IMAGING STUDIES

- Ultrasound is not proven to be effective.
- Plain radiographs, MRI, and triple-phase bone scan may help identify osteomyelitis when clinically suspected. A comparison study of 44 patients scheduled for open biopsy showed that MRI has superior diagnostic benefit over plain radiography.

Rx PREVENTION & TREATMENT

- The most effective strategies for prevention and resolution of pressure injuries are designed to provide a systematic approach involving risk assessment, continuous monitoring, education, and multiple interventions.
- Conduct a structured and individualized risk assessment on a regular basis, especially when the clinical condition changes.
- Identify high-risk patients using standardized risk assessment scales and risk prediction tools (e.g., Braden and Norton in the US; Waterlow scale in the UK; Cubbin and Jackson scale for ICU patients).
- Use standardized assessment tools to monitor wound healing on a weekly basis. Examples include the Pressure Sore Status Tool (PSST), Pressure Ulcer Scale for Healing (PUSH), Wound Healing Scale, and the Sessing Scale. The PUSH tool in conjunction with the NPUAP staging system is the most readily applied tool.
- Use of prophylactic dressings in high-risk patients is being studied in small randomized pilot studies in the U.S. and Australia. Foam and silicone dressings may be promising and cost-effective. However, no consensus has been reached.
- Focus on controlling the microclimate (moisture and temperature).
  1. Minimize prolonged skin exposure to moisture, urine, or stool.
  2. Treat dry, cracked skin.
- Use of repositioning and pressure-reducing devices (e.g., foam mattresses, air-fluidized beds, low–air loss beds, pillows, gel pads, or foam wedges when in bed or in a chair).
  1. Patient repositioning (based on individual tissue tolerance): Current studies assume repositioning is effective for prevention and healing. Focus is on education, positioning devices, most effective position, and turning frequency. Studies range from basic techniques and devices such as pillows to pressure mapping imaging and ultrasound to detect changes indicating deep tissue injury. Pilot studies continue in acute care hospitals, critical care, rehabilitation facilities, nursing homes, and in home-bound populations.
  2. Bed surface:
     a. There is consensus that pressure-reducing mattresses are effective in prevention and healing of pressure injuries compared with standard bed surfaces. Data comparing reactive vs. nonreactive support surfaces are inconsistent and inconclusive.
     b. Two randomized controlled trials (RCTs) found that use of air-fluidized beds contributed to the healing of a greater number of pressure injuries after 15 days compared with standard care.
     c. A systematic review revealed no differences in the rate of pressure injury healing with the use of either alternating-pressure mattresses or low air-loss beds compared with standard care. A small Belgian prospective RCT compared a static air mattress vs alternating pressure mattress in high risk, bed or chair-dependent nursing home residents over age 65. Results noted pressure injuries presented 50% sooner in the alternating pressure mattress group compared with the static air mattress.
  3. Support surface:
     a. The first meta-analysis of support surfaces and pressure injury prevention concluded with moderate certainty that powered active air surfaces and powered hybrid air surfaces probably reduced the incidence of pressure injuries by 58% and 78% when compared with standard hospital surfaces.
     b. There is low certainty that nonpowered reactive surfaces reduce pressure injuries.
     c. Based on the results of 19 RCTs, a Cochrane Review concluded based on current evidence: no support surface is more effective at healing pressure injuries than standard support surfaces.
     d. Pressure-relieving overlays: One RCT demonstrated that a viscoelastic pad on the operating table significantly reduced incidence of postoperative pressure injuries compared with a standard operating table.
     e. Use adequate support surfaces while in bed or in a chair to prevent "bottoming out" (defined as less than 1 inch between patient and support surface; measured by putting hand under support surface and feeling thickness to patient).
  4. Foam alternatives:
     a. Forty-one RCTs demonstrated that patients lying on standard hospital mattresses are more likely to develop pressure injuries than those patients lying on higher-specification foam mattresses.
- Recent systematic review of pressure injury prevention strategies showed poor methodology in most studies. Use of support surfaces, repositioning, optimized nutrition, and sacral skin moisturizing was most appropriate.

NONPHARMACOLOGIC THERAPY

- Pressure injuries should be cleaned at each dressing change.
- Avoid agents that are cytotoxic to epithelial cells (e.g., iodine, iodophor, sodium hypochlorite, hydrogen peroxide, acetic acid, alcohol).
- Wound irrigation should not exceed 15 psi and is best done with an 18-gauge angiocatheter. Necrotic tissue should be debrided quickly because it delays wound healing and increases risk of infection.

- Do not debride hard, dry, stable eschar on heels or ischemic limbs.
- No single dressing or product is superior; keep wound bed moist and protect it from urine/stool. Silver dressings, topical phenytoin, and growth factors should be limited to difficult-to-heal wounds, chronic ulcers, and extensive burns given their extra cost and limited scientific validation. Reduce pressure by using foam mattress, dynamic support surface (e.g., low–air loss bed), and frequent repositioning (e.g., every 2 hours or, in case of poor perfusion, more frequently).
- Hyperbaric oxygen therapy when used for some wounds provided temporary benefit. There have been no studies specifically looking at treatment of pressure injuries. Moreover, serious adverse events such as pneumothorax and seizures can occur.
- The data on the efficacy of ultrasound as wound therapy is limited. Similarly RCTs on electromagnetic therapy found no evidence of benefit on wound healing.
- Use of topical agents such as phenytoin, becaplermin gel, sucralfate, and medicinal manuka honey showed limited evidence for the healing of stage 2 ulcers.
- Negative-pressure wound therapy (NPWT) may be useful for wounds that have significant drainage. They help improve healing by promoting angiogenesis, improving tissue perfusion, and decreasing bacterial count. Calcium alginate and foam dressings may also be beneficial for such wounds. Randomized studies have not identified any significant differences to quantitative wound healing; however, it provided some level of patient and provider comfort.
- Although controlling poor nutrition has been shown to be beneficial, a recent large investigation demonstrated that feeding tubes did not prevent or heal pressure injuries, but increased the risk for their development.
- Minimize or promptly remove urinary and/or fecal contamination.
- No RCTs have compared debridement versus no debridement in the treatment of pressure injuries.
  1. Thirty-two RCTs have compared different debridement agents, but there is insufficient evidence to promote the use of one particular agent.
  2. One RCT demonstrated pressure injuries treated with collagenase healed significantly more quickly than those treated with hydrocolloid.
  3. One RCT comparing honey-treated dressings with saline-soaked dressings showed faster healing times with the honey-treated group.
  4. A meta-analysis and one RCT found significant benefit in rates of healing with use of hydrocolloid dressings versus traditional saline gauze dressings but not over other forms such as hydrogels, foam dressings, or collagenase.
- Malnutrition is an independent risk factor for pressure injury. However no benefit was found with nutritional and vitamin supplementation for those without known nutritional deficiencies. There is inconclusive evidence that vitamin C and zinc are effective in wound healing. Data is limited to support enteral or parenteral nutrition for patients whose oral intake is inadequate.
- There is insufficient data to recommend the use of anabolic steroids such as oxandrolone therapy to promote weight gain and repletion of protein stores.

ACUTE GENERAL Rx

- The cornerstone of therapy involves the use of appropriate wound dressings, pressure-reducing devices, treatment of infection, debridement, and surgical consultation when appropriate.
- Traditional bedside debridement provides excellent results in reducing the surface area for a majority of the wounds. Sharp debridement can effectively remove devitalized tissue and is a proven significant component to advancing wound closure.
- All pressure injuries are colonized with bacteria. Clinically evident infections should be assessed with culture and treated appropriately with topical and systemic antibiotics.
- A randomized controlled trial in 2017 showed significant reduction in stage 2 to 4 pressure injuries using anode and cathode high-voltage electrical stimulation.
- Pain medications are necessary if pressure injuries are present. One study found that excruciating pain was more prevalent in nursing home residents with pressure injuries. Local factors that may be contributing to pain such as ischemia, infection, or breakdown of surrounding skin should be properly addressed.

CHRONIC Rx

- Continue vigilance with pressure reduction because pressure injuries can recur with minimal trauma.
- There are no randomized trials available to identify whether repositioning makes a difference in the healing rates of pressure injuries or what the optimal repositioning regimen should be.
- Consider radiologic evaluation for infected ulcer bed, occult osteomyelitis, or abscess.

DISPOSITION

- When systematic risk assessments are done and preventive measures are followed, most pressure injuries can be prevented. Most injuries heal when appropriate management strategies are followed.
- Stage 4 pressure injuries in high-risk patients (e.g., paraplegics) can take mos to yrs to heal.

REFERRAL

- Physical and occupational therapists to help improve bed and chair mobility, as well as basic activities of daily living
- Wounds with necrotic tissue need referral to providers trained in sharp debridement
- Role of plastic surgeons for operative repair for large stage 3 or 4 pressure injuries that do not respond to optimal care
- To a specialty wound care center for non-healing complex pressure injuries

PATIENT & FAMILY EDUCATION

- Educate patient and family members on the risk factors for pressure injury formation.
- Encourage mobility and adequate nutritional intake as well as avoidance of bed rest.
- There is a need for patient involvement and education during periods of care transition and service changes by health care providers.

Considerations for palliative wound care for pressure injuries that exist and occur in serious illness to include the end-of-life stage

- Palliative patient populations have the highest incidence of all types of wounds. Pressure injuries comprise about 60% of them.
- Pressure injuries are unavoidable at the end of life. The term SCALE (skin changes at life's end) was introduced in 2008 to describe the group of wound phenomena that result from the complex failure of homeostatic mechanisms at the end of life.
- Kennedy Terminal Ulcer (KTU) has been described in the literature as an unavoidable and rapid onset skin breakdown or skin failure that occurs as part of the dying process. It occurs in the sacrococcygeal area, heel, calf, and elbows. Its classic configuration could be shaped like a pear, butterfly, or horseshoe. In contrast, the 3:30 syndrome of KTU was coined due to the rapidity of change, i.e., the patient's skin was normal when examined in the morning and by 3:30 pm shift change, the ulcer had emerged.
- The basic steps in pressure injury management at the end of life mirror that conventional pressure injury except that the primary intent is not necessarily for wound healing. Rather emphasis on quality of life and symptom control is the overarching goal. These steps include cleansing/debridement, management of exudate, slough, or infection, protection of the periwound skin, and dead space management.
- Common wound cleansing solutions used in this population include Dakin solution, cadexomer iodine, acetic acid, and topical phenytoin. All promote some improvement in inflammation, bacterial burden, healing, odor, pain, and granulation tissue development.
- The factors associated with increased likelihood of healing include age less than 70 yr, palliative performance score >30, and in exceptional circumstances, the use of artificial nutrition for those with good performance status.

PEARLS & CONSIDERATIONS

COMMENTS

- Up to 10% of older persons will have a pressure injury.

- Because 70% of pressure injuries occur in older persons, the approach should be similar to other multifactorial geriatric syndromes with an interprofessional team approach.
- Identify and reduce all modifiable risk factors for pressure injuries.
- Treat the pain associated with pressure injuries.
- Proper skin care, use of support surfaces, mobilization, and nutritional support are integral for prevention and treatment. Of these, pressure redistribution is the most important factor for prevention.
- Effective prevention practices consist of timely wound reassessments, regular communication with team members, patient and caregiver empowerment, and utilization of clinical decision support tools for health care providers.
- Clinical studies have not revealed that any one dressing product is superior to another.
- Nonhealing pressure injuries require assessment for debridement, infection, abscess, and/or referral to a wound center.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Bed Sores (Patient Information)

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SUGGESTED READINGS

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Ricci JA et al: Evidenced-based medicine: the evaluation and treatment of pressure injuries, *Plast Reconstr Surg* 139:275-286, 2017.

BASIC INFORMATION

DEFINITION

Preterm labor is defined as regular contractions that result in cervical dilation or effacement prior to 37 wk gestation. Preterm birth is one that occurs after 20 wk gestation and before the completion of 37 wk gestational age.

SYNONYM

Premature labor

ICD-10CM CODES

O60.0	Preterm labor without delivery
O60.1	Preterm spontaneous labor with preterm delivery
O60.2	Preterm spontaneous labor with term delivery

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The incidence of preterm births in the U.S. increased from 9.5% in 1981 to 12.7% in 2006 before falling gradually to 11.4% by 2013. The increase since 1981 is attributed to improvements in pregnancy dating by ultrasound, increased use of assisted reproductive technology, and increased preterm induction or preterm operative delivery for maternal or fetal indications. Between 40% and 45% of these births follow spontaneous preterm labor; either the remaining preterm births result from preterm premature rupture of membranes (PPROM), or they occur secondary to intentional delivery for maternal or fetal indications.

PREDOMINANT AGE AND RACIAL DIFFERENCES: Pregnant women at the extremes of reproductive age (<17 yr and >35 yr) are at greatest risk. Black race is one of the most significant risk factors with the rate of preterm birth averaging 18.4% between 2005 and 2007 compared to 10.8% among Asian Americans and 11.6% in white women. The disparity between African-American and other ethnic American races persists after adjusting for income, education, and other medical risk factors.

GENETICS: A genetic component has been suggested. Women with sisters who have had preterm births and women with grandparents who were born preterm may be at increased risk for having preterm deliveries themselves. Single-nucleotide polymorphisms have also been associated with preterm labor.

RISK FACTORS: Risk factors for premature labor include a prior preterm delivery, intrauterine infection, systemic or genital tract infections, periodontal disease, short interpregnancy interval (<6 mo), short cervical length (<25 to 30 mm), low pre-pregnancy body mass index (BMI) (<19.8 kg/m^2), age (<17 yr or >35 yr), a history of elective pregnancy termination, history of prior stillbirth, African-American ethnicity, vaginal bleeding, polyhydramnios or oligohydramnios, multiple gestation, structural abnormalities of the uterus, history of cervical cone biopsy or loop electrocautery excision, in vitro fertilization or ovulation induction, tobacco use, heavy alcohol consumption, cocaine use, heroin use, and psychological or social stress. The strongest historic risk factor for preterm birth is a previous birth between 16 and 36 wk gestation.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Presenting symptoms include increased pelvic pressure, abdominal cramping or contractions, increased vaginal discharge, vaginal bleeding or spotting, or leakage of fluid.

ETIOLOGY

Causes of premature labor are varied and often difficult to determine. Premature labor may be secondary to infection, systemic illness, trauma, anatomic abnormalities (i.e., uterine anomaly), or a combination of factors. It is thought that cervical ripening is the most common first step to premature labor or delivery. Subsequently, decidual-membrane activation occurs followed by contractions (Box 1).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for preterm labor should include preterm rupture of membranes, preterm contractions (contractions before 37 wk gestation that do not result in cervical change), and abdominal pain or cramping secondary to other medical conditions. There are many medical conditions that may cause preterm contractions or premature labor. Treating some of these underlying conditions may improve the prognosis for stopping the preterm labor.

Possible medical conditions include:

- Infection
  1. Chorioamnionitis
  2. Genital tract infections, including bacterial vaginosis, gonorrhea, chlamydia
  3. Urinary tract infections, including pyelonephritis, cystitis, or asymptomatic bacteriuria
  4. Gastroenteritis
- Trauma
- Placental abruption
- Illicit drug use
- Preterm premature rupture of membranes
- Appendicitis
- Nephrolithiasis
- Pancreatitis
- Cholelithiasis
- Uterine fibroids

WORKUP

- History and physical exam to rule out trauma, abuse, other causes of abdominal pain, and infection
- Fetal heart rate monitoring and tocometry to determine fetal status and contraction frequency
- Speculum exam to visually assess the cervix and assess for rupture of membranes, bleeding, infection, or advanced cervical dilation
  1. If the patient is <35 wk gestation, a Fetal Fibronectin (FFN) test should be collected prior to performing a digital exam or transvaginal ultrasound. A FFN test can help predict preterm delivery if the patient has a cervical length on transvaginal ultrasound of <30 mm
- Digital exam in the unruptured patient with normal placentation to determine cervical dilation and effacement, and fetal station

LABORATORY TESTS

- CBC
- Urine analysis and culture

BOX 1 Factors Linked to Preterm Labor

Demographic and Psychosocial
- Extremes of age (>40 yr, teenagers)
- Lower socioeconomic status
- Tobacco use
- Cocaine abuse
- Prolonged standing (occupation)
- Psychosocial stressors

Reproductive and Gynecologic
- Prior preterm delivery
- Diethylstilbestrol exposure
- Multiple gestations
- Anatomic endometrial cavity anomalies
- Cervical incompetence
- Low pregnancy weight gain
- First-trimester vaginal bleeding
- Placental abruption or previa

Surgical
- Prior reproductive organ surgery
- Prior paraendometrial surgery other than genitourinary (appendectomy)

Infectious
- Urinary tract infections
- Nonuterine infections
- Genital tract infections (bacterial vaginosis)

From Marx JA et al: *Rosen's emergency medicine: concepts and clinical practice,* ed 7, Philadelphia, 2010, Elsevier.

- Urine toxicology screen
- Collect tests for GBS, gonorrhea, and *Chlamydia*
- Perform a wet prep for yeast, bacterial vaginosis, and *Trichomonas*
- Fetal fibronectin swab as described earlier
- Consider PT, PTT, INR, CMP, amylase, and lipase
- Amniocentesis may be performed if an intraamniotic infection is suspected

IMAGING STUDIES

A formal ultrasound is indicated to determine estimated fetal weight, fetal presentation, amniotic fluid volume, placental location and appearance, and cervical length.

The diagnosis of preterm labor is confirmed in the presence or regular contractions if the patient is >3 cm dilated, ≥80% effaced, or <2 cm cervical length by cervical ultrasonography. Diagnosis may also be confirmed if the patient is <3 cm dilated or <80% effaced or 2–3 cm cervical length if FFN is positive or if cervical change is documented over time.

Rx TREATMENT

Patients with premature labor should be delivered promptly when an intraamniotic infection is suspected or when they have cervical dilation >5 cm, a persistently nonreassuring fetal heart rate tracing, or significant vaginal bleeding concerning for placental abruption having maternal or neonatal implications.

NONPHARMACOLOGIC THERAPY

- Smoking cessation.
- Bedrest, activity restriction, and pelvic rest are often recommended by clinicians, but there are insufficient data to support this practice.

ACUTE GENERAL Rx

- Antenatal administration of corticosteroids between 24 wk and 33 6/7 wk gestation is recommended for women at risk of preterm delivery to prevent neonatal respiratory distress syndrome and decrease the incidence of intraventricular hemorrhage and necrotizing enterocolitis. It is also recommended between 34.0 and 36.5 wk gestation if there is no prior steroid exposure.
- Numerous tocolytic agents have been used in an attempt to inhibit contractions (Box 2). Although efficacy is unclear, they can be utilized during an observation period in an effort to prolong gestation for administration and exposure of steroids or to transfer the mother to a facility capable of caring for preterm infants. This, of course, assumes there are no maternal or fetal medical contraindications to use of tocolytic drugs and no indications for rapid delivery. The most commonly used tocolytics are beta-mimetics (terbutaline), magnesium sulfate, calcium channel blockers (nifedipine), or prostaglandin synthetase inhibitors (indomethacin, ketorolac, sulindac). Table E1 summarizes side effect profiles of tocolytic agents.

BOX 2 Commonly Used Tocolytic Agents

Magnesium sulfate
- 4-6 g IV bolus over 30 min
- 2-4 g/hr IV infusion

Terbutaline
- 5-10 mg PO q4-6h
- 0.25-0.5 mg SC q30 min-6 h
- 10-80 μg/min IV

Ritodrine*
- 10 mg PO q2-4 h
- 5-10 mg IM q2-4 h
- 50-350 μg/min IV

Isoxsuprine
- 20 mg PO q4-6 h
- 0.05-0.5 mg/min IV

*Ritodrine is currently discontinued in the U.S. *IV,* Intravenously; *PO,* orally; *SC,* subcutaneously.
From Marx JA et al: *Rosen's emergency medicine: concepts and clinical practice,* ed 7, Philadelphia, 2010, Elsevier.

Routine antibiotic use has failed to show benefit in the absence of a known infection. But all mothers in preterm labor (without a documented negative group B strep culture) should be given antibiotics to prevent neonatal GBS infection.

Intravenous magnesium sulfate has been shown to decrease cerebral palsy in children exposed antenatally with premature labor or premature rupture of the membranes.

PROPHYLACTIC OR CHRONIC Rx

- Patients with a history of prior spontaneous preterm birth may be candidates for prophylactic use of 17 alpha-hydroxyprogesterone caproate between 16 wk and 36 wk gestation.
- Patients with a history of preterm birth and short cervix may also be candidates for prophylactic or rescue cerclage.
- There is no evidence supporting the use of maintenance tocolytic therapy.

REFERRAL

- Women who present in preterm labor should be referred to an obstetrician and transferred to a facility with a neonatal intensive care unit.
- For women who present for prenatal care with a history of preterm delivery, early referral to an obstetrician is also recommended.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Abruptio Placentae (Related Key Topic)
Breech Birth (Related Key Topic)

AUTHOR: **Ghamar Bitar, MD**

TABLE E1 Side Effect Profiles of Tocolytic Agents

	Side Effects		
Agent or Class	**Maternal**	**Fetal or Neonatal**	**Contraindications**
β-adrenergic receptor agonists	Tachycardia and hypotension, tremor (39% vs. 4% with placebo), shortness of breath (15% vs. 1% with placebo), chest discomfort (10% vs. 1% with placebo), pulmonary edema (0.3%), hypokalemia (39% vs. 6% with placebo), hyperglycemia (30% vs. 10% with placebo)	Tachycardia	Tachycardia-sensitive maternal cardiac disease, poorly controlled diabetes mellitus
Magnesium sulfate	Flushing, diaphoresis, nausea, loss of deep-tendon reflexes (at serum levels of 9.6-12 mg/dl), respiratory paralysis (at serum levels of 12-18 mg/dl), cardiac arrest (at serum levels of 24-30 mg/dl); when used with calcium channel blockers, suppression of heart rate, contractility and left ventricular systolic pressure, and neuromuscular blockade	Data conflict with regard to effect on perinatal mortality	Myasthenia gravis
Calcium channel blockers	Dizziness, flushing, hypotension when used with magnesium sulfate, suppression of heart rate, contractility, and left ventricular systolic pressure and neuromuscular blockade; elevation of hepatic aminotransferase levels, reflexive headache		Hypotension, preload-dependent cardiac lesions (e.g., aortic insufficiency)
Cyclo-oxygenase inhibitors	Nausea, esophageal reflux, gastritis, and emesis; platelet dysfunction (rarely of clinical significance in patients without underlying bleeding disorder)	In utero closure of ductus arteriosus (risk associated with use for >48 hr), patent ductus arteriosus in neonate (conflicting data), oligohydramnios (reversible), NEC (conflicting data)	Platelet dysfunction or bleeding disorder, hepatic or renal dysfunction, gastrointestinal or ulcerative disease, asthma (in women with hypersensitivity to aspirin)
Oxytocin receptor antagonists	Hypersensitivity injection-site reactions	For atosiban, an increased rate of fetal or infant death (may be attributable to the lower gestational age of infants in the atosiban group)	None
Nitric oxide donors	Dizziness, flushing, hypotension		Hypotension, preload-dependent cardiac lesions (e.g., aortic insufficiency)

From Gabbe SG et al: *Obstetrics: normal and problem pregnancies,* ed 7, Philadelphia, 2017, Saunders.

SUGGESTED READINGS

Iams JD et al: Care for women with prior preterm birth, *Am J Obstet Gynecol* 203:89-100, 2010.

Martin JA et al: Preterm births–United States 2007, *MMWR Surveill Summ* (Suppl 60)78-79, 2011.

BASIC INFORMATION

DEFINITION

Priapism is the persistent, usually painful erection associated or unassociated with sexual stimulation. There are two major forms: Low-flow (venoocclusive) priapism and high-flow priapism (associated with increased arterial inflow without increased venous outflow resistance).

ICD-10CM CODES

N48.30 Priapism, unspecified
N48.31 Priapism due to trauma
N48.32 Priapism due to disease classified elsewhere
N48.33 Priapism, drug-induced
N48.39 Other priapism

EPIDEMIOLOGY & DEMOGRAPHICS

- Peak incidence is seen from ages 5 to 10 yr and 20 to 50 yr.
- In the younger group, priapism is often associated with sickle cell disease or neoplasm. In the older group it is often caused by pharmacologic agents.
- Low-flow (venoocclusive priapism [type I]) is much more common than high-flow (type II).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- In idiopathic priapism the initial erection is associated with prolonged sexual excitement. Previous transient episodes are frequently reported. The erection involves the corpora cavernosa alone. Detumescence does not occur spontaneously.
- In secondary priapism, sexual excitement need not be involved. Otherwise the clinical picture is the same as in idiopathic priapism.
- Table E1 compares normal erection and priapism.

ETIOLOGY

Idiopathic: Prolonged sexual arousal

- Secondary or associated causes:
  1. Sickle cell disease
  2. Diabetes
  3. Leukemia (especially chronic myelogenous leukemia)
  4. Solid tumor (malignant) penile infiltration
  5. Spinal cord injury
  6. Perineal or penile trauma
  7. Iatrogenic
  8. Total parenteral nutrition, which includes a fat emulsion
  9. Hyperosmolar IV contrast
  10. Spinal or general anesthesia
  11. Anticoagulant therapy
  12. Phenothiazines
  13. Trazodone
  14. Intracorporeal injection therapy for impotence
  15. Phosphodiesterase type 5 inhibitors (e.g., sildenafil [Viagra], tadalafil [Cialis], vardenafil [Levitra])
  16. Box E1 summarizes the various causes of priapism

PATHOPHYSIOLOGY

- Low-flow priapism: Prolonged erection leads to edema of the cavernosal trabeculae, resulting in a sequence of stasis, thrombosis, venous occlusion, fibrosis, scarring, and possibly impotence.
- High-flow priapism: Cavernosal artery rupture leading to an arteriocavernous fistula.

DIAGNOSIS

WORKUP

None if the associated underlying causes are known to be present. Otherwise they should be ruled out. Box E2 summarizes key elements in taking the history in patients with priapism. Low-flow priapism can be distinguished from high-flow priapism by obtaining a corporeal blood gas value. A PO_2 <30 mm Hg, PCO_2 >60 mm Hg, and a pH <7.25 are consistent with low-flow priapism. High-flow priapism can be confirmed by a perineal Doppler ultrasound (Fig. E1) or arteriography (useful to identify arterial-lacunar fistula).

TREATMENT

- Fig. E2 illustrates an algorithm for managing ischemic priapism. An approach to the management of high-flow priapism is shown in Fig. E3.
- Goal: Achieve detumescence with preservation of potency.
- Medical therapies:
  1. Ice packs
  2. Ice water enemas
  3. Hot water enemas
  4. Pressure dressing
  5. Sedatives
  6. Analgesics
  7. Antispasmodic/anticholinergic drugs
  8. Estrogens
  9. Anticoagulants
  10. Procaine
  11. Amyl nitrite
  12. Local or general anesthesia
  13. Ketamine (1 mg/lb)
- In the patient with sickle cell disease: Intravenous hydration, alkalinization, transfusion or exchange transfusion, oxygen.
- Corporeal irrigation with normal saline may be used for low-flow priapism. The midshaft of the penis can be injected with a small-gauge butterfly needle and irrigated with 10 to 20 ml of normal saline, followed by an intracorporeal injection of an alpha-adrenergic agonist every 5 min until detumescence. Commonly used intracavernous vasoconstrictor agents are epinephrine (10 to 20 mcg), phenylephrine (250 to 500 mcg), and ephedrine (50 to 100 mg). It is mandatory to monitor the patient's blood pressure and pulse when using alpha-adrenergic agonists.
- Surgery:
  1. Cavernospongiosum shunt
  2. Glans-cavernosum shunt
  3. Cavernosaphenous shunt
  4. In the less common situation of high-flow priapism (diagnosed by the finding of bright red arterial blood on aspiration), arterial embolization or surgical ligation is recommended.

PROGNOSIS

Impotence is associated with the duration of priapism, with 36 hr being an important threshold.

REFERRAL

To urologist

RELATED CONTENT

Priapism (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

TABLE E1 Comparison of Normal Erection and Priapism

Factor	Normal Erection	Priapism
Portion of penis involved	Corpora cavernosa and corpus spongiosum and glans	Corpora cavernosa
Cause	Vasodilation of penile arteries	Obstruction of venous outflow Disturbance of neuroarterial mechanism (imbalance between it and adrenergic activity) Increased viscosity
Sexual desire	Present	Absent
Pain	Absent	Present
Duration	Min to hours	Hours to days

From Nseyo UO (ed): *Urology for primary care physicians,* Philadelphia, 1999, Saunders.

BOX E1 Causes of Priapism

α-Adrenergic Receptor Antagonists
Prazosin, terazosin, doxazosin, tamsulosin

Antianxiety Agent
Hydroxyzine

Anticoagulants
Heparin, warfarin

Antidepressants and Antipsychotics
Trazodone, bupropion, fluoxetine, sertraline, lithium, clozapine, risperidone, olanzapine, chlorpromazine, thioridazine, phenothiazines

Antihypertensives
Hydralazine, guanethidine, propranolol

Attention-Deficit/Hyperactivity Disorder Agents
Methylphenidates (Concerta, Daytrana, Focalin, Metadate, Methylin, Quillivant, Ritalin)
Atomoxetine (Strattera)

Recreational Drugs
Alcohol, cocaine (intranasal and topical), crack cocaine, marijuana

Genitourinary Conditions
Straddle injury, coital injury, pelvic trauma, kick to penis or perineum, arteriovenous or arteriocavernous bypass surgery, urinary retention

Hematologic Dyscrasias
Sickle cell disease, thalassemia, granulocytic leukemia, myeloid leukemia, lymphocytic leukemia, multiple myeloma, hemoglobin Olmsted variant, fat emboli associated with hyperalimentation, hemodialysis, glucose-6-phosphate dehydrogenase deficiency

Hormones
Gonadotropin-releasing hormone, testosterone

Infectious (Toxin-Mediated) Causes
Scorpion sting, spider bite, rabies, malaria

Metabolic Conditions
Amyloidosis, Fabry disease, gout

Neoplastic Causes (Metastatic or Regional Infiltration)
Prostate, urethra, testis, bladder, rectum, lung, kidney

Neurogenic Conditions
Syphilis, spinal cord injury, cauda equina compression, autonomic neuropathy, lumbar disk herniation, spinal stenosis, cerebral vascular accident, brain tumor, spinal anesthesia, cauda equina syndrome

Vasoactive Erectile Agents
Papaverine, phentolamine, prostaglandin E_1, oral phosphodiesterase type 5 inhibitors, combination intracavernous therapy

Modified and updated from Lue TF: Physiology of penile erection and pathophysiology of erectile dysfunction and priapism. In Walsh PC et al (eds): *Campbell's urology,* Philadelphia, 2002, Saunders.

BOX E2 Elements in Taking the History of Priapism

Duration of erection
Presence of pain
Previous episodes of priapism and method of treatment
Baseline erectile function
Use of any erectogenic therapies (both prescription and nutritional supplements)
Medications and recreational drugs
Sickle cell disease, hemoglobinopathies, hypercoagulable states
Trauma to the pelvis, perineum, or penis

From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

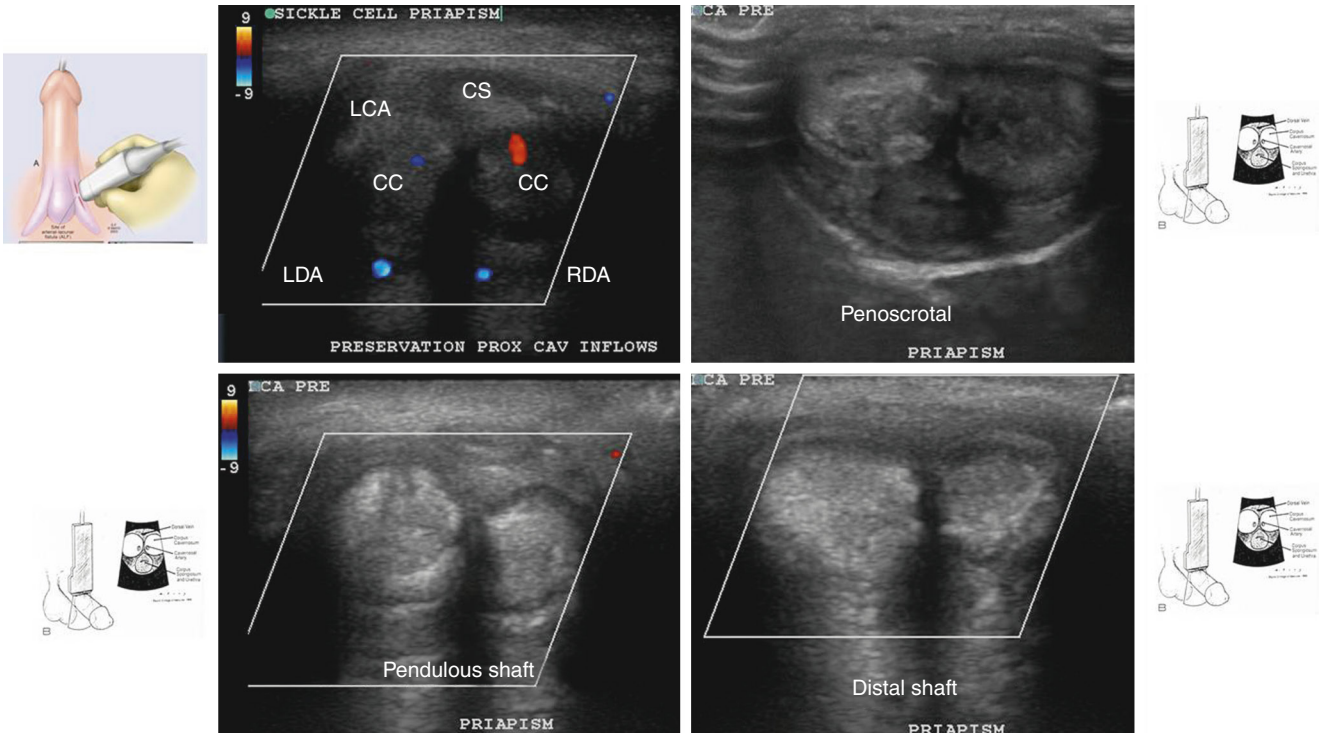

FIG. E1 This 21-year-old Nigerian man had erectile dysfunction after recurrent episodes of sickle cell ischemic priapism. A, Transperineal imaging with color Doppler shows preservation of cavernous arterial inflow at the origin in the corpora cavernosa. **B–D,** Increasing echogenicity on gray-scale ultrasonography of the penile shaft: Penoscrotal, pendulous shaft, and distal shaft. These findings are the result of recurring ischemic priapism, which leaves the patient with distal corporal fibrosis. *CC,* Corpora cavernosa; *CS,* corpus spongiosum; *LCA,* left cavernous artery; *LDA,* left dorsal artery; *RDA,* right dorsal artery. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

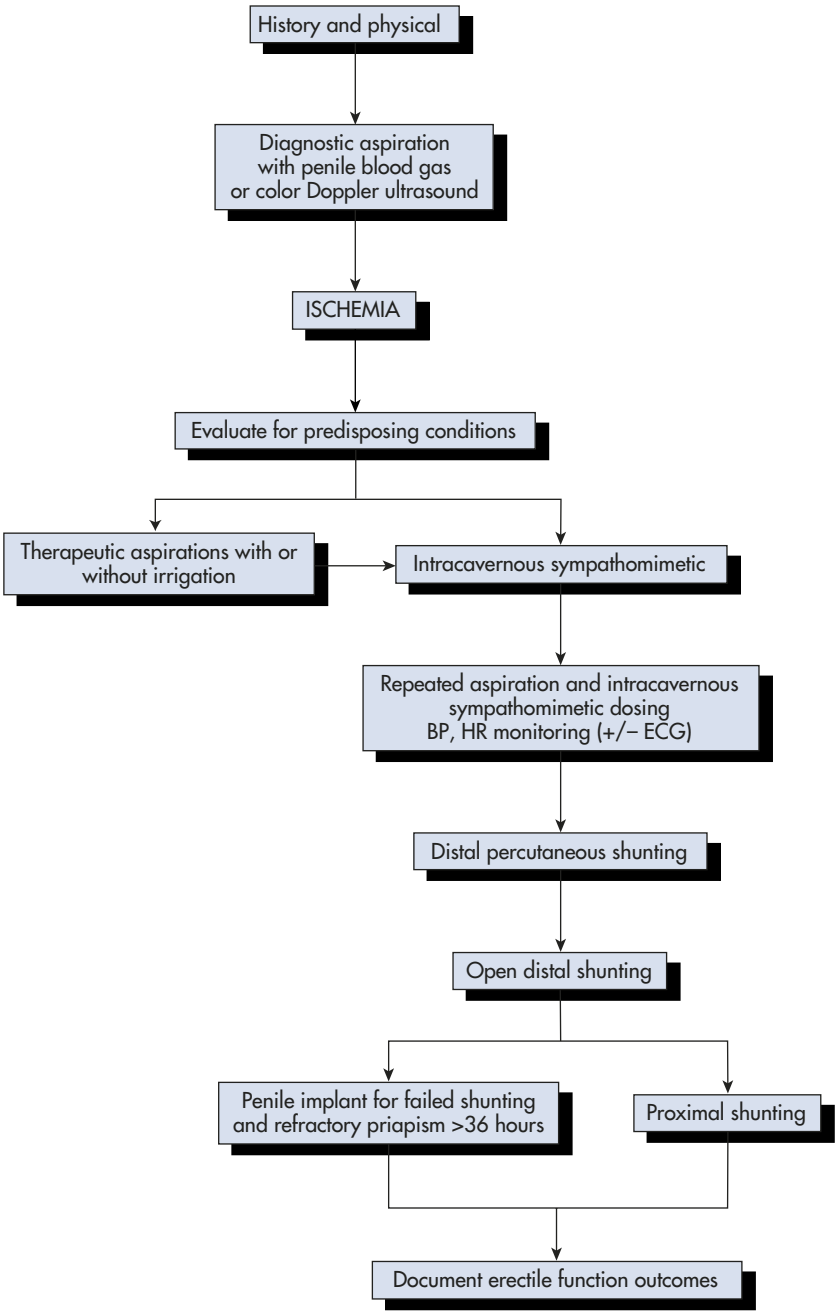

FIG. E2 Algorithm for managing ischemic priapism. *BP,* Blood pressure; *ECG,* electrocardiogram; *HR,* heart rate. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

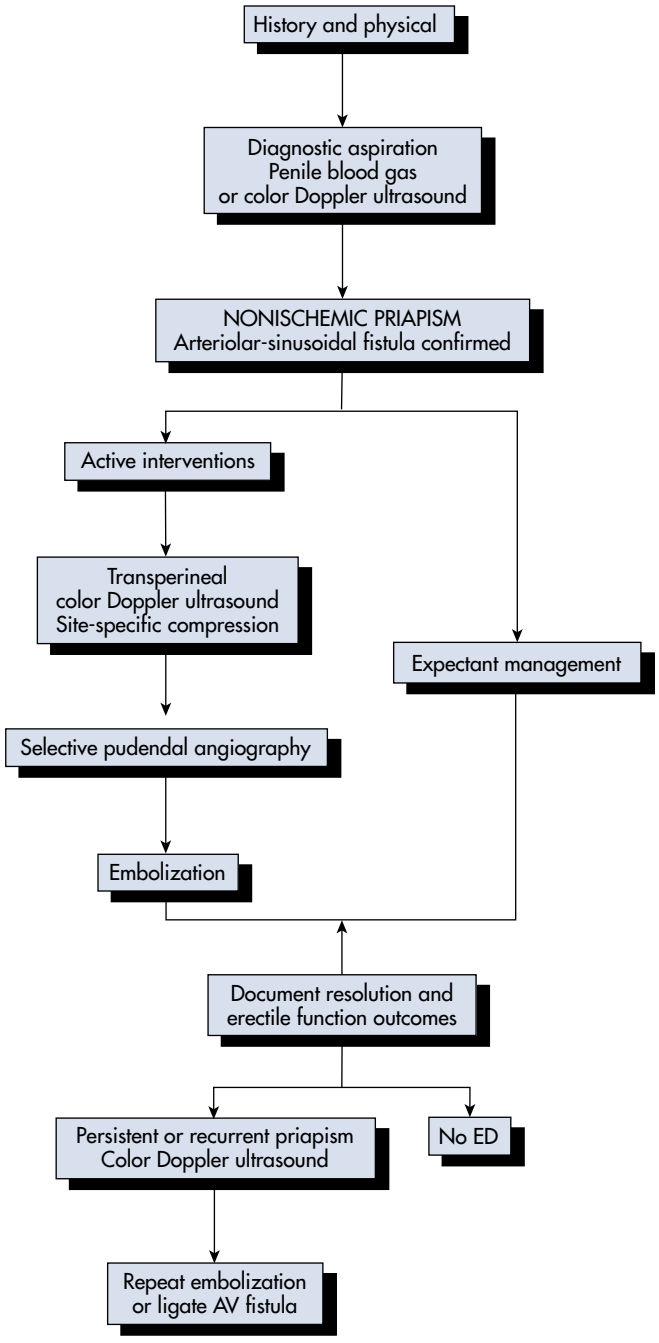

FIG. E3 Algorithm for managing high-flow priapism. *AV,* Arteriovenous; *ED,* erectile dysfunction. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

- Primary angiitis of the central nervous system (PACNS) is the preferred name for vasculitis that is confined to the CNS.
- CNS vasculitis is considered secondary when it occurs in the context of a systemic inflammatory disease, such as a systemic vasculitis or systemic lupus erythematosus (SLE), or an infectious process such as varicella zoster virus.
- PACNS predominantly affects small- and medium-sized arteries of the brain parenchyma, spinal cord, and leptomeninges, resulting in symptoms and signs of CNS dysfunction.
- It is defined by inflammation of the cerebral vasculature without angiitis in other organs.

SYNONYMS

PACNS
CNS vasculitis

ICD-10CM CODE
I67.7 Cerebral endarteritis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: PACNS is a rare disease. A retrospective analysis of 101 patients with PACNS reported an annual incidence rate of 2.4 cases per 1,000,000 person-yr.
PREDOMINANT SEX: There is a 2:1 male predominance among reported cases.
PREDOMINANT AGE: The median age at diagnosis is 50 yr, although PACNS can occur at almost every age.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- PACNS is characterized by a long prodromal period, with few patients presenting acutely.
- The vasculitis can affect any part of the CNS, causing the clinical manifestations to be highly variable and nonspecific.
- Headache is the most commonly reported symptom, usually subacute and insidious, in contrast to the sudden-onset thunderclap headache that is observed with reversible cerebral vasoconstriction syndromes (RCVS).
- Other symptoms include cognitive impairment, stroke, and transient ischemic attack.
- Patients with PACNS who develop strokes usually present with more than a single stroke in different anatomic territories.
- Other, less common symptoms may appear, including cranial neuropathies, ataxia, and seizure.
- Signs and symptoms suggestive of systemic vasculitis, such as peripheral neuropathy, fever, weight loss, or rash, are usually lacking.
- Spinal cord involvement occurs alone or coincides with parenchymal brain involvement.
- Angiitis affecting the spinal cord usually presents as a myelopathy, with pain, motor weakness, and sensory findings.
- Symptoms and signs of untreated PACNS progress over the course of months.

ETIOLOGY

- The cause of PACNS is unknown.
- Several potential etiologic agents or mechanisms have been proposed, but understanding of the cause of PACNS remains highly speculative.
- Various infectious agents have been proposed as etiologic factors, such as varicella zoster virus, West Nile virus, *Mycoplasma gallisepticum*, and HIV.
- Cerebral amyloid angiopathy and PACNS have been described together in some patients, and associations between amyloid depositions have also been proposed as a trigger.
- Although the cause of PACNS is unknown, inflammation of the CNS causes the vessels to become narrowed, occluded, and thrombosed, resulting in tissue ischemia and necrosis of the territories of the involved vessels.
- PACNS is more likely to affect blood vessels in the cerebral cortex and leptomeninges than subcortical regions.
- Blood vessels supplying cranial nerves may also be involved.

DIAGNOSIS

- The diagnosis of PACNS is based upon a constellation of symptoms and signs in the `setting of supportive studies and the exclusion of alternative diagnoses
- The diagnosis can usually be made when all of the following are present:
  1. An acquired otherwise unexplained neurologic deficit
  2. Evidence of either classic angiographic or histopathologic features of angiitis within the CNS (Table E1)
  3. No evidence of systemic vasculitis or any other condition that could elicit the angiographic or pathologic findings

DIFFERENTIAL DIAGNOSIS

PACNS can be mimicked closely in both its clinical presentation and radiologic manifestations by a number of other disorders (Box E1). The most frequent mimic of PACNS is a group of disorders known collectively as the reversible cerebral vasoconstriction syndromes (RCVS) (Box E2).

LABORATORY TESTS

- Laboratory testing and serological assays (Box E3) are used primarily to exclude other etiologies of CNS dysfunction.
- Analysis of the cerebrospinal fluid (CSF) is a crucial part of the evaluation of patients with potential PACNS and should be performed in all patents unless there are contraindications.
- The CSF is abnormal in 80% to 90% of patients with pathologically documented disease.

TABLE E1 Demographic Characteristics, Clinical Features, and Imaging Studies Distinguishing Primary Angiitis of the Central Nervous System from Reversible Cerebral Vasoconstriction Syndrome

Feature	PACNS	RCVS
	Demographics	
Age at onset (yr)	40-50	20-40
Gender predilection	Men	Women
Clinical features	Variable	Cephalgia Catastrophic stroke or edema
Onset of symptoms	Insidious	Acute or subacute
Provocative factors	None	Vasoactive medication Eclampsia or postpartum status Migraine
Headache	Progressive	Thunderclap
Stroke, onset	During the course of illness	Early, a few days after initial normal imaging
Course	Progressive	Uniphasic Rapid dynamic nature
Diagnosis		
CSF	Abnormal	Normal
High-resolution MRI of the vessel wall	Arterial wall enhancement	Lack of contrast enhancement
Treatment	Glucocorticoids or immunosuppressives	Calcium channel blockers or nimodipine Magnesium
Resolution at follow-up angiography	Months	Within 3 months

CSF, Cerebrospinal fluid; *MRI,* magnetic resonance imaging; *PACNS,* primary angiitis of the central nervous system; *RCVS,* reversible cerebral vasoconstriction syndrome.
From Hochberg MC et al: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

BOX E1 Clinical Syndromes of Cerebral Vasculitis

I. Primary CNS vasculitis or PACNS
   1. Granulomatous angiitis of the central nervous system
II. Secondary CNS vasculitis
   1. Systemic vasculitis
      a. Behçet disease
      b. Necrotizing arteritis of the polyarteritis type (PAN)
      c. Systemic granulomatous vasculitis/ANCA-associated vasculitis (GPA, EGPA)
      d. Giant cell arteritis
      e. Hypersensitivity vasculitis and cryoglobulinemic vasculitis
      f. Kawasaki disease
   2. Systemic rheumatic diseases
      a. Systemic lupus erythematosus
      b. Sjögren syndrome
      c. Rheumatoid arthritis
      d. Mixed connective tissue disease or overlap syndrome
      e. Scleroderma
      f. Sarcoidosis
      g. Inflammatory bowel disease
   3. Infection-associated cerebral vasculitis
      a. Virus (varicella-zoster virus, West Nile virus, cytomegalovirus, hepatitis B and C viruses)
      b. Retroviral infection/HIV-1
      c. Spirochete *(Treponema pallidum, Borrelia burgdorferi)*
      d. Fungi (*Aspergillus, Coccidioides, Histoplasma* spp.)
      e. *Bartonella* spp.
      f. *Rickettsia* spp.
      g. Bacterial meningitis
      h. *Mycoplasma* spp.
      i. *Mycobacterium tuberculosis*
      j. Protozoal, amebiosis, cysticercosis
   4. Cerebral vasculitis associated with amyloidosis, amyloid angiitis
   5. Cerebral vasculitis associated with paraneoplastic disorders, paraneoplastic angiitis

ANCA, Antineutrophil cytoplasmic antibody; *CNS*, central nervous system; *EGPA,* eosinophilic granulomatosis with polyangiitis; *GPA,* granulomatosis with polyangiitis; *HIV,* human immunodeficiency virus; *PACNS,* primary angiitis of the nervous system.
From Hochberg MC et al: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

BOX E2 Noninflammatory Vasculopathic Disorders that Mimic Primary Angiitis of the Central Nervous System

Reversible Cerebral Vasoconstriction Syndromes
Intracranial atherosclerosis
Cerebral embolism
Hypercoagulable state
Intracranial vertebral artery dissection
Neurofibromatosis
Fibromuscular dysplasia
Susac syndrome
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
Moyamoya disease
Acute multifocal placoid pigment epitheliopathy
Mitochondrial encephalopathy, lactic acidosis, and strokelike illness (MELAS)
Progressive multifocal leukoencephalopathy
Reversible posterior leukoencephalopathy syndrome
Demyelinating syndrome

From Hochberg MC et al: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

BOX E3 Laboratory Evaluation for Suspected Primary Angiitis of the Central Nervous System

General Studies
Complete blood count
Complete metabolic panel and hepatic function test
Erythrocyte sedimentation rate
C-reactive protein
Lipid panel
Urinalysis and urine microalbumin
Urine toxicology screen
Prothrombin and thromboplastin time
Proteins S and C
Serum and urine protein electrophoresis and serum immunoglobulin electrophoresis
Quantitative immunoglobulin
Acute hepatitis panel, B and C virus
HIV
Serology panel
Rheumatoid factor
Antinuclear antibody
Antibodies to Ro/SSA, La/SSB, Sm, and RNP antigens
Anticardiolipin antibody and lupus anticoagulant
Serum complement level: C2, C3, C4, and CH^{50}
Antibody to double-stranded DNA
Antineutrophil cytoplasmic antibody
Angiotensin-converting enzyme
Lyme titer (ELISA and Western blot)
Serum cryoglobulins
Treponema pallidum, rapid plasma antigen, and fluorescent treponemal antigen
Cerebrospinal fluid studies
Protein
Glucose
Cell count
IgG level and index
Oligoclonal bands
Venereal Disease Research Laboratory (VDRL)
Viral antibodies and antigens and polymerase chain reaction for West Nile virus, cytomegalovirus, herpes simplex and herpes zoster, and HIV
Lyme titer
ANCA titer
ACE level
India ink, Gram stain, and routine cultures, including acid-fast bacillus stain

ACE, Angiotensin-converting enzyme; *ANCA,* antineutrophil cytoplasmic antibody; *CH^{50},* 50% hemolyzing dose of complement; *ELISA,* enzyme-linked immunosorbent assay; *HIV,* human immunodeficiency virus; *RNP,* ribonucleoprotein.
From Hochberg MC et al: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

- CSF findings are nonspecific but most commonly include an elevated CSF protein and a modest lymphocytic pleocytosis.
- Fig. E1 describes an algorithmic approach to the diagnosis of PACNS.

Small vessel PACNS may have normal cerebral angiography. However, PACNS is unlikely in the context of normal brain MRI and normal cerebrospinal fluid studies.

IMAGING STUDIES

- Various neuroimaging modalities can be used to assess for both parenchymal and vascular abnormalities in the evaluation of suspected PACNS.
- Magnetic resonance imaging (MRI) should be performed in all patients.
- The selection of additional neuroimaging modalities depends on the initial MRI findings and individual patient characteristics.
- Conventional angiography (Fig. E2) remains an important part of the diagnostic testing for suspected PACNS.
- Angiography can detect segmental narrowing in multiple vessels that are typical of, though

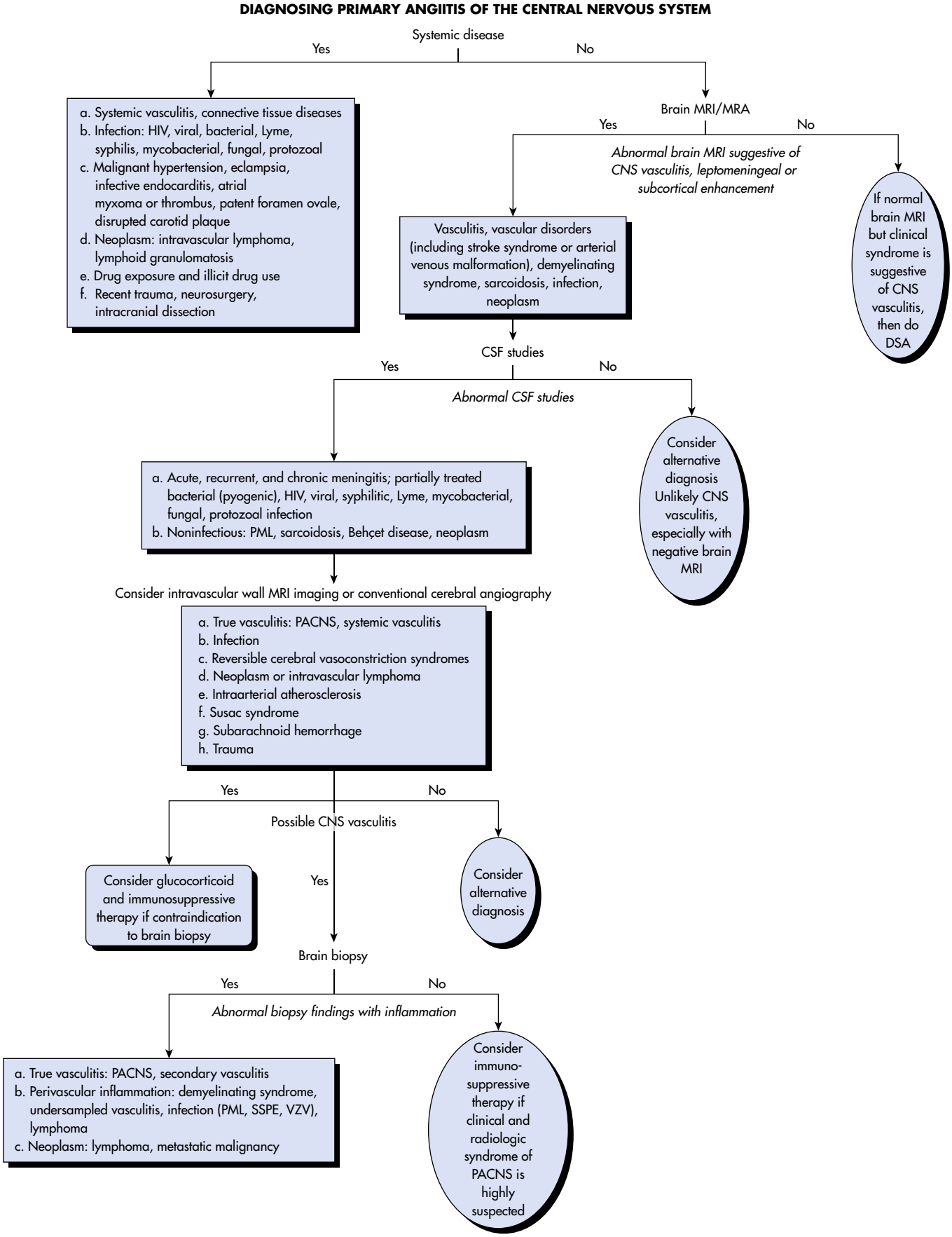

FIG. E1 Algorithmic approach to the diagnosis of primary angiitis of the central nervous system (PACNS). PACNS presents with a clinical syndrome of unclear etiology with altered mental status, headache, and seizure. *CSF,* Cerebrospinal fluid; *CNS,* central nervous system; *DSA,* digital subtraction angiography; *HIV,* human immunodeficiency virus; *MRA,* magnetic resonance angiography; *MRI,* brain magnetic resonance imaging; *PML,* progressive multifocal leukoencephalopathy; *SSPE,* subacute sclerosing panencephalitis; *VZV,* varicella-zoster virus. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

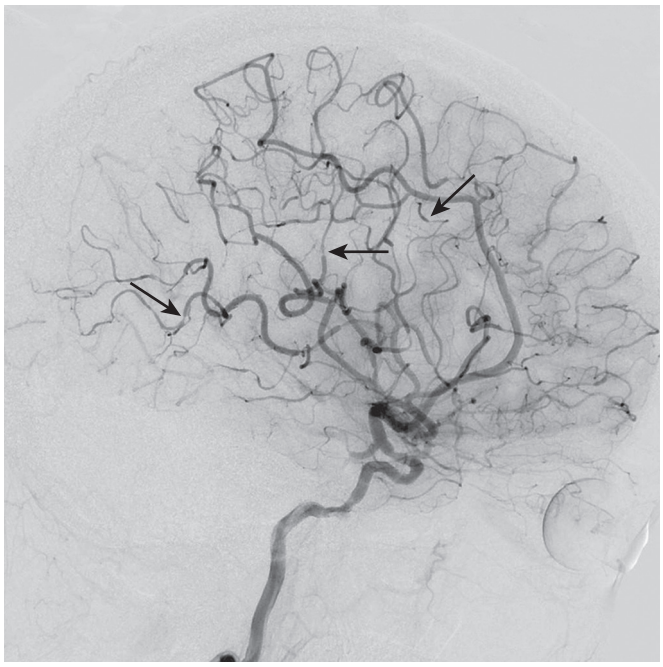

FIG. E2 Cerebral angiography of primary angiitis of the central nervous system (PACNS). Diffuse irregularity and severe multifocal narrowing in the distribution of large, intermediate, and small arteries. Typical PACNS features include beading, segmental narrowing, and dilation *(arrows),* aneurysmal dilatation, circumferential or eccentric vessel irregularities, and multiple occlusions with sharp cutoffs. (From Hochberg MC et al: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

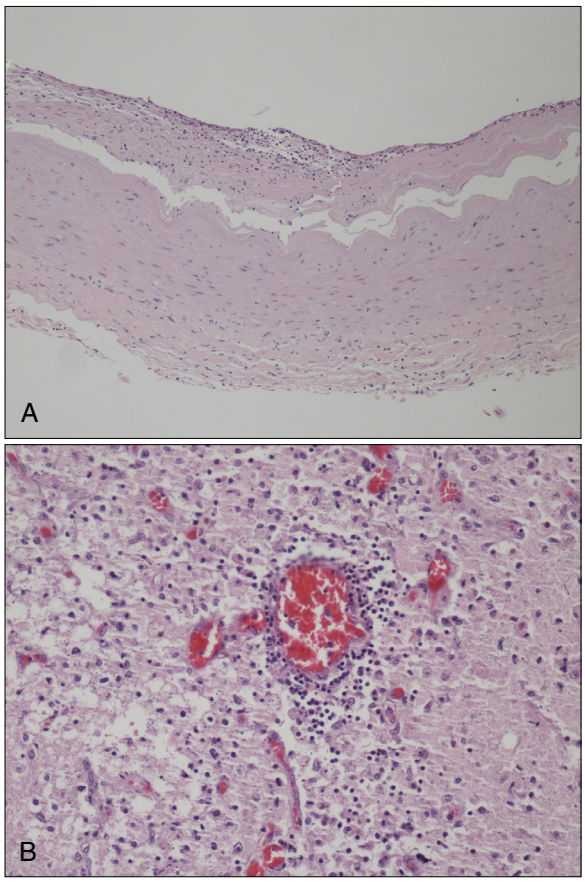

FIG. E3 Brain biopsy findings of granulomatous vasculitis. A, A large artery inflammatory vasculopathy with fibroblastic and smooth muscle proliferation accompanied by mononuclear cell infiltrate in the arterial wall (intima, media, and adventitia). **B,** Granulomatous vasculitis with a mixture of epithelioid cells, plasma cells, macrophages, and scattered granulomas (hematoxylin-eosin staining). (From Hochberg MC et al: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

not pathognomonic for, PACNS, and help further rule out alternative diagnoses such as atherosclerosis, moyamoya, and dissection. These tests may also be helpful in selecting a location for brain biopsy if needed.

- A brain biopsy should be performed in most patients with suspected PACNS. A biopsy will help histologically identify PACNS (Fig. E3) as well as exclude other lesions or vasculitis mimics, particularly infection or malignancy.

Rx TREATMENT

ACUTE GENERAL Rx

- PACNS should be treated with a combination of glucocorticoids and cyclophosphamide (Grade 2C).
- Treatment of atypical PACNS should be individualized according to the severity and the extent of the neurologic deficit.
- The response to treatment is monitored by periodic reassessment of symptoms, neurologic findings, and neuroimaging abnormalities.
- It is important to differentiate between disease damage and disease progression. Neurologic deficits due to cerebral or cerebellar infarction may resolve slowly or not at all.
- For some patients, a response to treatment may only be indicated by symptomatic improvement (e.g., resolution of headache) but not the resolution of magnetic resonance (MR) lesions.
- A lack of new lesions on MRI is a more reliable way to assess for progression of the disease.
- A follow-up MR should be obtained 4 to 6 wk after beginning treatment, then every 3 to 6 mo throughout therapy, and subsequently according to the evolution of the disease.

CHRONIC Rx

We recommend the use of measures to prevent osteoporosis and *Pneumocystis* infections during the treatment of PACNS (Grade 1A).

DISPOSITION

Usually inpatient due to severe disease presentation

REFERRAL

Rheumatology, neurology, infectious diseases

PEARLS & CONSIDERATIONS

- PACNS predominantly affects small- and medium-sized arteries of the brain parenchyma, spinal cord, and leptomeninges, resulting in symptoms and signs of CNS dysfunction.
- The most frequent mimic of PACNS is a group of disorders known collectively as the reversible cerebral vasoconstriction syndromes (RCVS).
- The diagnosis of PACNS is based upon a constellation of symptoms and signs in the setting of supportive studies and the exclusion of alternative diagnoses.
- CSF findings are nonspecific but most commonly include an elevated CSF protein and a modest lymphocytic pleocytosis.

- PACNS should be treated with a combination of glucocorticoids and cyclophosphamide (Grade 2C).

AUTHOR: **Catherine E. Najem, MD**

SUGGESTED READINGS

Hajj-Ali RA, Calabrese LH: Diagnosis and classification of central nervous system vasculitis, *J Autoimmun* 48–49:149-152, 2014, https://doi.org/10.1016/j.jaut.2014.01.007. Review.

Hajj-Ali RA, Calabrese LH: Primary angiitis of the central nervous system, *Autoimmun Rev* 12(4):463-466, 2013.

BASIC INFORMATION

DEFINITION

Primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis is a chronic, variably progressive cholestatic liver disease most often affecting middle-aged women and characterized by autoimmune destruction of intralobular bile ducts leading to portal inflammation, hepatic cell necrosis, fibrosis, cirrhosis and, ultimately, liver failure.

SYNONYMS

PBC
Primary biliary cirrhosis
Biliary cirrhosis
Nonsuppurative destructive cholangitis
Autoimmune cholangiopathy (AIC)

ICD-10CM CODE
K74.3 Primary biliary cholangitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Annual incidence rates range from 3.3 to 58 cases per million.
- PBC accounts for up to 2% of deaths from cirrhosis worldwide.

PREVALENCE: Prevalence is greatest in North America and Northern Europe and varies tremendously by time and geographic areas, ranging globally from 2.7 to 492 cases per million. Disease burden seems to be increasing, which may be a result of better detection rather than true rise in disease incidence.

PREDOMINANT SEX: Female:male ratio of 9:1

PREDOMINANT AGE: Onset typically occurs between the ages of 30 and 65 yr and is uncommon before age 25 yr.

PREDOMINANT RACE: Most often described in Caucasians but PBC affects all races.

GENETICS:

- Pathogenesis is unknown, but it is thought to be in the setting of environmental influences and genetic predisposition.
- There are no clearly identified genetic factors associated with PBC; however, there is a clear familial occurrence. Prevalence among familial clustering of PBC is approximately 3% to 9% in the U.S., Brazil, Japan, and Europe. The concordance rate among monozygotic twins is 63%.
- Up to 73% of patients with PBC have at least one other extrahepatic autoimmune disorder such as thyroiditis, Sjögren syndrome, rheumatoid arthritis, cutaneous scleroderma (which can include CREST syndrome), systemic lupus erythematosus, pernicious anemia, celiac disease, autoimmune thrombocytopenia purpura, autoimmune diabetes mellitus, and/or other autoimmune diseases.
- A variant form of PBC exists as an overlap syndrome with autoimmune hepatitis (AIH).
- PBC is closely associated with a greater risk of hepatocellular carcinoma as well as an overall greater risk of cancer.

ETIOLOGY

- Although the cause of PBC remains unknown, it is believed to require both a genetic susceptibility as well as an environmental trigger ultimately leading to the modification of mitochondrial proteins triggering a persistent T lymphocyte–mediated attack on intralobular bile ducts.
- PBC is associated most strongly with HLA alleles DRA, DRB1, DPB1, DQB1, BTNL2 and c6orf10. PBC is also associated with ORMDL3, CD80, STAT1/STAT4, IL12A, NF-κB, and RPL3/SYNGR1. However, there is variation across ethnic groups.
- Possible environmental triggers include infectious agents, cigarette smoking, environmental pollutants, radiation, urinary tract infections, reproductive hormone replacement, prior pregnancy, toxic waste sites (particularly exposure to halogenated hydrocarbons), electrophilic drugs, and xenobiotics found in food additives and cosmetics.
- The enzyme complex subunit PDC-E2 is an autoantigen that plays a major role in the early pathogenesis of PBC. Patients with PBC have a tenfold increased concentration of PDC-E2-specific cytotoxic $CD8^+$ lymphocytes in their livers compared to their blood, and antimitochondrial antibodies (AMAs), which are the serologic hallmark of this disease, react to the PDC-E2 subunit leading to a strong inflammatory response. In addition, biliary epithelial cells handle PDC-E2 in a unique way that exposes them to immune-mediated attack. Future therapies may be specific immunomodulation directed at these peptides.
- In addition, secondary damage to hepatocytes results from the chronic accumulation of bile acids.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical stages:

- Asymptomatic
- Symptomatic
- Cirrhotic
- Hepatic failure

Symptoms:

- 50% to 65% of patients may be asymptomatic; 50% of patients develop symptoms in 5 yr, 80% in 10 yr, and 95% in 20 yr.
- Fatigue (20% to 85% of patients) and pruritus (40% to 80% of patients) are the usual presenting symptoms and are independent of disease severity.
- Fatigue can be chronic and correlate with daytime somnolence and autonomic dysfunction.
- Pruritus is worse at night, with constricting, coarse garments, and in association with dry skin and hot, humid weather. The cause is unknown but elevated histamine, bile salt concentration, endogenous opioids, lysophosphatidic acid, and female steroid hormones and their metabolites have been discussed as potential causes. Pruritus may first occur during pregnancy but is distinguished from pruritus of pregnancy because it persists into the postpartum period and beyond.
- Symptoms include jaundice (10% to 60%), unexplained right upper quadrant pain (10%), manifestations of portal hypertension, dyslipidemia (76% to 96%), xanthomas (15% to 50%), osteoporosis (20% to 44%), Sjögren syndrome (4% to 73%), rheumatoid arthritis (2% to 6%), systemic lupus erythematosus (up to 4%), celiac disease (up to 6%), and thyroid disorders (6% to 24%) with the most common being Hashimoto thyroiditis.
- Other symptoms can include steatorrhea, fat-soluble vitamin deficiencies, and anemia.

Physical examination:

- Variable: Findings depend on stage of disease at time of presentation; patients at the early stage may be completely unaffected.
- Excoriations may be present due to extensive scratching from pruritus and can be severe enough to cause bleeding.
- Hepatomegaly and splenomegaly can worsen with disease progression.
- Xanthomas and jaundice generally appear in advanced disease. Kayser-Fleischer rings are rare and result from copper retention. Hyperpigmentation of the skin due to melanin deposition may also occur.
- Late physical findings mirror those of cirrhosis: spider nevi, caput medusae, temporal and proximal limb wasting, ascites, palmar erythema, digital clubbing, gynecomastia, and edema.

DIAGNOSIS

The diagnosis of PBC can be established when two of the following three criteria are met.

- Positive serum AMA, titer >1:40 or PBC-specific anti-nuclear antibody reactivity
- Biochemical evidence of cholestasis (mainly alkaline phosphatase elevation [ALP] $\geq$ 1.5 times the upper limit of normal [ULN])
- Characteristic liver histology demonstrating nonsuppurative destruction of small to medium-sized interlobular biliary ducts

DIFFERENTIAL DIAGNOSIS

- Drug-induced cholestasis (common medications: phenothiazines, anabolic steroids, some antibiotics as TMP-SMX, oxacillin, and ampicillin)
- PBC-AIH overlap syndrome; reported in 2% to 20% of patients initially diagnosed with PBC. Transition from stable PBC to AIH and vice versa also seen
- Other etiologies of chronic liver disease and cirrhosis, such as alcoholic cirrhosis, chronic viral hepatitis, primary sclerosing cholangitis, AIH, sarcoidosis, hepatic amyloidosis, chemical/toxin-induced cirrhosis, other hereditary or familial disorders (e.g., cystic fibrosis, α-1-antitrypsin deficiency)
- Biliary obstruction
- Secondary biliary cirrhosis or secondary sclerosing cholangitis

WORKUP

History, physical examination, laboratory evaluation, liver biopsy

LABORATORY TESTS

- AMAs found in 90% to 95% of patients with PBC and are 98% specific.
- Antinuclear antibodies (ANAs) and AMAs found in 53% of patients. In approximately 5% to 10% of patients, AMAs are absent (AMA-negative PBC). Nearly all patients have ANA or AMAs, or both.
- Cholestatic pattern of liver biochemical markers; markedly increased ALP (of hepatic origin). ALP levels along with bilirubin levels correlate with the risk of liver transplantation or death.
- γ-Glutamyl transpeptidase is increased (indicate biliary origin of ALP).
- Serum IgM levels are increased (lower in AMA-negative PBC).
- Bilirubin level is normal early on and increases with disease progression (direct and indirect). Increased serum bilirubin level is a poor prognostic indicator.
- Aminotransferase level may be normal and, if increased, is rarely more than 5 x ULN.
- Markedly increased serum lipids in more than 50% of patients is largely due to increased lipoprotein X (LpX). Total cholesterol may surpass 1000 mg/dl (with increased xanthomas rather than xanthelasmas). In the early stages of PBC, patients can have relatively higher HDL in comparison to LDL and VLDL. This rise in HDL might explain the lack of increased risk for cardiovascular disease. However, cardiovascular risk may still exist due to other risk factors (e.g., family history and metabolic syndrome).
- Percutaneous liver biopsy confirms or rules out the diagnosis, allows staging, but is not essential to make the diagnosis or to initiate medical therapy in patients with typical liver chemistry and positive AMA test.
- Histology is not uniform, so histologic stage is based on the most advanced lesion present.
  1. Stage I: Nonsuppurative cholangitis indicated by lymphocytic infiltration of small bile ducts with or without epithelioid granulomas or plasma cells, limited to portal areas
  2. Stage II: Extension of inflammatory cells to periportal parenchyma, ductular proliferation
  3. Stage III: Bridging necrosis or fibrous septa linking portal triads
  4. Stage IV: Frank cirrhosis with regenerative nodules

IMAGING STUDIES

If history, physical examination, blood tests, and liver biopsy are all consistent with PBC neither imaging nor cholangiography is necessary (Fig. E1).

PROGNOSIS

- Median survival is 7.5 to 16 yr in untreated patients but is getting longer with earlier diagnosis and initiation of treatment. Table 1 summarizes time course of histologic progression to a higher stage in patients with PBC.
- 80% of patients progress one stage within 3 yr, and 31% of patients progress from stage I to stage IV within 4 yr.
- Neither presence nor total titer level of AMAs predicts survival, disease progression, or response to therapy.
- Prognostic laboratory measures: Serum bilirubin is the best predictor of survival and the most heavily weighted factor in prognostic models. Box 1 summarizes independent predictors of survival in patients with PBC.
- Response to ursodeoxycholic acid (UDCA) therapy can be prognostic, with approximately 40% of patients failing to respond. There are multiple biochemical response criteria that, if met after 1 yr of treatment with UDCA, are associated with improved clinical outcomes. Three of these criteria are Barcelona (decrease in ALP level of at least 40% or to the reference range), Paris I (ALP <3 x ULN, AST <2 x ULN and bilirubin within normal limits), and Paris II (ALP <1.5 x ULN, ALT <1.5 x ULN and bilirubin within normal limits). Similarly, the Mayo Risk score, a predictor of short-term survival probability in non-transplanted patients (www.mayoclinic.org/medical-professionals/transplant-medicine/calculators/the-updated-natural-history-model-for-primary-biliary-cirrhosis/itt-20434724), can also reliably predict life expectancy when calculated after 6 mo of UDCA therapy.

Poorer prognosis is associated with jaundice, advanced histologic stage, elevated bilirubin or ALP, low albumin, hepatocellular carcinoma, non-response to UDCA, and esophageal varices.

TABLE 1 Time Course of Histologic Progression to a Higher Stage in Patients with PBC

Histologic Progression*	Initial Histologic Stage		
	1	2	3
1 yr	41	43	35
2 yr	62	62	50

*Percent of patients in whom the histologic stage increases at 1 yr and 2 yr.

From Feldman M et al: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

BOX 1 Independent Predictors of Survival in Patients with PBC in Various Clinical Studies

Clinical
Age
Ascites
Edema
Hepatomegaly
Variceal bleeding

Laboratory
Serum albumin level
Serum alkaline phosphatase level
Serum bilirubin level
Prothrombin time

Liver Histology
Cholestasis
Cirrhosis
Fibrosis
Mallory hyaline

PBC, Primary biliary cholangitis.
From Feldman M et al: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

Rx TREATMENT

- Treatment is according to the clinical stage of the disease.
- Asymptomatic stage:
  - Follow liver function tests every 3 mo.
  - Once ALP is elevated up to 1.5 x ULN, begin UDCA at 13 to 15 mg/kg/day in two to four divided doses regardless of histologic stage.
    1. Side effects may include headaches, dizziness, diarrhea or constipation, dyspepsia, nausea, weight gain, back pain, and upper respiratory infections.
    2. Watch for interactions with fibric acid derivatives, bile acid sequestrants, estrogen derivatives, as well as aluminum hydroxide, which may interfere with the therapeutic effect or serum concentration of UDCA.
    3. Efficacy is best if started during stage I or II disease but should be started at any stage of disease. Lifelong therapy is currently recommended.
- Treatment also includes treatment of associated conditions such as fatigue, pruritus, osteoporosis, hypercholesterolemia, malabsorption, fat-soluble vitamin deficiencies, anemia, hypothyroidism, and any complications of cirrhosis.

ACUTE GENERAL Rx

- Symptomatic stage: Goals of treatment are resolution of symptoms such as pruritus, treatment of chronic cholestatic complications, and delay of liver failure.
- Obeticholic acid has recently been approved as a second line treatment for PBC.
  1. It is a farnesoid X receptor agonist and is used in combination with UDCA for patients who have an inadequate response to UDCA or as monotherapy for patients who are UDCA non-responders.
  2. It is initially dosed at 5 mg once daily and can be increased to 10 mg once daily after 3 mo if there has been an inadequate decrease in bilirubin and/or ALP.
  3. The most common adverse event noted is pruritus and therefore this drug may not be ideal for patients with that symptom.
- Prednisone, azathioprine, colchicine, methotrexate, fibrates, penicillamine, cyclosporine, silymarin, and mycophenolate mofetil are no longer used because of limited efficacy and/or significant toxicity.
- For the pruritus of PBC, cholestyramine resin (4 to 16 g/day) reduces pruritus in most patients but must be given at least 4 hrs before UDCA to avoid reducing the efficacy of that drug. Antihistamines at bedtime help nighttime symptoms. Rifampin (150 to 300

mg bid), oral opiate antagonists such as naltrexone (12.5 to 50 mg daily) and sertraline (75 to 100 mg daily) can be used for pruritus refractory to bile acid sequestrants. Table 2 summarizes treatment recommendations for pruritus in PBC. Intractable pruritus can be an indication for liver transplantation.
- Newer agents that are being investigated for pruritus include ileal bile acid transporter inhibitors and fibrates.

CHRONIC Rx

- Liver function tests should be checked every 3 to 6 mo.
- Management of sicca syndrome: Artificial tears can be used initially for dry eyes. Saliva substitutes can be used for xerostomia and dysphagia; pilocarpine or cevimeline can be used for refractory cases. Moisturizers can be given for vaginal dryness.
- Treatment/Prevention of osteopenia/osteoporosis: Patients with PBC should be given 1000 to 1200 mg calcium daily in divided doses and 1000 IU of vitamin D daily in the diet and as supplements if needed. Weight-bearing exercises are also recommended. Bone densitometry should be done at time of diagnosis, after a fragility fracture, in patients with cirrhosis, prior to transplant, or in patients receiving steroids more than 3 mo. It should then be performed every 2 to 4 yr. Alendronate (70 mg weekly) or other bisphosphonates should be considered if patients have osteopenia in the absence of acid reflux or known varices.
- Hyperlipidemia is common in patients with PBC. However, there is no elevated risk of cardiovascular disease. Statins are safe and effective in patients who may need treatment even if liver chemistry is abnormal.
- Vitamin A, K, and E deficiencies can be clinically important in advanced cases and respond to oral replacement.
- Upper endoscopy to assess for varices is indicated every 1 to 3 yr in patients with cirrhosis or Mayo risk score >4.1. Nonselective beta-blockers or endoscopic banding can be considered for prevention of variceal hemorrhage.
- Regular screening for hepatocellular carcinoma with ultrasound and α-fetoprotein every 6 mo is recommended for patients with cirrhosis.
- Liver transplantation is the only effective treatment for patients with liver failure, and approximately 25% of PBC patients ultimately need a liver transplant. Indications for transplantation include hepatic decompensation (encephalopathy, recurrent variceal bleeding, intractable ascites and spontaneous bacterial peritonitis), hepatocellular carcinoma fulfilling Milan criteria (see "Hepatocellular Carcinoma"), and intractable pruritus. Liver transplant should also be considered with a Mayo risk score >7.8, MELD score >12, and bilirubin ≥ 6 mg/dl.
- The outcome of liver transplantation for patients with PBC is more favorable than that of nearly all other liver disease categories. The survival rates at 1 yr are now up to 90% to 95%. Although recurrent disease may develop in 11% to 42% of patients after liver transplantation within a median of 47 mo, patient and graft survival is usually not affected.

DISPOSITION

Definitive treatment requires liver transplantation. Among untreated patients transplant-free survival is 79%, 59%, and 32% at 5, 10, and 15 yr, respectively.

REFERRAL

Gastroenterology and/or hepatology for treatment, evaluation for liver transplantation, and management of portal hypertension.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Primary Biliary Cirrhosis (PBC) (Patient Information)

AUTHORS: **Jeanette G. Smith, MD,** and **Dina A. Ibrahim, MD**

TABLE 2 Current Recommendations for Treatment of Pruritus in Primary Biliary Cholangitis

Approach	Drug	Mechanism of Action	Dose	Adverse Effects	Comments
First line	Cholestyramine	Bile acid resin	4-16 g/day	Unpleasant taste, bloating, constipation, and diarrhea	Morning dose preferred; separate at least 3 hr from other drugs
	Colesevelam	Bile acid resin	3.75 g/day in two or three divided doses	As above (but less frequent), headache, myalgia	Separate at least 3 hr from other drugs
Second line	Rifampicin (rifampin)	Pregnane X receptor (PXR) agonist and enzyme inducer	150-600 mg/day	Hepatitis, liver failure, hemolysis	150 mg/day when serum bilirubin level <3 mg/dl; 300 mg/day when serum bilirubin level >3 mg/dl; regular monitoring of blood count and liver biochemistry
Third line	Naltrexone	Opiate mu receptor antagonist	50 mg/day	Opioid withdrawal–like reaction—abdominal pain, high blood pressure, tachycardia, goose bumps, nightmares	Start at 12.5 mg/day; increase gradually; regular monitoring of liver biochemistry
Fourth line	Sertraline	Serotonin reuptake inhibitor (SSRI)	100 mg/day	Nausea, dizziness, diarrhea, visual hallucinations, increased fatigue	Start at 25 mg/day; increase gradually

From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, 2017, Elsevier.

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FIG. E1 Primary biliary cholangitis demonstrated by endoscopic retrograde cholangiopancreatography. (From Berk RN et al: *Radiology of the gallbladder and bile ducts: diagnosis and intervention,* Philadelphia, 1983, WB Saunders.)

Primary Chest Wall Tumors

BASIC INFORMATION

DEFINITION

Primary chest wall tumors are a heterogeneous group of rare neoplasms originating from soft tissue, bone, or cartilage of chest wall. Approximately 50% to 80% of chest wall tumors are malignant; approximately 55% arise from bone cartilage and 45% from soft tissue. Chondrosarcomas are the most common primary chest wall sarcoma. The most common soft-tissue primary malignant tumors are fibrosarcomas and malignant fibrous histiocytomas. The most common benign chest wall tumors are osteochondroma, chondroma, and fibrous dysplasia.

ICD-10CM CODES

R22	Localized swelling, mass and lump of skin, and subcutaneous tissue
R22.2	Localized swelling, mass and lump, trunk
C41	Malignant neoplasm of bone and articular cartilage of other unspecified sites
C49.9	Malignant neoplasm of connective and soft tissue, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- 1% to 2% of all new cancer diagnosed and 5% of all thoracic neoplasm.
- More common in the elderly.
- Ewing sarcoma and rhabdomyosarcoma are the most common tumors in children.
- Chondrosarcoma, lymphoma, or solitary plasmacytoma are more frequently seen in the adult.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Palpable enlarging mass over the chest wall or pain.
- Soft tissue masses are usually painless but skeletal lesions can be painful from periosteal invasion.
- Weakness and atrophy of upper extremities can be found from compression of a tumor on the brachial plexus.
- Patients with malignant neoplasms are typically older than patients with benign tumors (60 vs. 42 yrs) and have larger tumors (9 vs. 7 cm).

ETIOLOGY

- Most primary chest wall tumors arise sporadically
- Risk factors: Previous radiation treatment, chronic lymphedema, or exposure to chemicals
- Genetic predispositions: Neurofibromatosis type 1 or familial retinoblastoma

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bone tumors:
  1. Benign: Fibrous dysplasia, osteochondroma, chondroma, Langerhans cell/histiocytosis/eosinophilic granuloma, aneurysmal bone cyst, osteoid osteoma, osteoblastoma, and giant cell tumor
  2. Malignant: Chondrosarcoma, Ewing sarcoma, osteosarcoma, and solitary plasmacytoma
- Soft tissues:
  1. Benign: Lipomas, lipoblastoma, fibroma, fibromatosis, hemangiomas, benign peripheral nerve sheath tumors, and mesenchymal hamartomas
  2. Malignant: Malignant fibrous histiocytoma, synovial sarcomas, rhabdomyosarcoma, fibrosarcoma, and metastatic disease

IMAGING STUDIES

- Chest x-rays (CXR) can reveal sclerotic or lytic bone lesions.
- Chest CT to assess the extent of size, location, and structure involvement such as soft tissue, bone, pleura, vessels, mediastinal area, or lung metastasis. It is also useful in estimating post-resection defect to plan for reconstruction surgery.
- MRI is now a preferred imaging modality to assess primary chest wall tumors. It provides better-detailed information on soft tissue, vascular, and nerve involvement and extension to the spine or thoracic inlet. Malignant tumors usually appear dark on T1-weighted MRI and bright on T-weighted MRI images.

BIOPSY

- Excisional biopsy is preferred for lesions less than 2 cm, thought to be benign and possible for primary closure.
- Incisional biopsy should be considered for lesions larger than 2 cm. A minimum of 1 cm^3 is recommended.
- Fine-needle aspiration biopsy can give high diagnostic accuracy with ancillary techniques such as immunohistochemical stain or cytogenetic analysis.
- Core needle biopsy can be used for deep lesions under the guidance of imaging modalities.

LABORATORY TEST

Cytogenetic analysis is widely used to increase diagnostic accuracy and is sometimes helpful for making the therapeutic decision.

TREATMENT

- Surgical resection and reconstruction are the main principles of treatment.
- Baseline pulmonary function test should be obtained prior to the surgery to determine resection candidacy. Extensive chest wall resection can compromise pulmonary function.
- Systemic treatment and radiation are often combined with surgery as adjuvant or neoadjuvant treatment for malignant disease.
- Isolated plasmacytoma can be treated with chemotherapy or radiation (see “Multiple Myeloma”).
- Metastatic or locally advanced soft tissue sarcomas: Systemic treatment with cytotoxic agent or tyrosine kinase inhibitor (Pazopanib).

FOLLOW UP

- Evaluation for rehabilitation (OT, PT). Continue until maximal function is achieved.
- H&P every 3 to 6 mo for 2 to 3 y, then every 6 mo for next 2 yr, then annually.
- Imaging of chest and other known sites of metastatic disease.
- Consider obtaining postoperative baseline and periodic imaging of primary site based on estimated risk of locoregional recurrence.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Sarcoma (Related Key Topic)

AUTHORS: **Soontharee Congrete, MD,** and **Patan Gultawatvichai, MD**

SUGGESTED READINGS

Cipriano A, Burfeind Jr W: Management of primary soft tissue tumors of the chest wall, *Thorac Surg Clin* 27(2):139-147, 2017.

Shah AA, D'Amico TA: Primary chest wall tumors, *J Am Coll Surg* 210(3):360-366, 2010.

Smith SE, Keshavjee S: Primary chest wall tumors, *Thorac Surg Clin* 20(4):495-507, 2010.

Thomas M, Shen KR: Primary tumors of the osseous chest wall and their management, *Thorac Surg Clin* 27(2):181-193, 2017.

Primary Immunodeficiency Disease (ALG)

BASIC INFORMATION

DEFINITION

Primary immunodeficiency diseases (PIDDs) are a collection of >200 rare disorders involving the absence or malfunction of integral parts of the immune system. The etiologies of PIDDs are not communicable in the infectious sense, but vertically transmissible via transfer of inherited genetic defects. Although some defects affect a single part of the immune system, others cause multicomponent breakdown of combined innate and cellular immune responses and suggest the interplay of epigenetic influences. To be considered a PIDD, the cause must not be secondary to another disease, drug/chemical, or environmental exposure. Primary immunodeficiency disease onset may occur at birth, as most do, or at any subsequent developmental stage and may affect anyone, with only specific regard to gender or ethnicity.

SYNONYMS

PID
PIDD
PI

ICD-10CM CODES

D80.5	Immunodeficiency with increased immunoglobulin M [IgM]
D80.9	Immunodeficiency with predominantly antibody defects, unspecified
D81.0	Severe combined immunodeficiency [SCID] with reticular dysgenesis
D81.1	Severe combined immunodeficiency [SCID] with low T- and B-cell numbers
D81.2	Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
D81.9	Combined immunodeficiency, unspecified
D82.2	Immunodeficiency with short-limbed stature
D82.3	Immunodeficiency following hereditary defective response to Epstein-Barr virus
D82.8	Immunodeficiency associated with other specified major defects
D82.9	Immunodeficiency associated with major defect, unspecified
D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.1	Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
D83.2	Common variable immunodeficiency with autoantibodies to B- or T-cells
D83.9	Common variable immunodeficiency, unspecified
D84.9	Immunodeficiency, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

Overall about 1:500 are born with and 1:1200 currently live with a PIDD, these numbers generally exclude the milder forms of immunodeficiency (e.g., IgA deficiency). The predilection for age and gender varies according to the specific disorder.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The history, signs, and symptoms depend on the precise genetic disorder. Recurrent, persistent, or unusual infections, as well as developmental delay or congenital anomalies, are among the most common attributes present when considering a primary immunodeficiency as a potential diagnosis.

ETIOLOGY

Inherited

DIAGNOSIS

Criteria for the diagnosis of common variable immunodeficiency disease are summarized in Box E1. The International Union of Immunological Societies (IUSIS) PID expert committee has set forth a PID classification system that is updated every other year. The PIDs are grouped into eight categories, based on the primary mechanism of each disease. Due to the complexity of the classification system in clarifying a PID case and the reasoning that most PIDs will present in nonimmunological fields of medicine, a phenotype-based algorithmic approach highlighting the clinical and biological characteristics of a particular PID has been synthesized to aid in diagnosis (Fig. E1).

- Combined T-cell and B-cell immunodeficiencies (Boxes E2 and E3)
- Well-defined syndromes with immunodeficiency (Table E1)
- Predominantly antibody deficiencies (Table E2)
- Disease of immune dysregulation
- Congenital defects of phagocyte number, function, or both
- Defects of innate immunity (Box E4)
- Autoinflammatory disorders
- Complement deficiencies (Table E3)

DIFFERENTIAL DIAGNOSIS

Secondary immunodeficiency, primary infections

WORKUP

A thorough history detailing the type, location, and frequency of the infections, as well as any physical exam findings that may indicate recurrent or persistent infections (e.g., scarred tympanic membranes) is essential in the initial characterization of the suspect immunodeficiency (Table E4). Box E5 summarizes when to suspect an immunodeficiency disorder. Screening tests for suspected primary immunodeficiency disease are summarized in Table E5.

LABORATORY TESTS

- Screening tests:
  1. Complete blood count with a manual differential: The most important test upon initial evaluation is whether lymphocyte, neutrophil, and platelet counts are normal.
  2. Quantitative immunoglobulin levels (IgG, IgA, IgM, IgE): The specimen should be processed at a CLIA (Clinical Laboratories Improvement Act)-approved laboratory and be evaluated within the context of the patient's age and clinical presentation.
  3. Vaccine responsive antibody quantification: Important to the evaluation of an antibody deficiency disorder is evaluating whether there are truly low serum immunoglobulin responses to both polysaccharide- and protein-based vaccines. Table E6 describes antibody specificities commonly used in flow cytometry for immunodeficiency assessment.
  4. Any further investigation should defer to an immunologist for guidance based on history, symptoms, and clinical presentation and may involve a more precise analysis of immunoglobulin subtypes, T and B lymphocytic subsets, cell surface markers, complement levels, and gene sequencing.

TREATMENT

Treatment depends highly on the specific immunodeficiency and should always include

BOX E1 Criteria for the Diagnosis of Common Variable Immunodeficiency Disease

- At least one of the following:
  1. Increased susceptibility to infection
  2. Autoimmune manifestations
  3. Granulomatous disease
  4. Unexplained polyclonal lymphoproliferation
  5. Affected family member with antibody deficiency
- *And* marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2 standard deviations below the normal levels for age)
- *And* at least one of the following:
  1. Poor antibody response to vaccines (and/or absent isohemagglutinins)
  2. Low switched-memory B cells (<70% of the age-related normal value)
- *And* secondary causes of hypogammaglobulinemia have been excluded
- *And* diagnosis is established after the fourth yr of life (although symptoms may present before that age)
- *And* no evidence of severe T-cell deficiency, defined as two of the following:
  1. CD4+ cells/mm^3: 2-6 yr, <300; 6-12 yr, <250; >12 yr, <200
  2. Naive CD4+ %: 2-6 yr, <25; 6-16 yr, <20; >16 yr, <10
  3. Significantly decreased T-cell proliferation to stimulation

Ig, Immunoglobulin.
From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

primary treatment and prophylaxis of the offending infectious agents. Key concepts in the management of primary immunodeficiencies are summarized in Box E6. Education on the necessary precautions to minimize potential infections is crucial. A systematic consideration of the appropriate vaccinations is key to avoid any unnecessary infections or complications. Specific PIDDs carry the risk of malignancies and require regular screenings.

Immunoglobulin replacement is standard treatment for most primary immunodeficiencies to reduce the incidence of serious bacterial infections. Available immunoglobulin G products include Hyquia, Gammagard liquid, Gamune XC, and Hizentra. The newest FDA-approved product is Hyquia. It contains human immune globulin 10% with recombinant hyaluronidase. It is administered subcutaneously every 3 to 4 wk. It has dosing advantages compared to other immune globulin subcutaneous (IGSC) products, but may be more difficult to self-administer because of the need to give hyaluronidase first. The risk of immunogenicity with chronic exposure to recombinant human hyaluronidase is a concern, and its safety in children has not been established.[1]

[1]A new subcutaneous immune globulin (HyQvia) for primary immunodeficiency, *Med Lett Drugs Ther* 57(1476):121-122, 2015.

NONPHARMACOLOGIC THERAPY

Surgical intervention may be necessary for specific congenital malformations and possibly if malignancy is identified. In the case of a severe combined immune deficiency, patient bone marrow transplantation may be a therapeutic option.

PATIENT & FAMILY EDUCATION

Due to the nature of primary immunodeficiencies, affecting both the patient and family members, genetic counseling is key to comprehensive patient care. Although immunologists are well versed in the genetic inheritance of the PIDDs, referral to a genetic counselor is often advised.

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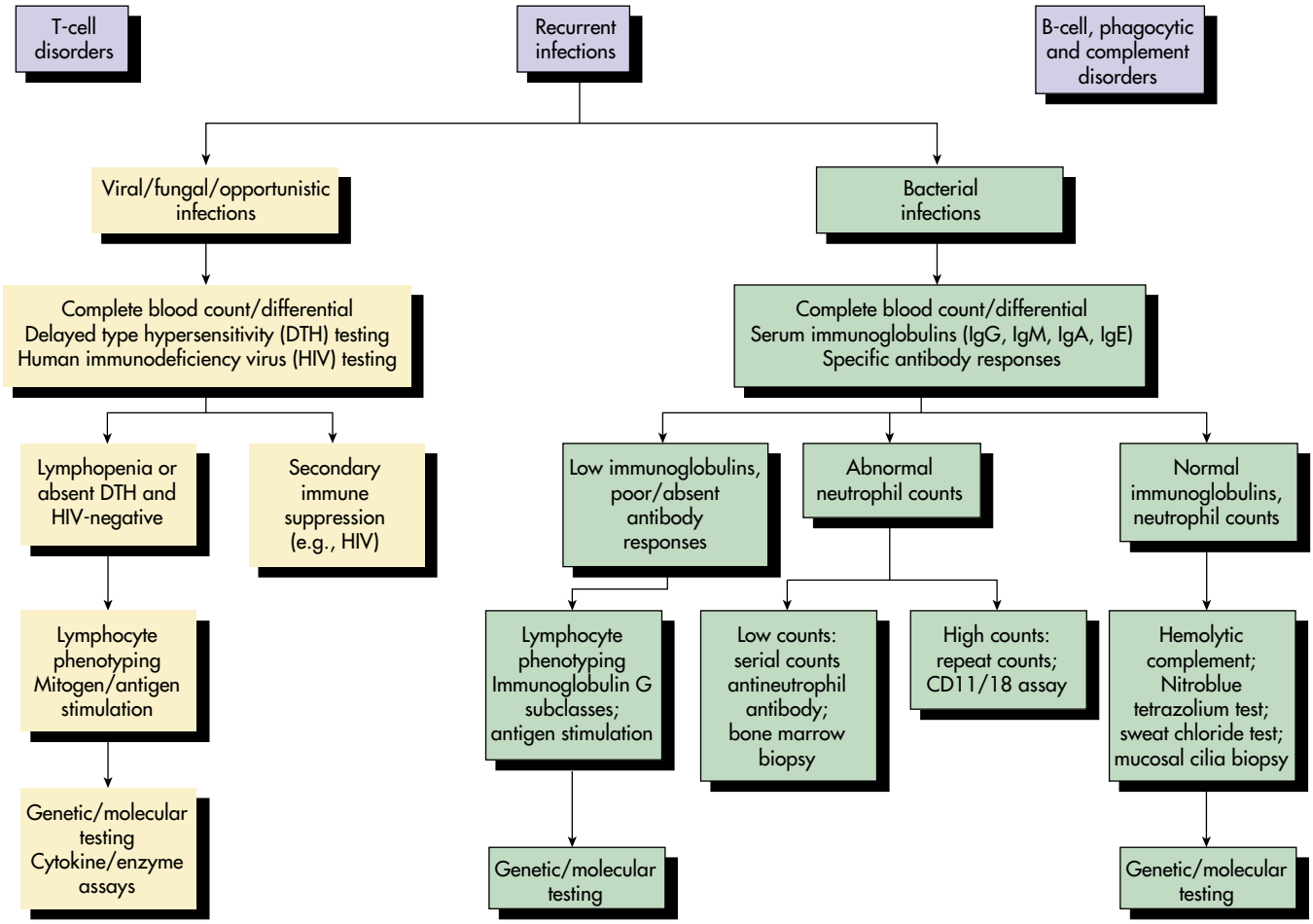

FIG. E1 A diagnostic testing algorithm for primary immunodeficiency diseases. (From Lindegren ML et al: Applying public health strategies to primary immunodeficiency diseases: a potential approach to genetic disorders, *MMWR Recomm Rep* 53[RR-1]:1-29, 2004.)

BOX E2 Screening Tests for B-Cell Immune Function

Screening Tests
- Quantitative serum immunoglobulins
- Specific antibodies to vaccine responses
  1. Tetanus, diphtheria (IgG1)
  2. Pneumococcal and meningococcal polysaccharides (IgG2)
  3. Viral respiratory pathogens (IgG1 and IgG3)
  4. Other vaccines: Hepatitis B, influenza, MMR, polio (killed vaccine)
- Isohemagglutinins (IgM antibodies to A and B blood group antigens)
- B-cell quantitation by flow cytometry

Advanced Testing
- In vitro B-cell immunoglobulin production
- Regulation of immunoglobulin synthesis
- CD40 ligand–CD40 interactions
- B-cell subsets: Nonswitched and switched memory B-cells
- Molecular analysis for gene deletions or mutations

IgG, Immunoglobulin G; *MMR,* measles, mumps, rubella vaccine.
From Adkinson NF et al: *Middleton's allergy: principles and practice,* ed 8, Philadelphia, 2014, WB Saunders.

BOX E3 Screening Tests for Innate Defense Factors

Screening Tests
- Absolute granulocyte count, cell morphology
- Serum total hemolytic complement (CH_{50}), alternative pathway hemolytic activity (AP_{50})
- Nitroblue tetrazolium (NBT) test or flow cytometry using dihydrorhodamine dye test
- Flow cytometry for leukocyte adhesion molecules (CD11/CD18 and CD15a)

Advanced Testing
- Phagocytic assays
- Chemotaxis assays
- Analysis of Toll-like receptor pathways
- Molecular analysis for specific defects

From Adkinson NF et al: *Middleton's allergy: principles and practice,* ed 8, Philadelphia, 2014, WB Saunders.

TABLE E1 Antibody and B-Cell Deficiencies

Disease	Functional Deficiencies	Mechanism of Defect
Agammaglobulinemia		
X-linked	Decrease in all serum Ig isotypes; reduced B-cell numbers	Pre-B receptor checkpoint defect; Btk mutation
Autosomal recessive forms	Decrease in all serum Ig isotypes; reduced B-cell numbers	Pre-B receptor checkpoint defect; mutations in IgM heavy chain (μ), surrogate light chains, Igα, BLNK
Hypogammaglobulinemia, isotype defects		
Selective IgA deficiency	Decreased IgA; may be associated with increased susceptibility to bacterial infections and protozoa such as *Giardia lamblia*	*TACI* mutations in some patients
Selective IgG2 deficiency	Increased susceptibility to bacterial infections	Small subset has deletion in IgG2 locus
Common variable immunodeficiency	Hypogammaglobulinemia; normal or decreased B-cell numbers	*ICOS* and *TACI* mutations in some patients
ICF syndrome	Hypogammaglobulinemia; occasional mild T-cell defects	*DNMT3B* mutations
Hyper-IgM Syndromes		
X-linked	Defects in helper T-cell–mediated B-cell, macrophage, and dendritic cell activation; defects in somatic mutation, class switching, and germinal center formation; defective cell-mediated immunity	*CD40L* mutations
Autosomal recessive with cell-mediated immune defects	Defects in helper T-cell–mediated B-cell, macrophage, and dendritic cell activation; defects in somatic mutation, class switching, and germinal center formation; defective cell-mediated immunity	*CD40, NEMO* mutations
Autosomal recessive with antibody defect only	Defects in somatic mutation and isotype switching	*AID, UNG* mutations

AID, Activation-induced cytidine deaminase; *BLNK,* B-cell linker; *Btk,* Bruton tyrosine kinase; *DNMT3B,* DNA methyltransferase 3B; *ICF,* immunodeficiencies, centromeric instability, and facial anomalies; *ICOS,* inducible costimulator; *Ig,* immunoglobulin; *NEMO,* NF-κB essential modulator; *TACI,* transmembrane activator and calcium modulator and cyclophilin ligand interactor; *UNG,* uracil *N*-glycosylase.
From Adkinson NF et al: *Middleton's allergy: principles and practice,* ed 8, Philadelphia, 2014, WB Saunders.

TABLE E2 Predominant Antibody Deficiencies

	Disease	Mode of Inheritance/Genetic Locus	Clinical Features
Severe reduction in all serum immunoglobulin isotypes with absent B cells	Bruton tyrosine kinase deficiency	XL/Xq21.3-22	Severe bacterial infections (especially of the respiratory tract), absent lymphoid tissue
	μ heavy chain deficiency	AR/14q32.3	Severe bacterial infections
	λ5 deficiency	AR/22q11.21	Severe bacterial infections
	Igα deficiency	AR/19q13.2	Severe bacterial infections
	Igβ deficiency	AR/17q23	Severe bacterial infections
	BLNK deficiency	AR/10q23.2	Severe bacterial infections
	SP110 deficiency	AR/2q37.1	Hepatic venoocclusive disease, some with frequent infection
	LRRC8A deficiency	AD/9q34.11	Facial anomalies
	PIK3R1	AR/5q13.1	Recurrent bacterial infection
	Thymoma with immunodeficiency (Good syndrome)	None	Recurrent infection with encapsulated bacteria and diarrhea, autoimmune phenomena
	Myelodysplasia	Variable/monosomy 7, trisomy 8, dyskeratosis congenita	Recurrent infections and pancytopenia
Severe reduction in at least two serum immunoglobulin isotypes with low or normal B-cell numbers	Common variable immunodeficiency syndromes	≈10% with family history AR or AD	Recurrent respiratory tract infections leading to chronic sinusitis, hearing loss, bronchiectasis, autoimmune disease, lymphoproliferation, malignancy (especially non-Hodgkin lymphoma and gastric carcinoma)
	TACI alterations	AD and AR/17p11.2	
	BAFFR alterations	AR/22q13	
	MSH5 alterations	Unk/6p22.1-p21.3	
	ICOS deficiency	AR/2q33	Recurrent infections
	CD19 deficiency	AR/16p11.2	Recurrent infections
	X-linked lymphoproliferative disease (mutation in SH2 domain protein 1A)	XL/Xq25-q26	Fulminant infection with EBV, lymphoma, dysgammaglobulinemia
	CD81 deficiency	AR/11p15.5	Recurrent infections
	CD20 deficiency	AR/11q12.2	Recurrent infections
	CD21 deficiency	AR/1q32.2	Recurrent infections
	LRBA deficiency	AR/4q31.3	Recurrent infections, inflammatory bowel disease, EBV infection
	TNSF12 deficiency	AD/17p13.1	Recurrent bacterial infections, thrombocytopenia, neutropenia
	NFKB2 deficiency	AD/10q24.32	Recurrent infections
	CXCR4 activation	AD gain of function/2q22.1	WHIM syndrome
Severe reduction in serum IgG and IgA with increased IgM and normal B-cell numbers (disorders of immunoglobulin class switching)	CD40 ligand deficiency	XL/Xq26.3-Xq27.1	Recurrent infections with bacteria and opportunistic pathogens, neutropenia, autoimmune disease
	CD40 deficiency	AR/20q11-20q13.2	Recurrent infections with bacteria and opportunistic pathogens, neutropenia, autoimmune disease
	NEMO hypomorphic mutations	XL/Xq28	Recurrent infections with bacteria and opportunistic pathogens, neutropenia, autoimmune disease
	AID deficiency	AR/12p13	Recurrent bacterial infections and diarrhea, marked enlargement of lymphoid organs
	UNG deficiency	AR/12q23-q24.1	Recurrent bacterial infections and diarrhea, marked enlargement of lymphoid organs
Isotype or light-chain deficiencies with normal B-cell numbers	Ig heavy-chain deficiency	AR/14q32	Most patients are healthy
	κ-chain deficiency	AR/2p11.2	Most patients are healthy
	Isolated IgG subclass deficiency	Variable/unknown	Most patients are healthy
	IgA deficiency associated with IgG subclass deficiency	Variable/unknown	Most patients are healthy
	Selective IgA deficiency	Variable/unknown	Most patients asymptomatic, but increased prevalence of infections, autoimmune disease, atopy, and celiac disease
	PRKCδ deficiency	AR/3p21.1	Recurrent infection, autoimmunity, and chronic EBV infection
	Activated PI3K-γ	AD gain of function/1p36.22	Recurrent infection, autoimmunity, chronic EBV, and CMV infection
Specific antibody deficiency with normal immunoglobulin level and B-cell number	Inability to make antibodies to specific antigens	Variable/unknown	Recurrent sinopulmonary infection, bronchiectasis, diarrhea, autoimmune disease
Transient hypogammaglobulinemia of infancy	IgG and IgA deficiency	Variable/unknown	More likely to be male (60%-80%), mild infections and diarrhea, atopy

λ5, Immunoglobulin lambda-like polypeptide (a surrogate light chain subunit that is part of the pre–B-cell receptor); *AD,* autosomal dominant; *AID,* activation-induced cytidine deaminase (thought to be essential for initiation of the DNA cleavage required for class-switch recombination and somatic hypermutation); *AR,* autosomal recessive; *BAFFR,* B-cell–activating factor receptor; *BLNK,* B linker (a cytoplasmic linker or adaptor protein that plays a critical role in B-cell development); *CMV,* cytomegalovirus; *CXCR4,* CXC-chemokine receptor 4 (mediates migration of resting leukocytes and hematopoietic progenitors in response to its ligand, stromal cell–derived factor 1 [SDF1]); *EBV,* Epstein–Barr virus; *ICOS,* inducible T-cell costimulator (belongs to CD28 family of costimulatory surface molecules); *Ig,* immunoglobulin; *Igα,* immunoglobulin-associated α (necessary for expression and function of the B-cell antigen receptor); *Igβ,* immunoglobulin-associated β (necessary for expression and function of the B-cell antigen receptor); *LRBA,* lipopolysaccharide-responsive, beige-like anchor protein (implicated in regulating endosomal trafficking, particularly endocytosis of ligand-activated receptors); *MSH5, mutS* homolog 5 (a protein involved with DNA mismatch repair and meiotic recombination); *NEMO,* NFκB essential modulator; *NFκB,* nuclear factor kappa-B; *PI3K-γ,* protein kinase C family member (critical for regulation of cell survival, proliferation, and apoptosis); *PRKCδ,* member of the protein kinase c family (involved in B-cell receptor-mediated signaling); *TACI,* transmembrane activator and CAML-interactor; *TNSF12,* tumor necrosis factor ligand superfamily, member 12 (weak inducer of apoptosis); *UNG,* uracil DNA glycosylase (allows creation of single-stranded breaks essential to class switch recombination and somatic hypermutation); *WHIM,* warts, hypogammaglobulinemia, infections, and myelokathexis; *XL,* X-linked.

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

BOX E4 Screening Tests for T-Cell Immunity

Screening Tests
- Newborn screening for TREC analysis (not available in all states)
- Absolute lymphocyte count
- Chest radiograph for thymus shadow in newborns
- Delayed skin hypersensitivity to recall antigens
- Quantification of T-cell subsets

Advanced Testing
- Lymphocyte proliferative responses to mitogens, antigens, and allogeneic cells in MLC
- Lymphocyte-mediated cytotoxicity: NK and ADCC activity
- Production of cytokines
- Functional response to cytokines
- Signal transduction studies
- Molecular analysis for specific defects

ADCC, Antibody-dependent cellular cytotoxicity; *MLC,* mixed lymphocyte culture; *NK,* natural killer; *TREC,* T-cell receptor excision circles.
From Adkinson NF et al: *Middleton's allergy: principles and practice,* ed 8, Philadelphia, 2014, WB Saunders.

TABLE E3 Inherited Complement Deficiencies

Deficiency	Chromosomal Location	Number of Cases Reported	Clinical Features; Diagnostic Strategy
C1q	1	10-100	SLE, infections; CH50 near zero
C1r/s	12	10-100	SLE, infections; CH50 near zero
C4	6	10-100	SLE, infections; CH50 near zero
C2	6	Many	SLE, infections, some asymptomatic; CH50 near zero
C3	19	10-100	Infections frequent and severe, glomerulonephritis; CH50 near zero
Factor D	19	<10	*Neisseria*; AH50 near zero
Factor B	6	<10	*Neisseria*; AH50 near zero
Properdin	X	>100	*Neisseria*; AH50 diminished
MBL	10	Millions	Most asymptomatic infections, SLE; CH50 normal, MBL assay required
C5	9	10-100	*Neisseria*; CH50 near zero
C6	5	>100	*Neisseria*; CH50 near zero
C7	5	>100	*Neisseria*; CH50 near zero
C8	1 and 9	>100	*Neisseria*; CH50 near zero
C9	5	Many	*Neisseria*; CH50 diminished
Factor I	4	10-100	*Neisseria*, HUS; C3 may be diminished, many require mutation analysis
Factor H	1	10-100	*Neisseria*, HUS; C3 may be diminished, many require mutation analysis
MCP	1	<10	HUS; mutation analysis required
C1 inhibitor	11	Many	Angioedema; C1 antigen and functional levels
CR3/CR4	16	>100	Leukocyte adhesion deficiency, very severe systemic infections, lack of pus; flow cytometry
CD59	11	<10	Paroxysmal nocturnal hemoglobinuria; flow cytometry

AH50, Serum dilution that lyses 50% of a red cell suspension; *CH50,* serum dilution that lyses 50% of a red cell suspension; *HUS,* hemolytic uremic syndrome; *MBL,* mannose-binding lectin; *MCP,* membrane cofactor protein; *SLE,* systemic lupus erythematosus.
From Adkinson NF et al: *Middleton's allergy: principles and practice,* ed 8, Philadelphia, 2014, WB Saunders.

TABLE E4 Physical Examination of Patients with Recurrent Infection

Diagnosis and Physical Findings	
Growth Failure	Sinusitis
SCID	Purulent nasal discharge
Dysmorphisms	Purulent postpharyngeal exudate
Micrognathia, short philtrum, ear anomalies	Pharyngeal cobblestoning
Short-limbed dwarfism	Dentition, gums
Hypertelorism, epicanthal folds, flat nasal bridge	Conical teeth
Ectodermal dysplasia	Periodontitis
Coarse facies	**Respiratory Tract**
Skin and oral mucosa	Digital clubbing
Rashes	Rales
Lupus-like malar rash	**Wheezing Cardiac System**
Dermatomyositis rash	Heart murmur (conotruncal abnormalities)
Erythroderma	**Lymphatic System**
Eczema	Absent tonsils, lymph nodes
Petechiae	Diffuse lymphoid hyperplasia
Pyoderma, abscesses	Lymphadenitis
Poor wound healing	**Musculoskeletal System**
Candidiasis	Arthralgia, arthritis
Telangiectasia	Dermatomyositis
Delayed umbilical cord separation	Lupus-like syndrome
Abnormal hair	Short-limb dwarfism
Ears, Nose, Throat, and Mouth	Craniosynostosis
Chronic otitis media	**Neurologic System**
Dull tympanic membranes	Ataxia
Poor light reflex	Enteroviral meningoencephalitis
Scarring	Neuropathies
Perforations of the tympanic membrane	Pernicious anemia

SCID, Severe combined immunodeficiency.
From Adkinson NF et al: *Middleton's allergy: principles and practice,* ed 8, Philadelphia, 2014, WB Saunders.

BOX E5 When to Suspect an Immunodeficiency Disorder

- Frequency of infectious illnesses higher than expected
- Unusual severity or duration of infectious disease
- Poor response to conventional antibiotic therapy
- Unusual organisms or opportunistic infections causing disease
- Failure to thrive secondary to frequent illnesses
- Poor wound healing
- Noninflammatory *Staphylococcus* spp. skin infection (or absence of pus)
- Recurrent periodontitis
- Low granulocyte or lymphocyte count

From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

TABLE E5 Screening Tests for Suspected Primary Immunodeficiency Disease

Immunodeficiency	Screening Tests
All types	Complete blood cell count
	Peripheral blood smear
Antibody deficiency	Quantitative serum immunoglobulins: IgG, IgA, IgM, IgE
	Postimmunization specific IgG antibody titers
	Isohemagglutinins
T-cell deficiency	Delayed hypersensitivity skin tests or lymphocyte proliferation response to mitogens
	Chest imaging studies for thymus size
	Lymphocyte subset phenotyping
Complement deficiency	Total hemolytic complement (CH50) assay
Phagocyte deficiency	Dihydrorhodamine (DHR)-1,2,3 reduction by flow cytometry
	Neutrophil CD18 and CD15 expression

Ig, Immunoglobulin.
From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

TABLE E6 Antibody Specificities Commonly Used in Flow Cytometry for Immunodeficiency Assessment

Antibody Designation	Detection on Normal Cells
CD2	Pan–T-cell, NK cells (80%-95% of T lymphocytes)
CD3	Mature pan–T-cell (95% of T lymphocytes)
CD4	Helper/inducer T-cells (65% of T lymphocytes) and monocytes
CD8	Cytotoxic/suppressor T-cells (35% of T lymphocytes)
CD14	Maturing monocytes
CD16	Granulocytes, NK cells
CD19	Pan–B-cell lymphocyte
CD20	Maturing B-cells (surface immunoglobulin–positive B lymphocytes)
CD34	Immature hematopoietic cells, stem cells
CD41	Platelets and megakaryocytes
CD45	Leukocyte common antigen
CD56	NK cells, some stem cell disorders
HLA-DR	Myeloid blasts, B-cells, activated T-cells (90% of B lymphocytes and monocytes)
Common Monoclonal Antibody Panel Specificities	
To evaluate lymphocyte purity and recovery	CD45, CD14 (two-color)
To evaluate helper/inducer T-cell population	CD3, CD4 (two-color)
	CD3, CD4, CD45 (three-color)
	CD3, CD4, CD45, CD8 (four-color)
To evaluate cytotoxic/suppressor T-cell population	CD3, CD8 (two-color)
	CD3, CD8, CD45 (three-color)
To evaluate B-cell lymphocyte population	CD3, CD19 (two-color)
	CD3, CD19, CD45 (three-color)
	CD3, CD19, CD45, CD16 (four-color)
To evaluate NK cell population	CD3, CD16 and/or CD56 (two-color)

HLA, Human leukocyte antigen; *NK,* natural killer.
From Adkinson NF et al: *Middleton's allergy: principles and practice,* ed 8, Philadelphia, 2014, WB Saunders.

BOX E6 Key Concepts in the Management of Primary Immunodeficiencies

Immune function: T- and B-cell number and function should be assessed periodically.
IgG replacement therapy: Infusions are indicated for patients with poor antibody responses to immunizations.
Immunizations: Live vaccines should not be administered to patients who have severe T-cell deficiencies unless they have received definitive treatment. Household contacts of children with immunodeficiency should not receive oral poliovirus vaccines because of the risk for transmission to the immunodeficient child. Other live vaccines (BCG, MMRV) may be administered to household contacts. If the vaccine recipient develops a rash, contact with the immunodeficient child should be avoided.*
Blood products: When needed, patients with immune deficiencies should receive only irradiated, cytomegalovirus-negative, leukocyte-depleted blood products.
Antibiotic prophylaxis: T-cell–deficient patients should be given antibiotic prophylaxis to prevent *Pneumocystis jirovecii* infection. Antibiotic prophylaxis is recommended for dental and surgical procedures and should be considered for patients with recurrent infections.
Infectious diseases: Infections should be recognized promptly, and unusual pathogens should be considered. Antibiotic therapy should be started early and discontinued cautiously.
Diet and activity: Patients with immune deficiency should have a regular diet and lifestyle but should be instructed to avoid eating raw food and playing in environments potentially highly contaminated with pathogens, including daycare centers. Strict hand-washing precautions and reverse isolation may be indicated for patients with poor T-cell function.

*American Academy of Pediatrics: Summaries of infectious diseases: meningococcal infections. In Pickering LK et al (eds): *2015 Red book: report of the Committee on Infectious Diseases*, ed 30, Illinois, 2015, American Academy of Pediatrics, pp. 547-558.
BCG, Bacille Calmette-Guérin; *Ig,* immunoglobulin; *MMRV,* measles, mumps, rubella, and varicella.
From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

SUGGESTED READINGS

Bousfiha AA et al: A phenotypic approach for IUIS PID classification and diagnosis: guidelines for clinicians at the bedside, *J Clin Immunol* 33(6):1078-1087, 2014.
Notarangelo LD: Primary immunodeficiencies, *J Allergy Clin Immunol* 125(2 Suppl 2):S182-S194, 2010.
Pravaneh N et al: Primary immunodeficiencies: a rapidly evolving story, *J Allergy Clin Immunol* 131(2):314-323, 2013.

Primary Myelofibrosis

BASIC INFORMATION

DEFINITION

Primary myelofibrosis (PMF) is a clonal stem cell disorder characterized by chronic myeloproliferation, atypical megakaryocytic hyperplasia, bone marrow fibrosis (Fig. E1), and extramedullary hematopoiesis in the spleen and liver primarily. Prefibrotic/early myelofibrosis is a recently defined World Health Organization entity with marrow findings typical of myelofibrosis but with less overt fibrosis.

ICD-10CM CODES

C94.40	Acute panmyelosis with myelofibrosis not having achieved remission
C94.41	Acute panmyelosis with myelofibrosis, in remission
C94.42	Acute panmyelosis with myelofibrosis, in relapse
D75.81	Myelofibrosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (U.S.): ~1.9 per 100,000, age >75 yr; 0.7 per 100,000, age 50 to 74 yr; 0.1 per 100,000, age 35 to 49 yr

PREDOMINANT SEX AND AGE:

- Women 35% lower risk, African ancestry 25% lower risk
- Median age of diagnosis is ~67 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

COMMON SYMPTOMS:

- Fatigue (variably reported 30% to 90%)
- Early satiety, abdominal fullness (~70%)
- Abdominal pain (~45%, may be severe if splenic infarction)
- Weight loss (~50%)
- Other reported symptoms: fever, bone pain, itching, night sweats, diarrhea (attributed to effect of splenic enlargement on bowel)
- Back pain and spinal cord compression from extramedullary hematopoiesis are rare complications of PMF

CLINICAL FINDINGS

- Splenomegaly (most)
- Hepatomegaly (~50%)
- Anemia (50% +), leukocytosis or leukopenia, thrombocytosis, or thrombocytopenia
- Elevated lactate dehydrogenase (LDH)
- Leukoerythroblastic changes in peripheral blood—immature myeloid cells (the bone marrow in the peripheral blood), nucleated red blood count (RBC), teardrop RBC. Rare blast may be seen in chronic-phase disease
- Portal hypertension (5% to 10%)—due to increased blood return from splenic vein, hepatic involvement with extramedullary hematopoiesis (EMH), or venous thrombosis. May cause variceal bleeding and ascites
- Unexpected bleeding, thrombosis including portal, splenic mesenteric and hepatic vein thrombosis (Budd-Chiari syndrome)
- Manifestations of EMH—rarely involving lung (pulmonary hypertension), paraspinal lesions with neurologic symptoms, central nervous system, kidney. More common after splenectomy
- Leukemic transformation 8% to 23% within first 10 yr; risk varies by risk score and genetics
- Table E1 summarizes symptoms and physical findings of patients with primary myelofibrosis detected at diagnosis. Medical disorders associated with myelofibrosis are summarized in Table E2

ETIOLOGY

- Clonal disorder of multipotent hematopoietic progenitors arising from the hematopoietic stem cell compartment.
- The *JAK-2* V617F mutation (present in 50% to 60% cases) results in a substitution of valine for phenylalanine at codon 617 in the pseudokinase domain of *JAK-2*, an enzyme in the Janus family of cytoplasmic nonreceptor tyrosine kinases in erythroid progenitors. The mutation causes constitutive activation of *JAK-2* and increased proliferation signals to hematopoietic precursors.
- Calreticulin exon 9 mutations (present in 20% cases) are either type I or type II; type I mutations confer a more favorable prognosis.
- Somatic mutations of *cMPL*, the gene coding for the thrombopoietin gene, are present in about 10%.
- Approximately 10% are "triple negative" for these mutations, which confers a worse prognosis.
- Table E3 describes genetic lesions identified in patients with primary myelofibrosis and outlines the prognostic relevance of the mutation profiles.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS (BOX E1)

- Myelofibrosis evolving from preexisting polycythemia vera or essential thrombocytosis
- Chronic myelogenous leukemia
- Myelodysplastic syndrome with marrow fibrosis
- Acute myelofibrosis of acute megakaryocytic leukemia

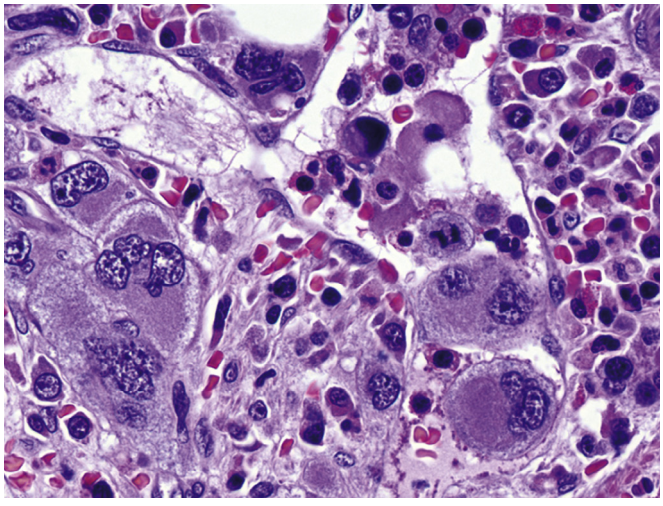

FIG. E1 Bone marrow biopsy in chronic idiopathic myelofibrosis, with increased spacing between cells suggesting fibrosis and intrasinusoidal hematopoiesis (500×). (From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, Philadelphia, 2017, Elsevier.)

TABLE E1 Summary of Symptoms and Physical Findings of Patients with Primary Myelofibrosis Detected at Diagnosis

Symptom or Finding	Incidence (%)
Asymptomatic	16-30
Fatigue	47-71
Fever	5-15
Weight loss	7-39
Night sweats	6-21
Symptoms due to enlarged spleen	11-48
Bleeding	5-20
Gout or renal stones	6-13
Pallor	60
Petechiae or ecchymoses	15-20
Splenomegaly	89-99
Hepatomegaly	39-70
Peripheral edema	13
Evidence of portal hypertension	2-6
Lymphadenopathy	1-10
Jaundice	0-4

From Hoffman R: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, WB Saunders.

TABLE E2 Conditions Associated with Myelofibrosis

Nonmalignant Conditions

Infections: Tuberculosis, histoplasmosis
Renal osteodystrophy
Vitamin D deficiency
Hypoparathyroidism
Hyperparathyroidism
Gray platelet syndrome
Systemic lupus erythematosus
Scleroderma
Radiation exposure
Osteopetrosis
Paget disease
Benzene exposure
Thorotrast exposure
Gaucher disease
Primary autoimmune myelofibrosis

Malignant Disorders

Primary myelofibrosis
Other chronic myeloproliferative disorders: polycythemia vera, chronic myeloid leukemia, essential thrombocythemia
Acute myelofibrosis
Acute myeloid leukemia
Acute lymphocytic leukemia
Hairy cell leukemia
Hodgkin lymphoma
Myelodysplasia with myelofibrosis
Multiple myeloma
Systemic mastocytosis
Non-Hodgkin lymphoma
Carcinomas: Breast, lung, prostate, stomach

From Hoffman R: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, WB Saunders.

- Marrow fibrosis associated with hairy cell leukemia, lymphoma, and multiple myeloma
- "TAFRO" syndrome (*t*hrombocytopenia, *a*nasarca, myelo*f*ibrosis, *r*enal dysfunction, *o*rganomegaly), a variant of multicentric Castleman disease
- Nonhematologic disorders with bone marrow fibrosis: solid tumor metastases to the bone marrow, autoimmune disorders, and secondary hyperparathyroidism with vitamin D deficiency
- Table E4 compares key features of major myeloproliferative and myelodysplastic/myeloproliferative disease

LABORATORY TESTS

- CBC:
  1. Anemia (hemoglobin <10g/dl) is common.
  2. Platelet count and white blood cell (WBC) count vary widely; WBC usually elevated.
  3. Peripheral blood smear: Nucleated RBCs, granulocyte precursors, and teardrop-shaped RBCs (leukoerythroblastosis).
  4. "Blasts" may be present in the chronic phase of PMF; this does not by itself indicate leukemic transformation.
- LDH, elevated uric acid
- Bone marrow biopsy: often is a "dry tap"; reveals reticulin fibrosis, increased megakaryocytes

TABLE E3 Diagnostic Molecular Defects in Primary Myelofibrosis and Related Myeloproliferative Neoplasms

Mutation	Chromosome Location	Incidence	Relevance
Janus kinase 2 (*JAK-2*) V617F, c1849G>T, exon 14	9p24	PMF ~60% P Vera ~95% ET ~55%	Causes constitutive activation of *JAK-2*, sending EPO-independent proliferation signals to bone marrow
Calreticulin (*CALR*) Exon 9 Most common variants (80%): Type I: 52 BP deletion c.1092_1143 Type II: 5 BP insertion C1154_1155insTTGTC	19p32.2	PMF ~20% ET ~20% P Vera 0%	Mainly localized to endoplasmic reticulum as "chaperone," involved with glycoprotein folding, calcium hemostasis, other processes
Myeloproliferative leukemia virus (*MPL*) W515L/K, exon 10	1p34	PMF ~10% ET ~3%	Codes for the thrombopoietin receptor

EPO, Erythropoietin; *ET,* essential thrombocytosis; *P Vera,* polycythemia vera; *PMF,* primary myelofibrosis.
Tests for *JAK-2 V617F*, calreticulin exon 9, and *c-mpl W515L/K* are commercially available and may be diagnostically helpful. Numerous other gene mutations have been described. Some, notably *ASXL1* (Additional Sex Combs-Like 1) appear to carry prognostic significance but are not readily available (see Tefferi A: Primary myelofibrosis: 2014 update on diagnosis, risk-stratification, and management, *Am J Hematol* 89:915-925, 2014 for more details).

BOX E1 Diagnostic Criteria for Primary Myelofibrosis

WHO Diagnostic Criteria for Primary Myelofibrosis and Prefibrotic (Early) Primary Myelofibrosis (2016)
Overt Primary Myelofibrosis

Major Criteria

1 Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grade 2 or 3.
2 Not meeting WHO criteria for essential thrombocytosis, polycythemia vera, BCR-ABL1+ chronic myeloid leukemia, myelodysplastic syndrome, or other myeloid neoplasms.
3 Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, in the presence of another clonal marker, or absence of reactive myelofibrosis.

Minor Criteria

1. Leukoerythroblastosis
2. LDH above institutional upper limit of normal
3. Anemia not attributed to a comorbid condition
4. Palpable splenomegaly
5. Leukocytosis ≥11 × 10^9/L

Diagnosis of overt PMF requires meeting all three major criteria and one minor criteria. Minor criteria should be confirmed in two consecutive determinations.

Preprimary Myelofibrosis
Major Criteria

1. Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis
2. Not meeting the WHO criteria for BCR-ABL1+ CML, PV, ET, myelodysplastic syndrome, or other myeloid neoplasm
3. Presence of *JAK2*, *CALR*, or *MPL* mutations, or in the absence of these mutations, presence of another clonal marker or absence of minor reactive bone marrow reticulin fibrosis

Minor Criteria

1. Presence of at least one of the following, confirmed in two consecutive determinations:
   a. Anemia not attributed to a comorbid condition
   b. Leukocytosis ≥11,000/mcl
   c. Palpable splenomegaly
   d. LDH increased to above upper limit of normal of institutional reference range

Diagnosis of pre-PMF requires all three major criteria and at least one minor criteria.
Arber DA et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, *Blood* 127(20):2391-2405, 2016. Details of grading of myelofibrosis can be found in this reference.

LDH, Lactic dehydrogenase; *WHO,* World Health Organization.
From Hoffman R: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, WB Saunders.

TABLE E4 Key Features of Major Myeloproliferative and Myelodysplastic/Myeloproliferative Disease

Disorder	Demographics	Laboratory Features, Morphology	Cytogenetics	Prognosis
CML	Middle-aged	*BCR-ABL* present	t(9:22)(q34;q11) *BCR-ABL1*	Dependent on response to TKI
CNL	Older adults	Neutrophilia >2K/μL	*CSF3R mutation*	Indolent
PV	Middle-aged, M > F	Major criteria: Hb >18.5 g/dl in M or >16.5 g/dl; *JAK2 V617F* (or Exon 12) Minor criteria: hypercellular marrow with panmyelosis; ↓EPO; endogenous erythroid colony formation in vitro; 2 major plus 1 minor, or first major plus 2 minor criteria	*JAK2 V617F* (or exon 12) negative t(9;22)	10-20 yr
PMF	>50 yr	Major criteria: Megakaryocyte proliferation/atypia with marrow fibrosis; CML, PV, MDS ruled out; *JAK2 V617F* Minor criteria: Leukoerythroblastosis, ↑LD, anemia, splenomegaly; all three major plus two minor criteria	*JAK2 V617F*Calreticulin; *TET2, ASXL1, EZH2, CBL,* IDH1/IDH2, TP53, and SRSF2 *mutations;* +8, +9, del(20q), del(13q), del(1p), negative t(9;22)	Dependent on phase: ≈10 yr in early prefibrotic phase; ≈5 yr in fibrotic phase
ET	5th decade (M = F), second peak in 30s (F > M)	Platelet count >450 K; BM with proliferation of mature megakaryocytes; PV, PMF, CML, MDS ruled out; *JAK2 V617F* NOTE: All four criteria must be met.	*JAK2 V617F* in 50%; Calreticulin 40%; del(13q22), +8, +9 seen in 5%-10% of cases; negative t(9;22)	Stable for many yr (most cases)
CMML	Median, 65-75 yr, M > F	Monocytosis >1000, cytopenias, myeloid dysplasias, <20% blasts	+8, –7, 12p abnormalities in 20%-40% of cases; negative t(9;22)	20-40 mo with progression to AML in 15%-30%
JMML	Younger than 3 yr, M > F	Monocytosis >1000, blasts <20%, plus two of ↑Hb F, immature granulocytes, WBC >10K, clonal abnormalities, GM-CSF hypersensitivity	Monosomy 7, negative t(9;22)	Poor; possible benefit from BMT
Myeloid/lymphoid neoplasms w/↑eos and *PDGFR/FGFR1*	M 25-55 yr	PB w/inc eos, BM eos with mast cells	*FIP1L1-PDGFRA, PDGFRB, FGFR*	Variable response to TKI
Mastocytosis	All ages	Mononuclear w/central nuclei, variable basophilic granules (often not seen in fixed tissue); dense aggregates of spindle cells	*KIT* D816V	Cutaneous, indolent; systemic, variable; leukemia, aggressive
CEL NOS, idiopathic HES	Usually adult M; any age or sex	PB ≥1.5 K eos/μL, <20% blasts	+8, i(17q) 8p11 w/various partners	Indolent, 80% 5-yr survival

AML, Acute myelogenous leukemia; *BM,* bone marrow; *BMT,* bone marrow transplant; *CEL,* chronic eosinophilic leukemia; *CIM,* chronic idiopathic myelofibrosis; *CML,* chronic myeloid leukemia; *CMML,* chronic myelomonocytic leukemia; *CNL,* chronic neutrophilic leukaemia; *eos,* eosinophils; *EPO,* erythropoietin; *ET,* essential thrombocythemia; *F,* female; *GM-CSF,* granulocyte-macrophage colony-stimulating factor; *Hb,* hemoglobin; *HES,* hypereosinophilic syndrome; *inc,* increased; *JMML,* juvenile myelomonocytic leukemia; *LD,* lactate dehydrogenase; *M,* male; *MDS,* myelodysplastic syndrome; *NAP,* neutrophil alkaline phosphatase; *NOS,* not otherwise specified; *PB,* peripheral blood; *PMF,* primary myelofibrosis; *PV,* polycythemia vera; *TKI,* tyrosine kinase inhibitor; *WBC,* white blood cell.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, Philadelphia, 2017, Elsevier.

- Chromosomes, either by FISH or conventional cytogenetics
- Molecular testing in peripheral blood for *BCR-ABL* (rule out chronic myeloid leukemia), *JAK2,* calreticulin, and *MPL* mutations for risk stratification. Distinguishing calreticulin type I vs. type II has clinical relevance for risk stratification
- Additional mutation testing for *ASXL1* or *SRSF2* if available

Rx TREATMENT

Prognostic scoring systems for primary myelofibrosis are summarized in Table E5. The Dynamic International Prognostic Scoring System plus (DIPSS-plus) identifies several risk factors for survival and leukemic transformation.

- Age >65 yrs
- Hemoglobin <10 g/dl
- Leukocyte count >25 × 10^9/L
- Circulating blasts >1%
- Presence of constitutional symptoms
- Red cell transfusion need
- Platelet <100 × 10^9/L
- Unfavorable karyotype (complex or presence of +8, –7/7q–, i(17q), inv(3), –5/5q–, 12p–, or 11q23 rearrangement)

Risk scoring:

- Low (zero risk factors);
- Intermediate-1 (one risk factor);
- Intermediate-2 (two or three risk factors), and
- High (greater than four risk factors).

Median survivals (Table E6) are as follows: low, 185 mo; INT-1, 78 mo; INT-2, 35 mo; high, 16 mo. Molecular correlates for survival independent of DIPSS plus have recently been identified, based on the presence/absence of calreticulin mutation type I and *ASXL1*. For *CALR+/ASLX1* patients, median survival is 10.5 yr; for *CALR–/ASXL+* survival was 2.3 yr; for patients with both or neither mutations, survival was 5.8 yr.

LOW AND INTERMEDIATE 1 RISK

- Asymptomatic—observation
- Conventional drug therapy if symptomatic (response rates to each of the following agents is ~15% to 25%):
  1. Anemia—androgens (e.g., oxymetholone), danazol, prednisone, lenalidomide or thalidomide +/– prednisone, erythroid-stimulating agents in some cases.

TABLE E5 Prognostic Scoring Systems for Primary Myelofibrosis

Risk Factor	Lille	IPSS	DIPSS	DIPSS Plus
Anemia (hemoglobin)	X (<10 g/dl)	X (<10 g/dl)	X (<10 g/dl)	X (<10 g/dl)
Leukocytosis (white blood cell count)	X (<4 or >30 × 10^9/L)	X (>25 × 10^9/L)	X (>25 × 10^9/L)	X (>25 × 10^9/L)
Peripheral blood blasts		X (≥1%)	X (≥1%)	X (≥1%)
Constitutional symptoms		X	X	X
Age (yrs)		X (>65)	X (adjusted for age)	X
Karyotype				X (unfavorable[a])
Platelet				X (<100 × 10^9/L)
Transfusion status				X

[a]Unfavorable karyotype includes complex or sole or two abnormalities that include +8, −7/7q−, i7/7q−, i(17q), −5/5q−, 12p−, inv(3), or 11q23 rearrangements.
DIPSS, Dynamic international prognostic scoring system; *IPSS,* international prognostic scoring system.
From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE E6 Median Survival of Each Risk Group in Four Prognostic Scoring Systems for Primary Myelofibrosis

Risk Group	Lille	IPSS	DIPSS	DIPSS Plus
Low	93 mo	135 mo	Not reached	185 mo
Intermediate-1	26 mo	95 mo	170 mo	78 mo
Intermediate-2		48 mo	48 mo	35 mo
High	13 mo	27 mo	18 mo	16 mo

DIPSS, Dynamic international prognostic scoring system; *IPSS,* international prognostic scoring system.
From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE E7 Relationship of Mutation Profile to Survival in Primary Myelofibrosis

Mutation	Incidence (%)*	Median Survival (yr)
JAK-2 V617F	60	5.9
CALR exon 9	21	15.9
"Triple negative"	12	9.9
MPL	6	2.3

*Based on 428 patients from Mayo Clinic, Bergamo and Florence, Italy.
Data from Tefferi A et al: Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis, *Blood* 124(16):2507-2513, 2014.

2. Lenalidomide response rates are higher if a 5q deletion is present.
3. Symptomatic splenomegaly—hydroxyurea (first line, helpful in about 40%), ruxolitinib, splenectomy.
4. Radiation offers transient palliation of splenic symptoms; treatment of choice for extramedullary hematopoiesis.

- Lower-risk patients who are positive for *ASXL1* or *SRSF2* should be considered for allogeneic transplant. Patients with these mutations have a median time to leukemic transformation of 5.6 yr, vs. 18 yr for those who do not have them.

INTERMEDIATE 2 AND HIGH RISK

- High-risk genetics include *ASLX1* and *SRSF2* mutations and absence of calreticulin mutations or "triple-negative" status.
- Allogeneic stem cell transplant is recommended for eligible, higher-risk patients but the timing is controversial. In a recent report from the European Society for Blood and Marrow Transplantation, for patients who were 2-yr survivors after undergoing allogeneic hematopoietic stem cell transplant, the overall survival was 74% at 10 yr. Excess mortality was 14% and 33% in patients aged <45 yr and patients aged ≥65 yr, respectively.
- Ruxolitinib is an inhibitor of Janus-associated kinases *JAK1* and *JAK2.* Survival benefit is suggested by longer follow-up, especially in symptomatic patients. Approximately 50% remain responsive to ruxolitinib at 5 yr.
- Splenectomy, especially for transfusion-dependent anemia or severe thrombocytopenia.

DISPOSITION

- Median survivals according to DIPSS plus risk groups are: low, 185 mo; INT-1, 78 mo; INT-2, 35 mo; high, 16 mo.
- Median survival based on genomic analysis (Table E7):
  1. *CALR* mutated 17.7 yr; *JAK2* mutated 9.2 yr; *MPL* mutated 9.1 yr; triple-negative 3.2 yr
- Molecular correlates for survival independent of DIPSS plus have recently been identified based on the presence/absence of CALR mutation type I and *ASXL1* mutation.
  1. *CALR+/ASLX1−* patients: median survival 10.5 yr
  2. *CALR−/ASXL+*, median survival 2.3 yr
  3. For patients with both or neither mutations, survival was 5.8 yr.

PEARLS & CONSIDERATIONS

- PMF entails a wide spectrum of prognosis according to numerous risk factors.
- The only curative treatment is allogeneic stem cell transplant, which entails high risk of treatment-related mortality and morbidity.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Ritesh Rathore, MD**

SUGGESTED READINGS

Arber DA et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, *Blood* 127(20):2391-2405, 2016.

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Primary Ovarian Insufficiency

BASIC INFORMATION

DEFINITION

- Women younger than 40 yr of age with amenorrhea, oligomenorrhea, or dysfunctional uterine bleeding for 4 mo or more along with follicle stimulating hormone (FSH) levels in the menopausal range meet diagnostic criteria for primary ovarian insufficiency.
- Menopause younger than the age of 40 yr.

SYNONYMS

POI
Hypergonadotropic hypogonadism
Premature ovarian failure
Premature menopause
Gonadal dysgenesis

ICD-10CM CODES

E28.3	Primary ovarian failure
E28.310	Symptomatic premature menopause
E28.39	Other primary ovarian failure
E28.9	Ovarian dysfunction, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Affects 1% to 4% of the female population in the U.S.
PREDOMINANT AGE: 1:250 incident cases by age 35 and 1:100 by age 40

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The most common presentation is disturbance in menstrual pattern due to intermittent ovarian function.
- Between 5% and 30% of affected women have another affected female relative.
- Between 10% and 30% of affected women already have a concurrent autoimmune condition, the most common of which is hypothyroidism.
- Symptoms of estrogen deficiency include hot flashes, night sweats, poor concentration, drying of the vagina, and infertility.
- Physical exam may reveal stigmata of an autoimmune condition such as vitiligo, thyroid enlargement, or Turner syndrome (webbed neck, short stature, and high-arched palate).

ETIOLOGY (SEE TABLE 1)

Idiopathic in 95% of cases

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pregnancy.
- Causes of secondary amenorrhea include eating disorder, exercise, drugs, sarcoidosis, polycystic ovarian disease, hypothalamic amenorrhea, hyperprolactinemia/prolactinoma, and Cushing disease.

WORKUP

- After pregnancy is ruled out, the initial evaluation should include the measurement of serum prolactin, FSH, and thyrotropin (TSH) levels.
- If the FSH level is in the menopausal range (>40 μIU/ml by radioimmunoassay), the test should be repeated in 1 mo along with a serum estradiol measurement to confirm the diagnosis of primary ovarian insufficiency.

LABORATORY TESTS

Once a diagnosis of premature ovarian failure is made, other evaluations include:

- Autoimmune disorders, adrenal insufficiency (seen in 3% of cases): Serum anti-adrenal and anti-21 hydroxylase antibodies should be measured.
- Hypothyroidism: Serum TSH, T_4, and anti-TPO antibodies.
- All cases should be screened for osteoporosis by DXA for bone mineral density.
- A karyotype analysis should be performed for all patients to look for chromosomal defects including Turner variant or deletions of the X chromosome.
- Permutations for the fragile X syndrome (*FMR1* gene) should be checked for as well.

IMAGING STUDIES

Pelvic ultrasound has no proven benefit in the management of these patients.

TREATMENT

NONPHARMACOLOGIC THERAPY

Counseling or patient support group should be offered to all women with low self-esteem and depression due to the psychological scar left by the diagnosis.

ACUTE GENERAL Rx

- Physiologic estrogen and progestin replacement is reasonable in the cases of young women until they reach the age of natural menopause.
- A dose of 100 mcg of estradiol per day, administered by transdermal patch, achieves average estradiol level observed in normal menstruating women and effectively treats symptoms.
- Cyclic medroxyprogesterone at a dose of 10 mg per day for 12 days each month is the preferred progestin to provide protection against endometrial cancer.
- Pregnancy may occur while a woman is taking estrogen and progesterone therapy and the therapy should be stopped immediately if the pregnancy test is found to be positive.

TABLE 1 Mechanisms and Causes of Primary Ovarian Insufficiency

Accelerated Follicular Depletion

Genetic: Turner syndrome, fragile X premutations, galactosemia
Toxic: Chemotherapy, radiation, infections such as mumps or cytomegalovirus
Autoimmune: Polyglandular failure, hypothyroidism, Addison disease, vitiligo, myasthenia gravis

Abnormal Follicular Stimulation

Gonadotropin receptor function: Follicle stimulating hormone/luteinizing hormone receptor mutation
Enzyme defects: Aromatase deficiency, luteinized follicles

CHRONIC Rx

- Intake of 1200 mg of elemental calcium and 800 units of vitamin D_3 per day should be encouraged to prevent bone loss. A serum 25-hydroxyvitamin D level of 30 ng per ml or higher should be maintained.
- Patients with positive tests for adrenal antibodies should be evaluated annually for adrenal insufficiency by corticotropin stimulation test.
- Patients who wish to avoid pregnancy should use a barrier method or an IUD.
- Options for parenthood include adoption, foster parenthood, egg donation, and embryo donation.

DISPOSITION

Women with the known diagnosis should be encouraged to maintain a lifestyle that optimizes bone and cardiovascular health, including regular weight-bearing exercises, adequate intake of calcium (1200 mg daily) and vitamin D (800 IU daily), healthy diet to prevent obesity, and screening for cardiovascular risk factors.

REFERRAL

Referral to gynecologist and reproductive endocrinologist may be helpful in patients who decide to pursue parenthood.

PEARLS & CONSIDERATIONS

COMMENTS

- Common etiologies should be ruled out, including chromosomal abnormalities, fragile X premutations, and autoimmune causes.
- Management directed at symptom resolution and bone protection primarily, but should include psychosocial support for women facing this devastating diagnosis.

PREVENTION

Early diagnosis of primary ovarian insufficiency important for osteoporosis prevention and possibly prevention of coronary artery disease.

PATIENT & FAMILY EDUCATION

- https://medlineplus.gov/primaryovarianinsufficiency.html
- www.earlymenopause.com
- www.nichd.nih.gov/health/topics/poi/resources/patients

RELATED CONTENT

Amenorrhea (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

BASIC INFORMATION

DEFINITION

Primary sclerosing cholangitis (PSC) is an autoimmune fibroinflammatory disease predominantly affecting the large bile ducts. It is characterized by segmental fibrosing and inflammation of intrahepatic and extrahepatic bile ducts complicated by recurrent cholangitis, cholangiocarcinoma (CCA), cirrhosis, and portal hypertension.

SYNONYMS

Chronic obliterative cholangitis
Fibrosing cholangitis
Stenosing cholangitis
PSC

ICD-10CM CODES
K83.0 Cholangitis
K83.9 Disease of biliary tract, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- The incidence and prevalence of PSC are 0.9 to 1.3 cases per 100,000 persons per yr and 8.5 to 16.2 cases per 100,000 persons, respectively.
- About 65% of patients with PSC are men.
- Mean age of presentation is 30 to 40.
- Over 80% of patients with PSC also have inflammatory bowel disease (IBD). 4% to 5% of patients with ulcerative colitis (UC) will develop PSC. A PSC-IBD phenotype may be present which carries a higher risk of colon cancer and is characterized by mild pancolitis, rectal sparing, and backwash ileitis. PSC is an independent risk factor for developing colon cancer in patients with IBD.
- PSC can coexist with other autoimmune liver diseases. Autoimmune hepatitis (AIH) and PSC overlap syndrome can be seen and is more common in young adults and children.
- Cholangiocarcinoma is present in 1% to 2% of PSC patients at diagnosis and should be considered a premalignant disease. The lifetime risk is 5% to 10%.
- Box 1 summarizes a classification of and diseases associated with sclerosing cholangitis.
- The median survival from time of diagnosis is 10 to 15 yr without liver transplantation.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Many patients are asymptomatic (up to 50%) at the time of diagnosis with normal physical examination findings. However, many patients will have abnormal liver tests and a known diagnosis of IBD.
- More than 75% of asymptomatic patients develop symptoms, the most common of which are nonspecific pruritus, abdominal pain, and fatigue. Physical findings of symptomatic patients may reveal jaundice, skin excoriation and hyperpigmentation from scratching, hepatosplenomegaly, and xanthelasma. Other symptoms include steatorrhea and weight loss, which are concerning for advanced PSC, sepsis, or mechanical obstruction (i.e., cholangitis), and malignancy (i.e., cholangiocarcinoma).
- Patients can also present with advanced liver disease and decompensated cirrhosis (i.e., ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and variceal hemorrhage) or hepatic failure. In patients with cirrhosis, physical findings may reveal a shrunken nodular liver and evidence of portal hypertension.

ETIOLOGY

- The cause of PSC is unknown, but the most likely mechanism is immunologic priming in a genetically susceptible patient causing phenotypic expression of PSC.
- Genetic and immunologic factors are supported by reports of familial occurrence of this disorder and increased frequency of HLA B8 and DR3. Genome-wide association studies have discovered novel loci associated with PSC, but the functional aspects of these genes are still unknown.
- Portosystemic inflammation caused by translocation of the gut microbiota is an increasing area of research. The close association with UC and PSC may be secondary to gut-activated T lymphocytes in IBD causing portal inflammation because of overlapping adhesion molecules in the gut and liver. Furthermore, intestinal dysbiosis in PSC has also been seen and remains an area of ongoing research.
- Dysregulated inflammatory cytokine production by cholangiocytes is also more recently suggested to be playing a role in the pathogenesis of PSC.

DIAGNOSIS

Diagnosis is based on characteristic cholangiographic findings in combination with clinical, biochemical, and in some cases histologic features. It is increasingly common to diagnose PSC based on imaging with magnetic resonance cholangiopancreatography (MRCP). Liver biopsy is now rarely used to diagnose disease. Table 1 describes staging of PSC. Work is being done to enable a diagnosis to be made based on biomarkers such as microRNA and fecal microbiota profiles.

DIFFERENTIAL DIAGNOSIS

- IgG4-associated cholangitis (IAC)
- Surgical biliary trauma
- Ischemic cholangitis, recurrent pyogenic cholangitis, recurrent pancreatitis
- Choledocholithiasis, cholangiocarcinoma
- Intraarterial chemotherapy (5-FU/floxuridine)
- Diffuse intrahepatic metastasis, sarcoidosis, or amyloidosis
- AIDS-related, eosinophilic, or mast cell cholangiopathy
- Histiocytosis X, graft-versus-host disease
- Hepatic inflammatory pseudotumor, portal hypertensive biliopathy

WORKUP

History, physical examination, laboratory evaluation, and imaging studies (MRCP). Liver biopsy is generally not necessary for diagnosis

LABORATORY TESTS

- Serum biochemical tests are abnormal in approximately 75% of patients with PSC, with a predominantly cholestatic pattern and an elevation in the serum alkaline phosphatase (3-10 times the upper limit of normal for more than 6 mo). However, this value can vary and be normal during the disease course. Serum aminotransferase levels are elevated in the majority of patients (2-3 times the upper limits of normal). Serum bilirubin is usually normal at the time of diagnosis unless the patient has advanced stricturing disease; an initial elevation of bilirubin at diagnosis may be related to worse prognosis.
- A wide range of autoantibodies can be detected in patients with PSC; however, they are nonspecific for PSC, including the perinuclear antineutrophil cytoplasmic antibody (pANCA), autoantibodies such as antinuclear antibody (ANA), and anti-smooth muscle antibody (ASMA).
  1. Perinuclear antineutrophil cytoplasmic antibody (pANCA) is positive in 33% to 88% of those with PSC but is not specific.
  2. Anti-mitochondrial antibody (AMA), which is characteristic of primary biliary cholangitis (PBC), is *NOT* found in PSC and can be helpful in excluding PSC.
  3. Serum IgG levels are useful in the diagnosis of PSC-AIH overlap syndrome (more common in pediatric patients) and IAC with autoimmune pancreatitis.
  4. In particular, elevated levels of IgG4 are found in 10% to 20% of PSC patients, with a subset of these patients displaying features of autoimmune pancreatitis. PSC patients with elevated IgG4 tend to have worse outcomes and seem to respond to corticosteroid therapy; hence, IgG4 levels should be checked at least once in all patients with PSC.

IMAGING STUDIES

- Cholangiography (Fig. E1), with magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP), is considered to be the gold standard for the diagnosis of PSC. Characteristic findings reveal segmental fibrosis of bile ducts with saccular dilatation of normal intervening areas resulting in a "beads-on-a-string" appearance.
- MRCP has an overall diagnostic accuracy rate of 90%. It is the first imaging modality of choice when PSC is suspected because ERCP can be associated with increased rates of serious complications (i.e., pancreatitis and cholangitis) in patients with PSC.
- Liver biopsy is not necessary for the diagnosis of PSC in patients with typical cholangiographic findings. Biopsies are subject to sample variation, and typical "onion skin"–type periductal fibrosis is rare. Liver biopsy

BOX 1 Classification of and Diseases Associated with Sclerosing Cholangitis

Primary Sclerosing Cholangitis
Principal Disease Associations
Inflammatory bowel disease:
- Crohn colitis or ileocolitis
- Ulcerative colitis

Other Disease Associations
Systemic diseases with fibrosis:
- Inflammatory pseudotumor
- Mediastinal fibrosis
- Peyronie disease
- Pseudotumor of the orbit
- Retroperitoneal fibrosis
- Riedel thyroiditis

Autoimmune or collagen vascular disorders:
- Autoimmune hemolytic anemia
- Celiac disease
- Chronic sclerosing sialoadenitis
- Membranous nephropathy
- PSS
- Rapidly progressive glomerulonephritis
- RA
- Sjögren syndrome
- SLE
- Type 1 diabetes mellitus

Alloimmune diseases:
- Hepatic allograft rejection
- Hepatic graft-versus-host disease after bone marrow transplantation

Infiltrative diseases:
- Hypereosinophilic syndrome
- Histiocytosis X
- Sarcoidosis
- Systemic mastocytosis

Immunodeficiency:
- Congenital immunodeficiency
  - Combined immunodeficiency
  - Dysgammaglobulinemia
  - X-lined agammaglobulinemia
- Acquired immunodeficiency:
  - AIDS
  - Angioimmunoblastic lymphadenopathy
  - Opportunistic infections (e.g., cryptosporidiosis, cytomegalovirus, microsporidiosis)
  - Selective IgA deficiency

Secondary Sclerosing Cholangitis
Obstructive
Autoimmune pancreatitis
Biliary parasites
Caroli disease
Choledocholithiasis
Chronic pancreatitis
Congenital abnormalities:
- CF
- Choledochal cyst

Fungal infection
Recurrent pyogenic cholangitis
Surgical stricture

Toxic
Intra-arterial floxuridine (FUDR)
Intraductal formaldehyde or hypertonic saline (echinococcal cyst treatment)

Ischemic
Hepatic allograft arterial occlusion
Paroxysmal nocturnal hemoglobinuria
Toxic vasculitis (FUDR)
Vascular trauma

Neoplastic
Cholangiocarcinoma
Hepatocellular carcinoma
Lymphoma
Metastatic cancer

AIDS, Acquired immunodeficiency syndrome; *CF,* cystic fibrosis; *FUDR*, 5-fluorouracil deoxyribonucleoside; *Ig,* immunoglobulin; *PSS,* progressive systemic sclerosis; *RA,* rheumatoid arthritis; *SLE,* systemic lupus erythematosus.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

may help in the diagnosis of PSC-AIH overlap syndrome, small-duct PSC (normal cholangiogram), or IAC.
- Noninvasive measurements of liver elastography including MR elastography are promising methods for evaluating for cirrhosis but have not yet been validated in this patient cohort.

Rx TREATMENT

- No medical therapy has been established to be effective in halting the disease progression of PSC. Liver transplantation is indicated in patients with decompensated cirrhosis, hilar cholangiocarcinoma, and in those with recurrent bacterial cholangitis.
- Ursodeoxycholic acid (UDCA) has shown variable benefit in randomized controlled trials.
- Although biochemical improvement has been seen with UDCA, there has been no proven benefit on survival.
- In two trials, high-dose UDCA (28-30 mg/kg/day) was associated with colorectal dysplasia, liver transplantation, and varices. Therefore, high-dose UDCA is *NOT* universally recommended as medical therapy in patients with PSC. A trial of medium- or low-dose UDCA ~20 mg/kg/day is used by some clinicians, since some trials have shown biochemical response.
- Oral vancomycin may show clinical and biochemical response in pediatric patients, but no randomized clinical trial has been performed. The benefit seen from the use of oral vancomycin may be related to the antibiotic effect on the microbiome of the gut. Investigations are ongoing.
- Manipulation of the microbiome is an exciting area being explored as a future treatment for PSC. Recent studies have shown that FMT in PSC is safe, improves liver biochemistries, and improves microbiome diversity. This is a rapidly expanding area of gastroenterology that shows promise. However, larger studies are needed to determine if such treatments can affect mortality or reduce liver transplantation.
- The use of corticosteroids and other immunosuppressive agents is not recommended in patients with PSC alone; however, it is recommended in patients with PSC-AIH overlap syndrome or elevated IgG4.
- Use of tumor necrosis factor inhibitors has been ineffective in PSC. Other monoclonal antibody therapies targeting lymphocyte trafficking, tyrosine kinase signaling, and liver fibrosis are being studied. Furthermore, other targets for treatment are ongoing and aimed at bile acid synthesis and mast cell inhibition.
- Bile acid–based therapeutic approaches are currently in clinical trials, including peroxisome proliferator-activated receptor agonists and farnesoid X receptor agonists.
- Management of PSC patients is aimed at symptom relief and management of complications from PSC (i.e., obstruction/strictures, cirrhosis, portal hypertension).

TABLE 1 Staging of Primary Sclerosing Cholangitis

Stage	Description
I—Portal	Portal edema, inflammation, ductal proliferation; abnormalities do not extend beyond the limiting plate
II—Periportal	Periportal fibrosis with or without inflammation extending beyond the limiting plate
III—Septal	Septal fibrosis, bridging necrosis, or both
IV—Cirrhotic	Biliary cirrhosis

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, WB Saunders.

ACUTE GENERAL Rx

- With mild pruritus, skin emollients and antihistamines are recommended as the first-line treatment.
- With moderate or severe pruritus, bile acid sequestrants (i.e., cholestyramine 16 g/day) are the preferred choice for the initial management of pruritus. Alternative agents for pruritus refractory to bile acid sequestrants include rifampicin 150 to 300 mg twice daily, naltrexone 50 mg daily, sertraline 75 to 100 mg daily, or phenobarbital 90 mg at bedtime.
- Patients who present with increasing serum bilirubin and/or worsening pruritus, progressive bile duct dilation on imaging studies, or cholangitis need to be evaluated for dominant strictures with imaging. A dominant stricture is a stenosis <1.5 mm in the common bile duct or <1 mm in the hepatic duct.
- ERCP with brushings, cytology, and fluorescent in situ hybridization (FISH) is recommended to evaluate dominant strictures for cholangiocarcinoma, which is found in 15% to 20% of cases. Once malignancy is excluded, balloon dilation with or without stenting is recommended to treat symptoms. Routine stenting is not required, but short-term stenting may be helpful in patients with severe stricture. If ERCP is unsuccessful, percutaneous cholangiopancreatography with stenting should be considered.
- In noncirrhotic patients with dominant strictures refractory to endoscopic or percutaneous management, surgery should be considered, although this may complicate future liver transplantation surgery.
- Antibiotic usage is recommended in patients with dominant strictures/obstructions both acutely and for long-term prophylaxis in patients with recurrent cholangitis.

CHRONIC Rx

- Avoidance of alcohol and vaccination against hepatitis A and B is advised.
- Patients with PSC are at risk for osteoporosis and osteopenia.
  1. The pathophysiology of bone loss is poorly understood but likely multifactorial. Impaired absorption of fat-soluble vitamins, such as vitamins D and K, and possible impairment of osteoblasts by bilirubin may be contributing factors. The risk of osteoporosis appears to be independent of cumulative corticosteroid exposure.
  2. DEXA scan should be performed at diagnosis and should be repeated in 2 to 4 yr.
  3. Calcium (1000-1500 mg) and vitamin D 600 to 800 IU daily are recommended for patients with osteopenia, and the addition of bisphosphonate is recommended in patients with osteoporosis.
- Patients with newly diagnosed PSC should have a full colonoscopy with biopsies to exclude concurrent IBD and for surveillance of colorectal cancer. In patients with IBD, continued surveillance colonoscopy with biopsies, or chromoendoscopy, at 1- to 2-yr intervals is recommended. In patients without IBD, a suggested 3- to 5-yr surveillance interval has been recommended due to an increased risk of colorectal cancer.
- Cholangiocarcinoma (CCA) development is common in PSC. Surveillance for CCA should be performed every 6 to 12 mo with ultrasound, CT, or MRI, with or without serum CA 19-9. Although CA19-9 may detect CCA, Sinakos et al[1] evaluated the long-term outcomes in patients with PSC and increased levels of CA 19-9 and found that one third of patients did not have CCA after 30 mo of follow-up. These differences may in part be due to genotypic differences in *FUT2/3* alleles that affect expression of CA19-9. Surveillance is not indicated in PSC patients <20 yr of age or those who have small duct PSC. Endoscopic retrograde cholangiopancreatography (ERCP) with brush cytology or cholangioscopy should be performed in patients who have biochemical or symptomatic deterioration or dominant stricture.
- Annual transabdominal ultrasound is recommended due to the increased risk of gallbladder malignancy, even in patients who are not cirrhotic. If masses or polyps >8 mm are detected, cholecystectomy should be performed.
- Patients with PSC and cirrhosis are recommended to have hepatocellular carcinoma (HCC) surveillance with ultrasound, with or without α-fetoprotein, every 6 mo and gastroesophageal variceal surveillance at regular intervals.
- With advanced disease, fat-soluble vitamin deficiencies such as A, E, and D should be assessed.
- In cases of HCC and CCA, depending on underlying liver disease, resection versus liver transplantation would be required.

[1]Sinakos E et al: Many patients with primary sclerosing cholangitis and increased serum levels of carbohydrate antigen 19-9 do not have cholangiocarcinoma, *Clin Gastroenterol Hepatol* 9:434-439, 2011, e1.

DISPOSITION

Liver transplantation is the only effective treatment for patients with end-stage liver disease, portal hypertension, liver failure, and recurrent or intractable bacterial cholangitis. Survival is excellent, with 90% and 80% survival rates at 1 and 5 yr, respectively. The recurrence of PSC after transplant is reportedly 5% to 20%. Transplant referral is warranted when MELD exceeds 14 or greater, or with worsening cholangitis or intractable pruritus.

REFERRAL

Gastroenterology and/or hepatology for treatment of PSC, management of its complications, surveillance of associated malignancy, and evaluation for liver transplantation.

PEARLS & CONSIDERATIONS

- Management of PSC targets symptom relief, complications of PSC, cirrhosis, early carcinoma detection, and timely referral for liver transplantation.
- High-dose UDCA is not universally recommended for treatment of PSC.
- Patients are at increased risk for the development of colorectal cancer, gallbladder cancer, and cholangiocarcinoma and need surveillance.
- Patients with PSC and ulcerative colitis have more common right-sided colon involvement and greater risk of pouchitis after colectomy with an ileal pouch-anal anastomosis.
- In patients with cirrhosis, surveillance for gastroesophageal varices and HCC is recommended.
- Liver transplant remains the only definitive therapy for complications of PSC.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Ulcerative Colitis (Related Key Topic)

AUTHORS: **Ronan Farrell, MD,** and **Amanda Pressman, MD**

SUGGESTED READINGS

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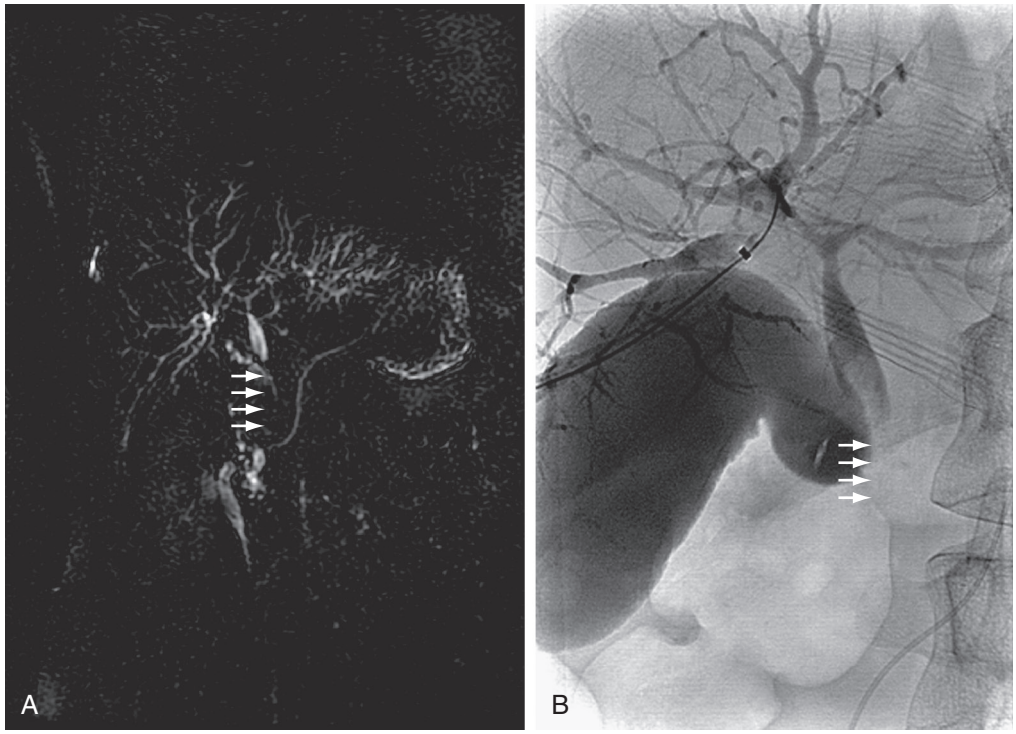

FIG. E1 A, Reconstructed magnetic resonance cholangiopancreatography images in a patient with primary sclerosing cholangitis. The intrahepatic biliary radicles are diffusely abnormal and characterized by pruning and a beaded appearance. There is a dominant stricture at the level of the distal bile duct *(arrows)* indicated by a signal void on magnetic resonance image. **B,** A percutaneous cholangiogram in the same patient. Note the high-grade, dominant, distal bile duct stenosis *(arrows)* with a markedly enlarged gallbladder, suggesting that the stricture involves the insertion of the cystic duct. Similar findings could be seen in a patient with a distal cholangiocarcinoma. (From Feldman M et al: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier)

Progressive Multifocal Leukoencephalopathy (PML)

BASIC INFORMATION

DEFINITION

Progressive multifocal leukoencephalopathy (PML) is an uncommon and often fatal subacute demyelinating disease of the white matter, caused by reactivation of the JC virus (JCV) infection, which has tropism for oligodendrocytes, in an immunocompromised individual. PML originally was described half a century ago by Astrom et al in patients with chronic lymphoid leukemia and Hodgkin lymphoma. JCV was isolated in 1971 and is named for the initials of the first patient from whose brain it was isolated.

SYNONYM

PML

ICD-10CM CODE

A81.2 Progressive multifocal leukoencephalopathy

EPIDEMIOLOGY & DEMOGRAPHICS

RISK FACTORS: Typically seen in patients with profound immunosuppression and impaired cell-mediated immunity. These include patients with AIDS, lymphoproliferative disorders, chronic infections such as tuberculosis, and, more recently, patients on immunosuppressive or immunomodulating medications such as natalizumab, rituximab, efalizumab, brentuximab vedotin, mycophenolate mofetil, anti-TNF-alpha agents, and oral agents used in the treatment of multiple sclerosis (dimethyl fumarate and fingolimod). In rare instances, it may be seen in the absence of apparent immunologic abnormality.

INCIDENCE AND PREVALENCE:

- The PML era can be broadly divided into four epochs: Pre-HIV, HIV (pre-ART), HIV (post-ART), and modern era.
- Prior to the HIV epidemic in the early 1980s, PML was rare and seen almost exclusively in patients with lymphoproliferative and myeloproliferative disorders.
- HIV: A fiftyfold increase in PML cases was reported with HIV epidemic. During the HIV pre-highly active antiretroviral therapy (HAART) era, 3% to 5% of patients with HIV developed PML. PML is an AIDS-defining illness. Highly active retroviral therapy (ART) has led to some decline in PML cases.
- Incidence of PML in natalizumab-treated patients depends on treatment duration. Incidence is 7.4/1000 without prior immunosuppressant use and 19.5/1000 with prior immunosuppressant use during mos 25 to 48.
- Seroepidemiologic studies have shown that asymptomatic primary infection with JCV occurs at an early age, and by adult life 30% to 90% of the population is seropositive. It becomes dormant in tissues such as kidney, bone marrow, tonsils, and lymphoreticular tissue.

PREDOMINANT SEX AND AGE: Males and females are equally affected. There is no specific age distribution.

GENETICS: Unknown

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Subacute neurologic deficits are common; can also present acutely as a stroke mimic.
- The clinical course spans wks to mos leading to severe disability and death.
- PML lesions usually involve cerebral hemispheres; cerebellar and brainstem involvement may be seen in AIDS. Multifocal asymmetric white matter involvement is common; rarely there can be gray matter involvement including cerebellar granular cells. Usually the optic nerve and spinal cord are not involved.
- Non–AIDS-associated PML: Early lesions involve occipital subcortical white matter and cause visual-field deficits (homonymous hemianopia) or cortical blindness. Motor weakness and altered mentation may be seen, while headache, seizures, and extrapyramidal syndromes are rare.
- AIDS-related PML: Motor weakness is more common. Abnormalities of speech, cognition, gait, sensation, and visual impairment are also seen.
- Natalizumab-associated PML: Frontal lobe is commonly involved, leading to cognitive impairment, neurobehavioral changes, motor disorders, language disorders, and visual defects.
- Immune reconstitution inflammatory syndrome (IRIS): A paradoxical clinical deterioration that occurs during immunologic recovery in previously immunocompromised patients, such as antiretroviral therapy–treated HIV-seropositive patients or cessation of immunomodulating treatment, such as natalizumab. An increase in the number or size of lesions on neuroimaging with contrast enhancement of brain lesions and brain edema may be seen.

ETIOLOGY & PATHOGENESIS

- JCV infection may be acquired through respiratory tissue or oropharyngeal route; seroconversion usually occurs in childhood.
- A cytotoxic-specific response against JCV acts as a containing mechanism for PML. Immunosuppression leads to development of PML either as primary infection of the CNS following immunosuppression or reactivation of a dormant infection. The virus produces lytic infection of the oligodendrocytes and causes oligodendrocyte death and demyelination. Neuronal infection does not usually occur except in granule cell neurons of the cerebellum. Infection of the astrocytes is abortive, leading to characteristic bizarre enlarged cells.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Multiple sclerosis
- Acute disseminated encephalomyelitis
- Vasculitis
- HIV encephalitis
- Mitochondrial encephalopathies (e.g., mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS])
- Posterior reversible encephalopathy syndrome

WORKUP

- Diagnosis is based on compatible clinical presentation, MRI brain features, and detection of JCV in cerebrospinal fluid (CSF).
- The two diagnostic approaches employed include:
  1. Demonstration of typical histopathologic findings (multifocal demyelination, enlarged bizarre astrocytes with lobulated hyperchromatic nuclei, and enlarged oligodendroglial nuclei) and JC virus in tissue specimen (electron microscopy, immunohistochemistry, or polymerase chain reaction [PCR] techniques); or
  2. Demonstration of JC virus in the CSF of patients who fulfill clinical and radiographic criteria.

LABORATORY TESTS

- CSF examination: Usually normal; may show mild lymphocytic pleocytosis (20 to 25 leukocytes/ml) and elevated protein (usually <65 mg/dl).
- CSF PCR for JCV has a sensitivity of 95% and specificity of 99% using ultrasensitive PCR techniques, but may be lower depending on the techniques used.

IMAGING STUDIES

- MRI brain (Fig. E1) is the neuroimaging of choice and shows demyelinating lesions that are hyperintense on T2 and fluid-attenuated inversion recovery (FLAIR) sequences, are hypointense on T1, and typically don't enhance with gadolinium in patients with AIDS unless associated with IRIS. However, in drug-related PML, contrast enhancement is more likely to occur and may be related to IRIS from medication withdrawal.
- CT head may show subcortical hypodensities.
- MR spectroscopy will demonstrate features of demyelination—decreased *N*-acetyl acetate, increased choline, and increased lactate.

TREATMENT

There is no specific treatment for PML. Treatment is aimed at reversal of the underlying causes of immunosuppression.

NONPHARMACOLOGIC THERAPY

Plasma exchange and immunoadsorption for natalizumab-treated patients to rapidly reduce blood levels of natalizumab and hasten restoration of immune function. However, IRIS-related complications will need treatment, often with intravenous steroids.

ACUTE GENERAL Rx

- HIV-positive patients: Antiretroviral therapy should be optimized.
- HIV-negative patients: Immunosuppressive medication should be discontinued; plasma exchange may be considered for natalizumab-treated patients.
- IRIS: Treatment with steroids should be considered.

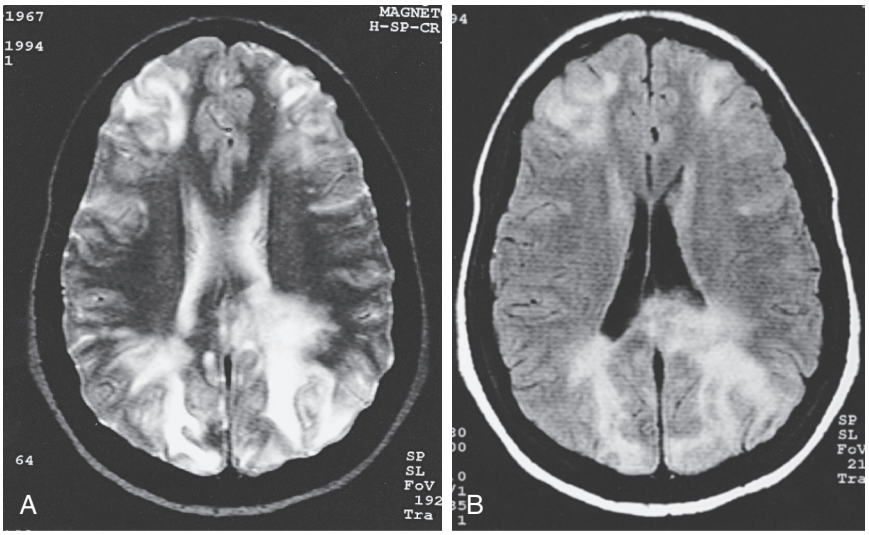

FIG. E1 Progressive multifocal leukoencephalopathy. Axial T2-weighted **(A)** and fluid-attenuated inversion recovery (FLAIR) **(B)** images of patient with human immunodeficiency virus (HIV). Multiple areas of white matter disease are identified; FLAIR image clarifies the involvement of periventricular white matter. These findings in an HIV-positive patient strongly suggest progressive multifocal leukoencephalopathy. (From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.)

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CHRONIC Rx

No specific pharmacologic therapy exists for chronic treatment.

DISPOSITION

Of all HIV-related cerebral disorders, PML probably has the worst prognosis. Pre-AIDS era survival was 6 mo. With ART, incidence and prognosis of PML has improved. A lower CSF JCV load and better CD4 counts have better prognoses. Natalizumab-treated patients have worse prognoses seen with longer time to diagnosis, presence of widespread disease, and brainstem involvement.

REFERRAL

Refer to neurology if patients have neurologic deficits of uncertain etiology, especially in the setting of AIDS or immunosuppression.

PEARLS & CONSIDERATIONS

COMMENTS

PML is a fatal opportunistic cerebral infection that should be considered in all immunosuppressed individuals presenting with neurologic deficits and demyelinating cerebral lesions. Early referral to a center with neurologic expertise, especially neuroimmunology or neuroinfectious diseases, should be considered.

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Progressive Supranuclear Palsy

BASIC INFORMATION

DEFINITION

Progressive supranuclear palsy (PSP) is an atypical parkinsonian syndrome characterized by supranuclear gaze impairment, prominent and early postural instability with falls, axial greater than appendicular rigidity, and poor or absent response to levodopa.

SYNONYMS

Steele-Richardson-Olszewski syndrome
Progressive supranuclear ophthalmoplegia
PSP

ICD-10CM CODES

G23.1 Progressive supranuclear ophthalmoplegia
G23.9 Degenerative disease of basal ganglia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1.1 per 100,000 (5.3 per 100,000 over age 50)
PREVALENCE: 4.9 per 100,000 (6.4 per 100,000 age-adjusted)
PREDOMINANT SEX AND AGE: Slight male predominance; mean age onset 65 yr, very uncommon for onset <50 yr
GENETICS: Familial cases have been reported only rarely. The vast majority of cases are sporadic.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Tremorless parkinsonism is the general clinical presentation, and differentiation from idiopathic Parkinson disease can be challenging early in the disease course. However, there are certain symptoms that can serve as "red flags" to consider PSP:

- Early postural instability and retropulsion leads to frequent falls; falls within the first yr of onset of symptoms is typically the rule.
- Supranuclear gaze palsy is often preceded by slowing of vertical saccades; square wave jerks may be present; blepharospasm is common.
- Dystonia of the frontalis and procerus muscles gives the PSP patient a "surprised" or "frightened" expression (Fig. E1) as opposed to the hypomimia of Parkinson disease (Fig. E2).
- Speech is typically strained, spastic, hypernasal, with a low-pitched dysarthria.
- Pseudobulbar affect and "emotional incontinence" can be seen, with easy crying or laughter.
- Early cognitive impairment, most commonly with apathy, disinhibition, and anxiety.

ETIOLOGY

PSP is caused by neuronal degeneration of nuclei in the brainstem and basal ganglia as a result of abnormal tau protein accumulation in tufted astrocytes and neurofibrillary tangles.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Parkinson disease: Responds robustly to levodopa, progresses more slowly, starts asymmetrically, and lacks "red flag" symptoms listed previously.
- Corticobasal syndrome: Also a tauopathy like PSP, but parkinsonism is associated with prominent asymmetric dystonia, cortical sensory signs such as astereognosis, apraxia, and sometimes an "alien hand" syndrome.
- Multiple system atrophy: Distinguished by dysautonomia (particularly orthostatic hypotension), cerebellar ataxia, and inspiratory stridor.
- Dementia with Lewy bodies: A syndrome of coinciding dementia and parkinsonism, visual hallucinations, and fluctuating mental status.

WORKUP

- PSP is a clinical diagnosis, best made by a neurologist familiar with the disorder, such as a movement disorders specialist.
- A robust response to levodopa may lead consideration away from PSP.
- Brain MRI (see the following) can be helpful.

LABORATORY TESTS

There are no diagnostic laboratory tests.

IMAGING STUDIES

- Dorsal midbrain atrophy is commonly seen on MRI and is referred to as the "hummingbird sign" due to the elongated beak appearance seen on the midsagittal plane.
- Dopamine transporter imaging (DaTscan with [^{123}I]β-CIT SPECT) shows reduced uptake in PSP and is therefore not useful in differentiating PSP from Parkinson disease or other causes of parkinsonism.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical and occupational therapy are essential for avoiding the morbidity associated with frequent falls. Assistive devices such as a walker or wheelchair should be encouraged.

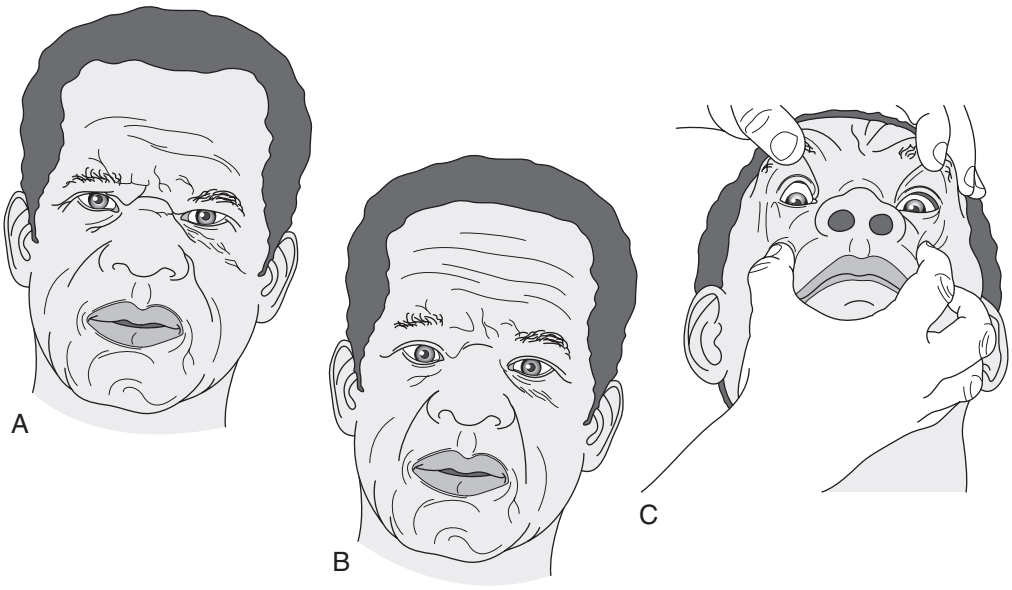

FIG. E1 A, PSP patients typically have a grimace because of continuous contractions of their facial muscles. **B,** Because of the loss of the ability to voluntarily move the eyes vertically, the hallmark of PSP, this patient cannot comply with the examiner's request to look downward. **C,** However, when the examiner rocks the patient's head back (performs an oculocephalic maneuver), his eyes dip well below the meridian. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists*, ed 8, Philadelphia, 2017, Elsevier.)

FIG. E2 A patient with progressive supranuclear palsy with staring expression, frontalis overactivity, and retrocollis. She is wearing a neck sling for a fractured wrist sustained in a fall. (From Burn D, Lees A: Progressive supranuclear palsy: where are we now? *Lancet Neurol* 1:359, 2002.)

- Dysphagia is a common finding that should be monitored closely in conjunction with a speech therapist.
- Prisms may be helpful to compensate for misalignment and diplopia resulting from the eye movement abnormalities; however, benefits, if noted, tend to be short-lived as the disease progresses.

CHRONIC Rx

- Although classically felt to be unresponsive to levodopa, there is often a transient but meaningful response to higher doses of levodopa (1200 mg/day). The poor response to levodopa is most likely due to the loss of postsynaptic dopamine receptors.
- Anticholinergic medications should be avoided.
- Blepharospasm can be effectively treated with botulinum toxin injections.

DISPOSITION

Median latency from symptom onset to wheelchair-bound state is 5 yr and to death is 7 yr in PSP-Richardson syndrome (classically described phenotype above). Lifespan improves to 10 to 12 yr in the PSP-parkinsonism. It is a closer clinical mimic to idiopathic PD and PSP-pure akinesia with gait freezing (no typical PSP features for first yrs, with freezing or gait, speech, and other activities being the primary manifestations) phenotypes.

REFERRAL

Referral to a movement disorders center is appropriate.

PEARLS & CONSIDERATIONS

COMMENTS

Consider PSP in a parkinsonian patient with the onset of falls within 1 yr of diagnosis, vertical eye movement abnormalities, early cognitive impairment, pseudobulbar affect, frontonasal dystonia, or poor response to levodopa.

PATIENT & FAMILY EDUCATION

Patient and caregiver information and resources can be found through CurePSP at www.psp.org.

RELATED CONTENT

Parkinson Disease (Related Key Topic)

AUTHORS: **Andrew P. Duker, MD,** and **Jennifer E. Vaughan, MD**

SUGGESTED READINGS

Colosimo C et al: Fifty years of progressive supranuclear palsy, *J Neurol Neurosurg Psychiatry* 85:938-944, 2014.

Respondek G et al: The phenotypic spectrum of progressive supranuclear palsy: a retrospective multicenter study of 100 definite cases, *Mov Disord* 29:1758-1766, 2014.

Prolactinoma ALG PTG

BASIC INFORMATION

DEFINITION

Prolactinomas are monoclonal tumors that secrete prolactin.

ICD-10CM CODES

D35.2 Benign neoplasm of pituitary gland
E22.8 Other hyperfunction of pituitary gland

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Most common pituitary tumor; nearly 30% of all pituitary adenomas secrete enough prolactin to cause hyperprolactinemia
PREDOMINANT SEX: Microadenomas are more common in women; macroadenomas are found more frequently in men.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Men: Decreased facial and body hair, infertility, small testicles; may also have decreased libido, erectile dysfunction, and delayed puberty (caused by decreased testosterone as a result of inhibition of gonadotropin secretion).
- Women: Physical examination may be normal; history may reveal amenorrhea, galactorrhea (Fig. E1), oligomenorrhea, and anovulation.
- Both sexes: Visual field defects and headache may occur depending on size of tumor and its expansion.

ETIOLOGY

Prolactin-secreting pituitary adenomas: Microadenomas (<10 mm diameter) or macroadenomas (>10 mm diameter). No risk factors have been identified for sporadic prolactinomas. Rarely prolactinomas can be part of multiple endocrine neoplasia (MEN) type 1 syndrome.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Secretion of prolactin is under tonic inhibitory control by hypothalamic dopamine. Hyperprolactinemia may be caused by the following:

- Drugs: Risperidone, phenothiazines, methyldopa, reserpine, monoamine oxidase inhibitors, androgens, progesterone, cimetidine, tricyclic antidepressants, haloperidol, meprobamate, chlordiazepoxide, estrogens, narcotics, metoclopramide, verapamil, amoxapine, cocaine, oral contraceptives
- Hepatic cirrhosis, renal failure, primary hypothyroidism
- Ectopic prolactin-secreting tumors (hypernephroma, bronchogenic carcinoma)
- Infiltrating diseases of the pituitary (sarcoidosis, histiocytosis)
- Head trauma, chest wall injury, spinal cord injury
- Polycystic ovary disease, pregnancy, nipple stimulation
- Idiopathic hyperprolactinemia, stress, exercise

WORKUP

- The diagnosis of prolactinoma is established by demonstration of an elevated serum prolactin level (after exclusion of other causes of hyperprolactinemia) and radiographic evidence of a pituitary adenoma.
  1. Normal mean prolactin levels are 8 ng/ml in women and 5 ng/ml in men.
  2. Prolactin levels >100 ng/ml are suspicious for prolactinomas. Most macroprolactinomas raise prolactin levels >250 ng/ml and levels >500 ng/ml are virtually diagnostic of macroprolactinomas.
  3. Prolactin levels can vary with time of day, stress, sleep cycle, and meals. More accurate measurements can be obtained 2 to 3 hr after awakening, preprandially, and when patient is not distressed.
  4. Serial measurements are recommended in patients with mild prolactin elevations.
- TSH, free T_4, BUN, Creat, ALT, AST are useful tests. Pregnancy test in all women of childbearing age.
- All patients with prolactinomas should undergo visual field testing. Serial evaluation is recommended, particularly during pregnancy in patients with macroadenomas.

IMAGING STUDIES

- MRI with gadolinium enhancement is the procedure of choice in the radiographic evaluation of pituitary disease.
- In absence of MRI, a radiographic diagnosis is best accomplished with a high-resolution CT scanner and special coronal cuts through the pituitary region.

TREATMENT

NONPHARMACOLOGIC THERAPY

Pregnancy and breastfeeding should be avoided because they can encourage tumor growth.

ACUTE GENERAL Rx

- Management of prolactinomas depends on their size and encroachment on the optic chiasm and other vital structures, the presence or absence of gonadal dysfunction, and the patient's desires regarding fertility. Patients with microprolactinomas without symptoms of hypogonadism do not require treatment. Fig. 2 describes a management algorithm for prolactinomas. Women with hypogonadism related to a microadenoma who do not desire fertility can be treated with a combined oral contraceptive.
- Medical therapy is preferred when fertility is an important consideration. Prolactinomas are treated with the dopamine agonists (DA) bromocriptine and cabergoline.
  1. Bromocriptine: Initial dose is 0.625 mg at bedtime for the first wk. After 1 wk, add morning dose of 1.25 mg. Gradually increase dose by 1.25 mg/wk until dose of 5 to 10 mg/day is achieved. Bromocriptine decreases size of the tumor and generally lowers the prolactin level into the normal range when the initial serum prolactin is <500 ng/ml. Side effects of bromocriptine are nausea, constipation, dizziness, and nasal stuffiness. Bromocriptine appears to be safe during pregnancy.
  2. Cabergoline is a longer-acting dopamine agonist that is more expensive but may be more effective and better tolerated than bromocriptine; initial dose is 0.25 mg twice weekly.
  3. After therapy is initiated, MRI should be repeated in 1 yr for microprolactinomas if the prolactin level normalizes. For macroprolactinomas, MRI is repeated after 2 mo and every 6 to 12 mo until stable on serial studies.
- Transsphenoidal resection: Option in an infertile patient who cannot tolerate bromocriptine or cabergoline or when medical therapy is ineffective. The success rate depends on the location of the tumor (entirely intrasellar), experience of the neurosurgeon, and size of the tumor (<10 mm in diameter); the recurrence rate may reach 80% within 5 yr. Possible complications of transsphenoidal surgery vary with experience and skill of the neurosurgeon and tumor anatomy and include transient diabetes insipidus, hypopituitarism, cerebrospinal fluid rhinorrhea, and infections (meningitis, wound infection).
- Pituitary irradiation is useful as adjunctive therapy of macroadenomas (>10 mm in diameter) and in patients with persistent hypersecretion after surgery. Potential complications include cranial nerve damage, radionecrosis, and cognitive abnormalities.
- Stereotactic radiosurgery (gamma knife) has become popular as a modality in the treatment of prolactinomas. A high dose of ionizing radiation is delivered to the tumor through multiple ports. Its advantage is minimal irradiation to surrounding tissues. Proximity of the tumor to the optic chiasm limits this therapeutic modality.

CHRONIC Rx

- Patients on medical therapy require periodic measurement of prolactin levels. An attempt to reduce the dose of bromocriptine or cabergoline can be made after the prolactin level has been normal for 2 yr. An MRI scan of the pituitary should be obtained to rule out tumor enlargement within 6 mo of initiation of tapering regimen.
- Evaluation and monitoring of pituitary function are recommended after transsphenoidal surgery.

DISPOSITION

- Transsphenoidal surgery will result in a cure in nearly 50% to 75% of patients with microadenomas and 10% to 20% of patients with macroadenomas.
- Nearly 20% of microprolactinomas resolve during long-term dopamine agonist treatment.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients must be monitored for several yrs after surgery because up to 50% of

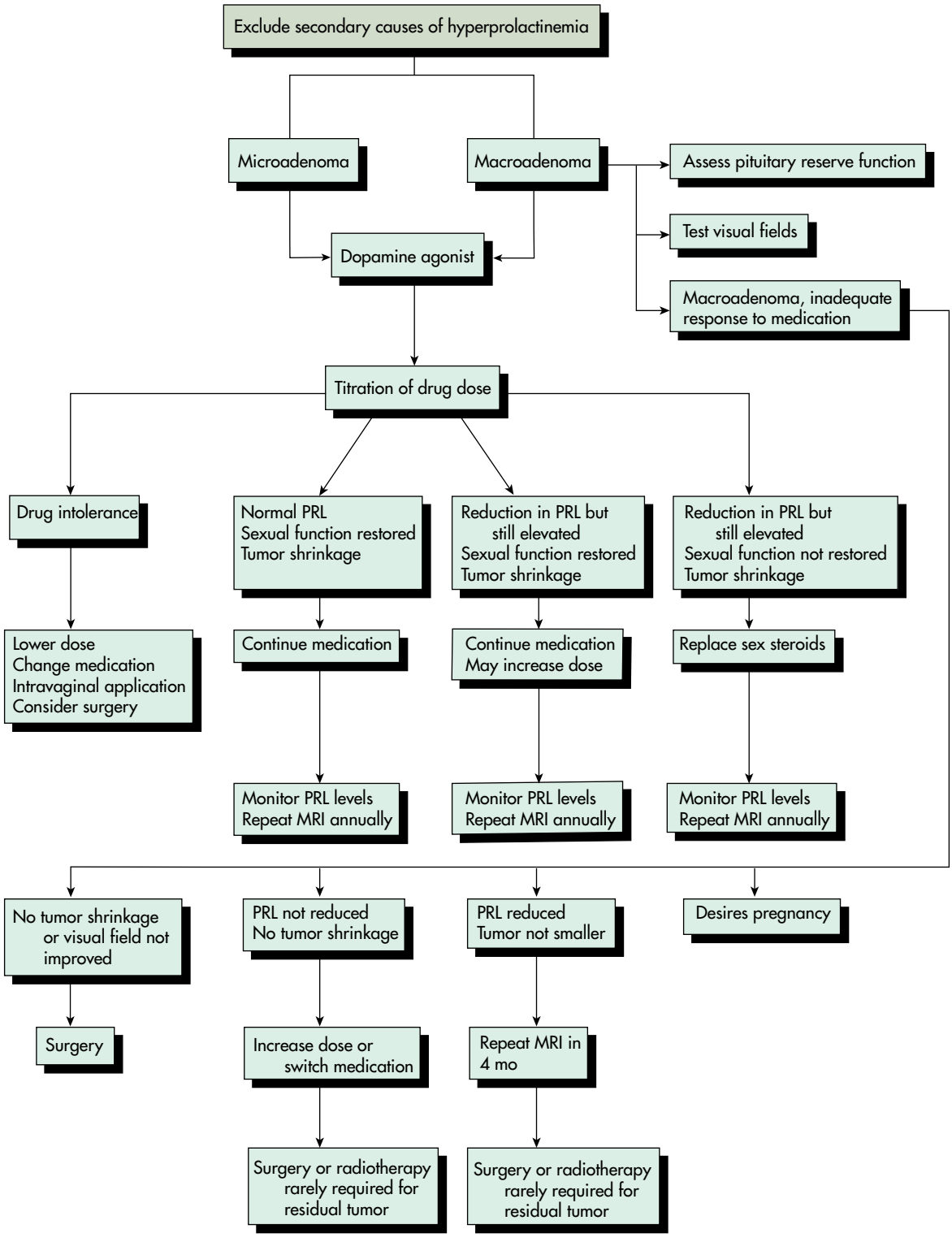

FIG. 2 Prolactinoma management. After secondary causes of hyperprolactinemia have been excluded, subsequent management decisions are based on clinical imaging and biochemical criteria. *MRI,* Magnetic resonance imaging; *PRL,* prolactin. (Modified from Larsen PR et al: *Williams textbook of endocrinology,* ed 11, Philadelphia, 2008, Saunders.)

microadenomas and nearly 90% of macroadenomas can recur.

- Pituitary microadenomas are found in 10.9% of autopsies, and 44% of these microadenomas are prolactinomas.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Prolactinoma (Patient Information)
Pituitary Adenoma (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READING

Klibansku A: Prolactinomas, *N Engl J Med* 362:1219-1226, 2010.

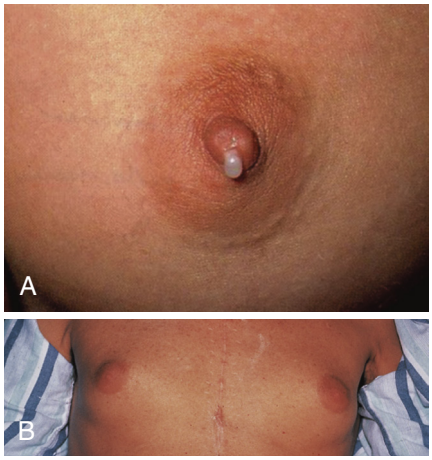

FIG. E1 Effects of prolactinoma. A, Galactorrhea in a female. **B,** Gynecomastia in a male. (**A,** From Bouloux PM: *Clinical medicine assessment questions in color,* St Louis, 1993, Wolfe. **B,** From Mir MA: *Atlas of clinical diagnosis,* Edinburgh, 2003, Saunders.)

Pronator Syndrome

BASIC INFORMATION

DEFINITION

Pronator syndrome is a form of compression neuropathy of the median nerve in the proximal forearm caused primarily by the pronator teres muscle; however, other areas of entrapment can also be encountered (Fig. E1). Occasionally, only the anterior interosseous motor branch is affected, causing a specific motor palsy of the median nerve.

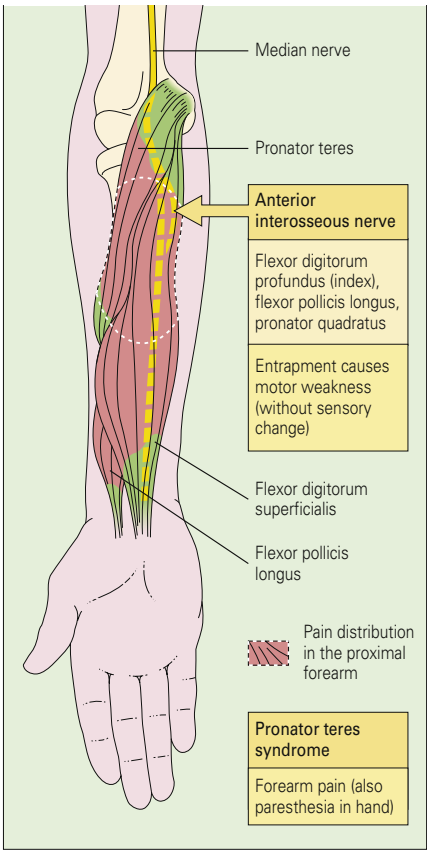

FIG. E1 Forearm entrapment regions. The median nerve may be compressed at several locations in the forearm, most commonly as it traverses the pronator teres muscle. The anterior interosseus branch of the median nerve is solely for motor, and thus entrapment produces no sensory deficit. (From Hochberg MC et al [eds]: Rheumatology, ed 3, St Louis, 2003, Mosby.)

SYNONYM

Kiloh-Nevin syndrome (anterior interosseous syndrome)

ICD-10CM CODES

G56.10	Other lesions of median nerve, unspecified upper limb
G56.90	Unspecified mononeuropathy of unspecified upper limb

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Rare (comprises <1% of median nerve entrapment disorders); most common in dominant arm.

PREDOMINANT SEX: Males are affected more often than females.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Forearm discomfort and fatigue, often resulting from repetitive pronation.
- Insidious onset.
- Nocturnal paresthesias are not typical.
- Vague numbness in hand, primarily in thumb and index finger, may be present, similar to carpal tunnel syndrome.
- Distinguished from carpal tunnel syndrome by paresthesias and/or numbness in the palmar cutaneous branch of the median nerve.
  - Palmar cutaneous branch supplies the radial palm including the thenar eminence.
- Tenderness and enlargement of the pronator teres may be present.
- Tinel sign may be positive at the site of compression in the proximal forearm.
- Although there are no reliable provocative tests, painful paresthesias may occasionally be elicited with forced pronation of the forearm against resistance.
- Motor impairment is rare.

Anterior interosseous nerve (AIN) syndrome:

- Forearm pain and weakness.
- Patient may be unable to form a circle when trying to pinch the index finger and thumb because of the inability to flex distal phalanges of thumb and index finger using the flexor pollicis longus and flexor digitorum profundus to the index finger, respectively.
- Sensation to the hand is not affected.

ETIOLOGY

- Localized anatomic compression
- Trauma
- Traumatic cutdown or phlebotomy

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Carpal tunnel syndrome
- Cervical disk syndrome with radiculopathy
- AIN syndrome
- Brachial plexopathy
- Tendon rupture
- Tendinitis

WORKUP

- Electrodiagnostic studies may be helpful but are not required; they are indicated if symptoms persist >4 to 6 wk or if motor weakness is suspected. Often these tests are normal or inconclusive.
- Plain radiography to rule out bony abnormalities causing compression.

TREATMENT

- Rest, activity modification, bracing of forearm, sling
- Flexor muscle stretching exercises, physical therapy
- Nonsteroidal antiinflammatory medications
- Corticosteroid injection

DISPOSITION

Patients whose symptoms are mainly subjective often respond to nonsurgical management. Motor deficits may not be reversible despite surgery. Six mo to a yr of nonoperative therapy is recommended.

REFERRAL

Surgical referral in cases of failed medical management or when motor weakness is present.

PEARLS & CONSIDERATIONS

COMMENTS

Prognosis for recovery is good. When indicated, surgical intervention is most effective if the compression can be confirmed by objective testing.

AUTHORS: **Kalpit N. Shah, MD,** and **Ryan M. O'Donnell, MD**

SUGGESTED READINGS

El-Haj M et al: Median nerve compression in the forearm: a clinical diagnosis, *Hand (N Y)*, 2019 Sep 20, https://doi.org/10.1177/F1558944719874137. [Epub ahead of print].

Neal S, Fields KB: Peripheral nerve entrapment and injury in the upper extremity, *Am Fam Physician* 81(2):147, 2010.

Presciutti S, Rodner CM: Pronator syndrome, *J Hand Surg* 36:907–909, 2011.

Rodner CM et al: Pronator syndrome and anterior interosseous nerve syndrome, *J Am Acad Orthop Surg* 21:268–275, 2013.

Strohl AB, Zelouf DS: Ulnar tunnel syndrome, radial tunnel syndrome, anterior interosseous nerve syndrome, and pronator syndrome, *J Am Acad Orthop Surg* 25(1):e1–e10, 2017.

BASIC INFORMATION

DEFINITION & CLASSIFICATION

Prostate cancer is a neoplasm involving the prostate. Various classifications have been developed to evaluate malignancy potential and prognosis.

- The degree of malignancy varies with the stage:
  1. Stage A: Confined to the prostate, no nodule palpable.
  2. Stage B: Palpable nodule confined to the gland.
  3. Stage C: Local extension.
  4. Stage D: Regional lymph nodes or distant metastases.
- In the Gleason classification (Box E1 and Fig. E1), two histologic patterns are independently assigned numbers 1 to 5 (best to least differentiated). These numbers are added to give a total tumor score between 2 and 10. Prognosis is best for highly differentiated tumors (e.g., Gleason score 2-4) compared with most poorly differentiated tumors (Gleason score 7-10).
- Another commonly used classification is the Tumor-Node-Metastasis (TNM) classification of prostate cancer (Table 1).
- Table 2 summarizes the definition of risk groups and biopsy criteria.

ICD-10CM CODES

C61 Malignant neoplasm of prostate
D07.5 Carcinoma in situ of prostate

EPIDEMIOLOGY & DEMOGRAPHICS

- Prostate cancer has surpassed lung cancer as the most common nonskin cancer in men.
- In the United States, more than 220,000 new cases are diagnosed yearly, and nearly 30,000 males die from prostate cancer each year (second leading cause of death from cancer in U.S. men).
- Incidence of prostate cancer increases with age: Uncommon <50 yr; 80% of new cases are diagnosed in patients aged ≥65 yr. Widespread prostate-specific antigen (PSA) testing has doubled the incidence of prostate cancer and the lifetime risk for prostate cancer to approximately 16%. Prostate cancer is also diagnosed earlier, and the incidence of clinically "silent" T_1 tumors has increased from 17% in 1989 to 48% in 2001 since the advent of PSA screening. Currently, approximately 80% of prostate cancer cases are diagnosed as localized disease and only 4% as metastatic disease.
- Prostate cancer is found at autopsy in more than half of U.S. men older than 50 yr but is the cause of death in only 3%.
- Average age at time of diagnosis is 72 yr.
- Blacks in the United States have the highest incidence of prostate cancer in the world (one in every nine males).
- Incidence is low in Asians.
- Approximately 9% of all prostate cancers may be familial. Obesity is a risk factor for prostate cancer. High-fat, low-fiber diet increases risk. High insulin levels may also increase the risk of prostate cancer. Dietary supplementation with vitamin E has been reported to significantly increase the risk of prostate cancer among healthy men. Linkage studies have implicated chromosome 17p21-22 as a possible location of a prostate-cancer susceptibility gene. Germline mutations in *HOXB13* are associated with a significantly increased risk of hereditary prostate cancer.
- Mortality rates of prostate cancer have declined substantially in the past 15 yr from 34% in 1990 to <20% currently.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Generally silent disease until it reaches advanced stages.
- Bone pain and pathologic fractures may be initial symptoms of prostate cancer.
- Local growth can cause symptoms of outflow obstruction.
- Digital rectal examination (DRE) may reveal an area of increased firmness; 10% of patients will have a negative DRE.
- Prostate may be hard, fixed, with extension of tumor to the seminal vesicles in advanced stages.

TABLE 1 Prostate Cancer

T Stage		
T_x	Primary tumor is not assessable	
T_0	There is no evidence of primary tumor	
T_1	Tumor is not clinically palpable or detected with imaging	
	T_{1a}	*An incidental histological finding in ≤5% of resected tissue (e.g., TURP)*
	T_{1b}	*An incidental histological finding in >5% of resected tissue (e.g., TURP)*
	T_{1c}	*Tumor is identified by needle biopsy*
T_2	Prostate-confined tumor that is clinically palpable or detected with imaging	
	T_{2a}	*Tumor involves ≤1/2 of one prostate lobe*
	T_{2b}	*Tumor involves >1/2 of one prostate lobe (but not both lobes)*
	T_{2c}	*Tumor involves both lobes*
T_3	There is tumor extension through the prostate capsule	
	T_{3a}	*Unilateral or bilateral tumor extension through the prostate capsule*
	T_{3b}	*Seminal vesical involvement*
T_4	Tumor invades structures other than the seminal vesicles (e.g., the bladder neck, rectum, or pelvic wall)	
N Stage		
N_x	The lymph nodes are not assessable	
N_0	There is no tumor spread	
N_1	There is tumor spread to one or more regional pelvic nodes	
M Stage		
M_0	There is no tumor spread beyond the regional pelvic nodes	
M_1	There is tumor spread beyond the regional pelvic nodes	
	M_{1a}	*Tumor spread to nodes outside of the pelvis*
	M_{1b}	*Tumor spread to bones*
	M_{1c}	*Tumor spread to other organs (e.g., lung, liver and brain) ± bone involvement*

From Grant, LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Benign prostatic hypertrophy
- Prostatitis
- Prostate stones

LABORATORY TESTS

- Measurement of PSA is controversial in early diagnosis of prostate cancer. PSA screening is associated with psychological harm, and its potential benefits remain uncertain. In asymptomatic men with no history of prostate cancer, screening using PSA does not reduce all-cause mortality or death from prostate cancer. Normal PSA is found in >20% of patients with prostate cancer, whereas only 20% of men with PSA levels between 4 ng/ml and 10 ng/ml have prostate cancer. Most guidelines encourage a shared decision-making approach between patient and physician regarding PSA testing. Available evidence favors clinician discussion of the pros and cons of PSA screening with average-risk men aged 65 to 69 yr. Only men who express a definite preference for screening should have PSA testing. Rather than widespread annual PSA screening, a reasonable approach may be to focus on high-risk men (those with PSA levels ≥2 ng/ml at age 60). The American Cancer Society recommends offering the PSA test and DRE yearly to men aged ≥50 yr who have a life expectancy of at least 10 yr. Earlier testing, starting at age 40 to 45 yr, is recommended for men at high risk (e.g., blacks, men with family history of prostate cancer). An isolated elevation in PSA level should be confirmed several weeks later before proceeding with further

TABLE 2 Definition of Risk Groups

Risk Group	Clinical Stage	PSA (ng/ml)	Gleason Score	Biopsy Criteria
Low	T_{1a} or T_{1c}	<10	2-6	Unilateral or <50% of core involved
Intermediate	T_{1b}, T_{1c}, or T_{2a}	<10	3 + 4 = 7	Bilateral
High	T_{1b}, T_{1c}, T_{2b}, or T_3	10-20	4 + 3 = 7	>50% of core involved or perineural invasion or ductal differentiation
Very high	T_4	>20	8-10	Lymphovascular invasion or neuroendocrine differentiation

From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

testing, including prostate biopsy. Screening for prostate cancer in men aged ≥75 yr is controversial and generally not recommended. The American College of Physicians (ACP) recommends that clinicians should not screen for prostate cancer using the PSA in average-risk men under age 50, men over age 69, or men with a life expectancy of <10 to 15 yr. The U.S. Preventive Services Task Force (USPSTF) recommends against PSA-based screening for prostate cancer in all age groups. According to the USPSTF:

1. The magnitude of harms from screening (e.g., falsely high PSA levels, psychological effects, unnecessary biopsies, overdiagnosis of indolent tumors) is "at least small."
2. The magnitude of treatment-associated harms (i.e., adverse effects of surgery, radiation, and hormonal therapy) is "at least moderate."
3. The 10-yr mortality benefit of PSA-based prostate cancer screening is "small to none."
4. The overall balance of benefits and harms results in "moderate certainty that PSA-based screening has no net benefit."

- Free PSA: The use of serum free PSA for prostate screening has been proposed by some urologists as a means to decrease unwarranted biopsies without missing a significant number of prostate cancers. This approach is based on the higher free PSA in men with benign prostatic hyperplasia and the higher protein-bound PSA levels in men with prostate cancer. For example, in men with total PSA levels of 4 to 10 ng/ml, the cancer probability is 0.25, but if the percentage of free PSA is ≤17%, the probability of cancer increases to 0.45.
- PSA velocity: The rate of increase of serum PSA over time (PSA velocity) can aid in the diagnosis of prostate cancer. A yearly PSA velocity >0.75 ng/ml increases the likelihood of later malignancy when total PSA is still within normal range. Proper interpretation of PSA velocity requires at least three PSA measurements over an 18-mo period because most PSA variations are physiologic. Recent trials have cast a doubt on the value of PSA velocity by showing that adding PSA velocity as a trigger for biopsy did not improve predictive accuracy beyond that of using PSA threshold values alone.
- Age-adjusted PSA: There is evidence that the current threshold of 4.0 ng/ml is inadequate for younger men, because in a recent study 22% of men with PSA levels between 2.6 and 4.0 were found to have prostate cancer. The concept of age-related cutoffs remains controversial. Lowering the upper limit of normal for PSA would improve sensitivity but decrease specificity.
- Prostatic acid phosphatase can be used for evaluation of nonlocalized disease.
- Prostate cancer gene 3 *(PCA3)* is overexpressed in prostate cancer cell, and high levels are suggestive of prostate cancer. Measurement of *PCA3* in urine specimens collected after digital exams is helpful to make decisions about prostate biopsy in men with elevated PSA.
- Transrectal biopsy and fine-needle aspiration of prostate can confirm the diagnosis. Indications for biopsy include an abnormal PSA level, an abnormal DRE, or a previous biopsy specimen that showed prostatic intraepithelial neoplasia or prostatic atypia. The number of cores taken is patient specific, typically including a minimum of 10 cores. Prostate volume negatively affects cancer detection rate (23% in glands >50 cm^3, 38% in glands <50 cm^3).

IMAGING STUDIES (FIGS. E2 THROUGH E5)

- Bone scan is useful to evaluate bone metastasis (present or eventually develops in almost 80% of patients). However, according to the American Urological Association (AUA), the routine use of bone scanning is not required for staging of prostate cancer in asymptomatic men with clinically localized cancer if the PSA level is ≤20 ng/ml.
- CT scan, MRI, and transrectal ultrasonography may be useful in selected patients to assess extent of prostate cancer. High-resolution MRI with magnetic nanoparticles has been used for the detection of small and otherwise undetectable lymph node metastases in patients with prostate cancer. However, according to the AUA, transrectal ultrasonography adds little to the combination of PSA and DRE. Similarly, CT and MRI imaging are generally not indicated for cancer staging in men with clinically localized cancer and PSA <25 ng/ml. With regard to pelvic lymph node dissection in staging, the AUA states that it may not be required in patients with PSA levels <10 ng/ml and when PSA level is <20 ng/ml and the Gleason score is <6.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Watchful waiting is reasonable in selected patients with early-stage (T_{1a}) and projected life expectancy <10 yr or in patients with focal and moderately differentiated carcinoma.

ACUTE GENERAL Rx

- Therapeutic approach varies with the following:
  1. Stage of the tumor
  2. Patient's life expectancy
  3. General medical condition
  4. Patient's treatment preference (e.g., patient may be opposed to orchiectomy)
- The optimal treatment of clinically localized prostate cancer is unclear. It is important to remember that all forms of treatment have potential adverse effects. Management requires careful consideration of the potential benefits and harms of intervention, the patient's age, health status, and individual preferences. A treatment algorithm for prostate cancer is described in Fig. 6. Table 3 summarizes recommended treatment based on risk group and life expectancy.
  1. Radical prostatectomy is generally performed in patients with localized prostate cancer and life expectancy >10 yr. Radical prostatectomy reduces disease-specific mortality, overall mortality, and the risks of metastasis and local progression. The absolute reduction in the risk of death after 10 yr is small, but the reductions in the risks of metastasis and local tumor progression are substantial. A 29 yr follow-up comparing radical prostatectomy with watchful waiting showed that men with clinically detected, localized prostate cancer and a long life expectancy benefited from radical prostatectomy with a mean 2.9 yr of life gained. Postoperative complications of radical prostatectomy include urinary incontinence (10% to 20% depending on degree of neurovascular bundle and urethral preservation, patient age, and correct mucosal apposition) and erectile dysfunction (percentage >50% and varies with patient age, preoperative erectile dysfunction, stage of tumor at time of surgery, and preservation of neurovascular bundle). Lower complication rates occur in hospitals that perform a large number of prostatectomies. Fewer men will have postsurgical erectile dysfunction after unilateral or bilateral nerve-sparing surgery. In men undergoing prostatectomy, robotic-assisted laparoscopic surgery represents an alternative to open retropubic radical prostatectomy. Despite advertisements that suggest that there

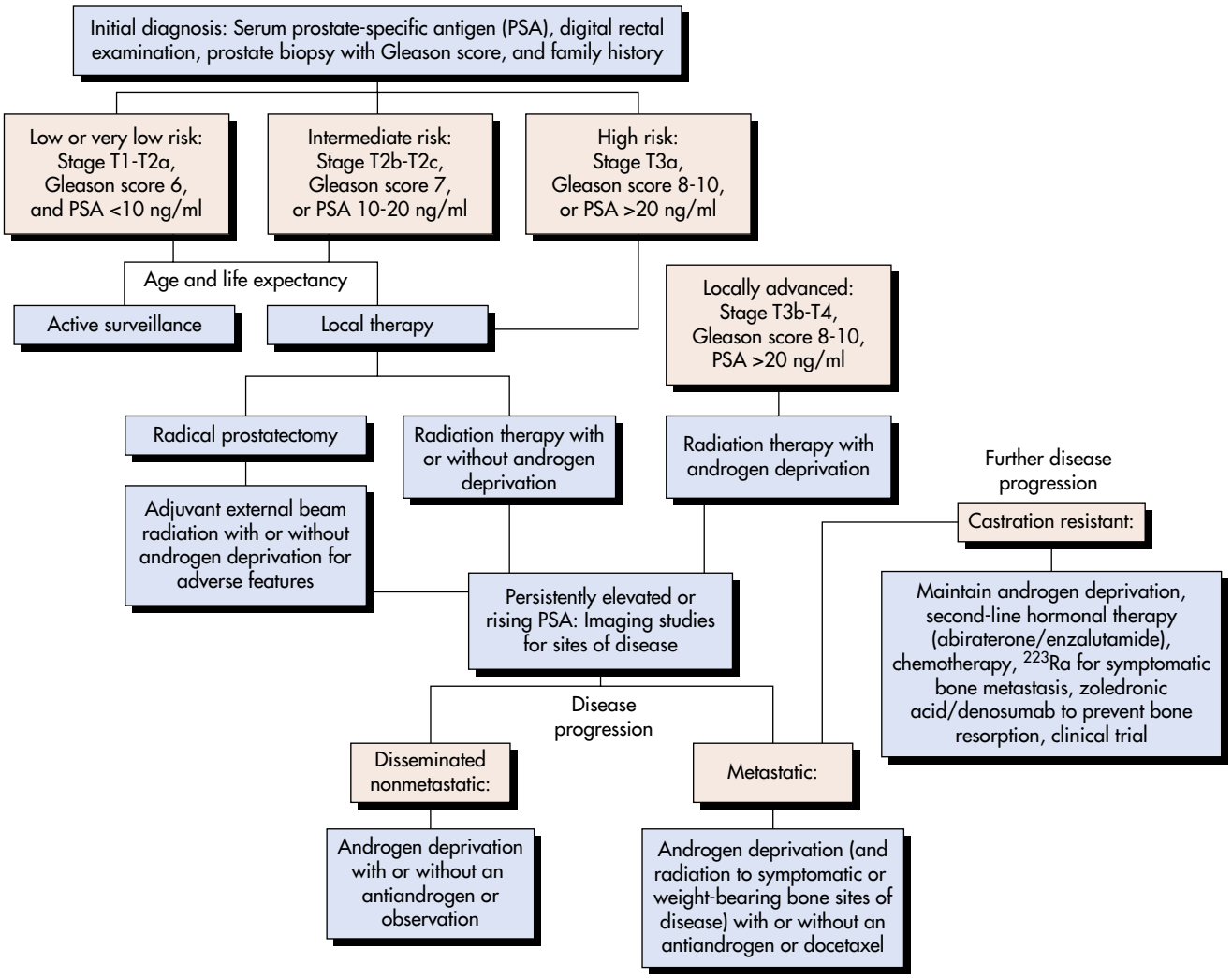

FIG. 6 Treatment algorithm. ^{223}Ra, Radium-223. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

TABLE 3 Recommended Treatment

Risk Group	Life Expectancy (Yr)	Recommended Treatment
Low	0-5	AS, HT
	5-10	AS, RT, HT, 0
	>10	RP, RT, AS, 0
Intermediate*	0-5	AS, HT, RT, 0
	5-10	RT, HT, RP, 0
	>10	RP, RT, 0, HT
High*	0-5	AS, RT + HT, 0
	5-10	RT + HT, HT, RP, 0
	>10	RT + HT, RP + RT + HT, HT
Very high*	0-5	AS, RT + HT, 0
	5-10	H, RT + HT, ST
	>10	RT + HT, RP + RT + HT, HT, ST, IT

AS, Active surveillance; *HT,* hormone therapy; *IT,* investigational multimodal therapy; *0,* others; *RP,* radical prostatectomy; *RT,* radiation therapy; *ST,* systemic therapy.
*If there is more than a 20% probability of positive lymph nodes, AS, HT, ST + HT.
From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

are fewer complications after robotic surgery, data show that sexual dysfunction occurs postoperatively in about 88% of patients who have undergone robotic-assisted or conventional prostatectomy and that incontinence problems are more prevalent (33%) with robotic surgery than with open retropubic radical prostatectomy (RPP) (27%). Trials have shown that prostatectomy is preferred over "watchful waiting" in patients with localized prostate cancer detected by PSA if the PSA level is >10 ng/ml. In this subgroup, the 10-yr mortality is 48.4% with prostatectomy versus 61.6% with watchful waiting. In men who have low-risk disease (PSA level <10 mcg/L, stage $<T_{2a}$, Gleason score ≤3 + 3), and <6% risk for prostate cancer–specific death at 15 yr, watchful waiting (WW) and active surveillance (AS) are reasonable and underutilized options.

TABLE 4 Major Circulating Androgens

Source	Androgen	Amount Produced/Day (mg)	Relative Potency	Relative Potency/Amount Produced
Testes	Testosterone	6.6	100	15.2
Testes and peripheral tissues	Dihydrotestosterone	0.3	160-190	533-633
Adrenal glands	Androstenedione	1.4	39	27.9
Adrenal glands	Dehydroepiandrosterone	29	15	0.5

From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

2. Radiation therapy (external-beam irradiation or brachytherapy with implantation of radioactive pellets [iodine-125 or palladium-103 seeds] into the prostate gland) represents an alternative in patients with localized prostate cancer, especially poor surgical candidates or patients with a high-grade malignancy. The efficacy of brachytherapy is comparable to external radiation. In patients receiving external-beam radiation, a total dose of 79.2 Gy (high dose) compared with a total dose of 70.2 Gy (conventional dose) has been reported to lower the risk of recurrence without increased risk of morbidity and mortality. Newer radiation treatments such as intensity-modulated radiation therapy (IMRT) and proton therapy are becoming increasingly popular and replacing the older technique of conformal radiation therapy over the past 10 yr. Trials have shown that among patients with nonmetastatic prostate cancer, the use of IMRT compared with conformal therapy is associated with less gastrointestinal morbidity and fewer hip fractures but more erectile dysfunction; IMRT compared with proton therapy is associated with less GI morbidity. Patients with localized prostate cancer and high risk for extraprostatic disease and disease recurrence (e.g., Gleason score ≤7 with multiple positive biopsy cores and clinical stage T_{1b}-T_{2b}) may benefit (increased overall survival) with the addition of 6 mo of androgen suppression therapy to radiation therapy.
3. Watchful waiting is reasonable in patients who are too old or too ill to survive longer than 10 yr. If the cancer progresses to the point where it becomes symptomatic, palliation can be attempted with several methods. Conservative management is also reasonable for patients with Gleason score of 2 to 4 because these patients do not have a shortened life expectancy and treatment is associated with long-term side effects. Watchful waiting also appears to be safe in older men with less-aggressive disease. Individual preferences play a central role in the decision whether to treat or to pursue active surveillance.

- Patients with advanced disease and projected life expectancy <10 yr are candidates for radiation therapy and hormonal therapy (diethylstilbestrol, luteinizing hormone–releasing hormone analogues, antiandrogens, bilateral orchiectomy).
- Recommended treatment of patients with regional metastatic prostate cancer with projected life expectancy ≥10 yr includes radiation therapy and hormonal therapy.
- Prostate cancer is an androgen-receptor-dependent disease, and the blocking of androgen-receptor signaling is an effective treatment modality. Table 4 summarizes major circulating androgens. Androgen deprivation therapy (ADT) is the mainstay of treatment for metastatic prostate cancer. Adverse effects of ADT include decreased libido, impotence, hot flashes, osteopenia with increased fracture risk, metabolic alterations, and changes in mood and cognition. Adjuvant treatment with luteinizing hormone-releasing hormone (LHRH) agonists (goserelin, leuprolide, or triptorelin) plus antiandrogens (flutamide, bicalutamide, or nilutamide), when started simultaneously with external-beam radiation, improves local control and survival in patients with locally advanced prostate cancer. Pamidronate inhibits osteoclast-mediated bone resorption and prevents bone loss in the hip and lumbar spine in men receiving treatment for prostate cancer. Gonadotropin-releasing hormone (GnRH) receptor antagonists can be used for rapid medical castration of men with advanced prostate cancer. Degarelix is an injectable GnRH agonist useful to suppress testosterone in patients with prostate cancer who are not good candidates for LHRH agonists and refuse surgical castration. Assessment of bone density and treatment with once-weekly oral alendronate can prevent and improve the bone loss that occurs in men receiving ADT for prostate cancer.
- Docetaxel plus prednisone or docetaxel plus estramustine can be used in metastatic hormone–refractory prostate cancer. Newer treatments for hormone–refractory prostate cancer (castration-resistant cancer) include immunotherapy with sipuleucel and cabazitaxel, a microtubule inhibitor that interferes with cell mitosis and replication. Both agents can prolong survival but adverse effects can be severe and both agents are very expensive. Abiraterone is an oral agent that blocks biosynthesis of androgens by inhibiting CYP17, an enzyme required for androgen biosynthesis. It has been FDA approved for oral treatment, in combination with prednisone, of metastatic castration-resistant prostate cancer in patients previously treated with docetaxel.
- Enzalutamide is a newer nonsteroidal antiandrogen. Trials have shown it to be highly effective in extending survival in patients with metastatic castration-resistant prostate cancer. It can be used sequentially with other agents such as docetaxel, abiraterone, cabazitaxel, and immunotherapy. Radium-223, an alpha emitter, selectively targets bone metastases and has been found effective in improving survival in men with castration-resistant prostate cancer and bone metastases.
- The polyadenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor has shown a high response rate in patients whose prostate cancers were no longer responding to standard treatments and who had defects in DNA-repair genes.

CHRONIC Rx

- Patients should be monitored at 3- to 6-mo intervals with clinical examination and PSA for the first yr, then every 6 mo for the second yr, then yearly if stable. For patients who have undergone radical prostatectomy, a rising PSA level suggests evidence of residual or recurrent prostate cancer. A recent study revealed that if the PSA level remains undetectable 3 to 5 yr after radical prostatectomy, the probability of biochemical recurrence is extremely low, and it is reasonable to stop PSA monitoring. [1]Salvage radiotherapy may potentially cure patients with disease recurrence after radical prostatectomy. Recent trials have shown that addition of 24 mo of antiandrogen therapy with daily bicalutamide to salvage radiation therapy results in significantly higher rates of long-term overall survival and lower incidences of metastatic prostate cancer and death from prostate cancer than radiation therapy plus placebo.[2]
- Chest radiography and bone scan should be performed yearly or sooner if patient develops symptoms.

[1]Matsumoto K et al: Determining when to stop prostate specific antigen monitoring after radical prostatectomy: the role of ultrasensitive prostate specific antigen, *J Urol* 197:655, 2017.
[2]Shirley WV et al: Radiation with or without antiandrogen therapy in recurrent prostate cancer, *N Engl J Med* 376:417-428, 2017.

TABLE 5 Common Pain Syndromes in Metastatic Castration-Resistant Prostate Cancer

Pain Syndrome	Initial Management	Other Therapeutic Alternatives
Localized bone pain	Pharmacologic pain management	Surgical stabilization of pathologic fractures or extensive bone erosions
	Localized radiotherapy (special attention to weight-bearing areas, lytic metastasis, and extremities)	Epidural metastasis and cord compression should be evaluated in all patients with focal back pain
		Radiopharmaceuticals should be considered if local radiation therapy fails
Diffuse bone pain	Pharmacologic pain management	Corticosteroids
	"Multispot" or wide-field radiotherapy	Bisphosphonates or RANK ligand inhibitors
	Radiopharmaceuticals	Calcitonin
		Chemotherapy
Epidural metastasis and cord compression	High-dose corticosteroids	Pharmacologic pain management
	Radiation therapy	Physical therapy for recovery of neurologic function
	Surgical decompression and stabilization are indicated in high-grade epidural compressions, extensive bone involvement, or recurrence after irradiation.	
Nerve plexopathies caused by direct tumor extension or previous therapy (rare)	Pharmacologic pain management	Tricyclic antidepressants (amitriptyline)
	Radiation therapy (if not previously used)	Anticonvulsants (gabapentin, pregabalin)
	Neurolytic procedures (nerve blocks)	
Miscellaneous neurogenic causes: Postherpetic neuralgia, peripheral neuropathies	Complete neurologic evaluation	Tricyclic antidepressants (amitriptyline)
	Pharmacologic pain management	Anticonvulsants (gabapentin, pregabalin)
	Discontinuation of neurotoxic drugs: Docetaxel, platinum compounds	
Other uncommon pain syndromes: Extensive skull metastasis with cranial nerve/skull base involvement, extensive painful liver metastasis, or pelvic masses	Radiation therapy	Chemotherapy
	Pharmacologic pain management	Intrathecal chemotherapy may ameliorate symptoms of meningeal involvement
	Corticosteroids (cranial nerve involvement)	

RANK, Receptor activator of nuclear factor-κB.
From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

DISPOSITION

- Prognosis varies with the stage of the disease and the Gleason classification (see "Definition"). For patients between ages 65 and 69 yr at diagnosis and a Gleason score of 2 to 4, the probability of dying from prostate cancer 15 yr after diagnosis is 0.06 and that of dying from other causes is 0.56. If the Gleason score is 7 to 10, the probability of dying from prostate cancer increases to 0.72 and from other causes varies from 0.25 to 0.36.
- The ploidy of the tumor also has prognostic value; prognosis is better with diploid tumor cells and worse with aneuploid tumor cells.
- For grade 1 tumors, the extended 10-yr, disease-specific survival is similar for patients with prostatectomy (94%), radiotherapy (90%), and conservative management (93%); survival rate is better with surgery than with radiotherapy or conservative management in patients with grade 2 or 3 localized prostate cancer.
- Expression of the gene *EZH2* has been identified as an important factor in the determination of the aggressiveness of prostate cancer. A recent study revealed that expression of the *EZH2* gene may be a better predictor of clinical failure than Gleason score, tumor stage, or surgical margin status. Testing for EZH2 protein in prostate cancer tissue may be useful to determine prognosis and direct treatment.
- Preoperative PSA level and PSA velocity have prognostic significance. Men whose PSA level increases by >2.0 mcg/ml during the year before the diagnosis of cancer may have a relatively high risk of death from prostate cancer despite undergoing radical prostatectomy.
- Extraprostatic disease is detected at radical prostatectomy in 38% to 52% of patients and is associated with a risk of disease recurrence, progression, and death. In these patients, adjuvant radiotherapy results in significantly reduced risk of PSA relapse and disease recurrence; however, the improvements in metastases-free survival and overall survival are not statistically significant. Table 5 summarizes common pain syndromes in metastatic castration-resistant prostate cancer.
- The Prostate Cancer Prevention trial revealed that the use of 5-alpha-reductase inhibitors lowers the incidence of prostate cancer but also increases the incidence of high-grade tumors (Gleason score >7). It is possible that these agents delay diagnosis of prostate cancer by lowering PSA levels and decreasing prostate size. The trade-off inherent in using 5-alpha-reductase inhibitors for prostate cancer prevention is risk of one additional high-grade cancer in order to avert three or four lower-grade cancers. Based on these results, the FDA's Oncologic Drugs Advisory Committee concluded that finasteride and dutasteride do not have a favorable risk-benefit profile for chemoprevention of prostate cancer in healthy men.
- Patients undergoing prostatectomy are more likely to have urinary incontinence than those undergoing radiotherapy at 2 yr and 5 yr. However, at 15 yr there are no significant relative differences in disease-specific functional outcomes among men undergoing prostatectomy or radiotherapy.
- Bone health is a significant concern in men with prostate cancer. Trials involving bisphosphonates and denosumab reveal that both improve bone mineral density (BMD) in men with nonmetastatic prostate cancer receiving androgen deprivation therapy. Denosumab has also been shown to reduce the risk of vertebral fractures.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Prostate Cancer (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

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BOX E1 2005 International Society of Urological Pathology Modified Gleason System

Pattern 1
Circumscribed nodule of closely packed but separate, uniform, rounded to oval, medium-sized acini (larger glands than pattern 3)

Pattern 2
Like pattern 1, fairly circumscribed, yet at the edge of the tumor nodule there may be minimal infiltration
Glands are more loosely arranged and not quite as uniform as Gleason pattern 1

Pattern 3
Discrete glandular units
Typically smaller glands than seen in Gleason pattern 1 or 2
Infiltrates in and among nonneoplastic prostate acini
Marked variation in size and shape

Pattern 4
Fused microacinar glands
Ill-defined glands with poorly formed glandular lumens
Large cribriform glands
Cribriform glands
Hypernephromatoid

Pattern 5
Essentially no glandular differentiation, composed of solid sheets, cords, or single cells
Comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses

From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

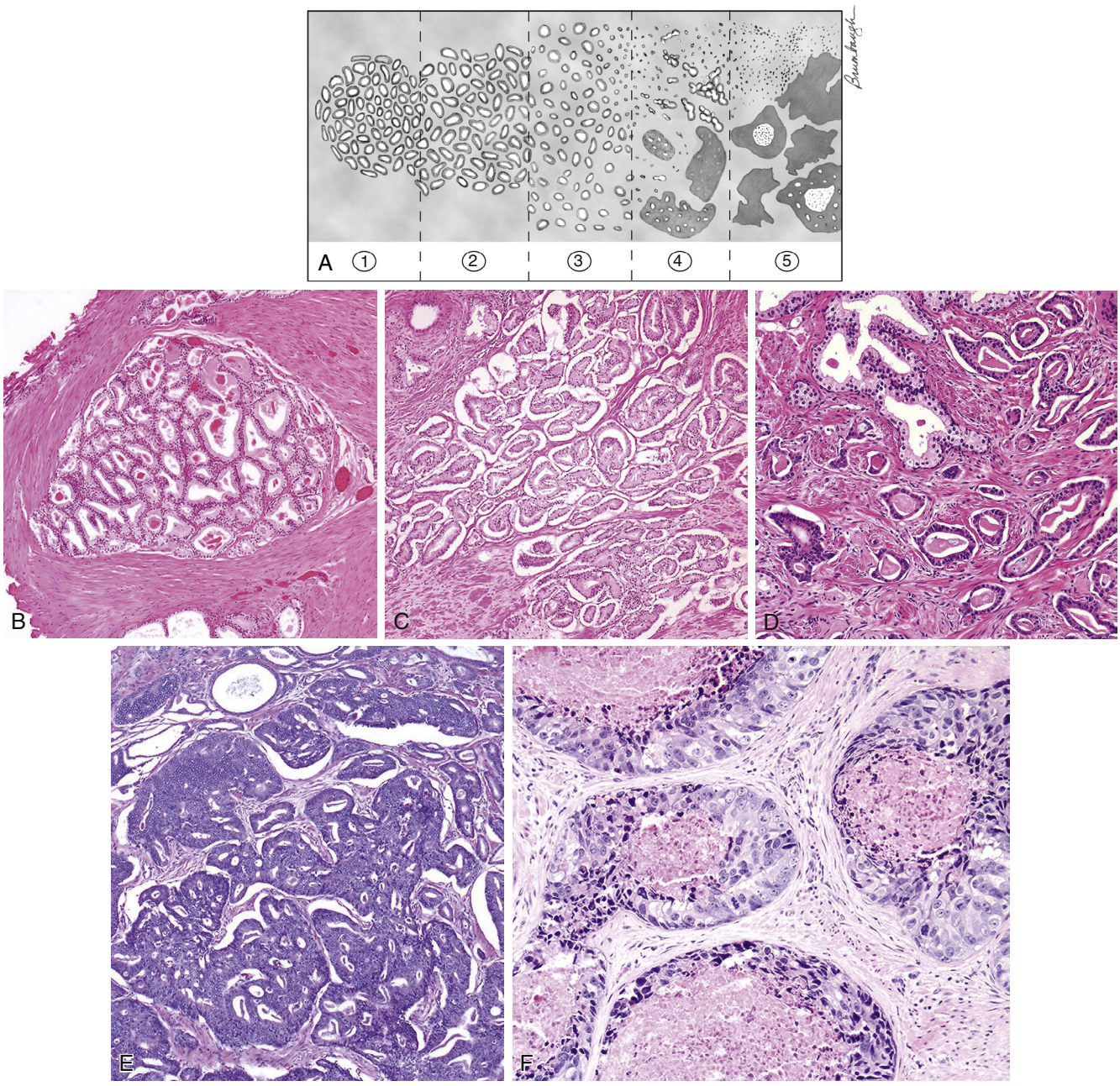

FIG. E1 The Gleason grading system. (A) Schematic diagram of the Gleason grading system. **(B)** Gleason pattern 1: Well-circumscribed nodule of closely packed glands. **(C)** Gleason pattern 2: Nodule with more loosely arranged glands. **(D)** Gleason pattern 3: Small glands with an infiltrative pattern between benign glands. **(E)** Gleason pattern 4: Large irregular cribriform glands. **(F)** Gleason pattern 5: Solid nests of tumor with central comedonecrosis. (From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.)

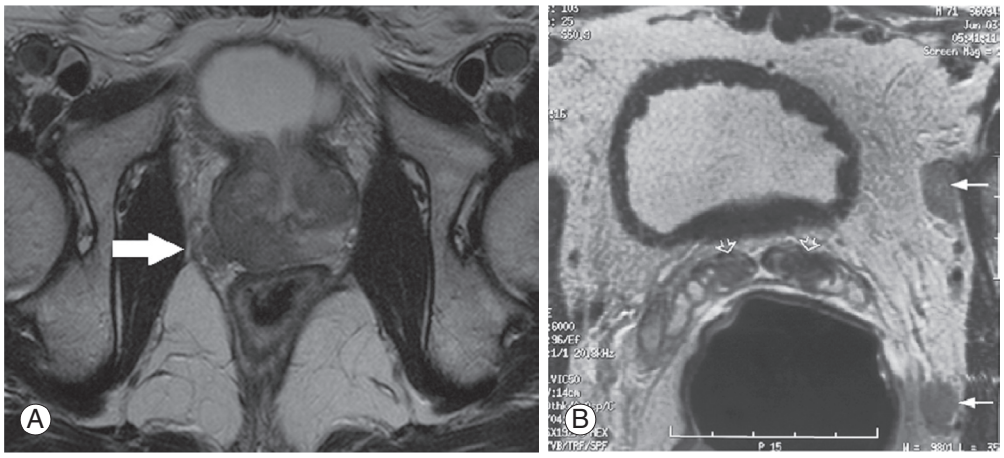

FIG. E2 Prostate carcinoma. (A) Axial T2WI demonstrating a low signal focus within the right peripheral lobe with extracapsular tumor extension (arrow). **(B)** Low SI within the medial aspects of both seminal vesicles representing invasion (open arrows). There is involvement of local pelvic lymph nodes (arrow). (From Adam A, Dixon AK, Grainger RG, Allison DJ: *Grainger & Allison's diagnostic radiology,* ed 5, 2017, Churchill Livingstone. In Grant, LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, 2019, Elsevier.)

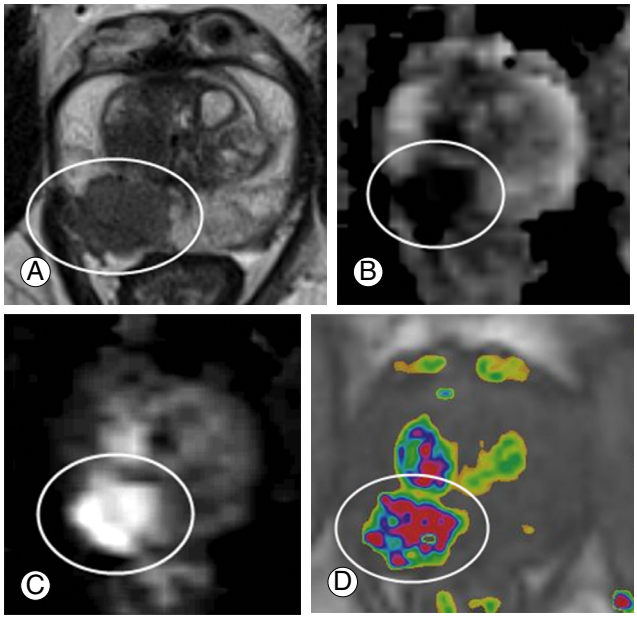

FIG. E3 Multi-parametric MR images of a 64-yr-old man with a PSA level of 13 ng/ml and 1 negative TRUS biopsy session, showing a typical case of a peripheral zone tumor. With MR-guided biopsy a GS 4 + 4 = 8 was found. **(A)** Axial T2-weighted image. **(B)** Axial ADC map. **(C)** Axial DWI with b = 1400. **(D)** Axial DCE image. (From Adam A, Dixon AK, Gillard JH, Schaefer-Prokop CM: *Grainger and Allison's diagnostic radiology,* ed 6, 2015, Elsevier. In Grant, LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, 2019, Elsevier.)

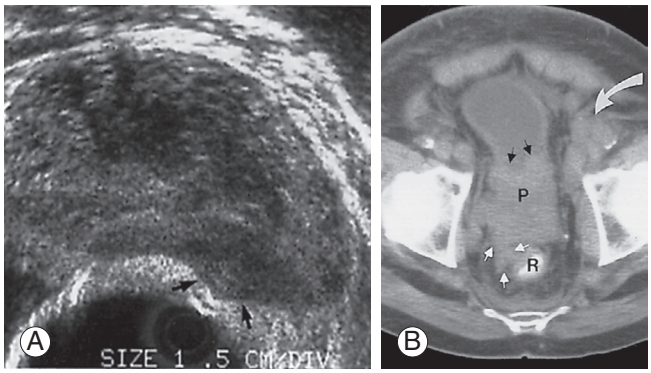

FIG. E4 (A) Stage T_3 prostate carcinoma. TRUS demonstrating an ill-defined hypoechoic area (arrows) within the peripheral zone. The tumor is causing a localized bulge of the prostatic outline beyond the expected contour of the gland. This is the most reliable finding in diagnosing transcapular invasion. **(B)** CT demonstration of prostatic carcinoma with regional lymph node metastasis. The prostate gland (P) is markedly enlarged, and there is direct tumor extension into the perirectal region (small white arrows), rectum (R), and the bladder base (small black arrows). Pronounced left external iliac adenopathy is present (curved arrow). (From Adam A, Dixon AK, Grainger RG, Allison DJ: *Grainger & Allison's diagnostic radiology,* ed 5, 2017, Churchill Livingstone. In Grant, LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, 2019, Elsevier.)

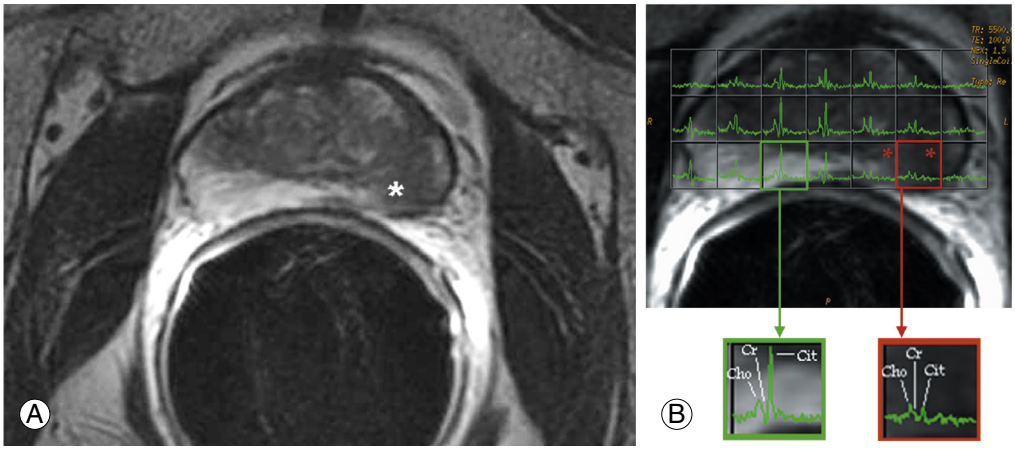

FIG. E5 MRI and 3D 1 H MR spectroscopy of prostate carcinoma. (A) Axial T2WI (endorectal coil), with **(B)** superimposed MR spectroscopic grid and corresponding spectral array to the superimposed grid. The tumor (*) is seen as a low SI in the left peripheral gland. The corresponding MR spectroscopic grid shows concordant results with abnormal metabolism in this area: Green box, healthy tissue ▸ red box, cancer ▸ Cho, choline ▸ Cr, creatine ▸ Cit, citrate. (From Adam A, Dixon AK, Grainger RG, Allison DJ: *Grainger & Allison's diagnostic radiology,* ed 5, 2017, Churchill Livingstone. In Grant, LA: *Grainger & Allison's diagnostic radiology essentials*, ed 2, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Prostatitis refers to inflammation of the prostate gland. There are four major categories (Table 1):

1. Acute bacterial prostatitis (type I)
2. Chronic bacterial prostatitis (type II)
3. Chronic prostatitis/pelvic pain syndrome (CP/CPPS) (type III): Subdivided into type IIIA (inflammatory) and IIIB (noninflammatory)
4. Asymptomatic inflammatory prostatitis (type IV)

ICD-10CM CODES
N41.0 Acute prostatitis
N41.1 Chronic prostatitis

EPIDEMIOLOGY & DEMOGRAPHICS

- 50% of men will have symptoms of prostatitis in their lifetime.
- Prostatitis accounts for >8% of visits to urologists and 1% of visits to primary care physicians.
- The prevalence of chronic bacterial prostatitis is 5% to 10%.
- CP/CPPS is the most common of the clinically defined prostatitis syndromes, with prevalence ranging from 9% to 12% of men.
- Acute bacterial prostatitis accounts for 10% of all cases of prostatitis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute bacterial prostatitis:
  1. Sudden or rapidly progressive onset of:
     a. Dysuria.
     b. Frequency.
     c. Urgency.
     d. Nocturia.
     e. Perineal pain that may radiate to the back, rectum, or penis.
  2. Hematuria or a purulent urethral discharge may occur.
  3. Occasionally urinary retention complicates the course.
  4. Fever, chills, and signs of sepsis can also be part of the clinical picture.
  5. On rectal examination the prostate is typically tender.
- Chronic bacterial prostatitis:
  1. Characterized by positive culture of expressed prostatic secretions. May cause symptoms such as suprapubic, low back, or perineal pain; mild urgency, frequency, and dysuria with urination; and possibly recurrent urinary tract infections.
  2. May be asymptomatic when the infection is confined to the prostate.
  3. May present as an increase in severity of baseline symptoms of benign prostatic hypertrophy (BPH).
  4. When cystitis is also present, urinary frequency, urgency, and burning may be reported.
  5. Hematuria may be a presenting complaint.
  6. In elderly men, new onset of urinary incontinence may be noted.
- CP/CPPS:
  1. Presents similarly with pain in the pelvic region lasting >3 mo. Symptoms also can include pain in the suprapubic region, low back, penis, testes, or scrotum.
  2. The symptoms can be of variable severity and may include lower urinary tract symptoms, sexual dysfunction, and reduced quality of life.

ETIOLOGY

- Acute bacterial prostatitis:
  1. Acute, usually gram-negative infection of the prostate gland. *E. coli* is the most commonly isolated organism.
     a. Generally associated with cystitis.
     b. Results from the ascent of bacteria into the urethra.
  2. Occasionally the route of infection is hematogenous or a lymphatogenous spread of rectal bacteria.
  3. Consider *Neisseria gonorrhoeae* or *Chlamydia trachomatis* in young patients (age <35 yr) with risk of sexually transmitted disease (STD).
- Chronic bacterial prostatitis:
  1. Often asymptomatic. *E. coli* is the most commonly isolated organism.
  2. Exacerbation of symptoms of BPH caused by the same mechanism as in acute bacterial prostatitis.
- CP/CPPS:
  1. Type IIIA: Refers to symptoms of prostatic inflammation associated with the presence of white blood cells in prostatic secretions with no identifiable bacterial organism.
  2. *Chlamydia* infection may be etiologically implicated in some cases.
  3. Type IIIB: Refers to symptoms of prostatic inflammation with no or few white blood cells in the prostatic secretion. Its cause is multifactorial (Fig. 1).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- BPH with lower urinary tract symptoms
- Prostate cancer
- Interstitial cystitis/bladder pain syndrome
- Pelvic floor dysfunction
- Bladder cancer
- Urolithiasis
- UTI
- Proctitis

WORKUP

- Rectal examination:
  1. Tender prostate most suggestive of acute bacterial prostatitis
  2. Enlarged prostate common in chronic bacterial prostatitis
  3. Normal prostate is consistent with chronic bacterial prostatitis and CP/CPPS
- Expression of prostatic secretions by prostate massage is contraindicated in acute bacterial prostatitis but is appropriate in the other three situations.

LABORATORY TESTS

- Urinalysis
- Urine culture and sensitivity
- Bacterial localization studies can be performed but are cumbersome and impractical in most clinical settings
- Cell count and culture of expressed prostatic secretions
- Prostate-specific antigen (PSA) is not used to diagnose prostatitis and is not recommended unless a nodule is present on digital examination. A rapid rise over baseline should raise the possibility of prostatitis even in the absence of symptoms. In such cases, a follow-up PSA after treatment of prostatitis is appropriate
- Complete blood count and blood cultures if fever, chills, or signs of sepsis exist

TABLE 1 Classification System for the Prostatitis Syndromes

Traditional	National Institutes of Health	Description
Acute bacterial prostatitis	Category I	Acute infection of the prostate gland
Chronic bacterial prostatitis	Category II	Chronic infection of the prostate gland
N/A	Category III Chronic pelvic pain syndrome (CPPS)	Chronic genitourinary pain in the absence of uropathogenic bacteria localized to the prostate gland employing standard methodology
Nonbacterial prostatitis	Category IIIA Inflammatory CPPS	Significant number of white blood cells in expressed prostatic secretions, postprostatic massage urine sediment (VB3), or semen
Prostatodynia	Category IIIB Noninflammatory CPPS	Insignificant number of white blood cells in expressed prostatic secretions, postprostatic massage urine sediment (VB3), or semen
N/A	Category IV Asymptomatic inflammatory prostatitis (AIP)	White blood cells (and/or bacteria) in expressed prostatic secretions, postprostatic massage urine sediment (VB3), semen, or histologic specimens of prostate gland

From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

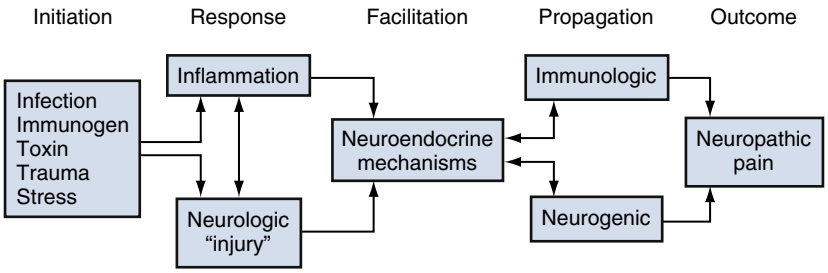

FIG. 1 The cause and pathogenesis of chronic prostatitis/chronic pelvic pain syndrome (category III chronic pelvic pain syndrome) appears to involve a pluricausal, multifactorial mechanism. An initiating stimulus, such as infection, reflux of some toxic or immunogenic urine substance, or perineal or pelvic trauma, starts a cascade of events in an anatomically or genetically susceptible man, resulting in a local response of inflammation or neurogenic injury or both. Further interrelated immunologic, neuropathic, endocrinologic, and psychologic mechanisms propagate or sustain the chronicity of the initial (or ongoing) event. The final outcome is the clinical manifestation of chronic perineal or pelvic pain and associated symptoms with local and central neuropathic mechanisms involving areas outside the prostate or pelvic area. (From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.)

BOX 1 Suggested Therapies for Chronic Prostatitis and Chronic Pelvic Pain Syndrome (National Institutes of Health Category III)

Recommended

1. α-Blocker therapy as part of a multimodal treatment strategy for newly diagnosed, α-blocker–naive patients who have voiding symptoms
2. Antimicrobial therapy trial for selected newly diagnosed, antimicrobial-naive patients
3. Selected phytotherapies: Cernilton and quercetin
4. Multimodal therapy directed by clinical phenotype
5. Directed physiotherapy. Although level 1 evidence is not available, evidence from multiple weak trials and vast clinical experience strongly suggests benefit for selected patients

Not Recommended

1. α-Blocker monotherapy, particularly in patients previously treated with α-blockers
2. Antiinflammatory monotherapy
3. Antimicrobial therapy as primary therapy, particularly for patients in whom treatment with antibiotics has previously failed
4. 5α-Reductase inhibitor monotherapy; can be considered in older patients with coexisting benign prostatic hyperplasia
5. Most minimally invasive therapies such as transurethral needle ablation (TUNA), laser therapies
6. Invasive surgical therapies such as transurethral resection of the prostate (TURP) and radical prostatectomy

Requiring Further Evaluation

1. Low-intensity shock wave treatment
2. Acupuncture
3. Biofeedback
4. Invasive neuromodulation (e.g., pudendal nerve modulation)
5. Electromagnetic stimulation
6. Botulinum toxin A injection
7. Medical therapies including mepartricin, muscle relaxants, neuromodulators, and immunomodulators

Modified from Nickel JC et al: Male chronic pelvic pain syndrome (CPPS). In Chapple C, Abrams P [eds]: *Male lower urinary tract symptoms (LUTS). An international consultation on male LUTS, Fukuoka, Japan, Sept 30–Oct 4, 2012*, Montreal, 2013, Société Internationale d'Urologie. From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.

Rx TREATMENT

- Acute bacterial prostatitis:
  1. Uncomplicated (with risk of STD, age <35 yr): Ceftriaxone 250 mg IM × 1 dose *or* cefixime 400 mg PO × 1 *then* doxycycline 100 mg bid × 10 days.
  2. Uncomplicated with low risk of STD: Levofloxacin 500 mg qid or ciprofloxacin 500 mg bid × 10 to 14 days.
- Chronic bacterial prostatitis:
  1. First-line choice is a quinolone (ciprofloxacin or levofloxacin) for 4 wk.
  2. Trimethoprim-sulfamethoxazole (TMP-SMX) is second-line choice for 1 to 3 mo if the organism is sensitive. Tissue penetration for TMP-SMX is not as good as quinolones, and there is evidence of increasing uropathogenic resistance.
- CP/CPPS:
  1. Suggested therapies for CP/CPPS are summarized in Box 1.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Prostatitis (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Anothaisintawee T et al: Management of chronic prostatitis/chronic pelvic pain syndrome, *JAMA* 305(1):78-86, 2011.

Coker TJ, Dierfeldt DM: Acute bacterial prostatitis: diagnosis and management, *Am Fam Physician* 93(2):114-120, 2016.

Holt JD et al: Common questions about chronic prostatitis, *Am Fam Physician* 93(40):290-296, 2016.

Shoskes DA et al: Phenotypically directed multimodal therapy for chronic prostatitis/chronic pain syndrome, *Urology* 75(6):1249-1253, 2010.

BASIC INFORMATION

DEFINITION

Pruritus ani refers to an intense chronic itching of the anus and perianal skin.

SYNONYM

Anal neurodermatitis

ICD-10CM CODE
L29.0 Pruritus ani

EPIDEMIOLOGY & DEMOGRAPHICS

- Any age can be affected
- Occurs in 1% to 5% of the population
- Male:female predominance of 4:1
- Many of these patients may not present to care
- More common in ages 40 to 60s

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Anal itching
- Anal fissures
- Hemorrhoids
- Excoriations
- Pinworms
- Fecal incontinence

ETIOLOGY

Anorectal diseases and fecal contamination:
- Diarrhea
- Anal incontinence
- Prolapsed internal hemorrhoids
- Fissures
- Fistulae
- Rectal prolapse
- Malignancy: Bowen disease, epidermoid cancer, perianal Paget disease

Infections:
- Fungal: Candidiasis, dermatophytes
- Parasitic: Pinworms, scabies
- Bacterial: *Staphylococcus aureus,* erythrasma
- Lymphogranuloma venereum, granuloma inguinale, chancroid
- Molluscum contagiosum
- Herpes, gonococcal syphilis, human papillomavirus, trichomoniasis

Local irritants:
- Moisture, obesity, excessive perspiration
- Soaps, hygiene products
- Toilet paper: Perfumed, dyed
- Underwear: Irritating fabrics, detergents
- Anal creams, suppositories
- Dietary: Coffee, beer, acidic foods
- Drugs: Mineral oil, ascorbic acid, hydrocortisone sodium succinate, quinine, colchicine

Dermatologic diseases:
- Inverse psoriasis
- Atopic dermatitis
- Seborrheic dermatitis
- Hidradenitis suppurativa

Squamous cell carcinoma or adenocarcinoma
- Contact dermatitis

Section II also describes the various causes of pruritus ani.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Allergies
- Anxiety
- Dermatologic conditions
- Infections
- Parasites
- Diabetes mellitus
- Chronic liver disease
- Neoplasia
- Proctalgia fugax

WORKUP

- Detailed history regarding bowel habits, hygiene, use of perfumed products, changes in diet, and medical history
- Inspection of perianal area
- Possible biopsy to exclude neoplasia
- Palpation of inguinal lymph nodes (if present suggestive of neoplasia)
- Microscopic inspection of scrapings
- Colposcopy

LABORATORY TESTS

- CBC, comprehensive metabolic panel (CMP) thyroid stimulating hormone (TSH)
- Urinalysis
- Cultures
- Stool for ova and parasites
- Tape test
- HIV test if risk factors are present
- Glucose tolerance test, if necessary

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of tight, nonbreathable clothing and underclothing
- Discontinuation or curtailment of coffee, beer, citrus fruits, tomatoes, chocolate, and tea. Dietary modification is frequently recommended, although its effectiveness has not been established. Cleansing of anal area after bowel movements with a premoistened pad or tissue and avoidance of perfumes and dyes present in toilet paper and soaps
- Avoidance of excessive perspiration
- Aggressive management of fecal leakage or incontinence to avoid soiling of perianal skin

ACUTE GENERAL Rx

- Minimization of frequent loose stools with antidiarrheals and fiber agents if appropriate
- Use of a 1% hydrocortisone cream sparingly bid during the acute phase of pruritus ani but not for >2 wk to avoid atrophy
- Protective ointments such as zinc oxide may be helpful
- For nighttime symptoms, an antihistamine taken orally to help quell itching
- Treatment of predisposing factors, such as parasites, diabetes, liver disease, hemorrhoids, and other infections

CHRONIC Rx

- Possible complications: Excoriation and secondary bacterial infection; must be treated aggressively
- Longstanding, intractable pruritus ani: Good response to topical capsaicin (depletes substance P) or intracutaneous injections of methylene blue (kills nerve endings), or steroid injections

DISPOSITION

- Usually good results with total resolution of symptoms
- In some, persistent and recurrent symptoms—these patients should be carefully reassessed for an underlying cause, and may require additional laboratory testing

REFERRAL

To colorectal specialist if conservative measures fail or if patient experiences rectal bleeding or change in bowel movements

RELATED CONTENT

Anal Itching (Patient Information)
Hemorrhoids (Related Key Topic)
Pinworms (Related Key Topic)

AUTHORS: **Anthony Sciscione, DO,** and **Gina Ranieri, DO**

SUGGESTED READINGS

Markell KW et al: Pruritus ani, *Surg Clin North Am* 90:125-135, 2010.
Nasseri YY et al: Pruritus ani: diagnosis and treatment, *Gastroenterol Clin North Am* 42:801-813, 2013.
Schaffer et al: Itching for a diagnosis, *N Engl J Med* 372:864-881, 2016.
Yosipovitch G, Bernhard JD: Chronic pruritus, *N Engl J Med* 372:964-968, 2015.

Pruritus Vulvae ALG

BASIC INFORMATION

DEFINITION

Pruritus vulvae refers to intense itching of the female external genitalia.

SYNONYMS

Lichen simplex chronicus
Atopic dermatitis
Squamous cell hyperplasia
Eczema

ICD-10CM CODES

L28.0 Lichen simplex chronicus
L29.2 Pruritus vulvae
L29.3 Anogenital pruritus, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- A disorder that can affect women at any age, including children.
- Lichen simplex is a common cause of itching in the anogenital area.
- Postmenopausal women: Frequently affected because of hypoestrogenic state (thinned skin is more susceptible to irritants).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Unrelenting, intense itching or burning of the vulva or anogenital skin.
- Scratching provides initial relief, but chronic scratching and rubbing exacerbates the sensation of itching.
- Itching can wake patients from sleep, and nighttime scratching is common.
- Physical findings often include erythema; erythematous plaques; papules; thickened, sometimes leathery-appearing skin; erosions and fissures from scratching; and pigment change (hyperpigmentation and hypopigmentation).

ETIOLOGY

- Severe pruritus is probably caused by triggering of terminal nerve fibers in a disrupted epidermal barrier layer (caused by inflammation, irritants, infection, scratching, etc.).
- The severe itching and skin changes in lichen simplex are the end result of chronic scratching and rubbing. This is in response to a number of initiating triggers, including environmental causes, infectious causes, and other underlying or associated skin conditions. Noninfectious causes of itching are more common in chronic itching. Environmental causes include heat, tight clothing, sweat, urine, moist toilet wipes, menstrual or urinary incontinence pads, panty liners, benzocaine, contraceptive gels, vaginal medications, feminine hygiene products, and soap.
- Infectious causes of itching include yeast, herpes simplex, condylomata acuminata, and molluscum contagiosum.
- Other causes:
  1. Neoplasms such as vulvar intraepithelial neoplasia (VIN), Paget disease, and squamous cell carcinoma
  2. Vulvar or vaginal atrophy
  3. Infestations with scabies, pediculosis pubis, or pinworms
- Children typically have nonspecific pruritus, lichen sclerosus, bacterial infections, or pinworm infestation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Contact or irritant dermatitis
- Vaginitis (yeast, trichomonas)
- Vulvar dermatoses, including lichen sclerosus, lichen planus, psoriasis
- VIN
- Pinworms
- Vulvar cancer
- Syringoma of the vulva

WORKUP

- Inspection of vulva and perianal area for skin texture change, erythema, papules, fissures, ulcerations, erosions, induration, or plaques.
- Must rule out infections, including trichomoniasis, candidiasis, and bacterial vaginosis with vaginal exam.

LABORATORY TESTS

- pH and wet prep of saline and potassium hydroxide of vaginal discharge
- Vaginal cultures
- Biopsy when needed (punch biopsy commonly used), especially if symptoms persist despite therapy, or if diagnosis is unclear
- Tape test to look for pinworms

TREATMENT

NONPHARMACOLOGIC THERAPY

- Stop scratching.
- Avoid excessive washing: Use plain water to gently wash.
- Wear loose-fitting clothing.
- Soak at comfortable temperature, and then apply barrier such as petrolatum or zinc oxide paste.
- Cool gel packs.
- Avoid perfumes; feminine hygiene products, including pads (if possible); benzocaine; antibiotic ointments; and body creams over vulvar area because they can cause irritation.
- Reduce stress and address psychological component.

ACUTE GENERAL Rx

- Local application of corticosteroids:
  1. One of the high- or medium-potency corticosteroids (such as 0.05% clobetasol ointment or 0.05% fluocinonide ointment) can be used to relieve itching.
  2. Apply to vulva twice daily for 2 to 4 wk, then once daily for 2 to 4 wk, and then three times weekly for 2 to 4 wk.
- Once itching is controlled, high-potency steroid can be discontinued and patient can be switched to hydrocortisone preparation to use intermittently.
- Stop itching and scratching, especially nighttime scratching, with hydroxyzine or diphenhydramine (1 to 25 mg, can increase to 50 mg) before bedtime.
- Selective serotonin reuptake inhibitors (SSRIs) may be helpful.
- Need to treat other underlying problems:
  1. Yeast infection: Any of the vaginal antifungal creams or fluconazole 150 mg every 3 days for three doses. Children and menopausal women not on estrogen are less likely to have yeast as cause.
  2. Trichomoniasis or bacterial vaginosis: Metronidazole 500 mg PO bid for 7 days.
  3. Antibiotics for superimposed infection—dicloxacillin 250 to 500 mg four times daily for 10 days, or treatment based on culture results.
  4. Urinary tract infection: Treatment of specific organism.
  5. Vaginal estrogen replacement therapy if atrophy is the cause of pruritus or burning.
  6. Pinworms: Mebendazole 100 mg 1 tablet at diagnosis and repeated in 1 to 2 wk; also treat other members in family aged >2 yr.
  7. Lichen sclerosus: High-potency topical steroid ointment such as clobetasol propionate ointment 0.05% applied twice daily until skin appearance/texture improves (several mo), and then can decrease to 3 times weekly.

CHRONIC Rx

- If not relieved by topical measures: Intradermal injection of triamcinolone (10 mg/ml diluted 2:1 saline); 0.1 ml of the suspension injected at 1-cm intervals and tissue gently massaged.
- If symptoms still uncontrollable: Consider systemic steroids, prednisone, or prednisolone, 40 mg daily for 7 days and then 20 mg daily for 7 days.

DISPOSITION

Usually controlled with conservative measures and topical steroids.

REFERRAL

- To a gynecologist for further workup if conservative measures do not give relief.
- When burning rather than itching predominates, the patient should be evaluated for vulvar dermatoses, vulvodynia, or signs of sensory neuropathy.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Lichen Sclerosus (Related Key Topic)
Vaginitis, Estrogen-Deficient (Related Key Topic)
Vaginitis, Fungal (Related Key Topic)
Vaginitis, Prepubescent (Related Key Topic)f
Vaginitis, Trichomonas (Related Key Topic)

AUTHORS: **Anthony Sciscione, DO,** and **Helen Toma, MD, MSPH**

SUGGESTED READINGS

Caro-Bruce E: Vulvar pruritus in a postmenopausal woman, *CMAJ (Can Med Assoc J)* 186:688-689, 2014.

Margesson L: Overview of treatment of vulvovaginal disease, *Skin Therapy Lett* 16(3):5-7, 2011.

Vulvovaginal disorders: an algorithm for basic adult diagnosis and treatment, vulvovaginaldisorders.com.

Psittacosis

BASIC INFORMATION

DEFINITION

Psittacosis is a systemic infection caused by the bacterium *Chlamydophila psittaci* (formerly known as *Chlamydia psittaci*) and is predominantly transmitted by birds.

SYNONYMS

Ornithosis
Parrot pneumonia

ICD-10CM CODE
A70 *Chlamydia psittaci* infections

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- In 2014, only eight cases were reported in the U.S. compared with an average of 10 cases (range 2 to 21) reported annually from 2005 to 2011. However, there was an outbreak of 13 cases in 2018 in Georgia and Virginia among poultry workers in two separate poultry slaughterhouses owned by the same corporation.
- True incidence is probably higher because infections may be subclinical.
- Highest incidence among pet owners and people working with birds.

PEAK INCIDENCE: Age 30 to 60 yr
PREVALENCE (IN U.S.):

- Low among humans.
- More than 130 avian species serve as hosts of the bacterium, and between 5% and 8% of birds, including poultry, seagulls, and geese, carry the organism.
- Most human infections are from birds of the order Psittaciformes, which includes cockatiels, parrots, cockatoos, and budgerigars.

PREDOMINANT SEX: Equal sex distribution
PREDOMINANT AGE: More common in adults

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation period of 5 to 15 days
- Subclinical infection
- Onset abrupt or insidious
- Most common symptoms:
  1. Fever
  2. Myalgias
  3. Chills
  4. Cough
- Most common clinical syndrome: Atypical pneumonia with fever, headache, dry cough, and a chest radiograph more dramatically abnormal than the physical examination
- Ranges from mild disease to respiratory failure and death, although this is extremely unusual
- Other clinical presentations:
  1. Mononucleosis-like syndrome
  2. Typhoidal form
- Most frequent physical findings:
  1. Fever
  2. Pharyngeal erythema
  3. Rales
  4. Hepatomegaly
- Less common findings:
  1. Somnolence
  2. Confusion
  3. Relative bradycardia
  4. Pleural rub
  5. Adenopathy
  6. Splenomegaly
  7. Horder spots (pink blanching maculopapular rash)
- Besides the lungs, other specific end-organ involvement:
  1. Pericarditis
  2. Myocarditis
  3. Endocarditis
  4. Hepatitis
  5. Joints
  6. Kidneys (glomerulonephritis)
  7. Central nervous system

ETIOLOGY

- *C. psittaci* is an obligate intracellular bacterium.
- Infection is usually spread by the respiratory route from infected birds, by direct contact or aerosolization of dried feces or bird feather dust, and rarely from a bite.
- There is a history of exposure to birds in 85% of patients, mostly with birds as pets.
- Strains from turkeys and psittacine birds are most virulent for human beings.
- Cows, goats, and sheep are occasionally implicated.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- *Legionella*
- *Mycoplasma*
- *Chlamydophila pneumoniae*
- Viral respiratory infections
- Typhoid fever
- Viral hepatitis
- Aseptic meningitis
- Mononucleosis

WORKUP

- Complete blood count, and renal and liver function tests
- *Chlamydophila* serology
- Chest x-ray
- Special immunostaining of respiratory secretions

LABORATORY TESTS

- White blood count is normal or slightly elevated
- ESR and C-reactive protein are generally elevated
- Mild liver function abnormalities are common (50%)
- Blood cultures are almost always negative
- Highly infectious in cultures and thus a biohazard to laboratory workers, and so specialized laboratories are required
- Studies on respiratory secretions:
  1. Direct immunofluorescent antibody of respiratory secretions with monoclonal antibodies to chlamydial antigens
  2. *Chlamydophila* lipopolysaccharide antigen by enzyme immunoassay
  3. Polymerase chain reaction can be done on respiratory secretions and also possibly on blood, sputum, and even urine
- Serologic studies:
  1. Complement-fixing (CF) antibodies
  2. Microimmunofluorescence (MIF) antibody test: Specialty labs only
  3. Possible false-negative results and cross-reaction with other chlamydial species with both techniques

IMAGING STUDIES

- Chest x-ray is abnormal in 50% to 90% with a variety of patterns.
- Pleural effusions are common.

TREATMENT

ACUTE GENERAL Rx

- Doxycycline (100 mg PO bid) for 10 to 14 days after fever declines *or*
- Tetracycline (500 mg PO qid)
- Macrolides, such as erythromycin or azithromycin, are considered second-line agents in adults but first-line agents in children
- Quinolones, such as ciprofloxacin and moxifloxacin, are effective in vitro, but more studies are needed for clinical use

CHRONIC Rx

In the rare cases of endocarditis, combination of heart valve replacement and prolonged antibiotic course may be the treatment of choice.

DISPOSITION

- Mortality rate is low (0.7%)
- Poor prognostic factors:
  1. Advanced age
  2. Leukopenia
  3. Severe hypoxemia
  4. Renal failure
  5. Confusion
  6. Multilobe pulmonary involvement
- Possible reinfection

REFERRAL

- To infectious disease expert:
  1. Complicated atypical pneumonia or other end-organ involvement
  2. Suspicion of an outbreak
- To pulmonologist for diagnostic bronchoscopy

PEARLS & CONSIDERATIONS

COMMENTS

- Hospitalized patients do not require specific isolation precautions.
- Any confirmed or suspected case of psittacosis should be reported to public health authorities.
- Recent evidence indicates that *C. psittaci* may be associated with induction of a rare form of lymphoma found in the ocular adnexa; case reports have described regression of ocular lymphoma with antibiotic treatment for *C. psittaci.*

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READING

Hogerwerf L et al: Chlamydia psittaci (psittacosis) as a cause of community-acquired pneumonia: a systematic review and meta-analysis, *Epidemiol Infect* 145:3096-3105, 2017.

Knittler MR, Sachse K: Chlamydia psittaci: update on an underestimated zoonotic agent, *Pathog Dis* 73:1-15, 2015.

Nieuwenhuizen AA et al: Laboratory methods for case finding in human psittacosis outbreaks: a systematic review, *BMC Infect Dis* 18:442, 2018.

Stewardson AJ, Grayson MK: Psittacosis, *Infect Dis Clin North Am* 24(1):7-25, 2010.

BASIC INFORMATION

DEFINITION

Psoriasis is a chronic skin disorder characterized by excessive proliferation of keratinocytes, resulting in the formation of thickened scaly plaques, itching, and inflammatory changes of the epidermis and dermis. Psoriasis is also associated with cardiovascular, metabolic, and neuropsychiatric effects. The various forms of psoriasis include plaque (most common), guttate, erythrodermic, pustular, inverse, and arthritis variants.

ICD-10CM CODES

L40	Psoriasis
L40.0	Psoriasis vulgaris
L40.1	Generalized pustular psoriasis
L40.4	Guttate psoriasis
L40.8	Other psoriasis
L40.9	Psoriasis unspecified
L40.54	Psoriatic juvenile arthropathy

EPIDEMIOLOGY & DEMOGRAPHICS

- Psoriasis affects 2% to 4% of the world's population. Most patients have limited psoriasis involving <5% of their body surface.
- There is a strong association between psoriasis and human leukocyte antigens (HLAs) B13, B17, and B27 (pustular psoriasis).
- Peak age of onset is bimodal (age 30 to 39 yr and at age 60 yr). Mean age at diagnosis is 34 yr.
- Men and women are affected equally. Approximately 20% of patients with psoriasis also have psoriatic arthritis. Median time from development of joint symptoms to diagnosis of psoriatic arthritis is 5 yr. Nail psoriasis affects over 50% of patients with psoriasis and can occur with any of the subtypes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Approximately 85% of patients with psoriasis have mild-to-moderate disease.
- The primary psoriatic lesion is an erythematous papule topped by a loosely adherent scale. Scraping the scale results in several bleeding points *(Auspitz sign).*
- Chronic plaque psoriasis generally manifests with symmetric, sharply demarcated, erythematous, silver-scaled patches affecting primarily the intergluteal folds, elbows, scalp, fingernails, toenails, and knees (Figs. 1 and 2). This form accounts for 80% of psoriasis cases. Psoriasis may also involve the forehead, particularly contiguous to the scalp (Fig. E3).
- Psoriasis can also develop at the site of any physical trauma (sunburn, scratching). This is known as *Koebner phenomenon.*
- Nail involvement is common (pitting of the nail plate), resulting in hyperkeratosis, onychodystrophy with onycholysis (Fig. E4).
- Pruritus is variable; soreness and bleeding may occur.
- Joint involvement can result in sacroiliitis and spondylitis.
- Guttate psoriasis is generally preceded by streptococcal pharyngitis and manifests with multiple droplike lesions on the extremities and the trunk.
- Erythrodermic psoriasis is characterized by widespread cutaneous erythema and scaling.
- Pustular psoriasis manifests with widespread pustules. Localized forms may affect palms and soles.
- Inverse psoriasis is characterized by red and sharply demarcated thinner patches involving intertriginous areas (axillae, inguinal areas).
- Adverse effect on psychological and social functioning, with affected persons often feeling stigmatized.

ETIOLOGY

- Unknown, but there is a strong genetic component and high heritability. There are at least nine chromosomal loci with linkage to psoriasis. These loci are called psoriasis susceptibility 1 through 9 (PSORS1-PSORS9). PSORS1 locus in the major histocompatibility complex (MHC) region on chromosome 6 is considered the most important susceptibility locus and is believed to account for 35% to 50% of the heritability of the disease.
- Familial clustering (genetic transmission with a dominant mode with variable penetrants).
- One third of persons affected have a positive family history.
- A high prevalence of celiac disease has been noted in patients with psoriasis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Contact dermatitis
- Atopic dermatitis
- Stasis dermatitis
- Tinea
- Nummular dermatitis
- Candidiasis
- Mycosis fungoides, Sezary syndrome
- Cutaneous systemic lupus erythematosus
- Secondary and tertiary syphilis
- Drug eruption
- Dermatomyositis (DM)

FIG. 1 Psoriasis. Variably sized erythematous plaques with moderately thick overlying scale. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

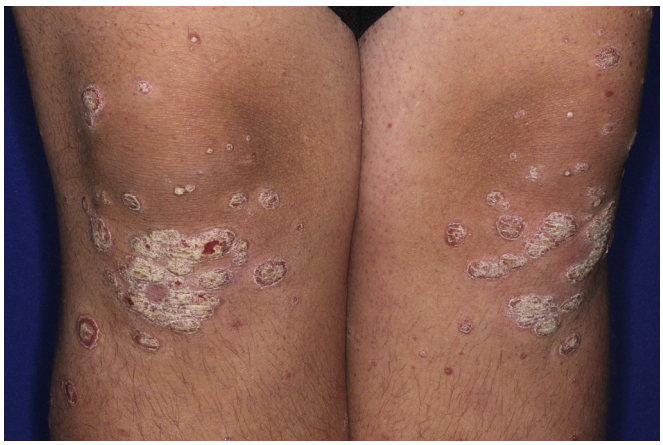

FIG. 2 Typical plaques of psoriasis with thick, micaceous scale overlying erythema. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, 2016, Elsevier.)

- Lupus erythematosus (LE)
- Seborrheic dermatitis
- Pityriasis rosea
- Lichen planus
- Pityriasis rubra pilaris

WORKUP

- Diagnosis is clinical. Blood work is rarely needed. A rapid plasma regain test is useful when ruling out syphilis. Antinuclear antibody (ANA) and anti-Ro and anti-La antibodies are helpful in ruling out subacute cutaneous lupus.
- Skin biopsy is rarely necessary.

LABORATORY TESTS

Generally not necessary for diagnosis

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Sunbathing generally leads to improvement.
- Eliminate triggering factors (e.g., stress, certain medications [e.g., lithium, beta-blockers, antimalarials]). Severe emotional stress tends to aggravate psoriasis.
- Patients with psoriasis benefit from a daily bath in warm water followed by application of a cream or ointment moisturizer. Regular use of an emollient moisturizer limits evaporation of water from the skin and allows the stratum corneum to rehydrate itself.
- Psoralen and ultraviolet A (PUVA) therapy (see "General Rx").
- Local hyperthermia has been used successfully to clear psoriatic plaques, but relapse is common.
- Occlusive treatment with surgical tape or dressings is effective as monotherapy or in combination with topical medications.
- Avoidance of tobacco. Smoking tobacco may worsen psoriasis.

GENERAL Rx

Therapeutic options vary according to the extent of disease. Approximately 70% to 80% of all patients can be treated adequately with topical therapy.

- Patients with limited disease (<20% of the body) can be treated with the following:
  1. Topical steroids: Disadvantages are brief remissions, expense, and decreased effect with continued use. Salicylic acid can be compounded by pharmacist in concentrations of 2% to 10% and used in combination with a corticosteroid to decrease the amount of scale.
  2. Calcipotriene: A vitamin D analogue effective for moderate plaque psoriasis. Adults should comb the hair, apply solution to the lesions, and rub it in, avoiding uninvolved skin. Disadvantages include its cost and potential burning and skin irritation. It should not be used concurrently with salicylic acid because calcipotriene is inactivated by the acidic nature of salicylic acid. Taclonex ointment and Enstilar aerosol foam formulation are a combination of calcipotriene and the high-potency corticosteroid betamethasone dipropionate. They are well tolerated and more effective than either agent used alone but also much more expensive.
  3. Tar products (Estar, liquor carbonis detergens [LCD], Psorigel) can be used overnight and are most effective when combined with ultraviolet B (UVB) light (Goeckerman regimen).
  4. Anthralin: Useful for chronic plaques; can result in purple-brown staining; best used with UVB light.
  5. Retinoids such as tazarotene 0.05%, 0.1% cream or gel, are effective in thinning plaques but are expensive and can cause irritation.
  6. Other useful measures include tape or occlusive dressing, UVB and lubricating agents, and interlesional steroids.
- Therapeutic options for persons with generalized disease (affecting >20% of the body) and for those with inadequate response to topical agents:
  1. UVB light exposure three times a wk: This therapy does not require administration of a systemic drug (unlike psoralen plus ultraviolet A [PUVA]), but to be effective, it requires removal of scale with keratolytic agents and emollients.
  2. Oral PUVA administered two to three times weekly is effective for generalized disease. It is often considered in patients for whom narrow-band UVB therapy is ineffective. However, many PUVA treatments are required, necessitating frequent office visits, and it may be associated with phototoxicity, such as erythema and blistering, and increased risk of skin cancer.
- Systemic treatments include methotrexate 25 mg/wk for severe psoriasis. Etretinate (a synthetic retinoid) is most effective for palmar-plantar pustular psoriasis. Dose is 0.5 to 1 mg/kg/day. It can cause liver enzyme and lipid abnormalities and is teratogenic.
- Apremilast is a phosphodiesterase type-4 inhibitor used in moderate to severe plaque psoriasis. Side effects include diarrhea, nausea, headache, and worsening depression.
- Cyclosporine is also effective in severe psoriasis; however, relapses are common.
- Chronic plaque psoriasis may be treated with alefacept, a recombinant protein that selectively targets T lymphocytes. Treatment with alefacept for 12 wk (0.025, 0.075, or 0.150 mg/kg of body weight IV weekly) may result in significant improvement. Some patients also demonstrate a sustained clinical response after the cessation of treatment. This medication is very expensive (a 12-wk course can cost >$8000).
- Biologic therapies are now routinely used when traditional systemic agents are ineffective or poorly tolerated. Screening for tuberculosis is necessary before initiating treatment with these agents. Active, serious infection is a contraindication to the use of biologics.
- Tumor necrosis factor (TNF) inhibitors (adalimumab [Humira], etanercept [Enbrel], infliximab [Remicade]): Trials revealed a reduction in severity of plaque psoriasis. Efalizumab, a humanized monoclonal antibody that inhibits the activation of T cells, has also been reported to produce significant improvement in plaque psoriasis treatment period. Adalimumab has been reported to be effective for joint and skin manifestations of psoriasis.
- Newer biologic agents in patients with moderate to severe plaque psoriasis are ustekinumab (Stelara; an interleukin-12 and interleukin-23 blocker), brodalumab (SILIQ), ixekizumab (Taltz), secukinumab (Cosentyx) anti–interleukin-17 receptor antagonists, and guselkumab (Tremfya), risankizumab (Skyrizi), and tildrakizumab (ILUMYA) interleukin-23 blockers. Cost is a limiting factor with all these agents.

DISPOSITION

The course of psoriasis is chronic, and the disease may be refractory to treatment.

REFERRAL

- Dermatology referral is recommended in all patients with generalized disease.
- Hospital admission may be necessary for severe diffuse or poorly responsive psoriasis. The Goeckerman regimen combines daily application of tar with UVB exposure and can result in prolonged remissions.

PEARLS & CONSIDERATIONS

COMMENTS

Psoriasis is more emotionally than physically disabling for most patients. Counseling may be indicated, particularly when it affects younger patients.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Psoriasis (Patient Information)
Psoriatic Arthritis (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Griffiths C et al: Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis, *N Engl J Med* 362:118-128, 2010.

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Papp KA et al: Brodalumab, an anti-interleukin 17 receptor antibody for psoriasis, *N Engl J Med* 366:1181-1189, 2012.

Reich K et al: A 52-week trial comparing briakinumab with methotrexate in patients with psoriasis, *N Engl J Med* 365:1586-1596, 2011.

FIG. E3 Psoriasis often involves the forehead, particularly contiguous to the scalp. Note the eyelid and brow involvement. Given the yellowish scaling, this has been called "sebopsoriasis." (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, 2016, Elsevier.)

FIG. E4 Nail psoriasis. Several fingers show severe onycholysis with oil spots and nail pitting, accentuated where the pits trapped old nail polish. Having just a few nails involved is common. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Psoriatic arthritis (PsA) is an inflammatory arthropathy, often included in a class of disorders called the *seronegative spondyloarthropathies (SpA),* a family of diseases characterized by inflammation of the spine, peripheral joints, and entheses (sites of insertion of tendon into bone). Both the Moll and Wright and CASPAR classification criteria are described in Table1.

ICD-10CM CODES

L40.5+	Arthropathic psoriasis
L40.54	Psoriatic juvenile arthropathy
L40.52	Psoriatic arthritis mutilans

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 6 per 100,000 per yr
PREVALENCE: One to two per 1000 in the general population. Variable estimates of 4% to 30% of patients with underlying psoriasis
PREDOMINANT SEX: Equal male-to-female distribution
PREDOMINANT AGE: Symptom onset generally between age 30 to 55

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Psoriasis precedes arthritis in 67% of cases by an average of 8 to 10 yr.
- Arthritis precedes psoriasis or occurs concomitantly in 33% of patients.
- Arthritis, dactylitis, spondylitis, and enthesitis are main features.
- On examination, about 15% of patients will have psoriasis without prior diagnosis of skin disease.
- Arthritis is inflammatory, commonly characterized by prolonged morning stiffness, improvement with activity, joint erythema, warmth, or swelling.
- There are five classically described patterns of joint involvement (Box 1).
- Some patients may present with more than one pattern, and patterns can evolve over time. The distal interphalangeal (DIP) joints (Fig. E1) and spine are each affected in 40% to 50% of cases. It is rare to have spondyloarthritis alone, and it usually occurs with peripheral involvement.
- Dactylitis, also known as "sausage digit," refers to diffuse swelling of a finger or toe (Fig. E2); it is fairly common and occurs in approximately 30% to 40% of patients during the disease course. It is associated with increased risk of radiographic joint damage.
- Enthesitis commonly occurs at the Achilles and plantar fascia (Fig. E3), and swelling and tenderness may be seen on exam. Subclinical disease may be evident by ultrasonography.
- Dystrophic changes of the nails (pitting, onycholysis, leukonychia) may occur in association with joint inflammation in involved digits.
- Spondyloarthritis may include sacroiliitis but is generally less likely to cause fusion to the extent seen in ankylosing spondylitis. More common to have asymmetric sacroiliac joint involvement (usually bilateral in ankylosing spondylitis).
- Ocular inflammation including conjunctivitis and uveitis can be seen.

ETIOLOGY

Remains unknown, but felt to be interplay of genetic, immunologic, and environmental factors. Fig. E4 illustrates the pathogenetic pathways in PsA. There is a higher frequency of HLA-B12, HLA-B17, HLA_B57, HLA-Cw*0602 in PsA. Those with PsA versus psoriasis alone have higher frequency of HLA-B7, HLA-B27.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rheumatoid arthritis (RA)
- Erosive osteoarthritis
- Crystalline arthritis, including gout and pseudogout
- Other seronegative spondyloarthropathies, which include reactive arthritis, enteropathic arthritis, and ankylosing spondylitis (also see differential diagnosis of SpA in Section III)

WORKUP

- Diagnosis is generally made on clinical grounds based on history, exam, and radiographic findings given lack of specific lab findings. An algorithm for the diagnosis of psoriatic arthritis is described in Fig. 5.
- Early diagnosis can be difficult to establish when the joint symptoms develop before skin and nail findings.

LABORATORY TESTS

- No specific diagnostic lab tests.
- Acute phase reactants such as ESR and CRP may be elevated, although less commonly than in patients with rheumatoid arthritis.
- Anemia of chronic disease may be seen.
- Rheumatoid factor (RF) and anti-CCP are generally negative but can be present in up to 15% of patients.
- *HLA-B27* is significantly more common in patients with axial inflammation.
- Arthrocentesis generally demonstrates inflammatory synovial fluid without crystals.

BOX 1 Subtypes of Psoriatic Arthritis

- Distal interphalangeal joint–predominant arthritis (10%)
- Symmetric polyarthritis–predominant arthritis (5%-20%)
- Asymmetric oligoarthritis or monoarthritis (70%-80%)
- Axial disease predominant (spondylitis, sacroiliitis, or both) (5%-20%)
- Arthritis mutilans (rare)

From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

TABLE 1 Classifications of Psoriatic Arthritis

	CASPAR*		
Moll and Wright	**Points**	**Category**	**Description**
Presence of PsO and an inflammatory arthritis (peripheral arthritis and/or sacroiliitis or spondylitis)	2	Current PsO	Psoriatic skin or scalp disease confirmed by a dermatologist or rheumatologist; history of PsO from the patient, family physician, dermatologist, rheumatologist, or other qualified practitioner; patient-reported history of PsO in a first- or second-degree relative
	1	Personal or family history of PsO	
The (usual) absence of serologic tests for RF	1	Psoriatic nail dystrophy on current physical examination	Includes onycholysis, pitting, and hyperkeratosis
	1	Negative test for RF	ELISA or nephelometry preferred (no latex) using the local laboratory reference range
	1	Current dactylitis or history of dactylitis documented by a rheumatologist	Swelling of the entire digit
	1	Radiographic evidence of juxtaarticular new bone formation	Ill-defined ossification near joint margins in the hand or foot, excluding osteophyte formation on plain radiographs

*Psoriatic arthritis is diagnosed when three or more points are assigned in the presence of inflammatory articular disease (joint, spine, or entheseal).
CASPAR, Classification Criteria for the Study of Psoriatic Arthritis; *ELISA,* enzyme-linked immunosorbent assay; *PsO,* psoriasis; *RF*, rheumatoid factor.
From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

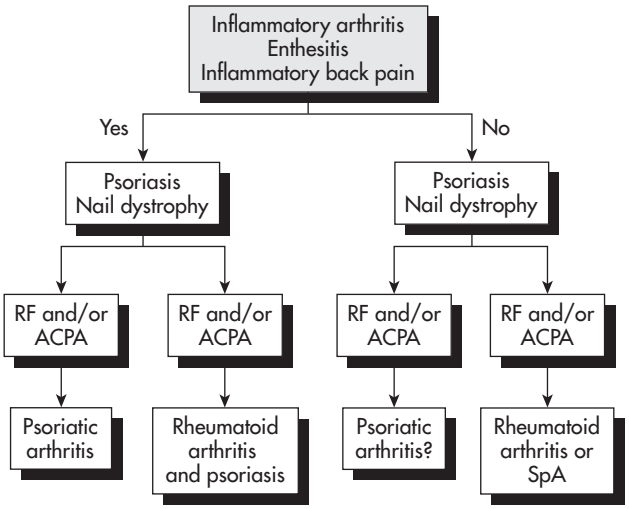

FIG. 5 Algorithm to be used in the diagnosis of individual patients presenting with possible psoriatic arthritis. Some patients may present with typical articular manifestations of psoriatic arthritis but in the absence of skin or nail disease. They can be diagnosed as having definite psoriatic arthritis only when psoriasis subsequently develops. *ACPA,* Anticitrullinated protein antibody; *RF,* rheumatoid factor; *SpA,* spondyloarthropathy. (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

IMAGING STUDIES

Radiographic findings of involved joints may include soft tissue swelling, joint space narrowing, subluxation, erosive changes, and new bone formation (periostitis, fusion). As opposed to RA, see more asymmetric joint involvement and DIP joint changes.

Severe digital erosive change with adjacent heterotopic bone formation may give rise to "pencil in cup" deformity. Can see whittling of the phalanges.

With axial involvement can see sacroiliac joint changes (sclerosis, erosions, pseudo-widening, ankylosis) and bridging vertebral syndesmophytes.

Musculoskeletal ultrasonography can be used in the evaluation of enthesitis or arthritis.

MRI may be helpful in further evaluation of sacroiliac and spinal involvement.

Rx TREATMENT

PHARMACOLOGIC THERAPY

The choice of therapeutic agent depends on the type of clinical manifestations, as not all agents are effective for all manifestations. For example, enthesis and spinal involvement are not responsive to traditional oral disease-modifying agents such as methotrexate or leflunomide but are responsive to tumor necrosis factor blocking agents (TNFi).

- NSAIDs may be used for mild or limited disease.
- Intraarticular corticosteroid injections can be used as adjunctive rx for involved joints.
- Oral glucocorticoids should generally be avoided, given increased risk for development of erythrodermic or pustular psoriasis.
- In patients with active peripheral joint disease, elevated acute phase reactants, or evidence of changes on imaging, traditional DMARDs such as methotrexate, sulfasalazine, and leflunomide should be considered early on, though data supporting their use is limited.
- Apremilast is an oral phosphodiesterase 4 (PDE 4) inhibitor and is safe to use, especially in those with multiple comorbidities. Can also be beneficial for enthesitis and dactylitis.
- In patients with peripheral arthritis who fail to respond to nonbiologic DMARDs, escalation of therapy should be considered. All five TNFi are FDA-approved to treat psoriatic arthritis (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol). In those resistant to a TNFi, a second TNFi can be tried. If adequate response is still not achieved, a different mechanism of action (IL-17i, IL-12/23 blockade) can be tried.
- Secukinumab, an IL-17 inhibitor, is approved to treat psoriasis, PsA, and AS. Ixekizumab, an anti-IL-17 monoclonal antibody, can also be used to treat psoriasis, PsA, and now AS. Brodalumab, an anti-IL17RA monoclonal antibody, treats psoriasis alone currently. Guselkumab, an anti-IL23 antibody, is also only approved for psoriasis.
- Ustekinumab is a human IgG monoclonal antibody that binds to the p40 subunit of interleukin (IL)-12 and -23 and is approved to treat psoriasis, psoriatic arthritis, and Crohns.
- Abatacept (selective T-cell costimulation modulator) was approved to treat PsA, but has shown limited efficacy in treatment of psoriasis but can help peripheral arthritis. Tofacitinib (oral Janus kinase inhibitor) has also been approved.
- In patients with predominantly axial disease not responsive to NSAIDs, TNFi or IL17i can be tried. For enthesitis/dactylitis TNFi, IL17i, IL12/23, and apremilast can be considered.

REFERRAL

Rheumatology, dermatology

PEARLS & CONSIDERATIONS

- Patients frequently have a positive family history of psoriasis or psoriatic arthritis.
- Severity of skin psoriasis and activity of inflammatory arthritis can be discordant.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Psoriatic Arthritis (Patient Information)

AUTHOR: **Daphne Scaramangas-Plumley, MD**

SUGGESTED READINGS

Gladman D et al: Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors, *N Engl J Med* 377:1525-1536, 2017.

McInnes IB et al: Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial, *Ann Rheum Dis* 73(2):349-356, 2014.

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Ritchlin CT et al: Psoriatic arthritis, *N Engl J Med* 376:957-970, 2017.

FIG. E1 Symmetric polyarthritis resembling rheumatoid arthritis. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

FIG. E2 Dactylitis of the second toe. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

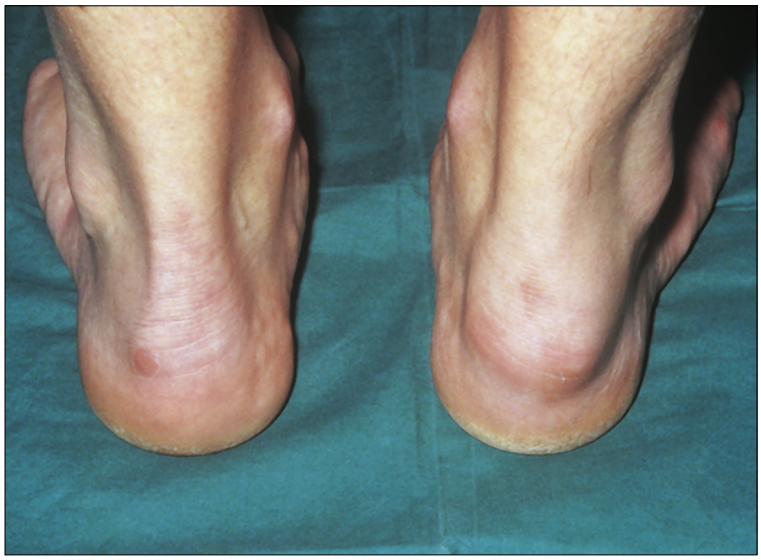

FIG. E3 Enthesitis involving the insertion of the right Achilles tendon. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

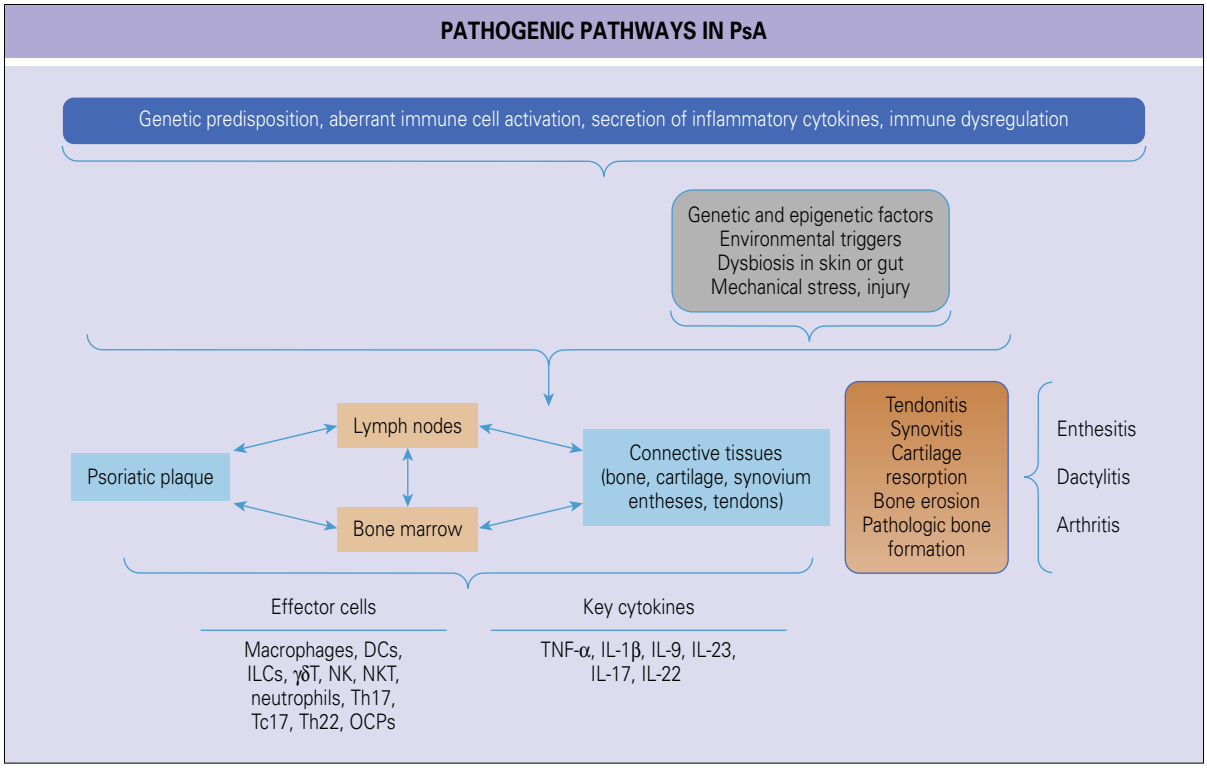

FIG. E4 Activation of Th1 and type 17 immune cells in genetically predisposed individuals by an array of poorly defined environmental factors results in psoriatic plaque formation. In a subset of patients with psoriasis, epigenetic and environmental events in patients with specific genetic risk variants result in musculoskeletal inflammation in an array of connective tissues. Effector cells are home to entheses and joints from the skin, lymph nodes, and bone marrow. They release cytokines that promote inflammation in tendon–ligament–synovial capsule insertion sites, tendons, synovium, and bone accompanied by bone and cartilage damage and pathologic new bone formation. The resulting clinical phenotypes manifest as enthesitis, synovitis, and dactylitis. *DC,* Dendritic cell; *ILC,* innate lymphocyte; *NK,* natural killer; *OCP,* osteoclast precursors; *Tc17,* CD8+ IL-17 secreting cell; *Th17,* CD4+ IL-17 secreting cell; *Th22,* IL-22 secreting CD4+ cell. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Psychosis is a state in which external reality is distorted by delusions and/or hallucinations (a delusion is a fixed false idiosyncratic belief; a hallucination is a false auditory, visual, olfactory, tactile, or taste perception).

Psychosis is a key finding in many mental illnesses, such as brief psychotic disorder, delusional disorder, schizoaffective disorder, schizophrenia, schizophreniform disorder, or shared psychotic disorder. Psychosis can also present as part of the evolution of a mood disorder (depression and bipolar disorder), a sign of an underlying medical condition, or a manifestation of a toxic state, i.e., abuse of substances or withdrawal state.

ICD-10CM CODES	
F05	Delirium not induced by alcohol and other psychoactive substances
F06.0	Organic hallucinosis
F09	Unspecified organic or symptomatic mental disorder
F10.5	Psychotic disorder due to psychoactive substance use
F30.2 and F31.2	Manic episode with psychosis and bipolar affective disorder with psychosis
F32.3	Major depressive disorder, single episode, severe with psychotic features
DSM-5 CODES	
Depends on specific diagnosis	

EPIDEMIOLOGY & DEMOGRAPHICS

1-yr prevalence: 4.5 per 1000. The (demographics of) psychosis depends on the underlying disorder.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

History:

- Past and current medical history important to identify potential medical etiologies
- Medication use
- Use of illicit substances or alcohol
- Identification of functional and social impairment
- Behavior that is odd or unpredictable; patient may be acting based on misinterpretation of their reality or false perceptions (delusions or hallucinations)

Examination:

- Examine for symptoms of:
  1. Mood disorder: Delusions or hallucinations are usually congruent with the mood (e.g., auditory hallucinations in a depressed patient may tell the patient what a terrible person he is)
  2. Altered or disorganized thought pattern: Usually reflected in disorganized speech (including word salad, thought blocking, rhyming, clang associations) or disorganized behavior
  3. Lack of insight into problems
  4. Signs of Parkinson disease, dementia

ETIOLOGY

- Involves an interaction among:
  1. Dopaminergic overactivity (particularly in the mesocortical, mesolimbic, and nigrostriatal systems)
  2. Environmental, social, or childhood factors
  3. Genetic predisposition

DIAGNOSIS

WORKUP

- Evaluate for potential confounding factors
- Underlying mental disorder: Schizophrenia, major depression, brief psychotic disorder, delusional disorder, schizoaffective disorder, schizophreniform disorder
- Underlying personality disorder: Borderline, paranoid, schizoid, schizotypal
- Underlying medical conditions: Infections ranging from urinary tract infections (UTIs) to HIV/AIDS, Parkinson disease, Huntington disease, leprosy, malaria, sarcoidosis, systemic lupus erythematosus, prion disease, hypoglycemia, postpartum state, cerebrovascular event, temporal lobe epilepsy, brain neoplasm
- Medications: Systemic steroids, anticonvulsants, antiparkinsonian medications, some chemotherapy, scopolamine
- Underlying dementia: Alzheimer disease, Lewy body dementia, vascular dementia
- Illicit drugs (usually with chronic use; can be caused by intoxication or withdrawal): lysergic acid diethylamide (LSD), phencyclidine (PCP), cocaine, gamma-hydroxybutyrate (GHB; withdrawal), alcohol, amphetamines, and marijuana. New substances of abuse (e.g., "bath salts," synthetic cannabinoids) may not be detected by current toxicology panels
- Traumatic brain injury
- Intensive care unit stay: Hypoxia, decreased cardiac output, infection, medications, sleep deprivation, alteration of diurnal cycle, sensory deprivation or overload, pain
- Emotional stress

LABORATORY TESTS

Consider checking chemistry panel (calcium), complete blood count, UA, liver function tests, cortisol, HIV, rapid plasma reagin, thyroid-stimulating hormone, vitamin B_{12} and folate levels, indirect unconjugated bilirubin, serum antinuclear antibody (ANA), serum angiotensin converting enzyme, toxicology screen, lumbar puncture (LP).

IMAGING STUDIES

Consider chest x-ray (rule out sarcoid), electroencephalography, head CT or MRI.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral therapy
- Social and behavioral skills training
- Training for self-management of disease
- Aforementioned strategies favored over psychoanalytic techniques given the relative inability for abstract thought and lack of insight in psychotic patients
- Family intervention, including education and strategies to reduce emotional expression
- Counseling for substance abuse

ACUTE GENERAL Rx

- Antipsychotics (first or second generation equally effective but different in side effect profile) consider combining with anticholinergics like benztropine to reduce motor side effects if such arise; low doses should control first episode. Use with caution in elderly patients because adverse effects limit effectiveness. Second-generation antipsychotics are also useful starting with low doses. Alternative formulations are available; e.g., rapid injectable form or oral disintegrating tablets. Obtain baseline lab work including lipid profile, glucose/A1c, CBC.
- Benzodiazepines for nonspecific sedation if agitation is severe.
- Discontinue offending medication if present.

CHRONIC Rx

Second-generation antipsychotics may reduce the incidence of tardive dyskinesia but may increase incidence of metabolic disorders compared with first-generation antipsychotics. Multicenter trials showed similar efficacy between first and second generation. Consider economic factors, including insurance formulary, when selecting a maintenance regimen.

DISPOSITION

Prognosis varies according to etiology of psychosis. In general, the more severe and longer the psychotic episode, the worse the prognosis.

REFERRAL

Patient should be admitted for acute stabilization if actively psychotic to prevent harm to self and others as well as ensure administration of medications.

PEARLS & CONSIDERATIONS

- Delusions and/or hallucinations are hallmarks of psychosis.
- Rule out medical or drug causes of psychosis.
- Antipsychotics are the mainstay of acute and chronic treatment.
- Brief psychotic disorder DSM-5 298.8 (F23) (brief reactive psychosis), which is a psychotic response to a severe stressor, usually responds well to low-dose neuroleptic treatment.
- Consider alternatives to antipsychotics in elderly or intellectually disabled patients (see "Nonpharmacologic Therapy").

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Psychosis (Patient Information)
Delirium (Related Key Topic)

AUTHORS: **Arnaldo A. Berges, MD**

SUGGESTED READINGS

Hackman DT et al: Prescription drug monitoring program inquiry in psychiatric assessment: detection of high rates of opioid prescribing to a dual diagnosis population, *J Clin Psychiatry* 75(7):750-756, 2014.

Leentjens AF et al: Delirium: an evidence-based medicine (EBM) monograph for psychosomatic medicine practice, commissioned by the Academy of Psychosomatic medicine (APM) and the European association of Consultation Liaison Psychiatry and Psychosomatics (EACLPP), *J Psychosom Res* 73(2):149-152, 2012.

Moreno C et al: Psychotic symptoms are associated with physical health problems independently of a mental disorder diagnosis: results from the WHO World Health Survey, *World Psychiatr* 12(3):251-257, 2012.

Wainwright LD et al: What do relatives experience when supporting someone in early psychosis? *Psychol Psychother*, 2014.

BASIC INFORMATION

DEFINITION

Acute cardiogenic pulmonary edema (ACPE) is a clinically observed consequence of increased capillary leakage of fluid into the interstitial space in the pulmonary vasculature, resulting in the constellation of clinical signs and symptoms of decreased gaseous exchange in the alveoli.

SYNONYMS

Cardiogenic pulmonary edema (CPE)
Acute cardiogenic pulmonary edema (ACPE)
Acute decompensated heart failure (ADHF) with pulmonary edema
Acute diastolic heart failure with pulmonary edema
Acute systolic heart failure with pulmonary edema

ICD-10CM CODES

I50.1	Left ventricular failure
J68.1	Pulmonary edema due to chemicals, gases, fumes and vapors
J81.0	Acute pulmonary edema
J81.1	Chronic pulmonary edema

EPIDEMIOLOGY & DEMOGRAPHICS

- The prevalence of heart failure (HF) is estimated around 6.5 million people and is expected to increase to 8 million by the yr 2030.
- In 2012, 1.7 million HF-related visits to U.S. physician offices, and half a million emergency department visits were reported.
- Within 30 days, 25% to 30% of these patients are readmitted with recurrent ADHF.
- In-hospital mortality rate is 10% to 20%, particularly when associated with acute MI.

CLINICAL PRESENTATION

- Altered mental status
- Dyspnea (exertional or at rest, paroxysmal nocturnal dyspnea, orthopnea)
- Cough and wheezing (cardiac asthma)
- Diaphoresis, cold and clammy skin
- Perioral and peripheral cyanosis
- Pink, frothy sputum

PHYSICAL EXAMINATION FINDINGS

- Hypertension (in cardiogenic shock could be hypotensive)
- Tachycardia
- Elevated jugular venous pressure with hepatojugular reflex
- Bilateral pulmonary rales/decreased or absent air entry
- S3 gallop/S4 and or laterally displaced apex
- Abdominal distention/ascites
- Peripheral edema
- Weight gain

ETIOLOGY

Common causes of acute pulmonary edema include the following:

- Acute myocardial infarction
- Poor dietary compliance or medication nonadherence
- Atrial and ventricular arrhythmias
- Valvular heart disease (mitral, aortic, tricuspid, and pulmonary valve disease)
- Renal and liver disease
- Endocrine (thyrotoxicosis, obesity, metabolic syndrome, diabetes)
- Toxin mediated (cocaine, alcohol, chemotherapy agents, ephedra)
- Peripartum cardiomyopathy/heart failure of pregnancy
- Infections (myopericarditis, endocarditis, HIV, Chagas)
- Uncontrolled hypertension
- Structural heart disease (ventricular septal defect, infiltrative heart disease, hypertrophic cardiomyopathy)
- Pulmonary embolism
- Box 1 summarizes common causes of cardiogenic and noncardiogenic pulmonary edema

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Noncardiogenic pulmonary edema (see Fig. E1 and Table 1)
- Viral pneumonitis and other pulmonary infections
- Pulmonary embolism
- Exacerbation of asthma/chronic obstructive pulmonary disease
- High altitude pulmonary edema (HAPE)
- Sarcoidosis
- Pulmonary fibrosis
- Lymphangitic carcinomatosis

BOX 1 Common Causes of Cardiogenic and Noncardiogenic Pulmonary Edema

Cardiogenic Pulmonary Edema
- Acute exacerbation of heart failure
- Acute valve dysfunction (e.g., mitral valve chordae tendineae rupture)
- Arrhythmia/myocardial infarction
- Hypertensive crisis
- Fluid overload following aggressive volume resuscitation (e.g., postoperative)
- Ventricular septal rupture
- Pericardial tamponade

Noncardiogenic Pulmonary Edema
- Direct lung injury
  - Pneumonia
  - Gastric aspiration
  - Toxic inhalation
  - Negative pressure related (e.g., strangulation)
- Indirect causes of lung injury
  - Sepsis
  - Trauma
  - Pancreatitis
  - Multiple blood transfusions
  - Burn injury

From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.

LABORATORY TESTS

- Arterial blood gases (ABGs): Respiratory and metabolic acidosis, decreased Pa_{O_2}, increased Pa_{CO_2}, low pH. (NOTE: The patient may initially show respiratory alkalosis as a result of hyperventilation in attempts to maintain Pa_{O_2}.)
- BNP and NT-pro BNP add diagnostic value to the history and physical examination as evidenced in the Breathing Not Properly (BNP) study.
- Cardiac biomarkers: Troponin T or I if suspicion for acute coronary syndrome.
- Basic metabolic profile: Assess for electrolyte abnormalities; renal failure can dictate diuretic choice.
- Complete blood count: Anemia can trigger acute pulmonary edema.
- Glucose, Hb A1C, fasting lipid profile, TSH for risk stratification.
- Urinalysis and urine toxicology if indicated.

IMAGING STUDIES

- ECG: May elucidate the specific cause of the pulmonary edema. Causes may include ischemia/infarct, arrhythmias, LV hypertrophy, atrial enlargement.
- Chest x-ray (Fig. 2):
  1. Bilateral interstitial and alveolar infiltrates
  2. Cephalization of the pulmonary vessels
  3. Kerley B lines; fluffy perihilar infiltrates
  4. Pleural effusions
  5. Enlarged cardiac silhouette
- Echocardiogram:
  1. Assess left and right ventricular systolic/diastolic function.
  2. Structural abnormalities (VSD, LV rupture).
  3. Evaluate valvular abnormalities.
  4. Engorged inferior vena cava (IVC) and IVC plethora, based on bedside ultrasound, suggests elevated filling pressures.
- Computed tomography of the chest; may differentiate between cardiogenic and noncardiogenic pulmonary edema.
- Right heart catheterization (RHC): Helps to differentiate between different types of shock and to guide tailored therapy (inotrope and pressor infusion) in cardiogenic shock. The ESCAPE trial failed to demonstrate the utility of pulmonary artery catheters in acute decompensated heart failure.
- Lung ultrasound has emerged as a tool to diagnose pulmonary edema. It is easy to use, accessible, noninvasive, and has a high accuracy. B lines and pleural effusions are suggestive of pulmonary edema.

TREATMENT

ACUTE GENERAL Rx (FIG. 3)

Nonpharmacologic treatment:

- Heart failure teaching.
- Sodium restriction in ACC/AHA class C and D heart failure patients has conflicting data.
- Restrict 1.5 to 2 L of free water in the setting of hyponatremia.

TABLE 1 Distinguishing Cardiogenic and Noncardiogenic Pulmonary Edema

	History	Exam	Labs	Imaging	Pulmonary Artery Catheter
Cardiogenic	Heart disease Renal disease Uncontrolled HTN Edema Orthopnea Recent administration of IV fluids or blood products	Heart failure exam findings: Distended neck veins S3 heart sound Dependent edema Elevated blood pressure Cool extremities	↑BNP >1200 pg/ml ↑Creatinine (in setting of volume overload) ↑Troponin	CXR: CMG Pleural effusions Kerley B lines TEE: ↓LVEF Diastolic filling defect Severe mitral or aortic valvular disease Pericardial effusion with tamponade VSD	PCWP >18 mm Hg Prominent V-waves (mitral regurgitation) Elevation and equilibration of right atrial pressure, pulmonary artery diastolic and PCWP (tamponade physiology) CVP >12 mm Hg
Noncardiogenic	Sepsis Aspiration event Trauma (long bone fractures) Burn injury Pancreatitis Multiple transfusions	Signs of active infection Extensive burn injury Evidence of trauma (absence of heart failure exam findings)	↑WBC BNP <200 pg/ml	CXR: Diffuse central and peripheral infiltrates Normal heart size No or minimal pleural effusions TEE: Normal LV and valvular function No evidence of volume overload	PCWP <18 mm Hg CVP <12 mm Hg

BNP, Brain natriuretic peptide; *CVP*, central venous pressure; *CXR*, chest x-ray; *HTN*, hypertension; *IV,* intravenous; *LVEF*, left ventricle ejection fraction; *PCWP*, pulmonary capillary wedge pressure; *S3*, third heart sound; *TEE*, transesophageal echocardiogram; *VSD*, ventricular septal defect; *WBC*, white blood count.
From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.

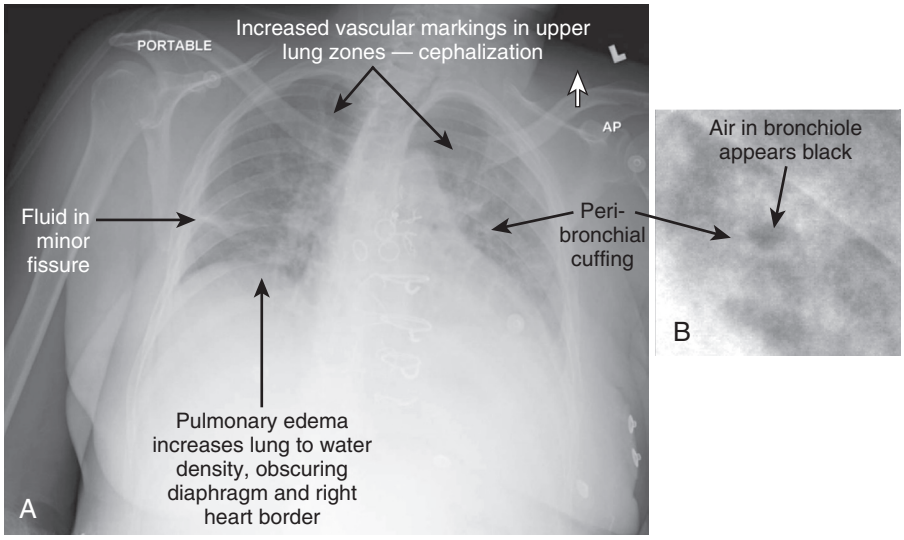

FIG. 2 Pulmonary edema. A, Anterior-posterior chest x-ray. **B,** Close-up from **A.** This 53-yr-old female with end-stage renal disease missed dialysis and presented to the emergency department. Her examination demonstrated bilateral rales. Her x-ray shows mild cardiomegaly, bilateral interstitial opacities, and cephalization of the pulmonary vascular markings. The minor fissure appears thickened. These findings are consistent with pulmonary edema. In addition, peribronchial cuffing is present. As discussed elsewhere, this is a nonspecific thickening of the bronchial wall that can occur from edema in the setting of heart failure, asthma, viral illness, or even infections such as pertussis. The thickened wall appears white, whereas the air-filled bronchiole appears black and has a circular short-axis cross section. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

- Risk factor modification (blood pressure and sugar control).
- Oxygen supplementation if signs of hypoxia are present.
- Noninvasive ventilation (continuous positive airway pressure [CPAP]) or bilevel noninvasive positive-pressure ventilation [NPPV]) reduces dyspnea and may reduce the need for endotracheal intubation. They improve oxygenation and lower carbon dioxide. Positive pressure ventilation (invasive or noninvasive) decreases preload and afterload and reduces the work of breathing, while positive end expiratory pressure improves oxygenation.

Pharmacologic treatment-afterload reducers:

- Loop diuretics such as furosemide, torsemide, bumetanide, and ethacrynic acid are the cornerstones of the treatment of volume overload. Intravenous treatment might be required in acute pulmonary edema. There is no difference in symptoms or kidney function whether the diuretic is given as a bolus versus continuous infusion (DOSE trial; NEJM March 3, 2011).
- Nitrates: Particularly useful if the patient has concomitant chest pain or is hypertensive.
  1. Nitroglycerin: 0.4 to 0.8 mg SL or nitroglycerin spray may be given immediately on arrival and repeated every 5 min up to three times if the patient remains symptomatic and blood pressure remains stable.
  2. 2% nitroglycerin ointment: 1 to 3 inches out of the tube applied continuously; absorption may be erratic.
  3. IV nitroglycerin for refractory chest pain or and hypertension: Start at 0.2 to 0.4 mcg/kg/min.
- Nitroprusside is useful for afterload reduction in severe hypertension, acute mitral regurgitation, or acute aortic regurgitation.
  1. Start at low-dose 0.5 μg/kg/min with an arterial line in place.
  2. Monitor for cyanide toxicity.
- ACE inhibitors, angiotensin II receptor blockers, aldosterone antagonist, and sacubitril-valsartan are vasodilators with long-term mortality benefit in patients with heart failure with reduced ejection fraction.
- Ultrafiltration/aquapheresis if diuretic resistant.

Pharmacologic-vasopressors:

- Patients with profound hypotension benefit from vasopressors.
  1. Norepinephrine: It is a powerful vasoconstrictor with small inotropic effect.

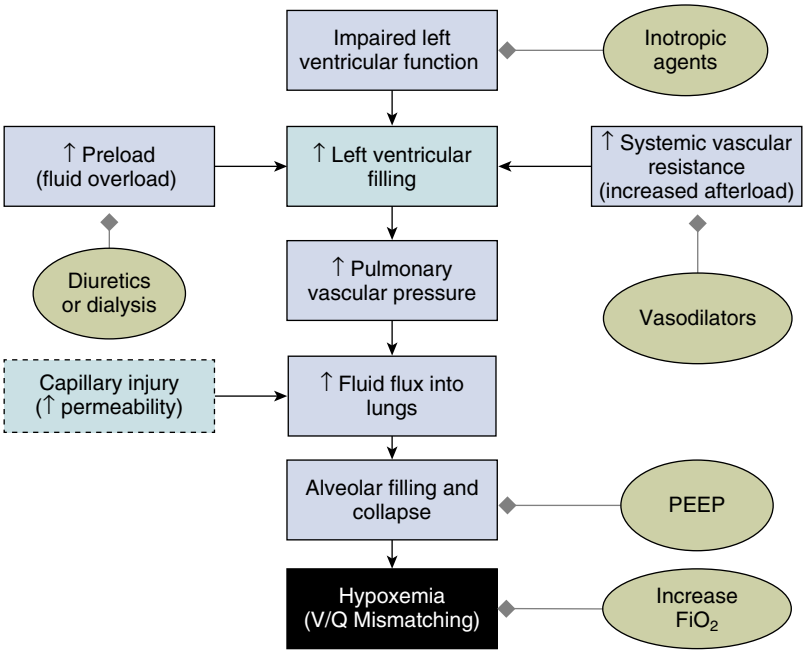

FIG. 3 Acute management of pulmonary edema. This schematic represents basic mechanisms distinguishing cardiogenic and noncardiogenic pulmonary edema and the contributing factors *(blue boxes)* that ultimately lead to impaired gas exchange *(black box)*. The *green circles* represent treatments that are available in the intensive care unit setting to reduce pulmonary edema or to mitigate its adverse consequences. *FiO2*, Fraction of inspired oxygen; *PEEP*, post end-expiratory pressure; *V/Q,* ventilation/perfusion. (From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.)

2. Dopamine: Low doses (0.5 to 3 μg/kg/min) increase blood flow to coronary, renal, and cerebral beds. Intermediate doses (3 to 10 μg/kg/min) increase cardiac contractility while high doses (10 to 20 μg/kg/min) have a pressor effect.

Pharmacologic-inotropes:

- Dobutamine: Potent inotrope, mild chronotropic effects. Dose ranges from 2.5 to 20 mcg/kg/min.
- Phosphodiesterase inhibitors (amrinone, milrinone, and enoximone [not available in U.S.]) may be useful in refractory cases. Milrinone may be associated with increased hypotension and new atrial arrhythmias with increased mortality in patients with ischemia.

Mechanical support:

- Intraaortic balloon pump (IABP): Decreases afterload, increases coronary blood flow.
- Impella: Axial-flow pump on a pigtail catheter that crosses the aortic valve and unloads the left ventricle.
- Tandem heart device: Oxygenated blood is pumped from the left atrium into the femoral artery. It can provide 3.5 to 4.5 L/min of cardiac output.
- Extracorporeal membrane oxygenation (ECMO) as a bridge to heart transplant.
- Durable mechanical circulatory support are advanced therapies that can be considered for those in cardiogenic shock refractory to medical therapy.

DISPOSITION

Admit to ICU/CCU if:

- Need for intubation
- Signs and symptoms of hypoperfusion
- SpO_2 <90% despite supplemental oxygen
- Use of accessory muscles/RR >25/min
- Heart rate <40 or >130, SBP <90

PEARLS & CONSIDERATIONS

COMMENTS

Accumulated evidence still favors the use of noninvasive ventilation, especially CPAP, in patients with ACPE, especially as this therapy reduces dyspnea and helps correct metabolic abnormalities more rapidly than standard oxygen therapy. The role of morphine in the treatment of ACPE has come into question.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Heart Failure (Related Key Topic)

AUTHORS: **Gemini Yesodharan, MD,** and **Maxwell Eyram Afari, MD**

SUGGESTED READINGS

Chen HH et al: Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial, *J Am Med Assoc* 310(23):2533-2543, 2013.

De Backer D et al: Comparison of dopamine and norepinephrine in the treatment of shock, *N Engl J Med* 362(9):779-789, 2010.

Maw AM et al: Diagnostic accuracy of point-of-care lung ultrasonography and chest radiography in adults with symptoms suggestive of acute decompensated heart failure: a systematic review and meta-analysis, *JAMA network open* 2(3):e190703, 2019.

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Weng CL et al: Meta-analysis: noninvasive ventilation in acute cardiogenic pulmonary edema, *Ann Intern Med* 152:590-600, 2010.

Yancy CW et al: 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, *J Am Coll Cardiol* 62(16):e147-e239, 2013.

Yancy CW et al: 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure, *J Am Coll Cardiol* 16:33024-33028, S0735-1097, 2016.

Signs	Cardiac	Renal	Lung Injury
Heart size	Enlarged	Normal	Normal
Blood flow	Inverted	Balanced	Normal
Kerley lines	Common	Common	Absent
Edema	Basilar	Central: Butterfly	Diffuse
Air bronchograms	Not common	Not common	Very common
Pleural effusions	Very common	Common	Not common

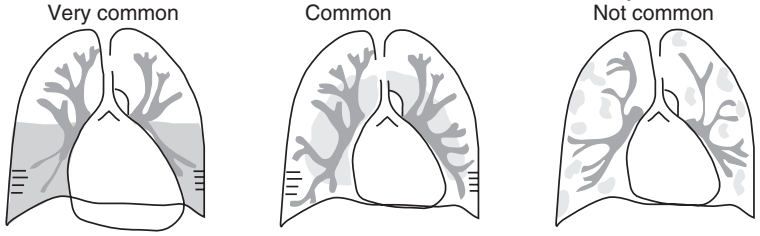

FIG. E1 Types of pulmonary edema. (From Weissleder R et al: *Primer of diagnostic imaging,* St Louis, 2007, Mosby.)

BASIC INFORMATION

DEFINITION

Pulmonary embolism (PE) refers to the lodging of a thrombus or other embolic material from a distant site in the pulmonary circulation. A classification of acute pulmonary embolism is described in Table 1.

SYNONYMS

Pulmonary thromboembolism
PE

ICD-10CM CODES

I26	Pulmonary embolism
I26.01	Septic pulmonary embolism with acute cor pulmonale
126.09	Other pulmonary embolism with acute cor pulmonale
126.90	Septic pulmonary embolism without acute cor pulmonale
126.99	Other pulmonary embolism without acute cor pulmonale
127.82	Chronic pulmonary embolism
Z86.711	Personal history of pulmonary embolism

EPIDEMIOLOGY & DEMOGRAPHICS

- 650,000 cases of PE occur in the U.S. each yr (increased incidence in women and with advanced age); annually, as many as 100,000 people in the U.S. die from acute PE, and the diagnosis is often not made until after autopsy. The incidence of PE is increasing with the increasing use of spiral CT scans, with a lower severity of illness and lower mortality, suggesting the increase is caused by earlier diagnosis.
- More than 90% of pulmonary emboli originate in the deep venous system of the lower extremities.
- Pulmonary thromboembolism is associated with >200,000 hospitalizations. 8% to 10% of victims of PE die within the first hour.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most common symptom: Dyspnea (82% to 85%)
- Tachypnea (30% to 60%)
- Cough (30% to 40%)
- Wheezing (20%)
- Chest pain: May be nonpleuritic or pleuritic (infarction) (40% to 49%)
- Syncope (massive PE) (10% to 14%)
- Fever, diaphoresis, apprehension
- Hemoptysis (2%)
- Evidence of DVT may be present (e.g., swelling and tenderness of extremities)
- Cardiac examination may reveal: Tachycardia (23%), increased pulmonic component of S2, murmur of tricuspid insufficiency, right ventricular heave, right-sided S3
- Pulmonary examination: May demonstrate rales, localized wheezing, friction rub

ETIOLOGY

- Thrombus, fat, or other foreign material
- Risk factors for PE:
  1. Prolonged immobilization, reduced mobility
  2. Postoperative state, major surgery
  3. Trauma to lower extremities, immobilizer, or cast
  4. Estrogen-containing birth control pills, hormone replacement therapy
  5. Prior history of DVT or PE
  6. CHF
  7. Pregnancy and early puerperium
  8. Visceral cancer (lung, pancreas, alimentary and genitourinary tracts)
  9. Spinal cord injury
  10. Advanced age
  11. Obesity
  12. Hematologic disease (e.g., factor V Leiden mutation, antithrombin III deficiency, protein C deficiency, protein S deficiency, lupus anticoagulant, polycythemia vera, dysfibrinogenemia, paroxysmal nocturnal hemoglobinuria, acquired protein C resistance without factor V Leiden, G20210A prothrombin mutation)
  13. COPD, diabetes mellitus, acute medical illness
  14. Prolonged air travel
  15. Central venous catheterization
  16. Autoimmune diseases (SLE, IBD, RA)

TABLE 1 Classification of Acute Pulmonary Embolism

Category (Frequency)	Presentation	Therapy
Massive PE (5%-10%)	Systolic blood pressure <90 mm Hg or poor tissue perfusion or multisystem organ failure plus extensive thrombosis, such as "saddle" PE or right or left main pulmonary artery thrombus	Anticoagulation (usually with high-dose intravenous UFH), plus advanced therapy: Systemic thrombolysis, pharmacomechanical catheter–directed therapy, surgical embolectomy, and/or inferior vena cava (IVC) filter.
Submassive PE, high risk (15%)	Hemodynamically stable but moderate or severe RV dysfunction or enlargement, coupled with biomarker elevation indicative of RV microinfarction and/or RV pressure overload	Anticoagulation until decision made regarding implementation of advanced therapy; controversy centers on this group. For systemic thrombolysis, reducing the rate of cardiovascular collapse and death must be balanced against the increased rate of hemorrhagic stroke.
Submassive PE, low risk (5%-10%)	Hemodynamically stable with RV dysfunction or biomarker elevation, but not both	Anticoagulation followed by "watch and wait." Implement advanced therapy if there is clinical deterioration.
Small to moderate PE (70%)	Normal hemodynamics and normal RV size and function	Anticoagulation and consider brief hospital stay or entirely home therapy.

PE, Pulmonary embolism; *RV*, right ventricular; *UFH*, unfractionated heparin.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Myocardial infarction
- Pericarditis
- Pneumonia
- Pneumothorax
- Chest wall pain
- GI abnormalities (e.g., peptic ulcer, esophageal rupture, gastritis)
- CHF
- Pleuritis
- Anxiety disorder with hyperventilation
- Pericardial tamponade
- Dissection of aorta
- Asthma

WORKUP

- Recent guidelines from the Clinical Guidelines Committee of the American College of Physicians for the Evaluation of Patients with Suspected Acute Pulmonary Embolism recommend the following:[1]
  1. Use of validated clinical prediction rules to estimate pretest probability in patients in whom acute PG is being considered.
  2. Not obtaining a D-dimer measurement or imaging studies in patients with low pretest probability of PE and who meet all pulmonary embolism rule-out criteria.
  3. Obtaining a high-sensitivity D-dimer measurement as the initial diagnostic test in patients who have an intermediate pretest probability of PE or in patients with low pretest probability of PE who do not meet all pulmonary embolism rule-out criteria. Clinicians should not use imaging studies as the initial test in patients who have a low or intermediate pretest probability of PE.
  4. Use age-adjusted D-dimer thresholds (age × 10 ng/ml rather than a generic 500 ng/ml) in patients older than 50 yr to determine whether imaging is warranted.
  5. Clinicians should not obtain any imaging studies in patients with a D-dimer level below the age-adjusted cutoff.

[1]Raja AS et al: Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the Clinical Guidelines Committee of the American College of Physicians, *Ann Intern Med* 163:701-711, 2015.

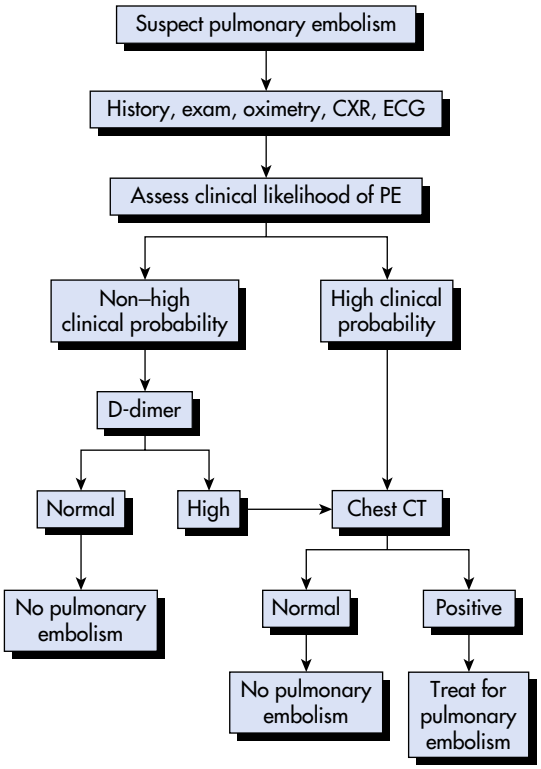

FIG. 1 Integrated diagnostic approach. *CT,* Computed tomography; *CXR*, chest x-ray [examination]; *ECG,* electrocardiogram; PE, pulmonary embolism. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

TABLE 2 Wells Score for Pulmonary Embolism*

Characteristic	Points
Risk Factors	
Previous pulmonary embolism or deep venous thrombosis	1.5
Immobilization or surgery in the previous 4 wk	1.5
Cancer	1
Clinical Findings	
Hemoptysis	1
Heart rate >100/min	1.5
Clinical signs of deep venous thrombosis	3
Other	
Alternative diagnosis is less likely than pulmonary embolism	3

Interpretation of total score: 0-1 point, low probability; 2-6 points, moderate probability; 7 or more points, high probability.

*Wells PS et al: Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED d-dimer, *Thromb Haemost* 83:416-420, 2000.

From McGee S: *Evidence-based physical diagnosis*, ed 4, Philadelphia, 2018, Elsevier.

TABLE 3 Revised Geneva Score for Pulmonary Embolism*

Characteristic	Points
Risk Factors	
Age >65 yr	1
Previous pulmonary embolism or deep venous thrombosis	3
Surgery (under general anesthesia) or fracture (of lower limbs) within 1 mo	2
Cancer (active or considered cured <1 yr)	2
Clinical Findings	
Unilateral leg pain	3
Hemoptysis	2
Heart Rate	
75-94 beats/min	3
≥95 beats/min	5
Pain on palpation of lower-limb deep veins and unilateral edema	4

Interpretation of total score: 0-3 points, low probability; 4-10 points, moderate probability; ≥11 points, high probability.

*Le Gal G et al: Prediction of pulmonary embolism in the emergency department: the revised Geneva score, *Ann Intern Med* 144:165-171, 2006.

From McGee S: *Evidence-based physical diagnosis,* ed 4, Philadelphia, 2018, Elsevier.

6. CTPA should be obtained in patients with high pretest probability of PE. Ventilation-perfusion scans should be reserved for patients who have a contraindication to CTPA or if CTPA is not available.
7. A D-dimer measurement should not be obtained in patients with a high pretest probability of PE.

- Clinical assessment alone is insufficient to diagnose or rule out PE. It is also important to remember that no single noninvasive test has both high sensitivity and high specificity for PE. Consequently, in addition to clinical assessment, most patients require an imaging test to diagnose PE. An integrated diagnostic approach to PE is illustrated in Fig. 1.

The Wells prediction rules (Table 2) and the revised Geneva score (Table 3) can be used to estimate the probability of PE. In the Wells prediction rules, each of the following findings is assigned a score:

1. Clinical signs/symptoms of deep vein thrombosis (score = 3.0).
2. No alternate diagnosis as likely or more likely than PE (score = 3.0).
3. Heart rate >100/min (score = 1.5).
4. Immobilization or surgery in last 4 wk (score = 1.5).
5. Previous history of DVT or PE (score = 1.5).
6. Hemoptysis (score = 1.0).
7. Cancer actively treated within last 6 mo (score = 1.0).

- The probability of PE is high if total score is >6, moderate if 2 to 6; and low if <2.
- The modified Wells score divides PE as likely (>4 points) or unlikely (<4 points).
- A low clinical probability of PE in association with a normal plasma D-dimer measurement essentially rules out PE, and further imaging is not needed. If clinical probability is intermediate or high, and/or the D-dimer measurement is abnormal, further workup with imaging is needed.
- The YEARS algorithm is a risk-adjusted D-dimer tool to rule out DVT that allows a threshold of 1000 ng/ml in patients without signs of DVT, no hemoptysis, and in whom PE is considered not to be the most likely diagnosis.
- CT pulmonary angiography (CTPA) (Fig. 2) is an excellent diagnostic modality (83% sensitivity and 96% specificity).
- V/Q scan is reserved for patients with clinically significant contrast allergies or renal insufficiency, or when CTPA is not available.
- Pulmonary angiogram (gold standard) can confirm the diagnosis in equivocal cases, but is rarely used.
- Serial compressive duplex ultrasonography of lower extremities can be used in patients with "low-probability" lung scan and high clinical suspicion (see "Imaging Studies"). It is useful if positive; negative results do not exclude PE.

LABORATORY TESTS

- ABGs may reveal hypoxemia and respiratory alkalosis (decreased Pa_{O_2} and Pa_{CO_2} and increased pH); normal results do not rule out PE.
- Alveolar-arteriolar (A-a) oxygen gradient, a measure of the difference in oxygen concentration between alveoli and arterial blood, may be elevated. However, a normal A-a gradient does not rule out PE.
- High-sensitivity plasma D-dimer measurement: D-dimer assays by ELISA detect the presence of plasmin-mediated degradation products of fibrin that contain cross-linked D fragments in the whole blood or plasma. A normal plasma D-dimer level is useful to exclude PE in patients with a low pretest probability of PE. However, it cannot be used to "rule in" the diagnosis because it increases with many other disorders (e.g., metastatic cancer, trauma, sepsis, postoperative state). Plasma D-dimer can also be used in conjunction with lower-extremity compression ultrasonography in patients with

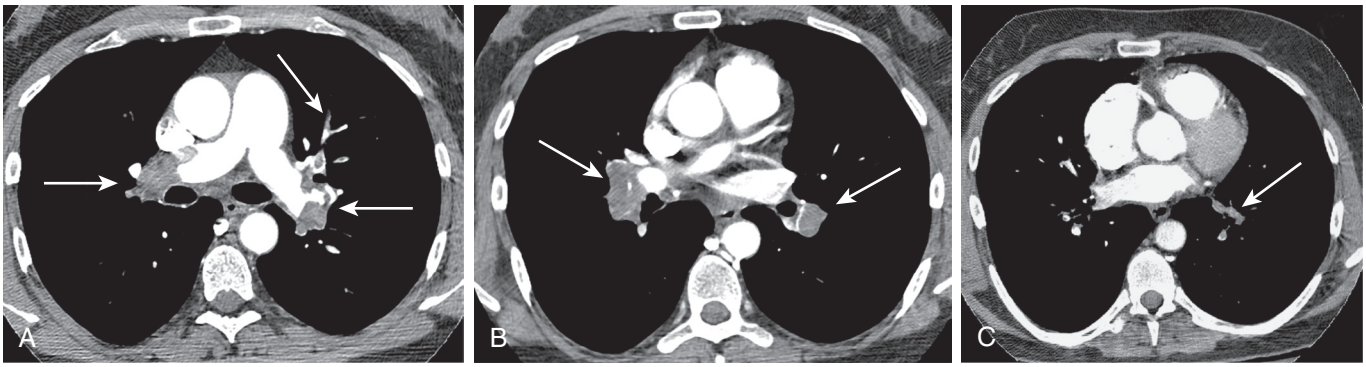

FIG. 2 A 46-yr-old woman presented with acute shortness of breath and hypoxia. Chest radiograph was normal. A, Chest computed tomography shows a low-attenuation filling defect in left and right main pulmonary arteries *(arrows)* and left upper lobe segmental artery *(arrow),* representing massive pulmonary embolism. Emboli extend to left and right interlobar arteries (*arrows),* as well as a left lower lobe segmental artery *(arrow),* seen in **B** and **C,** respectively. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.)

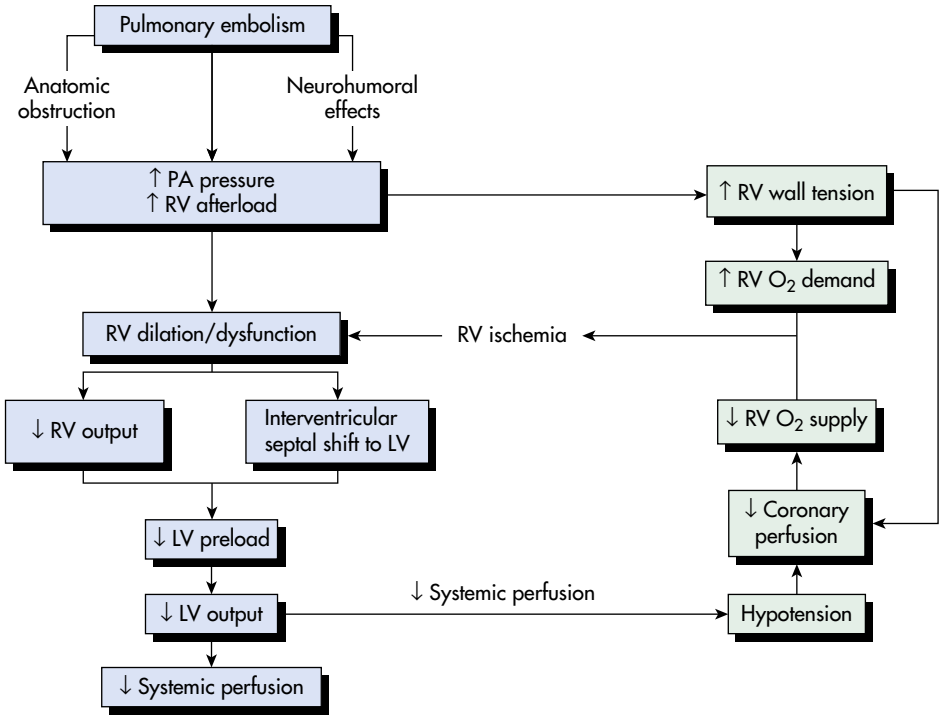

FIG. 3 Pathophysiology of right ventricular dysfunction and its deleterious effects of causing decreased systemic arterial pressure, decreased coronary perfusion, and deteriorating ventricular function. *LV,* Left ventricle/ventricular; *PA,* pulmonary artery; *RV,* right ventricle/ventricular. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

indeterminate V/Q and spiral CT scans. Absence of DVT and presence of a normal D-dimer level in these settings generally rule out clinically significant PE.

- Elevated cardiac troponin levels also occur in patients with PE because of right ventricular dilation and myocardial injury; therefore, PE should be considered in the differential diagnosis of all patients presenting with chest pain or dyspnea and elevated cardiac troponin levels.
- Elevated serum BNP levels in patients with acute PE may reflect RV overload. The pathophysiology of RV dysfunction in PE is illustrated in Fig. 3.
- ECG is abnormal in 85% of patients with acute PE. Frequent abnormalities are sinus tachycardia; nonspecific ST-segment or T-wave changes; S-1, Q-3, T-3 pattern (10% of patients); S-1, S-2, S-3 pattern; T-wave inversion in V_1 to V_6; acute RBBB; new-onset atrial fibrillation; ST segment depression in lead II; right ventricular strain. A right ventricular strain pattern on ECG in patients with PE and normal blood pressure is associated with adverse short-term outcome and adds incremental prognostic value to echocardiographic evidence of right ventricular function.

IMAGING STUDIES

- Chest x-ray may be normal; suggestive findings include elevated diaphragm, pleural effusion, dilation of pulmonary artery, infiltrate or consolidation, abrupt vessel cut-off, oligemia distal to the PE (*Westermark sign*), or atelectasis. A wedge-shaped consolidation in the middle and lower lobes is suggestive of a pulmonary infarction and is known as *Hampton hump.*
- CT angiography is an accurate, noninvasive tool in the diagnosis of PE at the main, lobar, and segmental pulmonary artery levels. A major advantage of CT angiography over standard pulmonary angiography is its ability to diagnose intrathoracic disease other than

PE that may account for the patient's clinical picture. It is also less invasive, less costly, and more widely available. Its major shortcoming is its poor sensitivity for subsegmental emboli.

- V/Q Lung scan (in patient with normal chest x-ray examination): This test must be interpreted within the pretest probability of having a PE.
  1. A normal lung scan rules out PE.
  2. A ventilation-perfusion mismatch is suggestive of PE, and a lung scan interpretation of high probability is confirmatory (Fig. E4).
  3. If the clinical suspicion of PE is high and the lung scan is interpreted as low probability, moderate probability, or indeterminate, a pulmonary arteriogram is diagnostic; a positive arteriogram confirms diagnosis; a positive compressive duplex ultrasonography for DVT obviates the need for an arteriogram, because treatment with IV anticoagulants is indicated in these patients; the overall sensitivity of compressive ultrasonography for DVT in patients with PE is 29%, specificity 97%; adding ultrasonography in patients with a nondiagnostic lung scan prevents 9% of angiographies; however, this improvement in efficacy is achieved at the cost of unnecessary anticoagulant therapy in 26% of patients who have false-positive ultrasonography results.
- Angiography: Pulmonary angiography is the historic gold standard; however, it is invasive, expensive, and not readily available in some clinical settings. False-positive pulmonary angiograms may result from mediastinal disorders such as radiation fibrosis and tumors.
- Gadolinium-enhanced magnetic resonance angiography (MRA/MRV) of the pulmonary arteries has a moderate sensitivity and high specificity for the diagnosis of PE at experienced centers, but obtaining acceptable images is technically challenging and should only be performed if other imaging tests are contraindicated.
- Echocardiography: Useful for identifying patients with PE who may have poor prognosis. Moderate or severe hypokinesis, persistent pulmonary hypertension, patent foramen ovale, and free-floating right heart thrombus are markers for increased risk of death or recurrent thrombosis. Such patients should be considered for thrombolysis or embolectomy.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Correction of risk factors (see "Etiology") to prevent future PE.

ACUTE GENERAL Rx

Patients with acute PE should be initially stratified according to risk so that higher-risk therapies (e.g., thrombolysis, embolectomy) are offered to patients with the greatest chance of benefit.

- Anticoagulants are recommended as initial therapy in patients with small to moderate PE.
- Oral rivaroxaban, a factor Xa inhibitor (15 mg bid for 3 wk, then 20 mg/d), has been studied as a treatment for DVT and for PE, without prior parenteral therapy. For both DVT and PE, treatment with rivaroxaban alone was noninferior to treatment with LMWH followed by a vitamin K antagonist with regard to the endpoint of recurrent venous thromboembolism. Use of rivaroxaban should be avoided in patients with severe renal failure.
- Apixaban, a Factor Xa inhibitor (10 mg twice a day for a week, followed by 5 mg twice a day), is also approved for the treatment of acute PE based on the data in the AMPLIFY and AMPLIFY-EXT trials, in which apixaban met its noninferiority mark in terms of efficacy and improved safety compared to warfarin.
- Unfractionated heparin (UFH) (IV or subcutaneous), subcutaneous low-molecular-weight heparin (LMWH), or subcutaneous fondaparinux can be used for the initial treatment for at least 5 days when used with warfarin or dabigatran. If IV unfractionated heparin is used, a bolus dose (80 U/kg) followed by a weight-based (18 U/kg/hr) continuous infusion to achieve therapeutic anti-factor Xa (or aPTT) levels should be used. LMWH and fondaparinux should be avoided in patients with severe renal failure.
- Thrombolytic agents (urokinase, tPA, streptokinase): Provide rapid resolution of clots with increased risk of major bleeding (up to 3% incidence of intracranial hemorrhage); thrombolytic agents are the treatment of choice in patients with massive PE who are hemodynamically unstable and with no contraindication to their use. Fig. 5 describes treatment of submassive pulmonary embolism. Fig. 6 illustrates the approach to "high-risk" submassive pulmonary embolus with right ventricular injury. The use of thrombolytic agent in the treatment of hemodynamically stable

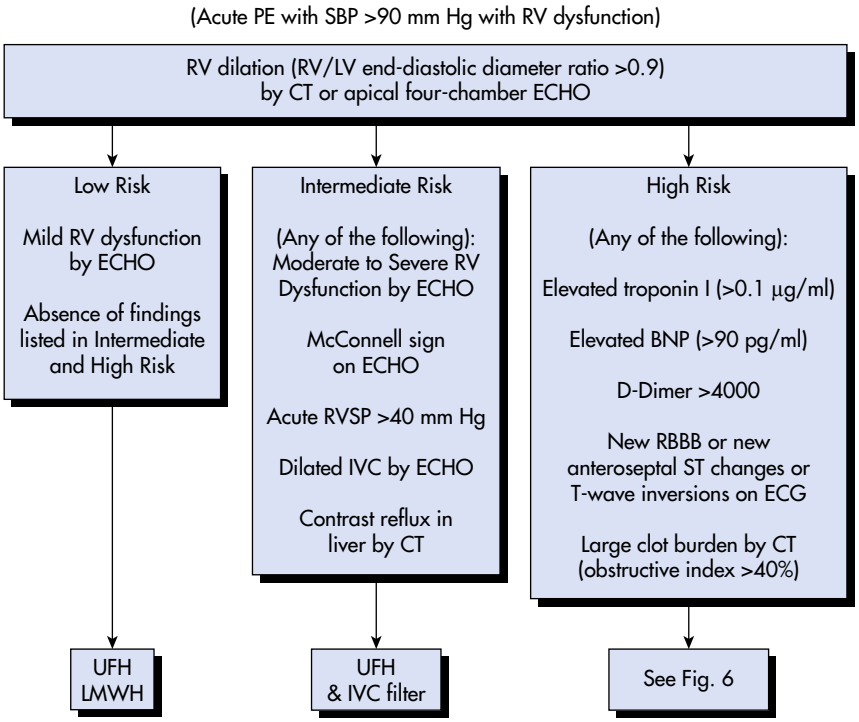

FIG. 5 Submassive pulmonary embolus algorithm. *BNP,* Brain natriuretic peptide; *CT,* computed tomography; *ECG,* electrocardiogram; *ECHO,* echocardiogram; *IVC,* inferior vena cava; *LMWH,* low-molecular-weight heparin; *PE,* pulmonary embolism; *RBBB,* right bundle branch block; *RV,* right ventricle; *RV/LV,* right ventricle/left ventricle; *RVSP,* right ventricular systolic pressure; *SBP,* systolic blood pressure; *UFH,* unfractionated heparin. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

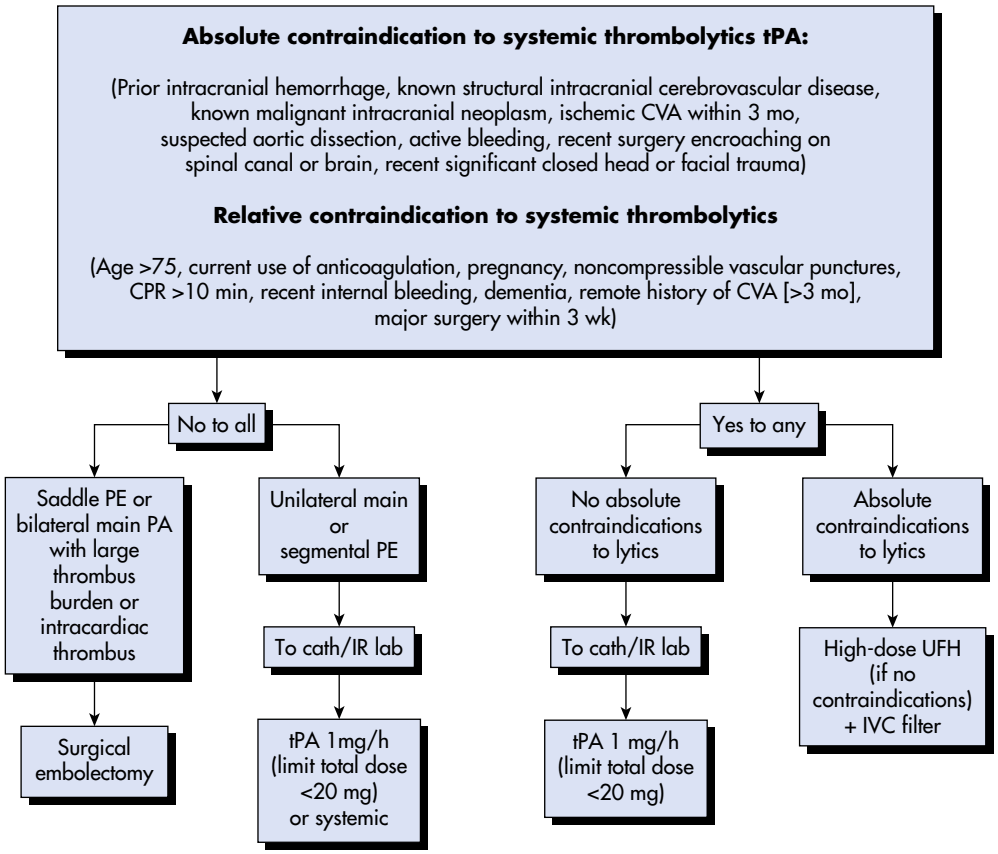

FIG. 6 "High-risk" submassive pulmonary embolus with right ventricular injury algorithm. *CPR,* Cardiopulmonary resuscitation; *CVA,* cerebrovascular accident; *IR,* interventional radiology; *IVC,* inferior vena cava; *PA,* pulmonary artery; *PE,* pulmonary embolism; *tPA,* tissue plasminogen activator; *UFH,* unfractionated heparin. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.)

patients with acute submassive PE remains controversial, although there is some evidence that half-dose tPA has some efficacy. Use of the thrombolytic agents alteplase (100 mg IV over 2-hr period) in normotensive patients with moderate or severe right ventricular dysfunction identified by ECG has been advocated by some physicians. Use of alteplase in conjunction with heparin has been shown to improve the clinical course of stable patients who have acute submassive PE without internal bleeding, mainly by reducing need for subsequent thrombolytic use. Additional studies are needed to confirm these findings before recommending routine use of this therapeutic approach. The Pulmonary Embolism Thrombolysis (PEITHO) trial revealed that in patients with intermediate risk of pulmonary embolism, fibrinolytic therapy prevented hemodynamic compensation but increased the risk of major hemorrhage and stroke.

- Long-term treatment for PE not associated with malignancy can be carried out with warfarin therapy or rivaroxaban.
- For PE associated with malignancy, LMWH is recommended for long-term therapy.
- For PE occurring in the setting of a reversible risk factor, anticoagulation should be continued for 3 mo. For patients with an unprovoked PE, longer-term anticoagulation should be considered, and indefinite long-term anticoagulation should be used in patients with recurrent unprovoked PE. Important factors to consider in the decision to extend anticoagulation include the patient's risk of bleeding and patient preferences after an informed discussion of risks and benefits.
- If thrombolytics and anticoagulants are contraindicated (e.g., GI bleeding, recent CNS surgery, recent trauma) or if the patient continues to have recurrent PE despite anticoagulation therapy, vena caval interruption is indicated by transvenous placement of an inferior vena caval filter.
- In older adults, IVC filters are associated with higher 30-day and 1-yr mortality (11.6% and 20.5%, respectively, versus 9.3% and 13.4% in those who do not); however, these patients tend to be sicker than those who are not.
- Acute pulmonary artery surgical embolectomy or catheter-based thrombectomy may be indicated in a patient with massive PE who cannot receive thrombolytic therapy. Pulmonary embolectomy is also recommended for those whose critical status does not allow sufficient time for thrombolytic therapy to be effective and for those who remain unstable after receiving fibrinolysis.

CHRONIC Rx

- Elimination of risk factors (see "Etiology").
- Patients with unprovoked DVT/PE have a high rate of recurrent VTE. Longer durations of chronic anticoagulation after unprovoked DVT/PE result in lower rates of recurrent DVT/PE while on anticoagulation, but benefits are lost once anticoagulation is halted. The use of indefinite anticoagulation in selected individuals with apparently unprovoked DVT/PE must be weighed against ongoing bleeding risk and other factors.
- Aspirin (100 mg daily) is superior to placebo in preventing recurrence of venous thromboembolism in patients with a first-ever unprovoked venous thromboembolism (VTE) who had already completed 6 to 18 mo of oral anticoagulation. This suggests that aspirin could be offered as an alternative to oral anticoagulants for prevention of recurrent VTE in patients who refuse to or cannot continue oral anticoagulant therapy but who have a high risk of recurrent VTE.
- Trials involving extending the treatment time of the novel oral anticoagulants (rivaroxaban, dabigatran, and apixaban) all showed superior

TABLE 4 Stratification of Risk of Death Associated with Pulmonary Embolism and Severity-Adjusted Treatment*

Early Risk of Death	Risk Factor: Shock or Hypotension (on Clinical Examination)	Risk Factor: Right Ventricular Dysfunction (on Echocardiography or Multidetector CT)	Risk Factor: Myocardial Injury (on Cardiac Troponin Testing)	Recommended Treatment
High	Present	Present†	NA‡	Unfractionated heparin plus thrombolysis or embolectomy
Intermediate§	Absent	Present	Present	Low-molecular-weight heparin or fondaparinux; as a rule, no early thrombolysis; monitor clinical status and right ventricular function
Low	Absent	Absent	Absent	Low-molecular-weight heparin or fondaparinux; consider outpatient treatment

CT, Computed tomography; *RV,* right ventricle.
*Adapted with modifications from the 2008 Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology. NA denotes not applicable.
†If RV function is normal on echocardiography, or if a CT scan shows no RV dilation in a patient with hemodynamic compromise and clinically suspected pulmonary embolism, an alternative diagnosis should be sought.
‡Troponin test results do not influence risk assessment or treatment in hemodynamically compromised patients with acute pulmonary embolism.
§Although it has been suggested that normotensive patients with both RV dysfunction and myocardial injury have a higher risk of death than those with only one of these risk factors, there is currently no definitive proof that they should receive more aggressive treatment.
From Konstantinides S: Acute pulmonary embolism, *N Engl J Med* 359:2804-2813, 2008.

TABLE 5 Original and Simplified Pulmonary Embolism Severity Index (PESI)

Variable	Original PESI	Simplified PESI
Age	Age, in yr	1 (if age >80 yr)
Male sex	+10	—
History of cancer	+30	1
History of heart failure	+10	1 for either or both of these items
History of chronic lung disease	+10	
Pulse >110 beats/min	+20	1
Systolic blood pressure <100 mm Hg	+30	1
Respiratory rate >30 breaths/min	+20	—
Temperature <36 °C	+20	—
Altered mental status	+60	—
Arterial oxyhemoglobin saturation (SaO_2) <90%	+20	1
30-DAY MORTALITY RISK STRATA (BASED ON THE SUM OF POINTS)		
LOW-RISK PESI	**LOW-RISK sPESI**	
Class I: <65 Points	**0 Points**	
(event rate 95% CI, 0-1.6)	(event rate 95% CI, 0-2.1)	
Class II: 66-85 Points		
(event rate 95% CI, 1.7-3.5)		
HIGH-RISK PESI	**HIGH-RISK sPESI**	
Class III: 86-105 Points	**≥1 Point**	
(event rate 95% CI, 3.2-7.1)	(event rate 95% CI, 8.5-13.2)	
Class IV: 106-125 Points		
(event rate 95% CI, 4.0-11.4)		
Class V: >125 Points		
(event rate 95% CI, 10.0-24.5)		

CI, Confidence interval; *PESI,* Pulmonary Embolism Severity Index; *sPESI,* Simplified Pulmonary Embolism Severity Index.
From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

efficacy and reduced morbidity compared to placebo as well as similar rate of major bleeding (though increased all bleeding).

DISPOSITION

- Mortality can be reduced to <10% by rapid and effective treatment. Stratification of risk of death associated with PE and severity-adjusted treatment is described in Table 4. Indicators of poor prognosis include hemodynamic instability/hypotension, signs of RV dysfunction, elevated BNP, elevated troponin, thrombus burden, coexisting DVT, and right ventricular thrombus. The Pulmonary Embolism Severity Index (PESI) is summarized in Table 5.
- Mortality from recurrent pulmonary emboli is 8% with effective treatment and >30% in patients with untreated pulmonary emboli.

PEARLS & CONSIDERATIONS

COMMENTS

- Use of clinical prediction rules in association with D-dimer testing may reduce the use of unnecessary imaging in patients in whom PE is unlikely. A combination of a low clinical pretest probability and a D-dimer level less than 1000 mg per milliliter can identify patients at low risk for pulmonary embolism.[3]
- Massive PE (PE associated with hypotension, shock, or circulatory arrest) remains the clearest situation in which thrombolytics should be employed. Submassive PE (PE associated with right ventricular dysfunction or injury but without hypotension) remains an area of controversy with regard to thrombolytic use.
- A recent prospective study revealed that suspected pulmonary embolism in pregnant patients can be ruled out by using a pregnancy-adapted YEARS diagnostic algorithm across all trimesters of pregnancy. The three following criteria from the YEARS algorithm were used: (1) Clinical signs of deep-vein thrombosis, (2) hemoptysis, (3) pulmonary embolism as the most likely diagnosis. A D-dimer level was also obtained. PE was ruled out if none of the three criteria were met and the D-dimer level was <1000 mg/ml or if one or more of the three criteria were met and the D-dimer level was <500 mg/ml.[2]

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pulmonary Embolism (PE) (Patient Information)
Deep Vein Thrombosis (Related Key Topic)
Hypercoagulable State (Related Key Topic)

AUTHOR: **Chakravarthy Reddy, MD**

[2]van der Pol LM et al: Pregnancy-adapted YEARS algorithm for diagnosis of suspected pulmonary embolism, *N Engl J Med* 380(12):1139-1149, 2019.
[3]Kearon C et al: Diagnosis of pulmonary embolism with d-dimer adjusted to clinical probability, N Engl J Med 381(22):2125-2134, 2019.

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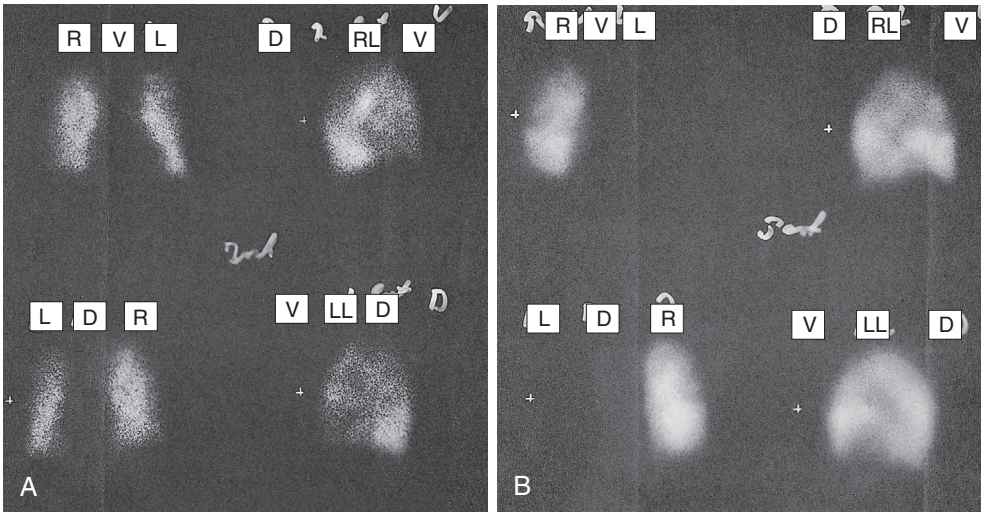


FIG. E4 Ventilation-perfusion lung scan in massive pulmonary embolism. A, A normal pattern on the ventilation scan. **B,** The complete disappearance of the entire left lung from the perfusion scan indicates proximal occlusion of the left pulmonary artery. *D,* Dorsal; *L,* left; *LL,* left lobe; *R,* right; *RL,* right lobe; *V,* ventral. (From Crawford MH et al [eds]: *Cardiology,* ed 2, St Louis, 2004, Mosby.)

BASIC INFORMATION

DEFINITION

Pulmonary hypertension (PH) is defined as the presence of an elevated mean pulmonary arterial pressure (PAP) ≥20 mm Hg at rest (previously ≥25 mm Hg). Pulmonary hypertension is classified into five major groups: pulmonary arterial hypertension (Group 1), pulmonary hypertension due to left heart disease (Group 2), pulmonary hypertension due to lung disease (Group 3), pulmonary hypertension due to chronic thromboembolic disease (Group 4), and miscellaneous (Group 5).

Pulmonary arterial hypertension (PAH) is a syndrome defined as mean pulmonary pressure ≥20 mm Hg with pulmonary capillary wedge pressure <15 mm Hg and a pulmonary vascular resistance ≥3 Wood units on right heart catheterization. Idiopathic pulmonary arterial hypertension (IPAH) is diagnosed when PAH is present without any apparent cause. It is a highly morbid disease characterized by progressive obliteration of precapillary arterioles. This topic will mostly focus on pulmonary arterial hypertension.

SYNONYMS

PH
Pulmonary arterial hypertension
Idiopathic pulmonary arterial hypertension
IPAH
Associated pulmonary arterial hypertension
PAHA, also known as secondary pulmonary hypertension
Heritable pulmonary arterial hypertension
HPAH
Group I pulmonary hypertension

ICD-10CM CODES
I27.0 Primary pulmonary hypertension
I27.2 Other secondary pulmonary hypertension

EPIDEMIOLOGY & DEMOGRAPHICS

- IPAH is rare, occurring in one to two cases per 1 million people per yr, with an overall prevalence estimated at 15 to 50 per 1 million.
- IPAH is more common in women than men (3:1), usually presenting in the third to fourth decades of life.
- In adults the most common cause of pulmonary hypertension is due to left-sided heart disease (Group 2).
- Prevalence of secondary PAH could range from 8% to 12% in cases of scleroderma, 0.5% of HIV, 23% to 53% of mixed connective tissue disorders, and 1% to 4% cases of systemic lupus erythematosus.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Insidious, may go undetected for yrs
- Exertional dyspnea most common presenting symptom (60%)
- Fatigue and weakness
- Anorexia/abdominal pain
- Syncope, classically exertion-related or after a warm shower with peripheral vasodilation
- Chest pain
- Hoarse voice from compression of recurrent laryngeal nerve by an enlarged pulmonary artery (Ortner syndrome)
- Hemoptysis
- Rarely, palpitations due to atrial fibrillation or atrial flutter
- Loud P2 component of the second heart sound and paradoxical splitting of second heart sound
- Right-sided S4
- Jugular venous distention
- Abdominal distention and ascites
- Prominent parasternal (right ventricular [RV]) impulse
- Holosystolic tricuspid regurgitation murmur heard best along the left fourth parasternal line that increases in intensity with inspiration
- Peripheral edema
- Features of the physical exam pertinent to the evaluation of pulmonary hypertension are summarized in Table 1

ETIOLOGY

- The etiology of IPAH is unknown.
- APAH (associated PAH) has several known risk factors: connective tissue disorders such as systemic sclerosis, portal hypertension and liver cirrhosis, appetite-suppressant drugs (e.g., fenfluramine), and infections, including schistosomiasis and HIV disease. High altitude, schistosomiasis, and HIV disease are common causes of PH worldwide; however, pulmonary venous hypertension from left ventricular failure and PH related to COPD are more common causes of PH in developed nations.
- Several genetic abnormalities have been associated with HPAH (heritable PAH), many of which are mutations in the genes that code for members of the tumor growth factor-beta family of receptors (BMPR-II, ALK-1, endoglin) on chromosome 2q33.
- Up to 25% of patients with IPAH have abnormal BMPR-II structure or function, while up to 80% of hereditary PAH is due to mutations in BMPR-II.
- Mutations in *KCNK3, SMAD9,* and *CAV1* have also been associated with both familial and idiopathic pulmonary arterial hypertension.
- Heritable PAH is an autosomal-dominant disease with variable penetrance, affecting only about 10% to 20% of carriers.
- Several factors play a role in the pathogenesis of PAH, including a genetic predisposition, endothelial cell dysfunction, abnormalities in vasomotor control, thrombotic obliteration of the vascular lumen, and vascular remodeling through cell proliferation and matrix production.
- SSRI use in late pregnancy is associated with increased persistent PAH in newborns.
- The updated clinical classification of pulmonary hypertension is described in Table 2.

DIAGNOSIS

- PAH is a hemodynamic diagnosis involving the detection of elevated pressure in the pulmonary arteries and elevated pulmonary vascular resistance in the pulmonary vascular bed, occurring in the absence of significant pulmonary venous hypertension.
- Right-sided heart catheterization must be performed in all patients suspected of having PAH to establish the diagnosis and to assess pulmonary hemodynamics including reactivity response to vasodilators.
- One of the most challenging differential diagnoses of IPAH is heart failure with preserved EF (HFpEF). In such patients, the PCWP may be at the higher limit of normal at rest. Exercise or fluid challenge at the time of right heart catheterization can result in disproportionate rise in PCWP, which favors group 2 pulmonary hypertension.
- IPAH is a diagnosis of exclusion; causes that lead to groups 2 to 5 pulmonary hypertension must be ruled out. TTE, HR-CT, PFT, and V/Q scan must be performed before the diagnosis of IPAH is established and treatment started.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is as listed under "Etiology." Table 3 summarizes distinguishing pulmonary arterial hypertension from heart failure with preserved ejection fraction.

EVALUATION

- Consists of establishing the diagnosis and etiology.
- Echocardiography with Doppler technique can provide a noninvasive but limited estimation of systolic PAP. Common findings include tricuspid regurgitation, right heart enlargement, abnormal movement of septum and, rarely, pericardial effusion. However, the diagnosis of PH cannot be established by echocardiography alone, as echocardiography can overestimate or underestimate PAP.
- ECG shows RV enlargement, strain pattern, and right axis deviation.
- Chest radiograph (Fig. 1) shows enlarged central pulmonary arteries and right heart enlargement. Chest radiography is abnormal in 90% of patients at diagnosis.
- A normal chest radiograph does not rule out the diagnosis. High-resolution computed tomography (CT) (Fig. E2) can assist in the evaluation for emphysema or interstitial lung disease. Ventilation-perfusion lung scan has high sensitivity for chronic thromboembolic disease. CT angiography is less sensitive for diagnosing chronic thromboembolic disease. The diagnosis can be confirmed by pulmonary angiography, which has high specificity. Pulmonary angiography is also useful in identifying patients who can benefit from pulmonary endarterectomy (PEA).
- Cardiac magnetic resonance imaging (CMR) can provide accurate noninvasive evaluation of the right ventricular size, morphology, and function.

TABLE 1 Features of the Physical Examination Pertinent to the Evaluation of Pulmonary Hypertension

Sign	Implication
PHYSICAL SIGNS THAT REFLECT THE SEVERITY OF PULMONARY HYPERTENSION	
Accentuated pulmonary component of S_2 (audible at the apex in >90%)	High pulmonary pressure that increases force of pulmonic valve closure
Early systolic click	Sudden interruption of opening of the pulmonary valve into a high-pressure artery
Midsystolic ejection murmur	Turbulent transvalvular pulmonary outflow
Left parasternal lift	High right ventricular pressure and hypertrophy present
Right ventricular S4 (in 38%)	High right ventricular pressure and hypertrophy present
Increased jugular A wave	Poor right ventricular compliance
PHYSICAL SIGNS THAT SUGGEST MODERATE TO SEVERE PULMONARY HYPERTENSION	
Moderate to severe pulmonary hypertension	
Holosystolic murmur that increases with inspiration	Tricuspid regurgitation
Increased jugular V waves	
Pulsatile liver	
Diastolic murmur	Pulmonary regurgitation
Hepatojugular reflux	High central venous pressure
Advanced pulmonary hypertension with right ventricular failure	
Right ventricular S3 (in 23%)	Right ventricular dysfunction
Distention of jugular veins	Right ventricular dysfunction or tricuspid regurgitation, or both
Hepatomegaly	Right ventricular dysfunction or tricuspid regurgitation, or both
Peripheral edema (in 32%)	
Ascites	
Low blood pressure, diminished pulse pressure, cool extremities	Reduced cardiac output, peripheral vasoconstriction
PHYSICAL SIGNS THAT SUGGEST A POSSIBLE UNDERLYING CAUSE FOR OR ASSOCIATIONS WITH PULMONARY HYPERTENSION	
Central cyanosis	Abnormal ventilation-perfusion ratio, intrapulmonary shunt, hypoxemia, pulmonary-to-systemic shunt
Clubbing	Congenital heart disease, pulmonary venopathy
Cardiac auscultatory findings, including systolic murmurs, diastolic murmurs, opening snap, and gallop	Congenital or acquired heart or valvular disease
Rales, dullness, or decreased breath sounds	Pulmonary congestion or effusion, or both
Fine rales, accessory muscle use, wheezing, protracted expiration, productive cough	Pulmonary parenchymal disease
Obesity, kyphoscoliosis, enlarged tonsils	Possible substrate for disordered ventilation
Sclerodactyly, arthritis, telangiectasia, Raynaud phenomenon, rash	Connective tissue disorder
Peripheral venous insufficiency or obstruction	Possible venous thrombosis
Venous stasis ulcers	Possible sickle cell disease
Pulmonary vascular bruits	Chronic thromboembolic pulmonary hypertension
Splenomegaly, spider angiomas, palmar erythema, icterus, caput medusae, ascites	Portal hypertension

From McLaughlin VV et al: ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc., and the Pulmonary Hypertension Association, *J Am Coll Cardiol* 53:1573, 2009; In Mann DL et al: *Braunwald's heart disease,* ed 11, Philadelphia, 2019, Elsevier.

TABLE 2 Updated Clinical Classification of Pulmonary Hypertension

1 PAH
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
- 1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease
- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to postcapillary PH

3 PH due to lung disease and/or hypoxia
- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

4 PH due to pulmonary artery obstructions
- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

5 PH with unclear and/or multifactorial mechanisms
- 5.1 Hematologic disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

HIV, human immunodeficiency virus*; LVEF,* left ventricular ejection fraction; *PAH,* pulmonary arterial hypertension; *PCH,* pulmonary capillary hemangiomatosis; *PH,* pulmonary hypertension; *PVOD,* pulmonary veno-occlusive disease.

From Simonneau G et al: Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 53(1):1801913, 2019; DOI: 10.1183/13993003.01913-2018.

TABLE 3 Distinguishing Pulmonary Arterial Hypertension (PAH) from Heart Failure with Preserved Ejection Fraction (HFpEF)

Characteristic	PAH More Likely	HFpEF More Likely
Age	Younger	Older
Comorbid conditions—DM, HTN, CAD, obesity (metabolic syndrome)	Often absent	Often multiple present
Symptoms—PND, orthopnea	Often absent	Often present
Cardiac examination	RV heave, loud P_2, TR murmur	Sustained LV impulse, LS4
CXR	Clear lung fields	Pulmonary vascular congestion, pleural effusions, pulmonary edema
Chest CT	Often clear lungs	Mosaic perfusion pattern, ground-glass opacities consistent with chronic interstitial edema
ECG	RAD, RVE	LAE, LVE, atrial fibrillation, no RAD
Natriuretic peptides	Often elevated	Often elevated
Echo—LAE, LVH	Absent	Often present
Echo—diastolic dysfunction	Grade 1 common	Grade 2, 3 common
Echo—right ventricle	Often enlarged, may share the apex	Often normal, mildly enlarged
Echo—pericardial effusion	Sometimes	Rare

CAD, Coronary artery disease; *CT,* computed tomography; *CXR,* chest x-ray; *DM,* diabetes mellitus; *ECG,* electrocardiogram; *Echo,* echocardiography; *HTN,* hypertension; *LAE,* left atrial enlargement; *LS4,* left-sided fourth heart sound; *LV,* left ventricular; *LVE,* left ventricular enlargement; *LVH,* left ventricular hypertrophy; *PND,* paroxysmal nocturnal dyspnea; *RAD,* right-axis deviation; *RV,* right ventricular; *RVE,* right ventricular enlargement; *TR,* tricuspid regurgitation.
From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

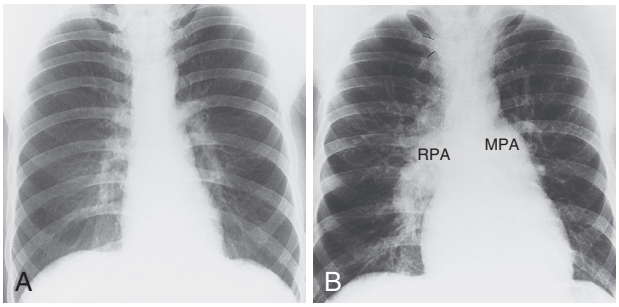


FIG. 1 Progressive pulmonary arterial hypertension. This patient initially presented with a relatively normal chest radiograph **(A).** However, several yrs later **(B)** there is increasing heart size and marked dilation of the main pulmonary artery *(MPA)* and right pulmonary artery *(RPA).* Rapid tapering of the arteries as they proceed peripherally is suggestive of pulmonary hypertension and is sometimes referred to as pruning. (From Mettler FA [ed]: *Primary care radiology,* Philadelphia, 2000, WB Saunders.)

- Pulmonary function tests may show obstructive (airway disease) and/or restrictive disease (parenchymal disease) depending on etiology. Diffusion capacity of carbon monoxide in the lung is reduced due to pulmonary vascular destruction in PAH.
- In asymptomatic patients the severity of pulmonary arterial hypertension (PAH) disease should be evaluated in a systematic and consistent manner, using a combination of World Health Organization (WHO) functional class (FC), exercise capacity, and echocardiographic, laboratory, and hemodynamic variables to inform therapeutic decisions.
- Right heart catheterization is required to assess pulmonary hemodynamics, exclude shunts and left heart disease, and perform acute vasoreactivity response testing.
- Symptomatic patients with PAH, in the absence of contraindications, should undergo acute vasoreactivity testing using a short-acting agent at a center with experience in the performance and interpretation of vasoreactivity testing.
- Screening for the presence of PAH with Doppler echocardiography is warranted in individuals with a known predisposing genetic mutation or first-degree relative with IPAH, connective tissue diseases (especially scleroderma), congenital heart disease with left-to-right shunt, HIV, sickle cell disease, or portal hypertension undergoing evaluation for orthotopic liver transplantation.
- Determining the degree of functional impairment, as assessed by the WHO functional classification system (Classes I-IV) and the 6-min walk test (6MWT), is a useful way to monitor disease progression and assess response to treatment.
- The longitudinal evaluation of patients with pulmonary arterial hypertension is summarized in Table 4.

LABORATORY AND DIAGNOSTIC TESTS

- Complete blood count is usually normal in PAH but may show secondary polycythemia.
- Arterial blood gases show low PO_2 and oxygen saturation.
- Overnight oximetry and/or sleep study to rule out sleep apnea or hypopnea.
- Other blood tests: Antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-Scl-70, anticentromere, antitopoisomerase, anti-Ro, anti-La, anti-RNA polymerase III, ribonucleoprotein antibody levels, and rheumatoid factor (RF) to screen for underlying connective tissue disease, HIV serology, liver function tests, and antiphospholipid antibodies.
- Brain natriuretic peptide (BNP) level can provide prognostic information, with elevation in BNP level being associated with increased mortality.
- Ventilation-perfusion lung scan has high sensitivity for chronic thromboembolic PAH. The diagnosis should be confirmed by pulmonary angiography, which has high specificity.

Rx TREATMENT (FIG. 3)

- Most of the evidence in management of PAH is limited to IPAH/HPAH. There is some evidence in treatment of APAH associated with connective tissue disease, especially scleroderma, and congenital heart disease. The recommendations for treating PAH associated with other causes are limited to case studies and expert opinions.
- There is some evidence for the use of advanced therapies for sarcoidosis-associated PH. The heterogeneity of sarcoid-associated PH complicates the interpretation.

GENERAL MEASURES AND TREATMENT:

- Patients should be encouraged to remain active within symptom limits and avoid excessive physical activity.
- Exercise training appears to be beneficial for patients with PH. It is associated with improved exercise capacity, muscular function, quality of life, and possibly right ventricular function and pulmonary hemodynamics.
- PAH is a contraindication to pregnancy as it carries a 30% to 50% mortality risk.
- PAH patients have a higher risk of death from infections and should receive age-appropriate vaccines as well as be vaccinated against influenza and pneumococcal pneumonia.
- Although there are no randomized data to suggest that long-term O_2 therapy is beneficial, oxygen administration has shown to

TABLE 4 Longitudinal Evaluation of Patients with Pulmonary Arterial Hypertension*

	Low Risk	High Risk
Clinical course	Stable; no increase in symptoms and/or decompensation	Unstable; increase in symptoms and/or decompensation
Physical examination	No evidence of right-sided heart failure	Signs of right-sided heart failure
Functional class†	I/II	IV
6MW distance†	>400 m	<300 m
Echocardiogram	RV size/function normal	RV enlargement/dysfunction
Hemodynamics	RAP normal CI normal	RAP high CI low
BNP	Nearly normal/remaining stable or decreasing	Elevated/increasing
Treatment	Oral therapy	Intravenous prostacyclin and/or combination treatment
Frequency of evaluation	Every 3-6 mo‡	Every 1-3 mo
FC assessment	Every clinic visit	Every clinic visit
6MW distance	Every clinic visit	Every clinic visit
Echocardiogram§	Yearly or center dependent	Every 6-12 mo or center dependent
BNP¶	Center dependent	Center dependent
RHC	Clinical deterioration and center dependent	Every 6-12 mo or clinical deterioration

BNP, Brain natriuretic peptide; *CI,* cardiac index; *FC,* functional class; *IV,* intravenous; *RAP,* right atrial pressure; *RV,* right ventricle; *6MW,* 6-min walk.

*For patients in the high-risk category, consider referral to a PAH specialty center for consideration of advanced therapies, clinical trials, and/or lung transplantation.

†The frequency of follow-up evaluation for patients in functional class III and/or 6MW distance between 300 and 400 m would depend on a composite of detailed assessments of the other clinical and objective characteristics listed.

‡For patients who remain stable with established therapy, follow-up assessments can be performed by referring physicians or PH specialty centers.

§Echocardiographic measurement of pulmonary artery systolic pressure is an estimation only, and it is strongly advised that its evaluation not be relied on as the sole parameter to make therapeutic decisions.

¶The usefulness of serial BNP levels to guide management in individual patients has not been established.

From McLaughlin VV et al: ACCF/AHA 2009 expert consensus document on pulmonary hypertension. A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association, *J Am Coll Cardiol* 53:1573, 2009.

From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

reduce PVR. Ambulatory O_2 may be considered for exercise-induced desaturations to maintain oxygen saturations of >90%.

- Diuretics (e.g., furosemide 40 to 80 mg qd) improve dyspnea by reducing preload and peripheral edema. Avoid excessive diuresis in patients who are preload dependent.
- Digoxin has been used in patients with IPAH with inconclusive benefits. It can be considered in patients who develop atrial tachyarrhythmia. There is no conclusive data regarding the use of beta-blockers, ACE inhibitors, or ARB in IPAH unless required by comorbidities such as concurrent hypertension or cardiomyopathy.
- Evidence for the use of oral anticoagulation with warfarin for IPAH is derived mostly from retrospective single-center experience. Data from RCT and registries remain heterogenous and inconclusive. A large multicenter observational longitudinal registry of patients with IPAH (REVEAL Registry) assessed the effect of warfarin treatment on survival and found no benefit; it also found poorer survival in patients with PAH associated with systemic sclerosis. Generally, patients with IPAH who are undergoing IV prostaglandin therapy are anticoagulated if there are no contraindications to anticoagulation, as they are at high risk for catheter-related thrombosis. There are no data regarding the role of novel oral anticoagulants in IPAH.
- Iron deficiency with or without anemia is common and is associated with reduced exercise capacity; it should be closely monitored and replenished as needed.

CHRONIC Rx

Calcium channel blocker (CCB):

- Acute vasoreactivity response testing should be done in all patients at the time of right heart catheterization. Epoprostenol, adenosine, or nitric oxide is generally used to assess the response. A positive response is a fall in mean PAP of ≥10 mm Hg to a value of <40 mm Hg, with increased or unchanged cardiac output. Fewer than 10% of patients are responders in IPAH, and they are the only patients who can be safely treated with this type of therapy. Acute vasoreactivity study is not recommended for patients in groups 2 to 5.
- The positive responders may benefit from treatment with calcium channel blockers (diltiazem, amlodipine, or nifedipine). All patients should be reassessed in 6 to 8 wk to demonstrate sustained benefit from the calcium channel blocker.
- CCBs should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity because of potential severe side effects.
- If patients do not show an adequate response, additional PAH therapy should be started.

PROSTANOIDS

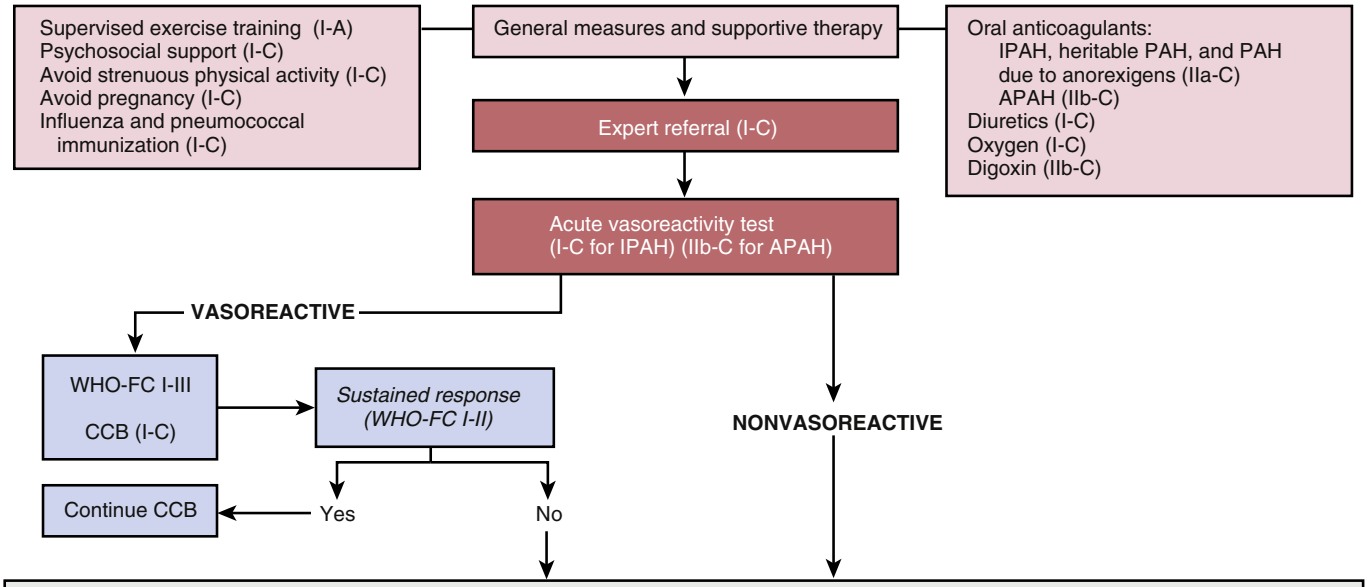
- These synthetic prostacyclin analogues act as potent vasodilators of pulmonary arteries and inhibitors of platelet aggregation. They all have shown improvement in symptoms, exercise capacity including 6MWD, and hemodynamics. They are ideal for WHO functional class III and IV patients.
  1. Epoprostenol: IV formulation with very short half-life (3 to 5 min). It is the most studied drug, and it is the only one that has shown to improve mortality. It requires long-term IV access with associated risks of infection and thrombosis. Rapid tachyphylaxis with dose escalation is seen. Common side effects include flushing, headache, jaw pain, abdominal cramping, and diarrhea. Limited evidence exists for use in secondary PAH patients.
  2. Treprostinil: IV and SQ formulation with longer half-life. Main disadvantage is pain at SQ pump site (no long-term evidence for IV formulation). Treprostinil is also available as a nebulized inhaled solution.
  3. Iloprost: Aerosolized formulation with short half-life requiring 6 to 8 treatments/day. Oral and IV forms are also available. Well tolerated, with flushing and jaw pain being the most frequent side effects.
  4. Beraprost: PO formulation. Not approved in the U.S.

RIOCIGUAT: GUANYLATE CYCLASE STIMULATORS

Guanylate cyclase stimulators enhance cGMP production and in preclinical studies show antiproliferative and antiremodeling properties in animal models. These oral agents are useful for class II and III patients and have shown favorable results on exercise capacity, hemodynamics (decrease in PVR), WHO functional class, and time to clinical worsening without any mortality benefit. There has also been reported benefit in patients with inoperable and persistent chronic group IV pulmonary hypertension with improvement in 6MWD and reduction in PVR. The most serious side effect is syncope.

Endothelin receptor antagonists (ERAs):

Activation of the endothelin system results in vasoconstriction of the pulmonary vascular smooth muscles. Most of these oral pulmonary vasodilators require monthly liver function tests, and often the response is delayed by wks. Thus it is not an ideal starting therapy for WHO class IV patients. It is effective in class II and III patients and improves symptoms, exercise capacity, and hemodynamics without any improvement in mortality.



INITIAL THERAPY WITH PAH-APPROVED DRUGS

RED: Morbidity and mortality as primary endpoint in randomized controlled study or reduction in all-cause mortality (prospectively defined)

* Level of evidence is based on the WHO-FC of most of the patients in the studies

† Approved only, in the United States (treprostinil inhaled), in New Zealand (iloprost IV), in Japan and S. Korea (beraprost)

‡ Drugs under regulatory approval

Recommendation	Evidence*	WHO-FC II	WHO-FC III	WHO-FC IV
I	A or B	Ambrisentan Bosentan Macitentan‡ Riociguat‡ Sildenafil Tadalafil	Ambrisentan Bosentan Epoprostenol IV Iloprost inhaled Macitentan‡ Riociguat‡ Sildenafil Tadalafil Treprostinil SC, inhaled†	Epoprostenol IV
IIa	C		Iloprost IV† Treprostinil IN	Ambrisentan, bosentan Iloprost inhaled, and IV† Macitentan‡ Riociguat‡ Sildenafil, tadalafil Treprostinil SC, IV, inhaled†
IIb	B		Beraprost†	
	C		Initial combination therapy	Initial combination therapy

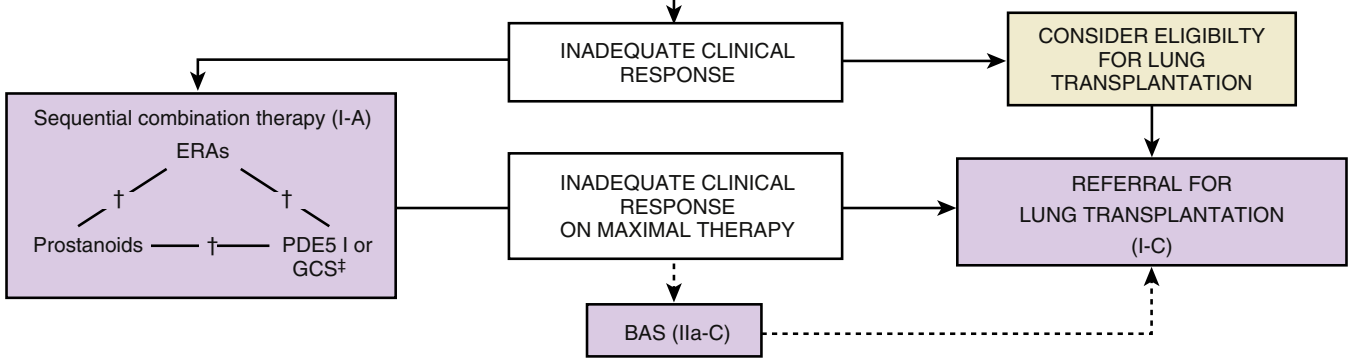


FIG. 3 Treatment algorithm for pulmonary arterial hypertension *(PAH)*. Background therapies include warfarin anticoagulation, which is recommended in all patients with IPAH and no contraindication. Diuretics are used for the management of right-sided heart failure. Oxygen is recommended to maintain oxygen saturation higher than 90%. Acute vasodilator testing should be performed in all patients with IPAH who may be potential candidates for long-term therapy with calcium channel–blocking agents (CCBs). Patients with PAH caused by conditions other than IPAH have a very low rate of long-term responsiveness to oral CCBs, and the value of acute vasodilator testing in such patients needs to be individualized. Patients with IPAH in whom CCB therapy would not be considered, such as those with right-sided heart failure or hemodynamic instability, should not undergo acute vasodilator testing. CCBs are indicated only for patients who have a positive acute vasodilator response, and such patients need to be monitored closely for both safety and efficacy. For patients who did not have positive acute vasodilatory testing and are considered to be at lower risk based on clinical assessment (see Table 5), oral therapy with an endothelin receptor antagonist (ERA) or phosphodiesterase-5 inhibitor (PDE5 I) would be the first line of therapy recommended. If an oral regimen is not appropriate, consideration of the other treatments would need to be based on the patient's profile, side effects, and risk associated with each therapy. For patients who are considered high risk based on clinical assessment (Table 5), continuous treatment with an intravenous prostacyclin (epoprostenol or treprostinil) would be the first line of therapy recommended. If a patient is not a candidate for continuous intravenous treatment, consideration of the other therapies would have to be based on the patient's profile and the side effects and risk associated with each treatment. Epoprostenol improves exercise capacity, hemodynamics, and survival in patients with IPAH and is the preferred treatment option for the most critically ill patients. Combination therapy should be considered when patients are not responding adequately to initial monotherapy. *APAH,* Associated PAH; *BAS,* balloon atrial septostomy; *GCS,* guanylate cyclase stimulators; *IPAH,* idiopathic pulmonary arterial hypertension; *IV,* intravenous; *SC,* subcutaneous; *WHO-FC,* World Health Organization functional class. (From Galiè N et al: Updated treatment algorithm of pulmonary arterial hypertension, *J Am Coll Cardiol* 62[25 Suppl]:D60, 2013. From Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.)

TABLE 5 Pulmonary Arterial Hypertension: Determinants of Prognosis*

Determinants of Risk (estimated 1-yr mortality)	Lower Risk (<5%)	Intermediate Risk (5-10%)	Higher Risk (>10%)
Clinical evidence of RV failure	No	No	Yes
Progression of symptoms	No	Gradual	Rapid
WHO class†	I, II	III	IV
6MW distance‡	>440 m	164-440 m	<165 m
CPET	Peak V_{O_2} >15 ml/kg/min	Peak V_{O_2} 11-15 ml/kg/min	Peak V_{O_2} <11 ml/kg/min
Echocardiography	No pericardial effusion, No RA enlargement, Minimal RV dysfunction	No or minimal pericardial effusion, minimal RA enlargement	Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement
Hemodynamics	RAP <8 mm Hg, CI >2.5 L/min/m^2	RAP 8-14mmHg CI 2-2.4 L/min/m2	RAP >14mm Hg, CI <2.0 L/min/m^2
BNP§	Not elevated	Mildly elevated	Significantly elevated

BNP, Brain natriuretic peptide; *CI,* cardiac index; *CPET,* cardiopulmonary exercise testing; *peak* V_{O_2}, average peak oxygen uptake during exercise; *RA,* right artrial; *RAP,* right atrial pressure; *RV,* right ventricular; *WHO,* World Health Organization.

*Most data available pertain to IPAH, with little data available for other forms of PAH. One should not rely on any single factor to make risk predictions.

†The WHO class is the functional classification for PAH and is a modification of the NHYA functional class.

‡6MW distance is also influenced by age, sex, and height.

§Because data regarding the influence of BNP on prognosis are currently limited and many factors, including renal function, weight, age, and sex, may influence BNP, absolute numbers are not given for this variable.

From McLaughlin VV et al: ACCF/AHA 2009 expert consensus document on pulmonary hypertension. A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association, *J Am Coll Cardiol* 53:1573, 2009. In Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

- Bosentan is an oral nonselective endothelin A and B receptor blocker, whereas sitaxsentan and ambrisentan are oral selective endothelin A receptor blockers. Ambrisentan does not require monitoring of liver function tests.
- ERAs have been shown to cause improvement in exercise capacity, WHO functional class, hemodynamic and echocardiographic variables without affecting mortality.
- Macitentan is a nonselective endothelin receptor antagonist that showed significant reduction in composite end point of death in patients with IPAH. It was thought not to cause liver toxicity, but postmarketing analysis suggested it can cause liver toxicity. It however more frequently can cause anemia and pharyngitis.

Phosphodiesterase (PDE-5) inhibitors:

- These are oral agents that act by inhibiting phosphodiesterase type 5 enzyme (PDE-5), resulting in increased concentration of nitric oxide causing vasodilation through the cGMP/NO pathway. In addition, they exert antiproliferative effects. Highly effective in WHO class II patients, both in IPAH and scleroderma-associated PAH. Improve symptoms, exercise capacity including 6MWD, hemodynamics, and time to clinical worsening. Mortality benefit was not studied. Most side effects are related to vasodilion including headache, flushing, and epistaxis.
- Sildenafil is administered as 20 mg PO tid. Tadalafil dose is 40 mg once daily. They are also used as combination therapy with epoprostenol and endothelin receptor antagonists.

Prostacyclin agonists:

Selexipag is an oral selective nonprostanoid prostacyclin IP receptor agonist approved for PAH. The IP receptor promotes vasodilation and antiproliferation. Selexipag has been shown to decrease disease progression and hospitalizations without any effect on mortality. Side effects are mild and consist of headache, jaw pain, flushing, and diarrhea.

Treatment considerations depending on WHO functional class:

- According to consensus definition, patients with PAH who demonstrate acute vasoreactivity should be considered candidates for therapy with an oral CCB, except in the case of right heart failure or other contraindications.
- CCBs should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity, as described previously.
- For treatment-naïve PAH patients with WHO functional class (FC) II or III symptoms who are not candidates for, or who have failed, CCB therapy, monotherapy should be initiated with an approved ERA, phosphodiesterase-5 (PDE5) inhibitor, or the soluble guanylate cyclase stimulator riociguat.

- For treatment-naïve PAH patients with WHO FC IV, prostanoids are first line.
- For treatment-naïve PAH patients with WHO FC III symptoms who have evidence of rapid progression of their disease or other markers of a poor clinical prognosis, consideration of initial treatment with a parenteral prostanoid is recommended.
- For treatment-naïve PAH patients in WHO FC IV who are unable, or do not desire, to manage parenteral prostanoid therapy, treatment with an inhaled prostanoid in combination with an ERA is recommended.
- For WHO FC III or IV PAH patients with unacceptable clinical status despite established PAH-specific monotherapy, addition of a second class of PAH therapy to improve exercise capacity is recommended. Such patients should be evaluated at centers with expertise in the evaluation and treatment of complex patients with PAH.
- Combination therapies: Considered when there is no improvement or deterioration on monotherapy. The FDA has approved the use of ambrisentan and tadalafil together as the first two-drug regimen for PAH because it is associated with a significant reduction in the rate of clinical failure compared with monotherapy with either drug alone (AMBITION trial). Starting dose is 5 mg for ambrisentan and 20 mg for tadalafil once daily.
- Bosentan + inhaled iloprost (STEP trial) showed some benefit over monotherapy.
- IV epoprostenol + oral bosentan (BREATH-2 trial) did not show a statistically significant difference when compared with monotherapy.
- IV epoprostenol + oral sildenafil (PACES trial) showed benefit over monotherapy.

INVASIVE Rx

- Lung transplantation and heart-lung transplantation are other options in patients with end-stage class IV disease.
- Atrial septostomy may be performed as a bridge to transplant. It involves creation of an interatrial communication, resulting in right-to-left shunt, which decreases right-sided pressure and increases LV preload and cardiac output. Atrial septostomy is recommended for individuals with a room air SaO_2 >90% who have severe right-sided heart failure (with refractory ascites) despite maximal diuretic therapy, or who have signs of impaired systemic blood flow (such as syncope) from reduced left heart filling.
- Extracorporeal membrane oxygenation (ECMO) is also commonly used as a bridge to transplant.
- Patients should be referred for lung transplant if:
  1. They have WHO FC III or IV during escalating treatment
  2. They have rapidly progressive disease
  3. Parenteral therapy is utilized
  4. Pulmonary venoocclusive disease (PVOD) or pulmonary capillary hemangiomatosis is known or suspected

Lung transplant recipients with IPAH have survival rates of 52% to 75% at 5 yr and 45% to 66% at 10 yr.

TREATMENT OF SECONDARY PAH, APAH:

- Directed toward cause. Some situations merit mention:
  1. PAH with uncorrected congenital heart disease: Eisenmenger syndrome. Medical treatment generally ineffective. Heart-lung transplantation required in most patients. PH may persist after surgical correction of congenital heart disease, and pulmonary vasodilators can be effective therapies in this patient population.
  2. PAH with scleroderma: Selective pulmonary vasodilators are effective.
  3. PAH with lung disease or hypoxia: Oxygen therapy for hypoxemia, CPAP for OSA, control of primary disease process.
  4. PAH with chronic thromboembolic disease: Pulmonary endarterectomy is curative; may consider pulmonary vasodilators, notably riociguat, after anticoagulation (for at least 3 mo and if endarterectomy is not an option) if continued symptoms and elevation in PVR and transpulmonary gradient.
  5. PAH with HIV: Control of viral load by antiretroviral therapy.

DISPOSITION

- The 6MWT is predictive of survival in patients with idiopathic PAH. A baseline 6MWT <250 m is associated with a 50% risk of death at 2 yr. Drop in O_2 saturation >10% during the test increases mortality risk 2.9 times over a median follow-up of 26 mo.
- Cardiopulmonary exercise testing (CPET) is also performed, during which gaseous exchange and ventilation are continuously measured during incremental exercise. A peak oxygen uptake (pVO_2) of <10 ml/kg/min independently predicts a worse prognosis.
- A BNP level ≥350 pg/ml at baseline evaluation is associated with a 25% risk of death at 2 yr.
- WHO class II and III patients with PAH have a mean survival of 3.5 yr.
- WHO class IV patients have a mean survival of 6 mo.
- As per the REVEAL (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) risk score, poor prognostic signs include:
  1. Signs of RV failure
  2. WHO functional class III or IV
  3. Walk a distance of <165 meters in 6-min walk test
  4. Peak VO2 <10 ml/min/kg in cardiopulmonary testing
  5. Elevated BNP levels >180 pg/ml
  6. Presence of pericardial effusion
  7. TAPSE [tricuspid annular plane systolic excursion] <2 cm on echo of right ventricle
  8. Right atrial pressure >20 mm Hg or pulmonary vascular resistance of >32 Wood units on right heart catheterization
  9. Increased heart rate >92 or BP <109 mm Hg
  10. Male gender >60 yr of age
  11. Concomitant renal dysfunction with estimated glomerular filtration rate ≤30/ml/min/m
  12. Diffusion capacity of lung for carbon monoxide (DLCO) <33%

REFERRAL

If the diagnosis of IPAH/HPAH is suspected, a consultation with a pulmonary specialist is recommended. PHA may require disease-specific consultations. Advanced cases need to be transferred to transplant centers.

PEARLS & CONSIDERATIONS

- The exertional dyspnea of PAH is typically described by patients as being relentlessly progressive over several mos to a yr, often out of proportion to, or in the absence of, underlying heart or lung disease.
- Over 20% of patients in the Registry to Evaluate Early and Long-term PAH Disease Management had symptoms for more than 2 yr before PAH was recognized. Consideration of the diagnosis of PAH in the differential diagnosis of unexplained dyspnea, especially in younger individuals, is essential.
- Chest x-ray may reveal evidence of interstitial fluid or fibrosis within the lungs in cases of secondary PH. IPAH is not associated with infiltrates on chest radiograph.

COMMENTS

- RV systolic pressure (RVSP) as estimated by echocardiography is not a good indicator of the presence of PAH because RVSP increases with age and body mass index. Athletically conditioned men also have a higher resting RVSP. Thus these measurements can be misleading.
- Abrupt development of pulmonary edema during acute vasodilator testing suggests pulmonary venoocclusive disease or pulmonary capillary hemangiomatosis and is a contraindication to long-term vasodilator treatment.
- In advanced PAH, heart rate increase is the main compensatory mechanism and reflects increased sympathetic tone. A higher heart rate at rest is an important marker of prognosis and should be assessed at frequent intervals after initiation of treatment for PAH.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pulmonary Hypertension (Patient Information)

AUTHOR: **Caroline Zahm, MD**

SUGGESTED READINGS

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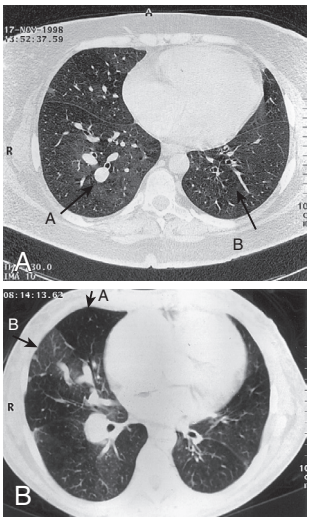

FIG. E2 Chest computed tomographic scans in a patient with chronic thromboembolic pulmonary hypertension. A, Helical scan with contrast medium enhancement of the pulmonary vasculature shows a marked disparity in vessel size between the involved vessels *(A),* which are enlarged from thrombus, and the uninvolved vessels *(B).* **B,** Non–contrast-enhanced high-resolution scan illustrates a marked mosaic pattern manifest by differences in density of regions of the lung parenchyma reflecting the perfused areas *(B)* and the nonperfused areas *(A),* also consistent with underlying thromboembolic disease. (From Zipes DP et al [eds]: *Braunwald's heart disease,* ed 7, Philadelphia, 2005, WB Saunders.)

BASIC INFORMATION

DEFINITION

Pulseless electrical activity (PEA) is defined as the presence of organized cardiac electrical activity without sufficient mechanical contraction to produce a palpable pulse.

SYNONYM

Electromechanical dissociation (EMD)

ICD-10CM CODES

I46.9	Cardiac arrest, cause unspecified
I49.9	Cardiac arrhythmia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Accounts for about 35% of cardiac arrest cases
- Increasingly recognized as the cause of sudden cardiac death in patients with implantable cardioverter-defibrillators

PHYSICAL FINDINGS & CLINICAL PRESENTATION

PRIMARY PEA:

- Organized electrical activity (not VT/VF)
- No detectable pulse

SECONDARY PEA: As in primary PEA and may also have:

- Bradycardia: Drug overdose, elevated vagal tone
- Tachycardia: Hypovolemia, massive PE
- Elevated JVP and no pulse with CPR: Cardiac tamponade, massive PE, tension pneumothorax
- Absent unilateral breath sounds and tracheal deviation: Tension pneumothorax
- Cyanosis: Hypoxia

ETIOLOGY

PRIMARY PEA: Myocardial electromechanical uncoupling secondary to advanced heart muscle disease

SECONDARY PEA: Related to changes in the loading conditions of the heart, ischemia, and/or myocardial depressants. Current guidelines suggest using the 5Hs and 5Ts as diagnostic tools when determining the etiology:

- **H**ypovolemia
- **H**ypoxia
- **H**ypothermia
- **H**ypo-/hyperkalemia
- **H**ydrogen ions (acidosis)
- **T**ension pneumothorax
- **T**amponade
- **T**hrombosis in the lungs (pulmonary embolism)
- **T**hrombosis in the heart (ACS)
- **T**oxins: β-blockers, calcium channel blockers, digoxin, tricyclic antidepressants, benzodiazepines, opioids

DIAGNOSIS

WORKUP

- Stabilizing patient and workup to establish etiology should proceed simultaneously
- History, physical examination, laboratory tests, imaging studies (refer to 5Hs/5Ts)

LABORATORY TESTS

- CBC, potassium, magnesium, CK-MB, troponin, toxicology screen
- Arterial blood gas
- ECG (Fig. E1):
  1. Low voltage: Tamponade
  2. Right heart strain (S1-Q3-T3 pattern, right axis deviation): PE, pneumothorax
  3. Arrhythmias: MI, metabolic abnormalities, drug effects
  4. ST changes, Q waves: MI

IMAGING STUDIES

- Chest radiograph: Rule out pneumothorax, aortic dissection (widened mediastinum).
- Echocardiogram: Rule out tamponade, ischemia (LV contractility, wall motion), valve dysfunction, tumors, and clots. May help diagnose aortic dissection and PE and assess intravascular volume status.
- Abdominal radiograph or ultrasound: Rule out ruptured abdominal aortic aneurysm.

TREATMENT

- Identifying and treating a reversible cause is critical.
- Physiologic parameters can help monitor quality of CPR and detect the return of spontaneous circulation (ROSC). Suggested methods include quantitative waveform capnography, arterial relaxation diastolic pressure, arterial pressure monitoring, or central venous oxygen saturation.

NONPHARMACOLOGIC THERAPY

- Activate emergency response service.
- Begin CPR; ensure high quality, minimize interruptions. Perform CPR for 2 min between pauses to assess rhythm and circulation.
- Attach cardiac monitor/defibrillator.
- Obtain IV/intraosseous (IO) access.
- Consider advanced airway placement.
- Confirm absence of blood flow with Doppler ultrasound, arterial line, or bedside echocardiogram.

ACUTE GENERAL Rx

- Treat specific cause if known.
- Give 100% oxygen.
- Epinephrine 1 mg IV push/IO, q3 to 5min.
- Give normal saline (20 ml) bolus after peripheral IV administration of medication to improve its distribution.
- Medication can be given via endotracheal tube if IV/IO access cannot be obtained; IV/IO routes preferred because they provide more predictable drug delivery and pharmacologic effects. Give 2 to 2.5× the IV dose in 10 ml of sterile water.
- If rhythm changes to VF or pulseless VT:
  1. Defibrillate.
  2. For refractory VF or pulseless VT consider amiodarone.
- If achieve ROSC, initiate postcardiac arrest care.

DISPOSITION

Of hospitalized patients who develop PEA, <15% survive to discharge. Survival rates much lower in patients with prehospital PEA. Survivors often have poor neurologic outcomes.

REFERRAL

As needed for underlying condition

PEARLS & CONSIDERATIONS

- The benefit of epinephrine in PEA resuscitation is uncertain; it may be associated with worse neurologic outcomes and increased long-term mortality. However, the 2015 American Heart Association guidelines support its continued use.
- Targeted temperature management (32 °C to 36 °C [89.6 °F to 96.8 °F] for 24 hr) may improve neurologic outcomes and reduce mortality in comatose cardiac arrest survivors; however, the evidence for therapeutic hypothermia in PEA is based on nonrandomized trials and its role continues to be evaluated. The current AHA guidelines published in 2015 recommend therapeutic hypothermia for all cardiac arrest patients without contraindications.
- Termination of resuscitation guidelines exist for out-of-hospital cardiac arrest. Similar guidelines for in-hospital cardiac arrest are not available; termination of resuscitation is based on multiple patient factors.
- Prognostication is more difficult in patients treated with hypothermia and may be guided by testing, but no single exam finding or test is definitive; a multimodal approach is needed. Delay neurologic testing for at least 72 hr after ROSC. In addition to neurologic examination (corneal and pupillary reflexes, motor response), testing may include median nerve somatosensory-evoked potentials, EEG, biomarkers, and neuroimaging. Wait >72 hr after return to normothermia before attempting to predict outcome.

AUTHOR: **Nathan Riddell, MD**

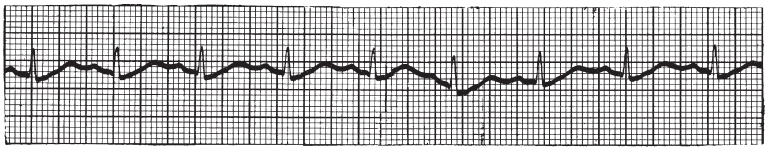

FIG. E1 Sinus rhythm with pulseless electrical activity (PEA). Although the electrocardiogram showed sinus rhythm, the patient had no pulse or blood pressure. In this case the PEA was a result of depressed myocardial function after a cardiac arrest. (From Goldberg AL: *Clinical electrocardiography,* ed 5, St Louis, 1994, Mosby.)

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BASIC INFORMATION

DEFINITION

Pure red cell aplasia (PRCA) is characterized by a triad of severe anemia, reticulocytopenia (<1%), and the absence of erythroid precursors in the bone marrow. All other cell lineages (namely, myeloid precursors and megakaryocytes) are normal. Table E1 describes the classification of PRCA.

SYNONYMS

PRCA
Congenital hypoplastic anemia
Joseph-Blackfan-Diamond syndrome
Acquired red cell aplasia

ICD-10CM CODES

D61.01	Constitutional (pure) red blood cell aplasia
D60.0	Chronic acquired pure red cell aplasia

EPIDEMIOLOGY & DEMOGRAPHICS

- The frequency of this disease has been underestimated mainly due to self-limiting nature of most of the cases.
- Rare disease (WHO classification).

PREDOMINANT SEX AND AGE: The male:female ratio is 2:1 for PRCA with thymoma. However, immune-mediated cases are seen more commonly in females.

GENETICS: A mutation in the gene *RPS19* located at 19q13.2 can be seen in 25% of congenital hypoplastic anemia patients.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Anemia is the primary problem in PRCA.
- Patients with severe anemia can present with fatigue, pallor, tachycardia, and dyspnea.
- Congenital hypoplastic anemia is usually associated with physical findings of short stature, abnormal thumbs, and mental retardation.
- Other stigmata of underlying illnesses such as splenomegaly, enlarged parotid glands, lymphadenopathy, leg ulcers, and thymomas may be evident.
- Physical findings related to complications from therapy including iron overload secondary to PRBC transfusions; corticosteroid therapy and immunotherapy may also be present.

ETIOLOGY (TABLE E2)

- Congenital: Usually sporadic caused by injury to stem cells in utero.
- Acquired: The inciting events in the development of PRCA are not known; however, viruses or exposure to chemicals can serve as potential triggers (Fig. E1).
  1. Acute and often self-limited (usually secondary to drugs, chemicals [Table E3], and viral infections)
  2. Chronic and often requiring treatment of the underlying disorder (hematologic and solid malignancies, thymomas, autoimmune disorders, and immunocompromised states)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- PRCA:
  1. Bone marrow findings: Diminished RBC precursors but otherwise normal cellularity
  2. Peripheral blood: Anemia only
  3. Cytogenetics: Usually normal
- Myelodysplastic syndrome:
  1. Bone marrow findings: Hypercellular with dysplasia
  2. Peripheral blood: Cytopenia(s) with cellular dysplasia
  3. Cytogenetics: Abnormal
- Hemolytic anemia:
  1. Bone marrow findings: Normal cellularity, potentially increased erythrocyte precursors
  2. Peripheral blood: Anemia with elevated LDH, bilirubin, and reticulocyte count; decreased haptoglobin, and positive direct antiglobulin (Coombs) test in autoimmune hemolytic anemia
  3. Cytogenetics: Normal
- Aplastic anemia:
  1. Bone marrow findings: Hypocellular
  2. Peripheral blood: Pancytopenia
  3. Cytogenetics: Usually normal

WORKUP

A search should always be made for the underlying condition. Bone marrow examination is required to diagnose PRCA. Fig. E2 is a diagnostic algorithm for PRCA.

LABORATORY TESTS

- CBC with peripheral smear: Normocytic, normochromic anemia
- Reticulocyte count: Diminished (<1% or <10,000/μL)
- No changes in WBC or platelet count unless

TABLE E1 Classification of Pure Red Cell Aplasia

	Congenital (DBA)	
Primary	Autoimmune Idiopathic	
Secondary	Thymoma	CLL
	Hematologic malignancies	T-LGL/chronic NK-LGL leukemia
		Myeloma
		NHL
		MDS
		ALL
	Solid tumors	Renal cell carcinoma
		Thyroid cancer
		Various adenocarcinomas
	Infections	Parvovirus B19
		EBV, mumps
		HIV, HTLV-1
		CMV
		Viral hepatitis (hepatitis A, hepatitis B)
		Leishmaniasis
		Gram-positive systemic infections (e.g., staphylococcemia)
		Meningococcemia
	Autoimmune conditions	SLE
		RA
		Sjögren syndrome
		Mixed connective tissue disease
		Autoimmune hepatitis
		Anti-EPO antibodies
		ABO-incompatible BMT
		Minor incompatibility
	Drugs and chemicals	
	Pregnancy	
	Severe nutritional deficiencies	
	Renal failure	

ALL, Acute lymphoblastic leukemia; *BMT*, bone marrow transplantation; *CLL*, chronic lymphocytic leukemia; *CMV*, cytomegalovirus; *DBA*, Diamond-Blackfan anemia; *EBV*, Epstein-Barr virus; *EPO*, erythropoietin; *HIV*, human immunodeficiency virus; *HTLV-1*, human T-lymphotrophic virus-1; *MDS*, myelodysplastic syndrome; *NHL*, non-Hodgkin lymphoma; *NK-LGL*, natural killer large granular lymphocyte; *RA*, refractory anemia; *SLE*, systemic lupus erythematosus; *T-LGL*, T-cell large granular lymphocyte. (See Hoffman R et al for multiple references within table.)

Modified from Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE E2 Causes of Acquired Red Cell Aplasia

Drugs	Viruses
Procainamide	Parvovirus B19
Phenytoin	Mumps
Sulfonamides	Hepatitis
Zidovudine	Infectious mononucleosis (Epstein-Barr virus)
Azathioprine	Atypical *Mycoplasma*
Chloramphenicol	
Isoniazid	
Recombinant erythropoietin therapy/anti-EPO antibodies	
Malignancies	**Autoimmune Conditions**
Thymomas (5%)	Systemic lupus erythematosus
Chronic lymphocytic leukemia, chronic myeloid leukemia	Rheumatoid disease
Hodgkin disease	Autoimmune hemolytic anemia
Large granular lymphocyte leukemia	
Immunocompromised States	**Others**
Human immunodeficiency virus	Pregnancy
Human T-lymphotrophic virus type 1	ABO-incompatible hematopoietic cell transplantation
Idiopathic	

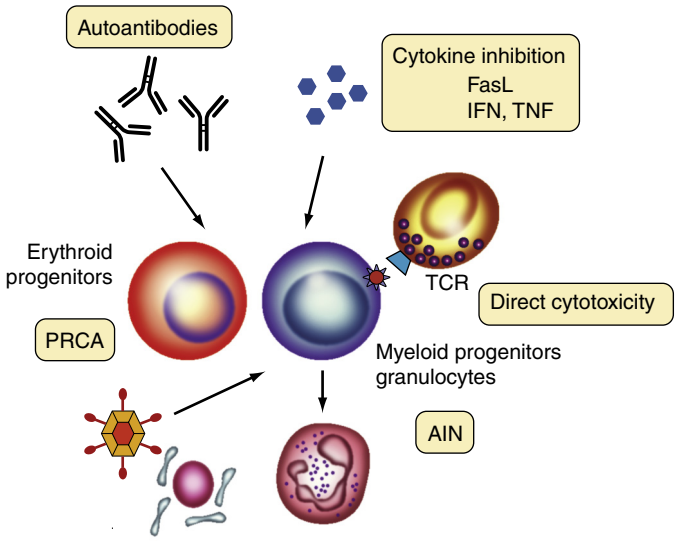

FIG. E1 Pathogenesis of pure red cell aplasia. *AIN,* Autoimmune neutropenia; *FasL,* Fas ligand; *IFN,* interferon; *PRCA,* pure red cell aplasia; *TCR,* T-cell receptor; *TNF,* tumor necrosis factor. (From Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.)

there is an underlying hematologic disorder (e.g., chronic lymphocytic leukemia, large granular lymphocyte leukemia)
- Bone marrow biopsy is essential to make this diagnosis and rule out other causes: Normocellular marrow with normal myeloid precursors and megakaryocytes but absent erythroid precursors
- Viral titers, if clinically indicated
- Antinuclear antibody testing
- Basic labs including hepatic and renal function tests and haptoglobin, LDH
- Negative direct antiglobulin (Coombs) test
- Chest x-ray or chest CT should be ordered in all cases to rule out underlying thymoma
- Specialized test may include karyotyping and immunophenotyping and peripheral flow cytometry if underlying hematologic disorder is suspected

Rx TREATMENT

NONPHARMACOLOGIC THERAPY
- Treatment of the underlying cause
- Discontinuation of possible offending drugs
- Packed red blood cell (PRBC) transfusion for severely symptomatic anemia
- Immediate hematologic consultation
- Viral infections usually resolve spontaneously in 2 to 3 wk
- About 10% to 15% of patients have thymomas. Surgical resection results in amelioration of anemia in 30% of cases

ACUTE GENERAL Rx
- PRBC transfusion is indicated for symptomatic anemia.
- A vast majority of patients have a protracted remitting and relapsing course, requiring long-term support of anemia with blood transfusions and long-term treatment with immunosuppressive agents.

CHRONIC Rx
- In refractory and relapsed cases, immunosuppressive therapy usually with prednisone as monotherapy or in combination with cyclosporine or cyclophosphamide or antithymocyte globulin (ATG) should be considered.
- Allogeneic hematopoietic stem cell transplantation is considered in the most severe cases refractory to initial immunotherapy.
- Immunocompromised hosts with PRCA secondary to parvovirus infection may not improve spontaneously and often benefit from high-dose intravenous immunoglobulin (IVIG) therapy.
- Certain cases of thymomas with PRCA that do not respond to surgery may respond to somatostatin analogs (e.g., octreotide) in combination with prednisone.
- In patients with pure cell aplasia caused by antierythropoietin antibodies, stopping erythropoietin therapy and transfusing RBCs can help to correct severe anemia.

DISPOSITION
- Acute self-limited PRCA has an excellent prognosis.
- The mortality rate is low in most of the acquired chronic cases but may have significant morbidity related to the underlying condition and complication of therapy.
- Patients with congenital red cell aplasia undergo remission in 15% to 25% of cases and may not need treatment again, or may relapse after reaching adulthood.

REFERRAL
All patients should be referred to a hematologist for complete workup, diagnosis, initiation of appropriate treatments, and monitoring of the response to therapy.

PEARLS & CONSIDERATIONS

COMMENTS
- Rare diagnosis.
- Many cases self-limiting; those associated with malignancies require treatment of the underlying condition.

PREVENTION
Medications implicated as the cause of PRCA should be avoided.

PATIENT & FAMILY EDUCATION
- The consequences of iron overload and secondary hemosiderosis from repeated transfusion therapy should be explained to patients.
- The possibility of the transmission of infections with transfusions and immunotherapy should be discussed with patients.
- Long-term use of corticosteroids, immunomodulators can result in significant adverse effects that should be explained to patients.

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TABLE E3 Drugs and Chemicals Implicated in Pure Red Cell Aplasia

Alemtuzumab	Isoniazid
Allopurinol	Lamivudine
α-Methyldopa	Linezolid
Aminopyrine	Maloprim
Azathioprine	Mycophenolate mofetil
Benzene	Penicillin
Carbamazepine	Phenylbutazone
Cephalothin	Phenytoin
Chloramphenicol	Procainamide
Chlorpropamide	Ribavirin
Cladribine	Rifampicin
Cotrimoxazole	Sulfasalazine
D-Penicillin amine	Sulfathiazole
Erythropoietin	Sulindac
Estrogens	Tacrolimus
Fludarabine	Thiamphenicol
FK506	Ticlopidine
Gold	Valproic acid
Halothane	Zidovudine
Interferon-α	

From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

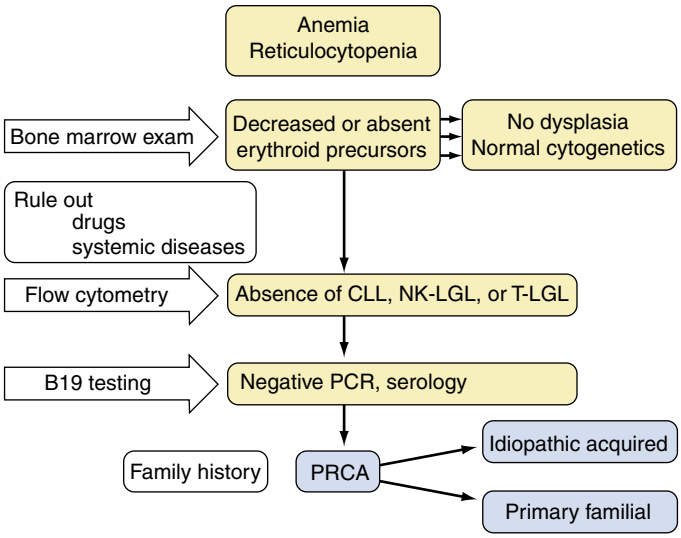

FIG. E2 Diagnostic algorithm in pure red cell aplasia. *CLL,* Chronic lymphocytic leukemia; *NK-LGL,* natural killer large granular lymphocyte; *PCR,* polymerase chain reaction; *PRCA,* pure red cell aplasia; *T-LGL,* T-cell large granular lymphocyte. (From Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.)

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BASIC INFORMATION

DEFINITION

Ascending infection of a bacterial pathogen that infects the renal pelvis and kidney. It primarily presents as a urinary tract infection (UTI) characterized by painful urination (dysuria) with associated flank pain/tenderness, nausea, vomiting, and/or fever. The elderly may also present with failure-to-thrive, unexplained anorexia, other organ system decompensation, or generalized deterioration.

CONSISTS OF TWO GROUPS:

- ***Uncomplicated:*** Can be treated as an outpatient with oral antibiotics.
- ***Complicated:*** Inpatient treatment with intravenous antibiotics is required. Hospitalization is indicated for persistent vomiting, progression of uncomplicated UTI, suspected sepsis, immunosuppression, or urinary tract obstruction. This is a potentially life-threatening infection that can lead to renal parenchymal damage. Timely diagnosis and management can significantly impact patient outcomes.

SYNONYMS

Acute pyelonephritis
Pyonephrosis
Renal carbuncle
Lobar nephronia
Acute bacterial nephritis

ICD-10CM CODES

N10	Acute tubulo-interstitial nephritis
N11	Chronic tubulo-interstitial nephritis
N11.0	Nonobstructive reflux-associated chronic pyelonephritis
N11.1	Chronic obstructive pyelonephritis
N11.8	Other chronic tubulo-interstitial nephritis
N11.9	Chronic tubulo-interstitial nephritis, unspecified
N12	Tubulo-interstitial nephritis, not specified as acute or chronic
N20.9	Calculus pyelonephritis

Use additional code (B95-B97) to identify infectious agent.

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Pyelonephritis is extremely common in the U.S. (450,000 cases per yr), with the highest incidence in the summer. Pyelonephritis accounts for 9.1% to 31% of severe sepsis cases annually, depending on geographic area. Mortality averages 16.1% annually, ranging from 5% for ages <25 yr to 43% for ages >64 yr.

PREDOMINANT SEX: Women are 5 times more likely to be hospitalized than men until age 65 yr. In males beyond age 65 yr, the difference in prevalence narrows. Risk factors associated with pyelonephritis in healthy women are sexual intercourse (3 or more times weekly over the previous 30 days), a new sex partner in the past yr, use of spermicide, UTI in the past 12 mo, mother with a history of UTI, diabetes mellitus, and urinary incontinence. Urinary tract obstruction is the most important risk factor for a complicated UTI.

PREDOMINANT AGE: Trimodal distribution described in females:

- Girls, ages 0 to 4 yr
- Women, ages 15 to 35 yr especially if sexually active
- Gradual increase in frequency after age 50 yr, with peak incidence at 80 yr

Bimodal distribution in males:

- Boys, ages 0 to 4 yr
- Gradual increase in prevalence after age 35 yr with peak incidence at 85 yr

GENETICS: Congenital urologic structural disorders associated with vesicoureteral reflux predispose to infections at an early age (<5 yr) and produce renal scarring in most males and some females. Pyelonephritis may produce an Ask-Upmark kidney (segmental renal hypoplasia) which is found more often in young females with severe hypertension.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Diagnosis established by clinical presentation, history, and physical examination.

Pyelonephritis is suspected in cases of lower urinary tract symptoms (e.g., urinary frequency, urgency, and dysuria) and frequently accompanied by any of the following:

- Fever, rigors, chills (fever may not be present in the elderly or immunosuppressed)
- Flank pain
- Hematuria: Gross hematuria occurs rarely in acute pyelonephritis and raises suspicion for acute cystitis, papillary necrosis, or lower genitourinary malignancy
- Toxic appearance
- Nausea and vomiting
- Headache
- Diarrhea

Physical examination may elicit costovertebral angle tenderness with exquisite flank pain, a nearly universal finding. Its absence suggests an alternative diagnosis. Patients presenting with nephrolithiasis/ureterolithiasis usually do not present with costovertebral angle tenderness. Usually, abdominal or suprapubic tenderness is present.

ETIOLOGY

Ascending infections from intestinal bacteria that colonize the perineum and vulva in women account for most infections. Less commonly, bacteria, viruses, or fungal pathogens may produce hematogenously induced pyelonephritis.

- Gram-negative bacilli cause 95% of cases (e.g., *E. coli* and *Klebsiella* species).
- Less common gram-negative bacteria may produce infection, particularly after urinary tract instrumentation (e.g., *Enterobacter, Serratia,* and *Proteus mirabilis, Pseudomonas*, among others).
- Resistant gram-negative organisms or fungi such as *Candida* may colonize indwelling catheters.
- Gram-positive organisms such as enterococci and rarely, *Staphylococcus saprophyticus.*
- *Staphylococcus aureus* indicates hematogenous spread to the kidneys.
- Viruses generally are limited to the lower urinary tract.
- Urea-splitting organisms generate alkaline urine, which fosters production of staghorn calculi. These stones may grow to large size and cause infection, obstruction, or both.

In the elderly, *E. coli* is less common (60%). Diabetics develop infections from *Klebsiella* species, Enterobacteriaceae, *Clostridia* species, or *Candida* species.

During the past decade, community-acquired bacteria (particularly *E. coli*) that produce extended-spectrum beta-lactamases have emerged as a cause of acute pyelonephritis worldwide. The most common risk factors for these uropathogens include frequent visits to health care centers, recent use of antimicrobials (e.g., cephalosporins and fluoroquinolones), older age, immunosuppression, recurrent pyelonephritis, nephrolithiasis, and comorbid conditions such as diabetes mellitus and recurrent UTIs.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes the following:

- Abdominal abscess
- Acute abdomen
- Appendicitis
- Basilar pleural process
- Diverticulitis
- Endometriosis
- Herpes zoster
- Lower rib fracture
- Metastatic disease
- Musculoskeletal disorders
- Nephrolithiasis
- Pancreatitis
- Papillary necrosis
- Pelvic inflammatory disease
- Prostatitis
- Pulmonary infarctions
- Renal corticomedullary necrosis
- Renal vein thrombosis
- Retroperitoneal hemorrhage or abscess
- Splenic abscess or infarct
- Urinary tract obstruction
- Vascular pathology

WORKUP

Evaluation includes prostate health assessment in older males.

URINALYSIS

Conducted on a clean-catch voided or catheterized specimen, if unable to void or cooperate. Dipstick and microscopic examination must be performed on a fresh specimen for preservation of formed elements (e.g., cells, casts, and microorganisms). Most cases demonstrate pyuria and positive leukocyte esterase in association with a positive blood reaction and

microhematuria. Leukocyte casts are generally of renal origin but may be absent.

URINE CULTURE

Historically, clean, midstream cultures are obtained from all patients suspected of having acute pyelonephritis to guide antibiotic therapy. However, a clean-catch specimen may not be necessary because recent evidence demonstrates no significant difference in the number of contaminated or unreliable culture results when collected with or without preparatory cleansing. Obtain a catheterized urine sample if the patient is unable to void, is uncooperative, or has a change in mental status. There is no difference in colony counts or organisms between catheterized and midstream voiding samples.

More than 95% of acute pyelonephritis cases exhibit more than 10^5 colony-forming units of a single bacterium per ml of urine. However, it is important to obtain an accurate history regarding the timing of culture acquisition and prior antibiotic administration. A negative culture with classic clinical and radiological findings does not rule out acute pyelonephritis as proven in a prospective study in which only 23.5% of 196 patients with clinical and radiological evidence of acute pyelonephritis demonstrated positive urine cultures. A urine Gram stain may aid in the choice of empiric antimicrobial therapy pending urine culture. If gram-positive cocci are seen, one should consider *Enterococcus* species or *Staphylococcus saprophyticus* as causative.

Post-treatment urinalysis and culture are unnecessary if symptomatic improvement occurs, but these studies should be obtained if symptomatic improvement does not occur within 2 to 3 days of antibiotic treatment, or symptoms recur within 2 wk of treatment. Urinary tract imaging is recommended in these cases.

BLOOD CULTURES

Cultures are obtained from hospitalized patients, but may not be routinely required in uncomplicated cases. Approximately 15% to 30% of patients with acute pyelonephritis are bacteremic. The elderly and individuals with complicated acute pyelonephritis are more likely to develop bacteremia and sepsis.

Urine cultures yield a causative organism in nearly all cases of acute pyelonephritis. Therefore, a positive blood culture may be diagnostically redundant. However, in unclear cases, or when an alternative diagnosis to acute pyelonephritis is considered, endometriosis, intraabdominal or psoas abscess, or cholangitis, blood cultures should be obtained.

RADIOLOGY

Most uncomplicated cases of acute pyelonephritis do not require imaging studies, unless symptoms do not improve or recurrence occurs or patient has prolonged fever (>72 hours) or persistent bacteremia. Abdominal radiographs (i.e., kidney, ureter, and bladder x-ray [KUB]) are of limited use in acute pyelonephritis, unless staghorn calculi are present. Retrograde or antegrade pyelography may be helpful in severe obstruction that is not evident after noninvasive evaluations. Voiding cystourethrography demonstrates vesicoureteral reflux and is generally performed routinely only in children.

Recommendations for radiologic tests:

- Healthy patients with uncomplicated pyelonephritis typically do not require radiologic evaluation when therapeutic responses occur within 72 hours of antibiotic therapy.
- If no response to therapy occurs within 72 hours, abdominal CT is the study of choice.
- Diabetics and immunocompromised patients should undergo precontrast and postcontrast abdominal and pelvic CT scans (Fig. 1) within 24 hours of diagnosis when the response to therapy is not prompt.
- Ultrasound (Fig. E2) is reserved for patients in whom exposure to contrast or radiation is considered hazardous. There is a high false-negative rate for renal abscess with ultrasound. In a prospective study of acute pyelonephritis of 213 patients submitted for CT/NMR study, 50 patients (23.5%) had a renal abscess, yet only two were detected by ultrasound.
- All other adults with complicated cases (i.e., history of stones or other urologic conditions, prior urologic surgery, repeated episodes of pyelonephritis) should be evaluated early by CT.
- Helical CT detects calculi with high sensitivity.
- Urologic imaging studies should be conducted in all young men and boys.

Although the risk of contrast nephropathy has declined substantially, exert caution during contrast administration to patients with chronic kidney disease or for those taking metformin. When evaluating kidney function, diagnostic decision-making must include eGFR trends, not serum creatinine, especially in the elderly. Patients with acute pyelonephritis and acutely elevated baseline serum creatinine may warrant CT imaging to rule out obstruction. If the risk of radiocontrast media administration outweighs its benefits, consider retrograde or antegrade pyelography.

The purpose of imaging is to identify underlying structural abnormalities, such as occult obstruction from a stone or abscess and serious complications such as emphysematous pyelonephritis. In a prospective study of 213 patients with acute pyelonephritis, there were no differences in frequency of fever, leukocytosis, C-reactive protein, pyuria, urine cultures, and duration of symptoms before hospitalization for positive or negative CT. Accordingly, systematic CT or magnetic resonance imaging is not required to exclude an anatomical abnormality. Such abnormalities cannot be predicted based on clinical, biochemical, or culture parameters.

Emphysematous pyelonephritis is a necrotizing infection that produces intraparenchymal kidney gas identifiable by renal imaging that is associated with high mortality. Risk factors include diabetes mellitus and/or urinary tract obstruction. Gas-forming bacteria, most commonly *E. coli*, produce gas that is usually restricted within Gerota fascia. If gas is localized to the kidney, mortality is 60%. If gas spreads to the perinephric space, mortality is 80%. In emphysematous pyelitis, the mortality is 20%. This must be differentiated from a renal abscess that can also be associated with a gas collection. With drainage and antibiotic treatment, a renal abscess has a favorable prognosis.

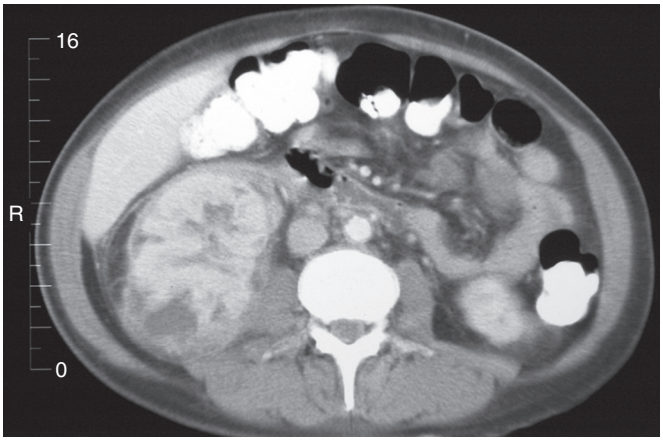

FIG. 1 Acute pyelonephritis: Contrast material–enhanced computed tomographic (CT) scan. The heterogeneous CT nephrogram shows the diffuse involvement of the right kidney. Stranding and some fluid are visible in the perinephric space with thickening of Gerota fascia. (From Skorecki K et al: *Brenner & Rector's the kidney*, ed 10, Philadelphia, 2016, Elsevier.)

LABORATORY TESTS

A basic metabolic profile and CBC with differential count are required for all patients with suspected acute pyelonephritis to estimate renal function. If the diagnosis is in doubt, other laboratory tests may be appropriate to clarify the differential diagnosis (e.g., lipase, transaminase, and β-HCG levels).

Rx TREATMENT

ACUTE GENERAL Rx

UNCOMPLICATED ACUTE PYELONEPHRITIS: Close outpatient follow-up is possible with minimal gastrointestinal symptoms and the ability to maintain fluid intake and oral medications. Prompt antibiotic therapy prevents progression of infection and must be initiated following acquisition of appropriate cultures. Begin empiric therapy based on risk of adverse effects, local community bacterial profiles, and resistance rates. Antibiotics are revised after urine culture results are available.

The concept of requiring long-term treatment of acute pyelonephritis has been questioned. Women with acute pyelonephritis were randomized to oral treatment with ciprofloxacin 500 mg twice daily for 7 days or 14 days, and 27% of these patients experienced bacteremia from *E. coli*. No differences in the cure rates were found (87% and 96%, respectively).

Outpatient regimens:

- Fluoroquinolones are preferred in communities where the local prevalence of resistant *E. coli* is ≤10%.
- Ciprofloxacin 500 mg by mouth twice daily or a single, 1000-mg dose in the extended-release form by mouth daily for 7 days.
- Levofloxacin 750 mg by mouth daily for 5 days.
- The initial dose may be administered intravenously (ciprofloxacin 400 mg or levofloxacin 500 mg).
- When a fluoroquinolone is contraindicated, alternative treatment with trimethoprim/sulfamethoxazole 160/800 mg PO twice daily for 10 to 14 days may be administered if the pathogen is susceptible. Recent data suggest that stopping treatment at 7 days may be equally effective.

Because of the high prevalence of resistance to oral beta-lactam antibiotics and trimethoprim/sulfamethoxazole, these agents usually are reserved for cases where susceptibility results are known. Additional factors (e.g., allergy history, potential drug–drug interactions, drug availability) may require empiric treatment with these agents before susceptibility results are known. For such cases, a long-acting, broad-spectrum parenteral drug (e.g., ceftriaxone 1 g or gentamicin 5 mg/kg) may be administered as a one-time dose or longer, until sensitivities of the organism are known. If the local prevalence of fluoroquinolone resistance to *E. coli* exceeds 10%, an initial intravenous dose of ceftriaxone or gentamicin is recommended, followed by an oral fluoroquinolone regimen.

Significant clinical improvement during appropriate empiric antibiotic therapy should occur within 48 to 72 hours. If improvement does not occur, a complication of acute pyelonephritis or an alternative diagnosis such as an abscess, emphysematous pyelonephritis, or an obstructing calculus should be considered. Any unexpected change in the clinical picture warrants immediate investigation with a CT scan, and with potential for surgical intervention.

COMPLICATED ACUTE PYELONEPHRITIS: Hospitalization is indicated for the following reasons:

- Toxic patients
- Complicated infections
- Diabetes or otherwise immunosuppressed
- Suspected bacteremia

Inpatient care includes supportive care, monitoring of culture results, adjustment of antibiotic regimen, and intravenous volume repletion as required. Intravenous antibiotics are continued until defervescence occurs and clinical improvement occurs. Next, there is conversion to an oral antibiotic regimen for a total duration of 10 to 14 days.

- Intravenous antibiotic options for more toxic patients pending cultures include ceftriaxone (1 to 2 g once daily), IV ciprofloxacin (400 mg every 12 hours) or IV levofloxacin (500 to 750 mg IV once daily), piperacillin/tazobactam (3.375 g IV every 6 hours), or carbapenems such as meropenem or imipenem (500 mg IV every 6 to 8 hours).
- Ceftazidime 1 to 2 g IV every 8 hours, piperacillin/tazobactam, or carbapenems are optimal choices for *Pseudomonas* due to this organism's increasing ciprofloxacin resistance.
- Aminoglycosides (2 mg/kg IV loading dose followed by 1 mg/kg IV every 8 to 12 hours, adjusted for kidney function) are potentially nephrotoxic, and are used only when there is no better alternative. Vancomycin 1 g IV every 12 hours, linezolid 600 mg IV or PO every 12 hours, or daptomycin 4 to 6 mg/kg IV daily for gram-positive cocci (e.g., enterococci, staphylococci).
- Ampicillin 1 to 2 g IV every 4 to 6 hours for ampicillin-sensitive enterococci with aminoglycoside for synergy. Urinary obstruction is promptly drained by nephrostomy tube. Surgical drainage of abscess formation(s).
- Pregnant females with acute pyelonephritis are hospitalized and treated initially with a second- or third-generation cephalosporin.

RENAL ABSCESSES (RENAL CARBUNCLES)

Cortical abscesses historically required surgical drainage; however, using current antibiotics is commonly sufficient for cure.

- Semisynthetic penicillin, cephalosporin, fluoroquinolone, or vancomycin, with guidance from culture and sensitivity results.
  1. Parenteral therapy for 10 to 14 days followed by oral therapy for 2 to 4 wk.
  2. Fever should resolve in 5 to 6 days and pain within 24 hours.
  3. If no clinical response occurs within 48 hours, percutaneous or open drainage should be considered. More extreme measures are occasionally required, including enucleation or nephrectomy.

CORTICOMEDULLARY ABSCESSES

- Parenteral therapy for at least 48 hours is typically successful.
- May require incision and drainage and possibly nephrectomy.
- If defervescence occurs, IV antibiotic treatment may be switched to complete a 2-wk course of oral antibiotic therapy.

PERINEPHRIC ABSCESSES

- Serious complication with mortality in the 25% to 50% range.
- Lesions require early recognition, surgical drainage, and parenteral antibiotics (not adequate alone) to reduce mortality.
- Initial antibiotic therapy should include an aminoglycoside and an antistaphylococcal agent.
  1. If *Pseudomonas* species grow in culture or are suspected, an antipseudomonal beta-lactam antibiotic should be administered with the aminoglycoside.
  2. For enterococcus, an aminoglycoside and ampicillin are recommended.
- Reported with tuberculosis or fungi as rare causes.
- Nephrectomy may be considered with clinical deterioration despite aggressive therapy.

CALCULI-RELATED INFECTIONS

Chronic pyelonephritis may lead to struvite stone formation, which is comprised of magnesium ammonium phosphate (struvite) and calcium carbonate-apatite. Formation requires infection with a urease-producing organism, such as *Proteus* or *Klebsiella*. Under normal conditions the urine is undersaturated with ammonium phosphate.

Symptoms directly attributable to struvite stones are uncommon. Most frequently, patients will present with symptoms of a urinary tract infection, mild flank pain, or hematuria. The stone may grow rapidly over a period of wks to mos and, if not adequately treated, can develop into a staghorn or branched calculus filling the entire renal pelvis and calyces.

Medical treatment for struvite stones is often ineffective and only indicated when surgery is not an option. Mortality is 28% with observation vs. 7.2% with surgical treatment. The most common surgical intervention is percutaneous nephrolithotomy. Open surgery, once the gold standard, is rarely used now.

Surgical intervention is generally recommended in patients with newly discovered stones or in patients with a solitary kidney or two equally functioning kidneys. Nephrectomy is a reasonable option in patients with a nonfunctional kidney, especially if chronic infection is present.

RENAL PAPILLARY NECROSIS

- Admission for parenteral antibiotics:
  1. Initial therapy should cover *E. coli*, *Enterobacter*, *Proteus*, and *Klebsiella* species, pending culture results.
  2. For more serious infections, *Pseudomonas* and *Enterococcus* should also be covered.
  3. Empiric therapy agent options include the following:
     a. Aminoglycosides
     b. Cefotaxime
     c. Ceftriaxone
     d. Ceftazidime
     e. Cefepime
     f. Piperacillin-tazobactam
     g. Imipenem-cilastatin
     h. Meropenem
     i. Ciprofloxacin
  4. Continue parenteral therapy until fever and clinical symptoms improve.

Xanthogranulomatous pyelonephritis: Rare variant of chronic pyelonephritis with destruction of renal parenchyma.

- Generally, unilateral
- Usually in individuals with obstructing stones
- CT is the diagnostic modality of choice and can provide staging information
- Can be confused with malignancy
- Treatment is surgical nephrectomy

CHRONIC Rx

- Repair underlying structural problems especially when kidney function is compromised.
  1. Reflux
  2. Obstruction
  3. Suspect nephrolithiasis
- Avoid urinary catheters.

DISPOSITION

- If pyelonephritis is uncomplicated with no significant GI symptoms, treatment may be initiated on an outpatient basis with close monitoring of therapeutic response(s) in 48 to 72 hours.
- If pyelonephritis is complicated and symptoms persist for >48 to 72 hours, admission is recommended for any of the following: Significant GI symptoms that preclude oral therapy, pregnancy, urinary tract obstruction, suspected renal or perinephric abscess, bacterial sepsis, diabetes or other immunocompromised states, recurrent or refractory pyelonephritis, or infection with unusual or antibiotic-resistant microorganisms.
- If sepsis is present, consider intensive care unit hospitalization.
- Acute pyelonephritis may be fatal when complications develop such as emphysematous pyelonephritis (mortality rate, 20% to 80%), perinephric abscess (mortality rate, 20% to 50%), or sepsis syndrome (>25% overall mortality rate).
- Acute deterioration or nonresponse to conventional therapy may be due to a complication, resistant organism, or unrecognized comorbidity.
- Diabetic patients with acute pyelonephritis are prone to bacteremia, longer hospital stays, and greater mortality. Diabetics should be considered complicated patients.
- Patients >65 yr of age experience greater mortality, septic shock, bedridden status, and immunosuppression. In males, mortality is also increased with the use of antibiotics in the previous mo.

REFERRAL

- General surgery or urology for suspected abscess
- Infectious disease for resistant organisms and poor response to routine antibiotic therapy as outlined
- Urology to correct underlying urologic problems (e.g., reflux and hydronephrosis)
- Nephrology consult for renal dysfunction or nephrolithiasis evaluation
- Critical care medicine if ICU admission is required

PEARLS & CONSIDERATIONS

- Consider acute pyelonephritis in patients with urinary symptoms, flank pain, and fever.
- Obtain a urinalysis and culture before starting empiric antibiotic therapy. Adjust treatment, pending antibiotic sensitivity testing.
- Evaluate clinical response in 48 to 72 hours during outpatient therapy. If there is no or delayed improvement, continue evaluation to rule out urinary tract obstruction.
- Urology consultation in all cases of urinary tract obstruction or detection of urinary tract gas (e.g., emphysematous pyelonephritis).
- Treat all diabetics as complicated acute pyelonephritis patients.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pyelonephritis (Patient Information)

AUTHORS: **James P. Reichart, MD,** and **Nelson Kopyt, DO**

SUGGESTED READINGS

AHRQ Guidelines: ACR Appropriateness Criteria acute pyelonephritis. www.ahrq.gov/gam/index.html.

Colgan R et al: Diagnosis and treatment of acute pyelonephritis in women, *Am Fam Physician* 84(5):51, 2011.

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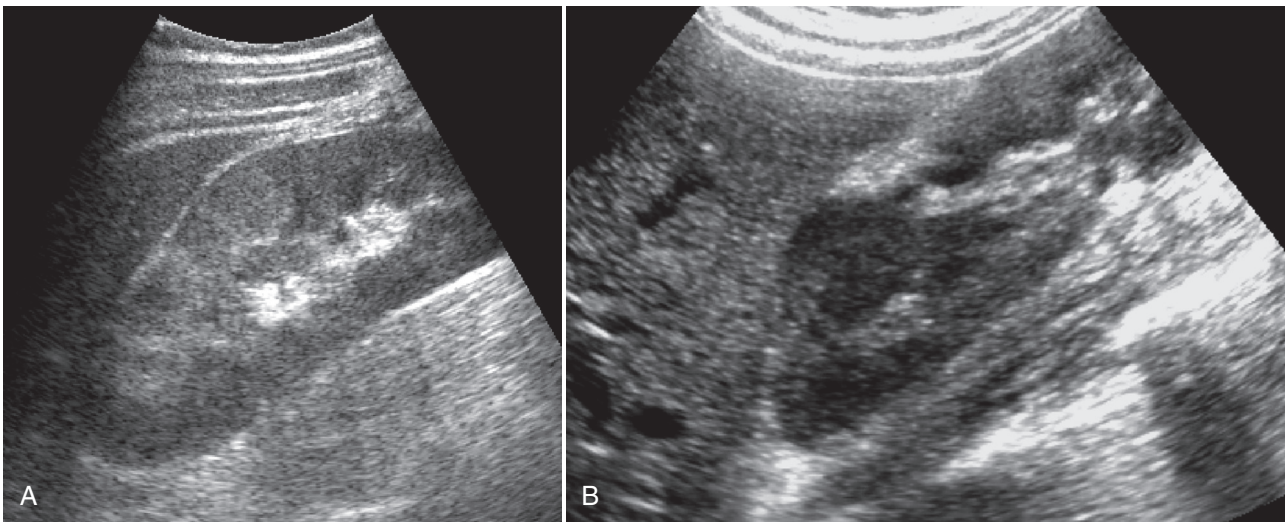

FIG. E2 Acute pyelonephritis. A, Subtle focal increased echogenic areas are seen in the anterior cortex of the right kidney. **B,** Single focal hypoechoic area is seen in the upper pole of the kidney in another patient. (From Rumack CM et al: *Diagnostic ultrasound*, ed 4, Philadelphia, 2011, Elsevier.)

Pyoderma Gangrenosum

BASIC INFORMATION

DEFINITION

Pyoderma gangrenosum (PG) is a rare, noninfectious neutrophilic dermatosis that presents as an inflammatory skin disease characterized by a papule or pustule that progresses to a painful ulcer with violaceous overhanging borders and a purulent base.

In contrast to its name, PG is neither an infectious nor gangrenous condition.

ICD-10CM CODE
L88 Pyoderma gangrenosum

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 10 cases per million people per yr.
PREDOMINANT AGE: Most common in young and middle-aged adults, with an average age of onset between 40 and 60 yr. Children can be affected.
PREDOMINANT SEX: Women are more frequently affected.
GENETICS: Familial cases of PG have been reported. PAPA syndrome is an autosomal dominant disorder linked to a mutation on chromosome 15q and characterized by pyogenic sterile arthritis, PG, and acne.
RISK FACTORS: Autoimmune diseases, particularly ulcerative colitis, Crohn disease, and rheumatoid arthritis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typically presents first as an inflammatory papule, pustule, vesicle, or nodule that rapidly and painfully progresses to an ulcer or erosion with tissue necrosis and enlargement of the area. The ulcer or erosion is surrounded by a violaceous border with a surrounding erythema (Fig. E1). Level of the pain is greater than expected based upon the appearance of the ulcer. Fever may be present.
- Classic PG is commonly found on the lower extremities (Fig. E2).
- Atypical PG occurs more frequently in the upper extremities, head, and neck. Atypical PG lesions begin as pustules and become plaques that may be studded with pustules.
- Peristomal PG lesions appear similarly to classic PG lesions; however, they occur around surgically created stomas such as in Crohn disease surgery.
- PG might also involve the genital area or might rarely affect extracutaneous sites (liver, lungs, intestines, cornea, heart, bones, CNS).
- As many as 30% of lesions occur via pathergy. Pathergy is the abnormal development of skin lesions at the sites of injury, including minor injuries. Pathergy-induced PG lesions can be misdiagnosed as cellulitis. Surgery can also induce pathergy.
- Some patients only present with a single episode of PG, while others can have multiple episodes or a chronic relapsing course.
- Approximately 50% of PG sufferers have an underlying systemic disease, including inflammatory bowel disease, myeloproliferative diseases, hematologic disorders (most frequently IgA monoclonal gammopathy), or inflammatory arthritis, pulmonary diseases, SLE, thyroid diseases, solid organ cancers, viral and autoimmune hepatitis, sarcoidosis, and major depression.

ETIOLOGY

Neutrophilic infiltration causing cutaneous damage seems to be a major part of the underlying mechanism. Abnormalities in neutrophil function, genetic variations, and dysregulation of the innate immune system are the primary factors causing PG.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

PG is often misdiagnosed due to its rareness, its similar appearance to other lesions, and a general lack of awareness of its existence.

- Cellulitis
- Vascular occlusion disorders
- Fungal infection
- Brown recluse spider bite
- Primary systemic vasculitides such as polyarteritis nodosa and granulomatosis with polyangiitis
- Malignancies such as squamous cell carcinoma, cutaneous lymphoma, and metastatic carcinoma
- Sporotrichosis
- Angiocentric T-cell lymphoma
- Cryoglobulinemia
- Drugs
- Livedoid vasculopathy
- Antiphospholipid syndrome
- Erythema nodosum
- Erythema elevatum diutinum

WORKUP

PG is a diagnosis of exclusion. Workup should include biopsy of lesions and evaluation for associated underlying illness such as inflammatory bowel disease, arthritis, or malignancy. History, particularly as to the timing and progression of the lesions and inciting injury, is particularly important, as well as the physical appearance and localization of the lesions.

LABORATORY TESTS

Skin biopsy is not diagnostic in itself because the findings are nonspecific. However, it may be helpful in excluding other diseases. Histopathologic findings show sterile dermal neutrophilia with or without mixed inflammation or lymphocytic vasculitis. Giant cells or leukocytoclastic vasculitis might be found. Other appropriate testing include rheumatologic lab work, hepatitis panel, or colonoscopy to evaluate for inflammatory arthritis, hepatitis, paraproteinemia, or inflammatory bowel disease (IBD). Tissue cultures should also be performed to rule out bacterial or fungal causes. Direct immunofluorescence studies might show deposition of IgM, C3, and fibrin in vessel walls.

IMAGING STUDIES

Consider colonoscopy and/or CT to evaluate for IBD. Chest radiography to evaluate for the

FIG. E1 Pyoderma gangrenosum. Note undermined hemorrhagic borders. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

FIG. E2 Pyoderma gangrenosum. Painful leg ulceration with an inflamed, undermined border. Note the pustule distal to the ulceration, often the earliest sign of a new site of involvement. The most common underlying condition in affected children is inflammatory bowel disease, although no underlying abnormality may be discovered. (From Paller AS et al: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E3 Pyoderma gangrenosum. Partial response to treatment with cyclosporine. Note the persistent inflammation and evidence of healing ulcerations with residual cribriform scarring. The pyoderma gangrenosum healed fully and remained quiescent while the child was given etanercept, but this young boy developed Takayasu disease several yr after onset of the pyoderma gangrenosum despite ongoing inhibition of tumor necrosis factor alpha activity. (From Paller AS et al: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

presence of extracutaneous involvement and for possible infection before the initiation of immunosuppressive therapy.

Rx TREATMENT

The major treatment modalities revolve around wound care for the ulcers themselves, as well as either topical or systemic therapy (Fig. E3).

NONPHARMACOLOGIC THERAPY

Surgery or aggressive debridement should be avoided in PG lesions because the surgery can cause pathergy and worsen the lesions. When needed, grafting should be performed concurrently with systemic immune-modulating therapy to prevent worsening of the lesions.

ACUTE GENERAL Rx

Care may include one or more of the following:

- Topical wound care and moist healing
- Topical high-potency steroids (e.g., clobetasol)
- Topical immune modulators (e.g., tacrolimus)
- Systemic glucocorticoids (e.g., prednisone)
- Systemic immune modulators (e.g., cyclosporine)
- Antibiotics—only in cases of superinfection and if used with one of above
- Infliximab in patients with Crohn disease
- Dapsone or colchicine have shown some benefit
- Second-line treatment includes immunomodulatory drugs (thalidomide, azathioprine, mycophenolate mofetil, methotrexate, IV immune globulin)

CHRONIC Rx

Similar to above except for longer durations or in pulse therapy

COMPLEMENTARY & ALTERNATIVE MEDICINE

Not relevant

DISPOSITION

Can be treated in both inpatient and outpatient settings depending on severity and therapeutic modalities

REFERRAL

- Dermatology
- Rheumatology
- Gastroenterology, especially in cases of IBD-related PG
- Hematology

PEARLS & CONSIDERATIONS

COMMENTS

- PG is a diagnosis of exclusion that should only be made after other diseases in the differential have been ruled out and the patient has been evaluated for the associated diseases seen in >50% of cases.
- Postoperative pyoderma gangrenosum (PG at site of surgical incision) has less association with systemic disease than its nonpostoperative counterpart. It is often misdiagnosed as wound infection, and affected sites are often debrided, causing additional wound breakdown.

PATIENT & FAMILY EDUCATION

Support for PG can often be found in the support groups for associated diseases, particularly Crohn disease, ulcerative colitis, erythema nodosum, and rheumatoid arthritis.

AUTHOR: **Catherine E. Najem, MD**

SUGGESTED READINGS

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Pyogenic Granuloma

BASIC INFORMATION

DEFINITION

Pyogenic granuloma is a benign vascular lesion of the skin and mucous membranes. The lesions are caused by capillary proliferation, generally the result of trauma.

SYNONYMS

Granuloma pyogenicum
Tumor of pregnancy
Eruptive hemangioma
Lobular capillary hemangioma
Granulation tissue–type hemangioma

ICD-10CM CODE
L98.0 Pyogenic granuloma

EPIDEMIOLOGY & DEMOGRAPHICS

- Common in children and young adults. Also found more frequently in pregnant women
- Equally prevalent in males and females, with no racial or familial predisposition
- Caused by trauma or surgery
- Gingival lesions occur more frequently during pregnancy

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Small (<1 cm), yellow to red, dome-shaped lesions
- May have surrounding scale at base (Fig. E1)
- Most commonly found on exposed surface of extremities, face, or on sites of trauma
- Often found on the gingiva during pregnancy (called *epulis*)
- Extremely friable, can easily ulcerate, and may bleed profusely with minor trauma

ETIOLOGY

- Trauma causing focal capillary growth. These lesions are neither infectious in etiology nor granulomatous in histology.
- Occurs more commonly in patients treated with certain medications (isotretinoin, indinavir, capecitabine, vemurafenib).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Amelanotic melanoma
- Bacillary angiomatosis
- Glomus tumor
- Hemangioma
- Irritated nevus
- Wart
- Kaposi sarcoma

WORKUP

Diagnosis is based on clinical history and appearance. Generally begins with trauma followed by the development of an erythematous papule. The lesion tends to bleed easily and develops over several days to weeks.

LABORATORY TESTS

Pathologic examination should be performed after excision to rule out melanoma.

TREATMENT

ACUTE GENERAL Rx

- Excision: Using 1% lidocaine for anesthesia, shave or curette at base and border. Follow with electrocauterization or cryotherapy.
- Pulsed-dye laser is also a safe and effective treatment modality.
- Pregnancy epulis generally resolves spontaneously after childbirth.
- Medication-related pyogenic granuloma may relapse after discontinuation or dose-lowering of culprit medication.

REFERRAL

Dermatology referral recommended if lesion recurs or multiple satellite lesions occur after excision.

PEARLS & CONSIDERATIONS

COMMENTS

- "Pyogenic granuloma" is a misnomer since these lesions are neither pyogenic nor granulomatous.
- Removal of entire lesion is essential because lesions may recur at the site of residual tissue.
- Patients and parents should be alerted to the possibility of recurrence after removal.
- Multiple satellite lesions occasionally develop near a primary pyogenic granuloma, usually after destruction of that lesion.

AUTHOR: **Fred F. Ferri, MD**

FIG. E1 Pyogenic granuloma. A, This is the classic appearance of a red, friable nodule growing rapidly on the finger. There is often a portion that extends under the skin laterally. **B,** Pyogenic granuloma on the finger. This lesion is more dry and crusted. **C,** Pyogenic granuloma on the chin of an adult. The fingers, lip, palms, soles, and face are typical sites. **D,** Pyogenic granuloma of the eyebrow. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

SUGGESTED READINGS

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Q Fever

BASIC INFORMATION

DEFINITION

Q fever is a zoonotic systemic febrile illness caused by *Coxiella burnetii* that may be acute or chronic. The concept of persistent localized disease may soon replace that of chronic Q fever.

SYNONYM

C. burnetii infection

ICD-10CM CODE
A78 Q fever

EPIDEMIOLOGY & DEMOGRAPHICS

- *C. burnetii* is found worldwide. Fig. E1 illustrates distribution in the U.S. in 2010.
- Common animal reservoirs are cattle, sheep, and goats.
- Pets such as cats, rabbits, and pigeons are also reservoirs.
- A parturient cat caused an outbreak in Nova Scotia just by delivering in the same room as a card game.
- Most cases are found in individuals who have direct contact with infected animals (e.g., farmers, veterinarians) or who are exposed to contaminated animal urine, feces, milk, or placental tissues.
- Q fever is seen more often in men than in women (ratio of 3:1).
- Its incidence in the U.S. is increasing, with more than 30 cases recently reported in U.S. military personnel recently deployed to Iraq and Afghanistan.
- Travel to Middle Eastern and African countries poses the greatest risk.
- *C. burnetii* is a CDC class B bioterrorism agent.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute Q fever presentation:
  1. Fever
  2. Pneumonia
  3. Hepatitis
  4. Meningoencephalitis
  5. Many cases are asymptomatic
- Chronic/persistent localized Q fever presentation (duration of infection >6 mo):
  1. Chronic endocarditis
  2. Vascular infection (aneurysms and vascular prostheses)
  3. Bone and joint infections (culture-negative osteomyelitis or prosthetic joint infection)
- Most common clinical symptoms:
  1. Chills
  2. Sweats
  3. Nausea
  4. Vomiting
  5. Cough, nonproductive
  6. Headache
  7. Fatigue
- Most frequent physical findings:
  1. Fever
  2. Inspiratory rales
  3. Purpuric rash
  4. Hepatomegaly
  5. Splenomegaly
- Infected pregnant women may be asymptomatic acutely, yet fetal wastage may occur

ETIOLOGY

- Q fever is caused by the Proteobacteria *C. burnetii.*
- *C. burnetii* is a gram-negative coccobacillus transmitted from arthropods to animals to human beings.
- The disease is acquired most often by inhalation of aerosols. In the lungs, it proliferates in macrophages and then gains access to the bloodstream, producing a transient bacteremia. Thereafter it can invade many organs, most commonly the lungs and liver.
- There is an incubation period of 3 to 30 days before systemic symptoms manifest.
- Persons with abnormal heart valves, prosthetic valves, and endovascular grafts are at high risk of progression to chronic Q fever. This includes individuals with bicuspid aortic valves.

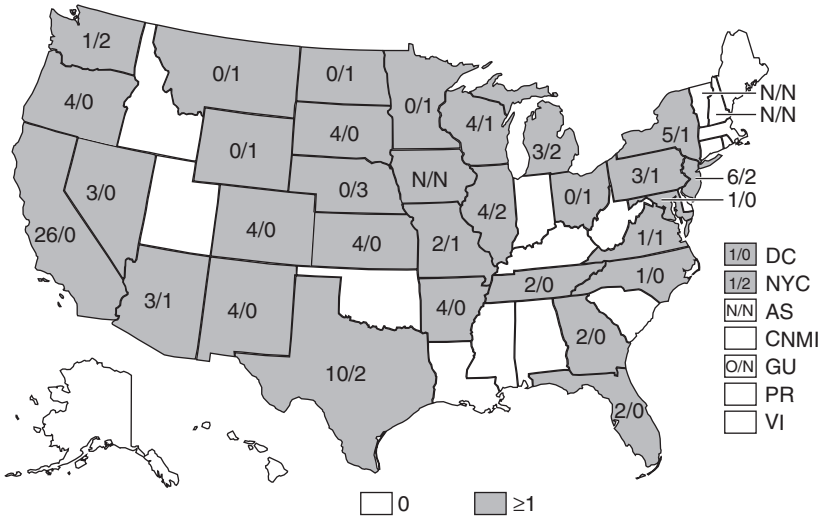

FIG. E1 Q Fever, acute and chronic. Number of reported cases: U.S. and U.S. territories, 2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59:1–111, 2012.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Q fever can have various presentations and must be in the differential diagnosis of fever, hepatitis, pneumonia, endocarditis, and meningitis. Situations that should prompt serologic testing for Q fever are described in Table E1.

WORKUP

- Complete blood count (CBC), erythrocyte sedimentation rate (ESR), and liver function tests
- Urinalysis
- Serology
- Chest radiography

LABORATORY TESTS

In acute Q fever:

TABLE E1 Situations that Should Prompt Serologic Testing for Q Fever

Acute Q Fever (Phase II Antigen and IgG ≥200 and IgM ≥50)
Fever in a patient in contact with ungulates
Unexplained prolonged fever (>7 days)
Granulomatous hepatitis
Fever and thrombocytopenia
Meningoencephalitis
Myocarditis
Erythema nodosum
Fever during pregnancy
Fever in a patient in contact with a parturient pet
Unexplained atypical pneumonia
Fever and an increase in transaminases (2-5 times the normal level)
Aseptic meningitis
Guillain-Barré syndrome
Pericarditis
Spontaneous abortion
Chronic Q Fever (Phase I Antigen and IgG ≥800 and IgA ≥100)
Blood culture–negative endocarditis
Patient with a valvulopathy and unexplained fever
Weight loss
Fatigue
Increased erythrocyte sedimentation rate
Increased transaminases
Thrombocytopenia
Patient with unusually rapid degradation of a prosthetic valve
Fever in a patient with a vascular aneurysm or prosthesis
Aseptic osteomyelitis
Chronic pericarditis
Multiple spontaneous abortions

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

- CBC and white blood cell count are usually normal.
- Thrombocytopenia can occur (25%).
- Elevation of hepatic transaminases (two to three times the normal range) may be seen.
- Antibody detection by immunofluorescence assay is the most commonly used method because of its high sensitivity and specificity. Complement fixation (CF) shows a fourfold rise in titer between acute and convalescent samples.
- Polymerase chain reaction is desirable in early disease.
- Testing has been approved by the FDA and can be obtained from the CDC through the state health department.

In chronic Q fever (almost always endocarditis):

- ESR is elevated.
- Anemia is present.
- Microscopic hematuria.
- Blood cultures are almost always negative.
- MIF (microimmunofluorescence) titer of >1:800 to phase I antigen is diagnostic.

IMAGING STUDIES

- Chest radiographs are abnormal, showing segmental lobe consolidation.
- Pleural effusions (35%).
- Transthoracic echocardiography after the diagnosis of acute Q fever can be used to stratify risk of progression to endocarditis.
- PET/CT imaging may be instrumental in determining the focus of persistent localized or chronic Q fever.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Oxygen as needed in patients with pneumonia

ACUTE GENERAL Rx

- Acute Q fever can be treated with doxycycline (100 mg bid) for 14 to 21 days *or*
- Clarithromycin is the macrolide of choice for acute infection given intolerance of doxycycline
- Ofloxacin 200 mg PO q8h or ciprofloxacin 875 mg PO bid for 14 to 21 days
- Hydroxychloroquine plus doxycycline for endocarditis associated with Q fever
- Fluoroquinolones are recommended for suspected meningoencephalitis because of excellent penetration into the CNS
- Pregnant women may be treated with trimethoprim-sulfamethoxazole until the seventh month of gestation

CHRONIC Rx

- Chronic Q fever is treated with a combination of two antibiotics, doxycycline 100 mg bid and rifampin 900 mg qd.
- Doxycycline 100 mg bid and hydroxychloroquine 200 mg PO tid is the preferred therapy.
- Duration of treatment: 2 to 3 yr, at minimum 18 mo.
- Strongly consider prophylactic treatment for exposed individuals with preexistent high-risk cardiac lesions.

DISPOSITION

- Patients with acute Q fever respond well with antibiotics, with deaths rarely reported.
- Up to 20% of patients develop a post–Q fever fatigue syndrome.

Mortality rate in chronic Q fever endocarditis is high (24%). Many patients will need valve replacement surgery.

REFERRAL

Referral to an infectious disease expert is recommended in any cases of suspected acute or chronic Q fever.

Drug levels must be monitored and serial serologies evaluated.

REPORTING

Q fever has been a reportable disease in the U.S. since 1999. The CDC must be notified of cases.

PEARLS & CONSIDERATIONS

COMMENTS

- An acellular (CMR) vaccine is available in the U.S. However, vaccines that are available in other countries such as Australia have been more thoroughly studied.
- Infected patients do not require specific isolation precautions.
- Q fever derived its name in 1935 from Derrick, who was suspicious of a new disease during a series of acute febrile illnesses in abattoir workers of Queensland, Australia, justifying the name of Q fever (for "query").

AUTHOR: **Patricia Cristofaro, MD**

SUGGESTED READINGS

American Academy of Pediatrics RED BOOK. Q FEVER. 2012 Report of the Committee on Infectious Diseases

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Quadrilateral Space Syndrome

BASIC INFORMATION

DEFINITION

The quadrilateral space is formed by the long head of the triceps brachii muscle medially, the teres minor muscle superiorly, the teres major inferiorly, and the medial aspect of the humerus laterally (Fig. E1). The axillary nerve (along with the posterior humeral circumflex artery) courses through the quadrilateral space and innervates the teres minor and deltoid muscles as well as the posterolateral cutaneous region of the shoulder and upper arm.

Quadrilateral space syndrome (QSS) is a rare neurovascular syndrome characterized by shoulder pain, paresthesias, and point tenderness in the quadrilateral space due to compression or mechanical injury of the axillary nerve/posterior humeral circumflex artery in the quadrilateral space.

SYNONYMS

QSS
Lateral axillary hiatus syndrome
nQSS (neurogenic quadrilateral space syndrome)
vQSS (vascular quadrilateral space syndrome)

ICD-10CM CODE
Code varies with specific etiology of syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Rare in general population, more common in participants in sports that involve abduction and external rotation of upper extremities (baseball, volleyball, swimming, yoga) and in professional window cleaners. Most common age group is 20 to 40 yr and most commonly involves the dominant shoulder.

DOMINANT SEX: 7:1 male:female ratio, most likely due to traditional sex distribution in overhead or "throwing" athletics

RISK FACTORS: Professional athletes, window cleaners

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Diffuse shoulder pain (slow onset, intermittent, poorly localized, posterior and lateral aspect of the shoulder and arm)
- Nondermatomal neuropathic pain, usually in the posterior or lateral aspect of the shoulder/arm
- Weakness and numbness in the shoulder, most commonly in posterior region
- Vascular manifestations may be present (thrombosis, digital or hand ischemia, decreased pulses, pallor, splinter hemorrhages, cold intolerance)
- Symptoms aggravated by abduction and external rotation of the affected shoulder
- Throwing athletes notice pain with the late cocking phase of throwing in the overhead position
- Point tenderness over the quadrilateral space and, sometimes, deep palpation cause lateral shoulder pain or paresthesias
- A separate entity with isolated atrophy of the teres minor may also be present without sensory findings or deltoid weakness; this process is often asymptomatic and found incidentally with MRI

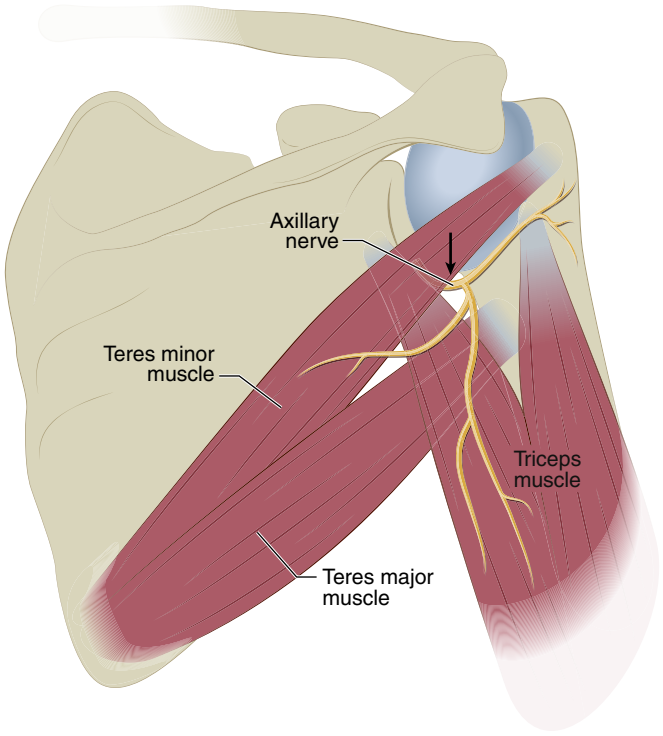

FIG. E1 Drawing of the quadrilateral space. View from the posterior aspect of the scapula demonstrating the four margins of the space: The teres minor muscle superiorly, the teres major muscle inferiorly, the medial aspect of the humerus laterally, and the triceps muscle medially. Note the axillary nerve passing though the quadrilateral space *(arrow)* and providing branches to the teres minor, triceps, and deltoid muscles. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2014, Saunders.)

ETIOLOGY

- Fibrous bands (generally posttraumatic) causing fixed structural compression of the quadrilateral space is the most common cause
- Muscle hypertrophy, especially in competitive athletes
- Repetitive mechanical injury to the posterior circumflex humeral artery
- Proximal humeral head fractures and callus formations
- Anterior shoulder dislocation resulting in traction and compression
- Soft tissue and osseous tumors, paralabral cysts
- Idiopathic

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Brachial neuritis/plexopathy
- Thoracic outlet syndrome/referred pain from cervical radiculopathy
- Parsonage-Turner syndrome
- Thrombosis or aneurysmal formation in more proximal branches of axillary artery
- Adhesive capsulitis
- Rotator cuff or labral pathology
- Glenohumeral instability
- Proximal humeral fracture

WORKUP

- Magnetic resonance imaging (MRI)
- Computed tomographic angiography (CTA)
- Digital subtraction angiography (DSA)
- Magnetic resonance angiography (MRA)
- Ultrasound (US)
- Electromyography (EMG): Indicated primarily to rule out alternative diagnoses
- Quadrilateral space lidocaine block test: 5 ml of 1% lidocaine injected in the quadrilateral space with or without ultrasound guidance

LABORATORY TESTS

None indicated

IMAGING STUDIES

- CTA, DSA, MRA: Fixed posterior circumflex humeral artery (PCHA) occlusion due to thrombosis with or without distal embolization
- MRI: Denervation edema (acute, increased T2 and STIR signal and size) or fatty atrophy (chronic) of the teres minor and/or deltoid muscle

TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical therapy: Soft tissue massage modalities, shoulder range of motion exercises, posterior rotator cuff strengthening, and scapular stabilization exercises
- Activity modification: Avoidance of abduction and external rotation

ACUTE GENERAL Rx

- Nonsteroidal antiinflammatory medications (NSAIDs), therapy, and activity modification

CHRONIC Rx

- Neurolysis/excision of existing fibrous bands or space-occupying lesions indicated after failed conservative treatment trial for at least 6 mo and a positive lidocaine test
- If fixed PCHA occlusion due to thrombosis: PCHA ligation with or without thrombolysis or surgical thromboembolectomy
  - Anticoagulation for 3 mo in patients with PCHA thrombosis

COMPLEMENTARY & ALTERNATIVE MEDICINE

None

DISPOSITION

In most cases, there is complete resolution of the symptoms with nonsurgical management and return to full activity after several wk

REFERRAL

Vascular surgery, orthopedics, neurology

AUTHORS: **Mohit Kukreja, MD,** and **E. Scott Paxton, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Rabies is a fatal zoonotic illness caused by a number of species of neurotropic viruses in the Rhabdoviridae family and transmitted to human beings by the bite of an infected animal.

SYNONYM

Hydrophobia

ICD-10CM CODE
A82.9 Rabies, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Approximately two U.S. cases annually; 83 human cases or rabies in the U.S. from 1980 to 2015. Of these, 25 cases were imported rabies in people who were exposed to rabid animals in endemic nations and 5 cases were in tissue or organ transplantation recipients. Since 2008, nine persons have died from rabies in the U.S. following a rabies exposure abroad.

In the U.S., most cases are transmitted by bats; in the world, most cases are transmitted by dogs.

PREDOMINANT SEX: Men are more commonly affected (70% of cases)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation period is usually 1 to 3 mo in humans but can range from several days to 8 yr
- Shorter incubation period with bites on the face. Longer if extremities involved
- In domestic animals, a quarantine of 10 days is usually mandated
- Prodrome:
  1. Fever
  2. Headache
  3. Malaise
  4. Pain or anesthesia at exposure site
  5. Sore throat
  6. Gastrointestinal symptoms
  7. Psychiatric symptoms
- Acute neurologic period, with objective evidence of central nervous system involvement
- Two types of presentation
- "Furious" (encephalopathic) rabies (80% of cases):
  1. Extreme hyperactivity and bizarre behavior alternating with periods of relative calm
  2. Hallucinations, disorientation
  3. Seizures
  4. Paralysis
  5. Fear, pain, and spasm of the pharynx and larynx caused by drinking
  6. Coma, death
- "Dumb" (paralytic) rabies (20% of cases):
  1. Ascending flaccid paralysis
  2. Often prominent in the bitten limb
  3. Deep tendon and plantar reflexes lost
  4. Fasciculations

ETIOLOGY

- Rabies virus: Bullet-shaped viruses that belong to Rhabdoviridae family, genus *Lyssavirus*
- Cases in the U.S. are associated with:
  1. Bats
  2. Raccoons
  3. Foxes
  4. Skunks
- Small rodents (squirrels, mice, rats, chipmunks) and lagomorphs such as rabbits almost never have rabies and in the U.S. have never been a source of transmission of rabies to humans
- In 17 of 19 cases of rabies occurring in the U.S. from 1997 to 2006, exposure to bats was felt to be the source, although many did not have a clinically evident bite or scratch
- Imported cases are usually associated with dogs
- Unusual acquisition:
  1. By organ transplantation: Kidney, liver, arterial segment
  2. By aerosol transmission in laboratory workers and spelunkers

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Delirium tremens
- Tetanus
- Hysteria
- Psychiatric disorders
- Other viral encephalitides (Box E1)
- Guillain-Barré syndrome
- Poliomyelitis

BOX E1 Differential Diagnosis of Rabies

Viral-borne encephalitis
Herpes simplex virus (HSV-1)
Arboviruses (e.g., Eastern equine encephalitis, Western equine encephalitis, West Nile, Japanese encephalitis, California encephalitis, Rift Valley fever)
Enterovirus: Enterovirus 71
Cerebral malaria
Acute disseminated encephalomyelitis (ADEM)
Limbic encephalitis
Guillain-Barré syndrome
Poliomyelitis
Post-rabies vaccine encephalomyelitis
Tetanus
Botulism
Drugs
  Direct toxicity: Drug-induced psychosis (e.g., phencyclidine [PCP])
  Drug syndromes: Serotonin syndrome, neuroleptic malignant syndrome
  Drug withdrawal: Severe alcohol withdrawal
Florid mental illness
Rabies hysteria

From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.

WORKUP

- Antemortem diagnosis requires multiple specimens (saliva, skin that requires a full-thickness biopsy from posterior neck at the hairline, cerebrospinal fluid, serum) and multiple testing modalities: PCR, antibodies, immunofluorescence of viral antigens, viral culture.
- Animals submitted for rabies testing should be euthanized in a way that maintains the integrity of the brain.
- Negri bodies are eosinophilic cytoplasmic inclusions found in neurons. They are the best-known histologic feature of rabies usually found at postmortem examination.
- The national case definition for animal rabies requires laboratory confirmation by either:
  1. A positive DFA test (preferably performed on CNS tissue).or
  2. Isolation of rabies virus (in cell culture or in a laboratory animal).
- Fig. E1 describes an approach to assessing rabies exposure and initiating post-exposure prophylaxis (PEP) in the U.S.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Isolation of the patient to prevent transmission to others
- Supportive therapy

ACUTE GENERAL Rx

- No known beneficial therapy. A case report from 2005 describes a 15-yr-old girl who survived rabies and had been treated with a combination of ketamine, midazolam, ribavirin, and amantadine. It is known as the Milwaukee protocol. The protocol has been unsuccessful in over 40 subsequent reports and is considered ineffective.
- Other nonproven agents include interferon, corticosteroids, therapeutic coma, minocycline, and prevention of cerebral vasospasm. Research is ongoing in vitro and mice with favipiravir, a viral RNA polymerase inhibitor.
- Emphasis is placed on prophylaxis of potentially exposed individuals after an exposure (Table E1):
  1. Thorough wound cleansing and irrigation of the wound with soap and water as soon as possible. If available, a viricidal agent (e.g., povidone-iodine solution) should be used to irrigate the wounds.
  2. Active and passive immunization is most effective when used within 72 hr of exposure.
- Vaccinations: The CDC has recently recommended reducing the number of vaccine doses for postexposure prophylaxis. Current recommendations for rabies postexposure prophylaxis are as follows:
  1. Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) 1 ml IM (deltoid area) 1 each on days 0, 3, 7, and 14 in patients not previously vaccinated. In patients previously vaccinated, administer HDCV or PCECV 1

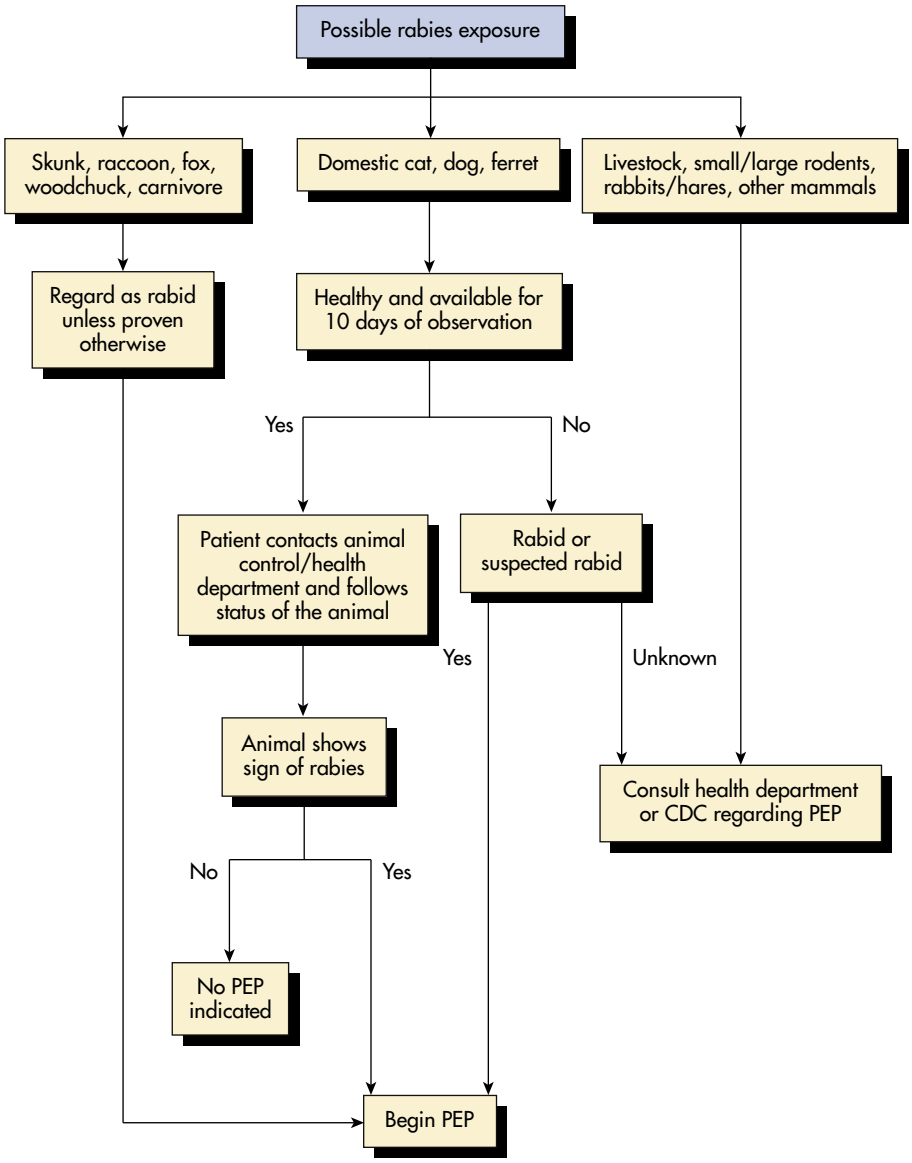

FIG. E1 Approach to assessing rabies exposure and initiating postexposure prophylaxis (PEP) in the U.S. *CDC,* Centers for Disease Control and Prevention. (From Adams JG et al: *Emergency medicine, clinical essentials,* 2nd ed, Philadelphia, Elsevier, 2013.)

TABLE E1 Regimen Examples for Preexposure and Postexposure Vaccination with Rabies Vaccines

Vaccination	Route	Days on Which Doses Are Given	Remarks
Preexposure	IM*	0, 7, 21, or 28	Standard U.S. and WHO three-dose regimen
	ID†	0, 7, 21, or 28	Economical, but not to be used in those taking antimalarial medications; unlicensed route in U.S.; WHO recommended
Postexposure‡	IM*	0, 3, 7, 14	Standard U.S. four-dose recommendation
	IM*	0 (2 doses), 7, 21	Used in some countries when RIG is not indicated; so-called 2-1-1 schedule
	ID†	0, 3, 7 (2 doses each), 28	Used in Thailand with PVRV, PCECV; so-called 2-2-2-0-1 schedule
	ID†,§	0 (8 doses), 7 (4 doses), 28, 90	Used in developing countries with HDCV, PCECV, or PVRV cell culture vaccines; so-called 8-0-4-0-1-1
Booster (for reexposure)	IM*	0, 3	Only after documented vaccination with cell culture vaccine¶
	ID†	0, 3	Only after documented vaccination with cell culture vaccine¶

HDCV, Human diploid cell vaccine; *ID,* intradermal; *IM,* intramuscular; *PCECV,* purified chick embryo cell vaccine; *PVRV,* purified Vero cell rabies vaccine; *RIG,* rabies immune globulin; *WHO,* World Health Organization.
*Together with rabies immunoglobulin.
†Give 0.1 ml, over the deltoids.
‡Give 0.5 ml (PVRV) or 1 ml, depending on the vaccine, into the deltoid.
§Give 0.1 ml at multiple sites (see text).
¶Or demonstrated presence of virus-neutralizing antibodies after other vaccines.
From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.

ml IM (deltoid area) 1 each on days 0 and 3. Human rabies hyperimmune globulin (RIG) 20 IU/kg body weight should be administered to persons not previously vaccinated. If anatomically feasible, the full dose should be infiltrated into the wound; any remaining volume should be given IM at a site separate from vaccine administration.

- Preexposure prophylaxis with HDCV or RVA (1 ml IM on days 0, 7, and 21 or 28) in individuals at high risk for acquisition:
  1. Veterinarians.
  2. Laboratory workers working with rabies virus.
  3. Spelunkers.
  4. Visitors to endemic areas.

DISPOSITION

Virtually always fatal. Rabies has one of the highest case/fatality ratios of any infectious disease.

REFERRAL

- To infectious disease consultant
- To local health authorities

PEARLS & CONSIDERATIONS

COMMENTS

- Most cases in the U.S. are caused by:
  1. Bat bites, often after minimal contact and inapparent exposure to infected bat saliva
  2. Dog bites occurring outside the U.S.
- Rare cases can be transmitted by mucous membrane contact with aerosolized virus (caves, laboratory-acquired cases)
- Rabies is preventable if exposed persons receive postexposure prophylaxis. Public understanding of rabies exposure risk from bat contact needs to be improved

RELATED CONTENT

Rabies (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Radial tunnel syndrome describes a form of compression neuropathy of the posterior interosseous nerve (PIN), a branch of the radial nerve, which presents mainly as pain over the dorso-radial aspect of the forearm (Fig. E1). The radial nerve branches 3 to 5 cm distal to the lateral epicondyle, into the superficial radial sensory nerve and PIN, which then enters the radial tunnel. The radial tunnel is approximately 5 cm and formed by the capitellum posteriorly; the brachioradialis, extensor carpi radialis longus, and brevis muscles anterolaterally; the brachialis muscle and biceps tendon medially; and ends at the proximal edge of the supinator. The PIN supplies the supinator and extensor muscles of the forearm (including the extensor carpi ulnaris, extensor digitorum, extensor digiti minimi, extensor indicis, extensor pollicis longus and brevis muscles, and abductor pollicis longus) as well as providing sensory innervation and proprioception to the wrist joint.

There is some controversy as to whether radial tunnel syndrome is a distinct entity or a variation of PIN syndrome. Patients may be found to have radial tunnel syndrome in the presence of forearm pain and localized tenderness over the radial nerve without weakness. Those with a primary complaint of weakness, rather than pain, are considered to have PIN syndrome.

SYNONYM

Radial pronator syndrome

ICD-10CM CODE

G56.30 Lesion of radial nerve, unspecified upper limb.

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Rare, annual incidence is <0.03%
PEAK INCIDENCE: Unknown
PREDOMINANT SEX & AGE: Peak between age 30 and 50, likely slight female predominance, studies range from a female:male ratio of 1:1 to 6:1
GENETICS: Unknown
RISK FACTORS: Trauma and heavy manual labor, especially those who perform forearm extensions in pronation or supination

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients with radial tunnel syndrome present with pain in the proximal forearm, which is often exacerbated by activities that involve repetitive forearm pronation, wrist extension, and elbow extension. Pain is usually felt over lateral epicondyle of the humerus radiating distally toward radial styloid and thumb with maximum pain 3 to 5 cm distal to the lateral epicondyle.

Physical examination shows localized tenderness over the radial nerve distal to the lateral epicondyle. Pain is worsened with forearm pronation, wrist flexion, and elbow extension. The findings of localized forearm pain (especially over the mobile wad, or at the proximal edge of the supinator) with extension of the middle finger against resistance and pain with resisted supination are thought to be specific for radial tunnel syndrome. It is important to carefully examine the lateral aspect of the elbow, as radial tunnel syndrome is often missed. Tenderness over the supracondylar ridge is consistent with lateral epicondyle tendinopathy (tennis elbow), while tenderness 5 cm distal to the radiocapitellar joint is consistent with radial tunnel syndrome.

ETIOLOGY

- Localized compression sometimes related to repetitive movements or work-force injury; but often idiopathic
- Rarely, space-occupying lesions, such as lipomas, ganglions, or synovitis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Lateral epicondylitis, which may often co-occur
- Posterior interosseous nerve syndrome

WORKUP

Anesthetic injection into the radial tunnel, which should provide pain relief, and can then serve as a marker for correct injection location for corticosteroids. Injections around the radial nerve should be undertaken with ultrasound guidance to minimize potential injury to nerve structures.

LABORATORY TESTS

N/A

IMAGING STUDIES

- Electromyogram (EMG)/nerve conduction velocity (NCV) studies are often done but rarely show evidence of radial tunnel syndrome. There is no consistent relationship between symptoms and study findings.
- MRI usually negative and has a limited role. Can be helpful in ruling out lipoma/ganglion as cause of compression, or rarely show denervation/edema within supinator/extensor.

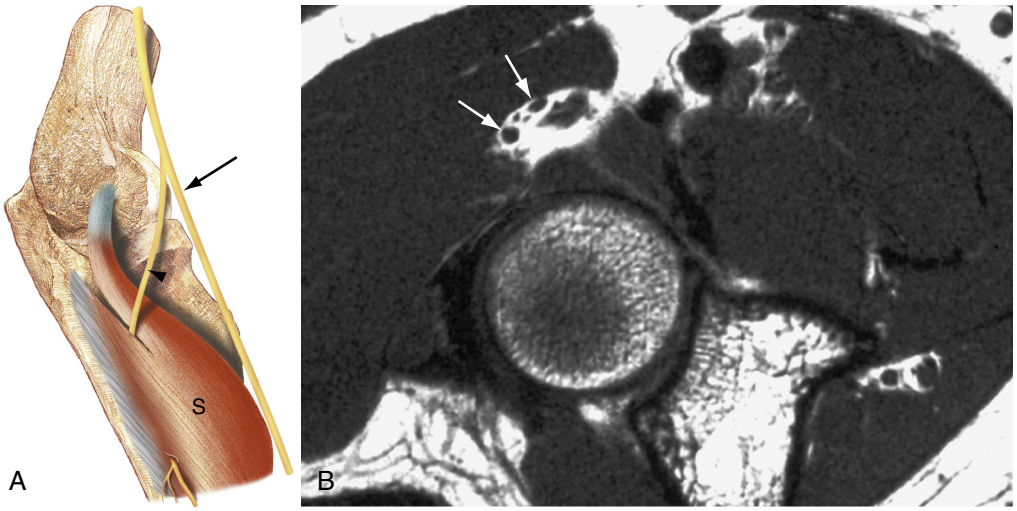

FIG. E1 Normal anatomy of the radial nerve in the elbow area. A, Lateral illustration. The radial nerve courses distally in the anterior aspect of the elbow and arm. At the level of the elbow joint it divides into two branches: The superficial sensory branch *(arrow)* and the deep motor branch or posterior interosseous nerve *(arrowhead)*. The posterior interosseous nerve penetrates the supinator muscle *(S)* between the superficial and the deep layers (the arcade of Fröhse). **B,** Axial T1-weighted magnetic resonance image. (From Pope TL et al: *Musculoskeletal imaging*, ed 2, Philadelphia, 2015, Elsevier.)

TREATMENT

ACUTE GENERAL Rx

- Wrist splinting (generally at nighttime), gentle stretching, and activity modification (limiting repetitive pronation and supination)
- NSAIDs
- Corticosteroid injection: Diagnostic and therapeutic

CHRONIC Rx

Activity modification

DISPOSITION

- Conservative treatment and steroid injection results in about 60% of patients being pain free at 2 yr.
- Radial tunnel release surgery has been reported to be effective in 70% of patients.

REFERRAL

Surgical referral for radial tunnel release surgery—if conservative measures fail >3-mo period

PEARLS & CONSIDERATIONS

COMMENTS

Radial tunnel syndrome coexists with lateral epicondylitis in about 5% of patients. In lateral epicondylitis, pain is directly over lateral epicondyle rather than more distal, as in radial tunnel syndrome. Muscle weakness, if present, is clinically insignificant.

PREVENTION

Activity modification and avoidance of forearm pronation, wrist flexion, and elbow extension

RELATED CONTENT

Epicondylitis (Related Key Topic)
Pronator Syndrome (Related Key Topic)

AUTHORS: **Avi D. Goodman, MD,** and **Manuel F. DaSilva, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Radiation is the emission of energy as electromagnetic waves or moving subatomic particles. It can be natural or man-made. Natural radiation can come from a cosmic source, such as the sun, or a terrestrial source, such as naturally occurring radionuclides. Man-made radiation can come from nuclear reactors and x-ray machines. There are two types of radiation, ionizing radiation and nonionizing radiation, both of which have the potential for human tissue injury. Ionizing radiation has more energy and can cause a direct effect with its interactions on cellular molecules such as DNA bases, proteins, and cellular membranes, or by indirectly affecting these molecules by influencing other molecules, primarily water, to generate free radicals. The different types of ionizing radiation include alpha and beta particles, gamma rays, and x-rays. An alpha particle is a helium nucleus without the electrons, two protons, and two neutrons. A beta particle is either an electron or a positron (which is a positively charged electron). Gamma rays and x-rays are photons of pure energy, and their biological effects are due to ionization. Nonionizing radiation has less energy and causes damage to biological tissues and aforementioned cellular components through the transfer of thermal (heat) energy. Examples of nonionizing radiation include radio waves, microwaves, and sun exposure. The most important risk from radiation exposure is cancer. Other risks include genetic mutations and birth defects.

UNITS OF RADIATION (TABLE E1)

The amount of radiation absorbed by the patient's tissues is highly predictive of its biological effects.

- Roentgen (R): A measure of radiation that quantifies the electrical charge; it generates in a volume of air divided by the air's mass (coulomb/kg).
- Grays (Gy): Energy deposited per unit mass. 1 J/kg of tissue = 1 Gy.
- Radiation absorbed dose (rad): Amount of radiation absorbed by a material; 1 rad = 1/100 gray (Gy).
- Roentgen equivalent man (rem): A measure of radiation biologic damage. It is the product of the absorbed dose and a quality factor. The quality factor considers differential sensitivity among tissues (Table E2).
- Sievert (Sv): Equal to 100 rem.
- Lethal dose of radiation (LD 50): Amount of radiation associated with death in 50% of those similarly exposed.
- Dose rate: Refers to amount of radiation delivered per unit of time and is often measured in Gy/hr or rads/hr.
- Effective dose: A measurement of dose that considers the type of radiation and the relative sensitivity of the exposed organ/tissue, as determined by the weighting factor for that organ/tissue.

SYNONYMS

For large exposures (deterministic, or nonstochastic, effects of radiation):
Acute radiation syndrome
Radiation sickness
Chronic low-dose exposures produce stochastic effects. This has no common synonyms

ICD-10CM CODES

W88	Exposure to ionizing radiation
T66	Unspecified effects of radiation
T66.XXXA	Radiation sickness, unspecified, initial encounter
T66.XXXS	Radiation sickness, unspecified, sequela
W88.8XXA	Exposure to other ionizing radiation, initial encounter
W90.2XXA	Exposure to laser radiation, initial encounter
W90.8XXA	Exposure to other nonionizing radiation, initial encounter
X39.08XA	Exposure to other natural radiation, initial encounter
Y63.2	Overdose of radiation given during therapy
Y63.3	Inadvertent exposure of patient to radiation during medical care
Z51.0	Encounter for antineoplastic radiation therapy
Z57.1	Occupational exposure to radiation
Z77.123	Contact with and (suspected) exposure to radon and other naturally occurring radiation
G62.82	Radiation-induced polyneuropathy
J70.0	Acute pulmonary manifestations due to radiation
J70.1	Chronic and other pulmonary manifestations due to radiation
K12.33	Oral mucositis (ulcerative) due to radiation
K52.0	Gastroenteritis and colitis due to radiation
K62.7	Radiation proctitis

EPIDEMIOLOGY & DEMOGRAPHICS

- High-dose radiation is limited to nuclear disasters.
- Low-dose radiation occurs from naturally occurring radiation (i.e., radon, terrestrial

TABLE E1 Radiation Exposure Units of Measurement

	SI Units	Common Units	Conversion Equivalents
Radioactivity	Becquerel (Bq)	Curie (Ci)	1 Bq = 3.7×10^{10} Ci
Absorbed dose	Gray (Gy)	Rad	1 rad = 0.01 Gy
Dose equivalent	Sievert (Sv)	Rem	1 Rem = 0.01 Sv
Exposure	Coulomb/kg (C/kg)	Roentgen (R)	1 R = 0.000258 C/kg

TABLE E2 Symptoms, Therapy, and Prognosis of Whole-Body Ionizing Radiation Injury

	0-1 SV	1-2 SV	2-6 SV	6-10 SV	10-20 SV	>50 SV
Therapeutic needs	None	Observation	Specific treatment	Possible treatment	Palliative	Palliative
Vomiting	None	5%-50%	>3 Gy, 100%	100%	100%	100%
Time to nausea, vomiting	—	3 hr	2 hr	1 hr	30 min	<30 min
Main locus of injury	None	Lymphocytes	Bone marrow	Bone marrow	Small bowel	Brain
Symptoms and signs	—	Moderate leukopenia, epilation	Leukopenia, hemorrhage, epilation	Leukopenia, hemorrhage, epilation	Diarrhea, fever, electrolyte imbalance	Ataxia, coma, convulsions
Critical period	—	—	4-6 wk	4-6 wk	5-14 days	1-4 hr
Therapy	Reassurance	Observation	Transfusion of granulocytes, platelets	Transfusion, antibiotics, bone marrow transplantation	Fluids and salts, possible bone marrow transplantation	Palliative
Prognosis	Excellent	Excellent	Guarded	Guarded	Poor	Hopeless
Lethality	0	0	0%-80%	80%-100%	100%	100%
Time of death	—	—	2 mo	1-2 mo	2 wk	1-2 days
Cause of death	—	—	Infection, hemorrhage	Hemorrhage, infection, pneumonitis	Enteritis, infection	Cerebral edema

Modified from Phillips TL: Radiation injury, In Wyngaarden JB et al [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.

and cosmic radiation), man-made radiation including radiation in medicine (CT, x-ray, radiopharmaceuticals), and radiation in industry such as nuclear power and radioactive waste.
- There is an increase in exposure to low-dose radiation among average Americans due to the expansion of medical imaging, which has been increasing continuously over the past 30 yr.
- Younger persons are particularly susceptible to injury from radiation exposure.
- The average natural background radiation is about 3.6 mSv per yr.
- Epidemiology of cumulative low-level radiation is not well understood and is based on the following two dose-dependent theories:
  1. Stochastic effects of radiation exposure: There is a probability of damage-increased effect with dose, but there is no dose threshold, and severity is not dose related.
  2. Deterministic effects: Severity of damage is dose related but with a threshold below which there is no negative outcome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Low-level radiation: Low-level radiation over time may present clinically with various malignancies that may be at increased incidence compared with background rates of malignancies, but there remains much controversy.
- Exposure to radiation from medical imaging tests has been implicated in secondary cancer. The rate of cancer has been found to be dose dependent, and exposure increases incremental risk. Data suggest clear evidence of increased radiation-induced cancer risk at doses >100 mSv, but the risk is more controversial with doses of 10 to 100 mSv, which is the range of most medical imaging, including CT.
- Occupational radiation exposure has been associated with cancer risk, both non-CLL leukemia and other cancers. Occupational exposure has been implicated to cause cataracts in medical professionals who get exposure in a dose-dependent relationship.
- Acute radiation syndrome (ARS): An acute illness caused by a high dose of penetrating radiation (≥0.7 Gy) over a large portion of the body delivered in a short period of time (usually minutes). Effects of acute radiation exposure are better studied based on previous nuclear disasters and are summarized in Table E3. The four stages of ARS are:
  1. Stage 1 (prodromal phase 0 to 2 days after exposure): Flulike syndrome with anorexia, apathy, nausea, vomiting, diarrhea, fever, tachycardia, and/or headache, usually occurring within 48 to 72 hr.
  2. Stage 2 (latent phase 2 to 20 days after exposure): A short period characterized by improvement in symptoms, lasting for several days to 1 mo. Duration is inversely related to dose of radiation received and may be absent at severe doses of 10 Gy or greater. Acute radiation pneumonitis may manifest characterized by dry cough and dyspnea.
  3. Stage 3 (manifest illness phase 21 to 60 days): If the person survives this stage, recovery is likely. There are three classic ARS syndromes:
     a. Hematopoietic syndrome: Effects can occur with exposure >1 Gy and include pancytopenia, increased infection risk, and bleeding disorders.
     b. Gastrointestinal syndrome: Radiation induces loss of intestinal crypts, resulting in abdominal pain, nausea, vomiting, anorexia, and diarrhea (5 to 12 Gy).
     c. Central nervous system: Symptoms occur with a very high level of acute radiation (>10 Gy) and include ataxia, confusion, seizures, and coma due to damage of the blood-brain barrier, interstitial edema, and acute inflammation.
     d. Cutaneous syndrome: Findings include erythema, edema, and dry desquamation of the skin that can involve the dermis, subcutaneous tissue, and even muscle or bone.
  4. Stage 4: Death or recovery, lasting wks to mos. Radiation exposure of greater than 5 Gy results in a high risk of death. No individual has survived doses of greater than 10 Gy of exposure. If patients survive, they need lifelong follow-up because of the potential for unusual infections, organ dysfunction, and carcinogenesis.
     a. Radiation "burn": Prolonged exposure from fluoroscopy can lead to acute radiodermatitis presenting as red patches but over a few wks can lead to tissue necrosis.
     b. Radiation-induced lung fibrosis may also arise in doses to the lungs in the range of 8 to 10 Gy. Such injury can lead to tissue hypoxia.
- The clinical course of acute radiation syndrome depends on absorbed radiation dose and distribution. Although all tissues composed of short-lived cells are affected by radiation, the most sensitive of cells in adults include:
  1. Crypt cells in the intestines
  2. Hematopoietic cells in the bone marrow
  3. Spermatocytes in the testis

PROGNOSIS

ACUTE RADIATION SYNDROME:
- Exposure <1 Gy: Almost certain survival
- Exposure 1 to 2 Gy: 90% survival with medical care
- Exposure 2 to 3.5 Gy: Probable survival with medical care
- Exposure 3.5 to 5.5 Gy: 50% survival with medical care
- Exposure 5.5 to 10 Gy: Probable death, even with ICU-level care, reverse isolation, and possible hematopoietic stem cell transplantation
- Exposure >10 to 12 Gy: Certain death

CHRONIC LOW-DOSE EXPOSURE: Excess cancer not detected below 100 mSv

Dx DIAGNOSIS

ACUTE RADIATION SYNDROME:
- Diagnosis usually accompanies a nuclear disaster and therefore suspicion is already very high. Diagnosis may be difficult, as prodromal stage may occur hours to days after exposure.
- Workup can include measuring radiation levels at site. Estimation of exposure may be accomplished using tools such as the METREPOL (Medical Treatment Protocols for Radiation Accident) clinical grading system, which is useful for prognosis.
- Laboratory studies: In the acute setting, serial CBCs with differential, chromosome analysis.
- Diagnostic imaging: Brain imaging.

TABLE E3 Dose Estimates for Common Life and Medical Activities

Activity	Dose Estimate
Natural background and human-made radiation (annual average dose equivalent, including radon)	360 mrem
Diagnostic chest x-ray	6-10 mrem
Flight from Los Angeles to Paris	800 mrem
Barium enema	5 mrem
Smoking 1.5 packs per day for 1 yr	16,000 mrem = 16 rem
Heart catheterization	45,000 mrad = 45 rad = 0.45 Gy
Mild acute radiation syndrome	200 rad = 2 Gy
LD_{50} for acute whole-body irradiation managed without supportive care	450 rad = 4.5 Gy
Occupational limit for a radiation worker	5 rem = 0.05 Sv
Limit of a member of the public	0.1 rem = 0.001 Sv = 1 mSv

Gy, Gray; *LD50,* median lethal dose; *mrad,* millirad; *mrem,* millirem; *mSv,* millisievert; *rad,* radiation absorbed dose; *rem,* roentgen equivalent man; *Sv,* sievert.

Modified from Goans RE: Medical management of radiation incidents, In Shannon MW et al [eds]: *Haddad and Winchester's clinical management of poisoning and drug overdose,* ed 4, Philadelphia, 2007, Saunders.

- Typical syndromes are hematopoietic (doses >3 Gy), gastrointestinal (doses 5 to 12 Gy), and cerebrovascular (10 to 12 Gy).

CHRONIC LOW-DOSE EXPOSURE:

- Currently impossible to determine whether a subsequently diagnosed malignancy is radiation induced. Recent study has shown that long-term exposure to low-dose radiation can lead to a small increase in the risk of leukemia.
- Workup is for underlying malignancy evaluation.
- Research is being performed to look at the effect of chronic low-dose exposure on diseases other than malignancy, such as stroke and heart attack.

ETIOLOGY

ACUTE RADIATION SYNDROME: Usually nuclear disaster

CHRONIC LOW-DOSE EXPOSURE: The average annual dose to residents of the U.S. is approximately 3.6 mSv.

- Cosmic: Positive-charged ions that interact with atmosphere to create secondary radiation
- Terrestrial: Radon, potassium-40, thorium, and uranium
- Man-made: Medical radiation including x-rays, CT scans, PET scans, nuclear stress tests, fluoroscopy, nuclear power, radioactive waste

Rx TREATMENT

- For all accidental radiation contamination, such as nuclear medicine materials, the following decontamination steps are considered mandatory:
  1. Perform at site of exposure unless there is continued radiation exposure.
  2. Remove all clothing (and treat as radioactive waste). Providers should use strict isolation precautions, including donning of gown, mask, cap, double gloves, and shoe covers, when evaluating and treating contaminated patients.
  3. Wash patient with mild soap (neutral pH) and lukewarm water. Dispose of contaminated water as radioactive waste.
  4. Scrub any open wound.
  5. Depending on the situation, the regional emergency response system should be called for additional measures such as evacuation.
- Management of acute radiation syndrome:
  1. Establish IV access.
  2. Monitor physiologic signs.
  3. Manage the airway.
  4. Manage burns.
  5. Identify and treat other injuries.
  6. Obtain CBC with differential, HLA typing prior to any transfusions.
  7. Repeat CBC every 2 to 3 hr for two to three times to assess lymphocyte depletion.
  8. Confirm initial dose estimate using chromosome aberration cytogenetic bioassay when possible.
  9. Provide analgesia and treat vomiting with antiemetics (e.g., ondansetron).
  10. Manage bleeding and transfuse if necessary.
  11. Document skin changes to monitor for radiation skin damage.
  12. Consult with radiation, radiotherapy, and hematology experts.
  13. Diagnose and treat sepsis. Administration of antibiotics reduces the mortality rate. In nonneutropenic patients, use of antibiotics should be reserved for obvious foci of infection secondary to extensive burns, penetrating wounds, and/or abdominal/visceral trauma.
  14. In the setting of neutropenic fever secondary to radiation exposure, one should follow Infectious Diseases Society of America (IDSA guidelines), including fluoroquinolone with streptococcal coverage, an antiviral agent, and an antifungal agent.
  15. Thyroid protection should be considered with exposure to radioactive iodine exposure (e.g., nuclear reactor incident, atomic blast). Prevention of significant uptake is achieved with administration of potassium iodide (KI) within 6 hr of exposure. Repeat doses (every 24 hr) of KI can be administered if radioactive iodine exposure is expected for more than 24 hr.
  16. Consider colony-stimulating factors (CSFs). In any adult with whole-body or significant partial body exposure >3 Gy, treatment with CSFs should be rapidly initiated (e.g., G-CSF or filgrastim, 5 mcg/kg of body weight per day). CSFs may be withdrawn when the absolute neutrophil count reaches a level greater than 1.0×10^9 after recovery from the nadir.
  17. Consider transfusion for radiation-associated bone marrow suppression and GI-associated blood losses. Transfusion thresholds are based upon transfusion guidelines for patients receiving chemotherapy. Consider leukoreduction and irradiation of blood products to prevent graft-versus-host disease.
  18. Consider stem cell transplantation in people with exposure dose of 7 to 10 Gy who do not have significant burns or other major organ toxicity and who have an appropriate donor.
  19. Provide counseling; 75% of individuals exposed to nuclear weapon detonations exhibit some form of psychological symptoms, ranging from insomnia to difficulty concentrating and social withdrawal.
  20. Table E4 summarizes radiation countermeasures for treatment of internal contamination.
- Chronic low-dose exposures: Treatment of radiation-induced organ damage would not differ significantly from non–radiation-induced cancers, cataracts, or skin lesions.
- Late sequelae of radiation exposure include cardiac manifestations such as restrictive cardiomyopathy, constrictive pericarditis, and coronary artery disease. Those at high risk are patients with a radiation exposure of >35 Gy to the heart and usually manifests after 10 yr of radiation exposure.

PEARLS & CONSIDERATIONS

COMMENTS

- Humans are consistently exposed to background/naturally occurring radiation.
- The main concern of radiation exposure is increased risk of cancer.
- X-rays and gamma rays are types of ionizing radiation that can have deleterious biologic effects by damaging DNA.
- The ionizing radiation from medical imaging procedures is not negligible. Since the early 1980s, the per capita dose of radiation from medical imaging has increased by a factor of nearly 6. There is concern that the greater exposure to low-dose radiation due to increased medical imaging will lead to a higher incidence of radiation-induced cancer.
- Efforts to reduce risk of radiation from imaging include justification, optimization, and limitation for imaging procedures.
- Optimization refers to a guiding principle named As Low As Reasonably Achievable (ALARA), which recommends that diagnostic imaging be protocoled to the lowest possible dose to the patient.
- It is difficult to make a link between exposure to chronic low-level radiation and a specific malignancy in an individual.
- Positioning patients for fluoroscopy procedures and monitoring amounts of x-ray radiation are very important to prevent radiation burns.

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TABLE E4 Radiation Countermeasures for Treatment of Internal Contamination

Medical Countermeasure	Administered for	Mechanism of Action	Route of Administration	Dosage	Duration of Treatment
Aluminum carbonate	Phosphorus (P-32)	Phosphate binder	PO	600-mg tablet tid or 400 mg/5 ml tid	
Aluminum hydroxide	Radium (Ra-226) Strontium (Sr-90)	Blocks intestinal absorption	PO	*Adults:* 60-100 ml (1200 mg) *Children:* 50 mg/kg, not to exceed the adult dose	Give one dose within 24 hr of radionuclide intake
	Phosphorus (P-32)	Phosphate binder	PO	600 mg tablet tid or 320 mg/5 ml tid	
Barium sulfate	Radium (Ra-226) Strontium (Sr-90)	Blocks intestinal absorption	PO	100-300 g (as a single dose in 250 ml water)	Give one dose within 24 hr of radionuclide intake
Calcium carbonate	Radium (Ra-226) Strontium (Sr-90)	Competes for bone binding sites	PO	Use as directed on label	Begin therapy within 12 hr of radionuclide intake if possible
Calcium gluconate	Radium (Ra-226) Strontium (Sr-90)	Competes for bone binding sites; phosphate binder	IV	5 ampoules (500 mg Ca/amp) in 500 ml 5% D5W; infuse over 4-6 hr	6 days; begin therapy within 12 hr of radionuclide intake if possible
Calcium phosphate	Radium (Ra-226) Strontium (Sr-90)	Increases excretion	PO	1200 mg	Give one dose within 24 hr of radionuclide intake
Deferoxamine (DFOA)	Plutonium (Pu-239)	Chelating agent	IM (preferred route)	2 ampoules (500 mg DFOA/amp)	• Give a single dose, then obtain bioassay to assess residual body burden of Pu-239 • Repeat as indicated: 500 mg IM (preferred) or IV q4h × 2 doses, then 500 mg IV q12h for 3 days
			IV (slow infusion)	2 ampoules (500 mg DFOA/amp) at 15 mg/kg/hr	
Dimercaprol (BAL)	Polonium (Po-210)	Chelating agent	IM (300 mg/vial for deep IM injection only)	2.5 mg/kg qid × 2 days (days 1 and 2), then bid × 1 day (day 3), then QD (days 4-10)	10 days
DTPA (calcium and zinc)	Americium (Am-241) Californium (Cf-252) Cobalt (Co-60) Curium (Cm-244) Plutonium (Pu-238 and Pu-239) Yttrium (Y-90)	Chelating agent	IV (give once daily as a bolus or as a single infusion; i.e., do not fractionate the dose)	*Adults:* 1 g in 5 ml 5% D5W or 0.9% NS slow IV push over 3-4 min or 1 g in 100-250 ml D5W or NS as an infusion over 30 min *Children <12 yr:* 14 mg/kg/day slow IV push over 3-4 min (not to exceed 1 g/day)	• Begin treatment with Ca-DTPA, then change to Zn-DTPA for maintenance, as indicated • Duration of therapy depends on total body burden and response to treatment
			Nebulized inhalation (for use in adults only)	1 g in 1:1 dilution with sterile water or NS over 15-20 min	
			Wound irrigation fluid	1 g Ca- or Zn-DTPA and 10 ml 2% lidocaine in 100 ml 5% D5W or 0.9% NS	• Irrigation can be accompanied by IV or inhaled DTPA • Amount of DTPA absorbed by wound tissues cannot be measured • Avoid overdosing with DTPA and/or 2% lidocaine
EDTA	Cobalt (Co-60)	Chelating agent	IV	1000 mg/m^2 /day in 500 ml 5% D5W or 0.9% NS; infuse over 8-12 hr	Given as a single dose
			IM	Divide IV dose equally into two doses and administer 8-12 hr apart	Given as a divided dose
D-penicillamine	Polonium (Po-210)	Chelating agent	PO	*Adults:* 0.75-1.5 g (250 mg/capsule) QD *Children:* 30 mg/kg/day (250 mg/capsule) divided into 4 doses	• Obtain bioassay to assess • Continue only if clinically indicated • D-penicillamine has a narrow therapeutic index; use is associated with high risk of toxicity

TABLE E4 Radiation Countermeasures for Treatment of Internal Contamination—cont'd

Medical Countermeasure	Administered for	Mechanism of Action	Route of Administration	Dosage	Duration of Treatment
Potassium iodide (KI)	Iodine (I-131)	Blocking agent	PO	*Adults >40 yr:* 130 mg/day (for projected thyroid dose ≥500 cGy) *Adults 18-40 yr:* 130 mg/day (projected thyroid dose ≥10 cGy) *Pregnant or lactating women of any age:* 130 mg/day (for projected thyroid dose ≥5 cGy) *Adolescents ≥70 kg:* 130 mg/day (for projected thyroid dose ≥5 cGy) *Children & adolescents 3-18 yr:* 65 mg/day (projected thyroid dose ≥5 cGy) *Infants & toddlers 1 mo-3 yr:* 32.5 mg/day (projected thyroid dose ≥5 cGy) *Neonates from birth to 1 mo:* 16 mg/day (projected thyroid dose ≥5 cGy)	• Some incidents will require only a single dose of KI • Incident managers may recommend additional daily doses if ongoing radioactive iodine ingestion or inhalation represents a continuing threat
Potassium phosphate	Phosphorus (P-32)	Phosphate binder	PO	600-1200 mg, given in divided doses	
Potassium phosphate, dibasic	Phosphorus (P-32)	Phosphate binder	PO (take with full glass of water with meals and at bedtime)	*Adults:* 1-2 tablets (250 mg/tab) qid *Children >4 yr:* 1 tablet (250 mg/tab) qid	
Propylthiouracil	Iodine (I-131)	Blocking agent	PO	*Adults:* 2 tablets (50 mg/tab) tid	8 days
Prussian blue, insoluble	Cesium (Cs-137)	Ion exchange; inhibits enterohepatic recirculation in GI tract	PO	*Adults, children >12 yr:* • 1-3 g (2-6 capsules; 0.5 g insoluble Prussian blue per cap) tid; up to 10-12 g/day (based on Goiânia incident data) • 3 g (6 capsules; 0.5 g insoluble Prussian blue per cap) tid (see FDA package insert) • *Children 2-12 yr:* 1 g (2 capsules; 0.5 g insoluble Prussian blue per cap) tid • Capsules may be opened and contents mixed with food • See FDA package insert for pediatric prescribing information • *Children <2 yr:* Prussian blue is not FDA-approved for use (IND or EUA may be required)	• Minimum 30 day course per FDA • Obtain bioassay and whole-body count to assess treatment of efficacy • Duration of therapy depends on total body burden and response to treatment
Sevelamer	Phosphorus (P-32)	Phosphate binder	PO	• 2-4 tablets (400 mg-800 mg/tab) tid • Not to exceed 1600 mg tid	5 days if possible; first dose is the most important
Sodium alginate	Radium (Ra-226) Strontium (Sr-90)	Blocks intestinal absorption	PO (take with a full glass of water)	5 g bid × 1 day, then 1 g qid	
Sodium bicarbonate	Uranium (U-235)	Facilitates increased renal excretion	IV	• 2 amps (44.3 mEq bicarbonate/amp) in 1000 ml 5% D5W or 0.9% NS • 250 ml (1-2 mEq/kg) slow infusion	Administer therapy until urine pH is 8-9; continue for 3 days
			PO	2 tablets/q4h	
Sodium glycerophosphate	Phosphorus (P-32)		PO	600-1200 mg, given in divided doses	
Sodium phosphate	Phosphorus (P-32)		PO	600-1200 mg, given in divided doses	
SumLimer (DMSA)	Polonium (Po-210)	Chelating agent	PO	• 100 mg capsules • Administer 10 mg/kg or 350 mg/m^2 every 8 hr for 5 days, then reduce; safety and efficacy in children <12 yr has not been established	Reduce frequency of administration to 10 mg/kg or 350 mg/m^2 every 12 hr for an additional 2 wk of therapy; typical treatment course 19 days
Water	Tritium (H-3)	Facilitates excretion	PO	>3-4 L/day	3 wk

bid, Twice daily; *EUA,* emergency use authorization; *FDA,* Food and Drug Administration; *IND,* investigational new drug; *IV,* intravenous; *PO,* by mouth; *qid,* four times daily; *tid,* three times daily.
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BASIC INFORMATION

DEFINITION

Ramsay Hunt syndrome is a localized herpes zoster infection involving the seventh nerve and geniculate ganglia, resulting in hearing loss, vertigo, and facial nerve palsy.

SYNONYMS

Herpes zoster oticus
Geniculate herpes
Herpetic geniculate ganglionitis

ICD-10CM CODE
B02.21 Postherpetic geniculate ganglionitis

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: Equal sex distribution
PREDOMINANT AGE:
- Increasingly common with advancing age
- Rare in childhood

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Characteristic vesicles:
  1. On pinna
  2. In external auditory canal (Fig. E1)
  3. In distribution of the facial nerve (VII cranial nerve) and, occasionally, adjacent cranial nerves can also be involved, such as V, IX, X
- Facial paralysis on the involved side
- Auditory symptoms include mild to severe tinnitus, deafness, vertigo, and nystagmus

FIG. E1 Herpes zoster of the geniculate ganglion resulting in vesicles on the ear (as shown here) and tympanic membrane occurs in Ramsay Hunt syndrome. Both seventh and eighth cranial nerve functions may be affected. (From White GM, Cox NH [eds]: *Diseases of the skin: color atlas and text,* ed 2, St Louis, 2006, Mosby.)

ETIOLOGY

- Reactivation of dormant infection with varicella-zoster virus after primary varicella.
- Herpetic inflammation of the geniculate ganglion is thought to be the cause of this syndrome.

DIAGNOSIS

- Usually made by recognition of the clinical features detailed previously
- Viral culture and/or microscopic examination of specimens taken from active vesicles

DIFFERENTIAL DIAGNOSIS

- Herpes simplex
- External otitis
- Impetigo
- Enteroviral infection
- Guillain-Barre syndrome
- Bell palsy of other etiologies, such as Lyme disease
- Acoustic neuroma (before appearance of skin lesions)

The differential diagnosis of headache and facial pain is described in Section II.

WORKUP

If the diagnosis is in doubt, confirm varicella-zoster virus infection.

LABORATORY TESTS

- Generally not necessary
- Viral culture of specimens of vesicular fluid and scrapings of the vesicle base
- Tzanck preparation, which may reveal multinucleated giant cells but has low sensitivity
- Direct immunofluorescent staining of scrapings

IMAGING STUDIES

MRI may demonstrate enhancement of the facial and vestibulocochlear nerves before appearance of vesicles.

TREATMENT

ACUTE GENERAL Rx

- Use of corticosteroids is controversial.
- Acyclovir (800 mg PO 5× qd for 10 days), famciclovir (500 mg tid for 7 days), or valacyclovir (1 g q8h for 7 days) may hasten healing.
- Use of prednisone (60 mg PO qd for 7 days or on a tapering regimen, 40 mg PO for 2 days, 30 mg for 7 days, followed by tapering course) is recommended by some authors, but its use remains controversial.
- Analgesics should be used as indicated.

CHRONIC Rx

- Duloxetine and amitriptyline are effective in postherpetic pain.
- Other agents for postherpetic pain include gabapentin and pregabalin.
- Narcotic analgesics may occasionally be necessary.

DISPOSITION

Recurrences are unusual.

REFERRAL

To otolaryngologist: Patients with persistent facial paralysis for potential surgical decompression of the facial nerve

PEARLS & CONSIDERATIONS

To prevent reactivation of herpes zoster, the herpes zoster vaccine is recommended. The Zoster Vaccine Recombinant, Adjuvanted (SHINGRX) is 90% effective after 2 doses and can be given to persons >50 yr of age.

COMMENTS

Immunodeficiency states, particularly HIV infection, should be considered in:
- Younger patients
- Severe cases
- Patients with a history of specific risk behavior

RELATED CONTENT

Ramsay Hunt Syndrome (Patient Information)
Herpes Zoster (Related Key Topic)

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Raynaud Phenomenon PTG

BASIC INFORMATION

DEFINITION

Raynaud phenomenon (RP) is a vasospastic disorder that causes an exaggerated response to cold temperatures and/or emotional stress, resulting in episodic digital ischemia. It presents as a cold-induced, symmetric, sharply demarcated white or blue discoloration of the distal fingers or toes, followed by erythema at a variable time after rewarming.

SYNONYMS

Primary Raynaud phenomenon or Raynaud disease
Secondary Raynaud phenomenon
RP

ICD-10CM CODES

I73.0 Raynaud syndrome
I73.00 Raynaud syndrome without gangrene
I73.01 Raynaud syndrome with gangrene

EPIDEMIOLOGY & DEMOGRAPHICS

- RP is classified clinically into primary or secondary forms and affects approximately 3% to 5% of the general population, 15% of children younger than 12 yr, and less than 1% of adults older than 60 yr.
- Occurs more commonly in colder climates.
- Primary RP usually occurs between the ages of 12 and 25 yr.
- It is more likely to affect more women than men (4:1).
- 5% to 15% of patients with primary Raynaud phenomenon develop a secondary cause later in the course of the disease (mostly a connective tissue disorder).
- Secondary RP tends to begin after age 35 to 40 yr.
- Secondary RP occurs in more than 90% of patients with scleroderma and in approximately 30% of patients with systemic lupus erythematosus or Sjögren syndrome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The typical manifestation of RP is the biphasic color response of the digits to cold exposure and rewarming, which may or may not be accompanied by pain. RP most often affects the hand (Fig. E1).
  1. White (pallor) or blue (cyanotic) discoloration of the digit(s) resulting from vasospasm on cold or vibration exposure.
  2. Red (rubor) with or without pain and paresthesia when vasospasm resolves and blood returns to the digit.
- Color changes can sometimes be induced by placing the hand in an ice bath, although this is not recommended as a diagnostic maneuver because responses may be inconsistent even in patients with definite RP.
- Color changes are well delineated, symmetric, and usually bilateral, involving the fingers and toes. The index, middle, and ring fingers are commonly involved and the thumb infrequently; however, if the thumb is involved, that suggests secondary causes of RP.
- Fingertips are most often involved, but feet, ears, nose, tongue, and nipples can also be affected.
- Patients with RP may exhibit a violaceous or reticular pattern of skin of arms and legs, sometimes with regular, unbroken circles (livedo reticularis).
- Duration of attacks can range from seconds to hours and averages 15 to 20 min.
- Chronic skin changes resulting from repeated attacks may include skin thickening and brittle nails. Ulcerations and, rarely, gangrene may occur.
- Physical examination should also include examination for symptoms associated with autoimmune disease, such as fever, rash, arthritis, dry eyes, dry mouth, myalgias, or cardiopulmonary abnormalities.

ETIOLOGY

- Primary RP can also be called idiopathic Raynaud phenomenon, primary Raynaud syndrome, or Raynaud disease. It occurs in the absence of any associated disease.
- With primary RP, the possibility that another first-degree family member is affected is reported as approximately 25%.
- Secondary RP is associated with an underlying pathologic condition or disorder, use of certain drugs, or related occupation. Secondary causes of Raynaud phenomenon are summarized in Box 1.

DIAGNOSIS

Clinical criteria:

- Definite RP: Repeated episodes of biphasic color change on cold exposure
- Possible RP: Uniphasic color changes plus numbness or paresthesia on cold exposure
- No RP: No color change on cold exposure

The suggested criteria for primary RP are:

- Symmetric attacks
- Absence of tissue necrosis, ulceration, gangrene, or peripheral vascular disease
- Absence of a secondary cause on the basis of a patient's history and general physical examination
- Negative nail-fold capillary examination
- Negative test for antinuclear antibody (ANA)
- Normal erythrocyte sedimentation rate (ESR)

Secondary RP is suggested by the following findings:

- Onset of symptoms after age 30 yr
- Male gender
- Episodes that are painful, asymmetric, or associated with ischemic skin lesions
- Clinical features suggestive of a connective-tissue disease
- Elevated specific autoantibody tests and ESR
- Evidence of microvascular disease on microscopy of nail-fold capillaries
- It is critical to differentiate primary and secondary RP since management is significantly different for the two conditions. Table 1 summarizes characteristics of primary and secondary Raynaud phenomenon

BOX 1 Secondary Causes of Raynaud Phenomenon

Rheumatologic
Systemic sclerosis (CREST syndrome)
Sjogren syndrome
Systemic lupus erythematosus
Ehlers-Danlos syndrome
Rheumatoid arthritis
Dermatomyositis
Polymyositis
Mixed connective tissue disease

Autoimmune
Reiter syndrome
Vasculitis (polyarteritis nodosa, Henoch-Schönlein purpura)
Antiphospholipid syndrome
Primary pulmonary hypertension

Endocrine
Hypothyroidism
Pheochromocytoma
Carcinoid

Infectious
Hepatitis B and C infection
Mycoplasma pneumonia

Medications
Cyclosporine
Ergotamine
Beta-blockers
Cytotoxic (bleomycin, cisplatin, vinblastine)
Bromocriptine
Nicotine
Cocaine
Sulfasalazine
Interferon-alpha and interferon-beta
Clonidine
Sympathomimetics
Estrogen in oral contraceptives
Caffeine

Occlusive Vascular
Arteriosclerosis
Vascular trauma (hypothenar hammer syndrome)
Buerger disease
Thoracic outlet syndrome
Thromboembolism

Hematologic Proliferative
Leukemia
Lymphoma
Polycythemia vera
Multiple myeloma
Disseminated intravascular coagulation
Cryoglobulinemia
Cold agglutinin disease

Neurologic
Migraines
Carpal tunnel syndrome
Polyneuropathy

Environmental
Emotional stress
Frostbite
Repetitive trauma or injuries to hand

Malignancy
Lung, stomach, small bowel
Paraneoplastic syndrome
Neurofibromatosis

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

TABLE 1 Characteristics of Primary and Secondary Raynaud Phenomenon

Characteristic	Primary	Secondary
Age	Younger (<30 yr)	Older (>30 yr)
Gender preference	Female	Male (depending on secondary cause)
Incidence	Most common	Less common
Familial predisposition	Yes	Yes
Combination with other disease	No, idiopathic	Associated with systemic disease
Vascular defect	Functional dysregulation of autonomic nervous system	Structural changes in connective tissue or vessels
Associated signs	None	Arthritis, sclerodactyly, cardiopulmonary abnormality, rash
Frequency	Precipitated by stimuli	Periodic and stimuli trigger
Severity of symptoms	Long history of mild attacks	Severe and disabling pain
Distribution	Symmetric	Asymmetric
Duration	Self-limited	Need for additional treatment (pharmacologic, surgery)
Critical complications	None	Ischemia and ulcers
Capillaroscopy	Normal (symmetric, thin, and uniform)	Abnormal (dilated, irregular, elongated, and tortuous vessel)
Vascular examination	Normal pulses	Abnormal pulses
Erythrocyte sedimentation rate	Normal	Elevated
Serologic studies	Negative	Antinuclear antibody, autoantibodies
C-reactive protein	Normal	Elevated

From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.

DIFFERENTIAL DIAGNOSIS

- Neurogenic thoracic outlet syndrome or carpal tunnel syndrome
- Frostbite or cold weather injury
- Medication reaction (ergotamine, chemotherapeutic agents)
- Atherosclerosis, thromboembolic disease
- Buerger disease, embolic disease
- Acrocyanosis
- Livedo reticularis
- Injury from repetitive motion

WORKUP

- Once the diagnosis of RP is established, differentiating primary from secondary is helpful in treatment and prognosis.
- Patients who are younger when their symptoms occur, have a normal history and physical examination and normal nail-fold capillaries, and have no history of digital ischemic lesions can be considered as having primary RP. These patients can be monitored clinically without any further testing.
- If a secondary cause of RP is suspected, appropriate laboratory testing is recommended (see "Laboratory Tests"). Secondary RP has associated abnormal nail-fold microscopy.

LABORATORY TESTS

- CBC, serum electrolytes, blood urea nitrogen, creatinine, ESR, ANAs, VDRL antibody test, rheumatoid factor, and urinalysis should be included in the initial evaluation.
- If the history, physical examination, and initial laboratory tests suggest a possible secondary cause, specific serologic testing (e.g., anticentromere antibodies, anti-Scl 70, cryoglobulins, complement testing, and serum protein electrophoresis) may be indicated.
- Noninvasive vascular testing includes finger systolic blood pressures, segmental blood pressure measurements, cold recovery time (measure vasoconstrictor and vasodilator responses of finger to cold), fingertip thermography, and laser Doppler with thermal challenge (measures relative change in skin blood flow with ambient warming).

IMAGING STUDIES

- The diagnosis of RP should not be made on the basis of laboratory tests, and imaging studies should not replace a good history and physical examination.
- Duplex ultrasound can image the palmar arch and digital arteries for patency.
- Magnetic resonance angiography is useful for imaging larger arteries.
- Contrast angiography is the gold standard for arterial imaging.
- Nail-fold capillary microscopy can differentiate primary from secondary RP.
- Videomicroscopy and thermography are also useful for diagnosis of RP.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid drugs that may precipitate RP (see "Etiology").
- Avoid cold exposure and sudden temperature shifts. Use warm gloves, hats, and garments during the winter months or before going into cold environments (e.g., air-conditioned rooms).
- Avoid stressful situations, and use relaxation techniques in preventing RP attacks.

ACUTE GENERAL Rx

- Acute measures to terminate an attack include rotating the arms in a windmill pattern, placing the hands under warm water or in a warm body fold such as the axilla, and the swing-arm maneuver.
- Medications are indicated in the treatment of RP if there are signs of critical ischemia or if the quality of life of the patient is affected to the degree that activities of normal living are no longer possible and preventive techniques do not work. Table 2 summarizes drugs commonly used in Raynaud phenomenon.

CHRONIC Rx

- Dihydropyridine calcium channel blockers (e.g., nifedipine, amlodipine, felodipine, nisoldipine, isradipine) are the most effective pharmacologic treatment for RP and are the drugs of choice. Amlodipine or nifedipine are commonly used.
- Amlodipine dosage ranges from 2.5 to 10 mg/day. Nifedipine is most often prescribed at a dose of 10 to 20 mg 30 min before cold exposure. If symptoms occur with long duration, nifedipine XL 30 to 180 mg PO qd is often effective.
- When calcium channel blockers do not appropriately control symptoms, phosphodiesterase inhibitors (cilostazol, pentoxifylline, and sildenafil) can be added or substituted. Sildenafil can be started at a dosage of 20 mg/day. Angiotensin 2 receptor antagonists (losartan), and selective serotonin reuptake inhibitors (fluoxetine) have also been used with some limited success.
- Some potential therapeutic options include direct vasodilators such as nitroprusside, hydralazine, papaverine, minoxidil, niacin, and griseofulvin. Topical 1% nitroglycerin or topical l-arginine, ethyl nicotinate, hexyl nicotinate, thurfyl salicylate may also be useful, particularly if low blood pressure is a concern.
- Alpha receptor antagonists such as prazosin and phenoxybenzamine have also shown some effectiveness in treating RP.
- The prostaglandins, including inhaled iloprost, IV epoprostenol, alprostadil, and tadalafil, may be promising in severe RP. However, additional experience and controlled studies are needed.
- Antioxidants like zinc gluconate have been used to decrease tissue damage.
- *N*-Acetylcysteine and probucol have been shown to lead to improvement in RP.
- Anticoagulation with IV unfractionated heparin or subcutaneous low-molecular-weight heparin and addition of aspirin can be considered during the acute phase of a severe ischemic event. Aspirin (81 mg/day) therapy can be considered in all patients with secondary RP with a history of ischemic ulcers or thrombotic events; however, caution should be exercised because aspirin can theoretically worsen vasospasm by the inhibition

TABLE 2 Drugs Commonly Used in Raynaud Phenomenon

Drug	Dosage
Oral	
Nifedipine (or other long-acting calcium channel blocker)	10-20 mg bid or tid
Sildenafil	25-50 mg tid
Naftidrofuryl oxalate	100-200 mg tid
Inositol nicotinate	1 g tid or inositol nicotinate forte 1.5 g bid
Thymoxamine	40-80 mg qid (stop after 2wk if no response)
Intravenous Infusion	
Iloprost	Start infusion (peripheral line) at 1 μg/hr; increase by 1 μg every 30 min until reach maximum tolerable dose (maximum dose should not be greater than 3 μg/hr). Infusions are given over 6 hr each day for 3-7 days on each occasion.
Prostaglandin E_1	60 μg in 250-ml physiologic infusion over 3 hr daily for 5-6 days. This could be repeated every 6 wk to cover the cold weather in severe cases, especially if associated with critical ischemia or digital ulceration, and should be given via a central line.

bid, Twice a day; *qid,* four times a day; *tid,* three times a day.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

BOX 2 Features Suggestive of Progression of RP

Clinical
- Older age at onset (>35 yr)
- Recurrence of chilblains as adult
- Vasospasm all yr round
- Asymmetric attacks
- Sclerodactyly or any other sign of CTD
- Digital ulceration
- Finger pulp pitting scars

Laboratory
- Increased inflammatory markers
- Detection of autoantibodies
- Increased von Willebrand factor antigen

Nail-fold Microscopy
- Abnormal vessels on videomicroscopy

CTD, Connective tissue disorder.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

of prostacyclin. Long-term anticoagulation with heparin or warfarin is not recommended unless there is evidence of a hypercoagulable state.
- Bypass surgery can be performed for severe RP associated with reconstructible arterial occlusive disease.
- Sympathectomy is available for unreconstructible occlusive disease or pure vasospastic disease refractory to medical treatment.
- Microsurgical revascularization of the hand and digital reconstruction may improve digital vascular perfusion and heal digital ulcers when proximal arterial occlusion is associated with digital vasospasm.
- Ischemic digital lesions should be treated with topical antibiotics and daily cleansing with soap and water. Digits that progress to dry gangrene should be permitted to undergo autoamputation. Surgical amputation is limited for intractable pain or deep tissue infection.

DISPOSITION

The prognosis of patients with RP depends on the etiology.
- Primary RP is fairly benign, usually remaining stable and controlled with nonpharmacologic medical treatment.
- Remission of primary RP can occur spontaneously.
- Patients with secondary RP, specifically those with scleroderma, CREST syndrome, or thromboangiitis obliterans, may develop severe ischemic digits with ulceration, gangrene, and autoamputation.
- Box 2 summarizes features suggestive of progression of Raynaud phenomenon.

REFERRAL

- Rheumatology consult is indicated if secondary collagen vascular disease is diagnosed.
- Vascular surgery consult is indicated if ulcers, gangrene, or threatened digit loss is noted.

PEARLS & CONSIDERATIONS

- Most patients with RP can be managed by a primary care provider
- It is important to differentiate primary from secondary forms. Secondary forms may become manifest as far out as 10 yr from the diagnosis of RP. It is important to take immediate action during an attack, and patients are encouraged to:
  1. Keep warm
  2. Not use tobacco products
  3. Avoid aggravating medications
  4. Control stress
  5. Exercise
  6. Follow up with a physician

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Raynaud Phenomenon (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Shapiro SC, Wigley FM: Treating Raynaud phenomenon: beyond staying warm, *Cleveland Clinic J Med* 84:797-804, 2017.

Wigley FM, Flavahan NA: Raynaud phenomenon, *N Engl J Med* 375:556-565, 2016.

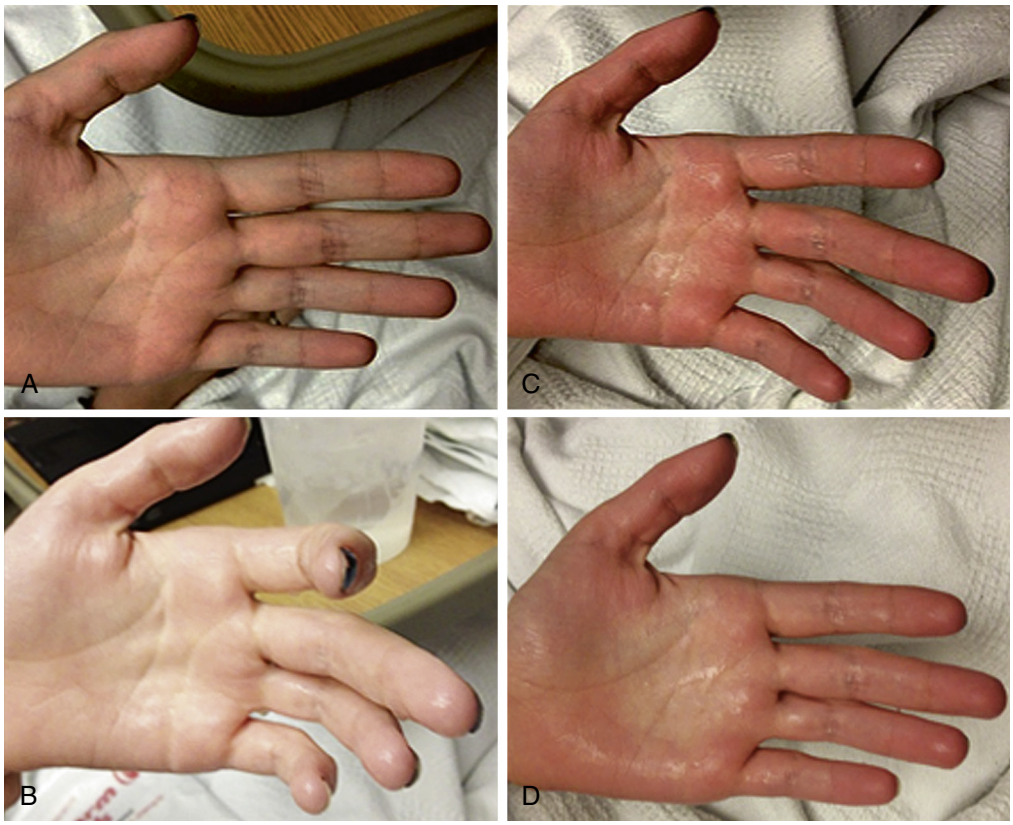

FIG. E1 Raynaud phenomenon in a patient with Ehlers-Danlos syndrome to illustrate the color changes associated with stressful stimuli. A, Normal-appearing hand. **B,** After cold stimuli, the pallor from vasoconstriction can be seen. **C,** After 30 seconds, the hyperemic red appears in fingers with blood reperfusion. **D,** Hand after 3 minutes exposed to stimuli. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

BASIC INFORMATION

DEFINITION

Reactive arthritis is one of the seronegative spondyloarthropathies, so called because serum rheumatoid factor is not present in these forms of inflammatory arthritis. Its characteristic clinical course consists of urethritis, conjunctivitis, and arthritis. Hans Reiter was a Nazi war criminal and many believe that he should no longer be given name recognition to designate this syndrome. Reactive arthritis is an asymmetric polyarthritis that affects mainly the lower extremities and is associated with one or more of the following:

- Urethritis
- Cervicitis
- Dysentery
- Inflammatory eye disease
- Mucocutaneous lesions

SYNONYMS

Reiter disease
Reiter syndrome
Seronegative spondyloarthropathy

ICD-10CM CODE
M02.30 Reiter disease, unspecified site

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 0.0035% annually of men ≤50 yr
PEAK INCIDENCE: Most common in the third decade
PREDOMINANT SEX: Male
PREDOMINANT AGE: 20 to 40 yr
GENETICS: Familial disposition: Strongly associated with HLA-B27 (63% to 96%)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Polyarthritis:
  1. Affecting the knee and ankle
  2. Commonly asymmetric
- Heel pain and Achilles tendinitis, especially at the insertion of the Achilles tendon
- Plantar fasciitis
- Large effusions
- Dactylitis, or "sausage toe"
- Urethritis
- Uveitis or conjunctivitis; uveitis can progress to blindness without treatment
- Keratoderma blennorrhagicum, circinate balanitis:
  1. Hyperkeratotic lesions on soles of the feet (Fig. E1), toes, penis (Fig. E2), hands
  2. Closely resembles psoriasis
- Aortic regurgitation similar to that seen in ankylosing spondylitis

ETIOLOGY

- Epidemic Reiter syndrome after outbreaks of dysentery has been well described.
- Genetically susceptible HLA-B27 individuals are at risk for developing reactive arthritis after infection with certain pathogens:
  1. *Salmonella*
  2. *Shigella*
  3. *Yersinia enterocolitica*
  4. *Chlamydia trachomatis*
- Symptom complex indistinguishable from reactive arthritis has been described in association with HIV infection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ankylosing spondylitis
- Psoriatic arthritis
- Rheumatoid arthritis
- Gonococcal arthritis-tenosynovitis
- Rheumatic fever
- Serum sickness
- Gout
- Chronic mucocutaneous candidiasis

WORKUP

- X-ray examination of affected joints
- Synovial fluid examination and culture
- Careful examination of eyes and skin
- Cultures for gonococcus (urethral, cervical, stool)

LABORATORY TESTS

- Elevated but nonspecific erythrocyte sedimentation rate
- No specific laboratory tests to diagnose reactive arthritis
- Do not use HLA-B27 testing as a diagnostic tool, as only positive in 30% to 50% of patients

IMAGING STUDIES

Plain radiographs:

- Juxtaarticular osteopenia of affected joints
- Erosions and joint space narrowing in more advanced disease
- Periostitis and reactive new bone formation at the insertions of the Achilles tendon and the plantar fascia
- Sacroiliitis:
  1. Unilateral or bilateral
  2. Indistinguishable from ankylosing spondylitis
- Vertebral bridging osteophytes

TREATMENT

NONPHARMACOLOGIC THERAPY

Physical therapy to maintain range of motion of the spine and other joints

ACUTE GENERAL Rx

- Flares treated with nonsteroidal antiinflammatory drugs such as indomethacin (25 to 50 mg PO tid). Refractory cases can be treated with methotrexate or infliximab.
- Mucocutaneous lesions are visually self-limited and clear with topical corticosteroids. Acitretin or cyclosporine can be used for refractory skin lesions.
- Enteric or urethral infection should be treated with appropriate antibiotic coverage.
- Uveitis should be treated with steroid eye drops in consultation with an ophthalmologist.
- Achilles tendinitis and plantar fasciitis should be treated with injections of methylprednisolone (40 to 80 mg).
- Sulfasalazine (500 to 1000 mg PO bid, then titrate up to maximum 3 g/day) may be effective.
- Careful monitoring for the following is essential:
  1. Gastrointestinal toxicity
  2. Hypersensitivity
  3. Bone marrow suppression
- Persistent and uncontrolled disease should be managed with cytotoxic drugs (methotrexate, azathioprine) in consultation with a rheumatologist.
- The role of tumor necrosis factor alpha inhibitors in therapy is evolving, but agents such as etanercept for 6 mo or infliximab have been shown to be helpful in small studies.

CHRONIC Rx

Chronic disease is best managed by a team approach with the collaboration of a rheumatologist or other experienced physician and physical therapist.

DISPOSITION

- Recurrences are frequent, even with treatment.
- Long-term sequelae:
  1. Persistent polyarthritis
  2. Chronic back pain
  3. Heel pain
  4. Progressive iridocyclitis
  5. Aortic regurgitation

REFERRAL

- To ophthalmologist if uveitis is suspected
- To rheumatologist if arthritis and tendinitis fail to improve rapidly after a course of nonsteroidal antiinflammatory drugs

PEARLS & CONSIDERATIONS

COMMENTS

- Infection with HIV is associated with particularly severe cases of reactive arthritis.
- HIV testing is recommended, especially if risk factors such as unprotected sexual activity or IV drug use are identified.
- The role of antibiotics seems useful in *Chlamydia*-triggered arthritis, but the role of antibiotics in arthritis triggered by enteric pathogens is less clear.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Reiter Syndrome (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Flagg SD et al: Decreased pain and synovial inflammation after etanercept therapy in patients with reactive and undifferentiated arthritis: an open-label trial, *Arthritis Rheum* 53:613, 2005.

Hannu T: Reactive arthritis, *Best Pract Res Clin Rheumatol* 25(3):347-357, 2011.

Honda K et al: Reactive arthritis caused by Yersinia enterocolitica enteritis, *Intern Med* 56:1239–1242, 2017.

Schmitt SK: Reactive arthritis., *Infect Dis Clin North Am* 31:265-277, 2017.

Selmi C, Gershwin ME: Diagnosis and classification of reactive arthritis, *Autoimmun Rev* 13:546-549, 2014.

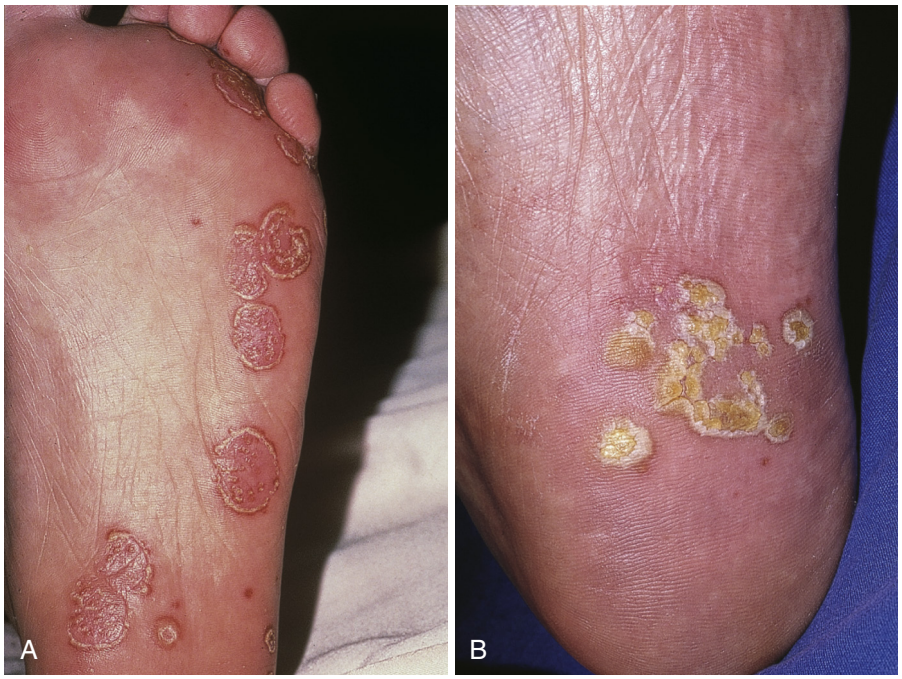

FIG. E1 Reiter syndrome. A and **B,** Examples of lesions on the soles; these annular lesions are typical of keratoderma blennorrhagicum. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

FIG. E2 Reiter syndrome. Circinate balanitis, with urethral discharge. (Courtesy Dr. B. Stanley. From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

Rectal Prolapse

BASIC INFORMATION

DEFINITION

Rectal prolapse is an often socially disabling condition characterized by the circumferential protrusion of part or all layers of the rectum beyond the anus. The two main types of rectal prolapse include: (1) Partial prolapse including the anal or rectal mucosa only, and (2) complete (full-thickness) prolapse involving all layers of the rectum (Fig. E1). A third and less common type is prolapse of the rectal wall that does not protrude through the anus, known as an occult prolapse or rectal intussusception.

SYNONYMS

Procidentia
Rectal intussusception

ICD-10CM CODES

K62.3	Rectal prolapse
K62.2	Anal prolapse

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown in general population. In children with cystic fibrosis it approaches 20%.
PEAK INCIDENCE: Women after the fifth decade represent between 80% and 90% of patients with rectal prolapse. Incidence increases with each decade in female patients until the seventh decade.
PREVALENCE: N/A
PREDOMINANT SEX AND AGE: Rectal prolapse occurs at the extremes of age, with an equal sex distribution in children. In adults, females predominate by a ratio of nine to one.
GENETICS: N/A
RISK FACTORS: Cystic fibrosis, hemorrhoids, laxity of the pelvic fascia/muscles due to prior pelvic surgery or obstetric trauma, anal sphincter dysfunction, chronic constipation, and increasing age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most patients detect a mass, usually after defecation or strenuous activity. Later in the course, patients may develop prolapse with activities such as standing or walking.
- In children, the prolapse usually appears as a painless, maroon-colored mass associated with mucus or blood.
- Anal sphincter weakness associated with rectal prolapse may cause fecal incontinence
- Other common symptoms include rectal bleeding, a change in bowel habits, incomplete evacuation or tenesmus, and a mucus-like discharge with bowel movements.
- Differentiating between mucosal and complete prolapse can be helpful yet challenging. Mucosal prolapse usually occurs distal to the dentate line, extending only a few centimeters beyond the anus. Complete prolapse may extend up to 15 cm and will usually have a normal-appearing anus as compared with mucosal prolapse, in which the anal edges appear everted.

ETIOLOGY

- Rectal prolapse is associated with chronic straining, leading to pelvic muscle and nerve dysfunction or weakness.
- Multiple conflicting theories exist for the etiology of rectal prolapse including: (1) A redundant sigmoid colon lying deep within the pelvis, (2) an intussusception due to poor anorectal tone, (3) injury to the pudendal nerves from repeated stretching of the pelvic floor, and (4) abnormal fixation of the rectum.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Rectal cancer, hemorrhoids, rectal polyps, intussusception

WORKUP

General principles of evaluation include a thorough physical examination including digital rectal examination, imaging studies to evaluate various etiologies, and colorectal surgical consultation for repair.

LABORATORY TESTS

- In general, patients with rectal prolapse do not need laboratory testing if they appear well or are mostly asymptomatic.
- A hemoglobin/hematocrit may be obtained if there is concern for significant bleeding. A metabolic panel may be obtained if there is concern for electrolyte abnormalities.
- All patients that require surgical intervention will need preoperative laboratory testing.

IMAGING STUDIES

- Screening evaluation of the colon with colonoscopy or a barium enema is recommended in most adult patients after reduction or repair of rectal prolapse.
- Additional studies such as cinedefecography, anorectal manometry, electromyography, and colonic transit studies may be considered in the evaluation of patients with rectal prolapse in consultation with a specialist.

TREATMENT

- Patients with a small rectal prolapse that reduces on its own may be managed conservatively with stool softeners. Early specialist referral is encouraged to exclude alternative diagnoses and for serial examinations.
- Operative intervention is the mainstay of treatment for rectal prolapse that requires manual reduction. Goals of surgical treatment include control of the prolapse, restoring continence, and preventing constipation.
- The choice of operative repair takes into account many factors, including coexisting slow transit constipation, postoperative rectal compliance, pelvic floor denervation, the possibility of postoperative sexual dysfunction in men, age, cardiac and pulmonary risk factors, prior abdominal surgeries or pelvic irradiation, and overall immune function.
- Given that many patients with rectal prolapse carry high operative risk due to age and concomitant disease, nonoperative treatment is appealing but only temporary.

NONPHARMACOLOGIC THERAPY

- Abdominal procedures such as suture rectopexy with sigmoid resection and/or subtotal colectomy yield better results in young, healthy patients and are associated with lower recurrence rates.
- Perineal procedures such as perineal rectosigmoidectomy with levatorplasty have a higher rate of recurrence and functional abnormality, yet carry a lower surgical risk and are thus reserved for high-risk, older surgical patients.

ACUTE GENERAL Rx

- Manual reduction can be attempted after appropriate analgesia or sedation. In children, the protruding mucosa proximal to the anorectal ring is replaced by applying slow and steady pressure to the prolapsed segment.
- In adults, manual reduction is more challenging and may take several minutes. The thumbs are placed over the prolapsed segment medially and the fingers grasp the outer walls laterally. Continuous, steady pressure starting with the thumbs followed by rolling of the fingers can aid in reduction.
- After reduction, a digital rectal examination should be performed on all patients to ensure that the reduction is complete, and to evaluate for mass or polyps. Gauze with a lubricant jelly can be placed over the anus and taped in place after reduction.
- Patients with severe rectal prolapse that cannot be reduced or have ischemia/gangrene of the prolapsed segment will require emergency surgical consultation and hospitalization.
- Granulated sugar applied for 15 min to a swollen prolapsed segment has been used to reduce edema before attempting manual reduction.

FIG. E1 Prolapse of the rectum. (Courtesy Gershon Effron, MD, Sinai Hospital of Baltimore. From Seidel HM et al: *Mosby's guide to physical examination,* ed 4, St Louis, 1999, Mosby.)

CHRONIC Rx

Patients with edematous rectal walls, venous engorgement, thrombosis, ulcerations, strangulation, or ischemia will likely not be candidates for manual reduction and will require more urgent surgical referral.

COMPLEMENTARY & ALTERNATIVE MEDICINE

N/A

DISPOSITION

- Patients with reducible and nonischemic rectal prolapse without significant bleeding can be referred for outpatient surgical consultation and intervention.
- Patients with ischemic or nonreducible segments associated with gangrene or severe bleeding will need to be hospitalized.

REFERRAL

Patients with rectal prolapse will require colorectal surgical consultation. Many patients will also require referral to a gastroenterologist for screening colonoscopy.

PEARLS & CONSIDERATIONS

COMMENTS

- Rectal prolapse is a relatively rare yet socially debilitating condition that appears at the extremes of age.
- Manual reduction is the mainstay of initial treatment after appropriate analgesia or sedation.
- Surgical referral is warranted for all patients and emergent referral should be made for all patients with ischemic, gangrene, or nonreducible prolapsed segments.

PREVENTION

Avoiding chronic constipation

AUTHOR: **Rory Merritt, MD, MEHP**

Relapsing Polychondritis

BASIC INFORMATION

DEFINITION

Relapsing polychondritis (RP) is a rare, progressive, autoimmune disorder characterized by episodic inflammation and destruction of cartilage and proteoglycan-rich tissues such as those present in the eyes, inner ear, cardiovascular system, and kidneys.

SYNONYMS

Chronic atrophic polychondritis
RPC
Generalized or systemic chondromalacia
Meyenburg-Altherr-Uehlinger syndrome
Relapsing perichondritis
von Meyenburg disease

ICD-10CM CODE
M94.1 Relapsing polychondritis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 3.5 cases per million. There is similar frequency of cases in both sexes. RP is associated with human leukocyte antigen-DR4. Box 1 summarizes conditions associated with relapsing polychondritis.
PREDOMINANT SEX: Males and females are affected equally.
PREDOMINANT AGE: Peak onset is between 40 and 60 yr, although RP has been described in children.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- RP affects cartilaginous and noncartilaginous structures.
- Acute unilateral or bilateral auricular chondritis affecting the pinna and sparing the earlobe (Fig. E1) is the classic clinical feature and the most common symptom. It presents with sudden onset of redness, swelling, warmth, and pain. RP may resolve with or without treatment in 5 to 10 days. Repeated attacks may progress to a pinna devoid of firmness and a cauliflower-like appearance. Swelling of the outer ear or inner ear artery vasculitis may cause deafness or vertigo.
- The second most common symptom is arthritis in an asymmetric pattern.
- RP may affect the nasal cartilage, causing saddle-nose deformity (Fig. E2), structures of the inner ear leading to auditory or vestibular complications, and ocular structures.
- Respiratory disease develops in 50% of patients and is noteworthy because of its association with lethal organ system involvement and worse prognosis. Patients may have symptoms such as hoarseness, aphonia, tenderness over the anterior neck (anterior trachea cartilage or thyroid cartilage [Fig. E3]), or persistent dry cough.
- Cardiovascular, ocular, renal, neurologic, and mucocutaneous manifestations are possible.
- Table 1 demonstrates frequency of initial findings at time of diagnosis with subsequent symptoms.
- Anemia at the time of diagnosis in individuals older than 50 may be a poor prognostic factor. Macrocytic anemia warrants suspicion of myelodysplasia.

ETIOLOGY

Unknown, felt to be an autoimmune condition. Some association with HLA-DR4 is seen.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infection (tuberculosis, fungal disease, leprosy, syphilis)
- Leukemia cutis, lymphoma
- Red ear syndrome
- ANCA-associated vasculitides
- Cogan syndrome
- Chondrodermatitis nodularis helicis

1. Diagnosis is clinical, and McAdams criteria (Box 2) commonly are used. Presence of any three of the following is diagnostic: 1) bilateral auricular chondritis, 2) nonerosive inflammatory polyarthritis, 3) chondritis of nasal cartilage, 4) inflammation of ocular structures (conjunctivitis, keratitis, scleritis, episcleritis, uveitis), 5) chondritis of the respiratory tract (laryngeal/tracheal cartilage), 6) cochlear and/or vestibular damage (hearing loss, tinnitus, vertigo).
2. Since RP is a remittent and rare disease, diagnosis may be delayed.

LABORATORY TESTS

- No specific blood tests to diagnose RP.
- Acute-phase reactants may be elevated during times of disease activity.
- Serologic testing as warranted if associated condition such as rheumatoid arthritis or ANCA-associated vasculitis is suspected.
- Synovial fluid analysis if arthritis is present.
- Cartilage biopsy (Fig. E4).

IMAGING STUDIES

- Pulmonary function tests (PFTs) should be obtained in all suspected cases. If abnormal, chest CT is warranted to look for abnormalities such as airway stenoses or dynamic airway collapse. Expiratory CT abnormalities are common. Findings may be missed if not obtained during expiratory phase.
- Echocardiogram can be used to characterize cardiopulmonary symptoms and assess heart valves.
- PET/CT and MRI may be used to monitor disease activity and response to treatment.
- Biopsy, though not required, demonstrates cartilage with loss of basophilic staining of cartilage matrix, perichondrial inflammation, and potential cartilage destruction (see Fig. E3). Infiltrates are mainly plasma cells and lymphocytes.

BOX 1 Conditions Associated with Relapsing Polychondritis

- Rheumatoid arthritis
- Systemic lupus erythematosus
- Scleroderma
- Sjögren syndrome
- Overlap connective tissue disease
- Ankylosing spondylitis and sacroiliitis
- Psoriatic arthritis
- Reactive arthritis
- Antineutrophil cytoplasmic antibody-associated granulomatous vasculitis
- Polyarteritis nodosa
- Churg-Strauss vasculitis
- Behçet syndrome
- Myelodysplastic syndromes
- Lymphoma
- Inflammatory bowel disease
- Primary biliary cirrhosis

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE 1 Clinical Manifestations of Relapsing Polychondritis

Finding	Frequency (%) Initial	Total
Auricular chondritis	39	85
Saddle-nose deformity	18	29
Hearing loss	9	30
Arthritis	36	52
Costochondral cartilage inflammation	2	2
Nasal cartilage inflammation	24	54
Ocular inflammation	19	51
Scleritis or episcleritis	19	47
Laryngotracheal-bronchial disease	26	48
Laryngotracheal stricture	15	23
Systemic vasculitis	3	10
Valvular dysfunction	0	6
Cutaneous features	7	28

Adapted from Isaak BL, Liesegang TJ, Michet CJ Jr. Ocular and systemic findings in relapsing polychondritis, *Ophthalmology* 93:681-9, 1986. In Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

BOX 2 Diagnostic Criteria for Relapsing Polychondritis

- Bilateral auricular chondritis
- Nonerosive seronegative inflammatory polyarthritis
- Nasal chondritis
- Ocular inflammation (conjunctivitis, keratitis, scleritis and/or episcleritis, uveitis)
- Respiratory tract chondritis (laryngeal and/or tracheal cartilages)
- Cochlear and/or vestibular dysfunction (neurosensory hearing loss, tinnitus, and/or vertigo)
- Cartilage biopsy confirmation of a compatible histologic picture

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Severe airway, cardiac, and sensorineural deficits require a holistic approach. Airway teams should be aware of pathologic airways. Tracheobronchomalacia may require tracheostomy, stenting of airway, or nighttime positive pressure ventilation. Cardiac intervention to treat aortic root dilation or valvular disease may be warranted. Cochlear implantation may restore hearing. Interventions ideally should take place during disease quiescence.

ACUTE GENERAL Rx

Initial management of patients with acute RP is dependent on severity. For minor inflammation (nose, ear, or chest wall), NSAIDs, low dose corticosteroids, colchicine, or dapsone may be used. Serious or life-threatening manifestations such as severe chondritis, laryngotracheal or ocular symptoms often require 1 mg/kg of prednisone with slow taper.

CHRONIC Rx

- Steroid dependence, relapses, or life-threatening manifestations may warrant disease modifying therapies. Case reports have demonstrated success with methotrexate, cyclophosphamide, mycophenolate mofetil, azathioprine, chlorambucil, cyclosporine, and IVIG.
- RP refractory to conventional treatments has been treated successfully with TNF inhibitors, tocilizumab, anakinra, and abatacept. Rituximab has more negative than positive case reports.

REFERRAL

- ENT for audiovestibular symptoms
- Pulmonology, anesthesia, and surgery for airway management
- Rheumatology

PEARLS & CONSIDERATIONS

- Prompt diagnosis is necessary to avoid severe complications.
- Respiratory involvement, number of manifestations, and anemia predict reduced survival.
- All patients should have airway and laryngotracheal involvement assessed through neck and chest x-rays and PFTs. Flow volume loops may reveal fixed extrathoracic obstruction.

AUTHOR: **Long Pham, MD**

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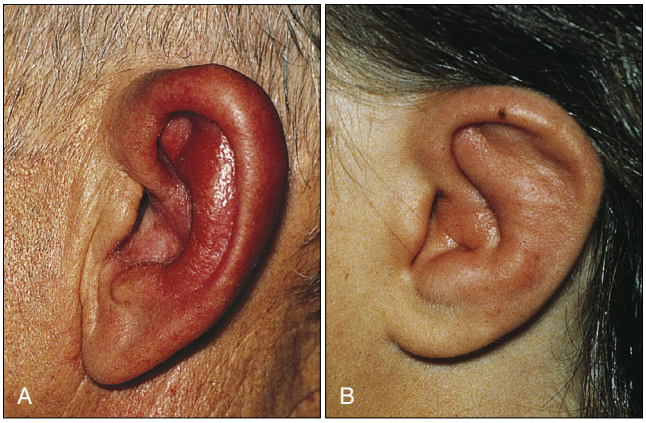

FIG. E1 Otorhinolaryngeal disease in relapsing polychondritis. A, The pinna of the ear becomes inflamed; note the sparing of the noncartilaginous portion of the ear. **B,** Recurrent attacks cause loss of cartilage, with the ear flopping over. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

FIG. E2 Otorhinolaryngeal disease in relapsing polychondritis. The saddle-nose deformity is caused by damage to the nasal bridge. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

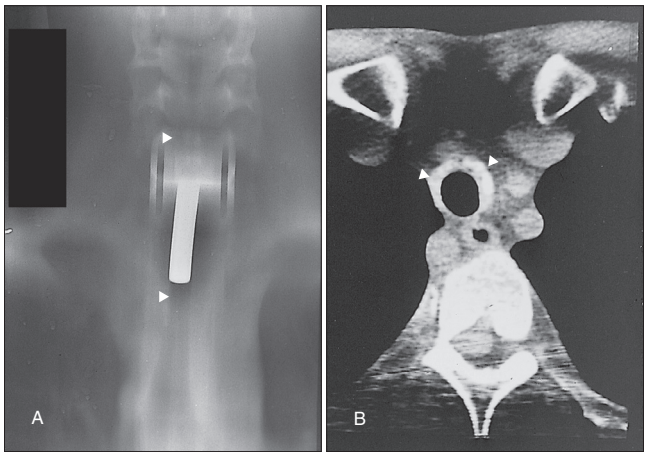

FIG. E3 Localized tracheobronchial obstruction caused by relapsing polychondritis. A, The radiograph shows both narrowing in the larynx above the tracheostomy tube and tracheal stenosis below *(arrowheads)*. **B,** Computed tomography scan of the trachea shows the thickening of the tracheal wall due to inflammatory changes *(arrowheads)*. Note how the posterior, noncartilaginous portion of the trachea is spared. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

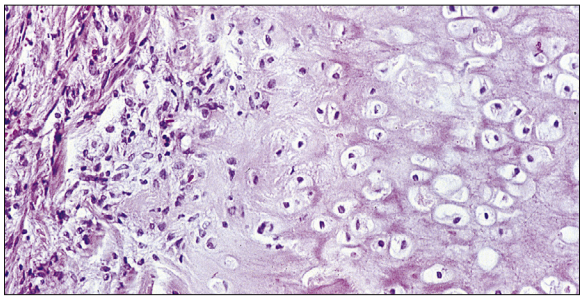

FIG. E4 Biopsy specimen from the ear shows perichondritis with the presence of mononuclear cells and occasional polymorphonuclear leukocytes at the fibrochondral junction (hematoxylin and eosin stain, ×200). (Courtesy Dr. Lester E. Wold. In Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

Renal Abscess

BASIC INFORMATION

DEFINITION

Renal abscess and perinephric abscess are purulent complications of an underlying urinary infection of the ascending tract with an obstructed pyelonephritis. Predisposing factors include diabetes and renal stones. There is lobar necrosis with renal abscess and perirenal fat necrosis in perinephric abscess.

SYNONYMS

Intrarenal abscess
Perinephric abscess
Kidney abscess

ICD-10CM CODE
N15.1 Renal and perinephric abscess

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Ranges from 1 to 10 per 10,000 hospital admissions
PREDOMINANT SEX AND AGE: In one study median age was 59.8 yr
RISK FACTORS: Diabetes and renal stones

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms include fever, flank pain, abdominal pain, and urinary frequency or dysuria.
- At times renal abscess can present insidiously in the elderly or persons with diabetes.

ETIOLOGY

These infections may be a complication of a urinary tract infection that ascends to the upper tract, usually due to gram-negative bacteria, or a complication of a bacteremia with hematogenous seeding to the kidney, usually secondary to a *Staphylococcus aureus* infection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute pyelonephritis with papillary necrosis
- Acute lobar nephronia: Acute nonsuppurative renal infection
- Renal cell carcinoma
- Malakoplakia: Rare granulomatous inflammatory disease seen with *Escherichia coli* infection
- Emphysematous pyelonephritis: Gas formation within the renal parenchyma caused by infection by facultative anaerobes or *Candida* spp.

WORKUP

Combination of laboratory tests and imaging

LABORATORY TESTS

- Blood cultures, urine cultures, urinalysis, and CBC are basic tests.
- Elevated ESR or C-reactive protein may be marker for a deep-seated infection.

IMAGING STUDIES

- Ultrasound may show thick-walled fluid-filled cavity in renal parenchyma. A perinephric abscess is confined to the perinephric space by Gerota fascia.
- CT with contrast (Fig. E1) is preferred over ultrasound for the diagnosis.
- MRI and nuclear scans are of limited value.

TREATMENT

Antibiotic therapy and, when necessary, interventional radiology or surgical drainage procedure

NONPHARMACOLOGIC THERAPY

- Therapy for a renal abscess greater than 5 cm in diameter should be percutaneous drainage by CT- or US-guided therapy along with intravenous antibiotics.
- A perinephric abscess should be drained percutaneously with CT or US guidance.
- At times a nephrectomy may be required for severe cases, usually in diabetic patients.

ACUTE GENERAL Rx

A renal abscess less than 5 cm in diameter can be treated successfully with targeted intravenous therapy (92% success rate for abscess 3 to 5 cm in diameter). Antibiotic choices are based on culture results but initially should target gram-negative bacteria unless infection is secondary to staphylococcal bacteremia. Empiric antibiotic therapy in geographic areas where fluoroquinolone resistance rates are <10% consists of ciprofloxacin 400 mg IV loading dose. In areas with high fluoroquinolone resistance rates, ceftriaxone 1 g IV is appropriate. If perinephric abscess is associated with staphylococcal bacteremia, give IV nafcillin if methicillin-susceptible *Staphylococcus aureus* (MSSA) or vancomycin 1 g IV q12h if methicillin-resistant *S. aureus*.

CHRONIC Rx

Antibiotic therapy generally continues for 2 to 3 weeks, some of which can be completed with oral therapy.

DISPOSITION

Antibiotics such as trimethoprim-sulfamethoxazole and quinolone antibiotics penetrate well in the kidney and are ideal oral agents for therapy.

REFERRAL

Interventional radiology, urologic surgeon, and infectious diseases consult

PEARLS & CONSIDERATIONS

COMMENTS

This diagnosis should be considered in patients who are being treated for pyelonephritis with appropriate antibiotics and fail to respond clinically after 5 days.

PREVENTION

Early and targeted therapy for urinary tract infections, especially in diabetic patients

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Pyelonephritis (Related Key Topic)
Urinary Tract Infection (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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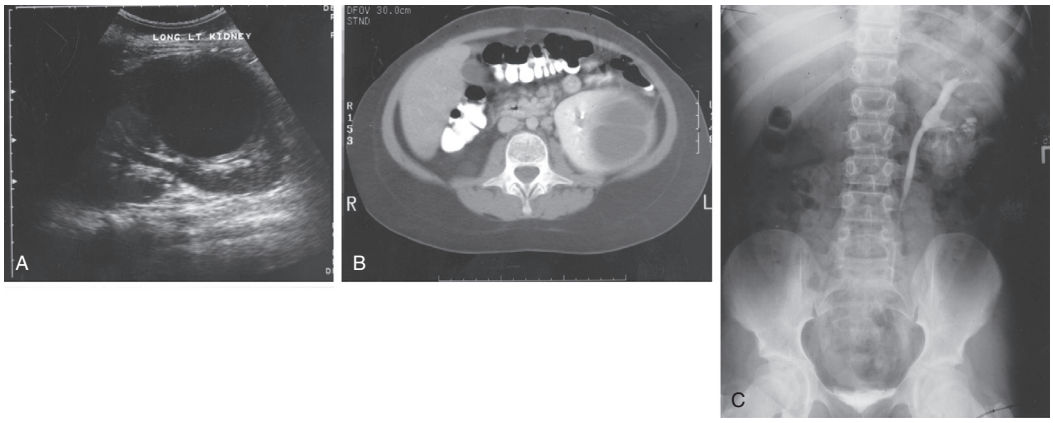

FIG. E1 Renal abscess complicating infundibular stenosis in a 10-year-old girl with low-grade fever, marked left costovertebral angle tenderness, leukocytosis, and pyuria but a negative urine culture (she had received outpatient antibiotics). The right kidney was absent. **A,** Sonogram of the left kidney revealed a large cystic mass with septa. **B,** The mass was confirmed by computed tomography. **C,** Intravenous pyelogram obtained after resolution of the abscess (by percutaneous and open drainage) reveals anomalous development of the lower infundibulum and calyces. (From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Renal artery stenosis (RAS) is the progressive narrowing of the renal artery, which is most commonly due to atherosclerosis or fibromuscular dysplasia (FMD). RAS is an important, potentially reversible cause of hypertension, ischemic nephropathy, and destabilizing cardiac syndromes. RAS increases the risk of renal artery occlusion via progression of the severity of the stenosis.

SYNONYMS

Fibromuscular disease
FMD
RAS
Renovascular disease

ICD-10CM CODES

I70.1	Atherosclerosis of renal artery
I15.0	Renovascular hypertension
I77.9	Disorder of arteries and arterioles, unspecified
Q27.1	Congenital renal artery stenosis

EPIDEMIOLOGY & DEMOGRAPHICS

- RAS:
  1. Atherosclerotic RAS (ARAS) accounts for about 90% of cases. True prevalence is unknown.
     a. General population autopsy studies: 10%, 27% over 50 yr; hypertensive patients: 0.2% to 5%.
     b. In the general population >65 yr of age, the prevalence is 6.8% by Doppler ultrasound (5.5% of women, 9.1% of men, 6.7% of African Americans, and 6.9% of Caucasians). Of those with ARAS, 12% had bilateral disease.
     c. In patients with malignant hypertension, the prevalence is 43% in Caucasians and 7% in African Americans. In patients with mild hypertension, the prevalence is <1%.
     d. In patients with peripheral artery disease, the prevalence is 22% to 59%.
  2. FMD accounts for approximately 10% of chronic RAS. It is typically seen in women (90%). FMD was previously thought to be a disease of the young and healthy with few risk factors, but recent data suggest an average age of diagnosis of 54 yr, and 26% have bilateral disease.

ETIOLOGY

- Atherosclerosis: ARAS is a process similar to atherosclerosis in other vascular beds with similar risk factors: family history, smoking, diabetes, hypertension, and hyperlipidemia. ARAS most often involves the ostium and proximal third of the main renal artery.
- Fibromuscular dysplasia (FMD) (Figs 1 and 2): Etiology unknown. Classified into three categories based on the layer of arterial wall affected: medial (>90%), intimal (<10%), adventitial (<1%). FMD typically involves the distal main renal artery and intrarenal branches.

PATHOGENESIS

- Pathogenesis of fibromuscular dysplasia is unknown. Fibromuscular dysplasia involves abnormal constrictions and dilations of the renal artery, leading to a typical "string of beads" finding on angiography.
- The pathogenesis of atherosclerotic RAS is similar to that of atherosclerosis in other vascular beds.
- The pathogenesis of renovascular hypertension is related to the neurohormonal cascade resulting from renal ischemia. The macula densa of the kidney senses a decreased systemic blood pressure caused by the reduced blood flow through the stenotic artery. Renal hypoperfusion or ischemia produces an increase in plasma renin that converts angiotensin I to angiotensin II, producing vasoconstriction and aldosterone secretion, sodium retention, and potassium wasting. Hypertension results and can be self-sustaining, even in the case of unilateral RAS, because of hypertensive damage to the contralateral kidney.
- The pathogenesis of ischemic nephropathy is a topic of current debate. Whether renal dysfunction develops purely from persistent ischemia related to progressively narrowed vessels or from repetitive small ischemic insults and upregulation of inflammatory mediators is yet to be fully elucidated.
- "Flash" or sudden-onset pulmonary edema, a manifestation usually seen in bilateral ARAS, results from sodium and water retention as well as upregulation of the sympathetic nervous system.

NATURAL HISTORY

- RAS caused by fibromuscular dysplasia rarely causes renal artery occlusion or ischemic nephropathy.
- ARAS rarely progresses to total occlusion. One study of serial ultrasounds of patients with RAS demonstrated that those with >60% stenosis progressed to total occlusion in 1 yr in only 5% of cases; an additional 11% progressed after 2 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Progressive RAS:

- Renal artery stenosis should be considered in any white female aged <30 yr with hypertension not attributed to any other cause, or in any patient aged >50 yr with new-onset refractory hypertension, or with stable hypertension that has abruptly and significantly worsened.
- RAS most often presents as a clinically asymptomatic finding. Manifestations can include renovascular hypertension, ischemic nephropathy, or flash pulmonary edema.
- Flash pulmonary edema in the absence of cardiac disease most often indicates severe bilateral renal artery stenosis.
- Renovascular hypertension should be considered if blood pressure control remains suboptimal on a medication regimen that includes 3 maximally dosed medications, including a diuretic.
- Ischemic nephropathy should be considered if kidney function is rapidly deteriorating or parenchymal sizes are decreasing on serial imaging, particularly with bilateral disease.
- Acute elevation of serum creatinine (>30%) after starting angiotensin–converting-enzyme inhibitors (ACEIs) or angiotensin type I receptor blockers (ARBs) may be seen in bilateral disease.
- A bruit heard in either upper quadrant on abdominal auscultation may suggest RAS. Patients with atherosclerotic RAS will often have bruits heard in other vascular beds.

DIAGNOSIS

SCREENING

American College of Cardiology and American Heart Association (ACC/AHA) guidelines for identification of patients who should be screened for RAS:

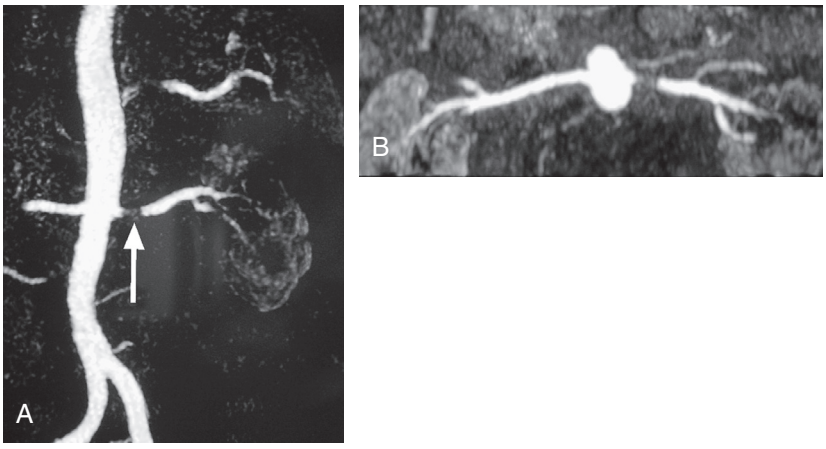

FIG 1. Magnetic resonance angiogram. **A,** Coronal maximum intensity projection (MIP) of a patient with significant left renal artery stenosis *(white arrow).* **B,** Axial MIP of the same patient. (From Adam A et al: *Grainger & Allison's diagnostic radiology,* ed 5, 2007, Churchill Livingstone. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

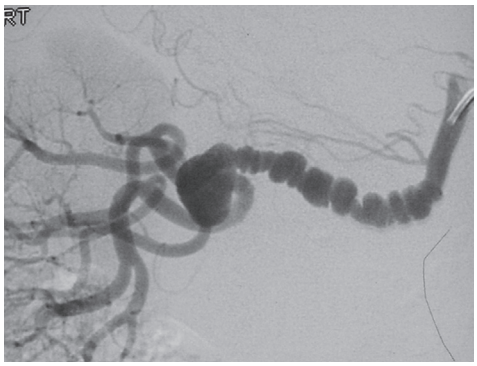

FIG. 2 Fibromuscular dysplasia. On a selective right anterior oblique (RAO) digital subtraction angiogram, the characteristic saccular dilatations and web-like stenoses are clearly evident. (From Adam A et al: *Grainger & Allison's diagnostic radiology,* ed 5, 2007, Churchill Livingstone. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

- Onset of hypertension at age <30 yr or severe hypertension at age >55 yr
- Clinical findings that suggest secondary hypertension as opposed to essential hypertension in the absence of a more likely cause of secondary hypertension such as pheochromocytoma
- Malignant hypertension: Hypertension with coexistent evidence of acute end-organ damage (acute renal failure, acute decompensated heart failure, new visual or neurologic disturbance, and/or advanced retinopathy)
- Accelerated hypertension: Sudden and persistent worsening of previously controlled hypertension
- Resistant hypertension: Full doses of a three-drug regimen that includes a diuretic
- Sudden unexplained pulmonary edema
- New azotemia or acute kidney injury following initiation of an ACEI or ARB
- Unexplained atrophic kidney or variation in size of both kidneys by >1.5 cm, smaller kidney likely affected by RAS
- Consider screening when renal asymmetry is noted with kidney lengths differing by ≥1.5 cm

LABORATORY TESTS

- Basic chemistry panel including sodium, potassium, blood urea nitrogen, and serum creatinine
- Urinalysis
- Renal vein renin sampling helps determine whether one or both kidneys are overproducing renin in cases of suspected renovascular hypertension (RVH). A positive result has strong predictive value. However, 50% of patients with no evidence for lateralization can still respond to unilateral intervention. This procedure is rarely performed except in specialized hypertension centers

IMAGING STUDIES

Renal Duplex Doppler ultrasonography, CT angiography, and magnetic resonance angiography (MRA) are effective diagnostic screening methods. The choice of imaging modality will depend on the availability of the diagnostic tool, the experience and local accuracy of each modality, patient characteristics including body size, renal function, and contrast allergy, and the presence of prior stents.

RENAL DOPPLER ULTRASOUND:

- Renal Doppler is a noninvasive, inexpensive screening study, and it can determine whether a stenosis of >60% is present.
- Abnormal results in RAS:
  1. Peak systolic velocity (PSV) >250 cm/sec
  2. Peak diastolic velocity >150 cm/sec
  3. Renal-to-aortic ratio (RAR) >3.5
  4. Acceleration time >100 msec
  5. Exact definitions of a positive renal Doppler for RAS will vary by institution
- Compared to renal angiography, Doppler studies have shown varied performance, with a sensitivity of 84% to 98% and a specificity of 62% to 99%.
- Limitations include high user variability. Valid test performance requires technicians who perform a high volume of these tests to reduce user error. If significant user variability exists at certain institutions, renal Doppler may be excluded from diagnostic algorithm. Patients with a large body habitus may have limited imaging results. It is not as sensitive or specific as MR or CT methods. Detection of RAS is limited to identifying whether stenosis of 60% to 99% is present.
- Duplex Doppler is a good modality for monitoring patency after a stent has been placed.

MAGNETIC RESONANCE ANGIOGRAPHY:

- MRA provides good visualization of both main and accessory renal arteries. The test has high sensitivity (90% to 100%) and a specificity of 76% to 94%. It is superior to renal Doppler ultrasonography and equivalent to CT angiography.
- Benefits include the lack of exposure to iodine contrast or radiation.
- Limitations include claustrophobia, high cost, and inability to image within a previously placed metallic stent. In addition, gadolinium exposure is relatively contraindicated in CKD patients with an estimated glomerular filtration rate (GFR) <30 ml/min per 1.73 m^2 due to the risk of inducing nephrogenic systemic fibrosis.

COMPUTED TOMOGRAPHY ANGIOGRAPHY:

- CT angiography is rapid and effective. When compared with angiography, CT has a sensitivity of 59% to 96% and a specificity of 82% to 99%. It is superior to renal Doppler and equivalent to MRA. Contrast uptake in kidneys can also be used to estimate viability of affected kidneys.
- CT has good spatial resolution and can detect restenosis through metal stents.
- CTA can be used more easily than MRA in obese or claustrophobic patients.
- Limitations include radiation exposure and potentially nephrotoxic, iodinated radiocontrast medium exposure to CKD patients. Heavily calcified arteries may appear narrower than in actuality.

DIRECT ANGIOGRAPHY:

- IV digital subtraction angiography (DSA) has an 88% sensitivity and 90% specificity. It is the gold standard for anatomic diagnosis of RAS. It is not a first-line screening tool, but it is recommended after a positive noninvasive test. DSA is also used for patients with a high clinical suspicion for RAS and inconclusive noninvasive tests and in whom the decision has already been made that correction of stenosis will produce clinical benefit. DSA allows for angioplasty with stenting during the same procedure. Renal fractional flow reserve at the time of DSA can evaluate the severity of RAS during maximal vasodilatation.
- This modality is reserved for patients with a high likelihood of intervention.
- Limitations include its invasive nature, requiring intraaortic catheterization that may lead to aortic and renal artery trauma with possible dissection, rupture, thrombosis, or embolization.
- Procedure requires a skilled interventionalist (radiologist, cardiologist, or vascular surgeon) knowledgeable in RAS.
- Procedure requires iodinated contrast and must be used cautiously with CKD. Carbon dioxide contrast imaging and limiting image acquisition number reduce kidney injury risk.

NUCLEAR RENOGRAPHY (WITHOUT CAPTOPRIL): A noninvasive test conducted when renal atrophy is present to document differential kidney function. This can be useful when determining whether to revascularize an atrophic kidney or to remove it in renovascular hypertension. Atrophic kidneys with <20% differential renal function are unlikely contributors to ongoing worsening kidney function but may still contribute to renovascular hypertension.

Rx TREATMENT

ACUTE GENERAL Rx

The treatment of renal artery stenosis must be targeted to the clinical presentation:

- Asymptomatic RAS requires no treatment.
- Patients with chronic hypertension in the setting of incidentally discovered RAS require only antihypertensive medical therapy.
- Patients in whom RVH is suspected should be initially treated with antihypertensive therapy, specifically medications that block the renin-angiotensin-aldosterone system. As discussed later, failure to control blood pressure

on an aggressive regimen represents a reason to consider renal revascularization.
- Patients with ischemic nephropathy should be considered for intervention only if the renal function is rapidly declining or flash pulmonary edema develops in the setting of bilateral renal artery stenosis.

PHARMACOLOGIC THERAPY

- Because of the activation of the renin-angiotensin-aldosterone system in RAS, ACEIs or ARBs are recommended and well tolerated (92%) for the treatment of RVH. Kidney function should be monitored carefully when initiating or titrating these medications, particularly when bilateral RAS (78% tolerability) or unilateral stenosis with solitary kidney is present to avoid precipitating AKI.
- Diuretics should be considered in patients with congestive heart failure or flash pulmonary edema.
- Antiplatelet therapy and statin therapy in patients with atherosclerotic RAS.

NONPHARMACOLOGIC THERAPY

- If either blood pressure cannot be controlled by medications alone, flash pulmonary edema occurs, or there is rapid decline in renal function, referral for renal angiography, angioplasty, and stenting may be indicated.
- Angioplasty without stenting is insufficient for atherosclerotic lesions due to a high failure rate of adequate dilation of the artery or a high rate of restenosis.
- Occasionally a kidney that has lost its function due to RAS may cause refractory hypertension. This situation would be discovered only by renal vein renin sampling in a patient with unilateral renal atrophy. In such cases, nephrectomy of the atrophied kidney may be the best method to control blood pressure.
- Rarely is renal artery bypass required.
- If RAS is suspected as the cause of flash pulmonary edema or rapidly declining kidney function, bilateral disease is likely, and, if confirmed by angiography, both renal arteries should be stented.
- Hypertension is rarely cured with revascularization in patients with atherosclerotic RAS due to high background essential hypertension. The goal of intervention is to gain control of blood pressure and reduce the number of blood pressure medications.
- The ACC/AHA guidelines for clinical indications of renal artery revascularization in the presence of significant stenosis include:
  1. Accelerated, resistant, or malignant hypertension (class IIa)
  2. Hypertension with unilateral small kidney (class IIa)
  3. Hypertension with intolerance to medication (class IIa)
  4. Treatment of cardiac destabilization syndromes such as unexplained heart failure exacerbations or episodes of flash pulmonary edema (class I) and refractory or unstable angina (class IIa)
  5. Progressive chronic kidney disease with bilateral RAS or RAS associated with a solitary functioning kidney (class IIa)
- Many patients who meet these criteria will not demonstrate a beneficial response to renal revascularization. Careful selection of patients for angiography and intervention must be made.
- Multiple randomized controlled trials (e.g., ASTRAL, CORAL, DRASTIC, and STAR) have not shown benefit to percutaneous therapy compared to medical therapy, with end points of blood pressure control, renal function, and cardiovascular events. However, these trials did have several inherent limitations.
  1. DRASTIC trial was a small angioplasty-only trial that demonstrated no difference in blood pressure, but it did show decrease in daily doses of antihypertensive drugs and number of drugs in the intervention group. Crossover was high from the medication arm to the intervention arm.
  2. The ASTRAL trial was a moderate-sized trial of stenting versus medication in RAS that showed no difference in blood pressure control or in the number of antihypertensive medications required to achieve blood pressure control. RAS severity was only moderate in the study population, decreasing the likelihood of finding a positive result.
  3. CORAL is a large, prospective, multicenter trial comparing stenting versus medication in severe RAS (>60% stenosis). This study confirms that with atherosclerotic renal artery stenosis and hypertension, clinical outcomes are not improved by stenting and that renal artery stenting is futile in general. RAS severity was moderate in many patients and may have diluted the beneficial effects of intervention on those with severe RAS.
  4. Follow-up of the CORAL population at 3 yr failed to show any difference in blood pressure control, change in GFR, end-stage renal disease, or death with stenting vs. medical therapy.
- With these limitations in mind, there is no prospective, randomized, controlled trial that has shown a benefit in any subgroup of patients with renal artery stenosis of revascularization over medical management. Therefore it is recommended that the decision to refer a patient for revascularization be made by specialists who are practiced and skilled in handling hypertension and renal artery stenosis.

FIBROMUSCULAR DYSPLASIA

- Medical therapy should include an ACEI or ARB to control blood pressure unless severe bilateral disease is present (rare).
- RVH from fibromuscular dysplasia (FMD) is often cured by renal artery revascularization because many younger patients do not have background essential hypertension.
- In most cases, patients should be referred for renal artery angioplasty regardless of whether blood pressure can be controlled medically.
- Stenting is not appropriate in patients with FMD because angioplasty alone usually yields a durable result. In addition, recurrence of FMD is common, and the presence of stents may hinder additional interventions.
- Renal artery bypass may be necessary in patients whose FMD recurs multiple times or in whom angioplasty failed to yield an improvement in blood pressure.

DISPOSITION & REFERRAL

- Patients with uncontrolled hypertension on multiple agents should be referred for management by a hypertension specialist.
- Percutaneous intervention for atherosclerotic RAS must be reserved for selected patients until further data are available.

PEARLS & CONSIDERATIONS

- Renal artery stenosis is most commonly an incidental finding and clinically silent.
- Renal artery stenosis may present as hypertension, renal dysfunction, or both, or flash pulmonary edema.
- Stenting is inappropriate for most patients with RAS. Consideration should be made only in high-risk patients and after consultation with a specialist in the field.
- The modality for the type of imaging should depend on the expertise of the institution.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Renal Artery Stenosis (Patient Information)
Hypertension (Related Key Topic)

AUTHOR: **James Simon, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Renal cell carcinoma (RCC) is a primary carcinoma originating in the renal parenchyma from the malignant transformation of proximal renal tubular epithelial cells. The majority of renal cell cancers are of clear cell type; papillary tumors comprise 15%, and chromophobe cancers comprise 10%.

SYNONYMS

Hypernephroma
RCC
Renal cell adenocarcinoma

ICD-10CM CODES

C64.9	Malignant neoplasm of kidney, except renal pelvis
C64.1	Malignant neoplasm of right kidney, except renal pelvis
C64.2	Malignant neoplasm of left kidney, except renal pelvis
C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.9	Malignant neoplasm of renal pelvis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: In 2019, there were an estimated 73,820 new cases and 14,770 deaths in the U.S. Two percent of cases of renal cancer are associated with inherited syndromes.
PREDOMINANT SEX: Male:female ratio is approximately 2:1.
PREDOMINANT AGE: Peak incidence is at age 50 to 70 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients are often asymptomatic until they have advanced disease. Paraneoplastic syndromes such as hypercalcemia, erythrocytosis, anemia, and hepatic dysfunction may occur with renal cell carcinoma. The classic triad of flank pain, hematuria, and a palpable abdominal mass currently represents an unusual presentation. Current presenting findings in RCC include:

Hematuria	50-60%
Elevated erythrocyte sedimentation rate	50%-60%
Abdominal mass	25%-45%
Anemia	20%-40%
Flank pain	35%-40%
Hypertension	20%-40%
Weight loss	30%-35%
Fever	5%-15%
Hepatic dysfunction	10%-15%
Classic triad (hematuria, abdominal mass, flank pain)	5%-10%
Hypercalcemia	3%-6%
Erythrocytosis	3%-4%
Varicocele	2%-3%

ETIOLOGY

Hereditary forms:
- Familial renal carcinoma
- Renal carcinoma associated with Von Hippel-Lindau disease
- Hereditary papillary renal cell carcinoma

Risk factors:
- Cigarette smoking
- Obesity
- Phenacetin-containing analgesics
- Asbestos, lead, Thorotrast, and chromium exposure
- Gasoline and other petroleum products
- Role of the *VHL* gene on chromosome 3

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Transitional cell carcinomas of the renal pelvis (8% of all renal cancers)
- Wilms tumor
- Other primary renal carcinomas and sarcomas
- Renal cysts
- Retroperitoneal tumors

WORKUP

LABORATORY TESTS:
- Urinalysis: Hematuria
- Complete blood count: Anemia or erythrocytosis
- Chemistry panel: Renal failure and electrolyte issues, including hypercalcemia
- Liver function tests: Hepatic dysfunction with elevated alkaline phosphatase, prolonged prothrombin time, and hypoalbuminemia

IMAGING STUDIES

Nearly 50% of renal cancers are now detected because a renal mass is incidentally detected on radiographic evaluation.
- Renal ultrasound
- Abdominal CT scan with contrast (Figs. E1 and 2); CT-guided biopsy is generally not necessary for diagnosis of solid masses >4 cm (high likelihood of cancer)
- MRI
- Renal arteriogram
- Intravenous pyelography

STAGING

See Table 1.

COMMON SITES OF METASTASES

Lung	50%-60%
Bone	30%-40%
Regional nodes	15%-30%
Main renal vein	15%-20%
Perirenal fat	10%-20%
Adrenal (ipsilateral)	10%-15%
Vena cava	10%-15%
Brain	10%-15%
Adjacent organs (colon, pancreas)	10%
Kidney (contralateral)	2%

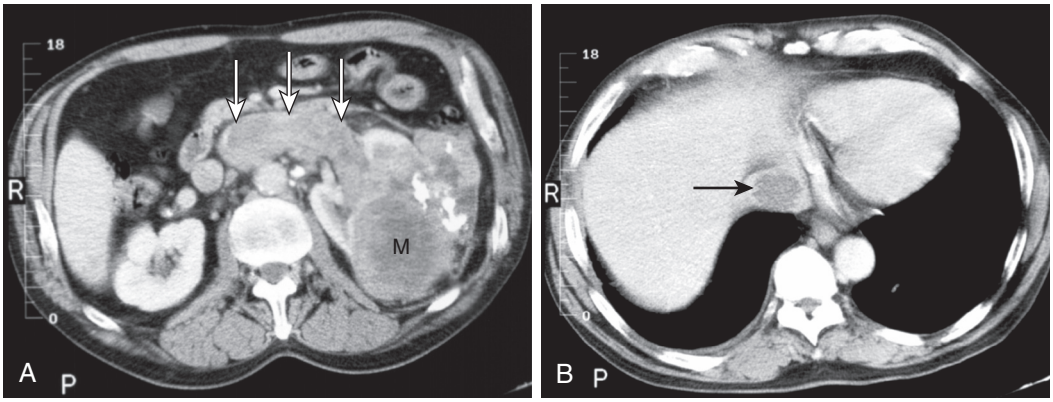

FIG. 2 Renal cell carcinoma. In this patient, the computed tomography scan at the midportion of the kidneys **(A)** demonstrates a large left renal mass *(M)* that extends into the renal vein and into the inferior vena cava *(arrows)*. **B,** An image at the level of the base of the heart shows that the tumor thrombus *(arrow)* extends into the right atrium. (From Mettler FA Jr: *Essentials of radiology,* ed 3, Philadelphia, 2014, Saunders.)

TABLE 1 TNM Staging of Renal Cell Carcinomas as per the AJCC Eighth Edition

T Stage	Description
T_x	Tumor cannot be assessed
T_1: Tumor ≤7 cm, limited to kidney	T_{1a}: Tumor <4 cm T_{1b}: Tumor ≥4 cm to ≤7 cm
T_2: Tumor >7 cm, limited to kidney	T_{2a}: Tumor >7 cm but ≤10 cm T_{2b}: Tumor >10 cm
T_3: Tumor extending into major veins or perinephric tissue but not into ipsilateral adrenal gland or beyond Gerota fascia	T_{3a}: Tumor extends to renal vein/branches or invades perirenal and/or renal sinus fat T_{3b}: Tumor extends into IVC below diaphragm T_{3c}: Tumor extends into IVC above diaphragm or wall of IVC
T_4	Tumor invades beyond Gerota fascia (including contiguous extension into ipsilateral adrenal gland)
N stage	**Description**
N_x	Regional nodes cannot be assessed
N_1	No regional nodes involved
N_2	Metastasis in regional node(s)
M stage	**Description**
M_0	No distant metastases
M_1	Distant metastasis present
Stage	**TNM grouping**
I	$T_1N_0M_0$
II	$T_2N_0M_0$
III	$T_3N_0M_0$ or $T_{1-3}N_1M_0$
IV	$T_4N_{any}M_{any}$ or $T_{any}N_{any}M_1$

AJCC, American Joint Committee on Cancer; *IVC,* intravenous cholangiography; *TNM,* tumor, node, metastases.

Rx TREATMENT

- Surgery:
  1. Surgical nephrectomy (open procedure or laparoscopic approach) is the only effective management for stages I, II, and some stage III tumors. Although radical nephrectomy had long been the standard treatment, retrospective studies have shown that partial rather than radical nephrectomy is associated with improved survival and is appropriate for patients with renal cell neoplasms <4 cm that are not adjacent to the renal pelvis or invading the vena cava.
  2. Laparoscopic robotic-assisted nephrectomy has been adopted in multiple centers, primarily for nephron-sparing surgery in the case of tumors <4 cm. Advantages include less blood loss, minimal effects on renal function, and similar oncologic outcomes. Disadvantages include increased costs and limitations in tumor size and locations eligible for robotic surgery.
  3. Various forms of partial nephrectomy may be available for patients with bilateral cancers or with a solitary kidney.
  4. Cytoreductive nephrectomy in patients with metastatic RCC before immunotherapy improved survival in patients compared with immunotherapy alone on the basis of randomized trials data. However, recent results from the randomized Clinical Trial to Assess the Importance of Nephrectomy (CARMENA) demonstrated no benefit for intermediate- and poor-risk patients in the setting of modern tyrosine kinase inhibitor (sunitinib) therapy. Additional trials data are awaited to assess the role of nephrectomy in favorable risk patients and with the use of neoadjuvant tyrosine kinase inhibitor therapy.
- Angioinfarction, cryoablation, or radiotherapy (for palliation).
- Systemic therapy:
  1. In patients with unresectable disease, therapy with the multi-targeted tyrosine kinase inhibitors axitinib, sunitinib, pazopanib, cabozantinib, lenvatinib, and sorafenib and also mTOR kinase inhibitors such as everolimus and temsirolimus can be used as therapy. Typically, patients are offered sequential therapy with either of these agents until maximum response duration or onset of major toxicity from each agent. The majority of responses with these agents are typically either partial or stable disease, and relapse is the norm.
  2. Checkpoint inhibitors: The checkpoint inhibitors have demonstrated efficacy in both treatment-naïve and previously treated patients. Combination checkpoint inhibition with ipilimumab combined with nivolumab has demonstrated superior efficacy for patients with IMDC intermediate and poor risk treatment-naïve patients. Furthermore, therapeutic regimens combining tyrosine kinase inhibition plus immune checkpoint inhibition also have demonstrated superiority in all risk groups for axitinib plus pembrolizumab and also axitinib plus avelumab compared to sunitinib monotherapy.
  3. Immunotherapy: High-dose interleukin-2 therapy may achieve a 15% response rate, which is often durable and associated with long-term survival in highly selected patients with excellent performance status. Severe toxicities associated with this therapy have limited the use of this approach.

PROGNOSIS

The 5-yr survival rate among patients with kidney cancer has increased from 57% in 1987-1989 to 74% in 2006-2012. The prognosis of surgically treated patients is shown in the following:

TNM Stage	5-yr Survival (%)
I	95
II	88
III (renal vein or vena cava)	50-60
III (nodal involvement)	15-25
IV	5-20

REFERRAL

- To urologist for staging and surgery
- To medical oncologist if metastatic disease is present

PEARLS & CONSIDERATIONS

- Patients should be considered for nephron-sparing surgery in case of smaller tumors (<4 cm).
- Laparoscopic robotic-assisted surgery is utilized for standard nephron-sparing surgery routinely; it is utilized for central tumors and tumors >4 cm in some experienced centers.
- Adjuvant therapy utilizing tyrosine kinase inhibitors has showed mixed results when used in the postresection setting and is not approved for use in this setting. An intergroup study showed no survival benefit, whereas a smaller study limited to high-risk patients showed a progression-free survival benefit.
- High-dose interleukin-2 can lead to long-term remissions in 10% to 15% of carefully selected patients.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Kidney Cancer (Patient Information)

AUTHOR: **Bharti Rathore, MD**

SUGGESTED READINGS

Choueiri TK, Motzer RJ: Systemic therapy for metastatic renal-cell carcinoma, *N Engl J Med* 376:354–366, 2017.

Motzer RJ et al: Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma, *N Engl J Med* 380(12):1103–1115, 2019.

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Rini BI et al: Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma, *N Engl J Med* 380(12):1116–1127, 2019.

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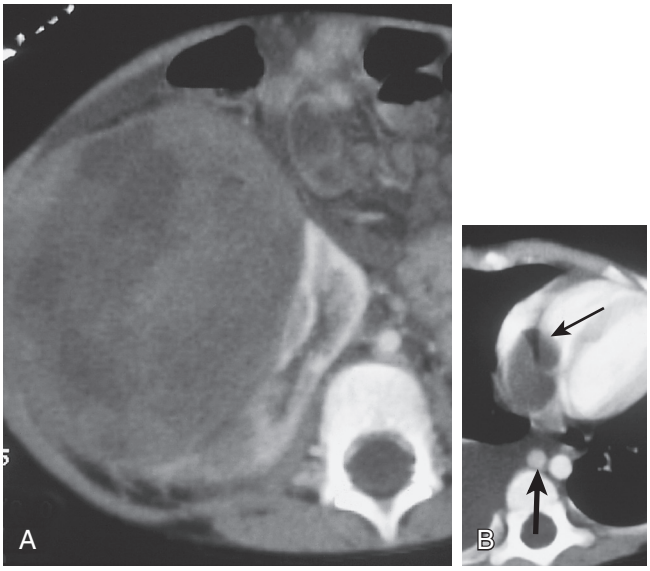

FIG. E1 Renal cell carcinoma. Ultrasonography demonstrates a 17mm hyperreflective mass in the left kidney with posterior shadowing. (From Grainger RG et al [eds]: *Grainger & Allison's diagnostic radiology,* ed 4, London, 2001, Harcourt.)

Renal Tubular Acidosis

BASIC INFORMATION

DEFINITION

Renal tubular acidosis (RTA) is a group of chronic diseases characterized by hyperchloremic metabolic acidosis (HCMA) produced by inability of the renal tubules to either excrete hydrogen ion (H^{+}) or retain bicarbonate ion (HCO_3^-). Factors differentiating types of RTA are described in Table 1. Four main types of RTA are described:

- Type 1 (classic, distal RTA): Abnormality in distal tubule hydrogen secretion, resulting in hypokalemic HCMA
- Type 2 (proximal RTA): Decreased proximal tubule bicarbonate reabsorption, resulting in hypokalemic HCMA
- Type 3 (mixed RTA): Rare autosomal recessive disorder with features of distal and proximal RTA
- Type 4 (hyporeninemic, hypoaldosteronism RTA): Aldosterone deficiency or a disease of the cortical collecting duct characterized by decreased distal sodium reabsorption and decreased distal tubule acidification hyperkalemic HCMA

SYNONYM

RTA

ICD-10CM CODE

N25.89 Other disorders resulting from impaired renal tubular function

EPIDEMIOLOGY & DEMOGRAPHICS

RTA type 4 affects primarily adults, whereas RTA types 1 and 2 are more frequent in children.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Examination may be normal.
- Reduced skin turgor may be present from polyuria and dehydration.
- Muscle weakness and aches, paralysis, and cardiac arrhythmias from hypokalemia may occur.
- Low back pain and bone pain may be present in patients with abnormalities of calcium and phosphorus metabolism (RTA type 2).
- Failure to thrive or delayed growth in children.
- Some patients may present with sensorineural deafness in RTA type 1 (H^+–ATPase mutations).

ETIOLOGY

- Type 1 RTA inherited as a primary disorder with mutation of the basolateral chloride–bicarbonate exchanger (*SLC4A1* gene) or apical proton–ATPase (H^+–ATPase). Acquired causes: Autoimmune disorders (SLE, Sjögren syndrome); primary biliary cirrhosis and other liver diseases; medications (amphotericin, NSAIDs, lithium carbonate, ifosfamide); genetic disorders (Ehlers–Danlos syndrome, Marfan syndrome, hereditary elliptocytosis); toxins (toluene); disorders with nephrocalcinosis (primary hyperparathyroidism, vitamin D intoxication, idiopathic hypercalciuria); and tubulointerstitial disease (renal transplantation, renal medullary cystic disease, obstructive uropathy, chronic urinary tract infections, and analgesic nephropathy)
- Type 2 RTA includes inherited disorders such as proximal tubule cell sodium bicarbonate co-transporter (NBCe1) defect, carbonic anhydrase type 2 deficiency, and Fanconi syndrome (caused by cystinosis, Wilson disease, hereditary fructose intolerance, Lowe syndrome, Fanconi-Bickel syndrome, Dent disease, tyrosinemia, galactosemia). Acquired causes include primary hyperparathyroidism, multiple myeloma, amyloidosis, light chain deposit diseases, heavy metals (copper, lead, mercury, and cadmium), chronic rejection of a transplanted kidney, and medications (acetazolamide, topiramate, outdated tetracycline, ifosfamide, zidovudine, didanosine, aminoglycosides)
- Type 3 RTA: Rare inherited recessive disorder with carbonic anhydrase (CA) 2 deficiency, drugs (topiramate)
- Type 4 RTA includes inherited disorders such as pseudohypoaldosteronism type 1 or type 2 (Gordon syndrome). Acquired causes include diabetes mellitus, HIV/AIDS, sickle cell disease, obstructive uropathy, lupus, amyloidosis, adrenal insufficiency, kidney transplant rejection, drugs (spironolactone, eplerenone, amiloride, angiotensin-converting enzyme [ACE] inhibitors, angiotensin-receptor blockers [ARBs], trimethoprim, pentamidine, heparin, NSAIDs, and calcineurin inhibitors [cyclosporine, tacrolimus])

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS: EXTRARENAL ORIGIN

- Diarrhea with significant bicarbonate loss
- External loss of biliary and pancreatic secretions
- Gastrointestinal-urinary diversion procedures (e.g., ureterosigmoidostomy, ileal conduit)
- Respiratory acidosis
- Drugs: Calcium chloride, magnesium sulfate, cholestyramine

WORKUP

Detection of HCMA by serum electrolyte and arterial blood gas (ABG) analysis followed by evaluation of potential causes (see "Etiology"). Fig 1 describes an approach to the patient with RTA.

LABORATORY TESTS

- ABG reveals metabolic acidosis.
- Anion gap is normal.
- Serum potassium is low in RTA types 1 and 2, normal in type 3, and high in type 4.
- First-morning urine pH is >5.5 in RTA type I, <5.5 in types 2 and 3, and <5.5 (low mineralocorticoid secretion) or >5.5 (collecting duct abnormality) in RTA type 4.
- Urinary anion gap (UAG) is an indirect evaluation of urinary ammonium excretion, which differentiates renal from extrarenal causes of normal anion gap metabolic acidosis (e.g., diarrhea). UAG is 0 or positive in all types of RTA.
- $UAG = U_{(Na + K)} - U_{Cl}$.
- UAG is valid only if U_{Na} >20 mEq/L and urine pH <6.5.
- Urine osmolar gap (UOG) is an independent surrogate of urinary ammonium concentration and is not affected by the presence of other non-reabsorbable anions (e.g., keto acids, 5-oxoproline/pyroglutamic acid, bicarbonate, or hippurate).
- Calculated $U_{NH4}^+ = 0.5$ (measured Uosm – calculated Uosm [2 (Na + K) + Urine Urea (mg/dl/2.8) + glucose (mg/dl/18]).
- Calculated urine ammonium ≥75 mEq/L denotes intact renal tubular function and supports an extrarenal origin of HCMA.

TABLE 1 Contrasting Features and Diagnostic Studies in Renal Tubular Acidosis

Finding	Types of Renal Tubular Acidosis		
	Proximal (Type 2)	Classical Distal (Type 1)	Generalized Distal Dysfunction (Type 4)
Plasma potassium	Low	Low	High
Urine pH during metabolic acidosis (ABG pH <7.3)	<5.5	>5.5	<5.5 or >5.5
Urine net charge	Positive	Positive	Positive
Fanconi lesion	Present	Absent	Absent
Fractional bicarbonate excretion	10%-15%	2%-5%	5%-10%
Urine–Blood PCO_2	Normal	Low	Low
H^+–ATPase defect		Low	
HCO_3^-/Cl^- transporter defect		High	
Amphotericin B		Normal	
Response to therapy	Least responsive	Responsive	Less responsive
Associated features	Fanconi syndrome	Nephrocalcinosis/ hypergammaglobulinemia	Chronic kidney disease

ATPase, Adenosine triphosphatase; (U – B) *PCO_2,* urine–blood CO_2 tension difference, <30 is low.
Modified from DuBose TD: Disorders of acid–base balance. In *Brenner and Rector's the kidney,* ed 9, Philadelphia, 2011, WB Saunders.

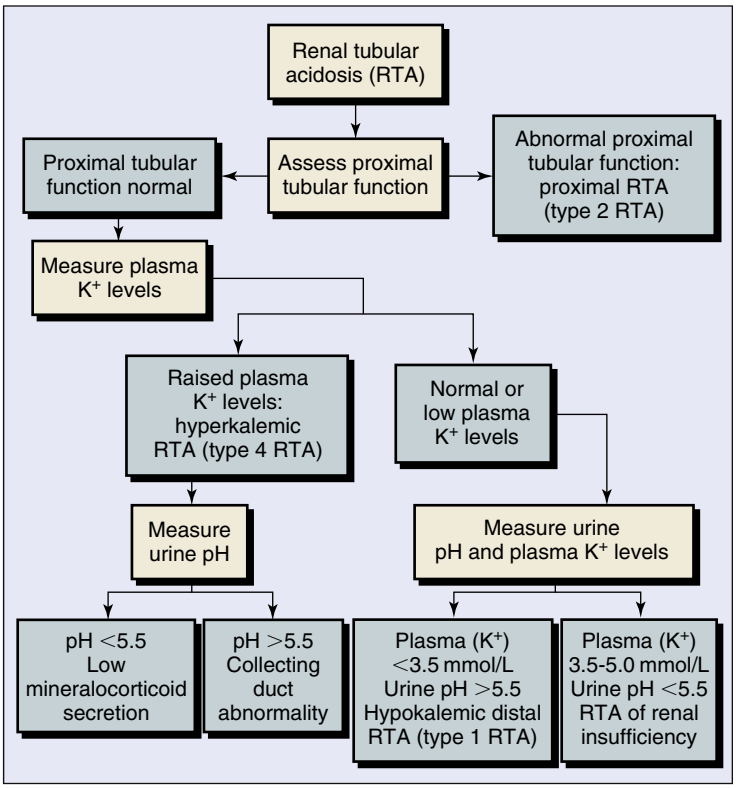

FIG. 1 Approach to the patient with renal tubular acidosis. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, WB Saunders.)

- Calculated urine ammonium ≤25 mEq/L denotes inappropriately low concentration.
- UOG cannot be used if there are other neutral substances in the urine (e.g., mannitol, alcohols) or during a urinary tract infection urease-producing bacteria.
- Additional studies include urine and serum calcium concentrations.
- Parathyroid hormone measurement when primary hyperparathyroidism is suspected (type 2 RTA).

IMAGING STUDIES

- Plain abdominal radiographs for evaluation of nephrocalcinosis
- Kidney ultrasound to determine kidney sizes or presence of stones
- Non–contrast-enhanced CT scan in patients with nephrocalcinosis or nephrolithiasis

Rx TREATMENT

ACUTE GENERAL Rx

- Types 1 and 2 are treated with oral sodium bicarbonate (1 to 2 mEq/kg/day in RTA type I, 2 to 4 mEq/kg/day in RTA type 2) titrated to correct metabolic acidosis (serum bicarbonate >22 mEq/L).
- Potassium supplementation is required for hypokalemic patients.
- Type 4 RTA can be treated with diuretics to lower elevated potassium levels and with sodium bicarbonate to correct significant acidosis. Fludrocortisone 0.1 to 0.3 mg/day can be used to correct mineralocorticoid deficiency.

CHRONIC Rx

- Monitor potassium levels in RTA type 4.
- Monitor for bone disease (osteomalacia) in RTA type 2.
- Monitor for nephrolithiasis and nephrocalcinosis in RTA type I.

DISPOSITION

- Prognosis varies with the associated conditions (see "Etiology").
- Untreated distal RTA may result in hypocalcemia, hypophosphatemia, nephrolithiasis, and nephrocalcinosis.

PEARLS & CONSIDERATIONS

- Non-anion gap metabolic acidosis: Check for urine ammonium (urine anion and osmolar gaps) to differentiate nonrenal vs. renal causes of HCMA.
- Examine serum potassium to differentiate between RTA types 1 or 2 vs. type 4.
- In type 4 hyperkalemic RTA, carefully review medication list and rule out urinary obstruction, especially in elderly males.

COMMENTS

Patient education material can be obtained from the National Kidney and Urologic Diseases Information Clearinghouse, Box NKUDIC, Bethesda, MD 20893.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Jian Li, MD, PhD**

SUGGESTED READINGS

Kraut JA, Madias NE: Differential diagnosis of nongap metabolic acidosis: value of a systematic approach, *Clin J Am Soc Nephrol* 7:671-679, 2012.

Kim S et al: The urine-blood PCO2 gradient as a diagnostic index of H^+–ATPase defect distal renal tubular acidosis, *KI* 66:761-767, 2004.

Renal Vein Thrombosis

BASIC INFORMATION

DEFINITION

Renal vein thrombosis (RVT) is the thrombotic occlusion of one or both renal veins.

ICD-10CM CODE

I82.3 Embolism and thrombosis of renal vein

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence unknown; probably an underdiagnosed condition
- May occur at any age with no gender preference
- Epidemiology tied to the underlying cause

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Acute bilateral renal vein thrombosis:
- Back and bilateral flank pain
- Acute renal failure

Acute unilateral renal vein thrombosis:
- Flank pain
- Decline in renal function
- Hematuria
- Increase in the amount of proteinuria if associated with nephrotic syndrome

Chronic unilateral renal vein thrombosis:
- May be silent
- Pulmonary emboli and hemolysis
- Back pain
- Deep vein thrombosis in lower extremities
- Edema
- Glycosuria
- Hyperchloremic acidosis
- Left varicocele (if the left renal vein is thrombosed)
- Dilated abdominal veins

ETIOLOGY & PATHOGENESIS

- Nephrotic syndrome, especially when the serum albumin is <2 g/dl
- Extrinsic compression by a tumor or retroperitoneal mass
- Invasion of the renal vein or inferior vena cava by tumor (almost always renal cell cancer)
- Trauma
- Other hypercoagulable states
- Severe dehydration

NOTE: For unknown reasons, diabetic nephropathy is not commonly associated with renal vein thrombosis, even if the nephrotic syndrome is present.

Controversy has existed regarding whether the renal vein thrombosis association with nephrotic syndrome is a complication of nephrotic syndrome or whether renal vein thrombosis occurring in the setting of increased renal vein pressure (e.g., with congestive heart failure, constrictive pericarditis, or extrinsic compression) can independently cause proteinuria. Current evidence is that renal vein thrombosis does not cause nephrotic syndrome.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The diagnosis of renal vein thrombosis does not include any differential consideration. The differential diagnosis is that of proteinuria. Renal vein thrombosis should be considered if proteinuria worsens or if renal function worsens in a patient with glomerulonephritis. Renal vein thrombosis should also be considered in patients with pulmonary emboli and no lower-extremity deep vein thrombosis.

WORKUP

Clinical suspicion (see "Differential Diagnosis") and imaging studies

IMAGING STUDIES

- Abdominal ultrasound with Doppler (Fig. E1)
- Abdominal MRI or CT with contrast (Fig. 2) in the absence of significant renal failure
- Renal arteriography (delayed films during venous phase)
- Selective renal vein venography
- Renal biopsy may be indicated if evidence of nephritis is present (e.g., active urinary sediment)

TREATMENT

- Anticoagulation with heparin or low-molecular-weight heparin as a bridge to coumadin in acute renal vein thrombosis to prevent pulmonary emboli and in attempt to improve renal function and decrease proteinuria.
- Note that patients with nephrotic syndrome can be resistant to heparin because of antithrombin III deficiency.
- Direct thrombin and factor Xa inhibitors have not been studied in patients with nephrotic syndrome. However, there are case reports of their effectiveness in patients who have contraindications or refuse warfarin or low-molecular-weight heparin.
- Local thrombolytic therapy with or without endovascular thrombectomy has also been reported to be effective, particularly for patients with acute renal vein thrombosis with evidence of acute renal failure.
- The value of anticoagulation in chronic renal vein thrombosis is dubious. The exception is in nephrotic patients with membranous glomerulonephritis with profound hypoalbuminemia, where prolonged prophylactic anticoagulation may be of benefit even if renal vein thrombosis has not been documented.

PROGNOSIS

Probable worsening of the underlying nephropathy by acute renal vein thrombosis; the effect of chronic renal vein thrombosis is unclear.

AUTHOR: **David J. Lucier, Jr., MD, MBA, MPH**

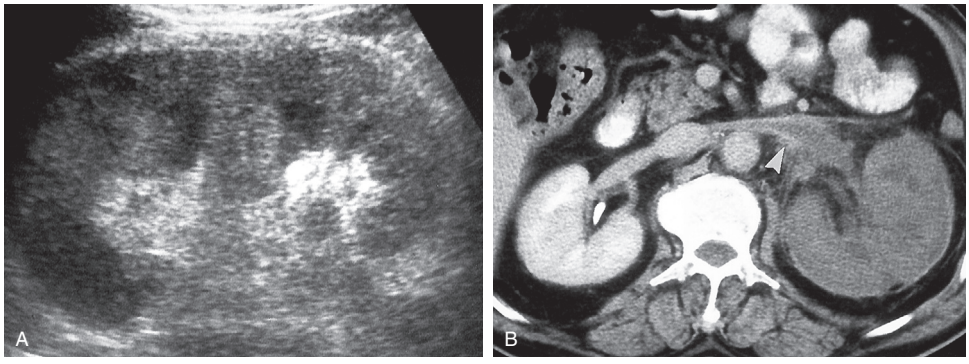

FIG. 2 Renal vein thrombosis. A, Sagittal sonogram demonstrates a diffusely enlarged, edematous left kidney with loss of corticomedullary differentiation. **B,** Confirmatory contrast-enhanced computed tomography shows a large, poorly perfused left kidney and thrombus in the left renal vein *(arrowhead).* (From Rumack CM et al: *Diagnostic ultrasound,* ed 4, Philadelphia, 2011, Elsevier.)

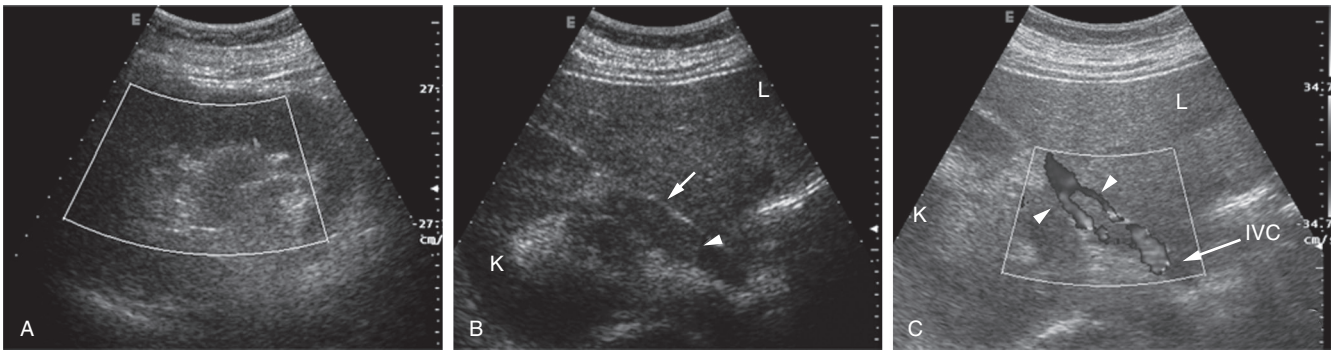

FIG. E1 Bilateral renal vein thrombosis in a patient with nephritic syndrome secondary to focal glomerulosclerosis. Male, age 23, with normal glomerular filtration rate (GFR) and proteinuria 12 to 17 g/day. Ultrasonographic evaluation was required after acute worsening of GFR and low back pain (serum creatinine was 3.7 mg/dl). Right kidney longitudinal diameter was 14 cm and it appeared hypoechoic, globose-shaped and hypoperfused **(A).** Resistive indexes were 0.68. Right renal vein showed a hypoechoic material *(white arrow)* filling most part of the lumen *(arrowhead)* **(B).** After systemic anticoagulant therapy **(C),** the vein showed a partial recanalization with thin flow signals *(arrowheads)* around the thrombus. The progressive improvement in vessel perfusion occurred together with functional recovery. *IVC,* Inferior vena cava; *K,* kidney; *L,* liver. (From Ronco C et al: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.)

Respiratory Syncytial Virus

BASIC INFORMATION

DEFINITION

Respiratory syncytial virus (RSV) is an RNA virus that tends to form syncytia in tissue culture. RSV causes repeated acute respiratory tract infections in people of all ages. It is highly contagious and is the leading cause of severe lower respiratory tract infections in infants and young children, while it usually manifests as upper respiratory infections, bronchiolitis, or tracheobronchitis in older children and adults.

SYNONYMS

Bronchiolitis
RSV

ICD-10CM CODES

B97.4	Respiratory syncytial virus as the cause of diseases classified elsewhere
J12.1	Respiratory syncytial virus pneumonia
J20.5	Acute bronchitis due to respiratory syncytial virus
J21.0	Acute bronchiolitis due to respiratory syncytial virus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Humans are the only source of infection. There are 64 million infections worldwide annually, resulting in 160,000 deaths; it is associated with >57,000 U.S. pediatric hospitalizations annually and 2 million outpatient visits each yr among children <5 yr. It is the leading cause of lower respiratory tract infection in young children worldwide.

PREVALENCE: Nearly everyone is infected by age 2, with reinfections occurring at all ages.

PREDOMINANT SEX AND AGE: Male sex may predispose to more severe respiratory disease in RSV infection. Age predominance in infancy and the elderly.

PEAK INCIDENCE: In nontropical areas of the Northern Hemisphere, seasonal outbreaks usually occur November to April, with a peak in January or February; in nontropical areas of the Southern Hemisphere, May to September, with a peak in May, June, or July. In the tropics, seasonal outbreaks usually occur during the rainy season. Incubation ranges from 2 to 8 days; although 4 to 6 days is most common.

RISK FACTORS: For children, risk factors include attending daycare or school and inpatient hospitalization. Severe disease is seen primarily in infants and young children (especially those born before 35 wk of gestation); the elderly; and in patients with cardiac, pulmonary, or immune system dysfunction.

GENETICS: Severe disease is associated with polymorphisms in various interleukins and CCR5.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Physical findings include fever, tachypnea, prolonged expiration, wheezes and rales, cough, rhinorrhea, coryza, conjunctivitis, and otitis media. Clinical presentation can include pneumonia and bronchiolitis.

ETIOLOGY

Humans are the only known reservoir. Transmission is by large respiratory droplets via close contact or contaminated surfaces, where it can survive for several hours. The CDC recommends hand washing, gowns, and gloves to prevent nosocomial infection, which is especially common on pediatric wards. However, the CDC does not recommend excluding children with respiratory illnesses who are well enough to attend school or daycare, as RSV is often spread during early stages of illness.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Influenza, parainfluenza, and adenovirus

WORKUP

- History with a focus on upper and lower respiratory symptoms, fever, and (in infants) apnea
- Focused physical exam including temperature and pulse oximetry, as well as lung and head, eyes, ears, nose, and throat (HEENT) exam

LABORATORY TESTS

Nasopharyngeal specimens can be analyzed using rapid diagnostic assays, such as immunofluorescent and enzyme immunoassay techniques for detection of viral antigen and are generally reliable in infants and young children. Virus isolation is also possible, but requires 1 to 5 days and accuracy may vary. Serologic testing (serum antibodies) is less useful because it is unreliable in infants and is confounded in other patients due to repeated infections.

IMAGING STUDIES

Chest x-ray for suspected pneumonia, but not routinely in suspected bronchiolitis

TREATMENT

NONPHARMACOLOGIC THERAPY

Early diagnosis and isolation techniques are important in limiting spread of RSV infections.

ACUTE GENERAL Rx

Primary treatment is predominantly supportive in nature. May include hydration, clinical assessment of respiratory status, measurement of oxygen saturation, supplemental oxygen, bronchodilators, suction of the upper airway, nebulized hypertonic saline, and, if required, intubation and mechanical ventilation.

- Mild disease: Symptomatic treatment and supportive therapy.
- Severe disease may require oxygen therapy, bronchodilators, hospitalization, intubation, and mechanical ventilation. The use of corticosteroids remains controversial, especially in infants, and is not recommended by the American Academy of Pediatrics.
- Avoid sports drinks, soft drinks, undiluted fruit juice, or water. These beverages may contain too much sugar, contain too few calories, or lack the proper balance of essential minerals.
- Reduce fever with acetaminophen or ibuprofen.
- Antibiotics may be used to treat a bacterial infection (such as pneumonia) that develops as a complication.
- Ribavirin is not recommended for routine use but may be indicated in specific situations, such as for treatment of severe lower respiratory tract RSV infections in pediatric and adult patient populations with additional underlying compromising conditions such as chronic lung conditions, prematurity, borderline personality disorder (BPD), congenital heart disease, immunodeficiency, immunosuppression, or organ transplantation. It may also be used in selected patients with documented, potentially life-threatening RSV. Updated eligibility criteria for treatment may change, and updates should be sought from the American Academy of Pediatrics Red Book in its print or online version. Further studies are needed. New research in the field of RNA interference-based agents has shown promising results for the treatment of acute RSV infection but is still in phase II trials. Ribavirin is a Federal Drug Administration Pregnancy Category X product, indicating that its use is contraindicated in women who are pregnant. It also should not be taken by women who are breastfeeding.

REFERRAL

To pulmonology and infectious disease specialists for severe disease or when use of ribavirin is considered; hospitalization for those with respiratory compromise

PEARLS & CONSIDERATIONS

PREVENTION

Primary prevention is through avoidance of transmission through hand washing, proper procedures to avoid spread in health care facilities, and diagnosis of suspected cases.

No benefit has been found from the use of RSV prophylaxis intravenous immunoglobulin (IVIG) or RSV immune globulin (IG) monoclonal antibody, and RSV-IVIG is no longer available. Palivizumab, a humanized mouse monoclonal antibody, may be used in certain infants and children to reduce the risk of lower tract disease, in those with chronic lung disease of prematurity, history of preterm birth, or with congenital heart disease. Updated eligibility criteria for prophylaxis may change, and consultation with pulmonary or infectious disease specialists is recommended.

PATIENT & FAMILY EDUCATION

Hand washing with soap and water for 15 to 20 seconds, covering mouth and nose when coughing or sneezing, avoiding sharing cups and eating utensils with those who may be infected, and refraining from kissing loved ones possibly infected may all aid in preventing future infection. Avoid visiting infected child in the hospital. Avoid secondhand smoke, which irritates the mucous membranes of the nose, sinuses, and lungs of the affected patients and makes them more susceptible to infections.

AUTHOR: **Maher Tabba, MD, FACP, FCCP**

SUGGESTED READINGS

Centers for Disease Control: www.cdc.gov.

Rose EB et al: Respiratory syncytial virus seasonality—United States, 2014-2017, *MMWR (Morb Mortal Wkly Rep)* 67(2), 2018.

Smith DK et al: Respiratory syncytial virus bronchiolitis in children, *Am Fam Physician* 95(2):94-99, 2017.

World Health Organization: Homepage. www.who.int.

BASIC INFORMATION

DEFINITION

Restless legs syndrome (RLS) is an awake phenomenon consisting of an urge to move legs, usually associated with feeling of discomfort in legs. Symptoms typically are present only at rest and at least partially improve with movement. Additionally, symptoms are usually worse at night. RLS can result in sleep disturbance with associated executive dysfunction and depression.

SYNONYMS

RLS
Wittmaack-Ekbom syndrome

ICD-10CM CODE
G25.81 Restless legs syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Average prevalence rate is 1% to 29%. Prevalence estimates in Europe are around 10%, and 0.1% to 12% in East Asian population.
PEAK PREVALENCE: 10% in persons aged 30 to 79 and 19% in persons aged 80 or above
PREDOMINANT SEX: Early-onset RLS is more common in females, with 2:1 female/male ratio.
PREDOMINANT AGE: Prevalence of RLS increases with age, and it is more commonly seen in the elderly population.
GENETICS: Genetic basis of RLS has been reported, particularly in early-onset RLS.

- Autosomal dominant disorder
- Common among first-degree relatives
- RLS associated with certain sequences in chromosomes 6p, 12q, 14q, 9p, 20p, 2p, 16p
- These include polymorphisms in the genes *BTBD9, MEIS1, PTPRD, MAP2K5, SKOR1,* and *TOX3*

RISK FACTORS:

- Iron deficiency anemia (IDA)—25% to 35%.
- Pregnancy: Increases in severity and prevalence with each passing trimester.
- End-stage renal disease (ESRD) requiring hemodialysis: Improves with transplant but not dialysis.
- Many neurologic diseases such as Parkinson disease, multiple sclerosis, neuropathy, and myelopathy increase risk as do mood disorders, other inflammatory disease, and cardiovascular disease.

CLASSIFICATION

- Primary RLS is without any obvious cause, with no associated disorder.
- Secondary RLS results from other medical conditions.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Wide spectrum of severity of clinical manifestations has been reported in RLS.
- Most common symptom is unpleasant sensations in legs ("dysesthesias"), reported as discomfort or "creepy-crawling" sensations, mostly bilateral. Arms are occasionally involved.
- There is an extreme urge to move legs, and relief is sustained as long as the movement continues.
- Symptoms are worse at night or evening. Best sleep is usually early in the morning.

ETIOLOGY

The exact etiology remains unknown. Pharmacologic, pathologic, physiologic, and imaging studies have implicated dopaminergic pathways, brain iron metabolism, and endogenous opioid pathways.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Periodic limb movement disorder (PLMD)
- Nocturnal leg cramps
- Painful peripheral neuropathy
- Akathisia
- Positional discomfort
- Volitional movements, foot tapping, leg rocking

WORKUP

- Diagnosis of RLS is based on established clinical criteria (Table 1) and normal neurologic examination.
- Testing is done to determine possible cause of secondary RLS. All patients with RLS should be screened for iron deficiency because iron supplementation in patients with iron deficiency may resolve the symptoms.
- Polysomnography with leg activity monitors to determine limb movements during sleep, but they are unable to distinguish periodic limb movements from periodic movements associated with sleep apnea.
- Nerve conduction studies and electromyography for associated peripheral neuropathy.

LABORATORY TESTS

- Iron status: Serum ferritin, total iron binding capacity, percent saturation
- CBC for anemia in case of iron deficiency
- Metabolic panel: Blood urea nitrogen and serum creatinine for renal insufficiency

IMAGING STUDIES

No imaging studies are required for diagnosis of RLS.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of caffeine, alcohol, and nicotine, which can exacerbate RLS.
- Review and adjustment of medications that may exacerbate or cause RLS (selective serotonin reuptake inhibitors, dopamine blocking agents, stimulants).
- Physical and mental activity.
- Good sleep hygiene.
- Monitoring for depression as RLS has an elevated suicide risk. Bupropion may be the best agent for depression in RLS due to lack of dopamine effects.

CHRONIC Rx

Once the diagnosis of RLS is considered based on clinical criteria as mentioned in Table 1 and causes impairment of quality of life, an anticonvulsant (gabapentin enacarbil or pregabalin) or dopamine agonist (bromocriptine, pramipexole, or ropinirole) should be started at low dose and then gradually tapered depending on tolerance.

Treatment options (Table 2) for RLS include:

- Anticonvulsants, such as gabapentin, have been shown to be effective in multiple studies. Gabapentin enacarbil and pregabalin would now be considered first-line agents in the treatment of RLS. These agents do not cause iatrogenic worsening (augmentation) of RLS with long-term treatment. Limited case reports support use of lamotrigine and topiramate in patients who are intolerant of other agents.
- Dopaminergic agents such as levodopa and dopamine agonists help to ameliorate RLS symptoms, decrease periodic limb movements, and improve sleep. Dopamine agonists, pramipexole and ropinirole, can be first-line agents in the treatment of RLS but often cause augmentation of RLS with long-term treatment.

TABLE 1 Diagnostic Criteria for Restless Legs Syndrome

Minimal Criteria

- Desire to move the legs usually associated with paresthesias
- Motor restlessness, as characterized by floor pacing, leg rubbing, stretching, and flexing
- Worse at rest, with relief by activity
- Worse at night

Additional Criteria

- Sleep disturbances, as difficulty in sleep onset and maintaining sleep, daytime fatigue, or somnolence
- Involuntary movements, as periodic limb or leg movements in sleep and periodic or aperiodic limb movements while awake
- Neurologic examination is normal in idiopathic restless legs syndrome
- Clinical course may begin at any age but most severe in middle and older age
- Family history suggests autosomal dominant mode of inheritance in one third of the cases

From Stiansy K et al: Clinical symptomatology and treatment of restless leg syndrome and periodic limb movement disorder, *Sleep Med Rev* 6(4):253-265, 2002.

TABLE 2 Management of Restless Legs Syndrome LS/WED

Agent and Daily Dosage	Side Effects	Countermeasures
Step 1: α2δ Agents		
First-line treatment, particularly if sleep disturbance, pain, or anxiety is present		
Gabapentin enacarbil, 300-600 mg Pregabalin, 50-450 mg* Gabapentin, 100-1800 mg*	Dizziness	Reduce dose and add alternate medication class as needed. If fall risk, then discontinue and change to alternate medication class.
	Somnolence, daytime fatigue	Reduce dose and add alternate medication class as needed. If significant, discontinue and change to alternate medication class.
	Tolerance	Discontinue, take drug holiday with return to medication. Switch to alternate medication class.
	Weight gain	Reduce dose and add alternate medication class as needed. If significant, discontinue and change to alternate medication class.
Step 2: Dopamine Agonists		
Alternative first-line treatment if depression is present and dose kept low.		
Pramipexole, 0.125-0.5 mg* (0.75 mg in Europe) Ropinirole, 0.5-4.0 mg* Rotigotine, 1-3 mg/24 h	Nausea and orthostatic hypotension	Slowly increase dosage or use domperidone if available (10-30 mg).
	Insomnia	Add or switch to α2δ agent. Use a small dose of benzodiazepines in association with dopamine agonists.
	Daytime fatigue and somnolence	Reduce dosage or discontinue dopamine agonists.
	Compulsive or impulsive behavior	Reduce dose and add alternate medication class as needed. If significant, discontinue and change to alternate medication class.
	Tolerance	Discontinue and switch to longer-acting dopamine agonist or alternate medication class.
	Augmentation	Discontinue and switch to alternate medication class or longer-acting dopamine agonist.
Step 3: Dopamine Precursors		
Useful for intermittent treatment, such as twice a wk		
Levodopa-benserazide or levodopa-carbidopa (regular or slow release), 100/25 or 200/50 mg†	Same as for dopamine agonists	See countermeasures for dopamine agonists.
	Morning rebound or augmentation of restless legs syndrome in early evening	Use small extra dose of levodopa during daytime or reduce dosage or combine levodopa with dopamine agonists or benzodiazepines or discontinue levodopa (if severe and persistent).
	Augmentation	Do not use daily. Discontinue and switch to dopamine agonists or a nondopamine medication.
Benzodiazepines		
Useful for sleep promotion		
Clonazepam, 0.5-2.0 mg‡ Temazepam, 15-30 mg‡ Nitrazepam, 5-10 mg*	Daytime somnolence	Reduce dosage.
	Tolerance	Take drug holiday for 2 wk then return to lower dosage.
Opiates		
Second-line treatment		
Oxycodone-naloxone, 10/5 to 40/20 mg/day Methadone, 2.5-20 mg Oxycodone, 5-40 mg	Constipation	Use for symptom treatment.
	Dependency	Take a drug holiday. Discontinue and switch to alternate medication.
Oral Iron		
Always consider if serum iron ≤75 mcg/L *or* transferrin saturation ≤17%		
Ferrous sulfate, 650 mg (325 mg with vitamin C, 100 mg twice a day)	Constipation, stomach upset and pain	Reduce dose, discontinue, take with food.
	Diarrhea, nausea, vomiting	Reduce dose, discontinue, take with food.

*One hour before onset of symptoms in the evening or 1-2 hours before bedtime if symptoms are not present in the evening.
†Considered most appropriate for PRN dosing not more than 3 times a wk rather than daily use.
‡Before bedtime usually to promote sleep with restless legs syndrome.
From Kryger M et al: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.

- Rotigotine patch (Neupro) is also effective and FDA approved for moderate to severe RLS.
- Opiates, mostly methadone, are generally reserved as last line of treatment.
- Iron replacement should be started concurrently in case of iron deficiency. Iron supplements are indicated even with low-normal ferritin levels (<45 ng/ml). Sometimes IV iron replacement is used.

REFERRAL

Refer to neurologist if diagnosis is uncertain or an underlying disorder is suspected.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Restless Legs Syndrome (Patient Information)

AUTHORS: **Fariha Jamal, MD,** and **Corey Goldsmith, MD**

SUGGESTED READINGS

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Lee CS et a.: Symptom severity of restless leg syndrome predicts its clinical course, *Am J Med* 129:438-445, 2016.

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Winter AC et al: Vascular risk factors, cardiovascular disease, and restless legs syndrome in women, *Am J Med* 126:220-227, 2013.

Retinal Detachment

BASIC INFORMATION

DEFINITION

Retinal detachment is the separation of the neurosensory retina (NSR) from the retinal pigment epithelium (RPE). This results in the accumulation of subretinal fluid (SRF) in the potential space between the NSR and the RPE. The main types of retinal detachment are **rhegmatogenous** (caused by retinal tear with vitreous fluid passing through the defect), **tractional** (subretinal fluid caused by fibrous proliferation and pulling from vitreous gel), and **exudative** (accumulation of subretinal fluid due to inflammation or tumors).

ICD-10CM CODES

H33	Retinal detachment and breaks
H33.2	Serous retinal detachment
H33.5	Other retinal detachments
H33.0	Retinal detachment with retinal break

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.) OF RHEGMATOGENOUS RETINAL DETACHMENT:

- Annual incidence roughly 1 in 10,000
- Particularly common in patients with high myopia of 5 diopters or more
- Incidence 1% to 2% after cataract surgery

PEAK INCIDENCE: Incidence increases with increasing age or increasing myopia

PREVALENCE (IN U.S.): Busy ophthalmologists may see one or two acute retinal detachments per month.

PREDOMINANT AGE:

- Most common age group is 40 to 70 yr old.
- Peak age coincides with peak incidence of acute posterior vitreous detachment, as this is the most important cause of a retinal tear.
- Rare in children and almost always due to congenital ocular disorders (Stickler syndrome) or trauma.

RISK FACTORS:

- Myopia
- Lattice degeneration (peripheral retinal thinning)
- Previous ocular surgery (particularly cataract surgery)
- Family history
- Contralateral retinal detachment or retinal tear
- Ocular trauma
- MEK inhibitors (serous retinal detachment)
- Ocular inflammation (uveitis)
- Retinal vascular disease (particularly diabetic retinopathy)
- Intraocular tumor (ocular or metastatic)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Sudden onset of flashes of light and floaters associated with a peripheral shadow or curtain
- May progress rapidly over days to involve central vision
- Generally no pain unless associated with ocular inflammation
- Examination reveals elevation of retina and vessels associated with tears in the retina () and/or hemorrhage in the vitreous

ETIOLOGY

- The overwhelming majority of retinal detachments are caused by a retinal tear or hole (rhegmatogenous) occurring after acute separation of the vitreous (posterior vitreous detachment [PVD]).
- Cataract surgery is thought to cause biochemical changes in the vitreous resulting in PVD.
- High myopia and lattice degeneration cause thin areas of the retina resulting in holes.
- Most common cause of traction RD is severe proliferative diabetic retinopathy resulting in fibrovascular proliferation with contraction of fibrous tissue and secondary detachment of retina.
- Ocular tumors and inflammation including posterior uveitis and scleritis are the most common causes of exudative retinal detachment.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Degenerative retinoschisis
- Uveal effusion syndrome
- Choroidal detachment
- Hemorrhage
- Tumors

WORKUP

- Full eye examination with dilated fundus exam and retinal drawing to document tears and extent of detachment
- Visual fields
- Ultrasonography when the view of the fundus is limited due to hemorrhage or cataract to show the retinal detachment or tumors beneath it
- Medical workup only when inflammation or systemic disease considered

LABORATORY TESTS

Usually not necessary unless exudative detachment is being considered

IMAGING STUDIES

B scan ultrasonography (US) of the eye

TREATMENT

NONPHARMACOLOGIC THERAPY

Immediate surgery. The three principal methods for reattachment of the retina in patients with primary retinal detachment are scleral buckling, vitrectomy, and pneumatic retinopexy. There is a paucity of randomized trials comparing these procedures and the choice remains subjective. Some data suggest that vitrectomy may be preferable for detachment in pseudophakic eyes, whereas primary detachment in phakic eyes with complexity exceeding the original indications for pneumatic retinopexy may be treated with scleral buckling or vitrectomy.

ACUTE GENERAL Rx

- Early surgery to repair the detachment
- Treatment of the underlying disorder

CHRONIC Rx

Occasionally, steroids or other treatment of underlying inflammatory disease, if indicated

DISPOSITION

- Immediately refer to an ophthalmologist
- Early intervention improves outcomes

REFERRAL

Immediately

PEARLS & CONSIDERATIONS

COMMENTS

If treated early, most patients will recover a substantial portion of their vision.

AUTHOR: **Robert H. Janigian, Jr., MD**

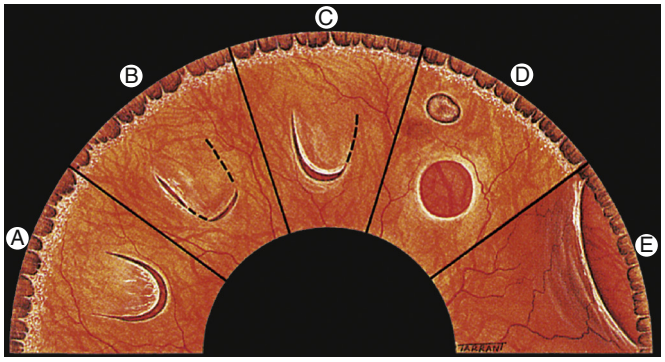

FIG. E1 Retinal tears. A, Complete U-shaped; **B,** linear; **C,** L-shaped; **D,** operculated; **E,** dialysis. (From Kanski JJ, Bowling B: *Clinical ophthalmology: a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

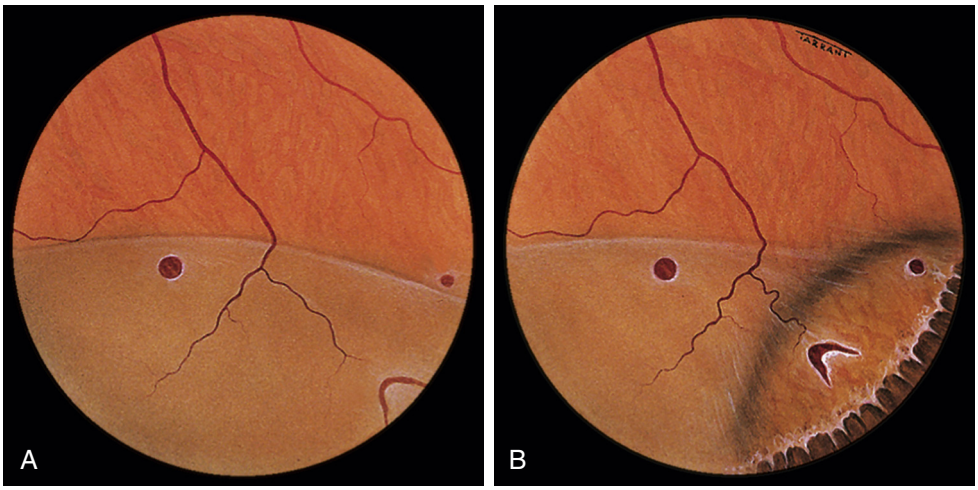

FIG. E2 Appearance of retinal breaks in detached retina. A, Without scleral indentation; **B,** with indentation. (From Kanski JJ, Bowling B: *Clinical ophthalmology: a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

SUGGESTED READINGS

Alves C et al. Risk of ophthalmic adverse effects in patients treated with MEK inhibitors: a systematic review and meta-analysis, *Ophthalmic Res* 57(1):60-69, 2017.

Kuhn F, Aylward B: Rhegmatogenous retinal detachment: a reappraisal of its pathophysiology and treatment, *Ophthalmic Res* 51(1):15-31, 2014.

Retinal Hemorrhage (PTG)

BASIC INFORMATION

DEFINITION

Retinal hemorrhages occur as a result of rupture of the rich retinal capillary network. The location of the vascular pathology determines the type of hemorrhage and may aid in the differential diagnosis. Preretinal hemorrhage usually implies neovascularization or traction, intraretinal hemorrhage is caused by rupture of capillaries or aneurysms within the retina, and subretinal hemorrhage occurs when there is rupture of choroidal vessels or subretinal neovascularization. Retinal hemorrhages are abnormal, and causes should be sought (see "Etiology").

SYNONYMS

Subretinal or preretinal hemorrhages
Splinter hemorrhage, dot and blot hemorrhages
Roth spots (small white centered blood, traditionally associated with endocarditis)

ICD-10CM CODES

H35.60	Retinal hemorrhage, unspecified eye
H35.61	Retinal hemorrhage, right eye
H35.62	Retinal hemorrhage, left eye
H35.63	Retinal hemorrhage, bilateral

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Busy ophthalmologists see one or two cases a mo.
PREDOMINANT AGE: Usually vascular disease in older patients
PEAK INCIDENCE:

- In children: Associated primarily with trauma and hematologic disorders (must consider shaken baby syndrome and leukemia in every child with retinal hemorrhages), rare retinal vascular diseases of children (Coat syndrome, Eales disease)
- Associated with trauma, diabetes, vascular disease (hypertensive retinopathy, retinal vascular occlusions, sickle cell disease, anemia, radiation retinopathy), macular degeneration, altitude changes (mountain climbing)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Retinal hemorrhages in general do not cause loss of vision or ocular symptoms unless associated with other ocular pathology; symptoms, when present, are generally from the systemic cause.
- Ophthalmoscopy reveals hemorrhage within the retina, or on the nerve or subretinal area.
- Evidence of diabetes, hypertension, tumors, inflammation, macular degeneration, and drug use.

ETIOLOGY

- Vascular: Diabetic retinopathy, hypertensive retinopathy, retinal vein occlusion, carotid occlusive disease, Valsalva retinopathy, radiation retinopathy, retinal macroaneurysm, ischemic optic neuropathy
- Elevated intracranial pressure (hemorrhages generally located around or on optic nerve)
- Trauma
- Inflammatory diseases: Retinal vasculitis, lupus
- Infectious: HIV retinopathy, acute retinal necrosis (herpes virus mediated), endocarditis
- Neoplastic: Leukemia, vascular tumors of the retina, choroidal melanoma, metastatic tumors
- Degenerative diseases: Age-related macular degeneration, myopia, angioid streaks
- Rapid changes in altitude (mountain climbing or scuba diving)
- Drugs: Interferon, cocaine
- NOTE: In general, anticoagulants and antiplatelet drugs do not by themselves cause retinal hemorrhages

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Evaluate patients for local and systemic diseases (diabetes is most common).
- Trauma in children or adults.
- Venous or arterial occlusion associated with atherosclerotic heart disease may cause retinal hemorrhage.
- Rule out malignant melanoma, trauma, hypertensive, or cardiovascular disease.
- Section II describes the differential diagnosis of acute painless loss of vision.

WORKUP

- Complete history and general physical examination; evaluate for trauma; look for systemic diseases and medication etiologies
- Complete eye exam, including dilated fundus exam

LABORATORY TESTS

- Minimum: Complete blood count, erythrocyte sedimentation rate, complete blood chemistries
- Visual field testing

IMAGING STUDIES

- Color photography and fluorescein angiography (assess for retinal vascular causes, vasculitis, macular degeneration) (Fig. E1)
- Ocular ultrasound if tumor is in differential
- Carotid Doppler scan
- Trauma: Skull radiographs or head CT (evaluate for fractures)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Laser or treatment of underlying disorder
- Carotid endarterectomy if indicated

ACUTE GENERAL Rx

- Laser treatment may be indicated for certain retinal diseases (diabetic retinopathy, retinal vein occlusion, retinal macroaneurysm).
- Treatment may be indicated for wet macular degeneration or diabetic retinopathy (intravitreal injection).
- Treat underlying systemic disease.
- Repair any damage from trauma.

CHRONIC Rx

- Vitamin therapy: Age-Related Eye Disease Study 2 formulation for macular degeneration.
- Treatment will differ depending on various causes of bleeding.
- Treat medical problems (e.g., diabetes, hypertension).
- Encourage adequate control of underlying medical disorders.

DISPOSITION

If present, hemorrhage in the retina is generally considered abnormal; refer to ophthalmologist for evaluation.

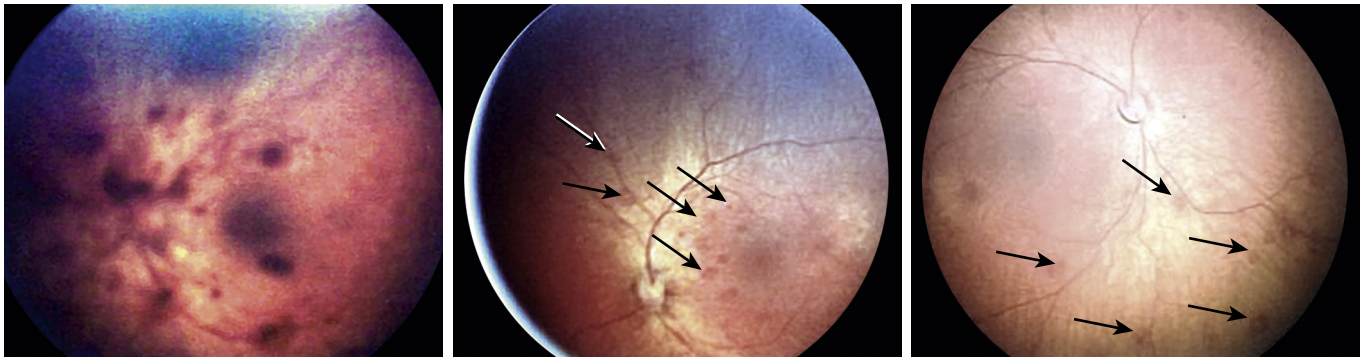

FIG. E1 Retinal hemorrhages. *Arrows* point to hemorrhages of various sizes. (From Kliegman RM [ed]: *Nelson textbook of pediatrics*, ed 19, 2011, Saunders.)

REFERRAL

Immediate referral to an ophthalmologist, especially if there is a significant change in vision or distorted vision; early treatment significantly affects outcome.

PEARLS & CONSIDERATIONS

COMMENTS

- Vision may not be affected if macula is not involved.
- Complete recovery of vision depends on cause.
- Chronic situations may have poor prognosis.

RELATED CONTENT

Diabetic Retinopathy (Related Key Topic)

AUTHOR: **Robert H. Janigian, Jr., MD**

SUGGESTED READING

Binenbaum G, Forbes BJ: The eye in child abuse: key points on retinal hemorrhages and abusive head trauma, *Pediatr Radiol* 4(Suppl 44):S571-S577, 2014.

Retinitis Pigmentosa (PTG)

BASIC INFORMATION

DEFINITION

Retinitis pigmentosa (RP) refers to a group of phenotypically variable and genetically diverse retinal dystrophies resulting in predominantly rod photoreceptor cell death. Subsequent cone and retinal pigment epithelial involvement can also be seen. The term "retinitis" is a misnomer as inflammation plays a very minor role in the pathology. Visual manifestations usually include night blindness (nyctalopia) and loss of peripheral vision.

SYNONYM

RP

ICD-10CM CODE
H35.5 Hereditary retinal dystrophy

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.):
- Approximately 1 in 4000 in the U.S. and 1 in 5000 worldwide.
- It is the most commonly encountered hereditary fundus dystrophy.

PREDOMINANT SEX: X-linked presents only in males, but there is no gender predilection with the other genetic varieties.

PREDOMINANT AGE: Onset usually in young adulthood but can present at any time from infancy up to 30s to 50s, depending on mode of inheritance.

PEAK INCIDENCE:
- Autosomal recessive incidence: In the 20s
- Autosomal dominant form: In the 40s

GENETICS:
- Over 100 genetic loci have been mapped on more than 50 genes representing all inheritance patterns
- 20% autosomal recessive
- 10% to 20% autosomal dominant
- 10% X-linked
- Up to 40% have no family history and an unknown molecular genetic basis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Classic triad: Bone spicule and pigment clumping in the mid periphery (Fig. E1), "waxy pallor" of the optic nerve and arteriolar attenuation.
- Findings almost always bilateral but may be asymmetric.
- Other findings: Depigmentation and atrophy of retinal pigment epithelium (RPE), cataracts, and macular edema.
- Typical symptoms: Decrease in night vision and peripheral vision. Patients typically lose night vision to a greater extent than they lose day vision, and they lose peripheral vision before losing central vision.

ETIOLOGY

RP may occur as an isolated sporadic disorder, or may be inherited as autosomal dominant, autosomal recessive, or x-linked. Gene mutations that cause RP generally affect the biological function of the photoreceptors and RPE. The end result is photoreceptor apoptosis and cell death. XL is the least common but most severe form, and may result in complete blindness by the third or fourth decade.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Previous chorioretinitis: Syphilis, cytomegalovirus (CMV) retinitis, rubella, diffuse unilateral subacute retinitis
- Must consider other genetic disorders that cause retinal degeneration, including gyrate atrophy, choroideremia, Refsum disease, cone-rod dystrophy, cone dystrophy, and Leber congenital amaurosis
- Toxic retinopathies (phenothiazines, chloroquine)

WORKUP

- Electrophysiologic studies (electroretinogram results are most important)
- Dark adaptation studies
- Visual fields
- Medication history

LABORATORY TESTS

- Usually not necessary
- Venereal disease research laboratory (VDRL) if syphilis is a consideration
- Consider other conditions that cause pigmentary degeneration of the retina: Serum ornithine level or ornithine-lysine ratio (for gyrate atrophy of the retina and choroid) and serum phytanic acid level (for Refsum disease)

IMAGING STUDIES

- Color fundus photography
- Optical coherence tomography
- Fluorescein angiography

TREATMENT

CHRONIC Rx

- No proven therapy to prevent photoreceptor cell death.
- Nutritional and supplement therapy is controversial: High-dose vitamin A palmitate (15,000 IU) was shown to slow the decline of electroretinogram (ERG) response, but whether it translates to better visual prognosis is not clear.
- Docosahexaenoic acid (DHA), an omega-3 fatty acid thought to be important for photoreceptor function, has been evaluated in two clinical trials for its potential to slow vision loss in RP, but neither study showed a clear benefit.
- Based on clinical trial results, some experts recommend a regimen of 15,000 IU of vitamin A palmitate daily, lutein 12 mg daily, and two portions of oily fish weekly.
- Use of UV-absorbing sunglasses and brimmed hats for protection from high levels of light exposure seems prudent.
- Drugs that may negatively impact RP include isotretinoin (Accutane), sildenafil (Viagra), and vitamin E.
- Cystoid macular edema should be treated with carbonic anhydrase inhibitors including topical dorzolamide and acetazolamide, periocular or intravitreal steroid, and possibly intravitreal anti-vascular endothelial growth factor (anti-VEGF).
- Emerging therapies: Argus II retinal implant is a phototransducing chip that is surgically placed on the retinal surface and is FDA approved for RP patients with bare light perception or no light perception. Trials are

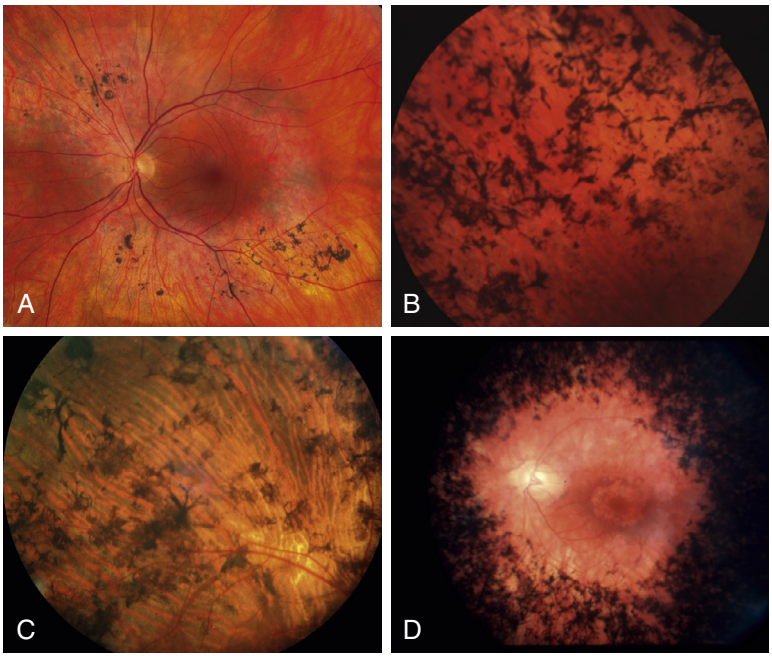

FIG. E1 Progression of retinitis pigmentosa. A, Early changes. **B,** Advanced changes. **C,** Unmasking of choroidal vessels. **D,** End-stage disease. (**A,** Courtesy P. Saine; from Kanski JJ, Bowling B. *Clinical ophthalmology: a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

under way using gene therapy targeted for specific gene mutations. Ciliary neurotrophic factor (CNTF) has been shown to slow retinal degeneration, and clinical trials are presently in progress.

DISPOSITION

- Reassurance that total blindness is rare; the overwhelming majority of patients maintain sight in one eye
- Low-vision evaluation
- Annual comprehensive eye examination with visual fields and possibly ERG every 2 yr
- Liver function studies for those on high-dose vitamin A

REFERRAL

To ophthalmologist to confirm diagnosis

PEARLS & CONSIDERATIONS

COMMENTS

- Patient education material can be obtained from the Retinitis Pigmentosa Foundation Fighting Blindness, 1401 Mt. Royal Avenue, 4th Floor, Baltimore, MD 21217.
- Information regarding ongoing clinical trials for RP can be found at clinicaltrials.gov.

RELATED CONTENT

Retinitis Pigmentosa (Patient Information)

AUTHOR: **Robert H. Janigian, Jr., MD**

SUGGESTED READINGS

Cruz L et al: Argus II study group: five-year safety and performance results from the Argus II retinal Prosthesis System clinical trial, *Ophthalmology* 123(10):2248-2254, 2016.

Jacobson SG, Cideciyan AV: Treatment possibilities for retinitis pigmentosa, *N Engl J Med* 363(17), 2010.

Terrell T, Commander J: Current stem cell approaches for the treatment of inherited retinal degenerations, *Semin Ophthalmol* 34(4):287-292, 2019.

Zhang Q: Retinitis pigmentosa: progress and perspective, *Asia Pac J Ophthalmol* 5:265–271, 2016.

BASIC INFORMATION

DEFINITION

Retinoblastoma is a congenital neoplasm arising from the neural layers of the retina. It represents the most common childhood intraocular malignancy and accounts for 10% to 15% of cancers occurring within the first yr of life.

ICD-10CM CODES

C69.20 Malignant neoplasm of unspecified retina
C69.21 Malignant neoplasm of right retina
C69.22 Malignant neoplasm of left retina

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Retinoblastoma affects 1 in 15,000 children, with approximately 300 children newly diagnosed each yr in the U.S. The worldwide incidence is 1 in 15,000 to 1 in 20,000 live births, constituting a total of 9000 new cases per yr. The annual incidence of retinoblastoma in children less than 15 yr was 4.1 per million between 2005 and 2009.

PEAK INCIDENCE:

- 6 to 13 mo. Mean age at diagnosis is 12 mo for bilateral tumors and 24 mo for unilateral tumors.
- 72% diagnosed by age 3.
- 90% diagnosed by age 4.

PREDOMINANT AGE: 8 mo

GENETICS:

- First disease demonstrating a genetic basis for cancer development:
  1. Biallelic inactivation of the *RB1* gene.
  2. Mutation of *RB1* gene predisposes to other second malignancies such as lung, bladder, bone, skin, or brain cancers.
- Either heritable or nonheritable, with the majority of cases having no positive family history:
  1. Heritable form affects one eye or both.
  2. Nonheritable form affects only one eye.
- Gene mutation or an autosomal-dominant gene with 80% to 95% penetration

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Leukocoria in a child <3 yr old (white reflex or white pupil) (Fig. E1)
- White elevated retinal masses
- Strabismus
- Glaucoma
- Uveitis
- Vitreous masses and opacity

ETIOLOGY

The retinoblastoma (*RB1*) gene is a tumor suppressor gene located on the long arm of chromosome 13 at region 14 that codes for the RB protein. A second genetic abnormality accountable for retinoblastoma has been discovered recently: the amplification of the *MYCN* gene. All bilateral retinoblastomas are heritable and often present at an earlier age. Biallelic *RB1* inactivation is responsible for most bilateral, heritable retinoblastomas. Of all retinoblastomas, ~60% are attributable to somatic, nonhereditary mutations caused by biallelic *RB1* loss. The *MYCN* gene amplification contributes a small percentage of nonheritable retinoblastoma with normal *RB1* gene.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Eye examination (Fig. E2):

- Strabismus
- Retinal detachment
- Uveitis
- Other tumors
- Glaucoma
- Coats disease (pathologic telangiectatic retinal vessels that leak and lead to accumulation of subretinal fluid and lipid)
- Endophthalmitis
- Cataract
- Infectious

SCREENING

Screening should be conducted shortly after birth with frequent follow-up by an ophthalmologist for children with a positive family history of retinoblastoma or 13q deletion.

WORKUP

Diagnosis is by ophthalmologic examination. An awake examination to determine if the patient can fixate, and extent of eye mobility should be done. Examination should also include visual acuity, papillary examination, extraocular movements, slit-lamp examination for evidence of iris neovascularization, hyphemia or hypopyon, indirect ophthalmoscopy with 360 degrees of scleral depression, and fundus photographs documenting all lesions. Ophthalmologic examination is followed by ultrasonography of the eye and MRI of the orbits and brain to exclude extraocular extension and trilateral retinoblastoma. Metastatic disease is rare at diagnosis, but if there is evidence of disease invasion into the optic nerve or extensive choroidal involvement, a full metastatic workup may be warranted, including lumbar puncture, bone marrow biopsy and aspirate, or radionuclide bone scan.

CLASSIFICATION

Several classifications for retinoblastoma have been in place for many yrs. In 1969, the Reese-Ellsworth classification system was devised to predict the outcome of external beam radiation. However, this classification became outdated as chemotherapy strategies became widely used for salvage therapy. In 2003, a new international classification system for intraocular retinoblastoma (IIRC) was formulated (Table E1). This system accurately reflects response to standardized chemotherapy regimen used in conjunction with focal consolidative therapy. The international classification system is subdivided into:

- Group A (small, very low risk)
- Group B (medium, low risk)
- Group C (confined, medium, moderate risk)
- Group D (diffuse, large, high risk)
- Group E (enucleation, advanced, very high risk)

STAGING

Table E2 summarizes the International Retinoblastoma Staging System.

IMAGING STUDIES

- MRI: May show calcifications in retina
- Ultrasonography: Good delineation of mass

TREATMENT

Usually treated by a multidisciplinary team consisting of a pediatrician, an ophthalmologist, a pediatric oncologist, and a pediatric radiation oncologist. Table E3 summarizes a recommended approach to the treatment of intraocular retinoblastoma. Treatment depends on location and stage of tumor when diagnosed:

- Chemotherapy was introduced in the 1990s and has shown efficiency in control of tumor growth in various stages of retinoblastoma. The goal of chemotherapy is to reduce the tumor volume for focal therapy with cryotherapy, laser, thermotherapy, or plaque brachytherapy. Systemic chemotherapy involves a three-drug regimen comprising vincristine, cisplatin, and etoposide
- Plaque brachytherapy with iodine-125 or ruthenium-106 and cryotherapy
- Surgical enucleation of the eye in heavy tumor burden; i.e., group E to prevent metastasis
- Radiation and chemotherapy

DISPOSITION

Overall there is a high cure rate (93% 5-yr survival in the U.S.) for retinoblastoma. Group A tumors generally have good visual and survival prognosis with focal consolidative therapy alone, groups B and C are treated with chemotherapy and focal therapy with good results (vision salvage rates up to 93%), group D patients often eventually require enucleation despite treatment.

REFERRAL

- To ophthalmologist, pediatric oncologist, and pediatric radiation oncologist.
- Prospective parents with a family history of retinoblastoma should be referred for genetic counseling. Genetic testing should be carried out for most retinoblastoma patients unless it is declined.

PEARLS & CONSIDERATIONS

COMMENTS

- High incidence of second tumor in survivors compared with general population
- High incidence of lung cancer, bladder cancer, and other epithelial cancers

RELATED CONTENT

Retinoblastoma (Patient Information)

AUTHOR: **Donny V. Huynh, MD**

FIG. E1 Presentation of retinoblastoma. A, Leukocoria; **B,** secondary glaucoma and buphthalmos; **C,** red eye due to uveitis; **D,** iris nodules and pseudohypopyon; **E,** orbital inflammation; **F,** orbital invasion. (Courtesy of C Barry **[A]**; N Rogers **[B]**; U Raina **[C]**. From Bowling B: *Kanski's clinical ophthalmology, a systemic approach,* ed 8, Philadelphia, 2016, Elsevier.)

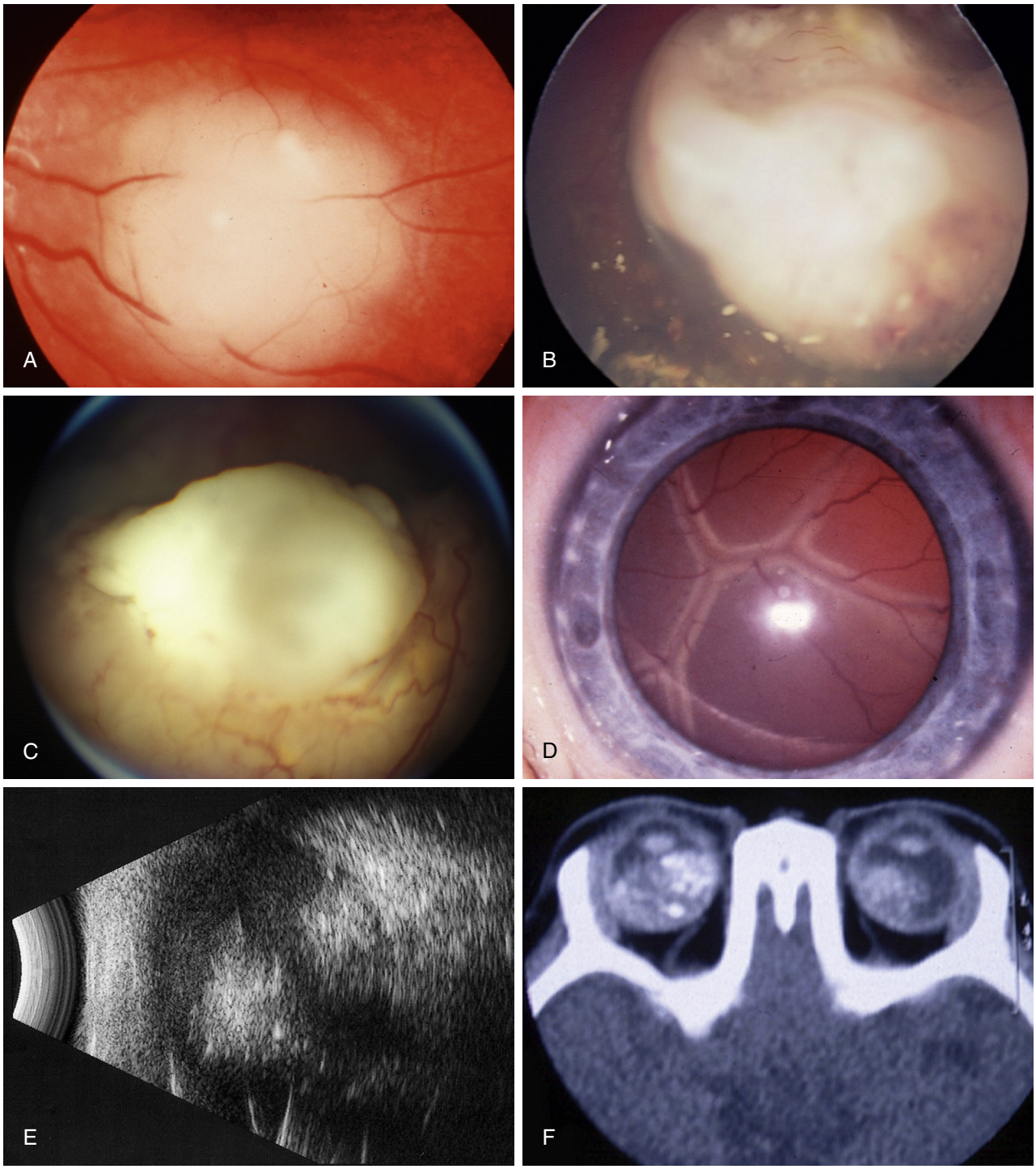

FIG. E2 Retinoblastoma. A, Intraretinal tumor; **B,** endophytic tumor with vitreous seeding; **C,** mixed endophytic and exophytic growth; **D,** total retinal detachment; **E,** B-scan shows echoes from calcification; **F,** axial computed tomography shows bilateral tumors with calcification. (Courtesy of B Dixon-Romanowska **[B]**; L MacKeen **[C]**; K Nischal **[F]**. From Bowling B: *Kanski's clinical ophthalmology, a systemic approach,* ed 8, Philadelphia, 2016, Elsevier.)

TABLE E1 International Classification for Intraocular Retinoblastoma

GROUP A

Small tumors away from foveola and disc
- Tumors ≤3 mm in greatest dimension confined to the retina, and
- Located at least 3 mm from the foveola and 1.5 mm from the optic disc

GROUP B

All remaining tumors confined to the retina
- All other tumors confined to the retina not in group A
- Subretinal fluid (without subretinal seeding) ≤3 mm from the base of the tumor

GROUP C

Local subretinal fluid or seeding
- Local subretinal fluid alone >3 to ≤6 mm from the tumor
- Vitreous seeding or subretinal seeding ≤3 mm from the tumor

GROUP D

Diffuse subretinal fluid or seeding
- Subretinal fluid alone >6 mm from the tumor
- Vitreous seeding or subretinal seeding >3 mm from tumor

GROUP E

Presence of any of these poor-prognosis features:
- More than two thirds of globe filled with tumor
- Tumor in anterior segment
- Tumor in or on the ciliary body
- Iris neovascularization
- Neovascular glaucoma
- Opaque media from hemorrhage
- Tumor necrosis with aseptic orbital cellulitis
- Phthisis bulbi

From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE E2 International Retinoblastoma Staging Systems

Stage 0: Patient treated conservatively
Stage I: Eye enucleated, completely resected histologically
Stage II: Eye enucleated, microscopic residual tumor
Stage III: Regional extension
a. Overt orbital disease
b. Preauricular or cervical lymph node extension
Stage IV: Metastatic disease
a. Hematogenous metastasis (without CNS involvement)
   1. Single lesion
   2. Multiple lesions
b. CNS extension (with or without any other site of regional or metastatic disease)
   1. Prechiasmatic lesion
   2. CNS mass
   3. Leptomeningeal and CSF disease

CNS, Central nervous system; *CSF,* cerebrospinal fluid.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE E3 Recommended Approach to the Treatment of Intraocular Retinoblastoma

		Treatment			
R-E Group	**ABC Group**	**Focal Tx**	**Intraarterial Chemotherapy**	**Systemic Chemotherapy**	**Radiation**
I-II	A	+	If PD	If PD	If PD
I-III	B	+	MEL 3-5 mg × 3-6 courses	VCR 0.05 mg/kg day 1 only CBP 18.6 mg/kg daily for 2 days for × 6 courses	If PD
IV-V	C-D[a]	+	MEL 3-5 mg × 3-6 courses Consider addition of second agent (TOP, CBP)	VCR 0.05 mg/kg day 1 only CBP 14 mg/kg day 1 and 2 ETO 6 mg/kg day 1 and 2 × 6 courses	If PD Consider early EBRT if massive vitreous seeding at completion of chemotherapy
V b	E	Enucleation			

[a]Consider upfront enucleation if unilateral.
CBP, Carboplatin; *EBRT,* external-beam radiation therapy; *ETO,* etoposide; *MEL,* melphalan; *PD,* progressive disease; *TOP,* topotecan; *Tx,* treatment; *VCR,* vincristine.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

SUGGESTED READINGS

Ghassemi F et al: Risk definition and management strategies in retinoblastoma: current perspective, *Clin Ophthalmol*, 2015.

Theriault B et al: The genomic landscape of retinoblastoma: a review, *Clin Experiment Ophthalmol* 42(1):33-52, 2014.

BASIC INFORMATION

DEFINITION

Retroperitoneal fibrosis (RPF) is a condition characterized by the presence of inflammation and fibrosis surrounding the infrarenal aorta and iliac arteries. To make the diagnosis, the following must be present:

- A soft tissue density surrounding the infrarenal aorta or iliac vessels demonstrated on enhanced computed tomography (CT) or magnetic resonance imaging (MRI)
- Absence of a biopsy in the retroperitoneum that is positive for malignancy
- Absence of a systemic, multicentric, fibrosing process such as IgG4-related disease or a histiocytic disease such as Erdheim-Chester disease

SYNONYMS

Ormond disease (idiopathic retroperitoneal fibrosis)
Periureteritis fibrosa
Periureteritis plastic
Chronic periureteritis
RPF
Sclerosing retroperitoneal granuloma

ICD-10CM CODE

N13.58	Crossing vessel and stricture of ureter without hydronephrosis

EPIDEMIOLOGY & DEMOGRAPHICS

Patients with RPF present to medical attention in the fifth, sixth, and seventh decades of life with a mean age of 54 yr. There is a slight male-to-female predominance, with ratios ranging from 1:1 to 3:1 depending on the report. All races appear to be affected equally. Few epidemiological studies exist that accurately characterize the incidence and prevalence of the disease. One report from the Netherlands suggests an incidence of 0.10/100,000 individuals.

RISK FACTORS: Definitive risk factors for RPF have not been established. Associations with atherosclerosis of the abdominal aorta, therapeutic radiation exposure, asbestos exposure, and certain medications (methysergide, ergotamine, pergolide, cabergoline, bromocriptine) have all been associated with RPF.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The disease onset may be preceded by systemic symptoms such as fatigue, anorexia, and weight loss
- May take months from the time symptoms start until a specific diagnosis is established
- Dull, noncolicky pain that does not modify with position is present in the lower back, flank, and lower abdomen and radiates to the inguinal area
- Testicular pain may often be accompanied by a hydrocele or varicocele due to spermatic vein encasement
- New or worsening hypertension
- Acute kidney injury secondary to ureteral obstruction
- Lower extremity edema secondary to caval compression
- Deep venous thromboembolism or pulmonary embolus
- Hypothyroidism (secondary to autoimmune thyroiditis)
- Physical findings on exam include:
  1. Abdominal or flank tenderness
  2. Lower extremity edema
  3. Hydrocele
  4. New onset or worsening hypertension

ETIOLOGY & PATHOGENESIS

There is no formal agreement on the clinical definition of RPF. Likely, several different mechanisms exist to explain the evolution of this disease process. Unfortunately no animal model has been developed to further study this family of diseases, thus making elucidation of these mechanisms protracted. There are currently two different hypotheses proposed to explain the pathogenesis of RPF. The first model is based on the finding that many patients with RPF have a significant burden of atherosclerosis in the abdominal aorta. The incidence of this finding

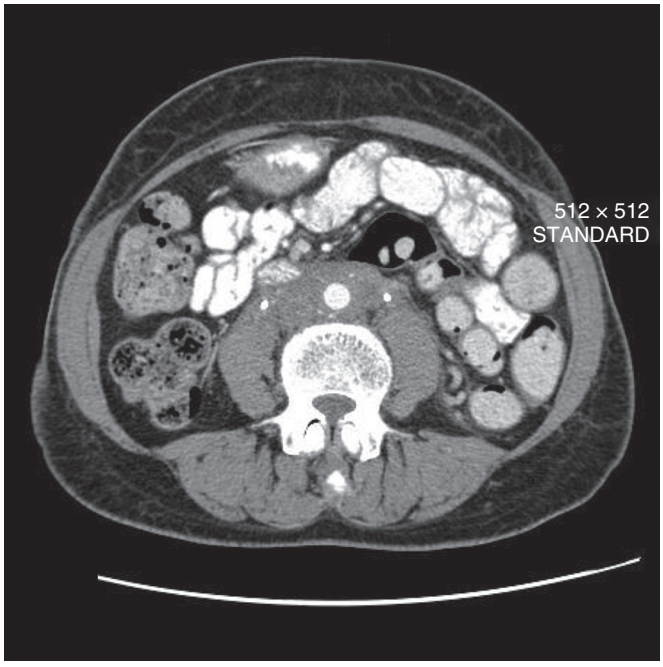

FIG. E1 Retroperitoneal fibrosis. Computed tomography scan of the abdomen with intravenous contrast reveals a soft tissue density surrounding the infrarenal aorta.

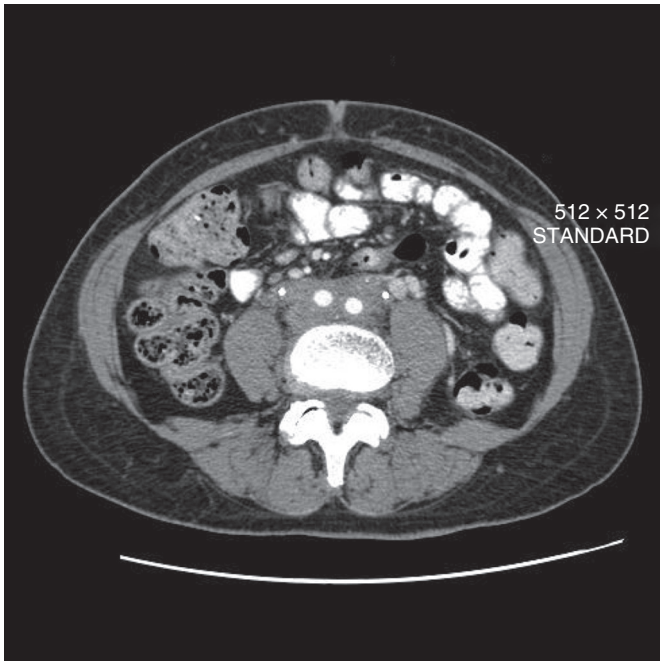

FIG. E2 Computed tomography scan of the pelvis reveals a soft tissue density surrounding the common iliac arteries.

varies by series. Other patients present with no evidence of an atherosclerotic burden, and alternative explanations have been proposed. Each may correctly explain a subset of patients with RPF, or components of each may uniformly apply to the broader heterogeneous population currently labeled as RPF.

1. Atherosclerosis model: This model was originally proposed by Michison and Parums in the mid-1980s. The authors noticed that the affected sections of the aorta had a heavy atherosclerotic burden. Microscopically the authors noted that the inflammatory reaction to the atherosclerosis was not limited to the intimal layer but expanded to the media and adventitial layers. The authors postulated that this "breach" into the media allowed lipid-laden macrophages to present oxidized low-density lipoprotein (LDL) and ceroid as antigens to T and B cells, thus initiating an immune reaction. This inflammatory reaction progressed to the adventitial layer and periaortic space, leading to the periaortitis and fibrosis.
2. These same authors could subsequently demonstrate that in patients with periaortitis, IgG could be shown to be in close apposition to extracellular ceroid. Additionally, they could show that ceroid-laden macrophages could be found in the adventitia and regional lymph nodes and that T and B cells found in the aorta media layer demonstrated markers of activation and proliferation. Finally, these authors showed evidence of elevated serum IgM and IgG antibodies to oxidized LDL and ceroid in patients with CP but not in a control population.
3. Autoimmune model: The evidence that RPF represents an autoimmune disease is broad but circumstantial. In one of his original papers, Ormond noted that the periaortic vessels in two of his patients resembled the vasculitis seen in polyarteritis nodosa. Similar findings of vasculitis of the vasa vasorum of the aorta have been documented by other authors. Moroni documented by flow cytometry that in patients with RPF there were increased numbers of circulating endothelial cells and that these cells were of microvascular origin. Similar findings were not found in patients with atherosclerosis or in healthy controls. These circulating endothelial cells returned to normal levels with suppression of the immune system. Vaglio has shown the presence of the HLA-DRB1* 03 allele in patients with RPF. This allele has also shown to be present in high numbers in other autoimmune diseases—namely, type 1 diabetes mellitus, myasthenia gravis, and systemic lupus erythematosus (SLE). Patients with RPF have been documented to also present with various other autoantibodies. There are also case reports of patients presenting with both RPF and with autoimmune diseases, such as seropositive inflammatory arthritis, ankylosing spondylitis, and SLE-associated and ANCA-associated vasculitis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Retroperitoneal lymphoma
- Erdheim-Chester disease
- IgG-4 RD
- Metastatic breast cancer
- Inflammatory aortic aneurysm

WORKUP

- The initial diagnosis is usually made via CT scan or MRI. Definitive diagnosis is established by laparoscopic biopsy or ultrasound-guided percutaneous needle biopsy, but these are usually not required unless the diagnosis is in question
- Workup usually also involves:
  1. Age-appropriate cancer screening
  2. Cross-sectional imaging

LABORATORY TESTS

- An increase in the erythrocyte sedimentation rate (ESR) is almost always present.
- Elevated C-reactive protein (CRP). CRP and ESR lack sensitivity and specificity for the diagnosis of RPF.
- Serum creatinine is variably increased: present in 50% to 75% of patients.
- Anemia (normochromic, normocytic) present in 45% of patients.
- TSH is abnormal in 25% of patients.
- Antithyroperoxidase antibodies present in 24%.

IMAGING STUDIES

- Radiographic imaging usually provides a tentative diagnosis.
- Contrast-enhanced CT scan is the preferred imaging method and demonstrates a homogeneous, circumferential soft tissue mass surrounding the infrarenal abdominal aorta and common iliac arteries. Medial deviation of the ureters and inferior vena cava encasement are common.
- MRI shows low intensity on T1-weighted images and variable by T2-weighted images. Secondary cases due to malignancy are often not homogeneous, are bulky, and less often cause medial ureteral deviation.

BIOPSY

The pathology of RPF is that of a fibroinflammatory disease marked by chronic inflammation and fibrous tissue. The inflammatory infiltrate consists of lymphocytes, plasma cells, and rare macrophages. Lymphoid aggregates contain T and B cells. If the ratio of IgG-4 to total IgG is >40%, consider IgG-4–related disease.

TREATMENT

GOALS OF TREATMENT

- Identify and discontinue the use of any inciting or suspected drug
- Suppress inflammatory process
- Preserve renal function by maintaining ureteral patency
- Exclude malignancy
- Relieve symptoms

NONPHARMACOLOGIC THERAPY

Therapy is initially directed toward drainage of the ureteral obstruction by a ureteral stent or percutaneous nephrostomy tube.

ACUTE GENERAL Rx/CHRONIC Rx

- The aim of pharmacologic treatment is to reduce or eliminate the inflammatory soft tissue mass. There are multiple approaches to medical therapy. The two most commonly used medical protocols are the following:
  1. Glucocorticoids are the initial immunosuppressant used, with doses of 0.75 to 1 mg/kg/day prednisone tapered over the 6 to 9 months.
  2. Mycophenolate mofetil 1000 mg by mouth twice daily with corticosteroids, starting at 40 mg per day, with a taper of 10 mg per month. After prednisone 10 mg daily has been taken for 1 month, reduce to 5 mg daily for 30 days and then discontinue prednisone. Mycophenolate mofetil is continued until ureteral stents or PCN have been removed for 6 months, with no evidence of recurrent obstruction. Mycophenolate mofetil is continued for 6 months in cases in which no obstruction is present for at least 6 months and after a 25% reduction in the periaortic mass.
  3. Although tamoxifen had historically been used as a steroid-sparing agent, randomized clinical trials have shown it to be of less benefit than prednisone.
  4. A randomized trial of prednisone alone versus prednisone plus mycophenolate mofetil has not been conducted. Both regiments report excellent response rates.

STENT MANAGEMENT

For patients with unilateral or bilateral stents in which cross-sectional imaging demonstrates a reduction of the periaortic or peri-iliac mass and in which the effected ureter(s) is free from the fibroinflammatory density, only one stent should be removed at a time.

After removal, patients are assessed for increased pain and decreased urine output. At 48 hr, blood is obtained for analysis of creatinine and potassium. If there is no clinical suspicion of obstruction, a technetium-99m nuclear scan with furosemide washout is obtained at 14 days. If excretion is normal ($T_{1/2}$ excretion, <12 min), the contralateral stent may be removed. At day 14, a partial obstruction may exist from ureteral edema. If a partial obstruction is demonstrated at day 14 ($T_{1/2}$ excretion, 12 to 20 minutes), the examination is repeated in 2 weeks. If a partial obstruction still exists, the ureteral stent is replaced. If the follow-up study indicates no obstruction, the stent can remain out and attention to remove the contralateral stent, if present, with a simi-

lar protocol proceeds. For patients in whom ureteral obstruction was relieved with a percutaneous nephrostomy and cross-sectional imaging suggests regression of the mass sufficient to relieve the obstruction, patency may be evaluated by closing the external stopcock and proceeding with a technetium-99m nuclear scan with furosemide washout, as described previously, or by formal Whittaker manometry.

DISPOSITION

- Long-term follow-up is required because of the potential for disease recurrence.
- After discontinuation of medications, renal function, inflammatory markers (e.g., erythrocyte sedimentation rate), and complete blood count are followed monthly for 6 months and quarterly afterward.
- Cross-sectional imaging by CT or MRI is performed 6 months after discontinuation of medications.
- For patients with normal labs and normal cross-sectional imaging at 6 months, annual follow-up is appropriate, unless new symptoms occur.
- Prognosis is usually good; however, if RPF chronically relapses, maintenance therapy and monitoring are required.

AUTHOR: **Paul J. Scheel, Jr., MD**

SUGGESTED READINGS

Brandt AS et al: Associated findings and complications of retroperitoneal fibrosis in 204 patients: results of urologic registry, *J Urol* 185:526-531, 2011.

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BASIC INFORMATION

DEFINITION

Retropharyngeal abscess is a soft tissue infection of the throat that involves retropharyngeal space and that primarily affects children. The anatomic boundaries of the retropharyngeal space are the buccopharyngeal fascia (middle layer of the deep cervical fascia) anteriorly and the alar fascia (deep layer of the deep cervical fascia) posteriorly. The space begins at the skull base superiorly and ends inferiorly where the two fasciae fuse at the level between the first and second thoracic vertebrae.

ICD-10CM CODE

J39.0 Retropharyngeal and parapharyngeal abscess

EPIDEMIOLOGY & DEMOGRAPHICS

Retropharyngeal abscess occurs most commonly in children between the ages of 2 and 4 yr, analogous to suppurative cervical adenitis. 70% of cases are in patients under the age of 6, and 50% are in patients under the age of 3. This represents the peak age group for numerous viral upper respiratory tract infections and their attendant complications, acute otitis media and sinusitis. Retropharyngeal space infection is less common in older children and adults because the lymph nodes generally atrophy by puberty.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The onset of a retropharyngeal infection may be insidious, with little more than fever, irritability, drooling, a muffled voice (dysphonia), or possibly nuchal rigidity.
- The acute symptoms relate to pressure and inflammation produced by the abscess on either the airway or the upper digestive tract and pharynx. The patient may have intense dysphagia, drooling, and odynophagia, or there may be some element of respiratory distress from edema and inflammation of the airway (stridor, tachypnea, or both).
- Unwillingness to move the neck because of discomfort is often a prominent presenting feature and should lead to consideration of retropharyngeal abscess if the child is febrile and irritable.
- Extension of the neck is usually affected more than flexion. This causes the patient to hold his or her neck stiffly or to present with torticollis.
- Trismus is unusual.
- On physical examination it may be possible to appreciate midline or unilateral swelling of the posterior pharyngeal wall. The mass may be fluctuant to the examining finger, and care must be taken to avoid rupture of the abscess into the upper airway.

Complications are numerous and could be fatal; these include airway obstruction, septicemia, thrombosis of the internal jugular vein, carotid artery rupture, and acute necrotizing mediastinitis. Aspiration with resultant pneumonia may complicate retropharyngeal abscess if rupture of the abscess occurs and empties into the airway. Infection can spread from one space in the neck to another.

The most dreaded complication is jugular vein suppurative thrombophlebitis (Lemierre syndrome), in which the vessels of the carotid sheath become infected, leading to bacteremia and spread of infection to the lungs, brain, and mediastinum.

ETIOLOGY

- The retropharyngeal space comprises two chains of lymph nodes that drain the nasopharynx, adenoids, posterior paranasal sinuses, middle ear, and Eustachian tube. Accordingly, suppurative infections in these areas may provide the seeds for infection for retropharyngeal abscess.
- The predominant bacterial species are *Streptococcus pyogenes* (group A *Streptococcus*), *Staphylococcus aureus,* and respiratory anaerobes (including *Fusobacteria, Prevotella,* and *Veillonella* species). *Haemophilus* species are also occasionally found.
- In young children, infection usually reaches this space by lymphatic spread from a septic focus in the pharynx or sinuses.
- In adults, infection may reach the retropharyngeal space from either local or distant sites. Penetrating trauma (e.g., from chicken bones or iatrogenic) is the usual source of local spread. More distant sources of infection include odontogenic sepsis and peritonsillar abscess (now a rare cause).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cervical osteomyelitis
- Pott disease
- Meningitis
- Calcific tendonitis of the long muscle of the neck
- Differentiating features of deep neck infections are summarized in Table 1

LABORATORY STUDIES

- CBC with differential.
- Blood cultures may be considered in refractory cases or for severe symptoms.

IMAGING STUDIES

- A lateral neck film should be obtained and can be helpful in delineating the presence of a retropharyngeal abscess and may demonstrate cervical lordosis; the retropharyngeal space is considered widened and pathologic if it is greater than 7 mm at C2 or 14 mm at C6 (Fig. E1).
  1. There must be attention to technical issues when performing the study, especially in children. The film should be a perfect lateral, and the child must keep the neck in extension during inspiration to avoid a false thickening of the retropharyngeal space. Crying, particularly in infants, may also cause false thickening of the retropharyngeal space.
- CXR should be considered to evaluate for mediastinitis or aspiration pneumonia.
- A CT scan of the neck is useful for patients with moderate or high suspicion of having a deep neck space abscess. It is the most useful imaging modality to identify abscesses in the retropharyngeal space, but it is not perfect. Both the sensitivity and specificity of the CT scan in predicting the presence of drainable purulent material are quite variable from study to study, ranging between 68% and 100%.
  1. The CT scan provides more information than the plain radiograph because it can generally differentiate between retropharyngeal cellulitis and retropharyngeal abscess and can demonstrate extension of the retropharyngeal abscess to contiguous spaces in the neck. Findings

TABLE 1 Differentiating Features of Deep Neck Infections

Space	Clinical Features*
Submandibular space (Ludwig angina)	Woody submental induration, protruding swollen/necrotic tongue, no trismus, rotted lower molars commonly present
Lateral pharyngeal space (anterior)	Fever, toxicity, trismus, neck swelling
Lateral pharyngeal space (posterior)	No trismus, no swelling (unless ipsilateral parotid is involved), cranial nerve IX-XII palsies, Horner syndrome, carotid artery erosion
Retropharyngeal space (retropharynx)	Neck stiffness, decreased neck range of motion, soft-tissue bulging of posterior pharyngeal wall, sore throat, dysphagia, dyspnea
Retropharyngeal space ("danger space")	Mediastinal or pleural involvement
Retropharyngeal space (prevertebral)	Neck stiffness, decreased neck range of motion, cervical instability, possible spread along length of vertebral column
Jugular vein septic thrombophlebitis (Lemierre syndrome)	Sore throat, swollen tender neck, dyspnea, chest pain, septic arthritis

*Fever and signs of systemic toxicity are common to all.
From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

TABLE 2 Therapeutic Options for Deep Neck Infections

Syndrome	Likely Flora	Therapeutic Options*
Submandibular space infection (community acquired)	Anaerobes, streptococci, *Staphylococcus aureus*	Ampicillin-sulbactam (3 g IV q6h) Ceftriaxone (1-2 g IV q24h) *plus* clindamycin (300-900 mg IV q8h) *or* metronidazole (500 mg IV q6h) Ertapenem (1 g IV q day)
Submandibular space infection (hospital/ICU acquired)	*Pseudomonas aeruginosa,* methicillin-resistant *S. aureus* (MRSA), anaerobes	Imipenem (500 mg IV q6h) *or* piperacillin-tazobactam (3.375 g IV q8h by continuous infusion) *plus* vancomycin (1 g IV q12h)
Retropharyngeal space infection	Anaerobes, streptococci, *S. aureus*	Ampicillin-sulbactam (3 g IV q6h) Ceftriaxone (1-2 g IV q24h) *plus* clindamycin (300-900 mg IV q8h) *or* metronidazole (500 mg IV q6h) Ertapenem (1 g IV q day)
Lateral pharyngeal space infection	Anaerobes, streptococci, *S. aureus*	Ampicillin-sulbactam (3 g IV q6h) Ceftriaxone (1-2 g IV q24h) *plus* clindamycin (300-900 mg IV q8h) *or* metronidazole (500 mg IV q6h) Ertapenem (1 g IV q day)
Internal jugular vein septic thrombophlebitis	*Fusobacterium necrophorum*	Metronidazole (500 mg IV q6h) Clindamycin (300-900 mg IV q8h) Ampicillin-sulbactam (3 g IV q6h)

ICU, Intensive care unit; *IV,* Intravenous.
*Antibiotic choices listed are examples, because for most infections, multiple different antibiotics are effective; individual choice will be influenced by patient factors (e.g., allergies, concurrent medications), local hospital bacterial resistance rates, and microbiological culture results.
From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

on CT common to both cellulitis and abscess are a low-density core, soft tissue swelling, obliterated fat planes, and mass effect. Findings on CT scan that are indicative of abscess are "complete rim enhancement" and scalloping of the abscess borders (Fig. E2). The abscess may be seen as a mass impinging on the posterior pharyngeal wall.

- MRI of the neck is rarely used for diagnosis, especially in the pediatric population because of the longer time to acquire the study and the need for sedation in the younger population. T2-weighted images may identify and localize areas of pus for drainage or aspiration. Gadolinium enhancement is important to accurately define the soft tissue component. It also can be useful for distinguishing inflammatory from congenital or neoplastic lesions. Magnetic resonance angiography can be helpful for imaging vascular lesions, such as jugular thrombophlebitis.

Rx TREATMENT

ACUTE GENERAL & CHRONIC Rx

- When the CT findings suggest cellulitis or phlegmon, a trial of IV antibiotic therapy without drainage is initiated, and the child is monitored as an inpatient for 48 hr. If the child is clinically improved, consider discharge home with a course of oral antibiotics. If the clinical course is not improved or is worse, a repeat CT scan should be obtained, and surgical drainage or prolonged IV antibiotic therapy may be warranted. Some investigators also support a trial of IV antibiotic therapy alone when small abscesses are identified by CT scans, as long as the airway is not compromised.
  1. Ampicillin-sulbactam (300 mg/kg/day IV divided q6h) or clindamycin (25 to 40 mg/kg/day IV divided q8h) are effective antimicrobial selections. In adults, ampicillin-sulbactam 3 g IV q6h or clindamycin 600 mg IV q8h. Antibiotics should be adjusted as culture data become available, and oral therapy is continued to complete at least a 14-day course. Therapeutic options for deep neck infections are summarized in Table 2.
- Surgical intervention has historically played a prominent role in the management of retropharyngeal abscess in conjunction with antibiotic therapy. Prompt surgical drainage is indicated when there is a large hypodense area suggestive of an abscess or when a patient has not responded to parenteral therapy alone.

PEARLS & CONSIDERATIONS

PREVENTION

The complications of deep neck infection in any space are numerous and potentially fatal. Early diagnosis, with prompt and appropriate management, is key to avoiding these complications.

SUGGESTED READING

Available at ExpertConsult.com

AUTHOR: **Louis Insalaco, MD**

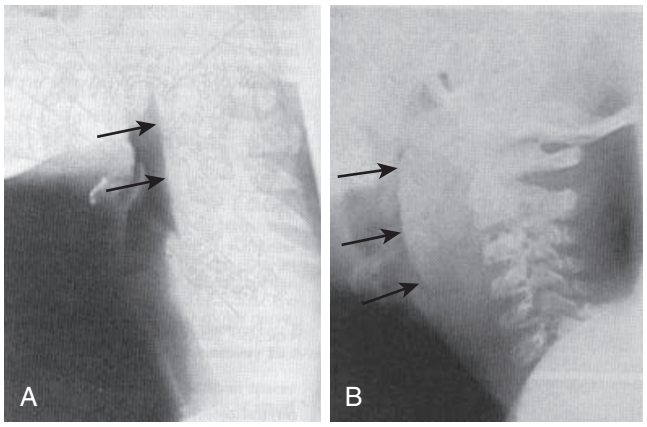

FIG. E1 Lateral radiographs of the neck show normal lateral cervical view (**A,** *arrows*) and expansion of the prevertebral soft tissues by a retropharyngeal abscess (**B,** *arrows*).

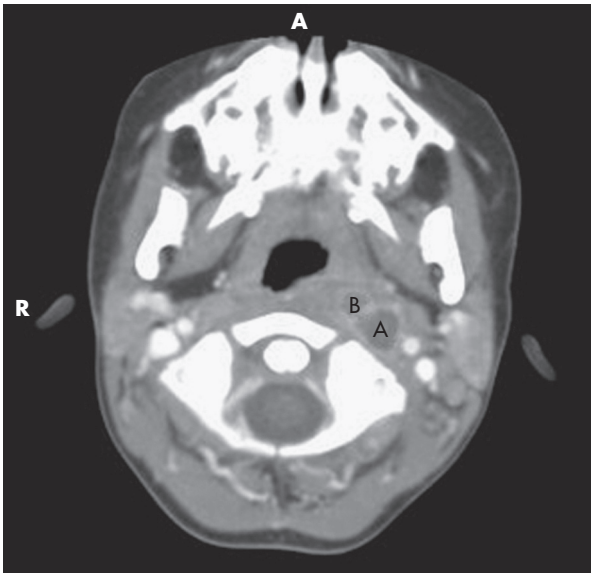

FIG. E2 Computed tomography scan of a retropharyngeal abscess (*A* and *B*) demonstrates a low-density core, soft tissue swelling, obliterated fat planes, mass effect, and rim enhancement.

SUGGESTED READING

Saluja S et al: A prospective study of 113 deep neck infections managed using a clinical practice guideline, *Laryngoscope* 123(12):3211-3218, 2013.

Reye Syndrome

BASIC INFORMATION

DEFINITION

Reye syndrome is a postinfectious triad consisting of encephalopathy, fatty liver degeneration, and transaminase elevation.

ICD-10CM CODE
G93.7 Reye syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- During the 1970s, 300 to 600 cases were being reported yearly in the U.S.
- Since the mid-1980s, after the understanding that aspirin is associated with Reye syndrome, the yearly count has fallen to <20 cases.
- Seasonal relation with influenza and varicella outbreaks.
- Age: Rare in persons aged >18 yr; peak age (in the U.S.) is 6 to 8 yr.
- Case-fatality rate: 25% to 50%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Shortly after recovery from a viral infection (flu or chickenpox), an afebrile child begins to vomit intractably. Hepatomegaly is often present. The vomiting can lead to dehydration. Occasionally, symptoms of hypoglycemia are present. After 2 days symptoms of encephalopathy dominate the clinical picture (lethargy, confusion, stupor, coma, seizures, decorticate or decerebrate posture) (Table E1).

ETIOLOGY

- Temporal association with influenza and varicella infection
- Epidemiologic association with aspirin or other salicylate use to treat the viral infection
- Possible association with aflatoxin and pesticides
- Pathology
- Liver: No inflammation; the striking finding is panlobular microvesicular hepatocyte infiltration on light microscopy and mitochondrial injury on electron microscopy
- Brain: No inflammation but cerebral edema and anoxic degeneration
- Pathogenesis: Not fully understood but mitochondrial dysfunction is clearly center stage

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Inborn errors of metabolism (e.g., carnitine deficiency, ornithine transcarbamylase deficiency)
- Salicylate or amiodarone intoxication
- Jamaican vomiting sickness
- Hepatic encephalopathy of any cause

Table E2 describes diseases that present a clinical or pathologic picture resembling Reye syndrome.

TABLE E2 Diseases That Present a Clinical or Pathologic Picture Resembling Reye Syndrome

Metabolic disease:
Organic aciduria
Disorders of oxidative phosphorylation
Urea cycle defects (carbamoyl phosphate synthetase, ornithine transcarbamylase)
Defects in fatty acid oxidation metabolism
Acyl-CoA dehydrogenase deficiencies
Systemic carnitine deficiency
Hepatic carnitine palmitoyltransferase deficiency
3-OH, 3-methylglutaryl-CoA lyase deficiency
Fructosemia
Central nervous system infections or intoxications (meningitis), encephalitis, toxic encephalopathy
Hemorrhagic shock with encephalopathy
Drug or toxin ingestion (salicylate, valproate)

CoA, Coenzyme A.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

WORKUP

According to the Centers for Disease Control and Prevention (CDC) case definition, the following conditions must be met for consideration as a Reye syndrome case:

- Acute noninflammatory encephalopathy documented by:
  1. Alteration in the level of consciousness and, if available, a record of cerebrospinal fluid containing ≤8 leukocytes per mm^3 or
  2. Histologic specimen demonstrating cerebral edema without perivascular or meningeal inflammation
- Hepatopathy documented either by a liver biopsy or autopsy considered to be diagnostic of Reye syndrome or by a threefold or greater rise in the levels of serum aspartate aminotransferase, serum alanine aminotransferase, or serum ammonia
- No more reasonable explanation for the cerebral and hepatic abnormalities

LABORATORY TESTS

- Elevated transaminase (alanine aminotransferase and aspartate aminotransferase)
- Elevated ammonia level
- Occasional elevation of creatine phosphokinase, lactate dehydrogenase, and bilirubin and prolongation of prothrombin time
- Occasional hypoglycemia (in patients <4 yr)
- Cerebrospinal fluid is normal or contains <8 white blood cells per milliliter
- Rarely a liver biopsy is indicated (in infants or in recurrent cases)

TREATMENT

- Supportive
- Mannitol, glycerol, or hyperventilation for cerebral edema if present
- Interferon-alfa (experimental)
- Prevention:
  1. Influenza vaccine
  2. Varicella vaccine
  3. Avoidance of aspirin in children, especially during influenza and varicella outbreaks

TABLE E1 Clinical Staging of Reye Syndrome

Grade	Symptoms at Time of Admission
I	Usually quiet, **lethargic** and sleepy, vomiting, laboratory evidence of liver dysfunction
II	Deep lethargy, **confusion,** delirium, combative, hyperventilation, hyperreflexic
III	Obtunded, **light coma,** seizures, decorticate rigidity, intact pupillary light reaction
IV	Seizures, deepening coma, **decerebrate rigidity,** loss of oculocephalic reflexes, fixed pupils
V	Coma, loss of deep tendon reflexes, respiratory arrest, fixed dilated pupils, **flaccidity/decerebrate** intermittent isoelectric electroencephalogram

From Behrman RE: *Nelson textbook of pediatrics,* ed 17, Philadelphia, 2005, Saunders.

AUTHOR: **Fred F. Ferri, MD**

BASIC INFORMATION

DEFINITION

Rhesus (Rh) incompatibility is a clinical scenario where discordance of the maternal and fetal Rh type leads to the development of maternal Rh sensitization and hemolytic disease of the neonate. Individuals whose RBCs express the Rh D antigen are classified as Rh-positive, whereas those whose RBCs do not express the antigen are classified as Rh-negative.

ICD-10CM CODES

036.0910	Maternal care for other rhesus isoimmunization, first trimester, not applicable or unspecified
T80.4	Rh incompatibility reaction
T80.4	Unspecified complication following infusion, transfusion, and therapeutic injection

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- The absence of the D antigen (Rh negative blood type) occurs in 15% to 17% of Caucasians, 4% to 8% of blacks, and <1% of the Native American and Asian populations. If the father's blood type is not known, the chance that an Rh– pregnant woman is bearing an Rh+ fetus is approximately 60%.
- Of those pregnancies complicated by Rh incompatibility, the risk of maternal isoimmunization to the D antigen is approximately 8% for each ABO-compatible pregnancy if no prophylaxis is given.
- Maternal-fetal ABO incompatibility is somewhat protective against Rh isoimmunization.

GENETICS: Five major loci determine Rh status: C, D, E, c, e. The presence of the D antigen results in an Rh+ individual, while its absence results in an Rh– individual. Of Rh+ fathers, 45% are homozygotes, and 55% are heterozygotes. For homozygous Rh+ fathers, the probability of an Rh+ offspring is 100%. The probability for heterozygotes is approximately 50%.

RISK FACTORS:

- RhD-negative woman
- Antepartum: Fetal-to-maternal transfusion
- Intrapartum: Fetal-to-maternal transfusion, spontaneous abortion, ectopic pregnancy, abruptio placentae, abdominal trauma, chorionic villus sampling, amniocentesis, percutaneous umbilical blood sampling (PUBS), external cephalic version, manual removal of the placenta, therapeutic abortion, autologous blood product administration
- Maternal history of hydrops or sensitization to RhD

ETIOLOGY

The initial response to D antigen exposure is production of immunoglobulin (Ig) M that does not cross the placenta. With a repeated exposure, IgG is produced. Hemolysis in the fetus results once maternal IgG is present in the fetal circulation by crossing the placenta. This may result in a spectrum of hemolytic disease in the newborn, resulting in antepartum or neonatal death or neurologic damage to the fetus because of hyperbilirubinemia and kernicterus.

DIAGNOSIS

LABORATORY TESTS

ABO and Rh blood type and an antibody screen as part of the initial prenatal profile.

- If antibody screen negative:
  1. Repeat antibody screen at 28 weeks of gestation.
  2. Obtain neonatal blood type after delivery.
  3. If Rh incompatibility is confirmed by the neonatal blood type, a Kleihauer-Betke/flow cytometry or rosette test should be performed to determine the amount of fetomaternal transfusion in the following high-risk circumstances: abruptio placentae, placenta previa, cesarean delivery, intrauterine manipulation, manual removal of the placenta.
- If anti-D antibody screen is positive:
  1. Maternal indirect Coombs test is needed to determine antibody titer.
  2. Determine paternal Rh status and zygosity.
  3. If father is heterozygous, PUBS or amniotic fluid is needed to determine fetal Rh status.

IMAGING STUDIES

- Ultrasound evaluation may show subcutaneous edema, ascites, pleural effusion, pericardial effusion, or hepatomegaly. It can diagnose hydrops fetalis, but it cannot predict it.
- Doppler ultrasound of middle cerebral artery can predict moderate to severe anemia.

TREATMENT

PREVENTION OF D-ISOIMMUNIZATION

- 50 mcg of D immunoglobulin: After spontaneous or induced abortion or ectopic pregnancy <13 weeks' gestation
- 300 mcg of D immunoglobulin (protects against 30 ml of fetal blood)
  1. After spontaneous or induced abortion >13 weeks' gestation, amniocentesis, chorionic villous sampling, PUBS, external cephalic version, or other intrauterine manipulation
  2. As antepartum prophylaxis at 28 weeks' gestation. Maternal anti-D prophylaxis does not cause hemolysis in the fetus or newborn
  3. At 40 weeks' gestation or at delivery if the neonate is D- or Du-positive
  4. If Kleihauer-Betke or rosette test confirms >30 ml of fetal red blood in maternal circulation, additional D immunoglobulin is indicated. Confirm adequacy of therapy by a maternal indirect Coombs test 48 to 72 hr after Rh immunoglobulin is given

MANAGEMENT OF D-ISOIMMUNIZED PREGNANCIES

- Serial amniocentesis for assessment of amount of fetal bilirubin in fluid (OD_{450}) after 25 weeks' gestation with interpretation of the Delta OD_{450} according to criteria established by Liley
- PUBS if ultrasonographic evidence of hydrops, rising zone II Delta OD_{450} values on amniocentesis, or maternal history of a severely affected child
- Intrauterine exchange transfusion if severe anemia is documented remote from term
- Initiation of steroids for lung maturation at 28 weeks in severely affected pregnancies with delivery at lung maturity
- Delivery as soon as lung maturation is achieved in mild to moderately affected pregnancies

Fig. 1 shows an algorithm for clinical management of a patient with red cell sensitization in the first affected pregnancy and Fig. 2 shows an algorithm for clinical management of a patient with red cell sensitization and a previously affected fetus or infant.

DISPOSITION

Survival of nonhydropic infants is 90%. Of infants with hydrops, 82% survive.

REFERRAL

Refer all Rh isoimmunized pregnancies to a tertiary care center before 18 to 20 weeks of gestation.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Bharti Rathore, MD**

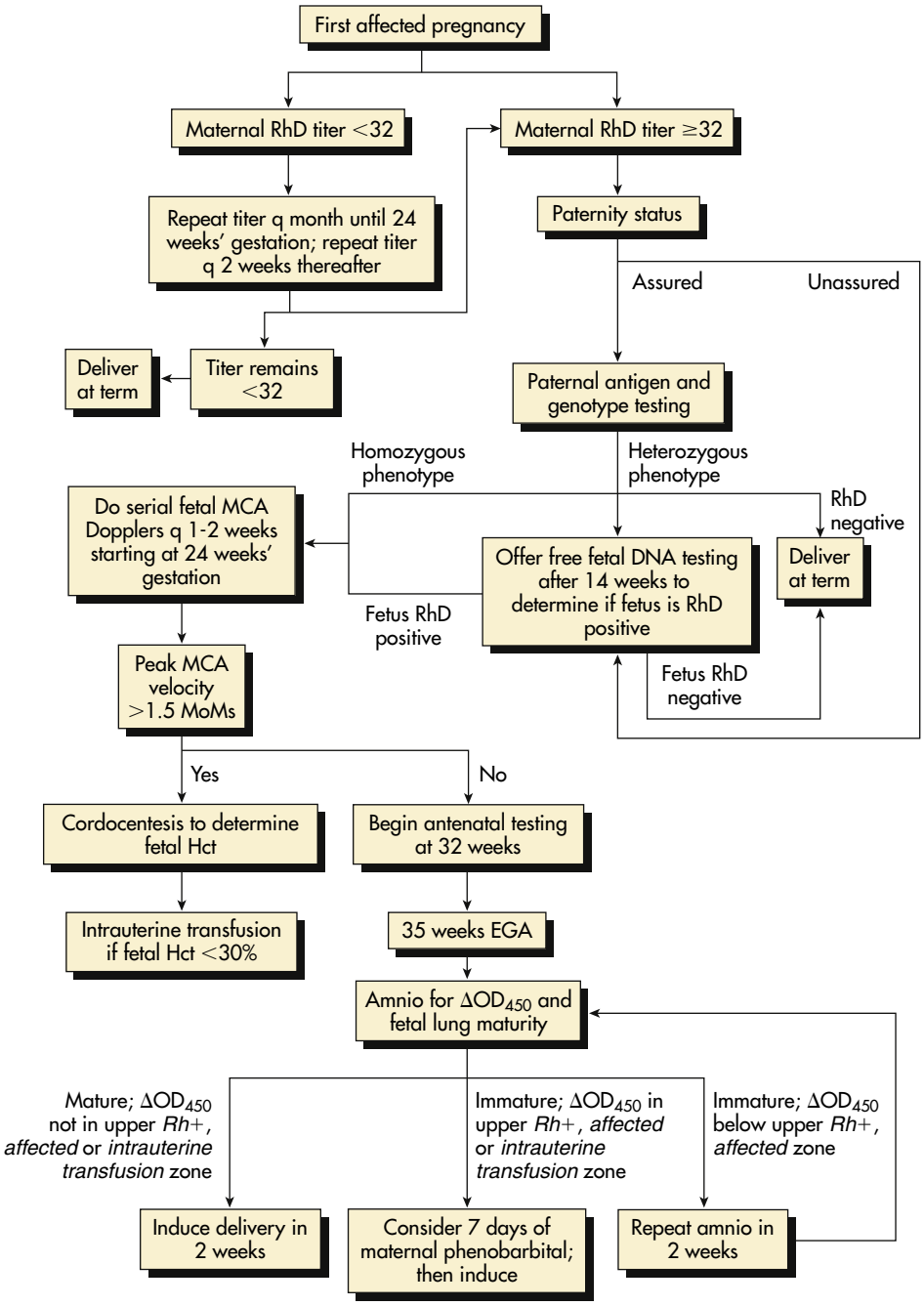

FIG. 1 Algorithm for clinical management of a patient with red cell sensitization in the first affected pregnancy. *ΔOD450,* Deviation of optical density of amniotic fluid by spectrophotometer at 450nm; *DNA,* deoxyribonucleic acid; *EGA,* estimated gestational age; *Hct,* hematocrit; *MCA,* middle cerebral artery; *MoMs,* multiples of the median; *Rh+,* Rhesus positive; *RhD,* Rhesus D antigen. (From Gabbe SG: *Obstetrics,* ed 6, Philadelphia, 2012, Saunders.)

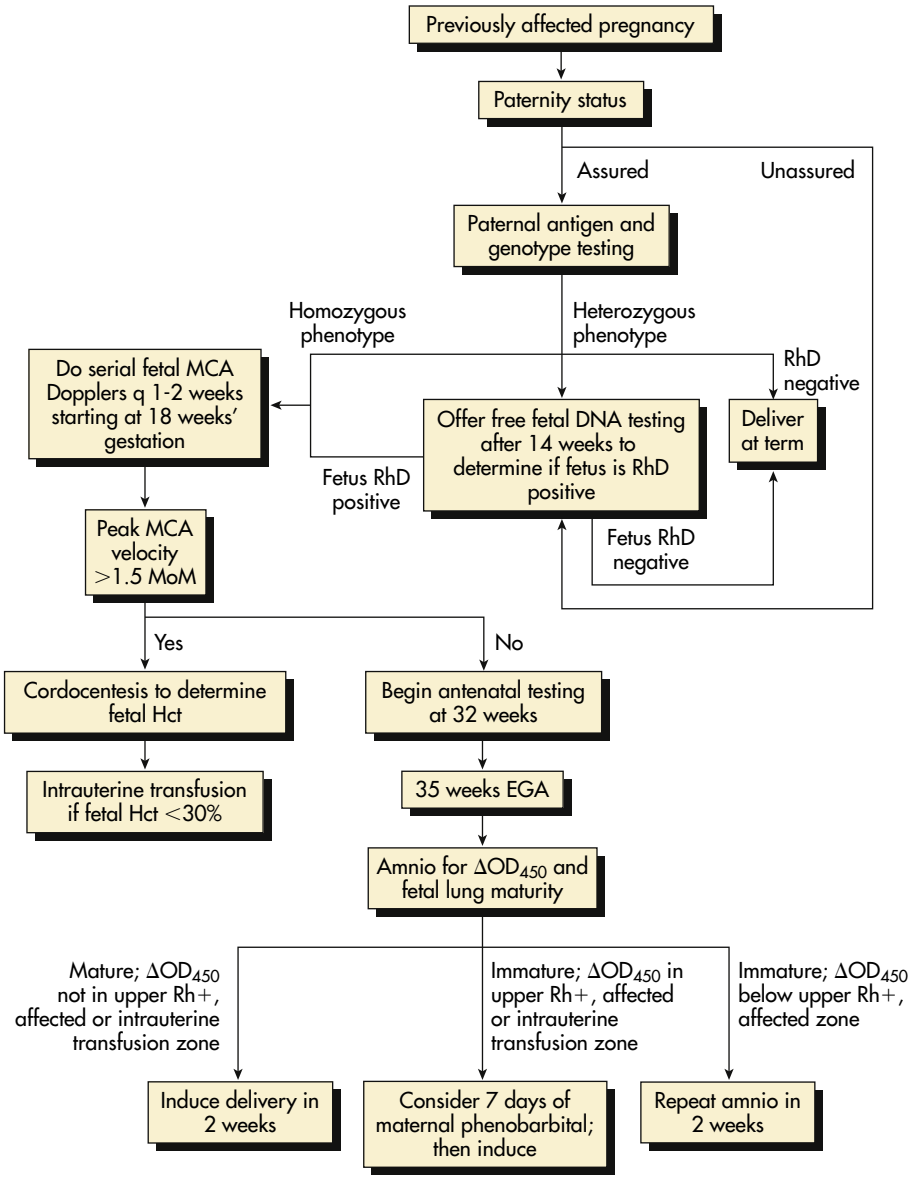

FIG. 2 Algorithm for clinical management of a patient with red cell sensitization and a previously affected fetus or infant. *OD450,* Deviation of optical density of amniotic fluid by spectrophotometer at 450nm; *DNA,* deoxyribonucleic acid; *EGA,* estimated gestational age; *Hct,* hematocrit; *MCA,* middle cerebral artery; *MoMs,* multiples of the median; *Rh+,* Rhesus positive; *RhD,* Rhesus D antigen. (From Gabbe SG: *Obstetrics,* 6 ed, Philadelphia, 2012, Saunders.)

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BASIC INFORMATION

DEFINITION

Rhabdomyolysis is a syndrome characterized by striated muscle lysis with resulting muscle damage and leakage of intracellular contents into the circulation. The presentation may range from asymptomatic elevation of creatine kinase (CK) to severe muscle injury with irreversible kidney failure. In general, five- to tenfold elevations of CK levels, muscle pain, and myoglobinuria in an appropriate clinical setting (see below) are sufficient criteria for the diagnosis of rhabdomyolysis. Acute renal injury occurs from a combination of factors, including volume depletion, tubular obstruction, direct heme-induced proximal tubular cell injury, and associated renal vasoconstriction.

ICD-10CM CODES

M62.82	Rhabdomyolysis (idiopathic)
T79.6	Traumatic ischemia of muscle
M62.89	Other specified disorders of muscle

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT AGE: Incidence of 1 in 10,000 in the U.S.

- Rare in children. Increased risk with advanced age, i.e., >80 yr
- Reported incidence of AKI with rhabdomyolysis is 10% to 55%
- 7% to 10% of cases of AKI are due to rhabdomyolysis

MORTALITY RATE: 5% to 8%. Prognosis is better in the absence of AKI.

ONSET: Evidence is limited regarding the onset of physical exertion-induced rhabdomyolysis. Exercise levels exceeding usual exercise tolerance levels for individuals are commonly causative. Extracellular volume depletion and vasoconstriction are common predisposing features. Patients with risk factors (e.g., metabolic myopathies, advanced age) develop symptoms associated with rhabdomyolysis within 2 to 6 hr after activity. Patients without such risk factors generally become symptomatic 12 to 36 hr after muscle injury. The presence of concurrent electrolyte abnormalities such as hypokalemia, hyponatremia, hypernatremia, hypomagnesemia, hypophosphatemia, and hypocalcemia increases the risk for rhabdomyolysis.

CK levels rise within 2 to 12 hr of the onset of muscle injury, peak generally by 24 to 72 hr, and decline within 3 to 5 days after cessation of muscle injury. Peak CK concentrations may predict development of renal injury. In patients with rhabdomyolysis secondary to malignant hyperthermia, CK concentrations peak approximately 14 hr after an acute episode.

Cholesterol-lowering therapy with HMG-CoA synthetase inhibitors (statins) in association with severe clinical rhabdomyolysis requiring hospitalization is reported in less than 0.1% of cases, although myalgia is a frequent complaint. Studies have demonstrated that glycolytic skeletal muscles have a low antioxidant defense, which limits their potential for metabolizing reactive oxygen species (ROS) leading to damage of muscle cells. The mechanism by which this occurs is multifactorial: uptake efficacy of transport proteins in hepatocytes, level of systemic circulation of statins, level of extrahepatic inhibition of mitochondrial respiration, bioavailability, and lipophilicity. Among the statins, pravastatin has been reported to have a lower risk of rhabdomyolysis, presumably due to its lower lipid solubility. The average duration of statin therapy before the onset of myopathy is 6 mo. Symptom resolution with normalization of serum CK concentrations occurs in days to weeks following drug discontinuation. The average time for onset of rhabdomyolysis after addition of fibrate to statin therapy is 32 days. There are very rare genetic variants associated with statin-induced myopathy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Classic triad: (1) Muscle pain, (2) weakness, and (3) dark urine from myoglobinuria
- Muscle tenderness is present only 50% of the time
- Muscle swelling
- Muscular rigidity
- Fever
- Altered consciousness
- In statin-induced rhabdomyolysis, fatigue (74%) is nearly as common as muscle pain (88%)
- Oliguria or anuria in the presence of kidney injury

ETIOLOGY

Causes can be divided into three categories:

- Traumatic or muscle compression:
  1. High-current electrical injury
  2. Crush injury and compartment syndrome
  3. Tourniquet and limb ischemia
  4. Reperfusion after revascularization procedures for ischemia
  5. Extensive surgical (spinal) dissection, bariatric surgery
- Nontraumatic exertional:
  1. Exercise: More than 10 genetically predisposing mutations are associated with exertional rhabdomyolysis
  2. Sickle cell trait, rarely; usually additional predisposing factors are involved (e.g., BMI >30 kg/m^2, tobacco use, statin use, antipsychotic use, high altitude)
  3. Heat stroke
  4. Metabolic myopathies
  5. Malignant hyperthermia and neuroleptic malignant syndrome
  6. Seizure activity
- Nontraumatic, nonexertional:
  1. Drug-induced (statins alone, combination of statins with fibrates, or erythromycin, simvastatin and amiodarone, amphetamines, haloperidol, levofloxacin, macrolide antibiotics)
  2. Alcoholism
  3. Hypothyroidism
  4. Infectious and inflammatory myositis

Table 1 summarizes the various causes of rhabdomyolysis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

"Creatine Kinase Elevation" in Section IV describes a clinical algorithm for the evaluation of CK elevation.

LABORATORY TESTS

- Creatine kinase: Usually CK is 5 to 10 times the upper limit of normal and typically peaks 24 to 72 hours after the initial insult (Fig. 1). Levels >15,000 IU/L are more likely to be associated with renal injury. However, in patients with concomitant risk factors such as hypokalemia or volume depletion, CK levels as low as 5000 U/L have been associated with AKI.
- Myoglobin: Excreted in urine with visible changes in urine ("port wine") at levels >100 to 300 mg/dl. Myoglobinuria can be suspected by a positive urine dipstick test for blood and minimal or no microhematuria. Due to its more rapid hepatic metabolism, myoglobin lacks sensitivity in detecting rhabdomyolysis. Therefore, serum and/or urine myoglobin measurement is not recommended to establish diagnosis. Blood urea nitrogen and creatinine help monitor the severity of AKI.
- Potassium, calcium, phosphorus, and uric levels are released from damaged muscle, and levels should be monitored.
- Calcium: Hypocalcemia from influx and deposition of calcium phosphate in damaged muscle tissue. Hypercalcemia may follow

TABLE 1 Causes of Rhabdomyolysis

Muscle injury/ischemia	Trauma, pressure necrosis, electric shock, burns, acute vascular disease
Myofiber exhaustion	Seizures, excessive exercise, heat exhaustion
Toxins	Alcohol, cocaine, heroin, amphetamines, ecstasy, phencyclidine, snakebite
Drugs	Statins, fibrates, zidovudine, neuroleptic malignant syndrome, azathioprine, theophylline, lithium, diuretics, colchicine
Electrolyte disorders	Hypophosphatemia, hypokalemia, excess water shifts (hyperosmolality)
Infections	Viral (influenza, HIV, coxsackievirus, Epstein-Barr virus), bacterial *(Legionella, Francisella, Streptococcus pneumoniae, Salmonella, Staphylococcus aureus)*
Familial	McArdle disease, carnitine palmitoyl transferase deficiency, malignant hyperthermia
Other	Hypothyroidism, polymyositis, dermatomyositis

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

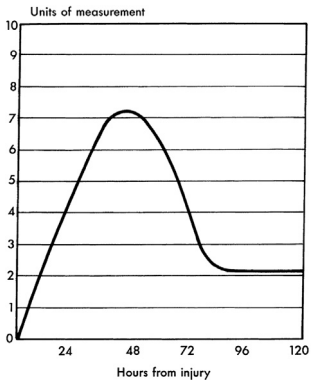

FIG. 1 Typical creatine kinase elimination curve.

resolution of rhabdomyolysis from subsequent release of muscle-sequestered calcium back into the circulation and increased gastrointestinal calcium absorption from enhanced vitamin D production.
- Anion gap metabolic acidosis may occur from release of organic acids and phosphates from damaged muscle.
- Urinalysis: Myoglobin is detected as blood on dipstick, but erythrocytes are absent on microscopy. Presence of pigmented tubular casts establishes acute tubular necrosis.
- Unlike most other causes of acute tubular necrosis, rhabdomyolysis may result in a fractional excretion of sodium (FENa) of <1% due to renal vasoconstriction.
- Box 1 summarizes laboratory abnormalities observed with rhabdomyolysis.

BOX 1 Laboratory Abnormalities Observed with Rhabdomyolysis

Potassium
Elevated
Risk for acute kidney injury

Bicarbonate
Decreased (20 mEq/L)
Metabolic acidosis

Uric Acid
Elevated (>7 mg/dl)
Marker of acute renal failure

Sodium
Usually normal
Can decrease with mannitol therapy
Use serum osmolality values as a guide

Phosphate
Elevated
Risk for precipitation of calcium phosphate
May need phosphate binders if phosphate >7 mg/dl

Creatine Kinase
Elevated
Associated with creatine kinase level of 15 to 75,000

Blood Urea Nitrogen
Elevated (>20 mg/dl)

Creatinine
Elevated

Calcium
Initially low
Rebound phase may demonstrate hypercalcemia

Liver Function Tests
Occasionally elevated
Serum aspartate transaminase, lactate dehydrogenase, aldolase, muscle enzyme levels elevated

Troponin
Normal
Suspect myocardial damage as a cause (or effect) if elevated
7% false-positive rate for troponin I

Anion Gap
Sometimes elevated
May predict acute kidney injury

Prothrombin Time, Partial Thromboplastin Time, D-Dimer
Disseminated intravascular coagulation in up to 30% of severe cases
Associated with greater mortality

From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

Rx TREATMENT

ACUTE GENERAL Rx

- Identify precipitating factor(s) and discontinuation of drugs or toxins that might be a contributing factor.
- Early, aggressive, high-volume IV fluid replacement with normal saline. Extracellular fluid volume loading and diuresis reduce the risk for renal damage by elimination of urate and phosphate that can precipitate in the kidneys. Fig. 2 describes a treatment algorithm for rhabdomyolysis.
- Fasciotomy is indicated in compartment syndrome for preservation of muscle and nerve function.
- Initiate volume repletion with normal saline at a rate of 200 to 1000 ml/hour depending on the clinical circumstances and severity of muscle damage. Titrate to maintain a urine output of at least 200 ml/hr. Consider treatment with mannitol (up to 200 g/day with cumulative dose up to 800 g) to GFR, diuresis, and scavenge free radicals. Typically, a 20% mannitol infusion at a dose of 0.5 g/kg is given over a 15-min period followed by an infusion at 0.1 g/kg/hour. Discontinue mannitol and volume resuscitation if diuresis (>20 ml/hr) is not established. Maintain volume repletion until myoglobinuria stops (negative urine dipstick blood test) or plasma CK levels decrease to <5000 U/L.
- Correct hypocalcemia if symptomatic or hyperkalemia is severe enough to produce electrocardiographic changes.
- Treatment of all electrolyte imbalances.
- Urine alkalinization: Maintain urine pH at 6 to 7 pH units and serum pH at ~7.50. This recommendation is controversial but appears helpful in research models when administered early in the course of rhabdomyolysis. Urine alkalization may prevent renal tubular myoglobin precipitation and reduce lipid peroxidation, reactive oxygen species formation, and myoglobin-induced vasoconstriction. However, early volume resuscitation and expansion is the most important treatment.
- Initiation of renal replacement therapy is guided by the severity of renal injury and electrolyte imbalances. The use of continuous renal replacement therapy or high-flux membranes to enhance myoglobin clearance has not been validated.

DISPOSITION

Early diagnosis and management are required to avoid AKI that occurs in 30% of cases. Rhabdomyolysis accounts for 7% to 10% of all cases of AKI in the U.S.

REFERRAL

Renal consultation and surgical consultation if compartment syndrome develops

PEARLS & CONSIDERATIONS

COMMENTS

- Statin-induced rhabdomyolysis occurs 12 times more frequently when statins are combined with fibrates than when used alone.
- Short-term, high-dose glucocorticoid steroid administration (500-1000 mg methylprednisolone) has been used for treatment of alcohol-induced rhabdomyolysis, refractory to volume repletion. This treatment may be efficacious in cases of severe rhabdomyolysis by retarding secondary leukocyte inflammatory muscle injury.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Rhabdomyolysis (Patient Information)
Statin-Induced Muscle Syndrome (Related Key Topic)

AUTHORS: **Jayanth Lakshmikanth, MD,** and **Hesham Shaban, MD**

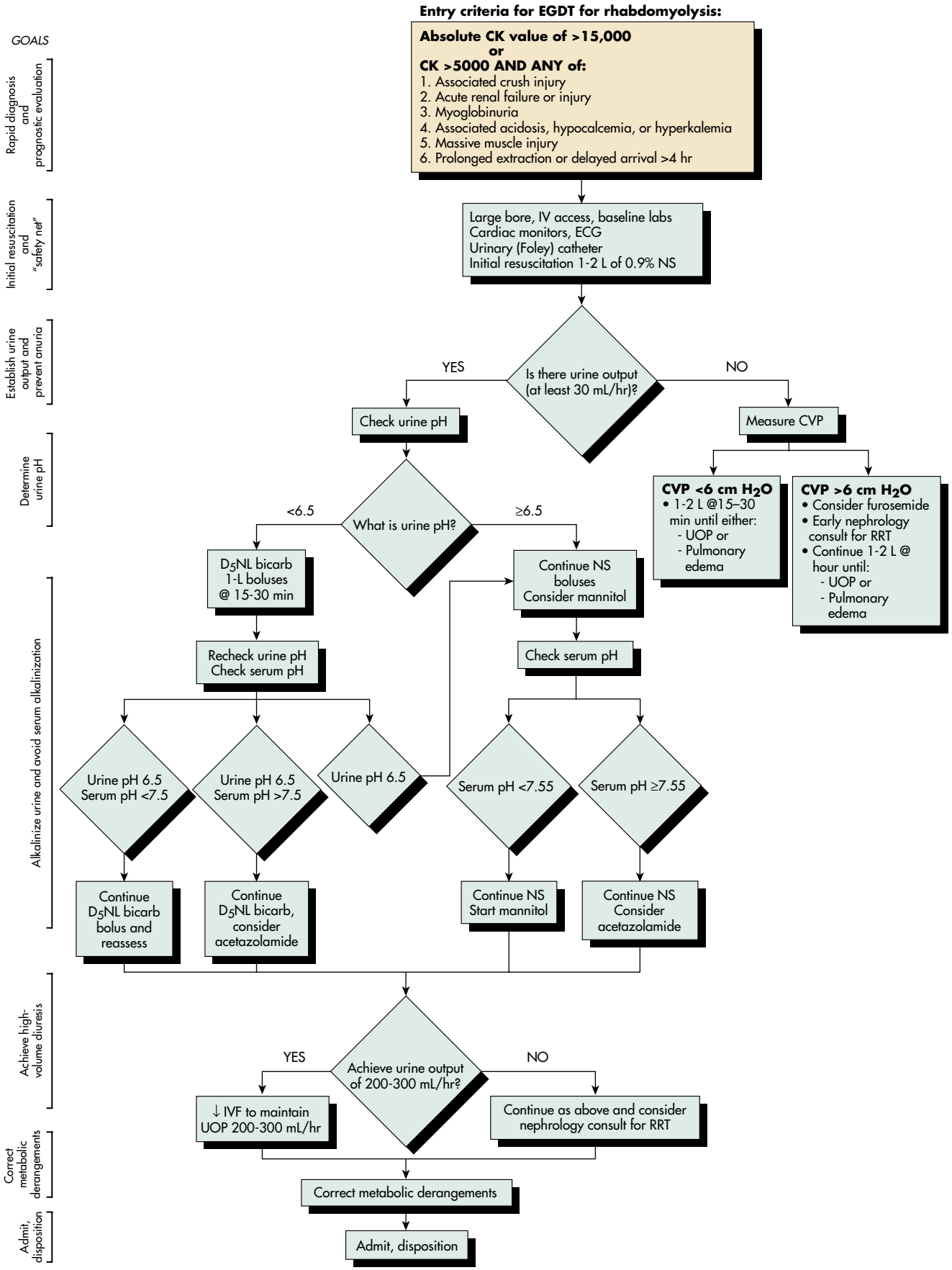

FIG. 2 Early goal-directed therapy for rhabdomyolysis. *CK,* Creatine kinase; *CVP,* central venous pressure; *D5NL bicarb,* 5% dextrose in normal sodium bicarbonate solution; *EGDT,* early goal-directed therapy; *IV,* intravenous; *IVF,* intravenous fluid; *NS,* normal saline; *RRT,* renal replacement therapy; *UOP,* urinary output. (From Adams JG et al: *Emergency medicine, clinical essentials,* 2nd ed, Philadelphia, Elsevier 2013.)

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BASIC INFORMATION

DEFINITION

Rheumatic fever is a multisystem inflammatory disease that occurs in the genetically susceptible host 2 to 4 wk after a pharyngeal infection with group A streptococci.

SYNONYMS

ARF
Acute rheumatic fever
Rheumatic carditis

ICD-10CM CODES

I00	Rheumatic fever without heart involvement
I01	Rheumatic fever with heart involvement
I01.0	Acute rheumatic pericarditis
I01.1	Acute rheumatic endocarditis
I01.2	Acute rheumatic myocarditis
I01.8	Other acute rheumatic heart disease
I01.9	Acute rheumatic heart disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Has declined in the last 4 to 6 decades

- 0.1% to 3% in patients with untreated streptococcal pharyngitis
- Higher incidence of streptococcal pharyngitis with:
  1. Crowding
  2. Poverty
  3. Young age

INCIDENCE (WORLD): ARF remains one of the most important causes of cardiovascular morbidity and mortality among socially and economically disadvantaged people around the world.

PREDOMINANT AGE (IN U.S.):

- Age 5 to 15 yr for first attack, rare before the age of 3
- Possible relapses later

PEAK INCIDENCE (IN U.S.): School-age children

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute streptococcal pharyngitis, which may be subclinical and not reported by the patient.
- After latent period of 2 to 4 wk (average, 19 days), acute rheumatic attack.
- Patient is febrile, with a migratory polyarthritis of knees, ankles, wrists, elbows; typically severe for 1 wk, remits by 3 to 4 wk.
- Carditis:
  1. New heart murmur:
     a. Mitral regurgitation
     b. Aortic insufficiency
     c. Diastolic mitral murmur
  2. Cardiomegaly
  3. CHF
  4. Pericardial friction rub or effusion
- Rarely, pancarditis is severe and fatal.
- Subcutaneous nodules (Fig. E1) can be palpated over extensor tendon surfaces or bony prominences, such as the skull.
- Chorea (Sydenham chorea) is characterized by rapid involuntary movements affecting all muscles:
  1. Muscular weakness
  2. Emotional lability
  3. Rarely seen after adolescence and almost never in adult males
- Erythema marginatum (Fig. E2):
  1. Evanescent, pink, well-demarcated spreading to trunk and proximal extremities
  2. Not specific
- Arthralgias (joint pain without swelling).
- Abdominal pain.

ETIOLOGY

- Fig. E3 illustrates the pathophysiology of rheumatic fever. • Both initial attacks and recurrences can be completely prevented by prompt treatment of streptococcal pharyngitis with penicillin.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rheumatoid arthritis
- Juvenile rheumatoid arthritis (Still disease)
- Bacterial endocarditis
- Systemic lupus
- Viral infections
- Poststreptococcal reactive arthritis: Severe arthritis but no carditis

WORKUP

- "Jones Criteria for Guidance in the Diagnosis of Rheumatic Fever" updated in 2015 to take into consideration low-risk populations vs. moderate- and high-risk populations
- Low-risk populations: ARF incidence less than or equal to 1 per 100,000 school-aged children, or all-age rheumatic heart disease prevalence of less than or equal to 1 per 1000 population per yr
- Diagnosis, initial ARF: Two major manifestations or one major plus two minor manifestations with evidence of preceding group A *Streptococcus* (GAS) infection
- Diagnosis, recurrent ARF: Two major or one major and two minor or three minor with evidence of preceding GAS infection
- Major criteria, low-risk populations and percentage of patients with each:
  1. Carditis: Clinical and or subclinical as determined by echocardiographic valvulitis: 50% to 70%
  2. Arthritis: Polyarthritis only: 35% to 66%
  3. CNS involvement (e.g., chorea): 10% to 30%
  4. Erythema marginatum: <6% (pink, nonpruritic rash of trunk and possibly limbs)
  5. Subcutaneous nodules: 0% to 10% (firm, painless a few millimeters to 2 cm in size)
- Minor criteria, low-risk populations:
  1. Fever: Greater than or equal to 38.5° C (101.3° F)
  2. Polyarthralgia
  3. Erythrocyte sedimentation rate (ESR) >60 mm in first hour and/or C-reactive protein greater than or equal to 3.0 mg/dl
  4. Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)
- Major criteria, moderate- and high-risk populations:
  1. Carditis, clinical and/or subclinical
  2. Arthritis:
     a. Monoarthritis or polyarthritis
     b. Polyarthralgia
  3. Chorea
  4. Erythema marginatum
  5. Subcutaneous nodules
- Minor criteria:
  1. Monoarthralgia
  2. Fever greater than or equal to 38.5° C (101.3° F)
  3. ESR >30 mm/hr and/or C-reactive protein >3.0 mg/dl
  4. Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion). For moderate- to high-risk patients (ARF> 2 per 100,00 school-aged children per yr or all-age rheumatic heart disease prevalence >1 per 1000 population),

FIG. E1 Subcutaneous nodules of rheumatic fever over the bony prominences of the elbow. (From Beerman LB et al: Cardiology. In Zitelli BJ et al [eds]: *Atlas of pediatric physical diagnosis,* ed 6, Philadelphia, 2012, Saunders.)

Jones criteria may underdiagnose cases, so criteria modified as follows:

a. Criterion of arthritis includes monoarthritis or polyarthralgia in addition to polyarthritis.
b. Minor criteria of joint involvement is monoarthralgia vs. polyarthralgia.
c. A lower cutoff for fever is used: ≥100.4° F (38° C).
d. A lower cutoff for sed rate is used: ≥30 mm/hr instead of ≥60 mm/hr. CRP cutoff is unchanged.

LABORATORY TESTS

- Throat cultures are usually negative at presentation of clinical manifestations of rheumatic fever.
- Streptococcal antibody tests are more useful in establishing the diagnosis.
  1. Peak at the beginning of the attack.
  2. Can document a recent streptococcal infection.
- ASO (antistreptolysin O) titers peak:
  1. 4 to 5 wk after the actual streptococcal throat infection
  2. Which coincides during the second or third wk of rheumatic fever illness
- Anti-DNase B (Streptozyme) can be detected for 6 to 9 mo following infection and can be tested if ASO titer negative.
- Other antistreptococcal antibody tests include streptokinase and antihyaluronidase.
- High-titer streptococcal antibodies:
  1. Are supportive of diagnosis, but not proof
  2. Should be interpreted in the context of clinical criteria

IMAGING STUDIES

- Chest x-ray to assess heart size.
- Echocardiogram:
  1. Echocardiography with Doppler should be performed in all cases of confirmed or suspected ARF to evaluate evidence of mitral or aortic valve regurgitation. Specific criteria exist for Doppler findings for the pathological mitral regurgitation and pathological aortic regurgitation of ARF.
  2. To rule out pericardial effusion.

FIG E2 Erythema marginatum in acute rheumatic fever. The pen mark shows the location of the rash approximately 60 min previously. (From Cohen J, Powderly WG: *Infectious diseases,* ed 2, St Louis, 2004, Mosby.)

Rx TREATMENT

ACUTE GENERAL Rx

- Course of penicillin to eradicate throat carriage of group A streptococci
- Arthralgia or arthritis without carditis: Aspirin 90 to 100 mg/kg/day for 2 wk, followed by 60 to 70 mg/kg/day for the subsequent 4 to 6 wk if needed

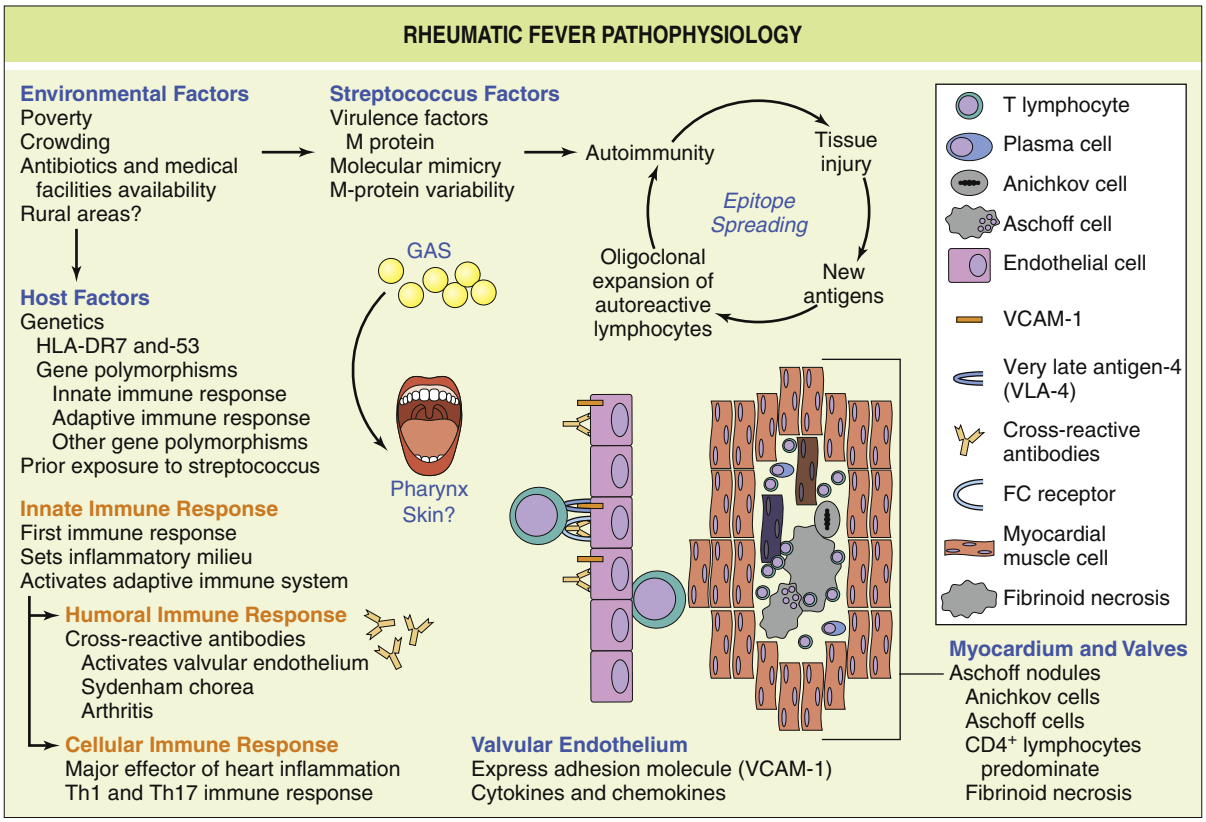

FIG. E3 Rheumatic fever pathophysiology. *GAS,* Group A β-hemolytic *Streptococcus*; *VCAM-1,* vascular adhesion molecule-1. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

- Carditis and heart failure:
  1. Prednisone 40 to 60 mg/day
  2. IV corticosteroids, such as methylprednisolone, 10 to 40 mg/day for severe carditis

CHRONIC Rx

Secondary prevention (prevention of recurrences):

- Monthly treatment with benzathine penicillin 1.2 million U IM or penicillin V: 250 mg orally bid
- Erythromycin in patients with penicillin allergy: 250 mg bid or sulfadiazine orally at 0.5 g once a day for patients <27 kg and 1.0 g daily for patients >27 kg

Duration of prophylaxis (American Heart Association recommendations):

- Rheumatic fever without carditis: 5 yr or until 21 yr of age, whichever is longer
- Rheumatic fever with carditis but without residual heart disease (no clinical or echocardiographic evidence of persistent valvular disease): 10 yr or until 21 yr of age, whichever is longer
- Rheumatic fever with carditis and residual heart disease (clinical or echocardiographic evidence of persistent valvular disease): 10 yr or until 40 yr of age, whichever is longer, sometimes lifelong prophylaxis

DISPOSITION

- Damage of heart valves because of fibrosis:
  1. Late sequela of recurrent attacks
  2. Frequent cause of valvular heart disease in developing countries
- May progress to heart failure

REFERRAL

To cardiologist for management of severe carditis

RELATED CONTENT

Rheumatic Fever (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Gewitz MH et al: Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association, *Circulation* 131:1806-1818, 2015.

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Rhodes KL et al: Acute rheumatic fever: revised diagnostic criteria, *Pediatr Emerg Care* 34:436-440, 2018.

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BASIC INFORMATION

DEFINITION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory polyarthritis which affects peripheral joints, especially the small joints of the hands and feet. It is a chronic, progressive disease in which untreated inflammation may lead to cartilage and bone erosions and joint destruction resulting in functional impairment.

SYNONYM

RA

ICD-10CM CODES

M06.9	Rheumatoid arthritis, unspecified
M05.10	Rheumatoid lung disease with rheumatoid arthritis of unspecified site
M05.20	Rheumatoid vasculitis with rheumatoid arthritis of unspecified site
M05.30	Rheumatoid heart disease with rheumatoid arthritis of unspecified site
M05.39	Rheumatoid heart disease with rheumatoid arthritis of multiple sites
M05.40	Rheumatoid myopathy with rheumatoid arthritis of unspecified site
M05.49	Rheumatoid myopathy with rheumatoid arthritis of multiple sites
M05.50	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified site
M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis of multiple sites
M05.60	Rheumatoid arthritis of unspecified site with involvement of other organs and systems
M05.69	Rheumatoid arthritis of multiple sites with involvement of other organs and systems
M05.70	Rheumatoid arthritis with rheumatoid factor of unspecified site without organ or systems involvement
M05.79	Rheumatoid arthritis with rheumatoid factor of multiple sites without organ or systems involvement
M05.80	Other rheumatoid arthritis with rheumatoid factor of unspecified site

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Annual incidence in northern Europe and the U.S. 0.15 to 0.60 per 1000

TYPICAL AGE AT DIAGNOSIS: Usually between age 30 and 60. Steadily increases with age until the mid-70s

PREVALENCE: 0.5% to 1.0% of the worldwide population, with different rates in different ethnic groups

PREDOMINANT SEX: Females > males (2 to 3:1)

RISK FACTORS:

- Female gender, age, tobacco use, silica exposure, and obesity, family history. Smoking has an additive detrimental effect in RA patients (two-fold excess mortality risk).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Initial presentation:

- Pain, swelling, warmth in one or more peripheral joints, frequently with symmetric small joint involvement, often associated with >1 hour of morning stiffness and constitutional symptoms such as fatigue, malaise, low-grade fevers, and weight loss occurring over a period of weeks to months. A subset of patients can also present with acute-onset polyarthritis instead of insidious symptoms.
- Most common joints involved include metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints (Fig. E1), and metatarsophalangeal (MTP) joints (Fig. E2), as well as wrists.
- Other affected joints involved include elbows, shoulders, hips, knees, and ankles.
- Distal interphalangeal (DIP) joints are spared.
- Sacroiliac and vertebral joints are spared, except for the C1 and C2 articulations.

Chronic longstanding disease:

- "Swan-neck" (DIP flexion and PIP hyperextension) (Fig. E3), "boutonniere" (DIP hyperextension and PIP flexion), and "Z-thumb" (MCP flexion and IP hyperextension) deformities (Fig. 4), ulnar deviation and subluxation of the MCP joints as well as radial deviation of the wrists.
- C1-C2 (atlantoaxial) inflammation can lead to odontoid erosion and transverse ligament laxity/rupture, resulting in atlantoaxial subluxation and cord compression.
- Joint damage of wrists, elbows, shoulders, hips, and knees can lead to severe secondary osteoarthritis, necessitating joint surgery and/or replacement.

Extraarticular manifestations:

- Secondary Sjögren syndrome (~35%): Immune-mediated inflammation of lacrimal and salivary glands, resulting in dry mouth (xerostomia) and eyes (keratoconjunctivitis sicca).
- Rheumatoid nodules (25%): Nontender, firm nodules on extensor surfaces and pressure points, usually in rheumatoid factor positive (RF+) disease. Histopathology demonstrates palisading histiocytes surrounding a central area of fibrinoid necrosis.
- Felty syndrome: RA with splenomegaly and leukopenia. Most patients are positive for HLA-DR4 and RF.

Pulmonary disease:

- Pleural disease (exudative effusions, pleuritis)
- Interstitial lung disease (up to 10% clinically significant)
- Bronchiolitis obliterans
- Cryptogenic organizing pneumonia
- Pulmonary nodules: A combination of RA and pneumoconiosis is called Caplan syndrome

Neuromuscular:

- Entrapment neuropathy (carpal tunnel, tarsal tunnel, cubital tunnel most commonly involved)
- Mononeuritis multiplex
- Peripheral neuropathy
- Cervical myelopathy and cord compression in atlantoaxial subluxation
- Pachymeningitis (rare)

Vasculitis.

Cardiac disease:

- Pericarditis (most common)
- Myocarditis
- Valvular nodules
- There is an increased risk of cardiovascular disease compared to the general population, probably due to accelerated atherosclerosis from systemic inflammation

Ocular disease:

- Keratoconjunctivitis sicca (dry eye, without dry mouth) (10%)
- Episcleritis, scleritis, scleral thinning, scleromalacia perforans, ulcerative keratitis

Amyloidosis: Occurs in longstanding, poorly controlled RA. Usually presents as nephrotic syndrome. Can affect heart, kidney, liver, spleen, intestines, and skin.

Osteoporosis

ETIOLOGY

The exact cause of RA remains unknown despite extensive research. It is likely that a combina-

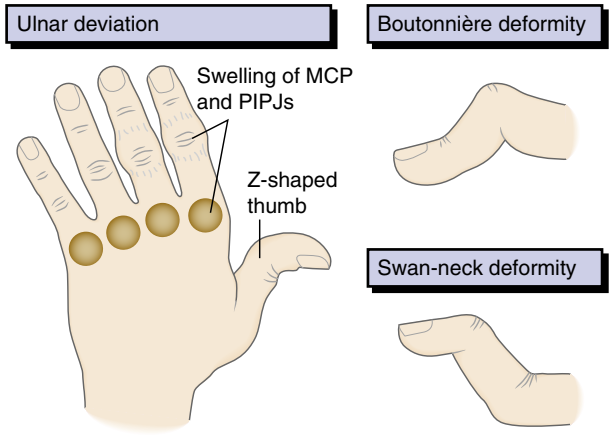

FIG. 4 Characteristic hand deformities in rheumatoid arthritis. *MCP,* Metacarpophalanges; *PIPJs,* proximal interphalangeal joints. (From Ballinger A: *Kumar & Clark's essentials of clinical medicine,* ed 6, Edinburgh, 2012, Saunders.)

tion of genetic, hormonal, and environmental factors lead to aberrant immune activation and inflammatory response in the joint. A common genetic background plays a role in susceptibility to disease, as twins and first-degree relatives of RA patients are at increased risk of developing the disease compared to the general population. Patients with HLA-DR4, DR1, and DR14 alleles have increased susceptibility to RA; in particular, one amino acid sequence in the DR β chain, known as the shared epitope, is overrepresented in these patients. Other identified genetic associations include polymorphisms in *PTPN22, PADI4*, *CTLA4*, *TRAF1-C5*, *STAT4*, *TNFAIP3*. Epigenetic factors are also likely to be involved. Multiple environmental factors have also been implicated as possible etiologic factors, including cigarette smoking, silica exposure, and low socioeconomic class. Infectious agents such as *P. gingivalis*, Epstein-Barr virus, and parvovirus B19 have also been reported as possible triggers.

Stages of disease development presumably include:

- Initiation of the innate immune response through toll-like receptor (TLR) activation by a stimulating signal.
- Perpetuation of inflammatory response through activation of the adaptive immune system. There is migration of inflammatory cells (autoreactive B and T cells, monocytes) into the joint space, activation of macrophage-like and fibroblast-like synoviocytes, and development of a "synovial pannus," a thickened synovial membrane.
- The pannus releases pro-inflammatory cytokines (TNF-α, IL-1, IL-6, IL-15, IL-17, IL-18) as well as proteases, which erode cartilage and bone. Bone erosions are caused mainly by osteoclasts, which express the receptor activator of NF-κB (RANK). TNF-α, IL-1, IL-6, and IL-17 promote the expression of RANK ligand (RANKL) on T cells and fibroblast-like synoviocytes, thus creating a positive feedback loop. IL-6 and TNF-α act synergistically to increase vascular endothelial growth factor levels, which in turn stimulate angiogenesis, thereby maintaining pannus formation. B-cell differentiation is also promoted by IL-6, leading to the production of autoantibodies.
- Many of the new "biologic" disease-modifying antirheumatic drugs (DMARDs) are engineered to target these cytokines (see "Treatment" section).

Dx DIAGNOSIS

The American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) developed new classification criteria for RA in 2010. These are based on a point system where patients with score ≥6/10 are considered to have "definite RA." Four variables constitute the new criteria:

- The number and size of involved joints (0 to 5 points, with higher scores for a larger number of small joints affected).
- Levels of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibody (0 to 3 points, with a higher score for a high-titer positive RF or anti-CCP).
- Elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) (1 point).
- Symptom duration ≥6 wk (1 point).

TABLE 1 Factors Useful for Differentiating Early Rheumatoid Arthritis from Osteoarthritis

	Rheumatoid Arthritis	Osteoarthritis
Age at onset	Childhood and adults, peak incidence in 50s	Increases with age
Predisposing factors	Susceptibility epitopes (HLA-DR4, HLA-DR1, HLA-DR14)	Trauma
	Polymorphisms, epigenetic factors, infectious agents	Congenital abnormalities (e.g., shallow acetabulum)
	Smoking, silica exposure	
Early symptoms	Morning stiffness, pain, swelling	Pain increases through the day and with use
Joints involved	Wrists, MCP, PIP, and MTP joints; DIP joints are almost never involved.	DIP joints (Heberden nodes), PIP joints (Bouchard nodes), carpometacarpal joints, weight-bearing joints (hips, knees)
Physical findings	Soft tissue swelling, warmth	Bony osteophytes, minimal soft tissue swelling early on, crepitus
Radiologic findings	Periarticular osteopenia, marginal erosions	Subchondral sclerosis, osteophytes
Laboratory findings	Increased CRP, RF, and anti-CCP antibody, anemia, thrombocytosis	Normal

anti-CCP, Anticitrullinated protein; *CRP-RF,* C-reactive protein-rheumatoid factor; *DIP,* distal interphalangeal joint; *MCP,* metacarpophalangeal joint; *MTP,* metatarsophalangeal joint; *PIP,* proximal interphalangeal joint.

DIFFERENTIAL DIAGNOSIS

- Infectious causes: Parvovirus B19, hepatitis B, hepatitis C, poststreptococcal reactive arthritis, acute rheumatic fever
- Connective tissue diseases: Systemic lupus erythematosus, scleroderma, mixed connective tissue disease, Sjögren syndrome
- Seronegative spondyloarthropathies
- Calcium pyrophosphate deposition (CPPD or "pseudo-RA")
- Polyarticular gout
- Polymyalgia rheumatica
- Remitting seronegative symmetric synovitis with pitting edema (RS3PE) can resemble seronegative RA in elderly patients
- Hemochromatosis
- Paraneoplastic syndromes
- Osteoarthritis, a degenerative arthritis that lacks prolonged morning stiffness and that usually lacks synovitis, should not be confused with RA (see Table 1)

LABORATORY TESTS

- RF (sensitivity ~60%; specificity ~80%). False positives are seen with hepatitis C, subacute bacterial endocarditis, primary biliary cirrhosis, sarcoidosis, malignancy, Sjögren syndrome, SLE, and increasing age.
- Anti-CCP antibodies. Sensitivity is similar to RF, but it is more specific for RA than RF (up to 95% to 98%).
- The presence of either RF or anti-CCP ("seropositive RA") is associated with more severe disease, more extraarticular manifestations, and worse prognosis.
- Elevated ESR and/or CRP. Will decline with treatment; thus can be used to monitor disease activity along with physical examination and clinical presentation.
- CBC with differential. Possible anemia of chronic disease (through production of the iron-regulating hormone, hepcidin) and thrombocytosis.
- Hypoalbuminemia and hypergammaglobulinemia.
- ANA is present is 20% to 30% of patients. However, complement will usually be normal or increased, in contrast to patients with systemic lupus erythematosus. Many patients will have secondary Sjögren syndrome (positive ANA with negative SSA and SSB).
- Inflammatory synovial fluid with >2000 PMNs. Of note, patients with RA have an increased risk of developing septic arthritis. Hence, synovial fluid with white blood cells >50,000 cells/mm^3 is concerning for an infectious process and must always be ruled out.

IMAGING STUDIES

Plain radiography (Table E2):

- Early changes include soft tissue swelling, symmetrical joint space narrowing, and periarticular osteopenia.
- Later changes include periarticular erosions and deformities. This reflects cartilage and bone destruction secondary to pannus formation (Fig. E5).
- Radiographs of hands and feet should be obtained at disease onset and repeated to monitor disease progression and to ensure that adequate treatment is achieved.

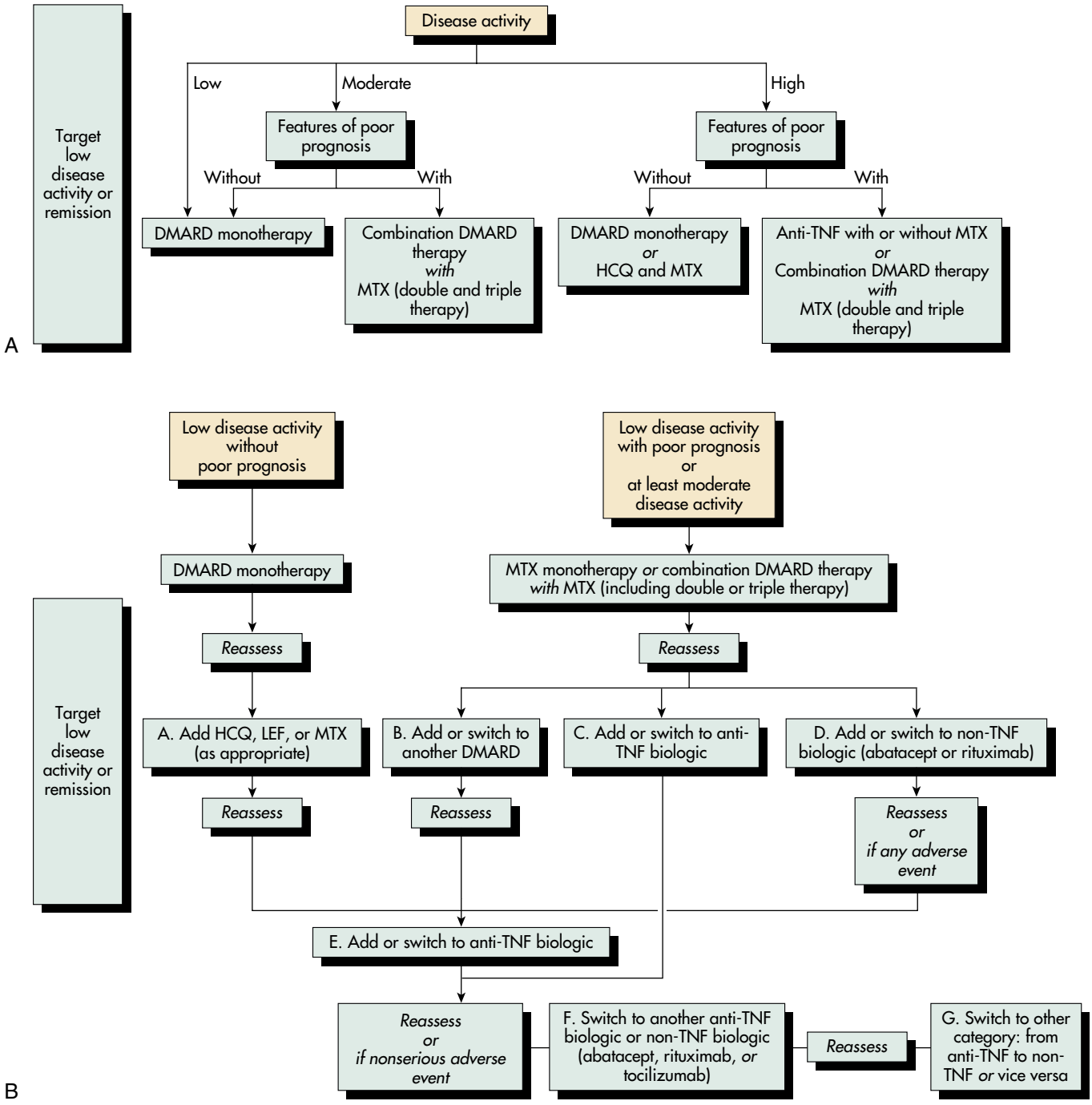

FIG. 6 American College of Rheumatology recommendations for treatment of rheumatoid arthritis. **A,** Early disease. **B,** Established disease. *DMARD,* Disease-modifying antirheumatic drug; *HCQ,* hydroxychloroquine; *LEF,* leflunomide; *MTX,* methotrexate; *TNF,* tumor necrosis factor. (From Firestein GS et al [eds]: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

MRI and musculoskeletal US:

- More sensitive for detecting erosive disease and joint effusions/synovitis

Rx TREATMENT

- Early identification and treatment of RA with DMARDs is crucial. More than half of patients have radiographic joint damage within 2 yr of disease onset, but early aggressive treatment with DMARDs and/or biologic agents is associated with decreased progression of synovitis and bone erosions, and with decreased disability. Fig. 6 describes the American College of Rheumatology recommendations for treatment of rheumatoid arthritis. Goal of therapy is to "treat to a target" of low disease activity or remission.
- There are several tools to measure disease activity and define remission in rheumatoid arthritis, including (but not limited to) the following: Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), Disease Activity Score (DAS) 28, Routine Assessment of Patient Index Data 3 (RAPID3), Stanford Health Assessment Questionnaire (HAQ), and Patient Activity Scale (PAS).

ACUTE GENERAL Rx

- NSAIDs: Can be used initially to relieve pain and mild inflammation, or used later in the disease course for additional control of mild pain. NSAIDs are not disease modifying.
- Corticosteroids: Oral or intraarticular, frequently used initially to reduce inflammation rapidly until oral DMARD treatments take

effect. They may also be used during acute flares or in low doses for additional control of inflammation. The use of corticosteroids at the lowest dose possible and shortest duration is recommended. Corticosteroids have many side effects, including but not limited to weight gain, increased risk of diabetes, osteoporosis, cataract formation, peptic ulcer disease (especially when used in combination with NSAIDs), and avascular necrosis.

CHRONIC Rx

- DMARDs: Can be classified into "nonbiologic" and "biologic" treatments.
  1. Nonbiologic DMARDs: Most commonly used agents are methotrexate (MTX), hydroxychloroquine (HCQ), sulfasalazine (SSZ), and leflunomide (LEF). Most of these are associated with potential toxicity and require close monitoring. They are also slow-acting drugs that generally require >8 wk to start taking effect.
  2. MTX is the most commonly used DMARD worldwide for the treatment of RA. It is effective as monotherapy in about 30% of patients with RA.
  3. "Triple therapy"—MTX, HCQ, and SSZ—has been shown to be superior to MTX alone.
- Biologic DMARDs: Newer biologically engineered therapies, which target cytokines and cells involved in the RA inflammatory response. Major side effects include an increased risk of infections, most notably reactivation of tuberculosis with anti-TNF agents. A negative PPD or interferon γ-release assay is a prerequisite to initiate therapy. Biologic DMARDs are most effective when used in combination with a nonbiologic DMARD, usually MTX.
- The five approved tumor necrosis factor α inhibitors (TNFI) include infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab.
- Abatacept (CTLA-4Ig) is a recombinant protein that prevents costimulatory binding of antigen presenting cell to T cell, preventing T-cell activation.
- Tocilizumab (anti–IL-6) is a monoclonal antibody against the IL-6 receptor.
- Sarilumab is another IL-6 inhibitor monoclonal antibody, approved by the FDA in 2017 for treatment of RA, and can be used as monotherapy or in combination with MTX or other conventional DMARDs.
- Tofacitinib (JAK1/2/3 inhibitor) inhibits the JAK-STAT intracellular signaling pathway, thus preventing the production of inflammatory mediators. The first oral biologic DMARD, it can be used as monotherapy or in combination with MTX. Baricitinib, an oral, once-daily Janus kinase (JAK1 and JAK2) inhibitor, has been approved by the FDA in May 2018 for treatment of moderate to severe RA in patients who did not respond adequately to one or more TNFIs. A dose of 2 mg was approved, with concerns that higher doses had increased adverse events. Upadacitinib (JAK1 > JAK2/3 inhibitor) was approved in 2019 at 15 mg once daily for moderate to severely active RA resistant or intolerant to MTX, or in combination with MTX with other nonbiologic DMARDs.
- Rituximab (anti-CD20) is a monoclonal antibody against the CD20 antigen on B lymphocytes.
- Biosimilars are beginning to be available. These molecules are highly similar, but not identical, to the original drugs. Legal disputes have delayed the widespread adoption of these drugs in the U.S., but they are likely to be of increasing prevalence in the future.
- Treatment recommendations in RA patient with high-risk comorbidities:
  1. TNFI should be avoided in patients with congestive heart failure, as it can worsen the condition.
  2. In patients with hepatitis B, immunosuppressive therapy can be safely prescribed along with concomitant antiviral therapy.
  3. Treatment of hepatitis C patients with RA should be done following standard guidelines in collaboration with gastroenterology/hepatology. Immunosuppressive therapy can be used safely in conjunction with antiviral therapy; avoidance of DMARDs such as MTX and LEF should be taken into consideration.
  4. In patients with a history of skin cancer, DMARDs are recommended over the use of biologics. For patients with previously treated lymphoproliferative disorders, use of rituximab should be considered first, as well as combination DMARDs and non-TNF biologics. One should avoid TNFI, as there is an increased risk of lymphoma with these agents. Recommendations for treatment of patients with previously treated solid organ malignancy are the same as for patients without the condition.

Immunization, cardiovascular disease prevention (smoking cessation, blood pressure control, cholesterol control), and osteoporosis prevention (with calcium and vitamin D supplementation and bisphosphonate therapy) should be addressed in all RA patients.

DISPOSITION

- Remissions and exacerbations are common, but condition is chronically progressive in the majority of cases.
- Joint degeneration and deformity often lead to disability. Joint replacement is indicated for patients with severe joint damage whose symptoms are poorly controlled by medical management. The ACR published guidelines in 2017 concerning the perioperative management of antirheumatic medications in patients undergoing elective total hip or total knee arthroplasty.
- Early and aggressive diagnosis and treatment are crucial in preventing or slowing joint destruction.

REFERRAL

- Early referral to rheumatologist
- Orthopedic consultation for corrective surgery

PEARLS & CONSIDERATIONS

RA sometimes develops acutely in the postpartum patient; conversely, as high as 75% of pregnant RA patients will experience remission during pregnancy.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Rheumatoid Arthritis (Patient Information)

AUTHOR: **Daphne Scaramangas-Plumley, MD**

SUGGESTED READINGS

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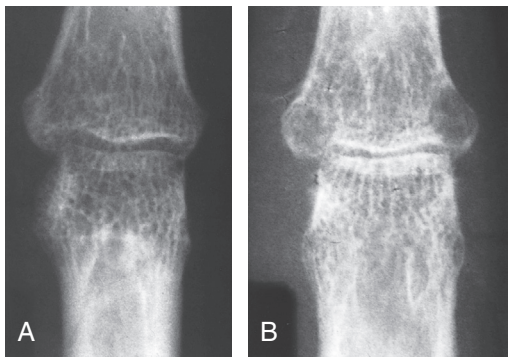

FIG. E1 Rheumatoid arthritis. (A) Initial x-ray shows early trabecular loss around the finger proximal interphalangeal joint with joint space preservation. **(B)** Subsequently there is erosive change with joint space narrowing. (From Sutton D: *Textbook of radiology and imaging,* ed 7, 1998, Churchill Livingstone. In Grant LA *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

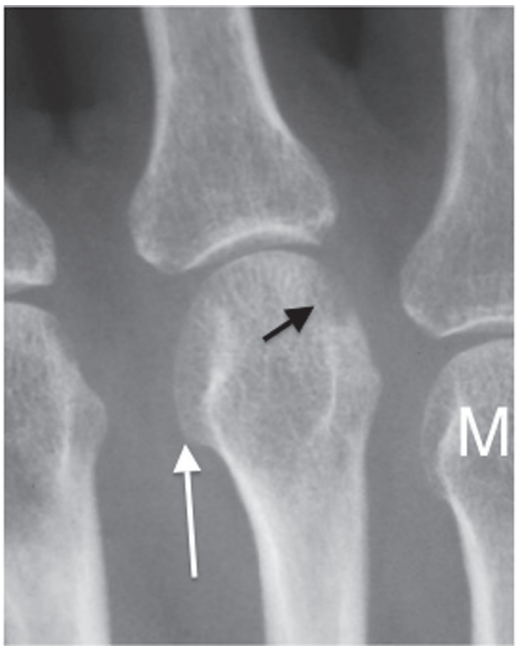

FIG. E2 Rheumatoid arthritis with the earliest feature of erosive change seen along the radial border of this middle metacarpal head. There is localized osteopenia with a "dot-dash" pattern of deossification *(white arrow)*. Note also the symmetrical soft-tissue swelling and frank erosion of the ulna border *(black arrow)*. (From Adam A et al: *Grainger and Allison's diagnostic radiology,* ed 6, 2015, Elsevier. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

FIG. E3 Rheumatoid arthritis. Bilateral symmetrical changes with soft tissue swelling (especially over the ulnar styloids). Erosions are seen at the carpus, metacarpophalangeal joints, distal radius and ulna with joint space narrowing and bone collapse. There is a swan neck deformity of the right 5th distal interphalangeal joint. (From Sutton D: *Textbook of radiology and imaging,* ed 7, 1998, Churchill Livingstone. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

TABLE E2 Plain Radiographic Findings in Rheumatoid Arthritis and Corresponding Pathophysiological Causes

Radiological Findings	Pathological Cause
Periarticular osteoporosis	This reflects localized hyperemia and is most pronounced during the acute stages of the disease
Soft tissue swelling	This represents synovial hypertrophy, joint effusion and periarticular soft tissue edema, and is typically symmetrical
Erosions	These are marginal in location caused by the inflammatory and erosive effect of the inflamed synovium on the "bare area" of the joint (that part of the joint adjacent to the synovium which is not covered by cartilage)
Joint space narrowing	This results from cartilage loss. Early uniform cartilage loss results from interruption of the flow of synovial fluid nutrients by the pannus. Later the hypertrophied synovium causes direct destruction with undermining of the cartilage and destruction of the subchondral bone. There may be joint widening in the early stages or ankylosis in the end stages of the disease
Subchondral cysts	These result from destruction of the subchondral plate by pannus, which allows joint fluid to be forced into the subchondral bone under pressure
Joint subluxation and dislocation	These are due to damage or destruction to tendons and ligaments as a result of the inflammatory pannus. In the early stages the deformity may be reversible and therefore underestimated on plain films
Generalized regional osteoporosis	This results from pain-induced disuse and may be exacerbated by the effects of therapy (e.g., steroids)

From Adam A et al: *Grainger & Allison's diagnostic radiology,* ed 5, 2007, Churchill Livingstone. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.

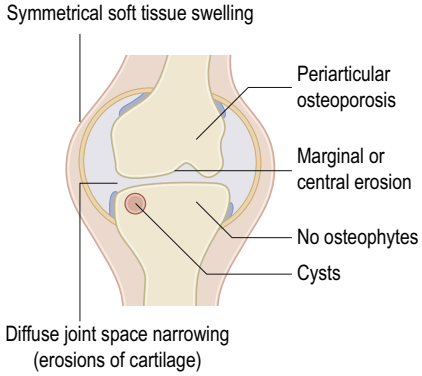

FIG. E5 Diagram showing the typical radiographic changes in rheumatoid arthritis. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

Rocky Mountain Spotted Fever PTG

BASIC INFORMATION

DEFINITION

Rocky Mountain spotted fever (RMSF) is a life-threatening, tickborne febrile illness caused by infection with *Rickettsia rickettsii*. The infection occurs when *R. rickettsii* in the salivary glands of a vector tick is transmitted into the dermis, spreading and replicating in the cytoplasm of endothelial cells and eliciting widespread vasculitis and end-organ damage.

SYNONYM

RMSF

ICD-10CM CODE

A77.0 Spotted fever due to *Rickettsia rickettsii*

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.18 to 0.32 cases per 100,000 person/yr. Infections have been reported throughout the U.S.

PREVALENCE: Most prevalent in the Southeast, followed by the South Central states, but seen nywhere (Fig. E1). The RMSF main territory" extends from North Carolina to Oklahoma. It has recently been reported in eastern Arizona, with common brown dog ticks *(Rhipicephalus sanguineus)* implicated as a vector of *R. rickettsii.*

PREDOMINANT SEX: Affects both genders equally

PREDOMINANT AGE: Occurs at any age, but more likely in children ages 5 to 14 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation: 3 to 12 days
- First symptoms: Fever, headache, malaise, myalgias

Common History, Signs, or Symptom	%
Tick bite	65
Fever	100
Rash	>90
Rash on palms and soles (Fig. E2)	80
Headache	90
Myalgia	75
Nausea or vomiting	60
Abdominal pain	40
Conjunctivitis	30
Edema	20
Pneumonitis	15
Any severe neurologic complication (including stupor, delirium, seizures, ataxia, papilledema, focal neurologic deficits, and coma)	30

- Rash: A petechial rash is the hallmark of RMSF:
  1. Appears during first 3 days in 50%; by day 5, 90% have it. No rash in <10%.
  2. Initial appearance: Blanching erythematous macules on wrists and ankles that then spread to trunk, palms, and soles (Fig. E3). The rash involves palms and soles in more than 30% of cases and usually spares the face.
  3. Lesions may evolve into papules and eventually become nonblanching (petechiae or palpable purpura).
- Gastrointestinal symptoms:
  1. Nausea, vomiting, and abdominal pain are common
  2. Occasionally may mimic an "acute abdomen" (e.g., appendicitis, cholecystitis)
  3. Mild hepatitis
- Cardiopulmonary involvement:
  1. Interstitial pneumonitis
  2. Myocarditis
- Renal problems:
  1. Prerenal azotemia
  2. Interstitial nephritis
  3. Glomerulonephritis
- Neurologic involvement:
  1. Encephalitis (confusion, lethargy, delirium)
  2. Ataxia
  3. Convulsion
  4. Cranial nerve palsy
  5. Speech impediment
  6. Hemiparesis or paraparesis
  7. Spasticity
- Fulminant RMSF:
  1. Early, widespread vascular necrosis leading to multisystem illness and death

ETIOLOGY & PATHOGENESIS

- Infectious agent: *R. rickettsii* (an intracellular bacterium).
- Vector: Dog tick and wood tick (vertical transmission exists in ticks, but horizontal transmission involving rodents represents an important reservoir for the agent). In the U.S., *R. rickettsii* is transmitted mainly by the American dog tick *(Dermacentor variabilis)* and the Rocky Mountain wood tick *(D. andersoni).*
- Pathogenesis: The spread of *R. rickettsii* is hematogenous with attachment to the vascular endothelium, causing a vasculitis. The manifestations of this illness are caused by increased vascular permeability.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Influenza A, enteroviral infection, typhoid fever, leptospirosis, infectious mononucleosis, viral hepatitis, sepsis, ehrlichiosis, gastroenteritis, acute abdomen, bronchitis, pneumonia, meningococcemia, disseminated gonococcal infection, secondary syphilis, bacterial endocarditis, toxic shock syndrome, scarlet fever, rheumatic fever, measles, rubella, typhus, rickettsialpox, Lyme disease, drug hypersensitivity reactions, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, Kawasaki syndrome, immune complex vasculitis, connective tissue disorders.

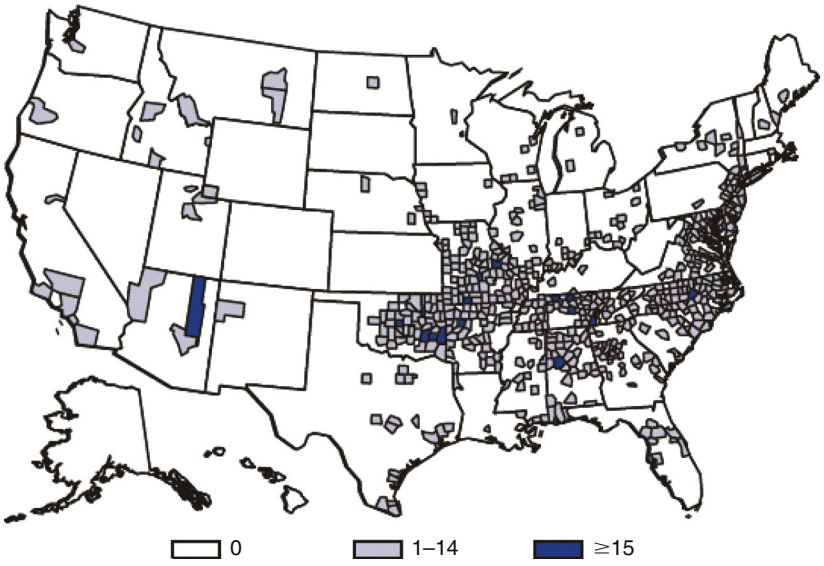

FIG. E1 Spotted fever rickettsiosis. Number of reported cases, by county, U.S., 2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59[53]:1-111, 2012.)

FIG. E2 Palmar rash associated with Rocky Mountain spotted fever. (From Walker DH, Raoult D: *Rickettsia rickettsii* and other spotted fever group rickettsiae [Rocky Mountain spotted fever and other spotted fevers]. In Mandell GL et al [eds]: *Principles and practice of infectious diseases,* ed 5, New York, 2000, Churchill Livingstone.)

FIG. E3 Late appearance of rash: Rocky Mountain spotted fever manifesting on lower extremity. (Courtesy of Theodore Woodward, MD. From Marx JA et al: *Rosen's emergency medicine: concepts and clinical practice,* 7 ed, Philadelphia, 2010, Elsevier.)

WORKUP

- Consider RMSF in any patient with an acute febrile illness with headache and myalgia, especially with an associated history of tick exposure. Absence of rash does not rule out the diagnosis.
- Rickettsial antibodies take several weeks to develop; therefore, serologic testing is of limited utility in acute illness.
- Box E1 shows the diagnostic criteria for Rocky Mountain spotted fever.

LABORATORY TESTS

- Thrombocytopenia and elevated aminotransferase are common (see the following).
- Cerebrospinal fluid analysis reveals a lymphocyte-predominant pleocytosis.

Routine Tests	%
White cell count	
<10,000/mm^3	72
>10% bands	69
Platelet count	
<150,000/mm^3	52
<99,000/mm^3	32
Serum sodium value <132 mEq/L	56

BOX E1 Diagnostic Criteria for Rocky Mountain Spotted Fever

Laboratory Criteria

- Serologic evidence of a significant change in serum antibody titer reactive with *Rickettsia rickettsii* antigens between paired serum specimens, as measured by a standardized assay conducted in a commercial, state, or reference laboratory
- Demonstration of *R. rickettsii* antigen in a clinical specimen by immunohistochemical methods
- Detection of *R. rickettsii* DNA in a clinical specimen by the polymerase chain reaction (PCR) assay
- Isolation of *R. rickettsii* from a clinical specimen in cell culture

For confirmed cases, a significant change in titer must be determined by the testing laboratory; examples of commonly used measures of significant change include, but are not limited to, a fourfold or greater change in antibody titer as determined by indirect immunofluorescent antibody (IFA) assay or an equivalent change in optical density measured by enzyme-linked immunosorbent assay (EIA or ELISA).

Case Classification (CDC Case Definition, 2004)

Confirmed: The patient has a clinically compatible illness that is laboratory confirmed.
Probable: The patient has a clinically compatible illness and serologic evidence of antibody reactive with *R. rickettsii* in a single serum sample at a titer considered indicative of current or past infection (cutoff titers are determined by individual laboratories).

CDC, Centers for Disease Control and Prevention.
From Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States. *MMWR Recomm Rep* 55(RR-4):18, 2006, and from Marx JA et al: *Rosen's emergency medicine: concepts and clinical practice,* 7 ed, Philadelphia, 2010, Elsevier.

Routine Tests	%
Aspartate aminotransferase ≥2× normal	62
Alanine aminotransferase ≥2× normal	39
Bilirubin value >1.4 mg/dl	30
Cerebrospinal Fluid	
Opening pressure ≥250 mm H_2O	14
Glucose value ≤50 mg/dl	8
Protein value ≥50 mg/dl	35
White cell count ≥5/mm^3	38
Mononuclear cell predominance	46
Polymorphonuclear cell predominance	50

- Etiologic tests:
  1. Antibody titers to *R. rickettsii* (by indirect fluorescent antibody test). The diagnosis of RMSF requires a fourfold increase 2 wk apart and thus is not helpful in the care of the patients despite a sensitivity and specificity of near 100%.
  2. The only test that can provide a timely diagnosis is the immunohistologic demonstration of *R. rickettsii* in skin biopsy specimens.

Rx TREATMENT

- Oral or IV doxycycline is first-line treatment. Administer 200 mg/day in 2 divided doses for 7 days or for 2 days after defervescence.
- Chloramphenicol, 50 mg/kg/day in 4 divided doses is an alternative treatment; chloramphenicol may be preferred during pregnancy because of the effects of doxycycline on fetal bones and teeth; therapy continued for at least 2 days after defervescence.

PROGNOSIS

- It is imperative to give antibiotic treatment empirically when RMSF is suspected.
- Fatality rate: 5% to 10% (five times greater if treatment is initiated after day 5 of illness, which is more likely in the absence of rash and during seasonal nonpeak tick activity). Long-term sequelae seen in patients who recover from severe RMSF: Paraparesis, hearing loss; peripheral neuropathy; bladder and bowel incontinence; cerebellar, vestibular, and motor dysfunction; language disorders; limb amputation; and scrotal pain after cutaneous necrosis.

RELATED CONTENT

Rocky Mountain Spotted Fever (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

BASIC INFORMATION

DEFINITION

Rosacea is a chronic skin disorder characterized by papules and pustules affecting the face and often associated with flushing and erythema.

SYNONYM

Acne rosacea

ICD-10CM CODES

L71 Rosacea
L71.9 Rosacea unspecified
L71.1 Rhinophyma
L71.8 Other rosacea
L71.0 Perioral dermatitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Rosacea occurs in 1 in 20 Americans
- Onset often between ages 30 and 50 yr
- More common in people of Celtic origin; however, this disease may be overlooked in nonwhites because skin pigmentation results in atypical presentation
- Female:male ratio of 3:1

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Facial erythema, presence of papules, pustules, and telangiectasia (Fig. E1).
- Excessive facial warmth and redness are the predominant presenting symptoms.
- Itching is generally absent.
- Comedones are absent (unlike acne).
- Women are more likely to show symptoms on the chin and cheeks, whereas in men the nose is commonly involved.
- Ocular findings (mild dryness and irritation with blepharitis, conjunctival injection, burning, stinging, tearing, eyelid inflammation, swelling, and redness) are present in 50% of patients.

Rosacea can be classified into four major subtypes (Table E1):

1. Erythematotelangiectatic (vascular): Erythema in central part of face, telangiectasia, flushing
2. Papulopustular (inflammatory): Presence of dome-shaped erythematous papules and small pustules, in addition to facial erythema, flushing, and telangiectasia
3. Phymatosis/glandular rosacea (Fig. E2): Presence of thickened skin with prominent pores that may affect the nose (rhinophyma) (Fig. E3), chin (gnathophyma), forehead (metophyma), eyelids (blepharophyma), and ears (otophyma)
4. Ocular: Conjunctival injection, sensation of foreign body in the eye, telangiectasia and erythema of lid margins, scaling

ETIOLOGY

- The pathophysiology of rosacea is incompletely understood but believed to involve the vasculature.
- Hot drinks, alcohol, and sun exposure may accentuate the erythema by causing vasodilation of the skin.
- Flare-ups may also result from reactions to medications (e.g., simvastatin, angiotensin-converting enzyme inhibitors, vasodilators, fluorinated corticosteroids), stress, extreme heat or cold, wind, humidity, strenuous exercise, spicy drinks, menstruation.

DIAGNOSIS

The presence of at least one of the following primary features in a central distribution of the face is generally sufficient to diagnose rosacea: Papules and pustules, telengiectasia, flushing (transient erythema), nontransient erythema.

DIFFERENTIAL DIAGNOSIS

- Drug eruption
- Acne vulgaris
- Contact dermatitis
- Systemic lupus erythematosus
- Carcinoid flush
- Idiopathic facial flushing
- Seborrheic dermatitis
- Facial sarcoidosis
- Photodermatitis
- Mastocytosis
- Perioral dermatitis
- Granulomas of the skin

WORKUP

Diagnosis is based on clinical findings. Distinguishing features between acne and rosacea are the presence of telangiectasia and deep diffuse erythema and absence of comedones in rosacea.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Instruct patients to keep a diary to identify stimuli and triggers that exacerbate rosacea (e.g., spicy foods, drugs, cosmetics) and avoid identified triggers.
- Avoid alcohol, excessive sun exposure, and hot drinks of any type.
- Use of mild, nondrying soap or soap-free cleansers and nonoily moisturizers is recommended; local skin irritants should be avoided. General recommendations for skin care in patients with rosacea are summarized in Table 2.
- Sunscreens are an important component of therapy and should be applied each morning.
- Daily circular massage for several minutes of the central portion of the face is helpful in decreasing lymphedema and inflammation in this area.
- Reassure patient that rosacea is completely unrelated to poor hygiene.
- Vascular laser surgery is effective for telangiectasia.
- Surgical options are available for telangiectasia and rhinophyma and include

TABLE 2 General Recommendations for Facial Skin Care and Education in Patients With Rosacea

Facial Skin Care

- Wash with lukewarm water and use soap-free cleansers that are pH balanced.
- Cleansers are applied gently with fingertips.
- Use sunscreens with both UVA and UVB protection and an SPF ≥30.
- Sunscreens containing the inorganic filters titanium dioxide and/or zinc oxide are usually well tolerated.
- Use cosmetics and sunscreens that contain protective silicones.
- Water-soluble facial powder containing inert green pigment helps to neutralize the perception of erythema.
- Moisturizers containing humectants (e.g., glycerin) and occlusives (e.g., petrolatum) help to repair the epidermal barrier.
- Avoid astringents, toners, and abrasive exfoliators.
- Avoid cosmetics that contain alcohol, menthols, camphor, witch hazel, fragrance, peppermint, and eucalyptus oil.
- Avoid waterproof cosmetics and heavy foundations that are difficult to remove without irritating solvents or physical scrubbing.
- Avoid procedures such as glycolic peels or dermabrasion.

Patient Education

- Reassure the patient about the benign nature of the disorder and the rarity of rhinophyma, particularly in women.
- Emphasize the chronicity of the disease and the likelihood of exacerbations.
- Direct patients to information websites such as those of the National Rosacea Society (www.rosacea.org) or the American Academy of Dermatology (www.aad.org).
- Advise to avoid recognized triggers.
- Explain the importance of compliance with topical regimens.
- Educate on the importance of sun avoidance.•

SPF, Sun protective factor; *UVA,* ultraviolet A; *UVB,* ultraviolet B.

Adapted from Del Rosso JQ, Baum EW: Comprehensive medical management of rosacea: an interim study report and literature review, *J Clin Aesthet Dermatol* 1:20-25, 2008; Powell FC: Rosacea, *N Engl J Med* 352:793-803, 2005; and Pelle MT et al: Rosacea: II. Therapy, *J Am Acad Dermatol* 51:499-512, 2004; In From Bolognia J: *Dermatology,* ed 4, 2018, Elsevier.

dermabrasion, laser ablation, heated scalpel, electrocautery, and radiofrequency electrosurgery.

GENERAL Rx

- Several classes of drugs are used in treatment of rosacea, including the metronidazole family, the tetracycline family, ivermectin cream, and azelaic acid.
- Vascular rosacea: Topical therapy with metronidazole aqueous gel (MetroGel) applied bid is effective as initial therapy for mild cases. A new 1% formulation of metronidazole (Noritate) applied daily may improve patient compliance. Clindamycin lotion (Cleocin), sulfacetamide, or erythromycin 2% solution may also be effective. Brimonidine (Mirvaso) is a selective alpha$_2$-adrenergic receptor agonist FDA-approved as a gel preparation for topical treatment of adults with persistent facial erythema of rosacea. Oxymetazoline (Rhofane) 1% cream is also an FDA-approved selecting alpha1a-adrenergic receptor agonist for topical treatment of persistent facial erythema in adults. Neither brimonidine or oxymetazoline are indicated for the treatment of inflammatory lesions of rosacea.
- Pustular and ocular rosacea: Systemic antibiotics (doxycycline 100 mg qd or tetracycline 250 mg qid until symptoms diminish, then taper off). Minocycline 50 to 100 mg qd should be used only in resistant cases because this medication is expensive. Oral metronidazole (200 mg qd to bid) for 4 to 6 wk is also effective. A 1% cream formulation of the antiparasitic drug ivermectin (Soolantra) is effective for papulopustular rosacea with minimal adverse effects. After 3 months of therapy, it will produce clearing of rosacea lesions in up to 80% of patients with moderate to severe symptoms. Its mechanism of action is unknown, but it may be due to the combination of its antiinflammatory effects and its antiparasitic effects on the Demodex mite, which may contribute to the symptoms of rosacea. Cost may be a limiting factor ($320 for one 30-g tube).
- Isotretinoin (Accutane) 0.5 to 1 mg/kg/day in two divided doses for 15 to 20 wk can be used for refractory papular and pustular rosacea; use of retinoids may, however, worsen erythema and telangiectasis.
- Erythema and flushing may respond to low-dose clonidine (0.05 mg bid).
- Treatment of phymatous rosacea: Oral tetracyclines, oral isotretinoin, ablative/pulsed dye laser therapy, electrosurgery.
- Treatment of ocular rosacea: Topical or oral tetracyclines, artificial tears, and/or lid cleansing for eyelid hygiene. Medical and surgical therapies for rosacea are summarized in Table E3.

DISPOSITION

- Rosacea is often resistant to initial treatment and recurrent. Periods of remission and relapse are common.
- The progression of rosacea is variable. Typical stages include:
  1. Facial flushing
  2. Erythema and/or edema and ocular symptoms
  3. Papules and pustules
  4. Rhinophyma

PEARLS & CONSIDERATIONS

COMMENTS

- The course of the disease is typically chronic, with remissions and relapses.
- Patients with resistant cases may have *Demodex folliculorum* mite infestation or tinea infection (diagnosis can be confirmed with potassium hydroxide examination); the role of *D. folliculorum* in rosacea is unclear. These mites can sometimes be found in large numbers in the lesions; however, their numbers do not generally decline with treatment.
- Rosacea can result in emotional and social stigmas, especially because many people associate rosacea and rhinophyma with alcohol abuse.
- Early consultation with an ophthalmologist is recommended in patients with suspected ocular involvement.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Rosacea (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Del Rosso JQ: Management of facial erythema of rosacea, *J Am Acad Dermatol* 69:S44-S56, 2013.

Del Rosso JQ et al: Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 1, *Cutis* 92:234-240, 2013.

van Zuuren EJ: Rosacea, *N Engl J Med* 377:1754-1764, 2017.

FIG. E1 Papulopustular rosacea. (Courtesy Curt Samlaska, MD. From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

TABLE E1 Differential Diagnosis of the Four Subtypes of Rosacea

Rosacea Subtype and Differential Diagnosis	Distinguishing Feature(s) from Rosacea
Erythematotelangiectatic rosacea	
Actinic damage (telangiectatic photoaging)	• Also characterized by facial telangiectasias and erythema, but the latter favors the lateral more than the central face • There tends to be less transient and nontransient erythema • Some patients have both disorders
Seborrheic dermatitis	• Erythema with greasy scale in the eyebrows, nasolabial folds, auditory meatus, retroauricular sulcus, and scalp • Involvement of eyelid creases • Patients often have both disorders
Keratosis pilaris rubra	• Onset usually during adolescence • Background erythema of the lateral cheeks with superimposed tiny follicular papules
Acute cutaneous lupus erythematosus	• Absence of inflammatory papulopustules and ocular changes • At least 75%-80% of patients have systemic signs/symptoms of SLE • Often more well-demarcated edematous plaques with sparing of the nasolabial fold
Flushing (idiopathic or secondary)	• Intermittent erythema and warmth • Flushing in patients with rosacea is usually limited to the face • Consider other common etiologies (e.g., menopause, anxiety disorder) or a tumor-related phenomenon (carcinoid syndrome, occult pheochromocytoma, mastocytosis) when additional anatomic sites are involved or there are associated symptoms such as tachycardia and sweating
Papulopustular rosacea	
Acne (vulgaris)	• Onset at a younger age • Comedones, both open and closed, and cysts • Greater involvement of the upper trunk
Steroid-induced rosacea	• Clinical overlap with periorificial dermatitis
Demodicosis (*Demodex* folliculitis)	• Patients often immunosuppressed (HIV infection, leukemia) • Involves face, especially the nose, and upper chest • Responds to topical permethrin ± oral ivermectin

Continued

TABLE E1 Differential Diagnosis of the Four Subtypes of Rosacea—cont'd

Rosacea Subtype and Differential Diagnosis	Distinguishing Feature(s) from Rosacea
Pityriasis folliculorum	• See text
Tinea incognito, candidiasis	• Both can mimic rosacea, especially if topical corticosteroids have been used • KOH examination demonstrates hyphae or budding yeasts
Papulopustular eruptions due to EGFR inhibitors	• Occurs in up to 90% of patients on these drugs • Abrupt onset • May also involve scalp, neck, and trunk
Follicular mucinosis	• Multiple papules but not pustules
Ocular rosacea	
Seborrheic dermatitis	• Involvement beyond the eyelid margin; may be accentuated in the eyelid creases
Drug-induced ocular rosacea	• Eyedrops used to treat other ocular disorders, e.g., glaucoma
Phymatous rosacea	
Lupus pernio (sarcoidosis)	• Violaceous indurated plaque of the distal nose
Discoid lupus erythematosus	• Erythema, scaling, follicular plugging, and tendency to scarring
Lupus vulgaris (cutaneous TB)	
Neoplasms	• Basal cell carcinoma, lymphoma, angiosarcoma, cutaneous metastases ("clown nose")

Occasionally, trichostasis spinulosa has associated erythema, but detection of multiple hairs within the follicular orifice by dermoscopy or microscopic examination of follicular contents establishes the diagnosis. *EGFR,* Epidermal growth factor receptor; *KOH,* potassium hydroxide; *SLE,* systemic lupus erythematosus; *TB,* tuberculosis.
From Bolognia J: *Dermatology,* ed 4, 2018, Elsevier.

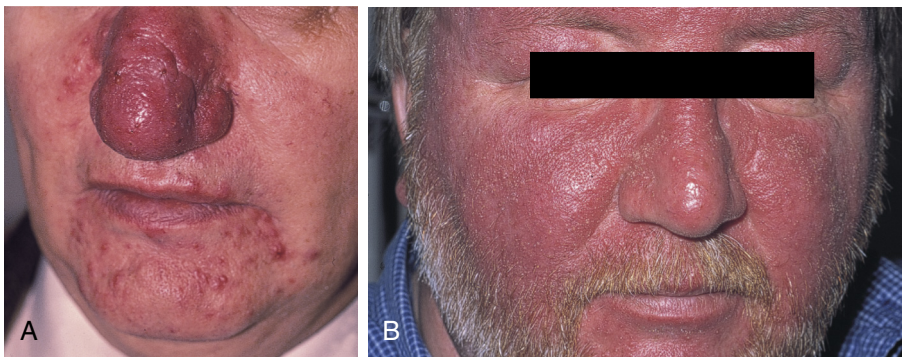

FIG. E2 Severe rosacea. A, Note the scattered papules on the face and the confluent involvement of the nose. Alcohol ingestion is not related to this appearance. **B,** Note the severe inflammation with confluent redness and significant edema. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

FIG. E3 Glandular rosacea. (From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

TABLE E3 Medical and Surgical Therapies For Rosacea

Treatment	Comments and/or Doses
Erythematotelangiectatic	
Facial skin care recommendations (see Table 2)	Particularly useful as this subtype is prone to skin irritation and "sensitivity"
Photoprotection	UVR may potentiate dermal matrix damage
Topical agents, e.g., azelaic acid, metronidazole	May reduce erythema, but their use is often limited by their irritant effects
Topical brimonidine tartrate (0.33% gel)*,†	Selective α_2-adrenergic agonist that improves erythema
Topical oxymetazoline HCl (1% cream)*	Selective α_{1A}-adrenergic agonist that improves erythema
Laser therapy†	Use of vascular lasers (e.g., pulsed dye, potassium titanyl phosphate) as well as intense pulsed light may improve grades 2 and 3
Papulopustular	
Topical	
Metronidazole (0.75% gel or cream; 1% cream)*,† once or twice daily	Can be used as initial treatment to clear inflammatory lesions or as indefinite maintenance therapy
Ivermectin (1% cream)*,† once daily	More effective than placebo and slightly more effective than topical metronidazole in randomized controlled trials
Azeleic acid (15% gel)*,† twice daily	Appears to be more effective than topical metronidazole but with more side effects, e.g., irritation Azeleic acid (20% cream twice daily) is a non–FDA-approved alternative dose
Sodium sulfacetamide (10%) and sulfur (5%) in a cream or lotion* once or twice daily	May include 10% urea
Erythromycin (2% solution) twice daily	Alcohol in solution may reduce tolerance
Clindamycin (1% lotion) daily	
Benzoyl peroxide 5% plus clindamycin 1% daily	May cause skin irritation
Tretinoin (0.025% cream; 0.05% cream; 0.01% gel) daily	Alters epidermal keratinization and may improve photodamage Poorly tolerated by some patients
Permethrin (5% cream) daily–weekly	Shown to be as effective as topical metronidazole for the treatment of papules and erythema May have future role in combination with antibiotics, but further studies needed
Pimecrolimus (1% cream) or tacrolimus (0.03%, 0.1% ointment) twice daily	Some studies have shown improvement in erythema, but there have been case reports of exacerbations, so further studies needed
Systemic	
Doxycycline*,†	40 mg daily (30 mg immediate release and 10 mg delayed release) for 4-8 weeks As effective as the 100 mg dose but with fewer adverse effects
Doxycycline	50-100 mg once or twice daily for 4-8 weeks
Minocycline	50-100 mg twice daily or sustained action formula (1 mg/kg) daily for 4-8 weeks**
Tetracycline†	250-500 mg twice daily for 4-8 weeks
Erythromycin	250-500 mg once or twice daily for 4-8 weeks
Azithromycin	250-500 mg (5-10 mg/kg) thrice weekly for 4-8 weeks
Metronidazole	200 mg once or twice daily for 4-8 weeks
Isotretinoin†	0.3 mg/kg/day
Phymatous	
Isotretinoin	May reduce nasal volume and halt the progression of rhinophyma
Surgical excision	Can effectively debulk and resculpt the nose
Electrosurgery	
CO_2 laser	
Ocular	
Eyelid hygiene and artificial tears	Frequently used to treat mild disease
Fusidic acid	Useful for maintaining remission following treatment of grades 2 and 3 disease with systemic antibiotics
Metronidazole gel	
Cyclosporine 0.5% ophthalmic emulsion†	More effective than artificial tears in treatment of ocular rosacea
Systemic antibiotics (see above section)	For grade 2-3 disease

If moderate to severe flushing persists despite avoidance of triggers, beta-blockers (e.g., carvedilol, nadolol) can be tried. *CO_2;* Carbon dioxide; *FDA,* U.S. Food and Drug Administration; *HCl,* hydrochloride; *UVR*, ultraviolet radiation.
*FDA-approved treatments for rosacea (evidence-based support = 1).
†In a Cochrane review of randomized controlled trials conducted for moderate to severe rosacea, these were the treatments shown to be effective.
**In a 16-week trial, minocycline 100 mg daily was noninferior to doxycycline 40 mg daily.
From Bolognia J: *Dermatology,* ed 4, 2018, Elsevier.

BASIC INFORMATION

DEFINITION

Roseola is a benign viral illness found in infants and characterized by high fevers that last 3 or 4 days, followed by defervescence, and development of a macular or maculopapular rash.

SYNONYMS

Exanthem subitum
Sixth disease
Roseola infantum
Pseudorubella
Human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7)

ICD-10CM CODE
B08.2 Exanthema subitum (sixth disease)

EPIDEMIOLOGY & DEMOGRAPHICS

- Nearly one-third of all infants develop roseola before the age of 2 yr.
- Peak prevalence is between 7 and 13 mo.
- More than 90% of children older than 2 yr of age are seropositive for the virus causing roseola.
- Roseola is spread from person to person. It is not known how it is spread, but it must be very efficiently spread and presumably via the respiratory tract.
- There is no predilection for gender or time of yr.
- Like other herpesviruses, HHV-6 induces a lifelong latent infection in humans.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typically the child develops a high fever, usually up to 104 °F (40 °C), that lasts for 3 to 5 days.
- Fever may be associated with a runny nose, irritability, and fatigue.
- A rash appears within 48 hr of defervescence; it begins on the neck or trunk and then spreads to the extremities, and persists for a few hours to 2 days.
- Faint pink maculopapular rash that blanches when palpated (Fig. E1) and generally nonpruritic. The mucous membranes are spared.
- Other common findings: Cervical and/or occipital adenopathy, erythematous tympanic membranes, anorexia.
- Nagayama spots: Red papules on the soft palate or base of the uvula.
- Seizures.
- Less common: Febrile seizures (≤6% of cases), cough, diarrhea, aseptic meningitis.

ETIOLOGY

- Roseola is usually caused by human herpesvirus-6 (HHV-6) in the great majority of cases but other causes include human herpesvirus-7, enteroviruses, adenoviruses, and parainfluenza virus type 1. A small percentage of children may have primary infection with HHV-7.
- The incubation period is between 5 and 15 days.

DIAGNOSIS

The diagnosis of roseola is usually made by the clinical presentation as stated previously. It can be confirmed serologically by indirect immunofluorescence assays, ELISA, neutralization assays, and immunoblot. Viral culture is the gold standard to document active viral replication but is expensive, time consuming, and available only in research laboratories.

DIFFERENTIAL DIAGNOSIS

- Rubeola (measles)
- Rubella
- Fifth disease (erythema infectiosum) caused by parvovirus B19
- Enteroviral infections
- Drug eruption
- Mononucleosis
- All causes of fever (e.g., otitis media, pneumonia, and urinary tract infection)
- Meningitis

WORKUP

- If unsure of the diagnosis of roseola in a febrile infant, a fever workup is done to rule out other infectious causes.
- The decision to proceed with a fever workup is a clinical judgment call.

LABORATORY TESTS

- CBC with differential usually shows relative neutropenia and mild atypical lymphocytosis
- Erythrocyte sedimentation rate (ESR), blood cultures as indicated
- Urinalysis and urine cultures
- Stool cultures if diarrhea is present
- Lumbar puncture if needed to rule out meningitis in patients with mental status changes
- Commercial assays can be used to detect HHV-6-specific IgG antibody responses but IgM assays are not always reliable for acute infection
- A quantitative PCR real-time assay for HHV-6 can be performed on whole blood, serum, plasma, or CSF and can be used to detect reactivation of latent virus in immunocompromised patients, such as hematopoietic stem cell transplant patients

IMAGING STUDIES

Chest x-ray to rule out pneumonia

TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive care
- Maintain hydration by drinking clear fluids: water, fruit juice, lemonade, and so forth
- Sponge bath with lukewarm water if febrile

ACUTE GENERAL Rx

- Acetaminophen 10 to 15 mg/kg per dose at 4-hr intervals for fever
- Ibuprofen 5 to 10 mg/kg per dose at 6-hr intervals (maximal dose 600 mg)

CHRONIC Rx

Roseola is a viral disease that is short lasting; chronic treatment is usually not an issue.

DISPOSITION

- Roseola is generally a benign, self-limited disease that usually lasts approximately 1 wk
- Complications, although rare, can occur and include:
  1. Febrile seizures
  2. Meningitis
  3. Encephalitis
  4. Pneumonitis
  5. Hepatitis

REFERRAL

Subspecialty consultation is made with the appropriate discipline if any of the previously mentioned complications occur (e.g., neurology for seizures).

PEARLS & CONSIDERATIONS

COMMENTS

- A child with fever and rash should be excluded from day care.
- HHV-6 is named accordingly because it is the sixth herpesvirus discovered after herpes simplex 1 (HSV-1), HSV-2, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and varicella-zoster virus (VZV).
- Roseola is called sixth disease because it represents the sixth childhood "exanthem"; the other five are measles, scarlet fever, rubella, Dukes disease, and erythema infectiosum.
- Reactivation of latent virus in immunocompromised patients such as AIDS patients or hematopoietic stem cell or solid organ transplant recipients can be serious or fatal. In these patients, options include ganciclovir, foscarnet, and cidofovir.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Roseola (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Agut H et al: Human herpesviruses 6A, 6B, and 7, *Microbiol Spectr* 4(3): DMIH2-0007-2015.

Agut H et al: Laboratory and clinical aspects of human herpesvirus 6 infections, *Clin Microbiol Rev* 28:313-335, 2015.

Caserta MT et al: Roseoloviruses: unmet needs and research priorities: perspective, *Curr Opin Virol* 9:167-169, 2014.

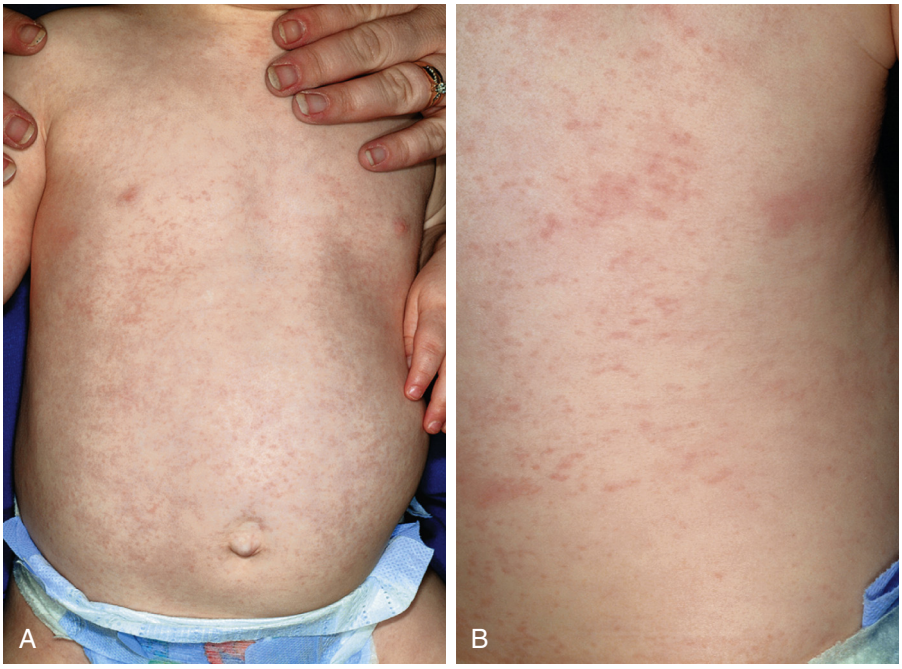

FIG. E1 Roseola infantum. Erythematous blanching macules and papules **(A)** in an infant who had high fever for 3 days preceding development of the rash. On closer inspection **(B),** some lesions reveal a subtle peripheral halo of vasoconstriction. (From Paller AS, Mancinin AJ [eds]: *Hurwitz clinical pediatric dermatology,* ed 3, Philadelphia, 2006, Saunders.)

Rotator Cuff Disease (PTG)

BASIC INFORMATION

DEFINITION

- The rotator cuff includes the supraspinatus, infraspinatus, teres minor, and subscapularis muscles that encompass the shoulder joint and facilitate both movement and stabilization of the joint.
- Rotator cuff disease is composed of subacromial bursitis, rotator cuff tendinopathy, impingement syndrome, and partial- or full-thickness muscle or tendon tears (Fig. E1).

SYNONYMS

Rotator cuff syndrome
Shoulder impingement syndrome
Painful arc syndrome
Supraspinatus syndrome

ICD-10CM CODES

M75.1	Rotator cuff tear or rupture, not specified as traumatic
M75.100	Unspecified rotator cuff tear or rupture of unspecified shoulder, not specified as traumatic
M75.11	Incomplete rotator cuff tear or rupture not specified as traumatic
M75.12	Complete rotator cuff tear or rupture, not specified as traumatic
M75.80	Other shoulder lesions, unspecified shoulder
M75.40	Impingement syndrome of unspecified shoulder
S46.001A	Unspecified injury of muscle(s) and tendon(s) of the rotator cuff of right shoulder, initial encounter
S46.002A	Unspecified injury of muscle(s) and tendon(s) of the rotator cuff of left shoulder, initial encounter
S43.421A	Sprain of right rotator cuff, initial encounter
S43.422A	Sprain of left rotator cuff capsule, initial encounter
S46.019A	Strain of muscle(s) and tendon(s) of the rotator cuff of unspecified shoulder, initial encounter
S46.099A	Other injury of muscle(s) and tendon(s) of the rotator cuff of unspecified shoulder, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 5% to 10% of the population. Can be prevalent in up to 39% of asymptomatic individuals with up to 64% prevalence in symptomatic individuals. Rotator cuff disease is the most common cause of shoulder pain, which is the third most frequent musculoskeletal reason to present to primary care. Up to 10% of all referrals to physical therapists are for shoulder pain.
PREDOMINANT SEX: Both sexes have been quoted as being equally predisposed to the development of rotator cuff pathology.
PREDOMINANT AGE: >40 yr. Advancing age has been consistently held accountable as a major risk factor for development of cuff tears.
RISK FACTORS: Advanced age, genetics, obesity, smoking and alcohol consumption, diabetes mellitus, repetitive overhead activity, occupational and sporting activities, trauma, and falls

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain located in the upper arm near the deltoid insertion and aggravated by overhead motions. Figs. E2 through E4 illustrate useful tests in the evaluation of rotator cuff disorders.
- Worse pain at night, exacerbated by lying on the affected shoulder.
- Muscle weakness indicates a tear.
- Atrophy and sunken appearance of the scapular muscles, especially infraspinatus, with longstanding disease.

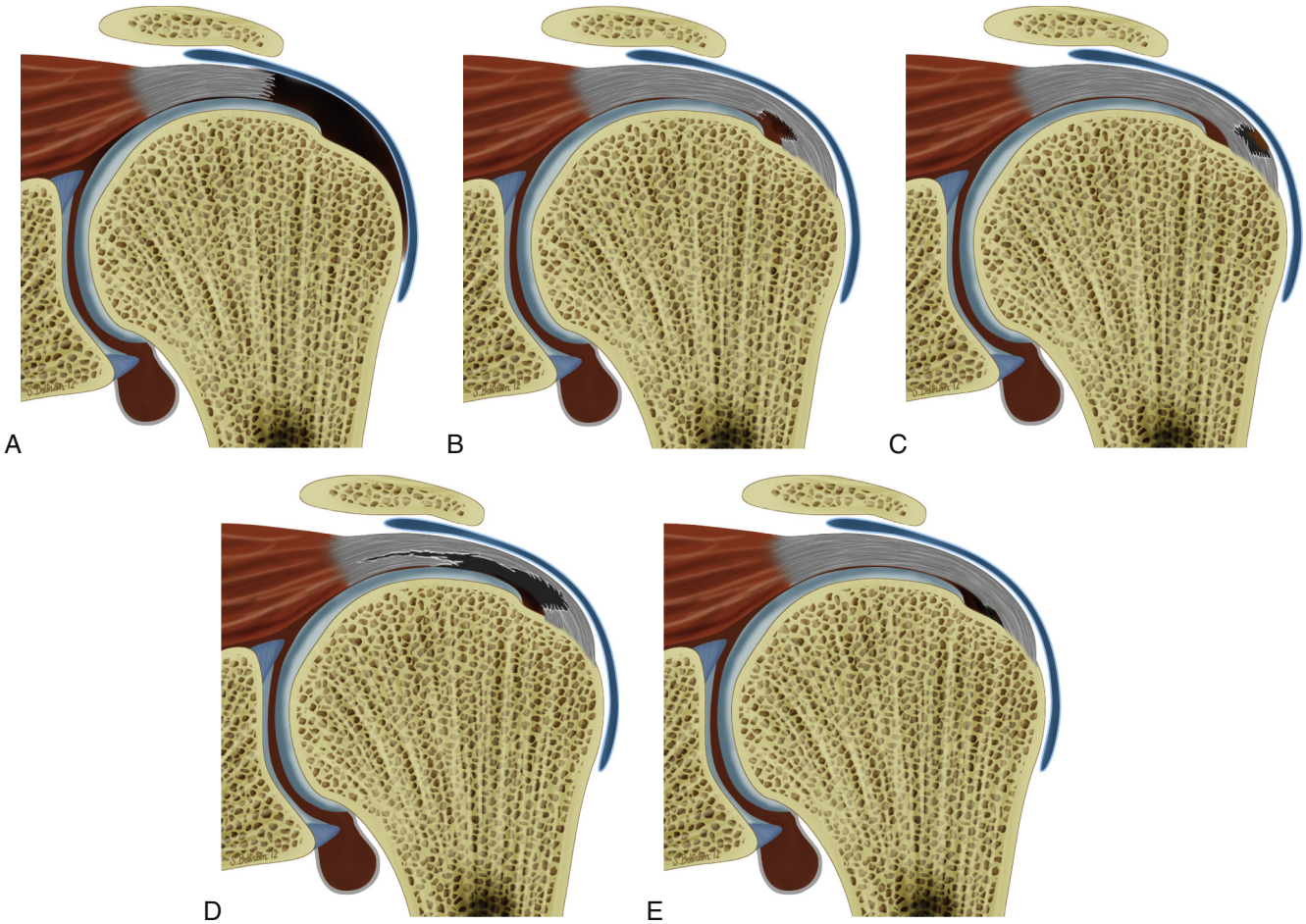

FIG. E1 Illustration of different types of rotator cuff tears. A, Full-thickness tear; **B,** partial articular surface tear; **C,** partial bursal surface tear; **D,** delaminating tear; **E,** rim-rent tear. (Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2014, WB Saunders.)

- Tenderness over the affected muscle or under the acromion suggests rotator cuff disease (Fig. E5).
- Useful clinical tests to assess for impingement include Hawkins-Kennedy sign, Neer sign, and the painful arc sign. The drop arm test is useful for evaluating for a rotator cuff tear.
- ***Hawkins-Kennedy sign:*** Shoulder and elbow are flexed at 90 degrees; shoulder pain is elicited with passive internal rotation.
- ***Neer sign:*** Pain with forced passive full-forward flexion.
- ***Painful arc sign:*** Pain with passive abduction of the shoulder between 60 and 120 degrees.
- ***Drop arm test:*** Examiner passively abducts patient's shoulder to 90 degrees. Patient is asked to slowly lower or adduct shoulder to their side. If patient is unable to control this motion, patient's arm falls to their side, suggesting a possible tear.
- Pain or weakness with resisted external rotation indicates involvement of the infraspinatus muscle.
- The combination of Hawkins-Kennedy sign, the painful arc sign, and weakness in external rotation yields the best probability (95%) for any degree of impingement.
- The combination of the drop arm sign, the painful arc sign, and weakness in external rotation accurately predicts full-thickness tears (91%).
- Studies suggest that a positive painful arc test result and a positive external rotation resistance test result are the most useful findings for detecting rotator cuff disease, whereas the presence of a positive lag test (external or internal rotation) is most useful for diagnosis of a full-thickness rotator cuff tear.
- A subacromial injection of local anesthetic can be used to distinguish weakness from rotator cuff tendinopathy and true tears—normal strength after injection indicates tendinopathy.

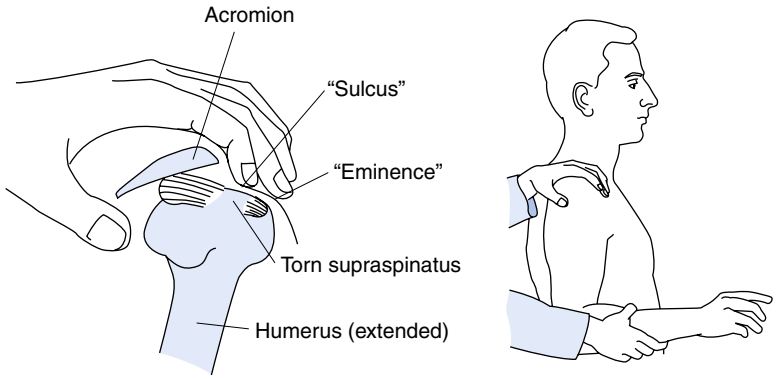

FIG. E2 Palpation of rotator cuff tears. The clinician stands behind the patient, and the patient's arm is relaxed at the side with the elbow flexed 90 degrees. The clinician palpates just below the patient's acromion with one hand and holds the patient's forearm with the other. The clinician then gently extends the patient's arm as far as possible and rotates the shoulder internally and externally to fully reveal the greater tuberosity and attached tissues. In patients with tears of the supraspinatus tendon (which inserts on the greater tuberosity), the clinician detects both an abnormal eminence and an abnormal sulcus posterior to this eminence. The abnormal eminence is the greater tuberosity with attached remnant of tendon, and the sulcus just behind it is the actual rent in the supraspinatus tendon. Comparison with the contralateral shoulder helps to determine whether the suspected tear is real or not. (From McGee S: *Evidence-based physical diagnosis*, ed 4, Philadelphia, 2018, Elsevier.)

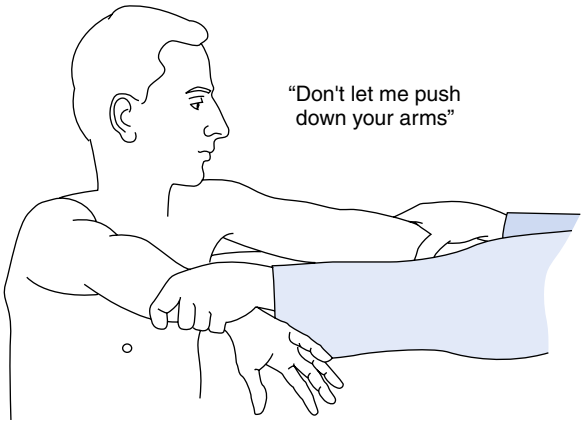

FIG. E3 Supraspinatus test (empty can test, Jobe test). The clinician stands in front of the patient and elevates the patient's arms to 90 degrees in the plane of the scapula (i.e., *scaption*, midway between forward flexion and sideways abduction). The patient's arms are internally rotated with thumbs pointing down (as if emptying a can). The patient is asked to hold this position and resist attempts to lower the arms to the side. Some investigators propose testing the supraspinatus muscle in a slightly different way, with the arms externally rotated and thumbs pointing up (i.e., **full can test**), because this position causes less pain than the empty can test. In clinical studies, both versions have similar diagnostic accuracy. (From McGee S: *Evidence-based physical diagnosis*, ed 4, Philadelphia, 2018, Elsevier.)

ETIOLOGY

A combination of tendon overload, microvascular compromise, and compression by surrounding structures. About 95% of all rotator cuff pathology occurs as an outcome from irritation onto the subacromial bursa and rotator cuff tendons from the undersurface of the overlying anterior aspect of the acromion. Recent studies show diabetes and hyperlipidemia may be associated with rotator cuff disease.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bicipital tendinitis, labrum tears, adhesive capsulitis, glenohumeral osteoarthritis, acromioclavicular injury, subscapularis bursitis, avascular necrosis. Table E1 describes the differential diagnosis of shoulder pain.
- Neurologic and visceral etiologies need to be ruled out.

IMAGING STUDIES

- Evidence-based guidelines do not support imaging for shoulder pain unless there is an indication of underlying pathology.
- Plain radiography: Anteroposterior view can reveal tendon calcifications and migration of humeral head, indicating a large tear.
- Ultrasonography: Accurate tool for initial evaluation, but has limitations as it is highly operator dependent; partial tears are difficult to identify.
- MRI (Fig. E6 and E7): Test of choice for shoulder soft tissue pathology when surgery is being considered. Lower sensitivity for partial tears, especially in the setting of severe osteoarthritis (OA).
- MRI arthrography: Useful when MRI is normal but a tear is clinically suspected. Better than MRI for picking up partial tears and labral tears. Can use CT arthrography instead if patient has a contraindication to an MRI.
- In-office needle arthroscopy has been shown in a recent systematic review to cost less but be diagnostically inferior to MRI for the diagnosis of rotator cuff tears.

Rx TREATMENT

ACUTE GENERAL Rx

- Ice and rest without aggravating activity.
- Physical therapy and a structured exercise program are unequivocally the main intervention for symptomatic rotator cuff pathology.
- Acetaminophen and/or topical or oral NSAIDs for 7 to 10 days, then as needed.
- Subacromial glucocorticoid injections (usually mixed with local anesthetic) can be used

in patients with severe pain and without suspected tears. Ultrasound-guided injection of an inflamed or thickened bursa has better outcomes.
- Intraarticular injections with hyaluronic acid in combination with physical therapy are more effective than physical therapy alone in reducing pain and improving function. However, the use of platelet-rich plasma injections in treating chronic rotator cuff tears may not be beneficial.
- Surgery is reserved for healthy patients with acute full-thickness tears or with chronic partial tears who fail conservative management. However, a recent systematic review showed subacromial decompression did not improve outcomes for painful shoulder impingement compared with placebo.

DISPOSITION

Return to work or sport should be gradual and based upon the ability to exhibit full range of motion (ROM) and appropriate strength without discomfort.

REFERRAL

- Physical therapy.
- Orthopedic consultation should be obtained in patients with a clinically significant rotator cuff tear and in patients who fail to improve with conservative management.

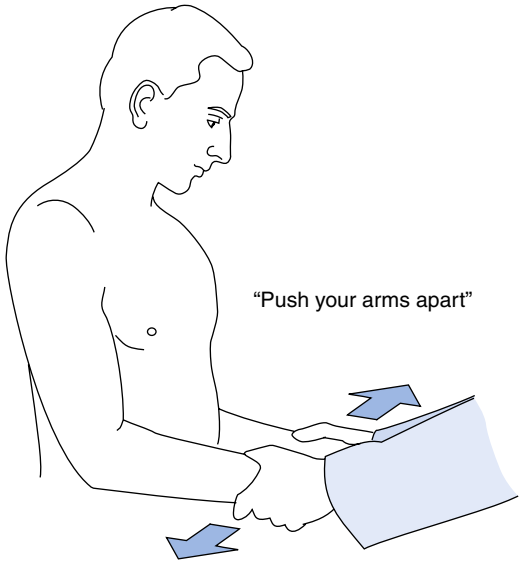

FIG. E4 Infraspinatus test. The clinician stands in front of the patient, and the patient's arms are at his or her side with elbows flexed 90 degrees and thumbs up. The examiner places his or her hands outside those of the patient's and directs the patient to move his arms out (i.e., direction of arrow), resisting the clinician's opposing inward pressure. (From McGee S: *Evidence-based physical diagnosis*, ed 4, Philadelphia, 2018, Elsevier.)

PEARLS & CONSIDERATIONS

COMMENTS

- Supraspinatus is the most commonly injured muscle.
- Rotator cuff tears can be asymptomatic, especially in the elderly.
- Identification of partial tears remains a clinical challenge, and imaging is often needed.
- It is important to differentiate tears from tendinopathy because they require different management.
- Most patients respond to conservative management. However, 50% of patients with shoulder pain have symptoms for over 6 mo.
- Untreated longstanding rotator cuff tendinopathy can cause significant loss in range of motion and adhesive capsulitis.

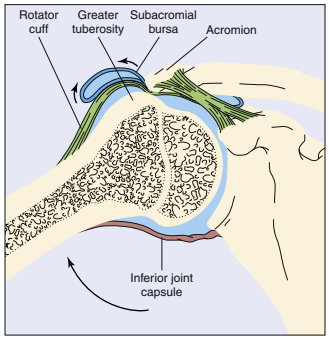

FIG. E5 Impingement of the rotator cuff and subacromial bursa. Mechanism of impingement of the rotator cuff and subacromial bursa between the humeral head and overlying coracoacromial arch. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

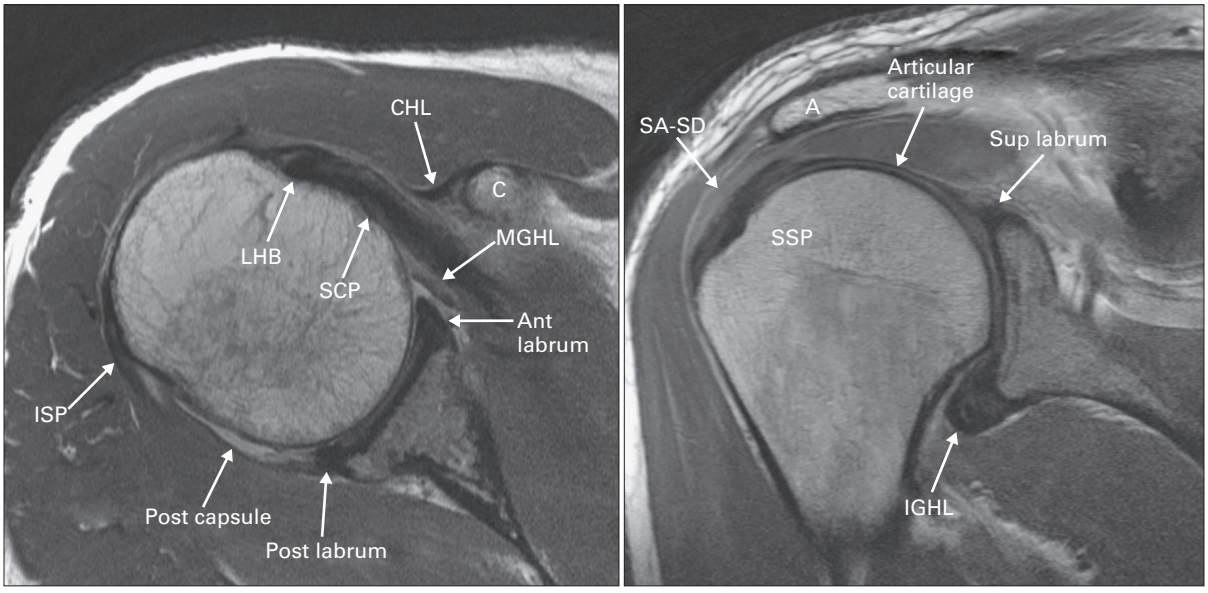

FIG. E6 Magnetic resonance imaging of the shoulder showing the anatomic features of the glenohumeral joint. *A,* Acromion; *Ant,* anterior; *C,* cyst; *CHL,* coracohumeral ligament; *IGHL,* inferior glenohumeral ligament; *ISP,* infraspinatus; *LHB,* long head of biceps; *MGHL,* middle glenohumeral ligament; *Post,* posterior; *SA-SD,* subacromial/subdeltoid; *SCP,* subscapularis; *SSP,* supraspinatus; *Sup,* superior. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

TABLE E1 Differential Diagnosis of Shoulder Pain: Clinical and Radiographic Features of Common Causes of Shoulder Pain

Diagnosis	Age	Type of Onset	Location of Pain	Night Pain	Active Range of Motion	Passive Range of Motion	Impingement Signs	Radiation of Pain	Paresthesia	Weakness	Instability	Radiographic Changes	Special Features
Rotator cuff tendinitis	Any	Acute or chronic	Deltoid region	+	↓↓ guarding	Normal	+++	–	–	Only due to pain	Look for	In chronic cases	Painful arc of abduction
Rotator cuff tears (chronic)	>40 yr	Often chronic	Deltoid region	++	↓↓↓	Normal (may ↓ later)	++	–	–	++	–	+	Wasting of cuff muscles
Bicipital tendinitis	Any	Overuse	Anterior	–	↓ guarding	Normal	+	Occasionally into biceps	–	Only due to pain	Look for	None	Special examination tests
Calcific tendinitis	30-60 yr	Acute	Point of shoulder	++	↓↓↓ guarding	Normal except for pain	+++	–	–	Only due to pain	–	++	Tenderness ++
Capsulitis ("frozen shoulder")	>40 yr	Insidious	Deep in shoulder	++	↓↓	↓↓	+	–	–	–	–	–	Global range of motion ↓
Acromioclavicular joint	Any	Acute or chronic	Over joint	Lying on side	↓ full elevation	Normal	–	–	–	–	–	In chronic cases	Local tenderness
Osteoarthrosis of glenohumeral joint	>40 yr	Insidious	Deep in shoulder	++	↓↓	↓↓	–	–	–	May have mild	–	+++	Crepitus
Glenohumeral instability	Usually <25 yr	Episodic	Anterior or posterior	–	Only apprehension	Only apprehension	Possible	–	+ with acute episodes	+ with acute episodes	+++	Often	Stress tests
Cervical spondylosis	>40 yr	Insidious	Suprascapular	Often	Normal	Normal	–	++	+++	+	–	In cervical spine	Pain with neck movement
Thoracic outlet syndrome	Any	Usually with activity	Neck, shoulder, arm	–	Normal	Normal	–	++	++	++	–	–	Special examination tests

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

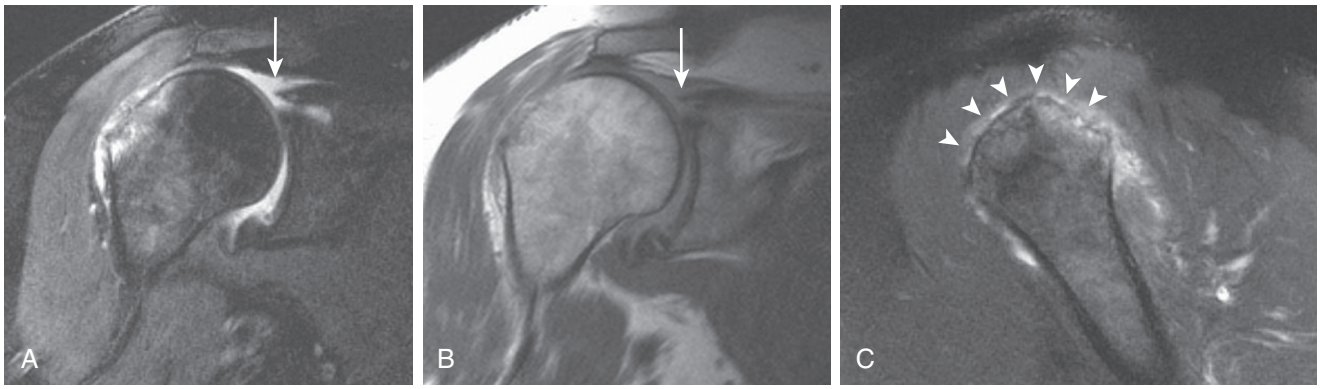

FIG. E7 Oblique coronal fat-suppressed proton density–weighted **(A),** oblique coronal proton density–weighted **(B),** and oblique sagittal fat-suppressed T2-weighted **(C)** magnetic resonance images demonstrate a massive full-thickness rotator cuff tear. Note the retraction of the myotendinous junction to the level of the glenoid (**A** and **B,** *arrows*). There is involvement of the entire supraspinatus and infraspinatus tendons as demonstrated by the complete stripping of the tendons from the greater tuberosity (**C,** *arrowheads*). Also note the markedly narrowed acromiohumeral interval. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2014, WB Saunders.)

- A recent trial showed that older patients with symptomatic, nontraumatic, supraspinatus tears do not benefit from surgery. Patients who underwent surgery and physiotherapy fared no better than those who underwent physiotherapy alone.

RELATED CONTENT

Rotator Cuff Pain (Patient Information)
Rotator Cuff Tear (Patient Information)
Rotator Cuff Tendinitis (Patient Information)
Rotator Cuff Tendinosis (Patient Information)

Bursitis (Related Key Topic)

AUTHORS: **Jeremy E. Raducha, MD,** and **Manuel F. DaSilva, MD**

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BASIC INFORMATION

DEFINITION

Rubella is a mild illness caused by the rubella virus that can cause severe congenital problems by in vitro transmission to a fetus when a pregnant woman becomes infected.

SYNONYM

German measles

ICD-10CM CODES

B06.9	Rubella without complication
B06	Rubella
B06.8	Rubella with other complications
P35.0	Congenital rubella syndrome
Z23	Encounter for immunization
B06.00	Rubella with neurological complication, unspecified
B06.01	Rubella encephalitis
B06.02	Rubella meningitis
B06.09	Other neurological complications of rubella
B06.81	Rubella pneumonia
B06.82	Rubella arthritis
B06.89	Other rubella complications
B06.9	Rubella without complication
Z20.4	Contact with and (suspected) exposure to rubella

EPIDEMIOLOGY & DEMOGRAPHICS

- Before vaccination (i.e., before 1969):
  1. 28 reported cases per 100,000 person-yr, eight of which were in persons >15 yr.
  2. Four cases of congenital rubella syndrome per 100,000 live births.
- Since mass vaccination (i.e., after 1980), most cases have occurred in unimmunized people, with <1 case per 100,000 person-yr (acquired and congenital) (Fig. E1).
- Currently, 10% to 20% of childbearing-age women are susceptible.
- The highest risk of developing long-term complications of congenital infection exists during the first trimester of gestation; both risk of congenital infection and long-term complications drop during the second trimester, and although the risk of congenital infection increases during the third trimester, there is no risk of long-term complication at that point.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acquired infection:
  1. Incubation: 14 to 21 days
  2. Prodrome: 1 to 5 days; low-grade fever, headache, malaise, anorexia, mild conjunctivitis, coryza, pharyngitis, cough, and cervical, suboccipital, and postauricular lymphadenopathy
  3. Rash: 1 to 5 days
- Enanthema: Palatal macules
- Exanthema (rash): Blotchy eruption beginning on face and neck (Fig. E2) and then spreading to trunk and limbs:
  1. Occasional splenomegaly and hepatitis (during rash)
  2. Complications: Arthritis (15%, mostly in adult women), thrombocytopenia, myocarditis, optic neuritis, encephalitis (all <0.1%)
- Congenital infection (see Table E1):
  1. Deafness: 85%
  2. Intrauterine growth retardation: 70%
  3. Cataracts: 35%
  4. Retinopathy: 35%
  5. Patent ductus arteriosus: 30%
  6. Pulmonary artery hypoplasia: 25%
  7. In utero death: 20%
  8. Mental retardation: 10% to 20%
  9. Meningoencephalitis: 10% to 20%
  10. Behavior disorder: 10% to 20%
  11. Hepatosplenomegaly: 10% to 20%
  12. Bone radiolucencies: 10% to 20%
  13. Diabetes mellitus (type 1): 10% to 20% by age 35 yr
  14. Other congenital heart defects: 2% to 5%

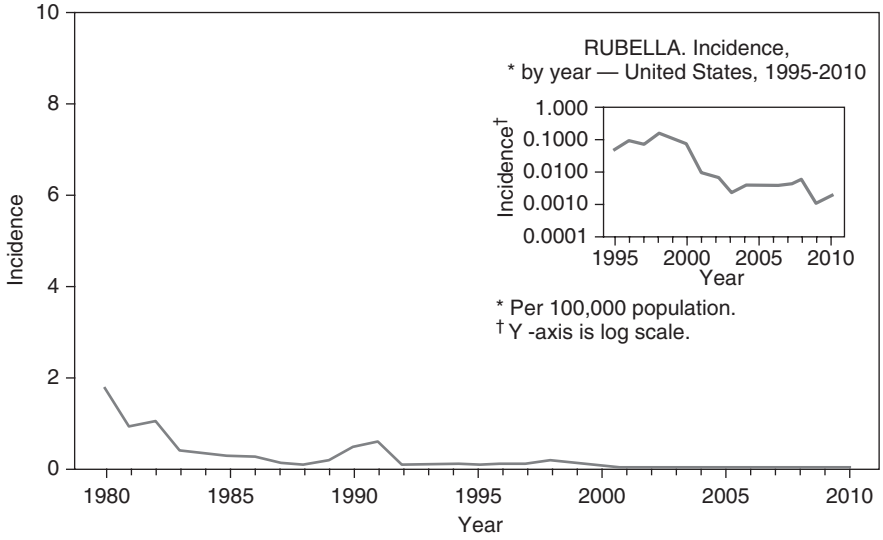

FIG. E1 Rubella. Incidence by yr in the U.S., 1980 through 2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR* 59:1–111, 2012.)

ETIOLOGY & PATHOGENESIS

- Acquired infection:
  1. Viral portal of entry is upper respiratory tract.
  2. Viral replication occurs in lymph nodes; then hematogenous dissemination occurs to many organs, including placenta if present.
  3. Immune complexes may be cause of rash and arthritis.
- Congenital infection:
  1. Fetus is infected by the placenta during maternal-acquired infection.
  2. Cellular damage in the fetus results from cytolysis of fetal cells, mostly by fetal vasculitis or from immune-mediated inflammation and damage.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acquired rubella syndrome
  1. Other viral infections by enteroviruses, adenoviruses, human parvovirus B-19, measles
  2. Scarlet fever
  3. Allergic reaction
  4. Kawasaki syndrome
- Congenital rubella syndrome
  1. Congenital syphilis, toxoplasmosis, herpes simplex, cytomegalovirus, and enterovirus can cause a similar set of problems

WORKUP

- Acquired infection
  1. Serologic test (hemagglutination inhibition, neutralization tests, complement fixation tests, passive agglutination, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA])
  2. Immunoglobulin (Ig) M antibodies (by EIA) are detected early (by second to fourth week)
  3. IgG antibodies (by ELISA) can be measured as acute phase (7 days after rash onset) and convalescent phase (14 days later)
- Congenital infection
  1. Viral culture (from nasopharynx)
  2. Serologic studies: IgM anti–rubella virus detection by EIA is the method of choice (after the newborn is age 5 mo)

IMMUNIZATION

- Four existing vaccines provide persisting immunity in 92% of vaccines. Indications:
  1. All children ≥12 mo (as part of the measles-mumps-rubella [MMR] vaccine)
  2. Postpubertal women
- Vaccinate if not known to be immunized (advise not to become pregnant within 3 mo of vaccination)
- Premarital serologic screening for rubella immunity

FIG. E2 Rash of rubella. (From Kliegman RM et al: *Nelson textbook of pediatrics*, ed 19, Philadelphia, 2011, Saunders.)

TABLE E1 Pathologic Findings in Congenital Rubella Syndrome

System	Pathologic
Cardiovascular	Patent ductus arteriosus Pulmonary artery stenosis Ventriculoseptal defect Myocarditis
Central nervous system	Chronic meningitis Parenchymal necrosis Vasculitis with calcification
Eye	Microphthalmia Cataract Iridocyclitis Ciliary body necrosis Glaucoma Retinopathy
Ear	Cochlear hemorrhage Endothelial necrosis
Lung	Chronic mononuclear interstitial pneumonitis
Liver	Hepatic giant cell transformation Fibrosis Lobular disarray Bile stasis
Kidney	Interstitial nephritis
Adrenal gland	Cortical cytomegaly
Bone	Malformed osteoid Poor mineralization of osteoid Thinning cartilage
Spleen, lymph node	Extramedullary hematopoiesis
Thymus	Histiocytic reaction Absence of germinal centers
Skin	Erythropoiesis in dermis

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

- Prenatal or antepartum serologic screening for rubella
- Vaccinate susceptible women postpartum
- Serologic screening for female workers likely to be exposed to rubella (e.g., teachers, child-care employees, health care workers)

CONTRAINDICATIONS

- Pregnancy
- Recent receipt of immune globulin or blood transfusion (2 wk before to 3 mo after)
- Immunodeficiency (except AIDS)
- Adverse reactions:
  1. Fever, rash, or lymphadenopathy: 5% to 15%
  2. Arthralgias: 0.5% in children; 25% in adult women
  3. Transient peripheral neuropathy (rare)

Rx TREATMENT

- No known effective antiviral therapy
- Management of specific congenital problems as appropriate

RELATED CONTENT

Rubella (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

BASIC INFORMATION

DEFINITION

Salivary gland neoplasms are benign or malignant tumors of the salivary glands (parotid, submandibular, or sublingual).

SYNONYMS

These tumors are often named according to their histologic type (see "Diagnosis").

ICD-10CM CODES

C08.9	Malignant neoplasm of major salivary gland, unspecified
C07	Malignant neoplasm of parotid gland
C08.0	Malignant neoplasm of submandibular gland
C08.1	Malignant neoplasm of sublingual gland

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: One to two cases per 100,000 person-yr (1% of all head and neck tumors)

RISK FACTORS:

- The causes are not fully understood.
- Prior radiation, cancer history, and genetic predisposition may play a role.
- Workers involved in rubber manufacturing and beauty shops and those with exposure to nickel compounds may have an increased risk of salivary gland cancers.
- Chronic inflammation of salivary glands is not clearly defined as a risk factor.

DISTRIBUTION:

- Parotid gland, 85% (80% are benign)
- Submandibular gland, 10% (55% are benign)
- Sublingual and minor glands, 5% (35% are benign)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Parotid gland:
  1. Painless swelling overlying the masseter muscle (under the temporomandibular joint)
  2. Pain
  3. Facial nerve palsy
  4. Cervical lymph nodes
  5. Mass in oral cavity
- Submandibular gland: Swelling under anterior portion of the mandible.
- Sublingual gland: Intraoral swelling under the tongue, medial to the mandible.
- Initial spread is by local invasion. Parotid tumors present fixation to surrounding structures in approximately 20% of cases, skin invasion in 10%, and facial nerve involvement in 25%.
- Neck lymph node metastases are more common in the submandibular gland than in the parotid gland, about 40% vs. 25%, respectively.
- Distant metastases at presentation are rare. At 10 yr they account for approximately 30% to 40%, primarily depending on histologic type (adenoid cystic carcinoma, squamous cell, undifferentiated, and salivary duct carcinoma). Lung and bone are the most common sites, depending on histologic type.
- Lung and bone are the most common sites of metastasis.
- Risk factors for recurrence postoperatively include locally advanced tumor, pathologic T_3-T_4 stage, invasion into adjacent structures, nodal involvement, high-grade histology, perineural invasion, angiolymphatic invasion, positive margins, and recurrent disease.

ETIOLOGY AND PATHOGENESIS:

- Several salivary gland tumors are characterized by tumor-type–specific gene fusions. The major targets of the translocations are transcriptional coactivators, tyrosine kinase receptors, and transcription factors involved in growth factor signaling and cell cycle regulation.
- Adenoid cystic carcinoma (ACC) is characterized in more than 80% cases by a t(6;9)(q22–23;p23–24) translocation, resulting in a fusion of the *MYB* oncogene to the transcription factor gene *NFIB. MYB* is a transcription factor involved in the control of cell proliferation, apoptosis, and differentiation that is highly expressed in immature, proliferating cells and is downregulated as cells become differentiated.
- Mucoepidermoid carcinoma (MEC), the most common subtype, is characterized by a t(11;19)(q21–22;p13) translocation, resulting in a *CRTC1-MAML2* gene fusion. The fusion oncoprotein has transforming activity and activates transcription of several target genes.

DIAGNOSIS

PATHOLOGY

HISTORY

Benign Tumors:

- Mixed tumor (usually parotid)
- Adenolymphoma (Warthin tumor)
- Pleomorphic adenoma
- Capillary hemangioma, lymphangioma (in children)
- Intraductal papilloma
- Other (e.g., myoepithelioma, canalicular adenoma, basal cell adenoma)

Malignant Tumors:

- Mucoepidermoid carcinoma (most common malignant tumor of the parotid gland)
- Adenoid cystic carcinoma
- Adenocarcinoma
- Malignant mixed tumor
- Squamous cell carcinoma
- Other

STAGE (TNM):

T_0	No evidence of primary tumor
T_1	Tumor <2 cm
T_2	Tumor 2-4 cm
T_3	Tumor 4-6 cm
T_4	Tumor >6 cm

All subdivided into:

- Without local extension
- With local extension

N_0	No lymph node metastasis
N_1	Single ipsilateral node <3 cm
N_2	Ipsilateral, contralateral, or bilateral node <6 cm
N_3	Any node >6 cm
M_0	No distant metastasis
M_1	Distant metastasis
Stage I	T_{1a} or $_{2a}N_0M_0$
Stage II	$T_{1b,2b,3a}$ N_0M_0
Stage III	$T_{3b,4a}$ N_0M_0 or any T except $_{4b}N_1M_0$
Stage IV	T_{4b} N any M any or T any $N_{2,3}M_0$ or T any N_1M_1

WORKUP

- Fine-needle aspiration. The sensitivity, specificity, and accuracy of parotid gland aspirates are approximately 92%, 100%, and 98%, respectively
- Imaging by CT scan or MRI (Fig. E1)
- Open biopsy (rarely indicated)

TREATMENT

Malignant tumors:

- Surgery is the mainstay of treatment; gland resection and neck dissection if lymph nodes are involved is the standard approach.
- A lateral lobectomy with preservation of facial nerve should be considered for tumors confined to the superficial lobe of the parotid gland. Gross tumor should not be left in situ, but if the facial nerve is able to be preserved by "peeling" tumor off the nerve, it should be

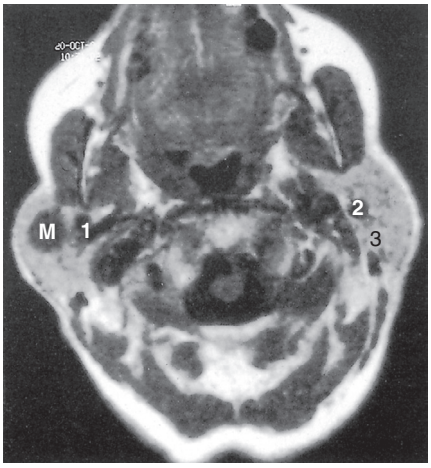

FIG. E1 Pleomorphic adenoma of parotid gland. Pleomorphic adenoma in the right parotid *(M)* is a well-defined, low-signal intensity mass on the axial T1-weighted MRI. Note displacement of the retromandibular vein *(1)* medially by the mass compared with the normal left retromandibular vein *(2).* The left facial nerve *(3)* branching through the normal left parotid is seen. (From Skarin AT: *Atlas of diagnostic oncology,* ed 4, St Louis, 2010, Mosby.)

attempted, followed by radiation therapy for microscopic disease.
- Postoperative radiotherapy is indicated for high-risk malignant tumors and has demonstrated improved overall survival.
- Cisplatin chemotherapy can be considered in combination with radiotherapy for high-risk or unresectable disease.
- Single-agent chemotherapy (cisplatin, doxorubicin, methotrexate, taxanes) or multiagent regimens can be used if metastatic spread-through response rates are low.
- The immune checkpoint inhibitor pembrolizumab has demonstrated promising antitumor activity and a manageable safety profile in patients with advanced salivary gland cancers.

Targeted therapies targeting EGFR (cetuximab) and c-kit (imatinib) have been evaluated with limited efficacy in metastatic patients.

PROGNOSIS OF MALIGNANT TUMORS

Five-yr survival rates:
- Mucoepidermoid carcinoma: 75% to 95%
- Adenoid cystic carcinoma: 40% to 80%
- Adenocarcinoma: 20% to 75%
- Malignant mixed tumor: 35% to 75%
- Squamous cell carcinoma: 25% to 60%

RELATED CONTENT

Salivary Gland Tumors (Patient Information)

AUTHOR: **Ritesh Rathore, MD**

SUGGESTED READINGS

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Cohen RB et al: Pembrolizumab for the treatment of advanced salivary gland carcinoma: findings of the Phase 1b KEYNOTE-028 Study, *Am J Clin Oncol* 41(11):1083-1088, 2018.

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BASIC INFORMATION

DEFINITION

Salmonellosis is an infection caused by one of several serotypes of a gram-negative bacillus of the genus *Salmonella.* Salmonella infection can be typhoidal (serotype Typhi or Paratyphi) or nontyphoidal. Current *Salmonella* nomenclature is described in Table 1.

SYNONYMS

Typhoid fever
Paratyphoid fever
Enteric fever

ICD-10CM CODES

A02.0	*Salmonella* enteritis
A02.1	*Salmonella* sepsis
A02.2	Localized *Salmonella* infections
A02.8	Other specified *Salmonella* infections
A0.9	*Salmonella* infection, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Epidemiologically, the clinical syndromes are divided into those that cause a typhoidal type of infection (systemic illness with fever and abdominal pain) such as *Salmonella typhi* and those that do not: Nontyphoidal *Salmonella* infections (gastroenteritis) such as *S. enteritidis*, *S. newport*, and *S. typhimurium.*
- Estimated 1 million cases/yr of nontyphoidal salmonellosis in the United States (leading cause of foodborne illness in the U.S.). In 2017 an outbreak occurred linked to live poultry in backyard flocks with over 960 cases in 48 states caused by several different *Salmonella* bacteria.
- Largest outbreak of gastroenteritis syndrome (nontyphoidal): 200,000 who ingested contaminated milk.
- Approximately 500 cases of *Salmonella typhi* infection are reported each yr, of which nearly 80% is associated with foreign travel.

PREDOMINANT AGE:

- <20 yr old
- >70 yr old
- Highest rates of infection in infants, especially neonates

PEAK INCIDENCE: Summer and fall

GENETICS:

Neonatal Infection:

- Highly susceptible to infection with nontyphoidal *Salmonella*

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Infections:
  1. Localized to GI tract (gastroenteritis)
  2. Systemic (typhoid fever)
  3. Localized outside of GI tract
- Gastroenteritis:
  1. Incubation period: 12 to 48 hr
  2. Nausea, vomiting
  3. Diarrhea, abdominal cramps
  4. Fever
  5. Bacteremia: Occurs mostly in the immunocompromised host or those with underlying conditions, including HIV infection
  6. Self-limited illness lasting 3 or 4 days
  7. Colonization of GI tract persistent for months, especially in those treated with antibiotics
- Typhoid fever:
  1. Incubation period of few days to several wk
  2. Prolonged fever, often with a stepwise-increasing temperature pattern
  3. Myalgias
  4. Headache, cough, sore throat
  5. Malaise, anorexia
  6. Abdominal pain
  7. Hepatosplenomegaly
  8. Diarrhea or constipation early in the course of illness
  9. Rose spots (faint, maculopapular, blanching lesions) sometimes seen on chest or abdomen
- Untreated disease:
  1. Fever lasting 1 to 2 mo
  2. Main complication: GI bleeding caused by perforation from ulceration of Peyer patches in the ileum
  3. Rare complications:
     a. Mental status changes
     b. Shock
  4. Relapse rate of approximately 10%
- Infections outside GI tract:
  1. Can occur in virtually any location
  2. Usually occur in patients with underlying diseases
  3. Endocarditis, endovascular infections are caused by seeding of atherosclerotic plaques or aneurysms
  4. Hepatic or splenic abscesses in patients with underlying disease in these organs
  5. Urinary tract infections in patients with renal tuberculosis (TB) or schistosomiasis
  6. *Salmonellae* are a frequent cause of gram-negative meningitis in neonates
  7. Osteomyelitis in children with hemoglobinopathies (particularly sickle cell disease)

ETIOLOGY

- More than 2000 serotypes of *Salmonella* exist, but only a few cause disease in humans. Host factors and conditions predisposing to the development of systemic disease with nontyphoidal *Salmonella* strains are described in Table 2 and Table 3.
- Raw produce is an increasingly recognized vehicle for salmonellosis. In 2008 there was a large outbreak due to contaminated jalapeno and Serrano peppers with *Salmonella Saintpaul* involving 1500 persons, of whom 21% were hospitalized and two died. In 2009 there was an outbreak associated with contaminated peanut butter and peanuts. In 2017 there was an outbreak associated with papaya.
- Some found only in humans are the cause of enteric fever:
  1. *S. typhi*
  2. *S. paratyphi*
- Some responsible for gastroenteritis and frequently isolated from raw meat and poultry and uncooked or undercooked eggs:
  1. *S. typhimurium*
  2. *S. enteritidis*
- *S. choleraesuis* is a prototype organism that causes extraintestinal nontyphoidal disease.
- Transmission generally via ingestion of contaminated food or drink.
- Outbreaks of gastroenteritis related to contaminated poultry, meat, and dairy products are common.
- Typhoid fever is a systemic illness caused by serotypes exclusive to humans:
  1. Acquisition by ingestion of food or water contaminated by other humans.
  2. Most cases in the United States are:

TABLE 1 *Salmonella* Nomenclature

Traditional Usage	Formal Name	CDC Designation
S. typhi	*S. enterica** subsp. enterica ser. Typhi	*S.* ser. Typhi
S. dublin	*S. enterica* subsp. enterica ser. Dublin	*S.* ser. Dublin
S. typhimurium	*S. enterica* subsp. enterica ser. Typhimurium	*S.* ser. Typhimurium
S. choleraesuis	*S. enterica* subsp. enterica ser. Choleraesuis	*S.* ser. Choleraesuis
S. marina	*S. enterica* subsp. houtenae ser. Marina	*S.* ser. Marina

CDC, Centers for Disease Control and Prevention; *ser.,* serovar; *subsp.,* subspecies.
*Some authorities prefer *S. choleraesuis* or *S. enteritidis* rather than *S. enterica* to describe the species.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

TABLE 2 Host Factors and Conditions Predisposing to the Development of Systemic Disease with Nontyphoidal *Salmonella* Strains

Neonates and young infants (≤3 mo of age)
HIV/AIDS
Other immunodeficiencies and chronic granulomatous disease
Immunosuppressive and corticosteroid therapies
Malignancies, especially leukemia and lymphoma
Hemolytic anemia, including sickle cell disease, malaria, and bartonellosis
Collagen vascular disease
Inflammatory bowel disease
Achlorhydria or use of antacid medications
Impaired intestinal motility
Schistosomiasis, malaria
Malnutrition

AIDS, Acquired immunodeficiency syndrome; *HIV,* human immunodeficiency virus.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

TABLE 3 Susceptibility to *Salmonella* spp. Infection

Patient Group at Risk	Mechanism
Newborn	Achlorhydria, rapid gastric emptying
	Poorly developed cell-mediated immunity
	Complement deficiency
	Immunoglobulin deficiency in premature infants
Sickle-cell anemia	Reticuloendothelial system overload owing to hemolysis
	Functional asplenia
	Tissue infarcts
	Defective opsonization
Neutropenia (congenital or acquired)	Polymorphonuclear neutrophils needed for killing
Chronic granulomatous disease	Defective killing by polymorphonuclear neutrophils
Defects of immune system IL-12/interferon-γ axis	Defective signaling resulting in failure to activate macrophages and recurrent/persistent infection by nontyphoid *Salmonella*
Acquired immunodeficiency syndrome	Low CD4
	Effects of malnutrition on cell-mediated immunity
	Survival of organisms in macrophages (owing to *Salmonella* genes *PhoP/PhoQ, spvA-D, R*)
Organ transplantation, immunosuppression	Defective cell-mediated immunity
Gastrectomy	Loss of stomach acid barrier
Malaria	Reticuloendothelial overload during hemolysis
	Abnormal complement levels
	Abnormal macrophage function
Bartonellosis (verruga peruana)	Reticuloendothelial overload during hemolysis
Schistosomiasis	*Salmonella* sequestered in schistosomes protected from host defenses and antibiotics

From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.

   a. Acquired during foreign travel: 80% of cases.
   b. Acquired by ingestion of food prepared by chronic carriers, many of whom have acquired the organism outside of the United States.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other causes of prolonged fever:
  1. Malaria
  2. TB
  3. Brucellosis
  4. Amebic liver abscess
- Other causes of gastroenteritis:
  1. Bacterial: *Shigella, Yersinia, Campylobacter* spp.
  2. Viral: Norwalk virus, rotavirus
  3. Parasitic: *Entamoeba histolytica, Giardia lamblia*
  4. Toxic: *Enterotoxigenic E. coli, Clostridium difficile*

WORKUP

- Typhoid fever:
  1. Cultures of blood, stool, urine; repeat if initially negative.
  2. Blood cultures are more likely to be positive early in the course of illness.
  3. Stool and urine cultures are more commonly positive in the second and third wk of illness.
  4. Highest yield with bone marrow biopsy cultures: 90% positive.
  5. Serology using Widal test is helpful in retrospect, showing a fourfold increase in convalescent titers.
- Gastroenteritis: Stool cultures
- Extraintestinal localized infection:
  1. Blood cultures.
  2. Cultures from the site of infection.

LABORATORY TESTS

- Neutropenia is common.
- Transaminitis is possible.
- Culture to grow organism: Blood, body fluids, biopsy specimens.

IMAGING STUDIES

- Not routinely indicated.
- Radiographs of bone may be suggestive of osteomyelitis (particularly in patients with sickle cell disease and bone infarctions).
- CT scan or sonogram of abdomen:
  1. May reveal hepatic or splenic abscesses or pleural involvement.
  2. May reveal aortic aneurysm.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Adequate hydration and electrolyte replacement in people with diarrhea.

TABLE 4 Treatment of Salmonella Gastroenteritis in Children

Organism and Indication	Dose and Duration of Treatment
Salmonella infections in infants <3 mo of age or immunocompromised persons (in addition to appropriate treatment for underlying disorder)	Cefotaxime 100-200 mg/kg/day every 6 hr for 5-14 days *or* Ceftriaxone 75 mg/kg/day once daily for 7 days *or* Ampicillin 100 mg/kg/day every 6 hr for 7 days *or* Cefixime 15 mg/kg/day for 7-10 days

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

ACUTE GENERAL Rx

Treatment decisions must consider the severity of infection and the risk for extraintestinal disease.

- Typhoid fever:
  1. Levofloxacin 750 mg PO/IV q24h or ciprofloxacin 500 mg PO bid or 400 mg IV bid for 7 to 10 days. Should not be used as first line in patients from South Asia due to resistance unless known to be susceptible
  2. Ceftriaxone 2 g IV qd for 7 to 14 days or cefixime (20 to 30 mg/kg/day orally divided into q12h dosing for 7 to 14 days)
  3. Another alternative agent: Azithromycin (1 g orally then 500 mg daily for 5 to 7 days)
  4. Children: See Table 4. In general, quinolones are avoided in children unless a multidrug-resistant strain is involved due to concerns of possible cartilage damage. Another alternative for children: Azithromycin (10 to 20 mg/kg to 1 g maximum once daily for 5 to 7 days)
  5. If tests show susceptibility, can also use amoxicillin or trimethoprim/sulfamethoxazole in adults and children (Table 5)
  6. Dexamethasone 3 mg IV initially, followed by 1 mg IV q6h for eight doses for patients with shock or mental status changes
- Gastroenteritis:
  1. Usually not indicated for gastroenteritis alone because this illness usually self-limited
  2. Treatment may prolong the carrier state and is discouraged for healthy patients <50 yr of age who have relatively mild disease
  3. Prophylactic treatment for patients who are at high risk of developing complications from bacteremia (see Table 4):
     a. Neonates
     b. Patients with hemoglobinopathies
     c. Patients with atherosclerosis
     d. Patients with aneurysms
     e. Patients with prosthetic devices
     f. Immunocompromised patients

TABLE 5 Antibiotics Commonly Used in the Treatment of *Salmonella* Infections

Drug	Dose	Comments
Ciprofloxacin	20-30 mg/kg per day in 2 doses PO or IV	First-line therapy[a]
Ceftriaxone	75-100 mg/kg per day in 1 or 2 doses IM or IV	First-line therapy
Cefotaxime	100-300 mg/kg per day in 3-4 doses IM or IV	First-line therapy
Cefixime	20-30 mg/kg per day in 1 or 2 doses PO	Alternative therapy
Azithromycin	10 mg/kg per day in 1 dose PO	Alternative therapy
Chloramphenicol	50-100 mg/kg per day in 4 doses PO	High frequency of resistance; use only for susceptible strains
Ampicillin	200-400 mg/kg per day in 4 doses PO, IM, or IV	High frequency of resistance; use only for susceptible strains
TMP-SMX	10 mg/kg per day TMP, 50 mg/kg per day SMX in 2 doses PO or IV	High frequency of resistance; use only for susceptible strains

IM, Intramuscular; *IV,* intravenous; *PO,* by mouth; *TMP-SMX,* trimethoprim-sulfamethoxazole.
[a]Not approved by the US Food and Drug Administration in children <18 yr; current expert opinion agrees in recommending this agent as an effective therapy for regions with susceptible *Salmonella* strains and especially for severe infections.
From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

CHRONIC Rx

- Carrier states are possible in those with typhoid fever.
- More common in people >60 yr of age and in people with gallstones.
- Usual site of colonization is the gallbladder.
- Treatment should be considered for those with persistently positive stool cultures and for food handlers.
- Suggested regimens for eradication of carrier state:
  1. Ciprofloxacin 500 mg PO bid for 4 wk.
  2. SMX/TMP 1 to 2 DS tabs PO bid for 6 wk (if susceptible).
  3. Amoxicillin 2 g PO q8h for 6 wk (if susceptible).
- Cholecystectomy may be required in carriers with gallstones who fail medical therapy, but this is rarely indicated for nontyphoidal salmonellosis currently.
- Prolonged course of oral therapy or lifetime suppression for patients with AIDS who have chronic infection.

DISPOSITION

- Typhoid fever:
  1. Treated patients usually respond to therapy; small percentage of chronic carriers.
  2. Untreated patients may have serious complications.
- Gastroenteritis:
  1. Usually self-limited
  2. May be recurrent or persistent in AIDS patients

PEARLS & CONSIDERATIONS

COMMENTS

- Fluoroquinolones remain the most reliably effective class of antibiotics for empiric therapy despite increasing resistance. They should not be used in children or pregnant women.
- Infections should be reported to local health departments.
- Other recent outbreaks in the U.S. have been traced back to raw tomatoes, peanut butter, pet turtles, and frozen pot pies.
- Vaccine is available for *Salmonella typhi*: Oral live weakened vaccine (four doses, one every other day) for age >6 yr and lasts for 5 yr or one dose of inactivated injectable vaccine for persons >2 yr old that lasts for 2 yr, but neither vaccine is greater than 75% effective.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Salmonellosis (Patient Information)
Typhoid Fever (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Behravesh CB et al: 2008 outbreak of Salmonella Saintpaul infections associated with raw produce, *N Engl J Med* 364:918-927, 2011.

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DuPont HL: Acute infectious diarrhea in immunocompetent adults, *N Engl J Med* 370:1532-1540, 2014.

Gaffga NH: Outbreak of salmonellosis linked to live poultry from a mail-order hatchery, *N Engl J Med* 366:2065-2073, 2012.

Haselbeck AH et al: Current perspectives on invasive nontyphoidal Salmonella disease, *Curr Opin Infect Dis* 30:498-503, 2017.

BASIC INFORMATION

BASIC INFORMATION

Sarcoidosis is a chronic multisystem granulomatous disease characterized histologically by the presence of nonspecific, noncaseating granulomas.

SYNONYM

Boeck sarcoid

ICD-10CM CODES

D86	Sarcoidosis
D86.0	Sarcoidosis of lung
D86.1	Sarcoidosis of lymph nodes
D86.2	Sarcoidosis of lung with sarcoidosis of lymph nodes
D86.3	Sarcoidosis of skin
D86.8	Sarcoidosis of other and combined sites
D86.9	Sarcoidosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Incidence is 11 in 100,000 in whites and 35 in 100,000 in blacks; presents most commonly in the winter and early spring. (The adjusted annual incidence among black Americans is roughly three times higher than among white Americans [35.5 cases/100,000, as compared with 10.9/100,000] and is likely more chronic and fatal in black Americans.)

PREDOMINANT SEX: Increased incidence in females

PREDOMINANT AGE: 20 to 40 yr

GENETICS: Familial clustering has been described. Having a first-degree relative with sarcoidosis increases the risk for disease fivefold (ACCESS study). There have been reports of association between sarcoidosis and gene products, specifically HLA class II antigens, encoded by HLA-DRB1 and DQB1 alleles.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical manifestations often vary with the stage of the disease and degree of organ involvement. Patients may be asymptomatic, but a chest radiograph may demonstrate findings consistent with sarcoidosis (see "Imaging Studies"). Nearly 50% of patients with sarcoidosis are diagnosed by incidental findings on chest radiograph. Lung involvement occurs in >90% of patients with sarcoidosis.
- Frequent manifestations:
  1. Pulmonary manifestations: Dry, nonproductive cough; dyspnea; chest discomfort.
  2. Constitutional symptoms: Fatigue, weight loss, anorexia, malaise, night sweats.
  3. Visual disturbances: Blurred vision, ocular discomfort, conjunctivitis, iritis, uveitis (65% of patients).
  4. Dermatologic manifestations (30% of patients): Erythema nodosum (10% of patients), macules, papules, subcutaneous nodules, hyperpigmentation, lupus pernio (indurated violaceous lesions on the nose, lips, ears, and cheeks that can erode into underlying cartilage and bone) (Fig. E1).
  5. Myocardial disturbances, arrhythmias, cardiomyopathy, various conduction abnormalities, and pericardial effusion. Cardiac sarcoidosis is much more common than clinically appreciated and is found in up to 25% of patients in the U.S.
  6. Splenomegaly, hepatomegaly.
  7. Rheumatologic manifestations: Arthralgias have been reported in up to 40% of patients. It typically affects the ankles but can also involve the knees, wrists, and small joints of the hands and feet.
  8. Löfgren syndrome, consisting of triad of arthritis, erythema nodosum, and bilateral hilar adenopathy, occurs in 9% to 34% of patients. Fever is frequently present.
  9. Neurologic and other manifestations: Cranial nerve palsies, diabetes insipidus, meningeal involvement, parotid enlargement, hypothalamic and pituitary lesions, peripheral adenopathy. Neurosarcoidosis is detected in up to 25% of patients and can occur in the absence of apparent disease elsewhere. The presence of anterior uveitis, parotiditis, fevers, and facial nerve palsy is known as Heerfordt syndrome.

ETIOLOGY & PATHOGENESIS

A cardinal feature of sarcoidosis is the presence of CD4+ T cells that interact with antigen-presenting cells to initiate the formation and maintenance of granulomas (Fig. 2). Multiple lines of evidence suggest that sarcoidosis may result from the interaction of multiple genes with environmental exposures or infection.

GENETIC PREDISPOSITION TO SARCOIDOSIS

Various HLA antigens have been implicated in diverse patient populations. Familial predisposition has been reported dating back to 1923, with a wide percentage of variability of affected relatives (0.4% to 21%) and heterogeneity based on genetic background. A more recent study was published by the ACCESS (A Case Controlled Etiologic Survey of Sarcoidosis) study group, which confirmed increased risk for family members with an odds ratio of 4.6 for all relatives. Absolute risk, however, for a family member to be affected was less than 1%. This study also showed a higher risk in white versus African-American siblings and parents.

IMMUNOPATHOGENESIS OF SARCOIDOSIS: Numerous chemokines and cytokines have been implicated in the development and/or resolution of the disease. In sarcoidosis, the alveolitis seen at disease presentation represents an increase in primarily lymphocytic cellularity, predominated by CD4 cells. Presence of increased neutrophils in the bronchoalveolar lavage of patients with sarcoidosis has been associated with persistence of disease, with spontaneous remission noted in 36% of patients with elevated neutrophil counts. Other interstitial lung diseases in which neutrophils have been associated with worse outcomes include interstitial pulmonary fibrosis hypersensitivity pneumonitis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Tuberculosis
- Lymphoma
- Hodgkin disease
- Metastases
- Pneumoconioses
- Enlarged pulmonary arteries
- Infectious mononucleosis
- Lymphangitic carcinomatosis
- Idiopathic hemosiderosis
- Alveolar cell carcinoma
- Pulmonary eosinophilia
- Hypersensitivity pneumonitis
- Fibrosing alveolitis
- Collagen disorders
- Parasitic infection

Section II describes the differential diagnosis of granulomatous lung disease and a classification of granulomatous disorders.

WORKUP

- No pathognomonic diagnostic test exists for sarcoidosis, so the diagnosis remains one of exclusion. Workup is aimed at excluding critical organ involvement, determining extent and severity of disease, and excluding other disease. The presence of noncaseating granulomas does not establish the diagnosis, because conditions such as tuberculosis and malignancies, among others, can cause granulomas. A complete neurologic and ophthalmologic examination is mandatory. A complete occupational and environmental exposure history is recommended.
- Initial laboratory evaluation should include complete blood count, serum chemistries (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes, blood urea nitrogen, creatinine, serum calcium), urinalysis, 24-hour urinary excretion of calcium, CRP, ESR, and tuberculin skin test.
- Chest radiograph and ECG should also be obtained in all patients with sarcoidosis.
- Pulmonary function testing: Spirometry, diffusion capacity of carbon monoxide–single breath.
- Biopsy should be done on accessible tissues suspected of sarcoid involvement (conjunctiva, skin, lymph nodes); bronchoscopy with transbronchial biopsy (85% diagnostic yield) is often performed in patients without any readily accessible site. Endobronchial ultrasound-guided fine-needle aspiration of intrathoracic lymph nodes also has high diagnostic yield and makes use of mediastinoscopy usually unnecessary. Among patients with suspected Stage I/II pulmonary sarcoidosis undergoing tissue confirmation, the use of endosonographic nodal aspiration compared with bronchoscopic biopsy resulted in greater diagnostic yield.

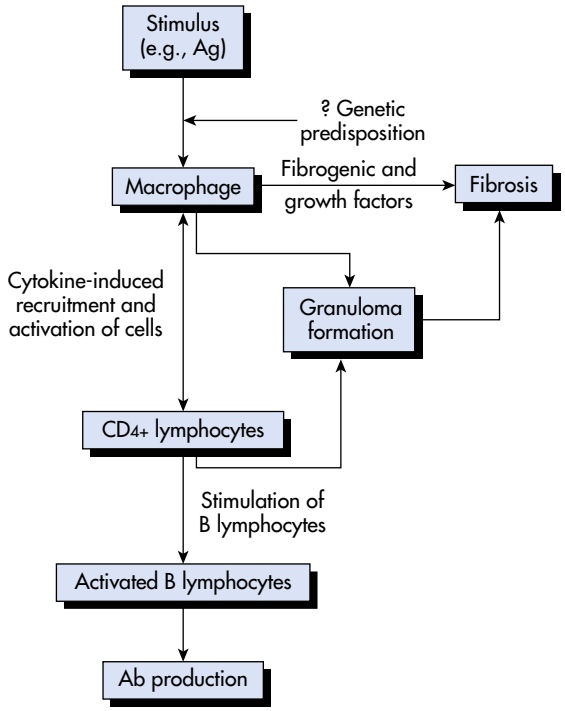


FIG. 2 Simplified proposed pathogenetic sequence in sarcoidosis. *Ab*, Antibody; *Ag*, antigen. (From Weinberger SE: *Principles of pulmonary medicine*, ed 7, Philadelphia, 2019, Elsevier.)

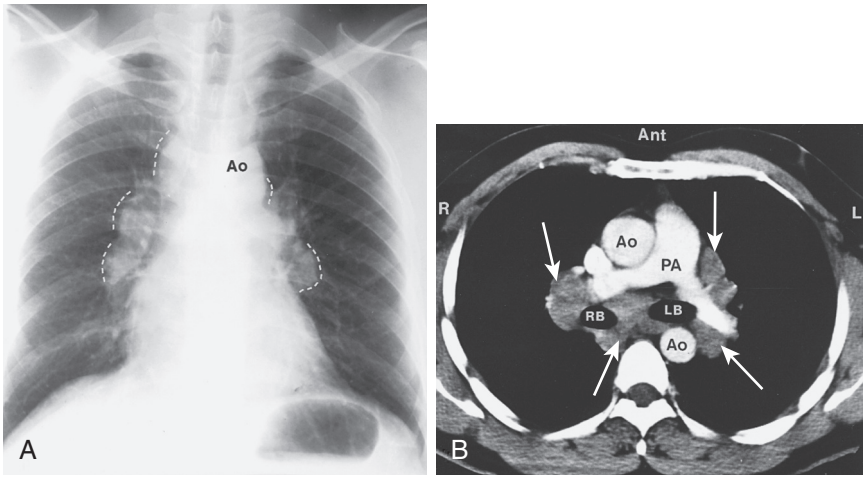


FIG. 3 Sarcoid. Marked lymphadenopathy *(dotted lines)* is seen in the region of both hila in the right paratracheal region **(A).** The transverse contrast-enhanced CT scan of the upper chest **(B)** clearly shows the ascending and descending aorta *(Ao)* as well as the pulmonary artery *(PA)* and superior vena cava. The right and left mainstem bronchus area is also seen. The *arrows* indicate the extensive lymphadenopathy. *LB,* Left bronchus; *RB,* right bronchus. (From Mettler FA [ed]: *Primary care radiology*, Philadelphia, 2000, Saunders.)

LABORATORY TESTS

Laboratory abnormalities:

- Hypergammaglobulinemia, anemia, leukopenia may be present
- Liver function test abnormalities are common, e.g., elevated alkaline phosphatase
- Hypercalcemia (11% of patients), hypercalciuria (40% of patients; attributable to increased gastrointestinal absorption, abnormal vitamin D metabolism, and increased calcitriol production by sarcoid granuloma)
- Angiotensin-converting enzyme: Elevated in approximately 75% of patients with untreated sarcoidosis; nonspecific and poor sensitivity; generally not useful as a diagnostic tool or in following the course of the disease
- Serum adenosine deaminase (ADA); serum amyloid A (SAA) elevated but nonspecific

IMAGING STUDIES

- Chest radiograph (Fig. 3): Pulmonary sarcoidosis is classified based on radiographic pattern. Adenopathy of the hilar and paratracheal nodes is a frequent finding. Parenchymal changes may also be present, depending on the stage of the disease (stage 0, normal radiograph; stage I, bilateral hilar adenopathy; stage II, stage I plus pulmonary infiltrate; stage III, pulmonary infiltrate without adenopathy; stage IV, advanced fibrosis with evidence of "honeycombing," hilar retraction, bullae, cysts, and emphysema).
- Pulmonary function tests (spirometry and diffusing capacity of the lung for carbon dioxide): May be normal or may reveal a restrictive ventilatory defect with reduced forced vital capacity, reduced DLCO, or both. Endobronchial sarcoidosis may exhibit obstructive physiology, depending on severity.
- For patients without apparent lung involvement, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is useful in identifying sites for diagnostic biopsy.
- CT imaging, more specifically high-resolution CT, may help detect early parenchymal abnormalities. It is indicated when the chest radiograph is atypical for sarcoidosis.
- FDG-PET and MRI with gadolinium are useful in patients with suspected cardiac and neurologic involvement.
- Gallium-67 scan: Represents an older testing modality. It will localize in areas of granulomatous infiltrates; however, it is not specific and not necessary. The "panda" sign (localization in the lacrimal and salivary glands, giving a "panda" appearance to the face) is suggestive of sarcoidosis.
- Bronchoscopy: Flexible bronchoscopy and bronchoalveolar lavage (BAL) with transbronchial biopsy (showing noncaseating granulomas) are traditional methods for the minimally invasive diagnosis of sarcoidosis. With hilar adenopathy, endobronchial ultrasound (EBUS) is the preferred method for lymph node sampling. BAL may show predominantly lymphocytosis, elevated ADA levels, and elevated CD4:CD8 ratio (4:1).
- Mediastinoscopy: Rarely used nowadays for lymph node sampling and diagnosis.

Rx TREATMENT

ACUTE GENERAL Rx

- Many patients with sarcoidosis will not require any treatment. In general, treatment should be instituted when organ function is threatened. Corticosteroids (Table 1) are the mainstay of therapy when treatment is required (e.g., prednisone 40 mg qd for 8 to 12 wk with gradual tapering of the dose to 10 mg qod over 8 to 12 mo); corticosteroids should be considered in patients with severe symptoms (e.g., dyspnea, chest pain); hypercalcemia; ocular, central nervous system, or cardiac involvement; or progressive pulmonary disease. Patients with interstitial lung disease benefit from oral steroid therapy for 6 to 24 mo.
- A lack of benefit from steroid therapy may be due to the presence of irreversible fibrotic disease. Patients with progressive disease refractory to corticosteroids may be treated with methotrexate 7.5 to 15 mg once per

TABLE 1 Indications for Use of Corticosteroids in Sarcoidosis

Disorder	Treatment
Iridocyclitis	Corticosteroid eye drops; local subconjunctival deposit of cortisone
Posterior uveitis	Oral prednisone
Pulmonary involvement	Steroids rarely recommended for stage I; typically used if infiltrate remains static or worsens over 3-mo period or the patient is symptomatic
Upper airway obstruction	Rare indication for intravenous steroids
Lupus pernio	Oral prednisone shrinks the disfiguring lesions
Hypercalcemia	Responds well to corticosteroids
Cardiac involvement	Corticosteroids usually recommended if patient has arrhythmias or conduction disturbances
Central nervous system involvement	Response is best in patients with acute symptoms
Lacrimal/salivary gland involvement	Corticosteroids recommended for disordered function, not gland swelling
Bone cysts	Corticosteroids recommended if symptomatic

From Andreoli TE [ed]: *Cecil essentials of medicine*, ed 8, Philadelphia, 2010, Saunders.

week or another immunosuppressant such as azathioprine or mycophenolate mofetil.
- Methotrexate, at a dose of 7.5 to 10 mg per week, has been demonstrated to be relatively safe and can also be used as a steroid-sparing agent. Additional agents that have been used with limited clinical experience include pentoxifylline, infliximab, cyclosporine, minocycline, and leflunomide.
- Immunomodulators: Etanercept has not been found to be useful in sarcoidosis. Infliximab has been used with some benefits in cutaneous, pulmonary, and neurologic disease.
- NSAIDs are useful for musculoskeletal symptoms and erythema nodosum.
- Pulmonary rehabilitation in patients with significant respiratory insufficiency. Consider liver and lung transplantation in patients unresponsive to conventional treatment.
- Pulmonary hypertension is a dreaded complication of advanced pulmonary sarcoidosis. The prognosis for patients with sarcoidosis-associated pulmonary hypertension is not known.

DISPOSITION

- The majority of patients with sarcoidosis have spontaneous remission within 2 yr and do not require treatment. Their course can be followed by periodic clinical evaluation, chest radiographs, and pulmonary function tests.
- Blacks have increased rates of pulmonary involvement, a worse long-term prognosis, and more frequent relapses.
- Up to one third of patients have unrelenting disease, leading to clinically significant organ impairment. Adverse prognostic factors in sarcoidosis include age of onset >40 yr, cardiac involvement, neurosarcoidosis, progressive pulmonary fibrosis, chronic hypercalcemia, chronic uveitis, involvement of nasal mucosa, nephrocalcinosis, and presence of cystic bone lesions and lupus pernio.
- Prognosis for Loeffler syndrome is good with remittance within 16 wk in most patients. Symptoms can generally be controlled with NSAIDs. Low-dose glucocorticoids, hydroxychloroquine, and colchicine are also effective.

REFERRAL

Ophthalmologic examination is indicated in all patients with suspected sarcoidosis because ocular findings (iridocyclitis, uveitis, conjunctivitis, and keratopathy) are found in ≥25% of documented cases.

PEARLS & CONSIDERATIONS

COMMENTS

- Serial spirometry and measurement of DLCO can be useful in following response to therapy and disease progression.
- Approximately 15% to 20% of patients with lung involvement advance to irreversible lung impairment (bronchiectasis, cavitation, progressive fibrosis, pneumothorax, and respiratory failure). Death from pulmonary failure occurs in 5% to 7% of patients with sarcoidosis.
- Newer treatment approaches are aimed at targeting mechanisms involving CD4 type 1 helper T cells.
- The diagnosis of sarcoidosis should be reconsidered in the presence of atypical manifestations or persistent/progressive disease despite appropriate therapy.
- Diagnostic biopsy may not be necessary in most patients presenting with asymptomatic bilateral lymphadenopathy (with no other evidence of malignancy), in those with Lofgren syndrome, or in those with Heerfordt syndrome.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Sarcoidosis (Patient Information)

AUTHOR: **Imrana Qawi, MD**

SUGGESTED READINGS

Iannuzzi MC, Fontana JR: Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics, *J Am Med Assoc* 305(4):391-399, 2011.

Soto-Gomez N et al: Diagnosis and management of sarcoidosis, *Am Fam Physician* 93(10):840-848, 2016.

Spagnolo P et al: Sarcoidosis: challenging diagnostic aspects of an old disease, *Am J Med* 125:118-125, 2012.

FIG. E1 Sarcoidosis. A, Erythema nodosum. **B,** Bilateral hilar lymphadenopathy. **C,** Seventh nerve palsy. **D,** Lupus pernio. **E,** Lacrimal gland enlargement. (**D,** courtesy MA Mir. From Mir MA: *Atlas of clinical diagnosis*, Philadelphia, 2003, Saunders.)

BASIC INFORMATION

DEFINITION

Sarcomas are heterogenous groups of malignant cancers of connective tissue, with a wide range of differentiation—blood vessels (angiosarcoma), fat tissue (liposarcoma), and bone (osteosarcoma), among others. Sarcomas can be classified into two basic types: Soft tissue sarcoma (STS) (Table E1) and primary bone sarcoma. Affecting virtually all tissues, they are more common in soft tissues, but 75% occur in the limbs.

ICD-10CM CODES

C22.3	Angiosarcoma of liver
C40	Malignant neoplasm of bone and articular cartilage of limbs
C41	Malignant neoplasm of bone and articular cartilage of other unspecified sites
C49.0	Malignant neoplasm of connective and soft tissue of head, face, and neck
C49.9	Malignant neoplasm of connective and soft tissue, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Sarcoma of bone: Eight cases per million per annum.
  1. In the U.S. there are approximately 2600 new cases annually, and these represent 0.2% of newly diagnosed cancers.
  2. Osteosarcoma (Fig. E1) and Ewing sarcoma occur predominantly during childhood and adolescence.
- STS: 30 cases per million per annum.
  1. In the U.S. there are approximately 11,000 new cases annually, and these represent <1% of newly diagnosed cancers.
  2. The incidence increases with age, with the median age of diagnosis 57 yr.
  3. Men and women are affected equally.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Bone sarcomas. Clinical presentation usually includes:
  1. Pain—at rest or at night
  2. Swelling or mass at the site
  3. Pathologic fractures
- Soft tissue sarcomas:
  1. Present with painless mass (usually >5 cm)
  2. Mass grows slowly for months or years

ETIOLOGY

- Most sarcomas arise sporadically.
- Genetic predispositions:
  1. Familial retinoblastoma (mutation of the RBI gene at 13q14) predisposes to osteosarcoma.
  2. Neurofibromatosis type 1 (mutation of NF1 gene at 17q11) predisposes to malignant peripheral nerve sheath tumor (malignant schwannomas and neurofibrosarcomas).
  3. Diaphyseal aclasis (an autosomal inherited condition) is associated with increased risk of peripheral chondrosarcoma.
  4. Germline mutations associated with soft tissue sarcoma are summarized in Table E2.
- Environmental causes:
  1. Previous radiotherapy for solid tumors predisposes to sarcoma 4 to 10 yr after exposure.
  2. Chronic lymphedema: Associated with the development of angiosarcoma.
  3. Exposure to chemicals (e.g., dioxins, phenoxyacetic herbicides, vinyl chloride increase the risk of hepatic angiosarcoma).
  4. Viruses (e.g., human herpesvirus 8 plays a role in the development of Kaposi sarcoma).
  5. Foreign body (shrapnel, medical implants).
  6. Predisposing environmental factors for soft tissue sarcomas are summarized in Table E3.

DIAGNOSIS

WORKUP

- Soft tissue sarcoma: Any unexplained superficial soft tissue mass >5 cm, or any deep-seated soft tissue mass should be regarded as malignant until proven otherwise.
- Bone sarcoma: Patients with unexplained bone pain, persistent bone tenderness, or nonmechanical bone pain (especially when it disturbs sleep or rest) have bone cancer until proven otherwise.
- Patients with suspected spontaneous fracture or recurrence of the fracture with minor trauma should be considered as having bone cancer.

TABLE E1 Histologic Classification of Soft Tissue Sarcoma

Adipocytic Sarcomas
Atypical lipomatous tumor/well-differentiated liposarcoma
Dedifferentiated liposarcoma
Myxoid liposarcoma
Pleomorphic liposarcoma

Fibroblastic and Myofibroblastic Sarcomas
Malignant solitary fibrous tumor
Inflammatory myofibroblastic tumor
Myxoinflammatory fibroblastic sarcoma
Infantile fibrosarcomas
Adult fibrosarcomas
Myxofibrosarcoma (myxoid undifferentiated pleomorphic sarcoma)
Low-grade fibromyxoid sarcoma (Evans tumor)
Sclerosing epithelioid fibrosarcoma

So-called Fibrohistiocytic Sarcomas
Undifferentiated pleomorphic sarcoma (UPS)

Smooth Muscle Sarcomas
Leiomyosarcoma

Skeletal Muscle Sarcomas
Embryonal rhabdomyosarcoma
Alveolar rhabdomyosarcoma
Pleomorphic rhabdomyosarcoma

Vascular Sarcomas
Epithelioid hemangioendothelioma
Angiosarcoma
Kaposi sarcoma
Solitary fibrous tumor (formerly hemangiopericytoma)

Osseous Sarcomas
Extraskeletal osteosarcoma

Sarcomas of Uncertain Differentiation
Synovial sarcoma
Epithelioid sarcoma
Alveolar soft part sarcoma
Clear cell sarcoma of soft tissue
Extraskeletal myxoid chondrosarcoma
Desmoplastic small round cell tumor
Extrarenal rhabdoid tumor
Extraskeletal Ewing sarcoma
Intimal sarcoma

Notochord-derived Tumor Behaving Like Sarcomas
Chordoma

From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

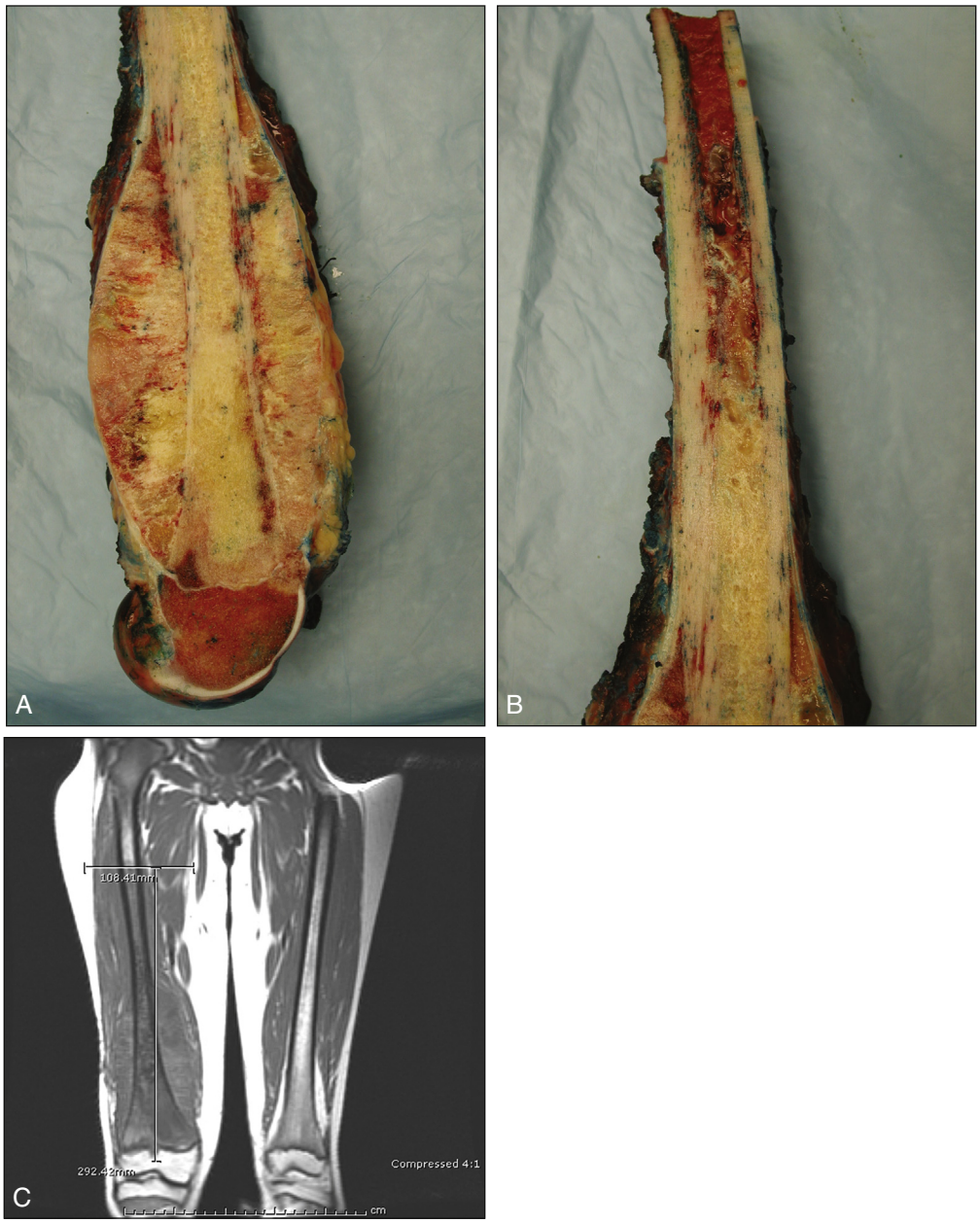


FIG. E1 **A,** Gross photograph of an osteosarcoma of the distal femur. The medullary cavity is filled with tumor, which has replaced the normal marrow contents. The tumor has penetrated and incompletely destroyed the cortex and penetrated the growth plate distally. The Codman triangle, an incomplete host periosteal response, is well demonstrated. Histologically, this would show woven periosteal bone. One also can appreciate how this tumor could enter the joint under the synovium, anteriorly in this case. **B,** A section from higher in the femur shows where the medullary extent of the tumor ends rather abruptly. There is a margin of normal marrow proximal to the marrow extent. **C,** Coronal T1-weighted image of this case nicely shows the extent of the tumor in the medullary cavity and the penetration of the growth plate. It corresponds to the preceding findings seen on the gross specimen. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

- Referral to a sarcoma treatment center of all patients with a suspected sarcoma is recommended.

IMAGING STUDIES (TABLE E4)

- A chest computed tomography (CT) scan (Figs. E2 and E3) is compulsory for staging purposes. Chest spiral CT helps detect lung metastases because hematogenous dissemination to the lungs is the principal form of spread.
- The American Joint Committee on Cancer (AJCC) and International Union Against Cancer (IUCC) are widely used for staging classification.
- Soft tissue sarcoma:
  1. Magnetic resonance imaging (MRI) is the initial imaging modality of choice, especially for soft tissue sarcoma of the extremities, trunk, and head and neck. CT with IV contrast is also useful for diagnosis.
  2. Ultrasound is used to help differentiate between benign and suspicious lesions.
- Bone sarcoma: Radiograph (Fig. E4) is the initial imaging of choice. It helps to rule out bone tumor, shows calcification, and reveals bone erosions. Fig. E5 summarizes radiographic features that may help differentiate benign from malignant lesions. Diagnostic workup for bone sarcomas is summarized in Table E5.
- A multidisciplinary team approach is essential and should include a radiologist, surgeon, pathologist, medical oncologist, and radiation oncologist.

BIOPSY

- In nearly all cases a biopsy is needed to establish a tissue diagnosis. Guidelines for biopsy are summarized in Box E1.
- Multiple core needle biopsies are usually done.
- An excisional biopsy may be used for superficial lesions <5 cm.

TABLE E2 Germline Mutations Associated with Soft Tissue Sarcoma

Syndrome	Inheritance Pattern	Locus	Gene	Associated Soft Tissue Sarcomas
Familial gastrointestinal stromal tumor syndrome	AD	4q12	*KIT*	Gastrointestinal stromal tumor
Familial desmoid fibromatosis (Gardner syndrome)	AD	5q21	*APC*	Desmoid fibromatosis
Li-Fraumeni syndrome	AD	17p13,22q11	*TP53, CHK2*	Multiple types
Neurofibromatosis type I (von Recklinghausen disease)	AD	17q11	*NF1*	Malignant peripheral nerve sheath tumors
Retinoblastoma	AD	13q14	*RB1*	Multiple types
Rhabdoid predisposition syndrome	AD	22q11	*SNF5/INII*	Malignant rhabdoid tumors
Werner syndrome	AR	8p11–12	*WRN*	Multiple types

AD, Autosomal dominant; *AR,* autosomal recessive.
From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

TABLE E3 Soft Tissue Sarcoma: Predisposing Environmental Factors

Factor	Agent	Patient Population	Comment
Radiotherapy	Orthovoltage and megavoltage radiation	Therapeutic radiation patients	Most commonly undifferentiated pleomorphic sarcoma and osteosarcoma; dose-response relationship
Chemotherapy	Alkylating agents: Cyclophosphamide, melphalan, procarbazine, nitrosourea, and chlorambucil	Pediatric cancer patients	Relative risk of bone sarcoma increased with cumulative drug exposure
Chemical exposure	Phenoxyacetic acids: 2,4-dichlorophenoxyacetic acid (2,4-D); 2,4,5 trichlorophenoxyacetic acid (2,4,5-T); 2 methyl-4 chlorophenoxyacetic acid (MCPA)	Forestry and agricultural workers	Phenoxy herbicide and defoliant exposure
	2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD); dioxin	Vietnam veterans	No clear link demonstrable for dioxin (Agent Orange)
	Chlorophenols	Sawmill workers	
	Thorotrast	Diagnostic x-ray patients	Hepatic angiosarcoma
	Vinyl chloride	Vinyl chloride workers	Hepatic angiosarcoma
	Arsenic	Vineyard workers	Hepatic angiosarcoma after exposure to arsenical herbicides
Chronic lymphedema		Postsurgery patients Postradiation patients Patients with congenital lymphedema or filariasis	Stewart-Treves syndrome (lymphangiosarcoma)

From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

TABLE E4 Radiographic Techniques Available

1. Plain films: Loss of trabeculation, matrix identification, calcification, etc.
2. Bone scan: Whole body, three phases to evaluate vascularity, static skeletal survey to evaluate for skeletal metastatic disease
3. MRI (magnetic resonance imaging): Excellent soft tissue contrast, sometimes nearly diagnostic; T1 best for anatomy, contrast enhancement, magnetic resonance angiography capability, best overall single study when properly monitored by a physician
4. CT (computed tomography): Margination, matrix identification, calcification, cortical disruption, axial localization of lesion; imaging for pulmonary metastatic disease
5. Rapid whole-body short tau inversion recovery (STIR) MRI: Excellent survey study with cooperative patients and in institutions using these techniques
6. PET (positron emission tomography): Adds metabolic parameter used to monitor effectiveness of neoadjuvant chemotherapy; staging in Ewing sarcoma

From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

- In carefully selected cases an open biopsy may be done (rarely used because of its high complication rate).
- For difficult to palpate or necrotic soft sarcomas, ultrasound or CT–guided biopsies are performed.
- Biopsy results are interpreted collaboratively by the specialist sarcoma pathologist, surgeon, and radiologist together.

HISTOLOGIC DIAGNOSIS

- Treatment planning is guided by a histologic diagnosis.
- Histologic diagnosis is made according to the World Health Organization (WHO) classification.
- WHO has defined >50 histologic subtypes of soft tissue sarcoma.
- Newer methods such as immunocytochemistry and cytogenetics can aid diagnosis by identifying tumor lineage.
- Sarcomas with complex karyotypes are summarized in Table E6.

Rx TREATMENT

Treatment depends on the extent of the disease and falls into several groups.

ACUTE GENERAL Rx

- Surgical resection: Most cases are treated by surgery. For example, in most adults soft tissue sarcoma and sarcoma of bone are not very sensitive to chemotherapy. Fig. E6 illustrates a management strategy for soft tissue sarcomas.
  1. Surgery must be done by surgeon trained to treat this disease.
  2. Wide excision with negative margins is the standard surgical procedure.
  3. For bone sarcomas amputation has been the standard procedure. Recent advances

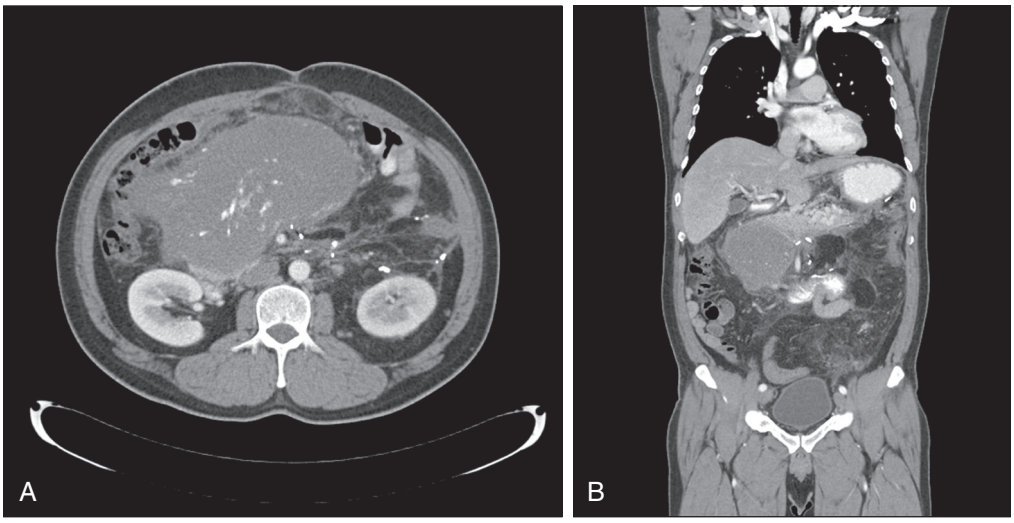


FIG. E2 A, A 48-yr-old man with retroperitoneal and intraabdominal well-differentiated and dedifferentiated liposarcoma. Axial contrast-enhanced computed tomography (CT) images show a large, heterogeneous mass with foci of calcification, consistent with osteosarcoma divergent differentiation sometimes seen with this form of sarcoma. In this situation, the finding of osteoblasts does not merit the use of chemotherapy for osteosarcoma; the risk of tumor recurrence rests entirely with the dedifferentiated liposarcoma portion of the diagnosis. **B,** The same patient as in **A,** with coronal sectioning from data existing from the axial CT scans. This technique is commonly used with both magnetic resonance imaging and CT. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

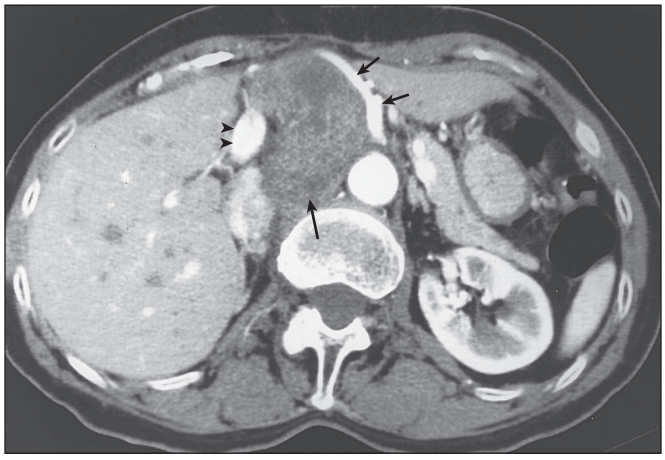


FIG. E3 Contrast-enhanced computed tomography scan of the abdomen demonstrating a retroperitoneal undifferentiated pleomorphic sarcoma. Note the large mass *(bottom arrow)* between the aorta and inferior vena cava with abutment and displacement of celiac axis and hepatic artery *(top arrows).* The portal vein *(arrowheads)* is well visualized, and low-attenuation foci in the liver, which are unopacified hepatic veins, are incidentally visualized. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

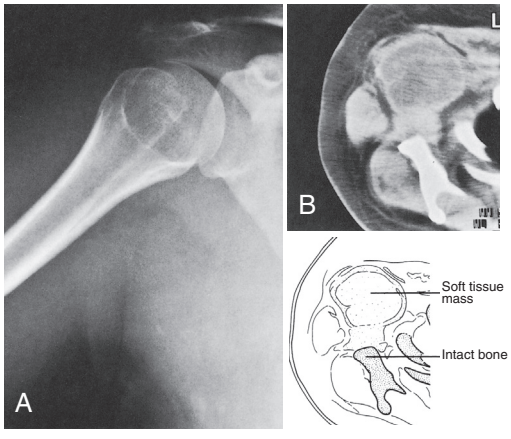
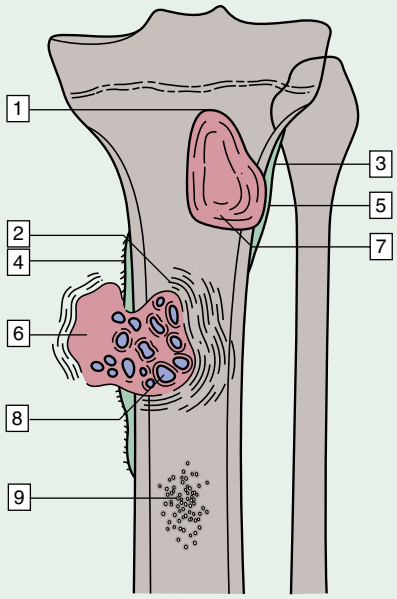


FIG. E4 Fibrosarcoma. A, Anteroposterior plain film of the shoulder of a 40-yr-old woman with a history of an enlarging mass in the right axilla shows an ill-defined mass adjacent to the lateral border of the scapula. **B,** CT section with contrast enhancement shows the extent of the mass and the lack of bone involvement. The tumor proved to be a fibrosarcoma. (From Skarin AT: *Atlas of diagnostic oncology,* ed 3, St Louis, 2003, Mosby.)



Feature	Benign (slow-growing process)	Malignant (aggressive process)
Border	1. Sharply outlined, sclerotic (narrow zone of transition)	2. Poorly defined (wide zone of transition)
Periosteal reaction	3. Solid, uninterrupted	4. Interrupted (sunburst, Codman triangle)
Soft tissue extension/mass	5. Absent or contained by shell of periosteal new bone	6. Frank extension through destroyed periosteum
Type of bone destruction	7. Geographic: Uniformly destroyed area with sharply defined border	8. "Moth-eaten" (likely malignant): Destroyed areas with ragged borders
		9. Permeative (aggressive/malignant): Ill-defined destruction spreading through marrow space

FIG. E5 Benign versus malignant bone lesions. The radiographic features illustrated may help differentiate benign from malignant lesions. (From Bullough PG, Vigorita VJ: *Atlas of orthopedic pathology,* Baltimore/New York, 1984, University Park Press/Gower Medical Publishing; in Skarin AT: *Atlas of diagnostic oncology,* 4 ed, St Louis, 2010, Mosby.)

TABLE E5 Diagnostic Workup Algorithm for Bone Sarcomas

1. Anteroposterior and lateral radiographs of the bone/joint involved
2. If a malignant bone lesion is suspected, proceed to:
   - Magnetic resonance imaging (MRI) of the lesion and coronal T1 images of the entire bone
   - Chest computed tomography (CT) to screen for pulmonary metastases
   - Radionuclide bone scan to look for "skip" and other bony metastases
3. Review with multidisciplinary team (surgeon, oncologist, radiotherapist, radiologist, and pathologist); decide whether tissue will be needed for cytogenetics or other special biologic studies
4. Plan open or needle biopsy by surgeon or interventional radiologist (after reviewing images with the radiologist who will perform the biopsy)

From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

BOX E1 Guidelines for Biopsy

Needle Biopsy

1. Planning: Biopsy tract must be in line of potential resection.
2. Traverse only one compartment and only one muscle if possible.
3. Avoid contamination of joint.
4. Microbiologic culture.
5. Prolonged gentle pressure for hemostasis.

Incisional Biopsy

1. Planning: Plan most appropriate biopsy tract and avoid transverse incisions.
2. Use pneumatic tourniquet after gravity exsanguination.
3. Avoid contamination of joint.
4. Avoid exposure of neurovascular structures.
5. Monitor biopsy with frozen sections.
6. Microbiologic culture if there is question.
7. Maintain integrity of deep tumor-host margin; could extend necessary surgical margin.
8. Absolute hemostasis; thrombogenic agents (e.g., thrombin, Oxycel, Avitene).
9. Hemostatic closure of pseudocapsule.
10. Subcuticular closure.

From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

TABLE E6 Sarcomas with Complex Karyotypes

Type of Sarcoma	Resembles
Fibrosarcoma (other than congenital)	Fibrous tissue
Leiomyosarcoma	Smooth muscle
Undifferentiated pleomorphic sarcoma	Poorly differentiated
Osteosarcoma	Bone
Chondrosarcoma (types other than extraskeletal myxoid)	Cartilage
Liposarcoma (types other than myxoid)	Fat
Embryonal rhabdomyosarcoma	Skeletal muscle
Malignant peripheral nerve sheath tumor*	Nerve sheath
Angiosarcoma	Endothelium

*Some have NF1 mutations.
From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.

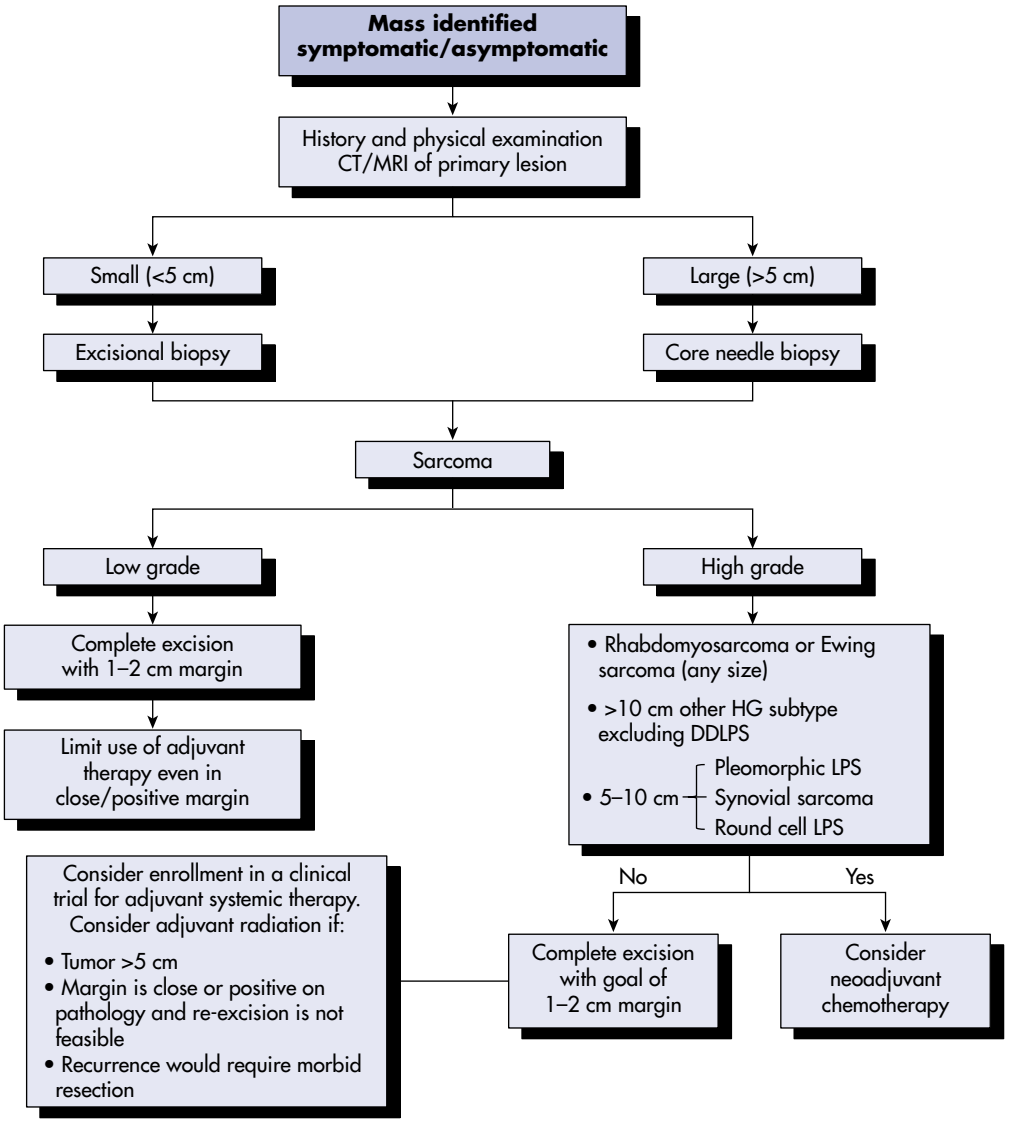


FIG. E6 Management strategy for soft tissue sarcoma. *CT*, Computed tomography; *DDLPS*, dedifferentiated liposarcoma; *HG*, high-grade; *LPS*, liposarcoma; *MRI*, magnetic resonance imaging. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

permit the avoidance of amputation with limb-sparing surgery followed by reconstruction by endoprosthetic replacement.

- Radiotherapy is used often in adjuvant fashion after primary sarcoma resection as a means to decrease local recurrences, e.g., in extremity or retroperitoneal sarcomas.
- Chemotherapy is typically used followed by surgery in cases of advanced sarcoma or palliatively in case of metastatic disease.
  1. Upfront chemotherapy is used to reduce disseminated micrometastases and to reduce tumor size preoperatively. Recent data support use of chemotherapy combined with hyperthermia in selected soft tissue sarcomas of the extremities before resection.
  2. Systemic chemotherapy regimens for advanced STS typically comprise multiple drugs such as the MAID regimen (mesna, doxorubicin, ifosfamide, dacarbazine) and the AIM regimen (doxorubicin, ifosfamide, mesna). Single-agent therapy with either doxorubicin or ifosfamide is also appropriate in the palliative setting.
  3. More recently, pazopanib, a tyrosine kinase inhibitor, has been approved for patients with metastatic or recurrent sarcoma. Trabectedin (an agent derived from a marine sponge) and eribulin (a microtubule inhibitor) have now been approved in advanced leiomyosarcoma or liposarcoma after showing an overall survival benefit.
  4. Olaratumab, a monoclonal antibody directed against platelet-derived growth factor (PDGF), had been approved based on early survival data when used in combination with doxorubicin as a first-line option in metastatic soft tissue sarcomas, but the mature survival results did not confirm a survival benefit.
- Follow-up of bone sarcoma after treatment includes:
  1. Periodic monitoring with radiographs and other imaging modalities.
  2. CT scan of the chest.
  3. Bone scan.
- Follow-up of soft tissue sarcoma (extremities):
  1. Physical exam detects 97% of recurrence.
  2. Physical exam is done every 3 to 6 mo for 3 yr, then every 6 mo for the next 2 yr for stage II and III cancers, then annually.
  3. Imaging.
- Stage I: CXR every 6 to 12 mo.
- Stages II and III: Image the primary site with MRI or CT.
- Chest x-ray or chest CT every 3 to 6 mo for 5 yr, then annually.

REFERRAL

- Sarcomas are relatively uncommon yet comprise a wide variety of different entities; as such, evaluation by multidisciplinary oncology teams with expertise in this field is recommended.
- Treatment and follow-up guidelines have been published by the National Comprehensive Cancer Network (www.nccn.org).

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SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Scabies is a contagious disease caused by the mite *Sarcoptes scabiei.*

ICD-10CM CODE
B86 Scabies

EPIDEMIOLOGY & DEMOGRAPHICS

- Scabies is generally acquired by sleeping with or in the bedding of infested individuals.
- It is generally associated with poor living conditions and is also common in hospitals and nursing homes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Primary lesions are caused when the female mite burrows within the stratum corneum, laying eggs within the tract she leaves behind; burrows (linear or serpiginous tracts, see Fig. E1) end with a minute papule or vesicle.
- Primary lesions (Fig. E2) are most commonly found in the web spaces of the hands, wrists, buttocks, scrotum, penis, breasts, axillae, and knees. They are often confused with eczema (Fig. E3).
- Secondary lesions result from scratching or infection.
- Intense pruritus, especially nocturnal, is common; it is caused by an acquired sensitivity to the mite or fecal pellets and is usually noted 1 to 4 wk after the primary infestation.
- Examination of the skin may reveal burrows, tiny vesicles, excoriations, inflammatory papules.
- Widespread and crusted lesions (Norwegian or crusted scabies) may be seen in elderly and immunocompromised patients (Fig. E4). Pruritus may be mild or absent due to impaired host immune response.
- Table 1 summarizes the different presenting forms of scabies.

ETIOLOGY

- Human scabies is caused by the mite *S. scabiei,* var. *hominis* (Fig. 5). After impregnation on the skin surface, the gravid female burrows in the stratum corneum within 30 min and gradually extends the tract along the boundary with the stratum granulosum depositing 10 to 25 oval eggs in a 4- to 5-wk period. The eggs hatch in 3 to 5 days, and larvae move to the skin surface and mature in 2 to 3 wk, resuming the cycle.
- Clinical manifestations result from a delayed type IV hypersensitivity reaction to the mite, eggs, saliva, or scybala.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pediculosis
- Atopic dermatitis
- Flea bites
- Seborrheic dermatitis
- Dermatitis herpetiformis
- Contact dermatitis
- Nummular eczema
- Syphilis
- Other insect infestation

WORKUP

Diagnosis is made on the clinical presentation and on the demonstration of mites, eggs, or mite feces.

LABORATORY TESTS

- Microscopic demonstration of the organism, feces, or eggs: A drop of mineral oil may be placed over the suspected lesion before removal (Box 1); the scrapings are transferred directly to a glass slide; a drop of potassium hydroxide is added and a cover slip is applied.
- Skin biopsy is rarely necessary to make the diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Clothing, underwear, and towels used in the 48 hours before treatment must be laundered.

ACUTE GENERAL Rx

- Permethrin 5% cream is usually effective with one treatment; it should be massaged into the skin from head to soles of feet and applied under fingernails and toenails (it is best if applied in the evening and left overnight to maximize exposure); remove 8 to 14 hr later by washing. Repeat in 1 to 2 wk. Permethrin is safe for children >2 mo old.
- A single dose (150 to 200 μg/kg in 6-mg tablets) of ivermectin, an antihelmintic agent, is also effective for the treatment of scabies. It is the best treatment for generalized crusted scabies. Three to seven doses of ivermectin given on days 1, 2, 8, 9, 15, 22, and 28 may be needed for crusted scabies.
- Pruritus generally abates 24 to 48 hr after treatment but can last up to 2 wk; oral antihistamines are effective in decreasing postscabietic pruritus.
- Topical corticosteroid creams may hasten the resolution of secondary eczematous dermatitis.
- If the patient is a resident of an extended care facility, it is important to educate the patients, staff, family, and frequent visitors about scabies and the need to have full cooperation in treatment. Scabicide should be applied to all

TABLE 1 Different Presenting Forms of Scabies

Presenting Forms of Scabies	Specific High-Risk Populations	Clinical Manifestations	Limited Differential Diagnoses
Classic scabies (scabies vulgaris)	Infants and children; sexually active adults; men who have sex with men	Intense generalized pruritus, worse at night; inflammatory pruritic papules localized to finger webs, flexor aspects of wrists, elbows, axillae, buttocks, genitalia, female breasts; lesions and pruritus spare the face, head, and neck; secondary lesions include eczematization, excoriation, impetigo	Dermatitis herpetiformis, drug reactions, eczema, pediculosis corporis, lichen planus, pityriasis rosea
Scalp scabies	Infants and children; institutionalized older adults; AIDS patients; patients with preexisting crusted scabies	Atypical crusted papular lesions of the scalp, face, palms, and soles	Dermatomyositis, ringworm, seborrheic dermatitis
Crusted scabies (Norwegian scabies, scabies norvegica, scabies crustosa)	Institutionalized older adults; institutionalized developmentally disabled (Down syndrome); homeless, especially HIV-positive; all immunocompromised patients, particularly those with AIDS or positive for HIV or HTLV-1; transplant recipients; patients on prolonged systemic corticosteroids and chemotherapy	Psoriasiform hyperkeratotic papular lesions of the scalp, face, neck, hands, feet, with extensive nail involvement; eczematization and impetigo common	Contact dermatitis, drug reactions, eczema, erythroderma, ichthyosis, psoriasis
Nodular scabies	Sexually active adults; men who have sex with men; HIV-positive men > HIV-positive women	Violaceous pruritic nodules localized to male genitalia, groin, axillae, representing hypersensitivity reaction to mite antigens	Acropustulosis, atopic dermatitis, Darier disease, lupus erythematosus, lymphomatoid papulosis, papular urticaria, necrotizing vasculitis, secondary syphilis

AIDS, Acquired immunodeficiency syndrome; *HIV*, human immunodeficiency virus; *HTLV-1*, human T-cell lymphotropic virus type 1.
From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

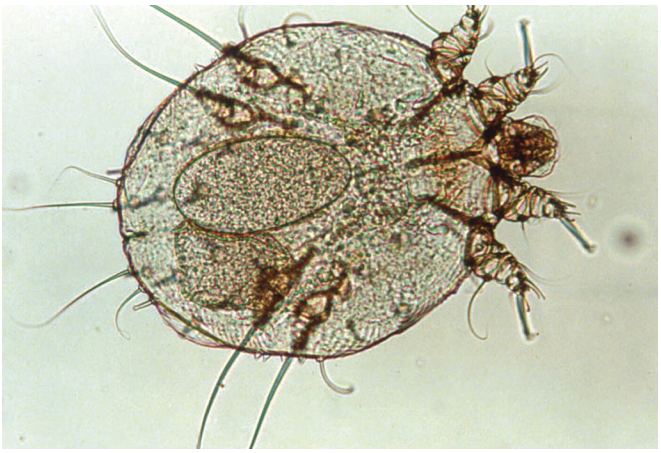

FIG. 5 Scabies mite. Note the eggs within the body of the mite. (Live scabies mite, ×40 magnification.) (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

BOX 1 Performing a Mineral-Oil Examination for Scabies

1. Apply a drop of mineral oil to the lesion(s) to be scraped.
2. Scrape through the lesion with a number 15 scalpel blade (a small amount of bleeding is expected with appropriately deep scrapings).
3. Smear contents of scraping on a clean glass slide.
4. Add a few more drops of mineral oil.
5. Place cover slip over oil and examine under microscope at low power.

Criteria for a positive mineral oil examination:
Scabies mite.
or
Ova (eggs).
or
Scybala (feces).

From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.

patients, staff, and frequent visitors, whether symptomatic or not; symptomatic family members of staff and visitors should also receive treatment.
- Table 2 summarizes currently recommended treatment for scabies.

DISPOSITION

Refractory cases usually are seen with immunocompromised hosts or patients with underlying skin diseases. ***Norwegian scabies*** refers to a highly contagious variant often found in institutions caring for physically and mentally disabled individuals.

PEARLS & CONSIDERATIONS

COMMENTS

- Lindane is potentially neurotoxic and should not be used on infants or pregnant women (permethrin is safe in pregnancy and infants over 2 mo old).
- Sexual partners should be notified and treated.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Scabies (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

TABLE 2 Currently Recommended Treatment for Scabies

Scabicides	FDA Approved?	Pregnancy Category*	Dosing Schedule	Safety Profile	Contraindications
5% Permethrin cream (Actin, Nix, Elimite)	Yes	B	Apply from neck down; wash off after 8-14 hr; good residual activity, but second application recommended after 1 wk	Excellent; itching and stinging on application	Prior allergic reactions; infants <2 mo of age; breastfeeding
1% Lindane lotion or cream	Yes	B	Apply 30-60 ml from neck down; wash off after 8-12 hr; no residual activity; increasing drug resistance	Potential for central nervous system toxicity from organochloride poisoning, usually manifesting as seizures, with overapplication and ingestions	Preexisting seizure disorder; infants and children <6 mo of age; pregnancy; breastfeeding
10% Crotamiton cream or lotion (Eurax)	Yes	C	Apply from neck down on two consecutive nights; wash off 24 hr after second application	Excellent; not very effective; exacerbates pruritus	None
2%-10% Sulfur in petrolatum ointments	No	C	Apply for 2-3 days, then wash	Excellent; not very effective	Preexisting sulfur allergy
10%-25% Benzoyl benzoate lotion	No	None	Two applications for 24 hr with 1-day to 1-wk interval	Irritant; exacerbates pruritus; can induce contact irritant dermatitis and pruritic cutaneous xerosis	Preexisting eczema
0.5% Malathion lotion (Ovide), 1% malathion shampoo (unavailable in the U.S.)	No	B	95% ovicidal; rapid (5 min) killing; good residual activity; increasing drug resistance	Flammable 78% isopropyl alcohol vehicle stings eyes, skin, mucosa; increasing drug resistance; organophosphate poisoning risk with overapplication and ingestions	Infants and children <6 mo of age; pregnancy; breastfeeding
Ivermectin (Stromectol)	Yes	C	200 μg/kg single PO dose, may be repeated in 14-15 days; not ovicidal, second dose on day 14 or 15 highly recommended; recommended for endemic or epidemic scabies in institutions and refugee camps	Excellent; may cause nausea and vomiting; take on empty stomach with water	Safety in pregnancy uncertain; probably safe during breastfeeding; not recommended for children younger than 5 yr of age or weighing <15 kg

FDA, U.S. Food and Drug Administration; *PO*, by mouth.
*U.S. Food and Drug Administration (FDA) safety in pregnancy categories: A, safety established; B, presumed safe; C, uncertain safety; D, unsafe; X, highly unsafe.
From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

FIG. E1 Scabies. Curvilinear burrow of the lateral hand. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

FIG. E2 Scabies nodules. Early scabies nodules developing at sites of crusting; these lesions persisted long after adequate therapy for the infestation. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

FIG. E3 Scabies in an infant. Diffuse pruritic, eczematous lesions on an infant are often confused with eczema. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

FIG. E4 Norwegian scabies. (From Swartz MH: *Textbook of physical diagnosis,* 7 ed, Philadelphia, 2014, Saunders, 2014.)

SUGGESTED READINGS

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Scarlet Fever (PTG)

BASIC INFORMATION

DEFINITION

Scarlet fever is a rash involving the skin and tongue and complicating streptococcal group A pharyngitis.

SYNONYMS

Scarlatina
SF

ICD-10CM CODES

A38	Scarlet fever
A38.0	Scarlet fever with otitis media
A38.1	Scarlet fever with myocarditis
A38.8	Scarlet fever with other complications
A38.9	Scarlet fever, uncomplicated

EPIDEMIOLOGY & DEMOGRAPHICS

- Same as streptococcal pharyngitis; namely, children ages 5 to 15 yr. May also complicate impetigo
- Most common in cooler climates during the late fall, winter, and early spring
- Most cases follow tonsillitis or pharyngitis; however, it has also been reported after wounds ("surgical scarlet fever"), burns, and pelvic or puerperal infections

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Diffuse erythema, beginning on face and spreading to neck, back, chest, rest of trunk, and extremities (Fig. E1, A). Most intense on inner aspects of arms and thighs.
- Erythema blanches, but nonblanching petechiae may be present or produced by a tourniquet.
- Strawberry or raspberry tongue (Fig. E1, B, C).
- Rash lasts approximately 1 wk and then desquamates.
- Febrile illness with headache, malaise, anorexia, and pharyngitis begins after a 2- to 4-day incubation period.
- Scarlatinal rash begins 1 or 2 days after the onset of pharyngitis.

ETIOLOGY

Caused by group A beta-hemolytic *Streptococcus* infection, which produces one of three erythrogenic toxins (NOTE: Some streptococcal species have the ability to cause both scarlet fever and rheumatic fever).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Viral exanthems (covered in Section II)
- Kawasaki syndrome
- Toxic shock syndrome
- Drug rashes

See "Differential Diagnosis" of "Pharyngitis/Tonsillitis" in Section I.

WORKUP

- Identification of group A *Streptococcus* by throat culture
- Streptolysin O antibody titers

TREATMENT

- Penicillin 250 mg PO qid for 10 days or erythromycin 250 mg PO qid for 10 days in penicillin-allergic patients. A clinical response can be expected in 24 to 48 hr.
- Benzathine penicillin 1 to 2 million U IM once; may be used for a patient who cannot swallow pills.

COMPLICATIONS (RARE)

- Peritonsillar abscess
- Mastoiditis
- Otitis media
- Pneumonia
- Sepsis and distant foci of infection
- Acute rheumatic fever
- Inability to swallow liquids or upper airway obstruction requiring hospitalization

NOTE: Failure to respond to penicillin should raise doubt about the diagnosis because *Streptococcus* may be carried in the pharynx without causing infection.

PEARLS & CONSIDERATIONS

COMMENTS

Patients with antibodies against the toxin are spared the rash but still develop other symptoms of the infection (e.g., sore throat).

RELATED CONTENT

Scarlet Fever (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

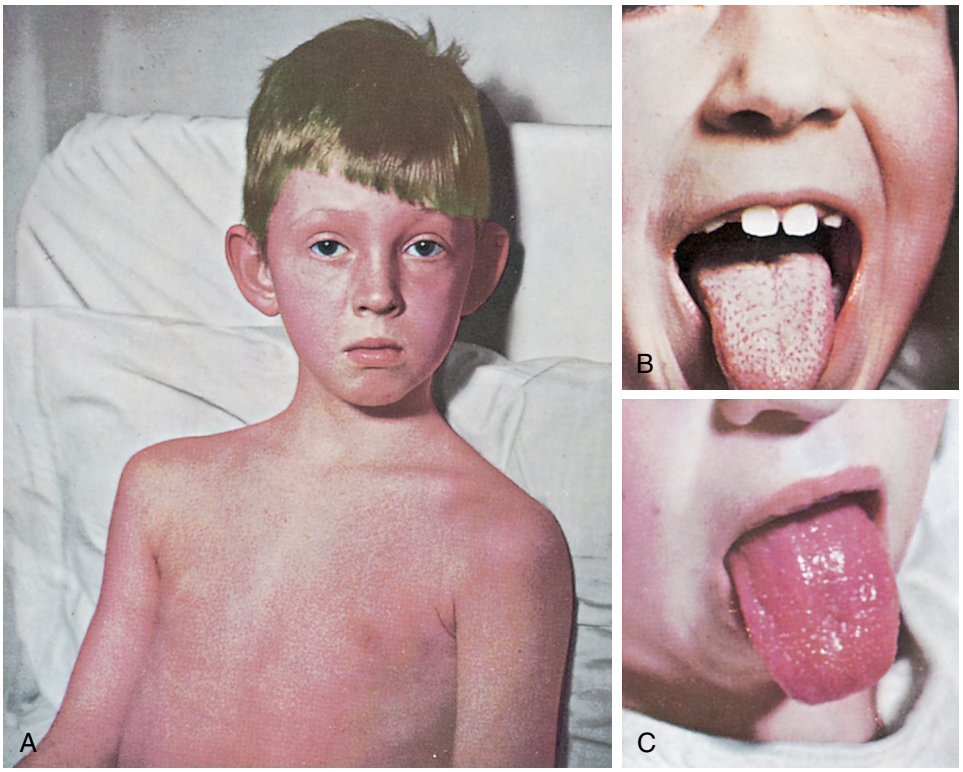

FIG. E1 Scarlet fever. A, Punctate, erythematous rash (second day). **B,** White strawberry tongue (first day). **C,** Red strawberry tongue (third day). (Courtesy Dr. Franklin H. Top, Professor and Head of the Department of Hygiene and Preventive Medicine, State University of Iowa, College of Medicine, Iowa City, IA; and Parke, Davis & Company's Therapeutic Notes. From Gershon AA et al: *Krugman's infectious diseases of children*, ed 11, Philadelphia, 2004, Mosby.)

BASIC INFORMATION

DEFINITION

Schistosomiasis is caused by infection with parasite blood flukes known as schistosomes. Their life cycle is illustrated in Fig. E1.

SYNONYMS

Bilharziasis
Urinary schistosomiasis
Hepatosplenic schistosomiasis
Swimmer's itch
Katayama fever
Snail fever

ICD-10CM CODES

B65	Schistosomiasis (bilharziasis)
B65.0	Schistosomiasis due to *Schistosoma haematobium*
B65.1	Schistosomiasis due to *Schistosoma mansoni*
B65.2	Schistosomiasis due to *Schistosoma japonicum*
B65.8	Other schistosomiasis
B65.9	Schistosomiasis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Worldwide >230 million people, 20 million people with severe disease, and >200,000 deaths annually. Roughly 85% of cases globally occur in Africa, although incidence may be increasing in southern Europe. U.S. travelers to endemic areas are at risk of infection.
- Geographic distribution of schistosomiasis (see Fig. E2) is confined to an area between 36° north and 34° south latitude, where freshwater temperatures average 25° to 30° C (77° to 86° F), and where freshwater snail (intermediate host) habitats are located.

PREVALENCE: The greatest cercarial exposure usually occurs in boys ages 5 to 10 yr.

DISTRIBUTION:

- *Schistosoma mansoni* in tropical and subtropical areas of sub-Saharan Africa, the Middle East, South America, and the Caribbean
- *S. haematobium* in North Africa, sub-Saharan Africa, the Middle East, and India
- *S. japonicum* in Asia, particularly in China, the Philippines, Thailand, and Indonesia
- *S. intercalatum* in Cameroon and the Democratic Republic of the Congo
- *S. mekongi* in Mekong River (Laos and Cambodia)

ETIOLOGY & PATHOGENESIS

- Human infections are caused by five main schistosome species (three major ones and two less common): *S. mansoni, S. haematobium, S. japonicum, S. mekongi,* and *S. intercalatum.*
- Acquisition of disease occurs via contact with fresh water containing infectious free-living cercarial larvae that penetrate intact skin and transform into schistosomulae.

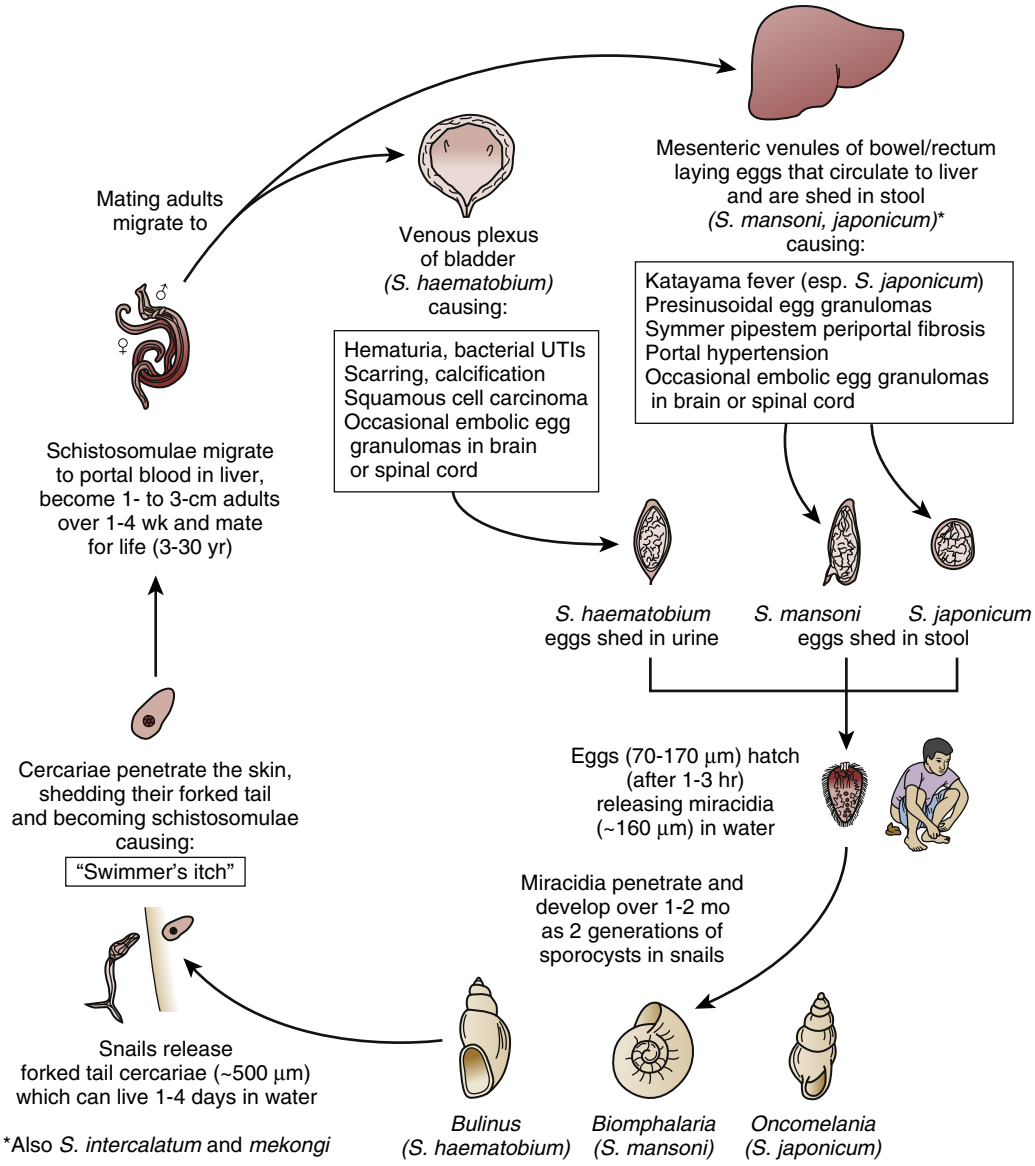

FIG. E1 Life cycle of a schistosome. *UTIs,* Urinary tract infections. (From King CH: Schistosomiasis. In Guerrant RL, et al. [eds]: *Tropical infectious diseases, principles, pathogens, and practice*, ed 2, Philadelphia, 2006, Churchill Livingstone.)

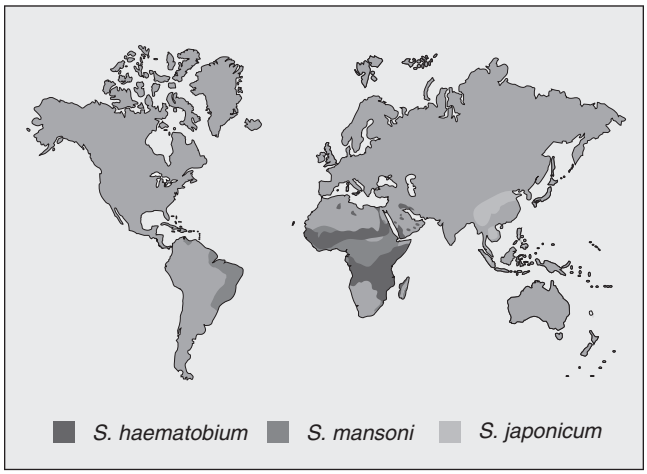

FIG. E2 World map showing the geographic distribution of the main pathogenic schistosomes. (From Floege J, et al.: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

- Once inside humans, they ultimately reach, depending on the species, the venules of the target organs and develop into adult worms. Male and female worms mate continuously at this point.
- Adult worms are 1 to 3 cm in length and live 3 to 7 yr. Females lay eggs that on contact with fresh water become miracidium larvae that then enter freshwater snails (an intermediate host). The miracidia develop further and exit the snail in water as cercarial larvae that will enter humans as the definitive host.
- The eggs produced by adult worms are released into the bloodstream and can invade local tissue. This tissue insult induces a granulomatous reaction that involves T-helper-2 cytokines, eosinophils, and macrophages.
- These granulomas contain the egg and the proteolytic enzymes it releases to prevent tissue necrosis. Granuloma formation results in chronic inflammation and disease manifestation in humans.
- In the U.S., most cases are acquired during foreign travel or appear in immigrants.
- Incubation period is typically 2 to 12 wk for acute illness, but chronic infection can remain asymptomatic for years.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

ACUTE SYMPTOMS:
- Swimmer's itch: Initial penetration of the skin by cercariae. Most commonly seen with *S. japonicum* infection.
- Katayama fever: Systemic hypersensitivity reaction to migrating parasites early in infection and lasting 2 to 10 wk.

CHRONIC SYMPTOMS:
- Failure to thrive in children from regions where schistosomiasis is endemic
- Intestinal schistosomiasis:
  1. Abdominal pain
  2. Poor appetite
  3. Bloody diarrhea
  4. Iron-deficiency anemia
  5. Intestinal polyp
  6. Bowel ulcer and strictures
- Hepatic schistosomiasis:
  1. Hepatomegaly
  2. Splenomegaly
  3. Portal hypertension
  4. Esophageal varices and hematemesis
  5. Ascites
- Urinary schistosomiasis:
  1. Hematuria (micro- or macroscopic)
  2. Dysuria
  3. Urinary frequency
  4. Fibrosis of bladder, ureters, and female genital tract
  5. Squamous cell cancer of bladder
  6. Proteinuria
  7. Nephrotic syndrome

COMPLICATIONS:
- Neurologic complications:
  1. Granuloma of spinal cord or brain
  2. Transverse myelitis
  3. Epilepsy or focal neurologic deficit
  4. Impaired cognitive function
- Pulmonary complications:
  1. Granulomatous pulmonary endarteritis
  2. Pulmonary hypertension
  3. Cor pulmonale
- Other complications include tubal obstruction and infertility
- Recurrent bacteremia and recurrent UTI
- Significant systemic associations: Malnutrition, impaired growth, and development

COMORBIDITIES:
- HIV: Schistosomiasis may increase the risk of HIV infection.
- Hepatitis B and C: People who have coinfection appear to have more severe disease.
- Malaria: Possible protective effect of schistosomiasis on malaria infection.

DX DIAGNOSIS

DIFFERENTIAL DIAGNOSIS
- Amebiasis
- Bacillary dysentery
- Bowel polyp
- Prostatic disease
- Genitourinary tract cancer
- Bacterial infections of the urinary tract

WORKUP
- Microscopy in urine or stool
- Tissue biopsy (rectal, ideally under direct visualization)
- Serology
- CBC
- LFT
- US of abdomen, including bladder
- CT scan of abdomen
- Urine/serum antigen assay

LABORATORY TESTS
- CBC can show eosinophilia, anemia, thrombocytopenia
- LFT with mild increase in alkaline phosphatase and GGT
- Microscopy: Stool and urine to examine for eggs
- Serology: ELISA for detecting both schistosomal antibodies and antigen, especially for symptomatic travelers
- Limited ability to discern between active and prior infection for patients in endemic regions
- Rectal biopsy or bladder mucosal biopsy
- While not yet in widespread use, PCR testing, particularly in patients previously treated or with negative microscopy and positive serology results

IMAGING STUDIES
- An x-ray of the abdomen shows "fetal head" calcification.
- Sonography can detect thickened bladder wall, hydronephrosis and hydroureter, and bladder polyps or calcification. It can also detect thickened fibrosed portal tracts.
- Esophagoscopy documents esophageal varices.
- Liver biopsy may also demonstrate granuloma and periportal fibrosis (also called Symmer pipestem fibrosis).
- Cystoscopy should be considered in cases of persistent urinary symptoms as there is risk of bladder cancer, even in pediatric cases.

RX TREATMENT

- Oral antihistamines can relieve symptoms of swimmer's itch (reaction from skin penetration of cercariae after water exposure). Regardless, dermatologic symptoms resolve gradually.
- Drug of choice for *S. haematobium* and *S. mansoni* is praziquantel 40 mg/kg of body weight PO in one or two doses. *S. japonicum* and *S. mekongi* require a dose of 60 mg/kg divided in three doses.
- Any pregnant or lactating women with evidence of schistosomiasis should receive treatment with praziquantel. In pregnant women, praziquantel administration is preferred after the first trimester.
- Alternatives: Oxamniquine 15 mg/kg PO once or 20 mg/kg PO daily for 3 days for recalcitrant infections of *S. mansoni* and metrifonate for urinary schistosomiasis, but currently not available.
- Oral steroids are indicated with Katayama fever and central nervous system involvement.

DISPOSITION

Treated patients usually respond to therapy. Definitive cure has occurred only when there is total disappearance of viable eggs from the excreta for a total of 6 mo after treatment. Patients may excrete nonviable eggs for months to years after effective therapy and may require examination to confirm nonviability early after initial treatment.

REFERRAL

- To an infectious disease specialist knowledgeable in parasitology and geographic medicine for treatment and follow-up
- To a gastroenterologist for sclerotherapy of bleeding esophageal varices, if needed in advanced hepatosplenic schistosomiasis
- To a urologist for management and follow-up of urinary complications of *S. haematobium* infection of the genitourinary tract

PEARLS & CONSIDERATIONS

COMMENTS

Prevention:

- Chemotherapy with yearly praziquantel:
  1. Mass, nationwide preventative chemotherapy
  2. Targeted endemic populations
- Snail control:
  1. Mollusciciding (historically not effective)
  2. Environmental modification
  3. Biologic control
- Reduction of water contact and contamination:
  1. Provision of domestic water supplies to prevent exposure to humans
  2. Provision of sanitary disposal of excreta to prevent exposure to snail habitat
- Vaccines are in development
- Improved living standards

Screening:

- Travelers and refugees from endemic areas and those who have been exposed to fresh water:
  1. Serology
  2. Urine and stool microscopy

AUTHOR: **Russell J. McCulloh, MD**

SUGGESTED READINGS

Cavalcanti MG et al: The advances in molecular and new point-of-care (POC) diagnosis of schistosomiasis pre- and post-praziquantel use: in the pursuit of more reliable approaches for low endemic and non-endemic areas, *Front Immunol* 28(10):858, 2019, https://doi.org/10.3389/fimmu.2019.00858.

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Wu W, Huang Y: Application of praziquantel in schistosomiasis japonica control strategies in China, *Parasitol Res* 112(3):909-915, 2013.

Schizophrenia

BASIC INFORMATION

DEFINITION

Schizophrenia is a disorder that causes significant distortions in thinking, perception, speech, and behavior. Characteristics include psychosis, apathy, social withdrawal, and cognitive impairment, which result in significant social impairment.

SYNONYM

Dementia praecox

ICD-10CM CODES

F20 Schizophrenia
F20.0 Paranoid schizophrenia
F20.1 Hebephrenic schizophrenia
F20.2 Catatonic schizophrenia
F20.3 Undifferentiated schizophrenia
F20.5 Residual schizophrenia
F20.6 Simple schizophrenia
F20.8 Other schizophrenia
F20.9 Schizophrenia, unspecified

DSM-5 CODE

295.90

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.2 per 1000

PREVALENCE: 0.5%; lifetime prevalence risk, 0.4%

PREDOMINANT SEX: Males have a more severe illness with earlier onset. Prevalence in males approximately 1.4 times higher.

PREDOMINANT AGE:

- Age of onset of psychotic symptoms is the early 20s for males and the late 20s for females.
- Age of onset of negative symptoms is usually earlier (i.e., the mid-teenage yr).

PEAK INCIDENCE: Between ages of 16 and 30 yr

GENETICS:

- Genetics accounts for 70% of risk; the remaining 30% associated with other factors such as urban environments, migration, or cannabis use.
- First-degree relatives have a 10 times greater chance of becoming schizophrenic.
- Discordant rates among identical twins are higher than expected with the simple inheritance pattern.
- Associations with several chromosomes have been described, but none has been replicated.
- Evidence exists that triple nucleotide repeat expansion (e.g., such as that seen with Huntington disease) may play a role in the inheritance of the disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Schizophrenia is best defined as a dilapidating illness that begins early in life and that progresses slowly throughout the lifetime.
- Frequent structural brain imaging findings include the enlargement of the ventricular system, a loss of brain volume and cortical gray matter, and an alteration of the white matter tracts.
- The initial "negative" symptoms of adolescence (prodromal phase)—cognitive decline, social withdrawal and awkwardness, loss of motivation and pleasure, and loss of emotional expressiveness—begin after a period of normal development.
- During early adulthood, positive symptoms of psychosis and thought disturbance occur; psychotic symptoms then wax and wane throughout life. Treatment ameliorates positive symptoms, but generally does little for negative ones.
- The condition is also accompanied by cognitive impairment, including problems with attention and concentration, psychomotor speed, learning, memory, and executive functions (e.g., abstract thinking, problem solving, planning).
- Social and occupational dysfunction can be profound.

ETIOLOGY

- The basic determination of whether this is a neurodegenerative or neurodevelopmental condition has not been made.
- The major hypothesis is that abnormality of the mesocortical pathways produces the hypofrontality and the negative symptoms. This occurs along with a compensatory hyperactivation of the mesolimbic pathways, which produces the positive symptoms of psychosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Schizophrenia is diagnosed when an individual has experienced at least 6 mo (1 mo if using ICD-10 criteria) of hallucinations, delusions, thought disorders, catatonia, or negative symptoms (e.g., avolition, anhedonia, social isolation, affective flattening).
- Any medical condition, medicine, or substance that can affect brain homeostasis can cause psychosis; this is distinguished from schizophrenia by a relatively brief course and an alteration in mental status that suggests an underlying delirium.
- Other neurologic conditions that have psychosis as the initial presentation (e.g., Huntington disease) need to be ruled out.
- Mood disorders with psychosis: These are indistinguishable from schizophrenia cross-sectionally but have a longitudinal course that includes full recovery.
- Delusional disorder involves nonbizarre delusions and lacks the thought disturbance, hallucinations, and negative symptoms of schizophrenia.
- Autism in the adult has an early age of onset and lacks significant hallucinations or delusions.

WORKUP

- History and physical examination to help determine whether the psychosis is primary or secondary.
- Neurologic examination to uncover the soft neurologic signs (e.g., clumsiness, cortical thumb, loss of fine motor movements) that are common with schizophrenia.

LABORATORY TESTS

- No laboratory tests are specific.
- Laboratory examinations (e.g., chemistry profile, blood count, sedimentation rate, toxicology screen, and urinalysis) are geared toward excluding a primary medical condition or toxic state. Note that new common drugs of abuse may not be detectable with regular screening tests.

IMAGING STUDIES

- CT or MRI of the brain during the initial workup; repeated if the course of the illness varies from what is expected.
- EEG may reveal slowing when psychosis is the result of an encephalopathy. Findings can be similar as a result of common medication use for treatment of psychosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Significant social support is required by most schizophrenic patients, but available support services are often grossly inadequate. Schizophrenic patients constitute nearly one third of all homeless individuals and approximately 5% of the incarcerated population. They usually require help with basic social, occupational, and interaction skills.
- Family stress can precipitate relapse and re-hospitalization. Family interventions can reduce morbidity.
- Cognitive behavioral therapy can reduce the severity of both psychotic and negative symptoms.
- Illness management training for patients can increase medication adherence and reduce symptom distress.
- Integrated treatment that includes assertive community treatment, family involvement programs, and social skills training reduces the severity of both psychotic and negative symptoms, reduces comorbid substance misuse, reduces hospital days, increases adherence to treatment, and increases satisfaction with treatment.

ACUTE GENERAL Rx

- Acute psychosis is usually adequately controlled with antipsychotic agents.
- Few differences in effectiveness exist between first-generation antipsychotics (e.g., haloperidol, perphenazine, fluphenazine, chlorpromazine) and second-generation antipsychotics (e.g., risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, clozapine, lurasidone) for nonrefractory patients. First-generation antipsychotics are slightly more likely than second-generation antipsychotics to cause a parkinsonian state and eventual tardive dyskinesia (rate of tardive dyskinesia, 15% to 30%). Antiparkinsonian drugs (e.g., benztropine, amantadine) are used to ameliorate the parkinsonism. Risperidone has been shown to be superior to haloperidol for the prevention of acute psychotic relapse.

- Sedatives (i.e., benzodiazepines and, to a lesser degree, barbiturates) can be used transiently if a patient is in an agitated state. Benzodiazepines like lorazepam are essential for schizophrenic patients who present with catatonia.
- ECT may be needed in cases of catatonic schizophrenia unresponsive to lorazepam.

CHRONIC Rx

- Relapse prevention is a major goal of treatment. Noncompliance is common and leads to high relapse rates. Antipsychotic agents usually must be continued at the same doses that controlled psychosis. For noncompliant patients, long-acting injectable preparations given biweekly, monthly, or every 3 mo can be used.
- Most patients frequently switch among antipsychotics; there is considerable individual variability with regard to antipsychotic response and vulnerability to specific adverse effects.
- Clozapine is more effective than other agents for treatment-refractory patients. However, it requires monitoring to prevent life-threatening adverse effects. Regular monitoring of WBC and absolute neutrophil count (ANC) during the therapy is required due to a greater risk of developing agranulocytosis.
- Olanzapine may also be more effective than less expensive first-generation drugs but has substantial adverse metabolic effects. Lurasidone is a newer second-generation antipsychotic that appears to be better tolerated, but longer-term studies are needed.
- Neurocognitive improvement associated with antipsychotic treatment among patients with schizophrenia is small and does not differ between first-generation and second-generation antipsychotics.
- Antiparkinsonian agents may also need to be continued for the long term.
- Tardive dyskinesia (i.e., choreoathetoid movements of the muscles of tongue and face and occasionally of other muscle groups) can occur in as many as 30% of patients with the long-term use of neuroleptics.
- The negative symptoms of schizophrenia can resemble depression. In addition, depressive disorders may occur in schizophrenic patients. Antidepressant treatment of the negative symptoms is usually not effective. However, antidepressants can improve the symptoms of a comorbid depressive episode.
- Mood stabilizers (e.g., lithium, valproate, carbamazepine) are of little use unless the patient has a comorbid impulse control disorder.
- Substance abuse is a major problem for more than a third of schizophrenic patients. More than half of these patients smoke cigarettes. Unfortunately, these individuals do poorly in traditional substance abuse treatment programs. Specialized "dual-diagnosis" programs with highly structured aftercare are required.
- Specific antipsychotic medications have been associated with weight gain (i.e., olanzapine and clozapine) and QT prolongation. Hyperlipidemia and diabetes mellitus are associated with second-generation antipsychotics, and hyperprolactinemia is associated with first-generation antipsychotics. (Risperidone, a second-generation antipsychotic, can also produce hyperprolactinemia.) Clozapine is associated with agranulocytosis and a decrease in intestinal motility, which can lead to bowel obstruction. Metabolic status and weight should be screened before the start of treatment and at regular intervals.
- Patients with schizophrenia have a higher lifetime incidence of suicide, with 20% attempting on one or more occasions and 5% to 10% completing suicide. Comorbid use of substances and hopelessness are associated risk factors. Clozapine has shown the ability to decrease the incidence of suicidal attempts in schizophrenia patients.
- Several first- and second-generation antipsychotics are available in long-acting injectable preparations that may be helpful in addressing issues of poor compliance or difficulty when treatment needs to be supervised. Current preparation can be given in intervals that range between every 2 to every 3 mo. Consider economic factor and importance of regular checks when using long-acting injectables.

DISPOSITION

- The positive symptoms of as many as 20% to 30% of schizophrenic patients do not respond to available treatments. A much higher fraction of patients experience relapse as a result of poor compliance.
- Negative symptoms are responsible for the 50% to 70% of patients in whom deterioration in occupational and social function continues.
- Approximately 5% to 10% of schizophrenic patients will complete suicide.
- The course of the illness is most strongly predicted by the level of social development attained at the onset of psychosis.
- Schizophrenic patients die 12 to 15 yr sooner than the average population, mostly as a result of physical causes related to a lack of access to health care or as a result of health risk factors (e.g., smoking, obesity).

REFERRAL

- If hospitalization is required
- If patient is noncompliant
- If patient is resistant to treatment

PEARLS & CONSIDERATIONS

- Rule out delirium caused by medical conditions, medications, or substance abuse before diagnosing an individual's psychotic behavior as schizophrenia.
- All antipsychotic medications have high discontinuation rates in chronic schizophrenia treatment. Olanzapine and clozapine may be more effective than other antipsychotics for chronic treatment, but they have significant side effects.
- Significant social support is required for most patients with schizophrenia. Nonpharmacologic therapy should be used in conjunction with pharmacotherapy.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Schizophrenia (Patient Information)

AUTHOR: **Arnaldo A. Berges, MD**

SUGGESTED READINGS

Hackman DT et al.: Prescription drug monitoring program inquiry in psychiatric assessment: detection of high rates of opioid prescribing to a dual diagnosis population, *J Clin Psychiatry* 75(7):750-756, 2014.

McDonagh MS et al: *AHRQ comparative effectiveness reviews. Treatments for schizophrenia in adults: a systematic review*, Rockville (MD), 2017, Agency for Healthcare Research and Quality (US).

Rosenheck RA et al: Long-acting risperidone and oral antipsychotics in unstable schizophrenia, *N Engl J Med* 364:842-851, 2011.

Sin J, Norman I: Psychoeducational interventions for family members of people with schizophrenia: a mixed-method systematic review, *J Clin Psychiatry* 74(12):e1145-e1162, 2014.

Tiihonen J et al: Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29823 patients with schizophrenia, *JAMA Psychiatry* 74(7):686-693, 2017.

BASIC INFORMATION

DEFINITION

Sciatica refers to the neuralgia following the sciatic nerve down the leg along its distribution. Sciatica usually occurs unilaterally. Pain is described as sharp or aching, and it typically radiates from the buttock down the leg posteriorly, laterally, or anteriorly depending on the level of nerve root compression.

SYNONYMS

Bilateral sciatica
Deep gluteal syndrome
Gout of the hip
Ischialgia
Left-sided sciatica
Low back pain with left sciatica
Low back pain with right sciatica
Low back pain—sciatica
Lumbago with sciatica
Lumbar nerve root pain
Lumbar radiculopathy (LBP)—sciatica
Neuropathy—sciatic nerve
Right-sided sciatica
Sciatic nerve dysfunction
Sciatic neuritis

ICD-10CM CODES

G57.00	Lesion of sciatic nerve, unspecified lower limb
G57.01	Lesion of sciatic nerve, right lower limb lesion
G57.02	Lesion of sciatic nerve, left lower limb
M54.30	Sciatica, unspecified side
M54.31	Sciatica, right side
M54.32	Sciatica, left side
M54.40	Lumbago with sciatica, unspecified side
M54.41	Lumbago with sciatica, right side
M54.42	Lumbago with sciatica, left side
M54.5	Low back pain
M54.9	Dorsalgia, unspecified
M62.838	Other muscle spasm

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Very few studies have determined the incidence of sciatica. However, 5% to 10% of patients with low back pain have sciatica. The highest incidence recorded is 40%.
PEAK INCIDENCE: Age 30 to 64 yr
PREVALENCE: Annual prevalence of disc-related sciatica in the general population is estimated at 2.2%.
RISK FACTORS:

- Increasing risk with height
- Smoking
- Diabetes
- Obesity
- Prolonged sitting and sedentary lifestyle
- Occupational factors:
  1. Strenuous physical activity (e.g., frequent lifting while bending and twisting)
  2. Driving

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Unilateral leg pain greater than low back pain
- Pain radiating to foot or toes
- Numbness and paresthesia in the same distribution
- Straight leg raising test induces more leg pain
- Localized neurology limited to one nerve root

ETIOLOGY

- Sciatica is usually caused by disc herniation at the L4 to L5 and L5 to S1 level, less commonly at the L3 to L4 level.
- Other causes include lumbar spinal stenosis, facet joint osteoarthritis or other arthropathies, spinal cord infection or tumor, sacroiliac joint dysfunction, degenerative disc disease, or isthmic spondylolisthesis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Nonspecific low back pain
- Piriformis syndrome
- Muscular problems (sprain, spasm)
- Vascular problems (claudication, compartment syndrome)
- Chronic edema
- Box 1 summarizes the differential diagnosis for low back pain

WORKUP

History taking and the physical examination are important steps in the evaluation of sciatica. Historical clues to the cause of low back pain are summarized in Table 1. Red flags that may indicate cauda equina or spinal infection mandate emergent workup. Fig. 1 summarizes an algorithm for the management of low back pain.
HISTORY TAKING:

- Severity of pain
- Duration
- Influence of coughing, movement, or rest
- Complaints of radiating pain in the leg following a dermatomal pattern
- Low back pain, less severe than leg pain
- Pain generally radiates below the knee, into the foot
- Dermatome maps used to locate origin of the pain
- Sensory symptoms

PHYSICAL EXAMINATION: Neurological testing

- Myotomes
- Reflexes (L4 to S3)
- Sensations (dermatomes; see Fig. 2)

LUMBAR MOBILITY ASSESSMENT: Neural tension tests (preferable seated position)

- Straight leg raise test
- Reversed straight leg raise test
- Bragard test
- Crossed straight leg raise test
- Slump test
- Femoral nerve tension test

BOX 1 Differential Diagnosis for Low Back Pain

Localized and Common
Uncomplicated musculoskeletal back pain
Intervertebral disk herniation
Spinal stenosis
Spondylolisthesis
Osteoarthritis
Fracture

Localized and Uncommon
Infection
Spondylitis
Epidural abscess
Diskitis
Herpes zoster

Malignancy
Metastatic
Breast
Lung
Prostate
Kidney, thyroid, colon (less common)
Primary
Multiple myeloma
Lymphoma
Leukemia
Primary cord or extradural tumors
Osteoid osteoma
Other primary bone tumors

Pediatric
Spondylolisthesis, spondylolysis
Severe scoliosis
Scheuermann disease

Rheumatologic
Ankylosing spondylitis
Psoriatic arthritis
Polymyalgia rheumatica
Reiter syndrome

Vascular
Arteriovenous malformation of spinal cord
Epidural hematoma

Life-Threatening Referred Pain
Abdominal aortic aneurysm

Gastrointestinal System
Biliary pathology
Pancreatitis
Peptic ulcer disease
Diverticulitis

Genitourinary System
Renal colic
Pyelonephritis
Prostatitis
Cystitis

Gynecologic System
Menstrual cramps
Spontaneous abortion
Labor
Ectopic pregnancy
Pelvic inflammatory disease
Endometriosis
Ovarian cyst
Ovarian torsion

Hematologic System
Sickle cell crisis

Functional
Somatization disorder
Depression
Fibrositis
Malingering

From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Elsevier.

TABLE 1 Historical Clues to the Cause of Low Back Pain

Questions for Patient	Potential Diagnosis
Does the back pain radiate down past the knees?	Radiculopathy and likely a herniated disk
Is the pain worse with walking and better with bending forward and sitting?	Spinal stenosis
Do you have morning back stiffness that improves with exercise?	Ankylosing spondylitis
Are you older than 50 yr?	Osteoporotic fracture, spinal malignancy
Has there been any recent history of blunt trauma?	Fracture
Do you take long-term corticosteroids?	Fracture, spinal infection
Do you have a history of cancer?	Spinal metastatic malignancy
Does your pain persist at rest?	Spinal malignancy, spinal infection
Has there been persistent pain for longer than 6 wk?	Spinal malignancy
Has there been unexplained weight loss?	Spinal malignancy
Is the pain worse at night?	Spinal malignancy, spinal infection
Are you immunocompromised (e.g., HIV infection, alcoholism, diabetes)?	Spinal infection
Have you had fevers or chills?	Spinal infection
Do you have pain, weakness, or numbness in both legs?	Cauda equina syndrome
Do you have bladder or bowel control problems?	Cauda equina syndrome

HIV, Human immunodeficiency virus.
From Walls RM et al: *Rosen's emergency medicine: concepts and clinical practice*, ed 9, Philadelphia, 2018, Elsevier.

Major maneuvers:
- Lumbar lateral bending
- Hip flexion
- Lasegue test
- Bechterew test
- Fajersztajn test
- Knee extension

Minor maneuvers:
- Cervical flexion
- Spinal flexion
- Hip internal rotation
- Hip adduction
- Great toe dorsiflexion
- Increased intrathecal/intradiscal pressure

LABORATORY TESTS

No laboratory tests specifically identify sciatica; it is a clinical diagnosis.
- Occasionally laboratory tests such as complete blood count (CBC) may suggest infection, anemia due to certain cancers, or other unusual causes of sciatica.
- Elevated erythrocyte sedimentation rate may suggest inflammation somewhere in the body.
- Urinalysis may suggest a kidney stone if there is blood in the urine, or infection if bacteria and white blood cells are present in the urine.

IMAGING STUDIES

- If pain does not resolve on its own, computed tomography (CT) or magnetic resonance imaging (MRI) scans of spine can be ordered to evaluate for other causes.
- If patient has a history of cancer, HIV infection, or IV drug use, or has been taking steroids over a period of time, imaging or bone scan are recommended.
- Electromyography (EMG).
- X-ray of spine may be examined for compression of nerve due to bone overgrowth.

Rx TREATMENT

Treatment for sciatica is activity modification and pain medication.

- Prescription-strength nonsteroidal anti-inflammatory drugs, such as meloxicam and diclofenac
- Analgesics, such as acetaminophen
- Muscle relaxants, such as cyclobenzaprine and tizanidine
- Corticosteroids
- Nerve pain medication (e.g., gabapentin)
- If pain is severe and not relieved by previous measures, then narcotic medications may be prescribed for a short period

NONPHARMACOLOGIC THERAPY

- Back surgery may be recommended if the pain continues and the CT and MRI indicate an anatomic problem with disc or bone and all other methods of treatment do not work. In a recent trial[1] involving patients with sciatica lasting more than 4 mo and caused by lumbar disk herniation, microdiskectomy was superior to nonsurgical care with respect to pain intensity at 6 mo of follow-up
- Ice or heat on affected area for 20 min every 2 hr
- Physical therapy
- Acupuncture, relaxation techniques
- Epidural injections
- Exercise therapy, including walking, yoga, Pilates
- Reducing pressure on the nerve root
- Bed rest is not recommended

ACUTE GENERAL Rx

- Acetaminophen for mild pain.
- Prescription-strength nonsteroidal anti-inflammatory drugs, such as meloxicam and diclofenac for moderate pain. Muscle relaxants, such as cyclobenzaprine and tizanidine are frequently used but efficacy is questionable. They are contraindicated in elderly patients.
- Gabapentin or pregabalin are frequently prescribed, but trials have failed to show reduced intensity of leg pain or improved outcomes.

[1]Bailey CS et al, Surgery versus conservative care for persistent sciatica lasting 4 to 12 months, *N Engl J Med* 382(12):1093-1102, 2020.

CHRONIC Rx

If pain is severe and not relieved by previous measures, then narcotic medications may be considered for a short period, although the medical community is increasingly turning away from long-term opioids due to the associated morbidity and mortality

COMPLEMENTARY AND ALTERNATIVE MEDICINE

- Acupuncture
- Spinal manipulation/chiropractic treatment techniques
- Physical therapy

DISPOSITION

Outpatient workup and assessment, including:
- Checking for red flags that may indicate malignancies, osteoporotic fractures, infection, or cauda equina syndrome
- Taking a history to determine localization, severity, loss of strength, sensation, duration, course, influence of coughing, rest or movement
- Physical examination, including straight leg raising test
- Imaging or laboratory diagnostic testing if red flags are present
- Prescribe medication as needed

REFERRAL

- Orthopedic surgeon
- Pain management
- Physical therapist
- Refer to neurosurgeon immediately in cases of cauda equina syndrome or acute severe paresis or progressive paresis (within a few days)
- Refer to neurologist, neurosurgeon, or orthopedic surgeon for consideration of surgery in cases of intractable radicular pain (not responding to morphine) or if pain does not diminish after 6 to 8 wk of conservative care

PEARLS & CONSIDERATIONS

COMMENTS

- Most people recover fully from sciatica and often without treatment, but it can potentially cause nerve damage. Important to seek immediate medical attention with loss of feeling in affected leg, weakness in affected leg, or loss of bowel or bladder function, as this could indicate cauda equina or epidural abscess.
- Sciatica does have a tendency to recur.
- Bed rest is not recommended.

PREVENTION

- Exercise regularly.
- Maintain proper posture when you sit.
- Use good body mechanics.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Lumbar Disk Syndrome (Related Key Topic)
Piriformis Syndrome (Related Key Topic)

AUTHORS: **Samantha Ni, MD,** and **Mark F. Brady, MD, MPH, MMSc**

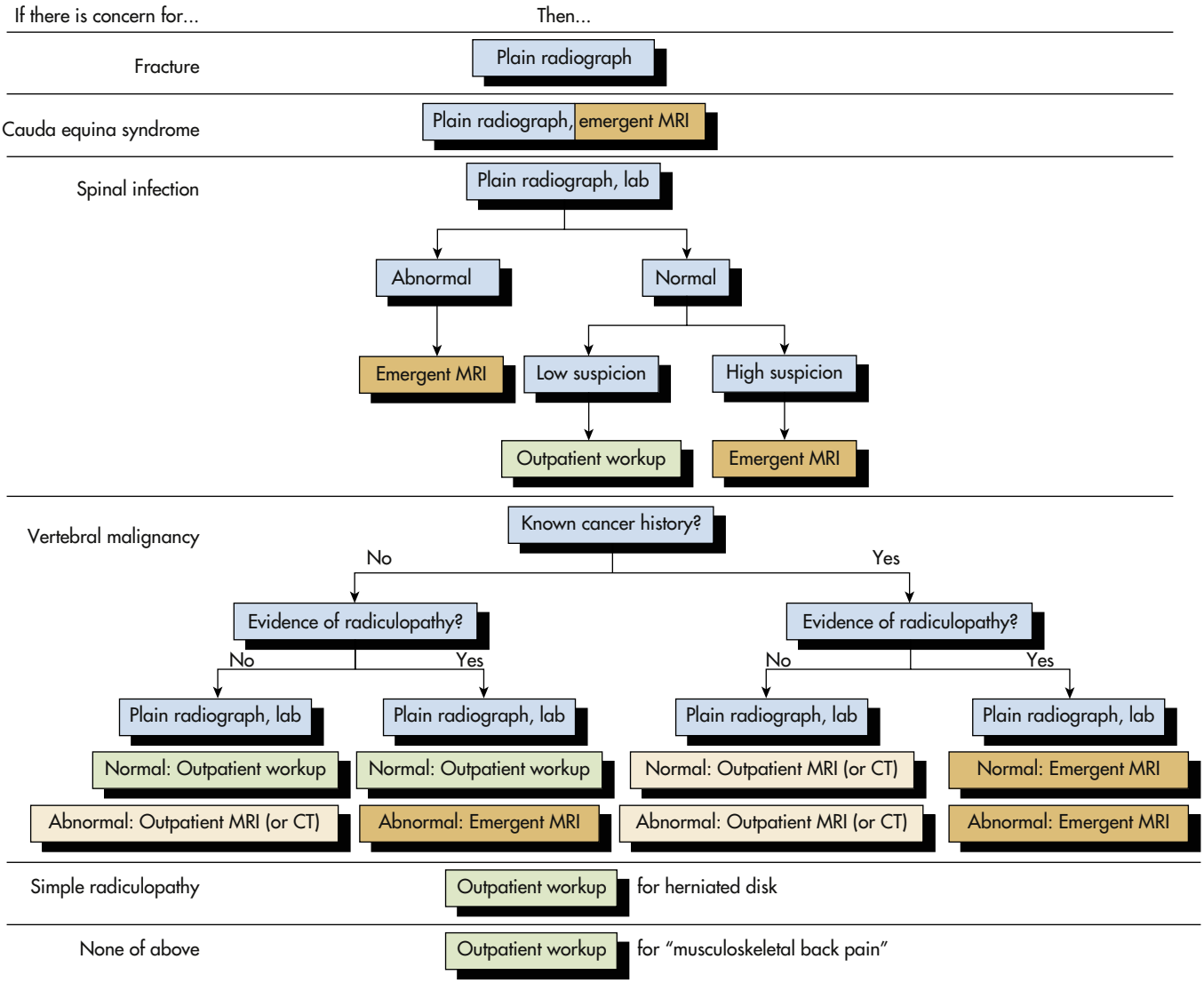

FIG. 1 Algorithm for management of low back pain. The patient's history may be concerning for more than one red flag diagnosis. *CT,* Computed tomography; *MRI,* magnetic resonance imaging. (From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Elsevier.)

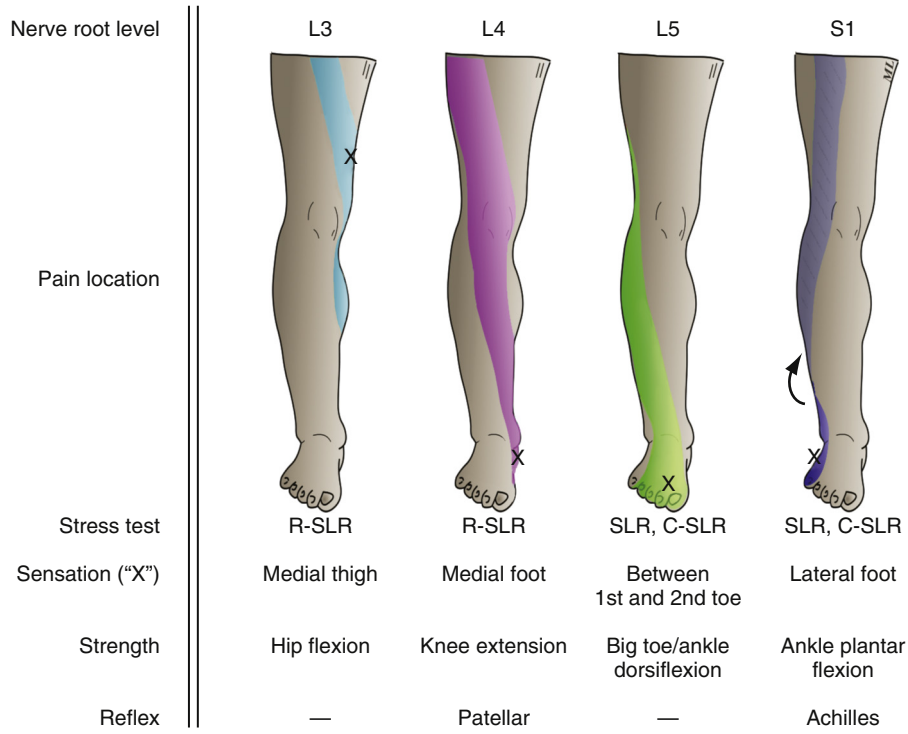

FIG. 2 Physical examination findings for L3-S1 radiculopathy. The *X* marks the ideal location to test for sensation for each nerve root. *C-SLR,* Crossed straight leg raise; *R-SLR,* reverse straight leg raise; *SLR,* straight leg raise. (From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Elsevier.)

SUGGESTED READINGS

Deyo R, Mirza SK: Herniated lumbar intervertebral disk, *N Engl J Med* 374:1763-1772, 2016.

Koes BW et al: Diagnosis and treatment of sciatica, *BMJ* 334:1313-1317, 2007.

Mathieson S et al: Trial of pregabalin for acute and chronic sciatica, *N Engl J Med* 376:111-120, 2017.

Miller KJ: Physical assessment of lower extremity radiculopathy and sciatica, *J Chiroprac Med* 6:75-82, 2007.

Ropper AH, Zafonte RD: Sciatica, *N Engl J Med* 372:1240-1248, 2015.

Visser LH et al: Sciatica-like symptoms and the sacroiliac joint: clinical features and differential diagnosis, *Eur Spine J* 22:1657-1664, 2013.

BASIC INFORMATION

DEFINITION

Scleritis is inflammation of the sclera (the fibrous layer of the eye underlying the conjunctiva and episclera). It is characterized by edema and cellular infiltration of the entire thickness of the sclera.

Classification of immune-mediated scleritis:

- Anterior nonnecrotizing scleritis: Can be subdivided into diffuse or nodular.
- Anterior necrotizing scleritis with inflammation: Can be subdivided into vasoocclusive, granulomatous, or surgically induced. Aggressive form of scleritis. Average age of onset is 60 yr. Bilateral in 60% of patients.
- Scleromalacia perforans: Typically affects elderly women with longstanding rheumatoid arthritis.
- Posterior scleritis: Involves the deeper tissues of the eye and is potentially blinding. Age of onset is often under 40 yr. Bilateral in 35% of cases.

SYNONYMS

Anterior scleritis
Diffuse nodular, necrotizing scleritis
Scleromalacia perforans
Scleral melt syndrome

TABLE E1 Classification of Immune-Mediated (Noninfectious) Scleritis

Anterior

- Nonnecrotizing
  - Diffuse
  - Nodular
- Necrotizing with inflammation
  - Vasoocclusive
  - Granulomatous
  - Surgically induced (can also be infective)
- Scleromalacia perforans (necrotizing without inflammation)

Posterior

From Bowling B: *Kanski's clinical ophthalmology, a systemic approach*, ed 8, Philadelphia, 2016, Elsevier.

ICD-10CM CODES
H15.0 Scleritis
H15.1 Episcleritis

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Increases with increasing age
INCIDENCE (IN U.S.): Busy ophthalmologists may see one or two cases/yr
PREVALENCE (IN U.S.): Relatively rare
PREDOMINANT SEX: 61% women
PREDOMINANT AGE: 52 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Deep, boring (dull) eye pain that may awaken patient from sleep
- Photophobia
- Tearing
- Painful eye movements
- Globe is tender to touch
- Conjunctival injection
- Thinning of the sclera
- An underlying systemic autoimmune disease is found in >50% of patients. Most common rheumatic problem is rheumatoid arthritis. Most patients with systemic disease are diagnosed before development of scleritis

ETIOLOGY

- Inflammatory (seen with rheumatoid arthritis, granulomatosis with polyangiitis [Wegener granulomatosis], relapsing polychondritis, polyarteritis nodosa), lupus, sarcoidosis. A classification of immune-mediated scleritis is described in Table E1.
- Allergic.
- Infectious scleritis (herpes zoster, tuberculosis, Lyme disease, syphilis, *Pseudomonas aeruginosa, Nocardia,* leprosy) is uncommon, accounting for 4% to 18% of cases.
- Approximately 50% of patients with scleritis have an underlying systemic disease (vasculitis, infectious disease).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Most common causes are rheumatoid arthritis and other collagen-vascular diseases.

- Occasionally there are allergic, infectious, or traumatic causes.
- Conjunctivitis, iritis, and episcleritis should be considered in the differential diagnosis. Patients with episcleritis generally have less pain and vision is unaffected.

WORKUP

- Eye examination. Figs. E1 to E6 illustrate the various types of scleritis
- Visual field examination
- Workup for autoimmune disease (e.g., vasculitis, collagen vascular diseases)

LABORATORY TESTS

Rheumatoid factor, antinuclear antibody, erythrocyte sedimentation rate, ANCA (c-ANCA, p-ANCA), antiphospholipid antibodies, HLA-B27 may be useful for underlying etiology

IMAGING STUDIES

Usually not necessary; CT scan of orbit may be useful in selected patients for collagen vascular disease or vasculitis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Bandage lenses
- Surgery if thinning of the sclera is severe to prevent eye rupture

ACUTE GENERAL Rx

Immunotherapy:

- Steroids (topical, periocular, and systemic)
- Cycloplegic drops
- NSAIDs (topical and systemic); systemic more effective than topical. Some NSAID and

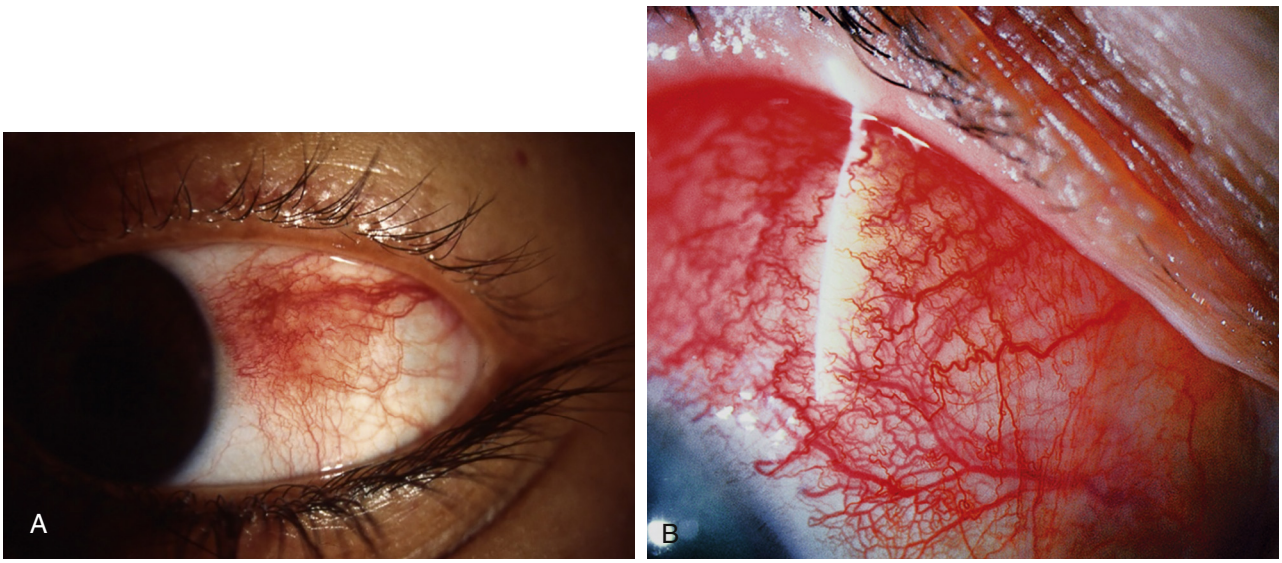

FIG. E1 Simple episcleritis. A, Sectoral. **B,** Diffuse. (Courtesy of JH Krachmer, MJ Mannis, and EJ Holland, from *Cornea*, 2005, Mosby; **B,** from Bowling B: *Kanski's clinical ophthalmology: a systemic approach*, ed 8, Philadelphia, 2016, Elsevier.)

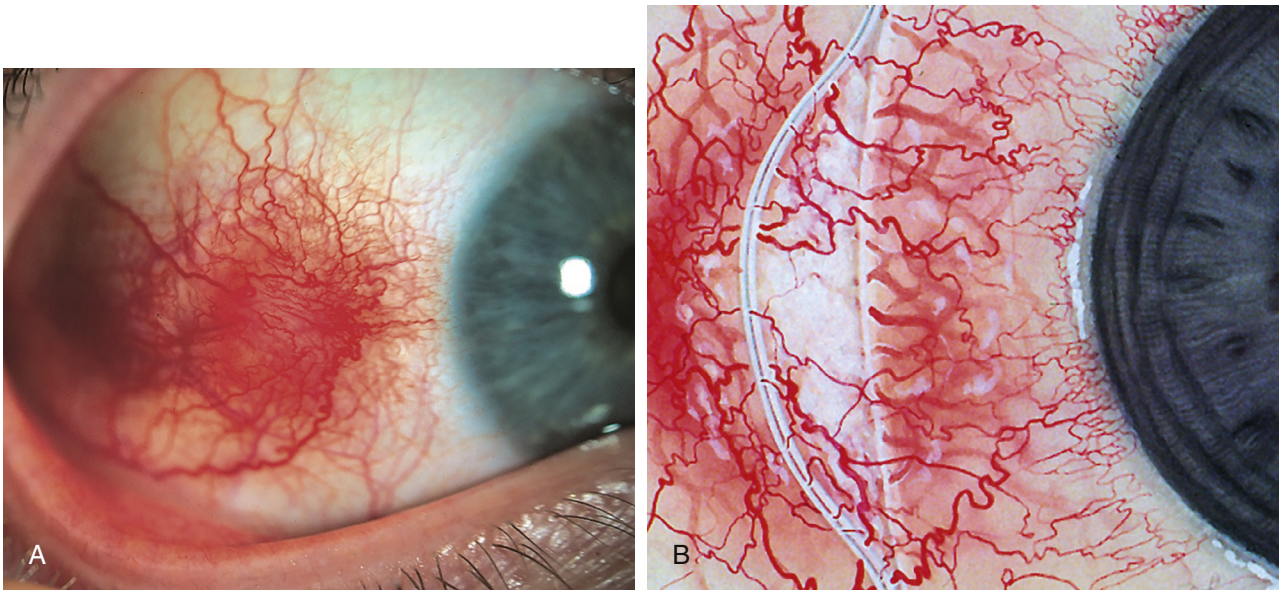

FIG. E2 A, Nodular episcleritis. **B,** Slit illumination shows that the deep beam is not displaced above the scleral surface. (From Bowling B: *Kanski's clinical ophthalmology: a systemic approach*, ed 8, Philadelphia, 2016, Elsevier.)

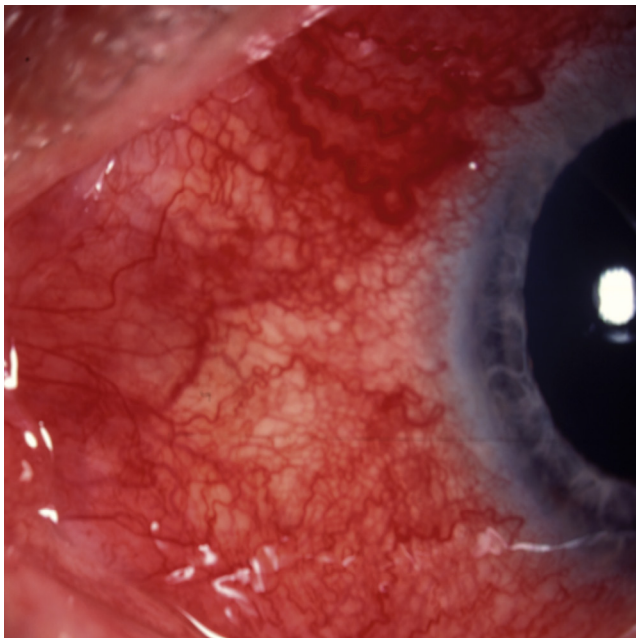

FIG. E3 Diffuse nonnecrotizing anterior scleritis. (From Bowling B: *Kanski's clinical ophthalmology: a systemic approach*, ed 8, Philadelphia, 2016, Elsevier.)

steroid drops have been shown to increase risk of corneal peripheral ulceration, so should be closely observed
- Cytotoxic agents (cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate) for severe unresponsive cases
- Immune modulators (cyclosporin, tacrolimus)
- Specific antibodies (infliximab, rituximab)

CHRONIC Rx

- Systemic corticosteroids can be given for the underlying disease.
- Local steroids may be helpful. Topical steroids should be used judiciously since these can potentiate the collagenase activity and worsen the scleral loss.
- Control underlying disease.

DISPOSITION

Urgent referral to ophthalmologist because this disorder can be a sight-threatening condition.

REFERRAL

Should be managed by ophthalmologist; complications of scleritis can be severe, including scleral melt, inflammation, corneal involvement. An ophthalmologist may also enlist the help of a rheumatologist for severe cases that may require long-term immunotherapies.

PEARLS & CONSIDERATIONS

COMMENTS

Necrotizing scleritis can be an ominous diagnosis because these patients often have other severe underlying debilitating vasculitic disease processes.

AUTHOR: **R. Scott Hoffman, MD**

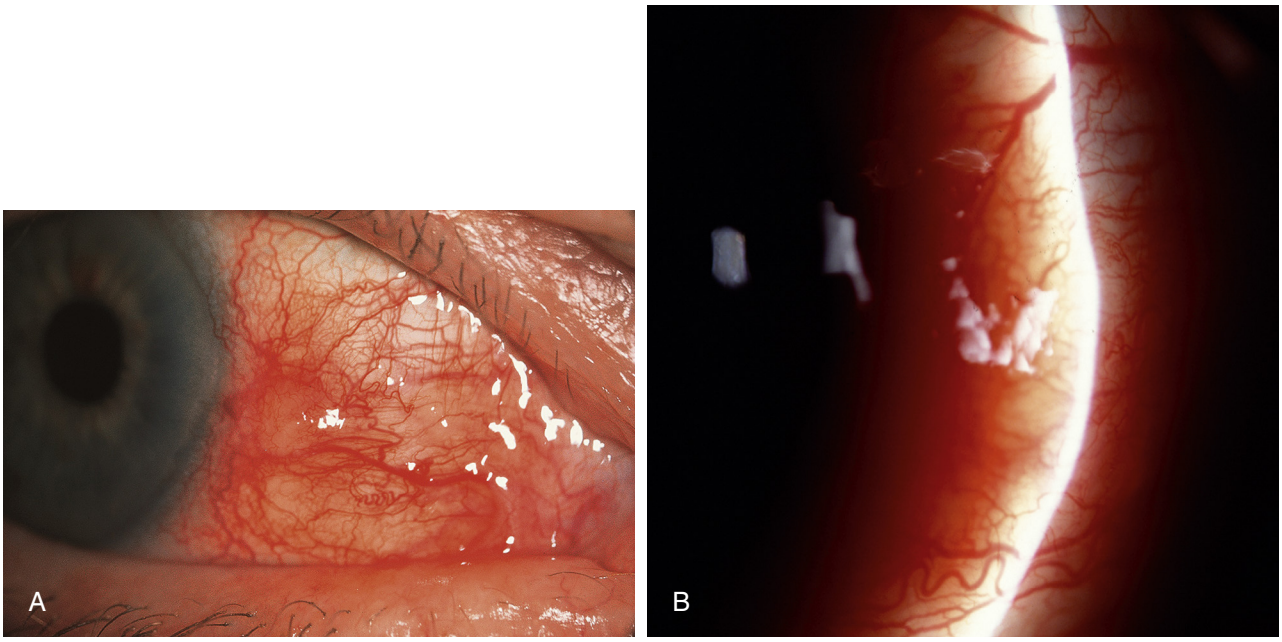

FIG. E4 A, Nodular nonnecrotizing anterior scleritis. **B,** Slit illumination shows superficial displacement of the entire beam. (Courtesy of P Watson—**A,** from Bowling B: *Kanski's clinical ophthalmology: a systemic approach*, ed 8, Philadelphia, 2016, Elsevier.)

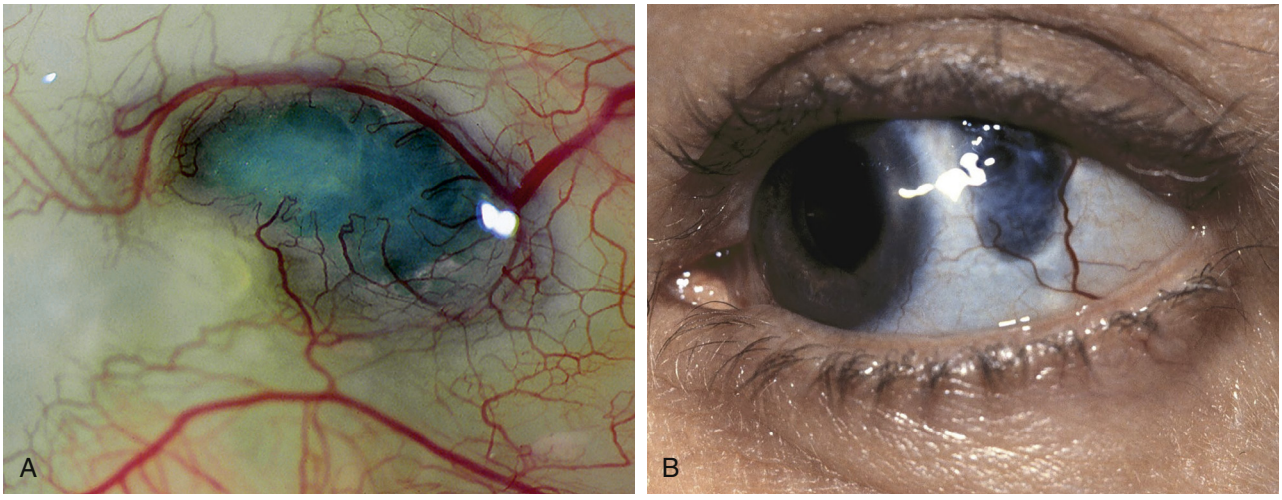

FIG. E5 Vasoocclusive necrotizing scleritis with inflammation. A, Early stage. **B,** Moderate disease—inflammatory signs are commonly more marked than in these cases. (Courtesy of C Barry. **B,** from Bowling B: *Kanski's clinical ophthalmology: a systemic approach*, ed 8, Philadelphia, 2016, Elsevier.)

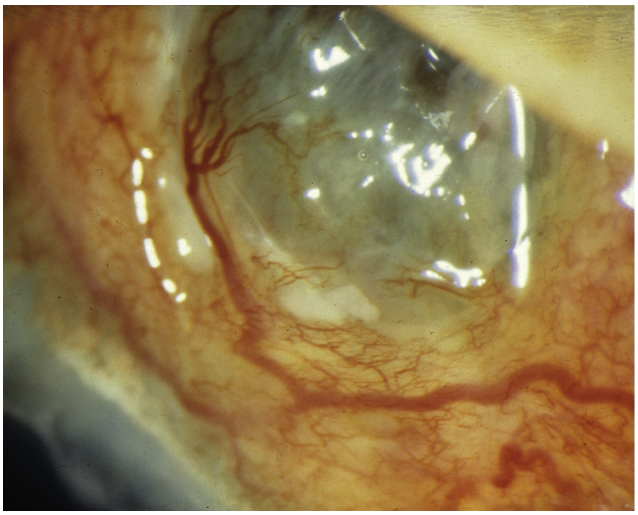

FIG. E6 Granulomatous necrotizing scleritis with inflammation. (Courtesy of P Watson. From Bowling B: *Kanski's clinical ophthalmology: a systemic approach*, ed 8, Philadelphia, 2016, Elsevier.)

SUGGESTED READING

Etminan M et al: Inflammatory ocular adverse events with the use of oral bisphosphonates: a retrospective cohort study, *CMAJ* 184:E431, 2012.

Scleroderma (Systemic Sclerosis)

BASIC INFORMATION

DEFINITION

Scleroderma or systemic sclerosis (SSc) is a term used to describe a connective tissue disorder that is characterized by thickening and fibrosis of the skin. Scleroderma is divided into two forms: Localized scleroderma and systemic sclerosis. Systemic sclerosis is a multiorgan disease characterized by fibrosis and vasculopathy. Skin thickening without any organ involvement is known as localized scleroderma and includes three subset conditions (see Box 1). Systemic sclerosis includes skin fibrosis along with variable severe involvement of diverse internal organs. It is further divided into two major subgroups: (1) Limited cutaneous SSc (lcSSc), which involves skin thickening of the face, neck, and distal to the elbows and knees; and (2) diffuse cutaneous SSc (dcSSc), which affects the skin in a more generalized distribution including the proximal and distal extremities, face, neck, and trunk. Clinical features of the major subsets of systemic sclerosis are summarized in Box 2.

SYNONYMS

SSc
Systemic sclerosis
Morphea applies to localized scleroderma that affects only the skin.
Scleredema is a disease of the skin that mimics but is distinct from scleroderma.

ICD-10CM CODES

L94.0	Localized scleroderma (morphea)
L94.1	Linear scleroderma
M34.0	Progressive systemic sclerosis
M34.1	CREST syndrome
M34.2	Systemic sclerosis induced by drug and chemical
M34.81	Systemic sclerosis with lung involvement
M34.82	Systemic sclerosis with myopathy
M34.83	Systemic sclerosis with polyneuropathy
M34.89	Other systemic sclerosis
M34.9	Systemic sclerosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

Incidence and prevalence of SSc differs between studies due to variations between geographic regions and time periods.

BOX 1 Classification of Scleroderma

I. Localized scleroderma
  A. Morphea
  B. Linear scleroderma
  C. Scleroderma en coup de sabre
II. Systemic sclerosis
  A. Limited cutaneous systemic sclerosis
  B. Diffuse cutaneous systemic sclerosis

From Hochberg MC, et al.: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

INCIDENCE: There are an estimated 19 cases per 1 million persons/yr, but many mild cases go unrecognized.
PREVALENCE: 276 cases per 1 million persons per yr
PREDOMINANT SEX: Female/male ratio of 4:1
PREDOMINANT AGE: 30 to 50 yr
DISTRIBUTION: Worldwide

PHYSICAL FINDINGS & CLINICAL PRESENTATION

PHYSICAL FINDINGS:

- Skin:
  1. Initial presentation of puffy hands and fingers may occur in some patients.
  2. Tightening of the skin begins on the hands and then can progress to the forearms, face, and neck. The skin is shiny, taut, and sometimes red, with loss of creases and hair. Skin thickening involving the fingers or toes is known as sclerodactyly (Fig. E1). Skin involvement in scleroderma is classified as lcSSc or dcSSc, depending on the distribution of the skin thickening (see previously) (Fig. E2). Fig. E3 illustrates the method used to quantify skin thickness in scleroderma.
  3. Skin tightening may limit movement by causing flexion contractures of the fingers, wrists, and elbows. Perioral skin tightening (Fig. E4) results in decreased oral aperture, furrowing around the lips, and dry membranes.
  4. Pigmentary skin changes (hypo or hyperpigmentation) may occur (e.g., "salt and pepper").
  5. Telangiectasias (dilated capillaries) may be seen on face, hands, mucous membranes (Fig. E4), and trunk.
  6. Subcutaneous calcinosis, calcinosis cutis
  7. In dsSSc patients, the skin fibrosis can soften over time (generally occurring at least 2 yr after onset of skin manifestation), with improved joint mobility.
  8. Skin atrophy and thinning can also occur in the late stages of SSc.
- Musculoskeletal:
  1. Arthralgias and swelling
  2. Inflammatory arthritis, tendinitis
  3. Myalgias, myopathy
  4. Joint contractures
  5. Tendon friction rubs (physical exam finding of a palpable rub felt over tendon sheaths—fingers, wrists, elbows, knees, and/or ankles)
- Gastrointestinal involvement:
  1. Esophageal dysmotility with heartburn
  2. Esophageal stricture with dysphagia and odynophagia
  3. Delayed gastric emptying
  4. Gastrointestinal bleeding from mucosal telangiectasias, gastric antral vascular ectasias, or gastritis
  5. Small bowel dysmotility with abdominal cramps, bloating, and diarrhea
  6. Colon dysmotility with constipation
  7. Intestinal bacterial overgrowth resulting in irregular bowel movements (diarrhea alternating with constipation)
  8. Pseudo-obstruction (functional ileus)
  9. Primary biliary cholangitis
- Pulmonary:
  1. Interstitial lung disease (ILD): Pulmonary fibrosis with symptoms of dyspnea and nonproductive cough as well as fine inspiratory crackles on examination. Seen in both lcSSc and dcSSC, but it is more common and severe in dcSSC
  2. Pulmonary arterial hypertension (PAH): Presenting with dyspnea and/or fatigue. Can be identified in both lcSSc and dcSSc, but it is more commonly seen in lcSSc
- Cardiac:
  1. Pericarditis or pericardial effusion
  2. Myocardial fibrosis or ischemia that can lead to CHF or arrhythmias
  3. Left or right systolic or diastolic dysfunction
- Renal:
  1. Rapidly progressive renal failure also known as scleroderma renal crisis (SRC): New-onset hypertension, anemia with schistocytes on peripheral blood smear, thrombocytopenia and renal insufficiency with active urinary sediment and proteinuria

BOX 2 Clinical Features of the Major Subsets of Systemic Sclerosis

Limited SSc
- Skin sclerosis, distal limbs and face
- Long preexisting RP symptoms
- Lower frequency of severe lung fibrosis and renal crisis
- High burden of nonlethal morbidity

Diffuse SSc
- Proximal skin sclerosis
- Shorter preexisting RP history
- High frequency of severe lung fibrosis
- Increased risk of scleroderma renal crisis
- Inflammatory skin changes and pruritus common for first 1-3 yr

Sine SSc
- Features of RP with scleroderma-associated ANA reactivity and at least one internal organ manifestation of SSc
- Frequency uncertain because of likely underdiagnosis

Overlap SSc
- Cases that fulfill classification criteria for SSc and that are diagnosed as SSc but also show features of another autoimmune rheumatic disease
- Most often myositis
- Other cases of lupus, arthritis, or vasculitis
- Comprise up to 20% of SSc cohorts

ANA, Antinuclear antibody; *RP,* Raynaud phenomenon; *SSc,* systemic sclerosis.
From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

- Vascular:
  1. Raynaud phenomenon (RP): Vasospasm of the fingers with exposure to cold, resulting in color changes of the digits along with numbness/tingling and discomfort
  2. Complications of vascular involvement can include digital pitted scars or ulcers, nonreversible ischemic changes with impending tissue loss, dry gangrene, and auto-amputation
  3. Nailfold capillary abnormalities: Seen with nailfold capillaroscopy, including capillary dilatation, avascularity, or "drop out" of capillaries
- Other organ involvement:
  1. Hypothyroidism
  2. Erectile dysfunction
  3. Sjögren syndrome
  4. Entrapment neuropathies
  5. Depression

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Raynaud phenomenon: Initial complaint in 70% of patients (NOTE: The prevalence of Raynaud phenomenon is 5% to 10% in the general population; most cases do not progress to scleroderma)
- Finger or hand swelling that is sometimes associated with carpal tunnel syndrome
- Arthralgias/arthritis
- Internal organ involvement (Table E1, Table E2, Fig. E5, Fig. E6)
- LcSSc (previously known as CREST syndrome): Calcinosis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly telangiectasias—skin fibrosis is limited to the distal extremities. This acronym is now considered obsolete by many because it does not accurately reflect the burden of internal organ involvement

ETIOLOGY

The etiology of this condition is unknown, but genetic and environmental factors (infectious agents, occupational exposures, drugs) contribute to the manifestation of the disease. Genetic profiles show clustering of different alleles according to the subtype of SSc.

Pathologically, small- and medium-sized arteries become injured, leading to fibrin deposition and ultimately luminal occlusion, causing chronic tissue hypoxia. There is also an abnormal selection of fibroblasts and aberrant control of connective tissue synthesis by fibroblasts and other cells. This fibrosis occurs in different organs, causing dysfunction and eventual failure. Although there are characteristic autoantibodies detected, it is not clear that they directly participate in the pathogenesis of the disease.

DIAGNOSIS

The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) have created criteria as a guide in diagnosing and classifying SSc (Table 3). These include a scoring system for both clinical and laboratory findings (sclerodactyly, fingertip lesions, telangiectasias, abnormal nailfold capillaries, Raynaud phenomenon, PAH/ILD, and SSc-related autoantibodies).

DIFFERENTIAL DIAGNOSIS

DERMATOLOGIC:

- Scleredema
- Amyloidosis
- Porphyria cutanea tarda
- Eosinophilic fasciitis
- Reflex sympathetic dystrophy
- Nephrogenic systemic fibrosis
- Table 4 summarizes distinguishing features of scleroderma and scleroderma-like conditions

SYSTEMIC:

- Idiopathic pulmonary fibrosis
- Primary pulmonary hypertension
- Primary biliary cirrhosis
- Cardiomyopathies
- Gastrointestinal dysmotility problems
- Systemic lupus erythematosus and overlap syndromes

WORKUP

Laboratory tests and imaging studies

TABLE 3 ACR/EULAR 2013 Classification Criteria for Systemic Sclerosis*

Item	Subitem	Weight or Score
Skin thickening of fingers on both hands extending proximal to the MCP joints (sufficient criterion)	—	9
Skin thickening on the fingers (only count the higher score)	Puffy fingers	2
	Sclerodactyly of fingers (distal to MCP joints but proximal to proximal interphalangeal joints)	4
Fingertip lesions (only count higher score)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	—	2
Abnormal nailfold capillaries	—	2
Pulmonary arterial hypertension or ILD (maximum score, 2)	PAH	2
	ILD	2
Raynaud phenomenon	—	3
SSc-related antibodies (anti-centromere, anti-topoisomerase 1 [anti-SCL-70], anti-RNA polymerase III (max score 3)	Anti-centromere	3
	Anti-topoisomerase I	
	Anti-polymerase III	

*The score is determined by adding the maximum weight or score in each category. Patients with scores ≥9 have definite systemic sclerosis (SSc).

ACR, American College of Rheumatology; *EULAR,* European League Against Rheumatism; *ILD,* interstitial lung disease; *MCP,* metacarpophalangeal; *PAH,* pulmonary arterial hypertension; *SSc,* systemic sclerosis.

From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

TABLE 4 Distinguishing Features of Scleroderma and Scleroderma-like Conditions

Condition	Skin Changes and Distribution	Extradermal Involvement	Dermatopathology	Other
Localized scleroderma	Amorphous plaques (morphea) or lines involving the face (linear) and extremities and sparing the fingers	None	Dermal sclerosis, mononuclear inflammation	Linear especially common in children, autoantibodies common
Scleredema	Trunk, back, neck	Rare	Swollen collagen bundles, mucin accumulation	
Scleromyxedema	Induration, sclerodactyly Limited mouth opening	Rare	Excessive dermal mucin deposition	Serum paraprotein (especially IgG λ)
Nephrogenic systemic fibrosis	Extremities, fingers; symmetric	Frequent, mild (muscle, fascia, lungs)	Fibroblast proliferation, mucin deposition, dermal spindle cell proliferation	After gadolinium exposure in end-stage renal disease
Eosinophilic fasciitis	Extremities, trunk; spares fingers	Rare; low-grade myositis	Dermal and hypodermal sclerosis, normal epidermis, muscle inflammation occasionally	Peripheral blood eosinophilia frequent

From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

LABORATORY TESTS

- Antinuclear antibodies (ANA): Nucleolar (more common), homogeneous, or speckled patterns
- Rheumatoid factor positive in 20% of patients
- Routine biochemistry tests may indicate specific organ involvement (e.g., liver, kidney, muscle); should check CBCD, CK, CMP, UA

The following extractable nuclear antigens are either present or absent in SSc:

- Anticentromere antibodies: Generally positive in one third of patients with lcSSc
- Anti-Scl-70 antibody (antitopoisomerase I): Positive in 40% of patients with dcSSc and has an increased risk of developing ILD
- Anti-RNA polymerase III antibody: Portends a worse prognosis, with rapidly progressive skin fibrosis and increased risk of developing SRC. May also indicate increased cancer risk
- Anti-ribonucleoprotein (anti-RNP): Positive in 20%, can see with overlap conditions
- Other possible antibodies include U3 RNP, U1 RNP, PM-Scl, Th/To, Anti-Ku
- Table 5 summarizes autoantigens and autoantibodies in scleroderma

IMAGING AND OTHER STUDIES

- Arthritis: Joint radiographs
- Gastrointestinal:
  1. Upper endoscopy (diagnostic procedure of choice; may be therapeutic)
  2. Cine-esophagography (in rare circumstances)
  3. Barium swallow (occasionally indicated)
  4. Esophageal manometry
- Pulmonary:
  1. Chest x-ray
  2. Pulmonary function tests (especially single-breath diffusion capacity for carbon monoxide—DLCO)
  3. Thoracic high-resolution computed tomography (HRCT) scan
  4. Bronchoscopy with biopsy, bronchoalveolar lavage
- Cardiac:
  1. ECG
  2. Ambulatory (Holter) ECG monitoring
  3. Echocardiography (screen for pulmonary arterial hypertension)
  4. Cardiac catheterization
- Kidney: Renal biopsy
- Skin: Skin biopsy
- Vascular: Nailfold capillaroscopy

Rx TREATMENT

Currently, there is no disease-modifying therapy available for SSc. Generally, the internal organ involvement of the disease is treatable. Fig. 7 illustrates management strategies in SSc. Immunosuppressive agents are used in individual patients. Prednisone should be used with extreme caution, especially in doses >20 mg/day (can precipitate SRC).

- Raynaud phenomenon:
  1. Keep hands and body warm
  2. Avoid smoking and using vasoconstricting drugs
  3. Calcium channel blockers (i.e., long-acting dihydropyridines)
  4. Peripheral α1-adrenergic blockers
  5. Angiotensin II receptor blockers
  6. Topical nitrate
  7. Phosphodiesterase inhibitors
  8. Stellate ganglion blockades
  9. Digital sympathectomy
  10. Table E6 summarizes vascular therapies for Raynaud phenomenon
- Arthralgias: NSAIDs or low-dose corticosteroids (5-10 mg of prednisone per day)
- Myositis: Methotrexate or azathioprine with low-dose corticosteroids
- Skin: For skin fibrosis, immunomodulatory drugs have been used, generally started within 3 yr of onset (methotrexate, mycophenolate mofetil). Cyclophosphamide can be used for refractory or rapidly progressive involvement. Table E7 summarizes immunomodulatory and antifibrotic strategies for disease-modifying treatment of systemic sclerosis skin disease
- GI tract: Table E8 summarizes treatment of GI tract complications in systemic sclerosis
- Esophageal reflux:
  1. H_2-receptor blockers
  2. Proton pump inhibitors
- Interstitial lung disease:
  1. Mycophenolate mofetil or cyclophosphamide for symptomatic ILD
  2. Nintedanib, a small molecule that inhibits several kinases linked to the pathogenesis of interstitial lung diseases (receptor tyrosine kinases and nonreceptor tyrosine kinases), recently received FDA approval for the treatment of ILD associated with systemic sclerosis
  3. Lung transplantation for patients with advanced pulmonary involvement
- Pulmonary hypertension:
  1. Oxygen
  2. Diuretics (with caution)
  3. Prostacyclins (epoprostenol, iloprost, treprostinil)
  4. Endothelin-1 receptor inhibitors (bosentan, ambrisentan)
  5. Phosphodiesterase 5 inhibitors (sildenafil, tadalafil)
  6. Table E9 summarizes approved therapies for treatment of pulmonary arterial hypertension
- Renal involvement:
  1. Angiotensin-converting enzyme inhibitors
  2. Dialysis
  3. Renal transplantation

TABLE 5 Autoantigens and Autoantibodies in Scleroderma

Autoantigen	Molecular Structure	Autoantibody Frequency
Scl-70	100-kD native and 70-kD degradation product; DNA topoisomerase I	75% in diffuse scleroderma; 20%-59% in all patients; 13% in CREST
Centromere	Proteins 17, 80, and 140 kD; localized at inner and outer kinetochore plates	57%-82% in CREST; 8% in diffuse form
RNA Pol I	RNA Pol I complex of subunit proteins, 210-211 kD	4%-30% in scleroderma; 13% in diffuse form
RNA Pol II	Transcripts mRNA	4%
RNA Pol III	Transcripts 5S rRNA, tRNA	23% in scleroderma; 45% in diffuse form; 6% in CREST
Fibrillarin	Protein 34 kD, component of U3 RNP particle	6%-8%; 5% in diffuse form; 10% in CREST
U1nRNP	Spliceosome complex	2%-5% in all patients; 24% in PM/scleroderma overlap
PM-Scl	Complex of 11 proteins, 110-120 kD	4%-11%; 24% in PM/scleroderma overlap
Ku	DNA-binding protein	1%-14% in scleroderma; 26%-55% in PM/scleroderma overlap
Th/To	Protein 40 kD, complexes with 7S and 8S RNAs	1%-13% in scleroderma; 1%-11% in diffuse form; 8%-19% in CREST; up to 3% in PM/scleroderma overlap
NOR-90	Protein 90 kD, human upstream binding factor, localized in nucleolus organizer region	Rare

CREST, Calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia; *DNA,* deoxyribonucleic acid; *mRNA,* messenger RNA; *PM,* polymyositis; *RNA,* ribonucleic acid; *RNP,* ribonucleoprotein; *rRNA,* ribosomal RNA; *tRNA,* transfer RNA.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, Philadelphia, 2017, Elsevier.

REFERRAL

Rheumatology consultation is indicated. Consider pulmonary, cardiology, or gastrointestinal consultations depending on organ involvement.

PEARLS & CONSIDERATIONS

COMMENTS

Autologous hematopoietic stem cell therapy (HSCT) has shown some benefit in patients with severe diffuse cutaneous systemic sclerosis, but there was greater treatment-related mortality and morbidity associated with HSCT.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Scleroderma (Patient Information)

AUTHOR: **Joanne Szczygiel Cunha, MD**

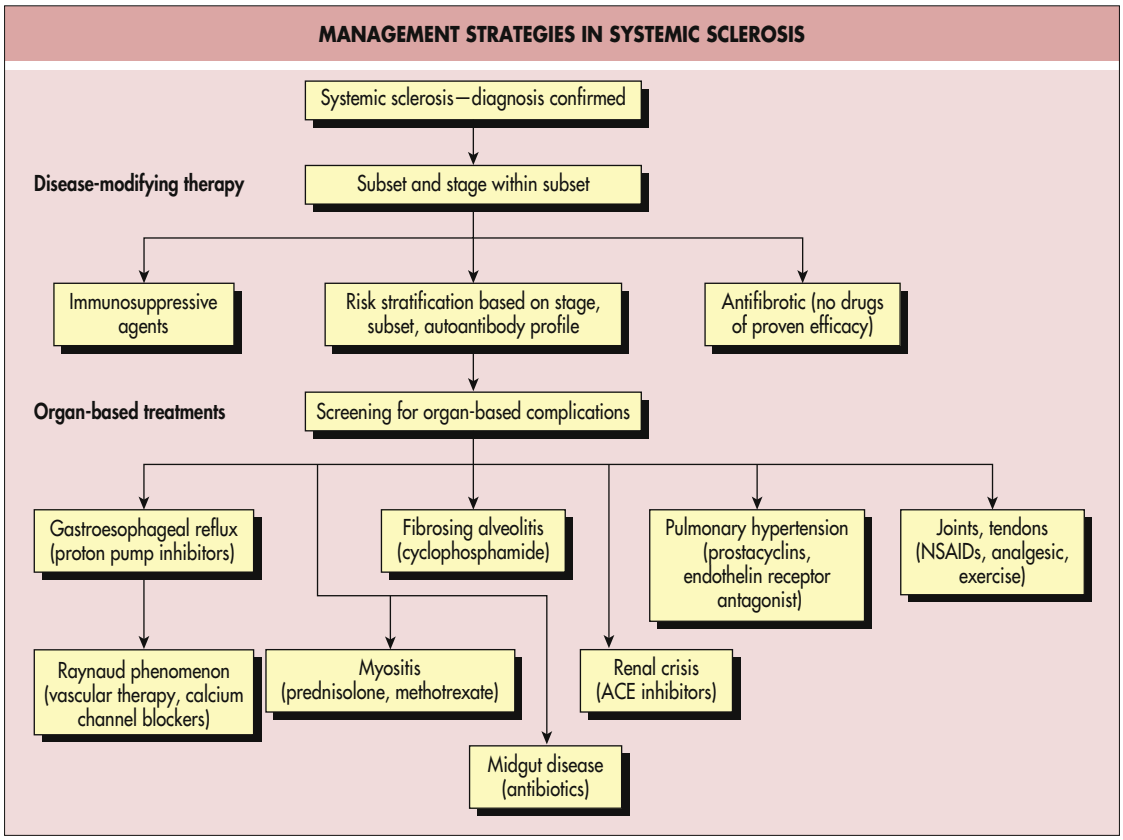

FIG. 7 Management of scleroderma requires multiple strategies depending on the specific problems that are present in individual patients. *ACE,* Angiotensin-converting enzyme; *NSAID,* nonsteroidal antiinflammatory drug. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

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FIG. E1 Sclerodactyly in a patient with systemic sclerosis. (From Hochberg MC, et al.: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

FIG. E2 Skin involvement in scleroderma is subdivided into "limited" and "diffuse" cutaneous forms. A, Sclerodactyly in limited cutaneous disease. **B,** Truncal changes in diffuse cutaneous disease. **C,** Inflammatory signs in early active skin disease. **D,** Finger contracture in the chronic fibrotic phase of skin involvement in scleroderma. (From Firestein GS, et al.: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

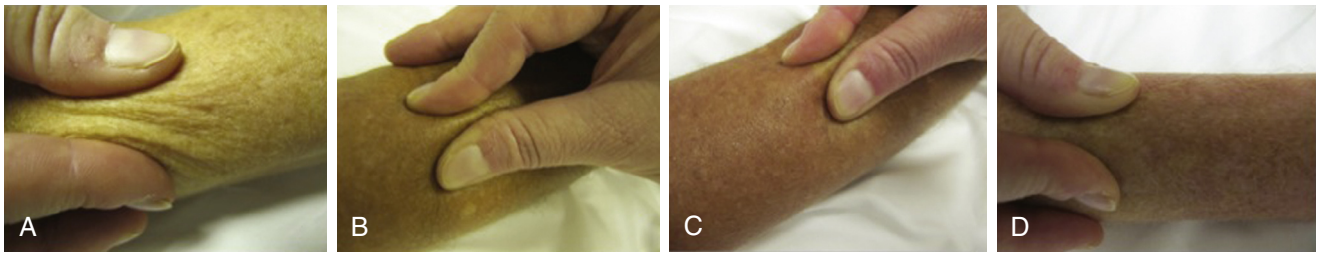

FIG.E3 Method used to semi-quantify skin thickness in scleroderma. The modified Rodnan skin score is obtained by clinical palpation of 17 different body areas (fingers, hands, forearms, upper arms, chest, abdomen, thighs, lower legs, and feet) and subjective averaging of the thickness of each specific site: 0 = normal **(A)**; 1 = mild **(B)**; 2 = moderate **(C)**; and 3 = severe **(D)**. The maximum score is 51. (From Firestein GS, et al.: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

FIG. E4 Oral manifestations. A, Perioral skin tightening with decreased oral aperture, furrowing around the lips, and dry membranes. **B,** Periodontal disease with regression of gum and loosening of teeth. **C** and **D,** Telangiectasias on lips and tongue. (From Firestein GS, et al.: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

TABLE E1 Overview of Musculoskeletal Complications of Systemic Sclerosis

Manifestation	Clinical Features	Serologic Associations
Contractures	Typical feature of dcSSc Associated with ARA positivity Palmar fibrosis	ARA, ATA, RF, ACPA
Tendonitis or tendon friction rubs	Overlap arthritis	ARA
Arthritis	May resemble RA in overlap Associated with RF positivity and ACPA positivity More with U1RNP reactivity Contributes to deformity and contractures May have Jaccoud pattern but with fixed deformity	U1RNP, ACPA, RF
Myositis	Minor elevation in CK common, especially in dcSSc Weakness and loss of muscle bulk Severe myositis less frequent Overlap syndromes with myositis most common Serologic associations include anti–PM-Scl, anti-U1RNP, anti-fibrillarin	U1RNP, PM-Scl, U3RNP
Acro-osteolysis	More common in environmentally triggered SSc Association with vasculopathy and Raynaud phenomenon Possible association with calcinosis	ACA, ATA

ACA, Anticentromere; *ACPA,* anti-cyclic citrullinated protein antibody; *ARA,* anti-RNA polymerase III antibody; *ATA,* antitopoisomerase; *CK,* creatine kinase; *dcSSc,* diffuse cutaneous systemic sclerosis; *PM-Scl,* anti-polymyositis scleroderma antibody; *RA,* rheumatoid arthritis; *RF,* rheumatoid factor; SSc, systemic sclerosis; *U1RNP,* anti-U1-ribonucleoprotein antibody; *U3RNP,* anti-U3-ribonucleoprotein antibody.
From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

TABLE E2 Patterns of Parenchymal Lung Involvement in Systemic Sclerosis

Classification	HRCT Appearance	Frequency (%)	Outcome	Treatment
NSIP	Homogeneous interstitial shadowing with traction bronchiectasis and predilection for bases and subpleural locations	50	Variable depending on extent of disease	Supportive Antireflux MMF or CYC RTX Experimental agents
UIP	Heterogeneous interstitial shadowing with architectural distortion, traction bronchiectasis, and cystic changes	15	Variable depending on extent of disease and may have worse outcome than NSIP but not as much as in IPF	Supportive Antireflux MMF or CYC RTX Experimental agents
OP	Patchy and asymmetric changes with homogeneous appearance and later patchy scarring	5	Potential for improvements and recovery if treated effectively	Steroids and anti-infective treatment MMF or CYC if associated with significant fibrosis
PF with emphysema	Interstitial fibrotic change that may have NSIP or UIP features and is associated with airspace enlargement and concurrent emphysematous change	10	Variable depending on extent and severity	Supportive Antireflux MMF or CYC RTX for fibrosis Manage airway disease according to severity and responsiveness
Pleuroparenchymal fibroelastosis	Interstitial fibrosis with additional pleural-based dense fibrosis and scarring extending to the upper zones	1	Progressive and difficult to treat with poor outcome	Supportive Antireflux MMF or CYC RTX for fibrosis
Aspiration pneumonia	Asymmetric changes often associated with esophageal dilatation; leaves patchy scarring	20	Potential for improvements and recovery if treated effectively; may be aggravated by immunosuppression	Vigorous antireflux and acid suppressive therapy Prophylactic antibiotics and prompt treatment of intercurrent infection

CYC, Cyclophosphamide; *IPF,* idiopathic pulmonary fibrosis; *MMF,* mycophenolate mofetil; *NSIP,* nonspecific interstitial pneumonia; *OP,* organizing pneumonia; *PF,* pulmonary fibrosis; *RTX,* rituximab; *UIP,* usual interstitial pneumonia.
From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

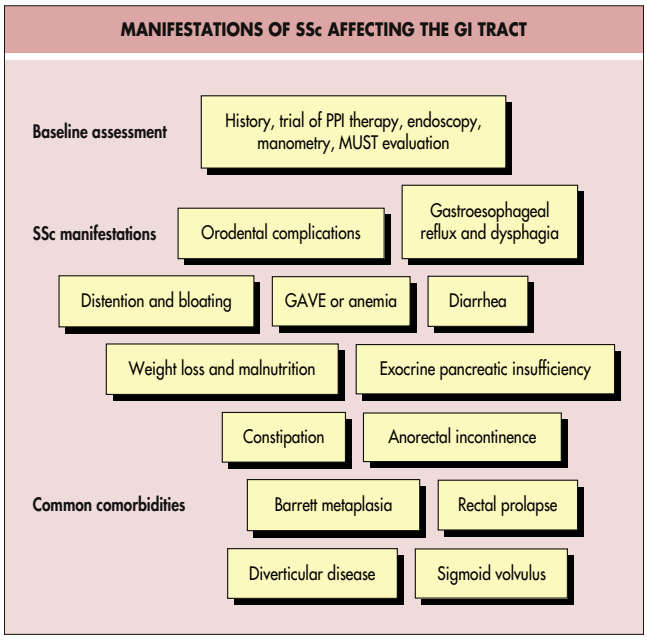

FIG. E5 Manifestations of systemic sclerosis within the gastrointestinal (GI) tract are frequent and require careful assessment. The major features are summarized for the upper, mid-, and lower GI tract along with important comorbidities that may need additional assessment and treatment. *GAVE,* Gastric antral vascular ectasia; *MUST,* Malnutrition Universal Screening Tool; *PPI,* proton pump inhibitor. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

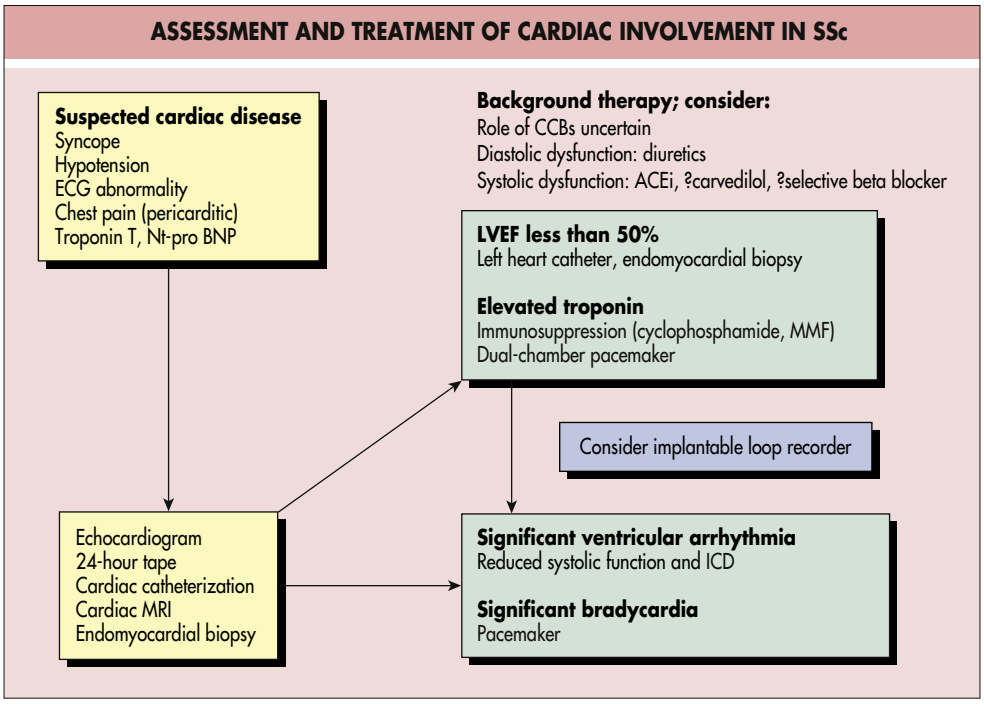

FIG. E6 Cardiac manifestations of systemic sclerosis (SSc) are common but can be challenging to diagnose and manage. This is because minor changes in rate or imaging may not be significant, and other manifestations can be unpredictable. Cardiac involvement should be investigated systematically, and hemodynamically significant disease may be treated as outlined in the figure. The use of loop recording reveal devices in cases with suspected sporadic significant arrhythmias may be considered to identify patients who may benefit from an implantable defibrillator (ICD). *ACEI,* Angiotensin-converting enzyme inhibitor; *CCB,* calcium channel blocker; *ECG,* electrocardiogram; *LVEF,* left ventricular ejection fraction; *MMF,* mycophenolate mofetil; *MRI,* magnetic resonance imaging; *Nt-pro BNP,* N-terminal pro b-type natriuretic peptide. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

TABLE E6 Vascular Therapies for Raynaud Phenomenon

Treatment	Examples	Comments	Reference	Grade*
Nondrug	Hand warmers, protective clothing	Universally helpful		
Nutritional	Evening primrose oil	Symptoms improve		
	Fish oil capsules	Symptoms improve only in primary Raynaud, not scleroderma		
	Antioxidant vitamins	Theoretical benefit but no controlled trial evidence		
Pharmacologic Agents for Raynaud Phenomenon				
Calcium channel blockers	Nifedipine, amlodipine, diltiazem	Variable and differential response to different agents; slow titration of dose reduces the severity of adverse effects	1	A
Angiotensin-converting enzyme inhibitors (quinapril)		No evidence of effectiveness	2	A
Angiotensin receptor blockers	Losartan	Effective in clinical trial but limited effectiveness in practice	3	A
Selective serotonin reuptake inhibitor	Fluoxetine	Readily available; clinically less effective but fewer adverse vasodilatory effects than calcium channel blockers	4	A
Topical nitrates	Nitroglycerin patch MQX-503, topical nitroglycerin	Long-acting patch helpful but many side effects; multiple studies new agent with significant results but not approved by FDA	5, 6	A
Treatment for Ulcers				
Phosphodiesterase inhibitors	Sildenafil, tadalafil	Clinical trials show improvement in Raynaud manifestations and ulcer healing	7, 8	A
Parenteral vasodilators	Iloprost, prostaglandin E_1, treprostinil	Effective in healing ulcers and reducing severity and frequency of Raynaud attacks; expensive with limited long-term benefit (not available in U.S.)	9	C
Endothelin receptor antagonists	Bosentan	Clinical trials show decrease in new ulcers but no effect on healing (approved for prevention of ulcers in Europe but not in U.S.)	10, 11	A
Statins		Single study showing decreased occurrence of ulcers	12	A
Local management of ulcers		Wound-healing techniques, topical antibiotics, soaking, occlusion, debridement; systemic antibiotics as necessary; adequate analgesia (including narcotics if necessary)		
Surgical Procedures				
Radical microarteriolysis, digital sympathectomy		Division of adventitia of digital arteries; sometimes termed *digital sympathectomy.* Useful treatment for individual critically ischemic digits; experimental treatment showing improved pain and mobility; phase 3 trial of adipose-derived stromal injections ongoing	13	B
Autologous adipose–derived stromal injections and fat grafting			14-16	B
Botulinum toxin A (Botox) "sympathectomy"		Small studies promising but clinical trials needed	17	C
Debridement, amputation		Autoamputation is best to allow maximum preservation of healthy tissue. Surgery should be conservative and reserved for cases of infection or intractable pain.		

*Findings of studies include these types of evidence:
Level A: Randomized controlled clinical trial, cohort study.
Level B: Retrospective cohort, exploratory cohort, outcomes research, case-control study; or extrapolations from level A studies.
Level C: Case-series study or extrapolations from level B studies.
Level D: Expert opinion without explicit critical appraisal; or based on physiology, bench research, or first principles.
FDA, Food and Drug Administration.
From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

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TABLE E7 Evidence-Based Review of Immunomodulatory and Antifibrotic Strategies for Disease-modifying Treatment of Systemic Sclerosis Skin Disease

Agent	Clinical Trial Data	Reference	Grade*
Immunomodulatory Agents			
Methotrexate	Placebo-controlled trial, 30 patients; significant improvement in skin score	18	A
	Larger North American study; inconclusive results	19	A
Mycophenolate	Favorable outcomes in skin, lung, and survival rate in uncontrolled trials and observational cohorts	20, 21	B
Rituximab	Small, open, randomized trial showed favorable skin and lung outcomes, but prospective open study found no effect on skin	22, 23	B
	Observational cohort study found positive effect on joints, skin, and PFTs	24	A
Immunoablation	Observational experience marked improvement in skin	25	B
	Small, short-term study comparing stem cell transplantation with high-dose intravenous cyclophosphamide (Cytoxan); very favorable results	26	A
	ASTIS controlled trial with improved skin and survival	27	A
Cyclosporine	Open study, 10 patients; improvement in skin score	28	C
Intravenous immunoglobulin	Improved skin and joint status in open study	29	C
Extracorporeal photopheresis	First study suggested benefit but later evaluation equivocal	30	A
Oral induction of tolerance to type I collagen	Favorable pilot data; trial results positive for late-stage disease	31	A
Anti–IL-6, tocilizumab	Phase 2 trial with improved skin and less loss of lung function	32	A
Antifibrotic Agents			
D-Penicillamine	Uncontrolled studies with positive effects but controlled trial without evidence of response	33	B
		34	A
Minocycline	Small, open study with cured patients but larger uncontrolled study showing no effect	35	C
		36	B
Tyrosine kinase	Variable effects in several uncontrolled inhibitor trials showing increased toxicity and a controlled trial that was negative	37, 38, 39	B A

*Findings of studies include these types of evidence:
Level A: Randomized controlled clinical trial, cohort study.
Level B: Retrospective cohort, exploratory cohort, outcomes research, case-control study; or extrapolations from level A studies
Level C: Case-series study or extrapolations from level B studies
Level D: Expert opinion without explicit critical appraisal; or based on physiology, bench research, or first principles
ASTIS, Autologous Stem Cell Transplantation International Scleroderma Trial; *IL-6,* interleukin-6; *PFT,* pulmonary function test.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

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TABLE E8 Treatment of Gastrointestinal Tract Complications in Systemic Sclerosis

Site	Disorder	Symptom	Investigation	Treatment
Mouth	Tight skin	Cosmetic	None	Facial exercises
	Dental caries	Toothache	Dental radiograph	Dental treatment
	Sicca syndrome	Dry mouth	Salivary gland biopsy	Artificial saliva
Esophagus	Dysmotility or esophageal spasm	Dysphagia	Barium swallow	PPIs
	Reflux esophagitis	Heartburn	Esophageal scintigraphy	Minimize NSAID and CCB use
	Stricture	Dysphagia	Manometry, endoscopy	Elevate head of bed, avoid late meals
Stomach	Gastroparesis	Anorexia, nausea, early satiety	Scintigraphy	Erythromycin (as motility agent), metoclopramide, domperidone, PPIs
	NSAID-related ulcer	Pain	Endoscopy, barium UGI	PPIs
	Gastric antral vascular ectasia or watermelon stomach	Severe anemia, silent blood loss	Endoscopy	Laser coagulation
Small bowel	Hypomotility	Weight loss	Barium follow-through	Rotational antibiotics, metronidazole, ciprofloxacin, rifaximin, octreotide (low dose) for severe disease; TPN in rare cases
	Stasis	Postprandial bloating	^{14}C glycocholate or hydrogen breath tests	
	Bacterial overgrowth	Malabsorption	Breath tests	Domperidone, metoclopramide, rotational antibiotics, metronidazole, ciprofloxacin, rifaximin
	NSAID enteropathy	Steatorrhea	Jejunal aspiration	
	Pseudo-obstruction	Abdominal pain	Fecal microscopy	Oral nutritional supplements
		Distention	Plain abdominal radiography	Parenteral nutritional support
	Pneumatosis intestinalis	Diarrhea with blood, benign pneumoperitoneum	Plain abdominal radiography	Conservative management
Large bowel	Hypomotility	Alternating constipation and diarrhea	Barium enema, CT of abdomen	Dietary manipulation, stool expanders for constipation, loperamide for diarrhea
	Colonic pseudodiverticula	Rare perforation	Barium enema, CT of abdomen	Resection as a last resort
	Pseudo-obstruction	Abdominal pain, distention	Plain abdominal radiography	Conservative management
Anus	Sphincter involvement	Fecal incontinence	Rectal manometry	Kegel exercises, protective measures, sacral nerve stimulation

CCB, Calcium channel blocker; *CT,* computed tomography; *NSAID,* nonsteroidal antiinflammatory drug; *PPI,* proton pump inhibitor; *TPN,* total parenteral nutrition.
From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

TABLE E9 Approved Therapies for Treatment of Pulmonary Arterial Hypertension

Class of Drug	Drug	Route of Administration	Main Adverse Effects	Comments
Endothelin receptor antagonists	Bosentan	Oral twice a day	LFT abnormalities in up to 10% (bosentan); reduces oral anticoagulant efficacy (bosentan); potentially teratogenic; fluid retention and anemia	Nonselective ET_A and ET_B blockade
	Ambrisentan	Oral daily dose	Potentially teratogenic; fluid retention and anemia	Partially selective ERA with specificity for ET_A
	Macitentan	Oral daily dose	Potentially teratogenic; fluid retention and anemia	Nonselective ET_A and ET_B blockade (more tissue-specific)
Nitric oxide stimulation	Sildenafil, PDE5 inhibitor	Oral: 3 times a day	Headache, visual disturbance, epistaxis; generally well tolerated	Different formulation licensed for erectile dysfunction
	Tadalafil, PDE 5 inhibitor	Oral: Once daily	Headache, visual disturbance, epistaxis	Generally well tolerated; longer duration of action than sildenafil
	Riociguat, guanylin cyclase stimulator	Oral: Twice a day	Headache, hypotension, bleeding	Cannot be used with PDE5 inhibitors reserved for severe disease
Prostacyclin analogues	Epoprostenol	Continuous IV infusion	Headaches, muscle cramps, diarrhea; severe worsening if infusion interrupted; sepsis and other risks from IV administration	Reserved for severe disease; Side effects for all prostacyclins are similar and often limit dose
	Treprostinil	SC or IV infusion Nebulized inhaled: 4 times a day Oral: 3 times a day	Headaches, muscle cramps, diarrhea; worsening if infusion interrupted but less immediate than with epoprostenol; sepsis and other risks from IV administration; severe local site pain from SC infusion	
	Iloprost	Nebulized inhaled: 6-9 times a day	Headaches, muscle cramps, diarrhea	Inhaled drug PAH
	Beraprost	Oral: 60 μg a day	Headaches, muscle cramps, diarrhea	Licensed only in Japan
	Selexipag, prostacyclin receptor stimulator	Oral: Twice a day	Headaches, muscle cramps, diarrhea	Recently approved; will need to see if as effective as IV drugs

ERA, Endothelin receptor antagonist; *ET_A,* endothelin receptor type A; *ET_B,* endothelin receptor type B; *IV,* intravenous; *LFT,* liver function test; *PAH,* pulmonary arterial hypertension; *PDE5,* phosphodiesterase type 5; *SC,* subcutaneous.

From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

BASIC INFORMATION

DEFINITION

Scoliosis is a three-dimensional spine deformity characterized by lateral and rotational curvature of the spine. The two main types are adolescent idiopathic scoliosis (AIS) and adult degenerative scoliosis (ADS), which are distinguished by age of onset. Scoliosis may be classified as either structural (fixed, nonflexible) or nonstructural (flexible, correctable, and secondary to nonspinal pathology). Scoliosis is often detected on physical examination (Adams forward bend test) and confirmed radiographically.

ICD-10CM CODES	
M41	Scoliosis
M41.0	Infantile idiopathic scoliosis
M41.1	Juvenile idiopathic scoliosis
M41.20	Other idiopathic scoliosis, site unspecified
M41.3	Thoracogenic scoliosis
M41.40	Neuromuscular scoliosis, site unspecified
M41.80	Other forms of scoliosis, site unspecified
Q67.5	Congenital deformity of spine

EPIDEMIOLOGY & DEMOGRAPHICS (IDIOPATHIC FORM)

PREDOMINANT SEX: The incidence of AIS is similar in males and females; however, females have up to a tenfold greater risk of curve progression. Females are roughly seven times as likely to require orthopedic surgical intervention for idiopathic scoliosis. ADS has an equal gender distribution.
PREVALENCE: 1.5% to 3% of adolescents
PREDOMINANT AGE:
- Onset variable
- Most curves found in adolescents (age ≥11 yr)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typical presentation involves postural complaints rather than pain or neurologic symptoms.
- Record patient age (in yrs plus mos) and height.
- Perform neurologic examination to rule out neuromuscular disease.
- Inspect the shoulders and iliac crests to determine if they are level.
- Palpate the spinous processes to determine their alignment.
- Have the patient bend forward at the waist to approximately 45 degrees with the arms hanging free (Adams position); observe from the back to detect whether one side of the back appears higher than the other (Fig. 1).
- May repeat forward bending test in a sitting position to eliminate leg length inequality.

ETIOLOGY

- 90% unknown, referred to as *idiopathic* (genetic)
- Congenital spine deformity
- Neuromuscular disease
- Leg-length inequality
- Local inflammation or infection
- Acute pain (disk disease)
- Chronic degenerative disk disease with asymmetric disk narrowing

Curves of an idiopathic nature or those accompanying congenital deformity or neuromuscular disease are associated with structural changes. The nonstructural types (leg-length discrepancy, muscle spasm, inflammation, or acute pain) disappear when the offending disorder is corrected.

DIAGNOSIS

WORKUP

- Curvatures associated with congenital spine abnormalities, neuromuscular disease, and other less common forms of scoliosis can usually be identified by history or associated radiographic or physical findings.
- The diagnosis of scoliosis is suspected on the basis of physical examination and confirmed by radiography performed while the patient is in a standing position. Physical examination with the Adams forward bend test and scoliometer measurement can identify scoliosis, and the radiologic testing for Cobb angle measurement can confirm the diagnosis. The Cobb angle is measured on a thoraco-lumbar radiograph and is defined as the intersecting angle between lines drawn parallel to the endplates of the two vertebrae with the greatest amount of tilt. The Risser grade measures ossification of the iliac apophysis. It consists of five grades ranging from 25% ossification in grade 1 to full ossification of the apophysis in grade 5. Lower Risser scores are associated with higher spinal growth potential. Patients with Risser scores of 0 or 1 are at greatest risk of scoliosis curve progression. Scoliosis screening is described in Fig. 2.

IMAGING STUDIES

- PA, lateral, and side-bending radiographs of the entire spine and pelvis.
- There is high potential for repeated radiation exposure in adolescents evaluated for scoliosis. Use breast and gonadal shielding whenever possible. If you are referring to a specialist that will be unable to view the images obtained, instruct the patient's family to bring a printed copy to their visit.
- Diagnosis of idiopathic scoliosis is confirmed by a Cobb angle greater than 10 degrees as measured on a radiograph.
- Severity of the curve is measured in degrees, usually by the Cobb method (Fig. 3).
- MRI is usually not indicated unless there is pain, neurologic deficit, or a left thoracic curve (which is often associated with an underlying spinal disorder).

TREATMENT

ACUTE GENERAL Rx

- Treatment or correction of cause if curve is nonstructural
- Early detection is key in treating genetic (idiopathic) curve
- Regular observation for curves <20 degrees
- If no curve progression, repeat imaging may be limited to once per yr
- Bracing for idiopathic curves of 25 to 45 degrees in patients with an immature skeleton (Risser score 0 to 2) to prevent progression
- Surgery (Fig. E4) for idiopathic curves >45 degrees in patients with an immature skeleton

DISPOSITION

- The larger the curve at detection, the greater the chance of progression.
- Progression is more common in young children who are beginning their growth spurt.
- Curves in females are more likely to progress.
- Curves <20 degrees will improve spontaneously >50% of the time.
- Failure to diagnose and treat these curves may allow progressive deformity, pain, and cardiopulmonary compromise to develop.
- Spinal deformities >50 degrees in adults may progress and eventually become painful or compromise pulmonary function.
- There is no difference in the rate of back pain in the general population and patients with adolescent idiopathic scoliosis.

REFERRAL

Refer for orthopedic consultation if structural curve >20 degrees is present or if structural curve <20 degrees progresses 5 degrees or more upon follow-up evaluation.

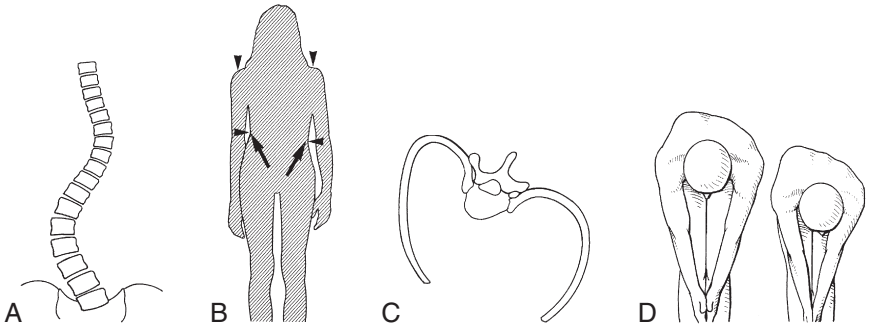
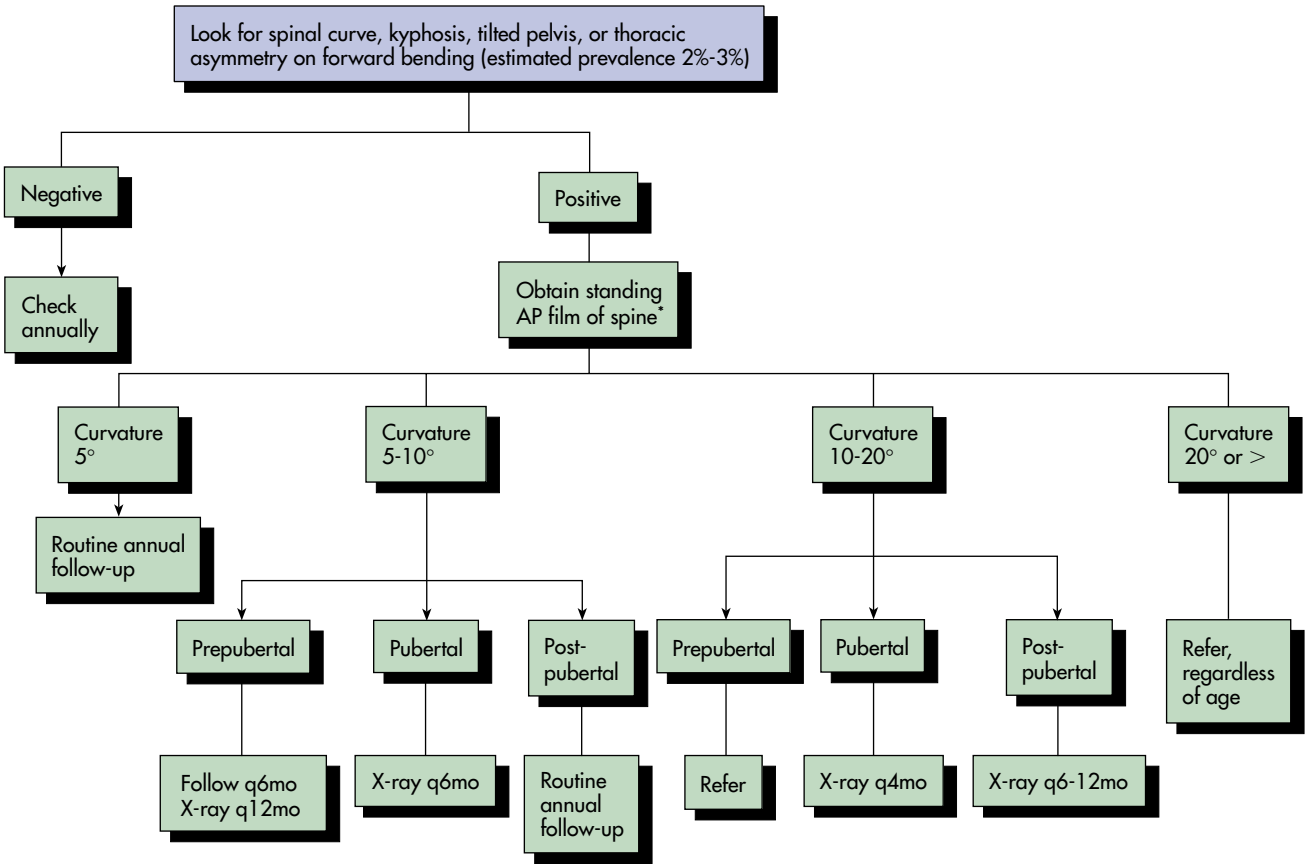


FIG. 1 Structural changes in idiopathic scoliosis. A, As curvature increases, alterations in body configuration develop in both the primary and compensatory curve regions. **B,** Asymmetries of shoulder height, waistline, and the elbow-to-flank distance are common findings. **C,** Vertebral rotation and associated posterior displacement of the ribs on the convex side of the curve are responsible for the characteristic deformity of the chest wall in scoliosis patients. **D,** In the school screening examination for scoliosis, the patient bends forward at the waist. Rib asymmetry of even a small degree is obvious.



*Cobb method of angle measurement.

1. Find the lowest vertebra whose bottom tilts toward concavity of curve.
2. Erect a perpendicular line from extension of bottom surface.
3. Find highest vertebra as in #1 and erect perpendicular from extension of top surface.
4. Measure intersecting angle = angle of scoliosis.

FIG. 2 Scoliosis screening and follow-up. *AP,* Anteroposterior.

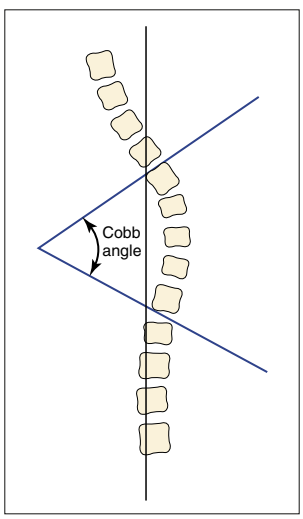


FIG. 3 Cobb angle. This is measured using the superior and inferior end plates of the most tilted vertebrae at the end of each curve. (From Tschudy MM, Arcara KM: *The Harriet Lane handbook,* ed 19, Philadelphia, 2012, Mosby.)

PEARLS & CONSIDERATIONS

COMMENTS

- Congenital scoliosis has a high incidence of cardiac and urinary tract abnormalities.
- Bracing is not intended to completely straighten the idiopathic curve. It may improve the curvature, but is mainly used to stabilize and prevent progression.
- The initial Cobb angle magnitude (≥25 degrees) is the most important predictor of long-term curve progression.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Scoliosis (Patient Information)

AUTHOR: **Michael Bergen, MD**

SUGGESTED READINGS

American Academy of Orthopedic Surgeons: *Position Statement: screening for the early detection of idiopathic scoliosis in adolescents*. www.aaos.org/uploadedFiles/1122%20Screening%20for%20the%20Early%20Detection%20of%20Idiopathic%20Scoliosis%20in%20Adolescents%202%201%2016.pdf, February 2016.

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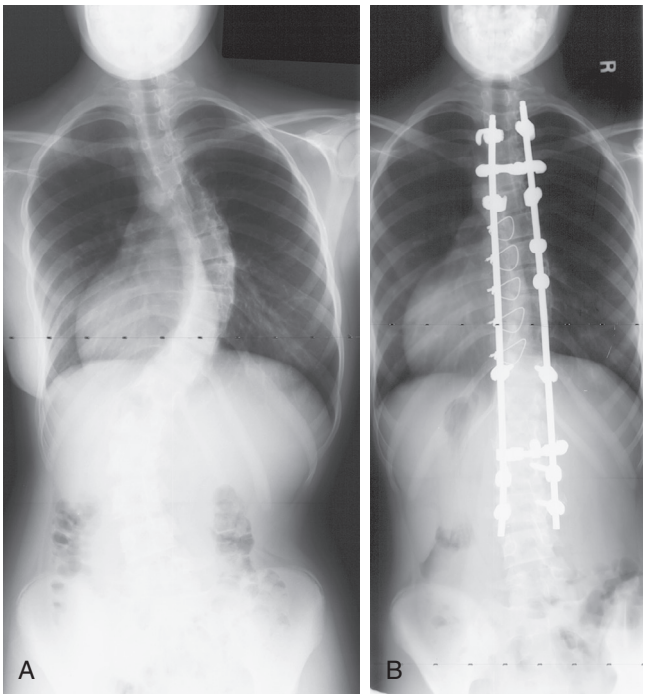

FIG. E4 Preoperative standing posteroanterior radiograph of a 14-yr-old girl who was skeletally immature and developed a 68-degree right thoracic and a 53-degree left lumbar scoliosis **(A).** Her trunk was shifted to the right, and the left shoulder was slightly depressed. Based on the risk of future progression, she was treated with an instrumented posterior spinal fusion from T3 to L3 with correction of the right thoracic curve to 20 degrees and the left lumbar curve to 10 degrees **(B).** Coronal spinal balance was restored, and shoulder height was maintained. (From Kliegman RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.)

Scombroid Poisoning

BASIC INFORMATION

DEFINITION

Foodborne illness from improperly stored fish causing histamine toxicity when consumed, mimicking a type I hypersensitivity reaction

SYNONYMS

Scombroid fish poisoning

ICD-10CM CODES

T61.11 Scombroid fish poisoning, accidental
T61.12 Scombroid fish poisoning, intentional
T61.13 Scombroid fish poisoning, assault
T61.14 Scombroid fish poisoning, undetermined

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: According to the CDC's Foodborne Disease Outbreak surveillance system, data collected from U.S and Puerto Rico show the following:

- Between 1998 and 2008, there were 333 outbreaks and 1383 patient cases, no mortalities.
- Between 2009 and 2015, there were 101 total outbreak cases (95 were confirmed outbreak cases); 299 total patient cases (280 of these were confirmed individual patient cases); and 2 hospitalizations, no mortalities.

PEAK INCIDENCE: Summer

RISK FACTORS: Improperly stored fish at temperatures >4° C or >40° F

- Risk factors for more severe reaction
  1. Immunocompromised
  2. Patients with preexisting chronic pulmonary conditions
  3. Medications that inhibit metabolism of histamine
  4. Chronic diseases impairing normal cardiac response to hypotension

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typically within 30 min to 1 hour after ingestion, patients will experience symptoms of overwhelming levels of histamine that include:
  1. Metallic or peppery taste
  2. Cutaneous flushing
  3. Urticarial rash
  4. Perioral burning or edema
  5. Tachycardia/palpitations
  6. Dizziness
  7. Headache
  8. GI symptoms: Abdominal pain, nausea, vomiting, diarrhea
  9. Hypotension
- Rarer symptoms
  1. Bronchospasm
  2. Cardiac arrhythmias
  3. Shock

ETIOLOGY

There are certain types of fish whose flesh naturally has high levels of histidine. When they are not stored properly, bacteria (generally gram-negative Enterobacteriaceae) can grow and metabolize histidine into histamine. Once histamine is present, cooking, freezing, smoking will NOT destabilize it. Extent of poisoning is related to the quantity of histamine ingested, which is dependent on the growth of bacteria producing histamine and the amount of fish ingested.

Fish known to cause scombroid poisoning include:

- Scombridae family
  1. Tuna
  2. Mackerel
  3. Bonito
- Other examples
  1. Mahi-mahi
  2. Anchovies
  3. Sardines
  4. Albacore
  5. Marlin
  6. Herring
- Cheese
  1. Most notably, Swiss cheese

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Allergic reaction/anaphylaxis
- Asthma exacerbation
- Serum sickness
- Angioedema
- Ciguatera poisoning
- Table 1 summarizes marine biotoxins

WORKUP

- Unnecessary for diagnosis, however can obtain:
  1. Plasma levels of histamine
  2. Urine levels of histamine metabolites
  3. Plasma levels of tryptase: Should be negative in scombroid cases

LABORATORY TESTS

Not generally indicated unless there is a suspicion of intentional overdose

IMAGING STUDIES

Generally not indicated

TREATMENT

- Supportive care
- Antihistamines (PO if patient can tolerate)
  1. H_1 blocker: Benadryl
  2. H_2 blocker: Ranitidine, cimetidine, famotidine
  3. Can have patients take H_1/H_2 blockers scheduled after initial symptoms resolve to prevent recurrence
- If patient becomes anaphylactic, may need crystalloids, steroids, and epinephrine
- Hypotensive patients requiring fluids or epinephrine should be observed as an admit

NONPHARMACOLOGIC THERAPY

Fluids, no known benefit of crystalloid type

ACUTE GENERAL Rx

H_1 and H_2 blocker (PO or IV)

DISPOSITION

- Supportive care is normally sufficient. Symptoms should resolve in 1 to 2 days, and most patients can be discharged home if they have no airway compromise or hypotension during their stay and are observed to be improving. There is no standard of care for length of observation.
- In cases of patients with preexisting illnesses or medications that predispose them to a more severe manifestation of the illness:
  1. The duration of illness may be prolonged.
  2. May need admission for observation until toxicity has resolved.

REFERRAL

The local health department should be notified when a scombroid case is suspected.

PEARLS & CONSIDERATIONS

COMMENTS

This is not a true allergy. Histamine already is present in the fish or cheese consumed, as opposed to a Type I hypersensitivity reaction, in which the patient's immune system reacts to the fish's antigens and generates histamine. In the case of scombroid, only the histamine consumed is part of the reaction.

PREVENTION

Store fish immediately after it is caught to prevent bacterial growth and conversion of histidine in dark meat into histamine (<44° C or <40° F). In some instances, fish is caught and stored improperly long before the market or restaurant takes possession of it. When histamine levels are high, no cooking, smoking, or boiling will eradicate it. Fish with high histamine levels may not taste bad or have any distinguishing features until consumed. All persons consuming contaminated fish should react to the stored histamine, so an isolated case in which several people share a meal of the same fish should raise suspicion of an alternate diagnosis.

PATIENT & FAMILY EDUCATION

- California Department of Public Health Scombroid Fish Poisoning Fact Sheet available at www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/ScombroidFishPoisoningFactSheet.pdf
- Hungerford JM Scombroid Poisoning: A Review available at www.sciencedirect.com/science/article/pii/S0041010110000450?via%3Dihub
- Poison Control Food Poisoning from Fish: Ciguatera and Scombroid available at www.poison.org/articles/2009-jun/what-you-cant-smell-can-hurt

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Samantha Ni, MD,** and **J. Richard Walker III, MD, MS, FACEP**

TABLE 1 Marine Biotoxins

Syndrome	Symptoms	Incubation Period	Toxin	Mechanism of Action	Food Source	Geographic Distribution	Seasonality
Paralytic shellfish poisoning	Facial and perioral paresthesias, headache, muscular weakness, mental status changes, nausea, vomiting, death	30 min-4 h	Saxitoxin	Blocks sodium channels	Shellfish	NE and NW U.S., Chile, Japan	May-November
Diarrheic shellfish poisoning	Diarrhea, nausea, vomiting, abdominal pain, chills	30 min-12 h	Okadaic acid	Inhibits protein phosphatase	Shellfish	Japan, Europe, Africa	
Amnesic shellfish poisoning	Nausea, vomiting, abdominal cramps, diarrhea, headache, visual disturbance, anterograde amnesia, confusion, coma	15 min-6 h	Domoic acid	Stimulates glutamate receptors	Shellfish	Canada, NE and NW U.S.	
Neurotoxic shellfish poisoning	Paresthesia, abdominal pain, dizziness, diplopia, gait disturbance, reversed temperature perception, respiratory difficulty	5 min-4 h	Brevetoxins	Opens sodium channels	Shellfish and other fish	Western Florida, Caribbean	Spring-fall
Ciguatera	Nausea, vomiting, abdominal cramps, facial and perioral paresthesias, headache, reverse temperature perception, extremity pain, arthralgia, myalgia, sharp pain in the legs and teeth	1-6 h	Ciguatoxin, maitotoxin	Opens Na^+ channels; opens Ca^{2+} channels	Predatory fish reef	Tropical areas	February-September
Scombroid fish poisoning	Pruritic rash, flushing, sweating, perioral tingling, dizziness, facial and lingual swelling, vomiting, diarrhea, urticaria, bronchospasm	Min-h	Histamine	Histamine receptors	Tuna, mahi-mahi, mackerel, sardines	Worldwide	Yr-round
Puffer fish	Facial paresthesia, ascending paralysis, respiratory failure, circulatory collapse, death	30 min-3 h	Tetrodotoxin, saxitoxin	Blocks Na^+ channels	Puffer fish	East Asia	

From Cherry JD: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.

SUGGESTED READINGS

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Divers Alert Network. *Scombroid fish poisoning*. www.diversalertnetwork.org/health/hazardous-marine-life/scombroid-fish-poisoning.

Gould LH et al: Surveillance for foodborne disease outbreaks – United States 1998-2008. Centers for Disease Control and Prevention. MMWR. *Surveillance Summaries* June 28, 2013 / 62(SS02);1-34.
www.cdc.gov/mmwr/preview/mmwrhtml/ss6202a1.htm?s_cid=ss6202a1_w

California Department of Public Health, Division of Communicable Disease Control. *Scombroid fish poisoning Fact Sheet*. November 2015. www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/ScombroidFishPoisoningFactSheet.pdf.

Hungerford JM: Scombroid poisoning: a review, *Toxicon* 56(15):231-243, 2010. www.sciencedirect.com/science/article/pii/S0041010110000450?via%3Dihub.

Soloway RA: *Food poisoning from fish: Ciguatera and scombroid*. Poison Control, National Capital Poison Center. 2012. www.poison.org/articles/2009-jun/what-you-cant-smell-can-hurt.

Seasonal Affective Disorder (PTG)

BASIC INFORMATION

DEFINITION

Recurrent depressive episodes during autumn and winter alternating with nondepressive episodes during spring and summer (less frequently, recurring depressive episodes during spring and summer, alternate with nondepressive episodes during autumn and winter). Patients with seasonal affective disorder (SAD) have experienced two episodes of major depression in the past 2 yr that demonstrate the temporal seasonal relations and have had no nonseasonal episodes over this period. Furthermore, seasonal depressive episodes substantially outnumber nonseasonal depressive episodes throughout the individual's lifetime.

SYNONYMS

SAD
Seasonal depression
Winter depression
Wintertime blues

ICD-10CM CODES

F33	Recurrent depressive disorder
F33.0	Recurrent depressive disorder, current episode, mild
F33.1	Recurrent depressive disorder, moderate
F33.2	Recurrent depressive disorder, severe without psychotic symptoms
F33.3	Recurrent depressive disorder, severe with psychotic symptoms
F33.4	Recurrent depressive disorder, currently in remission
F33.9	Recurrent depressive disorder, unspecified

DSM-5 CODE

There is no DSM-5 code for seasonal affective. It is now categorized as a specifier under major depression.

EPIDEMIOLOGY & DEMOGRAPHICS

- Climate, genetic vulnerability, and psychological and sociocultural factors all play a role. The risk of seasonal mood swings is clearly associated with northern latitudes. The prevalence of SAD is estimated to be 0.5% to 1.5% in northern European populations, but up to 10% to 20% of these populations report milder, recurrent episodes consistent with subsyndromal SAD. In the U.S., it is estimated that about 5% of the population experiences SAD.
- As with other depressive disorders, women are affected disproportionately.
- Younger age, as well as greater familiarity with SAD, is associated with increased prevalence.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The symptoms of SAD can be identical to those of other depressive episodes, but tend to include features associated with atypical major depression, including low energy, oversleeping, irritability, weight gain, and overeating. The onset of neurovegetative symptoms often precedes the onset of cognitive and affective symptoms.
- Average duration is 5 mo, generally beginning in November.

ETIOLOGY

- Explanations focus on diathesis-stress models. An interaction between biologic and cognitive-affective factors appears to contribute to SAD. Retinal sensitivity anomalies and emotional reactivity to light stimuli, genetic variables predisposing to seasonal shift in sleep patterns in response to shorter photoperiod, circadian rhythm disturbance, and irregularities in melatonin, serotonin, and melatonin-serotonin interaction have been identified as potential risk factors. Shorter photoperiod and decrease in sunlight are hypothesized to be the triggers.
- Several neurotransmitters implicated, including dopamine, serotonin, and norepinephrine.
- Cognitive risk factors include elevated rumination and negative cognitions related to the winter season and its impact on one's mood.
- Low activity and exercise levels, which are also implicated in nonseasonal depression, have been shown in some studies to characterize SAD.
- Patients with nonseasonal depression and/or anxiety may also show symptom exacerbations during the winter mos.

DIAGNOSIS

Diagnostic workup similar to that for major depression

DIFFERENTIAL DIAGNOSIS

- Major depressive disorder
- Minor depression or adjustment disorder
- Bipolar affective disorder
- Evaluate for substance use (especially alcohol)
- Medical illness or medications that may contribute to depression (e.g., endocrine disorders, neurologic disease)

WORKUP

- As with major depression, consider medical etiologies and rule out as indicated by the presenting signs and symptoms. Consider endocrine evaluation, especially thyroid function; sleep studies and a toxicology screen might be considered.
- Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorders Version (SIGH-SAD) used in research settings.
- In patients with major depressive disorder treated longitudinally, the routine use of depression scales to monitor outcome can help identify seasonal fluctuations of symptoms. Self-report scales to assess seasonal fluctuations in depressive symptoms have been developed but are not routinely used in clinical settings.

LABORATORY TESTS

As directed by presenting symptoms

IMAGING STUDIES

Generally not indicated

TREATMENT

NONPHARMACOLOGIC THERAPY

- Phototherapy presupposes that artificial light at a similar strength to natural sunlight will prevent the biologic changes that mediate SAD.
- Many studies have demonstrated efficacy of light therapy in individuals with SAD. Recent studies indicate that light therapy may also be efficacious with various subtypes of depression, including both melancholic and atypical, and for individuals with nonseasonal depression, though more research is needed. Transcranial photobiomodulation approaches are now under study.
- Light therapy may be used as a first-line treatment; choice of light therapy versus medication or psychotherapy depends on various factors, however, including severity of symptoms and suicidality, prior response to medication or light therapy, feasibility, and patient preference, and patient treatment expectations may also play a role.
- Some studies showing retinal sensitivity and neurotransmitter (e.g., serotonin) anomalies in SAD normalize following phototherapy, but more research is needed.
- Phototherapy tends to use 2500 to 10,000 lux delivered by a commercial light box or a portable head-mounted unit. Phototherapy is recommended to begin within 2 wk of the start of symptoms and continue through the winter mos. Patients are instructed to sit ~18 in from the light box for 30 min up to several hours once or twice per day for a minimum of 1 wk. Most studies have examined broad-wavelength (bright white) light: Studies are currently underway to examine potential advantages of short-wavelength (blue) light, though more research is needed.
- A recent meta-analysis demonstrated efficacy of high-density negative ions in reducing depressive severity, although further research is needed to determine whether efficacy is comparable to light therapy.
- Growing research demonstrates the efficacy of cognitive-behavioral therapy tailored specifically for SAD, either alone or with possible additive effects to light therapy. Cognitive behavioral therapy (CBT) for SAD appears to operate through distinct mechanisms than light therapy (e.g., reducing rumination and negative SAD-related cognitions). Patients with elevated cognitive symptoms of depression may benefit from CBT or combined CBT with light therapy over light therapy alone, and a recent study found a lower recurrence rate following CBT compared with light therapy, but further research is needed.

PHARMACOLOGIC THERAPY

Bupropion is effective in preventing recurrence.

ACUTE GENERAL Rx

Necessary if patient is suicidal

CHRONIC Rx

- Growing support for use of selective serotonin reuptake inhibitors (SSRIs) for SAD (e.g., fluoxetine, sertraline), although more research is needed.
- Preliminary studies demonstrated efficacy of novel antidepressants that act on melatonin (i.e., agomelatine), but further research is needed.

DISPOSITION

Psychiatric referral may be helpful to confirm diagnosis. Recommended for high-risk and suicidal patients.

REFERRAL

For active suicidal ideation, psychosis, symptoms suggestive of bipolar disorder

PEARLS & CONSIDERATIONS

Patients with SAD may present with a complaint of overeating, particularly food high in carbohydrates.

RELATED CONTENT

Seasonal Affective Disorder (SAD) (Patient Information)

AUTHORS: **Mark Zimmerman, MD,** and **Catherine D'Avanzato, PhD**

SUGGESTED READINGS

Kurlansik SL et al: Seasonal affective disorder, *Am Fam Physician* 86(11):1037-1041, 2012.

Meesters Y et al: Seasonal affective disorder, winter type: current insights and treatment options, *Psychol Res Behav Manag* 9:317-327, 2016.

Seborrheic Dermatitis (SD) PTG

BASIC INFORMATION

DEFINITION

Seborrheic dermatitis (SD) is a common, inflammatory skin condition characterized by a mild to severe rash with scaling and erythema that occurs in areas of the skin rich in sebaceous glands.

SYNONYMS

SD
Dandruff
Cradle cap (Fig. E1)
Sebopsoriasis
Seborrheic eczema
Pityriasis capitis
Seborrhea

ICD-10CM CODES
L21.9 Seborrheic dermatitis, unspecified
L21.1 Seborrheic infantile dermatitis
L21.8 Other seborrheic dermatitis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Affects 3% to 5% of otherwise healthy adults; increases to 34% to 83% in immunocompromised patients
PREDOMINANT SEX AND AGE: Can occur from infancy through old age, with peak incidence in adolescents and young adults and increasing again after age 50 yr. More common in men than women.
RISK FACTORS: More common in patients with HIV/AIDS, Parkinson disease, other neurologic disorders, mood disorders, chronic alcoholic pancreatitis, hepatitis, cancer, and genetic disorders (e.g., Down syndrome). Recent evidence linking obesity and metabolic syndrome with an increased occurrence of SD. Occurs more often during winter season and during periods of increased stress.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Mild, greasy scaling of the scalp and nasolabial folds (Fig. E2); postauricular skin, beard area, eyebrows, trunk, and sometimes the central face. Blepharitis, otitis externa, and coexisting acne vulgaris or pityriasis may also be present. Itching and stinging of lesions can occur. Increased occurrence during times of stress or sleep deprivation.
- The scale often has a yellow, greasy appearance.

ETIOLOGY

- Fungal infections of the *Malassezia* species have been associated with SD, and the skin changes are thought to result from an inflammatory response to *Malassezia* yeast.
- Altered immune function may play a role. Patients with SD may show upregulation of interferon (IFN)-α, expressed interleukin-6 (IL-6), expressed IL-1β, and IL-4.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Atopic dermatitis
- Candidiasis
- Dermatophytosis
- Impetigo
- Psoriasis
- Rosacea
- Systemic lupus erythematosus
- Tinea infection
- Contact dermatitis
- Nummular dermatitis

WORKUP

- Diagnosis usually based on clinical identification of lesions (distribution and appearance).
- Skin biopsies can be performed, if warranted, to distinguish SD from similar disorders.

LABORATORY TESTS

- Microscopic examination with special stains can be used to determine whether yeast cells are present in keratinocytes.
- Biopsy can demonstrate parakeratosis in the epidermis, plugged follicular ostia, and spongiosis.
- HIV testing.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient education that SD is a chronic condition and treatment is aimed at resolving lesions but does not prevent recurrence.
- General recommendations: Wash skin regularly, soften and remove scales, and apply moisturizing emollients after washing.
- Scale removal can be accomplished through the application of mineral or olive oil and removed with a comb or brush after 1 hr.

ACUTE GENERAL Rx

- Antifungals (e.g., Nizoral, selenium sulfide, ketoconazole [the most evidence for effectiveness among antifungals], ciclopirox, fluconazole). Considered first-line therapy. Shampoos should be kept on the skin for 5 min before washing off.
- Reserve oral antifungal therapy for patients with widespread SD, or SD that is refractory to topical therapy.
- Topical steroids: Can be in the form of shampoos, creams, or ointments. Can be used alone or in more severe SD with antifungals. Desonide and mometasone display the lowest recurrence rates and highest clearance. Avoid prolonged use due to side effects.
- Calcineurin inhibitors (e.g., tacrolimus ointment, pimecrolimus cream): Good when face and ears are affected. Limit use due to potential side effects. Can be used in combination with topical nonsteroidal antiinflammatory agents
- Keratolytics (e.g. coal tar, salicylic acid, zinc pyrithione).
- Treatment of any secondary bacterial infection with oral antibiotics.

CHRONIC Rx

Recalcitrant SD: Topical azole combined with desonide regimen (limit use to 2 wk), pimecrolimus cream

COMPLEMENTARY & ALTERNATIVE MEDICINE

Borage and tea tree oil (melaleuca oil)
Crude honey
Aloe vera

REFERRAL

Consider referral to dermatology for recalcitrant cases or uncertain diagnosis.

PEARLS & CONSIDERATIONS

- Use a combination of topical steroids and antifungal cream for severe SD.
- Limit use of steroids to 2-wk course of treatment due to risk of cutaneous atrophy and telangiectasias.
- SD of the scalp can be treated with an antifungal (e.g., 2% ketoconazole) or keratolytic shampoo. Limit use of antifungal shampoos to twice a wk to prevent drying of the scalp. Alternate the use of antifungal shampoos with a moisturizing shampoo.
- In patients with widespread SD, consider testing for HIV infection. In patients with HIV/AIDS, the severity of seborrheic dermatitis is inversely correlated with the CDs counts.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Seborrheic Dermatitis (Patient Information)

AUTHOR: **Anngene Anthony, MD, MPH, FAAFP**

SUGGESTED READINGS

Borda LJ et al: Treatment of seborrheic dermatitis: a comprehensive review, *J Dermatolog Treat* 30(2):158-169, 2019.

Clark GW et al: Diagnosis and treatment of seborrheic dermatitis, *Am Fam Physician* 91(3):185-190, 2015.

Gupta AK et al: Topical treatment of facial seborrheic dermatitis: a systematic review, *Am J Clin Dermatol* 18(2):193-213, 2017.

Uzuncakmak TK et al: Cutaneous manifestations of obesity and the metabolic syndrome, *Clin Dermatol* 36(1):81-88, 2018.

FIG. E1 Cradle cap in an infant. (From Kliegman RM, et al.: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

FIG. E2 Seborrheic dermatitis. (From Swartz MH: *Textbook of physical diagnosis,* ed 7, Philadelphia, 2014, Saunders, 2014.)

BASIC INFORMATION

DEFINITION

Tonic clonic seizures are characterized by sudden loss of consciousness, muscle contraction (tonic phase), followed by rhythmic jerking activity (clonic phase).

SYNONYMS

Bilateral tonic-clonic seizures
Convulsive seizures
Grand mal seizures
Generalized tonic clonic seizures

ICD-10CM CODES
G40.6 Grand mal seizures, unspecified
G41.0 Grand mal status epilepticus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Thirty to fifty cases per 100,000 person-yr (epilepsy incidence)
PEAK INCIDENCE: Not applicable
PREVALENCE: Five to eight cases/1,000 persons (epilepsy incidence)
PREDOMINANT SEX AND AGE: No gender preference

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with tonic clonic seizures usually have normal physical and neurologic examinations.
- During the seizures, the patients are unresponsive and can have violent postures with severe repetitive muscle contractions (Fig. 1).
- After the seizure, the patients are usually lethargic and confused.
- Tonic clonic seizures are associated with injuries, bladder incontinence, and tongue biting.
- Any warning or aura before onset of the seizure or focal postictal weakness (Todd paralysis) may point toward a focal neurologic lesion.

ETIOLOGY

- Seizures are a cardinal sign of cortical neurologic injury. Generalized seizures include both hemispheres of the brain at onset. However, seizures can start focally and then quickly generalize across both hemispheres of the brain and be almost identical to primary generalized seizures. Any warning or aura symptoms before the generalized seizure starts would point to a focal onset.
- The etiology of seizures can be genetic or due to an acquired injury to the brain.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Convulsive syncope
- Psychogenic nonepileptic spells, conversion disorder, somatic symptom disorder, dissociative disorder
- EPI
- TIA
- Vertigo
- Factitious disorder
- Malingering
- Myoclonus (from metabolic disturbance)

WORKUP

- EEG (Fig. 2). An EEG can help confirm the presence of epilepsy but cannot be used to exclude the diagnosis.
- Ambulatory EEG and/or video EEG recommended for patients with diagnostic uncertainty.

LABORATORY TESTS

- Routine blood workup (CBC, CMP, glucose, electrolytes)
- Urine drug screen
- Lumbar puncture is recommended in patients with suspicion of meningitis

IMAGING STUDIES

- Neurodiagnostic imaging studies such as CT of the head or, preferably, MRI of the brain should be performed in all patients with first unprovoked seizure.
- CT scans of the head should be avoided in children due to unnecessary exposure to radiation and the low yield of the test. CT scans of the head are reserved for neurologic emergencies and are adjusted for weight in children.

TREATMENT

- The immediate management of a seizure focuses on stabilization of the patient with focus on the airway and vital signs and rapid identification and correction of reversible causes.
- Seizures lasting >5 minutes or multiple seizures without return to baseline in between should be treated as status epilepticus.
- Treatment is based on the type and etiology of seizures (i.e., metabolic disturbance, infectious, etc.).
- Provoked seizures due to metabolic derangements, infections, fever, alcohol, or drug-withdrawal are typically generalized and likely do not need long-term treatment.
- Multiple antiepileptic medication choices are available. Choice depends on side effect profile as well as whether the seizure started focally or is secondary to an idiopathic generalized epilepsy syndrome.

NONPHARMACOLOGIC THERAPY

Not applicable

GENERAL Rx

- First unprovoked seizure with normal imaging, EEG, and laboratory workup requires no treatment.
- Recurrent seizures and seizures with abnormal studies require treatment depending on the etiology.
- Primary generalized epilepsies:
  1. Levetiracetam (Keppra): Initial dose 250 to 500 bid, maximum dose 1500 mg bid.
  2. Lamotrigine (Lamictal): Initial dose 25 mg daily and increase slowly to goal dose 150-250 mg daily (depends on combination of other medications).
  3. Topiramate (Topamax): Initial dose 25 mg bid and increase to usual dose of 100 to 200 mg bid.
  4. Perampanel (Fycompa): Initial dose of 2 mg once daily at bedtime, increments of 2 mg once daily at weekly intervals to a recommended maintenance dose of 8 to 12 mg (adjunctive treatment in patients with epilepsy 12 yr of age and older).
  5. Valproic acid (Depakote): Initial dose: 10 to 15 mg/kg/day (divided bid), maximum dose 60 mg/kg/day. Valproic acid should be avoided in girls and women with childbearing potential due to the risk of teratogenicity.
- Focal epilepsies with secondary generalization: Almost all antiepileptic drugs are approved for focal seizures, either in monotherapy or in adjunct. Carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, levetiracetam, or lacosamide are all possibilities among others.

CHRONIC Rx

According to a recent joint American Academy of Neurology and American Epilepsy Society evidence-based guideline on the management of a first unprovoked seizure in adults, there is strong evidence that the risk of a second seizure is highest in the first 2 yr and ranges from 21% to 45%. This risk is higher for patients with prior brain insults such as traumatic brain injury or stroke or those with epileptiform abnormalities on EEG. Significant brain imaging abnormalities and nocturnal seizures also indicate a more elevated risk of recurrent seizures. Chronic treatment with antiepileptic drugs is indicated for ≥2 unprovoked seizures or in patients with one seizure with abnormal workup. However, moderate evidence supports advising the patient that immediate antiepileptic therapy, compared with delaying treatment until a second unprovoked seizure, is likely to reduce the risk of a seizure recurrence in the next 2 yr. Furthermore, the risk of adverse events with antiepileptics ranges from 7% to 31%, with most of these adverse events being mild and reversible. Thus, the practice guideline suggests that under certain circumstances adults with one provoked seizure, even without high-risk EEG or MRI findings, can be treated with antiepileptic drugs because at least in the next 2 yr the risk of a recurrent seizure is reduced. Although there is no strong evidence that such treatment improves quality of life, even one seizure can have negative consequences on social and occupational functioning such as driving, making treatment an attractive option for many.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Not applicable

DISPOSITION

- Patients should avoid situations that may cause injuries or accidents in the event of a seizure, such as climbing ladders, swimming unsupervised, or taking baths (rather than showers).
- No driving until seizure-free in accordance with local laws and regulations.

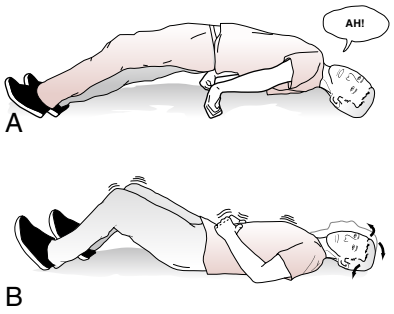

FIG. 1 A, This man in the tonic phase of a tonic-clonic seizure arches his torso and extends his arms and legs. He assumes this position because of the relatively greater strength of the extensor muscles compared to the flexor muscles. Simultaneous diaphragm, chest wall, and laryngeal muscle contractions force air through his tightened larynx to produce the shrill "epileptic cry." During this phase, he may also bite his tongue and lose control of his urine. **B,** In the clonic phase, his head, neck, and legs contract symmetrically and forcefully for about 10 to 20 seconds. Saliva, aerated and often blood-tinged from tongue lacerations, froths from his mouth. His pupils dilate, and he sweats profusely. Finally, his muscular contractions lose strength. The seizure usually ends with stertorous breathing. In the immediate postictal period, he remains unresponsive. Before regaining consciousness, he may pass through a state of confusion and agitation. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists*, ed 8, Philadelphia, 2017, Elsevier.)

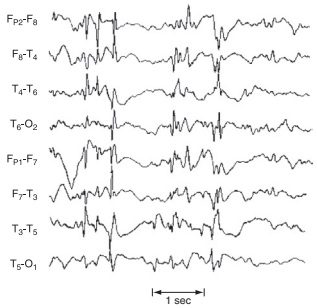

FIG. 2 During a tonic-clonic seizure, the EEG ideally shows paroxysms of spikes, polyspikes, and occasional slow waves in all channels; however, muscle artifact can obscure this pattern. Even during interictal periods, the EEG contains multiple bursts of generalized spikes in the background. In contrast to occasional temporal lobe spikes, this pattern confirms a diagnosis of epilepsy in patients with seizures. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists*, ed 8, Philadelphia, 2017, Elsevier.)

REFERRAL

Patients with epilepsy and seizures should be referred for a consultation by a neurologist, preferably one with epilepsy training.

PEARLS & CONSIDERATIONS

COMMENTS

- It is crucial to understand that tonic clonic seizures can occur in variety of acute neurologic diseases.
- Successful treatment depends on the correct choice of antiepileptic drugs based on the type (focal onset versus generalized onset) and etiology of the seizures.
- All women of childbearing age taking antiepileptic drugs should take folic acid supplementation (1 to 4 mg/day) for the prevention of neural tube defects.
- Many antiepileptic drugs also affect vitamin D absorption or metabolism, prompting attention to patients' bone health.

PREVENTION

Sleep deprivation and alcohol consumption should be avoided.

PATIENT & FAMILY EDUCATION

Patients with ongoing seizures are forbidden to drive; check your state regulations and laws regarding driving and epilepsy.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Generalized Tonic-Clonic Seizures (Patient Information)
Status Epilepticus (Related Key Topic)

AUTHORS: **Patricio Sebastian Espinosa, MD, MPH,** and **Corey Goldsmith, MD**

SUGGESTED READING

Krumhold A et al: Evidence-based guideline: management of an unprovoked first seizure in adults. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society, *Neurology* 84(16):1705-1713, 2015.

BASIC INFORMATION

DEFINITION

Sepsis is an exaggerated inflammatory response to an infectious stimulus. It is usually caused by generalized bacterial or fungal infection and characterized by evidence of infection, fever or hypothermia, hypotension, and evidence of end-organ compromise. The Sepsis Definitions Task Force in 2016 updated definitions for sepsis and septic shock (Table 1). A major change in the definitions is the elimination of mention of SIRS*. According to the new definitions, sepsis is now defined as evidence of infection plus life-threatening organ dysfunction, clinically codified by an acute change in 2 points or greater in the SOFA score (Table 2). The new clinical criteria for septic shock include sepsis with fluid, unresponsive hypotension, serum lactate level greater than 2 mmol/L, and the need for vasopressors to maintain mean arterial pressure of 65 mm Hg or greater.[1,2]

*SIRS (Systemic Inflammatory Response Syndrome): Variables in SIRS criteria include respiratory rate (breaths/min), white blood cell count (109/L), hands (%), heart rate (beats/min), temperature (°C), and arterial carbon dioxide tension (mm Hg). Score range is 0-4.

[1]Abraham E: New definitions for sepsis and septic shock: continuing evolution but with much still to be done, *JAMA* 315(8):757-759, 2016.

[2]Shankar-Hari M et al: Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), *JAMA* 315(8):775-787, 2016.

SYNONYMS

Septicemia
Sepsis syndrome
Severe sepsis
Systemic inflammatory response syndrome
Septic shock

ICD-10CM CODES

A41.9	Sepsis, unspecified organism
A41.50	Gram-negative sepsis, unspecified
A41.2	Sepsis due to unspecified *Staphylococcus*
A41.4	Sepsis due to anaerobes
A41.51	Sepsis due to *Escherichia coli* [E. coli]
A41.52	Sepsis due to Pseudomonas
A54.86	Gonococcal sepsis
B37.7	Candidal sepsis
A32.7	Listerial sepsis
A40.0	Sepsis due to streptococcus, group A
A40.1	Sepsis due to streptococcus, group B
A40.3	Sepsis due to Streptococcus pneumoniae
A40.8	Other streptococcal sepsis
A40.9	Streptococcal sepsis, unspecified
A41.01	Sepsis due to Methicillin susceptible *Staphylococcus aureus*
A41.02	Sepsis due to Methicillin resistant *Staphylococcus aureus*

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Sepsis occurs in 6% of hospitalized patients; approximately half require ICU admission.
- More than 1 million cases of sepsis occur each yr in the U.S. 15% of sepsis patients die in the hospital; 6% are discharged to hospice.

PREDOMINANT SEX: Males are slightly more commonly affected than females.

PREDOMINANT AGE:

- Neonatal period.
- Patients >65 yr of age account for 60% of all cases of sepsis.

GENETICS:

- Familial disposition: A great variety of congenital immunodeficiency states and other inherited disorders may predispose to septicemia.
- Neonatal infection: Incidence is high in neonatal period.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever or hypothermia
- Hypotension
- Tachycardia
- Tachypnea
- Altered mental status
- Bleeding diathesis
- Skin rashes
- Symptoms that reflect primary site of infection: Urinary tract, GI tract, CNS, respiratory tract
- Table 3 describes some clinical signs and symptoms of sepsis

ETIOLOGY

- Disseminated infection with a great variety of bacteria:
  1. Gram-negative bacteria:
     a. *Escherichia coli*
     b. *Klebsiella* spp.
     c. *Pseudomonas aeruginosa*
     d. *Proteus* spp.
     e. *Neisseria meningitides*
  2. Gram-positive bacteria:
     a. *Staphylococcus aureus* (including MRSA)
     b. *Streptococcus* spp.
     c. *Enterococcus* spp.
- Less common infections:
  1. Fungal

TABLE 1 Proposed New Definitions of Sepsis

Term	Definition	Criteria	Notes
Sepsis[a] (previously severe sepsis)	Life-threatening organ dysfunction caused by a dysregulated host response to infection	Organ dysfunction is identified as an acute change in the SOFA score, ≥2 points from the baseline consequent to the infection.	qSOFA (quick Sequential Organ Failure Assessment) Prolonged ICU stay or in-hospital mortality can be identified at the bedside with qSOFA. 1. Respiratory rate ≥22 breaths/min 2. Acute mental status change 3. Systolic blood pressure ≤100 mm Hg An increase in SOFA of ≥2 predicts a 10% mortality in the general hospital population. Presume a baseline SOFA of 0 unless the patient has known (acute or chronic) organ dysfunction before the onset of infection.
Septic shock	It is a subset of sepsis in which the underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.	A clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level ≥2 mmol/L despite adequate volume resuscitation	Septic shock portends hospital mortality in excess of 40%.

[a]Note that the proposed new definitions abandon the previous term "severe sepsis" to describe infection-induced organ dysfunction and now use "sepsis" in its place. The previous condition called "sepsis" is now just called "infection," and when infection is not associated with organ dysfunction, there is no differentiation between infection with or without systemic manifestations.

MAP, Mean arterial pressure.

From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.

TABLE 2 The Sequential Organ Failure Assessment (SOFA) Score

Score	0	1	2	3	4
Respiration					
PaO_2/FiO_2, mm Hg	>400	≤400	≤300	≤200 With respiratory support	≤100
Coagulation					
Platelets × $10^3/mm^3$	>150	≤150	≤100	≤50	≤20
Liver					
Bilirubin, mg/dl (μmol/L)	<1.2 (<20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (>204)
Cardiovascular					
Hypotension	No hypotension	MAP <70 mm Hg	Dopamine ≤5 or dobutamine (any dose)*	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1*	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1*
Central Nervous System					
Glasgow coma score	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dl (μmol/L) OR urine output	<1.2 (<110)	1.2-1.9 (110- 170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) <500 ml/d	>5.0 (>440) <200 ml/d

*Adrenergic agents administered for at least 1 hour (doses given are in mcg/kg per min).
From Ronco C et al: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.

TABLE 3 Clinical Signs and Symptoms of Sepsis

Infection	General	Inflammatory	Hemodynamic	Tissue Perfusion
Documented or suspected	Temperature >38° C (100.4° F) or <36° C (96.8° F) Heart rate >90 beats/min Respiratory rate ≥20 breaths/min Altered mental status Hyperglycemia Third spacing of fluid	WBC count <4000 or >12,000 cells/μL or ≥10% bands	Hypotension: Systolic blood pressure <90 mm Hg MAP <70 mm Hg SV_{O_2} >70 CI >3.5 L/min/m^2	Hypoxemia: (Pao_2/Fio_2 <300) Acute oliguria (urine output <0.5 ml/kg/hr) Coagulopathy Abnormal liver function tests Platelet count <100,000 cells/μL Lactic acidosis Skin mottling

CI, Cardiac index; *MAP,* mean arterial pressure; *SVo_2,* mixed venous oxygen saturation; *WBC,* white blood cell.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

2. Viral
3. Rickettsial
4. Parasitic

- Sepsis is a complex dysregulation of both inflammation and coagulation (Fig. E1). There is activation of coagulation, inflammatory cytokines, complement, and kinin cascades with release of a variety of vasoactive endogenous mediators. The innate immune system recognizes pathogens by means of pattern-recognition receptors (toll-like receptors [TLRs], Table 4). TLRs bind to structures on microorganisms and, based on the composite information gained, generate a tailored response to the invading pathogen.
- Predisposing host factors:
  1. General medical condition
  2. Extremes of age
  3. Immunosuppressive therapy
  4. Recent surgery
  5. Granulocytopenia
  6. Hyposplenism
  7. Diabetes
  8. Instrumentation

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cardiogenic shock
- Acute pancreatitis
- Pulmonary embolism
- Systemic vasculitis
- Toxic ingestion
- Exposure-induced hypothermia
- Fulminant hepatic failure
- Collagen-vascular diseases

WORKUP

- Evaluation should focus on identifying a specific pathogen and localizing the site of primary infection. Box 1 summarizes a general approach to shock.
- Hemodynamic, metabolic, coagulation disorders should be carefully characterized.
- Intensive monitoring.

LABORATORY TESTS

- Cultures of blood and examination and culture of sputum, urine, wound drainage, stool, and CSF, depending on the presenting signs and symptoms for each patient
- CBC with differential, coagulation profile
- Routine chemistries, LFTs
- ABGs, lactic acid level
- Procalcitonin can be useful as a serum marker of bacterial infection as a cause of the sepsis, and has been shown to improve survival and facilitate earlier discontinuation of antibiotics
- Urinalysis

IMAGING STUDIES

- Chest x-ray
- Other radiographic and radioisotope procedures according to suspected site of primary infection

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Tissue oxygenation: Mixed venous oxygen saturation maintained >70% if possible; early mechanical ventilation with low tidal volume (6 ml/kg predicted body weight) to protect lung parenchyma from overstretching and "volutrauma." Recommended plateau pressure for sepsis-related ARDS is ≤30 cm H_2O.
- Focal infection should be drained if possible, and potentially infected catheters should be removed.

ACUTE GENERAL Rx

- Blood pressure support, rapid IV fluid resuscitation and vasopressors (Table 5), if needed, with the goal of reestablishing a mean arterial blood pressure >65 mm Hg; reduction in blood lactate and improved mixed venous oxygen saturation >70% within 6 hr of recognition of septic shock is associated with improved survival. If possible, measure vena cava oxygen

TABLE 4 Toll-Like Receptors

Toll-Like Receptor	Pathogen or Disease State
TLR1	Lyme disease
	Neisseria meningitidis
TLR2	*Mycobacterium tuberculosis*
	Chagas disease
	Leptospirosis
	Fungal sepsis
	CMV viremia
TLR3	Many
TLR4	Gram-negative bacteria
	Septic shock
	Chlamydia trachomatis
	Chlamydia pneumoniae
	Certain viruses
	Mycobacterium tuberculosis
TLR5	Flagellated bacteria (e.g., *Salmonella*)
TLR7	Viral infections
TLR8	Viral infections
TLR9	Bacterial and viral infections
TLR10	Unknown

CMV, Cytomegalovirus; *TLR,* Toll-like receptor.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.

BOX 1 General Approach to Shock: Initial Diagnosis and Evaluation

- Clinical (primary diagnosis)
  - Tachycardia, hypotension (systolic blood pressure <90 mm Hg) tachypnea, oliguria, encephalopathy (confusion), peripheral hypoperfusion (mottled extremities), cyanosis
- Laboratory (confirmatory)
  - Hemoglobin, WBC, platelets
- Prothrombin time/partial thromboplastin time
  - Electrolytes, arterial blood gases, Ca, Mg, BUN, creatinine, serum lactate
  - ECG
- Monitoring (continuous ECG and respiratory monitors)
  - Pulse oximetry
  - Urinary catheter (urine output)
  - Point-of-care ultrasonography (heart, lung, abdominal, and major vessels)
  - Arterial pressure catheter
  - Central venous pressure monitor (uncomplicated shock)
  - Pulmonary artery flotation catheter
    - Cardiac output
    - Pulmonary artery occlusion pressure
    - Central and/or mixed venous oxygen saturation (intermittent or continuous)
  - Oximetry[a]
- Imaging (chest x-ray)
  - X-ray views of abdomen[a]
  - Computed tomographic scan: Abdomen or chest[a]
  - Formal transthoracic and/or transesophageal echocardiogram[a]

[a]Optional.
BUN, Blood urea nitrogen; *Ca,* calcium; *ECG,* electrocardiogram; *Mg,* magnesium; *WBC,* white blood cell.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.

TABLE 5 Relative Potency of Intravenously Administered Vasopressors/Inotropes Used in Shock[a]

		CARDIAC		PERIPHERAL VASCULATURE			
Drug	**Dose**	**Heart Rate**	**Contractility**	**Vasoconstriction**	**Vasodilation**	**Dopaminergic**	**Typical Clinical Use**
Dopamine	1-4 μg/kg/min	1+	1-2+	0	1+	4+	All shock
	5-10 μg/kg/min	2+	2+	1-2+	1+	4+	
	11-20 μg/kg/min	2+	2+	2-3+	1+	4+	
Norepinephrine	0.01-0.3 μg/kg/min	2+	2+	4+	0	0	Refractory shock
Dobutamine	1-20 μg/kg/min	1-2+	3+	1+	2+	0	CHF; cardiogenic, obstructive and septic shock
Dopexamine[b]	0.5-6 μg/kg/min	2+	1+	0	3-4+	4+	CHF; cardiogenic shock
Epinephrine	0.05-0.2 μg/kg/min	4+	4+	4+	3+	0	Refractory or anaphylactic shock
Phenylephrine	0.1-1 μg/kg/min	0	1+	4+	0	0	Neurogenic or septic shock
Isoproterenol	1-8 μg/min	4+	4+	0	4+	0	Cardiogenic shock (bradyarrhythmia), torsades de pointes, ventricular tachycardia
Vasopressin	0.02-0.04 U/min	0	0	4+	0	0	Vasodilatory (e.g., septic) shock
Milrinone	37.5-75 μg/kg bolus over 10 min; 0.375-0.75 μg/kg/min infusion	1+	3+	0	2+	0	CHF; cardiogenic shock

[a]The 1 to 4+ scoring system represents an arbitrary quantitation of the comparative potency of different vasopressors/inotropes.
[b]Not clinically released in the U.S.
CHF, Congestive heart failure.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.

saturation ($ScvO_2$) to assess adequacy of resuscitation. If the $ScvO_2$ is <70%, consider packed red blood cell transfusion to achieve Hct >30%. Start inotropic agents if $ScvO_2$ is <70% despite transfusion and adequate fluid resuscitation.

1. IV hydration; patients receiving balanced crystalloids as resuscitation fluids. appear to have a lower 30-day mortality compared with patients who received saline (26% versus 31%) in a recent trial.[1] Use the fluid challenge technique to evaluate the effect (and safety) of fluid administration. For sepsis-induced hypoperfusion, give 30 ml/kg of IV crystalloids within 3 hours, with additional fluid based on frequent reassessment using dynamic variables (e.g., passive leg raise test or pulse or stroke volume variations induced by mechanical ventilation) rather than previous guidelines using target-specific values of central venous pressure. Fluid administration should be discontinued when the response to fluids is no longer beneficial. Most patients need 4 to 6 L of fluid in the first 6 hours. Trials have shown that resuscitation with balanced crystalloids or albumin compared with other fluids seems to be associated with reduced mortality, and that albumin replacement in addition to crystalloids alone does not improve the rate of survival at 28 and 90 days.

[1]Brown RM et al: Balanced Crystalloids versus Saline in Sepsis. A Secondary Analysis of the SMART Clinical Trial *Am J Respir Crit Care Med* 200:1487-1495, 2019.

TABLE 6 Empirical Antibiotic Options for Patients with Severe Sepsis or Septic Shock

	Suspected Source				
	Lung	**Abdomen**	**Skin/Soft Tissue**	**Urinary Tract**	**Source Uncertain**
Major Community-Acquired Pathogens	*Streptococcus pneumoniae* *Haemophilus influenzae* *Legionella* *Chlamydia pneumoniae*	*Escherichia coli* *Bacteroides fragilis*	*Streptococcus pyogenes* *Staphylococcus aureus* Polymicrobial	*E. coli* *Klebsiella* species *Enterobacter* species *Proteus* spp. *Enterococci*	
Empirical Antibiotic Therapy	Moxifloxacin *or* levofloxacin *or* azithromycin *plus* cefotaxime *or* ceftazidime *or* cefepime *or* piperacillin-tazobactam	Imipenem *or* meropenem *or* doripenem *or* Piperacillin-tazobactam ± aminoglycoside If biliary source: Piperacillin-tazobactam, ampicillin-sulbactam, *or* ceftriaxone with metronidazole	Vancomycin *or* daptomycin *plus either* imipenem *or* meropenem *or* piperacillin-tazobactam; ± clindamycin (see text)	Ciprofloxacin *or* levofloxacin (if gram-positive cocci, use ampicillin *or* vancomycin ± gentamicin)	Vancomycin *plus either* doripenem *or* ertapenem *or* imipenem *or* meropenem
Major Commensal or Nosocomial Microorganisms	Aerobic gram-negative bacilli	Aerobic gram-negative rods Anaerobes *Candida* spp.	*Staphylococcus aureus* (? MRSA) Aerobic gram-negative rods	Aerobic gram-negative rods *Enterococci*	Consider MDRO if in area of high prevalence. Consider echinocandin if neutropenic or indwelling intravascular catheter
Empirical Antibiotic Therapy	Imipenem *or* meropenem *or* doripenem *or* cefepime (if *Acinetobacter baumannii* or carbapenem-resistant *Klebsiella* in ICU, add colistin)	Imipenem *or* meropenem ± aminoglycoside (consider echinocandin)	Vancomycin *or* daptomycin *plus* imipenem-cilastatin *or* meropenem *or* cefepime, ± clindamycin	Vancomycin *plus* imipenem *or* meropenem *or* cefepime	Cefepime *plus* vancomycin ± caspofungin

Dosages for intravenous administration (normal renal function):
- Imipenem-cilastatin, 0.5-1.0 g q6-8h
- Meropenem, 1-2 g q8h
- Doripenem, 0.5 g q8h
- Piperacillin-tazobactam, 3.375 g q4h or 4.5 g q6h
- Vancomycin, load 25-30 mg/kg, then 15-20 mg/kg q8-12h
- Cefepime, 1-2 g q8h
- Levofloxacin, 750 mg q24h
- Ciprofloxacin, 400 mg q8-12hr
- Moxifloxacin, 400 mg qd
- Ceftriaxone, 2 g q24h
- Caspofungin, 70 mg, followed by 50 mg q24h
- Colistin: loading dose = 5 mg/kg body weight.

ICU, Intensive care unit; *MDRO*, multidrug-resistant organisms; *MRSA*, methicillin-resistant *Staphylococcus aureus*.
For MDRO, resistance usually includes carbapenems.
Carbapenems are less susceptible to extended-spectrum β-lactamases; base choice on local resistance pattern.
From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

2. Therapy with vasopressors if mean arterial blood pressure of >65 mm Hg cannot be maintained by hydration alone. Use norepinephrine as a first-choice vasopressor and target a mean arterial pressure (MAP) of 65 mm Hg.

- Correction of acidosis by improving the tissue perfusion, not by giving bicarbonate. Mechanical ventilation as needed
- Antibiotics:
  1. Directed at the most likely sources of infection. Table 6 describes initial antibiotic recommendations for septic patients.
  2. Should generally provide broad coverage of gram-positive and gram-negative bacteria (or fungi if clinically indicated).
  3. Antibiotics should be administered within 1 hr of the diagnosis of septic shock—this is a medical emergency.
- The role of corticosteroids in the acute management of septicemia has long been debated. Previous trials had shown that corticosteroid therapy improved hemodynamic outcomes in patients with severe septic shock. Patients with relative adrenal insufficiency may benefit from low-dose therapy with hydrocortisone (200 mg IV by continuous infusion for 7 days). Recent trials, however, revealed that hydrocortisone did not improve survival or reversal of shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed. Until definitive data are available, the decision to administer corticosteroids for septic shock should be based on the individual patient's severity of illness versus risk of corticosteroid administration. Current evidence and guidelines support limiting the use of IV hydrocortisone for patients with septic shock to these instances with fluid resuscitation and vasopressor therapy are inadequate to restore hemodynamic stability.[2] A recent meta-analysis revealed that although 28 day mortality is lower with corticosteroids in adult patients with sepsis, that effect does not persist at 90 days.[3] The corticotropin (ACTH) stimulation test is not helpful and should not be used to determine the need for corticosteroid in these patients.
- Blood transfusion: A lower hemoglobin threshold is preferred. Trials have shown that among patients with septic shock, mortality at 90 days and rates of ischemic events and use of life support is similar among those assigned to blood transfusion at a higher hemoglobin threshold (hemoglobin level of 9 g/dl or less) and those

[2]Yende S, Thompson T: Evaluating glucocorticoids for sepsis. Time to change course, *JAMA* 316(17):1769–1770, 2016.
[3]Fang F et al: Association of corticosteroid treatment with outcomes in adult patients with sepsis: a systematic review and meta-analysis, *JAMA Intern Med* 179(2):213–223, 2019.

assigned to blood transfusion at a lower threshold (hemoglobin level of 7 g/dl or less).

CHRONIC Rx

- Adjust antibiotic therapy on the basis of culture results.
- In general, continue antibiotic therapy for a minimum of 7 to 10 days.
- Infection source control (e.g., removal of catheter/device suspected to be infected).
- If hyperglycemia develops during treatment, start continuous insulin IV infusion, maintain blood glucose in the 110 to 180 mg/dl level, and avoid insulin-induced hypoglycemia.

DISPOSITION

- All patients with sepsis should be hospitalized and given access to intensive monitoring and nursing care.
- Among adults with suspected infection admitted to an ICU, an increase in SOFA score of 2 or more has greater prognostic accuracy for in-hospital mortality than SIRS criteria or the qSOFA score (quick SOFA).[4] The qSOFA can be done at bedside and consists of increased respiratory rate ≥ 22/min, altered mentation and systolic BP ≤100 mm Hg with each allocated 1 point.

REFERRAL

- To infectious diseases expert
- To physician experienced in critical care

PEARLS & CONSIDERATIONS

COMMENTS

- Mortality rises quickly if antibiotic therapy is not instituted promptly (preferably within 1 hr of onset of shock) and metabolic derangements are not treated aggressively.
- The Surviving Sepsis Campaign hour-1 bundle 2018 update recommends: Measure lactate level. Re-measure if initial lactate is >2 mmol/L. [weak recommendation, low quality of evidence] Obtain blood cultures prior to administration of antibiotics. [best practice statement] Administer broad spectrum antibiotics. [strong recommendation, moderate quality of evidence] Rapidly administer 30 ml/kg crystalloid for hypotension or lactate ≥4 mmol/L [strong recommendation, low quality of evidence] and apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg. [strong recommendation, moderate quality of evidence]
- Recent trials have shown that early, goal-directed therapy (EGDT) does not result in better outcomes than usual care and is associated with higher hospitalization costs across a broad range of patient and hospital characteristics.[5]

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Glenn G. Fort, MD, MPH,** and **Fred F. Ferri, MD**

[4]Raith EP et al: Prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit, *JAMA* 310(3):290–300, 2016.

[5]The PRISM Investigators: Early, goal-directed therapy for septic shock–a patient-level meta-analysis, *N Engl J Med* 376:2223–2234, 2017.

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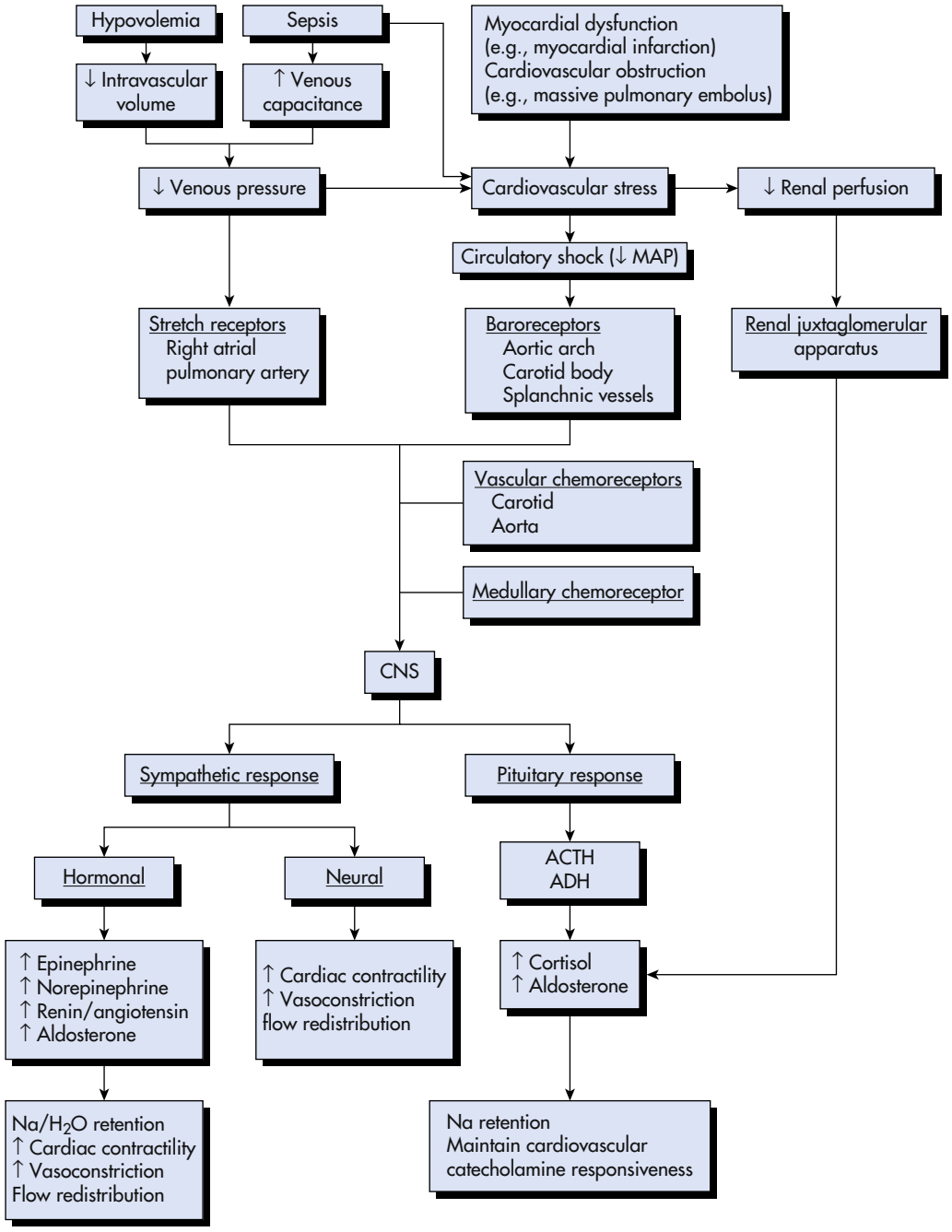

FIG. E1 Neurohormonal response to shock. During early cardiovascular stress, the neurohormonal response may be limited to increased activity of the juxtaglomerular apparatus and stimulation of right atrial and pulmonary artery low-pressure mechanoreceptors. With further hypotension, high-pressure vascular baroreceptors, vascular chemoreceptors, and the medullary chemoreceptor are stimulated sequentially. This results in augmented neurohormonal activity with increased pituitary hormone (adrenocorticotropic hormone *[ACTH]* and antidiuretic hormone *[ADH]*) release and increased sympathetic outflow from the central nervous system *(CNS)*. Volume retention, increased venous tone, increased cardiac contractility, and blood flow redistribution to vital organs are the results. *MAP,* Mean arterial pressure; *Na,* sodium; *H_2O,* water. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.)

Septic Arthritis ALG PTG

BASIC INFORMATION

DEFINITION

Septic arthritis is a highly destructive form of joint disease most often caused by hematogenous spread of organisms from a distant site of infection. Direct penetration of the joint as a result of trauma or surgery and spread from adjacent osteomyelitis may also cause bacterial arthritis. Any joint in the body may be affected.

SYNONYMS

Infectious arthritis
Bacterial arthritis
Pyogenic arthritis

ICD-10CM CODE
M00.9 Pyogenic arthritis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Between 2 and 6 cases per 100,000 people per yr
PREVALENCE (IN U.S.): Unknown
PREDOMINANT SEX: Gonococcal arthritis in females
PREDOMINANT AGE: Gonococcal arthritis in sexually active adults
PEAK INCIDENCE:
- Gonococcal arthritis: Young adults
- Other bacterial causes: All ages

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hallmark: Acute onset of monoarticular joint pain, erythema, heat, and immobility
- Limited range of motion of the joint
- Effusion, with varying degrees of erythema and increased warmth around the joint
- Single joint affected in 80% to 90% of cases of nongonococcal arthritis
- Gonococcal dermatitis-arthritis syndrome:
  1. Typical pattern is a migratory polyarthritis or tenosynovitis
  2. Small pustules on the trunk or extremities
- Febrile patient at presentation
- Most commonly affected joints in adult: Knee and hip, but any joint may be involved; in children—hip

ETIOLOGY

- Bacteria spread from another locus of infection.
  1. Highly vascular synovium is invaded by hematogenously spread bacteria.
  2. WBC enzymes cause necrosis of synovium, cartilage, and bone.
  3. Extensive joint destruction is rapid if infection is not treated with appropriate IV antibiotics and drainage of necrotic material.
- Predisposing factors: Rheumatoid arthritis, prosthetic joints, advanced age, immunodeficiency (HIV, DM, immunosuppressive drugs), gout, sexual activity (gonococcal arthritis), skin infections, cutaneous ulcers (contiguous spread), recent joint surgery, recent intraarticular infection. Fig. E1 illustrates routes by which bacteria can reach the joint.
- The most common nongonococcal organisms are staphylococci (40%), streptococci (28%), and gram-negative bacilli (19%). Less common are mycobacteria (8%), gram-negative cocci (3%), anaerobes (1%), and gram-positive bacilli (1%).
- Staphylococci (*S. aureus* and coagulase-negative staphylococcal species) account for >50% of prosthetic-hip and prosthetic-knee infections. *S. aureus* is very common in patients with rheumatoid arthritis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gout
- Pseudogout
- Trauma
- Hemarthrosis
- Rheumatic fever
- Adult or juvenile rheumatoid arthritis
- Spondyloarthropathies such as reactive arthritis (Reiter syndrome)
- Osteomyelitis
- Viral arthritides
- Septic bursitis
- Lyme disease caused by *Borrelia burgdorferi*

WORKUP

- Joint aspiration, Gram stain, and culture of the synovial fluid. Fig. 2 describes an algorithm for synovial fluid analysis in septic arthritis.
- Immediate arthrocentesis before other studies are undertaken or antibiotics instituted. Synovial fluid should be evaluated at bedside and then sent for lab evaluation.

LABORATORY TESTS

- Joint fluid analysis:
  1. Synovial fluid leukocyte count is usually elevated >50,000 cells/mm^3 with >80% polymorphonuclear cells.
  2. Counts are highly variable, with similar findings in gout, pseudogout, or rheumatoid arthritis. Lower WBC counts can occur in joint replacement, disseminated gonococcal disease, and peripheral leukopenia.
  3. Synovial fluid glucose or protein is not helpful because results are not specific for septic arthritis. The differential diagnosis of synovial fluid abnormalities is described in Section IV.
  4. PCR testing: Useful for detection of uncommon organisms (e.g., Lyme disease).
  5. Crystal analysis: Septic arthritis can coexist with crystal arthropathy; therefore, the presence of crystals does not preclude a diagnosis of septic arthritis.
- Blood cultures: Positive in 25% to 50% of patients with septic arthritis.
- Culture of possible extraarticular sources of infection.
- Elevated peripheral WBC count, ESR (nonspecific), C-reactive protein (CRP) (nonspecific). When elevated, ESR and CRP may be useful to monitor therapeutic response.
- If gonococcus is suspected, perform nucleic acid amplification tests (NAATs) on synovial fluid.

IMAGING STUDIES

- Radiograph of the affected joint (Fig. E3): Useful to rule out osteomyelitis, fractures, chondrocalcinosis, or inflammatory arthritis
- MRI: Findings that suggest an acute intraarticular infection include the combination of bony erosions with marrow edema
- CT scan: Useful for early diagnosis of infections of the spine, hips, and sternoclavicular and sacroiliac joints
- Ultrasound: Can be useful for detecting effusions in joints that are more difficult to examine (e.g., hip)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Affected joints aspirated daily to remove necrotic material and to follow serial WBC counts and cultures
- If no resolution with IV antibiotics and closed drainage: Open debridement and lavage, particularly in nongonococcal infections
- Prevention of contractures:
  1. After acute stage of inflammation, range-of-motion exercises of the affected joint
  2. Physical therapy helpful

ACUTE GENERAL Rx

- IV antibiotics immediately after joint aspiration and Gram stain of the synovial fluid. Empiric antibiotic therapy (Table E1) is based on organism found on Gram stain of synovial fluid:
  1. Gram-positive cocci: Vancomycin: 15 to 20 mg/kg IV q8 to 12h. Keep trough levels at 15 to 20 mcg/ml. Alternatives include daptomycin and linezolid
  2. Gram-negative cocci: Ceftriaxone: 1 to 2 g IV q day in adults (children: 50 to 100 mg/kg IV q day). Alternative includes cefotaxime
  3. Gram-negative rods: Ceftriaxone, cefepime: 1 to 2 g IV q8 to 12h in adults (children: 100 to 150 mg/kg/day divided in q8h dosing), piperacillin-tazobactam: 3.375 g IV to 4.5 g IV q6h. Aztreonam or fluoroquinolones can be used in patients with allergy to penicillin or cephalosporins
  4. Negative Gram stain: Vancomycin plus either cefepime or a carbapenem such as meropenem: 1 g IV q8h in adults (children: 60 mg/kg/day divided in q8h dosing) or ertapenem

The optimal duration of antibiotic use in septic arthritis has traditionally been 3 to 6 wk usually following surgical drainage. Recent trials (Gjika et al, *Ann Rheum Dis* Aug 2019, 78: 1114) support a 2-wk course in conjunction with surgery.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Septic Arthritis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

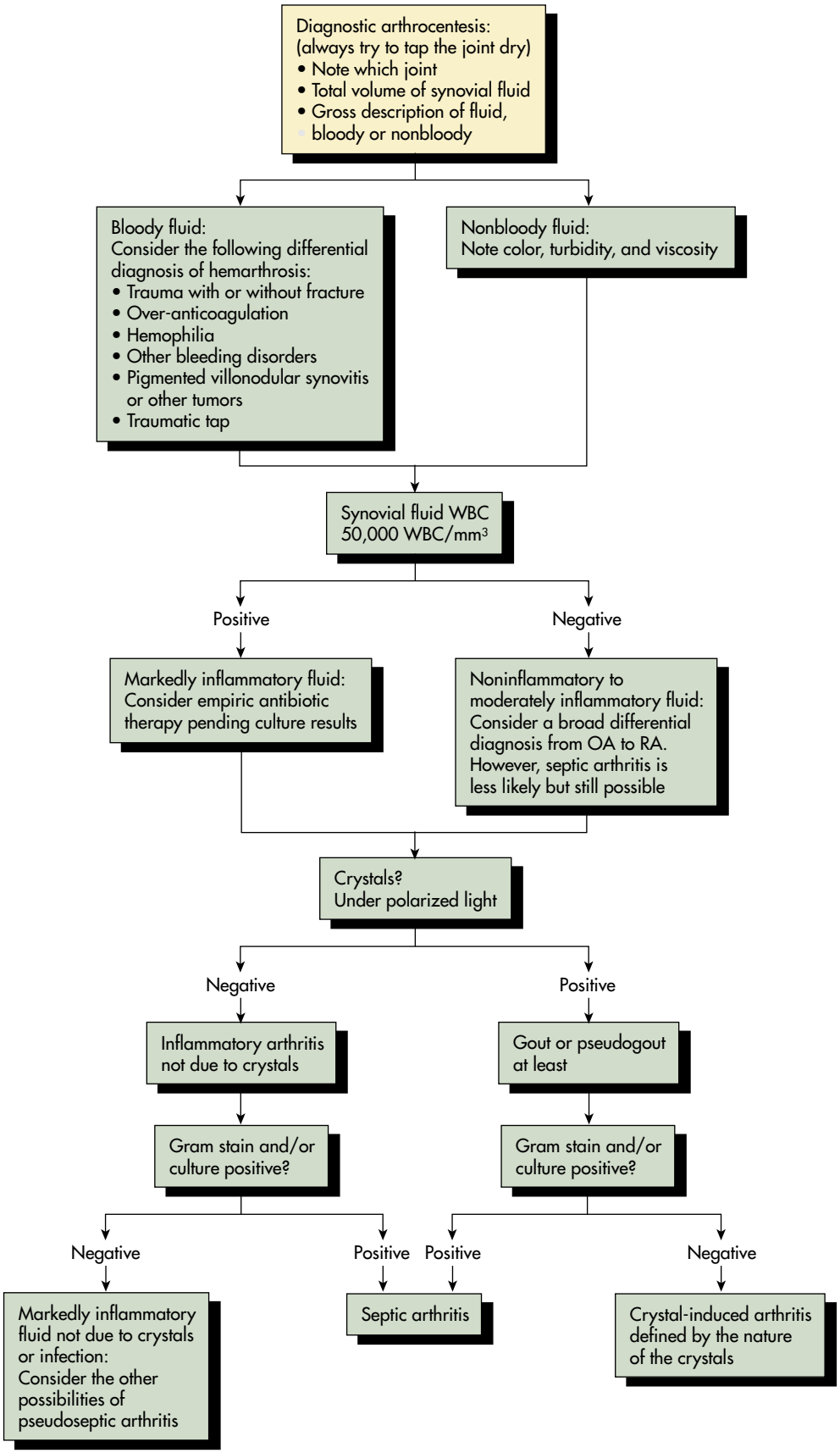

FIG. 2 Algorithm for synovial fluid analysis in septic arthritis. *OA,* Osteoarthritis; *RA,* rheumatoid arthritis; *WBC,* white blood cell count. (From Harris ED et al: *Kelley's textbook of rheumatology,* ed 7, Philadelphia, 2005, Saunders.)

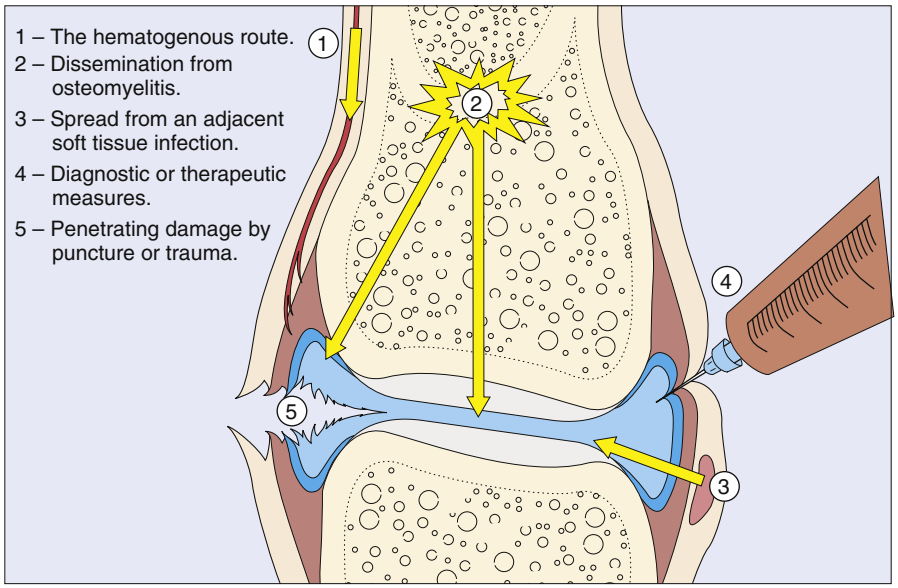

FIG. E1 Routes by which bacteria can reach the joint. (From Hochberg MC et al: *Rheumatology,* ed 5, St. Louis, Mosby, 2011.)

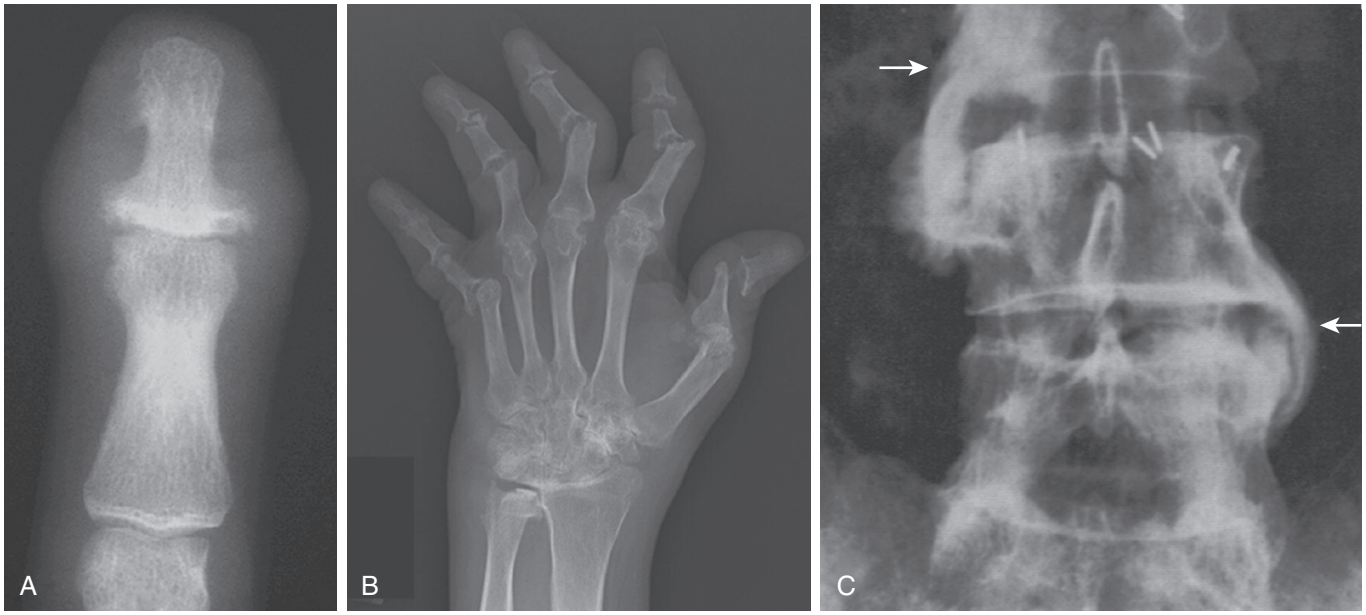

FIG. E3 Septic arthritis (x-ray and magnetic resonance imaging [MRI]). A, X-ray in anteroposterior view of sacroiliac joints shows destruction of the right sacroiliac joint as part of septic arthritis *(arrows).* **B,** In another patient, short tau inversion recovery (STIR) coronal MRI through sacroiliac joints shows erosive changes in the right sacroiliac joint with extensive bone marrow edema. **C** and **D,** Tuberculous spondylitis. **C,** X-ray of the lumbar spine in lateral view shows disk space narrowing at the L3-L4 level with destructive changes involving the superior end plate of the L4 vertebral body *(arrow).* **D,** Coronal STIR MRI of the lumbar spine of the same patient confirms focal destruction of the L4 vertebral body *(arrow).* Enlargement of both psoas muscles (P) with increased signal is noted, owing to paraspinal extension of the infection. (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

TABLE E1 Recommended Empiric Therapy for Adult Native Joint Bacterial Arthritis

Gram Stain	Preferred Antibiotic*	Alternative Antibiotic
Gram-positive cocci	Vancomycin, 15-20 mg/kg (ABW) daily every 8-12 hr†	Daptomycin, 6-8 mg/kg daily™™ *or* linezolid, 600 mg IV or PO every 12 hr‡
Gram-negative cocci§	Ceftriaxone, 1 g every 24 hr	Cefotaxime, 1 g every 8 hr ‖
Gram-negative rods¶	Ceftazidime, 2 g every 8 hr *or* cefepime, 2 g every 8 hr *or* piperacillin-tazobactam, 4.5 g every 6 hr	Aztreonam, 2 g every 8 hr *or* fluoroquinolone *or* carbapenem
Gram stain negative¶	Vancomycin plus ceftazidime *or* cefepime	Daptomycin‡ *or* linezolid‡ plus piperacillin-tazobactam *or* aztreonam *or* fluoroquinolone** *or* carbapenem

*Unless noted otherwise, dosages are IV for persons with normal renal function.
†Therapeutic monitoring should target a serum trough of 15-20 mg/L.
‡For patients allergic to, or intolerant of, vancomycin.
§Equivocal gram-negative morphology should be considered as gram-negative rods.
‖ Gram-negative cocci with epidemiology or history suggestive of gonococcal infection should be initially treated per Centers for Disease Control and Prevention Sexually Transmitted Disease Guidelines. Alternative therapies have not been suggested for patients with a history of a Stevens-Johnson syndrome or severe IgE-mediated allergy to β-lactam antibiotics. Possible empiric options for penicillin-allergic patients, pending culture sensitivities, include azithromycin, ciprofloxacin, tobramycin, gentamicin, and spectinomycin (not available in U.S.).
¶For patients with risk factors for resistant gram-negative pathogens (significant health care exposure, immunosuppression, or history of extended-spectrum β-lactamase gram-negative infection or colonization), drug selection should consider regional or local antibiograms.
**Ciprofloxacin, 400 mg IV q8h or 750 mg PO q12h *or* levofloxacin, 750 mg IV or PO q24h.
Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

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Lim SY et al: Septic arthritis in gout patients: a population-based cohort study, *Rheumatology (Oxford)* 54:2095-2099, 2015.

Serotonin Syndrome

BASIC INFORMATION

DEFINITION

Serotonin syndrome (SS) is a potentially life-threatening condition resulting from excessive serotonergic stimulation of 5-HT_{1A} and 5-HT_{2A} receptors in the CNS and PNS. SS is a drug-induced disorder that is classically characterized by mental status changes, neuromuscular hyperactivity, and autonomic dysfunction.

SYNONYMS

SS
Hyperserotonemia
Serotonergic syndrome
Serotonin toxicity

ICD-10CM CODES

Y49	Adverse effects due to psychotropic drugs
Y49.0	Adverse effects due to tricyclic and tetracyclic antidepressants
Y49.1	Adverse effects due to monoamine-oxidase-inhibitor antidepressants
Y49.2	Adverse effects due to other and unspecified antidepressants
Y49.3	Adverse effects due to phenothiazine antipsychotics and neuroleptics
G25.89	Other specified extrapyramidal and movement disorders

EPIDEMIOLOGY & DEMOGRAPHICS

- The true incidence of SS is not known, as clinical manifestations may go unnoticed or be attributed to another condition.
- SS is seen in all age groups.
- SS classically occurs in patients receiving two or more serotonergic drugs, but it can also occur with monotherapy—selective serotonin reuptake inhibitor (SSRI) monotherapy has an incidence of 0.5 to 0.9 cases of SS per 1000 patient-mo. Although there is an FDA alert, it has been argued that there is a lack of sufficient evidence showing that SSRIs and triptans cause serious SS.
- Concomitant use of an SSRI with a monoamine oxidase inhibitor (MAOI) poses the greatest risk of developing SS.
- Combination of SSRIs with other serotonergic drugs (e.g., tryptophan, illicit drugs like cocaine and MDMA, "Ecstasy") or drugs with serotonergic properties (e.g., methylene blue, lithium, meperidine, triptans, linezolid) may also lead to SS.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Findings of clonus with hyperreflexia in the setting of recent (<5 wk) use of serotonergic agents strongly suggest the diagnosis of SS.
- Symptoms can manifest within min to hours after starting a new psychopharmacologic treatment, increasing the dose of a serotonergic drug, or administering a second serotonergic drug.
- Clonus (inducible, spontaneous, and ocular) is the key finding in establishing a diagnosis of SS.
- Classic triad of clinical features:
  1. Neuromuscular excitation: Hyperreflexia, myoclonus, muscle rigidity, tremor
  2. Autonomic nervous system excitation: Nausea/vomiting, diarrhea, hypertension, tachycardia, diaphoresis, fever >38° C (100° F) to severe hyperthermia
  3. Altered mental status: Anxiety, agitation, confusion, coma

ETIOLOGY

- Hyperstimulation of the brain stem and spinal cord serotonin receptors leading to the neuromuscular and autonomic symptoms.
- Psychopharmacologic drugs—in particular, fluoxetine and sertraline co-administered with MAOI (e.g., tranylcypromine and phenelzine)—have been cited as a common cause of SS. Triptans (serotonin-receptor agonists used in the treatment of migraines) may also precipitate the SS when used in combination with SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs). Box 1 describes classes of medications that produce SS.

BOX 1 Classes of Medications That Produce Serotonin Syndrome in Psychiatric Patients

Selective serotonin reuptake inhibitors
Monoamine oxidase inhibitors
Atypical antipsychotics
Heterocyclic antidepressants
Trazodone
Dual-uptake inhibitors
Psychostimulants
Buspirone
Mood stabilizers
Analgesics
Antiemetics
Cough suppressants
Dietary supplements
Linezolid

From Goldman L, Schafer AI: *Goldman-Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.

DIAGNOSIS

- SS is a clinical diagnosis. There are no specific laboratory tests for SS. A high index of suspicion along with a detailed medication history is the mainstay of diagnosis.
- Diagnostic criteria: Most accurate is Hunter Serotonin Toxicity Criteria (sensitivity 84%, specificity 97%, confirmation by toxicologist). Sternbach diagnostic criteria (Table 1) are also commonly used.
- To fulfill Hunter criteria a patient must have consumed a serotonergic drug and have one of the following:
  1. Spontaneous clonus
  2. Inducible clonus plus agitation or diaphoresis
  3. Ocular clonus plus agitation or diaphoresis
  4. Tremor and hyperreflexia
  5. Temperature >38° C (100° F) plus hypertonia plus ocular clonus or inducible clonus

DIFFERENTIAL DIAGNOSIS

- Neuroleptic malignant syndrome (NMS), substance abuse (e.g., cocaine, amphetamines), anticholinergic toxicity, malignant hyperthermia, thyroid storm, infection (e.g., meningitis, encephalitis), alcohol and opioid withdrawal.
- Classic features in differentiation of NMS from SS are that SS develops over 24 hr, involves neuromuscular hyperactivity (hyperreflexia, myoclonus), and begins to resolve within 24 hr with appropriate therapy, whereas NMS develops gradually over days to wks, involves sluggish neuromuscular response, and resolves over an average period of 1 wk to 10 days.

WORKUP

- Because SS is a clinical diagnosis, there is no laboratory test that confirms the diagnosis, and serum serotonin concentration does not correlate with the clinical picture. Other causes

TABLE 1 Criteria to Determine Serotonin Syndrome and Toxicity

Sternbach diagnostic criteria for serotonin syndrome	1. Recent addition or increase of proserotonergic medication 2. At least three of the following: 1. Agitation 2. Ataxia 3. Diaphoresis 4. Diarrhea 5. Hyperreflexia 6. Hyperthermia 7. Mental status changes 8. Myoclonus 9. Shivering 10. Tremor 3. Neuroleptic agent not added or dose increased before the onset of symptoms 4. Diagnosis of infections, withdrawal, and other poisoning or metabolic disruptions excluded
Hunter criteria for serotonin toxicity (context of serotonergic medications)	1. If patient has spontaneous clonus, serotonin toxicity present 2. If no spontaneous clonus, one of the following needed for a diagnosis of serotonin toxicity: 1. Inducible clonus *and* agitation *or* diaphoresis 2. Ocular clonus *and* agitation *or* diaphoresis 3. Tremor *and* hyperreflexia 4. Temperature >38° C *and* ocular clonus *or* inducible clonus

From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

are described in "Differential Diagnosis." Thus, all patients should have blood tests and diagnostic imaging studies to rule out infectious, toxic, and metabolic causes.
- Additional laboratory tests are performed to exclude complicating features of SS (e.g., renal failure secondary to rhabdomyolysis).

LABORATORY TESTS

- CBC with differential when considering sepsis
- Urine and blood cultures
- Electrolytes, BUN, and creatinine to rule out acidosis and renal failure
- Coagulation studies to rule out disseminated intravascular coagulation
- Blood and urine toxicology screen, including acetaminophen and salicylate levels if overdose was intentional
- Thyroid function tests
- Creatine-phosphokinase (CPK) with isoenzymes
- ECG because ventricular rhythm disturbance is a potentially fatal complication
- CSF studies to rule out meningitis

IMAGING STUDIES

Imaging studies are not specific in the diagnosis of SS and are only ordered to exclude other causes with similar clinical presentations as SS.

Rx TREATMENT

- Once a diagnosis of SS is established, consultation with a medical toxicologist, clinical pharmacologist, and/or poison control center should be considered
- Management includes:
  1. Discontinue use of all potential precipitating drugs.
  2. Provide supportive management.
  3. Control agitation.
  4. Administer serotonin antagonists.
  5. Control autonomic instability.
  6. Control hyperthermia.
  7. Reassess the need to resume the use of the serotonergic agent once the symptoms have resolved.

NONPHARMACOLOGIC THERAPY

- Discontinuation of the drug is the mainstay of therapy.
- Treatment is supportive: Maintaining oxygenation and blood pressure and monitoring respiratory status. Hypotensive patients may require both IV fluids and vasopressor therapy.
- Patients who are severely hyperthermic with temperatures >41° C (106° F) should be given IV sedation, paralyzed, and intubated. Cooling blankets can be used for patients with mild to moderate hyperthermia. There is no role for acetaminophen here.
- Intubation is recommended for patients unable to protect their airways as a result of mental status changes or seizures.

ACUTE GENERAL Rx

- Benzodiazepines for control of agitation are preferred to physical restraints.
  1. Lorazepam 1 to 2 mg IV every 30 min has been used effectively in treating agitation, muscle rigidity, myoclonus, and seizure complications.
  2. Diazepam is an alternative choice.
- Blood pressure management with short-acting agents such as esmolol and nitroprusside.
- Serotonin antagonists should be titrated to clinical effectiveness in patients for whom nonpharmacologic therapy and benzodiazepines are not achieving adequate response, although substantial and rigorous data are lacking.
  1. Cyproheptadine 4 mg tablet or 2 mg/5 ml syrup is given 12 mg initially followed by 2 mg every 2 hr until therapeutic response is achieved in adults (up to 32 mg/day); children ages 7 to 14 should receive 4 mg every 6 hr (up to 16 mg/day), children ages 2 to 6 should receive 2 mg every 6 hr (up to 12 mg/day), and children younger than 2 yr should receive a maximum of 0.25 mg/kg/day as 0.06 mg/kg every 6 hr.
  2. Atypical antipsychotic agents with serotonin antagonist properties (e.g., olanzapine 10 mg SL) have been tried with some success.
  3. Chlorpromazine 50 to 100 mg IM may be considered in severe cases, but intravenous fluid loading is essential to prevent hypotension.

CHRONIC Rx

For patients not requiring hospital admission, cyproheptadine and lorazepam can be given in an oral dose on a prn basis with close follow-up.

DISPOSITION

- SS is a potentially life-threatening condition if not recognized early, although it does exist on a spectrum.
- Prompt diagnosis and withdrawal of the medication result in improvement of symptoms within 24 hr.
- Seizures, rhabdomyolysis, hyperthermia, ventricular arrhythmia, respiratory arrest, and coma are all complicating features of SS.

REFERRAL

All cases of SS secondary to psychotropic medications should be referred to a psychiatrist.

PREVENTION

Modify prescription practices by avoiding multidrug regimens.

PEARLS & CONSIDERATIONS

The combined use of SSRIs and MAOIs is contraindicated.

COMMENTS

- The use of SSRIs and other serotonergic agents is not an absolute contraindication; however, prompt withdrawal of the medication is recommended if any symptoms suggesting SS occur.
- SS is usually found in patients being treated for depression, bipolar disorders, obsessive-compulsive disorder, attention deficit disorder, and Parkinson disease.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Neal Bucher, MD,** and **J. Richard Walker III, MD, MS, FACEP**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Sexual assault is any sexual act performed against someone who has not freely given their consent or who is unable to give consent.

SYNONYM

Rape

ICD-10CM CODES

Y05	Sexual assault by bodily force
Z04.41	Encounter for examination and observation following alleged adult rape
Z04.42	Encounter for examination and observation following alleged child rape

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 19% of women, 3% of men
PEAK INCIDENCE: As high as 25%
PREVALENCE (IN U.S.): 23 million women, 2.8 million men
PREDOMINANT SEX AND AGE: Female, ages 12 to 34
RISK FACTORS: Alcohol/drug consumption, prior history of being sexually/physically abused, multiple sexual partners, involvement in sex work, poverty, incarceration/institutionalization, intellectual disability

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Extragenital trauma: 70%: Erythema, bruises, abrasions, lacerations, or fractures on thigh, arms, face, neck
- Anogenital trauma: 27%: Injury to breasts, external genitalia, vagina, anus, rectum
- Other: Pregnancy (5%), bullet wounds, death

Physical findings more likely if examined within 72 hr of event, if event occurred outdoors, and if perpetrator was unknown

DIAGNOSIS

WORKUP

Preliminary issues and strategies in preparing for taking the history from a sexual assault victim (SAV) are described in Box E1. Consent issues are summarized in Box E2.

- History:
  1. Circumstances of assault: Date, time, location
  2. Physical description of perpetrator
  3. Areas of trauma, specifically details of oral, vaginal, anorectal contact, or penetration
  4. Condom use
  5. Ejaculation: Presence or absence
  6. Presence of bleeding in victim or perpetrator
  7. Recent consensual sexual activity
  8. Showering, bathing, changing of clothes since event
- Physical examination:
  1. Ideally performed by individual trained to perform sexual assault examinations, i.e., SANE (Sexual Assault Nurse Evaluation) providers: www.sane-sart.com
  2. Physical exam can take 3 to 6 hr to complete
  3. Components:
     a. Physical examination of entire body
     b. Forensic evidence collection
     c. STD evaluation and treatment
     d. Pregnancy risk evaluation
     e. Care of injuries
  4. General physical exam components:
     a. Documentation of any physical trauma, including photographs
     b. Colposcopy: May reveal areas of minor genital trauma
     c. Wood's light: To reveal foreign debris or semen
  5. Forensic evaluation: Not required, but should be offered; written informed consent needed:
     a. Commercially made specimen collection kits available: Once completed, kits need to be sealed and handled according to kit instructions
     b. U.S.: States required to provide free specimen collection
     c. Samples of blood, saliva, mucosal swabs: Buccal/vaginal/rectal, fingernail scrapings/clippings, hair specimens
     d. Clothing: If unchanged since event
- Box E3 summarizes potential specimens to be gathered for forensic evidence collection.
- Fig. E1 describes an algorithm for emergency department management of patients after sexual assault.

LABORATORY TESTS

- Laboratory evaluation of sexual assault is summarized in Table E1
- Pregnancy test (if applicable)
- STD testing:
  1. GC/CT: Recommended for all, may be excluded if individual elects prophylactic treatment
  2. Wet mount or vaginal swab for *Trichomonas*
  3. Baseline HIV/hepatitis/syphilis testing: Individual basis
  4. Retest for HIV/syphilis at 6 wk, 3 mo, and 6 mo from incident

IMAGING STUDIES

Use of imaging studies as dictated by other injuries sustained for diagnosis/treatment of fractures, soft tissue, and other traumatic injuries

TREATMENT

NONPHARMACOLOGIC THERAPY

Acute crisis counseling: To support mental health needs of victim in immediate post-assault period

ACUTE GENERAL Rx

- Post-exposure prophylaxis (PEP) for acute sexual assault victims is summarized in Table E2
- Sexually transmitted infections:

BOX E1 Preliminary Issues and Strategies in Preparing for Taking A Patient History From a Sexual Assault Victim (SAV)

Provide a quiet, confidential, safe environment.
Briefly review the interview and examination process in private with the SAV.
Explain the sensitive, personal, embarrassing nature of questions and the right to be interviewed in private.
Show concern for the SAV's immediate comfort (e.g., if thirsty, take oral swabs first so SAV may drink).
Provide advocacy.
Try to conduct the interview the same way.
Leave difficult questions until the end; some may need to be repeated during appropriate parts of the physical examination.
Explain why you are asking the question and the possible responses.
Explain that all questions will be asked.

From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, WB Saunders.

BOX E2 Consent Issues in Sexual Assault Cases

Consent should specify that the sexual assault victim's signature acknowledges the following:

- That hospitals and health care professionals are mandated reporters and that an anonymous Jane Doe report can be made
- Receipt of information about victim compensation funds
- Specific understanding of examination and evidence collection procedures
- Specific understanding of the use of photography in documenting physical and genital injuries
- That information collected will be sent to law enforcement and is obtainable by defense counsel
- That data without patient identity can be collected for valid educational and scientific purposes
- That consent may be withdrawn at any time
- That there is no charge for the examination, whether reported to law enforcement or not

From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, WB Saunders.

BOX E3 Potential Specimens to Be Gathered for Forensic Evidence Collection

Clothing
- Each article of clothing should be packaged in a separate paper bag to avoid cross-contamination.
- If the patient has changed her clothing, only underwear should be collected.

Known blood sample
- Crime laboratory assesses for secretor status and blood type of the patient.
- Toxicology testing (urine and blood)
- For use in cases in which drug-facilitated sexual assault is suspected
- Collect for evaluation less than 72 to 96 hr after the assault (the time varies by crime laboratory).

Oral swabs and smears
- Collect for evaluation up to 24 hr after the assault.

Head hair combings
Fingernail scrapings
Foreign material collection
Swabs of bite marks or areas where the assailant's mouth touched the patient
Pubic hair combings
External genital swabs

Vaginal swabs and smears
- Cervical sampling should be considered for evaluation between 96 and 120 hr after the assault.

Perianal swabs
Anorectal swabs and smears
- Collect for evaluation up to 24 hr after the assault.

Forensic photography
- Three views per injury, one with a ruler for scale.

From Adams JG et al: *Emergency medicine: clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

1. Empiric treatment recommended secondary to poor follow-up rates
2. Gonorrhea: Ceftriaxone 250 mg IM *or* cefixime 400 mg PO
3. *Chlamydia:* Azithromycin 1 g (single dose) *or* doxycycline 100 mg bid × 7 days
4. Trichomoniasis: Metronidazole 2 g PO (single dose)

- Hepatitis B:
  1. If perpetrator is known to be infected: HBIG + Hep B vaccination.
  2. If perpetrator disease status unknown: Hep B vaccination alone.
  3. If victim has already been vaccinated with documented immunity: No treatment necessary.
- HIV:
  1. Use of antiretrovirals after sexual assault is controversial.
  2. Overall risk of acquiring HIV is unknown but higher in certain situations:
     a. Male-on-male rapists
     b. Assault occurring in area with high local prevalence
     c. Multiple assailants
     d. Anal sexual assault
     e. Presence of trauma, bleeding, or genital lesions in either victim/assailant
  3. Antiretroviral drugs should be offered in all situations.
  4. Ideally, antiretrovirals are initiated within 4 hr; should not start if >72 hr.
- Pregnancy:
  1. Pregnancy risk is estimated to be 5% per rape in women age 12 to 45.
  2. Emergency contraception should be offered in all cases.
     a. Levonorgestrel: 0.75 mg q12h for two doses or 1.5 mg single dose
     b. Yuzpe regimen: 100 mcg ethinyl estradiol + 0.5 mg levonorgestrel, repeated in 12 hr
     c. Ulipristal (selective progesterone receptor modulator): Preferred method when >72 hr from assault
  3. Antiemetics: EC + antibiotics for STD prophylaxis commonly causes nausea.

CHRONIC Rx

- No chronic prescriptions.
- Long-term psychiatric counseling may be needed.

REFERRAL

Mental health professional

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Chlamydia Genital Infections (Related Key Topic)
Contraception (Related Key Topic)
Gonorrhea (Related Key Topic)
Syphilis (Related Key Topic)
Human Immunodeficiency Virus (Related Key Topic)

AUTHORS: **Yaneve Fonge, MD,** and **Sarah L. Chisholm, MD**

TABLE E1 Laboratory Evaluation of Sexual Assault

Within 8-12 hr (if indicated by history)

Urine and blood for date rape drugs (GHB, Rohypnol, ketamine)

Within 24 hr (if indicated by history)

Blood for comprehensive toxicology screen (for other classes of drugs)

Within 72 hr (or up to 96 hr depending on the protocol used)

Forensic evidence kit
Pregnancy test
Hepatitis B screen (hepatitis B surface antigen, surface antibody, and core antibody)
Syphilis (rapid plasma reagin [RPR], Venereal Disease Research Laboratories [VDRL])
HIV infection
Bacterial vaginosis (BV) and candidiasis: Point-of-care testing and/or wet mouth with measurement of vaginal pH and KOH application for whiff test
Trichomonas vaginalis: Nucleic acid amplification tests (NAATs) by urine or vaginal specimen or point-of-care testing (DNA probes) from vaginal specimen
Chlamydia and Neisse*ria gonorrhoeae*: Nucleic acid amplification testing (NAATs) at sites of penetration or possible penetration:
1. *N. gonorrhoeae:* Oropharynx, rectum, urine*
2. *Chlamydia*: Urine,* rectum

*Dirty urine sample may be used as alternate for genital swab.

From Centers for Disease Control and Prevention: Sexually transmitted diseases: Treatment guidelines 2015, *MMWR Recomm Rep* 64(RR-3):1–140, 2015, and Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States, 2016. In Kliegman, RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

TABLE E2 Postexposure Prophylaxis (PEP) for Acute Sexual Assault Victims

Routine

Recommended Regimen for STI Prophylaxis

Ceftriaxone 250 mg intramuscularly
plus
Azithromycin 1g orally in a single dose
plus
Metronidazole 2 g orally in a single dose or
Tinidazole 2 g orally in a single dose

Pregnancy Prophylaxis*

Levonorgestrel (Plan B) 1.5 mg orally in a single dose
or
Ulipristal acetate (Ella) 30 mg is effective for up to 120 hr.

Human Papillomavirus (HPV)

Assess HPV vaccine history; to the unimmunized, administer initial vaccine at initial exam, with 2 follow-up doses at 1 to 2 mo and at 6 mo if >15 yr old or a single follow-up dose at 6-12 mo if ≤15 yr old.

As Indicated

All persons offered PEP should be prescribed a 28-day course of a two- or three-drug antiretroviral regimen.

Human Immunodeficiency Virus (HIV)†

Preferred regimen:
Tenofovir 300 mg and fixed-dose combination emtricitabine, 200 mg (Truvada) once daily
plus
Raltegravir 400 mg twice daily *or*
Dolutegravir 50 mg daily‡

Hepatitis B Virus (HBV)

Specific indications for vaccine, immunoglobulin and/or Booster dependent upon assailant's status

*Provided for patients with negative urine pregnancy screen. In addition, antiemetic (Compazine, Zofran) can be prescribed for patients receiving emergency contraception.

†HIV PEP is provided for patients with penetration and when the assailant is known to be HIV-positive or at high risk because of a history of incarceration, intravenous drug use, or multiple sexual partners. If provided, laboratory studies must be drawn before administration of medication (HIV, CBC, LFTs, BUN/Cr, amylase, lipase), and follow-up must be arranged.

‡Dolutegravir has been associated with neural tube defects if exposure occurs within the first trimester of pregnancy. Therefore, it should be avoided in pregnant patients or those at risk for becoming pregnant.

U.S. Department of Health and Human Services, U.S. Food & Drug Administration. Juluca, Tivicay, Triumeq (dolutegravir): *FDA to evaluate potential risk of neural tube birth defects*. May 18, 2018. In Kliegman, RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

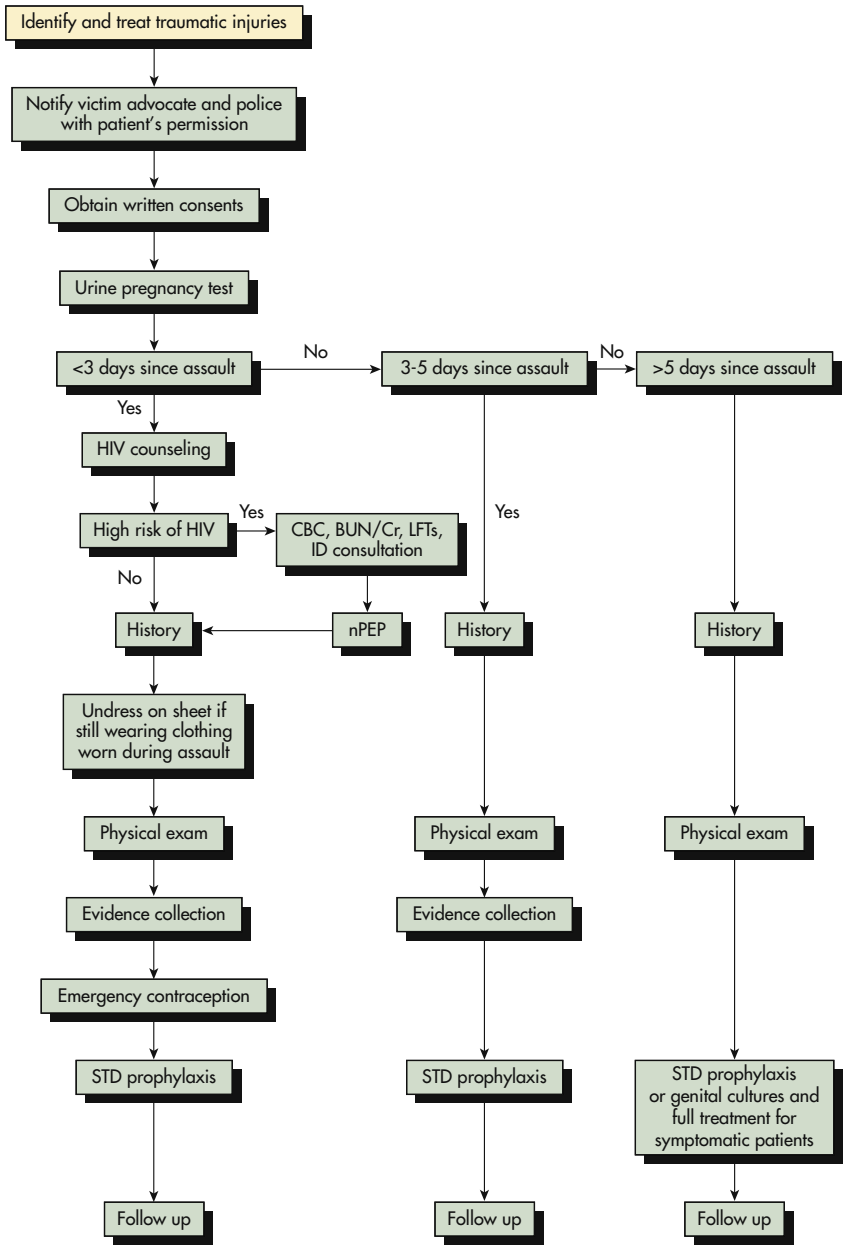

FIG. E1 Emergency department management of patients after sexual assault. *BUN*, Blood urea nitrogen; *CBC*, complete blood count; *Cr*, creatinine; *HIV*, human immunodeficiency virus; *ID*, infectious disease; *LFTs*, liver function tests; *nPEP*, nonoccupational postexposure prophylaxis; *STD*, sexually transmitted disease. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

SUGGESTED READINGS

American College of Obstetricians and Gynecologists: Committee on health care for underserved women: Committee opinion no. 499: sexual assault, *Obstet Gynecol* 118(2 Pt 1):396-399, 2014.

American College of Obstetricians and Gynecologists: Sexual assault. ACOG Committee opinion No. 777, *Obstet Gynecol* 133:e296-302, 2019.

Bates CK et al: Evaluation and management of adult sexual assault victims. Available at www.uptodate.com.

CDC: *MMWR: Sexually Transmitted Diseases Treatment Guidelines* 64, 2015. No. 3.

Fisher BS et al: *The sexual victimization of college women.* Department of Justice, National Institute of Justice, Publication No. NCJ 182369: Washington, DC.

Senn CY et al: Efficacy of a sexual assault resistance program for university women, *N Engl J Med* 372:2326-2335, 2015.

Tjaden P, Thoennes N: *Extent, nature, and consequences of rape victimization: findings from the National Violence against Women Survey*, Department of Justice, 2006. Available at: www.ncjrs.gov/pdffiles1/nij/210346.pdf.

BASIC INFORMATION

DEFINITION

A sexual dysfunction in a woman is any disorder that interferes with female sexuality and that causes marked distress to that person. The DSM-5 reclassified these disorders into the following categories:

- Female sexual arousal disorder (FSIAD): Hypoactive sexual desire disorder (HSDD) and female sexual arousal disorder (FSAD) were merged into this category
- Female orgasmic disorders
- Genito-pelvic pain/penetration disorder (GPPD): Combines the diagnoses of dyspareunia and vaginismus
- Sexual dysfunction due to secondary causes (e.g., medication, substance abuse, medical conditions)

Female sexual dysfunction is also further categorized as lifelong (primary) or acquired (secondary—present for 6 mo or more). The updated classification system has a high rate of false negatives due to the elimination of individuals reporting mild-to-moderate symptoms. The symptoms must also cause significant distress to the individual. The change in criteria was established to avoid overmedicalization of normal sexual function.

SYNONYMS

Female sexual dysfunction
Hypoactive sexual desire disorder (HSDD)

ICD-10CM CODES (NOTE: The new classification categories will be included in the ICD-11)

R37	Sexual dysfunction, unspecified
F52.0	Hypoactive sexual desire disorder
F52.22	Female sexual arousal disorder
F52.31	Female orgasmic disorder
N94.1	Dyspareunia
N94.81	Vulvodynia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: According to the National Health and Social Life Survey, in 1999, ~20% to 50% of women reported some form of sexual dysfunction during their lifetimes. One third of women reported a decrease in sexual interest, and one fourth reported an inability to achieve orgasm.

PREVALENCE (TABLE E1): A more recent survey of women 18 yr of age and older found an age-adjusted prevalence of any sexual problem to be ~43%.

PREDOMINANT AGE: Sexually related personal distress was more common in middle-aged women (aged 45 to 64) than in younger or older women.

RISK FACTORS:

- Correlates of distressing sexual problems include poor self-assessed health, low education level, depression, anxiety, thyroid conditions, and urinary incontinence.
- Higher insomnia scores and shorter sleep duration are associated with decreased sexual function.
- Obesity and overweight body status have been associated with lower sexual satisfaction and desire.
- Comorbid conditions such as arthritis, diabetes mellitus, hypertension, malignancy, neuromuscular disorders, renal failure, and gynecologic (e.g., chronic pelvic pain) and dermatologic conditions (e.g., lichen sclerosis, psoriasis) can contribute to sexual dysfunction.
- Aging is associated with decreased sexual responsiveness, sexual activity, and libido.
- Decreased hormonal levels associated with menopause can cause decreased vaginal lubrication and dyspareunia.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History: Important to obtain the patient's definition of the dysfunction, including its onset and duration; to determine whether the dysfunction is situational or global; and to determine whether more than one dysfunction exists and the interrelationship among the dysfunctions. Dysfunction is diagnosed if the symptoms are causing distress to the patient.
- Related medical and gynecologic conditions (including prior gynecologic surgery)
- Psychosocial factors, including sexual abuse, sexual orientation, depression and anxiety, status of current relationships and sexual activity, personal and family beliefs about sexuality
- Current medications including OTC and herbal preparations; alcohol, tobacco, and drug use; and birth control method, substance use/misuse
- Physical examination:
  1. The gynecologic examination can aid in identifying signs of decreased estrogen and androgen levels, infection, endometriosis, pelvic floor dysfunction, and systemic disease
  2. Cotton swab test when concern exists for provoked vulvodynia
  3. Other body systems as indicated (e.g., cardiovascular, thyroid)

ETIOLOGY

- Chronic medical conditions (e.g., diabetes, coronary vascular disease, arthritis, urinary incontinence).
- Medication induced (e.g., antihypertensives, narcotics, hormonal preparations, antihistamines, amphetamines, psychotropic medications). SSRIs are the most common medications linked to sexual dysfunction.
- Gynecologic conditions (e.g., cystitis, posthysterectomy, gynecologic cancers, breast cancer [femininity/self-image issues; chemotherapy effects], postpregnancy, postmenopausal). Premenopausal BSO is associated with a higher risk of HSDD.

TABLE E1 Prevalence and Definition of Female Sexual Dysfunctions

	Prevalence*	Definition†
Hypoactive sexual desire/low libido	9%-60%	Diminished feelings of sexual interest or desire, absence of sexual thoughts, and/or lack of receptivity to sexual activity‡
Sexual arousal disorder/sex not pleasurable	5%-51%	**Genital Female Sexual Arousal Disorder (GFSAD)**: Disruption of clitoral erection, vaginal vasocongestion, vaginal lubrication
Difficulty with genital lubrication	8%-60%	**Psychological Female Sexual Arousal Disorder (PFSAD):** Absent or markedly diminished feelings of excitement or pleasure in response to sexual stimuli
		Mixed Female Sexual Arousal Disorder: GFSAD and PFSAD
Persistent genital arousal disorder	~1%	Persistent, recurrent, intrusive, and/or distressing sensations of genital arousal not related to sexual stimulation and that do not resolve after orgasm
Female orgasmic disorder	7%-65%	Lack of experience of orgasm or diminished orgasm intensity despite high sexual arousal after a period of sufficient sexual stimulation and arousal
Sexual pain disorders	4%-42%	**Dyspareunia**: Persistent/recurrent pain with attempted/complete vaginal entry with a penis, finger, or other object
		Vaginismus: Vaginal spasm or pain in response to penetration with a penis, finger, or other object despite a desire for penetration to occur‡
Anxiety about sexual performance	6%-16%	N/A

*Laumann et al, 1999; Nicolosi et al, 2005, 2006a, 2006b; Shifren et al, 2008; West et al, 2008; Witting et al, 2008; Garvey et al, 2009.
†Waldinger et al, 2009; Basson et al, 2010b.
‡The term *vaginismus* is no longer preferred, as it includes significant semantic baggage as a psychological disorder.

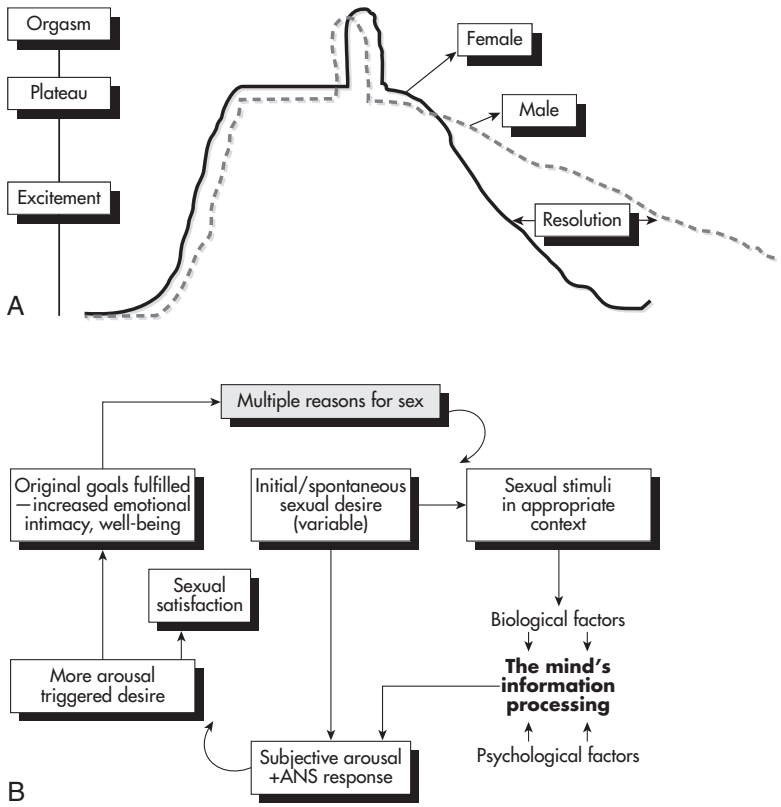

FIG. E1 A, The four phases of the human sexual response cycle as postulated by Masters and Johnson. Because the resolution phase is prolonged considerably in men, men can experience refractoriness to further stimulation for varying lengths of time before they can achieve another orgasm. As discussed in the text, understanding of the human sex response cycle has evolved substantially since the publication of this work. **B,** The circular human response cycle of overlapping phases. It is increasingly recognized that the human sexual response involves much more complexity, circularity, and flexibility than is reflected in Masters and Johnson's original model. "Desire" may or may not be present initially; it can be triggered during the experience. Arousal and desire overlap. Multiple psychologic and biologic factors influence the information processing of sexual stimuli. Underlying this processing may be the individual's unique tendency for excitation versus inhibition. *ANS,* Autonomic nervous system. (From Melmed S: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

- Psychosocial (e.g., religion, taboos, identity conflicts, guilt, relationship problems, abuse, rape, life stressors).
- Fig. E1 illustrates the four phases of the human sexual response as postulated by Masters and Johnson.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Depression
- Psychosocial stressors
- Medical disease (e.g., thyroid dysfunction)
- Menopausal status can be assessed using STRAW + 10 tool

LABORATORY TESTS

- Cervical cultures and vaginal swabs for infectious disease
- Cervical cancer screening as per current guidelines
- Appropriate laboratory tests if comorbid or chronic disease is suspected
- Measurement of prolactin, thyroid function tests, estrogen, progesterone, LH, testosterone, and sex hormone binding globulin is indicated only if a hormonal etiology is suspected from history

IMAGING STUDIES

Appropriate imaging studies if comorbid or chronic disease is suspected

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Treat genital arousal and pelvic pain symptoms before addressing HSDD
- Education including a discussion of normal sexual behavior
- Stress management
- Behavioral therapy (e.g., cognitive-behavioral therapy) and mindfulness-based interventions can treat low sexual desire and arousal disorders
- Counseling (individual or couples) for relationship issues
- Activities to enhance stimulation and eliminate routine
- Distraction techniques
- Noncoital behavior
- Position changes (e.g., female astride)
- Lubricants (e.g., nonpetroleum based). There are several over-the-counter lubricants and massage oils, some of which are hypoallergenic, that can be safely applied to female genitalia
- Physical therapy may be useful for patients with pelvic floor dysfunction and pain
- Eros clitoral therapy device: An FDA-approved device for targeting symptoms of FSAD

ACUTE GENERAL Rx

NSAIDs before intercourse for sexual pain disorders

CHRONIC Rx

- Treat underlying medical, gynecologic, or psychological conditions.
- Reduce comorbidities, including weight loss.
- Increase physical activity (associated with increased satisfaction and sexual engagement).
- For medication-induced conditions, decrease dose or change medication.
- For postmenopausal women or those with hypoestrogenism, try estrogen replacement therapy with or without progesterone. Local vaginal estrogen therapy is preferred over systemic therapy. Transdermal estradiol is superior to oral estradiol for improving sexual function because oral estradiol increases circulating sex hormone-binding globulin (SHBG) and lowers free testosterone, thus effecting libido adversely. Estrogen replacement is associated with improvements in dyspareunia and vaginal dryness.
- For postmenopausal vaginal and/or vulvar atrophy, ospemifene has been associated with improved sexual function.
- Transdermal testosterone therapy: Results show increase in satisfying sexual activity and sexual desire. Must weigh risks (hirsutism, acne, virilization, and cardiovascular complications) vs. benefits of use. Monitoring of testosterone levels to avoid supraphysiologic therapy is recommended.
- Sildenafil (evidence from RCTs for use in patients with neurodegenerative disease and antidepressant-induced FSD after traditional therapy has failed). Data are conflicting. Phosphodiesterase inhibitors may increase blood flow to the genitalia but generally appear to have little benefit in treating arousal disorders. Sildenafil has been helpful in patients with SSRI-induced sexual dysfunction.
- Bupropion 300 to 400 mg/day was shown to increase sexual arousal and orgasm completion in a recent trial. In addition, adjunctive treatment with bupropion significantly improved key aspects of sexual function in women with SSRI-induced sexual dysfunction.
- Flibanserin (Addyi): A nonhormonal treatment for HSDD. It is an agonist at serotonin 5-HT receptors and an antagonist at 5-HT_{2A} receptors. Its mechanism of action in treating HSDD is unknown. The recommended dose is

TABLE E2 Investigational Pharmacotherapy for Women's Sexual Dysfunctions

Sexual Dysfunction	Mechanisms of Dysfunction	Drug Type	Off-Label and Investigational Drugs	Comments
Sexual interest/ desire disorder	Loss of brain's arousability to sexual stimuli	Drugs with specific serotonin receptor subtype or agonist/ antagonist profile	Flibanserin: 5-HT1A agonist and 5-HT2A antagonist, weak partial D4 agonist	Flibanserin is now FDA approved for treatment of hypoactive sexual desire disorder
Subjective arousal disorder		Melanocortin agonists	Bremelanotide: Synthetic peptide, α-MSH analog agonist at MC1R, MC3R, MC4R	Small RCT showed benefit for women's arousal disorder with in-home use of nasal drug 45 min before sex. Sponsor has discontinued trials.
Combined arousal disorder		Dopamine agonists	Bupropion	One small 4-mo study in nondepressed premenopausal women showed increased arousability and sexual response, no increase in initial desire.
Genital arousal disorder: Estrogen deplete	Loss of genital vasocongestion in response to sexual stimulation	To provide local substrate for estrogen and testosterone intracrine synthesis	Local vaginal DHEA	Phase 3 RCT showed increased maturation of vaginal epithelium, lower pH, and sexual benefit in all domains of response from local vaginal DHEA for 12 wk.
		Selective tissue estrogenic activity regulator with androgenic and progestogenic properties	Tibolone	RCT of dysfunctional women showed tibolone marginally superior to 50 μg/140 μg combined transdermal estradiol/norethisterone. Major problem is distinguishing the subgroup of women with genital arousal disorder who have reduced genital vasocongestion. Small RCTs in diabetes and MS showed only modest benefit from sildenafil.
Genital arousal disorder despite estrogen replete	Loss of genital vasocongestion in response to sexual stimulation	To enhance the action of NO–PDEIs	Sildenafil, tadalafil, vardenafil	
Serotoninergic antidepressant–associated orgasmic disorder	Former orgasmic response absent or extremely delayed	PDEIs	Sildenafil	8-wk RCT with very strict entry criteria showed benefit from 50-100 mg sildenafil.

D4, Dopamine 4 receptor; *DHEA,* dehydroepiandrosterone; *5-HT,* serotonin; *ISSWSH,* International Society for the Study of Women's Sexual Health; *MC1R,* melanocortin-1 receptor; *MS,* multiple sclerosis; *MSH,* melanocyte-stimulating hormone; *NO,* nitric oxide; *PDEIs,* phosphodiesterase inhibitors; *RCTs,* randomized controlled trials.

100 mg once daily at bed time. Side effects include hypotension, syncope, and CNS depression. Consumption of alcohol increases risk of side effects and is contraindicated. It is mostly effective with approximately 10% of women reporting "much" or "very much" improvement in HSDD symptoms.

- Ospemifene: A selective estrogen receptor agonist/antagonist (SERM). Clinical trials demonstrated a significant improvement in sexual pain, arousal, and desire.
- Table E2 summarizes investigational pharmacotherapy for women's sexual dysfunctions.

REFERRAL

- Gynecologic referral for conditions that may be amenable to surgical therapy (e.g., pelvic floor disorders)
- Psychological referral for conditions (e.g., depression, abuse) that may benefit from counseling or psychotherapy
- Social services referrals for active abuse issues

RELATED CONTENT

Female Sexual Dysfunction (Patient Information)
Hypoactive Sexual Desire Disorder (Related Key Topic)

AUTHOR: **Anngene Anthony, MD, MPH, FAAFP**

SUGGESTED READINGS

American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Gynecology: ACOG Practice Bulletin No. 119: female sexual dysfunction, *Obstet Gynecol* 117:996, 2011.

Clayton AH et al: The International Society for the Study of Women's Sexual Health process of care for the management of hypoactive sexual desire disorder in women, *Mayo Clin Proc* 93:467-487, 2018.

Clayton AH et al: Female sexual dysfunction, *Med Clin North Am* 103:681-698, 2019.

Faubion SS et al: Sexual dysfunction in women: a practical approach, *Am Fam Phys* 92(4):281-288, 2015.

Lorenz T et al: Antidepressant-induced female sexual dysfunction, *Mayo Clin Proc* 91(8):1280-1286, 2016.

Taylor HS et al: Effects of oral vs transdermal estrogen therapy on sexual function in early postmenopause: ancillary study of the Kronos early estrogen prevention study (KEEPS), *JAMA Intern Med* 177(10):1471-1479, 2017.

BASIC INFORMATION

DEFINITION

Shaken baby syndrome is a potentially life-threatening and severe form of abuse in which an infant or child is violently shaken. Intracranial injury is caused by rapid acceleration and rotation of the cranium (sometimes associated with impact on a solid object which leads to rapid angular deceleration). The classic injury pattern associated with shaking includes diffuse subdural hemorrhage, retinal hemorrhages, and diffuse brain injury (Fig. E1). The diagnosis is often difficult to make because the clinical manifestations are nonspecific, perpetrators are unlikely to report a history of trauma, and there may be little to no external signs of injury.

SYNONYMS

Shaken infant syndrome
Abusive head trauma
Nonaccidental head injury

ICD-10CM CODES	
T74.1	Physical abuse
T74.4	Shaken infant syndrome, initial encounter
T74.4XXD	Shaken infant syndrome, subsequent encounter
T74.4XXS	Shaken infant syndrome, sequela

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Most common cause of death or serious neurologic injury resulting from child abuse. It is specific to infancy, when children have unique anatomic features. A population-based study conducted in the U.S. showed an incidence of abusive head trauma in children <2 yr of 17 per 100,000 persons with a higher incidence in the first yr of life compared to the second. Population-based studies in Europe show similar incidence in the first yr.

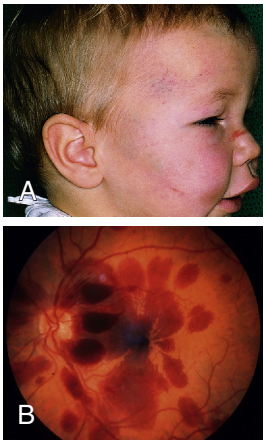

FIG. E1 Shaken baby syndrome. A, Facial bruising. **B,** Fundus hemorrhages involving different levels. (Courtesy R. Bates. From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

PEAK INCIDENCE: Shaken babies are typically younger than 1 yr; with median age of 4 mo.
PREVALENCE: ~25% of clinically diagnosed babies with shaken baby syndrome die, and ~80% of the remaining suffer lifelong neurologic damage.
PREDOMINANT SEX: About 60% of identified victims of shaking injury are male. Children of families who live at or below the poverty level are at an increased risk for these injuries as well as any type of child abuse.
RISK FACTORS: History of abuse, history of domestic violence, low socioeconomic status, perinatal illness, incessant crying, and family dysfunction. The perpetrators in 65% to 90% of cases are males and are most commonly the father.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

In several retrospective series, no history of a traumatic event was offered in 64% to 97% of cases. One study of 364 children with shaken baby syndrome found that 40% had no signs of external injury on initial evaluation. Majority will have an abnormal neurologic examination. Generally present with nonspecific symptoms (i.e., seizures, failure to thrive, vomiting associated with lethargy or drowsiness, decreased feeding, hypothermia, bradycardia, hypertension or hypotension, respiratory irregularities, apnea, coma, or death). Retinal and cranial hemorrhages and brain injury are hallmarks of the syndrome. Other signs of abuse such as skull fractures, occult fractures (particularly of ribs and long bone diaphysis), abdominal injury, and hearing loss, may be present.

ETIOLOGY

Angular deceleration forces cause primary parenchymal injury including traumatic axonal injury. Neuropathology and imaging techniques have established the cause of brain injury as hypoxic ischemic encephalopathy.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Head trauma from other etiology vs. infection vs. bleeding disorder vs. other etiology

WORKUP

Imaging of the brain, skeletal survey

LABORATORY TESTS

CBC, chemistry, coagulation study, lumbar puncture if meningitis is considered

IMAGING STUDIES

Initial study of unenhanced CT scan and skeletal survey. MRI should be done as follow up in patients with abnormal CT findings and is indicated for infants who are asymptomatic but require neuroimaging after finding noncranial injuries.

TREATMENT

Treatment focused on targeting specific injuries and also on prevention of future injuries.

NONPHARMACOLOGIC THERAPY

Admission to a hospital for observation

ACUTE GENERAL Rx

Supportive care and interventions as dictated by the clinical, laboratory, and imaging findings

CHRONIC Rx

Counseling, working with the child's school to optimize academic development

REFERRAL

Neurologist and neurosurgery (if needed)

PEARLS & CONSIDERATIONS

PREVENTION

The National Center on Shaken Baby Syndrome offers a prevention program. Additionally, researchers like Harvey Karp have suggested ideas.

PATIENT & FAMILY EDUCATION

Shaken baby syndrome can result in lifelong, irreversible injuries. Prevention is a key component. Infants crying most commonly leads to shaking. Therefore the National Center on Shaken Baby Syndrome offers a prevention program, the **Period of Purple Crying,** which seeks to help parents and other caregivers understand crying in normal infants. By defining and describing the sometimes inconsolable infant crying that can sometimes cause stress, anger, and frustration in parents and caregivers, the program hopes to educate and empower people to prevent abusive head trauma.

Another method that may help is one suggested by author Dr. Harvey Karp's "five S's":

1. Shushing: Use "white noise" or rhythmic sounds that mimic the constant whir of noise in the womb.
2. Side/stomach positioning: Place the baby on the left side to help digestion.
3. Sucking: Let the baby breast-feed or bottle-feed, or give the baby a pacifier or finger to suck on.
4. Swaddling: Wrap the baby up snugly in a blanket to help him or her feel more secure.
5. Swinging gently: Rock in a chair, use an infant swing, or take a car ride to help duplicate the constant motion the baby felt in the womb.

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Fujiwara T et al: Effectiveness of educational materials designed to change knowledge and behavior about crying and shaken baby syndrome: a replication of a randomized controlled trial in Japan, *Child Abuse Negl* 36(9):613-620, 2012.
National Center on Shaken Baby Syndrome: homepage. Available at: http://dontshake.org.

Sheehan Syndrome

BASIC INFORMATION

DEFINITION

Sheehan syndrome is a state of postpartum hypopituitarism resulting from infarction of the pituitary secondary to postpartum hemorrhage or shock. The enlarged pituitary gland in pregnancy is more susceptible to ischemia following hemorrhage and severe hypotension, causing partial or complete loss of the anterior pituitary hormones (adrenocorticotropic hormone [ACTH], follicle-stimulating hormone [FSH], luteinizing hormone [LH], growth hormone [GH], prolactin [PRL], thyroid-stimulating hormone [TSH]) and their target organ functions.

ICD-10CM CODES

E23.0 Hypopituitarism
E23.6 Other disorders of pituitary gland
E23.7 Disorder of pituitary gland, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Approximately 1 case in 10,000 deliveries. Actual frequency is not known but is thought to be higher in developing countries.
PREDOMINANT SEX: Affects only females
RISK FACTORS:

- Hypovolemic shock
- Type 1 (insulin-dependent) diabetes mellitus (secondary to microvascular disease)
- Sickle cell anemia (secondary to occlusion of the small vessels in the pituitary)
- Presence of small sella

ONSET OF SYMPTOMS: Symptoms may be acute or chronic. The severity of the disease depends on the extent of the damage to particular pituitary gland cell types. In the acute form, severe symptoms occur immediately postpartum, although this is rare. Chronic symptoms may appear months to yr after the initial insult.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Failure to lactate or difficulty with lactation
- Failure to resume menses after delivery
- Failure of axillary or pubic hair growth
- Diminished libido
- Infertility
- Skin depigmentation (including areola)
- Breast atrophy
- Vaginal atrophy causing pain with intercourse
- Superinvolution of the uterus
- Hypothyroidism (cold intolerance, dry skin, fatigue, weight gain, constipation)
- ACTH insufficiency (fatigue, chronic hypotension)
- Diabetes insipidus (rare)

ETIOLOGY

- Compromise of the blood supply to the low-pressure pituitary sinusoidal system may occur with postpartum hemorrhage or shock, resulting in pituitary infarct and/or necrosis.
- The extent of damage to pituitary determines the severity of resulting hormonal dysfunction.
- Antibodies against hypothalamic and/or pituitary cells have been reported, suggesting an autoimmune cause.
- Severity of postpartum hemorrhage does not always correlate with the presence of Sheehan syndrome. Although rare, Sheehan syndrome has also been reported with normal postpartum bleeding.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Postpartum autoimmune hypophysitis
- Chronic infections
- HIV
- Sarcoidosis
- Amyloidosis
- Rheumatoid disease
- Hemochromatosis
- Metastatic carcinoma
- Lymphocytic hypophysitis
- Pituitary tumor

WORKUP

- Target gland deficiency should be investigated by measuring levels of ACTH, FSH, LH, TSH (which may be normal or low), and T_4. Cortisol and estradiol (which may be low) should also be measured.
- Provocative testing of pituitary hormone reserves (e.g., metyrapone test, insulin tolerance test, and cosyntropin test): Normal, subnormal, or delayed responses may suggest the presence of islands of pituitary cells that no longer have the support of the hypothalamic-portal circulation.
- Measurement of insulin-like growth factor-1 to screen for GH deficiency: Subnormal levels suggest decreased GH.
- Impaired prolactin response to TRH or dopamine antagonist stimulation is frequently found.
- During pregnancy, adjustments must be made in interpreting both hormone levels and responses to various stimuli because of normal physiologic changes.

IMAGING STUDIES

- MRI of the pituitary:
  1. Early findings: Enlarged enhancing pituitary
  2. Late findings: Empty sella
  3. Rules out mass lesion
- CT scan of the pituitary when MRI is unavailable or contraindicated

TREATMENT

ACUTE GENERAL Rx

- Early identification and treatment are essential. Clinicians should have a high index of suspicion with any woman experiencing related symptoms following postpartum hemorrhage and/or shock.
- Acute form can be lethal, presenting with hypotension, tachycardia, failure to lactate, and hypoglycemia.
- IV corticosteroids and fluid replacement should be given initially.
- Diagnosis is confirmed with a full endocrinologic workup.
- Treatment involves replacement of deficient pituitary hormones such as corticosteroids, levothyroxine, estrogen, and growth hormone.

CHRONIC Rx

- With late-onset disease (symptoms of general hypopituitarism, such as oligomenorrhea or amenorrhea, vaginal atrophic changes, and loss of libido): A full endocrinologic workup and replacement of the appropriate hormones are needed.
- With symptoms of adrenal insufficiency: Corticosteroids should be given.
  1. A maintenance dose of cortisone acetate or prednisone may be given.
  2. Adrenal production of cortisol is not entirely dependent on ACTH; thus, replacement of mineralocorticoids is rarely necessary.
  3. Stress doses of glucocorticoids should be administered during surgery or during labor and delivery.

DISPOSITION

- Patients who receive early diagnosis and adequate hormonal replacement may expect favorable outcomes, including subsequent pregnancy.
- Central adrenal insufficiency is the primary cause of mortality in Sheehan syndrome.

REFERRAL

Patients should have yearly examinations by an endocrinologist.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hypopituitarism (Related Key Topic)

AUTHOR: **Emelia Argyropoulos Bachman, MD**

SUGGESTED READINGS

Karaca Z, Kelestimur F: Pregnancy and other pituitary disorders (including GH deficiency), *Best Practice Res Clin Endocrinol Metab* 25:897-910, 2011.

Kilicli F et al: Sheehan syndrome, *Gynecol Endocrinol* 29(4):292-295, 2013.

Shift Work Disorder

BASIC INFORMATION

DEFINITION

- Shift work refers to nonstandard work schedules, including permanent or intermittent night work, early morning work, and rotating schedules.
- Shift work disorder (SWD) is defined as the development of sleep disturbances and impairment of waking alertness and performance that some, but not all, individuals experience when adapting to shift work.

SYNONYMS

Circadian rhythm sleep disorder of shift work type
SWD

ICD-10CM CODE
G47.26. Circadian rhythm sleep disorder, shift work type

EPIDEMIOLOGY & DEMOGRAPHICS

- The disorder is caused by the patient working at a time when his/her circadian rhythm is trying to initiate and maintain sleep.
- It is not known why some people are more resilient to the effects of shift work than others.
- Most people will have some difficulty tolerating shift work and may benefit from the same interventions as those with more significant problems associated with SWD.

INCIDENCE: Not known
PEAK INCIDENCE: Not known
PREVALENCE:

- Prevalence of SWD is difficult to estimate because the boundary between a "normal response" to night work, and a diagnosable disorder is not sharp.
- Approximately 16% to 20% of the total work force is engaged in night-shift work. Survey data suggest that 5% to 10% of all shift workers experience clinically significant problems that would warrant a diagnosis of SWD.

PREDOMINANT SEX AND AGE: More prevalent in shift workers aged above 50 yr and worsens with passage of time if the work hours persist.
GENETICS: No known genetic contribution to SWD
RISK FACTORS: SWD is more likely in shift workers who have a morning-type disposition, sleep need greater than 8 hours, or strong competing social and/or personal demands (e.g., child rearing).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Diagnosis is based on history of the patient working outside 8:00 A.M. to 6:00 P.M. daytime window on a regular basis.
- Sleep logs and actigraphy (devices that estimate sleep/wake schedule based on movement) can be helpful but are not required for the diagnosis.

ETIOLOGY

SWD is understood to be a circadian rhythm disorder primarily caused by exogenously determined alterations in the timing of sleep and wakefulness rather than disturbances of the endogenous circadian rhythm itself.

DIAGNOSIS

Diagnostic criteria include persistent sleep disruption that leads to excessive sleepiness or difficulty sleeping or both. The sleep disturbance causes clinically significant distress or impairment and problems occur as a result of shift work schedule. Diagnostic criteria for SWD are summarized in Table E1.

DIFFERENTIAL DIAGNOSIS

- Normal variations in sleep with shift work (e.g., short-term or mild difficulties adjusting to new shift)
- Insomnia disorder (sleep problems not specifically linked to shift work)
- Other circadian rhythm disorder (e.g., jet lag, free running disorder)
- Sleep apnea (a common comorbidity that can make shift work more difficult)

WORKUP

- Ideally, SWD is assessed by clinical interview, supplemented with sleep logs and actigraphy. Actigraphy is the estimation of sleep and wake times based on movement. Several medical-grade devices are available that have been validated in relation to polysomnography (the gold standard for sleep assessment).
- Clinical interview should address difficulties with performance during night shift, problems sleeping during the day, and assess other sleep, psychiatric, and medical conditions that can co-occur with SWD and exacerbate symptoms (see Differential Diagnosis earlier).

LABORATORY TEST

Polysomnography (i.e., a comprehensive, in-lab sleep study) is usually not necessary in diagnosis or treatment of SWD but may be helpful for ruling out other sleep disorders with overlapping symptoms.

TREATMENT

SWD requires behavioral changes to minimize impact of scheduling on sleep and circadian biology. Pharmacological interventions must be carefully timed in order to be most beneficial. Table E2 summarizes clinical guidelines for assessment and management of SWD.

NONPHARMACOLOGIC THERAPY

- Planned naps before night shifts improve performance without compromising sleep after shift has ended. Planned naps during shifts can also be helpful when feasible, but workers can be impaired immediately after awakening.

TABLE E1 Diagnostic Criteria for Shift Work Disorder

***International Classification of Sleep Disorders* (ICSD3) Criteria: General Criteria for Any Circadian Rhythm Sleep-Wake Disorder**

A. A chronic or recurrent pattern of sleep-wake rhythm disruption due primarily to alteration of the endogenous circadian timing system or misalignment between the endogenous circadian rhythm and the sleep-wake schedule desired or required by the person's physical environment or social/work schedules.
B. The circadian rhythm disruption leads to insomnia symptoms, excessive sleepiness, or both.
C. The sleep and wake disturbances cause clinically significant distress or impairment in mental, physical, social, occupational, educational, or other important areas of functioning.

Specific Criteria for Circadian Rhythm Sleep-Wake Disorder, Shift Work Disorder (ICD-9-CM code: 327.36)*

A. There is a report of insomnia and/or excessive sleepiness, accompanied by a reduction of total sleep time, which is associated with a recurring work schedule that overlaps the usual time for sleep.
B. The symptoms have been present and associated with the shift work schedule for at least 3 mo.
C. Sleep log and actigraphy monitoring (whenever possible and preferably with concurrent light exposure measurement) for at least 14 days (work and free days) demonstrate a disturbed sleep and wake pattern.
D. The sleep and/or wake disturbance are not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, poor sleep hygiene, or substance use disorder.

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition: DSM-5*: Diagnostic Criteria for Circadian Rhythm Sleep Disorder (307.45)

A. A persistent or recurrent pattern of sleep disruption that is due primarily to an alteration of the circadian system or to a misalignment between the endogenous circadian rhythm and the sleep-wake schedule required by the person's physical environment or social or professional schedule.
B. The sleep disruption leads to excessive sleepiness or insomnia, or both.
C. The sleep disturbance causes clinically significant distress or impairment in social, occupational, and other important areas of functioning.

Specify Type:

Shift work type: Insomnia during the major sleep period and/or excessive sleepiness (including inadvertent sleep) during the major awake period associated with a shift work schedule (i.e., recurring unconventional work hours).

*ICD-10CM code: G47.26 circadian rhythm sleep-wake disorder, shift work type.
ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification.
From Kryger M et al: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.

TABLE E2 Clinical Guidelines for Assessment and Management of Shift Work Disorder

Assessment

I. Determine circadian misalignment (sleep diaries and actigraphy with concurrent light exposure).
II. Assess sleep disturbance.
  A. Determine difficulty falling asleep, staying asleep, or having nonrestorative sleep (both during daytime and nighttime sleeps).
  B. Measure degree of alertness.
  C. Assess falling asleep during inappropriate circumstances or times (using Epworth Sleepiness Scale [ESS]), with special attention to drowsy driving.
  D. Determine important job-related factors: Duration of commute after shift, number of consecutive shifts, type of shift, time between shifts.
III. Determine impact on social and domestic responsibilities.[1]

Management[2]

I. Shift workers should have regular physical examinations with attention to psychological (e.g., depression), gastrointestinal, cardiovascular, and potential cancer risks associated with shift work.[2]
  A. Sleep-related comorbidity: Determine risk of sleep-disordered breathing, restless legs syndrome, or other potential sleep disorder.
  B. Other comorbidity: Identify medical or psychiatric disorders that may contribute to the symptoms of insomnia or excessive sleepiness.
II. Determine if removal from shift work is appropriate or practically feasible. If patient meets criteria for a diagnosis of shift work disorder, cessation of the shift work schedule should be the first option discussed with the patient.
III. Determine patient-specific therapeutic approach.
  A. Circadian adaptation
    1. Consider individual difference factors (e.g., age, phase preference).
    2. Consider compromise phase position (e.g., partial phase delay using bright light during first half of night and increased darkness during daytime).
    3. *Night workers*: On days off, adopt a late sleep schedule (i.e., bedtime of 3:00 to 4:00 A.M.).
  B. Symptom management
    1. Insomnia
      a. Good sleep behaviors
        i. Target inappropriate sleep behaviors and encourage use of eye mask, ear plugs, and light-blocking shades during daytime sleep.
      b. Sleep maintenance a primary concern
        i. Consider intermediate-acting hypnotic (half-life of 5 to 8 hours).
        ii. Consider melatonin treatment for daytime sleep (~3 mg).
      c. Sleep initiation problems
        i. Consider short-acting hypnotic.
      d. Sleep problems on days off
        i. Consider fixed sleep-wake schedule and consider anchor sleep.
        ii. Excessive sleepiness (i.e., ESS score <10)
    2. Address sleep disturbance if present.
      a. Consider wake-enhancing medication before shift (e.g., modafinil, armodafinil) or off-label stimulants (e.g., amphetamine, methylphenidate).
      b. Prophylactic nap before work shift is recommended.
      c. Judicious use of brief to moderate-length naps (30 to 60 min), with recognition of risk of sleep inertia (consider prenap caffeine to reduce sleep inertia).
      d. Consider combined treatment strategies during the work shift (alerting medications, bright light, anchor sleep, and naps).
IV. Address additional work, social, and domestic factors.
  A. Social/family/psychological: Improve balance between family/social, work, and sleep time and treat psychosocial stress, depression, or marital discord if present,[1] educate patient's family regarding shift worker's need of protected time for sleep.
  B. Health and safety: Promote improved healthy eating habits with respect to regularity and timing relative to the major sleep period (not within 2 to 4 hours of bedtime), reduce inappropriate substance use, increase exercise at appropriate times (not within 2 to 4 hours of bedtime), educate on risks of drowsy driving and critical times of performance vulnerability.
  C. Work-related: Reduce number of consecutive shifts (<4),[1] reduce shift duration (<12 hours), use clockwise rotation,[3] ensure adequate time between shifts (>11 hours),[1] move heavy workload outside circadian nadir (4:00 to 7:00 A.M.), address commute time (longer = greater accident risk), move to day or evening shift,[4] consider incorporation of a shift work awareness program.[5]

[1]Knauth P, Hornberger S: Preventive and compensatory measures for shift workers, *Soc Occup Med* 53:109-116, 2003.
[2]Costa G: Guidelines for the medical surveillance of shift workers, *Scand J Work Environ Health* 24(Suppl. 3):151-155, 1998.
[3]Monk TH: What can the chronobiologist do to help the shift worker? *J Biol Rhythms* 15:86-94, 2000.
[4]Pilcher JJ et al: Differential effects of permanent and rotating shifts on self-report sleep length: a meta-analytic review, *Sleep* 23:155-163, 2000.
[5]Monk TH, Folkard S: *Making shift work tolerable,* Boca Raton, 1992, CRC Press.
From Kryger M et al: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.

- Bright light during night shift work improves alertness. Both short- and long-duration light exposure has been shown to be helpful relative to normal lighting.
- Bright light should be avoided in the morning when feasible to protect daytime sleep. Darkened glasses can be helpful provided that they do not compromise driving ability (if shift worker must drive home after shift).
- Daytime sleep environment should be protected from both light and noise. Sleep masks, black-out curtains, ear plugs, and noise machines can be helpful.
- Circadian adaptation during jet travel is illustrated in Fig. E1.

ACUTE GENERAL Rx

- Wake-promoting medications such as modafinil/armodafinil, caffeine, and amphetamine have been shown to improve performance during the night shift. Modafinil and caffeine have established safety records and are generally considered as first-line treatments. Ideally, medications would be administered at times and doses where daytime sleep after the shift work is not affected.
- Hypnotic medications can be helpful for promoting daytime sleep after night shift work. Carryover sedation must be evaluated to ensure performance during night shift work is not impaired. Specific agents that have been tested include triazolam, temazepam, and zopiclone. Evidence is stronger for promoting sleep during day than improving waking performance during night shift work.
- Melatonin administered before daytime sleep (after night shift work) has been shown to be effective. Melatonin is not regulated by the FDA, and so it is important to avoid brands with poor performance in independent laboratory tests. Fig. E2 illustrates using light and melatonin to phase shift the internal biologic time.

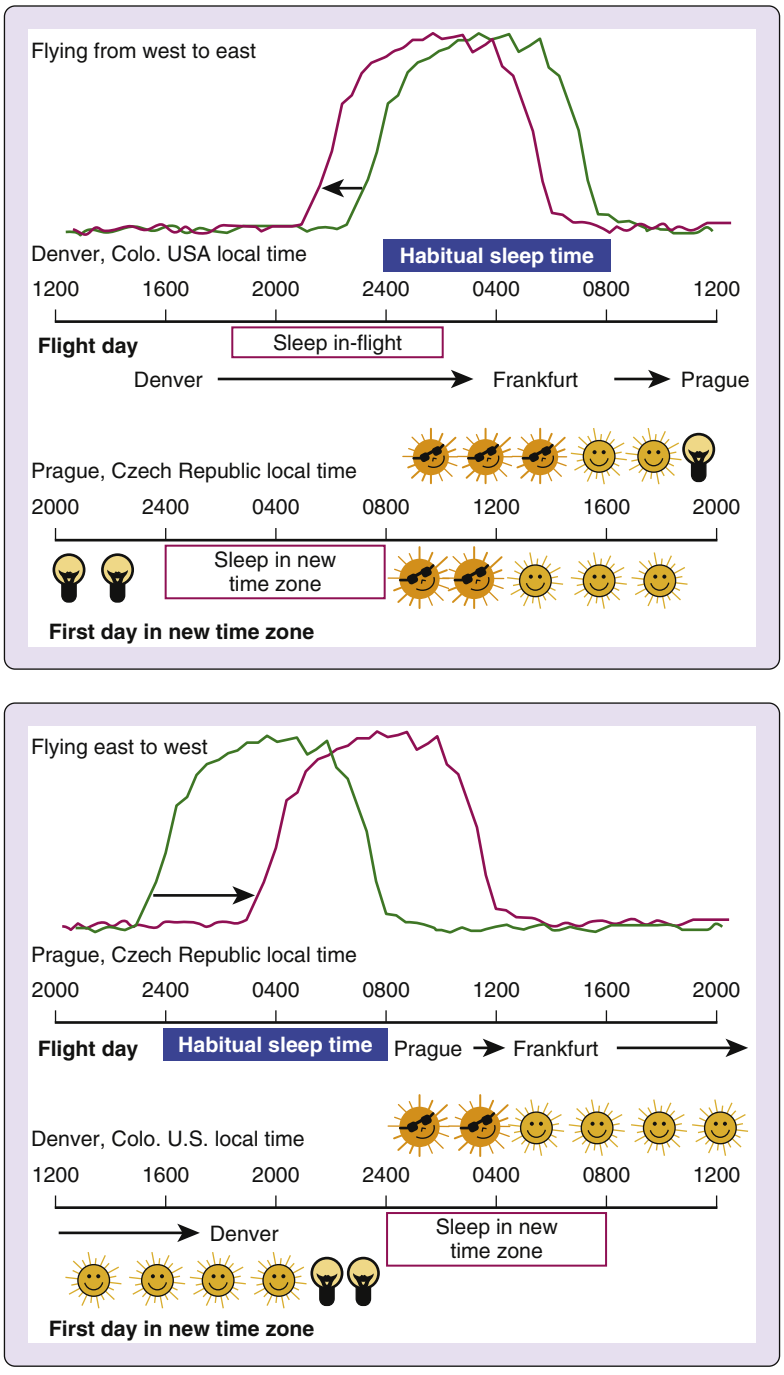

FIG. E1 Circadian adaptation during jet travel. *Top:* When traveling eastward, the jet traveler needs to advance the timing of his or her sleep schedule as well as the phase of the internal circadian clock so that both occur earlier. In the current example of a trip from Denver, Colorado, to Prague, Czech Republic, the primary plane flight to Frankfurt *(long black arrows)* occurs during the beginning of the biologic night, when endogenous melatonin levels are high *(green line; top panel).* The traveler should sleep as much as possible on the plane flight to reduce the negative impact of sleep deprivation during jet travel. Exogenous melatonin taken shortly after boarding the plane may help the traveler fall asleep earlier than normal when endogenous melatonin levels are low. In this example, the traveler spends several hours in Frankfurt before the flight connection to Prague. Light exposure during most of the biologic night will induce a westward phase delay, opposite to what is needed for an eastward shift; accordingly, the traveler should avoid exposure to bright light *(sun with sunglasses)* and wear an eye mask or sunglasses until after the habitual time of awakening in the home time zone. Subsequent exposure to bright light *(sun without sunglasses and light bulb)* will facilitate the eastward phase advance of the traveler's circadian clock *(red line; top panel).* Sleep timing should be consistent with the local time zone in Prague, and melatonin may again help phase shift the clock and promote sleep onset if taken when endogenous melatonin levels are low. The next day, the traveler should at first continue to avoid exposure to bright light. Each day, the time of exposure to bright light can be moved earlier by 1 to 2 hours per day. *Bottom:* When traveling westward, the jet traveler needs to delay the timing of his or her sleep schedule as well as the phase of the internal circadian clock *(green line; bottom panel)* so that both occur later. In the example of a trip from Prague to Denver, plane flights occur across the biologic day when endogenous melatonin levels are low, and the traveler should remain awake for much of the trip, assuming that sleep was adequate before travel. Caffeine and/or a nap can help to support subsequent wakefulness. Exposure to bright light should occur across the entire plane flight and until just before bedtime in the new time zone, to facilitate a westward phase delay *(red line; bottom panel).* (From Kryger M et al: *Principles and practice of sleep medicine*, ed 6, Philadelphia, 2017, Elsevier.)

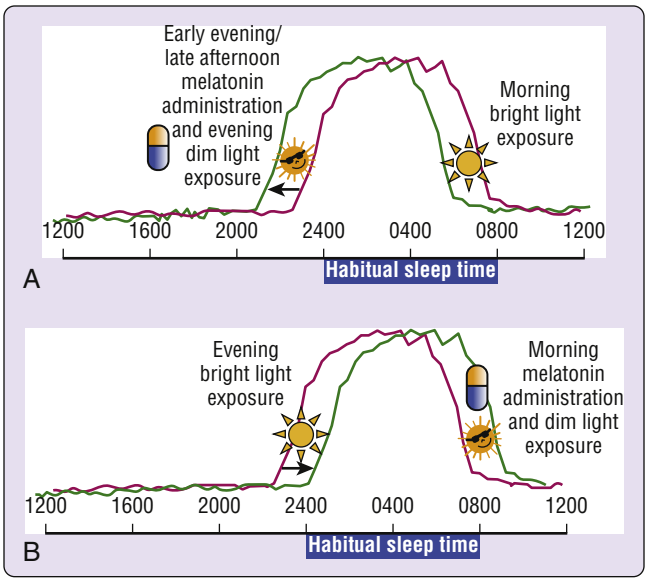

FIG. E2 Using light and melatonin to phase shift the internal biologic time. A, When the traveler is entrained to local time, light exposure during the morning and melatonin ingestion in the afternoon will induce an eastward phase advance shift of the internal circadian clock. *Red line* shows initial melatonin rhythm and *green line* shows advanced melatonin rhythm after treatment. **B,** Light exposure during the evening and melatonin administration in the morning will induce a westward phase delay shift of the internal circadian clock. *Red line* shows initial melatonin rhythm and *green line* shows delayed melatonin rhythm after treatment. Adjustment to eastward travel should include exposure to dim light or darkness in the evening. This can be achieved by wearing sunglasses if the sun has not set and by turning down the lights in the house. Adjustment to westward travel should include exposure to dim light or darkness in the morning. Administration of melatonin when the jet traveler is required to be awake (e.g., for work or driving) should be avoided, because melatonin has been reported to impair performance. (From Kryger M et al: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.)

CHRONIC Rx

Patients with chronic difficulty adapting to shift work despite adequate treatment may need to find other work. Many shift work jobs can be dangerous if completed by individuals who are impaired by sleepiness.

COMPLEMENTARY & ALTERNATIVE MEDICINE

No evidence-based recommendations currently available

REFERRAL

- Sleep medicine specialists in pulmonology, neurology, or psychiatry generally have expertise to treat SWD.
- Psychologists specializing in behavioral sleep medicine can be consulted (where available).

PEARLS & CONSIDERATIONS

COMMENTS

- Most people who work night shifts will experience difficulties and can benefit from treatment strategies for SWD.
- All shift workers should be educated about dangers associated with working while impaired by sleep deprivation.
- Co-occurring sleep disorders, especially sleep apnea, are common and can exacerbate symptoms of SWD. All shift workers should be screened for sleep disorders.
- When possible, inconsistent shifts and rotating schedules should be avoided.
- Treatment strategies are designed around delaying circadian rhythms as much as possible, then providing countermeasures for fatigue during shift, and protecting or promoting sleep during the day.

PREVENTION

SWD can be prevented by avoiding night shift work. However, many essential services require night shift workers. Early detection and treatment for mild SWD is essential. Those with more severe SWD may need to consider working earlier shifts.

PATIENT & FAMILY EDUCATION

The National Sleep Foundation (sleepfoundation.org) provides high-quality information on SWD and ways to manage symptoms.

RELATED TOPIC

Insomnia (Related Key Topic)

AUTHOR: **Jared D. Minkel, PhD**

Shigellosis PTG

BASIC INFORMATION

DEFINITION

Shigellosis is an inflammatory disease of the bowel caused by one of four species of *Shigella.* It is the third most common cause of diarrhea in the United States after *Salmonella* and *Campylobacter* and the most common cause of bacillary dysentery in the United States.

SYNONYM

Bacillary dysentery

ICD-10CM CODES

A03.9	Shigellosis, unspecified
A03.0	Shigellosis due to *Shigella dysenteriae*
A03.1	Shigellosis due to *Shigella flexneri*
A03.2	Shigellosis due to *Shigella boydii*
A03.3	Shigellosis due to *Shigella sonnei*
A03.8	Other shigellosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 6.59 cases per 100,000 population with approximately 450,000 cases/yr

PREDOMINANT SEX: Male homosexuals are at increased risk.

PREDOMINANT AGE: Shigellosis predominantly affects children (Box E1), with 28 cases per 100,000 population in children <4 yr old and 25.67 cases per 100,000 population in children aged 4 to 11.

PEAK INCIDENCE: Summer

GENETICS: Neonatal infection: Rare but severe

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Possibly asymptomatic, but incubation period can range from 1 to 7 days with an average of 3 days
- Mild illness that is usually self-limited, resolving in a few days
- High fever
- Watery diarrhea. Dysentery (abdominal cramps, tenesmus, and numerous, small-volume stools with blood, mucus, and pus)
- Descending intestinal tract illness, reflecting infection of small bowel first and then the colon
- Severe disease is more common in children and elderly and outside of the U.S.

BOX E1 Risk Factors for Severe Disease

Infants, and adults >50 yr
Children who are not breastfed
Children recovering from measles
Patients with HIV
Malnourished children and adults
Any patient who develops dehydration, unconsciousness, hypothermia, or hyperthermia, or has a history of convulsion

From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

- Complications of severe illness (Box E2):
  1. Seizures
  2. Megacolon
  3. Intestinal perforation
  4. Death
- Extraintestinal manifestations are uncommon (reactive arthritis in up to 3% of patients)
- Bacteremia is more common in children; in adults it has been described in patients with AIDS, the elderly, and diabetics
- Hemolytic-uremic syndrome (HUS): Can be caused by *S. dysenteriae*
- Reactive arthritis, sometimes as part of Reiter syndrome following *S. flexneri* infection

ETIOLOGY

- *Shigella:* Gram-negative rod bacteria that are less susceptible to stomach acid and thus as few as 10 to 100 bacteria can cause disease. The bacteria invade colonic tissue and cause inflammation.
  1. *S. flexneri.*
  2. *S. dysenteriae.*
  3. *S. sonnei.*
  4. *S. boydii.*
- *S. sonnei* is the most commonly isolated species in the United States (over 75% of cases), and it usually causes a mild, watery diarrhea.
- Direct person-to-person transmission by consumption of contaminated food or water is thought to be the most common route. Outbreaks among men who have sex with men have occurred because of direct or indirect oral-anal contact.
- Contaminated food or water may transmit disease.
- Outbreaks have occurred in day care centers, a community wading pool frequented by toddlers, and residential institutions.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- May mimic other bacterial gastroenteritis, such as *Clostridium difficile, Salmonella, Campylobacter,* and *Yersinia.*
- Dysentery can also be caused by *Entamoeba histolytica.*
- Bloody diarrhea may resemble disease caused by invasive *E. coli* (IEC).
- Hemolytic-uremic syndrome caused by enterohemorrhagic *E. coli* (O157:H7).

LABORATORY TESTS

- The diagnosis is established by bacterial stool culture.
- Stool should be cultured from fresh samples, because the yield is increased by processing the specimen soon after passage. The best yield is from the mucoid part of the stool.
- Serology is available but rarely useful.
- Polymerase chain reaction (PCR) is available but due to cost used mainly for outbreak investigations.
- Fecal leukocyte preparation may show WBCs.
- Total WBCs may be low, normal, or high. Leukemoid reactions can occur in children.
- Blood cultures should be obtained in patients with severe disease or sepsis syndromes.

IMAGING STUDIES

Abdominal radiographs may suggest megacolon or perforation in rare, severe cases.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Adequate hydration
- Electrolyte replacement

BOX E2 Complications of Shigellosis

Abdominal
- Persistent diarrhea
- Postdysenteric irritable bowel syndrome
- Ileus, toxic megacolon, intestinal perforation
- Protein-losing enteropathy, malnutrition
- Surgical complications: Intestinal perforation and obstruction, appendicitis, intraabdominal abscesses

Neurologic
- Seizures
- Headache, lethargy, disorientation, hallucinations
- Coma
- Severe toxin encephalopathy or ekiri syndrome

Bacteremia
- In malnourished children, young infants, and HIV-AIDS patients

Hemolytic-Uremic Syndrome
- Only with *Shigella dysenteriae* serotype 1

Urogenital
- Vulvovaginitis, urinary tract infections

Other
- Conjunctivitis, keratitis, corneal ulcers
- Reactive arthritis
- Reiter syndrome
- Hepatitis
- Myocarditis

From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

ACUTE GENERAL Rx

Antibiotics recommended in all patients with positive stool cultures, severe illness, immunocompromised status:

- To shorten course of illness.
- To limit transmission of illness.
- For adults: Pending susceptibilities, ciprofloxacin 750 mg PO bid for 3 days or levofloxacin 500 to 750 mg q day for 3 days should be used. An alternative is azithromycin 500 mg q day for 3 days.
- For children: IV ceftriaxone (50 mg/kg/day) for 5 days in cases of severe disease. For oral therapy, can use cefixime: 8 mg/kg/day as single daily dose or divided q12h for 5 days *or* azithromycin: 10 mg/kg/day in a single daily dose for 3 days. A short course of an oral quinolone can also be used safely although they are not approved for children.

DISPOSITION

- Most disease is self-limited and resolves without treatment.
- Severe illness may be fatal.

REFERRAL

For severe illness or complications

PEARLS & CONSIDERATIONS

COMMENTS

- Shigella is one cause of "gay bowel syndrome."
- Illness is worsened by agents that decrease intestinal motility.
- Food handlers, child care providers, and health care workers should have a negative stool culture documented following treatment.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Shigellosis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Dekker JP, Frank KM: Salmonella, Shigella, and Yersinia, *Clin Lab Med* 35:225-246, 2015.

DuPont HL: Acute infectious diarrhea in immunocompetent adults, *N Engl J Med* 370:1532-1540, 2014.

Kotloff KL et al: Shigellosis, *Lancet* 391:801-812, 2018.

Short Bowel Syndrome ALG PTG

BASIC INFORMATION

DEFINITION

Short bowel syndrome (SBS) is a malabsorption syndrome that results from extensive small intestinal resection or congenital causes (Table 1).

SYNONYMS

Short bowel
SBS

ICD-10CM CODE
K91.2 Postsurgical malabsorption, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

- Parallels Crohn disease (see "Crohn Disease" in Section I), which is the most common cause of the syndrome in adults.
- In children, two thirds of short bowels are related to congenital abnormalities (intestinal atresia, gastroschisis, volvulus, aganglionosis) and one third are related to necrotizing enterocolitis.
- Prevalence: 10,000 to 20,000 cases are estimated to exist in the U.S.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Diarrhea and steatorrhea
- Weight loss
- Anemia related to iron or vitamin B_{12} absorption
- Bleeding diathesis related to vitamin K malabsorption
- Osteoporosis/osteomalacia related to vitamin D and calcium malabsorption
- Hyponatremia, hypokalemia
- Hypovolemia
- Other macronutrient or micronutrient deficiency states

ETIOLOGY

- Extensive bowel resection for treatment of the conditions mentioned previously (see "Epidemiology"). SBS typically does not occur until less than 200 cm of healthy small intestine remains. Risk for SBS is decreased if colon is intact.
- Congenital.
- Box 1 summarizes causes of short bowel syndrome.

The human intestine is 3 to 8 m in length. Removal of up to half of the small intestine produces no disruption in nutrient absorption, and most patients can maintain nutritional balance on oral feeding if they have more than 100 cm (3 ft) of jejunum. Similarly, 100 cm of intact jejunum can maintain a normal water, sodium, and potassium balance under normal circumstances. The presence of an intact colon can compensate for some small intestine loss.

Site-specific functions (Fig. 1):

- Calcium, magnesium, phosphorus, iron, and vitamins are absorbed in the duodenum and proximal jejunum.
- Vitamin B_{12} and bile acids are absorbed in the ileum. The resection of more than 60 cm of ileum results in vitamin B_{12} malabsorption. The loss of more than 100 cm results in fat malabsorption (from the loss of bile acids).
- The loss of gastrointestinal endocrine hormones can affect intestinal motility.
- Intestinal bacterial overgrowth may also occur, especially if the ileocecal valve is lost.

BOX 1 Causes of Short Bowel Syndrome (SBS) and Intestinal Failure in Adults and Children

Adults
Catastrophic vascular accidents:
  Superior mesenteric arterial embolism
  Superior mesenteric arterial thrombosis
  Superior mesenteric venous thrombosis
Chronic intestinal pseudoobstruction
Intestinal resection for tumor or trauma
Midgut volvulus
Multiple intestinal resections for Crohn disease
Radiation enteritis
Refractory sprue
Scleroderma and mixed connective tissue disease

Children
Congenital villus atrophy
Extensive aganglionosis
Gastroschisis
Jejunal or ileal atresia
*Necrotizing enterocolitis

*Functional SBS can also occur in conditions associated with severe malabsorption and intact bowel length.

From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

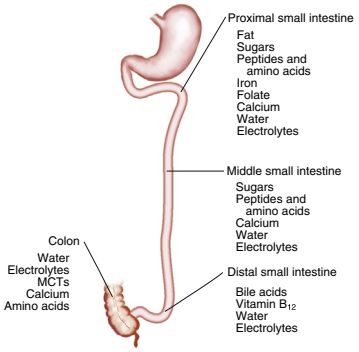

FIG. 1 Specific areas of absorption of dietary constituents and secretions in the small intestine and colon. Macronutrients and micronutrients are absorbed predominantly in the proximal jejunum. Bile acids and vitamin B_{12} (cobalamin) are absorbed only in the ileum. Electrolytes and water are absorbed in both the small and large intestine. Medium-chain triglycerides *(MCTs),* calcium, and some amino acids can be absorbed in the colon. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

- Macronutrient requirements in patients with short bowel syndrome are summarized in Table 2.

DIAGNOSIS

Presence of macronutrient and/or micronutrient loss in a patient with a known history of bowel resection. Daily stromal or fecal losses of electrolytes, minerals, and trace elements in SBS are summarized in Table 1.

DIFFERENTIAL DIAGNOSIS

Because the history of significant bowel resection is typically known, there is no differential diagnosis. If that history is not known, all causes of weight loss, malabsorption, and diarrhea must be considered.

TREATMENT

Extensive small bowel resection with colectomy (<100 cm of jejunum):

- Rx: Long-term total parenteral nutrition (TPN). Some patients can switch to oral intake after 1 to 2 yr of TPN. In jejunostomy patients, excessive fluid loss can be reduced with H_2 blockers, proton pump inhibitors, or octreotide. Micronutrients are supplemented.

Extensive small bowel resection with partial colectomy (usually patients with Crohn disease):

- Rx: Oral intake alone is possible in all patients with >100 cm of jejunum. In addition to vitamin B_{12} deficiency, these patients often have diarrhea. Consider lactose malabsorption and bacterial overgrowth treated, respectively, with lactose restriction and antibiotics (tetracycline 250 mg tid or metronidazole 500 mg tid for 2 wk). Nonspecific antidiarrheal agents may also be indicated (e.g., Imodium or codeine). The patient must be monitored for micronutrient losses.
- Table 3 and Fig. 2 summarize management strategies for SBS. Intestinal transplantation is performed mostly in children at selective centers.
- Therapeutic agents used to decrease intestinal transit and diarrheal volume are summarized in Table E4.
- FDA-approved medications for SBS in patients receiving nutritional support are:
  1. Recombinant growth hormone somatropin (Zorbtive): Effective in increasing weight and reducing parenteral nutrition volume. These effects do not persist when the drug is stopped.
  2. Teduglutide (Gattex), a recombinant DNA analog of glucagon-like peptide-2. It promotes mucosal growth in the small bowel through stimulation of crypt cell proliferation and inhibition of enterocyte apoptosis. This drug may have to be continued indefinitely for effects to persist.

COMPLICATIONS

- Oxalate kidney stones
- Cholesterol gallstones
- D-Lactic acidosis

TABLE 1 Daily Stomal or Fecal Losses of Electrolytes, Minerals, and Trace Elements in Severe Short Bowel Syndrome*

Component	Amount Lost
Sodium	90-100 mEq/L
Potassium	10-20 mEq/L
Calcium	772 (591-950) mg/day
Magnesium	328 (263-419) mg/day
Iron	11 (7-15) mg/day
Zinc	12 (10-14) mg/day
Copper	1.5 (0.5-2.3) mg/day

*For sodium and potassium, the average concentration per liter of stomal effluent is given. Values for minerals and trace elements are mean 24-hour losses, with the range in parentheses.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE 2 Macronutrient Requirements in Patients with Short Bowel Syndrome

Colon Present	Colon Absent
Carbohydrate	
Complex carbohydrates/starches	Variable types
30-35 kcal/kg per day	30-35 kcal/kg per day
Soluble fiber	
Fat	
MCT/LCT	LCT
20%-30% of caloric intake	20%-30% of caloric intake
Protein	
Intact protein	Intact protein
1.0-1.5 g/kg per day	1.0-1.5 g/kg per day

LCT, Long-chain triglycerides; *MCT,* medium-chain triglycerides.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

TABLE 3 Management Strategies for Short Bowel Syndrome

1. Acute phase
   a. Treat postoperative complications
   b. Maintain full support via the parenteral route
   c. Initiate low-rate trophic enteral feeds
   d. Document amount and site of remaining bowel and underlying disease
2. Early adaptation (up to 1 yr postsurgery)
   a. Increase enteral nutrition to tolerance; supplement with glutamine
   b. Achieve permanent parenteral access, if indicated
   c. Maximize antiperistaltic agents
   d. Octreotide for high-output ostomy or fistula
   e. Dietary counseling
   f. Clinical trials of trophic growth factors
3. Long-term adaptation (>1 yr postsurgery)
   a. Recruit bypassed bowel
   b. Bowel-lengthening procedure (Bianchi or STEP)
   c. Monitor for development of TPN-associated complications, and refer for transplant before recurrent sepsis, thrombosis, or end-stage liver disease

STEP, Serial transverse enteroplasty; *TPN,* total parenteral nutrition.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

PROGNOSIS

- Directly dependent on the extent of the bowel resection and in the case of Crohn disease by the underlying illness.
- Whether the colon remains in continuity with the small bowel is an important factor in the patient's ability to adapt after significant small bowel resection.

RELATED CONTENT

Short Bowel Syndrome (Patient Information)
Malabsorption (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

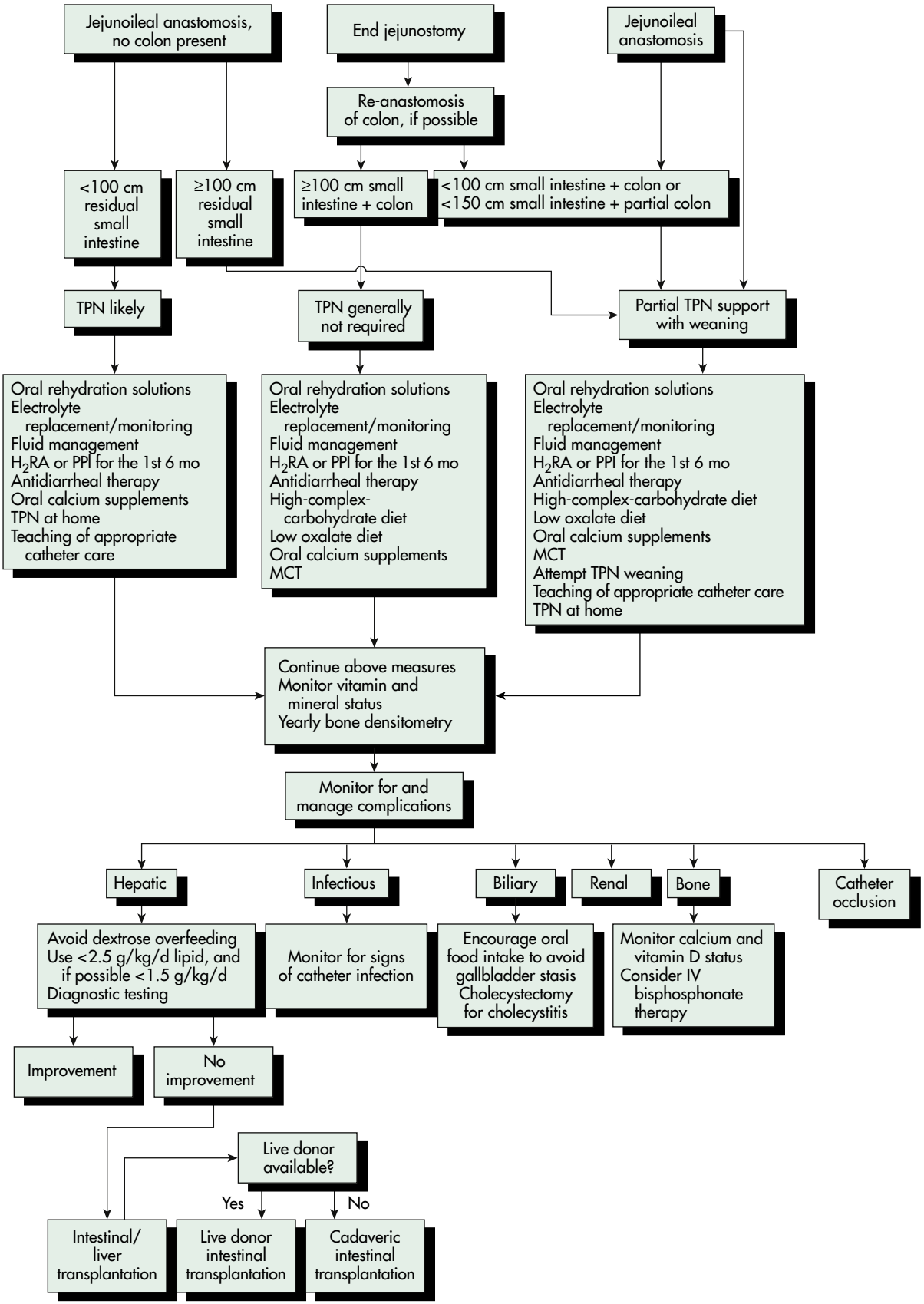

FIG. 2 Algorithm for management of the patient with short bowel syndrome. *H2RA,* Histamine 2 receptor antagonist; *IV,* intravenous; *MCT,* medium-chain triglycerides; *PPI,* proton pump inhibitor; *TPN,* total parenteral nutrition. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

TABLE E4 Therapeutic Agents Used to Decrease Intestinal Transit and Diarrheal Volume in Patients with Short Bowel Syndrome (SBS)

Agent	Dosage
Loperamide*	4-6 mg 4× daily
Diphenoxylate-atropine*	2.5-5 mg 4× daily
Codeine phosphate*	15-60 mg 2-4× daily
Tincture of opium	0.6 ml (2.5 mg) 2-4× daily
Ranitidine†	300 mg twice daily
Omeprazole‡	40 mg twice daily
Octreotide	50-100 μg SC twice daily
Clonidine	0.3 mg transcutaneous patch once weekly

*The antidiarrheal agents loperamide, diphenoxylate-atropine, and codeine phosphate are given 1 hr before meals and at bedtime. Dosages may be increased over those recommended because of incomplete absorption in patients with SBS.
†Cimetidine, famotidine, and nizatidine are alternatives.
‡Esomeprazole, lansoprazole, rabeprazole, and pantoprazole are alternatives.
SC, subcutaneously.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

BASIC INFORMATION

DEFINITION

Short QT syndrome (SQTS) is a genetically inherited disorder of cardiac repolarization characterized by a severely shortened QT interval on the ECG, leading to atrial and ventricular arrhythmias and sudden cardiac death in affected individuals. This is a primary electrical disorder and patients have structurally normal hearts.

SYNONYM

SQTS

ICD-10CM CODE
I45.89 Other specified conduction disorders

EPIDEMIOLOGY AND DEMOGRAPHICS

- The disease is a relative new entity, first documented in 2000. In most (but not all) cases of SQTS, the QT or QTc (correct QT interval) has been <360 ms; however, there are many individuals with that QT interval who are clinically unaffected. Although poorly defined, the estimated prevalence of short QTc ≤340 ms is estimated to be 5 in 10,000 in persons less than 21 yr of age. Males are more commonly affected.
- Genetics: The disease is genetically heterogeneous and transmitted in an autosomal dominant fashion. Different genes encoding various cardiac ion channels have been attributed to SQTS, including a carnitine transporter and a chloride-bicarbonate anion exchanger. Based on this, eight SQTS have been described, from SQTS 1 to SQTS 8. SQT 1 is the most common variant described, due to a mutation in the cardiac ion channel KCNH2(HERG). SQTS 2 has been described to be sporadic, while the others are familial in nature.

PHYSICAL FINDINGS AND CLINICAL PRESENTATION

- Seen across all age groups, though most patients are children or young adults.
- Syncope and cardiac arrest are the most common presenting features. Syncope is likely due to ventricular arrhythmias. Sudden death can happen with exercise as well as at rest. Cardiac arrest is often the first manifestation of the disease with a peak incidence in the first yr of life and second peak between 20 and 40 yr of age; overall risk cardiac arrest is 40% before age 41.
- Atrial fibrillation and flutter are well described as being part of the syndrome.
- A significant percentage of patients are asymptomatic.

ETIOLOGY

- Cardiac repolarization abnormality
- A total of 22 different mutations have been found in 9 different genes, 15 in single families. At present, the chance of finding a causative mutation in a family with SQTS is approximately 20%. Mutations cause an increase in net outward current from either a reduction in inward depolarizing currents INa or ICa or augmentation of outward repolarizing currents I to I K1, I K-ATP, I ACh, I Kr or I Ks as well as defects in Cl/HCO_3 exchanger. The resultant shortening of the action potential causes a shortening of the effective refractory period, with subsequent increased susceptibility of both atrial and ventricular muscle to premature depolarizations that lead to AF and VF
- Acquired causes—see "Differential Diagnosis"

DIAGNOSIS

- The 2013 HRS guidelines define SQTS as follows:
  1. SQTS is diagnosed in the presence of a QTc ≤330 ms.
  2. SQTS can be diagnosed in the presence of a QTc ≤360 ms and one or more of the following: a pathogenic mutation, family history of SQTS, family history of sudden death at age ≤40, survival of a ventricular tachycardia/ventricular fibrillation episode in the absence of heart disease.
  3. Notably, more recent studies suggest the use of somewhat more liberal cutoffs of 340 ms as standalone and 370 ms in combination with additional risk factors.
- A proposed scoring system (Table 1) for the diagnosis of SQTS incorporates the above criteria but has not yet been fully endorsed by the current guidelines.
- The differential diagnosis of a short QT includes various conditions such as hyperkalemia, hypercalcemia, acidosis, digitalis toxicity, effect of acetylcholine or epinephrine, sinus tachycardia, or hyperthermia. All these are possible causes of an acquired short QT interval that must be ruled out before a diagnosis of SQTS can be entertained.

WORKUP

- Evaluation of any survivor of sudden death starts with a detailed history and physical examination, with particular emphasis on family history. Many patients with SQTS have unexplained syncope or palpitations prior to resuscitated sudden death. Atrial fibrillation is common in SQTS patients and a family history of lone AF should also be sought, in addition to resuscitated VF arrest.
- Physical examination is mostly normal in patients with SQTS.
- ECG findings in SQTS include not only an abnormally short QT interval (usually <360 msec), but usually also a short or even absent ST interval, with the T-wave appearing to emanate directly from the S-wave. T-waves are usually any combination of tall, narrow, and symmetric, with a prolonged Tpeak-Tend ratio (Fig. E1). Additionally, PQ-segment depression (PQD), defined as 0.05-mV PQ depression from the isoelectric TP segment, is more typically present in patients with SQTS. Another feature to look for is the lack of adaptation of the QT interval to the heart rate (diminished rate dependence) as a result of which the corrected QT interval can be misleading; therefore, QT measurement on resting ECG in SQTS is more accurate with heart rate as close to 60 as possible.

TABLE 1 SQTS Diagnostic Criteria

	Points
QTc, msec	
<370	1
<350	2
<330	3
Jpoint-Tpeak interval <120 msec	1
Clinical history	
History of sudden cardiac arrest	2
Documented polymorphic VT or VF	2
Unexplained syncope	1
Atrial fibrillation	1
Family history	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

SQTS, Short QTS syndrome; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia.
A minimum of 1 point must be obtained in the electrocardiographic section in order to obtain additional points.
High-probability SQTS: ≥4 points; intermediate-probability SQTS: 3 points; low-probability SQTS: ≤2 points. Electrocardiogram: Must be recorded in the absence of modifiers known to shorten the QT. Jpoint-Tpeak interval must be measured in the precordial lead with the greatest amplitude T-wave. Clinical history: Events must occur in the absence of an identifiable etiology, including structural heart disease. Points can only be received for 1 of cardiac arrest, documented polymorphic VT, or unexplained syncope. Family history: Points can only be received once in this section.
Adapted from Gollob MH, Redpath CJ, Roberts JD: The short QT syndrome: proposed diagnostic criteria, *J Am Coll Cardiol* 57(7):802-812, 2011.

- Echocardiogram and cardiac MRI should be performed to confirm a lack of structural heart disease.
- Holter recordings and stress tests can document a lack of variation of the QT interval in relation to the RR cycle; this is an important aspect of establishing the diagnosis. The QT interval shortens only slightly with increasing heart rates, so the QT and QTc values approach normal levels during faster heart rates. The QT fails to lengthen at slower heart rates.
- At electrophysiology study, the atrial and ventricular refractory periods are usually very short (140 to 200 msec at a CL of 400 to 600 msec). Sustained atrial fibrillation or flutter with rapid ventricular rates is often induced with programmed stimulation in the atrium. The inducibility of VF in SQTS patients at EPS is about 60%. EPS has a role in adding to the diagnosis by demonstrating short A and V refractory periods (also seen in other channelopathies such as Brugada syndrome), but given its low sensitivity, it cannot be used for risk stratification.

LABORATORY TESTS

- Genetic testing is recommended for all patients in whom a diagnosis of SQTS is suspected. This is especially true if they have a clinical or family history of syncope or sudden death.
- Screening family members: Mutation-specific genetic testing is recommended for all first-degree relatives of a patient diagnosed with a genotype-positive short QT syndrome.

Rx TREATMENT

- There is no significant clinical data on how to approach patients with an isolated short QT interval ≤330 but no family or clinical history or genotype criterion (low and intermediate probability of SQTS). Risk stratification of these patients is not possible at this time; however, they should be referred to an electrophysiologist with expertise on this topic for comprehensive testing, including genetic testing.
- Asymptomatic patients with incidentally found SQTS should be followed without any prophylactic medication.
- Patients with QT <330 msec and one criterion from clinical/family history or genetic testing fall in the high probability category of SQTS and hence a higher-risk subgroup for sudden cardiac death. An ICD implant is recommended in this group for secondary and possibly also primary prevention against sudden cardiac death.
- ICD implantation is a class I indication in patients with the diagnosis of SQTS and who are survivors of cardiac arrest or have sustained ventricular arrhythmia if meaningful survival greater than 1 yr is expected.
- A peculiar issue in patients with SQTS implanted with an ICD is double counting of peaked T-waves that are closely coupled to the QRS complex. This often leads to inappropriate ICD shocks. Most ICDs have programming modifications that can be made to avoid this problem.
- Pharmacologic therapy is usually only advised in patients with multiple and frequent appropriate ICD shocks. Quinidine is the preferred agent in these cases.
- However, medications may be the mainstay of therapy in patients in whom an ICD cannot be implanted for various reasons, including in children in whom technical challenges are significant.
- Isoproterenol infusion is effective in the setting of refractory VF storm and SQTS.
- While many drugs, such as flecainide, sotalol, ibutilide, hydroquinone, and amiodarone, have been used in an attempt to increase the QT interval, most of the available data favor hydroquinidine as the drug of choice across all forms of the SQTS.
- On a special note, primary carnitine deficiency, which presents with SQTS and is associated with VF, is a rare autosomal recessive disorder caused by a defective transport of carnitine into the cell. Administration of oral DL-carnitine or L-carnitine 5g/day over time abolishes the changes on ECG.

REFERRAL

Consultation with an electrophysiologist is strongly recommended if SQTS is suspected.

PEARLS AND CONSIDERATIONS

- SQTS is a rare genetic syndrome causing arrhythmias and sudden death.
- Should be suspected in patients with QT interval <370 msec presenting with syncope, sudden cardiac death, or atrial fibrillation and a family history of the same.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Simon Gringut, MD,** and **Shruti Hegde, MD**

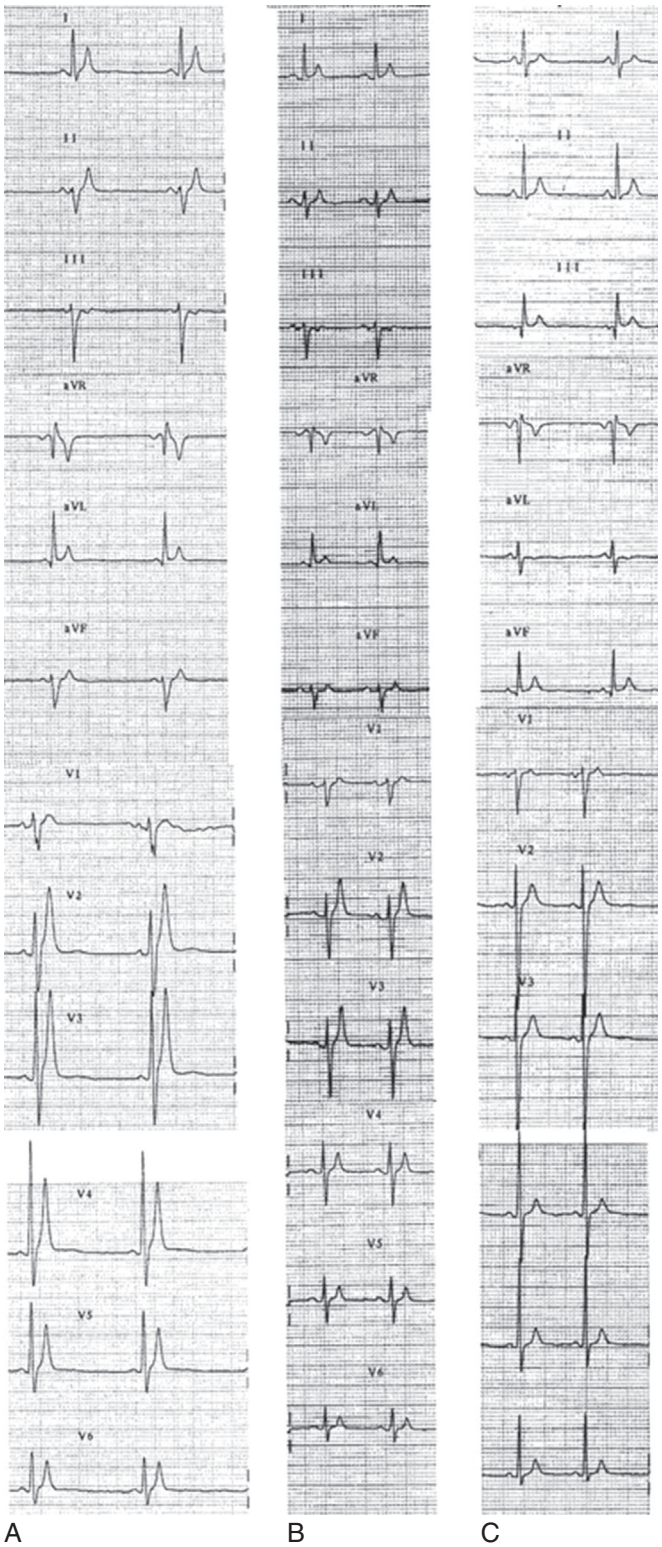

FIG. E1 Twelve-lead electrocardiogram (25 mm/s paper speed) of family 1 patients. A, Patient 1 (IV, 3): Sinus rhythm, heart rate 52 beats per minute (bpm); left-axis deviation, QT 280 msec. **B,** Patient 2 (IV, 2): Sinus rhythm, heart rate 96 bpm; left-axis deviation, QT 220 msec. **C,** Patient 3 (V, 1): Sinus rhythm with mean heart rate 92 bpm, QT 260 msec. (Adapted with permission from Gaita F et al: Short QT syndrome: a familial cause of death, *Circulation* 108:965-970, 2003.)

SUGGESTED READINGS

Al-Khatib SM et al: 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society, *J Am Coll Cardiol* 72:e91, 2018.

Bjerregaard P: Diagnosis and management of short QT syndrome, *Heart Rhythm* 15(8):1261-1267, 2018.

Gollob MH, Redpath CJ, Roberts JD: The short QT syndrome: proposed diagnostic criteria, *J Am Coll Cardiol* 57:802-812, 2011.

Mazzanti A et al: Novel insight into the natural history of short QT syndrome, *J Am Coll Cardiol* 63:1300-1308, 2014.

Priori SG et al: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes, *Heart Rhythm* 10(12):1932-1963, 2013.

Roussel J et al: Carnitine deficiency induces a short QT syndrome, *Heart Rhythm* 13:165, 2016.

BASIC INFORMATION

DEFINITION

Sialadenitis is an inflammation of one or multiple salivary glands. It may present as acute or chronic disease with multiple potential etiologies. This section focuses mainly on the workup and management of acute sialadenitis.

ICD-10CM CODE
K11.20 Sialadenitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Accounts for approximately 0.01% to 0.02% of hospital admissions.
- 30% to 40% of affected patients are postoperative patients.
- Parotid gland is most frequently affected, followed by the submandibular glands (Fig. E1).

PREDOMINANT SEX AND AGE:

- Affects men and women equally.
- Patients are usually in the sixth and seventh decades of life.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain and swelling of the affected salivary gland
- Increased pain with meals
- Erythema and localized tenderness at the duct opening
- Massage may express purulent discharge from duct orifice
- Induration and pitting of the skin, with involvement of the masseteric and submandibular spatial planes in severe cases

ETIOLOGY

- Ductal obstruction is generally from salivary stasis and increased salivary viscosity as a result of dehydration, medication-induced xerostomia, or poor dental hygiene. This predisposes patients to retrograde migration of bacteria, which can then lead to suppurative sialadenitis.
- Acute suppurative sialadenitis is a bacterial infection of the salivary gland. Most frequent infecting organisms are *Staphylococcus aureus* (50% to 90% of cases), streptococcal species, *Haemophilus influenzae,* and *E. coli;* more recently, anaerobic infections have been increasing in prevalence.
- Recent surgery, Sjögren syndrome, diabetes mellitus, hypothyroidism, renal failure, trauma, radiation therapy, chemotherapy, dehydration, and chronic illness are predisposing factors.
- Mumps is the most common cause of nonsuppurative acute sialadenitis. Majority of cases (>80%) occur in children younger than 15 yr.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Salivary gland neoplasm
- Ductal stricture
- Sialolithiasis
- Decreased salivary secretion as a result of medications (e.g., amitriptyline, diphenhydramine, anticholinergics)
- Dental infections
- Lymphoma
- Cervical adenitis
- Infected branchial cleft or sebaceous cysts

WORKUP

- Generally not necessary. Fig. E2 describes a diagnostic algorithm.
- Ultrasound or CT scan in patients not responding to medical treatment.

LABORATORY TESTS

- Generally not indicated
- Complete blood count with differential to possibly reveal leukocytosis with left shift
- Mumps antibodies if there is clinical suspicion
- Culture of purulent drainage from salivary duct opening or percutaneously should be obtained to provide useful information in tailoring antibiotic therapy if the patient is not responding to empiric therapy

IMAGING STUDIES

- Ultrasound or CT scan may be needed in patients with no improvement or clinical worsening after 48 to 72 hours of medical therapy. This can provide information on the presence of a drainable collection.
- Sialography should not be performed during the acute phase, as it can worsen symptoms.
- MRI is also of little utility in acute sialadenitis.

TREATMENT

Nonpharmacologic therapy—these interventions are crucial in expediting resolution of symptoms.

- Massage of the gland: May express pus and relieve some of the pressure
- Hydration with intravenous fluid or aggressive oral hydration along with electrolyte repletion
- Warm compresses
- Oral cavity irrigations
- Administration of sialagogues such as lemon drops or vitamin C lozenges

ACUTE GENERAL Rx

- Amoxicillin-clavulanate 500 to 875 mg bid or cefuroxime 250 to 500 mg bid should be given for 10 days. Clindamycin is an alternative choice in patients allergic to penicillin.
- In patients coming from nursing homes or in cases of nosocomial infections, consider empiric treatment with vancomycin given the prevalence of methicillin-resistant *S. aureus.*
- IV antibiotics (e.g., cefoxitin, nafcillin) can be given in severe cases.
- Patients generally improve with 48 to 72 hours of medical treatment. If there is no improvement, consider imaging with CT or ultrasound.
- Surgical drainage is indicated for the rare cases that are refractory to medical management and that are found to have an abscess on CT or ultrasound.

DISPOSITION

Complete recovery unless the patient has underlying obstruction (e.g., ductal stricture, tumor, or stone)

REFERRAL

- To ear-nose-throat specialist for cases refractory to appropriate medical therapy
- For salivary gland incision and drainage, which may be necessary in resistant cases

PEARLS & CONSIDERATIONS

COMMENTS

Prevention of dehydration will decrease the risk of sialadenitis.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Salivary Gland Inflammation (Patient Information)
Sialolithiasis (Related Key Topic)
Salivary Gland Neoplasms (Related Key Topic)

AUTHOR: **Louis Insalaco, MD**

SUGGESTED READINGS

Maresh A et al: Sialoendoscopy in the diagnosis and treatment of obstructive sialadenitis, *Laryngoscope* 121(3):495-500, 2011.

Wilson KF et al: Salivary gland disorders, *Am Fam Physician* 89(11):882-888, 2014.

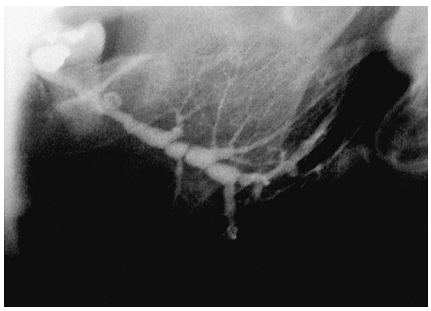

FIG. E1 Sialogram of patient with chronic sialadenitis showing sausage link–like patterns and massive duct dilation. (From Blitzer CE et al: Sialadenitis, In Johnson JT, Yu VL [eds]: *Infectious diseases and antimicrobial therapy of the ears, nose, and throat,* Philadelphia, 1997, Saunders.)

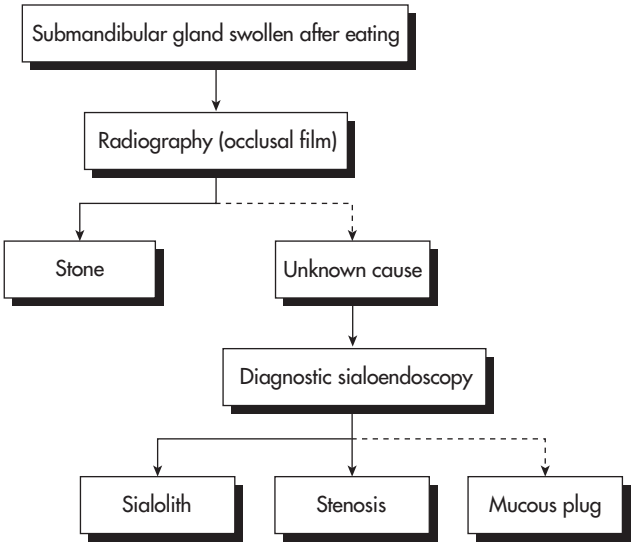

FIG. E2 Diagnostic algorithm. (From Yu C-Q et al: Selective management of obstructive submandibular sialadenitis, *Br J Oral Maxillofacial Surg* 46[1]:46-49, 2008.)

Sialolithiasis ALG PTG

BASIC INFORMATION

DEFINITION

Sialolithiasis is the existence of hardened intraluminal deposits in the ductal system of a salivary gland.

SYNONYMS

Salivary gland stone
Salivary calculus

ICD-10CM CODE
K11.5 Sialolithiasis

EPIDEMIOLOGY & DEMOGRAPHICS

Affects patients mostly in the fifth to eighth decades and occurs most commonly in the submandibular gland (85%); 15% of occurrences are located in a parotid gland (Table E1).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms: Colicky postprandial pain and swelling of a salivary gland. Tends to have a remitting/relapsing course.
- Signs: Swelling and tenderness of a salivary gland. The stone may be felt with bimanual palpation of the floor of the mouth or inner cheek.

ETIOLOGY

- The cause is unknown. Contributing factors include saliva stagnation, sialadenitis (inflammation of a salivary gland), ductal inflammation, or injury (Fig. 1).
- Gout is a known cause of salivary gland calculi.
- Salivary calculus composition is mainly calcium phosphate and carbonate, often combined with small proportions of magnesium, zinc, ammonium salts, and organic materials or debris.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Lymphadenitis
- Salivary gland tumor
- Salivary gland bacterial (*Staphylococcus* or *Streptococcus*), viral (mumps), or fungal infection (sialadenitis)
- Noninfectious salivary gland inflammation (e.g., Sjögren syndrome, sarcoidosis, lymphoma)
- Salivary duct stricture
- Dental abscess

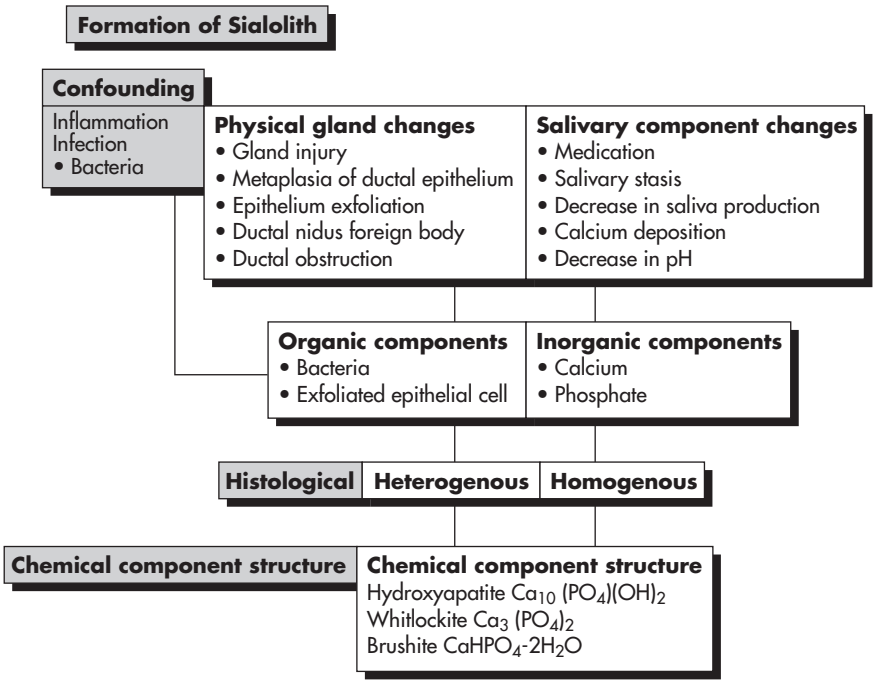

FIG. 1 Algorithm of clinical findings and pathogenesis of sialolithiasis. (From Lee LT, Wong YK: Sialolithiasis in minor salivary glands, *J Oral Maxillofac Surg*, 2010.)

IMAGING STUDIES

- X-ray: 90% of submandibular stones are radiopaque and will show up on x-ray. 90% of parotid stones are radiolucent and will not show up on x-ray.
- Non–contrast-enhanced computed tomography is very useful in detecting nearly all salivary stones.
- Ultrasound can detect 90% of salivary stones >2 mm.
- Sialography has a 95% to 100% sensitivity in detecting stones (Figs. E2 and E3), although it is more invasive than the above options and requires contrast injection into the affected duct.

TREATMENT

- Nonsurgical management is usually the first-line treatment.
  1. Warm compresses, gland massages, sialogogues (lemon wedges, sour candies), IV or oral hydration.
  2. Antibiotics if associated bacterial sialadenitis is present.
- Surgical treatment:
  1. The surgical approach depends on the location of the stone. Submandibular stones in the distal aspect of the duct that are palpable may be excised transorally under local anesthesia. More proximal stones may require removal of the submandibular gland. Sialoendoscopy is a newer technique where a rigid endoscope and specialized instruments and/or lasers are used to visualize and remove the stones. Stones in the parotid duct also may be accessible via the transoral approach or may require parotidectomy. Sialoendoscopy is also an option for parotid stones.
  2. Extracorporeal shock wave lithotripsy is an alternative technique that breaks up the stones into smaller fragments that can be secreted naturally through the duct.

REFERRAL

To otorhinolaryngologist

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Salivary Gland Stones (Patient Information)
Sialadenitis (Related Key Topic)

AUTHOR: **Louis Insalaco, MD**

SUGGESTED READINGS

Maresh A et al: Sialoendoscopy in the diagnosis and treatment of obstructive sialadenitis, *Laryngoscope* 121(3):495-500, 2011.

Wilson KF et al: Salivary gland disorders, *Am Fam Physician* 89(11):882-888, 2014.

TABLE E1 Salivary gland calculi

	Submandibular gland	Parotid gland
Incidence of calculi	85%	15%
Radiopaque calculi	60%-80%	20%-40%
Common location of calculi	At the duct genu (where it makes an acute bend over the posterior free border of the mylohyoid muscle)	The parotid hilum or main duct overlying the masseter muscle

From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.

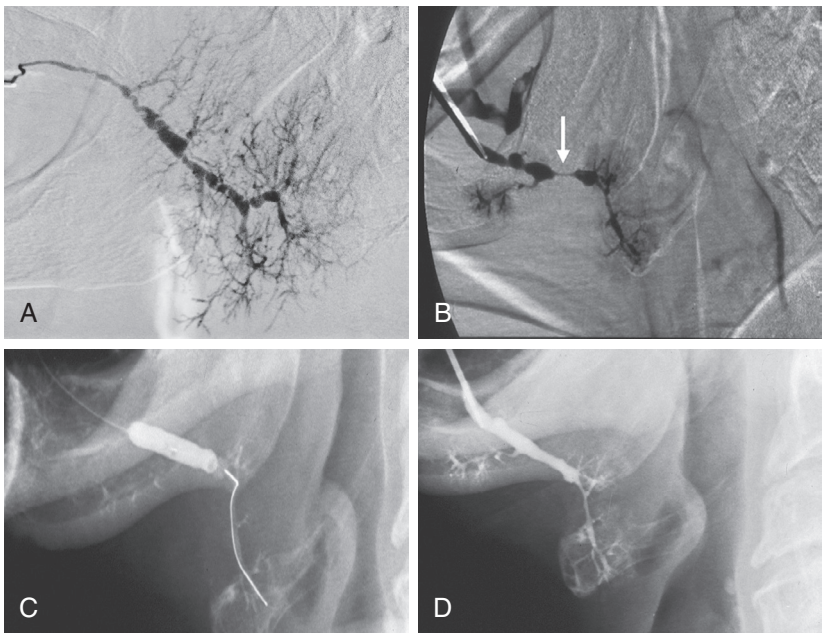

FIG. E2 Parotid sialogram. A, Multiple strictures in the main and some branch ducts. Digital subtraction image. **B,** Parotid sialogram shows an inflammatory parotid duct stricture *(arrow)* secondary to stone disease. Digital subtracted image. **C,** Balloon dilatation of the stricture. **D,** Postprocedure sialogram. (From Sutton D: *Textbook of radiology and imaging,* ed 7, 1998, Churchill Livingstone. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

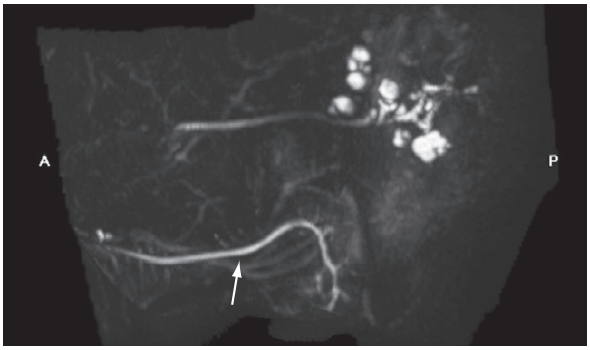

FIG. E3 Magnetic resonance sialography image showing chronic sialadenitis of the parotid gland with focal globular high signal areas of sialectasis within the parenchyma of the gland. The main duct appears normal. The submandibular duct and gland *(arrow)* appear normal. (From Adam A, Dixon AK et al: *Grainger & Allison's diagnostic radiology,* ed 5, 2007, Churchill Livingstone, 2007. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Sinus node dysfunction is a group of cardiac rhythm disturbances characterized by abnormalities of the sinus node leading to the inability of the SA node to react to heart rate changes to meet physiological demands. This entity includes (1) chronic, inappropriate bradycardia; (2) sinus pauses or arrest; (3) sinoatrial exit block; and (4) alternating sinus bradycardia with paroxysmal supraventricular tachyarrhythmias (frequently atrial fibrillation) known as tachycardia-bradycardia syndrome. When sinus node dysfunction is associated with symptoms, it is called sick sinus syndrome (SSS).

SYNONYMS

Sinus pause
Sinus arrest
Inappropriate persistent sinus bradycardia
Tachycardia-bradycardia syndrome
Sinoatrial exit block
SSS
Bradycardia-tachycardia syndrome

ICD-10CM CODE
I49.5 Sick sinus syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- In children: Associated with congenital and acquired heart disease, particularly after cardiac surgery.
- In adults: It is primarily a disease of the elderly secondary to progressive idiopathic degenerative disease. A modern population study has suggested that white race, increased BMI, prolonged baseline QRS or right bundle branch block, elevated N-terminal pro-B-type natriuretic peptide, HTN, or other cardiovascular diseases are associated with increased incidence of sick sinus syndrome. With an aging population, the annual incidence of SSS is projected to increase significantly.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fatigue, light-headedness, syncope, presyncope, palpitations. Other manifestations include dyspnea on exertion and worsening angina.
  1. Usually symptoms are progressive; however, abrupt symptoms are not uncommon (i.e., syncope).
- Physical examination may be normal or reveal abnormalities (e.g., irregular heart rhythm, signs of congestive heart failure, heart murmurs or gallop sounds) associated with the underlying heart disease.

ETIOLOGY

- Sinus node fibrosis is the primary etiology, which may also affect the atrioventricular node, the His bundle, or its branches. Polypharmacy should be considered and obtaining an accurate medicine list is essential.
  1. Common medications include beta blockers, nondihydropyridine calcium channel blockers, digoxin, and antiarrhythmic medications.
- Additional etiologies include acute coronary syndromes, diseases of the SA nodal artery, inflammatory and infiltrative diseases such as hemochromatosis, amyloidosis, sarcoidosis, collagen vascular diseases (SLE and scleroderma), epicardial and pericardial diseases, trauma following cardiac surgery, hypothyroidism, hypothermia, hypoxia, sepsis, muscular dystrophies (e.g., myotonic dystrophy, Friedreich ataxia), infectious etiologies such as Lyme disease, increased intracranial pressure.
  1. The sinus node artery arises from right coronary artery in 55% to 60% of people and the left circumflex artery in 40%.

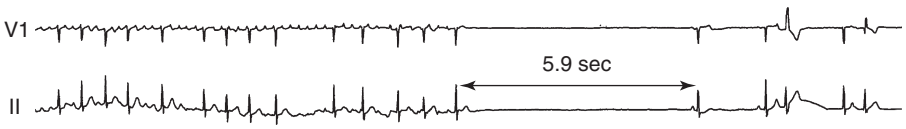

FIG. 1 Tachycardia-bradycardia syndrome. Two surface electrocardiogram leads show atrial fibrillation that spontaneously terminates followed by a 5.9-second pause before sinus rhythm resumes. The patient became light-headed during this period. (From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, Saunders.)

TABLE 1 Indications for Permanent Pacing in Sinus Node Dysfunction

Class	Indications
I	• Sinus node dysfunction with documented symptomatic bradycardia or sinus pauses that produce symptoms • Symptomatic sinus bradycardia that is iatrogenic and will occur as a consequence of essential long-term therapy of a type and dose of drugs for which there are no acceptable alternatives • Symptomatic chronotropic incompetence
IIa	• Sinus node dysfunction, occurring spontaneously or as a result of necessary drug therapy, with a heart rate of less than 40 beats/min when a clear association between significant symptoms consistent with bradycardia has not been documented • Unexplained syncope when sinus abnormalities are observed or provoked with electrophysiologic study
IIb	• A chronic heart rate of less than 40 beats/min, while awake, in the minimally symptomatic patient
III	• Sinus node dysfunction in asymptomatic patients, including those in whom substantial sinus bradycardia (heart rate of less than 40 beats/min) is a consequence of long-term drug treatment • Sinus node dysfunction in which symptoms suggestive of bradycardia are clearly documented as not associated with a slow heart rate • Symptomatic bradycardia associated with nonessential drug therapy

ACC, American College of Cardiology; *AHA,* American Heart Association; *HRS,* Heart Rhythm Society.
Adapted from ACC/AHA/HRS 2008 revised guidelines with 2012 update.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bradycardia: Atrioventricular block
- Tachycardia: Atrial fibrillation or atrial flutter, sinus tachycardia
- Medication toxicity
- Carotid sinus hypersensitivity
- Metabolic abnormality (e.g., hyperkalemia in acute kidney injury)

WORKUP

- ECG (Fig. 1)
- Ambulatory cardiac rhythm monitoring
- Twenty-four-hour ambulatory ECG (Holter) with diary to correlate symptoms to findings:
  1. Event recorder or an implantable loop recorder if symptoms are less frequent.
  2. Establishment of diagnosis is more effective with longer-term recording (at least 2-4 wk) compared with 24-hour ambulatory ECG.
  3. Exercise stress testing to evaluate the severity of chronotropic incompetence.
  4. The term *chronotropic incompetence* is felt to represent the inability to augment heart rates appropriately in response to exercise or activities of daily living.
- Electrophysiologic testing, including sinus node recovery time and sinoatrial conduction time

TREATMENT

- Permanent pacemaker placement is primarily indicated if bradycardia is symptomatic and a reversible etiology is not identified. Indications for permanent pacemaker in sinus node dysfunction are described in Table 1.
- In tachycardia-bradycardia syndrome, drug treatment is indicated for tachycardia, primarily with AV node blocking agents, after placement of the permanent pacemaker.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Daniel R. Frisch, MD**

SUGGESTED READINGS

Brignole M et al: ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA), *Eur Heart J* 34(29):2281-2329, 2013, https://doi.org/10.1093/eurheartj/eht150.

Epstein AE et al: ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: executive summary, *Heart Rhythm* 5:934-955, 2008.

Jensen PN et al: Incidence of and risk factors for sick sinus syndrome in the general population, *J Am Coll Cardiol* 64(6):531-538, 2014.

Semelka M et al: Sick sinus syndrome: a review, *Am Fam Physician* 87(10):691-696, 2013.

BASIC INFORMATION

DEFINITION

- Sickle cell disease (SCD) is a hemoglobin disorder in which the substitution of valine for glutamic acid at position six of the beta globin chain yields a variant hemoglobin, hemoglobin S. When hemoglobin S is not bound to oxygen (deoxy HgbS) it can polymerize into long strands, deforming red blood cells (RBCs) into a characteristic sickle shape. Chronic RBC membrane damage from this process locks cells into the sickle shape. These abnormal cells can obstruct the microcirculation because of abnormal adherence to vascular endothelium, causing painful crises, which are the hallmark of sickle cell disease.
- Patients with SCD include those who are homozygous for sickle cell hemoglobin (HbSS), also called sickle cell anemia (SCA), and those with one sickle hemoglobin gene inherited with other hemoglobin abnormalities, notably beta thalassemia (Hgb S/β^0 or Hgb S/β^+ thalassemia) and hemoglobin C (HbSC).

SYNONYMS

Sickle cell anemia
SCA
SCD
Hemoglobin S disease

ICD-10CM CODES

D57.1	Sickle-cell disease without crisis
D57.20	Sickle-cell/Hb-C disease without crisis
D57.211	Sickle-cell/Hb-C disease with acute chest syndrome
D57.212	Sickle-cell/Hb-C disease with splenic sequestration
D57.219	Sickle-cell/Hb-C disease with crisis, unspecified
D57.3	Sickle-cell trait
D57.40	Sickle-cell thalassemia without crisis
D57.411	Sickle-cell thalassemia with acute chest syndrome
D57.412	Sickle-cell thalassemia with splenic sequestration
D57.419	Sickle-cell thalassemia with crisis, unspecified
D57.80	Other sickle-cell disorders without crisis
D57.811	Other sickle-cell disorders with acute chest syndrome
D57.812	Other sickle-cell disorders with splenic sequestration
D57.819	Other sickle-cell disorders with crisis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Sickle cell disease is an autosomal-recessive disorder. In African Americans, the incidence of sickle cell anemia at birth is 1 in 600 and the incidence of all genotypes of sickle cell disease is 1 in 300. Approximately 90,000 people in the U.S. have sickle cell disease.
- Sickle cell trait occurs in approximately 300 million people worldwide, with the highest prevalence of approximately 30% to 40% in sub-Saharan Africa, but also in the southern Mediterranean region (usually as Hgb S/β^0 or Hgb S/β^+), parts of the Middle East, and India. In the U.S., it is found in nearly 10% of African Americans.
- An estimated 2000 babies are born with sickle cell disease in the U.S. each yr, and worldwide 275,000 infants are born with the disease annually.
- There is no predominant sex.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination is variable depending on the degree of anemia and presence of acute vasoocclusive syndromes, as well as acute pulmonary, neurologic, cardiovascular, genitourinary, and musculoskeletal complications. Table 1 summarizes organ damage seen in sickle cell disease.
- A study of the prevalence of pain in sickle cell patients found that patients complained of pain on 55% of days surveyed; another study showed 40% to 80%. Chronic pain may be due to avascular necrosis of joints and is sometimes poorly explained.
- There is no clinical laboratory finding that is pathognomonic of painful crisis of sickle cell disease. The diagnosis of a painful episode is made solely on the basis of the medical history and physical examination. Elevated total bilirubin and lactate dehydrogenase (LDH) are sometimes seen with crisis due to increased hemolysis. However, hemolytic anemia is typical for sickle cell disease at baseline. "Aplastic crisis" refers to crisis presenting with severe anemia and low reticulocyte count, usually caused by B19 parvovirus infection.
- Bones are the most common site of pain. Dactylitis, or hand-foot syndrome (acute, painful swelling of the hands and feet), is the first manifestation of sickle cell disease in many infants. Irritability and refusal to walk are other common symptoms. After infancy, musculoskeletal pain can be symmetric, asymmetric, or migratory, and it may or may not be associated with swelling, low-grade fever, redness, or warmth.
- In both children and adults, sickle vasoocclusive episodes are difficult to distinguish from osteomyelitis, septic arthritis, synovitis, rheumatic fever, or gout.
- Cholecystitis should be considered when abdominal pain is present because this is common in patients with chronic hemolysis. In general, localizing symptoms for infection (e.g., urinary symptoms) should be evaluated because these can trigger sickle crisis. Whereas patients with severe sickle cell disease have splenic atrophy in adulthood, patients with milder disease (e.g., Hgb S/C) may have splenic infarct pain in adulthood.
- The acute chest syndrome is a potentially life-threatening complication of sickle cell disease that manifests with chest pain, fever, wheezing, tachypnea, and cough. Chest radiograph may reveal pulmonary infiltrates. Causes include infection (*Mycoplasma, Chlamydia,* viruses), infarction, and fat embolism, but often no cause is identified.
- Musculoskeletal and skin abnormalities seen in sickle cell anemia include leg ulcers (particularly on the malleoli) and limb-girdle deformities caused by avascular necrosis of the femoral and humeral heads. Osteonecrosis of the heads of the femur and humerus is found in nearly 50% of adults with Hgb S/S sickle cell disease.
- Endocrine abnormalities include delayed sexual maturation and late physical maturation, especially evident in boys.
- Neurologic abnormalities on examination may include seizures and altered mental status. Strokes occur in about 10% of children and adults with sickle cell anemia and approximately 35% of children with sickle cell anemia have cerebrovascular disease.
- Infections, particularly involving *Salmonella, Staphylococcus aureus, Mycoplasma,* and *Streptococcus,* are relatively common. Catheter-associated bacteremia should be considered if a vascular access device is present; these may present without fever.
- Severe splenomegaly as a result of sequestration often occurs in children before splenic atrophy.

TABLE 1 Organ Damage Seen in Sickle Cell Disease

Organ or System	Injury
Skin	Stasis ulcer
Central nervous system	Cerebrovascular accident
Eye	Retinal hemorrhage, retinopathy
Cardiac	Congestive heart failure
Pulmonary	Intrapulmonary shunting, embolism, infarct, infection
Vascular	Occlusive phenomenon at any site
Liver	Hepatic infarct, hepatitis resulting from transfusion, hepatic sequestration, intrahepatic cholestasis
Gallbladder	Increased incidence of bilirubin gallstones caused by hemolysis
Spleen	Acute sequestration
Urinary	Hyposthenuria, hematuria
Genital	Decreased fertility, impotence, priapism
Skeletal	Bone infarcts, osteomyelitis, aseptic necrosis
Placenta	Insufficiency with fetal wastage
Leukocytes	Relative immunodeficiency
Erythrocytes	Chronic hemolysis

From Marx J et al: *Rosen's emergency medicine: concepts and clinical practice,* ed 7, Philadelphia, 2010, Mosby.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Thalassemia
- Other hemolytic anemias
- The differential diagnosis of patients presenting with a painful crisis is discussed in "Physical Findings"

TABLE 2 Baseline Evaluations to Consider

	Tests
Blood tests	CBC with differential
	Reticulocyte count
	Hemoglobin HPLC or electrophoresis
	LDH
	Renal function tests
	Liver function tests
	Mineral panel
	Serum iron, ferritin, TIBC
	Vitamin D level
	Hepatitis B sAg
	Hepatitis C antibody
	RBC alloantibody screen
	RBC typing
	D-dimer[a]
	C-reactive protein[a]
	Brain natriuretic peptide
Urine and kidney tests	Urinalysis
	Renal ultrasonography[b]
Radiology	MRI or MRA brain (adults)[c] or transcranial Doppler ultrasonography starting at age 2 yr (children)
	Chest radiography[d]
	Hip or shoulder radiograph or MRI (or both)[c]
	Bone density in teenagers and adults
Cardiology and pulmonary	Echocardiogram
Neurocognitive	Neurocognitive testing[d]

CBC, Complete blood count; *HPLC,* high performance liquid chromatography; *LDH,* lactate dehydrogenase; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging; *RBC,* red blood cell; *sAg,* surface antigen; *TIBC,* total iron-binding capacity.
[a]Consider following as surrogate markers after initiation of disease-modifying intervention.
[b]If hematuria with red blood cells in urine.
[c]As clinically indicated.
[d]If the patient has poor school performance, an abnormal memory, or abnormal MRI findings.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

WORKUP (TABLE 2)

- Screening of all newborns regardless of racial background is performed in the U.S. Screening can be performed with sodium metabisulfite reduction test (Sickledex test).
- Hemoglobin electrophoresis will also confirm the diagnosis and is useful to identify hemoglobin variants such as fetal hemoglobin and hemoglobin C.
- Patients will have evidence of hemolysis (elevated reticulocyte count, low haptoglobin, variable elevation of LDH and total bilirubin).
- Chest x-ray often reveals typical vertebral body changes ("fish mouth" vertebrae) caused by chronic vasoocclusive injury to vertebral bodies.
- For prenatal diagnosis, initial step is identification of parenteral globin gene mutation by DNA-based testing. If positive, then DNA-based testing of chorionic villus sampling or amniotic fluid cells is performed.

LABORATORY TESTS

- Anemia (resulting from chronic hemolysis), reticulocytosis, leukocytosis, and thrombocytosis are common. Hgb S/β^0 and Hgb S/β^+ thalassemia will have microcytosis; Hgb S/C is also typically microcytic. Hgb S/C may have normal or near-normal hematocrit, but will have characteristic changes on peripheral smear (target cells).
- Elevations of bilirubin and lactate dehydrogenase are also common, as is low haptoglobin, consistent with chronic hemolysis.
- Peripheral blood smear may reveal sickle cells, target cells, poikilocytosis, and hypochromia (Fig. 1).
- Elevated blood urea nitrogen and creatinine may be present in patients presenting acutely with dehydration or chronically with progressive renal insufficiency.
- Urinalysis may reveal hematuria and proteinuria. Patients with SCD should be screened for microalbuminuria and proteinuria with spot urine testing by 10 yr of age.

IMAGING STUDIES (FIGS. E2 AND E3)

- Chest x-ray or noncontrast chest CT scan to evaluate acute and chronic lung changes is helpful.
- Routine skeletal imaging is rarely helpful in acute crisis and should usually be reserved for pain that is not consistent with transient acute crisis.
- MRI or bone scan is useful to address chronic avascular necrosis or, in the acute setting, osteomyelitis.
- CT scan or MRI of brain is not indicated in asymptomatic adults and children with SCD but is often needed in patients with neurologic complications such as transient ischemic attack, cerebrovascular accident, seizures, or altered mental status.
- Transcranial Doppler ultrasonography (TCD) is used to identify children with sickle cell anemia who are at risk for stroke. There should be an annual screening starting at age 2 until age 16. Patients determined to be at risk (transcranial Doppler velocity ≥200 cm/s) should be enrolled in long-term transfusion programs. These are effective in reducing risk of stroke by >90%. In adults, magnetic resonance angiography (MRA) can be used instead of TCD to identify those at risk for stroke.
- Doppler echocardiography should be performed in patients with unexplained respiratory symptoms to evaluate for pulmonary hypertension, with right heart catheterization performed if abnormal. Screening for vasculopathy is done by estimating the tricuspid regurgitant jet velocity (TRV). Elevated values are predictive of early mortality. The prevalence of pulmonary hypertension when right heart catheterization is performed is approximately 6% in adults with sickle cell disease.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Patients should be instructed to avoid conditions that may precipitate sickling crisis, such as extremes of cold and heat and dehydration.
- Maintain adequate hydration (PO or IV).
- Correct hypoxia when present.

ACUTE GENERAL Rx

- Initiate aggressive IV or oral hydration; most patients in crisis have evidence of dehydration.
- Aggressively diagnose and treat suspected infections such as urinary infection, respiratory infections, or catheter-associated line infections. Table 3 summarizes bacteria and viruses that most frequently cause serious infection in patients with sickle cell disease.
- Provide pain relief during the vasoocclusive crisis (Table 4). Most patients will have a treatment history that can guide dosing. Opiate management is complicated by high levels of tolerance in patients often treated over many yrs. Patient-controlled analgesic pumps are often helpful; caution should be used when employing continuous infusions, which are usually not necessary or helpful. Morphine and hydromorphone are most commonly used. Meperidine is rarely used now and generally discouraged because of neurologic side effects, although some patients state a preference for it.
- Oral diphenhydramine (Benadryl) is used to control pruritus, which is commonly associated with opiate analgesics; preferred to IV therapy in guidelines.

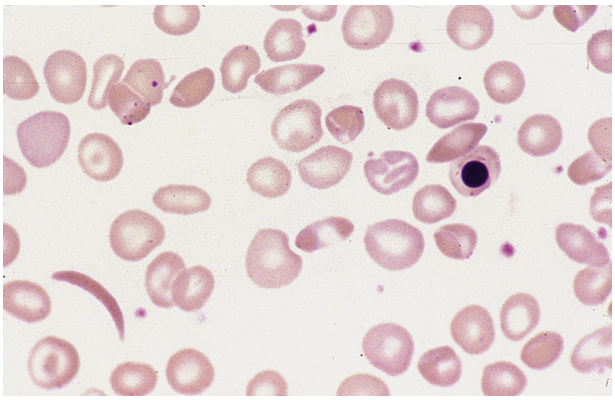

FIG. 1 Photomicrograph of a blood film. Sickle cell anemia (homozygosity for hemoglobin S). Shown are a sickle cell, boat-shaped cells, a nucleated red cell, and target cells. (From Bain BJ et al: *Dacie and Lewis practical haematology,* ed 12, Philadelphia, 2017, Elsevier.)

TABLE 3 Bacteria and Viruses That Most Frequently Cause Serious Infection in Patients with Sickle Cell Disease

Microorganism	Type of Infection	Comments
Streptococcus pneumoniae	Septicemia	Common despite prophylactic penicillin and pneumococcal vaccine
	Meningitis	Less frequent than in yrs past
	Pneumonia	Rarely documented except in infants and young children
	Septic arthritis	Uncommon
Haemophilus influenzae type b	Septicemia	
Meningitis		
Pneumonia	Much less common in recent yrs because of immunization with conjugate vaccine	
Salmonella species	Osteomyelitis	
Septicemia	Most common cause of bone and joint infection	
Escherichia coli and other gram-negative enteric pathogens	Septicemia	
Urinary tract infection		
Osteomyelitis	Focus sometimes not apparent	
Staphylococcus aureus	Osteomyelitis	Uncommon
Mycoplasma pneumoniae	Pneumonia	Pleural effusions; multilobe involvement
Chlamydia pneumoniae	Pneumonia	
Parvovirus B19	Bone marrow suppression (aplastic crisis)	High fever common; rash and other organ involvement infrequent
Hepatitis viruses (A, B, and C)	Hepatitis	Marked hyperbilirubinemia

Data from Buchanan GR, Glader BE: Benign course of extreme hyperbilirubinemia in sickle cell anemia: analysis of six cases, *J Pediatr* 91:21, 1977. From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

- Table 5 summarizes overall strategies for the management of acute chest syndrome.
- Follow oxygenation in patients presenting with chest pain or respiratory symptoms; assess for evolving acute chest syndrome if oxygenation deteriorates.
- Urology evaluation for priapism.

CHRONIC Rx

- Hydroxyurea increases hemoglobin F levels and reduces the incidence of vasoocclusive complications. It is helpful in patients with Hgb S/S and S/β^0 thalassemia; its value in other variants is less certain. A study of hydroxyurea with 17.5 yr of follow-up showed evidence of improved survival and no safety signals. There is strong evidence to support use of hydroxyurea therapy in children 9 mo and older to decrease the frequency of vasoocclusive crises and acute chest syndrome. Hydroxyurea therapy is also strongly recommended for adults with three or more vasoocclusive crises during any 12-mo period, with SCD pain or chronic anemia interfering with daily activities, or with severe or recurrent episodes of acute chest syndrome. Recommended starting doses are 15 mg/kg/day in adults, 5 to 10 mg/kg/day in patients with renal disease, and 20 mg/kg/day in children. It should be stopped in pregnancy and contraception counseling should be given to patients taking it.
- Pharmaceutical grade L-glutamine is approved to decrease crisis symptoms in patients with Hgb S/S and Hgb S/β^0 thalassemia; benefits include decrease in acute crisis episodes, reduced hospitalization, and decrease in episodes of acute chest syndrome. Dosing is 5 to 15 g twice daily, taken with food or 8 oz of cold or room-temperature fluid. Constipation, nausea, headache, and abdominal discomfort were common side effects, occurring in about 15% to 20% of patients. It may work with or without concomitant use of hydroxyurea. Caution may be warranted in prescribing L-glutamine to patients with clinically significant renal or hepatic dysfunction.
- Replace folic acid (1 mg PO qd) due to loss from increased utilization of folic acid stores from to chronic hemolysis. Sickle cell patients also often have mineral and vitamin deficiencies (calcium, zinc, and vitamins A, C, D, and E) and may need vitamin and nutritional supplementation.
- Chronic pain management represents an enduring challenge, made more difficult by the current opiate addiction and overdose epidemic. In one study, patients reported pain 55% of days. Review of guidelines for safe opiate prescribing is strongly recommended and management with pain management specialists is also strongly recommended.
- Indications for transfusion in sickle cell disease are described in Table 6. Urgent exchange transfusion for acute chest syndrome with progressive hypoxia (arterial oxygen saturation <90%) or multiorgan failure may be lifesaving. Simple transfusion may be adequate in milder cases with a target Hgb of 10 g/dl. Transfusion therapy is appropriate for patients with stroke or at high risk by transcranial Doppler study (see earlier) if possible. Transfusion has shown benefit in children with silent infarcts by MRI in preventing progression. Transfusion to Hgb 10 g/dl is recommended in anemic patients undergoing general anesthesia to reduce crisis and respiratory complications after surgery. Patients on chronic transfusion therapy should receive RBC matched at C, E, and K antigens to avoid alloimmunization. Transfusion is not recommended for asymptomatic anemia. Serum ferritin level should be monitored quarterly. Iron overload due to blood transfusions (transfusional hemosiderosis) can be treated with chelating agents (deferoxamine [SC infusion], deferasirox [PO], and deferiprone [PO]).
- Annual screening for proteinuria is recommended. Angiotensin-converting enzyme inhibitor therapy should be started for microalbuminuria in adults with SCD to prevent progression of renal injury. Progressive renal injury may cause worsening anemia and responds to erythropoietin.

TABLE 4 Recommended Dose and Interval of Analgesics Necessary to Obtain Adequate Pain Control in Patients with Sickle Cell Disease

	Dose/Rate	Comments
Severe to Moderate Pain		
Morphine	Parenteral: 0.1-0.15 mg/kg every 3-4 h Recommended maximum single dose, 10 mg PO: 0.3-0.6 mg/kg every 4 h	Drug of choice for pain; lower doses in elderly adults and infants and in patients with liver failure or impaired ventilation
Meperidine	Parenteral: 0.75-1.5 mg/kg every 2-4 h Recommended maximum dose, 100 mg PO: 1.5 mg/kg every 4 h	Increased incidence of seizures; avoid in patients with renal or neurologic disease and those who receive MAOIs
Hydromorphone	Parenteral: 0.01-0.02 mg/kg every 3-4 h PO: 0.04-0.06 mg/kg every 4 h	
Oxycodone	PO: 0.15 mg/kg/dose every 4 h	
Ketorolac	IM: Adults: 30 or 60 mg initial dose followed by 15-30 mg; children: 1 mg/kg load followed by 0.5 mg/kg every 6 h	Equal efficacy to 6 mg MS; helps narcotic-sparing effect; not to exceed 5 days; maximum, 150 mg first day, 120 mg maximum on subsequent days; may cause gastric irritation
Butorphanol	Parenteral: Adults: 2 mg every 3-4 h	Agonist–antagonist; can precipitate withdrawal if given to patients who are being treated with agonists
Mild Pain		
Codeine	PO: 0.5-1 mg/kg every 4 h Maximum dose, 60 mg	Mild to moderate pain not relieved by aspirin or acetaminophen; can cause nausea and vomiting
Aspirin	PO: Adults: 0.3-6 mg every 4-6 h; children: 10 mg/kg every 4 h	Often given with a narcotic to enhance analgesia; can cause gastric irritation; avoid in febrile children
Acetaminophen	PO: Adults: 0.3-0.6 g every 4 h; children: 10 mg/kg	Often given with a narcotic to enhance analgesia
Ibuprofen	PO: Adults: 300-400 mg every 4 h; children: 5-10 mg/kg every 6-8 h	Can cause gastric irritation
Naproxen	PO: Adults: 500 mg/dose initially and then 250 every 8-12 h; children: 10 mg/kg/day (5 mg/kg every 12 h)	Long duration of action; can cause gastric irritation
Indomethacin	PO: Adults: 25 mg every 8 h; children: 1-3 mg/kg/day given 3 or 4 times	Contraindicated in psychiatric, neurologic, renal diseases; high incidence of gastric irritation; useful in gout

IM, Intramuscular; *MAOI,* monoamine oxidase inhibitor; *MS,* morphine sulphate; *PO,* oral.

Adapted from Charache S et al: Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia: Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia, *N Engl J Med* 332:1317, 1995. In Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 5 Overall Strategies for the Management of Acute Chest Syndrome

Prevention

Incentive spirometry and periodic ambulation in patients admitted for sickle cell pain, surgery, or febrile episodes
Watchful waiting in any hospitalized child or adult with sickle cell disease (pulse oximetry monitoring and frequent respiratory assessments)
Cautious use of intravenous fluids
Intense education and optimum care of patients who have sickle cell anemia and asthma

Diagnostic Testing and Laboratory Monitoring

Blood cultures, if febrile
Nasopharyngeal samples for viral culture (respiratory syncytial virus, influenza), depending on clinical setting
Complete blood counts every day and appropriate chemistries
Continuous pulse oximetry
Chest radiographs for persistent or progressive illness

Treatment

Blood transfusion (simple or exchange) depending on clinical features; consider maintaining an active type and crossmatch
Supplemental O_2 for drop in pulse oximetry by 4% over baseline, or values <90%
Empirical antibiotics (third-generation cephalosporin and macrolide)
Continued respiratory therapy (incentive spirometry and chest physiotherapy as necessary)
Bronchodilators and corticosteroids for patients with asthma
Optimum pain control and fluid management

From Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

- Annual retinopathy screening should be performed beginning at age 10, especially for patients with Hgb S/C variant, in whom proliferative retinopathy occurs in about 30% to 50%. It is less common in Hgb S/S and other variants.
- Gene therapy for patients with sickle cell disease represents a novel approach. Clinical trials with lentiviral vector-mediated addition of an antisickling β-globin gene into autologous hematopoietic stem cells are ongoing with encouraging early results in terms of reduction of sickle cell crises and correction of the biologic hallmarks of the disease.
- Allogeneic stem cell transplantation can be curative in young patients with symptomatic sickle cell disease.
- A recent phase 2 trial for the prevention of pain crises in sickle cell disease involving crizanlizumab, an antibody against the adhesion molecule p-selectin, revealed a significantly lower rate of sickle cell–related pain crisis than placebo and was associated with a low incidence of adverse events.
- A recent phase 3 trial with Voxelotor, an inhibitor of sickle hemoglobin (HbS) polymerization revealed that Voxelotor significantly increased hemoglobin levels and reduced markers of hemolysis.[1]
- Penicillin V 125 mg PO bid should be administered by age 2 mo and increased to 250 mg bid by age 3 yr. Penicillin prophylaxis can be discontinued after age 5 yr except in children who have had splenectomy.
- Table 7 summarizes disease-modifying treatments to consider.

REFERRAL

- Hospitalization for pain crisis unresponsive to oral analgesics, or involving fever, respiratory symptoms, or vomiting and diarrhea.
- Optimal management requires coordination with hematology, blood banking, pain management, and psychosocial counseling and support. ferral for patients with organ-specific complications, notably pulmonary hypertension,

[1]Vichinsky E et al: A phase 3 randomized trial of Voxelotor in sickle cell disease, *N Engl J Med* 381:509-519, 2019.

TABLE 6 Indications for Transfusion in Sickle Cell Disease

	Duration	Consensus	Method	Goal*
Stroke, acute	Single	+	Ex	HbS <30%
Stroke, ongoing care	Chronic	+	Either	HbS <30%
High-velocity transcranial Doppler	Chronic	+	Either	HbS <30%
ACS, initial episode	Single	+	Dir > Ex	Hgb 10
ACS, recurrent	6-12 mo	+	Either	
Pulmonary hypertension	Chronic	+	Either	
Multiorgan failure	Single	+	Ex	
Major surgery	Single	+	Dir	Hgb 10
Acute anemia	Single	+	Dir	
Recurrent spleen sequestration	Chronic	+		
Sepsis/meningitis	Single	+	Dir	
Severe chronic pain	6-12 mo	+		
Congestive heart failure	Chronic	+		
Silent infarct with abnormal neuropsychology	Chronic	–		
Pregnancy		–		
Anemia/renal failure	Chronic	–		
Leg ulcers	6-12 mo	–		
Severe growth delay		–		
Severe eye disease		–		
Priapism		–		

ACS, Acute chest syndrome; *Dir,* direct; *Ex,* exchange; *Hb,* hemoglobin type; *Hgb,* hemoglobin concentration; +, consensus reached; –, consensus not reached.
*Goal of transfusion if a consensus has been reached.
From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

TABLE 7 Disease-Modifying Treatments to Consider[a]

Robust clinical data	Penicillin prophylaxis
	Streptococcus pneumoniae vaccination
	Hydroxyurea
	Chronic exchange transfusion
	Iron chelation for chronic iron overload[b]
Limited clinical data	Daily multivitamin without iron or folate supplementation *and* vitamin D replacement[c]
	Haemophilus influenzae vaccination
	Influenza vaccination
	Erythropoietin
	Phlebotomy
Experimental	Hb F reactivation with decitabine, histone deacetylase inhibitors, or imids
	Erythropoietin for chronic relative reticulocytopenia
	Nutritional supplements and antioxidants (e.g., glutamine, zinc, multivitamins)
	N-acetylcysteine

Hb F, Fetal hemoglobin.
[a]See text for specific indications and limitations.
[b]Best data from thalassemia patient experience.
[c]Risks minimal; therefore, it is generally done.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

acute/chronic kidney disease, and ophthalmologic complications.
- Referral to an ophthalmologist for an annual dilated retinal examination beginning at 10 yr of age.

PEARLS & CONSIDERATIONS

COMMENTS

- The average life span of individuals with sickle cell trait is similar to that of the general population. It may be associated with hematuria, often painless, and rhabdomyolysis under extreme conditions. Chronic pain and acute pain are not typical of sickle cell trait. It is also associated with a higher incidence of renal medullary cancer.
- Regular immunizations, especially pneumococcal vaccination, are recommended. The prophylactic administration of penicillin soon after birth and the timely administration of pneumococcal and *Haemophilus influenzae* type b vaccines have resulted in a significant decline in the incidence of these infections. The heptavalent conjugated pneumococcal vaccine (Prevnar) should be administered from 2 mo of age. The 23-valent unconjugated pneumococcal vaccine (Pneumovax) is given from age 2 yr and can be boosted once 3 yr later. Influenza vaccination can be given after 6 mo of age.
- Pulmonary hypertension is a complication of chronic hemolysis and is associated with a high risk of death. It can be detected by Doppler echocardiography in more than 30% of adult patients with sickle cell disease. Cardiac catheterization will confirm the diagnosis. It is resistant to hydroxyurea therapy.
- Metformin increases fetal hemoglobin (HbF) levels in patients with SCD. A recent study revealed that metformin use in SCD patients with diabetes is associated with fewer episodes of consequential SCD complications and with lower health care utilization.[2]

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Sickle Cell Anemia (Patient Information)

AUTHOR: **Bharti Rathore, MD**

[2]Badawy SM, Payne AB: Association between clinical outcomes and metformin use in adults with sickle cell disease and diabetes mellitus, *Blood Adv* 3:3297-3306, 2019.

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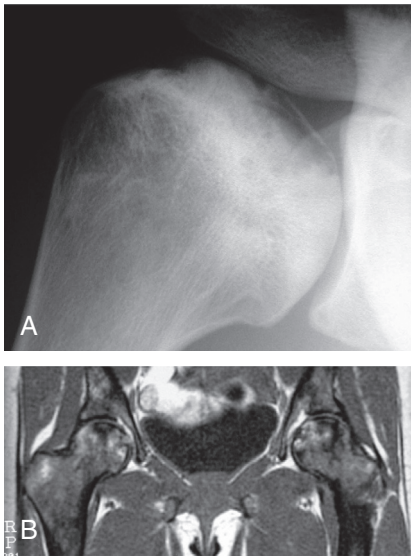

FIG. E2 Sickle cell disease. A, Infarction of the humeral head has led to the separation of an osteochondral fragment of the subarticular bone with adjacent reactive medullary sclerosis. **B,** Coronal T1 weighted image of the proximal femora showing patchy hypointensity within the marrow due to marrow hyperplasia and bilateral femoral head osteonecrosis. (From Adam A et al: *Grainger & Allison's diagnostic radiology,* ed 5, 2007, Churchill Livingstone. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

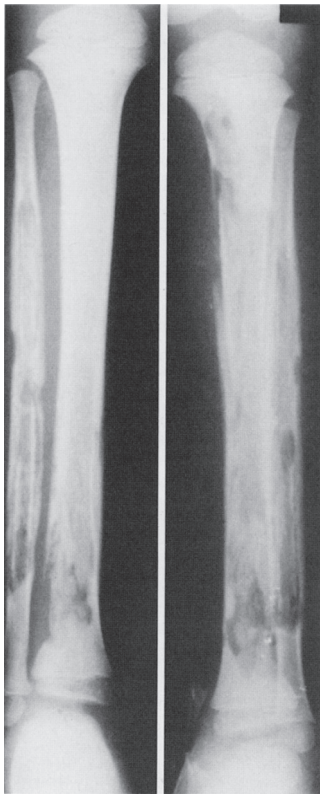

FIG. E3 Sickle cell disease with salmonella osteomyelitis. Extreme destructive changes in the long bones have been caused by infection superimposed upon infarction. Numerous sequestra are present. (From Sutton D: *Textbook of radiology and imaging,* ed 7, 1998, Churchill Livingstone. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Silicosis is a spectrum of lung disease attributable to the inhalation of silica (silicon dioxide) in crystalline form.

SYNONYM

Pneumoconiosis caused by silica

ICD-10CM CODE

J62.8 Pneumoconiosis due to other dust containing silica

EPIDEMIOLOGY & DEMOGRAPHICS

- Occupational disease affecting men and women involved in gathering, milling, processing, or using silica-containing rock or sand. Jobs that can lead to silicosis are described in Box 1.
- According to the Occupational Safety and Health Administration (OSHA), an estimated 200,000 miners and 1.7 million others have experienced an occupational exposure to silica.
- African Americans have a seven times greater rate of developing silicosis compared to whites at the same level of exposure. The annual number of silicosis deaths declined 40% from 185 in 1999 to 111 in 2013, but the decline appears to have leveled off during 2010 to 2013, according to the Centers for Disease Control and Prevention.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- There are three patterns of silicosis: Acute, chronic, and accelerated. The chronic form can be further subdivided in chronic simple silicosis and chronic complicated silicosis (progressive massive fibrosis).
- Acute silicosis is also known as silicoproteinosis. Develops several wk to <5 yr after silica exposure. Presents with rapid onset of cough, weight loss, fatigue, and pleuritic chest pain.
- Chronic silicosis is the most common clinical presentation, and onset occurs after decades of repeated exposure. It has two types:
  1. Simple silicosis, which may be asymptomatic, with the only manifestation being an abnormal chest radiograph. Latency period is 10 to 20 yr and progression to massive fibrosis is rare.
  2. Progressive massive fibrosis characterized by radiographic progression and resulting fibrosis.
- Accelerated silicosis may have an initial asymptomatic phase followed by rapidly increasing frequency of symptoms parallel with worsening radiographic abnormalities. Develops <10 yr after initial high-level exposure.

BOX 1 Jobs That Can Lead to Silicosis

Mining: Surface or underground mining (tunneling)
Milling: Ground silica for abrasives and filler
Quarrying
Sandblasting (e.g., of buildings, preparing steel for painting)
Pottery; ceramic or clay work
Grinding, polishing using silica wheels
Stone work: Strong fabrication, especially with engineered stone.
Foundry work: Grinding, molding, chipping
Refractory brick work
Glass making: To polish and as an abrasive
Boiler work: Cleaning boilers
Manufacture of abrasives

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

ETIOLOGY

- Silica particles are ingested by alveolar macrophages, which in turn release oxidants causing cell injury and cell death, attract fibroblasts, and activate lymphocytes, increasing immunoglobulins in the alveolar space.
- Hyperplasia of alveolar epithelial cells occurs.
- Collagen accumulates in the interstitium.
- Neutrophils also accumulate and secrete proteolytic enzymes, which leads to tissue destruction and emphysema.
- Silica dust may be carcinogenic (not proven).
- Exposure to silicosis predisposes to tuberculosis.
- Some patients develop rheumatoid silicotic pulmonary nodules and may have arthritic symptoms of rheumatoid arthritis (Caplan syndrome). Scleroderma has also been associated with silicosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other pneumoconiosis, berylliosis, hard metal disease, asbestosis
- Sarcoidosis
- Tuberculosis
- Interstitial lung disease
- Hypersensitivity pneumonitis
- Lung cancer
- Langerhans cell granulomatosis (histiocytosis X)
- Granulomatous pulmonary vasculitis

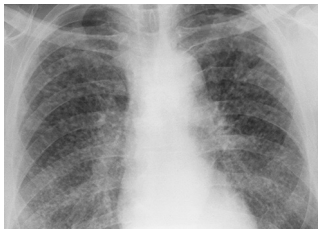

FIG. 1 Simple silicosis. There are multiple small (2- to 4-mm) nodules distributed throughout the lungs with an upper lobe predominance. (From McLoud TC: *Thoracic radiology: the requisites,* St Louis, 1998, Mosby.)

WORKUP

- History of occupational exposure
- Chest radiograph (Fig. 1)

Acute silicosis:

- Chest radiograph demonstrates bilateral, diffuse ground-glass opacities.
- Chest CT demonstrates diffuse nodular and patchy consolidative opacities with enlargement of hilar lymph nodes.
- Milky and lipoproteinaceous effluent is seen on bronchoalveolar lavage (BAL).
- Lung biopsy is not necessary in the setting of a definite exposure history.
- Exclusion of other causes like pulmonary edema, alveolar hemorrhage, and pulmonary alveolar proteinosis is necessary.

Chronic silicosis:

- Chest radiograph demonstrates multiple small, rounded opacities (<10 cm in diameter) distributed in the upper lung zones.
- Progressive massive fibrosis (PMF) refers to coalescence of the nodules of chronic silicosis with calcified hilar adenopathy.
- Pulmonary function tests (PFT) show mixed obstructive and restrictive defect.
- High resolution CT scan (HRCT), bronchoscopy, and lung biopsies have limited diagnostic role unless atypical radiographic features are noted.

Accelerated silicosis:

- Radiographic pattern is that of simple silicosis, although development of radiographic abnormalities is more rapid. This has greater risk for PMF.

TREATMENT

- Treatment is symptomatic (supplemental O_2 for hypoxemia, bronchodilators, antibiotics for infections).
- Prevention (industrial hygiene).
- Smoking cessation.
- Vaccination against influenza and pneumococcus.
- Whole-lung lavage may have a role in acute silicoproteinosis.
- Treatment of associated tuberculosis if present.
- Consider lung transplant for patients who develop chronic respiratory failure.
- Once patients progress to fibrosis, no therapies can alter the course of the disease.

ASSOCIATED COMPLICATIONS

Silicosis is associated with increased risk of mycobacterial infections, including tuberculosis, chronic necrotizing aspergillosis, lung cancer, rheumatic disorders, and chronic airflow obstruction.

RELATED CONTENT

Silicosis (Patient Information)

AUTHORS: **Javeryah Safi, MD,** and **Samaan Rafeq, MD**

BASIC INFORMATION

DEFINITION

Sinusitis is inflammation of the mucous membranes lining one or more of the paranasal sinuses. The various presentations are:

- Acute sinusitis: Infection lasting <4 wk, with complete resolution of symptoms.
- Subacute infection: Lasts from 4 to 12 wk, with complete resolution of symptoms.
- Recurrent acute infection: Episodes of acute infection lasting <30 days, with resolution of symptoms, which recur at intervals at least 10 days apart.
- Chronic sinusitis: Inflammation of the paranasal sinuses and nasal cavities lasting >12 wk, with persistent upper respiratory symptoms. It accounts for 1% to 2% of total physician encounters.
- Acute bacterial sinusitis superimposed on chronic sinusitis: New symptoms that occur in patients with residual symptoms from prior infection(s). With treatment, the new symptoms resolve but the residual ones do not.

SYNONYM

Rhinosinusitis: Sinusitis is almost always accompanied by inflammation of the nasal mucosa; thus it is now the preferred term.

ICD-10CM CODES

J32.9	Chronic sinusitis, unspecified
J01.90	Acute sinusitis, unspecified
J01.00	Acute maxillary sinusitis, unspecified
J01.01	Acute recurrent maxillary sinusitis
J01.10	Acute frontal sinusitis, unspecified
J01.11	Acute recurrent frontal sinusitis
J01.20	Acute ethmoidal sinusitis, unspecified
J01.21	Acute recurrent ethmoidal sinusitis
J01.30	Acute sphenoidal sinusitis, unspecified
J01.31	Acute recurrent sphenoidal sinusitis
J01.80	Other acute sinusitis
J01.81	Other acute recurrent sinusitis
J01.91	Acute recurrent sinusitis, unspecified
J32.0	Chronic maxillary sinusitis
J32.1	Chronic frontal sinusitis
J32.2	Chronic ethmoidal sinusitis
J32.3	Chronic sphenoidal sinusitis
J32.8	Other chronic sinusitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Seems to correlate with the incidence of upper respiratory tract infections and higher in women than men; 30 million cases a yr in the U.S.

PEAK INCIDENCE:

- Fall, winter, spring: September through March
- In adults: Greatest incidence between 45 and 74 yr of age
- Approximately 6% to 7% of children presenting with respiratory symptoms have acute sinusitis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients often give a history of a recent upper respiratory illness with some improvement, then a relapse
- Mucopurulent secretions in the nasal passage:
  1. Purulent nasal and postnasal discharge lasting 7 to 10 days
  2. Facial tightness, pressure, or pain
  3. Nasal obstruction
  4. Headache
  5. Decreased sense of smell
  6. Purulent pharyngeal secretions, brought up with cough, often worse at night
- Erythema, swelling, and tenderness over the infected sinus in a small proportion of patients:
  1. Diagnosis cannot be excluded by the absence of such findings.
  2. These findings are not common, and do not correlate with number of positive sinus aspirates.
- Intermittent low-grade fever in about half of adults with acute bacterial sinusitis
- Toothache is a common complaint when the maxillary sinus is involved
- Periorbital cellulitis and excessive tearing with ethmoid sinusitis:
  1. Orbital extension of infection: Chemosis, proptosis, impaired extraocular movements
- Characteristics of acute sinusitis in children with upper respiratory tract infections:
  1. Persistence of symptoms
  2. Cough
  3. Bad breath
- Symptoms of chronic sinusitis (may or may not be present):
  1. Nasal or postnasal discharge
  2. Fever
  3. Facial pain or pressure
  4. Headache
- Nosocomial sinusitis is typically seen in patients with nasogastric tubes or nasotracheal intubation

ETIOLOGY

- Each of the four paranasal sinuses is connected to the nasal cavity by narrow tubes (ostia), 1 to 3 mm in diameter; these drain directly into the nose through the turbinates. The sinuses are lined with a ciliated mucous membrane (mucoperiosteum).
- Acute viral infection:
  1. Infection with the common cold or influenza
  2. Mucosal edema and sinus inflammation
  3. Decreased drainage of thick secretions/obstruction of the sinus ostia
  4. Subsequent entrapment of bacteria
     a. Multiplication of bacteria
     b. Secondary bacterial infection
- Other predisposing factors:
  1. Tumors
  2. Polyps
  3. Foreign bodies
  4. Congenital choanal atresia
  5. Other entities that cause obstruction of sinus drainage
  6. Allergies
  7. Asthma
- Dental infections lead to maxillary sinusitis.
- Viruses recovered alone or in combination with bacteria (in 16% of cases):
  1. Rhinovirus
  2. Coronavirus
  3. Adenovirus
  4. Parainfluenza virus
  5. Respiratory syncytial virus
- The principal bacterial pathogens in sinusitis are *Streptococcus pneumoniae,* nontypable *Haemophilus influenzae,* and *Moraxella catarrhalis.*
- In the remainder of cases *Streptococcus pyogenes, Staphylococcus aureus,* beta-hemolytic streptococci, and mixed anaerobic infections (*Peptostreptococcus, Fusobacterium, Bacteroides, Prevotella* spp.) are found.
- Infection is polymicrobial in about one third of cases.
- Anaerobic infections are seen more often in cases of chronic sinusitis and in cases associated with dental infection; anaerobes are unlikely pathogens in sinusitis in children.
- Fungal pathogens are isolated with increasing frequency in immunocompromised patients but remain uncommon pathogens in the paranasal sinuses. Fungal pathogens include *Phaeohyphomycosis, Aspergillus, Pseudallescheria, Sporothrix, and Zygomycetes spp.*
- Nosocomial infections: Occur in patients with nasogastric tubes, nasotracheal intubation, cystic fibrosis, and immunocompromised state.
  1. *S. aureus* (including MRSA)
  2. *Pseudomonas aeruginosa*
  3. *Klebsiella pneumoniae*
  4. *Enterobacter* spp.
  5. *Proteus mirabilis*
- Organisms typically isolated in chronic sinusitis:
  1. *S. aureus*
  2. *S. pneumoniae*
  3. *H. influenzae*
  4. *P. aeruginosa*
  5. Anaerobes

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Temporomandibular joint disease
- Migraine headache
- Cluster headache
- Dental infection
- Trigeminal neuralgia
- Allergic rhinitis
- Drugs (cocaine, decongestant overuse)
- Gastroesophageal reflux disease
- Wegener granulomatosis
- Cystic fibrosis

WORKUP

- The diagnosis is generally based on clinical signs and symptoms (purulent rhinorrhea and facial pain). Radiologic tests and cultures are not recommended initially and should be considered only when treatment is ineffective and sinusitis persists.
- In the normal healthy host, the paranasal sinuses should be sterile. Although the contiguous structures are colonized with bacteria and likely contaminate the sinuses, the mucociliary lining functions to remove these bacteria.
- Gold standard for diagnosis: Recovery of bacteria in high-density $\geq 10^4$ colony-forming

units/ml from a paranasal sinus, in the setting of a patient with history of upper respiratory infection and symptoms persisting for 7 to 10 days. Sinus aspiration is the best method for obtaining cultures; however, it must be performed by an otorhinolaryngologist and is not practical for the primary care practitioner. Therefore, most diagnoses are based on the clinical history and presentation, possibly supported by radiologic evaluations.

1. Overall, standard radiographs are of limited use in diagnosis, although negative films are strong evidence against the diagnosis
2. CT scans:
   a. Much more sensitive than plain radiographs in detecting acute changes and disease in the sinuses
   b. Recommended for patients requiring surgical intervention, including sinus aspiration; it is a useful adjunct to guide therapy
3. Transillumination:
   a. Used for diagnosis of frontal and maxillary sinusitis
   b. Absence of light transmission indicates that sinus is filled with fluid
   c. Dullness (decreased light transmission) is less helpful in diagnosing infection
4. Endoscopy:
   a. Used to visualize secretions coming from the ostia of infected sinuses
   b. Culture collection via endoscopy often contaminated by nasal flora; not nearly as good as sinus puncture
5. Sinus puncture:
   a. Gold standard for collecting sinus cultures
   b. Generally reserved for treatment failures, suspected intracranial extension, and nosocomial sinusitis

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

To help promote sinus drainage:

- Air humidification with vaporizers (for steam) or humidifiers (for a cool mist)
- Application of hot, wet towel over the face
- Sipping hot beverages
- Hydration

ACUTE GENERAL Rx

- Sinus drainage:
  1. Nasal vasoconstrictors, such as phenylephrine nose drops, 0.25% or 0.5%.
  2. Topical decongestants should not be used for more than a few days because of the risk of rebound congestion.
  3. Systemic decongestants.
  4. Corticosteroids: Nasal or systemic corticosteroids, such as nasal beclomethasone. Oral corticosteroids combined with antibiotics may be associated with modest benefit for short-term relief of symptoms in adults with severe symptoms of acute sinusitis compared with antibiotics alone. Oral corticosteroids as monotherapy are not associated with improved clinical outcomes in adults with clinically diagnosed acute sinusitis.[1]
  5. Nasal irrigation, with hypertonic or normal saline (saline may act as a mild vasoconstrictor of nasal blood flow).
  6. Use of antihistamines has no proven benefit, and the drying effect on the mucous membranes may cause crusting, which blocks the ostia, thus interfering with sinus drainage.
- Analgesics, antipyretics

Antimicrobial therapy:

- Most cases of acute sinusitis have a viral cause and will resolve within 2 wk without antibiotics.
- Current treatment recommendations favor symptomatic treatment for those with mild symptoms. 85% of persons have a reduction or resolution of symptoms within 7 to 15 days without antibiotic therapy. Physicians grossly overprescribe antibiotics for presumed bacterial sinusitis despite a much higher prevalence of viral infections.
- Antibiotics should not be prescribed for mild to moderate sinusitis within the first wk of illness. They should be reserved for those with persistent symptoms for more than 10 days, high fever and purulent nasal discharge or facial pain lasting for at least 3 consecutive days, or worsening symptoms after a typical viral illness lasting >5 days that had initially improved ("double sickening").
- Antibiotic therapy is usually empiric, targeting the common pathogens:
  1. First-line antibiotics in children include amoxicillin or amoxicillin/clavulanate. For adults amoxicillin/clavulanate or doxycycline is first-line agent, with quinolones (levofloxacin or moxifloxacin) reserved as second-line agents unless patient is penicillin allergic.
  2. Second-line antibiotics include the newer macrolides: clarithromycin, and oral cephalosporins: cefuroxime axetil, cefprozil, cefaclor, loracarbef, but high rate of resistance of *S. pneumoniae* is a concern with these agents as is *H. influenzae* resistance with TMP-SMX and azithromycin such that they should no longer be used as first-line agents.
  3. For patients with uncomplicated acute sinusitis, the less expensive first-line agents appear to be as effective as the costlier second-line agents.
- Hospitalization and IV antibiotics may be required for more severe infection and those with suspected intracranial complications. Broader-spectrum antibiotic coverage may be indicated in severe cases, to cover for MRSA, *Pseudomonas*, and fungal pathogens.
- Duration of therapy generally 5 to 7 days in adults rather than 10 to 14 days as recommended in the past.
  1. Optimal duration of treatment in children varies from 10 to 28 days.

Surgery:

- Surgical drainage indicated
  1. If intracranial or orbital complications suspected
  2. Many cases of frontal and sphenoid sinusitis
  3. Chronic sinusitis recalcitrant to medical therapy
- Surgical debridement imperative in the treatment of fungal sinusitis

Complications:

- Untreated, sinusitis may lead to a number of serious, life-threatening complications.
- Intracranial complications include meningitis, brain abscess, and epidural and subdural empyema.
- Intracranial sequelae are more common with frontal and ethmoid infections.
- Extracranial complications include orbital cellulitis, blindness, orbital abscess, osteomyelitis.
- Extracranial sequelae are more commonly seen with ethmoid sinusitis.

CHRONIC Rx

- Chronic sinusitis: Evidence supports daily high-volume saline irrigation with topical corticosteroid therapy as a first-line therapy for chronic sinusitis. A short course of systemic corticosteroids (1 to 3 wk), short course of doxycycline (3 wk), or a leukotriene antagonist may be considered in patients with nasal polyps. A prolonged course (3 mo) of macrolide antibiotic may be considered for patients without polyps.
- Dupilumab (Dupixent), a monoclonal antibody that targets interleukin (IL)-4 and -13 was recently FDA approved for chronic rhinosinusitis with nasal polyps (CRSwNP). Cost is a limiting factor.
- Surgical intervention may be necessary in nonresponders.

REFERRAL

- To infectious disease specialist if failure to respond to initial therapy
- To otorhinolaryngologist for:
  1. Failure to respond to therapy
  2. Suspected fungal infection
  3. Suspected intracranial or orbital complications

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Sinusitis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

[1]Venekamp RP et al: Systemic corticosteroid therapy for acute sinusitis, *JAMA* 313(12):1258-1259, 2015.

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Sjögren Syndrome PTG ALG

BASIC INFORMATION

DEFINITION

Sjögren syndrome (SS) is a chronic autoimmune disorder that targets exocrine glands. It is characterized by lymphocytic and plasma cell infiltration and destruction of salivary, lacrimal, and parotid glands, resulting predominantly in dry eyes and dry mouth, but it can affect other organ systems as well.

Primary and secondary forms have been described:

- Primary: Dry mouth (xerostomia) and dry eyes (xerophthalmia) develop as isolated entities. Is immunogenetically associated with HLA-DRB1*0301 and DRB1*1501 and serologically associated with antibodies to Ro/SS-A and La/SS-B.
- Secondary: Associated with other autoimmune connective tissue diseases. The immunogenetic and serologic findings are usually those of the accompanying disease (e.g., HLA-DR4 if associated with RA).

SYNONYMS

SS
Sicca syndrome
Keratoconjunctivitis sicca
Sicca complex
Dry eye syndrome/dysfunctional tear syndrome

ICD-10CM CODES

M35.00	Sicca syndrome, unspecified
M35.01	Sicca syndrome with keratoconjunctivitis
M35.02	Sicca syndrome with lung involvement
M35.03	Sicca syndrome with myopathy
M35.04	Sicca syndrome with tubulo-interstitial nephropathy
M35.09	Sicca syndrome with other organ involvement

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 4 per 100,000; of these cases, 70% had primary SS.

PREVALENCE: Prevalence is 0.2% to 2.7% of population; secondary SS is also common and can affect up to 19% of patients with systemic lupus erythematosus (SLE) and 26% to 31% of rheumatoid arthritis (RA) and scleroderma patients.

PREDOMINANT SEX: Female:male ratio is approximately 10:1.

PREDOMINANT AGE: Peak incidence is the fourth and fifth decade, but can occur in all ages. Rarely reported in children.

RISK FACTOR: Seen in all races/ethnicities, but more common in Caucasians.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

SS is one of the most common autoimmune diseases and should be considered in any patient with unexplained symptoms and a positive antinuclear antibody.

2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary SS: A score of >4 when the weights from the criteria are summed:

- Labial salivary gland with focal lymphocytic sialadenitis and focus of >1 foci/4 mm^2—score 3
- Anti-SSA/Ro positive—score 3
- Ocular staining score >5 in at least one eye—score 1
- Schirmer test <5 mm/5 min in at least one eye—score 1
- Unstimulated whole saliva flow rate <0.1 ml/min—score 1

Diagnosis of SS based on the prior diagnostic criteria was presence of at least two of three objective diagnostic tests below:

1. Positive serum levels of anti-SS-A/Ro and/or anti-SS-B/La or a positive rheumatoid factor and antinuclear antibody (ANA) titer of at least 1:320
2. Salivary gland biopsy exhibiting focal sites of inflammation. One or more sites of inflammation per 4 mm^2 are considered to be positive
3. Keratoconjunctivitis sicca with ocular staining score of three or more (the dissipation rate of a specialized dye that is applied to the tear film that bathes the surface of the eye; a score of three or more is considered to be positive)

Manifestations:

- Dry mouth, dry lips (cheilosis), erythema and hyperlobulation of tongue (Fig. E1) and other mucosal surfaces, carious teeth
- Dry eyes (conjunctival injection, corneal ulceration, blurred vision, decreased luster, enlargement of lacrimal glands, and irregularity of the corneal light reflex)
- Salivary gland enlargement (Fig. E2) and dysfunction, with subsequent difficulty in chewing and swallowing food and in speaking without frequent water intake, thickened saliva, and burning sensation in mouth
- Extra-glandular involvement occurs in 50% of patients. There are multiple systemic manifestations associated with SS, which include the following:
  1. Fever/fatigue.
  2. Cutaneous vasculitis may be present, usually of lower extremities.
  3. Skin ulceration, photosensitivity, Raynaud phenomenon.
  4. Dyspareunia and pruritus can occur secondary to vaginal dryness.
  5. Pulmonary involvement includes interstitial lung disease (NSIP, UIP); lymphocytic interstitial pneumonitis (LIP) and cryptogenic organizing pneumonia (COP); chronic obstructive pulmonary disease; fibrosis; and xerotrachea.
  6. Gastrointestinal: Celiac disease, esophageal dysmotility, type I autoimmune hepatitis, primary biliary cirrhosis, and pancreatitis can occur.
  7. Renal manifestations: Type 1 renal tubular acidosis, Fanconi syndrome, glomerulonephritis, and interstitial nephritis.
  8. Neurologic involvement: Peripheral, cranial, or autonomic neuropathy; CNS involvement also possible, cognitive dysfunction ("brain fog").
  9. Musculoskeletal: Arthralgias and myopathy.
  10. Hematologic: Cytopenias, hypergammaglobulinemia, cryoglobulins. Increased lymphoma risk, with 5% to 10% developing non-Hodgkin lymphoma.
  11. RA and other connective tissue diseases are seen commonly with secondary SS.
  12. Autoimmune thyroiditis may be observed in patients with SS.
  13. Pregnancy: Patients with anti-SSA antibodies have an increased risk of delivering a baby with neonatal lupus, with cutaneous manifestations or congenital heart block.

ETIOLOGY

Sjögren syndrome is an autoimmune disorder of unclear etiology. It is associated with certain HLA-DQ and HLA-DR alleles. It has been postulated that viral agents (e.g., hepatitis C and Epstein-Barr virus) may trigger the clinical manifestations. The pathogenesis involves a complex interplay of several factors, including genetic and epigenetic controls of immune homeostasis and gene expression, age, gender, and environmental insults.

Over 90% of the infiltrating cells are CD4+ T lymphocytes with memory phenotype (70%) and B lymphocytes (20%). The remaining 10% are an admixture of plasma cells, CD8+ T lymphocytes, T regulatory cells, natural killer cells, and dendritic cells. Predominantly Th1- and Th17-driven response.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Medication-related dryness (e.g., anticholinergics, antihistamines, diuretics, benzodiazepines, antidepressants)
- Age-related exocrine gland dysfunction
- Mouth breathing, anxiety
- Infections such as viruses, HIV, hepatitis C
- Diabetes mellitus, acromegaly, Type V hyperlipidemia
- Chronic sialadenitis
- Graft-versus-host diseaselg
- G4-related disease
- Ocular herpetic lesions, blepharitis, corneal abrasions, contact lens irritation
- Vitamin A deficiency
- Other: Sarcoidosis, primary salivary hypofunction, radiation injury, amyloidosis
- An algorithm for the diagnosis of SS is provided in Fig. 3

WORKUP

Workup involves ocular and oral examination and laboratory and radiographic testing to demonstrate the following criteria for diagnosis of primary and secondary SS.

- Symptoms and objective signs of ocular dryness:
  1. Schirmer test (Fig. E4): <5 mm wetting per 5 min. (Normal wetting is >15mm in

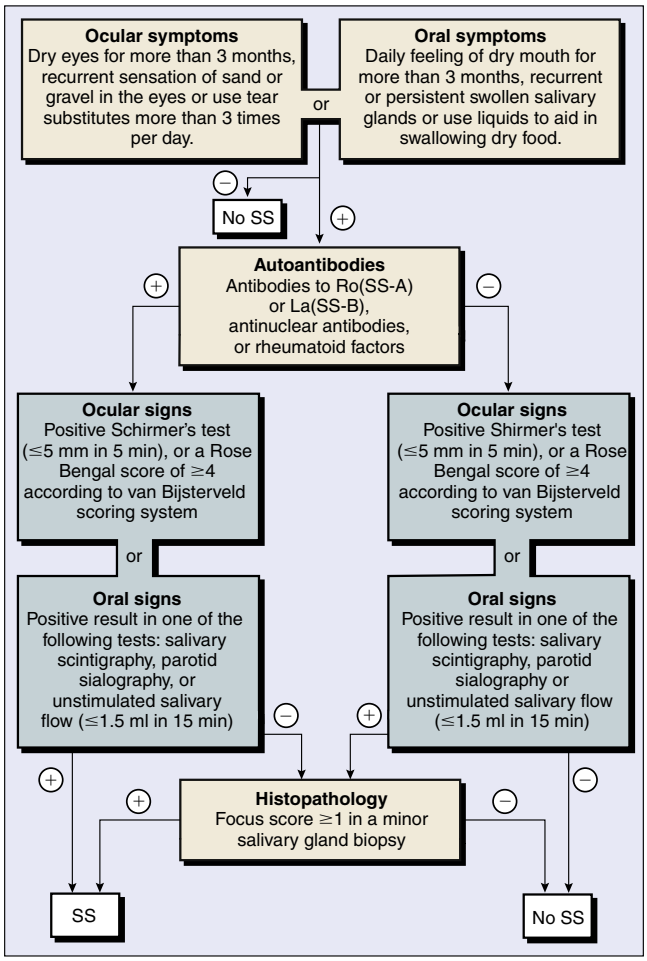

FIG. 3 Suggested algorithm for the diagnosis of Sjögren syndrome. Exclusion criteria include hepatitis C or human immunodeficiency virus infection, sarcoidosis, graft-versus-host disease, preexisting lymphoma, previous head or neck irradiation, and use of anticholinergic drugs. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

5 minutes). There is a 15% false-positive and false-negative rate.
2. Zone-quick diagnostic threads: A sterile cotton thread with pH indicator, phenol red. Yellow turns to red in contact with tears.
3. Positive Rose Bengal stains dead/dying cells.
4. Tear breakup time and tear osmolality measured after instillation of fluorescein.

- Symptoms and objective signs of dry mouth:
  1. Decreased parotid flow using Lashley cups or other methods
  2. Abnormal biopsy result of minor salivary gland (focus score >1 based on average of four assessable lobules)
  3. Sialometry (sensitivity 56%, specificity 81%): Assessment of rate of saliva production in which collection of ≤1.5 ml after two expectorations 15 min apart is considered positive
- Evidence of systemic autoimmune disorder:
  1. Elevated rheumatoid factor (70% to 90% of patients)
  2. Elevated titer of ANA >1:320 (80% of patients)
  3. Presence of anti-SS-A (Ro) (>60% of patients) or anti-SS-B (La) antibodies (40% of patients)

SECONDARY:
- Characteristic signs and symptoms of SS
- Clinical features sufficient to allow a diagnosis of RA, SLE, polymyositis, or scleroderma

LABORATORY TESTS

- Positive ANA (80% of patients) with autoantibodies anti-SS-A and anti-SS-B may be present.
- Additional laboratory abnormalities may include elevated erythrocyte sedimentation rate, anemia, leukopenia, thrombocytopenia, abnormal liver function studies, elevated serum beta$_2$ microglobulin levels, rheumatoid factor (50% to 60%), hypergammaglobulinemia, antibodies to double-stranded DNA (in cases with proteinuria), depressed C3 and C4, and the presence of cryoglobulins (30% of patients).
- A definite diagnosis of SS can be made with a salivary gland biopsy (gold standard) showing focal lymphocytic sialadenitis with focus score of 1 per 4 mm^2 of glandular tissue.
- Salivary gland ultrasound can be done to characterize changes in salivary gland parenchyma (sensitivity 75%, specificity 78%). Diseased gland shows hypoechoic areas with convex borders.
- MRI of the gland shows inhomogeneous parenchyma. Finding generally correlates with biopsy of the gland.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Adequate fluid replacement. Ameliorate skin dryness by gently blotting dry after bathing, leaving a small amount of moisture, and then applying a moisturizer
- Increased environmental moisture by using humidifiers
- Proper oral hygiene (daily topical fluoride use, antimicrobial mouth rinses, and stabilization of oral cavity pH) to reduce the incidence of caries
- Sugar-free chewing gum and sour lemon lozenges to stimulate salivary secretion
- Periodic dental and ophthalmologic evaluations to screen for complications
- Reduce caffeine intake and smoking

GENERAL Rx

- Use artificial tears frequently.

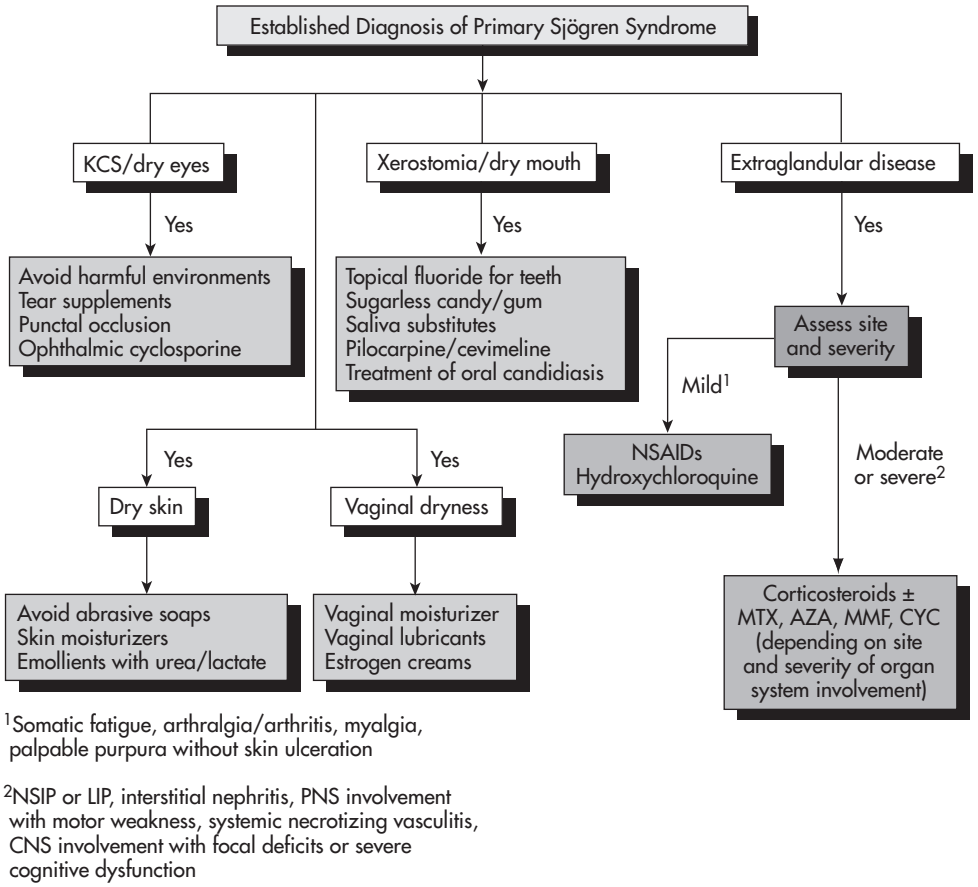

FIG. 5 Treatment algorithm for Sjögren syndrome. The treatment of Sjögren syndrome usually requires a multidisciplinary approach involving rheumatologists, ophthalmologists, dentists/oral surgeons, otolaryngologists, and other subspecialists, depending on the extent of extra-glandular disease. In all cases, it is prudent to minimize the use of medications that can exacerbate the symptoms of dryness, such as antihistamines, antidepressants, muscle relaxers, and other drugs with anticholinergic properties. The treatment of extra-glandular disease is individualized according to the site and severity of organ system involvement. The approaches indicated in the algorithm for the treatment of extra-glandular disease are not supported by evidence from randomized, controlled trials, but rather from expert opinion based on retrospective case series and clinical experience. *AZA,* Azathioprine; *CNS,* central nervous system; *CYC,* cyclophosphamide; *KCS,* keratoconjunctivitis sicca; *LIP,* lymphocytic interstitial pneumonitis; *MMF,* mycophenolate mofetil; *MTX,* methotrexate; *NSAIDs,* nonsteroidal antiinflammatory drugs; *NSIP,* nonspecific interstitial pneumonitis; *PNS,* peripheral nervous system. (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

- Muscarinic agonists: Pilocarpine (5mg PO QID) or cevimeline (30mg PO TID) can be useful to improve oral dryness.
- Ophthalmic cyclosporine and lifitegrast drops may be useful for dry eyes.
- Hydroxychloroquine alone or in conjunction with methotrexate may be useful for arthralgias and cutaneous manifestations.
- Oral cyclosporine only improves the symptoms of subjective dryness.
- Tumor necrosis factor (TNF) antagonists have not shown benefit in short-duration placebo-controlled trials.
- Rituximab (RTX) has shown some improvement in oral dry mouth symptoms, relieving marked salivary and lacrimal gland swelling in a retrospective review.
- Propionic acid gel can be used for vaginal dryness.
- Systemic manifestations are treated according to symptoms and complications.
- Cyclophosphamide, azathioprine, and mycophenolate mofetil are generally reserved for life-threatening extra-glandular manifestations.
- Fig. 5 describes a treatment algorithm for Sjögren syndrome.

REFERRAL

- Rheumatology referral is generally indicated.
- Referral should be made to an oncologist when lymphoma is suspected.
- During pregnancy, if patient tests positive for SSA/SSB antibody, she should seek consultation with a perinatologist.

PEARLS & CONSIDERATIONS

COMMENTS

- Unusual presentations of SS may occur in association with polymyalgia rheumatica, chronic fatigue syndrome, fever of unknown origin, and inflammatory myositis.
- The most serious complication of primary SS is the development of non-Hodgkin lymphoma and other lymphoproliferative disorders, which occur at a ten- to forty-fourfold increased rate as compared to age-matched controls.
- The presence of parotid gland enlargement, rheumatoid factor, low C4, cryoglobulinemia, lymphopenia, and higher levels of disease activity as measured by EULAR Sjögren Syndrome Disease Activity Index (ESSDAI) predicts a higher lymphoma risk.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Sjögren Syndrome (Patient Information)

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SUGGESTED READINGS

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Vivino FB et al: New treatment guidelines for Sjögren's disease., *Rheum Dis Clin North Am* 42(3):531-551, 2016, https://doi.org/10.1016/j.rdc.2016.03.010.

FIG. E1 Hyperlobulation of the tongue. Hyperlobulation and fissuring of the tongue are characteristic changes associated with salivary hypofunction in patients with Sjögren syndrome. The papillary atrophy can be a manifestation of oral candidiasis and may be reversed with antifungal therapy. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

FIG. E2 Bilateral parotid gland enlargement. Marked enlargement of both parotid glands is evident in this young woman with Sjögren syndrome. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

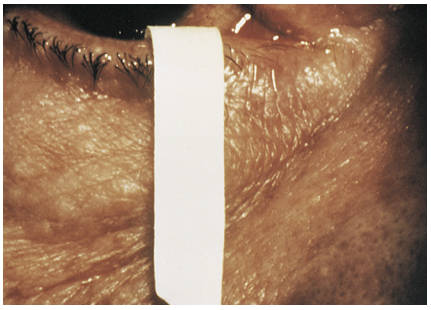

FIG. E4 Schirmer test in a patient with Sjögren syndrome. Wetting of less than 5 mm/5 min of the filter paper strip is shown. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

BASIC INFORMATION

DEFINITION

The *International Classification of Sleep Disorders, Third Edition,* classifies sleep-disordered breathing disorders into five categories: central sleep apnea syndrome (Table 1), obstructive sleep apnea disorders (OSA), sleep-related hypoventilation disorders, sleep-related hypoxemia disorder, and isolated symptoms and normal variants. The American Academy of *Sleep Medicine* defines OSA as repetitive episodes of upper airway obstruction that occur during sleep and that are typically associated with oxyhemoglobin desaturations.

SYNONYMS

Sleep apnea syndrome
Sleep-disordered breathing
Obstructive sleep apnea syndrome (OSA)
Obstructive sleep apnea–hypopnea syndrome

ICD-10CM CODES

G47.30	Sleep apnea, unspecified
G47.31	Primary central sleep apnea
G47.33	Obstructive sleep apnea (adult) (pediatric)
G47.37	Central sleep apnea in conditions classified elsewhere
G47.39	Other sleep apnea
P28.3	Primary sleep apnea of newborn

EPIDEMIOLOGY & DEMOGRAPHICS

OSA is a common disease in the U.S. Data from the Wisconsin Cohort Study indicated that the current prevalence of moderate to severe sleep-disordered breathing (apnea-hypopnea index, measured as events/hour, ≥15) is 10% among 30- to 49-yr-old men; 17% among 50- to 70-yr-old men; 3% among 30- to 49-yr-old women; and 9% among 50- to 70-yr-old women. The prevalence of OSA with associated excessive daytime somnolence is approximately 3% to 7% in adult men and 2% to 5% in adult women.[2] The prevalence seems to be higher in obese and hypertensive patients. The prevalence of OSA in the general pediatric population is estimated to be 1% to 6%. However, in obese children and adolescents, OSAH is reported to occur in 19% to 61%. Risk factors include obesity, craniofacial and upper airway abnormalities, and retrognathia, while family history of OSA, current tobacco smoking, nasal congestion, and diabetes are clinical associations. There are an estimated 24 million persons in the U.S. who remain undiagnosed.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Many patients are unaware that their breathing is affected and may not visit a physician for evaluation. Others may not consider sleepiness a relevant topic to discuss with their health care provider.
- Nocturnal symptoms, including gastroesophageal reflux symptoms, nocturia, and angina pectoris
- Snoring (potentially loud, habitual, and bothersome to others)
- Witnessed apneas that often interrupt snoring and end with a snort
- Gasping, choking, or smothering sensations that arouse the patient from sleep
- Restless sleep associated with frequent arousals
- Daytime symptoms:
  1. Nonrestorative sleep
  2. Not feeling refreshed upon awakening
  3. Morning headache
  4. Dry mouth or throat upon awakening
  5. Excessive daytime sleepiness, typically during quiet activities
  6. Daytime fatigue or tiredness
  7. Problems with memory, concentration, and cognitive function, especially with executive functioning
  8. Easily angered, short tempered, and inattentive
  9. Hyperactivity in children
  10. Symptoms of fibromyalgia
  11. Cognitive decline (older population)
- Obesity (body mass index >30 kg/m2). A 10% increase in weight predicts a sixfold increase in the likelihood of developing clinically significant OSA
- Insulin resistance or type 2 diabetes mellitus
- Mood swings, irritability, anxiety, and/or depression
- Decreased libido and/or impotence
- Neck circumference (surrogate marker for central obesity) of >43 cm (17 in) in men and >37 cm (15 in) in women
- Erythematous oropharynx because of snoring
- Adenotonsillar hypertrophy, excessive soft tissue, high-arched hard palate, pendulous uvula, prominent tongue, large degree of overjet, and retrognathia or micrognathia can be present
- Narrowing of lateral airway walls is independent predictor of OSA in men but not women
- Craniofacial skeletal abnormalities can lead to OSA, particularly among children and nonobese adults
- Systemic hypertension (HTN)
- Pulmonary HTN
- Family history of OSA increases risk with each additional close family member further increasing odds
- Table 2 summarizes clinical characteristics of patients with sleep apnea

TABLE 1 Pathophysiologic Classification of Central Sleep Apneas

Physiologic	Pathologic
• Sleep transition • Phasic REM	Nonhypercapnic • Medical condition related 1. Congestive heart failure 2. Poststroke 3. ESRD 4. PAH 5. Atrial fibrillation • High altitude • Idiopathic Hypercapnic • Congenital central hypoventilation syndrome • Primary chronic alveolar hypoventilation syndromes • Other CNS disorders associated with CSA 1. Encephalitis, tumors, strokes 2. Anatomic abnormalities 3. Neurodegenerative disorders • Muscular and PNS disorders associated with CSA (selected examples) 1. Muscular dystrophies 2. Acid maltase deficiency 3. Charcot-Marie-Tooth disease and other neuropathies 4. Postpolio syndrome 5. Myasthenia gravis Disintegrative (e.g., brainstem injury, opioid induced) CSA with OSA or upper airway disorders (including treatment emergent CSA)

CNS, Central nervous system; *CSA,* central sleep apnea; *ESRD,* end-stage renal disease; *OSA,* obstructive sleep apnea; *PAH,* pulmonary arterial hypertension, *PNS,* peripheral nervous system; *REM,* rapid eye movements.
From Kryger M et al: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.

ETIOLOGY

- Narrowing of upper airway as a result of obesity or increased peripharyngeal fat deposition, retrognathia and/or micrognathia, adenotonsillar hypertrophy, macroglossia, or neuromuscular weakness (Fig. E1)
- Upper airway muscular weakness as a result of neuromuscular disorders, primary CNS disorders (e.g., stroke), or metabolic disorders
- Other diseases associated with the development of OSAH (e.g., hypothyroidism, acromegaly)
- Fig. E2 illustrates the pathophysiologic consequences of OSA

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Anemia
- Anxiety or panic disorder
- Behaviorally induced insufficient sleep syndrome
- Cardiac or heart disease
- Central sleep apnea
- Circadian rhythm disorder

TABLE 2 Clinical Characteristics of Patients with Sleep Apnea

Central		
Nonhypercapnic	**Hypercapnic**	**Obstructive**
Insomnia	Daytime sleepiness Morning headache	Daytime sleepiness
Mild intermittent snoring	Snoring	Prominent snoring
Awakenings (choking, dyspnea)	Respiratory failure	Witnessed apneas, gasping
Normal body habitus	Normal or obese Polycythemia Cor pulmonale	Commonly obese Upper airway narrowing

From Kryger M et al: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.

Epworth Sleepiness Scale

Situation	Score
Sitting and reading	
Watching TV	
Sitting inactive in public place	
Passenger in car	
Lying down to rest in afternoon	
Sitting talking to someone	
Sitting after lunch without alcohol	
In a car, stopped for minutes in traffic	
Total (normal #10)	

Dozing

0 = Never

1 = Slight chance

2 = Moderate chance

3 = High chance

FIG. 3 The Epworth Sleepiness Scale. This instrument asks patients about their likelihood of dozing in eight different situations over the past mo. (From Mason RJ et al: *Murray and Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, WB Saunders.)

- Depression
- Drug or alcohol abuse
- Gastroesophageal reflux
- Hypothyroidism
- Idiopathic hypersomnia with long or short sleep time
- Inadequate sleep hygiene
- Insomnia
- Medication effect
- Narcolepsy
- Nocturnal asthma
- Nocturnal gastroesophageal reflux
- Nocturnal seizures
- Obesity-hypoventilation syndrome
- Parasomnias
- Parkinson disease
- Periodic limb movement disorder
- Primary snoring
- Pulmonary or lung disease
- Restless legs syndrome
- Shift work sleep disorder
- Sleep fragmentation (multiple causes)

WORKUP

- Evaluation should include questions about snoring, witnessed apneas, gasping or choking episodes, restless sleep, and excessive daytime sleepiness. Fig. 3 describes the Epworth Sleepiness Scale, an instrument that evaluates the likelihood of dozing in eight different situations in the preceding 30 days. The Berlin Questionnaire and the STOP-BANG screening test are also widely used and well validated screening instruments.
- Mood swings and personality changes should be addressed.
- Job performance and difficulty driving or previous motor vehicle accidents related to excessive daytime sleepiness should be discussed.
- Additional concerns include morning dry mouth/throat, morning headaches, alcohol intake, weight gain, mood or personality changes.
- A thorough drug history should be performed that includes the use of narcotics, muscle relaxants, and sedatives.
- A family history should target the presence of OSA.
- Physical exam is frequently normal in patients with OSA except for the presence of obesity, enlarged neck circumference, and possibly HTN.
- OSAH is confirmed by nocturnal polysomnography (PSG), which is the gold standard for diagnosis (Fig. 4). The PSG should be performed during the patient's typical sleeping hours; it should include all stages of sleep in the supine position. A growing trend is evaluating patients with home testing rather than in-lab polysomnography, although this is not yet approved for routine pediatric testing.
- The severity of the OSA is determined by the apnea-hypopnea index (AHI) (Table 3), which is derived from the total number of apneas and hypopneas divided by the total sleep time.
- Recommended severity cutoff levels for the AHI in adult patients are as follows:
  1. Mild: 5 to 15 respiratory events per hour (with symptoms)
  2. Moderate: 15 to 30 respiratory events per hour
  3. Severe: >30 respiratory events per hour
- In children, the thresholds for severity of OSA are lower compared to adults.
- Criteria for the treatment of mild OSAH often require symptoms, including excessive daytime sleepiness, cardiovascular disease, HTN, and mood swings.
- In certain patients, portable sleep studies or pulse oximetry may be an effective alternative to PSG for evaluation of OSA.

LABORATORY TESTS

- Arterial blood gas testing should be performed if a patient has suspected pulmonary HTN or cor pulmonale to rule out daytime hypoxemia and/or hypercapnia.
- Thyroid studies should be obtained if thyroid dysfunction is suspected.
- Fasting glucose level is recommended because OSA increases risk of diabetes mellitus independent of other risk factors.
- Complete blood count is helpful to look for anemia; iron studies if anemia is detected

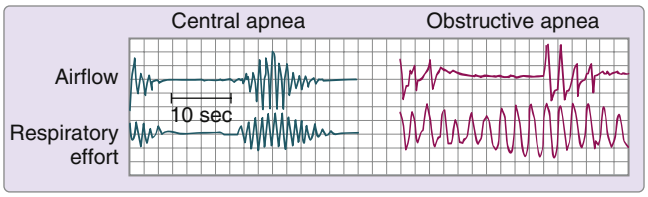

FIG. 4 Central and obstructive sleep apnea: The relationship between airflow and respiratory effort in central and obstructive apnea. During central apnea, cessation of airflow occurs without associated ventilatory effort. Respiratory effort is present during an obstructive apnea. (From Wellman A, White DP: Central sleep apnea and periodic breathing. In Kryger M, Dement W [eds]: *Principles and practice of sleep medicine,* ed 5, Philadelphia, 2011, WB Saunders, 1140-1152.)

TABLE 3 Definitions*

Events

Apnea: Cessation of breathing lasting 10 seconds or longer. Obstructive—continued respiratory effort with paradoxical motion of rib cage and abdomen; central—absent respiratory effort.

Hypopnea: Different definitions used. Two alternative definitions are part of the scoring criteria advanced by the American Academy of Sleep Medicine:

1. Score a hypopnea if all of the following are present:
   a. Nasal pressure signal excursions; drop ≥30% of baseline for at least 10 seconds.
   b. There is a ≥4% desaturation from pre-event baseline.
   c. At least 90% of the event's duration must meet the amplitude reduction of criteria for hypopnea.
2. Score a hypopnea if all of the following are present:
   a. Nasal pressure signal excursions; drop ≥50% of baseline for at least 10 seconds.
   b. There is a ≥3% desaturation from pre-event baseline *or* the event is associated with an arousal. (The latter does not require a desaturation.)
   c. At least 90% of the event's duration must meet the amplitude reduction of criteria for hypopnea.
3. *Respiratory Effort–Related Arousal (RERA):* Pattern of progressively more negative esophageal pressure terminated by a sudden change in pressure to a less negative level and an arousal; events last 10 seconds or longer.

Metrics of Severity

Apnea-Hypopnea Index: Average number of apneas plus hypopneas per hour of sleep.
Respiratory Disturbance Index: Average number of apneas plus hypopneas plus RERAs per hour of sleep.

Consensus Definitions of Severity

Normal: <5 episodes/hr
Mild sleep apnea: ≥5 and <15 episodes/hr
Moderate sleep apnea: ≥15 and <30 episodes/hr
Severe sleep apnea: ≥30 episodes/hr

Concept of Sleep Apnea Syndrome

Sleep-disordered breathing with complaint of excessive sleepiness

*See also American Academy of Sleep Medicine.
From Mason RJ et al: *Murray and Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, WB Saunders.

and ferritin level if concomitant restless legs syndrome is present.
- Pulmonary function testing if lung disease is suspected or to assess severity of neuromuscular disease in that patient population.
- 12-lead electrocardiogram (ECG) or echocardiogram is indicated if cardiac dysfunction is suspected.

IMAGING STUDIES

- Plain radiography of the neck can be helpful to assess the soft tissues of patients with anatomic abnormalities.
- Chest x-ray if lung disease is suspected.

Rx TREATMENT

Fig. 5 illustrates medical therapies for obstructive sleep apnea stratified by mechanisms targeted.

NONPHARMACOLOGIC THERAPY

- Behavioral modifications:
  1. Weight loss in overweight and obese patients. Evidence exists that weight loss is effective for reducing the severity of OSA, and if significant, it may potentially allow some patients to discontinue continuous positive airway pressure (CPAP) therapy.
  2. 10% weight gain predicted an approximate 32% increase in the AHI and sixfold increase in the odds of developing moderate to severe sleep disordered breathing.
  3. 10% weight loss predicted a 26% decrease in the AHI.
  4. Weight loss with bariatric surgery may improve OSA in some patients, but its definitive role remains unclear. In a recent trial in obese patients with OSA, bariatric surgery compared with conventional weight loss therapy did not statistically reduce AHI despite major differences in weight loss.
  5. Exercise without weight loss may improve OSA.
  6. Avoid alcohol for 4 to 6 hours before bedtime.
  7. Avoid narcotics, muscle relaxants, and sedating medications.
  8. Sleep hygiene training, especially avoidance of sleep deprivation.
  9. Avoid or reduce supine sleeping positions.
  10. Avoid medications that may worsen OSA.
- Medical treatment:
  1. CPAP is the primary therapy for OSA. It delivers a constant airway pressure that serves as a pneumatic splint relieving upper airway obstruction.
  2. Other methods of delivering positive pressure include:
     a. Bilevel positive airway pressure (BiPAP), which delivers predetermined inspiratory and expiratory airway pressures.
     b. Auto-titrating positive airway pressure (APAP), which increases or decreases the level of pressure in response to change in airflow, vibratory snoring, or changes in circuit pressure.
  3. Oral appliances constructed by a reputable and qualified dentist may be effective for the treatment of mild OSA in certain patients, especially those with retrognathia. Mandibular advancement devices (MADs) are a good alternative to CPAP in patients who are unable to tolerate CPAP. Trials have shown that although CPAP is more effective than MADs in reducing AHI (4.5 vs. 11 events/h, respectively), self-reported adherence with use of MADs is higher (6.5 vs. 5.2 h/night for CPAP use). Important health outcomes were similar after 1 mo of optimal MAD and CPAP treatment in patients with moderate-severe OSAH, which may be explained by the greater efficacy of CPAP being offset by inferior compliance relative to MAD, resulting in similar effectiveness. There was no overall difference between MADs and CPAP with respect to improvement in blood pressure, daytime sleepiness, or quality of life.
  4. Optimal treatment of allergic rhinitis should be pursued, including nasal irrigation and direct antiinflammatory therapies.
  5. Symptoms of excessive daytime sleepiness that linger despite good compliance to CPAP may require further investigation or medical therapy with stimulants.
  6. Patients should be considered for surgery if multiple attempts at CPAP therapy have failed and if an oral appliance is not an option. If the patient opts for surgery, ensure that it is performed by a reputable and qualified otolaryngologist and is based on the location of airway collapse.

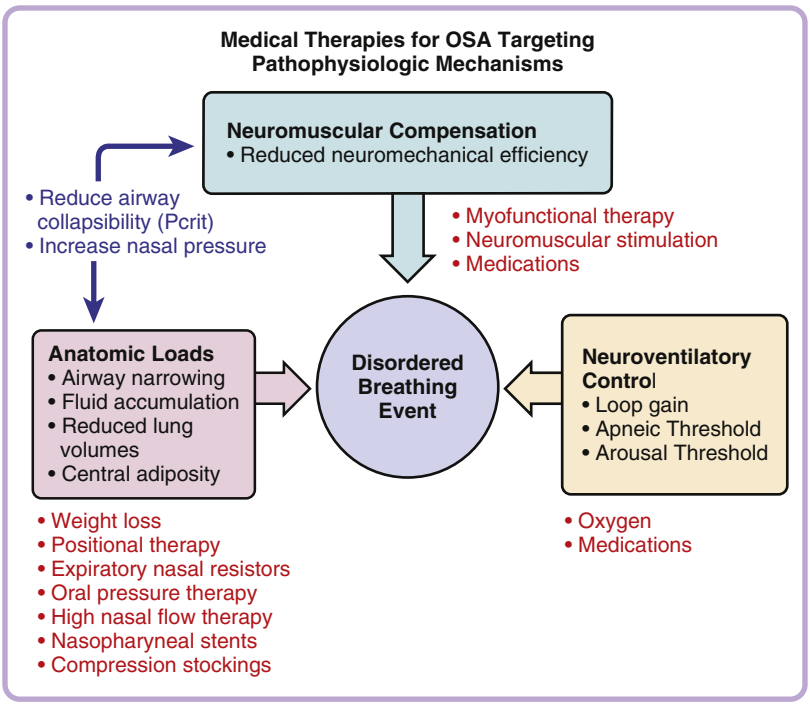

FIG. 5 Medical therapies for obstructive sleep apnea *(OSA)*, stratified by mechanisms targeted. Certain therapies can be considered on the basis of the pathophysiologic mechanisms targeted. OSA is thought to occur as a consequence of increases in anatomic loads on the upper airway, impairments in neuromuscular compensation, or alterations in neuroventilatory control. Traditional therapies such as continuous positive airway pressure (CPAP) use nasal pressure to overcome anatomic loads. By contrast, upper airway surgery or weight loss results in reduced airway collapsibility (Pcrit). Other therapies that may relieve anatomic loads on the upper airway include positional therapy, use of expiratory nasal resistors, oral pressure therapy, nasopharyngeal stenting, and application of compression stockings. Therapies that address impairments in neuromuscular function include myofunctional therapies, use of certain medications, and neuromuscular stimulation. Therapies that may affect neuroventilatory control include use of medications to increase the arousal threshold and supplemental oxygen, which can affect loop gain. (From Kryger M et al: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.)

- Surgical treatment:
  1. Surgery is done to correct specific anatomic areas of narrowing: nasal, pharyngeal, and tongue base/hypopharynx.
  2. Adenotonsillectomy is often curative for children with OSA.
  3. Nasal septoplasty/turbinectomy should be considered for patients with nasoseptal deformities.
  4. Uvulopalatopharyngoplasty, which involves resection of the uvula and soft palate, is effective for a small number of patients. Predicting which patients will benefit from this surgical treatment is difficult.
  5. Palatal implant surgery and distraction osteogenesis maxillary expansion (DOME) for high-arched palates are other surgical options.
  6. Hypoglossal nerve stimulation (by surgical placement of an implant in the upper chest) helps recruit lingual muscles, reduce pharyngeal collapsibility, and decrease upper airway resistance.
  7. Tracheostomy is typically reserved for patients with very severe OSA who failed medical therapy or who have cor pulmonale.

DISPOSITION

- The short-term prognosis for excessive daytime sleepiness and snoring is good to excellent with the regular use of CPAP, but no studies have been performed to address the long-term effects in a large population of patients.
- Residual symptoms of excessive daytime sleepiness can occur in some patients with OSA despite regular CPAP use. This has led the FDA to approve modafinil for the management of residual sleepiness.

REFERRAL

- Highly trained sleep specialists with expertise in caring for patients with OSA are recommended, especially for complex cases.
- Surgical referral to otolaryngology should be considered for children with adenotonsillar hypertrophy and for adults who are unresponsive to weight loss and CPAP therapy.
- Referral to a qualified dentist for treatment with an oral appliance may be useful for certain patients with mild OSA.

PEARLS & CONSIDERATIONS

- OSAH is a common disorder that is underrecognized and underdiagnosed, so the identification of risk factors is crucial for making the correct diagnosis.
- The prevalence of OSA increases among women after menopause.
- The single most effective therapy for OSA is CPAP administered by nasal or facial masks or other interfaces if required.
- Patients with OSA are more vulnerable than healthy persons to the effects of alcohol consumption and sleep restriction with regard to various driving performance variables.
- OSA is a risk factor for systemic and pulmonary HTN, stroke, atrial fibrillation, and coronary artery disease. In patients with untreated HTN and OSA, the use of CPAP results in small but statistically significant reductions in blood pressure. Therapy with CPAP has not been shown to prevent cardiovascular events in patients with moderate-to-severe obstructive sleep apnea and established cardiovascular disease.
- OSA may also be an independent risk factor for peptic ulcer bleeding.
- Ethnic differences may exist for some populations, with South Asians having a higher prevalence and risk for cardiovascular side effects.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Sleep Apnea (Patient Information)

AUTHORS: **Grace Rebecca Paul, MBBS, MD,** and **Don Hayes Jr., MD, MS, MEd**

SUGGESTED READINGS

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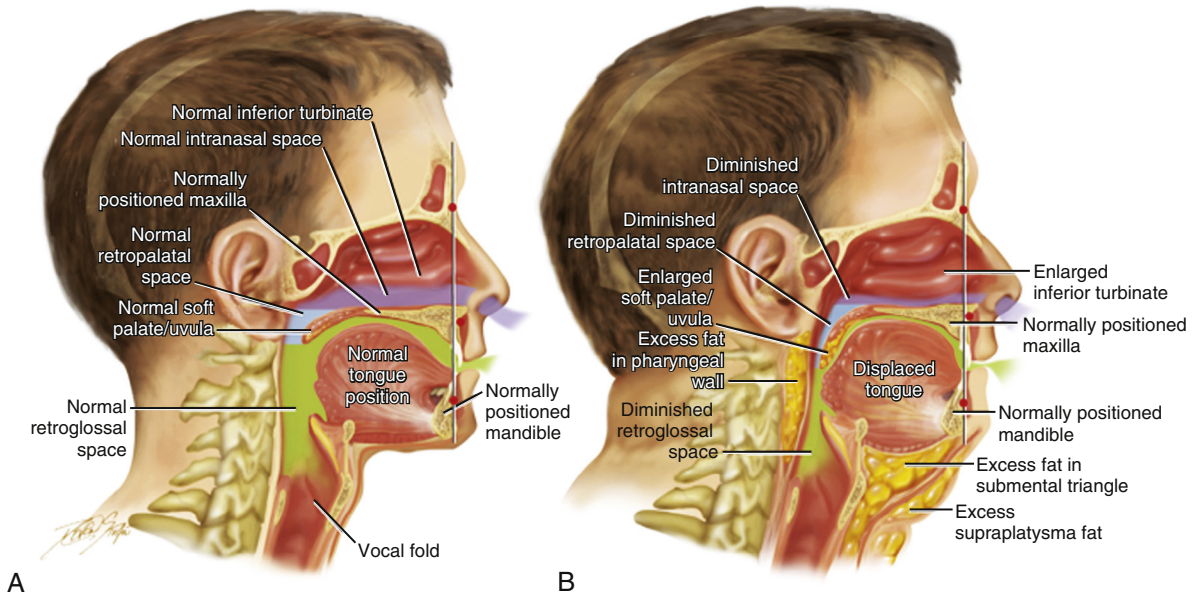

FIG. E1 Normal and abnormal airway anatomy. A, This illustrated midline sagittal cross section of the head and neck depicts the normal upper airway and maxillofacial spaces and anatomy of a healthy, normal-weight 20-yr-old man. The patient has a normal upper and lower facial skeleton and normal soft tissue indicators (soft palate, tongue, tonsils, and adenoids), without any compromise of the intranasal cavity. **B,** With increasing age and weight gain, the same individual, 3 decades later, has an elevated body mass index. Although the anatomy of the upper and lower facial skeleton remains fixed without any changes, fatty tissue consisting of adipose cells has expanded and infiltrated the crevices and space in the upper airway. Particularly compromised are the retropharyngeal and the lateral pharyngeal tissues, the soft palate, and the floor of the mouth, culminating in restricted airflow. At age 20 yr, the patient had normal upper airway space (the intranasal, retropalatal, and the retroglossal sites were all well visualized and with appropriate space for air flow to proceed smoothly and unimpeded). At age 50 yr, he has developed obstructive sleep apnea: The normal airspace *(green)* is severely compromised because of restriction of the upper airway, intranasal space, and retropalatal and the retroglossal spaces. A *perfect storm* indeed. (From Posnick JC: *Orthognathic surgery: principles and practice,* St Louis, 2014, Elsevier, 992-1058.)

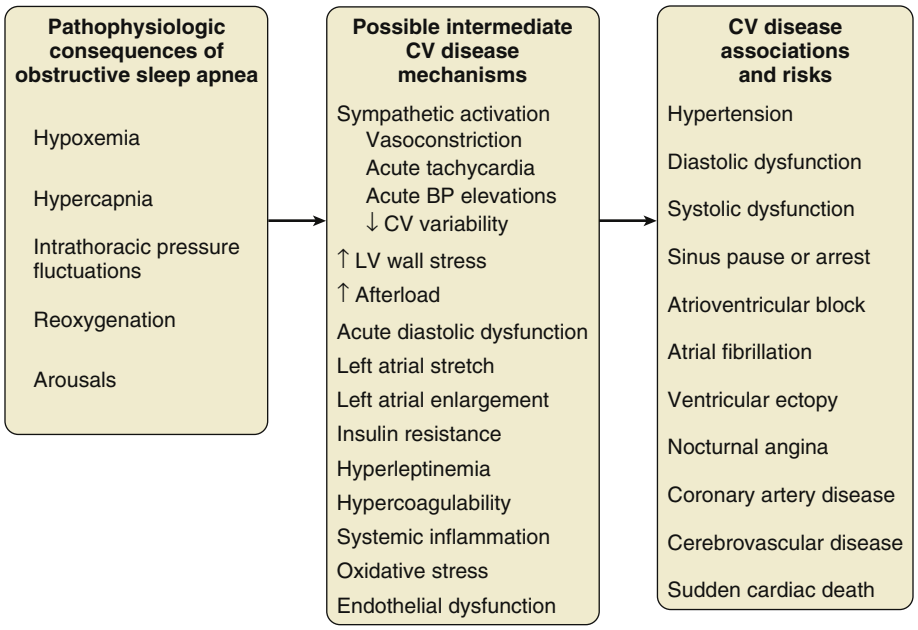

FIG. E2 The pathophysiologic consequences of obstructive sleep apnea disorders (OSA) may acutely and chronically elicit multiple intermediate cardiovascular *(CV)* disease mechanisms, which may promote the association of OSA with a number of cardiovascular conditions and diseases. *BP,* Blood pressure; *LV,* left ventricular. (From Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.)

BASIC INFORMATION

DEFINITION

Slipped capital femoral epiphysis (SCFE) is characterized by displacement of the metaphysis (femoral neck) anteriorly on the capital femoral epiphysis (femoral head) at the level of the physis (growth plate). It commonly presents with hip or knee pain and an abnormal gait.

- Unilateral, but bilateral in about one fourth of cases. When bilateral or if age <10 yr old, may be associated with endocrinopathies.
- Classified as stable when the child is able to walk and bear weight, or unstable when the child is not.
- The child should remain non–weight-bearing pending orthopedic evaluation.

SYNONYMS

Slipped capital femoral epiphysis
SCFE

ICD-10CM CODES

M93.001	Unspecified slipped upper femoral epiphysis (nontraumatic), right hip
M93.002	Unspecified slipped upper femoral epiphysis (nontraumatic), left hip
M93.003	Unspecified slipped upper femoral epiphysis (nontraumatic), unspecified hip
M93.011	Acute slipped upper femoral epiphysis (nontraumatic), right hip
M93.012	Acute slipped upper femoral epiphysis (nontraumatic), left hip
M93.013	Acute slipped upper femoral epiphysis (nontraumatic), unspecified hip
M93.021	Chronic slipped upper femoral epiphysis (nontraumatic), right hip
M93.022	Chronic slipped upper femoral epiphysis (nontraumatic), left hip
M93.023	Chronic slipped upper femoral epiphysis (nontraumatic), unspecified hip
M93.031	Acute on chronic slipped upper femoral epiphysis (nontraumatic), right hip
M93.032	Acute on chronic slipped upper femoral epiphysis (nontraumatic), left hip
M93.033	Acute on chronic slipped upper femoral epiphysis (nontraumatic), unspecified hip

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The incidence is 10 cases per 100,000, with a 1.4:2.0 female:male ratio. Left hip is more commonly affected than right hip.
PEAK INCIDENCE: Average age at diagnosis is 12 yr, with range of 10 to 16 yr.
PREVALENCE: 10.8 cases per 100,000 children
GENETICS: Greater incidence in blacks, Hispanics, and Pacific Islanders
RISK FACTORS:

- Obesity is by far the greatest risk factor
- Metabolic/endocrine disorder, radiation exposure
- Genetic

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presents with pain in the knee, hip, groin, or thigh and altered gait. Often presents with patient's refusal to bear weight.
- May note limited range of motion of the affected hip on internal rotation (Fig. E1), with obligatory external rotation if passively flexed up to 90 degrees.

ETIOLOGY

- Occurs when shearing forces at the femoral head exceed the strength of the capital femoral physis. Most commonly occurs during the preadolescent growth spurt.
- Multifactorial: Predisposing factors include obesity, trauma, history of radiation exposure, and endocrine/metabolic disorders.
- Obesity: 63% of affected patients are >90% for weight. Elevated leptin may be independently associated with increased odds of development of SCFE.
- Endocrine disorders: Consider an underlying endocrinopathy in patients who are <10 yr old or less than the fiftieth percentile for weight. Hypothyroidism, hypogonadism, panhypopituitarism, or growth hormone deficiency may be identified. Consider a screening of TSH/T_4 and bone age assessment at diagnosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Stress fracture or apophyseal avulsion fracture
- Avascular necrosis (Legg-Calvé-Perthes disease)
- Hip apophysitis
- Transient synovitis
- Septic arthritis or osteomyelitis
- Adductor muscle strain (groin pull)

WORKUP

- Diagnosis based on examination and radiologic findings.
- Laboratory testing can be done to look for secondary causes.

LABORATORY TESTS

Consider renal and endocrine (growth hormone and thyroid function) tests, especially in patients who are <10 yr or less than the fiftieth percentile for weight.

IMAGING STUDIES

- Obtain bilateral hip radiographs with both AP and frog-leg lateral views (Figs. E2 and E3), as about one fourth of cases are bilateral. Plain radiographs are both sensitive and specific enough to make the diagnosis.
- Widening, irregularity, and lucency of the physis may be noted, as well as incongruency of the proximal femoral epiphysis.
- The slip occurs at the weakest part of the physeal plate and results in the displacement of the head from the metaphysis, giving the characteristic "ice cream falling off the cone" appearance on radiographs.
- If the radiograph is normal but suspicion remains high, MRI may be diagnostic and is helpful in diagnosing complications of SCFE, such as osteonecrosis.

TREATMENT

- When suspicious for SCFE, place the child on non–weight-bearing crutches or in a wheelchair pending further evaluation.
- The initial goals of treatment are to prevent slip progression and avoid complications.
- Surgical management is required, and orthopedic referral is imperative. The gold standard procedure is insertion of a single or two cannulated screws at the center of the epiphysis. A second screw may be required to confer greater rotational stability but this carries higher risk of compromising the blood supply.

NONPHARMACOLOGIC THERAPY

- The standard treatment for SCFE is fixation with one or two cannulated screws.

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FIG. E1 Clinical examination of a patient with a stable slipped capital femoral epiphysis. Hip flexion and external rotation are limited. With flexion of the affected hip, the limb rotates externally. (From Herring JA: Slipped capital femoral epiphysis. In Herring JA (ed): *Tachdjian's pediatric orthopaedics,* ed 5, Philadelphia, 2014, Elsevier, Fig. 18.5. In Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.)

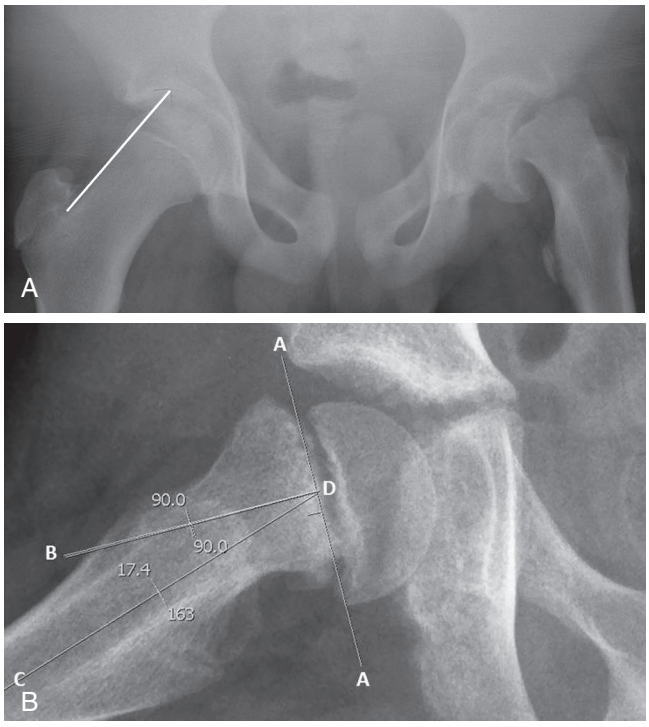

FIG. E2 Slipped capital femoral epiphysis. A, Left slipped capital femoral epiphysis. Klein's line is shown on the right. This line normally intersects approximately the lateral sixth of the capital femoral epiphysis in the AP projection. **B,** The slip angle—between (1) a line [BD] perpendicular to the plane of the growth plate [AA] and (2) a line [CD] parallel to the longitudinal axis of the femoral shaft in the frog lateral projection—is 17.4°. (From Adam A et al (ed): *Grainger and Allison's diagnostic radiology,* ed 6, London, 2015, Churchill Livingstone. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

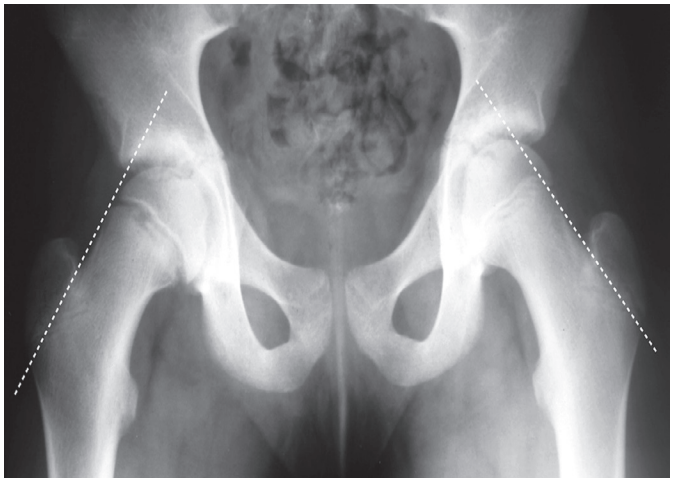

FIG. E3 Slipped capital femoral epiphysis. Klein's line. (From Adam A, Dixon AK: *Grainger & Allison's diagnostic radiology,* ed 5, London, 2007, Churchill Livingstone. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

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Zaltz I et al: Unstable SCFE: review of treatment modalities and prevalence of osteonecrosis, *Clin Orthop Relat Res* 471(7):2192-2198, 2013.

- Prophylactic treatment of the contralateral hip in SCFE is not recommended in most patients but can be considered for high-risk patients, such as those with endocrine disorders, young age, and obesity.

DISPOSITION

- SCFE is a common preadolescent disorder in which early diagnosis and proper management can prevent future complications such as osteonecrosis and chondrolysis.
- Chondrolysis: Acute dissolution of articular cartilage and narrowing of the joint space. The patient presents with pain, stiffness, and decreased range of motion. May be a complication of surgery but occurs in about 10% of cases of untreated SCFE.
- Osteonecrosis has a higher risk in unstable SCFE and is increased by the degree and angle of the slippage. Diagnose with MRI or bone scan.
- Recent studies have shown that postoperative AVN is prevented by monitoring physeal hemodynamics intraoperatively, including assessment of intracranial pressure by laser Doppler flowmetry and by confirmation of bleeding after drilling the femoral head.

PEARLS & CONSIDERATIONS

- Physicians should consider SCFE when a child between the ages of 10 to 15 yr presents with limping and groin, hip, thigh, or knee pain. One quarter of cases are bilateral, especially if there is underlying endocrinopathy.
- Endocrinopathy workup should be considered if age <10 yrs or less than fiftieth percentile by weight.
- Physical exam shows decreased internal rotation of the hip and obligatory external rotation.
- Radiography to evaluate for SCFE should include AP and frog-leg lateral views of the hips. Obtain cross table lateral views for unstable SCFE.
- Standard treatment of stable SCFE is in situ fixation with one or two cannulated screws.

RELATED CONTENT

Slipped Femoral Epiphysis (Patient Information)

AUTHOR: **Jacob Modest, MD**

BASIC INFORMATION

DEFINITION

Small bowel bacterial overgrowth (SIBO) is the presence of excessive native and/or nonnative bacteria in the small intestine (bacterial count $>10^5$/ml per jejunal aspirate) causing chronic diarrhea and malabsorption.

SYNONYMS

Bacterial overgrowth syndrome
SIBO

ICD-10CM CODES

K90.4 Malabsorption due to intolerance, NEC
K90.89 Other intestinal malabsorption

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: The prevalence of SIBO is varied based on the population studied and the diagnostic tests used. It has shown to be prevalent in up to 12.5% to 20% of the healthy population using glucose and lactulose breath test.

PREDOMINANT SEX AND AGE: SIBO affects predominantly the elderly population or those with recent UGI surgery, including bariatric surgery. The elderly population has decreased gastric secretion and hypomotility due to age-associated decline as well as increased use of motility-altering medications.

RISK FACTORS:

- Advanced age is a known risk factor as there is thought to be an age-associated decline in GI motility.
- Patients with irritable bowel syndrome have a higher prevalence of SIBO compared to the general population. Initial studies have shown up to 65% to 80% of IBS patients with confirmed SIBO with an abnormal lactulose breath test.
- Other risk factors include UGI tract surgery, inflammatory bowel disease, chronic pancreatitis, immunodeficiency, liver disease, and obesity.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients will present with nonspecific findings, which include abdominal distention, bloating, and/or pain. Other common symptoms include diarrhea and subsequent weight loss and weakness. Pathophysiology of symptoms and clinical consequences of SIBO are summarized in Table 1.
- The severity of symptoms reflects the extent of bacterial overgrowth.
- Severe malabsorption can present as symptoms secondary to vitamin deficiencies. Fat-soluble vitamin deficiencies can present as night blindness (vitamin A), osteomalacia and hypocalcemia (vitamin D), or prolonged bleeding (vitamin K). Bacterial overgrowth can affect vitamin B_{12} absorption in the ileum leading to neuropathies with sensory ataxia.

ETIOLOGY

Disorders that disrupt protective mechanisms against bacterial burden predispose patients to SIBO. Box 1 summarizes diseases and disorders linked to SIBO based on pathophysiology.

- Patients with structural or anatomical abnormalities are at greater risk. These include patients with small bowel diverticula, small intestinal strictures, surgical blind loops, ileocecal resections, or gastric resections (increasing common cause of SIBO).
- Motility disorders predispose to SIBO because of the ineffective clearance of bacteria from the proximal bowel into the colon. Examples of this include gastroparesis and small bowel dysmotility, both suggestive of poorly controlled diabetes. Long-standing celiac disease can also interfere with small bowel motility.
- It is thought that recent antibiotic use as well as antacid medication can alter the normal bacterial flora in the small intestine, contributing to SIBO.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Celiac disease
- Chronic pancreatitis
- Inflammatory bowel disease
- Irritable bowel syndrome
- Tropical sprue
- Whipple disease
- Lactose intolerance

WORKUP

Diagnostic testing should include workup for diarrhea, anemia, and malabsorption. While endoscopy with jejunal aspirate and culture was a diagnostic tool of choice, its role is limited because of low specificity. While hydrogen breath tests have their limitations as well, they are noninvasive and easy to perform.

LABORATORY TESTS

- Breath tests have become more commonplace in diagnosing SIBO. Typically fermenting bacteria reside in the colon. In SIBO, fermenting bacteria is present in the small intestine as well. A carbohydrate test dose (typically lactulose or glucose) is given and its byproduct (hydrogen) is measured as it is excreted in the breath. In SIBO, exhaled hydrogen concentrations rise early.
- Standard anemia workup is essential. CBC may suggest macrocytic anemia secondary to B_{12} deficiency.
- Nutritional status should be evaluated with albumin levels.
- Stool evaluation can aid in the diagnosis as well. An increase in fecal fat may be suggestive of SIBO. Stool WBC, culture, ova, and parasites should be ordered as well to rule out other infectious etiology.

TABLE 1 Pathophysiology of Symptoms and Clinical Consequences in Small Bowel Bacterial Overgrowth

Process	Mechanisms of Action	Clinical Consequences
Mucosal injury induced by bacteria and/or their toxins or products	Loss of brush-border enzymes	Carbohydrate maldigestion
	Injury to epithelial barrier leading to enhanced intestinal permeability	Protein-losing enteropathy; bacterial translocation and portal and systemic endotoxemia
	Inflammatory response generating inflammatory cytokines	Liver injury and inflammation, systemic inflammatory responses
Luminal competition with the host for nutrients	Consumption of dietary protein	Hypoproteinemia, edema
	Consumption of vitamin B_{12}	B_{12} deficiency, megaloblastic anemia, neurologic symptoms
	Consumption of thiamine	Thiamine deficiency
	Consumption of nicotinamide	Nicotinamide deficiency
Bacterial metabolism	Fermentation of unabsorbed carbohydrates	Bloating, distension, flatulence
	Deconjugation of primary bile acids	Diarrhea due to the effects of deconjugated bile acids in the colon; depletion of the bile acid pool leading to fat and fat-soluble vitamin malabsorption
	Synthesis of vitamin K	Interference with dosing of vitamin K antagonists (e.g., warfarin)
	Synthesis of folate	High serum folate levels
	Synthesis of D-lactic acid	D-lactic acidosis
	Synthesis of alcohol	Liver injury
	Synthesis of acetaldehyde	Liver injury

From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

BOX 1 Diseases and Disorders Linked to Small Bowel Bacterial Overgrowth (SIBO) Based on Pathophysiology

Dysmotility
Acromegaly:
- Amyloidosis
- Chronic opiate use
- Diabetic autonomic neuropathy
- Gastroparesis
- Hypothyroidism
- Idiopathic intestinal pseudo-obstruction
- Long-standing use of motility-suppressing drugs
- Myotonic muscular dystrophy
- Systemic sclerosis/scleroderma

Altered Anatomy
Blind loops:
- Gastrocolic or jejunocolic fistula
- Ileocecal valve resection
- Small intestinal diverticulosis
- Strictures (Crohn disease, radiation, surgery)
- Surgically induced alterations in anatomy (Billroth II gastrectomy, end-to-side anastomosis)

Hypochlorhydria
Long-term acid suppression (?)
- Postsurgical

Immune Deficiency
Acquired immune deficiency (e.g., AIDS, severe malnutrition)
- Inherited immune deficiencies

Multifactorial Causes
Advanced age:
- Celiac disease
- Chronic pancreatitis
- Crohn disease
- Cystic fibrosis
- End-stage kidney disease
- Intestinal failure
- Liver disease
- Radiation enteropathy
- Tropical sprue

Unclear or Undefined Relationship to SIBO
Erosive esophagitis:
- Interstitial cystitis
- IBS
- Parkinson disease
- Restless legs syndrome
- Rosacea
- Severe obesity

From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

IMAGING STUDIES

- Endoscopic evaluation of the small intestine can be useful in finding structural and motility causes of bacterial overgrowth such as diverticula and strictures. Small bowel biopsy may aid in the diagnosis of celiac disease as well.
- Jejunal aspirate cultures via endoscopy are considered a standard of diagnosis. Aspirate cultures that exceed 10^5 organisms/ml suggest the presence of SIBO.
- There are several limitations to jejunal aspirate cultures. Bacterial overgrowth is not uniform and may be in inaccessible areas to endoscopist and can easily be missed. Contamination from oropharyngeal flora can lead to false-positive tests. Also endoscopy is an invasive test and other methods of testing such as a breath test may be a more practical initial approach.

Rx TREATMENT

The goal is to treat the underlying cause and treat the bacterial overgrowth with antibiotic therapy.

NONPHARMACOLOGIC THERAPY

Structural disorders such as strictures, fistula, and diverticula may require surgical intervention.

ACUTE GENERAL Rx

- 7- to 10-day course of antibiotic therapy with rifaximin, amoxicillin-clavulanate, or metronidazole and ciprofloxacin has been shown to be beneficial.
- Nutritional support with vitamin replacement and dietary modification (lactose-free diet).

CHRONIC Rx

- Recurrence is common after antibiotic therapy. These patients may require subsequent courses of antibiotic therapy.
- Avoid using antacid medication.
- Avoid drugs that reduce GI motility (opioids).
- Consider lactose-free diet if the response to antimicrobial agents is incomplete.

DISPOSITION

Prognosis is dependent on underlying cause of SIBO. Although recurrence rate is high, antibiotic therapy remains the mainstay of therapy often requiring repeated courses if the underlying condition cannot be resolved.

REFERRAL

- Gastroenterology consultation for small bowel evaluation
- Surgical consultation with an underlying structural disorder

PEARLS & CONSIDERATIONS

COMMENTS

- SIBO is due to a disruption of protective mechanisms against bacterial burden
- Look for risk factors including UGI tract surgery, structural disorders, IBD, IBS, and disorders decreasing GI motility.
- Diagnosis can be made with hydrogen breath test or endoscopic jejunal aspirate culture.
- Treatment is with antibiotics.
- The combination of vitamin B_{12} deficiency (due to bacterial consumption) and an elevated serum folate level (due to bacterial production) is suggestive of SIBO.
- SIBO can contribute to symptoms of IBS or IBD.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Small Intestinal Bacterial Overgrowth (Patient Information)
Irritable Bowel Syndrome (Related Key Topic)
Malabsorption (Related Key Topic)

AUTHOR: **George Cholankeril, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

- Small bowel obstruction can be **functional** (as a result of intrinsic abnormal intestinal pathology) or **mechanical** (which may occur acutely or may be chronic).
- Small bowel obstruction is due to intraluminal or extraluminal mechanical compression.
- Mechanical obstruction means the blockage of the intestinal lumen, preventing the passage of luminal contents through the gut tube. Adhesion disease is the most common cause of mechanical small bowel obstruction in developed countries.
- Mechanical obstruction may be either:
  1. **Simple obstruction:** In which the lumen may be *partially* or *completely blocked* but with intact intestinal blood flow *OR*
  2. **Strangulated obstruction:**
     a. This is a surgical emergency.
     b. Usually the obstruction is complete; blood flow to the obstructed segment is cut off; and tissue necrosis, gangrene, and perforation may occur.

ICD-10CM CODES

K56	Paralytic ileus and intestinal obstruction
K56.1	Intussusception
K56.2	Volvulus
K56.3	Gallstone ileus
K56.4	Other impaction of intestine
K56.5	Intestinal adhesions (bands) with obstruction
K56.6	Other and unspecified intestinal obstruction
K56.9	Ileus, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- The most frequently encountered surgical disorder of the small intestines is mechanical small bowel obstruction (SBO). This is a common surgical emergency.
- 75% of all cases of small bowel obstruction are due to intraabdominal adhesion related to prior abdominal surgery, such as appendectomy, colorectal surgery, and gynecologic procedures.

PREDOMINANT SEX AND AGE: None

RISK FACTORS

- Previous abdominal or pelvic surgery—most important risk factor for mechanical SBO in the U.S.
- Hernia (abdominal wall or groin)
- Prior abdominal irradiation
- Bowel neoplasm
- Foreign-body ingestion
- Parasitic infestation
- Gallstones
- Inflammatory/ischemic stricture

PHYSICAL FINDINGS & CLINICAL PRESENTATION

PHYSICAL FINDINGS: These may include:

- Dehydration (manifested by tachycardia, decreased urine output, orthostatic hypotension, dry mucous membrane)
- Abdominal distention may suggest an abnormal accumulation of air or fluid
- Hyperactive bowel sounds (an early occurrence)
- Tympany to abdominal percussion over a distended abdomen may indicate the presence of air
- Percussion dullness over a distended abdomen may indicate fluid
- High-pitched "tinkling" sound on auscultation of the abdomen
- Hypoactive bowel sounds (late finding)
- Hernia
- Rectal examination may reveal:
  1. Blood (suggestive of neoplasm or strangulation or mucosal ischemia)
  2. Masses (may suggest obturator hernia)
  3. Fecal impaction

CLINICAL PRESENTATION: There are four key symptoms: abdominal pain, vomiting, distention, p0185 and constipation.

- Abdominal pain (abrupt onset):
  1. Intermittent, crampy, or colicky
  2. Constant pain (that is, change in pain's character) signifies serious complication
- Abdominal distension: Indicates abnormal accumulation of air or fluid
- Nausea
- Vomiting (bilious vomiting seen in proximal obstructions)
- Diarrhea (early finding)
- Constipation (a late finding)
- Obstipation (inability to pass gas)

Hypotension, fever, tachycardia, leukocytosis, and peritoneal signs (these late findings may be seen with strangulation or intestinal ischemia) should compel urgency toward operative management

- It is important to perform serial abdominal examinations to detect changes early

ETIOLOGY

- Postoperative adhesions, especially prior abdominopelvic operations (may cause acute obstruction usually within 1 mo of surgery; or chronic obstructions can occur yrs later)
- Incarcerated inguinal hernia
- Malignant tumor
- IBD
- Gallstone ileus
- Stricture
- Cystic fibrosis
- Volvulus
- In children consider pyloric stenosis, intussusception, congenital atresia

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Paralytic ileus
- Pseudo-obstruction
- Acute cholangitis
- Cholecystitis
- Gastroenteritis
- Inflammatory bowel disease
- Diverticulitis
- Endometriosis
- Mesenteric ischemia
- Pancreatitis
- Dysmenorrhea
- Ovarian torsion

WORKUP

During the initial evaluation of patients with suspected SBO, the primary objectives are to gauge the degree of metabolic derangement and volume depletion and to assess the need for and expediency of surgery. It is also important to exclude sepsis, perforation, and bowel ischemia. As with many surgical conditions, determining the correct diagnosis and management strategy hinges on a focused yet thorough history and physical examination.

LABORATORY TESTS

- Laboratory abnormalities are not diagnostic of bowel obstruction but instead may indicate complications of obstruction. Essential laboratory tests include:
  1. Basic metabolic panel (hyponatremia, hypokalemia)
  2. CBC: Hemoconcentration, leukocytosis
  3. Urinalysis
  4. Serum amylase: May be elevated
  5. LDH
  6. Hepatic panel
  7. Check serum lactate, blood cultures, ABG in patients with signs such as fever, hypotension, or change in mental status
  8. Type and cross-match (in anticipation of possible surgical intervention)

IMAGING STUDIES

- Image to confirm diagnosis, identify the location of the obstruction, and access the type of obstruction.
- Imaging also helps identify complications (perforation, necrosis, etc.) and possible cause of the obstruction.
- Initial radiographic evaluation begins with plain x-ray films of the abdomen (supine and upright) and an upright chest radiograph. An upright chest radiograph is of paramount importance to inspect for pneumoperitoneum and also for evidence of aspiration in a patient with a history of vomiting. A supine and upright plain abdominal x-ray in patients with suspected small bowel obstruction may show:
  1. Ladder-like pattern of dilated small bowel loops with air-fluid levels (Fig. 1) indicating small bowel obstruction
  2. Accumulation of air and fluid proximal and clearance of fluid and air distal to the post of obstruction
- Enteroclysis (a fluoroscopic x-ray of the small intestine) is useful in detecting obstruction and can distinguish partial from complete blockage and adhesions from metastases.
- CT scan is the study of choice if the patient has fever, tachycardia, abdominal pain, and leukocytosis. It can reveal the etiology of the obstruction: abscess, inflammatory process, extra-luminal pathology, and/or metastases.
- CT can elucidate the cause, such as the presence of a mass (Fig. 2) or a hernia with subsequent obstruction (Fig. 3). In addition, CT has high sensitivity for detecting strangulation and pneumoperitoneum indicative of a perforation and is particularly useful in the early postoperative setting to rule out ischemia, intraabdominal abscess, or morbidity as the underlying cause. It is also useful in patients with a history of

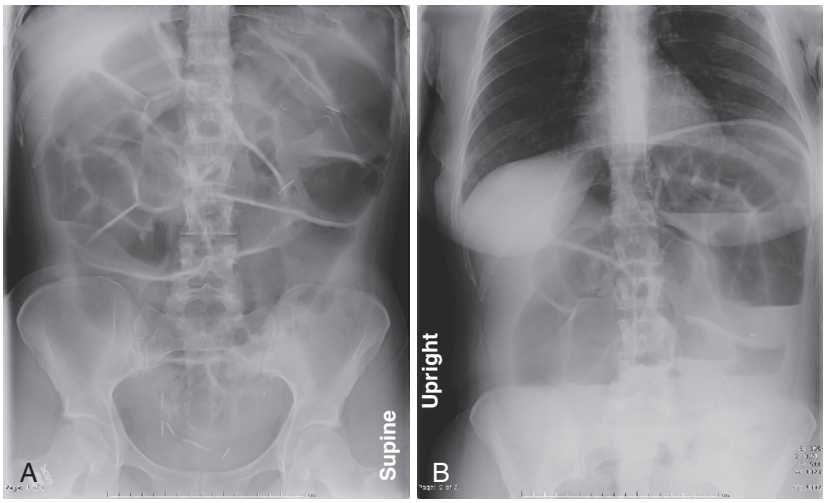

FIG. 1 A, Supine film showing dilated loops of small bowel in a patient with small bowel obstruction. **B,** Upright abdominal film revealing multiple air-fluid levels and small bowel dilation, consistent with a diagnosis of small bowel obstruction. (From Marx J: *Rosen's emergency medicine: concepts and clinical practice,* ed 6, Philadelphia, 2006, Saunders.)

FIG. 2 Computed tomography scan of small bowel volvulus with notable mesenteric torsion. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

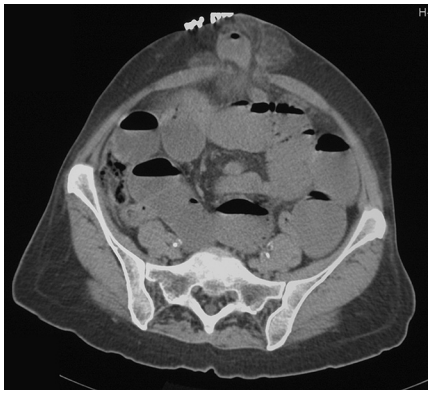

FIG. 3 Computed tomography scan of complete small bowel obstruction due to incisional hernia. (From Cameron IL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

malignancy to differentiate potentially recurrent disease from adhesions (Fig. 4).

- CT enterography, in which intraluminal distention is achieved with administration of large volumes of oral contrast such as water-methylcellulose solution, can be useful. This modality is most often used to diagnose patients with Crohn disease–related strictures, and its benefit is high-resolution imaging of the bowel wall; however, it is impractical in the patient with gastrointestinal (GI) distress who is nauseated and vomiting.

Rx TREATMENT

EMERGENCY ROOM CARE

- Vigorous fluid resuscitation and correction of electrolyte disorders underpin the initial therapeutic goals of both nonoperative and preoperative management strategies. Placing a Foley catheter to measure urinary output, establishing adequate intravenous access, and reassessing hemodynamic and electrolyte status are all essential in the initial management.

FIG. 4 Coronal image of computed tomography scan showing mass in proximal small bowel with decompressed loops of small bowel distal to obstruction. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

- Initial treatment consists of:
  1. Designate the patient nothing by mouth ("NPO")
  2. Fluid resuscitation (with isotonic Ringer or normal saline solution)
  3. Bowel decompression (via nasogastric [NG] tube placement): A standard NG tube provides symptomatic relief, prevents added gas and fluid accumulation proximally, and enables the serial assessment of antegrade fluid movement
  4. Correction of metabolic and electrolyte abnormalities
  5. Pain management
  6. Antiemetic administration
  7. Surgical consultation: Must be done early
  8. Antibiotic administration

NONSURGICAL INPATIENT CARE

General Principles:

- Bowel rest.
- Continue NG suction for decompression.
- Serial abdominal examination (q4 to 6h).
- Check labs, for example, CBC, BMP, lactic acid q6h.
- Provide adequate fluid.

Patients with low-grade partial SBOs are prone to spontaneous resolution with conservative interventions such as bowel rest, NG decompression, and appropriate fluid resuscitation. For partial or simple obstructions resolution usually occurs within 72 hr.

SURGICAL CARE

More than 25% of inpatients admitted because of SBO will require an operation. Patients with complete or high-grade partial SBO are most likely to need surgery, with less than 20% successfully managed nonoperatively. Surgery is indicated in:

- Strangulated obstruction (which is a surgical emergency)
- Patients with signs of necrosis or perforation (require prompt surgery)
- Simple complete obstruction: After failed nonoperative care

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BASIC INFORMATION

DEFINITION

Smallpox infection is caused by the variola virus, a DNA virus member of the genus *Orthopoxvirus.* It is a human virus with no known nonhuman reservoir of disease. Natural infection occurs after implantation of the virus on the oropharyngeal or respiratory mucosa.

ICD-10CM CODES

B03	Smallpox
T50.B11A	Poisoning by smallpox vaccines, accidental (unintentional), initial encounter
T50.B11D	Poisoning by smallpox vaccines, accidental (unintentional), subsequent encounter
T50.B11S	Poisoning by smallpox vaccines, accidental (unintentional), sequela
T50.B12A	Poisoning by smallpox vaccines, intentional self-harm, initial encounter
T50.B12D	Poisoning by smallpox vaccines, intentional self-harm, subsequent encounter
T50.B12S	Poisoning by smallpox vaccines, intentional self-harm, sequela
T50.B13A	Poisoning by smallpox vaccines, assault, initial encounter
T50.B13D	Poisoning by smallpox vaccines, assault, subsequent encounter
T50.B13S	Poisoning by smallpox vaccines, assault, sequela
T50.B14A	Poisoning by smallpox vaccines, undetermined, initial encounter
T50.B14D	Poisoning by smallpox vaccines, undetermined, subsequent encounter
T50.B14S	Poisoning by smallpox vaccines, undetermined, sequela
T50.B15A	Adverse effect of smallpox vaccines, initial encounter
T50.B15D	Adverse effect of smallpox vaccines, subsequent encounter
T50.B15S	Adverse effect of smallpox vaccines, sequela
T50.B16A	Underdosing of smallpox vaccines, initial encounter
T50.B16D	Underdosing of smallpox vaccines, subsequent encounter
T50.B16S	Underdosing of smallpox vaccines, sequela
Z20.89	Contact with and (suspected) exposure to other communicable diseases

EPIDEMIOLOGY & DEMOGRAPHICS

- Smallpox infection was eliminated from the world in 1977. The last cases of smallpox, from laboratory exposure, occurred in 1978. The threat of bioterrorism has brought on renewed interest in the smallpox virus.
- Routine vaccination against smallpox ended in 1972.
- Smallpox is spread from person to person by infected saliva droplets in face-to-face contact with the ill person. Criteria for the suspicion of smallpox in patients with acute generalized vesicular or pustular rash are described in Box E1. Categorization of risk of smallpox from clinical criteria is described in Box E2.
- Persons with smallpox are most infectious during the first wk of illness, when the largest amount of virus is present in saliva; however, some risk of transmission lasts until all scabs have fallen off.
- The incubation period is approximately 12 days (range, 7 to 17 days) after exposure.
- Contaminated clothing or bed linens can also spread the virus. Special precautions need to be taken to ensure that all bedding and clothing of patients are cleaned appropriately with bleach and hot water. Disinfectants such as bleach and quaternary ammonia can be used for cleaning contaminated surfaces.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Initial symptoms include high fever, fatigue, and headaches and backaches. A characteristic rash, most prominent on the face, arms, and legs, follows in 2 to 3 days (Fig. E1).
- The rash starts with flat red lesions that evolve at the same rate. The rash follows a centrifugal pattern.
- Lesions are firm to the touch, domed, or umbilicated. They become pus filled and begin to crust early in the second wk.
- Scabs develop and then separate and fall off after approximately 3 to 4 wk. Depigmentation persists at the base of the skin lesions for 3 to 6 mo after illness. Scarring is usually most extensive on the face.
- Associated with the rash may be fever, headache, generalized malaise, vomiting, and colicky abdominal pain.
- Variola major may produce a rapidly fatal toxemia in some patients.
- Complications of smallpox include dehydration, pneumonia, blepharitis, conjunctivitis, and corneal ulcerations.

ETIOLOGY

Smallpox is caused by the variola virus. There are at least two strains of the virus, the most virulent known as *variola major* and a less virulent strain known as *variola minor* (alastrim).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rash from other viral illnesses (e.g., hemorrhagic chickenpox, measles, Coxsackievirus). Table E1 summarizes distinguishing features of smallpox and varicella
- Abdominal pain may mimic appendicitis
- Meningococcemia
- Insect bites
- Impetigo
- Dermatitis herpetiformis
- Pemphigus
- Papular urticaria

WORKUP & LABORATORY TESTS

- Laboratory examination requires high-containment (BL-4) facilities.

BOX E1 Criteria for Suspicion of Smallpox in Patients with Acute Generalized Vesicular or Pustular Rash

- Febrile prodrome:
  1. >101° F (>38.3° C), 1-4 days before rash onset
  2. With headache, backache, or abdominal pain
- Firm, deep-seated, well-circumscribed vesicles/pustules
- Lesions in the same stage of development in any one area of the body

Minor Smallpox Criteria

- Centrifugal distribution
- First lesions in the pharynx, oral mucosa
- Patient appears "toxic"
- Slow evolution of the rash:
  1. 1-2 days each stage: Macule, papule, vesicle
- Lesions on palms and soles

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.

BOX E2 Categorization of Risk of Smallpox from Clinical Criteria

High Risk of Smallpox

- Febrile prodrome *and*
- Classic smallpox lesion *and*
- Lesions in the same stage of development

Moderate Risk of Smallpox

- Febrile prodrome *and* one other *major* smallpox criterion *or*
- Febrile prodrome *and* four or more minor smallpox criteria

Low Risk of Smallpox

- No febrile prodrome or
- Febrile prodrome *and* fewer than four minor smallpox criteria

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.

FIG. E1 Smallpox. Multiple, tense pustules of the face in a patient from Ghana with smallpox. (Courtesy Centers for Disease Control and Prevention, Dr. J. Noble Jr. From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.)

TABLE E1 Distinguishing Features of Smallpox and Varicella

	Smallpox	Varicella
Prodrome	High fever, headache, backache, malaise	Mild fever, constitutional symptoms
Skin examination	Centrifugal distribution; pustules all in same stage of development; deep involvement	Central distribution; vesicles and crusted papules in different stages at one time; superficial
Scarring	Common; often severe	Occasional; usually mild (unless secondary bacterial infection)
Complications	Bacterial infection, pneumonia, arthritis, encephalitis, blindness, death	Bacterial infection; rarely pneumonia, encephalitis, arthritis

From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, Philadelphia, 2016, Elsevier.

- Electron microscopy of vesicular scrapings can be used to distinguish poxvirus particles from varicella-zoster virus or herpes simplex. To obtain vesicular or pustular fluid it may be necessary to open lesions with the blunt edge of a scalpel. A cotton swab may be used to collect the fluid.
- In the absence of electron microscopy, light microscopy can be used to visualize variola viral particles (Guarnieri bodies) after Giemsa staining.
- Polymerase chain reaction techniques and restriction fragment-length polymorphisms can rapidly identify variola.

IMAGING STUDIES

Chest radiograph in patients with suspected pneumonia

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive therapy
- IV hydration in severe cases
- A suspected case of smallpox should be placed in strict respiratory and contact isolation

ACUTE GENERAL Rx

- There is no proven treatment for smallpox. Vaccination administered within 3 to 4 days may prevent or significantly ameliorate subsequent illness. Vaccinia immune globulin can be used for treatment of vaccine complications and for administration with vaccine to those for whom vaccine is otherwise contraindicated.
- Patients can benefit from supportive therapy (e.g., IV fluids, acetaminophen for pain or fever).
- Antibiotics are indicated only if secondary bacterial infections occur. Penicillinase-resistant antimicrobial agents should be used if smallpox lesions are secondarily infected.
- Topical idoxuridine should be considered for corneal lesions.

DISPOSITION

- The mortality rate for variola major is 20% to 50%. Variola minor has a mortality rate of 1%.
- After severe smallpox, pitted lesions (most commonly on the face) are seen in up to 80% of survivors.
- Panophthalmitis and blindness from viral keratitis or secondary eye infection occur in 1% of patients.
- Arthritis caused by viral infection of the metaphysis of growing bones occurs in 2% of children.

REFERRAL

ID consultation and notification of local health authorities is mandatory in all cases of smallpox.

PEARLS & CONSIDERATIONS

- The smallpox virus is fragile; in the event of an aerosol release, all viruses will be inactivated or dissipated within 1 to 2 days. Buildings exposed to the initial aerosol release of the virus do not need to be decontaminated. By the time the first cases are identified, typically 2 wk after release, the virus in the building will be gone. Infected patients, however, will be capable of spreading the virus and possibly contaminating surfaces while they are sick. Standard hospital-grade disinfectants such as quaternary ammonias are effective in killing the virus on surfaces and should be used for disinfecting hospitalized patients' rooms or other contaminated surfaces. In the hospital setting, patients' linens should be autoclaved or washed in hot water with bleach added. Infectious waste should be placed in biohazard bags and autoclaved before incineration.
- Symptomatic patients with suspected or confirmed smallpox are capable of spreading the virus. Patients should be placed in medical isolation to avoid spread of the virus. In addition, people who have come into close contact with smallpox patients should be vaccinated immediately and closely watched for symptoms of smallpox.
- Traditional smallpox vaccines are based on replicating vaccinia viruses and have considerable side effects. Recent phase 3 trials of modified vaccinia Ankara (MVA) as a vaccine against smallpox did not identify any safety concerns. Immune responses and attenuation of the major cutaneous reaction suggest that this MVA vaccine protected against variola infection.[1]

COMMENTS

- In people exposed to smallpox, the vaccine can lessen the severity of or even prevent illness if given within 4 days of exposure.
- The vaccine against smallpox contains another live virus called *vaccinia.* The vaccine does not contain smallpox virus. Smallpox vaccination produces a skin lesion that is infectious. Vaccine virus in the skin lesion can be transferred to others if the skin lesion is touched directly or if the bandage is handled casually with ungloved hands. The vaccination site is infectious until the scab falls off, approximately 21 days after vaccination.
- Primary vaccination confers full immunity to smallpox in more than 95% of persons for up to 10 yr.

AUTHOR: **Fred F. Ferri, MD**

[1] Pittman PR et al: Phase 3 Efficacy Trial of Modified Vaccinia Ankara as a Vaccine against Smallpox, *N Engl J Med* 381(20):1897-1908, 2019.

BASIC INFORMATION

DEFINITION

Social anxiety disorder (SAD) is a persistent and intense fear of being embarrassed, humiliated, or negatively evaluated in social situations. SAD commonly presents as excessive anxiety or fear in situations involving social interactions (e.g., conversing with one or a group of other individuals, with sexually attractive others, with authority figures), performance situations (e.g., public speaking, acting/performing in front of an audience), or situations in which one is being observed (e.g., while eating). Individuals with SAD fear that they will behave in these situations in ways that will cause them to be embarrassed or that others will judge them negatively. Many individuals also fear that they will show anxiety symptoms that will be observed by others. The anxiety must persist in these situations for at least 6 mo, and for children it must occur with peers and not just with adults. The anxiety often results in avoidance of these situations, thus leading to significant occupational, academic, and/or social impairment as well as marked distress. A specifier of "performance only" should be given when the fears are confined to speaking or performing in public.

SYNONYMS

Social phobia
SAD

ICD-10CM CODES

F93.2	Social anxiety disorder of childhood
F40.1	Social phobias
F40.9	Phobic anxiety disorder, unspecified

DSM-5

300.23	Social phobia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Ranges from 4 to 5 to 9/1000 person-yr; cumulative incidence of 11.0% in first 3 decades of life

PEAK INCIDENCE: Highest standardized incidence rates per person-yr between 10 and 19 yr of age

PREVALENCE (IN U.S.): Lifetime prevalence of 12% in epidemiologic samples, and 12-mo prevalence of 7%; point prevalence of up to 30% in outpatient clinical settings

PREDOMINANT SEX: More common in women than in men (odds ratio of 1.5 to 2.2) in epidemiologic samples, but men are more likely to seek treatment

PREDOMINANT AGE: Mean age at onset ~16 yr of age; median age at onset, 13 yr of age; onset rarely occurs after age 25, with 75% having an onset between 8 and 15 yr of age

GENETICS:

- Heritability ranges from 20% to 50%.
- 15% to 26% risk of SAD among first-degree relatives of those with SAD.
- There have been no consistent findings to demonstrate specific genes associated with SAD.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical symptoms during social interactions such as heart palpitations, sweating, shaking, and/or blushing, which may take the form of a panic attack.
- Fear that others will observe these physical symptoms in social situations and negatively judge them; fears that they will "say something stupid," make a mistake, or offend others also are common.
- Report being "shy" most of their lives.
- Comorbid psychiatric disorders (e.g., major depression, other anxiety disorders) and substance abuse (e.g., alcohol/cannabis) are common.
- Common sociodemographic features include younger age, female gender, unmarried status, lower education, and lower income.
- Few seek treatment specifically for SAD, and instead initially seek treatment for other psychiatric disorders (e.g., major depression, other anxiety disorders).
- The onset of SAD often precedes that of the other comorbid psychiatric conditions.

ETIOLOGY

- There is no clear etiology and likely is a combination of multiple factors.
- Research has examined developmental psychology factors (e.g., lack of modeling of socialization by parents), temperamental factors (e.g., behavioral inhibition), and occurrence of prior traumatic social experiences (e.g., significant teasing by peers, being embarrassed or humiliated in a social or performance situation).
- The risk of SAD also may be increased with family history.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other anxiety disorders (e.g., panic disorder with agoraphobia)
- As a consequence of mood disorders (e.g., avoidance of social situations associated with major depression)
- Pervasive developmental disorder (e.g., autism spectrum disorder)
- Personality disorders (e.g., schizoid personality disorder); however, in the case of avoidant personality disorder, both may be diagnosed
- Anxiety associated with medical conditions such as stuttering or Parkinson disease

WORKUP

- Psychiatric history is required for a diagnosis.
- Screening measures may improve detection of SAD as it is a chronic, disabling condition for which many individuals do not seek treatment.
- Physical examination may be useful in ruling out other explanations for physical symptoms that are present, and to rule out presence of social anxiety due to a medical condition.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavior therapy (CBT)
- Acceptance and Commitment Therapy (ACT)
- Interpersonal Psychotherapy (IPT)
- Exposure therapy
- Social skills training

PHARMACOLOGIC THERAPY

- SSRIs/SNRIs
- Benzodiazepines (less favored)
- MAOIs (less favored)
- Beta-blockers (e.g., propranolol, atenolol—for performance-related anxiety)

ACUTE GENERAL Rx

- SAD is a chronic condition; therefore acute treatment is rarely indicated.
- However, benzodiazepines or beta-blockers may be prescribed on an as-needed basis for acute performance anxiety. Caution should be taken when prescribing benzodiazepines due to the possibility of dependence or misuse and high incidence of relapse following discontinuation, and long-term use of these medications generally is discouraged.
- Beta-blockers may also be prescribed on an as-needed basis, particularly for physical symptoms experienced during performance situations. However, evidence does not support their use for more generalized forms of SAD.

CHRONIC Rx

- CBT is effective and an appropriate first-line treatment.
- SSRIs/SNRIs (e.g., sertraline, escitalopram, paroxetine, venlafaxine) are also effective in the treatment of SAD and are a first-line pharmacologic treatment.
- MAOIs previously were considered gold-standard treatment for SAD, but currently are less favorable due to side effects and dietary restrictions.
- Combination treatment of SSRI/SNRI and CBT is effective for SAD; ensuring CBT as an intervention may result in greater long-term benefit.

DISPOSITION

- SAD is a chronic condition, typically unremitting without treatment.
- Treatment may significantly improve SAD, although symptoms and impairment may continue to be present for some individuals following treatment.

REFERRAL

- If comorbid psychiatric conditions are present
- If the symptoms do not improve upon treatment or response to treatment is not optimal

RELATED CONTENT

Anxiety (Generalized Anxiety Disorder) (Related Key Topic)

AUTHOR: **Kristy L. Dalrymple, PhD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Somatic cough syndrome, formerly psychogenic cough, is a disorder of chronic, debilitating cough that is medically unexplained despite extensive medical evaluation. It is a diagnosis of exclusion. The cough is considered to have a psychologic or psychiatric etiology and is not intentionally produced or feigned.

SYNONYMS

Psychogenic cough
Tic cough
Habit cough
Functional cough
Involuntary cough syndrome
Psychogenic cough tic
Psychosomatic cough

ICD-10CM CODES

F45.8	Other somatoform disorders (NOTE: ICD-10 uses DSM-IV terminology)
F45.1	Undifferentiated somatoform disorder
F95.9	Tic disorder, unspecified (referring to tic cough)
F95.1	Chronic vocal tic disorder (referring to tic cough)

DSM-5 CODES

300.82	Somatic symptom disorder
307.20	Other specified tic disorder (tic cough)
307.22	Chronic motor or vocal tic disorder

EPIDEMIOLOGY & DEMOGRAPHICS

There is a paucity of data on somatic cough syndrome. The evidence that exists is of limited quality due to the lack of control groups, the retrospective nature of all the studies, varying definitions and terminology, and evolving diagnostic criteria. For example, the most recent American College of Chest Physicians (ACCP) guidelines published in 2015 recommended replacing the terms "psychogenic cough" and "habit cough" with "somatic cough syndrome" and "tic cough," to align with the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*), classification of diseases. However, these recommendations have not been readily adopted in research or in practice based on the subsequent literature.

INCIDENCE: Unknown

PEAK INCIDENCE: Somatic cough disorder incidence peaks at age 8 to 14 yr.

PREVALENCE: Unknown

PREDOMINANT SEX AND AGE: There is no gender difference in children. In adults, there may be a female predominance, although limited data exist. Somatic cough syndrome is more common in children, adolescents, and young adults and is one of the most common causes of chronic cough in 6- to 16-yr-olds. Somatic cough syndrome is thought to be uncommon in adults, although it may be underreported or underdiagnosed.

GENETICS: None known

RISK FACTORS

- There are no systematic studies identifying risk factors for somatic cough syndrome.
- Because the 2015 ACCP guidelines recommend that for a diagnosis of somatic cough syndrome the patient must meet criteria for somatic symptom disorder (see later), the risk factors should be similar. These include a complex interplay of:
  1. Predisposing factors: Early adverse life events
  2. Precipitating factors: Recent illness, problems at work/school, and psychiatric illness
  3. Perpetuating factors: Poor health, chronic stress, isolation, sick role/illness behavior, and misdiagnosis/mistreatment
- In population studies of individuals with chronic cough, anxiety and depression were increased in some but not all individuals.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Although there are no distinguishing clinical features that reliably differentiate somatic cough syndrome from other causes of chronic cough, certain characteristics are considered supportive of the diagnosis (see Table E1). These include:

- A loud, dry, honking cough, absent during sleep, and prominent during clinic visits.
- The cough often begins at the time of an upper respiratory infection, fails to resolve, and may lead to excessive work/school absences.
- There is no consistent response to antitussive medication, bronchodilators, steroids, or antibiotics.
- Cough duration is highly variable, lasting from several wk to decades.
- In children, the cough is often much more bothersome to parents/other adults than to the patient and rarely affects play, speech, or eating.
- The cough is not intentionally produced or feigned.
- In both children and adults with unexplained chronic cough despite extensive medical evaluation, the presence of the core clinical features of tics, including suppressibility, distractibility, suggestibility, variability, and the presence of a premonitory sensation whether the cough is single or one of many tics is supportive of the diagnosis of tic cough. However, the distinction between somatic cough syndrome and tic cough is not entirely clear.
- Cases of Tourette syndrome presenting with unexplained chronic cough have been reported, and an evaluation for a tic disorder should be considered if other suggestive signs are present.

ETIOLOGY

- The exact cause of somatic cough syndrome is not clear. Various factors may play a role, including:
  1. Genetic and biological factors, for example, resulting in a vulnerability trait
  2. Family influence, which may be genetic or environmental, or both
  3. Decreased awareness of or difficulty processing emotions, causing the patient to shift the focus to physical symptoms rather than emotional or psychological issues
  4. Learned behavior—for example, the attention or other benefits gained from having an illness, which is often not recognized at a conscious level

TABLE E1 Clinical Features Suggestive of Somatic Cough Syndrome

Prominent during clinic visits
Often, but not always, absent during sleep
Rarely interrupts play, speech, or eating in children
May have a barking or honking quality after short inhalation, though this is not diagnostic
May lead to excessive absences from school or work
Often begins at the time of an upper respiratory tract infection and fails to resolve
No consistent response to antitussive medication, bronchodilators, steroids, or antibiotics

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

In children:

- Medical: Cough-dominant asthma, airway malacia, postviral cough, increased cough receptor sensitivity, foreign body ingestion, otogenic cough, protracted bacterial bronchitis
- Psychiatric: Tourette syndrome

In adults:

- Medical: Asthma, gastroesophageal reflux disease, medication-associated (ACE inhibitors), lung cancer, chronic bronchitis

WORKUP

- A comprehensive medical evaluation should be undertaken for common and uncommon causes of chronic cough. Chronic cough management algorithms are helpful to guide evaluation.
- Clinical interview should query for a history of psychiatric illness, history of substance abuse, recent and past psychosocial stressors, adverse early life experiences, and preceding medical (specifically respiratory) illness, along with previous pharmacologic and nonpharmacologic treatment trials. The impact of symptoms on work/school should also be assessed.
- Laboratory, imaging, and other diagnostic studies, such as chest x-ray and pulmonary function testing, should be undertaken if indicated by history or physical examination.

- 2015 ACCP guidelines on somatic cough syndrome recommend against anchoring a somatic cough syndrome diagnosis on the presence or absence of nighttime cough or cough with a barking or honking quality.
- A recently described "cough monitoring method" may be helpful in objectively identifying variation in cough characteristics during daytime compared to during sleep, based on the rationale that nighttime cough in somatic cough syndrome is significantly different from daytime cough. The method involves measuring cough sounds and thoracoabdominal movement with specialized equipment; however, more research is needed to validate this novel technique.
- The patient should meet *DSM-5* criteria for somatic symptom disorder, which include:
  1. One or more somatic symptoms that result in disruption of daily life.
  2. Excessive thoughts, feelings, and behaviors related to these somatic symptoms or associated health concerns. At least two of the following are needed to meet this criterion:
     a. High level of health-related anxiety
     b. Disproportionate and persistent concerns about the medical seriousness of one's symptoms
     c. Excessive time and energy devoted to these symptoms or health concerns
  3. The symptom lasts >6 mo.
- An isolated cough tic lasting greater than 1 yr would be considered chronic vocal tic disorder by *DSM-5* criteria.

Rx TREATMENT

- The mainstay of treatment for somatic cough syndrome involves nonpharmacologic approaches. Guidance on treatment is limited by the lack of controlled studies. Many interventions, including pharmacotherapy, behavioral modifications, and psychotherapy, have been used. There is no evidence that pharmacologic approaches are effective.
- In general, studies reported lack of benefit of pharmacologic interventions (antibiotics, cough suppressants, antihistamines, bronchodilators, and steroids).
- In contrast to a common view in individuals with chronic cough, that the cough is a reflex and involuntary, functional MRI studies demonstrate the role of the supramedullary pathways, including the cerebral cortex during cough, and changes in brain behavior during active cough suppression, suggesting a voluntary component to cough.
- Behavioral treatments where patients are taught to identify precipitating sensations to the cough are designed to help the patient "take control" of the cough and take an active role in their treatment.
- Hypnosis, suggestion therapy (see Table E2), reassurance, and counseling, along with appropriate psychotropic medication for psychiatric comorbidities, have been shown to be effective.
- Referral to psychologist or psychiatrist may be appropriate.
- In a systematic review of "psychogenic cough" treatment studies, which included 18 uncontrolled studies, Haydour et al. found that hypnosis (three studies), suggestion therapy (four studies), and counseling and reassurance (seven studies) were the most commonly used interventions.
  1. Hypnosis was effective in resolving cough in 78% of the patients and improving it in another 5%.
  2. Suggestion therapy resolved cough in 96% of patients.
  3. Pediatric patients had the most benefit from these forms of therapy.
- Vocal-fold injection of botulinum toxin type A was reported in three pediatric cases of debilitating chronic cough and was effective in disrupting the cough cycle. However, the cough recurred from 10 days to 2.5 mo later, and behavioral therapy was subsequently successful in controlling the cough.
- Patient values, preferences, and availability of potential therapies should guide treatment choice.

COMPLEMENTARY & ALTERNATIVE MEDICINE

None known

DISPOSITION

- Somatic cough syndrome has a good prognosis if diagnosed and treated early and often resolves with behavioral therapies (see earlier).
- Delay in diagnosis, misdiagnosis, and mistreatment can exacerbate the numerous physical, social, and emotional side effects of chronic cough, such as avoidance of daily activities, difficulty with interpersonal relationships, stress urinary incontinence, and avoidance of talking.
- It is therefore important to include somatic cough syndrome in the differential diagnosis of persistent or recurrent chronic cough and asthma that is difficult to control and refractory to standard pharmacologic approaches.

REFERRAL

Referral to psychologist and/or psychiatrist should be considered if diagnosis is complicated by difficult-to-treat comorbid psychiatric conditions.

PEARLS & CONSIDERATIONS

COMMENTS

- Consider that there may be more than one cause of a chronic cough.
- Newer concepts, including idiopathic cough, unexplained cough, cough hypersensitivity syndrome, and laryngeal hypersensitivity, are also used to describe medically unexplained cough. Further research is needed to better elucidate these entities and how they diverge from somatic cough syndrome.

PREVENTION

There are no known preventive measures.

SUGGESTED READINGS

Available at ExpertConsult.com

TABLE E2 Steps to Suggestion Therapy in Somatic Cough Syndrome

1. Explain to the patient that the irritant that originally caused the cough is now gone, and their current cough is contributing to an ongoing cycle of more irritation and more coughing.
2. Advise the patient that each second the cough is delayed will make the cough easier to suppress.
3. Instruct the patient to focus all of their attention on suppressing the urge to cough for 1 min. After this is accomplished, progressively increase the amount of time while concurrently offering an alternative behavioral strategy to reduce irritation, such as sipping lukewarm water or inhaling a cool mist from a vaporizer.
4. As the patient demonstrates the ability to voluntarily resist coughing for increasing time periods, continue to confidently acknowledge this success.
5. When the patient is able to suppress the urge to cough for about a 10-min interval, inquire, "you're beginning to feel you can resist the urge to cough, aren't you?"
6. When the patient is able to consistently answer affirmatively to the question, "Do you feel that you can now resist the urge to cough on your own?" then the session can be ended. Note: Only ask this question after the patient has suppressed the cough for at least 5 min.
7. Finally, express confidence and encouragement that the patient can resist the urge to cough at home (autosuggestion).

Adapted from Weinberger M, Lockshin B: When is a cough functional and how should it be treated? *Breathe* 13:22-30, 2017.

AUTHOR: **Danielle Goldfarb, MD**

SUGGESTED READINGS

Haydour Q et al: Management and diagnosis of psychogenic cough, habit cough, and tic cough: a systematic review, *Chest* 146:355-372, 2014.

Imai E et al: An objective evaluation of nocturnal cough count and cough pattern in children with psychogenic cough, *Respir Investig* 55:334-337, 2017.

Leech J et al: Brain activity associated with placebo suppression of the urge-to-cough in humans, *Am J Respir Crit Care Med* 188:1069-1075, 2013.

Vertigan AE: Somatic cough syndrome or psychogenic cough—what is the difference? *J Thorac Dis* 9:831-838, 2017.

Vertigan AE et al: Somatic cough syndrome (previously referred to as psychogenic cough) and tic cough (previously referred to as habit cough) in adults and children: chest guideline and expert panel report, *Chest* 148:24-31, 2015.

Weinberger M, Lockshin B: When is a cough functional and how should it be treated? *Breathe* 13:22-30, 2017.

Somatic Symptom Disorder

BASIC INFORMATION

DEFINITION

Somatic symptom disorder is a new diagnostic entity subsumed within *DSM-5* under somatic symptom and related disorders. It replaces somatization disorder. Patients with these disorders are usually encountered in primary medical settings, and thus the diagnoses have been reconceptualized to make them more useful for nonpsychiatric providers. Previous criteria overemphasized the concept of the medically unexplained symptom, which has now been dropped in favor of incorporating affective, cognitive, and behavioral components to more accurately reflect the clinical picture. In this particular condition, patients often present with one or more somatic symptoms that are perceived as distressing, which significantly disrupt daily life. They interpret or understand bodily symptoms as harmful and threatening. It is crucial to understand that somatic symptoms without a medical explanation are not sufficient to make the diagnosis. *DSM-5* somatic symptom disorder (SSD) with predominant pain replaces *DSM-IV-TR* pain disorder. The differential diagnosis of SSD includes related conditions that are in the same *DSM-5* category: illness anxiety disorder; conversion disorder, factitious disorder, and other specified somatic symptom and related disorders such as pseudocyesis (a false belief of being pregnant with associated signs and reported symptoms).

SYNONYMS

Functional syndrome
Nonorganic symptoms
Medically unexplained symptoms
Somatization syndrome
Somatoform disorder

ICD-10CM CODE	
F45.1	Somatoform disorder
ICD-10CM CODE	
300.82	Somatic symptom disorder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Not known
PEAK INCIDENCE: Not known
PREVALENCE: Estimated to be around 5% to 7%
PREDOMINANT SEX AND AGE: Females tend to report more somatic symptoms.
GENETICS: Not known, but thought to contribute along with other factors
RISK FACTORS: Tendency to experience negative affect (neuroticism), limited education, lower socioeconomic status, recent stressful life events, childhood adversity, or abuse

PHYSICAL FINDINGS & CLINICAL PRESENTATION

These patients usually present with multiple somatic symptoms that are distressing and disrupt life and function. Symptoms can be specific, such as localized pain, but often are not. These somatic symptoms can coexist with another medically diagnosable condition. They present with high levels of anxiety about their symptoms, which they focus on excessively and perceive as unduly threatening. They have a high level of utilization of medical services.

ETIOLOGY

Thought to be the result of multiple contributing factors such as genetic predisposition, early traumatic experiences, learning, cultural, and social issues

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other medical conditions: Symptoms of unknown etiology are insufficient to make the diagnosis of somatic symptom disorder. Multisystemic disorders (e.g., autoimmune disorders), pheochromocytoma, and carcinoid and endocrinopathies may present with multiple somatic complaints and psychological symptoms.
- Illness anxiety disorder: Distress about the meaning of the complaint, not the symptom itself.
- Conversion disorder: Voluntary motor or sensory symptom not compatible with known neurological condition.
- Factitious disorder: Falsification of physical or psychological symptoms or induction of injury/disease.
- Mood and anxiety disorders.
- Obsessive-compulsive disorder: Intrusive thoughts, images about the symptoms.
- Delusional disorder: If beliefs about somatic symptoms are rigid and firmly held.
- Malingering.

WORKUP

Rule out general medical conditions. With patients suspected or known to experience recurrent somatic symptoms, a conservative approach that limits the use of tests is best, as testing may only serve to reinforce the underlying beliefs about the nature of the symptoms.

LABORATORY TESTS

No specific laboratory test is required, except as indicated by history and physical examination.

IMAGING STUDIES

No specific imaging test is required, except as indicated by history and physical examination.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Establish a therapeutic alliance with the patient.
- Validate concerns and suffering.
- Elicit expectations and help set goals that are realistic.
- Preliminary studies using cognitive behavioral therapy or acceptance and commitment therapy or mindfulness-based stress reduction show feasibility and early promise.

ACUTE GENERAL Rx

- Brief examination that focuses on complaint area.
- Explore current psychosocial issues.
- Provide empathy and support.
- Benefit from antidepressant medication for somatic symptoms is unclear, but this benefit may be independent of depression.
- Serotonergic and noradrenergic transmission mediates endogenous analgesic mechanisms via descending inhibitory pathways in the central nervous system and may play a role in the heightened pain sensitivity seen in many of these patients.

CHRONIC Rx

- Single provider to manage overall care.
- Safeguard against patient's doctor-shopping tendency when possible.
- Provide empathy and support while reinforcing previously set goals, particularly restoration of function.
- Regular follow-up to support therapeutic relationship.
- Avoid invasive or extensive testing unless clinically warranted.
- Treat coexisting mood and anxiety disorders.

DISPOSITION

This is a chronic condition with frequent exacerbations requiring close follow-up.

REFERRAL

To a psychiatrist and/or a psychotherapist if patient is psychologically minded and open to referral

PEARLS & CONSIDERATIONS

- Some mental disorders may initially manifest with somatic symptoms; with multiple somatic symptoms, there is a higher likelihood of psychopathology.
- It is important to elicit the patient's own explanatory models for his or her symptoms.
- When more psychological explanations are reported, the patient is more likely to be disabled.
- Some patients have a negative self-perception that can persist and is a strong predictor of poor outcome.
- Patients may have catastrophic thinking and may be hostile to previous doctors, whom they may blame.
- Help patients reframe thoughts and keep focus on restoring function rather than on diagnosis and elimination of symptoms.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Christina D. Scully, MD,** and **Dwayne R. Heitmiller, MD, FAPM**

SUGGESTED READINGS

Creed FH et al: The epidemiology of multiple somatic symptoms, *J Psychosom Res* 72:311-317, 2012.

Katsamanis M et al: Psychophysiologic treatment for patients with medically unexplained symptoms: a randomized controlled trial, *Psychosomatics* 52(3):218-229, 2011.

Lacourt T et al: "Functional somatic syndromes, one or many?" an answer by cluster analysis, *J Psychosom Res* 74:6-11, 2013.

Tomenson B et al: Total somatic symptom score as a predictor of health outcome in somatic symptom disorders, *Br J Psychiatry* 203:373-380, 2013.

Southern Tick-Associated Rash Illness (STARI)

BASIC INFORMATION

DEFINITION

A rash, similar to the erythema migrans (EM) rash of Lyme disease, and flulike illness associated with the bite of the Lone Star tick *(Amblyomma americanum)* in eastern, southeastern, and south-central U.S.

SYNONYMS

Master disease
Southern Lyme disease

ICD-10CM CODE

A93.8 Other specified arthropod-borne viral fevers

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown as not a reportable disease in the U.S.
PEAK INCIDENCE: As it is temporally associated with tick bites, occurs more often in spring and summer
RISK FACTORS: Activities that lead humans to enter wooded areas where the ticks reside, such as hiking, lawn care, hunting, and walking in the woods

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The rash of STARI is an expanding erythematous lesion (Fig. E1) with irregular borders and central clearing that develops around the site of the Lone Star tick bite. Usually appears within 7 days of the bite and can expand to a diameter of 8 cm or more. It is described as being similar to erythema migrans rash of Lyme disease.
- Other associated symptoms include headache, fatigue, generalized achiness, and/or nausea similar to Lyme disease but without clinical progression or complications.

ETIOLOGY

The cause of STARI remains unknown. At one point a putative causative organism, *Borrelia lonestari,* was identified but it has never been isolated from a human patient. The organism has been isolated in Lone Star ticks (Fig. E2) and deer.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Lyme disease: Caused by the bite of the *Ixodes scapularis* tick and also causes a similar rash called erythema migrans. Causative organism is *Borrelia burgdorferi.*

WORKUP

Diagnosis should be considered in a patient from geographic areas that harbor the Lone Star tick and have a compatible rash, clinical syndrome, and a recent tick bite.

LABORATORY TESTS

- There is no definitive serology test for STARI.
- The ELISA for Lyme disease may be equivocal or weakly positive in patients with STARI but the Lyme Western blot test and Lyme C6 peptide assay will be negative.

TREATMENT

Doxycycline 100 mg orally twice a day for 10 days has been shown to produce rapid resolution of symptoms. This is also the antibiotic used for Lyme disease. For patients allergic to doxycycline or pregnant women or small children, amoxicillin can be used. Adults: 500 mg PO 3× a day.

PEARLS & CONSIDERATIONS

COMMENTS

A study by Wormser et al looked at the differences between STARI and Lyme disease:

- Patients with STARI were more likely to recall tick bite than patients with Lyme disease.
- The time period from tick bite to onset of skin lesion was shorter in STARI (average of 6 days).
- STARI patients with an erythema migrans rash were less likely to have other symptoms than were Lyme disease patients with erythema migrans rash.
- STARI patients were less likely to have multiple skin lesions, had lesions that were smaller in size than Lyme patients (6 to 10 cm for STARI vs. 6 to 28 cm for Lyme disease), and had lesions that were more circular and with more central clearing.
- With antibiotic therapy, patients with STARI had resolution of symptoms faster than patients with Lyme disease.

PREVENTION

Insect repellants can be useful in preventing attachment of the tick. Examples include DEET, picaridin, oil of lemon eucalyptus (OLE) or PMD, and the synthetic version of OLE.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Lyme Disease (Related Key Topic)
Ehrlichiosis and Anaplasmosis (Related Key Topic)
Babesiosis (Related Key Topic)
Rocky Mountain Spotted Fever (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

CDC.: Southern tick-associated rash illness (STARI). . . Available at: www.cdc.gov/stari/disease/index.html.

Goldstein IM et al: Hitting the target: Lyme or STARI, *J La State Med Soc* 165: 83-87, 2013.

Philpp MT et al: Serologic evaluation of patients from Missouri with erythema migrans-like skin lesions with the C6 Lyme test, *Clin Vaccine Immunol* 13:1170-1171, 2006.

Wormser GP et al: Prospective clinical evaluation of patients from Missouri and New York with erythema migrans-like skin lesions, *Clin Infect Dis* 41:958, 2005.

FIG. E1 Rash commonly seen with southern tick-associated rash illness.

FIG. E2 Tick vector for southern tick-associated rash illness.

BASIC INFORMATION

DEFINITION

Spasticity is an exaggerated tone that displays a velocity-dependent increase in resistance of muscles to a passive stretch stimulus.

SYNONYM

Hypertonicity

ICD-10CM CODES

G80.9	Cerebral palsy, unspecified
G81.10	Spastic hemiplegia affecting unspecified side
G83.9	Paralytic syndrome, unspecified
M62.838	Other muscle spasm
R25.0	Abnormal head movements
R26.0	Ataxic gait

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Spasticity affects between 47% and 70% of people with multiple sclerosis, 32% to 36% of those with spinal cord injury, approximately 20% of those with stroke, more than 90% with cerebral palsy, and approximately 50% of patients with traumatic brain injury.

PREDOMINANT SEX AND AGE: Spasticity is not affected by sex, race, or age group, nor is it more prevalent in any of those groups.

RISK FACTORS: Central nervous system diseases, including multiple sclerosis, stroke, spinal cord injury, cerebral palsy, traumatic brain injury.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patient may present with impaired gait, impaired limb function, decreased mobility, or discomfort due to increased muscle tone.
- While increased tone may preserve strength in the affected muscles, function may be impaired, especially fine motor. Examine active and passive motion, reflexes, and functions:
  1. Strength may be normal or decreased. Isometric strength is typically greater than concentric strength.
  2. Tone may be variably increased to passive range of motion (modified Ashworth scale; see Table E1).
  3. Reflexes are typically brisk.
  4. Patient may have accompanying extensor plantar signs, clonus, or spontaneous flexor spasms.
  5. Function may be impaired or enhanced due to increased tone.

ETIOLOGY

Upper motor neuron injury, most commonly due to multiple sclerosis, stroke, spinal cord injury, cerebral palsy, traumatic brain injury

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Rigidity, clonus, dystonia, dyskinesia, myotonia, tetanus, muscle contracture, cramps

WORKUP

- A diagnosis is established clinically.
- Investigate reversible exacerbating causes of spasticity: Underlying infection, bladder distention, bowel impaction, fracture, pain.

LABORATORY TESTS

Urinalysis, complete blood count, metabolic panel

IMAGING STUDIES

Chest x-ray, abdominal x-ray series, bladder ultrasound

TREATMENT

First treat reversible causes of spasticity (see "Workup"), then proceed to physical and pharmacologic therapeutics. Lastly, consider surgical intervention in severe, refractory cases.

NONPHARMACOLOGIC THERAPY

- Physical therapeutics include range of motion and muscle stretching, serial casting or orthotics, muscle cooling, electrical stimulation.
- Surgical procedures include tenotomy, tendon lengthening, and tendon transfers. More invasive surgical interventions include peripheral neurectomy, myelotomy, and rhizotomy.

ACUTE GENERAL Rx

- Oral medications: Baclofen, tizanidine, diazepam, dantrolene (Table E2)
- Other interventions: Intrathecal baclofen, botulinum toxin intramuscular injections, chemical nerve blocks (with bupivacaine, phenol, or ethyl alcohol)

COMPLEMENTARY & ALTERNATIVE MEDICINE

EMG biofeedback

DISPOSITION

Typically nonprogressive, but medications may lose efficacy after long duration of use. Drug holidays (with use of alternative spasmolytic) may be beneficial.

REFERRAL

- Physicians: Neurologist or physiatrist with expertise in botulinum toxin injection and/or intrathecal spasmolytic therapy is recommended when oral medications are ineffective or not tolerated.
- Physical and occupational therapy.

TABLE E1 Modified Ashworth Scale

0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end range of motion when the part is moved in flexion or extension/abduction or adduction
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion
2	More marked increase in muscle tone through most of the range of motion, but the affected part is easily moved
3	Considerable increase in muscle tone, passive movement is difficult
4	Affected part is rigid in flexion or extension (abduction or adduction)

From Stein J: Spasticity. In Frontera WR et al (eds): *Essentials of physical medicine and rehabilitation,* ed 2, Philadelphia, 2008, WB Saunders.

TABLE E2 Commonly Used Oral Spasmolytic Medications

Medication	Mechanism of Action	Starting Dose	Maximum Dose	Common Side Effects	Considerations*
Baclofen	GABA-B agonist	5 mg tid	20 mg qid†	Sedation, rare hepatotoxicity	Cognitive impairment
Diazepam	GABA-A agonist	2 mg bid	10 mg qid	Sedation, dependence or tolerance	History of substance abuse, cognitive impairment
Tizanidine	Alpha-2 agonist	2 mg tid	12 mg tid	Sedation, hypotension, hepatotoxicity	Cognitive impairment
Dantrolene	Blocks Ca^{2+} release from sarcoplasmic reticulum	25 mg daily	100 mg qid	Weakness, hepatotoxicity	Liver disease

*Baclofen, diazepam, and tizanidine are centrally acting and may exacerbate cognitive impairment. Dantrolene acts peripherally; however, it has the rare but fatal side effect of hepatotoxicity.
†Approved by the U.S. Food and Drug Administration only up to 80 mg/day, but many clinicians exceed this in patients who tolerate this medication well but do not respond to smaller doses.
bid, Twice a day; *qid,* four times a day; *tid,* three times a day. Modified from Stein J: Spasticity. In Frontera WR et al (eds): *Essentials of physical medicine and rehabilitation,* ed 2, Philadelphia, 2008, WB Saunders.

PEARLS & CONSIDERATIONS

- Assess whether the spasms recently increased in severity or intensity (as would occur with reversible exacerbating causes).
- Consider whether patient's tone is beneficial or detrimental to patient's functionality or overall health status.
- Spasticity may assist posture and mobility, as well as maintain muscle mass and bone mineralization, reduce dependent edema, and prevent deep venous thrombosis.
- Spasticity may impair patient's functionality, interfere with activities of daily living, interfere with sleep, and cause discomfort.
- Monitor liver function with dantrolene and tizanidine, as these drugs may cause hepatotoxicity.

AUTHOR: **Joseph S. Kass, MD, JD, FAAN**

Spina Bifida

BASIC INFORMATION

DEFINITION

Spina bifida refers to a group of neural tube disorders that involve the spinal column and include spina bifida occulta and spina bifida cystica (Fig. E1). Anencephaly and cranium bifidum (i.e., encephalocele) are also classified as neural tube disorders.

Spina bifida occulta is a midline defect of closure of the posterior vertebral arches and laminae and usually involves the L5 to S1 area of the spinal cord.

Spina bifida cystica includes both meningocele and myelomeningocele. Meningocele is a midline defect in which only the meninges herniate through the posterior vertebral arch defect with a normal spinal cord in a normal position in the spinal canal; this condition makes up about 5% of cases of spina bifida cystica. Myelomeningocele is the most severe form of disease in the spectrum of spina bifida. The meninges, fragments of bone and cartilage, and the spinal cord herniate through the vertebral arches or the skin; this condition makes up about 95% of cases. Most of these defects (~75%) are located in the lumbosacral area (Figs. E2 and E3).

SYNONYMS

Dysraphism
Meningomyelocele
Neural tube disorders

ICD-10CM CODES

Q76.0 Spina bifida occulta
Q05.8 Sacral spina bifida without hydrocephalus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Spina bifida occulta: 10% of the general pediatric population
- Spina bifida cystica: 0.15% of Caucasians, 0.04% of African Americans
- Highest in Ireland and lowest in Japan
- Within the U.S., rate is approximately 0.2 per 1000 live births and is much higher in the Latino population
- Influenced by season, economic status, maternal age, heat exposure, and history of prior children with neural tube defects
- Neural tube defects are the second-most common congenital anomaly (after cardiac malformations) and are the cause of chronic disability of between 70,000 and 100,000 individuals in the U.S.

PREDOMINANT SEX: Females are affected more frequently than males.

RISK FACTORS:

- Nutritional deficiency (specifically folate)
- Prior children with neural tube defects (risk increases 1.5% to 2%)
- If two prior children had spinal column defects, the risk increases 6% to 10%.

GENETICS:

- Unknown.
- New data suggest that epigenetic alteration in placental DNA methylation may be associated with spina bifida, particularly with genes involving *TRIM 26* and *GNAS.*

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Spina bifida occulta:
  1. Most patients are asymptomatic and have a normal neurologic examination.
  2. In some cases, patients may have a patch of hair, a lipoma, skin discoloration, or a dermal sinus overlying the defect.
  3. The condition is occasionally associated with syringomyelia, diastematomyelia, and a tethered cord.
- Meningocele:
  1. Patients typically have a normal neurologic examination; however, lesions may be accompanied by tethering, syringomyelia, or diastematomyelia.
  2. Constipation or bladder dysfunction can develop as a result of an enlargement of the lesion.
- Myelomeningocele:
  1. The lesion can be completely exposed, or it may have a skinlike membrane.
  2. The extent of the neurologic deficits depends on the level of the lesion.
     a. Thoracolumbar: Hypertonic or spastic bladder with normal anal tone

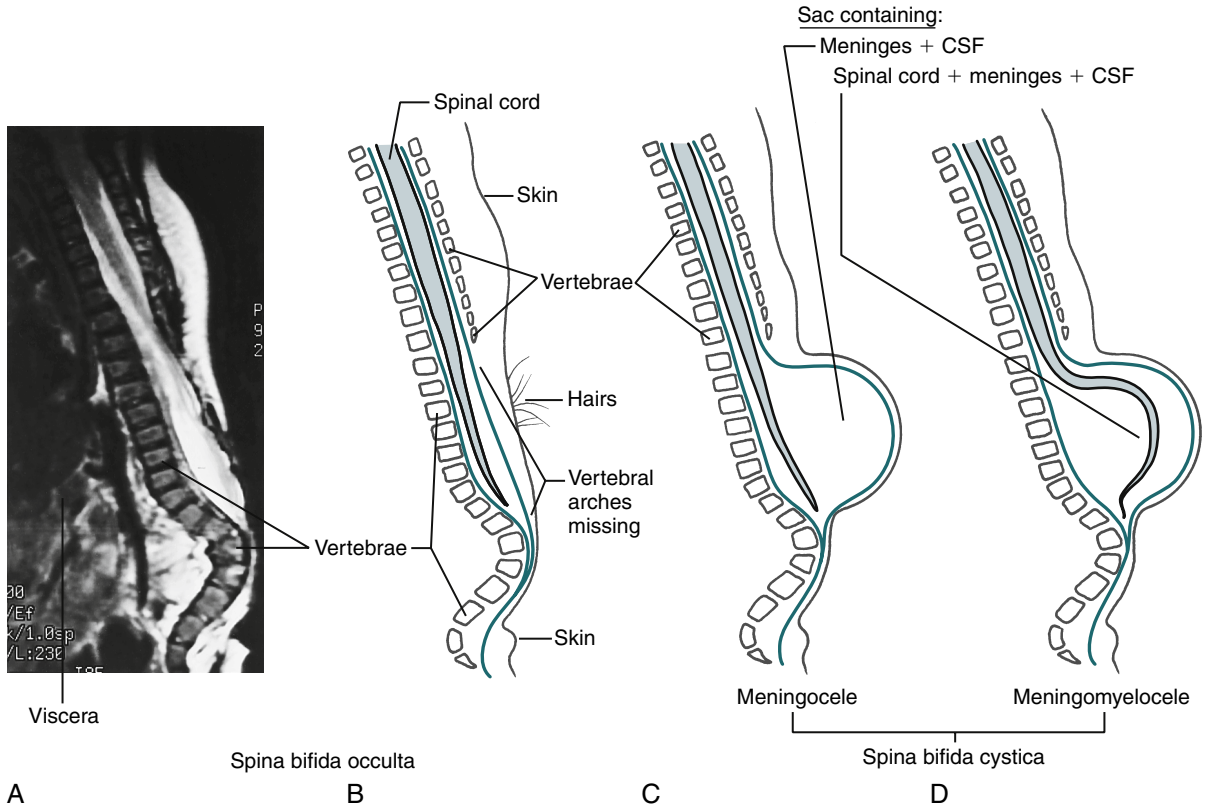


FIG. E1 Sagittal views of spina bifida malformations. Magnetic resonance image **(A)** and corresponding views showing spina bifida occulta **(A, B)** and spina bifida cystica (**C,** meningocele; **D,** meningomyelocele). *CSF,* Cerebrospinal fluid. (From Haines DE: *Fundamental neuroscience for basic and clinical applications,* ed 3, Philadelphia, 2006, Churchill Livingstone.)

b. Below L2: Flaccid tone; areflexic paraparesis; sensory loss in L3 to L4 dermatomes; bladder and bowel incontinence; and poor anal sphincter tone, which can result in rectal prolapse
c. Below S3: Motor deficits are absent; bladder and anal sphincter paralysis with saddle anesthesia

- Joint deformities include contractures, hip dislocations, scoliosis, clubfoot, and rocker-bottom foot.
- Hydrocephalus with Chiari malformations type II occurs in up to 90% of lumbosacral myelomeningoceles, and it is seen in more than half of cases at birth.
- Tethered cord disease manifests with a loss of motor function, spasticity with contractures, rapid progression of scoliosis with bent posture, back pain, and changes in urodynamics.

FIG. E2 Lumbosacral myelomeningocele covered by an epithelialized membrane. (From Kliegman RM [ed]: *Nelson textbook of pediatrics,* ed 18, Philadelphia, 2007, Saunders.)

- The condition is associated with disorders of cell migration that cause brain malformations, including heterotopia and schizencephaly.
- With this disease, there may also be multiorgan developmental disease (e.g., renal agenesis/anomalies, duodenal atresia, cardiac malformations, tracheoesophageal fistulas).

ETIOLOGY

- The posterior neuropore closes at about 26 to 28 days of gestation, which is typically prior to maternal knowledge of the pregnancy. The failure of the closure results in any of the neural tube disorders, with the severity being dependent on the stage of development at closure (i.e., earlier in development results in spina bifida cystica vs. spina bifida occulta).
- The cause of the failure to close is unknown, but it is thought to be multifactorial and to involve genetic defects, environmental toxins, and folate deficiency.

Dx DIAGNOSIS

This section will be further divided into prenatal diagnosis and diagnosis after birth.

PRENATAL DIAGNOSIS

- All pregnant women should be offered screening for NTDs. Unlike screening for fetal aneuploidy in women of advanced maternal age, selective screening based on maternal risk factors is not effective, because 90% to 95% of NTDs will occur in pregnancies with no risk factors. Thus, universal NTD screening would identify the majority of affected pregnancies.
- The benefit of screening is that early diagnosis can allow parents the option of terminating the pregnancy, deciding on a therapeutic intervention such as fetal surgery, or preparing for the birth of a child with an NTD. Furthermore, advanced knowledge of NTD may affect the mode and site of delivery, as these infants should be delivered at a center with level III neonatal intensive care unit and pediatric neurosurgery services.
- There are two approaches to prenatal screening for NTDs: Measurement of maternal serum alpha-fetoprotein (MSAFP) and ultrasound (screening and diagnostic). While intricate details of MSAFP interpretation and prenatal ultrasonographic screening for NTDs are beyond the scope of this book, MSAFP screening basics are discussed in the following.
  1. MSAFP screening is ideally performed at 16 to 18 wks gestation but can be performed as early as 15 wk or as late as 20 wk. First-trimester screening is not recommended, due to low sensitivity.
  2. It is important to consider gestational age, multiple pregnancy, maternal weight, and maternal diabetes mellitus when interpreting MSAFP values, as these can all affect interpretation. Furthermore, abdominal wall defects are commonly associated with elevated MSAFP.

DIAGNOSIS AFTER BIRTH

DIFFERENTIAL DIAGNOSIS: Isolated to this group of disorders

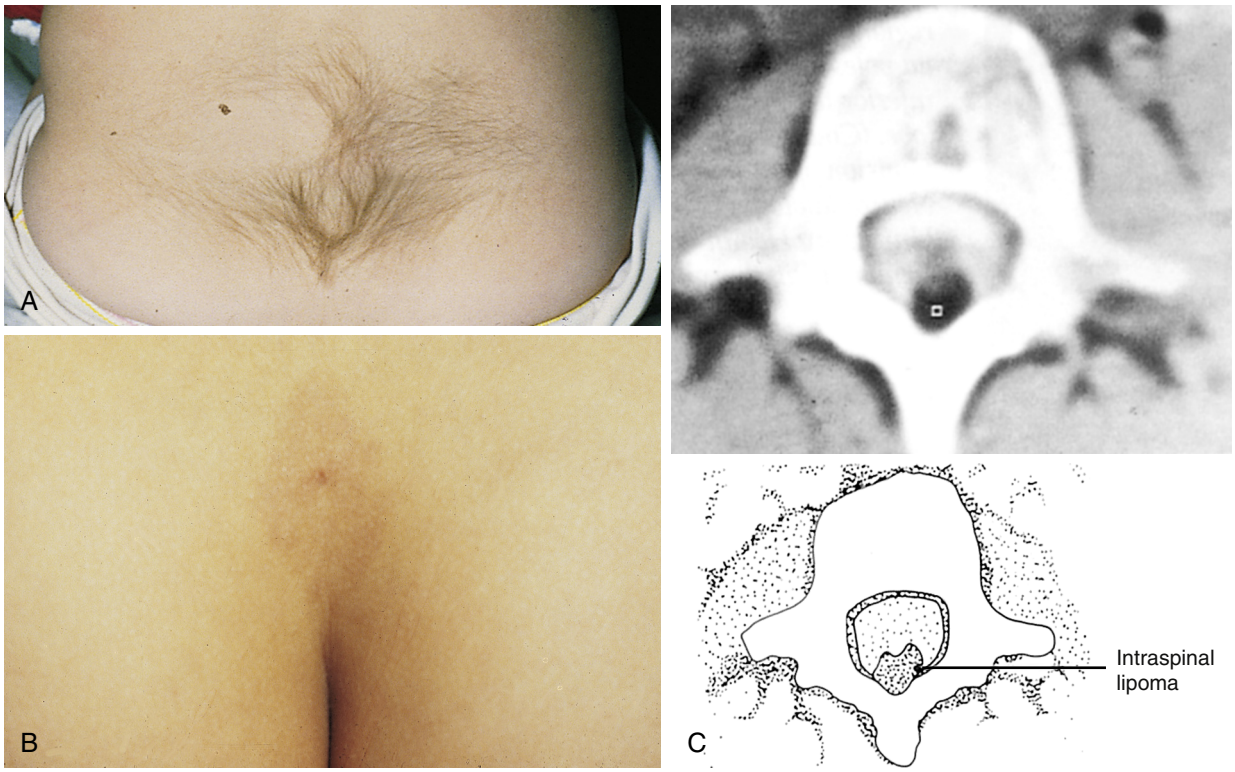


FIG. E3 Examples of cutaneous malformations associated with spina bifida occulta. A, Tuft of hair. **B,** Sacral lipoma. **C,** Sinus tract that communicates with a dermoid tumor. (From Zitelli BJ, Davis HW [eds]: *Atlas of pediatric physical diagnosis,* ed 5, Philadelphia, 2007, Saunders.)

WORKUP

- Spina bifida occulta: None, unless foot deformities, neurogenic bladder, or neurologic deficits develop, which would be concerning for spinal cord pathology
- Spina bifida cystica: Mostly includes imaging studies

LABORATORY TESTS

None

IMAGING STUDIES

- Ultrasound of affected areas
- MRI of head and spine
- Computed tomography is a quicker study and would not require sedation; however, this method exposes the patient to radiation and therefore should be minimized

Rx TREATMENT

- Spina bifida occulta: If asymptomatic with normal examination, none
- Meningocele: None
- Myelomeningocele: Antiepileptic medications, if warranted

NONPHARMACOLOGIC THERAPY

- Spina bifida occulta: There is no nonpharmacologic therapy used for this condition, unless the patient develops neurologic disease that is suggestive of underlying spinal cord disease.
- Meningocele: Most of these defects are covered by skin, so there is minimal risk of infection. If the patient has a normal examination with full-thickness skin, surgery can be delayed. However, if cerebrospinal fluid begins to leak or if the skin is thin, then immediate surgical correction is warranted.
- Myelomeningocele: Initial sac closure with a ventriculoperitoneal shunt is usually performed during the first 48 hr of life. It is important to use nonlatex gloves and equipment to minimize the risk of latex sensitization in these infants, as they are at increased risk for developing life-threatening latex allergy.
- The in utero closure of spinal lesions has been successful in a few centers, but there is a lack of evidence to support this procedure. The theory is that early closure possibly results in less severe motor disease, joint deformities, and sensory loss.

CHRONIC Rx

- Involves a multidisciplinary approach that includes primary care, neurology, urology, orthopedic surgery, neurosurgery, and physical and occupational therapy
- Bladder catheterization to ensure complete emptying of urinary bladder and minimization of renal scarring
- Urodynamic evaluations
- Bowel training with stool softeners and enemas (an appendicostomy may be placed for antegrade enemas, if warranted)
- The goal is to prevent the further loss of function and to maximize ambulation:
  1. Close monitoring via physical examination for further worsening of clubfoot, spasticity, sensory loss as a result of possible shunt malfunction, or tethering of cord, which would warrant neurosurgical intervention
  2. Orthotics
  3. Physical and occupational therapy
- Frequent skin examinations to monitor for decubitus ulcer formation

DISPOSITION

- 70% of patients have normal intelligence; this is affected by episodes of meningitis and encephalitis.
- Most patients with spina bifida have normal intelligence, but almost all will have some degree of learning disability, including attention deficits, memory problems, and poor executive functioning.
- Seizures occur in 10% to 25% of children with myelomeningocele and are correlated to poor cognitive performance.

PEARLS & CONSIDERATIONS

PREVENTION

All women of childbearing age should take a daily multivitamin for folate supplementation (0.4 mg/day), because more than half of pregnancies are unplanned, and the greatest benefit is seen when supplements are taken for about 1 mo before conception. Daily dose should be increased to 0.6 mg/day during pregnancy. Women who have had a previous child with NTD and those taking medications that affect folate metabolism (e.g., valproic acid, carbamazepine, methotrexate, sulfamethoxazole/trimethoprim) are recommended to take folic acid supplementation of 4 to 5 mg per day prior to conception to reduce occurrence/recurrence of NTD. This high dose should be taken as folic acid alone, not as a multivitamin, as there is a risk of excessive vitamin intake with ingestion of several multivitamins, such as vitamin A, which is dangerous during pregnancy.

RELATED CONTENT

Meningomyelocele (Related Key Topic)

AUTHORS: **Stephanie Michelle Allen, MS, Donita Dillon Lightner, MD,** and **Joseph S. Kass, MD, JD, FAAN**

SUGGESTED READINGS

Bernard JP et al: Combined screening for open spina bifida at 11-13 weeks using fetal biparietal diameter and maternal serum markers, *Am J Obstet Gynecol* 209(3):223.e1-223.e5, 2013.

Bredaki FE et al: First-trimester screening for neural tube defects using alpha-fetoprotein, *Fetal Diagn Ther* 31:109, 2012.

Dennis M, Barnes MA: The cognitive phenotype of spina bifida meningomyelocele, *Dev Disabil Res Rev* 16(1):31-39, 2010.

Spencer K et al: First trimester maternal serum alpha-fetoprotein is not raised in pregnancies with open spina bifida, *Prenat Diagn* 34:168, 2014.

BASIC INFORMATION

DEFINITION

- Spinal cord compression is characterized by direct compression of the spinal cord within the spinal canal. This may result in loss of neurologic function from compression of the spinal cord in the cervical, thoracic, and upper lumbar spinal canal. Compression may also occur at the cauda equina in the lower lumbar spinal canal, which is anatomically below the level of the spinal cord. Fig. 1 illustrates a schematic demarcation of principal dermatomes shown as distinct segments. Depending on the underlying etiology, symptoms may develop gradually or acutely and may result in complete or incomplete deficits. Neurologic deficits related to compression of the cord itself are referred to as myelopathy, whereas deficits caused by compression on nerve roots are described as radiculopathy.
- Signs and symptoms of myelopathy:
  1. Upper motor neuron signs (Hoffman sign, inverted radial reflex, Babinski sign, spasticity, hyperreflexia, clonus) in chronic cases
  2. Weakness
  3. Sensory deficits
  4. Clumsiness, difficult ambulation, ataxic gait (secondary to loss of proprioception in legs)
- Signs and symptoms of radiculopathy:
  1. Lower motor neuron signs (hyporeflexia, hypotonicity, fasciculations, muscle atrophy)
  2. Weakness
  3. Sensory deficits

Incomplete spinal cord lesions may classically present in distinct syndromic patterns (Table 1), for example, as follows:

- Anterior cord syndrome
- Central cord syndrome (most common)
- Cauda equina syndrome (not a true example of spinal cord compression but rather of cauda equina compression, affecting lower motor neurons in lumbosacral nerve roots)
- Conus medullaris syndrome
- Brown-Séquard syndrome

SYNONYMS OR RELATED TERMS

Central cord syndrome
Anterior cord syndrome
Brown-Séquard syndrome
Acute spinal cord compression
Cauda equina syndrome
Conus medullary syndrome

ICD-10CM CODES	
S14.13XX	Anterior cord syndrome
G83.81	Brown-Séquard syndrome
G83.4	Cauda equina syndrome
S14.12XX	Central cord syndrome
G95.81	Conus medullaris syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

Dependent on etiology of cord compression

DEGENERATIVE SPINE DISORDERS

May affect the cervical, thoracic, and/or lumbar spine. Underlying pathology involves changes in keratin sulfate-to-chondroitin sulfate ratio in intervertebral disks with aging. This leads to a cascade of secondary events, including loss of disk height, disk herniation, spondylosis, increased intersegmental motion, formation of osteophytes, ligamentum flavum hypertrophy, and arthrosis of the facet joints. Compression of the nerve roots and/or spinal cord may result.

Spinal cord and nerve root compression from degenerative conditions are more common with increasing age, although any age group may be affected. Specific epidemiology and demographics are dependent on the type of degenerative changes.

TUMOR

Epidemiology dependent entirely on tumor type. Malignant tumors in the spine are most commonly metastatic disease, although primary musculoskeletal tumors are possible. The spine is the third-most common site for tumor metastases, after the lung and liver. Common metastatic lesions to the spine include lung cancer, breast cancer, prostate cancer, cancer of the GI tract, multiple myeloma, and lymphoma.

INFECTION

Diskitis/osteomyelitis may progress to epidural abscess, causing spinal cord or cauda equina compression. If not adequately addressed in a timely manner, this may result in permanent neurologic deficit. Epidural abscess incidence is approximately 0.2 to 3.0 per 10,000 hospital admissions. *Staphylococcus aureus* is the most common offending organism. Risk factors include increasing age, diabetes mellitus, end-stage renal disease, chronic hepatitis/cirrhosis, known endocarditis, immunocompromise, and IV drug abuse.

SPINAL CORD INJURY

Occurred most commonly in males with a mean age of 37 yr in 2010. Alcohol plays a major role in at least 25% of spinal cord injury (SCI).

INCIDENCE: 12,400 new cases/yr in 2010 in the U.S.

PREVALENCE: 250,000 persons in 2005 in the U.S.

COST (IN U.S.): >$5 billion/yr

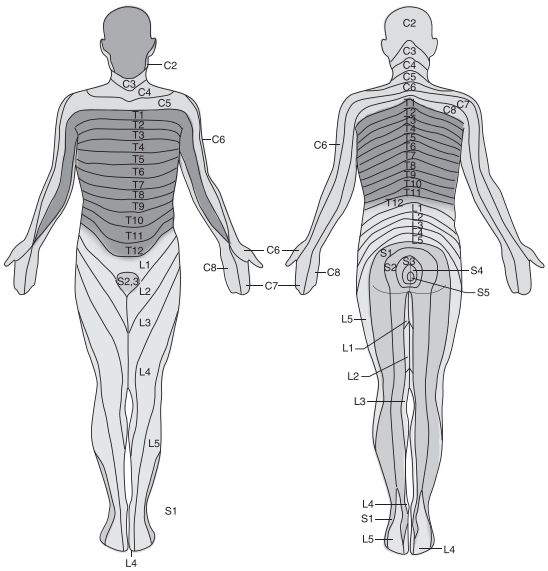
RISK FACTORS: Underlying spinal disease can predispose to SCI:

- Inflammatory spondyloarthropathies, especially ankylosing spondylitis
- Diffuse idiopathic skeletal hyperostosis (DISH)
- Congenital spinal disorders
- Preexisting spinal canal stenosis or compromise
- Atlantoaxial instability
- Osteoporosis
- Rheumatoid arthritis (cervical spine)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical features reflect the amount of spinal cord involvement:

- Weakness, sensory changes (dependent on level of compression/lesion/injury).
- Myelopathy if cord involvement, radiculopathy if nerve root involvement (may involve both).



Levels of principal dermatomes

C5	Clavicles
C5,6,7	Lateral parts of upper limbs
C8, T1	Medial sides of upper limbs
C6	Thumb
C6,7,8	Hand
C8	Ring and little fingers
T4	Level of nipples
T10	Level of umbilicus
T12	Inguinal or groin regions
L1,2,3,4	Anterior and inner surfaces of lower limbs
L4,5 S1	Foot
L4	Medial side of great toe
S1,2, L5	Posterior and outer surfaces of lower limbs
S1	Lateral margin of foot and little toe
S2,3,4	Perineum

FIG. 1 Schematic demarcation of levels of principal dermatomes shown as distinct segments. There is actually considerable overlap between any two adjacent dermatomes. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2011, Saunders.)

TABLE 1 Spinal Cord Syndromes

Syndrome	Sensory	Motor	Sphincter Involvement
Central cord syndrome	Variable	Upper extremity weakness, distal > proximal	Variable
Brown-Séquard syndrome	Ipsilateral position and vibration sense loss Contralateral pain and temperature sensation loss	Motor loss ipsilateral to cord lesion	Variable
Anterior cord syndrome	Loss of pin and touch sensation Vibration, position sense preserved	Motor loss or weakness below cord level	Variable
Transverse cord syndrome—complete	Loss of sensation below level of cord injury	Loss of voluntary motor function below cord level	Sphincter control lost
Cauda equina syndrome	Saddle anesthesia may be present, or sensory loss may range from patchy to complete transverse pattern	Weakness may be of lower motor neuron type	Sphincter control impaired

From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, WB Saunders.

TABLE 2 Physical Examination Findings Associated with Vertebral Fractures and Spinal Cord Injuries

Injury	Physical Examination Area	Associated Findings
Vertebral fracture	Spine	Tenderness of the neck and/or back. Examine the entire spine because vertebral fractures may occur in multiples.
	Neurologic	See "Spinal cord injury" later.
	Chest	*Thoracic spine fractures:* Check for chest tenderness, unequal breath sounds, and arrhythmia, which are suggestive of an associated intrathoracic injury or myocardial contusion.
	Abdomen/pelvis	*Thoracolumbar and lumbar spine fractures:* Check for abdominal or pelvic tenderness. A transverse area of ecchymosis on the lower abdominal wall (seat belt sign) increases the chance of an abdominopelvic injury.
	Extremity	*Thoracolumbar and lumbar spine fractures*: Check for calcaneal tenderness because 10% of calcaneal fractures are associated with a low thoracic or lumbar fracture. Mechanistically, these areas are fractured as a result of axial loading.
Spinal cord injury	Neurologic, motor (anterior column)	Assess motor function on a scale of 0 to 5. The *motor level* is defined as the most caudal segment with at least 3/5 strength. Injuries to the first eight cervical segments result in tetraplegia (previously known as quadriplegia); lesions below the T1 level result in paraplegia.
	Neurologic, sensory (spinothalamic tract)	Assess sensory function via pinprick and light touch on the following scale: 0 = absent; 1 = impaired; 2 = normal. The *sensory level* is defined as the most caudal segment of the spinal cord with normal sensory function. The highest intact sensory level should be marked on the patient's spine to monitor for progression.
	Neurologic, sensory (dorsal column)	Assess vibratory sensory function on a scale of 0 to 2 by using a tuning fork over bony prominences. Assess position sense (proprioception) by flexing and extending the great toe.
	Neurology, deep tendon reflex	On a scale of 0 to 4, assess the deep tendon reflexes in the upper (biceps, triceps) and lower (patellar, Achilles) extremities.
	Anogenital	Assess rectal tone, sacral sensation, signs of urinary or fecal retention or incontinence, and priapism. Also check the anogenital reflexes. An *anal wink* (S2-S4) is present if the anal sphincter contracts in response to stroking the perianal skin area. The *bulbocavernosus reflex* (S3-S4) is elicited by squeezing the glans penis or clitoris (or pulling on an inserted Foley catheter), which results in reflexive contraction of the anal sphincter.
	Head-to-toe examination	A spinal cord injury may mask a patient's ability to perceive and localize pain. Imaging of high-risk areas, such as the abdomen, and areas of bruising or swelling may be required to exclude occult injuries.

From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

- ***Central cord syndrome (most common incomplete spinal cord injury):*** Motor impairment greater in upper than in lower extremities, variable degree of sensory loss below the injury level. Weakness and poor hand dexterity are especially common. Classically occurs after mild trauma including cervical hyperextension in the setting of preexisting cervical spondylosis.
- ***Anterior cord syndrome (worst prognosis of incomplete spinal cord injury):*** Affects the anterior or ventral two thirds of the spinal cord, sparing the dorsal columns. May be caused by a vascular injury to the anterior spinal artery or by a flexion/compression injury. Impairment usually is worse in the lower extremities than upper extremities. Physical manifestations include motor, pain, and temperature loss below the lesion. Proprioception and vibratory sense may be preserved as dorsal columns are preserved.
- ***Brown-Séquard syndrome:*** Rare in isolation. Caused by injury to half of the spinal cord and resulting in the loss of motor function, position, vibration, and light touch on the side of injury, as well as loss of pain and temperature sense on the contralateral side. Typically, secondary to a knife wound.
- ***Conus medullaris syndrome:*** Results in variable motor loss in the lower extremities with loss of bowel and bladder function. In general, more bowel and bladder is affected earlier than motor.
- ***Cauda equina syndrome:*** Low back pain, weakness in bilateral lower extremities, saddle anesthesia, and loss of voluntary bladder and/or bowel control, often presenting as bladder retention and/or bowel incontinence.

ETIOLOGY

- Trauma (most SCIs result from high-speed motor vehicle accidents, falls, sports injuries, or violence)
- Tumor
- Infection (e.g., epidural abscess)
- Inflammatory processes
- Degenerative disk disease with associated spinal stenosis
- Acute disk herniation
- Cystic abnormalities
- Ankylosing spondylitis, DISH. Patients with underlying DISH or ankylosing spondylitis are at high risk of SCI with otherwise relatively minor fractures of the spine
- Table 2 summarizes physical examination findings associated with vertebral fractures and spinal cord injuries

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

See "Synonyms or Related Terms."

WORKUP

- Signs and symptoms of spinal cord or cauda equina compression often indicate urgent surgical conditions and thus require urgent imaging and early referral for assessment by a spine specialist.

- In cases of acute trauma in which spinal cord injury is suspected, patient should undergo full trauma evaluation following advanced trauma life support protocol in emergency room setting. With suspected injury to the cervical spine, the patient should be immobilized in a hard cervical collar or in-line traction at all times during evaluation. Log-roll precautions may be indicated as well to immobilize the spine during acute injury evaluation.
- Inflammatory labs will usually be elevated both in cases of trauma and infectious processes. Laboratory tests ordered should be specific to the suspected etiology or differential diagnosis for spinal cord compression.

IMAGING STUDIES

- Signs and symptoms of spinal cord compression in most cases will mandate advanced imaging, often including CT and CT myelogram and/or MRI.
- Plain x-rays may be helpful; however, normal plain films do not negate the need for further advanced imaging in the setting of signs and symptoms of spinal cord compression or spinal cord injury. This is especially true in the setting of ankylosing spondylitis or DISH.
- In the trauma setting, after primary and secondary surveys, fine-cut helical CT scans with axial, coronal, and sagittal reconstructions have replaced plain cervical radiographs in most trauma centers as the initial evaluation of choice in detecting fractures of the cervical spine.
- Detection of injury to any part of the spine during trauma evaluation mandates full imaging evaluation of the entire spine, as noncontiguous injuries are common.
- While CT scan is excellent at imaging bony structures and detecting fractures, MRI provides more detailed imaging of the soft-tissue structures, including neural structures, discoligamentous structures, the posterior ligamentous complex, and paraspinal soft tissues. MRI is very sensitive for detecting ligamentous injury, spinal cord edema, spinal cord compression from soft-tissue structures, epidural hematoma, diskitis, osteomyelitis, and epidural abscess. Of note, gadolinium contrast may increase the sensitivity of the MRI study for the detection of tumors or infections.

Rx TREATMENT

- Depending on the etiology of spinal cord compression as well as the specific signs and symptoms during physical examination and history-taking, urgent surgical decompression and/or stabilization may be indicated. Referral to a spine specialist is indicated in most cases of spinal cord compression.
- Corticosteroids: Controversial in cases of acute spinal cord injury. Methylprednisolone was thought to reduce the amount of secondary injury that occurs after SCI and was previously used in many trauma centers. However, current evidence is insufficient to support corticosteroids for this use, and most spine trauma centers no longer utilize steroids in cases of acute spinal cord injury.

Vasopressors: Current evidence supports the use of vasopressors in cases of spinal cord injury to maintain spinal cord perfusion and to prevent ischemic damage to the cord. The ideal mean arterial pressure and duration of treatment are yet to be defined. Both the treatment modality and the injury itself mandate admission to ICU level of care in most cases for close monitoring.

DISPOSITION

Indicators regarding prognosis:

- Patients with acute traumatic SCI need monitoring in the ICU and evaluation for potential life-threatening complications, including cardiovascular instability and respiratory failure.
- In general, the greater the distal motor and sensory sparing, the greater the expected recovery.
- In most cases of spinal cord compression and/or spinal cord injury, the primary goal of surgical decompression and/or stabilization should be to spare the remaining functional levels and to prevent worsening of the injury. Return of function should not be guaranteed.
- Prophylaxis against deep vein thrombosis and pulmonary embolism should always be provided. In acute injuries to the spine or postoperatively, this may consist of mechanical prophylaxis including TEDs and SCDs. Pharmacologic deep vein thrombosis/pulmonary embolism prophylaxis is often held initially to prevent development of epidural hematoma. The optimal timing for initiation of pharmacologic prophylaxis is controversial, and no strict guidelines are currently in place.

REFERRAL

Signs and symptoms of spinal cord or cauda equina compression often indicate urgent surgical conditions and thus require urgent imaging and early referral for assessment by a spine specialist.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Spinal Stenosis (Patient Information)
Lumbar Disk Syndrome (Related Key Topic)
Spinal Epidural Abscess (Related Key Topic)
Spinal Stenosis, Lumbar (Related Key Topic)

AUTHORS: **Daniel Brian Carlin Reid, MD, MPH,** and **Shyam A. Patel, MD**

SUGGESTED READINGS

Eltorai AEM et al: Recent developments in the treatment of spinal epidural abscesses, *Orthop Rev* 9(2):7010, 2017.

Martin AR et al: Can microstructural MRI detect subclinical tissue injury in subjects with asymptomatic cervical spinal cord compression? A prospective cohort study, *BMJ Open* 8(4):e019809, 2018.

O'Phelan KH: Emergency neurologic life support: spinal cord compression, *Neurocrit Care* 27(Suppl 1):144-151, 2017.

Ropper AE, Ropper AH: Acute spinal cord compression, *N Engl J Med* 376:1358-1369, 2017.

Spinal Epidural Abscess

BASIC INFORMATION

DEFINITION

A spinal epidural abscess (SEA) is a focal suppurative infection occurring in the spinal epidural space.

SYNONYM

SEA

ICD-10CM CODE
G06.1 Intraspinal abscess and granuloma

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- 2 to 25 cases/100,000 hospitalized patients/yr
- May be increasing over the past 3 decades

PREDOMINANT AGE:

- Median age of onset approximately 50 yr (35 yr in intravenous drug users)
- Peak incidence in seventh and eighth decades of life

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The presentation of SEA can be nonspecific.
- Fever, malaise, and back pain are the most consistent early symptoms.
- Pain is often focal. It may initially be mild but can progress to become severe.
- As the disease progresses, root pain can occur, followed by motor weakness, sensory changes, bladder and bowel dysfunction, and paralysis.
- Physical findings may be limited to fever or spinal tenderness.
- The evolution to neurologic deficits can occur as quickly as a few hours, or over wks to mos.
- Once paralysis occurs, it may quickly become irreversible without the appropriate intervention.

ETIOLOGY

- SEA most commonly results from hematogenous dissemination.
- Pyogenic bacteria account for the majority of cases in the U.S. Immigrants from TB-endemic areas may present with tuberculous SEAs. Fungi and parasites can also cause this condition. The most common causative organism is *Staphylococcus aureus.* Gram-negative bacilli and anaerobes may be seen if the infection has a urinary or GI source.
- Most posterior SEAs are thought to originate from distant focus (e.g., skin and soft tissue infections), while anterior SEAs are commonly associated with diskitis or vertebral osteomyelitis. No source was found in approximately one third of cases.
- Associated predisposing conditions include diabetes mellitus, alcoholism, cancer, AIDS, and chronic renal failure, or following epidural anesthesia, spinal surgery or trauma, prolonged epidural catheter placement, paraspinal glucocorticoid or analgesic injections, acupuncture, or IV drug use. No predisposing condition is found in approximately 20% of patients.
- Damage to the spinal cord can be caused by direct compression of the spinal cord, vascular compromise, bacterial toxins, and inflammation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Herniated disk
- Vertebral osteomyelitis and diskitis
- Metastatic tumors
- Meningitis

LABORATORY TESTS

- WBC may be normal or elevated.
- ESR and C-reactive proteins are usually elevated.
- Blood cultures are positive in approximately 60% of patients with SEA and should be obtained prior to starting antibiotics.
- CSF cultures are positive in 19%, but lumbar puncture is unnecessary, and may be contraindicated.
- Once imaging is done, CT-guided aspiration or open biopsy should be done to determine causative organism. Abscess content culture is positive in 90% of patients.

IMAGING STUDIES

- MRI with gadolinium is the imaging modality of choice (Fig. 1); CT scan with contrast may show the abscess (Fig. 2) but is less sensitive than MRI.
- CT with myelography is more sensitive for cord compression.

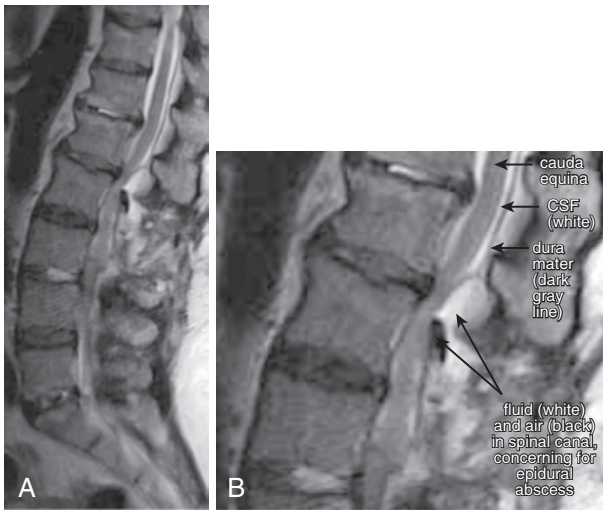


FIG. 1 Same patient as in Fig. 2, in whom noncontrast computed tomography showed air in the spinal canal, concerning for epidural abscess. Magnetic resonance imaging (MRI) of the lumbar spine without contrast was performed, as the patient was in acute renal failure. **A,** This T2-weighted sagittal MRI provides useful information even without gadolinium contrast. **B,** Close-up. On T2-weighted MRI sequences, fluid including cerebrospinal fluid *(CSF)* appears white. Fat-containing tissues such as bone marrow and the spinal cord or cauda equina appear dark gray. Calcified bone appears nearly black due to an absence of resonating protons. Air appears completely black for the same reason. The midline sagittal image shows the cauda equina to be impinged upon by an epidural fluid collection containing air—an epidural abscess. The dura mater is visible as a thin, dark-gray line parallel to the spinal cord. It is indented in the region of the epidural abscess. (From Broder JS: *Diagnostic imaging for the emergency physician*, Philadelphia, 2011, WB Saunders.)

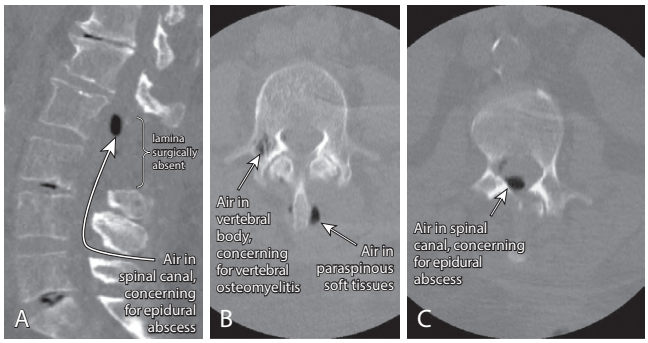


FIG. 2 This 67-yr-old female presented with delirium and fever. 3 mo prior, she had undergone lumbar laminectomy, and her wound had been treated with a wound VAC dressing. Magnetic resonance imaging was not initially available, so noncontrast computed tomography (CT) was performed. Noncontrast CT is excellent at delineating air, which appears black on bone windows. **A,** The midsagittal view demonstrates air *(black)* in the spinal canal at the L2 and L3 levels. On the axial views **(B, C),** air is visible in the spinal canal, in paraspinal soft tissues, and within the vertebral body. These findings are concerning for a paraspinal infection that has developed into an epidural abscess with vertebral osteomyelitis. (From Broder JS: *Diagnostic imaging for the emergency physician*, Philadelphia, 2011, WB Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Surgical decompression is the mainstay of treatment. Decompression within the first 24 hr has been related to an improved prognosis.
- Nonsurgical treatment is effective in some patients, but failure rate may be excessive. This approach should not be considered and should only be attempted in the absence of signs of compressive myelopathy and with very careful follow-up.

ACUTE GENERAL Rx

- In addition to surgery, antibiotics directed at the most likely organism should be initiated. Fig. 3 describes an algorithm for the management of patients with SEA.
- If the organism is unknown, broad coverage against staphylococci, streptococci, and gram-negative bacilli should be initiated. Empiric antimicrobial intravenous therapy typically includes vancomycin (loading dose: 25 to 30 mg/kg, then 15 to 20 mg/kg q8-12h, aiming for trough levels of 15 to 20) plus an antipseudomonal cephalosporin such as piperacillin/tazobactam at high dose (4.5 g IV q6h) or carbapenem such as meropenem (1 to 2 g IV q8h) or imipenem. The regimen can be adjusted according to culture results. Therapy should continue for at least 4 to 6 wk.

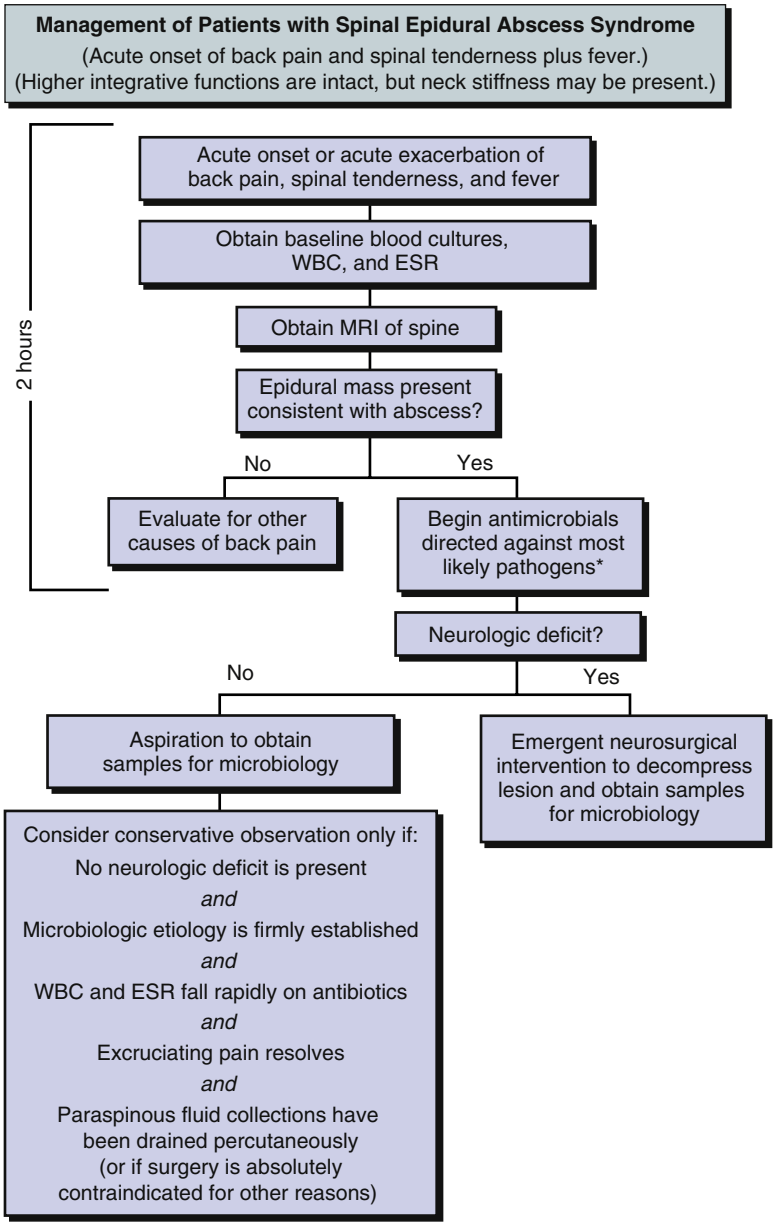


FIG. 3 Algorithm for the management of patients with spinal epidural abscess syndrome. If magnetic resonance imaging *(MRI)* cannot be performed, myelography, high-contrast computed tomography (CT), or CT-myelography may be an acceptable alternative to localize an epidural abscess. *If abscess drainage can be performed promptly, antimicrobial drugs may be withheld until specimens for microbial analysis are obtained. *ESR,* Erythrocyte sedimentation rate; *MRI,* magnetic resonance imaging; *WBC,* white blood cell. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.)

CHRONIC Rx

Neurologic deficits may remain despite aggressive treatment.

DISPOSITION

Irreversible paralysis and death can occur in up to 25% of patients.

REFERRAL

All cases should be referred to a neurosurgeon and an infectious disease specialist.

PEARLS & CONSIDERATIONS

- Follow-up imaging with MRI is not necessary unless patient develops new neurologic signs or symptoms, has poor clinical response, or has persistent elevation of inflammatory markers.
- It is critically important to recognize this process early; the prognosis is generally excellent if treatment is initiated while symptoms are localized and before evidence of myelopathy develops.
- The likelihood of success postsurgery is low in patients who have developed complete paralysis for longer than 36 hours.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Shah AA et al: Nonoperative management of spinal epidural abscess: development of predictive algorithm for failure, *J Bone Joint Surg Am* 100(7):546-555, 2018.

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Spinal Stenosis, Cervical Spine

BASIC INFORMATION

DEFINITION

Cervical spinal stenosis is defined as any abnormal narrowing of the cervical spinal canal. Radiographically, absolute cervical stenosis is defined as a canal diameter less than 10 mm, and relative stenosis is defined as a canal diameter between 10 and 13 mm. Stenosis of any part of the spinal canal (cervical, thoracic, or lumbar) may be congenital or, more commonly, acquired. Congenital spinal stenosis is due to a skeletal hypoplasia, whereas acquired stenosis is a multifactorial process that usually evolves with advanced age and as a result of degenerative disease. Symptoms arising from cervical spinal stenosis are due to compression of the exiting nerve root or on the spinal cord itself.

SYNONYMS

Cervical myelopathy
Cervical radiculopathy
Degenerative disease of the spine
Spinal foramina narrowing

ICD-10CM CODES

M47.12	Other spondylosis with myelopathy—cervical region
M47.22	Other spondylosis with radiculopathy—cervical region
M47.812	Cervical spondylosis without myelopathy or radiculopathy
M48.02	Spinal stenosis in cervical region
M50.0	Cervical disc disorder with myelopathy
M50.1	Cervical disc disorder with radiculopathy

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: In acquired cases, >50 yr
PREVALENCE: 1:1000 persons >65 yr old and 5:1000 persons >50 yr old
PREDOMINANT SEX AND AGE: Males and females affected equally; age depends on etiology (congenital vs. acquired); in acquired cases, most common between 20 and 65 yr of age

GENETICS: Genetic factors play a role in degenerative disease of the vertebrae and disc desiccation, but no one associated gene has been identified.
RISK FACTORS: Systemic diseases, rheumatoid arthritis, osteoarthritis; degenerative disc disease, repetitive microtrauma (spear tackler's spine), poor ergonomics

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Neurologic symptoms related to cervical stenosis may include:
  1. Chronic neck pain
  2. Unilateral or bilateral upper limb pain, often radiating
  3. Numbness of hands
  4. Arm or hand clumsiness
  5. Loss of hand dexterity
  6. Progressive loss of fine motor function of the hands
  7. Weakness of the upper extremities and proximal lower extremities
  8. Decreased sensation of the arm or hands
  9. Gait disturbances
  10. Hyperreflexia
- A positive Hoffman sign has somewhat low sensitivity but can be specific for cervical myelopathy in the context of other signs and symptoms.
- Central cord syndrome should be considered if a patient with existing cervical stenosis falls and develops weakness greater in the upper extremities than lower extremities.

ETIOLOGY

- Congenital or developmental cervical spinal stenosis is associated with skeletal hypoplasia resulting in diminished space within the spinal canal. Possible causes include:
  1. Vertebral segmentation failure
  2. Achondroplasia
  3. Incomplete vertebral arch fusion
  4. Anterior vertebral wedging or beaking
  5. Thoracolumbar kyphosis
  6. Early vertebral arch ossification
- Acquired stenosis accounts for the majority of cases; most arise from degenerative changes at the disk space level. It is a complex process that can also involve systemic, traumatic, and iatrogenic etiologies (Fig. E1). Several causes include:
  1. Facet joint and ligamentum flavum hypertrophy
  2. Stenosis from herniated disks
  3. Ossification of the posterior longitudinal ligament
  4. Spondylolisthesis
  5. Previous spinal fusions
  6. Paget disease
  7. Acromegaly
  8. Ankylosing spondylitis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ankylosing spondylitis
- Rheumatoid arthritis
- Diffuse idiopathic skeletal hyperostosis (DISH)
- Epidural, subdural, or intradural abscess
- Metabolic diseases (osteomalacia, vitamin B_{12}, or folate deficiency)
- Vascular disease (peripheral with claudication)
- Lumbar muscle strain
- Thoracic outlet syndrome
- Metastatic disease, Paget disease
- Conversion disorder, malingering
- Various intracranial processes

WORKUP

- Imaging modalities are of greatest utility in diagnosing cervical stenosis
  1. AP and lateral cervical spine x-rays
  2. Cervical spine CT scan can be helpful to describe the bony architecture
  3. Cervical spine MRI immediately if neurologic deficit or if pain >4 wk; most useful diagnostic test (Fig. E2)
  4. CT myelography if MRI is contraindicated (pacemaker)
- Consider nerve conduction studies if imaging equivocal

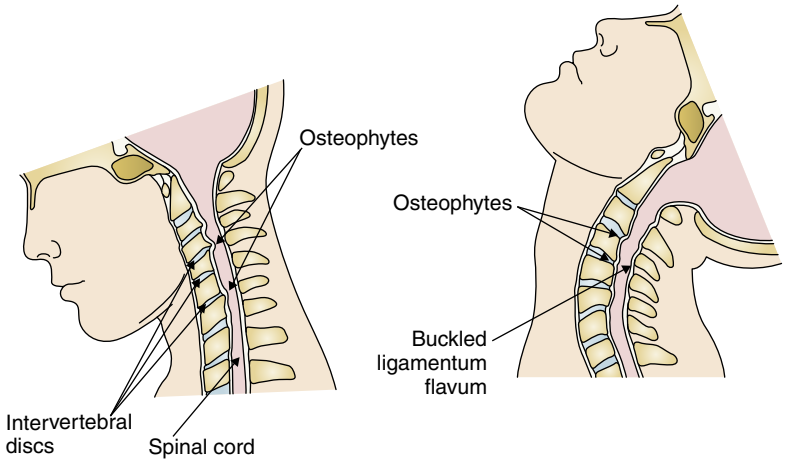

FIG. E1 Illustration of cervical spinal stenosis with associated causes (disc protrusion, osteophyte formation, hypertrophied ligamentum flavum). (From Frontera WR et al: *Essentials of physical medicine and rehabilitation*, Philadelphia, 2015, Elsevier.)

FIG. E2 T2 magnetic resonance image of the cervical spine demonstrating stenosis within the canal at the C4 to C5 and C5 to C6 level. (From Crowley P, Oxon BA: Neuroimaging of spinal canal stenosis, *MRI Clin N Am* 24:523-539, 2016.)

LABORATORY TESTS

Appropriate blood tests or CSF examination to rule out conditions on differential diagnosis

TREATMENT

Management of cervical spinal stenosis is geared toward symptom relief, preservation of function, and prevention of further neurologic decline. The decision between conservative or operative treatment depends on symptom severity, chronicity, and presence of neurologic deficits.

NONPHARMACOLOGIC THERAPY

- Physical/occupational therapy
- Mechanical measures (soft collar, heat, firm pillow) for pain relief
- Lifestyle changes
- Cervical traction

PHARMACOLOGIC THERAPY

- Analgesics
- Antiinflammatory agents:
  1. Use of PO or IV steroids
  2. Epidural steroid injections
- Antispasmodics
- Membrane stabilizing anticonvulsants (e.g., gabapentin) for neuropathic/radicular pain

DISPOSITION

- Nonoperative management of symptomatic patients is usually a temporizing measure; however, physicians must exhaust all nonsurgical options before referral for surgery in the absence of major neurologic deficits or progressive decline.
- Between 5% and 25% of patients with cervical stenosis will require surgery, with 33% of those experiencing favorable outcomes.
- Surgical intervention often involves decompression of the spinal cord/canal and fusion of the bony elements for stabilization. Laminoplasty, in which the spine is decompressed but the posterior processes are not resected, may be an option for eligible patients to retain motion.

REFERRAL

- Physical therapy
- Orthopedic or neurosurgical spine specialist for possible surgical decompression and fusion

PEARLS & CONSIDERATIONS

COMMENTS

As the population ages, cervical spinal stenosis will increase in prevalence. In general, treatment is initiated when the patient becomes symptomatic. The majority of patients can be treated conservatively, and in the primary care setting, immediate intervention for asymptomatic cervical stenosis is not necessary. However, any patient presenting with a neurologic deficit should be referred urgently to a spine specialist.

PREVENTION

Measures to strengthen neck musculature, improve the ergonomics of one's work environment, as well as avoiding chronic repetitive trauma may play a role in prevention of acquired cases.

PATIENT & FAMILY EDUCATION

Patient information on cervical spinal stenosis is available at www.spine-health.com/conditions/spinal-stenosis.

AUTHORS: **Lindsay R. Kosinski, MD,** and **Shyam A. Patel, MD**

SUGGESTED READINGS

Aljuboori Z, Boakye M: The natural history of cervical spondylotic myelopathy and ossification of the posterior longitudinal ligament: a review article, *Cureus* 11(7):e5074, 2019.

Clarencon F et al: The degenerative spine, *Magn Reson Imaging Clin N Am* 24(3):495–513, 2016.

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Gutierrez GJ, Chirumamilla D: Cervical spinal stenosis. In Desai M, O'Brien J, (eds): *The spine handbook*, New York, 2018, Oxford University Press, pp. 132-146.

Lund T, Santos de Moraes OJ: Cervical, thoracic and lumbar stenosis. In Winn HR et al: *Youmans and Winn neurological surgery*, Philadelphia, 2017, Elsevier, pp. 2373-2383.

Meleger AL, Egyhazi R: Cervical spinal stenosis. In Frontera WR et al (eds): *Essentials of physical medicine and rehabilitation*, Philadelphia, 2015, Elsevier, pp. 35-39.

Toledano M, Bartleson JD: Cervical spondylotic myelopathy, *Neurol Clin* 31:287-305, 2013.

Spinal Stenosis, Lumbar

BASIC INFORMATION

DEFINITION

Lumbar spinal stenosis (LSS) is an anatomical impairment characterized by narrowing of the spinal canal or nerve root foramen (Fig. E1).

SYNONYMS

Central spinal stenosis
Lateral spinal stenosis
Spondylosis
Lumbar spinal stenosis
LSS

ICD-10CM CODE
M48.06 Spinal stenosis, lumbar region

EPIDEMIOLOGY & DEMOGRAPHICS

More common between 50 and 60 yr of age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms caused by direct mechanical compression or indirect vascular compression of the nerve roots or the cauda equina
- Neurogenic claudication: Leg, buttock, or back pain precipitated by walking and relieved by sitting
- Pain may radiate down to ankles and is associated with numbness, tingling, and weakness
- Taking a flexed posture reduces symptoms because it increases the available space in the lumbar spinal canal
- Decreased lumbar extension
- Normal peripheral pulses
- Positive Romberg sign (decreased proprioception)
- Wide-based gait
- Reduced knee and ankle reflex
- Urine incontinence

ETIOLOGY

Spinal stenosis may be primary or secondary.

- Primary stenosis (congenital or developmental narrowing):
  1. Idiopathic
  2. Achondroplasia
  3. Morquio-Ullrich syndrome
- Secondary stenosis (acquired):
  1. Degenerative (hypertrophy of the articular processes, disk degeneration, ligamentum flavum hypertrophy, spondylolisthesis)
  2. Fracture/trauma
  3. Postoperative (postlaminectomy)
  4. Paget disease
  5. Ankylosing spondylitis
  6. Tumors
  7. Acromegaly

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Osteoarthritis of the knee or hip
- Acute cauda equina syndrome, resulting from compression by epidural abscess or tumors
- Pain and weakness caused by multiple myeloma or osteomyelitis
- Intermittent claudication—peripheral vascular disease
- Peripheral neuropathy such as that caused by a herniated nucleus pulposus
- Scoliosis or spondylolisthesis
- Rheumatoid diseases: Ankylosing spondylitis, Reiter syndrome, fibromyalgia
- Box E1 summarizes the differential diagnosis for low back pain. Table E1 compares clinical features of spinal stenosis, peripheral vascular disease, and disk disease

WORKUP

History, physical examination (Fig. E2), and specific imaging studies. Historical clues to the cause of low back pain are summarized in Table E2. Fig. E3 illustrates an algorithm for the management of low back pain.

IMAGING STUDIES

- Lumbar spine film sensitivity 66%, specificity 93%.
- Ultrasound of the spinal canal has also been used.
- CT scan of the lumbosacral spine: Sensitivity (75% to 85%), specificity (80%).
- MRI of the lumbosacral spine (Fig. E4): Sensitivity (80% to 90%), specificity (95%).
- Myelogram: Sensitivity (77%), specificity (72%). Absolute stenosis is defined as the anterior-posterior (AP) diameter of the spinal canal <10 mm. Relative stenosis: 10 to 12 mm AP diameter.
- Electromyography (EMG) and nerve conduction velocity (NCV) are additional studies particularly useful in differentiating peripheral neuropathy from lumbar spinal stenosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Physiotherapy
- Lumbar corsets
- Back exercises
- Abdominal muscle strengthening
- Aquatic exercises

ACUTE GENERAL Rx

- Surgery should be considered in patients with significant compression of nerve roots as determined by MRI or CT and incapacitating symptoms limiting activities of daily living or bladder and bowel incontinence.
- Surgical procedures include decompressive laminectomy, arthrodesis, hemilaminectomy, and medial facetectomy.
- Lumbar interspinous process decompression using X-STOP device: A titanium oval spacer placed between the two adjacent spinous processes of the affected level; provides an unloading distractive force to the stenotic middle column part of the motion segment.
- There is little value in adding fusion to decompression surgery. For most patients, spinal stenosis surgery should be limited to decompression when no overt instability is present. Trials have shown that fusion for the treatment of spinal stenosis should be restricted to patients who have proven spinal

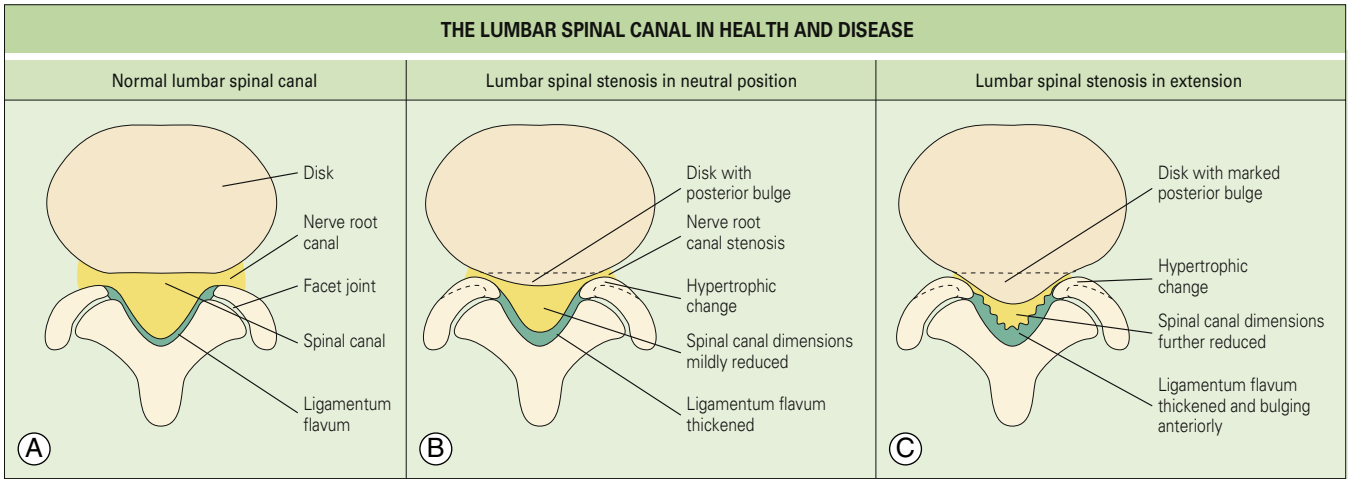

FIG. E1 A, The normal spinal canal. **B,** The spinal canal with central spinal and nerve root canal stenosis in the neutral position. **C,** The effect of lumbar extension on the spinal canal. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

BOX E1 Differential Diagnosis for Low Back Pain

Localized and Common
Uncomplicated musculoskeletal back pain
Intervertebral disk herniation
Spinal stenosis
Spondylolisthesis
Osteoarthritis
Fracture

Localized and Uncommon
Infection
Spondylitis
Epidural abscess
Diskitis
Herpes zoster

Malignancy
Metastatic
Breast
Lung
Prostate
Kidney, thyroid, colon (less common)
Primary
Multiple myeloma
Lymphoma
Leukemia
Primary cord or extradural tumors
Osteoid osteoma
Other primary bone tumors

Pediatric
Spondylolisthesis, spondylolysis
Severe scoliosis
Scheuermann disease

Rheumatologic
Ankylosing spondylitis
Psoriatic arthritis
Polymyalgia rheumatica
Reiter syndrome

Vascular
Arteriovenous malformation of spinal cord
Epidural hematoma

Life-Threatening Referred Pain
Abdominal aortic aneurysm

Gastrointestinal System
Biliary pathology
Pancreatitis
Peptic ulcer disease
Diverticulitis

Genitourinary System
Renal colic
Pyelonephritis
Prostatitis
Cystitis

Gynecologic System
Menstrual cramps
Spontaneous abortion
Labor
Ectopic pregnancy
Pelvic inflammatory disease
Endometriosis
Ovarian cyst
Ovarian torsion

Hematologic System
Sickle cell crisis

Functional
Somatization disorder
Depression
Fibrositis
Malingering

From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Saunders.

TABLE E1 Comparative Clinical Features of Spinal Stenosis, Peripheral Vascular Disease, and Disk Disease

Feature	Spinal Stenosis	Disk Prolapse	Peripheral Vascular Disease
Reduced straight leg raise	Rarely	Usually	No
Neurologic deficit	Sometimes	Often	No
Leg pain on walking	Yes	Usually	Yes
Leg pain on sitting	No	Yes	No
Pain relief on standing still	No	No	Yes
Pain relief on sitting	Yes	No	Yes
Numbness/paresthesia	Yes	Yes	Sometimes

From Carr A, Hamilton W: *Orthopedics in primary care,* ed 2, Philadelphia, 2005, Butterworth-Heinemann.

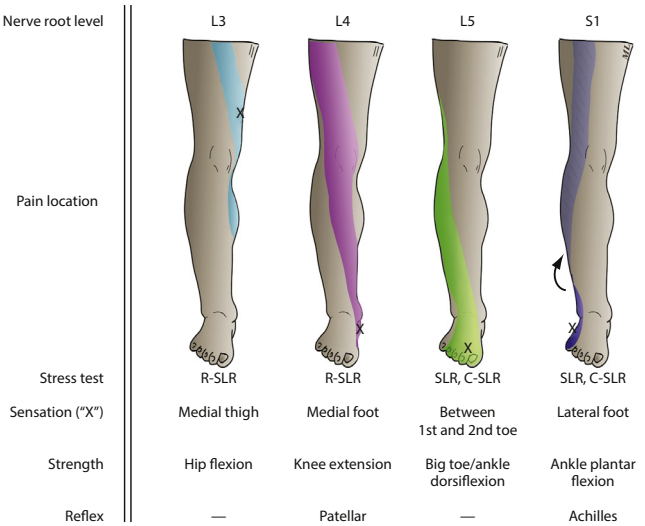

FIG. E2 Physical examination findings for L3 to S1 radiculopathy. The X marks the ideal location to test for sensation for each nerve root. *C-SLR,* Crossed straight leg raise; *R-SLR,* reverse straight leg raise; *SLR,* straight leg raise. (From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Saunders.)

instability, as confirmed on flexion-extension radiographs; vertebral destruction caused by trauma, tumors, infections, or spinal deformities, such as congenital spondylolisthesis or adult scoliosis.[1]

CHRONIC Rx

- Conservative therapy with NSAIDs (ibuprofen 800 mg PO tid, naproxen 500 mg PO bid) may be tried for symptomatic relief in addition to acetaminophen.
- Epidural glucocorticoid injections are widely used to treat symptoms of lumbar spinal stenosis; however, rigorous data are lacking regarding the effectiveness and safety of these injections. A recent trial revealed that in the treatment of lumbar spinal stenosis, epidural injection of glucocorticoids plus lidocaine offered minimal or no short-term benefit as compared with epidural injection of lidocaine alone.

DISPOSITION

- Approximately 20% of patients having surgery require repeat surgery within 10 yr. Nearly one third of these patients continue to experience pain.
- The natural history of spinal stenosis is one of slow progression. Although not very common, cord compression with resultant bowel and bladder incontinence and paresis can occur.
- Operative treatment in patients with LSS has been reported as being more effective in reducing pain and disability than nonoperative treatment. However, in a recent randomized trial comparing surgery vs. nonsurgical treatment of lumbar spinal stenosis, surgical decompression and a physical therapy regimen yielded similar effects among patients with LSS who were surgical candidates. Patients and health care providers should engage in shared decision-making conversations that include full disclosure of evidence involving surgical and nonsurgical treatments for LSS.[2]

[1]Peul WC, Moojen WA: Fusion for spinal stenosis, safeguard or superfluous surgical implant? *N Engl J Med* 374(15):1478-1479, 2016.

[2]Delitto A et al: Surgery versus nonsurgical treatment of lumbar spinal stenosis: a randomized trial, *Ann Intern Med* 162:465-473, 2015.

TABLE E2 Historical Clues to the Cause of Low Back Pain

Questions for Patient	Potential Diagnosis
Does the back pain radiate down past the knees?	Radiculopathy and likely a herniated disk
Is the pain worse with walking and better with bending forward and sitting?	Spinal stenosis
Do you have morning back stiffness that improves with exercise?	Ankylosing spondylitis
Are you older than 50 yr?	Osteoporotic fracture, spinal malignancy
Has there been any recent history of blunt trauma?	Fracture
Do you take long-term corticosteroids?	Fracture, spinal infection
Do you have a history of cancer?	Spinal metastatic malignancy
Does your pain persist at rest?	Spinal malignancy, spinal infection
Has there been persistent pain for longer than 6 wk?	Spinal malignancy
Has there been unexplained weight loss?	Spinal malignancy
Is the pain worse at night?	Spinal malignancy, spinal infection
Are you immunocompromised (e.g., HIV infection, alcoholism, diabetes)?	Spinal infection
Have you had fevers or chills?	Spinal infection
Do you have pain, weakness, or numbness in both legs?	Cauda equina syndrome
Do you have bladder or bowel control problems?	Cauda equina syndrome

HIV, Human immunodeficiency virus.
From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Saunders.

REFERRAL

- Patients who have spinal stenosis should be referred to an orthopedic surgeon specializing in back surgery or to a neurosurgeon.
- Pain clinic referrals should be made if surgery is contraindicated or if the patient does not want surgery.

PEARLS & CONSIDERATIONS

COMMENTS

- Approximately one third of patients have coexisting peripheral vascular disease.
- The severity of cauda equina constriction is directly related to the walking ability and the pain intensity in the legs and back.
- Spinal stenosis is also a cause of chronic low back pain in the young.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Spinal Stenosis (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

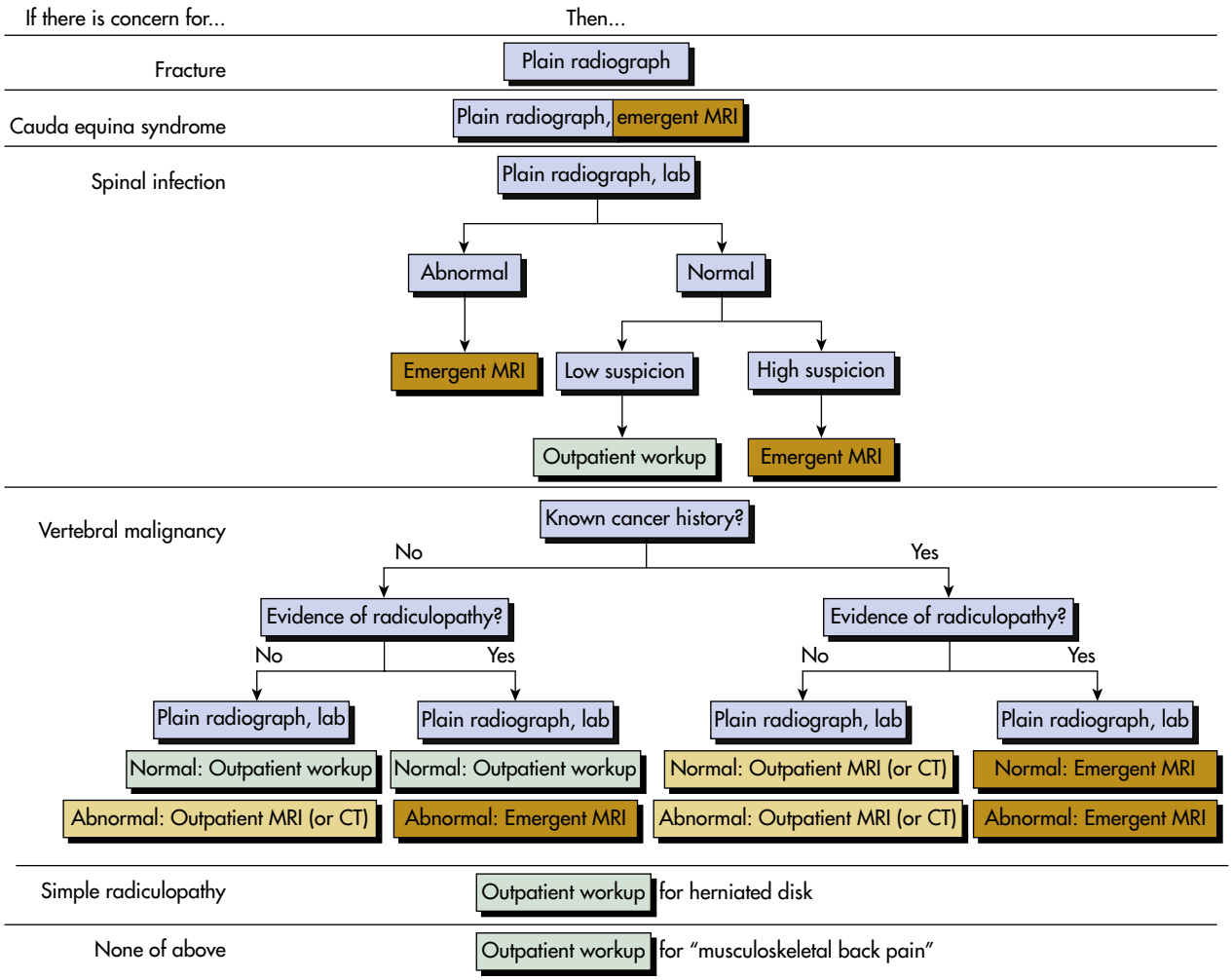

FIG. E3 Algorithm for management of low back pain. The patient's history may be of concern for more than one red flag diagnosis. *CT,* Computed tomography; *MRI,* magnetic resonance imaging. (From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Saunders.)

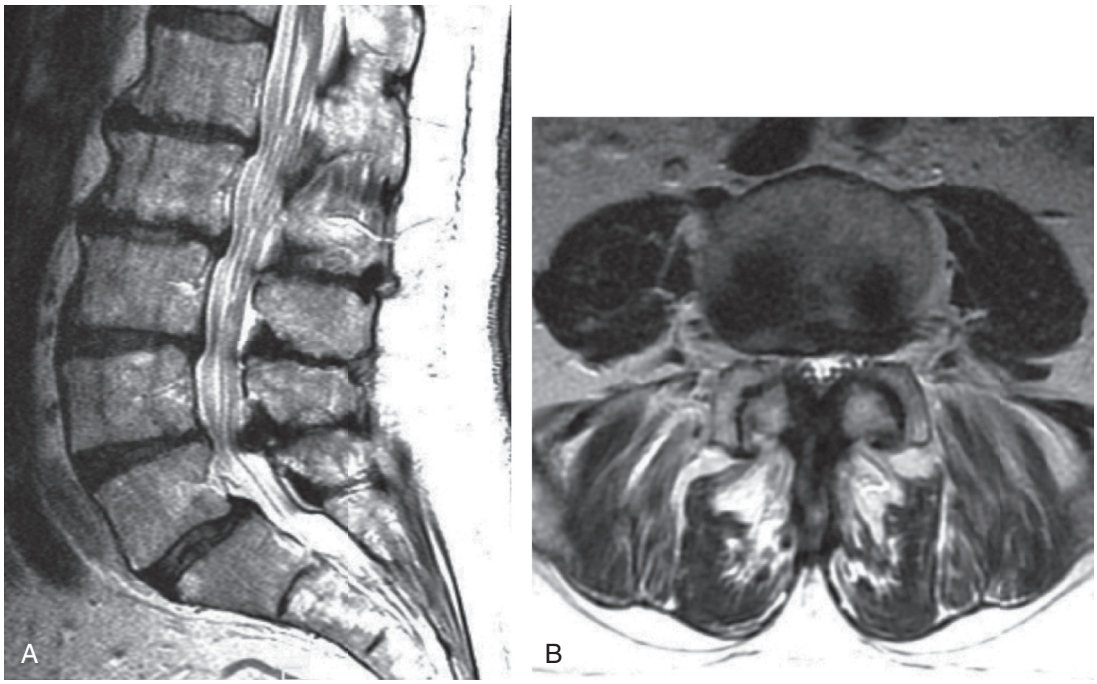

FIG. E4 Degenerative spinal stenosis. A, The sagittal T2-weighted magnetic resonance image shows decreased anteroposterior diameter of the neural canal at the L4 to L5 level due to redundancy of the ligamentum flavum. **B,** The axial image through the L4 to L5 disk shows decreased cross-sectional area of the thecal sac from hypertrophic changes of the facet joints posterolateral to the thecal sac. (Courtesy Dr. John Crues, University of California, San Diego.)

SUGGESTED READINGS

Forsth P et al: A randomized, controlled trial of fusion surgery for lumbar spinal stenosis, *N Engl J Med* 374:1413-1423, 2016.

Friedly JL et al: A randomized trial of epidural glucocorticoid injections for spinal stenosis, *N Engl J Med* 371:11-21, 2014.

Ghogawala Z, et al: Laminectomy plus fusion versus laminectomy alone for lumbar spondylolisthesis, *N Engl J Med* 374:1423-1434, 2016.

BASIC INFORMATION

DEFINITION

The spinocerebellar ataxias (SCAs) are a heterogeneous group of autosomal-dominant inherited genetic conditions that cause progressive ataxia and other neurologic symptoms.

SYNONYMS

Autosomal-dominant cerebellar ataxia (ADCA)
Machado-Joseph disease (eponym for SCA3; this may be the most common SCA)

ICD-10CM CODES
G11.8 Other hereditary ataxias
G11.9 Hereditary ataxia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: The prevalence of the condition is approximately 3 persons per 100,000. The most common SCAs are 1, 2, 3, 6, and 7.
PREDOMINANT SEX: SCA demonstrates no gender preference.
PREDOMINANT AGE: The age of onset is often during the 30s or 40s. However, this can be highly variable, even within family groups; SCAs can occur anytime from childhood to late adulthood.
GENETICS: All SCAs are inherited in an autosomal dominant fashion; however, reduced penetrance can be present.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Chronically progressive cerebellar ataxia is the predominant symptom of all of the SCAs. It typically presents as a combination of balance and gait difficulty, limb incoordination, nystagmus, and dysarthria.
- More than 36 different genetic subtypes of SCA have been described to date. Although certain clinical characteristics are common to specific SCA subtypes, these conditions have significant overlap and variability; therefore, making a diagnosis based on the clinical presentation alone can be challenging and sometimes impossible without genetic testing. The more common SCAs may include the following distinguishing features in addition to ataxia:
  1. SCA1 can be characterized by nystagmus, spasticity, and neuropathy.
  2. SCA2 can be characterized by slow saccades, gaze palsy, neuropathy, and sometimes parkinsonism or dementia.
  3. SCA3, also known as Machado-Joseph disease (Fig. E1), can be characterized by neuropathy, amyotrophy, parkinsonism, and dystonia.
  4. SCA6 is generally felt to be a pure cerebellar syndrome with ataxia and nystagmus (gaze evoked and downbeat) as well as having a frequently later age of onset.
  5. SCA7 is characterized by dementia, vision loss caused by a pigmentary maculopathy, and spasticity.
  6. Knowledge in this area is constantly expanding and being updated. Online sources of information (e.g., Online Mendelian Inheritance in Man [http://www.ncbi.nlm.nih.gov/omim]) can be invaluable for tracking new developments.

ETIOLOGY

Several of the SCAs are the result of polyglutamine CAG repeat expansions; this leads to the accumulation of mutant proteins inside neurons, which is thought to cause neuronal dysfunction and cell death. Higher numbers of repeats are correlated with an earlier onset of symptoms, and anticipation in subsequent generations may be present. Other types of repeat expansions and point mutations have been found with several SCAs; for others, the affected gene has not been identified.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Structural cerebellar abnormality: Includes cerebellar tumor, inflammation (e.g., multiple sclerosis), stroke, or hemorrhage; the time course for these causes is typically more acute or subacute than chronic.
- Endocrine dysfunction: Hypothyroidism or hypoparathyroidism can uncommonly cause ataxia.
- Alcoholic cerebellar degeneration: Caused by heavy alcohol use; gait ataxia predominates.
- Other toxin-induced ataxias: Antiepileptic medications, lithium, heavy metals (lead, manganese, mercury, bismuth), and chemotherapeutic agents.
- Creutzfeldt-Jakob disease: Rapidly progressive ataxia, dementia, and myoclonus.
- Paraneoplastic cerebellar degeneration: Found in association with primary malignancies (e.g., small cell lung cancer, breast cancer); subacute-onset ataxia that progresses rapidly.
- Celiac disease: Gluten-sensitive enteropathy with malabsorption may be associated with ataxia; autoantibodies such as antigliadin, antitissue transglutaminase (TTG), and/or IgA endomysial antibodies are typically present.
- Antiglutamic acid decarboxylase (GAD) antibody-associated cerebellar ataxia: A rare autoimmune cause of late-onset ataxia that may be partially responsive to immunotherapy.
- Multiple system atrophy (MSA): The cerebellar variant of this disorder causes ataxia; there is typically associated parkinsonism with some degree of autonomic dysfunction (e.g., orthostatic hypotension, urinary incontinence); brain MRI may reveal pontocerebellar atrophy.
- Friedreich ataxia: Autosomal recessive inheritance, generally younger age of onset (i.e., mean 15 yr of age), lower limb areflexia, and posterior column dysfunction.
- Ataxia associated with vitamin E deficiency: Can be an autosomal recessive disorder or acquired; clinically resembles Friedreich ataxia, with areflexia and loss of position sense.
- Ataxia telangiectasia: Autosomal recessive inheritance, childhood onset, oculocutaneous telangiectasias, and immunodeficiency.
- Wilson disease: Can cause hepatic dysfunction, psychiatric symptoms, and a variety of movement disorders, including ataxia; particularly important to screen for this in patients who are young at onset because it is treatable.
- Dentatorubral-pallidoluysian atrophy (DRPLA): Autosomal dominant like SCA but typically has ataxia with associated choreoathetosis, myoclonus, epilepsy, and dementia; frequently grouped with the SCAs due to its shared pathogenic CAG repeat expansion.
- Fragile X–associated tremor/ataxia syndrome: Premutation of the fragile X mutation gene; more common among males than females; late onset of ataxia (i.e., >50 yr),

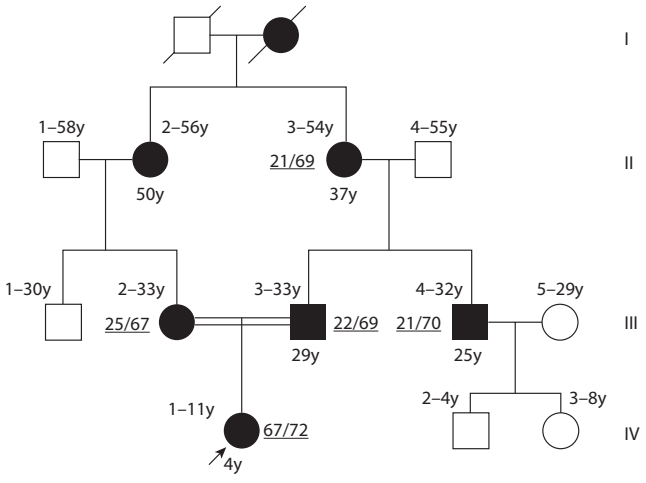

FIG. E1 Family pedigree of proband (IV-1). Age at onset of spinocerebellar ataxia type 3 symptoms is given beneath symbols (*italics*). Above the symbols, the actual age of the members of the family is given. If tested, the number of CAG repeat units of the *ATXN3* allele pair is also given (*underscored italics*). (From Daniel RC et al: Homozygosity enhances severity in spinocerebellar ataxia type 3, *Pediatri Neurol* 38[4]:296-299, 2008.)

tremor, and sometimes parkinsonism; MRI often shows T2 hyperintensities in the middle cerebellar peduncle.
- Episodic ataxias: Autosomal dominant, transient ataxia lasting seconds to days depending on the mutation; pediatric onset in most; ataxia may be responsive to acetazolamide.
- Spastic ataxias: Distinguished by prominent, symmetric spasticity, particularly of the lower extremities. Most of these conditions have an autosomal recessive pattern of inheritance and include autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), hereditary spastic paraplegia (HSP), and cerebrotendinous xanthomatosis.
- Box E1 shows the classification of the various causes of ataxia.

LABORATORY TESTS

- Rule out acquired causes of ataxia, depending on the clinical scenario, with thyroid studies, toxicology screening, and the determination of the vitamin E level or presence of paraneoplastic antibodies.
- For pediatric patients, screen for ataxia telangiectasia with serum alpha-fetoprotein (AFP).
- Screen for Wilson disease with ceruloplasmin and, if indicated, a 24-hour urinary copper determination.
- Genetic testing is commercially available for many but not all of the SCAs (SCA 1, 2, 3, 5, 6, 7, 8, 10, 12, 13, 14, 17, 28, DRPLA).

IMAGING STUDIES

- MRI of the brain should be performed to exclude structural abnormalities.
- Cerebellar or brain stem atrophy can be seen with several of the SCA subtypes.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Speech therapy for dysarthria and dysphagia
- Physical therapy
- Occupational therapy

CHRONIC Rx

Treatment is symptomatic and supportive. In some cases, parkinsonism can respond to levodopa. Clonazepam can be helpful if tremor is prominent. Spasticity can be treated with baclofen or tizanidine. Focal spasticity or dystonia may benefit from botulinum toxin injections.

DISPOSITION

All SCA disorders are progressive, although the speed is variable from subtype to subtype and from patient to patient. On average, patients become wheelchair bound 15 yr after the onset of ataxia, and death can occur after 20 to 25 yr.

REFERRAL

Referral to a general neurologist or to a movement disorders center is appropriate.

PEARLS & CONSIDERATIONS

COMMENTS

- Genetic testing can have consequences for both the patient and the family. These issues should be discussed during the informed consent process. Patients who desire asymptomatic testing as a result of a relevant family history should undergo genetic counseling before testing.
- In symptomatic patients with a family history of dominantly inherited ataxia, the diagnostic process is relatively straightforward. Genetic testing that is directed toward likely mutations by phenotype and ethnic origin should be the first step, rather than an extensive workup for other causes.

PATIENT & FAMILY EDUCATION

Patient educational materials, as well as contact information for support and advocacy groups, are available through the National Ataxia Foundation: http://www.ataxia.org.

AUTHORS: **Andrew P. Duker, MD,** and **Jennifer E. Vaughan, MD**

SUGGESTED READINGS

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BOX E1 Classification of Ataxia

Congenital Ataxias

Hereditary Ataxias

Autosomal Recessive Ataxias
- Friedreich ataxia
- Ataxia–telangiectasia
- Ataxia with oculomotor apraxia type 1
- Ataxia with oculomotor apraxia type 2
- Autosomal recessive spastic ataxia of Charlevoix-Saguenay
- Abetalipoproteinemia
- Ataxia with isolated vitamin E deficiency
- Refsum disease
- Cerebrotendinous xanthomatosis
- Marinesco-Sjögren syndrome
- Autosomal recessive ataxia with known gene locus
- Early-onset cerebellar ataxia

X-Linked Ataxias
- Fragile X tremor ataxia syndrome

Autosomal Dominant Ataxias
- Spinocerebellar ataxias
- Dentatorubral-pallidoluysian atrophy
- Episodic ataxias

Nonhereditary Degenerative Ataxias
- Multiple system atrophy, cerebellar type
- Sporadic adult-onset ataxia of unknown etiology

Acquired Ataxias
- Alcoholic cerebellar degeneration
- Ataxia as a result of other toxic causes (e.g., antiepileptic medications, lithium, solvents)
- Paraneoplastic cerebellar degeneration (e.g., anti-Hu, anti-VGKC, anti-CV2)
- Other immune-mediated ataxias (e.g., gluten ataxia, ataxia associated with anti-glutamic acid decarboxylase antibodies)
- Acquired vitamin E deficiency
- Hypothyroidism
- Ataxia as a result of physical causes (e.g., heat stroke, hyperthermia)

From Goetz CG: *Textbook of clinical neurology*, ed 3, Philadelphia, 2007, WB Saunders.

BASIC INFORMATION

DEFINITION

Spondyloarthropathies (SpAs) are a group of interrelated systemic autoinflammatory conditions that are serologically negative for rheumatoid factor, connected by an underlying genetic risk with similar patterns of inflammation. This group encompasses ankylosing spondylitis, psoriatic arthritis, reactive arthritis, enteropathic arthritis, and undifferentiated spondyloarthritis (Table 1). SpAs are broadly classified by axial versus peripheral joint involvement, with or without radiographic progression.

SYNONYMS

Spondyloarthritis
Spondylopathy
Spondylitis
Spondylosis
SPAs

ICD-10CM Codes

M46.80	Other specified inflammatory spondylopathies, unspecified site
M46.82	Other specified inflammatory spondylopathies, cervical region
M46.83	Other specified inflammatory spondylopathies, cervicothoracic region
M46.86	Other specified inflammatory spondylopathies, lumbar region
M46.87	Other specified inflammatory spondylopathies, lumbosacral region
M46.89	Other specified inflammatory spondylopathies, multiple sites
M46.81	Other specified inflammatory spondylopathies, occipito-atlantoaxial region
M46.88	Other specified inflammatory spondylopathies, sacrococcygeal region
M46.84	Other specified inflammatory spondylopathies, thoracic region
M46.85	Other specified inflammatory spondylopathies, thoracolumbar region

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Worldwide prevalence of SpA is 0.2% to 1.6%, with over 1% of the U.S. population affected. Varies regionally with prevalence of HLA-B27.

PREDOMINANT SEX AND AGE: Males younger than age 45 yr are predominantly affected. Previously, male:female ratio was thought to be 10:1; more recently, about 3:1.

Patients older than 45 yr may present with chronic, severe disease due to diagnostic delays.

GENETICS: Association with the *HLA-B27* allele is the strongest known genetic risk factor.

RISK FACTORS: *HLA-B27* allele*, male sex*, smoking*, ethnic background, family history of SpA, and certain infections (*Associated with more severe disease)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History:
  1. Inflammatory low back pain may be the primary presenting symptom:
     a. Pain and stiffness in low back or buttocks that is worst in the morning, may awaken the patient from sleep, and improves with exercise
     b. Morning stiffness generally lasting longer than 1 hour
     c. Improvement with NSAIDs
     d. Sensitivity up to 90% and positive likelihood ratio up to 2.2 for axial SpA
  2. Symptoms of systemic and peripheral inflammation are additional clues that can be elicited in a comprehensive review of systems:
     a. Uveitis: Painful ocular inflammation
     b. Psoriasis: Chronic skin inflammation with red patches and silvery scales
     c. Inflammatory bowel disease: Crohn disease and ulcerative colitis
     d. Synovitis: Inflammation of the synovial membrane of joints
     e. Enthesitis: Inflammation at the site of tendon or ligament insertion onto bone
     f. Dactylitis: Tenosynovitis of the digits causing classic sausage-like appearance
- Physical exam:
  1. Axial joints: Spine and sacroiliac (SI) joints
  2. Inspect curvature, palpate for tenderness, and evaluate range of motion for cervical, thoracic, and lumbar spine. Measure degree of axial involvement with occiput wall, thoracic expansion. Patients with SpA may have an abnormal Schober test result (Fig. E1). This test is performed by having the patient stand erect and marking the distance between the midpoint of the posterior superior iliac spines ("dimples of Venus") and 10 cm above that point. The patient is then asked to maximally flex forward while the more caudal spot is kept stationary. The more cephalad point on the tape measure should demonstrate at least 5 cm of excursion. This abnormality also can be seen with lumbar degenerative disk disease. Test for sacroiliitis with Patrick and Gaenslen tests
  3. Peripheral joints: Lower extremity predominance
  4. Inspect for signs of inflammation, including dactylitis, synovitis, and enthesitis
  5. Evaluate for systemic involvement manifesting as anterior uveitis and psoriasis:
     a. Slit lamp is necessary to diagnose anterior uveitis
     b. Full skin exam is critical to detect occult psoriasis; look for nail changes
- Musculoskeletal manifestations commonly affect weight-bearing joints with high mechanical stress; thus, it is particularly important to examine the lumbar spine, SI joints, and lower extremities
- Degree of axial involvement can be measured via specialized exam techniques, which are used to track disease activity and response to treatment over time

ETIOLOGY

- Genetic:
  1. The *HLA-B27* allele has a strong association with SpA, through mechanisms not fully understood.
- Environmental:
  1. Microbial infections, disruptions in barrier defense mechanisms (skin and intestinal mucosa), and mechanical articular stressors may trigger an inflammatory response, which then develops into signs and symptoms specific to each type of SpA.
- Autoinflammatory:
  1. Key components of the inflammatory cascade involved in the pathogenesis of SpA are TNF, IL-12, IL-17, IL-23, and prostaglandins. Success in treatment with targeted therapies to each of these molecules has helped us understand their role in the etiology of SpA.

TABLE 1 Comparison of Ankylosing Spondylitis and Related Disorders

Feature	Ankylosing Spondylitis	Psoriatic Arthritis	Reactive Arthritis	Enteropathic Arthropathy
Sex (male:female)	2-3:1	1:1	1:1	1:1
Age of onset	<40 yr	35-55 yr	20-40 yr	Any age
Sacroiliitis or spondylitis (%)	100	~20	~40	<20
Symmetry of sacroiliitis	Symmetrical	Asymmetrical	Asymmetrical	Symmetrical
Peripheral arthritis (%)	~25	95	90	5-20
Distribution	Axial and lower limbs	Variable	Lower limbs	Variable
HLA-B27 positivity (%)	85-95	25-60*	30-70	7-70†
Uveitis	0-40	~20	~50	<15

*60% when spondylitis is present.
†70% when spondylitis is present.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE 2 Criteria for Spondyloarthritis (SpA)*

Amor Criteria	ESSG Criteria
A. Past or current clinical manifestations:	Inflammatory back pain *or* synovitis
1. Back pain at night and/or back stiffness in the morning (1 point)	• Asymmetric synovitis or • Predominantly lower limb synovitis
2. Asymmetric oligoarthritis (2 points)	AND
3. Gluteal pain without other details (1 point) or alternating gluteal pain (2 points)	One or more of the following: • Positive family history • Psoriasis
4. Sausage-like digit or toe (2 points)	• Inflammatory bowel disease
5. Heel pain or other enthesopathy (2 points)	• Urethritis, cervicitis, or acute diarrhea within 1 mo before arthritis
6. Iritis (2 points)	• Buttock pain alternating between right and left gluteal areas
7. Nongonococcal urethritis within 1 mo before the onset of arthritis (1 point)	• Enthesopathy • Sacroiliitis (radiography)
8. Acute diarrhea within 1 mo before the onset of arthritis (1 point)	
9. Past or current psoriasis and/or balanitis and/or inflammatory bowel disease (2 points)	
B. Radiographic changes:	
10. Sacroiliitis grade 2 or more if bilateral, grade 3 or more if unilateral (3 points)	
C. Predisposing genetic factors:	
11. Presence of HLA-B27 antigen and/or family history of ankylosing spondylitis, Reiter syndrome, psoriasis, uveitis, or chronic bowel disease (2 points)	
D. Responsiveness to treatment:	
12. Improvement within 48 hours after initiation of an NSAID and/or recurrence within 48 hours after discontinuation of a nonsteroidal antiinflammatory drug (2 points)	

*Definite SpA if ≥6 points; probable SpA if 5 points.
ESSG, European Spondyloarthropathy Study Group; *NSAID,* nonsteroidal antiinflammatory drug.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

Dx DIAGNOSIS

Table 2 summarizes diagnostic criteria for SpA.

DIFFERENTIAL DIAGNOSIS

- Seronegative rheumatoid arthritis (peripheral presentation)
- Degenerative disc disease (axial presentation) or DISH
- Inflammatory osteoarthritis (axial or peripheral presentation)
- Hypertrophic osteoarthropathy (peripheral presentation)

WORKUP

- Young patients, particularly men younger than 45 yr, with chronic inflammatory low back pain responsive to NSAIDs should be screened.
- Patients with psoriasis, inflammatory bowel disease, or recent gastrointestinal or genitourinary infections presenting with new-onset low back or peripheral joint pain should also be screened.
- Screening begins with a comprehensive history and physical exam.
- HLA-B27 testing and imaging of SI joints and/or lumbar spine are indicated based on clinical suspicion.

LABORATORY TESTS

- HLA-B27:
  1. Negative test does not rule out SpA.
  2. Sensitivity: 95% for ankylosing spondylitis, 80% for reactive arthritis, 70% for psoriatic arthritis, and 50% for enteropathic arthritis
- Elevated ESR and CRP, anemia of chronic disease, leukocytosis, and thrombocytosis may reflect active inflammation. A normal CRP or ESR does not rule out spondyloarthropathies
- Testing for rheumatoid arthritis antibodies is generally negative (RF, CCP)
- Synovial fluid is inflammatory and nonspecific, with WBC >2,000/mm^2

IMAGING STUDIES

- **X-Ray:** SI joints and lumbar spine:
  1. May not detect early inflammation
  2. 20% to 80% have non-radiographic disease at time of presentation
  3. May show signs of structural damage such as erosions, syndesmophytes, sclerosis, and ankylosis in chronic axial disease
- **MRI:** SI joints and lumbar spine:
  1. Subchondral bone marrow edema in early disease
  2. Useful when x-ray and clinical findings are nondiagnostic but clinician's suspicion for axial SpA remains high

Rx TREATMENT

Improvement in symptoms, preservation of function, and prevention of structural damage can be achieved through a multidisciplinary approach.

NONPHARMACOLOGIC THERAPY

- Physical and occupational therapies improve functional outcomes
- Surgery:
  1. Joint replacements (high-impact joints such as hips)
  2. Spinal wedge osteotomy (advanced axial disease)
  3. Colectomy (advanced enteropathic arthritis)

ACUTE GENERAL Rx

- NSAIDs are first line.
- Avoid steroids in psoriatic arthritis due to risk of life-threatening pustular psoriasis and erythroderma.

CHRONIC Rx

- **NSAIDs:**
  1. Up to 35% of patients may achieve remission
  2. Best response in early disease
  3. Continuous dosing may prevent radiographic progression of axial disease
- **DMARDs:** Effective for peripheral involvement only, not effective in axial disease
  1. Methotrexate, leflunomide, sulfasalazine
- **TNF inhibitors:** NSAID or DMARD failure
  1. Infliximab, adalimumab, golimumab, etanercept, certolizumab pegol
- **IL-17 and IL-12/23 inhibitors:** 2nd TNF inhibitor failure
  1. Recent studies show similar efficacy compared to TNF inhibitors
  2. Ixekizumab (IL-17 inhibitor) recently approved for ankylosing spondylitis
  3. Ustekinumab (IL-12/23 inhibitor) and secukinumab (IL-17 inhibitor) are effective in psoriatic arthritis. Secukinumab also is approved for ankylosing spondylitis

4. Ustekinumab is also effective in Crohn-enteropathic arthritis

- **JAK inhibitors:** Phase II clinical trial
  Tofacitinib (JAK 1, 2, 3 inhibitor) was shown to improve clinical and imaging outcomes in axial SpA, with phase III trial data pending.
  1. Tofacitinib is approved to treat both UC and psoriatic arthritis.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Strong clinical trials are lacking.
- Small studies have shown Pilates, tai chi, deep tissue massage, and hydroelectric therapy can be beneficial in axial SpA.

DISPOSITION

- Function and mobility may be limited in advanced axial disease.
- Psoriatic arthritis is an independent risk factor for cardiovascular disease.

REFERRAL

Rheumatology, dermatology, ophthalmology, gastroenterology, infectious disease

PEARLS & CONSIDERATIONS

COMMENTS

Young patients with chronic inflammatory low back pain deserve referral to a rheumatologist. HLA-B27 positivity is not required for diagnosis if strong clinical features are present. MRI may be needed to detect early axial disease. Repeated spinal x-rays at scheduled intervals (e.g. every 2 yr) are not recommended in patients with active or stable non-radiographic axial SpA. Track axial disease activity with clinical scoring systems and physical exam measurements. Traditional DMARDs are not effective in axial disease.

PREVENTION

High index of suspicion and prompt referral allows for early diagnosis. Early treatment with treat-to-target approach may prevent symptomatic and radiographic progression.

PATIENT & FAMILY EDUCATION

Smoking cessation is key. Discuss with family the implications of strong genetic component. Educate patients with psoriasis and inflammatory bowel disease about symptoms of inflammatory low back or peripheral joint pain to monitor for development of SpA in these high-risk individuals.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Ankylosing Spondylitis (Related Key Topic)
Psoriatic Arthritis (Related Key Topic)
Reactive Arthritis (Reiter Syndrome) (Related Key Topic)
Enteropathic Arthritis (Related Key Topic)

AUTHOR: **Matthew J. White, DO**

SUGGESTED READINGS

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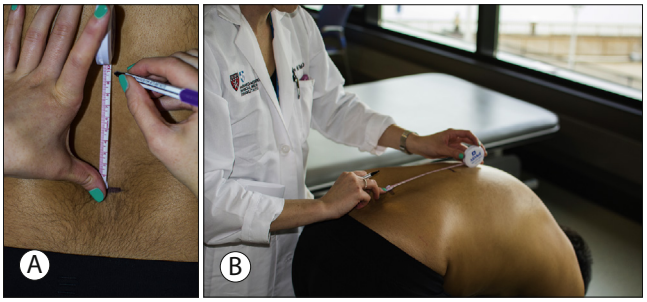

FIG. E1 Schober test. A, With the patient standing, measure 10 cm superior from the midpoint of the posterior superior iliac spines. **B,** The patient then is asked to maximally flex forward while the more caudal spot is kept stationary. The total length between the lines should be greater than 15 cm. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Spontaneous abortion is fetal loss before wk 20 of pregnancy, calculated from the patient's last menstrual period, or the delivery of a fetus weighing <500 g. Early loss is before menstrual wk 12, whereas late loss refers to losses from wks 12 to 20.

Spontaneous abortion can also be classified as incomplete (partial passage of fetal tissue through partially dilated cervix), complete (spontaneous passage of all fetal tissue), threatened (uterine bleeding without cervical dilation or passage of tissue), inevitable (bleeding with cervical dilation without passage of fetal tissue), or missed abortion (intrauterine fetal demise without passage of tissue).

Recurrent spontaneous abortion involves three or more spontaneous pregnancy losses before wk 20. It affects approximately 1% of couples attempting to conceive. However, in actual practice, most reproductive experts consider two spontaneous pregnancy losses sufficient to initiate an evaluation for habitual or recurrent spontaneous abortion, since the risk of another loss is similar at this point, and the emotional stress is high. As many as 5% of couples and probably even a higher proportion of couples in which the woman is over the age of 35 are affected by two or more consecutive spontaneous abortions.

SYNONYMS

Spontaneous miscarriage
Miscarriage
Spontaneous pregnancy loss

ICD-10CM CODES

O03.89	Complete or unspecified spontaneous abortion with other complications
O03.9	Complete or unspecified spontaneous abortion without complication

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 10% to 20% of clinically recognized pregnancies; 80% of miscarriages occur in the first trimester. Recurrent miscarriage occurs in <1% of couples attempting to have children.

GENETICS:

- Fetal chromosomal aneuploidy and polyploidy account for the overwhelming majority of first-trimester losses.
- Autosomal trisomy accounts for the majority of abnormalities, followed by monosomy X, tetraploidy, and, lastly, structural chromosomal abnormalities.
- The incidence of trisomy increases as maternal age increases.

MATERNAL CAUSES:

- Uterine anomalies: Müllerian abnormalities such as unicornuate, bicornuate, or septated uterus are associated with increased miscarriage risk, although rates vary in different studies. A septated uterus is most highly associated with recurrent loss and can be surgically corrected and thus is important to diagnose. Other intrauterine pathologies such as synechiae, leiomyomas, or prior DES exposure are important to rule out also.
- Incompetent cervix (iatrogenic or congenital, associated with 20% of mid-trimester losses).
- Antiphospholipid antibody syndrome.
- Uncontrolled diabetes mellitus.
- Rare or controversial causes include HLA associations between mother and father; infections such as tuberculosis, *Chlamydia,* and *Ureaplasma;* smoking and alcohol use; irradiation; progesterone deficiency; and environmental toxins. Most of the literature is observational in nature, which may skew risk factor data.
- With two or more spontaneous miscarriages, a karyotype can be performed on the products of conception to evaluate for aneuploidy, which may be associated with a balanced translocation in one of the parents, and which has a substantially increased risk for abortion (depending on the actual type of translocation); if the pregnancy is carried to term, it has a 3% to 5% risk for an unbalanced karyotype. In patients with habitual abortion, evaluation for anatomic defects such as uterine septum and for antiphospholipid syndrome (lupus anticoagulant, beta 2 glycoprotein IgG/IgM, and anticardiolipin antibody IgG/IgM) should also be obtained.

RISK FACTORS:

- Vaginal bleeding, especially >3 d, carries with it a 15% to 20% chance of miscarriage
- Advancing maternal age
- Two or more prior miscarriages
- Significant underlying maternal health issues such as uncontrolled diabetes, thyroid disease, or other endocrine disturbances
- Illicit substance use
- Obesity
- Alcohol, smoking, and excessive caffeine intake
- Use of fluconazole in pregnancy is associated with a statistically significant increased risk of spontaneous miscarriage

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Profuse bleeding and cramping have a higher association with miscarriage than bleeding without cramping, which is more consistent with a threatened miscarriage.
- Cervical dilation with history or finding of fetal tissue at cervical os may be present.
- In cases of missed abortion, uterine size may be smaller than menstrual dating, in contrast to molar gestation, where size may be greater than dates.
- The presence of nausea and vomiting in early pregnancy is associated with a reduced risk for pregnancy loss.

ETIOLOGY

In a general overview, the etiology can be classified in terms of maternal (environmental) and fetal (genetic) factors, with the majority of miscarriages being related to genetic or chromosomal causes.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Normal pregnancy
- Hydatidiform molar gestation
- Ectopic pregnancy
- Dysfunctional uterine bleeding
- Pathologic endometrial or cervical lesions

WORKUP

- All patients with bleeding in the first trimester should have an evaluation for possible ectopic pregnancy.
- If there are three early, prior pregnancy losses, a workup and treatment for recurrent miscarriage should begin before next conception. If there is a strong history for second-trimester loss, consideration for cerclage should be given if the history is consistent with incompetent cervix (e.g., painless cervical dilation).
- Most providers will initiate an evaluation for couples who have had two previous losses.
- One unexplained fetal loss beyond 10 wk or 1 birth before 34 wk because of preeclampsia should prompt an evaluation for antiphospholipid antibody syndrome.

LABORATORY TESTS

- Type and antibody screen are used to evaluate the need for Rh immune globulin.
- Recurrent pregnancy loss: During the preconception period in patients with recurrent pregnancy loss, hemoglobin A_{1c}, TSH, prolactin, anticardiolipin antibody, lupus anticoagulant, 20210A beta 2 glycoprotein antibodies, karyotyping, and anatomic evaluation with hysterosalpingography, or saline ultrasonography to assess for uterine septum. With increasing age, oocyte quality is a factor, and some practitioners will perform day 3 of the menstrual cycle FSH and antimüllerian hormone to assess for diminished ovarian reserve. Progesterone level <5 mg/dl suggests nonviable gestation vs. >25 mg/dl, which suggests a good prognosis.

IMAGING STUDIES

Transvaginal sonogram (preferred) (Figs. 1 through 3) can be used with menstrual dating and serum quantitative human chorionic gonadotropin to document pregnancy location, fetal heart presence, gestational sac size, and adnexal pathology.

TREATMENT

NONPHARMACOLOGIC THERAPY

Depending on the patient's clinical status, desire to continue the pregnancy, and certainty of the diagnosis, expectant management can be considered. In pregnancies <6 wk or >14 wk, complete expulsion of fetal tissue usually occurs, and surgical intervention such as D&C can be avoided.

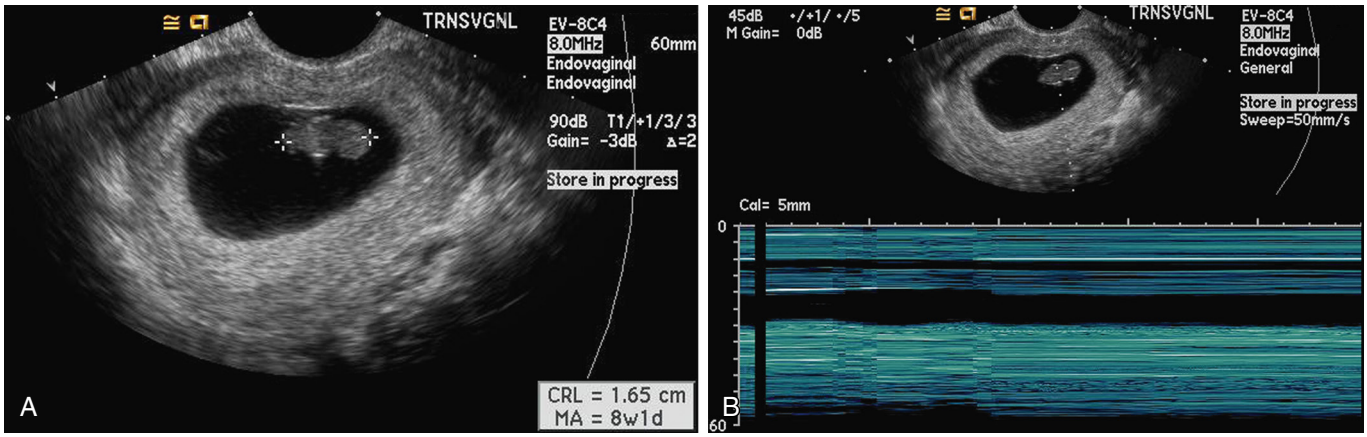

FIG. 1 Embryonic demise. Transvaginal **(A)** and M-mode **(B)** ultrasound. There was no cardiac activity in an embryo measuring more than the threshold of 5 mm. (From Fielding JR et al: *Gynecologic imaging*, Philadelphia, 2011, WB Saunders.)

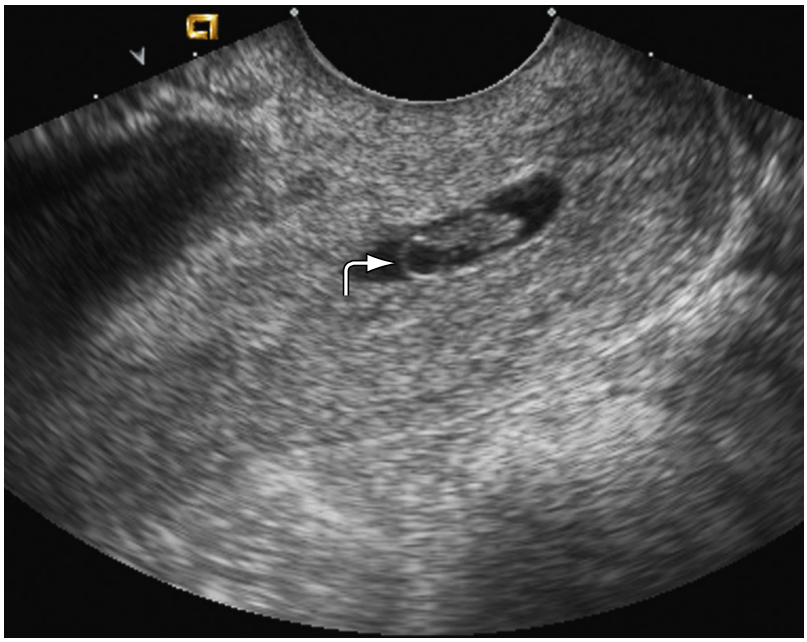

FIG. 2 Inevitable abortion. Transvaginal ultrasonography shows a sac in the cervical canal, past the internal os. The embryo *(curved arrow)* was nonviable. (From Fielding JR et al: *Gynecologic imaging*, Philadelphia, 2011, WB Saunders.)

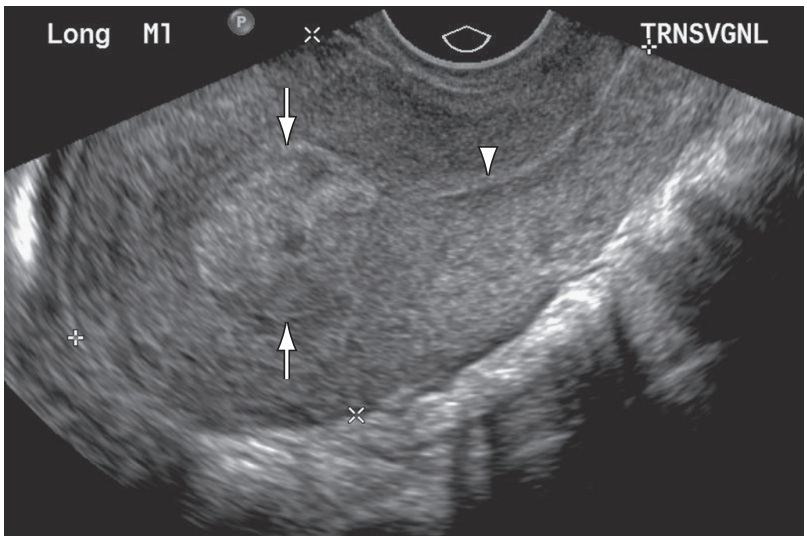

FIG. 3 Incomplete abortion. Transvaginal ultrasonography shows an echogenic mass *(arrows)* in the fundal endometrial cavity. The lower-segment endometrium *(arrowhead)* is normal. (From Fielding JR et al: *Gynecologic imaging*, Philadelphia, 2011, WB Saunders.)

ACUTE GENERAL Rx

- Incomplete miscarriage between 6 and 14 wk can be associated with great blood loss; these patients should undergo D&C.
- In cases of missed abortion, if fetal demise has occurred >6 wk before or gestational age is >14 wk, there is an increased risk of hypofibrinogenemia with disseminated intravascular coagulation. Thus D&C or manual vacuum aspiration should be performed early in the disease course. Consider use of misoprostol (Cytotec) in appropriate cases where the patient wishes to avoid surgery.
- There is evidence that a surgical approach leads to quicker resolution of the pregnancy event with fewer visits being required.
- Rh-negative patients should be given RhoGAM 50 mcg IM to prevent Rh isoimmunization.

PEARLS & CONSIDERATIONS

Spontaneous pregnancy loss is recommended as a replacement for the term *abortion* and to acknowledge the emotional aspects of losing a pregnancy.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Miscarriage (Patient Information)

AUTHOR: **Adrienne B. Neithardt, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Spontaneous bacterial peritonitis (SBP) is an inflammatory reaction of the peritoneum secondary to the presence of bacteria or other microorganisms. More specifically, SBP is defined as an ascitic fluid infection without an evident intraabdominal surgically treatable source occurring primarily in patients with advanced cirrhosis of the liver.

SYNONYMS

Primary peritonitis
SBP
Peritonitis, spontaneous bacterial

ICD-10CM CODE
K65.2 Spontaneous bacterial peritonitis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: The prevalence of SBP in cirrhotic patients admitted to the hospital has been estimated at 10% to 30%.
PREDOMINANT SEX: Males are affected more often than females.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute fever with accompanying abdominal pain/ascites, nausea, vomiting, diarrhea.
- In cirrhotic patients, presentation may be subtle with a low-grade temperature (100° F; 37.8° C) with or without abdominal abnormalities.
- In patients with ascites, a heightened degree of awareness is necessary for detection.
- Jaundice and encephalopathy.
- Deterioration of mental status and/or renal function.
- Table 1 summarizes symptoms and signs of ascetic fluid infection.

ETIOLOGY

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Streptococcus pneumoniae*
- *Streptococcus* and *Enterococcus* spp.
- *Staphylococcus aureus*
- Anaerobic pathogens: *Bacteroides, Clostridium* organisms
- Other: Fungal, mycobacterial, viral

DIAGNOSIS

The diagnosis of SBP is established by a positive ascitic fluid bacterial culture and an elevated ascitic fluid absolute polymorphonuclear leukocyte count (≥250 cells/mm^3).

DIFFERENTIAL DIAGNOSIS

- Appendicitis (in children)
- Perforated peptic ulcer
- Secondary bacterial peritonitis
- Peritoneal abscess
- Splenic, hepatic, or pancreatic abscess
- Cholecystitis
- Cholangitis

WORKUP

Paracentesis and ascitic fluid analysis will confirm diagnosis (see "Laboratory Tests").

LABORATORY TESTS

Ascitic fluid analysis reveals the following:

- Cell count with an absolute polymorphonuclear cell count >250/mm^3
- Presence of bacteria on Gram stain
- pH <7.31
- Lactic acid >32 mg/dl
- Protein <1 g/dl
- Glucose >50 mg/dl
- Lactate dehydrogenase <225 μU/ml
- Positive culture of peritoneal fluid
- Measurement of the serum/ascites/albumin gradient: The serum/ascites/albumin gradient indirectly measures portal pressure. The albumin concentration of ascitic fluid and serum must be obtained on the same day. The ascitic fluid value is subtracted from the serum value to obtain the gradient. If the difference (not a ratio) is >1.1 g/dl, the patient has portal hypertension, with 97% accuracy. If the difference is <1.1 g/dl, portal hypertension is not present. The majority of patients with SBP have portal hypertension as a result of cirrhosis

IMAGING STUDIES

- Abdominal ultrasound: If there is clinical difficulty in performing paracentesis
- CT scan: To rule out secondary peritonitis (if indicated) and to exclude abscess, mass

TABLE 1 Symptoms and Signs of Ascitic Fluid Infection

	Frequency (%)				
Symptom or Sign	**SBP**	**Bacterascites**	**CNNA**	**Secondary Peritonitis**	**Polymicrobial Bacterascites**
Fever	68	57	50	33	10
Abdominal pain	49	32	72	67	10
Abdominal tenderness	39	32	44	50	10
Rebound tenderness	10	5	0	17	0
Altered mental status	54	50	61	33	0

CNNA, Culture-negative neutrocytic ascites; *SBP,* spontaneous bacterial peritonitis.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

TREATMENT

ACUTE GENERAL Rx

- Cefotaxime (2 g IV q8h) or ceftriaxone (2 g IV q24h). Alternative agents include ticarcillin-clavulanate, piperacillin-tazobactam, cefoxitin, and meropenem. Continue therapy for 5 to 7 days. Repeat diagnostic paracentesis can be done at day 2. Repeat paracentesis at 48 hr will demonstrate a significant decrease in polymorphonuclear count in patients with SBP. If ascites PMN count decreases by at least 25% at day 2, IV therapy can be switched to PO (levofloxacin 500 to 750 mg qd) to complete 7 days of therapy if organisms are susceptible.
- IV albumin (1.5 g/kg of body weight upon initial diagnosis and 1 g/kg of albumin on day 3) if BUN >30 mg/dl, serum creatinine >1 mg/dl, bilirubin >4 mg/dl.

PROPHYLAXIS

- Ciprofloxacin 500 mg PO qd or levofloxacin 250 mg PO qd.
- Alternative therapy: TMP-SMX one double-strength tablet PO qd.
- Rifaximin 1200 mg a day was shown in a recent study to be superior to norfloxacin.
- Prophylaxis should be continued until disappearance of ascites or until liver transplantation.

DISPOSITION

The overall mortality rate from an episode of SBP is 20%, and following an episode, the 1-yr mortality rate approaches 70%. Patients that develop SBP should be considered for liver transplantation.

PEARLS & CONSIDERATIONS

COMMENTS

- Renal failure is a major cause of morbidity in cirrhotic patients with SBP. The use of IV albumin (1.5 g/kg at the time of diagnosis and 1 g/kg on day 3) may lower the rate of renal failure and mortality in patients with SBP.
- The criteria for the diagnosis of SBP require that abdominal paracentesis be performed and ascitic fluid be analyzed before a diagnosis of SBP can be made.
- Culturing ascitic fluid as if it were blood (with bedside inoculation of at least 10 ml of ascitic fluid directly into blood culture bottles at the bedside) has been shown to significantly increase the culture positivity of the ascitic fluid in the 80% to 100% range.
- Avoid therapeutic paracenteses during active infection.
- Positive blood cultures in an individual with ascites require exclusion of a peritoneal source by paracentesis.
- Follow-up paracentesis is indicated only in selected cases (worsening clinical status, nosocomial SBP, infection with atypical organism, recent β-lactam exposure).

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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Sporotrichosis

BASIC INFORMATION

DEFINITION

Sporotrichosis is a granulomatous/pyogenic disease commonly caused by pathogenic strains of the dimorphic fungus *Sporothrix schenckii,* although at least six other pathogenic *Sporothrix* species exist in various geographic regions, such as *Sporothrix brasiliensis*.

SYNONYMS

Lymphocutaneous sporotrichosis
Cutaneous sporotrichosis
Pulmonary sporotrichosis

ICD-10CM CODES

B42.0 Pulmonary sporotrichosis
B42.1 Lymphocutaneous sporotrichosis
B42.7 Disseminated sporotrichosis
B42.8 Other forms of sporotrichosis
B42.9 Sporotrichosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: The most common form, lymphocutaneous sporotrichosis, occurs equally in both sexes. Males predominate in both pulmonary and osteoarticular sporotrichosis.
PREDOMINANT AGE: Generally, lymphocutaneous sporotrichosis occurs in people 35 yr of age or younger, usually through occupation or hobbies such as landscaping or gardening. Pulmonary sporotrichosis occurs in people between the ages of 30 and 60 yr, often alcoholic men with COPD and diabetics. Those with HIV are at risk for disseminated infection.
GENETICS: Neonatal infection: At least one case of transmission from the cheek lesions of the mother to the skin of the infant has been reported.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Cutaneous disease:
  1. Arises at the site of inoculation, often the site of soil exposure (Fig. E1)
  2. Initial lesion usually located on the distal part of an extremity (Fig. E2), although any area may be affected, including the face
  3. Variable incubation period of approximately 3 wk once introduced into the skin
  4. Granulomatous reaction provoked
  5. Lesion becomes papulonodular, erythematous, elastic, variable in size
  6. Subsequently, nodule becomes fluctuant, undergoes central necrosis, breaks down, discharges mucoid pus from which fungus may be isolated
  7. Indolent ulcer with raised erythematous or violaceous borders
  8. Secondary lesions:
     a. Develop along superficial lymphatic channels
     b. Evolve in the same manner as the primary lesion, with subsequent inflammation, induration, and suppuration
- Fixed, or plaque form:
  1. Erythematous verrucous, ulcerated, or crusted lesions
  2. Does not spread locally
  3. Does not involve lymphatic vessels
  4. Rarely undergoes spontaneous resolution
  5. More often persists for yrs without systemic symptoms and within a setting of normal laboratory examinations
- Osteoarticular involvement:
  1. Most common extracutaneous form
  2. Usually presents as monoarticular arthritis
  3. Left untreated, may progress to:
     a. Synovitis
     b. Osteitis
     c. Periostitis
     d. All involving elbows, knees, wrists, and ankles
  4. Joint inflamed:
     a. Associated with an effusion
     b. Painful on motion
- Early pulmonary disease:
  1. Usually associated with a paucity of clinical findings:
     a. Low-grade fever
     b. Cough
     c. Fatigue
     d. Malaise
     e. Weight loss
  2. Untreated:
     a. Cavitary pulmonary disease
     b. Frank pulmonary dysfunction
     c. Hemoptysis
     d. Mimics tuberculosis
  3. Meningitis:
     a. Uncommon except perhaps in the immunocompromised patient
     b. Presents with few signs or symptoms of neurologic involvement, usually headache
  4. Few reported cases:
     a. Infection of the ocular adnexa
     b. Endophthalmitis without antecedent trauma
     c. Infection of the testes and epididymis
     d. Certain strains favor cooler body areas such as the scrotum, lower extremities

ETIOLOGY

- *Sporothrix schenckii:*
  1. Global in distribution
  2. Often isolated from soil, plants, and plant products

FIG. E1 Sporotrichosis. Erythematous papules and nodules on the plantar surface with early lymphangitic (sporotrichoid) spread. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

FIG. E2 Sporotrichosis of the fifth finger in a gardener. Three nodular lesions are visible on the hand and arm. (From Mandell GL et al: *Principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, WB Saunders.)

3. Majority of case reports from tropical and subtropical regions of the Americas
- Occupational or recreational exposure:
  1. Hay
  2. Straw
  3. Sphagnum moss
  4. Timber
  5. Thorny plants (e.g., roses and barberry bushes)
- Animal contact:
  1. Armadillos
  2. Cats
  3. Squirrels
- Tattooing

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Fixed, or plaque, sporotrichosis:
  1. Bacterial pyoderma
  2. Foreign body granuloma
  3. Tularemia
  4. Anthrax
  5. Other mycoses: Blastomycosis, chromoblastomycosis
- Lymphocutaneous sporotrichosis:
  1. *Nocardia brasiliensis*
  2. *Leishmania braziliensis*
  3. Atypical mycobacterial disease: *Mycobacterium marinum, Mycobacterium kansasii*
- Pulmonary sporotrichosis:
  1. Pulmonary TB
  2. Histoplasmosis
  3. Coccidioidomycosis
- Osteoarticular sporotrichosis:
  1. Pigmented villonodular synovitis
  2. Gout
  3. Rheumatoid arthritis
  4. Infection with *Mycobacterium tuberculosis*
  5. Atypical mycobacteria: *Mycobacterium marinum, Mycobacterium kansasii, Mycobacterium avium-intracellulare*
- Meningitis:
  1. Histoplasmosis
  2. Cryptococcosis
  3. TB

WORKUP

- The diagnosis should be considered in individuals who are occupationally exposed to soil, decaying plant matter, and thorny plants (gardeners, horticulturists, farmers) who present with chronic nonhealing ulcers or lesions with or without associated arthritis or pulmonary symptoms.
- Diagnosis is made by culture:
  1. Pus
  2. Joint fluid
  3. Sputum
  4. Blood
  5. Skin biopsy
- Isolation of the fungus from any site is considered diagnostic of infection.
- Saprophytic colonization of the respiratory tract has been described.
- A positive blood culture may indicate infection in an immunocompromised host.
- Increasingly sensitive laboratory culturing systems may detect the fungus in the normal host.
- Biopsy specimens are diagnostic if characteristic cigar-shaped, round, oval, or budding yeast forms are seen.
- Despite special staining, the yeast may remain difficult to detect unless multiple sections are examined, as organisms are rare.
- No standard method of serologic testing is available.

LABORATORY TESTS

- CBCs and serum chemistries are generally normal.
- Elevated ESR is seen with extracutaneous disease.
- CSF analysis in meningeal disease reveals:
  1. Lymphocytic pleocytosis
  2. Elevated protein
  3. Hypoglycorrhachia
- Nested polymerase chain reaction (PCR) assay represents a future clinical modality to rapidly detect *Sporothrix schenckii*.
- Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) has been used to identify *Sporothrix* grown in culture to the species level.

IMAGING STUDIES

- Chest x-ray examination: Unilateral or bilateral upper lobe cavitary or noncavitary lesions
- Radiographic findings of affected joints:
  1. Loss of articular cartilage
  2. Periosteal reaction
  3. Periarticular osteopenia
  4. Cystic changes

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Local heat and prevention of bacterial superinfection in cutaneous or plaque form. This treatment is important for pregnant women as azoles are teratogenic.

ACUTE GENERAL Rx

CUTANEOUS AND LYMPHOCUTANEOUS SPOROTRICHOSIS:

- Itraconazole at doses of 200 mg/day is the drug of choice and should be given for 2 to 4 wk after the lesions have resolved.
- Alternative treatment: Use saturated solution of potassium iodide (SSKI) 5 to 10 drops PO tid or 1.5 ml PO tid, gradually increasing to 40 to 50 drops PO tid or 3 ml PO tid after meals.
- Maximum tolerated dose should be continued until cutaneous lesions have resolved, approximately 6 to 12 wk.
- Adjunctive therapy with heat is useful and occasionally curative.
- Side effects of SSKI:
  1. Nausea
  2. Anorexia
  3. Diarrhea
  4. Parotid or lacrimal gland hypertrophy
  5. Acneiform rash

DEEP-SEATED MYCOSES (OSTEOARTICULAR, NONCAVITARY PULMONARY DISEASE):

- Itraconazole:
  1. Appropriate initial chemotherapy
  2. Less toxic than amphotericin B
  3. 200 mg PO bid for 1 to 2 yr with continued lifelong suppressive therapy in selected patients
  4. Absence of relapses from 40 to 68 mo has been documented when at least 200 mg/day administered for 24 mo
  5. Insufficient data for use in disseminated disease (e.g., fungemia and meningitis)
  6. Drug levels should be monitored to assess absorption
- Parenteral amphotericin B, total course of 2 to 2.5 g or more, results in cure in approximately two thirds of cases. Lipid AmB 3 to 5 mg/kg/day is also recommended and less toxic.
  1. Relapses are common.
  2. Amphotericin B-resistant isolates of *Sporothrix schenckii* have been reported.
  3. Remains the drug of choice for severely ill patients with disseminated disease.
  4. In cavitary pulmonary disease, given perioperatively as an adjunct to surgical resection.
  5. When patient is improved, can continue treatment with itraconazole 200 mg PO bid.
  6. Treat for at least 12 mo.
  7. The latest IDSA guidelines recommend fluconazole only as an alternative treatment for lymphocutaneous disease.
  8. Requires daily doses of 400 mg/day for lymphocutaneous disease and 800 mg/day for visceral or osteoarticular disease.
  9. Fluconazole much less effective than itraconazole.
  10. All azoles are teratogenic in pregnancy.

CHRONIC Rx

For lymphocutaneous and visceral disease, therapy with itraconazole 200 mg/day for periods of 24 mo or greater. *Sporothrix* is resistant to voriconazole. It is sensitive in vitro to posaconazole, but existing data are very limited at present.

DISPOSITION

- Prognosis for cutaneous disease is good.
- Prognosis is less satisfactory for extracutaneous disease, especially if associated with abnormal immunologic states or other underlying systemic diseases.

REFERRAL

- To surgeon; with an established diagnosis of pulmonary sporotrichosis, cavitary lesions require resection of involved tissue and possible pretreatment with amphotericin
- To infectious disease physician

PEARLS & CONSIDERATIONS

COMMENTS

- In patients with underlying immunosuppression (e.g., hematologic malignancy or infection with HIV), progression of the initial infection may develop into multifocal extracutaneous sporotrichosis.

- In this subset of patients, dissemination of cutaneous lesions is accompanied by hematogenous spread to lungs, bone, mucous membranes, CNS.
- Osteoarticular and pulmonary manifestations predominate with the development of polyarticular arthritis and osteolytic bone lesions.
- In the absence of therapy, the infection is ultimately fatal.
- Patients with underlying immunosuppressive states should be carefully evaluated even when presenting with single cutaneous lesions.
- Diagnostic modalities should include:
  1. Radiographic examination of chest
  2. Technetium pyrophosphate bone scan
  3. Culture of synovial fluid, blood, skin lesion(s)
- In patients with AIDS, itraconazole appears to be the drug of choice, although meningitis and pulmonary disease may warrant the use of amphotericin B.
- In patients with AIDS, lifetime suppressive therapy with itraconazole should follow initial therapy because of the potential for relapse and dissemination. Treatment may be terminated when CD4 counts exceed 200 for more than 1 yr.
- Disseminated cases have been reported with the use of TNF-alpha inhibitors.

AUTHOR: **Patricia Cristofaro, MD**

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Squamous Cell Carcinoma ALG PTG

BASIC INFORMATION

DEFINITION

Squamous cell carcinoma (SCC) is a malignant neoplasm of keratinocytes.

SYNONYMS

SCC
Skin cancer

ICD-10CM CODES

C44.5	Malignant neoplasm of skin of trunk
C44.4	Malignant neoplasm of skin of scalp and neck
D04	Carcinoma in situ of skin
C44.9	Malignant neoplasm of skin, unspecified
C44.0	Malignant neoplasm of skin of lip
C44.2	Malignant neoplasm of skin of ear and external auricular canal
C44.3	Malignant neoplasm of skin of other and unspecified parts of skin
C44.02	Squamous cell carcinoma of skin of lip
C44.121	Squamous cell carcinoma of skin of unspecified eyelid, including canthus
C44.122	Squamous cell carcinoma of skin of right eyelid, including canthus
C44.129	Squamous cell carcinoma of skin of left eyelid, including canthus
C44.221	Squamous cell carcinoma of skin of unspecified ear and external auricular canal
C44.222	Squamous cell carcinoma of skin of right ear and external auricular canal
C44.229	Squamous cell carcinoma of skin of left ear and external auricular canal
C44.320	Squamous cell carcinoma of skin of unspecified parts of face
C44.321	Squamous cell carcinoma of skin of nose
C44.329	Squamous cell carcinoma of skin of other parts of face
C44.42	Squamous cell carcinoma of skin of scalp and neck
C44.520	Squamous cell carcinoma of anal skin
C44.521	Squamous cell carcinoma of skin of breast
C44.529	Squamous cell carcinoma of skin of other part of trunk
C44.621	Squamous cell carcinoma of skin of unspecified upper limb, including shoulder
C44.622	Squamous cell carcinoma of skin of right upper limb, including shoulder
C44.629	Squamous cell carcinoma of skin of left upper limb, including shoulder
C44.721	Squamous cell carcinoma of skin of unspecified lower limb, including hip
C44.722	Squamous cell carcinoma of skin of right lower limb, including hip
C44.729	Squamous cell carcinoma of skin of left lower limb, including hip
C44.82	Squamous cell carcinoma of overlapping sites of skin

EPIDEMIOLOGY & DEMOGRAPHICS

- SCC is the second most common cutaneous malignancy, comprising 20% of all cases of nonmelanoma skin cancer.
- Incidence is highest in lower latitudes (e.g., southern U.S., Australia).
- Male:female ratio is 2:1.
- Incidence increases with age and sun exposure.
- In black patients, SCC are 20% more common than basal cell carcinomas (BCC).
- Average age at diagnosis is 66 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- SCC frequently begins at the site of actinic keratosis and commonly affects the scalp, neck region, back of hands (Fig. E1), superior surface of the pinna, and the lip (Fig. E2). On the lower lip, SCC often develops on actinic cheilitis. A history of smoking is a significant predisposing factor.
- Bowen disease refers to SCC in situ (Fig. E3).
- SCC lesions may have a scaly, erythematous macule or plaque (Fig. E4).
- Telangiectasia, central ulceration may also be present. The ulcer may be superficial and hidden by a crust. Removal of the crust may reveal a well-defined papillary base.
- Most SCCs present as exophytic lesions that grow over a period of mo.
- Although most SCCs are relatively slow growing and nonaggressive, some (2% to 5%) can exhibit rapid growth and metastases. Aggressive tumors are more common in immunocompromised patients and when arising from scars, burns, or prior injury (Marjolin ulcer). Presence of SCC on ears, lips, or size >2 cm are high-risk features of SCC.

ETIOLOGY

Risk factors include ultraviolet B radiation, immunosuppression (kidney transplant recipients have a significantly increased risk), arsenic exposure, HPV infection, medications (azathioprine, sorafenib, tumor necrosis factor [TNF] inhibitors), discoid LE, erosive lichen planus, chronic ulcers, prior radiation exposure, and tobacco abuse.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Keratoacanthomas
- Actinic keratosis
- Amelanotic melanoma
- Basal cell carcinoma
- Benign tumors
- Healing traumatic wounds
- Spindle cell tumors
- Warts

WORKUP

Diagnosis is made by full-thickness skin biopsy (incisional or excisional).

TREATMENT

ACUTE GENERAL Rx

- Electrodesiccation and curettage for small SCCs (<2 mm in diameter), superficial tumors, and lesions located in extremity and trunk.
- Tumors thinner than 4 mm can be managed by simple local removal.
- Lesions 4 to 8 mm thick or those with deep dermal invasion should be excised.
- Tumors penetrating the dermis can be treated with several modalities, including excision and Mohs surgery, radiation therapy, and chemotherapy. Mohs surgery is commonly used for lesions on the face.
- Metastatic SCC can be treated with cryotherapy and combination of chemotherapy using 13-*cis*-retinoic acid and interferon-alpha 2A.
- A treatment algorithm for squamous cell carcinoma is illustrated in Fig. 5.
- In a recent phase 1 study of PD-1 blockade with cemiplimab among patients with advanced cutaneous squamous cell carcinoma, cemiplimab induced a response in approximately half the patients.[1]

DISPOSITION

- Survival is related to size, location, degree of differentiation, immunologic status of the patient, depth of invasion, and presence of metastases. Risk factors for metastasis include lesions on the lip or ear, increasing lesion depth, and poor cell differentiation. Table 1 summarizes risk factors for metastasis of invasive squamous cell carcinoma.
- Patients whose tumors penetrate through the dermis or exceed 8 mm in thickness are at risk of tumor recurrence.
- The most common metastatic locations are regional lymph nodes, liver, and lung.
- Tumors on the scalp, forehead, ears, nose, and lips also carry a higher risk.
- The rate of SCC metastasis from all skin sites ranges from 0.5% to 5.2%.
- SCCs originating in the lip and pinna metastasize in 10% to 20% of cases.
- 5-yr survival for metastatic SCC is 34%.

REFERRAL

Oncology referral for metastatic SCC

PEARLS & CONSIDERATIONS

COMMENTS

- SCC arising in areas of prior radiation, thermal injury, and areas of chronic ulcers or chronic draining sinuses are more aggressive and have a higher frequency of metastasis than those originating in actinic damaged skin.

[1] Migden MR et al: PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma, *N Engl J Med* 379:341-51, 2018.

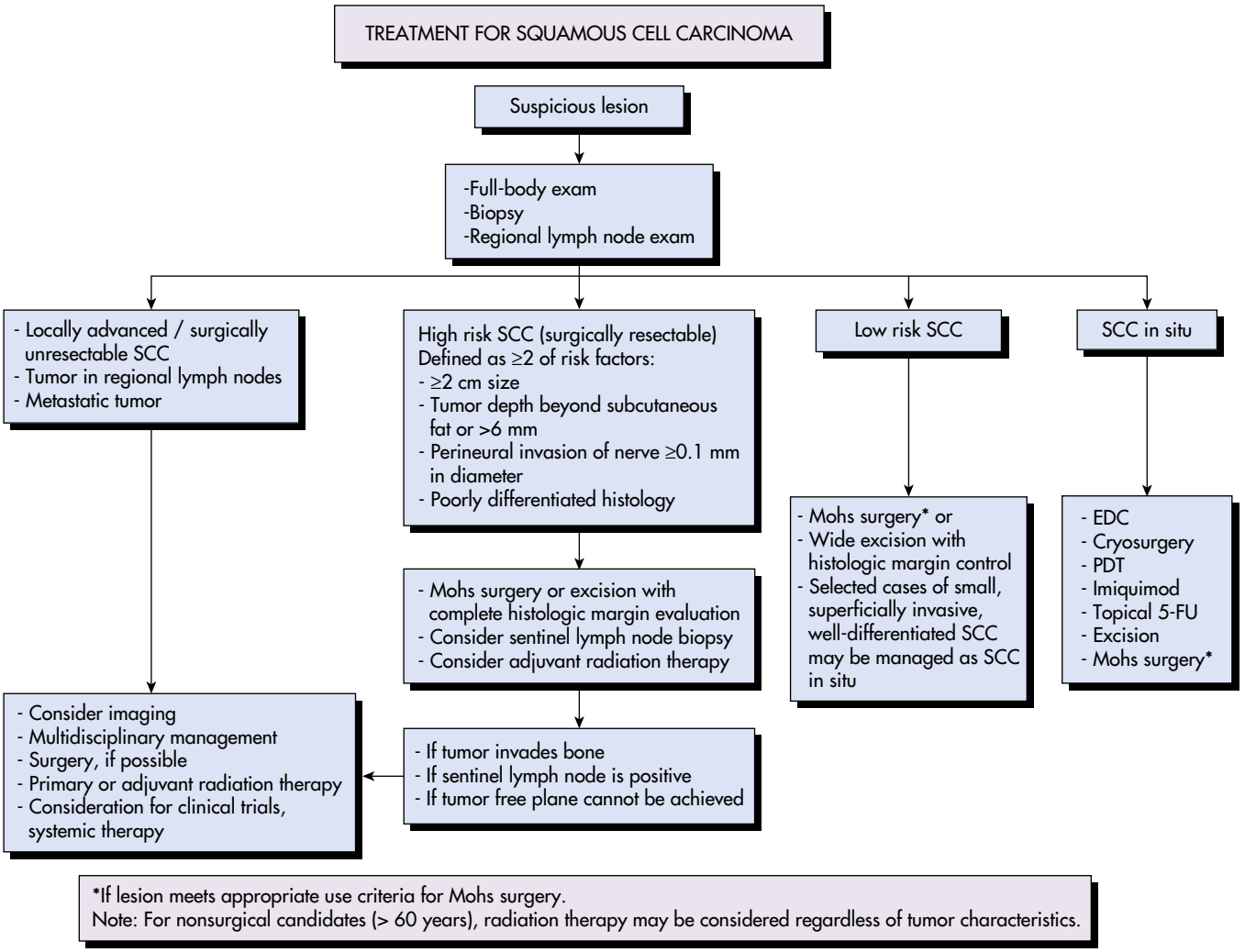

FIG. 5 Treatment algorithm for squamous cell carcinoma *(SCC).* *EDC,* Electrodesiccation and curettage; *5-FU,* 5-fluorouracil; *PDT,* photodynamic therapy. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

TABLE 1 Risk Factors for Metastasis of Invasive Squamous Cell Carcinoma

Tumor thickness: >2 mm (high risk: tumor thickness >6 mm)
Diameter: >2 cm
Location: Ear, lips, and mucosae, including tongue, vulva, and penis (perineural growth may be an additional risk factor in these locations)
Arising within a scar (e.g., burn, radiation)
Histopathologic features: Poorly differentiated or undifferentiated, acantholytic,* developing within Bowen disease
Immunosuppression

*Recently questioned Ogawa T et al: Acantholytic squamous cell carcinoma is usually associated with hair follicles, not acantholytic actinic keratosis, and is not "high risk": diagnosis, management, and clinical outcomes in a series of 115 cases, *J Am Acad Dermatol* 76:327-333, 2017.

Based in part on Brantsch KD et al: Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study, *Lancet Oncol* 9:713-720, 2008.

- Oral retinoids may be useful as a preventive strategy in patients with immunosuppression.
- Nicotinamide (500 mg bid, available over the counter) mitigates some of the deleterious effects of UV radiation and has been reported to lower the incidence of nonmelanoma skin cancer (NMSC0) by 23%.[2]

RELATED CONTENT

Squamous Cell Carcinoma (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

[2] Chen AC et al: A phase 3 randomized trial of nicotinamide for skin cancer chemoprevention, *N Engl J Med* 373:1618, 2015.

FIG. E1 Squamous cell carcinoma. (From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

FIG. E2 Squamous cell carcinoma of the lip. The lower lip **(A)** is a relatively commonly affected site. Smoking is a risk factor for this site, and the prognosis is poorer compared to similar-sized lesions at other sun-exposed sites. Treatment is usually by wedge excision or with radiotherapy. By contrast, the upper lip margin **(B)** is a relatively uncommon site. The chronic trauma from the patient's only three teeth may have been relevant. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

FIG. E3 Squamous cell carcinomas *in situ,* Bowen disease type. A, Scaly red plaque on the chest with skip areas and background photodamage. **B,** Larger broken-up pink plaque with scale-crust in the pubic region, a sun-protected site. This type of lesion often is misdiagnosed as dermatitis or psoriasis and treated with topical corticosteroids. **C,** Bright red, well-demarcated plaque on the proximal nail fold with associated horizontal nail ridging; the possibility of HPV infection needs to be considered. **D,** Dermoscopic findings of tiny dotted vessels in the upper half of the lesion combined with superficial scales. **E,** Extensive involvement of the finger that was misdiagnosed clinically as an inflammatory dermatosis and treated for yrs with corticosteroid creams. (From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier. **B,** Courtesy Kalman Watsky, MD; **D,** Courtesy, Iris Zalaudek, MD)

FIG. E4 Squamous cell carcinoma *in situ,* erythroplasia of Queyrat type. Large, eroded erythematous plaque with well-demarcated borders. The lesion began on the shaft of the penis. (From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.)

Statin-Induced Muscle Syndromes

BASIC INFORMATION

DEFINITION

Statin-induced muscle syndromes (SIMS) include myopathy, myalgia, myositis, and rhabdomyolysis. Definitions for these syndromes are inconsistent in the medical literature.

- Myopathy: A general term defined as any disease of muscles.
- Myalgia: Muscle weakness or pain without serum creatinine kinase elevation.
- Myositis: Muscle weakness or pain with an increased serum creatinine kinase level.
- Rhabdomyolysis: Muscle weakness or pain and a marked serum creatinine kinase level usually greater than 10× the upper limit of normal and serum creatinine elevation as well as signs of brown urine and elevated urine myoglobin. A rare **immune-mediated necrotizing myopathy (IMNM),** also known as **statin-associated autoimmune myopathy,** has also been associated with the use of statins with symptoms persisting after discontinuation of the drug. This condition presents with symmetric proximal arm and leg weakness and severe elevations of muscle enzymes.

SYNONYMS

SIMS
Statin-induced myopathies
Statin-induced myositis
Statin-induced myalgias
Statin-induced rhabdomyolysis
Statin-associated autoimmune myopathy

ICD-10CM CODES

M60.9	Myositis, unspecified
M62.82	Rhabdomyolysis
G72.2	Myopathy due to other toxic agents
G72.9	Myopathy, unspecified
G72.81	Critical illness myopathy
G72.89	Other specified myopathies
M60.89	Other myositis, multiple sites

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Risk of statin-induced rhabdomyolysis is 1.2 per 10,000 persons/yr. Rhabdomyolysis risk of death is 0.15 deaths per 1 million prescriptions. SIMS most commonly occur in people aged 51 to 75, which may reflect the pattern of statin use. Statin-associated autoimmune myopathy occurs in an estimated 2 or 3 of every 100,000 patients treated with statins.

PEAK INCIDENCE: Patients on high-dose statins have a 0.9% incidence of statin-induced rhabdomyolysis.

PREVALENCE: The prevalence of statin-induced myalgias is about 1% to 5%, similar to placebo in clinical trials, although observational studies have suggested a prevalence of 10% or higher. Statins may cause elevated transaminases (ALT, AST) at a prevalence of 0.5% to 2.0% and rhabdomyolysis ~0.08%.

PREDOMINANT SEX AND AGE: The mean age of hospitalized patients with statin-induced myopathy or rhabdomyolysis was 64 yr old and was slightly more common in women (56%).

GENETICS: Interpatient variability exists in the activity of the *CYP3A4* gene for the metabolism of simvastatin, atorvastatin, and lovastatin. Homozygous carriers of *CYP2D6* (poor metabolizers) had a higher rate of discontinuation of simvastatin due to muscle syndromes compared with the *CYP2D6* wild-type genotype; patients taking atorvastatin and having a muscle event were more likely to have the CYP2D6*4 allele. *SLCO1B1* polymorphisms encode for the organic anion transport of statins into the liver cells. The variant C allele may increase the risk of the *SLCO1B1* statin–induced myopathy. Simvastatin-induced myopathy is more likely to be associated with *SLO1B1* genotype and not *ABCB1* genotype. However, a statin-associated autoimmune myopathy has shown a link to class II HLA allele DRB1*11:01 in the development of anti-HMG CoA reductase antibodies, leading to an increase in expression of the antibodies in the muscles of patients exposed to statins. Deficiencies in ubiquinone (coenzyme Q10) may exist in patients with a mutation in the *COQ2* gene. The *EYS* gene can affect neuromuscular tissue and may have a role. In addition, *RYR1* and *CACNA1S* genetic variants may be associated with statin-induced muscle syndromes and elevated CK levels.

RISK FACTORS: Small body frame; age over 80 yr; women, particularly frail elderly women; patients taking multiple drugs, especially gemfibrozil, niacin, cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, verapamil, amiodarone; renal or liver impairment; pharmacogenetic variability; hypothyroidism; excessive alcohol intake; vigorous exercise; severe infections; excessive grapefruit juice ingestion; low vitamin D levels; inherited defects of muscle metabolism such as carnitine palmityl transferase II deficiency, McArdle disease, and myoadenylate deaminase deficiency; acquired myopathies such as postpoliomyelitis syndrome; lipophilic statins (simvastatin, atorvastatin, lovastatin); multiple conditions such as diabetes; renal impairment, and prior elevated CK; and drugs of abuse (amphetamines, heroin, cocaine, phencyclidine).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Myopathy can occur at any time, although it is more common within the first 4 wk of therapy; statin-associated necrotizing myopathy may occur after mos of using statins
- Proximal generalized muscle aches, body aches, and pains, and may be mild or severe
- Dark-colored urine
- Muscle cramps, spasms, tenderness, or stiffness
- Unusually tired or weak
- Nocturnal cramping
- Tendon pain

ETIOLOGY

- History of current statin use.
- May be explained by one of three deficiencies of end products of the 3-hydroxy-3-methylglutaryl-coA reductase pathway: cell signaling and apoptosis, mitochondrial function and ubiquinone concentrations, and cholesterol concentrations and cell membrane integrity.
- The risk may be enhanced by drug interactions that interfere with hepatic metabolism and gut wall transport of interacting medications and by pharmacodynamic effects.
- Underlying metabolic muscle disorder may predispose a patient to develop myopathy.
- Patients with statin-associated autoimmune myopathy have been found to have anti-HMG-CoA reductase antibodies even prior to exposure to statin therapy.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Bursitis, tendinitis, radiculopathy, osteoarthritis, muscle strain, myofascial pain, hypothyroidism, proton pump inhibitor–induced polymyositis, viral illness, polymyositis, idiopathic inflammatory myositis, and polymyalgia rheumatica

WORKUP

Workup consists of a thorough history, including exercise history, urine color, medication history, and physical exam to palpate tenderness and obtain blood tests to evaluate muscle and kidney damage.

LABORATORY TESTS

If severe myopathy or rhabdomyolysis is suspected:

- Elevated CPK, positive serum myoglobin, elevated BUN, serum creatinine, AST, ALT, LDH, and potassium
- Urine creatinine, positive casts, and hemoglobin in urine with absence of red blood cells
- Anti-3-hydroxy-3-methylglutaryl-conenzyme A (anti-HMG-CoA) antibody
- Consider electrocardiogram and assessment of calcium, phosphate, and uric acid

If mild to moderate myopathy is suspected:

- Monitor TSH and CPK levels; CPK may only be elevated when sudden severe myopathy occurs.
- If the patient has brown or dark urine or elevated CPK, monitor BUN and serum creatinine.
- In statin-associated autoimmune myopathy, the creatine kinase level is usually ≥10 times the upper limit of normal. In these patients, muscle biopsy specimens will be positive for autoantibodies against HMG-CoA reductase and may have necrosis.

IMAGING STUDIES

- Not recommended.
- In statin-associated autoimmune myopathy, electromyography shows small-amplitude motor-unit potentials with increased spontaneous activity characteristic of an active myopathic process. Muscle edema is evident on MRI.[1]
- Statin Intolerance Tool:
  1. The American College of Cardiology has created a tool to assess statin muscle symptoms and to guide clinicians that can be of value: http://tools.acc.org/statinintolerance/#!/

[1]Mammen AL: Statin-associated autoimmune myopathy, *N Engl J Med* 374:664-669, 2016.

TREATMENT

NONPHARMACOLOGIC THERAPY

Treatment of rhabdomyolysis is generally supportive in nature (see "Rhabdomyolysis" topic).

ACUTE GENERAL Rx

- Stop statin therapy immediately if muscle symptoms occur. Check history, potential drug-drug interactions, CPK, TSH, renal function, hepatic function, and urinalysis.
- If patients have suspected rhabdomyolysis, they should be hospitalized and treated with supportive therapy and monitoring of complications.
- If CPK <10× the upper limit of normal without symptoms, continue statin therapy at the same or lower dosage.
- If CPK <10× the upper limit of normal with intolerable symptoms, discontinue statin.
- If CPK >10× the upper limit of normal, discontinue statin.

Box E1 describes recommendations of the National Lipid Association Statin Safety Assessment Task Force regarding statin and muscle safety.

CHRONIC Rx

- After stopping the statin and symptom or CPK resolution, which may take up to 4 mo, consider the same statin at a lower dosage or a different statin at an equivalent or lower dosage.
- When restarting therapy, consider statins such as low-dose rosuvastatin; pravastatin; and alternate-day dosing of rosuvastatin or atorvastatin.
- If patient had rhabdomyolysis secondary to statin therapy, consider nonstatin treatments.
- If the patient develops myopathy after a second trial of therapy, statin treatment should be permanently discontinued and nonstatin cholesterol-lowering therapy initiated.
- For IMNM (statin-associated autoimmune myopathy and idiopathic inflammatory myositis), immunosuppressive therapy with prednisone (1 mg per kg of body weight per day) and at least one agent (methotrexate, azathioprine, or mycophenolate mofetil) have been used. In resistant cases, IV immune globulin or another agent such as rituximab may be added.

INTEGRATIVE MEDICINE

- The effect of coenzyme Q10 on reducing or preventing SIMS remains controversial; although it may be effective in reducing muscle pain, weakness, cramps, and tiredness, it has no effect on lowering CK levels. Given its safety, coenzyme Q10 can be recommended if the actions listed under "Chronic Rx" are insufficient to continue the use of the statin and if the muscle symptoms have been limited to myalgias. Use coenzyme Q10 with caution in patients taking warfarin, as its anticoagulant effect may be decreased.
- A 2015 meta-analysis of observational studies reported that vitamin D levels were lower in patients with statin-induced myalgias than in individuals who did not have these symptoms.
- In a study of 282 patients with vitamin D levels less than 32 ng/ml and with myalgia-myositis from statins, vitamin D supplementation (median 50,000 IU D_3/wk) for 6 mo improved symptoms and statin tolerance in 74% to 85% of patients; another study showed that replacement of vitamin D in patients with low-serum vitamin D may be able to maintain or restart previously failed statin therapy.

DISPOSITION

- Usually resolves within 1 wk up to 4 mo after discontinuing statin therapy.
- Once the patient has a full recovery, an alternative statin can be tried.
- Statins should not be restarted in IMNM or idiopathic inflammatory myositis.

REFERRAL

If rhabdomyolysis is suspected, immediate referral for hospitalization is suggested.

PEARLS & CONSIDERATIONS

COMMENTS

SIMS are usually mild and will resolve within a few wk after discontinuing statin therapy. However, such syndromes may progress to rhabdomyolysis.

PREVENTION

- Follow the 2013 AHA/ACC treatment guidelines and the 2017 ACC focused update on nonstatin therapies for LDL cholesterol and limit the concomitant use of fibrates with statins.
- Discontinue statin therapy prior to and during surgical procedures.
- If patient requires a short-term therapy with an interacting medication such as an azole antifungal, temporarily discontinue statin therapy until interacting therapy is completed.
- If statin–fibric acid therapy is warranted, fenofibrate is preferred over gemfibrozil to decrease risk of myopathy.
- Baseline liver function testing before initiation of statin therapy and only if clinically indicated thereafter.

PATIENT & FAMILY EDUCATION

- Inform patients to promptly report muscle weakness, unexpected muscle pain, or brownish urine.
- Ensure that the pharmacist and/or primary care physician checks for drug-drug interactions with every new prescription, including those from dentists and physicians from other specialties.
- Coenzyme Q10 may lessen milder muscle symptoms from statins, but patients should inform their physician and pharmacist if they decide to use this supplement.
- A recent clinical trial comparing lipid-lowering efficacy for two nonstatin therapies, ezetimibe and evolocumab, among patients with statin intolerance revealed that evolocumab resulted in a significantly greater reduction in LDL-C levels after 24 wk. Further studies are needed to assess long-term efficacy and safety.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Rhabdomyolysis (Related Key Topic)

AUTHORS: **Lisa Cohen, PharmD** , and **Anne L. Hume, PharmD**

SUGGESTED READINGS

Bitzur R et al: Intolerance to statins: mechanisms and management, *Diabetes Care* 36(Suppl 2), 2014.

Caughey GE et al: Association of statin exposure with histologically confirmed idiopathic inflammatory myositis in an Australian population, *JAMA Intern Med* 178:1224-1229, 2018.

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Norata GD et al: Statins and skeletal muscle toxicity: from clinical trials to everyday practice, *Pharmacol Res 88C* 107-113, 2014.

Patel AM: Statin toxicity from macrolide antibiotic coprescription, *Ann Int Med* 158:868-876, 2013.

Qu H et al: Effects of coenzyme Q10 on statin-induced myopathy: an updated meta-analysis of randomized controlled trials, *J Am Heart Assoc* 7(19), 2018.

BOX E1 Recommendations to Health Care Professionals Regarding Statin and Muscle Safety

- Whenever muscle symptoms or an increased CK level is encountered in patients receiving statin therapy, health professionals should attempt to rule out other causes, because these are most likely to explain the findings. Other common causes include increased physical activity, trauma, falls, accidents, seizure, shaking chills, hypothyroidism, infections, carbon monoxide poisoning, polymyositis, dermatomyositis, alcohol abuse, and drug abuse (cocaine, amphetamines, heroin, or PCP).
- Obtaining a pretreatment, baseline CK level can be considered in patients who are at high risk of experiencing muscle toxicity (e.g., older patients or those combining a statin with an agent known to increase myotoxicity), but this is not routinely necessary in other patients.
- It is unnecessary to measure CK levels in asymptomatic patients during the course of statin therapy, because marked, clinically important CK elevations are rare and are usually related to physical exertion or other causes.
- Patients receiving statin therapy should be counseled about the increased risk of muscle symptoms, particularly if initiation of vigorous, sustained endurance exercise or a surgical operation is being contemplated; they should be advised to report such muscle symptoms to a health professional.
- Creatine kinase measurements should be obtained in symptomatic patients to help gauge the severity of muscle damage and facilitate decision of whether to continue therapy or alter doses.
- In patients who develop intolerable muscle symptoms with or without CK elevation and for whom other etiologies have been ruled out, the statin should be discontinued. Once symptoms disappear, the same or different statin at the same or a lower dose can be restarted to test the reproducibility of symptoms. Recurrence of symptoms with multiple statins and doses requires initiation of other lipid-altering therapy.
- In patients who develop tolerable muscle symptoms or have no symptoms but have a CK level <10× ULN, statin therapy may be continued at the same or reduced doses and symptoms may be used as the clinical guide to stop or continue therapy.
- In patients who have positive anti-HMG-CoA antibodies and statin-associated necrotizing autoimmune myopathy, more aggressive immunosuppressant treatments may be necessary.
- In patients who develop rhabdomyolysis (CK >10,000 IU/L or >10× ULN with an elevation in serum creatinine or need for intravenous hydration therapy), statin therapy should be stopped. Intravenous hydration therapy in a hospital should be instituted if indicated for patients experiencing rhabdomyolysis. Once patients recover, risk versus benefit of statin therapy should be carefully reconsidered.

CK, Creatine kinase; PCP, phencyclidine; ULN, upper limit of normal.
From McKenney JM et al: Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force, *Am J Cardiol* 97(suppl 8A):89C-94C, 2006.

Status Epilepticus

BASIC INFORMATION

DEFINITION

Status epilepticus is a medical neurologic emergency. It is historically defined as 30 min of continuous seizure activity or two or more seizures without full recovery of consciousness between seizures. However, in practice a continuous seizure that lasts >5 min is treated as status epilepticus.

SYNONYMS

Convulsive status epilepticus
Nonconvulsive status epilepticus

ICD-10CM CODES

G41	Status epilepticus
G40.301	Generalized idiopathic epilepsy and epileptic syndromes, not intractable, with status epilepticus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 40 to 100 cases per 100,000 persons
PEAK INCIDENCE: It is most common among children younger than 1 yr and adults older than 60 yr.
PREDOMINANT SEX AND AGE: No gender preference

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients can present with repetitive tonic-clonic movements of the body (convulsive status epilepticus); other patients are comatose and nonresponsive (nonconvulsive status epilepticus).
- Patients may also present with lethargy, intermittent confusion, and involuntary movements.

ETIOLOGY

- Status epilepticus can be the result of an acute neurologic injury, such as stroke, meningitis, brain tumor, etc. Table 1 summarizes causes of status epilepticus in adults presenting in the community.
- In patients with epilepsy, abrupt discontinuation of antiepileptic drugs can result in status epilepticus.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Convulsive syncope
- Encephalopathies: Metabolic, infectious, toxic, etc.
- Nonepileptic spells

WORKUP

- ABCs
- ICU admission
- Emergent electroencephalogram (EEG)
- Continuous video EEG in refractory cases
- Table 2 describes a suggested timetable for emergency diagnosis and treatment of status epilepticus. A treatment approach is summarized in Table 3 and Fig. 1.

LABORATORY TESTS

- Routine blood workup (CBC, CMP, glucose, electrolytes)

TABLE 1 Causes of Status Epilepticus in Adults Presenting from the Community

Previous Seizures	No Previous Seizures
Common	
Subtherapeutic anticonvulsant	Ethanol-related
Ethanol-related	Drug toxicity
Intractable epilepsy	CNS infection
	Head trauma
	CNS tumor
Less Common	
CNS infection	Metabolic aberration
Metabolic aberration	Stroke
Drug toxicity	
Stroke	
CNS tumor	
Head trauma	

CNS, Central nervous system.
From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

- Urine drug screen
- Lumbar puncture and CSF analysis in patients with suspected infectious meningitis or encephalitis or suspected autoimmune or paraneoplastic encephalitis

IMAGING STUDIES

- Immediate CT scan of the head.
- MRI of the brain with and without contrast should be performed once the patient is in a stable condition.

TREATMENT

- Patients with continuous seizure activity over 3 min need intravenous lorazepam 0.1 mg/kg at 2 mg/min (or diazepam 0.2 mg/kg at 5 mg/min only when lorazepam is not available).
- In the absence of intravenous access, intramuscular administration of midazolam 10 mg in an adult is a superior alternative.
- Failure of response to lorazepam or midazolam is referred to as established status epilepticus and should be followed by second-line therapy of intravenous fosphenytoin 20 mg/kg (PE) at a rate not greater than 150 mg/min, phenytoin 20 mg/kg IV at up to 50 mg/min as tolerated, intravenous valproic acid 40 mg/kg IV, or intravenous levetiracetam 60 mg/kg IV. Vital signs should be monitored during the infusion.
- If seizures continue, an additional infusion of intravenous valproate, levetiracetam, lacosamide, or brivaracetam or continuous

TABLE 2 Suggested Timetable for Emergency Diagnosis and Treatment of Status Epilepticus

Time	Exam/Intervention	Testing
Initial presentation: 0 min	Airway, breathing, circulation, IV access, monitoring	Glucose, oxygenation via pulse oximetry ± blood gas analysis
Primary survey: 5 min	Neurologic exam Administer antiepileptic drugs Lorazepam, 0.1 mg/kg IV Phenobarbital, 20 mg/kg IV Normal saline maintenance IV Reduce fever	Electrolytes, renal and liver function, ammonia, anticonvulsant levels, toxicology, complete blood cell count, urinalysis
Secondary survey: 15-30 min	Evaluate treatment results Second-line antiepileptic drug if seizure persists Fosphenytoin, 20 mg/kg IV, or phenytoin, 20 mg/kg IV	Patient-specific: Cranial imaging (CT vs. MRI), lumbar puncture, EEG, ECG
Status epilepticus: >30 min	Intubation and mechanical ventilation	
Refractory status epilepticus: >60 min	Titrate antiepileptic drug to burst suppression Pentobarbital, 10 mg/kg IV given over 30 min, then 5 mg/kg every hour for 3 doses, then 1 mg/kg/h; titrate to effect Midazolam, 0.15 mg/kg IV, then 1-2 μg/kg/min, titrate to effect Phenobarbital, 5-10 mg/kg IV every 20 minutes to achieve burst suppression, then every 12 hours Evaluate need for vasopressors	Continuous EEG Neurologic consultation Consider anesthesia consultation for treatment with inhaled anesthetic

CT, Computed tomography; *ECG,* electrocardiogram; *EEG,* electroencephalogram; *IV,* intravenous; *MRI,* magnetic resonance imaging.
From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

TABLE 3 Treatment Approach to Status Epilepticus

1. Appropriate critical care treatment should be provided as soon as possible and simultaneously with emergent initial therapy for seizures. Treatment should be escalated quickly until seizures are controlled.
   1a. Critical care treatment (dictated by clinical circumstances):
   a. Intubation for airway protection and mechanical ventilation
   b. Vital sign monitoring
   c. Peripheral IV access
   d. Treatment of hypotension with vasopressors
   e. Finger stick blood glucose
   f. Nutrient resuscitation (thiamine before dextrose)
   g. Hypertension may be related to ongoing seizure activity, and termination of status epilepticus often substantially corrects it. Additionally, many agents used to terminate status epilepticus can produce hypotension.
   1b. Emergent initial therapy with benzodiazepines:
   a. Lorazepam 0.1 mg/kg up to 4 mg per dose, may repeat after 5-10 min
   b. Midazolam 0.2 mg/kg IM/IV up to 10 mg
   c. Diazepam 0.15 mg/kg up to 10 mg per dose, may repeat after 5 min
2. Urgent control therapy—antiseizure drugs available in IV formulations:
   a. Fosphenytoin/phenytoin 20 mg PE/kg IV, may repeat bolus of 5 mg/kg IV:
   b. Valproic acid 20-40 mg/kg IV, may repeat bolus of 20 mg/kg IV
   c. Levetiracetam 1000-3000 mg IV
   d. Phenobarbital 20 mg/kg IV, may repeat bolus of 5-10 mg/kg
   e. Lacosamide 200-400 mg IV
   f. Midazolam bolus 0.2 mg/kg IV, followed by 0.05-2 mg/kg/h continuous infusion
3. Refractory therapy–continuous infusion of antiseizure drugs, titrated to either seizure cessation, suppression-burst, or complete suppression on EEG:
   a. Midazolam bolus 0.2 mg/kg IV, followed by 0.05-2 mg/kg/h continuous infusion
   b. Propofol bolus 1-2 mg/kg, followed by 20 mcg/kg/min continuous infusion, titrate up to 30-200 mcg/kg/min
   c. Pentobarbital 5-15 mg/kg, may repeat bolus of 5-10 mg/kg, followed by 0.5-5 mg/kg/h continuous infusion
4. Treat complications.
5. Complications of status epilepticus are numerous and can involve multiple organ systems. In particular, convulsive status epilepticus is associated with cardiac complications such as hypertension and tachycardia, as well as rhabdomyolysis and hyperthermia. Respiratory complications, including respiratory failure, hypoxia, and neurogenic pulmonary edema, may be seen. Status epilepticus is associated with neuronal damage and cerebral edema with increased intracranial pressure, which may require intracranial pressure monitoring and aggressive treatment with hypertonic agents.

From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

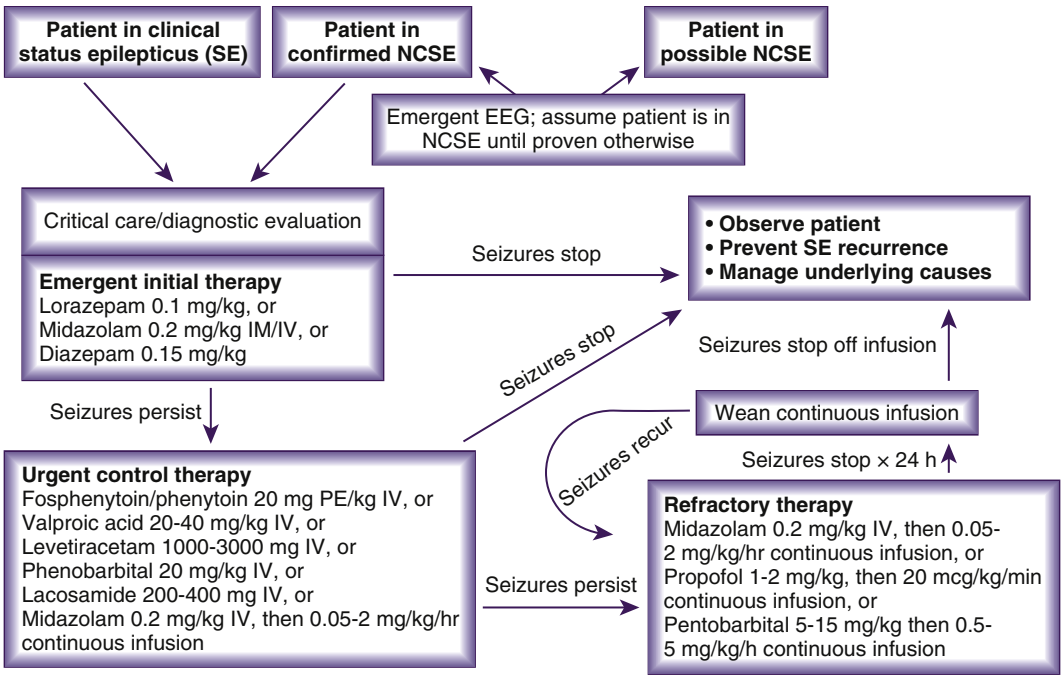

FIG. 1 Management algorithm for status epilepticus. *EEG,* Electroencephalogram; *IM,* intramuscular; *IV,* intravenous; *NCSE,* nonconvulsive status epilepticus; *SE,* status epilepticus. (From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.)

TABLE 4 Treatment Alternatives for Refractory and Super-Refractory Status Epilepticus

	Comments	Adverse Events
Thiopental	Metabolized to pentobarbital	Hypotension Respiratory depression Cardiac depression
Ketamine	Mechanism of action particularly well-suited to treat refractory and super-refractory SE (NMDA receptor antagonist)	High intracranial pressure Hypotension Hallucinations
Inhaled anesthetics	High rate of complications Needs closed system (gas recovery)	Hypotension Infection Paralytic ileus
Ketogenic diet	Relatively safe (no respiratory and cardiocirculatory instability) Slow onset of action Requires skilled dietician	Gastroesophageal reflux Constipation Acidosis Hypertriglyceridemia
Lidocaine	Minor respiratory depression compared with other drugs	Cardiocirculatory instability Possible induction of seizures
Hypothermia	Only transitory control (cannot be a prolonged therapy)	Hypotension Cardiovascular instability Impaired coagulation (bleeding risks)
Resective surgery	Long-term treatment of seizures Not all patients are eligible	Surgical risks

NMDA, N-methyl-D-aspartate; *SE,* status epilepticus.
From Swaiman KF et al: *Swaiman's pediatric neurology, principles and practice,* ed 6, Philadelphia, 2017, Elsevier. See original table for references.

infusions of phenobarbital, midazolam, and propofol are alternatives. Many of these drugs remain under investigation, and superiority of any one agent is not established. Treatment alternatives for refractory and super-refractory status epilepticus are summarized in Table 4.

NONPHARMACOLOGIC THERAPY

None

GENERAL Rx

It is important to find out the etiology of the status epilepticus (e.g., metabolic disturbance, infection). The appropriate treatment/understanding of the underlying cause of the status epilepticus will impact successful treatment.

CHRONIC Rx

- Chronic treatment of status epilepticus depends on underlying etiology.
- Patient with status epilepticus due to epilepsy will need chronic treatment.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Not applicable

DISPOSITION

- Response to treatment depends on the etiology of the status epilepticus.
- When there is no CNS injury as a cause or result of the status epilepticus, the prognosis is good.
- No driving until seizure freedom in accordance with local laws and regulations.

REFERRAL

Status epilepticus is a neurologic emergency; therefore immediate inpatient neurologic consultation is warranted.

PEARLS & CONSIDERATIONS

COMMENTS

- Status epilepticus is a medical emergency that carries a high risk of mortality. Mortality among patients who present in status epilepticus is 15% to 22%. Among those who survive, functional ability will decline in 25% of cases.
- Continuous video EEG is crucial in the treatment of these patients because some of them may not be clinically seizing (convulsing) but electrographically they may still have subclinical repetitive seizures or subclinical status epilepticus.
- In the context of benzodiazepine-refractory convulsive status epilepticus, the anticonvulsant drugs levetiracetam, fosphenytoin, and valproate each led to seizure cessation and improved alertness by 60 min in approximately half the patients, and the three drugs were associated with similar incidences of adverse events.[1]

PREVENTION

Medication compliance is crucial in patients with epilepsy.

PATIENT & FAMILY EDUCATION

- Patients with epilepsy have normal lives.
- The goal of treatment is no seizures and no side effects to medications.
- Patient education and information can be obtained at the Epilepsy Foundation: www.epilepsyfoundation.org
- Pregnant women with epilepsy should visit the Antiepileptic Drug Pregnancy Registry website for information and assistance: www.aedpregnancyregistry.org
- Patients with ongoing seizures are forbidden from driving; check state regulations and laws regarding driving and epilepsy.

AUTHORS: **Patricio Sebastian Espinosa, MD, MPH,** and **Corey Goldsmith, MD**

[1]Kapur J et al: Randomized trial of three anticonvulsant medication for status epilepticus, *N Engl J Med,* 381:2103-13, 2019

BASIC INFORMATION

DEFINITION

Stevens-Johnson syndrome (SJS) is a rare, severe vesiculobullous form of erythema multiforme (EM) affecting the skin, mouth, eyes, and genitalia. SJS is defined as affecting <10% of body surface area (BSA). When it affects 10% to 30% of BSA, it is known as SJS-toxic epidermal necrolysis (TEN) overlap syndrome. TEN affects >30% of BSA. Table E1 provides a classification of SJS and TEN.

SYNONYMS

SJS
Herpes iris
Febrile mucocutaneous syndrome

ICD-10CM CODE
L51.1 Stevens-Johnson syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- SJS affects predominantly children and young adults.
- Male:female ratio is 2:1.
- Prevalence: 1:100,000 for SJS and 1:1,000,000 for TEN

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The cutaneous eruption generally occurs within 4 wk of drug initiation and is generally preceded by vague, nonspecific symptoms of low-grade fever and fatigue (influenza-like symptoms) occurring 1 to 14 days before the skin lesions. Cough is often present. Fever may be high during the active stages. The acute phase of the disease lasts 1 to 2 wk.
- Enlarging red-purple macules (Fig. E1) or papules and bullae generally occur on the conjunctiva, mucous membranes of the mouth (Fig. E2), nares, and genital regions. Lesions rapidly spread to their maximum extent usually within 2 days.
- Corneal ulcerations may result in blindness.
- Ulcerative stomatitis results in hemorrhagic crusting (Fig. E3).
- Nikolsky sign (shearing off of epidermis with pressure on skin) can be present.
- Flat, atypical target lesions or purpuric maculae may be distributed on the trunk or be widespread.
- The pain from oral lesions may compromise fluid intake and result in dehydration.
- Thick, mucopurulent sputum and oral lesions may interfere with breathing.
- Box E1 summarizes features of SJS and TEN.

ETIOLOGY

- Drugs (see Box E2). Upper respiratory tract infections (e.g., *Mycoplasma pneumoniae*) and HSV infections have also been implicated.
- Increased rash of SJS with *HLA-B*1502* and *HLA-B*5801,* HIV, kidney disease, and unconfirmed autoimmune diseases.

TABLE E1 Classification of Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, and Stevens-Johnson Syndrome–Toxic Epidermal Necrolysis Overlap

	SJS	SJS-Ten	Ten
Lesional morphology	Targetoid lesions, dusky red macules, bullae	Targetoid lesions, dusky red macules, bullae	Targetoid lesions, dusky erythematous macules and plaques; detachment of epidermis
Localization of skin lesions	May be scattered and isolated; may be confluent, especially on the trunk and face	May be scattered and isolated; often confluent	Usually extensive involvement with widespread confluence
Involved skin	<10%	10%-30%	>30%
Biopsy features	More interface dermatitis	Significant interface dermatitis + necrolysis	Predominantly necrolysis
Mucosal changes	Prominent	Prominent	May be less than in SJS
Systemic involvement	Often present	Always present	Always present

SJS, Stevens-Johnson syndrome; *TEN,* toxic epidermal necrolysis.
From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.

FIG. E1 Stevens-Johnson syndrome (SJS). Intensely erythematous macules are nearly confluent on the palms of this boy with SJS from carbamazepine. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

FIG. E2 Stevens-Johnson syndrome. Purpuric macules became bullous. Note the inflammation of the conjunctivae and lips. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence*, ed 5, 2016, Elsevier.)

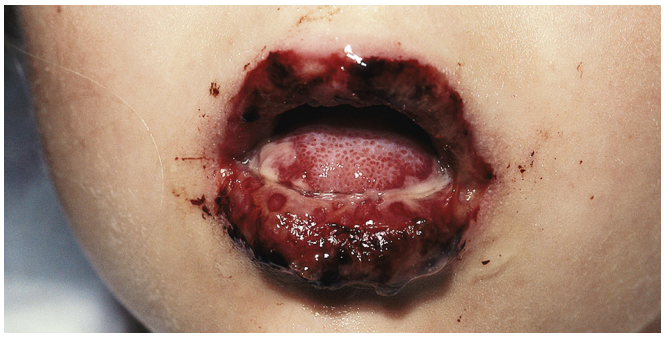

FIG. E3 Stevens-Johnson syndrome. Mucous membrane involvement with severe swelling and hemorrhagic crusting of the lips. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

BOX E1 Features of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

- Constitutional
  - Fever
  - Dehydration
- Mucocutaneous
  - Stomatitis with hemorrhagic crusts
  - Oral and genital erosions
  - Dysphagia
  - Purulent conjunctivitis with photophobia
  - Occasionally esophageal and pulmonary mucosal sloughing
  - Dusky erythematous macules, targetoid lesions, bullae, and skin sloughing
- Visceral
  - Lymphadenopathy
  - Hepatosplenomegaly with hepatitis
  - Uncommonly: Pneumonitis, arthritis, myocarditis, and nephritis
- Laboratory abnormalities
  - Increased erythrocyte sedimentation rate (100%)
  - Leukocytosis (60%)
  - Eosinophilia (20%)
  - Anemia (15%)
  - Elevated hepatic transaminase levels (15%)
  - Leukopenia (10%)
  - Proteinuria, microscopic hematuria (5%)

From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.

BOX E2 Most Common Pharmacologic Triggers of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

- Allopurinol
- Barbiturates
- Carbamazepine
- Lamotrigine
- NSAIDs
- Penicillins
- Phenytoin
- Sulfonamides

NSAIDs, Nonsteroidal antiinflammatory drugs.
From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Toxic erythema (drugs or infection)
- Pemphigus
- Pemphigoid
- Urticaria
- Hemorrhagic fevers
- Serum sickness
- *Staphylococcus* scalded-skin syndrome
- Behçet syndrome

WORKUP

- Diagnosis is generally based on clinical presentation and characteristic appearance of the lesions.
- Skin biopsy is generally reserved for when classic lesions are absent and diagnosis is uncertain. Biopsy reveals epidermal necrolysis but cannot distinguish between SJS, TEN, and EM.

LABORATORY TESTS

CBC with differential, cultures in cases of suspected infection

IMAGING STUDIES

Chest x-rays may show patchy changes in patients with pulmonary involvement.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Withdrawal of any potential drug precipitants
- Careful skin nursing to prevent secondary infection

ACUTE GENERAL Rx

- Treatment of associated conditions (e.g., acyclovir for HSV infection, azithromycin for *Mycoplasma* infection)
- Antihistamines for pruritus
- Treatment of the cutaneous blisters with cool, wet Burow compresses
- Relief of oral symptoms by frequent rinsing with lidocaine (Xylocaine Viscous)
- Liquid or soft diet with plenty of fluids to ensure proper hydration
- Treatment of secondary infections with antibiotics
- Corticosteroids: Use remains controversial and there is a clear risk of sepsis; they should be used only in severe cases early in the disease; when used, prednisone 20 to 30 mg bid until new lesions no longer appear, then rapidly tapered
- Topical steroids: May use to treat papules and plaques; however, should not be applied to eroded areas
- Vitamin A: May be used for lacrimal hyposecretion
- Consider IVIG in severe cases

DISPOSITION

- Prognosis varies with severity of disease. It is generally good in patients with limited disease; however, mortality rate may approach 10% in patients with extensive involvement. A severity of illness score known as SCORETEN that incorporates increased glucose level (>252 mg/dl), increased BUN (>28 mg/dl), electrolytes (serum bicarbonate <20 mEq/L), age (>40 yr), immunosuppression (presence of cancer), involvement >10% of BSA, and increased heart rate (>120 beats/min) can be used to calculate mortality risk.
- Oral lesions may continue for several mo.
- Scarring and corneal abnormalities may occur in 20% of patients.

REFERRAL

- Management of SIS is similar to those with extensive burns. Hospital admission in a unit used for burn care is recommended in severe cases.
- Urethral involvement may necessitate catheterization.
- Ocular involvement should be monitored by an ophthalmologist.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Stevens-Johnson Syndrome (Patient Information)
Toxic Epidermal Necrolysis (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READING

Wetter DA, Camilleri MJ: Clinical, etiologic, and histopathologic features of Stevens-Johnson during an 8-year period at Mayo Clinic, *Mayo Clin Proc* 85(2):131-138, 2010.

BASIC INFORMATION

DEFINITION

Stomatitis is inflammation involving the oral mucous membranes. Mucositis is inflammation and ulceration of the mucous membranes. It is most commonly seen in the mouth but can occur anywhere in the GI, genitourinary (GU), or respiratory tract. It is most often due to side effects of chemotherapy or radiation therapy (Fig. E1) in cancer patients.

SYNONYM

Heterogeneous grouping of unrelated illnesses, each with its own designation(s)

ICD-10CM CODES

A69.0	Necrotizing ulcerative stomatitis
B08.4	Enteroviral vesicular stomatitis with exanthem
B08.61	Bovine stomatitis
B37.0	Candidal stomatitis
K12	Stomatitis and related lesions
K12.0	Recurrent oral aphthae
K12.1	Other forms of stomatitis
K12.30	Oral mucositis (ulcerative), unspecified
K12.31	Oral mucositis (ulcerative) due to antineoplastic therapy
K12.32	Oral mucositis (ulcerative) due to other drugs
K12.33	Oral mucositis (ulcerative) due to radiation
K12.39	Other oral mucositis (ulcerative)
K13.0	Other and unspecified lesions of oral mucosa

PHYSICAL FINDINGS & CLINICAL PRESENTATION

WHITE LESIONS:

- Candidiasis (thrush)
  1. Caused by yeast infection *(Candida albicans)*
  2. Examination: White, curdlike material (Fig. E2) that, when wiped off, leaves a raw, bleeding surface
  3. Epidemiology: Seen in the very young and the very old, those with immunodeficiency (AIDS, cancer), persons with diabetes, and patients treated with antibacterial agents
- Other:
  1. Leukoedema: Filmy opalescent-appearing mucosa, which can be reverted to normal appearance by stretching. This condition is benign.
  2. White sponge nevus: Thick, white corrugated folds involving the buccal mucosa. Appears in childhood as an autosomal dominant trait. Benign condition.
  3. Darier disease (keratosis follicularis): White papules on the gingivae, alveolar mucosa, and dorsal tongue. Skin lesions also present (erythematous papules). Inherited as an autosomal dominant trait.
  4. Chemical injury: White sloughing mucosa.
  5. Nicotine stomatitis: Whitened palate with red papules.
  6. Lichen planus: Linear, reticular, slightly raised striae on buccal mucosa. Skin is involved by pruritic violaceous papules on forearms and inner thighs.
  7. Discoid lupus erythematosus: Lesion resembles lichen planus.
  8. Leukoplakia: White lesions that cannot be scraped off; 20% are premalignant epithelial dysplasia or squamous cell carcinoma.
  9. Hairy leukoplakia: Shaggy white surface that cannot be wiped off; seen in HIV infection, caused by Epstein-Barr virus.

RED LESIONS:

- Candidiasis may present with red lesions instead of the more frequent white. Median rhomboid glossitis is a chronic variant.
- Benign migratory glossitis (geographic tongue): Area of atrophic depapillated mucosa surrounded by a keratotic border. Benign lesion, no treatment required.
- Hemangiomas.
- Histoplasmosis: Ill-defined, irregular patch with a granulomatous surface, sometimes ulcerated.
- Allergy.
- Anemia: Atrophic reddened glossal mucosa seen with pernicious anemia.
- Erythroplakia: Red patch usually caused by epithelial dysplasia or squamous cell carcinoma.
- Burning tongue (glossopyrosis): Normal examination; sometimes associated with denture trauma, anemia, diabetes, vitamin B_{12} deficiency, psychogenic problems.

DARK LESIONS (BROWN, BLUE, BLACK):

- Coated tongue: Accumulation of keratin; harmless condition that can be treated by scraping
- Melanotic lesions: Freckles, lentigines, lentigo, melanoma, Peutz-Jeghers syndrome, Addison disease
- Varices
- Kaposi sarcoma: Red or purple macules that enlarge to form tumors; seen in patients with AIDS

RAISED LESIONS:

- Papilloma
- Verruca vulgaris
- Condyloma acuminatum
- Fibroma
- Epulis
- Pyogenic granuloma
- Mucocele
- Retention cyst

BLISTERS:

- Primary herpetic gingivostomatitis (Fig. E3)
  1. Caused by herpes simplex virus type 1 or, less frequently, type 2
  2. Typical course of herpetic gingivostomatitis: Day 1: Malaise, fever, headache, sore throat, cervical lymphadenopathy; days 2 and 3: appearance of vesicles that develop into painful ulcers of 2 to 4 mm in diameter; duration of up to 2 wk
  3. Recurrent intraoral herpes: Rare; recurrences typically involve only the keratinized epithelium (lips). Table E1 summarizes distinctions between aphthous and herpetic oral ulcers
- Pemphigus and pemphigoid
- Hand-foot-mouth disease: Caused by coxsackievirus group A
- Erythema multiforme
- Herpangina: Caused by echovirus
- Traumatic ulcer
- Primary syphilis
- Perlèche (or angular cheilitis)
- Recurrent aphthous stomatitis (canker sores): Most common oral mucosa lesion; may be associated with many systemic diseases
- Behçet syndrome (aphthous ulcers, uveitis, genital ulcerations, arthritis, and aseptic meningitis)
- Reiter syndrome (conjunctivitis, urethritis, and arthritis with occasional oral ulcerations)
  1. Unknown cause
  2. Solitary or multiple painful ulcers may develop simultaneously and heal over 10 to 14 days. The size of the lesions and the frequency of recurrences are variable.

FIG. E1 Oral mucositis caused by radiation therapy. (From Keefe ZDM, Logan R: Oral complications of cancer and its treatment. In Walsh TD et al [eds]: *Palliative medicine,* Philadelphia, 2008, WB Saunders.)

FIG. E2 Stomatitis and mucositis. A, Marked stomatitis in a patient receiving methotrexate. **B,** Aphthous stomatitis related to severe granulocytopenia after chemotherapy. The ulcers may be due to herpes simplex or other infection. **C,** Mucositis in a patient receiving combination chemotherapy for head and neck cancer. **D,** Marked ulcer of the tongue in a 32-yr-old man receiving induction chemotherapy for acute leukemia. **E,** Mucositis of the tongue due to *Monilia* infection (thrush) in a patient receiving corticosteroids for brain metastases. **F,** Marked oral mucositis due to mixed infection in a patient receiving chemotherapy for acute leukemia. (From Skarin AT: *Atlas of diagnostic oncology,* 4 ed, St Louis, 2010, Mosby.)

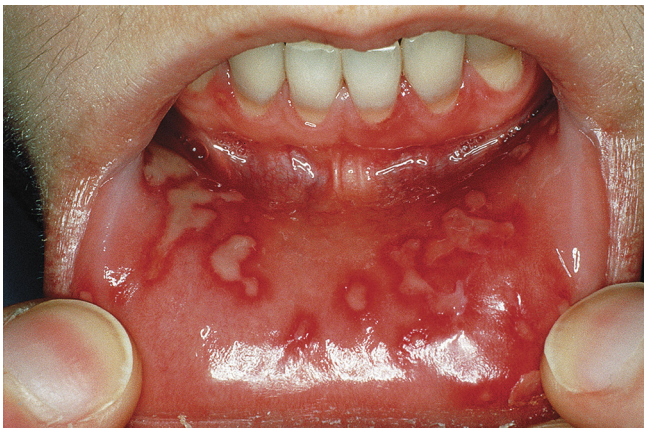

FIG. E3 Herpetic gingivostomatitis, extensive erosions of the oral mucosa. (James WD et al: *Andrews' diseases of the skin*, ed 12, Philadelphia, 2016, WB Saunders.)

TABLE E1 Distinctions between Aphthous and Herpetic Oral Ulcers

Condition	Mucosa	Location
Aphthous ulcers	Unkeratinized	Lateral tongue, floor of the mouth, labial and buccal mucosa, soft palate, pharynx
Herpetic ulcers	Keratinized	Gingiva, hard palate, dorsal tongue

From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

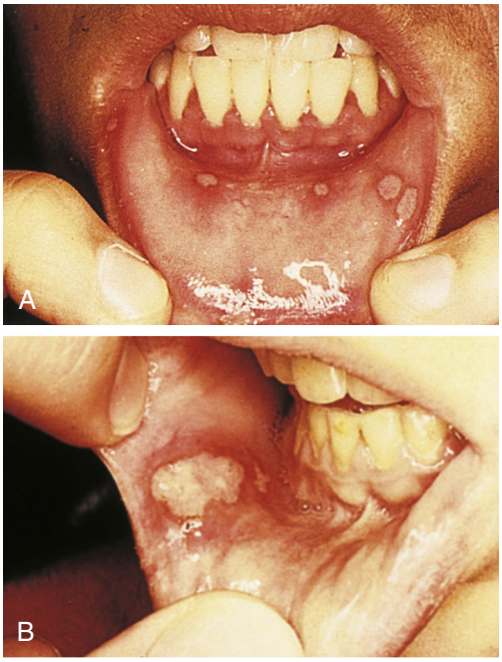

FIG. E4 A, Multiple minor aphthous ulcers. **B,** A major aphthous ulcer. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

DIAGNOSIS

WORKUP

- White lesions: Candidiasis (thrush) diagnosis—ovoid yeast and hyphae seen in scrapings treated with KOH culture
- Blisters:
  1. Exfoliative cytology
  2. Viral culture
  3. Immunofluorescence for herpes antigen

TREATMENT

White lesions: Candidiasis (thrush) treatment:
- Topical with nystatin or clotrimazole
- Systemic with ketoconazole or fluconazole

Blisters:
- Supportive
- Consider acyclovir

Recurrent intraoral herpes/aphthous ulcerations (Fig. E4): Topical corticosteroids (dexamethasone ointment applied to the identified ulcer tid) or systemic steroids for severe cases.

RELATED CONTENT

Stomatitis (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

Strabismus PTG

BASIC INFORMATION

DEFINITION

Strabismus is a condition of the eyes in which the visual axes of the eyes are not aligned. The misalignment may be constant or intermittent, and it may vary depending on the gaze direction (comitant or incomitant).

SYNONYMS

Esotropia
Exotropia
Heterotropia
Hypertropia
Hypotropia
Restrictive eye movement
Crossed eyes
Walleye
Squint
Lazy eye
Floating eye

ICD-10CM CODES

H50.0	Convergent concomitant strabismus
H50.1	Divergent concomitant strabismus
H50.2	Vertical strabismus
H50.3	Intermittent heterotropia
H50.4	Other and unspecified heterotropia
H50.5	Heterophoria
H50.6	Mechanical strabismus
H50.8	Other specified strabismus
H50.9	Strabismus, unspecified
H51.9	Unspecified disorder of binocular movement

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 2% of the population
PEAK INCIDENCE: Childhood
PREDOMINANT SEX: None
PREDOMINANT AGE: Variable depending on type, but more common in childhood
GENETICS: Most childhood forms suggest polygenic inheritance patterns with variable penetrance, although certain types (i.e., accommodative esotropia, intermittent exotropia) show a definite hereditary predisposition.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Conjugate gaze loss with the eyes fixing independently
- Diplopia in acquired adult-onset strabismus
- Decreased range of eye movements in paralytic and restrictive forms
- Compensatory head posture
- Amblyopia (a decrease in best-corrected visual acuity in an otherwise structurally healthy eye) may occur with untreated strabismus with a childhood onset

ETIOLOGY

- Often obscure in childhood strabismus.
- Many cases of esotropia are infantile, or present in first yr of life
- Accommodative esotropia occurs later, with the peak incidence between 2 and 4 yr of age
- Higher risk with neurologic disease, vision loss, or severe refractive errors
- Orbital or ocular trauma and/or surgery
- Thyroid disorders or other orbital inflammatory disease

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Evaluation of eye position and movement
- Vision testing
- Refractive errors
- Central nervous system (CNS) tumors
- Orbital tumors
- Brain and CNS dysfunction
- Thyroid disease
- Myasthenia gravis

WORKUP

- Eye examination: Fig. E1 illustrates diagnostic tests that help differentiate between common causes of strabismus. Strabismus is classified according to the type and magnitude of misalignment. Esotropia refers to an inward deviation of the nonfixing eye and exotropia to the outward deviation of the nonfixing eye. Hypertropia is a vertical deviation in which the nonfixing eye is higher, and hypotropia is a vertical deviation in which the nonfixing eye is lower.
- Measurement of deviation: The Hirschberg test (Fig. E2) gives a rough estimate of the angle of a manifest strabismus and is especially useful in young or uncooperative patients or when fixation in the deviating eye is poor.
- Visual field testing.
- MRI or CT to rule out tumors or other intracranial pathology in paralytic strabismus.
- Thyroid function tests in acquired restrictive strabismus.
- Myasthenia gravis workup in acquired, unstable strabismus.

LABORATORY TESTS

- Generally not needed, except in suspected myasthenia gravis where blood testing for acetylcholine receptor antibodies may be helpful, or thyroid function tests in suspected thyroid related eye disease.
- Single-fiber EMG in suspected myasthenia gravis.

IMAGING STUDIES

Necessary only if other neurologic findings are found.

TREATMENT

THERAPY

- Glasses
- Surgery
- Prisms
- Occlusion to relieve diplopia
- Orthoptic exercises
- Botulinum toxin
- Pharmacologic treatment, i.e., pyridostigmine in myasthenia gravis–induced strabismus

CHRONIC Rx

- Glasses
- Prisms
- Ocular occluding devices for intractable diplopia caused by strabismus
- Botulinum toxin

DISPOSITION

Glasses, prisms, and/or surgery may reestablish normal or improved ocular alignment and recover binocular single vision.

REFERRAL

- Early for full evaluation and rehabilitation of functional and cosmetic ocular alignment
- To an ophthalmologist for management (usually)

RELATED CONTENT

Strabismus (Patient Information)

AUTHORS: **David Robbins Tien, MD,** and **Alexandra Meyer Tien, MD**

FIG. E1 Diagnostic tests that help differentiate between common causes of strabismus. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 23, Philadelphia, 2008, WB Saunders.)

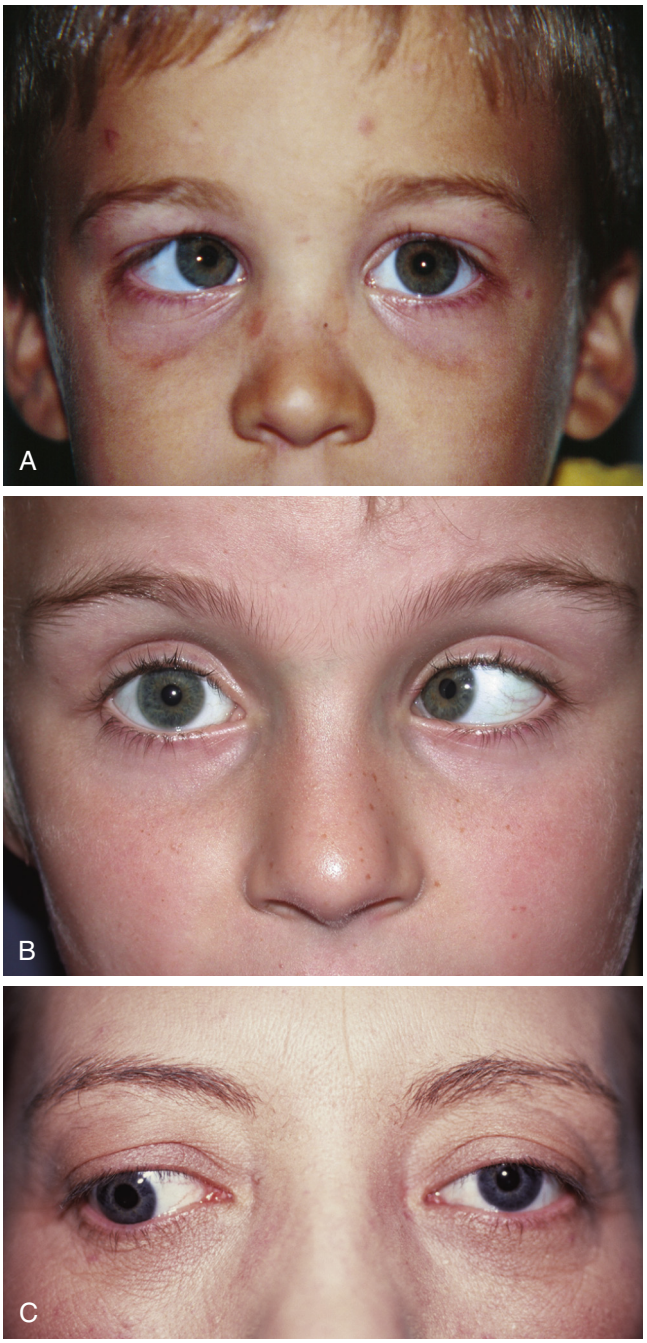

FIG. E2 Hirschberg test. A, The right corneal reflex is near the temporal border of the pupil, indicating an angle of about 15 degrees. **B,** The left corneal reflex is at the limbus, indicating an angle of about 45 degrees. **C,** The right corneal reflex is at the limbus in a divergent squint. (**A,** Courtesy J. Yanguela. From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, WB Saunders.)

BASIC INFORMATION

DEFINITION

Ischemic stroke is the sudden onset of a focal neurologic deficit as a result of cerebral ischemia resulting in cell death. The purpose of this chapter is to help the provider make decisions about the management of the acute stroke patient within the first several hours of symptoms; this is the crucial time for definitive treatment interventions.

SYNONYMS

Stroke
Brain attack
Cerebrovascular accident (this is a nonspecific term and should not be used)

ICD-10CM CODES

I63	Cerebral infarction
I63.3	Cerebral infarction due to thrombosis of cerebral arteries
I63.4	Cerebral infarction due to embolism of cerebral arteries
I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I63.8	Other cerebral infarction
I63.9	Cerebral infarction, unspecified
I67.89	Other cerebrovascular disease

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- ~795,000 new or recurrent strokes occur each yr in the U.S.
- Stroke is the number five cause of death (165,000 deaths every yr) and the leading cause of long-term disability in the U.S.

PREVALENCE: There are ~4.5 million stroke survivors in the U.S.

RISK FACTORS: Hypertension, dyslipidemia, diabetes mellitus, and smoking are the four major modifiable risk factors. Other risk factors include age, gender, atrial fibrillation (most common cause of cardioembolic stroke), mechanical heart valve, patent foramen ovale, recent myocardial infarction, metabolic syndrome, carotid artery stenosis, vertebral artery stenosis, intracranial artery stenosis, hypercoagulable states, subclinical atrial tachyarrhythmias without clinical atrial fibrillation, sickle cell disease, and obesity.

GENETICS: Multifactorial

PHYSICAL FINDINGS & CLINICAL PRESENTATION

When a patient presents with an acute ischemic stroke acutely, the most important considerations are determination of the time the patient was last known normal, the etiology (ischemic or hemorrhagic), and the severity, because these aspects will determine acute treatment. The time last known normal was when the patient was last seen normal (by themselves or by someone else). If they awoke with the deficits, the time last seen normal was when they went to bed.

Clinical presentation varies with the artery and region of CNS affected. Clinical presentation cannot reliably distinguish between hemorrhagic and ischemic causes, and so imaging must be done. Below is a noncomprehensive list of common stroke syndrome presentations based on the cerebral vascular territory affected. Please note that this list is not comprehensive and that all findings for a particular syndrome may not be listed here.

- Large- to medium-sized arteries:
  1. Dominant middle cerebral artery (MCA): Dominant face and arm > leg weakness and sensory loss with aphasia (expressive, receptive, or both); possible hemianopia
  2. Nondominant MCA: Nondominant face and arm > leg weakness and sensory loss with hemineglect; possible hemianopia
  3. Anterior cerebral artery (ACA): Contralateral leg weakness and sensory loss
  4. Internal carotid artery: Combination of contralateral MCA and ACA
  5. Basilar artery: Typically an acute loss of consciousness preceded by vertigo, nausea, vomiting, and diplopia; quadriparesis or quadriplegia may be seen, including "locked-in" syndrome
  6. Posterior cerebral artery: Unilateral hemianopia; blindness with anosognosia (Anton syndrome) if bilateral
  7. Posterior inferior cerebellar artery: Lateral medullary (Wallenberg) syndrome—ipsilesional loss of pinprick and temperature on the face and contralateral loss of pinprick and temperature on the body; ipsilesional Horner syndrome and ipsilesional palatal weakness with resulting dysphagia, dysarthria. Also with vertigo, nystagmus, ataxia.
- Small arteries: Lacunar syndromes; no cortical signs are present in lacunar syndromes.
  1. Pure motor hemiparesis: Typically due to an ischemic lesion in either the internal capsule or pons.
  2. Pure hemisensory loss: Typically due to an ischemic lesion of the thalamus.
  3. Ataxic hemiparesis: Ataxia out of proportion to the hemiparesis; typically due to an ischemic lesion of either the internal capsule or pons.
  4. Sensorimotor stroke: Typically due to ischemic lesion involving both the thalamus and internal capsule.
  5. Dysarthria–clumsy hand syndrome: Multiple localizations possible but typically the pons; facial weakness, dysarthria, and mild clumsiness and weakness of the hand.

ETIOLOGY

Etiologies include atherosclerosis, cardioembolism, artery-to-artery embolism, small-vessel lipohyalinosis, arteritis, arterial dissection, and vasospasm.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute ischemic stroke includes hemorrhagic stroke (intracerebral hemorrhage), subarachnoid or subdural hemorrhage, seizure with postictal paralysis, migraine with hemiparesis or other aura, syncope, hypoglycemia, hypertensive encephalopathy, and conversion disorder.

BOX 1 Immediate Diagnostic Studies: Evaluation of a Patient with Suspected Acute Ischemic Stroke

All Patients
Noncontrast brain computed tomographic scan (magnetic resonance imaging, if available)
Blood glucose level
Serum electrolyte and renal function tests
Electrocardiography
Markers of cardiac ischemia
Complete blood count, including platelet count
Prothrombin time/international normalized ratio
Activated partial thromboplastin time
Oxygen saturation

Selected Patients
CT angiogram head and neck or MR angiogram head and neck
CT or MR perfusion
Hepatic function tests
Toxicology screen
Blood alcohol level
Pregnancy test
Arterial blood gas tests (if hypoxia is suspected)
Chest radiography (if lung disease is suspected)
Lumbar puncture (if subarachnoid hemorrhage is suspected and computed tomography scan is negative for blood)
Electroencephalogram (if seizures are suspected)

CT, Computed tomography; *MR,* magnetic resonance.
From Christensen H et al: Abnormalities on ECG and telemetry predict stroke outcome at 3 months, *J Neurol Sci* 234:99-103, 2005.

TABLE 1 National Institutes of Health Stroke Scale

1A. Level of Consciousness (LOC)	1B. LOC Questions	1C. LOC Commands
0 = Alert 1 = Not alert, but arousable 2 = Not alert, obtunded 3 = Coma	Ask the month and his/her age. 0 = Answers both correctly 1 = Answers one correctly 2 = Answers neither correctly	Open and close the eyes. Open and close the nonparetic hand. 0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly
2. Best Gaze (Horizontal)	**3. Visual Fields**	**4. Facial Palsy**
0 = Normal 1 = Partial gaze palsy 2 = Forced deviation or total gaze paresis	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia	0 = Normal 1 = Minor paralysis 2 = Partial paralysis (total or near total paralysis of lower face) 3 = Complete paralysis of upper and lower face
5. Motor Arm	**6. Motor Leg**	**7. Limb Ataxia**
Right Arm extended with palms down 90 degrees (if sitting) or 45 degrees (if supine) for 10 s 0 = No drift 1 = Drift; limb drifts down from position and does not hit bed or support in 10 s 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement **Left**	**Right** Leg extended at 30 degrees, always tested supine for 5 s 0 = No drift 1 = Drift; limb drifts down from position and does not hit bed or support in 5 s 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement **Left**	The finger-nose-finger and heel-shin tests 0 = Absent 1 = Present in one limb 2 = Present in two limbs
8. Sensory	**9. Best Language**	**10. Dysarthria**
To Pinprick or Noxious Stimuli 0 = Normal 1 = Mild to moderate sensory loss 2 = Severe to total sensory loss	0 = No aphasia, normal 1 = Mild-to-moderate aphasia 2 = Severe aphasia 3 = Mute, global aphasia, coma	0 = Normal 1 = Mild-to-moderate 2 = Severe (including mute/anarthric due to aphasia) Do not score if intubated.
11. Extinction and Inattention	**Total Score:**	
0 = No abnormality 1 = Present 2 = Profound (two modalities)		

From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

LABORATORY TESTS

- Immediate (Box 1): Complete blood count, metabolic panel that includes blood glucose and renal function, PT/INR, aPTT, troponin I, and urinalysis. Blood glucose is the only test required before initiation of IV tPA
- National Institutes of Health Stroke Scale (Table 1): A brief, focused neurologic examination aimed at providing a numeric estimate of the severity of stroke; can be performed by any health care provider trained in its use; may increase the likelihood of the correct assessment of stroke
- ECG and telemetry monitoring
- Echocardiogram to look for potential cardiogenic source of embolism, infective endocarditis, and intracardiac shunts

IMAGING STUDIES

- Immediate (Fig. 1): Computed tomography (CT) of the head without contrast to rule out hemorrhage.
- CT angiogram of the head and neck is necessary acutely in selected patients if deficits are severe to assess whether there is a thrombus that is amenable to intervention as well as CT head perfusion to assess for the degree of salvageable tissue (Table 2).
- MRI of the brain with stroke protocol to assess the extent of stroke (because CT typically will not show an ischemic stroke for several hours), but it is rarely needed in the hyperacute setting to determine appropriateness of reperfusion strategy.

Cross reference: See "Transient Ischemic Attack" for general workup, which is identical to that for ischemic stroke.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

GENERAL CONSIDERATIONS:

- Airway and breathing should be maintained.
- Supplemental oxygen should be provided to keep the oxygen saturation at ≥92%.
- Pneumatic compression devices or pharmacologic means should be applied to help prevent deep venous thrombosis.
- Avoid any and all oral intake until swallowing is evaluated and found to be unimpaired; this helps to avoid aspiration pneumonia.
- Early mobilization for rehabilitation is desirable.
- Consider neurosurgical intervention for craniectomy in select cases. Typical cases in which craniectomy may be performed include cerebellar ischemia with compression of the brain stem and/or the fourth ventricle as well as large middle cerebral artery ischemia. Available evidence suggests that it may be better to perform early hemicraniectomy (<48 hr) to achieve better outcomes in malignant hemispheric strokes. Decompressive hemicraniectomy has shown good benefit in terms of mortality but not much benefit in terms of disability and functional outcomes.

ACUTE GENERAL Rx

INTRAVENOUS THROMBOLYSIS:

- IV t-PA, or alteplase, is the only medical therapy approved by the U.S. FDA for the treatment of acute ischemic stroke.
- The time window for administration is generally accepted to be within 4.5 hours of symptom onset, although the FDA indication is still within 3 hours. The American Heart Association/American Stroke Association recommends a t-PA administration window of up to 4.5 hours with certain additional exclusion criteria when compared to the 3-hour administration.
- There are strict criteria for the administration of IV t-PA (see Table 3).
- The protocol is weight based, with 90 mg being the maximum allowable dose.
- The risk of brain hemorrhage with IV t-PA is about 6% in stroke patients. The management of suspected intracranial hemorrhage after use of t-PA is summarized in Box 2.
- Endovascular intervention is useful only for large, accessible thrombi. Therefore if a stroke patient is a candidate for IV t-PA, treatment with IV t-PA should be started and then the patient should be assessed for possible endovascular therapy. Table 4 summarizes AHA recommendations for endovascular therapy in patients with acute ischemic stroke.

IMMEDIATE CATHETER CEREBRAL ANGIOGRAPHY FOR ENDOVASCULAR INTERVENTION

(Figs. E2 and E3): Methods available:

- The American Heart Association/American Stroke Association 2018 guidelines now recommend mechanical thrombectomy with a stent-retriever device for highly selected patients who present with large vessel occlusion (LVO) up to 16 hours after last known normal and suggest that it is reasonable up to 24 hours.
  1. IV tPA should be administered in this group if eligible.
  2. All patients should be assessed with CT angiogram head and neck or MRA head and neck for possible LVO if they have an NIHSS of ≥6 or suspicion of a large vessel stroke.
  3. In selected patients with acute ischemic stroke within 6 to 24 hours of last known normal who have LVO on noninvasive angiogram, obtaining a CT perfusion, DW-MRI, or perfusion is recommended

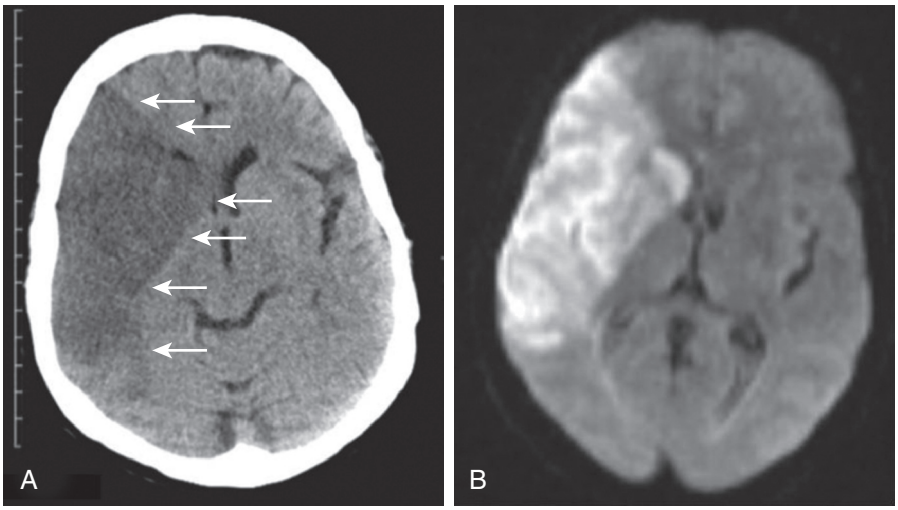

FIG. 1 Large right middle cerebral artery infarct on an unenhanced computed tomographic scan **(A)** and a diffusion-weighted magnetic resonance image **(B).** There is a mass effect, and this patient is at risk for cerebral herniation syndromes.

TABLE 2 Imaging Modalities for Stroke

Imaging Modality	Advantage	Disadvantage
Cerebral catheter angiography	• Allows for the definitive assessment of cerebral circulation (gold standard) • Allows for the deployment of intra-arterial thrombolysis and thrombectomy devices if a thrombus is found • Allows for the assessment of collateral circulation	• Invasive (significant risks) • High cost • Not available at all facilities
Doppler studies	• Noninvasive • May be performed at the patient's bedside	• Can be limited by the patient's body habitus • Operator dependent
Magnetic resonance angiography	• Excellent view of the large arteries of the neck and brain • No contrast material needed	• Cannot be performed in patients who are critically ill, who are unable to tolerate supine positioning, who have a pacemaker or other ferromagnetic hardware, or who are claustrophobic
Magnetic resonance perfusion	• Assesses cerebral hemodynamics • May show ischemic penumbra (i.e., the area of the brain that may be saved by timely intervention)	• Not commonly available • Not well standardized
CT angiography	• Excellent view of the large arteries of the neck and brain • Similar to magnetic resonance angiography with regard to resolution	• Requires intravenous contrast
CT perfusion	• Assesses cerebral hemodynamics • May show ischemic penumbra (i.e., the area of the brain that may be saved by timely intervention)	• Challenging to interpret in some cases • Not routinely available at many facilities • Requires intravenous contrast

CT, Computed tomography.

to aid in patient selection for mechanical thrombectomy.

- Adult patients should receive mechanical thrombectomy with a stent retriever if they present within 6 hours of last known normal with a causative LVO (especially of the internal carotid artery or MCA segment 1 [M1] but reasonable in the setting of a causative MCA segment 2 or 3 [M2/3] or other large vessel cerebral artery) if they were relatively independent before the stroke and have an NIHSS score of ≥6 and an ASPECTS score of ≥6. Treatment needs to be able to be initiated (groin puncture) within 6 hours of symptom onset.
- Patients should receive mechanical thrombectomy with a stent retriever if treatment can be initiated within 16 hours (and possibly up to 24 hours) of last known normal with a large anterior circulation LVO and they meet the DAWN or DEFUSE-3 criteria (a defined mismatch between clinical severity and/or infarct volume compared to the penumbra [tissue at risk]). The number needed to treat to improve functional outcomes is only 2.8, and so patients should be aggressively evaluated for possible treatment.
- Complications can ensue from the endovascular procedure itself, including an intracerebral hemorrhage rate that is similar to that associated with IV t-PA. A recent meta-analysis revealed that among patients with acute ischemic stroke, endovascular therapy with mechanical thrombectomy versus standard medical care with t-PA was associated with improved functional outcomes and higher rates of angiographic revascularization, but no significant difference in symptomatic intracranial hemorrhage or all-cause mortality at 90 days.[1,2]
- Endovascular intervention is typically available only at comprehensive stroke centers.

HYPERTENSION: Elevated blood pressure is common during acute stroke, and it often subsides without specific therapy. In general, hypertension is not treated acutely unless it is extremely high (e.g., >220 mm Hg systolic blood pressure); there is evidence of hypertension-induced organ damage; or thrombolysis is being considered, in which case the blood pressure needs to be reduced (if it can be safely accomplished) to <185/110 mm Hg. It is risky to decrease blood pressure dramatically and quickly in the presence of acute ischemic stroke as it can cause an extension of the infarcted tissue into the ischemic penumbra. A 15% to 25% decrease over the first 24 hours is recommended when more acute lowering is not required.

HYPOTENSION: The presence of systemic hypotension in acute ischemic stroke portends a poor outcome. The cause should be sought, and volume depletion should be corrected with normal saline. Cardiac arrhythmias should be treated. Induced hypertension with vasopressor agents may be useful for select cases with an ischemic penumbra that is at risk, but caution is strongly advised.

HYPOGLYCEMIA: Hypoglycemia can mimic stroke. Prompt assessment of serum glucose level and replacement as necessary are important.

HYPERGLYCEMIA: Hyperglycemia should be treated with sliding scale insulin, taking into consideration the patient's oral intake. The presence of hyperglycemia worsens ischemic stroke outcomes, but recent evidence has not shown that aggressive treatment with an insulin pump improves outcomes.

FEVER: Fever is harmful during acute stroke. Ascertaining and addressing the cause while lowering an elevated temperature is strongly advised.

[1]Only test recommended before initiation of IV rtPA.
[2]Although it is desirable to know the results of these tests before giving a patient tissue plasminogen activator, thrombolytic therapy should not be delayed while awaiting the results unless (1) there is clinical suspicion of a bleeding abnormality or thrombocytopenia; (2) the patient has received heparin or warfarin; or (3) the patient's use of anticoagulants is not known.

TABLE 3 Eligibility Criteria for Acute Thrombolysis in Acute Ischemic Stroke

Eligibility Criteria

- Diagnosis of ischemic stroke causing measurable neurological deficit
- The neurological signs should not be minor and isolated. Caution should be exercised in treating a patient with major deficits
- Onset of symptoms <4.5 hours before beginning treatment
- The neurologic signs should not be clearing spontaneously
- The symptoms of stroke should not be suggestive of subarachnoid hemorrhage
- The patient or family members should understand the potential risks and benefits from treatment

Contraindications for Thrombolysis

- Evidence of intracranial hemorrhage on CT
- Head trauma or prior stroke in previous 3 months
- Myocardial infarction in the previous 3 months
- Gastrointestinal or urinary tract hemorrhage in previous 21 days
- Arterial puncture at a noncompressible site in the previous 7 days
- Major surgery in the previous 14 days
- History of previous intracranial hemorrhage
- Elevated blood pressure (systolic >185 mm Hg and diastolic >110 mm Hg)
- Evidence of active bleeding or acute trauma (fracture) on examination
- Taking an oral anticoagulant or, if taking anticoagulant, INR ≥1.7 is a contraindication
- If receiving heparin in previous 48 hours, aPTT must be in normal range
- Platelet count ≤100,000 mm^3
- Blood glucose concentration ≥50 mg/dl (2.7 mmol/L)
- Seizure with postictal residual neurologic impairments
- CT shows a multilobar infarction (hypodensity >1/3 cerebral hemisphere)

aPTT, Activated partial thromboplastin time; *CT,* computed tomography; *INR,* international normalized ratio.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

BOX 2 Management of Suspected Intracerebral Hemorrhage after Use of Tissue Plasminogen Activator

Discontinue the tPA infusion if it remains in progress.
Obtain noncontrast CT scan of the head stat.
Order PT, PTT, platelet count, fibrinogen level, type and cross-match stat.
In event of hemorrhage, consult hematology and neurosurgery.
Give 6 to 8 units of cryoprecipitate, then 6 to 8 units of platelets.
Administer aminocaproic acid 4 to 5 gm IV over 1 hour, followed by 1 gm PO or IV per hour.
Check fibrinogen every 4 hours and give cryoprecipitate to keep fibrinogen >150 mg/dl.
Monitor blood pressure every 15 min.
Periodically repeat CBC, PT, PTT.
Consider repeat head CT.

CBC, Complete blood cell count; *CT,* computed tomography; *IV,* intravenous; *PO,* oral; *PT,* prothrombin time; *PTT*, partial thromboplastin time; *stat,* immediately; *tPA,* tissue plasminogen activator.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

TABLE 4 AHA Recommendations for Endovascular Therapy in Patients with Acute Ischemic Stroke

Patients should receive endovascular therapy with a stent retriever if they meet all of the following criteria (class I; level of evidence, A):

1. Prestroke modified Rankin score 0 to 1 (functionally independent)
2. Acute ischemic stroke receiving intravenous recombinant tissue plasminogen activator within 4.5 hours of onset according to guidelines from professional medical societies
3. Causative occlusion of the internal carotid artery or proximal middle cerebral artery
4. Age 18 years or older
5. National Institutes of Health Stroke Scale (NIHSS) score of 6 or greater
6. Alberta Stroke Program Early CT Score (ASPECTS) of 6 or greater
7. Treatment can be initiated (groin puncture) within 6 hours of symptom onset

CT, Computed tomography.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

ANTIPLATELET THERAPY: Oral, rectal, or feeding tube administration of aspirin (325 mg/day) within 48 hours of stroke onset is advised to decrease the likelihood of a repeat ischemic stroke. Other oral antiplatelet regimens approved for secondary stroke prophylaxis (e.g., clopidogrel, aspirin plus extended-release dipyridamole) may also be used. Patients who have received t-PA cannot be given antithrombotic or anticoagulant agents within the first 24 hr after administration. In patients with acute ischemic stroke and atrial fibrillation, full dose anticoagulation with heparin infusion or low molecular weight heparin should be avoided in the acute setting, as this could potentially harm the patient by causing symptomatic intracranial hemorrhage, and there is very little evidence to suggest any benefit. However, chronic anticoagulation is indicated after the acute period has passed.

DISPOSITION

Patients with acute ischemic stroke should be cared for in a stroke unit or an intensive care unit. Nurses with skills in stroke care and telemetry monitoring should be routine. Once the patient is stable and the workup is complete, rehabilitation should be arranged.

REFERRAL

Patients with acute ischemic stroke should be transported to a hospital in which providers are skilled in stroke care. Depending on the severity and duration of symptoms, the patient may qualify for immediate endovascular intervention at a comprehensive stroke center, even if he or she is not a candidate for IV tPA. If complications from brain edema develop, further evaluation by a neurosurgeon may be helpful during the acute phase.

PEARLS & CONSIDERATIONS

PREVENTION

- The prevention of acute ischemic stroke depends on the aggressive management of risk factors in individual patients.
- Cross reference: Stroke, secondary prevention.
- Paroxysmal atrial fibrillation is common in patients with cryptogenic stroke. A recent study found that noninvasive ambulatory ECG monitoring for 30 days significantly improved the detection of atrial fibrillation by a factor of >5 and nearly doubled the rate of anticoagulant treatment compared to the standard practice of short-duration ECG monitoring.

PATIENT & FAMILY EDUCATION

Patients and families need to be taught about ways to reduce the risk for recurrent stroke, including lifestyle modifications. Education about rehabilitation goals, when appropriate, should also be accomplished.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Stroke (Patient Information)
Stroke, Secondary Prevention (Related Key Topic)
Transient Ischemic Attack (Related Key Topic)
Atrial Fibrillation (Related Key Topic)

AUTHORS: **Corey Goldsmith, MD,** and **Prashanth Krishnamohan, MBBS, MD**

SUGGESTED READINGS

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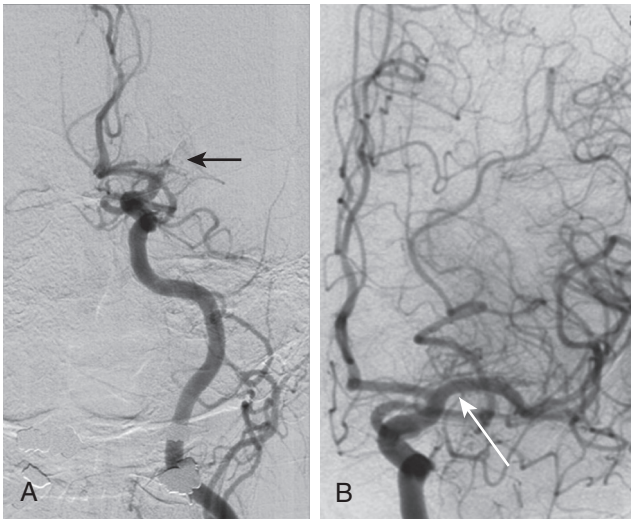

FIG. E2 A, A catheter angiogram showing left middle cerebral artery occlusion, which caused severe stroke symptoms for several hours. **B,** The artery was opened with the Merci clot retrieval system, and this resulted in normal flow.

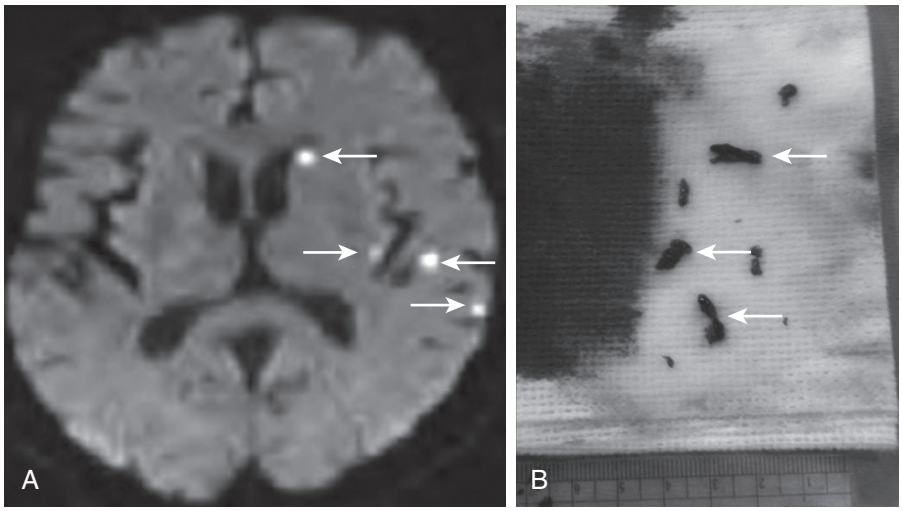

FIG. E3 **A,** A diffusion-weighted magnetic resonance image of the same patient as shown in previous figure, this time showing only mild left cerebral ischemia after intervention. The patient was clinically normal. **B,** Thrombi removed from the middle cerebral artery using the Merci clot retrieval system.

BASIC INFORMATION

DEFINITION

Hemorrhagic stroke is the sudden onset of a focal neurologic deficit caused by hemorrhage into or around the brain.

SYNONYMS

Intracerebral hemorrhage (ICH)
Intracranial hemorrhage
Cerebrovascular attack (this is a nonspecific term and should not be used)
The term *subarachnoid hemorrhage* refers to a specific location for hemorrhage, which commonly occurs as a result of a ruptured aneurysm. Please see "Subarachnoid Hemorrhage" for additional information.

ICD-10CM CODES

I61	Intracerebral hemorrhage
I61.0	Intracerebral hemorrhage in hemisphere, subcortical
I61.1	Intracerebral hemorrhage in hemisphere, cortical
I61.2	Intracerebral hemorrhage in hemisphere, unspecified
I61.3	Intracerebral hemorrhage in brainstem
I61.4	Intracerebral hemorrhage in cerebellum
I61.5	Intracerebral hemorrhage, intraventricular
I61.6	Intracerebral hemorrhage, multiple localized
I61.9	Nontraumatic intracerebral hemorrhage, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: There are approximately 795,000 new or recurrent strokes per yr in the U.S., of which approximately 10% are hemorrhagic.[1]

RISK FACTORS:

- Hypertension
- Anticoagulant use
- Thrombolysis
- Alcoholism
- Illicit drug use (e.g., cocaine)
- Cerebral amyloid angiopathy
- Increased age
- African American race
- Low cholesterol, low-density lipoprotein, and triglycerides
- Minuscule increase in absolute risk from antiplatelet therapy
- Questionable effect of chronic kidney disease and selective use of serotonin reuptake inhibitors

GENETICS: Multifactorial

[1]Chatterjee S et al: New oral anticoagulants and the risk of intracranial hemorrhage: traditional and Bayesian meta-analysis and mixed treatment comparison of randomized trials of new oral anticoagulants in atrial fibrillation, *JAMA Neurol* 70(12):1486-1490, 2013.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The presentation varies with the region of the brain that is affected. Table 1 summarizes correlation between levels of brain function and clinical signs. There is no clinical way to distinguish between a primary cerebral hemorrhage and an ischemic stroke; therefore imaging is required. Imaging can also help determine if the diagnosis is ischemic stroke with hemorrhagic conversion versus primary hemorrhage.

The following are common locations for hypertensive hemorrhage:

- Basal ganglia
- Cerebellum
- Pons

Lobar hemorrhage in an older adult is likely due to amyloid angiopathy.

A systematic, detailed examination is necessary when approaching a comatose patient (Box 1). The ICH score is a widely used grading scale to estimate mortality based on CT scan results. Parameters used to calculate the ICH score include Glasgow Coma Scale (GCS) (0 to 2 points) at presentation, patient age ≥80 (1 point), ICH volume ≥30 ml (1 point), presence of intraventricular blood (1 point), and infratentorial origin of blood (1 point). Scores range from 0 to 6, with a score of 0 conferring 0% mortality and a score of 6 with estimated 100% mortality.

ETIOLOGY

- Rupture of vessels
- Aneurysm
- Arteriovenous malformation
- Brain tumor
- Amyloid angiopathy

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ischemic stroke
- Seizure with postictal paralysis
- Syncope
- Migraine with hemiparesis
- Conversion disorder

LABORATORY TESTS

- Complete blood count, metabolic panel including blood glucose and renal function, prothrombin time/international normalized ratio, activated partial thromboplastin time, urinalysis, and toxicology screens
- ECG and telemetry monitoring

IMAGING STUDIES

- Immediate: CT scan of the head without contrast is highly sensitive for hemorrhage (Fig. 1).
- CT or MR angiogram to rule out an underlying vascular malformation. CT spot sign on the CTA has been shown to be a reliable early predictor of hematoma expansion.

TABLE 1 Correlation between Levels of Brain Function and Clinical Signs

Structure	Function	Clinical Sign
Cerebral cortex	Conscious behavior	Speech (including any sounds) Purposeful movement Spontaneous To command To pain
Brainstem activating and sensory pathways (reticular activating system)	Sleep-wake cycle	Eye opening Spontaneous To command To path
Brainstem motor pathways	Reflex limb movements	Flexor posturing (decorticate) Extensor posturing (decerebrate)
Midbrain CN III	Innervation of ciliary muscle and certain extraocular muscles	Pupillary reactivity
Pontomesencephalic MLF	Connects pontine gaze center with CN III nucleus	Internuclear ophthalmoplegia
Upper pons		
CN V	Facial and corneal	Corneal reflex-sensory
CN VIII	Facial muscle innervation	Corneal reflex-motor response Blink Grimace
Lower pons		
CN VIII (vestibular portion) connects by brainstem pathways with CN III, IV, VI	Reflex eye movements	Doll's eyes Caloric responses
Pontomedullary junction pressure	Spontaneous breathing Maintained blood pressure	Breathing and blood pressure do not require mechanical or chemical support
Spinal cord	Primitive protective responses	Deep tendon reflexes Babinski response

CN, Cranial nerve; *MLF,* medial longitudinal fasciculus.
Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Elsevier.

BOX 1 Neurologic Profile: A Modified Glasgow Coma Scale

Verbal Response
Oriented speech
Confused conversation
Inappropriate speech
Incomprehensible speech
No speech

Eye Opening
Spontaneous
Response to verbal stimuli
Response to noxious stimuli
None

Motor Response
Obeys
Localizes
Withdraws (flexion)
Abnormal flexion
None

Pupillary Reaction
Present
Absent

Spontaneous Eye Movement
Orienting
Roving conjugate
Roving disconjugate
Miscellaneous abnormal movements
None

Oculocephalic Response
Normal (unpredictable)
Full
Minimal
None

Oculovestibular Response
Normal (nystagmus)
Tonic conjugate
Minimal or disconjugate
None

Deep Tendon Reflexes
Normal
Increased
Absent

From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Elsevier.

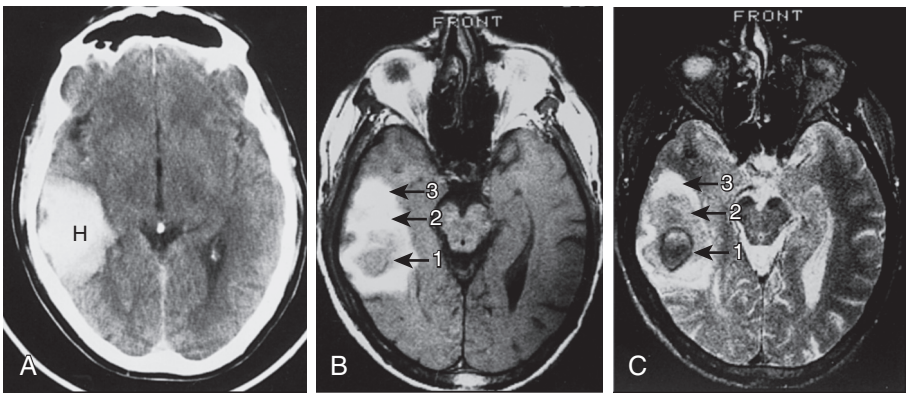

FIG. 1 Hemorrhage. Axial computed tomography image **(A)** demonstrates a large area of acute hemorrhage *(H)* in right temporal lobe. T1-weighted **(B)** and T2-weighted **(C)** magnetic resonance imaging scans demonstrate the hemorrhage in various stages of breakdown. Center of lesion is dark on T1- and T2-weighted images, indicating oxyhemoglobin *(1).* Intermediate zone is bright on T1-weighted image and gray on T2-weighted image, indicating intracellular methemoglobin *(2).* Outer rim is bright on both T1- and T2-weighted images, indicating extracellular methemoglobin *(3).* (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

- MRI of the brain with a gradient echo sequence is also highly sensitive for hemorrhage, including intracerebral microhemorrhages that may not be visible with computed tomography scanning. MRI may also help to identify underlying brain tumors or vascular malformations, especially if the bleeding occurs at atypical sites. In the acute setting the MRI may show only the hematoma, but repeat MRI approximately 6 weeks after initial hemorrhage may help exclude these other etiologies.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Urgent neurosurgical evaluation is needed in many cases either for evacuation of the hematoma or for relieving raised intracranial pressure by procedures such as EVD placement or decompressive surgeries.
- Surgery should be performed promptly for cases of cerebellar hemorrhage of >3 cm when the patient is deteriorating clinically, showing brain stem edema or hydrocephalus.
- Surgery for lobar or deep brain clots may be considered for select cases, although the level of evidence for efficacy is not high. Currently, guidelines recommend standard craniotomy for patients with lobar clots >30 ml within 1 cm of the cerebral cortex.
- Recent innovative surgical techniques, such as instillation of thrombolytic agents for intraventricular hemorrhage and minimally invasive surgery for hematoma evacuation, appear to be promising. Clinical trials are currently in progress to assess whether these approaches improve mortality and neurologic outcomes.

ACUTE GENERAL Rx

The cornerstones of medical management of acute intracerebral hemorrhage include:

- Control of hypertension
- Correction of coagulopathy
- Management of elevated intracranial pressure
- Treatment of seizures

HYPERTENSION (BOX 2): Blood pressure should be quickly lowered by 15% and then gradually and safely brought to the individual patient's target range. In theory, this may diminish the expansion of the hematoma. More aggressive control of systolic blood pressure (SBP) to 140 or less in the acute setting has been shown to be safe in clinical trials (INTERACT2 trial) with nonsignificant improvement in outcomes compared to less aggressive BP control (target SBP <180 mm Hg). ATACH 2 studied aggressive blood pressure lowering in patients randomized within 4.5 hr of symptom onset. Patients were randomized to aggressive blood pressure lowering to a target SBP of 110 to 139 mm Hg compared to standard blood pressure lowering to target SBP of 179 to 140 mm Hg. The trial was stopped early because there was no difference in neurological outcome or death, but patients in the aggressive blood pressure lowering arm suffered more kidney injury. Evidence suggests that a more sustained BP control with continuous IV medications might be more beneficial than using intermittent medications resulting in significant BP variability. The most recent guidelines, published in 2015, state that for ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe and can be effective for improving functional outcome. For ICH patients presenting with SBP >220 mm Hg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring.

CORRECTION OF COAGULOPATHY:

- Early hematoma expansion has been associated with poor outcome.
- Protamine sulfate is used to treat cases of heparin-induced intracerebral hemorrhage. Protamine dosage is 1 mg IV for every 100 units of heparin administered in the previous 2 to 3 hours (maximum dose is 50 mg).
- Prothrombin concentrate complex (PCC) is now recommended for reversal of warfarin-associated ICH. FFP may also be used for this purpose, although it carries the disadvantage of administering more volume, potentially leading to complications such as pulmonary edema and slightly longer times to reversal of coagulopathy compared to PCC. Vitamin K should be administered IV along with flash-frozen plasma (FFP)/PCC for sustained effects. Routine use of recombinant factor VII concentrates is not recommended due to insufficient evidence and concern for increased risk of thromboembolic events.
- Idarucizumab (Praxbind) is a humanized monoclonal antibody fragment that can be used for urgent reversal of the anticoagulant effect of the direct thrombin inhibitor dabigatran (Pradaxa).

BOX 2 Suggested Recommended Guidelines for the Treatment of Elevated Blood Pressure in Patients with Spontaneous Intracerebral Hemorrhage

1. SBP of >200 mm Hg or MAP of >150 mm Hg: Consider the aggressive reduction of BP with continuous intravenous infusion, with BP monitoring every 5 min.
2. SBP of >180 mm Hg or MAP of >130 mm Hg with evidence or suspicion of elevated ICP: Consider ICP monitor and reducing BP with intermittent or continuous intravenous medications to keep cerebral perfusion pressure >60 to 80 mm Hg.
3. SBP of >180 mm Hg or MAP of >130 mm Hg without evidence or suspicion of elevated ICP: Consider a modest reduction of BP (e.g., MAP of 110 mm Hg or target blood pressure of 160/90 mm Hg) with intermittent or continuous intravenous medications, and clinically reexamine the patient every 15 min.

BP, Blood pressure; *ICP,* intracranial pressure; *MAP,* mean arterial pressure; *SBP,* systolic blood pressure.
Modified from Broderick J et al: Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update, *Stroke* 38:2001-2023, 2007.

- Andexanet alfa, a recombinant modified human factor X2 decoy protein, has been effective for reversion of the anticoagulant effect of apixaban (Eliquis), rivaroxaban (Xarelto), and edoxaban (Savaysa).
- Recommendations for thrombolytic-associated intracerebral hemorrhage treatment include the consideration of the infusion of platelets and cryoprecipitate.
- Hemostatic therapy has not been shown convincingly to improve outcomes, despite reducing hematoma expansion. Efforts are under way to identify patients at high risk of early hematoma expansion by using clinical and radiographic information to determine who may benefit from more aggressive hemostatic intervention.
- Platelet transfusion for patients experiencing ICH while on aspirin appears to result in worse outcomes than no platelet transfusion according to the PATCH trial. The odds of death or dependence at 3 mo were significantly higher in the transfused group as compared to the nontransfused group.

ELEVATED INTRACRANIAL PRESSURE: This condition should be treated with a graded approach, which may include the elevation of the head of the bed, analgesia/sedation, hyperventilation, and osmotic therapy. In patients clinically suspected to have elevated ICP or with GCS <8, invasive monitoring of the ICP may be required. If conservative treatment fails to control ICP, external ventricular drain (EVD) placement or other decompressive procedures like craniotomy should be pursued.

SEIZURES: If seizures occur, they should be treated aggressively, including with intravenous medications, if needed. Although widely practiced, routine use of prophylactic antiepileptic medications is not recommended. Continuous EEG monitoring should be employed in patients with suspected seizures or unexplained low levels of consciousness.

SUPPORTIVE TREATMENT:

- Hyperglycemia: A high blood glucose level predicts a worse outcome. Markedly elevated glucose levels should be lowered to <200 mg/dl.
- Antipyretics should be administered for fever in addition to searching for a cause of the fever.
- Care should be taken to avoid hypoxia. Airway and ventilatory management should happen early and concurrently with the primary management of ICH.
- Pneumatic compression devices should be applied to help prevent deep venous thrombosis. Chemical deep venous thrombosis prophylaxis can be started after 48 to 72 hours in most situations once the bleed has been determined to be stable.
- Early mobilization for rehabilitation is desirable.

DISPOSITION

For large hemorrhages or unstable patients, immediate referral to a stroke center

REFERRAL

Patients with hemorrhagic stroke should be transported to a hospital where providers are skilled in the treatment of stroke and cerebrovascular diseases including the availability of neurosurgery services and neurocritical care. Depending on the severity and duration of symptoms, the patient may require neurosurgical intervention.

PEARLS & CONSIDERATIONS

- Outcomes are inversely correlated with hemorrhage size.
- Specific reversal agents may be useful for warfarin-, heparin-, direct oral anticoagulant- (DOAC), or thrombolysis-associated hemorrhage.
- No procoagulant medications have yet been shown to be safe and effective for the mitigation of spontaneous intracerebral hemorrhage in placebo-controlled trials.

PREVENTION

- Prevention depends on the aggressive management of risk factors in individual patients, including hypertension, smoking, alcohol use, and cocaine use.
- DOACs dabigatran, apixaban, rivaroxaban, and edoxaban are uniformly associated with an overall reduced risk of iatrogenic ICH when used for stroke prevention in atrial fibrillation when compared to warfarin. Any of the currently available DOACs can be considered first line for patients at high risk for ICH.

PATIENT & FAMILY EDUCATION

Patients and families need to understand that most patients will not soon achieve functional independence and that rehabilitation will be a long process. Education about avoiding antithrombotic agents should be stressed as appropriate for individual circumstances.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Stroke (Patient Information)

AUTHORS: **A. Basit Khan, MD, Corey Goldsmith, MD,** and **Prashanth Krishnamohan, MBBS, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Secondary prevention of stroke involves preventing the recurrence of a cerebral vascular ischemic or hemorrhagic stroke after a primary event (including transient ischemic attack) and early rehabilitation.

SYNONYMS

Brain attack
Stroke
Cerebral thrombosis
Cerebral hemorrhage
Brain infarct

ICD-10CM CODES

I65.2	Occlusion and stenosis of carotid artery
I65.0	Occlusion and stenosis of vertebral artery
I65.9	Occlusion and stenosis of unspecified precerebral artery
I66	Occlusion and stenosis of cerebral artery, not resulting in cerebral infarction
I65.1	Occlusion and stenosis of basilar artery

EPIDEMIOLOGY & DEMOGRAPHICS

Stroke is the fifth leading cause of death in the U.S. and the leading cause of disability. Each yr, there are a total of 795,000 strokes, of which 185,000 are recurrent strokes. Thus, secondary prevention of ischemic stroke remains good treatment strategy. Secondary prevention is specifically targeted toward modifiable risk factors.

RISK FACTORS: Age is the most important nonmodifiable risk factor. Modifiable risk factors include hypertension, hyperlipidemia, cigarette smoking, excessive alcohol consumption, physical inactivity, obesity (i.e., a body mass index of >25 kg/m^2), obstructive sleep apnea, illegal drug use (amphetamines, cocaine), and diabetes mellitus.

GENETICS: Multifactorial and strong family correlation if idiopathic strokes occur in parents <65 yr old.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Stroke can have a varied presentation. Typically, the individual has a sudden definable loss of motor, sensory, visual, or cognitive functions that have a clear time of onset and that are noticed by others or by the individuals themselves.
- Physical findings such as weakness and/or numbness in one limb or on one side of the body, facial droop, visual field loss, or the inability to understand or communicate with others raises one's suspicion of a stroke event.

ETIOLOGY

- Strokes are broadly divided into ischemic or hemorrhagic (i.e., intraparenchymal or subarachnoid hemorrhage). It is impossible to distinguish ischemic from hemorrhagic intracerebral hemorrhage by history alone; therefore imaging is required to confirm stroke subtype.
- Ischemic strokes can be caused by large-vessel atherosclerosis, cardioembolism due to atrial fibrillation or cardiomyopathy, or small vessel disease such as lacunar stroke. Rare causes such as recreational drug use (e.g., cocaine abuse); arterial dissection; and hypercoagulable states need to be considered when ischemic stroke occurs in younger individuals.
- The most common cause of intracerebral hemorrhage is uncontrolled hypertension. Older patients with lobar hemorrhages likely have amyloid angiopathy as the cause of their hemorrhagic stroke. Spontaneous rupture of a brain aneurysm causes subarachnoid hemorrhage.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Seizure and postictal states
- Brain tumor
- Complicated migraine
- Hypoglycemia
- Psychogenic disorder

WORKUP

- Blood glucose level, HBA1c
- Activated partial thromboplastin time, prothrombin time/international normalized ratio complete blood count, and comprehensive metabolic panel
- Fasting lipid panel
- Hypercoagulability tests for young stroke patients with no obvious risk factors

IMAGING STUDIES

- Computed tomography scanning of the head without contrast can differentiate between ischemic and hemorrhagic stroke. MRI of the brain is a more specific and prognostic study.
- Carotid ultrasound and transcranial Doppler are used to detect large-vessel extracranial carotid atherosclerosis but are not useful for visualizing the intracranial vasculature or the posterior circulation. Magnetic resonance angiography (MRA) and computed tomography angiography (CTA) of the head and neck provide imaging of the entire extracranial and intracranial vascular supplying both the anterior and posterior circulations. MRA can be performed without contrast, whereas CTA requires iodinated contrast and may be inappropriate for patients with renal dysfunction.
- Echocardiogram to look for structural abnormalities that could be the source of cardioembolism.
- Heart rhythm monitoring to detect atrial fibrillation. It is rare for an isolated ECG to detect paroxysmal atrial fibrillation that may be the source of the ischemic stroke or transient ischemic attack (TIA). It can even be missed under 24 hr of telemetry in many patients. If a high index of suspicion for a cardioembolic source exists, working with a cardiologist to place a monitoring device should be considered because many cases of paroxysmal atrial fibrillation require more prolonged monitoring for detection.

TREATMENT

The secondary prevention of stroke is targeted toward modifiable risk factors. These include lifestyle modifications such as appropriate diet, exercise, weight loss, and smoking cessation, avoidance of heavy alcohol use, and risk factor modification as listed in the following.

Antiplatelet or Anticoagulant Choice:

All patients with noncardioembolic ischemic stroke or TIA should be on aspirin (50 to 325 mg/day), a combination of aspirin and extended-release dipyridamole, or clopidogrel. Long-term treatment with a combination of clopidogrel and aspirin in secondary stroke prevention when no other pressing medical conditions require their use is no longer recommended due to increased mortality from intracerebral hemorrhage. In some circumstances, short-term treatment with the combination of clopidogrel and aspirin is reasonable in the first 30 to 90 days. Ticagrelor failed to show benefit for secondary stroke prevention compared with aspirin in general, though it may have an improved efficacy in intracranial stenosis. Prasugrel is contraindicated in patients with a history of stroke or TIA. If a patient is already on an antiplatelet drug at the time of stroke or TIA, then consideration of switching to another agent is reasonable, although a holistic approach that includes assessment of compliance with the antiplatelet agent and the extent other risk factors have been controlled is recommended.

PREVENTING STROKE IN SPECIFIC CONDITIONS

- Cardioembolic strokes as a result of nonvalvular atrial fibrillation (AF): All patients with an ischemic stroke secondary to nonvalvular atrial fibrillation would have a CHA2DS2-VASc score of >2, and therefore anticoagulation is recommended. Two first-line drug therapies can be recommended: direct oral anticoagulants (DOACs) such as apixaban, dabigatran, edoxaban, and rivaroxaban; and warfarin with an international normalized ratio (INR) between 2.0 and 3.0. DOACs have been shown to result in a lower rate of intracerebral hemorrhage. Although more expensive than warfarin, DOACs do not require monitoring, do not have the dietary issues associated with warfarin, and have fewer drug-drug interactions. However, patients on enzyme-inducing medications such as phenytoin or HIV patients on protease inhibitors cannot use DOACs. Warfarin is still preferred in patients with marked renal impairment (see specific information available from the FDA about renal impairment and dosing for each DOAC) and in patients with mechanical heart valves or valvular causes of atrial fibrillation. Reversible therapies for some of the DOACs have recently been made available. A patient on a DOAC experiencing a recurrent stroke should only receive tissue plasminogen activator (t-PA) if the patient has been off the medication for at least 48 hr. For patients on warfarin, an INR of less than 1.7 allows for administration of t-PA. There is no evidence that aspirin monotherapy is helpful in reducing cardioembolic events. The Active-A trial suggested that a combination of aspirin and clopidogrel is slightly better than aspirin alone for those unable to tolerate warfarin,

but patients on dual therapy experienced an increased risk of hemorrhagic complications. Because dual-antiplatelet therapy and DOACs have similar rates of bleeding complications but different levels of efficacy for prevention of cardioembolic stroke, the use of aspirin/clopidogrel dual therapy instead of a DOAC is almost never indicated. Furthermore, apixaban and aspirin monotherapies have been shown to have similar rates of bleeding. Thus, patients at risk of bleeding who previously were put on aspirin rather than warfarin could now be prescribed apixaban and experience the same bleeding risk but with actual benefit in terms of stroke risk reduction.

- Cardioembolic strokes as a result of a prosthetic metallic valve: Anticoagulant therapy with warfarin is recommended with a goal INR between 2.5 and 3.5.
- Strokes as a result of large-vessel extracranial atherosclerosis (i.e., symptomatic carotid stenosis): For patients with recent TIA or ischemic stroke and ipsilateral severe (70% to 99%) carotid artery stenosis, carotid endarterectomy (CEA) or carotid stenting is recommended, preferably within 14 days of the event if no contraindication. For patients with recent TIA or ischemic stroke and ipsilateral moderate (50% to 69%) carotid stenosis, intervention is recommended on a case-by-case basis only if the surgeon's perioperative morbidity and mortality rate is <6%.When the degree of stenosis is <50%, there is no indication for CEA. Carotid stenting can be an alternative to CEA in patients with low or average risk of periprocedural complications. In older patients (>70), CEA is associated with better outcomes.
- Symptomatic intracranial atherosclerosis (i.e., cavernous carotid stenosis, basilar stenosis): The symptomatic intracranial artery stenosis stenting trial (SAMMPRIS) demonstrated superiority of aggressive medical management of intracranial atherosclerosis compared with angioplasty and stenting for secondary stroke prevention. Therefore the use of aspirin plus clopidogrel 75 mg daily for 90 days is reasonable in addition to modifiable risk factor management, including high-intensity statin and SBP <140. There is no advantage to using warfarin over aspirin.
- Patent foramen ovale (PFO): The American Academy of Neurology's 2016 guidelines recommend medical therapy with antiplatelets for stroke patients with PFO though recent trials (CLOSE and REDUCE trials) suggest a benefit for PFO closure devices especially in the setting of an atrial septal aneurysm or large interatrial shunt.
- Intracerebral hemorrhage: For immediate management, please refer to the chapter on intracerebral hemorrhage. Anticoagulation or antiplatelet agents should be held for 3 to 4 weeks and can be restarted if there is a compelling indication such as nonvalvular atrial fibrillation. The American Stroke Association/American Heart Association 2014 guideline recommends avoiding long-term anticoagulation (e.g., warfarin, heparin) after spontaneous lobar intracerebral hemorrhage, but antiplatelet therapy (e.g., aspirin, clopidogrel, Aggrenox) may be considered in all cases of intracerebral hemorrhage where there is a definite indication. Consider a neurology consultation in these cases.
- Antiplatelet therapy is recommended in cases of cryptogenic strokes. A consultation with a neurologist should be considered for young stroke patients and for patients with no obvious cause or with stroke from unusual causes (e.g., hypercoagulable states, dissections).

PREVENTING LONG-TERM COMPLICATIONS AFTER A STROKE

- Evaluation by a physical, occupational, and speech therapist will reduce the long-term disability that can follow a stroke event. The American Stroke Association 2014 guideline recommends a multidisciplinary approach to rehabilitation. Studies have shown an improved survival and recovery. Home-based rehabilitation can be considered after discussion with the rehabilitation specialist.
- Depression rates are high after an ischemic stroke, and patients should be screened.

RISK FACTOR MODIFICATION

- Hypertension: Antihypertensive treatment is recommended for both the prevention of recurrent stroke and the prevention of other vascular events in persons who have had an ischemic stroke or a TIA. Absolute target blood pressure level and reduction should be individualized, but a target of <140/90 is reasonable. Blood pressure should be lowered gradually over the first several days after an ischemic stroke to prevent cerebral hypoperfusion and extension of stroke. After a hemorrhagic stroke, blood pressure should be lowered quickly. Lifestyle modifications as listed previously should be included as part of a comprehensive antihypertension treatment plan.
- Diabetes: Uncontrolled hyperglycemia can lead to acceleration of both intracranial and extracranial arteriosclerosis. The goal for the hemoglobin A_{1c} level should be <7%.
  1. In a recent trial involving patients with a history of ischemic stroke or TIA, the risk of stroke or MI was lower among patients who received pioglitazone than among those who received placebo. Pioglitazone was also associated with a lower risk of diabetes but with a higher risk of weight gain, edema, and fracture.
- Hyperlipidemia: For patients with ischemic stroke or TIA with elevated cholesterol levels, statin agents are recommended with a goal low-density lipoprotein <70 mg/dl. The SPARCL study demonstrated that, compared with patients taking placebo, patients taking atorvastatin 80 mg daily experienced a statistically significant reduction in the risk of experiencing a recurrent ischemic stroke.
- Cigarette smoking: Absolute cessation is required. Try to offer pharmacologic therapy or counseling services to the patient. Secondhand tobacco exposure is just as dangerous, so inquire about secondhand exposure.
- Obesity: Weight reduction may be considered for all overweight ischemic stroke and TIA patients to maintain the goal of a body mass index of between 18.5 and 24.9 kg/m^2 and a waist circumference of <35 in for women and <40 in for men.
- Excessive alcohol consumption: Patients with ischemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption of alcohol. Light to moderate levels of no more than two drinks per day for men and one drink per day for nonpregnant women may be considered.
- Obstructive sleep apnea: A sleep study should be considered due to high prevalence of obstructive sleep apnea in this population and improvement in outcomes.

DISPOSITION

Secondary stroke prevention is a multifaceted approach of lifestyle modification and pharmacologic intervention that is aimed at preventing or limiting disability.

REFERRAL

For complicated recurrent strokes, a referral to a neurologist who specializes in stroke is recommended.

PEARLS & CONSIDERATIONS

The modification of risk factors is the best preventive measure for stroke. Lifestyle modification is a very important aspect of secondary stroke prevention. Always consider the patient's ability to afford the therapy and prescribed follow-up tests. Experience teaches us that patients sometimes will not let us know about their ability to afford therapies unless we inquire.

PREVENTION

Prevention is the goal of treatment, and compliance is the most important factor. Review risk factor reduction and pharmacologic therapy as previously discussed.

PATIENT & FAMILY EDUCATION

More information can be obtained from the following sources:

- American Heart Association, National Center, 7272 Greenville Avenue, Dallas, TX 75231
- American Stroke Association, 1-888-4-STROKE or 1-888-478-7653
- H.O.P.E. for Stroke, 250 Duck Pond Drive, Wantagh, NY 11793, 516-804-8495

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Stroke (Patient Information)
Transient Ischemic Attack (Related Key Topic)

AUTHORS: **Joseph S. Kass, MD, JD, FAAN,** and **Corey Goldsmith, MD**

SUGGESTED READINGS

Furie KL: Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, *Stroke* 42:227-276, 2011.

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Sturge-Weber Syndrome

BASIC INFORMATION

DEFINITION

Sturge-Weber syndrome (SWS) is a sporadic congenital disorder characterized by a dermal capillary malformation (port-wine stain) occurring in association with vascular malformations of the leptomeninges and the eye.

Sturge first described a patient with epilepsy, a facial capillary malformation, and buphthalmos in 1879. Parkes Weber better characterized the pattern and distribution of the characteristic intracranial calcifications. The complete syndrome generally includes the triad of facial dermal capillary malformation (port-wine stain), ipsilateral central nervous system (CNS) vascular malformation (leptomeningeal angiomatosis), and vascular malformation of the choroid of the eye associated with glaucoma. Partial forms have been reported.

SYNONYMS

Sturge (-Weber) (-Dimitri) disease or syndrome
Encephalocutaneous angiomatosis
SWS

ICD-10CM CODE

Q85.8 Other phakomatoses, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

SWS is not a heritable disorder; thus, recurrence is unlikely.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

SWS is characterized by a facial angioma (port-wine stain) and an associated leptomeningeal angioma. These vascular malformations are associated with specific ocular and neurologic abnormalities.

CUTANEOUS MANIFESTATIONS:

- Cutaneous port-wine stain is the most common type of vascular malformation, occurring in 0.3% of newborns. However, only a small number of children with port-wine stains have SWS.
- In SWS, the port-wine stain typically is present on the forehead and upper eyelid (Fig. E1), primarily in the distribution of the first or second division of the trigeminal nerve. Extension of the skin lesion to both sides of the face and the trunk and extremities is common.
- The distribution of the cutaneous angioma influences the risk of an associated leptomeningeal angioma. Leptomeningeal angioma occurs in approximately 90% of cases when the port-wine stain involves both the upper and lower eyelids, compared with 10% when only one eyelid is affected.
- The skin lesion usually is obvious at birth. However, its appearance changes with age and its size increases as the patient grows. In the newborn, the lesion is flat and usually light pink in color. It typically darkens with age to a deep red, port-wine appearance and vascular ectasias develop. The vascular ectasias produce nodularity and superficial blebbing, which lead to overgrowth of the underlying soft tissues and sometimes the bone.
- It may extend to mucosal surfaces with concomitant gingival hypertrophy, which may be even further accentuated in patients being treated with phenytoin for seizures. Some patients exhibit accelerated eruption of teeth.

LEPTOMENINGEAL ANGIOMA:

- Leptomeningeal angioma occurs in 10% to 20% of cases when a typical facial lesion is present. The intracerebral lesion usually occurs on the same side as the port-wine stain. Leptomeningeal angiomatosis seldom occurs without an accompanying facial angioma.
- The parietal and occipital areas are affected most commonly, although any portion of the cerebrum can be involved.
- The pathologic appearance of the leptomeninges includes thickening and discoloration caused by the increased vascularity. The angiomatous tissue typically fills the subarachnoid space in the sulci, and large, tortuous venous structures drain superficially or into the deep venous system. The underlying parenchyma may be atrophic and contain multiple calcific granular deposits. The intraparenchymal calcification may result from chronic tissue hypoxia caused by venous stasis.

OCULAR MANIFESTATIONS:

- Ocular features of SWS include glaucoma and vascular malformations of the conjunctiva, episclera, choroid, and retina.
- The predominant ocular abnormality is glaucoma (increased intraocular pressure), which occurs in 30% to 70% of affected patients. The risk of glaucoma is highest in the first decade. Congenital glaucoma is seen in approximately one half of patients with SWS and presents in newborns with enlargement of the globe *(buphthalmos).* Patients occasionally develop glaucoma as adults. Thus, continued vigilance is needed, even in patients with initially normal intraocular pressure.
- Angioma of the choroid occurs in 30% to 40% of patients with SWS and can lead to increased intraocular pressure. These lesions may be diffuse or localized within the retina.
- Episcleral and conjunctival lesions include anomalous vessels or true angiomata. These may be caused by increased venous pressure in the eye.
- Weber originally noted heterochromia of the iris. The more deeply pigmented iris usually is ipsilateral to the facial angioma. The pigmentation is caused by aggregated melanocytic hamartomata on the anterior surface of the iris.

FIG. E1 A unilateral port-wine stain is present in this man with Sturge-Weber syndrome. (From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

NEUROLOGIC FEATURES:

- The neurologic features of SWS are progressive and include seizures, focal neurologic deficits, and mental retardation. These disorders occur with variable severity. A small proportion of patients have no neurologic abnormalities.
- The reasons for neurologic progression are uncertain. A possible mechanism is hypoxic-ischemic injury to tissue adjacent to the leptomeningeal angioma. Other proposed mechanisms are venous occlusion and increased venous pressure.

SEIZURES:

- Seizures occur in 80% of patients with SWS and are more common with bilateral than unilateral port-wine stains. Seizures may develop at any age, although they usually start in early childhood.
- Seizures are often the first symptom to appear. Initially, seizures are typically focal but often become generalized tonic clonic. Less often, infantile spasms or myoclonic or atonic seizures are seen. The occurrence of seizures, the age at onset, and the response to treatment affect prognosis. Onset before age 1 yr and poor response to anticonvulsant therapy are associated with a greater likelihood of cognitive impairment.
  1. Hemiparesis: Often develops acutely in conjunction with the onset of seizures. The deficit occurs contralateral to the facial and intracranial lesions. The affected extremity usually does not grow at a normal rate, resulting in hemiatrophy. Some affected children have progressive loss of motor function or have a series of strokelike events.
  2. Intellectual disability: Children with SWS typically develop normally for several months after birth, then manifest developmental delay. However, impairment can be obvious soon after birth, especially in infants with extensive brain involvement. Cognitive function is poorest in patients

with bilateral intracerebral lesions. In one report, only 8% of patients with bilateral leptomeningeal angiomata were intellectually normal.

3. Behavior problems: Are more common in SWS patients than in their unaffected siblings. Higher risk for psychological problems is associated with poorer cognitive function and frequent seizures. However, behavior problems can occur in patients with normal intelligence.
4. Other deficits: Many patients have visual field defects, typically homonymous hemianopia. This is from the involvement of the leptomeningeal angioma with one or both occipital lobes or optic tracts. Hydrocephalus also may occur. This disorder is believed to result from increased venous pressure caused by thrombosis of the deep venous channels or extensive arteriovenous anastomoses.

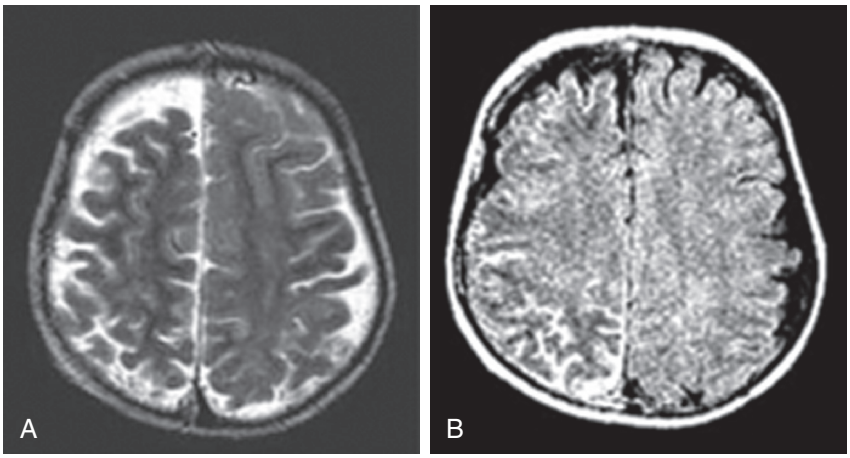

FIG. E2 Axial magnetic resonance image of child with Sturge-Weber syndrome demonstrating atrophy of the left hemisphere and contrast enhancement of the surface of the left hemisphere particularly prominent over the occipital lobe.

ETIOLOGY

The Sturge-Weber syndrome and port-wine stains are caused by a somatic activating mutation in *GNAQ*.[1]

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Klippel-Trenaunay-Weber syndrome (extensive capillary angiomata associated with dysplastic veins involving the limbs and trunk, often with hypertrophy of the affected extremity)
- Von Hippel-Lindau disease (associated with capillary retinal angiomata in contrast to cavernous angiomata seen in SWS)

WORKUP

SWS should be suspected in all patients with facial capillary malformations involving the trigeminal dermatome. At-risk infants should undergo careful physical examination to determine the extent of the malformation.

IMAGING STUDIES

- Most children with facial port-wine stains without an intracranial lesion would be expected to develop normally. Therefore performing neuroimaging studies is helpful to provide prognostic information.
- Plain radiographs of the skull may detect intracranial calcifications, revealing the classic "tram line" appearance, but calcifications are often not present before age 2 yr. Newer radiographic techniques have made plain films obsolete.
- The preferred technique is MRI with gadolinium contrast, which demonstrates the presence of the leptomeningeal angioma and the extent of involvement with brain structures (Fig. E2).
- If MRI is not readily available, cranial CT reliably identifies brain calcification and provides some anatomic information.
- In some cases leptomeningeal involvement may not be detected by neuroimaging during infancy and only becomes apparent later. There is no absolute way to exclude intracerebral lesions during the first yr after birth.

Rx TREATMENT

No specific treatment exists for SWS. The cutaneous, ocular, and neurologic manifestations are treated with mixed success.

ACUTE GENERAL & CHRONIC Rx

Port-wine stain:

- Port-wine stains can be treated by selective photothermolysis with a pulsed-dye laser. Treatment can be further optimized for individual patients so that blanching of the lesion can be accomplished in the fewest possible sessions.
- The response of facial port-wine stains to laser treatment depends on the location and size of the lesion and the patient's age. The greatest decrease in size occurs in the smallest lesions and in the youngest children (<1 yr). The greater success in the youngest patients may reflect treatment before the development of ectasias.
- Complications of laser therapy include scarring and transient hyperpigmentation. Retinal injury can occur if the eyes are not shielded properly.

Glaucoma:

- The development of new medications has improved the medical management of glaucoma in SWS. However, topical treatment often is ineffective in normalizing intraocular pressure. In these cases, the surgical treatment depends on the etiology of the glaucoma.

Seizures:

- Management of seizures in SWS often is difficult. The success of controlling seizures with anticonvulsant medication is variable and unpredictable. Carbamazepine is the recommended antiepileptic of choice. In refractory cases, hemispherectomy or more limited surgical resection of epileptogenic tissue may be beneficial, although risks often outweigh benefits.

REFERRAL

- Initial ophthalmologic evaluation should be performed in the neonatal period because of the risk of congenital glaucoma.
- If the first complete ophthalmologic evaluation is normal, it should be repeated frequently (some authors have suggested quarterly evaluations) for the first 2 yr of life.
- If the examination results remain normal, the vision should be reevaluated at least annually throughout the patient's lifetime.
- Periodic evaluation by a pediatric neurologist is an essential component of the management of SWS.

! PEARLS & CONSIDERATIONS

COMMENTS

- The prognosis for SWS depends on the extent of the leptomeningeal angioma and its effect on the perfusion of the cerebral cortex as well as the severity of ocular involvement.
- Prognosis also is affected by the age of onset of seizures and whether they can be controlled.
- Neurologic function may deteriorate with age. As a result, approximately half of affected adults are impaired, including those who initially were normal.

PATIENT & FAMILY EDUCATION

The Sturge-Weber Foundation is an active support group for patients and families (www.sturge-weber.org).

AUTHOR: **Fred F. Ferri, MD**

[1]Shirley MD et al: Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ, *N Engl J Med* 368:1971-1979, 2013.

Stuttering

BASIC INFORMATION

DEFINITION

Stuttering is a neurodevelopmental communication disorder characterized by disruptions in the flow of speech, otherwise known as dysfluencies. Dysfluencies include repetitions of part and whole words, prolongations of sounds, and blocks. Dysfluencies can also be accompanied by physical tension of the speech muscles, secondary characteristics, and feelings and attitudes associated to the stutter.

SYNONYM

Childhood-onset fluency disorder

ICD-10CM CODE
F80.81 Stuttering
DSM-5 CODE
315-35

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Approximately 2% of adults stutter and 5% of children exhibit stuttering. The prevalence of stuttering in the teenage and adult populations is approximately 1% worldwide.
PREDOMINANT SEX AND AGE: During childhood, twice as many boys stutter as girls. More girls than boys recover from stuttering, approximately 80% of those children recover either with or without treatment. Male-to-female ratio is 3:1 in older children and adults, and 1.5:1 in very young children (30 to 48 months). Stuttering is three to four times more common in males than in females. Stuttering begins around 18 mo and puberty but mostly between 2 and 5 yr of age.
GENETICS: Studies show higher rates of stuttering within families of those who stutter and a higher concordance for stuttering in identical twins compared to fraternal twins; 30% to 60% of individuals who stutter have a family history of stuttering.
RISK FACTORS: Presence of other speech or language disorders, family history of stuttering, onset after 3.5 yr of age, male sex, and stuttering over 6 months in duration. Adult onset may occur after head injury, neurological disorder, or intense fear.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Stuttering usually presents between the ages of 2 and 5, when normal language development begins and children are transitioning from using simple phrases to more complex sentences. Characteristics of stuttered speech include repetitions of part or whole words (e.g., I I I like to go go go shopping), prolongations (e.g., I lllllike to go shopping), and interjections (e.g., I like to, um, go shopping).
- Stuttering is often accompanied by behaviors and feelings that can lead to significant impairment in academic, social, and occupational spheres. Affected individuals show fear and embarrassment around speech and may avoid speaking in some situations. People who stutter develop secondary behaviors that can be broken into two categories: escape behaviors and avoidance behaviors.
- Differentiating stuttering from normal developmental dysfluency is important. Normal dysfluency occurs in many children, is self-limited, and does not need treatment. It is characterized by occasional stuttering events (6-8/100 words and 2/100 syllable and word repetitions) and brief stuttering events (<0.5 second). The child does not seem concerned about the dysfluency, the disrupted speech tends to come and go based on whether the child is tired, excited, or talking about new or complex topics, and speech is typically tension-free with no secondary behaviors. Stuttering, in contrast, occurs in more speaking situations (15/100 words and 9/100 syllable and word repetitions), the stuttering event is of longer duration (>0.5 s), there are signs and symptoms or tension and secondary behaviors, and there is an emerging awareness of difficulties.

ETIOLOGY

- Findings in twin studies consistently demonstrate strong phenotype inheritance in identical twins compared with fraternal twins.
- Researchers at present are utilizing genome-wide association study (GWAS) and functional genome-wide association study (fGWAS) techniques to better understand specific genetic variations that are associated with stuttering. Genes on chromosomes 9, 10, 12, 13, and 18 have been associated with stuttering, although the functions of these candidate genes have not been reliably determined.
- Stuttering might be related to abnormal elevations of cerebral dopamine activity.
- Brain imaging studies show distinct differences in sensorimotor integration centers in the brains of those who stutter compared to controls. It is unclear whether observed brain differences are part of the pathophysiology of stuttering or arise as an adaptation to prolonged stuttering.
- Although parents do not cause their child's stuttering, a critical, impatient, or interrupting speech environment can lead to worsening stuttered speech. Early emotional trauma and other parenting behaviors can also be substantial factors to onset and worsening of stuttering in children.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Stuttering is classified as developmental, neurogenic, or psychogenic.
- Normal fluency development is different from stuttered speech and occurs between 2 and 6 yr of age. Examples of normal dysfluencies include whole-word and phrase repetitions, revising sentences, pauses filled with "filler words" (e.g., um, ah, uh), silent pauses such as hesitations, and infrequent, single, part-word repetitions.
- Developmental stuttering, known simply as stuttering, is the most common form of speech dysfluency and usually presents in the preschool yrs.
- Neurogenic stuttering, by contrast, is much less common and can be caused or exacerbated by a traumatic brain injury, infection, or cerebrovascular accident and is typically acquired after childhood. Neurogenic stuttering may be an early diagnostic sign of a neurological problem.
- Psychogenic stuttering, like neurogenic, is much less common than developmental stuttering. It is a later-onset disorder and has an identifiable precipitant, which most often takes the form of an emotional stressor/injury as opposed to a physical injury.
- Psychogenic stuttering can be differentiated from developmental stuttering because those affected with it are usually not overly concerned about their dysfluency. Additionally, unlike developmental stuttering, psychogenic stuttering does not improve when the affected individual sings or recites something in a chorus, or when the auditory processing of his own voice is blocked, i.e., with ear plugs or when music is played in headphones.
- Differentiating neurogenic stuttering from developmental and psychogenic stuttering can be more challenging, especially in cases where no clear history exists or no visual evidence is available. Similar to individuals with psychogenic stuttering, some with neurogenic stuttering do not notice their stuttered speech and thus can appear unconcerned about it. Other times, affected individuals do notice their speech dysfluency and are troubled by it, as is the case in developmental stuttering.
- History of developmental stuttering is a risk factor for the emergence of neurogenic stuttering; that is, successfully treated developmental stuttering can reemerge after a brain injury.

WORKUP

- Diagnostic information should include a client interview, review of developmental and family history, assessment of speech fluency (context, quality, frequency, duration, and presence of secondary behaviors), and assessment of the emotional, cognitive, and attitudinal impact of stuttering on academic, social, or occupational spheres. Formalized assessments can also be used to assess the frequency and duration of stuttered speech, physical concomitants associated with dysfluencies, and the naturalness of the individual's speech.
- A parent or caregiver interview should be completed to assess the parental response to the child's stuttering (intrusive/critical/anxious vs. accepting/patient/calm).
- A full physical exam should be conducted with special attention to the mental status exam and neurologic exam.
- No laboratory tests or imaging studies are indicated unless neurogenic stuttering is suspected.

- Evaluation by an audiologist for a formal hearing assessment to rule out hearing loss or discrimination disorder may be beneficial in some cases.
- The use of a cognitive neuroscience approach to understanding the relationships between language processing and stuttering has utilized electrophysiological measures of time-locked brain activity–event related potentials.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Typically, provided by a speech language pathologist. Medications are not first-line treatment.
- Requires a synergistic approach of speech and language, attitudinal, and environmental factors. Speech and language factors include fluency-shaping mechanisms, stuttering modification tools, delayed auditory feedback devices, message therapy (primarily for preschoolers), and the Lidcombe approach (parental use of operant conditioning techniques for children under the age of 6 yr). Attitudinal factors include treatment of self-esteem, locus of control, and assertiveness as they are related to the stutter. Lastly, treatment of environmental factors include any stimuli, events, or ongoing characteristics that have an impact on the person's fluency level, cultural factors, and the family component.
- The above therapies help the person who stutters reduce fear about stuttering and produce speech more easily. Treatment focuses on helping the child speak slower and decreasing physical tension and struggle. Families are encouraged to create an atmosphere of acceptance and calm for their child to speak, including providing the children full attention when they are speaking, turn taking, decreased demands to speak, repetition of utterances, and modeling of slow speech.

ACUTE GENERAL Rx

- Clinical trials have not resulted in effective, practical medication options for the treatment of stuttering. Smaller-scale trials and case studies have been conducted with a variety of agents, including clonidine, antipsychotics, and GABA-A partial agonists. Clonidine was found to be ineffective in reducing speech dysfluency. A recent double-blind, randomized, placebo-controlled study of the GABA-A partial agonist pagoclone showed a significant reduction in speech dysfluency. A phase III trial of this medication not been conducted.
- Case reports of deep brain stimulation of the ventral intermediate nucleus of the thalamus have shown some reduction in speech dysfluency in adults with severe stuttering.

DISPOSITION

Research suggests that as many as 70% of children who stutter will outgrow it without therapy; however, if a child has been stuttering for more than 1 yr, the likelihood of outgrowing it without therapy is reduced.

REFERRAL

Children with severe stuttering should be referred immediately to a speech-language pathologist for further evaluation and treatment. Those presenting with a mild stutter should be referred if stuttering continues for longer than 6 to 8 wk or if there is significant concern by the parent or child.

AUTHOR: **Rebecca Craine, MSEd, CCC-SLP**

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Stye (Hordeolum) PTG

BASIC INFORMATION

DEFINITION

A hordeolum is an acute inflammatory process affecting the eyelid and arising from the meibomian (posterior) or Zeis (anterior) glands. It is most often infectious and usually caused by *Staphylococcus aureus*. When infection involves the meibomian glands, it is called meibomianitis.

SYNONYMS

Hordeolum
Meibomianitis

ICD-10CM CODES

H00.011	Hordeolum externum right upper eyelid
H00.012	Hordeolum externum right lower eyelid
H00.013	Hordeolum externum right eye, unspecified eyelid
H00.014	Hordeolum externum left upper eyelid
H00.015	Hordeolum externum left lower eyelid
H00.016	Hordeolum externum left eye, unspecified eyelid
H00.019	Hordeolum externum unspecified eye, unspecified eyelid
H00.021	Hordeolum internum right upper eyelid
H00.022	Hordeolum internum right lower eyelid
H00.023	Hordeolum internum right eye, unspecified eyelid
H00.024	Hordeolum internum left upper eyelid
H00.025	Hordeolum internum left lower eyelid
H00.026	Hordeolum internum left eye, unspecified eyelid
H00.029	Hordeolum internum unspecified eye, unspecified eyelid

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Unknown
PREVALENCE (IN U.S.): Unknown
PREDOMINANT SEX: No gender predilection
PREDOMINANT AGE: May occur at any age
NEONATAL INFECTION: Rare in the neonatal period
PEAK INCIDENCE: May occur at any age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abrupt onset with pain and erythema of the eyelid
- Localized, tender mass in the eyelid (Fig. E1)
- May be associated with blepharitis
- External hordeolum: Points toward the skin surface of the lid and may spontaneously drain
- Internal hordeolum: Can point toward the conjunctival side of the lid and may cause conjunctival inflammation

ETIOLOGY

- 75% to 95% of cases are caused by *S. aureus*, which includes MRSA strains.
- Occasional cases are caused by *Streptococcus pneumoniae*, other streptococci, gram-negative enteric organisms, or mixed bacterial flora.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Eyelid abscess
- Chalazion
- Allergy or contact dermatitis with conjunctival edema
- Acute dacryocystitis
- Herpes simplex infection
- Cellulitis of the eyelid

LABORATORY TESTS

- Generally, none are necessary.
- If incision and drainage are performed, specimens should be sent for bacterial culture.

TREATMENT

NONPHARMACOLOGIC THERAPY

External stye (eyelash follicle): Usually responds to warm compresses and will drain spontaneously.

ACUTE GENERAL Rx

- Systemic antibiotics generally not necessary for an external stye.
- For internal stye, use hot packs *plus* oral dicloxacillin 500 mg qid × 7 days. If suspecting methicillin-resistant *Staphylococcus aureus* (MRSA), use trimethoprim-sulfamethoxazole DS bid in place of dicloxacillin. In patients with hospital-acquired infection, consider linezolid 600 mg PO bid.
- For external stye, topical erythromycin ophthalmic ointment applied to the lid margins two to four times daily until resolution may be helpful in some cases.
- Incision and drainage: Rarely needed but should be considered for progressive infections.

DISPOSITION

- Usually sporadic occurrence
- Possible relapse if resolution is not complete

REFERRAL

- For evaluation by an ophthalmologist if visual acuity or ocular movement is affected or if the diagnosis is in doubt
- For surgical drainage if necessary

PEARLS & CONSIDERATIONS

COMMENTS

Seborrheic dermatitis may coexist with hordeolum.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Chalazion (Patient Information)
Stye (Hordeolum) (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

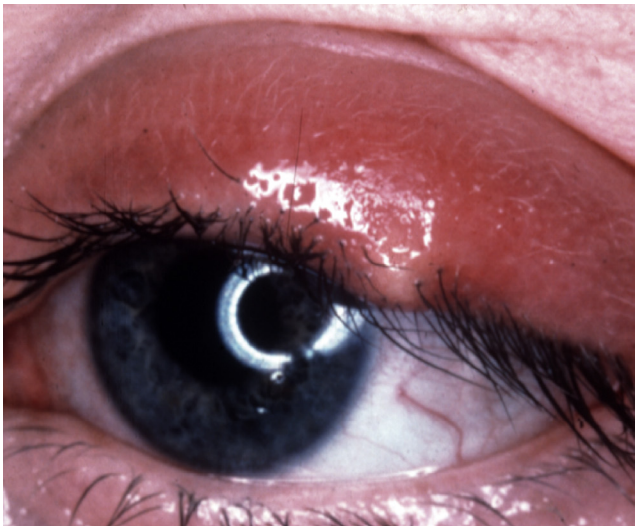

FIG. E1 External hordeolum (stye). (From Bowling B: *Kanski's clinical ophthalmology, a systemic approach,* ed 8, Philadelphia, 2016, Elsevier.)

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Subarachnoid Hemorrhage PTG

BASIC INFORMATION

DEFINITION

Subarachnoid hemorrhage (SAH) is defined as hemorrhage into the subarachnoid space surrounding the brain. This can be either nontraumatic (typically due to cerebral aneurysm rupture) or traumatic in nature. Here we will focus upon nontraumatic subarachnoid hemorrhage. Box 1 describes the Hunt and Hess clinical classification of patients presenting with aneurysmal SAH.

SYNONYMS

Subarachnoid bleed
SAH

ICD-10CM CODES

I60	Subarachnoid hemorrhage
I60.1	Subarachnoid hemorrhage from middle cerebral artery
I60.2	Subarachnoid hemorrhage from anterior communicating artery
I60.3	Subarachnoid hemorrhage from posterior communicating artery
I60.4	Subarachnoid hemorrhage from basilar artery
I60.5	Subarachnoid hemorrhage from vertebral artery
I60.7	Subarachnoid hemorrhage from intracranial artery, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Nontraumatic: 6 to 8 cases/100,000 persons per yr.

PREDOMINANT SEX: Women aged >55 yr were found to have a 25% greater risk of developing SAH compared with men of the same age.

PREDOMINANT AGE: The mean age at onset is 55 yr.

PEAK INCIDENCE: Most aneurysmal SAH occurs in people who are between the ages of 55 and 60 yr.

GENETICS:

- First-degree relatives have a 5 to 12 times greater risk of developing SAH compared with the general population.
- Autosomal dominant polycystic kidney disease is known to be associated with cerebral aneurysms in 8% of cases; screening is recommended in families with this condition. in which one family member has experienced a ruptured aneurysm.
- Collagen vascular diseases such as Marfan syndrome, Ehler Danlos syndrome have also been implicated in the formation of aneurysms.

RISK FACTORS: Although genetics seem to play a factor in SAH, lifestyle factors are more important for determining overall risk. These risk factors include smoking, hypertension, oral contraception, pregnancy, and amphetamine/cocaine use.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The primary symptom is a sudden, severe headache in >90% of cases. About 50% have a headache that is classically described as the "worst headache of my life" and reaches maximal intensity within 1 min—the so-called thunderclap headache. This headache may be associated with nausea/vomiting, neck pain, seizure, or complete loss of consciousness.
- 30% to 60% of patients report a history of headaches during the weeks preceding the actual hemorrhage event. These are most likely sentinel bleeds that represent microhemorrhages.
- Altered mental status and coma may result from the direct effect (hemorrhagic mass effect), but more likely is the result of acutely increased intracranial pressure.
- A posterior communicating artery aneurysm may present as oculomotor (cranial nerve III) palsy, typically involving the pupillary fibers, even in a nonruptured setting.
- Table 1 describes the World Federation of Neurologic Surgeons clinical classification of SAH.

ETIOLOGY

- A ruptured saccular (berry) aneurysm is the most common cause of spontaneous SAH (75% to 80% of spontaneous SAH).
- Idiopathic SAH, also known as angiogram-negative SAH, accounts for 5% to 20% of spontaneous SAH. In these cases, no angiographic cause of the hemorrhage is found. This entity is also known as benign perimesencephalic SAH and is thought to occur due to rupture of venous plexus in the cisterns surrounding the brain stem.
- Other causes of spontaneous SAH include arteriovenous malformations, bleeding into preexisting tumors, vasculitis, and rarely reversible cerebral vasoconstriction syndrome, cerebral venous sinus thrombosis, or intracranial cerebral artery dissection.
- Cocaine abuse, sickle cell anemia, coagulopathies, and pituitary apoplexy can also result in SAH.
- Trauma.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Intracerebral hemorrhage as a result of spontaneous rupture of intracerebral arteries or arterioles (rather than arteries passing through the subarachnoid space) due to hypertension or amyloid angiopathy, as well as trauma, intratumoral bleed, ischemic stroke with hemorrhagic conversion, cerebral venous sinus hemorrhage associated with venous sinus thrombosis, mycotic aneurysm rupture.
- Other headache syndromes: Thunderclap headaches due to reversible cerebral vasoconstriction syndrome (often with recurrent thunderclap headaches), migraine headache, sexual headache, cough headache, exertional headache, secondary causes including, but not limited to, pituitary apoplexy or acute hydrocephalus.

WORKUP

IMAGING STUDIES:

- Computed tomography (CT) of the head (Fig. E1) shows hemorrhage in more than 95% of cases, especially during the acute phase (i.e., 24 to 48 hr) after the onset of bleeding. Box 2 describes the Fisher grade of SAH on initial CT (Fisher III being associated with highest risk of vasospasm). About 3% to 5% of SAH may be missed on initial CT of the head. MRI brain, specifically FLAIR sequence, is helpful in detecting subarachnoid blood if clinically suspected.
- Lumbar puncture should be performed in all cases of suspected SAH with "normal CT of the head" between 6 and 12 hours after the onset of the headache for highest yield. The following suggest SAH:
  1. An RBC count of more than 100,000/m^3 in tubes 1 AND 4. This is to differentiate

BOX 1 Hunt and Hess Clinical Classification of Subarachnoid Hemorrhage

I	Asymptomatic or mild headache and neck stiffness
II	Moderate to severe headache and neck stiffness ± cranial nerve palsy
III	Mild focal deficit, lethargy, or confusion
IV	Stupor, moderate to severe hemiparesis
V	Deep coma, extensor posturing

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

TABLE 1 World Federation of Neurologic Surgeons Clinical Classification of Subarachnoid Hemorrhage

Grade	Glasgow Coma Scale	Motor Deficits
I	15	Absent
II	13-14	Absent
III	13-14	Present
IV	7-12	Present or absent
V	3-6	Present or absent

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

BOX 2 Fisher Grade of Subarachnoid Hemorrhage on Initial Computed Tomography

1	No blood detected
2	Diffuse or vertical layers <1 mm thick
3	Localized subarachnoid clot and/or vertical layers ≥1 mm thick
4	Intraparenchymal or intraventricular clot with diffuse or no SAH
Modified Fisher CT Rating Scale	
1	Minimal or diffuse thin SAH without IVH
2	Minimal or thin SAH with IVH
3	Thick cisternal clot without IVH
4	Thick cisternal clot with IVH

CT, Computed tomography; *IVH,* intraventricular hemorrhage; *SAH,* subarachnoid hemorrhage.
From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

from a traumatic tap in which there will be a drop in RBC count from tube 1 to 4.
2. Presence of xanthochromia or bilirubin in the cerebrospinal fluid.
3. SAH can also be excluded by the following two criteria: CSF RBC count <2000 × 10^6/L and no xanthochromia.

- CT angiogram of the brain (Fig. E2).
- Digital subtraction angiography with 3D processing when indicated is the gold standard for diagnosis of etiology in subarachnoid hemorrhage.

LABORATORY TESTS

- Basic laboratory values, including CBC, chemistry panel, prothrombin time, partial thromboplastin time, and platelet count.
- Serum troponin to evaluate for severe cardiac stress; elevated troponins indicate cardiac ischemia secondary to catecholamine surge and is associated with poor outcome.
- Patients with SAH are prone to developing cerebral salt wasting, resulting in hyponatremia. Sodium levels should be monitored frequently.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Airway, breathing, and circulation
- Once stabilized, good neurologic exam
- Cerebrospinal fluid (CSF) drainage may be required for patients who develop hydrocephalus and increased intracranial pressure. It is also recommended for patients with Hunt and Hess grade 3 or higher.

ACUTE GENERAL Rx

- Critical care management: Initial management strategies are geared toward stabilizing the patient and preventing re-hemorrhage and hydrocephalus. Re-hemorrhage occurs within 72 hours in up to 23% and is associated with very high mortality rates.
- Blood pressure control: Tight blood pressure control is paramount before securing the aneurysm to protect against re-rupture. Blood pressure control can be achieved with the use of antihypertensive infusions such as intravenous nicardipine. A systolic blood pressure of less than 140 mm Hg is recommended. Placement of arterial line is recommended. After securing of the aneurysm, liberalization of blood pressure parameters is the standard.
- Intracranial pressure control: Raised intracranial pressure occurs in more than 50% of patients with subarachnoid hemorrhage secondary to hydrocephalus, cerebral edema, cerebral infarction or other causes. Insertion of a ventricular catheter to treat acute hydrocephalus and maintain intracranial pressure <20 mm Hg can be lifesaving. Patients who are unable to be weaned may require permanent CSF diversion.
- In cases of aneurysmal SAH, treatment focuses on occlusion/exclusion of the aneurysm to prevent rebleeding. The most common treatment methods are:
  1. Microsurgical clipping: Performed through a craniotomy by placing a clip around the neck of the aneurysm
  2. Endovascular coiling (Fig. E3): Performed via digital subtraction angiography; it consists of deploying platinum coils inside the aneurysm or stents in the parent artery to cause thrombosis of the aneurysmal sac. Most aneurysms currently are treated endovascularly.
- Vasospasm: Cerebral vasospasm is a morbid complication leading to cerebral ischemia, disability, and death after SAH. It typically develops between day 4 and 14 (but may occur up to day 21) after the hemorrhage, and it reaches a peak on day 6 to 8. Treatment strategies include:
  1. Current medical therapy for vasospasm focuses upon hypertension, with typical mean arterial pressure goals of 90 to 100 (after aneurysm is secured) and with euvolemia instead of hypervolemia, as the latter was found to lead to significant cardiopulmonary and hemodynamic complications. "Triple H" therapy—*H*ypertension, *H*ypervolemia, and *H*emodilution—was originally employed to maintain cerebral perfusion, but it has fallen out of favor due to its many complications.
  2. Nimodipine (60 mg q4h or 30 mg q2h if blood pressure is low) has been shown to improve outcomes if it is administered between days 4 and 21 after the hemorrhage, even if it does not significantly reduce the amount of vasospasm detected on angiography.
  3. Intraarterial therapies such as intraarterial calcium channel blockers and balloon angioplasty may be employed as needed.
- Seizures occur in about 3% of patients during the acute phase; use of prophylactic antiepileptics is controversial and not recommended, but patients presenting with seizures should be treated appropriately with anticonvulsants.
- Pain control: Use short-acting and less-sedating medications (e.g., codeine, low-dose morphine).
- Monitor and treat for cerebral salt wasting and any other electrolyte abnormalities or anemia.
- Maintain normothermia.

CHRONIC Rx

- Management of reversible risk factors mentioned above (smoking, hypertension, drug use)
- Management of neurologic disability through physical therapy and rehabilitation

DISPOSITION

- SAH is often associated with a poor outcome with a death rate between 30% and 40%; 10% to 15% of patients die before they reach the hospital though outcomes have been improving over the past two decades.
- Almost half of those who survive hospitalization have cognitive impairments or disability that affect their lifestyles.

REFERRAL

Patients should be managed in a cerebrovascular center that maintains capacity to perform open surgical and endovascular procedures, with a critical care unit experienced in caring for neurosurgical patients.

PEARLS & CONSIDERATIONS

COMMENTS

- "Thunderclap" headaches should be considered SAH until proven otherwise and evaluated by CT of the head with/without LP. MRI FLAIR sequence is also a helpful modality.
- All SAH should be managed in a critical care setting (preferably neurocritical care unit) with neurosurgical care available.
- Measures to prevent rebleeding include adequate control of blood pressure and aneurysm treatment with the use of coiling or clipping.

PREVENTION

Controlling some of the modifiable risk factors, especially smoking and blood pressure, may help to decrease the risk of aneurysmal rupture.

PATIENT & FAMILY EDUCATION

- SAH is a devastating condition, with most survivors developing significant neurologic or cognitive deficits. A good support system and an adequate physical and cognitive rehabilitation program may prove useful to survivors.
- Screening may be useful for patients with two or three first-degree relatives with SAH.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Subarachnoid Hemorrhage (Patient Information)

AUTHORS: **Farhan A. Mirza, MD,** and **Justin F. Fraser, MD**

SUGGESTED READINGS

Lawton MT, Vates GE: Subarachnoid hemorrhage, *N Engl J Med* 377:252-266, 2017.

Perry JJ et al: Differentiation between traumatic tap and aneurysmal subarachnoid hemorrhage: prospective cohort study, *BMJ* 350:h568, 2015.

Perry JJ et al: Validation of the Ottawa subarachnoid hemorrhage rule in patients with acute headache, *CMAJ* 189:E1379-E1385, 2017.

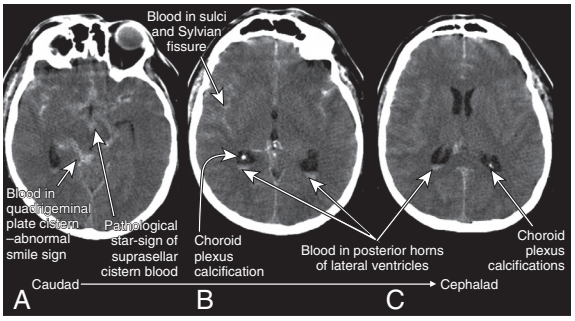

FIG. E1 Subarachnoid hemorrhage (SAH), noncontrast computed tomography (CT), brain windows. Acute SAH appears white on noncontrast CT brain windows. **A** through **C,** nonconsecutive axial slices, progressing from caudad to cephalad. In this case of diffuse SAH, note the presence of subarachnoid blood filling the sulci, as well as extending into the cisterns, Sylvian fissures, and even lateral ventricles. In **A,** blood *(white)* fills the suprasellar cistern. This star-shaped structure is normally filled with cerebrospinal fluid (CSF) *(black).* The quadrigeminal plate cistern is normally a smile-shaped black crescent, filled with CSF, but in this case is filled with blood. Extremely bright calcifications in the choroid plexus of the posterior horns of the lateral ventricles are common, normal findings—do not mistake these for hemorrhage. Note their similarity in density to bone of the calvarium. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

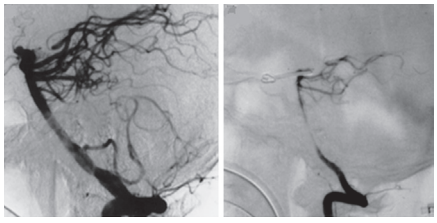

FIG. E2 Baseline angiogram obtained shortly after subarachnoid hemorrhage (*left*) and repeat angiogram obtained 7 days later (*right*) showing severe vasospasm of basilar artery, with reduced distal flow. (From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.)

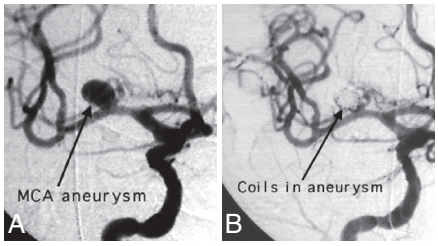

FIG. E3 Angiogram demonstrating middle cerebral artery aneurysm before **(A)** and after placement of detachable coils to thrombose the aneurysm **(B).** (From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.)

Subclavian Steal Syndrome

BASIC INFORMATION

DEFINITION

Subclavian steal syndrome is an occlusion or severe stenosis of the proximal subclavian artery leading to decreased antegrade flow or retrograde flow in the ipsilateral vertebral artery and neurologic symptoms referable to the posterior circulation.

SYNONYM

Proximal subclavian (or innominate) artery stenosis or occlusion

ICD-10CM CODE

G45.8 Other transient cerebral ischemic attacks and related syndromes

EPIDEMIOLOGY & DEMOGRAPHICS

- Similar to that of other manifestations of atherosclerosis (coronary artery disease, cerebrovascular disease, or peripheral vascular disease)
- Affects middle-aged persons (men somewhat younger than women on average) with arteriosclerotic risk factors, including family history, smoking, diabetes mellitus, hyperlipidemia, hypertension, and sedentary lifestyle

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms:

- Many patients are asymptomatic.
- Upper-extremity ischemic symptoms: Fatigue, exercise-related aching, coolness, numbness of the involved upper extremity.
- Neurologic symptoms are reported by 25% of patients with known unilateral subclavian steal. These include brief spells of:
  1. Vertigo
  2. Diplopia
  3. Decreased vision
  4. Oscillopsia
  5. Gait unsteadiness

These spells are only occasionally provoked by exercising the ischemic upper extremity (classic subclavian steal). Left subclavian steal is more common than right, but the latter is more serious.

- Posterior circulation stroke related to subclavian steal is rare.
- Innominate artery stenosis can cause decreased right carotid artery flow and cerebrovascular symptoms of the anterior cerebral circulation, but this is uncommon.

Physical findings:

- Delayed and smaller volume pulse (wrist or antecubital) in the affected upper extremity
- Lower blood pressure in the affected upper extremity
- Supraclavicular bruit

NOTE: Inflating a blood pressure cuff will increase the bruit if it originates from a vertebral artery stenosis and decrease the bruit if it originates from a subclavian artery stenosis.

ETIOLOGY & PATHOGENESIS

Etiology:

- Atherosclerosis
- Arteritis (Takayasu disease and temporal arteritis)
- Embolism to the subclavian or innominate artery
- Cervical rib
- Long-term use of a crutch
- Occupational (baseball pitchers and cricket bowlers)

Pathogenesis: The vertebral artery originates from the subclavian artery. For subclavian steal to occur, the occlusion must be proximal to the takeoff of the vertebral artery. On the right side, only a small distance separates the bifurcation of the innominate artery and the takeoff of the vertebral artery, explaining why the condition occurs less commonly on the right side. Occlusion of the innominate artery must affect right carotid artery flow.

DIAGNOSIS

The carotid arteries should be evaluated at least noninvasively in all cases.

DIFFERENTIAL DIAGNOSIS

- Posterior circulation transient ischemic attack or stroke
- Upper-extremity ischemia:
  1. Distal subclavian artery stenosis or occlusion
  2. Raynaud phenomenon
  3. Thoracic outlet syndrome

WORKUP

- Noninvasive upper-extremity arterial flow studies
- Doppler sonography of the vertebral, subclavian, and innominate arteries
- Arteriography, magnetic resonance arteriogram (Fig. 1)

TREATMENT

- In most patients the disease is benign and requires no treatment other than atherosclerosis risk factor modification and aspirin. Symptoms tend to improve over time as collateral circulation develops.
- Vascular surgical reconstruction requires a thoracotomy; it may be indicated in innominate artery stenosis or when upper-extremity ischemia is incapacitating.

AUTHOR: **Fred F. Ferri, MD**

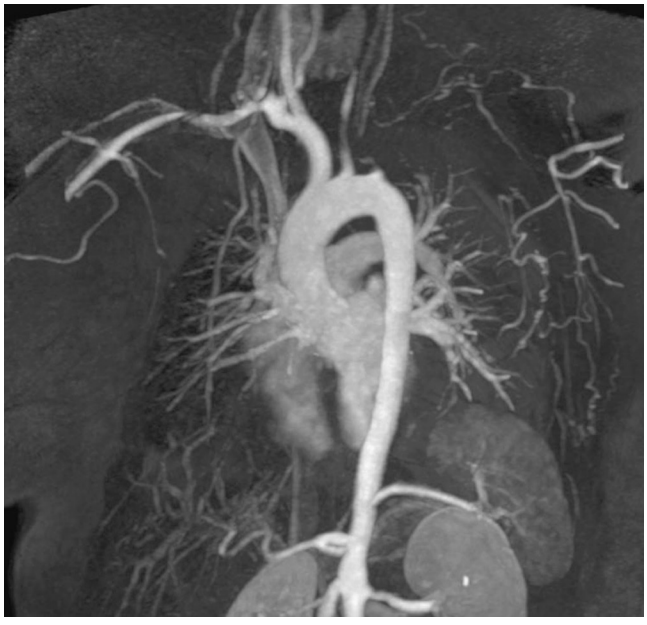

FIG. 1 Magnetic resonance arteriogram demonstrating diffuse moderate stenosis of the proximal left common carotid and proximal occlusion of the left subclavian artery coming off the aortic arch with development of an extensive collateral network. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

BASIC INFORMATION

DEFINITION

Subclinical brain infarct (SBI) is defined as the presence of infarcted brain tissue without a history of transient neurologic or strokelike symptoms. It was initially identified in clinicopathological studies. The advent of neuroimaging has made it easier to detect and characterize. On a CT scan, it often is described as areas of hypodensity resembling cerebrospinal fluid (CSF). On a brain MRI, it is defined as well circumscribed, usually circular lesions greater than 3 mm, iso to hypointense on T1 and hyperintense on T2 weighted images.

SYNONYMS

SBI
Silent brain infarction
Covert brain infarction

ICD 10-CM CODE
I63.9 Cerebral infarction, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Annual incidence 2% to 4% per year over the age of 50 with incidence rates increasing with age
PEAK INCIDENCE: Peak incidence occurs in the aging population and those with prior history of a stroke or a transient ischemic attack (TIA). The incidence of SBIs can be as high as 19% annually in people with prior history of transient ischemic attacks and as high as 23% in those undergoing carotid endarterectomies.
PREVALENCE: The overall prevalence of SBIs ranges from 8% to 62% depending on the population being studied. It increases with age and cardiovascular risk factors.
GENETICS: Genetic polymorphisms of endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), methylenetetrahydrofolate reductase (MTHFR), and protein kinase Cη (PRKCH) have been associated with increased risk of SBIs.
RISK FACTORS: Age, hypertension, metabolic syndrome, carotid artery disease, chronic kidney disease, coronary artery disease, heart failure, hyperhomocysteinemia, obstructive sleep apnea and other cardiovascular risk factors

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- By definition, a subclinical brain infarct is silent or asymptomatic when it occurs in isolation. It tends to occur in multiples in at-risk populations, and the effect is clinically apparent when episodes accumulate.
- The condition is associated most significantly with cognitive decline, and it increases the risk of dementia as well as functional decline.
- The presence of SBIs also doubles the risk of ischemic stroke or TIA, and multiple SBIs are associated with more severe, subsequent ischemic stroke.

ETIOLOGY

The etiology of an SBI is very similar to any other infarct. That is, it occurs due to cessation of blood supply to a particular area of the brain. SBIs are subclinical and asymptomatic likely due to the fact that they occur in noneloquent areas of the brain or are small enough to allow neural plasticity to take over.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Dilated perivascular spaces
Chronic symptomatic infarction
Chronic cerebral microvascular disease

WORKUP

- CT scan though the sensitivity is low
- SBIs can be readily identified on MRI using T1 and T2 sequences.

LABORATORY TESTS

There are no laboratory tests to detect SBIs, but elevated low-density lipoprotein and c-reactive protein are associated.

IMAGING STUDIES

Brain CT scan or MRI

TREATMENT

Aggressive control of vascular risk factors to reduce subsequent risk of stroke, cardiovascular disease, and dementia

PEARLS & CONSIDERATIONS

COMMENTS

- A subclinical brain infarct in isolation has no clinical manifestations, but accumulation of these lesions can lead to cognitive decline and increase the risk of dementia.
- SBIs increase subsequent risk of stroke more than 50%. Hence, when these are detected in asymptomatic individuals, they may point toward unidentified vascular risk factors. Identification and modification of these risk factors may have significant benefit.

PATIENT & FAMILY EDUCATION

None

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Stroke, Acute Ischemic (Related Key Topic)
Stroke, Secondary Prevention (Related Key Topic)

AUTHORS: **Khawja A. Siddiqui, MD,** and **Corey Goldsmith, MD**

SUGGESTED READINGS

Fanning JP, Wong AA, Fraser JF: The epidemiology of silent brain infarction: a systematic review of population-based cohorts, *BMC Med* 12:119, 2014.

Kovacs KR et al: Silent brain infarction–a review of recent observations, *Int J Stroke* 8(5):334-347, 2013.

Windham BG et al: Small brain lesions and incident stroke and mortality: a cohort study, *Ann Int Med* 163:22-31, 2015.

BASIC INFORMATION

DEFINITION

A subdural hematoma (SDH) is a collection of blood or blood products between the brain and dura mater. Subdural hematomas can be acute (ASDH) or chronic (CSDH) and vary significantly in presentation and treatment.

SYNONYM

Subdural hemorrhage

ICD-10CM CODES

I62.01 Acute subdural hematoma
I62.03 Chronic subdural hematoma
S06.5 Traumatic subdural hemorrhage

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- The exact incidence of ASDH is unknown, but it is commonly seen in patients with head injury.
- CSDH is most common in the elderly with an estimated incidence of 1.72 to 13.1 per 100,000.

PREVALENCE: Unknown

PREDOMINANT AGE AND SEX:

- Peak incidence of CSDH is in the eighth decade and is notably higher in males.
- ASDHs usually present in the trauma setting and can happen in all age groups. In particular, shaken baby syndrome can be associated with SDH in the infant population.

RISK FACTORS:

- Trauma and antithrombotic therapy are the most common risk factors for ASDH and CSDH.
- Brain atrophy secondary to advanced age and alcoholism are common risk factors, especially with the coagulopathy/thrombocytopenia seen in chronic alcoholics.
- Intracranial hypotension associated with CSF shunts or leaks is uncommon but can result in acute or chronic SDH.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms vary on the basis of acuity, size, and location. Acute traumatic SDHs are often seen in traumatic brain injury patients, and their Glasgow Coma Scale may vary according to the extent of brain injury, size of hematoma, and associated compression. When associated with a midline shift (i.e., >5 mm), they can cause signs of cerebral herniation (e.g., ipsilateral pupil dilation, contralateral weakness) requiring prompt surgical evacuation.
- Patients with CSDH may present with diverse nonspecific symptoms such as headaches, confusion, gait disturbance, incontinence, aphasia, hemiparesis, transient ischemic attack-like symptoms, and seizures.

ETIOLOGY

SDH is usually the result of shearing and tearing of a bridging vein between the brain parenchyma and the dura mater. Other causes of bleeding into the subdural space include contusion, extension of parenchymal hemorrhage. In the setting of spontaneous SDH, other vascular abnormalities, such as arteriovenous (AV) malformation, aneurysm, and dural AV fistula, should be kept in mind.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Cerebrospinal fluid (CSF) hygromas, abscesses, and tumor infiltrations

WORKUP

- Clinical assessment: Patient history, including medications, specifically anticoagulants/antiplatelets; alcohol abuse; recent trauma; cancer; and recent bacterial infections
- Neurologic examination: Glasgow Coma Scale, cranial nerves, motor/sensory exam CT head

LABORATORY TESTS

Assessment of the patient's coagulation status including CBC with platelet count, prothrombin time, partial thromboplastin time, and liver function test (especially with a history of alcoholism or liver failure)

IMAGING STUDIES

CT head (Fig. 1): Demonstrates the classic crescentic collection between the brain and inner table. For comatose and trauma patients, include a cervical spine CT scan. ASDH is usually hyperdense, whereas a CSDH is usually hypodense on noncontrast CT. Contrast is only needed if there are concerns about tumor or infection.

TREATMENT

- Correction of underlying coagulopathy, if present (e.g., warfarin/ASA/clopidogrel reversal).
- Admission for monitoring in the setting of acute SDH.
- The majority of SDH can be managed without surgery in awake patients with normal neurologic examinations.

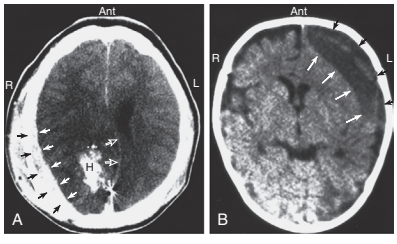

FIG. 1 A, Noncontrast computed tomography scan of an acute subdural hematoma shows a crescentic area of increased density in the right posterior parietal region between the brain and the skull *(black and white arrows).* An area of intraparenchymal hemorrhage *(H)* is also seen. **B,** A chronic subdural hematoma for a different patient is shown. There is an area of decreased density in the left frontoparietal region *(arrows)* that effaces the sulci, compresses the anterior horn of the left lateral ventricle, and shifts the midline somewhat to the right. (From Mettler FA [ed]: *Primary care radiology,* Philadelphia, 2000, WB Saunders.)

- Medical management of CSDH using antifibrinolytic therapy with tranexamic acid 650 mg per day has shown promising results, although a small, randomized, placebo-controlled trial showed no statistically significant difference.
- Seizure prophylaxis with phenytoin or levetiracetam for seven days should be considered in almost all cases, as there is underlying injury to the brain tissue associated with acute subdural hematoma. The irritative effects of blood products on the brain can also contribute to seizures, in both acute and chronic subdural hematomas. If seizures do occur, video EEG monitoring should be instituted and aggressive treatment undertaken.

NONPHARMACOLOGIC THERAPY

Surgical treatment is indicated in:

- ASDHs measuring >10 mm in thickness with a midline shift >5 mm on CT scan and a compromised neurologic status (Glasgow Coma Scale <9, pupillary asymmetry or fixation) should be immediately evacuated.
- In CSDH with a mass effect, a clear change in the neurologic examination from baseline, and/or enlargement of the hematoma size, evacuation via craniotomy or burr hole should be considered.

DISPOSITION

Depending on the size and location of the SDH and the examination of the patient, observation can range from the ICU to outpatient management. When observation of the patient is considered, clinical examinations should be serially performed. Patient baseline and follow-up clinical examinations are more important than CT scan findings.

REFERRAL

Neurosurgical and operative consultation should be made available.

PEARLS & CONSIDERATIONS

COMMENTS

- Many elderly patients have small CSDHs or hygromas. Unless these are associated with seizures or clinical or radiographic progression, they are usually not emergent and usually do not require neurosurgical intervention. Recurrence after surgical management for CSDH is common.
- SDHs in elderly patients can have a mixed hyperdense and hypodense appearance on noncontrast CT scan; this finding is suggestive of subdural membranes and chronic components.

PATIENT & FAMILY EDUCATION

Individuals with SDHs are at higher risk for seizure, so surveillance is important.

RELATED CONTENT

Subdural Hematoma (Patient Information)

AUTHORS: **Farhan A. Mirza, MD,** and **Justin F. Fraser, MD**

BASIC INFORMATION

DEFINITION

A localized accumulation of infected fluid, often encapsulated, located under the diaphragm and may also involve the liver and spleen

SYNONYMS

Subdiaphragmatic abscess
Infradiaphragmatic abscess

ICD-10CM CODES

K65.1 Peritoneal abscess
K68.11 Postprocedural retroperitoneal abscess

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Not well known but intraabdominal abscess occurs in 1% to 2% of all cases of abdominal surgery. It increases to 10% to 30% in cases with preoperative perforation of a hollow viscus, spillage of fecal material into peritoneum, or intestinal ischemia.

RISK FACTORS:

- Abdominal surgery, especially with accidental viscus perforation
- Peptic ulcer perforation
- Appendiceal perforation
- Diverticulitis with perforation
- Mesenteric ischemia with bowel infarction
- Abdominal trauma especially penetrating trauma
- Foreign body ingestion with subsequent viscus perforation

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Constitutional symptoms include:
  1. Fever, malaise, or chills
  2. Cough, increased respiratory rate with shallow or grunting respiration
  3. Shoulder-tip pain on affected side (referred pain)
- Physical findings can include:
  1. Dullness to percussion on affected side
  2. Diminished or absent breath sounds on affected side
  3. Tenderness over the eighth to eleventh ribs

ETIOLOGY

Infection is usually polymicrobial: Aerobic gram-negative rods, most commonly *Escherichia coli, Klebsiella* species, *Enterobacter* species, and *Pseudomonas aeruginosa,* and gram-positive cocci: *Streptococcus viridians,* enterococci and *Staphylococcus aureus,* and anaerobes (found in 60% to 70% of cases) such as *Bacteroides fragilis* and *Clostridia* species.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Liver abscess
- Subhepatic abscess
- Lesser sac abscess
- Empyema of the lung
- Diaphragmatic hernia

WORKUP

Should be started in patients with recent abdominal surgery (weeks to months) with the constitutional symptoms and physical findings mentioned above

LABORATORY TESTS

- Complete blood count with differential may show an elevated white blood count with left shift
- Blood cultures may be positive in up to 50% of the cases
- Gram stain and culture, aerobically and anaerobically, of any aspiration procedure

IMAGING STUDIES

- Plain x-ray films can suggest the location of the abscess in about 50% of the cases and can demonstrate elevation of the hemidiaphragm and/or subphrenic air-fluid level
- Ultrasonography and CT (Fig. 1) are more sensitive
- Other options include leukocyte tagged with gallium 67 and indium 111 scans and MRI

TREATMENT

Includes source control with either percutaneous drainage or surgery and intravenous antibiotics:

- Percutaneous drainage via interventional radiology:
  1. Percutaneous drainage with catheter placement remains the preferred treatment despite the fact that the subphrenic location can be problematic for imaging-guided percutaneous drainage.
  2. Approaches include subcostal approach or intercostal approach. The intercostal approach is associated with a higher risk for pleural complications, but these tend to be minor.
  3. Radiographic modalities used include ultrasonography, CT, and fluoroscopy.
  4. Complications of drainage procedures can include pleural effusion, pneumothorax, or empyema.
- Surgery: May be required in recurrence of abscess or due to multiple abscesses not amenable to percutaneous drainage procedure
- Antibiotics: Broad-spectrum antibiotics should be used to cover Gram-negative rods, Gram-positive bacteria, and anaerobes until cultures are resulted and should be continued at least 4 to 7 days after adequate drainage procedure. Examples include:
  1. Piperacillin/tazobactam 3.375 g IV q6h or 4.5 g IV q8h
  2. Meropenem 1 g IV q8h or imipenem 0.5 to 1 g IV q6h
  3. Ciprofloxacin IV 400 mg IV q12h plus IV metronidazole 500 mg IV q8h for penicillin allergic patients

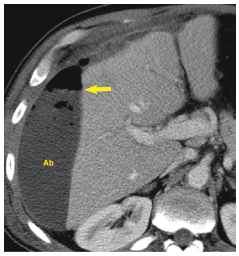

FIG. 1 Subphrenic abscess. A postoperative abscess *(Ab)* is seen as a fluid collection between the diaphragm and the liver. Mass impression on the liver is evidence of fluid loculation. An air–fluid level *(arrow)* is evident, caused by gas-producing *Escherichia coli.* This abscess was successfully treated using percutaneous catheter drainage guided by computed tomography. (From Webb WR et al: *Fundamentals of body CT,* ed 4, Philadelphia, 2015, Saunders.)

REFERRAL

- Interventional radiology
- General surgery
- Infectious diseases

PEARLS & CONSIDERATIONS

COMMENTS

Success of percutaneous drainage procedures is greater than 85%, and recurrence rates are about 1% to 10%.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Peritonitis, Secondary (Related Key Content)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Preece SR et al: Safety of an intercostal approach for imaging-guided percutaneous drainage of a subdiaphragmatic abscesses, *AJR Am J Roentgenol* 202:1349-1354, 2014.

Solomkin JS et al: Diagnosis and management of complicated intraabdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America, *Clin Infect Dis* 50:133-164, 2010.

BASIC INFORMATION

DEFINITION

The recurrent use of alcohol and/or drugs that causes clinically and functionally significant impairment, such as health problems, disability, and failure to meet major responsibilities at work, school, or home. The recent opiate crisis has resulted in high morbidity and mortality rates, highlighting its importance as a public health problem. The issue has been magnified by recent abuse of the highly potent synthetic opioid fentanyl and other agents.

SYNONYMS

Drug use
Addiction
Substance abuse

ICD-10CM CODE
F10-F19 Defined by specific substance
DSM-5
Depends on specific substance of abuse

EPIDEMIOLOGY & DEMOGRAPHICS

Genetic factors have a major influence on progression of substance use to dependence, whereas environmental factors unique to the individual play an important role in exposure and initial use of substances.

INCIDENCE: Peak period of both alcohol and illicit drug use disorders occurs in late adolescence and early adulthood, with a substantial reduction in substance use disorders after age 26 yr.

PREVALENCE: The lifetime prevalence of alcohol use disorders is approximately 8%, and prevalence of illicit drug use disorders is 2% to 3%.

PREDOMINANT SEX AND AGE: Substance abuse in general is more common among males than among females (1.3 times more).

GENETICS: Multiple biological mechanisms are involved in tolerance, craving, anxiety, dysphoria, executive cognitive function, and reward. Genome's role in neuroadaptation to drugs and the ways in which genetic variations and environmental exposures cause vulnerability to addictions are still under investigation. Addictive drugs induce adaptive changes in gene expression in brain reward regions, causing tolerance and habit formation with craving and negative affect. A specific effect of the μ-opioid receptor polymorphism (*OPRM1*; Asn40Asp) Asp40 to predict favorable naltrexone treatment response in alcoholism was recently replicated.

RISK FACTORS: Offspring of substance abusers were at twofold increased risk for any substance use disorder and a threefold risk for alcohol and marijuana abuse or dependence compared with offspring of control parents. Individuals who develop substance use disorders in adolescence are more likely to have those symptoms persist into adulthood.

Common risk factors are:

- Family history of addiction
- Being male
- Having another mental health disorder
- Peer pressure
- Lack of family involvement
- Taking a highly addictive drug

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Physical and behavioral symptoms are helpful to determine drug use. Bloodshot or glazed eyes, dilated or constricted pupils (7 or 8 mm pupil size may suggest the influence of cocaine, crack, meth, hallucinogens, or other stimulant; 1 or 2 mm pupil size may indicate the influence of heroin, opiates, or other depressant), abrupt weight changes, bruises, infections, and track marks are common physical signs. Behavioral changes occur as individual becomes more dependent on the drug. Increased aggression or irritability, sudden changes in social network, dramatic changes in habits and/or priorities, involvement in criminal activity, and financial problems are commonly observed.

ETIOLOGY

Theories are categorized into three main subgroups: social, psychological, and biological. There has been an emphasis on the role of personality, age of starting drug abuse, and hereditary and genetic factors. Some studies identified family as the most important and crucial risk factor for drug abuse in youth (lack of a safe and warm environment at home, insecure attachment between children and the parents, role modeling of the parents, loss of a parent, and lack of supervision). Peer pressure is also a strong risk factor. Although there is no general agreement on the gateway effect of drugs such as cannabis, poverty, neighborhood, living in poor and polluted suburbs, and low level of leisure facilities have been identified as impacting factors.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Use a motivational interviewing (MI) style and evidence-based interventions; identify and treat co-occurring medical and psychiatric conditions. Open-ended questions, affirmation, reflective listening, and summary reflections (OARS) are basic MI techniques.

WORKUP

Screening and assessment tools are available. CAGE (Cutdown, Guilty, Annoyed, Eyeopener) and AUDIT (Alcohol Use Disorders Identification Test) are commonly used for alcohol use disorder, and DAST (Drug Abuse Screening Test) is for drugs. CIWA-Ar (revised Clinical Institute Withdrawal Assessment for Alcohol scale assessment) and COWS (Clinical Opiate Withdrawal Scale) are used to assess the severity of alcohol and opioid withdrawal symptoms consequently.

LABORATORY TESTS

Blood alcohol levels, breathalyzer test results, urine drug screens, and, less commonly, hair and saliva analysis can be used to assess patients for possible alcohol and other drug use. Chemicals and their metabolites can be detected in the samples for limited times. Therefore, tests should be chosen and timed carefully.

IMAGING STUDIES

Imaging techniques such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG) have been used to investigate these behaviors in drug-addicted human populations. However, there is no current therapeutic use or monitoring the outcome.

TREATMENT

Multiple treatment options for substance use disorders exist that can help individuals reach treatment goals. No single treatment is right for everyone. Treatment options should be discussed with patients and families to help them decide which ones are best for the patients' conditions. The outcomes of self-change efforts and treatment experiences should be reviewed frequently.

NONPHARMACOLOGIC THERAPY

Talk therapy has been shown to teach skills to avoid relapse, to reduce harmful substance use, and to improve health and quality of life. Cognitive behavioral therapy for substance use disorders and 12-step facilitation and motivational enhancement therapy are commonly used techniques. Peer support by Alcoholics Anonymous, Narcotics Anonymous, and SMART Recovery are also helpful.

ACUTE GENERAL Rx

Inpatient medically supervised withdrawal may be necessary for patients with symptoms of at least moderate alcohol withdrawal and patients with histories of severe withdrawal seizures. CIWA-Ar is a symptom-triggered approach to treatment of alcohol withdrawal with benzodiazepines. Diazepam (Valium), lorazepam (Ativan), and chlordiazepoxide (Librium) are the most frequently used benzodiazepines, with treatment often commencing when CIWA-Ar scores reach 8 to 10, with standing or as-needed dosing for scores from 11 to 20. Benzodiazepine use disorder also requires inpatient admission; tapering the drug in outpatient settings should be closely monitored. Comfort medications (clonidine, dicyclomine, loperamide, ibuprofen) are useful in management of opioid withdrawal symptoms. Buprenorphine, which requires a special DEA X license to prescribe, can be used for both withdrawal and long-term maintenance treatment. The *combo* product (Suboxone) contains buprenorphine, a partial mu opiate receptor agonist, and naloxone, a mu receptor antagonist, which is included to prevent dissolving of the buprenorphine for injectable use. Naloxone is not absorbed significantly when sublingually dissolved, while buprenorphine is. However, naloxone is potent when injected, causing acute withdrawal and thus serving as a

deterrent to buprenorphine abuse. Before starting buprenorphine, patients must be tapered off their opiates to avoid the acute withdrawal that comes with use of buprenorphine, which is strongly bound to the mu receptor. When buprenorphine is used for medically supervised opiate withdrawal, patients are required to go through mild to moderate withdrawal (COWS of >12) before the first dose of buprenorphine is given. Antipsychotics (i.e., haloperidol) may be considered for agitation, hallucinations, and other behavioral disturbances.

CHRONIC Rx

Acamprosate, disulfiram, naltrexone (oral or injectable), and topiramate are the medications that are commonly used for alcoholism treatment. Benzodiazepines should be avoided due to their own risk of addiction, and risk of triggering alcohol relapses. Because these are chronic conditions, the length of the treatment will depend on the individual treatment plan and the patient's success in achieving goals. Maintenance programs with methadone and buprenorphine may be continued for years.

COMPLEMENTARY & ALTERNATIVE MEDICINE

The top three therapies—religious/spiritual healing, relaxation techniques, and meditation—are commonly used adjunctive approaches. Neurofeedback and acupuncture are also reported as supportive.

DISPOSITION

Because of the nature of this chronic/relapsing condition, individuals should be referred to and monitored at outpatient drug and/or alcohol treatment centers. Other health conditions and co-occurring psychiatric disorder treatment can be provided at general mental health clinics. Drug rehabilitation may require a controlled environment, such as those in sober houses and long-term recovery clinics. Alcoholics Anonymous (AA) programs are also effective in providing peer support.

REFERRAL

https://findtreatment.samhsa.gov/

PEARLS & CONSIDERATIONS

COMMENTS

Goals of substance use disorder treatment:

- Stop the harmful use of addictive substances.
- Improve health and wellness.
- Live a self-directed life.
- Strive to reach full potential.
- Improve quality of life.

PREVENTION

Efforts typically focus on children and teens. Besides national recognition of substance use prevention, family-based, school-based, and community prevention programs focus on changing community conditions or policies so that the availability of substances is reduced.

PATIENT & FAMILY EDUCATION

Individuals are provided information to understand the many aspects of what substance abuse is; warning signs of addiction; information about how alcohol and specific drugs affect the mind and body; and the consequences of addiction. Family therapy and education play important roles in the change process. It remains to be seen how legalization of cannabis will affect the rate of early-onset psychotic illness, since cannabis is a known risk factor.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Alcohol Use Disorder (Related Key Topic)
Drug Use Disorder (Related Key Topic)
Hallucinogenic Overdose (Related Key Topic)
Opioid Overdose (Related Key Topic)
Opioid Use Disorder (Related Key Topic)
Synthetic Cannabinoids (Related Key Topic)

AUTHOR: **Tahir Tellioglu, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

The Centers for Disease Control and Prevention (CDC) defines suicide and suicidal behavior as:

- Suicide.
- Death caused by self-directed injurious behavior with intent to die as a result of the behavior.
- Suicide attempt:
  1. A nonfatal self-directed potentially injurious behavior with intent to die as a result of the behavior. A suicide attempt may or may not result in injury.
     a. An estimated 1.3 million adults aged 18 or older (0.6) attempted suicide in the past yr.
     b. There is one suicide for every 25 attempted suicides.
- Suicidal ideation.
- Thinking about, considering, or planning for suicide:
  1. Among adults aged ≥18 yr in the U.S. during 2013.
     a. An estimated 9.3 million adults (3.9% of the adult U.S. population) reported having suicidal thoughts in the past yr (CDC 2015).
     b. An estimated 2.7 million adults (1.1% of the adult U.S. population) made a plan about how they would attempt suicide in the past yr (CDC 2015).
     c. Percentage of adults having serious thoughts about suicide was highest among adults aged 18 to 25 (7.4%), followed by adults aged 26 to 49 (4%) and then by adults aged 50 or older (2.7%).

SYNONYM

Self-murder

ICD-10CM CODES

X64	Intentional self-poisoning by an exposure to other and unspecified drugs, medicaments, and biological substances
X70	Intentional self-harm by hanging, strangulation and suffocation
X71	Intentional self-harm by drowning and submersion
X72	Intentional self-harm by handgun discharge
X75	Intentional self-harm by explosive material
X76	Intentional self-harm by smoke, fire and flames
X78	Intentional self-harm by sharp object
X81	Intentional self-harm by jumping or lying before moving object
X83	Intentional self-harm by other specific means

DSM-5: Categorized by method

EPIDEMIOLOGY & DEMOGRAPHICS

- Suicide was the tenth-leading cause of death for all ages in 2013. There were 41,149 suicides in 2013 in the U.S.—a rate of 12.6 per 100,000, which is equal to 113 suicides each day or 1 every 13 min (CDC 2015).
- CDC researchers wrote in a 2018 report that suicide rates in the U.S. have risen nearly 30% since 1999, and mental health conditions are one of several factors contributing to suicide. In addition, from 1999 to 2015, suicide rates increased among both sexes, all racial/ethnic groups, and all urbanization levels.
- During 2000 to 2016, the suicide rate among U.S. persons ages 16 to 64 yr increased 34%, from 12.9 per 100,000 population to 17.3.

DATA AND STATISTICS: Firearm suicides (CDC 2014):

- Number of deaths: 17,352
- Deaths per 100,000 population: 5.8

Suffocation suicides:

- Number of deaths: 8161
- Deaths per 100,000 population: 2.7

Poisoning suicides:

- Number of deaths: 6358
- Deaths per 100,000 population: 2.1

Suicidal deaths are only part of the problem. More people survive suicide attempts than actually die. They are often seriously injured and need medical and rehabilitative care.

AGE-RELATED DATA:

- Suicide is the third-leading cause of death among persons aged 10 to 14 yr, the second-leading among persons aged 15 to 34, the fourth-leading among persons aged 45 to 54, the eighth-leading among persons aged 55 to 64, and the seventeenth-leading among persons 65 yr and older.
- During 2002 to 2006, the greatest percentage of suicides occurred by firearm among all race/ethnicity groups for persons ages 65 yr and older. Except for Asian/Pacific Islanders, suffocation accounted for the highest percentage of suicides among those 65 yr and older (52.6%).

GENDER DIFFERENCES:

- Women attempt suicide about two to three times as often as men.
- Males succeed at taking their own lives at nearly four times the rate of females and represent 77.9% of all U.S. suicides.
- Suicide is the seventh-leading cause of death for males and the fourteenth-leading cause for females.
- Firearms are the most common method of suicide among males (56.9%).
- Poisoning is the most common method in women (34.8%).

ENVIRONMENTAL FACTORS:

- Suicide rates traditionally decrease in times of war and increase in times of economic crises.
- After adjusting for age, suicide rates are highest in the western and northwestern regions of the U.S.

MARITAL STATUS: Suicide rates are highest among the divorced, separated, and widowed and lowest among the married.

SUBSTANCE USE: CDC data from 16 National Violent Death Reporting System states in 2010: 33.4% of suicide decedents tested positive for alcohol, 23.8% for antidepressants, and 20% for opiates including heroin and prescription painkillers.

FINANCIAL IMPACT OF SUICIDES:

- Suicide results in an estimated $51 billion in combined medical and work lost costs to society (CDC 2015).
- The average suicide costs $1,164,499 (the estimate is based on 2010 CDC data and refers to people aged 10 and above).

SURVIVORS (CDC):

- A survivor of suicide is a family member or friend of a person who died by suicide.
- Surviving the loss of loved one to suicide is a risk factor for suicide.
- Surviving family members and close friends are deeply impacted by each suicide and experience a range of complex grief reactions including guilt, anger, abandonment, denial, helplessness, and shock.
- No exact figure exists, but it is estimated that a median of between 6 and 32 survivors exist for each suicide, depending on the definition used.
- According to another estimate, approximately 7% of the U.S. population knew someone who died of suicide during the past 12 months.

RISK FACTORS (CDC) (TABLE E1):

- Family history of suicide
- Family history of child maltreatment
- Previous suicide attempt(s)
- History of mental disorders, particularly clinical depression
- History of alcohol and substance abuse
- Feelings of hopelessness
- Impulsive or aggressive tendencies
- Cultural and religious beliefs (e.g., belief that suicide is noble resolution of a personal dilemma)
- Local epidemics of suicide
- Isolation, a feeling of being cut off from other people
- Barriers to accessing mental health treatment
- Loss (relational, social, work, or financial)
- Physical illness
- Easy access to lethal methods
- Unwillingness to seek help because of the stigma attached to mental health and substance abuse disorders or to suicidal thoughts
- Rates are higher in developing countries.
- Rates vary by occupation, ethnicity, and employment status.

PROTECTIVE FACTORS (CDC):

- Effective clinical care for mental, physical, and substance abuse disorders
- Easy access to a variety of clinical interventions and support for help seeking
- Family and community support (connectedness)
- Support from ongoing medical and mental health care relationships
- Skills in problem solving, conflict resolution, and nonviolent ways of handling disputes
- Cultural and religious beliefs that discourage suicide and support instincts for self-preservation

SUICIDAL BEHAVIOR:

- All suicidal behavior should be taken seriously, as a failed attempt may lead to a completed suicide in the future.
- Nearly half of suicides are preceded by an attempt that does not end in death.

TABLE E1 Suicide and Risk Factors: A Summary

Primary Diagnosis	Demographics	Personality Factors	Comorbidities	Social Factors	Other Factors
Bipolar	Male	Borderline	Substance abuse	Divorced	Means available
Schizophrenia	Older age	Narcissistic	Panic disorder	Widower	History of child abuse
Major depressive disorder	White race	Antisocial	Anxiety	Lives alone	Few reasons to live
Dysthymia	Homosexuality	Conduct disorder	Axis III dx	Isolated	Many adverse events
Adjustment disorder	History of attempt	Impulsive		Money worries	Change in grades
Conduct disorder	Family history			Other losses	Change in friends
Psychosis	Suicidal ideas			No religion	Giving things away
	Hopeless				Guns in the home
	Helpless				

dx, Diagnosis.
From Sadock BJ et al: *Kaplan & Sadock's comprehensive textbook of psychiatry,* ed 9, Philadelphia, 2009, Wolters Kluwer Health/Lippincott Williams & Wilkins.

- Those with a history of attempts are 23 times more likely to eventually end their own lives than those without.
- A suicidal gesture does not have death as a goal, but can serve as a dramatic way of alerting others to some type of ongoing distress.
- Risky behaviors such as speeding or disregarding traffic laws, or abusing drugs, are considered parasuicide when the person shows total disregard for whether the actions might result in his or her death.
- Unsuccessful suicide attempts may also result from miscalculations in the plan. These people are at high risk for attempting suicide again.

EVALUATION:

- Directly inquire into the presence of suicidal ideation. Approximately one half to two thirds of individuals who commit suicide visit physicians within 1 mo of taking their lives. Key components of the suicide evaluation are summarized in Table E2.
- Emergency evaluation: See https://www.nimh.nih.gov/research/research-conducted-at-nimh/asq-toolkit-materials/emergencydepartment/pdfs/bssa_155388.pdf
- Explicit suicidal intent, hopelessness, and a well-formulated plan indicate high risk. Clinicians can use the mnemonic SAL: Is the method specific? Is it available? Is it lethal? Remember to inquire about gun availability.
- The concurrence of multiple psychiatric problems, substance abuse, and multiple physical problems increases the risk.
- Covert suicidal ideation occurs in patients primarily with multiple vague physical complaints, depression, anxiety, or substance abuse.
- Primary care-feasible screening tools might help to identify some adults at increased risk for suicide but have limited ability to detect suicide risk in adolescents. Psychotherapy may reduce suicide attempts in some high-risk adults, but effective interventions for high-risk adolescents are not yet proven.

TABLE E2 Components of the Suicide Evaluation

- Conduct a thorough psychiatric examination.
  1. Establish initial rapport.
  2. Combine open-ended and direct questions.
  3. Gather information from family, friends, and coworkers.
  4. Conduct a mental status examination.
- Complete a suicide assessment.
  1. Ask specifically about thoughts of suicide and plans to commit suicide.
  2. Examine the details of the suicide plan.
  3. Determine the risk/rescue ratio.
  4. Assess the level of planning and preparation.
  5. Evaluate the degree of hopelessness.
  6. Identify precipitants.
- Establish a psychiatric and/or medical diagnosis.
  1. Obtain history.
  2. Use data from a psychiatric examination.
  3. Incorporate data from prior or current treaters.
- Estimate suicide risk.
  1. Evaluate risk factors.
  2. Evaluate available social supports.

From Stern TA et al: *Massachusetts General Hospital handbook of general hospital psychiatry,* ed 7, Philadelphia, 2018, Elsevier.

ACUTE INTERVENTIONS:

- Place patient in a safe environment (usually hospitalization in a psychiatric unit or a medical unit with continuous observation).
- Emergency medical stabilization and clearance as required, related to severity and lethality of attempt, age, comorbid medical issues, and overall clinical presentation.

ACUTE PSYCHOPHARMACOLOGIC INTERVENTIONS:

- Benzodiazepines may be useful in reducing extreme anxiety and dysphoria in an acutely suicidal patient; however, these agents should not be prescribed until the means of the suicidal attempt are known (not a benzodiazepine overdose) and patient is medically stable (i.e., respiratory system, vital signs, cognitive functioning are stable).
- Antipsychotics (typicals or atypicals) can be used if psychosis is present (e.g., voices telling patient to hurt self) and to manage acute agitation.
- If indicated, mood stabilizers and antidepressants can be started in the acute setting but may have up to a 2-wk latency period. However, awareness of increased risk of suicidal thoughts/behavior with these medications in some populations is required.

THERAPY:

- Long-term: Psychotherapy aimed at factors that underlie the decision to pursue suicide or at the risk factors contributing to suicidal behavior. Remember that the basic suffering reflected in suicidality with its hopelessness and despair is often fueled by disconnectedness and loss of attachments.
- Substance abuse treatment (e.g., Alcoholics Anonymous, Narcotics Anonymous) when substance use disorder is present.
- Therapy should be aimed at the underlying condition (e.g., antidepressants for depression, anxiolytics or antidepressants for anxiety, substance abuse treatment, or psychotherapy for chronic low self-esteem, hopelessness).
- In elderly, loneliness and medical disability are major reasons for suicide and therefore major targets for intervention.
- Involvement of family members, spouse, loved one, caregivers if possible for therapy and management.
- A history of adverse childhood experiences increases suicide risk.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Ali Kazim, MD**

SUGGESTED READINGS

Alliance of Hope: For Suicide Survivors. Website: https://allianceofhope.org/
American Association of Suicidology. Website. www.suicidology.org.
Anglemyer A et al: The accessibility of firearms and risk for suicide and homicide victimization among household members, *Ann Intern Med* 160:101-110, 2014.
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Horowitz L et al: Ask suicide-screening questions (ASQ), a brief instrument for the pediatric emergency department, *Arch Pediatr Adolesc Med* 166(12):1170-1176, 2012.
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Snyder L et al: Ethics and the legalization of physician-assisted suicide: an American College of Physicians position paper, *Ann Intern Med* 167:576-578, 2017.
Tsai A et al: Social integration and suicide mortality among men: 24-year cohort study of U.S. health professionals, *Ann Intern Med* 161:85-95, 2014.

Superior Vena Cava Syndrome ALG

BASIC INFORMATION

DEFINITION

Superior vena cava (SVC) syndrome is a set of symptoms that results when a mediastinal mass compresses the SVC or the veins that drain into it, resulting in obstruction of blood flow from the head, neck, upper torso, or extremities to the right atrium.

SYNONYM

SVC

ICD-10CM CODES

I87.1	Compression of vein
S25.20XA	Unspecified injury of superior vena cava, initial encounter
S25.29XA	Other specified injury of superior vena cava, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

- SVC syndrome occurs in 15,000 persons in the U.S. every yr.
- More than 50% of patients present with SVC on presentation of malignancy.
- Mirrors lung cancer (especially small cell carcinoma) and lymphoma.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The pathophysiology of the syndrome involves increased pressure in the venous system draining into the SVC producing edema of the head, neck, and upper extremities. Symptoms develop over a period of 2 weeks in one third of patients and include:

- Shortness of breath
- Chest pain
- Cough
- Dysphagia, hoarseness, stridor
- Headache
- Syncope
- Visual trouble

Signs:

- Chest wall vein distention (Fig. E1)
- Neck vein distention
- Facial edema, facial plethora
- Upper-extremity swelling
- Cyanosis

ETIOLOGY

- Lung cancer (65% of all cases, of which half are small cell lung cancer)
- Lymphoma (15%)
- Thymoma
- Tuberculosis
- Goiter
- Aortic aneurysm (arteriosclerotic or syphilitic)
- SVC thrombosis:
  1. Primary: Associated with a central venous catheter
  2. Secondary: Complication of SVC syndrome associated with one of the above-mentioned causes
- Inflammatory process, fibrosing mediastinitis
- Fig. E2 illustrates the anatomy of superior vena cava syndrome. Table 1 summarizes common malignancies associated with SVC syndrome in adults.

DIAGNOSIS

Diagnostic imaging (Fig. E3 and E4): CT scan of the chest with contrast is the most useful diagnostic study. MRI is usually adequate to establish the diagnosis of SVC obstruction and to assist in the differential diagnosis of probable cause.

DIFFERENTIAL DIAGNOSIS

The syndrome is characteristic enough to exclude other diagnoses. The differential diagnosis concerns the underlying etiologies listed previously.

WORKUP

- Chest radiograph (mediastinal widening, pleural effusion)
- Chest CT with contrast or MRI (in patient who cannot tolerate contrast medium) usually confirms the diagnosis
- Venography: Rarely needed. Warranted only when an intervention (e.g., stent or surgery) is planned
- Percutaneous needle biopsy, endobronchial ultrasound-guided needle biopsy, or

TABLE 1 Malignancies Associated with Superior Vena Cava (SVC) Syndrome in Adults*

Neoplastic Diagnosis	Percentage of SVC	Percentage of Disease-Associated SVC
Lung cancer, stage 3B or 4:	48-81	
Small cell lung cancer		15-45
Squamous cell cancer		20-25
Adenocarcinoma		5-25
Large cell carcinoma		4-30
Lymphoma:	2-21	
Diffuse large cell lymphoma		64
Lymphoblastic lymphoma		33
Breast cancer	11	

*Includes lung cancer, lymphomas, and metastases from other solid tumors. 75% to 85% of patients with SVC have neoplastic disease.
From Zipes DP et al (eds): *Braunwald's heart disease,* ed 7, Philadelphia, 2005, Saunders.

BOX 1 Approach to Patients with Superior Vena Cava Obstruction

The diagnosis is established by physical examination and clinical presentation (see text).

- Respiratory status should be assessed promptly. Only patients in extremis should be treated urgently with radiation therapy or stent placement without a histologic diagnosis. Emergency therapy is necessary in fewer than 5% of all superior vena cava (SVC) obstruction cases.
- Diagnostic evaluation should proceed with the least invasive procedures performed initially followed by more invasive procedures as needed to obtain histologic diagnosis:
  1. Chest radiography
  2. Sputum cytology
  3. Thoracentesis with cytologic evaluation of fluid
  4. Node biopsy if a palpable node is present; avoid fine-needle aspiration if lymphoma is suspected
  5. Fiber-optic bronchoscopy with endobronchial ultrasound
  6. Mediastinoscopy with video-assisted imaging
  7. Thoracostomy with video-assisted imaging
- Evaluation may vary depending on the age and sex of the patient:
  1. In older adults (i.e., ≥50 years), the most common cause of SVC obstruction is lung cancer; lymphoma and metastatic cancer are less common, and benign processes are uncommon.
  2. In young adults (<50 years old), the most common cause of SVC obstruction is lymphoma (usually large cell lymphoma or lymphoblastic lymphoma; rarely Hodgkin disease). Lung cancer and thoracic malignancy are less common. Germ cell cancer (almost never in female patients) and benign causes are uncommon. The preceding evaluation should be modified to include the following studies before more invasive procedures are performed:
     a. Serum tumor markers (i.e., β-human chorionic gonadotropin, α-fetoprotein, and lactate dehydrogenase)
     b. Bone marrow aspiration and biopsy

From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE 2 Comparison of Treatment Modalities for Malignancy-Related Superior Vena Cava Obstruction

Modality	Time to Symptom Relief	Percentage with Symptom Response	Potential for Combined Modality Therapy
Radiation therapy	3-30 days	56-96	Yes
Chemotherapy	1-2 weeks	59-77	Yes
Stent placement	0-72 hours	78-95	Yes

From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

mediastinoscopy are usually the initial diagnostic modalities used to establish a histologic diagnosis
- Box 1 summarizes an approach to patients with superior vena cava obstruction.

Rx TREATMENT

- Tissue diagnosis is usually needed before commencing therapy. EBUS is now considered the first step in evaluation. Mediastinoscopy would be considered if EBUS is non-diagnostic or there is high clinical suspicion for lymphoma.
- Management is guided by the severity of the symptoms and the underlying etiology. Table 2 compares treatment modalities for malignancy-related superior vena cava obstruction.
- Most patients with SVC do not require emergency intervention. Emergency empiric radiation is indicated in critical situations such as respiratory failure or central nervous system signs associated with increased intracranial pressure.
- Treatment of the underlying malignancy:
  1. Radiotherapy: The majority of tumors causing SVC syndrome are sensitive to radiotherapy
  2. Systemic chemotherapy
- Anticoagulant or fibrinolytic therapy in patients who do not respond to cancer treatment within a week or if an obstructing thrombus has been documented.
- Loop diuretics are often used, but their effect is limited.
- Upright positioning and fluid restriction until collateral channels develop and allow for clinical regression are useful modalities for SVC syndrome secondary to benign disease.
- Steroids (dexamethasone 4 mg q6h) may be useful in reducing the tumor burden in lymphoma and thymoma after definitive diagnosis is made.
- Percutaneous self-expandable stents that can be placed under local anesthesia with radiologic manipulation are useful in the treatment of SVC syndrome to bypass the obstruction, especially in cases associated with malignant tumors.
- Surgical bypass grafting is infrequently used to treat SVC syndrome.
- Fig. 5 illustrates a management algorithm for superior vena cava obstruction.

REFERRAL

To a thoracic surgeon, pulmonary specialist, or oncologist

AUTHOR: **Gaetane Michaud, MD**

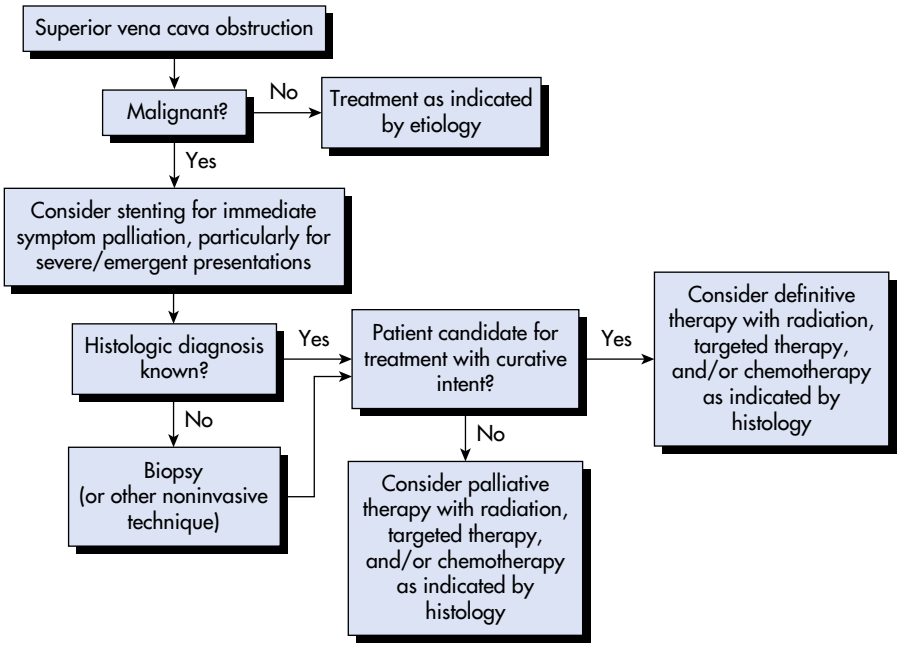

FIG. 5 A management algorithm for superior vena cava obstruction. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

FIG. E1 A patient with characteristic venous dilation and facial edema. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

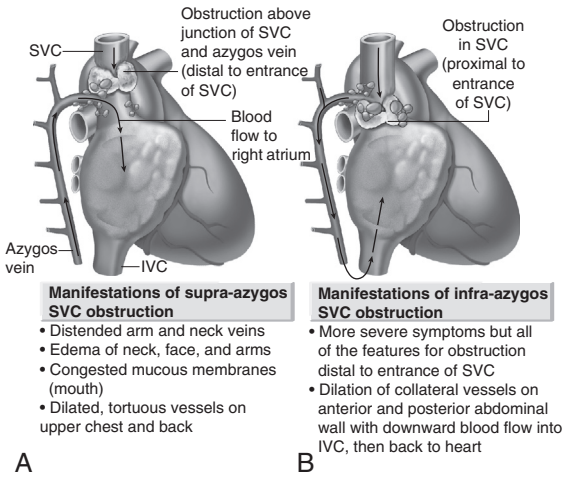

FIG. E2 Superior vena cava (SVC) syndrome secondary to external compression of the SVC by a lung tumor and thrombosis of the SVC. A, Initial venogram showing compression of the superior vena cava and filling defects because of thrombus. **B,** Venogram after 24 hours of catheter-directed thrombolysis with resolution of the thrombus but residual stenosis. **C,** Balloon venoplasty. **D,** Final angiogram after deployment of a self-expanding stent. *RA,* Right atrium. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.)

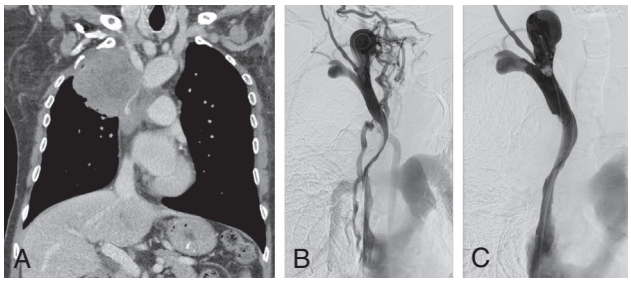

FIG. E3 A 58-year-old man presented with facial edema, bilateral upper extremity swelling and shortness of breath. A coronal reconstruction image **(A)** from a contrast-enhanced computed tomography scan shows a large right upper lobe mass extending into the mediastinum with severe compression of the superior vena cava. Venography **(B)** confirms severe stenosis of the superior vena cava with multiple mediastinal collaterals. The obstruction is inferior to the azygos vein confluence with the superior vena cava. The patient was treated with placement of an intravascular stent (Wall Stent, Boston Scientific, Natick, MA). Post-stent venography **(C)** shows a widely patent superior vena cava and disappearance of collaterals in the thorax. The symptoms improved within 12 hours. Subsequently, a biopsy was performed, which confirmed small cell lung cancer. The patient received radiation therapy. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

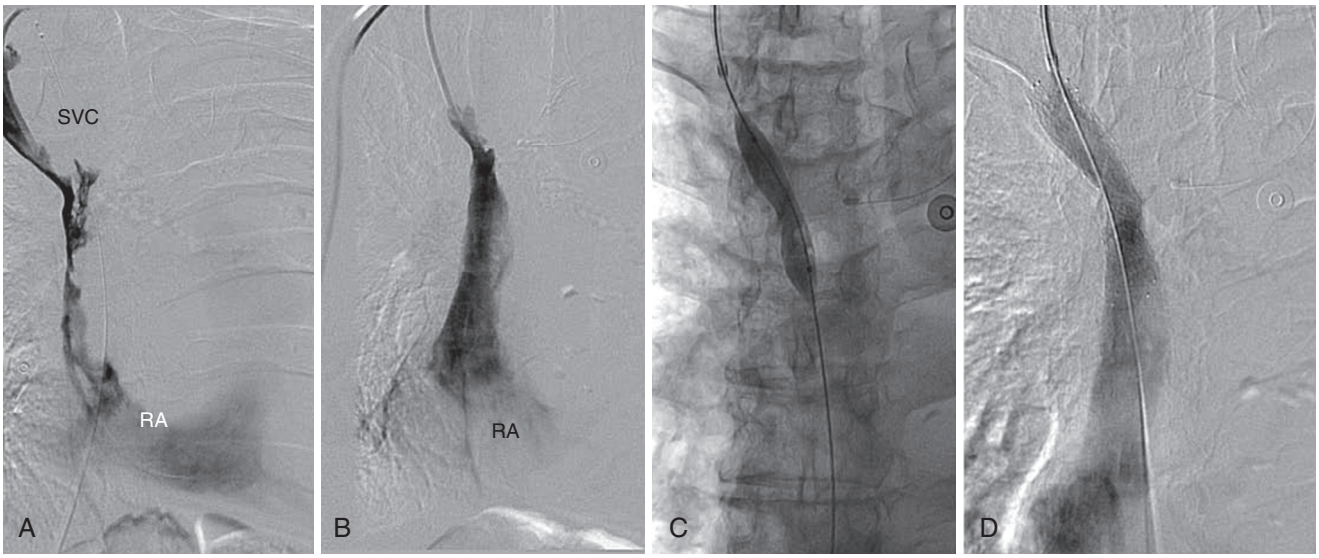

FIG. E4 Anatomy of superior vena cava (SVC) syndrome. Lymph nodes may obstruct blood return above the entrance of the azygos vein **(A),** resulting in edema of the face, neck, and arms and distended veins in the neck and arms and over the upper chest. Obstruction below the return of the azygos vein **(B)** results in retrograde flow through the azygos through collateral veins to the inferior vena cava (IVC), with all the symptoms and signs in **A** plus dilation of the veins over the abdomen as well. (Modified from Skatin AT [ed]: *Atlas of diagnostic oncology,* ed 3, Philadelphia, 2003, Elsevier.)

BASIC INFORMATION

DEFINITION

Supraventricular tachycardia (SVT) is a group of rapid regular tachyarrhythmia. There are three major categories of SVT:

1. Atrial tachycardia (AT): An arrhythmia that originates from the atrium and does not involve the AV node. This is usually a focal arrhythmia. In some cases, the underlying mechanism may be a reentry circuit, either a small circuit (microreentry) or a large circuit (macroreentry)
2. AV nodal reentrant tachycardia (AVNRT)
3. AV reentrant tachycardia (AVRT) (Fig. 1)

The latter two are reentrant arrhythmia that always involve the AV node as part of the circuit (Fig. 1).

Other forms of arrhythmia that involve the atria, such as atrial fibrillation and atrial flutter, have distinct electrocardiographic features and are covered in separate chapters. Rare forms of SVT such as inappropriate sinus tachycardia, sinus mode reentry tachycardia, and junctional tachycardia are beyond the scope of this chapter.

SYNONYMS

SVT
Paroxysmal supraventricular tachycardia
PSVT

ICD-10CM CODE
I47.1 Supraventricular tachycardia

EPIDEMIOLOGY & DEMOGRAPHICS

SVT is most commonly diagnosed between the ages of 12 and 30. SVT occurs most commonly in patients with no prior cardiac conditions. AVNRT is the most common type of SVT in both genders and in all ages. It occurs most commonly in young women. AVRT is the second most common SVT, and it is typically diagnosed in younger patients as compared to the age of patients with AVNRT. AT is more commonly associated with structural heart disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients may be either symptomatic or asymptomatic.
- Patient may be aware of "fast" regular heartbeat (but sometimes complain of irregular heartbeat: palpitations); may complain of weakness, dyspnea, dizziness, chest pain, presyncope or, rarely, syncope.
- Patients with AVNRT may complain of neck pounding during the episode due to simultaneous contraction of the atria and ventricles with closed AV valves causing a sharp increase in atrial and jugular venous pressure.
- In some cases the episodes can be triggered by physical activity or psychological stress, but in others there may not be an obvious trigger. In patients with AVNRT, sometimes the arrhythmia is reproducibly initiated when bending forward to pick up an item from the floor.
- Hemodynamic status during the arrhythmia may vary and depend on the patient's comorbidities and presence of underlying structural heart disease. Usually, patients are hemodynamically stable.
- Physical examination is most commonly normal and unrevealing, except rapid regular heart rate and occasionally hypotension. In patients with AVNRT sharp tall jugular vein A waves may be seen when the right atrium contracts against a closed tricuspid valve.

ETIOLOGY (SEE FIG. 1)

- AVNRT: Dual electrical pathways within the AV node. In typical AVNRT the anterograde limb conducts slowly (slow pathway) and the retrograde limb has fast conduction properties (fast pathway), and vice versa in atypical AVNRT.
- AVRT is accessory pathway mediated, either orthodromic (antegrade through the AV node and retrograde through the accessory pathway) or, much less commonly, antidromic (antegrade through the accessory pathway and retrograde through the AV node). In the case of antidromic tachycardia, the QRS will be wide and fully preexcited. In some patients, the presence of accessory pathway is not evident on the baseline ECG (concealed accessory pathway), while in others it is manifest in the baseline ECG, presenting the typical features of the Wolff-Parkinson-White (WPW) syndrome.
- Paroxysmal atrial tachycardia and multifocal atrial tachycardia: abnormal automaticity of atrial tissue or triggered activity. In some cases (especially in patients who underwent previous cardiac surgery such as valve replacement or ASD closure), the underlying mechanism is macroreentrant AT.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of SVT relies principally on the 12-lead ECG. Every patient suspected of having an episode of SVT should have a 12-lead ECG done immediately. Typically, patients with SVT will present with a narrow complex QRS tachycardia with a ventricular rate faster than 100 beats per minute (bpm) and typically faster than 130 to 150 bpm.

P wave morphology can be useful in discriminating rhythms. P waves with a similar axis to the sinus node can be atrial tachycardias and sinus tachycardias. P waves with retrograde depolarization of the atria (seen as inverted in the inferior leads) can be seen in AVNRT, AVRT, and atrial tachycardia. Sawtooth P waves are indicative of classical counterclockwise typical type I flutter, and an absence of P waves with irregular R-R intervals points to atrial fibrillation. Variable (>3) morphologies of P wave are suggestive of multifocal atrial tachycardia. Wide QRS complex (>0.12 sec) with initial slurring (delta wave) during sinus rhythm and short PR (<0.12 sec) is characteristic of Wolff-Parkinson-White syndrome.

In typical AVNRT, due to the small size of the circuit within the AV node and the fast retrograde conduction, there is simultaneous depolarization of the ventricles and atria, thus making the P wave "buried" in the QRS and

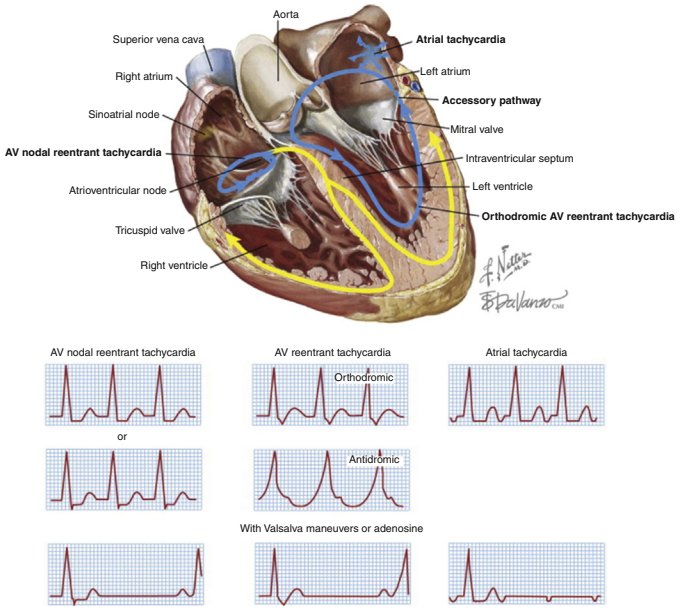

FIG. 1 Typical electrocardiographic recordings and anatomic representation of the common supraventricular tachycardias. *AV,* Atrioventricular. (From Runge MS et al [eds]: *Netter's cardiology,* ed 2, Philadelphia, 2010, Saunders. Adapted from Delacretaz E: Clinical practice: supraventricular tachycardia, *N Engl J Med* 354:1039-1051, 2006.)

therefore not visible or inscribed very close to the QRS at the final part of the QRS complex, and sometimes creating a "pseudo terminal S wave" usually seen in leads II, III, and aVF and "pseudo terminal R waves" at the end of the QRS in V1 and avR (Fig. 1).

In orthodromic AVRT, the P wave is usually visible close after the QRS due to the rapid conduction properties of the accessory pathway (short RP tachycardia). In AT, the P wave is usually noticed farther away after the QRS (long RP tachycardia) (Fig. 1).

Other diagnostic maneuvers that may assist in the differential diagnosis are vagal maneuvers (such as carotid sinus massage) or giving intravenous AV nodal blocking agents such as adenosine or verapamil) to produce AV nodal conduction block. This will terminate reentrant arrhythmia dependent on the AV node—AVNRT and AVRT—but not AT, which will continue, albeit with nonconducted P waves.

Other arrhythmias that present with narrow complex tachycardia like PSVT are:

- Fascicular VT
- Junctional tachycardias
- Artifact such as with Parkinson disease

SVT can conduct with bundle branch block (BBB) and wide QRS either due to preexisting BBB on the baseline ECG or due to aberrant conduction (rapid rate–dependent BBB). When a patient presents with wide QRS tachycardia, VT must be excluded first. Features to distinguish SVT from ventricular tachycardia are outlined in Table 1.

WORKUP

- Electrocardiography
- Echocardiography to exclude structural heart disease
- Thyroid function tests
- Complete blood count to exclude anemia or infection as an underlying trigger for the event
- In most cases the workup will be negative, with no underlying cardiac or systemic pathology and no clear triggers for an acute episode
- Holter or event monitor to document the arrhythmias if they are paroxysmal and not documented yet

TABLE 1 Features That May Differentiate Ventricular Tachycardia from Supraventricular Tachycardia with Aberrancy

Helpful Features	Implications
Positive QRS concordance	Diagnostic of VT
Presence of AV dissociation, capture beats, or fusion beats	Diagnostic of VT
Atypical RBBB (monophasic R, QR, RS, or triphasic QRS in V1; R:S ratio <1, QS or QR, monophasic R in V6)	Suggests VT
Atypical LBBB (R >30 min or R to S [nadir or notch] >60 min in V1 or V2; R:S ratio <1, QS or QR in V6)	Suggests VT
Shift of axis from baseline	Suggests VT
History of CAD	Suggests VT
QRS during tachycardia identical to QRS during sinus rhythm	Suggests SVT
Termination with adenosine	Suggests SVT

AV, Atrioventricular; *CAD,* coronary artery disease; *LBBB,* left bundle branch block; *RBBB,* right bundle branch block; *SVT,* supraventricular tachycardia; *VT,* ventricular tachycardia.

Stambler BS et al: Etripamil nasal spray for rapid conversion of supraventricular tachycardia to sinus rhythm, *J Am Coll Cardiol* 72:489-497, 2018.

Rx TREATMENT (FIG. 2)

NONPHARMACOLOGIC THERAPY

Acute termination: If the patient is hemodynamically unstable, prompt synchronized cardioversion with an external defibrillator using 50 to 100 J should be performed.

If the patient is stable, Valsalva maneuver in the supine position is the most effective way to terminate most types of SVT; carotid sinus massage (after excluding occlusive carotid disease and murmurs over the carotid arteries) is also commonly used to elicit vagal efferent impulses. These are effective in terminating AVRT, AVNRT, and may occasionally terminate some types of atrial tachycardia, but in the case of sinus tachycardia, atrial flutter, and atrial fibrillation, they only transiently slow down AV conduction without terminating the actual tachycardia.

PHARMACOLOGIC THERAPY

- Adenosine is useful to terminate acutely orthodromic AVRT and AVNRT and can uncover the underlying rhythm in paroxysmal atrial tachycardia (Fig. 3); it is the first choice of therapy for treatment of almost all episodes of SVT unresponsive to vagal maneuvers. The dose is 6 mg given as a rapid IV bolus; tachycardia is usually terminated within a few seconds. If this fails, one may repeat with 12

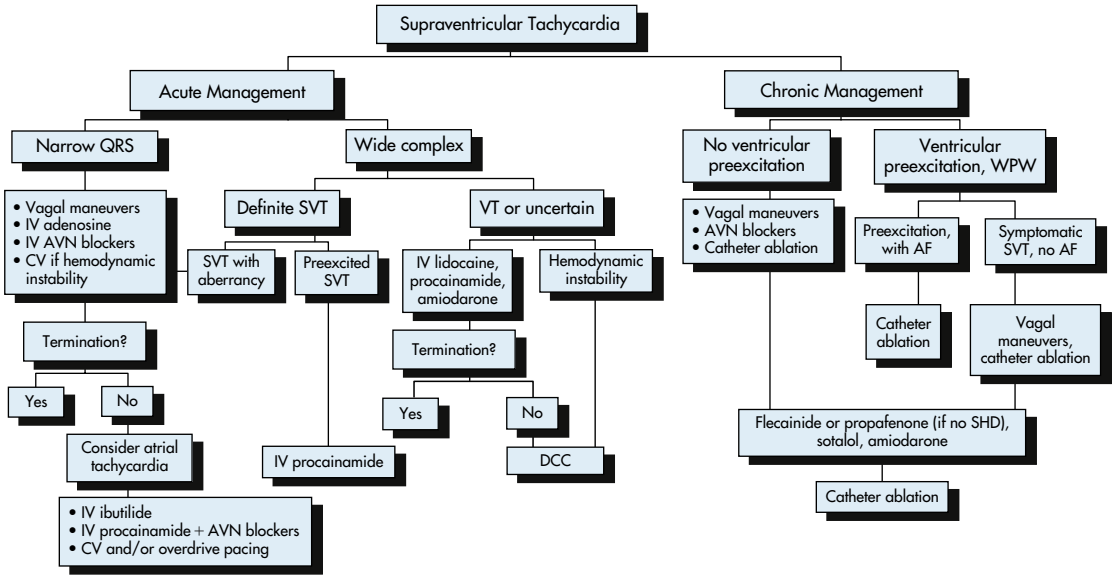

FIG. 2 Supraventricular tachycardia. *AF,* Atrial fibrillation; *AVN,* atrioventricular node; *CV,* cardioversion; *IV,* intravenous; *DCC,* direct current cardioversion; *SHD,* structural heart disease (no overt evidence of myocardial, valvular, congenital or coronary heart disease); *SVT,* supraventricular tachycardia; *VT,* ventricular tachycardia; *WPW,* Wolff-Parkinson-White. (From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

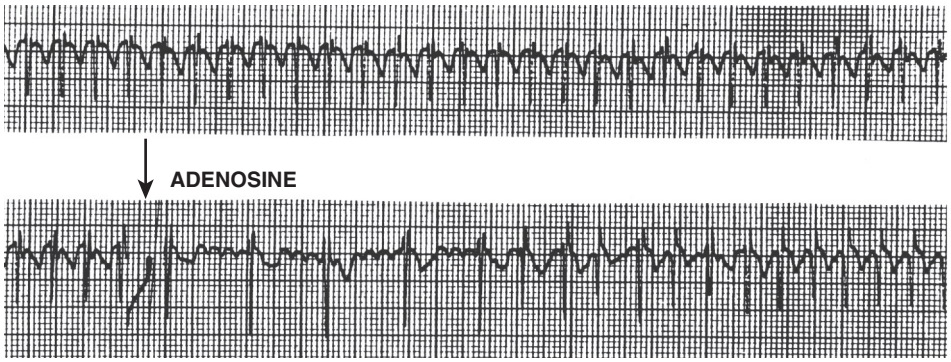

FIG. 3 Adenosine can uncover the mechanism of supraventricular tachycardia. A 3-month-old infant developed an extremely fast, narrow QRS complex tachycardia and a heart rate of 220 beats/min after insertion of a central line through a jugular vein. Adenosine produced a transient atrioventricular block and unmasked very rapid atrial fibrillation waves (570 beats/min). (From Park MK: *Park's Pediatric cardiology for practitioners,* ed 6, Philadelphia, Elsevier, 2014.)

mg IV bolus. Contraindications are second- or third-degree atrioventricular block; WPW with atrial fibrillation; sick sinus syndrome; and chronic use of drugs such as dipyridamole, theophylline, or aminophylline; and heart transplant. Adenosine may cause bronchospasm in asthmatics.

- Verapamil 5 to 10 mg IV is given over 5 min; if no effect, may repeat in 30 min.
  1. Verapamil should be used cautiously in patients with SVT associated with hypotension.
  2. Slow injection of calcium chloride (10 ml of a 10% solution given over 5 to 8 min before verapamil administration) decreases the hypotensive effect without compromising its antiarrhythmic effect.
- Metoprolol (IV 5 mg/2 min up to 15 mg) or esmolol (500 μg/kg IV bolus, then 50 μg/kg/min) may be effective in the treatment of SVT.
  - IV digoxin (0.75 to 1 mg slow IV loading in increments of 0.25 mg over several hours) is rarely used in SVT but may tried if other agents are not effective.
  - Digoxin, beta-blockers, and calcium-channel blockers should be avoided in patients with pre-excitation syndrome and antidromic AVRT or preexcited atrial fibrillation to avoid increased conduction through the accessory pathway.
  - Recently a new rapidly acting intranasal calcium-channel blocker—etripamil—was reported to be effective in rapid conversion of SVT to sinus rhythm. This may prove in the future to be an important treatment modality but is not yet available for routine clinical use.

CHRONIC TREATMENT

The goal is prevention of recurrent episodes. In patients with infrequent and minimally symptomatic episodes without preexcitation, it is optional to provide treatment only during acute episodes. In patients with recurrent symptomatic episodes, regular treatment with beta-blockers or nondihydropyridines calcium channel blockers can be tried; if these fail, class Ic antiarrhythmics are an option. It is also possible to treat patients who have infrequent symptomatic episodes with a "pill-in-the-pocket" strategy with either beta-blockers or other antiarrhythmics. Patients who fail antiarrhythmic therapy, develop side effects due to medications, or refuse medical therapy should be referred for catheter ablation. This is a highly effective mode of treatment with low risk of complications. Recent studies show that ablation therapy is highly effective, safe, and associated with a very low recurrence rate.

DISPOSITION

Most patients respond well with resolution of the SVT upon treatment (see "Acute General Rx"). Some patients may need chronic AV blocking agents for recurrence.

REFERRAL

Radiofrequency ablation (RFA) is the procedure of choice in symptomatic patients who are refractory to medical therapy especially in AVRT, AVNRT, and atrial flutter. RFA has high efficacy rates (single procedure success is 93.2%), low all-cause mortality (0.1%), and low adverse events (2.9%). Despite high reported success rates, RFA appears to be underused in clinical practice.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Supraventricular Tachycardia (Patient Information)

AUTHORS: **Moti Haim, MD,** and **Yuval Konstantino, MD**

SUGGESTED READINGS

Colucci RA et al: Common types of supraventricular tachycardia: diagnosis and management, *Am Fam Physician* 82(8):942-952, 2010.

Page RM et al: 2015ACC/AHA/HRS Guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society, *J Am Coll Cardiol* 67(13):e27-e115, 2016, https://doi.org/10.1016/j.jacc.2015.08.856.

Katritsis DG et al: Catheter ablation vs. antiarrhythmic drug therapy in patients with symptomatic atrioventricular nodal re-entrant tachycardia: a randomized, controlled trial, *Europace* 19 :602-606, 2017.

Brachmann J et al: Long-term symptom improvement and patient satisfaction following catheter ablation of supraventricular tachycardia: Insights from the German ablation registry, *Eur Heart J* 38:1317-1326, 2017.

BASIC INFORMATION

DEFINITION

Syncope is the transient loss of consciousness with spontaneous recovery that results from an acute global reduction in cerebral blood flow. There are three major types: neurocardiogenic, orthostatic, and cardiac. Syncope is a symptom, and the goal is to distinguish lethal causes from benign causes of transient loss of consciousness.

ICD-10CM CODE
R55 Syncope and collapse

EPIDEMIOLOGY & DEMOGRAPHICS

- Syncope accounts for 3% to 5% of emergency department visits.
- 30% of the adult population will experience at least one syncopal episode during their lifetimes.
- Incidence of syncope is highest in elderly men and young women.
- 15% of children and adolescents experience syncope; fewer than 5% have cardiac causes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Blood pressure: If low, consider orthostatic hypotension; if unequal in both arms (difference >20 mm Hg), consider subclavian steal or dissecting aneurysm. (NOTE: Blood pressure [BP] and heart rate should be recorded in the supine and standing positions, waiting at least 5 minutes between each position.) If there is a drop in BP but no change in heart rate (HR), the patient may be taking a beta-blocker or may have an autonomic neuropathy.
- Pulse: If patient has tachycardia, bradycardia, or irregular rhythm, consider arrhythmia.
- Heart: If there are murmurs present, consider syncope attributable to left ventricular outflow obstruction (aortic stenosis or idiopathic hypertrophic subaortic stenosis); if there are jugular venous distention and distal heart sounds, consider cardiac tamponade.
- Carotid sinus pressure: Can be diagnostic if it reproduces symptoms and other causes are excluded; a pause >3 sec or a systolic BP drop >50 mm Hg without symptoms or <30 mm Hg with symptoms when sinus pressure is applied separately on each side for <5 sec is considered abnormal. This test should be avoided in patients with carotid bruits or cerebrovascular disease. ECG monitoring, IV access, and bedside atropine should be available when carotid sinus pressure is applied.

ETIOLOGY

- Neurocardiogenic or neurally mediated syncope: most common type, accounting for two-thirds of cases. It includes vasovagal, situational, carotid hypersensitivity, and postexertional syncope (Box 1).
  1. Psychophysiologic (emotional upset, panic disorders, hysteria, hyperventilation)
  2. Visceral reflex (micturition, defecation, food ingestion, coughing, ventricular contraction, glossopharyngeal neuralgia)
  3. Carotid sinus pressure
  4. Reduction of venous return caused by Valsalva maneuver
  5. Postural tachycardia syndrome (POTS)
- Orthostatic hypotension (10% of cases):
  1. Hypovolemia
  2. Vasodilator medications
  3. Autonomic neuropathy (diabetes, amyloid, Parkinson disease, multisystem atrophy)
  4. Pheochromocytoma
  5. Carcinoid syndrome
- Cardiac (10% to 20%):
  1. Reduced cardiac output:
     a. Left ventricular outflow obstruction (aortic stenosis, hypertrophic cardiomyopathy)
     b. Obstruction to pulmonary flow (pulmonary embolism, pulmonic stenosis, primary pulmonary hypertension)
     c. Myocardial infarct with pump failure
     d. Cardiac tamponade
     e. Mitral stenosis
     f. Reduction of venous return (atrial myxoma, valve thrombus)
     g. Beta-blocker therapy
  2. Arrhythmias or asystole:
     a. Extreme tachycardia (>160 to 180 beats/min)
     b. Severe bradycardia (<30 to 40 beats/min)
     c. Sick sinus syndrome
     d. Atrioventricular block (second or third degree)
     e. Ventricular tachycardia or fibrillation
     f. Long QT syndrome
     g. Pacemaker malfunction
     h. Psychotropic medications and beta-blockers (Table 1)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Seizure (see "Workup").
- Vertebrobasilar transient ischemic attack (TIA) usually manifests as diplopia, vertigo, or ataxia but not loss of consciousness. Isolated episodes of transient loss of consciousness (TLOC, Fig. E1) without accompanying neurologic symptoms are unlikely to be TIAs.

BOX 1 Causes of Syncope

Reflex Syncopal Syndromes
- Vasovagal faint (common faint)
- Carotid sinus syncope
- Situational faint:
  1. Acute hemorrhage
  2. Cough, sneeze
  3. Gastrointestinal stimulation (swallow, defecation, visceral pain)
  4. Micturition (postmicturition)
  5. Postexercise
  6. Pain, anxiety
- Glossopharyngeal and trigeminal neuralgia

Orthostatic
- Aging
- Antihypertensives
- Autonomic failure:
  1. Primary autonomic failure syndromes (e.g., pure autonomic failure, multiple system atrophy, Parkinson disease with autonomic failure)
  2. Secondary autonomic failure syndromes (e.g., diabetic neuropathy, amyloid neuropathy)
- Medications
- Volume depletion:
  1. Hemorrhage, diarrhea, Addison disease, diuretics, febrile illness, hot weather

Cardiac Arrhythmias
- Sinus node dysfunction (including bradycardia-tachycardia syndrome)
- Atrioventricular conduction system disease
- Paroxysmal supraventricular and ventricular tachycardias
- Implanted device (pacemaker, implantable cardioverter defibrillator) malfunction
- Drug-induced proarrhythmias

Structural Cardiac or Cardiopulmonary Disease
- Cardiac valvular disease:
  1. Acute myocardial infarction, ischemia
  2. Obstructive cardiomyopathy
  3. Atrial myxoma
  4. Acute aortic dissection
  5. Pericardial disease, tamponade
  6. Pulmonary embolus, pulmonary hypertension

Cerebrovascular
- Vascular steal syndromes

Multifactorial

Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

TABLE 1 Drugs That Can Cause or Contribute to Syncope

Drug	Mechanism
Diuretics	Volume depletion
Vasodilators: • Angiotensin-converting enzyme inhibitors • Calcium channel blockers • Hydralazine • Nitrates • α-Adrenergic blockers • Prazosin	Reduction in systemic vascular resistance and venodilation
Other antihypertensive drugs: • α-Methyldopa • Clonidine • Guanethidine • Hexamethonium • Labetalol • Mecamylamine • Phenoxybenzamine	Centrally acting antihypertensives
Drugs associated with torsades de pointes: • Amiodarone • Disopyramide • Encainide • Flecainide • Quinidine • Procainamide • Sotalol	Ventricular tachycardia associated with a prolonged QT interval
Digoxin	Cardiac arrhythmias
Psychoactive drugs: • Tricyclic antidepressants • Phenothiazines • Monamine oxidase inhibitors • Barbiturates	Central nervous system effects causing hypotension; cardiac arrhythmias
Alcohol	Central nervous system effects causing hypotension; cardiac arrhythmias

Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

- Recreational drugs or alcohol.
- Functional causes such as somatoform disorders.
- Sleep disorders, such as sleep attacks and narcolepsy, are also in the differential for TLOC.
- Head trauma.

WORKUP

The history is crucial to diagnosing the cause of syncope and may suggest a diagnosis that can be evaluated with directed testing. History is also important to determine other etiologies for TLOC, such as seizure.

- Sudden loss of consciousness (LOC): Consider cardiac arrhythmias.
- Gradual LOC: Consider orthostatic hypotension, vasodepressor syncope, hypoglycemia.
- History of aura before LOC or prolonged confusion (>1 min), amnesia, or lethargy after LOC suggests seizure rather than syncope.
- Patient's activity at the time of syncope:
  1. Micturition, coughing, defecation: Consider syncope caused by decreased venous return.
  2. Turning head or while shaving: Consider carotid sinus syndrome.
  3. Physical exertion in a patient with murmur: Consider aortic stenosis.
  4. Arm exercise: Consider subclavian steal syndrome.
  5. Assuming an upright position: Consider orthostatic hypotension.
- Associated events:
  1. Chest pain: Consider myocardial infarction, pulmonary embolism.
  2. Palpitations: Consider arrhythmias or POTS.
  3. Incontinence (urine or fecal) and tongue biting are associated with seizure or syncope.
  4. Brief, transient shaking after LOC may represent myoclonus from global cerebral hypoperfusion and not seizures. However, sustained tonic/clonic muscle action is more suggestive of seizure.
  5. Focal neurologic symptoms or signs point to a neurologic event such as a seizure with residual deficits (e.g., Todd paralysis) or cerebral ischemic injury.
  6. Psychologic stress: Syncope may be vasovagal.
  7. Multiple nonspecific symptoms (fatigue, diffuse weakness, headache, "brain fog," exercise intolerance, "coat hanger sign") can be seen in POTS and neurogenic orthostatic hypotension and may have psychophysiologic or functional causes.
- Review current medications, particularly antihypertensive and psychotropic drugs.
- Carotid sinus massage (CSM) may be reasonable in patients older than 40 with syncope of unknown origin and possibly due to vasovagal mechanism. It is contraindicated in patients with carotid disease.
- Table 2 differentiates syncope caused by neutrally mediated hypotension, arrhythmias, seizures, and psychogenic causes.
- Fig. 2 illustrates an approach to the evaluation of syncope.

LABORATORY TESTS

Routine blood tests rarely yield diagnostically useful information and should be done only if they are specifically suggested by the results of the history and physical examination. The following are commonly ordered tests:

- Pregnancy test in women of childbearing age
- Complete blood count to look for anemia and signs of infection
- Electrolytes, blood urea nitrogen, creatinine, magnesium, and calcium to look for electrolyte abnormalities and evaluate fluid status
- Serum glucose level
- Cardiac troponins, especially if the patient gives a history of chest pain before the syncopal episode
- Drug and alcohol levels with suspected toxicity

IMAGING STUDIES

- ECG to rule out arrhythmias; may be diagnostic in 5% to 10% of patients.
- Echocardiography. Indicated in patients where initial evaluation suggests structural heart disease (based on physical exam and/or ECG) or have known heart disease.
- If seizure is suspected, MRI of the brain and electroencephalogram may be useful.
- If head trauma or neurologic signs on examination, CT or MRI may be helpful.
- If arrhythmias are suspected, a 24-hr Holter monitor or admission to a telemetry unit in high risk patients is appropriate. In general, Holter monitoring is rarely useful, revealing a cause for syncope in <3% of cases. Loop recorders that can be activated after syncopal episode to retrieve information about the cardiac rhythm during the preceding 4 min add considerable diagnostic yield in patients with unexplained syncope.
- Implantable cardiac monitors that function as permanent loop recorders or implantable cardioverter-defibrillators, which are placed subcutaneously in the pectoral region with the patient under local anesthesia, are useful in patients with cardiac syncope.
- Electrophysiologic studies may be indicated in patients with structural heart disease and/or recurrent syncope.

TILT-TABLE TESTING

- Useful to support a diagnosis of neurocardiogenic syncope. Patients age >50 yr should have stress testing before tilt-table testing. Positive results would preclude tilt-table testing.
- Indicated in patients with recurrent episodes of unexplained syncope as well as patients in high-risk occupations (e.g., pilots, bus drivers). The test is also useful for identifying patients with prominent bradycardic

TABLE 2 Differentiation of Syncope Caused by Neurally Mediated Hypotension, Arrhythmias, Seizures, and Psychogenic Factors

	Neurally Mediated Hypotension	Arrhythmias	Seizures	Psychogenic
Demographics and clinical setting	Female > male sex Younger age (<55 yr) More episodes (>2) Standing, warm room, emotional upset	Male > female sex Older age (>54 yr) Fewer episodes (<3) During exertion or when supine Family history of sudden death	Younger age (<45 yr) Any setting	Female > male sex Occurs in presence of others Younger age (<40 yr) Many episodes (often many episodes in a day) No identifiable trigger
Premonitory symptoms	Longer duration (>5 sec) Palpitations Blurred vision Nausea Warmth Diaphoresis Lightheadedness	Shorter duration (<6 sec) Palpitations less common	Sudden onset or brief aura (déjà vu, olfactory, gustatory, visual)	Usually absent
Observations during the event	Pallor Diaphoresis Dilated pupils Slow pulse, low BP Incontinence may occur Brief clonic movements may occur	Blue, not pale Incontinence may occur Brief clonic movements may occur	Blue face, no pallor Frothing at the mouth Prolonged syncope (duration >5 min) Tongue biting Horizontal eye deviation Elevated pulse and BP Incontinence more likely* Tonic-clonic movements if grand mal	Normal color Not diaphoretic Eyes closed Normal pulse and BP No incontinence Prolonged duration (minutes) common
Residual symptoms	Residual symptoms common Prolonged fatigue common (>90%) Oriented	Residual symptoms uncommon (unless prolonged unconsciousness) Oriented	Residual symptoms common Aching muscles Disorientation Fatigue Headache Slow recovery	Residual symptoms uncommon Oriented

*May be observed with any of these causes of syncope but more common with seizures.
BP, Blood pressure.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

response who may benefit from implantation of a permanent pacemaker. The test is contraindicated in patients with recent stroke, MI, and severe coronary or carotid disease.
- It is performed by keeping the patient strapped in an upright posture on a tilt table with footboard support. The angle of the tilt table varies from 60 to 80 degrees. The duration of upright posture during tilt-table testing varies from 25 to 45 min.
- The hallmark of neurocardiogenic syncope is severe hypotension associated with a paradoxic bradycardia triggered by a specific stimulus. The diagnosis of neurocardiogenic syncope is likely if upright tilt testing reproduces these hemodynamic changes in <15 min and causes presyncope or syncope.
- Postural orthostatic tachycardia syndrome is diagnosed if there is a sustained heart rate increase of not less than 30 beats/minute or above 120 beats/min within 10 min of active standing or head-up tilt without associated orthostatic hypotension and with reproduction of symptoms.

PSYCHIATRIC EVALUATION

- May be indicated in young patients without heart disease who have frequently recurring transient loss of consciousness and other somatic symptoms.
- Generalized anxiety disorder, pain disorder, and major depression predispose patients to neurally mediated reactions and may result in syncope.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Ensure proper hydration; consider compression stockings and salt tablets in appropriate patients.
- Eliminate medications that may induce hypotension.
- Elevate the head of the bed by 10 to 30 degrees while sleeping.

ACUTE GENERAL Rx

- Varies with the underlying etiology of syncope (e.g., pacemaker in patients with syncope resulting from complete heart block). Clinical variables for identification of high-risk syncope patients who may benefit from hospitalization or an accelerated outpatient evaluation are summarized in Table E3.
- Syncope caused by orthostatic hypotension is treated with volume replacement in patients with intravascular volume depletion. Also consider midodrine to promote venous return by adrenergic-mediated vasoconstriction and fludrocortisone for its mineralocorticoid effects to increase intravascular volume, although these medications can cause supine hypertension. Droxidopa is approved for neurogenic orthostatic hypotension in pure autonomic failure or multiple system atrophy.

DISPOSITION

Prognosis varies with the age of the patient and the etiology of the syncope. In general:
- Benign prognosis (very low 1-yr morbidity rate) in patients:
  1. Age <30 yr and having noncardiac syncope
  2. Age <70 yr and having vasovagal or psychogenic syncope or syncope of unknown cause
- Poor prognosis (high mortality and morbidity rates) in patients with cardiac syncope, with presenting systolic BP <90 mm Hg.
- Patients with the following risk factors have a higher 1-yr mortality rate: Abnormal ECG, history of ventricular arrhythmia, history of congestive heart failure.

REFERRAL

Hospital admission in elderly patients without prior history of syncope or unknown etiology of their syncope and in any patients suspected of having cardiac syncope, with presenting systolic BP <90 mm Hg.

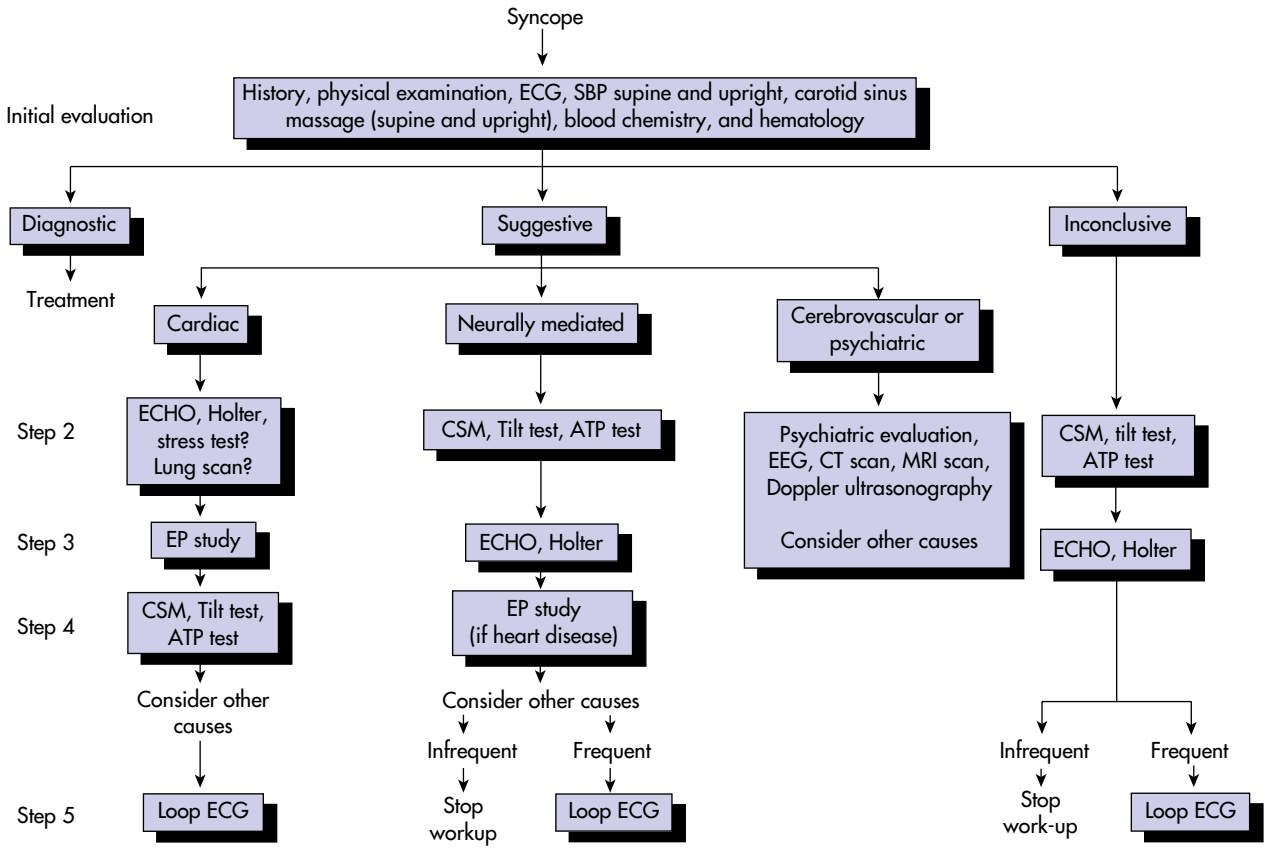

FIG. 2 An approach to the evaluation of syncope for all age groups. *ATP test,* Adenosine provocation test; *CSM,* carotid sinus massage; *ECG,* electrocardiogram; *ECHO,* echocardiogram; *EEG,* electroencephalography; *EP study,* electrophysiologic study; *SBP,* systolic blood pressure. (Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.)

PEARLS & CONSIDERATIONS

COMMENTS

- The etiology of syncope is identified in <50% of cases during the initial evaluation.
- A thorough history and physical examination are the most productive means of establishing a diagnosis in patients with syncope.
- Driving restrictions vary based on state but consider restricting driving if syncope is frequent or unpredictable.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Syncope (Patient Information)
Orthostatic Hypotension (Related Key Topic)

AUTHORS: **Corey Goldsmith, MD,** and **Tzu-Ching (Teddy) Wu, MD, MPH**

SUGGESTED READINGS

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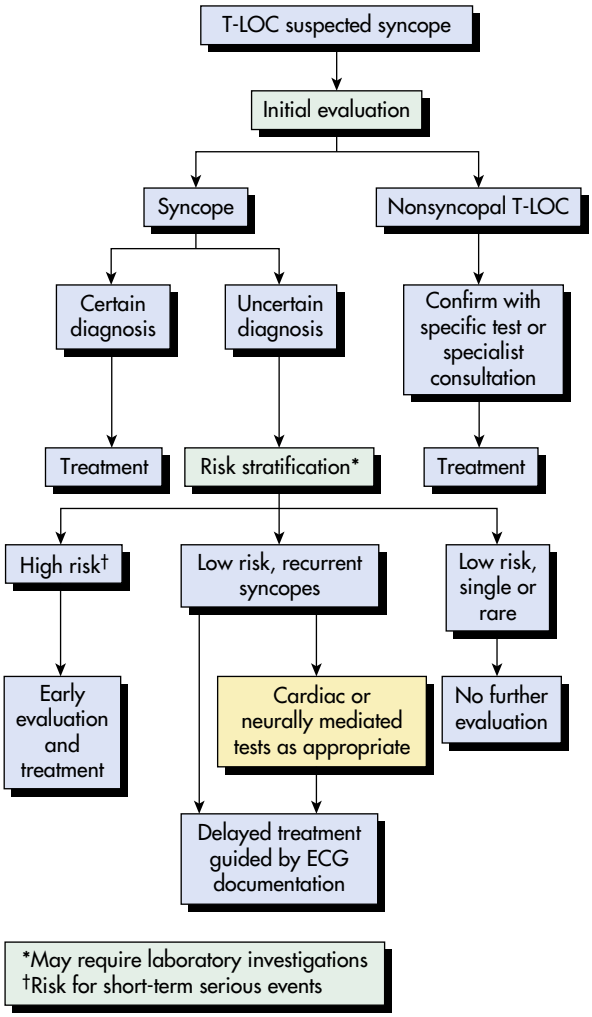

FIG. E1 Diagnostic approach to the evaluation of patients with transient loss of consciousness (T-LOC) and syncope. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

TABLE E3 Clinical Variables for Identification of High-Risk Syncope Patients Who May Benefit from Hospitalization or an Accelerated Outpatient Evaluation

Severe structural heart disease (low ejection fraction, previous myocardial infarction, heart failure)
Clinical or ECG features suggesting arrhythmic syncope:
Syncope during exertion or while supine
Palpitations at the time of syncope
Family history of sudden death
Nonsustained ventricular tachycardia
Bifascicular block or QRS >120 msec
Severe sinus bradycardia (<50 beats/min) in the absence of medications or physical training
Preexcitation
Prolonged or very short QT interval
Brugada ECG pattern (right bundle branch block with ST elevation in leads V1-V3)
Arrhythmogenic right ventricular dysplasia ECG pattern (T wave inversion in leads V1-V3 with or without epsilon waves)
ECG suggestive of hypertrophic dilated cardiomyopathy
Clinical evidence or suspicion of a pulmonary embolus (clinical setting, sinus tachycardia, shortness of breath)
Severe anemia
Important comorbid conditions:
Significant electrolyte abnormalities
Severe anemia

ECG, Electrocardiogram.
(From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

In healthy individuals, the expected physiologic response to serum hypotonicity is inhibition of antidiuretic hormone/arginine vasopressin (ADH/AVP) hypothalamic synthesis and posterior pituitary gland release. Decreased binding to renal medullary collecting duct vasopressin (V2) receptors results in the increased excretion of urine that is dilute (low osmolality) and hypotonic (low sodium and potassium concentrations). The syndrome of inappropriate antidiuresis (SIAD) is defined by "inappropriately" concentrated urine in patients with hypotonic hyponatremia and normal extracellular fluid (ECF) volume. In the absence of an elevated serum glucose or exogenous osmole such as mannitol, the serum sodium concentration (S_{Na}) is determined primarily by the ratio of total body exchangeable sodium plus potassium (Na + K) (mmol) to total body water (TBW) (L):

$$S_{Na} = \frac{(Na + K)e}{TBW}$$

Hyponatremia results from a reduction of the numerator, increase of the denominator, or both. To correct hyponatremia, the normal, appropriate renal response is excretion of urine with [Na] + [K] concentrations that are significantly less than S_{Na}. In SIAD, TBW is increased primarily by expansion of the volume of electrolyte-free water (EFW), or water that essentially contains neither sodium nor potassium or any other electrolyte. The presence of urea in electrolyte-free water does not change tonicity. The severity of hyponatremia in SIAD reflects a defect of urinary dilution and the magnitude of electrolyte-free fluid intake. The definition of SIAD excludes hemodynamic stimuli that stimulate ADH, including ECF volume (decreased total body sodium content), hypotension, and disorders characterized by decreased effective arterial blood volume. The latter group is characterized by increased ECF volume (edema or ascites) from increased total body sodium content. This group includes cardiac disease (e.g., congestive heart failure or chronic pericardial disease), nephrotic syndrome, and cirrhosis.

The term *syndrome of inappropriate antidiuretic hormone* (SIADH) has fallen into disfavor because 10% to 15% of so-called SIADH patients manifest suppressed or undetectable serum ADH concentrations. The group with suppressed ADH may have increased sensitivity of renal collecting duct cells to ADH, secretion of other ADH-like peptides, or altered renal hemodynamics that reduce sodium and water delivery to distal diluting sites, thereby preventing maximal urinary dilution. Establishing a diagnosis of SIAD does not require the measurement of ADH levels. Patients with hypothyroidism and adrenal insufficiency are excluded from the definition of SIAD. SIAD is not diagnosed in acute or chronic kidney disease. However, thiazide-induced hyponatremia is considered a drug-induced form of SIAD or SIAD-type physiology. Drugs that decrease electrolyte-free water excretion also may cause SIAD and represent a separate diagnostic entity.

SYNONYMS

SIADH
SIAD
Syndrome of inappropriate antidiuretic hormone secretion
Syndrome of inappropriate ADH release
Inappropriate secretion of antidiuretic hormone

ICD-10CM CODE
E22.2 Syndrome of inappropriate secretion of antidiuretic hormone

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Hyponatremia occurs in nearly 14% of hospitalized patients and represents an acquired disorder in the majority of cases. Nearly half of these patients have SIAD. The adjusted odds ratio for in-hospital mortality in patients with hyponatremia at hospital admission is 1.47 (95% Confidence Interval, 1.33 to 1.62).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Chronic hyponatremia is defined as an S_{Na} <130 mmol/L persisting for more than 48 hours with normal ECF volume. Patients are hemodynamically stable with no evidence of edema, ascites, pleural, or pericardial effusion.
- Manifestations: Marathon running or other extreme endurance exercise, fever and delirium after 3,4-methylenedioxy-methamphetamine (MDMA, ecstasy) administration, stigmata of alcoholism or malnutrition, fever and/or localizing symptoms related to pneumonia or other pulmonary disease, or headaches and visual field defects from an intracranial mass.
- If hyponatremia occurs rapidly, generally in less than 24 h, delirium, lethargy, or seizures may occur. Diminished reflexes and extensor plantar responses may occur with severe hyponatremia or an S_{Na} <120 mmol/L.
- Neurologic abnormalities, including ataxia, mood changes, and proximal muscle weakness, are frequent in chronic hyponatremia. Abnormalities may be subtle, despite severe hyponatremia.
- Drugs: Thiazide diuretics and selective serotonin reuptake inhibitor (SSRI) antidepressants are the two most common causes of drug-related hyponatremia. Narcotic analgesics, carbamazepine, phenothiazines, tricyclic antidepressants, MDMA (ecstasy), nicotine, clofibrate, haloperidol, nonsteroidal antiinflammatory drugs (NSAIDs), monoamine oxidase inhibitors, chlorpropamide, vasopressin, desmopressin, oxytocin, and chemotherapeutic agents (vincristine, vinblastine, cyclophosphamide) represent additional etiologies.
- Neoplasms: Lung, oropharynx, stomach, duodenum, pancreas, brain, thymus, bladder, prostate, endometrium, mesothelioma, lymphoma, and Ewing sarcoma.
- Pulmonary disorders: Pneumonia, aspergillosis, pulmonary abscess, tuberculosis, bronchiectasis, emphysema, cystic fibrosis, status asthmaticus, and respiratory failure associated with positive-pressure breathing.
- Intracranial pathology: Trauma, neoplasms, infections (meningitis, encephalitis, brain abscess), hemorrhage, hydrocephalus, multiple sclerosis, and Guillain-Barré syndrome.
- Postoperative period: Surgical stress, positive pressure ventilation, anesthetic agents, and pain.
- Other: Acute intermittent porphyria, psychosis, delirium tremens, general anesthesia, and endurance exercise.
- Table 1 summarizes common etiologies of SIAD.

DIFFERENTIAL DIAGNOSIS

- Hyponatremia associated with subclinical hypovolemia
- Solute-limited water excretion (e.g., "tea-and-toast" diet, beer-drinker's potomania). This is an acquired disorder and is the renal inability to excrete sufficient electrolyte-free water due to an insufficient osmolar intake (sodium and potassium) and/or metabolism (generation of urea from protein metabolism).
- Primary polydipsia or water intake that exceeds renal dilutional capability and is frequently accompanied by solute-limited water excretion
- Endocrine disorders, including hypothyroidism and adrenal insufficiency
- Severe hypokalemia occurs because the pool of exchangeable potassium ions is twice the size of the exchangeable sodium pool. When intracellular potassium is in severe deficit, sodium ions exit the plasma, enter cells, and cause hyponatremia.
- Hypertonic hyponatremia (hyperglycemia, iatrogenic administration of mannitol, sorbitol, glycine)
- Hyponatremia from subclinical heart or liver disease
- Pseudohyponatremia caused by extreme hyperglobulinemia or hyperlipidemia
- Reset osmostat: Regulation of ADH occurs at a lower-than-normal osmotic threshold, with intact urinary dilution and concentration

WORKUP

- Normal ECF volume by history and physical examination. No history of large-volume fluid losses. No generalized edema, ascites, or large pleural effusions.
- Laboratory evaluation (see "Laboratory Tests") is consistent with excessive ADH secretion or sensitivity in the absence of osmotic or hemodynamic stimuli for ADH secretion.
- Normal thyroid, adrenal, and cardiac function.
- No recent or concurrent use of loop diuretics.
- Failure to correct hyponatremia after ECF volume repletion by isotonic 0.9% saline solution.
- Correction of hyponatremia by solely fluid restriction is generally unsuccessful.
- Diagnostic criteria for SIADH are described in Table 2.

TABLE 1 Common Etiologies of the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

Tumors

Pulmonary/mediastinal (bronchogenic carcinoma, mesothelioma, thymoma)

Extrapulmonary (duodenal carcinoma, pancreatic carcinoma, ureteral/prostate carcinoma, uterine carcinoma, nasopharyngeal carcinoma, leukemia)

Central Nervous System Disorders

Mass lesions (tumors, brain abscesses, subdural hematoma)

Inflammatory diseases (encephalitis, meningitis, systemic lupus erythematosus, acute intermittent porphyria, multiple sclerosis)

Degenerative/demyelinating diseases (Guillain-Barré syndrome, spinal cord lesions)

Miscellaneous (subarachnoid hemorrhage, head trauma, acute psychosis, delirium tremens, pituitary stalk section, transsphenoidal adenomectomy, hydrocephalus)

Drug-Related

Stimulated release of AVP (nicotine, phenothiazines, tricyclics)

Direct renal effects and/or potentiation of AVP antidiuretic effects (desmopressin, oxytocin, prostaglandin synthesis inhibitors)

Mixed or uncertain actions (ACE inhibitors, carbamazepine and oxcarbazepine, chlorpropamide, clofibrate, clozapine, cyclophosphamide, 3,4-methylenedioxy-methamphetamine (ecstasy), omeprazole; serotonin reuptake inhibitors (SSRIs), vincristine

Pulmonary

Infections (tuberculosis, acute bacterial and viral pneumonia, aspergillosis, empyema)

Mechanical/ventilatory causes (acute respiratory failure, COPD, positive-pressure ventilation)

Other Causes

Acquired immunodeficiency syndrome (AIDS) and AIDS-related complex

Prolonged strenuous exercise (marathon, triathlon, ultramarathon, hot-weather hiking)

Senile atrophy

Idiopathic

ACE, Angiotensin-converting enzyme; *AVP,* arginine vasopressin; *COPD,* chronic obstructive pulmonary disease.
From Melmed S: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

TABLE 2 Diagnostic Criteria for the Syndrome of Inappropriate Antidiuretic Hormone Release

Essential Diagnostic Criteria

Decreased extracellular fluid effective osmolality (<270 mOsm/kg H_2O)
Inappropriate urinary concentration (>100 mOsm/kg H_2O)
Clinical normovolemia
Elevated urinary sodium concentration under conditions of normal salt and water intake
Absence of adrenal, thyroid, or pituitary insufficiency
Absence of chronic kidney disease
Absence of diuretic use

Supplemental Criteria

Abnormal water loading test (inability to excrete at least 90% of a 20 ml/kg H_2O load in 4 hours and/or failure to dilute urine osmolality to <100 mOsm/kg H_2O)
Plasma vasopressin level inappropriately elevated relative to the plasma osmolality
No significant correction of S_{Na} with volume expansion, but improvement after fluid restriction

S_{Na}, Serum sodium.
From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

LABORATORY TESTS

- Normal or low BUN and/or serum creatinine
- Normal thyroid stimulating hormone
- S_{Na} lower than the limit of the normal range
- Decreased serum osmolality (<275 mOsm/kg H_2O) corrected for serum glucose and exogenous osmoles
- Decreased serum uric acid
- Urine osmolality >100 mOsm/kg H_2O with plasma hypotonicity
- Urine sodium usually >40 mmol/L with normal dietary salt intake

IMAGING STUDIES

Imaging is not routinely required for diagnosis. Imaging may facilitate the diagnosis of an associated underlying pulmonary or CNS disease or rule out intracranial pathology.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

With mild SIAD, fluid restriction (10 to 15 ml/kg/day) combined with increased solute loads (diets high in protein, urea powder, sodium chloride, and potassium chloride) may normalize S_{Na}. The enhanced solute load produces an osmotic diuresis that increases electrolyte-free water loss. Urea administration should be undertaken with a consulting nephrologist; it has been proven safe for decades.

ACUTE GENERAL Rx

PHARMACOLOGIC THERAPY:

Rate of Correction: In chronic hyponatremia, rapid S_{Na} correction rates are avoided to prevent brain injury from osmotic demyelination syndrome. Patients with moderate-to-severe hyponatremia should undergo serial monitoring of S_{Na} and serum potassium concentration (S_K), urine volumes, and urine chemistries (osmolality, K, and Na). Most SIAD patients have chronic hyponatremia (developing over more than 24 hours) and mild symptoms. Target S_{Na} correction rates are 6 to 8mmol/L/day in chronic hyponatremia. The S_{Na} should be actively lowered in patients who experience increases of >10 mmol/L during a 24-hour period. The rate of S_{Na} change during conservative therapy or 0.9% infusion should be slow or even flat because sodium is excreted while water is mostly retained. In cases of hyponatremia from undiagnosed ECF volume depletion or unrecognized limitation of EFW excretion because of inadequate urinary solute (tea and toast diet or beer potomania), the administration of saline may produce rapid excretion of large volumes of hypotonic urine with overly rapid S_{Na} correction. Therefore, close monitoring of serum and urine electrolytes, osmolality, and volume is recommended.

Acute Hyponatremia: In the small fraction of patients with acute hyponatremia (duration <24 hours), the goal of therapy is to increase S_{Na} sufficiently to prevent or reduce the severity of cerebral edema. S_{Na} should be increased by up to 6 mmol/L within the first 3 hours if symptoms are mild-to-moderate and within the initial hour with severe symptoms (seizures, coma, obtundation).

Rapid correction of S_{Na} in acute hyponatremia may involve hypertonic saline therapy (3% saline, 513 mmol/L). As a rule of thumb, 1 ml/kg body weight of 3% saline is expected to increase S_{Na} by 1mmol/L. Rates of S_{Na} correction may be greater than anticipated when unrecognized ECF volume depletion is concurrently corrected. The simultaneous delivery of the synthetic ADH analog desmopressin can mitigate S_{Na} overcorrection. Intravenous furosemide therapy may augment urinary EFW loss and prevent unintended ECF volume expansion during hypertonic saline therapy.

Chronic Hyponatremia: The therapeutic goals of chronic hyponatremia from SIAD are normalization of TBW and restoration of sodium and potassium stores to their respective normal levels. These goals may be achieved in the following manner:

- Choose a 24-hour target S_{Na} based on current S_{Na} and safe rates of correction (see "Rate of Correction").
- Estimate current TBW and total body cation content. Estimation of current TBW should consider the patient's baseline TBW, volume of additional retained water, and changes in total body content of sodium and potassium.
- Determine target TBW that achieves the target S_{Na} from Step 1.
- Determine 24-hour net EFW loss to attain the TBW from Step 3.
- Estimate and total all sources of EFW intake and loss (including insensible). Add/subtract this total volume to/from net target EFW (Step 4) to determine total EFW volume loss required to attain the target S_{Na}.
- Select an appropriate strategy to achieve the target EFW volume loss: Collecting duct V2 receptor antagonist (e.g., tolvaptan), urea therapy, or loop diuretic combined with electrolyte replacement such as sodium chloride ("salt") tablets.

The following example demonstrates the method to determine the target TBW and EFW loss required to reach an appropriate S_{Na} target after 24 hours of therapy for a patient with chronic hyponatremia:

- S_{Na} is 115 mmol/L in 75kg, minimally symptomatic elderly woman who chronically takes an SSRI and hydrochlorothiazide.
  1. *Step 1: Establish target S_{Na}:*
     a. Target S_{Na} after 24 hours = Current S_{Na} + 6 = 121 mmol/L
  2. *Step 2: Estimate current TBW and total body cations:*
     a. Current weight = 75 kg
     b. Estimated TBW fraction = 0.55 (55%)
     c. Current TBW = 0.55 × 75 = 41.2 L
     d. Current total body cation quantity = Current TBW × S_{Na} = 41.2 × 115 = 4743 mmol
  3. *Step 3: Calculate target TBW:*
     a. Target TBW (L) = Current Na and K cation/Target S_{Na} = 4743 mmol/121 mmol/L = 39.2 L
  4. *Step 4: Calculate net EFW loss:*
     a. Target *net EFW loss* after 24 hours = Current TBW – Target TBW = 41.2 L – 39.2 L = 2 L
  5. *Step 5: Calculate total urine EFW volume:*
     a. Target *total urine EFW excretion* (estimate: 1 L oral fluid intake and 0.5 L net insensible loss) Urine EFW volume = 2 + (1 – 0.5) = 2.5 L
  6. *Step 6: Establish therapeutic strategy*
  7. *Step 7: Implementation strategy*
- From Step 6, a 24-hour net EFW loss of 2.5 L is required. With loop diuretic administration, this volume of EFW loss entails an equal volume of isotonic cation loss for a 5L urine output. Cation losses can be repaired with 0.9% saline or 3% saline. Administration of the latter requires 70% less volume than 0.9% saline and elevates S_{Na} more rapidly. Alternatively, cation replacement can be carried out by oral administration of NaCl and KCl tablets. Periodic monitoring of S_{Na}, S_K, urine volume, and urine chemistries (osmolality, sodium, and potassium) is recommended to prevent overly rapid correction of S_{Na}.

Loop Diuretic Plus Saline Strategy: Before the advent of specific V2 receptor antagonists, SIAD was typically treated by increasing urine volume and EFW loss with a loop diuretic. Half of the urine volume can be assumed to consist of electrolyte-free water because the sum of urine sodium and potassium cation concentrations will approximate 75 mmol/L, i.e, half-normal saline concentration. Isotonic or hypertonic IV fluids can be administered to correct urine sodium loss. A 1L volume 0.9% saline is equivalent to 0.3 L of 3% saline. Its use should be guided by an expert. Urine potassium loss must not be ignored and corrected separately.

Vasopressin (V2) Receptor Antagonists: Selective V2 receptor antagonist therapy is straightforward and convenient for patients and medical personnel. Two agents are available in the U.S.: IV conivaptan (20 mg IV × 1 followed by continuous IV infusion of 20 to 40 mg/day for 2 to 4 days) and oral tolvaptan (15 to 90 mg/day, as needed). Tolvaptan must be initiated in-hospital. Urinary electrolyte losses are minimal, meaning that administration produces virtually electrolyte-free urine (Step 5).

CHRONIC Rx

- When SIAD is chronic, fluid restriction (<15 ml/kg) may be required indefinitely and combined with high dietary electrolyte and protein.
- NaCl tablets, electrolyte supplements, protein powders to generate urea production, and pharmaceutical-grade urea may be used to correct hyponatremia. Periodic monitoring of electrolytes is recommended in patients with chronic SIAD.
- Tolvaptan has been administered successfully in clinical trials. FDA-labeling states that initial therapy must take place in-hospital. Tolvaptan use is restricted to 30 days due to concerns regarding hepatotoxicity, which was detected during clinical trials for polycystic kidney disease. Additional contraindications include volume contraction and concomitant use of strong cytochrome P3A inhibitors. Patients undergoing tolvaptan therapy should not be fluid-restricted.
- Demeclocycline variably increases urine electrolyte-free water losses. This agent is contraindicated in hepatic disease and rarely is used today.

DISPOSITION

- Mortality exceeding 40% has been reported in patients with S_{Na} <110 mmol/L.
- Hospital readmission rates are common in chronic SIAD when an underlying cause cannot be eliminated, especially if patients are unwilling or unable to restrict their fluid intake and follow dietary recommendations.
- Chronic, mild-to-moderate hyponatremia is associated with bone loss, falls, and increased fracture risk, particularly in elderly patients.

REFERRAL

Emergency department evaluation and hospital admission are appropriate for moderate-to-severe hyponatremia due to SIAD, especially when acute or symptomatic. Due to a high complication risk from overly aggressive or ineffective treatment, consultation by a nephrologist, endocrinologist, or critical care physician is recommended.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Syndrome of Inappropriate Secretion of Antidiuretic Hormone (Patient Information)

AUTHORS: **Mark D. Faber, MD,** and **Jerry Yee, MD**

SUGGESTED READINGS

Hoorn EJ, Zietse R: Diagnosis and treatment of hyponatremia: compilation of the guidelines, *J Am Soc Nephrol* 28:1340-1349, 2017.

Kirkman MA et al: Hyponatremia and brain injury: historical and contemporary perspectives, *Neurocrit Care* 18:406-416, 2013.

Peri A et al: SIADH: differential diagnosis and clinical management, *Endocrine* 55:311-319, 2017.

Wehling M et al: Filling the gap—improving awareness and practice in hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in the older patient: a European consensus view, *Drug Res (Stuttg)* 67(1):5-12, 2017.

Synthetic Cannabinoids

BASIC INFORMATION

DEFINITION

Synthetic cannabinoids are manufactured variants of natural cannabinoids found in marijuana. Most are modeled after delta-9-tetrahydrocannabinol (THC), which is among the most psychoactive of the cannabinoids. The chemical structures of these substances are frequently altered in order to circumvent regulations and law enforcement. They often are sold as incense or herbal products combined with various other herbal ingredients.

SYNONYMS

There are more than 700 commonly used synonyms for synthetic cannabinoids.
Chill out
Chill x
Crazy monkey
Herbs
Incense
K2
Spice
Spice diamond
Spice gold

ICD-10CM CODES	
F12.1	Cannabis abuse
F12.15	Cannabis abuse with psychotic disorder
F12. 98	Cannabis use, unspecified with other cannabis-induced disorder
F19.1	Other psychoactive substance abuse

EPIDEMIOLOGY & DEMOGRAPHICS

- Synthetic cannabinoids were developed in research laboratories in the 1980s and first emerged as a recreational drug around 2008.
- Prevalence and incidence have steadily increased, with over 7000 annual cases reported to regional poison control centers in the U.S.
- The majority of exposures occur in young men aged 20 to 30 yr as a result of intentional ingestion as a recreational drug. Adolescents 13 to 18 yr account for up to 25% of hospitalizations after ingestions.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Synthetic cannabinoids are manufactured experimentally, with each variation carrying a new chemical signature. Frequently they are sold as a mixture with various herbs and other compounds. As such, physical symptoms may vary widely depending upon the route and type of substance ingested.
- The majority of symptoms are mild and self-limited; however, severe toxicities are common.
- Synthetic cannabinoids have much higher potency than natural marijuana, and thus greater potential for delirium, agitation, and psychosis.
- The most common symptoms across multiple studies are sinus tachycardia and neuropsychiatric symptoms (toxic psychosis, agitation, coma, CNS symptoms).
- Among the most commonly reported symptoms are:
  1. Tachycardia, palpitations, chest pain, hypotension, bradycardia, cardiac arrest
  2. Conjunctival injection, nystagmus, ataxia, sedation, seizures, syncope, respiratory depression, CNS depression, coma, emesis, hyperthermia, rhabdomyolysis, acute kidney injury
  3. Psychotic effects: Irritability, paranoia, anxiety, racing thoughts, hallucinations, delusions, psychosis, delirium
- There have been reports of myocardial infarction, subarachnoid hemorrhages, pneumothorax, and acute ischemic strokes after ingestion. Superwarfarin adulterants of synthetic cannabinoids can lead to clinically significant coagulopathy.[1]

ETIOLOGY

- The majority of synthetic compounds are cannabinoid receptor 1 and 2 (CB1 and CB2) agonists. Some versions have NDMA, serotonin, and other receptor affinity.
- Current compounds have higher cannabinoid receptor binding affinity, with resulting potency up to 800 times greater than THC.
- Metabolized by glucuronidation and oxidation by liver cytochrome oxidase enzymes and renally excreted.

DIAGNOSIS

- Intoxication with synthetic cannabinoids is primarily a clinical diagnosis.
- Rapid urine drug screens designed to detect THC will not detect the presence of synthetic cannabinoids.
- Mass spectrometry and liquid chromatography can confirm the presence of synthetic compounds but have limited use in the timely treatment of the acutely toxic patient.

DIFFERENTIAL DIAGNOSIS

- Drug or alcohol intoxication
- Hypoglycemia
- Acute psychosis
- Status epilepticus or seizure disorder
- Toxidromes (tricyclic antidepressants, anticholinergic agents, organophosphates, sympathomimetics)

WORKUP

The diagnosis of synthetic cannabinoid intoxication is clinical. Workup is dictated by clinical symptoms and degree of toxicity.

LABORATORY TESTS

- Mild intoxication usually does not require extensive laboratory studies.
- For severe toxicity:
  1. Serum electrolytes
  2. Blood urea nitrogen and creatinine, as there is increased risk for acute kidney injury
  3. Creatine kinase and urine myoglobin if concern for rhabdomyolysis
  4. Venous blood gas if concern for respiratory depression
  5. Serum lactate for increased risk of lactic acidosis
  6. Drug abuse screen for contaminants or coingestions
  7. Troponin or cardiac biomarkers, as there is increased risk for myocardial infarction in patients with chest pain

IMAGING STUDIES

Neuroimaging (CT or MRI of the brain) would be indicated if seizure is part of toxidrome.

OTHER TESTS

12-Lead electrocardiogram

TREATMENT

Treatment is supportive and directed at symptoms and complications of toxicity.

- Acute kidney injury is common. Fluid resuscitation should be started for the prevention and treatment of renal injury and rhabdomyolysis in most patients.
- Reassurance, decreased stimulation in a dimly lit room, and benzodiazepines for anxiety are useful in mild-to-moderate toxicity.
- Psychosis and agitation can usually be adequately controlled with benzodiazepines.
- Hyperthermia from seizures, myoclonus, and rhabdomyolysis should be treated aggressively. Evaporative cooling, benzodiazepines, and cooling blankets are usually sufficient.
  1. If intubation and paralysis are necessary, depolarizing agents such as succinylcholine should be avoided, as hyperkalemia from rhabdomyolysis is of concern.
  2. Antipyretics have no effect in temperature management.
- Seizures should be treated with benzodiazepines. Frequently, seizures are reported as a single nonsustained episode. Seizures unresponsive to benzodiazepines should be treated with pharmacologically induced coma and continuous EEG. Neuroimaging is recommended in patients with seizures.
- Dystonic symptoms are best treated with benzodiazepines rather than with anticholinergic agents such as diphenhydramine, which have the potential to worsen hyperthermia.
- Early administration of haloperidol in addition to antiemetics for the treatment of cannabinoid hyperemesis syndrome.

[1]Kelkar AH et al: An outbreak of synthetic cannibinoid-associated coagulopathy in Illinois, *N Engl J Med* 379:1216-1223, 2018.

NONPHARMACOLOGIC THERAPY

Counseling addressing psychological and social issues

DISPOSITION

- Patients with mild-to-moderate symptoms can be observed for 6 hr in the emergency department and safely discharged after resolution of symptoms.
- Patients who remain symptomatic warrant admission to an appropriate level of care, based on the severity of their symptoms.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Craig Blakeney, MD**

SUGGESTED READINGS

Adams AJ et al: "Zombie" outbreak caused by the synthetic cannabinoid AMB-fubinaca in New York, *N Engl J Med* 346:235-242, 2017.

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Rosenbaum CD et al: Here today, gone tomorrow… and back again? A review of herbal marijuana alternatives (K2, spice), synthetic cathiones (bath salts), kratom, saliva divinorum, methoxetamine, and piperazines, *J Med Toxicol* 8:15-32, 2012.

BASIC INFORMATION

DEFINITION

Syphilis is a systemic sexually transmitted disease caused by the bacteria *Treponema pallidum*, with acute and chronic manifestations, characterized by primary skin lesions; secondary eruption involving skin and mucous membranes; long periods of latency; and late lesions of the skin, bone, viscera, central nervous system, and cardiovascular system.

SYNONYM

Lues

ICD-10CM CODES

A50	Congenital syphilis
A51.0	Primary genital syphilis
A51.1	Primary anal syphilis
A51.2	Primary syphilis of other sites
A51.3	Secondary syphilis of skin and mucous membranes
A51.4	Other secondary syphilis
A51.5	Early syphilis, latent
A51.9	Early syphilis, unspecified
A52	Late syphilis
A52.0	Cardiovascular and cerebrovascular syphilis
A52.1	Symptomatic neurosyphilis
A52.2	Asymptomatic neurosyphilis
A52.3	Neurosyphilis, unspecified
A52.8	Late syphilis, latent
A52.9	Late syphilis, unspecified
A53.9	Syphilis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Most commonly diagnosed in people 20 to 30 yr old.
- Slightly more prevalent in men than women.
- Rates reached historic lows in the U.S. in 2000 but began increasing among males in 2001, and increase has continued. The number of cases reported to the CDC increased by 71% from 2014 to 2018. In 2018 men accounted for 86% of all patients with syphilis. Rates are disproportionately higher among black and Hispanic men who have sex with men (MSM), compared with white MSM and among young MSM. Rates are also increasing in women, with highest rates in black women compared with Hispanic and white women. The rates of primary and secondary syphilis among women more than doubled between 2014 and 2018. Congenital syphilis rates also have been increasing, with 1306 cases reported in 2018.
- Usually more prevalent in urban areas and among people of lower socioeconomic status.
- Communicability is indefinite and variable. Communicable during primary, secondary, and latent mucocutaneous lesions in up to first 4 yr of latency. Most probable congenital transmission occurs in early maternal syphilis. Adequate penicillin treatment ends infectivity within 24 to 48 hr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

PRIMARY SYPHILIS:

- Characteristic lesion is a painless chancre on genitalia (Figs. E1 and E2), mouth, or anus; atypical primary lesions may occur.
- May appear 3 days to 12 wk (usually 3 wk) after exposure and may resolve without treatment within 6 wk.

SECONDARY SYPHILIS:

- Bacteremia associated with generalized lymphadenopathy and a characteristic maculopapular rash including palms, soles, trunk, and mucous membranes. Lesions may also be pustular, involve the mucosal surfaces. Constitutional, flulike symptoms may also occur, as well as mild disturbances of multiple organ systems.
- 60% to 80% have maculopapular lesions on palms and soles (Fig. E3).
- 21% to 58% have mucocutaneous or mucosal lesions (pharyngitis, tonsillitis, "mucous patch" lesion on oral and genital mucosa).
- Condylomata lata intertriginous papules (raised, gray-white lesions) form at areas of friction and moisture, such as the vulva (Fig. E4).
- Occurs 4 to 6 wk after appearance of chancre. Resolves within 1 wk to 12 mo. Can have relapsing episodes up to 5 yr after initial episode.

LATENT SYPHILIS—EARLY VS. LATE LATENT:

- Generally asymptomatic, can occur between 1 and 30 yr after a primary infection
- Seroreactivity without other evidence of primary or secondary disease
- Not sexually transmitted but may be transmitted from a pregnant woman to her fetus for up to 4 yr after acquiring the disease
- In early latent syphilis, disease can be transmitted even without the current presence of an active lesion. This is not the case in late latent syphilis
- Early latent: <12 mo from acquisition
- Late latent: >12 mo from acquisition, or time since infection is unknown

TERTIARY SYPHILIS:

- A form of late syphilis characterized by gummas (nodular, ulcerative lesions) that can involve the skin, mucous membranes, skeletal system, and viscera.
- Manifestations of cardiovascular syphilis include aortitis, aneurysm, or aortic regurgitation.
- Neurosyphilis may be asymptomatic or symptomatic. Tabes dorsalis, meningovascular syphilis, general paralysis, or insanity may occur.
- Ocular syphilis can affect any part of the eye. Posterior uveitis is the most common. Iritis, choroidoretinitis, and leukoplakia may also occur.

ETIOLOGY

- *Treponema pallidum,* a spirochete
- Spread by sexual intercourse or by intrauterine transfer

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other genitoulcerative diseases such as herpes, chancroid (see Table 1)
- See Section III for a clinical algorithm for the evaluation of genital ulcer disease

WORKUP

Confirmation is primarily through laboratory diagnosis.

- Culture of lesions
- Serologic testing (see the following lab tests)
- Cerebrospinal fluid (CSF) testing

LABORATORY TESTS

- Dark-field microscopy of fluid from lesion to look for treponeme is the definitive method for diagnosis of early syphilis.
- Serologic testing:
  1. Nontreponemal tests: Venereal disease research laboratory (VDRL) or rapid plasma reagin (RPR).
  2. Treponemal tests: Fluorescent treponemal antibody absorbed (FTA-ABS) tests, the *T. pallidum* passive particle agglutination (TP-PA) assay, various enzyme immunoassays (EIAs), chemiluminescence immunoassays, immunoblots, or rapid treponemal assays.
  3. Antibody titers can assess for response to treatment and for reinfection in previously treated patients.
- Screening methods:

TABLE 1 Genital Ulcer Disease

Disease	Lesions	Lymphadenopathy	Systemic Symptoms
Primary syphilis	**Painless,** indurated, with a clean base, usually singular	Nontender, rubbery, nonsuppurative bilateral lymphadenopathy	None
Genital herpes	**Painful** vesicles, shallow, usually multiple	Tender, bilateral inguinal adenopathy	Present during primary infection
Chancroid	Tender papule, then **painful,** undermined purulent ulcer, single or multiple	Tender, regional, painful, suppurative nodes	None
Lymphogranuloma	Small, **painless** vesicle or papule progresses to an ulcer	Painful, matted, large nodes with fistulous tracts	Present after genital lesion heals

From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

1. Traditional: Screen with nontreponemal tests; confirmation with treponemal testing.
2. Alternative: Screen with treponemal testing, confirm with nontreponemal testing. More false positives, less likely to miss early or latent syphilis.

- When the nontreponemal test is negative despite a positive screen, an additional treponemal screen may be helpful. Trials have shown that two positive treponemal screens help identify a population with likely prior or current syphilis, and treatment of these patients may be justifiable.
- In patients with neurosyphilis, serologic criteria for response to therapy is a fourfold or greater decrease in VDRL titer over 6 to 12 mo.
- Lumbar puncture (LP) for cerebrospinal fluid VDRL (CSF-VDRL) in patients with evidence of latent syphilis (good specificity, poor sensitivity). If negative with high suspicion, can also perform a CSF FTA-ABS (good sensitivity, less specificity). When reactive in the absence of substantial contamination of CSF with blood, it is considered diagnostic of neurosyphilis. The Centers for Disease Control and Prevention indications for LP are neurologic symptoms, treatment failure, any eye or ear involvement, or evidence of active syphilis (aortitis, gumma, iritis).
- HIV testing in all patients.

Rx TREATMENT

ACUTE GENERAL Rx

- Primary, secondary, early latent:
  1. Penicillin G benzathine 2.4 million U IM once.
  2. Infants and children: Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose.
  3. Nonpregnant penicillin-allergic patients: Doxycycline 100 mg bid × 14 days.
  4. Alternative regimens (contraindicated in MSM, persons with HIV, or pregnant women):
     a. Azithromycin 2 g PO × 1 dose
     b. Ceftriaxone 1-2 g IM or IV for 10-14 days
     c. Tetracycline 500 mg PO QID for 14 days
     d. Amoxicillin 3 g PO BID + probenecid 500 mg PO BID for 14 days
  5. Careful clinical and serologic follow-up of persons receiving any alternative therapy is essential.
  6. Persons with a penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin.
- Late latent syphilis, tertiary syphilis (not neurosyphilis):
  1. Penicillin G benzathine 2.4 million U IM q wk × 3 wk.
  2. Infants and children: Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose.
  3. Nonpregnant penicillin-allergic patients: Doxycycline 100 mg PO BID × 4 wk.
- Neurosyphilis:
  1. Aqueous crystalline penicillin G 18 to 24 million U/day, administered as 3 to 4 million U IV q4h or continuous infusion for 10 to 14 days.
  2. Alternative regimen: Procaine penicillin 2.4 million U IM/day plus probenecid 500 mg PO qid, both for 10 to 14 days.
- Congenital syphilis:
  1. Aqueous crystalline penicillin G 50,000 U/kg/dose IV q12h × first 7 days of life and q8h after that for a total of 10 days OR procaine penicillin G 50,000 U/kg/dose IM/day × 10 days.
  2. An algorithm for evaluation and treatment of infants born to mothers with reactive serologic tests for syphilis is illustrated in Fig. E5.

DISPOSITION

- Repeat quantitative nontreponemal tests at 6 and 12 mo to ensure adequate treatment. For HIV-infected patients, repeat testing at 3, 6, 9, 12, and 24 mo. Pregnancy requires monthly tests until delivery.
- Findings indicating need for retreatment of syphilis and additional testing for HIV:
  1. If a fourfold increase in titer occurs and is sustained over testing performed >2 wk apart.
  2. If initial high titer fails to drop by fourfold within a yr for early syphilis or 24 mo for late syphilis
  3. If signs persist, or patient develops new signs of infection
- Because treatment failure may be the result of unrecognized CNS infection, CSF examination can be considered in such situations. For retreatment, weekly infusions of benzathine penicillin G 2.4 million units IM for 3 wk is recommended, unless CSF examination indicates that neurosyphilis is present.
- Pregnant women without a fourfold drop in titer by 6 mo compared to pretreatment titer need to be retreated. Inadequate treatment is likely if patient delivers fewer than 30 days after treatment, or if titers are fourfold higher than pretreatment at delivery. Titers should be repeated monthly during pregnancy for those infected.
- Cases should be reported to local or state health department for referral, follow-up, and partner notification.

REFERRAL

- Pregnant and possible congenital syphilis
- Pregnant and allergic to penicillin, who need to be desensitized for treatment
- Late latent syphilis with serious central nervous system, cardiovascular, or other organ system compromise

PEARLS & CONSIDERATIONS

- Jarisch-Herxheimer reaction (fever, myalgia, tachycardia, hypotension) may occur within 24 hr of treatment.
- Fig. E6 illustrates the course of untreated syphilis. One third of untreated patients develop CNS and/or cardiovascular sequelae.
- Up to 80% of those treated during late stages remain seropositive indefinitely.
- Treponemal tests remain positive even after adequate therapy.
- Male circumcision does not decrease the incidence of syphilis (unlike HIV, HSV-2, and HPV infection).
- Partner notification and treatment:
  1. Persons who are exposed within 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in a sex partner might be infected even if seronegative; therefore, such persons should be treated presumptively.
  2. Persons who were exposed ≥90 days before the diagnosis of syphilis in a sex partner should be treated presumptively if serologic test results are not available immediately and the opportunity for follow-up is uncertain.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Syphilis (Patient Information)
Tabes Dorsalis (Related Key Topic)

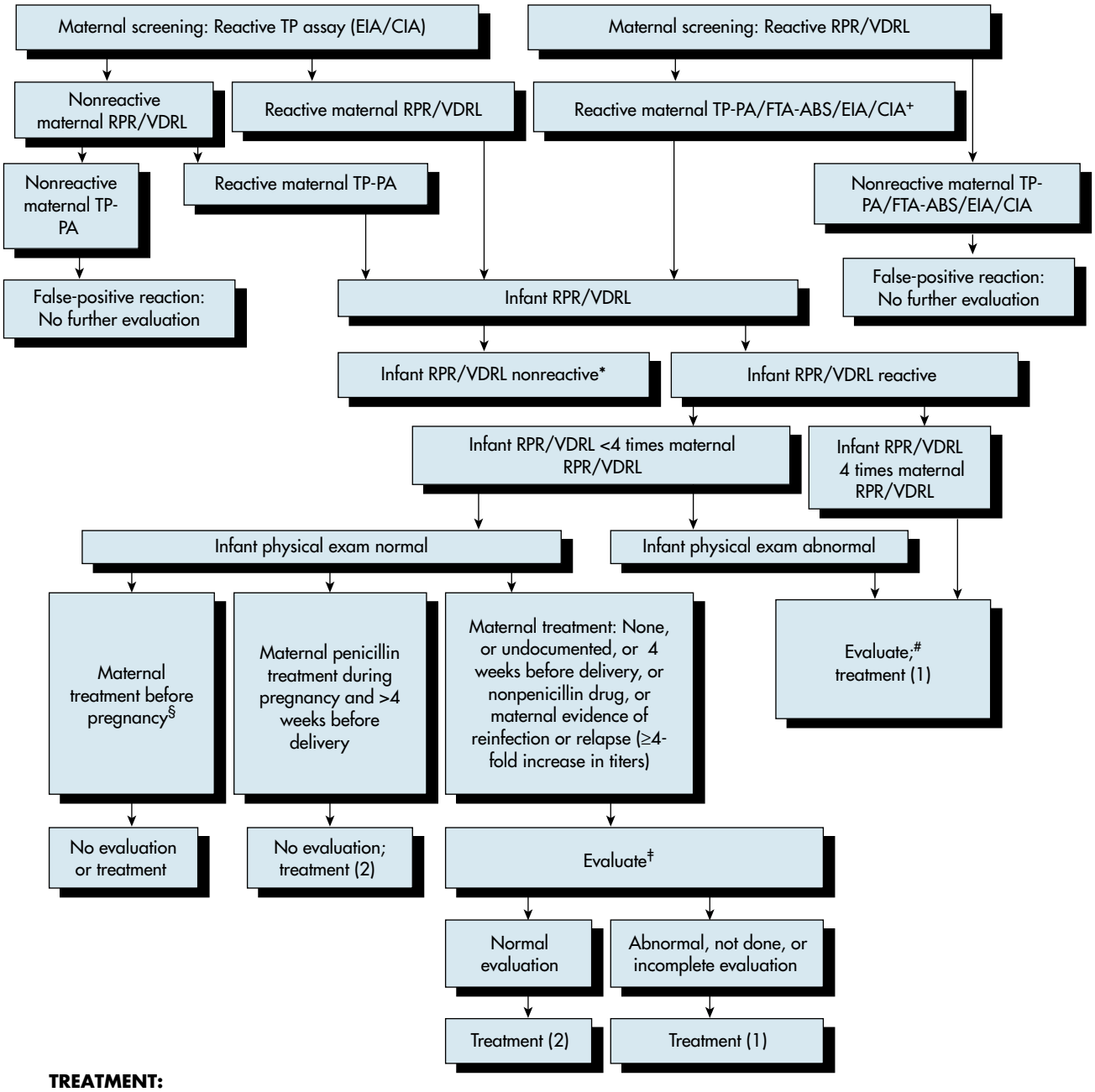
AUTHORS: **Anthony Sciscione, DO,** and **Ashwini U. Dhokte, MD**

FIG. E1 Penile chancres. Single **(A)** and multiple **(B),** with characteristic clean, moist bases. (Courtesy Yale Residents' Slide Collection. From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

FIG. E2 Syphilis with vulvar chancre. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

FIG. E3 Pink-brown to dark brown palmar **(A)** and plantar **(B)** lesions of secondary syphilis. Note the peripheral collarette of scale. (Courtesy Yale Residents' Slide Collection. From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

FIG. E4 Condyloma lata—genital lesions of secondary syphilis. (From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)



TREATMENT:

(1) Aqueous penicillin G 50,000 U/kg IV q 12 hr (1 wk of age), q 8 hr (>1 wk), or procaine penicillin G 50,000 U/kg IM single daily dose, x 10 days

(2) Benzathine penicillin G 50,000 U/kg IM x 1 dose

FIG. E5 Algorithm for evaluation and treatment of infants born to mothers with reactive serologic tests for syphilis. +, Test for HIV antibody. Infants of HIV-infected mothers do not require different evaluation or treatment. *If the mother has had no treatment, undocumented treatment, treatment ≤4 weeks before delivery, or evidence of reinfection or relapse (fourfold or higher increase in titers) *and* the infant's physical examination is normal, *then* treat infant with a single intramuscular injection of benzathine penicillin (50,000 U/kg). No additional evaluation is needed. §Women who maintain a VDRL titer ≤1:2 (RPR ≤1:4) beyond 1 year after successful treatment are considered serofast. #Evaluation consists of CBC, platelet count, CSF examination for cell count, protein, and quantitative VDRL. Other tests as clinically indicated: Long-bone x-rays, neuroimaging, auditory brain stem response, eye examination, chest radiograph, liver function tests. ‡CBC, platelet count; CSF examination for cell count, protein, and quantitative VDRL; long-bone radiographs. Treatment regimens are as follows: (1) aqueous penicillin G 50,000 units/kg IV every 12 hours (≤1 week old) or every 8 hours (>1 week old) or procaine penicillin G 50,000 units/kg IM single daily dose × 10 days; (2) benzathine penicillin G 50,000 units/kg IM × 1 dose. *CBC,* Complete blood count; *CIA,* chemiluminescence; *CSF,* cerebrospinal fluid; *EIA,* enzyme immunoassay; *FTA-ABS,* fluorescent treponemal antibody absorption; *IM,* intramuscular; *IV,* intravenous; *RPR,* rapid plasma reagin; *TP, Treponema pallidum; TP-PA, Treponema pallidum* particle agglutination; *VDRL,* Venereal Disease Research Laboratory. (From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.)

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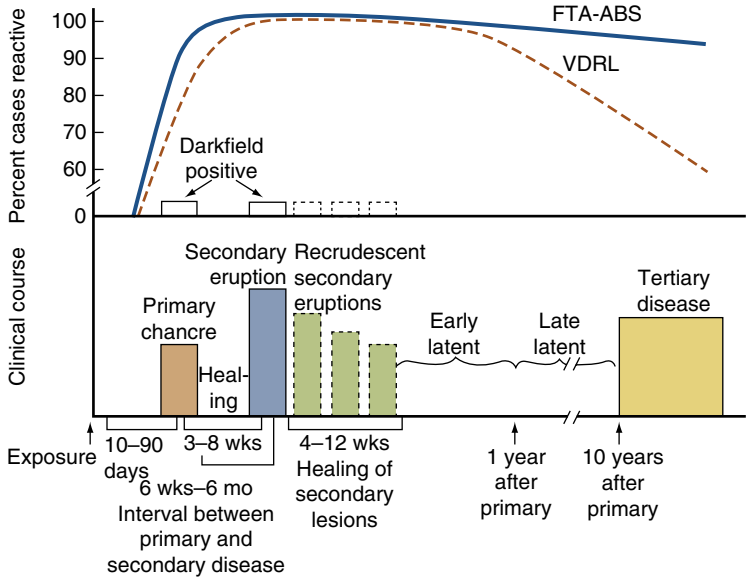

FIG. E6 The course of untreated syphilis. *FTA-ABS,* Fluorescent treponemal antibody absorption; *VDRL,* Venereal Disease Research Laboratory. (From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Syringomyelia is a condition characterized by the formation of any fluid-filled tubular cavity within the spinal cord. When syringomyelia involves the medulla oblongata, it is called syringobulbia, and when it involves the cerebral pons, it is described as syringopontia. When the cavity is in direct continuity with the fourth ventricle, it is called communicating syringomyelia. *Hydromyelia* is sometimes used as a term that indicates a focal dilatation of the spinal cord central canal.

SYNONYM

Syrinx

ICD-10CM CODES

G95.0 Syringomyelia, syringobulbia, and syringopontia
Q06.4 Hydromyelia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- A rare condition
- No accurate figures for the incidence of syringomyelia
- Incidence of posttraumatic syringomyelia is between 1.9% and 4.5%

PREVALENCE:

- Prevalence can vary from 1.9 per 100,000 people in Japan to 8.4 per 100,000 people in Western countries
- About 40% to 75% of patients with Chiari malformations have syringomyelia
- 90% of patients with syringomyelia have an associated Chiari malformation
- 50% of cases are due to cerebrospinal fluid (CSF) blockage
- 10% communicate with fourth ventricle

PREDOMINANT SEX AND AGE:

- Symptoms commonly begin in late adolescence or early adulthood
- Both sexes are equally affected

RISK FACTORS:

- Congenital defects such as neural tube defects (myelomeningocele and tethered cord syndrome), Chiari malformations, and Klippel-Feil syndrome
- Base of skull anomalies such as achondroplasia
- Spinal cord trauma, including birth trauma and postsurgical. More prevalent in a complete spinal cord injury. Diagnosed 12 to 15 years after spinal cord injury.
- Intramedullary tumors (ependymomas, astrocytomas, and hemangioblastomas are most common)
- Extramedullary tumors and arachnoid cysts
- Inflammatory conditions such as sarcoidosis, multiple sclerosis, and transverse myelitis
- Spinal arteriovenous malformations
- Spinal canal stenosis (cervical most common)
- Infection such as meningitis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Onset is usually insidious, often asymptomatic until the third or fourth decade
- More acute course if it involves the brain stem
- Cervical spine is the most commonly affected area:
  1. Neuropathic joints (Fig. E1) (especially in the shoulder or elbow), intrinsic hand atrophy, hand and/or arm weakness
  2. Neck, back, arm, and/or leg pain and stiffness
  3. Cape-like loss of pain and temperature in the upper extremity with preservation of light touch, vibration, and proprioception
  4. Painless burns or other injuries in the hand
  5. Sharp testing elicits no pain, but patient often perceives the sharpness of the object
  6. Impaired walking, toe walking in children
  7. Bowel and bladder dysfunction are signs of late-stage disease
  8. Loss of upper limb reflexes and hyperreflexia in the lower extremities
- Scoliosis is common, especially in children
- Nystagmus and Horner syndrome may also occur
- Hemangiomas or midline tuft of hair can indicate underlying spine deformities

ETIOLOGY

- Two current theories of syrinx development:
  1. Obstruction of CSF outflow from the fourth ventricle at the level of the foramen magnum
  2. Difference in spinal pressure and intracranial pressure during Valsalva-like maneuvers
- Congenital malformations, any acquired trauma, or spinal inflammatory/infection conditions could cause the abnormal CSF flow dynamics

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Amyotrophic lateral sclerosis/motor neuron disease
- Diabetic neuropathy
- Spinal cord tumor
- Spinal cord infarction
- Spinal cord epidural abscess
- Multiple sclerosis
- Transverse myelitis
- Tabes dorsalis
- Vitamin B_{12} deficiency

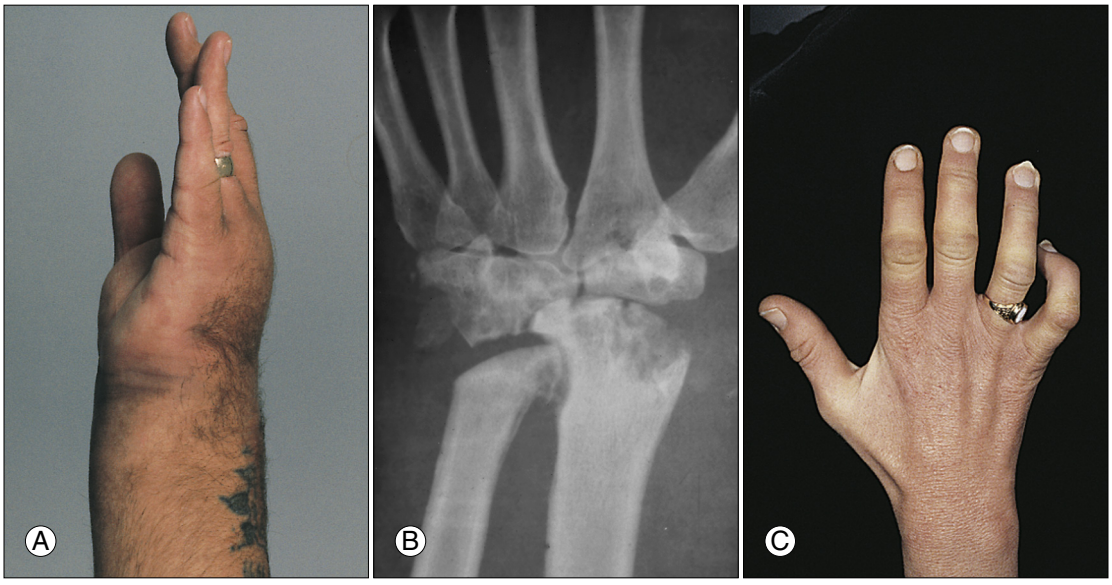

FIG. E1 Syringomyelia. A, A neuropathic wrist joint in a patient with mild syringomyelia. Note the swelling and deformity of the joint. **B,** Radiograph showing the gross destruction of the proximal carpal row with attrition and simplification of the bony margins. Residual fragments of bone and considerable soft tissue swelling also can be seen. **C,** Wasting of the intrinsic muscles of the hand and claw deformity. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

- Copper deficiency
- Progressive spinal muscular atrophy

IMAGING STUDIES

- Plain radiographs usually reveal widening of the bony canal in the region of involvement
- Bony anomalies are often present at the base of the skull and at the C1 to C2 spinal segments
- MRI (Fig. E2 and E3) of the spine with contrast is the gold standard study of choice. Gadolinium contrast is necessary to rule out spinal tumors
- Four-dimensional phase-contrast MRI can best evaluate CSF flow dynamics
- CT myelography is an alternative test if MRI is contraindicated

Rx TREATMENT

- No medical treatment is currently available
- Asymptomatic syringomyelia can be treated expectantly, as there have been cases of spontaneous resolution
- Decompressive laminectomy is standard of care for patients with normal CSF flow and mild neurologic symptoms
- Direct drainage of the syrinx by syringoarachnoid, syringoperitoneal, and synringopleural shunts
- Syringotomy
- Terminal ventriculostomy
- Neuroendoscopic surgery
- Cell transplantation with autologous bone marrow-derived mesenchymal stromal cells in symptomatic post-traumatic syringomyelia

DISPOSITION

- The condition is slowly progressive in most cases, but the course of the disease may be quite variable, ranging from death in a few months to slow incapacitation over several years; progression may halt at any time.
- Surgical intervention leads to improvement in neurologic findings in 30% of patients
- Physical and occupational therapies prevent further loss of function

REFERRAL

Neurology and neurosurgery referral when diagnosis is suspected

RELATED CONTENT

Syringomyelia (Patient Information)

AUTHORS: **Emil Stefan Vutescu, MD,** and **Shashank Dwivedi, MD**

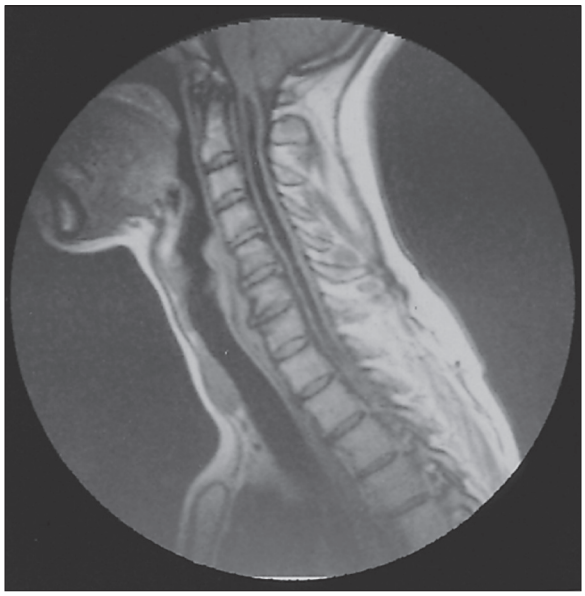

FIG. E2 Magnetic resonance image of the cervical spine in a patient with syringomyelia, showing the fluid-filled syrinx in the center of the spinal cord. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

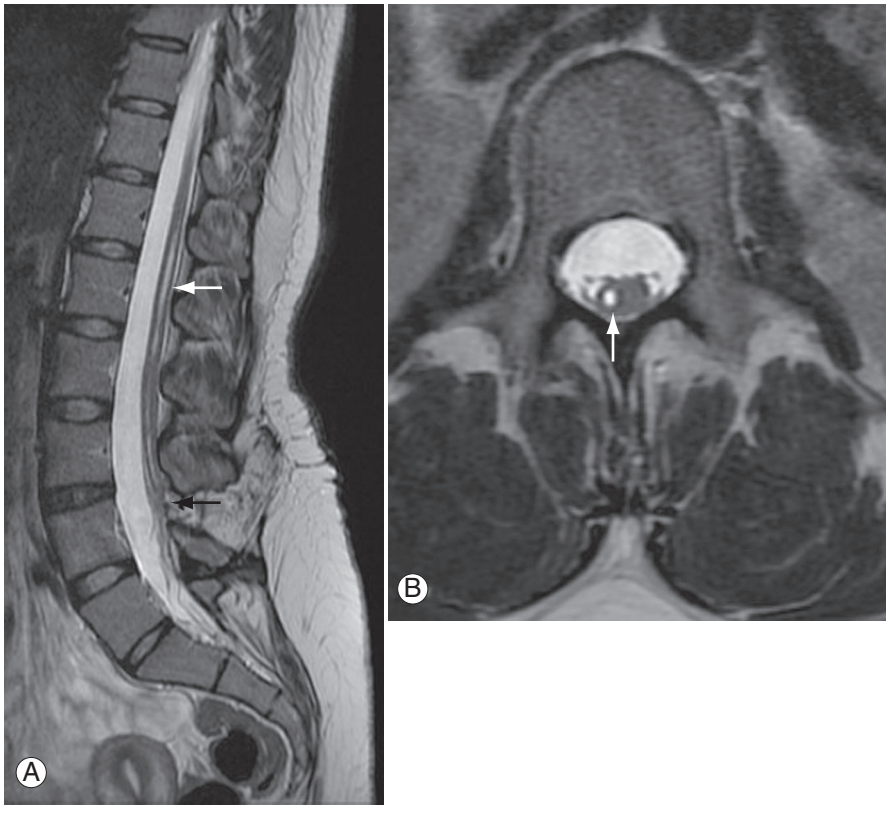

FIG. E3 Syringohydromyelia, tethered cord, in a 21-year-old female. Sagittal **(A)** and axial **(B)** T2-weighted magnetic resonance images show eccentric syringohydromyelia *(white arrow)* associated with tethered cord *(black arrow).* (From Naidich T et al: *Imaging of the spine,* 2011, WB Saunders. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

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BASIC INFORMATION

DEFINITION

Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder characterized by autoantibody production responsible for antibody-mediated and immune complex deposition tissue damage. SLE involves multiple organs and systems and has heterogeneous disease patterns. Relapses and remissions are a common feature.

SYNONYMS

SLE
Lupus

ICD-10CM CODES

M32	Systemic lupus erythematosus
M32.0	Drug-induced systemic lupus erythematosus
M32.8	Other forms of systemic lupus erythematosus
M32.9	Systemic lupus erythematosus, unspecified
M32.10	Systemic lupus erythematosus, organ or system involvement unspecified
M32.11	Endocarditis in systemic lupus erythematosus
M32.12	Pericarditis in systemic lupus erythematosus
M32.13	Lung involvement in systemic lupus erythematosus
M32.14	Glomerular disease in systemic lupus erythematosus
M32.15	Tubulo-interstitial nephropathy in systemic lupus erythematosus
M32.19	Other organ or system involvement in systemic lupus erythematosus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Varies across gender, race/ethnic groups, and geography from 20 to 70 cases per 100,000 persons. Prevalence higher among African Americans, Asian Americans, and Hispanics. There are an estimated 350,000 people with SLE in the U.S.
PREDOMINANT SEX: Female:male ratio is 9:1. The ratio is highest in reproductive age group, and about half of that in patients younger than 16 and older than 55.
PREDOMINANT AGE: Mean age at diagnosis is 31.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Constitutional: Unexplained fever, fatigue (80% to 100% patients), malaise (Table 1)
- Mucocutaneous lesions (more than 80% of patients): Acute (associated with + Ro antibody): malar rash (Fig. E1) sparing nasolabial folds (acute cutaneous lupus); annular or papulosquamous rash (subacute cutaneous lupus); Chronic: raised erythematous patches with subsequent edematous plaques and adherent scales (discoid cutaneous lupus), lupus profundus, lupus tumidus; alopecia, photosensitivity, nasal, or oropharyngeal ulcerations (classically painless, but discoid lesions [Fig. E2] may be painful); Raynaud phenomenon; leukocytoclastic vasculitis, chilblains; livedo reticularis or livedo racemosa (secondary to antiphospholipid antibody syndrome); skin biopsy hallmark: interface dermatitis
- Musculoskeletal (about 90% of lupus patients): Arthralgias are more common than true arthritis, but nonerosive deforming arthritis is not rare; myositis
- Cardiac: Pericardial rub (pericarditis) is most common; valvular heart disease: valve nodules and thickening (Libman-Sacks endocarditis); congestive heart failure, myocarditis, premature atherosclerotic heart disease
- Pulmonary: Pleuritis (most common), acute or chronic pneumonitis, diffuse alveolar hemorrhage, pulmonary hypertension
- Gastrointestinal: Dysphagia, mesenteric vasculitis, peritonitis, pancreatitis, hepatitis
- Neuropsychiatric: Headache, psychosis, seizure, acute confusional states, peripheral or cranial neuropathy, transverse myelitis, stroke (may be associated with antiphospholipid syndrome), cognitive dysfunction
- Hematologic (about 50% of lupus patients): Anemia (hemolytic, anemia of chronic disease, aplastic anemia), thrombocytopenia, leukopenia, lymphadenopathy, secondary antiphospholipid antibody syndrome
- Renal: Acute renal failure, proteinuria, nephritic syndrome, nephrotic syndrome

ETIOLOGY

Lupus may develop in genetically susceptible individuals, triggered by endogenous and exogenous factors. SLE susceptibility involves MHC class II polymorphism with commonly observed association with *HLA-DR-2, DR3, DR4,* and *DR8.* SLE is also associated with inherited deficiencies of C1q, C2, C4a, others. There is predilection for familial clustering of SLE with risk in monozygotic twins—about 25% to 50%—and 5% in dizygotic twins. Environmental factors such as UV light, Epstein-Barr virus infection, and tobacco smoking may have a triggering role. Autoantibody production is the hallmark of disease development and diagnosis of SLE. Evidence supports the improper processing of nuclear proteins and nucleic acid from cell death. Impairments in neutrophil cell death via a process termed NET-osis (nuclear extracellular trap) contribute to the accumulation of nuclear debris. This, in turn, can lead to the presentation of self-nuclear material to plasmacytoid dendritic cells. Plasmacytoid dendritic cells propagate antibody and immune complex production via a type I interferon-dependent mechanism.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rheumatoid arthritis, mixed connective tissue disease, systemic vasculitis
- Neoplastic disorder
- Hematologic malignancy, paraneoplastic syndrome
- Systemic infection
- Other: Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, primary antiphospholipid antibody syndrome

EVALUATION

The diagnosis of SLE is clinical. The 2019 European League Against Rheumatism/American College of Rheumatology (ACR) classification criteria for SLE include positive antinuclear antibody (ANA) at least once as obligatory entry criterion, followed by additive weighted criteria grouped in 7 clinical (constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal) and 3 immunologic (antiphospholipid antibodies, complement proteins, SLE-specific antibodies) domains, and weighted from 2 to 10. Patients accumulating ≥10 points are classified as having systemic lupus. The new criteria had a sensitivity of 96.1% and specificity of 93.4%, compared with 82.8% sensitivity and 93.4% specificity of the ACR 1997 (see below) and 96.7% sensitivity

TABLE 1 Potential Clinical Manifestations of Systemic Lupus Erythematosus

Target Organ	Potential Clinical Manifestations
Constitutional	Fatigue, anorexia, weight loss, fever, lymphadenopathy
Musculoskeletal	Arthritis, myositis, arthralgias, myalgias, avascular necrosis, osteoporosis
Skin	Malar rash, discoid rash, photosensitive rash, cutaneous vasculitis, livedo reticularis, periungual capillary abnormalities, Raynaud phenomenon, alopecia, oral and nasal ulcers
Renal	Hypertension, proteinuria, hematuria, edema, nephrotic syndrome, renal failure
Cardiovascular	Pericarditis, myocarditis, conduction system abnormalities, Libman-Sacks endocarditis
Neurologic	Seizures, psychosis, cerebritis, stroke, transverse myelitis, depression, cognitive impairment, headaches, pseudotumor, peripheral neuropathy, chorea, optic neuritis, cranial nerve palsies
Pulmonary	Pleuritis, interstitial lung disease, pulmonary hemorrhage, pulmonary hypertension, pulmonary embolism
Hematologic	Immune-mediated cytopenias (hemolytic anemia, thrombocytopenia or leukopenia), anemia of chronic inflammation, hypercoagulability, thrombocytopenic thrombotic microangiopathy
Gastroenterology	Hepatosplenomegaly, pancreatitis, vasculitis affecting bowel, protein-losing enteropathy
Ocular	Retinal vasculitis, scleritis, episcleritis, papilledema

and 83.7% specificity of the Systemic Lupus International Collaborating Clinics 2012 criteria.

1997 ACR Criteria:

- Malar rash
- Discoid rash
- Photosensitivity (recurrence of unusual skin rash in sun-exposed areas)
- Oral or nasopharyngeal painless ulceration, observed by physician
- Arthritis (nonerosive)
- Serositis (pleuritis, pericarditis)
- Renal disorder (persistent proteinuria >0.5 g/day, or ≥3+ on dipstick if quantification not performed; cellular casts)
- Neurologic disorder (seizures, psychosis [in absence of offending drugs or metabolic derangement])
- Hematologic disorder:
  1. Hemolytic anemia with reticulocytosis
  2. Leukopenia (<4000/mm^3 total on two or more occasions)
  3. Lymphopenia (<1500/mm^3 on two or more occasions)
  4. Thrombocytopenia (<100,000/mm^3 in the absence of offending drugs)
- Immunologic disorder:
  1. Anti–double-stranded DNA antibody (anti-dsDNA)
  2. Anti-Smith antibody (anti-Sm)
  3. Antiphospholipid antibodies (anticardiolipin IgM or IgG, lupus anticoagulant, anti-beta-2 glycoprotein IgM or IgG, or false-positive fluorescent treponemal antibody absorption test or *Treponema pallidum* immobilization for 6 months)
- ANA: An abnormal titer of ANA by immunofluorescence or equivalent assay at any time in the absence of drugs known to be associated with drug-induced lupus syndrome

2012 SLICC Criteria: SLE can be diagnosed if:

- Biopsy-proven nephritis with either ANA or anti-dsDNA antibodies *or*
- Patient satisfies four clinical criteria, requiring at least one clinical and at least one immunologic criterion
- Clinical criteria:
  1. Acute cutaneous lupus (malar rash, bullous lupus, toxic epidermal necrolysis, photosensitive lupus rash, maculopapular lupus, subacute cutaneous lupus)
  2. Chronic cutaneous lupus (discoid, hypertrophic verrucous, panniculitis, mucosal lupus, lupus tumidus, chilblains lupus, lichen planus)
  3. Oral ulcers or nasal ulcers
  4. Nonscarring alopecia
  5. Synovitis (more than two joints or inflammatory arthralgias of more than two joints)
  6. Serositis (pleurisy for more than 1 day, pericardial pain for more than 1 day)
  7. Renal (>500 mg proteinuria/24 hr) or RBC casts)
  8. Neurologic (seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confusional state)
  9. Hemolytic anemia
  10. Lymphopenia (<1000/mm^3 at least once)
  11. Thrombocytopenia (<100,000/mm^3 at least once)
- Immunologic criteria:
  1. ANA
  2. Anti-dsDNA (>2× laboratory reference range)
  3. Anti-Smith
  4. Antiphospholipid antibodies (lupus anticoagulant, RPR, anti-cardiolipin IgA, IgG, IgM, anti-β2 glycoprotein IgA, IgG, IgM)
  5. Low complement
  6. Direct Coombs test in the absence of hemolytic anemia

Definitions of SLE classification criteria are included in Table 2.

LABORATORY TESTS

Suggested initial laboratory evaluation of suspected SLE:

- ANA by immunofluorescence or similar high-quality method
  1. Complete blood count with differential, blood urea nitrogen and serum creatinine, urinalysis, ESR, PTT, complements (C3, C4)

Consider additional laboratory testing in a patient with strong suspicion for systemic lupus:

- Anti-dsDNA, anti-Smith, anti-SSA, anti-SSB, anti-RNP antibodies. Table 3 summarizes autoantibodies and clinical significance in SLE
- Lupus anticoagulant, RPR, anticardiolipin antibodies, anti-beta-2 glycoprotein

TABLE 2 Definitions of SLE Classification Criteria 2019

Criteria	Definition
Antinuclear antibodies (ANA)	ANA at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test at least once. Testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended.
Fever	Temperature >38.3° C (100.9° F)
Leukopenia	White blood cell count <4,000/mm^3
Thrombocytopenia	Platelet count <100,000/mm^3
Autoimmune hemolysis	Evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated LDH, *AND* positive Coombs (direct antiglobulin) test
Delirium	Characterized by 1) change in consciousness or level of arousal with reduced ability to focus, 2) symptom development over hours to <2 days, 3) symptom fluctuation throughout the day, 4) either 4a) acute/subacute change in cognition (e.g., memory deficit or disorientation), or 4b) change in behavior, mood, or affect (e.g., restlessness, reversal of sleep/wake cycle)
Psychosis	Characterized by 1) delusions and/or hallucinations without insight and 2) absence of delirium
Seizure	Primary generalized seizure or partial/focal seizure
Non-scarring alopecia	Non-scarring alopecia observed by a clinician†
Oral ulcers	Oral ulcers observed by a clinician†
Subacute cutaneous OR discoid lupus	Subacute cutaneous lupus erythematosus observed by a clinician:† Annular or papulosquamous (psoriasiform) cutaneous eruption, usually photodistributed If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted). OR Discoid lupus erythematosus observed by a clinician:† Erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/plugging (scalp), leading to scarring alopecia on the scalp If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular and/or periappendageal lymphohistiocytic infiltrate. In the scalp, follicular keratin plugs may be seen. In longstanding lesions, mucin deposition may be noted.)
Acute cutaneous lupus	Malar rash or generalized maculopapular rash observed by a clinician† If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted. Perivascular neutrophilic infiltrate may be present early in the course.)
Pleural or pericardial effusion	Imaging evidence (such as ultrasound, x-ray, CT scan, MRI) of pleural or pericardial effusion, or both
Acute pericarditis	≥2 of 1) pericardial chest pain (typically sharp, worse with inspiration, improved by leaning forward), 2) pericardial rub, 3) EKG with new widespread ST elevation or PR depression, 4) new or worsened pericardial effusion on imaging (such as ultrasound, x-ray, CT scan, MRI)

TABLE 2 Definitions of SLE Classification Criteria 2019—cont'd

Criteria	Definition
Joint involvement	Either 1) synovitis involving 2 or more joints characterized by swelling or effusion, or 2) tenderness in 2 or more joints and at least 30 minutes of morning stiffness
Proteinuria >0.5 g/24 hours	Proteinuria >0.5 g/24 hours by 24-hour urine or equivalent spot urine protein-to-creatinine ratio
Class II or V lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	Class II: Mesangial proliferative lupus nephritis: purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposit. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy. Class V: Membranous lupus nephritis: global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
Class III or IV lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	Class III: Focal lupus nephritis: Active or inactive focal, segmental, or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations Class IV: Diffuse lupus nephritis: Active or inactive diffuse, segmental, or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.
Positive antiphospholipid antibodies	Anticardiolipin antibodies (IgA, IgG, or IgM) at medium or high titer (>40 APL, GPL, or MPL, or >the 99th percentile) or positive anti-β_2GPI antibodies (IgA, IgG, or IgM) or positive lupus anticoagulant
Low C3 OR low C4	C3 OR C4 below the lower limit of normal
Low C3 AND low C4	Both C3 AND C4 below their lower limits of normal
Anti-dsDNA antibodies OR anti-Sm antibodies	Anti-dsDNA antibodies in an immunoassay with demonstrated ≥90% specificity for SLE against relevant disease controls OR anti-Sm antibodies

anti-β_2GPI, Anti–β_2-glycoprotein I; *anti-dsDNA,* anti-double-stranded DNA; *CT,* computed tomography; *EKG,* electrocardiography; *ISN,* International Society of Nephrology; *LDH,* lactate dehydrogenase; *MRI,* magnetic resonance imaging; *RPS,* Renal Pathology Society; *SLE,* systemic lupus erythematosus.
†This may include physical examination or review of a photograph.

TABLE 3 Autoantibodies and Clinical Significance in Systemic Lupus Erythematosus (SLE)

Autoantibody	Prevalence in SLE	Clinical Significance
Antinuclear Antibody		
Anti-dsDNA	60%	95% specificity for SLE; fluctuates with disease activity; associated with glomerulonephritis
Anti-Smith	20%-30%	99% specificity for SLE; associated with anti-U1RNP antibodies
Anti-U1RNP	30%	Antibody associated with mixed connective tissue disease and lower frequency of glomerulonephritis
Anti-Ro/SSA	30%	Associated with Sjögren syndrome, photosensitivity, SCLE, neonatal lupus, congenital heart block
Anti-La/SSB	20%	Associated with Sjögren syndrome, SCLE, neonatal lupus, congenital heart block, anti-Ro/SSA
Antihistone	70%	Also associated with drug-induced lupus
Antiphospholipid	30%	Associated with arterial and venous thrombosis, pregnancy morbidity

Anti-dsDNA, Anti-double-stranded deoxyribonucleic acid; *SSA,* Anti-Sjögren-syndrome-related antigen A; *SSB,* Anti-Sjögren-syndrome-related antigen B; *SCLE,* subacute cutaneous lupus erythematosus.
From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.

antibodies especially in patients with thrombotic events or recurrent miscarriages
- Urinalysis for RBC, cellular casts
- Random spot urine protein: Urine creatinine ratio, 24-hr urine protein collection if proteinuria; >0.5 or >500 mg/24 hr is abnormal, respectively. Evaluation of renal biopsy specimens in lupus nephritis is summarized in Table 4.
- Direct Coombs test

IMAGING STUDIES

- Chest x-ray for evaluation of pulmonary involvement (pleural effusion, infiltrates)
- Electrocardiogram for chest pain
- Echocardiogram if murmur, evidence of new or unexplained congestive heart failure, or suspected pericarditis

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of sunlight and use of high-SPF sunscreen (>35).
- Screening and counseling for modifiable cardiovascular risk factors such as cigarette smoking, diet, exercise, cholesterol, and uncontrolled HTN.
- Counseling for pregnancy planning for patients of childbearing age.
- Calcium and vitamin D supplementation for prevention of early osteoporosis (see "Clinical Pearls").

GENERAL Rx

- There are only four FDA-approved SLE medications: aspirin, steroids, hydroxychloroquine (1955), and belimumab (2011).
- Treatment should be targeted toward the involved organ(s).
- Limited and defined courses of corticosteroids are useful for a variety of SLE symptoms. Steroid therapy should be restricted to acute or subacute control of symptoms, due to the increased cardiovascular risk and increased organ damage associated with chronic steroid use.
- Consider checking G6PD in certain ethnic groups more predisposed to antimalarial-induced hemolytic anemia.
- Hydroxychloroquine has best evidence for reducing flares, organ damage, lipids, thrombosis; improving survival; augmenting action of mycophenolate mofetil (MMF) in lupus nephritis; and preventing seizures. Currently recommend not to exceed dose of 5 mg/kg/day to decrease risk of retinal toxicity.
- Methotrexate and azathioprine are used as steroid-sparing agents. Indications include cutaneous and joint involvement.
- Joint pain and mild serositis are generally well controlled with NSAIDs or low-dose corticosteroids. Hydroxychloroquine and methotrexate are also effective for arthritis. Belimumab does well for joint and cutaneous manifestations. Leflunomide and rituximab may be considered for refractory arthritis. Treatment approach for musculoskeletal features of SLE is summarized in Table 5.

- Cutaneous manifestations:
  1. Topical or intradermal corticosteroids are helpful for individual discoid lesions, especially in the scalp.
  2. Hydroxychloroquine alone or in combination with quinacrine and/or chloroquine can be considered for refractory skin disease.
  3. Refractory cases may be treated with belimumab, MMF, dapsone, or combination treatment.
  4. Table 6 summarizes general management of cutaneous lesions in SLE.
- Hematologic manifestations:
  1. Corticosteroids are first-line therapy. Table E7 summarizes the treatment and main hematologic features of SLE.
  2. Azathioprine can be used for thrombocytopenia or hemolytic anemia. Check for TPMT genetic mutation before the first use.
  3. Intravenous immunoglobulin (IVIG) or rituximab may be considered for severe leukopenia, autoimmune hemolytic anemia, or autoimmune thrombocytopenia.
- Central nervous system manifestations:
  1. Headaches are treated symptomatically. Most headaches will not be SLE-related and should be treated according to underlying cause.
  2. Anticonvulsants and antipsychotics may be indicated.
  3. Standard therapy for other neuropsychiatric SLE symptoms is not established.
- Renal disease: The histologic classification of lupus nephritis according to the International Society of Nephrology/Renal Pathology Society is summarized in Table E8. Severity of lupus nephritis is described in Table E9. Treatment recommendations for lupus nephritis are summarized in Table E10. (Class III, IV or IV/V with cellular crescents lupus nephritis; see Table 11). INDUCTION: 6-mo treatment
- The typical treatment induction period is 6 months. The use of intravenous cyclophosphamide (CYC) with corticosteroids given at monthly intervals is more effective in preserving renal function than is treatment with glucocorticoids alone. Low-dose "Euro-Lupus" protocol may be equally efficacious and less toxic for certain populations (e.g., Caucasians) than high-dose regimen. MMF is considered equivalent to CYC based on high-quality studies, with better tolerability and fertility profile. MMF may be preferred in African Americans and Hispanics. MMF and azathioprine are good options for maintenance treatment.
- Severe nonrenal organ disease:
  1. Evidence from systematic randomized controlled trials for nonrenal lupus treatment is comparatively limited.
  2. High-dose intravenous CYC is used as induction treatment. Azathioprine or MMF may be used as maintenance.
  3. IVIG may be considered in severe disease especially when concomitant infection is present.
  4. Plasmapheresis or plasma exchange may be considered in critical situations: First-line therapy in Guillain-Barré syndrome, TTP, second line for SLE-related hemolytic anemia, cerebritis, and DAH. Infectious complications are common.
- Therapy targeting B cells:
  1. Rituximab: Anti-CD 20 monoclonal antibody. Randomized controlled trials for rituximab as an adjunct induction agent were negative in terms of both renal and nonrenal outcomes but were felt to be limited by study design. Some observational studies have shown efficacy in those who have failed other regimens.
  2. Epratuzumab: An anti-CD 22 agent. Studies initially showed positive data, but in July 2015 both phase III trials for SLE failed to meet their primary endpoint and this medication is no longer studied.
  3. Belimumab: Decreases activation of B cells. When used in addition to standard therapy, patients on belimumab showed improvement in cutaneous and musculoskeletal disease. Belimumab-treated patients had decreased SLE activity, a reduced time to disease flare, and lower glucocorticoid exposure. Safety data were good. Patients with central nervous system or serious kidney disease were excluded.
  4. Abatacept: Downregulates T cell activation. Data is limited regarding improvement in arthritis, fatigue, sleep if added to routine therapy. Negative data as adjunct agent for lupus arthritis when added to MMF or CYC.
  5. Interferon therapy: Interferon α (INFα) has been linked to increased disease activity in SLE. INFα blocking therapies are in phase II clinical trials. Sifalimumab, a monoclonal antibody against INFα, reduced moderate to severe mucocutaneous involvement in SLE and decreased active joint count and fatigue scores in preliminary data analysis. Development of sifalimumab has been terminated in favor of anifrolumab, a similar INFα blocking agent.
  6. There is continuous interest in studying B cell- and interferon-based treatment, but no FDA approved treatment, other than above, is currently used clinically. Novel

TABLE 4 Evaluation of Renal Biopsy Specimens in Lupus Nephritis

Renal biopsy parameters	Evaluation
Ensure that sample is adequate	Specimens with <10 glomeruli are suboptimal.
Light microscopy stains	*Hematoxylin and eosin:* Best to identify inflammatory cells
	Trichrome (Masson): Best for interstitial fibrosis, glomerulosclerosis
	Periodic acid–Schiff (PAS): Identify basement membrane abnormalities
Immunofluorescence studies	Useful for identification of immune deposits
Electron microscopy	Helps to define distribution (subendothelial, epithelial, membranous deposits) of immune complexes and detection of podocytopathy
Activity and chronicity indexes	Useful in organizing renal biopsy report as a complement to ISN/RPS 2003 classification
Important elements to consider	Activity index (especially crescents, fibrinoid necrosis)
	Chronicity index (especially interstitial fibrosis, tubular atrophy, glomerular sclerosis)
	Renal vascular lesions (related to presence of antiphospholipid antibodies)

ISN, International Society of Nephrology; *RPS,* Renal Pathology Society.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE 5 Treatment Approach for Musculoskeletal Features of Systemic Lupus Erythematosus

	First-line therapy	Second-line therapy	Third-line therapy	Experimental therapy
Arthritis	HCQ or CQ	MTX	Belimumab	Abatacept
	Low doses of glucocorticoids	Leflunomide	RTX	Sifalimumab
			Anti-TNF	
AVN	Avoid high doses of corticosteroid	Antiaggregation in aPL positivity	Core decompression	
			Percutaneous drilling	
			Arthroplasty	
Myositis	High-dose corticosteroid	MTX	IVIG	
		Azathioprine	RTX	

aPL, Antiphospholipid; *AVN,* avascular necrosis; *CQ,* chloroquine; *HCQ,* hydroxychloroquine; *IVIG,* intravenous immunoglobulin; *MTX,* methotrexate; *RTX,* rituximab; *TNF,* tumor necrosis factor.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE 6 General Management of Cutaneous Lesions in Systemic Lupus Erythematosus

	Acute	SCLE	DLE
Nonpharmacologic measures			
	Photoprotection	Photoprotection	Photoprotection
	Avoidance of photosensitizing drugs	Avoidance of photosensitizing drugs	Avoidance of photosensitizing drugs
	Smoking cessation	Smoking cessation	Smoking cessation
Topical treatment			
	Topical calcineurin inhibitors	Topical glucocorticoids	Topical corticosteroids
		Topical calcineurin inhibitors	Topical calcineurin inhibitors
		Intralesional glucocorticoids	Intralesional glucocorticoids
			R-salbutamol
Systemic treatment			
First line	Antimalarials	Antimalarials	Antimalarials
	Glucocorticoids		Glucocorticoids
Second line		Systemic retinoids	MTX
			Systemic retinoids
			Antimalarial combination
Refractory cases			
	According to systemic involvement	Thalidomide	Dapsone
	RTX	Leflunomide	Thalidomide
	Belimumab	MMF	Belimumab
		IVIGs	RTX
		RTX	Lenalidomide
		Belimumab	
Therapies under investigation			
	Abatacept	Abatacept	Abatacept
		Sifalimumab	Sifalimumab
		Apremilast	Apremilast

DLE, Discoid lupus erythematosus; *IVIG,* intravenous immunoglobulin; *MMF,* mycophenolate mofetil; *MTX,* methotrexate; *RTX,* rituximab; *SCLE,* subacute cutaneous lupus erythematosus; *SLE,* systemic lupus erythematosus.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE 11 Severity of Lupus Nephritis*

Proliferative Disease	
Mild	Type III without severe histologic features (e.g., crescents, fibrinoid necrosis); low chronicity index (i.e., ≤3); normal renal function; nonnephrotic-range proteinuria
Moderately severe	Mild disease as defined above with partial or no response after the initial induction therapy or delayed remission (>12 months), or focal proliferative nephritis with adverse histologic features or reproducible increase of at least 30% in serum creatinine levels, or diffuse proliferative nephritis (class IV) without adverse histologic features
Severe	Moderately severe as defined above but not remitting after 6 to 12 mo of therapy, or proliferative disease with impaired renal function and fibrinoid necrosis or crescents in >25% of glomeruli, or mixed membranous and proliferative nephritis, or proliferative nephritis with high chronicity alone or in combination with high activity (chronicity index >4 or chronicity index >3 and activity index >10), or rapidly progressive glomerulonephritis (doubling of serum creatinine within 2 to 3 mo)
Membranous Nephropathy	
Mild	Nonnephrotic-range proteinuria with normal renal function
Moderate	Nephrotic-range proteinuria with normal renal function at presentation
Severe	Nephrotic-range proteinuria with impaired renal function at presentation (at least 30% increase in serum creatinine)

*Concomitant therapy with corticosteroids or other immunosuppressive drugs may modify urinary sediment and/or histologic findings and should be taken into consideration.
From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

potential targeted treatment approaches may include blocking IL17, IL12/23 and JAK. Research remains very active and ongoing to find new therapeutic targets.

- Recommended assessment and monitoring of patients with SLE with nonrenal, noncentral nervous system manifestations are summarized in Box 1.

DISPOSITION

- Most patients with SLE experience remissions and exacerbations.
- Five-yr survival rate has improved to more than 90% in patients with newly diagnosed SLE since the advent of potent immunosuppressive therapy. The 15-yr survival rate is now 85%.
- Early death related to SLE activity and infections; late death due to CVD.
- Lupus nephritis progression rate to ESRD in 10% to 30% within 15 yr.
- African Americans, Asian Americans, and Hispanic Americans in general have a worse prognosis. The leading cause of death in SLE patients in developed countries is premature atherosclerosis. The quality of life for many SLE patients is poor due to fatigue, chronic pain, and cognitive impairment.

REFERRAL

- Rheumatology consultation for all patients with SLE
- Hematology consultation for patients with significant hematologic abnormalities (e.g., severe hemolytic anemia or thrombocytopenia)

BOX 1 Recommended Assessment and Monitoring of Patients with Systemic Lupus Erythematosus with Nonrenal, Non-Central Nervous System Manifestations

Patient general assessment
In addition to the standard care of patients without lupus of the same age and sex, the assessment of patients with SLE must include the evaluation of:
- Disease activity by a validated index at each visit
- Organ damage annually
- General quality of life by patient history and/or by a 0–10 VAS (patient global score) at each visit
- Comorbidities
- Drug toxicity

Cardiovascular risk factors
At baseline and during followup at least once a year:
- Assess smoking, vascular events (cerebral and cardiovascular), physical activity, oral contraceptives, hormonal therapies, and family history of cardiovascular disease
- Perform blood tests: Blood cholesterol, glucose
- Examine for blood pressure and BMI (and/or waist circumference)
- NB: Some patients may need more frequent followup (e.g., those taking glucocorticoids).

Osteoporosis risk
All patients with SLE:
- Should be assessed for adequate calcium and vitamin D intake, regular exercise, and smoking habits
- Should be screened and followed for osteoporosis according to existing guidelines (1) for postmenopausal women and (2) for patients taking glucocorticoids or on any other medication that may reduce BMD

Cancer risk
Cancer screening is recommended according to the guidelines for the general population, including cervical smear tests.

Infection risk
Screening: Patients with SLE should be screened for:
- HIV based on the patient's risk factors
- HCV and HBV based on the patient's risk factors, particularly before IS drugs including high-dose glucocorticoids are given
- Tuberculosis, according to local guidelines, especially before IS drugs including high-dose glucocorticoids are given
- CMV testing should be considered during treatment in selected patients.

Vaccination: Patients with SLE are at high risk of infections, and prevention should be recommended. The administration of inactivated vaccines (especially flu and pneumococcus), following CDC guidelines for patients who are immunosuppressed, should be encouraged strongly in patients with SLE who take IS drugs, preferably administered when the SLE is inactive. For other vaccinations, an individual risk–benefit analysis is recommended.

Monitoring: At followup visits, continuous assessment of the risk of infection by taking into consideration the presence of:
- Severe neutropenia (<500 cells/mm^3)
- Severe lymphopenia (<500 cells/mm^3)
- Low IgG (<500 mg/dL)

Frequency of assessments
In patients with no activity, no damage, and no comorbidity, assessments are recommended every 6 to 12 months. During these visits, preventive measures should be emphasized.

Laboratory assessment
It is recommended to monitor the following autoantibodies and complement:
- At baseline: ANA, anti-dsDNA, anti-Ro, anti-La, anti-RNP, anti-Sm, antiphospholipid, C3, C4
- Reevaluation of aPLs in previously negative patients before pregnancy, surgery, transplant, and use of estrogen-containing treatments or in the presence of a new neurologic or vascular event; anti-Ro and anti-La antibodies before pregnancy; anti-dsDNA/C3 C4 may support evidence of disease activity or remission

Other laboratory assessments. At 6- to 12-month intervals, patients with inactive disease should have:
- CBC
- ESR
- CRP
- Serum albumin
- Serum creatinine (or eGFR)
- Urinalysis and urine protein-to-creatinine ratio

NB: If a patient is on a specific drug treatment, monitoring for that drug is required as well.

Mucocutaneous involvement
Mucocutaneous lesions should be characterized, according to existing classification systems, as to whether they may be:
- LE specific
- LE nonspecific
- LE mimickers
- Drug-related

Lesions should be assessed for activity and damage using validated indices (e.g., CLASI).

Eye assessment
In patients treated with glucocorticoids or antimalarials, a baseline eye examination is recommended according to standard guidelines. An eye examination during followup is recommended:
- In selected patients taking glucocorticoids (high risk of glaucoma or cataracts)
- In patients on antimalarial drugs. (Low risk: HCQ: No further testing is required until after 5 years of baseline, and after the first 5 years of treatment, eye assessment is recommended yearly; High risk: Eye assessment is recommended yearly, especially when using CQ).

ANA, Antinuclear antibodies; *aPL,* antiphospholipid antibody; *BMD,* bone mineral density; *BMI,* body mass index; *CBC,* complete blood count; *CDC,* Centers for Disease Control and Prevention; *CLASI,* Cutaneous Lupus Erythematosus Disease Area and Severity Index; *CMV,* cytomegalovirus; *CQ,* chloroquine; *CRP,* C-reactive protein; *eGFR,* estimated glomerular filtration rate; *ESR,* erythrocyte sedimentation rate; *HBV,* hepatitis B virus; *HCQ,* hydroxychloroquine; *HCV,* hepatitis C virus; *IgG,* immunoglobulin G; *IS,* immunosuppressors; *LE,* lupus erythematosus; *NB,* nota bene; *SLE,* systemic lupus erythematosus; *VAS,* visual analog scale.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

- Nephrology consultation in patients with proteinuria and/or suspected renal involvement
- Dermatology consultation for patients with unexplained or unusual skin rash
- Cardiology consultation for patients with lupus carditis, arrhythmias
- Ophthalmology referral for all patients on hydroxychloroquine and chloroquine

PEARLS & CONSIDERATIONS

- Arthritis in SLE often has no prolonged morning stiffness and is not erosive on x-rays; reversible joint deformities in lupus are termed Jaccoud arthropathy.
- Myocardial infarction is 50 times more common in young female patients than in age-matched control group.
- Prevent adverse effects of medications: Consider prophylaxis for infections and appropriate vaccinations, ensure yearly Pap and other cancer screening as clinically indicated; for patients taking CYC, intervention to preserve bladder and fertility should be considered; manage bone health.
- Based on small clinical data a vitamin D level >40 may have modest reduction in disease activity; in addition vitamin D may reduce risk of thrombosis, based on oncology research.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Systemic Lupus Erythematosus (Patient Information)
Discoid Lupus (Related Key Topic)

AUTHOR: **Katarzyna Gilek-Seibert, MD, RhMUS**

FIG. E1 Systemic lupus erythematosus. This young man has the typical malar rash of systemic lupus erythematosus. Note the prominent nasolabial sparing. (From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

FIG. E2 Erosive lesions of discoid lupus erythematosus involving the palms. Typical lesions of discoid lupus erythematosus are present elsewhere. (From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

TABLE E7 Treatment of Main Hematologic Features of Systemic Lupus Erythematosus

	First-line therapy	Second-line therapy	Third-line therapy	Experimental therapy
Thrombocytopenia	Glucocorticoids	Azathioprine CYC IVIG	RTX MMF Cyclosporine	Thrombopoietin-receptor agonists
Autoimmune anemia	Glucocorticoids*	CYC IVIG	MMF RTX Danazol	
Pure RBC aplasia	Glucocorticoids*	CYC IVIG	Danazol Cyclosporine MMF	EPO
Hemophagocytosis syndrome	Glucocorticoids*	CYC Cyclosporine PE	IVIG† RTX	
TTP	Glucocorticoids*	PE CYC	RTX	

CYC, Cyclophosphamide; *EPO,* erythropoietin; *IVIG,* intravenous immunoglobulin; *MMF,* mycophenolate; *PE,* plasma exchange; *RBC,* red blood cell; *RTX,* rituximab; *TTP,* thrombotic thrombocytopenic purpura.
*Methylprednisolone pulses (3 × 1000 mg) are recommended.
†In patients with concomitant infection.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE E8 Histologic Classification of Lupus Nephritis According to the International Society of Nephrology/Renal Pathology Society (2003)

Class	Description
I	Minimal mesangial lupus nephritis
	Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
II	Mesangial proliferative lupus nephritis
	Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits
	A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy but not by light microscopy
III	Focal lupus nephritis
	Active or inactive focal, segmental, or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
IV	Diffuse lupus nephritis
	Active or inactive diffuse, segmental, or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into *diffuse segmental* (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions and diffuse global (IV-G) when ≥50% of the involved glomeruli have global lesions. *Segmental* is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.
V	Membranous lupus nephritis
	Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
	Class V nephritis may occur in combination with class III or class IV, in which case both will be diagnosed.
	Class V nephritis may show advanced sclerotic lesions.
VI	Advanced sclerotic lupus nephritis ≥90% of the glomeruli globally sclerosed without residual activity

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE E9 Severity of Lupus Nephritis*

	Histologic class (ISN/RPS 2003)	↓ GFR†	Proteinuria >3 g per 24 hr	Adverse histologic features‡
Mild	III	–	–	–
	V	–	–	
Moderately severe	III	+/–	+/–	–
	IV	–	+/–	–
	V	–	+	
Severe	III–IV	+/–	+/–	+
	IV	+	+/–	+/–
	III-IV	+§	+/–	+/–
	V	+	+	
	V + III–IV	+/–	+/–	+/–

+, Presence of feature; –, absence of feature; *ISN,* International Society of Nephrology; *RPS,* Renal Pathology Society.
*Concomitant treatment with corticosteroids or other immunosuppressive drugs may modify urinary sediment or histologic findings and should be taken into consideration.
†Reproducible increase of ≥30% in serum creatinine levels and/or decrease of ≥10% in glomerular filtration rate (GFR).
‡Cellular crescents in ≥30% of glomeruli and/or fibrinoid necrosis in ≥25% of glomeruli and/or activity index ≥12 and/or chronicity index ≥4 and/or combination of activity index ≥11 and chronicity index ≥3.
§Rapidly progressive glomerulonephritis (doubling of serum creatinine within 2 to 3 mo.)
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

TABLE E10 Recommended Treatment of Lupus Nephritis

Histologic type or severity	Type of therapy	
	Induction	**Maintenance**
Proliferative		
Mild	• High-dose glucocorticoids (0.5-1 mg/kg/day for 4-6 wk with gradual tapering to 0.125 mg/kg every other day within 3-4 mo) alone or in combination with AZA (1-2 mg/kg/day) • If no response within 3-6 mo, treat as moderately severe.	• Low-dose glucocorticoids (≤0.125 mg/kg on alternative days) alone or with AZA (1-2 mg/kg/day) • Consider further gradual tapering at the end of each year of response.
Moderate	• MPA (MMF 3 g/day) with glucocorticoids (0.5 mg/kg/day for 4 wk; then taper) for 6 mo. Consider three initial pulses of IV MP (500-750 mg/pulse), or • Pulse IV CYC (3 g over 3 mo) with glucocorticoids as above • If no response within 6-12 mo, treat as severe.	• Low-dose glucocorticoids (≤0.125 mg/kg on alternative days) with MPA (MMF 2 g/day) for 18-24 mo after initial response; then consider gradual tapering, or • AZA (2 mg/kg/day)
Severe	• Monthly pulses of IV CYC (0.5-1 g/m^2) in combination with pulse IV MP for 6 mo. Background glucocorticoids (0.5 mg/kg/day for 4 wk; then taper), or • MPA (MMF 3 g/day) • If no improvement, consider MPA, combination of MPA with calcineurin inhibitor, or rituximab.	• Low-dose glucocorticoids (≤0.125 mg/kg on alternative days) in combination with quarterly pulses of IV CYC for at least 1 yr beyond response, or • MPA (MMF 2 g/day)
Membranous		
Mild	• High-dose glucocorticoids alone or in combination with AZA (2 mg/kg/day)	• Low-dose glucocorticoids alone or with AZA (1-2 mg/kg/day)
Moderate to severe	• High-dose glucocorticoids in combination with MPA (MMF 3 g/day), or • Bimonthly pulse IV CYC (0.5-1 g/m^2, six pulses), or • CsA (3-5 mg/kg/day) or tacrolimus	• Low-dose glucocorticoids • AZA (2 mg/kg/day) • CsA (3 mg/kg/day) or tacrolimus • MPA (MMF 2 g/day)

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

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Tabes Dorsalis

BASIC INFORMATION

DEFINITION

Tabes dorsalis is a form of late neurosyphilis affecting the dorsal columns of the spinal cord and peripheral nerves, characterized by paroxysmal pain, particularly in the abdomen and legs; sensory ataxia; normal strength; autonomic dysfunction; and Argyll Robertson pupils.

SYNONYMS

Posterior spinal sclerosis
Tabetic neurosyphilis
Syphilitic myeloneuropathy
Neurosyphilis

ICD-10CM CODE
A52.11 Tabes dorsalis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Rare, but increasing with HIV/AIDS
PEAK INCIDENCE: 15 to 20 yr after initial infection
PREVALENCE (IN U.S.): Rare; more common with HIV/AIDS epidemic. Ten percent of untreated patients with syphilis develop neurosyphilis, 2% to 5% of whom may develop tabes dorsalis. Relative prevalence of tabes dorsalis is reduced compared with the preantibiotic era. This may be the only clinical manifestation of neurosyphilis that has been altered during the antibiotic era.
PREDOMINANT SEX: Male

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Argyll Robertson pupils are common. The pupil reacts poorly to light but well to accommodation (light-near dissociation)
- Loss of position and vibration at ankles (wide-based gait, inability to walk in the dark, sensory ataxia)
- Loss of deep pain sensation, resulting in deep foot ulcers
- Degenerative joint disease (Fig. E1), especially in knees, caused by severe neuropathy (Charcot joints)
- Normal strength with areflexia in the legs
- Lightning pains in the legs
- Severe intermittent visceral pains, such as gastrointestinal and laryngeal (visceral crises)
- Autonomic dysfunction (urinary and fecal incontinence due to sphincter dysfunction)

ETIOLOGY

Infectious *(Treponema pallidum).* Neurosyphilis occurs as a consequence of treponemal penetration of the blood-brain barrier and destruction of adjacent neural tissue, sometimes coupled with cerebral infarction due to meningovascular disease.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Vitamin B_{12} deficiency (subacute combined degeneration of the spinal cord)
- Vitamin E deficiency
- Chronic nitrous oxide abuse
- Spinal cord neoplasm (involving conus medullaris)
- Lyme disease

WORKUP

Thorough neurologic history and examination

LABORATORY TESTS

- Lumbar puncture: The diagnosis of neurosyphilis requires a CSF mononuclear pleocytosis of 20 WBC/μL or a reactive Venereal Disease Research Laboratory (VDRL) or a positive intrathecal *T. pallidum* antibody index. Pleocytosis is less specific in patients with HIV due to HIV-related meningitis.
- False-positive serum RPR may occur in Lyme disease, nonvenereal treponematoses, genital herpes simplex, pregnancy, systemic lupus erythematosus, alcoholic cirrhosis, scleroderma, and mixed connective tissue disease.
- All patients with syphilis should be tested for HIV.
- Persons who are HIV positive are at increased risk of developing neurosyphilis. A new development in the detection of neurosyphilis in patients who are HIV positive is the use of the B-cell chemoattractant chemokine (CXC motif) ligand 13 as a CSF marker.

IMAGING STUDIES

Not necessary if diagnosis confirmed clinically and serologically

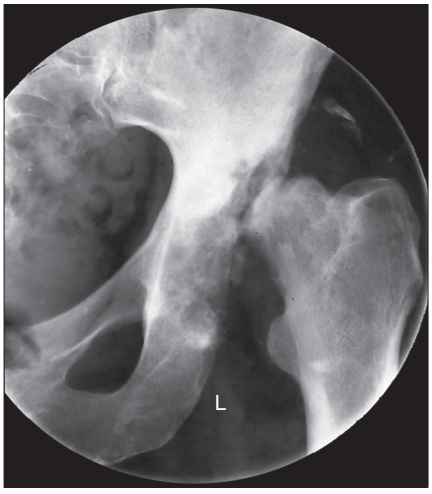

FIG. E1 Neuropathic hip secondary to tabes dorsalis. (Courtesy Dr. I. Watt. From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

TREATMENT

ACUTE GENERAL Rx

- CDC guidelines: Aqueous crystalline penicillin G 18 to 24 million units per day, administered as 3 to 4 million units IV every 4 hours, or continuous infusion for 10 to 14 days; or if adherence can be ensured, penicillin G procaine, 2.4 million units IM daily, plus probenecid 500 mg orally four times a day for 10 to 14 days
- If patient is penicillin allergic, either desensitize to penicillin or obtain an infectious disease (ID) consultation.
- Many of the symptoms—degenerative neuropathic joint disease, lightning pains—persist after treatment.

CHRONIC Rx

- Physical therapy
- Analgesics, carbamazepine, gabapentin, or steroids may help lightning pain
- Supportive care (wheelchair, toileting issues, etc.)

DISPOSITION

- Close follow-up required. Repeat lumbar puncture is recommended every 6 mo until CSF pleocytosis normalizes. If pleocytosis does not normalize in 6 mo or CSF is still abnormal in 2 yr, repeat treatment. Serologic criterion for response to therapy is a fourfold or greater decrease in VDRL titer over 6 to 12 mo.
- Further indication for retreatment: If there is a fourfold increase in titers or a failure of titers >1:32 to decrease at least fourfold by 6 to 12 mo.

REFERRAL

- Joint replacement in moderate cases
- ID consult for patients with penicillin allergy

PEARLS & CONSIDERATIONS

COMMENTS

- Diagnosis should be considered in all patients with a progressive neuropsychiatric disorder with signs of spinal cord dysfunction and peripheral neuropathy.
- Penicillin does not improve late neurosyphilitic syndromes but usually halts their progression.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Syphilis (Related Key Topic)

AUTHOR: **Joseph S. Kass, MD, JD, FAAN**

SUGGESTED READINGS

Marra CM et al: CXCL13 as a cerebrospinal fluid marker for neurosyphilis in HIV-infected patients with syphilis, *Sex Transm Dis* 37(5):283-287, 2010.

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BASIC INFORMATION

DEFINITION

Takayasu arteritis is a large-vessel vasculitis that primarily affects the aorta and its main branches. Chronic inflammation of involved vessels commonly leads to stenosis, occlusion, dilation, and aneurysms in the arterial wall.

SYNONYMS

Pulseless disease
Aortitis syndrome
Aortic arch arteritis
Nonspecific aortoarteritis

ICD-10CM CODE
M31.4 Aortic arch syndrome [Takayasu]

EPIDEMIOLOGY & DEMOGRAPHICS

In the U.S., the incidence is 2.6 per 1 million people. The highest prevalence of Takayasu arteritis has been described in Japan, where all cases of Takayasu arteritis are registered by the government, and it has been estimated that 100 to 200 new cases occur each yr.

The female:male ratio is 8:1. Age of onset is between 10 and 40 yr with three quarters of patients presenting between the ages of 10 and 20 yr.

GENETICS: Some HLA alleles, including HLA-B52, HLA-B39, and HLA-B67, have been reported to be associated with Takayasu.

CLINICAL PRESENTATION & PHYSICAL FINDINGS

Takayasu arteritis manifests with clinically nonspecific signs and symptoms of systemic inflammation, including general fatigue, weight loss, generalized arthralgias and myalgias, and low-/high-grade fever. These symptoms are usually subacute, which leads to delay in the diagnosis from mos to yrs. Vascular symptoms are rare at presentation, and localized symptoms and signs vary depending on the location of the affected arteries.

- Table E1 summarizes common symptoms and signs in Takayasu arteritis. "Red flags" for Takayasu arteritis are summarized in Table E2.
- The occlusive stage of Takayasu arteritis may progress to stenosis or aneurysm of the aorta and its primary branches, and may manifest as a variety of clinical signs and symptoms, such as:
  1. Arm or leg claudication, weakness, and numbness
  2. Amaurosis fugax, diplopia, headache, orthostasis, vertigo, memory loss, or syncope
  3. Angina or myocardial infarction
  4. Vascular bruits of the carotid artery, subclavian artery, and aorta
  5. Discrepancy of blood pressures between the upper extremities, typically of ≥10 mm Hg
  6. Diminished or absent pulses, ischemic ulcerations, or gangrene in advanced disease
  7. Hypertension
  8. Retinopathy
  9. Aortic insufficiency as a result of aortic root dilatation and aneurysm formation
  10. Weakness of the arterial walls may give rise to localized aneurysms/dissection.
  11. Dyspnea or hemoptysis
  12. Skin lesions similar to erythema nodosum
- Gastrointestinal (GI) symptoms (abdominal pain, diarrhea, and GI bleed) secondary to mesenteric artery ischemia

ETIOLOGY & PATHOGENESIS

The cause of Takayasu arteritis is poorly understood. Cell-mediated mechanisms (cytotoxic T cell, macrophage, natural killer cells, and others) and cytokine release (such as tumor necrosis factor-alpha [TNF-α], interleukin-6 [IL-6], and interferon-gamma [IFN-γ]) are thought to be important to the pathogenesis. Both pathways contribute to the induction and amplification of inflammation and tissue injury.

- Infiltration by inflammatory cells (lymphocytes, macrophages, and multinucleated giant cells) into the vasa vasorum and media of the large elastic arteries (Fig. E1) leads to production of matrix metalloproteinases (MMP), which cause destruction of elastic fibers in the arterial wall, neovascularization, and other inflammatory changes. An intermediate stage, driven in part by TNF-alpha, leads to mucopolysaccharide deposition and proliferation of fibroblasts and smooth muscle cells, causing intimal hypertrophy.
- With chronic disease, inflammatory lesions progress to either thick fibrotic calcified narrowings (≥90% of cases) or aneurysms if fibrosis is insufficient and the arterial wall is instead thinned and dilated (≥25% of cases).
- Infection, in particular, tuberculosis, has been implicated in the pathogenesis, with several studies reporting an increased incidence of caseating granulomas in patients with Takayasu arteritis. Additional immunologic studies lend support to a pathogenic role of CD4 and CD8 T cells in this patient population.

DIAGNOSIS

Diagnostic criteria for Takayasu arteritis were established by the American College of Rheumatology in 1990. A diagnosis is made if at least three of the six criteria are present; this

TABLE E1 Common Symptoms and Signs (%) in Takayasu Arteritis

	Study					
Symptom/Sign	**Japan (n = 52)**	**India (n = 106)**	**China (n = 530)**	**Korea (n = 129)**	**U.S. (n = 60)**	**Mexico (n = 107)**
Fatigue/constitutional	27%	—	—	34%	43%	78%
Weight loss	—	9%	—	11%	20%	22%
Musculoskeletal	6%	5%	—	—	53%	53%
Claudication	13%	—	25%	21%	90%	29%
Headache	31%	44%	—	60%	42%	57%
Visual changes	6%	12%	10%	20%	30%	8%
Syncope/dizziness	40%	26%	14%	36%	35%	13%
Palpitations	23%	19%	—	23%	10%	43%
Dyspnea	21%	26%	11%	42%	—	72%
Carotidynia	21%	—	—	2%	32%	—
Hypertension	33%	77%	60%	40%	35%	72%
Bruit	—	35%	58%	37%	80%	94%
Decreased pulses	62%	—	37%	55%	60%	96%
Asymmetric blood pressure	—	—	—	—	47%	—

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

results in a sensitivity of 91% and specificity of 98%. The criteria are:

- Age of disease onset <40 yr
- Claudication of the extremities
- Decreased brachial artery pulse
- Systolic blood pressure difference ≥10 mm Hg between left and right arms
- Bruit over one or both of the subclavian arteries or the abdominal aorta
- Abnormal arteriogram, not related to arteriosclerosis or fibromuscular dysplasia

TABLE E2 "Red Flags" for Takayasu Arteritis

In patients younger than 40 yr, the following may be indicative of TA:
Unexplained acute-phase response (raised ESR and/or CRP)
Carotidynia
Hypertension
Discrepant blood pressure between the arms (>10 mm Hg)
Absent or weak peripheral pulse or pulses
Limb claudication
Arterial bruit
Angina

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

DIFFERENTIAL DIAGNOSIS

Table E3 describes pathologic characteristics of selected forms of vasculitis. Other causes of inflammatory arteritis must be excluded:

- Temporal arteritis (giant cell arteritis)
- Atherosclerosis
- Infectious aortitis
- Syphilis
- Tuberculosis
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Buerger disease
- Behçet disease
- Marfan syndrome
- Ehlers-Danlos syndrome

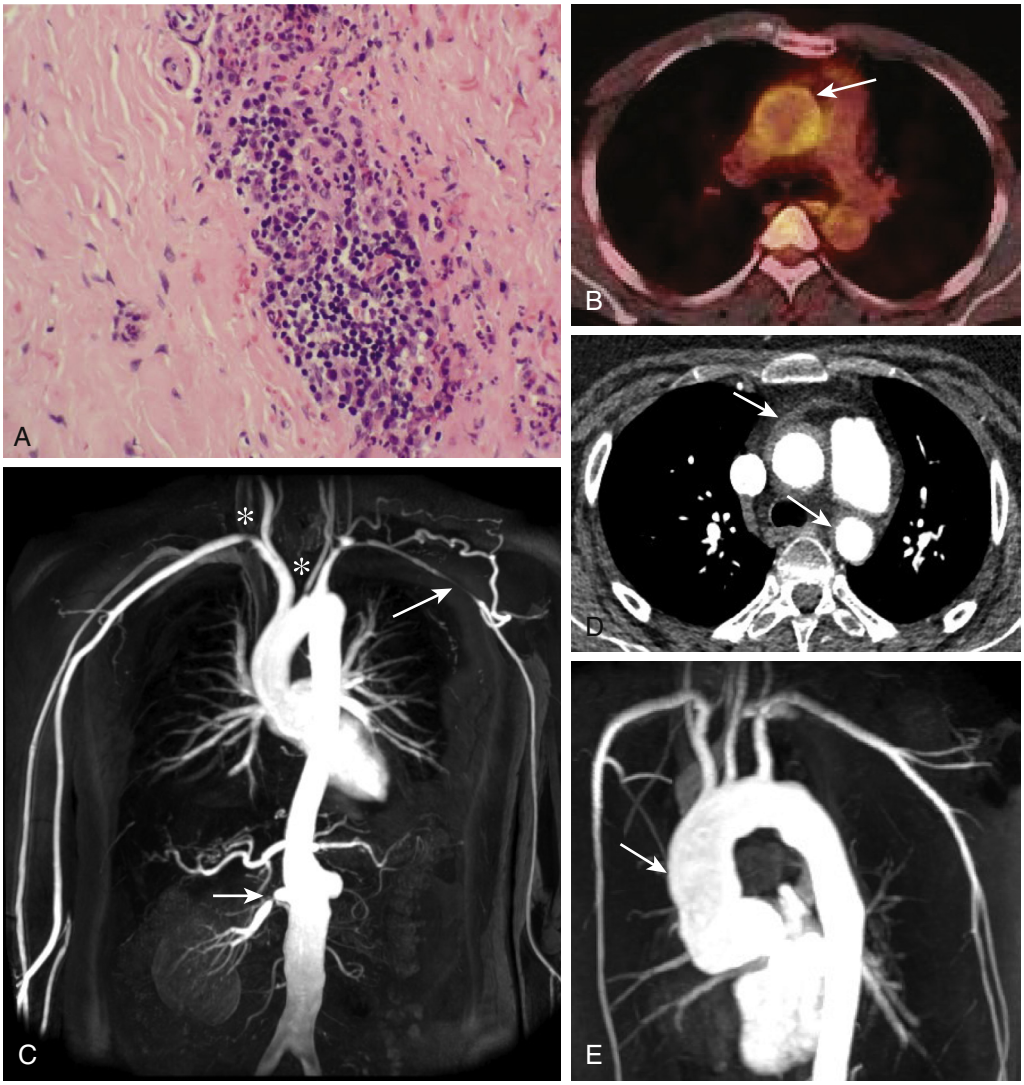

FIG. E1 Takayasu arteritis A, Hematoxylin-eosin staining of a common carotid artery biopsy specimen obtained at surgery shows a focal mixed mononuclear cell inflammatory infiltrate with a multinucleated giant cell. **B,** ^{18}FDG-PET-CT scan demonstrating uptake in the aortic arch *(arrow)*, consistent with active arteritis. **C,** Magnetic resonance angiogram (MRA) demonstrating stenosis of the left subclavian artery with collateral formation *(long arrow)*, proximal stenoses in the right subclavian and left common carotid arteries *(stars)*, proximal stenosis in the right renal artery *(short arrow)*, and an atrophic left kidney. **D,** Computed tomography angiogram demonstrating thickening of the wall of the ascending and descending aorta *(arrows).* **E,** MRA revealing severe dilatation of the ascending aorta *(arrow)* requiring aortic valve replacement. (Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

- Cogan syndrome
- Kawasaki disease
- Spondyloarthropathies
- Fibromuscular dysplasia
- Relapsing polychondritis

WORKUP

Any young patient with findings of absent pulses and loud bruits merits a workup for Takayasu arteritis. There are no diagnostic laboratory tests to diagnose Takayasu arteritis. Nonspecific inflammatory biomarkers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are useful markers for diagnosis, but normal values shouldn't be used to rule out the disease. In most patients, the diagnosis is made by clinical findings and imaging of the arterial branches. Advanced imaging modalities, including contrast-enhanced magnetic resonance angiography (MRA) and computed tomography angiography (CTA), allow for not only early diagnosis but also detailed assessment of vascular lesions. Three-dimensional reconstructions of the whole aorta and neck arteries using CTA are especially useful for surveying lesions. Ultrasound and FDG-PET are commonly used for diagnosis as well as in serial monitoring of disease activity. Catheter-based angiography is used to rule out ischemia and to measure core blood pressure when all four limbs arterial stenosis prevent accurate blood pressure measurement.

LABORATORY TESTS

- ESR and serum CRP levels are usually but not always elevated.
- A CBC may reveal a normal or elevated white blood cell count as well as anemia.
- Immunologic studies may include elevated immunoglobulins (IgG and IgA) and complement components (C3 and C4).
- Hypercoagulation and increase in platelet aggregation.
- Recent studies have attempted to establish a link between elevated levels of various interleukins and other inflammatory markers and active disease.

IMAGING STUDIES

- Imaging of the entire aorta and major branch vessels using angiography, CTA, or MRA.
- CTA can detect changes in the vessel wall and provide an accurate representation of luminal diameters.
- MRA provides information on vessel lumen and wall thickening, cardiac morphology and function, and myocardial tissue characterization.
- Angiography can show the narrowing of the aorta and its branches, aneurysm formation, poststenotic dilation, and the development of any collateral circulation. Angiographic findings are classified into five major types:
  1. Type I: Lesions that involve only branches of the aortic arch
  2. Type IIa: Lesions that involve the ascending aorta, the aortic arch, and its branches
  3. Type IIb: Lesions from IIa plus the thoracic descending aorta
  4. Type III: Lesions that involve the thoracic descending aorta, abdominal aorta, and/or renal arteries
  5. Type IV: Lesions that involve the abdominal aorta and/or renal arteries
  6. Type V: Lesions that involve the entire aorta and its branches
- Chest radiography: Pathologic changes of the aorta are often visible, with areas of alternating stenosis and dilation seen. Segmental calcification outlining areas of aortic narrowing is characteristic of Takayasu disease.
- Ultrasound: Carotid, thoracic, and abdominal ultrasound are useful adjunctive imaging studies to diagnose the occlusive disease that results from Takayasu arteritis. The addition of Doppler is helpful to assess blood flow and absent pulses.
- Positron emission tomography using radioisotope fluorodeoxyglucose (FDG-PET) as a marker for tissue with high glucose uptake has shown promising results in terms of specificity and sensitivity. The yield of using PET scans to measure disease activity is still under study.

Rx TREATMENT

Treatment of Takayasu arteritis consists of two parts: Induction and maintenance of remission and management of arterial complications.

ACUTE GENERAL Rx

High-dose glucocorticoids are first-line therapy for suppressing systemic symptoms and stopping disease progression. Prednisone (1 mg/kg/day, up to a maximum daily dose of 60 to 80 mg) can be used for 3 mo or intravenous steroids can be administered initially.

Attempts to taper prednisone can be made with resolution of constitutional symptoms, significant decline in the ESR and C-reactive protein levels, and in accordance with imaging studies.

Because of steroids' side effects and the high rate of relapse while tapering, it is recom-

TABLE E3 Pathologic Characteristics of Selected Forms of Vasculitis

	Takayasu Arteritis	Polyarteritis Nodosa	Wegener Granulomatosis	Churg-Strauss Syndrome	Henoch-Schönlein Purpura	Cutaneous Leukocytoclastic Angiitis
Vessels involved	Elastic (large) or muscle (medium-sized) arteries	Medium-sized and small muscle arteries	Small arteries and veins; sometimes medium-sized vessels	Small arteries and veins; sometimes medium-sized vessels	Capillaries, venules, arterioles	Capillaries, venules, arterioles
Organ involvement	Aorta, aortic arch and major branches, pulmonary arteries	Skin, peripheral nerve, gastrointestinal tract, other viscera	Upper respiratory tract, lungs, kidneys, skin, eyes	Upper respiratory tract, lungs, heart, peripheral nerves	Skin, joints, gastrointestinal tract, kidneys	Skin, joints
Type of vasculitis and inflammatory cells	Granulomatous with some giant cells; fibrosis in chronic stages	Necrotizing, with mixed cellular infiltrate	Necrotizing or granulomatous (or both); mixed cellular infiltrate plus occasional eosinophils	Necrotizing or granulomatous (or both); prominent eosinophils and other mixed infiltrate	Leukocytoclastic, with some lymphocytes and variable eosinophils; IgA deposits in affected tissues	Leukocytoclastic, with occasional eosinophils

IgA, Immunoglobulin A.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

mended to use a glucocorticoid sparing agent at the time prednisone is prescribed. Commonly used second agents include:

- Leflunomide
- Methotrexate
- Mycophenolate mofetil
- Azathioprine
- Tocilizumab
- Anti-TNF agents
- Cyclophosphamide

CHRONIC Rx

- Patients with Takayasu arteritis are monitored closely for signs of relapse and disease complications with clinical assessment, inflammatory biomarkers (e.g., ESR and CRP), and imaging. Multiple indexes exist for the assessment of disease activity, including the NIH criteria for active disease, the Disease Extent Index-Takayasu (DEI.Tak), and the Indian Takayasu Arteritis Score (ITAS).
- Percutaneous angioplasty or bypass grafts should be considered for irreversible arterial stenoses with severe ischemia (cardiac or cerebral), severe hypertension in renal artery stenosis, or aneurysmal enlargement with risk of rupture. Five-yr arterial complication rate after surgical or endovascular revascularization is around 40%. The likelihood of complications increases sevenfold when inflammation is present at the time of revascularization.
- Aortic regurgitation may require valve replacement or repair by surgery, although the need to manipulate inflamed, friable tissue can lead to complications such as valvular detachment after replacement.
- Treatment of hypertension in patients with Takayasu arteritis can be difficult, especially because there is usually concurrent glucocorticoid therapy and there is the potential for renovascular hypertension. Special monitoring should be employed when using ACE inhibitors due to the high frequency of renal artery stenosis in this population.

DISPOSITION

- Immunosuppressant therapy may achieve clinical remission.
- With the addition of a second agent for patients with treatment resistance or relapse, approximately half of patients will achieve remission.
- Quality of life is comparable to that of patients with rheumatoid arthritis or ankylosing spondylitis.
- In the absence of major complications (MI, stroke, severe hypertension, heart failure, and aneurysm), 5-yr survival rates reach 80% to 90%. In the presence of major complications, 5-yr survival is 50% to 70%.
- Death can occur suddenly from a ruptured aneurysm, a myocardial infarction, or a cerebrovascular accident.

Pregnancy may exacerbate cardiovascular complications and can increase the risk for maternal and fetal morbidity and mortality. Heart failure, embolism, and thrombosis are common complications during pregnancy. If a pregnant woman is diagnosed with the disease, oxytocin should be injected to the corpus uteri directly (when needed), and the intravenous route should be avoided. It is important to maintain the mother's blood pressure in a stable range and to avoid fluctuations in hemodynamics.

REFERRAL

Whenever the diagnosis of vasculitis is suspected, a rheumatology consultation is appropriate. Vascular surgery and cardiology consultations are recommended for any evidence of carotid, peripheral, or coronary artery disease or if a large abdominal aneurysm is found.

PEARLS & CONSIDERATIONS

With long-term glucocorticoid use, consider measures to protect against bone loss. Bisphosphonates have been studied prospectively with corticosteroid use in this fashion; remember to ensure adequate dietary calcium and vitamin D intake as well.

COMMENTS

- No studies have proved that treatment results in regression of stenosis, although there are limited case reports describing the return of pulses with treatment.
- Only one fifth of patients have a self-limited course. The majority show a progressive or relapsing remitting course that requires long-term immunosuppressive therapies.
- Although short-term prognosis of the disease is favorable, long-term prognosis depends on the incidence of complications and the presence of progressive course. The presence of both major complications along with progressive course is associated with the worst prognosis. The prognosis and vascular complications of Takayasu arteritis are improving. Fatal or serious complications have diminished in the past decade.

RELATED CONTENT

Vasculitis, Systemic (Related Key Topic)

AUTHORS: **Ihab Alomari, MD,** and **Pranav M. Patel, MD, FACC, FAHA, FSCAI**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Takotsubo cardiomyopathy, also known as stress cardiomyopathy (SC), is a syndrome characterized by transient systolic and diastolic dysfunction with a characteristic ballooning of the apical and/or mid segments of the left ventricle (LV). It mimics acute myocardial infarction (MI), but there is no evidence of obstruction of an epicardial coronary artery. Typically, but not always, it is preceded by severe illness or intense emotional, physical, or psychological stress. Initially described in the 1990s in Japan, the systolic LV on left angiogram has a distinctive shape similar to a *tako-tsubo* pot with a narrow neck and round bottom, used by fishermen to trap octopi. The variants of SC include apical (81.7%), midventricular (14.6%), basal/reverse takotsubo (2.2%), and focal (1.5%).

SYNONYMS

Stress cardiomyopathy (SC)
Left ventricular apical ballooning syndrome (LVABS)
Ampulla cardiomyopathy
Broken heart syndrome

ICD-10CM CODE
I51.81 Takotsubo syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: An estimated 15 to 30 new cases per 100,000 per yr
PREVALENCE: About 1% to 2% of patients presenting with troponin-positive acute coronary syndrome (ACS) have SC.
PREDOMINANT SEX AND AGE: On presentation, 90% are females, and 80% are females >50 yr of age. Mean age of presentation is 68.8 yr.
RISK FACTORS: SC can be triggered by severe medical illness, intense emotional psychosocial stress or physical stress (death of loved ones, domestic abuse, fierce arguments, financial hardships, severe pain, natural disasters, etc.), or chronic stress/distress. A positive life event (happy heart syndrome) also can cause SC. Familial case series have raised the possibility of a genetic predisposition.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute substernal chest pain, dyspnea, and syncope are the most common presenting complaints (International Takotsubo Registry study).
- On physical examination, a systolic ejection murmur (due to left ventricular outflow tract obstruction and mitral regurgitation) may be present.
- SC can manifest as heart failure (30%), ventricular arrhythmias, cardiogenic shock (10%), or sudden cardiac death.

ETIOLOGY

The proposed mechanisms for SC include the following:

- In postmenopausal women, estrogen deficiency leads to endothelial vasomotor dysfunction. Lack of endothelial-dependent vasodilation causes excessive coronary vasoconstriction.
- Increased catecholamine from an acute event can be directly toxic to the myocardium. The increased density of beta-adrenoreceptors in the apex makes it more sensitive to catecholamine and accounts for the apical ballooning.
- Impaired microvascular perfusion resulting in ischemic stunning.
- Fig. 1 depicts the interplay among triggers, pathogenic factors, and predisposing factors in SC.

DIAGNOSIS

Mayo Clinic proposed criteria (2008) for diagnosis of SC: All four criteria required to make diagnosis.

- Transient wall motion abnormalities that extend beyond a single epicardial vascular distribution (Fig. 2). A stressful trigger is often, but not always, present
- Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture
- New ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponins
- Absence of pheochromocytoma or myocarditis

DIFFERENTIAL DIAGNOSIS

- Acute coronary syndrome
- Cardiac syndrome X/microvascular angina
- Prinzmetal angina
- Acute myocarditis
- Cocaine cardiomyopathy
- Cardiomyopathy associated with pheochromocytoma

WORKUP

- A high index of suspicion is required when a postmenopausal woman presents with ACS after intense stress.
- Cardiology consult should be immediately obtained.
- Obstructive coronary artery disease needs to be ruled out.

LABORATORY TESTS

- Cardiac biomarkers (troponin, CK-MB) are often modestly elevated.
- Cardiac natriuretic peptide (brain natriuretic peptide [BNP] and pro-BNP) levels are also commonly elevated.

IMAGING STUDIES

- ECG: ST elevation in precordial leads (reciprocal changes typically absent), T-wave inversions (which may be dramatic) in the anterior or lateral leads, QT prolongation, and abnormal Q waves.
- Echocardiography (ECHO) typically shows the characteristic apical ballooning. Contrast ECHO is quite useful to exclude apical thrombus.
- Obstructive coronary artery disease should be excluded with a coronary angiogram.
- Cardiac magnetic resonance imaging (Fig. 3) can show the absence of late gadolinium enhancement (seen in MI).
- Coronary computed tomography angiography may help evaluate for stenosis in epicardial coronary arteries in specific clinical settings (e.g., poor MRI acoustic windows).

COMPLICATIONS

- Approximately 20% have in-hospital complications including heart failure, cardiogenic shock requiring mechanical support, life-threatening arrhythmias, acute mitral regurgitation, LV outflow tract (LVOT) obstruction, free wall rupture, and death.
- Due to the Venturi effect, mitral valve systolic anterior motion could cause LVOT obstruction and mitral regurgitation (14% to 45% of patients), which further impede LV systolic function.

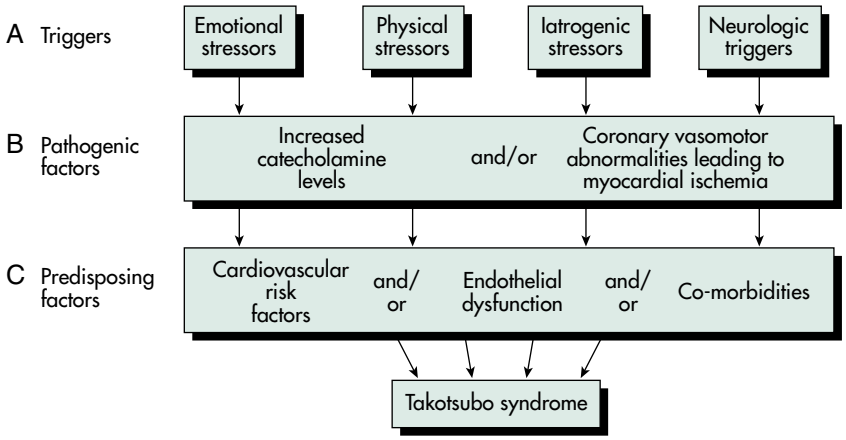

FIG. 1 The interplay among triggers, pathogenic factors, and predisposing factors in Takotsubo disease. (From Pelliccia F et al: Takotsubo syndrome [stress cardiomyopathy]: an intriguing clinical condition in search of its identity, *Am J Med* 127:699-704, 2014.)

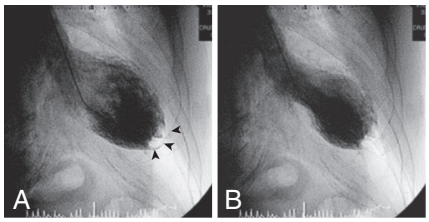

FIG. 2 A and **B,** Left ventriculogram showing apical ballooning characteristic of stress-induced cardiomyopathy. (From Mitsuma W et al: *JACC* 51[1]: cover, 2008.)

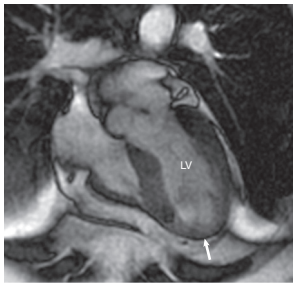

FIG. 3 Takotsubo cardiomyopathy. The patient was a 58-yr-old woman who was referred for cardiovascular magnetic resonance (CMR) after a coronary angiogram revealed no obstructive disease despite the presence of ST-segment elevations on electrocardiogram and positive biomarker assays. A diagnosis of Takotsubo cardiomyopathy was made on the basis of the CMR image, which shows LV apical akinesis and ballooning (*arrow*). *LV,* Left ventricle. (From Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.)

- Arrhythmias (25%) include supraventricular tachycardia and ventricular arrhythmias.
- Systemic thromboembolism and increased risk of stroke.
- Intramyocardial hemorrhage and rupture.

Rx TREATMENT

Initially, patients should be treated for presumptive acute coronary syndrome until this is excluded.

NONPHARMACOLOGIC THERAPY

Supportive care such as the elimination of the physical or emotional trigger is important.

ACUTE GENERAL Rx

- Hemodynamically stable: Treat with diuretics, vasodilators, and venodilators (nitroglycerin, nitroprusside).
- Cardiogenic shock *without* LVOT obstruction: Vasopressor (phenylephrine, vasopressin) and inotropic support (dobutamine, milrinone, dopamine) may be required. When treatment is refractory to medical therapy, percutaneous and surgical mechanical circulatory support will be required.
- Cardiogenic shock *with* LVOT obstruction: Increase preload by leg elevation and fluid resuscitation if no significant pulmonary congestion. Avoid inotropic agents, since increased basal contractility will increase the LVOT obstruction. Beta blockers can improve the obstruction. Phenylephrine should be used cautiously because it could increase the after-load and thus increase the gradient.

CHRONIC Rx

- 3 to 6 mo of guideline-directed medical therapy for heart failure with reduced ejection fraction (beta blockers, ACE inhibitors, angiotensin II receptor blocker, aldosterone antagonist, angiotensin receptor-neprilysin inhibitor)
- Repeat ECHO (in 4 to 6 wk) to ensure normalization of systolic function.
- 3 mo of anticoagulation is suggested if an intraventricular thrombus is detected.

DISPOSITION

- Carries a favorable prognosis compared to STEMI or NSTEMI; in-hospital mortality is up to 5%. The recurrence rate is around 2% to 4% per yr.
- In a Medicare cohort, patients ≥85 yr of age had higher in-hospital, 30-day, 1-yr mortality, and 30-day readmission rates; hence, the need for good discharge planning is key.

REFERRAL

Follow up with a cardiologist.

PEARLS & CONSIDERATIONS

COMMENTS

- The term *takotsubo* is the Japanese name for an octopus trap (*tako-tsubo*), which has a similar shape of the LV in systole during a left ventriculogram (see Fig. 2).
- Patients with takotsubo cardiomyopathy have a higher prevalence of neurologic or psychiatric disorders than those with an acute coronary syndrome.

PREVENTION

Minimizing stress may reduce incidence but no data to support this.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Mostafa Ghanim, MD,** and **Maxwell Eyram Afari, MD**

SUGGESTED READINGS

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Tapeworm Infestation PTG

BASIC INFORMATION

DEFINITION

Four species of adult tapeworm (cestodes) may infect humans as the definitive host: *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tapeworm), *Diphyllobothrium latum* (fish tapeworm), and *Hymenolepis nana* (dwarf tapeworm). In addition, several tapeworms (*T. solium, T. crassiceps, T. multiceps*) can infect human tissue in their larval form, resulting in cysticercosis. Others infect in their intermediate forms, resulting in hydatid disease (see "Echinococcosis" in Section I). Table 1 describes common cestode parasites of humans, their typical vectors, and their usual symptoms.

SYNONYM

Cysticercosis (larval infection by *T. solium*)

ICD-10CM CODES

B68.0	*Taenia solium* taeniasis
B68.1	*Taenia saginata* taeniasis
B68.9	Taeniasis unspecified
B70.0	Diphyllobothriasis
B71.0	Hymenolepiasis
B71.9	Cestode infection, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Diagnosed primarily in immigrants, particularly those from Latin America and Southeast Asia
- Varies widely by country of origin and dietary practices

PREVALENCE (IN U.S.):

- *T. saginata:* <0.1%
- *D. latum:* <0.05%
- *T. solium:* <0.1%
- *H. nana:* Sporadic, often in setting of outbreak

PREDOMINANT SEX: Equal sex distribution

PREDOMINANT AGE:

- *T. saginata, T. solium, D. latum:* 20 to 39 yr of age
- *H. nana* in setting of institution outbreaks: Children

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Adult worms:

- Attach to bowel mucosa via suckers, hooks, or grooves depending on species
- Feed and grow, producing digestive/body/reproductive segments called proglottids
- Cause minimal or no symptoms or sequelae but occasionally can cause nausea, anorexia, or epigastric pain

Cysticercosis: Larval infection by *T. solium*:

- Mass lesions of brain (neurocysticercosis), soft tissue, viscera
- Neurocysticercosis may cause seizures, hydrocephalus (due to ventricle obstruction)

Prolonged infection with *D. latum*:

- Vitamin B_{12} deficiency
- Megaloblastic anemia

ETIOLOGY

TAPEWORM:

- Adult worms consist of a head (scolex), neck, and hundreds or thousands of proglottids. Each proglottid contains male and female reproductive organs, including eggs.
- Adult worm resides in small or large bowel; proglottids and eggs are passed in stool.
- *T. saginata* may produce up to 100,000 eggs/proglottid and *T. solium* up to 50,000 eggs/proglottid.
- Eggs are ingested by the animal intermediate host (Fig. 1).
- Eggs hatch into larvae.
- Larvae perforate the host intestinal wall and disseminate into skeletal muscle, brain, viscera.
- Develop into cysticerci (scolex inside a cyst) over several wk.
- Humans eat infected beef *(T. saginata),* pork *(T. solium),* or fish *(D. latum).*
- Larval scolex attaches to intestinal wall and matures into adults within the GI lumen.
- *H. nana* infection is acquired by ingesting eggs in human or rodent feces.

CYSTICERCOSIS:

- Humans ingest eggs of *T. solium* in food contaminated with human feces that contain the eggs.
- Eggs hatch into larvae in gut and cross intestinal wall.
- Larvae disseminate widely through tissues (particularly soft tissue and CNS) forming cystic lesions containing either viable or nonviable larvae.

DIAGNOSIS

WORKUP

- Stool examination for eggs or proglottids (tapeworm):
  1. Eggs of *Taenia* spp. cannot be differentiated by microscopy, but the species can be identified through examination of the proglottids in stool.
  2. Eggs of *Taenia* spp. are round and measure 30 to 40 μm.
- Cerebral noncontrast CT scan and MRI (neurocysticercosis)
- Serum antibody with ELISA confirmatory testing recommended for neurocysticercosis
- Confirmatory serologic test is enzyme-linked immunotransfer blot (EITB), as ELISA has poor sensitivity/specificity
- CBC may show eosinophilia

TABLE 1 Common Cestode Parasites of Humans, Their Typical Vectors, and Their Usual Symptoms

Parasite Species	Developmental Stage Found in Humans	Common Name	Transmission Source	Symptoms Associated with Infection
Diphyllobothrium latum	Tapeworm	Fish tapeworm	Plerocercoid cysts in freshwater fish	Usually minimal; with prolonged or heavy infection, vitamin B_{12} deficiency
Hymenolepis nana	Tapeworm, cysticercoids	Dwarf tapeworm	Infected humans	Mild abdominal discomfort
Taenia saginata	Tapeworm	Beef tapeworm	Cysts in beef	Abdominal discomfort, proglottid migration
Taenia solium	Tapeworm	Pork tapeworm	Cysticerci in pork	Minimal
Taenia solium (Cysticercus cellulosae)	Cysticerci	Cysticercosis	Eggs from infected humans	Local inflammation, mass effect; if in central nervous system, seizures, hydrocephalus, arachnoiditis
Echinococcus granulosus	Larval cysts	Hydatid cyst disease	Eggs from infected dogs	Mass effect leading to pain, obstruction of adjacent organs; less commonly, secondary bacterial infection, distal spread of daughter cysts
Echinococcus multilocularis	Larval cysts	Alveolar cyst disease	Eggs from infected canines	Local invasion and mass effect leading to organ dysfunction; distal metastasis possible
Taenia multiceps	Larval cysts	Coenurosis, bladder worm	Eggs from infected dogs	Local inflammation and mass effect
Spirometra mansonoides	Larval cysts	Sparganosis	Cysts from infected copepods, frogs, snakes	Local inflammation and mass effect

Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

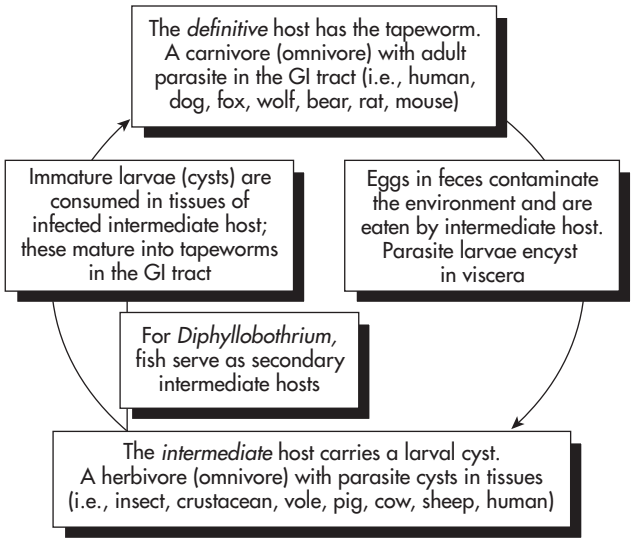

FIG. 1 Cestode parasites alternate larval and adult stages in two different hosts. *GI,* Gastrointestinal. (Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.)

IMAGING STUDIES

- Tapeworm: Incidental finding on upper GI series
- Neurocysticercosis:
  1. Cerebral cysts are readily demonstrated by CT scan or MRI.
  2. Calcified lesions are an incidental finding.

Rx TREATMENT

ACUTE GENERAL TREATMENT

- All adults and children with intestinal tapeworm infections should be treated with a single oral dose of praziquantel.
  1. *T. solium:* 5 to 10 mg/kg
  2. *T. saginata:* 5 to 10 mg/kg
  3. *D. latum:* 5 to 10 mg/kg
  4. *H. nana:* 25 mg/kg and a repeat dose 7 to 10 days later if heavy infection
- Praziquantel acts by causing changes in the teguments of the worms, allowing increased permeability to calcium ions, which then accumulate inside worm and cause paralysis.
- Repeat stool screening at 1 and 3 mo to confirm cure.
- Can use purgatives adjunctively to hasten clearance of deceased worms from intestine.
- An alternative therapy to praziquantel for fish, beef, or pork tapeworm infections is niclosamide, 2 g PO once for adults or 50 mg/kg orally once for children. For *H. nana* infections alternative is for adults: niclosamide 2 g PO × 7 days and for children 11 to 34 kg: niclosamide 1 g PO on day 1 and then 500 mg/day for 6 days and 1.5 g for children over 34 kg PO on day 1 and then 1 g/day for 6 days.
- Therapy that may be considered for symptomatic cysticercosis:
  1. May regress spontaneously (i.e., no treatment, also okay for calcified parenchymal neurocysticercosis)
  2. Surgery, especially in cases of ventricular obstruction (neurocysticercosis)
  3. Albendazole 15 mg/kg/day (maximum: 1200 mg) PO for 10 to 14 days plus
  4. Praziquantel 50 mg/kg/day PO for 10 to 14 days plus
  5. Dexamethasone: 0.1 mg/kg/day often beginning 1 to 3 days before antiparasitic therapy ×10 to 14 days, plus/minus
  6. Antiseizure medication ×1 yr. Use of steroids in neurocysticercosis may reduce CNS inflammation and increase levels of albendazole in CNS.
  7. If increased intracranial pressure is present, treat it alone before considering antiparasitic therapy
- Medical therapy second line with:
  1. Ocular infections.
  2. Cerebral infections in which local inflammation caused by destruction of the parasite may cause significant damage/inflammation (e.g. 4th ventricle infection).
- Adjunctive antiepileptics may be necessary for neurocysticercosis.

CHRONIC TREATMENT AND PREVENTION

- Retreatment if required
- Avoidance of undercooked pork, meat, or fish
- Cysticercosis: Proper hand washing, proper disposal of human waste

DISPOSITION

- Neurologic follow-up for patients with neurocysticercosis
- Ophthalmologic follow-up for patients with ocular involvement

REFERRAL

Patients treated for neurocysticercosis should be evaluated by a physician experienced in managing this infection if possible.

PEARLS & CONSIDERATIONS

COMMENTS

T. solium is the most dangerous of the tapeworms because of the potential for cysticercosis by means of autoinfection.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Tapeworm Infection (Patient Information)
Cysticercosis (Related Key Topic)

AUTHORS: **Lisa Sieczkowski, MD,** and **Russell J. McCulloh, MD**

SUGGESTED READINGS

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Tardive Dyskinesia PTG

BASIC INFORMATION

DEFINITION

Tardive dyskinesia (TD) is a neurological disorder of involuntary movements associated with the long-term use of antipsychotic medication, particularly first-generation antipsychotics. Patients exhibit rapid, repetitive, stereotypic movements that mostly involve the oral, lingual, trunk, and limb areas.

SYNONYMS

Orofacial dyskinesia
Tardive syndrome
TD

ICD-10CM CODE
G24.01 Drug induced subacute dyskinesia
DSM-5 CODE
335.85

EPIDEMIOLOGY & DEMOGRAPHICS

- The disorder is caused by dopamine-blocking antipsychotics (e.g., haloperidol) and antiemetics (e.g., metoclopramide, prochlorperazine, and promethazine).
- With first-generation antipsychotics, at least 20% of patients are affected with TD, and ~5% are expected to develop TD with each yr of antipsychotic treatment.
- The incidence of TD with second-generation antipsychotics is reduced only by about one third. With the increasing use of these medications, TD remains a serious problem.
- Risk increases with the duration of antipsychotic treatment, in female and in elderly patients, in patients with brain damage or dementia, with concurrent anticholinergic use, and in patients with nonschizophrenia diagnoses.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- TD is classically described as a chronic condition of insidious onset, but symptoms are variable over time and may even improve despite continued antipsychotic therapy.
- The condition typically appears with the reduction or withdrawal of the antipsychotic medications.
- TD classically involves stereotypic movements of the mouth and tongue, including lip smacking and puckering, tongue twisting and protrusion, and facial grimacing.
- TD may also involve slow, writhing movements of the trunk or choreoathetoid movements of the fingers and toes.
- The involuntary mouth movements associated with TD may be suppressed by voluntary actions (e.g., putting food in the mouth, talking).
- Variants of TD with similar treatment include tardive dystonia (e.g., torticollis, blepharospasm), tardive myoclonus, tardive akathisia, and tardive tics.

ETIOLOGY

TD is caused by chronic exposure to dopamine receptor antagonists that is thought to result in the upregulation of dopamine receptors in the basal ganglia as well as damage to striatal cholinergic neurons. Dysfunction of striatal GABAergic interneurons has also been implicated. It has been proposed that dopamine receptor hypersensitivity and neurodegenerative changes might cause altered synaptic plasticity of excitatory synapses onto striatal interneurons, resulting in an imbalance between the direct and indirect basal ganglia pathways.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute extrapyramidal symptoms (e.g., short-term withdrawal dyskinesias, Parkinsonism, akathisia)
- Basal ganglia movement disorders (e.g., Huntington chorea, Tourette syndrome, levodopa-induced dyskinesia in Parkinson disease, Wilson disease)
- Autoimmune diseases (Sydenham chorea, multiple sclerosis)
- Other causes of neurologic damage (e.g., lead or mercury toxicity, HIV, neurosyphilis, head injury, neurodegeneration from illicit substances)
- Mannerisms associated with disorganized type or catatonic type schizophrenia or catatonic syndrome associated with mood disorder or medical illness
- Hyperthyroidism-induced choreoathetosis
- Edentulous dyskinesias and improperly fitted dentures
- Rabbit syndrome (a rare variant of extrapyramidal symptoms with rapid vertical orofacial movements without tongue involvement); may respond to anticholinergic agents

WORKUP

TD is a diagnosis of exclusion, with emphasis on a complete neuropsychiatric and medication history and a thorough physical examination.

IMAGING STUDIES

Standard brain imaging is normal in patients with TD.

TREATMENT

ACUTE GENERAL Rx

- Treatment is predicated on prevention: Limit the indications for antipsychotics; use the lowest effective dose; discontinue the drugs, when feasible; and monitor patients frequently. Anticholinergic medications may worsen symptoms.
- Switch to second-generation antipsychotics, if possible.

CHRONIC Rx

- If continued antipsychotic treatment is needed, switching to clozapine or quetiapine is the preferred initial treatment.
- Valbenazine and deutetrabenazine, inhibitors of the vesicular monoamine transporter 2 (VMAT2), are centrally acting synaptic dopamine depleters that are the first FDA-approved treatments for TD and are recommended as first-line treatment options when discontinuation of antipsychotic not indicated. The older version, tetrabenazine, may also improve TD and might be considered.
- Clonazepam and *Ginkgo biloba* probably improve TD.
- Amantadine also has been helpful in some cases.
- For treatment-resistant, disabling TD, deep brain stimulation of internal globus pallidus seems to provide significant symptom reduction without exacerbation of psychiatric symptoms.
- TD is potentially irreversible in nearly two thirds of patients; thus, patients undergoing long-term treatment with dopamine receptor blocking agents require frequent monitoring and aggressive management at the onset of TD symptoms.

REFERRAL

Movement disorder specialist consultation if symptoms are severe

PEARLS & CONSIDERATIONS

- After removal of the causative medication, symptoms of tardive dyskinesia can take mos to resolve or may become permanent (higher risk in elderly, female sex, prolonged use, and higher dose of causative medication).
- First-generation antipsychotics should be resumed to treat TD in the absence of active psychosis only as a last resort for persistent, disabling, and treatment-resistant TD.
- Avoid anticholinergic medications (e.g., benztropine), which may exacerbate TD symptoms.
- Recent evidence suggests increased overall mortality among patients with TD, which highlights the need for referral for more aggressive specialized interventions.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Tardive Dyskinesia (Patient Information)

AUTHOR: **John A. Gray, MD, PhD**

SUGGESTED READINGS

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Tarsal Tunnel Syndrome (PTG)

BASIC INFORMATION

DEFINITION

Tarsal tunnel syndrome (TTS) is the most common compressive neuropathy in the foot and ankle. TTS may be secondary to pathologic, structural, or biomechanical factors that cause compression of the tibial nerve and/or its terminal branches (medial calcaneal, medial plantar, lateral plantar nerves) within or distal to the tarsal tunnel (Figs. E1 and E2).

SYNONYMS

Posterior tibial nerve neuralgia
Tibial nerve entrapment neuropathy
TTS

ICD-10CM CODES

G57.50	Tarsal tunnel syndrome, unspecified lower limb
G57.51	Tarsal tunnel syndrome, right lower limb
G57.52	Tarsal tunnel syndrome, left lower limb

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Rare entrapment neuropathy, but the most common entrapment neuropathy in the foot/ankle

PREDOMINANT SEX: The incidence of TTS is higher in females than in males.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Medial heel or ankle pain, distal shooting pain/burning, and generalized foot or ankle pain that is worse after prolonged standing or walking. Pain is usually relieved with rest. Numbness may be present along the plantar foot.
- Localized edema, varicosities, palpable soft tissue masses, biomechanical abnormalities, and signs of trauma.
- Positive Tinel sign: Percussion over the course of the tibial nerve results in distal or proximal radiation of paresthesia (25% to 75% sensitivity and 70% to 90% specificity).
- Compression test: Plantar flexion and eversion of the ankle or digital pressure over the tarsal tunnel reproduces symptoms and is both sensitive and specific.
- Muscle weakness/complete loss of motor function of the plantar foot muscles (late and rare outcome). Atrophy of intrinsic foot musculature if severe nerve injury.
- Heel pain triad: Adult-acquired flatfoot (posterior tibial tendon deficiency), plantar fasciitis, tarsal tunnel syndrome.

ETIOLOGY

- Most common cause: Fracture/dislocation/trauma involving the talus, calcaneus, or medial malleolus (scar tissue, bone, or cartilage fragments, or bony spurs may compress the nerve)
- Intrinsic factors:
  1. Tendinopathy
  2. Osteophytes
  3. Space-occupying lesions/varicosities (most common space-occupying lesion), tumors, ganglion cyst, lipoma, neuroma, perineural fibrosis
  4. Hypertrophic musculature such as abductor hallucis
- Extrinsic factors:
  1. Trauma: Ankle sprain, fracture
  2. Repetitive stress on the tibiotalar joint (jumping, running, etc.)
  3. Constrictive footwear or constrictive cast/bandage
  4. Biomechanical: Tarsal coalition, valgus hindfoot, other hindfoot anomalies

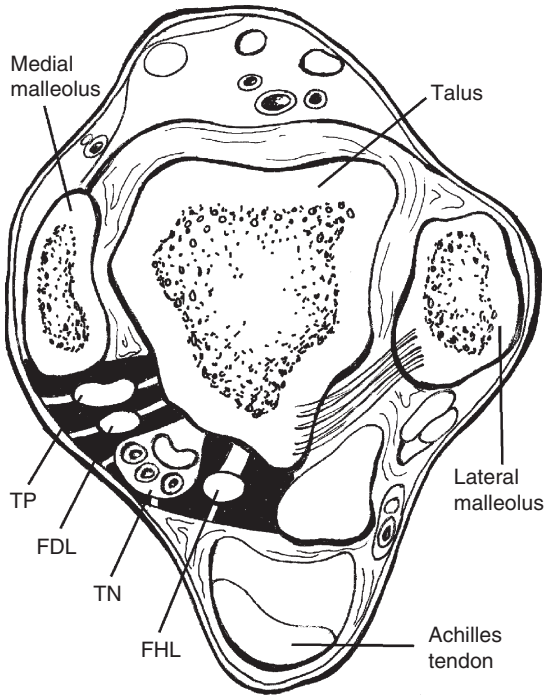

FIG. E1 Anatomy of tarsal tunnel syndrome. Transverse view of ankle. Tendons and neurovascular elements are included in individual fibrous septa that connect periosteum with the deep fascia. *FDL,* Flexor digitorum longus; *FHL,* flexor hallucis longus tendon; *TN,* tibial nerve (single contour), posterior tibial artery, veins; *TP,* tibialis posterior tendon. (From Canoso J: *Rheumatology in primary care,* Philadelphia, 1997, WB Saunders.)

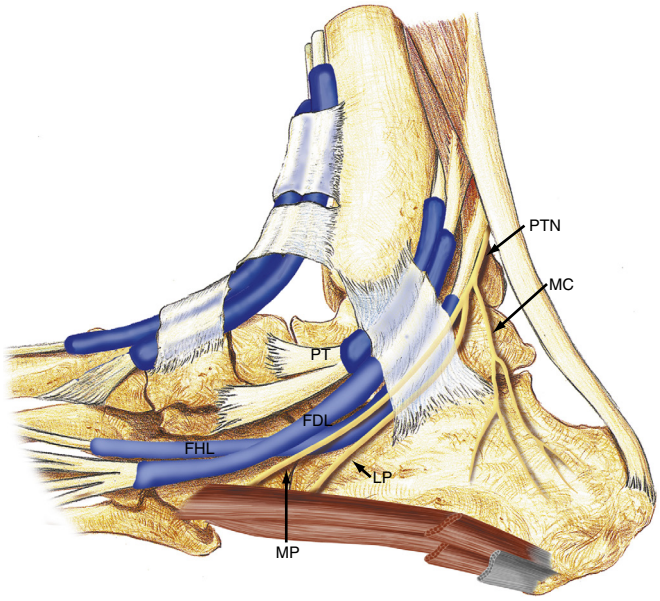

FIG. E2 Normal anatomy of the tarsal tunnel. Drawing of the tarsal tunnel illustrates the flexor retinaculum forming the roof of the tarsal tunnel. The structures contained within the tarsal tunnel include the posterior tibialis tendon *(PT),* flexor digitorum longus tendon *(FDL),* posterior tibial nerve *(PTN)* and its branches, and the flexor hallucis longus *(FHL).* The branches of the PTN are the medial calcaneal nerve *(MC),* the medial plantar nerve *(MP),* and the lateral plantar nerve *(LP).* (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2014, WB Saunders.)

5. Systemic: Diabetes mellitus, hypothyroidism, gout, hyperlipidemia
6. Inflammatory factors/edema: Venous congestion, pregnancy, post-trauma/surgical, rheumatoid arthritis, ankylosing spondylitis

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Plantar fasciitis
- Calcaneal fracture or other osseous trauma
- Ankle sprain/strain or chronic soft tissue injury
- Calcaneal spur
- Tumor
- Posterior tibial tendonitis
- Posterior tibial tendon dysfunction
- Peripheral neuropathy
- Radiculopathy
- Achilles tendonitis or retrocalcaneal bursitis
- Compartment syndrome of deep flexor compartment
- Lumbar spinal stenosis (often bilateral, unlike TTS pain)

WORKUP

- Detailed history and physical
- Biomechanical evaluation and examination

DIAGNOSTIC STUDIES

- X-rays: Can help rule out trauma, bone tumor, structural deformity.
- MRI (Fig. E3): Can identify edema, fibrosis, tumors, varicosities, ganglionic cysts, tenosynovitis, muscle hypertrophy, and evidence of trauma. MRI may enhance surgical planning by revealing the extent of decompression required.
- Electromyography/nerve conduction studies: Prolonged tibial motor distal latencies and slowing of conduction velocities across the flexor retinaculum when studying medial and lateral plantar nerves. Comparison studies with unaffected extremity may be helpful. The sensory nerve conduction velocity is arguably the most accurate study, with a sensitivity of about 90%.
- Ultrasound: Can help identify, aspirate, or perform a biopsy on space-occupying lesions.
- Diagnostic local injections: Relief following an injection of an anesthetic around the affected nerve can help confirm diagnosis.

Rx TREATMENT

CONSERVATIVE

- Rest, ice, elevation, immobilization with night splint or removable boot walker
- Address shoe gear problems
- NSAIDs, antidepressants, antiseizure medications, vitamin B_6
- Topical lidocaine or fentanyl patches, capsaicin, transdermal clonidine, compound mixtures
- Custom orthotics: Heel lifts, medial arch support, medial heel wedge, heel seat
- Bracing/taping: Ankle brace/stirrup brace for ankle instability, plantar arch taping
- Physical therapy: Iontophoresis, interferential current therapy, stretching, strengthening
- Local steroid injections: Anesthetics to reduce pain and/or corticosteroids to help decrease inflammation
- Support hose to control edema
- All of these are usually ineffective due to the structural nature of problem

SURGICAL

- Indicated in patients who have failed conservative treatment for 3 to 6 mo and in those with reproducible physical exam findings, EMG findings, and correctible surgical abnormality
- Nerve decompression: Open or endoscopic release of retinaculum, mass excision, etc. (reported success rates range from 75% to 91%, and recurrence rates of 17% have been reported)
- Correction of associated deformity/adjacent pathologic structure, if present
- Patients with symptoms for <1 yr often have significantly better outcomes after surgery than patients with a longer history
- Postoperative instructions: Elevation, partial weight bearing with assistance of crutches, sutures remain in place for 10 to 12 days
- Complications: New neurological deficits, complex regional pain syndrome, impaired wound healing, infection, keloid formation, swelling, worsening of symptoms

DISPOSITION

TTS can lead to pain and dysesthesias in the calf and sole of the foot as well as dysfunction of the foot flexors and intrinsic muscles. Patients with TTS may experience lifelong chronic pain with unknown etiology or a limited course once the causative factor is resolved (mechanical, healed ankle sprain, soft tissue mass resection, etc.).

REFERRAL

- Foot and ankle surgery referral should be initiated early
- Physical therapy or sports medicine
- Pain management

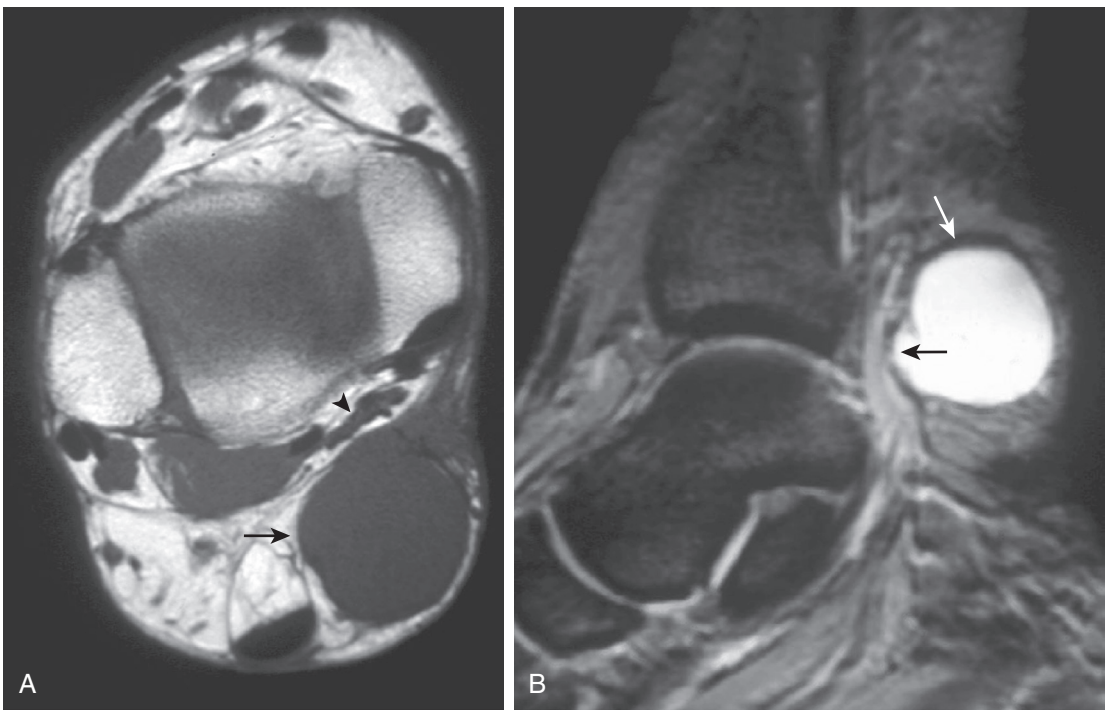

FIG. E3 Tarsal tunnel syndrome. Axial T1-weighted **(A)** and sagittal gradient-recalled echo **(B)** images demonstrate a large ganglion cyst *(arrow)* producing compression of the posterior tibial nerve (*black arrow,* **B**) at the level of the tarsal tunnel. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2014, WB Saunders.)

PEARLS & CONSIDERATIONS

TTS can be mistaken for plantar fasciitis or Achilles tendonitis. Differentiation between these entities is important for proper treatment (refer to "Plantar Fasciitis").

SUGGESTED READINGS

Ahmad M et al: Tarsal tunnel syndrome: a literature review, *Foot Ankle Surg* 18(3):149-152, 2012.

Coughlin MJ et al: *Mann's surgery of the foot and ankle e-book: expert consult-online*, Elsevier Health Sciences, 2013.

De Prado M et al: The tarsal tunnel syndrome, *Fuß & Sprunggelenk* 13(4):227-236, 2015, https://doi.org/10.1016/j.fuspru.2015.09.001.

McSweeney SC, Cichero M: Tarsal tunnel syndrome: a narrative literature review, *Foot* 25(4):244-250, 2015.

RELATED CONTENT

Tarsal Tunnel Syndrome (Patient Information)

AUTHORS: **Christopher McDonald, MD,** and **Brad Blankenhorn, MD**

BASIC INFORMATION

DEFINITION

Temporomandibular joint (TMJ) syndrome refers to a group of disorders leading to symptoms of the TMJ. Box 1 describes a classification of temporomandibular joint disorder (TMD), which also can be classified as intraarticular (within the joint) or extraarticular (involving the surrounding musculature). The TMJ is a diarthrotic joint, meaning neither joint can move independently of the other because each is hinged at both ends. The joint is a true synovial joint capable of two actions of movement: translational and rotational. The articulating surfaces are the glenoid fossa of the temporal bone and the condylar process of the mandible, with the articular disk interposed between the two.

SYNONYMS

Temporomandibular dysfunction
Painful temporomandibular joint
TMJ
Temporomandibular disorders (TMD)

ICD-10CM CODE
N26.60 Temporomandibular joint disorder, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- 15% to 25% of the population have symptoms of TMJ disorders at some point in their lives.
- Females are affected more often than males (up to 4:1 ratio).
- Occurs between the second and fourth decades of life.
- Usually unilateral, affecting either side with equal frequency.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms may appear or be worse during stressful life events.
  1. Often unilateral pain in the muscles of mastication, usually described as a "dull" ache
  2. Otalgia
  3. Odontalgia
  4. Headaches (frontal, temporal, retroorbital)
  5. Tinnitus
  6. Dizziness
  7. Clicking or popping sounds with movement of the TMJ
  8. Joint locking
- Fig. E1 illustrates the clinical examination of the temporomandibular joint, range of mandibular motion, and muscle palpation.
- Physical exam findings:
  1. Tender to palpation over TMJ in external auditory meatus or preauricular region anterior to tragus
  2. Limited jaw opening or trismus
  3. Clicking or popping of TMJs with joint mobility
  4. Lateral deviation of mandible
  5. TMJ crepitus

ETIOLOGY

- Myofascial pain-dysfunction syndrome: The most common cause of TMJ syndrome and results from teeth grinding and clenching the jaw (bruxism)
- Internal TMJ derangement: Abnormal connection of the articular disk to the mandibular condyle as a result of disk displacement or chronic dislocations
- Degenerative joint disease
- Rheumatoid arthritis
- Gouty arthritis
- Pseudogout
- Ankylosing spondylitis
- Trauma (i.e., fractures)
- Congenital defects (i.e., aplasia, hypoplasia)
- Prior surgery (orthodontic, intraarticular steroid injection)
- Tumors

DIAGNOSIS

Can be made based on history and physical examination in most cases.

DIFFERENTIAL DIAGNOSIS

Includes the list provided earlier. Myofascial pain-dysfunction syndrome, internal TMJ derangement, and degenerative joint disease represent >90% of all causes of TMJ syndrome. Others not mentioned include dental problems such as dental caries, loss of posterior teeth support, and Eagle syndrome (stylohyoid syndrome, carotidynia, and trigeminal neuralgia). Alternative diagnoses such as otitis, mastoiditis, salivary gland disorders, migraine headache, sinusitis, postherpetic neuralgia, trigeminal neuralgia, glossopharyngeal neuralgia, and giant cell arteritis should always be excluded.

WORKUP

The diagnosis is based largely on history and physical examination findings. Radiographic imaging evaluation is used to exclude anatomic or systemic causes of disease when conservative management has failed.

LABORATORY TESTS

Laboratory examination is often not needed but may be helpful in ruling out certain conditions. CBC if infection is suspected. Rheumatoid factor if rheumatoid arthritis is suspected.

IMAGING STUDIES

- Plain radiographs: The most common views are the panoramic, transorbital, and transpharyngeal in both opened and closed positions.
- CT scan is highly accurate in diagnosing osseous derangements of the TMJ.
- MRI is the procedure of choice and has replaced arthrography in cases of disabling pain or if locking occurs. It is used to determine disk position and morphology along with degenerative bony changes.
- Arthrography is helpful in looking for meniscus involvement but is seldom performed anymore, as it is more invasive and less accurate than MRI for TMJ imaging.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Soft diet to rest the muscles of mastication
- Heat 15 to 20 min 4 to 6 times per day
- Massage of the masseter and temporalis muscles
- Formed splints or bite appliances to reduce compression of retrodiscal tissue (Fig. 2)
- Range-of-motion exercises
- Cognitive-behavioral therapy and biofeedback have been shown to reduce pain.
- Acupuncture

ACUTE GENERAL Rx

- NSAIDs: Ibuprofen 800 PO mg tid prn or naproxen 500 mg PO bid prn, titrated to relieve symptoms
- Muscle relaxants or benzodiazepines at bedtime: Diazepam 2.5 to 5 mg PO tid prn or amitriptyline 5 to 100 mg PO qd prn

BOX 1 Classification of Temporomandibular Joint Disorder

Myofascial pain disorder and dysfunction
Most common; primarily of muscular origin
Characterized by myogenous pain and limited mandibular function
May be associated with parafunctional habits, stress, anxiety, depression, or trauma

Temporomandibular joint internal displacement (disk displacement)
Reducing or nonreducing (closed lock) with joint sounds and deviation with opening
Most common is anteromedial displacement of the disk
Results in a mechanical interference, leading to moderate to severe restriction in range of motion

Systemic diseases (arthritides, e.g., rheumatoid arthritis, psoriatic arthritis, osteoarthritis)
Affect the joint through inflammation or degenerative processes
May result in condylar remodeling and degenerative joint disease
Also may be related to infectious processes triggering joint inflammation

Congenital and developmental diseases (including trauma and neoplasms)
Hemifacial microsomia or condylar hyperplasia
Idiopathic condylar resorption
Ankylosis
Tumors (e.g., osteochondroma)

From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

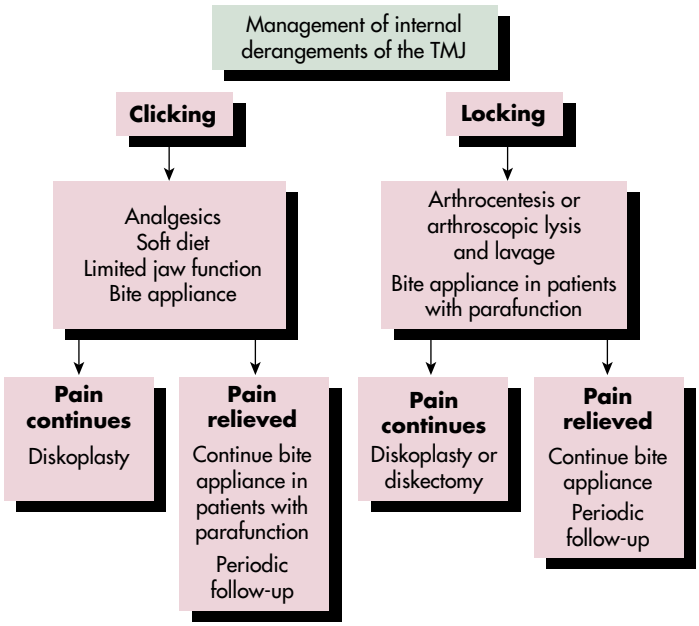

FIG. 2 Management of internal derangements of the temporomandibular joint *(TMJ)*. Patients with painful clicking or locking are treated medically initially, whereas those with locking require surgical intervention. (From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

- In degenerative joint disease of the TMJ, intraarticular steroid injection can be tried
- Botulism toxin injections into the masticatory muscles
- Arthrocentesis with joint lavage and lysis of adhesions (Fig. E3)
- In patients with pain and clicking in the TMJ that is unresponsive to nonsurgical treatment, the disc should be repositioned arthroscopically or by open surgery (discoplasty) (see "Chronic Rx")

CHRONIC Rx

- Most of the above treatments are used for myofascial pain-dysfunction syndrome; however, they can be applied to other causes of TMJ syndrome. Surgery is usually a measure of last resort in patients who do not respond to nonpharmacologic and acute general treatment. Absolute indications for surgical therapy include neoplasms, growth abnormalities, and joint ankylosis.
- Surgical procedures include:
  1. Meniscoplasty
  2. Meniscectomy
  3. Subcondylar osteotomy
  4. TMJ reconstruction

DISPOSITION

The course depends on the underlying etiology; however, less than 5% of adults with temporomandibular symptoms develop chronic symptoms.

REFERRAL

All patients with TMJ syndrome refractory to conservative nonpharmacologic and acute therapy should be referred to a periodontist, oral maxillofacial surgeon, or ear-nose-throat surgeon.

PEARLS & CONSIDERATIONS

Patients with rheumatoid arthritis involving the TMJ usually have bilateral involvement.

COMMENTS

Frequently, emotional stress initiates the myofascial pain-dysfunction, which accounts for 85% of all cases of TMJ syndrome.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Temporomandibular Joint (TMJ) Syndrome (Patient Information)

AUTHOR: **Louis Insalaco, MD**

SUGGESTED READING

Gauer RL, Semidey MJ: Diagnosis and treatment of temporomandibular disorders, *Am Fam Physician* 91(6):378-386, 2015.

FIG. E1 Clinical examination of the temporomandibular joint, range of mandibular motion, and muscle palpation. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

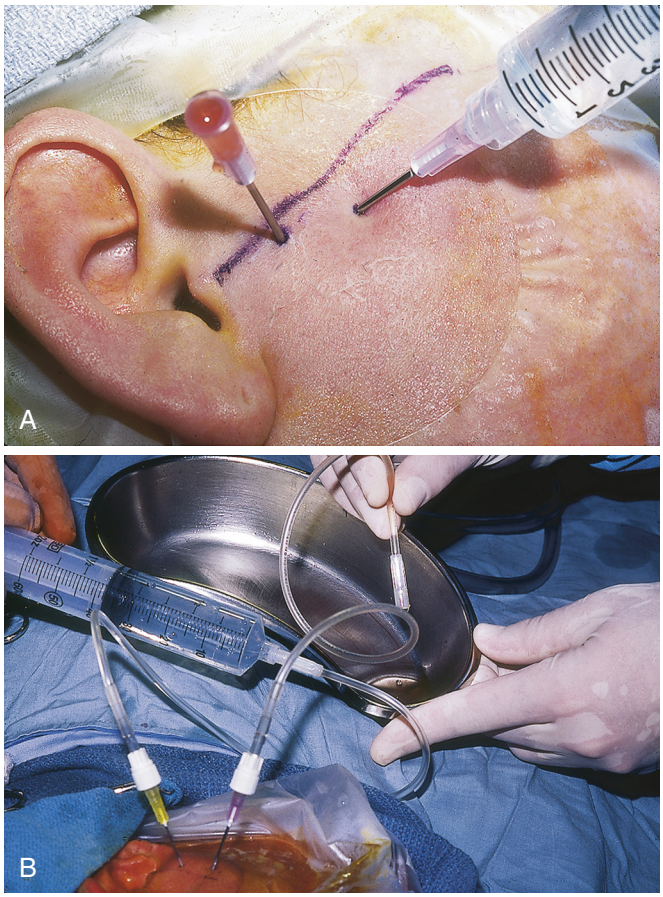

FIG. E3 A, Hypodermic needles inserted into the upper joint space to allow lavage of the joint. **B,** Joint being irrigated with lactated Ringer solution. (From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, WB Saunders.)

BASIC INFORMATION

DEFINITION

Tension-type headache (TTH) is a highly prevalent primary headache disorder not associated with nausea or vomiting. Although previously thought to be caused by psychological factors and muscle contraction, current thinking implicates neurobiological mechanisms.

ICD-10CM CODES

G44.201	Tension-type headache, unspecified, intractable
G44.209	Tension-type headache, unspecified, not intractable

EPIDEMIOLOGY & DEMOGRAPHICS

Most common type of headache, representing 70% of all headaches presenting to primary care physicians. Women are affected more often than men.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Headaches have an insidious progression, ranging from infrequent (<1 day per mo) to chronic. Although considered a "featureless" headache disorder, either photophobia or phonophobia may still be present. Concurrent problems, such as anxiety, depression, and analgesic overuse, may aggravate the headaches. Patients may have pericranial tenderness to palpation on exam. The rest of the examination should be normal.

PATHOPHYSIOLOGY

- TTH is no longer thought to be due to either a psychological problem or abnormal muscle contraction. Similar to migraine, TTH is likely a heterogeneous disorder with several possible pathophysiologic mechanisms.
- In episodic TTH, peripheral mechanisms may predominate, whereas in chronic TTH, central mechanisms are involved.

DIAGNOSIS

The International Headache Society criteria for tension-type headache are as follows:

- At least 10 headaches
- Lasting from 30 min to 7 days
- Having at least two of the following features:
  1. Bilateral
  2. Pressure or tightening (non-pulsating) quality
  3. Mild or moderate intensity
  4. Not aggravated by routine physical activity such as walking or climbing stairs
- Both of the following:
  1. No nausea or vomiting
  2. No more than one of either photophobia or phonophobia
- Not better accounted for by another diagnosis

DIFFERENTIAL DIAGNOSIS

- Migraine (would expect associated symptoms [i.e., nausea]; see topic "Migraine Headache")
- Cervical spine disease
- Intracranial mass (may present with focal neurologic signs, seizures, or headache awakening patient from sleep)
- Idiopathic intracranial hypertension (found more often in obese women of childbearing age)
- Medication overuse headache
- Secondary headache (e.g., obstructive sleep apnea, temporomandibular joint syndrome, hypo- or hyperthyroidism, drug side effects)
- Section II describes the differential diagnosis of headaches

WORKUP

- Routine testing is not needed; the diagnosis may be established clinically.
- Thorough history to identify any red flag features (see topic "Migraine Headache," SSNOOP5 mnemonic in Differential Diagnosis) and physical examination (looking for papilledema) for all patients being evaluated for headache.
- Neuroimaging, preferably with contrast-enhanced MRI, should be performed only when red flag features are identified by history or unexplained neurologic findings are present on examination.
- Erythrocyte sedimentation rate and C-reactive protein in patients 50 yr of age and older to screen for giant cell arteritis.

TREATMENT

Current evidence supports synergistic benefits of combined nonpharmacologic and pharmacologic interventions. Nonpharmacologic therapy may include behavioral sleep modification, acupuncture, cognitive-behavioral therapy, relaxation training, and biofeedback.

ACUTE Rx

- Simple analgesics (i.e., NSAID, acetaminophen).
- Combination analgesics containing caffeine may be used as second-line treatment, although use on more than 10 days per mo may lead to medication overuse headache.
- As with migraine headaches, narcotic- and barbiturate-containing analgesics should be avoided in tension-type headaches.

PREVENTIVE Rx

- Tricyclic antidepressants (e.g., amitriptyline 10 to 50 mg qhs) (first choice)
- Other options: Mirtazapine, venlafaxine, and tizanidine

DISPOSITION

The headache prognosis is generally favorable. Some patients will not respond to treatment.

REFERRAL

If red flags are present on history or exam or if the patient is not improving with treatment

PEARLS & CONSIDERATIONS

It is imperative to avoid overuse of caffeine as well as narcotic-, and barbiturate-containing medications because of the risk of rebound headaches.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Tension Headache (Patient Information)

AUTHOR: **Jonathan H. Smith, MD**

SUGGESTED READINGS

Bendtsen L et al: EFNS guideline on the treatment of tension-type headache: report of an EFNS task force, *Eur J Neurol* 17:1318, 2010.

Kaniecki RG: Tension-type headache, *Continuum* 18(4), 2012.

Linde K et al: Acupuncture for tension-type headache, *Cochrane Database Syst Rev* 4:CD007587, 2016.

BASIC INFORMATION

DEFINITION

Testicular cancers are primary germ cell cancers originating in the testis. They are the most common cancers in men between the ages of 15 and 44 yr, and incidence has been increasing gradually since 1975.

SYNONYMS

Testis tumor
Testicular neoplasms

ICD-10CM CODES

C62.00	Malignant neoplasm of unspecified undescended testis
C62.01	Malignant neoplasm of undescended right testis
C62.02	Malignant neoplasm of undescended left testis
C62.10	Malignant neoplasm of unspecified descended testis
C62.11	Malignant neoplasm of descended right testis
C62.12	Malignant neoplasm of descended left testis
D40.10	Neoplasm of uncertain behavior of unspecified testis
D40.11	Neoplasm of uncertain behavior of right testis
D40.12	Neoplasm of uncertain behavior of left testis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: There were an estimated 9560 new cases and 410 deaths associated with testicular cancer in the U.S. in 2019. The incidence is 5.4 cases per 100,000 men annually. White men have the highest incidence, whereas black men have the lowest incidence.

PREVALENCE: It accounts for 1% to 2% of all cancers in males.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Testicular cancer typically presents as a painless mass in the testis. Any mass within the testicle should be considered cancer until proven otherwise. It may be found by the patient, who brings it to the attention of a physician, or it may be found by a physician on a routine examination.
- Symptoms other than scrotal or testicular swelling are typically absent unless the cancer has metastasized (10% of patients at diagnosis). Occasionally a patient may report scrotal fullness or heaviness. About 10% of patients present with acute pain. Back pain secondary to enlarged retroperitoneal lymph nodes can occur. Gynecomastia from tumors that secrete beta-human chorionic gonadotropin (hCG) is found in 5% of men with testicular cancer.
- Testicular palpation should be performed with two hands. Transillumination may distinguish a solid mass (e.g., cancer) and a fluid-filled lesion (e.g., hydrocele or spermatocele). The mass is nontender; indeed, it is less sensitive than a normal testicle.

ETIOLOGY, CLASSIFICATION, & PATHOLOGY

- Cryptorchidism (undescended testes) is a major risk factor even if corrected by orchiopexy; however, treatment of undescended testis before puberty decreases the risk of testicular cancer from fivefold to twofold.
- Family history is an important risk factor (risk is four to eight times as high in a brother of a person with testicular cancer and four to six times higher in sons of a father with testicular cancer)
- Other risk factors include genetic disorders (Down syndrome, testicular dysgenesis syndrome), Klinefelter syndrome, infertility, tobacco use, and white race (risk is highest among whites and lowest among blacks).
- Classification: Testicular cancers can be classified as pure seminomas or nonseminomatous germ cell tumors (embryonal carcinoma, choriocarcinoma, yolk sac carcinoma, teratoma, or mixed germ cell tumors).
- Germ-cell tumors appear to develop as a result of a tumorigenic event in utero that leads to a precursor lesion classified as intratubular germ-cell neoplasia. Approximately 90% of germ-cell tumors are associated with adjacent intratubular germ-cell neoplasia, which carries a 50% risk of testicular cancer within 5 yr. Table 1 summarizes germ cell tumors and serum markers.
- A genetic locus that confers a predisposition to testicular cancer is at 12q21, the location of the genes encoding the proteins involved in KITLG–KIT signaling. The development of intratubular germ-cell neoplasia may involve aberrantly activated KITLG–KIT in utero, which induces arrest of embryonic germ cells at the gonocyte stage; subsequently, overexpression of embryonic transcription factors leads to suppression of apoptosis, increased proliferation, and accumulation of mutations in gonocytes.
- The incidence of various subtypes of testicular cancers is as below:

Cell Type	Frequency (%)
Seminoma	42
Embryonal cell carcinoma	26
Teratocarcinoma	26
Teratoma	5
Choriocarcinoma	1

- Other rare types:
  1. Yolk sac carcinoma
  2. Mixed germ cell tumors
  3. Carcinoid tumor
  4. Sertoli cell tumors
  5. Leydig cell tumors
  6. Lymphoma
  7. Metastatic cancer to the testes

STAGING

- TNM staging system for testicular cancer is described in Table 2 and Table 3.
- The clinical stages consist of stage I, with tumor confined to the testis; stage II, with positive regional lymph nodes; and stage III, with metastases. Fig. 1 shows the clinical staging of testicular cancer.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Spermatocele
- Varicocele
- Hydrocele
- Epididymitis/orchitis
- Epidermoid cyst of the testicle
- Epididymis tumors
- Inguinal hernia
- Hematocele or testicular rupture
- Torsion of testicular appendage
- Skin cancer

WORKUP

Physical examination, laboratory tests, and imaging studies (Fig. 2). A radical inguinal orchiectomy is diagnostic and therapeutic. Immunohistochemical analysis is used to determine the histologic composition of the tumor. Staging involves CT of chest, abdomen, and pelvis and measurement of beta subunit

TABLE 1 Germ Cell Tumors and Serum Markers

Histology	Marker Negative (%)	Elevated hCG Alone (%)	Elevated AFP Alone (%)
Seminoma	90	10 (usually <100 IU/ml)	0 (if +, by definition, NSGCT)
All NSGCTs	15	50-60	40
Embryonal		0	10-40
Yolk sac tumors		Rare	80-90 (alone or with elevated hCG)
Choriocarcinoma (or syncytiotrophoblast elements)		>90 (level can be very high)	0

AFP, α-Fetoprotein; *hCG,* human chorionic gonadotropin; *NSGCT,* nonseminoma germ cell tumor.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE 2 TNM Staging for Testicular Cancer (*AJCC 8th Edition Staging Cancer Manual*)

pT Stage	Primary Tumor
pT_X	Primary tumor cannot be assessed
pT_0	No evidence of primary tumor
pT_{is}	Germ cell neoplasia *in situ*
pT_1	Tumor limited to testis (including rete testis invasion) without lymphovascular invasion pT_{1a}: Tumor smaller than 3 cm in size (seminoma only) pT_{1b}: Tumor 3 cm or larger in size (seminoma only)
pT_2	Tumor limited to testis (including rete testis invasion) with lymphovascular invasion OR tumor invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer covering the external surface of tunica albuginea with or without lymphovascular invasion
pT_3	Tumor directly invades spermatic cord soft tissue with or without lymphovascular invasion
pT_4	Tumor invades scrotum with or without lymphovascular invasion
N Stage	**Regional Lymph Nodes**
N_x	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Metastasis with a lymph node mass 2 cm or smaller in greatest dimension OR multiple lymph nodes, none larger than 2 cm in greatest dimension
N_2	Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension OR multiple lymph nodes, any one mass larger than 2 cm but not larger than 5 cm in greatest dimension
N_3	Metastasis with a lymph node mass larger than 5 cm in greatest dimension
M Stage	**Distant Metastasis**
M_0	No distant metastasis
M_1	Distant metastasis present M_{1a}: Nonretroperitoneal nodal or pulmonary metastases M_{1b}: Nonpulmonary visceral metastases
S	**Serum Tumor Markers**
S_x	Not available
S_0	Markers within normal levels
S_1	LDH <1.5 × N *and* hCG (mIU/ml) <5000 *and* AFP (ng/ml) <1000
S_2	LDH 1.5-10 × N *or* hCG (mIU/ml) 5000–50,000 *or* AFP (ng/ml) 1000-10,000
S_3	LDH >10 × N *or* hCG (mIU/ml) >50,000 *or* AFP (ng/ml) >10,000

AJCC, American Joint Committee on Cancer; *TNM,* tumor, necrosis, metastases.

TABLE 3 AJCC Prognostic Stage Groupings

Stage	T	N	M	S
0	pT_{is}	N_0	M_0	S_0
I	pT_{1-4}	N_0	M_0	S_X
I_A	pT_1	N_0	M_0	S_0
I_B	pT_{2-4}	N_0	M_0	S_0
I_S	Any T	N_0	M_0	S_{1-3}
II	Any T	N_{1-3}	M_0	S_X
II_A	Any T	N_1	M_0	S_0-S_1
II_B	Any T	N_2	M_0	S_0-S_1
II_C	Any T	N_3	M_0	S_0-S_1
III	Any T	Any N	M_1	S_X
III_A	Any T	Any N	M_{1a}	S_0-S_1
III_B	Any T	Any N	M_0-M_{1a}	S_2
III_C	Any T	Any N	M_0-M_{1a}	S_3
	Any T	Any N	M_{1b}	Any S

AJCC, American Joint Committee on Cancer.

of human chorionic gonadotropins (β-hCG), alpha-fetoprotein (AFP), and lactate dehydrogenase (LDH).

LABORATORY TESTS

- Serum β-hCG is elevated in approximately 20% of patients with pure seminomas.
- Serum AFP is elevated in nonseminoma tumors, never elevated in patients with pure seminomas.

One or both of these tumor markers will be elevated in 70% of cases of testicular cancer.

- Serum lactate LDH level is elevated with rapid turnover of malignant cells.
- Testicular biopsy is contraindicated.

IMAGING STUDIES

- Testicular ultrasound
- CT scan of chest, pelvis, and abdomen
- MRI of the brain in patients with neurologic symptoms
- PET scan is not recommended (frequent false positives)

Rx TREATMENT

- Box E1 summarizes a treatment algorithm for testicular cancer.
- Seminoma:
  1. Stage I: Most patients with clinical stage 1 are cured with orchiectomy. Radical inguinal orchiectomy plus one cycle of single-agent carboplatin chemotherapy or radiation therapy (RT) to the paraaortic lymph nodes is a standard treatment option. However, it has been replaced in many instances with active surveillance postorchiectomy. More relapses are associated with surveillance (20% vs. 4% with radiotherapy or chemotherapy), but long-term survival approaches 100% irrespective of initial option chosen.[1]
  2. Stage II_A or II_B: RT or cisplatin-based chemotherapy (e.g., bleomycin, etoposide, and cisplatin [BEP]).
- Nonseminoma:
  1. Stage I_A: Radical orchiectomy plus nerve-sparing retroperitoneal lymph node dissection (RPLND)
  2. Stage I_B: Same as stage I_A plus two cycles of chemotherapy (bleomycin, etoposide, and cisplatin [BEP])
  3. Stages II-III: Multiagent cisplatin-based chemotherapy regimens for three or four cycles depending on risk stratification (low/intermediate or high). RPLND is offered for residual lymph nodal disease after chemotherapy
- Relapsed disease:
  1. Salvage chemotherapy using multiagent regimens is offered. Active drugs include ifosfamide, paclitaxel, cisplatin, vinblastine, and cisplatin.
  2. Chemotherapy-sensitive patients can be successfully treated with high-dose chemotherapy followed by autologous stem cell transplantation (ASCT).
- Posttreatment surveillance for testicular cancer survivors (annually):
  1. Fertility assessment
  2. Physical examination and skin examination (increased risk of dysplastic nevi)
  3. Testicular examination (3% to 4% risk of second testicular cancer)
  4. Serum tumor markers (hCG, AFP)
  5. Abdominal and pelvic CT every 3 to 4 mo for 2 yr, every 6 to 12 mo in third and fourth yr, and annually thereafter

[1]Hanna NH, Einhorn LH: Testicular cancer, discoveries and updates, *N Engl J Med* 371:2005-2016, 2014.

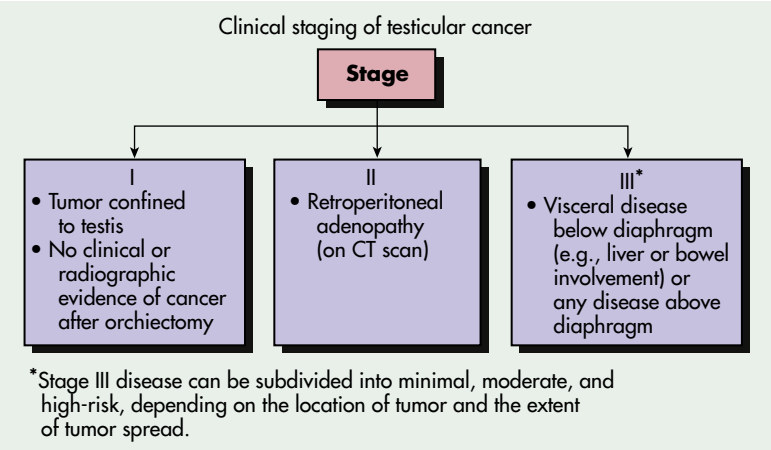

FIG. 1 Clinical staging of testicular cancer. The American Joint Committee on Cancer TNM staging system is less commonly used, because it is based upon histologic evaluation of the orchidectomy specimen and retroperitoneal periaortic lymph node dissection. Because the latter may not be performed in every patient, the clinical staging system is generally more practical. (From Skarin AT: *Atlas of diagnostic oncology,* ed 4, St Louis, 2010, Mosby.)

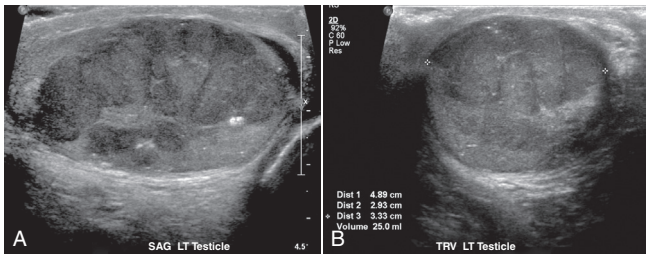

FIG. 2 Seminoma in an 18-year-old patient with painless left scrotal mass. A and **B,** Sagittal and transverse sonograms of the left testis demonstrate a testicular volume of 25 ml, with a lobulated, heterogeneous, relatively hypoechoic mass occupying most of the testis with a thin rim of normal testis and a few tiny clusters of calcification, as well as multiple, tiny, brightly echoic speckles both inside and outside the mass. The tiny speckles represent microlithiasis. (From Rumack CM et al: *Diagnostic ultrasound,* ed 4, Philadelphia, 2011, Elsevier.)

DISPOSITION

- The overall cure for testicular cancer is >95% (80% for metastatic disease). Patients with pure seminomas have a better prognosis. Prognosis can be determined by criteria established by the International Germ Cell Consensus Criteria (Table E4). Because treatment produces favorable outcomes even in advanced stages, the U.S. Preventive Services Task Force recommends against screening asymptomatic men for testicular cancer.
- There is an increased risk for metabolic syndrome (insulin resistance, hypertension, dyslipidemia, abdominal obesity) after radiation or chemotherapy. Additionally, effects on long-term reproductive health, lower fertility, hearing impairment, neuropathy, and Raynaud phenomenon are long-term toxicities seen with chemotherapy use.
- Therapeutic radiation and chemotherapy are risk factors for cancers of thyroid, lymphoma, kidney, pancreas, stomach, and leukemia. There is also an increased risk for metabolic syndrome (insulin resistance, hypertension, dyslipidemia, abdominal obesity) after radiation or chemotherapy.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Testicular Cancer (Patient Information)

AUTHOR: **Bharti Rathore, MD**

BOX E1 Treatment Algorithm

1. Suspicious testicular mass:
   - History and physical examination (H&P)
   - α-fetoprotein (AFP)
   - β-human chorionic gonadotropin (β-hCG)
   - Lactate dehydrogenase (LDH)
   - Chemistry profile
   - Testicular ultrasonography
2. Radical inguinal orchiectomy:
   - Consider inguinal biopsy of contralateral testis if ultrasound findings raise suspicion for intratesticular abnormalities, cryptorchid testis, or marked atrophy.
3. If orchiectomy shows pure seminoma:
   - Abdominal and pelvic computed tomography (CT)
   - Chest radiography
   - Consider chest CT if positive abdominal CT or abnormal chest radiograph
   - Discuss sperm banking, if clinically indicated

   3a. For stage I_A/I_B pure seminoma, consider the following:
      - Surveillance
      - Single-agent carboplatin (area under the curve [AUC] 7 × 1-2 cycles)
      - Radiation therapy

   3b. For stage II_A pure seminoma, consider the following:
      - Radiation therapy
      - Chemotherapy (BEP × 3 cycles of EP × 4 cycles)

   3c. For stage II_B pure seminoma, consider the following:
      - Chemotherapy (BEP × 3 cycles of EP × 4 cycles)
      - Radiation therapy (only for nonbulky, <3 cm cases)

   3d. For stage II_C/III pure seminoma, consider the following:
      - Chemotherapy
      - Good-risk disease: BEP × 3 cycles of EP × 4 cycles
      - Intermediate-risk disease: BEP × 4 cycles or VIP × 4 cycles

   3e. Postchemotherapy management for pure seminoma:
      - Residual mass >3 cm: PET-CT, resection of disease if positive, second-line chemotherapy if viable seminoma detected
      - Residual mass <3 cm or no residual mass: Surveillance
4. If orchiectomy shows nonseminoma or any mixed histologic types:
   - Chest, abdominal, pelvic CT
   - Repeat tumor marker testing (AFP, β-hCG, LDH)
   - Brain magnetic resonance imaging (MRI) if clinically indicated
   - Discuss sperm banking, if clinically indicated

   4a. For stage I_A/I_B pure seminoma, consider the following:
      - Surveillance
      - Adjuvant chemotherapy (BEP × 1-2 cycles)
      - Nerve-sparing RPLND

   4b. For stage II_A/II_B without elevated markers, consider the following:
      - Primary nerve-sparing RPLND (use cautiously for II_B)
      - If pathologic N_1, then consider surveillance vs adjuvant BEP × 2 cycles or EP × 2 cycles
      - If pathologic N_2, then consider adjuvant BEP × 2 cycles or EP × 2 cycles
      - If pathologic N_3, then consider adjuvant BEP × 3 cycles or EP × 4 cycles
      - Primary chemotherapy (BEP × 3 cycles or EP × 4 cycles)

   4c. For stage I_s, II_A with elevated markers, II_B with elevated markers, II_C, or III, consider the following:
      - Chemotherapy (BEP × 3 or EP × 4 if good risk; if intermediate or poor risk, then BEP × 4 or VIP × 4)

   4d. Postchemotherapy management for nonseminoma and mixed histologic types:
      - Residual mass >1 cm: Resection of disease if possible (RPLND or lung resection)
      - Consider adjuvant chemotherapy (BEP × 2 cycles or EP × 2 cycles) if residual viable germ cell tumor disease present at time of resection
5. Recurrence after initial therapy:
   - Referral to specialized center for evaluation
   - Consider surgical salvage if late relapse (>2 yr)
   - Consider conventional-dose chemotherapy (TIP × 4 or VeIP × 4) vs high-dose chemotherapy with autologous transplant

BEP, Bleomycin, etoposide, and cisplatin; *EP,* etoposide and cisplatin; *PET-CT,* positron emission tomography–computed tomography; *RPLND,* retroperitoneal lymph node dissection; *TIP,* paclitaxel, ifosfamide, and cisplatin; *VeIP,* vinblastine, ifosfamide, and cisplatin; *VIP,* ifosfamide, cisplatin, and etoposide.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE E4 International Germ Cell Consensus Criteria for Testicular Cancer

Nonseminoma	Seminoma
Good Prognosis	
Testis/retroperitoneal primary	Any primary site
And	*And*
No nonpulmonary visceral metastases	No nonpulmonary visceral metastases
And	*And*
Good markers—all of • AFP <1000 ng/ml and • hCG <5000 IU/L (1000 ng/ml) and • LDH <1.5× upper limit of normal	Normal AFP, any hCG, any LDH
58% of nonseminomas	90% of seminomas
5-yr PFS 89%	5-yr PFS 82%
5-yr survival 92%	5-yr survival 86%
Intermediate Prognosis	
Testis/retroperitoneal primary	Any primary site
And	*And*
No nonpulmonary visceral metastases	Nonpulmonary visceral metastases
And	*And*
Intermediate markers—any of • AFP ≥1000 and ≤10,000 ng/ml or • hCG ≥5000 IU/L and ≤50,000 IU/L or • LDH ≥1.5× normal and ≤10× normal	Normal AFP, any hCG, any LDH
28% of nonseminomas	10% of seminomas
5-yr PFS 75%	5-yr PFS 67%
5-yr survival 80%	5-yr survival 72%
Poor Prognosis	
Mediastinal primary	No patients classified as
Or	poor prognosis
Nonpulmonary visceral metastases	
Or	
Poor markers—any of • AFP >10,000 ng/ml or • hCG >50,000 IU/L (10,000 ng/ml) or • LDH >10× upper limit of normal	
16% of nonseminomas	
5-yr PFS 41%	
5-yr survival 48%	

AFP, α-fetoprotein; *hCG,* human chorionic gonadotropin; *LDH,* lactate dehydrogenase; *PFS,* progression-free survival.
From Skarin AT: *Atlas of diagnostic oncology,* ed 4, St Louis, 2010, Mosby.

SUGGESTED READINGS

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Hanna N et al: Testicular cancer: a reflection on 50 years of discovery, *J Clin Oncol* 32(28):3085-3092, 2014.

Lin K, Sharangpani R: Screening for testicular cancer: an evidence review for the U.S. Preventive Services Task Force, *Ann Intern Med* 153:396-399, 2010.

Rajpert-De Meyts E et al: Testicular germ cell tumours, *Lancet* 387:1762-1774, 2016.

Siegel RL et al: Cancer statistics, *CA Cancer J Clin* 69(1):7-34, 2019.

BASIC INFORMATION

DEFINITION

Testicular torsion is a twisting of the spermatic cord leading to cessation of testicular blood flow, ischemia, and infarction if left untreated.

SYNONYM

Spermatic cord torsion

ICD-10CM CODE
N44.03 Torsion of testis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Affects 1 in 4000 males <25 yr
PREDOMINANT AGE: Two thirds of all cases occur between the ages of 12 and 18 yr but may occur at any age, including antenatally.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typical sequence is sudden onset of hemiscrotal pain, then swelling, nausea, and vomiting without fever or urinary symptoms.
- Physical examination may reveal a tender firm testis, high-riding testis, horizontal lie of testis, absent cremasteric reflex, and no pain with elevation of testis. Absence of the cremasteric reflex (stroking or pinching the medial thigh causing contraction of cremaster muscle and elevation of testis) is the most sensitive physical finding.
- Painless testicular swelling occurs in 10%.
- One out of three patients reports previous episodes of spontaneously remitting scrotal pain.
- In the neonate, testicular torsion should be presumed in patients with a painless, discolored hemiscrotal swelling.
- In rare cases, torsion may involve an undescended testicle. In such situations an empty hemiscrotum is palpated with a tender lump in the inguinal area.

ETIOLOGY

- There are three types of testicular torsion: extravaginal, caused by nonadherence of the tunica vaginalis to the dartos layer; intravaginal torsion, caused by malrotation of the spermatic cord with the tunica vaginalis; and torsion of the testis below the epididymis (Fig. E1). Intravaginal torsion accounts for 90% of cases.
- Torsion usually occurs in the absence of any precipitating events. Trauma accounts for <10% of cases.

DIAGNOSIS

Diagnosis made mainly by clinical suspicion (Table E1). Color Doppler ultrasound evaluation or a nuclear testicular scan (Figs. E2 and E3) may help with diagnosis. Ultrasonography shows absent or decreased blood flow; scintigraphy reveals decreased perfusion on symptomatic side.

DIFFERENTIAL DIAGNOSIS

- Torsion of the testicular appendages (appendix testis)
- Testicular tumor
- Epididymitis
- Incarcerated inguinoscrotal hernia
- Orchitis
- Spermatocele
- Hydrocele, varicocele

WORKUP

The diagnosis is usually based on history and physical examination.

IMAGING STUDIES

- Doppler ultrasonic stethoscope (Doppler flowmetry) (Fig. E3)
- Radionuclide scrotal scanning (technetium-99m): Cold testicle (Fig. E2)

TREATMENT

Surgical derotation of the spermatic cord followed by bilateral testicular fixation with nonabsorbable sutures. If affected testis is nonviable, orchiectomy of affected testis and orchiopexy of contralateral side are performed. Attempts at manual detorsion should not delay surgical consultation.

PROGNOSIS

- The degree of ischemia depends on the duration of torsion and the degree of rotation of the spermatic cord.
- There is an 80% testicular salvage rate if detorsion occurs within 12 hr of onset.
- After 24 hr, irreversible testicular infarction is expected.
- Because contralateral testes can be affected (immunologic process), if treatment delayed and blood flow does not return after detorsion, some recommend orchiectomy of the infarcted testicle.

PEARLS & CONSIDERATIONS

- Manual detorsion by external rotation of the testis toward the thigh can be attempted for adolescent intravaginal torsion if an operating facility is not readily available.
- Extravaginal torsion is diagnosed in the newborn. Intravaginal torsion can occur at any age but is usually diagnosed in males ages 12 to 18 yr.

RELATED CONTENT

Testicular Torsion (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

TABLE E1 Differentiation of Testicular Torsion, Epididymitis, and Appendage Torsion

	Testicular Torsion	Epididymitis*	Appendage Torsion
Historical Features			
Age	Peak incidence in neonatal and adolescent groups but may occur at any age	Primarily adolescents and adults but may occur at any age	Typically prepubertal boys
Risk factors	Undescended testicle (neonate), rapid increase in testicular size (adolescent), failure of previous orchiopexy	Sexual activity or promiscuity, GU anomalies, GU instrumentation	Presence of appendages
Pain onset	Sudden	Gradual	Gradual or sudden
Previous episodes of similar pain	Possible (spontaneous detorsion)	Unlikely	Occasional
History of trauma	Possible	Possible	Possible
Nausea, vomiting	More likely	Less likely	Less likely
Dysuria	Less likely	More likely	Less likely
Physical Findings			
Fever	Less likely	More likely, particularly with advanced disease (epididymo-orchitis)	Less likely
Location of swelling and tenderness	Testicle, progressing to diffuse hemiscrotal involvement	Epididymis, progressing to diffuse hemiscrotal involvement	Localized to head of affected testicle or epididymis
Cremasteric reflex	Testicular torsion less likely if present	May be present or absent	May be present or absent
Testicle position	High-riding testicle, transverse alignment	Normal position, vertical alignment	Normal position, vertical alignment
Pyuria	Less likely	More likely	Less likely

GU, Genitourinary.
*Including epididymo-orchitis
From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

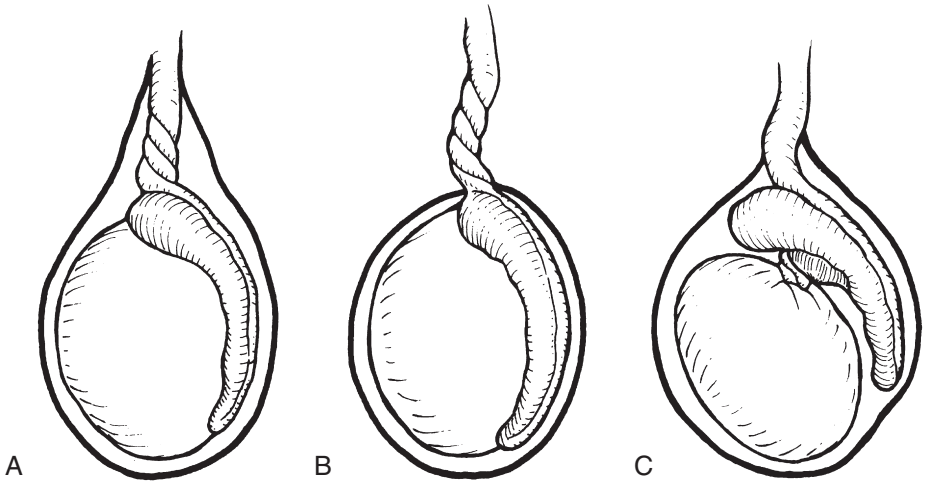

FIG. E1 Types of testicular torsion. A, Intravaginal torsion above the epididymis. **B,** Extravaginal torsion. **C,** Torsion of the testis below the epididymis. (From Rumack CM et al: *Diagnostic ultrasound,* ed 4, Philadelphia, 2011, Elsevier.)

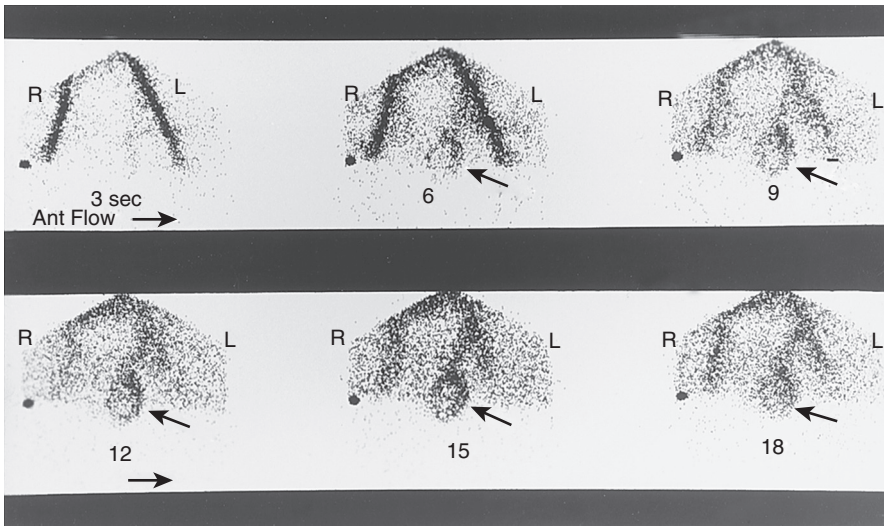

FIG. E2 Testicular torsion. Evaluation of blood flow to the testicle has been done by giving an intravenous bolus of radioactive material. The right and left iliac vessels are clearly identified, and sequential images are obtained every 3 seconds. Here, increased flow is seen to the rim of the left testicle *(arrows),* and there is no blood flow centrally. This is the appearance of a testicular torsion in which the torsion has been present for more than approximately 24 hr. *Ant,* Anterior. (From Mettler FA [ed]: *Primary care radiology,* Philadelphia, 2000, WB Saunders.)

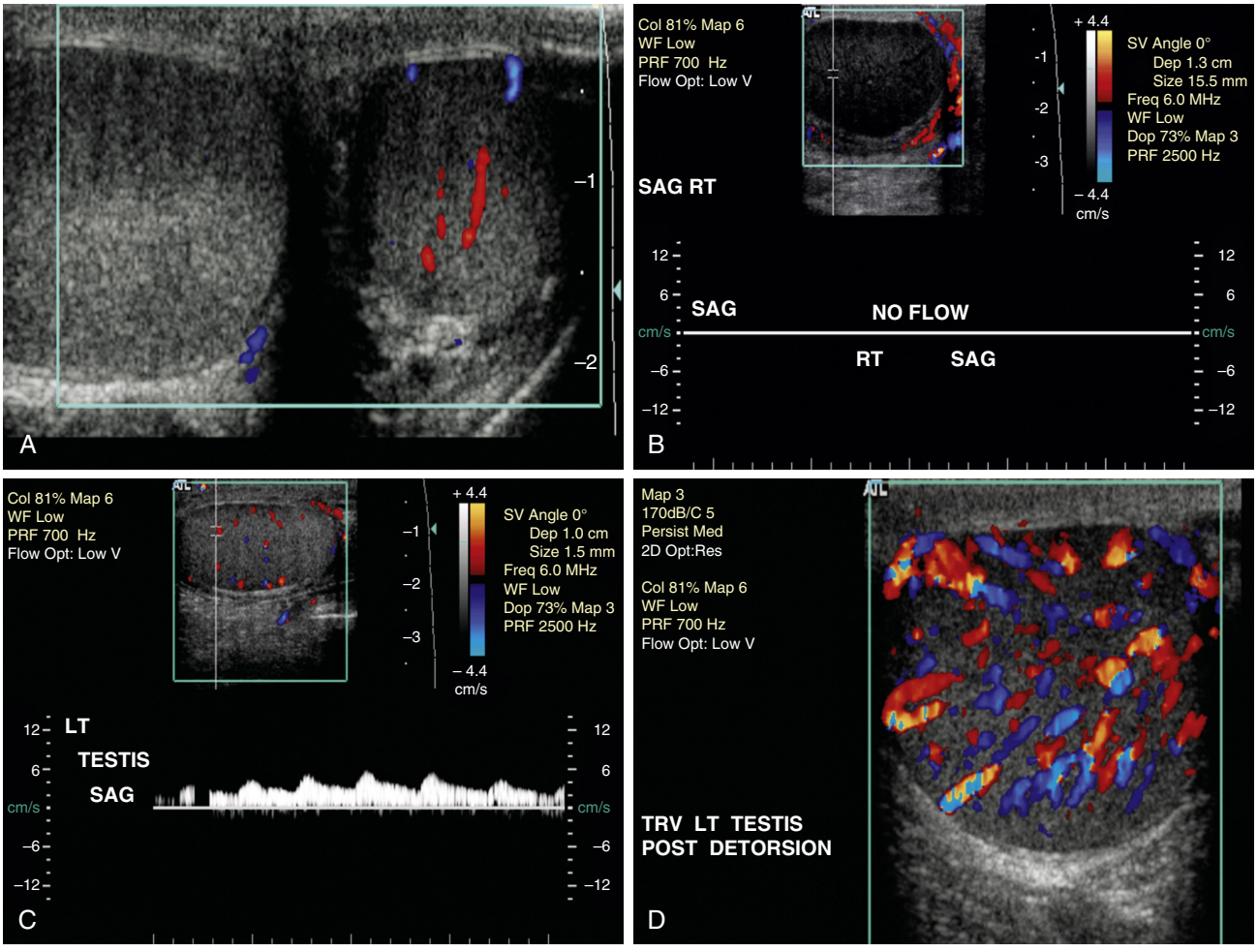

FIG. E3 Acute testicular torsion. **A** to **C,** This 13-year-old boy presented with acute, excruciating right-sided scrotal pain. **A,** Transverse gray-scale image of both testes demonstrates enlargement of the avascular right testis. **B,** Absence of both color and pulsed Doppler flow is noted on this sagittal image of the right testis. **C,** Normal pulsed and color Doppler flow confirmed in asymptomatic, normal-appearing left testis. **D,** Teenage boy with acute left-sided testicular torsion. Closed manual detorsion of the left testis was done at diagnosis in the ultrasound suite. Color Doppler sonogram of the left testis obtained immediately after detorsion shows dramatic hyperemia throughout the left testis. *LT,* Left; *RT,* right; *SAG,* sagittal; *TRV,* transverse. (From Rumack CM et al: *Diagnostic ultrasound,* ed 4, Philadelphia, 2011, Elsevier.)

BASIC INFORMATION

DEFINITION

Tetanus is a life-threatening illness manifested by muscle rigidity and spasms; it is caused by a neurotoxin (tetanospasmin) produced by *Clostridium tetani.*

SYNONYMS

Lockjaw
Generalized tetanus
Neonatal tetanus
Cephalic tetanus
Localized tetanus

ICD-10CM CODES
A33 Tetanus neonatorum
A34 Obstetrical tetanus
A35 Other tetanus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 264 cases between 2009 and 2017. Overall case fatality was 13.2%, but 31.3% for people over 65. More than 60% of cases were among people aged 20 to 64 yr. Diabetes, immunosuppression, and IVDA may be risk factors for tetanus. Diabetes accounted for 13% of cases and a quarter of all tetanus deaths. IVDA accounted for 17% of the cases.
INCIDENCE (WORLDWIDE): About 1 million cases of tetanus are reported worldwide annually, suggesting a global incidence of about 18 per 100,000 persons per yr and an estimated 300,000 to 500,000 deaths per yr. Tetanus is an expected complication when disasters strike in developing countries where tetanus immunization coverage is low.
PREDOMINANT AGE: >60 yr of age
GENETICS: Neonatal infection:

- Rare in the U.S.
- Among the leading causes of neonatal mortality in many parts of the world (caused by infection of the umbilical cord stump)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Trismus ("lockjaw")
- Risus sardonicus (peculiar grin), characteristic grimace that results from contraction of the facial muscles (Fig. E1)

FIG. E1 Facial muscle involvement in tetanus, producing characteristic "risus sardonicus." (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

- Generalized muscle spasms causing severe pain and, at times, respiratory compromise and death
- Rigid abdominal muscles, flexed arms, and extended legs (Fig. E2)
- Autonomic dysfunction several days after onset of illness
- Leading cause of death: Fluctuations in heart rate and blood pressure
- Usually, absence of fever
- Localized tetanus
  1. Rigidity of muscles near the injury
  2. Weakness as a result of lower motor neuron injury
  3. May be self-limited and resolve spontaneously
  4. More often progresses to generalized tetanus
  5. Cephalic tetanus:
     a. May occur with head injuries or chronic otitis with localized ear or mastoid infection with *C. tetani*
     b. Can manifest as cranial nerve dysfunction

ETIOLOGY

- *C. tetani* is a gram-positive, spore-forming bacillus (Fig. E3) that resides primarily in the soil.
- Majority of cases are caused by punctures and lacerations (Fig. E4).
- Toxin is elaborated from organisms in a contaminated wound.
- Local symptoms are caused by inhibition of neurotransmitter at presynaptic sites.
  1. Over the next 2 to 14 days, the toxin travels up the neurons to the CNS, where it acts on inhibitory neurons to prevent neurotransmitter release.
  2. Unopposed motor activity results in tonic contractions of muscles.

FIG. E2 Neonatal tetanus. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Strychnine poisoning
- Dystonic reaction caused by neuroleptic agents: Neuroleptic malignant syndrome
- Local infection (dental or masseter muscle) causing trismus
- Severe hypocalcemia
- Hysteria

WORKUP

- Positive wound culture is not helpful in diagnosis.
- Isolation of organism is possible in patients without the illness.

LABORATORY TESTS

- Usually, normal blood counts and chemistries
- Toxicology of serum and urine to rule out strychnine poisoning

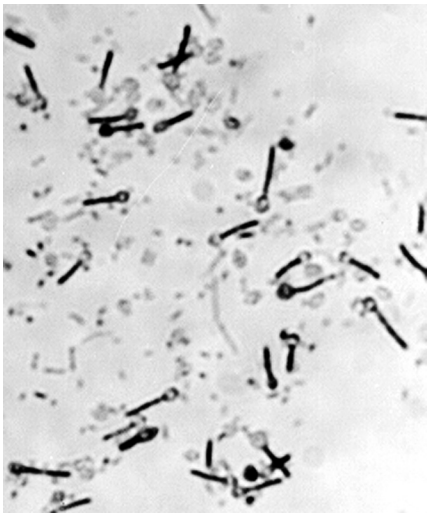

FIG. E3 *Clostridium tetani:* A gram-positive bacillus with terminal spores. (Courtesy J. Campbell, Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam. From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

FIG. E4 Lacerations to the feet are the most common focus of *Clostridium tetani* infection. Note clawing of toes secondary to increased tone in surrounding muscles. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Monitoring in a hospital ICU: Keep surroundings dark and quiet
- Intubation or tracheostomy for severe laryngospasm
- Prompt irrigation and debridement of wound to eliminate spores and necrotic tissue that can favor germination

ACUTE GENERAL Rx

- Passive immunization with human tetanus immunoglobulin (HTIG) 500 U as soon as possible via IM injection in thigh or deltoid muscle. Some studies recommend 3000 to 6000 U for generalized tetanus.
- Tetanus toxoid (Td) 0.5 ml by IM injection at a different site. Redose later for a total of 3 doses spaced at least 2 weeks apart to elicit active immunization.
- Antibiotics alone may fail without adequate debridement. Metronidazole 500 mg IV q6h to 8 h, or penicillin G 2 to 4 million U IV q4h to q6h for 7 to 10 days, or doxycycline 100 mg IV q12h.
- IV diazepam 10 to 30 mg to control muscle spasms. Alternative agents are midazolam, baclofen, IV magnesium sulfate, propofol, dantrolene, barbiturates, and chlorpromazine. Intrathecal antitoxin also can be used to control muscle spasms and avoid intubation.
- Neuromuscular blockade if necessary with pancuronium or vecuronium.
- Beta-blockers (e.g., labetalol: 0.25 to 1 mg/min) to control sympathetic hyperactivity.

CHRONIC Rx

- Supportive care. Beta-blockers (labetalol), magnesium sulfate, and morphine (0.5-1.0 mg/kg/h continuous infusion) can improve autonomic dysfunction
- Possible mechanical ventilation. Consider tracheostomy. If ventilator support is not available, benzodiazepines are the preferred agent to manage respiratory failure
- Minimal external stimuli
- Control of heart rate and blood pressure:
  1. Labetalol for sympathetic hyperactivity
  2. Pacemaker for sustained bradycardia
- Physical therapy once spasms subside

DISPOSITION

Full recovery over weeks to months if complications can be avoided

REFERRAL

- To emergency department
- To infectious disease specialist

PEARLS & CONSIDERATIONS

COMMENTS

- Illness is preventable. Table E1 describes tetanus prophylaxis in routine wound management.
- Boosters of Td should be given every 10 yr to maintain immune status.
- The tetanus-diphtheria-acellular pertussis vaccine (Tdap) may be used instead of Td, but if used, Tdap should be used only once in adults, except in pregnant women, who should receive Tdap during each pregnancy.
- Passive as well as active immunization (HTIG and Td) should be given for patients with tetanus-prone wounds who have not been adequately immunized in the previous 5 yr.
- A recent U.S. study showed that only 72% of people older than 6 yr had protective levels of antibody.

RELATED CONTENT

Tetanus (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

TABLE E1 Tetanus Prophylaxis in Routine Wound Management

	Clean, Minor Wounds		Other Wounds*	
History of Absorbed Tetanus Toxoid	**Tdap or Td†**	**TIG‡**	**Tdap or Td†**	**TIG‡**
Uncertain, or <3 doses	Yes	No	Yes	Yes
3 or more doses	No§	No	No¶	No

DT, Diphtheria and tetanus toxoid vaccine; *DTaP,* combined diphtheria toxoid–tetanus toxoid–acellular pertussis vaccine; *Td,* tetanus toxoid and reduced diphtheria toxoid vaccine; *Tdap,* tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; *TIG,* tetanus immune globulin.

*Such as, but not limited to, wounds contaminated with dirt, feces, or saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.

†For children <7 yr of age, DTaP is preferred to tetanus toxoid alone if <3 doses of DTaP have been given previously. If pertussis vaccine is contraindicated, DT is given. For persons ≥7 yr of age, Td (or Tdap for adolescents 11 to 18 yr of age) is preferred to tetanus toxoid alone. Tdap is preferred to Td for adolescents 11 to 18 yr of age who have never received Tdap. Td is preferred to tetanus toxoid for adolescents who received Tdap previously or when Tdap is not available.

‡TIG should be administered for tetanus-prone wounds in HIV-infected patients regardless of the history of tetanus immunizations.

§Yes, if ≥10 yr since the last tetanus toxoid–containing vaccine dose.

¶Yes, if ≥5 yr since the last tetanus toxoid–containing vaccine dose. (More frequent boosters are not needed and can accentuate adverse events.)

SUGGESTED READINGS

Afshar M et al: Narrative review: tetanus—a health threat after natural disasters in developing countries, *Ann Intern Med* 154:329-335, 2011.

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BASIC INFORMATION

DEFINITION

Tetralogy of Fallot (TOF) is a congenital heart deformity that consists of the following four features (Fig. E1):

1. Malalignment ventricular septal defect (VSD)
2. Infundibular stenosis and/or pulmonary valve stenosis that leads to the obstruction of the right ventricular (RV) outflow tract (less frequent subtypes include pulmonary valve atresia and absent pulmonary valve)
3. An aorta that overrides the VSD by <50% of its diameter with rightward conal deviation
4. Concentric RV hypertrophy (result of right ventricular outflow tract [RVOT] obstruction)

SYNONYM

TOF

ICD-10CM CODE
Q21.3 Tetralogy of Fallot

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- TOF is the most common cyanotic congenital heart defect.
- TOF accounts for nearly 3% to 5% of all cases of congenital heart disease.
- Occurs in approximately 0.28/1000 live births in the U.S.
- It is the most common cyanotic malformation to reach adulthood without reparative surgery.

PREDOMINANT SEX: Slightly higher incidence in males than females

GENETICS: Genetic influence is suspected (22q11 deletion).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Of the four major features of TOF, infundibular and pulmonary stenosis that lead to RV outflow tract obstruction and the presence of a VSD are the defects that result in abnormal intracardiac circulation and lead to clinical manifestations:
  1. Right-to-left shunting and hypoxemia
  2. Decreased pulmonary blood flow
  3. Altered RV hemodynamics
- The aforementioned pathophysiology results in common manifestations of TOF, including the following:
  1. Low birth weight and growth rate.
  2. Dyspnea on exertion.
  3. Physical examination findings:
     a. Cyanosis of the nail beds and lips
     b. Digital clubbing (less common as a result of early surgical correction)
     c. Palpable RV impulse
     d. Systolic thrill along the left sternal border
     e. Single second heart sound comprised of aortic component only
     f. A grade 3 to 5 crescendo/decrescendo systolic murmur is heard along the left mid to upper sternal border with posterior radiation (pulmonic stenosis)
  4. In TOF with pulmonary atresia, murmur is softened/absent and the patient is deeply cyanotic.
  5. Hypercyanotic ("tet") spells occur with events that cause sudden decreases in oxygenation, increase in right ventricular outflow tract obstruction/increase in pulmonary vascular resistance, or with decreased systemic vascular resistance leading to an increase in right to left shunting across the VSD. Hypercyanotic spells are characterized by paroxysmal episodes of worsening cyanosis and rapid and deep breathing. Provoking events include crying, defecation, and exercise. Relieved with increased systemic vasoconstriction (i.e., squatting). Prolonged episodes can result in syncope.
  6. The degree of RV outflow obstruction determines the age and symptoms at presentation. In neonates with severe obstruction, profound cyanosis may result from insufficient pulmonary blood flow. Cases with mild to moderate obstruction and adequate pulmonary flow ("pink tet") may be diagnosed while patient is being evaluated for murmur or heart failure.
  7. After repair, patients may have a low-pitched diastolic murmur at the pulmonic area that is consistent with pulmonary regurgitation or occasionally a pansystolic murmur that is consistent with a VSD patch leak. If the patient only has a palliative shunt, a continuous murmur may be heard over the chest on the side of the shunt.
  8. Fig. E2 shows the pathophysiologic mechanisms of a hypoxic (tet) spell.

ETIOLOGY

TOF results from the abnormal septation of the embryologic conotruncus and is associated with some genetic disorders, but the exact molecular mechanism leading to the defect is unknown.

DIAGNOSIS

- The diagnosis of TOF is suspected in any neonate, infant, or child who presents with cyanosis and a heart murmur (see "Physical Findings & Clinical Presentation").

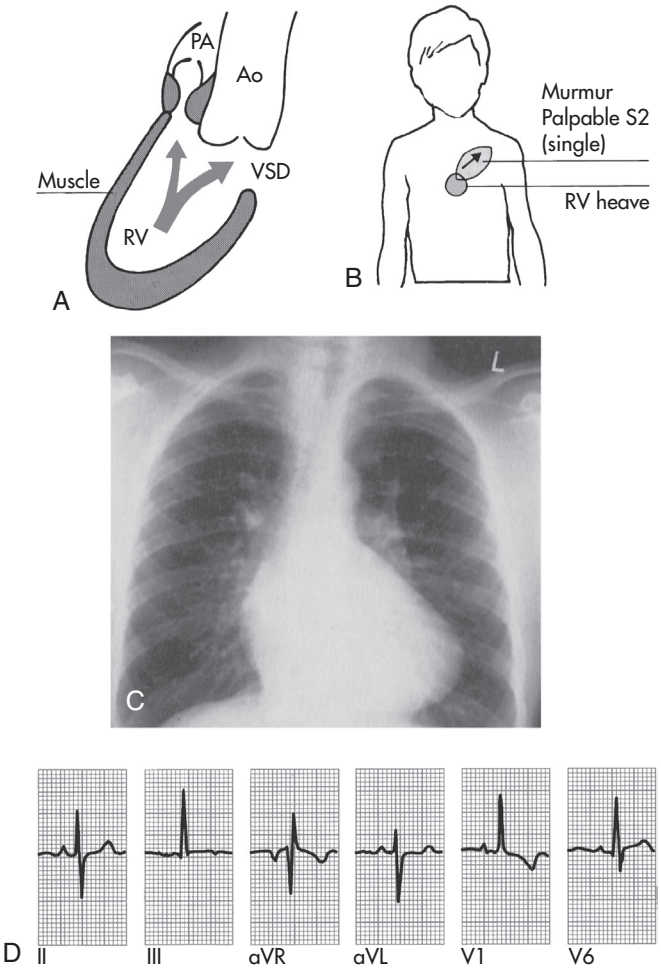

FIG. E1 Features of Fallot tetralogy. A, Diagram of abnormality. **B,** Physical signs. **C,** Chest x-ray showing right ventricular hypertrophy, typical "coeur en sabot." **D,** ECG showing right atrial and ventricular hypertrophy and right axis deviation. *Ao,* Aorta; *aVL,* augmented vector left; *aVR,* augmented vector right; *ECG,* electrocardiogram; *PA,* pulmonary artery; *RV,* right ventricle; *VSD,* ventricular septal defect. (From Souhami RL, Moxham J: *Textbook of medicine,* ed 4, London, 2002, Churchill Livingstone.)

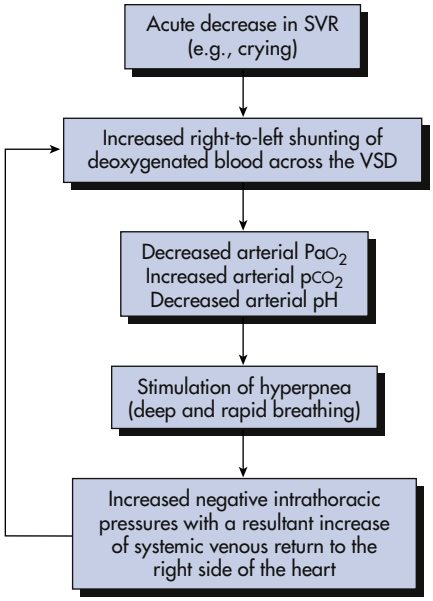

FIG. E2 Pathophysiologic mechanisms of a hypoxic (tet) spell. *PaO_2,* Partial pressure of oxygen in arterial blood; *pCO_2,* partial pressure of carbon dioxide; *SVR,* systematic vascular resistance; *VSD,* ventricular septal defect. (From Marx et al: *Rosen's emergency medicine: concepts and clinical practice,* 7 ed, 2010, Elsevier.)

- TOF is associated with other cardiac defects:
  1. Persistent foramen ovale/atrial septal defect
  2. Pulmonary artery anomalies
  3. Right aortic arch (25%)
  4. Left superior vena cava to coronary sinus (persistent left superior vena cava)
  5. Additional VSDs
  6. Coronary artery anomalies (LAD arising from RCA)
  7. Aortic valve regurgitation
- Associated anomalies and syndromes include the following:
  1. DiGeorge
  2. De Lange
  3. Goldenhar
  4. Klippel-Feil
  5. VACTERL
  6. CHARGE
  7. Pierre Robin
  8. Trisomies 21, 13, and 18
  9. Fetal alcohol
  10. Alagille
  11. MTHFR polymorphism

DIFFERENTIAL DIAGNOSIS

- Asthma
- Isolated VSD
- Pulmonary atresia
- Patent ductus arteriosus
- Aortic stenosis
- Pneumothorax

WORKUP

- Detailed history and physical examination, including pulse oximetry
- Echocardiogram, chest radiograph, 12-lead ECG, and routine laboratory tests

LABORATORY TESTS

- Pulse oximetry to determine oxygenation.
- The CBC shows polycythemia from long-standing hypoxemia.
- Arterial blood gas levels show hypoxemia, normal pH, and pCO_2 (carbon dioxide levels).

DIAGNOSTIC STUDIES

- ECG commonly demonstrates right axis deviation, RV hypertrophy, and right atrial enlargement.
- Exercise testing may help to evaluate functional capacity and exertional arrhythmias.
- Chest radiography reveals a boot-shaped heart that is commonly described as *coeur en sabot;* a prominent RV with decreased pulmonary vascularity; and a heart size that is usually normal. However, in patients with increased aortopulmonary collateral blood flow or with associated large patent ductus arteriosus, the heart size is increased with increased pulmonary vascularity.
- Echocardiography demonstrates VSD(s), anatomy and severity of right ventricular outflow tract obstruction, and aortic arch anatomy.
- Cardiac catheterization and angiography help to determine hemodynamics, the severity of right-to-left shunting, the localization of the VSD, coronary artery anatomy, right ventricular outflow obstruction, pulmonary artery stenosis, and assessment of aortopulmonary collaterals. Catheterization should be performed by centers with experts in ACHD and should be performed before intervention for RVOT obstruction to delineate coronary artery delineation with coronary artery compression testing (Class I, Level of evidence B) as the LAD may arise from the RCA crossing the RVOT.
- Cardiac MRI (CMR) can be used for the localization of a residual VSD after prior surgery and is the gold standard for serial anatomic assessment of the RV outflow tract, the assessment of RV volumes and function, the quantification of degree of pulmonary regurgitation, and the detection of RV myocardial fibrosis. Magnetic resonance angiography (MRA) can be a noninvasive alternative to cardiac catheterization for the evaluation of pulmonary vascular anatomy and the ascending aorta. 3D echocardiography can be a supplemental tool for evaluation of need for pulmonary valve replacement.
- Multislice spiral computed tomography may occasionally be used for diagnosis, and may be helpful during the planning of the repair procedure when the anatomy is unusual or complex. Its use in children may be limited by the risks associated with radiation exposure. It can also be used to make assessments that are similar to those usually made by MRI for patients who are unable to undergo MRI (such as those with permanent pacemakers).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Oxygen
- Prostaglandins at time of birth to keep a patent ductus and to maintain ductal flow to the lungs
- Knee-chest position during hypoxemic spells to help reduce venous return and to increase systemic vascular resistance, thereby decreasing right-to-left shunting

ACUTE GENERAL Rx

- The acute treatment of any infant or child with TOF who is cyanotic with respiratory distress is aimed at increasing systemic vascular resistance and decreasing right-to-left shunting (e.g., phenylephrine 0.1 to 0.5 mcg/kg/min intravenously to increase systemic vascular resistance, and oxygen and morphine to decrease pulmonary vascular resistance).
- Intravenous sodium bicarbonate for metabolic acidosis and, if more is necessary, respiratory support with intubation and sedation are required to control respiratory distress in cyanotic spells.
- Intravenous β-blockers (propranolol) are used to decrease RV outflow tract contractility.
- Emergent complete surgical repair or subclavian artery to pulmonary artery shunt (Blalock-Taussig shunt) is required if all of the previous treatments fail.

CHRONIC Rx

- Palliative surgery includes procedures to increase pulmonary blood flow, thus improving oxygen saturation and allowing for pulmonary artery growth. Examples of palliative procedures include the modified Blalock-Taussig shunt, in which a Gore-Tex tube is used to create a connection between the subclavian artery and the pulmonary artery; the Waterston shunt, which attaches the ascending aorta to the right pulmonary artery; and the Potts shunt, which attaches

the descending aorta to the left pulmonary artery (the latter two operations are no longer performed as they tended to lead to unpredictable pulmonary blood flow). These are generally performed in patients who are not candidates for complete surgical repair due to prematurity, hypoplastic pulmonary arteries, and/or coexistent cardiac anomalies.
- Complete surgical repair has good success and involves closing the VSD with a Dacron patch and relieving the RV outflow tract obstruction by resection of the infundibular stenosis, patch augmentation of the RV outflow, or the placement of a transannular patch. Surgical outcomes are superior if surgery is allowed to be delayed until the age of 3 to 6 mo when feasible. Following surgical repair most patients have dramatic improvement in symptoms and are generally able to lead a relatively normal life.
- Postoperative issues include the following:
  1. Residual pulmonic regurgitation
  2. Progressive RV dilation and dysfunction from pulmonary regurgitation leading to need for pulmonary valve replacement
  3. Residual RV outflow tract obstruction
  4. Branch pulmonary artery stenosis or hypoplasia
  5. Sustained ventricular tachycardia
  6. Sudden cardiac death
  7. Atrioventricular block, atrial flutter, and atrial fibrillation
  8. Progressive aortic regurgitation
  9. Syndromal associations

DISPOSITION

- In the current era, almost all patients with TOF have either palliative or complete surgical repair before they reach adulthood.
- <3% of patients with TOF survive to 40 yr without surgery.
- Survival after successful complete operative repair of TOF is excellent (35-yr survival rate for patients after TOF repair is 85%).
- Adults who underwent palliative surgery during childhood can present with cyanosis and clubbing, polycythemia, and pulmonary hypertension where there is excessive pulmonary blood flow.
- Pulmonary regurgitation (PR), residual pulmonary stenosis, and tricuspid regurgitation are the most common long-term sequelae in adults who underwent repair in childhood.
- Current guidelines and studies support pulmonary valve replacement with a bioprosthesis if there is moderate to severe PR with cardiovascular symptoms (Class I, level of evidence B) or in asymptomatic patients with evidence of ventricular enlargement/dysfunction in a setting of moderate to severe PR (Class IIa, level of evidence B). Pulmonary valve replacement is also reasonable if at least 2 of the following are present: RV diastolic volume by cardiac MRI is >160 ml/m^2 or RV systolic volume >80 ml/m^2, mild or greater RV or LV dysfunction, RV end diastolic volume >2 times the LV end diastolic function, RV systolic pressure 2/3 of systemic pressure or higher, reduction in exercise capacity. Pulmonary valve replacement can be performed either surgically or percutaneously.
- MRI or echocardiographic right ventricular global longitudinal strain assessment is a useful method to quantify remodeling of the right ventricle after repaired TOF and can guide management.
- Aortic root dilatation and aortic regurgitation are less common long-term issues. Aortic dissection is extremely rare in patients with TOF.
- Ventricular arrhythmia can lead to sudden cardiac death (SCD), and risk increases with time after surgical repair, particularly in the third and fourth decades of life (incidence of approximately 2% per decade). Monomorphic ventricular tachycardia is likely the result of a reentry circuit from an isthmus in the RV outflow tract due to scar caused by surgical repair. Patients are also susceptible to polymorphic VT/VFib due to progressive RV/LV dilation similar to other dilated cardiomyopathies. ICD is indicated for secondary prevention of SCD. Primary prevention ICD is indicated in patients who meet standard criteria (i.e., LVEF <35% with NYHA class II or III symptoms) and can be considered in those with additional risk factors that have been identified for SCD such as nonsustained ventricular tachycardia, QRS duration >180 ms, LV dysfunction, and extensive RV fibrosis on CMR. In those with moderate risk for SCD, programmed ventricular stimulation can assist in risk stratifying (Class IIa, level of evidence B).
- Atrial tachyarrhythmias are more prevalent than ventricular arrhythmias. Predisposition may be from scars at prior surgical access sites or from atrial dilation.
- A prolonged QRS duration on the preoperative ECG predicts an increased risk of postoperative supraventricular or ventricular arrhythmia. Prolongation of the QRS beyond 180 msec identifies patients who are at increased risk of ventricular tachycardia after surgery.
- Patients with signs or symptoms of arrhythmia may need to undergo invasive electrophysiologic testing and may require mapping and/or ablation of arrhythmias, antiarrhythmic medications, or the placement of an implantable cardiac defibrillator.
- Reduced exercise capacity is frequently the result of chronic pulmonary regurgitation or residual RV outflow tract obstruction.
- Patients with left ventricular dysfunction may benefit with angiotensin-converting enzyme inhibitors, β-blockers, and diuretics.
- Women with repaired TOF should be assessed by a cardiologist before considering pregnancy to determine if pulmonic valve replacement is needed first, as severe pulmonary regurgitation and RV dysfunction are associated with cardiac events during pregnancy, although many will tolerate pregnancy and delivery well. Consult with a geneticist prior to pregnancy should be offered (Class I, level of evidence B).
- Selected patients with normal RV pressures and function without evidence of residual shunt and without atrial or ventricular tachyarrhythmia are eligible to participate in competitive sports.

REFERRAL

- Infants and children with cyanotic heart disease should be referred to a pediatric cardiologist for further diagnostic evaluation. After being diagnosed with TOF, patients should be referred to centers with experience in palliative and complete surgical repair.
- Adult patients with repaired TOF should be comanaged with a cardiologist who specializes in adults with congenital heart disease. Routine followup is based on burden of symptoms and cardiac dysfunction, but the patient should be seen on at least an annual basis.

PEARLS & CONSIDERATIONS

- TOF was first described by the French physician Etienne Fallot in 1888.
- The first palliative surgical treatment for TOF was performed by Dr. Alfred Blalock at Johns Hopkins University in 1945 (i.e., the Blalock-Taussig shunt).
- The first surgical repair for TOF was performed by Dr. C. Walton Lillehei at the University of Minnesota in 1954.

COMMENTS

- The severity of RV outflow tract obstruction is the primary determinant of clinical symptoms and outcomes.
- There is a 3% increased risk of congenital heart disease in the children of parents with TOF.
- Unrepaired TOF requires subacute bacterial endocarditis prophylaxis before any dental work or nonsterile surgical procedures (e.g., surgery of the bowel or bladder).
- Children with TOF are at risk for neurodevelopmental delay when they reach school age.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Tetralogy of Fallot (Patient Information)

AUTHORS: **Johannes Steiner, MD,** and **Trace Barrett, MD**

SUGGESTED READINGS

Al-Habib HF et al: Contemporary patterns of management of tetralogy of Fallot: data from the Society of Thoracic Surgeons database, *Ann Thorac Surg* 90(3):813-819, 2010; discussion 819-820.

Loomba RS et al: Complete repair of tetralogy of Fallot in the neonatal versus non-neonatal period: a meta-analysis, *Pediatr Cardiol* 38:893-901, 2017.

Stout KK et al: 2018 AHA/ACC guideline for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines, *J Am Coll Cardiol* 73(12):1494-1563, 2019.

BASIC INFORMATION

DEFINITION

Thalassemias are a heterogeneous group of disorders of hemoglobin synthesis. Patients with thalassemia have abnormalities of synthesis of one of the alpha- or beta-globin chains. Patients with thalassemia have an excess of either alpha-globin chains or beta-globin chains, which impair red blood cell production and may decrease red blood cell survival. Table E1 summarizes clinical syndromes of thalassemias.

SYNONYMS

Mediterranean anemia
Cooley anemia

ICD-10CM CODES

D56	Thalassemia
D56.0	Alpha thalassemia
D56.1	Beta thalassemia
D56.2	Delta-beta thalassemia
D56.3	Thalassemia trait
D56.4	Hereditary persistence of fetal hemoglobin (HPFH)
D56.8	Other thalassemias
D56.9	Thalassemia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Thalassemia is among the most common genetic disorder worldwide. Approximately 4.83% of the world's population carries globin variants, including 1.67% of the population that are heterozygous for alpha-thalassemia and beta-thalassemia.
- The highest concentration of alpha-thalassemia is found in Southeast Asia and the African west coast. The prevalence is 5% to 10% in Thailand and approximately 5% among blacks.
- The worldwide prevalence of beta-thalassemia is approximately 3%; it is 15% to 30% in certain regions of Italy and Greece.
- The distribution of thalassemia in Europe, Africa, and Asia parallels that of malaria, suggesting that thalassemic persons are more resistant to the parasite, thus permitting evolutionary survival advantage.

CLASSIFICATION

Beta-thalassemia:

- It is increasingly common to classify thalassemia as transfusion dependent versus nontransfusion dependent. Historically, beta thalassemia has been classified as thalassemia minor, intermedia, and major
- Thalassemia minor: Associated with low normal Hgb or mild, asymptomatic anemia and microcytosis, with no organ failure
- Thalassemia major: PRBC transfusion dependence with severe complications related to bone marrow expansion and iron overload
- Thalassemia intermedia: In-between thalassemia minor and major; typically with Hgb 7.0 and 11.0 g/dl without transfusion dependence, but may have complications more typical of thalassemia major
- The designation beta+ (β^+) or beta-0 (β^0) is used to describe the severity of the beta-globin gene abnormality when combined with other abnormal Hgb, β^+ indicating a mild abnormality, β^0 a severe abnormality, usually from absent beta-globin gene synthesis. For example, β^0/Hgb S is more severe than β^+/Hgb S disease
- Other variant beta-globin gene abnormalities:
  1. Hemoglobin E, common in Southeast Asia, an abnormal Hgb caused by a Glu → Lys substitution at position 26 of the beta-globin chain. The resulting mRNA is unstable, causing decreased Hgb E production and a picture of beta thalassemia. Homozygous Hgb E is associated with mild anemia and microcytosis, similar to thalassemia minor, and is not usually symptomatic. Hgb E inherited with other beta globin abnormalities (e.g., β^0 thalassemia) may cause clinically significant anemia
  2. Delta-beta-thalassemia (total absence of both delta-globin and beta-globin synthesis)
  3. Lepore hemoglobin (synthesis of small amounts of fused delta-beta-globin and total absence of delta- and beta-globin)
  4. Hereditary persistence of fetal hemoglobin (HPHF) (increased hemoglobin F synthesis and reduced or absence of delta- and beta-globin)

Alpha-thalassemia:

- The alpha globin genes are found on chromosome 16, two on each. Alpha$^+$ refers to a chromosome with one gene missing (most common cause) or dysfunctional. Alpha^0 indicates that two genes are missing (most common) or dysfunctional. The severity of the abnormality depends on the number of deleted genes.
- Silent carrier (one alpha globin gene missing).
- Alpha-thalassemia trait (two alpha-globin genes missing). It is important to know in this situation whether the two genes are on the same or different chromosomes because this has genetic counseling consequences (risk of hydrops fetalis or Hgb H disease).
- Hemoglobin H disease (three alpha-globin genes missing). Hgb H is formed when excess beta-globin chains self-associate—that is, instead of two alpha and two beta-globin chains, the Hgb has four beta-globin chains (β^4). It is unstable and associated with anemia and hemolysis.
- Hydrops fetalis (all alpha-globin genes missing).
- Hemoglobin constant spring (Hgb_{cs}) is a "nondeletional" alpha thalassemia variant, that is, the gene is present but abnormal. Hgb_{cs} is caused by a mutation in the stop codon in the alpha-globin gene; the alpha chain is 31 amino acids longer, but is produced at only 1% of normal. It is common in Southeast Asia.

Thalassemic hemoglobinopathies:

- Hb Terre Haute, Hb Quong Sze, HbE, Hb Knossos

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Beta-thalassemia:

- Heterozygous beta-thalassemia (thalassemia minor): No or mild anemia, microcytosis and hypochromia, mild hemolysis, and splenomegaly
- Homozygous beta-thalassemia (thalassemia major): Intense hemolytic anemia; transfusion dependency; bone deformities (skull and long bones [Figs. E1 to E5]); osteopenia, hepatomegaly; splenomegaly; iron overload leading to cardiomyopathy, diabetes mellitus, and hypogonadism; growth retardation; pigment gallstones; susceptibility to infection, pulmonary hypertension, thrombophilia,

TABLE E1 Clinical Syndromes of Thalassemia

Clinically Asymptomatic

Silent carriers

α^+ thalassemia heterozygotes (some cases)

Rare forms of β-thalassemia heterozygosity

Thalassemia Minor (Low MCH and MCV, with or without Mild Anemia)

α^+ thalassemia heterozygotes (some cases)

α^0 thalassemia heterozygotes

α^+ thalassemia homozygotes

β^0 thalassemia trait

β^+ thalassemia trait

Some cases of hemoglobin E/β-thalassemia

Thalassemia Intermedia (Transfusion Independent)*

Some β^+/β^+ thalassemia homozygotes and compound heterozygotes

Interaction of β^0/β^0, β^0/β^+, or β^+/β^+ with αthalassemia

Interaction of β^0/β or β^+/β with triple α

Hemoglobin H disease

α^0/hemoglobin Constant Spring thalassemia

$\beta^0/\delta\beta$ or $\beta^+/\delta\beta$ thalassemia compound heterozygotes

$\delta\beta/\delta\beta$-thalassemia

Some cases of hemoglobin E/β-thalassemia and hemoglobin Lepore/β-thalassemia

Rare cases of heterozygotes for β-thalassemia mutation, particularly involving exon 3 ("dominant β-thalassemia")

Thalassemia Major (Transfusion Dependent)

β^0/β^0 thalassemia

β^+/β^+ thalassemia

β^0/β^+ thalassemia

Some cases of β^0/hemoglobin Lepore and β^+/hemoglobin Lepore thalassemia

Some cases of β^0/hemoglobin E and β^+/hemoglobin E thalassemia

MCH, Mean cell hemoglobin; *MCV,* mean cell volume.
*β-thalassemia intermedia is defined as a symptomatic condition in which regular transfusion is not essential to maintain life; however, some patients have a poor quality of life and may benefit from transfusion as their condition progresses (e.g., when there is increasing splenomegaly).
From Bain BJ et al: *Dacie and Lewis practical haematology,* ed 12, Philadelphia, 2017, Elsevier.

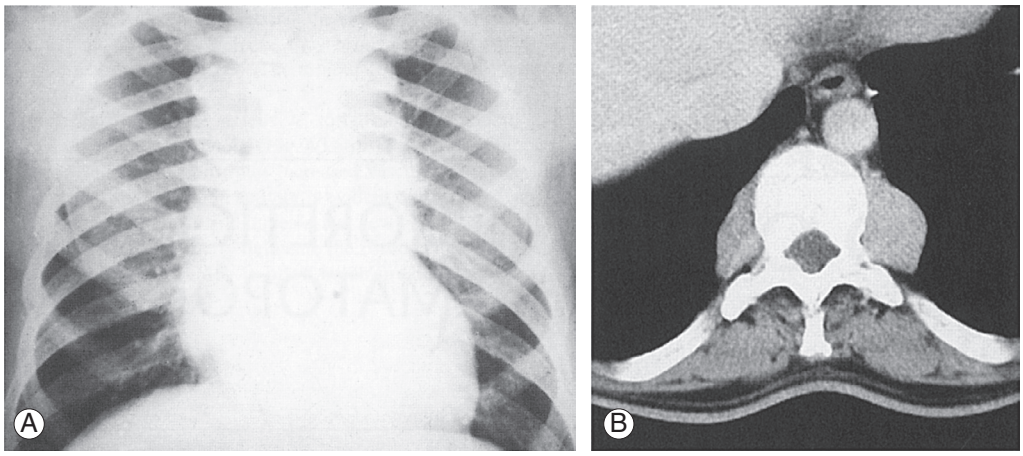

FIG. E1 Thalassemia. A, Lobulated soft tissue masses due to extramedullary hematopoiesis are present adjacent to the thoracic spine. **B,** In another patient, paravertebral extramedullary hematopoietic tissue is shown in the lower sections of a computed tomography examination of the thorax. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

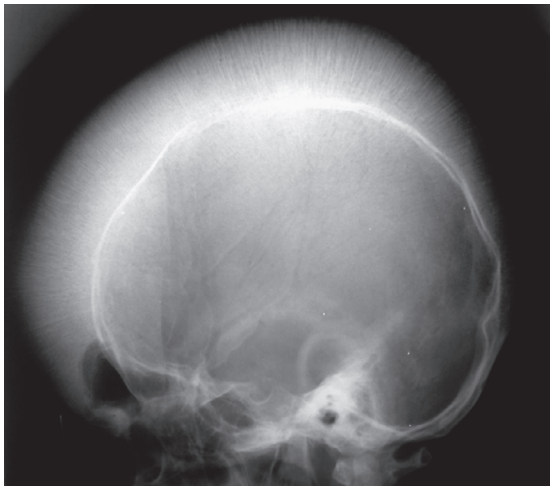

FIG. E2 Thalassemia. Lateral SXR (skull x-ray) showing gross expansion of the diploë and loss of definition of the outer table with sparing of the occipital bone. A gross "hair-on-end" appearance is shown. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

FIG. E3 Thalassemia. Sagittal T1-weighted image of the ankle showing diffuse reduction of marrow signal intensity due to reconversion. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

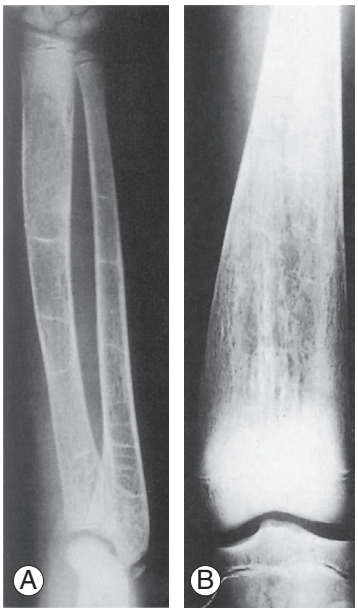

FIG. E4 Thalassemia. A, Considerable bone expansion, cortical thinning, and simplification of the trabecular pattern. **B,** Considerable marrow expansion has produced a flask shape of the distal femur. The coarsened trabecular pattern and cortical thinning are obvious. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

FIG. E5 Thalassemia (boy aged 7). Gross marrow hyperplasia has expanded and thinned overlying cortical bone. Medullary trabeculae have been destroyed, and the residual ones are coarsened. Inset: Early changes of the same type in a finger of a child aged 4 yr. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

hematopoietic "pseudotumors" (areas of hematopoiesis outside the marrow that may cause morbidity such as nerve compression)
- Thalassemia intermedia is a spectrum of disorder of resembling thalassemia major but manageable without transfusion therapy

Alpha-thalassemia:
- Silent carrier: No symptoms, often low normal MCV
- Alpha-thalassemia trait: Mild microcytic anemia, no symptoms
- Hemoglobin H disease: Moderately severe hemolysis with microcytosis and splenomegaly
- The loss of all four alpha-globin genes is incompatible with life (stillbirth of hydropic fetus). NOTE: Pregnancies with hydrops fetalis are associated with a high incidence of toxemia

ETIOLOGY

- Beta-thalassemia: It is caused by more than 200 point mutations and, rarely, by deletions. Many of these mutations decrease the amount of beta-globin produced to varying degrees, accounting for the spectrum of disease. The reduction of beta-globin synthesis results in excess, unbound alpha-globin chains that are cytotoxic and cause intramedullary hemolysis and ineffective erythropoiesis. The pathophysiology of beta-thalassemia is illustrated in Fig. E6. Hgb A_2 and fetal hemoglobin (Hgb F) may be increased.
- Alpha-thalassemia: Duplication of the α-globin chain on chromosome 16 results in 4α-globin genes ($\alpha\alpha/\alpha\alpha$); α-thalassemia results from

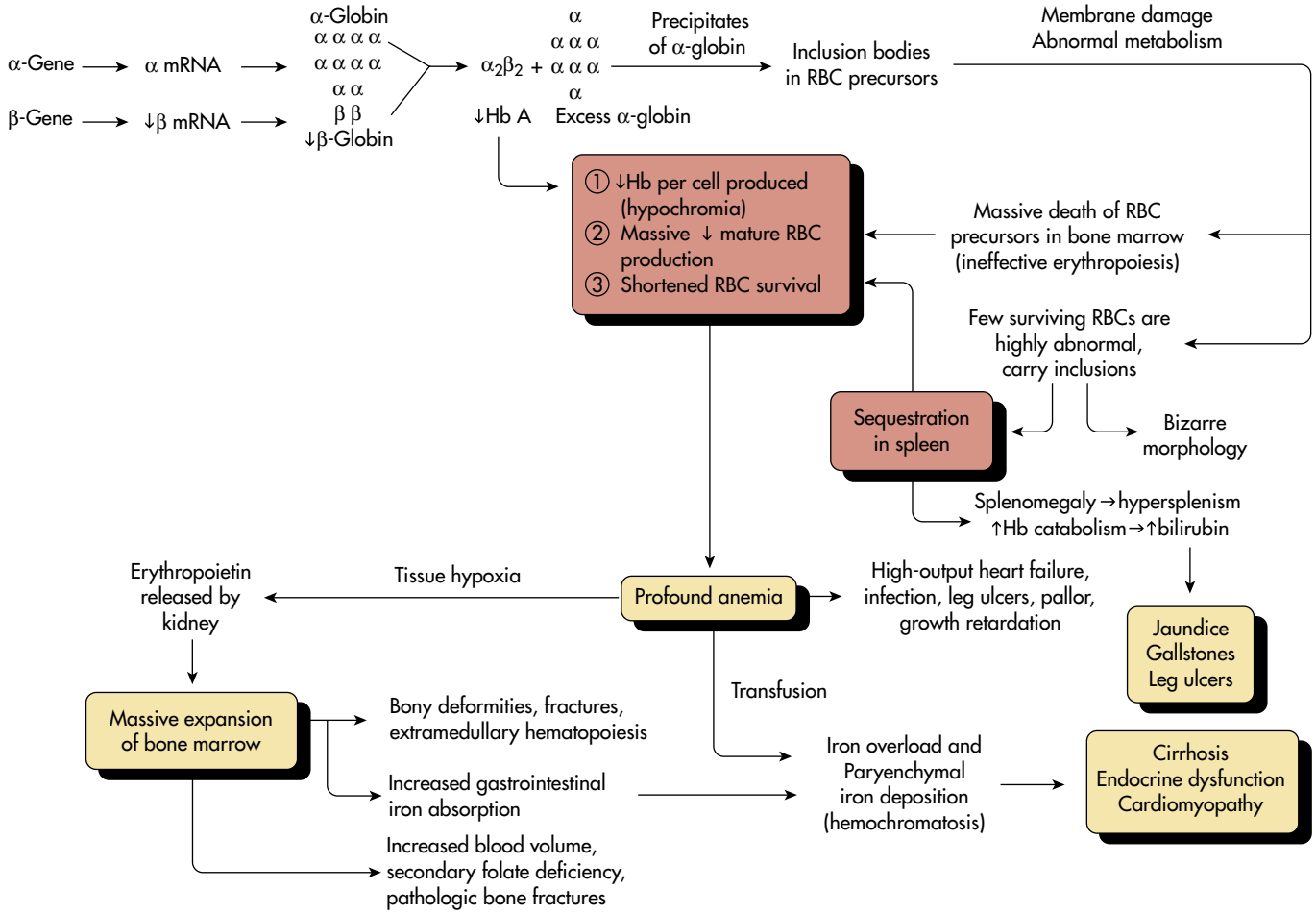

FIG. E6 Pathophysiology of severe forms of β-thalassemia. The diagram outlines the pathogenesis of clinical abnormalities resulting from the primary defect in β-globin chain synthesis. *Hb,* Hemoglobin; *RBC,* red blood cell. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

deletion or dysfunction (usually deletion) of one or more of these. Excess beta-globin chains may self-associate to form Hgb H (β^4), which is unstable and causes chronic hemolytic anemia.

Dx DIAGNOSIS

LABORATORY TESTS (TABLE E2, FIG. E7)

Beta-thalassemia:

- Microcytosis (mean cell volume: 55-80 fL)
- Mild anemia (Hgb <13.0 g/dl) with normal absolute RBC number
- Normal red blood cell (RBC) distribution width index (RDW)
- Smear (Fig. E8): Nucleated RBCs, target cells, anisocytosis, poikilocytosis, polychromatophilia, Pappenheimer and Howell-Jolly bodies
- Hemoglobin electrophoresis: Variable increase in hemoglobin A_2 and possibly increased Hemoglobin F
- Hemolysis: Elevated indirect bilirubin and lactate dehydrogenase, decreased haptoglobin

Alpha-thalassemia:

- Microcytosis without iron deficiency
- Hemoglobin electrophoresis normal (though Hgb H seen in hemoglobin H disease)
- Alpha-globin chain analysis may be performed at a reference laboratory and may be important for genetic counseling purposes, especially with alpha thalassemia trait

Rx TREATMENT

- Thalassemia minor: No treatment, but avoid iron administration for incorrect diagnosis of iron deficiency.
- Beta-thalassemia major (and hemoglobin H disease):
  1. PRBC transfusion therapy: Standard guidelines are available (Tables E3, E4, E5). For patients requiring transfusions for symptoms or to suppress complications, maintaining the pretransfusion hemoglobin level at 9 to 10.5 g/dl is typically recommended, with some patients (heart disease or other complications) benefiting from a target of 11 to 12 g/dl. To minimize the risk of complications, extended phenotyping of RBC is used for matching RBC in regularly transfused patients. RBCs are leukoreduced.
  2. Chelation therapy: Iron overload (transfusion hemosiderosis) is the major cause of late morbidity and mortality in patients with transfusion-dependent thalassemia. Serum ferritin <1000 ng/ml is associated with minimal risk of organ injury. MRI is used to assess hepatic and cardiac iron overload. Three iron chelators are available:
     a. Deferasirox (oral, first line in the U.S.), 20 to 40 mg/kg/day (transfusion dependent), 5 to 20 mg/kg/day (nontransfusion dependent).
     b. Deferoxamine (intravenous/subcutaneous) 75 to 100 mg/kg over 8 to 12 h 5 days/wk.
     c. Deferiprone (oral) 75 to 100 mg/kg/day.
  3. Splenectomy can decrease or eliminate transfusion requirement in thalassemia intermedia and for symptoms of enlarged spleen. Splenectomy increases infections, thrombotic complications, and pulmonary hypertension in thalassemia.
  4. Hematopoietic stem cell transplantation (HSCT): Allogenic transplantation should be considered in patients with severe disease before the onset of end-organ damage. Although HSCT is the only curative approach available, it has been limited by the high cost and scarcity of

TABLE E2 Laboratory Findings in Thalassemia

Phenotype	Genotype	Usual MCV	Usual MCH	Hemoglobin A_2	Hemoglobin H Inclusions
α thalassemia					
α^+ thalassemia heterozygosity	$-\alpha/\alpha\ \alpha$	N	N	N or ↓	–
α^+ thalassemia homozygosity	$-\alpha/-\alpha$	N or ↓	N or ↓	N or ↓	±
α^0 thalassemia heterozygosity	$--/\alpha\ \alpha$	↓	↓	N or ↓	+
Hemoglobin H disease					
Mild or moderate	$--/-\alpha$	↓	↓	N or ↓	+++
Severe	$--/\alpha^T\ \alpha$	↓	↓	N or ↓	+++
Hemoglobin Bart hydrops fetalis (α thalassemia major) α^0 homozygosity	$--/--$	↓	↓	–	–
β thalassemia					
β thalassemia trait	β^0/β or β^+/β	↓	↓	↑	–
β thalassemia trait with normal Hb A_2	β^+/β	↓	↓	N	–
δβ thalassemia trait	$\delta\beta^0/\beta$	↓	↓	N or ↓	–
Hb Lepore trait	$\delta\beta^{Lepore}/\beta$	↓	↓	N or ↓	–
β thalassemia intermedia	Heterogeneous	↓	↓	↑ or N	–
β thalassemia major	β^0/β^0, β^0/β^+, β^+/β^+	↓	↓	↑ or N	

MCH, Mean cell hemoglobin; *MCV,* mean cell volume; *N,* normal.
Bain BJ et al: *Dacie and Lewis practical haematology,* ed 12, Philadelphia, 2017, Elsevier.

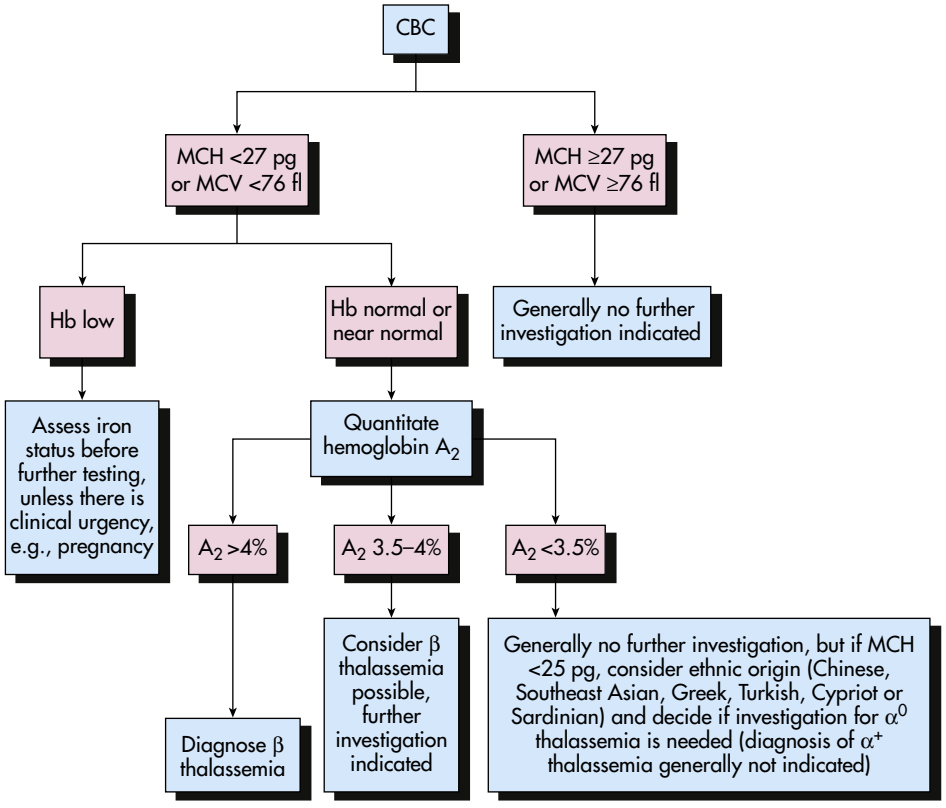

FIG. E7 Suggested scheme of investigation for thalassemia. (From Bain BJ et al: *Dacie and Lewis practical haematology,* ed 12, Philadelphia, 2017, Elsevier.)

human leukocyte antigen (HLA)-matched donors and carries a 5% to 10% transplant related mortality risk. Before transplantation, it is necessary to administer myeloablative regimens to eradicate the endogenous thalassemic bone marrow. Alternative donors (HLA-matched unrelated donor, unrelated cord blood, HLA-haploidentical relative) have been increasingly explored, translating into the expansion of the number of patients treatable with HSCT.

5. Exciting results have been obtained in early studies in 22 transfusion-dependent β-thalassemia patients with gene therapy. Autologous cells were transduced ex vivo with LentiGlobin BB305 vector, which encodes adult hemoglobin (HbA); the cells

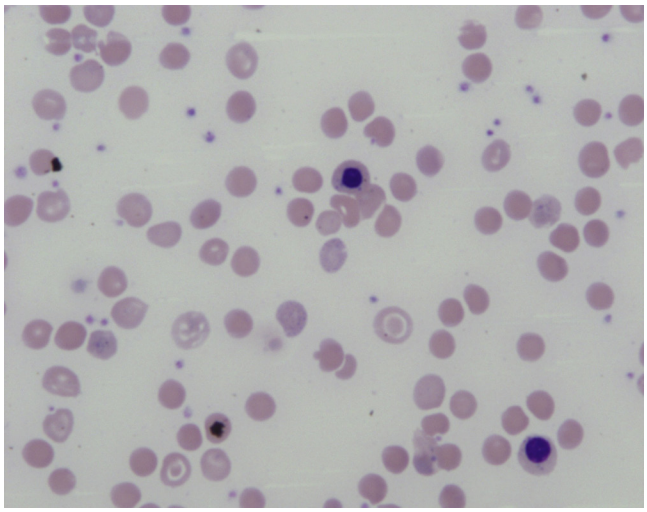

FIG. E8 Morphologic appearance of the peripheral blood film in a case of severe β-thalassemia. Note the bizarre cells, hypochromia, nucleated red blood cells, target cells, and polychromasia. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

were then reinfused after the patients had undergone myeloablative busulfan conditioning. This procedure reduced or eliminated the need for long-term red-cell transfusions in all patients with severe β-thalassemia without serious adverse events related to the drug product.

6. This product, named Zynteglo, has gained conditional market approval from the European Commission to treat transfusion-dependent β-thalassemia in patients >12 yr who have no other treatment options.
7. Members of the transforming growth factor β superfamily of ligands, including growth differentiation factors and activins, have been shown to act as inhibitors of late-stage erythropoiesis. Luspatercept is a novel recombinant fusion protein that acts as a trap for the transforming growth factor β superfamily of ligands. It was recently approved for treatment of anemia in adult patients with beta-thalassemia who require regular red blood cell transfusions.
8. Organ-specific toxicity should be managed with standard agents and protocols—for example, bisphosphonates for osteopenia and sildenafil citrate for pulmonary hypertension. Hematopoietic pseudotumors are managed with radiation, surgery, and transfusion.

PEARLS & CONSIDERATIONS

- Polymerase chain reaction can be used to detect point mutations or deletions in chorionic villous samples, enabling first-trimester, DNA-based testing for thalassemia.
- Genetic counseling is recommended for patients with thalassemia considering starting a family.

TABLE E3 Indications to Initiate Regular Transfusion Therapy in Nontransfusion-dependent Thalassemia

- Declining hemoglobin with enlargement of the spleen
- Growth failure
- Poor school performance
- Pregnancy
- Surgery
- Decreased exercise tolerance
- Failure of secondary sexual development
- Bony changes
- Frequent hemolytic crisis (hemoglobin H disease)
- Poor quality of life
- Primary prevention and management of the following:
  - Thrombotic or cerebrovascular disease
  - Pulmonary hypertension/heart failure
  - Extramedullary hematopoiesis
  - Leg ulcers

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Ritesh Rathore, MD**

TABLE E4 Nontransfusion-dependent Thalassemia Screening Recommendations

Test Name	Measurement	Frequency
MRI with T2 liver iron content	Liver iron	Every 1-2 yr
MRI with T2 cardiac iron content*	Cardiac iron	Every 1-2 yr
Ferritin	Total body iron	Every 3 mo
History and physical exam	General health, medication compliance	Every 3-4 mo
Echocardiogram	Pulmonary hypertension TRV	Every 1-2 yr
Liver function panel	Liver failure, hepatitis	Every 3 mo
Liver ultrasound (if LIC >5/ferritin >800)	Cirrhosis	Annually
AFP (if >40 or presence of clinical cirrhosis)	Hepatocellular carcinoma	Annually
Hepatitis B, C serologies (if receiving blood transfusions)	Hepatitis B and C viral infection/exposure	Annually
Tanner stage/sexual development evaluation	Sexual development	Annually
Standing and sitting height	Growth and development	Every 6 mo
Free T4, TSH	Thyroid function	Annually
Calcium, phosphate, vitamin D	Parathyroid function	Annually
Fasting blood sugar/oral glucose tolerance test	Diabetes mellitus screening	Annually
ACTH test	Adrenal insufficiency	Annually
DEXA	Bone mineral density	Annually

ACTH, Adrenocorticotropic hormone; *AFP,* α-fetoprotein; *DEXA,* dual-energy x-ray absorptiometry; *LIC,* liver iron concentration; *MRI,* magnetic resonance imaging; *TRV,* tricuspid regurgitant velocity; *TSH,* thyroid stimulating hormone.

*Cannot be widely recommended because no correlation with LIC.

TABLE E5 Transfusion-dependent Thalassemia Screening Recommendations

MRI with T2* liver iron content	Liver iron	Every 1-2 yr
MRI with T2* cardiac iron content	Cardiac iron	Every 1-2 yr
Ferritin	Total body iron	Every 3 mo
History and physical exam	General health, medication compliance	Every 3-4 mo
Echocardiogram	Pulmonary hypertension TRV	Every 1-2 yr
Liver function panel	Liver failure, hepatitis	Every 3 mo
Liver ultrasound (if LIC >5/ferritin >800)	Cirrhosis screening	Annually
AFP (if >40 or presence of clinical cirrhosis)	Hepatocellular carcinoma screening	Annually
Hepatitis B, C serologies (if receiving blood transfusions)	Hepatitis B and C viral infection/exposure	Annually
Tanner stage/sexual development evaluation	Sexual development	Annually
Standing and sitting height	Growth and development	Every 6 mo
Free T4, TSH	Thyroid function	Annually
Calcium, phosphate, vitamin D	Parathyroid function	Annually
Fasting blood sugar/oral glucose tolerance test	Diabetes mellitus screening	Annually
ACTH test	Adrenal insufficiency screening	Annually
DEXA	Bone mineral density	Annually
NTX, CTX, AP	Bone mineral density	Annually
Dental evaluation	Maxillofacial disease, periodontal disease, caries	6-12 mo

ACTH, Adrenocorticotropic hormone; *AFP,* α-fetoprotein; *AP,* alkaline phosphatase; *CTX,* collagen type 1 cross-linked C-telopeptide; *DEXA,* dual-energy x-ray absorptiometry; *LIC,* liver iron concentration; *MRI,* magnetic resonance imaging; *NTX,* N-terminal telopeptide; *TRV,* tricuspid regurgitant velocity; *TSH,* thyroid stimulating hormone.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

SUGGESTED READINGS

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Thoracic Outlet Syndrome PTG ALG

BASIC INFORMATION

DEFINITION

Thoracic outlet syndrome (TOS) describes a condition producing upper extremity symptoms believed to result from neurovascular compression at the thoracic outlet (Fig. E1, Table 1). Three types are described on the basis of point of compression: (1) cervical rib and scalenus syndrome, in which abnormal scalene muscles or the presence of a cervical rib may cause compression; (2) costoclavicular syndrome, in which compression may occur under the clavicle; and (3) hyperabduction syndrome, in which compression may occur in the subcoracoid area. The compression occurs in three anatomical structures: arteries, veins, and nerves. TOS usually is caused by a combination of two factors: (1) having abnormal anatomy that creates compression in the thoracic outlet, (2) having some injury at the thoracic outlet.

- Neurogenic TOS: Caused by compression of brachial nerve plexus
- Arterial TOS: Caused by subclavian artery compression
- Venous TOS: Caused by compression of subclavian vein

SYNONYM

TOS

ICD-10CM CODE
G54.0 Brachial plexus disorders

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: TOS is an uncommon disorder. Varies from source to source; presence of cervical ribs in 0.5% to 1% of population (50% bilateral), but most are asymptomatic. Approximately 90% of all TOS disorders are neurogenic, and the remaining 10% are arterial or venous.
PREDOMINANT SEX: Females affected more often than males (ratio of 3.5:1)
PREDOMINANT AGE: Rare in those aged <20 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms and signs are related to the degree of involvement of each of the various structures at the level of the first rib.
- True venous or arterial involvement is not common.
- Diagnosis is most often used in the consideration of neural pain affecting the arm, which suggests involvement of the brachial plexus.
  1. Arterial compression: Pallor, paresthesias, diminished pulses, coolness, Raynaud phenomenon, digital gangrene, supraclavicular bruit or mass, and stroke
  2. Venous compression: Edema and pain, thrombosis causing superficial venous dilation in the shoulder area
  3. Neurologic compression: Pain and/or paresthesia of neck, shoulder region, arm or hand, depending on the root involved with difficulty; intrinsic weakness and diminished sensation on examination
  4. Possible supraclavicular tenderness
  5. Provocative tests (Adson (Fig. E2), Wright): May reproduce pain but are of disputed usefulness

ETIOLOGY

- Congenital cervical rib or fibrous extension of cervical rib
- Abnormal scalene muscle insertion
- Drooping of shoulder girdle from generalized hypotonia or trauma
- Narrowed costoclavicular interval as a result of downward and backward pressure on shoulder (sometimes seen in individuals who carry heavy backpacks), poor posturing, pregnancy
- Acute venous thrombosis with exercise (effort thrombosis)
- Bony abnormalities of first rib
- Abnormal fibromuscular bands
- Malunion of clavicle fracture

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Carpal tunnel syndrome
- Cervical radiculopathy
- Brachial neuritis
- Ulnar nerve compression (cubital tunnel syndrome)
- Complex regional pain syndrome
- Superior sulcus tumor

WORKUP

Fig. 3 describes a diagnostic algorithm for thoracic outlet syndrome. Preliminary criteria for the clinical diagnosis of neurogenic thoracic outlet syndrome are summarized in Table 2. Except for venous or arterial pathology, no ancillary diagnostic tests are reliable for diagnostic confirmation.

IMAGING STUDIES

- Electromyography, nerve conduction velocity studies to rule out carpal tunnel syndrome, cervical radiculopathy
- Ultrasound for initial evaluation for arterial or venous thoracic outlet syndrome
- Cervical spine radiographs to rule out cervical disk disease
- Chest radiograph to rule out lung tumor
- Computed tomography (CT) for detailed anatomical relationship of vascular structure to surrounding muscles and bones
- Contrast-enhanced magnetic angiography can be very useful in assessing vessel imaging while using provocative arm positions
- Arteriography or venography (Fig. E4) can be used for dynamic studies while performing upper extremity maneuvers and also performing thrombolysis, if needed

TREATMENT

ACUTE GENERAL Rx

- Sling for pain relief
- Physical therapy modalities plus shoulder girdle–strengthening exercises
- Postural reeducation
- Nonsteroidal antiinflammatory drugs
- Muscle relaxants

CHRONIC Rx

Surgical treatment is indicated:

- After failure of physical therapy
- With complications such as thrombosis, aneurysms
- With neurologic compressions
- With sympathetic cervical rib

Surgical options:

- Thoracic outlet decompression
- Cervical rib resection
- Thoracic sympathetectomy
- Vascular repair
- Catheter-directed thrombolysis

TABLE 1 Sites and Structures Compressed in Thoracic Outlet Syndrome

Site	Description	Abnormalities	Structures Compressed
Sternal-costovertebral circle	This aperture can be narrowed by bony variations	• Cervical first rib • First rib • Long transverse process	• Subclavian artery • Subclavian vein • Brachial plexus
Scalene muscle triangle	The scalenus anterior and middle muscle insert on the first rib, creating a tunnel	Scalenus anterior and middle	• Subclavian artery • Brachial plexus
First rib, clavicular space	The neurovascular structures lie above the rib and below the clavicle	• Costoclavicular ligament • Clavicle • First rib	• Subclavian vein • Subclavian artery • Brachial plexus
Behind the pectoralis minor muscle	The neurovascular structures travel to and from the arm behind this muscle	• Pectoralis minor • Costocoracoid ligament	• Subclavian vein • Subclavian artery • Brachial plexus

From Sellke FW et al: *Sabiston & Spencer surgery of the chest*, ed 9, Philadelphia, 2016, Elsevier.

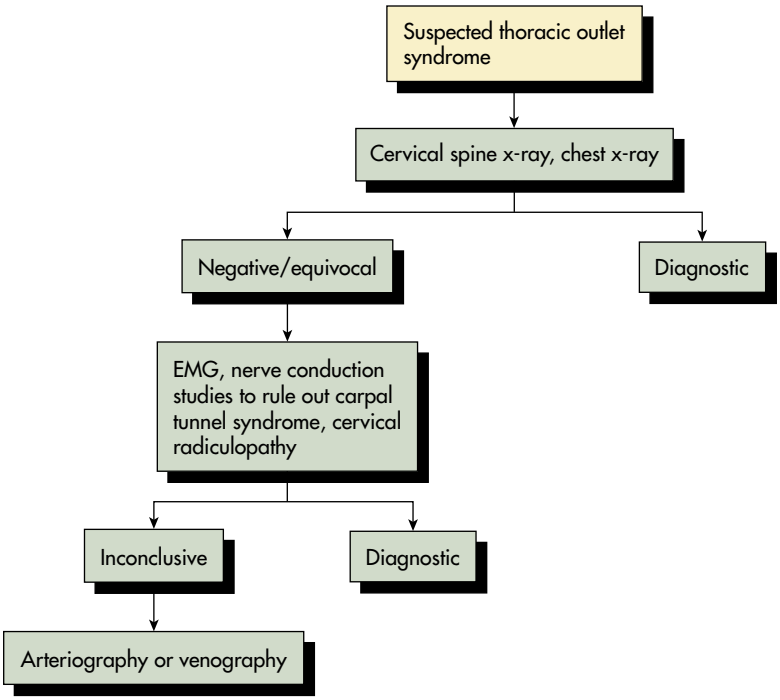

FIG. 3 Thoracic outlet syndrome. *EMG,* Electromyogram.

TABLE 2 Preliminary Criteria for the Clinical Diagnosis of Neurogenic Thoracic Outlet Syndrome

Unilateral or bilateral upper extremity symptoms that:
(1) Extend beyond the distribution of a single cervical nerve root or peripheral nerve
(2) Have been present for at least 12 wk
(3) Have not been explained satisfactorily by another condition
(4) Meet at least one criterion in at least four of the following five categories:

1. Principal symptoms	1A. Pain in the neck, upper back, shoulder, arm, or hand
	1B. Numbness; paresthesias; or weakness in the arm, hand, or digits
2. Symptom characteristics	2A. Pain, paresthesias, or weakness exacerbated with elevated arm positions
	2B. Pain, paresthesias, or weakness exacerbated by prolonged or repetitive arm or hand use or by prolonged work on a keyboard or other repetitive strain
	2C. Pain or paresthesias radiate down the arm from the supraclavicular or infraclavicular space
3. Clinical history	3A. Symptoms began after occupational, recreational, or accidental injury of the head, neck, or upper extremity, including repetitive upper extremity strain or overuse activity
	3B. Previous clavicle or first rib fracture or known cervical rib(s)
	3C. Previous cervical spine or peripheral nerve surgery without sustained improvement
	3D. Previous conservative or surgical treatment for thoracic outlet syndrome
4. Physical examination	4A. Local tenderness on palpation over scalene triangle or subcoracoid space
	4B. Arm, hand, or digit paresthesias on palpation over scalene triangle or subcoracoid space
	4C. Weak handgrip, intrinsic muscles, or digit 5 or thenar or hypothenar atrophy
5. Provocative maneuvers	5A. Positive upper limb tension test (ULTT)
	5B. Positive 1- or 3-min elevated arm stress test (EAST)

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

DISPOSITION

- Nonsurgical treatment: Often successful for patients with pain as the primary symptom
- Complications of surgical treatment include transient dysesthesia, venous injury, arterial injuries, or brachial plexus injuries.

REFERRAL

For vascular surgery consultation when venous or arterial impairment is present

PEARLS & CONSIDERATIONS

COMMENTS

- True thoracic outlet syndrome is probably an uncommon condition.
- Diagnosis is often used to describe a wide variety of clinical symptoms.
- Considerable disagreement exists regarding the frequency of this disorder.

RELATED CONTENT

Thoracic Outlet Syndrome (Patient Information)

AUTHOR: **Hisashi Tsukada, MD, PhD**

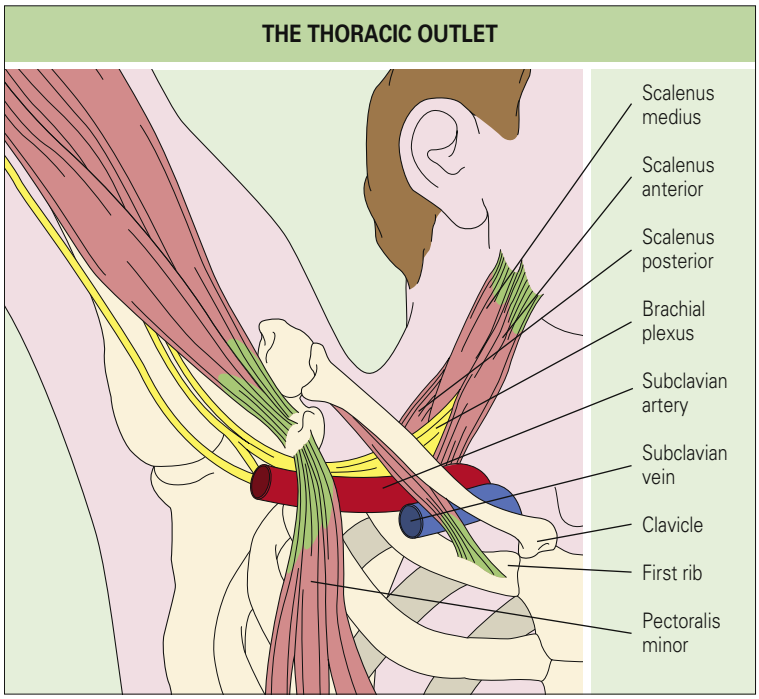

FIG. E1 The three narrow channels of the thoracic outlet include the scalene triangle, the costoclavicular passage, and the pectoralis minor attachment at the coracoid process. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

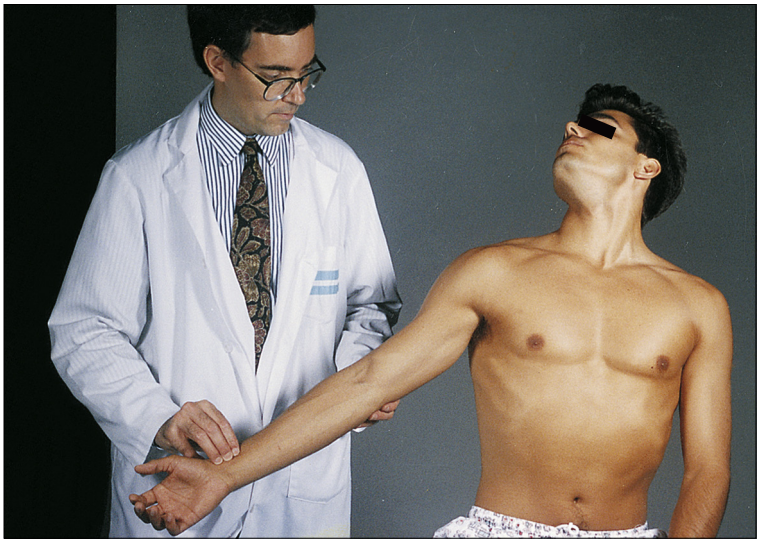

FIG. E2 The Adson maneuver. The patient inhales deeply, extends the neck fully, and turns the head to the side being examined. This tests for compression in the scalene triangle; the test result is positive if the radial pulse diminishes and the patient's symptoms are reproduced. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

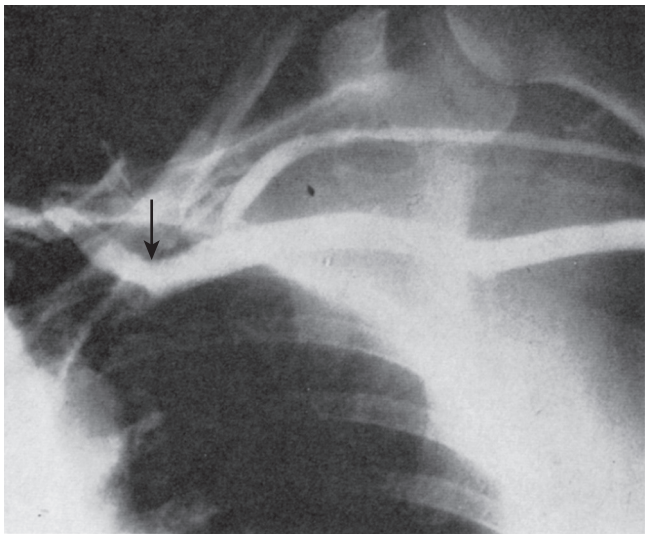

FIG. E4 Phlebogram showing total occlusion *(arrow)* with minimal collateral circulation of the left subclavian vein resulting from thoracic outlet compression. At operation, no thrombus was present in the vein, and obstruction was relieved by removing the first rib. (From Sellke FW et al: *Sabiston & Spencer surgery of the chest,* ed 9, Philadelphia, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Thromboangiitis obliterans (TAO), also known as Buerger disease, is an uncommon, segmental nonatherosclerotic, inflammatory vascular disease that most commonly affects small- and medium-sized arteries, veins, and nerves of the extremities. It is strongly associated with tobacco use and is characterized by the segmental presence of highly cellular and inflammatory thrombotic occlusions with relative sparing of the vascular wall. In contrast to other forms of vasculitis, TAO does not involve disruption of the intima or the media.

SYNONYMS

Buerger disease
TAO
Presenile gangrene

ICD-10CM CODE
I73.1 Thromboangiitis obliterans (Buerger's disease)

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Although TAO has been observed worldwide, it is most prevalent in the Mediterranean, Asia, the Middle East, and Eastern Europe, where the rate of tobacco use is higher. Overall prevalence is declining.

- In the U.S., the prevalence is 12.6 in 100,000.
- Among patients with peripheral artery disease, the prevalence of TAO has been reported to range as low as 0.5% to 5.6% in Western Europe to as high as 45% to 63% in India and 16% to 66% in Korea and Japan, although there are reports of changing demography including an increase in the number of non-Asians affected.

PREDOMINANT SEX AND AGE: TAO affects predominantly males (70% to 91%), typically between the ages of 25 and 45, with one report suggesting a median age at diagnosis of 38.5. However, recent studies suggest an increasing incidence among women (11% to 23%), likely reflecting increasing use of cigarettes among women.

RISK FACTORS:

- Tobacco use
- Male sex
- Asian ethnicity
- Chronic periodontal infections have been linked; however, a causative association has not been firmly established

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typical presentation: Asian males between 25 and 45 with a strong history of tobacco use.
- Signs of digital ischemia on physical exam:
  1. Prolonged capillary refill with dependent rubor
  2. Absent or diminished distal pulses
  3. Digital skin discoloration/cyanosis, Raynaud phenomenon
  4. Digital ulcerations
  5. Gangrene
  6. Superficial thrombophlebitis in a migratory pattern of tender nodules (helps distinguish TAO from other vasculitis)
- Common symptoms:
  1. Rest pain
  2. Paresthesias
  3. Claudication with involvement of proximal arteries including that of the foot, arch, or calf
- The predominance of distal limb involvement helps distinguish TAO from peripheral artery disease. One case series reported 46% of TAO patients with only lower-extremity ulcers, 28% with only upper-extremity ulcers, and 25% with involvement of both upper and lower extremities.
- On rare occasions, it has been reported that with advancement of disease, the proximal arteries can become involved, and more dramatic presentations can develop involving the visceral, cerebral, renal, ocular, and coronary arteries, including case reports of coronary artery dissection, acute kidney injury, papillophlebitis.

ETIOLOGY

- The etiology of TAO remains unclear; however, a multifactorial mechanism has been proposed that involves a combination of genetic susceptibility, tobacco exposure, prothrombotic factors, and autoimmune response.
- Impaired endothelium-dependent vasorelaxation in the peripheral vasculature of patients has been noted.
- There is a growing body of evidence to suggest that alterations in the autoimmune response play a role in disease progression. Cell-mediated sensitivity to types I and III collagen are detected with increased frequency in patients with thromboangiitis obliterans. The immunology of TAO is complex, with multiple pathways implicated. It is a matter of current study.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Atherosclerosis
- Acquired or inherited hypercoagulability
- Thromboembolic disease
- Vasculitides including polyarteritis nodosa
- Autoimmune and connective tissue diseases, i.e., SLE, CREST, and scleroderma
- Diabetic angiopathy
- Acrocyanosis
- Traumatic arterial thrombosis
- Occupational (chronic vibration syndrome, hypothenar hammer syndrome)
- Ergotamine, lead, or drug poisoning
- Disseminated intravascular coagulation
- Marijuana-associated peripheral arteriopathy (subject of a case report)

WORKUP

Diagnostic evaluation for thromboangiitis obliterans is summarized in Table E1. There are no universally accepted diagnostic criteria, but several have been proposed over the yrs by Papa, Mills, Olin, and Shionoya. Biopsy would provide a definitive diagnosis but is rarely needed, and a clinical diagnosis can be established in patients who meet the following criteria:

- History of smoking or tobacco use
- Onset before the age of 50 yr
- Evidence of distal extremity ischemia
- Typical angiographic findings of TAO (sensitive but not specific)
- Absence of atherosclerotic risk factors other than smoking

LABORATORY TESTS

- There are no specific tests to diagnose TAO. The primary goal of laboratory testing is to exclude alternative diagnoses. The following labs are usually normal or negative in patients with TAO and should be obtained:
  1. Inflammatory markers: ESR and CRP
  2. Autoimmune panel: ANA, RF, anti-centromere and anti-SCL70
  3. Hypercoagulability workup: Lupus anticoagulant, anticardiolipin antibody, proteins C and S, antithrombin III, prothrombin gene mutation, and factor V Leiden
  4. Toxicology screen: Cocaine, amphetamine, cannabis
  5. Complete blood count and metabolic panel
- If there is clinical suspicion for the disease but the patient denies use of tobacco, a urine

TABLE E1 Diagnostic Evaluation for Thromboangiitis Obliterans

Clinical	Laboratory	Imaging and Physiologic Testing
Digit ulcers	Complete blood cell count	Echocardiography
Gangrene	Liver function tests	Arteriography
Venous nodules or cords	Serum creatinine	Segmental pressures
Sensory deficits	Fasting blood glucose	Arterial waveform analysis
Allen test	Sedimentation rate	
Ankle-brachial index	Antinuclear antibody	
	Rheumatoid factor	
	Complement	
	CREST serology	
	Scleroderma serology	
	Hypercoagulability	
	Toxicology screen	

CREST, Calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

BOX E1 Angiographic Findings in Thromboangiitis Obliterans (Buerger Disease)

- Involvement of small- and medium-sized vessels; Palmar, plantar, tibial, peroneal, radial, and ulnar arteries; and digital arteries of fingers and toes
- Normal extremity arteries proximal to the popliteal and distal brachial levels
- Absence of proximal atherosclerosis and vascular calcification
- No source of thrombus
- Abrupt transition from a normal, smooth proximal artery to an area of occlusion
- Symmetric and segmental arterial involvement
- Tortuous "corkscrew" collaterals are suggestive, but not pathognomonic, of Buerger disease

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

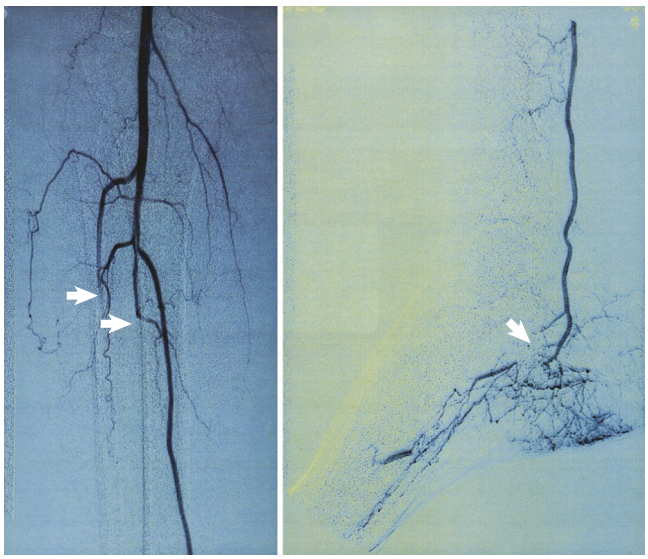

FIG. E1 Angiograms of a young woman with thromboangiitis obliterans. *Left,* Occlusion of anterior tibial and peroneal arteries *(arrows). Right,* Occlusion of distal portion of posterior tibial artery *(arrow)* with bridging collateral vessels. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

cotinine level can be ordered to confirm suspicion of recent smoking.
- Recent data has suggested the utility of a neutrophil/lymphocyte ratio in routine evaluation. Another recent study also associated TAO with elevated homocysteine levels.

NONINVASIVE VASCULAR EVALUATION

- Ankle-brachial index if lower-extremity signs or symptoms, wrist-brachial index for upper-extremity signs or symptoms with digit pressures should be performed.
- Digital plethysmography may demonstrate attenuated, flattened arterial waveforms.
- Allen test.
- Some investigative modalities are laser doppler luometry and laser speckle imaging, which have been suggested as adjuvant imaging modalities to assist with diagnosis.
- These nonspecific tests assess perfusion to distal extremities and do not distinguish TAO from other forms of peripheral vascular disease.

IMAGING STUDIES

- Noninvasive evaluation with computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or duplex ultrasonography can assist.
- Echocardiography may be required to rule out thromboembolic causes.
- Angiography remains the gold standard and may be performed to define the extent of disease, to confirm the diagnosis, and potentially to deliver therapeutic interventions.
- Typical angiography findings in TAO are described in Box E1. Fig. E1 shows an angiogram of a patient with TAO (Martorell Sign: Corkscrew Collaterals, sensitive but not specific for TAO).

PATHOLOGY: Although not necessary, biopsy helps confirm diagnosis and is useful in atypical presentations.
- May show highly cellular thrombus within artery or vein in the acute phase with evidence of organization and recanalization in later stages.
- Segmental obliteration of involved vessels ("skip" lesions) with preservation of the internal elastic membrane of the vessel wall.

Rx TREATMENT

MEDICAL THERAPY

- Box E2 summarizes treatment options for thromboangiitis obliterans. Smoking cessation is the only definitive treatment for TAO. Complete abstinence may halt progression

BOX E2 Treatment Options for Thromboangiitis Obliterans

Tobacco cessation*

Medical
- Prostacyclin and its analogues
- Aspirin
- Selective low-dose intraarterial streptokinase
- Bosentan, a dual endothelin-1 receptor antagonist
- Cyclophosphamide
- Guanethidine sympathetic blocks
- Serotonin blockers
- Sarpogrelate
- Intramuscular injections of vascular endothelial growth factor
- Phosphodiesterase type 5 (PDE5) inhibitors
- Omalizumab

Endovascular Therapies
- Extended angioplasty of each tibial and foot artery obstruction

Surgical Treatment
- Sympathectomy
- Arterial reconstruction
- Omental transfer
- Kirschner wire in medullary canal of tibia

Experimental Therapies
- Intramuscular injection of vascular endothelial growth factor
- Autologous whole bone marrow stem cell transplantation by fenestration
- Immunoadsorption
- Beperminogene perplasmid use

Interventional therapy
- Pneumatic compression has been used to augment perfusion to the lower extremities in patients with severe claudication or critical limb ischemia who are not revascularization candidates.
- Endovascular treatment with extended angioplasty at the tibial and foot arteries remains an option for patients with TAO and critical limb ischemia. This modality has prevented major amputations, with studies reporting a technical success rate of 66.7% to 91%, a limb salvage rate of 92% to 100%, and sustained clinical improvement in 84.2% of patients.
- Surgical revascularization usually is not feasible due to the distal and diffuse nature of the disease. However, bypass may be considered in patients with more proximal disease or suitable distal target vessels.
- Use of a spinal cord stimulator has been shown to improve regional perfusion and symptoms. It relieves pain through several mechanisms, including preventing transmission of painful stimuli through the corresponding dermatomes, stimulating the production of inhibitory neurotransmitters, and inhibiting sympathetic vasoconstriction, which improves peripheral microcirculation.
- Sympathectomy may be considered for patients with refractory pain and digital ischemia (Box E3).

*Only known, proven, established, and effective therapy.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

BOX E3 Treatment Options in Thromboangiitis Obliterans (Buerger Disease)

- Cessation of tobacco products
- Local wound care
- Arterial reconstruction with vein graft
- Prostaglandin analog iloprost or treprostinil sodium
- Cilostazol
- Hyperbaric oxygen therapy
- Calcium channel blockers (e.g., amlodipine or nifedipine for vasospasm)
- Intermittent pneumatic compression pump
- Implantable spinal cord stimulator
- Therapeutic angiogenesis
- Amputation

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

of disease and prevent flares. Use of nicotine replacement should be avoided due to risk of keeping disease active, but use of other smoking-cessation pharmacotherapy (e.g., bupropion or varenicline) is reasonable. The hazards of continued smoking in patients with TAO seem to be independent of factors such as number of cigarettes smoked per day.

- To date, there is no proven standard-of-care pharmacotherapy, and thus therapeutic options have been limited to prostaglandin analogs and vasodilators for palliative treatment.
  1. Iloprost, a prostaglandin analog, has been associated with reduced rest pain and greater healing of ischemic ulcers; however, it is not associated with a reduction in the amputation rate. The oral formulation has been shown to be no more effective than placebo.
  2. Vasodilators (calcium channel blockers, alpha blockers, cilostazol, sildenafil) may be helpful in symptom relief but have not been studied in prospective clinical trials.
  3. Bosentan, an endothelin receptor antagonist most commonly used in pulmonary arterial hypertension, has been used as a non-FDA approved therapy.
- There is no evidence to support the routine use of antiplatelet, anticoagulant, or thrombolytic agents; however, aspirin is routinely administered.
- Daily foot and hand hygiene will prevent ischemic ulcers, as well as avoidance of trauma, vibration, and cold.

OUTCOMES:

- Periods of exacerbation and remission are characteristic of TAO. The disease typically intensifies at the age of 30 to 40 and then abates. Patients aged 60 yr or older rarely have recurrence of symptoms.
- The risk of major amputation was 11% at 5 yr, 21% at 10 yr, and 23% at 20 yr. Risk of amputation was eliminated by 8 yr after smoking cessation. Multiple amputations and progressive disability cause decline in quality of life.
- One long-term followup of 224 patients demonstrated that in a mean of 5.7 yr, vascular events occurred in 58.9% of patients, amputation in 21.4%, and death in 1.4%.
- Patients with TOA are prone to premature atherosclerosis, and thus the incidence of peripheral and coronary atherosclerosis is higher in this patient population.

REFERRAL

Smoking cessation counseling, rheumatology consultation, and vascular surgery consultation are recommended for any young smokers with claudication and ischemic ulcers.

PEARLS & CONSIDERATIONS

- The pathogenesis of the disease is poorly understood, but tobacco use plays a key role.
- A multifactorial mechanism has been proposed that involves a combination of genetic susceptibility, tobacco exposure, prothrombotic factors, and autoimmune response.
- The diagnosis is predominantly clinical, and there are no universally accepted diagnostic criteria. Biopsy can confirm diagnosis but is rarely needed.
- Discontinuation of tobacco use is the only known definitive therapy for TAO.

PATIENT & FAMILY EDUCATION

Patients with TAO must be warned about tobacco use and secondhand passive smoke. Information for patients can be obtained from the following organizations:

- Vascular Disease Foundation (www.vdf.org)
- Mayo Foundation for Medical Education and Research (www.mayoclinic.com)

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Thromboangiitis Obliterans (Buerger Disease) (Patient Information)

AUTHORS: **Leo Ungar, MD,** and **Pranav M. Patel, MD, FACC, FAHA, FSCAI**

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BASIC INFORMATION

DEFINITION

Thrombocytosis is defined by an elevated platelet count (>450,000/ml) in peripheral blood. It is caused by overproduction of platelets (reactive thrombocytosis) or clonal expansion of megakaryocytes (clonal thrombocytosis). Reactive thrombocytosis is driven by excessive cytokines induced by various stimuli, such as trauma or inflammation. Clonal thrombocytosis is defined as chronic myeloproliferative neoplasms (MPNs), of which four subgroups are well characterized: chronic myelogenous leukemia (CML), polycythemia vera (PV), primary myelofibrosis (PMF), and essential thrombocythemia (ET). In addition, platelet count can be spuriously elevated in some conditions (see "Differential Diagnosis"). Extreme thrombocytosis is defined as platelet count >1 million/ml.

SYNONYMS

Thrombocythemia
Essential thrombocythemia
ET

ICD-10CM CODES

D47.3	Essential (hemorrhagic) thrombocythemia
D75.89	Other specified diseases of blood and blood-forming organs
D75.9	Disease of blood and blood-forming organs, unspecified
D77	Other disorders of blood and blood-forming organs in diseases classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

Reactive thrombocytosis is much more frequent than clonal thrombocytosis (70% vs. 22% in one series).

Epidemiology for essential thrombocythemia:
INCIDENCE: 1.2 to 3.0 per 100,000 population/yr
PREVALENCE: Estimated as 24 cases/100,000 population
PREDOMINANT SEX AND AGE: The median age at diagnosis is 58 yr. Female:male ratio is 2:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Regardless of the cause, a high platelet count may be associated with vasomotor symptoms such as headache, visual disturbances, dizziness, atypical chest pain, acral dysesthesia, and erythromelalgia.
- Thrombotic and bleeding complications can occur.
- Symptoms and complications are much more likely to occur in association with clonal thrombocytosis than reactive thrombocytosis.
- The degree of thrombocytosis does not predict the likelihood of clonal thrombocytosis and does not generally correlate to the risk of thrombosis.
- Splenomegaly is common with MPNs.
- Coexistent leukocytosis and erythrocytosis are common with CML and PV.
- Disease transformation from ET to PV, PMF, and acute myeloid leukemia (AML) is uncommon. In patients with ET, the 20-yr rate of leukemic transformation is estimated at 5%.

ETIOLOGY

- Essential thrombocytosis, a myeloproliferative neoplasm, is a clonal disorder of a multipotent hematopoietic progenitor cell.
- Abnormality in JAK2-STAT pathway (including *JAK2, CALR*, and *MPL* gene mutations) may play a role in pathogenesis of MPN.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Spurious thrombocytosis:
  1. Mixed cryoglobulinemia—precipitated cryoglobulin particles are counted as platelets by automatic counters; generally occurs at low temperatures.
  2. Circulating cytoplasmic fragments miscounted as platelets—seen mainly in patients with leukemia, lymphoma, severe hemolysis, or burns
- Reactive thrombocytosis:
  1. Benign hematologic disorders
  2. Acute hemorrhage, iron deficiency anemia, hemolytic anemia
  3. Chronic infection, such as tuberculosis
  4. Acute and chronic inflammatory disorders
  5. Rheumatologic disorders
  6. Inflammatory bowel disease
  7. Celiac disease
  8. Functional and surgical asplenia
  9. Tissue damage
  10. Trauma, thermal burn
  11. Myocardial infarction
  12. Acute pancreatitis
  13. Recent surgery
  14. Renal failure, nephrotic syndrome
  15. Exercise
  16. Medications, such as vincristine, epinephrine
- Clonal thrombocytosis:
  1. CML
  2. PV
  3. PMF
  4. Myelodysplastic syndrome (5q-syndrome)
  5. AML with inv(3), t(3;3)
  6. Essential thrombocytosis (Box 1)

WORKUP

- Comprehensive history and physical examination to exclude many of the common causes of reactive thrombocytosis: History and physical examination suggestive of acute blood loss, iron deficiency, acute or chronic infection/inflammation, medication use, asplenia, malignancy, and trauma should be evaluated. Fig. E1 describes a diagnostic algorithm for thrombocytosis. The diagnosis of ET requires platelet counts >450 × 10^3/ml on two separate occasions >4 weeks apart, absence of Philadelphia chromosome, and exclusion of secondary causes of thrombocytosis.
- Repeat CBC with peripheral blood smear and bone marrow biopsy (Figs. E2 and E3) to exclude spurious thrombocytosis.

LABORATORY TESTS

- CBC with peripheral blood smear: Howell-Jolly bodies and target cells are present in patients with asplenia; nucleated RBC, teardrop RBC and WBC precursors in patients with PMF.
- Serum ferritin level: Low ferritin level suggests iron deficiency.

BOX 1 World Health Organization Diagnostic Criteria for Essential Thrombocythemia

Diagnosis requires that all of the following criteria be met:
- Sustained platelet count ≥450 × 10^9/L*
- Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes; no significant increase or left shift of neutrophil granulopoiesis or erythropoiesis
- Failure to meet the WHO criteria for polycythemia vera,† primary myelofibrosis,‡ BCR-ABL1–positive chronic myelogenous leukemia,§ myelodysplastic syndrome,¶ or other myeloid neoplasms
- Demonstration of *JAK2 V617F* or other clonal marker; or, in the absence of *JAK2 V617F*, no evidence of reactive thrombocytosis¶

WHO, World Health Organization.
*Sustained during the workup process.
†Requires the failure of iron replacement therapy to increase the hemoglobin level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels; red cell mass measurement is not required.
‡Requires the absence of relevant reticulin fibrosis, collagen fibrosis, peripheral blood leukoerythroblastosis, or markedly hypercellular marrow accompanied by megakaryocyte morphology typical for primary myelofibrosis—small to large megakaryocytes with an aberrant nuclear-to-cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering.
§Requires the absence of BCR-ABL1.
¶Requires the absence of dyserythropoiesis and dysgranulopoiesis.
¶Causes of reactive thrombocytosis include iron deficiency, splenectomy, surgery, infection, inflammation, connective tissue disease, metastatic cancer, and lymphoproliferative disorders.
From Swerdlow SH et al (eds): *WHO classification of tumours of haematopoietic and lymphoid tissues,* Lyon, France, 2008, IARC Press.

- Serum C-reactive protein (CRP), ESR, and plasma fibrinogen: Nonspecific markers of infection or inflammation.
- Philadelphia chromosome or BCR-ABL rearrangement: Positive in CML.
- Serum erythropoietin assay: Low to normal in PV and ET.
- *JAK2* mutation analysis: PV and ET; *JAK2* mutation is found in 95% to 99% of patient with PV, in 40% to 60% of patients with PMF, and in about 50% to 55% of patients with ET.
- *MPL* and *CALR* mutation analysis: Frequency is reported as 4% and 15% to 36%, respectively, in ET:
  1. These mutations are associated with differences in prognosis and risk of thrombosis.
  2. *JAK2, CALR,* and *MPL* mutations are mutually exclusive. They are not confined to a particular myeloproliferative neoplasm, and their absence does not exclude any of the MPNs.
  3. About 17% of patients with ET will be negative for *JAK2, CALR,* and *MPL* mutations.
- Bone marrow chromosome analysis: 5q- syndrome and other myelodysplastic syndrome, CML.
- Bone marrow exam in ET may show clusters of abnormal megakaryocytes and increased reticulin fibrosis (see Fig. E3).

Rx TREATMENT

No therapies are known to alter survival or leukemic transformation in ET. Reactive thrombocytosis has been rarely associated with thrombosis or bleeding and generally does not require specific therapy.

ACUTE GENERAL Rx

- Vasomotor symptoms easily manageable with low-dose aspirin (<100 mg/day).
- Bleeding:
  1. Discontinue any platelet antiaggregating agent, such as aspirin or nonsteroidal antiinflammatory agents.
  2. Evaluate for disseminated intravascular coagulopathy and coagulation factor deficiency. Acquired factor V deficiency is occasionally present in association with clonal thrombocytosis. In that case, treat with fresh frozen plasma infusion.
  3. In case of extreme thrombocytosis (platelet count generally >1,000,000/uL [1000×10^9/L]), acquired von Willebrand disease may occur. Immediate definitive therapy with a platelet-lowering agent is essential in this instance. Platelet pheresis should be reserved for cases of acute thrombosis or bleeding.
- Thrombosis:
  1. Arterial or venous thrombosis occurs in 20% to 30% of patients.
  2. If the platelet count is >800,000/ml, platelet apheresis coupled with a platelet-lowering agent should be considered with the goal of platelet count <400,000/mm^3.
  3. Anticoagulant therapy for 3 months to indefinite based on the presence or absence of additional thrombophilic defects.

CHRONIC Rx

Treatment strategies for ET are based on the presence or absence of risk factors for thrombosis. Smoking cessation and obesity management should be discussed with all patients with ET. In low-risk patients (age <60 yr, no history of thrombosis or hemorrhage, platelet count <1 million/ml), observation may be adequate. Treatment with low-dose aspirin is indicated in low-risk patients with vasomotor symptoms or with other indications for aspirin use. The cytoreductive therapy along with low-dose aspirin therapy is indicated in high-risk patients (age >60 yr and/or with previous history of thrombosis) regardless of vasomotor symptoms.

- Low-dose aspirin (81 mg/day) may be safe and effective in preventing vascular events. It is also effective in preventing recurrent vascular events in high-risk patients and in treating the vasomotor symptoms.
- Cytoreductive therapy (Table 1):
  1. First-line therapies typically include hydroxyurea and interferon in the majority of cases. Anagrelide and interferon (if not used previously) generally are considered second line.
  2. Hydroxyurea (HU) versus anagrelide: HU plus aspirin is suggested to be safer and more effective than anagrelide plus aspirin in regard to thrombosis, bleeding, and transformation to PMF at 5 yr in a randomized trial. Monitor liver function tests and the degree of neutropenia or anemia with HU therapy.
  3. The incidence of leukemic conversion in patients with ET treated with HU alone is reported as <1%. Interferon alpha may be effective for controlling platelet count in patients failing treatment with HU.

TABLE 1 Choice of Drugs for Treatment of Patients with High-Risk Essential Thrombocythemia

Age (yr)	Treatment of Choice	Second Line
<50	Interferon	Anagrelide Hydroxyurea
50-75	Hydroxyurea	Interferon Anagrelide
>75	Hydroxyurea	Anagrelide

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

DISPOSITION

- Although long survival is expected in patients with ET, it is inferior to the sex- and age-matched U.S. population.
- An International Prognostic Score for Essential Thrombocythemia (IPSET) was proposed by International Working Group on Myelofibrosis Research and Treatment based on age, WBC count, and history of thromboembolism at diagnosis.

REFERRAL

Refer to hematologist/oncologist when platelet count is consistently elevated >450,000/mm^3 without causes for reactive thrombocytosis.

PEARLS & CONSIDERATION

COMMENTS

- Some patients with clinically apparent ET have Philadelphia chromosome or BCR-ABL rearrangement, even in the absence of other features of CML. It is suggested that it should be tested in all ET patients due to its potential therapeutic implications.
- The risk of bleeding with aspirin use in patients with ET paradoxically increases when the platelet count is >1 million/ml, likely due to acquired von Willebrand disease.

PATIENT & FAMILY EDUCATION

Smoking cessation is encouraged in both patients with ET and reactive thrombocytosis.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Robert Matera, MD,** and **John L. Reagan, MD**

SUGGESTED READINGS

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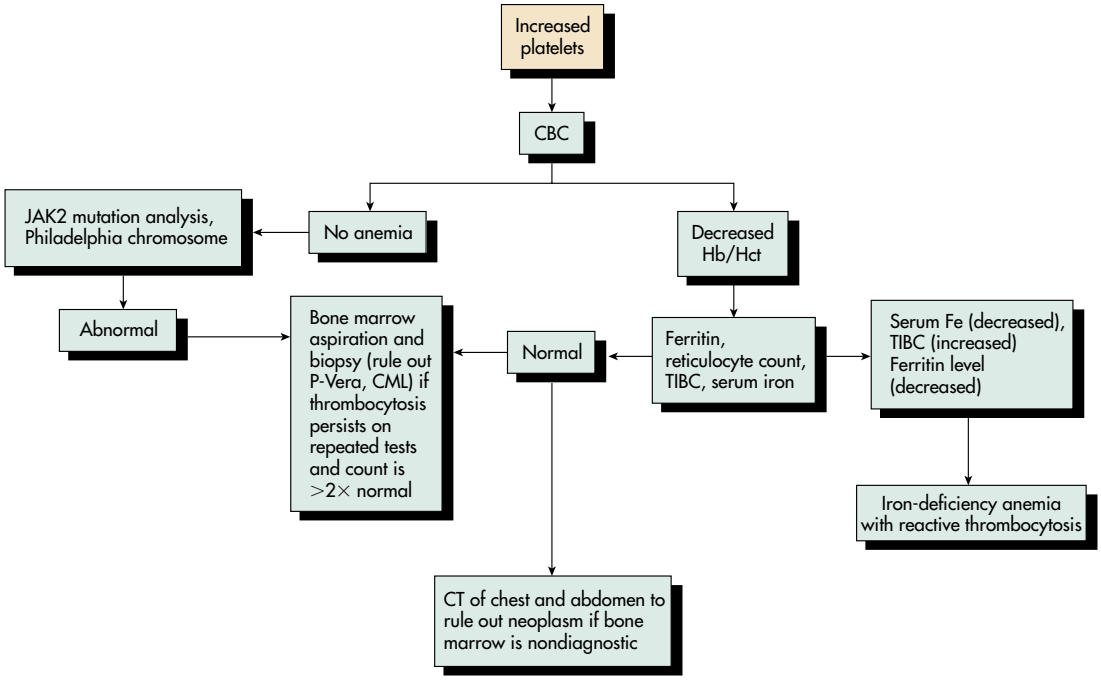

FIG. E1 Thrombocytosis diagnosis. *CBC,* Complete blood count; *CML,* chronic myelogenous leukemia; *CT,* computed tomography; *Fe,* iron; *Hb/Hct,* hemoglobin/hematocrit; *P-Vera,* polycythemia vera; *TIBC,* total iron-binding capacity. (From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Churchill Livingstone.)

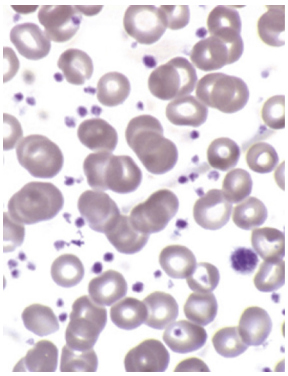

FIG. E2 Essential thrombocythemia (ET): Peripheral blood smear. The peripheral blood smear in ET shows a marked thrombocytosis with anisocytosis (varying sizes) of the platelets. (From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Churchill Livingstone.)

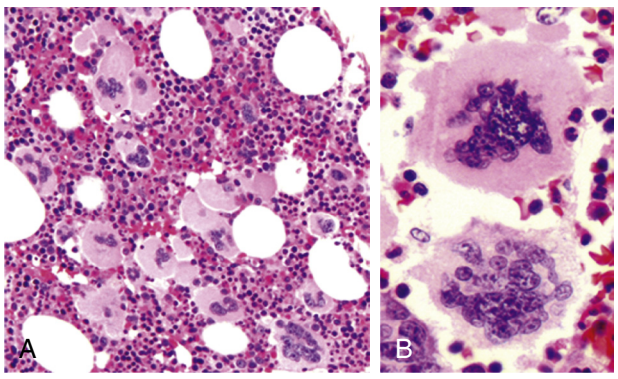

FIG. E3 Essential thrombocytosis: Bone marrow biopsy. The bone marrow **(A)** is hypercellular and exhibits a marked proliferation of large and giant megakaryocytes in loose clusters with other hematopoietic elements in the background. The large megakaryocytes **(B)** tend to be extensively lobulated. (From Hoffman R et al: *Hematology: basic principles and practice,* ed 7, Philadelphia, 2018, Churchill Livingstone.)

Thrombophlebitis, Superficial Venous PTG

BASIC INFORMATION

DEFINITION

Superficial venous thrombophlebitis (SVT) is an inflammation of a vein with subsequent secondary thrombus formation. SVT most frequently involves superficial veins of the leg, but any superficial vein can be affected. SVT has been reported to occur in 125,000 people in the U.S. per yr; however, the actual incidence is likely far greater. SVT is not always a benign condition. SVT should be regarded as the superficial venous manifestation of a systemic process known as venous thromboembolism (DVT, PE).

SYNONYMS

SVT
Superficial phlebitis
Superficial suppurative thrombophlebitis
Suppurative thrombophlebitis

ICD-10CM CODES

I80.00	Phlebitis and thrombophlebitis of superficial vessels of unspecified lower extremity
I80.8	Phlebitis and thrombophlebitis of other sites
I80.9	Phlebitis and thrombophlebitis of unspecified site

EPIDEMIOLOGY & DEMOGRAPHICS

- Approximately 30% to 45% of patients diagnosed with SVT are men with an average age of 54 yr.
- Approximately 55% to 70% of patients diagnosed with SVT are women with an average age of 58 yr.
- The overall recurrence of SVT is 18% over an average observation period of 15 mo, equally involving varicose and nonvaricose veins.
- The lifetime incidence of SVT in those with untreated varicose veins has been estimated at 25% to 50%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Subcutaneous vein is palpable as a tender cord or "wormlike" mass with increased warmth and erythema.
- Induration, redness, and tenderness are localized along the course of the vein. This linear appearance rather than circular appearance is useful to distinguish thrombophlebitis from other conditions (cellulitis, erythema nodosum).
- There is some swelling of the overlying skin and subcutaneous tissue but without generalized edema of the limb.
- Low-grade fever may be present.

ETIOLOGY

- In the lower extremity, 70% of SVT occurs in patients with varicose veins, with the great saphenous vein being most commonly involved (60% to 80%)
- Intravenous catheters and infusion of caustic drugs are the most common cause of upper-extremity SVT
- Malignancy
- Pregnancy/puerperium
- Hypercoagulable states
- Previous DVT/SVT
- OCP (oral contraceptive pill)/HRT (hormone replacement therapy)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Lymphangitis
- Cellulitis
- Erythema nodosum
- Panniculitis
- Acute lipodermatosclerosis

WORKUP

The clinical investigation includes not only the local findings but also the presence of varicose veins with or without the stigmata of chronic venous insufficiency. Today, duplex ultrasound is the most important additional diagnostic tool.

IMAGING STUDIES

- Duplex ultrasound offers the advantage of being inexpensive, noninvasive, and repeatable for follow-up examination.
- Ultrasonography confirms the diagnosis, shows the location of the thrombus and its location regarding the saphenofemoral and/or saphenopopliteal junctions.
- Ultrasound examination of patients with SVT has revealed that a concomitant DVT can exist in 15% to 20%.
- In up to 25% of these patients, the DVT may not be contiguous with the SVT and may be found in the contralateral leg.
- Therefore, bilateral duplex exam is recommended in all cases of SVT that involve the main trunk of the great saphenous vein (GSV) or small saphenous vein (SSV).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Warm, moist compresses
- Do not restrict activity. Immediate mobilization with walking exercises

ACUTE GENERAL Rx

- Treatment guidelines for SVT are not well established because of the lack of controlled clinical trials. In general, the primary goal of management should be to prevent thrombus extension and the risk of venous thromboembolism. All other therapy is directed at patient comfort with analgesics and NSAIDs (in patients not receiving anticoagulants).
- In patients with migratory SVT, recurrent SVT, or SVT without varicose veins, the underlying condition should be investigated, and treatment directed accordingly.
- The most common cause of upper-extremity SVT is an intravenous catheter. Treatment starts with removal of the cannula and application of warm compresses. The resultant lump may persist for mos. No anticoagulant therapy is required.
- In patients with lower-extremity SVT in a varicose vein branch, control of pain with analgesics and the use of gradient compression stockings are usually sufficient. Patients are encouraged to continue their usual daily activities.
- Many investigators favor systemic anticoagulation when there is superficial thrombosis of 5 cm or more in length, the thrombus is within 1 cm of the saphenous junctions, or more than 5 cm of the saphenous trunk is involved, as shown by duplex ultrasonography. Anticoagulation is also reasonable for patients with SVT and cancer or previous DVT.
- The American College of Chest Physicians guidelines recommend anticoagulation for 45 days over no anticoagulation in patients with lower-extremity SVT within 1 cm of the saphenofemoral or saphenopopliteal junction.
- In the case of patients with varicose veins secondary to saphenous vein reflux, a catheter vein ablation procedure should be performed only after the acute SVT episode is over in order to avoid the thromboembolic complications induced by such procedures.

PEARLS & CONSIDERATIONS

SUPERFICIAL SUPPURATIVE THROMBOPHLEBITIS

- Superficial suppurative thrombophlebitis is associated with an intravenous catheter or multiple puncture sites secondary to IV drug abuse and is located primarily in the upper extremity.
- Clinical presentation is similar to that of nonsuppurative SVT but with associated fever, leukocytosis, and/or septicemia.
- Most cases of intravenous catheter sepsis are not complicated by suppurative thrombophlebitis; local IV catheter site infections occur in about 7% of cases and septicemia is found in only 1 of every 400 IV catheterizations.
- The incidence of peripheral vein suppurative thrombophlebitis is highest in patients with specific risk factors such as burns, steroids, and IV drug abuse.
- Treatment consists of antibiotics with adequate coverage of gram-negative rods and *Staphylococcus aureus,* including MRSA. Initial empirical treatment is with IV vancomycin 1 g q12h *plus* ceftriaxone 1 g IV q24h. Alternative regimen consists of daptomycin 6 mg/kg IV q 12h *plus* ceftriaxone 1 g IV q24h.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Thrombophlebitis (Patient Information)
Deep Vein Thrombosis (Related Key Topic)

AUTHOR: **Frank G. Fort, MD, FACS, RPHS**

SUGGESTED READINGS

Decousus H et al: Fondaparinux for the treatment of superficial-vein thrombosis in the legs, *N Engl J Med* 363:1222-1232, 2010.

DiNisio M, Middeldorp S: Treatment of lower extremity superficial thrombophlebitis, *JAMA* 311:729, 2014.

BASIC INFORMATION

DEFINITION

Thrombotic thrombocytopenic purpura (TTP) is a rare autoimmune disorder characterized by thrombocytopenia and microangiopathic hemolytic anemia that can be associated commonly with other hallmarks such as neurologic impairment, renal dysfunction, and fever. The laboratory hallmark of TTP is a severe deficiency of the *ADAMTS13* factor (activity <10%).

SYNONYMS

TTP
Upshaw-Schulman Syndrome

ICD-10CM CODE
M31.1 Thrombotic microangiopathy

EPIDEMIOLOGY & DEMOGRAPHICS

- About 90% of new TTP cases are seen in adults (mostly females between 18 and 50 yr).
- The incidence of new TTP is 3 to 11 cases per million population per yr. The prevalence is ~10 cases per million population.
- There is increased incidence in HIV/AIDS and during pregnancy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The disease often begins as a flulike illness ultimately followed by clinical and laboratory abnormalities.
- Most patients present with nonspecific constitutional symptoms (weakness, nausea, abdominal pain, vomiting).
- Purpura (secondary to thrombocytopenia).
- Jaundice, pallor (from hemolysis).
- Mucosal bleeding.
- Fever.
- Fluctuating levels of consciousness (caused by thrombotic occlusion of the cerebral vessels). However, one third of patients have no neurologic abnormalities.
- Renal failure and neurologic events are usually end-stage features.

ETIOLOGY

- Acquired TTP is an autoimmune disorder caused by autoantibody inhibition of ADAMTS13 activity. Hereditary TTP (also called Upshaw-Schulman syndrome) is caused by homozygous or compound heterozygous *ADAMTS13* mutations (Table 1).
- Many drugs, including clopidogrel, ticlopidine, penicillin, antineoplastic agents (gemcitabine, mitomycin C), calcineurin inhibitors (cyclosporine), oral contraceptives, and quinine, have been associated with TTP.
- Other precipitating causes include infectious agents, pregnancy, malignancies, allogeneic stem cell transplantation, and neurologic disorders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

It is challenging to differentiate TTP from other thrombotic microangiopathies given the significant overlap in clinical presentation, but this distinction is critical in selecting an appropriate therapy for patients.

- Disseminated intravascular coagulation (DIC)
- Malignant hypertension
- Vasculitis
- Eclampsia or preeclampsia
- Hemolytic-uremic syndrome (HUS) and atypical HUS
- Gastroenteritis as a result of a serotoxin-producing serotype of *Escherichia coli*

WORKUP

A comprehensive history, physical examination, and laboratory evaluation usually confirm the diagnosis (Fig. 1).

LABORATORY TESTS

- Severe anemia and thrombocytopenia (platelet count <50,000 or >50% reduction from previous counts)
- Peripheral blood smear (Fig. E2, Fig. E3) reveals numerous red cell fragments (schistocytes)
- Elevated blood urea nitrogen and creatinine
- Evidence of hemolysis: Elevated reticulocyte count, indirect bilirubin, lactate dehydrogenase, decreased haptoglobin
- Urinalysis: Hematuria (red blood cells [RBCs] and RBC casts in urine sediment) and proteinuria
- Peripheral smear: Severely fragmented RBCs (schistocytes). More than 4% RBC fragments in the peripheral blood
- No laboratory evidence of DIC (normal fibrin degradation product, fibrinogen)
- The diagnosis of hereditary TTP requires documentation of *ADAMTS13* deficiency and an absence of *ADAMTS13* autoantibody inhibitor, and confirmation requires documentation of *ADAMTS13* mutations. Diagnostic criteria for acquired TTP are the presence of microangiopathic hemolytic anemia and thrombocytopenia without another apparent cause. An *ADAMTS13* level indicating less than 10% of normal activity supports the clinical diagnosis of acquired TTP while moderately decreased levels of >20% suggest the presence of other diagnoses.

TREATMENT

ACUTE GENERAL Rx

- Discontinue potential offending agents. Initiate *ADAMTS13* replacement by plasma infusion in patients with hereditary TTP.
- Current therapy for TTP is built on two complementary pillars: therapeutic plasma exchange (TPE) and immunosuppression.
- Daily TPE with replacement of 1.0 to 1.5 times the predicted plasma volume of the patient is standard therapy for TTP. TPE should be continued for a minimum of 2 days after the platelet count returns to normal (>150,000 cells/m^3).
- High-dose plasma infusion (25 ml/kg/day) may be useful only if TPE cannot be promptly started and for patients with very severe or refractory disease between plasma exchange sessions. High-dose plasma infusions can cause volume overload in patients with renal insufficiency.
- Patients with hereditary TTP who experience severe plasma allergic reactions have been effectively treated with plasma-derived factor VIII concentrate that contains *ADAMTS13*.
- Immunosuppression with the use of corticosteroids (prednisone 1 to 2 mg/kg/day) typically is administered concomitantly with TPE for a period of 3 to 4 wk.
- The monoclonal anti-CD20 antibody rituximab has been traditionally used for treatment of suboptimally responsive TTP and results in remissions in the majority of patients. Frontline use of rituximab results in shorter hospitalization with fewer relapses but is likely resulting in overtreatment in many cases.

TABLE 1 Etiology, Epidemiology, and Pathogenesis of TTP, HUS, and ADAMTS13–Related Parameters

	Congenital TTP	Acquired TTP	HUS
Etiology	*ADAMTS13* mutation	Antibody to *ADAMTS13,* endothelial cell activation	*Escherichia coli* or other microorganisms
Epidemiology	5-10 cases per yr per million	≤1 case per yr per million	1-5 cases per yr per million, mainly in children
Pathogenesis	Defective cleavage of vWF multimers, massive secretion of ultra-large vWF multimers, increased platelet deposition under shear condition, occlusion of blood vessels in microcirculation		Intoxication with Shiga-like toxin, damage of endothelial cells, enterohemorrhagic colitis, renal disorder
ADAMTS13 antigen	Very low or absent	Low or variable	Normal or moderately decreased
ADAMTS13 activity	≤5%-10%	≤5%-10% or variable	30%-100%
Inhibitor against ADAMTS13	No	Mostly yes	No

ADAMTS13, A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; *HUS,* hemolytic uremic syndrome; *TTS,* thrombotic thrombocytopenic purpura; *vWF,* von Willebrand factor.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, Philadelphia, 2017, Elsevier.

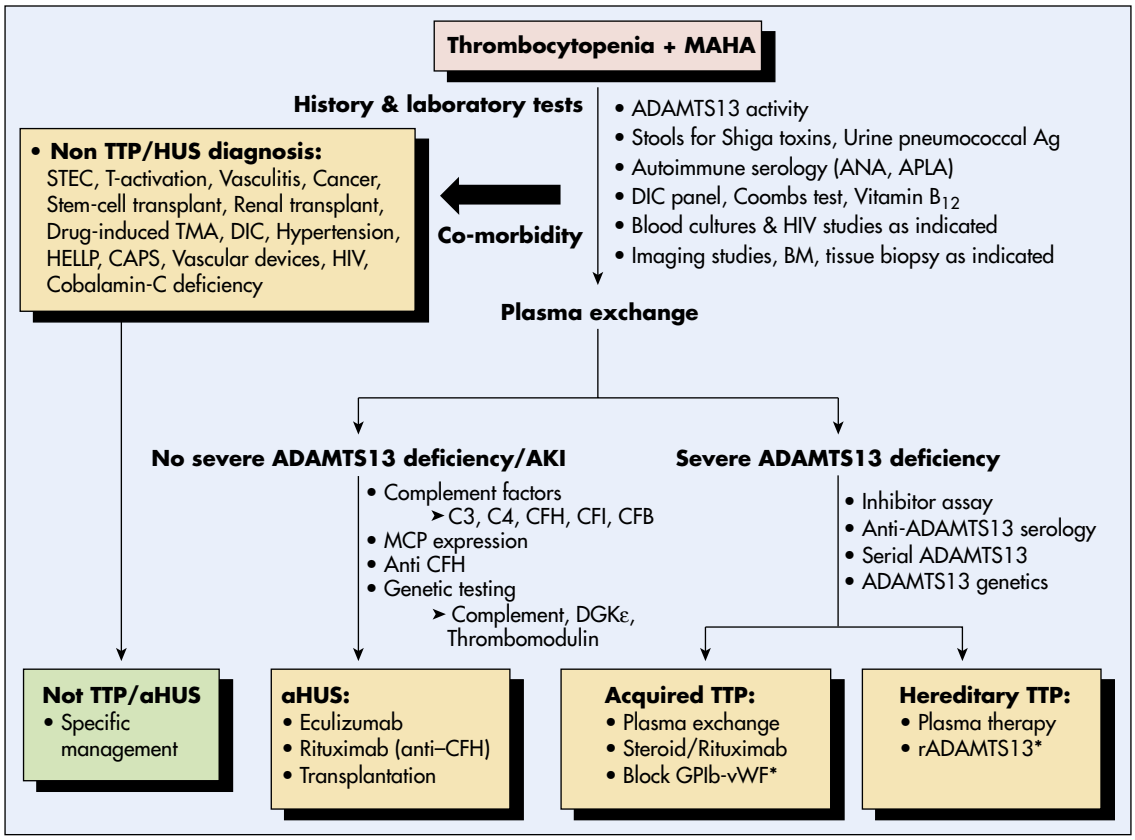

FIG. 1 An approach to diagnosis and management of thrombotic microangiopathies. *ADAMTS13,* A disintegrin and metalloproteinase with thrombospondin type 1 motifs, member 13; *Ag,* antigen; *aHUS,* atypical hemolytic uremic syndrome; *AKI,* acute kidney injury; *ANA,* antinuclear antibody; *APLA,* antiphospholipid antibodies; *BM,* bone marrow; *CAPS,* catastrophic antiphospholipid syndrome; *CFB,* complement factor B; *CFH,* complement factor H; *CFI,* complement factor I; *DGKE,* diacyl glycerol kinase ε; *DIC,* disseminated intravascular coagulation; *GP,* glycoprotein; *HELLP,* hemolysis, elevated liver enzymes, and low platelet count; *HIV,* human immunodeficiency virus; *HUS,* hemolytic uremic syndrome; *MAHA,* macroangiopathic hemolytic anemia; *MCP,* membrane cofactor protein; *rADAMTS13,* recombinant ADAMTS13; *STEC,* Shiga toxin-producing *E. coli*; *TMA,* thrombotic microangiopathy; *TTP,* thrombotic thrombocytopenic purpura; *vWF,* von Willebrand factor. *Bullet points* are diagnoses or therapies. *Indicates therapies under investigation. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

- Caplacizumab, an anti–von Willebrand factor humanized, bivalent, variable-domain-only immunoglobulin fragment, inhibits interaction between von Willebrand factor multimers and platelets. In a randomized trial, treatment with caplacizumab and plasma exchange was associated with faster normalization of the platelet count and lower incidence of a composite of TTP-related death, recurrence of TTP, or a thromboembolic event during the treatment period than placebo.
- Platelet transfusions are contraindicated except in severely thrombocytopenic patients with documented bleeding or those who are facing surgery or other invasive procedures in the setting of severe thrombocytopenia.
- Use of antiplatelet agents (acetylsalicylic acid, dipyridamole) is controversial.
- Splenectomy is performed in refractory cases.
- Dialysis is rarely required.

CHRONIC Rx

- Relapsing TTP may be initially retreated with TPE.
- TTP unresponsive to conventional therapy is usually effectively treated with rituximab and occasionally with chemotherapy agents (vincristine, cyclophosphamide).
- Splenectomy done while patients are in remission has been used historically to decrease the frequency of relapses.

DISPOSITION

- Survival of patients with TTP currently exceeds 80% with TPE.
- Relapse occurs in 20% to 40% of patients who have achieved initial remission.

PEARLS & CONSIDERATIONS

COMMENTS

- TTP should be considered in pregnant women with vague neurologic, gastrointestinal, or renal symptoms in either the obstetric triage or emergency department areas.
- TTP is fatal in 90% of patients without therapy.
- Case reports have suggested a benefit of the proteasome inhibitor bortezomib, possibly due to elimination of the autoreactive plasma cells producing anti-ADAMTS13 antibodies in patients who are refractory to TPE and rituximab administration.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hemolytic-Uremic Syndrome (Related Key Topic)

AUTHOR: **Bharti Rathore, MD**

SUGGESTED READINGS

Joly BS et al: Thrombotic thrombocytopenic purpura, *Blood* 129(21):2836-2846, 2017.

Kremer Hovinga JA, George JN: Hereditary thrombotic thrombocytopenic purpura, *N Engl J Med* 38:1653-1662, 2019.

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Scully M et al: Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura, *N Engl J Med* 380(4):335-346, 2019.

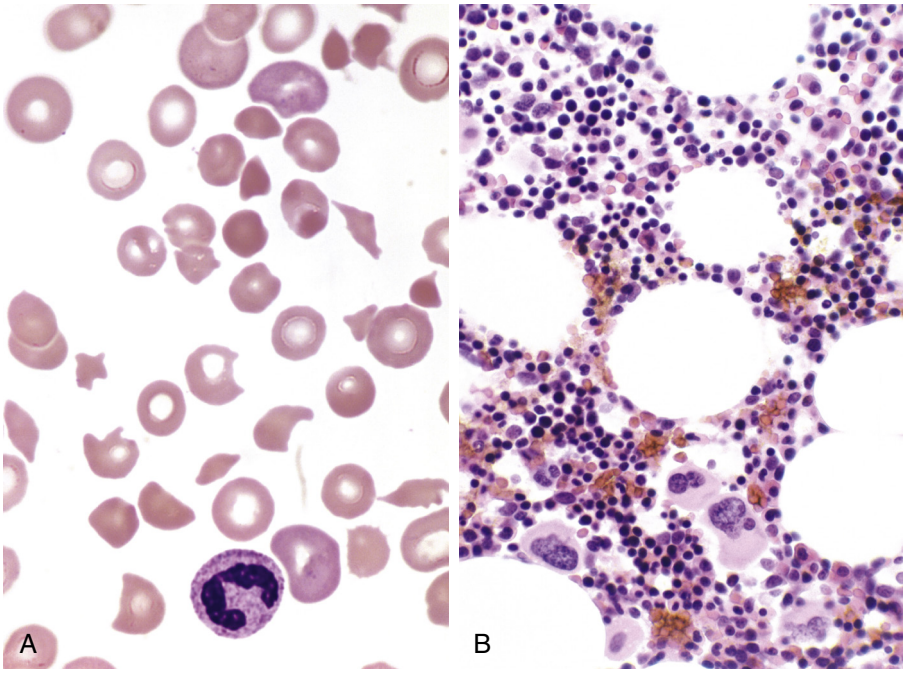

FIG. E2 A, Peripheral blood smear of thrombotic thrombocytopenic purpura. Numerous red cell fragments (schistocytes) are present. No platelets are seen in this field. **B,** The bone marrow trephine biopsy section demonstrates increased numbers of megakaryocytes. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

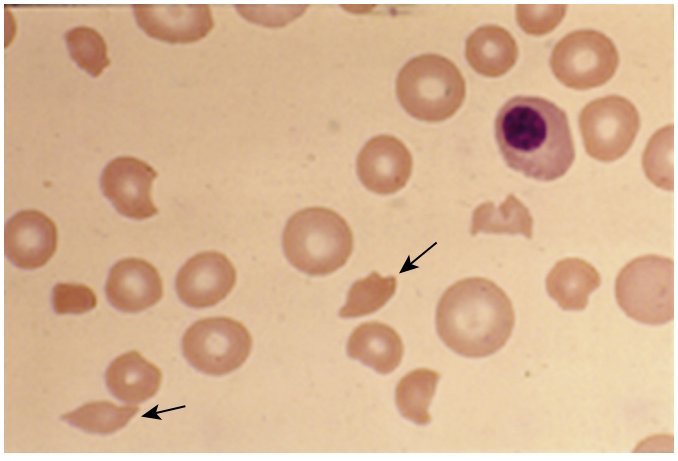

FIG. E3 Peripheral blood film obtained from a 28-year-old woman who presented with fever, epistaxis, and altered mental status. Note the absence of platelets and the presence of a nucleated erythrocyte and schistocytes *(arrows)* consistent with a microangiopathic process. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

BASIC INFORMATION

DEFINITION

Thyroid carcinoma is a primary neoplasm of the thyroid and consists of four major subtypes: papillary, follicular, anaplastic, and medullary.

SYNONYMS

Papillary carcinoma of thyroid
Follicular carcinoma of thyroid
Anaplastic carcinoma of thyroid
Medullary carcinoma of thyroid

ICD-10CM CODES

C73	Malignant neoplasm of thyroid gland
D09.3	Carcinoma in situ of thyroid and other endocrine glands
D34	Benign neoplasm of thyroid gland
D44.0	Neoplasm of uncertain behavior of thyroid gland

EPIDEMIOLOGY & DEMOGRAPHICS

- Thyroid cancer is the most common endocrine cancer, with an estimated 52,070 new cases and 2,170 deaths occurring in 2019 in the U.S.
- Incidence is 13.9 per 100,000 people in the U.S. and increasing over last 4 decades.
- Female:male ratio is 3:1.
- Median age at diagnosis: 45 to 50 yr.
- Occult thyroid cancer is identified in 20% of autopsy specimens.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Thyroid cancer is often identified incidentally. Physical exam may reveal:
  1. Presence of thyroid nodule
  2. Hoarseness and cervical lymphadenopathy
  3. Painless swelling in the region of the thyroid

ETIOLOGY

- Risk factors: Prior neck irradiation.
- Multiple endocrine neoplasia II (medullary carcinoma).
- Inherited syndromes associated with thyroid cancer are described in Table 1.
- GLP-1 receptor agonists for the treatment of type 2 DM (e.g., exenatide, albiglutide) can increase the risk of medullary thyroid carcinoma (MTC).

TABLE 1 Inherited Syndromes Associated with Thyroid Cancer

Multiple endocrine neoplasia (MEN) 2A and 2B
Isolated familial medullary thyroid cancer
Gardner syndrome
Familial adenomatous polyposis
Carney complex
Cowden syndrome
Familial nonmedullary thyroid cancer

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

- Although formerly thought to be a single entity, papillary thyroid carcinoma encompasses several tumor types that have mutually exclusive mutations. BRAF V600E accounts for 60% of these mutations.
- Pathways to the development of thyroid cancer are depicted in Fig. E1.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Multinodular goiter
- Lymphocytic thyroiditis
- Ectopic thyroid

WORKUP

The workup of thyroid carcinoma includes laboratory evaluation and diagnostic imaging. Key features of thyroid malignancies are summarized in Table 2. Diagnosis is confirmed with fine-needle aspiration or surgical biopsy. At diagnosis, the vast majority of thyroid cancers are well differentiated, with excellent prognosis. The characteristics of thyroid carcinoma vary with the type:

- Papillary carcinoma (85%):
  1. Most frequently occurs in women during second or third decades
  2. Histologically, psammoma bodies (calcific bodies present in papillary projections) are pathognomonic; found in 35% to 45% of papillary thyroid carcinomas
  3. Majority are not papillary lesions but mixed papillary follicular carcinomas
  4. Spread is by lymphatics and by local invasion
- Follicular carcinoma (10%):
  1. More aggressive than papillary carcinoma
  2. Incidence increases with age
  3. Tends to metastasize hematogenously to bone, producing pathologic fractures
  4. Tends to concentrate iodine (useful for radiation therapy)
- Anaplastic carcinoma (1%):
  1. Very aggressive neoplasm
  2. Two major histologic types: Small cell (less aggressive, 5-yr survival approximately 20%) and giant cell (death usually within 6 mo of diagnosis)
- MTC (4%):
  1. Unifocal lesion: Found sporadically in elderly patients
  2. Bilateral lesions: Associated with pheochromocytoma and hyperparathyroidism; this combination is known as MEN-II and is inherited as an autosomal-dominant disorder

LABORATORY TESTS

- Thyroid function studies are generally normal. Thyroid-stimulating hormone (TSH), T4, and serum thyroglobulin levels should be obtained before thyroidectomy in patients with confirmed thyroid carcinoma. Serum thyroglobulin levels can be useful postoperatively to monitor recurrence of thyroid carcinoma (Fig. E2).
- Increased plasma calcitonin assay in patients with medullary carcinoma (tumors produce thyrocalcitonin). RET proto-oncogene sequencing and measurement of plasma free metanephrine and normetanephrine levels to rule out coexistent pheochromocytoma are recommended in all patients with medullary thyroid cancer.
- Fine-needle aspiration biopsy is the best method to assess a thyroid nodule (see "Thyroid Nodule" in Section I). Table 3 describes the Bethesda system for thyroid cytopathology.

IMAGING STUDIES (FIG. E3)

- Thyroid ultrasound can detect solitary solid nodules that have a high risk of malignancy. However, a negative ultrasound does not exclude diagnosis of thyroid carcinoma.
- Thyroid scanning with iodine-123 or technetium-99m can identify hypofunctioning (cold) nodules, which are more likely to be malignant. However, warm nodules can also be malignant.

STAGING

- Stage I: Thyroid cancer of any size without distal spread in patient <45 yr. In patients >45 yr, tumor size ≤2 cm without local invasion or positive cervical lymph nodes
- Stage II: Distal spread in patient <45 yr. In patients >45 yr, tumors >2 cm but <4 cm without local invasion or positive cervical lymph nodes
- Stage III: Tumors >4 cm in patient >45 yr of age
- Stage IV: Distal spread in patient >45 yr of age

TREATMENT

ACUTE GENERAL Rx

- Papillary carcinoma:
  1. Total thyroidectomy is indicated if the patient has:
     a. Extrapyramidal extension of carcinoma.
     b. Papillary carcinoma limited to thyroid but a positive history of irradiation to the neck.
     c. Lesion >2 cm.
  2. Lobectomy with isthmectomy may be considered in patients with intra-thyroid papillary carcinoma <2 cm and no history of neck or head irradiation; surgery should be followed with suppressive therapy with thyroid hormone because these tumors are TSH responsive. The accepted practice is to suppress serum TSH concentrations to <0.1 microunit/ml in patients with persistent disease, suppression to 0.1 to 0.5 microunit/ml in patients who are disease free but are at high risk of recurrence, and a goal TSH level of 0.3 to 2.0 microunits/ml in patients who are disease free and have a low risk of recurrence.

3. Radioiodine ablation reduces rates of death and recurrence (Table 4). Radioiodine is administered for stages III and IV disease.
4. In cases that have progressed after radioiodine therapy, oral targeted inhibitors (lenvatinib, sorafenib) have significant survival benefit.

- Follicular carcinoma:
  1. Total thyroidectomy followed by TSH suppression, as previously noted.
  2. Radiotherapy with iodine-131 followed by thyroid suppression therapy with triiodothyronine is useful in patients with metastasis (Table 4).
  3. In cases that have progressed after radioiodine therapy, oral targeted inhibitors (lenvatinib, sorafenib) have significant survival benefit.
- Anaplastic carcinoma:
  1. At diagnosis, this neoplasm is rarely operable; palliative surgery is indicated for extremely large tumor compressing the trachea.
  2. Management is usually restricted to radiation therapy or chemotherapy (combination of doxorubicin, cisplatin, and other antineoplastic agents) (Table 4); these measures rarely provide significant palliation.
- Medullary carcinoma:
  1. Thyroidectomy should be performed, followed by TSH suppression.
  2. Vandetanib and cabozantinib are oral tyrosine kinase inhibitors that are FDA-approved for treatment of symptomatic or progressive, unresectable, locally advanced or metastatic medullary thyroid cancer.
  3. Patients and their families should be screened for pheochromocytoma and hyperparathyroidism.

DISPOSITION

Overall 5 yr survival rate is 98.17, but prognosis varies with the type of thyroid carcinoma: 5-yr survival is over 80% for follicular carcinoma and is approximately 5% with anaplastic carcinoma (see Table 5).

PEARLS & CONSIDERATIONS

COMMENTS

- Follow-up surveillance involves neck ultrasound 6-12 mo after initial treatment and periodically and lab evaluation with TSH, serum thyroglobulin (T8), and thyroglobulin antibody (T8 Ab).
- Family members of patients with medullary carcinoma should be screened; DNA analysis for the detection of mutations in the *RET* gene structure permits the identification of *MEN IIA* gene carriers.
- While there is little controversy regarding the benefit of radioactive iodine in iodine-avid advanced-stage well-differentiated thyroid cancer, the indications for radioactive iodine

TABLE 2 Thyroid Malignancies—Key Features

	Description	Pattern of Spread
Papillary carcinoma (70%-80%)	Low-grade tumors with a good prognosis (histologically multicentric) ▸ Tumors concentrate radio-iodine	Early lymph node spread (metastatic lymph nodes may be normal in size, cystic, calcified, hemorrhagic or contain colloid) ▸ Distant metastases are rare (and usually to the lungs)
Follicular carcinoma (10%-20%)	Slow growing ▸ Tumors concentrate radio-iodine	It rarely metastasizes to the regional lymph nodes ▸ The tendency is to spread via the bloodstream and disseminate to the lungs, bones, or liver
Anaplastic carcinoma (1%-2%)	Undifferentiated malignant tumors that do not concentrate radio-iodine ▸ There is a poor prognosis ▸ They tend to occur in older patients ▸ Punctate calcification and necrosis frequently are present	Lymphatic metastases occur in the majority of patients
Medullary carcinoma (5%-10%)	This originates from the parafollicular C cells ▸ It does not concentrate radio-iodine ▸ It may be sporadic or familial (and associated with the MEN type II syndrome or other endocrine neoplasms) ▸ It is usually a unilateral, solitary lesion ▸ Calcification is seen in 10% ▸ ^{123}I-MIBG and somatostatin analogs (e.g. octreotide) can be used for evaluation ▸ Circulating calcitonin levels are usually elevated	It may invade locally, spread to the regional nodes, or demonstrate hematogenous spread to the lungs, bones, or liver
Lymphoma (10%)	It is usually a non-Hodgkin lymphoma ▸ It occurs in one third of patients with Hashimoto thyroiditis (a MALT-type lymphoma) ▸ It presents as a rapidly enlarging, solitary nodule (80%) or as multiple nodules (imaging cannot distinguish between a lymphoma and thyroiditis) ▸ Necrosis and calcification are uncommon	It can involve the nodes with spread to the GI tract
Metastases (<1%)	The most common primary is renal cell carcinoma	

From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.

TABLE 3 The Bethesda System for Thyroid Cytopathology

Category	Risk of Malignancy (%)	Recommended Management
Nondiagnostic or unsatisfactory	1-4	Repeat FNA with ultrasound guidance
Benign	0-3	Clinical follow-up
Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)	5-15	Repeat FNA*
Follicular neoplasm or suspicious for follicular neoplasm	15-30	Lobectomy
Suspicious for malignancy	60-75	Lobectomy with or without frozen section or total thyroidectomy
Malignant	97-99	Total thyroidectomy

*Lobectomy also can be considered depending on clinical or sonographic characteristics.
FNA, Fine-needle aspiration.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE 4 Indications for Iodine-131 Treatment in Patients with Papillary, Follicular, or Hürthle Cell Thyroid Carcinoma after Initial Definitive Near-Total Thyroidectomy

No Indication
Adult patients at very low risk for cause-specific mortality or relapse: Complete surgical resection, favorable histology, and limited extent of disease (e.g., PTC patients with MACIS scores <6; patients with tumor size <1 cm, N0, and M0).
Definite Indications
Distant metastasis at diagnosis
Incomplete tumor resection
Complete tumor resection but high risk for mortality or recurrence (e.g., PTC patients with MACIS scores ≥6 and pTNM stage II/III FTC or HCC)
Probable Indications
Incomplete surgery (less than near-total thyroidectomy, no lymph node dissection)
PTC or FTC in a child younger than 16 yr
If PTC, tall cell or columnar cell variant and diffuse sclerosing variant
If FTC, widely invasive or poorly differentiated tumor
Bulky nodal metastases

FTC, Follicular thyroid carcinoma; *HCC,* Hürthle cell carcinoma; *MACIS,* scoring system based on metastasis, age, completeness of resection, invasion, and size; *PTC,* papillary thyroid carcinoma; *pTNM,* pathologic tumor-node-metastasis classification.
From Melmed S et al (eds): *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

TABLE 5 Characteristics of Thyroid Cancers

Type of Cancer	Percentage of Thyroid Cancers	Age of Onset (yr)	Treatment	Prognosis
Papillary	88	40-80	Thyroidectomy, followed by radioactive iodine ablation and TSH suppression	Good
Follicular	10	45-80	Thyroidectomy, followed by radioactive iodine ablation and TSH suppression	Fair to good
Medullary	3-4	20-50	Thyroidectomy and central compartment lymph node dissection and TSH suppression	Fair
Anaplastic	1	50-80	Isthmusectomy followed by palliative x-ray treatment	Poor
Lymphoma	<1	25-70	X-ray therapy and/or chemotherapy	Fair

From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

following total thyroidectomy in patients with very low risk disease is controversial. Proponents argue that its use may destroy microscopic metastases, while opponents counter that the risk of secondary cancer due to radioactive iodine is not warranted in patients whose prognosis is typically excellent.

- Metastatic thyroid cancers that are refractory to radioiodine (iodine-131) are associated with a poor prognosis.
- Small-molecule tyrosine kinase inhibitors, including vandetanib, cabozantinib, sorafenib, and lenvatinib, are now FDA-approved and have shown clinical benefit with improved survival in advanced differentiated and medullary thyroid cancer.
- Targeted therapy with a combined regimen of BRAF inhibitors and MEK inhibitors (dabrafenib plus trametinib) is efficacious and approved in patients with metastatic BRAFV600E-mutated anaplastic thyroid cancer.
- In a subset of patients with anaplastic thyroid cancer, the immune checkpoint inhibitor pembrolizumab may be an effective salvage therapy when added to kinase inhibitors at the time of progression on these drugs. In patients with advanced, differentiated thyroid cancer, pembrolizumab has a manageable safety profile and demonstrates evidence of antitumor activity in a minority of treated patients.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Thyroid Cancer (Patient Information)
Thyroid Nodule (Related Key Topic)

AUTHOR: **Bharti Rathore, MD**

SUGGESTED READINGS

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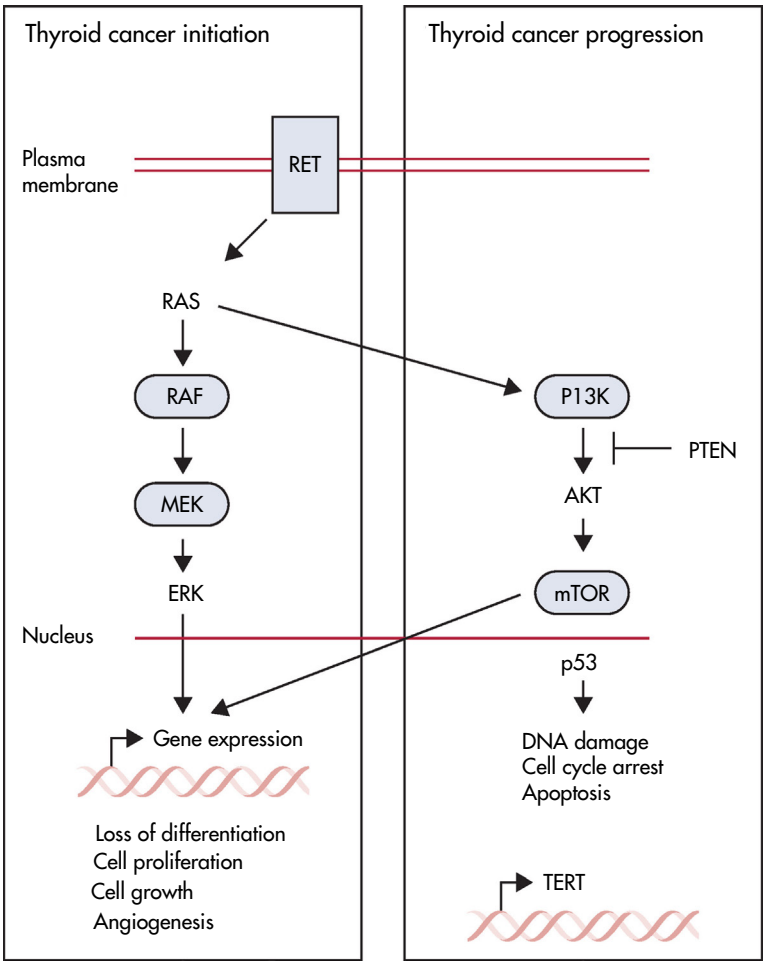

FIG. E1 Thyroid cancer pathways. Diagram shows the key molecular signaling pathways involved in thyroid cancer. The box on the left shows the mitogen-activated protein kinase pathway, which is activated by mutation in most thyroid cancers. These events are believed to initiate thyroid cancer development and lead to altered gene expression, which promotes cell proliferation, cell growth, angiogenesis, and loss of differentiation. The box on the right shows pathways altered in advanced thyroid cancers, which are believed to promote tumor progression. This includes the PI3K–mTOR pathway, the p53 tumor suppressor, and alterations in the promoter for TERT. Blue boxes represent factors for which targeted treatments are available that have been approved by the U.S. Food and Drug Administration. *mTOR,* Mammalian target of rapamycin; *PI3K,* phosphatidylinositol-3-kinase; *TERT,* telomerase reverse transcriptase. (From Cabanillas ME et al: Thyroid cancer, *Lancet* 388[10061]:2783-2795, 2016.)

FIG. E2 This patient was being monitored for a papillary thyroid carcinoma treated by total thyroidectomy and postoperative radioiodine. The serum thyroglobulin level was 45 ng/ml during levothyroxine suppressive treatment. **A,** A total-body scan was performed 3 days after administration of 100 mCi (3.7 GBq). There is no visible uptake in the neck or thorax. Notice the accumulation of radioiodine in the stomach, colon, and bladder. **B,** Positron emission tomography scan using [18F]-fluorodeoxyglucose (18FDG) with maximal intensity projection demonstrates significant uptake in the upper mediastinum. **C,** In fusion images of 18FDG-PET and CT scans, axial and coronal slices localized the FDG uptake in the right paratracheal mediastinum, corresponding to a lymph node metastasis that subsequently was excised. Serum thyroglobulin became undetectable during thyroid hormone treatment. (From Melmed S et al [eds]: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

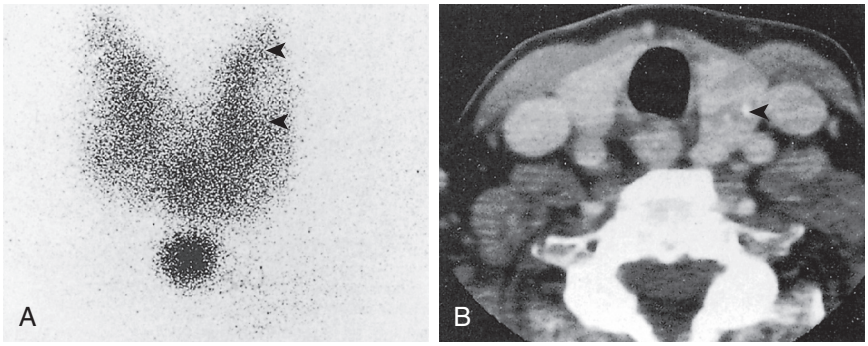

FIG. E3 Papillary adenocarcinoma. A 74-year-old woman presented with a thyroid nodule. **A,** An ^{123}I thyroid scan (anterior view) demonstrates a "cold" nodule *(arrows)* in the upper portion of the left thyroid lobe. The "hot" spot below the thyroid is a suprasternal marker. **B,** An axial computed tomography scan demonstrates an irregular density in the left thyroid lobe at the level of the lesion seen on the radionuclide scan. The lesion contains a single area of calcification *(arrow)* and is not demarcated sharply from normal thyroid tissue. At operation, there proved to be extracapsular extension. (From Skarin AT: *Atlas of diagnostic oncology,* ed 3, St Louis 2003, Mosby.)

Thyroid Nodule PTG ALG

BASIC INFORMATION

DEFINITION

A thyroid nodule is an abnormality found on physical examination of the thyroid gland; nodules can be benign (70%) or malignant.

ICD-10CM CODES

E04.1	Nontoxic single thyroid nodule.
E05.2	Thyrotoxicosis with toxic single thyroid nodule.
E05.11	Thyrotoxicosis with toxic single thyroid nodule with thyrotoxic crisis or storm

EPIDEMIOLOGY & DEMOGRAPHICS

- Thyroid nodules are detected in 40% of the U.S. population.
- Thyroid nodules can be found in 50% of autopsies; however, only one in 10 is palpable.
- Malignancy is present in 5% to 15% of all thyroid nodules and in 7% to 9% of palpable nodules.
- Incidence of thyroid nodules increases after 45 yr. They are found more frequently in women (5% of women; 1% of men).
- History of prior head and neck irradiation increases the risk of thyroid cancer.
- Increased likelihood that nodule is malignant: Nodule increasing in size or >3 cm, regional lymphadenopathy, fixation to adjacent tissues, age <40 yr, symptoms of local invasion (dysphagia, hoarseness, neck pain, male sex, family history of thyroid cancer or polyposis [Gardner syndrome]), rapid growth during levothyroxine therapy, microcalcification within the nodule, and high intranodular vascular flow.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Palpable, firm, and nontender nodule in the thyroid area should prompt suspicion of carcinoma. Signs of metastasis are regional lymphadenopathy and inspiratory stridor.
- Signs and symptoms of thyrotoxicosis can be found in functioning nodules.

ETIOLOGY

- History of prior head and neck irradiation
- Family history of pheochromocytoma, carcinoma of the thyroid, and hyperparathyroidism (medullary carcinoma of the thyroid is a component of MEN-II)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Thyroid carcinoma
- Multinodular goiter
- Thyroglossal duct cyst
- Epidermoid cyst
- Laryngocele
- Nonthyroid neck neoplasm
- Branchial cleft cyst

WORKUP

- Ultrasonography is an inexpensive and effective modality to stratify malignancy risk.
- Fine-needle aspiration (FNA) biopsy is the best diagnostic study; the accuracy can be >90%, but it is directly related to the level of experience of the physician and the cytopathologist interpreting the aspirate. FNA is not routinely recommended for thyroid nodules <1 cm in diameter unless there are significant risk factors (see earlier).
- FNA biopsy is less reliable with thyroid cystic lesions; surgical excision should be considered for most thyroid cysts not abolished by aspiration.
- A diagnostic approach to thyroid nodule is described in Fig. 1. Preoperative, ultrasonically guided FNA accurately classifies 62% to 85% of thyroid nodules as benign; however, 15% to 30% of aspirations yield indeterminate cytologic findings. Table 1 describes the probability of malignancy at histology based on FNA biopsy cytology.

LABORATORY TESTS

- Serum TSH should be obtained in all patients with thyroid nodules. If suppressed, obtain free T4 and free T3 and thyroid scan to rule out "hot nodule," indicative of hyperthyroid adenoma. Less than 1% of hyperfunctioning nodules are malignant. Typically FNA biopsy is not necessary in hot nodules.
- Thyroid-stimulating hormone (TSH), T4, and serum thyroglobulin levels should be obtained before thyroidectomy in patients with confirmed thyroid carcinoma on FNA biopsy.
- Serum calcitonin at random or after pentagastrin stimulation is useful when suspecting medullary carcinoma of the thyroid and in anyone with a family history of medullary thyroid carcinoma.
- Serum thyroid autoantibodies (see "Thyroiditis" in Section I) are useful in patients with multinodular goiter and when suspecting thyroiditis.
- Molecular analysis of thyroid tissue for the presence of *BRAF* and *RAS* mutations and for *RET/PTC* and *PAX8-PPAR* gamma 1 gene rearrangements can be used as a diagnostic tool, since 60% to 70% of thyroid cancers harbor at least one genetic mutation. The gene expression classifier profile can be used to identify a subpopulation of patients with a low likelihood of cancer, thereby avoiding unnecessary surgery in patients with indeterminate FNA. The gene expression classifier test has a high negative predictive value for cytologically indeterminate nodules (95% for an atypical or follicular lesion of undetermined significance, 94% for a follicular neoplasm, and 85% for a lesion suggestive of cancer).

IMAGING STUDIES

- Thyroid ultrasound (Fig. E2) is useful to evaluate the size of the thyroid and the number, composition (solid versus cystic), and dimensions of the thyroid nodule; solid thyroid nodules have a higher incidence of malignancy, but cystic nodules can also be malignant. Table E2 summarizes ultrasound features of benign and malignant thyroid nodules. The three characteristics on thyroid ultrasound most predictive of cancer are nodules >2 cm, microcalcifications, and entirely solid nodules.
- Thyroid scan can be performed with technetium-99m pertechnetate, iodine-123, or iodine-131. Iodine isotopes are preferred because up to 35% of nodules that appear functioning on pertechnetate scanning may appear nonfunctioning on radioiodine scanning. A thyroid scan:
  1. Classifies nodules as hyperfunctioning (hot), normally functioning (warm), or nonfunctioning (cold); cold nodules have a higher incidence of malignancy.
  2. Scan has difficulty evaluating nodules near the thyroid isthmus or at the periphery of the gland.
  3. Normal tissue over a nonfunctioning nodule might mask the nodule as "warm" or normally functioning.
- Both thyroid scan and ultrasound provide information about the risk of malignant neoplasia based on the characteristics of the thyroid nodule, but their value in the initial evaluation of a thyroid nodule is limited because neither provides a definite tissue diagnosis.

TREATMENT

GENERAL Rx

- Evaluation of results of FNA:
  1. Normal cells: May repeat biopsy during present evaluation or reevaluate patient after 3 to 6 mo of suppressive therapy (L-thyroxine, prescribed in doses to suppress the TSH level to 0.1 to 0.5).
     a. Failure to regress indicates increased likelihood of malignancy.
     b. Reliance on repeat FNA biopsy is preferable to routine surgery for nodules not responding to thyroxine.
- Indeterminate: Use of gene expression classifier profile. If suspicious, perform surgery; if benign, monitor with subsequent repeat FNA and gene expression classifier profile.
- Malignant cells: Surgery.

DISPOSITION

Variable with results of FNA biopsy

REFERRAL

Surgical referral for FNA biopsy

PEARLS & CONSIDERATIONS

COMMENTS

- Most solid, benign nodules grow; therefore, an increase in nodule volume alone is not a reliable predictor of malignancy.
- Thyroid nodules incidentally identified on fluorodeoxyglucose-PET (FDG-PET) scan done for other disorders has a much higher malignancy rate (30% to 50%).

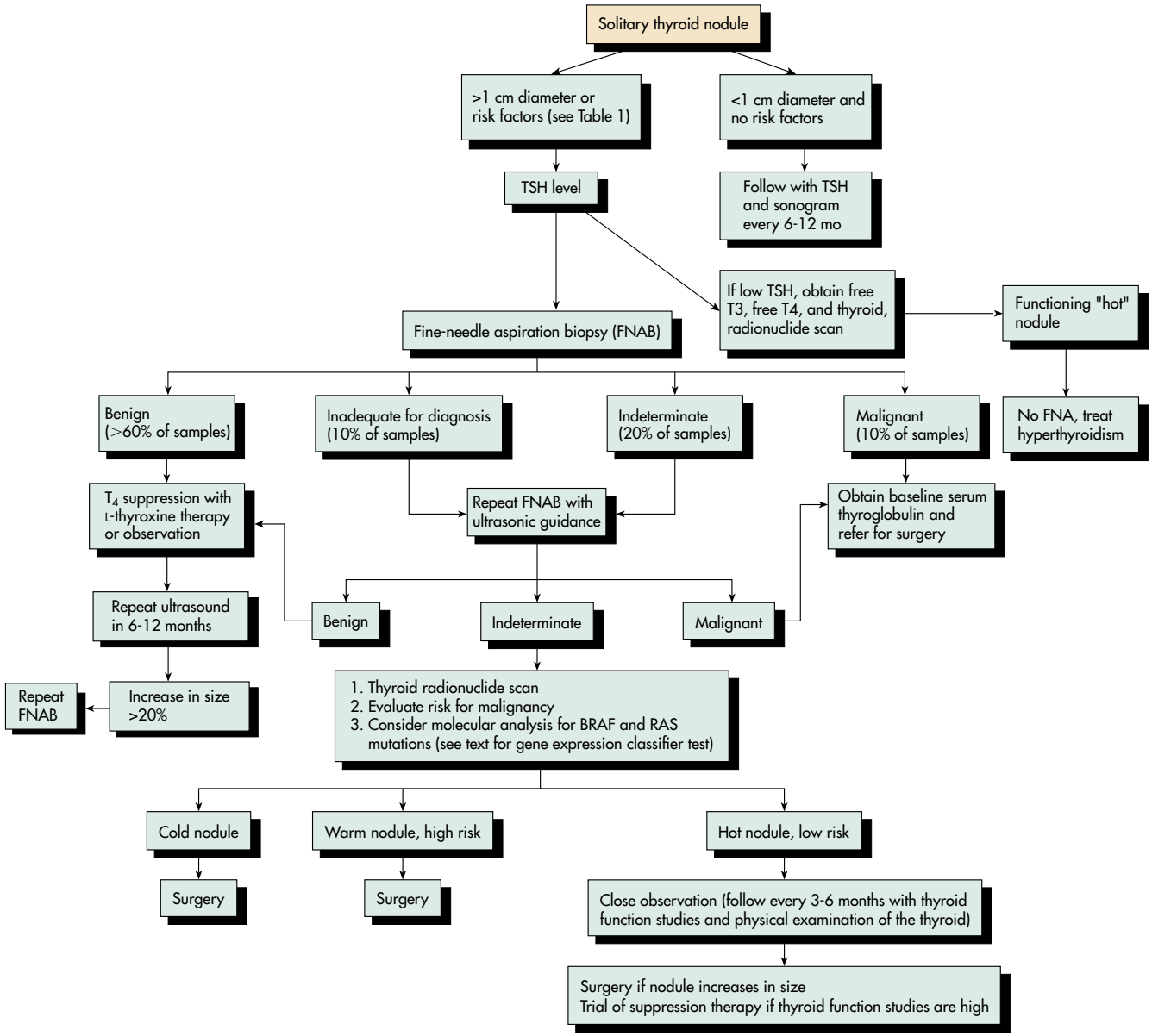

FIG. 1 Diagnostic algorithm for thyroid nodule. *FNA,* Fine needle aspiration; *T3,* triiodothyronine; *T4,* thyroxine; *TSH,* thyroid-stimulating hormone. (From Ferri F: *Ferri's best test,* ed 4, Philadelphia, Elsevier, 2017.)

TABLE 1 Clinical and Ultrasound Findings in Favor of Malignant Thyroid Nodules

Clinical Features	Ultrasound Findings
History	Higher suspicion
Young age (<20 yr) or older age (>60 yr)	Hypoechoic lesions
Male gender	Irregular margins
Neck irradiation during childhood or adolescence	Presence of microcalcifications
Rapid growth	Absence of halo
Recent changes in speaking, breathing, or swallowing	Internal or central blood flow
Family history of thyroid malignancy or MEN2	
Physical examination	Low suspicion
Firm and irregular consistency of nodule	Echo-free (cystic) lesion
Fixation to underlying or overlying tissues	Spongiform lesion
Vocal cord paralysis	
Regional lymphadenopathy	

MEN2, Multiple endocrine neoplasia II.
From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Elsevier.

- Surgery is indicated in hard or fixed nodule, presence of dysphagia or hoarseness, and rapidly growing solid masses regardless of "benign" results on FNA.
- Suppressive therapy of malignant thyroid nodules postoperatively with thyroxine is indicated. The use of suppressive therapy for benign solitary nodules is controversial.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Thyroid Nodule (Patient Information)
Thyroiditis (Related Key Topic)
Thyroid Carcinoma (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Alexander EK et al: Pre-operative diagnosis of benign thyroid nodules with indeterminate cytology, *N Engl J Med* 367:705-715, 2012.

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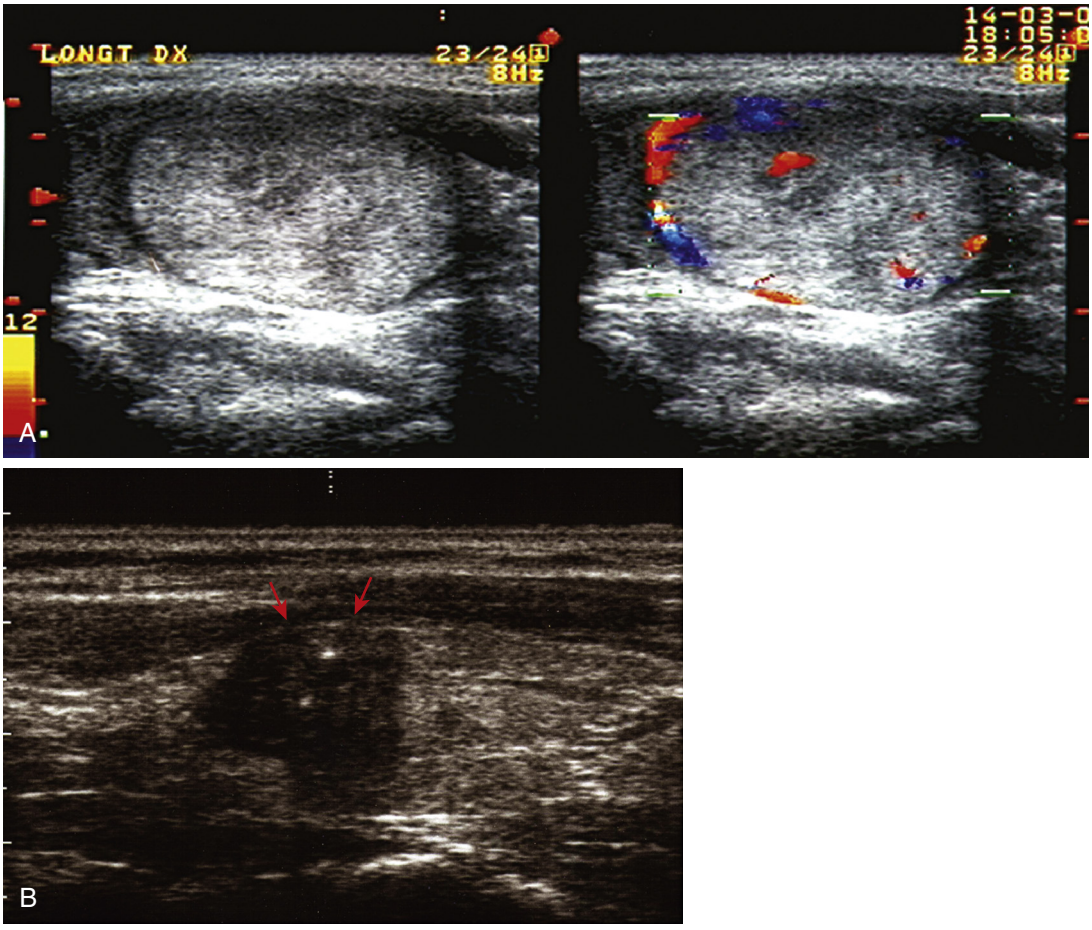

FIG. E2 Conventional and color flow Doppler ultrasonography. A, Benign lesion. Sonogram shows well-defined, oval, hyperechoic nodule with perinodular and slight intranodular blood flow. **B,** Malignant lesion. Sonogram shows a nodule with inhomogeneous hypoechoic aspect, microcalcifications, irregular borders, and invasion of the thyroid capsule *(arrows).* (From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Elsevier.)

TABLE E2 US Features of Benign and Malignant Thyroid Nodules (FNAC is still required for suspicious lesions)

	Benign	Malignant
Nodule characteristics	• A cystic nodule ± debris ± septations ▸ A sponge-like nodule • Posterior acoustic shadowing • A hyperechoic nodule • 'Comet tail' artefact (colloid nodule) • Multiple isoechoic nodules (multinodular goiter) • Multiple hypoechoic nodules (Hashimoto thyroiditis) • Indeterminate: A solid, well-defined nodule ± cystic components	• Solid nodules protruding into the cystic space • No posterior acoustic shadowing
Peripheral halo	• A thin, uniform halo	• An incomplete, irregular, or thickened halo
Nodule margin	• Smooth, regular margins	• An irregular, lobulated, or poorly defined margin
Calcification	• This is generally absent (eggshell calcification may be present)	• Microcalcification ▸ Fine or coarse calcification (commonly papillary or medullary carcinomas)
Metastatic spread		• Invasion of the adjacent tissues ± enlarged ipsilateral or bilateral cervical lymph nodes

From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.

BASIC INFORMATION

DEFINITION

Thyroiditis is an inflammatory disease of the thyroid. It is a multifaceted disease with various etiologies, different clinical characteristics (depending on the stage), and distinct histopathology. Thyroiditis can be subdivided into three common types (Hashimoto, painful, and painless) and two rare forms (suppurative and Riedel). To add to the confusion, there are various synonyms for each form, and there is no internationally accepted classification of autoimmune thyroid disease.

SYNONYMS

Hashimoto thyroiditis: Chronic lymphocytic thyroiditis, chronic autoimmune thyroiditis, lymphadenoid goiter

Painful subacute thyroiditis: Subacute thyroiditis, giant cell thyroiditis, de Quervain thyroiditis, subacute granulomatous thyroiditis, pseudogranulomatous thyroiditis

Painless postpartum thyroiditis: Subacute lymphocytic thyroiditis, postpartum thyroiditis

Painless sporadic thyroiditis: Silent sporadic thyroiditis, subacute lymphocytic thyroiditis

Infectious thyroiditis: Acute suppurative thyroiditis, bacterial thyroiditis, microbial inflammatory thyroiditis, pyogenic thyroiditis

Riedel thyroiditis: Fibrous thyroiditis

ICD-10CM CODES

E06.3 Autoimmune thyroiditis
E06.1 Subacute thyroiditis
E06.9 Thyroiditis, unspecified
E06.0 Acute thyroiditis
E06.5 Other chronic thyroiditis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Thyroiditis typically has three phases: thyrotoxic and hypothyroid (each lasting approximately 3 mo) and return to euthyroidism.
- Hashimoto: Patients may have signs of hyperthyroidism (tachycardia, diaphoresis, palpitations, weight loss) or hypothyroidism (fatigue, weight gain, delayed reflexes) depending on the stage of the disease. Usually there is diffuse, firm enlargement of the thyroid gland; the gland may also be of normal size (atrophic form with clinically manifested hypothyroidism).
- Painful subacute: Exquisitely tender, enlarged thyroid, fever; signs of hyperthyroidism are initially present; signs of hypothyroidism can subsequently develop.
- Painless thyroiditis: Clinical features are similar to subacute thyroiditis except for the absence of tenderness of the thyroid gland.
- Suppurative: Patient is febrile with severe neck pain, focal tenderness of the involved portion of the thyroid, erythema of the overlying skin.
- Riedel: Slowly enlarging hard mass in the anterior neck; often mistaken for thyroid cancer; signs of hypothyroidism occur in advanced stages.

ETIOLOGY

- Hashimoto: Autoimmune disorder that begins with the activation of CD4 T-helper lymphocytes specific for thyroid antigens. The etiologic factor for the activation of these cells is unknown
- Painful subacute: Possibly postviral; usually follows a respiratory illness not considered to be a form of autoimmune thyroiditis
- Painless thyroiditis: Frequently occurs postpartum
- Infectious (suppurative): Infectious etiology, generally bacterial, although fungi and parasites have also been implicated; often occurs in immunocompromised hosts or after a penetrating neck injury
- Riedel: Fibrous infiltration of the thyroid; etiology unknown
- Drug induced: Typically painless due to lithium, interferon-alfa, amiodarone, interleukin-2
- Radiation thyroiditis: Occurs 5 to 10 days after treatment with radioactive iodine; it is painful and may result in transient exacerbation of hyperthyroidism

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- The hyperthyroid phase of Hashimoto, subacute, and silent thyroiditis can be mistaken for Graves disease.
- Riedel thyroiditis can be mistaken for carcinoma of the thyroid.
- Painful subacute thyroiditis can be mistaken for infections of the oropharynx and trachea or for suppurative thyroiditis.
- Factitious hyperthyroidism can mimic silent thyroiditis.

WORKUP

- The diagnostic workup includes laboratory and radiologic evaluation to rule out other conditions that may mimic thyroiditis (see previously) and differentiate the various forms of thyroiditis.
- The patient's medical history may be helpful in differentiating the various types of thyroiditis (e.g., presentation after childbirth is suggestive of silent [postpartum, painless] thyroiditis; occurrence after a viral respiratory infection suggests subacute thyroiditis; history of penetrating injury to the neck indicates suppurative thyroiditis).

LABORATORY TESTS

- Thyroid-stimulating hormone, free T4: May be normal or indicative of hypothyroidism or hyperthyroidism depending on the stage of the thyroiditis.
- White blood cell (WBC) with differential: Increased WBC with left shift occurs with subacute and suppurative thyroiditis.
- Antimicrosomal antibodies: Detected in >90% of patients with Hashimoto thyroiditis and 50% to 80% of patients with silent thyroiditis.
- Serum thyroglobulin levels are elevated in patients with subacute and silent thyroiditis; this test is nonspecific but may be useful in monitoring the course of subacute thyroiditis and distinguishing silent thyroiditis from factitious hyperthyroidism (low or absent serum thyroglobulin level).

IMAGING STUDIES (FIGS. E1 and E2)

24-hr radioactive iodine uptake (RAIU) is useful to distinguish Graves disease (increased RAIU) from thyroiditis (normal or low RAIU). Table E1 summarizes factors that influence 24-hr thyroid iodide uptake.

TREATMENT

ACUTE GENERAL Rx

- The duration of the thyrotoxic phase of thyroiditis is usually 10 to 12 wk. This phase is followed by a hypothyroid phase typically lasting up to 12 wk.
- Treat hypothyroid phase in symptomatic patients somatic with levothyroxine 25 to 50 mcg/day initially and monitor serum thyroid-stimulating hormone initially every 6 to 8 wk.
- Control symptoms of hyperthyroidism with beta-blockers (e.g., propranolol 20 to 40 mg PO q6h or atenolol).
- Control pain in patients with subacute thyroiditis with nonsteroidal antiinflammatory drugs. Prednisone 20 to 40 mg qd may be used if nonsteroidals are insufficient, but it should be gradually tapered off over several wk.
- Use IV antibiotics and drain abscess (if present) in patients with suppurative thyroiditis.

DISPOSITION

- Hashimoto thyroiditis: Long-term prognosis is favorable; most patients recover their thyroid function.
- Painful subacute thyroiditis: Permanent hypothyroidism occurs in 10% of patients.
- Painless thyroiditis: 6% of patients have permanent hypothyroidism.
- Infectious thyroiditis: There is usually full recovery after treatment.
- Riedel thyroiditis: Hypothyroidism occurs when fibrous infiltration involves the entire thyroid.

REFERRAL

- Surgical referral in patients with compression of adjacent neck structures and in some patients with infectious (suppurative) thyroiditis
- Total thyroidectomy has been shown to improve symptoms in patients with Hashimoto thyroiditis who still have symptoms despite having normal thyroid gland function while receiving medical therapy.[1]

RELATED CONTENT

Thyroiditis (Patient Information)
Hyperthyroidism (Related Key Topic)
Hypothyroidism (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

[1] Guldvog I et al: Thyroidectomy versus medical management for euthyroid patients with Hashimoto disease and persisting symptoms: a randomized trial, *Ann Int Med* 170:453-464, 2019.

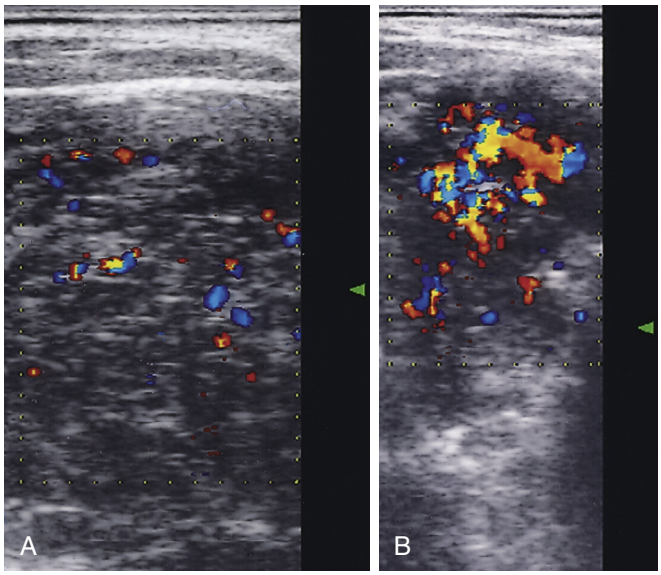

FIG. E1 A, Longitudinal ultrasound through the left lobe of the thyroid in a patient known to have Hashimoto thyroiditis reveals a loose, heterogeneous echotexture with abnormal color flow. There are enlarged neck nodes **(B),** again with abnormal color flow in this patient, who has developed lymphoma. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

FIG. E2 Thyroid scintigraphy demonstrating chronic thyroiditis affecting only the right lobe. (From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.)

TABLE E1 Factors That Influence 24-Hour Thyroid Iodide Uptake

Factors that Increase Uptake

Increased Hormone Synthesis

Hyperthyroidism

Response to glandular hormone depletion:
- Recovery from thyroid suppression
- Recovery from subacute thyroiditis
- Antithyroid agents

Excessive Hormone Losses
- Nephrotic syndrome
- Chronic diarrheal states
- Soybean ingestion

Normal Hormone Synthesis

Iodine deficiency:
- Dietary insufficiency
- Excessive loss (dehalogenase defect, pregnancy)

Hormone biosynthetic defects

Factors that Decrease Uptake

Decreased Hormone Synthesis

Primary hypofunction:
- Primary hypothyroidism
- Antithyroid agents
- Hormone biosynthetic defects
- Hashimoto disease
- Subacute thyroiditis

Secondary hypofunction

Exogenous thyroid hormones

Not Reflecting Decreased Hormone Synthesis

Increased availability of iodine:
- Diet or drugs
- Cardiac or renal insufficiency

Increased hormone release

Very severe hyperthyroidism (rare)

From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Elsevier.

Thyrotoxic Storm

BASIC INFORMATION

DEFINITION

Thyrotoxic storm is the abrupt and severe exacerbation of thyrotoxicosis. It is an acute, life-threatening complication of hyperthyroidism.

SYNONYM

Thyroid storm

ICD-10CM CODE
E05.5 Thyroid crisis or storm

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Tremor, tachycardia/tachyarrhythmias, fever (as high as 105.8 °F [41 °C])
- Sweating, diarrhea, vasodilation
- Lid lag, lid retraction, proptosis
- Altered mental status (psychosis, coma, seizures)
- Goiter
- Other: Evidence of precipitating factors (infection, trauma), congestive heart failure [CHF], hepatosplenomegaly, jaundice

ETIOLOGY

- Precipitating factors: Surgery, infection, myocardial infarction or cardiac disease, diabetic ketoacidosis, labor, iodinated IV contrast agents, radioactive iodine therapy
- Inadequate therapy in a hyperthyroid patient

DIAGNOSIS

The clinical presentation is variable. The patient may present with the following signs and symptoms:

- Fever
- Marked anxiety and agitation, psychosis
- Hyperhidrosis, heat intolerance
- Marked weakness and muscle wasting
- Tachyarrhythmias, palpitations
- Diarrhea, nausea, vomiting
- Elderly patients may have a combination of tachycardia, CHF, and mental status changes Although the diagnosis is based on clinical presentation, it can generally be ruled out if T_4 and T_3 levels are within normal limits

DIFFERENTIAL DIAGNOSIS

- Psychiatric disorders
- Alcohol or other drug withdrawal
- Pheochromocytoma
- Metastatic neoplasm

WORKUP

- Laboratory evaluation to confirm hyperthyroidism (elevated free T4, decreased thyroid-stimulating hormone [TSH])
- Evaluation for precipitating factors (e.g., ECG and cardiac enzymes in suspected MI, blood and urine cultures to rule out sepsis)
- Elimination of disorders noted in the differential diagnosis (e.g., psychiatric history, evidence of drug and alcohol abuse)

LABORATORY TESTS

- Free T_4, TSH
- Complete blood count with differential
- Blood and urine cultures
- Glucose
- Liver enzymes
- Blood urea nitrogen, creatinine
- Serum calcium
- Creatine phosphokinase

IMAGING STUDIES

Chest x-ray to exclude infectious process, neoplasm, CHF in suspected cases

TREATMENT

NONPHARMACOLOGIC THERAPY

- Nutritional care: Replace fluid deficit aggressively (daily fluid requirement may reach 6 L); use solutions containing glucose and add multivitamins to the hydrating solution.
- Monitor for fluid overload and CHF in the elderly and in those with underlying cardiovascular or renal disease.
- Treat significant hyperthermia with cooling blankets.

ACUTE GENERAL Rx

- Inhibition of thyroid hormone synthesis:
  1. Administer propylthiouracil (PTU) 800 mg initially (PO or by nasogastric tube)/PR, then 200 to 300 mg PO/PR q6h. PTU is preferred over methimazole because it has the added benefit of blocking peripheral conversion of T_4 to T_3
  2. If the patient is allergic to PTU, use methimazole 80 to 100 mg (PO or by nasogastric tube)/PR followed by 40 mg PO/PR q8h. Methimazole can also be administered IV 60 to 120 mg daily, divided doses
- Inhibition of stored thyroid hormone release from the gland:
  1. Sodium iodide 1 g IV over 24 hours or potassium iodide (oral) 5 drops 4 times/day (super-saturated potassium iodide). It is important to administer PTU or methimazole 1 hr *before* the iodide to prevent the oxidation of iodide to iodine and its incorporation in the synthesis of additional thyroid hormone
  2. Corticosteroids: Dexamethasone 1 to 2 mg IV q6h or hydrocortisone 100 mg IV q6h for approximately 48 hr is useful to inhibit thyroid hormone release, impair peripheral conversion of T_3 from T_4, and provide additional adrenocortical hormone to correct deficiency (if present)
- Suppression of peripheral effects of thyroid hormone:
  1. Beta-adrenergic blockers: Administer propranolol 60 to 80 mg every 4 hours. Propranolol may also be given IV 1 mg/min for 2 to 10 min under continuous ECG and blood pressure monitoring. Beta-adrenergic blockers must be used with caution in patients with severe CHF or bronchospasm. Cardioselective beta-blockers (e.g., esmolol 500 mg IV over 1 min, then 50 to 100 mg/kg/min or metoprolol 5 to 10 mg IV every 2 to 4 hours) may be more appropriate for patients with bronchospasm, but these patients must be closely monitored for exacerbation of bronchospasm because these agents lose their cardioselectivity at high doses. The calcium channel blocker diltiazem can also be given to reduce the heart rate. Dose is 0.25 mg/kg over 2 min, then infusion of 10 mg/min. Oral dose is 60 to 90 mg every 6 to 8 hours
- Control of fever with acetaminophen 325 to 650 mg q4h; avoidance of aspirin because it displaces thyroid hormone from its binding protein
- Treatment of any precipitating factors (e.g., antibiotics if infection is strongly suspected)

DISPOSITION

Patients with thyrotoxic crisis should be treated and appropriately monitored in the ICU.

REFERRAL

Endocrinology referral is appropriate in patients with thyrotoxic crisis.

PEARLS & CONSIDERATIONS

COMMENTS

If the diagnosis is strongly suspected, therapy should be started immediately without waiting for laboratory confirmation.

RELATED CONTENT

Graves Disease (Related Key Topic)
Hyperthyroidism (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READING

McDermott MT: In the clinic: hyperthyroidism, *Ann Intern Med ITC* 3:1-14, 2012.

BASIC INFORMATION

DEFINITION

Tinea capitis is a dermatophyte infection of hair shaft and follicles of the scalp, eyebrows, and eyelashes. It is a form of superficial mycosis. Etiologic agents are fungal species of the genera *Microsporum* and *Trichophyton*.

SYNONYMS

Ringworm of the scalp
Ringworm of the head
Gray patch tinea capitis
Black dot tinea capitis
Tinea tonsurans
Herpes tonsurans
Kerion
Favus

ICD-10CM CODE
B35.0 Tinea barbae and tinea capitis

EPIDEMIOLOGY & DEMOGRAPHICS

Tinea capitis primarily affects prepubertal children with peak age between 3 and 7 yr old. Adult cases are rare, possibly because of the fungistatic effect of the sebum found in older persons. Urban living, large family size, low socioeconomic status, and crowded living conditions may contribute to an increased incidence of tinea capitis. The elderly and immunocompromised individuals have an increased risk of infection. The incidence of the disease varies worldwide; however, it is relatively low in the U.S. It is reportedly widespread in parts of Central and South America, India, and Africa.

In the U.S., peak incidence occurs in school-aged children of low socioeconomic status, with African American male children accounting for the greatest proportion of cases. About 3% to 8% of American children are affected, and 34% of household contacts are asymptomatic carriers.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Classic triad of scalp scaling, alopecia, and cervical adenopathy. Table 1 summarizes clinical manifestations of tinea capitis in children.
- Most forms of tinea capitis begin with one or few round patches of scale (Fig. E1) or alopecia (Fig. E2).
- Primary lesions include plaques, papules, pustules, or nodules on the scalp (usually occipital region).
- Secondary lesions include scales, alopecia (usually reversible), erythema, exudates, and edema.
- Scalp pruritus may be present.
- Fever, pain, and lymphadenopathy (commonly postcervical) may occur with inflammatory lesions.
- Different clinical patterns of tinea capitis have been described:
  1. Gray patch: Lesions are scaly and well demarcated. The hairs within the patch break off a few millimeters above the scalp. One or several lesions may be present; sometimes the lesions join to form larger ones.
  2. Black dot: Early lesions with erythema and scaling patch are easily overlooked until areas of alopecia develop. Hairs within the patches break at the surface of the scalp, leaving behind a pattern of swollen black dots.
  3. Kerion (Fig. E3): Inflamed, exudative, pustular, boggy, tender nodules exhibiting marked edema, and hair loss seen in severe tinea capitis. Caused by immune response to the fungus. May lead to some scarring.
  4. Favus: Production of scutula (hair matted together with dermatophyte hyphae and keratin debris), characterized by yellow cup-shaped crusts around hair shafts. A fetid odor may be present.

TABLE 1 Clinical Manifestations of Tinea Capitis in Children

Clinical Feature	Comment
Scalp	
Alopecia	One or multiple patches; may simulate alopecia areata
Scaling	May be minimally inflammatory; may mimic seborrheic dermatitis
Erythema	Localized or widespread
Pustules	Differential diagnosis includes sterile folliculitis or bacterial folliculitis
"Black dots"	Alopecia with hair shafts broken off at surface of skin; may simulate trichotillomania
Kerion	Boggy, tender plaque with pustules and purulent discharge; represents a vigorous host immune response
Scarring	Rarely seen when untreated; usually follows kerion
Favus	Yellow, cup-shaped crusts around the hair
Other	
Lymphadenopathy	Common; cervical or occipital
Id reaction	Widespread, papular or papulovesicular eruption; extremity-predominant; usually seen after initiation of therapy; must be recognized as distinct from true drug reaction

From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.

ETIOLOGY

Although fungi of the *Microsporum* or *Trichophyton* genera cause most cases of tinea capitis, causative species vary between geographical areas and across time. *T. tonsurans* is the predominant cause of tinea capitis, present in more than 90% of cases in North and Central America. *Microsporum canis, M. audouinii,* and *Trichophyton mentagrophytes* are less common. The most common causative species for black dot tinea capitis is *T. tonsurans*, while gray patch tinea capitis tends to be caused by *M. audouinii* and *M. canis.* Infection of the hair shaft is preceded by invasion of the stratum corneum of the scalp. Transmission of *T. tonsurans* occurs from person-to-person via infected persons or asymptomatic carriers, fallen infected hairs, animal vectors, and fomites. *M. audouinii* is commonly spread by dogs and cats. Infectious fungal particles may remain viable for many mo. Even though the organism remains viable on combs, hairbrushes, and other fomites for long periods of time, the role of fomites in spreading the infection may vary in different geographic areas.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Seborrheic dermatitis and psoriasis may be confused with tinea capitis. Other conditions that resemble tinea capitis include alopecia areata, impetigo, pediculosis, trichotillomania, traction alopecia, folliculitis, pseudopelade, seborrhea/atopic dermatitis, psoriasis, carbuncles, pyoderma, lichen ruber planus, and lupus erythematosus; these should also be considered in the differential. Table 2 highlights distinctive features of conditions that may be confused for tinea capitis.

WORKUP

- KOH testing of hair shaft extracted from the lesion, not the scale, because the *T. tonsurans* spores attach to or reside inside hair shafts and will rarely be found in the scales.
- Wood's ultraviolet light fluoresces blue-green on hair shafts for *Microsporum* infections but will fail to identify *T. tonsurans.*
- Fungal culture of hairs and scales on fungal medium such as Sabouraud agar may be used to confirm the diagnosis, especially if uncertain.
- Histology of biopsies with fungal staining in cases where mycology tests are negative because of treatment initiation.

TREATMENT

- Griseofulvin is the gold standard FDA-approved treatment. Published studies show mean efficacy for griseofulvin treatment of about 68% for *Trichophyton* species and 88% for *Microsporum.* It is less costly than other drug options and has an excellent long-term safety profile. Micronized and ultramicronized preparations are absorbed better, and side effects are infrequent, especially when administered with fatty meals. Periodic monitoring of hematologic, liver, and renal function may be indicated, especially in prolonged treatment over 8 wk.
  1. **Children:** Griseofulvin is approved for children older than 2 yr of age: microsize griseofulvin 10 to 25 mg/kg PO per day in one single dose or two divided doses (maximum, 1 g/day; for tinea capitis, higher doses [20 to 25 mg/kg/day] have been recommended) or ultramicrosize

TABLE 2 Differential Diagnosis of Tinea Capitis

Disorder	Differentiating Features
Psoriasis	Red skin with thick, uniform, silvery scale, sharply demarcated; often psoriasis at other body sites also.
Dermatitis	Main possibility is seborrheic dermatitis: Usually more diffuse and has uniform fine scaling, rather than localized areas; doesn't typically cause alopecia or significant inflammation. May also be present on the face, especially the nasolabial fold, or as otitis externa. Atopic dermatitis is generally diffuse on scalp and almost inevitably present at other sites, but may coexist with tinea capitis, especially in children.
Pityriasis amiantacea	Thick sheets of asbestos-like scale, very adherent, generally a solitary patch. This may occur in various dermatoses.
Lichen simplex	Usually nape of neck; cobblestoned or lichenified skin thickening, with broken hairs that are not coated with scale.
Alopecia areata	Usually not inflamed (may be mildly so), not scaly, usually sharply defined. "Exclamation mark" hairs occur but are not coated with fungus; "cadaverized" hairs especially cause difficulty, as they mimic black dot alopecia.
Scarring alopecias	Examples: Discoid lupus erythematosus, lichen planus of scalp; cause perifollicular inflammation around intact hairs; usually associated with lesions at other sites also. Dissecting cellulitis of scalp is also in this differential.
Bacterial infections	Impetigo causes crusting but little inflammation, and hairs are intact; carbuncle is deeper and very tender but may be in the differential of kerion.
Trichotillomania	Broken hairs of unequal length, but hair shafts themselves and the scalp are normal.
Damage from hairdressing processes	Usually clear from the timescale.
Neoplasm	May be in the differential of kerion; usually slower-growing and mainly on elderly, balding scalp, whereas kerion is in children or young adults with previously intact hair.

From White GM, Cox NH (eds): *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.

griseofulvin, 5 to 15 mg/kg PO per day (maximum, 750 mg/day), in one single dose or two divided doses. Optimally, griseofulvin is given after a meal containing fat (e.g., peanut butter or ice cream). Recommended treatment length is 6 to 8 wk and should be continued 2 wk beyond clinical resolution (until hair regrowth occurs). Some children may require higher doses to achieve clinical cure.

2. **Adults and elderly persons:** Microsize griseofulvin 500 mg PO per day in one single dose or divided doses. The other option is ultramicrosize griseofulvin 375 mg PO per day in one single dose or divided doses. Recommended treatment length is 4 to 6 wk.

- Newer alternative treatments: Oral terbinafine, itraconazole, or fluconazole are comparable in efficacy and safety to griseofulvin, with possibly shorter treatment and better patient compliance. Preferred when resistant or when an allergy to griseofulvin is of concern. Monitoring of CBC, liver function tests, and renal function may be indicated.
  1. Terbinafine—4-wk course of therapy as effective as with griseofulvin. Dosages are 67.5 mg/day for patients weighing <20 kg; 125 mg/day for patients weighing 20 to 40 kg; and 250 mg for patients weighing >40 kg
  2. Itraconazole—3.5 mg/kg daily for 4 to 6 wk or pulse therapy of 5 mg/kg daily for 1 wk each mo for 2 to 3 mo (not approved for children)
  3. Fluconazole—the only oral antifungal agent approved for children <2 yr, 6 mg/kg/day for 6 wk in children (3 to 6 wk in adults) or 8 mg/kg weekly for 8 to 12 wk (cap at 150 mg weekly for adults)
- The adjuvant use of antifungal shampoos may be recommended for all patients and household contacts. Shampoo like selenium sulfide 2.5% used for 5 min or ketoconazole shampoo used 2 to 3 times/wk can help prevent infection or eradicate asymptomatic carrier state by inhibiting fungal growth.
- Severe inflammatory kerion can be managed with additional prednisone 40 mg daily (1 mg/kg/day in children) and tapering over 2 wk.
- Prompt treatment is indicated, as is examination of siblings and other household contacts for evidence of tinea capitis.
- Recommend follow-up visit every 2 to 4 wk with Wood's light, microscopic study, and fungal culture. A mycologic documented cure is the goal of treatment.
- Pets that are infected or asymptomatic carriers should be treated.
- Children receiving treatment for tinea capitis may attend school once they start therapy with griseofulvin or other effective systemic agent.

PEARLS & CONSIDERATIONS

- Systemic antifungal therapy is required for tinea capitis because topical antifungal medications are not effective.
- Shaving of the head, haircuts, or wearing a cap or scarf during treatment is unnecessary.
- Sharing of combs, hair ribbons, and hairbrushes should be discouraged.

COMMENTS

- Confirming the diagnosis of tinea capitis with a laboratory specimen is important because misdiagnosis will result in delay or improper treatment.
- Patients and their families should look for sources of infections and disinfect contaminated objects such as combs, brushes, towels, and headgear. Avoid sharing personal hygiene utensils.
- Culture of hairs and scalp dander facilitates carrier identification and prevention.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Tinea Capitis (Patient Information)

AUTHORS: **Priya Sarin Gupta, MD, MPH, Nadine Mbuyi, MD,** and **Alvaro M. Rivera, MD**

SUGGESTED READING

Gupta AK, Drummond-Main C: Meta-analysis of randomized, controlled trials comparing particular doses of griseofulvin and terbinafine for the treatment of tinea capitis, *Pediatr Dermatol* 30(1-6), 2013.

FIG. E1 Tinea capitis. Diffuse scaling with minimal erythema and patchy alopecia. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

FIG. E2 "Black dot" tinea capitis. This well-demarcated patch of alopecia is composed of numerous broken-off hair shafts (black dots). (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

FIG. E3 Kerion. This fluctuant, erythematous, boggy, crusted plaque was exquisitely tender to palpation. *Trichophyton tonsurans* was isolated in fungal culture. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Tinea corporis is a dermatophyte fungal infection caused by the genera *Trichophyton* or *Microsporum*. Tinea corporis includes all superficial dermatophyte infections of the skin other than those involving the scalp, beard, face, hands, feet, and groin.

SYNONYMS

Ringworm
Body ringworm
Tinea circinata

ICD-10CM CODE
B35.4 Tinea corporis

EPIDEMIOLOGY & DEMOGRAPHICS

- The disease is more common in warm climates.
- There is no predominant age or sex.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typically appears as single (Fig. E1) or multiple annular lesions with an advancing scaly border (Fig. E2); the margin is slightly raised, reddened (Fig. E3), and may be pustular.
- The central area becomes hypopigmented and less scaly as the active border progresses outward, thus the name "ringworm."
- The trunk and legs are primarily involved.
- Pruritus is variable.
- It is important to remember that recent topical corticosteroid use can significantly alter the appearance of the lesions.
- Tinea gladiatorum is a common problem for wrestlers.

ETIOLOGY

Trichophyton rubrum is the most common pathogen. Other common causes in the U.S. are *M. canis* and *T. mentagrophytes*. Table 1 summarizes common dermatophytes that cause tinea corporis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pityriasis rosea
- Erythema multiforme
- Psoriasis
- Cutaneous systemic lupus erythematosus
- Secondary syphilis
- Nummular eczema
- Eczema
- Granuloma annulare
- Lyme disease
- Tinea versicolor
- Contact dermatitis

WORKUP

Diagnosis is usually made on clinical grounds. It can be confirmed by direct visualization under the microscope of a small fragment of the scale using wet mount preparation and potassium hydroxide solution; dermatophytes appear as translucent branching filaments (hyphae) with lines of separation appearing at irregular intervals.

LABORATORY TESTS

- Microscopic examination of hyphae.
- Mycotic culture is usually not necessary.
- Biopsy is indicated only when the diagnosis is uncertain and the patient has not responded to treatment.
- HIV (widespread tinea corporis may be a presenting sign of AIDS).

TREATMENT

NONPHARMACOLOGIC THERAPY

Affected areas should be kept clean and dry.

ACUTE GENERAL Rx

- Various creams are effective; the application area should include normal skin approximately 2 cm beyond the affected area:
  1. Butenafine cream applied qd for 14 days
  2. Terbinafine cream applied bid for 7 to 14 days
  3. Other effective topical agents are sulconazole, miconazole, clotrimazole, ketoconazole, naftifine, ciclopirox olamine, and efinaconazole
- Systemic therapy is reserved for severe cases and is usually given up to 4 wk; commonly used agents:
  1. Fluconazole, 150 mg once a week for 4 wk
  2. Terbinafine, 250 mg qd for 7 to 14 days
  3. Itraconazole, 200 mg/day for 1 wk

DISPOSITION

Majority of cases resolve without sequelae within 3 to 4 wk of therapy.

REFERRAL

Dermatology referral in patients with persistent or recurrent infections

RELATED CONTENT

Ringworm (Patient Information)
Tinea Capitis (Related Key Topic)
Tinea Cruris (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

TABLE 1 Common Dermatophytes that Cause Tinea Corporis

Dermatophyte	Clinical Features
Anthropophilic	
Trichophyton rubrum	Commonly harbored by hair follicles; may produce concentric rings; can recur; causative organism in nodular perifolliculitis (Majocchi granuloma) and most common cause of tinea corporis
T. tonsurans	Commonly seen in adults who care for children with tinea capitis caused by this organism
Epidermophyton floccosum	Generally restricted to groin or feet; responsible for eczema marginatum
T. concentricum	Responsible for tinea imbricata; infections typically chronic
T. interdigitale (previously *T. mentagrophytes* var. *interdigitale*)	Causes interdigital tinea pedis, tinea cruris, and onychomycosis
Zoophilic	
T. mentagrophytes (previously *T. mentagrophytes* var. *mentagrophytes*)	May be associated with dermatophytid reaction; causes inflammatory tinea pedis and tinea barbae; associated with exposure to small mammals
Microsporum canis	Associated with pet exposure (cat or dog)
T. verrucosum	May mimic bacterial furunculosis; associated with exposure to cattle
Geophilic	
M. gypseum	Frequently associated with outdoor/occupational exposure; lesions may be inflammatory or bullous

From Bolognia J et al: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

FIG. E1 Tinea corporis. An expanding, erythematous, annular plaque. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

FIG. E2 Tinea corporis. Multiple annular, erythematous, scaly plaques with hyperpigmentation of the upper back and shoulders of a teenage boy. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

FIG. E3 Tinea corporis. Multiple annular, erythematous plaques with confluence and a polycyclic configuration occurred in this immunocompromised patient. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

Tinea Cruris PTG

BASIC INFORMATION

DEFINITION

Tinea cruris is a dermatophyte infection of the groin.

SYNONYMS

Jock itch
Groin ringworm
Crotch itch

ICD-10CM CODE
B35.6 Tinea cruris

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common during the summer in adolescent and young adult males.
- Males are affected more frequently than females; however, it has become more common in postpubertal females who are overweight or who often wear tight jeans or pantyhose.
- The infection often coexists with tinea pedis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- It begins as a small erythematous, and scaling or crusted patch that spreads peripherally.
- Erythematous plaques have a half-moon shape and a scaling border.
- The acute inflammation tends to move down the inner thigh (Fig. E1) and usually spares the scrotum; in severe cases the fungus may spread onto the buttocks.
- Itching may be severe.
- Red papules, vesicles, and pustules may be present.
- An important diagnostic sign is the advancing well-defined border with a tendency toward central clearing.

ETIOLOGY

- Dermatophytes of the genera *Trichophyton, Epidermophyton,* and *Microsporum. T. rubrum* and *E. floccosum* are the most common infecting agents. Table 1 summarizes common causative agents of tinea cruris.
- Transmission from direct contact (e.g., infected persons, animals). The patient's feet should be evaluated as a source of infection because tinea cruris is often associated with tinea pedis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Candidal intertrigo
- Psoriasis
- Seborrheic dermatitis
- Erythrasma
- Contact dermatitis
- Tinea versicolor

WORKUP

Diagnosis is based on clinical presentation and demonstration of hyphae microscopically using potassium hydroxide.

LABORATORY TESTS

- Microscopic examination.
- Cultures are generally not necessary.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Keep infected area clean and dry.
- Boxer shorts are preferred to briefs. The reduction of perspiration and enhancement of evaporation from the crural area are necessary prophylactic measures.

ACUTE GENERAL Rx

- Various topical antifungal agents are available:
  1. Butenafine cream, applied qd × 14 days
  2. Terbinafine cream, applied bid × 14 days
- Drying powders (e.g., miconazole nitrate) may be useful in patients with excessive perspiration.
- Oral antifungal therapy is generally reserved for cases unresponsive to topical agents or can be used along with topical agents in severe cases. Effective medications are fluconazole 200 mg qd × 7 days or 150 mg once a wk for 4 wk, terbinafine 250 mg qd × 14 days, or itraconazole 200 mg/day for 7 days.

DISPOSITION

Most cases respond promptly to therapy with complete resolution within 2 to 3 wk.

RELATED CONTENT

Tinea Cruris (Patient Information)
Tinea Capitis (Related Key Topic)
Tinea Corporis (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

TABLE 1 Tinea Cruris: Common Causative Pathogens

Dermatophyte	Clinical features
Trichophyton rubrum	• Most common cause of tinea cruris • Infection tends to be chronic • Fungus not viable in scale (e.g., on furniture, rugs, linens) for long periods of time • Frequent extension to buttocks, waist, and thighs
Epidermophyton floccosum	• Commonly associated with "epidemics" of tinea cruris in locker rooms or dormitories • Infection is acute (rarely chronic) • Arthroconidia are viable in scale (e.g., on furniture, rugs, linens) for long periods of time • Infection rarely extends beyond groin region • Causative agent of "eczema marginatum" (well demarcated borders with multiple small vesicles or, sometimes, vesiculopustules)
T. mentagrophytes (previously *T. mentagrophytes* var. *mentagrophytes*)	• Infection tends to be more severe and acute, with intense inflammation and pustule formation • May rapidly spread to the trunk and lower extremities, causing a severe inflammatory condition • Often acquired from animal dander

From Bolognia J et al: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

FIG. E1 Dermatophyte infection. A, *Tinea cruris* showing areas of postinflammatory hyperpigmentation and active infection at the border of the lesions. **B,** Histologically, fungal hyphae are localized within a compact stratum corneum layer. **C,** Potassium hydroxide preparation from a scraping showing fungal forms. (**A,** From Callen JP et al: *Color atlas of dermatology,* Philadelphia, 1993, Saunders, p. 318; **B** and **C,**from Elston DM, Ferringer T: *Dermatopathology,* Edinburgh, 2009, Saunders, p. 275.)

BASIC INFORMATION

DEFINITION

Tinea pedis is a dermatophyte infection of the feet.

SYNONYM

Athlete's foot

ICD-10CM CODE
B35.3 Tinea pedis

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common dermatophyte infection
- Increased incidence in hot humid weather; occlusive footwear is a contributing factor
- Occurrence is rare before adolescence
- More common in adult males

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typical presentation is variable and ranges from erythematous scaling plaques and isolated blisters to interdigital maceration (Fig. E1). The four major types of tinea pedis are summarized in Fig. E2.
- The infection usually starts in the interdigital spaces of the foot. Most infections are found in the toe webs or on the soles.
- Fourth or fifth toes are most commonly involved.
- Pruritus is common and is most intense after removal of shoes and socks.
- Infection with *Trichophyton rubrum* often manifests with a "moccasin" distribution affecting the soles and lateral feet.

Tinea pedis caused by *Trichophyton mentagrophytes* (interdigitale) can present with:

- Erythema and desquamation between the toes
- Multilocular bullae involving the thin skin of the plantar arch and along the sides of the feet and heel
- White superficial onychomycosis

ETIOLOGY

- Dermatophyte infection caused by *T. rubrum, Trichophyton mentagrophytes,* or less commonly *Epidermophyton floccosum.*
- There may be an autosomal dominant predisposition to this form of infection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Contact dermatitis
- Toe web infection (bacterial or candidal infection)
- Eczema
- Psoriasis
- Keratolysis exfoliativa
- Juvenile plantar dermatosis

WORKUP

- Diagnosis is usually made by clinical observation.
- Laboratory testing, when performed, generally consists of a simple potassium hydroxide preparation with mycologic examination under a light microscope to confirm the presence of dermatophytes.

LABORATORY TESTS

- Microscopic examination of a scale or the roof of a blister with 10% KOH under low or medium power will reveal hyphae.
- Mycologic culture is rarely indicated in the diagnosis of tinea pedis.
- Biopsy is reserved for when the diagnosis remains in question after testing or failure to respond to treatment.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Hyperhidrosis is a predisposing factor for tinea pedis. Keep infected area clean and dry. Aerate feet by using sandals when possible.
- Use 100% cotton socks rather than nylon socks to reduce moisture.
- Areas likely to become infected should be dried completely before being covered with clothes.

ACUTE GENERAL Rx

- Benzylamines: Butenafine HCl 1% cream applied bid for 1 wk or qd for 4 wk is effective in interdigital tinea pedis.
- Allylamines: Terbinafine cream applied bid × 14 days, or naftifine 1% cream applied qd or naftifine gel applied bid for 4 wk produces a significantly high cure rate.
- Imidazoles: Econazole, ketoconazole, miconazole, luliconazole, and clotrimazole cream are also effective agents. Clotrimazole 1% cream is an over-the-counter treatment. It should be applied to affected and surrounding area bid for up to 4 wk.
- Ciclopirox and tolnaftate are other antifungal agents available in cream, suspension, or gel. Tolnaftate is also available as a lotion, spray, or powder.
- When using topical preparations, the application area should include normal skin approximately 2 cm beyond the affected area.
- Areas of maceration can be treated with Burow solution soaks for 10 to 20 min bid followed by foot elevation.
- Oral agents (fluconazole 150 mg once per wk for 4 wk, terbinafine 250 mg/day for 14 days, itraconazole 200 mg bid × 7 days, or griseofulvin 500 to 1000 mg/day for 14 days) can be used in combination with topical agents in resistant cases.

PEARLS & CONSIDERATIONS

- Use of tolnaftate powder (Tinactin) or Zeasorb medicated powder on the feet after bathing may be helpful in preventing recurrent tinea pedis in susceptible persons.
- Combination therapy of antifungal and corticosteroid (clotrimazole/betamethasone [Lotrisone]) should only be used when the diagnosis of fungal infection is confirmed and inflammation is a significant issue.
- Nystatin is not effective and should not be used.

RELATED CONTENT

Athlete's Foot (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

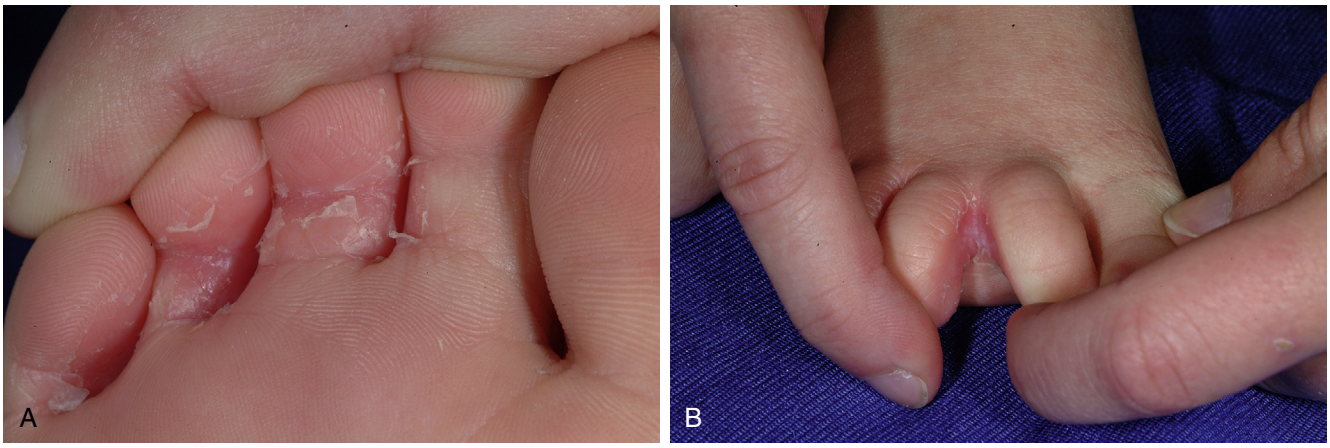

FIG. E1 Tinea pedis. This 6-year-old girl showed erythema and desquamation of the plantar foot and toes **(A)** and toe-web erythema and maceration **(B).** (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

THE FOUR MAJOR TYPES OF "TINEA PEDIS" CAUSED BY DERMATOPHYTES AND NON-DERMATOPHYTES			
Type	**Causative organism**	**Clinical features**	**Treatment considerations**
Moccasin	*Trichophyton rubrum* *Epidermophyton floccosum* *Neoscytalidium hyalinum* *N. dimidiatum*	Diffuse hyperkeratosis, erythema scaling and fissures on one or both plantar surfaces; frequently chronic and difficult to cure;* occasionally associated with immune deficiency	Topical antifungal plus product with urea or lactic acid; may require oral antifungal therapy
Interdigital	*T. interdigitale* (previously *mentagrophytes* var. *interdigitale*) *T. rubrum* *E. floccosum* *N. hyalinum* *N. dimidiatum* *Candida* spp. *Fusarium* spp.	Most common type; erythema, scaling, fissures and maceration in the web spaces; the two lateral web spaces are most commonly affected; "dermatophytosis complex" (fungal infection followed by bacterial invasion†) can develop; pruritus common; may extend to dorsum and sole of foot	Topical antifungal; may require topical or oral antibiotic if superimposed bacterial infection
Inflammatory (vesicular)	*T. mentagrophytes* (previously *T. mentagrophytes* var. *mentagrophytes*)	Vesicles and bullae on the medial foot; often associated with a dermatophytid reaction‡	Topical antifungal usually sufficient
Ulcerative	*T. rubrum* *T. interdigitale* (previously *T. mentagrophytes* var. *interdigitale*) *E. floccosum*	Typically an exacerbation of interdigital tinea pedis; ulcers and erosions in the web spaces; commonly secondarily infected with bacteria; seen in immunocompromised and diabetic patients	Topical antifungal; may require topical or oral antibiotics if secondary bacterial infection (common)

Dermatophytes Non-dermatophytes

*Because of the thickness of stratum corneum on plantar surfaces and the inability of *T. rubrum* to elicit a sufficient immune response to eliminate the fungus.
†Often *Pseudomonas, Proteus* spp., or *Staphylococcus aureus*.
‡Reaction to fungal elements presenting as a dyshidrotic-like eruption on the fingers and palms (culture negative for fungus).

FIG. E2 The four major types of tinea pedis caused by dermatophytes and nondermatophytes. (From Bolognia J et al: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.)

Tinea Unguium PTG

BASIC INFORMATION

DEFINITION

Tinea unguium is defined as a persistent fungal infection affecting the toenails and fingernails.

SYNONYMS

Onychomycosis
Ringworm of the nails

ICD-10CM CODE
B35.1 Tinea unguium

EPIDEMIOLOGY & DEMOGRAPHICS

- Tinea unguium is most commonly found in people between the ages of 40 and 60 yr.
- Tinea unguium rarely occurs before puberty.
- Incidence: 20 to 100 cases/1000 population.
- Toenail infection is 4 to 6 times more common than fingernail infection.
- Tinea unguium affects men more often than women.
- Occurs more frequently in patients with diabetes, peripheral vascular disease, and any conditions resulting in the suppression of the immune system.
- Occlusive footwear, physical exercise followed by communal showering, and incompletely drying the feet predispose the individual to developing tinea unguium.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Tinea unguium causes nails to become thick, brittle, hard, distorted, and discolored (yellow to brown color) (Fig. E1). Eventually, the nail may loosen, separate from the nail bed, and fall off (Fig. E2).
- Tinea unguium is frequently associated with tinea pedis (athlete foot).

ETIOLOGY

- The most common causes of tinea unguium are dermatophyte, yeast, and nondermatophyte molds
- The dermatophyte *Trichophyton rubrum* accounts for 80% of all nail infections caused by fungus
- *Trichophyton interdigitale* and *Trichophyton mentagrophytes* are other fungi causing tinea unguium
- The yeast *Candida albicans* is responsible for 5% of the cases of tinea unguium and tends to involve fingernails more than toenails
- Nondermatophyte molds *Scopulariopsis brevicaulis* and *Aspergillus niger,* although rare, can also cause tinea unguium
- Tinea unguium is classified according to the clinical pattern of nail bed involvement. The main types are:
  1. Distal and lateral subungual tinea unguium (DLSO)
  2. Superficial tinea unguium
  3. Proximal subungual tinea unguium
  4. Endonyx tinea unguium
  5. Total dystrophic tinea unguium

DIAGNOSIS

The diagnosis of tinea unguium is based on the clinical nail findings and confirmed by direct microscopy and culture.

DIFFERENTIAL DIAGNOSIS

- Psoriasis
- Contact dermatitis
- Lichen planus
- Subungual keratosis
- Paronychia
- Infection (e.g., *Pseudomonas*)
- Trauma
- Peripheral vascular disease
- Yellow nail syndrome

WORKUP

The workup of suspected tinea unguium is directed at confirming the diagnosis of tinea unguium by visualizing hyphae under the microscope by KOH prep or by culturing the organism. Although the standard for the diagnosis of fungal nail disease is a positive result on microscopic examination and culture of nail clippings with subungual debris or from surface debris in superficial white tinea unguium, treatment is often prescribed in the absence of confirmatory findings.

LABORATORY TESTS

- KOH prep: Specificity is high but sensitivity is variable.
- Fungal cultures on Sabouraud medium: Culture may take 4 to 6 wk.
- Dermatophyte test medium (DTM): An alternative to Sabouraud that takes only 3 to 7 days and can be done in office setting. A color change indicates dermatophyte growth.
- Nail plate biopsy with periodic acid–Schiff (PAS) stain.
- Blood tests are not specific in the diagnosis of tinea unguium and therefore not useful.

IMAGING STUDIES

- Imaging studies are not very specific in making the diagnosis of tinea unguium and not useful.
- If an infection is present and osteomyelitis is a consideration, an x-ray of the specific area and a bone scan may help establish the diagnosis.

CLASSIFICATION

- The Onychomycosis Severity Index (OSI) is a new classification system for grading the severity of tinea unguium.
- The OSI score is obtained by multiplying the score for the area of involvement (range, 0-5) by the score for the proximity of the disease to the matrix (range, 1-5). Ten points are added for the presence of a longitudinal streak or a patch (dermatophytoma) or for >2 mm of subungual hyperkeratosis.
- Mild tinea unguium corresponds to a score of 1 to 5; moderate to a score of 6 to 15; severe to a score of 16 to 35.
- Indicators of more severe onychomycosis are summarized in Table 1.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Surgical removal of the nail plate is a treatment option; however, the relapse rate is high.
- Prevent reinfection by wearing properly fitted shoes, avoiding public showers, and keeping feet and nails clean and dry.
- Short-pulse laser therapy is fungicidal and is a newer treatment modality for tinea unguium. Most patients will require two to four treatments, each lasting 15 to 30 min. Laser therapy is useful in patients with contraindications to oral agents. It is, however, expensive ($250 to $1000 per treatment) and not covered by most insurance plans.

ACUTE GENERAL Rx

- Topical antifungal creams are used for early superficial nail infections
  1. Miconazole 2% cream applied over the nail plate bid
  2. Clotrimazole 1% cream bid
  3. Ciclopirox: Topical antifungal nail lacquer can be used for moderate tinea unguium that spares the lunula. Success rate <10%.
  4. Efinaconazole 10% topical solution (Jublia) is modestly effective in treating

TABLE 1 Indicators of More Severe Onychomycosis with a Poor Response to Treatment

Nail factors	• Subungual hyperkeratosis >2 mm thick • Significant lateral involvement • Dermatophytoma • >50% involvement of nail bed • Slow nail growth rate • Total dystrophic onychomycosis • Matrix involvement
Patient factors	• Immunosuppression • Peripheral arterial disease • Poorly controlled diabetes mellitus

Adapted from Carney C et al: A new classification system for grading the severity of onychomycosis: Onychomycosis severity index, *Arch Dermatol* 147:1277-1282, 2011. From Bolognia J et al: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

toenail tinea unguium due to *Trichophyton rubrum* and/or *Trichophyton mentagrophytes.* Dosage is 1 drop (2 drops for big toenail) once daily for 48 wk. Cost and formulary are limiting factors with this agent.

5. Tavaborole 5% solution (Kerydin) is an oxaborole antifungal drug approved by the U.S. Food and Drug Administration (FDA) for topical treatment of toenail tinea unguium due to *T. rubrum* or *T. mentagrophytes*. It is applied to affected toenails once daily for 48 wk. It is modestly effective but much more expensive than topical ciclopirox 8% nail lacquer.

- Oral agents:
  1. Terbinafine:
     a. For toenails: 250 mg/day for 3 mo
     b. For fingernails: 250 mg/day for 6 wk
  2. Itraconazole:
     a. For toenails: 200 mg PO daily for 3 mo
     b. For fingernails: 200 mg PO daily for 6 wk
  3. Fluconazole: Not as effective as terbinafine or itraconazole:
     a. For toenails: 150 to 300 mg once weekly for 18 to 26 wk
     b. For fingernails: 150 to 300 mg once weekly for 12 to 16 wk
- All oral agents used for tinea unguium require periodic monitoring of liver function blood tests. Patients should be advised to watch for symptoms of drug-induced hepatitis (anorexia, fatigue, nausea, right upper quadrant pain) while taking these oral antifungal agents. They should stop their medication and contact their physician immediately if symptoms occur
- Itraconazole is contraindicated in patients taking cisapride, astemizole, triazolam, midazolam, and terfenadine. Statins should be discontinued during itraconazole therapy. Itraconazole requires gastric acidity for absorption; patients should be advised not to take oral antacids, H_2 blockers, or proton pump inhibitors while taking itraconazole
- Fluconazole is contraindicated in patients taking cisapride and terfenadine
- Oral antifungal agents should not be initiated during pregnancy

DISPOSITION

- Spontaneous remission of tinea unguium is rare.
- A disease-free toenail is reported to occur in approximately 25% to 50% of patients treated with the oral antifungal agents mentioned previously.

REFERRAL

- Podiatry consultation is indicated in diabetic patients for proper instruction in foot care, footwear, and nail debridement or surgical removal of the toenail.
- Dermatology consultation is indicated in patients refractory to treatment or if another diagnosis is considered (e.g., psoriasis).

PEARLS & CONSIDERATIONS

COMMENTS

- The growth of fungus on an infected nail typically begins at the end of the nail and spreads under the nail plate to infect the nail bed as well.
- Carefully consider the informational insert regarding drug-drug interactions and contraindications before initiating oral antifungal agents.
- Meta-analysis showed cure rates with the oral agents as follows: Terbinafine (about 75%), itraconazole (60% to 65%), and fluconazole (about 50%).

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Nail Fungus (Patient Information)
Ringworm (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Carney C et al: A new classification system for grading the severity of onychomycosis: onychomycosis severity index, *Arch Dermatol* 147(11):1277-1282, 2011.

Gupta AK et al: Onychomycosis therapy: past, present, future, *J Drugs Dermatol* 9:1109-1113, 2010.

Gupta AK, Simpson FC, Heller DF: The future of lasers in onychomycosis, *J Dermatolog Treat* 27(2):167-172, 2016.

Rosen T et al: Onychomycosis: epidemiology, diagnosis and treatment in a changing landscape, *J Drugs Dermatol* 14:223-233, 2015.

Vlahovic TC: Onychomycosis: evaluation, treatment options, managing recurrences, and patient outcomes, *Clin Podiatr Med Surg* 33(3):305-318, 2016.

FIG.E1 Distal subungual onychomycosis in a 5-year-old child. Note how heavily infected nails occur adjacent to totally normal nails. Cutting back the big toe's nail plate has revealed the friable subungual debris. This material is the most desirable for culture. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

FIG. E2 Collection of nail for culture. The subungual debris is the most valuable material for culture. After the nail is cut back, a curette may be used. Clippings of the nail may be added to the culture. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

Tinea Versicolor PTG

BASIC INFORMATION

DEFINITION

Tinea versicolor is a fungal infection of the skin caused by the yeast *Pityrosporum orbiculare (Malassezia furfur),* a commensal lipophilic fungus that lives in the hair follicles and stratum corneum.

SYNONYM

Pityriasis versicolor

ICD-10CM CODE
B36.0 Pityriasis versicolor

EPIDEMIOLOGY & DEMOGRAPHICS

- Increased incidence in adolescence and young adulthood
- More common during the summer (hypopigmented lesions are more evident when the skin is tanned)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most lesions begin as multiple small, circular macules of various colors (Fig. E1) on the trunk and upper arms.
- The macules may be darker (Fig. E2) or lighter (Fig. E3) than the surrounding normal skin and will scale with scraping.
- Most frequent site of distribution is trunk.
- Facial lesions are more common in children (forehead is most common facial site).
- Eruption is generally of insidious onset and asymptomatic.
- Lesions may be hyperpigmented in blacks.
- Lesions may be inconspicuous in fair-complexioned individuals, especially during the winter.
- Most patients become aware of the eruption when the involved areas do not tan.
- Mild itching and inflammation around the patches may be present.
- Facial lesions may occur in infants and immunocompromised patients.

ETIOLOGY

The infection is caused by *Malassezia* species (*M. globosa, M. restricta, M. sympodialis, M. furfur, M. obtusa,* and *M. slooffiae*). Factors that favor proliferation are pregnancy, malnutrition, immunosuppression, oral contraceptives, and excess heat and humidity.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Vitiligo
- Pityriasis alba
- Secondary syphilis
- Pityriasis rosea
- Seborrheic dermatitis
- Postinflammatory hyperpigmentation or hypopigmentation
- Pityriasis rubra pilaris
- Syphilis
- Hansen disease

WORKUP

Diagnosis is based on clinical appearance. The *Malassezia* fungus is easily demonstrated in scraping of the profuse scales that cover the lesions. Identification of hyphae and budding spores ("spaghetti and meatballs" appearance) with microscopy confirms diagnosis.

LABORATORY TESTS

Microscopic examination with potassium hydroxide confirms diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Sunlight accelerates repigmentation of hypopigmented areas.

ACUTE GENERAL Rx

- Topical treatment: Selenium sulfide 2.5% suspension (Selsun or Exsel) applied daily for 30 min for 7 consecutive days results in a cure rate of 80% to 90%. The scalp can be shampooed monthly with selenium sulfide to reduce scalp colonization.
- Antifungal topical agents (e.g., miconazole, ciclopirox, clotrimazole) are also effective.
- Oral treatment can be given along with topical agents but is generally reserved for resistant cases. Effective agents are fluconazole and itraconazole. Table 1 summarizes treatment options for tinea versicolor.

DISPOSITION

The prognosis is good, with eradication of the fungus usually occurring within 3 to 4 wk of treatment; however, recurrence is common. After initial therapy, use of monthly application of selenium sulfide may lower risk of recurrence.

PEARLS & CONSIDERATIONS

COMMENTS

Patients should be informed that the hypopigmented areas will not disappear immediately after treatment and that several mo may be necessary for the hypopigmented areas to regain their pigmentation.

RELATED CONTENT

Tinea Versicolor (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

TABLE 1 Treatment of Tinea (Pityriasis) Versicolor

Initial therapy (often combination)	*Topical**
	• Antifungal shampoo applied as a body cleanser for 10-15 minutes before rinsing, twice weekly for 2-4 wk 1. Selenium sulfide shampoo, 1% (OTC) or 2.5% 2. Ketoconazole shampoo, 1% (OTC) or 2% 3. Zinc pyrithione shampoo 4. Ciclopirox olamine shampoo, 1%
	• Antifungal cream applied several hand-widths beyond clinically visible lesions, daily to twice daily for 2 wk 1. Imidazole, e.g., ketoconazole 2% cream 2. Ciclopirox olamine 0.77% cream, gel, or lotion
	Oral†
	• Fluconazole: 200 mg PO daily × 5-7 days‡; 200-300 mg weekly × 2-3 wk; or 400 mg once • Itraconazole: 200 mg PO daily × 5-7 days
Maintenance therapy to prevent recurrence	• Treat previously affected sites with topical imidazole daily for 2 wk prior to anticipated sun exposure • Apply antifungal shampoo (see earlier) 1-2 times weekly

Oral ketoconazole is no longer indicated for treatment of superficial fungal infections due to risks of severe hepatotoxicity, QT prolongation, and serious drug interactions.
*Treatment of all the skin from the neck down to the knees may lead to higher success rates.
†Although there are few comparative studies of oral antifungal medications, cure rates of 98% to 100% have been reported in several randomized controlled trials of itraconazole 200 mg daily × 5 days and an open-label study of fluconazole 300 mg weekly × 2 wk.
‡Based upon authors' personal experience.
OTC, Over-the-counter; *PO,* by mouth. From Bolognia J et al: *Dermatology*, ed 4, Philadelphia, 2018, Elsevier.

FIG. E1 Tinea versicolor. Hypopigmented, minimally scaly macules and patches of seborrheic areas of the trunk. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

FIG. E2 Tinea versicolor. This immunosuppressed teenager with inflammatory bowel disease had hyperpigmented (rather than hypopigmented) scaly papules and plaques. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

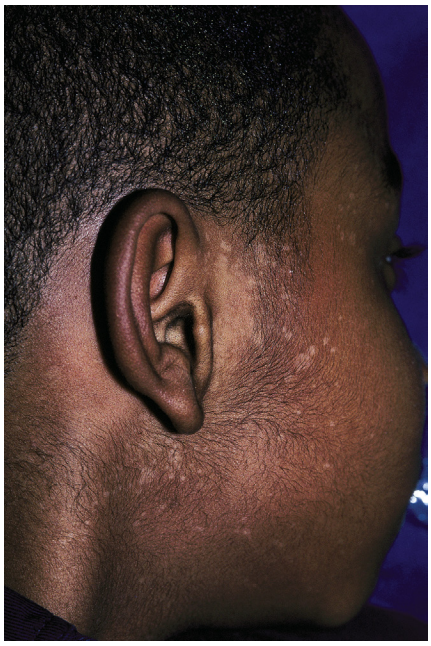

FIG. E3 Tinea versicolor. Occasional involvement of the face and/or neck is noted, especially in darkly pigmented individuals. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Tinnitus is a perceived sound in the absence of acoustic stimulus external to the head. It may be unilateral, bilateral, or lateral dominant. It is commonly described as a ringing, buzzing, roaring, hissing, whistling, humming, cricket-like, or pulsing sound. It is frequently a symptom associated with hearing loss, Ménière disease, acoustic neuroma, drug toxicity, depression, or an autoimmune inner ear disease. The sound may be internal and perceived only by the patient, called subjective or tonal tinnitus, or it may be heard by both the patient and the examiner, called objective or nontonal tinnitus.

ICD-10CM CODES

H93.1	Tinnitus
H93.2	Other abnormal auditory perceptions
H93.11	Tinnitus, right ear
H93.12	Tinnitus, left ear
H93.13	Tinnitus, bilateral
H93.19	Tinnitus, unspecified ear

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- The American Tinnitus Association reports 50 to 60 million Americans have tinnitus for >6 mo.
- Prevalence increases steadily with age, peaking for persons aged 60 to 69 yr.
- Prevalence in the U.S. based on National Health Interview Survey (NHIS) in 1996:
  1. 2.98% all ages
  2. 0.26% for persons <18 yr old
  3. 1.6% for persons aged 18 to 44 yr
  4. 5.96% for persons aged 45 to 64 yr: 7.7% males, 4.3% females
  5. 9.6% for persons aged 65 to 74 yr: 12% males, 7.7% females
  6. 7.6% for persons >75 yr: 11.4% males, 5.3% females
  7. 2:1 South/Northeast regions
- Up to 18% of people in industrialized societies are mildly affected by chronic tinnitus, and 0.5% report tinnitus having a severe effect on their daily life.
- Only 20% of patients with persistent tinnitus ever seek medical evaluation.

PREDOMINANT SEX AND AGE: Persons most affected are male, Caucasian, elderly, persons with hearing impairment, persons living in southern U.S. For military veterans, tinnitus is the third most common service-related disability.

RISK FACTORS: Any condition causing hearing loss or damage to the auditory system can produce tinnitus. Cochlear damage from exposure to noise is the most common cause. Exposure to ototoxic drugs is also important.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History should focus on exposure to loud noises, evidence of hearing loss, and ototoxic drugs.
- Patient should be screened for depression.
- Patient who complains of sound in ear may also complain of ear pain or fullness.
- Objective tinnitus is pulsatile and coincides with patient's pulse.
- Physical examination should focus on HEENT, neck, and neurologic exam.
- There may be no significant physical findings.

ETIOLOGY

- The mechanism behind tinnitus is poorly understood. It may originate at any point along the auditory pathway. Causes of tinnitus include injured cochlear hair cells, spontaneous activity in auditory nerve fibers, hyperactivity in the auditory nuclei in the brain stem, or a reduction in the suppressive activity of the central auditory cortex.
- Medications implicated in causing tinnitus include salicylates, NSAIDs, aminoglycosides, loop diuretics, valproate, quinine, chemotherapeutic agents, cisplatin, vincristine, and heavy metals such as lead.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Subjective/tonal tinnitus:
  1. Otologic: Tympanic membrane disorder, inner ear disorder (hair cells, organ of Corti), Ménière disease
  2. Ototoxic medications
  3. Neurologic: Multiple sclerosis, head trauma, cochlear nerve lesion, acoustic schwannoma, neurofibroma, meningioma
  4. Metabolic: Thyroid disorder, hyperlipidemia (leading to plaque formation), vitamin B_{12} deficiency
  5. Psychogenic: Depression, anxiety, fibromyalgia
  6. Infectious: Otitis media, Lyme disease, meningitis, syphilis
- Objective/nontonal tinnitus:
  1. Vascular: Arterial bruit, venous hum, arteriovenous malformation, vascular tumors
  2. Neurologic: Contraction of muscles of the eustachian tube, contraction of the stapedius muscle, contraction of the tensor tympani muscles, or a palatal myoclonus, glomus jugulare tumor
  3. Conductive: Patulous (wide-open) eustachian tube

WORKUP

- Audiometry.
- Tympanometry.
- Electronystagmography is used to evaluate for Ménière disease.
- An algorithm for tinnitus evaluation is described in Fig. E1 and Fig. E2.

LABORATORY TESTS

Evaluate for metabolic abnormalities: TSH, CBC, B_{12}, and lipid panel.

IMAGING STUDIES

- CT/MRI: To evaluate for subjective tinnitus
- MRI/MRA: To evaluate objective tinnitus
- Imaging should not be part of routine management. Clinicians must distinguish patients with bothersome tinnitus from patients with nonbothersome tinnitus. For patients without persistent and bothersome tinnitus, audiometric testing is optional.

TREATMENT

NONPHARMACOLOGIC THERAPY

- It is best to avoid exposure to excessive noise, ototoxic agents, and to wear protective equipment in noisy environments, or mask the tinnitus through amplification of normal sounds with a hearing aid. Habituation techniques such as tinnitus retraining therapy may help. Cognitive-behavioral therapy helps patients cope with tinnitus distress through biofeedback.
- Recent trials involving brain stimulation in the form of repetitive transcranial magnetic stimulation (rTMS have shown reduction in the perception or severity of tinnitus).[1]

ACUTE GENERAL Rx

- If the tinnitus is severe enough to cause suicidal symptoms, immediate referral to a psychiatrist and an otolaryngologist is recommended to minimize the time to diagnosis and optimize treatment.
- Patients with persistent symptoms or tinnitus accompanied by visual changes or headache should be evaluated for tumors such as acoustic neuroma.
- Clinicians should not routinely recommend anxiolytics, anticonvulsants, or intratympanic medications.

CHRONIC Rx

There is insufficient evidence to support the use of any medication, vitamin, or nutritional supplement to treat tinnitus. Empirical use of over-the-counter supplements or prescription medications should be discouraged.

DISPOSITION

Clinical course is variable. About 20% to 25% of patients with chronic tinnitus consider it a significant problem. Individualized tinnitus management programs can be beneficial in most patients.

PEARLS & CONSIDERATIONS

PREVENTION

- Avoid loud, chronic noise and ototoxic drugs.
- Higher caffeine intake is associated with a lower risk of incidence of tinnitus in women.

RELATED CONTENT

Tinnitus (Patient Information)

AUTHORS: **Vicky H. Bhagat, MD, MPH,** and **Dawn Hogan, MD**

[1]Folmer RL et al: Repetitive transcranial magnetic stimulation treatment for chronic tinnitus: a randomized clinical trial, *JAMA Otolaryngol Head Neck Surg* 141(8):716-722, 2015.

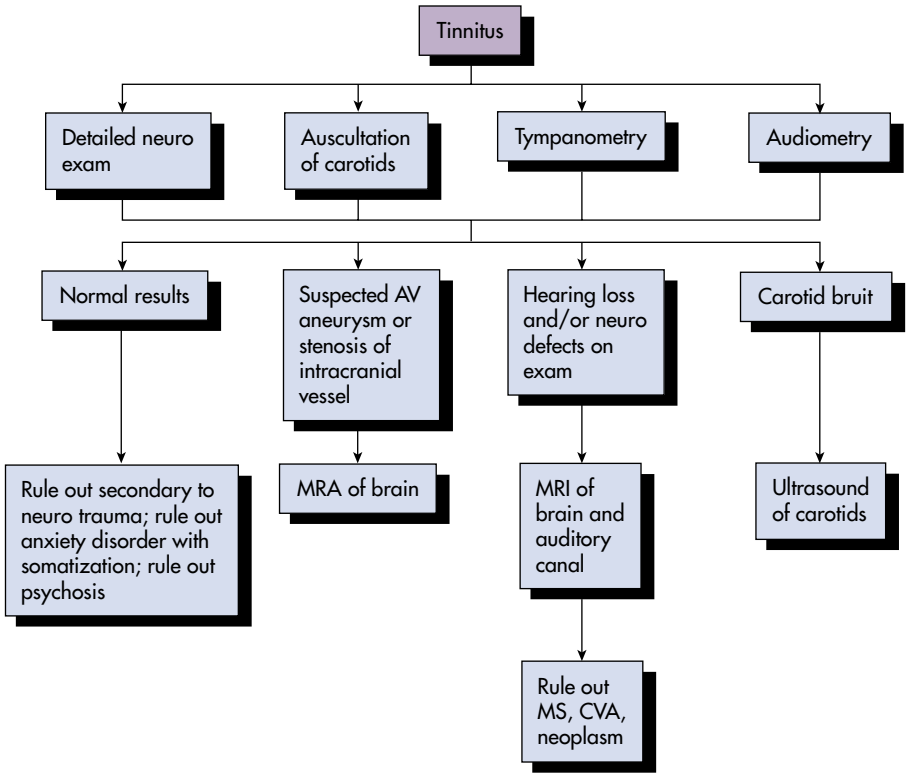

FIG. E1 Tinnitus evaluation. *AV,* Atrioventricular; *CVA,* cerebrovascular accident; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging; *MS,* multiple sclerosis. (From Ferri FF: *Ferri's best test: A practical guide to clinical laboratory medicine and diagnostic imaging,* ed 4, Philadelphia, 2017, Elsevier.)

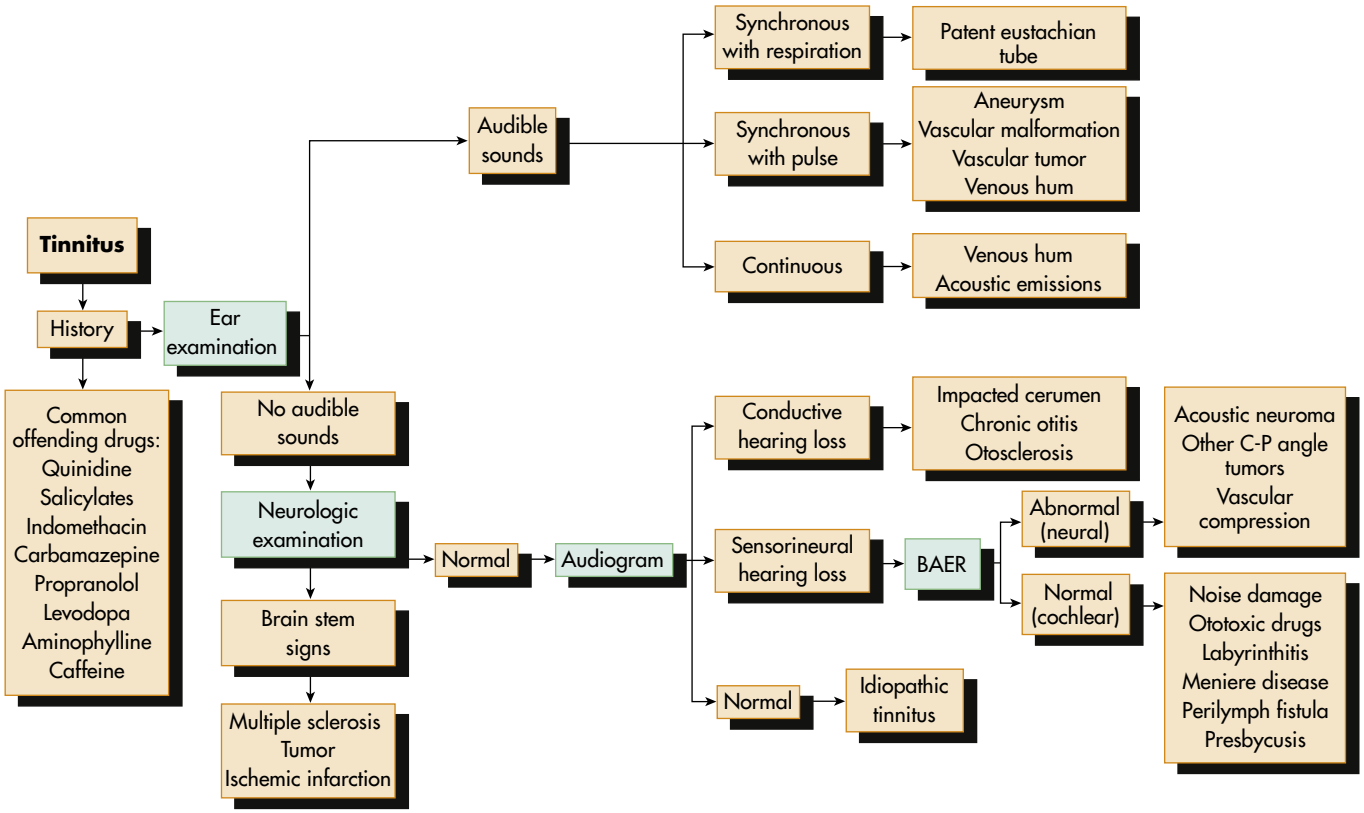

FIG. E2 Evaluation of tinnitus. *BAER,* Brain stem auditory evoked response; *C-P,* cerebellopontine. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

BASIC INFORMATION

DEFINITION

The term *Torsade de Pointes* (TdP) refers to a polymorphic ventricular tachycardia (VT) associated with a prolonged QT interval and electrocardiographically characterized by QRS complexes of changing amplitude that appear to twist around the isoelectric line, hence the name *Torsade de Pointes*, or "twisting of the points" (Fig. 1).

Torsade is typically initiated by a short-long-short sequence of ventricular beats but can also be initiated by a short-coupled variant. Typically, TdP occurs in the setting of a markedly prolonged QT interval (>500 msec); the QTc prolongs even further during the long diastolic interval of a compensatory pause after an early beat, leading to a polymorphic VT with a ventricular rate of 160 to 250 beats per minute, irregular RR intervals, and a cycling of the QRS axis through 180 degrees every 5 to 20 beats. It may be repetitive, nonsustained, or sustained and may degenerate into ventricular fibrillation. In some cases, the result is sudden cardiac death.

SYNONYMS

Torsades
TdP

ICD-10CM CODE
I47.2 Ventricular tachycardia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The precise incidence of TdP is unclear but accounts for fewer than 5% of all sudden cardiac arrests. In congenital long QT syndromes (LQTS), TdP may occur in up to 6% of cases at rest and 9% of cases during an exercise test. Among drug-induced causes of TdP, the incidence may vary between <1% in cases of antibiotics and antipsychotics to 2% to 4% when caused by class III anti-arrhythmics such as sotalol, ibutilide, and dofetilide.

PREDOMINANT SEX AND AGE: Because testosterone shortens the QT interval, women have a longer baseline QT interval, which is believed to be the reason for a two- to threefold increased incidence of TdP in women.

GENETICS: Of the congenital LQTS channelopathies, long QT syndromes 1, 2, and 3 account for >70% of all cases. In general, the risk of TdP increases as the QT lengthens; however, there are also genotype-phenotype relationships that help define risk; for example, LQTS3 carries a higher risk of TdP than LQTS1. Similarly, the Jervell and Lange-Nielsen syndrome and Romano-Ward syndrome may lead to TdP.

It is also likely that genetic factors are at play in acquired LQT and in the development of TdP. For example, in large populations, the QT interval prolongs very little with the administration of QT-prolonging drugs such as fluoroquinolones; however, certain individuals will have markedly exaggerated QT prolongation that leads to TdP; this is likely due to some underlying genetic factor.

RISK FACTORS: TdP in patients with congenital LQTS is often initiated by an external trigger (Table 1). Triggers can include exercise, noise, emotion, sudden waking from sleep by an alarm clock, telephone ringing, thunder, swimming, or diving. TdP in LQT1 patients is classically triggered by vigorous exercise or swimming; in LQT2 by emotion, pregnancy, or noise; and in LQT3 when at rest or asleep. Risk factors for drug-induced TdP are outlined in Table 2.

The risk factors for developing TdP in patients with acquired long QT are extensive and are outlined in Table 3.

PATHOPHYSIOLOGY:

- Changes in the balance of transmembrane ionic currents lead to lengthening of the QT interval and to abnormal action potentials called early afterdepolarizations (EADs). An EAD, in the setting of electrical instability induced by the prolonged QT, initiates the torsades. Perpetuation may be caused by transmural entry, triggered activity, or abnormal automaticity. A distinct group of cells called the M cells, located in the mid-myocardium, has a less rapid delayed rectifier potassium current (IKr), and these cells are central to the genesis of TdP.
- Drugs with the potential to cause TdP most frequently inhibit the rapid potassium channels and result in prolongation of the action potential duration, producing a prolonged QT on ECG.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical features depend on whether the TdP is caused by acquired or congenital long QT syndrome. Congenital LQTS patients may have certain specific triggers, such as noise, exercise, and emotions (see "Risk Factors").
- Symptoms of the tachycardia itself include palpitations, pre-syncope, syncope (sometimes with jerking movements from myoclonus, often misinterpreted as seizures), and sudden cardiac death (SCD).
- Patients resuscitated from SCD have an especially ominous prognosis, with a relative risk of 12.9% of experiencing another cardiac arrest.

ETIOLOGY

The etiology or triggers of TdP may be congenital or acquired causes of QT prolongation (see Table 1). For a comprehensive list of drugs that can cause or have the potential to cause TdP, see "Patient/Family Education."

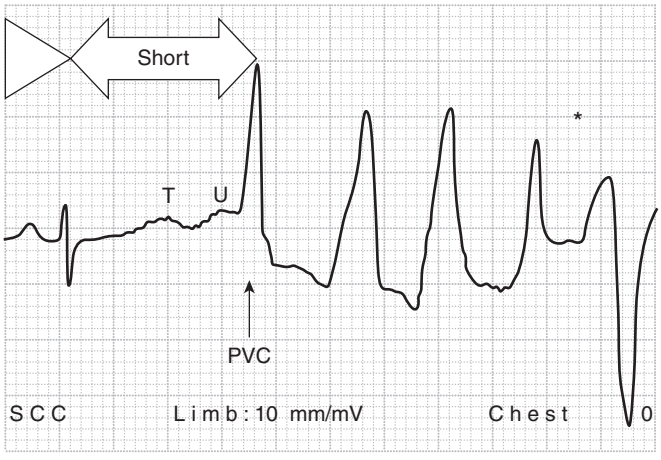

FIG. 1 Onset of Torsade de Pointes during the recording of a standard 12-lead electrocardiogram (ECG) in a young male with a history of drug addiction treated with chronic methadone therapy who presented to a hospital emergency department after ingesting an overdose of prescription and over-the-counter drugs from his parent's drug cabinet. Classic ECG features evident in this rhythm strip include a prolonged QT interval with distorted T-U complex, initiation of the arrhythmia after a short-long-short cycle sequence by a PVC that falls near the peak of the distorted T-U complex, "warm-up" phenomenon with initial R-R cycles longer than subsequent cycles, and abrupt switching of QRS morphology from predominantly positive to predominantly negative complexes (asterisk). (From Drew BJ et al: Prevention of Torsade de Pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation, *J Am Coll Cardiol* 55:934-947, 2010.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other causes of syncope:

- Other causes of broad complex tachycardia such as:
  1. Polymorphic VT
  2. Wolff-Parkinson-White (WPW) syndrome with rapid atrial fibrillation
  3. ECG artifact

WORKUP

- ECG (Fig. 2) and telemetry are the mainstays of diagnosing TdP as they detect the arrhythmia, the preceding prolonged QT interval, and the long-short cycles that trigger it.
- Determination and treatment of the etiology of TdP (see Table 1) is key.

TABLE 1 Causes and Triggers of Torsade de Pointes

Congenital	
	• Romano-Ward syndrome (autosomal dominant)
	• Jervell and Lange-Nielsen syndrome (autosomal recessive)
	• LQTS channelopathies
Acquired	
Metabolic syndromes	• Hypokalemia
	• Hypocalcemia
	• Hypomagnesemia
	• Starvation
	• Anorexia nervosa
	• Liquid protein diets
	• Hypothyroidism
Bradyarrhythmias	• Sinus node dysfunction
	• Second- or third-degree AV block
Antiarrhythmic drugs	• Quinidine
	• Procainamide
	• Disopyramide
	• Amiodarone and dronedarone
	• Sotalol
	• Dofetilide, ibutilide, azimilide
Antimicrobial drugs	• Erythromycin, clarithromycin, azithromycin
	• Pentamidine
	• Azole antifungals like voriconazole
	• Fluoroquinolones such as levofloxacin and moxifloxacin
	• Chloroquine
Antihistaminics	• Terfenadine
	• Astemizole
Psychiatric drugs	• Phenothiazines
	• Thioridazine
	• Tricyclic antidepressants
	• Haloperidol
	• Risperidone
	• Selective serotonin reuptake inhibitors
Antineoplastic agents	• Tyrosine kinase inhibitors such as sunitinib, dasatinib
	• Vorinostat
	• Arsenic
Gastric motility agents	• Cisapride, domperidone
Opioid dependence drugs	• Methadone
Other factors	• Myocardial ischemia
	• Hypothermia
	• Intracranial disease
	• HIV infection
	• Connective tissue disease with anti-Ro/SSA antibodies
	• Periodic paralysis (Andersen syndrome)
	• Cocaine

LABORATORY TESTS

- Electrolytes: Assess for hypokalemia, hypocalcemia, and hypomagnesemia
- Thyroid function tests
- Genetic studies if suspicion of congenital LQT syndrome

IMAGING STUDIES

- Echocardiography to rule out structural heart disease as a cause of VT
- Stress test to rule out myocardial ischemia. Stress ECG with dynamic assessment of the QT interval during varying heart rates may be diagnostic of long QT syndromes and related TdP
- CT scan of the head if intracranial disease is suspected

Rx TREATMENT

The cornerstone of treatment comprises intravenous magnesium and acceleration of the heart rate, either by mechanical overdrive pacing or by infusion of isoproterenol. Withdrawal of causative drugs and correction of underlying causes such as electrolyte imbalances, hypothermia, and ischemia are also important.

NONPHARMACOLOGIC THERAPY

- Withdrawal of any offending drugs and correction of electrolyte abnormalities are recommended in patients presenting with TdP (Class I recommendation).
- Temporary atrial or ventricular overdrive pacing is a Class I recommendation for all causes of TdP if intravenous magnesium fails.
- Acute and long-term pacing is recommended for patients presenting with TdP due to heart block and symptomatic bradycardia (Class 1) or those with recurrent pause-dependent torsades (Class IIa).
- Active internal and external rewarming if hypothermia is the etiology.

TABLE 2 Risk Factors for Drug-induced Torsade de Pointes

- Congenital long QT
- Female gender
- Electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia)
- Diuretic use
- Bradycardia
- Cardiac hypertrophy
- Myocardial fibrosis
- Congestive heart failure
- Renal and liver insufficiency
- Coadministration of drugs blocking P450 isoenzyme CYP3A4
- High doses or rapid intravenous infusion of the drug
- Baseline electrocardiographic abnormalities (prolonged QT, T-wave lability)

From Gowda RM et al: Torsades de Pointes: the clinical considerations, *Int J Cardiol* 96(1):1-6, 2004.

TABLE 3 Risk Factors for Torsade de Pointes in Hospitalized Patients

- Clinically recognizable risk factors
- QTc >500 msec
- LQT2-type repolarization: Notched or "bifid" T-wave
- Use of QT-prolonging drugs
- Concurrent use of more than one QT-prolonging drug
- Rapid infusion by intravenous route
- Structural heart disease
- Congestive heart failure
- Myocardial infarction
- Advanced age
- Female sex
- Hypokalemia
- Hypomagnesemia
- Hypocalcemia
- Treatment with diuretics
- Impaired hepatic drug metabolism
- Bradycardia
- Sinus bradycardia, heart block, incomplete heart block with pauses
- Premature QRS complexes leading to short-long-short cycles
- Multiple clinically recognizable risk factors
- Occult (latent) congenital LQTS
- Genetic polymorphisms

From Drew BJ et al: Prevention of Torsade de Pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation, *Circulation* 121(8):1047, 2010.

- If TdP degenerates into ventricular fibrillation, defibrillation and advanced cardiac life support protocol should be followed.

ACUTE GENERAL Rx

- Intravenous magnesium sulfate 1 to 2 g given over 1 to 2 min is first-line therapy for patients who present with LQTS and few episodes of TdP (Class IIa). Magnesium is not likely to be effective in patients with a normal QT interval.
- Isoproterenol is reasonable as temporary treatment in patients with acute disease who present with recurrent pause-dependent TdP

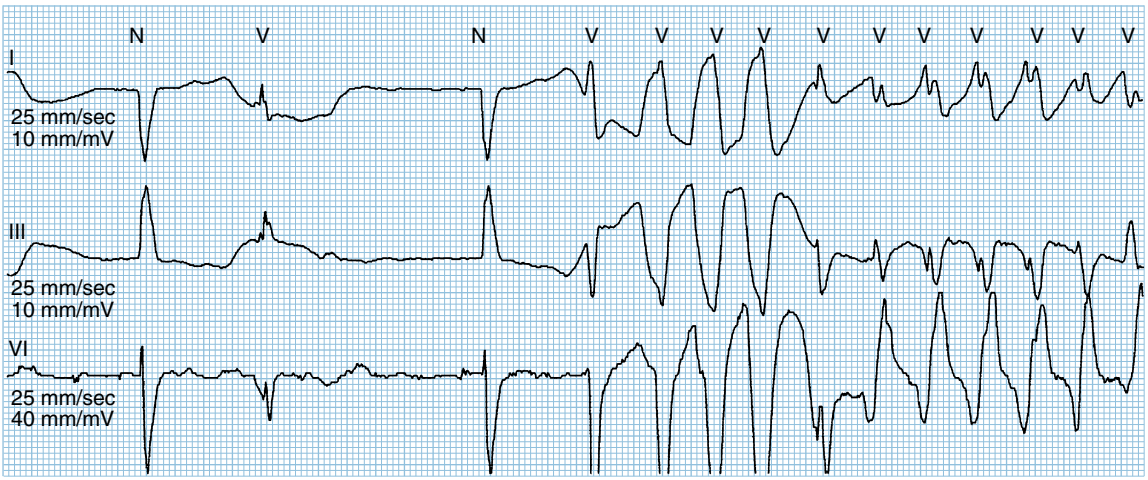

FIG. 2 Torsade de Pointes. This lead I, III, and V_1 rhythm strip shows sinus bradycardia with left bundle branch block and marked QT prolongation with premature ventricular contractions (R-on-T) that initiates a very rapid polymorphic ventricular tachycardia with the characteristic twisting of the QRS complex around the isoelectric baseline. Torsade de Pointes literally means "twisting of the points." (From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

and who do not have congenital LQTS (Class IIa).
- Beta-blockade combined with pacing is reasonable acute therapy for patients who present with TdP and sinus bradycardia (Class IIa).
- Potassium repletion to 4.5 to 5 mmol/L may be considered for patients who present with TdP and hypokalemia (Class IIb).
- Intravenous lidocaine, oral mexiletine, or phenytoin may be considered in patients who present with LQT3 and TdP (Class IIb).
- TdP is usually self-limited, and cardioversion should be performed only as a last resort in the setting of pulseless VF because of the high likelihood of immediate recurrence of the TdP after cardioversion.

CHRONIC Rx

- TdP resulting from congenital LQTS is treated with beta-blockade (propranolol or nadolol are preferred), pacing, and implantable cardioverter-defibrillator (ICD) in high-risk cases. For patients who continue to have syncope despite maximal drug therapy, cervical-thoracic sympathectomy may be considered.
- Long-term pacing is recommended for patients presenting with TdP due to heart block and symptomatic bradycardia.
- Avoid use of QT-prolonging drugs.
- Lifestyle modification in case of congenital LQTS.
- In patients with eating disorders, nutritional rehabilitation will correct the QT prolongation over the long term (3-18 mo).
- Psychiatric evaluation of patients with drug overdose and eating disorders.

DISPOSITION

Patients with TdP should be monitored in an intensive care setting.

REFERRAL

Patients should have an urgent cardiology consultation.

PEARLS & CONSIDERATIONS

COMMENTS

- Identification of the etiology for TdP is key in diagnosis, management, and prognosis of this condition.
- Drugs associated with TdP vary greatly in their risk for arrhythmia; an updated list can be found at https://crediblemeds.org. The risk-benefit ratio should be assessed for each individual to determine whether the potential therapeutic benefit of a drug outweighs the risk for TdP.
- Risk factors for drug-induced TdP include older age, female sex, heart disease, electrolyte disorders (especially hypokalemia and hypomagnesemia), renal or hepatic dysfunction, bradycardia or rhythms with long pauses, treatment with more than one QT-prolonging drug, and genetic predisposition.
- After initiation of a drug associated with TdP, ECG signs indicative of risk for arrhythmia include an increase in QTc from predrug baseline of >60 msec, marked QTc interval prolongation >500 msec, T-U wave distortion that becomes more exaggerated in the beat after a pause, visible T-wave alternans, new-onset ventricular ectopy, and couplets and nonsustained polymorphic ventricular tachycardia initiated in the beat after a pause.

PREVENTION

The 2011 AHA/ACC scientific statement on prevention of TdP suggests a strategy of documenting the QTc interval before and at least every 8 to 12 hr after the initiation, increased dose, or overdose of QT-prolonging drugs. If QTc prolongation is observed, documentation of more frequent measurements is recommended. The duration of QTc monitoring depends upon the duration of treatment with the QT-prolonging drug and the drug half-life.

PATIENT & FAMILY EDUCATION

- Patients should be educated about avoiding use of QT-prolonging drugs. A complete list of these drugs can be found at https://crediblemeds.org.
- First-degree relatives of all patients with congenital LQTS should undergo genetic testing.
- Congenital LQTS patients should avoid certain specific triggers (e.g., swimming and exercise in LQTS 1 and LQTS 2 and acoustic stimuli in LQTS 2).
- It is recommended that all patients affected by LQTS avoid competitive sports activity.

RELATED CONTENT

Long QT Syndrome (Related Key Topic)

AUTHOR: **Christopher Pickett, MD**

BASIC INFORMATION

DEFINITION

The most common definition of torticollis is the contraction or contracture of the muscles of the neck that causes the head to be tilted to one side (Fig. E1). It is often accompanied by rotation of the chin to the opposite side with flexion. Usually torticollis is a symptom of some underlying disorder. Torticollis can also be defined as posttraumatic or inflammatory in cases of fixed positional disorders of the head and neck.

SYNONYMS

Twisted neck
"Wry neck"
Spasmodic torticollis
Grisel syndrome
Posttraumatic painful torticollis (posttraumatic cervical dystonia)
Cervical dystonia

ICD-10CM CODES

G24.3	Spasmodic torticollis
M43.6	Torticollis
Q68.0	Congenital deformity of sternocleidomastoid muscle

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Congenital muscular torticollis:
  1. Palpable soft tissue "mass" in the sternocleidomastoid shortly after birth
  2. Mass gradually subsides, leaving a shortened, contracted sternocleidomastoid muscle
  3. Head characteristically tilted toward the side of the mass and rotated in the opposite direction
  4. Facial asymmetry and other secondary changes persisting into adulthood
- Spasmodic torticollis:
  1. "Spasms" in the cervical musculature; may be bilateral and uncontrollable
  2. Head often tilted toward the affected side
- Grisel syndrome:
  1. Painful nontraumatic subluxation of the atlanto-axial joint from inflammatory ligamentous laxity from an infectious process in the head or neck
  2. Often presents associated with recent upper respiratory tract infection or retropharyngeal abscess
  3. Rare postoperative complication after head and neck surgery (e.g., adenotonsillectomy)
- Posttraumatic painful torticollis:
  1. Abnormal posturing of the head after local injury to the neck or cervical spine; also known as posttraumatic cervical dystonia (PTCD)
  2. Severe pain with abnormal fixed posture of the head
  3. Presents after trauma, commonly motor vehicle crashes and falls from height
  4. May have an associated psychological component
- Findings in other cases depend on etiology. In *cervical dystonia*, the most frequent focal dystonia, one or more neck muscles involuntarily contract to rotate or tilt the head and neck (Fig. E2). The resultant posture may consist of turning of the head to one side (torticollis), tilting to one side (laterocollis), flexion (anterocollis), or extension (retrocollis); most often these occur in complex combinations. The movements initially occur intermittently, but as the condition progresses, the abnormal postures become sustained and a superimposed "dystonic tremor" often complicates the picture. Unlike other forms of dystonia, cervical dystonia causes pain because the muscle contractions forcefully compress and rotate the cervical vertebra on each other and irritate the cervical nerve roots that emerge between them.

ETIOLOGY

Torticollis has been found to have more than 50 different causes:

- Localized fibrous shortening of unknown cause involving the sternocleidomastoid, leading to the condition termed *congenital muscular torticollis*
- Spasmodic torticollis: Of uncertain etiology, possibly a variant of dystonia musculorum deformans
- Infection, specifically pharyngitis, tonsillitis, retropharyngeal abscess
- Miscellaneous rare causes: Congenital musculoskeletal deformities, trauma, inflammation from rheumatoid arthritis, vestibular disturbances, posterior fossa tumor, syringomyelia, neuritis of spinal accessory nerve, and drug reactions

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Table E1 summarizes the differential diagnosis of torticollis.

WORKUP

- Workup depends on the clinical situation.
- Laboratory studies are usually not helpful unless infection or rheumatoid disease is suspected.
- Any child with a gradually increasing torticollis should have a complete eye examination.

IMAGING STUDIES

- Plain radiographs in cases of trauma or to rule out congenital abnormalities
- MRI in appropriate cases
- Electrodiagnostic studies: Only rarely indicated to rule out neurologic causes
- US can be used to define neck masses in suspected congenital muscular torticollis

FIG. E1 Cervical dystonia consists of neck muscle contraction that causes rotation (torticollis), tilting (laterocollis), flexion (anterocollis), or extension (retrocollis)—usually in combination—of the head and neck. Shoulder elevation often accompanies the other movements. Continuous contractions result in muscle hypertrophy and pain. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.)

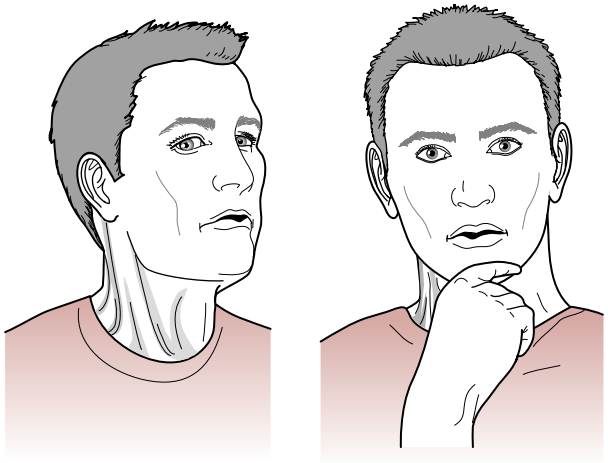

FIG. E2 As with blepharospasm and other focal dystonias, patients with cervical dystonia instinctively learn sensory tricks such as lightly touching the chin, which is a classic *geste antagoniste.* (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.)

TABLE E1 Differential Diagnosis of Torticollis

Congenital
- Muscular torticollis
- Positional deformation
- Hemivertebra (cervical spine)
- Unilateral atlanto-occipital fusion
- Klippel-Feil syndrome
- Unilateral absence of sternocleidomastoid
- Pterygium colli

Trauma
- Muscular injury (cervical muscles)
- Atlanto-occipital subluxation
- Atlantoaxial subluxation
- C2-3 subluxation
- Rotary subluxation
- Fractures

Inflammation
- Cervical lymphadenitis
- Retropharyngeal abscess
- Cervical vertebral osteomyelitis
- Rheumatoid arthritis
- Grisel syndrome (nontraumatic subluxation of the atlantoaxial joint due to local inflammation)
- Upper lobe pneumonia

Neurologic
- Visual disturbances (nystagmus, superior oblique or lateral rectus paresis)
- Dystonic drug reactions (phenothiazines, haloperidol, metoclopramide)
- Cervical cord tumor
- Posterior fossa brain tumor
- Syringomyelia
- Wilson disease
- Dystonia musculorum deformans

Other
- Acute cervical disk calcification
- Sandifer syndrome (gastroesophageal reflux, hiatal hernia)
- Benign paroxysmal torticollis
- Bone tumors (eosinophilic granuloma)
- Soft tissue tumor
- Psychogenic

From Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

Rx TREATMENT

- Congenital muscular torticollis: Gentle stretching exercises carried out by the parent; surgical release can benefit fixed deformities or those associated with secondary cervicothoracic scoliosis
- Spasmodic torticollis: Physical therapy, psychotherapy, cervical braces, biofeedback, and pain control
- Focal dystonia responds well to injections of botulinum toxin type A or B
- Grisel syndrome: Treatment of the underlying inflammatory process
- Posttraumatic painful torticollis: Treatment of psychological component, physical therapy, treatment of any initially unrecognized injury
- Other forms: Treated according to etiology

DISPOSITION

- Most patients with congenital muscular torticollis respond well to conservative treatment.
- Spasmodic torticollis is often resistant to normal conservative treatment.
- Prognosis of other forms of torticollis depends on etiology.

REFERRAL

- Torticollis often requires a multidisciplinary approach unless the etiology is obvious.
- Children usually do not require any specific studies; however, an orthopedic consultation is recommended.
- Fixed deformity in the child; may need orthopedic referral for surgical release.

RELATED CONTENT

Torticollis (Patient Information)

AUTHOR: **Jeremy E. Raducha, MD**

SUGGESTED READINGS

Amaral DM et al: Congenital muscular torticollis: where are we today? A retrospective analysis at a tertiary hospital, *Porto Biomed J* 4(3):e36, 2019.

Kim J-H et al: Secondary cervicothoracic scoliosis in congenital muscular torticollis, *Clin Orthop Surg* 11(3):344-351, 2019.

Heidenreich E et al: Informing the update to the physical therapy management of congenital muscular torticollis evidence-based clinical practice guideline, *Pediatr Phys Ther* 30(3):164-175, 2018.

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Nilesh K, Mukherji S: Congenital muscular torticollis, *Ann Maxillofac Surg* 3(2):198-200, 2013.

Reichman EF, Shah J: Grisel syndrome: an unusual and often unrecognized cause of torticollis, *Pediatr Emerg Care* 31(8):577-580, 2015.

BASIC INFORMATION

DEFINITION

Tourette syndrome (TS) is an inherited neuropsychiatric disorder characterized by motor, vocal, and phonic tics that change during the course of illness. Onset of symptoms is typically before the age of 18.

Tics are sudden, brief, intermittent, involuntary or semi-voluntary movements (motor tics), or sounds (phonic or vocal tics) that mimic fragments of normal behavior.

SYNONYMS

Gilles de la Tourette syndrome
TS
Tourette disorder

ICD-10CM CODE

F95.2 Combined vocal and multiple motor tic disorder [de la Tourette]

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.): Unknown; estimates range from 0.3% to 0.9% in children
PREDOMINANT SEX: Approximate male:female ratio of 4:1
PREDOMINANT AGE: Typical age of onset is between 2 and 15 yr (mean 5 to 7 yr).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Neurologic examination is normal.
- Vocal and phonic tics are characterized as simple (e.g., clearing of throat, sniffing, grunting, sucking) or complex (e.g., repetition of short phrases, swearing [coprolalia]).
- Motor tics can be simple (e.g., blinking, grimacing, head jerking [Fig. 1]) or complex (e.g., gesturing [Fig. 2]). Tics wax, wane, change over time, and are often suppressed for short periods. Commonly, they are preceded by an urge to perform the tic.
- TS is often associated with a variety of behavioral symptoms, most commonly attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD).

TS can be diagnosed using the DSM-5 criteria as follows:

- Both multiple motor and one or more vocal tics must be present at some time during the illness, although not necessarily concurrently.
- The tics may wax and wane in frequency but have persisted for more than 1 yr since first tic onset.
- Age at onset is less than 18 yr.
- Disturbance is not attributable to the direct physiologic effects of a substance (e.g., stimulants) or another medical condition (e.g., Huntington disease or postviral encephalitis).

ETIOLOGY

The exact pathogenesis is unknown. Genetic predisposition is likely as there is a strong family history of OCD or TS in patients with tics, and twin studies provide evidence for the importance of genetic factors. Recent analysis of linkage in a two-generation pedigree has led to the identification of a mutation in the HDC gene encoding l-histidine decarboxylase, the rate-limiting enzyme in histamine biosynthesis, pointing to a role for histaminergic neurotransmission in the mechanism and modulation of TS and tics. Immunologic dysfunction is also being explored in the pathogenesis of this complex disorder.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Sydenham chorea: Occurs after infection with group A *Streptococcus.*
- Pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS).
- Sporadic tic disorders: Tics tend to be motor or vocal but not both.
- Head trauma.
- Drug intoxication: Many drugs are known to induce or exacerbate tic disorders, including methylphenidate, amphetamines, anticholinergics, and antihistamines.
- Postinfectious encephalitis.
- Inherited disorders: Huntington disease, neurodegeneration with brain iron accumulation, and neuroacanthocytosis. These conditions should have other observed abnormalities on neurologic examination.

WORKUP

Clinical observation and history to confirm diagnosis

LABORATORY TESTS

No definitive laboratory tests

IMAGING STUDIES

CT scan and MRI of brain are unremarkable in TS and unnecessary if the neurologic examination is within normal limits.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Multidisciplinary: Education of parents, teachers, psychologists, and school nurses is essential.
- Watchful waiting without intervention is an appropriate treatment if tics are not bothersome, since the natural history of tics is to improve with time. 60% of patients have minimal or no tics 6 yr after initial diagnosis.
- Cognitive behavioral therapy, termed habit-reversal treatment or Comprehensive Behavioral Intervention for Tics (CBIT), is efficacious in suppressing tics and is the first-line treatment.
- Screening for ADHD, OCD, and depression on a regular basis is important.

ACUTE GENERAL Rx

Dopamine-blocking agents may be used to acutely reduce the severity of tics. However, these agents carry a risk of side effects, such as acute dystonic reactions.

CHRONIC Rx

Tics only require long-term treatment when they interfere with an individual's psychosocial, educational, and occupational function.

TICS:

- Alpha-2 agonists, such as clonidine and guanfacine, are used for treatment of motor tics and are considered by some experts

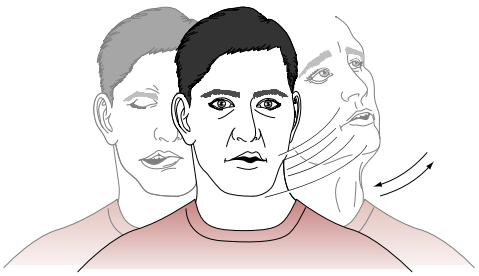

FIG. 1 This young man with Tourette disorder has multiple motor tics, including head jerking (head toss), grimacing of the right side of his mouth (half-smile), and depression of his forehead (frowning). Vocal tics of throat clearing and a short blowing sound accompany his motor tics. All of his tics continue throughout the day and briefly during sleep. Conversation, eating, and social situations have little influence, but with effort he can suppress his tics for several minutes. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.)

FIG. 2 This woman has compulsive obscene gestures—copropraxia. Similar to coprolalia, they have no affective or sexual content. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.)

as first-line medications after behavioral therapy because of their favorable adverse effect profile. However, they are more beneficial for treatment of behavioral symptoms and are preferred for patients with predominant psychiatric disorders.

- Haloperidol and pimozide are the only U.S. Food and Drug Administration-approved neuroleptics for the treatment of tics in TS. Pimozide is started at a dose of 0.5 to 1.0 mg at night and increased every 5 to 7 days to a therapeutic dose of 2 to 8 mg. Haloperidol is started at a dose of 0.25 to 0.5 mg and can be increased to 1 to 4 mg depending on response and side effects. Use of neuroleptics carries a small but significant risk of tardive dyskinesia.
- Tetrabenazine is a dopamine-depleting agent that can be used effectively in TS patients to control tics. Tetrabenazine does not cause many of the typical side effects of neuroleptic medication. However, severe depression may occur with use of tetrabenazine. Newer deutetrabenazine and valbenazine (VMAT2 inhibitors) also can be considered and have randomized placebo-controlled trials in progress.
- Topiramate is an antiepileptic used off-label to treat tics.
- Botulinum toxin (local injection) is effective for focal tics like eye blinking and neck and shoulder tics. The benefits are temporary, lasting 3 to 6 mo.
- Surgical treatment with deep brain stimulation is effective in some patients with disabling tics that are refractory to medications.

ADHD: Stimulants are useful for symptoms of ADHD but may exacerbate tics in 25% of patients. These medications should be used if troublesome behavioral symptoms persist.

OCD: Selective serotonin reuptake inhibitors, such as fluoxetine, are the most effective treatment for OCD.

DISPOSITION

- The intensity and frequency of tics typically diminishes during the later teenage years.
- One third of patients will achieve significant remission, although complete, lifelong remission is rare.
- One third will have mild, persistent, but "non-impairing" tics.

REFERRAL

Neurologist to confirm the initial diagnosis and for treatment in difficult cases

PEARLS & CONSIDERATIONS

- Tics do not need treatment unless they interfere with an individual's ability to function.
- Greater improvement in symptom severity among children with TS and chronic tic disorder has been reported with a comprehensive behavioral intervention compared with supportive therapy and education.
- An important part of treatment is appropriate evaluation and therapy of coexisting conditions (e.g., ADHD, OCD), as these conditions often cause more disability than the tics themselves.
- Deep brain stimulation has shown promising results as an alternative therapy in patients with medically refractory disease.

COMMENTS

Patient education may be obtained from the Tourette Syndrome Association, 4240 Bell Blvd., Bayside, NY 11361-2864; 800-237-0717 or 718-224-2999; http://www.tsa-usa.org.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Tourette Syndrome (Patient Information)

AUTHORS: **Corey Goldsmith, MD,** and **Fariha Jamal, MD**

SUGGESTED READINGS

Ercan-Sencicek AG et al: l-Histidine decarboxylase and Tourette's syndrome, *N Engl J Med* 362:1901-1908, 2010.

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Piacentini J et al: Behavior therapy for children with Tourette disorder, *J Am Med Assoc* 303(19):1929-1937, 2010.

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Toxic Epidermal Necrolysis

BASIC INFORMATION

DEFINITION

Toxic epidermal necrolysis (TEN) is a rare, acute, life-threatening mucocutaneous disease that is characterized by whole epidermal keratinocyte death resulting in dermal-epidermal separation of more than 30% body surface area (BSA). TEN and Steven-Johnson Syndrome (SJS) were initially described as separate entities, but are now considered to be variants of the same spectrum of disease, with similar clinical, histopathologic, and pathogenic features. SJS involves less than 10% BSA, SJS-TEN overlap involves 10% to 30% BSA, and TEN involves more than 30% BSA. TEN and SJS are caused by a hypersensitivity reaction to medications.

SYNONYM

Lyell syndrome

ICD-10CM CODE
L51.2 Toxic epidermal necrolysis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Annual incidence is two to seven cases per million per year
PREDOMINANT SEX AND AGE: Women:men ratio 1.5:1
GENETICS: Some ethnic groups are more susceptible to developing TEN to certain medications when having specific human leukocyte antigen (HLA) alleles: e.g., to carbamazepine in Asians and East Indians with HLA-B*1502 and Europeans with HLA-A*3101, or to allopurinol in Han Chinese with HLA-B*5801.
RISK FACTORS: Slow acetylator genotypes, immunosuppression, and concomitant administrations of radiotherapy and anticonvulsants increase the risk for TEN.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The lesions in TEN are dynamic and follow a sequence of changes characterized below.

- *Early*: Fever, stinging eyes, pain upon swallowing may precede cutaneous manifestations by 2 to 7 days.
- *Later*: Generalized, dusky red, purpuric macules of irregular size and shape, with tendency to coalesce (Fig. E1). Nikolsky sign positive (top layers of the skin slip away from the lower layers when slightly rubbed), detachment of large sheets of necrotic epidermis, extreme skin pain, mucosal involvement, anxiety, and asthenia. As the necrotic epidermis detaches from the underlying dermis, flaccid blisters form. The blisters can be extended sideways by slight pressure with a finger as more necrotic epidermis is displaced laterally (Asboe–Hansen sign). TEN patients resemble burn victims clinically, as well as in morbidity and mortality.
- *Resolution:* Scarring may develop when healing (joint contractures, eye complications, strictures of esophagus, anus, vagina, urethra).

ETIOLOGY

Exfoliation of the epidermis is due to extensive keratinocyte apoptosis. Several mechanisms have been postulated to explain the keratinocyte apoptosis. These include drug- or cytotoxic T-cell–mediated expression of FasL, perforin, granulysin, and granzyme B by keratinocytes via a molecular bridge involving tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and inducible nitric oxide synthase (iNOS).

Medications most commonly associated with the development of TEN are shown in Table E1. Medications other than those listed in Table E1 have been classified to carry a lower risk, a doubtful risk, or being without evidence for a risk to induce TEN (see "Suggested Readings").

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Steven-Johnson syndrome +SJS/TEN overlap
- Erythema multiforme-major (mostly postinfectious)
- Staphylococcal scalded skin syndrome
- Generalized fixed drug eruptions
- Paraneoplastic pemphigus
- Drug-induced linear IgA bullous dermatosis

WORKUP

Identification of TEN is based on the clinical findings of epidermal detachment of more than 30% BSA, mucous membrane involvement, and full-thickness epidermal necrolysis, as described by pathology. A complete medication history should be taken including a time line outlining when new medications were started before the onset of the clinical symptoms. TEN most commonly occurs between 1 and 4 wk after starting a new drug, but can occur at any time. Risk assessment should be done by using the SCORTEN mortality prognostic indicator (see Table E2). Workup for the patient is similar to burn patients.

FIG. E1 Toxic epidermal necrolysis. (Courtesy David Effron, MD. From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, WB Saunders.)

TABLE E1 Medications Most Commonly Causing Toxic Epidermal Necrolysis

Allopurinol	Cotrimoxazole
Sulfa drugs	Aminopenicillins
Carbamazepine	Cephalosporins
Phenobarbital	Quinolones
Phenytoin	Minocycline
Phenylbutazone	Trimethoprim-sulfamethoxazole
Lamotrigine	
Nevirapine	Amithiozone (thioacetazone)
Oxicam NSAIDs	Antiretroviral drugs, especially NNRTIs
Thioacetazone	

NNRTIs, Non-nucleoside reverse transcriptase inhibitors; *NSAIDs,* nonsteroidal antiinflammatory drugs.

TABLE E2 SCORTEN Mortality Prognostic Indicator

Prognostic Factor	Points	SCORTEN	Mortality (%)
Age >40 yr	1	0-1	3.2
Heart rate >120 bpm	1	2	12.1
Cancer/hematologic malignancy	1	3	35.8
BSA involved more than 10% on day 1	1	4	58.3
Serum urea level >28 mg/dl	1	>5	90
Serum bicarbonate level <20 mEq/L	1		
Serum glucose level >252 mg/dl	1		

BSA, Body surface area; *SCORTEN,* SCORe of Toxic Epidermal Necrosis.

LABORATORY TESTS

In addition to the skin biopsy, no specific laboratory test is available to diagnose TEN. Standard chemistry to monitor electrolyte and fluid balance and organ function (e.g., serum urea, bicarbonate, glucose; see Table E2) should be monitored as in burn patients.

IMAGING STUDIES

N/A

TREATMENT

Withdrawing the offending drug reduces the risk of death by 30% per day and is the single most important measure in the management of TEN.

NONPHARMACOLOGIC THERAPY

- *Symptomatic treatment:*
  1. SCORTEN >1: Transfer to intensive care unit/burn unit
  2. Fluid replacement
  3. Peripheral venous access (preferably in non-involved areas)
  4. Increased environmental temperature (30°C; 86° F)
  5. Air-fluidized bed
  6. Early nutritional support through nasogastric tube
  7. Aseptic procedures, frequent culturing of skin, blood, urine specimens
  8. No prophylactic antibiotics
  9. Prophylactic anticoagulation
  10. Nonadhesive wound dressings, porcine xenografts, human allografts, autologous skin grafts, skin substitutes
  11. Daily ophthalmologic exam/consultation; artificial tears, antibiotic eyedrops every 2 hours; early mechanical disruption of synechia
  12. Regular mouth washes with antiseptic/antifungal solutions

ACUTE GENERAL Rx

There is no consensus for the optimal pharmacologic treatment of TEN.

- High-dose steroids may be effective in the initial course of the disease, but probably increase mortality later on due to infectious complications (sepsis).
- Administration of high-dose IVIG over 3 to 4 days may reduce TEN-associated mortality (e.g., by blocking Fas-FasL interaction).
- Newer studies have found that cyclosporine offers a greater mortality benefit and decreases morbidity because the mean duration of re-epithelialization and duration of hospital stay was significantly lower (e.g., by targeting granulysin).
- Several reports in the literature suggest efficacy of TNF-α inhibitors, notably infliximab and etanercept.
- Other agents that may also be effective in the treatment of TEN include cyclophosphamide, plasmapheresis, and N-acetylcysteine.

DISPOSITION

Late withdrawal of the causative drug is associated with a less favorable outcome/increased mortality. If he/she survives, the patient may suffer debilitating and disfiguring scars and contractures, requiring extensive physical therapy and/or surgical interventions.

PEARLS & CONSIDERATIONS

COMMENTS

Early recognition and prompt discontinuation of the culprit drug saves lives.

PREVENTION

In order to prevent recurrences, it is of pivotal importance that patients are never again exposed to the drug that caused TEN. This also includes chemically related medications. Avoiding any drugs that have caused less severe drug reactions in the past is important for primary prevention of TEN.

RELATED CONTENT

Erythema Multiforme-Major (Related Key Topic)
Steven-Johnson Syndrome (Related Key Topic)

AUTHOR: **Ganary Dabiri, MD, PhD**

SUGGESTED READINGS

Ng QX et al: A meta-analysis of cyclosporine treatment for SJS/TEN, *J Inflam Research* 11:135-142, 2018.

Paradisi A et al: Etanercept therapy for TEN, *J Am Acad Dermatol* 71:278-283, 2014.

Scarf JM et al: Population prevalence of tourette syndrome: a systematic review and meta-analysis, *Mov Disord* 30(2):221-228, 2015.

Schwartz RA et al: Toxic epidermal necrolysis: Part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis, *J Am Acad Dermatol* 69(2):173.e1-13, 2013.

Schwartz RA et al: Toxic epidermal necrolysis: Part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment, *J Am Acad Dermatol* 69(2):187.e1-16, 2013.

Villano JH, Lovell EO: Mixed signals: toxic epidermal necrolysis, *Am J Med* 128(3):254-256, 2015.

BASIC INFORMATION

DEFINITION

Toxic megacolon is a rare but severe complication of colonic inflammation, usually inflammatory bowel disease (IBD). It is characterized by total or segmental nonobstructive colonic distention (>6 cm) associated with systemic toxicity of inflammatory or infectious etiology.

SYNONYM

Toxic dilation of the colon

ICD-10CM CODES

A04.7 Megacolon due to *Clostridium difficile*
K59.3 Megacolon, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Varies depending on etiology. Incidence in patients with ulcerative colitis (UC) is approximately 10% and nearly 5% in patients with Crohn disease. *Clostridium difficile* infections may be complicated by toxic megacolon in up to 3% of cases.
PEAK INCIDENCE: N/A
PREVALENCE: N/A
PREDOMINANT SEX AND AGE: With increasing rates of *Clostridium difficile (C. diff)* infections, patients ages 65 and older are at higher risk for developing toxic megacolon as a result of *C. diff* infection.
GENETICS: There are no known genetic factors that predispose patients to developing toxic megacolon associated with an inflammatory or infectious etiology.
RISK FACTORS: Major risk factors include inflammatory, infectious, and ischemic conditions of the colon, especially in individuals who are immunocompromised. Other risk factors include hypokalemia, use of narcotics or antidiarrheal agents, pregnancy, and recent instrumentation (such as colonoscopy).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with toxic megacolon usually appear severely ill. Clinical symptoms are similar to those of IBD and acute colitis and may include abdominal pain, diarrhea (usually bloody) and vomiting.
- Physical exam findings may include a distended, tender, and tympanic abdomen with reduced or absent bowel sounds. The patient may also present with signs of shock such as fever, tachycardia, mental status changes, and hypovolemia. Older patients are less likely to demonstrate a peritoneal abdominal examination.
- Laboratory findings may include leukocytosis, lactic acidosis, anemia, and electrolyte abnormalities such as hypokalemia and hypoalbuminemia.

ETIOLOGY

- Most common etiologies are inflammatory conditions such as UC, Crohn disease, and Behçet disease.
- Infections such as *C. diff, Salmonella, Shigella, E. coli,* cytomegalovirus, and *Entamoeba* can also be complicated by toxic megacolon.
- Other less common etiologies include ischemic colitis, malignancy such as lymphoma, and Kaposi sarcoma. In general, toxic megacolon is more likely to be associated with pancolitis than segmental colitis (Box 1).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Ischemic colitis, Crohn disease, ulcerative colitis

WORKUP

- General principles of workup include physical examination to evaluate for an acute abdomen, laboratory testing and radiography to evaluate for colonic dilation.
- Clinical criteria for toxic megacolon, proposed by Jalan et al in 1969, are still used. A diagnosis can be made if radiographic evidence of colonic distention >6 cm is present with at least three of the following: Fever >38° C (100.4° F), heart rate >120, leukocytosis >10.5, or anemia. In addition, at least one of the following must also be present: Dehydration, altered level of consciousness, electrolyte abnormalities, or hypotension.
- Patients with suspected toxic megacolon should be triaged emergently to an emergent care setting to facilitate rapid diagnosis and treatment.

LABORATORY TESTS

Initial testing should include a CBC, full chemistry panel, lactic acid, coagulation panel, liver function panel, and a type and screen.

IMAGING STUDIES

- All patients should initially receive a plain abdominal radiograph (Fig. 1) to assess for colonic dilation. Common findings include mucosal irregularity, loss of haustrations, "thumb printing" due to bowel wall edema, and thickening of the colonic wall with a continuous segment of air-filled colon >6 cm in diameter. The transverse or right colon is usually the most dilated segment seen.
- Computed tomography (CT) has been increasingly used to assess disease extent and for surgical planning (Fig. 2). It can also be helpful when differentiating between the various etiologies of toxic megacolon and to assess for complications such as intraabdominal hemorrhage or abscess.

BOX 1 Disorders Associated with Toxic Megacolon

- Inflammatory bowel disease
  1. Ulcerative colitis
  2. Crohn disease
- Infectious colitis
  1. *Salmonella, Shigella*, amoebic colitis
  2. *Clostridium difficile*
  3. Cytomegalovirus colitis
  4. HIV infection
- Cancer chemotherapy
- Ischemia

HIV, Human immunodeficiency virus.
From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, WB Saunders.

TREATMENT

Treatment includes both medical and surgical options. Principles of initial management include treating the underlying cause, managing shock, analgesia, and early surgical and gastroenterology consultation.

NONPHARMACOLOGIC THERAPY

- Surgery may be required in up to 50% of patients with toxic megacolon who do not show clinical improvement within 24 to 48 hr. The preferred first-line surgical treatment is subtotal colectomy with an end ileostomy. Other options include total proctocolectomy or colon decompression via the Turnbull method.
- Timing of surgical treatment is still controversial, with many advocating for aggressive medical treatment and observation before surgical intervention. Definitive indications for early surgical treatment include perforation, persistent colonic hemorrhage, or rapid clinical deterioration.

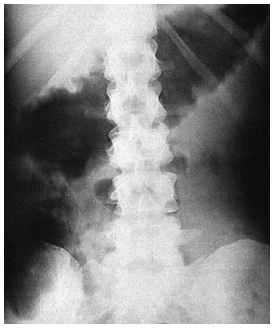

FIG. 1 Toxic megacolon secondary to ulcerative colitis. The smooth indentations seen along the margin of the colon represent pseudopolyps. (From Marx JA et al [eds]: *Rosen's emergency medicine: concepts and clinical practice,* ed 7, Philadelphia, 2010, Elsevier.)

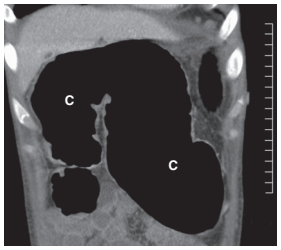

FIG. 2 Toxic megacolon. In a young patient with severe ulcerative colitis, coronal computed tomography demonstrates marked dilation of the colon *(c)* with thinning of its walls. The diameter of the lumen of the colon exceeds 7 cm. This finding places the patient at high risk of colon perforation. (From Webb WR et al: *Fundamentals of body CT,* ed 4, Philadelphia, 2015, WB Saunders.)

ACUTE GENERAL Rx

- Medications that impact colonic motility such as anticholinergics, opioids, and antidiarrheal agents should be discontinued and avoided.
- Electrolyte abnormalities, dehydration, and anemia are common clinical findings and should be addressed early. Fluid resuscitation with an isotonic solution and correction of electrolyte disturbances (especially hypokalemia) can help prevent worsening atony of the colonic wall. Patients with anemia from colonic hemorrhage should receive blood transfusion(s).
- Patients with toxic megacolon should receive broad-spectrum antibiotics as soon as possible. Infections due to *C. diff* should be treated with vancomycin (oral or rectal) or metronidazole (oral or IV). Toxic megacolon due to cytomegalovirus should be treated with ganciclovir IV.
- Patients with inflammatory etiologies such as UC or Crohn should receive high-dose IV steroids, either hydrocortisone 100 mg IV or methylprednisolone 60 mg IV. Steroids should not be used in patients with a confirmed infectious etiology.
- There are currently no data to support empiric treatment of toxic megacolon due to IBD with cyclosporine or infliximab. These treatment options should be reserved for patients who are not steroid responsive and should be limited to one attempt at clinical improvement so as not to delay surgical intervention.
- A management algorithm for toxic megacolon is outlined in Fig. 3.

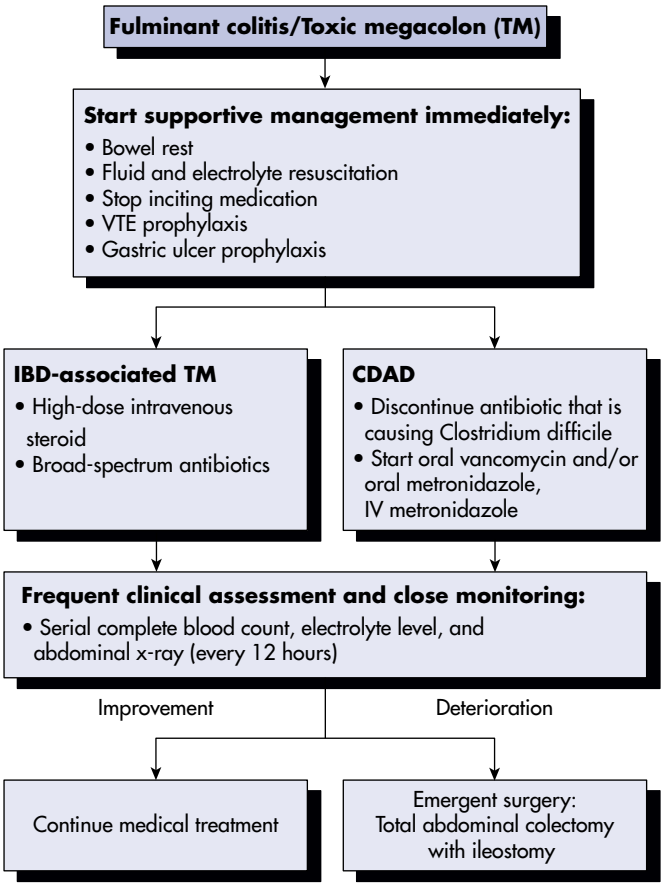

FIG. 3 Management algorithm for toxic megacolon. *CDAD, C. difficile*-associated disease; *IBD,* inflammatory bowel disease; *VTE,* venous thromboembolism. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.)

CHRONIC Rx

Patients with IBD will need continued treatment for the underlying disease process once the acute processes associated with toxic megacolon have resolved.

COMPLEMENTARY & ALTERNATIVE MEDICINE

N/A

DISPOSITION

All patients with toxic megacolon will require admission, possibly to the intensive care unit, depending on their clinical presentation.

REFERRAL

- Patients with suspected toxic megacolon presenting outside an emergency department should be referred there immediately.
- Surgical consultation in all cases.
- All patients with toxic megacolon due to newly diagnosed IBD who are discharged from the hospital should be referred to a gastroenterologist for continued treatment.

PEARLS & CONSIDERATIONS

COMMENTS

- Early recognition and treatment of toxic megacolon is critical given the associated high morbidity and mortality.
- Anticholinergic medications, antidiarrheal agents, and opioids can precipitate or worsen toxic megacolon.
- Management includes medical and surgical treatment with inpatient hospitalization and treatment of the underlying cause.

PREVENTION

Prevention focuses on treatment of underlying causes of colitis to prevent complications such as toxic megacolon.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Clostridium difficile Infection (Related Key Topic)
Crohn Disease (Related Key Topic)
Small Bowel Obstruction (Related Key Topic)
Ulcerative Colitis (Related Key Term)

AUTHORS: **Steven Rougas, MD, MS, FACEP,** and **Rory Merritt, MD, MEHP**

SUGGESTED READINGS

Autenrieth DM, Baumgart DC: Toxic megacolon, *Inflamm Bowel Dis* 18:584-591, 2012.

Strong SA: Management of acute colitis and toxic megacolon, *Clin Colon Rectal Surg* 23:274-284, 2010.

BASIC INFORMATION

DEFINITION

Toxic shock syndrome (TSS) is an acute febrile illness resulting in multiple organ system dysfunction caused most commonly by a bacterial exotoxin. Disease characteristics also include hypotension, vomiting, myalgia, watery diarrhea, vascular collapse, and an erythematous sunburn-like cutaneous rash that desquamates during recovery. Box 1 summarizes the clinical case definition of toxic shock syndrome.

SYNONYM

TSS

ICD-10CM CODE
A48.3 Toxic shock syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- Case reported incidence peak: 14 cases per 100,000 menstruating women annually in 1980; has since fallen to 1 case per 100,000 persons
- Occurs most commonly between ages 10 and 30 yr in healthy, young, menstruating white females
- Case fatality ratio of 3%

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever (>38.0° C; 100.4° F)
- Diffuse macular erythrodermatous rash that involves both skin and mucous membranes, resembles sunburn, and also involves the palms and soles. The rash then desquamates 1 to 2 wk after disease onset in survivors
- Orthostatic hypotension
- Gastrointestinal symptoms: Vomiting, diarrhea, abdominal tenderness
- Constitutional symptoms: Myalgia, headache, photophobia, rigors, altered sensorium, conjunctivitis, arthralgia
- Respiratory symptoms: Dysphagia, pharyngeal hyperemia, strawberry tongue
- Genitourinary symptoms: Vaginal discharge, vaginal hyperemia, adnexal tenderness
- End-organ failure
- Severe hypotension and acute renal failure
- Hepatic failure
- Cardiovascular symptoms: Disseminated intravascular coagulation, pulmonary edema, acute respiratory distress syndrome (ARDS), endomyocarditis, heart block

ETIOLOGY

- Menstruation-associated TSS: 45% of cases associated with tampons, diaphragm, or vaginal sponge use. There has been a decline in these cases and in the case-fatality ratio.
- Non–menstruation-associated TSS: 55% of cases associated with puerperal sepsis, post-cesarean section endometritis, mastitis, sinusitis, wound or skin infection, septorhinoplasty (nasal packings), pelvic inflammatory disease, respiratory infections following influenza, enterocolitis, and burns. The number of cases is increasing and the case-fatality ratio has not declined.
- Causative agent: *Staphylococcus aureus* infection of a susceptible individual (10% of population lacking sufficient levels of antitoxin antibodies), which liberates the disease mediator TSST-1 (exotoxin). While most cases are caused by methicillin-susceptible *S. aureus* (MSSA), cases of TSS from methicillin-resistant *S. aureus* (MRSA) have occurred, particularly those due to the more virulent, community-associated MRSA strains.
- *S. aureus* exotoxins are superantigens that can activate large numbers of T cells (up to 20% at one time), resulting in a massive cytokine production: Interleukin (Il-1), Il-2, TNF, and interferon gamma that then mediate the signs and symptoms of the disease.
- Other causative agents: Coagulase-negative staphylococci producing enterotoxins B or C, and exotoxin A–producing group A beta-hemolytic streptococci.
- Risk factors for staphylococcal toxic shock syndrome are summarized in Box 2.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Staphylococcal food poisoning
- Septic shock
- Mucocutaneous lymph node syndrome
- Scarlet fever
- Rocky Mountain spotted fever
- Meningococcemia
- Toxic epidermal necrolysis
- Kawasaki syndrome
- Leptospirosis
- Legionnaires' disease
- Hemolytic-uremic syndrome
- Stevens-Johnson syndrome
- Scalded skin syndrome
- Erythema multiforme
- Acute rheumatic fever

WORKUP

Broad-spectrum syndrome with multiorgan system involvement and variable but acute clinical presentation, including the following diagnostic criteria for staphylococcal toxic shock syndrome:

- Fever (>38° C; 100.4° F)
- Classic desquamating rash (1 to 2 wk)
- Hypotension/orthostatic systolic blood pressure ≤90 mm Hg
- Syncope
- Negative throat and cerebrospinal fluid cultures
- Negative serologic test for Rocky Mountain spotted fever, rubeola, and leptospirosis
- Clinical involvement of three or more of the following:
  1. Cardiopulmonary: ARDS, pulmonary edema, endomyocarditis, second- or third-degree atrioventricular block
  2. Central nervous system: Altered sensorium without focal neurologic findings
  3. Hematologic: Thrombocytopenia (platelets <100,000)
  4. Liver: Elevated liver function test results

BOX 1 Clinical Case Definition of Toxic Shock Syndrome

Clinical Findings

- Fever: Temperature of ≥38.9° C (102° F)
- Rash: Diffuse macular erythroderma
- Desquamation: 1 to 2 weeks after onset of illness, particularly on palms, soles, fingers, and toes
- Hypotension: Systolic blood pressure ≤90 mm Hg for adults; <5th percentile by age for children <16 years; orthostatic drop in diastolic blood pressure of ≥15 mm Hg from lying to sitting; orthostatic syncope or orthostatic dizziness
- Involvement of three or more of the following organ systems:
  - Gastrointestinal: Vomiting or diarrhea at onset of illness
  - Muscular: Severe myalgia or creatinine phosphokinase level greater than twice the upper limit of normal for the laboratory
  - Mucous membrane: Vaginal, oropharyngeal, or conjunctival hyperemia
  - Renal: Blood urea nitrogen or serum creatinine greater than twice the upper limit of normal, or 5 or more white blood cells per high-power field in the absence of a urinary tract infection
  - Hepatic: Total bilirubin, aspartate transaminase, or alanine transaminase greater than twice the upper limit of normal for the laboratory
  - Hematologic: Platelets <100,000/mm^2
  - Central nervous system: Disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent
- Negative results on the following tests, if obtained:
  - Blood, throat, or cerebrospinal fluid cultures; blood culture may be positive for *Staphylococcus aureus*
  - Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles

Case Classification

- *Probable:* A case with 5 of the 6 clinical findings above
- *Confirmed:* A case with all 6 of the clinical findings above, including desquamation, unless the patient dies before desquamation can occur

From Wharton M et al: Case definitions for public health surveillance, *MMWR Recomm Rep* 39[RR-13]:1-43, 1990. In Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.

BOX 2 Risk Factors for Staphylococcal Toxic Shock Syndrome

I. Colonization of infection with toxin-producing *Staphylococcus aureus*
II. Absence of protective antitoxin antibody
III. Infected site
  A. Primary *S. aureus* infection:
    - Carbuncle
    - Cellulitis
    - Dental abscess
    - Empyema
    - Endocarditis
    - Folliculitis
    - Mastitis
    - Osteomyelitis
    - Peritonitis
    - Peritonsillar abscess
    - Pneumonia
    - Pyarthrosis
    - Pyomyositis
    - Sinusitis
    - Tracheitis
  B. Postsurgical wound infection:
    - Abdominal
    - Breast
    - Cesarean section
    - Dermatologic
    - Ear, nose, and throat
    - Genitourinary
    - Neurosurgery
    - Orthopedic
  C. Skin or mucous membrane disruption:
    - Burns (chemical, scald, etc.)
    - Dermatitis
    - Influenza
    - Pharyngitis
    - Postpartum (vaginal delivery)
    - Superficial/penetrating trauma (insect bite, needle stick)
    - Viral infection
    - Varicella
  D. Foreign body placement:
    - Augmentation mammoplasty
    - Catheters
    - Contraceptive sponge
    - Diaphragm
    - Surgical prostheses, stents, packing material, sutures
    - Tampons
  E. No obvious focus of infection (vaginal or pharyngeal colonization)

Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

5. Renal: >5 cells/high-power field, negative urine cultures, azotemia, and increased creatinine (double normal)
6. Mucous membrane involvement: Vagina, oropharynx, conjunctiva
7. Musculoskeletal: Myalgia, creatine phosphokinase twice normal
8. Gastrointestinal: Vomiting, diarrhea

For streptococcal toxic shock syndrome the diagnostic criteria is as follows:

- Definite case: Isolation of group A β-hemolytic streptococci (GABHS) from a sterile site
- Probable case: Isolation of GABHS from a nonsterile site
- Hypotension: Presence of two of the following findings:
  1. Acute kidney injury or failure
  2. Elevated aminotransferase
  3. Erythematous macular rash, soft tissue necrosis
  4. Coagulopathy, including thrombocytopenia and disseminated intravascular coagulation
  5. Acute respiratory distress syndrome

TABLE 1 Staphylococcal Versus Streptococcal Toxic Shock Syndrome

Feature	Staphylococcal	Streptococcal
Age	Primarily 15-35 yr	Primarily 20-50 yr
Gender	Higher frequency in women	Men and women equally affected
Severe pain	Rare	Common
Hypotension	100%	100%
Erythroderma rash	Very common	Less common
Renal failure	Common	Common
Bacteremia	Low frequency	60%
Tissue necrosis	Rare	Common
Predisposing factors	Tampons, surgery	Cuts, burns, varicella
Thrombocytopenia	Common	Common
Mortality rate	<3%	30%-70%

From Mandell GL et al: *Principles and practice in infectious diseases,* ed 7, Philadelphia, 2008, Churchill Livingstone.

BOX 3 Therapeutic Principles for Management of Toxic Shock Syndrome

1. Identify the focus of infection; debride and irrigate extensively and remove any foreign material
2. Isolate the organism for antimicrobial susceptibility studies
3. Administer parenteral antimicrobial therapy to stop toxin production and eradicate the organism
4. Manage systemic multiorgan actions of toxins or mediators
5. Administer fluid therapy to maintain adequate venous return and cardiac filling pressure and prevent end-organ damage
6. Consider intravenous immunoglobulin for the following:
   - Disease refractory to initial fluid replacement and vasopressor support
   - A focus of infection that cannot be drained

Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

LABORATORY TESTS

- Pan culture (cervix and vagina, throat, nasal passages, urine, blood, cerebrospinal fluid, wound) for *Staphylococcus, Streptococcus* (Table 1), and other pathogenic organisms
- Electrolytes to detect hypokalemia, hyponatremia
- Complete blood count with differential and clotting profile for anemia (normocytic or normochromic), thrombocytopenia, leukocytosis, coagulopathy, and bacteremia
- Chemistry profile to detect decreased protein, increased aspartate aminotransferase, increased alanine aminotransferase, hypocalcemia, elevated blood urea nitrogen and creatinine, hypophosphatemia, increased lactate dehydrogenase, increased creatine phosphokinase
- Urinalysis to detect white blood cells (>5 cells/high-power field), proteinemia, microhematuria
- Arterial blood gases to assess respiratory function and acid-base status
- Serologic tests considered for Rocky Mountain spotted fever, rubeola, and leptospirosis

IMAGING STUDIES

- Chest x-ray to evaluate pulmonary edema
- ECG to evaluate arrhythmia
- Sonography, CT scan, or MRI considered if pelvic abscess or tuboovarian abscess suspected

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Therapeutic principles for management of toxic shock syndrome are outlined in Box 3.
- For optimal outcome: High index of suspicion and early and aggressive supportive management in an ICU setting
- Aggressive fluid resuscitation (maintenance of circulating volume, cardiac output, systolic blood pressure)
- Thorough search for a localized infection or nidus: Incision and drainage, debridement, removal of tampon or vaginal sponge
- Central hemodynamic monitoring, Swan-Ganz catheter, and arterial line for surveillance of hemodynamic status and response to therapy
- Foley catheter to monitor hourly urine output
- Possible military anti-shock trousers as temporary measure
- Acute ventilator management if severe respiratory compromise

- Renal dialysis for severe renal impairment
- Surgical intervention for indicated conditions (i.e., ruptured tubo-ovarian abscess, wound abscess, mastitis)
- Hyperbaric oxygen treatment can be used adjunctively

ACUTE GENERAL Rx

- Isotonic crystalloid (normal saline solution) for volume replacement following "7-3" rule (refers to the response in millimeters of mercury [mm Hg] of the pulmonary artery wedge pressure to volume replacement).
- Electrolyte replacement (K^+, C^+).
- Packed red blood cells, coagulation factor replacement, fresh frozen plasma to treat anemia or dilation and curettage.
- Vasopressor therapy for hypotension refractory to fluid volume replacement (e.g., dopamine beginning at 2 to 5 μg/kg/min).
- Steroids have been used but are not generally recommended due to lack of evidence of benefit.
- It is not clear whether antibiotics alter the course of acute TSS. Most authors recommend that patients receive 10 to 14 days of combination antibiotic therapy. In staphylococcal TSS, effective agents are clindamycin (900 mg IV every 8 hr in adults or 25 to 40 mg/kg per day in children) plus vancomycin (adults: 30 mg/kg per day IV in two divided doses; children: 40 mg/kg per day IV in four divided doses). Oxacillin or nafcillin sodium (2 g IV every 4 hr in adults; children: 100 to 150 mg/kg per 24 hr divided in four doses) can be used instead of vancomycin if TSS is due to MSSA. An alternative to vancomycin is linezolid.
- In streptococcal TSS, effective agents are penicillin G 24 million units/day in divided doses *plus* clindamycin 900 mg IV q8h. Alternative agents are ceftriaxone 2 g IV q24h *plus* clindamycin 900 mg IV q8h.
- Broad-spectrum antibiotic including gram-negative coverage added if concurrent sepsis suspected with TSS.
- Intravenous immune globulin (IVIG): While no controlled trials exist, most authors recommend IVIG (400 mg/kg in a single dose administered over several hours) in severe cases of TSS that are not responding to fluids or vasopressors. It may neutralize superantigen and decrease tissue damage.
- Tetracycline added if considering Rocky Mountain spotted fever.

CHRONIC Rx

- Severely ill patient: May require prolonged hospitalization and supportive management with gradual recovery and/or sequelae from severe end-organ involvement (ARDS or renal failure requiring dialysis)
- Majority of patients: Complete recovery
- Early-onset complications (within 2 wk):
  1. Skin desquamation
  2. Impaired digit sensation
  3. Denuded tongue
  4. Vocal cord paralysis
  5. Acute tubular necrosis
  6. ARDS
- Late-onset complications (after 8 wk):
  1. Nail splitting and loss
  2. Alopecia
  3. Central nervous system sequelae
  4. Renal impairment
  5. Cardiac dysfunction
- Recurrent TSS:
  1. More common in menstruation-related cases.
  2. Less common in patients treated with beta-lactamase–resistant antistaphylococcal antibiotics.
  3. Patients with history of TSS: If suspect signs and symptoms occur, have high index of suspicion and low threshold for evaluation and treatment.
  4. Screen for nasal carriage of *S. aureus* in patients with *S. aureus* TSS and treat with mupirocin in those with positive cultures.

PREVENTION

- Avoidance of tampons or use of low-absorbency tampons only (<4 hr in situ) and alternate with napkins
- Education for patients concerning signs and symptoms of TSS
- Avoidance of tampons for patients with history of TSS

DISPOSITION

- Complete recovery for most patients
- Long-term management of early- and late-onset complications for minority of patients

REFERRAL

- For multidisciplinary management, involving primary physician, gynecologist, internist, infectious disease specialist, and other supportive care specialists
- To tertiary-level hospital

PEARLS & CONSIDERATIONS

COMMENTS

Antibiotic prophylaxis against invasive group A streptococcal infection with benzathine penicillin G plus rifampin, clindamycin, or azithromycin is recommended for immunocompromised household contacts of patients with streptococcal TSS-like syndrome.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Toxic Shock Syndrome (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Al-ajmi JA et al: Group A streptococcus toxic shock syndrome: an outbreak report and review of the literature, *J Infect Public Health* 5(6):388-393, 2012.

Berger S et al: Menstrual toxic shock syndrome: case report and systematic review of the literature, *Lancet Infect Dis* 2019 May 28. Pii:S1473-3099 (19) 30041-6.

Linner A et al: Clinical efficacy of polyspecific intravenous immunoglobulin therapy in patients with streptococcal toxic shock syndrome: a comparative observational study, *Clin Infect Dis* 59(6):851-857, 2014.

Low DE: Toxic shock syndrome: major advances in pathogenesis, but not treatment, *Crit Care Clin* 29(3):651-675, 2013.

Schmitz M et al: Streptococcal toxic shock syndrome in the intensive care unit, *Ann Intensive Care* 8(1):88, 2018.

BASIC INFORMATION

DEFINITION

Toxoplasmosis is an infection caused by the protozoal parasite *Toxoplasma gondii* transmitted through ingestion of undercooked meat, undercooked shellfish, or cat feces.

ICD-10CM CODES

B58.9	Toxoplasmosis, unspecified
B58.3	Pulmonary toxoplasmosis
B58.89	Toxoplasmosis with other organ involvement
P37.1	Congenital toxoplasmosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Seroprevalence varies widely between different geographic locations, increasing with age, prevalence of cats in the area, and certain activities such as working in slaughterhouses or owning cats.
- Seroprevalence among women of childbearing age was 9.1% between 2009 and 2010.
- 0.23 cases of congenital toxoplasmosis per 10,000 live births between 2006 and 2014.
- Among patients with HIV, seroprevalence is approximately 11% in the U.S.

PREDOMINANT SEX: Equal gender distribution

PREDOMINANT AGE:

- Infancy (congenital infection)
- Prevalence increases with age

PEAK INCIDENCE: Seroprevalence is much higher in Latin America, Africa, and other temperate climates than in the U.S.

GENETICS: Congenital infection:

- Incidence and severity vary with the trimester of gestation during which the mother acquired infection.
  1. 10% to 25% (first trimester)
  2. 30% to 54% (second trimester)
  3. 60% to 65% (third trimester)
- Congenital infection occurring in the first trimester is the most severe.
- 89% to 100% of infections in the third trimester are asymptomatic.
- Risk to the fetus is not correlated with symptoms in the mother.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acquired (immunocompetent host): Usually subclinical, though may develop adenopathy, fatigue, and other constitutional symptoms that, while generally mild, can take weeks to resolve.
- Acquired (in patients with AIDS especially with CD4 count <100, hematopoietic stem cell transplant recipients): Most common presentation is encephalitis with headache, confusion, and fever. May have motor weakness or other focal neurologic abnormalities and seizures. Can also present as pneumonitis, chorioretinitis, or other end-organ involvement.
- Acquired (immunocompromised patients):
  1. Encephalitis
  2. Myocarditis (especially in heart transplant patients)
  3. Pneumonitis
- Ocular infection in the immunocompetent host: If not congenital, then presents in second or third decade of life as a focal necrotizing retinitis with photophobia, blurred vision, pain, and potentially loss of central vision if the macula is involved.
- Congenital: Results from acute infection acquired by the mother within 6 to 8 weeks before conception or during gestation and is usually asymptomatic in the mother. In the infant, symptomatic disease is estimated at 40%. Ocular disease can include chorioretinitis and blindness, while CNS manifestations can include intracranial calcifications resulting in epilepsy, hydrocephalus, microcephaly, psychomotor or mental retardation, and encephalitis.

ETIOLOGY

- *Toxoplasma gondii:*
  1. Ubiquitous intracellular protozoan
  2. Present worldwide
  3. Cat is the definitive host (Fig. E1)
  4. Oocysts can remain viable up to a year in moist soil, despite freezing temperatures.
- Human infection:
  1. Ingestion of oocysts shed by cats in soil, litter boxes, vegetables
  2. Ingestion of inadequately cooked meat or shellfish containing tissue cysts
  3. Vertical transmission

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Lymphadenopathy:
  1. Infectious mononucleosis
  2. Cytomegalovirus (CMV) mononucleosis
  3. Cat-scratch disease
  4. Sarcoidosis
  5. Tuberculosis
  6. Lymphoma
  7. Metastatic cancer
- Cerebral mass lesions in immunocompromised host:
  1. Lymphoma
  2. Tuberculosis
  3. Bacterial abscess
- Pneumonitis in immunocompromised host:
  1. *Pneumocystis jiroveci (carinii)* pneumonia
  2. Tuberculosis
  3. Fungal infection
- Chorioretinitis:
  1. Syphilis
  2. Tuberculosis
  3. Histoplasmosis (competent host)
  4. CMV
  5. Herpes simplex
  6. Fungal infection
  7. Tuberculosis
- Myocarditis:
  1. Organ rejection in heart transplant recipients
- Congenital infection:
  1. Rubella
  2. CMV
  3. Herpes simplex
  4. Syphilis
  5. Listeriosis
  6. Erythroblastosis fetalis
  7. Sepsis

WORKUP

- Acute infection, immunocompetent host:
  1. Complete blood count
  2. *Toxoplasma* serology (IgG, IgM) in serial blood specimens 3 weeks apart
  3. Lymph node biopsy if diagnosis uncertain
- Immunocompromised host:
  1. Central nervous system (CNS) symptoms:
     a. Cerebral CT scan or MRI if CNS symptoms present
     b. Spinal tap, if safe
     c. Brain biopsy if no response to empiric therapy
  2. Ocular symptoms:
     a. Funduscopic examination
     b. Serologic studies
     c. Rarely, vitreous tap
  3. Pulmonary symptoms:
     a. Chest x-ray examination
     b. Bronchoalveolar lavage
     c. Transbronchial or open-lung biopsy
  4. Myocarditis:
     a. Cardiac enzymes
     b. Electrocardiogram
     c. Endomyocardial biopsy for definitive diagnosis
- Toxoplasmosis in pregnancy (Fig. 2):
  1. Initial maternal screening with IgM and IgG
     a. If negative, mother at risk of acute infection and should be retested monthly
     b. If both IgG and IgM positive, obtain IgA and IgE ELISA, AC/HS test
     c. IgA and IgE ELISA, AC/HS test elevated in acute infection
     d. Ig high for 1 yr or more
     e. IgG repeated 3 to 4 weeks later to determine if titer is stable
  2. Acute maternal infection not excluded or documented:
     a. Fetal blood sampling (for culture, Ig, IgA, IgE)
     b. Amniotic fluid polymerase chain reaction (PCR)
  3. Fetal ultrasound every other week if maternal infection documented to look for ventriculomegaly, calcifications in the brain, and enlarged liver and spleen
- Congenital toxoplasmosis (Fig. 3):
  1. Placental histology
  2. Specific IgM or IgA in infant's blood

LABORATORY TESTS

- Antibody studies:
  1. More than one test necessary to establish diagnosis of acute toxoplasmosis (look for seroconversion or 4x increase)
  2. IgM antibody:
     a. Appears 5 days into infection
     b. Peaks at 2 weeks

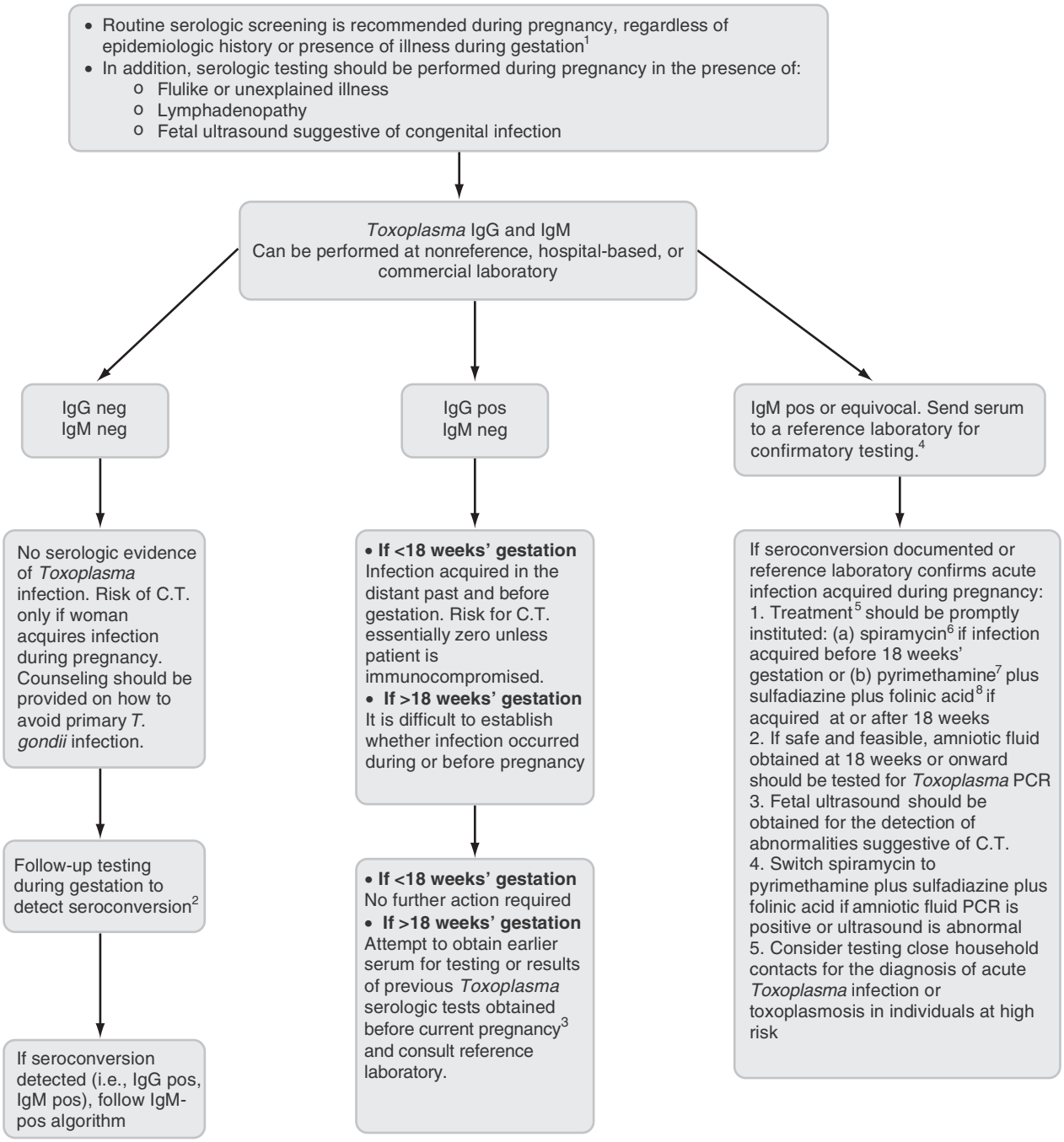

FIG. 2 Diagnostic approach and management algorithm of toxoplasmosis during pregnancy. Most of the initial serologic screening can be accomplished by nonreference or commercial laboratories. Only positive immunoglobulin M results should be considered for additional testing and consultation with medical experts at a reference laboratory. *CT,* Congenital toxoplasmosis; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M; *neg,* negative test result; *pos,* positive test result. [1]Up to 50% of women who acquire *Toxoplasma* infection during gestation do not have a known risk factor for acute infection or an illness suggestive of toxoplasmosis. Thus to identify all women at risk, serologic screening should be performed in all pregnant women, along with other routine screening tests. [2]In a recent study from Lyon, France, monthly screening of seronegative pregnant women was reported to significantly decrease the risk of vertical transmission and of clinical signs at 3 years of age. Consider consultation with a physician expert in management of toxoplasmosis during pregnancy (e.g., in the U.S., Palo Alto Medical Foundation–*Toxoplasma* Serology Laboratory [PAMF-TSL], www.pamf.org/serology/; 650-853-4828; e-mail, toxolab@pamf.org; or U.S. [Chicago] National Collaborative Treatment Trial Study [NCCTS]; 773-834-4152). [4]Consider sending serum sample to a reference laboratory (e.g., PAMF-TSL). [5]Treatment regimens vary by country. The pyrimethamine-sulfadiazine-folinic acid regimen should not be offered to any pregnant woman before 12 weeks of gestation because of potential teratogenicity. In some centers in Europe, this regimen is offered at 14 weeks of gestation or later; in the U.S., it is recommended at 18 weeks or later. [6]Spiramycin is not commercially available in the U.S. It can be obtained at no cost and after consultation (with PAMF-TSL or the NCCTS through the U.S. Food and Drug Administration). [7]When using pyrimethamine, folic acid should be discontinued from the prenatal multivitamins. Folic acid can potentially counteract the antiparasitic effect of the drug. [8]Folic acid should not be erroneously used instead of folinic acid. (From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.)

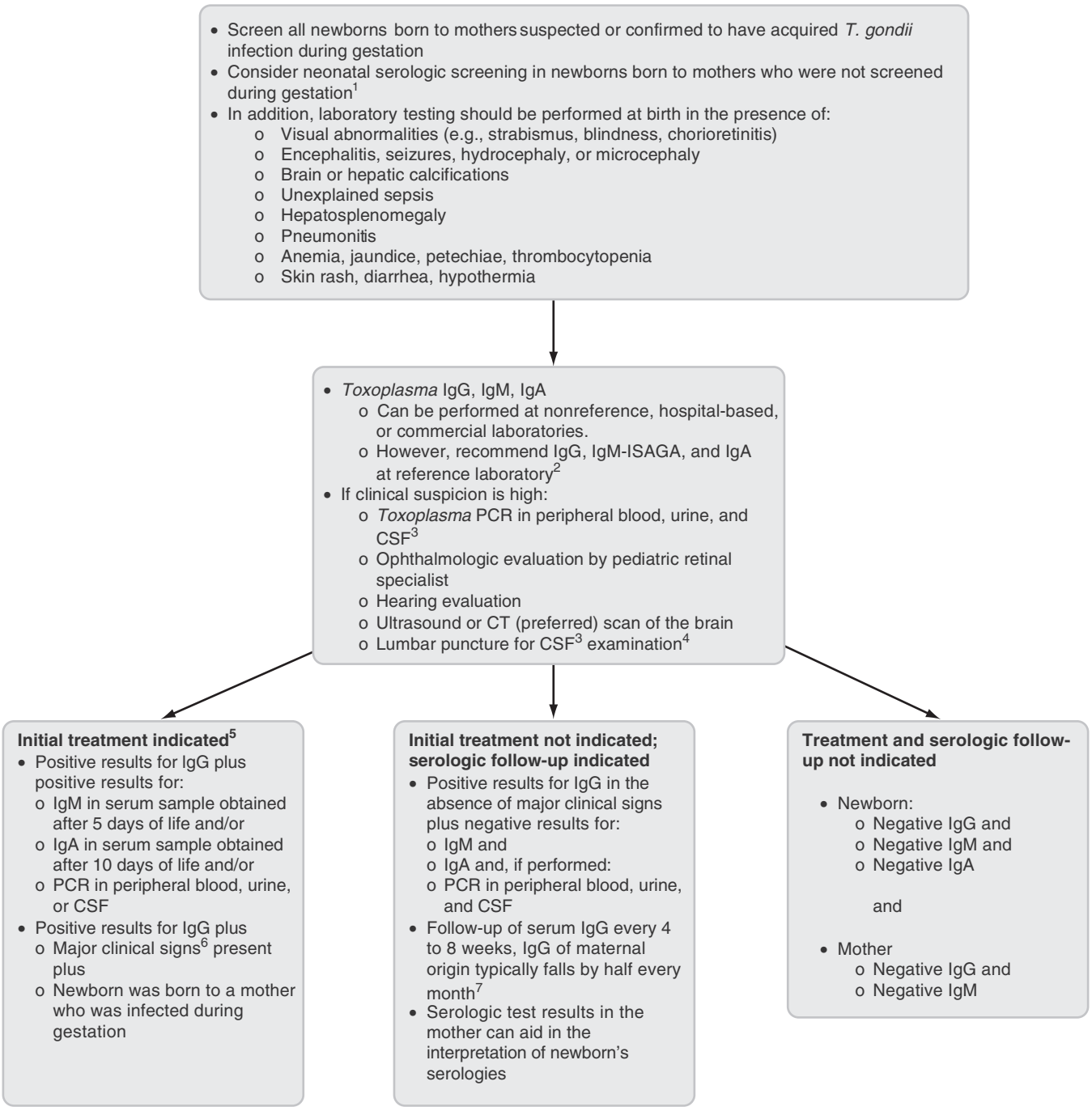

FIG. 3 Diagnostic approach and management algorithm of the newborn whose mother has been suspected or confirmed to have acquired toxoplasmosis during gestation. *CSF,* Cerebrospinal fluid; *CT,* computed tomography; *IgG, IgM,* and *IgA,* immunoglobulins G, M, and A, respectively; *ISAGA,* immunosorbent agglutination assay; *PCR,* polymerase chain reaction. [1]Consider consultation with a physician expert in management of toxoplasmosis during pregnancy (e.g., in the U.S., Palo Alto Medical Foundation–*Toxoplasma* Serology Laboratory [PAMF-TSL], www.pamf.org/serology/; 650-853-4828; e-mail, toxolab@pamf.org; or U.S. [Chicago] National Collaborative Treatment Trial Study, 773-834-4152). [2]Consider sending serum sample to a reference laboratory (e.g., PAMF-TSL). [3]If lumbar puncture is clinically indicated, deemed safe, and feasible. [4]In an attempt to confirm the diagnosis of congenital toxoplasmosis, CSF should be sent for cell count and differential (congenital toxoplasmosis is one of the few causes of eosinophilic meningitis), protein (congenital toxoplasmosis is one of the few causes of extreme elevation of CSF protein), glucose, and *T. gondii* PCR. [5]The recommended regimen is pyrimethamine plus sulfadiazine plus folinic acid (see text). [6]Major clinical signs are referred here: chorioretinitis, brain calcifications, and hydrocephalus. [7]Maternally transferred IgG antibodies usually decline and disappear within 6 to 12 months of life. (From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.)

TABLE 1 Guidelines for Interpretation of Serologic Tests for Toxoplasmosis

IgG	IgM	IgG Avidity	Interpretation
Positive	Negative	—	Remote infection, immune. IgG avidity testing is best used when both IgG and IgM are positive and timing of infection is crucial, as in pregnancy (see below). False-negative IgM results occur in approximately 25% of cases when evaluating infection in the newborn. If infection is suspected in this setting, further testing (dye test, IgM EIA, IgA EIA, IgE EIA/ISAGA, PCRs, ideally with paired maternal serology tests—see text) is necessary in a reference laboratory (*Toxoplasma* Serology Laboratory, PAMF Research Institute, 795 El Camino Real, Ames Building Palo Alto, CA, 94301; 650-853-4828).
Positive	Positive or equivocal	High	Infection within the past 18 mo but likely >12 wk ago. If pregnant and beyond first trimester, consider sending specimen to reference laboratory for dye test, repeat IgG avidity and IgM EIA, IgA EIA, IgE EIA/ISAGA, and AC/HS testing (see above).
Positive	Positive or equivocal	Low	Infection within the past 12 wk. Consider sending specimen to a reference laboratory (see above) to time infection more accurately (dye test, repeat IgG avidity and IgM EIA, IgA EIA, IgE EIA/ISAGA, and AC/HS) in the setting of pregnancy.
Equivocal	Negative	—	Indeterminate. Test a new specimen or consider a different assay (IFA or ELISA).
Equivocal	Equivocal	—	Indeterminate. Test a new specimen or consider a different assay (IFA or ELISA).
Equivocal	Positive	—	Acute infection or false-positive IgM result. Test a second specimen; if IgG becomes positive or remains equivocal, consider sending specimen to a reference laboratory to time infection more accurately (dye test, IgG avidity, IgM EIA, IgA EIA, IgE EIA/ISAGA, AC/HS—see text) in the setting of pregnancy.
Negative	Negative	—	No evidence of *Toxoplasma* infection; not immune.
Negative	Equivocal	—	Either false-positive IgM result or possible recent infection. Obtain a new specimen and retest. If infection is recent, IgM and IgG should become positive, with low IgG avidity. If repeated testing is still IgG negative and IgM equivocal, patient is likely uninfected. Consider IgM ISAGA.
Negative	Positive	—	Acute infection or false-positive IgM result. Repeat testing on new specimen. If the result is the same, it is likely a false-positive IgM result. Consider IgM ISAGA.

AC/HS, Differential agglutination test; *EIA,* enzyme immunoassay; *ELISA,* enzyme-linked immunosorbent assay; *IFA,* immunofluorescence assay; *Ig,* immunoglobulin; *ISAGA,* immunosorbent agglutination assay; *PCR,* polymerase chain reaction.
From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

   c. Falls to low level or disappears within 2 months
   d. May persist at low levels for 1 year or more
3. Antibody not measurable:
   a. Ocular toxoplasmosis
   b. Reactivation
   c. Immunocompromised hosts
4. IgG antibody:
   a. Appears 1 to 2 weeks after infection
   b. Peaks at 6 to 8 weeks
   c. Gradually declines over months to years
5. Guidelines for interpretation of serologic tests for toxoplasmosis are summarized in Table 1.

IMAGING STUDIES

- Chest x-ray if pulmonary involvement suspected
- Cerebral CT scan (Fig. E4) or MRI if encephalitis suspected

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Selected cases of ocular infection:
  1. Photocoagulation
  2. Vitrectomy
  3. Lentectomy
- Selected cases of congenital cerebral infection:
  1. Ventricular shunting

ACUTE GENERAL Rx

- Acute infection, immunocompetent, nonpregnant host:
  1. Usually requires no treatment, unless severe and persistent symptoms or vital organ damage
- Acute infection, immunocompromised host, non-AIDS:
  1. Treat even if asymptomatic
  2. Duration:
     a. Until 4 to 6 weeks after resolution of all signs and symptoms
     b. Usually 6 months or longer
- Reactivated infection, immunocompromised host, non-AIDS:
  1. Treat if symptomatic
- Acute or reactivated infection, AIDS:
  1. Treat in all cases
  2. Induction course:
     a. 3 to 6 weeks
     b. Maintenance therapy continued for life; consider discontinuation of suppressive therapy if the patient has a good response to antiretroviral therapy and if the CD4 count remains >200 cells/mm^3 for more than 3 months
  3. Empiric therapy:
     a. AIDS with positive IgG
     b. Multiple ring-enhancing lesions on cerebral CT scan or MRI
     c. Response seen by day 7 in 71% and day 14 in 91%
- Ocular infection:
  1. Treat in all cases
  2. Therapy continued for 1 month or longer if needed
  3. Response seen in 70% within 10 days
  4. Retreat as needed
  5. Steroids may be indicated in patients with signs or symptoms of increased intracranial pressure
  6. Surgical treatment in selected cases
- Treatment regimens (Table 2):
  1. Pyrimethamine 200 mg loading dose once PO, then 50 mg (<60 kg) to 75 mg (>60 kg) q day; *plus*
  2. Leucovorin 10 to 20 mg PO qid; *plus*
  3. Sulfadiazine 1 (<60 kg) to 1.5 g (>60 kg) PO q6h

  Other treatment options (if sulfa hypersensitivity or allergy is present): Pyrimethamine 50 to 75 mg/day PO with leucovorin 10 to 20 mg/day PO and either (1) clindamycin 600 mg q6h PO or IV (up to 1200 mg IV) q6h, or (2) clarithromycin 1 g PO bid, or (3) dapsone 100 mg/day PO, or (4) atovaquone 750 mg PO q6h.
- Acute infection in pregnancy:
  1. Treat immediately
  2. Risk of fetal infection reduced by 60% with treatment
     a. Seroconversion in the first trimester
        (1) Spiramycin 1 g every 8 hours
     b. Seroconversion beyond the first trimester or positive amniotic fluid PCR/ultrasound findings consistent with congenital toxoplasmosis:
        (1) Sulfadiazine 75 mg/kg/day in two divided doses ×2 days, then 50 mg/kg twice daily, *plus*
        (2) Pyrimethamine 50 mg bid ×2 days, then 50 mg PO daily, *plus*
        (3) Leucovorin 10 to 20 mg PO daily
- Postnatal treatment of congenital infection:
  1. Sulfadiazine 50 mg/kg PO bid, *plus*
  2. Pyrimethamine 2 mg/kg PO for 2 days, then 1 mg/kg PO daily for the first 2 to 6 months, then three times weekly, *plus*
  3. Leucovorin 5 to 20 mg PO three times weekly
  4. Minimum duration of treatment: 12 months

TABLE 2 Treatment of Toxoplasmosis

Disease	Medication	Dosage	Length of Therapy
Acute acquired—generally not treated unless severe or persistent symptoms, vital organ damage, or host immunosuppression[a]	Pyrimethamine *plus*	2 mg/kg/day for 2 days, then 1 mg/kg/day	4-6 wk or 2 wk after symptoms resolve for normal host; 4–6 wk beyond resolution for immunosuppressed hosts. In AIDS patients, treat until $CD4^+$ count >200
	Sulfadiazine *plus*	75-100 mg/kg/day divided twice daily (maximum 4 g/day); consider the lower dose in children >20 kg (see text)	
	Folinic acid	5-20 mg 3 times weekly; use higher doses if marrow suppression	
Ocular, older child	Pyrimethamine *plus*	2 mg/kg/day for 2 days, then 1 mg/kg/day (maximum 50 mg/day)	4-6 wk or 2 wk after symptoms resolve
	Sulfadiazine *plus*	75-100 mg/kg/day divided twice daily (maximum 4 g/day); consider the lower dose in children >20 kg (see text)	Prednisone should be continued until resolution of sight-threatening active chorioretinitis
	Folinic acid *plus*	5-20 mg 3 times weekly	
	Prednisone	1 mg/kg/day divided twice daily	
Congenital	Pyrimethamine *plus*	2 mg/kg per day for 2 days, then 1 mg/kg/day for 6 mo, then 3 times weekly (M-W-F) for 6 mo	1 yr
	Sulfadiazine *plus*	100 mg/kg per day divided twice daily	
	Folinic acid *plus*	5-10 mg 3 times weekly	
	Prednisone	1 mg/kg/day divided twice daily	Until resolution of elevated CSF protein level or sight-threatening active chorioretinitis
Pregnant women—acute infection first 21 wk of gestation	Spiramycin	3 g/day divided twice daily without food	Until fetal infection documented or excluded at 21 wk of gestation; if fetus infected, change to pyrimethamine plus sulfadiazine plus folinic acid until delivery
Pregnant women—fetal infection confirmed (amniotic fluid PCR positive)	Pyrimethamine *plus*	100 mg/day divided twice daily for 2 days, then 50 mg/day	Until delivery
	Sulfadiazine *plus*	3 g/day divided twice daily	
	Folinic acid	5-20 mg/day	

AIDS, Acquired immunodeficiency syndrome; *CSF,* cerebrospinal fluid; *PCR,* polymerase chain reaction.
[a]For more detailed recommendations for patients with human immunodeficiency virus infection/AIDS, see http://aidsinfo.nih.gov/guidelines.
From Cherry JD et al: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

CHRONIC Rx

Maintenance therapy in AIDS patients because of the high risk (80%) of relapse:
- Pyrimethamine 25 mg PO qid
- Sulfadiazine 500 mg PO qid
- Leucovorin 10 to 20 mg PO qid

DISPOSITION

- Prognosis:
  1. Excellent in the immunocompetent host
  2. Good in ocular infection (although relapses are common)
- Treatment of acute infection in pregnancy:
  1. Reduces incidence and severity of congenital toxoplasmosis
- Treatment of congenital infection:
  1. Improvement in intellectual function
  2. Regression of retinal lesions
- AIDS:
  1. 70% to 95% response to therapy

REFERRAL

- To infectious disease expert:
  1. Immunocompromised hosts
  2. Pregnant women
  3. Difficulty in making a diagnosis or deciding on treatment
- To pediatric infectious disease expert:
  1. Congenital infection
- To obstetrician:
  1. Pregnant seronegative mother
  2. Acute seroconversion
- To ophthalmologist:
  1. Congenital infection
  2. Any case of ocular infection

PEARLS & CONSIDERATIONS

COMMENTS

- Prevention of toxoplasmosis is most important in seronegative pregnant women and immunocompromised hosts.
- Patient instructions:
  1. Cook meat to 66° C (150.8° F).
  2. Cook eggs.
  3. Do not drink unpasteurized milk.
  4. Wash hands thoroughly after handling raw meat.
  5. Wash kitchen surfaces that come in contact with raw meat.
  6. Wash fruits and vegetables.
  7. Avoid contact with materials potentially contaminated with cat feces.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Toxoplasmosis (Patient Information)

AUTHORS: **Tara C. Bouton, MD, MPH, TM, Philip A. Chan, MD, MS,** and **Glenn G. Fort, MD, MPH**

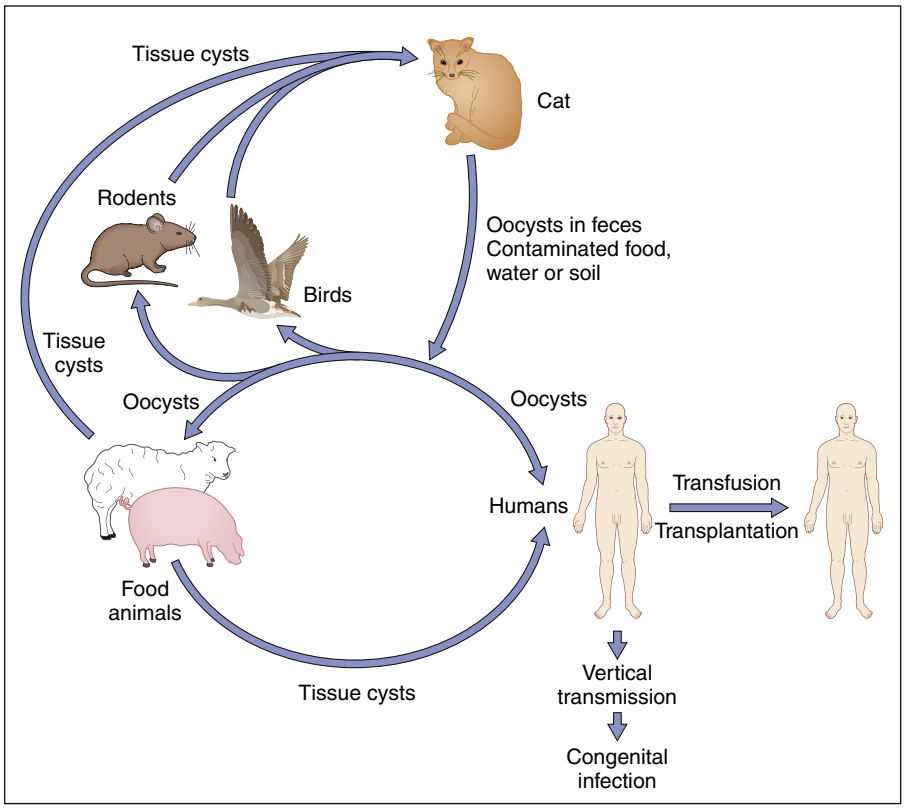

FIG. E1 Life cycle of *Toxoplasma gondii*. (From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

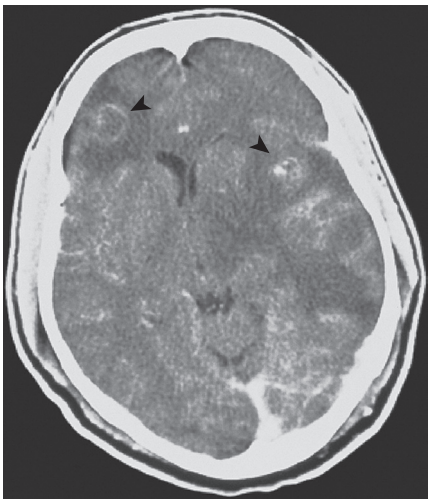

FIG. E4 Toxoplasmic encephalitis in a person who has acquired immunodeficiency syndrome. A cranial computed tomography scan shows bilateral contrast-enhanced ring lesions with peripheral edema and mass effect. (From Cohen J, Powderly WG: *Infectious diseases,* ed 2, St Louis, 2004, Mosby.)

SUGGESTED READINGS

Maldonado YA, Read JS: Committee on infectious diseases: diagnosis, treatment, and prevention of congenital toxoplasmosis in the United States, *Pediatrics* 139(2):e20163860, 2017.

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents: Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.

BASIC INFORMATION

DEFINITION

Bacterial tracheitis is an acute infectious disease affecting the trachea and large conducting airways. Tracheal inflammation may be caused by a large number of inhaled stimuli, but bacterial infection is a life-threatening illness associated with purulent secretions and subglottic edema.

SYNONYMS

Bacterial tracheobronchitis
Pseudomembranous croup
Membranous laryngotracheobronchitis

ICD-10CM CODES

J04.1 Acute tracheitis
J04.10 Acute tracheitis without obstruction
J04.11 Acute tracheitis with obstruction

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Uncommon
- May be the most common cause of acute upper airway obstruction requiring admission to pediatric ICUs

PEAK INCIDENCE: Three fourths of cases reported in winter

PREDOMINANT SEX: Boys > girls in one series

PREDOMINANT AGE:

- 1 mo to 8 yr
- Almost all <13 yr (most <3 yr)

GENETICS:

- Down syndrome is a possible predisposing factor.
- Congenital infection: Some cases have been found in those with anatomic abnormalities of the upper airways.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Croupy or "brassy" cough
- Inspiratory stridor (frequent)
- Wheezing (unusual)
- Fever (often >102° F [38.9° C])
- Thick, purulent secretions expectorated:
  1. Minority of patients expectorate "ricelike" pellets.
  2. Most patients are unable to mobilize secretions.
     a. Become inspissated
     b. Form pseudomembranes

ETIOLOGY

- *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA])
- *Haemophilus influenzae*
- Beta-hemolytic streptococcal infection
- Secondary to viral infections of the respiratory tract:
  1. Primary influenza
  2. Respiratory syncytial virus (RSV)
  3. Parainfluenza
- Many cases follow measles:
  1. Especially when accompanied by chest radiographic infiltrates
  2. Sometimes fatal outcome
  3. Associated with prolonged endotracheal intubation

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Viral croup
- Epiglottitis
- Diphtheria
- Necrotizing herpes simplex infection in the elderly
- Cytomegalovirus in immunocompromised patients
- Invasive aspergillosis in immunocompromised patients

WORKUP

DIRECT LARYNGOSCOPY:

- Typical secretions:
  1. May form pseudomembranes
  2. Airway obstruction
- Normal epiglottis rules out epiglottitis
- Possible subglottic edema

LABORATORY TESTS

- White blood count is sometimes elevated.
- On differential, left shift is almost universal.
- Gram stain and culture of tracheal secretions confirm diagnosis.
- Blood cultures are positive in a minority.
- Viral respiratory panels using PCR technology are available on throat and nasopharyngeal swabs and can detect multiple viruses including influenza, parainfluenza and RSV, and thus can differentiate between bacterial and viral infections.

IMAGING STUDIES

- Lateral x-ray examination of neck:
  1. Normal epiglottis
  2. Vague density or a "dripping candle" appearance of tracheal mucosa:
     a. Secretions
     b. Pseudomembranes
- Chest radiograms:
  1. Not diagnostic
  2. Should not be performed on patients in acute respiratory distress, because severe or fatal upper airway obstruction can develop suddenly
- Pneumonic infiltrates frequent
- Atelectasis: Unusual but can lead to lobar collapse

TREATMENT

NONPHARMACOLOGIC THERAPY

- Aggressive maintenance of a patent airway:
  1. Laryngoscopy or bronchoscopy used diagnostically and therapeutically to strip away pseudomembranes
  2. Voluminous and tenacious secretions suctioned from the underlying friable mucosa:
     a. May extend from between the vocal cords to the main carina
     b. Larger channels of rigid instruments for more effective suctioning
- Prevention of complete large airway obstruction:
  1. Nasotracheal intubation
  2. Humidification of inspired gas
  3. Frequent saline instillation and suctioning
  4. Intubation with general anesthesia, performed in the operating room, is preferred by some
- Ventilatory support necessary with initial management in ICU

ACUTE GENERAL Rx

- Antibiotic therapy: Start immediately, generally continued for 1 to 2 wk
- Initial therapy directed against *H. influenzae* and *S. aureus* (e.g., ceftriaxone and vancomycin (if MRSA suspected)
- Oral therapy is usually sufficient after 5 or 6 days of IV administration

DISPOSITION

- Most patients are extubated in 5 to 6 days after initiating antibiotic therapy.
- Anoxic encephalopathy is reported in 7% of survivors.

REFERRAL

Suspected diagnosis

PEARLS & CONSIDERATIONS

COMMENTS

- Infants are at increased risk of airway obstruction because of the small airway dimension.
- Presence of pneumonia and a staphylococcal cause are thought to worsen prognosis.
- Reported complications: Toxic shock syndrome, persistent postextubation stridor, pneumothorax, and volutrauma

RELATED CONTENT

Croup (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Heilman JA et al: Acute tracheitis, *Ear Nose Throat J* 89(7):E39, 2010.
Kuo CY, Parikh SR: Bacterial tracheitis, *Pediatr Rev* 35:497-499, 2014.
Miranda AD et al: Bacterial tracheitis, *Pediatr Emerg Care* 27:950-953, 2011.

BASIC INFORMATION

DEFINITION

Hemolytic transfusion reactions may be acute (occurring during or immediately after the transfusion) or delayed (occurring more than 24 hours after the transfusion). Acute hemolytic transfusion reaction (AHTR) is in vivo hemolysis most commonly caused by an alloantibody in a recipient's plasma to a cognate antigen on the donor red cells. The most commonly involved alloantibodies are to ABO antigens, but alloantibodies to minor blood group antigens have also been implicated. Typically the alloantibodies are of the IgM class, but complement fixing IgGs may also cause such a reaction. The clinical features vary, but usually there are high fever, chills, nausea, and backache. Red or brown urine may be passed due to hemoglobinuria. The plasma may show hemoglobinemia, and the direct Coombs test can be either positive or negative. Delayed hemolytic reactions are usually caused by an anamnestic alloantibody response upon re-exposure to cognate erythrocyte antigen. They are typically IgG and usually noncomplement fixing. They occur 1 to 10 days after transfusion. In delayed transfusion reactions, hemoglobinemia is unusual, and the only clinical manifestations may be fever, the serological finding of a newly positive indirect antiglobulin (indirect Coombs test), and/or the presence of a positive direct Coombs test. Delayed reactions can be clinically silent (called delayed serological hemolytic reactions) or manifest with fever, chills, nausea, vomiting, unexplained anemia, or jaundice. There is no specific treatment other than supportive care.

SYNONYMS

AHTR
DSTR
DHTR
Acute hemolytic transfusion reaction

ICD-10CM CODES

T80.3 ABO incompatibility reaction
T80.4 Rh incompatibility reaction
T80.8 Other complications following infusion, transfusion, and therapeutic injection
T80.9 Unspecified complication following infusion, transfusion and therapeutic injection

EPIDEMIOLOGY & DEMOGRAPHICS

- Approximately 1% of transfused products result in serious adverse reactions; hemolytic transfusion reactions account for up to 5% of these serious adverse reactions.
- Acute intravascular hemolysis occurs in one to five per 50,000 transfusions.
- Delayed reactions occur about 1:1500 red cell transfusions.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever, chills, nausea, tachycardia, chest pain, dyspnea, dizziness, bronchospasm.
- Lower back pain due to ischemic muscle pain or vasospasm hypotension.
- Severe reactions may occur in surgical patients under anesthesia who are unable to give any warning signs.
- Patients with delayed hemolytic transfusion reactions typically do not present as a clinical emergency. In most cases, presentation is with a low-grade fever from the generation of IL-1 or other proinflammatory cytokines. Hemoglobinuria and hemoglobinemia are rarely present. Unexplained anemia and jaundice are other possible presentations.
- Tables 1 and 2 summarize signs and symptoms of acute adverse reactions to blood transfusion. In the differential diagnosis of hemolysis.

ETIOLOGY

Most fatal hemolytic reactions are caused by clerical errors and mislabeled specimens.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Septic reaction
- Transfusion-related acute lung injury

MANAGEMENT

The transfusion must be stopped immediately. The blood bank must be notified, and the donor transfusion bag must be returned to the blood bank along with a freshly drawn posttransfusion specimen. Table 3 summarizes immediate investigations in the case of an acute transfusion reaction.

LABORATORY TESTS

- The direct antiglobulin test (DAT) is usually positive in a delayed reaction, and preparation of an eluate will help identify the offending antibody.
- In some delayed reactions, the only finding is a positive indirect Coombs test, and the implicated alloantibody can be identified in an antibody panel.
- In acute reactions, the urine may show hemoglobinuria (wine-colored urine) and the plasma hemoglobinemia (pink plasma).
- Labs (Table 4): Decreased hematocrit and serum haptoglobin (haptoglobin low to 0 mg/dl). Elevated LDH, indirect bilirubin and creatinine, if acute.
- In acute cases, monitor coagulation status (PT, aPTT, fibrinogen) for disseminated intravascular coagulation.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Stop transfusion immediately. Test anticoagulated blood from the recipient for the presence of free hemoglobin in the plasma.
- Monitor vital signs closely and maintain IV access with a suitable crystalloid or colloid solution.
- Maintain an adequate airway.

ACUTE GENERAL Rx

- Treatment is supportive and consists of fluid resuscitation, vasopressor support, and mannitol.
- Vigorous IV hydration (0.9% NaCl or some other suitable crystalloid solution) to maintain urine flow at >100 ml/hr until hypotension is corrected and hemoglobinuria clears. IV furosemide may be necessary to maintain adequate renal flow.
- The addition of mannitol may prevent renal damage (controversial). Mannitol, if chosen,

TABLE 1 Signs and Symptoms of Acute Adverse Reactions to Blood Transfusion

Reaction	Fever	Chills/ Rigors	Nausea/ Vomiting	Chest Discomfort/Pain	Facial Flushing	Wheezing/ Dyspnea	Back/ Lumbar Pain	Discomfort at Infusion Site	Hypotension
Acute hemolytic	X	X	X	X	X	X	X	X	X
Febrile nonhemolytic	X	X		X	X				
Nonimmune hemolysis									
Acute lung injury	X			X		X			X
Allergic									
Massive transfusion complications									
Anaphylaxis	X	X	X	X	X	X	X	X	X
Passive cytokine infusion	X	X	X			X			
Hypervolemia						X			
Bacterial sepsis	X	X	X				X	X	X
Air embolus				X		X			

From Goldman L, Bennett JC (eds): *Cecil's textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.

TABLE 2 Types of Acute Transfusion Reactions

Reaction Type	Presenting Signs and Symptoms
Acute hemolytic	Fever, chills, dyspnea, vomiting, hypotension, tachycardia, infusion site pain, back pain, hemoglobinuria, hemoglobinemia, indirect hyperbilirubinemia, renal failure, DIC
Febrile reaction	Fever, chills, rigors
Allergic	Urticaria, pruritus, flushing, angioedema, dyspnea, bronchospasm stridor, hypotension, tachycardia, abdominal cramping
Hypervolemic	Dyspnea, tachycardia, hypertension, headache, jugular venous distention
Septic	Fever, chills, hypotension, tachycardia, vomiting
Transfusion-related acute lung injury	Dyspnea, hypoxemia, fever, hypotension

DIC, Disseminated intravascular coagulation.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 3 Immediate Investigations in the Case of an Acute Transfusion Reaction

Check for hemolysis.
Perform visual examination of patient's plasma and urine (plasma and urine hemoglobin can be checked, but this is not essential).
Blood film may show spherocytosis.
Bilirubin and lactate dehydrogenase (LDH) levels will be raised.
Check for incompatibility.
Check the documentation and the patient's identity.
Repeat ABO group of patient on pretransfusion and posttransfusion samples and of the donor unit(s).
Screen the patient for red cell antibodies pretransfusion and posttransfusion.
Repeat crossmatch with pretransfusion and posttransfusion samples.
Direct antiglobulin test (DAT) on pretransfusion and posttransfusion samples.
Eluate from patient's red cells.
Check for disseminated intravascular coagulation.
Perform blood count and film, coagulation screen, and fibrin degradation products (or D-dimers).
Check for renal dysfunction.
Check blood urea, creatinine, and electrolytes.
Check for bacterial infection.
Take blood cultures from the patient and donor unit including immediate Gram stain.

From Bain BJ, Bates I, Laffan MA: *Dacie and Lewis practical haematology,* ed 12, Philadelphia, 2017, Elsevier.

TABLE 4 Hemolytic Transfusion Reactions: Serologic Presentation

Type	Antibody Detectable Initially	Primary Antibody Type	Degree of Complement Binding	Example
Acute intravascular	Yes	IgM	Full (C1-9)	ABO system
Acute extravascular	Yes	IgG	None/partial	Rh system
Delayed intravascular	No	IgG	Full (C1-9)	Kidd system
Delayed extravascular	No	IgG	None/partial	Duffy system

From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

must be used with caution; if acute tubular necrosis occurs before mannitol infusion, pulmonary edema may occur as a result of the acute increase in intravascular volume secondary to fluid expansion.
- Monitor for the presence of disseminated intravascular coagulation. PT, aPTT, and fibrinogen levels should be closely monitored.
- If sepsis is suspected, culture as appropriate.

DISPOSITION

Mortality rate is 3% to 10% in severe transfusion reactions.

PEARLS & CONSIDERATIONS

COMMENTS

Hemolysis caused by minor antigen systems is generally less severe and may be delayed 1 to 10 days after transfusion.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Joseph Sweeney, MD, FACP, FRCPath**

SUGGESTED READINGS

Hendrickson JE et al: ncidence of transfusion reactions: a multicenter study utilizing systematic active surveillance and expert adjudication, *Transfusion* 56:2587-2596, 2016.

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BASIC INFORMATION

DEFINITION

A clinical syndrome lasting up to 24 hours of sudden onset, severe anterograde and variable retrograde amnesia without loss of other neurologic function.

SYNONYM

TGA

ICD-10CM CODE
G45.4 Transient global amnesia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 3.4 to 10.4 per 100,000 people.
PEAK INCIDENCE: Most between ages 50 to 70 and equally common in men and women. In population older than 50 the incidence increases to 23.5 per 100,000 per year. TGA is also more common in individuals with migraine.[1]
RECURRENCE RATE: 2.9% to 23.8%

PHYSICAL FINDINGS & CLINICAL PRESENTATION[2]

- Cannot recall novel episodic information, repeatedly asking the same questions
- No impairment in consciousness or nonmemory cognitive domains, no focal neurologic deficit
- Complex procedural memory is often preserved (i.e., driving)
- Triggers include Valsalva maneuver, immersion in cold or hot, sexual intercourse, emotional stress
- Typically a single attack that is self-limited, with amnestic gap of the duration of episode
- Those with recent head injury or epilepsy diagnosis are excluded

[1] Arena JE et al: Transient global amnesia, *Mayo Clin Proc* 90(2):264-272, 2015.
[2] Arena JE et al: Long-term outcome in patients with transient global amnesia: a population-based study, *Mayo Clin Proc* 92(3):399-405, 2017.

ETIOLOGY

- Several proposed mechanisms of pathophysiology:
  1. Hypoperfusion or arterial ischemia of the hippocampi
  2. Internal jugular venous flow reversal causing venous hypertension to the medial temporal lobe
  3. Migraine phenomena with cortical spreading depression

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Posterior cerebral artery transient ischemic attack: Can be associated with confusion or memory loss. Commonly with vascular risk factors and other focal neurologic signs (homonymous hemianopsia, aphasia, hemiparesis, hemisensory loss, hemi-body pain, oculomotor nerve palsy or vertical gaze palsy).
- Transient epileptic amnesia: Epilepsy syndrome, consisting of atypical TGA or recurrent attacks of amnesia, often less than one hour and upon waking, responsive to antiepileptic medications. Associated with olfactory hallucinations or oral automatisms. Interictal EEG may be abnormal. Hippocampal atrophy on MRI may be seen.
- Dissociative fugue, or transient dissociative amnesia: Extensive retrograde amnesia, loss of personal identity may occur, unlike in TGA where such is preserved.
- Hypoglycemia: Metabolic dysfunction can cause impairment in consciousness, focal signs, or prolonged cognitive impairment unlike TGA.

WORKUP

- Largely a clinical diagnosis, workup should focus on exclusion of vascular or epileptic source of symptoms.
- Collateral history of witnessed event and exclusion of prior event.
- Cognitive examination with evaluation of registration, delayed recall, and orientation.
- Careful cranial nerve examination to exclude posterior circulation stroke.

LABORATORY TESTS

- Complete blood count with erythrocyte sedimentation rate and C-reactive protein
- Serum chemistries, including lipid profile
- Troponins and electrocardiogram

DIAGNOSTIC STUDIES

- MRI of the brain may show reversible T2 hyperintensity or diffusion restriction exclusive to the hippocampi.
- Electroencephalogram (EEG) to exclude epileptiform activity.

TREATMENT

NONPHARMACOLOGIC THERAPY

Self-limited, not requiring specific pharmacologic or nonpharmacologic treatment

ACUTE GENERAL Rx

Investigate as an emergency.

CHRONIC Rx

- Does not lead to long-term sequela of memory loss. Complete recovery of cognitive function has been reported 5 days to 6 mo after the episode.
- Low risk of subsequent ischemic cerebral stroke or seizures though possible increased risk of future dementia

DISPOSITION

Due to the benign nature of transient global amnesia, rarely is continued followup necessary.

REFERRAL

Referral to a neurologist is necessary when the diagnosis is uncertain or with atypical features of the clinical presentation.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Rituparna Das, MD**

SUGGESTED READINGS

Arena JE, Rabinstein AA: Transient global amnesia, *Mayo Clin Proc* 90(2):264-272, 2015.

Mangla A, Navi BB: Transient global amnesia and the risk of ischemic stroke, *Stroke* 45(2):389-393, 2014.

Nicastro N, Picard F: Transient global amnesia mimics: transient epileptic amnesia, *Epilepsy Behav Case Rep* 2:100-101, 2014.

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Szabo K: Transient global amnesia, *Front Neurol Neurosci* 34:143-149, 2014, https://doi.org/10.1159/000356431. Epub 2014 Apr 16.

Sugiyama A, Kobayashi M: Transient global amnesia with a hippocampal lesion followed by transient epileptic amnesia, *Seizure* 31:141-143, 2015.

Transient Ischemic Attack ALG PTG

BASIC INFORMATION

DEFINITION

Transient ischemic attack (TIA) is a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction on MRI. TIA symptoms typically resolve within 60 min and by definition within 24 hours. Despite complete symptom resolution, 20% to 50% of patients clinically suspected to have suffered a TIA have evidence of acute tissue infarction on MRI.

SYNONYMS

TIA
Amaurosis fugax
Ophthalmologic TIA
"Mini-stroke"
Pre-stroke

ICD-10CM CODES

G45.9	Transient cerebral ischemic attack, unspecified
G45.8	Other transient cerebral ischemic attacks and related syndromes
Z86.73	Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 70 to 101 cases per 100,000 persons annually
PEAK INCIDENCE: After age 60 yr
PREVALENCE: 200,000 to 500,000 persons in the United States. The annual risk of stroke after either a TIA or minor stroke is approximately 3% to 4%.
PREDOMINANT SEX AND RACE: Males > females; African American > Caucasian
RISK FACTORS: Same as for ischemic stroke

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- TIAs often present with transient neurologic symptoms including ipsilateral transient monocular blindness (amaurosis fugax), contralateral numbness or weakness, contralateral homonymous hemianopsia, and/or aphasia.
- Box 1 summarizes carotid artery TIAs.
- Vertebrobasilar artery TIAs are described in Box 2.

ETIOLOGY

Embolic (cardioembolism in 10% to 15%) large vessel atherothrombotic disease (20% to 25%) lacunar disease, hypoperfusion, hypercoagulable state, arteritis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Seizures, hypoglycemia, hemiplegic migraine, intracranial hemorrhage, mass lesion, vestibular disease, Bell palsy, meningitis, multiple sclerosis, subdural hematoma, brain abscess, cervical or lumbar spine disease, conversion disorder

WORKUP

Given the high risk of stroke within the first 48 hours following TIA (up to 10%), hospital admission for workup is advised. Most of the immediate risk of stroke is secondary to carotid disease.

The American Heart Association recommends that the ABCD2 score be used in the evaluation of TIA. It consists of 1 point for age ≥60 yr, 1 point for BP ≥140 mm Hg systolic or ≥90 mm Hg diastolic, clinical features (2 points for unilateral weakness, 1 point for speech impairment), duration of TIA (2 points for duration ≥60 min, 1 point for duration 10-59 min), presence of diabetes mellitus (1 point). According to the guidelines, it is reasonable to hospitalize patients with TIA if they present within 72 hours and have an ABCD2 score ≥3. There is some debate about the usefulness of this scale since it fails to account for changes seen on echocardiogram, carotid Dopplers, or ECG that may place the patient at more imminent risk of stroke (carotid stenosis, Afib, cardiac thrombus, etc.). Alternatives to this scoring system are being investigated.

LABORATORY TESTS

Complete blood count, basic metabolic panel, prothrombin time, activated partial thromboplastin time, sedimentation rate, fasting lipid panel, serum glucose and hemoglobin A_{1c} (to detect latent diabetes mellitus), and TSH.

IMAGING STUDIES

- CT scan should be obtained to exclude hemorrhage; MRI with diffusion-weighted images if immediately available to determine whether infarction occurred.
- Imaging of the vessels should be obtained via magnetic resonance angiography (MRA) head and neck, computed tomography angiography (CTA) head and neck, or carotid Doppler/transcranial Doppler (CD/TCD). If symptoms are localizable to the posterior circulation, MRA or CTA should be obtained in lieu of CD/TCD.
- Transthoracic echocardiogram should be obtained.

BOX 1 Carotid Artery Transient Ischemic Attacks

Symptoms
- Contralateral hemiparesis, hemianopsia, hemisensory loss
- Aphasia, if dominant hemisphere
- Neglect and hemi-inattention, if nondominant hemisphere
- Ipsilateral amaurosis fugax

Associated findings
- Carotid bruit
- Retinal artery emboli

Tests
- Ultrasonography (carotid Doppler studies)
- Magnetic resonance imaging angiography (MRA)
- Cerebral arteriography

Therapy
- Medical: Platelet inhibitors (e.g., aspirin)
- Risk-reduction measures (e.g., control blood pressure, glucose levels, cholesterol)
- Surgical: Carotid endarterectomy, if stenosis >70% and symptomatic
- Endovascular: Placement of stent

From Kaufman DM, Geyer HL, Milstein MJ: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.

BOX 2 Vertebrobasilar Artery Transient Ischemic Attacks

Symptoms
- Vertigo, vomiting, tinnitus
- Circumoral paresthesias or numbness
- Dysarthria, dysphasia
- Drop attacks

Associated findings
- Nystagmus
- Ataxia
- Cranial nerve abnormalities

Tests
- Ultrasonography (transcranial Doppler studies)
- Magnetic resonance imaging angiography (MRA)
- Cerebral arteriography

Therapy
- Medical: Platelet inhibitors*
- Risk-reduction measures
- Surgical: None

*See Box 1.
From Kaufman DM, Geyer HL, Milstein MJ: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.

- An echocardiogram with bubble should be obtained in all patients younger than 50 yr with TIA symptoms.
- Electrocardiogram should be obtained to exclude the presence of arrhythmias, namely atrial fibrillation.
- At least 24 hours of heart rhythm monitoring should be accomplished to screen for arrhythmia. Many stroke centers now utilize prolonged ambulatory cardiac rhythm monitoring over several weeks to months to identify paroxysmal atrial fibrillation in select patients when there is a high index of clinical suspicion.
- Paroxysmal atrial fibrillation is common in patients with TIA. A recent study found that noninvasive ambulatory ECG monitoring for 30 days significantly improved the detection of atrial fibrillation by a factor of more than five and nearly doubled the rate of anticoagulant treatment as compared with the standard practice of short-duration ECG monitoring.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Carotid endarterectomy or carotid stenting should be considered for patients found to have carotid stenosis of ≥50% as the cause for TIA. Efficacy is greatest in the two weeks immediately following a TIA or ischemic stroke. Please refer to the "Carotid Artery Stenosis" chapter for more information.
- The practice of intracranial angioplasty and stenting has largely declined following the publication of negative results from clinical trials and is only used in select patients who fail maximal medical management with aggressive platelet inhibition, strict risk factor control such as hyperlipidemia, hypertension, diabetes mellitus, weight loss, treatment of sleep apnea, and smoking cessation among others.

ACUTE GENERAL Rx

- In the absence of contraindications, patients with atrial fibrillation should be considered for anticoagulation. Choices for anticoagulants include the direct oral anticoagulants (such as dabigatran, rivaroxaban, apixaban, edoxaban, betrixaban) and/or warfarin. In patients with TIA and atrial fibrillation or a cardiac thrombus, therapeutic anticoagulation should be achieved rapidly. Those who are not candidates for a direct oral anticoagulation and who will need chronic warfarin should first be started on either intravenous heparin or therapeutic anticoagulant doses of Lovenox, along with warfarin, until target INR between 2.0 and 3.0 is achieved, at which point warfarin should be continued as monotherapy.
- Although no compelling evidence exists for the use of heparin in the acute treatment of TIAs without cardioembolic source, patients who develop recurrent symptoms within the same vascular territory that increase in duration, severity, and/or frequency (crescendo TIA/stuttering TIA) may benefit from its use pending cardiac and vascular imaging and identification of a possible source.

CHRONIC Rx

- Chronic therapy includes antiplatelet or anticoagulation therapy and modifying the four major risk factors: hypertension, dyslipidemia, diabetes mellitus, and smoking cessation.
- Antiplatelet therapy should be used to reduce the risk of recurrent TIAs or subsequent stroke. Three antiplatelet agents are commonly used in stroke prevention: aspirin, aspirin/dipyridamole, and clopidogrel. All are reasonable choices, but practitioners should consider their individual patient's comorbidities when selecting an antiplatelet agent.
- A direct oral anticoagulant of dose-adjusted warfarin (INR 2.0 to 3.0) or use of direct oral anticoagulants instead of an antiplatelet is indicated for prevention of future strokes in atrial fibrillation patients.

PEARLS & CONSIDERATIONS

- All cause mortality in 1 yr is 25% in patients diagnosed TIA.
- Dual antiplatelet therapy in acute TIA and minor stroke is being evaluated. A recent trial revealed that among patients with TIA or minor stroke who can be treated within 24 hours after the onset of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 days but did increase the risk of hemorrhage. Most of the benefit was concentrated in the first seven to 30 days, so dual antiplatelet therapy may be reasonable in the first 30 days after TIA.
- Previous studies conducted between 1987 and 2003 estimated the risk of stroke or an acute coronary syndrome was 12% to 20% during the first 3 mo after a TIA. New data estimate the 1-yr risk to be 6.2%. Multiple infarctions on brain imaging, large-artery atherosclerosis, and an ABCD[1] score of 6 or 7 were each associated with more than a doubling of the risk of stroke.[2]

PREVENTION

- A healthy lifestyle and management of cardiovascular risk factors should be encouraged.
- Antiplatelet therapy has not been proven efficacious in primary prevention of TIA or stroke but is very beneficial in secondary prevention.

PATIENT & FAMILY EDUCATION

Patients should be counseled on the early signs of stroke symptoms and instructed to promptly seek medical attention if they develop symptoms concerning for stroke. Patients should be encouraged to pursue a healthy lifestyle to include exercise and smoking cessation. In addition, patients should take an active role in controlling blood pressure and blood glucose. Further educational materials can be found online at http://www.strokecenter.org/.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Transient Ischemic Attack (TIA) (Patient Information)
Carotid Artery Stenosis (Related Key Topic)
Atrial Fibrillation (Related Key Topic)
Stroke, Acute Ischemic (Related Key Topic)
Stroke, Secondary Prevention (Related Key Topic)

AUTHORS: **Corey Goldsmith, MD, Joseph S. Kass, MD, JD, FAAN,** and **Prashanth Krishnamohan, MBBS, MD**

[1] Amarenco P et al: One-year risk of stroke after transient ischemic attack or minor stroke, *N Engl J Med* 374:1533-1542, 2016.
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Kernan WN et al: Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, *Stroke* 45:2160-2236, 2014.

Giles MF, Rothwell PM: Systematic review and pooled analysis of published and unpublished validations of the ABCD and ABCD2 transient ischemic attack risk scores, *Stroke* 41(4):667-673, 2010.

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Wang Y et al: Clopidogrel with aspirin in acute minor stroke or transient ischemic attack, *N Engl J Med* 369:11-19, 2013.

BASIC INFORMATION

DEFINITION

Demyelination in a transverse region of the spinal cord due to an inflammatory process that leads to sensory and motor changes below the lesion as well as autonomic dysfunction. The term "transverse myelitis" of late refers to any cause of inflammatory myelopathy, irrespective of severity or degree of structural or functional interruption of pathways through a transverse spinal cord section. Transverse myelitis that extends across three or more segments of the cord is referred to as longitudinally extensive transverse myelitis. The pathologic hallmark of transverse myelitis is the presence of focal collections of lymphocytes and monocytes with varying degrees of demyelination, axonal injury, and astroglial and microglial activation within the spinal cord.

SYNONYMS

Idiopathic transverse myelitis (ITM)
TM
ITM

ICD-10CM CODES

G37.3	Acute transverse myelitis in demyelinating disease of central nervous system
G04.89	Other myelitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Annual incidence ranges from 1.3 to 8 cases per million. The incidence increases to 24.6 cases per million annually if causes of acquired demyelination such as multiple sclerosis (MS) or neuromyelitis optic spectrum disorder are included.
PREVALENCE: Unknown
PREDOMINANT SEX: None, but female preponderance seen in cases associated with multiple sclerosis and neuromyelitis optica spectrum disorder.
GENETICS: No genetic predisposition has been shown.
PEAK INCIDENCE: Can occur at any age. Bimodal peak in the incidence between 10 to 19 yr and 30 to 39 yr. 20% of cases occur in children with a bimodal peak of incidence between 0 to 2 yr and 5 to 17 yr.
RISK FACTORS: Infection, vaccination

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Rapid onset of symmetric or asymmetric paraparesis or paraplegia of the lower extremities over a few days, ascending paresthesia, sensory level at the trunk, back pain, sphincter dysfunction, and positive Babinski, which can be bilateral. The arms may also be involved if the cervical cord is involved, but cervical involvement is less common than thoracic involvement. In the acute phase the weakness is flaccid, with diminished deep tendon reflexes mimicking a peripheral neuropathy such as Guillain-Barré syndrome.
- One third to one half of patients present with localizing back pain or a bandlike area of altered sensation, usually at the dermatomal level corresponding to the lesion within the cord.
- There is progression to nadir of clinical deficits between 4 hr and 21 days after symptom onset.
- Urinary incontinence or retention, GI disturbances (incontinence or constipation), and sexual dysfunction are common.
- Acute flaccid myelitis is a subtype of myelitis in which patients present with acute limb weakness and have primarily involvement of gray matter on spinal cord imaging.

ETIOLOGY

- The clinical signs are caused by an interruption in ascending and descending sensory, motor, and autonomic pathways in the transverse plane of the spinal cord, resulting in sensory-level weakness and autonomic dysfunction at and below the level of the lesion due to demyelination or inflammation of the spinal cord.
- Can be idiopathic demyelination (15% to 30%) that is a monophasic one-time event or demyelination secondary to neurologic or systemic conditions (Box 1).
- Secondary causes include postinfection, postvaccination, acute demyelinating encephalomyelitis (where transverse myelitis tends to be monophasic), and others such as multiple sclerosis, neuromyelitis optica spectrum disorder (NMOSD), connective tissue disorders such as systemic lupus, Sjögren syndrome, antiphospholipid antibody syndrome, sarcoidosis, and paraneoplastic conditions, which can be progressive or relapsing.
- Infectious causes of myelitis include HIV, syphilis, varicella zoster (associated with shingles), HTLV-1, Lyme disease, arboviruses such as West Nile virus (typically causing a poliomyelitis-type acute flaccid paralysis), or enteroviruses (typically causing acute flaccid paralysis mainly in children).
- About 50% of patients have had a recent upper respiratory infection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- MS (Table 1)
- Neuromyelitis optica spectrum disorder (NMOSD)
- Metastatic disease
- Spinal cord tumors
- Herniated or slipped discs
- Spinal stenosis
- Spinal epidural abscess
- Vascular malformation

BOX 1 Central Nervous System and Systemic Autoimmune Disorders Associated with Acute Transverse Myelitis

Central Nervous System Disorders
Acute disseminated encephalomyelitis
Multiple sclerosis
Neuromyelitis optica

Systemic Autoimmune Disorders
Antiphospholipid antibody syndrome
Behçet disease
Mixed connective tissue disorder
Neurosarcoidosis
Sjögren syndrome
Systemic lupus erythematosus

From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

TABLE 1 Distinguishing Acute Transverse Myelitis from Other Central Nervous System Demyelinating Disorders

Finding	ATM	ADEM	MS	NMO
Myelitis	+	+/–	+/– (partial)	+
Acute mental status changes	–	+	–	+/–
Optic neuritis	–	+/–	+/–	+/–
Abnormal brain MRI	–	+	+	+/–
CSF oligoclonal bands	–	+/–	+	+/–
Serum AQP4-IgG	–	–	–	+/–
Recurrences	+/–	+/–	+	+

+, Always present; +/–, variably present; –, usually absent.
ADEM, Acute disseminated encephalomyelitis; *AQP,* aquaporin 4; *ATM,* acute transverse myelitis; *CSF,* cerebrospinal fluid; *MRI,* magnetic resonance imaging; *MS,* multiple sclerosis; *NMO,* neuromyelitis optica.
From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

TABLE 2 Suggested Diagnostic Workup for Recurrent Central Nervous System Demyelinating Disorders and Systemic Autoimmune Disorders Associated with Acute Transverse Myelitis

All Patients	Suggestive of Neuromyelitis Optica	Also Consider
Brain MRI with gadolinium	Ophthalmology consultation	Angiotensin-converting enzyme (serum, CSF)
CSF oligoclonal bands	Visual evoked potentials	Other autoantibodies
Antinuclear antibodies	Formal visual field testing	Anti-dsDNA
Antiphospholipid antibodies		Anti-La
Serum AQP4-IgG		Anti-Ro
		Anti-Smith

CSF, Cerebrospinal fluid; *MRI,* magnetic resonance imaging; *NMO,* neuromyelitis optica.
From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

TABLE 3 Suggested Diagnostic Workup for Infections Associated with Acute Transverse Myelitis

Blood	Cerebrospinal Fluid	Other
• Blood cultures • Acute and convalescent titers to *Borrelia burgdorferi,* EBV, *Mycoplasma pneumoniae*	• Bacterial culture • Viral culture • PCR testing for CMV, EBV, Enterovirus, HSV, *M. pneumoniae*, VZV	• Viral culture of stool and respiratory secretions • Consider stool ova and parasite testing and serum titers if parasitic infection is suspected

CMV, Cytomegalovirus; *EBV,* Epstein-Barr virus; *HSV,* herpes simplex virus; *PCR,* polymerase chain reaction; *VZV,* varicella zoster virus.
From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

1. Spinal dural arteriovenous fistula (most common)
2. Arteriovenous malformation of the spinal cord

- Spinal cord infarction due to either anterior spinal artery or posterior spinal artery occlusion

WORKUP

Transverse myelitis (TM) should be suspected in patients with a history of rapid (hours to days) onset of motor weakness and sensory abnormalities with bladder or bowel dysfunction that is referable to the spinal cord. The dysfunction is bilateral (not necessarily symmetric), and there is a clearly defined sensory (dermatomal) level. It is important to distinguish idiopathic TM from TM due to MS or neuromyelitis optica spectrum disorder because idiopathic TM does not relapse and does not require long-term immunomodulatory therapy. A suggested diagnostic workup for recurrent CNS demyelinating disorders and systemic autoimmune disorders associated with acute transverse myelitis is summarized in Table 2.

IMAGING STUDIES

- Gadolinium-enhanced magnetic resonance imaging (MRI) of brain and MRI of the entire spine (Fig. E1, Fig. E2). This will show demyelinating lesion on T_2 with contrast enhancement. In MS there is usually a short segment lesion (less than three vertebral segments) that is dorsally located. Longitudinally extensive transverse myelitis that spans more than three or more segments of the cord is more typical of NMOSD, postinfectious, vascular, or other inflammatory causes.
- Computed tomography (CT) of the spine with and without contrast should be obtained if MRI is unavailable, but CT does not allow for visualization of the spinal cord itself.
- CT myelogram may also be obtained if MRI unavailable to evaluate for compression.
- Chest CT with and without contrast if sarcoidosis is suspected.

LABORATORY TESTS

- Lumbar puncture looking for CSF pleocytosis, oligoclonal bands for MS, or serology and PCR looking for infection (Table 3) such as varicella zoster virus and enterovirus PCR.
- ANA, hepatitis B serology, Lyme disease serology, VDRL, SSA, SSB, anticardiolipin antibody, lupus anticoagulant, copper, ceruloplasmin, vitamin B_{12}, RPR.
- Serum NMO-IgG and myelin oligodendrocyte glycoprotein (MOG) antibodies to evaluate for neuromyelitis optica spectrum disorder.
- If a paraneoplastic etiology is suspected, then appropriate antibodies should be ordered and appropriate cancer screening undertaken.

Rx TREATMENT

Corticosteroids (IV methylprednisolone 1 g/day for 3 to 7 days) are the first-line treatment for transverse myelitis.

NONPHARMACOLOGIC THERAPY

- Physical therapy
- Respiratory and oropharyngeal support

ACUTE GENERAL Rx

- High-dose IV corticosteroid (e.g., methylprednisolone 1000 mg/day for 3 to 7 days) to stop inflammatory damage to the spinal cord.
- Rescue therapy with plasma exchange may be helpful in patients who do not respond to corticosteroids.
- Combination therapy with plasmapheresis and corticosteroids or other immunosuppressive agents (e.g., rituximab or cyclophosphamide) may also be effective.
- Analgesia for pain.

CHRONIC Rx

- Baclofen or tizanidine for muscle spasms
- Gabapentin or pregabalin for neuropathic pain
- Low-molecular-weight heparin for DVT prophylaxis in patients with immobility
- Need for chronic immunosuppression will depend on underlying etiology

DISPOSITION

- One third of patients with transverse myelitis will have complete recovery, one third will have fair recovery, and one third have permanent disability and do not recover. Recurrence or relapse is possible, especially if the patient has MS, NMOSD, or sarcoidosis.
- Patients who need further care, including those with urinary retention, may need home nursing assistance. Some patients may benefit from rehabilitation, either inpatient or outpatient.

REFERRAL

- Referral to a neurologist to evaluate need for long-term therapy.
- Referral for physical and occupational therapy.
- Consider psychiatric consultation (high incidence of long-term mood and anxiety disorders).

SUGGESTED READINGS

Available at ExpertConsult.com

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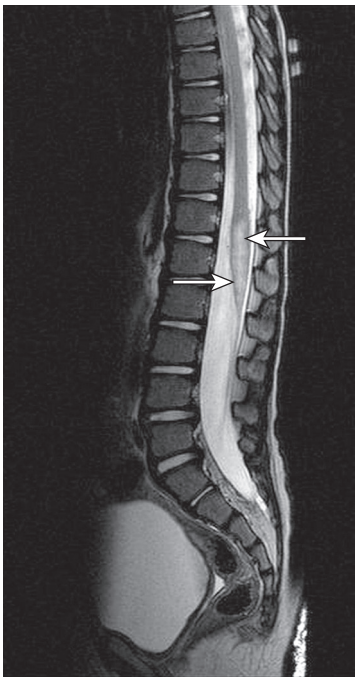

FIG. E1 Patient with clinical picture of transverse myelitis. Sagittal T2-weighted magnetic resonance image of the distal cord shows central T2 hyperintensity within the conus medullaris *(arrows)* in this case of acute disseminated encephalomyelitis. An acute spinal cord infarct also could have this imaging appearance. (From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.)

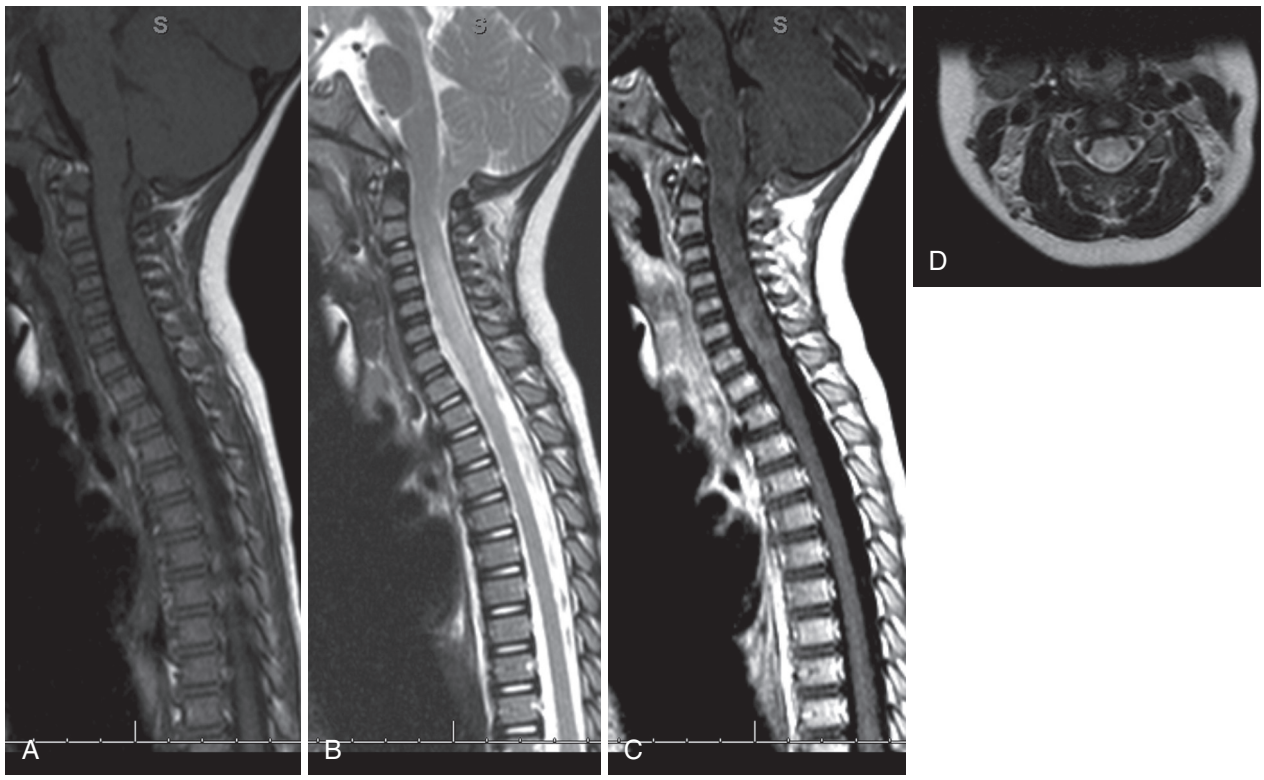

FIG. E2 Acute transverse myelitis of the cervical cord. (A) Sagittal T1-weighted magnetic resonance imaging (MRI) sequence through the cervical spinal cord demonstrating swelling of the cord. **(B)** T2-weighted MRI sequence of same patient revealing longitudinally extensive hyperintensity through the cervical cord. **(C)** T1-weighted MRI sequence with gadolinium revealing patchy enhancement of the cervical cord. **(D)** T2-weighted axial MRI sequence through the cervical cord revealing hyperintensity of both gray and white matter. (From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.)

SUGGESTED READINGS

Frohman EM, Wingerchuk DM: Transverse myelitis, *N Engl J Med* 363:564, 2010.
Wingerchuk DM et al: International consensus diagnostic criteria for neuromyelitis optica spectrum disorders, *Neurol* 85(2):177-189, 2015.

Traumatic Brain Injury (TBI)

BASIC INFORMATION

DEFINITION

- Impact to the head resulting in varying levels of cellular and macroscopic changes, detected with clinical examination supplemented by imaging studies.
- Mild traumatic brain injury (TBI) is defined as loss of consciousness <30 minutes, a Glasgow Coma Scale (GCS) of 13 to 15, and normal imaging.
- Moderate TBI is defined as loss of consciousness for 30 minutes to 24 hours with even longer alteration in consciousness, a GCS of 9 to 12, and may or may not have abnormal imaging.
- Severe TBI is defined as >24 hours of loss of consciousness with a GCS of 3 to 8 and prolonged posttraumatic amnesia with normal or abnormal imaging.

SYNONYMS

TBI
Head injury
Concussion
Intracranial contusion

ICD-10CM CODES

S06.9 X0A	Intracranial injury
S06.1X7A	Traumatic cerebral edema with loss of consciousness of any duration with death due to brain injury prior to regaining consciousness, initial encounter
S06.2X9A	Diffuse traumatic brain injury with loss of consciousness of unspecified duration, initial encounter
S06.300A	Unspecified focal traumatic brain injury without loss of consciousness, initial encounter
S06.305A	Unspecified focal traumatic brain injury with loss of consciousness greater than 24 hours with return to pre-existing conscious level, initial encounter
S06.309A	Unspecified focal traumatic brain injury with loss of consciousness of unspecified duration, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

Traumatic brain injury (TBI) is a worldwide leading cause of mortality in young individuals. Urbanization and increasing use of motor vehicles has led to an overall increase in TBI, especially in high-income and developing countries.
INCIDENCE: Globally, more than 10 million people suffer TBI resulting in mortality or requiring hospitalization each yr. By 2020, it is projected that TBI will surpass many diseases as the major cause of death and disability worldwide. TBI likely accounts for 9% of global mortality and is a threat to health in every country in the world. The financial burden of TBI has been estimated to be greater than $80 billion per yr in the United States alone. According to estimates from the CDC, about 2.87 million emergency department visits, including deaths and hospitalizations, were associated with TBI in 2014.
PREVALENCE: The prevalence of TBI in the United States has been estimated at approximately 5.3 million. In the European Union with 330 million inhabitants, approximately 7,775,000 new TBI cases occur each yr. According to the CDC, combined rates of TBI-related hospitalizations, emergency department visits, and deaths have risen from 521/100,000 in 2000 to 823.7/100,000 in 2010.
PEAK INCIDENCE: Approximate incidence in the US per CDC data is 103/100,000 population. In the European Union, this is estimated to be at 235/100,000.
PREDOMINANT SEX AND AGE: TBI occurs more frequently in young adults, particularly males 15 to 25 yr of age, and has a high cost to society because of life years lost. Hospitalizations and deaths are the highest in older adults >75 yr of age.
GENETICS: TBI and Apo E ε4 synergistically are also associated with a tenfold increased risk for Alzheimer disease as well as larger intracerebral hematomas and greater ischemia after TBI.
RISK FACTORS: N/A.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

TBI patients can present with a spectrum of clinical symptoms including nausea, vomiting, headache, seizures, altered mental status, and/or coma. Stigmata of trauma, including bruises, scalp lacerations, and periorbital or mastoid ecchymosis suggesting skull base fractures, are telltale signs of possible underlying traumatic brain injury. Box 1 describes risk stratification in patients with minor head trauma. The spectrum of TBI is most commonly assessed using the GCS, which ranges from 3 to 15 and utilizes eye, motor, and verbal exams (Table 1).

ETIOLOGY

Mechanical falls (35%), motor vehicle accidents (17%), and assaults resulting in direct or indirect trauma to the head are the most common etiologies. The most deaths occur from motor vehicle accidents.

An estimated 283,000 children seek care in U.S. emergency departments each yr for a sport- or recreation-related TBI. TBIs sustained in contact sports account for approximately 45% of these visits. Football, bicycling, basketball, playground activities, and soccer account for the highest number of emergency department visits.[1]

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of TBI is quite limited; however, there are several considerations and diagnoses considered as a possibility within the realm of TBI. These are enumerated in the imaging section.

WORKUP

TBI workup is always a part of the advanced trauma life support (ATLS) protocol. Primary and secondary survey followed by imaging studies constitutes the standardized approach to TBI. Focused TBI workup includes:

- History: Including timing of injury, duration of loss of consciousness if applicable, seizures (if any), comorbidities, use of anticoagulants and antiplatelet agents (requires reversal in the event of intracranial blood on imaging).
- Neurological examination: Glasgow Coma Scale, cranial nerves, motor/sensory exam. Assess for scalp lacerations, specifically overlying a skull fracture as well as CSF otorrhea or rhinorrhea.

BOX 1 Risk Stratification in Patients with Minor Head Trauma

High Risk
- Focal neurologic findings
- Asymmetrical pupils
- Skull fracture on clinical examination
- Multiple trauma
- Serious, painful, distracting injuries
- External signs of trauma above the clavicles
- Initial Glasgow Coma Scale score of 14 or 15
- Loss of consciousness
- Posttraumatic confusion or amnesia
- Progressively worsening headache
- Vomiting
- Posttraumatic seizure
- History of bleeding disorder or anticoagulation
- Recent ingestion of intoxicants
- Unreliable or unknown history of injury
- Previous neurologic diagnosis
- Previous epilepsy
- Suspected child abuse
- Age above 60 yr or below 2 yr

Medium Risk
- Initial Glasgow Coma Scale score of 15
- Brief loss of consciousness
- Posttraumatic amnesia
- Vomiting
- Headache
- Intoxication

Low Risk
- Currently asymptomatic
- No other injuries
- No focality on examination
- Normal pupils
- No change in consciousness
- Intact orientation and memory
- Initial Glasgow Coma Scale score of 15
- Accurate history
- Trivial mechanism
- Injury less than 24 hours ago
- No or mild headache
- No vomiting
- No preexisting high-risk factors

[1]Sarmiento K et al: Emergency Department Visits for Sports- and Recreation-Related Traumatic Brain Injuries Among Children—United States, 2010–2016, *MMWR* 68;241, 2019.

TABLE 1 Glasgow Coma Scale (GCS)

Adult		Infant
Eye Opening	**E**	**Eye Opening**
Spontaneous	4	Spontaneous
To speech	3	To speech
To pain	2	To pain
No response	1	No response
Best Motor Response	**M**	**Best Motor Response**
Obeys verbal command	6	Normal movements
Localizes to pain	5	Localizes to pain
Withdraws to pain	4	Withdraws to pain
Flexion (decorticate)	3	Flexion (decorticate)
Extension (decerebrate)	2	Extension (decerebrate)
No response	1	No response
Best Verbal Response	**E**	**Best Verbal Response**
Oriented speech	5	Coos, babbles
Disoriented speech	4	Cries but consolable
Inappropriate words	3	Persistently irritable
Incomprehensible sounds	2	Grunts to pain/restless
No response	1	No response

Mild TBI: GCS 13-15, Moderate TBI: GCS 9-12, Severe TBI GCS 8 or less.
GCS can range from 3 to 15. If intubated, then verbal component is replaced by 'T'. Best possible score if intubated is 10T, and worst is 3T.
In obtunded patients, pain stimulus can be central or peripheral. In patients with suspected spinal cord injury and paralysis, central stimulus to elicit facial grimace can be used to assess motor and eye component.

BOX 2 American College of Emergency Physicians Clinical Policy Regarding Neuroimaging in Adults with Mild Traumatic Brain Injury

A noncontrast head CT is indicated (level-1 recommendation) in adults with LOC or posttraumatic amnesia only if one or more of the following is present:
- Headache
- Vomiting
- Age >60 yr
- Drug or alcohol intoxication
- Deficits in short-term memory
- Physical evidence of trauma above the clavicle
- Posttraumatic seizure
- GCS score <15
- Focal neurologic deficit
- Coagulopathy

A noncontrast head CT should be considered (level-2 recommendation) in head trauma patients with no LOC or posttraumatic amnesia if there is:
- Focal neurologic deficit
- Vomiting
- Severe headache
- Age ≥ 65 yr
- Physical signs of a basilar skull fracture
- GCS score <15
- Coagulopathy
- A dangerous mechanism (e.g., ejection from motor vehicle, pedestrian struck, fall of more than 3 feet or 5 stairs)

CT, Computed tomography; *GCS,* Glasgow Coma Scale; *LOC,* loss of consciousness.
From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Elsevier.

- CT imaging of the head if there is a significant history of impact to the head, polytrauma, positive loss of consciousness, or stigmata of trauma to the head. The American College of Emergency Physicians Clinical Policy Regarding Neuroimaging in adults with mild TBI is summarized in Box 2.

LABORATORY TESTS

- Basic labs including CBC, basic metabolic panel, prothrombin time, activated partial thromboplastin time, urine drug screen, and ethanol blood level.
- Consider tests for platelet function analysis for unknown antiplatelet use.
- No blood biomarker currently exists. (Figs. 1 and E2)

IMAGING STUDIES (TABLE 2)

CT imaging forms the current cornerstone of imaging modalities for head trauma. Usually, in addition to a plain CT of the head (Fig. 3), CTA head/neck and CT of the spine is helpful if arterial or C-spine injury is suspected, respectively. Other imaging modalities such as MRI can be helpful in certain situations but are typically adjuncts in the acute setting to CT-guided management. Canadian CT head rules are a useful guide in determining utility of obtaining a CT scan. These are based on risk factors:

HIGH RISK:
- Failure to reach GCS of 15 within 2 hours
- Suspected open or any signs of basal skull fracture
- More than two episodes of vomiting
- Age older than 65

LOW RISK:
- Dangerous mechanism of injury or polytrauma
- Loss of consciousness lasting >30 minutes

Pathologies that can be identified with imaging are noted in the following:
- Primary extraaxial: Epidural, subdural, subarachnoid hemorrhage
- Primary intraaxial: Axonal injury, cortical contusion, intracerebral or intraventricular hemorrhage, encephalomalacia (from prior TBI or vascular insult)
- Skull fracture: Linear, depressed, open, involving frontal sinus or skull base
- Penetrating brain injury: Gunshot wounds, sharp objects resulting in parenchymal and vascular injury
- Vascular injury: Dissection, traumatic carotid-cavernous fistula (CCF), dural arteriovenous fistula (dAVF), pseudoaneurysm formation
- Secondary acute injury: Diffuse cerebral swelling/dysautoregulation (seen more commonly in children from posttraumatic hyperemia), infarction, infection from penetrating trauma, brain herniation from mass lesion or cerebral edema
- Secondary chronic injury: Hydrocephalus (posttraumatic due to disruption of normal CSF absorption pathways), encephalomalacia, CSF leak (from skull base fractures, manifests as otorrhea or rhinorrhea, leptomeningeal cyst (seen most commonly in infants, skull fracture resulting in underlying dural injury)

Rx TREATMENT

Prevention of secondary injury is the primary goal of prehospital and early in-hospital management. Most common mechanisms of secondary injury are either intracranial (ICP, hematoma) or systemic (hypoxia, hypovolemia, hypotension). Early categorization of head trauma patients according to the severity (based on GCS) and transport to facilities equipped with personnel and technology to deal with issues pertaining to head trauma has improved the overall management of head injury patients and prevention of secondary injury. Airway, breathing, and circulation, however, still remain the most important parameters to be stabilized and both directly and indirectly affect GCS and overall outcome. Trauma guidelines suggest intubation should be performed in any patient

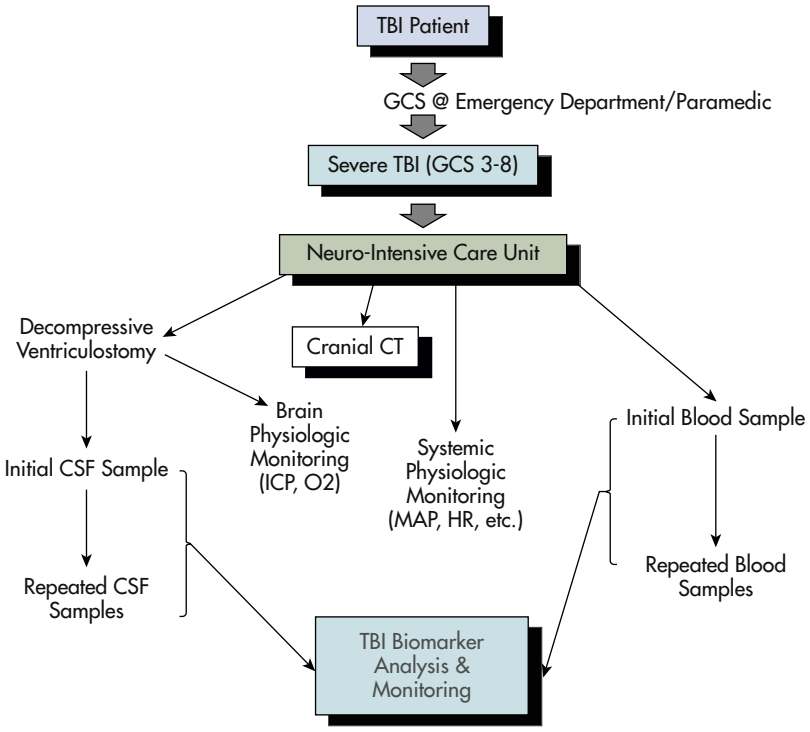

FIG. 1 Envisioned uses of brain biomarkers for severe traumatic brain injury *(TBI)* patient management. *CSF,* Cerebrospinal fluid; *CT,* computed tomography; *GCS,* Glasgow Coma Scale; *HR,* heart rate; *ICP,* intracranial pressure; *MAP,* mean arterial blood pressure. (From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.)

TABLE 2 Comparison of Head Imaging Modalities

	Computed Tomography Scans	Magnetic Resonance Imaging	Angiography	Skull Radiography
Advantages	Fast Patient accessible for monitoring Defines acute hemorrhages, mass effects, bone injuries, hydrocephalus, intraventricular blood, edema	Defines contusions and pericontusion edema, posttraumatic ischemic infarction, brainstem injuries	Helps localize acute traumatic lesions Defines vascular injuries, injuries to venous sinuses Detects mass effects	Readily available May help screen some patients for further imaging studies
Disadvantages	Artifacts arise from patient's movement, foreign bodies Streak artifacts may obscure brainstem or posterior fossa	Slow Patients not easily accessible for monitoring Does not define most acute hemorrhagic lesions Not useful for bone injuries	Does not define nature of acute lesion Does not detect infratentorial masses	Does not indicate presence or absence of intracranial injury
Indications	Acute severe head trauma Acute moderate head trauma Suspected depressed skull fracture High-risk minor head trauma Suspected child abuse in minor head trauma Deteriorating neurologic status	Persistent symptoms with postconcussive syndrome Suspected posttraumatic ischemic infarction Suspected contusions not seen on CT scan	Suspected vascular injury CT scan not available	CT scan may not be done Penetrating head trauma

CT, Computed tomography.
From Marx JA et al: *Rosen's emergency medicine: concepts and clinical practice,* J.A. Marx, 7 ed, 2010, Elsevier.

with a GCS of 8 or less to prevent hypoxemia and hypercapnia. Intravenous fluid resuscitation should also be started early to prevent hypovolemia resulting in hypotension, shown to double mortality. Transfer to and care in a Level I trauma center are associated with better outcomes.

Details of in-hospital management including critical care and surgical intervention is beyond the scope of this text. Some important points are summarized below.

- ATLS protocol (airway, breathing, circulation, disability, exposure).
- Ventilatory support.
- Optimization of oxygenation, ventilation, and fluid status.
- CT head (Fig. E4) to evaluate for mass lesion (hematoma) or cerebral edema. These findings may necessitate either surgical intervention or ICP monitor placement. ATLS guidelines recommend maximum 30 minutes between initial assessment and CT head.
- In case of either a severe TBI (GCS 8 or less) or a moderate TBI (GCS 8 to 13) with an unreliable neurological exam, patients should be admitted to the intensive care unit for frequent neurological checks. TBI guidelines suggest ICP monitor placement for GCS 8 or less to monitor intracranial pressure closely. ICP monitors are of various kinds, and the most commonly used include external ventricular drain, intraparenchymal pressure monitor, and a bolt device with

FIG. 3 Noncontrast-enhanced computed tomography scan of acute epidural hematoma at the level of right midconvexity. There is an associated mass effect and moderate midline shift. (From Marx JA et al: *Rosen's emergency medicine: concepts and clinical practice,* 7 ed, 2010, Elsevier.)

brain tissue oxygen pressure monitoring with fiberoptic pressure monitor. Recent research has also supported the use of brain tissue oxygen monitoring for severe TBI patients. Surgical decompression may involve evacuation of hematoma (epidural, subdural intraparenchymal contusion) through craniotomy alone (replacement of bone after completion of operation) versus decompressive craniectomy (complete removal of bone without replacement) in certain cases where cerebral edema is out of proportion to the presence of mass lesion. Skull fractures are treated depending on the morphology of the fracture. Open, depressed fractures require surgical debridement and elevation in most cases, in addition to broad-spectrum antibiotics.

- Avoid electrolyte imbalance, especially hyponatremia and hyperglycemia, which may contribute to cerebral edema and increase intracranial pressure.
- Elevation of head of bed to allow better venous drainage to reduce intracranial pressure.
- ICP management, which may include the following: Drainage of cerebrospinal fluid via external ventricular drain, surgical hematoma evacuation, administration of hyperosmotic fluids to reduce edema, pharmacologic sedation and paralysis, pentobarbital-induced coma, and surgical decompression of the brain. Decompressive craniectomy in patients with TBI and refractory intracranial hypertension results in lower mortality and higher rates of vegetative state, lower severe disability, and upper severe disability than medical care.[23] In patients with traumatic brain injury, hypothermia can reduce intracranial hypertension, but recent trials in patients with an intracranial pressure of more than 20 mm Hg after TBI, therapeutic hypothermia, plus standard care to reduce intracranial pressure did not result in outcomes better than those with standard care alone. The new TBI guidelines do not recommend hypothermia.
- Prevention of seizures in the acute setting. The most commonly used and studied drug is phenytoin. Indications for acute seizure prophylaxis in severe head trauma are described in Box 3. Levetiracetam (Keppra) is also a beneficial antiepileptic now commonly used in the TBI setting. Seizure prophylaxis, however, has not shown to prevent long-term development of traumatic epilepsy.
- DVT prophylaxis is recommended in almost all patients on hospital day 1 in addition to sequential compression devices (SCDs) for immobile or bedbound patients to prevent DVTs.
- Early initiation of parenteral nutrition.
- Early tracheostomy for ventilator-dependent patients is recommended to reduce mechanical ventilation days.

BOX 3 Indications for Acute Seizure Prophylaxis in Severe Head Trauma

- Depressed skull fracture
- Paralyzed and intubated patient
- Seizure at the time of injury
- Seizure at emergency department presentation
- Penetrating brain injury
- Severe head injury (Glasgow Coma Scale score ≤8)
- Acute subdural hematoma
- Acute epidural hematoma
- Acute intracranial hemorrhage
- Prior history of seizures

CHRONIC Rx

- TBI can lead to short- or long-term emotional, physiologic, and cognitive sequelae. Patients suffering from TBI are shown to benefit from neurocognitive, occupational, and physical therapy. The Glasgow Outcome Scale is a comprehensive measure of severity and eventual outcome of brain injury. Posttraumatic amnesia, age, length of coma, GCS score within the first 24 hours, and imaging study scales are some of the factors affecting outcome and dictating long-term prognosis.
- Chronic treatment addresses several sequelae of TBI, including, but not limited to, the following: dysautonomia, agitation, sleep disturbance, posttraumatic epilepsy, spasticity, dysphagia, syndrome of the trephined, posttraumatic hydrocephalus, apathy, fecal/urinary incontinence, headache, and neuropathic pain syndromes.
- Neurostimulants such as amantadine, zolpidem, bromocriptine, amphetamine, and methylphenidate are used in the rehabilitation phase with anecdotal data, but good RCTs are lacking in this area.

DISPOSITION

Depending on severity of head injury, patients may require admission to a rehabilitation facility or discharge to home with outpatient neurocognitive therapy.

REFERRAL

Early transfer to a Level 1 Trauma Center with neurosurgical personnel if high-risk findings are noted on clinical exam or CT head, and is associated with better outcomes.

PEARLS & CONSIDERATIONS

TBI is major healthcare issue. Guidelines have been developed to address TBI in a timely and effective fashion. Clinical acumen and judgment, however, is irreplaceable and should be exercised for better patient care and outcomes. Early recognition of high-risk patients and early imaging and early evaluation at a Level 1 Trauma Center by a specialist are associated with improved outcomes. The goal of healthcare providers in the field or in the community is to identify patients who need this attention.

PATIENT & FAMILY EDUCATION

- Brain Injury Association of America http://www.biausa.org/
- Brain Injury Resource Center http://www.headinjury.com/linktbisup.htm

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Concussion (Related Key Topic)
Postconcussion Syndrome (Related Key Topic)

AUTHORS: **Farhan A. Mirza, MD,** and **Justin F. Fraser, MD**

[2]Andrews PJD et al: Hypothermia for intracranial hypertension after traumatic brain injury, *N Engl J Med* 373:2103-2112, 2015.
[3]Hutchinson PJ: Trial of decompressive craniectomy for traumatic intracranial hypertension, *N Engl J Med* 379:1119-30, 2016.

SUGGESTED READINGS

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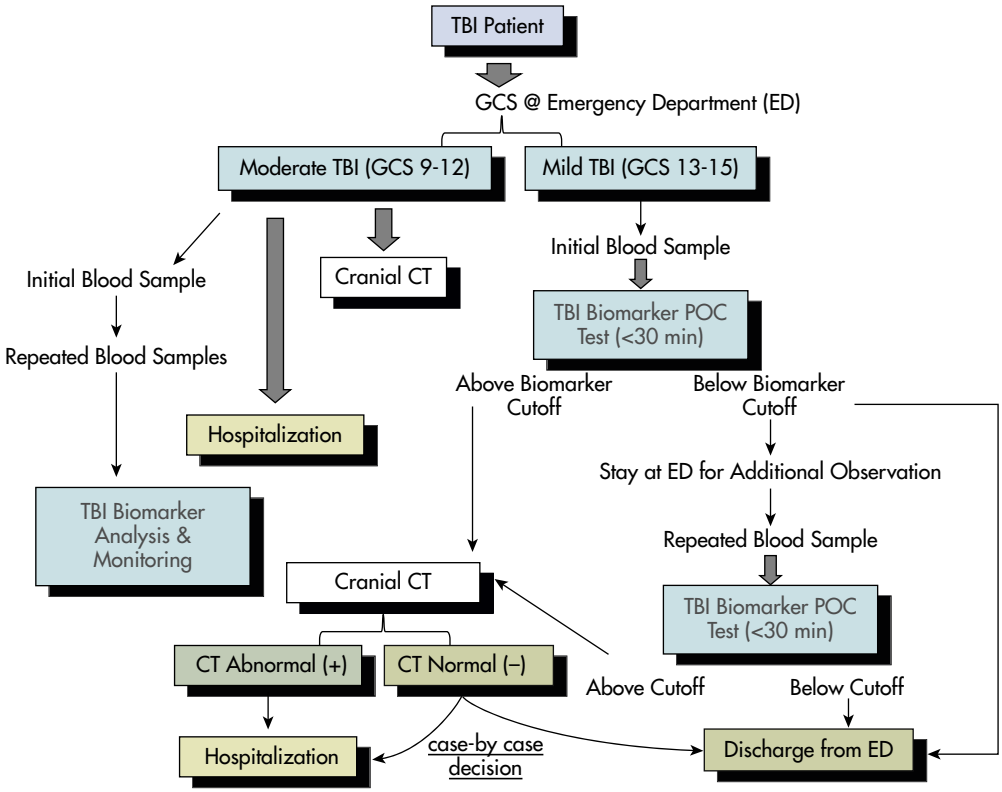
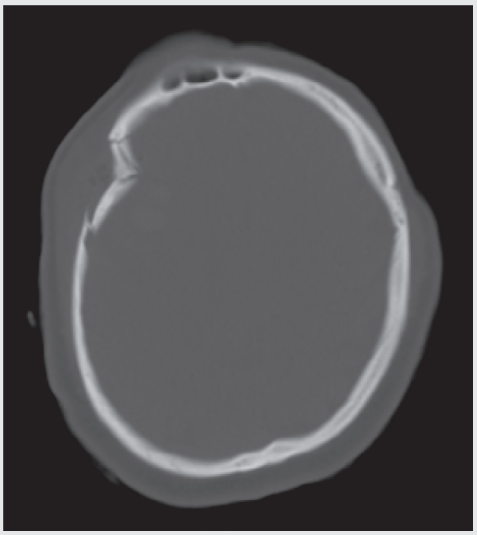
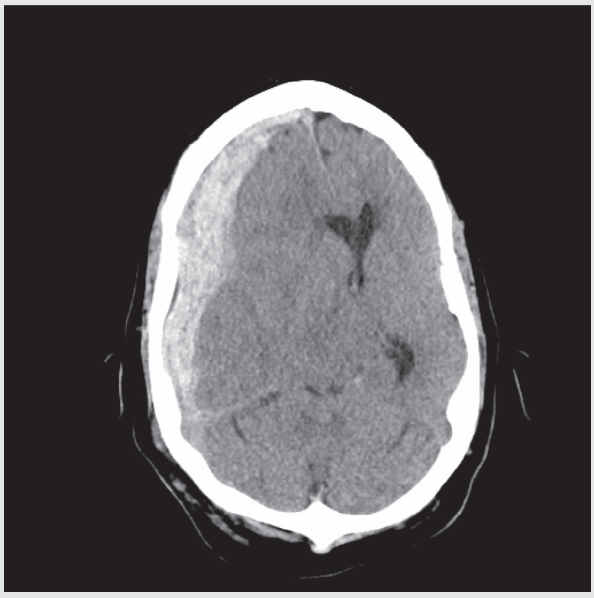


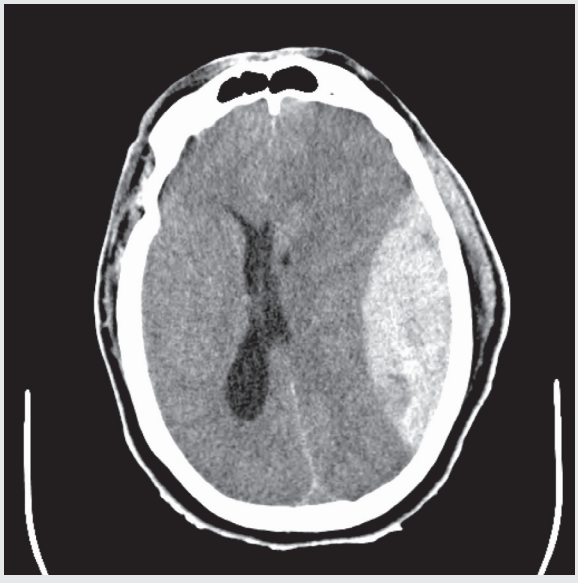
FIG. E2 Envisioned uses of brain biomarkers for mild-moderate traumatic brain injury *(TBI)* patient management. *CT,* Computed tomography; *GCS,* Glasgow Coma Scale; *POC,* point-of-care. (From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.)



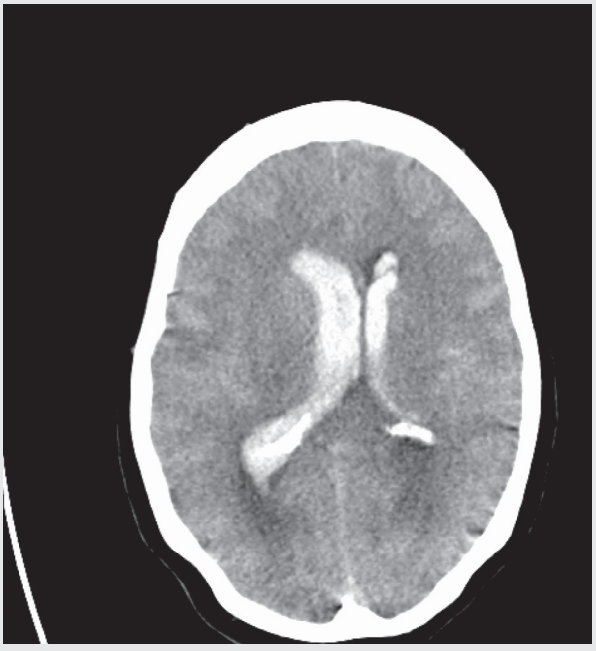
Right frontal depressed skull fracture



Right subdural hematoma with severe brain compression and midline shift



Left epidural hematoma with severe brain compression and midline shift



Intraventricular blood with casting of the ventricles

FIG. E4 Indications for acute seizure prophylaxis in severe head trauma. (From Marx JA et al: *Rosen's emergency medicine: Concepts and clinical practice,* 7th ed, Philadelphia, 2010, Elsevier.)

BASIC INFORMATION

DEFINITION

Traveler diarrhea (TD) is defined as 3 or more loose-to-watery stools, with or without associated fever, abdominal cramps, and vomiting, within a 24-hr period. It develops during or within 10 days of traveling to developing areas of the world.

SYNONYMS

TD
Enterotoxigenic *E. coli*
Enteroaggregative *E. coli*
Infectious diarrhea
Postinfectious irritable bowel syndrome

ICD-10CM CODE
A09 Infectious diarrhea

EPIDEMIOLOGY & DEMOGRAPHICS

Traveler diarrhea is mostly caused by bacteria and other pathogens in food and water.

At least 1 episode of diarrhea occurs in 40% to 50% of travelers during their stay abroad. Table 1 describes pathogens and epidemiologic features associated with traveler diarrhea.

INCIDENCE: High risk (>20%): South and Southeast Asia, Africa (except South Africa), South and Central America, and Mexico

Moderate risk (10% to 20%): Caribbean Islands, South Africa, Central and East Asia (including Russia and China), Eastern Europe, and the Middle East, including Israel

Low risk (<10%): Northern and Western Europe, Australia, New Zealand, United States, Canada, Singapore, Japan

PEAK INCIDENCE:

- Peak incidence occurs during the first week of travel and progressively declines after that
- Seasonal variation does exist for TD, with lower rates in the winter months

PREVALENCE: Acute and chronic diarrhea account for a third of medical visits by returned travelers as per the GeoSentinel database.

PREDOMINANT SEX AND AGE:

- Travelers in their 30s are at highest risk, possibly secondary to more adventurous travel.
- Gender does not seem to influence the risk for TD.
- Infants and toddlers are more likely to have a more severe form of TD and are more likely to need hospitalization.

GENETICS: Travelers with the O blood group are at higher risk for diarrhea caused by Norovirus and *Shigella*.

RISK FACTORS:

- Gastric acid protects against enteropathogens, so medications that reduce gastric acid secretion (i.e., PPI or H2-receptor blockers) are known to increase risk for TD by a factor of 12.
- Immunocompromised travelers such as those with HIV/AIDS are at higher risk for parasitic infections.
- Backpackers are at higher risk than those staying at a resort.
- Food bought from street vendors or prepared by persons not wearing gloves carries a higher risk.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The clinical presentation does not allow determination of infectious cause.
- Ninety percent of cases occur within 2 weeks of stay.
- Acute watery diarrhea predominates in 90% of patients.
- Signs of invasive infection, including fever and bloody/mucoid diarrhea, occur in 3% to 30%.
- Most patients report 3 to 5 bowel movements a day, but in 20% a higher frequency of up to 20 daily bowel movements occurs.
- Nausea (10% to 70%), vomiting (4% to 36%), abdominal cramps/tenesmus (80%), urgency (90%).
- Other: Myalgia, arthralgia, headache.
- Average episode resolves in 3 to 5 days.
- Prolonged symptoms lasting more than a week: 8% to 15%; chronic diarrhea >30 days: 1% to 3%.
- Severe episodes may result in electrolyte imbalance (K+ loss).
- Fifty percent of all travelers are incapacitated for at least 24 hours, but up to 20% are ill in bed for 1 to 2 days.

ETIOLOGY

- *E. coli* (Table E2): Accounts for up to 60% of all cases of TD and is most prevalent in Central and South America, South Asia, and Africa. Table E3 summarizes etiology of traveler diarrhea in Latin America, Africa, and Asia.
  1. Enterotoxigenic *E. coli* (ETEC): Produce heat labile and heat stable toxin and are the most common cause, accounting for 10% to 45% of cases. Frequently seen in Latin America, Africa, and South Asia.
  2. Enteroaggregative *E. coli* (EAEC): More commonly seen in Latin America.
  3. Other *E. coli* (enteropathogenic [EPEC], enteroinvasive [EIEC], enterohemorrhagic [EHEC]): Shiga toxin-producing or diffuse adhering *E. coli* are much less common.
- *Campylobacter:* 2% to 32% of cases. More common in Southeast Asia, where it is more frequent than ETEC.
- Shigella: 2% to 9%. More common in Africa.
- Salmonella: <5% of cases except in Asia, where it is seen in up to 10% of cases.
- Other bacteria: *Aeromonas, Arcobacter, Plesiomonas,* enterotoxigenic *Bacteroides fragilis, Vibrio cholera,* noncholera vibrios.
- Viral pathogens:
  1. Norovirus: Up to 17% of cases from Caribbean and Africa.
  2. Rotavirus: 4% to 7% of cases.
- Protozoans:
  1. *Entamoeba histolytica:* More common in South and Southeast Asia.
  2. *Giardia lamblia:* More common in South and Southeast Asia, especially Nepal.
  3. *Cryptosporidium, Cyclospora, Isospora.*

TABLE 1 Pathogens and Epidemiologic Features Associated with Traveler Diarrhea

Organism	Approximate Percentage of Cases (%)	Epidemiologic Features
Enterotoxigenic *Escherichia coli*	15-50	Most important causative agent of traveler diarrhea overall; not diagnosed by routine microbiologic methods
Enteroaggregative *E. coli*	20-35	Not diagnosed by routine microbiologic methods
Shigella spp. and enteroinvasive *E. coli*	10-25	Most important causes of dysentery; enteroinvasive *E. coli* not diagnosed by routine microbiologic methods
Nontyphoidal *Salmonella* spp.	5-10	
Campylobacter jejuni	3-15	More common in Asia; antimicrobial resistance a concern
Aeromonas	5	
Plesiomonas	5	
Giardia lamblia	<2	Affects hikers and campers who drink from contaminated freshwater streams
Cryptosporidium hominis/parvum	<2	Occasional large-scale waterborne outbreaks
Cyclospora cayetanensis	<2	
Vibrio cholerae		Ongoing outbreaks in Haiti and Zimbabwe, and endemic in many countries in Asia; rare cause of disease in travelers
Norovirus		Outbreaks on cruise ships
Entamoeba histolytica		May cause liver abscess

From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Malaria
- Dengue fever
- Influenza
- Rocky Mountain spotted fever
- Irritable bowel syndrome
- Inflammatory bowel disease
- Shellfish poisoning
- Mushroom poisoning

WORKUP

- Most cases of TD are self-limiting, do not require workup, and are treated symptomatically without regard to etiologic agent.
- In patients with diarrhea, fever, and colitic symptoms (bloody stools, cramping), a stool culture should be obtained to look for specific bacterial pathogens.

LABORATORY TESTS

- Stool culture ×3 for bacterial pathogens.
- Stool for ova and parasites to help identify protozoans. Special stains such as modified acid fast or trichrome stain may be necessary for *Cryptosporidium, Cyclospora,* and *Isospora.*
- Blood cultures in patients with systemic illness to rule out *Salmonella* species.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Fluid replacement to treat volume depletion of diarrhea is important.
- Mild cases: Alternate fluids that contain salts and fluids that contain sugars, such as broths or fruit juices. Pedialyte is effective as an over-the-counter product.
- Severe cases: Oral rehydration solution (ORS) packets are available in most pharmacies. They should be mixed with clean water to replace lost electrolytes and are used until patient is urinating regularly. An alternative home-based solution can be made with: ½ teaspoon of salt, ½ teaspoon of baking soda, and 4 tablespoons of sugar in one liter of clean water.

ACUTE GENERAL Rx

- Antisecretory agents may reduce symptoms but do not treat underlying cause:
  1. Bismuth subsalicylate: 1 dose of 525 mg (2 tablets of Pepto-Bismol) PO every 30 min up to 8 doses a day. Can reduce number of bowel movements by 50%. Dosages are available for children based on weight, and the product is available in liquid or chewable tablet form.
  2. Loperamide: 4 mg PO, then 2 mg after each loose bowel movement, not to exceed 16 mg per day. Use for up to 48 hrs. Has antisecretory and antimotility effect. Antimotility drugs should not be used in cases of bloody diarrhea or dysentery (increased risk of colitis and colonic perforation). When used, they should be given only in conjunction with antimicrobial therapy.
- Antibiotics are warranted only for moderate to severe diarrhea (i.e., >4 bowel movements a day, fever, or blood, pus, or mucus in stool. Antibiotics can reduce duration of diarrhea by 1 to 2 days.
  1. Azithromycin: The preferred antibiotic for empiric treatment of moderate to severe TD. It is also the preferred agent for children and pregnant women. Dose of 1 gram PO is the single dose for women. Children: 10 mg/kg/day single dose or for 3 days. Particularly effective against quinolone-resistant *Campylobacter* infections in Southeast Asia. Another option for children: Ceftriaxone 50 mg/kg/day IV once daily ×3 days.
     a. Ciprofloxacin: 500 mg twice a day for 1 to 3 days
     b. Levaquin: 500 mg a day for 1 to 3 days
  2. Fluoroquinolones are also effective agents for bacterial causes of TD, but resistance to fluoroquinolones is increasing. Cannot be used in children under 15 and in pregnant women:
  3. Rifaximin: 200 mg PO tid for 3 days for children age >12 and adults is effective for afebrile, noncolitic diarrhea such as ETEC. Does not treat *Salmonella, Shigella,* or *Campylobacter.*
  4. Rifamycin is now FDA approved for TD caused by non-invasive strains of *E. coli.* It is not recommended for TD complicated by fever and/or bloody stools. Dosage is 388 mg (2 tablets) bid ×3 days.
- Concerns of use of antibiotics:
  1. Widespread use of antibiotics has led to resistance. Tetracycline and sulfa agents such as Bactrim are no longer used due to widespread resistance.
  2. Antibiotic treatment may lead to prolonged colonization in infections with *Salmonella* and nontyphoid *Salmonella.*
  3. In cases of EHEC (Shiga toxin production) treatment with quinolones, but not rifaximin, may increase risk of complications such as hemolytic uremic syndrome.
  4. *Clostridia difficile* infection can occur with use of antibiotics.

PREVENTION BY ANTIBIOTICS AND NONANTIBIOTIC AGENTS

- Antibiotic prophylaxis can be considered for certain groups, such as persons with underlying illness, athletes, and politicians for up to 2 to 3 weeks. Ciprofloxacin 250 to 500 mg a day is effective in preventing 90% of TD. Rifaximin dosed daily has been shown to help prevent TD for U.S. travelers to Mexico, but not as effectively as Ciprofloxacin.
- Bismuth subsalicylate can be used. It must be given 4× daily and can cause black tongue and stools. As it contains salicylates, it can interact with anticoagulants and lead to toxicity in patients on long-term salicylate therapy.
- Probiotics are being studied for their potential use but evidence of their effectiveness is limited.

REFERRAL

Infectious diseases physician for more difficult cases lasting more than 72 hours

PEARLS & CONSIDERATIONS

- Travelers on cruises have lower incidence of TD than land-based trips, but cruise ship passengers and staff are at higher risk of large outbreaks of Norovirus that are difficult to contain. Norovirus infection needs only a low inoculum of virus to cause illness, and the virus is relatively resistant to cleaning.
- In up to 40% of cases of TD, no pathogen is identified.
- *Giardia* is the most frequent cause of long-lasting TD.

PREVENTION

- There are oral and injectable vaccines against *Salmonella typhi* available in the U.S.
- Dukoral oral vaccine is available in some countries such as Canada and Australia and in Europe to help prevent cholera and ETEC.

PATIENT & FAMILY EDUCATION

Food hygiene education: Wash hands often, especially after going to bathroom and before eating. Avoid raw fruits and vegetables (unless peeled and washed in clean water). Avoid undercooked meats, fish, and seafood. Avoid tap water and ice. Choose beverages in factory-sealed containers (such as bottled water and carbonated soft drinks). Try to avoid buffet-style foods.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Traveler Diarrhea (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

TABLE E2 Etiology of Traveler Diarrhea*

Characteristic	Latin America	Africa	Asia
Duration of stay (days)	21 (2-42)	28 (28-35)	(28-42)
Attack rate (%)	52 (21-100)	54 (36-62)	(39-57)
Organism (%)			
Enterotoxigenic *Escherichia coli*	46 (28-72)	36 (31-75)	(20-34)
Shigella	0 (0-30)	0 (0-15)	(4-7)
Salmonella	—	0 (0-0)	(11-15)
Campylobacter jejuni	—	—	(2-15)
Vibrio parahaemolyticus	—	—	(1-13)
Rotavirus	23 (0-36)	0 (0-0)	—

*Values shown are the median (and range) from multiple studies.
From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

TABLE E3 Frequency of Enterotoxigenic *Escherichia coli* in Association with Traveler Diarrhea in Latin America, Africa, and Asia

	Reported Frequency (%)				
Feature	Gastroenterologists in Mexico	Peace Corps Volunteers in Kenya	Yale Glee Club in Latin America	Japanese Travelers Returning to Tokyo from India, Southeast Asia, Orient	Total
Illness attack rate	49% in 16 days	69% in 5 wk	74% in 1 mo	—	
Type of enterotoxin					
LT only	16	33	25	4.8	21
LT and ST	16	15	12.5	11.8	38
ST only	9.8	2	19	13.6	41
% of ill patients with ETEC	41 (21/51 cases)	52 (14/27 cases)	56 (9/16 cases)	32 (270/843 cases)	33.5

ETEC, Enterotoxigenic *E. coli; LT,* heat-labile; *ST,* heat-stable.
From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

SUGGESTED READINGS

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Riddle MS et al: Guidelines for the prevention and treatment of traveler's diarrhea: a graded expert panel report, *J Travel Med* 24(Suppl 1):s57-S74, 2017.

Steffer R et al: Traveler diarrhea: a clinical review, *J Am Med Assoc* 313(1):71-80, 2015.

Zaidi D: Wine E: an update on traveler diarrhea, *Curr Opin Gastrenterol* 31:7-13, 2015.

BASIC INFORMATION

DEFINITION

Trichinellosis (trichinosis) is an infection by one of various species of the nematode parasite *Trichinella.*

SYNONYMS

Trichinella spiralis muscle infection
Trichinosis

ICD-10CM CODE
B75 Trichinellosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- About 90 cases were reported in the U.S. between 2008 and 2012 from 24 states and District of Columbia.
- In January 2017, 12 cases were reported in California among persons attending a dinner at which larb, a traditional Laotian raw pork dish, was served. Nine infected persons were hospitalized with sepsis and seven had acute kidney injury.
- Most cases occur outside the United States worldwide. Table E1 summarizes hosts and geographic distribution of species of the genus *Trichinella.*

GENETICS: Congenital infection:

- Abrupt delivery of stillbirths in infected pregnant women
- Vertical infection of the fetus

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms:
  1. Incubation period is usually 7 to 30 days and may vary widely depending on the time from ingestion of contaminated meat and on worm burden.
  2. Mild infections can be subclinical.
- Enteral phase:
  1. Correlates with penetration of ingested larvae into the intestinal mucosa
  2. May last from 2 to 6 wk
  3. Mild, transient diarrhea and nausea
  4. Abdominal pain
  5. Diarrhea or constipation
  6. Vomiting
  7. Malaise
  8. Low-grade fevers
- Migratory or parenteral phase:
  1. In the intestine, maturation and mating
  2. Newborn larvae:
     a. Penetrate into lymphatic and blood vessels
     b. Migrate to muscles, where they penetrate into muscle cells, enlarge, coil, and develop a cyst wall
  3. Patients may present with:
     a. Fever
     b. Myalgias
     c. Periorbital or facial edema
     d. Headache
     e. Skin rash, splinter hemorrhages under fingernails
     f. Other symptoms caused by the penetration of tissues by the newborn migrating larvae
  4. Peak in symptoms 2 to 3 wk after infection, then slowly subside
- Severe complications:
  1. Brain damage by granulomatous inflammation or occlusion of arteries
  2. Myocarditis with arrhythmias
  3. Respiratory myositis due to diaphragmatic involvement

ETIOLOGY

- *Trichinella* is a parasitic intracellular round worm. Larvae of *trichinella* species invade columnar epithelium cells of villi of the small intestine and develop into adult worms (Fig. E1).
- It is one of the most ubiquitous parasites in the world and may be found in virtually all warm-blooded animals. Most infections are due to *T. spiralis.*
- Humans are incidental hosts and infections in humans occur by the ingestion of contaminated animal meat that is raw or partially cooked and contains viable cysts.
- Most cases are now related to the consumption of poorly processed pork or wild game (bear, wild boar, cougar, and walrus).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Different presentations have different differential diagnoses.
- Early illness may resemble gastroenteritis.
- Later symptoms may be confused with:
  1. Measles
  2. Dermatomyositis
  3. Glomerulonephritis
  4. Cysticercosis
  5. Strongyloidiasis

TABLE E1 Hosts and Geographic Distribution of Species of the Genus *Trichinella*

Species	Code	Common Hosts	Geographic Distribution	Encapsulated
Trichinella spiralis	T1	Pigs, rodents, horses, bears, foxes	Worldwide	Yes
Trichinella nativa	T2	Bears, foxes, dogs	Arctic, subarctic	Yes
Trichinella britovi	T3	Dogs, cats, bears	Temperate areas, subarctic	Yes
Trichinella pseudospiralis	T4	Birds, omnivorous mammals	Arctic, Tasmania	No
Trichinella murrelli	T5	Bears	North America	Yes
Not yet defined	T6	Bears	Subarctic	Yes
Trichinella nelsoni	T7	Hyenas, cats	Tropical Africa	Yes
Not yet defined	T8	Lions, panthers	Southern Africa	Yes
Not yet defined	T9	Sylvatic carnivores	Japan	No

From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.

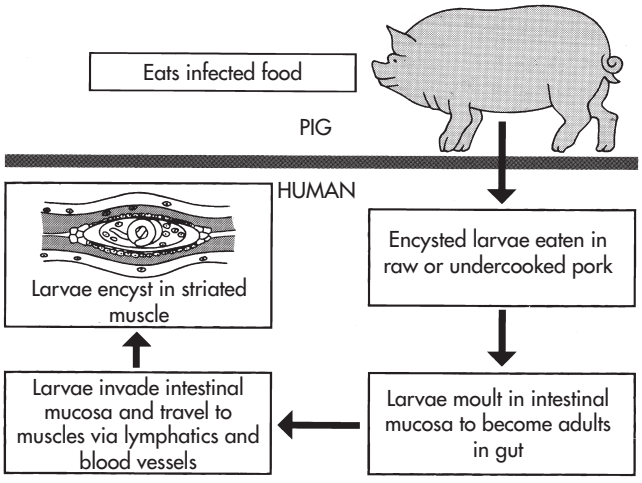

FIG. E1 Life cycle of *Trichinella spiralis.* (From Souhami RL, Moxham J: *Textbook of medicine,* ed 4, London, 2002, Churchill Livingstone.)

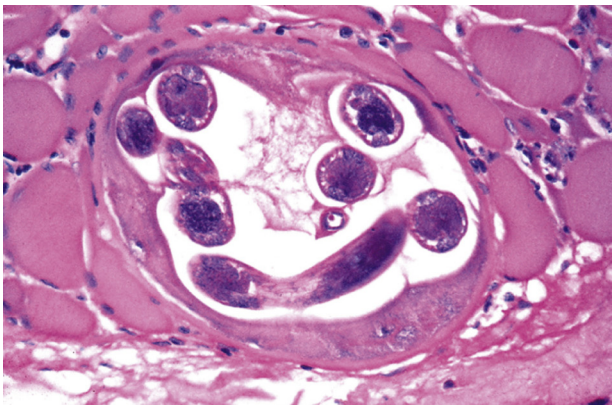

FIG. E2 Coiled *Trichinella spiralis* larvae within a skeletal muscle cell. (From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.)

WORKUP

- Antibody assay of serum is usually positive by approximately 2 to 4 wk after infection and can remain positive for years.
- Muscle biopsy is used to detect the larva in muscle tissue if diagnosis unclear; best done by placing the tissue between two slides.

LABORATORY TESTS

- Complete blood count: Leukocytosis with prominent eosinophilia (20% to 90%).
- Erythrocyte sedimentation rate: Usually normal.
- Elevation of muscle enzymes common (i.e., creatine phosphokinase, lactate dehydrogenase, aldolase).
- Serology: Antibodies detected by ELISA and Western blot but not useful in early disease.
- Muscle biopsy to look for larvae directly (Fig. E2). Biopsy is best done in symptomatic muscles and near insertion of a tendon.

IMAGING STUDIES

Soft-tissue radiographs may show calcified cyst walls.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Bed rest for myalgias

ACUTE GENERAL Rx

- Most infections are self-limited and do not require specific treatment.
- Albendazole: 400 mg twice a day for 10 to 14 days.
- Mebendazole: 200 to 400 mg tid for 3 days then 400 to 500 mg tid for 10 days but not available in the U.S.
- These agents are not advisable in pregnancy or children less than 2 yr of age.
- Steroids can be added in severe cases: Prednisone at 30 to 60 mg/day for 10 to 15 days.
- Salicylates to decrease muscle discomfort.

DISPOSITION

- Most symptoms subside over time.
- Reports of long-term sequelae:
  1. Myalgias
  2. Headaches
- Occasionally, death occurs.

REFERRAL

Diagnosis uncertain

PEARLS & CONSIDERATIONS

COMMENTS

- Prevention by thorough cooking of meats to at least 77° C (170.6° F).
- Inadequate to smoke, cure, or dry meats.
- Freezing at –15° C (–59° F) for 3 wk will kill *T. spiralis* larvae in pork.
- *T. nativa* is a freeze-resistant species that remains viable after freezing, even for months or years; it has been associated with infection from ingestion of bear meat.

RELATED CONTENT

Trichinosis (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Heaton D et al: Trichinosis outbreak linked to consumption of privately raised raw boar meat–California, 2017, *MMWR (Morb Mortal Wkly Rep)* 67(8):247-249, 2018.

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Tricuspid Regurgitation PTG

BASIC INFORMATION

DEFINITION

Tricuspid regurgitation (TR) refers to an abnormal retrograde flow of blood from the right ventricle to the right atrium (Fig. E1).

SYNONYMS

TR
Tricuspid insufficiency
Tricuspid incompetence

ICD-10CM CODES

I07.1	Rheumatic tricuspid insufficiency
I07.2	Rheumatic tricuspid stenosis and insufficiency
I36.1	Nonrheumatic tricuspid (valve) insufficiency
I36.2	Nonrheumatic tricuspid (valve) stenosis with insufficiency

EPIDEMIOLOGY & DEMOGRAPHICS

- In the adult population, the principal cause of TR is usually functional rather than structural, secondary to the dilation of the right ventricle and the tricuspid annulus.
- Approximately 10% of all TR is primary.
- In adolescents and young adults, most cases of TR are the result of congenital cardiac abnormalities.
- In patients with rheumatic heart disease, TR rarely occurs alone; it is usually associated with mitral or aortic valve disease.
- Flail leaflet is uncommon but can occur with chest trauma, endomyocardial biopsy, or pacemaker insertion.
- A small degree (i.e., trace to mild) of TR is present in approximately 70% of normal adults. On echocardiography, this "normal" degree of regurgitation is localized to a small region adjacent to valve closure, it often does not extend throughout systole, and it has low signal strength.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Isolated TR can cause nonspecific symptoms (e.g., exercise intolerance).
- Signs and symptoms of TR are usually the result of an underlying cause.
- Signs and symptoms may be caused by accompanying right-sided heart failure (e.g., jugular venous distention, peripheral edema, parasternal lift, ascites, hepatomegaly, right-sided S_3).
- A lower-left parasternal holosystolic murmur may be found; the murmur becomes louder during inspiration (Carvallo sign) and during maneuvers that increase venous return such as squatting, leg lifts, and isotonic exercises.
- Prominent "c-V" wave in the jugular venous waveform can occur analogous to prominent V-wave in the Swan-Ganz catheter pressure waveform in the setting of significant MR.
- Severe TR may produce systolic propulsion of the eyeballs, pulsatile varicose veins, a venous systolic thrill and murmur in the neck, a mid-diastolic murmur in severe regurgitation, and systolic hepatic pulsation.
- Atrial fibrillation or flutter is common as a result of right atrial enlargement secondary to elevated right atrial pressure.
- Table E1 summarizes the stages of tricuspid regurgitation.

ETIOLOGY

- Tricuspid valve dysfunction can occur with structurally normal (functional TR) or abnormal valves (primary TR).
- Functional TR involves conditions that lead to the dilation of the tricuspid annulus or right ventricular enlargement, including the following:
  1. Any cause of pulmonary hypertension (e.g., chronic obstructive pulmonary disease, pulmonary embolism, restrictive lung disease, collagen vascular disease, primary pulmonary hypertension, left to right shunts [i.e., ASD, VSD, anomalous pulmonary venous return]).
  2. Left-sided heart failure that leads to right-sided heart failure (this is the most common cause of right-sided heart failure).
  3. Dilated cardiomyopathy.
  4. Right ventricular infarction.
  5. Mitral stenosis or regurgitation.
- Primary TR involves conditions directly affecting the tricuspid valve apparatus, including the following:
  1. Rheumatic heart disease
  2. Congenital conditions (e.g., Ebstein anomaly—apical displacement of tricuspid valve, tricuspid atresia, cleft valve associated with atrioventricular canal malformations—primum ASD)
  3. Ischemic heart disease involving right ventricle with papillary muscle rupture
  4. Endocarditis, either bacterial (particularly related to intravenous drug use) or marantic (e.g., systemic lupus erythematosus, rheumatoid arthritis, and adenocarcinoma)
  5. Tricuspid valve prolapse or chordae rupture
  6. Carcinoid syndrome—can also lead to tricuspid stenosis
  7. Marfan syndrome
  8. Iatrogenic damage to the valve (e.g., pacemaker, implantable cardioverter-defibrillator, endomyocardial biopsy, anorectic drugs)
  9. External trauma (e.g., deceleration injury)
  10. Right atrial myxoma
  11. Collagen vascular diseases
  12. Myxomatous degeneration associated with tricuspid valve prolapse
  13. Radiation injury
  14. Endomyocardial fibrosis (important cause in tropical Africa)
  15. Metastatic cardiac tumors such as renal cell carcinoma, etc.

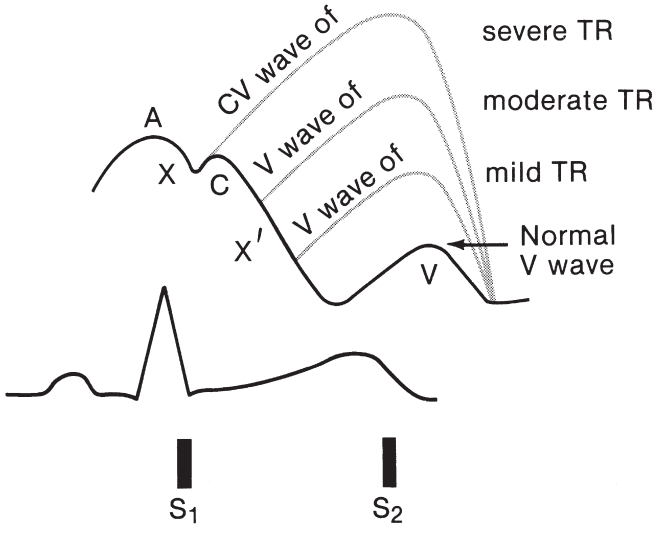

FIG. E1 The jugular venous pulse in tricuspid regurgitation. The jugular venous pulse wave normally drops during ventricular systole. As tricuspid regurgitation becomes more severe, the CV wave becomes more obvious during ventricular systole. *TR,* Tricuspid regurgitation. (From Conn R: *Current diagnosis,* ed 9, Philadelphia, 1997, Saunders.)

DIAGNOSIS

The diagnosis of TR is made noninvasively by physical examination and imaging techniques (e.g., echocardiography) and invasively by right-sided heart catheterization in selected cases.

DIFFERENTIAL DIAGNOSIS

On the basis of heart auscultation, the diagnosis of TR may be confused with other causes of systolic murmurs, such as mitral regurgitation, aortic stenosis, pulmonary stenosis, ventricular septal defect, and hypertrophic cardiomyopathy.

WORKUP

Any patient suspected of having significant TR should undergo the following:

- Chest x-ray
- ECG
- Echocardiogram (confirmatory) (Fig. E2)

TABLE E1 Stages of Tricuspid Regurgitation

Stage	Definition	Valve Anatomy	Valve Hemodynamics*	Hemodynamic Consequences	Symptoms
A	**At risk of TR**	*Primary:* Mild rheumatic change Mild prolapse Other (e.g., IE with vegetation, early carcinoid deposition, radiation) *Intraannular:* RV pacemaker or ICD lead Postcardiac transplantation (biopsy-related) *Functional:* Normal Early annular dilation	No or trace TR	None	None or in relation to other left heart or pulmonary/pulmonary vascular disease
B	**Progressive TR**	*Primary:* Progressive leaflet deterioration/ destruction Moderate to severe prolapse, limited chordal rupture *Functional:* Early annular dilation Moderate leaflet tethering	***Mild TR:*** Central jet area <5 cm^2 Vena contracta width not defined CW jet density and contour: Soft and parabolic Hepatic vein flow: Systolic dominance **Moderate TR:** Central jet area 5-10 cm^2 Vena contracta width not defined, but <0.70 cm CW jet density and contour: Dense, variable contour Hepatic vein flow: Systolic blunting	***Mild TR:*** RV/RA/IVC size normal **Moderate TR:** No RV enlargement No or mild RA enlargement No or mild IVC enlargement with normal respirophasic variation Normal RA pressure	None or in relation to other left heart or pulmonary/pulmonary vascular disease
C	**Asymptomatic severe TR**	*Primary:* Flail or grossly distorted leaflets *Functional:* Severe annular dilation (>40 mm or 21 mm/m^2) Marked leaflet tethering	***Severe TR:*** Central jet area >10 cm^2 Vena contracta width >0.7 cm CW jet density and contour: Dense, triangular with early peak Hepatic vein flow: Systolic reversal	RV/RA/IVC dilated with decreased IVC respirophasic variation Elevated RA pressure with "*c-V*" wave Diastolic interventricular septal flattening may be present	None, or in relation to other left-heart or pulmonary/pulmonary vascular disease
D	**Symptomatic severe TR**	*Primary:* Flail or grossly distorted leaflets *Functional:* Severe annular dilation (>40 mm or >21 mm/m^2) Marked leaflet tethering	***Severe TR:*** Central jet area >10 cm^2 Vena contracta width >0.70 cm CW jet density and contour: Dense, triangular with early peak Hepatic vein flow: Systolic reversal	RV/RA/IVC dilated with decreased IVC respirophasic variation Elevated RA pressure with "*c-V*" wave Diastolic interventricular septal flattening Reduced RV systolic function in late phase	Fatigue, palpitations, dyspnea, abdominal bloating, anorexia, edema

CW, Continuous-wave; *ICD,* implantable cardioverter-defibrillator; *IE,* infective endocarditis; *IVC,* inferior vena cava; *RA,* right atrium; *RV,* right ventricle; *TR,* tricuspid regurgitation.
*Several valve hemodynamic criteria are provided for assessment of TR severity, but not all criteria for each category are present in every patient. Classification of TR severity as mild, moderate, or severe also depends on image quality and integration of these parameters with clinical findings.
From Nishimura RA et al: 2014 AHA/ACCF guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 63:e57, 2014.

- Right-sided heart catheterization (in selected cases)
- CMR (in selected cases)

LABORATORY TESTS

ECG may show evidence of the following:
- Right atrial enlargement (e.g., P-wave amplitude in leads II or III or aVF of >2.5 mV)
- Right ventricular enlargement or hypertrophy (e.g., R:S ratio >1 in V_1, R >7 mm in V_1, or R wave in V_1+, S wave in V_5, or V_6 >10.5 mm)
- Right axis deviation—mean QRS axis between 100 and 270 degrees
- Atrial fibrillation

IMAGING STUDIES

- A chest x-ray may show the following:
  1. Evidence of chronic obstructive pulmonary disease (e.g., flattened diaphragms, barrel chest, dilated pulmonary arteries, increased retrosternal air space) or restrictive lung disease
  2. Enlarged right atrium
  3. Enlarged right ventricle
  4. Enlarged/prominent pulmonary arteries
- An echocardiogram (either transthoracic or transesophageal) will do the following:
  1. Distinguish primary from functional TR

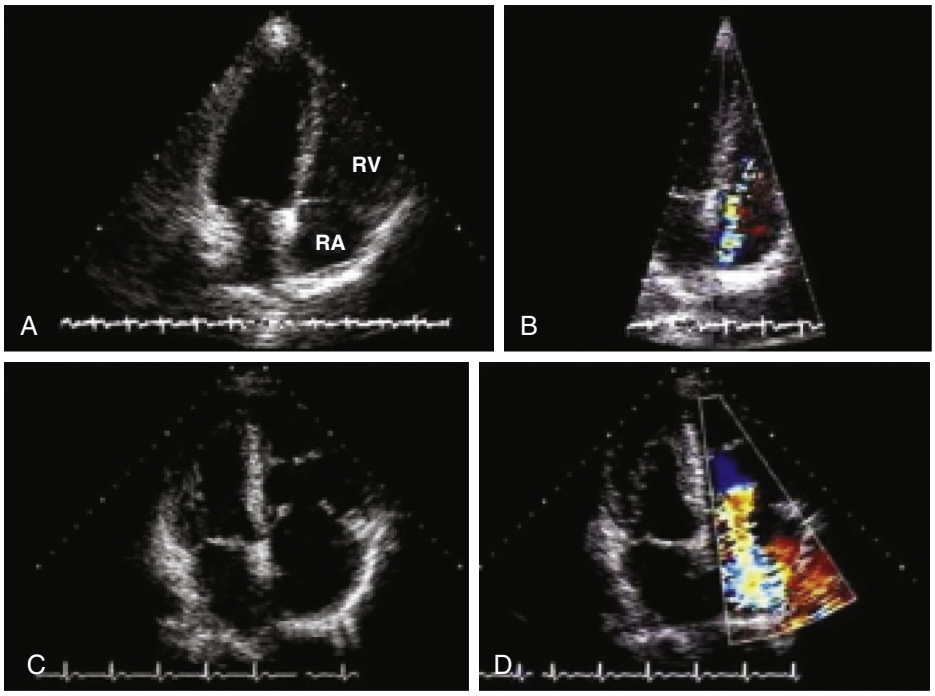

FIG. E2 Tricuspid regurgitation (TR) caused by carcinoid involvement of the tricuspid valve. Serial two-dimensional echocardiograms **(A** and **C)** and color Doppler studies **(B** and **D)** separated by 3 years are shown. **C,** After 3 years, severe thickening and fixation of the tricuspid leaflets are evident, with consequent severe TR and associated right ventricle *(RV)* and right atrial *(RA)* enlargement. (From Møller JE et al: Factors associated with progression of carcinoid heart disease, *N Engl J Med* 348:1005, 2003. In Mann DL et al: *Braunwald's heart disease,* ed 10, Philadelphia, 2015, Elsevier.)

2. Assess tricuspid valve structure and motion, measure annular size, and identify other cardiac abnormalities. Transesophageal echocardiogram is not typically needed since the tricuspid valve is an anterior structure easily assessed on transthoracic echocardiogram. Right ventricle, right atrium, and tricuspid annulus are often dilated in moderate to severe TR. 3D echocardiography can be helpful in analyzing complex valve anatomy and when tethering from a pacemaker or ICD lead is suspected
3. Estimate the severity of TR (vena contracta width >0.7 cm and systolic flow reversal in hepatic veins)
4. Estimate the pulmonary artery pressure
5. Exclude vegetation, mass, or prolapse
6. Assess left and right ventricular function

- CMR (cardiovascular magnetic resonance):
  1. If echocardiographic evaluation is poor
  2. Quantitative measurements of TR volume and regurgitant fraction
  3. RV volumes
  4. RV systolic function and ejection fraction
- Right-sided heart catheterization shows the following:
  1. Elevated right atrial and right ventricular systolic and end-diastolic pressures
  2. Large c-V waves

Rx TREATMENT

The treatment of TR is usually directed at the underlying cause.

NONPHARMACOLOGIC THERAPY

Oxygen therapy is beneficial for patients with functional TR caused by underlying pulmonary hypertension provoked by alveolar hypoxia.

ACUTE GENERAL Rx

- Severe TR with right-sided heart failure is typically treated with loop diuretics and aldosterone antagonists.
- In functional TR with left-sided heart failure, treatment should be targeted to the underlying disease process. If left ventricular systolic dysfunction is present, treatment includes standard therapies of preload reduction, afterload reduction, and inotropic therapy (see "Heart Failure").
- Improvement in functional TR can be seen with reversal of pulmonary hypertension by vasodilators, pulmonary thromboendarterectomy, or treatment of mitral stenosis. Structural TR treatment depends on the underlying cause.

CHRONIC Rx

- The American College of Cardiology/American Heart Association Guidelines Pertaining to the Surgical Management of Tricuspid Valve Disease/Regurgitation are summarized in Table E2.
- Moderate or severe TR of any cause is associated with increased mortality regardless of pulmonary artery systolic pressure or left ventricular ejection fraction.
- During recent years, annuloplasty has become an established surgical approach to significant TR. A recent study showed that tricuspid valve (TV) repair with an annuloplasty ring results in improved long-term outcomes.
- When the valve leaflet anatomy is not suitable for repair, valve replacement with a low-profile mechanical valve or bioprosthesis is often necessary. A bioprosthesis is almost always used due to the high rate of thromboembolic complications with mechanical prosthesis in the tricuspid position.
- In patients with TR due to refractory endocarditis (e.g., intravenous drug users), total excision of the diseased valve is done to eradicate the endocarditis without immediate replacement of the valve to avoid reinfection, and antibiotics are resumed. Initially, most patients tolerate the loss of the tricuspid valve without any difficulty. However, RV dysfunction usually occurs subsequently, and therefore a bioprosthetic valve may be inserted 6 to 9 mo after valve excision and control of infection.
- Some of the novel transcatheter approaches for TR that are currently under investigation include heterotopic implantation of the Edwards-Sapien XT valve in the inferior vena cava, and the use of other valve repair devices such as the MitraClip, the Mitralign or Trialign system, the TriCinch system, and the Forma spacer.

DISPOSITION

- Regardless of the cause, a greater-than-mild degree of TR is associated with decreased survival.

TABLE E2 ACC/AHA Guidelines for Intervention for Tricuspid Valve Disease[1]

Class	Indication	Loe
I	Tricuspid valve surgery is recommended for patients with severe TR (stages C and D) undergoing left-sided valve surgery.	C
	Tricuspid valve surgery is recommended for patients with severe TS at operation for left-sided valve disease.	C
	Tricuspid valve surgery is recommended for patients with isolated, symptomatic severe TS.	C
IIa	Tricuspid valve repair can be beneficial for patients with mild, moderate, or greater functional TR (stage B) at left-sided valve surgery with either tricuspid annular dilation or prior evidence of right-sided heart failure.	B
	Tricuspid valve surgery can be beneficial for patients with symptoms due to severe primary TR that are unresponsive to medical therapy (stage D).	C
IIb	Tricuspid valve repair may be considered for patients with moderate functional TR (stage B) and pulmonary artery hypertension at left-sided valve surgery.	C
	Tricuspid valve surgery may be considered for asymptomatic or minimally symptomatic patients with severe primary TR (stage C) and progressive degrees of moderate or greater RV dilation and/or systolic dysfunction.	C
	Reoperation for isolated tricuspid valve repair or replacement may be considered for persistent symptoms caused by severe TR (stage D) in patients who have undergone previous left-sided valve surgery and who do not have severe pulmonary hypertension or significant RV systolic dysfunction.	C
	Percutaneous balloon tricuspid commissurotomy might be considered in patients with isolated, symptomatic severe TS without accompanying TR.	C

LOE, Level of evidence; *RV,* right ventricular; *TR,* tricuspid regurgitation; *TS,* tricuspid stenosis.

[1]Nishimura R et al: 2013 AHA/ACCF guideline for valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 63:e57-e185, 2014.

From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

- Clinically insignificant TR can be detected by color Doppler imaging in many normal people. This is not an indication for either routine follow-up or prophylaxis against bacterial endocarditis.
- Mild and moderate TR are well tolerated during pregnancy. Women with severe TR are at higher risk for right-sided heart failure and atrial arrhythmias during pregnancy.
- Isolated TR with normal right ventricular function does not preclude an individual's involvement in competitive sports.

REFERRAL

For patients with significant symptomatic TR, a cardiology consultation is recommended.

PEARLS & CONSIDERATIONS

- TR that results from tricuspid valve prolapse is often associated with concurrent MV prolapse.
- Secondary TR commonly occurs in combination with left-sided valvular heart disease. It often does not improve, despite correction of the left-sided valve dysfunction.
- Functional tricuspid insufficiency, if left uncorrected, carries serious long-term consequences.
- Antibiotic prophylaxis for dental, gastrointestinal, or genitourinary procedures is no longer recommended for patients with only structural tricuspid valve abnormalities.
- Tricuspid annuloplasty at the time of MV surgery results in improved functional capacity without any increase in perioperative morbidity or mortality.
- If a donor heart develops TR after cardiac transplantation, tricuspid valve replacement with a biologic prosthesis is a safe, durable, and effective method of treating TR after transplantation. This allows for future endomyocardial biopsies to be performed. Mechanical valves should be avoided.
- In TR due to endocarditis in intravenous drug users, the diseased tricuspid valve is commonly excised without immediate replacement of the valve, and interval TV replacement is done 6 to 9 mo after the endocarditis has been completely treated with antibiotics to avoid re-infection of the bioprosthesis.

RELATED CONTENT

Tricuspid Regurgitation (Patient Information)

AUTHORS: **Reema Qureshi, MD,** and **Aravind Rao Kokkirala, MD, FACC**

SUGGESTED READING

Nishimura RA et al: AHA/ACC guideline for management of patients with valvular heart disease: a report of the American College of cardiology/American heart association Task Force on Practice guidelines, *Circulation* 129(23):e521-e643, 2014.

Tricuspid Stenosis

BASIC INFORMATION

DEFINITION

Tricuspid stenosis (TS) is an uncommon valvular pathology that is caused by the narrowing of the tricuspid valve orifice, which results in the restriction of right atrial emptying. TS is most often rheumatic in origin, and it often presents with a combination of regurgitation and stenosis.

SYNONYMS

Tricuspid valve stenosis
TS

ICD-10CM CODE
I07.0 Tricuspid stenosis

EPIDEMIOLOGY & DEMOGRAPHICS

- TS is most commonly caused by rheumatic heart disease, and it almost always occurs with associated mitral or aortic valve disease. In rheumatic heart disease, mitral and aortic valve involvement are much more common than tricuspid valve involvement.
- Carcinoid syndrome or prosthetic valve degeneration are the most common causes for TS in United States.
- Antibiotic therapy has made rheumatic heart disease and TS in the U.S. very rare.
- TS is present at autopsy in 15% of patients with rheumatic heart disease, but it is clinically significant in only 5%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Obstruction to tricuspid flow limits cardiac output and leads to elevated mean right atrial pressures even with a gradient as small as 5 mm Hg.
- As a result, most patients with significant TS have systemic venous congestion, jugular venous distention, ascites, and peripheral edema.
- Symptoms and physical examination findings usually depend on the presence and severity of concomitant mitral or aortic valve disease.
- Symptoms of right heart failure include fatigue, right upper quadrant abdominal pain (from hepatic congestion), ascites, hepatomegaly, and peripheral edema. Some complain of a fluttering discomfort in the neck caused by the tall "a" waves. The lungs are clear in isolated tricuspid stenosis, although tricuspid stenosis often coexists with mitral stenosis.
- Jugular venous distention, a prominent a wave that can sometimes approach the level of the right ventricular systolic pressure, slow rate of y descent that is barely appreciated, and palpable hepatic pulsations are noted during sinus rhythm.
- A right atrial pulsation may be palpated to the right of the sternum, and a diastolic thrill that increases with inspiration may be felt over the left sternal edge.
- An opening snap and a low-frequency diastolic murmur are best heard along the left lower sternal border of the fourth intercostal space. The murmur is softer, high-pitched, and shorter in duration as compared to mitral stenosis. The murmur is augmented by inspiration (i.e., Carvallo sign), leg raises, isotonic exercise, and squatting (all maneuvers that increase venous return to the right side of the heart).

ETIOLOGY

- Rheumatic heart disease results in the scarring of the valve leaflets starting at the leaflet tips, shortening of the chordae tendineae, and fusion of the commissures, thereby leading to the immobility of the valve leaflets and the narrowing of the tricuspid valve orifice.
- Other causes are congenital, infectious (e.g., endocarditis), metabolic, and enzymatic abnormalities (e.g., carcinoid syndrome, Whipple disease, Fabry disease); systemic rheumatic disease (Libman-Sacks endocarditis); right atrial or metastatic tumors; hypereosinophilic syndromes; and, rarely, scarring and adhesions as a result of complications of pacemaker placement. Other unusual causes include endocardial fibroelastosis and as a sequela to ergot alkaloid (methysergide or ergotamine) therapy. Most causes of tricuspid stenosis will result in tricuspid regurgitation as well.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Congenital tricuspid atresia or stenosis, as can be seen in Noonan syndrome (autosomal dominant disorder characterized by congenital heart defects, typically pulmonary valve stenosis and ASDs)
- Right heart diastolic dysfunction: Endomyocardial fibrosis or constrictive pericarditis, restrictive cardiomyopathies (however, restrictive cardiomyopathy and constrictive pericarditis demonstrate a steep y wave descent in the right atrial pressure tracings)
- Extrinsic compression of the right ventricle: Severe pectus excavatum, massive ascites, pleural effusion, pericardial effusion, or tumor
- Obstruction of right atrial emptying: Right atrial myxoma (although myxomas are typically found in the left atrium), metastatic tumor, right atrial thrombi, or tricuspid valve vegetation (particularly in association with a permanent pacemaker lead)

WORKUP

- Echocardiography is the diagnostic test of choice to evaluate the tricuspid valve.
- ECG is recommended to look for atrial arrhythmias, atrial fibrillation, or atrial flutter as a result of an enlarged right atrium. ECG in tricuspid stenosis may show tall atrial P waves more than 2.5 mm in the inferior leads (P pulmonale) with no right ventricular hypertrophy.
- Chest x-ray, which can demonstrate enlargement of the right atrium and IVC without enlarged pulmonary artery segment.
- Right heart catheterization is an option when echocardiography cannot be used to make a definitive diagnosis. Right heart catheterization can demonstrate prominent a wave and slow rate of Y descent.

IMAGING STUDIES

- Echocardiography reveals thickening and shortening of the tricuspid valve leaflets, restricted movement of the leaflets and the leaflet tips, a reduction in the diameter of the annulus, and diastolic doming of the valve. Evidence of right atrial enlargement and dilated IVC is present in most cases. For severe TS the mean gradient is typically more than 5 mm Hg at a heart rate of 60 to 80 bpm. Lower gradients may be seen with low stroke volume, and higher gradients can occur with coexisting tricuspid regurgitation. Transesophageal echocardiography is typically not of use since the tricuspid valve is an anterior structure and is easily visualized via transthoracic echocardiogram.
- Doppler echocardiography or cardiac catheterization demonstrates a reduced tricuspid valve area (characterized as severe when <1 cm^2), prolonged pressure half-time (severe when >190ms), and a diastolic pressure gradient across the tricuspid valve (normal gradient <1 mm Hg, and TS can be diagnosed with a mean pressure gradient as low as 2 mm Hg).
- Chest radiography may reveal an enlarged right atrium, dilated superior vena cava, and azygos vein with reduced pulmonary blood volume.

TREATMENT

NONPHARMACOLOGIC THERAPY

Salt and fluid restriction is essential to decrease peripheral edema.

GENERAL Rx

- Assess and treat the underlying cause of the valvular pathology.
- Treat bacterial endocarditis with antibiotics.
- Treat right atrial thrombus obstructing RV inflow with systemic anticoagulation (typically seen with dialysis catheters).
- Treat right atrial myxoma obstructing RV inflow with surgical resection.
- Manage right atrial volume overload with loop diuretics.
- Prescribe rate-controlling atrioventricular nodal blocking agents and anticoagulants for patients with atrial arrhythmias (atrial fibrillation and atrial flutter).

CHRONIC Rx

- Symptoms of systemic venous hypertension and congestion can be controlled with diuretics and angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, along with generalized salt and fluid restriction.

- Balloon valvuloplasty or dilation of the stenosed tricuspid valve has been shown to be effective, especially in patients with transvalvular pressure gradients 3 mm Hg and above, along with valve areas less than 1.5 cm^2. Patients with clinical evidence of systemic venous hypertension and congestion should be considered for valvotomy. However, tricuspid regurgitation that is characterized as more than mild is generally considered a contraindication to valvotomy because this can further worsen the tricuspid regurgitation. Tumor masses, vegetations, and thrombi are also contraindications to valvotomy.
- Tricuspid surgery is indicated in patients with severe TS at the time of left heart surgery or in patients with isolated symptomatic severe TS (class I recommendation). TS surgery is preferred over percutaneous balloon commissurotomy given that most TS is associated with regurgitation. Also, there is lack of long-term follow-up data on patients managed by percutaneous balloon commissurotomy.
- Tricuspid valve replacement is usually preferentially done with a large bioprosthesis, though no major difference in survival or adverse events has been identified when compared with mechanical valves in long-term follow-up. The current recommendation is that the choice of prosthesis should be individualized.

DISPOSITION

The natural course of severe TS is not well known.

REFERRAL

TS may be difficult to diagnose, so consultation with a cardiologist is recommended.

PEARLS & CONSIDERATIONS

- Rheumatic heart disease accounts for >90% of stenotic tricuspid valves.
- Rheumatic TS almost always occurs in association with mitral valve disease and sometimes with aortic valve disease.
- The majority of cases present with tricuspid regurgitation or a combination of regurgitation and stenosis.

COMMENTS

Tricuspid valve replacement carries a 30-day operative morbidity and mortality rate of 5% to 7% in addition to a high risk of right heart thrombus formation. Therefore, surgical procedures are reserved for patients who are not candidates for balloon dilation techniques. Unlike patients with mitral stenosis, patients with TS typically do not report dyspnea, orthopnea, or paroxysmal nocturnal dyspnea symptoms.

RELATED CONTENT

Tricuspid Stenosis (Patient Information)

AUTHORS: **Reema Qureshi, MD,** and **Aravind Rao Kokkirala, MD, FACC**

SUGGESTED READINGS

Nishimura RA et al: AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines, *Circulation* 129:e521-e643, 2014.

Rodés-Cabau J et al: Diagnosis and treatment of tricuspid valve disease: current and future perspectives, *Lancet* 388:2431-2442, 2016.

Tricyclic Antidepressant Overdose

BASIC INFORMATION

DEFINITION

Tricyclic antidepressants (TCAs) are secondary or tertiary amines that have variable abilities to inhibit reuptake of neurotransmitters (norepinephrine, dopamine, and serotonin) and to be anticholinergic, antihistaminic, and sedating. These properties are important to consider when prescribing these agents and when managing an intentional or accidental overdose.

SYNONYMS

Tricyclic antidepressant intoxication or poisoning
TCA OD

ICD-10CM CODE
T43.0 Poisoning by tricyclic and tetracyclic antidepressants

EPIDEMIOLOGY & DEMOGRAPHICS

- Pharmacokinetic interactions of TCAs are often clinically important. Table E1 summarizes selected drug interactions with tricyclic antidepressants.
- Commonly used TCAs include amitriptyline, imipramine, desipramine, nortriptyline, doxepin, amoxapine, clomipramine, and protriptyline.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Cardiovascular:
- Intraventricular conduction delay (QRS prolongation)
- Sinus tachycardia
- Atrioventricular block
- Prolongation of the QT interval
- Ventricular tachycardia
- Wide complex tachycardia without P waves.
- Refractory hypotension (the most common cause of death from TCA overdose)
- Late arrhythmias or sudden death (in addition to the arrhythmias, which occur during the first 24 to 48 hr; late problems can occur up to 5 days after the overdose)
- Fig. E1 illustrates common ECG rhythm abnormalities in tricyclic overdose

Central nervous system:
- Coma
- Delirium
- Myoclonus
- Seizures

Other:
- Hyperthermia
- Ileus
- Urinary retention
- Rhabdomyolysis
- Kidney failure
- Pulmonary complications (e.g., aspiration pneumonitis)
- Life-threatening overdose exists with the ingestion of >1 g of a TCA. Among patients who reach a hospital, most deaths occur within the first 24 hr; lack of initial symptoms can be deceptive

ETIOLOGY AND PATHOGENESIS

- Mechanisms of TCA cardiovascular toxicity (Table E2).
- CNS toxicity:
  1. Cholinergic blockade is believed to cause hyperthermia, ileus, urinary retention, pupillary dilation, delirium, and coma.
  2. The mechanism of myoclonus and seizures is not fully understood.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Cardiotoxicity from TCA can be confused with intoxication by drugs that cause QRS prolongation. These include class Ia antiarrhythmic agents (disopyramide, procainamide, quinidine), class Ic antiarrhythmic agents (encainide, flecainide, propafenone), cocaine, propranolol, quinine, chloroquine, neuroleptics, propoxyphene, and digoxin. Other causes of QRS prolongation include hyperkalemia, ischemic heart disease, cardiomyopathy, and cardiac conduction system dysfunction.

WORKUP

- Clinical presentation
- Knowledge of the overdose
- Although serum drug levels do not correlate well with toxicity, TCA concentration >1 mcg/ml can be life threatening; TCA concentration >3 mcg/ml is often fatal

TABLE E1 Selected Drug Interactions with Tricyclic Antidepressants

Drug	Potential Interaction
Carbamazepine	Decreased TCA plasma levels
Phenobarbital	
Rifampin	
Isoniazid	
Antipsychotics	Increased TCA plasma levels
Methylphenidate	
SSRIs	
Quinidine	
Propafenone	
Antifungals	
Macrolide antibiotics	
Verapamil	
Diltiazem	
Cimetidine	
Class I antiarrhythmics	Depression of cardiac conduction; ventricular arrhythmias
Guanethidine	Interference with antihypertensive effect
Clonidine	
Sympathomimetic amines (e.g., epinephrine)	Arrhythmias, hypertension (e.g., isoproterenol, epinephrine)
Antihypertensives	Hypotension
Vasodilator drugs	
Low-potency antipsychotics	
Anticholinergic drugs	Additive anticholinergic toxicity
MAOIs	Delirium, fever, convulsions
Sulfonylurea hypoglycemics	Hypoglycemia

MAOI, Monoamine oxidase inhibitor; *SSRI,* selective serotonin reuptake inhibitor; *TCA,* tricyclic antidepressant.
From Stern TA et al: *Massachusetts General Hospital handbook of general hospital psychiatry,* ed 7, Philadelphia, 2018, Elsevier.

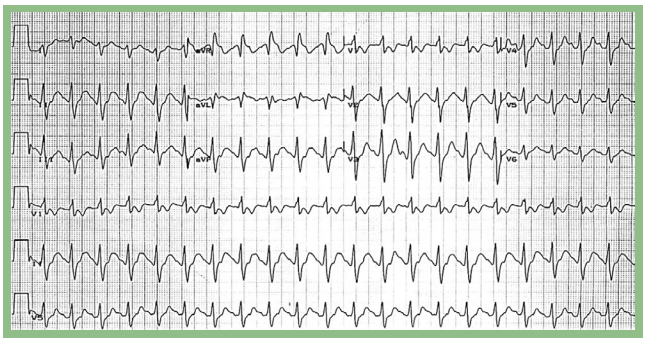

FIG. E1 Electrocardiographic findings in tricyclic antidepressant toxicity. Note the tachycardia, widened QRS interval (144 msec), and prominent R wave in lead aVR. These findings are consistent with blockade of fast sodium channels. (From Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.)

TABLE E2 Mechanism of Tricyclic Antidepressant Cardiovascular Toxicity

Toxic Effect	Mechanism
Conduction delays, arrhythmias	
QRS prolongation atrioventricular block	Cardiac sodium channel → slowed depolarization in atrioventricular node, His-Purkinje fibers, and ventricular myocardium
Sinus tachycardia	Cholinergic blockade, inhibition of norepinephrine reuptake
Ventricular tachycardia	
Monomorphic	Cardiac sodium channel inhibition → reentry
Torsades de pointes	Cardiac potassium channel inhibition → prolonged repolarization
Ventricular bradycardia	Impaired cardiac automaticity
Hypotension	
Vasodilation	Vascular alpha-adrenergic receptor blockade
Decreased cardiac contractility	Cardiac sodium channel inhibition → impaired excitation-contraction coupling

TABLE E3 Treatment of Complications of Tricyclic Antidepressant Toxicity

Toxic Effect	Treatment
Cardiovascular	
QRS prolongation	Hypertonic $NaHCO_3$ if QRS prolongation is marked or progressing; not clear if treatment is needed in the absence of hypotension or arrhythmias.
Hypotension	Intravascular volume expansion, $NaHCO_3$ vasopressors (norepinephrine) or inotropic agents (dopamine). Correct hyperthermia, acidosis, seizures. Consider mechanical support.
Ventricular tachycardia	$NaHCO_3$, lidocaine, overdrive pacing. Correct hypotension, hypothermia, acidosis, seizures.
Torsade des pointes	Overdrive pacing.
Ventricular bradycardia	Chronotropic agent (epinephrine), pacemaker.
Sinus tachycardia	Treatment rarely needed.
Atrioventricular block type II second or third degree	Pacemaker.
Hypertension	Rapidly titratable antihypertensive agent (nitroprusside).
Central Nervous System	
Delirium	Restraints, benzodiazepine. Neuromuscular blockade for hyperthermia, acidosis.
Seizures	Benzodiazepine. Neuromuscular blockade for hyperthermia, acidosis.
Coma	Intubation, ventilation if needed.
Other	
Hyperthermia	Control seizures, agitation. Cooling measures.
Acidosis	$NaHCO_3$ Correct hypotension, hypoventilation

- Baseline complete blood count, prothrombin time, blood urea nitrogen, creatinine, and electrolytes

Rx TREATMENT

ACUTE GENERAL Rx

- Initial measures:
  1. Hospitalization with cardiac monitoring as well as monitoring of vital signs and temperature.
  2. Initiate IV access.
  3. Administer activated charcoal with sorbitol.
  4. Large-bore tube gastric lavage is of unproven benefit.
  5. Ipecac is contraindicated.
  6. 12-lead ECG.
  7. If no evidence of cardiotoxicity has been noted during the first 6 hr of observation, further monitoring is not necessary; if there is evidence of cardiotoxicity, monitoring should continue for 24 hr after all signs of toxicity have resolved.
- See Table E3 for treatment of specific complications of TCA toxicity.
- Hemodialysis is not effective.
- When the patient is medically stable, psychiatric evaluation should be obtained.
- An algorithm for treatment of tricyclic antidepressant overdoses is described in Fig. E2.

AUTHOR: **Fred F. Ferri, MD**

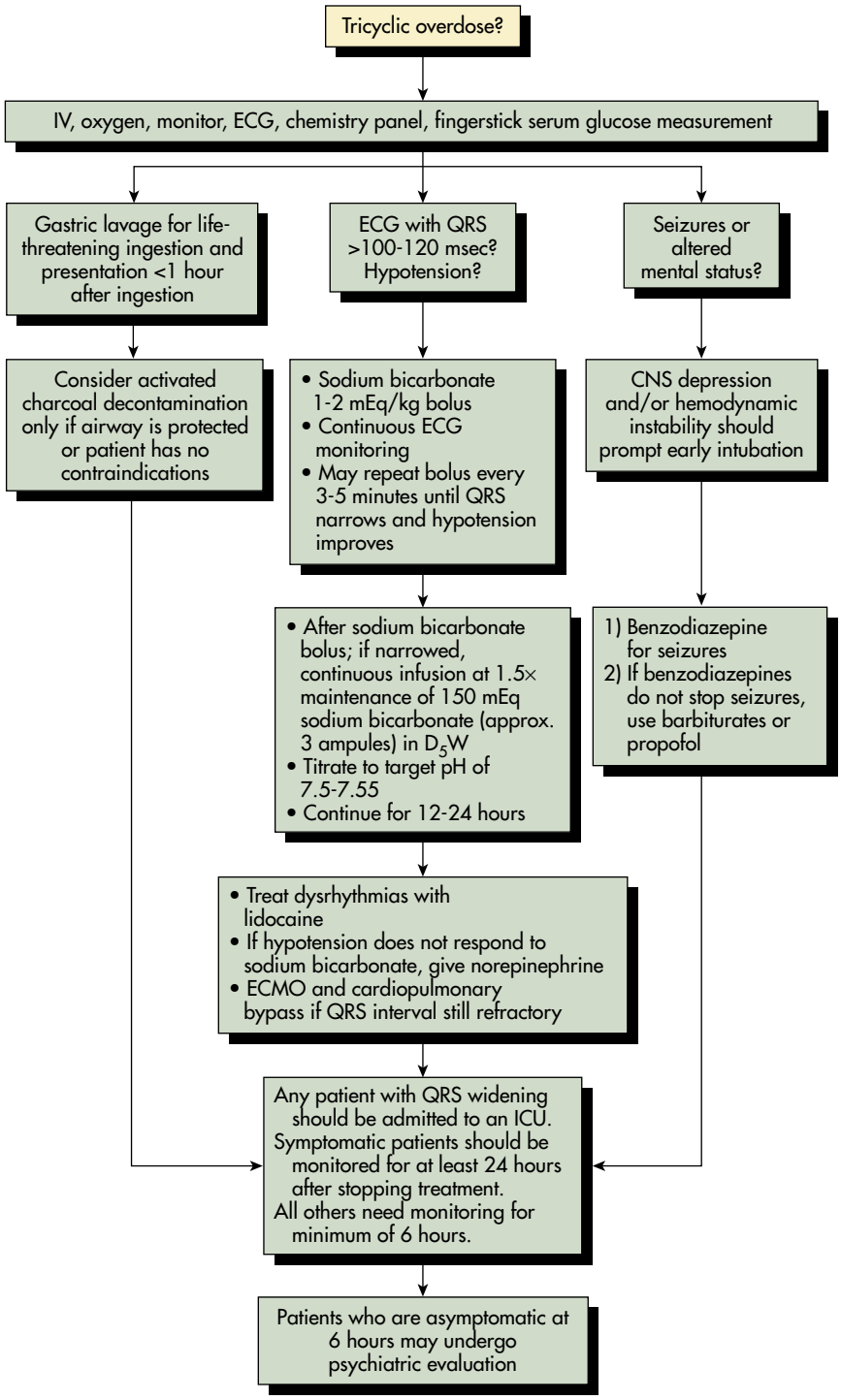

FIG. E2 Algorithm for treatment of tricyclic antidepressant overdoses. *CNS,* Central nervous system; *D5W,* 5% dextrose in water; *ECG,* electrocardiogram; *ECMO,* extracorporeal membrane oxygenation; *ICU,* intensive care unit; *IV,* intravenous. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

Trigeminal Neuralgia PTG

BASIC INFORMATION

DEFINITION

Trigeminal neuralgia is an intense, usually unilateral, paroxysmal, stabbing pain in the sensory distribution of the trigeminal (cranial nerve V) nerve.

SYNONYM

Tic douloureux ("painful tics/spasms")

ICD-10CM CODE
G50.0 Trigeminal neuralgia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 4 per 100,000
PEAK INCIDENCE: Incidence increases with age and peaks at 67 yr of age; onset in 90% of patients is after age 40.
PREVALENCE: 155 in 1 million
PREDOMINANT SEX AND AGE: Male:female ratio is 1:1.5.
RISK FACTORS: Most cases are idiopathic; age and multiple sclerosis are risk factors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients present with paroxysmal, unilateral facial pain that is usually described as shock-like, stabbing, or electric (Fig. 1).
- Pain can be spontaneous or triggered by touch, an air current, or activities such as shaving, eating, or brushing teeth.
- In severe cases, facial spasms can accompany the pain.
- Pain is usually described in distribution of the second (V2-maxillary) and third (V3-mandibular) divisions of the trigeminal nerve.
- The pain seldom lasts more than a few seconds to a minute.
- There is usually no sensory or motor loss.

ETIOLOGY

- Idiopathic or "classical": Cause usually unknown, likely an aberrant artery or vein compressing cranial nerve V at or near the pons. Neurovascular contact is also commonly found incidentally on imaging in asymptomatic individuals.
- Secondary: Accounts for up to 15% of cases; caused by nonvascular lesions such as a demyelinating plaque from multiple sclerosis or compression from a tumor near the pons.
- Box 1 summarizes causes of trigeminal neuralgia.

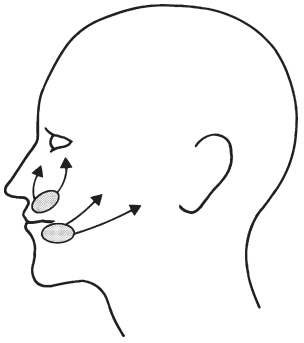

FIG. 1 Trigeminal neuralgia. The two most common sites of origin and radiation of pain are shown: mouth-ear and nose-orbit. Pain usually starts in the region of the encircled area and radiates in the directions shown.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Trigeminal neuropathy
- Primary stabbing headache
- Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT)
- Postherpetic neuralgia
- Glossopharyngeal neuralgia
- Dental pain

WORKUP

Trigeminal neuralgia is a clinical diagnosis (see previously).

IMAGING STUDIES

Neuroimaging (contrast-enhancing brain MRI) should be considered in young patients (<40 yr) with atypical symptoms (sensory loss, bilateral symptoms). MRI is useful to identify potential compressors or demyelinating causes. It detects nonvascular structure pathology in 15% of patients. Brain MRI is useful to identify neurovascular contact between trigeminal nerve and superior cerebellar artery.

TREATMENT

PHARMACOLOGIC Rx

- Carbamazepine 400 to 800 mg, 2 to 3 times daily divided dosing is the recommended initial treatment. This can be titrated to pain relief by 100 to 200 mg every 3 days to a maximum of 1200 mg divided bid or tid. HLA phenotype must be sent prior to starting in patients of East Asian ancestry due to high association with risk of Stevens-Johnson syndrome with carbamazepine.
- Oxcarbazepine can be used if carbamazepine is not tolerated due to side effects. Other medications include botulinum toxin type A, lidocaine, baclofen, phenytoin, gabapentin, clonazepam, lamotrigine, and levetiracetam.
- Drug combinations can be tried when one medication is partially effective before proceeding with secondary intervention.
- Spontaneous remissions may be seen in trigeminal neuralgia, and therefore periodic medication tapers should be considered if the patient is pain free.
- In the elderly population, caution should be used when initiating and titrating the above medications. Caution and extensive counseling should also be used in women of childbearing age when initiating treatment with anti-seizure medications.

BOX 1 Causes of Trigeminal Neuralgia

Classical
Neurovascular compression by an artery or vein

Symptomatic
Saccular aneurysm
Arteriovenous malformation
Tumors/mass-lesions at cerebellopontine angle:
- Vestibular schwannoma
- Meningioma
- Epidermoid

Primary demyelinating disorders:
- Multiple sclerosis
- Charcot-Marie-Tooth disease (rare)

Infiltrative disorders:
- Trigeminal amyloidoma

Nondemyelinating lesions:
- Small infarct or angioma in the brainstem

Familial

Modified from Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

NONPHARMACOLOGIC THERAPY

Patients with refractory pain eventually need secondary intervention such as microvascular decompression, selective nerve fiber destruction (rhizotomy), glycerol injection, thermal lesioning, chemical ablation, or gamma knife radiosurgery. Microvascular decompression is the only available nondestructive procedure and is effective in 75% of patients, and possesses observed long-term benefits.

DISPOSITION

- Most patients are responsive to initial pharmacologic treatment. Spontaneous remission is possible.
- Medical management is eventually ineffective in 30% to 50% of patients.

REFERRAL

Referral to a neurologist is appropriate if there is uncertainty about diagnosis or if symptoms are refractory to conservative management.

PEARLS & CONSIDERATIONS

In a young patient with trigeminal neuralgia, secondary causes such as multiple sclerosis should be considered, and an MRI of the head obtained. In secondary disease, initial therapy should address underlying secondary causes.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Trigeminal Neuralgia (Patient Information)

AUTHOR: **Jonathan H. Smith, MD**

SUGGESTED READING

Maarbjerg S et al: Significance of neurovascular contact in classical trigeminal neuralgia, *Brain* 138:311-319, 2015.

Yang F et al: Efficacy of 8 different drug treatments for patients with trigeminal neuralgia: a network meta-analysis, *Clin J Pain* 34:686-690, 2018.

BASIC INFORMATION

DEFINITION

Trigger finger refers to an inflammatory process involving the flexor tendon and A1 pulley that can lead to triggering of the digit. Fibroosseous pulleys along the fingers serve to tether down the flexor tendon and prevent bowstringing. Degenerative and inflammatory changes to the pulley can result in pain and difficulty flexing or extending the affected digit, as its tendon is no longer able to smoothly glide along the pulley (Fig. E1) (the fibroosseous tunnel that guides the flexor tendons of the fingers during flexion and extension). Over time, a nodule can develop on the flexor tendon at level of the A1 pulley causing a catching and popping phenomenon in patients, which can be painful and limit function. At the end stage of the condition, the patient may have to manually flex or extend the digit, as active motion is now completely limited.

SYNONYMS

Digital stenosing tenosynovitis
Stenosing flexor tenosynovitis
Stenosing tendovaginitis

ICD-10CM CODES

M65.30	Trigger finger, unspecified finger
M65.321	Trigger finger, right index finger
M65.322	Trigger finger, left index finger
M65.329	Trigger finger, unspecified index finger
M65.331	Trigger finger, right middle finger
M65.332	Trigger finger, left middle finger
M65.339	Trigger finger, unspecified middle finger
M65.341	Trigger finger, right ring finger
M65.342	Trigger finger, left ring finger
M65.349	Trigger finger, unspecified ring finger
M65.351	Trigger finger, right little finger
M65.352	Trigger finger, left little finger
M65.359	Trigger finger, unspecified little finger

EPIDEMIOLOGY & DEMOGRAPHICS

Trigger finger is one of the most common causes of hand pain in adults, with general prevalence of about 2% to 3% in the general population. Diabetics have almost a 10% lifetime risk of developing a trigger finger and tend to do worse with nonoperative management. The thumb and ring fingers are the most commonly affected digits; however, the condition can occur in any finger.
PREDOMINANT SEX AND AGE: Female:male ratio of 4:1. Trigger finger can be found in all age groups but is most commonly found in patients in the fifth and sixth decade of life.
RISK FACTOR: Most cases are spontaneous, without preceding trauma or alteration in activity level. However, some authors consider trigger finger to be associated with repetitive use occupations or jobs involving gripping or lifting. Patients with diabetes mellitus and rheumatoid arthritis are at increased risk.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Tenosynovitis of the flexor tendon always precedes the mechanical symptoms of triggering, resulting in pain over the flexor tendon around the palmar metacarpophalangeal (MCP) joint with palpation, passive finger extension, or isometric flexion.
- Triggering may be actively correctable (patient can extend finger with a click) or passively correctable (patient can extend finger using another finger or hand).
- Prolonged triggering may result in a flexion contracture at the proximal interphalangeal (PIP) joint; treatment at this stage often results in a poorer outcome.
- A palpable tender nodule may be noted just proximal to the palmar aspect of the MCP joint of the affected digit.

ETIOLOGY

Although there are many theories, there is no definitive cause of trigger finger. While most cases are idiopathic in nature, there are increased incidences in patients with diabetes, rheumatoid arthritis, and hypothyroidism, suggesting that alteration to the collagen or other components of the flexor tendon or A1 pulley may be a cause. Histologic review of the A1 pulley shows chondrocyte proliferation and an increase in matrix glycosaminoglycans, suggesting that repetitive compression of the A1 pulley and the flexor tendon may be implicated.

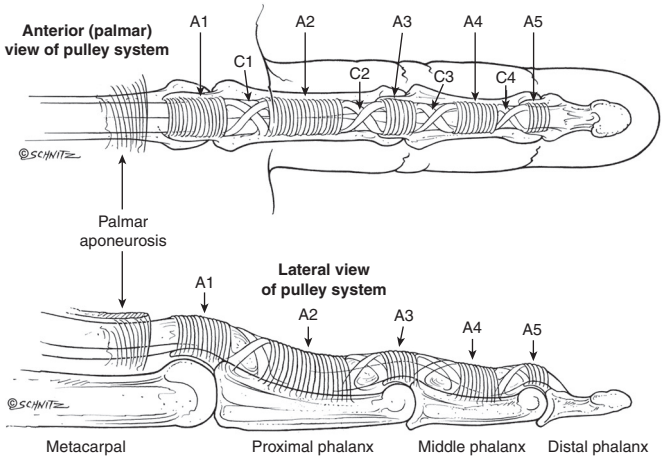

FIG. E1 The digital pulley system of the fingers. (From Ryzewicz M, Wolf JM: Trigger digits: principles, management, and complications, *J Hand Surg* 31(1):135, 2006.)

DIAGNOSIS

Based primarily on clinical history and physical examination

DIFFERENTIAL DIAGNOSIS

- Dupuytren contracture
- Infectious flexor tenosynovitis
- Proliferative tenosynovitis
- Ulnar collateral ligament injury (gamekeeper's thumb)
- Carpal tunnel syndrome
- Extensor tendon rupture
- Sagittal band rupture
- PIP contracture
- MCP arthritis
- Diabetic cheiroarthropathy

WORKUP

Rarely indicated unless an undiagnosed systemic cause (diabetes, rheumatoid arthritis, hypothyroidism) is considered or to rule out infection. It is a clinical diagnosis mostly obtained by history and physical examination.

LABORATORY TESTS

- Indicated when concerned for specific contributing factors or differential diagnosis
- Complete blood count with differential, C-reactive protein, sedimentation rate if concerned for infection
- Blood glucose, Hb^{A1c}
- Thyroid function tests
- Rheumatoid factor/anti-CCP antibody

IMAGING STUDIES

- X-rays are usually not indicated unless there is concern for fracture, foreign body, or dislocation/subluxation/erosion of a joint.
- MRI or ultrasound may be indicated for differential diagnoses of the surrounding soft tissues (e.g., ulnar collateral ligament tear).

TREATMENT

The goals of treatment are to reduce pain, swelling and inflammation in the flexor tendon sheath and allow smooth movement of the tendon when the finger is flexed or extended.

INITIAL NONOPERATIVE TREATMENT

- Rest, including ice, night splinting, or buddy taping to the adjacent finger, as much as possible for 4 to 6 wk.
- Pediatric trigger thumb responds well to intermittent extension splinting for flexible (nonfixed) deformities

- Use of gloves and damping tape to widen grips
- Physiotherapy with stretching and heat
- Oral nonsteroidal antiinflammatory medications have little supporting evidence

SUBSEQUENT NONOPERATIVE TREATMENT

- Injection of the tendon sheath or subcutaneous tissue around the sheath with a mixture of a steroid (usually triamcinolone, methylprednisolone, or betamethasone) and local anesthetic (e.g., lidocaine) is indicated for adult patients (Fig. E2). Steroid injections can transiently increase blood glucose levels in diabetic patients and are typically not as effective. Patients must be informed of this possibility before an injection is undertaken.
- If symptoms do not resolve or permanently improve, up to two repeat injections can be safe and efficacious.

SURGICAL TREATMENT

- Surgical release is indicated in patients with symptoms refractory to nonoperative care.

FIG. E2 Injection into the palm for trigger finger. (From Carr A, Hamilton W: *Orthopedics in primary care,* ed 2, Philadelphia, 2005, WB Saunders.)

- Percutaneous or open surgical release can be performed.
- Postoperative recurrence rate is about 3%.

DISPOSITION

- After steroid injection, symptoms usually resolve in 3 to 5 days, and locking resolves in most cases around 2 to 3 wk.
- If symptoms recur, one or two repeat steroid injections have a good chance to improve symptoms.
- Classically, diabetic patients have a lower success rate with steroid injections and surgical intervention compared to nondiabetic patients.

REFERRAL

Consultation with hand specialist is indicated with failure of nonsurgical management.

PEARLS & CONSIDERATIONS

COMMENTS

If more than one digit is involved, a workup for a contributing systemic disorder may be prudent.

RELATED CONTENT

Trigger Finger (Patient Information)

AUTHORS: **Shyam A. PateL, MD,** and **Devan D. Patel, MD**

SUGGESTED READINGS

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Womack ME et al: Treatment of paediatric trigger finger: a systematic review and treatment algorithm, *J Child Orthop* 12(3):209-2017, 2018.

Trochanteric Pain Syndrome (Trochanteric Bursitis) PTG

BASIC INFORMATION

DEFINITION

Greater trochanteric pain syndrome (GTPS) is a term used to describe chronic pain overlying lateral aspect of the hip. There are overlaps of trochanteric bursitis (TB) and GTPS. Unlike TB, GTPS is rarely accompanied by the principal symptoms of inflammation including erythema, edema, or warmth. GTPS often mimics pain generated from other sources such as myofascial pain, degenerative joint disease, and spinal pathology. Components of GTPS include tendinopathies and tears, bursal inflammation, and effusion.

SYNONYMS

Greater trochanteric pain syndrome
GTPS
Trochanteric bursitis
Trochanteric tendinitis

ICD-10CM CODES

M70.60 Trochanteric bursitis, unspecified hip
M70.61 Trochanteric bursitis, right hip
M70.62 Trochanteric bursitis, left hip

EPIDEMIOLOGY & DEMOGRAPHICS

- This commonly diagnosed regional pain syndrome is estimated to affect between 10% and 25% of the general population.
- In the primary care setting, the incidence of greater trochanteric pain is reported to be around 1.8 patients per 1000 per yr.
- Incidence peaks between the fourth and sixth decades of life but can occur at any age.
- Occurs more often in females than males (ratio of 4:1).
- One study found the prevalence of GTPS to be 17.6%, being higher in women and in patients with coexisting LBP, OA, ITB tenderness, and obesity.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- GTPS typically presents as chronic, persistent pain in the lateral hip and/or buttock that is exacerbated by lying on affected side, prolonged standing, driving, climbing stairs, running, or other high-impact activities.
- Pain may radiate along lateral aspect of the ipsilateral knee.
- Tenderness along the lateral or posterior aspect of the greater trochanter (Fig. E1).
- Pain can be reproduced by 10 provoking tests: Palpation of the greater trochanter, resisted external derotation test, modified resisted external derotation test, standard and modified Ober test, Patrick or FABER test, resisted hip abduction, single-leg stance test, and the resisted hip internal rotation test.

ETIOLOGY

- GTPS can be caused by repetitive high-intensity use of the tensor fasciae and gluteus medius over the outer femur trauma, infections such as tuberculosis, and crystal deposition.
- It can occur with other conditions such as osteoarthritis of the knee and hip, RA, sacroiliac joint disorders, leg length discrepancy, ankle sprain, and bunions of the feet causing changes in the patient's gait placing varus stress on the hip joint.
- It can also occur as a complication resulting from arthroscopic surgery of the hip (estimated 1.4% of cases). Cases with previous joint replacement were associated with worse outcomes.

DIFFERENTIAL DIAGNOSIS

- Piriformis tendinopathy
- L2 and L3 lumbar radiculopathy, and lumbar facet syndrome
- Iliotibial band syndrome
- Osteoarthritis of the hip
- Osteonecrosis of the hip
- Stress fracture of the femoral neck
- Meralgia paresthetica
- Acetabular labral tear
- Iliopsoas bursitis
- Osteomyelitis
- Metastatic bone disease
- Septic or pyogenic arthritis
- Gluteal medius tendon tears
- Abductor tendon tear (Table E1)

WORKUP

Since there is a wide differential for lateral hip pain, GTPS can be a challenging diagnosis to reach. Complete neurologic and musculoskeletal examination should be performed, including back, bilateral hip, knee, and observation of gait. Usually tenderness to palpation over the greater trochanter, pain with resisted abduction, and positive Patrick/FABER test are found.

LABORATORY TESTS

Not indicated in straightforward cases

IMAGING STUDIES

- Plain radiography: Plain x-rays are usually normal, but other potential causes can be excluded, including OA, femoroacetabular impingement, and fractures. Calcifications over the greater trochanter may be seen in 40% of patients presenting with GTPS.
- Ultrasound: Simple, dynamic, inexpensive test that can be very useful in establishing the cause of lateral hip pain.

FIG. E1 Typical location of pain in trochanteric bursitis syndrome. This is also a frequent pain radiation site for lumbar spine lesion, various nerve compression syndromes, and hip disease, particularly in osteonecrosis of the femoral head.

- CT and MRI will depict both osseous and soft tissue pathology but are not usually warranted unless the physician suspects associated conditions that would affect treatment decisions. MRI shows increased signal in bursitis, which can be found in symptomatic as well as asymptomatic patients.

Rx TREATMENT

Most cases of GTPS are self-limiting and tend to resolve with conservative measures.

NONPHARMACOLOGIC THERAPY

- Physical therapy and iliotibial band stretching exercises can reduce irritation of the trochanteric bursa area
- Warm compresses
- Ultrasound therapy
- Cryotherapy
- Treat gait disturbance by knee brace, shoe lift, ankle supports, and foot orthotics for the specific underlying conditions

ACUTE GENERAL Rx

- NSAIDs for pain relief: Ibuprofen 800 mg PO tid or naproxen 500 mg PO bid
- Topical corticosteroids delivered by percutaneous phonophoresis
- Corticosteroid injection
- Regional anesthetic block can be used as a treatment and may also help differentiate from referred pain

CHRONIC Rx

- Most patients respond to NSAIDs and/or nonpharmacologic therapy.
- Steroid injection: ~70% of patients respond after first injection and >90% respond after the second injection.
- Twenty-five percent of patients who receive steroid injection may experience relapse.
- A recent trial revealed that hip function improvement was greater with education plus exercise than with corticosteroid injections.[1]
- While the majority of patients with GTPS will improve with nonoperative management, endoscopic iliotibial band release and trochanteric bursectomy, with or without iliotibial band release, have shown significant benefit with minimum postoperative complications; gluteal tendon repair may also be effective treatment for severe recalcitrant cases.

REFERRAL

- Physical therapy
- Rheumatology or orthopedics referral if steroid injection therapy is indicated
- Orthopedics for possible bursectomy in chronic refractory cases

[1] Mellor R et al: Education plus exercise versus corticosteroid injection use versus a wait and see approach on global outcome and pain from gluteal tendinopathy: prospective, single blinded, randomised clinical trial, *BMJ* 361:k:1662, 2018.

TABLE E1 Trochanteric Bursitis Versus Abductor Tendon Tear

	Trochanteric bursitis	Abductor tendon tear
Symptoms	Peritrochanteric pain and tenderness to palpation over the greater trochanter Night pain	Peritrochanteric pain and tenderness to palpation over the greater trochanter Night pain
Examination	± Abductor limp ± Trendelenburg gait ± Abductor weakness	Abductor limp Trendelenburg gait Abductor weakness
MRI findings	Evidence of bursitis and increased signals at the greater trochanter Although tendinitis can be present, the tendon is intact with no tears	Tendinosis and tear of the abductor tendons with alterations in tendon signal and caliber Partial thickness and complete tears of the gluteus minimus or medius tendons
Nonoperative treatment	Walking aids (walker vs cane) NSAIDs Selective use of peritrochanteric injection with corticosteroid Structured physical therapy for strengthening	Walking aids (walker vs cane) NSAIDs Selective use of peritrochanteric injection with corticosteroid Structured physical therapy for strengthening
Operative treatment	Bursectomy (bursitis is recalcitrant to nonoperative treatment)	Tendon repair with suture anchors

MRI, Magnetic resonance imaging; *NSAID,* nonsteroidal antiinflammatory drug.
From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.

PEARLS & CONSIDERATIONS

Patients with GTPS will commonly report "hip" pain. The physical examination readily distinguishes GTPS from other hip pathologies. Relief of pain with local corticosteroid injection is helpful in differentiating trochanteric bursitis from referred pain.

COMMENTS

- The absence of limitation in range of motion differentiates trochanteric bursitis from degenerative joint disease of the hip.
- Localization of pain over the lateral hip and thigh differentiates trochanteric bursitis from meralgia paresthetica located over the anterolateral thigh and osteoarthritis located over the inner thigh groin area.

RELATED CONTENT

Trochanteric Bursitis (Patient Information)

AUTHOR: **Rasha B. Alqadi, MD**

SUGGESTED READINGS

Bolton WS et al: Do ultrasound-guided trochanteric bursa injections of corticosteroid for greater trochanteric pain syndrome provide sustained benefit, and are imaging features associated with treatment response?, *Clin Radiol* 73(5):505.e9 -505.e15, 2018. PMID: 29273226.

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Drummond J et al: The outcome of endoscopy for recalcitrant greater trochanteric pain syndrome, *Arch Orthop Trauma Surg* 138(11):1547-1554, 2016.

Ganderton C et al: Demystifying the clinical diagnosis of greater trochanteric pain syndrome in women, *J Womens Health (Larchmt)* 26(6):633-643, 2016.

Ganderton C et al: Gluteal loading versus sham exercises to improve pain and dysfunction in postmenopausal women with greater trochanteric pain syndrome: a randomized controlled trial, *J Womens Health (Larchmt)* 27(6):815-829, 2018. PMID: 29715073.

Lustenberger D et al: Efficacy of treatment of trochanteric bursitis: a systemic review, *Clin J Sport Med* 21:447, 2011.

Mallow M, Nazarian LN: Greater trochanteric pain syndrome diagnosis and treatment, *Phys Med Rehabil Clin N Am* 25(2):279–289, 2014.

Nurkovic J et al: Treatment of trochanteric bursitis: our experience, *J Phys Ther Sci* 28(7):2078-2081, 2016.

Zeman P et al: Clinical results of endoscopic treatment of greater trochanteric pain syndrome, *Acta Chir Orthop Traumatol Cech* 84(3):168-174, 2017.

Tropical Sprue

BASIC INFORMATION

DEFINITION

Tropical sprue is a malabsorption syndrome occurring primarily in tropical regions, including Puerto Rico, India, and Southeast Asia. The clinical features of tropical sprue include anorexia, diarrhea, weight loss, abdominal pain, and steatorrhea; these symptoms can develop in expatriates even several months after returning to temperate regions.

SYNONYMS

Postinfectious tropical malabsorption
"Tropical enteropathy," referring to a subclinical form of tropical sprue

ICD-10CM CODE
K90.1 Tropical sprue

EPIDEMIOLOGY & DEMOGRAPHICS

- Tropical sprue is endemic in tropical regions of Venezuela, Colombia, the Middle East, the Far East, the Caribbean (Puerto Rico, Haiti, Dominican Republic, Cuba), and India.
- The disease affects mainly adults, although it has been reported in all age groups.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The classic clinical features of tropical sprue are nonspecific and simply reflect the symptom of malabsorption. Onset is generally not insidious, and most patients can pinpoint when their disorder began.
- Diffuse, nonspecific abdominal tenderness and distention. Abdominal pain is crampy in nature.
- Low-grade fever.
- Glossitis, cheilosis, hyperkeratosis, hyperpigmentation (Fig. E1).
- Diarrhea, often with mucus and foul-smelling stools from fat malabsorption.
- Nausea, which leads to decreased appetite and decreased oral intake.
- Lactose intolerance often develops early in the course of tropical sprue.

ETIOLOGY

Fig. E2 illustrates the etiopathogenesis of sprue.

DIFFERENTIAL DIAGNOSIS

- Celiac disease
- Parasitic infestation
- Inflammatory bowel disease
- Other causes of malabsorption (e.g., Whipple disease)
- Lymphoma
- Pancreatic tumor
- Intestinal tuberculosis
- Microsporidia-associated HIV enteropathy

WORKUP

Diagnostic workup includes a comprehensive history (especially travel history), physical examination, laboratory evidence of malabsorption (see the following), and jejunal biopsy; the biopsy results are nonspecific, with blunting, atrophy, and even disappearance of the villi and subepithelial lymphocytic infiltration (Fig. E3). Partial villus atrophy distinguishes tropical sprue histologically from celiac sprue, which reveals flattened mucosa.

LABORATORY TESTS

- Megaloblastic anemia (>50% of cases)
- Vitamin B_{12} deficiency, folate deficiency
- Abnormal D-xylose absorption (72-hr fecal fat determination or serum carotene concentration)
- Stool examination to exclude *Giardia* spp.

IMAGING STUDIES

Gastrointestinal series with small-bowel follow-through may reveal coarsening of the jejunal folds.

FIG. E1 Hyperpigmentation of the palms in a patient with tropical sprue. This finding often is seen in southern Indian patients with tropical sprue and has been ascribed to vitamin B_{12} deficiency. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Saunders.)

TREATMENT

NONPHARMACOLOGIC THERAPY

Monitoring of weight and calorie intake

ACUTE GENERAL Rx

- Folic acid therapy (5 mg bid for 2 wk followed by a maintenance dose of 1 mg tid) will improve anemia and malabsorption in more than two thirds of patients.
- Tetracycline 250 mg qid for 4 to 6 wk in individuals who have returned to temperate zones, up to 6 mo in patients in endemic areas; ampicillin 500 mg bid for at least 4 wk in patients intolerant to tetracycline.
- Correction of vitamin B_{12} deficiency: Vitamin B_{12} 1000 mcg IM weekly for 4 wk, then monthly for 3 to 6 mo.
- Correction of other nutritional deficiencies (e.g., calcium, iron).

DISPOSITION

Complete recovery with appropriate therapy

REFERRAL

Gastrointestinal referral for jejunal biopsy

PEARLS & CONSIDERATIONS

COMMENTS

- Tropical sprue should be considered in any patient who presents with chronic diarrhea, weight loss, and malabsorption, especially if there is significant travel and exposure history.
- Important factors in the medical history in addition to travel history are use of medications that may predispose to a small-bowel overgrowth, HIV exposure (increased risk of chronic diarrhea), and any surgical procedure that may predispose to blind loop syndrome.
- Most of the functional changes in tropical sprue may be related to small-bowel mucosal damage; however, there is also dysfunctional hormonal regulation of the gut (increased enteroglucagon and motilin levels, decreased postprandial insulin and gastric inhibitory peptide), and decreased ability of the colon to absorb water.
- Even with prolonged therapy relapses can occur; however, some may be attributable to reexposure to an infecting organism rather than relapsing disease.

AUTHOR: **Fred F. Ferri, MD**

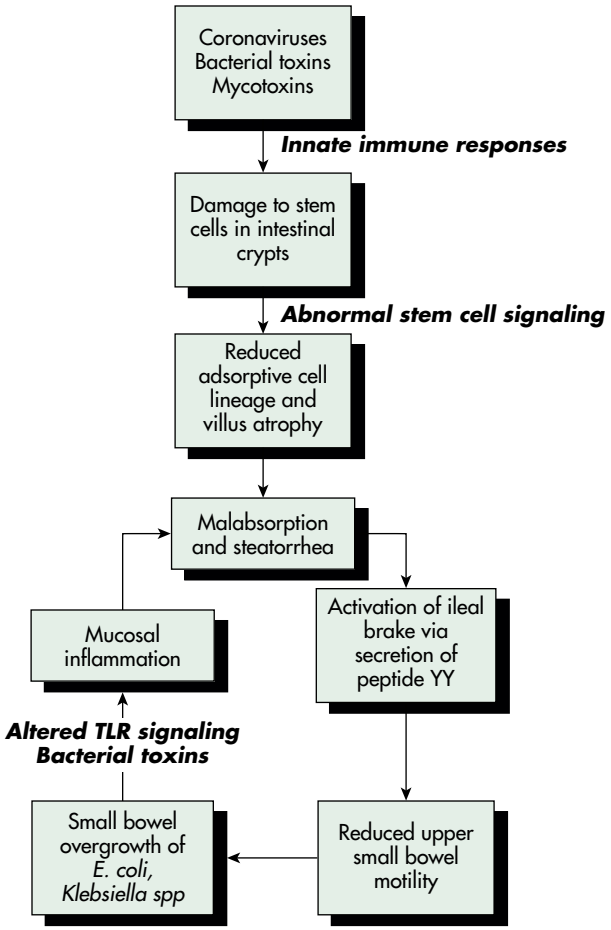

FIG. E2 Etiopathogenesis of sprue. This figure summarizes our current understanding of how etiologic agents that target intestinal epithelial stem cells lead to mucosal damage and malabsorption. This is perpetuated by small intestinal bacterial colonization because of ileal production of peptide YY, with resultant small bowel dysmotility. *TLR,* Toll-like receptor. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

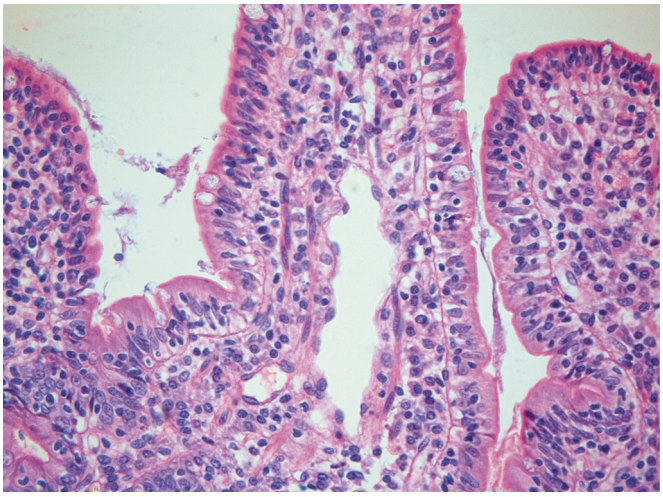

FIG. E3 Small intestinal mucosal biopsy from a patient with tropical sprue, showing an increase in intraepithelial lymphocytes. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

Tuberculosis, Miliary

BASIC INFORMATION

DEFINITION

Miliary tuberculosis (TB) is an infection of disseminated hematogenous disease, caused by the bacterium *Mycobacterium tuberculosis* (Mtb), and is often characterized as resembling millet seeds on pathologic or radiologic examination. Extrapulmonary disease may occur in virtually every organ site.

SYNONYM

Disseminated TB

ICD-10CM CODE
A19.9 Miliary tuberculosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): More than 38% of AIDS patients with TB have disseminated disease, often with concurrent pulmonary and extrapulmonary active sites. (See "Tuberculosis, Pulmonary" in Section I.)

PREVALENCE (IN U.S.):

- Undetermined
- Highest prevalence:
  1. AIDS patients
  2. Minorities
  3. Children
  4. Foreign-born persons
  5. Elderly

PREDOMINANT SEX:

- No specific predilection
- Male predominance in AIDS, shelters, and prisons reflected in disproportionate male TB incidence

PREDOMINANT AGE: Predominantly among 24 to 45 yr

PEAK INCIDENCE: HIV-positive patients, regardless of age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- See also "Etiology"
- Common symptoms:
  1. High intermittent fever (93%)
  2. Night sweats (79%)
  3. Weight loss (85%)
  4. Dyspnea (64%)
  5. Cough (82%)
- Symptoms referable to individual organ systems may predominate:
  1. Meninges
  2. Pericardium
  3. Liver
  4. Kidney
  5. Bone
  6. GI tract
  7. Lymph nodes
  8. Serous spaces:
     a. Pleural
     b. Pericardial
     c. Peritoneal
     d. Joint
  9. Skin
  10. Lung: Cough, shortness of breath
- Adrenal insufficiency possible, caused by infection of adrenal gland
- Pancytopenia:
  1. With fever and weight loss *or*
  2. Without other localizing symptoms or signs *or*
  3. With only splenomegaly
- TB hepatitis:
  1. Tender liver
  2. Obstructive enzymes (alkaline phosphatase) elevated out of proportion to minimal hepatocellular enzymes (SGOT, SGPT) and bilirubin
- TB meningitis:
  1. Gradual-onset headache
  2. Minimal meningeal signs
  3. Malaise
  4. Low-grade fever (may be absent)
  5. Sudden stupor or coma
  6. Cranial nerve VI palsy
- TB pericarditis:
  1. Effusions resembling TB pleurisy
  2. Cardiac tamponade
- Skeletal TB:
  1. Large joint arthritis (with effusions resembling TB pericarditis)
  2. Bone lesions (especially ribs)
  3. Pott disease:
     a. TB spondylitis, especially of lower thoracic spine
     b. Paraspinous TB abscess
     c. Possible psoas abscess
     d. Frequent cord compression (often relieved by steroids)
- Genitourinary TB:
  1. Renal TB:
     a. Papillary necrosis
     b. Destruction of renal pelvis
     c. Strictures of upper third of ureters
     d. Hematuria
     e. Pyuria with misleading bacterial cultures
     f. Preserved renal function
  2. TB orchitis or epididymitis:
     a. Scrotal mass
     b. Draining abscess
  3. Chronic prostatic TB
- GI TB:
  1. Diarrhea
  2. Pain
  3. Obstruction
  4. Bleeding
  5. Especially common with AIDS
  6. Bowel lesions:
     a. Circumferential ulcers
     b. Short strictures
     c. Calcified granulomas
     d. TB mesenteric caseous adenitis
     e. Abscess, but rare fistula formation
     f. Often difficult to distinguish from granulomatous bowel disease (Crohn disease)
- TB peritonitis:
  1. Fluid resembles TB pleurisy
  2. Purified protein derivative (PPD) often negative
  3. Tender abdomen
  4. Doughy peritoneal consistency, often with ascites
  5. Peritoneal biopsy indicated for diagnosis
- TB lymphadenitis (scrofula):
  1. May involve all node groups
  2. Common adenopathies:
     a. Cervical
     b. Supraclavicular
     c. Axillary
     d. Retroperitoneal
  3. Biopsy generally needed for diagnosis
  4. Surgical resection of nodes may be necessary
  5. Especially common with AIDS
- Cutaneous TB:
  1. Skin infection from autoinoculation or dissemination
  2. Nodules or abscesses
  3. Tuberculids (possibly allergic reactions)
  4. Erythema nodosum
- Miscellaneous presentations:
  1. TB laryngitis
  2. TB otitis
  3. Ocular TB:
     a. Choroidal tubercles
     b. Iritis
     c. Uveitis
     d. Episcleritis
  4. Adrenal TB
  5. Breast TB

ETIOLOGY

- See also "Tuberculosis, Pulmonary" in Section I.
- Mtb, a slow-growing, aerobic, nonspore-forming, nonmotile, acid-fast bacillus.
- Humans are the only reservoir for Mtb.
- Pathogenesis:
  1. Mtb are ingested by macrophages in alveoli, then transported to regional lymph nodes where spread is contained.
  2. Some Mtb reach the bloodstream and disseminate widely.
  3. Immediate active disseminated disease may ensue or a latent period may develop.
  4. During latent period, T-cell immune mechanisms contain infection in granulomas until later reactivation occurs as a result of immunosuppression or other undefined factors in conjunction with reactivated pulmonary TB or alone.
- Miliary TB may occur as a consequence of the following:
  1. Primary infection: Inability to contain primary infection leads to a hematogenous spread and progressive disseminated disease.
  2. In late chronic TB and in those with advanced age or poor immunity, a continuous seeding of the blood may develop and lead to disseminated disease.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Widespread sites of possible dissemination associated with myriad differential diagnostic possibilities:

- Lymphoma
- Typhoid fever

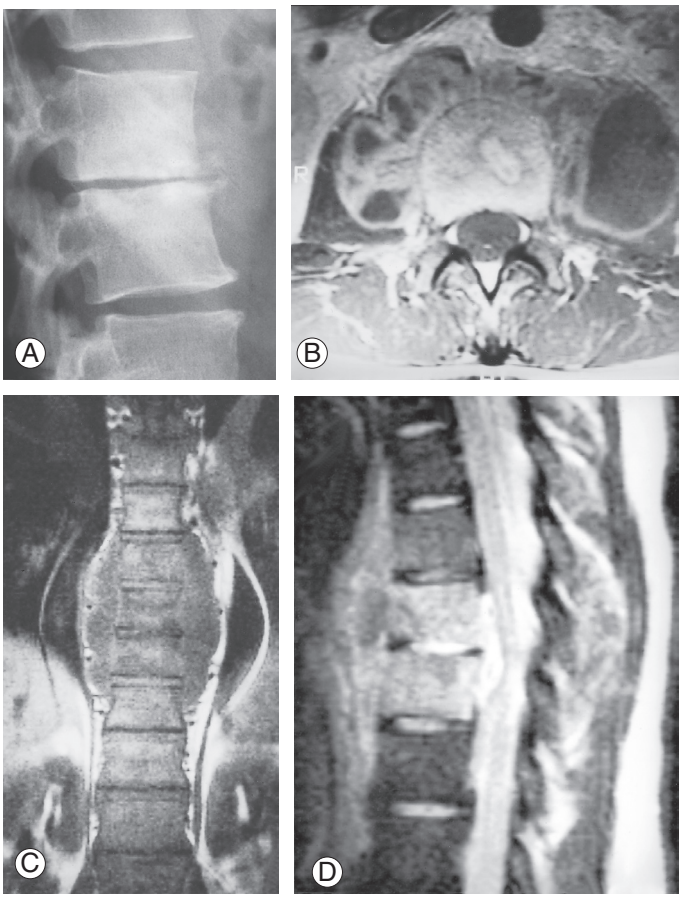

FIG. E1 Tuberculous discitis. (A) The plain x-ray changes are similar to a normal discitis with end-plate irregularity and reactive sclerosis. **(B)** Axial T1-weighted image shows the end-plate defect as well as psoas abscesses with central necrosis. **(C)** Coronal image in a different patient demonstrates intervertebral disc destruction at the point of maximal paraspinal widening and associated vertebral body signal change. **(D)** With fat suppression there is increased SI in adjacent vertebral bodies together with anterior and posterior masses (the latter compressing the spinal cord). (From Sutton D: *Textbook of radiology and imaging,* ed 7, 1998, Churchill Livingstone. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

- Brucellosis
- Other tumors
- Collagen-vascular disease

WORKUP

- Prompt evaluation is essential.
- Sputum for acid-fast bacilli (AFB) stain and culture and chest x-ray.
- High-resolution CT is more sensitive for miliary TB than CXR.
- Fluid analysis and mycobacterial culture wherever available.
  1. Sputum
  2. Blood: Particularly helpful in patients with AIDS
  3. Urine
  4. CSF
  5. Pleural
  6. Pericardial
  7. Peritoneal
  8. Gastric aspirates
- Biopsy of any involved tissue is advisable to make immediate diagnosis.
  1. Transbronchial biopsy preferred and easily accessible
  2. Bone marrow
  3. Lymph node
  4. Lumbar puncture for cerebrospinal fluid evaluation
  5. Scrotal mass if present
  6. Any other involved site
  7. Positive granuloma or AFB on biopsy specimen is diagnostic
- Imaging studies as needed (Fig. E1).

LABORATORY TESTS

- Culture and fluid analysis as described previously.
- Smear-negative sputum often is positive weeks later on culture (especially in HIV).
- CBC is usually normal.
- ESR is usually elevated.
- While not FDA approved for use in the U.S., internationally, assays to detect Mtb cell wall lipoarabinomannan in the urine (urine LAM assay) are used in HIV-infected patients with signs/symptoms of TB and CD4 <100 or severe illness.

IMAGING STUDIES

- Chest x-ray examination (may or may not be positive) (see "Tuberculosis, Pulmonary" in Section I)
- CT scan or MRI of brain and spinal cord (Fig. E2):
  1. Tuberculoma
  2. Basilar arachnoiditis
- Imaging of other sites based on clinical suspicion of involvement

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Bed rest or limited physical activity during acute phase of treatment
- High-calorie, high-protein diet to reverse malnutrition and enhance immune response to TB
- Isolation in negative-pressure rooms with high-volume air replacement and circulation (with health care provider wearing proper protective 0.5- to 1-micron filter respirators):
  1. Until three consecutive sputum AFB smears are negative or at least 2 weeks on multidrug treatment, if pulmonary disease coexists
  2. Isolation not required for closed-space TB infections such as peritonitis, osteomyelitis, and scrofula

ACUTE GENERAL Rx

- See "Tuberculosis, Pulmonary" in Section I.
- Therapy should be initiated immediately. Do not wait for definitive diagnosis.
- More rapid response to chemotherapy by disseminated TB foci than cavitary pulmonary TB.
- The American Thoracic Society/Centers for Disease Control and Prevention guidelines (2016) recommend 6 to 9 mo of treatment in patients with drug-susceptible acute TB. A four drug regimen is given for 2 mo followed by isoniazid and rifampin daily for 4 mo.
  1. Treatment for 12 mo often required for bone and renal TB.
  2. Prolonged treatment often required for CNS and pericardial.
  3. Prolonged treatment often required for all disseminated TB in infants.
- Compliance (rigid adherence to treatment regimen) is the chief determinant of success.
  1. Supervised directly observed therapy (DOT) is recommended for all patients.
  2. Supervised DOT is mandatory for patients at high risk of loss to follow-up.
- Steroids may be helpful in fulminant miliary disease with the hypoxemia and disseminated intravascular coagulation (DIC).

CHRONIC Rx

- Generally not indicated beyond treatment described previously
- Prolonged treatment supervised by infectious disease expert required in a few complicated infections caused by resistant organisms

DISPOSITION

- Monthly follow-up by physician experienced in TB treatment
- Confirm sensitivity testing, and alter treatment appropriately (see "Tuberculosis, Pulmonary" in Section I)

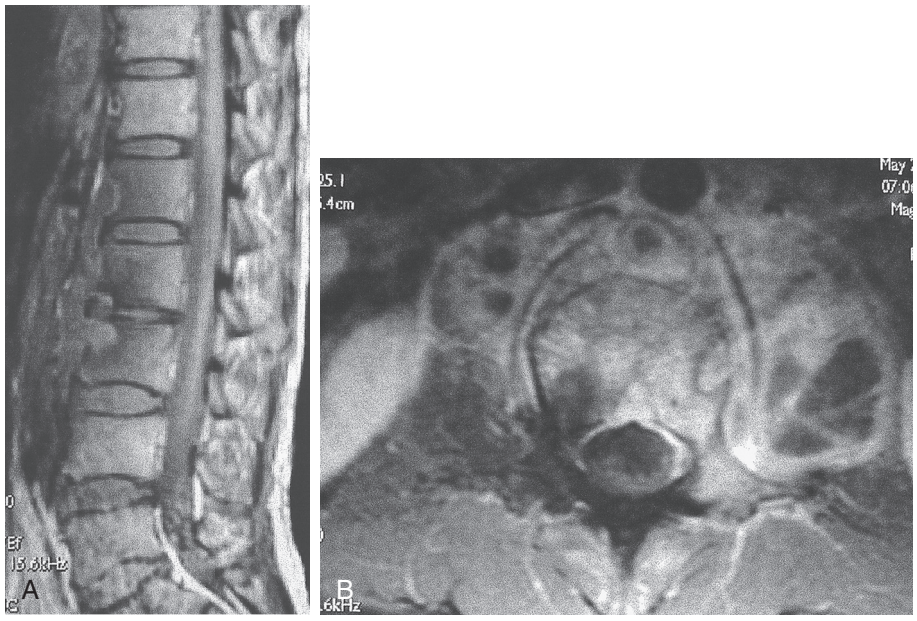

FIG. E2 A and **B,** Magnetic resonance images of tuberculous spinal osteomyelitis with scalloping of the vertebrae (tuberculous caries) and paraspinal "cold" abscesses. (From Grainger RG, Allison D: *Grainger & Allison's diagnostic radiology, a textbook of medical imaging,* ed 4, London, 2001, Churchill Livingstone.)

REFERRAL

- To infectious disease expert for extrapulmonary disease
- To pulmonary, orthopedic, or GI physicians for examinations or biopsy

PEARLS & CONSIDERATIONS

COMMENTS

- Consider acute TB in critically ill patients with enigmatic acute respiratory distress syndrome, shock, or DIC.
- All contacts (especially close household contacts and infants) should be properly tested for PPD conversions >3 mo following exposure.
- Those with positive PPD should be evaluated for active TB and properly treated or given prophylaxis.

RELATED CONTENT

Tuberculosis, Pulmonary (Related Key Topic)

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SUGGESTED READINGS

Garg RK, et al: Neurological complications of miliary tuberculosis, *Clin Neurol Neurosurg* 112:188-192, 2010.

Nahid P et al: Official American Thoracic Society/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. *Clinical Infectious Diseases* 20016;63(7):e147-e195.

Sharma SK, Mohan A, Sharma A, Mitra DK: Miliary tuberculosis: new insights into an old disease, *Lancet Infect Dis* 5:415, 2005.

BASIC INFORMATION

DEFINITION

Pulmonary tuberculosis (TB) is an infection of the lung and, occasionally, surrounding structures, caused by the bacterium *Mycobacterium tuberculosis* (Mtb). Multidrug-resistant (MDR) TB is defined as disease caused by strains of Mtb that are at least resistant to treatment with isoniazid and rifampin (two of the most effective first-line drugs); extensively drug-resistant (XDR) TB refers to disease caused by MDR strains that are also resistant to treatment with any fluoroquinolone and any of the injectable drugs used in second-line anti-TB treatment regimens.

SYNONYM

TB

ICD-10CM CODES
A15.0 Tuberculosis of lung
A15.7 Primary respiratory tuberculosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (WORLDWIDE):

- One fourth of the world's population is infected with TB, and it is still one of the deadliest diseases known to humans.
- In 2017, there were an estimated 10 million new cases of active tuberculosis; 9% involved coinfection with HIV; 1.3 million deaths from TB, including 300,000 among HIV-infected patients; 457,560 incident cases of multidrug-resistant TB worldwide.

INCIDENCE (IN U.S.):

- In 2018, a total of 9,029 new TB cases were reported in the U.S., representing a 0.7% decrease from 2017. The U.S. TB incidence in 2018 was 2.8 per 100,000 persons.
- The rate among non–U.S.-born persons was >14 times that in the U.S.-born persons.[1] Since 1993, TB case counts and rates have declined in the U.S (Fig. E1). As the number of cases decreases overall, an increasing percentage of cases occurs among non-U.S. born persons.
- More than 90% of new cases each yr from reactivated prior infections, while 9% represent new infections.
- Only 10% of patients with purified protein derivative (PPD) conversions will develop TB, most within 1 to 2 yr, though this is higher in HIV-positive patients (8%/yr).
- Two thirds of all new cases in racial and ethnic minorities and 80% of new cases in children occur in racial and ethnic minorities.
- Occurs most frequently in geographic areas and among populations with highest AIDS prevalence.
  1. Urban blacks and Hispanics between 25 and 45 yr old.
  2. Poor, crowded urban communities.
- Two thirds of new TB cases in 2018 occurred in non–U.S.-born persons, where the top five countries of birth were Mexico, the Philippines, India, Vietnam, and China.
- In 2017 in the U.S., 1.9% of cases were MDR TB, which is a decline from 8.2% in 2008. There were three cases of XDR TB in the U.S. in 2017.

PREVALENCE (IN U.S.):

- Between 3.1% and 5.0% of the U.S. population is estimated to be infected with latent TB infection
- Varies widely among population groups

PREDOMINANT SEX:

- Globally, in 2017, 6 million men contracted TB compared to 3.2 million women
- Male predominance in AIDS, shelters, and prisons reflected in disproportionate male incidence (Box 1)

PREDOMINANT AGE:

- Ages 24 to 45
- Childhood cases common among minorities
- Nursing home outbreaks among elderly

PEAK INCIDENCE:

- Infancy
- Teenage yr
- Pregnancy
- Elderly
- HIV-positive patients at highest risk regardless of age

BOX 1 High-risk Groups for Tuberculosis Infection and Disease

Groups at High Risk for Exposure or Infection
Close contacts of persons with tuberculosis
Foreign-born persons from high-risk regions (Asia, Africa, Latin America, Russia, eastern Europe)
Residents and employees of high-risk congregate settings (correctional institutions, nursing homes, homeless shelters, hospitals serving high-risk populations, drug treatment centers)
Medically underserved, low-income populations
High-risk racial or ethnic minority populations
Injectable drug users
Children exposed to adults in high-risk categories

Groups at Higher Risk for Disease Once Infected
Immunosuppressed patients, including those with HIV
Patients with recent tuberculosis infection (within past 2 yr)
Persons with certain medical conditions (diabetes mellitus, silicosis, cancer, end-stage renal disease, gastrectomy, body weight ≤90% of ideal)
Injectable drug users
History of inadequately treated tuberculosis
Children age ≤4 yr, especially infants

From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

GENETICS:

- Populations with widespread low native resistance have been intensely infected when initially exposed to TB.
- Following elimination of those with least native resistance, incidence and prevalence of TB tends to decline.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- See "Etiology"
- Primary pulmonary TB infection generally asymptomatic
- Reactivation pulmonary TB:
  1. Fever
  2. Night sweats
  3. Cough
  4. Hemoptysis
  5. Scanty nonpurulent sputum
  6. Weight loss
  7. Chest pain
- Progressive primary pulmonary TB disease: Same as reactivation pulmonary TB
- TB pleurisy:
  1. Pleuritic chest pain
  2. Fever
  3. Shortness of breath
- Rare massive, suffocating, fatal hemoptysis secondary to erosion of pulmonary artery within a cavity (Rasmussen aneurysm)
- Chest examination:
  1. Not specific
  2. Usually underestimates extent of disease
  3. Rales accentuated following a cough (posttussive rales)

ETIOLOGY

- Mtb, a slow-growing, aerobic, non-spore-forming, nonmotile bacillus, with a lipid-rich cell wall:
  1. Lacks pigment
  2. Produces niacin
  3. Reduces nitrate
  4. Produces heat-labile catalase
  5. Mtb staining, acid-fast and acid-alcohol fast by Ziehl-Neelsen method, appearing as red, slightly bent, beaded rods 2 to 4 microns long (acid-fast bacilli [AFB]), against a blue background
  6. Polymerase chain reaction (PCR) to detect <10 organisms/ml in sputum (compared with the requisite 10,000 organisms/ml for AFB smear detection)
  7. Culture:
     a. Growth on solid media (Löwenstein-Jensen; Middlebrook 7H11) in 2 to 6 weeks
     b. Growth in liquid media (BACTEC, using a radioactive carbon source for early growth detection) often in 9 to 16 days
     c. Enhanced in a 5% to 10% carbon dioxide atmosphere
  8. DNA fingerprinting (based on restriction fragment length polymorphism [RFLP]):
     a. Facilitates immediate identification of MTB strains in early growing cultures
     b. False negatives possible if growth suboptimal

[1]Colangeli R et al: Bacterial factors that predict relapse after tuberculosis therapy, *N Engl J Med* 379:823-833, 2018.

9. Humans are the only reservoir for Mtb
10. Transmission:
    a. Aerosolized droplets containing AFB generated through cough, speaking, singing, bronchoscopy, or autopsy are inhaled directly into alveoli
    b. Facilitated by close exposure to high-velocity cough (unprotected by proper mask or respirators) from patients with AFB-positive sputum and cavitary lesions.
    c. Locations of increased TB transmission risk include hospitals, homeless shelters, correctional facilities, nursing homes, and residential homes for those with HIV

- Pathogenesis:
  1. Mtb are ingested by macrophages in alveoli, then transported to regional lymph nodes, where spread is contained
  2. Some Mtb may reach bloodstream and disseminate widely
  3. Primary TB (often asymptomatic, minimal pneumonitis in lower or midlung fields, with hilar lymphadenopathy) is essentially an intracellular infection, with multiplication of organisms continuing 2 to 12 weeks after primary exposure, until cell-mediated hypersensitivity (detected by positive skin test reaction to tuberculin PPD) matures, and results in subsequent containment of infection
  4. Local and disseminated Mtb are thus contained by the following T-cell–mediated immune responses:
     a. Recruitment of monocytes
     b. Transformation of lymphocytes with secretion of lymphokines
     c. Activation of macrophages and histiocytes
     d. Organization into granulomas, where Mtb may survive within macrophages (Langhans giant cells), but within which multiplication essentially ceases (95%) and from which spread is prohibited
  5. Progressive primary pulmonary disease:
     a. May immediately follow the asymptomatic phase:
     b. Necrotizing pulmonary infiltrates
     c. Tuberculous bronchopneumonia
     d. Endobronchial TB
     e. Interstitial TB
     f. Widespread miliary lung lesions
  6. Postprimary TB pleurisy with pleural effusion:
     a. Develops after early primary infection, although often before conversion to positive PPD
     b. Results from pleural seeding from a peripheral lung lesion or rupture of lymph node into pleural space
     c. May produce a large (sometimes hemorrhagic) exudative effusion (with polymorphonuclear cells early, rapidly replaced by lymphocytes), frequently without pulmonary infiltrates
     d. Generally resolves without treatment
     e. Portends a high risk of subsequent clinical disease, and therefore must be diagnosed and treated early (pleural biopsy and culture) to prevent future catastrophic TB illness
     f. May result in disseminated extrapulmonary infection
  7. Reactivation pulmonary TB:
     a. Occurs months to yr following primary TB
     b. Preferentially involves the apical posterior segments of the upper lobes and superior segments of the lower lobes
     c. Associated with necrosis and cavitation of involved lung, hemoptysis, chronic fever, night sweats, weight loss
     d. Spread within lung occurs via cough and inhalation
  8. Reinfection TB:
     a. May mimic reactivation TB
     b. Ruptured caseous foci and cavities, which may produce endobronchial spread
  9. Mtb in both progressive primary and reactivation pulmonary TB:
     a. Intracellular (macrophage) lesions (undergoing slow multiplication)
     b. Closed caseous lesions (undergoing slow multiplication)
     c. Extracellular, open cavities (undergoing rapid multiplication)
     d. INH and rifampin are bactericidal in all three sites
     e. Pyrazinamide (PZA) especially active within acidic macrophage environment
     f. Extrapulmonary reactivation disease also possible
  10. Rapid local progression and dissemination in infants with devastating illness before PPD conversion occurs
  11. Most symptoms (fever, weight loss, anorexia) and tissue destruction (caseous necrosis) from cytokines and cell-mediated immune responses
  12. Mtb has no important endotoxins or exotoxins
  13. Granuloma formation related to tumor necrosis factor (TNF) secreted by activated macrophages

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Necrotizing pneumonia (anaerobic, gram-negative)
- Histoplasmosis
- Coccidioidomycosis
- Melioidosis
- Interstitial lung diseases (rarely)
- Cancer
- Sarcoidosis
- Silicosis
- Rare pneumonias:
  1. *Rhodococcus equi* (cavitation)
  2. *Bacillus cereus* (50% hemoptysis)
  3. *Eikenella corrodens* (cavitation)

WORKUP

- Sputum for AFB stains and Mtb culture.
- Chest x-ray (Fig. E2).
- PPD (tuberculin skin test [TST]) or interferon gamma release assays (IGRA) can be used for baseline testing:
  1. Recent conversion from negative to positive within 3 months of exposure is highly suggestive of recent infection.
  2. Single positive PPD is not helpful diagnostically.
  3. Negative PPD never rules out acute TB.
  4. Be certain that positive PPD does not reflect "booster phenomenon" (prior positive PPD may become negative after several yr and return to positive only after second repeated PPD; repeat second PPD within 1 wk), which thus may mimic skin test conversion.
  5. Positive PPD reaction is determined as follows:
     a. Induration after 72 hours of intradermal injection of 0.1 ml of 5 TU-PPD.
     b. 5-mm induration if HIV-positive (or other severe immunosuppressed state affecting cellular immune function), close contact of active TB, fibrotic chest lesions.
     c. 10-mm induration if in high–medical risk groups (immunosuppressive disease or therapy, renal failure, gastrectomy, silicosis, diabetes), foreign-born high-risk group (Southeast Asia, Latin America, Africa, India), low socioeconomic groups, IV drug addict, prisoner, health care worker.
     d. 15-mm induration if low risk.
  6. Anergy antigen testing (using mumps, *Candida,* tetanus toxoid) may identify patients who are truly anergic to PPD and these antigens, but results are often confusing. Not recommended.
  7. Patients with TB may be selectively anergic only to PPD.
  8. PPD cannot distinguish between TB disease and TB infection.
- Interferon gamma release assays (IGRAs): Diagnostic test for latent TB infection, known as the QuantiFERON TB Gold test (QFT-G) and T-SPOT.TB Assay. These blood tests measure interferon response to specific Mtb antigens. The test may assist in distinguishing true positive reactions from individuals with latent TB, from PPD reactions related to nontuberculous mycobacteria; prior BCG vaccination; or difficult-to-interpret skin-test results from people with dermatologic conditions or immediate allergic reactions to PPD. IGRAs have a specificity >95% for diagnosis of latent TB. The sensitivity of the T-SPOT assay (90%) appears to be higher than the QFT-G test (80%). It should be noted that IGRA sensitivity is diminished by HIV infection. Negative tests do not rule out active TB disease, and positive tests cannot distinguish between TB infection and disease.
- The Xpert MTB/RIF is an automated molecular test for Mtb and resistance to rifampin

(RIF) that provides sensitive detection of TB and rifampin resistance directly from untreated sputum in less than 2 hours with minimal hands-on time.

LABORATORY TESTS

- Sputum for AFB stains and culture:
  1. Induced sputum if patient not coughing productively
- Sputum from bronchoscopy if high suspicion of TB in patients unable to produce expectorated induced sputum for AFB:
  1. Positive AFB smear is essential before or shortly after treatment to ensure subsequent growth for definitive diagnosis and sensitivity testing
  2. Consider lung biopsy if sputum negative, especially if infiltrates are predominantly interstitial
- AFB stain-negative sputum may grow Mtb subsequently (especially in HIV)
- Gastric aspirates may be helpful, especially in children
- CBC:
  1. Variable values:
     a. WBCs: Low, normal, or elevated (including leukemoid reaction: >50,000)
     b. Normocytic, normochromic anemia often
  2. Rarely helpful diagnostically
- ESR usually elevated
- Thoracentesis:
  1. Exudative effusion:
     a. Elevated protein
     b. Decreased glucose
     c. Elevated WBCs (polymorphonuclear leukocytes early, replaced later by lymphocytes)
     d. May be hemorrhagic
  2. Pleural fluid usually AFB-negative
  3. Pleural biopsy often diagnostic—may need to be repeated for diagnosis
  4. Culture pleural biopsy tissue for AFB
- Bone marrow biopsy is often diagnostic in difficult-to-diagnose cases, especially miliary TB

IMAGING STUDIES

- Chest x-ray:
  1. Primary infection reflected by calcified peripheral lung nodule with calcified hilar lymph node
  2. Reactivation pulmonary TB:
     a. Necrosis
     b. Cavitation (especially on apical lordotic views)
     c. Fibrosis and hilar retraction
     d. Bronchopneumonia
     e. Interstitial infiltrates
     f. Miliary pattern
     g. Many of the previous findings may also accompany progressive primary TB
  3. TB pleurisy:
     a. Pleural effusion, often rapidly accumulating and massive
  4. TB activity not established by single chest x-ray examination
  5. Serial chest x-ray examinations are excellent indicators of progression or regression

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Increased rest during acute phase of treatment
- High-calorie, high-protein diet to reverse malnutrition and enhance immune response to TB
- Isolation in negative-pressure rooms with high-volume air replacement and circulation, with health care provider wearing proper protective 0.5- to 1-micron filter respirators, until three consecutive sputum AFB smears are negative during workup (taken in 8- to 24-hour intervals, with at least one being an early morning specimen) or a diagnosed case has been on standard multidrug treatment for at least 2 weeks and is clinically improving

ACUTE GENERAL Rx

- Generally, treatment of active tuberculosis consists of two phases: an intensive phase, followed by a continuation phase
- Compliance (rigid adherence to treatment regimen) chief determinant of success:
  1. Supervised directly observed therapy (DOT) recommended for all patients and mandatory for patients with high likelihood of loss to follow-up
- Adult initial regimen:
  1. Isoniazid 5 mg/kg (INH; max 300 mg), rifampin 10 mg/kg (RIF; max 600 mg), ethambutol by weight increments (EMB; 40 to 55 kg, 800 mg; 56 to 75 kg,1200 mg; 76 to 90 kg, 1600 mg), and pyrazinamide by weight increments (PZA; 40 to 55 kg, 1000 mg; 56 to 75 kg, 1500 mg; 76 to 90kg, 2000 mg) dosed daily
  2. Pyridoxine (vitamin B_6, 25 mg/day) should be given with INH to prevent peripheral neuropathy
  3. Usually decreased to INH and RIF after 8 weeks depending on susceptibilities, with ultimate duration of therapy dependent on HIV treatment status, extent of disease, regimen used, and treatment response, but generally at least 6 months
  4. Alternative, more complicated DOT regimens
- Monitor for clinical toxicity (especially hepatitis)
  1. Patient and physician awareness that anorexia, nausea, right upper quadrant pain, and unexplained malaise require immediate cessation of treatment
  2. Evaluation of liver function testing:
     a. Minimal SGOT/SGPT elevations without symptoms generally transient and not clinically significant
- Drug resistance (often multiple drug resistance TB [MDRTB]) increased by:
  1. 1 Prior treatment
  2. Acquisition of TB in high-TB-burden countries
  3. Homelessness, incarceration
  4. AIDS, intravenous drug use
  5. Known contact with MDRTB
- Other medications used in MDR or XDR TB include levofloxacin, moxifloxacin, cycloserine, aminoglycosides such as amikacin or kanamycin, PAS, clofazimine, bedaquiline, delaminid, pretomanid, linezolid, and ethionamide. A recent trial[2] with the combination of bedaquiline, pretomanid, and linezolid revealed a favorable outcome at 6 months after the end of therapy in a high percentage of patients with highly drug-resistant forms of TB
- Drug-resistant TB should be treated in consultation with a TB expert
- Preventive treatment for PPD conversion only (infection without disease):
  1. Must be certain that chest x-ray examination is negative and patient has no symptoms of TB
  2. Most important groups:
     a. HIV-positive and other severely immunocompromised patients
     b. Close contact with active TB
     c. Recent converter
     d. Old TB on chest x-ray examination
     e. IV drug addict
     f. Medical risk factor
     g. High-risk foreign country
     h. Homeless
     i. Box 2 summarizes persons in whom preventive therapy should be initiated to prevent progression to tuberculosis
  3. Treatment of **latent *M. tuberculosis***
- Infants generally given prophylaxis immediately if recent contact with active TB (even if infant PPD negative), then retested with PPD in 3 months (continuing INH if PPD becomes positive and stopping preventive treatment if PPD remains negative)

CHRONIC Rx

- Generally not indicated beyond treatment described previously

DISPOSITION

- Monthly follow-up by physician experienced in TB treatment.
- Confirm sensitivity testing and alter treatment appropriately.
- Frequent sputum samples until culture is negative.
- Confirm chest x-ray regression at 2 to 3 months.
- Approximately 5% of patients with drug-susceptible TB have a relapse after 6 months of first-line therapy. Higher MIC values of isoniazid or rifampin in predominant isolates of *M. tuberculosis* are associated with a greater risk of relapse.[3]

REFERRAL

- To infectious disease expert for:
  1. HIV-positive patient
  2. Patient with suspected drug-resistant TB
  3. Patients previously treated for TB

[2]Conradie F et al: Treatment of highly drug-resistant pulmonary tuberculosis, *N Engl J Med* 382:893-902, 2020.

[3]Talwar A et al: Tuberculosis-United States, 2018, *MMWR* 68(11):257-262, 2019.

BOX 2 Persons in Whom Treatment Should Be Initiated to Prevent Progression to Tuberculosis

Household members and other close associates of persons with potentially infectious tuberculosis
- Contacts of any age with a Mantoux tuberculin skin test reading of 5 mm or greater and no documented history of reaction in the past, or with a positive interferon gamma release assay (IGRA), should be considered recently infected and receive therapy if they have not been treated previously
- Newly infected people, regardless of age, who have had a tuberculin skin test or IGRA conversion within the past 2 yr
- People with HIV infection who have a reaction of 5 mm or greater to a Mantoux test or positive IGRA
- People of any age with past tuberculosis infection who received inadequate treatment
- People of any age with a positive tuberculin skin test or positive IGRA and an abnormal but stable chest radiograph
- People with significant tuberculin reactions or positive IGRAs who have special clinical situations, including silicosis, diabetes mellitus, prolonged corticosteroid therapy, immunosuppressive therapy, hematologic malignant disease, or end-stage renal disease
- All children and adolescents with a positive tuberculin skin test reaction or interferon release assay result

Adapted from Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

4. Patients whose fever has not decreased and sputum has not converted to negative in 2 to 4 weeks
5. Patients with overwhelming pulmonary or extrapulmonary TB

- To pulmonologist for bronchoscopy or pleural biopsy

PEARLS & CONSIDERATIONS

COMMENTS

- All contacts (especially close household contacts and infants) should be properly tested for PPD conversions during 3 months following exposure.
- Those with positive PPD should be evaluated for active TB and properly treated or given prophylaxis.
- Previous treatment is a common risk factor for XDR and MDR TB.
- In treatment of latent TB infections, evidence exists for the efficacy and safety of 6-month isoniazid monotherapy, rifampicin monotherapy, and combination therapies with 3 to 4 months of isoniazid and rifampicin.[4]
- Left untreated, 5% to 10% of patients with latent TB develop active TB. Updated guidelines from the CDC and the National Tuberculosis Controllers Association[5] for latent TB treatment include any of the following regimines:

1. Once-weekly isoniazid plus rifapentine for 3 mo administered under direct observation. The guideline recommends this regimen for adults and children (age < 2 yr), including patients who are HIV-positive.
2. Daily rifampin for 4 mo is also recommended strongly, especially for HIV-negative people, and perhaps has the lowest toxicity.
3. Daily rifampin plus isoniazid for 3 mo is another alternative.

[4]Zenner D et al: Treatment of latent tuberculosis infection, *Ann Intern Med* 167:248-255, 2017.

[5]Sterling TR et al: Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020, *MMWR Recomm Rep* 69(1);1-11, 2020.

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Available at ExpertConsult.com

AUTHORS: **Tara C. Bouton, MD, MPH, TM,** and **Glenn G. Fort, MD, MPH**

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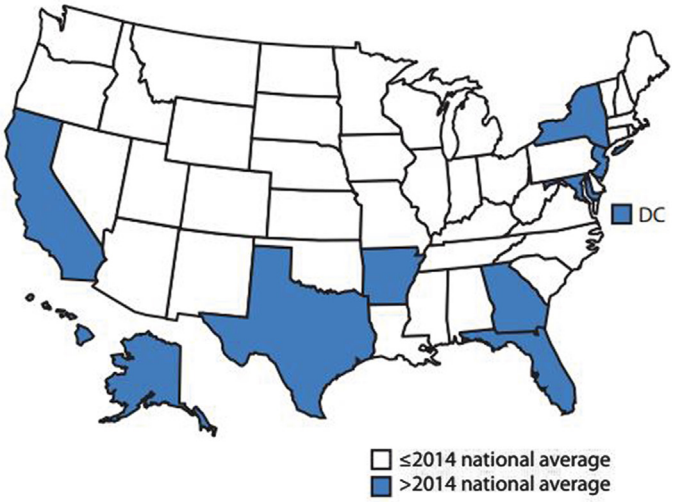

FIG. E1 Tuberculosis case rates (cases per 100,000) by state, 2014. (From Centers for Disease Control and Prevention: *Tuberculosis trends—United States*, 2014. *MMWR* 2015;64:265-9.)

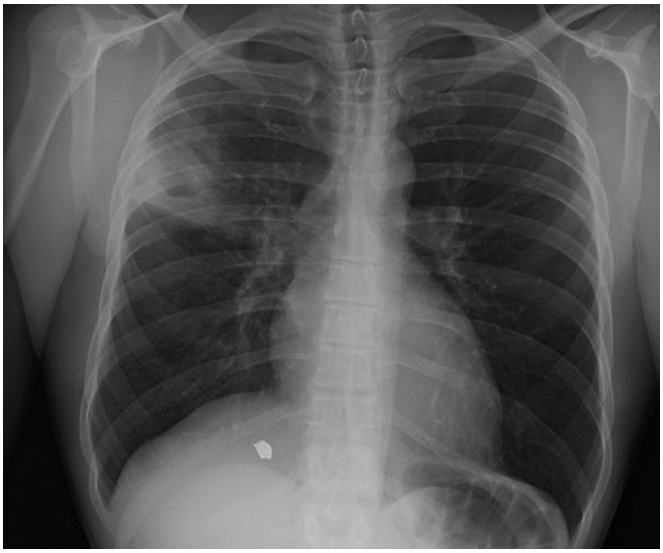

FIG. E2 Miliary pattern in tuberculosis consists of numerous nodules of uniform size. (From Grainger RG et al [eds]: *Grainger & Allison's diagnostic radiology,* ed 4, Philadelphia, 2001, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Tuberous sclerosis (TS) is an inherited neurocutaneous disorder that is characterized by pleomorphic features involving many organ systems, including multiple benign neoplasms (hamartomas) of the brain, kidney, and skin.

SYNONYMS

TS
TSC
Tuberous sclerosis complex

ICD-10CM CODE
Q85.1 Tuberous sclerosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: TS has an estimated incidence of 1 case per 6000 live births. Thus, it is the second most common neurocutaneous syndrome after neurofibromatosis.
PREVALENCE: The disorder affects about 1 in 10,000 persons in the general population.
PREDOMINANT SEX: TS has no predilection for gender or race.
GENETICS:

- TS is an autosomal dominant disorder with almost complete penetrance but a wide range of clinical severity. However, only one third of cases are familial. The apparently nonfamilial cases can represent either spontaneous mutations or mosaicism.
- Genetic research has identified two TS genes. One is located on chromosome 9 (*TSC1* gene) and the other on chromosome 16 (*TSC2* gene). About 68% of cases occur as a result of new gene mutations. Because of the genetic transmission and new mutations, antenatal diagnosis is difficult.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Dermatologic manifestations (Figs. E1, E2, and E3) may be the only clues the family physician has to the diagnosis of the disorder, which is also marked by childhood seizures and mental retardation.
- The diagnostic criteria for TS were recently revised at a consensus conference. Major and minor features are listed in Table E1.
- The classic diagnostic triad of seizures, mental retardation, and facial angiofibromas (Fig. E4) (Vogt triad) occurs in fewer than 50% of patients with TS.
- All of the clinical features of TS may not be apparent in the first yr of life. Thus, a child is often initially diagnosed with possible or probable TS, and the diagnosis of definite TS is made after additional features are identified.
- Dermatologic manifestations: A careful skin examination of patients at risk for TS continues to be the easiest and most accessible method of establishing the diagnosis (Table E2).
- Neurologic manifestations: These are the leading cause of morbidity and mortality in patients with TS. Brain hamartomas in the form of cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas are often responsible for intractable seizures, most commonly as infantile spasms. Approximately 90% to 96% of TS patients have seizures. Approximately 85% of patients have their first epileptic episode in the first 2 yr of life. Behavioral and cognitive dysfunction, including autism and mental retardation, can be seen in 40% to 50% of patients.
- Renal and pulmonary manifestations are strongly associated with TS.
- Angiomyolipoma is the most common renal lesion found in TS patients. Clinically evident pulmonary involvement in TS patients is relatively rare, with an estimated incidence of 1% to 6%. The most common lesion is lymphangiomyomatosis (LAM), a progressive cystic lung disease with progressive dyspnea and spontaneous pneumothorax in a childbearing woman.
- Cardiovascular manifestations: These are often the earliest diagnostic findings in patients with TS. Rhabdomyoma is the most common primary cardiac tumor in infants and children. Its incidence in TS patients ranges between 47% and 60%. In fact, 80% to 95% of patients with cardiac rhabdomyomas have TS.
- The most common ocular findings in TS are retinal hamartomas, appearing in 40% to 50% of patients.

ETIOLOGY

TS is an autosomal dominant disorder.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Cutaneous manifestations:

- Nevus anemicus
- Nevus depigmentosus (nevus achromicus)
- Vitiligo

FIG. E1 A hypopigmented, ash leaf-shaped spot on the thigh of a patient with tuberous sclerosis. (From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

FIG. E2 A periungual fibroma in a patient with tuberous sclerosis. (From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

FIG. E3 An erythematous plaque representative of a connective tissue nevus in a patient with tuberous sclerosis. (From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

TABLE E1 Revised Diagnostic Criteria for Tuberous Sclerosis Complex (TSC)

Major Features

1. Facial angiofibromas or forehead plaque
2. Nontraumatic ungual or periungual fibroma
3. Hypomelanotic macule (three or more)
4. Shagreen patch (connective tissue nevus)
5. Multiple retinal nodular hamartomas
6. Cortical tuber
7. Subependymal nodule
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma, single or multiple
10. Lymphangiomyomatosis
11. Renal angiomyolipoma

Minor Features

1. Multiple, randomly distributed pits in dental enamel
2. Hamartomatous rectal polyps
3. Bone cysts
4. Cerebral white matter radial migration lines
5. Gingival fibromas
6. Nonrenal hamartomas
7. Retinal achromic patch
8. "Confetti" skin lesions
9. Multiple renal cysts

Definite TSC: Either two major features or one major feature plus two minor features. Probable TSC: One major plus one minor feature. Possible TSC: Either one major feature or two or more minor features.

WORKUP

- The dermatologic manifestations of TS are helpful in diagnosing this disorder. When TS has been inherited in the autosomal dominant form, dermatologic signs are almost universally present in one of the patient's parents.
- No specific prenatal laboratory test is available.
- Early recognition of TS is vital because prompt implementation of the recommended diagnostic evaluation (neuroimaging studies, EEG, ECG, renal ultrasonography, brain MRI [Fig. E5] and chest CT) may prevent serious clinical consequences.
- Some findings in TS complex (TSC), notably renal angiomyolipomas and pulmonary lymphangioleiomyomatosis (LAM) emerge later, placing adults with undiagnosed TSC at increased risk for morbidity and mortality.

LABORATORY TESTS

- Molecular genetic testing: In recent yr, molecular genetic testing for TS has become clinically available. Such testing identifies mutations in the *TSC1* and *TSC2* genes by one of several methods, most commonly polymerase chain reaction (PCR) amplification of individual exons followed by DNA sequencing on DNA obtained from a patient's blood sample.
- DNA testing for TS is potentially useful in several settings:
  1. It can be helpful in confirming a clinical diagnosis of TS, especially in young patients in whom many clinical signs and symptoms have yet to develop.
  2. In many families with a history of TS in which there is a sporadic case of TS in a new child, genetic testing can provide reassurance to parents, children, and other family members that they do not carry the TS gene mutation.
  3. DNA testing is useful for prenatal diagnosis.

Rx TREATMENT

The management of TSC is presently symptomatic.

NONPHARMACOLOGIC THERAPY

Genetic counseling should be offered to families with affected members even though accurate counseling remains difficult because of the variability of gene expression.

ACUTE GENERAL Rx & CHRONIC Rx

- Treatment methods currently available for patients with disfiguring facial angiofibromas include cryosurgery, curettage, dermabrasion, chemical peeling, excision, and laser therapy.
- Some patients have been treated successfully with antiepileptic medications; unfortunately, there are multiple cases of intractable seizure in which medical treatment is ineffective. In some cases of intractable epilepsy, neurosurgical intervention becomes a lifesaving option.
- In such drug-resistant cases of TS, the early administration of vigabatrin (γ-vinyl-gamma aminobutyric acid), a selective irreversible inhibitor of GABA-transaminase, has been proved to result in 80% to 100% cessation rates of infantile spasms. Vigabatrin is marketed in many European countries but remains unavailable in the U.S. and has not been approved by the FDA.
- Embolization and/or renal sparing surgery are treatment options for renal angiomyolipomas.
- Oophorectomy, medroxyprogesterone, and tamoxifen have been advocated for patients with LAM, but the therapeutic benefit is unclear. Lung transplantation is reserved for patients with end-stage LAM.
- Most rhabdomyomas tend to regress with increasing age, although tumor growth has been documented in some at puberty. Surgery is recommended only for life-threatening situations, such as hemodynamic compromise.
- Oral rapamycin or sirolimus therapy can induce regression of brain astrocytomas associated with TS. Ongoing therapeutic trials with rapamycin in lymphangioleiomyomatosis appear promising.
- Neurosurgical resection is the standard treatment for subependymal giant cell astrocytomas in patients with the TSC. Trials with everolimus, which inhibits the mammalian target of rapamycin, a protein regulated by gene products involved in the TSC, have shown marked reduction in volume of subependymal giant cell astrocytomas and seizure frequency.

REFERRAL

A multidisciplinary team, including genetics, neurology, ophthalmology, nephrology, dermatology, neurosurgery, and plastic surgery, should evaluate children suspected of having TS.

! PEARLS & CONSIDERATIONS

PREVENTION

It is speculated that if one could establish the prenatal diagnosis of TS and have the patient begin using rapamycin early, one might prevent the development of TS manifestations.

RELATED CONTENT

Tuberous Sclerosis (Patient Information)

AUTHOR: **Ruby K. Satpathy, MD**

FIG. E4 Multiple facial angiofibromas in a patient with tuberous sclerosis. (From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

TABLE E2 Cutaneous Manifestations Associated with Tuberous Sclerosis Complex

Cutaneous Lesions	Descriptions	Age of Onset	Prevalence (%)	Diagnostic Classification
Hypomelanotic macules ("ash leaf" spots) or Fitzpatrick patches	Leaf-shaped or polygonal white spots enhanced by Wood lamp examination	Earliest cutaneous lesion; usually present on buttocks at birth or in infancy	97.2	Major
Facial angiofibromas	Red to pink papules with a smooth surface, symmetrically distributed over the centrofacial areas, sparing the upper lip	Second to fifth yr of life; become more prominent with age	74.5	Major
Shagreen patches	Slightly elevated patch or plaque, usually found on dorsal body surfaces, especially the lumbosacral area; its rough surface resembles an orange peel; represents a connective tissue nevus, sometimes called collagenoma	Rare during infancy; tend to increase in size and number with age	48.1	Major
Molluscum pendulum	Multiple soft pedunculated skin growths on neck; rarely in axillae or groin	More common during first decade of life; rare during infancy	22.6	Minor
Fibrous forehead plaque	Yellowish-brown or skin-colored plaques of variable size and shape, usually located on the forehead or scalp	Common at any age and can be seen at birth or in early infancy	18.9	Major
Periungual fibromas	Skin-colored or reddish nodules seen on the lateral nail groove or nail plate, or along the proximal nail folds; more commonly found on the toes than the fingers	Present at puberty or soon after; become more common with age	15.1	Major
"Confetti-like" macules	Multiple 1 mm to 2-mm white spots, symmetrically distributed over extremities	Second decade or adulthood	2.8	Minor

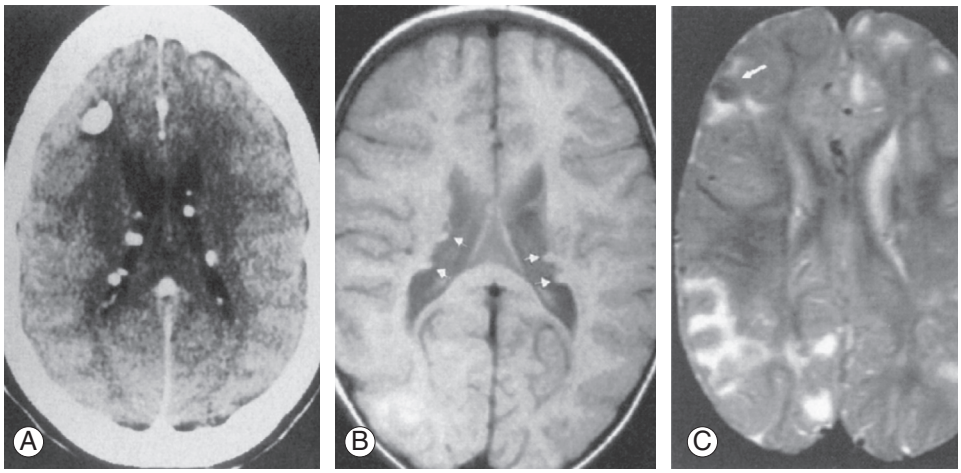

FIG. E5 Tuberous sclerosis. A, Computed tomography demonstrating periventricular calcified subependymal nodules. A cortical calcified tuber is also seen in the right frontal region. **B,** T1-weighted (WI) demonstrating the subependymal nodules *(arrows)* lining the lateral ventricles (isointense to white matter). **C,** T2WI demonstrating foci of abnormal SI throughout the subcortical white matter and in the cortex corresponding to cortical tubers. A right frontal tuber *(arrows)* is probably calcified (low SI). (From Grossman R, Yousem D: *Neuroradiology: the requisites,* 2003, Mosby. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

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Tularemia

BASIC INFORMATION

DEFINITION

Tularemia is a zoonosis caused by the small, facultative gram-negative intracellular coccobacillus *Francisella tularensis.* Clinical manifestations range from asymptomatic illness to septic shock and death.

SYNONYMS

Rabbit fever
Deerfly fever
O'Hara disease

ICD-10CM CODES
A21.9 Tularemia, unspecified
A21.0 Ulceroglandular tularemia
A21.1 Oculoglandular tularemia
A21.2 Pulmonary tularemia
A21.3 Gastrointestinal tularemia
A21.7 Generalized tularemia
A21.8 Other forms of tularemia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Overall incidence in the U.S. had been about 120 cases/yr with the highest reported incidence found in South Dakota, Arkansas, Missouri, and Oklahoma (Fig. E1). However, in 2015 there were 314 cases in the U.S. and 230 in 2016. It is also found in Canada, Mexico, European countries, Turkey, Israel, China, and Japan.

PREDOMINANT SEX: Male
PREDOMINANT AGE: Occurs at any age but is most common in 5- to 9-yr-old children and in men >55 yr of age
PEAK INCIDENCE: June through August and in December

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Physical findings:

- Incubation period is 3 to 5 days but may range from 1 to 21 days
- Most common initial signs and symptoms are abrupt onset of fever and respiratory symptoms. The following signs and symptoms may also be present:
  1. Chills
  2. Headache
  3. Malaise
  4. Anorexia
  5. Fatigue
  6. Cough
  7. Myalgias
  8. Chest discomfort
  9. Vomiting
  10. Abdominal pain
  11. Diarrhea
  12. Conjunctivitis
  13. Lymphadenitis

Clinical presentation:

- Ulceroglandular and glandular: Account for 75% to 80% of cases. Fever and a single erythematous papuloulcerative lesion with a central eschar (Fig. E2) accompanied by tender lymphadenopathy. Overall mortality rate for this form of tularemia is generally low (<2%).
- Oculoglandular: Accounts for 1% to 2% of cases. Painful inflamed conjunctiva with numerous yellowish nodules and pinpoint ulcers. Purulent conjunctivitis with regional lymphadenopathy. Corneal perforation may occur.
- Oropharyngeal and gastrointestinal: Account for 1% to 4% of cases. Acute, exudative, or membranous pharyngitis associated with cervical lymphadenopathy. Ulcerative intestinal lesion associated with mesenteric lymphadenopathy, diarrhea, abdominal pain, nausea, vomiting, and GI bleeding.
- Pulmonary: Occurs often in older adults and has a higher mortality rate. Symptoms include nonproductive cough, dyspnea, or pleuritic chest pain.
- Typhoidal: 10% of all cases of tularemia, usually after ingestion of viable *F. tularensis* bacteria. Rare in the U.S. Symptoms include high continuous fever, signs of endotoxemia, abdominal pain, and severe headache. Mortality rate can approach 30%.

COMPLICATIONS

- Intravascular coagulation
- Renal failure
- Rhabdomyolysis
- Jaundice
- Hepatitis
- Meningitis
- Encephalitis
- Pericarditis
- Peritonitis
- Osteomyelitis
- Splenic rupture
- Thrombophlebitis
- Myositis and sepsis

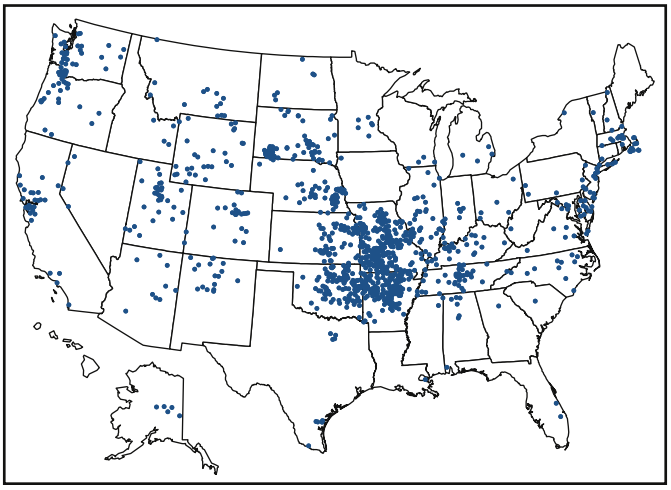

FIG. E1 Reported cases of tularemia in the United States, 2001 to 2010. One dot is placed randomly within the county of residence for each reported case. Cases were reported from 47 states. Six states accounted for 59% of reported cases: Missouri (19%), Arkansas (13%), Oklahoma (9%), Massachusetts (7%), South Dakota (5%), and Kansas (5%). (From Centers for Disease Control and Prevention [CDC]. Tularemia—United States, 2001-2010, *MMWR.* 2013;62:963-6, In Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.)

FIG. E2 Tularemia. (Courtesy of Steve Hess, MD. From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

ETIOLOGY

- Caused by infection with *F. tularensis*
- Two main biovars of *F. tularensis*: Types A and B. Type A produces severe disease in humans. Type B produces milder subclinical infection
- Transmitted by ticks, tabanid flies, and mosquitoes. Also acquired by inhalation and ingestion
- Cases also occur after exposure to animals (wild rabbit, squirrels, birds, sheep, beavers, muskrats, and domestic dogs and cats) or animal products
- Laboratory acquisition is possible
- Pathogenesis: After inoculation into the skin, the organism multiplies locally within 2 to 5 days; then it produces an erythematous tender or pruritic papule. The papule rapidly enlarges and forms an ulcer with a black base. The bacteria actively inhibit the protective host response by inducing antiinflammatory cytokines and spread to the regional lymph nodes, producing lymphadenopathy, and with bacteremia may spread to distant organs

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rickettsial infections
- Meningococcal infections
- Cat-scratch disease
- Infectious mononucleosis
- Atypical pneumonia
- Group A strep pharyngitis
- Typhoid fever
- Fungal infection—sporotrichosis
- Anthrax
- Plague
- Bacterial skin infections

WORKUP

- CBC
- Chest radiography
- Cultures of blood, lymph node, pleural fluid, wounds, sputum, and gastric aspirate
- Antigen detection in urine
- Polymerase chain reaction (PCR)
- Serology

LABORATORY TESTS

- Antibodies to *F. tularensis* demonstrated by tube agglutination, microagglutination, hemagglutination, and ELISA; definitive serologic diagnosis requires a fourfold or greater rise in titer between acute and convalescent specimens
- PCR to facilitate early diagnosis
- WBC count and ESR normal or elevated
- Rarely seen on Gram-stained smears or tissue biopsies; a tiny gram-negative bacillus

IMAGING STUDIES

Chest x-ray examination to show bilateral patchy infiltrate, lobar parenchymal infiltrate, cavitary lesion, pleural effusion, or emphysema

TREATMENT

ACUTE GENERAL Rx

- Immediate therapy to limit extent of acute illness and complications
- Streptomycin 15 mg/kg IV q12h (daily dose should not exceed 2 g) or gentamicin 5 mg/kg/day in 2 or 3 divided doses for 10 days or in the once-a-day dosing schedule
- Doxycycline 100 mg IV or PO bid
- Ciprofloxacin 400 mg IV or 750 mg PO bid for 14 to 21 days
- Combination antibiotics required for tularemic meningitis—chloramphenicol or doxycycline plus streptomycin
- Surgical therapies are limited to drainage of abscessed lymph nodes and chest tube drainage of empyemas

PROGNOSIS

The mortality rate of severe untreated infection (tularemic pneumonia and typhoidal tularemia) can be as high as 30%. The overall mortality rate associated with tularemia is 2% to 4% with appropriate treatment. Lifelong immunity usually follows tularemia.

DISPOSITION

Follow up as outpatient

PREVENTION

- Educate the public in the handling of sick or dead animals.
- Use only EPA-registered insect repellents, such as DEET or picaridin sprays.
- Remove ticks promptly.
- Drink only potable water.
- Adequately cook wild meats.
- Tularemia vaccine has been developed but is not commercially available in the U.S.; however, it is available from the CDC. Vaccination of high-risk individuals working with large quantities of cultured organism is recommended.
- Avoid skinning wild animals, especially rabbits; wear gloves while handling animal carcasses.
- Do not use wells or other water that is contaminated by dead animals.
- Hospitalized patients with tularemia do not need special isolation (no person-to-person transmission). Standard universal precautions for contaminated secretion are adequate when handling drainage from wounds.
- Laboratory personnel should be notified of potential danger of growing this organism in the laboratory and generation of an infectious aerosol from dried culture media.

REFERRAL

- For consultation with infectious diseases specialist in suspected cases.
- A cluster of tularemia cases, particularly in an urban area or nonendemic regions, should prompt concern over the possibility of bioterrorism; the local public health authorities should be contacted immediately to investigate the possibility of deliberate release of tularemia as a weapon of terror.

PEARLS & CONSIDERATIONS

- Alert the microbiology laboratory to the possibility of tularemia; this is a major biohazard in the laboratory.
- Do not use doxycycline or tetracycline in children or pregnant women.
- Because of its highly contagious nature with low inoculums, tularemia is considered an agent that could be used by terrorists. It is classified as a category A critical biologic agent by the CDC.

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

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Meagher KE, Decker CF: Other tick-borne illnesses: tularemia, Colorado tick fever, tick paralysis, *DM* 58(6):370-376, 2012.

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Yaglom H et al: Notes from the field: fatal pneumonic tularemia associated with dog exposure, Arizona, June 2016, *MMWR* 66:891, 2017.

BASIC INFORMATION

DEFINITION

- Tumor lysis syndrome (TLS) is an oncologic emergency referring to the acute release of potentially injurious intracellular contents into the systemic circulation from tumor cell breakdown.
- TLS is a constellation of metabolic disturbances that occurs typically in the setting of rapid tumor cell lysis induced by cancer-targeted treatment (chemotherapy and/or other interventions such as embolization or radiation). However, spontaneous tumor cell turnover has induced TLS without precipitation by chemotherapy.
- TLS is characterized by hyperuricemia, hyperphosphatemia, hypocalcemia, hyperkalemia, and acute kidney injury (AKI), often with progressive oliguria.
- In the current 2004 Cairo and Bishop classification system, TLS may be defined by laboratory or clinical parameters (Table 1). Grading of clinical tumor lysis syndrome is summarized in Table 2.
  1. **Laboratory TLS** is clinically silent and defined by the presence of at least two of the following biochemical variables within 3 days before or 7 days after initiation of chemotherapy despite adequate volume status and uric acid–lowering agents.
     a. Hyperuricemia:
        (1) Results from the rapid release and catabolism of intracellular nucleic acids.
        (2) Purine nucleic acids are metabolized to hypoxanthine, xanthine, and finally, uric acid.
        (3) In an acidic environment, uric acid can precipitate in the renal tubular lumen causing obstruction.
     b. Hyperkalemia.
     c. Hyperphosphatemia: Phosphate may precipitate with calcium to form calcium phosphate stones in renal tubules.
     d. Hypocalcemia: Occurs secondary to precipitation with phosphorus.
  2. **Clinical TLS** occurs when laboratory TLS is complicated by at least one of the following clinical complications (severe renal impairment, cardiac arrhythmias, central nervous system toxicity, and/or death) that are not attributed to chemotherapy regimen.

SYNONYM

TLS

ICD-10CM CODE
E88.3 Tumor lysis syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The frequency of TLS is unknown, but it is the most common disease-related emergency encountered by physicians who treat children or adults with hematologic cancers. Incidence depends on cancer mass (greater mass correlates with greater cellular content release at cell death), patient characteristics (e.g., preexisting chronic kidney disease, volume depletion, hypotension), and supportive care. Tumor bulk, proliferation rate, and treatment sensitivity are associated with greater frequency of TLS.

PREVALENCE: Variable

PREDOMINANT SEX AND AGE:

- No sex predilection exists.
- Occurs in all age groups. Older adults are more susceptible to TLS due to a decline in glomerular filtration rate with age.

GENETICS: No racial predilection

RISK FACTORS:

- High tumor burden:
  1. Large-size tumor
  2. LDH >1500 IU/L
  3. WBC >25,000/mm^3
  4. Risk of TLS is further stratified by tumor type:
     a. High risk:
        (1) Burkitt lymphoma
        (2) High-grade non-Hodgkin lymphoma
        (3) Lymphoblastic lymphoma
        (4) Acute T-cell leukemia
        (5) Other acute leukemias
     b. Moderate risk:
        (1) Low-grade lymphoma treated with chemotherapy/radiation/corticosteroids
        (2) Multiple myeloma
        (3) Breast carcinoma treated with chemotherapy/hormonal therapy
        (4) Small-cell lung carcinoma
        (5) Germ-cell tumors (e.g., seminoma, ovarian)
     c. Low risk:
        (1) Low-grade lymphoma treated with interferon
        (2) Merkel cell carcinoma
        (3) Adenocarcinoma of the gastrointestinal tract
- Administration of certain agents, including:
  1. Paclitaxel
  2. Hydroxyurea
  3. Etoposide
  4. Fludarabine
  5. Sorafenib
- Extensive bone marrow involvement
- Elevated pretreatment uric acid, potassium, or phosphorus levels
- Tumor highly sensitive to treatment
- Volume depletion
- Chronic kidney disease
- Decreased urine output
- Acidic urine
- Tumor involvement of the kidney/renal vasculature
- Advanced age
- Post-transcatheter arterial chemoembolization (TACE), radiofrequency thermal ablation
- Chimeric antigen receptor T-cells therapy (CAR-T cell)

ETIOLOGY

Most commonly occurs in patients with acute leukemias; bulky, solid tumors; or high-grade lymphomas. The pathophysiology of tumor lysis syndrome is illustrated in Fig. E1.

- Can occur spontaneously or after antitumor intervention (chemotherapy, radiation, etc.)
- Associated with administration of certain chemotherapeutic agents (whether intravenous, intrathecal, etc.):
  1. Paclitaxel
  2. Hydroxyurea
  3. Etoposide
  4. Fludarabine
- Spontaneous TLS:
  1. Rare
  2. Lysis of tumor cells without chemotherapy or in setting of minimal chemotherapy (e.g., steroid monotherapy in case of lymphomas)
  3. Related to rapid cell turnover rate

TABLE 1 Classification of Tumor Lysis Syndrome

Laboratory tumor lysis syndrome	Two or more of the metabolic abnormalities in the next column present on the same day Occurring within 3 days before initiation of therapy or 7 days after initiation of therapy Assumes the patient receives adequate hydration and a hypouricemic agent	Uric acid ≥476 μmol/L (8 mg/dl) in adults or the upper limits of normal in children Potassium ≥6.0 mmol/L Phosphorus ≥1.5 mmol/L (4.5 mg/dl) in adults or ≥2.1 mmol/L (6.5 mg/dl) in children Calcium ≤1.75 mmol/L (7 mg/dl) or ionized calcium <1.2 mmol/L (4.5 mg/dl)
Clinical tumor lysis syndrome	Laboratory tumor lysis syndrome plus any of the criteria in the next column (not attributable to other causes)	Acute kidney injury, defined as an increase in creatinine of 26.5 μmol /L (0.3 mg/dl) or when no baseline creatinine is documented, a single value ≥1.5 times the upper limits of normal for the patient's age and sex Symptomatic hypocalcemia (e.g., tetany or paresthesias), seizure, cardiac dysrhythmia, or sudden death attributed to hypocalcemia or hyperkalemia

From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE 2 Grading of Clinical Tumor Lysis Syndrome

Stage I	Stage II	Stage III	Stage IV	Stage V
Renal failure	Serum creatinine = 1.5 UNL or creatinine clearance 30-45 ml/min	Serum creatinine = 1.5-3 UNL or creatinine clearance 20-30 ml/min	Serum creatinine = 3-6 UNL or creatinine clearance 10-20 ml/min	Serum creatinine >6 UNL or creatinine clearance <10 ml/min
Cardiac arrhythmia	Intervention not indicated	Nonurgent intervention indicated	Symptomatic and incompletely controlled or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with heart failure, hypotension, syncope, shock)
Seizures	None	One brief, generalized seizure; seizure(s) well controlled by anticonvulsant, or infrequent focal motor seizures	Seizure in which consciousness is altered; poorly controlled seizure disorder, with generalized breakthrough seizures despite medical intervention	Seizure of any kind that is prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)

From Ronco C et al: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.

4. Can be associated with pregnancy; fever; and rarely, generalized anesthesia in predisposed individuals
5. Hyperphosphatemia may not recur because of the reutilization of released phosphorus for resynthesis of newer tumor cells

PHYSICAL FINDINGS & CLINICAL PRESENTATION

CLINICAL PRESENTATION: Patients may present with a number of symptoms either before starting chemotherapy or commonly within 3 days after initiating cytotoxic treatment. Common symptoms include:

- Nausea
- Vomiting
- Edema
- Shortness of breath (from fluid overload or CHF)
- Lethargy or weakness
- Seizure
- Syncope
- Muscle cramp
- Tetany

PHYSICAL FINDINGS:

- Associated with specific metabolic abnormalities, including hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia
- Findings often overlap for these metabolic derangements
  1. Hyperkalemia:
     a. Generalized weakness
     b. Paresthesias
     c. Paralysis
     d. ECG abnormalities:
        (1) Peaked T waves
        (2) Flattened P waves
        (3) Widened QRS complexes
        (4) Bradycardia
     e. Cardiac arrhythmias, including:
        (1) Ventricular tachycardia
        (2) Ventricular fibrillation
        (3) Asystole
        (4) Pulseless electrical activity
     f. Cardiac arrest
  2. Hyperphosphatemia:
     a. Oliguric or anuric AKI
     b. Cardiac arrhythmias
  3. Hypocalcemia:
     a. Paresthesias
     b. Tetany
     c. Neuromuscular irritability: Twitching, Chvostek sign (nonspecific), and carpopedal spasm
     d. Bronchospasm
     e. ECG abnormalities, including:
        (1) Inverted T waves
        (2) Prolonged QT interval
        (3) Ventricular arrhythmias
        (4) Heart block
     f. Cardiac arrest

ETIOLOGY

- TLS is caused by massive release of intracellular contents into the bloodstream at the time of death of neoplastic cells.
- Can occur spontaneously or after initiation of therapy in patients with:
  1. Acute leukemias
  2. Bulky solid tumors
  3. High-grade lymphomas
- Administration of certain agents:
  1. Paclitaxel
  2. Hydroxyurea
  3. Etoposide
  4. Fludarabine
- It has been reported in some cancer patients who received:
  1. Intrathecal administration of chemotherapy
  2. Rare causes: Pregnancy, fever, and rarely general anesthesia in predisposed individuals

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

See "Acute Kidney Injury" topic in Section I.

LABORATORY TESTS

- Early identification of abnormal laboratory values may prevent or reduce complications of TLS
- Laboratory TLS is defined by the presence of at least two of the following biochemical criteria within 3 days before or 7 days after initiation of chemotherapy despite adequate volume repletion or use of uric acid-lowering agents:
  1. Uric acid: >8.0 mg/dl in adults or above the upper limit of the normal range for age in children
  2. Phosphorus: >4.5 mg/dl in adults or >6.5 mg/dl in children
  3. Potassium: >6.0 mEq/L
  4. Calcium: Corrected calcium <7.0 mg/dl or ionized calcium <1.12 mg/dl
- Patients should have careful and frequent laboratory and clinic monitoring:
  1. Perform frequent ECGs or continuous cardiac monitoring for arrhythmia detection
  2. Monitor renal status closely and follow daily weights and fluid intakes and outputs
  3. Monitor BUN, creatinine, phosphorus, potassium, calcium, uric acid, and LDH in high-risk patients before and up to 72 hours after initiating therapy:
     a. If evidence of TLS develops, laboratory parameters should be checked twice daily

IMAGING STUDIES

- Consider abdominal/renal ultrasound if kidney failure present.
- Consider CT chest/abdominal/pelvis to evaluate for underlying malignancies.

Rx TREATMENT

GENERAL PRINCIPLES

- Prevention is mainstay of therapy.
- Identify high-risk patients (evaluate extent of tumor burden, kidney function, and pathologic findings) to initiate prophylactic measures in a timely fashion. Delayed treatment may lead to life-threatening complications.
- Optimal treatment involves preservation of renal function and prevention of cardiac dysrhythmias and neuromuscular irritability.
- Any metabolic derangements should be corrected before starting cancer treatment.
- Prevention for high-risk patients without TLS:
  1. Prompt, vigorous volume repletion and administration of uricosuric agent are mainstays of therapy. Box 1 summarizes treatment recommendations for tumor lysis syndrome.
     a. Volume repletion:
        (1) Prevents volume depletion and corrects electrolyte derangement.

(2) Fluid intake (whether oral or intravenous) should be maintained at 2 to 3 L/m^2 per day.
(3) Begin 24 to 48 hours before initiating cancer treatment and continue for up to 72 hours after treatment.
(4) If intravenous fluids are required, isotonic solutions are appropriate (e.g., 0.9% saline or 1 L D_5W plus 3, 50-ml ampules of 1 M $NaHCO_3$).
(5) Maintain urine output at 80–100 ml/m^2 per hour.
(6) Patients with underlying cardiac or kidney dysfunction should be monitored for volume overload and necessity for loop diuretics.
(7) Hypouricemic agents (e.g., allopurinol, rasburicase, and febuxostat). Uric acid is freely filtered at the glomerulus, and handling in the renal proximal tubule is a combination of reabsorption and secretion mediated by luminal urate/anion exchanger urate transporter 1 (URAT-1) and the basolateral organic anion transporter (OAT). When the capacity to transport luminal uric acid is overwhelmed, there is potential for uric acid to crystallize within the tubular lumen. An acidic urine pH favors this process. Uric acid crystals can cause direct tubular injury by obstruction. Furthermore, intratubular and parenchymatous uric acid precipitations causes renal injury by a granulomatous reaction and necrosis of the distal tubule epithelium through induction of chemokine-mediated inflammation from monocyte chemoattractant protein-1 (MCP-1) and macrophage migration inhibition factor (MIF). There are also crystal-independent mechanisms, which target hemodynamics: these include increased peritubular capillary pressures, increased vasoconstriction, and decreased blood flow. Uric acid also may prevent recovery from AKI in TLS, because it has been shown to inhibit proximal tubule cell proliferation. These diverse mechanisms are united in their propensity to cause AKI, as reported in Fig. 2.[1]
(8) Allopurinol:
  (a) Xanthine oxidase inhibitor, which prevents the conversion of xanthine and hypoxanthine to uric acid.
  (b) The prophylactic dose is 200 to 400 mg/m^2 daily in 1 to 3 divided doses, up to a maximum of 800 mg daily. The treatment dose is 300 to 900 mg/day.
  (c) In patients with high-grade liquid tumors, Allopurinol prophylaxis may cause xanthine nephropathy/nephrolithiasis:
    • Low serum uric acid levels and high urinary xanthine levels aid in diagnosis.
    • Consideration for reduction/cessation of allopurinol therapy should then be considered.
(9) Rasburicase:
  (a) Recombinant urate oxidase is used when uric acid levels cannot be lowered by standard measures.
  (b) Given by intravenous or intramuscular route in dosages from 50 to 100 units/kg per day for 1 to 5 days.
  (c) Should not be administered at same time as allopurinol, because allopurinol reduces uric acid levels and may reduce rasburicase efficacy.
  (d) Contraindicated in pregnancy and glucose-6-phosphate dehydrogenase deficiency due to hemolytic concerns.
  (e) Cost is a limiting factor.
(10) Febuxostat dose is 120 mg by mouth daily. It has fewer drug-drug interactions than allopurinol, and dose adjustment is not needed in patients with mild to moderate renal impairment. Cost is a limiting factor.
b. Urinary alkalinization:
  (1) Uric acid more soluble at urinary alkaline pH.
  (2) Remains controversial and has fallen out of favor.
  (3) Contraindicated with hyperphosphatemia because of risk of calcium phosphate deposition leading to stones/nephrocalcinosis.

[1]Ronco C: *Critical care nephrology,* 3rd ed, Elsevier 2019.

BOX 1 Tumor Lysis Syndrome: Treatment Recommendations

When no metabolic aberration exists:
- Allopurinol 300 mg/day, reduce to 100 mg/day after 3 days of chemotherapy

OR
- Rasburicase 0.2 mg/kg IV daily × 5 days
- Hydration: 0.45% saline 3000 ml/day
- Initiate chemotherapy within 24-48 hours of admission
- Monitor serum chemistry values every 12-24 hours

When metabolic aberration exists:
- Allopurinol or rasburicase as above; reduce dose if hyperuricemia is controlled or for renal insufficiency.
- Hydration with D_5W with 2 ampules/L of $NaCO_3$, add nonthiazide diuretics as needed.
- Urinary alkalization to keep urine pH >7.0; may discontinue when serum uric acid level is normal.
- Postpone chemotherapy until uric acid has decreased and electrolytes are stable.
- Monitor serum chemistries every 6-8 hours.
- Replace calcium with slow intravenous infusion of calcium gluconate (if symptomatic or for ECG changes).
- Treat hyperkalemia and hyperphosphatemia with exchange resins and phosphate binders, respectively.

Criteria for hemodialysis in patients unresponsive to the measures listed above:
- Serum potassium >6.0 mEq/L
- Serum uric acid >20 mg/dl
- Serum phosphorus >10 mg/dl
- Fluid overload unresponsive to diuretics

Symptomatic hypercalcemia D_5W, 5% dextrose in water; *ECG*, electrocardiogram; *$NaCO_3$*, sodium carbonate.

From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Elsevier. From Brudno JN et al: Toxicities of chimeric antigen receptor T cells: Recognition and management, *Blood*, May 20, 2016.

TREATMENT OF PATIENTS WITH TUMOR LYSIS SYNDROME

- Principles:
  1. Early consultations for nephrology and critical care teams
  2. Preventive measures as indicated previously
  3. Aggressive treatment of electrolyte disturbances to prevent cardiac arrhythmias and neuromuscular irritability
    a. Arrhythmias tend to be resistant to conventional therapy
    b. Arrhythmias are a leading cause of death in patients with severe TLS
  4. Treatment of kidney failure
- Management of electrolyte disturbances:
  1. Multiple, coexisting electrolyte abnormalities may make conservative management strategies difficult
    a. Systemic alkalinization may be required for concurrent hyperphosphatemia, hyperuricemia, and acidemia. Alkalinization may worsen hypocalcemia

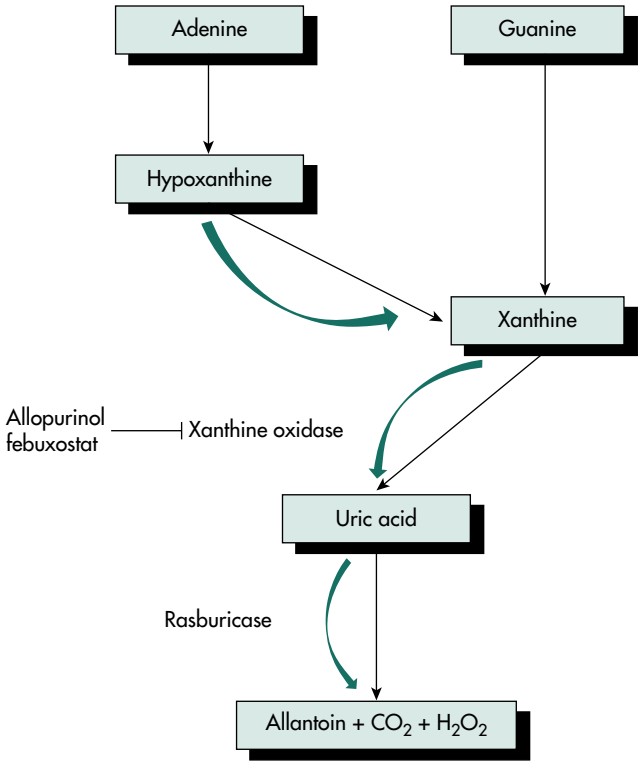

FIG. 2 Principles of therapy for the prevention and treatment of tumor lysis syndrome. (From Ronco C et al: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.)

2. Hyperuricemia:
   a. Uric acid–lowering agents including allopurinol or rasburicase
3. Hyperkalemia:
   a. Low-potassium diet
   b. Intravenous calcium chloride/gluconate for ECG changes of hyperkalemia
   c. Intravenous infusions of glucose and insulin to shift potassium into intracellular compartments
   d. Oral potassium-exchange resins (not for acute management)
   e. Hemodialysis
4. Hyperphosphatemia:
   a. Low phosphorus diet
   b. Intravenous infusion of glucose and insulin to shift phosphorus into cells
   c. Oral phosphate binders
5. Hypocalcemia:
   a. Treat only if neuromuscular irritability is present
   b. Intravenous calcium chloride/gluconate
   c. Calcitriol can be used if the serum phosphorus level is normal, but is a relatively slow form of therapy

- Management of kidney failure:
  1. Perform standard workup for kidney failure, including urinalysis, urine microscopy, urinary electrolytes, kidney ultrasound, etc.
  2. Supportive care with intravenous fluids and diuretics (if required)
  3. Consider early dialysis if above methods fail (especially if cardiac abnormalities present)

REFERRAL

- Nephrology
- Critical care

PEARLS & CONSIDERATIONS

COMMENTS

- TLS is an oncologic emergency, which can occur spontaneously, or, more commonly, during chemotherapy-related tumor cell lysis.
- TLS is associated with the release of several intracellular contents, including potassium, phosphorus, and uric acid. With concomitant renal failure, these products are retained to pathological levels, leading to cardiac and neurological abnormalities.
- Common risk factors for TLS include highly proliferative tumors and large tumor burdens (e.g., high-grade lymphomas and acute leukemias), and preexisting metabolic derangements and renal failure.
- High-risk patients should undergo prophylactic measures initiated 24 to 48 hours before initiation of cytotoxic agents.
- Prophylactic measures include aggressive intravenous volume repletion and administration of uric acid–lowering drugs.
- Frequent laboratory testing and monitoring of vital signs, intakes and outputs, and cardiac/neurological abnormalities are recommended.
- Complications may include continued electrolyte disturbances, renal failure, uremic complications, cardiac arrhythmias, and pulmonary edema from aggressive volume repletion.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Jesse Goldman, MD, FASH,** and **Sandeep Agarwal, MD**

SUGGESTED READINGS

Halfdanarson TR et al: Emergencies in hematology and oncology, *Mayo Clin Proc* 92(4):609-641, 2017.

Howard SC: The tumor lysis syndrome, *N Engl J Med* 364:1844-1854, 2011.

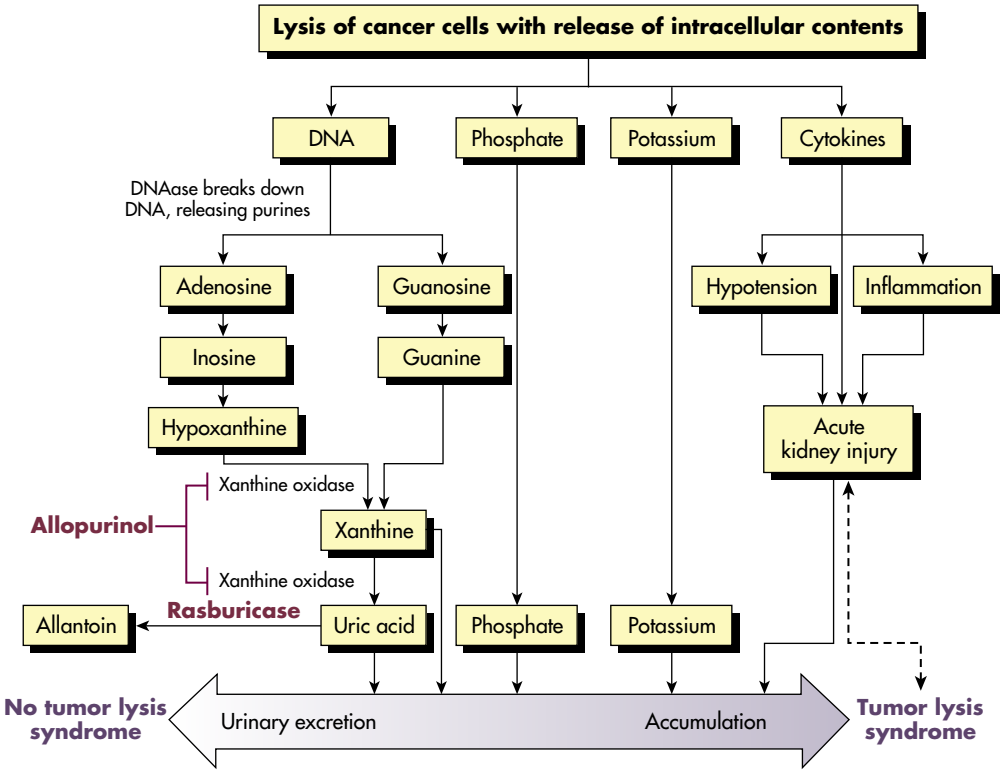

FIG. E1 Pathophysiology of tumor lysis syndrome. Lysis of cancer cells releases DNA, phosphate, potassium, and cytokines. DNA released from the lysed cells is metabolized into adenosine and guanosine, both of which are converted into xanthine. Xanthine is then oxidized by xanthine oxidase, leading to the production of uric acid, which is excreted by the kidneys. When the accumulation of phosphate, potassium, xanthine, or uric acid is more rapid than excretion, tumor lysis syndrome develops. Cytokines cause hypotension, inflammation, and acute kidney injury, which increase the risk for tumor lysis syndrome. The bidirectional dashed line between acute kidney injury and tumor lysis syndrome indicates that acute kidney injury increases the risk of tumor lysis syndrome by reducing the ability of the kidneys to excrete uric acid, xanthine, phosphate, and potassium. By the same token, development of tumor lysis syndrome can cause acute kidney injury by renal precipitation of uric acid, xanthine, and calcium phosphate crystals and by crystal-independent mechanisms. Allopurinol inhibits xanthine oxidase and prevents the conversion of hypoxanthine and xanthine into uric acid but does not remove existing uric acid. In contrast, rasburicase removes uric acid by enzymatically degrading it into allantoin, a highly soluble product that has no known adverse effects on health. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

Turner Syndrome

BASIC INFORMATION

DEFINITION

Turner syndrome is a pattern of malformation characterized by short stature, ovarian hypofunction, loose nuchal skin, and cubitus valgus, as described by Turner in 1938. An associated 45,X chromosome constitution was recognized by Ford et al in 1959.

ICD-10CM CODES

Q96.9 Turner syndrome, unspecified
Q96.8 Other variants of Turner syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

One case in every 2500 to 5000 live female births

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Turner phenotype is recognizable at any point on the developmental spectrum
- In spontaneous abortions, it is the most common sex chromosome abnormality detected (45,X chromosome constitution) and accounts for 20% of such cases
- In fetuses, it is suspected when ultrasonographic manifestations such as thickening of the nuchal folds, frank nuchal cystic hygromas, or mild shortness of the femur at midtrimester are identified
- In infants (Fig. E1):
  1. At birth may display loose nuchal skin (pterygium colli) and edema on the dorsa of hands and feet
  2. Canthal folds reflecting midface hypoplasia and redundant skin in the periorbital region
  3. Nipples appearing widely spaced (interthelial distance greater than one fourth the chest circumference)
  4. Heart and cardiovascular system: Murmur of aortic stenosis or bicuspid aortic valve or diminished femoral pulses suggestive of aortic coarctation
  5. Renal ultrasonography: Renal ectopia such as pelvic kidney or horseshoe kidneys
- In older children:
  1. Slow linear growth
  2. Short stature: May be improved with growth hormone therapy. Combining childhood ultra-low-dose estrogen with growth hormone may improve growth and provide other potential benefits associated with early initiation of estrogen replacement
  3. Delayed or absent menses: Secondary sex characteristics possibly normalized with estrogen replacement therapy
  4. Intelligence is often normal, but delays in spatial perception or visual-motor integration are commonly observed; frank mental retardation is rare

ETIOLOGY

- Abnormal phenotype caused by absence of the second sex chromosome, whether X or Y
- 45,X chromosome constitution in approximately 50% of affected individuals
- Other chromosome aberrations (40% of cases): Isochromosome Xq (46,X,i[Xq]) or mosaicism (XX/X)
- With deletions involving the short (or "p") arm of the X chromosome: Short stature but little ovarian hypofunction
- Deletions involving Xq13-q27: Ovarian failure
- Usually a deficiency of paternal contribution of sex chromosome, reflecting paternal nondisjunction

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Noonan syndrome (PTPN11 mutation), an autosomally dominant inherited disorder also characterized by loose nuchal skin, midface hypoplasia, canthal folds, and stenotic cardiac valvular defects and affecting males and females equally; also have normal chromosome constitutions
- Other conditions in the differential diagnosis of loose skin, whether or not associated with edema:
  1. Fetal hydantoin syndrome (loose nuchal skin, midface hypoplasia, distal digital hypoplasia)
  2. Disorders of chromosome constitution (trisomy 21, tetrasomy 12p mosaicism)
  3. Congenital lymphedema (Milroy edema)

WORKUP

- Giemsa banded karyotype to confirm clinical diagnosis
- Cardiologic consultation for evaluation for cardiac valvular abnormalities or aortic coarctation
- Renal ultrasonography after diagnosis is established
- Endocrine evaluations in older patients with short stature or amenorrhea
- Psychometrics to document known or suspected learning disabilities

LABORATORY TESTS

- As noted, routine Giemsa banded karyotype on peripheral lymphocytes is the gold standard to confirm the clinical impression in all suspected cases of Turner syndrome
- Important to exclude the presence of Y chromosome in mosaics
- Recognition of associated medical problems, such as hypergonadotropic hypogonadism or autoimmune thyroiditis, prompting periodic evaluation of these potential areas

IMAGING STUDIES

- Echocardiography
- Renal ultrasonography
- Abdominal ultrasonography for evaluation of ovarian and uterine size and morphology
- MRI of brain (especially in cases with known or suspected neurologic impairment)
- Radiography (for evaluation of carpal/metacarpal abnormalities, radioulnar synostosis)
- Bone age (for evaluation of short stature)

TREATMENT

Recognition of the multisystem involvement of Turner syndrome necessitates multiple medical specialists working in concert with the primary care provider to maximize and improve outcome while minimizing unnecessary or redundant testing.

NONPHARMACOLOGIC THERAPY

General medical care guided by normal medical standards with special attention paid to identifying such age-related problems as developmental delays, learning disabilities, slow growth, or amenorrhea

ACUTE GENERAL Rx

Specific treatment geared to the specific medical problem (e.g., cardiac or renal dysfunction)

CHRONIC Rx

- Estrogen-replacement therapy in early adolescents
- Some benefit from recombinant human growth hormone therapy

REFERRAL

- To geneticist: Clinical diagnosis, differential diagnosis, recurrence risk counseling, cytogenetic tests
- To endocrinologist (pediatric): Evaluation of short stature, estrogen or growth hormone replacement therapy
- To cardiologist: For cardiac valvular abnormalities or aortic coarctation

PEARLS & CONSIDERATIONS

COMMENTS

- Although newer studies are optimistic regarding outcomes, previous reports suffered from retrospective observations, case reports, and ascertainment bias, contributing to a generally poor interaction between the physician and patient.
- Affected individuals and families often benefit from the contemporary experiences and expertise of members of genetic support groups. The Turner Syndrome Society of the United States (800-365-9944; http://www.turnersyndrome.org) and the Alliance of Genetic Support Groups (800-336-4363 or 202-966-5557; http://geneticalliance.org) are valuable resources.
- A diagnosis of Turner syndrome should be considered in all girls with short stature or primary amenorrhea.
- Almost all women with Turner syndrome are infertile, although some conceive with assisted reproduction.

RELATED CONTENT

Turner Syndrome (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READING

Ross JL et al: Growth hormone plus childhood low-dose estrogen in Turner's syndrome, *N Engl J Med* 364:1230-1242, 2011.

FIG. E1 Physical manifestations associated with Turner syndrome. A, This newborn shows a webbed neck with low hairline, shield chest with widespread nipples, abnormal ears, and micrognathia. **B,** The low-set posterior hairline can be better appreciated in this older child, who also has protruding ears. **C,** In this frontal view, mild webbing of the neck and small, widely spaced nipples are evident, along with a midline scar from prior cardiac surgery. The ears are low set and prominent, protruding forward. **D** and **E,** The newborn shown in **A** also has prominent lymphedema of the hands and feet. (From Madan-Khetarpal S, Arnold G: Genetic disorders and dysmorphic conditions. In Zitelli BJ [eds]: *Zitelli and Davis' atlas of pediatric physical diagnosis,* ed 6, Philadelphia, 2012, Elsevier, Fig 1.25.)

BASIC INFORMATION

DEFINITION

Typhoid fever is a systemic infection caused by *Salmonella typhi* and S*almonella paratyphi* (A, B, and C).

SYNONYMS

Typhoid
Enteric fever

ICD-10CM CODES
A01.00 Typhoid fever, unspecified
A01.02 Typhoid fever with heart involvement
A01.09 Typhoid fever with other complications

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Approximately 400 cases of *S. typhi* infections are reported annually in the U.S. (Fig. E1). Over three quarters of the cases reported in the U.S. are now associated with foreign travel (most from Asia, Africa, and Central America).

PHYSICAL FINDINGS & CLINICAL PRESENTATION (TABLE E1)

- Incubation period is 8 to 16 days
- Usual manifestations:
  1. Prolonged fever (enteric fever). Temperature increases progressively and can remain elevated daily for 4 to 8 wk
  2. Myalgias
  3. Headache
  4. Cough
  5. Sore throat
  6. Malaise
  7. Anorexia, at times with abdominal pain and hepatosplenomegaly
  8. Diarrhea or constipation may occur early in the course of illness. One fifth of patients have constipation at diagnosis
  9. Rose spots, which are faint, maculopapular, blanching lesions, may sometimes be seen on the chest or abdomen
- Relative bradycardia (despite high fever) may occur
- Moderate hepatosplenomegaly may be present
- In an untreated patient, fever may last 1 to 2 mo. The main complication of untreated disease is GI bleeding as a result of perforation from ulceration of Peyer patches in the ileum. Mental status changes and shock are rare complications. The relapse rate is approximately 10%

ETIOLOGY

- *S. typhi* or *S. paratyphi* found only in humans
- Acquisition of disease by ingestion of food or water contaminated by human feces
- In the U.S., most cases are acquired either during foreign travel or by ingestion of food prepared by chronic carriers, many of whom acquired the organism outside of the U.S., most common in the Indian subcontinent (South, East, and Southeast Asia) and portions of sub-Saharan Africa

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Malaria
- Tuberculosis
- Brucellosis
- Amebic liver abscess
- Table E2 summarizes differential diagnoses of infectious diseases to consider in patients with possible typhoid or enteric fever

WORKUP

- Diagnosis is made by isolating *Salmonella typhi* from blood, stool, urine, or bone marrow.
- Blood, stool, and urine cultures are helpful.
- Cultures should be repeated if results are initially negative.
- Blood cultures are more likely to be positive early in the course of illness.
- Stool and urine cultures are more commonly positive in the second and third week of illness.
- Bone marrow biopsy cultures are 90% positive, although this procedure is usually not necessary.
- Rapid serologic tests can distinguish *Salmonella enterica* serotype *typhi* antibodies.

LABORATORY TESTS

- Neutropenia is common. Anemia and thrombocytopenia may be present
- Transaminitis is possible
- Culture:
  1. Blood
  2. Body fluids
  3. Biopsy specimens

DIAGNOSTIC IMAGING

- Chest x-ray may reveal pulmonary infiltrates.

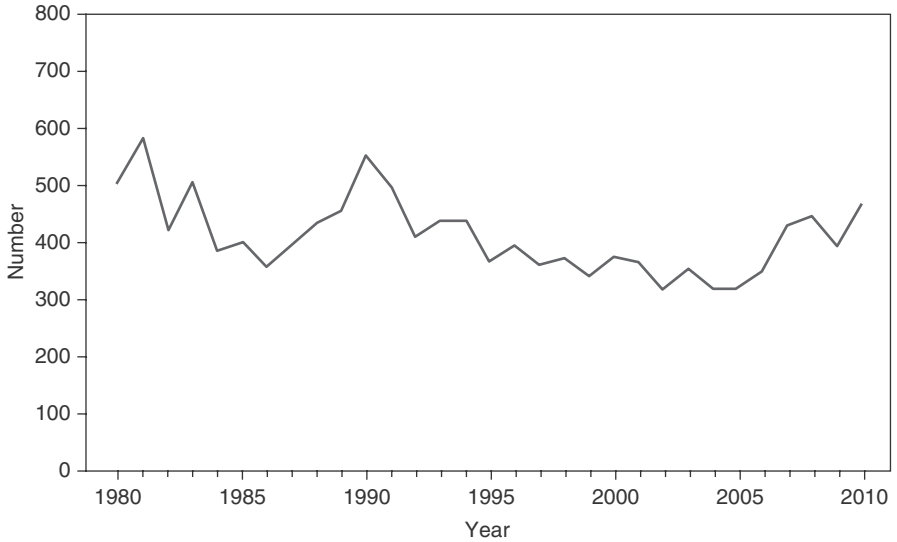

FIG. E1 Typhoid fever. Number of reported cases by yr, U.S., 1980 to 2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59[53]:1-111, 2012.)

TREATMENT

ACUTE GENERAL Rx

- Multidrug-resistant strains (MDR) are now common worldwide with resistance to ampicillin, Bactrim, and chloramphenicol. Resistance to quinolones is increasing, especially in Southeast Asia
- If not acquired in Asia: Ciprofloxacin 400 mg PO/IV q12h or levofloxacin 750 mg PO/IV q24h for 7 to 10 days
- If acquired in Asia: Ceftriaxone 2 g IV daily for 7 to 14 days
- An alternative agent for treatment remains azithromycin: Adults: 1 g PO on day 1, then 500 mg PO daily for 5 to 7 days. Children: 20 mg/kg orally on day 1, then 10 to 20 mg/kg (maximum 100 mg per day) for 5 to 7 days
- Dexamethasone, 3 mg/kg IV initially, followed by 1 mg/kg IV q6h for 8 doses for patients with septic shock or typhoid meningitis with antibiotic therapy
- Table E3 summarizes antibiotics commonly used in treating patients with enteric fever
- In vitro susceptibility testing should be done due to increasing antibiotic resistance

CHRONIC Rx

- Carrier states possible
- More common in age >60 yr and in people with gallstones
- Usual site of colonization: Gallbladder
- Treatment in those with persistently positive stool cultures and in food handlers
- Suggested regimens for eradication of carrier state:
  1. Ciprofloxacin 500 mg PO bid for 4 wk
  2. SMX/TMP 1 to 2 tabs PO bid for 6 wk (if susceptible)
  3. Amoxicillin, 2 g PO q8h for 6 wk (if susceptible)
- Cholecystectomy possibly required in carriers with gallstones who fail medical therapy

TABLE E1 Clinical Features of Typhoid and Paratyphoid Fever

	Clinical Feature	Approximate Frequency (%)*
Flulike symptoms	Fever	>95
	Headache	80
	Chills	40
	Cough	30
	Myalgia	20
	Arthralgia	<5
Abdominal symptoms	Anorexia	50
	Abdominal pain	30
	Diarrhea	20
	Constipation	20
Physical findings	Coated tongue	50
	Hepatomegaly	10
	Splenomegaly	10
	Abdominal tenderness	5
	Rash	<5
	Generalized adenopathy	<5

*The proportion of patients demonstrating these clinical features of enteric fever varies depending on the time, region, and type of clinical population (hospitalized or ambulatory) assessed. Estimates are drawn from recent case series in an endemic area, with patients presenting for ambulatory or inpatient care.

From Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.

TABLE E2 Differential Diagnoses of Infectious Diseases to Consider in Patients with Possible Typhoid or Enteric Fever

Common Infectious Causes of Nonspecific Acute Febrile Illness in Resource-limited Areas

- *Salmonella* bacteremia (typhoidal and nontyphoidal serotypes)
- Malaria
- Dengue and other arboviral fevers
- Leptospirosis
- Influenza
- Rickettsioses
- Bartonelloses

Infectious Causes of Typhoidal Illnesses, Including Prolonged Nonlocalizing Febrile Illnesses

- Persistent nontyphoidal bacteremia or abscess formation
- Typhus (rickettsiosis)
- Brucellosis
- Typhoidal tularemia
- Q fever
- Bartonellosis (including trench fever)
- Melioidosis
- Rat-bite fever, Haverhill fever *(Streptobacillus moniliformis)*
- Relapsing fever (borreliosis)
- Infective endocarditis
- Malaria
- Babesiosis
- Visceral leishmaniasis
- West African trypanosomiasis
- Tuberculosis
- Endemic mycoses (histoplasmosis)

From Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.

DISPOSITION

- Treated patients usually respond to therapy, with a small percentage becoming chronic carriers.
- The relapse rate is approximately 10%.
- Untreated patients may have serious complications.
- Complications of typhoid and paratyphoid fever are summarized in Table E4.

REFERRAL

- Failure of therapy
- Chronic carrier

PEARLS & CONSIDERATIONS

COMMENTS

- Live attenuated oral and IM parenteral vaccines are available for travelers to areas of high risk (Table E5).
- Oral vaccines are about 70% effective and last up to 5 yr. It is a series of four capsules taken on alternate days for persons ≥6 yr of age.
- The intramuscular vaccine is over 75% effective but lasts only 2 yr but can be given to persons ≥2 yr of age.
- Infection with antimicrobial-resistant *S. typhi* strains among U.S. patients with typhoid fever is associated with travel to the Indian subcontinent, and an increasing proportion of these infections are caused by *S. typhi* strains with decreased susceptibility to fluoroquinolones and beta-lactam antibiotics.
- Beginning in 2017 in the U.S., there has been an outbreak in 32 states of over 250 cases, including two deaths, with a strain of *Salmonella* resistant to cipro and azithromycin whose source is contaminated beef from the U.S. and soft Mexican cheese.

RELATED CONTENT

Typhoid Fever (Patient Information)
Salmonellosis (Related Key Topic)

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TABLE E3 Antibiotics Commonly Used in Treating Patients with Enteric Fever

	Antibiotic	Route	Typical Pediatric Dosage*	Adult Dosage	Typical Duration	Comments
Original first-line agents	Chloramphenicol	PO/IV	12.5-25 mg/kg qid	2-3 g/day (divided qid)	14-21 days	These agents are effective for susceptible strains; however, multidrug resistance to all of these agents is common in many areas.
	Amoxicillin	PO	25-35 mg/kg tid	1 g tid	14 days	
	Ampicillin	IV	25-50 mg/kg q6h	2 g q6h	14 days	
	TMP/SMX	PO/IV	8-12 mg/kg/day (TMP) 40-60 mg/kg/day (SMX) (divided qid)	160 mg/800 mg qid	14 days	
Fluoroquinolones	Ofloxacin	PO/IV	15 mg/kg bid	400 mg PO bid	5-14 days	Ofloxacin and ciprofloxacin are effective for nalidixic acid–susceptible strains. Short courses of 5-7 days are acceptable in uncomplicated cases. Courses of 10-14 days are recommended in patients requiring hospitalization or parenteral therapy. Gatifloxacin appears effective for uncomplicated cases caused by NaR strains.
	Ciprofloxacin	PO/IV	15 mg/kg bid	500 mg PO bid	5-14 days	
	Gatifloxacin	PO	10 mg/kg qd	10 mg/kg/day qd	7 days	
Third-generation cephalosporins	Ceftriaxone	IV	50-100 mg/kg qd	1-2 g IV qd	10-14 days†	These are an alternative to fluoroquinolones for NaR strains, and for empirical therapy in areas where NaR is common.
	Cefixime	PO	10 mg/kg bid	200 mg PO bid	7-14 days	
Macrolides	Azithromycin	PO	20 mg/kg qd	500-1000 mg PO qd	7 days	These are an alternative for uncomplicated infections caused by NaR strains and for empirical therapy where multidrug resistance and NaR are common.
Eradication of carriage	Ciprofloxacin	PO	—	500-750 mg bid	28 days	If eradication is indicated for public health reasons, a trial of medical therapy is justified, even in patients with evidence of cholelithiasis. Cholecystectomy may be considered.

NaR, Nalidixic acid resistant (see text); *TMP-SMX,* trimethoprim-sulfamethoxazole.
*Weight-based pediatric dosage should not exceed adult maximum.
†Recommended that treatment continue for at least 7 days post-defervescence to minimize relapse.
From Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.

TABLE E4 Complications of Typhoid and Paratyphoid Fever

System	Complication	Notes
Gastrointestinal	Hemorrhage	10%-15% in hospitalized patients
	Perforation	3% in hospitalized patients
Hepatobiliary	Jaundice	1%-3% in hospitalized patients
	Hepatitis	Usually subclinical (↑ ALT/AST)
	Acute cholecystitis	Rare; gallbladder may perforate
Neurologic	Mild encephalopathy	Confusion or apathy common
	Severe encephalopathy	Delirium, stupor, or coma
	Seizures	Common in children ≤5 yr
	Meningitis	Rare, primarily infants
	Guillain-Barré syndrome	Reported
Respiratory	Bronchitis	Dry cough is common
	Pneumonia	May be other concomitant bacterial infection (e.g., *Streptococcus pneumoniae*)
	Empyema	Rare reports
Cardiovascular	Myocarditis	Usually subclinical (ECG changes)
	Endocarditis	Rare reports
Hematologic	Anemia	Usually subclinical
	Disseminated intravascular coagulation	Usually subclinical (↑ PT/PTT)
Other	Musculoskeletal pyogenic infections	Osteomyelitis (particularly vertebral), psoas abscess and others reported
	Hemolytic-uremic syndrome	Reported
	Miscarriage	Reported

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase; *ECG,* electrocardiogram; *PT,* prothrombin time; *PTT,* partial thromboplastin time.
From Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.

TABLE E5 Typhoid Fever Vaccines Commercially Available Internationally

Vaccine	Type	Route	Dose and Interval	Minimum Age (yr)	Protection Against *S. Typhi*	Boosting Interval in Travelers
Ty21a	Live attenuated	Oral	Four doses (in U.S.) Administer one dose every other day until complete	5*	50%-80%†	Every 5 yr
Vi capsule antigen	Polysaccharide	Intramuscular	1	2	50%-80%	Every 2 yr

*Five yr and older per World Health Organization; 6 yr and older per U.S. Advisory Committee on Immunization Practices.
†Has some efficacy against *S. paratyphi* B (see text). Additional vaccines are in development, including conjugate vaccines.
From Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.

SUGGESTED READINGS

Andrews JR et al: Typhoid conjugate vaccines: a new tool in the fight against antimicrobial resistance, *Lancet Infect Dis* 19:e26-e30, 2019.

Anusha R et al: Comparison of the Enterocheck WB rapid antigen test with blood culture methods for the diagnosis of typhoid fever, *Ann Trop Paediatr* 31(3):231-234, 2011.

Crump JA, Mintz ED: Global trends in typhoid and paratyphoid fever, *Clin Infect Dis* 50(2):241-246, 2010.

de Jong HK, Parry CM, van der Poll T, Wiersinga WJ: Host-pathogen interaction in invasive Salmonellosis, *PLoS Pathog* 8(10):e1002933, 2012.

Gibani MM et al: Typhoid and paratyphoid fever: a call to action, *Curr Opin Infect Dis* 31:440-448, 2018.

BASIC INFORMATION

DEFINITION

Ulcerative colitis (UC) is an idiopathic, remitting and relapsing, chronic inflammatory bowel disease that starts in the rectum and extends proximally.

SYNONYMS

UC
Inflammatory bowel disease (IBD)
Idiopathic proctocolitis
Pancolitis

ICD-10CM CODES

K51.0	Ulcerative pancolitis
K51.2	Ulcerative proctitis
K51.3	Ulcerative rectosigmoiditis
K51.5	Left-sided colitis
K51.90	Ulcerative colitis, unspecified, without complications
K51.80	Other ulcerative colitis without complications
K51.811	Other ulcerative colitis with rectal bleeding
K51.812	Other ulcerative colitis with intestinal obstruction
K51.813	Other ulcerative colitis with fistula
K51.814	Other ulcerative colitis with abscess
K51.818	Other ulcerative colitis with other complication
K51.819	Other ulcerative colitis with unspecified complications
K51.911	Ulcerative colitis, unspecified with rectal bleeding
K51.912	Ulcerative colitis, unspecified with intestinal obstruction
K51.913	Ulcerative colitis, unspecified with fistula
K51.914	Ulcerative colitis, unspecified with abscess
K51.918	Ulcerative colitis, unspecified with other complication
K51.919	Ulcerative colitis, unspecified with unspecified complications

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The incidence of UC is 9 to 12 cases per 100,000 persons per yr in the U.S.; worldwide, the estimated incidence ranges from 1.2 to 20.3 cases per 100,000 person-yrs and its prevalence ranges from 7.6 to 246.0 per 100,000 persons. It is most common between ages 15 and 40 yr, with a second peak between 50 and 80 yr. The disease affects men and women at similar rates. Infection with nontyphoid salmonella or campylobacter is associated with an 8-10 times higher risk of developing ulcerative colitis in the following yr. Worldwide UC is more common than Crohn disease.

PREVALENCE: The prevalence of UC is 7.6 to 246.0 cases per 100,000 per yr. Higher prevalence in Ashkenazi Jewish descendants.

GEOGRAPHIC DISTRIBUTION: The highest incidence and prevalence of IBD are seen in northern Europe and North America, and the lowest in continental Asia.

GENETICS:

- Both specific and nonspecific gene variants are associated with UC.
- There are 47 loci associated with UC, of which 19 are specific for UC and 28 are shared with Crohn disease.
- Abnormalities in humoral and cellular adaptive immunity are also found in UC.

ETIOLOGY AND PATHOGENESIS

Accumulating evidence suggests that it may result from an inappropriate inflammatory response to environmental triggers and immune dysregulation involving CD4+ T-cell Th2 response in a genetically susceptible host.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with UC often present with acute onset of bloody diarrhea accompanied by tenesmus, fever, and dehydration. At presentation 40% of adults have proctitis, 40% have left-sided colitis, and 20% have pancolitis. Diarrhea is not always present in UC patients with proctosigmoiditis and proctitis, and patients may have constipation.
- Abdominal pain is not usually a prominent symptom. Abdominal distention and tenderness may indicate the presence of complications such as toxic megacolon.
- The onset of symptoms is typically acute and is generally followed by periods of spontaneous remission and frequent relapses.
- Fever, evidence of dehydration may be present during the acute flare-up.
- Evidence of extraintestinal manifestations may be present in nearly 25% of patients: Liver disease, sclerosing cholangitis, iritis, uveitis, episcleritis, arthritis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis. Box 1 summarizes common extraintestinal manifestations of UC.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS (TABLE 1, BOX 2)

- Crohn disease
- Bacterial infections:
  1. Acute: *Campylobacter, Yersinia, Salmonella, Shigella, Chlamydia, Escherichia coli, Clostridium difficile,* gonococcal proctitis
  2. Chronic: Whipple disease, tuberculosis, enterocolitis
- Irritable bowel syndrome
- Protozoal and parasitic infections (amebiasis, giardiasis, cryptosporidiosis)
- Neoplasm (intestinal lymphoma, carcinoma of colon)
- Ischemic bowel disease
- Diverticulitis
- Celiac sprue, lymphocytic or collagenous colitis, radiation enteritis, endometriosis
- Solitary rectal ulcer
- Acute self-limited colitis
- Medication (NSAIDs, chemotherapy)

WORKUP

An accurate diagnosis of UC should define the extent and severity of inflammation. Diagnostic workup includes:

- Comprehensive history, physical examination.
- Laboratory tests (see "Laboratory Tests").
- Colonoscopy to establish the presence of mucosal inflammation; typical endoscopic findings in UC are areas of continuous friable mucosa; diffuse, uniform erythema replacing the usual mucosal vascular pattern (Table 2); and pseudopolyps. The transition from abnormal to normal tissue tends to be abrupt. Rectal involvement is invariably present if the disease is active. Pathologic findings suggestive of UC include crypt abscesses and atrophy, mucin depletion, basal plasmacytosis, basal lymphoid aggregates, increased lamina propria cellularity, and Paneth cell metaplasia.

LABORATORY TESTS

- Anemia and high erythrocyte sedimentation rate (in severe colitis) are common but normal levels do not rule out the disorder.

BOX 1 Common Extraintestinal Manifestations of Ulcerative Colitis

Cutaneous/Oral
Angular stomatitis
Aphthous stomatitis
Erythema nodosum
Oral ulcerations
Psoriasis
Pyoderma gangrenosum
Pyostomatitis vegetans
Sweet syndrome (acute febrile neutrophilic dermatosis)

Ophthalmologic
Conjunctivitis
Episcleritis
Retinal vascular disease
Scleritis
Uveitis, iritis

Musculoskeletal
Ankylosing spondylitis
Osteomalacia
Osteonecrosis
Osteopenia
Osteoporosis
Peripheral arthropathy
Sacroiliitis

Hepatobiliary
Autoimmune hepatitis
Cholangiocarcinoma
Pericholangitis
PSC
Hepatic steatosis

Hematologic
Anemia of chronic disease
Autoimmune hemolytic anemia
Hypercoagulable state
Iron deficiency anemia
Leukocytosis or thrombocytosis
Leukopenia or thrombocytopenia

PSC, Primary sclerosing cholangitis.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

TABLE 1 Features That Distinguish Ulcerative Colitis from Other Diagnoses

Diagnosis	Clinical Features	Radiologic and Colonoscopic Features	Histologic Features
UC	Bloody diarrhea	Extends proximally from rectum; fine mucosal ulceration	Distortion of crypts; acute and chronic diffuse inflammatory cell infiltrate; goblet cell depletion; crypt abscesses; lymphoid aggregates
Crohn colitis	Perianal lesions are common; may be associated with ileitis; frank bleeding is less common than in UC	Segmental disease; rectal sparing; strictures, fissures, ulcers, fistulas; small bowel involvement	Focal inflammation; submucosal involvement; granulomas; goblet cell preservation; transmural inflammation; fissuring
Ischemic colitis	Occurs in older adults; sudden onset, often painful; usually resolves spontaneously in several days	Segmental splenic flexure and sigmoid involvement are most common, with thumbprinting early and ulceration after 24-72 hr; rectal involvement is rare	Mucosal necrosis with ghost cells; congestion with red blood cells; hemosiderin-laden macrophages and fibrosis (when disease is chronic)
Microscopic colitis	Watery diarrhea; normal-appearing mucosa at colonoscopy	Usually normal	Chronic inflammatory infiltrate; increased intraepithelial lymphocytes (lymphocytic colitis) and/or subepithelial collagen band (collagenous colitis)
Infectious colitis	Sudden onset; identifiable source in some cases (e.g., *Salmonella* spp.); pain may predominate (e.g., *Campylobacter* spp.); pathogens are present in stool	Nonspecific findings	Crypt architecture is usually normal; edema, superficial neutrophilic infiltrate, crypt abscesses
Amebic colitis	History of travel to endemic area; amebae may be detected in a fresh stool specimen but ELISA for amebic lectin antigen is the preferable diagnostic test	Discrete ulcers; ameboma or strictures	Similar to UC; amebae present in lamina propria or in flask-shaped ulcers, identified by periodic acid–Schiff stain
Gonococcal proctitis	Rectal pain; pus	Granular changes in rectum	Intense polymorphonuclear neutrophil infiltration; purulent exudate; Gram-negative diplococci
Pseudomembranous colitis	Often a history of antibiotic use; characteristic pseudomembranes may be seen on sigmoidoscopy; *Clostridium difficile* toxin is detectable in stools	Edematous; shaggy outline of colon; pseudomembranes may be identified radiologically or seen at colonoscopy	May resemble acute ischemic colitis; summit lesions of fibrinopurulent exudate

ELISA, Enzyme-linked immunosorbent assay; *UC,* ulcerative colitis.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

- Potassium, magnesium, calcium, and albumin may be decreased.
- Antineutrophil cytoplasmic antibodies (ANCA) with a perinuclear staining pattern (pANCA) can be found in >45% of patients; there is an increased frequency in treatment-resistant left-sided colitis, suggesting a possible association between these antibodies and a relative resistance to medical therapy in patients with UC.
- Calprotectin is a protein that is measured in feces as a marker of intestinal mucosa leukocyte activity that may be useful for screening of patients with suspected IBD. Trials have shown that based on a pretest probability of IBD of 32% in adults, an abnormal fecal calprotectin test would increase the posttest probability to 91% and a normal result would reduce the probability to 3%.
- Fecal lactoferrin is also a sensitive marker of intestinal inflammation.
- Stool examinations for ova and parasites, stool culture, and testing for *Clostridium difficile* toxin and *E. coli* O157:H7 may be useful to eliminate other causes of diarrhea in selected patients with risk factors.

IMAGING STUDIES

Image studies (plain radiography, CT scan [Fig. E1]) are generally reserved for suspected complications such as perforation of bowel or toxic megacolon.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Correct nutritional deficiencies; total parenteral nutrition with bowel rest may be necessary in severe cases. Folate supplementation may reduce the incidence of dysplasia and cancer in chronic UC.
- Avoid oral feedings during acute exacerbation to decrease colonic activity; a low-roughage diet may be helpful in early relapse.
- Psychotherapy is useful in most patients. Referral to self-help groups is also important because of the chronicity of the disease and the young age of the patients.

ACUTE GENERAL Rx

The therapeutic options vary with the degree of disease (mild, severe, fulminant) and areas of involvement (distal, extensive).

- Mild disease can be treated with 5-aminosalicylate agents (mesalamine, olsalazine, balsalazide, sulfasalazine). It can be administered as an enema (40 mg once daily at bedtime for 3 to 6 wk) or suppository (500 mg bid) for patients with distal colonic disease. Oral forms in which the 5-acetyl salicylic acid is in a slow-release or pH-dependent matrix (Pentasa 1 g qid, Asacol 800 mg PO tid) can deliver therapeutic concentrations to the more proximal small bowel or distal ileum. Olsalazine can be useful for maintenance of remission of UC in patients intolerant to sulfasalazine. Usual dose is 500 mg bid taken with food. Balsalazide is indicated for mild to moderately active UC. Usual dose is three 750-mg capsules tid. Probiotics may also be helpful in inducing remission in mild-to-moderate UC.
- Mild-to-moderate UC is often treated with a combination of rectal and oral 5-aminosalicylate. Refractory patients are candidates for oral glucocorticoids or immunosuppressive agents (e.g., cyclosporine). An algorithm for the management of mildly to moderately active UC is illustrated in Fig. 2.
- Severe disease usually responds to oral corticosteroids (e.g., prednisone 40 to 60 mg/day); the FDA has recently approved an extended-release formulation of the corticosteroid budesonide for induction of remission in mild to moderate ulcerative colitis. Corticosteroid suppositories or enemas are also useful for distal colitis. The immunosuppressant azathioprine or mercaptopurine also provides effective long-term treatment for Crohn disease. Fig. 3 describes an algorithm for the management of severely active UC.
- Biological agents are emerging treatment options for the management of ulcerative colitis. Infliximab, a chimeric monoclonal

BOX 2 Differential Diagnosis of Ulcerative Colitis

Infectious Causes
Aeromonas hydrophila
Campylobacter jejuni
Chlamydia spp.
Clostridium difficile
Cytomegalovirus
Entamoeba histolytica
Escherichia coli O157:H7, other EHEC
HSV
Listeria monocytogenes
Neisseria gonorrhoeae
Salmonella spp.
Schistosomiasis
Shigella spp.
Yersinia enterocolitica

Noninfectious Causes
Acute self-limited colitis
Behçet disease
Crohn disease
Diversion colitis
Diverticulitis
Drugs and toxins
  Chemotherapy
  Gold
  Penicillamine
Eosinophilic colitis
Graft-versus-host disease
Ischemic colitis
Microscopic colitis
  Collagenous
  Lymphocytic
Neutropenic colitis (typhlitis)
NSAIDs
Radiation colitis
SCAD
Solitary rectal ulcer syndrome

EHEC, enterohemorrhagic *Escherichia coli; HSV,* herpes simplex virus; *SCAD,* segmental colitis associated with diverticulosis.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

antibody, has been shown to be effective in patients who have not responded to corticosteroid therapy. Newer tumor necrosis factor inhibitors include adalimumab (ADA), golimumab, and vedolizumab for treatment of moderate-to-severe ulcerative colitis. These agents can be used for induction and maintenance of remission in patients that have not responded to other therapies or are corticosteroid-dependent. Head-to-head trials of these biologic agents are necessary to establish the best therapeutic option.

- Fulminant disease generally requires hospital admission and parenteral corticosteroids (e.g., IV hydrocortisone 100 mg q6h). When bowel movements have returned to normal and the patient is able to eat normally, oral prednisone is resumed. IV cyclosporine can also be used in severe refractory cases; renal toxicity is a potential complication.
- Surgery is indicated in patients who do not respond to intensive medical therapy. Fig. 4 illustrates the surgical management of chronic UC.
- Proctocolectomy is usually curative in these patients and also eliminates the high risk of developing adenocarcinoma of the colon (10% to 20% of patients develop it after 10 yr with the disease). Total proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the procedure of choice for most patients who require elective surgery, since it preserves anal sphincter function. Continent ileostomy is an alternative procedure.

TABLE 2 Endoscopic Differentiation of Ulcerative Colitis and Crohn Disease

Feature	Ulcerative Colitis	Crohn Disease
Distribution	Diffuse inflammation that extends proximally from the anorectal junction	Rectal sparing, frequent skip lesions
Inflammation	Diffuse erythema, early loss of vascular markings with mucosal granularity or friability	Focal and asymmetrical, cobblestoning; granularity and friability less commonly seen
Ulceration	Small ulcers in a diffusely inflamed mucosa; deep, ragged ulcers in severe disease	Aphthoid ulcers, linear or serpiginous ulceration; intervening mucosa is often normal
Colonic lumen	Often narrowed in long-standing chronic disease; tubular colon; strictures are rare	Strictures are common

From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

CHRONIC Rx

- Colonoscopic surveillance and multiple biopsies should be instituted approximately 10 yr after diagnosis because of the increased risk of colon carcinoma.
- Erythropoietin is useful in patients with anemia refractory to treatment with iron and vitamins.
- In patients on long-term steroid therapy, periodic bone density scans are recommended to screen for glucocorticoid-induced osteoporosis.

DISPOSITION

- The natural history of the disease is one of remission and episodic flares.
- The clinical course is variable. ~66% of patients will achieve clinical remission with medical therapy, and nearly 80% of treatment-compliant patients maintain remission. Fifteen percent to 20% of patients eventually require colectomy. Pouchitis is the most common long-term complication of IPAA (up to 40% of patients). >75% of patients treated medically will experience relapse.

REFERRAL

- Gastrointestinal consultation for initial diagnostic sigmoidoscopy/colonoscopy in suspected cases
- Surgical referral for patients with severe disease unresponsive to medical therapy. Indications for surgery in patients with UC are summarized in Box 3.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Ulcerative Colitis (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

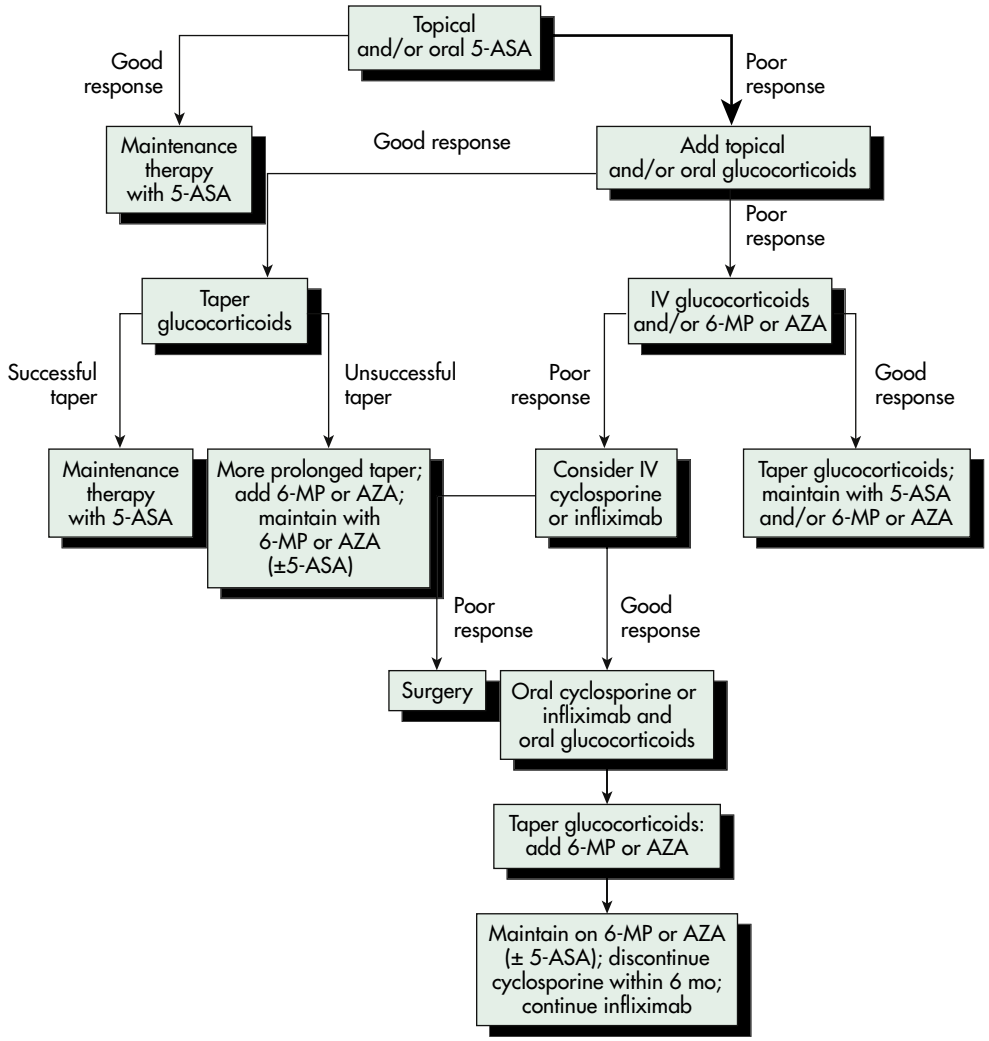

FIG. 2 Algorithm for the management of mildly to moderately active ulcerative colitis. *5-ASA,* 5-Aminosalicylate; *AZA,* azathioprine; *6-MP,* 6-mercaptopurine. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

BOX 3 Indications for Surgery in Patients with Ulcerative Colitis

- Colonic dysplasia or carcinoma
- Colonic perforation
- Growth retardation
- Intolerable or unacceptable side effects of medical therapy
- Medically refractory disease
- Systemic complications that are recurrent or unmanageable
- Toxic megacolon
- Uncontrollable colonic hemorrhage

From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

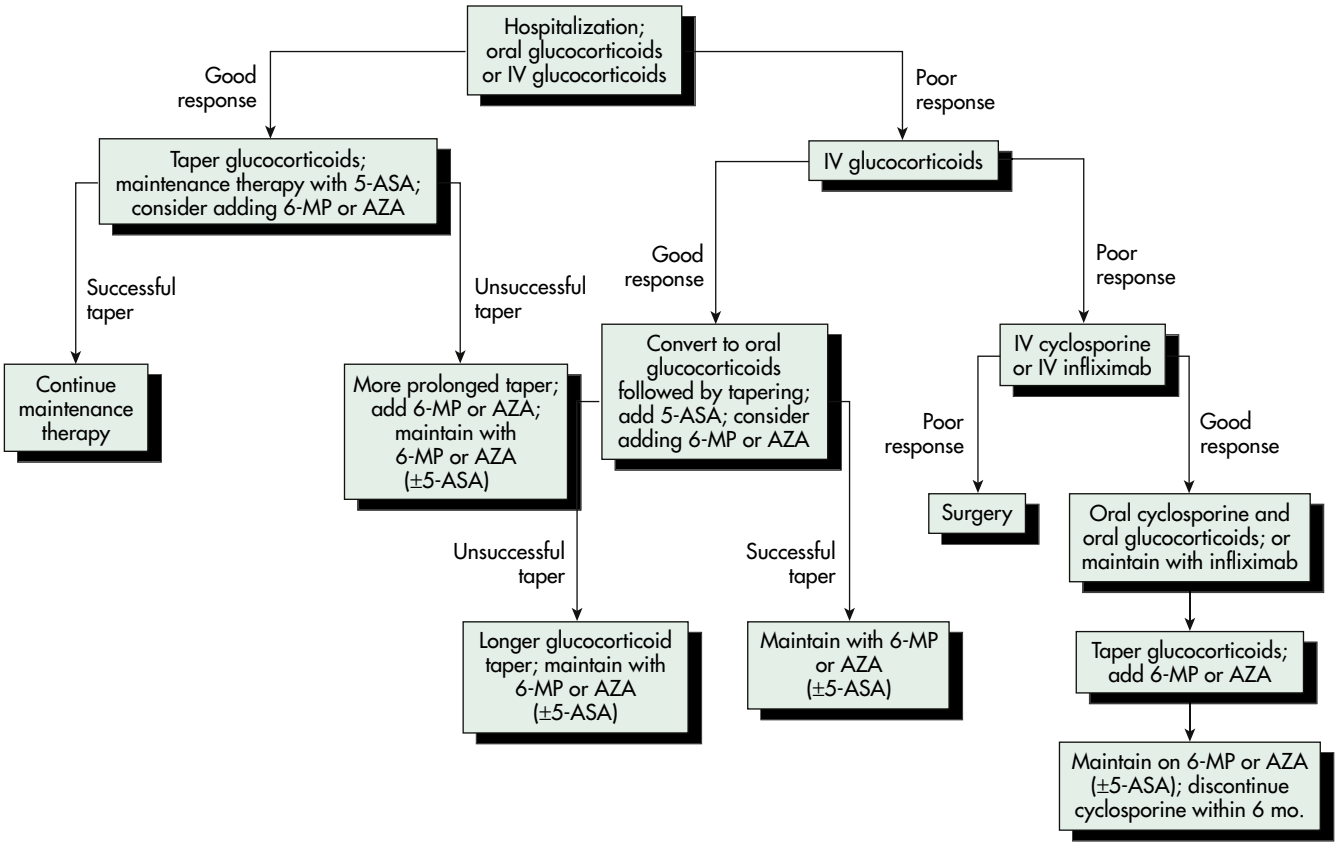

FIG. 3 Algorithm for the management of severely active ulcerative colitis. *5-ASA,* 5-Aminosalicylate; *AZA,* azathioprine; *6-MP,* 6-mercaptopurine. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

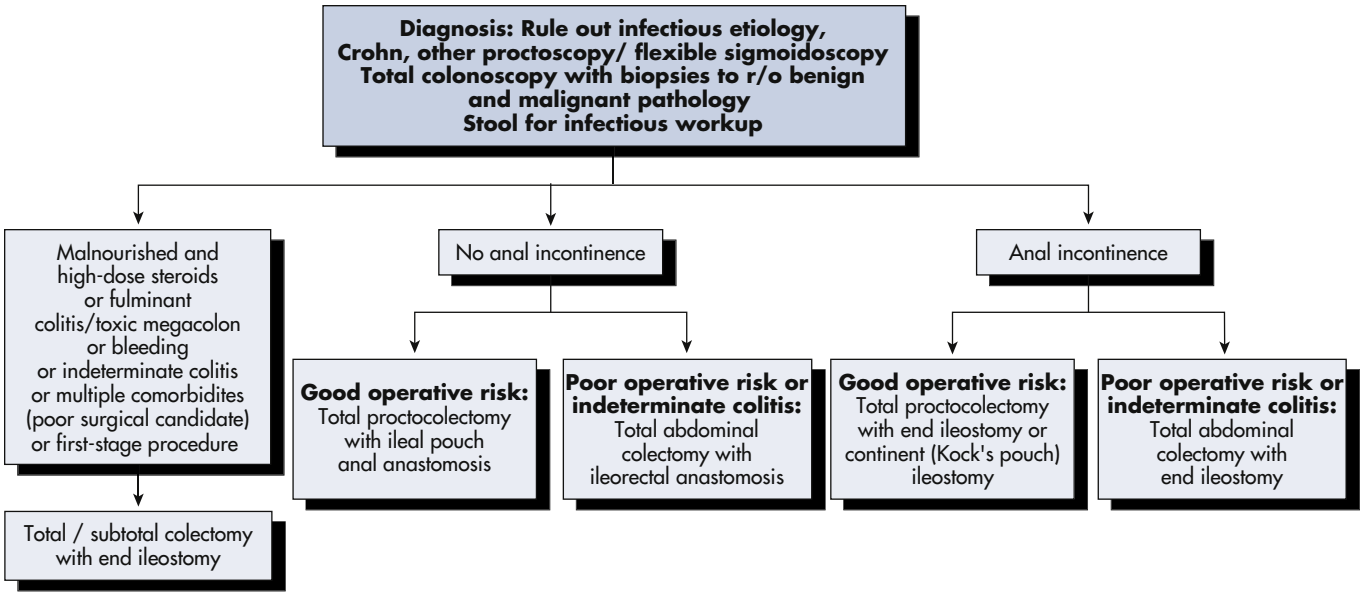

FIG. 4 Surgical management of chronic ulcerative colitis. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

SUGGESTED READINGS

Adams MA, Bornemann PH: Ulcerative colitis, *Am Fam Physician* 87(10):699-705, 2013.

Danese S, Fiocchi C: Ulcerative colitis, *N Engl J Med* 365:1713-1725, 2011.

Danese S et al: Biological agents for moderately active ulcerative colitis, a systematic review and network meta-analysis, *Ann Intern Med* 160:704-711, 2014.

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Sands BE et al: Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis, *N Engl J Med* 381:1215-1226, 2019.

Van Rheenen PF et al: Fecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis, *BMJ* 341:c3369, 2010.

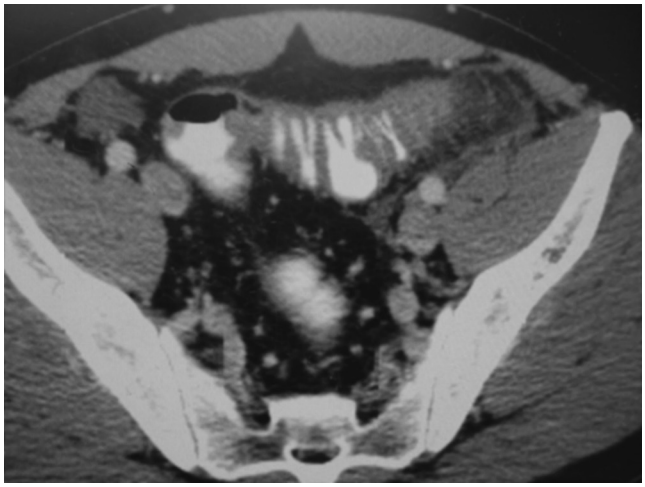

FIG. E1 Computed tomography scan showing colonic wall thickening in a patient with ulcerative colitis. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

Unruptured Intracranial Aneurysms (UIAs)

BASIC INFORMATION

DEFINITION

Unruptured intracranial aneurysms (UIAs) are acquired aneurysms found at bifurcations of major arteries. Most are found in the circle of Willis, with 85% being at the anterior circulation. Rupture of these aneurysms results in more than 80% of nontraumatic subarachnoid hemorrhages (SAH).

SYNONYMS

Berry aneurysms
Saccular aneurysms
UIAs

ICD-10CM CODE
I67.1 Cerebral aneurysm, nonruptured

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: The incidence of UIAs is currently unknown.

PREVALENCE: The prevalence of UIAs is approximately 3% in a population without comorbidity and with a mean age of 50 yr.

PREDOMINANT SEX & AGE: UIAs are 3× more common in women and are more likely to occur in those aged 60 and older. In the pediatric population, UIAs are twice as common in males.

GENETICS: No specific genetic mutations have been shown to cause UIAs. However, more than 19 single nucleotide polymorphisms (SNP) have been associated with sporadic aneurysms. SNPs on the *EDNRA, CDKN2B,* and *SOX17* genes located on chromosomes 4, 8, and 9 have been found to have the strongest association with developing UIAs.

- Genetic disorders that increase the risk of UIAs include autosomal dominant polycystic kidney disease, Marfan syndrome, Ehlers-Danlos syndrome type IV, multiple endocrine neoplasia type I, neurofibromatosis type 1, and hereditary hemorrhagic telangiectasia. Less commonly, aneurysms can occur with systemic lupus erythematosus, fibromuscular dysplasia, sickle-cell disease, and coarctation of the aorta.

RISK FACTORS: Risk factors include female gender, older age, family history, genetic factors, cigarette smoking, and hypertension.

- Risk factors that increase the risk of subarachnoid hemorrhage are also relevant to consider, as aneurysm rupture results in subarachnoid hemorrhages. These factors include heavy alcohol use, high dose estrogen, cocaine use in young populations, and low body mass index.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

UIAs often remain asymptomatic and undetected for long periods of time but also may present with nonspecific symptoms such as headaches or vertigo. A phase of aneurysm growth usually precedes any cases of rupture. Small aneurysms (<5 mm) are likely to remain asymptomatic, while those that grow to a large size may compress surrounding structures and present with specific neurological deficits. Examples include third cranial nerve palsy due to an aneurysm of the posterior communicating or basilar arteries, hemiparesis due to middle cerebral artery aneurysms, and cavernous sinus syndrome due to aneurysms in the cavernous sinus. In rare cases, emboli may originate from aneurysms and cause transient ischemic attacks or infarctions in other regions.

ETIOLOGY

The development of aneurysms is a multifactorial process that involves hemodynamic stress, inflammation, and molecular changes that result in a weakened arterial wall. Saccular aneurysms form as protrusions that are often thin-walled and lack tunica media. Fusiform aneurysms are less common and form due to dilatation of the artery itself. It's currently thought that hemodynamic stress causes endothelial dysfunction and starts the process of arterial wall inflammation and remodeling, while other factors such as smoking and connective tissue disorders are contributory.

DIAGNOSIS

WORKUP

- The presence of UIAs should be investigated in those with a history of SAH.
- Patients with significant family history (>2 first-degree relatives with UIA or SAH), autosomal dominant polycystic kidney disease, coarctation of the aorta, or microcephalic osteodysplastic primordial dwarfism should be offered screening with MRA or CTA.

LABORATORY TEST

Lab tests are unrevealing when investigating UIAs.

IMAGING STUDIES

- Most UIAs are discovered incidentally on brain MRI or CT. However, MRA and CTA have been shown to detect smaller aneurysms and are the tests of choice in screening for UIAs. Patients with contraindications to contrast administration can be screened with MRA.
- Digital subtraction angiography is used when surgical treatment of UIA is considered.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Reduction of risk factors such as smoking.
- Exercise is associated with a reduced risk of aneurysm formation and rupture.

ACUTE GENERAL Rx

- The main surgical treatments for UIAs are endovascular coiling and surgical clipping. However, there are few guidelines for surgical treatment of UIAs. Currently, it's believed that stable UIAs at <3 mm should not undergo surgical treatment, while patients who present with headaches or nerve palsies likely should be treated surgically. Beyond this, a detailed discussion of the risks and benefits and an individualized treatment plan are necessary.
- Patients with known UIAs presenting with severe headaches or symptoms of nerve compression should raise high suspicion for development of SAH.

CHRONIC Rx

- Blood pressure management, with the goal of systolic blood pressure <140.
- Aspirin use has been associated with lower risk of aneurysm rupture.

COMPLEMENTARY & ALTERNATIVE MEDICINE

None

DISPOSITION

The risk of rupture for patients managed conservatively is related to age, smoking status, blood pressure, size and location of the aneurysm, and history of previous SAH. This risk is estimated to be 1.4% in 1 yr and 3.4% in 5 yr. Currently, it's recommended that those with family history, multiple UIAs, or a high number of risk factors should be monitored for aneurysm growth.

REFERRAL

Vascular neurology or neurosurgery

PREVENTION

Decreasing modifiable risk factors such as smoking

PATIENT & FAMILY EDUCATION

American Association of Neurological Surgeons
www.aans.org/Patients/Neurosurgical-Conditions-and-Treatments/Cerebral-Aneurysm

RELATED CONTENT

Subarachnoid Hemorrhage (Related Key Topic)

AUTHORS: **Sudad Kazzaz, MD,** and **Joseph S. Kass, MD, JD, FAAN**

SUGGESTED READINGS

Brown R et al.: Unruptured intracranial aneurysms: epidemiology, natural history, management options, and familial screening, *Lancet Neurol* 13:393-404, 2014.

Burkhardt J et al: Management of small incidental intracranial aneurysms, *Neurosurg Clin N Am* 28:389-396, 2017.

Etminan N et al: Unruptured intracranial aneurysms: development, rupture and preventive management, *Nat Rev Neurol* 12:699-713, 2016.

Hackenberg K et al: Unruptured intracranial aneurysms contemporary data and management, *Stroke* 49:2268-2275, 2018.

Malhotra A et al: Growth and rupture risk of small unruptured intracranial aneurysms: a systematic review, *Ann Int Med* 167:26-33, 2017.

Signorell F et al: Hemodynamic stress, inflammation, and intracranial aneurysm development and rupture: a systematic review, *World Neurosurg* 115:234-244, 2018.

Thompson B et al: Guidelines for the management of patients with unruptured intracranial aneurysms, *Stroke* 46:2368-2400, 2015.

Upper Extremity Deep Vein Thrombosis

BASIC INFORMATION

DEFINITION

Deep vein thrombosis of the upper extremity (UEDVT) refers to the thrombosis of the subclavian, axillary, and brachial veins (Fig. E1). UEDVT has become more common due to the increased use of central venous catheters (CVCs), cardiac pacemakers, and defibrillators.

SYNONYMS

UEDVT
Upper extremity deep venous thrombosis

ICD-10CM CODES

I82.621	Acute embolism and thrombosis of deep veins of right upper extremity
I82.622	Acute embolism and thrombosis of deep veins of left upper extremity
I82.623	Acute embolism and thrombosis of deep veins of upper extremity, bilateral

EPIDEMIOLOGY & DEMOGRAPHICS

- UEDVT accounts for approximately 10% of all cases of deep vein thrombosis, resulting in an annual incidence of 0.4 to 1 case per 10,000 people.
- Complications of upper extremity deep vein thrombosis include pulmonary embolism (6%), recurrent venous thromboembolism (between 4% and 8%), and postthrombotic syndrome (15%).
- The overall 3-mo mortality rate of patients with UEDVT is 11%, which is significantly high compared to patients with lower extremity DVT.

RISK FACTORS:

- Prior line infection
- Obstructed central venous catheter
- Upper extremity surgery
- Casting of the arm with immobility
- Malignancy

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients with upper extremity deep vein thrombosis most commonly present with swelling, discoloration, or both, and pain and tenderness to palpation of the affected upper limb. Most thrombotic episodes secondary to indwelling CVCs remain subclinical and are only discovered during workup of catheter sepsis, catheter malfunction, or pulmonary embolism.

ETIOLOGY

- Primary UEDVT is a rare disorder (2 per 100,000 persons per yr) and includes idiopathic thrombosis and thrombosis associated with the thoracic outlet syndrome (TOS) or effort (Paget-Schroetter syndrome). TOS refers to compression of the neurovascular bundle as it exits the thoracic inlet. Effort thrombosis is frequently associated with TOS and occurs in young and physically active individuals.
- In contrast, individuals with idiopathic UEDVT have no known cause or underlying disease; however, it may be associated with an occult cancer.
- Secondary UEDVT represents the majority of cases and occurs in patients with CVCs, pacemakers, or cancer.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes superficial thrombophlebitis, cellulitis, venous congestion due to external vein compression, and lymphedema.

WORKUP

Clinical signs and symptoms are often nonspecific or unreliable. A venogram, once the gold standard, is no longer used; compression ultrasonography is now the preferred imaging exam for these patients.

LABORATORY TESTS

The D-dimer test cannot be recommended for use in screening patients with suspected upper extremity deep vein thrombosis because many of these patients have coexisting conditions that are associated with an elevated D-dimer level.

IMAGING STUDIES

Compression ultrasonography (Fig. E2), which relies on the noncompressibility of a thrombosed vein, is the preferred imaging modality for patients suspected of upper extremity deep vein thrombosis. A complete examination of the internal jugular vein, the brachial and axillary vein, as well as the subclavian vein distal to the clavicle is needed. The superficial veins, the cephalic and basilic, should also be insonated at their confluence with the deep system. A recent systemic review reported a sensitivity of 97% and a specificity of 96% for the diagnosis of UEDVT with ultrasonography.

TREATMENT

No randomized controlled trials have been performed to determine the optimal treatment and duration for patients with UEDVT.

NONPHARMACOLOGIC THERAPY

In patients with catheter-associated thrombosis of the upper extremity, routine catheter removal is not recommended. Removal is indicated when there is a nonworking catheter, infection, or a contraindication to anticoagulation therapy.

ACUTE GENERAL Rx

For acute upper extremity DVT, anticoagulation therapy should be started promptly on oral factor Xa inhibitors, rivaroxaban, or apixaban. Alternatives to these agents are unfractionated heparin or low–molecular-weight heparin, with simultaneous administration of vitamin K antagonists (warfarin). Warfarin treatment should be continued for at least 3 mo, with a goal INR of 2.0 to 3.0. The ultimate treatment duration with warfarin follows the same guidelines as treatment with an LEDVT.

Although prophylaxis is not routinely recommended, dosing 1 mg of warfarin beginning 3 days before subsequent CVC placement should be considered if patient requires a future CV.

For patients with extensive swelling, recent onset of functional impairment, and low risk for bleeding complications, catheter-directed thrombolysis should be considered. Mechanical catheter interventions (aspiration, thrombectomy, balloon angioplasty, or stenting) or surgical procedures (thrombectomy, venoplasty, venous bypass, or decompression at the venous thoracic outlet) should be considered only for patients with persistent evidence of severe DVT after anticoagulation therapy or thrombolysis,

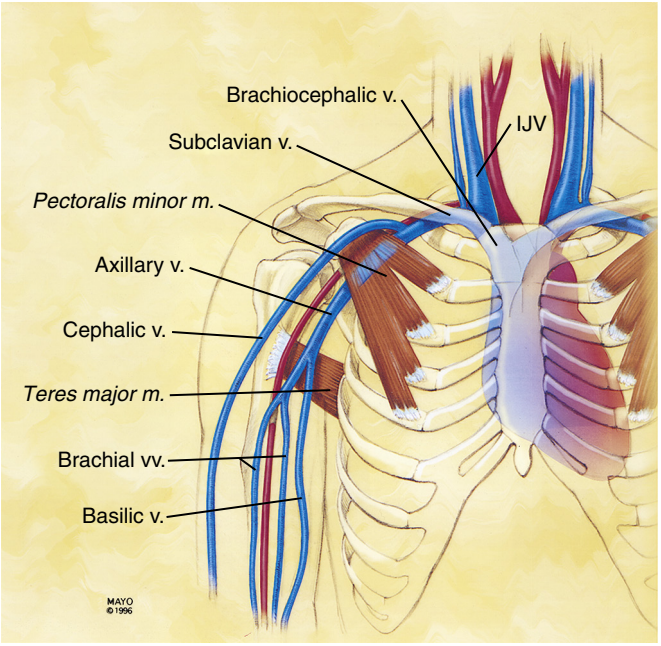

FIG. E1 Anatomy of the upper extremity veins. *IJV,* Internal jugular vein. (From Rumack CM et al: *Diagnostic ultrasound,* ed 4, Philadelphia, 2011, Elsevier.)

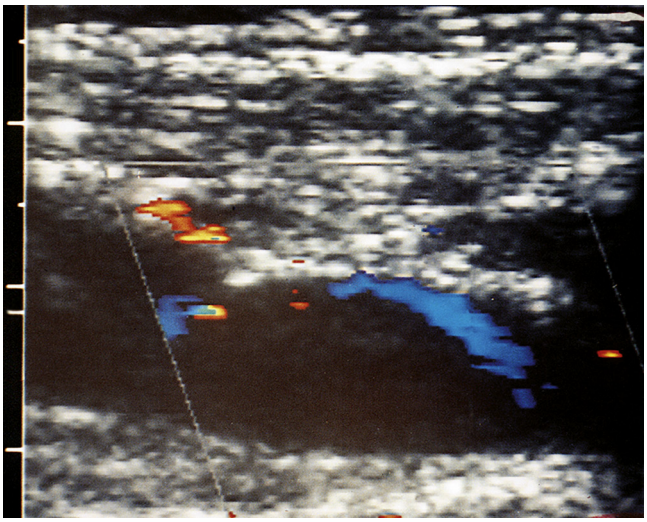

FIG. E2 Acute subclavian vein thrombosis. Color flow Doppler sonography of the subclavian vein shows extensive hypoechoic thrombus with minimal peripheral flow remaining. (From Rumack CM et al: *Diagnostic ultrasound,* ed 4, Philadelphia, 2011, Elsevier.)

and only in settings with sufficient expertise and resources.

PEARLS & CONSIDERATIONS

- Diagnosing UEDVT rapidly and accurately is essential to preventing thrombotic related morbidity and mortality.
- Catheter factors that increase the incidence of UEDVT include large luminal diameter, multiple ports, incorrect positioning, bacteremia, and prior line infection.
- The use of compression arm sleeves is recommended only in patients with persistent symptoms or in the postthrombotic syndrome.

SUGGESTED READING

Kucher N: Clinical practice. Deep vein thrombosis of the upper extremities, *N Engl J Med* 364(9):861-869, 2011.

PREVENTION

At this time, there is no convincing evidence to support routine thromboprophylaxis in all patients with central venous catheters; therefore, routine pharmacological prophylaxis is not recommended.

RELATED CONTENT

Deep Vein Thrombosis (Related Key Topic)
Pulmonary Embolism (Related Key Topic)
Thoracic Outlet Syndrome (Related Key Topic)

AUTHOR: **Frank G. Fort, MD, FACS, RPHS**

Urethritis, Gonococcal PTG ALG

BASIC INFORMATION

DEFINITION

Urethritis is a well-defined clinical syndrome manifested by dysuria, a urethral discharge, or both.

SYNONYMS

Gonococcal urethritis
GCU

ICD-10CM CODE

A54.00 Gonococcal infection of lower genitourinary tract, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Urethritis commonly is divided into two major categories based on etiology: gonococcal urethritis (GCU, *Neisseria gonorrhoeae* species) and nongonococcal urethritis (NGU, all other pathogens, most commonly *Chlamydia trachomatis*).
- This differentiation is based historically on *N. gonorrhoeae*'s easy visualization on Gram stain as gram-negative, kidney-shaped diplococci.
- In the U.S., rates of gonorrheal urethritis are rising; however, the incidence varies greatly based on race and geography; the prevalence of GCU is disproportionately higher in the South and among black, non-Hispanic men. The urethra is the most common site of infection in all men.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms of GCU: Dysuria is the most common chief complaint in patients with GCU. Additional common complaints include discharge and pruritus. Purulent discharge, meatal edema, and urethral tenderness to palpation also may occur, and 5% to 10% of patients with GCU remain asymptomatic.
- GCU may spread to other parts of the GU system. Prostatic involvement can cause urinary frequency, urgency, and nocturia and may present with mucopurulent discharge. Epididymal involvement can result in unilateral testicular pain and edema.
- Time frame: The incubation period of GCU is variable but is commonly 4 to 7 days. Without treatment, urethritis will persist for 3 to 7 wk, with 95% of men becoming asymptomatic after 3 mo.
- Complications: Periurethritis leading to urethral stenosis can occur. Additionally, disseminated infection can lead to tenosynovitis and arthritis. Rarely, hepatitis, myocarditis, endocarditis, and meningitis can occur.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- NGU
- Herpes simplex virus

LABORATORY TESTS

- If Gram staining is available, it is indicated and should be performed first, with modified Thayer-Martin media.
- Nucleic acid amplification tests (NAATs): These tests have largely replaced culture in many health care settings. They are not more sensitive than culture for detecting *N. gonorrhoeae* in cervical or urethral specimen; however, they have specificities of >99% and retain sensitivity when used to test first-catch urine or self-collected vaginal swabs. The performance of NAATs with respect to overall sensitivity, specificity, and ease of specimen transport is better than that of any of the other tests available for the diagnosis of chlamydial and gonococcal infections. NAATs should be used to detect chlamydia and gonorrhea except in cases of child sexual assault, rectal and oropharyngeal infections in prepubescent girls, and when evaluating a potential gonorrhea treatment failure in which case culture and susceptibility testing might be required.
- For culture and susceptibility testing: Rayon, Dacron, or calcium alginate tips with plastic or wire shafts should be used (not cotton-tipped swabs, which are bactericidal). A swab of the urethra should be performed within 2 to 4 hours after voiding to prevent bacterial washout with urination. Collect cultures of the pharynx and rectum when indicated for concomitant *Chlamydia* testing on all patients.
- Concomitant serologic testing for syphilis on all patients.
- Offer HIV counseling and testing to all patients.

TREATMENT

NONPHARMACOLOGIC THERAPY

Behavioral management: Avoid intercourse until cure has been attained and sexual partners have been evaluated and treated.

ACUTE GENERAL Rx

- Ceftriaxone 250 mg IM ×1 dose *plus* azithromycin 1 g orally single dose
- Dual therapy is intended for both cotreatment of potential *C. trachomatis* and to address the rising rates of gonococcal resistance to cephalosporins
- Severe allergy to cephalosporins: High-dose azithromycin with parenteral gentamicin or oral gemifloxacin

Alternative regimens:

- For penicillin-allergic patients, ceftriaxone still is recommended unless they have a history of an IgE-mediated penicillin allergy.
- Alternate regimens for those who cannot tolerate any penicillins include: Azithromycin, 2g orally plus either gentamicin 240 mg IM or gemifloxacin 320 mg orally.
- Fluoroquinolone antibiotics are no longer recommended to treat gonorrhea in the U.S. due to high rates of resistance.
- A test of cure is recommended by the CDC if any alternative regimen is administered, and should be a culture-based test collected 7 days after treatment.

CHRONIC Rx

Postgonococcal urethritis (PGU): Reinfection is the most common cause of recurrence. Repeat swab and culture of the urethra, pharynx, and rectum (where applicable) are mandatory. Persistence of polymorphonuclear cells (PMNs) with the absence of gram-negative intracellular diplococci suggests a diagnosis of PGU. This occurs when GCU is treated with a regimen that is ineffective against coincident nongonococcal infection; it represents NGU after GCU and should be treated as such. However, persistence of *N. gonorrhoeae* by smear or culture requires treatment for *N. gonorrhoeae*.

PEARLS & CONSIDERATIONS

COMMENTS

- Partner notification: The names and contact information of sexual partners should be gathered at the time of diagnosis and referred to the health department, or the patient can notify the contact directly. Expedited partner treatment is recommended by the Centers for Disease Control and Prevention (CDC) and is approved in most states. This consists of giving prescriptions to the infected patient for their partner(s) who has not been evaluated by a physician and is unlikely to seek medical care.
- On examination of the urethral smear, the presence of small numbers of PMNs provides objective evidence of urethritis. The complete absence of PMNs on a urethral smear argues against urethritis. If in addition to the PMNs there are gram-negative, intracellular diplococci, the diagnosis of gonorrhea is established.
- Patients should be advised to abstain from sex for 7 days after initiation of treatment.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Evaluation of Patients with Dysuria and/or Urethral/Vaginal Discharge (Algorithm, Section III)
Gonococcal Urethritis (Patient Information)
Gonorrhea (Related Key Topic)

AUTHORS: **Robin Metcalfe-Klaw, MD,** and **Rachel Wright Heinle, MD, FACOG**

SUGGESTED READINGS

www.cdc.gov/std/ept/legal/totals.htm

Brill JR: Diagnosis and treatment of urethritis in men, *Am Fam Physician* 81(70):873-879, 2010.

Workowski KA et al: Sexually transmitted diseases treatment guidelines 2015, *MMWR Morb Mortal Wkly Rep* 64(3), 2015.

BASIC INFORMATION

DEFINITION

Nongonococcal urethritis (NGU) is urethral inflammation caused by any of several organisms (see "Etiology").

SYNONYMS

NGU
Nongonococcal urethritis

ICD-10CM CODES

A56.0 Chlamydial infection of lower genitourinary tract
N34.1 Nonspecific urethritis

EPIDEMIOLOGY & DEMOGRAPHICS

- The occurrence is 50% in sexually transmitted disease clinics. *Chlamydia trachomatis* is the most common notifiable disease in the U.S., with >1.3 million infections reported to the Centers for Disease Control and Prevention (CDC) in 2010.
- NGU most commonly affects men in a higher socioeconomic class, affecting heterosexual men more frequently than men who have sex with men.
- NGU carries a greater morbidity rate than gonococcal urethritis (GCU).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation period: 2 to 35 days.
- Symptoms: Dysuria, whitish-clear urethral discharge, and urethral itching. The onset of symptoms in NGU is less acute than GCU. The majority of persons with *C. trachomatis* infection are not aware of their infection because they do not have symptoms that would prompt them to seek medical care.
- Signs: Whitish-clear urethral discharge, meatal edema, and erythema. Infected women manifest pyuria, and the disease can present as acute urethral syndrome.

COMPLICATIONS

- Epididymitis in heterosexual men may be linked to nonbacterial prostatitis, proctitis in men who have sex with men, or Reiter syndrome.
- Urethritis complications are more common in women and can be associated with pelvic inflammatory disease or infertility.

ETIOLOGY

- Most common agent is *Chlamydia* spp., an obligate intracellular parasite possessing both DNA and RNA, which replicates by binary fission. It causes 20% to 50% of NGU cases. Two species exist:
  1. *Chlamydia psittaci*
  2. *Chlamydia trachomatis* with its 15 serotypes:
     a. Serotypes A through C cause hyperendemic-blinding trachoma.
     b. Serotypes D through K cause genital tract infection.
     c. Serotypes L1 through L3 cause lymphogranuloma venereum.
- Other causes of NGU: *Mycoplasma genitalium* (found in 44% of treatment failures with double infection with *C. trachomatis* in up to 15% of cases); *Ureaplasma urealyticum*, causing 15% to 30% of the cases of NGU; *Trichomonas vaginalis*; herpes simplex virus; and Adenovirus. The cause of 20% of the cases of NGU has not been identified.
- Asymptomatic infection occurs in 28% of the contacts of women with chlamydial cervical infection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- GCU
- Herpes simplex virus
- Trichomoniasis

LABORATORY TESTS

- Requires demonstration of urethritis and exclusion of infection with *N. gonorrhoeae.*
- Nucleic acid amplification tests (NAATs): These tests have replaced culture in many settings where persons are screened for asymptomatic genital infection. The performance of NAATs with respect to overall sensitivity, specificity, and ease of specimen transport is better than that of any of the other tests available for the diagnosis of chlamydial and gonococcal infections. NAATs should be used to detect chlamydia and gonorrhea except in cases of child sexual assault involving boys, rectal and oropharyngeal infections in prepubescent girls, and when evaluating a potential gonorrhea treatment failure, in which case culture and susceptibility testing might be required.
- *Chlamydia* culture: The appearance of PMNs on urethral smear confirms the diagnosis of urethritis. Because *Chlamydia* is an intracellular parasite of the columnar epithelium, the best specimen for culture is an endourethral swab taken from an area 2 to 4 cm inside the urethra. For culture, a Dacron-tipped swab is used; avoid calcium alginate or cotton swabs. The organism can only be grown in tissue culture, which is expensive.

TREATMENT

- Because it is impossible to differentiate among the common etiologies of NGU, the condition is treated syndromically, including in the initial treatment regimen those drugs effective against the common causative agents.
- In patients with isolated uncomplicated NGU, recommended regimens are azithromycin 1 g orally single dose or doxycycline 100 mg bid × 7 days. Recommended regimen in pregnancy is azithromycin, 1 g orally as a single dose.
- In patients with confirmed urethritis and unclear etiology, concurrent treatment for gonorrhea and *Chlamydia* is recommended. In these patients, uncomplicated infections of the urethra can be treated with combination of a single 1-g dose of oral azithromycin or 100 mg doxycycline bid × 7 days *plus* ceftriaxone 250 mg × 1 dose.
- In areas where *T. vaginitis* is prevalent, men who have sex with women and have persistent or recurrent urethritis should be presumably treated with metronidazole 2 g orally in a single dose of tinidazole 2 g orally in a single dose.
- Recurrent NGU in patients initially treated with doxycycline should be treated with a single dose of azithromycin 1 g. If azithromycin was used for initial treatment, patients with recurrent NGU should be retreated with moxifloxacin 400 mg daily × 6 days.

PEARLS & CONSIDERATIONS

COMMENTS

- Partner notification: The names and contact information of all sexual partners within preceding 60 days should be gathered at the time of the visit and referred to the health department, or the patient notifies the contacts directly. Expedited partner treatment is recommended by the CDC and approved in several states. This consists of giving prescriptions to the infected patient for their partner(s) who have not been evaluated by a physician and are unlikely to seek medical care.
- Patients should abstain from intercourse for 7 days after therapy completion.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Nongonococcal Urethritis (Patient Information)
Cervicitis (Related Key Topic)
Chlamydia Genital Infections (Related Key Topic)

AUTHORS: **Rachel Wright Heinle, MD, FACOG,** and **Christine Burke, MD**

SUGGESTED READINGS

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BASIC INFORMATION

DEFINITION

Urinary tract infection (UTI) is a term that encompasses a broad range of clinical entities that have in common a positive urine culture. A conventional threshold is growth of >100,000 colony-forming units per milliliter from a midstream-catch urine sample with no more than two species of organisms and at least one sign or symptom of UTI (urgency, frequency, dysuria, suprapubic tenderness, fever >38.0° C [100.4° F]). In symptomatic patients, a smaller number of bacteria (between 100 and 10,000 colony-forming units per milliliter of midstream urine) is recognized as an infection.

ICD-10CM CODES

N39.0	Urinary tract infection, site not specified
N99.521	Infection of other external stoma of urinary tract
N99.531	Infection of other stoma of urinary tract
N30.00	Acute cystitis without hematuria
N30.30	Trigonitis without hematuria
N30.20	Other chronic cystitis without hematuria

CLASSIFICATION

- Uncomplicated UTI: Occurs in a normal urinary tract and resolves rapidly with conventional antimicrobials. Patients have a low risk of upper UTI.
- Complicated UTI: Occurs in patients with coexisting pathology (strictures, stones, comorbidities [diabetes mellitus, multiple sclerosis, spinal cord injuries]). Patients are considered at high risk for upper UTI.
- First infection: The first documented UTI; tends to be uncomplicated and is easily treated.
- Unresolved bacteriuria: UTI in which the urinary tract is not sterilized during therapy. Main causes are bacterial resistance, patient noncompliance with medication, mixed bacterial infection, rapid reinfection, azotemia, infected stones, Munchausen syndrome, and papillary necrosis.
- Bacterial persistence: UTI in which the urine cultures become sterile during therapy, but a persistent source of infection gives rise to reinfection by the same organism. Causes include infected stone, chronic bacterial prostatitis, atrophic infected kidney, vesicovaginal or enterovesical fistulas, obstructive uropathy, infected pyelocaliceal diverticula, infected ureteral stump after nephrectomy, infected necrotic papillae from papillary necrosis, infected urachal cysts, infected medullary sponge kidney, urethral diverticula, and foreign bodies.
- Reinfection: UTI in which a new infection occurs with new pathogens at variable intervals after a previous infection has been eradicated.
- Relapse: The less common form of recurrent infection; occurs within 2 wk of treatment when the same organism reappears in the same site as the previous infection. Relapsing infections of the urinary tract most commonly occur in pyelonephritis, kidney obstruction from a stone, foreign body, and prostatitis.

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- UTI is the most common bacterial infection encountered in the ambulatory care setting in the U.S. The self-reported annual incidence of UTI in women is 12%, and by age 32 half of all women report having had at least one UTI.
- UTIs account for 8 million health care visits per yr and 15% of all outpatient prescriptions.
- In neonates: More common in boys as a result of anatomic abnormalities such as the posterior urethral valves.
- In preschool children: More common in girls (4.5% vs. 0.5% for boys).
- In adulthood: More common in women, with a 1% to 3% prevalence in nonpregnant women. Table 1 describes factors modulating risk for acute uncomplicated UTIs in women. In pregnancy at 12 wk, the incidence of asymptomatic bacteriuria is similar to nonpregnant women, at 2% to 10%. However, 25% to 30% of pregnant women with untreated asymptomatic bacteriuria develop acute pyelonephritis, especially in the second and third trimesters, and have a pyelonephritic recurrence rate of 10%. In adults aged ≥65 yr, at least 10% of men and 20% of women have bacteriuria.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typical symptoms of UTI include:
  1. Urinary frequency, urgency
  2. Dysuria
  3. Suprapubic pain
  4. Gross or microscopic hematuria
- The probability of cystitis is greater than 50% in women with any symptom of UTI and greater than 90% in women who have dysuria and frequency without vaginal symptoms.
- Clinical symptoms alone can be used to make the diagnosis of uncomplicated UTI in women without a urine culture.
- When negative cultures are associated with significant pyuria, vaginal discharge, or hematuria, infections with *Chlamydia trachomatis, Neisseria gonorrhoeae*, and *Trichomonas vaginalis* should be considered.
- Acute pyelonephritis presents with fever, flank or abdominal pain, chills, malaise, and vomiting. It is these systemic symptoms that distinguish pyelonephritis from cystitis. Complications of acute pyelonephritis are renal abscess, perinephric abscess, emphysematous pyelonephritis, and pyonephrosis.

ETIOLOGY & PATHOGENESIS

- Most UTIs are caused by ascending fecal flora, which can colonize the vaginal and periurethral tissues and eventually enter the bladder.
- Other risk factors: Incomplete bladder emptying due to neurologic disease, bladder outlet obstruction or urethral stricture, renal failure, diabetes, vesicoureteral reflux, fistula, urinary diversion, infected stones, age, pregnancy, instrumentation, and poor patient compliance.
- Catheters: All patients who require a long-term Foley catheter eventually develop significant levels of bacteriuria. Treatment is reserved for individuals who become symptomatic (leukocytosis, fever, chills, malaise, loss of appetite, etc.) Using prophylactic antibiotics to treat patients who have chronic catheters is not indicated because of the risk of acquiring bacteria resistant to antibiotic therapy.
- Once bacteria reach the urinary tract, three factors determine whether symptomatic infection occurs (Box 1). These factors also determine the anatomic level of the UTI:
  1. Virulence of the microorganism
  2. Inoculum size
  3. Adequacy of the host defense mechanisms
- Urinary pathogens: In 90% of UTIs the infecting organism is gram-negative bacilli. *Escherichia coli* is the most common pathogen (85% of UTI cases). *Staphylococcus saprophyticus* causes 10% of infections, especially in young women. Other common urinary pathogens include *Klebsiella, Enterobacter, Serratia, Proteus,* and *Pseudomonas.*
- In contrast, the organisms that commonly colonize the distal urethra and skin of both men and women and the vagina of women

TABLE 1 Factors Modulating Risk for Acute Uncomplicated Urinary Tract Infections in Women

Host Determinants	Uropathogen Determinants
Behavioral: Sexual intercourse, use of spermicidal products, recent antimicrobial use, suboptimal voiding habits	*Escherichia coli* virulence determinants: P, S, Dr, and type I fimbriae; hemolysin; aerobactin; serum resistance
Genetic: Innate and adaptive immune response, enhanced epithelial cell adherence, antibacterial factors in urine and bladder mucosa, nonsecretor of ABO blood group antigens, P_1 blood group phenotype, reduced *CXCR1* expression, previous history of recurrent cystitis	
Biologic: Estrogen deficiency in postmenopausal women, micturition	

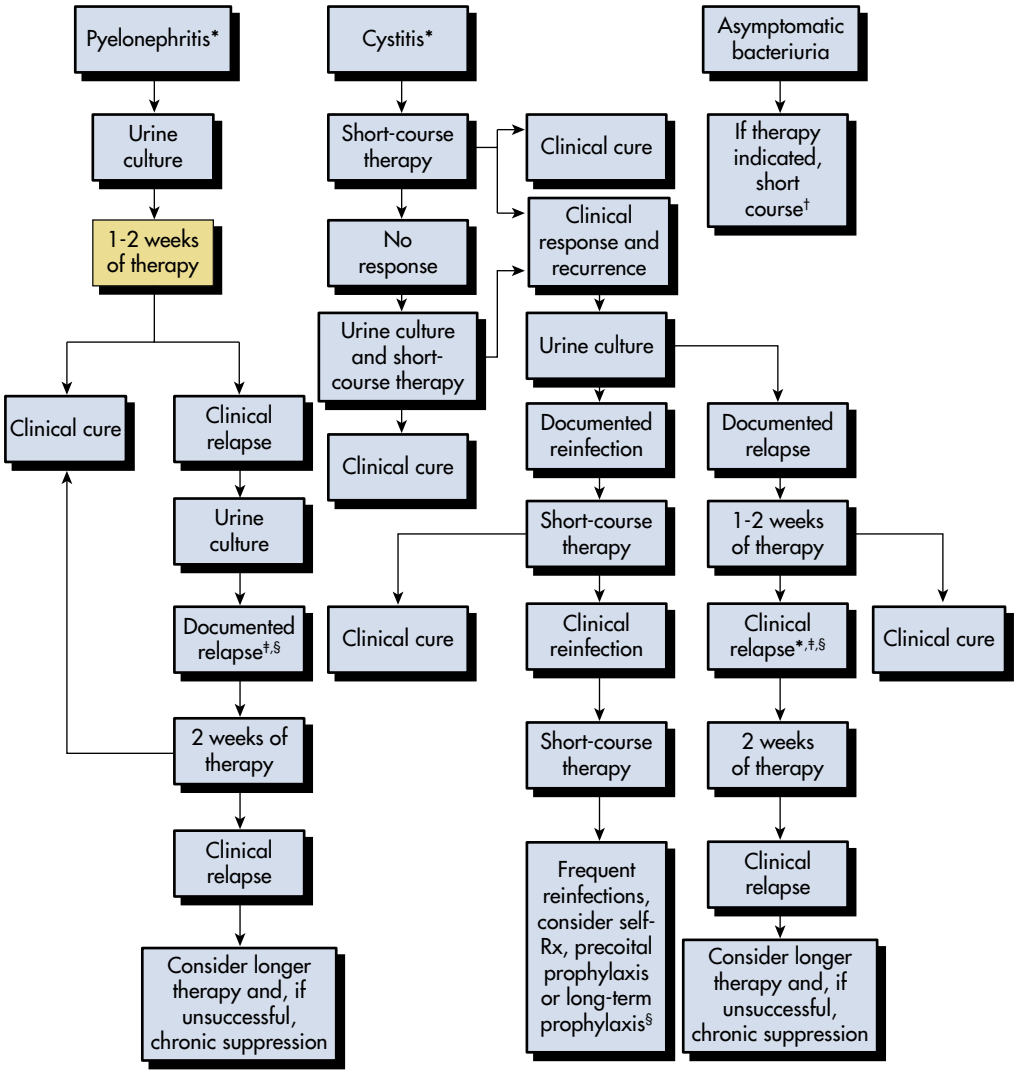
From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

BOX 1 Bacterial Factors

- The size of the inoculum
  1. The virulence of the infecting organism
  2. Virulence factors
     a. P-fimbriae facilitate the adherence of bacteria to biologic surfaces.
     b. K-antigens facilitate adherence and protect the organisms from the host-immune response.
     c. O-antigens are an important source of systemic reactions such as fever and shock that occur with bacterial infections.
     d. H-antigens are associated with flagella and are related to bacterial locomotion.
     e. Hemolysin may potentiate tissue damage and facilitate local bacterial growth.
     f. Urease alkalinizes the urine and facilitates stone formation, thus potentiating infection.
  3. Biofilms harbor bacteria on prosthetic devices and may be a source of recurrent infections.
  4. The presence of sialosyl galactosyl globoside on the surface of kidney cells. This compound is a highly powerful receptor for *Escherichia coli* bacteria.
  5. Women with a deficiency in human beta-defensin-1 are at greater risk for urinary tract infection.
- Adequacy of host defense mechanisms

are *Staphylococcus epidermidis*, diphtheroids, lactobacilli, *Gardnerella vaginalis*, and a variety of anaerobes that rarely cause UTIs. In general, the isolation of two or more bacterial species from a urine culture signifies a contaminated specimen unless the patient is being managed with an indwelling catheter or urinary diversion or has a chronic complicated infection.

- Defense mechanisms against cystitis: Low urine pH and high urine osmolarity, mucopolysaccharide glycosaminoglycan (GAG) protective layer, normal bladder that empties completely, and low vaginal pH due to the presence of estrogen and resulting colonization of the genital tract by lactobacillus. According to Walters and Karram, Tamm-Horsfall proteins are secreted in the kidney to help inhibit adherence of bacteria to urothelial cells.



*Consider imaging studies in all men and in women with complicated urinary tract infection.
†No therapy except for renal transplant patients or prior to urologic procedures. Follow-up culture only in transplant patients.
‡Evaluate men for chronic bacterial prostatitis.
§Consider imaging studies in women.

FIG. 1 Approach to the management of urinary tract infection in nonpregnant adults. (From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.)

- In uncomplicated, nonpregnant patients, cystitis rarely progresses to pyelonephritis or other serious infections such as bacteremia.

Dx DIAGNOSIS (FIG. 1)

DIFFERENTIAL DIAGNOSIS

- Vaginitis
- Urethritis (gonococcal, nongonococcal, *Trichomonas*)
- Interstitial cystitis (painful bladder syndrome)
- Pelvic inflammatory disease
- Nephrolithiasis
- Structural urethral abnormalities such as diverticulum or stricture

LABORATORY TESTS

- Microscopic urinalysis of clean-catch urine for bacteria and pyuria. The presence of ≥10 leukocytes/μl of unspun urine from a midstream catch indicates possible UTI. The absence of pyuria should call into question the diagnosis of UTI.
- Dipstick urinalysis with the presence of nitrites or leukocyte esterase is indicative of UTI. However, dipstick urinalysis may not be useful in symptomatic patients with typical symptoms and a negative dipstick urinalysis does not exclude the diagnosis of UTI such cases; additionally, dipsticks may be falsely positive when the urine is contaminated (dipstick nitrate and leukocyte esterase have a sensitivity of 75% and specificity of 82% in patients with >100,000 CFU/ml).
- Urine culture and sensitivity are useful in complicated UTIs and to help guide therapy in women who fail initial therapy. They are generally not needed in uncomplicated UTIs.

IMAGING STUDIES

- Warranted only if renal infection or genitourinary abnormality is suspected
- CT urogram, voiding cystourethrogram, renal ultrasound, and intravenous pyelogram
- Specialty examination: Cystoscopy and retrograde pyelography to rule out obstructive uropathy, if suspected urethral diverticulum, suspected mesh, or to rule out cancer in older patients.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Urinary analgesics such as phenazopyridine and aggressive hydration

ACUTE GENERAL Rx

- First-line antimicrobials for uncomplicated UTI as recommended by the Infectious Disease Society of North America, the American Urologic Society, and ACOG include: Nitrofurantoin bid for 5 days, trimethoprim plus sulfamethoxazole (TMP-SMX) bid for 3 days, or fosfomycin 3-g sachet in a single dose.
- Antimicrobial stewardship and drug resistance needs to be considered when choosing antibiotic therapy. Empiric treatment with TMP-SMX is considered appropriate when resistance rates are below 20%. Nitrofurantoin continues to have the lowest rates of antimicrobial resistance. Beta lactam antibiotics may be appropriate in cases of known patient hypersensitivity to conventional first-line agents.
  1. Nitrofurantoin may have lower rates of bioavailability in patients >65 yr due to decline in renal function (if Cr Cl < 30 ml/min) and thus should be avoided, as it may not reach therapeutic concentration in the urine.
- High rates of resistance and the potential for serious side effects should limit the use of fluoroquinolone antimicrobials. The U.S. FDA has warned against the use of fluoroquinolone antibiotics for routine infections when suitable alternatives are available.
- Pyelonephritis may be treated as an outpatient in stable, well-hydrated patients with close follow-up. Antimicrobial selection is ideally based on urine culture results. Empiric treatment with fluoroquinolone antimicrobials or TMP-SMX is acceptable. Initiation of treatment in the emergency room setting with a single parenteral dose of a long-acting beta lactam or aminoglycoside antibiotic followed by oral treatment with fluoroquinolones or TMP-SMX is an acceptable regimen. Patients should be assessed for a proper response to treatment within 48 hr. Nitrofurantoin and fosfomycin are not indicated for the treatment of pyelonephritis due to inadequate renal tissue levels.
- Inpatient management of pyelonephritis should begin with parenteral antimicrobials followed by transition to oral agents based on clinical response and culture results.
- Pyelonephritis requires a total duration of 10 to 14 days of therapy, although evidence exists that 7 to 10 days may be equally effective in low-risk patients.See Table 2.

PEARLS & CONSIDERATIONS

COMMENTS

- Asymptomatic bacteriuria occurs commonly in postmenopausal women. Treatment of asymptomatic bacteriuria with antimicrobials is discouraged because it seldom resolves and can result in the development of drug-resistant organisms. Patients with cloudy or foul-smelling urine should be encouraged to aggressively hydrate to eliminate these symptoms. Postmenopausal women with vaginal atrophy can be treated with vaginal estrogen to reduce the incidence of bacteriuria. Exceptions include immunocompromised patients, patients with structural urinary tract abnormalities, and pregnant patients.
- Pregnancy: 25% to 30% of pregnant women with untreated asymptomatic bacteriuria develop pyelonephritis. All pregnant women should be screened for asymptomatic bacteriuria and treated. Nitrofurantoin, TMP-SMX, and beta lactam antibiotics are appropriate first-line choices in pregnancy.
- Recurrent UTI: Two or more symptomatic UTIs over a 6-mo period or three or more episodes over a 12-mo period. Causes include unresolved infection, abnormal vaginal colonization by the originally infecting organism, or reinfection with a new strain. Management of recurrent UTI includes antibiotic prophylaxis for 6 months or longer, intermittent self-treatment, and postcoital prophylaxis depending on the circumstances. Patients with recurrent UTIs can be considered for an anatomic evaluation including office cystoscopy and upper urinary tract imaging (renal ultrasound or CT urography).

TABLE 2 Dosage and Toxicity of Antibiotics Commonly Used to Treat Urinary Tract Infections

Drug	Oral Dose and Frequency	Minor Toxicity	Major Toxicity
Trimethoprim-sulfamethoxazole	160 mg/800 mg, q12h	Allergic	Serious skin reactions, blood dyscrasia
Nitrofurantoin macrocrystals	100 mg, q12h	GI upset	Peripheral neuropathy, pneumonitis
Ampicillin	250-500 mg, q6h	Allergic, candidal overgrowth	Allergic reactions, pseudomembranous colitis
Tetracycline	250-500 mg, q6h	GI upset, skin rash, candidal overgrowth	Hepatic dysfunction, nephrotoxicity
Cephalexin	250-500 mg, q6h	Allergic	Hepatic dysfunction
Ciprofloxacin	250 mg, q12h	Nausea, vomiting, diarrhea, abdominal pain, headache, skin rash	Arrhythmias, angina, convulsions, gastrointestinal bleeding, nephritis

From Walters M, Karram M: *Urogynecology and reconstructive pelvic surgery, ed 4*, Philadelphia, 2015, Elsevier.

TABLE 3 Spectrum of Antimicrobial Activity against Common Lower Urinary Tract Pathogens

Organism	Nitrofurantoin	TMP-SMX	Ciprofloxacin	Levofloxacin	Cephalexin	Ampicillin	Fosfomycin
Escherichia coli	+	±	+	+	+	±	+
Pseudomonas	–	–	+	±	–	–	+
Klebsiella	–	±	+	+	+	–	+
Proteus	±	±	+	+	±	+	±
Enterobacter	±	±	+	+	–	–	±
Enterococcus	+	–	–	±	–	+	±
Staphylococcus	+	+	±	±	±	+	+
Serratia marcescens	–	±	+	+	–	–	±

From Walters M, Karram M: *Urogynecology and reconstructive pelvic surgery, ed 4,* Philadelphia, 2015, Elsevier.

- Nonantimicrobial strategies to prevent UTI have shown mixed results. Nonantimicrobial agents with antiseptic effects on the lower urinary tract include cranberry supplements with vitamin C, d-mannose, and methenamine. Studies demonstrating clinical effectiveness of these agents show at best modest effects with few side effects. Topical estrogen has been shown to normalize the vaginal flora and may increase the thickness of the urothelium over time and should be used as an adjunct in postmenopausal women with recurrent UTI. Oral probiotics may also be beneficial by decreasing the vaginal pH.

ANTIMICROBIAL RESISTANCE:

- Because of the overuse of antibiotics, organisms once sensitive to a number of antimicrobial agents are now increasingly resistant, making effective management of UTI and pyelonephritis more difficult and potentially more dangerous. Most important has been the increasing resistance to trimethoprim plus sulfamethoxazole (TMP-SMX), the current primary care provider drug of choice for acute uncomplicated UTI in women.
- Fluoroquinolone use for the treatment of acute cystitis in women should be avoided when suitable alternatives exist. The U.S. FDA has changed the labeling of quinolone antibiotics to reflect this recommendation.
- When choosing a treatment regimen, physicians should consider such factors as:
  1. In vitro susceptibility
  2. Adverse effects on individual patients
  3. Adverse effects on the population (stewardship)
  4. Cost-effectiveness
  5. Resistance rates in their respective communities
- Meropenem (1 g IV every 8 hr) or IV plazomicin (15 mg/kg BW once daily) are effective for the treatment of complicated UTIs and acute pyelonephritis caused by Enterobacteriaceae, including multidrug-resistant strains.See Table 3.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Urinary Tract Infection (Patient Information)
Urinary Tract Infection (Child) (Patient Information)
Pyelonephritis (Related Key Topic)

AUTHORS: **Matthew J. Fagan, MD, FACOC,** and **Meagan S. Cramer, MD**

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Urolithiasis (Nephrolithiasis) PTG ALG

BASIC INFORMATION

DEFINITION

Urolithiasis is the presence of calculi within the urinary tract. The five major types of urinary stones are calcium oxalate (60% to 70%), calcium phosphate (20%), uric acid (7%), struvite (7%), and cystine (1%) (Table 1).

SYNONYMS

Kidney stones
Kidney calculi
Renal stones
Renal calculi
Ureteral stones
Ureteral calculi
Nephrolithiasis
Ureterolithiasis

ICD-10CM CODES

N20.0	Calculus of kidney
N20.1	Calculus of ureter
N20.2	Calculus of kidney with calculus of ureter
N20.9	Urinary calculus, unspecified
N21.0	Calculus in bladder
N21.1	Calculus in urethra
N21.8	Other lower urinary tract calculus
N21.9	Calculus of lower urinary tract, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Urinary stones affect approximately 1 in 11 people in the U.S., with a lifetime prevalence of approximately 10% in males and 7% in females.
- Peak incidence is in the fourth to sixth decade of life.
- Urolithiasis appears to be more common among whites than Hispanics, Asians, or African Americans.
- The incidence of urinary stone disease is increasing, likely due to increased use of cross-sectional imaging and changing dietary and lifestyle factors.
- The incidence of symptomatic urolithiasis is greatest during the summer as a result of increased temperature with resulting dehydration and urinary concentration.
- Annually, between 1 and 2 million emergency department visits are due to kidney stones and renal colic.
- Approximately 90% of all urinary stones are radiopaque. Cystine stones are faintly radiopaque. Uric acid stones are radiolucent.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Stones may be asymptomatic, or may cause the following signs and symptoms, often from urinary tract obstruction:

- Acute, often severe, flank pain (renal colic)
- Pain radiating from the flank downward and anteriorly with referred pain to the groin and genitalia (common as the stone progresses down the ureter)
- Low back and lower abdominal pain, often ipsilateral to the stone
- Nausea and vomiting
- Hematuria, gross or microscopic
- Inability to find a comfortable position
- Urinary urgency and frequency with distal ureteral stones mimicking a urinary tract infection
- Fever and chills accompanying acute colic with superimposed infection
- Elderly patients, children, and patients with neurologic deficits may present with nonspecific and vague abdominal discomfort and pain

ETIOLOGY

- Urine composition: Supersaturation of various solutes and stone constituents is the driving force in kidney stone formation. Various metabolic abnormalities such as low or high urine pH, idiopathic hypercalciuria, hypocitraturia, hyperoxaluria, and hyperuricosuria predispose patients to urinary stone formation.
- Low urine volume is the most common cause in many stone–formers.
- Dietary factors: Diets high in sodium and animal protein increase the risk of urinary stone formation. Very high dietary oxalate consumption and heavy intake of phosphoric acid-containing carbonated drinks likely increase the risk of stone formation. Foods with high potential renal acid load such as cheese and meats increase the risk of urinary stone formation, while fruits and vegetables with low potential renal acid load may reduce the risk.
- Anatomic factors predisposing patients to urinary stasis: Malrotated, horseshoe or ectopic kidney; ureteropelvic junction obstruction; vesicoureteral reflux in young children; bladder outlet obstruction; and strictures affecting the urinary tract.
- Disease states:
  1. Hyperparathyroidism with hypercalcemia and hypercalciuria
  2. Sarcoidosis with hypercalcemia
  3. Malabsorption (e.g., inflammatory bowel disease) with increased oxalate absorption
  4. Chronic diarrheal states
  5. Gastric bypass surgery with enteric hyperoxaluria
  6. Metabolic syndrome (e.g., diabetes, overweight) produces acidic urine predisposing patients to uric acid stones; it has also been suggested that metabolic syndrome increases calcium oxalate stone formation by increasing the excretion of promoters of stone formation
  7. Gouty diathesis
  8. Primary hyperoxaluria: Genetic, rare, and usually presenting as a childhood disorder
  9. Medullary sponge kidney
  10. Hyperuricosuria (e.g., metabolic defects, dietary excess) (Box 1)
  11. Type I (distal tubule) renal tubular acidosis (>1% of calcium phosphate stones)
  12. Cystinuria: Autosomal recessive disorder produces 1% of stones
- Chronic infections: Urease-producing organisms (e.g., *Proteus* [most common], *Providencia, Pseudomonas, Klebsiella, Staphylococcus*) cause alkaline urine favoring struvite or magnesium ammonium phosphate crystal formation (Box 2).
- Medications: Protease inhibitors (e.g., indinavir, ritonavir), topiramate, and chronic laxative overuse.

TABLE 1 Types of Urinary Tract Stones and Their Etiology

Composition	Etiological factors	Percentage of all stones
Calcium oxalate/calcium oxalate mixed with calcium phosphate	An underlying metabolic disorder (e.g. idiopathic hypercalciuria or hyperoxaluria) ▸ in 25% no metabolic abnormality is identified	75
Struvite or matrix calculi (composed of magnesium ammonium phosphate)	Renal infection	10-15
Uric acid	Hyperuricemia or hyperuricosuria ▸ it is idiopathic in 50%	6
Cysteine	A renal tubular defect	1-2

Other stones (e.g., xanthine stones, which may be related to a metabolic abnormality, or indinavir stones, which are drug related) are uncommon and account for <5% of all renal stones.
From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.

BOX 1 Uric Acid Stones

Low urine pH (≤5.5)
High animal protein diet
Diarrhea
Insulin resistance (high body mass index, metabolic syndrome, type 2 diabetes)

Low Urine Volume
Inadequate fluid intake
Excessive extrarenal fluid losses
Diarrhea
Insensible losses (e.g., perspiration)

Hyperuricosuria
Excessive dietary purine intake
Hyperuricemia
- Gout
- Intracellular-to-extracellular uric acid shift
- Myeloproliferative disorders
- Tumor lysis syndrome

Inborn errors of metabolism
- Lesch-Nyhan syndrome
- Glucose-6-phosphatase deficiency

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

BOX 2 Factors Associated with Struvite Stone Formation

- Urease-producing bacteria:
  1. *Proteus*
  2. *Klebsiella*
  3. *Providencia*
  4. *Pseudomonas*
  5. *Staphylococcus epidermidis*
  6. *Haemophilus*
  7. *Yersinia species*
  8. *Serratia*
  9. *Citrobacter*
  10. *Ureaplasma*
- Elevated urinary pH

Modified from Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

BOX 3 Indications for a Metabolic Stone Evaluation

Recurrent stone formers
Strong family history of stones
Intestinal disease (particularly chronic diarrhea)
Pathologic skeletal fractures
Osteoporosis
History of urinary tract infection with calculi
Personal history of gout
Infirm health (unable to tolerate repeat stone episodes)
Solitary kidney
Anatomic abnormalities
Renal insufficiency
Stones composed of cystine, uric acid, struvite

From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Urinary tract infection (e.g., cystitis)
- Pyelonephritis
- Diverticulitis
- Appendicitis
- Pelvic inflammatory disease
- Ovarian pathology, including torsion
- Dysmenorrhea
- Ectopic pregnancy
- Small bowel obstruction
- Constipation
- Malignancy (primary urinary tract or retroperitoneal lymphadenopathy causing ureteral/kidney obstruction)
- Ureteropelvic junction obstruction
- Testicular torsion in children and teenagers
- Musculoskeletal back pain
- Renal infarction and renal bleeds
- Factitious (illicit substance-seeking behavior), often with recurrent stone formers

The differential diagnosis of obstructive uropathy is described in Section II.

WORKUP

- Stone composition of recovered stones should be determined by infrared spectroscopy or x-ray crystallography. Box 3 summarizes indications for a metabolic stone evaluation.
- Box 4 describes events in the medical history that may be significant with regard to urolithiasis.

LABORATORY TESTS

- Urinalysis: Hematuria is often present, but absence of hematuria does not exclude stones. Urine pH may help identify stone type: pH >7.5 is associated with struvite stones; pH <5.5 is generally associated with uric acid stones, and low serum bicarbonate concentration with urine pH ≥6 is consistent with a renal tubular acidosis.
- Urine culture and sensitivity results should be obtained selectively in patients who may have superimposed infections, based on clinical symptoms of dysuria, fever, chills or urinalysis suggestive of infection, or when surgical intervention is planned.
- Serum chemistries include electrolytes, BUN, creatinine, calcium, phosphate, uric acid and parathyroid hormone.
- Additional tests: 24-hr urine collection for volume, creatinine, calcium, uric acid, phosphate, oxalate and citrate excretion is generally reserved for patients with recurrent stones, young patients, bilateral stones and large stone burden. A 24-hr urine collection may be appropriate for motivated, first-time stone patients interested in preventing recurrent stones. An abbreviated evaluation of single-stone formers is described in Box 5. Table 2 summarizes diagnostic criteria for various disorders associated with urolithiasis.

IMAGING STUDIES

- Common diagnostic modalities for renal colic are summarized in Table 3.
- Noncontrast CT scanning ("low-dose") is rapid and accurate, has greatest sensitivity (nearly 100%) and specificity (94% to 96%), and can identify almost all stone types in essentially all locations. CT scan is the best test upon which to base stone treatment recommendations, evaluate stone persistence or passage, and plan for surgery. Indinavir antiviral therapy produces stones that are typically radiolucent and poorly visualized by noncontrast CT and usually require contrast-enhanced CT for visualization. A high index of suspicion is required for diagnosis.
- CT scans may be ordered by urologists planning surgical intervention because a CT yields information on adjacent organs and stone density that ultrasound and plain film radiography cannot reveal.
- Ultra-low-dose CT protocols specific to kidney stone evaluation are becoming more common and readily available.
- Ultrasonography or ultrasound (Fig. E1) may be an adequate initial study to detect stones or stone presence (i.e., hydronephrosis), especially in patients known to have a history of stones and in patients where radiation should be avoided (e.g., pregnancy and children). Ultrasonography is 50% to 70% sensitive in detecting stones within the kidneys, and about 90% sensitive in detecting hydronephrosis.
- Point-of-care ultrasound use is increasing in emergency departments and some clinic settings.
- Initial ultrasonography may be associated with lower cumulative radiation exposure than initial CT, without significant differences in missing, serious, or alternative diagnoses; adverse events; pain scores; return emergency department visits; or hospitalizations. It is reasonable to use ultrasonography as the initial imaging modality in suspected nephrolithiasis and to monitor known stones.
- Accuracy of sonography in detecting distal ureteral stones is variable due to variable stone size, body habitus, and operator expertise. The absence of an ipsilateral ureteral jet suggests the possibility of renal tract obstruction, but this sign is not pathognomonic.
- Abdominal radiography or a kidney-ureter-bladder x-ray (KUB) can identify radiopaque stones (e.g., calcium-containing but not radiolucent uric acid stones). However, 20% to 30% of stones will not be visible because of stone composition, poor film quality, or inadequate visualization due to overlying structures (bowel gas or bone).

Rx TREATMENT

ACUTE GENERAL Rx

- Diagnosis with labs, imaging, and patient history.
- Pain control: NSAIDs are excellent for managing renal colic (e.g., ketorolac, ibuprofen) and are preferred first-line agents. Opiates may be required for severe pain. Initial pain control with NSAIDs can reduce overall opiate dosing for renal colic. Fig. 2 illustrates a guideline algorithm for the evaluation, treatment and disposition of patients with presumed renal colic.
- IV fluids and antiemetics may be required.
- Patients with suspected urinary tract infections and obstructing stones require urgent kidney drainage (ureteral stent by a urologist or nephrostomy tube placement) and antibiotics. Patients with acute kidney injury or electrolyte derangements or those whose pain cannot be controlled also may require urgent kidney drainage.
- For patients who have a stone with a high probability of passage (i.e., small stone, especially distal ureter), medical expulsive therapy with α-blockers or calcium channel blockers (used less often due to side effects) may be helpful. New Level 1 evidence suggests that medical expulsive treatment may not be superior to placebo when considering all stone sizes; however, contemporary and numerous older studies have shown benefit to passage of distal stones ≥5 mm in size with the use of medical expulsive therapy.

BOX 4 Components of the Medical History that Are Significant for Urolithiasis

- Diseases associated with disturbances of calcium metabolism: Primary hyperparathyroidism, medullary sponge kidney, osteoporosis, immobilization, sarcoidosis, osteolytic metastases, plasmacytoma, neuroendocrine tumors, Paget disease
- Dietary history: Purine gluttony, calcium excess, milk alkali, oxalate excess, sodium excess, low citrus fruit intake
- Medications: Uricosurics, diuretics, analgesics, vitamins C and D, antacids (especially phosphorus-binding agents), acetazolamide, calcium channel blockers, triamterene, estrogens, theophylline, protease inhibitors (indinavir), sulfonamides
- Diseases associated with disturbances of oxalate metabolism: Primary hyperoxaluria types I and II, Crohn disease, ulcerative colitis, intestinal bypass surgery (especially jejunoileal bypass), ileal resection
- Diseases associated with disturbances of purine metabolism
- Intrinsic metabolic disorders: Anemia, neoplastic disorders (especially leukemias), intoxication, myocardial infarction, irradiation, cytotoxic chemotherapy
- Enzyme deficiency: Primary gout, Lesch-Nyhan syndrome
- Altered excretion: Renal insufficiency, metabolic acidosis
- Infectious history: Organisms (particularly *Proteus* and *Klebsiella*), febrile, upper tract involvement, and dates (if hospitalized)

Modified from Nseyo UO et al (eds): *Urology for primary care physicians,* Philadelphia, 1999, Saunders.

BOX 5 Abbreviated Evaluation of Single-Stone Formers

History
  Underlying predisposing conditions (as per Box 3 and Etiology section in text)
  Medications (calcium, vitamin C, vitamin D, acetazolamide, steroids)
  Dietary excesses, inadequate fluid intake, excessive fluid loss
Multichannel blood screen
  Basic metabolic panel (sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine)
  Calcium
  Intact parathyroid hormone
  Uric acid
Urine
  Urinalysis
    pH >7.5: Infection lithiasis
    pH <5.5: Uric acid lithiasis
    Sediment for crystalluria
  Urine culture
    Urea-splitting organisms: Suggestive of infection lithiasis
  Qualitative cystine
Radiography
  Radiopaque stones: Calcium oxalate, calcium phosphate, magnesium ammonium phosphate (struvite), cystine.
  Radiolucent stones: Uric acid, xanthine, triamterene
  CT scan, renal ultrasound or intravenous pyelogram: Radiolucent stones, anatomic abnormalities
Stone analysis

CT, Computed tomography.
Modified from Wein AJ et al: *Campbell–Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

TABLE 2 Diagnostic Criteria

	SERUM			URINARY							
	Ca	**P**	**PTH**	**Ca Fasting**	**Ca Load**	**Ca Restricted**	**UA**	**Ox**	**Cit**	**pH**	**Mg**
Absorptive hypercalciuria type I	N	N	N	N	↑	↑	N	N	N	N	N
Absorptive hypercalciuria type II	N	N	N	↑	N	N	N	N	N	N	N
Renal hypercalciuria	N	N	↑	↑	↑	↑	N	N	N	N	N
Primary hyperparathyroidism	↑	↓	↑	↑	↑	↑	N	N	N	N	N
Unclassified hypercalciuria	N	N/↓	N	↑	↑	↑	N	N	N	N	N
Hyperuricosuria	N	N	N	N	N	N	↑	N	N	N	N
Enteric hyperoxaluria	N/↓	N/↓	N/↓	↓	↓	↓	↓	↑	↓	N	N
Hypocitraturia	N	N	N	N	N	N	N	N	↓	N	N
Renal tubular acidosis	N	N	N/↑	↑	N	N/↑	N	N	↓	N/↑	N
Hypomagnesuria	N	N	N	N	N	N	N/↓	N	↓	N	↓
Gouty diathesis	N	N	N	N	N	N	N/↑	N	N/↓	↓	N
Infection lithiasis	N	N	N	N	N	N	N	N	↓	↑	N

Fasting samples represent 2-hr collections obtained in morning after an overnight fast. Calcium load samples were obtained over a 4-hr period subsequent to oral ingestion of 1 g calcium. ↑, High; ↓, low; *Cit,* citrate; *Mg,* magnesium; *N,* normal; *Ox,* oxalate; *PTH,* immunoreactive parathyroid hormone; *UA,* uric acid.
From Wein AJ et al: *Campbell–Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

TABLE 3 Common Diagnostic Imaging Modalities for Renal Colic

Modality	Information Provided	Radiation Dose	Contrast	Approximate Cost	Time
CT	Renal and ureteral stones, stone size, location, number, evidence of obstruction Alternative diagnoses, such as AAA, appendicitis, and free air	4-10 mSv	No	$750-$1000	Less than 5 min to perform, 30 min for interpretation
CT with IV contrast	Same as noncontrast CT Delineation of renal masses Additional information about vascular dissections and mesenteric ischemia	4-10 mSv	Yes	$750-$1000	Less than 5 min, after delay to measure creatinine
CT with IV and oral contrast	Same as CT with IV contrast Potentially improved diagnosis of bowel abnormalities	4-10 mSv	Yes	$750-$1000	Less than 5 min, after delay of approximately 2 hr to ingest oral contrast
Intravenous urogram	Structural and functional information about obstruction Rarely, identification of other pathology, such as AAA	1.5 mSv	Yes	$350	Approximately 75 min
X-ray	Possible identification of stone, but cannot assess for hydronephrosis or most other pathology	0.5-1 mSv	No	$250	Less than 5 min
Ultrasound	Identification of hydronephrosis or hydroureter Possible identification of stone Used to assess for AAA or biliary disease	No	No	$150	Approximately 15-30 min—bedside ultrasound is quicker

AAA, Abdominal aortic aneurysm; *CT*, computed tomography; *IV*, intravenous.
From Lipshultz LI et al: *Urology and the primary care practitioner*, ed 3, Philadelphia, 2008, Elsevier.

PREVENTION

- Increase low-calorie fluid intake. Generally, patients at increased risk for stones should increase fluid intake to maintain a urine volume of 2 to 3 L/day.
- Recommended daily allowance of dietary calcium: 800 to 1200 mg/day. Lower calcium consumption results in less gut oxalate-binding and greater colonic oxalate absorption, which in turn increases urinary oxalate and risk for calcium-based stones.
- Limiting animal protein to one serving daily is often recommended.
- Greater fruit and vegetable intake increases urinary excretion of citrate (stone inhibitor).
- Dietary sodium restriction is recommended to <2 grams daily to decrease renal calcium excretion.
- Dietary oxalate restriction in patients with hyperoxaluria may be beneficial. However, low oxalate diets can be difficult to comply with and restrict many foods that promote and maintain cardiovascular health. Box 6 describes foods containing high levels of oxalate.
- Increased dietary citrate (e.g., lemons, limes, oranges).
- Stone specific therapy (Fig. 3):
  1. Uric acid calculi can be prevented or even dissolved at urine pH levels greater than 6 to 6.5. This often is accomplished with potassium citrate or sodium bicarbonate taken 2 or 3 times daily with food. Correction of metabolic syndrome, obesity and diabetes is also preventative for uric acid stones.
  2. Calcium stones:
     a. In general, cannot be dissolved and either persist, pass or are removed.
     b. With hypercalciuria, thiazide diuretics and low-sodium diet are appropriate. Potassium citrate supplementation for patients with calcium stones and low 24-hr urine citrate excretion. Potassium citrate may also be effective with calcium stones even when urine citrate excretion is not low. Potassium citrate can treat the hypokalemia induced by thiazide diuretics.
     c. Urate-lowering treatment for patients with hyperuricosuria but not hypercalciuria.
  3. Struvite stones:
     a. Treating and preventing urinary tract infections reduces struvite stone formation and recurrence.
     b. Difficult to efficiently dissolve and rarely done due to treatment side effects and logistics.
     c. Urease inhibitor treatment by acetohydroxamic acid is considered for poor surgical candidates or those unable to fully clear stones. This agent is poorly tolerated and infrequently used in contemporary practice.
     d. Surgical interventions usually are required to remove struvite stones. Percutaneous nephrolithotomy (PCNL) and/or ureteroscopy are usually needed to adequately treat struvite stones as they facilitate active stone removal. Shock wave lithotripsy (SWL) can be used, but this does not actively remove the stones and may potentiate further UTIs.
  4. Cystine stones:
     a. High fluid intake of 3 to 4 L daily is the principal therapy, although it is hard to accomplish.
     b. Alkalinize urine to pH >6.5 to 7, often with potassium citrate.
     c. Thiol drugs such as D-penicillamine and tiopronin reduce the poorly soluble cystine to a soluble cysteine–drug complex. Tiopronin is better tolerated than penicillamine, but long-term compliance with both is infrequent.
- Surgical therapy
  1. Surgical treatment is needed for patients with severe pain unresponsive to medication, possible infection from an obstructing stone, acute kidney injury from ureteral obstruction, refractory nausea/vomiting and prolonged kidney obstruction (i.e., risk of irreversible renal damage).
  2. Ureteral stones can often be managed with ureteroscopy or SWL.
  3. Stones in the kidney can be managed with ureteroscopy or SWL if <1 to 2 cm in diameter and in a favorable location. As a stone becomes larger and more complex, PCNL becomes the preferred means of management.
  4. Indications for PCNL are described in Table 4.
- Guidelines for ureteral stone treatment:
  1. Proximal ureteral stones <1 cm diameter: SWL or ureteroscopy preferred.
  2. Proximal ureteral stones >1 cm diameter: SWL, ureteroscopy or PCNL for complex and/or large stones.
  3. Distal ureteral stones <1 cm diameter: Ureteroscopy or SWL, although ureteroscopy is generally preferred.
  4. Distal ureteral stones >1 cm diameter: Ureteroscopy or SWL; ureteroscopy is generally preferred.

CHRONIC Rx

Maintenance of proper hydration and dietary restrictions (see "Acute General Rx")

DISPOSITION

- More than 50% to 80% of patients will pass a ureteral stone within 4 to 6 weeks of presentation. Remember the "10 minus size of the stone in mm × 100% rule." For example,

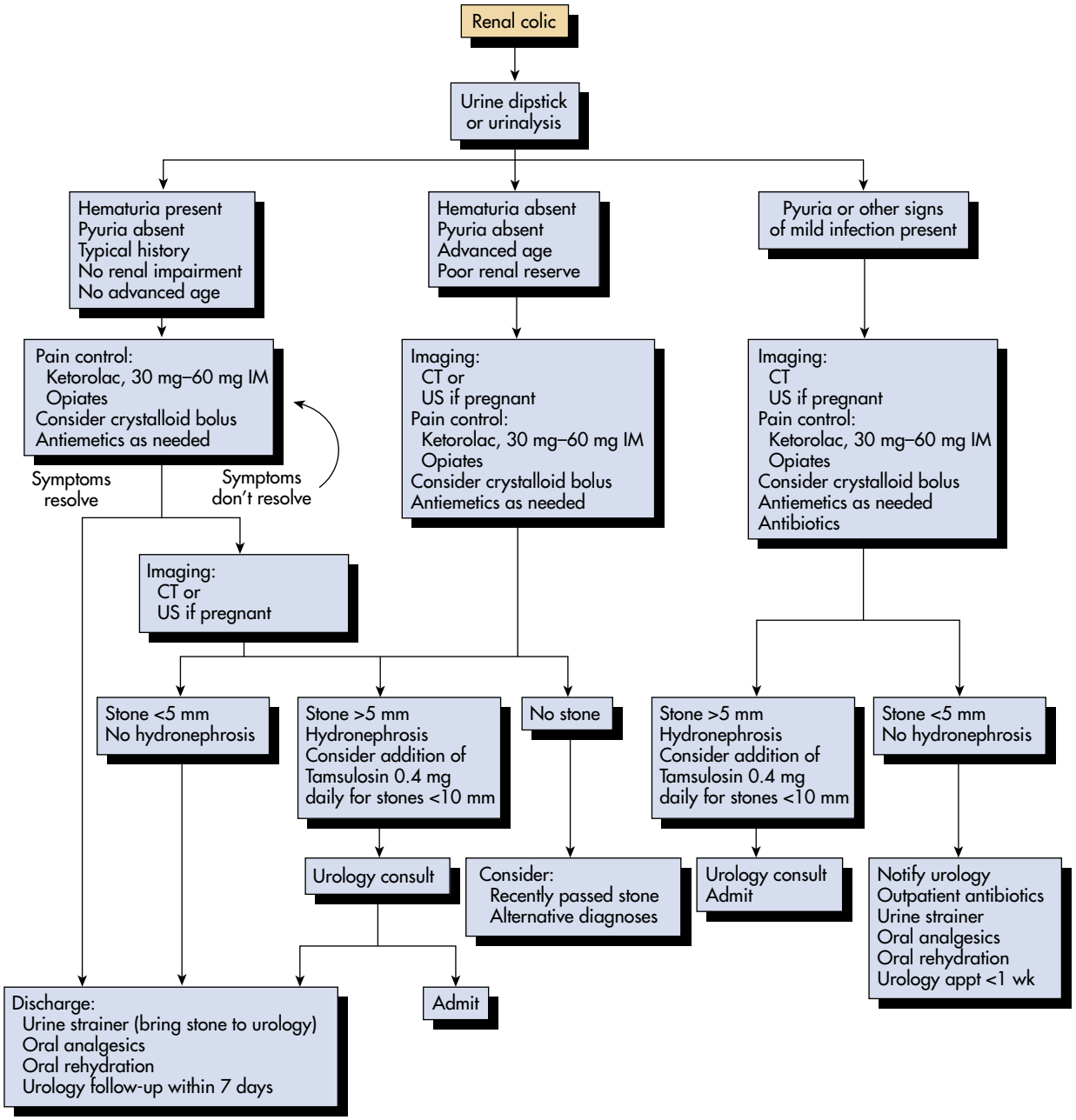

FIG. 2 Guideline algorithm for the evaluation, treatment, and disposition of patients with presumed renal colic. *CT,* Computed tomography; *IV,* intravenously; *US,* ultrasonography. (Modified from Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

a 3-mm stone has an approximately 70% probability of spontaneous passage while an 8-mm stone has only a 20% chance.

- Lifetime stone recurrence is as high as 50% and depends on stone factors (composition, size, location, and number of stones) and patient factors (anatomic, genetic, race, comorbidities, hydration status, diet, climate, and occupation).

REFERRAL

Urology referral is appropriate for any urinary stone patient, especially when spontaneous passage is unlikely; if a patient cannot be directly discharged from an emergency department; when there is an obstructing kidney stone and presumed or associated urinary tract infection; when there are large or recurrent stones; and when patients have solitary kidneys or complex anatomy that may predispose them to stones.

PEARLS & CONSIDERATIONS

COMMENTS

- Approximately 60% to 80% of ureteral stones will pass spontaneously within 4 to 6 weeks. Similarly, approximately 60% to 80% of patients will not require admission or surgery for a ureteral stone.

BOX 6 Foods Containing High Levels of Oxalate

Tea (black)
Cocoa
Spinach
Mustard greens
Pokeweed
Swiss chard
Beets
Rhubarb
Okra
Berries (some)
Chocolate
Nuts
Wheat germ
Soy crackers
Pepper

From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

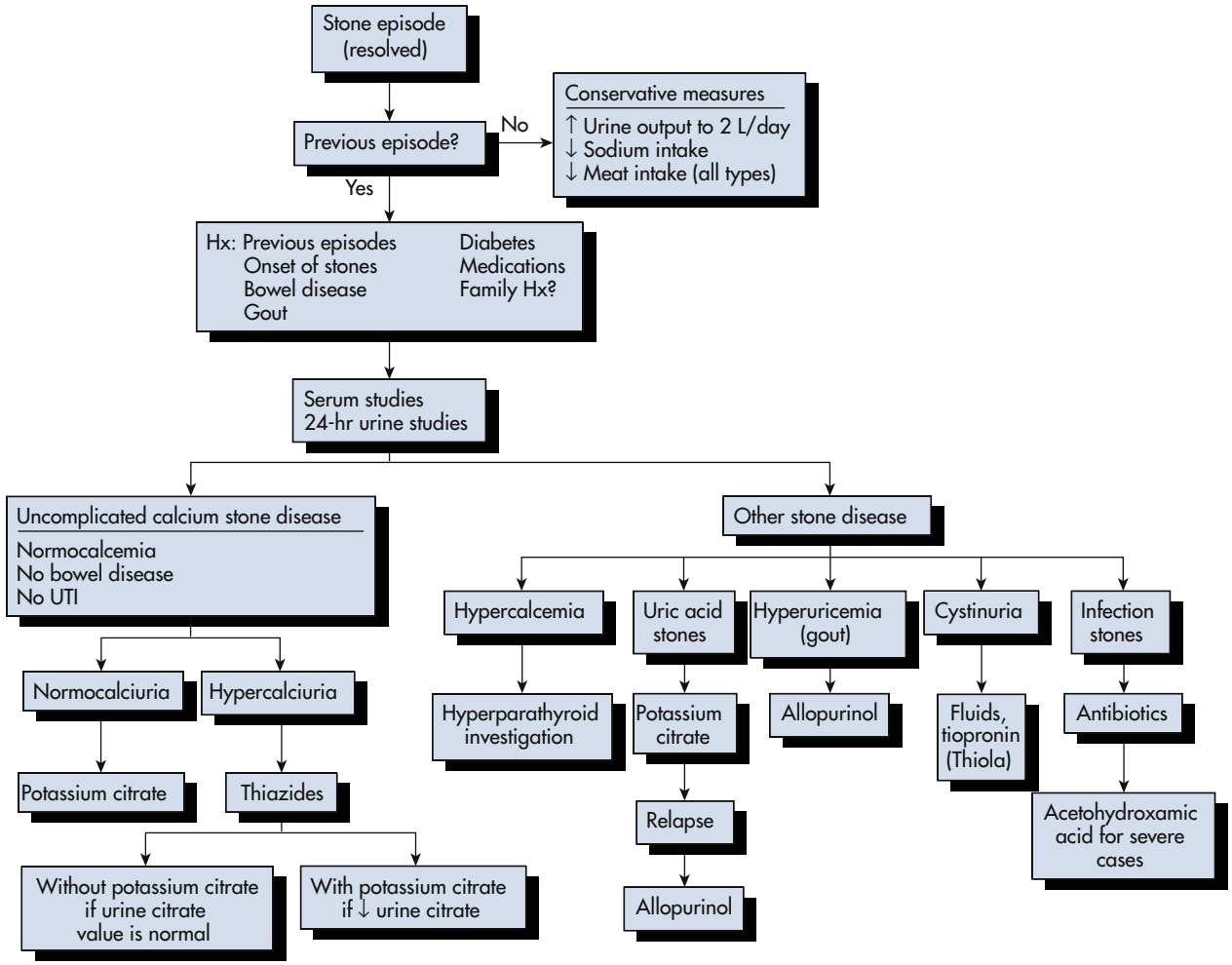

FIG. 3 Simplified treatment algorithm for the evaluation and medical management of urinary lithiasis. *Hx,* History; *UTI,* urinary tract infection. (Modified from CY Pak. From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

TABLE 4 Indications for Percutaneous Nephrolithotomy

Indicator	Description	Treatment
Stone size	≥1.5-2 cm or staghorn	
Composition*,**	Struvite stones	Complete removal necessary to reduce infection and minimize stone recurrence
	Calcium oxalate monohydrate and brushite stones	Difficult to pulverize by SWL
	Cystine stones	Difficult to pulverize by SWL
Stone position	Lower pole stones	Fragments less easily evacuated from dependent lower pole calyces; may not be accessible with ureteroscopy
Anatomic abnormalities	UPJ obstruction; caliceal diverticula; urinary diversion	Prevent passage of fragments after SWL; not always accessible with ureteroscopy
Patient characteristics	Morbid obesity; ureteral obstruction	Stone cannot be placed in focal point of SWL machine; not always accessible with ureteroscopy

SWL or ureteroscopy is the first choice for stone intervention, except in those circumstances that may favor PCNL. *SWL,* Extracorporeal shock wave lithotripsy; *PCNL,* percutaneous nephrolithotomy; *UPJ,* ureteropelvic junction.
*Stone composition can be defined with certainty only by direct stone analysis, but advances in imaging may ultimately provide a means to accurately assess stone composition in situ before treatment, thus allowing the urologist to select the treatment most likely to be successful.
**Ureteroscopy and laser lithotripsy also may be used to treat all stone types, including those listed in this table. Thus, stone size and location ultimately influence PCNL versus ureteroscopy decision.
Modified from Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

- Imaging is key to diagnosing urolithiases. Ultrasound or KUB is a suitable screening test, while CT scan is most accurate and often determines treatment recommendations.
- Consider NSAIDs as first-line therapy for pain control with kidney stones, unless there are contraindications (e.g., allergy or acute kidney injury).
- Patients should be referred to a urologist if they have large stones unlikely to pass spontaneously, multiple or bilateral stones at presentation, complex stones, or recurrent stones.
- An obstructing urinary stone in the setting of presumed urinary tract infection should be treated with prompt urinary tract drainage via insertion of a ureteral stent or percutaneous nephrostomy tube and with antibiotics. Delays in renal drainage can lead to rapid and life-threatening sepsis.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Kidney Stones (Patient Information)
Urinary Tract Infection (Patient Information)

AUTHORS: **Akshay Sood, MD,** and **David A. Leavitt, MD**

SUGGESTED READINGS

Assimos D et al: Surgical management of stones: American Urological Association/Endourological Society Guideline, PART I, *J Urol* 196:1153-1160, 2016.

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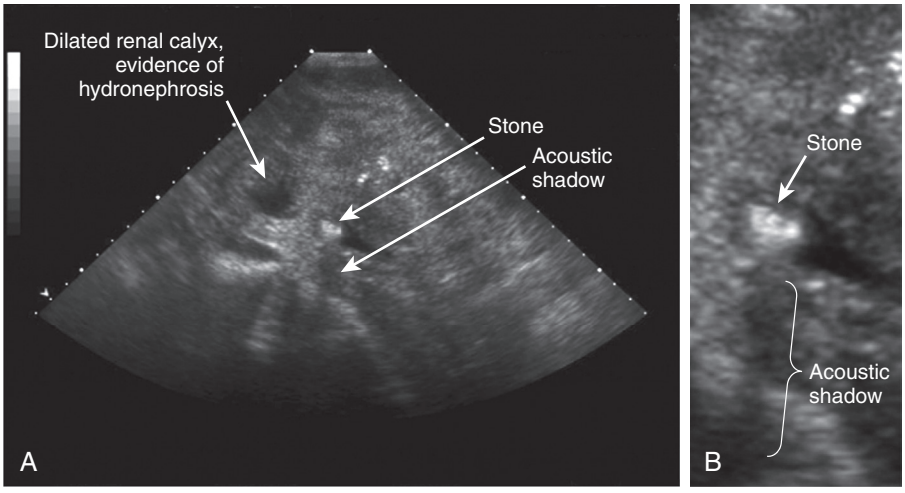

FIG. E1 Ultrasound of renal stone. Ultrasound can be used to assess for renal stones and complications such as hydronephrosis. Stones can be difficult to detect, whereas hydronephrosis is usually readily observed. Because stones are dense, they reflect sound and prevent its through transmission. As a result, stones are echogenic *(bright)* on ultrasound, and cast an acoustic shadow *(black).* **A,** Short-axis view of kidney. **B,** Close-up. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Urticaria is a pruritic rash involving the epidermis and the upper portions of the dermis caused by localized capillary vasodilation and the release of histamine and other vasoactive mediators. It is followed by transudation of protein-rich fluid in the surrounding tissue and manifests clinically with the presence of raised erythematous, circumscribed lesions with central pallor. Urticaria is classified according to its chronicity into acute (<6-wk duration) and chronic (>6-wk duration).

SYNONYMS

Hives
Wheals

ICD-10CM CODES

L50.0	Allergic urticaria
L50.1	Idiopathic urticaria
L50.2	Urticaria due to cold and heat
L50.8	Other urticaria
L50.9	Urticaria, unspecified
L50.6	Contact urticaria

EPIDEMIOLOGY & DEMOGRAPHICS

- Between 15% and 25% of the population will have at least one episode of urticaria during their lifetime.
- The incidence of chronic urticaria is thought to be around 1.4% annually. It is more common in adults, with the average age of occurrence between the third and fifth decades of life. Females are twice as likely to be affected as males.
- Incidence is increased in atopic patients.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presence of elevated, erythematous, or white circumscribed lesions that change in size and shape over time (Fig. E1) in no specific distribution; they are characterized by extreme pruritus and are evanescent in nature, with individual lesions generally lasting <24 hr in duration and disappearing without scarring. If the patient has persistent symptoms, new lesions typically have a novel distribution.
- Stroking of the skin can lead to urticarial reaction (dermatographism) (Fig. E2).
- Angioedema occurs in approximately 40% of cases of urticaria and is caused by mast cell mediator release in the subcutaneous tissue and deep dermis.

ETIOLOGY

Acute urticaria (Table 1):

- Food allergies (e.g., shellfish [Fig. E3], tree nuts, legumes, milk, eggs)
- Medication allergies (e.g., penicillin, aspirin, sulfonamides, hormone therapy)
- Insect sting allergies (e.g., honey bee, Hymenoptera, fire ant)
- Systemic diseases (e.g., systemic lupus erythematosus, serum sickness, autoimmune thyroid disease, cutaneous mastocytosis)
- Infections (viral infections such as hepatitis B and C, fungal infections, chronic bacterial infections, helminthic); viral upper respiratory infections are the predominant cause
- Contact (nonimmunologic) urticaria (e.g., caterpillars, plants)
- Other: Pregnancy, cryoglobulinemia, hair bleaches, chemicals, saliva, cosmetics, perfumes, pemphigoid, emotional stress, malignancy (lymphomas, endocrine tumors)
- Idiopathic urticaria is diagnosed in approximately 50% of patients with acute urticaria

Chronic urticaria:

- Chronic urticaria (CU) is classified as either chronic spontaneous urticaria (CSU) or chronic inducible urticaria (ClndU), depending on whether the skin lesions appear spontaneously or can be induced.
- Physical stimuli (e.g., pressure, cholinergic, solar, cold/heat, aquagenic, or vibration) are found in approximately 20% of patients.
- CSU results from the pathogenic activation of mast cells and basophils, which leads to the release of proinflammatory mediators.
- Up to 50% of CSU patients may have an autoimmune component with contributions from IgG- and IgE-specific autoantibodies (most commonly anti-IL-24 and anti-FcεR1 antibodies, with the latter found on the surface of dermal mast cells and basophils), although the significance of these antibodies is not known.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Erythema multiforme
- Erythema marginatum
- Erythema infectiosum
- Urticarial vasculitis
- Herpes gestationis
- Drug eruption
- Multiple insect bites
- Bullous pemphigoid
- Mastocytosis
- Mast cell activation syndrome
- Viral exanthema
- Pityriasis rosea
- Atopic dermatitis
- Contact dermatitis
- Henoch-Schönlein purpura

WORKUP

- It is useful to determine whether hives are acute or chronic; a medical history focused on various etiologic factors is necessary before embarking on additional laboratory testing.
- Most cases of acute urticaria resolve spontaneously and diagnostic testing is not required. However, in patients with acute urticaria, it is crucial to consider anaphylaxis before further workup of urticaria because this may require urgent management.
- The etiology of chronic urticaria (CU) is often never determined, and no diagnostic testing may be necessary based on a detailed history and physical examination. Targeted laboratory testing based on clinical findings is appropriate.

LABORATORY TESTS

- If the history is consistent with allergen-induced contact urticaria, skin testing with allergen extracts and screening for dermatographism by attempting to elicit a wheal after application of linear skin pressure should be performed only after withholding antihistamines for 36 to 72 hr to prevent false-negative results.
- CBC with differential, ESR, TSH, and liver function tests should be considered only in patients with a history or physical exam concerning for an underlying systemic condition. Routine testing is not indicated. Even with extensive testing, the cause of chronic urticaria is rarely established.
- Measurement of C4, C1 inhibitor antigenic level and function, and C1q may be helpful in patients who present with angioedema alone. In these patients, C1-inhibitor deficiency should be considered.
- Skin biopsy is helpful in patients with fever, arthralgias, and elevated erythrocyte sedimentation rate. Histologic evidence of leukocytoclasia (neutrophilic infiltration with fragmentation of nuclei) is indicative of urticarial vasculitis.
- When food or contact allergy is suspected in acute urticaria, testing can be performed using skin prick or ImmunoCAP testing.

TREATMENT

NONPHARMACOLOGIC THERAPY

Remove all suspected etiologic agents (e.g., stop aspirin and all nonessential drugs) and avoid any triggers that may have been observed to precipitate an attack.

ACUTE URTICARIA Rx

- Oral antihistamines: Use of second-generation H_1 antihistamines (e.g., cetirizine 10 mg/day, levocetirizine 5 mg/day, loratadine 10 mg/day, fexofenadine 180 mg/day) is preferred over first-generation sedating antihistamines (e.g., hydroxyzine, diphenhydramine). Higher doses of second-generation antihistamines up to 4 times the FDA-approved dose may be required to achieve adequate control of symptoms.
- Leukotriene receptor antagonists (e.g., montelukast) can be added to H_1 antagonists in refractory cases, although the utility of this has not been consistently shown.
- Oral corticosteroids should be reserved for refractory cases and prescribed for a very limited course (e.g., prednisone 20 mg daily or 20 mg twice daily for 5 days).

TABLE 1 Some Causes of Urticaria*

Infections	Eggs†
Bacterial infections	Cheese
Dental abscess	Inhalants
Sinusitis	Animal danders
Otitis	Pollen
Pneumonitis	Contactants
Gastritis	Wool
Hepatitis	Silk
Cholecystitis	Occupational exposure
Cystitis	Potatoes
Vaginitis	Antibiotics
Fungal infections	Cosmetics
Dermatophytes	Dyes
Candida	Hairspray
Other infections/infestations	Nail polish
Scabies	Mouthwash
Helminth	Toothpaste
Protozoa	Perfumes
Trichomonas	Hand cream
Drugs and Chemicals	Soap
Salicylates	Insect repellent
Indomethacin and other, newer nonsteroidal antiinflammatory agents†	Physical stimuli
Opiates†	Light
Radiocontrast material†	Pressure
Penicillin (medication, milk, blue cheese)	Heat
Sulfonamides	Cold
Sodium benzoate	Water
Douches	Vibration
Ear drops or eye drops	Endocrinopathies
Insulin	Thyroid disease
Menthol (cigarettes, toothpaste, iced tea, hand cream, lozenges, candy)	Diabetes mellitus
Tartrazine (vitamins, birth control pills, antibiotics, FDC yellow #5)	Pregnancy
Foods	Menstruation
Nuts	Menopause
Berries†	Systemic diseases
Fish	Rheumatic fever
Seafood	Connective tissue diseases (lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, Still disease, dermatomyositis, polymyositis, other)
Shellfish†	Leukemia
Bananas	Lymphoma
Grapes	Acquired immunodeficiency disease
Tomatoes	Ovarian tumors

*Partial list of most frequently described causes in each category.
†May be mediated by nonimmunologic mechanisms independent of IgE.
From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.

CHRONIC URTICARIA Rx

Stepwise approach for management of chronic urticaria is described in Fig. E4.

- Step 1: Monotherapy with second-generation H_1 antihistamines. Avoidance of triggers (e.g., NSAIDs, alcohol, opiates, physical triggers).
- Step 2: Dose advancement of second-generation antihistamine (up to 4× the daily recommended dose). Consider addition of leukotriene receptor antagonist (e.g., montelukast) or first-generation H_1 antihistamine (hydroxyzine or doxepin) to be taken at bedtime.
- Step 3: Referral to allergy specialist for evaluation and management. Add omalizumab (monoclonal anti-IgE antibody that downregulates surface IgE receptors) to second-generation antihistamine therapy. Ligelizumab is a newer high-affinity humanized monoclonal anti-IgE antibody that in recent trials has shown a higher percentage of patients with chronic spontaneous urticaria achieving compliance control of symptoms than omalizumab.[1]
- Step 4: If adequate control is not reached by 18 wk, alternative agents should be considered, including antiinflammatory (dapsone, hydroxychloroquine, sulfasalazine, methotrexate) or immunosuppressive agents (cyclosporine A, mycophenolate, tacrolimus, sirolimus).
- Step 5: Consider addition of immunomodulatory biologic agents (TNF-α inhibitor, IL-1 antagonist) or alternative therapies such as UV light therapy, IVIG, or plasmapheresis.
- Patients should be evaluated at each visit and if symptoms are well managed, should be considered for step down in treatment.

DISPOSITION

- Most cases of urticaria resolve within 6 wk.
- More than 50% of patients may not achieve satisfactory control of chronic urticaria with antihistamines alone and may require additional therapies. The median duration of CU is between 3 to 5 yr, but it can often be present for much longer durations.

PEARLS & CONSIDERATIONS

COMMENTS

- Topical treatment (e.g., starch baths or oatmeal baths) may be temporarily soothing in selected patients; however, they are not recommended for long-term control of CU.
- If individual urticarial lesions leave residual ecchymoses, pigmentation and/or lesions that typically last >24 hr at a single location, consider skin biopsy to evaluate for urticarial vasculitis.
- **Be judicious when prescribing NSAIDs in CU patients, as up to 30% of these patients will experience an exacerbation of urticaria and/or angioedema.**

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Hives (Patient Information)
Chronic Urticaria (Related Key Topic)

AUTHORS: **Shyam Joshi, MD,** and **Pinar Arikan, MD**

[1]Maurer M et al: Ligelizumab for chronic spontaneous urticaria, *N Engl J Med* 381: 1321-1332, 2019.

FIG. E1 Urticaria. Wheals may coalesce and cover large areas of the body. (From Paller AS et al: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E3 Urticaria. These annular and serpiginous wheals developed within minutes of eating shrimp. (From Paller AS et al: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E2 Dermatographism. Stroking of the skin leads to the urticarial reaction. (From Callen JP et al: *Dermatological signs of systemic disease,* ed 5, Philadelphia, 2017, Elsevier.)

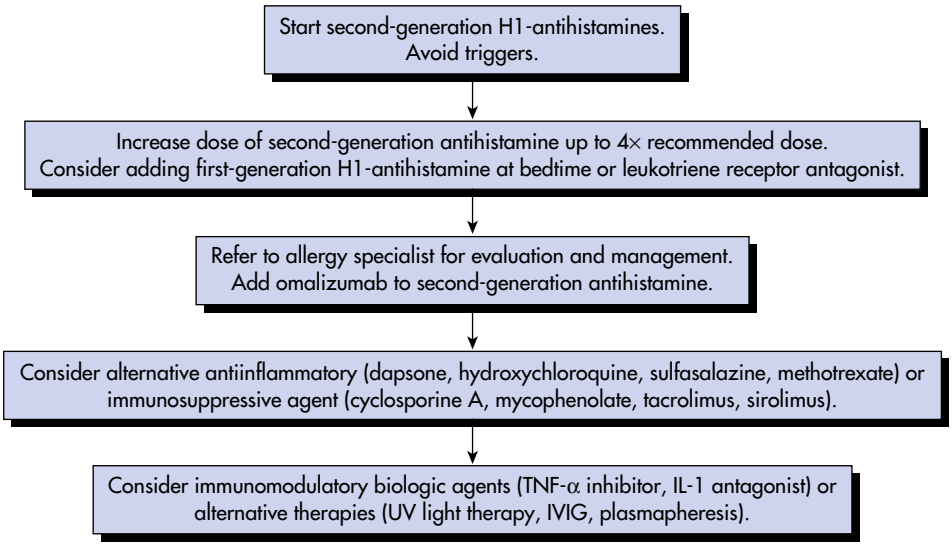

FIG. E4 Stepwise treatment diagram for chronic urticaria. Stepwise approach for management of chronic urticaria is described.

- Step 1: Monotherapy with second-generation H_1-antihistamines. Avoidance of triggers (e.g., NSAIDs, alcohol, opiates, physical triggers).
- Step 2: Dose advancement of second-generation antihistamine (up to 4 times the daily recommended dose). Consider addition of leukotriene receptor antagonist (e.g., montelukast) or first-generation H_1 antihistamine (hydroxyzine or doxepin) to be taken at bedtime.
- Step 3: Referral to allergy specialist for evaluation and management. Add omalizumab (monoclonal anti-IgE antibody that downregulates surface IgE receptors) to second-generation antihistamine therapy.
- Step 4: If adequate control is not reached by 18 wk, alternative agents should be considered including antiinflammatory (dapsone, hydroxychloroquine, sulfasalazine, methotrexate) or immunosuppressive agents (cyclosporine A, mycophenolate, tacrolimus, sirolimus).
- Step 5: Consider addition of immunomodulatory biologic agents (tumor necrosis factor-α [TNF-α] inhibitor, interleukin-1 [IL-1] antagonist) or alternative therapies such as ultraviolet (UV) light therapy, Intravenous immunoglobulin (IVIG), or plasmapheresis.
- Patients should be evaluated at each visit and if symptoms are well managed, should be considered for step down in treatment.

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Schaefer P: Acute and chronic urticaria: evaluation and treatment, *Am Fam Physician* 95(11):717-724, 2017.

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Uterine Fibroids PTG ALG

BASIC INFORMATION

DEFINITION

Uterine fibroids, also called leiomyomas or uterine myomas, are benign tumors of muscle cells of the myometrium and connective tissue. The incidence of malignancy is less than 1 in 1000. They are typically discrete nodular tumors that vary in size and number.

Fibroids are classified by location in the uterus relative to the myometrium.

- Subserosal: Located directly underneath the uterine serosa
- Intramural: Located in the myometrium proper
- Submucosal: Also known as intracavitary as they are located adjacent to the endometrium and protrude into the uterine cavity
- Pedunculated: Located on a pedicle or stalk, either from the serosa or in the cavity

Fibroids can also be located within the cervix, broad ligament, or diffusely in the body such as within the abdomen on peritoneum or within skin. Parasitic fibroids acquire a blood supply from a nonuterine source (Fig. 1).

SYNONYMS

Uterine leiomyomas
Uterine myomas
Fibroids
Leiomyomas

ICD-10CM CODES

D25.0 Submucous leiomyoma of uterus
D25.1 Intramural leiomyoma of uterus
D25.2 Subserosal leiomyoma of uterus
D25.9 Leiomyoma of uterus, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Estimated cumulative incidence of 70% to 80% in women by age 50.
- The most common benign solid pelvic tumor diagnosed in women and the most common reason for benign hysterectomy.
- More common in African American women than in Caucasian women.
- May occur singly but are often multiple.
- Approximately 50% of all fibroids are estimated to produce symptoms that impact women including restriction of social, physical, and work activities.
- Frequently diagnosed incidentally on pelvic examination.
- There is increased familial incidence.
- Potential to enlarge during pregnancy as well as regress after menopause.
- Approximately 200,000 hysterectomies, 30,000 myomectomies, and thousands of selective uterine-artery embolizations and high-intensity focused ultrasound procedures are performed annually in the U.S. to remove or destroy uterine fibroids.[1]

[1] Bulun SE: Uterine fibroids, *N Engl J Med* 369:1344-1355, 2013.

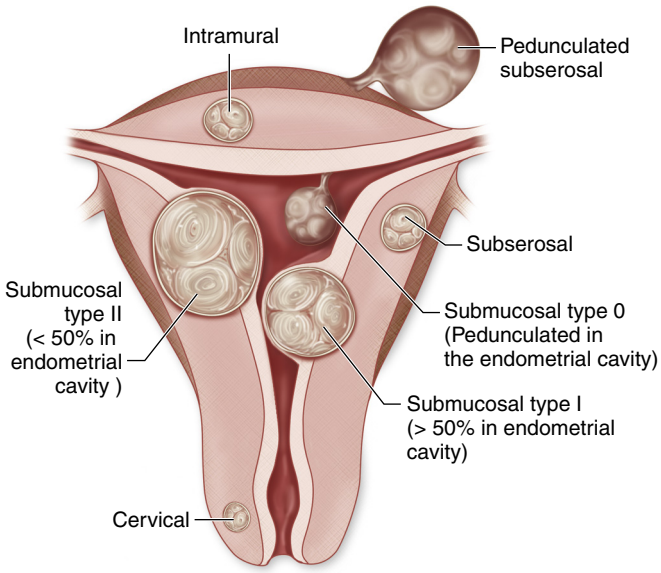


FIG. 1 Drawing of uterus in the coronal plane, illustrating possible location of uterine leiomyomas. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Enlarged, irregular uterus on pelvic examination
- Uterine fibroids are asymptomatic in up to 50% of affected women
- Presenting symptoms (when present):
  1. Abnormal uterine bleeding (most common)
  2. Chronic pelvic pain (dysmenorrhea, dyspareunia, pelvic pressure)
  3. Bulk symptoms (bloating, increase in abdominal girth)
  4. Anemia
  5. Acute pain (torsion of pedunculated fibroid, infarction, and degeneration)
  6. Urinary symptoms (frequency from bladder pressure, partial ureteral obstruction, complete ureteral obstruction, incontinence in setting of prolapse)
  7. GI symptoms (rectosigmoid compression with constipation or intestinal obstruction, pain with defecation)
  8. Prolapse through cervix of pedunculated submucosal fibroid
  9. Infertility
  10. Pregnancy complications including preterm birth, small fetus for gestational age, malpresentation, and potentially recurrent miscarriage

ETIOLOGY

Not well understood. It is suggested that fibroids arise from an original single smooth muscle cell in the myometrium. Each individual fibroid is monoclonal (all the cells are derived from one progenitor myocyte). Malignant degeneration of preexisting leiomyoma is extremely uncommon (<0.5%). There is a racial disparity in the prevalence, suggesting a genetic component, with most fibroids having a normal chromosomal makeup. A small group of women have an autosomal dominant disorder, hereditary leiomyomatosis and renal cell carcinoma syndrome, in which there is a genetic mutation in the fumarate hydratase gene, causing diminished suppressor function in fibroid formation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ovarian mass (neoplastic, nonneoplastic, endometrioma)
- Adenomyosis
- Endometriosis
- Endometrial polyp
- Endometrial carcinoma
- Leiomyosarcoma/uterine carcinosarcoma
- Inflammatory mass (reproductive organ or GI origin)
- Pregnancy

WORKUP

- Complete pelvic examination, including speculum exam as well as bimanual exam
- Estimation of size of uterus/mass and location of fibroids via imaging
- Endometrial sampling may be indicated (biopsy or dilation and curettage) when abnormal bleeding and pelvic mass are present
- If significant urinary symptoms are prominent, intravenous pyelogram to rule out impingement on urinary system

LABORATORY TESTS

- Pregnancy test
- Complete blood count
- Blood urea nitrogen/creatinine
- Thyroid stimulating hormone

IMAGING STUDIES

- Pelvic ultrasound (Fig. 2) is useful as a primary diagnostic modality. Transvaginal ultrasound commonly has higher diagnostic accuracy.
- MRI scan (Fig. E3) is helpful in planning treatment if malignancy is strongly suspected.

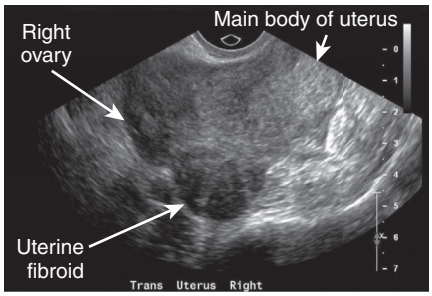


FIG. 2 Fibroid uterus: Endovaginal ultrasound. Ultrasound is the primary modality used for evaluation of uterine fibroids (leiomyomas). Typical features include a well-circumscribed appearance. Fibroids may be hypoechoic or hyperechoic relative to the uterus. They may be exophytic or intramural, or they may project into the uterine cavity. Whereas malignant uterine tumors may invade adjacent structures, a fibroid is contained within the uterine serosa. Uterine tumors, both benign and malignant, can show central necrosis, which usually appears hypoechoic with ultrasound. In this 38-yr-old woman, the fibroid is exophytic. The right ovary lies adjacent and is difficult to distinguish in this case. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

Also important to localize fibroids, especially if myomectomy is contemplated. Size, number, and location of fibroids are also important if a minimally invasive myomectomy is considered.

- Diagnostic hysteroscopy can be performed in the office and may provide direct evidence of intrauterine pathology or submucosal leiomyoma that distorts uterine cavity.
- Saline infusion sonography can be helpful in determining location and degree of intrusion into uterine cavity.

Rx TREATMENT

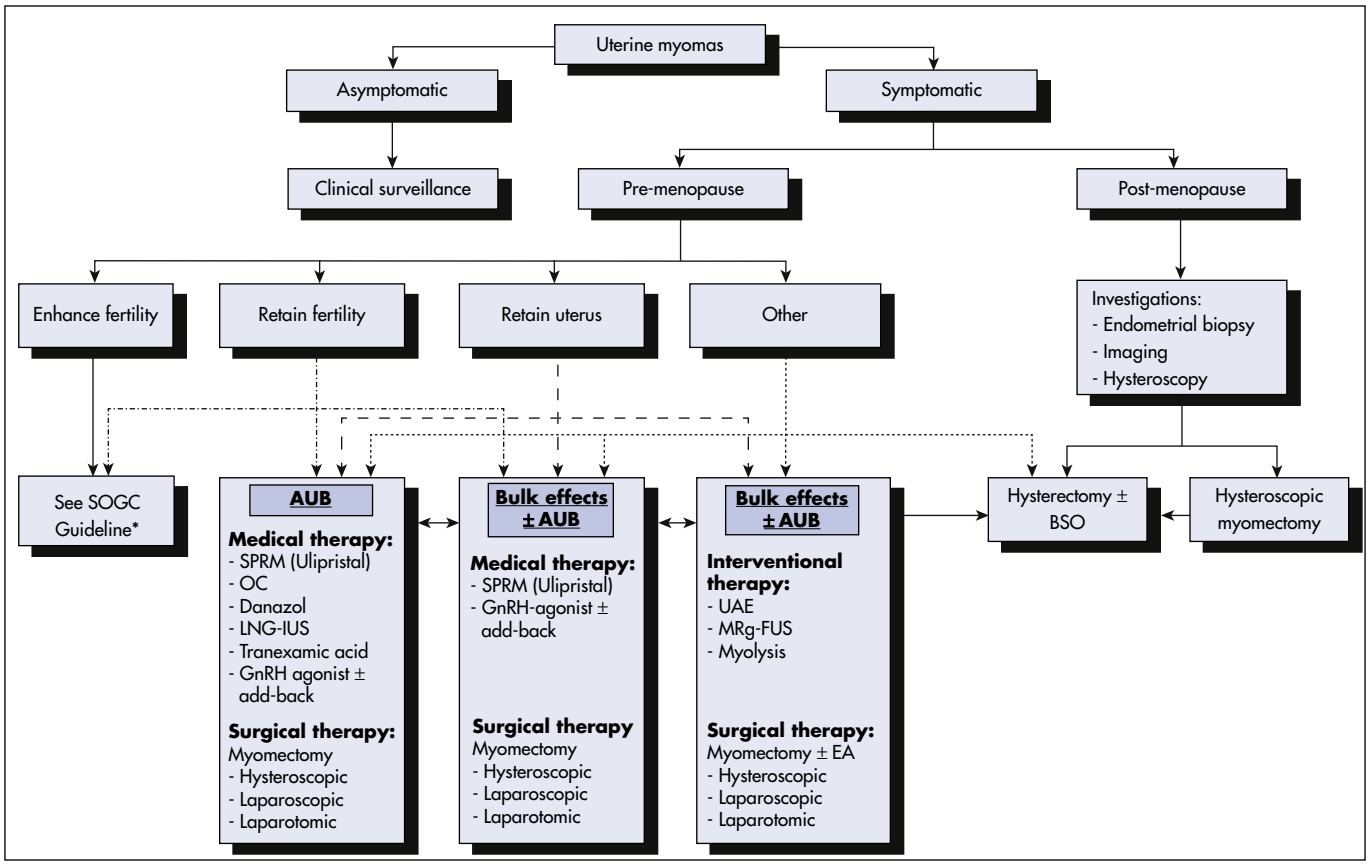
Management (Fig. 4) should be based on primary symptoms and may include observation with close follow-up, medical management, temporizing surgical therapies, embolization, or definitive surgical procedures. Treatment is generally indicated if bleeding is requiring blood transfusions, renal function is affected by size of the enlarged fibroid uterus, or when symptoms are present and are severe enough to be unacceptable to the patient.

NONSURGICAL Rx

- Patient observation and follow-up with periodic repeat pelvic examinations to ensure that tumors are not growing rapidly.
- Hormonal therapies can reduce bleeding symptoms and many have the added benefit of contraception. There is no evidence that exogenous estrogen or progestin increases risk of myomas.
  1. Combined hormonal methods with estrogen and progestin, including combined oral contraceptives, contraceptive patch, contraceptive vaginal ring.
  2. Progestin-only agents including oral progestins, intramuscular progestin injection, subcutaneous progestin implant, levonorgestrel intrauterine device (IUD).
  3. Progesterone IUD can be used to treat menorrhagia, but intracavitary fibroids may be a relative contraindication.
  4. Ulipristal acetate, not yet available in the U.S. for treatment of fibroids, is a selective progesterone-receptor modulator (SPRM) that acts on progesterone receptors in myometrial and endometrial tissue and inhibits ovulation without significant effects on estradiol levels or antiglucocorticoid activity. Recent trials showed that treatment with ulipristal acetate for 13 wk effectively controlled excessive bleeding due to uterine fibroids and reduced the size of the fibroids. Phase 3 trials for SPRM are ongoing in the U.S.
- Gonadotropin-releasing hormone (GnRH) agonist use results in 40% to 60% reduction in uterine volume within 3 months of initiating treatment. Hyperestrogenism, reversible bone loss, and hot flushes are associated with use. Consider low-dose progesterone replacement to minimize hypoestrogenic effects.
  1. Regrowth and return of bleeding symptoms occurs in approximately 50% of women treated within a few months after cessation.
  2. Indications for GnRH:
     a. Fertility preservation in women with large myomas before attempting conception or preoperative myectomy treatment
     b. Anemia treatment to normalize hemoglobin before surgery
     c. Women approaching menopause to avoid surgery
     d. Preoperative for large myomas to make vaginal hysterectomy, hysteroscopic resection/ablation, or laparoscopic destruction more feasible
     e. Women with medical contraindications for surgery
  3. Personal or medical indications for delaying surgery: Use of GnRH agonists may alter the consistency of the fibroid, making myomectomy more challenging.
- Nonhormonal medical therapies:
  1. Nonsteroidal antiinflammatory drugs.
  2. Tranexamic acid, an oral antifibrinolytic agent that prevents fibrinolysis of menstrual fluid, can decrease menorrhagia by 40% to 65%. Side effects include abdominal cramps, headaches, fatigue, and increase risk of venous thromboembolism.
- Other drugs used and under investigation:
  1. Danazol: Androgen and multienzyme inhibitor of steroidogenesis
  2. Mifepristone: Antiprogesterone shown to reduce the fibroid volume by 40% to 50% with amenorrhea
  3. Raloxifene: Selective estrogen receptor modulator, either alone or with a GnRH agonist, shown to reduce the fibroid volume 70% up to 1 yr but only in postmenopausal women
  4. Fadrozole: Aromatase inhibitor reported to have produced a 71% reduction in volume that is not yet available in the U.S.
  5. Vilaprisan: Selective progesterone receptor modulator (SPRM) currently in phase 3 trials showing decreasing amenorrhea rates and reduction in fibroid size

SURGICAL Rx

- Indications:
  1. Abnormal uterine bleeding with anemia refractory to hormonal therapy
  2. Chronic pain with severe dysmenorrhea, dyspareunia, or lower abdominal pressure/pain
  3. Acute pain, torsion, or prolapsing submucosal fibroid
  4. Urinary symptoms or signs such as hydronephrosis
  5. Rapid uterine enlargement premenopausal or any growth after menopause
  6. Infertility or recurrent pregnancy loss with submucous leiomyoma as only finding
  7. Enlarged uterus with compression symptoms or discomfort
- Procedures:
  1. Hysterectomy (definitive procedure): Vaginal, laparoscopic, robotic, or abdominal approach, dependent on surgical preference/expertise and uterine size.
  2. Myomectomy (to preserve fertility or due to patient preference): May be performed via abdominal, laparoscopic, or robotic approach.
  3. Vaginal myomectomy for prolapsed pedunculated submucous fibroid.
  4. Hysteroscopic resection: Typically at least 50% of the fibroid must be intracavitary for a hysteroscopic approach to be successful.
  5. Radiofrequency volumetric thermal ablation: FDA-approved uterine-sparing procedure in which laparoscopic ablation of individual fibroids is performed. This causes myolysis (necrosis of the tissue) resulting in the fibroid shrinking.
  6. Uterine artery embolization (UAE): Safe and effective short-term alternative to surgery, but its less invasive nature should be balanced against a higher rate for treatment failure or complications



BSO: Bilateral salpingo-oophorectomy; MRg-FUS: magnetic resonance-guided focused ultrasound; OC: oral contraceptives

FIG. 4 Algorithm for the management of uterine fibroids. *GnRH,* Gonadotropin-releasing hormone; *UAE,* uterine artery embolization. (From Vilos GA et al: The management of uterine leiomyomas, *J Obstet Gynaecol Can* 37(2):163, 2015. *Carranza-Mamane B, Havelock J, Hemmings R: Society of Obstetrics and Gynaecology Canada Reproductive Endocrinology and Infertility Committee: The management of uterine fibroids in women with otherwise unexplained infertility. SOGC Clinical Practice Guidelines, *J Obstet Gynaecol Can* 2015.)

at 5 yr (32%) versus the surgery group (4%). Age 40 yr and under at embolization and history of previous myomectomy are significant predictors of embolization failure. If the patient wishes to preserve future fertility, UAE should not be performed.

7. Endometrial ablation: Performed specifically to decrease menorrhagia.
8. MRI-guided focus ultrasound surgery for fibroids is a noninvasive thermoablative procedure that allows high-energy ultrasound waves to converge on a fibroid localized by MRI. Note, there is limited availability of this procedure.

COMPLICATIONS

- Red degeneration occurs when the fibroid outgrows its blood supply leading to hemorrhage in the center of the fibroid. This is typically seen in the second trimester of pregnancy but is a rare occurrence.
- Leiomyosarcoma (<0.1%). Recent concern has been voiced by the U.S. FDA regarding the use of morcellation in minimally invasive surgery because of the possibility of spreading occult malignancy in the peritoneal cavity.

REFERRAL

Consultation with gynecologic oncologist if suspicious of malignancy

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Uterine Fibroids (Patient Information)
Dysfunctional Uterine Bleeding (Related Key Topic)

AUTHORS: **Nima R. Patel, MD, MS,** and **Terri Q. Huynh, MD, MSCR**

SUGGESTED READINGS

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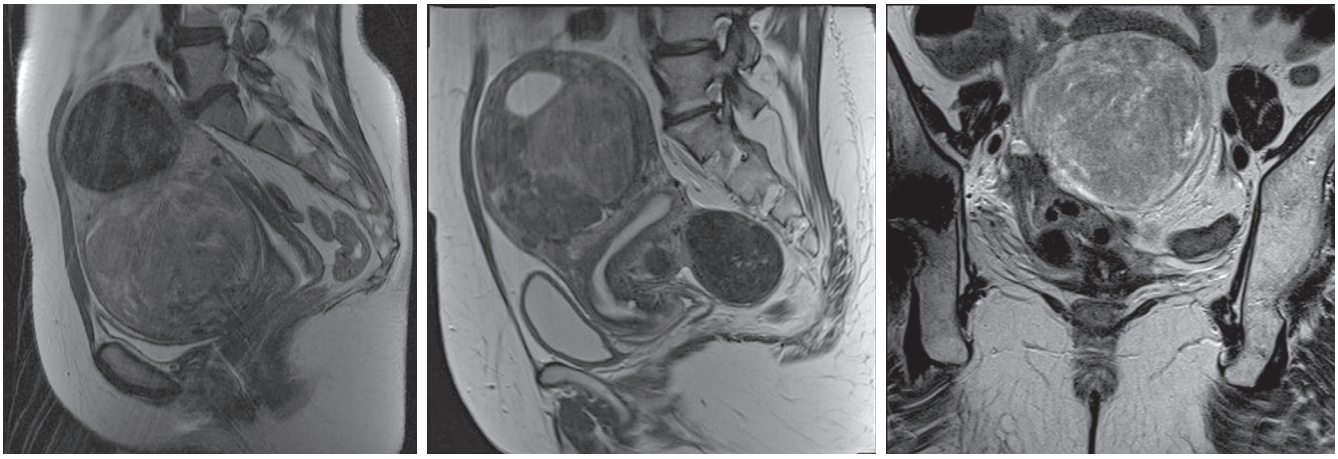

FIG. E3 Variable appearance of fibroids on magnetic resonance image (MRI). (A) Sagittal T2-weighted MRI showing an intermediate signal anterior myometrial fibroid. Patchy high signal areas indicate degeneration. A second fibroid at the fundus is of characteristic low signal. **(B)** There is cystic degeneration in the anterior fibroid, and a low signal intensity posterior fibroid that has displaced the rectum. Note retroverted uterus. **(C)** A large pedunculated fibroid is of mixed signal, indicating degeneration. Note multiple small low signal fibroids in the myometrium. (From Adam A et al: *Grainger and Allison's diagnostic radiology,* ed 6, 2015, Elsevier. In Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, 2019, Elsevier.)

BASIC INFORMATION

DEFINITION

Cancers of the uterine corpus include tumors originating from the endometrium (endometrial stromal cancers). The most common type of endometrial cancer is adenocarcinoma, which includes endometrioid, clear cell, mucinous, and papillary serous subtypes (see separate chapter on endometrial cancer). Uterine cancer also includes tumors that result from abnormal proliferation of cells originating from the connective, muscular, vascular, or fibrous tissue elements of the uterine wall (myometrium).

SYNONYMS

Leiomyosarcomas
Endometrial stromal sarcoma
Malignant mixed Müllerian tumors
Adenosarcomas

ICD-10CM CODES

C54.1 Malignant neoplasm of endometrium
C54.2 Malignant neoplasm of the myometrium
C54.0 Malignant neoplasm of isthmus uteri
C54.8 Malignant neoplasm of overlapping sites of corpus uteri

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Incidence of uterine cancer (including endometrial) is 27 per 100,000 women per yr, with 5 deaths per 100,000 women as of 2016. Endometrial cancer remains the most common gynecologic malignancy in the U.S. Uterine cancer is one of the few cancers with increasing incidence and mortality in the U.S., reflecting in part increases in the prevalence of obesity since the 1980s. It is the fourth most common cancer diagnosed and the sixth most common cause of cancer death among U.S. women.[1]
PREVALENCE: Uterine sarcoma accounts for approximately 8% of all cancers of the uterine corpus and is associated with poor prognosis.
MEAN AGE AT DIAGNOSIS: 60 yr
RISK FACTORS: Box 1 describes risk factors for uterine sarcoma

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abnormal vaginal bleeding is the most common symptom (90% of women with diagnosis).
- Vaginal discharge also may be a presenting symptom (10% of these patients have nonbloody discharge).
- May also present as pelvic pain or pressure and pelvic mass on examination (10% of women with uterine sarcoma)
- Urinary symptoms
- Abdominal pain or distension
- Weight loss

[1]Henley SJ et al: Uterine cancer incidence and mortality—United States, 1999-2016, *MMWR* 67(48):1333-1338, 2018.

ETIOLOGY

- The exact etiology is unknown.
- Endometrial cancer is possibly related to the balance between progesterone and estrogen in the body.

DIAGNOSIS

- Endometrial cancer: Endometrial biopsy or dilation and curettage with histologic evidence of malignancy.
- Uterine sarcoma: Postsurgical histological examination of uterine tissue

DIFFERENTIAL DIAGNOSIS

- Endometrial hyperplasia
- Leiomyoma

WORKUP

Diagnosis is made histologically by biopsy for abnormal bleeding. Workup includes biopsy (in the office or operating room, in conjunction with hysteroscopy) and imaging (see below). Histologic criteria include mitotic index, cellular atypia, and coagulative necrosis.

LABORATORY TESTS

- CBC depending on level of bleeding
- CA-125 (high levels can be a sign of metastasis, not diagnostic, not always elevated)

IMAGING STUDIES

- Pelvic ultrasound is a lower-cost method of detecting uterine corpus mass or thickened endometrial lining. Features concerning for uterine sarcoma: heterogeneous texture, central necrosis, irregular vessel distribution.
- Chest x-ray is usually done as routine preoperative testing.
- CT scans (Fig. 1), MRI, and PET are useful for assessing tumor spread once diagnosis is made.

STAGING

Staging of endometrial carcinoma and uterine adenosarcoma is summarized in Tables 1 and 2.

TREATMENT (TABLE 3)

NONPHARMACOLOGIC THERAPY

- Surgical excision is the mainstay of treatment, with or without lymph node mapping and with or without peritoneal lavage or peritoneal biopsies. Degree of removal and exploration depends on grading, staging, and type of cancer.
- Endometrial stromal sarcoma: Stage 1 disease is usually followed up by surveillance. Stage 2 or higher can be offered endocrine therapy or radiation therapy.
- Leiomyosarcoma: Usually followed with surveillance. Chemotherapeutic agents can be considered for stage 3 or higher; they have produced only partial and short-term responses

BOX 1 Risk Factors for Uterine Sarcoma

- Nulliparity
- Obesity
- History of pelvic radiation
- Exposure to tamoxifen

From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.

DISPOSITION

- Survival varies with each type of sarcoma but is generally very poor. Box 2 describes uterine prognostic factors.
- Five-yr survival for grade I endometrial stromal sarcoma is 91% and drops to 42% for grade III.
- Five-yr survival for leiomyosarcoma ranges from 76% for stage 1 to 29% for stage 4.
- Five-yr survival for undifferentiated sarcoma ranges from 70% for stage 1 to 23% for stage 4.

REFERRAL

Uterine sarcoma should be managed by a gynecologic oncologist and radiation oncologist. Key

TABLE 1 International Federation of Gynecology and Obstetrics 2009 Staging for Endometrial Carcinoma (Including Carcinosarcoma)

Stage	
I_A	Tumor confined to uterine corpus, <50% myometrial invasion
I_B	Tumor confined to uterine corpus, ≥50% myometrial invasion
II	Tumor invades cervical stroma but confined to uterus
III_A	Tumor invades uterine serosa or adnexa
III_B	Involvement of vagina or parametrium
III_{C1}	Metastasis to pelvic lymph nodes
III_{C2}	Metastasis to paraaortic lymph nodes
IV_A	Invasion of bladder or bowel mucosa
IV_B	Distant metastases including intraabdominal metastasis, inguinal lymph nodes, or both

From Niederhuber JE:*Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE 2 International Federation of Gynecology and Obstetrics 2009 Staging for Uterine Adenosarcoma

Stage	
I_A	Tumor limited to endometrium
I_B	Tumor limited to uterus, <50% myometrial invasion
I_C	Tumor limited to uterus, ≥50% myometrial invasion
II_A	Adnexal involvement
II_B	Extrauterine pelvic tissue involvement
III	Involvement of abdominal tissues
III_A	1 site
III_B	>1 site
III_C	Metastases to pelvic, paraaortic lymph nodes, or both
IV_A	Tumor invades bladder or rectum
IV_B	Distant metastases

From Niederhuber JE:*Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

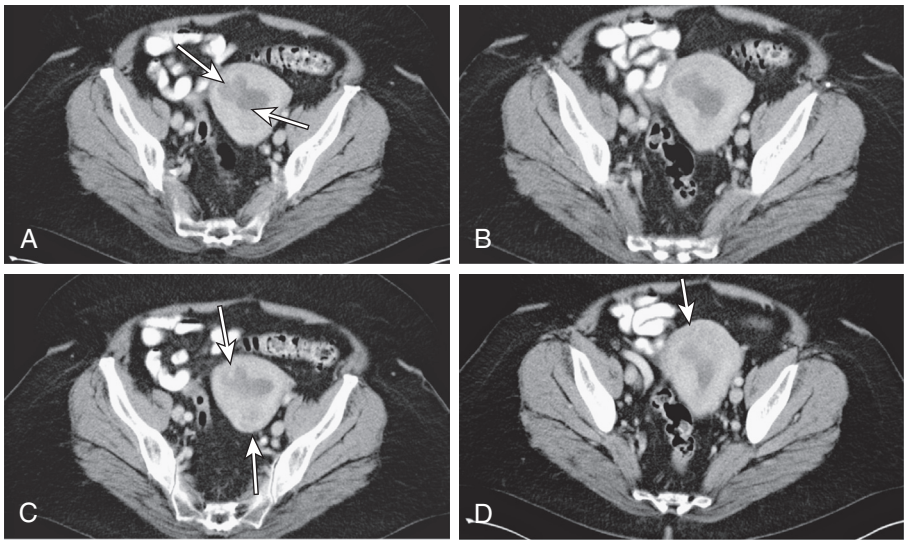

FIG. 1 A 50-year-old patient with uterine sarcoma. A, Axial contrast-enhanced computed tomographic (CT) image. Low-attenuation lobulated and infiltrating soft tissue fills the endometrial canal *(arrows),* extending into the myometrium. **B,** Axial contrast-enhanced CT image showing same as **A.** Low-attenuation, lobulated and infiltrating soft tissue fills the endometrial canal, extending into the myometrium. **C,** Axial contrast-enhanced CT image. Low-attenuation lobulated and infiltrating soft tissue fills the endometrial canal. Subtle myometrial invasion is seen anterior and posterior *(arrows).* **D,** Axial contrast-enhanced CT image. Low-attenuation lobulated and infiltrating soft tissue fills the endometrial canal *(arrow),* showing same. Subtle myometrial invasion is seen fundally. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

TABLE 3 National Comprehensive Cancer Network Guidelines for Treatment of Uterine Serous, Clear Cell Endometrial Carcinoma, and Carcinosarcoma

Stage	Adjuvant Treatment
I_A without myometrial invasion	Observe, or chemotherapy, or VBT, or combination therapy
I_A with myometrial invasion, I_B, II	Chemotherapy ± tumor-directed RT, or whole abdominopelvic RT ± VBT
III, IV (adequately debulked)	Chemotherapy ± tumor-directed RT, or whole abdominopelvic RT ± VBT
III, IV (inadequately debulked)	Chemotherapy

RT, Radiation therapy; *VBT,* vaginal brachytherapy.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

BOX 2 Uterine Sarcoma Prognostic Factors

- Tumor stage
- Tumor grade
- Tumor size
- Patient age
- Vascular space involvement
- Mitotic count
- Residual disease at surgery
- Adjuvant chemotherapy

From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.

BOX 3 Uterine Sarcoma: Key Points

- The disease mainly affects postmenopausal women.
- Most patients present early with postmenopausal bleeding.
- The primary treatment is hysterectomy.
- Adjuvant radiotherapy to the pelvis is used if poor prognosis features in stage 1 or if spread has occurred beyond the corpus.

From Greer IA et al: *Mosby's color atlas and text of obstetrics and gynecology,* London, 2001, Harcourt.

points in the management of uterine sarcoma are described in Box 3.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Uterine Cancer (Patient Information)
Endometrial Cancer (Related Key Topic)

AUTHORS: **Ashwini U. Dhokte, MD,** and **Rachel Wright Heinle, MD, FACOG**

SUGGESTED READINGS

Amant F et al: Gynecologic cancer intergroup (GCIG) consensus review for endometrial stromal sarcoma, *Int J Gynecol Cancer* 24:S67-S72, 2014.

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Center for Disease Control: gis.cdc.gov/Cancer/USCS/DataViz.html.

Uveitis

BASIC INFORMATION

DEFINITION

Uveitis is inflammation of the uveal tract, including the iris, ciliary body, and choroid. It may also involve other contiguous structures such as the sclera, cornea, retina, and vitreous humor (Fig. E1).

SYNONYMS

Anterior uveitis (iritis, iridocyclitis)
Intermediate uveitis (pars planitis)
Posterior uveitis (choroiditis)
Acute or chronic uveitis
Granulomatous or nongranulomatous uveitis

ICD-10CM CODES

H20.0	Acute and subacute iridocyclitis
H20.1	Chronic iridocyclitis
20.8	Other iridocyclitis
H20.9	Unspecified iridocyclitis
H44.131	Sympathetic uveitis, right eye
H44.132	Sympathetic uveitis, left eye
H44.133	Sympathetic uveitis, bilateral
H44.139	Sympathetic uveitis, unspecified eye

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Common; busy ophthalmologist will see two or more cases per wk.
PEAK INCIDENCE: Middle age or older
PREVALENCE (IN U.S.): 17 cases per 100,000 persons
PREDOMINANT SEX: None
PREDOMINANT AGE: 38 yr. Although uveitis is less common in children than adults, it is believed to be more severe with an increased risk for vision-threatening complications.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms of uveitis depend on the site of involvement and whether process is acute or insidious:
  1. Acute anterior uveitis: Pain and photophobia. Vision may not be affected initially.
  2. Posterior uveitis: Floaters, hazy vision. Involvement of the retina may produce blind spots or flashing lights.
  3. Insidious anterior uveitis: Symptoms may not be present until scarring, cataracts, and loss of vision occur.
- Photophobia
- Blurred visual acuity
- Irregular pupil (with synechiae, inflamed iris attaching to the lens)
- Hazy cornea
- Abnormal cells and flare in anterior chamber or vitreous humor noted with slit lamp examination
- Retinal hemorrhage, vascular sheathing
- Conjunctival injection, particularly around the iris (ciliary flush)
- Keratitic precipitates (white precipitates on the posterior surface of the cornea)
- Hazy vitreous
- Retinal inflammation
- Iris nodules

ETIOLOGY

- Infections: Herpes simplex and zoster virus, cytomegalovirus, toxoplasmosis, tuberculosis, syphilis, HIV
- Systemic disorders (autoimmunity): Sarcoidosis, Behçet syndrome, HLA-B27–associated diseases (e.g., ankylosing spondylitis, psoriatic arthritis), inflammatory bowel disease, juvenile idiopathic arthritis (Fig. E2)
- Idiopathic (>50% of patients)
- Significant intraocular inflammation after any eye surgery should alert one to the possibility of infection (endophthalmitis); this should be immediately referred to the ophthalmologist/surgeon

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Glaucoma (particularly acute angle closure)
- Conjunctivitis
- Retinopathy or neovascular glaucoma
- Keratitis
- Scleritis
- Episcleritis
- Masquerading syndromes: Lymphoma, uveal melanoma, metastases (breast, lung, renal), leukemia, retinitis pigmentosa, retinoblastoma

WORKUP

Comprehensive eye examination including slit lamp exam, dilated ophthalmoscopy

LABORATORY TESTS

- Complete blood count
- Laboratory tests for specific inflammatory causes cited previously in "Workup" (e.g., antinuclear antibody, erythrocyte sedimentation rate, syphilis [VDRL], HLA-B27, purified protein derivative, Lyme titer, angiotensin converting enzyme [ACE])
- Urinalysis

IMAGING STUDIES

- Chest radiograph in suspected sarcoidosis, tuberculosis, histoplasmosis
- Sacroiliac radiograph in suspected ankylosing spondylitis

TREATMENT

ACUTE GENERAL Rx

- Corticosteroids are the mainstay of therapy for noninfectious causes. The route and dosage of medication depends on the location of inflammation, the severity, and the presence of systemic disease. Cycloplegic drops (cyclopentolate, homatropine bid to qid) and topical steroids (prednisone acetate 1% 1 gtt qh during day, prn at night until favorable response, then q4 to 6h); avoid topical corticosteroids in infectious uveitis. Periocular corticosteroid injections can be used for posterior disease; they have the advantage of achieving high intraocular levels of steroids without the systemic side effects of oral corticosteroids.
- Antibiotics for bacterial infections and antiviral agents, when infection is suspected, should be started to prevent retinal damage.
- Systemic steroids if appropriate for the underlying disease. Systemic corticosteroid therapy is generally reserved for patients with systemic disorders and those with bilateral disease that is refractory to local medication or those with major ocular disability or retinitis.
- Antimetabolites when indicated. Immunosuppressive medications used in steroid-dependent or refractory uveitis include methotrexate, sulfasalazine, azathioprine, cyclosporine, and tacrolimus. These medications can have significant toxicity and should be prescribed only by physicians experienced with their use. May work in cooperation with rheumatologist.
- High-dose IV daclizumab has been reported as effective in reducing active inflammation in active juvenile idiopathic arthritis (JIA)-associated anterior uveitis. Additional trials are needed to better assess efficacy and safety. Phase 3 trials with adalimumab as a glucocorticoid-sparing agent for the treatment of noninfectious uveitis revealed a lower risk of uveitic flare or visual impairment and more adverse events and serious adverse events than placebo.

REFERRAL

Urgent referral to ophthalmologist for diagnosis and treatment[1]

PEARLS & CONSIDERATIONS

COMMENTS

Chronic anterior uveitis is the most common form of intraocular inflammation in children. JIA is the most common cause.

SUGGESTED READING

Available at ExpertConsult.com

AUTHOR: **R. Scott Hoffman, MD**

[1]Jaffe GJ et al: Adalimumab in patients with active non-infectious uveitis, *N Engl J Med* 375:932-943, 2016.

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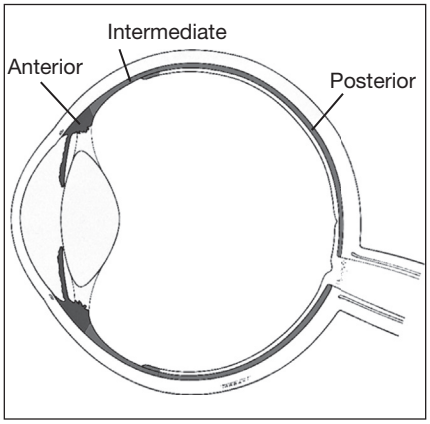

FIG. E1 Anatomic classification of uveitis. (From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

FIG. E2 Chronic anterior uveitis associated with oligoarticular and polyarticular rheumatoid factor-negative juvenile idiopathic arthritis, demonstrating posterior synechiae and absence of significant sclera inflammation. (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

Vaginal Bleeding During Pregnancy

BASIC INFORMATION

DEFINITION

Bleeding per vagina at any time during pregnancy must be regarded as abnormal and is associated with an increased likelihood of pregnancy complications.

SYNONYM

Hemorrhage

ICD-10CM CODES

O20.8	Other hemorrhage in early pregnancy
O20.9	Hemorrhage in early pregnancy, unspecified
O03.9	Complete or unspecified spontaneous abortion
O44.10	Placenta previa with hemorrhage, unspecified trimester
O45.8X9	Other premature separation of placenta, unspecified trimester

EPIDEMIOLOGY & DEMOGRAPHICS

- Common in U.S. and occurs in women of childbearing age.
- 20% to 25% of patients have vaginal spotting/bleeding in the first trimester.
- Early vaginal bleeding increases the risk of miscarriage (50%) and preterm birth. Some studies have also noted an increased risk of small-for-gestational-age fetal measurements, low birth weight, and possible intrauterine fetal demise.
- Ectopic pregnancy is the leading cause of maternal mortality in the first trimester. 1% to 2% of all pregnancies are ectopic with a recently increased risk of cesarean scar pregnancy.
- Placental abruptions are noted in 1 in 150 pregnancies with an increased recurrence rate in subsequent pregnancies (6% to 17% after one episode, up to 25% after two episodes).
- The increased cesarean rate over the past few decades has been associated with an increased diagnosis of placental implantation disorders—an important cause of vaginal bleeding in pregnancy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Bleeding: Ranges from scant to life-threatening with hemodynamic instability
- Color: Brown to bright red
- Can be painless or painful (cramps, back pain, severe abdominal pain)
- Fetal compromise: Ranges from none to fetal demise

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Any gestational age:
  1. Cervical lesions: Polyps, decidual reaction, neoplasia
  2. Vaginal trauma
  3. Cervicitis/vulvovaginitis
  4. Postcoital trauma
  5. Bleeding dyscrasias
- Gestation <20 wk:
  1. Implantation bleeding
  2. Spontaneous abortion
  3. Presence of intrauterine device
  4. Ectopic pregnancy (including cesarean scar and cervical or abdominal pregnancy)
  5. Molar pregnancy
  6. Low-lying placenta/placenta previa
  7. hCG-secreting tumors, including gestational trophoblastic neoplasia or gestational choriocarcinoma (incidence is 1 in 1500 to 20,000 pregnancies)
- Gestation >20 wk:
  1. Molar pregnancy
  2. Placental disorders (low-lying placenta, placenta previa, placenta accreta spectrum)
  3. Placental abruption
  4. Vasa previa
  5. Marginal separation of the placenta
  6. Preterm labor
  7. Bloody show at term
  8. Uterine rupture
  9. Postpartum hemorrhage related to retroplacental myomas
  10. Rare etiologies such as uterine artery aneurysm/pseudoaneurysm or uterine arteriovenous malformations (AVM). AVMs may be diagnosed following persistent vaginal bleeding after delivery or other uterine procedures

WORKUP

- Gestation <20 wk
  1. Pelvic examination with vaginal/cervical cultures if appropriate
  2. Laparoscopy (if indicated)
  3. Laparotomy (rarely required)
  4. Ultrasound to verify viable intrauterine pregnancy when β-hCG levels achieve threshold values (≥1500 mIU/ml for transvaginal sonography). If viable intrauterine pregnancy, evaluate pregnancy and uterine cavity including placenta and placental location
- Gestation >20 wk:
  1. Before pelvic examination, ultrasound for placental location, placental cord insertion, and placental evaluation
  2. If placenta previa or low-lying placenta, no bimanual examination
  3. If viable fetus, evaluation of fetal well-being as appropriate based on gestational age
  4. If suspected preterm labor, evaluate as clinically appropriate

LABORATORY TESTS

- Urine pregnancy test: If positive, get quantitative serum beta human chorionic gonadotropin (β-hCG). The following are typical although not entirely exclusive patterns:
  1. Early pregnancy: Follow serially every 48 hr
  2. Normal pregnancy: β-hCG doubles approximately every 48 hr
  3. Spontaneous abortion: β-hCG level will fall
  4. Ectopic pregnancy: β-hCG level will rise inappropriately (less than expected; threshold increase over 48 hr should be ≥66%)
  5. Molar pregnancy: β-hCG level is higher than expected for gestational age
- CBC
- Blood type and screen (Rh-negative patients need RhoGAM)
- Coagulation profile (particularly if moderate to heavy bleeding)
- Cervical/vaginal cultures, wet mount
- Pap smear for cervical malignancy; caution with biopsy as cervical biopsy sites in pregnancy can bleed extensively

IMAGING STUDIES

Ultrasound:

- 5 to 6 wk: Gestational sac (transvaginally); β-hCG >1500 mIU/ml is discriminatory level for visualization of a singleton gestation
- 6 to 7 wk: Fetal cardiac activity
- Molar pregnancy: Characteristic cluster of placental cysts
- Evaluate for evidence of subchorionic/submembranous hemorrhage or placenta accreta spectrum
- Location of placenta and placental cord insertion (particularly if >20 wk)
- Degree of placental separation: Difficult to assess

TREATMENT

NONPHARMACOLOGIC THERAPY

- Pelvic rest: No coitus, douching, or tampons
- Counseling: Genetic, bereavement (if indicated)
- For viable fetuses, ultrasound assessment of fetal growth and assessment of fetal well-being via external fetal monitoring as clinically appropriate
- Bed rest, if >20 wk (Recent studies show limited to no benefit of bed rest and possible increased medical and psychological risk to patients on activity restriction.)

ACUTE GENERAL Rx

- Hemodynamic stabilization with intravenous fluid administration and transfusion of blood products as clinically indicated
- Emergency dilation and curettage, laparoscopy, laparotomy, or cesarean delivery as necessary

REFERRAL

- If patient is unstable and needs emergency OB/GYN management and/or surgery
- If patient has suspected ectopic or molar pregnancy as immediate surgical treatment or medical intervention is indicated

- Perinatal consultation for high-risk pregnancies (placental implantation disorders, cesarean scar or abdominal pregnancy, placental abruption, vasa previa)
- Gynecologic oncology consultation if cervical carcinoma or hCG secreting tumor is suspected

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Abruptio Placentae (Related Key Topic)
Cervical Insufficiency (Related Key Topic)
Ectopic Pregnancy (Related Key Topic)
Molar Pregnancy (Related Key Topic)
Placenta Previa (Related Key Topic)
Sheehan Syndrome (Related Key Topic)
Spontaneous Abortion (Related Key Topic)

AUTHOR: **Jennifer B. Merriman, MD**

SUGGESTED READINGS

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Bever AM et al: Fetal growth patterns in pregnancies with first-trimester bleeding, *Obstet Gynecol* 131:1021-1030, 2018.

Coppola PT et al: Vaginal bleeding in the first 20 weeks of pregnancy, *Emerg Med Clin North Am* 21(3):667-677, 2003.

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BASIC INFORMATION

DEFINITION

Vaginal cancer is an abnormal proliferation of vaginal epithelium demonstrating malignant cells below the basement membrane.

SYNONYMS

Squamous cell carcinoma of the vagina
Adenocarcinoma of the vagina
Melanoma of the vagina
Sarcoma of the vagina
Endodermal sinus tumor
Vaginal malignancy

ICD-10CM CODE
C52 Malignant neoplasm of vagina

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: There were an estimated 5170 new cases in 2018 and an estimated 910 deaths.
PREVALENCE: Vaginal cancer is the second rarest gynecologic cancer. It comprises 3% of malignancies of the female genital tract. It is more prevalent in women infected with HPV.
MEAN AGE AT DIAGNOSIS: This is predominantly a disease of menopause. The mean age at diagnosis is 65.7 +/-14.3 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The signs and symptoms of invasive vaginal cancer (Fig. E1) are similar to those of cervical cancer. Majority of cases are asymptomatic.
- Postmenopausal vaginal bleeding and/or vaginal discharge are the most common symptoms.
- May also present as pelvic pain or pressure, dyspareunia, dysuria, malodor, or postcoital bleeding.
- May present as a vaginal lesion or abnormal Pap test.

ETIOLOGY

- The exact etiology is unknown.
- Approximately 80% to 90% of primary vaginal cancers are squamous cell carcinomas and 4% to 10% are adenocarcinomas.
- Most vaginal cancers are related to infection with HPV. It has been found in 65% of samples of invasive vaginal cancer and 93% of high-grade dysplastic vaginal lesions. Cervical cancers have similar risk factors. Patients with cervical cancer have an increased risk of vaginal carcinoma.
- Vaginal intraepithelial neoplasia (VaIN) is believed to be a precursor for squamous cell carcinoma of the vagina.
- HIV, smoking, and immunosuppression are risk factors. Prior pelvic radiation may be a risk factor.
- Clear-cell adenocarcinoma may be related to in utero diethylstilbestrol exposure (DES). Treatment of pregnant women with DES ended in the early 1970s, and it is anticipated that this spike in clear cell tumors will abate in the future.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Extension from another primary carcinoma is more common than primary vaginal cancer
- Vaginitis (atrophic or infectious)
- Vaginal mass: Polyp, endometriosis

WORKUP

- Diagnosis is made histologically by biopsy.
- Colposcopy and biopsy should follow suspicious Pap test.
- Cystoscopy, proctosigmoidoscopy, chest radiography, IV urography, and barium enema may be used for clinical staging.
- CT scan (Fig. E2), FDG, PET scan, and MRI are used to evaluate spread.
- Vaginal cancer staging is summarized in Table E1.

IMAGING STUDIES

- Chest radiography, IV urography, and barium enema are used for staging.
- CT scan and MRI are good for assessing tumor spread and planning radiation therapy.
- PET scan may have higher sensitivity in detecting primary spread and abnormal lymph nodes compared to CT scan.

TREATMENT

- Radiation therapy is the mainstay of treatment.
- Stage I tumors that are small and confined to the posterior, upper third of the vagina may be treated with radical surgery.
- Other stages require a whole-pelvis, interstitial, and/or intracavitary radiation therapy.
- Chemotherapy is used in conjunction with radiotherapy in select cases.
- Table E2 summarizes management of clear cell adenocarcinoma of the cervix and vagina.

DISPOSITION

5-yr survival ranges from 85% for stage I to 13% for stage IV vaginal squamous cell carcinoma.

REFERRAL

Vaginal cancer should be managed by a gynecologic oncologist and radiation oncologist.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Vaginal Cancer (Patient Information)

AUTHOR: **Christine Burke, MD**

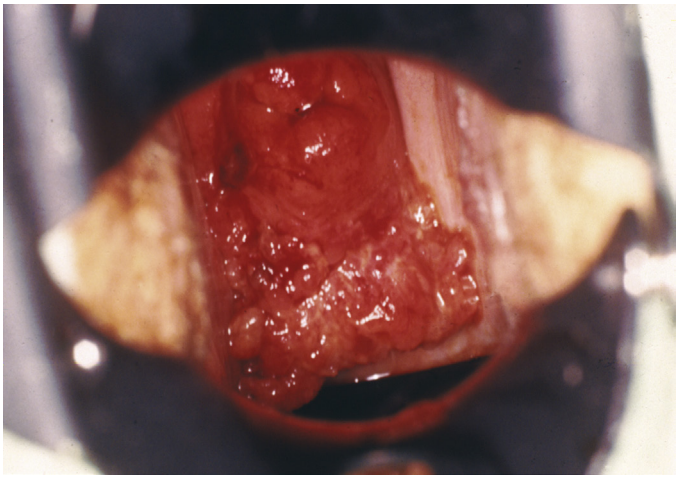

FIG. E1 Lesion of the posterior fornix in squamous cell carcinoma. (From DiSaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2018, Elsevier.)

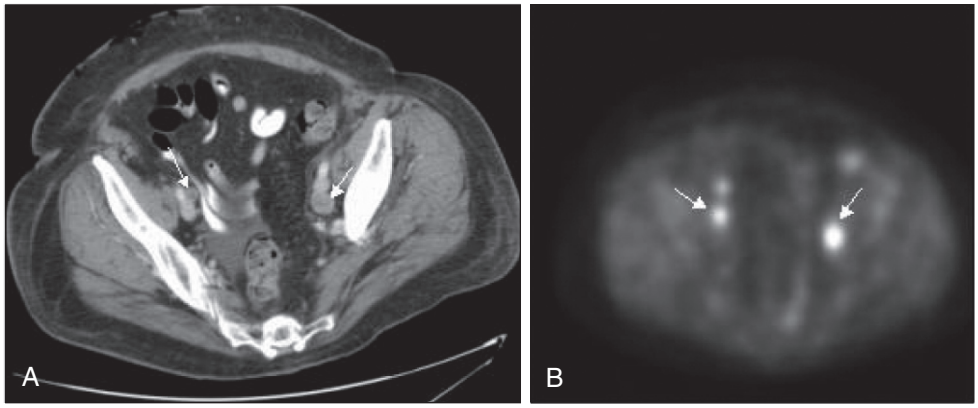

FIG. E2 Vaginal cancer with lymphadenopathy. (A) Computed tomography scan of pelvis showing mildly enlarged bilateral external iliac nodes suggestive of metastases *(arrows).* **(B)** Axial fluorodeoxyglucose–positron emission tomography scan showing hypermetabolic nodes as hyperintense spots confirming metastases *(arrows).* (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

TABLE E1 Vaginal Cancer: Staging Systems

Type	TNM	FIGO	Definition
Primary tumor	T_X		Primary tumor cannot be assessed
	T_0		No evidence of primary tumor
	T_{is}	0	Carcinoma in situ
	T_1	I	Tumor confined to the vagina
	T_2	II	Tumor invades paravaginal tissues but not to the pelvic wall
	T_3	III	Tumor extends to the pelvic wall
	T_4	IV_A	Tumor invades mucosa[a] of the bladder or rectum and/or extends beyond the true pelvis
		IV_B	Distant metastasis
Regional lymph nodes	N_X		Regional lymph nodes cannot be assessed
	N_0		No regional lymph node metastasis
Upper two-thirds of vagina	N_1		Pelvic node metastasis
Lower one-third of vagina	N_1		Unilateral inguinal node metastasis
	N_2		Bilateral inguinal node metastases
Distant metastasis	M_X		Presence of distant metastasis cannot be assessed
	M_0		No distant metastasis
	M_1		Distant metastasis

[a]Presence of bullous edema is not sufficient evidence to classify as T_4 or FIGO IV_A.
FIGO, International Federation of Gynecology and Obstetrics; *TNM,* tumor-node-metastasis.
From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

TABLE E2 Suggested Management of Clear Cell Adenocarcinoma of the Cervix and Vagina

Stage	Surgery	Radiation
Cervix		
I_b	Radical hysterectomy with clear vaginal margins and bilateral pelvic lymphadenectomy	5000 cGy of the whole pelvis in patients with positive pelvic nodes
II_a	Radical hysterectomy with bilateral pelvic lymphadenectomy and upper vaginectomy	5000 cGy of the whole pelvis in patients with positive pelvic nodes
II_b	Consider exenteration for radiation failures	5000 cGy of the whole pelvis, tandem, and ovoids
III_a and III_b	Consider exenteration for radiation failures	6000 cGy of the whole pelvis, tandem, and ovoids
IV	Individualize	
Vagina		
I (upper third of vagina)	Radical hysterectomy with bilateral pelvic lymphadenectomy and upper vaginectomy	5000 cGy of the whole pelvis in patients with positive nodes
I (lower two-thirds of vagina)	Radical hysterectomy with bilateral pelvic lymphadenectomy and total vaginectomy with vaginal reconstruction	5000 cGy of the whole pelvis, vaginal application, or interstitial implant
II	Consider exenteration for radiation failures	5000 cGy of the whole pelvis, interstitial implant
III	Consider exenteration for radiation failures	6000 cGy of the whole pelvis, interstitial implant
IV	Individualize	

From DiSaia PJ et al: *Clinical gynecologic oncology.* ed 9, Philadelphia, 2018, Elsevier.

SUGGESTED READINGS

Chiasson MA et al: Increased prevalence of vulvovaginal condyloma and vulvar intraepithelial neoplasia in women infected with human immunodeficiency virus, *Obstet Gynecol* 89(5 Pt1):690, 1997.

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BASIC INFORMATION

DEFINITION

Vaginal fistula is an abnormal passageway between the vagina and another epithelialized surface (Fig. E1).

SYNONYM

Vaginal sinus

ICD-10CM CODES

N82.0 Vesicovaginal fistula
N82.2 Fistula of vagina to small intestine
N82.3 Fistula of vagina to large intestine
N82.9 Female genital tract fistula, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: After benign hysterectomy: <1% (0.08% to 0.26%); after radical hysterectomy: 1% to 4%. Incidence is difficult to estimate in developing countries because of lack of medical care and medical follow-up after obstetric care.
PREVALENCE: Rare in the developed world from obstetric complications, but in developing countries, the best estimate of prevalence is as high as 124 in 100,000.
RISK FACTORS: In developing countries:

- Obstetric trauma
- Prolonged, protracted labor
- Cephalopelvic disproportion causing ischemia and necrosis of the tissue between the fetal head and maternal pubic bone

In developed countries:

- Hysterectomy, especially with the following:
  1. Extensive bladder dissection
  2. Iatrogenic injury of the bowel or bladder
  3. Prolonged operating times
  4. Laparoscopic approach has the greatest risk, vaginal approach the lowest
  5. Large blood loss
  6. Large volume uterus
  7. Coexisting pelvic adhesions distorting the normal pelvic anatomy
- Obstetric trauma:
  1. Rectovaginal fistulas are primarily related to severe vaginal lacerations. Risk factors for such include:
     a. Primiparity
     b. Midline episiotomies
     c. Increasing birth weights
     d. Use of vaginal forceps
  2. Bladder injury related to uterine rupture
- Invasive cancer
- Pelvic radiation, directly proportional to dosimetry:
  1. Also as a result of tumor necrosis after therapy
- Chronic inflammatory disease:
  1. Crohn disease
  2. Diverticulitis
- Pelvic infection:
  1. Tuberculosis
  2. Syphilis
  3. Lymphogranuloma venereum
- Trauma
- Previous pelvic surgery
- Diabetes mellitus
- Age >50, likely as a result of poor tissue quality from menopausal estrogen deficiency, although some studies have refuted this
- Tobacco usage
- Foreign bodies:
  1. Sub urethral slings for stress urinary incontinence have increased the incidence of urethrovaginal fistula
  2. Prolonged pressure between the fetal head and the maternal pubic bone, causing tissue necrosis
- Gynecologic:
  1. Extensive dissection about the urinary tract, including unidentified injury
  2. Poor-quality tissue with prolonged healing as a result of estrogen deficiency, infection, malignancy, or prior radiation therapy

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Flatus, stool, or urine per vagina
- Frequent urinary tract infections
- Urinary odor, hematuria
- Mucopurulent malodorous discharge per vagina
- Dyspareunia
- Perineal pain, perineal dermatitis
- Recurrent vaginal infections

ETIOLOGY (BOX E1)

- Obstetric:
  1. Incompletely repaired or unidentified vaginal lacerations

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rectal or urinary incontinence
- Pelvic inflammatory disease
- Vaginal infection
- Vaginal fistula:
  1. Vesicovaginal
  2. Urethrovaginal
  3. Ureterovaginal
  4. Rectovaginal
- Urinary tract infection

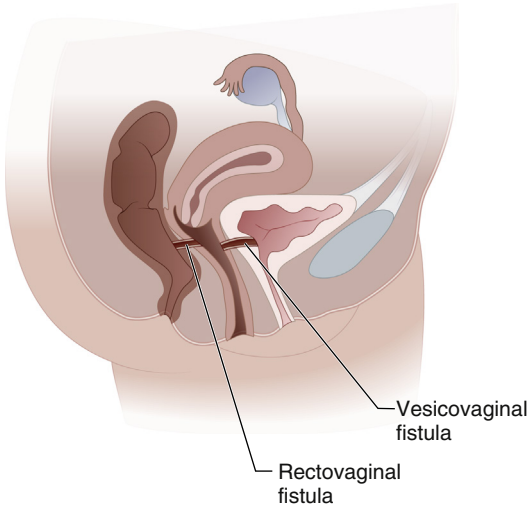

FIG. E1 The two most common types of vaginal fistulas are vesicovaginal and rectovaginal. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

BOX E1 Etiology of Vesicovaginal Fistula

Traumatic
  Postsurgical
    - Abdominal hysterectomy
    - Vaginal hysterectomy
    - Anti-incontinence surgery
    - Anterior vaginal wall prolapse surgery (e.g., colporrhaphy)
    - Vaginal biopsy
    - Bladder biopsy, endoscopic resection, laser therapy
    - Other pelvic surgery (e.g., vascular, rectal)
  External trauma (e.g., penetrating, pelvic fracture, sexual)
Radiation therapy
Advanced pelvic malignancy
Infectious or inflammatory cause
Foreign body
Obstetric
  Obstructed labor
  Forceps laceration
  Uterine rupture
  Cesarean section injury to bladder
Congenital

From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

WORKUP

- Thorough history and physical exam, specifically, questioning about Crohn disease symptomology; constitutional symptoms such as weight loss and fatigue, with malignancy in mind. An algorithm for the diagnosis of vesicovaginal fistulas is illustrated in Fig. E2
- Obtaining of past medical records specific to obstetric and surgical procedures
- Evaluation of patient's rectal and urinary continence
- Physical exam, looking for extraintestinal signs consistent with Crohn disease; lymphadenopathy; inspection of perineum and perianal area for evidence of abscess, obvious fistula, or scarring; pooling of urine; pelvic exam including lighted speculum exam for any vulvar, vaginal, or cervical anomaly, excluding pelvic inflammatory disease
- For rectovaginal fistulas: Can use gel mixed with methylene blue massaged into the rectal tissues; if visualized vaginally can aid in localizing fistulous tract
- For vesicovaginal fistulas: Bladder backfill. Administration of dyed sterile fluid (indigo carmine, methylene blue, sterile milk) into the bladder through a catheter. If the dye is seen vaginally, it is diagnostic of vesicovaginal fistula
- For ureterovaginal fistula: Double dye tampon test. Oral Pyridium with administration of blue dye into the bladder. If orange dye is present, indicates a ureterovaginal fistula. If blue dye is present, indicates vesicovaginal fistula
- Biopsy of fistula tract

LABORATORY TESTS

- Urinalysis
- Urine culture
- Complete blood count
- Wet prep
- Gonococcal and chlamydial testing

IMAGING STUDIES

- Proctoscopy for suspected rectovaginal fistula
- Vaginogram (Figs. E3 and E4)
- Cystoscopy
- CT of the abdomen and pelvis to exclude malignancy (especially in women with no history of obstetric trauma, previous fistula, inflammatory bowel disease, or known pelvic malignancy) (Fig. E3)
- Endoanal ultrasound, with or without hydrogen peroxide contrast injected into the suspected fistula tract
- Magnetic resonance imaging
- Intravenous urogram
- Retrograde ureteropyelography

Rx TREATMENT (FIG. E5)

NONPHARMACOLOGIC THERAPY

- Tension-free surgical repair, with multiple documented approaches (Table E1):
  1. Transvaginal
  2. Perineal
  3. Abdominal
  4. Laparoscopic
  5. Robot assisted
  6. Transrectal
  7. Transanal endoscopy
- If vesicovaginal fistula is small (<1 cm) and identified early:
  1. Prolonged urinary catheter placement, greater than 3 weeks

ACUTE GENERAL Rx

- Treatment of urinary or vaginal infection
- Estrogen replacement therapy, local vs. systemic if no contraindications
- Surgical repair of fistula with subsequent pelvic rest for 4 to 6 wk
- Minimizing Valsalva maneuvers
- Fig. E6 illustrates a treatment algorithm for primary and recurrent rectovaginal fistulas

CHRONIC Rx

If initial surgical management fails, repeat operations tailored to the cause of the fistula would be indicated, such as advancement flaps, sphincteroplasty, coloanal anastomosis (for rectovaginal fistula), gracilis flap. A 10-yr retrospective cohort study from the English National Health Service inpatient database showed that 11.9% of patients required repeat operations.

DISPOSITION

Cure rates after surgical repair vary in the literature, especially with the type of fistula repaired. With early intervention, estimated cure rates are between 84% and 100% in developed countries.

REFERRAL

If there is concern for vaginal fistula, the patient should be managed by a surgeon familiar with fistula surgery for repair and follow-up. Consider consulting with a urologist, colorectal surgeon, gynecologic oncologist, or urogynecologist.

PEARLS & CONSIDERATIONS

PREVENTION

- Prompt repair of obstetric lacerations.
- Screen patients most at risk before surgery.
- Avoid urologic complications in surgery (e.g., injury to bladder or ureters).
- Perform cystoscopy with complicated hysterectomy dissections to identify defects immediately.

AUTHORS: **Adrienne Werth, MD,** and **Anthony Sciscione, DO**

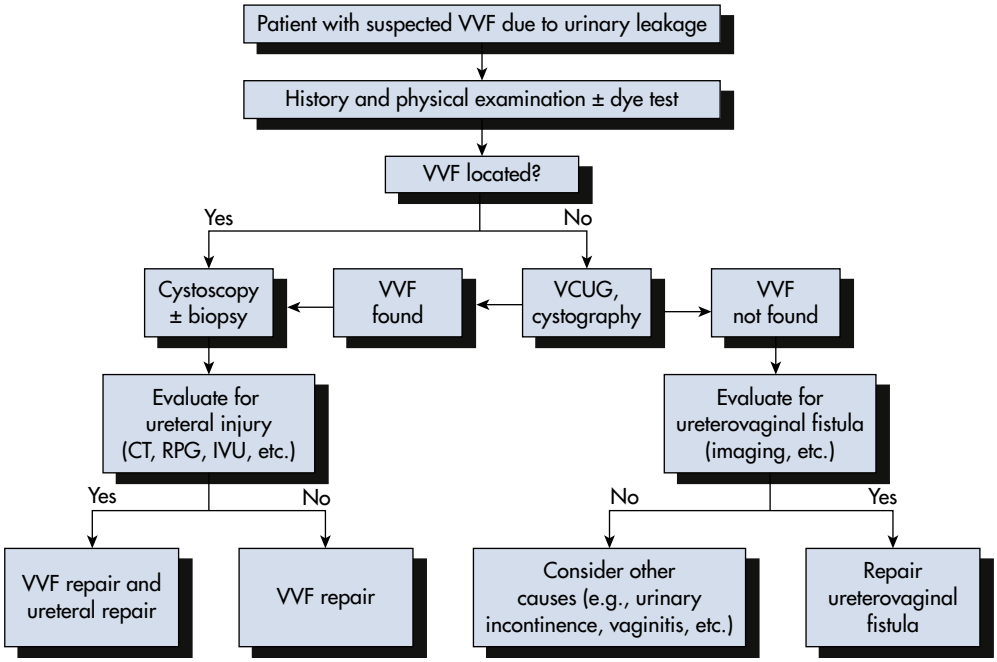

FIG. E2 Algorithm for the diagnosis of vesicovaginal fistula *(VVF).* *CT,* Computed tomography; *IVU,* intravenous urography; *RPG,* retrograde pyelography; *VCUG,* voiding cystourethrogram. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

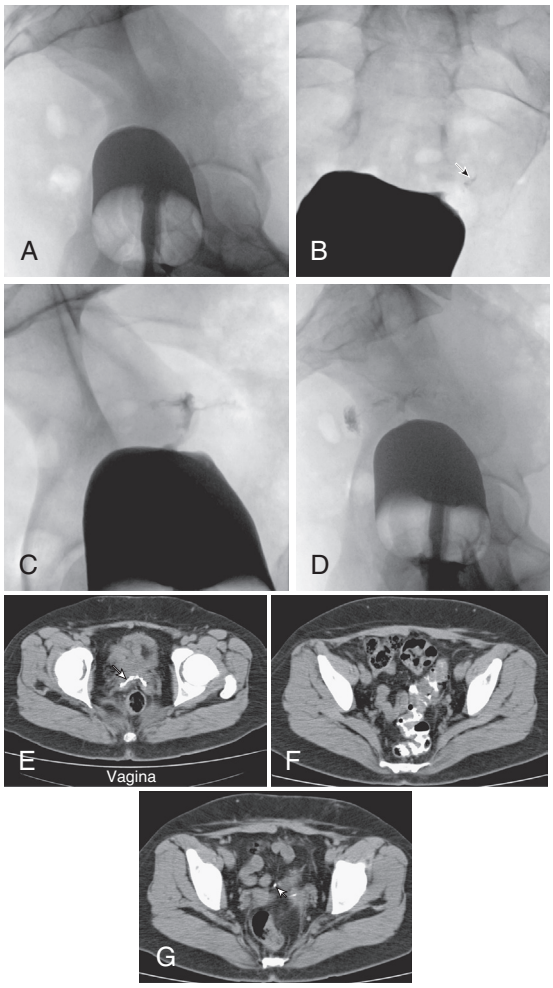

FIG. E3 A 44-year-old woman with gas and stool per vaginam 1 year after hysterectomy. Vaginal fistula was treated medically. **A,** Vaginogram, patient in left lateral position. **B,** Vaginogram, patient supine. The left apical vaginal fistula has just started to fill with contrast agent *(arrow).* **C,** Contrast agent is extending horizontally, likely in a loop of bowel. **D,** Vaginogram, patient in left lateral position, demonstrates small fistula to a loop of bowel, likely the rectosigmoid colon based on its relationship to the sacrum. **E,** Unenhanced computed tomographic (CT) scan of the pelvis immediately after the vaginogram demonstrates residual contrast agent in the vagina *(arrow).* **F,** CT scan confirms contrast agent from the vagina in the rectosigmoid colon. **G,** CT scan demonstrates 3 mm diameter short fistula to the rectosigmoid *(arrow).* (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

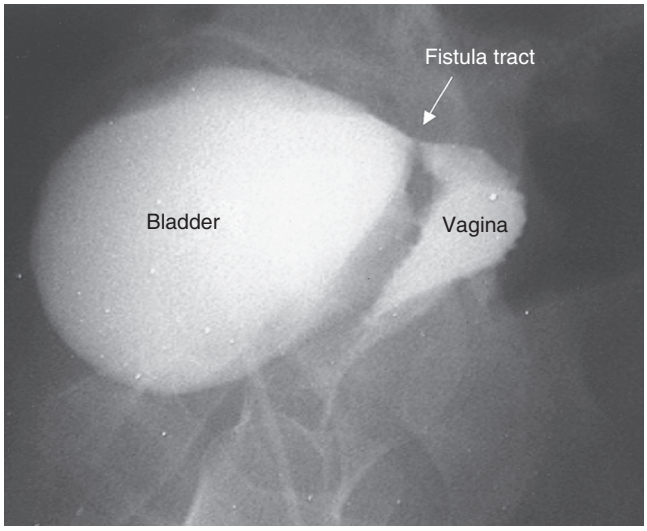

FIG. E4 Lateral image during cystography demonstrates the vesicovaginal fistula tract. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

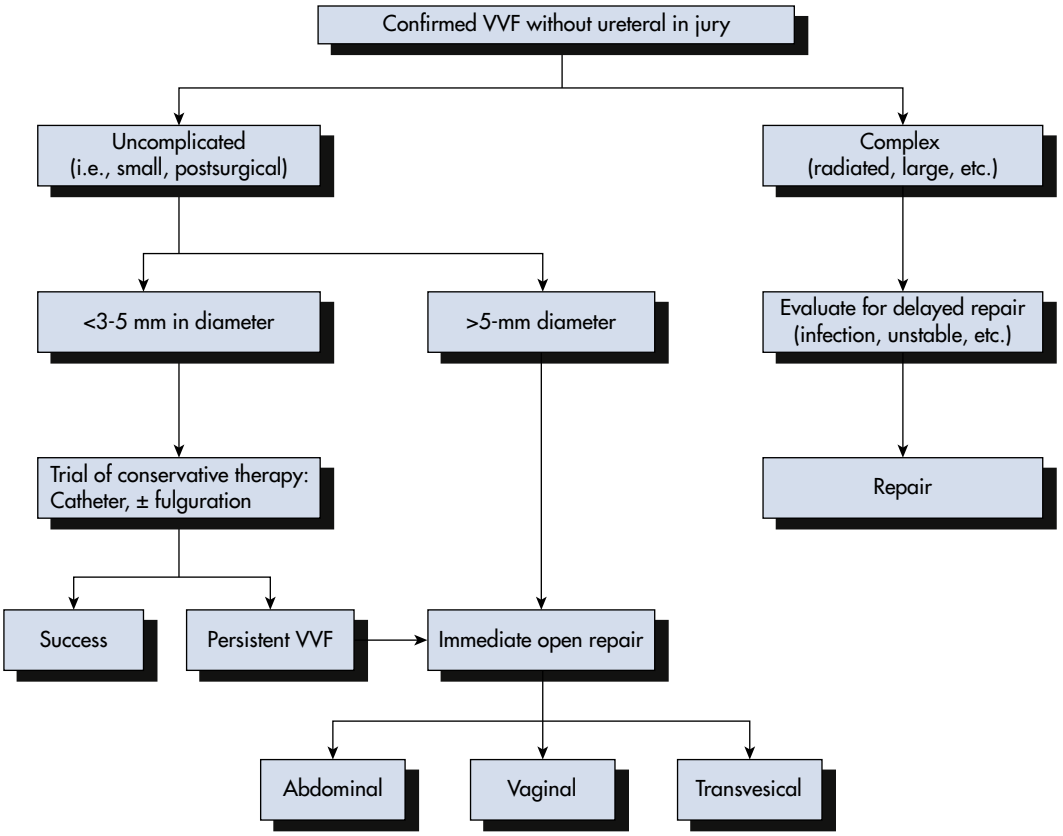

FIG. E5 Algorithm for management of vesicovaginal fistula *(VVF).* (From Wein AJ et al*: Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

TABLE E1 Abdominal versus Transvaginal Repair of Vesicovaginal Fistula

	Abdominal	Transvaginal
Incision	**Abdominal incision**	Vaginal incision(s) can be done immediately in the absence of infection or other complications.
Timing of repair (elapsed time from fistula creation)	Often delayed 3-6 months.	
Exposure	Fistula located low on the trigone or near the bladder neck may be difficult to expose transabdominally.	Fistula located high at the vaginal cuff may be difficult to expose transvaginally.
Location of ureters relative to fistula tract	Fistula located near ureteric orifice may necessitate reimplantation.	Reimplantation may not be necessary even if fistula tract is located near ureteric orifice.
Sexual function	No change in vaginal depth.	Risk of vaginal shortening (e.g., Latzko technique).
Use of adjunctive flaps	Omentum, peritoneal flap, rectus abdominis flap.	Labial fat pad (Martius fat pad), peritoneal flap, gluteal skin, or gracilis myocutaneous flap.
Relative indications	Large fistulae, location high in a deep narrow vagina, radiation fistulae, failed transvaginal approach, small-capacity bladder requiring augmentation, need for ureteral reimplantation, inability to place patient in the lithotomy position.	Uncomplicated fistulae, low fistulae.

From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

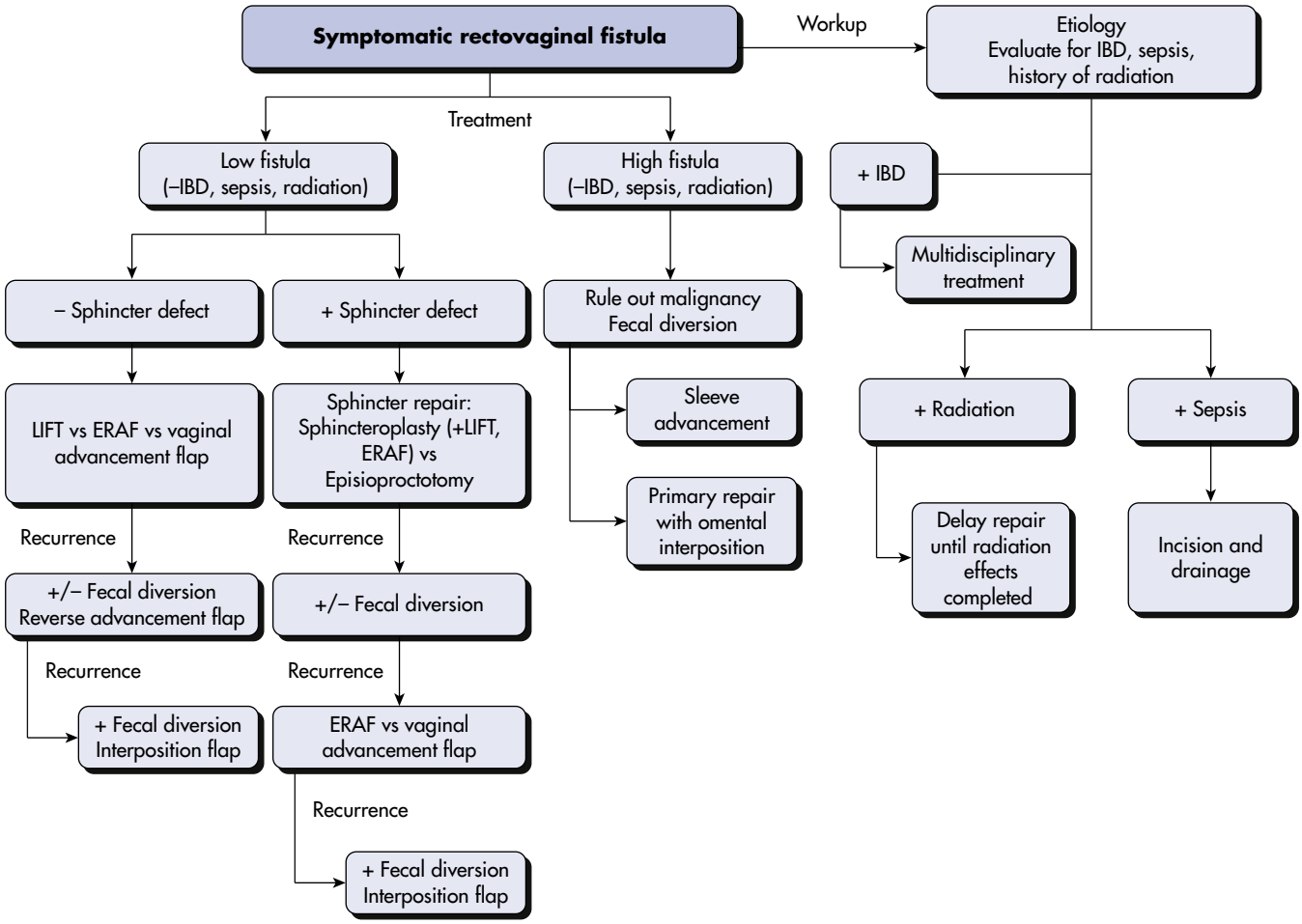

FIG. E6 Proposed treatment algorithm for primary and recurrent rectovaginal fistula. *ERAF,* Endorectal advancement flap; *IBD,* inflammatory bowel disease; *LIFT,* ligation of the intersphincteric fistula tract. (Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

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DeRidder D: An update on surgery for vesicovaginal and urethrovaginal fistulae, *Curr Opin Urol* 21:297-300, 2011.

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Jones HW, Rock JA, editors: *Te Linde's operative gynecology*, ed 11, Philadelphia, 2015, Wolters Kluwer.

Rogers RG et al: Current diagnosis and management of pelvic fistulae in women, *Obstet Gynecol* 128:635-650, 2016.

Vaginitis, Estrogen-Deficient

BASIC INFORMATION

DEFINITION

Estrogen-deficient vulvovaginitis is the irritation and/or inflammation of the vulva and vagina because of progressive thinning and atrophic changes secondary to estrogen deficiency.

SYNONYMS

Atrophic vaginitis
Vulvovaginal atrophy
Genitourinary syndrome of menopause

ICD-10CM CODE
N95.2 Postmenopausal atrophic vaginitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Postmenopausal women (average age 51 yr)
- Surgical menopause, ovarian failure or suppression, antiestrogenic medications, postpartum state
- Up to half of postmenopausal women are symptomatic, but a quarter of these will not seek treatment

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Thinning of pubic hair and epithelium, loss of vulvar architecture
- Decreased secretions from the vestibular glands with vaginal dryness
- Loss of elasticity and rugae
- Vulvar and vaginal itching
- Dyspareunia
- Dysuria and urinary frequency
- Vaginal spotting

ETIOLOGY

- Estrogen deficiency. Estrogen is essential to maintaining the urogenital environment. Postmenopausal thinning of the vaginal epithelium and increase in subepithelial connective tissue result in loss of rugal folds and elasticity. Reduced blood flow also contributes to a decline in vaginal secretions.
- Smoking and use of antiestrogen medications (e.g., aromatase inhibitors) increase the risk of vulvovaginal atrophy.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infectious vulvovaginitis
- Squamous cell hyperplasia
- Lichen sclerosus
- Vulvar, vaginal, cervical, and endometrial malignancy
- Irritant contact dermatitis
- Vulvodynia

WORKUP

- Pelvic examination
- Speculum examination
- Pap smear <65 yr of age
- Wet prep
- Possible ultrasound and/or endometrial biopsy if bleeding
- Possible vulvar or vaginal biopsy in the event of suspicious lesion

LABORATORY TESTS

Vaginal pH, culture or polymerase chain reaction for vaginal infections, urinalysis and culture if indicated, follicle-stimulating hormone and estradiol testing if in doubt of menopausal state

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of contact irritants such as scented soaps and feminine hygiene products
- Avoidance of synthetic undergarments, tight-fitting clothing
- Regular use of vaginal moisturizers (e.g., Replens) can decrease vaginal itching and irritation
- Use of water- or silicone-based personal lubricants (e.g., Astroglide) during intercourse is useful to reduce dyspareunia

GENERAL Rx

- Vaginal estrogen: Comes in cream, tablet inserts, and impregnated silastic ring. Tablets or cream can be used daily for the first 2 weeks, then 1 to 2× per week for maintenance therapy. Progesterone for endometrial protection is not required for vaginal estrogen.
- Systemic hormone replacement therapy (HRT): Utilize lowest effective dose. Estrogen use should be reviewed every 3 to 6 mo, with an attempt to taper or discontinue its use. Comes as a patch or pill. If uterus present, opposing progesterone therapy for protection of endometrial lining, either continuous low-dose pills, cyclic pills, or progesterone intrauterine device.
- Ospemifene: Selective estrogen receptor modulator, some systemic side effects (hot flashes, possible risk of venous thromboembolism).
- Other: Prasterone vaginal dehydroepiandrosterone is approved though less widely studied; vaginal laser therapy is being studied but is not approved for treatment.

DISPOSITION

The symptoms should be improved with the therapy. Caution for vaginal bleeding if uterus present.

REFERRAL

To obstetrician/gynecologist if vaginal bleeding, vaginal narrowing, or other visible changes in appearance or tissue architecture.

RELATED CONTENT

Pruritus Vulvae (Related Key Topic)

AUTHORS: **Christina M. Johnson, MD,** and **Nima R. Patel, MD, MS**

SUGGESTED READINGS

American College of Obstetricians and Gynecologists: Management of menopausal symptoms. Practice Bulletin No. 141, *Obstet Gynecol* 123:202-216, 2014.

Hainer BL, Gibson MV: Vaginitis: diagnosis and treatment, *Am Fam Physician* 83(7):807-815, 2011.

Hohenhaus MH: Vulvovaginal atrophy: a common and commonly overlooked problem, *Med Health R I* 94:138-140, 2011.

BASIC INFORMATION

DEFINITION

Inflammation of the vagina or vulva caused by a fungal infection.

SYNONYMS

Candidiasis, vulvovaginal
Monilial vulvovaginitis
Vulvovaginal candidiasis
VVC
Vulvovaginitis

ICD-10CM CODE
B37.3 Candidiasis of vulva and vagina

EPIDEMIOLOGY

- Fungal vaginitis is the second most common type of vaginitis.
- Ten percent of women have asymptomatic colonization of *Candida.*
- The lifetime incidence of fungal vaginitis is 75%.
- About 5% of episodes are recurring.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Intense vulvar and vaginal pruritus or burning
- Linear ulcers may be present on perineal skin (Fig. E1)
- External dysuria
- Dyspareunia edema and erythema, excoriations of skin of the labia majora due to scratching (Fig. E2)
- Thick, white discharge ("cottage cheese" discharge) (Fig. E3)
- Severe infections may present with cracks in the vaginal wall
- May be asymptomatic

ETIOLOGY

- There are at least 15 distinct species of *Candida.*
- *Candida albicans* is responsible for 80% to 92% of vaginal fungal infections.
- *Candida glabrata* is the most common of non-albican isolates that cause infection.
- In recurrent fungal vaginitis, *Candida glabrata, Candida parapsilosis, Candida tropicalis,* and *Candida Krusei* are the most common non-*albicans Candida* species that can induce vaginitis.

PREDISPOSING RISK FACTORS

- Diabetes mellitus with poor glycemic control
- Antibiotic use
- Immunosuppression
- Increased estrogen levels (oral contraceptive use, pregnancy, estrogen therapy)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bacterial vaginosis
- *Trichomonas* vaginitis
- Atrophic vaginitis
- Herpes simplex infection
- Cervicitis
- Vulvar intraepithelial neoplasia
- Lichen planus, lichen sclerosus
- Foreign body
- Hypersensitivity, allergic, or chemical reactions

WORKUP

- History and physical examination
- Pelvic and speculum examination: Pseudohyphae or blastospores seen with 10% KOH preparation on microscopy (positive in 50% to 70% of individuals with yeast infection) (Fig. E4)
- Vaginal pH <4.5
- Perform vaginal cultures if the infection is recurrent

FIG. E1 Vulvovaginal candidiasis. There is a linear ulcer of the perineal skin. (From Bennett et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.)

FIG. E2 Vulvovaginal candidiasis There are excoriations of the skin of the labia majora due to scratching. (From Bennett et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.)

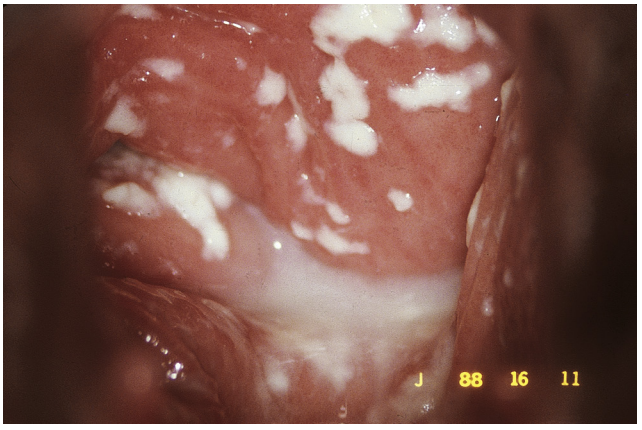

FIG. E3 Vulvovaginal candidiasis. There are adherent white patches with surrounding erythema on the cervical mucosa. (From Bennett et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.)

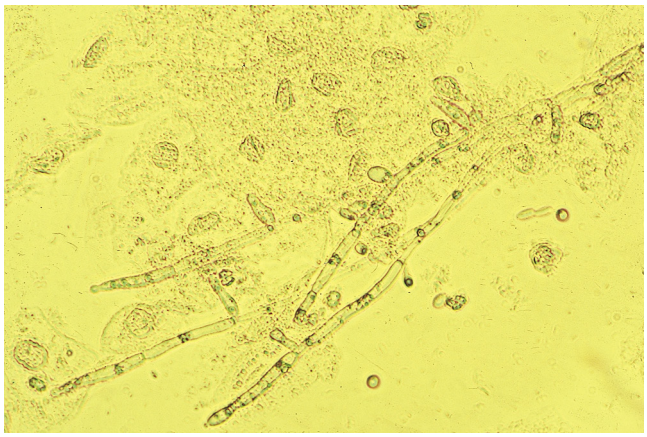

FIG. E4 Vulvovaginal candidiasis. Suspension of vaginal secretions in 0.9% NaCl. Mycelia can be seen. (From Bennett et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.)

- Classification of vulvovaginal candidiasis:
  1. Uncomplicated: Infrequent episodes (three or fewer/yr), mild to moderate symptoms, caused by *C. albicans*, nonpregnant patient and without medical complications.
  2. Complicated: Recurrent episodes (four or more/yr), severe symptoms, non-*albicans Candida*, poorly controlled diabetes, immunosuppression, severe medical illness, other vulvovaginal conditions and/or pregnancy.

Rx TREATMENT

PREVENTION

- Wear cotton underwear.
- Only take antibiotics when prescribed.

ACUTE GENERAL Rx

- Cure rate of the various azole derivatives is 85% to 90%; there is little evidence of superiority of one azole agent over another with similar efficacy when administered by either oral or vaginal route.
- For the treatment of acute, uncomplicated *Candida vulvovaginitis*, a single dose of fluconazole 150 mg PO is recommended.
- For severe infections, treatment with fluconazole 150 mg PO every 72 hr for two to three doses is recommended.
- Oral azoles may cause gastrointestinal side effects such as nausea, abdominal pain, headache, and liver function test elevations.
- The most common side effect of topical azoles is a local burning sensation or irritation.
- Alternatives:
  - Miconazole 200-mg suppository, one suppository ×3 days, 100 mg suppository ×7 days, 1200 mg suppository ×1 day, or 2% vaginal cream, one applicator (5 g) intravaginally ×7 days, or 4% vaginal cream, one applicator (5 g) intravaginally ×3 days.
  - Clotrimazole 1% vaginal cream (5 g) intravaginally qhs ×7 or 2% vaginal cream intravaginally (5 g) ×3 days.
  - Tioconazole 6.5% ointment (Monistat), one applicator intravaginally ×1.
- In pregnant patients, treat with topical clotrimazole or miconazole therapy for 7 days.

CHRONIC Rx (FOUR OR MORE SYMPTOMATIC EPISODES ANNUALLY)

- Resistance or recurrence:
  1. If recurrence is due to *C. albicans*: Induction therapy with oral fluconazole every 72 hours for a total of three doses or treat with 7 to 14 days of topical therapy or, then continue with fluconazole 150 mg PO weekly for 6 mo.
     a. If fluconazole not feasible, treat with topical azole or alternate oral azole 10 to 14 days then maintenance therapy for 6 mo.
  2. If recurrence is due to *C. glabrata* or *C. krusei*, there is a reduced susceptibility to fluconazole.
     a. *C. glabrata:*
        - Boric acid 600-mg capsule intravaginally daily ×14 days
        - Nystatin 100,000 units vaginal tablet daily ×14 days
        - For failure, 17% topical flucytosine cream, 5 g nightly ×14 days
     b. *C. krusei:*
        - Topical nonfluconazole (clotrimazole, miconazole, terconazole) regimen for 7 to 14 days

PEARLS & CONSIDERATIONS

COMMENTS

- Treatment indicated for symptom relief.
- No evidence that treating a woman's male sexual partner significantly improves woman's infection or reduces her rate of relapse.
- Various oral and topical preparations available, and patient preference, cost, and contraindications should be considered when prescribing.
- Vaginal creams and suppository regimens may weaken latex condoms and diaphragms.

RELATED CONTENT

Candidiasis (Patient Information)
Vaginal Yeast Infection (Patient Information)
Candidiasis, Cutaneous (Related Key Topic)
Pruritus Vulvae (Related Key Topic)
Vaginitis, Prepubescent (Related Key Topic)

AUTHORS: **Neha Rana, MD,** and **Emily Saks, MD, MSSCE**

SUGGESTED READINGS

Akimoto-Gunther L et al: Highlights regarding host predisposing factors to recurrent vulvovaginal candidiasis: chronic stress and reduced antioxidant capacity, *PloS One* 11(7):e0158870, 2016.

Goncalves B et al: Vulvovaginal candidiasis: epidemiology, microbiology and risk factors, *Crit Rev Microbiol* 42:905-927, 2016.

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Workowski KA, Bolan GA, Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, *MMWR Recomm Rep* 64(RR-03):1-1372015.

Yeoman CJ et al: Comparative genomics of Gardnerella vaginalis strains reveals substantial differences in metabolic and virulence potential, *PloS One* 65(8):e12411, 2010.

BASIC INFORMATION

DEFINITION

Prepubescent vulvovaginitis is an inflammatory condition of the vulva and vagina.

SYNONYM

Vulvovaginitis

ICD-10CM CODES
N76.0 Acute vaginitis
N76.1 Subacute and chronic vaginitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common gynecologic problem of premenarchal girls.
- Prepubertal girls are susceptible to irritation and trauma because of the absence of protective hair and labial fat pads, as well as a lack of estrogenization leading to atrophic vaginal mucosa.
- Symptoms of vulvovaginitis and introital irritation and discharge account for 80% to 90% of gynecologic visits.
- Nonspecific etiology in approximately 75% of children with vulvovaginitis.
- Majority of vulvovaginitis in girls involves a primary irritation of the vulva with secondary involvement of the lower third of the vagina.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Vulvar pain, dysuria, pruritus.
- Discharge is not a primary symptom but can occur.
- If present, vaginal discharge may be foul smelling or bloody.

ETIOLOGY

- Most commonly attributed to poor hygiene or nonspecific irritants. Etiologic factors in premenarcheal vulvovaginitis are summarized in Box 1.
- Hypoestrogenic state increases risk of infection or irritation due to:
  1. Higher vaginal pH (more hospitable to infectious agents)
  2. Underdeveloped labia minora and lack of significant adipose and hair of labia majora (less intrinsic protection of the vagina from trauma, irritants, infectious agents)
- Infections:
  1. Bacterial: Often respiratory or enteric organisms
  2. Protozoal/parasitic
  3. Mycotic
  4. Viral
- Endocrine disorders
- Labial adhesions
- Skin disorders
- Sexual abuse
- Allergic substance
- Trauma
- Foreign body
- Masturbation
- Constipation

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Physiologic leukorrhea
- Foreign body
- Bacterial vaginosis
- Fungal vulvovaginitis
- Precocious puberty
- Sexual abuse and possibly an associated sexually transmitted infection such as gonorrhea, *Chlamydia*, or *Trichomonas*
- Pinworms

WORKUP

- History regarding symptoms, hygiene practices, exposures to known irritants
- Examination, including Tanner staging, pelvic/genital examination; possibly speculum examination
  - May need rectal examination.
  - Knee-chest position for examination may be easier for the child to tolerate. May need to consider exam under anesthesia for more thorough evaluation if necessary.
- KOH and normal saline preparation of discharge
- Vaginoscopy if considering a foreign body

LABORATORY TESTS

- Urinalysis to rule out urinary tract infection and diabetes
- Cultures including sexually transmitted diseases

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid tight clothing
- Appropriate hygiene education
- Avoid chemical irritants
- If foreign body, removal via irrigation or exam under anesthesia
- If vulva is irritated, can use a topical over-the-counter emollient
- Reassurance

ACUTE GENERAL Rx

- *Streptococcal* and *staphylococcal* spp, *Haemophilus influenzae*: For children <20 kg, ampicillin 25 mg/kg q6h or amoxicillin 20 mg/kg q12h for 5 to 10 days; for children >20 kg, ampicillin 500 mg q6h or amoxicillin 20 mg/kg q12h for 5 to 10 days
- *Escherichia coli*: Azithromycin PO, 10 mg/kg on day 1 and then 5 mg/kg for 4 days.
- *Proteus vulgaris*: TMP-SMX 5 mg/kg q12h for 5 to 10 days
- *Chlamydia trachomatis*: For children <45 kg, treat with erythromycin base or ethylsuccinate 50 mg/kg/day PO qid ×14 days. For children ≥45 kg but younger than 8 yr, treat with azithromycin 1g PO single dose. If older than 8 yr, also can consider doxycycline 100 mg PO bid for 7 days
- *Neisseria gonorrhoeae*: For children ≤45 kg, treat with ceftriaxone 25 to 50 mg/kg IV or IM in a single dose, not to exceed 125 mg IM. Children >45 kg should be treated with ceftriaxone 250 mg IM plus azithromycin 1 g PO once
- *Trichomonas*: Metronidazole 15 mg/kg/day (divided into two doses per day) ×7 days or a single dose of 40 mg/kg.
- Pinworms: Mebendazole 100-mg chewable tablet, repeat in 2 to 3 wk
- Labial agglutination: Spontaneous resolution or topical estrogen cream for 7 to 10 days. High degree of efficacy with topical estrogen

CHRONIC Rx

See "Referral."

DISPOSITION

Further education:
- Discuss appropriate hygiene.
- If sexually active, discuss pregnancy prevention and safe sexual practices. Have a high suspicion of sexual abuse and report to child protective services with any concerns for abuse.

REFERRAL

- To obstetrician/gynecologist, preferably a physician with specialized training in pediatric and adolescent gynecology if available
- To pediatrician

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Chlamydia Genital Infections (Related Key Topic)
Pruritus Vulvae (Related Key Topic)
Vaginitis, Fungal (Related Key Topic)
Vaginitis, *Trichomonas* (Related Key Topic)
Vaginosis, Bacterial (Related Key Topic)

AUTHOR: **Margaret R. Hines, MD**

BOX 1 Etiologic Factors in Premenarcheal Vulvovaginitis

Bacterial Infections
Nonspecific mixed infections secondary to:
Poor perineal hygiene
Foreign body in vagina
Respiratory tract infections
Skin infections (impetigo)
Urinary tract infection
Specific nonvenereal infection:
Hemolytic streptococci (groups A, B, F)
Escherichia coli
Shigella flexneri, Shigella sonnei
Neisseria meningitidis, Neisseria sicca
Haemophilus influenzae type b, nontypeable strains
Streptococcus pneumoniae
Corynebacterium diphtheriae
Yersinia enterocolitica
Mycobacterium tuberculosis
Moraxella (Branhamella) catarrhalis
Staphylococcus aureus
Specific venereal infections:
Neisseria gonorrhoeae
Treponema pallidum
Chlamydia trachomatis
Chancroid *(Haemophilus ducreyi)*
Granuloma inguinale
Bacterial vaginosis:
Gardnerella vaginalis
Mobiluncus species
Fungal infections
Candida albicans
Other yeasts
Dermatophytes
Protozoan and parasitic infections
Trichomoniasis
Amebiasis
Enterobius vermicularis
Hirudiniasis
Schistosomiasis
Other parasitic infections (ascariasis, trichuriasis)
Viral infections
Venereal:
Herpes simplex
Condyloma acuminatum (papillomavirus)
Molluscum contagiosum
Involvement as part of systemic infection:
Measles
Varicella
Mononucleosis (Epstein-Barr virus)
Coxsackievirus
Smallpox
Infestations
Pediculosis
Scabies
Contact irritation or allergic reactions
Bubble bath preparations
Hair shampoos
Vulvar deodorant sprays
Soaps, laundry detergents
Other medications
Vulvar or perineal skin diseases
Local:
Seborrhea
Lichen sclerosus et atrophicus
Lichen planus
Lichen simplex chronicus
Premalignant leukoplakia
Erythrasma (*Corynebacterium minutissimum*)
Bartholinitis
Skenitis
Involvement as part of a systemic disorder:
Psoriasis
Bullous pemphigoid
Atopic dermatitis
Drug eruption
Generalized pruritus with excoriation
Chronic liver disease
Chronic renal disease
Metabolic errors
Psychosomatic
Crohn disease
Sjögren syndrome
Henoch-Schönlein purpura
Histiocytosis
Kawasaki disease
Stevens-Johnson syndrome
Typhoid
Zinc deficiency
Physical factors
Sand (sandbox)
Chemical or thermal trauma
Physical trauma (accidents, abuse, masturbation)
Nylon, rayon underclothing
Tight garments (maceration in warm climates)
Anatomic abnormalities:
Neoplasms (sarcoma botryoides)
Polyps
Labial agglutination, adhesion
Prolapsed urethra
Ectopic ureter
Rectal fistula
Draining pelvic abscess via fistula

From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

SUGGESTED READINGS

Centers for Disease Control and Prevention: 2015 sexually transmitted diseases treatment guidelines: Chlamydial infections, Division of STD prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB prevention, Centers for Disease Control and prevention. Available at: www.cdc.gov/std/tg2015/chlamydia.htm.

Centers for Disease Control and Prevention: 2015 sexually transmitted diseases treatment guidelines: Gonococcal Infections, Division of STD prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB prevention, Centers for Disease Control and Prevention. Available at: www.cdc.gov/std/tg2015/gonorrhea.htm.

Lewin LC: Sexually transmitted infections in preadolescent children, *J Pediatr Health Care* 21:153-161, 2007.

Randelović G et al: Microbiological aspects of vulvovaginitis in prepubertal girls, *Eur J Pediatr* 171:1203-1208, 2012.

Rome ES: Vulvovaginitis and other common vulvar disorders in children, *Endocr Dev* 22:72-83, 2012.

Van Neer PA, Korver CR: Constipation presenting as recurrent vulvovaginitis in prepubertal children, *J Am Acad Dermatol* 43(4):718, 2000.

Zuckerman A, Romano M: Clinical recommendation: vulvovaginitis, *J Pediatr Adolesc Gynecol* 29:673-679, 2016.

BASIC INFORMATION

DEFINITION

Trichomonas vulvovaginitis is the inflammation of vulva and vagina caused by *Trichomonas vaginalis*.

SYNONYMS

Trichomonas vaginalis
Trichomoniasis
TV

ICD-10CM CODE
A59.01 Trichomonal vulvovaginitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Acquired through sexual contact
- Diagnosed in:
  1. 50% to 75% of sex workers
  2. 5% to 15% of women visiting gynecology clinics
  3. 7% to 32% of women in sexually transmitted disease (STD) clinics
  4. 5% of women in family planning clinics
  5. 8% to 13% of black women, 0.8% to 1.8% of non-Hispanic white women
  6. More than 11% of women ≥40 yr old
- Most prevalent nonviral sexually transmitted infection in the U.S.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

These symptoms and physical findings may or may not be present depending on the case:

- Yellow-green, malodorous vaginal discharge
- Vaginal and/or vulvar pruritus
- Dysuria
- Dyspareunia
- Intense erythema of the vaginal mucosa
- Cervical petechiae ("strawberry cervix")
- Infected men may have symptoms of urethritis, epididymitis, or prostatitis
- Asymptomatic in ~50% of women and 90% of men

ETIOLOGY

Single-cell protozoan *Trichomonas vaginalis*

RISK FACTORS

- Multiple sexual partners
- History of previous STDs
- HIV infection

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS (TABLE E1)

- Bacterial vaginosis
- Fungal vulvovaginitis
- Atrophic vulvovaginitis
- Vaginal or cervical infection with other sexually transmitted infections such as gonorrhea or chlamydia

WORKUP

- Pelvic examination
- Speculum examination
- Evaluation for mobile trichomonads seen on normal saline preparation (Fig. E1): 30% to 70% sensitivity; sensitivity decreases if there is a delay in evaluating slides
- Assessment of vaginal pH: Trichomonas is associated with elevated pH (>5) of vaginal discharge
- Laboratory testing (see below)

LABORATORY TESTS

- Nucleic acid amplification tests (NAATs) have been developed that combine excellent performance characteristics (sensitivity and specificity >95%) with a more rapid turnaround time compared with culture. Thus, they are now considered better laboratory tests than culture. There are two commercially available NAATs in the U.S.:
  1. APTIMA assays (Hologic Gen-Probe, San Diego, CA)
  2. BD Probe Tec TV Q^X Amplified DNA Assay (Becton Dickinson, Franklin Lakes, NJ)
- Rapid tests are also available:
  1. The OSOM Trichomonas Rapid test (Sekisui Diagnostics, Framingham, MA) is an antigen detection test on vaginal secretions. It provides results in 10 min and can be done as a point-of-care test. It has a sensitivity of 82% to 95% and a specificity of 97% to 100%.
  2. The Affirm VP III (Becton Dickinson, Sparks, MD) is a DNA hybridization probe test; results are available within 45 min. Sensitivity is 63% and specificity >99%.
- Culture, when available, is considered the traditional gold standard laboratory test for diagnosis of trichomonas, with sensitivity 75% to 96% and specificity approaching 100%.

TREATMENT

NONPHARMACOLOGIC THERAPY

Condom use: The best way to prevent trichomoniasis is through consistent and correct use of condoms during all penile-vaginal sexual encounters

ACUTE GENERAL Rx

- Preferred initial treatment: Metronidazole 2 g PO × 1 *or* tinidazole single 2-g oral dose in both sexes. Treatment of the sexual partner is essential to prevent reinfection.
- Alternative regimen: Metronidazole 500 mg PO bid × 7 days.
- Alcohol consumption should be avoided during treatment with metronidazole (at least 24 hr after completion of therapy) and tinidazole (at least 72 hr after completion of therapy) to reduce possibility of disulfiram-like reaction.
- CDC recommends retesting sexually active women within 3 mo of treatment to assess for possible reinfection.

CHRONIC Rx

- For persistent infections, the CDC recommends first trying metronidazole 500 mg PO bid × 7 days.
- If treatment is still unsuccessful, proceed with metronidazole or tinidazole 2 g PO daily × 7 days.
- Allergy, intolerance, or adverse reactions: Alternatives to metronidazole or tinidazole are not recommended. Patients who are allergic to nitroimidazoles can be managed by desensitization.
- Pregnancy:
  1. Associated with adverse outcomes (i.e., premature rupture of membranes, preterm delivery), although it is unclear whether treatment decreases the incidence of these outcomes.
  2. Treat with metronidazole 2 g PO × 1 day; avoid tinidazole as there is little known about tinidazole in pregnancy.

DISPOSITION

- *Trichomonas* infection is considered an STD; therefore, treatment of the sexual partner is necessary.
- *T. vaginalis* infection is associated with two- to threefold increased risk for HIV acquisition.
- *T. vaginalis* infection in pregnancy is associated with premature rupture of membranes, preterm birth, and delivery of low birth weight infants.

REFERRAL

To obstetrician/gynecologist for recurrence and pregnancy

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Trichomoniasis (Patient Information)
Pruritus Vulvae (Related Key Topic)

AUTHOR: **Margaret R. Hines, MD**

SUGGESTED READINGS

Centers for Disease Control and Prevention: *2015 sexually transmitted diseases treatment guidelines: trichomoniasis, Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention*. Available at: www.cdc.gov/std/tg2015/trichomoniasis.htm.

Herbst de Cortina S et al: A systematic review of point of care testing for Chlamydia trachomatis, Neisseria gonorrhoeae, and Trichomonas vaginalis, *Infect Dis Obstet Gynecol* 2016:4386127, 2016.

Nye MB et al: Comparison of APTIMA Trichomonas vaginalis transcription-mediated amplification to wet mount microscopy, culture, and PCR for diagnosis of trichomoniasis in men and women, *Am J Obstet Gynecol* 200(2):188.e1–188.e7, 2009.

Patel EU et al: Prevalence and correlates of Trichomonas vaginalis infection among men and women in the United States, *Clin Infect Dis* 67(2):211–217, 2018.

TABLE E1 Differential Diagnosis of Vaginitis in Women

	Vaginal Discharge	pH	White Blood Cells	Microscopy	Symptoms
Normal	White, thick, smooth	≤4.5	Absent	Lactobacilli	None
Candidiasis	White, thick, curdlike	≤4.5	Absent	Mycelia	Vulvar pruritus, external or superficial dysuria
Trichomoniasis	Frothy or purulent	≥4.5	Present	Mobile trichomonads present Amine odor	Vulvar erythema and edema, punctate strawberry lesions on cervix
Bacterial vaginosis	Thin, white homogeneous	≥4.5	Absent	Paucity of lactobacilli (75% of patients) Amine odor Clue cells	Fishy odor and increased vaginal discharge

From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

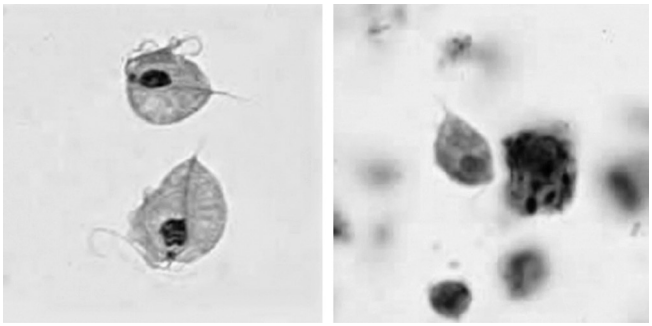

FIG. E1 *Trichomonas vaginalis* trophozoites stained with Giemsa *(left)* and iron hematoxylin *(right).* (From the Centers for Disease Control and Prevention: *Laboratory identification of parasites of public health concern, Trichomoniasis.*)

Vaginosis, Bacterial PTG

BASIC INFORMATION

DEFINITION

Bacterial vaginosis (BV) is a polymicrobial infection in which anaerobic bacteria overgrow and replace the normal hydrogen peroxide-producing lactobacilli, resulting in thin, gray, and malodorous vaginal discharge.

SYNONYMS

Bacterial vaginosis
BV
Nonspecific vaginitis
Gardnerella vaginalis vaginitis

ICD-10CM CODES

N76.0 Acute vaginitis
N77.1 Vaginitis, vulvitis and vulvovaginitis in diseases classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common cause of vaginal discharge in women of reproductive age.
- Most common organisms include *Gardnerella vaginalis*, *Porphyrmonas* species, *Mycoplasma hominis, Bacteroides* species, *Peptostreptococcus* species, *Ureaplasma urealyticum, Fusobacterium* species, *Prevotella* species, and *Atopobium vaginae*, and other facultative anaerobes.
- Women with BV are at increased risk for acquiring other sexually transmitted diseases (STDs) such as HIV, *N. gonorrhoeae, C. trachomatis,* and HSV-2. BV may contribute to persistent HPV infection. Also associated with pelvic inflammatory disease (PID) and complications after gynecologic surgery. Preoperative evaluation and treatment before planned hysterectomy or abortion decreases the infection complication rate.
- May be associated with low birth weight, premature rupture of membranes (PROM), and prematurity.
- BV may recur in 30% within the first 3 months after treatment, which may be due to:
  1. Persistence of pathogenic bacteria
  2. Reinfection from exogenous sources including sexual partners
  3. Failure of the normal lactobacillus-dominant flora to reestablish
- Risk factors: Multiple female or male sexual partners, sexually transmitted infections, douching, tobacco use, lack of condom use, and lack of vaginal lactobacilli.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- 50% to 75% of patients are asymptomatic.
- A thin, dull, and gray homogeneous discharge (Fig. E1)
- Characterized by a "fishy" odor from the vagina
- Vaginal pH >4.5
- BV alone does not typically cause dysuria or dyspareunia, and presence may suggest concomitant infection with another pathogen
- Clue cells on microscopic examination (Fig. E2)

ETIOLOGY

- *Gardnerella vaginalis* detected in 40% to 50% of vaginal secretions.
- Increase in vaginal pH secondary to decrease in hydrogen peroxide producing lactobacilli allows predominance of anaerobes that produce amines.
- It is unclear how the vaginal floral imbalance occurs and the role sexual activity plays in the pathogenesis of BV.
- *G. vaginalis* may be important in epithelial biofilm formation.
- Ethnicity and age may contribute to the vaginal microbial environment.

DIAGNOSIS

WORKUP

At least three of the Amsel clinical diagnostic criteria:

- Sensitivity of 92% and specificity of 77%:
  1. Thin, gray, and homogeneous, malodorous discharge that adheres to the vaginal walls.
  2. Vaginal pH >4.5.
  3. Positive whiff-amine test:
     a. Conducted by placing wet mount specimen and adding 10% potassium hydroxide, which creates a fishy odor.
  4. More than 20% of the epithelial cells are clue cells on microscopy.
- Gram staining: Considered the gold-standard laboratory method to determine the concentration of lactobacilli and gram-negative and gram-positive bacteria.
- If microscopy is unavailable, other diagnostic tests include Affirm VPIII (Becton Dickinson, Sparks, MD), which is a DNA-hybridization probe test for high concentrations of *G. vaginalis*, and the OSOM BV Blue test (Sekisui Diagnostics, Framingham, MA), which detects vaginal fluid sialidase activity. A molecular test for the vaginal microbiome for BV, candidiasis, and trichomonas (BD MAX Vaginal Panel) has also shown promising results in early studies.
- Cultures are unnecessary.
- Pap smear is not a reliable test for BV.
- Rule out other causes such as vulvar diseases, STDs, and atrophic vaginitis.

TREATMENT

ACUTE GENERAL Rx

- Recommended regimens (similar efficacy):
  1. Metronidazole 500 mg PO bid for 7 days *or*
  2. Metronidazole 0.75% gel, one full applicator (5 gm) intravaginally daily for 5 days *or*
  3. Clindamycin 2% cream, one full applicator (5 gm) intravaginally at bedtime for 7 days
- Alternate regimens:
  1. Clindamycin 300 mg PO bid for 7 days or clindamycin 100 mg ovules intravaginally once at bedtime for 3 days. May be associated with antimicrobial resistance.
  2. Tinidazole 1g PO once daily for 5 days. Longer half-life than metronidazole (~12 to 14 hr vs. ~6 to 7 hr)
  3. Secnidazole 2g PO once. Longer half life than metronidazole (~17 hr vs. ~8 hr). Shown to be superior to placebo in phase 3 trial and at least as effective as metronidazole 500 mg PO bid in noninferiority trial. Single 1-g oral dose appears to be effective also. Single dose improves compliance, but more expensive than multidose metronidazole therapy.
- Disulfiram-type reactions may occur while taking oral or topical metronidazole and patients should be advised to avoid alcohol while undergoing treatment.
- Sexual partners: It is not necessary to treat male partners of affected females; however, females who partner with females need to be aware of the signs and symptoms of BV, and treatment is indicated in this population if symptoms occur.
- Follow-up visits after treatment and resolution of symptoms are unnecessary, but patients are advised to return if symptoms recur.
- Not enough evidence for or against probiotic use for treatment and prevention.
- Clindamycin cream may weaken latex condoms if used together. Avoid treatment of asymptomatic patients.
- Treatment in pregnancy:
  1. Symptomatic pregnant patients with BV should be treated to relieve bothersome symptoms.
  2. Insufficient evidence to recommend routine screening for BV in asymptomatic pregnant women at high or low risk of preterm delivery.
  3. Can use oral or topical therapy for symptomatic pregnant women with same regimen as nonpregnant women.
  4. There is no evidence that metronidazole or clindamycin have any teratogenic effect during pregnancy. Tinidazole should be avoided in pregnancy.
- Recurrent BV:
  1. Condom use may help reduce the risk of recurrence.
  2. Chronic suppressive therapy has been proven to reduce the development or recurrence of BV.

PEARLS & CONSIDERATIONS

- BV is the most common cause of vaginitis in reproductive women.
- BV has been associated with PID, postprocedural gynecologic complications, and other STDs. It is reasonable to treat asymptomatic women who are to undergo gynecologic surgery and screen for other STDs.
- ACOG, USPSTF, and CDC all agree to not routinely screen and treat all pregnant women with asymptomatic BV to prevent preterm birth.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Bacterial Vaginal Infections (Patient Information)

AUTHORS: **Neha Rana, MD,** and **Emily Saks, MD, MSSCE**

SUGGESTED READINGS

ACOG Committee on Practice Bulletins–Gynecology: ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists, Number 72, May 2006: Vaginitis, *Obstet Gynecol* 107:1195-1206, 2006.

Paavonen J, Brunham RC: Bacterial vaginosis and desquamative inflammatory vaginitis, *N Engl J Med* 379:2246-2254, 2018.

Schwebke JR et al: A Phase 3, double-blind, placebo-controlled study of the effectiveness and safety of single oral doses of secnidazole 2 g for the treatment of women with bacterial vaginosis, *Am J Obstet Gynecol* 217(6), 2017. 678.e1-678.e9.

Workowski KA, Bolan GA, Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, *MMWR Recomm Rep* 64(RR-03) :1-137, 2015.

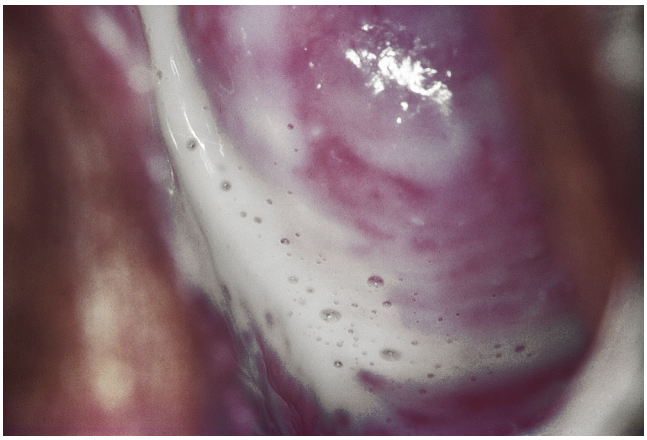

FIG. E1 Bacterial vaginosis. The gray, homogeneous discharge that coats the tissues is characteristic. (From Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.)

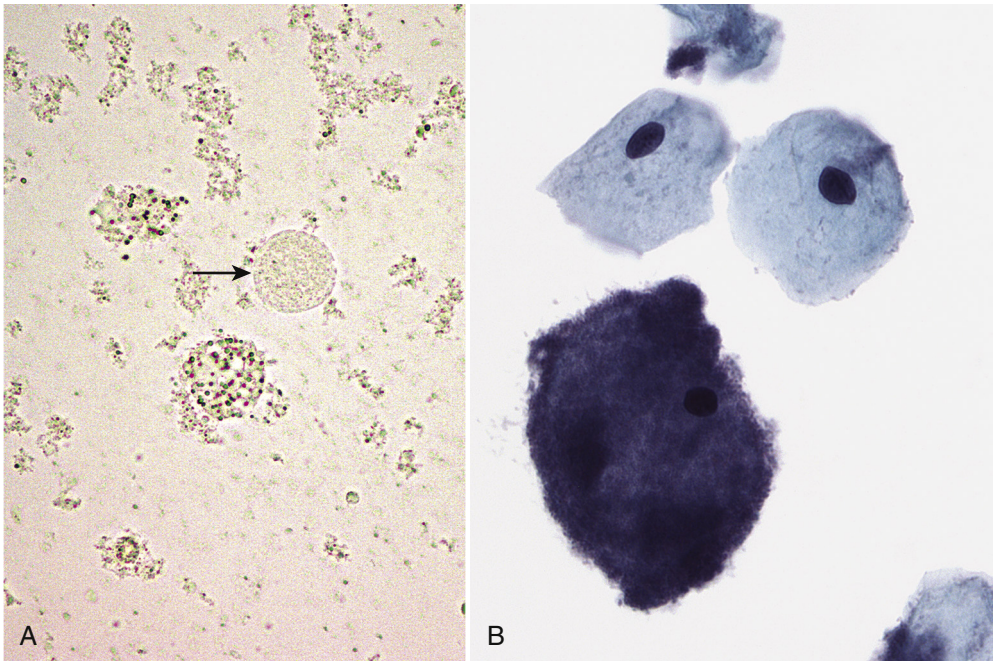

FIG. E2 Bacterial vaginosis, seen as dense, evenly distributed collections of rodlike bacterial forms in the squamous cells as seen on a wet prep **(A)** or Papanicolaou stain (clue cells; **B**). (From Crum CP et al: *Diagnostic gynecologic and obstetric pathology,* ed 3, Philadelphia, 2018, Elsevier.)

BASIC INFORMATION

DEFINITION

Enterococci are gram-positive, facultative anaerobic organisms usually oval in shape and can be seen as single cells, pairs, or chains. Vancomycin-resistant *Enterococcus* (VRE) are enterococci that have become resistant to vancomycin and several antibiotics normally used to treat enterococcal infections.

SYNONYM

VRE

ICD-10CM CODE

Z16.39 Resistance to other specified antimicrobial drug

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: VRE may be associated with the use of specific classes of antibiotics.

PEAK INCIDENCE: VRE was first reported in Europe in 1986, and there has been a steady rise in the incidence of enterococcal strains resistant to vancomycin. In 2007, 80% of *E. faecium* isolates and 7% of *E. faecalis* isolates were resistant to vancomycin.

PREVALENCE: Eighty percent of *E. faecium* are VRE; 69% of *E. faecalis* are VRE.

RISK FACTORS:

- Prior antimicrobial therapy, especially vancomycin
- Prolonged hospitalization
- Chronic medical conditions, renal failure
- Invasive devices
- ICU stay
- Colonization: VRE colonize the gastrointestinal tract; can be found on skin or perirectal swab culture or stool culture

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients may be asymptomatic and have gastrointestinal colonization; it can be associated with diarrhea. In hospitalized patients, infection is associated with colonization and can cause wound infections, bacteremia, abscesses (intraabdominal), and, rarely, pneumonia, urinary tract infections, and endocarditis.

ETIOLOGY

- The Clinical and Laboratory Standards Institute uses the following MIC definitions for vancomycin susceptibility and resistance in enterococci:
  1. Vancomycin susceptible: ≤4 mcg/ml
  2. Vancomycin resistant: ≥32 mcg/ml
  3. Vancomycin intermediate: 8 to 16 mcg/ml (vancomycin not recommended)
- Enterococci are primarily found in the human digestive tract and female genital tract, where they make up a significant portion of the normal bacterial population in healthy people. Enterococci can cause urinary tract, wound, bloodstream, heart valve, and brain infections. In the great majority of cases, VRE infections occur in hospitalized patients who have compromised immune systems. Most cases of VRE are caused by the *E. faecium* strains that have acquired resistance when they came in contact with other bacteria and shared genetic information.
- VRE is most commonly transmitted from one patient to another by health care workers whose hands have become contaminated inadvertently with feces or fluids of a person carrying the organism. VRE are not airborne but can survive on surfaces for several weeks.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other bacterial pathogens in blood, wounds, or urine.
- Once colonized, increased incidence to become infected

LABORATORY TESTS

- VRE rectal culture
- VRE stool culture
- Blood, urine, and wound cultures

TREATMENT

- For rectal or stool colonization, therapy is not recommended.
- Therapy is complicated by the fact that strains exhibit inherent resistance to many commonly used antibiotics.
- More than 80% of vancomycin-resistant *E. faecium* strains are also resistant to ampicillin.
- In symptomatic patients, if VRE strains are known to be susceptible, potential therapeutic agents include:
  1. Linezolid: 600 mg IV or PO q12h
  2. Daptomycin: 4 mg/kg/day IV for nonbacteremia infections and 6 mg/kg/day IV for bacteremias
  3. Tigecycline: 100 mg IV load dose, then 50 mg IV q12h. Although not specifically FDA approved for VRE strains, it offers an option for patients intolerant to other agents
  4. Quinupristin-dalfopristin (Synercid) only effective for *E. faecium* strains with no activity for *E. faecalis* strains: 7.5 mg/kg q8 to 12h. Can cause severe myalgias and arthralgias and venous irritation that often requires use of a central line, which has limited the use of this antibiotic
  5. Salvage regimens for severe VRE infections include:
     a. Daptomycin plus gentamicin and/or ampicillin or ceftaroline
     b. Daptomycin plus tigecycline
  6. The Healthcare Infection Control Practices Advisory Committee recommends that three negative stool/rectal cultures be obtained at weekly intervals to remove a patient from contact precautions.

REFERRAL

To infectious disease specialist

PEARLS & CONSIDERATIONS

COMMENTS

- Patients who are colonized with VRE have about an 8% rate of developing a true VRE infection in hospital or after discharge. The rate is higher in immunocompromised and severely ill patients.
- Incidence increases with comorbidity and hospitalization.
- The number of patients already colonized with VRE in a defined geographic area (colonization pressure) is the most significant factor for predicting new acquisition of VRE.
- An association between VRE colonization and *Clostridium difficile* infection has been reported in patients with hematologic malignancies.

PREVENTION

- Hand hygiene: Most important and practical method of preventing spread in hospital environment. Soap and water (used as a 30-sec wash) and alcohol-based hand rubs are effective, as is chlorhexidine.
- Cohorting and isolation techniques: Use of private rooms and use of gowns and gloves has been shown to decrease the risk of spread of multidrug-resistant bacteria.
- Cleaning contaminated objects or surfaces with standard hospital disinfectants, antibiotic management (prudent vancomycin use), and surveillance also help prevent spread.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Health Care-Related Infections (Related Key Topic)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Faron ML et al: Resistance mechanisms, epidemiology, and approaches to screening for vancomycin-resistant enterococcus in the health care setting, *J Clin Microbiology* 54:2436-2447, 2016.

Kohinke RM, Pakyz AL: Treatment of vancomycin-resistant enterococci: focus on daptomycin, *Curr Infect Dis Rep* 19:33, 2017.

Reyes K et al: Vancomycin-resistant enterococci: epidemiology, infection prevention, and control, *Infect Dis Clin North Am* 30:953-965, 2016.

BASIC INFORMATION

DEFINITION

Varicella is a viral illness caused by varicella-zoster virus and characterized by the acute onset of a generalized vesicular rash and fever.

SYNONYM

Chickenpox

ICD-10CM CODES

B01.9	Varicella without complication
B01.8	Varicella with other complications
B01.0	Varicella meningitis
B01.11	Varicella encephalitis and encephalomyelitis
B01.12	Varicella myelitis
B01.2	Varicella pneumonia
B01.81	Varicella keratitis
B01.89	Other varicella complications
Z20.820	Contact with and (suspected) exposure to varicella

EPIDEMIOLOGY & DEMOGRAPHICS

- Varicella is extremely contagious. More than 90% of unvaccinated contacts become infected.
- The incubation period of chickenpox ranges from 9 to 21 days.
- The peak incidence is during the springtime.
- The predominant age is 5 to 10 yr.
- The infectious period begins 2 days before the onset of clinical symptoms and lasts until all of the lesions have crusted.
- Most patients will have lifelong immunity after an attack of chickenpox; protection from the virus after a varicella vaccine is approximately 6 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Findings vary with the clinical course. Initial symptoms consist of fever, chills, backache, generalized malaise, and headache.
- Symptoms are generally more severe in adults.
- Initial lesions generally occur on the trunk (centripetal distribution) and occasionally on the face; these lesions consist primarily of 3- to 4-mm red papules with an irregular outline and a clear vesicle (Fig. E1) on the surface (i.e., the appearance of dewdrops on a rose petal).
- Intense pruritus generally accompanies the initial stage.
- New lesion development generally ceases by the fourth day, with subsequent crusting by the sixth day.
- Lesions generally spread to the face and the extremities (i.e., centrifugal spread).
- Patients generally present with lesions that are in different stages at the same time.
- Crusts generally fall off within 5 to 14 days. Scarring may occur in association with secondary bacterial infections (Figs. E2 and E3).
- The fever is usually highest during the eruption of the vesicles; the patient's temperature generally returns to normal after the disappearance of vesicles.
- Skin lesions may become superinfected with *Streptococcus pyogenes* or *Staphylococcus aureus*.
- Signs of potential complications (e.g., bacterial skin infections, neurologic complications, pneumonia, hepatitis) may be present on physical examination.
- Mild constitutional symptoms (e.g., anorexia, myalgias, headaches, restlessness) may be present; these are most common among adults.
- Excoriations may be present if scratching is prominent.

ETIOLOGY

Varicella-zoster virus (VZV) is a human herpes virus III (HHV-3) that can manifest with either varicella or herpes zoster (i.e., shingles, which is a reactivation of varicella).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other viral infection
- Impetigo
- Scabies
- Drug rash
- Urticaria
- Dermatitis herpetiformis
- Smallpox

WORKUP

The diagnosis is usually made on the basis of the patient's history and clinical presentation.

LABORATORY TESTS

- Laboratory evaluation is generally not necessary.
- The CBC may reveal leukopenia and thrombocytopenia.
- Serum varicella titers (i.e., a significant rise in the serum varicella immunoglobulin G antibody level), skin biopsies, or Tzanck smears are used only when diagnosis is in question.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Use antipruritic lotions for symptomatic relief.
- Avoid scratching to prevent excoriations and superficial skin infections.
- Use a mild soap for bathing.
- Hands should be washed often.

ACUTE GENERAL Rx

- Use acetaminophen for fever and myalgias; aspirin should be avoided because of the associated increased risk of Reye syndrome.
- Oral acyclovir (20 mg/kg qid for 5 days), valacyclovir, or famciclovir initiated at the earliest sign (i.e., within 24 hr of illness) is useful for healthy, nonpregnant individuals 13 yr old or older to decrease the duration and severity of signs and symptoms. Immunocompromised

FIG. E1 Chickenpox. (From Swartz MH: *Textbook of physical diagnosis,* ed 7, Philadelphia, 2014, WB Saunders.)

FIG. E2 Varicella scarring. Large, deep scars are present in this patient who had secondary bacterial infection of her primary varicella lesions. (From Paller AS et al: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

FIG. E3 Varicella, complicated. Deep, ulcerative lesions occurred in this young girl with underlying immunodeficiency and secondary infection of the skin with *Streptococcus pyogenes.* (From Paller AS et al: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, Philadelphia, 2016, Elsevier.)

hosts should be treated with intravenous acyclovir 500 mg/m^2 or 10 mg/kg q8h for 7 to 10 days.

- Varicella is most contagious from 2 days before to a few days after the onset of the rash. Varicella vaccine is available for children and adults; protection lasts at least 6 yr. Healthy, nonimmune adults and children exposed to varicella-zoster virus should receive prophylaxis with live attenuated varicella vaccine (Varivax). Patients with HIV or other immunocompromised patients should not receive the live attenuated vaccine.
- Exposed patients with contraindications to varicella vaccine can be treated with varicella-zoster immunoglobulin (VariZIG), which effectively prevents varicella in susceptible individuals. The dose is 12.5 U/kg IM up to a maximum of 625 U. VariZIG must be administered as early as possible after presumed exposure (i.e., within 10 days) for postexposure prophylaxis of varicella.
- Pruritus from chickenpox can be controlled with antihistamines (e.g., hydroxyzine 25 mg q6h) and antipruritic lotions (e.g., calamine).
- Oral antibiotics are not routinely indicated and should be used only in patients with secondary infection and infected lesions; the most common infective organisms are *Streptococcus* and *Staphylococcus* sp.

DISPOSITION

- The course is generally benign in immunocompetent adults and children.
- Infants who develop chickenpox are incapable of controlling the infection and should be given varicella-zoster immunoglobulin or gamma globulin if VariZIG is not available.

PEARLS & CONSIDERATIONS

COMMENTS

- VariZIG can be obtained from the nearest regional Red Cross Blood Center or the Centers for Disease Control and Prevention in Atlanta.
- Varicella immunization is recommended for all who have not had chickenpox; the dosage for adults and adolescents (>13 yr old) is two 0.5-ml doses 4 to 8 wk apart.

RELATED CONTENT

Chickenpox (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

BASIC INFORMATION

DEFINITION

A varicocele is a dilation of the testicular vein and pampiniform plexus within the scrotum.

SYNONYM

Sometimes referred to as "bag of worms" (Fig. E1)

ICD-10CM CODE
I86.1 Scrotal varices

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: A varicocele is present in up to 20% of all males. It occurs in approximately 40% of infertile men. However, only 10% to 15% of males with varicoceles have fertility problems.

RISK FACTORS: There are no reliable data on epidemiologic risk factors for varicocele, such as a family history or environmental exposures.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Although most varicoceles are painless, patients may complain of dull, aching pain that is relieved with lying down. They may also complain of testicular atrophy, one testicle being heavier than the other, a swollen testicle, or decreased fertility.
- Patients may report a mass lying posterior to and above the testis. When the patient is supine, dilation of the veins is generally decreased. Dilation and tortuosity of the veins are increased when the patient is upright and when the patient performs a Valsalva maneuver.
- The majority of cases (90%) occur more commonly on the left side because the left spermatic vein enters the left renal vein at a 90-degree angle, whereas the right testicular vein drains directly into the vena cava. Bilateral varicoceles occur in 33% of patients. A unilateral right-sided varicocele is very rare and should raise suspicion for an underlying disease causing obstruction of the vena cava.
- Physical examination reveals a soft scrotal mass that increases in size when standing and is typically described as a "bag of worms."
- Varicoceles can be graded based on physical exam. Grade 1 is small and is palpable only with Valsalva maneuver. Grade 2 is moderate and nonvisible on inspection but is palpable on standing. Grade 3 is large and visible on gross inspection.

FIG. E1 Varicocele. (From Swartz MH: *Textbook of physical diagnosis, history and examination,* ed 7, Philadelphia, 2014, Elsevier.)

ETIOLOGY

Varicoceles are caused by dysfunction of the valves in the spermatic vein, which allows pooling of blood in the pampiniform plexus.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hydrocele
- Spermatocele
- Epididymal orchitis
- Testicular tumor
- Table E1 describes the differential diagnosis of pediatric scrotal masses and pain

TABLE E1 Age-Based Differential Diagnosis of Pediatric Scrotal Masses and Pain

Diagnosis	Age at Onset	Pain	Position of Testes, Tenderness	Systemic Symptoms	Comment
Testicular torsion*	All ages; peak onset at 12-18 yr	60% sudden onset; diffuse tenderness	High-riding horizontal lie	Vomiting common; dysuria and fever uncommon	
Testicular appendix torsion	Prepuberty; average age, 10 yr	Acute or gradual; focal tenderness	Normal lie; blue dot	Vomiting, dysuria, and fever uncommon	
Epididymoorchitis	>16 yr	Gradual; posterior tenderness	Normal lie	Vomiting uncommon; dysuria and fever common	Adolescent etiology: STD
Hydrocele	Most common during first yr of life	Painless	Normal lie	None	Usually resolves by age 12 mo
Inguinal hernia (incarcerated hernia, strangulated hernia*)	Most common during first yr of life	Pain with incarceration or strangulation	Normal lie	Vomiting, abdominal pain with incarceration or strangulation	Occurs 10 times more frequently in males than in females; right-sided more common
Varicocele	10-15 yr	Painless, mild discomfort, "pressure or fullness"	Normal lie	None	Associated with infertility; right-sided varicocele should prompt evaluation for tumor causing IVC compression
Testicular tumor	Rare; most occur in patients <30 yr	Painless	Normal lie, nontender mass	None unless advanced tumor	

IVC, Inferior vena cava; *STD,* sexually transmitted disease.
*Emergency condition.
From Adams JG et al: *Emergency medicine: clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

WORKUP

Patient should undergo a testicular exam in the upright and supine position.

LABORATORY TESTS

- Laboratory evaluation is generally not indicated.
- Semen analysis may be performed if a varicocele is detected and the patient is infertile.

IMAGING

Usually varicoceles are diagnosed clinically. However, if there is suspicion for underlying malignancy, ultrasound may be used.

Rx TREATMENT

There are no clear guidelines or solid evidence for treatment. After a varicocele is identified, providers must document bilateral testicular size at regular intervals. Older men who do not want children and are asymptomatic can be treated conservatively. Surgical treatment is indicated for young men with retarded growth of a testis or abnormal sperm counts who want children.

MEDICAL MANAGEMENT

- NSAIDs are beneficial for pain relief.
- Scrotal support can reduce the feeling of "heaviness."

SURGERY

- If surgery is advisable, varicocelectomy is performed by ligation of the veins of the pampiniform plexus through an inguinal incision or by ligating the internal spermatic vein in the retroperitoneum. This is generally performed as an ambulatory surgery.
- Although surgery will reverse abnormal sperm counts, it will not necessarily reverse infertility.
- After surgery, the involved testis typically returns to its original size within 1 to 2 yr.
- The success rate of surgical repair is close to 98%; that of percutaneous repair is significantly lower.
- Sclerotherapy represents a less invasive option but is less effective in symptom reduction.

PEARLS & CONSIDERATIONS

- A varicocele in a young child may be indicative of an abdominal or retroperitoneal mass. Ultrasound should be performed.
- The sudden occurrence of a left-sided varicocele in an older man indicates occlusion of the spermatic vein and should prompt evaluation for a renal tumor.

RELATED CONTENT

Varicocele (Patient Information)

AUTHORS: **Emily Van Kirk, MD,** and **Andrew Caraganis, MD**

SUGGESTED READING

Will MA et al: The great debate: varicocele treatment and impact on fertility, *Fertil Steril* 95(3):841-852, 2011.

BASIC INFORMATION

DEFINITION

Veins in the leg are soft, thin-walled tubes that return blood to the heart. This is accomplished by the presence of one-way valves and the action of the calf pump. Superficial venous insufficiency develops when venous return is impaired by valvular incompetence, obstruction, or calf muscle pump failure.

Varicose veins, the most common clinical manifestation of chronic venous disease, are bulging (>3 mm in diameter), tortuous conduits (Fig. E1). Reticular veins, often called "feeder veins," are bluish subdermal veins about 1 to 3 mm in diameter that give rise to telangiectasia. Spider veins or telangiectasias are very small (≤1 mm in diameter) thread veins found commonly in clusters on the surface of the skin.

SYNONYM

Chronic venous disorder

ICD-10CM CODES

I83.90	Asymptomatic varicose veins of unspecified lower extremity
I83.899	Varicose veins of unspecified lower extremities with other complications

EPIDEMIOLOGY

PREVALENCE: One large U.S. cohort study found the biannual incidence of varicose veins was 3% in women and 2% in men.

- The prevalence of varicose veins in Western populations was estimated in one study to be about 25% to 30% in women and 10% to 20% in men.

RISK FACTORS:

- Gender: Female
- Genetics: Family history of varicose veins
- Increasing age
- Multiple pregnancies

SYMPTOMS AND PHYSICAL FINDINGS

Leg complaints consistent with chronic venous disease include aching, heaviness, subjective swelling, cramps, itching, tingling, and pain. These symptoms can be exacerbated by menses, heat, and prolonged standing.

CLINICAL PRESENTATION

- Chronic vein disease is the result of the introduction of high pressures into a normal low-pressure superficial venous system.
- This increased pressure or venous hypertension causes superficial veins to distend to such a degree that vein valves fail to close, causing reflux and pooling of blood in surface veins.
- Manifested clinically by two syndromes:
  1. Junctional: Failure of the terminal valve at the intersection between the saphenous vein trunks and the deep system. If the great saphenous vein is involved, large varicose veins are found mainly above medial knee or calf. When the small saphenous vein is involved, large varicose veins are found in posterior knee or calf area. If the anterior accessory of great saphenous vein is involved, large varicose veins are found mainly in anterior or lateral thigh.
  2. Perforator: Failure of valves located in perforating vein. Large varicose veins are found most commonly in medial calf and proximal thigh region.

CLASSIFICATION

Chronic venous disease can now be classified using the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) criteria to allow a precise description of the type of venous disease being discussed and provide an orderly framework for decision making (Table E1).

ETIOLOGY

- The underlying etiology of varicose veins remains uncertain.
- Important structural changes that occur: Failure of vein valve function and vein wall dilation from fragmentation of the muscle layer.

COMPLICATIONS

- Superficial venous thrombophlebitis (SVT): A very common disorder with an incidence of 125,000 new cases/yr in the U.S. The most frequent predisposing risk factors are varicose veins. The clinical findings include the presence of erythema, tenderness, and a palpable cord. Pain, increased warmth, and swelling are also present. Diagnosis is made by ultrasonography, which is useful to identify associated deep vein thrombosis that can occur in approximately 15% of patients. The location of the SVT determines the course of treatment; if the proximal great saphenous vein (GSV) is involved, a 1-mo course of low-molecular-weight heparin plus compression stockings has been found to be more effective than vein ligation. If SVT involves branch varicosities, treatment is usually symptomatic (control of pain).
- Bleeding is a more common complication than traditionally suspected. It is associated with thin-walled ectatic veins known as "blue blebs" that are found predominantly in the medial lower calf and ankle region. The best emergency treatment consists of pressure wrapping and not suture ligation, which results in delayed healing of the bleeding site. Sclerotherapy of these veins is the definitive treatment to prevent further bleeding.
- Dermal pathology of prolonged chronic venous disease (CEAP classes 4, 5, and 6).
  1. Varicose eczema
  2. Atrophie blanche
  3. Lipodermosclerosis
  4. Venous stasis ulcer
- Risks for peripheral artery disease and pulmonary embolism are slightly elevated in patients with varicose veins, but the clinical significance is unclear.[1]

FIG. E1 Varicose veins. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, S. Louis, 2006, Mosby.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other conditions that cause leg pain:

- Stress fracture
- Arthritis hip/knee joint
- Gout
- Degenerative disk disease of lower back

TABLE E1 CEAP Classification of Chronic Venous Disease

C: Clinical

C_0: No visible or palpable signs of venous disease
C_1: Telangiectasias or reticular veins
C_2: Varicose veins
C_3: Edema
C_4: Pigmentation or eczema
C_5: Healed venous ulcer
C_6: Active venous ulcer

E: Etiology

c: Congenital
p: Primary
s: Secondary or post-thrombotic
n: No venous cause identified

A: Anatomy

s: Superficial veins
p: Perforator veins
d: Deep veins
n: No venous location identified

P: Pathophysiology

r: Reflux
o: Obstruction
r,o: Reflux and obstruction
n: No venous pathophysiology identified

CEAP, Clinical-Etiology-Anatomy-Pathophysiology.

[1]Chang SL et al: Association of varicose veins with incident venous thromboembolism and peripheral artery disease, *JAMA* 319:807-817, 2018.

- Intermittent claudication secondary to peripheral arterial disease (PAD)
- Medications such as allopurinol and statins

Other conditions that cause leg swelling:

- Cellulitis
- Soft tissue injury to leg/ankle/foot
- Obesity
- Diabetes
- Advancing age
- Medications such as calcium channel blockers, steroids, monoamine oxidase inhibitors, and tricyclics

WORKUP

The diagnosis of chronic venous disorders is predominantly clinical. Initial evaluation consists of a thorough history and physical exam with classification of disease according to the CEAP criteria.

LABORATORY TESTS

Laboratory tests are not useful in patients with varicose veins.

IMAGING STUDIES

Duplex ultrasonography:

- Gold-standard imaging modality for the diagnosis, prognostic evaluation, pretreatment mapping, and posttreatment assessment of therapeutic intervention.
- Duplex ultrasound is used to identify and quantify points of valvular reflux within the superficial venous system.
- Assessment of valvular reflux is done with patient in the upright position, which physiologically approximates the condition in which valvular reflux occurs.
- Reverse flow of greater than 0.5 sec after distal compression is considered abnormal.

Other tests:

- Air plethysmography: May be useful in patients who have reflux in both superficial and deep venous systems or in patients with an unusual presentation of leg pain.
- Venography: Has been largely replaced by duplex ultrasonography but still retains a critical role in the evaluation of chronic venous insufficiency prior to venous reconstruction.

Rx TREATMENT

CONSERVATIVE THERAPY:

- Aerobic exercise regularly for 30 min a day.
- Elevate legs above heart level to reduce swelling.
- Flex ankles frequently at work and during air travel or long car travel.
- Maintain proper weight.
- Graduated compression stockings (below knee) to alleviate symptoms in patients who are not candidates or do not desire to undergo treatment of their varicose veins.

SCLEROTHERAPY:

- Small- to medium-sized varicose veins such as spider veins and reticular varices in the absence of reflux in saphenous trunks are best treated with liquid sclerotherapy.
- The three principal sclerosants used in the U.S. are hypertonic saline, sodium tetradecyl sulfate, and the newly FDA-approved solution, polidocanol.
- These agents are injected into vessels using 27-gauge or 30-gauge needles at concentrations of 23.4%, 0.1%, or 0.5%, respectively, causing injury to the endothelium with the resultant disappearance of the vein over period of time (usually 8 to 12 wk).

AMBULATORY PHLEBECTOMY:

- A procedure in which large varicose vein branches are removed with special hook instruments through a small puncture—incisions are made with an 18-gauge needle or No. 11 blade
- Performed safely under local anesthesia in an office setting and offers excellent cosmetic results and relief of symptoms
- Most commonly performed in conjunction with endovenous ablation procedures

ENDOVENOUS ABLATION:

- Ablation of diseased saphenous vein trunks, large incompetent tributaries, or perforating veins can be achieved by using:
  1. Radiofrequency energy
  2. Laser energy
  3. Ultrasound-guided foam sclerotherapy
- The first two accomplish thermal injury to the vein in situ via an intraluminal catheter or bare-tipped laser wire. Chemical ablation uses a solution (polidocanol or sodium tetradecyl sulfate) that is injected directly into the vein in the form of foam.
- Endovenous ablation can be performed in an office setting using local anesthesia. Patients can return to their normal daily activities immediately.
- The efficacy of these endovenous ablation procedures has been borne out by numerous published reports with occlusion rates over 95% and reflux free rates over 5-yr follow-up of 86%. A recent trial comparing ultrasound-guided foam sclerotherapy and endovenous laser ablation revealed that quality of life measures were generally similar among the study groups, with the exception of a slightly worse disease-specific quality of life in the foam group than in the surgery group. Both treatments had similar efficacy, but complications were less frequent after laser treatment and ablation rates were lower after foam treatment.

DISPOSITION

- In a recent randomized trial[2] of treatments for varicose veins, disease-specific quality of life 5 yr after treatment was better after laser ablation or surgery than after foam sclerotherapy.
- It is important that the physician educate the patient to understand that varicose veins are a chronic and progressive disease.
- Any treatment is at best palliative, as patients in time will develop varicose veins in other areas.

REFERRAL

To either a phlebologist, preferably board certified by the newly created American Board of Phlebology, or a residency-trained vascular surgeon

RELATED CONTENT

Varicose Veins (Patient Information)
Thrombophlebitis, Superficial Venous (Related Key Topic)
Venous Insufficiency, Chronic (Related Key Topic)

AUTHOR: **Frank G. Fort, MD, FACS, RPHS**

SUGGESTED READINGS

Brittenden J et al: A randomized trial comparing treatments for varicose veins, *N Engl J Med* 371:1218-1227, 2014.

[2]Brittenden J et al: Five-year outcomes of a randomized trial of treatments for varicose veins, N Engl J Med 381:912-922, 2019.

BASIC INFORMATION

DEFINITION

Vasculitis refers generically to inflammation occurring within the walls of blood vessels. Blood vessel inflammation can result in either perforation of affected vessels with hemorrhage into adjacent structures or thrombosis with subsequent ischemia and infarction of supplied tissues. Vasculitis can occur as a primary process or secondary to another connective tissue disease, infection, or drug exposure. The systemic vasculitides are a heterogeneous group of disorders (Table 1) characterized by blood vessel inflammation affecting vessels of varying size and location resulting in a wide range of clinical manifestations dictated largely by which vessels are affected (Fig. 1 and Fig. E2). Vasculitis is traditionally classified according to the size of the blood vessels predominantly affected (Table 2). Antineutrophilic cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA); microscopic polyangiitis (MPA), including renal-limited vasculitis (RLV); and eosinophilic granulomatosis with polyangiitis (EGPA). All are associated with ANCA and have similar features on renal histology (e.g., a focal necrotizing, and often crescentic, pauciimmune glomerulonephritis). Several of these are covered in individual topics, including topics on granulomatosis with polyangiitis (GPA), polyarteritis nodosa (PAN), giant cell arteritis (GCA), Takayasu arteritis, and Henoch-Schönlein purpura (HSP). Severity varies between and within specific vasculitides from a relatively benign, self-limited process to severe, life-threatening multisystem organ involvement with significant morbidity and mortality.

ICD-10CM CODES

M30.0	Polyarteritis nodosa
M30.3	Mucocutaneous lymph node syndrome [Kawasaki]
M31.30 31	Wegener granulomatosis without renal involvement
M31.5	Giant cell arteritis with polymyalgia rheumatica
M31.6	Other giant cell arteritis
M31.4	Aortic arch syndrome [Takayasu]
D 69.0	Allergic purpura
L95.9	Vasculitis limited to the skin, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- The epidemiology and demographics of the various vasculitides vary by the individual disease and, where applicable, are covered under the relevant vasculitis disease chapters.
- The most common form of systemic vasculitis in the U.S. is giant cell arteritis, with an approximate incidence of 170 cases per 1 million per yr in individuals older than 50 yr.
- Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis is significantly less common with aggregate incidence estimated at approximately 20 per million in the U.S.
- Age distribution can demonstrate significant variability between the vasculitides as shown by the fact that GCA generally does not occur before age 50, while 90% of cases of HSP occur in the pediatric population, and 80% of patients with Kawasaki disease are under age 5.
- Although genetic factors clearly play a role in disease susceptibility, familial cases of vasculitis are rare.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical presentation often includes nonspecific constitutional symptoms including fever, malaise, headache, and weight loss.

TABLE 1 Comparing the Vasculitides

Disease	Pathophysiology	Classic Features	Testing	Treatment
Giant cell arteritis	Mononuclear cell infiltration and giant cell formation	Headache, scalp tenderness, visual disturbance	ESR CRP biopsy	Prednisone and aspirin
Takayasu arteritis	Mononuclear cell infiltration and giant cell formation	Visual disturbance, chest pain, abdominal pain, differences in extremity blood pressure and pulses	Angiography	Prednisone Surgical or angiographic intervention
Polyarteritis nodosa	Polymorphonuclear infiltration	Fever, hypertension, myalgias, abdominal pain, hematuria, CHF, GI bleeding, orchitis	ESR, CRP biopsy Angiography	Prednisone (mild disease) plus cyclophosphamide (moderate-severe disease) Antiviral therapy if concurrent hepatitis B or C Azathioprine or methotrexate for maintenance of remission
Kawasaki disease	Polymorphonuclear infiltration	5-day fever, conjunctivitis, oral lesions, rash, red palms and soles, edema, cervical lymphadenopathy	ESR, CRP Leukocytosis Thrombocytosis Echocardiography	Aspirin plus IV gamma globulin
Granulomatosis with polyangiitis (Wegener granulomatosis)	Granuloma formation secondary to aggregating neutrophils	Upper and lower respiratory symptoms, renal insufficiency, skin lesions, visual disturbance	ESR CRP c-ANCA	Prednisone and methotrexate (mild disease) Cyclophosphamide or rituximab plus prednisone (moderate to severe disease)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Eosinophilic infiltration Allergic granulomas	Allergic rhinitis, nasal polyps, asthma	Leukocytosis Eosinophilia ESR, CRP biopsy	Prednisone with or without cyclophosphamide
Henoch-Schönlein purpura	IgA complex deposition	Palpable purpura, arthralgias, GI disturbances, glomerulonephritis	Leukocytosis Eosinophilia Ig A elevation, skin biopsy	Usually self-limited NSAIDs Prednisone if necessary Rituximab (refractory cases)
Cryoglobulinemic vasculitis	Cold precipitable monoclonal or polyclonal immunoglobulins	Palpable purpura, glomerulonephritis, myalgias, weakness, peripheral neuropathy	Low complement levels, hepatitis C Renal biopsy	Rituximab with or without prednisone Peg interferon plus ribavirin (HCV infection)
Cutaneous leukocytoclastic vasculitis	Neutrophilic infiltration Mononuclear and eosinophilic infiltration	Palpable purpura, macules, vesicles, bullae, urticaria	Skin biopsy	Prednisone Colchicine Dapsone
Behçet syndrome	Polymorphonuclear infiltration	Recurrent oral aphthous ulcers, genital ulcers, skin lesions, visual disturbance	ESR, CRP leukocytosis Oral mucosa autoantibodies	Topical corticosteroids Prednisone with azathioprine (end-organ disease) Colchicine (aphthous ulcer and arthritis) Infliximab (refractory disease)

c-ANCA, Cytoplasmic antineutrophil cytoplasmic antibody; *CHF,* congestive heart failure; *CRP,* C-reactive protein; *ESR,* erythrocyte sedimentation rate; *GI,* gastrointestinal; *IgA,* immunoglobulin A; *IV,* intravenous.
From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

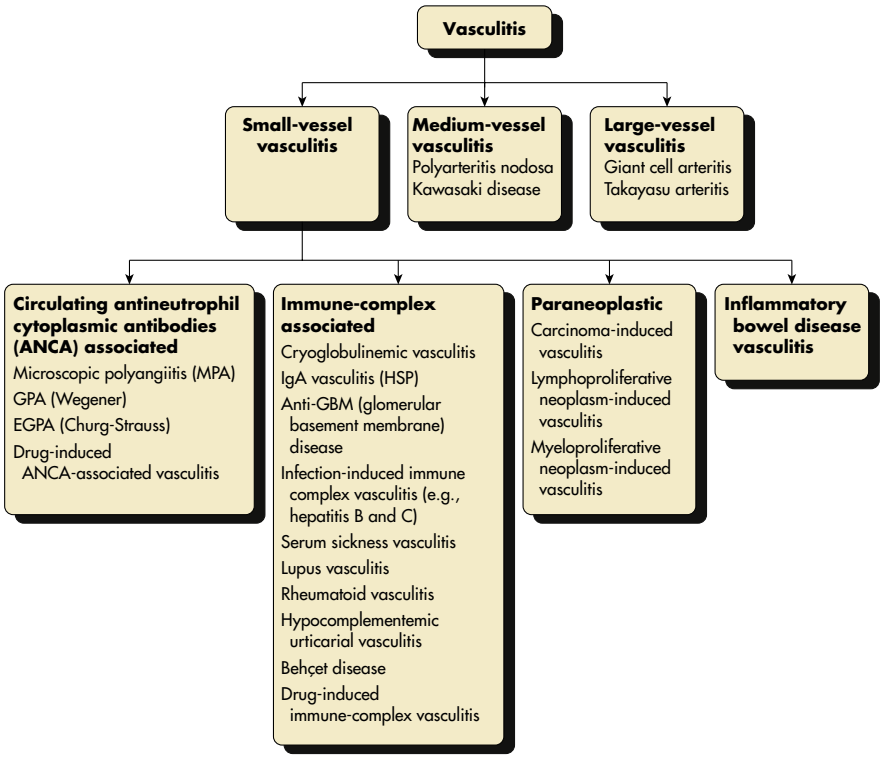

FIG. 1 Major categories of noninfectious vasculitis. Not included are vasculitides that are known to be caused by direct invasion of vessel walls by infectious pathogens, such as rickettsial vasculitis and neisserial vasculitis. *EGPA,* Eosinophilic granulomatous polyangiitis; *GPA,* granulomatous polyangiitis; *HSP,* Henoch-Schönlein purpura. (From Freehally J et al: *Comprehensive clinical nephrology,* ed 6, Philadelphia, 2019, Saunders.)

- Signs and symptoms are generally dictated by the tropism of involved vessels.
- Skin manifestations of vasculitis include petechiae, palpable purpura (Fig. E3), subcutaneous nodules, livedo reticularis, ulcerations, and digital ischemia.
- Kidney involvement of medium-sized and large vessel vasculitis is often in the form of renovascular hypertension. Glomerulonephritis may be seen in small vessel vasculitis.
- Pulmonary small vessel involvement can cause alveolar hemorrhage, which can present with cough, dyspnea, and alveolar hemorrhage.
- Mononeuritis multiplex is the characteristic finding of vasculitis affecting the vasa nervorum of the peripheral nervous system.
- Gastrointestinal involvement of the mesenteric vasculature can cause postprandial pain, bleeding, and perforation.
- Arthritis, while nonspecific, can be present.
- Significant clinical variability exists between the various vasculitides, although overlapping symptoms may be seen.

ETIOLOGY

Most forms of systemic vasculitis are of unknown etiology. Cryoglobulinemia vasculitis is often secondary to hepatitis C infection, and cutaneous leukocytoclastic vasculitis is often related to a drug exposure.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infective endocarditis
- Atrial myxoma
- Cholesterol emboli
- Malignancy
- Hypercoagulopathy
- Congenital collagen vascular disorder

WORKUP

- The diagnosis of most forms of systemic vasculitis relies on the history and physical examination as well as supportive laboratory testing. Table 3 describes differential diagnostic features of selected forms of small vessel vasculitis.
- Tissue biopsy is important in establishing an accurate diagnosis; biopsy sites should target affected tissues.
- Imaging such as mesenteric angiography can be supportive and may obviate the need for tissue biopsy.

LABORATORY TESTS

- Laboratory markers of systemic inflammation include elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and anemia of chronic disease.
- ANCA targeting myeloperoxidase (MPO) and proteinase 3 (PR3) are frequently found in several small vessel vasculitides, including GPA (Wegener), microscopic polyangiitis (MPA), and EGPA (Churg-Strauss).
- Hepatitis C antibodies and rheumatoid factor are often present in cryoglobulinemic vasculitis.
- Urinalysis in patients with glomerulonephritis due to small vessel ANCA-associated vasculitis will generally demonstrate hematuria with active urinary sediment, with red blood cell casts and proteinuria.

IMAGING STUDIES

- CTA, MRA, and angiography can demonstrate vascular narrowing and aneurysm formation in suspected medium-size and large-vessel vasculitis.
- Pulmonary and sinus CT scans can demonstrate active pulmonary and upper airway disease in ANCA-associated vasculitis.

TABLE 2 Classification Scheme of Vasculitides According to Size of Predominant Blood Vessels Involved

- Primary vasculitides
- Predominantly large vessel vasculitides
- Takayasu arteritis
- Giant cell arteritis (temporal arteritis)
- Cogan syndrome
- Behçet disease*
- Predominantly medium-sized vessel vasculitides
- Polyarteritis nodosa
- Cutaneous polyarteritis nodosa
- Buerger disease
- Kawasaki disease
- Primary angiitis of the central nervous system
- Predominantly small vessel vasculitides
- Immune complex mediated
- Goodpasture disease (anti-glomerular basement membrane disease)†
  1. Cutaneous leukocytoclastic angiitis ("hypersensitivity vasculitis")
  2. Henoch-Schönlein purpura
  3. Hypocomplementemic urticarial vasculitis
  4. Essential cryoglobulinemia‡
  5. Erythema elevatum diutinum
- ANCA-associated disorders§
  1. Granulomatosis with polyangiitis (GPA, Wegener granulomatosis)‡
  2. Microscopic polyangiitis (MPA)‡
  3. Eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome)‡
  4. Renal-limited vasculitis (RLV)
- Secondary forms of vasculitis
- Miscellaneous small vessel vasculitides
- Connective tissue disorders‡ (rheumatoid vasculitis, lupus erythematosus, Sjögren syndrome, inflammatory myopathy)
- Inflammatory bowel disease
- Paraneoplastic
- Infection
- Drug-induced vasculitis: ANCA-associated, other

*May involve small, medium-sized, and large blood vessels.
†Immune complexes formed in situ, in contrast to other forms of immune complex–mediated vasculitis.
‡Frequent overlap of small and medium-sized blood vessel involvement.
§Not all forms of these disorders are always associated with ANCA.
ANCA, Antineutrophil cytoplasmic antibody.
From Firestein G et al: *Kelley's textbook of rheumatology,* ed 8, Philadelphia, 2008, Saunders.

TABLE 3 Differential Diagnostic Features of Selected Forms of Small Vessel Vasculitis

Features	Microscopic Polyangiitis (MPA)	Granulomatosis with Polyangiitis (GPA)	Eosinophilic Granulomatosis with Polyangiitis	Henoch-Schönlein Purpura (HSP)	Cryoglobulinemic Vasculitis
Vasculitic signs and symptoms	+	+	+	+	+
IgA-dominant immune deposits	–	–	–	+	–
Cryoglobulins in blood and vessels	–	–	–	–	+
Antineutrophil cytoplasmic antibodies in blood	+	+	+	–	–
Necrotizing granulomas	–	+	+	–	–
Asthma and eosinophils	–	–	+	–	–

From Freehally J et al: *Comprehensive clinical nephrology,* ed 6, Philadelphia, 2019, Saunders.

Rx TREATMENT

Treatment of vasculitis depends on the specific type of vasculitis and is tailored to the severity of disease activity. Novel treatments are covered under the relevant vasculitis disease chapters.

ACUTE GENERAL Rx

- Systemic corticosteroids are generally required to gain initial control of active vasculitis, although mild cases of drug-induced cutaneous leukocytoclastic vasculitis often require cessation of the offending medication and at times, low-dose corticosteroid use.
- HSP and vasculitis limited to the skin, including cutaneous PAN, can often be managed without further immunosuppression.
- Major organ-threatening disease in systemic vasculitis has traditionally required pulse steroids and oral or intravenous cyclophosphamide for induction of remission.
- Studies have demonstrated noninferiority of rituximab compared to cyclophosphamide in ANCA-associated vasculitis with major organ involvement, and it is approved for this use.
- Rituximab with prednisone has also recently been shown to be effective in the treatment of relapsing flares of disease activity in ANCA-associated vasculitis.
- Similarly, rituximab has been used for maintenance of remission.
- Less severe disease such as granulomatosis with polyangiitis limited to the upper airways can be managed with methotrexate rather than cyclophosphamide.
- Trimethoprim/sulfamethoxazole should be used to prevent *Pneumocystis carinii* infection with concurrent immunosuppressive therapy.
- The goal of acute therapy is to induce remission of disease activity and is generally continued for 1 to 2 mo once this is achieved, at which point chronic therapy is used.

CHRONIC Rx

- The goal of chronic therapy is to prevent disease relapse and minimize medication side effects.
- Steroids are gradually tapered as allowed by disease activity.
- Immunomodulatory agents such as methotrexate or azathioprine are commonly used for maintenance therapy in place of cyclophosphamide to reduce side effects.
- Cryoglobulinemic vasculitis due to chronic hepatitis C will often improve with treatment of the underlying viral infection.
- Rituximab may also be an appropriate remission maintenance agent in ANCA-associated vasculitis, although frequency of dosing and duration of therapy are not yet well characterized.

DISPOSITION

Varies widely among the various vasculitides

REFERRAL

Systemic vasculitis care is generally coordinated by a rheumatologist. Renal, pulmonary, neurologic, and gastrointestinal consultation is often needed when vasculitis involves these organ systems. Isolated cutaneous leukocytoclastic vasculitis is often managed by dermatology.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Cogan Syndrome (Related Key Topic)
Cryoglobulinemia (Related Key Topic)
Eosinophilic Granulomatosis with Polyangiitis (Related Key Topic)
Giant Cell Arteritis (Related Key Topic)
Granulomatosis with Polyangiitis (Related Key Topic)
IgA Vasculitis (Related Key Topic)
Kawasaki Disease (Related Key Topic)
Microscopic Polyangiitis (Related Key Topic)
Polyarteritis Nodosa (Related Key Topic)
Takayasu Arteritis (Related Key Topic)

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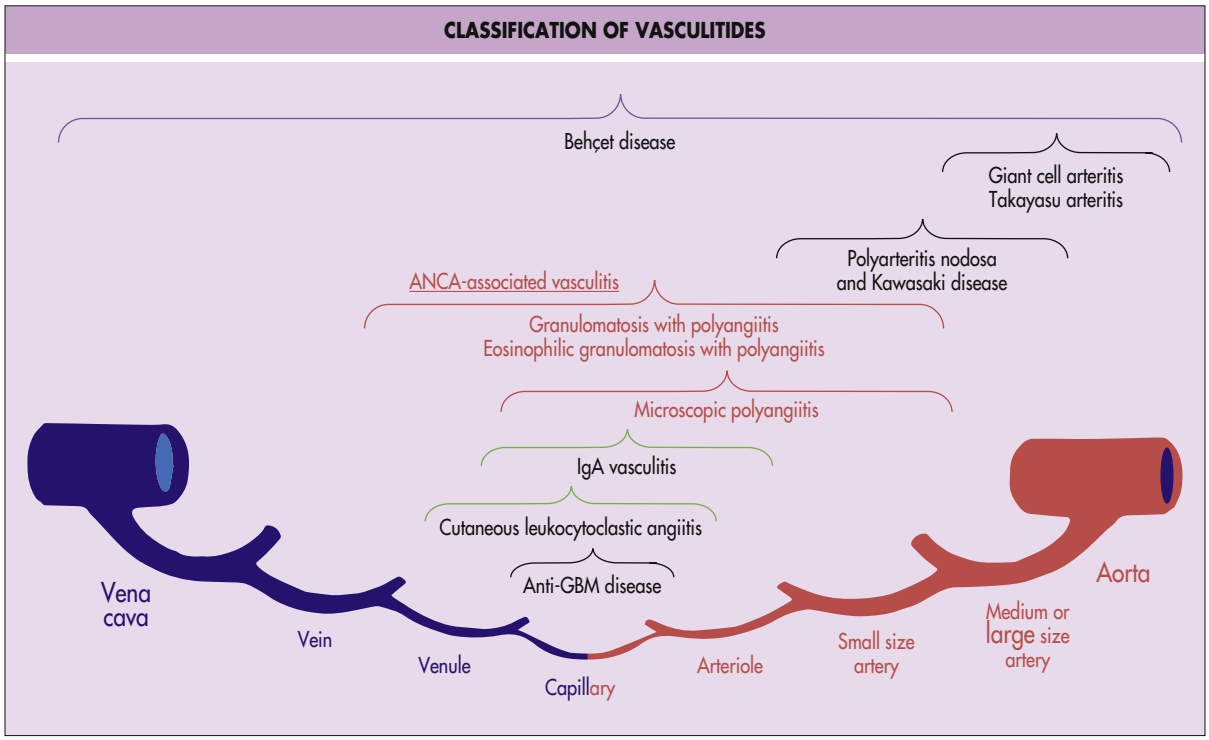

FIG. E2 The classification of vasculitides according to vessel size. *ANCA,* Antineutrophil cytoplasmic antibody; *anti-GBM,* anti–glomerular basement membrane; *IgA,* immunoglobulin A. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

FIG. E3 Leukocytoclastic vasculitis, palpable purpura. (From James W et al: *Andrews' diseases of the skin, clinical dermatology,* ed 10, Philadelphia, 2005, Saunders.)

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BASIC INFORMATION

DEFINITION

The spectrum of chronic venous disease (CVD) ranges from varicose veins to leg edema and skin manifestations consisting of hyperpigmentation, eczema, lipodermatosclerosis, and venous ulcer. These latter venous-specific skin changes constitute an advanced form of CVD known as chronic venous insufficiency (CVI).

SYNONYMS

Stasis dermatitis
Postthrombotic syndrome (PTS)
Chronic venous disease

ICD-10CM CODES

I87.2	Venous insufficiency (chronic) (peripheral)
I87.8	Other specified disorders of veins
I87.9	Disorder of vein, unspecified
I83.10	Varicose veins of unspecified lower extremity with inflammation

EPIDEMIOLOGY & DEMOGRAPHICS

- From 10% to 35% of adults in the United States have some form of CVI.
- Venous ulcers are the complication of CVI that results in the greatest morbidity and affects 4% of people over the age of 65.
- The population-based costs to the U.S. government for CVI treatment and venous ulcer care have been estimated at >$1 billion/yr.
- In addition, 4.6 million workdays/yr are lost to chronic venous-related diseases.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The manifestations of CVI can be viewed using the internationally accepted classification system, CEAP (clinical, etiology, anatomy, and pathophysiology) (Table 1). The spectrum of cutaneous changes of CVI in the affected leg include:

- Varicose eczema: The most common and earliest sign, this involves the skin above the medial ankle and consists of pruritic, red, and scaly eczematous patches and plaques.
- Hyperpigmentation: Caused by the breakdown of red blood cells and leads to hemosiderin deposition and dark staining of the skin (Fig. E1).
- Atrophie blanche: Usually presents as hypopigmented white patches with focal red punctate dots or telangiectasia surrounded by hyperpigmentation. Skin in this condition is avascular and prone to ulceration (Fig. E2).
- Lipodermatosclerosis: A chronic, brawny induration of the skin and underlying fat that usually involves the skin from medial malleolus up to the lower border of the calf. Progression of the disease leads to an "inverted champagne bottle" appearance. The induration and lack of perfusion of the skin in this area make it susceptible to ulcer formation.

TABLE 1 CEAP Classification

Clinical Classification	
C_0	No visible or palpable signs of venous disease
C_1	Telangiectasias or reticular veins
C_2	Varicose veins; diameter >3 mm
C_3	Edema
C_4	Changes in skin and subcutaneous tissue: Pigmentation, eczema, lipodermatosclerosis, or atrophie blanche
C_5	Healed venous ulcer
C_6	Active venous ulcer
	Each limb is further classified as asymptomatic (A) or symptomatic (S)
Etiologic Classification	
E_C	Congenital
E_P	Primary
E_S	Secondary (post-thrombotic)
E_N	No venous cause identified
Anatomic Classification	
A_S	Superficial veins
A_P	Perforator veins
A_O	Deep veins
A_N	No venous location identified
Pathophysiologic Classification	
P_R	Reflux
P_R	Obstruction
$P_{R,O}$	Reflux and obstruction
P_N	No venous pathophysiology identifiable

CEAP, Clinical-Etiological-Anatomical-Pathophysiological.
From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, 2017, Elsevier.

ETIOLOGY

- CVI occurs as a result of sustained venous hypertension in the leg, which can be caused by the following:
  1. Primary: Vein valve failure with reflux in the superficial venous system or perforating veins (most common cause of CVI).
  2. Secondary: Post-thrombotic syndrome in which a deep vein thrombosis causes outflow obstruction *or*
  3. Combination of the two previous processes.
- This sustained elevation in venous pressure or venous hypertension results in pathologic effects in the skin and subcutaneous tissues such as edema, eczema, hyperpigmentation, fibrosis, and ultimately venous ulceration.

DIAGNOSIS

The diagnosis and evaluation of CVI are directed primarily by a detailed history and physical examination.

DIFFERENTIAL DIAGNOSIS

- Contact dermatitis
- Atopic dermatitis
- Cellulitis
- Dermatophyte infection
- Pretibial myxedema
- Nummular eczema
- Xerosis
- Asteatotic eczema

WORKUP

The primary goal is to identify the cause of sustained venous hypertension. Fig. 3 describes the evaluation and management of chronic venous insufficiency.

LABORATORY TESTS

Generally not indicated

IMAGING STUDIES

- Evaluation of the patient is performed in the standing position with duplex ultrasonography to identify reflux in the superficial, deep, and perforating veins as well as obstruction of the deep veins.
- No exam of a leg with CVI is complete without palpation of pulses and/or determination of ankle-brachial index (ABI).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Leg elevation above heart level for 30 min three to four times a day
- Weight reduction because obesity is a risk factor for deep vein thrombosis and CVI
- Walking exercises to improve calf function
- Physical therapy to improve ankle joint mobility
- For weeping skin lesions, wet-to-dry dressing changes

ACUTE GENERAL Rx

- The fundamental role of compression in the treatment of CVI is well recognized and has been validated by randomized controlled trials (RCTs).
- The beneficial effects of gradient compression stockings (decrease in edema and control of discomfort) are due to their effect on microvascular hemodynamics and Starling forces.
- Below-knee compression stocking with a gradient of at least 20 to 30 mm Hg will control edema, alleviate pain, and improve the quality of life in CVI patients.
- Compression stockings are contraindicated in patients with an ABI of <0.6.
- Some patients (acute lipodermatosclerosis) may benefit from nonelastic compression with the Unna gel paste gauze boot to alleviate their symptoms and acute increase in their swelling. The Unna boot is changed once a week.
- Topical corticosteroid creams or ointments (e.g., triamcinolone 0.12% bid) may be used to help reduce inflammation and itching. Steroids should never be applied to ulcer.
- Antibiotics should only be used when treating a clinically apparent, culture-proved infection. Most secondary infections are the result of *Staphylococcus* or *Streptococcus* organisms.
- Diuretics have no role in the treatment of CVI-related edema.

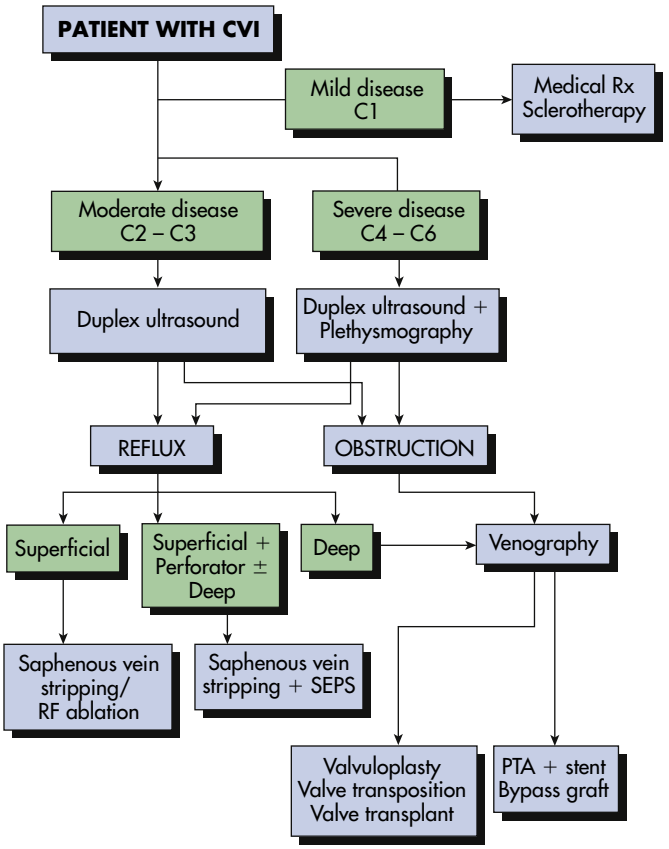

FIG. 3 Evaluation and management of chronic venous insufficiency. (From Cameron JA: *Current surgical therapy "varicose veins,"* Philadelphia, 2004, Saunders.)

CHRONIC Rx

- While conservative care is fundamental, patients with CVI should be considered for correction of their underlying venous hypertension.
- The majority of patients with CVI have superficial vein or perforator vein reflux as their underlying pathology and would benefit from the newer vein ablation procedures listed below.
  1. Endovenous ablation of superficial (saphenous) or perforator vein reflux.
  2. RF ablation with VNUS closure.
  3. Endovenous laser therapy (EVLT).
  4. Ultrasound-guided foam sclerotherapy.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Several groups of drugs have been evaluated in the treatment of CVI, including coumarins, flavonoids, and saponosides (horse chestnut extracts). These drugs have venoactive properties and are widely used in Europe but are not approved for use in the U.S. The precise mechanism of action is not known. Horse chestnut seed extract has been found, in the short term, to be as effective as compression stockings in reducing pain and edema, but long-term efficacy has not been established.

REFERRAL

- Phlebology
- Vascular surgery
- Indications for referral:
  1. Skin and subcutaneous changes consistent with CVI
  2. Associated peripheral arterial insufficiency (PAD)
  3. Longstanding varicose vein disease
  4. Consideration for vein ablation procedure

PEARLS & CONSIDERATIONS

COMMENTS

- Inflammatory skin changes from CVI are irreversible. The goal of therapy is to eliminate venous hypertension and prevent progression.
- Venous ulcers are often an end-stage manifestation of CVI. Refer to "Venous Ulcers" for more information.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Stasis Dermatitis (Patient Information)
Varicose Veins (Related Key Topic)
Venous Ulcers (Related Key Topic)

AUTHOR: **Frank G. Fort, MD, FACS, RPHS**

SUGGESTED READINGS

Singer AJ et al: Evaluation and management of lower-extremity ulcers, *N Engl J Med* 377:1559-1567, 2017.

Vivas A et al: In the clinic: venous leg ulcers, *Ann Intern Med* 165(3):ITC17-ITC32, 2016.

FIG. E1 Stasis dermatitis, venous insufficiency. (From James WD et al: *Andrews' diseases of the skin,* ed 12, Philadelphia, 2016, Elsevier.)

FIG. E2 Chronic venous ulcer likely to be resistant to treatment as it involves the space behind the medial malleolus, which is difficult to compress. (From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, 2017, Elsevier.)

BASIC INFORMATION

DEFINITION

Venous ulcers are defined as chronic defects of the skin that fail to heal spontaneously and persist for longer than 4 wk. Venous ulcers account for about 70% of all lower-extremity ulcerations. They are usually located in the "gaiter" region and can be accompanied by varicose veins, edema, hyperpigmentation, and lipodermatosclerosis. Venous ulceration develops in patients as a result of sustained venous hypertension.

SYNONYM

Stasis ulcers

ICD-10CM CODES	
I87.2	Venous insufficiency (chronic) (peripheral)
L97.909	Non-pressure chronic ulcer of unspecified part of unspecified lower leg with unspecified severity

EPIDEMIOLOGY & DEMOGRAPHICS

In industrialized nations, up to 1.5% of the population will suffer from venous ulcers. In patients ≥65 yr, the incidence increases to 4%. In the U.S., >500,000 people suffer from stasis ulcers.

RISK FACTORS

- Obesity
- Increasing age
- Family history of chronic venous insufficiency
- History of deep venous thromboembolism

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Venous ulcers are most commonly located in the lower leg just above the ankle (gaiter region). They are a partial-thickness, irregularly shaped wound with well-defined borders with granulation tissue and fibrin present in the ulcer base (Fig. E1). Venous ulcers are relatively painless and are surrounded by brown-stained skin and/or dry, itchy, and reddened skin. In about 50% of patients, there are visible varicose veins in an aching, swollen leg.

ETIOLOGY

The exact mechanism of the role of venous hypertension in the etiology of venous ulcers is not certain. Hemodynamic forces such as venous hypertension, circulatory stasis, and modified conditions of shear stress appear to play an important role in an inflammatory reaction accompanied by leukocyte activation that clinically leads to fibrosclerotic remodeling of the skin and then to ulceration.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Arterial ulcer
- Neurotrophic ulcers (located predominantly in the foot)
- Vasculitis
- Pyoderma gangrenosum
- Ulcerated skin tumors like basal cell or squamous cell carcinoma (Marjolin ulcer)
- Rheumatoid arthritis

WORKUP

- The history and clinical signs and symptoms of leg ulcers are often misleading and may not differentiate venous ulcers from other leg ulcers; about 30% of leg ulcers are not of venous origin.
- Measurement of the ankle-brachial index (ABI) is essential in excluding peripheral arterial disease (PAD), which can be present in 20% of patients and is required before starting compression therapy. Arterial insufficiency is suggested by an ABI <0.9.
- Patients with lower-extremity ulcers should also be evaluated for diabetes.
- Coagulation defects have been found in 40% of patients with leg ulcers. This finding suggests that many patients with leg ulcers have a known or suspected history of deep venous thrombosis and a thrombophilia workup is indicated.
- If vasculitis is suspected, a biopsy of the edge of the ulcer can confirm the diagnosis.
- Any wound that has failed to improve after therapy of 4 wk should have a biopsy to rule out malignancy.

IMAGING STUDIES

- Evaluation of patients with venous leg ulcer should include duplex sonography to identify reflux in the superficial, deep, and perforating veins as well as possible obstruction of the deep veins.
- If the ulcer appears to be infected, consider tissue for culture, plain x-ray films, and bone scan to evaluate for osteomyelitis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Fig. 2 describes an algorithm for the treatment of venous ulcers.
- Surgical debridement to remove all nonviable material can be accomplished in the office setting with the use of a topical xylocaine gel. Debridement produces the release of growth factors that allow the development of healthy granulation tissue and the initiation of the healing process.
- The first-line treatment of ulcers includes below-knee compression stockings to improve venous return to the heart, thereby decreasing edema, inflammation, and tissue ischemia (used only if the ABI is between 0.6 and 0.85 because compression can cause limb ischemia).
- There is Level A evidence that graduated compression stockings alone can lead to healing of a venous ulcer. The stockings should be worn during the day and removed at night.
- Regular, brisk walking 30 min a day, five times a week is recommended.
- Elevate leg above heart level and raise the foot of bed with 3-in blocks to reduce edema.
- Role of surgery: In a randomized controlled trial, endovenous catheter ablation of superficial reflux showed no improvement in the healing rate of ulcers but did demonstrate a reduction of ulcer recurrence from 28% to 12% at 12 mo.

ACUTE GENERAL Rx

- Dressings are used under compression stockings to provide a clean, moist environment to promote healing.
- Modern, more complex dressings have been developed and include occlusive and semiocclusive dressings, classified according to their physical composition and ability to control wound drainage.
- Semiocclusive dressings have varying ability to absorb wound drainage. Some examples of this type are hydrocolloids (DuoDerm), hydrogels (DuoDerm hydrogel), foam dressings (Allevyn), and alginates.
- Biologic wound dressings (Apligraf) and tissue-engineered products (Oasis) have been developed, and these products can either directly provide growth factors or indirectly stimulate growth factors in the ulcer bed.
- Pentoxifylline (800 mg tid) has been shown to be an effective adjuvant to compression therapy as reported in a meta-analysis of nine clinical trials.
- Skin grafting should be considered for large or refractory ulcers as long as the wound is clean and there is healthy granulation tissue.
- Published randomized clinical trials on the value of the different types of dressings in the management of leg ulcers have not shown effects on ulcer healing. Despite the lack of evidence to support their use, modern dressings remain a part of the standard of care. Decisions regarding their use should be based on local cost of the dressings and the physician's clinical experience.
- Trials involving the use of weekly, low-dose, high-frequency ultrasound for hard-to-heal venous leg ulcers do not support adding therapeutic ultrasound to standard care for venous leg ulcers.

DISPOSITION

The overall prognosis for this condition is poor; the healing rate depends on the initial size of the ulcer. Although 65% to 70% of venous ulcers are healed within 6 mo, the 5-yr recurrence rate of healed venous ulcers can be as high as 40%. Maintenance of lifelong compression therapy is recommended.

REFERRAL

All patients should be evaluated weekly during the first month of therapy. Nonhealing ulcers with little to no improvement should also be referred to a wound care clinic.

SUGGESTED READINGS

Available at ExpertConsult.com

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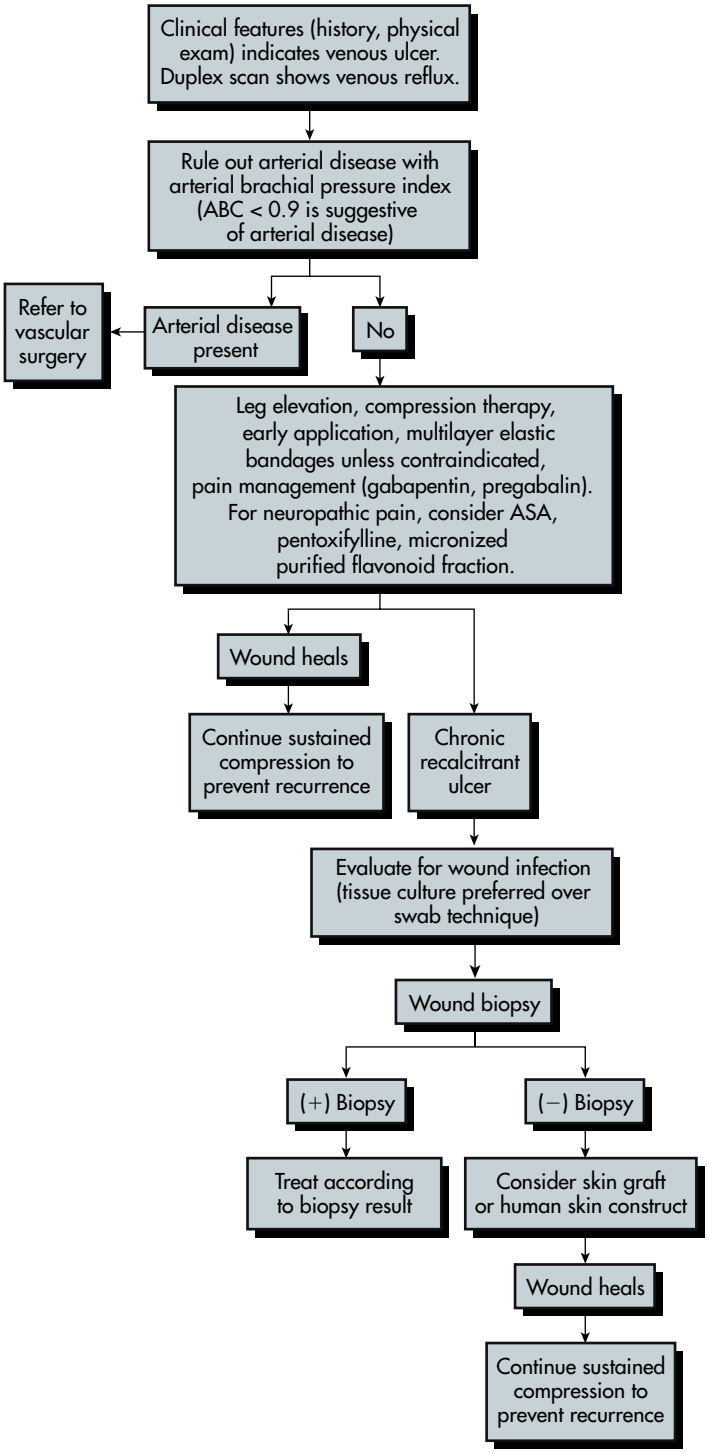

FIG. 2 Algorithm for the care of a patient with a venous leg ulcer.

SUGGESTED READINGS

Collins L, Seraj S: Diagnosis and treatment of venous ulcers, *Am Fam Physician* 81(8):989-996, 2010.

Singer AJ et al: Evaluation and management of lower-extremity ulcers, *N Engl J Med* 377:1559-1567, 2017.

Vivas A et al: In the clinic: venous leg ulcers, *Ann Intern Med* 165(3):ITC17-ITC32, 2016.

Watson JM et al: Use of weekly, low-dose, high-frequency ultrasound for hard to heal venous ulcers: the VenUS III randomized controlled trial, *BMJ* 342:d1092, 2011.

FIG. E1 Stasis ulcer. Any ulcer in this location with surrounding edema, redness, and scale is typical of a stasis ulcer. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

Ventricular Fibrillation

BASIC INFORMATION

DEFINITION

Ventricular fibrillation (VF) is a rapid, disorganized ventricular arrhythmia (Fig. E1) that renders the ventricle unable to contract in a synchronized manner resulting in no meaningful cardiac output or blood pressure and, if not rapidly interrupted, death. The ECG appearance of VF can evolve rapidly over the course of minutes as the heart becomes more ischemic. Upon initiation, QRST complexes in VF often appear coarse with grossly irregular oscillating complexes of variable rate, axis, and morphology. As VF continues, the QRST complexes become finer, lower amplitude, and slower, eventually resulting in asystole. VF is the leading mechanism of sudden cardiac death.

ICD-10CM CODE
I49.01 Ventricular fibrillation

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: A peak incidence of VF occurs in the first 48 hrs after an acute myocardial infarction (MI). The true incidence of VF is impossible to know because the majority of these episodes are in unmonitored patients and result in sudden cardiac death. Sudden cardiac death, as determined by death certificate analysis, is estimated to account for 400,000 to 450,000 deaths per yr in the U.S. In small studies in which patients were wearing monitoring at the time of death, the majority of sudden cardiac deaths were caused by VF (60% to 70%). The true proportion of sudden cardiac deaths caused by VF is highly dependent on the population studied.

RISK FACTORS:

- Between 80% and 90% of sudden cardiac death and VF cases occur in patients with coronary artery disease (CAD) or systolic dysfunction, with only about 15% of VF cases occurring in a "normal" heart at autopsy.
- Between 60% and 70% of patients with VF have CAD.
- Between 5% and 15% of events are secondary to structural heart disease (congenital coronary anatomy, myocarditis, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy). This frequency increases when under the age of 35 yr.
- Between 5% and 10% of events occur in the absence of ischemic or structural heart disease. These events are more common before the age of 35 and include inherited channelopathies and trauma-induced (commotio cordis) etiologies.
- Risk factors for VF in patients presenting with ischemic coronary heart disease:
  1. STEMI as opposed to NSTEMI
  2. Larger infarcts
  3. Inferior infarcts
  4. Baseline repolarization abnormalities
  5. Hypokalemia
  6. Male sex
  7. History of tobacco abuse
  8. Absence of pre-infarct angina

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients are unconscious, without blood pressure or pulse.
- Witnesses may describe a sudden loss of consciousness, without breathing along with a cyanotic appearance.
- Seizure activity may be witnessed after loss of consciousness caused by a lack of cerebral perfusion.

ETIOLOGY

In roughly 80% of patients with VT/VF there is increased ventricular ectopy prior to sustained ventricular arrhythmia. VF is thought to develop in one of three ways: (1) degeneration of sustained monomorphic VT, (2) degeneration of sustained polymorphic VT, or (3) development of VF as a primary event. The mechanism of VF is thought to involve multiple rotating spiral waves of micro reentry without any overall organized electrical activity. This is distinctly different from the predominant mechanism of monomorphic ventricular tachycardia, which is reentry around a fixed zone of slow conduction, typically ventricular scar. VF results from a substrate of heterogeneous repolarization and a triggering event such as critically timed PVC. In about one third of these cases the PVC initiates VT by an early R-on-T PVC, and the remaining two thirds occur after a late-cycle PVC. Repolarization of the heart is an active process requiring ATP to obtain and maintain a negative resting membrane potential via NA/K ATPase ion channels. By depriving a significant amount of myocardium to oxygen and thus the ability to generate ATP, ischemia can provide both the substrate of VF by impairing the ischemic area's ability to fully repolarize and allow for a triggering event by allowing spontaneous depolarization. Genetic conditions such as Long QT syndrome can also predispose to VF in absence of ischemia by providing more heterogeneous repolarization within the myocardium.

ETIOLOGIES OF VF IN ABSENCE OF STRUCTURAL OR CORONARY HEART DISEASE

- **Long QT syndrome:** Estimated prevalence of 1:2000 to 1:5000; the diagnosis is made based on combination of ECG findings and clinical and family history collectively compiled as Schwartz criteria. Typically inherited as autosomal dominant mutation with variable penetrance, making genetic testing helpful for confirming diagnosis or screening family members.
- **Short QT syndrome:** Inherited syndrome characterized by both a short QTc (<350 ms in males and 360 ms in females) and symptomatic atrial fibrillation and VF.
- **Brugada syndrome:** Prevalence is 5 to 50:10,000 of autosomal dominant inherited mutation characterized by a classic Brugada pattern on ECG in leads V1 to 2 combined with syncope or clinical sudden death. The ECG pattern is mutable and not always present. Genetic testing is limited.
- **Wolff-Parkinson-White syndrome:** 2% to 3% of sudden cardiac arrest due to WPW caused by AF conducting down bypass tract degenerating into VF.
- **Idiopathic VF:** Diagnosis of exclusion typified by VF induced by early coupled PVCs typically emanating from conduction system. Notably suppressed by isoproterenol and quinidine.
- **Early repolarization syndrome:** Typified by 1-mm ST elevation in two sequential inferior or lateral leads. This ECG pattern is quite nonspecific, occurring in 5% to 10% of general population and increasing risk of sudden death by threefold, or roughly 0.3%.
- **Commotio cordis:** VF as a result of low-velocity projectile impact on the chest wall inducing VF in the absence of sudden death. This is uncommon and occurs in young, typically male, individuals.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of an ECG suspicious of VF includes:

- ECG artifact
- Atrial fibrillation with aberration
- Polymorphic ventricular tachycardia

WORKUP

- Ischemia evaluation is paramount. Cardiac biomarkers should be checked and cardiac catheterization should be performed in most cases.
- A 12-lead ECG of the tachycardia should always be obtained and, whenever possible, compared to the ECG in sinus rhythm if there is any uncertainty about the diagnosis.
- Basic lab testing with focus on electrolytes levels (K and Mg) and hemoglobin.

LABORATORY TESTS

- Electrolyte levels potassium, magnesium
- Hemoglobin level
- Cardiac biomarkers
- Genetic testing should be reserved for specific situations such as when there is a concern for genetically mediated conditions such as hypertrophic cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia or Brugada syndrome

IMAGING STUDIES

- Echocardiogram (rule out structural heart disease).

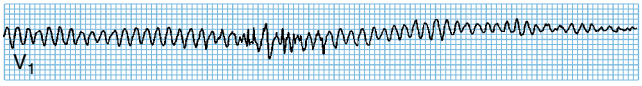

FIG. E1 Ventricular fibrillation. This rhythm strip shows ventricular fibrillation that degenerates further into fine ventricular fibrillation. (From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

- Diagnostic coronary angiography (rule out ischemic etiology).
- Cardiac MRI is indicated if the previous tests are unable to establish the cause of the arrhythmia and to rule out cardiomyopathies such as cardiac sarcoidosis, amyloid, LV noncompaction, arrhythmogenic right ventricular dysplasia.

Rx TREATMENT

ACUTE GENERAL Rx

- Patients with VF are hemodynamically unstable and require emergent unsynchronized defibrillation along with appropriate high-quality CPR as per ACLS protocols.
- Antiarrhythmic therapy with IV amiodarone and/or IV lidocaine is appropriate, particularly if patients have more than one event. IV lidocaine is particularly effective if VF is mediated by cardiac ischemia. Cardiac catheterization is recommended provided no contraindications exist. IV beta blockers are also recommended provided the patient is not in shock and blood pressure is permissive. If the patient is unresponsive after appropriate CPR a hypothermia protocol should be considered to aid in neurologic recovery. If the patient is having multiple episodes of VF despite these measures and is still awake between episodes, sedation and intubation are appropriate to reduce adrenergic drive. Cardiac electrophysiology consultation is appropriate for management of VF.
- Electrolyte supplementation is essential if hypokalemia or hypomagnesemia is detected.

CHRONIC Rx

After acute stabilization has occurred, chronic treatment is dependent on circumstances surrounding VF. If VF occurred within 48 hr of a large MI, then relief of ischemia via PCI, CABG, or lytic therapy is the primary treatment. A patient who has a well-defined ischemic trigger that has been satisfactorily treated likely will not require an implantable cardiac defibrillator, but a wearable external defibrillator could be considered under certain circumstances. Patients with VF in the periinfarction period who survive to hospital discharge have a prognosis similar to patients without arrhythmias in the peri-infarction period. ICD implantation is recommended in patients when there is no clearly reversible trigger, such as acute MI, commotio cordis, or drug overdose. If an inherited ion channelopathy is suspected, such as long QT, Brugada syndrome, or CPVT, genetic testing should be performed, but an ICD is appropriate even before definitive diagnosis is made for secondary prevention of sudden death from VF. If the etiology of VF is unknown after standard workup, cardiac MRI is suggested to work up cardiac sarcoid, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy. If indicated, then cardiac MRI should be done before ICD implantation. If a patient is subsequently diagnosed with inherited arrhythmia syndrome, familial screening should be discussed with the patient.

Cardiac echocardiography plays an important role in long-term risk stratification as well. If a patient's EF remains <35% 3 mo after appropriate revascularization and institution of appropriate heart failure therapy (ACE, beta-blocker therapy), then consideration of ICD is appropriate at that time.

Chronic therapy with antiarrhythmic medications such as amiodarone, mexiletine, or sotalol may be needed even after ICD implantation if the patient presents with multiple appropriate shocks. Continued focus on the trigger of VF such as ischemia or electrolyte disturbance is also critical. Cardiac ablation has been described in rare cases if a distinct triggering PVC is isolated, but this is not as commonly employed as ablation for VT.

DISPOSITION

Patients with sustained VF should be managed in an ICU because of the risk of degeneration to a hemodynamically unstable rhythm. A cardiologist or cardiac electrophysiologist should be consulted.

REFERRAL

All patients with VF should be referred to a cardiologist or a cardiac electrophysiologist.

PEARLS & CONSIDERATIONS

COMMENTS

- Effective VF treatment is strongly dependent on identifying and treating the inciting trigger (i.e., ischemia, cardiogenic shock) while using antiarrhythmic therapy IV amiodarone +/- IV lidocaine for stabilization.
- Hypothermia protocol should be considered in patients who have return of spontaneous circulation after VF arrest who remain comatose upon presentation or who were sedated prior to return of spontaneous circulation.
- ICDs are indicated for secondary prevention of VF independent of the substrate in the absence of a clearly reversible trigger.
- In the peri-infarction period, VT, particularly VT occurring more than 48 hr after MI, is far more predictive of subsequent out-of-hospital sudden death than VF and as such often warrants earlier ICD therapy consideration.
- In managing patients with multiple VF events (VF storm), therapies to reduce adrenergic drive are important, such as IV beta blockers as BP tolerates, aggressive IV sedation with propofol or Versed, or fentanyl along with intubation and electrolyte repletion.
- In patients with suspected long QT or Brugada syndrome, VF storm may be managed differently than VF in an ischemic setting or with structural cardiomyopathy. Long QT syndrome VF storm may prompt use of isoproterenol, magnesium repletion, and consideration of atrial pacing to prevent bradycardia. In treating Brugada syndrome VF storm, use of isoproterenol, quinidine and treatment of fever if it exists can be helpful.

PATIENT & FAMILY EDUCATION

Patients with familial or genetic causes of ventricular arrhythmias should have family screening of first-degree relatives.

RELATED CONTENT

Arrhythmogenic Right Ventricular Dysplasia (Related Key Topic)
Brugada Syndrome (Related Key Topic)
Hypertrophic Cardiomyopathy (Related Key Topic)
Long QT Syndrome (Related Key Topic)
Torsade de Pointes (Related Key Topic)

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SUGGESTED READING

Bunch TJ et al: Patients treated with catheter ablation for ventricular tachycardia after an ICD shock have lower long-term rates of death and heart failure hospitalization than do patients treated with medical management only, *Heart Rhythm* 11(4):533-540, 2014.

BASIC INFORMATION

DEFINITION

- *Ventricular septal defect* (VSD) refers to an abnormal communication through the septum that separates the right and left ventricles of the heart.
- VSDs may be large or small, single or multiple.
- VSDs can be classified according to their anatomic location:
  1. Perimembranous (75% to 80%): This is the most common type of defect. The septal leaflet of the tricuspid valve may become adherent and form a "pouch" of the septum that can limit the left-to-right shunting and lead to self-closure.
  2. Muscular/trabecular (5% to 20%): This defect is entirely surrounded by muscular tissue. Often has less hemodynamic impact, and spontaneous closure is common.
  3. Inlet (8%): Immediately inferior to atrioventricular valve apparatus. This defect commonly lies beneath the septal leaflet of the tricuspid valve; associated with Down syndrome.
  4. Outlet (5%): Includes doubly committed juxtaarterial, supracristal, subpulmonary, and infundibular. This is the least common type of defect. Lies beneath the semilunar valves and is usually found beneath the aortic valve, and it may lead to aortic regurgitation. High prevalence in Asian population, and spontaneous closure is uncommon.

SYNONYM

VSD

ICD-10CM CODES

Q21.0	Ventricular septal defect
I23.2	Ventricular septal defect as current complication following acute myocardial infarction

EPIDEMIOLOGY & DEMOGRAPHICS

- VSDs are one of the most common congenital heart abnormalities.
- VSD accounts for ~25% of all congenital heart defects in children and for approximately 10% of defects in adults (the decrease is a result of spontaneous closure that occurs by adulthood, with the majority occurring prior to 3 yr of age).
- The prevalence of VSD is 3 to 4 infants per 1000 live births and 0.5/1000 adults.
- VSD is found with equal frequency among both males and females.
- VSD may be associated with the following conditions:
  1. Atrial septal defect (35%)
  2. Patent ductus arteriosus (22%)
  3. Coarctation of the aorta (17%)
  4. Subvalvular aortic stenosis (4%)
  5. Subpulmonic stenosis, usually associated with progressive aortic regurgitation caused by prolapse of the aortic cusp through the defect
- Multiple VSDs are more prevalent among patients with tetralogy of Fallot and double-outlet right ventricular defects.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical presentation depends on the direction and volume of the VSD shunt, which is dictated by the size of the defect as well as by the relative resistances of pulmonary and systemic vascular beds. Fig. E1 illustrates the physiology of VSD.
  1. Defects of ≤25% of the aortic annulus diameter are small or restrictive defects (Q_p:Q_s <1.5:1). These typically involve small left-to-right shunts, no left ventricular volume overload, and no pulmonary artery hypertension (PAH).
  2. Defects that are 25% to 75% of aortic annulus diameter are considered to be moderate in size. Small to moderate left-to-right shunting (Q_p:Q_s 1.5 to 2:1), mild to moderate left ventricular volume overload, and mild or no PAH are seen. Patients may have symptoms of congestive heart failure that may improve with medical therapy or with age as the defect decreases in size relative to increasing body size.
  3. Defects of ≥75% of the aortic annulus diameter usually have moderate to large left-to-right shunting (Q_p:Q_s >2:1), left ventricular volume overload, and PAH. These patients usually have a history of congestive heart failure, or they may possibly develop right-to-left shunting (Q_p:Q_s <1:1) in the setting of Eisenmenger syndrome during late childhood, adolescence, or young adulthood. Eisenmenger syndrome—resulting from chronic elevations of pressure and flow—is associated with functional and structural alterations within the pulmonary vasculature.
- Infants may be asymptomatic at birth because of elevated pulmonary artery resistance. During the first few wk of life, pulmonary arterial resistance decreases, thereby allowing for more left-to-right shunting through the VSD. This results in a subsequent increase in flow into the lungs, the left atrium, and the left ventricle, which can potentially cause left ventricular volume overload. Tachypnea, failure to thrive, and congestive heart failure may then ensue.
- In adults with VSD, the shunt is left to right in the absence of pulmonary stenosis and pulmonary hypertension. Patients typically manifest symptoms of left-sided heart failure from left ventricular volume overload and associated eccentric hypertrophy (e.g., shortness of breath, orthopnea, dyspnea on exertion). Presence of relevant longstanding PAH could ultimately lead to right-ventricular hypertrophy and dilation.
- A spectrum of physical findings may be seen, including the following:
  1. Machine-like holosystolic murmur that is heard best along the left sternal border
  2. Murmur becomes shorter as right heart pressures increase
  3. Systolic thrill
  4. Mid-diastolic rumble heard at the apex (increased mitral flow)
  5. S3 heart sound
  6. Rales
- With the development of pulmonary hypertension, the following occur:
  1. An augmented pulmonic component of the S2 heart sound and decrescendo diastolic murmur indicating pulmonary regurgitation
  2. Cyanosis, clubbing, right ventricular heave, and signs of right heart failure (i.e., as seen with Eisenmenger complex, with a reversal of the shunt in a right-to-left direction)

ETIOLOGY

- VSD is usually congenital but can be acquired.
- Acquired VSD may result from myocardial infarction, procedural complication (postsurgical residual leak, aortic valve replacement, septal myectomy, or alcohol ablation for hypertrophic cardiomyopathy), severe endocarditis, or trauma.
- Postinfarct ventricular septal defect (PIVSD) typically occurs 1 to 5 days after the event in 0.2% of patients in the current fibrinolytic or primary angioplasty era.

DIAGNOSIS

The diagnosis of VSD can be suspected during a physical examination. Imaging studies—particularly transthoracic echocardiography with color Doppler—establish the diagnosis.

DIFFERENTIAL DIAGNOSIS

On the basis of the physical examination alone, the diagnosis of VSD may be confused with other causes of systolic murmurs, such as mitral regurgitation, tricuspid regurgitation, aortic stenosis, pulmonary stenosis, and hypertrophic cardiomyopathy.

WORKUP

Any person who is suspected of having a VSD should undergo an ECG, a chest radiograph, and an echocardiogram.

LABORATORY TESTS

- Laboratory tests are not specific.
- The CBC may show polycythemia, especially in patients with Eisenmenger complex.
- Arterial blood gas results may demonstrate hypoxemia, which does not correct with supplemental oxygen.

IMAGING STUDIES

- ECG findings vary in accordance with the size of the VSD and depending on whether pulmonary hypertension is present. Volume loading of the left ventricle might result in left-ventricular hypertrophy and left atrial enlargement, whereas raised right-ventricular pressure due to either pulmonary hypertension or obstruction to the pulmonary

outflow tract could lead to right-ventricular hypertrophy findings.
- Chest x-ray findings in patients with VSD include the following:
  1. Cardiomegaly that results from left ventricular volume overload that directly relates to the magnitude of the shunt
  2. The enlargement of the proximal pulmonary arteries along with the redistribution and pruning of the distal pulmonary vessels as a result of sustained pulmonary hypertension (Fig. E2, *A*)
- Echocardiography is the imaging modality of choice for the diagnosis of VSD:
  1. Two-dimensional echocardiography and color Doppler display the size and location of the VSD (Fig. E2, *B*), the chamber sizes, ventricular function, the presence of aortic valve prolapse or regurgitation, outflow tract obstruction, and the presence of tricuspid regurgitation.
  2. Continuous-wave Doppler approximates the gradient between the left and right ventricles and estimates the pulmonary artery pressure.
  3. The magnitude of the shunt can be determined by the calculation of the pulmonary-to-systemic flow ratio with the use of echocardiography.
- Heart catheterization is primarily indicated to assess operability of VSD patients with PAH based on their pulmonary vascular resistance (PVR) and in patients in whom the noninvasive testing was inconclusive, and further information, such as quantification of shunting and assessment of pulmonary pressures, is required.
- MRI, computed tomography or (3D) transesophageal echocardiography can be useful to assess the pulmonary artery, the pulmonary vein, and the aortic anatomy and to confirm the anatomy of unusual VSDs (e.g., inlet or apical defects) that are inadequately visualized with conventional surface echocardiography.

Rx TREATMENT

The decision to close a VSD depends on the type, size, and shunt severity as well as the patient's pulmonary vascular resistance, functional capacity, and associated valvular abnormalities.

NONPHARMACOLOGIC THERAPY

- Patients with a small VSD with a large left-to-right ventricular pressure gradient, a pulmonary-to-systemic blood flow ratio (Q_p:Q_s) of less than 1.5:1, no evidence of pulmonary hypertension (i.e., restrictive defect), and absence of associated infective endocarditis or valvular regurgitation can be observed.
- Oxygen for hypoxemia and a low-salt diet are recommended for patients with congestive heart failure.

ACUTE GENERAL & CHRONIC Rx

Closure of the VSD is indicated for the following patients:

- Infants with congestive heart failure and failure to thrive. Unrestrictive VSDs require surgical intervention within the first 2 yr of life to prevent PAH.
- Children between the ages of 1 and 6 yr with persistent VSD and a Q_p:Q_s of ≥2.
- Adults with a Q_p:Q_s of ≥1.5, clinical evidence of left-ventricular volume overload, and with pulmonary artery pressure that is less than two thirds of the systemic pressure and pulmonary vascular resistance that is less than two thirds of the systemic vascular resistance (class I, level of evidence B).
- Worsening aortic regurgitation caused by VSD (class II_a, level of evidence C).
- Positive history of infective endocarditis (IE) (class II_B, level of evidence C).
- Surgical closure is not indicated for VSD with severe irreversible PAH with high PVR (pulmonary artery systolic pressure greater than two thirds systemic pressure or pulmonary vascular resistance greater than two-thirds systemic) (class III, level of evidence C). In this population, pharmacotherapy with bosentan (class I) or combination with phosphodiester type-5 inhibitors can be considered.

Surgical closure with Dacron or Gore-Tex patches or primary surgical closure has long been the gold standard of therapy. It has low operative mortality (<2%) at experienced centers. However, surgery still carries a small risk of complete heart block, postpericardiotomy syndrome, wound infection, and neurologic sequelae related to cardiopulmonary bypass. The transcatheter approach to VSD closure is becoming an increasingly accepted modality of treatment for appropriately selected patients. Some studies have shown similar success rates for both surgical and percutaneous closures, and there are significantly fewer complications, days in the hospital, and blood transfusions after percutaneous closures. For patients with difficult vascular access, a periventricular approach using a partial median sternotomy allows for a less invasive repair, often without cardiopulmonary bypass.

Catheter-based closure in muscular VSD may be considered, especially if the VSD is remote from the tricuspid valve and the aorta. Device closure is indicated in residual defects after prior attempts at surgical closure, restrictive VSDs with either a significant left-to-right shunt (Q_p:Q_s >1.5:1) or history of IE, trauma, or iatrogenic artifacts after surgical replacement of the aortic valve.

Surgery still remains the treatment of choice in patients with large defects, coexistent congenital anomalies requiring surgical correction, and defects with close proximity to the aortic valve. Subpulmonic VSDs may require surgery due to the increased risk of aortic valve prolapse. Perimembranous VSD with more than trivial aortic regurgitation should be referred to surgery. Availability of early reperfusion therapy has led to a decline in incidence of postinfarct VSDs (PIVSDs). Surgical closure remains the gold standard in the acute setting or for large (>15 mm) septal ruptures. In the subacute or chronic setting, small or medium PIVSD (<15 mm) can be treated with percutaneous closure with comparable mortality to surgery. Percutaneous closure may also be considered as a temporizing measure to clinically stabilize patients prior to surgical correction. PIVSDs generally arise within 3 to 5 days of the acute event, and even earlier following reperfusion therapy. PIVSDs usually carry a high mortality rate of ~95% of those treated medically and ~50% with surgical repair. Surgical management within 10 days has better outcomes than waiting for cardiac stabilization.

DISPOSITION

- The natural history of an isolated VSD depends on the type of defect, its size, and any associated abnormalities.
- Approximately 75% to 80% of small VSDs close spontaneously by the time the patient reaches the age of 10 yr.
- Only 10% to 15% of large VSDs will close spontaneously.
- Large VSDs that are left untreated may lead to arrhythmias, congestive heart failure, PAH, and Eisenmenger complex.
- Eisenmenger complex carries a poor prognosis, with most patients dying before the age of 40 yr.
- Issues to monitor in adults with unrepaired or repaired and catheter-closed VSDs include the following:
  1. Development of aortic regurgitation
  2. Assessment of associated coronary artery disease
  3. Development of tricuspid regurgitation
  4. Assessment of the degree of left-to-right shunting (in unrepaired or residual VSD after repair)
  5. Ventricular dysfunction
  6. Assessment of pulmonary pressure
  7. Development of subpulmonary stenosis (usually as a result of midcavity obstruction of the right ventricle due to hypertrophy of muscle bands, also referred to as a double-chambered right ventricle)
  8. Development of discrete subaortic stenosis
  9. Development of arrhythmia or heart block
  10. Thromboembolic complications
  11. Infective endocarditis
- After closure, late survival is excellent when ventricular function is normal. PAH may improve, progress, or remain the same. Late operations may be required for tricuspid or aortic regurgitation.

REFERRAL

All infants and children diagnosed with VSD should be referred to a pediatric cardiologist. Adults with VSD should be referred to an adult cardiologist. Cardiothoracic surgeons who have experience with congenital heart disease surgery should be consulted if surgery is indicated.

FOLLOW-UP

- Adults with no residual VSD, no associated lesions, and normal pulmonary artery pressure do not require continued follow-up at a regional adult congenital heart disease (ACHD) center.

- Adults with VSD with residual heart failure, shunts, PAH, AR, or RV outflow tract (RVOT) or LV outflow tract (LVOT) obstruction should be seen at least annually at an ACHD regional center (class I, level of evidence C).
- Adults with a small residual VSD and no other lesions should be seen every 3 to 5 yr at an ACHD regional center (class I, level of evidence C).
- Adults with device closure of a VSD should be followed up every 1 to 2 yr at an ACHD center depending on the location of the VSD and other factors (class I, level of evidence C).
- Patients who develop bifascicular block or transient trifascicular block after VSD closure are at risk in later yrs for the development of complete heart block and should be followed up yearly by history and ECG and have periodic ambulatory monitoring and/or exercise testing.

PEARLS & CONSIDERATIONS

COMMENTS

- A loud murmur does not imply a large VSD. Small, hemodynamically insignificant VSDs can cause loud murmurs.
- In patients with Eisenmenger complex, the right-to-left shunting across the VSD is usually not associated with an audible murmur.
- Air-eliminating filters should be used on intravenous lines to prevent air embolism in patients with cyanosis indicating right-to-left shunting.
- The risk of patients with unrepaired VSD developing infective endocarditis is 4%. The risk is higher if aortic insufficiency is present.
- For patients with endocarditis, routine antibiotic prophylaxis for dental or surgical procedures is not indicated for isolated VSDs, except in the following circumstances:
  1. In the presence of complex congenital heart disease with cyanosis
  2. In the presence of a residual VSD after surgical closure
  3. During the first 6 mo after surgical patch or percutaneous transcatheter closure
- Any patient with a newly diagnosed murmur or hemodynamic compromise after a myocardial infarction should undergo evaluation for possible VSD.
- Pregnancy with a VSD is generally well tolerated in women with small VSDs, no pulmonary artery hypertension, and no associated lesions. Women with large shunts may experience arrhythmias, ventricular dysfunction, and the progression of pulmonary hypertension.
- Women with VSDs and severe pulmonary artery hypertension or Eisenmenger physiology should be counseled against pregnancy because of associated excessive maternal and fetal mortality.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Ventricular Septal Defect (VSD) (Patient Information)

AUTHORS: **Johannes Steiner, MD,** and **Trace Barrett, MD**

SUGGESTED READINGS

Bhatt A et al: Congenital heart disease in the older adult: a scientific statement from the American Heart Association, *Circulation* 131(21):1884-1931, 2015.

Penny DJ et al: Ventricular septal defect, *Lancet* 9771(377):1103-1112, 2011.

Stout KK et al: 2018 AHA/ACC guideline for the management Of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, *J Am Coll Cardiol* 73(12):1494-1563, 2019.

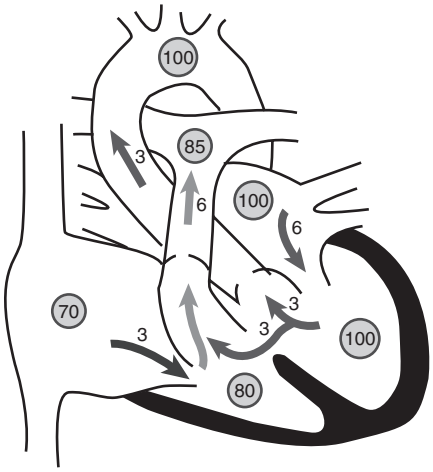

FIG. E1 Physiology of a large ventricular septal defect (VSD). Circled numbers represent oxygen saturation values. The numbers next to the arrows represent volumes of blood flow (in L/min/m^2). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Q_p:Q_s) of 2:1. Desaturated blood enters the right atrium from the vena cava at a volume of 3 L/min/m^2 and flows across the tricuspid valve. An additional 3 L of blood shunts left to right across the VSD, the result being an increase in oxygen saturation in the right ventricle. 6 L of blood is ejected into the lungs. Pulmonary arterial saturation may be further increased because of incomplete mixing at right ventricular level. 6 L returns to the left atrium, crosses the mitral valve, and causes a mid-diastolic flow rumble. 3 L of this volume shunts left to right across the VSD, and 3 L is ejected into the ascending aorta (normal cardiac output). (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, WB Saunders.)

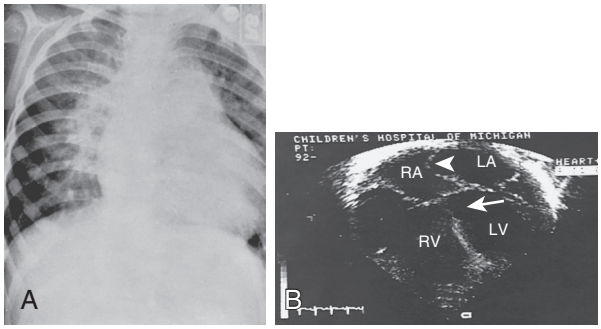

FIG. E2 A, Chest roentgenogram of a child with a large ventricular septal defect, large pulmonary blood flow, and pulmonary hypertension but only mild elevation of peripheral vascular resistance. This is reflected in the evidence of left and right ventricular enlargement, the enlargement of the main pulmonary artery, and a marked increase in pulmonary blood flow. **B,** Apical four-chamber echocardiographic view of ventricular septal defect (large arrow). The small arrow points to the interatrial septum. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. **(A,** From Pacifico AD et al: Surgical treatment of ventricular septal defect. In Sabiston DC Jr, Spencer FC [eds]: *Surgery of the chest,* ed 5, Philadelphia, 1990, WB Saunders. **B,** courtesy of Richard Humes, MD, Children's Hospital of Michigan, Detroit.)

Ventricular Tachycardia

BASIC INFORMATION

DEFINITION

- Ventricular tachycardia (VT) can be classified based on time (duration) or morphology.
- Nonsustained ventricular tachycardia (NSVT) is defined as beats originating from the ventricle, lasting from 3 to 30 seconds or for <30 seconds, at a rate >100/min.
- Sustained ventricular tachycardia is defined as above but lasts >30 seconds or produces symptoms in the patient and/or requires early intervention due to hemodynamic embarrassment.
- Ventricular tachycardia can be monomorphic or polymorphic, and the etiology, significance, and treatment of these two types of VT are different.

SYNONYMS

VT
Nonsustained paroxysmal ventricular tachycardia (NSVT) (Fig. E1)
Sustained ventricular tachycardia
Ventricular tachycardia, monomorphic
Ventricular tachycardia, nonsustained
Ventricular tachycardia, paroxysmal
Ventricular tachycardia, polymorphic
Ventricular tachycardia, sustained

ICD-10CM CODE
I47.2 Ventricular tachycardia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The actual incidence and prevalence of VT in the general population is unknown. VT, especially NSVT, can be seen in both structurally normal and abnormal hearts, although it is far more common in the latter. In apparently healthy, asymptomatic individuals, the incidence is estimated at 0% to 3%. The prevalence of ventricular arrhythmias is approximately 12 per 10,000 persons under age 55 and increased to between 20 (females) and 59 (males) per 10,000 persons ≥65 yr of age.

For details on incidence of NSVT in various cardiac conditions, please refer to Table E1.

RISK FACTORS: The presence of structural heart disease is a strong risk factor for VT, but there are multiple, specific types of VT seen in patients without any structural heart disease. Coronary heart disease is responsible for the majority of cases of VT.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients may be asymptomatic, or they may present with any combination of palpitations, dizziness, syncope, chest pain, shortness of breath, seizures, or even cardiac arrest.
- History of structural heart disease, especially coronary artery disease and a prior myocardial infarction, is a strong predictor of VT. Patients may also have a history of pacemaker or defibrillator implantation. A family history of sudden death must also be sought.
- Physical findings of AV dissociation may be seen by the astute observer. These include cannon A waves in the neck and variability in intensity of heart sounds. Marked fluctuations in the blood pressure because of the variability in the degree of left atrial contribution to left ventricular filling and cardiac output.
- The patient may also present physical findings of congestive heart failure including an S3 gallop, pedal edema, or crackles at the lung bases.

Fig. E2 shows initiation and termination of VT by means of programmed ventricular stimulation.

ETIOLOGY

Sustained monomorphic VT (Fig. E3) is mostly caused by reentry around a scar in the ventricular wall. The scar is most commonly the result of an old myocardial infarction, but arrhythmogenic RV cardiomyopathy (ARVC), nonischemic dilated cardiomyopathy, sarcoidosis, Chagas disease, tuberculosis, surgical incisions for repair of congenital heart disease, and ventricular volume reduction surgery can all cause scars in the myocardium. Fibrosis in the scar creates areas of anatomical conduction block, and fibrosis between surviving myocytes reduces cell-to-cell coupling, thereby distorting the path of propagation and causing areas of slow conduction, which promotes reentry.

Monomorphic VT can also be seen in patients without any evidence of structural heart disease (idiopathic VT). This subgroup represents 10% of all patients with VT and includes right ventricular outflow tract (RVOT) VT, which is due to triggered activity and is sensitive to adenosine; paroxysmal sustained VT, which is sometimes considered a variant of RVOT VT; and idiopathic left ventricular tachycardia, which originates from the posterior septum with underlying mechanism of reentry and is sensitive to verapamil.

Polymorphic VT is usually the result of active myocardial ischemia, electrolyte abnormalities (hypokalemia, hypomagnesemia), or genetic conditions such as LQTS, BRS, and CPVT. It may also be seen in HCM, various types of nonischemic cardiomyopathy, and idiopathic VF. The mechanisms are poorly understood but likely involve an initiating trigger that interacts with multiple rotors in the substrate to maintain the arrhythmia. Conditions that can cause polymorphic VT/VF in the absence of structural heart disease are summarized in Table E2.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of an ECG suspicious of VT includes:

- SVT with aberrancy, either with a preexisting bundle branch block or a rate-related bundle branch block
- SVT in a patient taking anti-arrhythmic drugs, e.g., IA or IC agents
- Antidromic tachycardia from ventricular preexcitation
- Ventricular paced rhythms
- ECG artifact

Differentiating sustained VT from other causes of wide complex tachycardia may be difficult, particularly if a high-quality 12-lead ECG is not available during the time of the arrhythmia. Stepwise criteria favoring VT in patients with wide-complex tachycardias using different algorithms are summarized in Table E3.

The following ECG characteristics strongly favor VT as opposed to SVT: Northwest (right superior) axis, QRS width >160 ms, AV dissociation fusion beats, and capture beats. The last three are highly specific for VT. The ECG hallmark for the diagnosis of VT is a wide complex tachycardia with the obvious presence of AV dissociation.

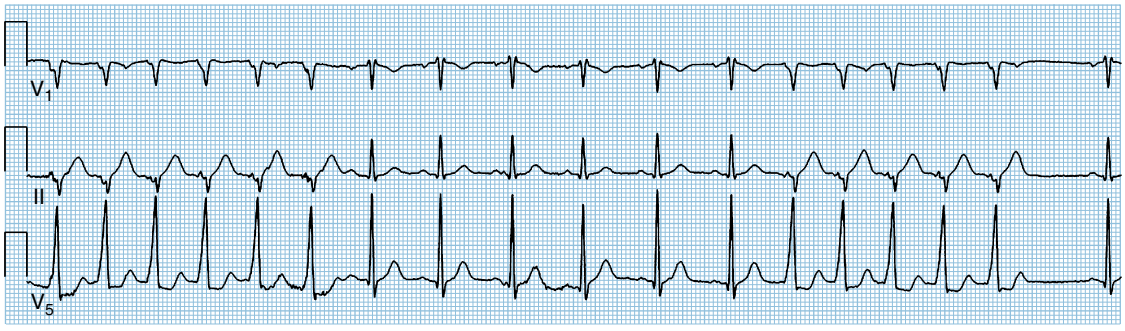

FIG. E1 Nonsustained ventricular tachycardia. This lead *V1, II,* and *V5* rhythm strip shows repetitive runs of nonsustained wide QRS complex tachycardias (five to six beats long, rate ~125 to 135 bpm) that represent nonsustained ventricular tachycardia. The second run is followed by a compensatory pause. There is atrioventricular dissociation evident in the first run on lead V1. (From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

TABLE E1 Reported Prevalence of Nonsustained Ventricular Tachycardia in Different Cardiac Conditions

Condition	Prevalence
Apparently healthy individuals	0%-3%
Non-ST ACS (2 to 9 days after admission)	18%-25%
Acute MI (early phase)	45%-75%
Reperfused acute MI (later than 1 week)	7%-13%
Heart failure (LVEF <30-40%)	30%-80%
DCM	40%-50%
HCM	25%-80%
Significant valve disease	≤25%
Hypertension	8%
Hypertension and left ventricular hypertrophy	12%-28%

DCM, Dilated cardiomyopathy; *HCM,* hypertrophic cardiomyopathy; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction; *Non-ST ACS,* non–ST-segment elevation acute coronary syndrome.
From Saksena S et al: *Electrophysiological disorders of the heart,* ed 2, Philadelphia, 2011, Saunders.

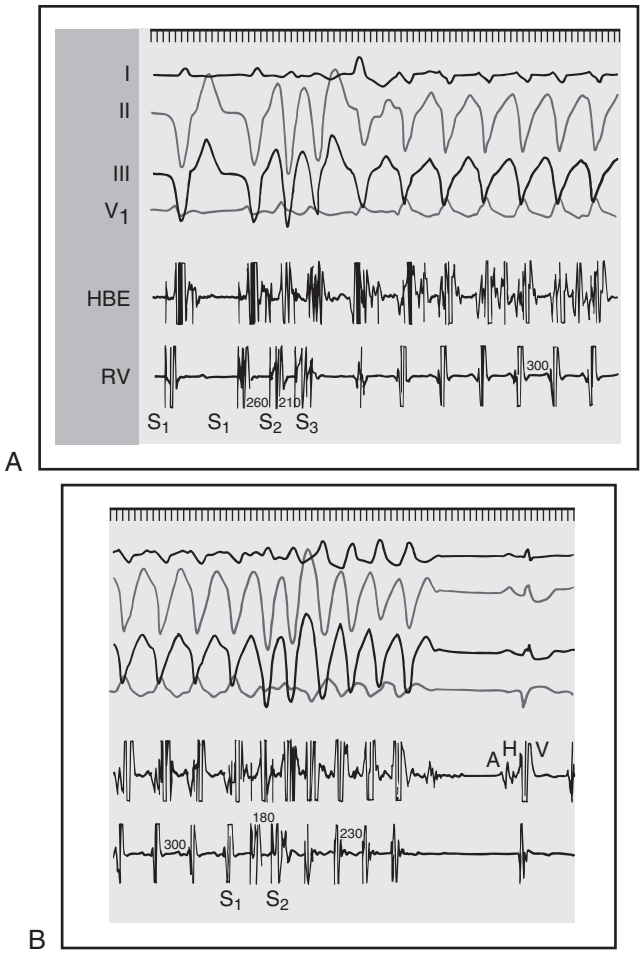

FIG. E2 Initiation and termination of ventricular tachycardia (VT) by means of programmed ventricular stimulation. The last two ventricular paced beats at a cycle length of 600 milliseconds are shown in **A.** A premature stimulus *(S2)* at an *S1-S2* interval of 260 milliseconds and another premature stimulus *(S3)* at a cycle length of 210 milliseconds initiate a sustained monomorphic VT at a cycle length of 300 milliseconds. **B,** Two premature ventricular stimuli *(S1-S2)* create an unstable VT that persists for several beats at a shorter cycle length (230 milliseconds) and then terminates, followed by sinus rhythm. *HBE,* His bundle electrogram; *RV,* right ventricle. (From Bonow RO et al: *Heart disease,* ed 9. Philadelphia, 2012, Saunders.)

Additional assessment is based upon QRS morphology. Most VT can be classified as either RBBB-type (overall positive in V1) or LBBB-type (overall negative in V1). The following criteria favoring VT can be applied for the respective types:

- RBBB type: Monophasic R; notched waveform with a taller left peak Rr'; biphasic RS or QR pattern.
- LBBB type in V1: R-wave >30 ms, slurred or notched S wave downstroke, delayed S nadir (QRS onset to S nadir >60 ms).
- RBBB-type tachycardias V6 shows QRS onset to predominant peak or nadir in lead V6 of 70 ms or rS pattern (R-to-S <1).
- LBBB type, criteria in V6: VT is favored in presence of a Q wave in v6.
- aVR: Presence of an initial R-wave in AVR and width of an initial r or q wave >40 ms.

WORKUP

- Lab testing should especially focus on checking K and Mg levels.
- A full 12-lead ECG of the tachycardia should always be obtained, whenever possible, and compared to the ECG in sinus rhythm if there is any uncertainty about the diagnosis. The electrocardiographic pattern of idiopathic VT by anatomic location is summarized in Table E4.
- This should be followed by an echocardiogram and ischemia evaluation with diagnostic coronary angiography and/or nuclear stress testing. Exercise testing should be performed because it may aid in provoking as well as establishing patient response to exercise-induced arrhythmias, including catecholaminergic *polymorphic* VT.
- An MRI of the heart is indicated if these tests are unable to establish the cause of the arrhythmia.
- Ambulatory ECG, event monitors, and implantable recorders are appropriate to evaluate for QT interval changes and T-wave alternans, judge therapy, evaluate risk, and to allow for symptom-rhythm correlation.
- Electrophysiologic testing is useful for the inducibility of VT, to guide ablation, the evaluation of drug effects, the assessment of the risk of recurrent VT, the loss of consciousness with arrhythmia as a suspected cause, and the assessment of indications for ICD therapy.

LABORATORY TESTS

- Potassium, magnesium
- Genetic testing should be reserved for specific situations, i.e., when there is a concern for genetically mediated conditions such as LQTS, HCM, CPVT, or BRS

IMAGING STUDIES

An echocardiogram and ischemia evaluation with diagnostic coronary angiography and/or nuclear stress testing is recommended to

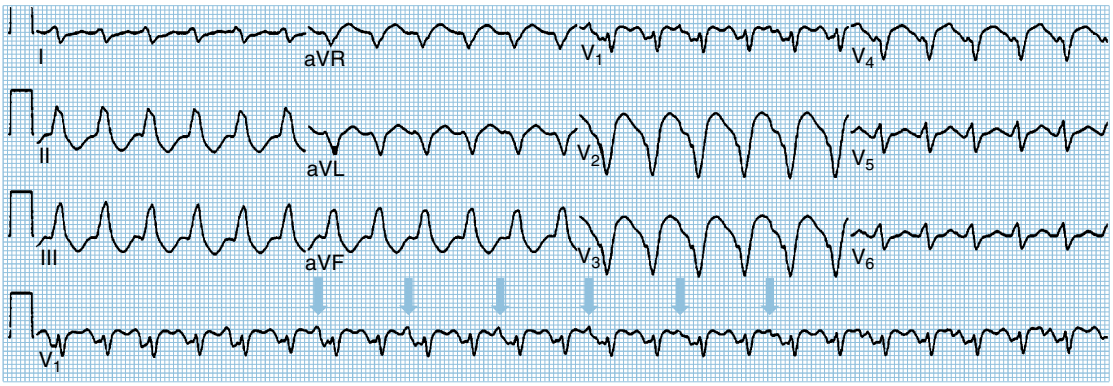

FIG. E3 Sustained monomorphic ventricular tachycardia. (From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

TABLE E2 Conditions That Can Cause Polymorphic VT/VF in the Absence of Structural Heart Disease and Potential Therapies

Clues	Test to Consider	Diagnoses	Therapies
Long QT/T-wave alternans	ECG/monitor	Congenital LQTS	Beta-blockers/stellatectomy
TdP pattern	Epinephrine challenge		Avoid QT-prolonging drugs
History of seizures	Genetic testing		Mexilitine/flecainide (LTQ3)
Specific trigger (loud noise)			Pacemaker/ICD
Long QT/T-wave alternans	ECG/Monitor	Acquired LQTS	Mg^{2+}/K^{+}
TdP pattern			Stop offending drug
Renal failure			Temporary pacing
New medication or drug abuse			
AV block	ECG/monitor	Bradycardia	Pacemaker
Incomplete RBBB with STE in leads V1 and V2	ECG	Brugada syndrome	Isoproterenol/quinidine
Fever	Drug challenge Genetic testing		Antipyretic Ablation ICD
Monomorphic PVC trigger	ECG/Monitor	Focal PVC origin	Ablation/ICD
J-point elevation	ECG	Early repolarization	ICD
Ventricular preexcitation	ECG	WPW	Ablation
Short QT interval	ECG	Short QTS	ICD
Bidirectional VT pattern exercise-induced	Digoxin level Exercise test Genetic testing	CPVT Andersen-Tawil syndrome Digoxin toxicity	Stop digoxin Beta-blockers/CCBs/flecainide ICD
STE and chest pain	Proactive testing	Coronary spasm	Vasodilators/coronary stent ICD
Short-coupled PVC trigger	ECG/Monitor	Idiopathic	ICD

CCBs, Calcium channel blockers; *CPVT,* catecholaminergic polymorphic ventricular tachycardia; *ECG,* electrocardiogram; *ICD,* implantable cardioverter-defibrillator; K^{+}, potassium ion; *LQTS,* long QT syndrome; Mg^{2+}, magnesium ion; *PVC,* premature ventricular complex; *RBBB,* right bundle branch block; *short QTS,* short QT syndrome; *STE,* ST elevation; *TdP,* torsade de pointes; *VT,* ventricular tachycardia; *WPW,* Wolff-Parkinson-White (syndrome).

rule out structural heart disease and ischemia. An MRI of the heart is indicated if these tests are unable to establish the cause of the arrhythmia, to rule out cardiomyopathies such as cardiac sarcoidosis, amyloid, LV noncompaction, arrhythmogenic right ventricular dysplasia, etc.

Rx TREATMENT

ACUTE GENERAL Rx

The initial management of a patient with VT depends on the hemodynamic stability of the patient. Emergent management is required in unstable patients, while additional time may be spent determining the etiology and treating any underlying precipitating factors in patients who are hemodynamically stable. All patients with VT should have a brief immediate assessment of the symptoms, vital signs, and level of consciousness to determine if they are hemodynamically stable or unstable. In unstable patients emergent synchronized cardioversion (or defibrillation for polymorphic rhythms) is needed. Those who subsequently become pulseless or unresponsive should be managed as per standard ACLS resuscitation protocols. An approach to nonsustained tachycardia is described in Fig. E4 and Table E5. Table E6 and Fig. E5 illustrate the management of sustained ventricular tachycardia.

If the patient is hemodynamically stable, either IV amiodarone, lidocaine (especially if there is a suspicion of ongoing ischemia), or procainamide may be used. In the case of a patient with sustained monomorphic VT and a known structurally normal heart, IV beta blockers or calcium blockers may be used. It must be remembered that use of all these agents may be associated with hemodynamic deterioration and an external defibrillator must be made available at all times.

Electrolyte supplementation is essential if hypokalemia or hypomagnesemia is detected.

TABLE E3 Stepwise Criteria Favoring Ventricular Tachycardia in Patients with Wide-Complex Tachycardias Using Different Algorithms

Kindwall Criteria[†]	Wellens Criteria[‡]	Brugada Criteria[§]	Miller Criteria[‖]
R >30 msec in V1 or V2 → VT	AV dissociation → VT	Absence of RS complex in all precordial leads → VT	Initial R wave in aVR → VT
Any Q in V6 → VT	QRS width >140 msec → VT	Longest R/S interval >100 msec in any precordial lead → VT	aVR with initial r or q >40 msec in duration → VT
>60 msec to S wave nadir in V1 or V2 → VT	Left axis deviation >−30 degrees → VT	AV dissociation → VT	aVR with a notch on the descending limb of a negative-onset and predominantly negative QRS in aVR → VT
Notched downstroke S wave in V1 or V2 → VT	If RBBB morphology, monophasic or biphasic QRS in V1 → SVT or R-to-S ratio of <1 in V6 → VT	If RBBB morphology, monophasic R or qR in V1 → VT R taller than R′ → VT rS in V6 → VT	In aVR, mV of initial 40 msec divided by terminal 40 msec ($v_i/v_t \leq 1$) → VT
	If LBBB morphology, S in V1-V2 → VT	If LBBB morphology, initial R >40 msec in duration → VT Slurred or notched S in V1 or V2 → VT Beginning Q or QS in V6 → VT	

LBBB, Left bundle branch block; *RBBB,* right bundle branch block; *VT,* ventricular tachycardia.
[†]Kindwall KE, Brown J, Josephson ME: Electrocardiographic criteria for ventricular tachycardia in wide complex left bundle branch block morphology tachycardias, *Am J Cardiol* 61:1279, 1988.
[‡]Wellens HJ, Bär FW, Lie KI: The value of the electrocardiogram in the differential diagnosis of a tachycardia with a widened QRS complex, *Am J Med* 64:27, 1978.
[§]Brugada P et al: A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex, *Circulation* 83:1649, 1991.
[‖]Vereckei A et al: New algorithm using only lead aVR for differential diagnosis of wide QRS complex tachycardia, *Heart Rhythm* 5:89, 2008.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

CHRONIC Rx

Chronic therapy of patients with VT usually requires multiple therapeutic modalities, including the ICD, antiarrhythmic drugs, catheter ablation, and surgery. An implantable cardioverter-defibrillator (ICD) is indicated for all patients who survive monomorphic VT in the setting of structural heart disease or prior MI, since it indicates the presence of a scar and risk of subsequent arrhythmias. Patients with idiopathic VT and structurally normal hearts generally do not require an ICD, but in cases of syncope associated with VT that cannot be successfully treated with ablation, it may be considered. Management of hemodynamically stable VT in patients with prior MI and normal LVEF remains under debate, but there is a consensus of considering VT ablation as initial therapy before ICD placement. For polymorphic VT, a reversible cause such as ischemia or electrolyte disturbances can sometimes be found, and an ICD may not be appropriate under these circumstances.

Chronic therapy with antiarrhythmic medications such as amiodarone, mexiletine, or sotalol may be needed even after ICD implantation if the patient presents with multiple appropriate shocks. No antiarrhythmic drug has shown mortality benefit in patients with monomorphic VT except beta-blockers. Use of antiarrhythmic medications is thus limited as an adjunct to catheter ablation in patients who cannot receive an ICD or in patients with frequent arrhythmia and ICD shocks. Catheter ablation of VT, particularly if performed early after first appropriate ICD discharge, is also very effective in preventing further ICD discharges and is associated with improved acute and long-term outcomes. For patients with refractory VT, surgical cardiac sympathetic denervation may be beneficial.

DISPOSITION

Patients with sustained VT, either monomorphic or polymorphic, should always be managed in an intensive care unit due to the risk of degeneration to a hemodynamically unstable rhythm. An electrophysiologist should be consulted.

REFERRAL

All patients with VT or NSVT should be referred to a cardiologist or a cardiac electrophysiologist.

PEARLS & CONSIDERATIONS

COMMENTS

- Use of antiarrhythmic drugs, especially IC agents, to treat NSVT is associated with increased mortality (CAST trial), while beta blockers have been shown to be helpful.
- In patients with coronary disease, NSVT has not been shown to have an adverse significance if LVEF is >40%. If the EF is below 40%, the MUSTT trial showed a benefit of EP-guided ICD therapy over antiarrhythmic agents such as mexiletine, propafenone, sotalol, or amiodarone. Patients with LVEF <35% are candidates for prophylactic ICD implantation based on the MADIT II and SCDHeFt trials.
- In hypertrophic cardiomyopathy, NSVT does seem to confer an increased risk of sudden death, especially if symptomatic, prolonged, or repetitive.
- There are certain conditions in which NSVT does not seem to have an adverse significance and does not predict sudden cardiac death. These include nonischemic dilated cardiomyopathy, mitral valve prolapse, mitral regurgitation, and absence of structural heart disease.

PATIENT & FAMILY EDUCATION

Patients with familial or genetic causes of ventricular tachycardia should have family screening of first-degree relatives.

RELATED TOPICS

Arrhythmogenic Right Ventricular Dysplasia (Related Key Topic)
Brugada Syndrome (Related Key Topic)
Long QT Syndrome (Related Key Topic)
Torsade de Pointes (Related Key Topic)

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TABLE E4 Electrocardiographic Pattern of Idiopathic Ventricular Tachycardia (VT) by Anatomic Location

Location	ECG Pattern
Outflow Tract VT	LBBB morphology and inferior axis
Right ventricular outflow tract (RVOT)	Later precordial transition (V3 or later) Narrower R wave duration and lower R/S wave amplitude ratio in V1 and V2
Left ventricular outflow tract (LVOT)	Early precordial transition (by V_3) Earlier precordial transition than SR Broader R wave duration and greater R/S wave amplitude ratio in V1 and V2 Notch (qrS) in V1 or V2
Left aortic cusp	"M" or "W" pattern in V1 Monophasic R by V1/V2 Greater R wave II/III ratio Lead I QS or rS
Right aortic cusp	Monophasic R by V2/V3 Positive notched R-wave in lead I
Aortomitral continuity	qR in lead V1 Positive concordance across precordium Rs/rs complex in lead I R wave ratio <1 in II/III
Epicardial	MDI >55% QS in lead I QS in leads II, III, and aVF (if superiorly directed, near MCV) Q-wave ratio in aVL/aVR >1.4 or S wave amplitude >1.2 mV "Transition break," specifically a loss of R from leads V1 to V2 (QS or rS) with prominent R by V3 (suggests near anterior interventricular vein)
Pulmonary artery	Tall R wave in the inferior leads Larger Q wave ratio in aVL/aVR Larger R/S amplitude in lead V2 Larger Q wave ratio in aVL/aVR Larger R/S amplitude in lead V2
Tricuspid annular	LBBB morphology and inferior or superior axis R wave in lead I R or r with overall positive polarity in aVL Later precordial transition (>V3)
Tricuspid inflow or parahisian	LBBB morphology and inferior axis Large R wave in lead I R wave with flat/positive polarity or "w" pattern in aVL
Mitral annular (MA)	RBBB pattern with concordance in leads V1 to V6 Anterior MAVT: positive QRS polarity in leads II, III, and aVF and negative QRS polarity in leads I and aVL Posterior or posteroseptal MAVT: negative QRS polarity in leads II, III, and aVF and positive QRS polarity in leads I and aVL
Fascicular VT	
Left posterior fascicle	RBBB and left axis deviation (LAFB pattern) rsR′ in V1 q in I and aVL Narrow QRS ≤140 msec
Left anterior fascicle	RBBB and right axis deviation (LPFB pattern) Narrow QRS <140 msec
Left septal	Incomplete RBBB (QRSd ~100-110 msec) and normal axis
Papillary Muscle VT	RBBB; can have varied axes
Posterior papillary muscle	qR or R in V1 Absent Q in leads I and aVL
Anterior papillary muscle	qR or R in V1 rS in leads I and aVL
Crux VT	Leftward-superior axis QRS Delayed intrinsicoid deflection Basal crux: LBBB pattern with early precordial transition Apical crux: midprecordial transition with QS in V5/V6

LBBB, Left bundle branch block; *RBBB*, right bundle branch block.

(Modified from Hoffmayer KS, Gerstenfeld EP: Diagnosis and management of idiopathic ventricular tachycardia *Curr Probl Cardiol* 38:131-158, 2013. In Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

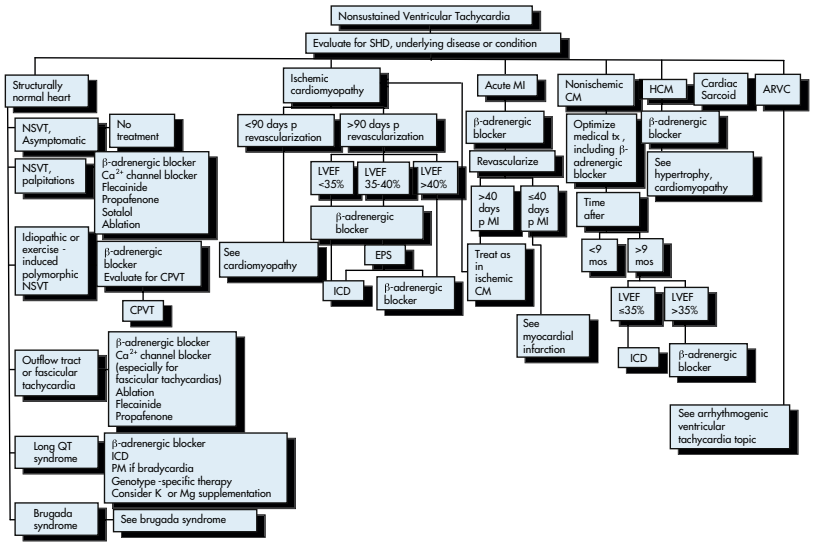

FIG. E4 Nonsustained ventricular tachycardia. *ARVC,* Arrhythmogenic right ventricular cardiomyopathy; *CM,* cardiomyopathy; *CPVT,* catecholaminergic polymorphic ventricular tachycardia; *EP,* electrophysiologic study; *HCM,* hypertrophic cardiomyopathy; *ICD,* implantable cardioverter defibrillator; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction; *NSVT,* nonsustained ventricular tachycardia; *PM,* pacemaker. (Modified from Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

TABLE E5 Management of Nonsustained Monomorphic and Polymorphic Ventricular Tachycardia

Setting	Therapy	Comments
Normal LV function	• No symptoms, no heart disease: No therapy • Young patient with bidirectional (or polymorphic) VT that may be life-threatening (CPVT): beta-adrenergic blocker • Symptoms of palpitations, no heart disease: beta-adrenergic blocker (e.g., acebutolol, 200-800 per day) • Idiopathic LV fascicular tachycardia (RBBB left axis QRS morphology): Verapamil • If LBBB (inferior axis morphology), beta-adrenergic blocker is first line. Other drugs: Sotalol (started in hospital), propafenone, flecainide, amiodarone. • RF ablation is curative for this type of VT in more than 95% if it can be initiated and mapped in the EP laboratory. • CAD, no symptoms: beta-adrenergic blocker, no additional antiarrhythmic therapy • CAD with symptoms, beta-adrenergic blocker, sotalol, amiodarone (started in the hospital) • Polymorphic NSVT 1. In the setting of long QT with syncope, treatment is required. 2. Genotyping is available. 3. Beta-adrenergic blockers are the first choice for long QT type I. 4. ICD is indicated for LQT2 or LQT3 with syncope or family history of sudden death	• Multiple clinical scenarios exist depending on the age of patient, heart disease, and symptoms. • If symptoms persist despite beta-adrenergic blockers or if they are not tolerated, nondihydropyridine calcium channel blockers can be utilized. • Idiopathic VT may occur in repetitive monomorphic variety and be symptomatic. 1. Not life-threatening. 2. Is exacerbated by exercise, mental stress, and catecholamines. • Idiopathic polymorphic VT in the young can be potentially life-threatening. 1. Treat with beta-adrenergic blocker. 2. Consider genotyping for CPVT. • Consider RV cardiomyopathy (dysplasia) with LBBB/noninferior axis morphology. • Consider ischemia. • The 12-lead morphology is helpful. 1. If LBBB with inferior axis, it is likely from the RV or LV/aortic cusp outflow tract in normal hearts and is ablatable. 2. If QRS is negative in I and aVL, it may be arising from the septum. 3. If it is positive in I and aVL, it may be arising from the free wall and may be adenosine sensitive. 4. VTs may respond to beta-adrenergic blockers, verapamil, and most antiarrhythmic drugs. • If it is a RBBB left axis QRS pattern, it may be a reentrant idiopathic VT from the LV apical septum. 1. Thought to be due to fascicular reentry. 2. Can be cured with RF ablation. 3. Is sensitive to verapamil (only use if known to be this type of VT). • Even patients with normal hearts may be at slightly higher risk for CA compared with the general population, but further evaluation and therapy is not beneficial. • Polymorphic tachycardia may be due to ischemia or infarction and may be transient.

TABLE E5 Management of Nonsustained Monomorphic and Polymorphic Ventricular Tachycardia

Setting	Therapy	Comments
Ischemic cardiomyopathy	• For LVEF ≤30%, 40 days after MI or 3 months after revascularization, ICD implantation is indicated for primary prevention • For LVEF ≤35%, NYHA FC II-III, ICD implantation is recommended for primary prevention • For LVEF ≤40%, EP study is recommended, and if sustained VT is induced, ICD should be implanted. • For NYHA FC II-ambulatory IV heart failure, LVEF ≤35%, LBBB and QRS duration ≥130 ms, cardiac resynchronization therapy is recommended after optimal medical therapy for at least 3 months or 40 days after MI.	• Increased risk of sudden death. • Increased risk is not related to length of episodes. • EP testing may risk stratify.
Nonischemic cardiomyopathy	• Beta-adrenergic blockers, ACE inhibitors, and other goal-directed medical therapy for heart failure. • For LVEF ≤35%, NYHA FC II-III, ICD is recommended. • For NYHA FC III-IV heart failure, LVEF ≤35%, and QRS duration >120 ms, cardiac resynchronization therapy is recommended.	
HCM	• Beta-adrenergic blocker, especially if symptomatic • Memory loop event recorders may be beneficial in correlating symptoms with arrhythmias. • No indication for amiodarone or other antiarrhythmic drugs if asymptomatic • Start amiodarone, if symptomatic, in the hospital. • ICD if 1. Septum >30 mm 2. Syncope 3. NSVT 4. Family history of sudden death 5. High-risk genotype 6. If prior CA 7. Sustained VT/VF 8. LV apical aneurysm 9. End-stage HCM with LVEF <50%	• Potentially indicative of a malignant, life-threatening ventricular arrhythmia. • EP testing of no proven benefit in this setting.
MI	• No specific therapy • Assess LV function. • Beta-adrenergic blocker as part of the post-MI regimen • If continued NSVT and impaired LV function (LVEF < 40%) after 4-6 wk, consider ICD and suppressive antiarrhythmic therapy to slow VT rate and prevent shocks.	• Little prognostic meaning early after MI. Predictive value increases with increasing time from MI. • If polymorphic, consider ischemia (or electrolyte disturbance if the QT interval is prolonged). • May represent a coronary reperfusion injury rhythm.
Preoperative	• If noncardiac surgery planned, assess symptoms, longevity of the problem, drugs • If recent onset: Assess LV function • If LVEF ≤40%, and if CAD, consider EP study. • If no CHF LVEF ≤ 30%, ICD. If CHF and LVEF ≤ 35%, ICD	
Postoperative	• No therapy • Has little prognostic meaning early after surgery • Resolves spontaneously in the great majority • Evaluate for underlying heart disease if risk factors are present. • Plan follow-up Holter monitor. If episodes continue, consider EP study. If induced VT, consider ICD if LVEF ≤ 40% or other criteria met (ischemic, nonischemic cardiomyopathy; discussed previously). • If asymptomatic, treat based on monitor results or based on EP study results.	

ACE, Angiotensin-converting enzyme; *CA,* cardiac arrest; *CABG,* coronary artery bypass graft; *CAD,* coronary artery disease; *CPVT,* catecholaminergic polymorphic ventricular tachycardia; *EP,* electrophysiologic; *FC,* functional class; *HCM,* hypertrophic cardiomyopathy; *ICD,* implantable cardioverter defibrillator; *LBBB,* left bundle branch block; *LV,* left ventricular; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction; *NSVT,* nonsustained ventricular tachycardia; *NYHA,* New York Heart Association; *RBBB,* right bundle branch block; *RF,* radiofrequency; *RV,* right ventricular; *VT,* ventricular tachycardia.

From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.

TABLE E6 Management of Sustained Ventricular Tachycardia

Setting	Therapy	Comments
Acute therapy • Monomorphic VT well tolerated (patient awake and alert, no angina, no CHF, stable BP)	• First line: Amiodarone 150 mg over 10 min followed by 1mg/min for 6 h followed by 0.5 mg/min 1. May combine amiodarone IV with oral drug and with IV lidocaine if needed 2. Lidocaine 1.5-2 mg/kg (but only effective in <15%) • Second line: Procainamide 10-15 mg/kg at 25 mg/min (or less), assessing the BP carefully 1. Procainamide can slow VT and may be effective in an additional 20% to 30% 2. Amiodarone is probably more effective than procainamide, safer, and better tolerated • Third line: Cardioversion after adequate anesthesia • Do not cardiovert while awake • Fourth line: Antitachycardia pacing via a temporary transvenous pacing lead	• Assess cause and hemodynamic tolerance. 1. Guidance of therapy is dependent on the clinical status of the patient. 2. VT can always degenerate to VF even if it is at first stable. • IV amiodarone is emerging as first-line therapy for sustained monomorphic VT due to lack of efficacy of other drugs. • Procainamide has a negative inotropic effect. • Temporary transvenous pacing requires time and experienced personnel to accomplish.
Acute therapy, MI	• Same as above but degree of urgency in treatment is greater. • The length of time in VT, even if apparently tolerated, should be minimized. • Lidocaine is associated with no improvement in mortality.	• Monomorphic VT 1. May not increase long-term mortality. 2. Can be ischemia induced but this is rare (<3% of all MIs). 3. Tends to indicate "an electrical reentry circuit" of damaged myocardium.
Acute therapy, polymorphic VT • Normal QT interval • Patient stable	• If stable and the patient is awake (very rare): 1. If ineffective, DC shock (200 J >300-360 J) after anesthetized • IV beta-adrenergic blockade as tolerated	• Very rare for patient to be stable and awake • Assess cause and hemodynamic tolerance. • Rule out ischemia, infarction, electrolyte abnormality (low K^+ or Mg^{2+}), or adverse drug effect. • Assess age, underlying disease process and LV function, potential causative factors (e.g., exercise). • Therapy depends on the clinical status, which can always degenerate to VF even if it appears to be stable. • IV amiodarone may be effective, but there are no data on well-tolerated polymorphic VT.
Chronic prevention No structural heart disease Idiopathic VT, usually in young patient Often exercise- or stress-induced Rule out RV cardiomyopathy (dysplasia) with MRI	• First line: beta-adrenergic blocker titrated to the highest tolerated dose • If recurrent episodes (with moderate or severe symptoms) occur: RF catheter ablation • The success for LBBB inferior axis and for RBBB superior axis VT ablation is 90% to 95% • RF ablation is first line if patient has syncope, hemodynamic intolerance, or patient preference	• Monomorphic VT can be highly symptomatic but is almost never "malignant" and life-threatening. • LBBB/inferior axis VT is usually from the outflow tract. 1. If the QRS is negative in I and aVL, suspect a septal or LV origin. 2. If it is positive in these leads, suspect a free wall origin. 3. The mechanism may be due to triggered automaticity. Highly amenable to RF ablation. • RBBB/superior axis VTs are likely due to reentry in the Purkinje system. 1. Are verapamil sensitive. 2. Can be successfully ablated. • For LBBB, noninferior axis morphology VTs, r/o ARVC.
Prior MI, ischemia can be provoked	• If monomorphic, suspect a substrate that is due to scar, not ischemia. • If polymorphic, suspect ischemia or infarction. • Consider a functional stress test or coronary angiogram and revascularization if ischemic. • ICD implantation if hemodynamically significant sustained VT/VF • Ablation can be successful in >50% but with a high rate of long-term recurrence 1. Used as adjunctive therapy to ICD implantation 2. May be used to reduce recurrent ICD shocks • Adjunctive antiarrhythmic drugs include amiodarone or sotalol	• May also be associated with VF. • Rarely, monomorphic VT is due to ischemia alone, but always suspect substrate even if episodes occur relatively soon after infarction. 1. If an antiarrhythmic drug is being used, consider the possibility of a proarrhythmic effect. • Most patients (>95%) with chronic VT due to CAD will be inducible in the EP laboratory, but this does not change treatment strategy.

ARVC, Arrhythmogenic right ventricular cardiomyopathy; *BP,* blood pressure; *EP,* electrophysiologic; *ICD,* implantable cardioverter defibrillator; *IV,* intravenous; *LBBB,* left bundle branch block; *LV,* left ventricular; *MI,* myocardial infarction; *MRI,* magnetic resonance imaging; *RBBB,* right bundle branch block; *RF,* radiofrequency; *RV,* right ventricular; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia.

From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.

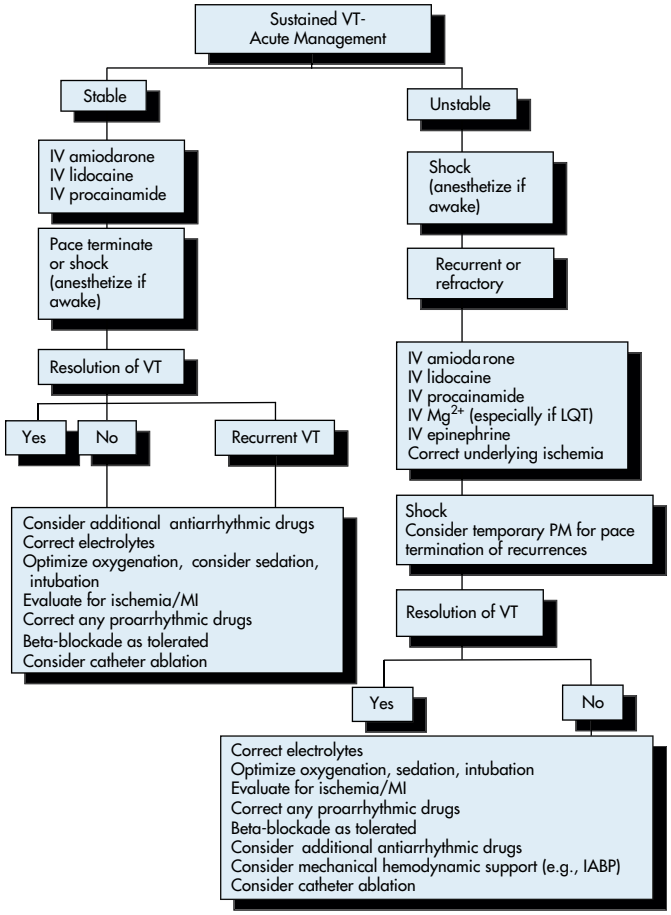

FIG. E5 Sustained ventricular tachycardia—acute management. *IABP,* Intra-aortic balloon pump; *IV,* intravenous; *LQT,* long QT interval; *MI,* myocardial infarction; *PM,* pacemaker; *VT,* ventricular tachycardia. (From Olshansky B et al: *Arrhythmia essentials,* ed 2, Philadelphia, 2017, Elsevier.)

SUGGESTED READINGS

Al-Khatib SM et al: *2017* AHA/ACC/HRS Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American heart association Task Force on Clinical Practice Guidelines and the heart rhythm Society, *Heart Rhythm* 2017.

Romero J et al: Early versus late referral for catheter ablation of ventricular tachycardia in patients with structural heart disease: a systematic review and meta-analysis of clinical outcomes, *JACC Clin Electrophysiol* 4(3):374-382, 2018.

Sapp JL et al: Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs, *N Engl J Med* 375:111-121, 2016.

Shivkumar K: V Catheter ablation of ventricular arrhythmias, *N Engl J Med* 380(16):1555-1564, 2019.

Vertebral Compression Fractures

BASIC INFORMATION

DEFINITION

Vertebral compression fractures (VCFs) are defined as fractures of spinal vertebrae in which a bony surface is driven toward another bony surface. These fractures are classified as radiographic reductions in vertebral body height of more than 15%.

SYNONYMS

Thoracolumbar vertebral compression fractures
Osteoporotic fractures
VCF

ICD-10CM CODES

M80.0	Post-menopausal osteoporosis with pathologic fracture
M80.4	Drug-induced osteoporosis with pathological fracture
M80.5	Idiopathic osteoporosis with pathological fracture
M80.8	Other osteoporosis with pathological fracture
M80.9	Unspecified osteoporosis with pathological fracture
S32.009A	Unspecified fracture of unspecified lumbar vertebra, initial encounter for closed fracture
S22.009A	Unspecified fracture of unspecified thoracic vertebra, initial encounter for closed fracture

EPIDEMIOLOGY & DEMOGRAPHICS

Approximately 700,000 VCFs occur in the United States each yr, and they affect up to 25% of postmenopausal women. They are the most common complication of osteoporosis. The prevalence increases with age, reaching a peak of 40% to 50% among women aged >80 yr. Compression fractures are also a major concern among men, although their rates of VCF are lower.

RISK FACTORS:

- Modifiable: Tobacco or alcohol use, osteoporosis, estrogen deficiency (i.e., early menopause, bilateral oophorectomy, premenopausal amenorrhea for >1 yr), frailty, impaired vision, abusive situations, inadequate physical activity, low body mass index, and deficiency of vitamin D or calcium.
- Nonmodifiable: Advanced age, female gender, dementia, Caucasian descent, history of fractures in adulthood and among first-degree relatives, and falls.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Asymptomatic: Most VCFs are asymptomatic, except for height loss or kyphosis (i.e., dowager's hump [Fig. 1]), which is often a sign of multiple VCFs and height loss of >6 cm has a sensitivity/specificity of 94% and 30%, respectively, for VCF.
- Symptomatic: When symptomatic, VCFs usually present as acute back pain after activity (e.g., bending, lifting) or coughing; neck strain and radicular rib pain may also be present.

ETIOLOGY

- VCFs take place when the combination of bending and the axial load on the spine exceed the strength of the vertebral body.
- The primary etiology of VCF is osteoporosis, though a pathologic fracture from an underlying malignancy, typically metastatic disease, must be ruled out.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Osteoporosis
- Malignancy, most often metastases
- Hyperparathyroidism
- Osteomalacia
- Granulomatous diseases (e.g., tuberculosis)
- Hematologic/oncologic diseases (e.g., multiple myeloma, primary bone malignancy)

WORKUP

- Only one third of VCFs are diagnosed. Guidelines for patient selection for vertebral fractural assessment are described in Box 1.
- VCFs can be clinically suspected from the history and physical alone, though they are often diagnosed incidentally by imaging performed for another indication.
- There may or may not be a specific injury or a remembered event that led to the VCF.

LABORATORY TESTS

Tests to rule out infection or cancer may be helpful, such as a complete blood count, an erythrocyte sedimentation rate, an alkaline phosphatase level, and a C-reactive protein level; these tests can be reserved for individuals for whom there is clinical suspicion.

IMAGING STUDIES

- Plain frontal and lateral radiographs (x-rays) are the initial imaging method and may be sufficient, particularly when no neurologic abnormalities are present. MRI and computed tomography (CT) scans may be uncomfortable or painful for the patient, especially during the acute phase.
- Although CT scans are not routinely necessary for the diagnosis, they can be helpful for visualizing fractures that are not seen on plain films, for evaluating the integrity of the posterior vertebral wall, for ruling out other causes of back pain, for detecting spinal canal narrowing, and for assessing instability.
- MRI may be useful when spinal cord compression is suspected, if neurologic symptoms are present, or to distinguish malignancy from osteoporosis (e.g., in patients <55 yr with VCF after minimal or no trauma).
- Bone density studies may be helpful to determine the severity of osteoporosis, which is a key risk factor for future fractures.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical therapy.
- External back braces: Frequently recommended to relieve pain and improve mobility, however, controlled trials have not shown any effect in patients with vertebral compression fractures.
- Exercise programs: Getting active as soon as possible is extremely important for both short-and long-term recovery.

ACUTE GENERAL Rx

- Analgesics are first line for pain control, including acetaminophen and opioids (oral or parenteral), and pain can be expected to diminish over 4 to 6 wk.
- Nonsteroidal antiinflammatory drugs are helpful but must be used with caution among elderly patients or when contraindicated.
- Muscle relaxants should be used judiciously because they have significant side effects, particularly in the elderly.
- Intranasal calcitonin (200 units once daily, alternating nostrils) has been shown in some small trials to hasten relief from pain when used as an adjunct to oral analgesics, and a

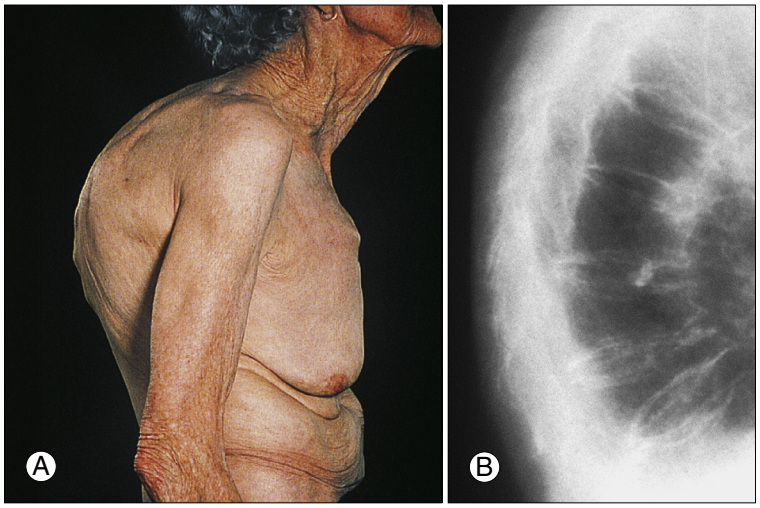

FIG. 1 Dowager's hump. (A) Marked thoracic kyphosis secondary to multiple osteoporotic fractures in an older woman. **(B)** Corresponding radiograph. (From Hochberg MC: *Rheumatology,* ed 7, Philadelphia, 2019, Elsevier.)

BOX 1 2007 ISCD Guidelines for Patient Selection for Vertebral Fractural Assessment

- Postmenopausal women with low bone mass (osteopenia) by BMD criteria, *plus* any one of the following: age >70 yr, historical height loss >4 cm (1.6 in), or prospective height loss >2 cm (0.8 in), self-reported vertebral fracture (not previously documented)
- Two or more of the following: age 60 to 69 yr, self-reported prior non-vertebral fracture, historical height loss of 2 to 4 cm, or chronic systemic diseases associated with increased risk of vertebral fractures (e.g., moderate to severe COPD or COAD, seropositive rheumatoid arthritis, Crohn disease)
- Men with low bone mass (osteopenia) by BMD criteria, *plus* any one of the following: age >80 yr, historical height loss >6 cm (2.4 in), prospective height loss >3 cm (1.2 in), self-reported vertebral fracture (not previously documented)
- Two or more of the following: age 70 to 79 yr, self-reported prior non-vertebral fracture, historical height loss of 3 to 6 cm, on pharmacologic androgen deprivation therapy or following orchiectomy, chronic systemic diseases associated with increased risk of vertebral fractures (e.g., moderate to severe COPD or COAD, seropositive rheumatoid arthritis, Crohn disease)
- Women or men on chronic glucocorticoid therapy (equivalent to 5 mg or more of prednisone daily for 3 mo or longer)
- Postmenopausal women or men with osteoporosis by BMD criteria, if documentation of one or more vertebral fractures will alter clinical management

BMD, Bone mineral density; *COAD,* chronic obstructive airways disease; *COPD,* chronic obstructive pulmonary disease; *ISCD,* International Society for Clinical Densitometry.
Reproduced with permission from the International Society for Clinical Densitometry. From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

2- to 4-wk course may be useful for patients who do not achieve adequate control with oral analgesics alone.

- Early mobilization with physical therapy is important for recovery and prevention of subsequent fractures.
- The efficacy of vertebroplasty versus kyphoplasty versus conservative treatment remains controversial.
- Percutaneous vertebroplasty involves the injection of acrylic bone cement into the affected vertebral body in an effort to stabilize the fracture and reduce pain, whereas in kyphoplasty, a high-pressure inflatable bone tamp or balloon is expanded within the body of the affected vertebra to restore prefracture vertebral height before the injection of bone cement. These two procedures were thought to be helpful in patients who did not respond to conservative therapy; however, further studies showed them to be no more effective than sham procedures (Buchbinder et al, 2009; Kallmes et al, 2009). Nonetheless, Klazen et al (2010) demonstrated in an open-label prospective randomized trial that for the subgroup of patients with acute osteoporotic VCFs and persistent pain, percutaneous vertebroplasty may provide immediate pain relief, sustained for at least a yr, which may be significantly greater than that achieved with conservative treatment. Zampini (2010) showed in a nonrandomized cohort study that elderly patients who underwent kyphoplasty were more likely to be discharged home. McCullough et al (2013) analyzed Medicare claims of patients with VCF treated with kyphoplasty or vertebroplasty compared with medical management and found no difference in mortality or major medical outcomes but decreased health care utilization in the conservatively managed group. These procedures are still in their infancy, and more answers should be forthcoming as to their efficacy, as well as questions regarding the amount of time that conservative therapy alone should be pursued and which procedure, if any, should be advised. Most current guidelines recommend 4 to 6 wk of medical therapy before pursuing surgical intervention in neurologically intact VCF.

CHRONIC Rx

Osteoporosis should be treated with the reduction of risk factors (e.g., smoking, alcohol), diet, exercise, calcium and vitamin D supplements, and with medications used to treat osteoporosis (e.g., bisphosphonates).

REFERRAL

Referral is indicated for neurologic abnormalities, unremitting pain, instability, continued disability, or when the investigation of the cause of the fracture reveals serious underlying pathology.

PEARLS & CONSIDERATIONS

Prevention of osteoporosis and conservative therapy remain the mainstay of treatment.

COMMENTS

- VCFs should be suspected in anyone aged >50 yr with the acute onset of low back pain. There are many opportunities for diagnosis and treatment that are easy to miss, especially for males.
- Solitary vertebral fractures higher than T7 are unusual and should raise suspicion for other pathologic causes.
- Diagnosing and treating osteoporosis reduce the incidence of VCFs.
- Getting people with VCF physically active as soon as possible will be efficacious both acutely and in the long term.
- In general, VCF will be best managed through a partnership of the patient, the primary care physician, an orthopedist, a physical therapist, a dietitian, and a social worker.

PREVENTION

Reducing the effects of modifiable risk factors is key.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

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McCarthy J, Davis A: Diagnosis and management of vertebral compression fractures, *Am Fam Physician* 94(1):44-50, 2016.

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Vestibular Neuronitis

BASIC INFORMATION

DEFINITION

Vestibular neuronitis is a syndrome of sudden-onset dysfunction of the peripheral vestibular system, often severe, with prolonged vertigo, nausea, and vomiting.

SYNONYMS

Vestibular neuritis
Acute neuritis
Neurolabyrinthitis
Vestibular neuropathy

ICD-10CM CODES

H81.2	Vestibular neuronitis
H81.23	Vestibular neuronitis, bilateral
H81.20	Vestibular neuronitis, unspecified ear
H81.21	Vestibular neuronitis, right ear
H81.22	Vestibular neuronitis, left ear

EPIDEMIOLOGY & DEMOGRAPHICS

Vestibular neuritis is the second most common cause of peripheral vestibular vertigo with an incidence of about 3.5:100,000 population. Although etiology remains uncertain, it is thought to result from viral infection causing selective inflammation of the vestibular nerve. Infectious origin is supported by the fact that it occurs in epidemics, may affect several family members, and occurs more commonly in spring and early summer. The male:female ratio is nearly 1:1. There is selective damage to the superior part of the vestibular labyrinth, supplied by the superior vestibular portion of the eighth cranial nerve.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Develops acutely over a period of hours and resolves over periods of days or wks, although long-term sequelae may occur, such as residual imbalance and nonspecific dizziness persisting for mos. Symptoms include sudden-onset, spontaneous, isolated vertigo; spontaneous peripheral nystagmus (horizontal and not direction changing); and imbalance. Patients report intense sensation of rotation and difficulty standing and walking and tend to veer toward the affected side; autonomic symptoms occur with pallor, sweating, nausea, and vomiting.

ETIOLOGY

Etiology remains uncertain but viral and post-viral inflammatory disorders are suspected. Herpes zoster, reactivation of herpes simplex type I, and other viruses have been implicated, but evidence is circumstantial.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cerebellar infarction
- Labyrinthitis: Similar symptoms of vertigo, with the addition of unilateral hearing loss
- Labyrinthine infarction
- Acoustic neuroma
- Perilymph fistula
- Migraine-associated vertigo
- Ménière disease
- Multiple sclerosis

WORKUP

- Patient may fall toward affected side when attempting ambulation or during Romberg tests.
- Hallpike maneuver: Checking for nystagmus and asking about re-creation of vertigo symptoms.
- Head-impulse test: Grasp patient's head, apply brief small-amplitude rapid head turn, first to one side and then the other; patient fixates on examiner's nose: positive test is lack of or slowing of corrective eye movements ("saccades") on affected side. A positive test supports the diagnosis of vestibular neuronitis.
- Laboratory testing and imaging are generally not indicated but may help rule out other etiologies.

LABORATORY TESTS

- Electronystagmography (ENG): A battery of eye movement tests that may provide an objective assessment of the vestibular and oculomotor systems and may help localize the lesion's site
- Audiogram: Normal

IMAGING STUDIES

Brain imaging: CT or MRI—normal

TREATMENT

NONPHARMACOLOGIC THERAPY

Vestibular exercises, when tolerated, will accelerate recovery.

ACUTE GENERAL Rx

Most treatments are empirical and related to symptoms. Further studies are needed.

- Corticosteroids: Corticosteroids are often prescribed, although a Cochrane review finds that there is insufficient evidence for administration. Some studies have shown that glucocorticoids administered within 3 days after onset of vestibular neuronitis may improve long-time recovery of vestibular function and reduce the length of hospital stay and may improve the caloric extent and recovery of canal paresis while others show no significant difference
- Antihistamines: e.g., meclizine, dimenhydrinate, promethazine
- Anticholinergics: Scopolamine
- Antiemetics: Droperidol, prochlorperazine
- Benzodiazepines: e.g., diazepam, valium, lorazepam
- Valacyclovir, either alone or in combination, is likely ineffective in treating vestibular neuronitis

CHRONIC Rx

- Vestibular rehabilitation exercises
- Anti-GABA agents
- Antihistamines

DISPOSITION

Most patients can be treated as outpatients, but inpatient care may be required in cases where vomiting is uncontrollable. If dehydrated because of severe vomiting, sufferers may require brief parenteral therapy.

REFERRAL

- ENT: If diagnosis uncertain, and if these patients are at risk for benign paroxysmal positional vertigo (BPPV) subsequently; also if symptoms linger
- Neurology: If question of central origin or migraine

PEARLS & CONSIDERATIONS

COMMENTS

- Diagnosis unlikely to be vestibular neuronitis if hearing is impaired or other neurologic signs and symptoms are present.
- Although patients may recover from dramatic acute symptoms, subtle vestibular deficits may linger for prolonged period, if not indefinitely (i.e., residual imbalance and nonspecific dizziness).
- Program of vestibular habituation head movement exercises can reduce imbalance symptoms.

PATIENT & FAMILY EDUCATION

Vestibular Disorders Association: https://vestibular.org/

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Benign Paroxysmal Positional Vertigo (Related Key Topic)
Ménière Disease (Related Key Topic)
Labyrinthitis (Related Key Topic)

AUTHOR: **Rocco J. Richards, MD**

SUGGESTED READINGS

Goudakos JK et al: Corticosteroids in the treatment of vestibular neuritis: a systematic review and meta-analysis, *Otol Neurotol* 31(2):183-189, 2010.

Karlberg ML, Magnusson M: Treatment of acute vestibular neuronitis with glucocorticoids, *Otol Neurotol* 32(7):1140-1143, 2011.

Saber Tehrani AS et al: Diagnosing stroke in acute dizziness and vertigo: pitfalls and pearls, *Stroke* 49:788-795, 2018.

Viral Bronchiolitis

BASIC INFORMATION

DEFINITION

Bronchiolitis is a common respiratory illness seen in children under 2 yr of age during the winter to early spring months. Most commonly caused by a viral infection, bronchiolitis often presents with fever, runny nose, cough, wheezing/crackles, and increased work of breathing. The upper respiratory illness leads to acute inflammation of the lower respiratory tract, causing increased mucus production, bronchospasms and edema, which impair air movement. The diagnosis of bronchiolitis is largely obtained through history and physical exam. The term bronchiolitis commonly has been associated with the first episode of wheezing within the first 12 mo of life. Most cases are self-limiting and rarely life-threatening.

ICD-10CM CODES

J11.1	Bronchiolitis due to influenza virus
J21	Acute bronchiolitis
J21.0	Acute bronchiolitis due to RSV
J21.1	Acute bronchiolitis due to human metapneumovirus
J21.8	Acute bronchiolitis due to other specified organisms
J44	Chronic bronchiolitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Approximately 20% of infants will need care for bronchiolitis in the first yr of life, and 2% to 3% of those younger than 12 mo will be hospitalized.

PEAK INCIDENCE: Bronchiolitis can occur throughout the yr but is most prevalent from December to March.

PREDOMINANT AGE & SEX:

- Children <2 yr old; it is most common in children 3 to 9 mo old due to their airways being smaller
- Affects both sexes equally

RISK FACTORS:

- Children under the age of 2 yr
- Children born prematurely
- Cardiopulmonary disease
- Formula feeding (those who are not breastfed)
- Children enrolled in day care
- Contact with an infected person
- Depressed immune system
- Cigarette smoke exposure

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Wheezing
- Rales (crackles)
- Cough
- Fever
- Rhinorrhea
- Nasal flaring, intercostal retractions
- Tachypnea
- Hypoxemia
- Apnea

ETIOLOGY

By far the most common cause of bronchiolitis is a viral infection. The following are the most common viruses that lead to bronchiolitis:

- Respiratory syncytial (50% to 80%)
- Rhinovirus (5% to 25%)
- Adenovirus (5% to 10%)
- Human metapneumovirus (5% to 10%)
- Parainfluenza virus (5% to 25%)
- Coronavirus (5% to 10%)
- Influenza virus and enterovirus (<5%)

Bronchiolitis in some cases has been caused by bacteria, such as *Mycoplasma pneumoniae*.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bronchitis
- Asthma
- Pneumonia
- Heart failure
- Croup

WORKUP

Diagnosis is based on symptoms, clinical presentation, patient's age, time of yr, and physical exam findings. Radiological and/or laboratory studies should not be obtained routinely. Clinical testing is used when the diagnosis of bronchiolitis is unclear or there is a need to risk stratify for complications. Table E1 describes a suggested assessment tool.

LABORATORY TESTS

- Routine lab testing for bronchiolitis is not recommended.
- For patients with concerns regarding severe bronchiolitis or alternative diagnoses, one can consider complete blood count, basic metabolic panel, arterial blood gas, and respiratory syncytial viral (RSV) testing.

IMAGING STUDIES

Although routine radiological studies are not recommended, a chest x-ray may have utility in evaluating for bacterial pneumonia or alternative diagnoses.

TREATMENT

The American Academy of Pediatrics recommends against the routine use of adjunct therapies such as albuterol, epinephrine, systemic corticosteroids, and antibiotics in the treatment of bronchiolitis. There may be a subset of patients who can benefit from adjunct therapies, especially when the diagnosis of bronchiolitis is unclear; however, the mainstay of bronchiolitis treatment is supportive.

NONPHARMACOLOGIC THERAPY

- Nasal bulb suction
- Bed rest
- Hydration
- Air humidifier

ACUTE GENERAL Rx

- Mild to moderate bronchiolitis:
  1. Tylenol and/or Motrin for fever
- Severe bronchiolitis:
  2. Supplemental oxygen for Sats <90
  3. Consider high-flow nasal cannula (HFNC), continuous positive airway pressure, and intubation for refractory hypoxia.
  4. IV or NG fluids for patients who cannot maintain oral hydration
  5. Nebulized hypertonic saline in hospitalized infants and children
  6. Antibiotics for patients with evidence of bacterial pneumonia
  7. Ribavirin in life-threatening disease or immunocompromised patients with documented RSV bronchiolitis

DISPOSITION

- Bronchiolitis symptoms peak around day 3 to day 5 and usually resolve completely within 3 weeks.
- Patients who are clinically stable, taking oral fluids, and maintaining oxygen saturation over 92% usually are considered appropriate to discharge. Ability of caretaker to care for the child, resources available, and access to follow-up should be considered for discharge.
- Clinicians should be aware of high-risk groups with bronchiolitis. These include infants with apnea, history of prematurity age <12 weeks, and chronic medical problems.
- Consider admission in patients with signs of respiratory distress, inability to keep saturation greater than 90% without oxygen, poor PO intake, apnea, cyanosis, and poor follow-up, and/or groups with higher risk of disease.

REFERRAL

The patient should follow up with the pediatrician within 24 hours of discharge for recheck.

PEARLS & CONSIDERATIONS

PREVENTION

- Hand hygiene
- Avoiding other young children with active viral respiratory illnesses
- Avoiding other young children with active viral respiratory illnesses
- Limit tobacco smoke exposure
- Breastfeeding

RELATED CONTENT

Acute Bronchitis (Related Key Topic)

AUTHORS: **Jordan Shull, MD,** and **Mark F. Brady, MD, MPH, MMSc**

SUGGESTED READINGS

Meissner HC: Viral bronchiolitis in children, *N Engl J Med* 374(1):62–72, 2016.

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Ricci V et al: Bronchiolitis in children: summary of NICE guidance, *BMJ* 350:h2305, 2015.

Scarfone RJ, Seiden JA: Pediatric respiratory emergencies: lower airway obstruction. In Walls R et al: *Rosen's emergency medicine: concepts and clinical practice,* ed 9, Philadelphia, 2017, Elsevier, pp 2081–2089.

TABLE E1 Suggested Bronchiolitis Assessment Tool

	Mild	Moderate	Severe
Feeding	Normal	Less	Poor
SaO_2 in room air	≥95%	92%-94%	<92%
Respiratory rate (breaths/min)	<60	60-70	>70
Retractions	None or minimal	Intercostal	Substernal
Accessory muscle use	None	None	Neck or abdominal
Wheeze	None or minimal	Moderate expiratory	Severe inspiratory-expiratory, audible without stethoscope
Air exchange	Good, equal breath sounds	Localized, decreased breath sounds	Multiple areas of decreased breath sounds

From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Elsevier.

BASIC INFORMATION

- Vitamin D is a hormone and a steroid and, by definition, not a vitamin. There are two forms of vitamin D: vitamin D_2 and vitamin D_3.
- Vitamin D_2 (ergocalciferol) is mainly found in some plant foods.
- Vitamin D_3 (cholecalciferol) is produced in skin exposed to ultraviolet (UV) B radiation from sunlight (Fig. E1). Gloson, Whistler, and DeBoot independently described rickets in the mid-seventeenth century. Sniadecki first reported the association of rickets with inadequate exposure to sunlight in 1822.
- The major functions of vitamin D include:
  1. Increasing calcium and phosphorus absorption from the small intestines
  2. Promoting the maturation of osteoclast to resorb calcium from bones

DEFINITION

Vitamin D deficiency is characterized by hypocalcemia and/or hypophosphatemia leading to impaired bone mineralization. It is classified as a serum 25-hydroxyvitamin D (25[OH]D) level of <20 ng/ml (50 nmol/L).This standard definition of vitamin D deficiency has been recently challenged, and some endocrinologists recommend a cutoff of 12 mg/ml for vitamin D deficiency.[1] Vitamin D insufficiency is defined as a 25(OH)D between 12 and 20 ng/ml.

The consequences of vitamin D deficiency include:

- Bone disease (rickets, osteoporosis, low bone mass)
- May impair reproductive success
- Decrease the ability to combat infection (especially TB, influenza, viral infection)
- May induce or worsen autoimmune disorders
- May increase the incidence of death due to heart disease, IBD, fracture, and cancer of the breast, colon, and prostate
- Subclinical vitamin D deficiency may occur in developed countries and be associated with increased fall risk, possible fractures, and osteoporosis.

SYNONYMS

The sunshine vitamin
The antirachitic factor
Cholecalciferol

ICD-10CM CODE
E55.9 Vitamin D deficiency, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Vitamin D insufficiency is very high among older adults and hospitalized and institutionalized people.
- Worldwide deficiency and insufficiency affect about 1 billion people.
- Children and young adults: 40% to 50% of preadolescent Caucasian girls, and Hispanic and African American adolescents, are vitamin D deficient.

PEAK INCIDENCE: In the U.S., 40% to 100% of the elderly are vitamin D deficient. Sixty percent of nursing home residents may be vitamin D deficient.

PREVALENCE: Forty-two percent of African American girls and women 15 to 49 yr old have 25(OH)D levels <20 ng/dl.

PREDOMINANT SEX AND AGE:

- Decreased skin production of vitamin D with age
- Increased prevalence among darker-skinned individuals

RISK FACTORS:

- Age (due to decreased ability to produce D_3)
- Sunshine-deficient areas (geographic location, living in higher latitudes)
- Dark-skinned individuals (melanin competes with vitamin D_3 precursors for UV photons and thus decreases pre-D_3 formation)
- Obese individuals
- Institutionalized individuals
- Pregnant and lactating women
- Use of sunscreen (sun radiation that causes skin cancer also produces pre-vitamin D_3 in skin)
- Patients on certain medications that antagonize vitamin D action (phenobarbital, phenytoin)
- Intestinal resection
- Severe chronic liver diseases (such as cirrhosis)
- Kidney disease (e.g., nephritic syndrome)
- Sarcoidosis and lymphomas (increased catabolism of 25[OH]D to 1,25[OH]2D)
- Intestinal malabsorption disease (caused by celiac sprue, cystic fibrosis, Whipple disease)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical presentation of vitamin D deficiency is dependent on the duration and severity of deficiency.
- Most patients with mild to moderate vitamin D deficiency are asymptomatic.
- Severe deficiency may lead to rickets (in children), osteomalacia (in adults), bone demineralization, hypokalemia, and phosphaturia.
- Rickets–seen in children; caused by defective mineralization in the skeleton (Fig. E2).
  1. Bowing of the legs
  2. Leg bone pain
  3. Delayed growth
  4. Seizure due to hypocalcemia
- Osteomalacia—seen in adults
  1. Periosteal bone pain (best detected by putting firm pressure on tibia or sternal bones)
  2. Proximal muscle weakness
  3. Chronic muscle aches/pain
- Fracture with very minimal trauma (brittle and easily broken bones)
- Severe hypocalcemia—especially in late vitamin D deficiency leading to seizure tetany
- Hypophosphatemia
- Paresthesia
- Tetany
- Muscle cramps

ETIOLOGY

- Inadequate exposure to sunlight, such as:
  1. During winter
  2. In nursing home and health care institution residents
  3. With excessive use of sunscreen
- Medications: Individuals on certain medications, such as phenobarbital, phenytoin, and rifampin (antagonize vitamin D action/increase vitamin D catabolism)
- Diseases and disease states:
  1. Diseases causing vitamin D malabsorption:
     a. Cystic fibrosis
     b. Whipple disease
     c. Celiac sprue
  2. Diseases increasing vitamin D catabolism:
     a. Lymphoma
     b. Sarcoidosis
  3. Intestinal resection
  4. Decreased 25(OH)D production:
     a. Kidney disease
     b. Liver cirrhosis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Arthritis
- Fibromyalgia

WORKUP

- Population-wide screening for vitamin D deficiency is not recommended because evidence to support this practice is lacking.
- Screening is needed for individuals at risk (osteoporosis, history of falls, obese persons, pregnant and lactating women, diseases causing vitamin D malabsorption, African Americans). Workup involves blood and urine tests as well as radiography, as outlined in the next section.

LABORATORY TESTS (TABLE 1)

- Serum 25(OH)D: This is the best test to determine vitamin D status.
- Parathyroid hormone (PTH): Increased levels in vitamin D insufficiency. It is a marker of vitamin D insufficiency.
- Increased (serum or bone) alkaline phosphatase.
- Decreased 24-hour urine calcium (patient should not be on a thiazide).
- In patients at risk for osteomalacia [s-25(OH)D is less than 10 ng/ml], check Ca, Ph, alkaline phosphatase, PTH, basic metabolic panel, and tissue transglutaminase antibodies.

IMAGING STUDIES

- Radiographs may show:
  1. Pseudofractures of the pelvis, femur, metatarsals
  2. Nontraumatic fractures
- Bone density:
  1. Decreased bone mineral density (osteopenia or osteoporosis). Note that bone mineral density is not routinely performed

[1] Shah S et al: Serum 25-hydroxyvitamin D insufficiency in search of a bone disease, *J Clin Endocrinol Metab* 102:2321-2328, 2017.

TABLE 1 Laboratory Tests

	SERUM			URINE
	Calcium	**Phosphorus**	**Alkaline phosphatase**	**Calcium**
Osteoporosis	N	N	N	N
Hyperparathyroidism				
Primary	↑		N or ↑	N or ↑
Secondary	N or ↑	↑	↑	↓
Tertiary	↑	N or ↓	N or ↑	N or ↑
Hypoparathyroidism	↓	↑	N	↓
Pseudohypoparathyroidism	↓	↑	N	↓
Rickets/osteomalacia				
Vit D deficient	↓	↓	↑	
Vit D refractory	N	↓	↑	↓
Hypophosphatasia	N or ↑	N	↓	N or ↑

Vit, Vitamin.
From Grant LA: *Grainger & Allison's diagnostic radiology essentials,* ed 2, Philadelphia, 2019, Elsevier.

in patients whose only risk factor is decreased Vitamin D levels.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Natural sources of vitamin D. These include:
  1. Exposure to sunlight. A mild sunburn is equivalent to consuming 10,000 to 25,000 IU of dietary vitamin D.
  2. Dietary sources are not enough to meet daily requirements. Oily fish such as salmon, cod, and mackerel are rich sources of vitamin D_3.
- Foods fortified with vitamin D.
  1. Mainly fortified dairy products.
  2. Fortified orange juice.

ACUTE GENERAL Rx

- Treating deficiency (general population): Cholecalciferol (vitamin D_3), when available, is preferred for vitamin D supplementation.
  1. 50,000 IU of vitamin D every week for 8 weeks, *or*
  2. 6000 IU daily to achieve a serum level of 25(OH)D of at least 30 ng/ml.
- Maintenance measures after treatment (general population): 1500 to 2000 IU daily.
- Treating deficiency (obese patients, patients with malabsorption syndromes, or those taking certain medications, as indicated earlier).
  1. 6000 to 10,000 IU daily.
- Maintenance measures after treatment (obese patients, patients with malabsorption syndromes, or those taking certain medications, as indicated earlier):
  1. 3000 to 6000 IU daily.
- After treating deficiency, recheck 25(OH)D in 12 to 16 weeks.

If deficiency persists after several attempts at treatment, try UV B light therapy

REFERRAL

Referral to an endocrinologist is recommended if there is no response to treatment.

PREVENTION

- Food fortification with vitamin D_2 or vitamin D_3.
- Adequate sun exposure, for example, exposure in the middle of the day (between 10:00 am and 3:00 pm).
- Use vitamin D_3 for supplementation when available.
- Vitamin D supplementation (per the Endocrine Society):
  1. Infants (age range 1 to 12 mo) require at least 400 IU/day of vitamin D
  2. Children (age range 1 to 18 yr) require 600 IU/day of vitamin D
  3. Adult supplementation (adults 19 to 70 yr): 600 IU of vitamin D daily
  4. Adult supplementation (persons ≥70 yr): 800 IU of vitamin D daily
  5. Exceptions: Pregnant or lactating women, obese persons, and patients on antiseizure medications, steroids, antifungals, and AIDS medications should be given 2× to 3× more vitamin D
  6. To reduce the risk of fracture and falls, the American Geriatric Society recommends a daily intake of at least 1000 IU and the National Osteoporosis Foundation 800 to 1000 IU in adults 65 yr or older

SCREENING: Routine screening for low-risk adults is not recommended. Screening is recommended only for individuals at high risk for vitamin D deficiency such as blacks and Hispanics, obese individuals (BMI >30 kg/m^2), patients with osteoporosis, the elderly, and patients with certain chronic diseases (see "Risk Factors"). According to the U.S. Preventive Services Task Force (USPSTF), current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults.

PEARLS & CONSIDERATIONS

- In the U.S., vitamin D supplements are available by prescription as vitamin D_2 (ergocalciferol) or over the counter as vitamin D_3 (cholecalciferol, usually in 400- to 1000-IU doses). Both vitamin D_2 and vitamin D_3 are acceptable as supplements. On average, oral vitamin D_3 raises blood levels more than does vitamin D_2.
- Upper limit of maintenance tolerability in healthy adults is 4000 IU a day. More than 4000 IU of vitamin D daily in nondeficient individuals increases the risk of harm. High-level supplements (>10,000 IU daily) are associated with kidney and tissue damage.
- Vitamin D supplementation is recommended for fall prevention. High-dose vitamin D supplementation (≥800 IU daily) has been shown to be favorable in the prevention of hip fracture and any nonvertebral fracture in persons 65 yr of age or older.
- Prescribing more than the recommended daily amount to improve quality of life or prevent cardiovascular disease or death is not advised.
- Trials have shown that low vitamin D levels are associated with depressive symptoms, especially in persons with a history of depression. These findings suggest that measuring vitamin D levels may be useful in patients with a history of depression.
- Vitamin D supplementation, administered with calcium, has been shown to lower the risk for falling and improve muscle strength in the elderly, especially in older vitamin D-deficient women who are at high baseline risk for falling.
- The treatment of vitamin D insufficiency in asymptomatic persons might reduce mortality risk in institutionalized elderly persons and risks for falls but not fractures.
- Recent data suggest that vitamin D deficiency is associated with the risk of developing certain cancers (including breast, colon, and prostate).
- Vitamin D deficiency is associated with some autoimmune diseases (types 1 and 2 diabetes, metabolic syndrome, multiple sclerosis).

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Vitamin D Deficiency (Patient Information)
Rickets (Related Key Topic)
Vitamin Deficiency (Related Key Topic)

AUTHOR: **Daniel K. Asiedu, MD, PhD, FACP**

SUGGESTED READINGS

Bischoff-Ferrari HA et al: A pooled analysis of vitamin D dose requirements for fracture prevention, *N Engl J Med* 367:40-48, 2012.

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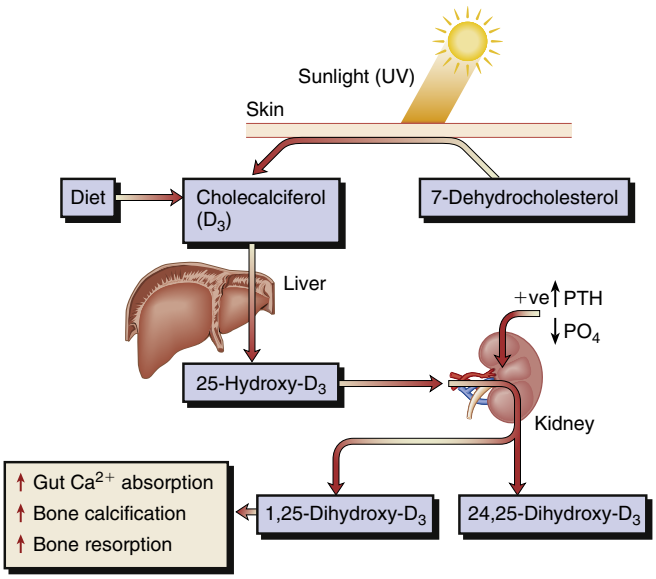

FIG. E1 The metabolism and actions of vitamin D. The primary source of vitamin D in humans is photoactivation in the skin of 7-dehydrocholesterol to cholecalciferol, which is then converted first in the liver to 25-hydroxyvitamin D and subsequently in the kidney to the much more active form, 1,25-dihydroxycholecalciferol ($1,25[OH]_2,D_3$). Regulation of the latter step is by parathyroid hormone *(PTH),* phosphate, and feedback inhibition by $1,25(OH)_2,D_3$. This step can also occur in lymphomatous and sarcoid tissue, resulting in the hypercalcemia that may complicate these diseases. (From Ballinger A: *Kumar & Clark's essentials of clinical medicine,* ed 6, Edinburgh, 2012, Saunders.)

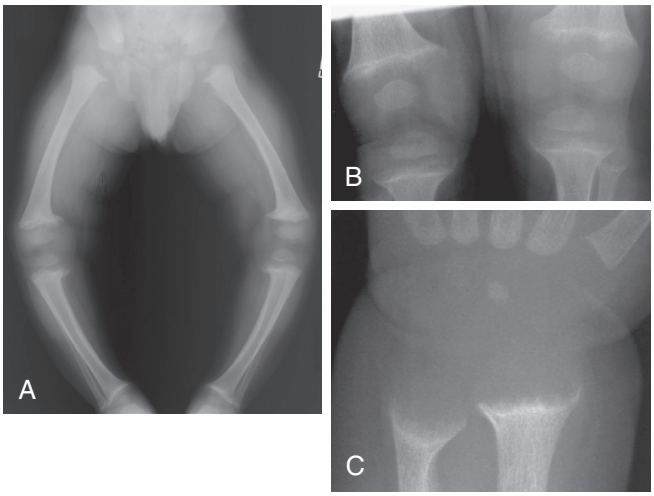

FIG. E2 Radiographs of a child with vitamin D deficiency rickets, demonstrating bowing of the femurs and tibias **(A)** and widened, frayed, demineralized epiphyseal plates **(B** and **C).** (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

BASIC INFORMATION

DEFINITION

Vitamins are organic compounds that cannot be synthesized by humans but are required as nutrients in minute amounts for normal metabolism. Vitamins have several different functions: They may regulate cell growth and differentiation, as catalysts, as antioxidants, and as co-enzymes. Vitamins are classified as either fat soluble (vitamins A, D, E, K) or water soluble (B group of vitamins and C). Deficiency of most vitamins is rare in Western countries. Certain groups may be prone to vitamin deficiency, and these are discussed here. Vitamin D deficiency is discussed in a separate topic.

SYNONYMS

Hypovitaminosis
Vitamin A: Retinol
Vitamin E: Alpha tocopherol
Vitamin K: Phytonadione or menadiol
Vitamin B_1: Thiamine
Vitamin B_2: Riboflavin
Niacin: Vitamin B_3; nicotinic acid
Vitamin B_5: Pantothenic acid
Vitamin B_6: Pyridoxine; pyridoxal phosphate
Folic acid: Vitamin B_9; folate
Vitamin B_{12}: Cyanocobalamin
Vitamin C: Ascorbic acid

ICD-10CM CODES

E50	Vitamin A deficiency
E51	Thiamine deficiency
E53	Deficiency of other B group vitamins
E55	Vitamin D deficiency
E56	Other vitamin deficiencies
E56.0	Deficiency of vitamin E
E56.1	Deficiency of vitamin K
E53.0	Riboflavin deficiency
E52	Niacin deficiency [pellagra]
E53.1	Pyridoxine deficiency
E53.8	Deficiency of other specified B group vitamins
E54	Ascorbic acid deficiency

EPIDEMIOLOGY & DEMOGRAPHICS

Deficiency can occur in all age groups but is most common in the elderly.

- Vitamin A deficiency: Affects 250 million preschool children worldwide.
- Vitamin K deficiency: Varies by geographic regions; no race predilection; affects both sexes equally. Encountered often in infants.
- Vitamin B_1 (thiamine) deficiency: Incidence is unknown; no sex, race, or age predilection.
- Vitamin B_2 (riboflavin): More common than previously appreciated. Deficiency is referred to as ariboflavinosis.
- Vitamin B_5 (pantothenic acid) deficiency: Rare, as it is present in all foods.
- Vitamin B_{12} (cobalamin) deficiency: Relatively common. Occurs in all age groups but more common in the elderly.
- Vitamin B_9 (folic acid) deficiency: Mandatory fortification started in 1998. Prevalence before fortification 16% and after 0.5%. Neural tube defect associated with low maternal folate status during pregnancy. Pregnant women and the elderly are at greatest risk of folic acid deficiency.
- Vitamin C (ascorbic acid) deficiency: Smokers and low-income persons are at increased risk.

Fig. 1 shows environmental and nutritional factors in disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Vitamin A: Xerophthalmia, xerosis of the cornea, keratomalacia, Bitot spots (abnormal squamous cell proliferation and keratinization of the conjunctiva), nyctalopia (poor adaptation to darkness)/night blindness, poor bone growth, dry skin and hair, follicular hyperkeratosis (caused by blockage of hair follicles by keratin), pruritus, broken fingernails
- Vitamin K: Clinical manifestation usually occurs if hypoprothrombinemia is present. Major symptom is bleeding to minor trauma. Also can show easy bruisability, epistaxis, hematoma, or gum bleeding
- Vitamin E: Nerve dysfunction (ataxia; hyporeflexia, peripheral neuropathy); bone weakness
- Vitamin B_1 (thiamine): Beriberi, which has two subtypes (infantile and adult). Adult type is described below:
  1. Dry beriberi (affecting the nervous system): Symmetrical peripheral neuropathy (with sensory and motor impairments), Wernicke encephalopathy (nystagmus, ataxia, ophthalmoplegia, and confusion), Korsakoff syndrome (impaired short-term memory loss and confabulation but normal cognition)
  2. Wet beriberi (affecting the cardiovascular system): Cardiomegaly, cardiomyopathy, heart failure, tachycardia, hypotension, chest pain, peripheral edema
  3. Gastrointestinal (GI): Anorexia; constipation
- Vitamin B_2 (riboflavin):
  1. Cheilosis (chapping and fissure of the lip)
  2. Glossitis (sore red tongue)
  3. Oily, scaly rashes on nasolabial folds, eyelids, scrotum, labia majora
  4. Red itchy eyes
  5. Normocytic or normochromic anemia
  6. Peripheral neuropathy
- Vitamin B_3 (niacin):
  1. Pellagra (4 *D*s—diarrhea, dermatitis, dementia, and ultimately death)
  2. Hyperpigmentation of sun-exposed skin
  3. "Raw beef" swollen and painful tongue
  4. Deficiency can be seen in prolonged use of Isoniazid, in carcinoid syndrome, and in Hartnup syndrome
- Vitamin B_5 (pantothenic acid):
  1. Deficiency is rare
  2. Deficiency leads to "burning feet syndrome" (distal paresthesia and dysesthesia)
  3. Anemia
  4. GI symptoms
- Vitamin B_6 (Pyridoxine): Rare to see overt deficiency.
  1. Mild deficiency—glossitis, cheilosis, impaired proprioception; sensory ataxia, confusion, depression
  2. Severe deficiency—seborrheic dermatitis, seizure, microcytic
- Vitamin B_{12} (cyanocobalamin):
  1. Megaloblastic anemia (pernicious anemia)
  2. Neurologic symptoms including peripheral neuropathy, ataxia (shuffling gait), paresthesia; subacute degeneration of the spinal cord (demyelination of the dorsal column), visual disturbances due to optic atrophy
  3. Glossitis and GI symptoms such as nausea, vomiting, and anorexia are also common
  4. Patients may also have dementia/mental sluggishness, depression, and weakness
- Vitamin B_9 (folic acid):
  1. Patchy hyperpigmentation of skin (especially between fingers and toes) and mucous membranes
  2. Moderate fever (temp <102° F; 38.9° C) despite the absence of infection
  3. Neural tube defect
  4. Angular stomatitis
  5. Red, beefy, smooth, and shiny tongue
  6. Megaloblastic anemia
- Vitamin C: Scurvy (bruising, petechiae, follicular hyperkeratosis, perifollicular hemorrhage), poor wound healing, fatigue, gingivitis/bleeding gums, weight loss, bone abnormalities (Fig. E2)

ETIOLOGY

- Fat-soluble vitamins (vitamins A, D, E, K):
  1. Decreased ingestion, malnutrition, eating disorders
  2. Diseases that affect fat absorption decrease the absorption of fat-soluble vitamins—for example, cystic fibrosis, celiac sprue, inflammatory bowel disease, cholestasis, hepatobiliary disease, small bowel surgery
  3. Change in vitamin metabolism:
     a. Alcoholism
     b. Drugs such as cholestyramine, warfarin, anticonvulsants, antibiotics (e.g., cephalosporins)
     c. Chronic kidney disease
- Increased risk in:
  1. Vegans
  2. Recent immigrants
  3. Refugees
  4. Toddlers/preschoolers living below the poverty line
- Water-soluble vitamins (the B group of vitamins and vitamin C)—there are several etiologic factors, including:
  1. Inadequate intake
  2. Decreased absorption
  3. Alcoholism
  4. Pregnancy/lactation
  5. Peritoneal dialysis
  6. Medications (e.g., isoniazid, phenothiazines, tricyclic antidepressants, metformin [vit B_{12}])
  7. Malabsorption
  8. Low income
  9. Advanced age
- Vitamin B_{12} deficiency—caused by:
  1. Insufficient dietary intake, as in strict vegans
  2. Decreased absorption secondary to intrinsic factor deficiency, decreased

Vitamin	Function	Consequences of deficiency
A	Retinal function, epithelial growth control	Night blindness, keratomalacia, xerophthalmia
B_1 (thiamine)	Co-enzyme	Beriberi, Wernicke's encephalopathy
B_2 (riboflavin)	Co-enzyme	Dermatitis, glossitis, keratitis, neuropathy, confusion
B_6 (pyridoxine)	Co-enzyme	Neuropathy
B_{12} (cobalamin)	Nucleic acid synthesis	Megaloblastic anemia Subacute combined degeneration of spinal cord
Niacin	Co-enzyme NAD, NADP	Pellagra (diarrhea, dermatitis, and dementia)
Folate	Co-enzyme in nucleic acid synthesis	Megaloblastic anemia, villous atrophy of gut
Vitamin C	Co-factor in hydroxylation	Scurvy
Vitamin D	Calcium and phosphate absorption	Rickets (childhood) Osteomalacia (adults)
Vitamin E	Antioxidant	Spinocerebellar degeneration
Vitamin K	Co-factor for coagulation factor synthesis	Bleeding due to coagulation defects

FIG. 1 Environmental and nutritional factors in disease. (From Stevens A: *Core pathology,* St Louis, 2009, Elsevier.)

intrinsic factor secretion, gastric atrophy, gastrectomy/gastric bypass
3. Terminal ileum disease such as celiac disease, enteritis, tropical sprue

- Folic acid deficiency:
1. Increased needs can lead to deficiency (e.g., pregnancy, lactation, malignancy)
2. Derangement of folate metabolism by:
   1. Medication (e.g., methotrexate)
   2. Disease (e.g., hypothyroidism)
   3. Increased excretion: As seen in alcoholics

DIAGNOSIS

WORKUP/LABORATORY TESTS

General initial laboratory tests include:
- Complete blood cell count (CBC)
- Liver function tests (LFTs)
- Basic metabolic panel (BMP)
- Albumin
- Measurement of serum levels of the specific vitamin in question

Specific tests may be considered in the following cases:
- Vitamin A:
1. Serum retinol level (best test, a direct measure, expensive)
2. Retinol binding protein (easier to perform, less expensive)
3. Dark-adaptation threshold test

- Vitamin K:
1. Prothrombin time/partial thromboplastin time (PT/PTT)
2. Prothrombin
3. Des-gamma-carboxyprothrombin (most sensitive test).
4. Niacin: Urine-*N*-methylnicotinamide (level <0.8 mg/day indicates niacin deficiency)

- Vitamin B_1 (thiamine):
1. Blood thiamine levels
2. Thiamine pyrophosphate levels in blood
3. Erythrocyte thiamine transketolase activity (ETKA)
4. Urinary thiamine excretion

- Vitamin B3 (niacin): Check urinary N-methylnicotinamide or erythrocyte NAD/NADP ratio (tests are not readily available)
- Vitamin B_2: Check plasma riboflavin concentration
- Vitamin B_{12}:
1. Serum vitamin B_{12} <190 pg/ml is diagnostic of vitamin B_{12} deficiency
2. Serum methylmalonic acid, which is elevated in B_{12} deficiency
3. Antiparietal antibody
4. Intrinsic factor antibody is decreased
5. Blood smear shows macrocytosis and hypersegmentation of megaloblasts
6. CBC shows increased mean corpuscle volume (MCV)
7. Megaloblastic anemia

- Folic acid:
1. Check serum folate level.
2. Additional testing includes checking for serum homocysteine level, which will be elevated.
3. Red cell folate level shows chronic folate status.

TREATMENT

Most of the vitamins are available over the counter individually or in different multivitamin formulations.
- Vitamin A deficiency: Treat with oral supplementation 10,000 IU daily.
1. Consume vitamin A–rich foods such as liver, beef, carrots, oranges, mangoes.
2. Five servings of fruit and vegetables give enough carotenoids for a day.

- Vitamin K deficiency: Treatment depends on the severity of bleeding, administered subcutaneously (SQ) or intramuscularly (IM).
- Vitamin B_1 (thiamine) deficiency: Give intramuscular thiamine 50 mg for several days.
1. If B_1 deficiency is suspected and patient needs intravenous glucose, give thiamine first before intravenous glucose. This prevents the development of Korsakoff psychosis.

- Vitamin B_{12} deficiency: Give 1000 mcg IM daily for 7 days, then once a wk for 1 mo, then once a mo indefinitely.
1. A potential option is oral supplementation.

- Folic acid deficiency: Daily requirement is 400 to 1000 mcg (1 mg) daily.
1. Centers for Disease Control and Prevention (CDC) recommend that women of childbearing age take 400 mcg of folic acid daily.

SUGGESTED READING

Available at ExpertConsult.com

RELATED CONTENT

Anemia, Pernicious (Related Key Topic)
Osteomalacia and Rickets (Related Key Topic)
Vitamin D Deficiency (Related Key Topic)
Wernicke Syndrome (Related Key Topic)
Vitamins and Their Functions (Appendix IIb)

AUTHOR: **Daniel K. Asiedu, MD, PhD, FACP**

FIG. E2 Scurvy. The knee shows widened metaphyses with spurs and reduced bone density. The ossific centers have a typical "white pencil" outline. Faint periosteal reaction is visible in the distal femur secondary to periosteal hemorrhage. The end plate is still well defined, and the physis is not widened (compared with rickets). Fractures are rare. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2014, WB Saunders.)

SUGGESTED READING

Jan A, Chow RD: Management of vitamin B_{12} deficiency: what is the role of oral therapy? *Clin Geriatr* 19(3):37-40, 2011.

BASIC INFORMATION

DEFINITION

Vitiligo is the acquired loss of epidermal pigmentation that is characterized histologically by the absence of epidermal melanocytes. There are 6 types based on the extent and distribution of the involved areas: localized (single or few macules in one anatomic area), segmental, generalized, universal (entire body surface is depigmented), acrofacial (fingers, lips), and mucosal.

ICD-10CM CODE
L80 Vitiligo

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Vitiligo affects 0.5% to 1% of the population; it is the most common depigmenting disorder.
PREDOMINANT AGE: Vitiligo can begin at any age, but the age at onset is <20 yr for half of patients. Peak onset is between ages 10 and 30. Onset is usually earlier in females.
GENETICS: A positive family history is present in 25% to 30% of patients, and both sexes are equally affected. There are no differences in the rates of occurrence with regard to skin type or race; however, it occurs in more than 8% in some regions of India.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hypopigmented and depigmented lesions (Fig. E1) favor sun-exposed regions, intertriginous areas, genitalia, and sites over bony prominences.
- Areas around the body orifices are also frequently involved.
- The lesions tend to be symmetric (Fig. E2).
- Segmental vitiligo (20% of childhood cases and 5% of adult cases) often has a dermatomal or quasidermatomal distribution.
- Vitiligo lesions may occur at trauma sites (i.e., Koebner phenomenon).
- The hair in affected areas may be white.
- The margins of the lesions are usually well demarcated; when a ring of hyperpigmentation is seen, the term *trichrome vitiligo* is used.
- The term *marginal inflammatory vitiligo* is used to describe lesions with raised borders.
- Initially the disease is limited, but the lesions tend to become more extensive over time.
- Focal vitiligo may affect nondermatomal areas (e.g., glans penis).
- Vitiligo may begin around pigmented nevi and produce a halo (i.e., Sutton nevus); in such cases, the central nevus often regresses and disappears over time.

ETIOLOGY & PATHOGENESIS

- Three pathophysiologic theories:
  1. Autoimmune theory (i.e., autoantibodies against melanocytes)
  2. Neural theory (i.e., neurochemical mediators selectively destroy melanocytes)
  3. Self-destructive process in which melanocytes fail to protect themselves against cytotoxic melanin precursors
- Although vitiligo is considered to be an acquired disease, 25% to 30% of cases are familial. The mode of transmission is unknown; the condition seems to be polygenic or autosomal dominant with incomplete penetrance and variable expression.
- Associated disorders:
  1. Alopecia areata
  2. Type 1 diabetes mellitus
  3. Adrenal insufficiency
  4. Hyperthyroidism and hypothyroidism

FIG. E1 Vitiligo. Depigmented, usually well-defined, white macules or patches that tend to have an oval or linear contour. (From Paller AS, Mancin AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

FIG. E2 Vitiligo. Symmetrical depigmentation of the knees and lower extremities. The dorsal aspect of the feet and hands are particularly hard to repigment. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

5. Mucocutaneous candidiasis
6. Pernicious anemia
7. Polyglandular autoimmune syndromes
8. Melanoma
9. Iritis and retinal pigmentary abnormalities

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acquired hypopigmentation disorders:
  1. Chemical-induced (e.g., chloroquine, imatinib, phenolic-catecholic derivatives [e.g., adhesives, deodorants, latex gloves, lacquer resins, varnish, soap antioxidants, insecticides, printing ink, paints, motor oil additives, disinfectants])
  2. Halo nevus
  3. Idiopathic guttate hypomelanosis
  4. Leprosy
  5. Leukoderma associated with melanoma
  6. Pityriasis alba
  7. Postinflammatory hypopigmentation
  8. Tinea versicolor
  9. Vogt-Koyanagi syndrome (i.e., vitiligo, uveitis, and deafness)
  10. Melasma
  11. Mycosis fungoides
- Congenital hypopigmentation disorders:
  1. Albinism, partial (piebaldism)
  2. Albinism, total
  3. Nevus anemicus
  4. Nevus depigmentosus
  5. Tuberous sclerosis
  6. Ito hypomelanosis

WORKUP

- Inquire about a personal and family history of autoimmune disease.
- A Wood's light examination may enhance the lesions of light-skinned individuals.

Rx TREATMENT

Treatment is indicated primarily for cosmetic purposes when depigmentation causes emotional or social distress. Depigmentation is more noticeable among patients with darker complexions. Combination therapies are associated with more improved repigmentation than monotherapies.

- Cosmetic masking agents (e.g., Dermablend, Covermark) or stains (e.g., Dy-O-Derm, Vitadye)
- Sunless tanning lotions (e.g., dihydroxyacetone)
- Repigmentation (This is achieved by the activation and migration of melanocytes from hair follicles; therefore, skin with little or no hair responds poorly to treatment.)
- Narrow-band ultraviolet B radiation (This is the preferred treatment for nonsegmental vitiligo. It is given twice weekly [not on successive days] during sessions that last from 5 to 10 min. The best results are achieved on the face, trunk, and limbs.)
- Psoralens and sunlight (e.g., PUVAsol)
- Topical mid-potency steroids (e.g., triamcinolone 0.1% or desonide 0.05% cream qd for 3 to 4 mo)
- Topical calcineurin inhibitors for face and neck lesions
- Intralesional steroid injection
- Systemic steroids (e.g., betamethasone 5 mg qd on two consecutive days per wk for 2 to 4 mo)
- Total depigmentation in cases of extensive vitiligo with 20% monobenzyl ether or hydroquinone (This is a permanent procedure, and patients will require lifelong protection from sun exposure.)
- Topical immunomodulators (e.g., tacrolimus, pimecrolimus) (These substances can also induce the repigmentation of vitiliginous skin lesions. However, their potential for systemic immunosuppression or for increasing the risk of skin cancer or other malignancies remains to be defined.)
- Calcipotriol, which is a synthetic analog of vitamin D_3 (This has also been used in combination with ultraviolet light or clobetasol, with limited results.)
- Surgical techniques can be applied to limited lesions

RELATED CONTENT

Vitiligo (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

Anbar TS et al: Beyond vitiligo guidelines: combined stratified/personalized approaches for the vitiligo patient, *Exp Dermatol* 23:219, 2014.

Ezzedine K et al: Interventions for vitiligo, *J Am Med Assoc* 316(6):1708-1709, 2016.

Von Hippel-Lindau Disease

BASIC INFORMATION

DEFINITION

Von Hippel-Lindau disease (VHL) is a rare, autosomal-dominant, inherited disorder that is characterized by the formation of hemangioblastomas, cysts, and malignancies that involve multiple organ systems.

SYNONYMS

Hippel-Lindau syndrome
Cerebelloretinal hemangioblastomatosis
Retinocerebellar angiomatosis
VHL

ICD-10CM CODE
Q85.8 Other phakomatoses, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

- The incidence of VHL is 1 case/36,000 live births.
- The mean age at the onset of clinical manifestations is 26 yr with median life expectancy of 49 yr, but the disease can present from infancy until the seventh decade of life.
- In the U.S., approximately 6000 to 7000 people have VHL.
- Affected individuals are at risk for the development of renal cell carcinoma (RCC), pheochromocytoma, pancreatic islet cell tumor, endolymphatic sac tumor, and hemangioblastomas of the cerebellum and the retina.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- There are two clinical types of VHL:
  1. Type 1 has decreased incidence of pheochromocytoma:
     a. Type 1A: Decreased risk of developing pheochromocytoma
     b. Type 1B: Decreased risk of developing both pheochromocytoma and renal cell carcinoma
  2. Type 2 has pheochromocytoma:
     a. Type 2A: Hemangioblastoma in the CNS with no RCC
     b. Type 2B: RCC and other tumors
     c. Type 2C: Only pheochromocytoma; associated with Chuvash polycythemia
- Retinal angiomas (60% prevalence):
  1. Usually occurs by age 25 yr with both VHL type 1 and VHL type 2
  2. Often multifocal and bilateral
  3. Detached retina
  4. Glaucoma
  5. Blindness
- CNS hemangioblastomas (70% prevalence):
  1. Cerebellum and spinal cord are the most common sites followed by the medulla
  2. Usually multiple; mean age at diagnosis is 25 yr; found with VHL types 1, 2A, and 2B
  3. Headache, ataxia, slurred speech, nystagmus, vertigo, nausea, and vomiting
- Renal cysts (50% to 70% prevalence) and clear cell RCC (~30% prevalence increasing to 70% at age 60):
  1. Usually occur by the age of 40 yr
  2. May be asymptomatic or cause abdominal and flank pain
  3. RCC is bilateral in 75% of patients
- Pancreatic cysts (~70% prevalence):
  1. Usually asymptomatic
  2. Large cysts can cause biliary obstructive symptoms
  3. Diarrhea and diabetes may develop if enough of the pancreas is replaced by cysts
- Pheochromocytoma (7% to 18% prevalence):
  1. Found with VHL types 2A, 2B, and 2C
  2. Bilateral in 50% to 80% of cases
  3. Hypertension, palpitations, sweating, and headache
  4. Commonly occurs with pancreatic islet cell tumors
- Papillary cystadenoma of the epididymis (25% to 60% of men with VHL):
  1. Palpable scrotal mass
  2. May be unilateral or bilateral
- Papillary cystadenoma of the broad ligaments (unknown prevalence):
  1. Usually asymptomatic
  2. Reported symptoms include pain, dyspareunia, and menorrhagia
- Endolymphatic sac tumors of the middle ear (10% to 15% prevalence):
  1. Vertigo
  2. Hearing loss
  3. Facial paralysis

ETIOLOGY

VHL is primarily caused by a mutation of the von Hippel-Lindau gene, which is located on the short arm of chromosome 3. Molecularly, the "two-hit" model of genetic dysfunction is thought to apply to VHL. Patients with one inactive VHL gene secondary to a VHL germlline mutation will develop disease following loss of the expression of the second allele through promoter hypermethylation. The VHL gene codes for a cytoplasmic protein that functions in tumor suppression.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Table E1 compares genetic diseases associated with the development of pancreatic or gut endocrine tumors.

DIAGNOSIS

- A clinical diagnosis is established in the presence of a positive family history plus a single CNS hemangioblastoma or a visceral lesion (e.g., RCC, pheochromocytoma, pancreatic cysts or tumors).
- If no clear family history is present, two or more hemangioblastomas or one hemangioblastoma with a visceral lesion is required to make the diagnosis.
- Genetic screening is up to 100% sensitive and specific, although in the 20% of patients with de novo VHL mutations, the test may be falsely negative as a result of somatic mosaicism.
- Screening family members is essential for the early detection of VHL disease.

WORKUP

Screening laboratory values and ophthalmoscopic, genetic, and imaging studies to look for sites of involvement

LABORATORY TESTS

- Complete blood count may reveal erythrocytosis that requires periodic phlebotomies.
- Electrolytes and renal function tests.
- Urine for norepinephrine, epinephrine, and vanillylmandelic acid to look for pheochromocytoma.
- Genetic studies: Complete sequencing of coding region, Southern blot, and fluorescent in situ hybridization.

IMAGING STUDIES

- Indirect and direct ophthalmoscopy, fluorescein angiography, and tonometry are used to screen for retinal angiomas and glaucoma.
- CT and MRI scanning of the abdomen is used for the screening, detection, and monitoring of patients with renal cysts or tumors, pheochromocytomas, and pancreatic cysts or tumors:
  1. Renal cysts grow an average of 0.5 cm/yr.
  2. Renal tumors grow an average of 1.5 cm/yr.
  3. Computed tomography scans are performed every 6 mo for the first 2 yr and every yr for life in patients who have had surgery for RCC.
- MRI with gadolinium (Fig. E1) is used for the screening and evaluation of CNS and spinal cord hemangioblastomas, endolymphatic sac tumors, and pheochromocytomas.
- Angiography may be performed before CNS surgery.

TABLE E1 Genetic Diseases Associated with the Development of Pancreatic or Gut Endocrine Tumors

Gene	Disease	Phenotype
Menin	Multiple endocrine neoplasia type 1	Parathyroid, pituitary, and pancreatic endocrine tumors
VHL	von Hippel-Lindau disease	Pancreatic endocrine tumors, hemangiomas, and multiple neoplasms
NF-1	Neurofibromatosis	Neurofibromas and pheochromocytomas
TSC1/2	Tuberous sclerosis	Pancreatic endocrine tumors and hamartomas

From Larsen PR et al: *Williams textbook of endocrinology,* ed 10, Philadelphia, 2003, Saunders.

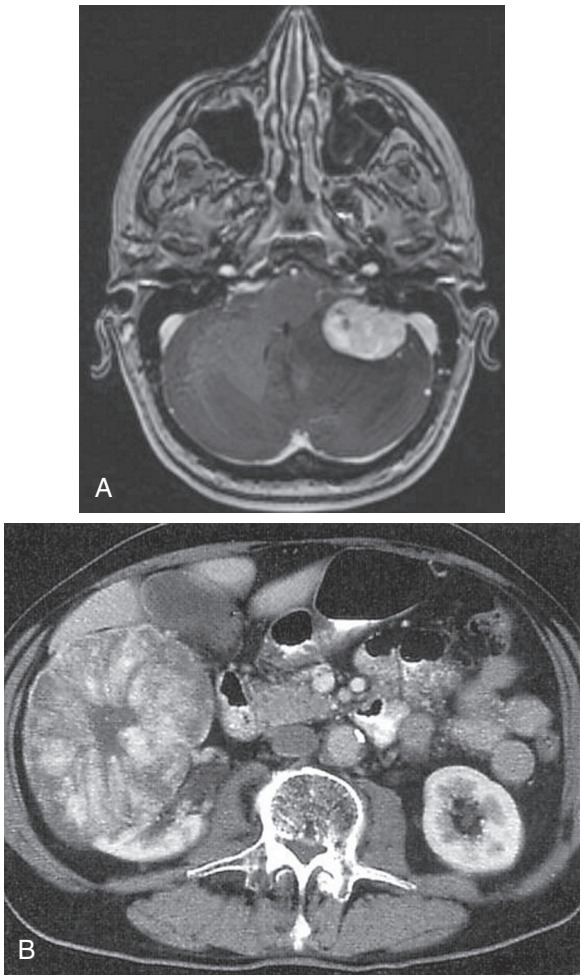

FIG. E1 Tumors in von Hippel-Lindau syndrome. A, Axial magnetic resonance image shows a cerebellar hemangioma. **B,** Axial computed tomography of the abdomen shows a renal carcinoma. (From Forbes CD, Jackson WF: *Atlas and text of clinical medicine,* 2003, Mosby.)

TREATMENT

NONPHARMACOLOGIC THERAPY

Genetic counseling

- VHL disease is inherited in an autosomal dominant fashion; thus, those with VHL have a 50% chance of passing the mutation on to their children.
- Patients with the somatic mosaicism form of VHL have varying risk of passing the condition to offspring, depending on whether or not the patient's germ cells carry the mutation. Therefore, risk may be as high as 50%.
- Patients should therefore be referred to a genetic counselor in conjunction with genetic testing.

ACUTE GENERAL Rx

- Laser photocoagulation and cryotherapy are used for patients with retinal angiomas to prevent blindness (Table E2).
- For cerebellar hemangioblastomas, treatment is surgical. External-beam radiation and stereotactic radiosurgery can also be performed.
- For renal tumors, surgery is delayed until one of the renal tumors reaches 3 cm in diameter. Nephron-sparing surgery is the preferred approach.
- Pancreatic islet cell tumors usually require surgical removal.
- Adrenalectomy is performed for pheochromocytoma.
- Antiangiogenic therapy has been shown to improve the survival of patients with RCC, with studies ongoing to assess combination therapy.

CHRONIC Rx

- Dialysis has been delayed for many patients with the use of nephron-sparing surgery.
- Renal transplantation is usually delayed for 1 yr after bilateral nephrectomy for renal tumors to ensure that no metastases have occurred.

REFERRAL

Geneticist, neurosurgeon, urologist, nephrologist, ophthalmologist, otolaryngologist, neurologist, endocrinologist, and radiation oncologist referrals should be considered

PEARLS & CONSIDERATIONS

- The most common cause of death in patients with VHL is RCC.
- More information for patients can be obtained from the von Hippel-Lindau Family Alliance (http://vhl.org).

AUTHORS: **River Cook, MD,** and **Alan Taylor, MD**

TABLE E2 Management of Different Manifestations of von Hippel-Lindau Disease

Tumor	Treatment	Screening
Retinal angiomas	Observation can be considered if angiomas are asymptomatic. If small, laser photocoagulation/ cryotherapy. in severe cases, the removal of the affected eye	Retinal examinations starting at 1 yr, repeating annually.
Central nervous system hemangioblastomas	Surgical resection for symptomatic patients or large tumors; gamma knife if difficult to remove from primary site	MRI brain and spinal cord for patients starting at 8 yr, repeating every 2-3 yr.
Renal cysts/carcinomas	For tumors <3 cm in diameter, observation; for one tumor >3 cm in diameter, remove all tumors by enucleation or partial nephrectomy; percutaneous radiofrequency ablation and cryosurgery are also performed; surgical resection is not recommended for any cyst without a tumor inside of it; nephrectomy is indicated for patients with end-stage renal disease who require dialysis because of the malignancy potential	MRI scan and quality ultrasound starting at 8 yr, repeating every yr.
Pancreatic cysts	Partial resection of the pancreas, depending on the site of the cyst	
Pheochromocytomas	Preferable to remove only the tumor itself and thus to conserve adrenal function	MRI scan and quality ultrasound starting at 8 yr, repeating every yr. Biochemical screening starting at 2 yr, repeating every yr. Bleed pressure at all visits starting at 2 yr old
Endolymphatic sac tumors	Early radical resection can preserve auditory function in majority of cases	Full audiological examination starting at 5 yr, repeated every 2-3 yr and MRI brain and spinal cord for patients starting at 8 yr, repeating every 2-3 yr. In patients with repeat ear infections, hearing loss, tinnitus, or vertigo, MRI with contrast utilizing thin slices is indicated.

CT, Computed tomography; *MRI,* magnetic resonance imaging.

SUGGESTED READINGS

Aufforth RD et al. Pheochromocytoma screening initiation and frequency in von Hippel-Lindau syndrome, *J Clin Endocrinol Metab* 100(12):4498-4504, 2015.

Ganeshan D et al: Tumors in von Hippel–Lindau Syndrome: From head to toe—comprehensive state-of-the-art review, *Radiographics* 38(3):849-866, 2018.

Maher ER et al: Von Hippel-Lindau disease: A clinical and scientific review, *Eur J Hum Genet* 19(6):617-623, 2011.

Varshney N et al: A review of Von Hippel-Lindau syndrome, *J Kidney Cancer VHL* 4(3):20-29, 2017.

BASIC INFORMATION

DEFINITION

von Willebrand disease is an inherited disorder of hemostasis characterized by a quantitative or qualitative deficiency in von Willebrand factor (vWF), a protein product of a gene located on the short arm of chromosome 12. The vWF factor is mostly synthesized in endothelial cells. von Willebrand disease results from a failure to synthesize or secrete vWF or an accelerated clearance of vWF. vWF is the carrier protein for clotting factor VIII (FVIII:C). vWF binds to denuded subendothelial collagen or glycosaminoglycans and causes platelets to adhere by acting as a ligand for glycoprotein IB on the platelet surface. This latter activity is measured in the laboratory by a test called the ristocetin cofactor (RCF). vWF circulates in plasma as a multimeric protein consisting of protomers attached by disulfide bonds. By definition, vWD is present if the level RCF is <30% of normal. A clinical entity known as low vWF exists when the level is between 30% and 60%. Such patients may exhibit a bleeding phenotype. Previously, this was considered mild vWD. There are several subtypes of von Willebrand disease. The most common type (80% of cases) is type I, where levels of vWF, FVIII:C, and RCF are reduced but concordant. Within type 1, there is type 1 mild, which is common; type 1 severe (T1S), which is rare; and type 1 C, in which the low vWF is due to accelerated clearance. There are four type 2 subtypes: type 2A, type 2B, type 2N, and type 2M. All the type 2 variants are due to a qualitative defect in vWF and show a discordancy between levels of RCF and FVIII:C. The type 2 vWD variants are characterized by low levels of RCF. Type 3 is rare and either an autosomal recessive disorder or double heterozygote and characterized by a near-complete quantitative deficiency of vWF and very low FVIII:C. Acquired vWD disease is a rare disorder that presents with mucocutaneous bleeding abnormalities and no clinical family history. It is seen often in association with hematoproliferative or autoimmune disorder or may occur in hypothyroidism. Successful treatment of the associated illness can reverse the clinical and laboratory manifestations.

SYNONYMS

Pseudohemophilia
vWD

ICD-10CM CODE
D68.0 von Willebrand disease

EPIDEMIOLOGY & DEMOGRAPHICS

- Autosomal-dominant disorder predominantly; rarely recessive or double-heterozygotic.
- Most common inherited bleeding disorder.
- Prevalence is 0.6% to 1.3% in general population, according to screening studies; estimates based on referral for symptoms of bleeding suggest a prevalence of 1 case per 10,000 persons.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Generally normal physical examination
- Mucosal bleeding (gingival bleeding, epistaxis) and gastrointestinal bleeding may occur
- Easy bruising
- Bleeding after surgery or dental extraction, menorrhagia
- Rarely, muscle or joint bleeding in type 3

ETIOLOGY

Quantitative or qualitative deficiency of vWF (see "Definition")

DIAGNOSIS

The diagnosis of von Willebrand disease generally requires two criteria: (1) a personal history, family history, or physical evidence of mucocutaneous bleeding and (2) a qualitative or quantitative decrease in functional activity of von Willebrand disease. The American Society of Hematology states that a definitive diagnosis of vWD may be made if RCF levels are <30 IU/dl.

DIFFERENTIAL DIAGNOSIS

Platelet function disorders, clotting factor deficiencies

WORKUP (FIG. 1)

SCREENING LABORATORY TESTS:

- Laboratory evaluation (Table 1).

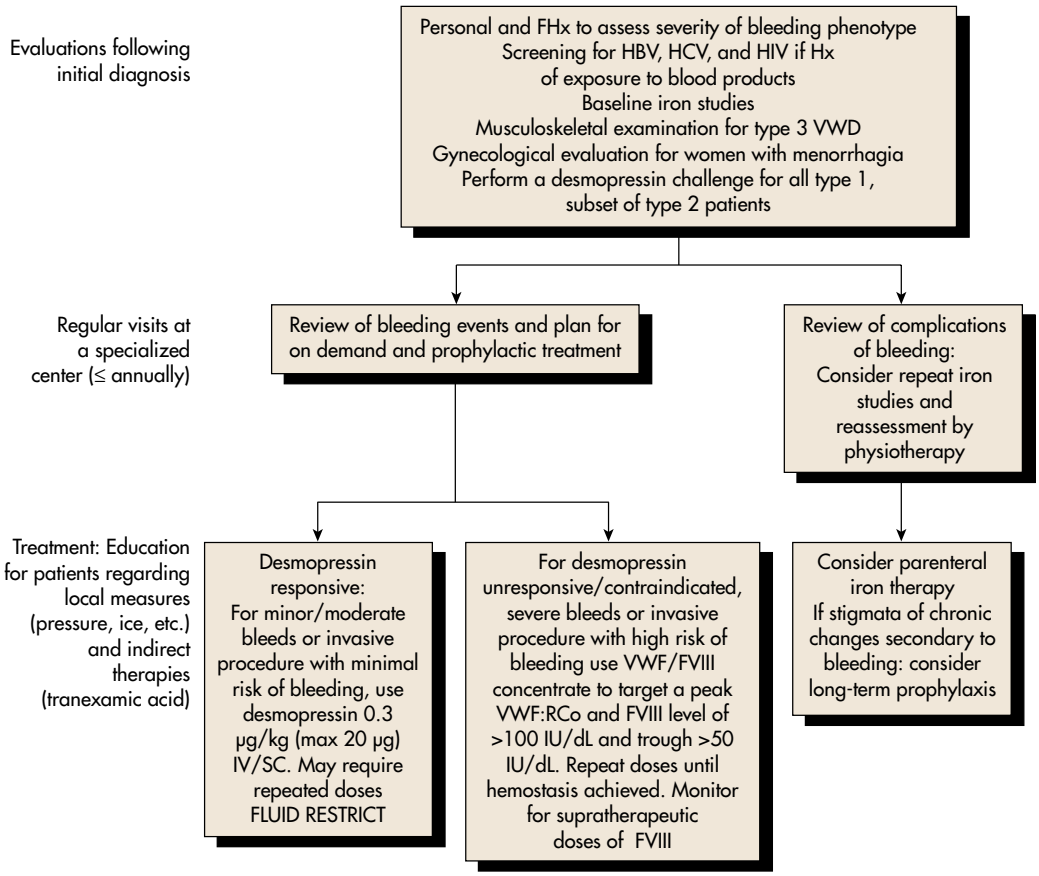

FIG. 1 Approach to the management of von Willebrand disease. *FHx,* Family history; *FVIII,* factor VIII; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HIV,* human immunodeficiency virus; *Hx,* history; *IV,* intravenous; *RCo,* ristocetin cofactor; *SC,* subcutaneous; *VWD,* von Willebrand disease; *VWF,* von Willebrand factor. (From Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

TABLE 1 Table of Investigations

vWD Type	vWF:RCo IU/dl[a]	vWF:Ag IU/dl[a]	RCo/Ag IU/dl[a]	FVIII:C IU/dl[a]	Multimer Pattern[b]	Other
1	Low	Low	Equivalent	~1.5× vWF:Ag	Normal	
2A	Low	Low	vWF:RCo < vWF:Ag	Low or normal	Abnormal ↓ HMWM	
2B	Low	Low	vWF:RCo < vWF:Ag	Low or normal	Abnormal ↓ HMWM	↑ RIPA[c](↓ platelet count)
2M	Low	Low	vWF:RCo < vWF:Ag	Low or normal	Normal	
2N	Normal/low	Normal/low	Equivalent	<30	Normal	↓ vWF:FVIIIB[d]
3	Absent	Absent	NA	<10	Absent	

Ag, Antigen; *FVIII:C,* FVIII level; *NA,* not applicable; *RCo,* ristocetin cofactor; *RIPA,* ristocetin-induced platelet aggregation; *vWD,* von Willebrand disease; *vWF:FVIIIB,* FVIII-binding assay.
[a]Relative to the reference range (approximate values); vWF:RCo (50-200 IU/dl); vWF:Ag (50-200 IU/dl); FVIII:C (50-150 IU/dl).
[b]HMWM, High-molecular-weight multimers.
[c]Increased agglutination at low concentrations of ristocetin.
[d]The ability of vWF to bind and protect FVIII is reduced. vWF and FVIII levels can look exactly like those in males with mild hemophilia A or in symptomatic hemophilia A carrier females.
From Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 2 Desmopressin Responsiveness in the Various Subtypes of von Willebrand Disease

vWD Type	vWF:RCo	vWF:Ag	RCo/Ag	FVIII:C IU/dl	vWF:CB	vWF:CB/vWF:Ag
1	Increase	Increase	Remains >0.7	Increase	Increase	Remains >0.7
2A	No/little change	Increase	Remains <0.7	Increase	No/little change	Remains <0.7
2M (GP1B-binding dysfunction)	No/little change	Increase	Remains <0.7	Increase	Increase	Remains >0.7
3	No/little change	No/little change		No/little change	No/little change	

Ag, Antigen; *FVIII:C,* factor VIII level; *GP1B,* glycoprotein 1B; *RCo,* ristocetin cofactor; *vWD,* von Willebrand disease; *vWF,* von Willebrand factor; *CB,* collagen assays-binding.
Modified from Favaloro EJ: Rethinking the diagnosis of von Willebrand disease, *Thromb Res* 127;Suppl 2:17, 2011; In Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

- Initial testing includes prothrombin time (normal), partial thromboplastin time (normal or slightly increased), platelet count (normal), and PFA-100 (abnormal or may show high normal values in type 1 vWD).

SPECIFIC LABORATORY TESTS:

- Factor VIII coagulant activity (FVIII:C, typically decreased, may be normal in some Type 2 variants).
- vWF antigen, ristocetin cofactor (RCF), and collagen binding assay (these typically are decreased and may be concordant as in type 1 and type 3, or discordant as in type 2 variants).
- Normal platelet number and morphology.
- Prolonged bleeding time, or more commonly, prolonged PFA-100 closure times.
- von Willebrand propeptide. This measures the N-terminal propeptide of vWF. This vWFpp is secreted in equimolar amounts to the mature vWF. The ratio of vWFpp to vWF can assist in identifying vWD due to rapid clearance, as in type 1C.
- Multimeric analysis: Type 2A von Willebrand disease can be distinguished from type I by absence of medium- and high-molecular-weight multimers.
- Type 2B von Willebrand disease is distinguished from type I by the absence of high-molecular-weight multimers.
- Type 2N is a defect in the factor VIII:C binding and has normal vWF levels but very low factor VIII:C with normal multimer pattern
- Type 2M is a defect in binding to platelets (low RCF, low CBA) but normal multimers.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of aspirin and other nonsteroidal antiinflammatory drugs
- Use of antifibrinolytics such as tranexamic acid, especially for menorrhagia or oral bleeding

GENERAL Rx

- Treatment of von Willebrand disease is based on normalizing factor VIII levels and von Willebrand factor at the time of spontaneous bleeding or before an intervention.
- Use of DDAVP (Table 2): DDAVP binds to V2 receptors in certain endothelial cells and causes the release of vWF. This is suitable for the management of the milder forms of vWD. Dose is 0.3 mcg/kg in 50 to 100 ml of normal saline solution IV infused over 20 min. DDAVP is also available as a nasal spray (dose of 150 mcg spray administered to each nostril) as a preparation for minor surgery and management of minor bleeding episodes.
- When a patient undergoes surgery or receives repeated therapeutic doses of concentrates, use of a plasma-derived vWF concentrate such as Humate-P or a new recombinant vWF (Vonvendi) may need to be administered.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHOR: **Joseph Sweeney, MD, FACP, FRCPath**

SUGGESTED READINGS

Laffan MA et al: The diagnosis and management of von Willebrand's disease, *Br J Haematol* 167:453-465, 2014.

Leebok F, Eikenboom JCJ: Von Willebrand's disease, *N Engl J Med* 375:2067-2080, 2016.

Lavin M et al: Novel insights into the clinical phenotype and pathophysiology underlying low VWF levels, *Blood* 130:2344-2353, 2017.

BASIC INFORMATION

DEFINITION

Vulvar cancer is an abnormal cell proliferation arising on the vulva and exhibiting malignant potential. The majority of vulvar cancers are of squamous cell origin (Table E1); however, other types include adenocarcinoma, basal cell carcinoma, sarcoma, and melanoma (Table E2).

SYNONYMS

Squamous cell carcinoma of the vulva (90%)
Basal cell carcinoma of the vulva
Adenocarcinoma of the vulva
Melanoma of the vulva
Bartholin gland carcinoma
Verrucous carcinoma of the vulva
Vulvar sarcoma

ICD-10CM CODE

C51.9 Malignant neoplasm of vulva, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: In 2019, it is estimated that there will be approximately 6070 new cases of vulvar cancer and that approximately 1280 women will die of the disease.

PREVALENCE: Vulvar cancer is uncommon. It comprises 3% to 5% of malignancies of the female genital tract and approximately 1% of all carcinomas found in women.

MEAN AGE AT DIAGNOSIS: Predominantly a disease of menopause, the mean age at diagnosis is 65 yr. However, the incidence shows a bimodal distribution, with both young and old women being affected.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Vulvar pruritus or pain is present (Table E3).
- May produce a malodorous discharge or present as bleeding.
- Raised lesion that may have fleshy (Fig. E1), ulcerated, leukoplakic (Fig. E2), or warty appearance; may have multifocal lesions.
- Lesions are usually located on labia majora but may be seen on labia minora, clitoris, and perineum.
- The lymph nodes of groin may be palpable.

ETIOLOGY

- There are two proposed independent pathways for the development of vulvar squamous cell carcinoma: Mucosal human papillomavirus (HPV) infection and chronic inflammatory (vulvar dystrophy) or autoimmune processes.
- Vulvar intraepithelial neoplasia has been reported in 20% to 30% of invasive squamous cell carcinoma of the vulva, but the malignant potential is unknown.
- Approximately 50% of vulvar cancers are thought to be attributable to HPV infection. HPV is more likely to be found in younger women with vulvar cancer; older women are less likely to have HPV-associated cancer.
- Other risk factors include a history of condyloma acuminatum, smoking, vulvar dystrophy, lichen sclerosis, chronic immunosuppression, hypertension, and diabetes.
- Vulvar cancer in younger women is more directly dependent on HPV infection, vulvar dysplasia, and tobacco use.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Lymphogranuloma inguinale
- Tuberculosis
- Vulvar dystrophies
- Vulvar atrophy
- Paget disease

WORKUP

- Diagnosis is made histologically by biopsy
- Thorough examination of the lesion and assessment of spread. Table E4 describes FIGO staging of vulvar cancer
- Possible colposcopy of adjacent areas
- Cytologic smear of vagina and cervix
- Cystoscopy and proctosigmoidoscopy may be necessary

IMAGING STUDIES

- Chest radiography
- CT scan and MRI for assessing local tumor spread

TABLE E1 Vulvar Intraepithelial Neoplasia Histologic Subtypes and Associations

	Usual (Warty-Basaloid, Undifferentiated)	Differentiated (Simplex)
Age	Premenopausal women (30s-40s)	Postmenopausal women (65 yr)
Overall %VIN	≈95	≈5
HPV associated	Yes	No
HPV type	16	NA
Risk factors	Smoking, immunosuppression	None identified
Distribution	Multifocal	Unifocal, unicentric
Background histology		Lichen sclerosus
Progression to	Warty, basaloid squamous cell cancer Invasive cancer	Keratinizing squamous cell cancer (Rare)

HPV, Human papillomavirus; *NA,* not applicable; *VIN,* vulvar intraepithelial neoplasia.
From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2017, Elsevier.

TABLE E2 Incidence of Vulvar Neoplasms by Histologic Type*

Tumor Type	Incidence (%)
Squamous	86.2
Melanoma	4.8
Sarcoma	2.2
Basal cell	1.4
Bartholin gland	
Squamous	0.4
Adenocarcinoma	0.6
Adenocarcinoma	0.6
Undifferentiated	3.9

*Based on 1378 reported cases.
From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2017, Elsevier.

TABLE E3 Signs and Symptoms of Vulvar Cancer

Sign or Symptom	Incidence (%)
Pruritus	45.0
Mass	45.0
Pain	23.0
Bleeding	14.0
Ulceration	14.0
Dysuria	10.0
Discharge	8.0
Groin mass	2.5

From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2017, Elsevier.

FIG. E1 Squamous cell carcinoma of the vulva. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

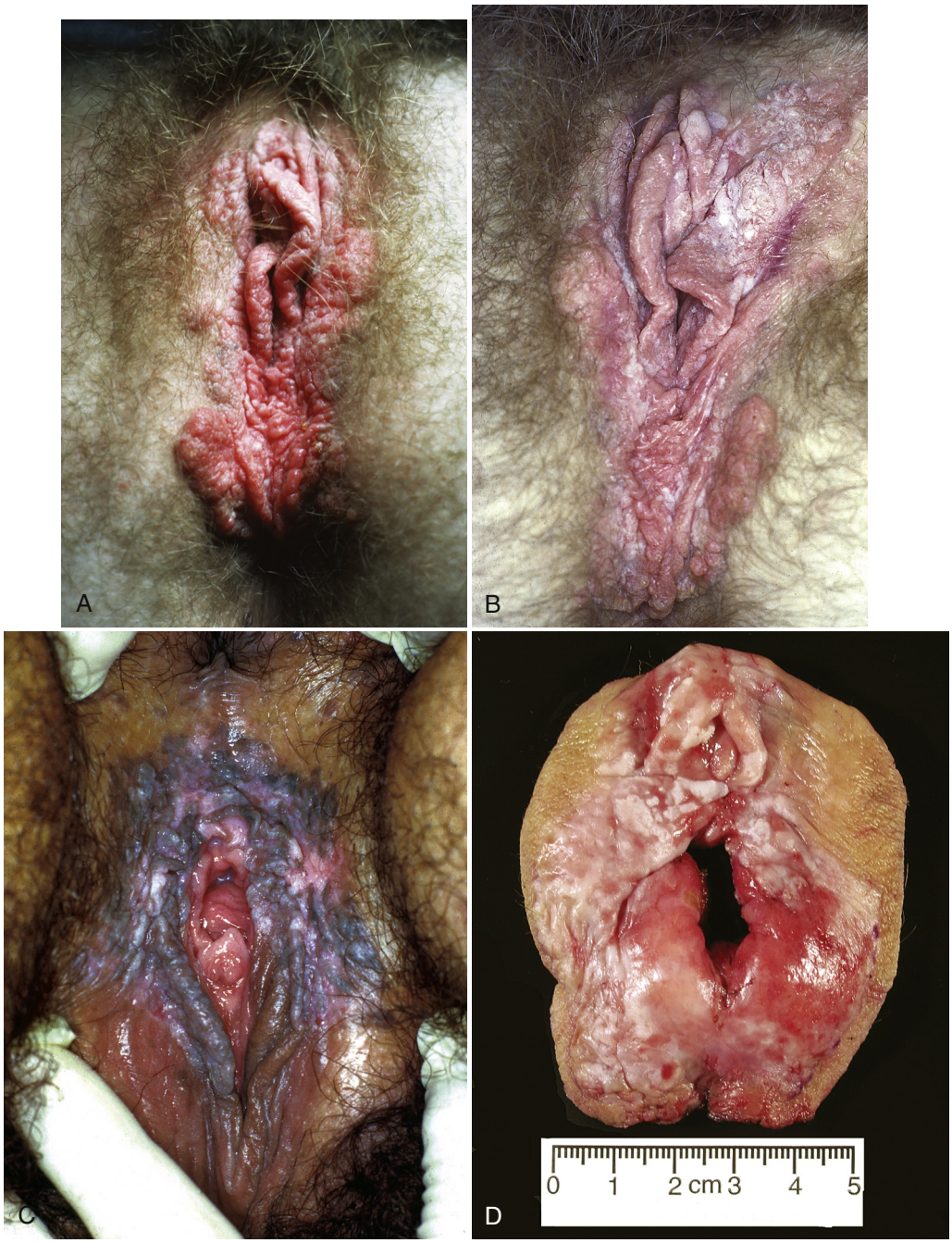

FIG. E2 Clinical presentations of classic vulvar intraepithelial neoplasia (VIN). A and **B,** Raised irregular lesions with variable hyperkeratosis. **C,** More macular pigmented VIN. **D,** Extensive confluent white plaques. (From Crum CP et al: *Diagnostic gynecologic and obstetric pathology,* ed 3, Philadelphia, 2018, Elsevier.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Treatment is individualized depending on the stage of the tumor. Figs. E3 through E5 describe treatment algorithm for management of patients with vulvar cancer.
- Stage I tumors with <1 mm stromal invasion are treated with complete local excision without groin node dissection. Imiquimod 5% cream, a topical immune response modulator, is also effective in the treatment of vulvar intraepithelial neoplasia.
- Stage I tumors with >1 mm stromal invasion are treated with complete local excision with groin node dissection.
- Stage II tumors require radical vulvectomy with bilateral groin node dissection.
- Advanced-stage disease may require the addition of radiation and chemotherapy to the surgical regimen.

DISPOSITION

Five-yr survival ranges from 98% for stage I to 15% for stage IV.

REFERRAL

Vulvar cancer should be managed by a gynecologic oncologist and radiation oncologist.

RELATED CONTENT

Vulvar Cancer (Patient Information)

AUTHOR: **Anthony Sciscione, DO**

TABLE E4 Federation of International Gynecologists and Obstetricians Staging of Invasive Cancer of the Vulva

Stage	Description
I	Tumor confined to the vulva
I_A	Lesions ≤2 cm in size confined to the vulva or perineum and with stromal invasion ≤1.0 mm*; no nodal metastasis
I_B	Lesions >2 cm in size confined to the vulva or perineum with stromal invasion greater than 1.0 mm*; no nodal metastasis
II	Tumor of any size with extension to adjacent perineal structures (one third lower urethra, one third lower vagina, anus); no nodal metastasis
III	Tumor of any size with or without extension to adjacent perineal structures (one third lower urethra, one third lower vagina, anus) with positive inguinofemoral lymph nodes
III_A	(i) With 1 lymph node metastasis (≥5 mm), or
	(ii) With 1-2 lymph node metastasis(es) (<5 mm)
III_B	(i) With ≥2 lymph node metastases (≥5 mm), or
	(ii) With ≥3 lymph node metastases (<5 mm)
III_C	With positive nodes with extracapsular spread
IV	Tumor invades other regional (two thirds upper urethra, two thirds upper vagina) or distant structures
IV_A	Tumor invades any of the following:
	(i) Upper urethra or vaginal mucosa, bladder mucosa, rectal mucosa, fixed to pelvic bone, or
	(ii) Fixed or ulcerated inguinofemoral lymph nodes
IV_B	Any distant metastasis, including pelvic lymph nodes

*The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.
From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2017, Elsevier.

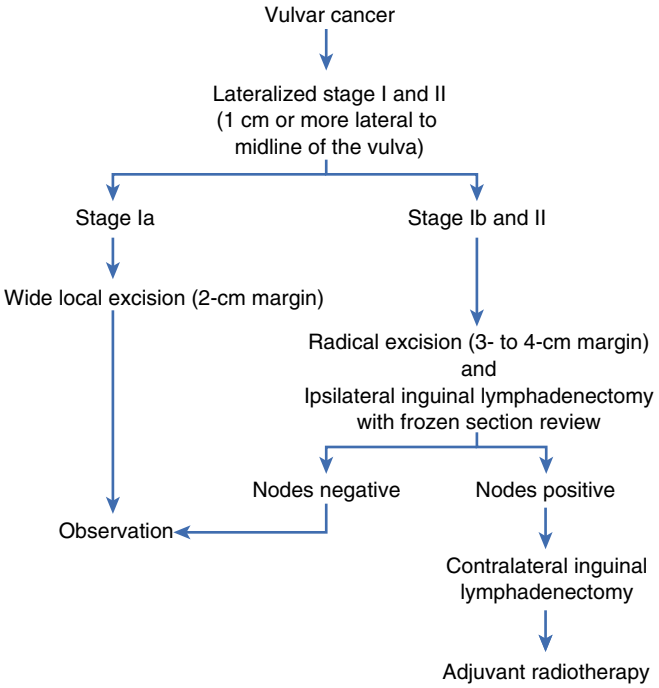

FIG. E3 Algorithm for management of lateralized stage I or II vulvar cancer. (From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2017, Elsevier.)

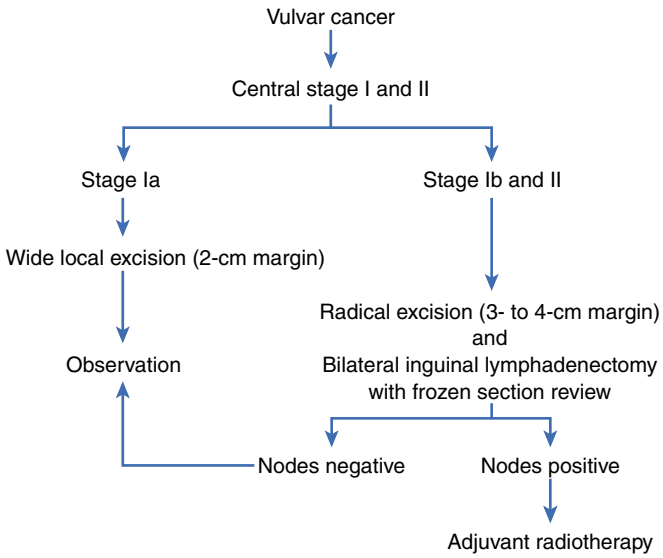

FIG. E4 Algorithm for management of central stage I or II vulvar cancer. (From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2017, Elsevier.)

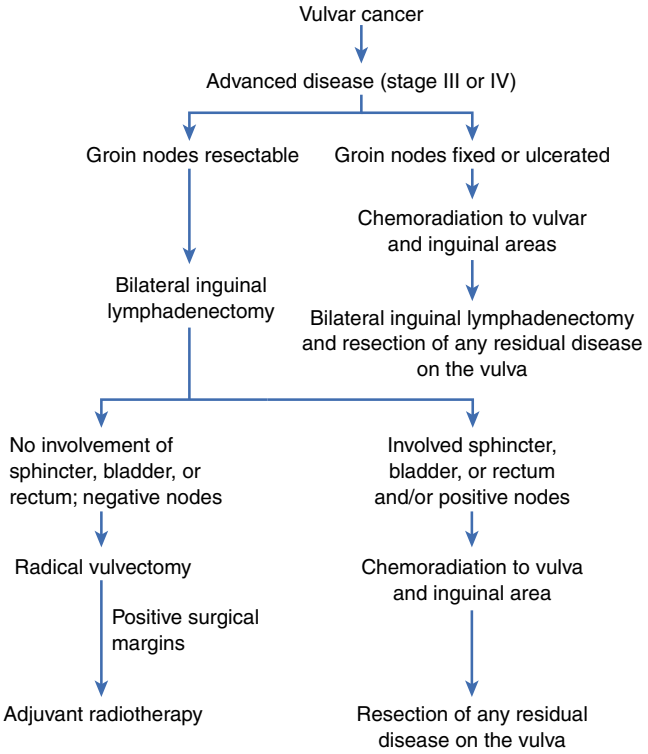

FIG. E5 Algorithm for management of advanced stage III or IV vulvar cancer. (From Disaia PJ et al: *Clinical gynecologic oncology,* ed 9, Philadelphia, 2017, Elsevier.)

BASIC INFORMATION

DEFINITION

Waldenström macroglobulinemia (WM) is an indolent B-cell lymphoplasmacytic lymphoma (LPL) characterized by lymphoplasmacytic infiltration in the bone marrow (BM) and other organs, and a monoclonal immunoglobulin M (IgM) paraprotein in the serum. Less than 5% of LPL secrete IgG, IgA, or light chains. Rare nonsecretory cases exist.

SYNONYMS

WM
Monoclonal macroglobulinemia
Lymphoplasmacytic lymphoma

ICD-10CM CODE
C88.0 Waldenström macroglobulinemia

EPIDEMIOLOGY & DEMOGRAPHICS

- Accounts for 2% of all hematologic cancers
- A reported 1500 new cases diagnosed every yr in the U.S.
- Overall incidence: 3.4 per million person-yr in men, 1.7 per million person-yr in women
- Median age at diagnosis: 69 yr
- More common among men than women and among whites than blacks

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- 30% to 50% of patients can be asymptomatic at presentation
- Weakness, fatigue, and pallor, usually associated with anemia (50%)
- Fever, night sweats, and weight loss (30%)
- Peripheral sensory neuropathy associated with IgM demyelinating antibodies, usually affecting the feet symmetrically (20%)
- Lymphadenopathy (15%)
- Hepatosplenomegaly (15%)
- Hyperviscosity syndrome (10%), characterized by headaches, recurrent nosebleeds, blurry vision due to retinal hemorrhages (Fig. E1); retinal vein link: sausage shaped
- Acrocyanosis, livedo reticularis, purpura, and/or peripheral ulcerations usually associated with symptomatic cryoglobulinemia (5% to 10%)
- Hemolytic anemia caused by cold agglutinin disease (5%)
- Amyloidosis causing renal dysfunction, neuropathy, and/or cardiac dysfunction (<5%)
- Meningeal signs caused by CNS involvement by WM (Bing Neel syndrome; 1%)

ETIOLOGY

- The main risk factor for development of WM is having IgM monoclonal gammopathy of unknown significance (MGUS).
- Other risk factors are older age and male sex.
- Multiple reports suggest familial clustering in about 20% of the patients, which may indicate a genetic predisposition to WM and other blood cancers.
- Approximately 20% of the patients have an Ashkenazi Jewish ancestry.
- There is an increased risk of WM in people with a personal history of autoimmune diseases.
- Radiation exposure, occupational chemicals, viral infection (hepatitis C), and chronic inflammatory stimulation have been suggested, but there is insufficient evidence to substantiate these hypotheses.

DIAGNOSIS

The diagnosis of WM is usually established by laboratory blood tests and by bone marrow (BM) biopsy. Diagnosis requires demonstration of LPL involving the BM space and the presence of an IgM monoclonal paraprotein (Table 1). *MYD88 L265P* is a commonly recurring mutation in WM seen in >90% of the patients with WM and 50% to 60% of patients with IgM MGUS and can be useful in differentiating WM from other IgM-secreting B-cell disorders such as marginal zone lymphoma, IgM multiple myeloma, and atypical forms of chronic lymphocytic. Non-*L265P MYD88* mutations rarely have been described (<5%) and should be excluded in patients who test negative for *MYD88 L265P* by PCR-based assays. Mutations in the *CXCR4* gene have been described in 40% of patients, and may impact clinical presentation and response to ibrutinib treatment.

DIFFERENTIAL DIAGNOSIS

- IgM MGUS
- IgM multiple myeloma
- Marginal zone lymphoma
- Atypical chronic lymphocytic leukemia

WORKUP

In any patient suspected of having WM, specific blood tests (CBC, serum or urine protein electrophoresis [SPEP or UPEP, respectively], serum IgM level, beta 2-microglobulin, serum viscosity) should be ordered. BM biopsy confirms the diagnosis. *MYD88* mutation testing can be helpful in supporting the diagnosis of WM.

LABORATORY TESTS

- CBC with differential:
  1. Anemia is a common finding, with a median hemoglobin value of approximately 10 g/dl. WBC count is usually normal; thrombocytopenia can occur.
  2. Peripheral smear may reveal "stacked coin" rouleaux formations and malignant lymphoid cells in some patients.
- SPEP: Homogeneous M spike (monoclonal gammopathy).
- Immunoelectrophoresis: Confirms IgM responsible for the M spike.
- Serum IgM levels are high, generally >3000 mg/dl.
- High serum beta 2-microglobulin levels are associated with poor prognosis.
- Serum viscosity. Hyperviscosity usually occurs when the serum viscosity is four times the viscosity of normal serum; classic feature although presents in only 10% of cases.
- Cryoglobulins or cold agglutinins may be present.
- BM biopsy: BM reveals infiltration by a lymphoplasmacytic cell population constituted by small lymphocytes with evidence of plasmacytoid and plasma cell

TABLE 1 Physicochemical and Immunologic Properties of the Monoclonal Immunoglobulin M Protein in Waldenström Macroglobulinemia

Properties of IgM Monoclonal Protein	Diagnostic Condition	Clinical Manifestations
Pentameric structure	Hyperviscosity	Headaches, blurred vision, epistaxis, retinal hemorrhages, leg cramps, impaired mentation, intracranial hemorrhage
Precipitation on cooling	Cryoglobulinemia (type I)	Raynaud phenomenon, acrocyanosis, ulcers, purpura, cold urticaria
Autoantibody activity to myelin-associated glycoprotein, ganglioside M_1, sulfatide moieties on peripheral nerve sheaths	Peripheral neuropathies	Sensorimotor neuropathies, painful neuropathies, ataxic gait, bilateral foot drop
Autoantibody activity to IgG	Cryoglobulinemia (type II)	Purpura, arthralgia, renal failure, sensorimotor neuropathies
Autoantibody activity to red blood cell antigens	Cold agglutinins	Hemolytic anemia, Raynaud phenomenon, acrocyanosis, livedo reticularis
Tissue deposition as amorphous aggregates	Organ dysfunction	Skin: bullous skin disease, papules, Schnitzler syndrome Gastrointestinal: diarrhea, malabsorption, bleeding Kidney: proteinuria, renal failure (light-chain component)
Tissue deposition as amyloid fibrils (light-chain component most commonly)	Organ dysfunction	Fatigue, weight loss, edema, hepatomegaly, macroglossia, organ dysfunction of involved organs (heart, kidney, liver, peripheral sensory and autonomic nerves)

IgM, Immunoglobulin M.
From Hoffman R: Hematology, *basic principles and practice,* ed 7, 2018, Elsevier.

TABLE 2 Summary of Consensus Response Criteria for Waldenström Macroglobulinemia

Response Type	Abbreviation	Criteria
Complete response	CR	Absence of serum monoclonal IgM protein by immunofixation Normal serum IgM level Complete resolution of extramedullary disease (i.e., lymphadenopathy/splenomegaly if present at baseline) Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response	VGPR	Monoclonal IgM protein is detectable 90% reduction in serum IgM level from baseline or normalization of serum IgM level Complete resolution of extramedullary disease (i.e., lymphadenopathy/splenomegaly if present at baseline) No new signs or symptoms of active disease
Partial response	PR	Monoclonal IgM protein is detectable ≥50% but <90% reduction in serum IgM level from baseline Reduction in extramedullary disease (i.e., lymphadenopathy/splenomegaly if present at baseline) No new signs or symptoms of active disease
Minor response	MR	Monoclonal IgM protein is detectable ≥25% but <50% reduction in serum IgM level from baseline No new signs or symptoms of active disease
Stable disease	SD	Monoclonal IgM protein is detectable <25% reduction and <25% increase in serum IgM level from baseline No progression in extramedullary disease (i.e., lymphadenopathy/splenomegaly) No new signs or symptoms of active disease
Progressive disease	PD	>25% increase in serum IgM level from lowest nadir (requires confirmation) and/or progression in clinical features attributable to the disease

IgM, Immunoglobulin M.

Owen RG et al: Response assessment in Waldenström macroglobulinemia, *Br J Haematol* 160:171, 2013. In Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

differentiation. The BM infiltration should be confirmed by immunophenotypic studies (flow cytometry and immunohistochemistry) showing the following profile: sIgM+CD19+CD20+CD22+CD79+.

IMAGING STUDIES

CT of the chest, abdomen, and pelvis may show lymphadenopathy, hepatosplenomegaly, and rarely, extralymphatic/extramedullary areas of disease.

Rx TREATMENT

- Because of the incurable nature of WM, the aim of treatment is to relieve symptoms and reduce the risk of organ damage. Initiation of therapy should not be based on the IgM levels alone because this may not correlate with either disease burden or symptomatic status. Patients with smoldering or asymptomatic WM and preserved hematologic function should be observed without therapy.
- Initiation of therapy is appropriate for patients with constitutional symptoms. Considerations for the initiation of treatment include the following: significant adenopathy or organomegaly, symptomatic hyperviscosity, moderate to severe neuropathy, amyloidosis, symptomatic cryoglobulinemia or cold agglutinin disease, hemoglobin concentration <10 g/dl, or evidence of disease transformation.
- Treatment is directed at both hyperviscosity and the lymphoproliferative disorder itself.

NONPHARMACOLOGIC THERAPY

Asymptomatic patients do not require treatment, and these patients should be monitored periodically for the onset of symptoms or changes in blood tests (e.g., worsening anemia, thrombocytopenia, rising IgM levels, and serum viscosity). Plasmapheresis should be the initial treatment in patients with symptoms of hyperviscosity or cryoglobulinemia followed immediately by more definitive therapy. Serum IgM level, percentage of bone marrow involvement, serum albumin level, and serum beta 2-microglobulin level can be used to estimate the risk of requiring therapy (awmrisk.com).

INITIAL Rx

- Treatment of the lymphoproliferative disorder includes single or combination therapy. There is no universally agreed upon standard of care:
  1. Combination regimens include alkylating agents (cyclophosphamide and bendamustine) or proteasome inhibitors (bortezomib, carfilzomib, and ixazomib) in combination with rituximab. These should be used in patients with severe constitutional symptoms, symptomatic bulky disease, hyperviscosity, or profound hematologic compromise. Response rates are 80% to 90% with any of these regimens.
  2. Rituximab, a monoclonal anti-CD20 antibody, can be used in symptomatic patients who are not candidates for combination therapy. Response rates are 40% to 50%. Rituximab can be used as maintenance therapy after rituximab-containing combination regimens.
  3. In April 2015, the FDA granted approval for the oral Bruton tyrosine kinase inhibitor ibrutinib to be used in patients with symptomatic WM. The response rate to ibrutinib is 90%, with a median time to response of 4 wk. Major responses were absent in patients who do not carry the *MYD88* mutation. The response was delayed in patients who carry any *CXCR4* mutation.
  4. In August 2018, the FDA approved the combination of ibrutinib and rituximab for the treatment of symptomatic WM patients. The combination was associated with higher response rate and longer median progression-free survival than rituximab and placebo.

Rx ON RELAPSED/REFRACTORY DISEASE

- Previously treated patients can be retried on original therapy if length of response from initial therapy was substantial. If the response from the initial therapy was short, alternative first-line agents can be used.
- Other treatment options: Fludarabine, ofatumumab, thalidomide, everolimus, and clinical trials. Autologous stem cell transplantation should be considered in heavily pretreated patients.

DISPOSITION

- The progression of WM is slow and insidious, with median survival from time of diagnosis of about 10 yr. Table 2 summarizes consensus response criteria for Waldenström macroglobulinemia.
- Younger patients tend to have more prolonged survival.
- About 10% to 20% of patients die from progression of the disease.
- Some patients develop acute myelogenous leukemia, usually secondary to exposure to chemotherapy, and some patients can develop more aggressive lymphomas.

TABLE 3 Prognostic Scoring Systems in Waldenström Macroglobulinemia

Study	Adverse Prognostic Factors	Number of Groups	Survival
Gobbi et al[1]	Hgb <9 g/dl	0-1 prognostic factors	Median: 48 mo
	Age >70 yr	2-4 prognostic factors	Median: 80 mo
	Weight loss		
	Cryoglobulinemia		
Morel et al[2]	Age ≥65 yr	0-1 prognostic factors	5-yr: 87% of patients
	Albumin <4 g/dl	2 prognostic factors	5-yr: 62%
	Number of cytopenias:	3-4 prognostic factors	5-yr: 25%
	Hgb <12 g/dl		
	Platelets $<150 \times 10^9$/L		
	WBC $<4 \times 10^9$/L		
Dhodapkar et al[3]	β_2M ≥3 g/dl	β_2M <3 mg/dl + Hgb ≥12 g/dl	5-yr: 87% of patients
	Hgb <12 g/dl	β_2M <3 mg/dl + Hgb <12 g/dl	5-yr: 63%
	IgM <4 g/dl	β_2M ≥3 mg/dl + IgM ≥4 g/dl	5-yr: 53%
		β_2M ≥3 mg/dl + IgM <4 g/dl	5-yr: 21%
Dimopoulos et al[4]	Albumin ≤3.5 g/dl	Albumin ≥3.5 g/dl + β_2M <3.5 mg/dl	Median: NR
	β_2M ≥3.5 mg/L	Albumin ≤3.5 g/dl + β_2M <3.5 or	Median: 116 mo
		β_2M 3.5-5.5 mg/dl	Median: 54 mo
		β_2M >5.5 mg/dl	
Morel et al[5]	Age >65 yr	0-1 prognostic factors (excluding age)	5 yr: 87% of patients
	Hgb <11.5 g/dl	2 prognostic factors (or age >65 yr)	5 yr: 68%
	Platelets $<100 \times 10^9$/L	3-5 prognostic factors	5 yr: 36%
	β_2M >3 mg/L		
	IgM >7 g/dl		

β_2M, β_2-microglobulin; *Hgb,* hemoglobulin; *IgM,* immunoglobulin M; *NR,* not reported; *WBC,* white blood cell count.

[1]Gobbi PG et al: Study of prognosis in Waldenström's macroglobulinemia: a proposal for a simple binary classification with clinical and investigational utility, *Blood* 83:2939, 1994.
[2]Morel P et al: Prognostic factors in Waldenström macroglobulinemia: a report on 232 patients with the description of a new scoring system and its validation on 253 other patients, *Blood* 96:852, 2000.
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[4]Dimopoulos M et al: The international staging system for multiple myeloma is applicable in symptomatic Waldenström's macroglobulinemia, *Leuk Lymphoma* 45:1809, 2004.
[5]Morel P et al: International prognostic scoring system for Waldenström macroglobulinemia, *Blood* 113:4163, 2009.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

- The risk of thyroid cancer, kidney cancer, and melanoma is increased in patients with WM.
- A staging system using age, serum beta 2-microglobulin level, hemoglobin level, platelet count and serum IgM concentration before treatment provide insight into prognosis and survival. Prognostic scoring systems in Waldenström macroglobulinemia are summarized in Table 3.

REFERRAL

A hematology consultation is helpful in guiding future workup, treatment, and monitoring. Participation in clinical trials is highly encouraged in patients with WM.

PEARLS & CONSIDERATIONS

COMMENTS

WM was first described in 1944 by the Swedish physician Jan Gösta Waldenström, who also described the X-linked Bruton agammaglobulinemia.

SUGGESTED READINGS

Available at ExpertConsult.com

AUTHORS: **Jorge J. Castillo, MD,** and **Steven P. Treon, MD**

SUGGESTED READINGS

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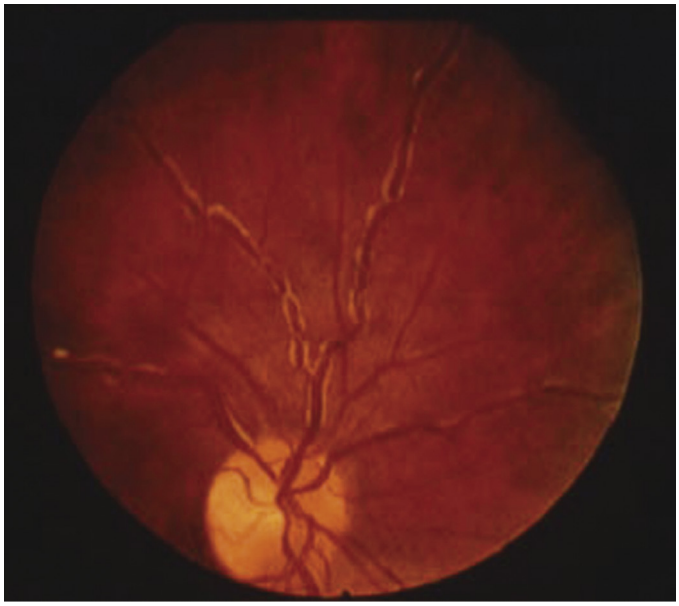

FIG. E1 Funduscopic examination of a patient with Waldenström macroglobulinemia with hyperviscosity-related changes, including dilated retinal vessels, hemorrhages, and "venous sausaging." The white material at the edge of the veins may be cryoglobulin. (Used with permission from Marvin J. Stone, MD. In Hoffman R: *Hematology, basic principles and practice,* ed 7, 2018, Elsevier.)

BASIC INFORMATION

DEFINITION

Warts are benign epidermal lesions caused by human papillomavirus (HPV).

SYNONYMS

Verruca vulgaris (common warts)
Verruca plana (flat warts)
Condyloma acuminatum (venereal warts)
Verruca plantaris (plantar warts)
Mosaic warts (cluster of many warts)
HPV infection

ICD-10CM CODES
B07.9 Viral wart, unspecified
B07.8 Other viral warts
A63.0 Anogenital (venereal) warts
B07.0 Plantar wart

EPIDEMIOLOGY & DEMOGRAPHICS

- Risk factors include use of communal showers, occupational handling of meat, and immunosuppression. Common warts occur most frequently in children and young adults.
- Anogenital warts are most common in young, sexually active patients. Genital warts are the most common viral sexually transmitted disease in the U.S., with up to 79 million Americans carrying the causative virus, and 14 million persons are newly infected each yr in the U.S.
- Persistent infection with oncogenic HPV types can cause cervical cancer in women as well as other anogenital and oropharyngeal cancers in women and men. 66% of cervical cancers, 55% of vaginal cancers, 79% of anal cancers, and 62% of oropharyngeal cancers are attributable to HPV types 16 or 18.
- Common warts are longer lasting and more frequent in immunocompromised patients (e.g., lymphoma, AIDS, immunosuppressive drugs).
- Plantar warts occur most frequently at points of maximal pressure (over the heads of the metatarsal bones or on the heels).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Common warts (Fig. E1) have an initial appearance of a flesh-colored papule with a rough surface; they subsequently develop a hyperkeratotic appearance with black dots on the surface (thrombosed capillaries). They may be single or multiple and are most common on the hands.
- Warts obscure normal skin lines (important diagnostic feature). Cylindrical projections from the wart may become fused, forming a mosaic pattern.
- Flat warts (Fig. E2) generally are pink or light yellow, slightly elevated, and often found on the forehead, back of hands, mouth, and beard area. They often occur in lines corresponding to trauma (e.g., a scratch), are often misdiagnosed (particularly when present on the face), and are inappropriately treated with topical corticosteroids.
- Filiform warts have a fingerlike appearance with various projections; they are generally found near the mouth, beard, or periorbital and paranasal regions.
- Plantar warts (Fig. E3) are slightly raised and have a roughened surface; they may cause pain when walking; as they involute, small hemorrhages (caused by thrombosed capillaries) may be noted.
- Genital warts (Fig. E4) are generally pale pink with several projections and a broad base. They may coalesce in the perineal area to form masses with a cauliflower-like appearance. Intraanal warts occur predominantly in patients who have had receptive anal intercourse, in contrast with perianal warts, which may occur in men and women without a history of anal sex.
- Genital warts on the cervical epithelium can produce subclinical changes that may be noted on Pap smear or colposcopy.

ETIOLOGY

- HPV infection; >150 types of viral DNA have been identified. Transmission of warts is by direct contact. Approximately 40 different types of HPV are transmitted through sexual contact.
- Genital warts: 90% are caused by HPV types 6 or 11. HPV types 16, 18, 31, 33, and 35 are found occasionally in visible genital warts (usually as coinfections with HPV 6 or 11) and can be associated with foci of high-grade, intraepithelial neoplasia, particularly in persons who are infected with HIV infection. In addition to warts on genital areas, HPV types 6 and 11 have been associated with conjunctival, nasal, oral, and laryngeal warts.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Molluscum contagiosum
- Condyloma latum
- Acrochordon (skin tags) or seborrheic keratosis
- Epidermal nevi
- Hypertrophic actinic keratosis
- Squamous cell carcinomas
- Acquired digital fibrokeratoma
- Varicella-zoster virus in patients with AIDS
- Recurrent infantile digital fibroma
- Plantar corns (may be mistaken for plantar warts)

WORKUP

- Diagnosis is generally based on clinical findings.
- Suspect lesions should be biopsied.
- The application of 3% to 5% acetic acid, which causes skin color to turn white, has been used by some providers to detect HPV-infected genital mucosa. However, acetic acid application is not a specific test for HPV infection. Therefore, the routine use of this procedure for screening to detect mucosal changes attributed to HPV infection is not recommended.

LABORATORY TESTS

- Screening for cervical cancer with cytology, which is performed by either Pap smear or liquid-based cytology. Screening guidelines recommend starting screening at age 21. Annual cytology is recommended until at least three normal cytology results are obtained.
- Colposcopy with biopsy is recommended in patients with cervical squamous cell changes.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Importance of use of condoms to reduce transmission of genital warts should be emphasized.
- Watchful waiting is an acceptable option in the treatment of nongenital cutaneous warts because many warts will disappear without intervention over time. However, many patients often request treatment because of social stigma or discomfort.
- Plantar warts that are not painful do not need treatment.
- Factors that influence selection of treatment include wart size, wart number, anatomic site of the wart, wart morphology, patient preference, cost of treatment, convenience, adverse effects, and provider experience. Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy.

GENERAL Rx

- Common warts:
  1. Application of topical salicylic acid 17%. Soak area for 5 min in warm water and dry. Apply thin layer once or twice daily for up to 12 wk, avoiding normal skin. Bandage.
  2. Liquid nitrogen and electrocautery are also common methods of removal. Cure rates for cryotherapy are 50% to 70% after three to four treatments.
  3. Blunt dissection can be used in large lesions or resistant lesions.
  4. Duct tape occlusion is also effective for treating common warts. It is cut to cover warts and left in place for 6 days. It is removed after 6 days and the warts are soaked in water and then filed with pumice stones. New tape is applied 12 hr later. This treatment can be repeated until warts resolve.
  5. Recalcitrant warts can be treated with injection of *Candida* or mumps skin antigen into the wart every 3 to 4 wk for up to three treatments, photodynamic therapy with aminolevulinic acid, pulsed dye laser, and intralesional bleomycin.
- Filiform warts: Surgical removal is necessary.

- Flat warts: Generally more difficult to treat.
  1. Tretinoin cream applied at bedtime over the involved area for several weeks may be effective.
  2. Application of liquid nitrogen.
  3. Electrocautery.
  4. 5-Fluorouracil cream applied once or twice a day for 3 to 5 wk is also effective. Persistent hyperpigmentation may occur after Efudex use.
- Plantar warts:
  1. Salicylic acid therapy (e.g., Occlusal-HP). Soak wart in warm water for 5 min, remove loose tissue, dry. Apply to area, allow to dry, reapply. Use once or twice daily; maximum 12 wk. Use of 40% salicylic acid plasters (Mediplast) is also a safe, nonscarring treatment; it is particularly useful in treating mosaic warts covering a large area.
  2. Blunt dissection is also a fast and effective treatment modality.
  3. Laser therapy can be used for plantar warts and recurrent warts; however, it leaves open wounds that require 4 to 6 wk to fill with granulation tissue.
  4. Interlesional bleomycin is also effective but generally used when all other treatments fail.
- Genital warts:
  1. Can be effectively treated with 20% podophyllin resin in compound tincture of benzoin applied with a cotton tip applicator by the treating physician and allowed to air dry. The treatment can be repeated weekly if necessary.
  2. Podofilox (Condylox 0.5% gel) is available for application by the patient. Local adverse effects include pain, burning, and inflammation at the site.
  3. Cryosurgery with liquid nitrogen delivered with a probe or as a spray is effective for treating smaller genital warts.
  4. Carbon dioxide laser can also be used for treating primary or recurrent genital warts (cure rate >90%).
  5. Imiquimod cream, 5%, is a patient-applied immune response modifier effective in the treatment of external genital and perianal warts (complete clearing of genital warts in >70% of females and >30% of males in 4 to 16 wk). Sexual contact should be avoided while the cream is on the skin. It is applied 3 times per wk before normal sleeping hours and is left on the skin for 6 to 10 hr.
  6. Sinecatechins (Veregen), a botanical drug product, is also effective for treatment of external genital and perianal warts. Formulation is a 15% ointment applied to affected area tid for up to 16 wk.
- Application of trichloroacetic acid or bichloracetic acid 80% to 90% is also effective for external genital warts. A small amount should be applied only to warts and allowed to dry, at which time a white "frosting" develops. This treatment can be repeated weekly if necessary.

DISPOSITION

- Warts can be effectively treated with the previous modalities with complete resolution in the majority of patients; however, the recurrence rate is high.
- Cervical carcinomas and precancerous lesions in women are associated with genital papillomavirus infection.
- Squamous cell anal cancer is also associated with a history of genital warts.

REFERRAL

- Dermatology referral for warts resistant to conservative therapy
- Surgical referral in selected cases
- Sexually transmitted disease counseling for patients with anogenital warts

PEARLS & CONSIDERATIONS

COMMENTS

- Subungual and periungual warts are generally more resistant to treatment. Dermatology referral for cryosurgery is recommended in resistant cases.
- Examination of sex partners is not necessary for the management of genital warts because no data indicate that reinfection plays a role.

PREVENTION

- Two HPV vaccines (Gardasil, Gardasil-9, Cervarix) have been licensed in the U.S. Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with HPV4 or HPV2 for females aged 11 to 12 yr and HPV4 for males aged 11 to 12 yr. Vaccination is also recommended for females aged 13 to 26 yr and for males aged 13 through 21 yr who were not vaccinated previously. Males aged 22 through 26 may be vaccinated. ACIP recommends vaccination of men who have sex with men and immunocompromised persons (including those with infection) through age 26 yr if not previously vaccinated. The 9-valent HPV vaccine (Gardasil-9) is approved for use in girls and women 9 to 26 yr old and boys 9 to 15 yr old. It is indicated to prevent diseases associated with HPV infection with types 6, 11, 16, 18, 31, 33, 45, 52, and 58. It appears to be more effective than the other 2 currently available vaccines. It consists of two doses. The first dose is administered at 11 to 12 yr of age, and the second dose 6 to 12 mo later. However, if the second dose is given less than 5 mo apart, a third dose will be needed at age 9 to 14. Patients with a weak immune system and in those starting vaccination at age 15 to 26 yr will need three doses. ACIP does not recommend catch-up HPV vaccination for all adults over 26 years old. Shared decision making regarding HPV vaccination is recommended for some adults age 27 through 65 who are unvaccinated.
- Male circumcision decreases heterosexual transmission of HPV.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Human Papillomavirus Infection (Patient Information)
Warts (Patient Information)
Condyloma Acuminatum (Related Key Topic)

AUTHOR: **Fred F. Ferri, MD**

SUGGESTED READINGS

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Mulhem E, Pinelis S: Treatment of nongenital cutaneous warts, *Am Fam Physician* 84(3):288–293, 2011.

FIG. E1 Common warts. A dome-shaped lesion of the lateral nose and a filiform lesion of the columella. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

FIG. E2 Flat warts with koebnerization. Flat papules on the forehead, with a linear configuration (Koebner phenomenon) at sites of autoinoculation. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

FIG. E4 Condylomata acuminata. Verrucous papules of the labial surfaces, with a large, vegetative lesion protruding from the vagina. This toddler had been sexually abused. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

FIG. E3 Plantar warts. Verrucous papules on the plantar surfaces. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology, a textbook of skin disorders of childhood and adolescence,* ed 5, 2016, Elsevier.)

BASIC INFORMATION

DEFINITION

Wernicke syndrome is an acute neuropsychiatric disorder characterized by the classic triad of ophthalmoplegia, ataxia, and disturbances of mental activity or consciousness due to a deficiency of thiamine often associated with chronic alcoholism or other causes of malnutrition.

SYNONYMS

Wernicke encephalopathy (WE)
Gayet-Wernicke encephalopathy
Cerebral beriberi
Wernicke superior hemorrhagic polioencephalitis

ICD-10CM CODES

E51.2	Wernicke encephalopathy
E51.8	Other manifestations of thiamine deficiency
F04	Amnestic disorder due to known physiological condition
F10.96	Alcohol use, unspecified with alcohol-induced persisting amnestic disorder

EPIDEMIOLOGY & DEMOGRAPHICS

- A higher prevalence of WE noted on autopsy studies (0.4% to 2.8%) compared with clinical studies (0.04% to 0.13%), and the majority of affected patients are alcoholic.
  1. WE lesions on autopsy of alcohol abusers: 12.5%
  2. WE lesions on autopsy patients with alcohol-related deaths: 29% to 59%

PREDOMINANT SEX AND AGE:

- Male:female ratio of 1.7 to 1
- Estimated mortality: 17%

GENETICS:

- Biochemical studies in fibroblasts from patients with WE show transketolase, a thiamine-dependent enzyme, to have a decreased affinity for thiamine pyrophosphate.
- Variants in the high-affinity thiamine transporter gene have also been implicated.
- Thiamine deficiency causes wet (cardiovascular) beriberi more commonly in the Asian population and dry beriberi (polyneuropathy and WE) in the European population.

RISK FACTORS:

- Alcohol abuse/misuse
- Diet:
  1. Malnutrition, unbalanced nutrition, thiamine-deficient infant formulas
  2. IV hyperalimentation without thiamine supplementation
  3. Magnesium depletion–cofactor required by enzymes: Transketolase and thiamine pyrophosphokinase
- GI disorders, including recurrent vomiting (i.e., hyperemesis gravidarum) or chronic diarrhea
- GI surgical procedures (i.e., GI resection) that cause malabsorption secondary to reduced surface area of gastric and duodenal mucosa such as bariatric surgery
- Systemic cancers:
  1. Consumption of thiamine by fast-growing neoplastic cells
  2. Most common underlying disorder causing WE in children
- Chemical compounds/drugs or chemotherapeutic treatments
- Systemic diseases:
  1. Peritoneal dialysis and hemodialysis
  2. HIV/AIDS
  3. Prolonged infectious febrile disease
  4. Hypermetabolic states
  5. Thyrotoxicosis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- WE is a clinical diagnosis with a classic triad of ophthalmoplegia, ataxia, and disturbances of mental activity or consciousness, although this full triad is only seen in 16% of all patients.
- Eye movement abnormalities include nystagmus, external rectus palsies, and reduced conjugate gaze.
- Ophthalmoscopic findings include swelling of the optic discs and retinal hemorrhages.
- Clinical suspicion must remain high in patients with risk factors listed above, especially in the setting of poor nutrition.
- Diagnosis is confirmed by improvement of neurologic signs after administration of parenteral thiamine.
- Labs and radiologic studies may aid diagnosis, but these should not delay a trial of parenteral administration of thiamine.

ETIOLOGY

- The biologically active form of vitamin B_1, thiamine pyrophosphate (TP), is a coenzyme for several important biochemical pathways involved in energy production, lipid metabolism, and production of amino acids and glucose-derived neurotransmitters.
- Body's reserve for thiamine is sufficient for 18 days.
- Malnutrition for 2 to 3 weeks or a diet disproportionately high in carbohydrates and low in thiamine intake can lead to an impaired function of enzymes requiring TP.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other acute encephalopathies (Table E1)
- Paramedian thalamic infarction
- Ventriculoencephalitis, paraneoplastic encephalitis, herpes simplex encephalitis
- Miller-Fisher syndrome
- Primary central nervous system lymphoma
- Multiple sclerosis, Behçet disease, Leigh disease
- Variant Creutzfeldt-Jakob disease

WORKUP

- WE is a clinical diagnosis based on the triad of features listed previously, though the full triad is rarely seen.
- Laboratory tests and radiologic studies as listed below may be obtained to confirm diagnosis.

LABORATORY TESTS

- Do not hold thiamine treatment for the results of blood tests or imaging when there is clinical suspicion.
- Blood thiamine concentration.
- Functional measurement of erythrocyte thiamine transketolase (ETKA) before and after administration of parenteral thiamine. A diagnosis may be confirmed if ETKA is low followed by a 25% increase after thiamine supplementation.
- High-performance liquid chromatography for assessment of thiamine, thiamine mono- and di-phosphate in human erythrocytes.
- Serum magnesium concentration (depletion of magnesium may mimic features of WE).

IMAGING STUDIES

MRI of the brain may show bilaterally symmetric increase in T2 signal at the paraventricular regions of the thalamus and mammillary bodies. Other areas of increased signal include hypothalamus, periaqueductal region, floor of the fourth ventricle, and midline cerebellum.

TREATMENT

ACUTE GENERAL Rx

- Treatment should be initiated in all patients with clinical suspicion of WE. Thiamine supplementation should precede glucose administration in all patients at risk for WE.
- Alcoholics with WE: Treat with 500 mg of thiamine hydrochloride (dissolved in 100 ml of normal saline) infused intravenously over 30 minutes three times daily for 2 to 3 days.

TABLE E1 Acute and Subacute Presentation of Nutritional Deficiency Syndromes

Syndrome	Clinical Setting
Wernicke-Korsakoff syndrome	Administration of intravenous glucose to a thiamine-deficient alcoholic patient
Wernicke-Korsakoff syndrome	Intractable vomiting due to hyperemesis gravidarum or gastroplasty
Postgastroplasty neuropathy	Intractable vomiting and severe weight loss in patients following weight reduction surgical procedures
Vitamin B_{12} myeloneuropathy	Nitrous oxide administration in cobalamin-deficient patients
Central pontine myelinolysis	Sudden change in tissue osmolarity in critically ill patients or alcoholics

From Goetz CG: *Textbook of clinical neurology,* ed 3, Philadelphia, 2007, Saunders.

- If a response is observed, continue with 250 mg of thiamine hydrochloride intravenously or intramuscularly daily until clinical improvement ceases.
- Nonalcoholics with WE: Treat with 200 mg of thiamine hydrochloride (dissolved in 100 ml of normal saline) infused intravenously over 30 minutes three times daily for 2 to 3 days.
- Parenteral magnesium must be infused concurrently with thiamine.
- Side effects of parenteral thiamine hydrochloride may include generalized pruritus, transient local irritation, or rarely, anaphylactic or anaphylactoid reactions.

CHRONIC Rx

Recommended oral dose after completed parenteral treatment for WE: Thiamine 30 to 100 mg twice daily

DISPOSITION

- If prompt treatment with thiamine is not administered during the potential reversible stages of WE, Korsakoff syndrome may develop consisting of a typical pattern of irreversible memory loss emerging after the acute global confusional state of WE resolves.
- Approximately 80% of patients who survive WE develop Korsakoff syndrome.

REFERRAL

In cases of altered mental status, ophthalmoplegia, or ataxia of gait, consider neurology consultation. Treatment should be initiated as soon as WE is suspected.

PEARLS & CONSIDERATIONS

COMMENTS

- WE should be suspected in all patients with poor nutrition.
- WE is a clinical diagnosis composed of a triad of confusion, ataxia, and ophthalmoplegia, but the full triad is rarely present.
- Thiamine infusion should be initiated upon clinical suspicion of WE.
- Thiamine infusion should precede infusion of fluids with glucose in all patients with poor nutrition or clinical suspicion of WE.

PREVENTION

- Prophylactic treatment for patients with severe alcohol withdrawal, poor nourishment, or signs of malnutrition: Thiamine 250 mg IM daily for 3 to 5 days.
- In individuals susceptible to WE, 100 mg of IV thiamine should precede any glucose infusion.
- Recommended daily dose of thiamine for an average, healthy adult: 1.4 mg or 0.5 mg per 1000 kcal of carbohydrates consumed.
- Higher daily dose of thiamine recommended for children, critically ill patients, and during pregnancy and lactation.

PATIENT & FAMILY EDUCATION

In cases of known alcohol abuse, severe illness, or after bariatric surgery, the patient and family should be counseled on the importance of proper nutrition, including vitamin supplementation.

RELATED CONTENT

Alcohol Use Disorder (Related Key Topic)
Korsakoff Psychosis (Related Key Topic)
Vitamin Deficiency (Related Key Topic)

AUTHORS: **Danyelle Evans, MD, Corey Goldsmith, MD,** and **D. Brandon Burtis, DO**

BASIC INFORMATION

DEFINITION

Arthropod-borne viruses (arboviruses) are transmitted to humans primarily through the bites of infected mosquitoes. West Nile virus (WNV) is the leading cause of domestically acquired arboviral disease in the U.S.

SYNONYMS

WNV
West Nile virus fever
West Nile virus encephalitis
Neuroinvasive West Nile virus infection
Nonneuroinvasive West Nile virus infection

ICD-10CM CODE
A92.30 West Nile virus infection, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Before 1999, WNV infection was confined to areas in the Middle East, with occasional outbreaks in Europe. The infection began being diagnosed in the Western Hemisphere in 1999. First seen in the northeast and mid-Atlantic states, WNV virus infection has spread steadily each yr to new regions of the U.S., with a general westward migration pattern. Since 2004, the incidence of WNV infection waxed and waned as it spread to the western states. Human cases of WNV infection have now been reported across all the contiguous continental U.S. (sparing only Hawaii and Alaska). From 1999 through 2016, more than 780,000 cases of WNV infection occurred in the U.S., with 21,574 cases of neuroinvasive disease and 2017 deaths attributable to WNV. The overall mortality rate from reported cases of symptomatic patients with WNV is about 4%. The virus has now become the most prevalent, reportable, arthropod-borne form of viral encephalitis in North America and is likely to remain for decades to come. In 2017, 48 states and the District of Columbia reported 1425 cases of neuroinvasive WNV disease (e.g., meningitis, encephalitis, acute flaccid paralysis) for a national incidence of 0.44 cases per 100,000 population. California, Texas, and Colorado had the highest reported numbers of cases. In 2018 WNV neuroinvasive disease incidence was 25% higher than the median incidence during 2008-2017.
- The virus is carried by a number of species of birds, as well as horses and several other animals. It is transmitted to humans through the bite of an infected mosquito. For this reason, WNV infection is seen primarily from mid-summer to mid-autumn, the period of maximum mosquito intensity (Fig. E1).
- The majority of severe cases have been reported among individuals >50 yr of age. There is no gender predilection. Certain HLA haplotypes appear to predispose to severe disease (e.g., HLA-A68 and HLA-C08).
- Person-to-person transmission is fortunately rare but has been reported to occur by blood transfusion, organ transplantation, breastfeeding, and perhaps perinatal transmission; the blood supply is now routinely tested by nucleic acid testing methods to reduce the risk of transmission-acquired WNV in the U.S.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Less than 20% of infected individuals develop symptomatic disease. The initial phase of illness is nonspecific, with abrupt onset of fever (West Nile fever) accompanied by malaise, eye pain, anorexia, headache, and, occasionally, rash and lymphadenopathy. Less commonly, myocarditis, hepatitis, or pancreatitis may occur.
- Encephalitis is the most common neurologic manifestation of WNV infection. Aseptic meningitis may also occur.
- In approximately 1 in 150 cases, especially among older patients (>70 yr), severe neurologic sequelae will occur (West Nile neuroinvasive disease [WNND]). Most common among these are ataxia, cranial nerve palsies, optic neuritis, seizures, myelitis, and polyradiculitis.

ETIOLOGY

The WNV is a member of the flavivirus group, along with the yellow fever, dengue, St. Louis, and Japanese encephalitis viruses. It has a large reservoir in nature, infecting many species of birds, as well as certain mammals, and is spread to humans primarily by the bite of an infected *Culex* mosquito or other various species of mosquito, with a peak incidence in the late summer and early fall. Neurologic disease is caused by direct invasion of the CNS.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Meningitis or encephalitis caused by more common viruses (e.g., enteroviruses, herpes simplex)
- Bacterial meningitis
- Vasculitis
- Fungal meningitis (e.g., cryptococcal infection)
- Tuberculous meningitis

LABORATORY TESTS

- Complete blood count, electrolytes (hyponatremia common).
- Spinal tap and cerebrospinal fluid (CSF) examination: Typically demonstrates lymphocytic pleocytosis with normal level of glucose and elevated level of protein.
- CSF WNV IgM antibody level: Detection in symptomatic patients is diagnostic of WNND. The antibody can be detected within 9 days of fever onset and can persist for several months. There can be rare false-positive results in people recently vaccinated against Japanese encephalitis or yellow fever viruses.

IMAGING STUDIES

MRI of the brain to exclude mass lesions and cerebral edema

TREATMENT

NONPHARMACOLOGIC THERAPY

Hospitalization, IV hydration, and ventilator support may be necessary.

ACUTE GENERAL Rx

No specific therapy has been established in clinical trials. Ribavirin and interferon alfa-2b have been shown to have in vitro activity against the virus. IV immunoglobulin (IVIG) from convalescent patient plasma is under study, but one clinical trial using high-titered IVIG already has not shown clinical significance in WNND.

CHRONIC Rx

Chronic rehabilitation therapy is usually necessary for patients with severe neurologic impairment. Mental status defects following WNND appear to be more common and severe than initially recognized.

DISPOSITION

Chronic rehabilitation as needed following recovery from acute infection. Physical and mental outcome measures seem to normalize within approximately 1 yr in patients with WNV. The presence of preexisting comorbid conditions is associated with longer recovery.

REFERRAL

- Infectious disease consultant
- Public health authorities

PEARLS & CONSIDERATIONS

COMMENTS

- Diagnosis requires a high index of suspicion because disease course may be nonspecific and may mimic other, more common disorders.
- Specific laboratory diagnostic studies are available only through public-health laboratories.
- Mosquito prevention with a DEET (N,N-diethyl-meta-toluamide) spray, picaridin spray, or oil of lemon eucalyptus (OLE) or para-menthane-diol (PMD) during peak season can prevent transmission through mosquito avoidance. OLE and PMD should not be used in children aged <3 yr.
- Equine vaccines are available, but human vaccines remain years away.

RELATED CONTENT

West Nile Virus Infection (Patient Information)

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Centers for Disease Control and Prevention: West Nile virus disease and other nationally notifiable arboviral diseases—United States, 2017, *MMWR* 67:1137-1141, 2018.

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Petersen LR et al: West Nile virus: Review of the literature, *J Am Med Assoc* 310:308-315, 2013.

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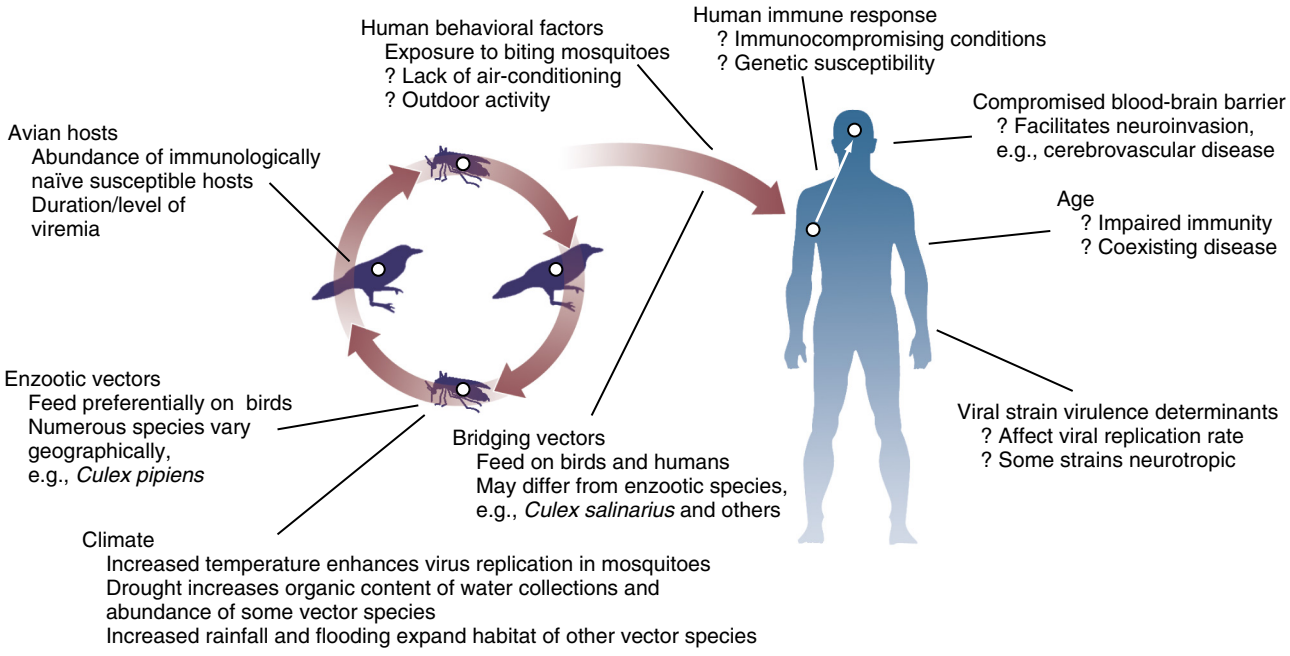

FIG. E1 West Nile virus transmission cycle and examples of modifying climatologic, vertebrate, mosquito, and human factors on infection and illness. (Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Saunders.)

BASIC INFORMATION

DEFINITION

Whiplash refers to a hyperextension injury to the neck (Fig. E1), often the result of being struck from behind by a fast-moving vehicle.

SYNONYMS

Acceleration flexion-extension neck injury
Cervical strain
Whiplash-associated disorder (WAD)

ICD-10CM CODE
S13.4 Sprain and strain of cervical spine

EPIDEMIOLOGY & DEMOGRAPHICS

- Whiplash occurs in more than 1 million people each yr, with a worldwide incidence of 15 to 200 per 100,000 people.
- Most injuries (40%) are the result of rear-end motor vehicle accidents.
- Whiplash occurs at all ages, in both sexes, and at all socioeconomic levels.
- Whiplash is more common in women than men.
- Nearly 50% of patients with whiplash seek legal advice.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Many present with a history of being involved in a motor vehicle accident and being rear-ended by another vehicle.
- Pain does not present initially but usually develops over the ensuing days.
- Symptoms include neck stiffness, headache, shoulder and back pain, tinnitus, temporomandibular joint (TMJ) pain, and mood changes.
- The presence of weakness or numbness in the arms or legs may be indicative of a more severe injury and should be evaluated by a clinician.

ETIOLOGY

- The mechanism of injury is the result of the sudden acceleration of the body forward, forcing the neck to hyperextend backward, causing injury to ligaments, muscles, bone, and/or intervertebral disk. At the end of the accident the head is thrust forward in a flexion position, sometimes causing injury to the cervical spine.
- Motor vehicle accidents, trauma from falls, contact sports, physical abuse, and altercations are all possible causes of whiplash.
- Patients with preexisting cervical facet degeneration are at higher risk for poor recovery.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Osteoarthritis
- Cervical disk disease
- Fibromyalgia
- Myofascial neck pain
- Torticollis
- Spinal cord tumor
- TMJ syndrome
- Tension headache
- Migraine headache

WORKUP

- Any patient who presents with symptoms of whiplash and musculoskeletal or neurologic signs merits a workup to exclude cervical spine fracture or herniated disk disease.
- The neck disability index has shown to have high reproducibility for quantifying disease burden related to whiplash.

LABORATORY TESTS

Laboratory studies are not helpful.

IMAGING STUDIES

- Plain cervical spine films (anteroposterior, lateral, and odontoid views)
- Flexion/extension x-rays
- CT scan to exclude fracture
- MRI as alternative or in addition to CT in selected cases of neurologic compromise

TREATMENT

NONPHARMACOLOGIC THERAPY

- Soft cervical collar for no longer than 72 hr. Prolonged courses of cervical immobilization have been found to delay the return of normal, pain-free motion.
- Nonimmobilization rehabilitation has shown faster and more complete pain relief.
- Moist heat 15 to 20 min four to six times per day.
- Continue with usual activities.
- Neck-specific exercises (isometric strengthening followed by resisted pulleys) have been shown to decrease associated radiating pain.

ACUTE GENERAL Rx

- Analgesics:
  1. NSAIDs
  2. Acetaminophen
- Muscle relaxants (short-term use)

CHRONIC Rx

NSAIDs and Tylenol can be used on a long-term basis, as needed. Referral to a physiatrist may also aid in providing multimodal therapy, such as stretching and strengthening.

DISPOSITION

- Many patients recover from the acute whiplash injury within wks.
- Factors associated with persistent and severe whiplash injuries are described in Table E1.
- 20% to 40% may develop chronic whiplash syndrome (symptoms of headache, neck pain, and psychiatric complaints that persist for 6 mo).

TABLE E1 Factors Associated with Persistent and Severe Whiplash Injuries

Severe Whiplash Injury
- High-speed injury
- Intense and rapid onset of pain
- Severe restriction of movement at presentation
- Abnormal neurology
- Bony injuries

Persistent Whiplash Injury
- High-speed injury
- Intense and rapid onset of pain
- Severe restriction of movement at presentation
- Abnormal neurology
- Bony injuries
- Increasing age
- Upper limb paresthesias
- Cervical spondylosis

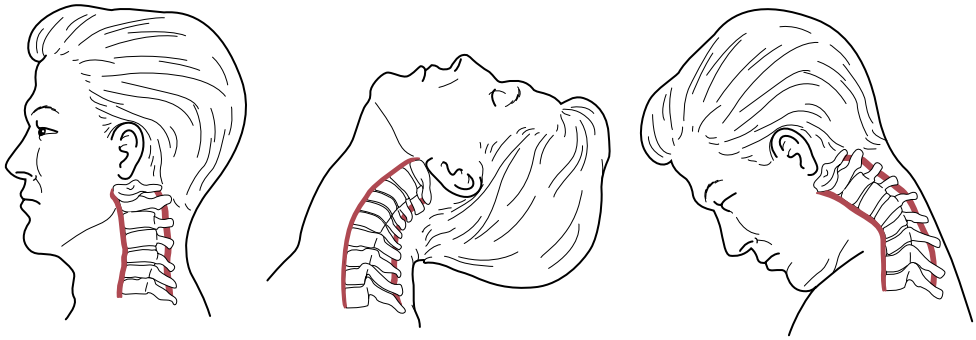

FIG. E1 Cervical flexion–extension injuries, popularly called whiplash, may tear the anterior and posterior longitudinal ligaments *(red)* and other soft tissues, herniate intervertebral disks, and exacerbate cervical spondylosis. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.)

- Older age, female gender, legal issues, preexisting cervical facet degeneration, and work status were found to be prognostic factors associated with a negative outcome.

REFERRAL

Orthopedic and physical therapy consultation should be sought for symptoms >6 mo.

PEARLS & CONSIDERATIONS

- Nearly one-third of all personal injury cases involve cervical injuries.
- Medical attention should be sought sooner for new weakness or numbness, changes with bowel or bladder function, or loss of dexterity.
- Recent studies have shown that patients with the quickest resolution of symptoms after an acute whiplash incident tend to have the best prognosis regarding long-term function and range of motion.

COMMENTS

The entity of chronic whiplash syndrome remains elusive. Some authorities argue that financial motivation is a factor leading to persistent neck symptoms. Other studies do not substantiate this, showing a true chronic injury to the soft tissues of the neck.

RELATED CONTENT

Whiplash (Patient Information)

AUTHOR: **Steven L. Bokshan, MD**

SUGGESTED READINGS

Malik AA et al: Assessment of range of movement, pain and disability following a whiplash injury, *Open Ortho J* 11:541-545, 2017.

Söderlund A et al: Exploring patients' experiences of the whiplash injury recovery process–A meta-synthesis, *J Pain Res* 11:1263, 2018.

Rydman E et al: Association between cervical degeneration and self-perceived non-recovery after whiplash injury, *Spine J*(19)30899–X, pii: S1529-9430 2019.

BASIC INFORMATION

DEFINITION

Whipple disease is a multisystem illness characterized by malabsorption and its consequences, lymphadenopathy, arthritis, cardiac involvement, ocular symptoms, and neurologic problems; it is caused by the gram-positive bacillus *Tropheryma whippelii.*

SYNONYM

Intestinal lipodystrophy (name used by Whipple in 1907)

ICD-10CM CODE
K90.81 Whipple disease

EPIDEMIOLOGY & DEMOGRAPHICS

- Uncommon illness (only about 1000 cases have been reported to date).
- Peak age: 30 to 60 yr; mean age at diagnosis, 50 yr.
- More frequent in men than women and in whites.
- Specific environmental factors have not been associated with Whipple disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

PHYSICAL FINDINGS:

- Abdominal distention, sometimes with tenderness and less commonly fullness or mass, which represents enlarged mesenteric lymph nodes
- Signs of weight loss, cachexia
- Clubbing
- Lymphadenopathy
- Inflamed joints
- Heart murmur or rub
- Sensory loss or motor weakness related to peripheral neuropathy
- Abnormal mental status examination
- Pallor

CLINICAL PRESENTATION: Whipple disease is characterized by various stages (Box E1): The prodromal stage is marked by protean symptoms and chronic arthralgias and arthritis. The steady-state stage, which follows the prodromal stage by an average time of 6 yr, is manifested by weight loss, diarrhea, or both. When the disease presents with extraintestinal symptoms (e.g., arthralgia), few clinicians will suspect the diagnosis unless or until GI symptoms are present. Weight loss, diarrhea, and arthropathies are found together in 75% of patients at time of diagnosis. The GI manifestations are those seen in malabsorption of any cause:

- Diarrhea: 5 to 10 semiformed, malodorous steatorrheic stools per day
- Abdominal bloating and cramps
- Anorexia

Extraintestinal manifestations of malabsorption:

- Weight loss, fatigue
- Anemia
- Bleeding diathesis
- Edema and ascites
- Osteomalacia

Extraintestinal involvement (Table E1):

- Arthritis (intermittent, migratory; affecting small, large, and axial joints)
- Pleuritic chest pain and cough
- Pericarditis, endocarditis
- Dementia, ophthalmoplegia, myoclonus, and many other symptoms because any portion of the CNS may be a disease site. Box E2 summarizes central nervous system symptoms and signs of classic Whipple disease
- Fever

ETIOLOGY & PATHOGENESIS

- Infectious disease caused by *T. whippeli,* an actinobacteria.
- The bacillus has never been cultured, nor has direct transmission from patient to patient ever been documented; however, the agent can be seen in tissue samples by electron microscopy and identified by polymerase chain reaction (PCR).
- Predictable response to appropriate antibiotic therapy confirms the pathogenic role of the infection.
- Tissue infiltration by macrophages is believed to be the mechanism of specific organ dysfunction and symptoms.
- Subtle defects of the cell-mediated immunity exist in active and inactive Whipple disease that may predispose certain individuals to clinical manifestations. HLA-B27 positivity is found in 26% of patients (four times higher than expected).

BOX E1 Clinical Presentations of *T. whipplei* Infection

Acute infection:
  Gastroenteritis
  Bacteremia
  Pneumonia
Asymptomatic carriage
"Classic" Whipple disease

From Cherry JD: *Feigin and Cherry's pediatric infectious diseases,* ed 8, 2019, Elsevier.

TABLE E1 Major Symptoms and Signs in Classic Whipple Disease

	Cases (%)
Symptoms	
Weight loss	65-100
Chronic diarrhea	65-85
Arthralgia	65-80
Abdominal pain	60
Fever	10-55
CNS-related complaints	10-40
Signs	
Malnutrition	90-95
Hypotension	70
Abdominal tenderness	50
Edema	30
Abdominal mass	20
Hepatomegaly	1-14
Splenomegaly	5-10
Ascites	8

CNS, Central nervous system.
From Cherry JD: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Malabsorption/maldigestion:

- Celiac disease
- *Mycobacterium avium-intracellulare* intestinal infection in patients with AIDS
- Intestinal lymphoma
- Abetalipoproteinemia
- Amyloidosis
- Systemic mastocytosis
- Radiation enteritis
- Crohn disease
- Short bowel syndrome
- Pancreatic insufficiency
- Intestinal bacterial overgrowth
- Lactose deficiency
- Postgastrectomy syndrome
- Other cause of diarrhea
- Seronegative inflammatory arthritis
- Pericarditis and pleuritis

BOX E2 Central Nervous System Symptoms and Signs of Classic Whipple Disease

Ataxia
Confusion
Convulsions
Dementia
Depression
Diplopia
Dizziness
Facial pain
Headache
Hearing loss
Hemiparesis
Hyperphagia
Hyperreflexia (± Babinski sign)
Incoordination
Lethargy, coma
Loss of vibratory and position sense
Meningoencephalitis
Mental and personality changes
Motor weakness
Muscle jerks and twitches
Muscle rigidity
Numbness
Nystagmus
Ophthalmoplegia
Papilledema
Polydipsia
Ptosis
Pupillary abnormalities
Sensory loss
Sleep disorders
Slurred speech
Stiff neck
Tinnitus
Visual difficulties (diplopia, blurring)

From Cherry JD: *Feigin and Cherry's pediatric infectious diseases,* ed 8, 2019, Elsevier.

- Lymphadenitis
- Neurologic disorders

WORKUP

Laboratory tests and imaging studies are useful; however, the diagnosis of Whipple disease is usually made by upper endoscopy and biopsy. Endoscopic findings reveal a pale yellow, shaggy mucosa alternating with an erythematous, erosive, or friable mucosa in the duodenum or jejunum.

LABORATORY TESTS

- Anemia (iron, folate, or vitamin B_{12} deficiency)
- Hypokalemia
- Hypocalcemia
- Hypomagnesemia
- Hypoalbuminemia
- Prolonged prothrombin time
- Low serum carotene
- Low cholesterol
- Leukocytosis
- Steatorrhea demonstrated by a Sudan fecal fat stain
- 72-hr stool collection demonstrating more than 7 g/24 hr of fat in the stool is impractical to perform, especially in ambulatory patients
- Defective D-xylose absorption

IMAGING STUDIES

Small bowel radiographs after barium ingestion often show thickening of mucosal folds.

BIOPSY

Infiltration of the intestinal lamina propria by PAS-positive macrophages containing gram-positive, acid-fast negative bacilli, associated with lymphatic dilation (diagnostic); PCR of the involved tissue in uncertain cases. If PAS staining of the small-bowel biopsy specimen is positive and the PCR assay is negative, the diagnosis of Whipple disease must be confirmed; this can be done by immunohistochemical testing with an antibody to *T. whippeli.* If this test result is positive, Whipple disease is confirmed.

Rx TREATMENT

- Antibiotics: TMP/SMX DS bid for 12 mo, usually preceded by parenteral administration of ceftriaxone (2 g/day) for 2 wk *or* penicillin G 2 million units q4h for 2 wk.
- Alternative regimen for sulfa-allergic patients consists of doxycycline (200 mg/day) *plus* hydroxychloroquine (200 mg tid) for 12 mo after parenteral ceftriaxone or penicillin G for 2 wk.
- Treat specific vitamin, mineral, and nutrient deficiencies.
- Patients with a neurologic recurrence of Whipple disease have a poor prognosis. Interferon gamma has been proposed for treatment of recurrent CNS disease.

AUTHOR: **Fred F. Ferri, MD**

BASIC INFORMATION

DEFINITION

Wilson disease is an autosomal recessive disorder of copper transport with inadequate biliary copper excretion, leading to an accumulation of the metal in liver, brain, kidneys, and corneas.

SYNONYM

Progressive hepatolenticular degeneration

ICD-10CM CODE
E83.00 Disorder of copper metabolism

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: One case in 30,000
PREDOMINANT SEX: Affects men and women equally (autosomal recessive gene)
ONSET OF SYMPTOMS: Ages 3 to 40 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Most older patients present with chronic liver disease and/or neurologic manifestations, whereas younger patients may present with acute liver failure. Hepatic presentation:

- Acute hepatitis with malaise, anorexia, nausea, jaundice, elevated transaminase, prolonged prothrombin time; rarely fulminant hepatic failure
- Chronic active (or autoimmune) hepatitis with fatigue, malaise, rashes, arthralgia, elevated transaminase, elevated serum immunoglobulin G, positive antinuclear antibody and antismooth muscle antibody
- Chronic liver disease/cirrhosis with hepatosplenomegaly, ascites, low serum albumin, prolonged prothrombin time, portal hypertension

Neurologic presentation:

- Movement disorder: Tremors (Fig. E1), ataxia
- Spastic dystonia: Masklike facies, rigidity, gait disturbance, dysarthria, drooling, dysphagia
- The most common neurologic presentation in a young adult is parkinsonism

Ophthalmic:

- Kayser-Fleischer ring; indicates copper deposition in the Descemet membrane of the iris. They are most common in patients with neurologic manifestations. Typically, they are only visualized with slit-lamp examination.
- Sunflower cataracts.

Psychiatric presentation:

- Depression, obsessive-compulsive disorder, psychopathic behaviors, neuroses

Other organs:

- Hemolytic anemia due to the sudden release of copper from liver cells
- Renal disease (i.e., Fanconi syndrome with hematuria, phosphaturia, renal tubular acidosis, vitamin D–resistant rickets)
- Cardiomyopathy
- Arthritis
- Hypoparathyroidism
- Hypogonadism

PHYSICAL FINDINGS:

- Ocular: The Kayser-Fleischer ring is a gold-yellow ring seen at the periphery of the iris (Fig. E2). It is present in virtually all persons with neurologic involvement. These should be sought with slit-lamp examination by a skilled examiner
- Stigmata of acute or chronic liver disease
- Neurologic abnormalities: See previous

ETIOLOGY & PATHOGENESIS

- Dietary copper is transported from the intestine to the liver, where normally it is metabolized into ceruloplasmin. In Wilson disease, defective incorporation of copper into ceruloplasmin and a decrease of biliary copper excretion lead to accumulation of this mineral.
- The disease results from an autosomal recessive inborn error of metabolism caused by a mutation of the copper P-type adenosine triphosphatase encoded on chromosome 13q14.3 (*ATP7B* gene).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hereditary hypoceruloplasminemia.
- Menkes disease.
- Consider the diagnosis of Wilson disease in all cases of acute or chronic liver disease for which another cause has not been established.
- Consider Wilson disease in patients with movement disorders or dystonia even without symptomatic liver disease.

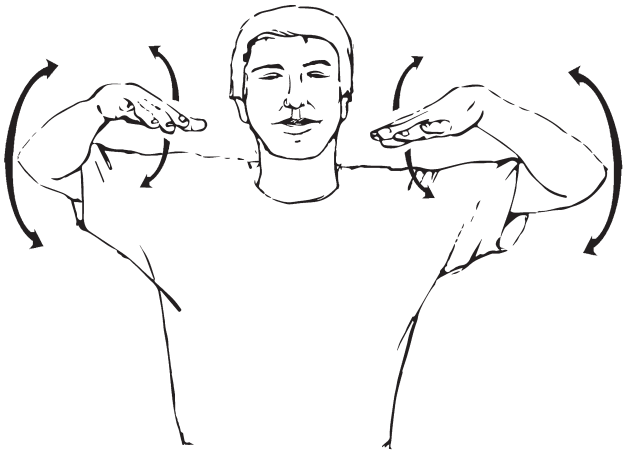

FIG. E1 Wilson disease characteristically induces parkinsonism, dystonia, dysarthria, and various tremors, including a *wing-beating tremor*. This particular tremor, which is a hallmark of the disease but only occurs in about one third of cases, consists of rhythmic, coarse, up-and-down arm movements based at the shoulders. It gives patients the appearance of flapping their arms as though they are attempting to fly. (From Kaufman DM et al: *Kaufman's clinical neurology for psychiatrists,* ed 8, Philadelphia, 2017, Elsevier.)

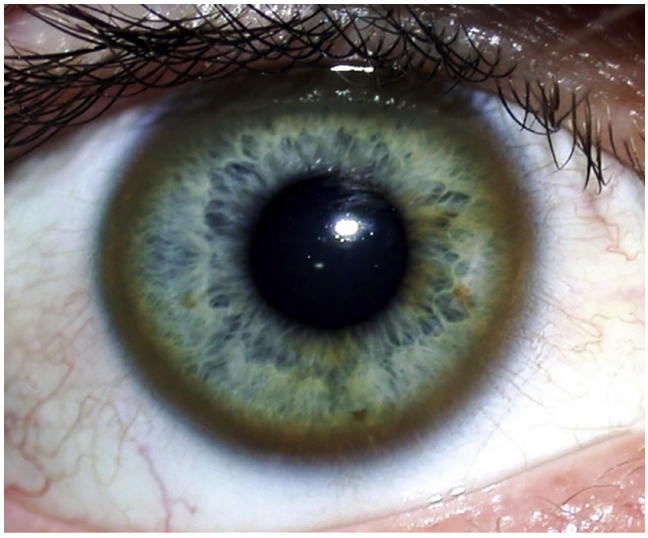

FIG. E2 Wilson disease. (Courtesy of S. Chen. From Bowling B: *Kanski's clinical ophthalmology, a systemic approach,* ed 8, Philadelphia, 2016, Elsevier.)

LABORATORY TESTS

- Table E1 compares biochemical parameters in normal adults and in patients with Wilson disease
- Low serum ceruloplasmin level (<200 mg/L) present in 95% of affected patients
- 24-hr urinary copper excretion greater than 250 mcg (normal <60 mcg); increases to greater than 1200 mcg/24 hr after 500 mg of d-penicillamine (normal <500 mcg/24 hr)
- Low serum copper
- Abnormal liver function tests (note that aspartate aminotransferase may be higher than alanine aminotransferase)
- Low serum uric acid and phosphorus
- Abnormal urinalysis (hematuria)
- Coombs-negative hemolytic anemia (due to sudden release of copper from hepatocytes)
- Molecular genetic testing for mutations of the *ATP7B* gene can also be used for diagnosis

BIOPSY

- Early:
  1. Steatosis, focal necrosis, glycogenated hepatocyte nuclei
  2. May reveal inflammation and piecemeal necrosis
- Late: Cirrhosis
- Hepatic copper content (>250 mcg/g of dry weight) (normal is 20 to 50 mcg) gold standard for diagnosis
- Histochemical confirmation of excess copper can be helpful in diagnosis, but if absent, does not exclude Wilson disease. The lack of immunoreactivity to copper-binding protein can occur because of the diffuse presence of copper in the cytoplasm and because of the assay's low sensitivity. Rhodamine and rubeanic acid stains can show dense granular lysosomal copper deposition in hepatocytes at the stage of cirrhotic nodular regeneration

Rx TREATMENT (TABLE E2)

- Trientine (triethylenetetramine): Chelator therapy; preferred agent due to fewer side effects than penicillamine
  1. 1 to 1.2 g/day divided tid
  2. Monitor CBC, iron studies
- Penicillamine (Chelator therapy):
  1. 0.75 to 1.5 g/day divided bid (with pyridoxine 25 mg/day)
  2. Monitor complete blood count (CBC) and urinalysis weekly
- Zinc: Inhibits intestinal copper absorption
  1. 50 mg tid
  2. Monitor zinc level
- Ammonium tetrathiomolybdate for neurologic symptoms
- Antioxidants
- Liver transplantation (for severe hepatic failure unresponsive to chelation); liver transplantation corrects the underlying pathophysiology and can be lifesaving

PROGNOSIS

Good with early chelation treatment

REFERRAL

To gastroenterologist, neurologist

PEARLS & CONSIDERATIONS

COMMENTS

Family screening of first-degree relatives must be undertaken. Genetic diagnosis is also useful in patients with indeterminate clinical and biochemical features.

RELATED CONTENT

Wilson Disease (Patient Information)

AUTHOR: **Fred F. Ferri, MD**

TABLE E1 Biochemical Parameters in Normal Adults and in Patients with Wilson Disease

	Normal Adults	Wilson Disease*
Serum ceruloplasmin (mg/L)	200-350	0-200
Serum copper (μg/L)	700-1520	190-640
(μmol/L)	11-24	3-10
Basal 24-hr urinary copper (μg/day)	<40	40-10,000
(μmol/day)	≤0.6	>0.6
Liver copper (μg/g dry weight)	20-50	>250 (possibly >70)

*For all the assays, results in homozygotes and heterozygotes may overlap.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

TABLE E2 Recommendations for the Treatment of Wilson Disease

Drug	Dose*	Tests for Monitoring Efficacy	Tests for Monitoring Side Effects
D-penicillamine (+ pyridoxine 25 mg daily)	Initial: 1-1.5 g/day (adults) or 20 mg/kg/day (children) divided into two or three doses	24-hour urinary copper: 200-500 μg (3-8 μmol)/day as target; estimated non–ceruloplasmin-bound copper <200 μg/L	Complete blood count; urinalysis; skin examination
	Maintenance: 0.75-1 g/day as needed to maintain cupruresis	Estimated non–ceruloplasmin-bound copper <100 μg/L	
Trientine†	Initial: 1-1.2 g/day divided into two or three doses‡	Same as for D-penicillamine	Complete blood count; iron studies
	Maintenance: Same	Same as for D-penicillamine	
Zinc	Initial: 50 mg elemental zinc three times daily (adults)§	24-hour urinary copper: <75 μg (1.2 μmol)/day as target	Serum zinc level Serum AST and ALT levels
	Maintenance: Titrate the dose based on efficacy monitoring data¶	Estimated non–ceruloplasmin-bound copper <100 μ/L	

*All medications should be taken before or after mealtime if possible, but the timing of the dose may have to be adjusted to enhance consistent adherence to treatment.
†Requires refrigeration.
‡The dose of trientine in children is not established (≈20 mg/kg/day).
§The dose of zinc in children is not established. Typical dosing is 25 mg of elemental zinc three times daily until adult stature (≈50 kg body weight) is achieved, when the adult dose of 50 mg of elemental zinc three times daily is used. The dose is not well defined for children younger than 5 yr. The dose in children also can be titrated to achieve optimal 24-hr urinary copper excretion.
¶The 24-hr urinary copper excretion reflects total body copper load and thus can be used to monitor zinc treatment although zinc does not cause cupruresis; some groups prefer to use the estimated non-ceruloplasmin-bound copper determination as a guide.

Wolff-Parkinson-White Syndrome PTG

BASIC INFORMATION

DEFINITION

Wolff-Parkinson-White (WPW) syndrome is a congenital heart condition in which, in addition to the normal electrical conduction through the atrioventricular (AV) node, there is an accessory pathway (AP) that connects the atria to the ventricles. Consequently, a portion of the ventricular myocardium is depolarized via the AP earlier than the normal AV nodal conduction, resulting in ventricular preexcitation. The terms "WPW syndrome" and "WPW pattern" often are used in describing patients with ventricular preexcitation. Patients with WPW syndrome have ECG findings of preexcitation, including short PR and slurring of the initial segment of the QRS complex known as the delta wave together with symptoms suggestive of arrhythmia or documented arrhythmia, which may be atrioventricular (AV) reentrant tachycardia, atrial fibrillation (AF), or both. Patients with the WPW pattern have characteristic ECG findings of preexcitation without evidence of arrhythmia.

SYNONYMS

Preexcitation syndrome
WPW

ICD-10CM CODE
I45.6 Preexcitation syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- The prevalence of a WPW pattern on the surface ECG is 0.1% to 0.3% in the general population. The prevalence is increased to 0.55% in first-degree relatives of affected patients. It is estimated that approximately 65% of adolescents and 40% of individuals older than 30 yr with WPW pattern on a resting ECG are asymptomatic.
- The prevalence of WPW is higher among males and decreases with age.
- Most patients with WPW have structurally normal hearts, but it may also occur in patients with congenital heart disease, most notably in patients with Ebstein anomaly, which is associated with right-side AP and often multiple and slowly conducting APs.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The physical examination is usually unremarkable.
- Symptoms are typically related to tachyarrhythmias, including the following:
  1. Palpitations, lightheadedness, anxiety, dyspnea, or chest pain
  2. Syncope or near syncope
  3. Sudden cardiac death
- The common arrhythmias in WPW syndrome are:
  1. Supraventricular tachycardia: AV reciprocating tachycardia (AVRT). This is the most common arrhythmia, further classified as orthodromic AVRT (narrow complex tachycardia, with antegrade conduction through the AV node and retrograde conduction via the AP that occurs in 70% of symptomatic patients) or antidromic AVRT (wide complex tachycardia with antegrade conduction via the AP and retrogradely through the AV node, which occurs in 4% to 5% of patients).
  2. AF (~10% to 38%), the second most common tachycardia, can be complicated by a very rapid ventricular response due to conduction over the AP, which can lead to ventricular fibrillation (VF) and sudden death. This risk is dependent on the antegrade refractory period of AP during AF.
  3. The risk of sudden death in symptomatic patients with WPW syndrome is estimated to be approximately 0.25% per yr or 3% to 4% over a lifetime.
- In a meta-analysis including approximately 2000 subjects with asymptomatic WPW, children had a sudden death rate of 1.9 compared with 0.9 in adults per 1000 patient-yrs of follow-up. This incidence is comparable with the estimated 0.1% per yr risk of death in the general population in Europe, Japan, and the U.S.

ETIOLOGY & PATHOGENESIS

- APs are thought to be an embryologic remnant, as substantiated by reports of SVT in uterus and by a greater prevalence of WPW in newborns and infants.
- Left free wall APs are most common followed by posteroseptal, right free wall, and anteroseptal locations.
- Some patients with WPW syndrome (~5% to 10%) have multiple APs.
- In subjects with WPW, two parallel routes of AV conduction are present: One is subject to delay through the AV node, and the other occurs without delay through the AP and results in preexcitation of the ventricles. The resulting QRS complex is a fusion beat, as a portion of the ventricle is preexcited and activated via the AP giving rise to the delta wave, and the remainder of the ventricle is activated by the normal activation pathway (Fig. 1).

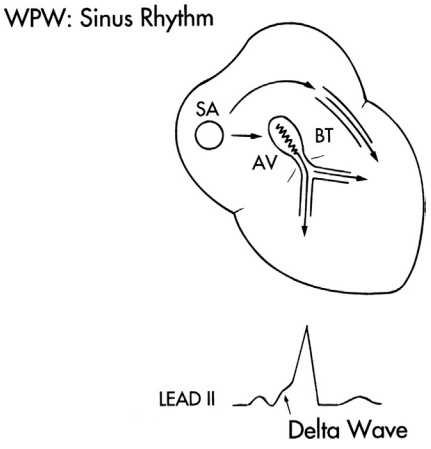

FIG. 1 With Wolff-Parkinson-White (WPW) syndrome, an abnormal accessory pathway called a bypass tract connects the atria and the ventricles. (From Goldberger AL [ed]: *Clinical electrocardiography: a simplified approach,* ed 6, St Louis, 1999, Mosby.)

- Reciprocating tachycardias occur when conduction is anterograde in one pathway (usually the AV node, i.e., orthodromic AVRT) and retrograde in the other (usually the AP) as a result of different refractory periods. This is usually initiated by a premature atrial or ventricular depolarization.

DIAGNOSIS

- Three basic features characterize the ECG abnormalities associated with WPW pattern:
  1. PR interval <120 ms.
  2. QRS complex can be >120 ms with a slurred, slowly rising onset of QRS in some leads (delta wave) and a normal terminal QRS portion. The width of the QRS complex depends on the amount of preexcitation ventricular tissue.
  3. Secondary ST-T wave changes directed in an opposite direction to the major delta and QRS vectors may be present.
- ECG patterns with abnormal QRS complexes and ST and T changes can mask or mimic myocardial infarction (in particular posteroseptal AP with negative delta waves in the inferior wall, which mimics old inferior wall myocardial infarction), bundle branch block (Fig. 2), or ventricular hypertrophy.
- Most commonly seen tachycardia (orthodromic AVRT) is characterized by a normal QRS with a regular rate of 150 to 250 bpm. Onset and termination are abrupt.
- Variants of preexcitation:
  1. Lown-Ganong-Levine syndrome is characterized by a short PR interval, a narrow QRS complex without a delta wave, and a clinical syndrome of paroxysmal SVTs. Postulated mechanisms to the short PR interval include a variant of the normal, enhanced sympathetic tone or specialized intra-nodal fibers with enhanced AV nodal conduction.
  2. Atriofascicular accessory pathway (Mahaim fiber): A slowly conducting AP with AV-nodal like properties, which connects the right atrium with the right bundle branch or the apical myocardium. In the baseline state, minimal or no preexcitation may be present. During preexcitation the QRS appears like a typical LBBB pattern.
  3. Nodoventricular or nodofascicular APs: Rare variants that connect the AV node and the ventricle or the bundle branch appropriately.
- An electrophysiology study is the gold standard to confirm the diagnosis, determine the location, and assess the conduction properties of the AP.

RISK STRATIFICATION

- Intermittent and abrupt loss of preexcitation on a beat-to-beat basis is indicative of lower risk, assessed with Holter monitoring or with an exercise stress test. The loss of preexcitation after administration of the antiarrhythmic drug procainamide has also been used to indicate a low-risk subgroup.

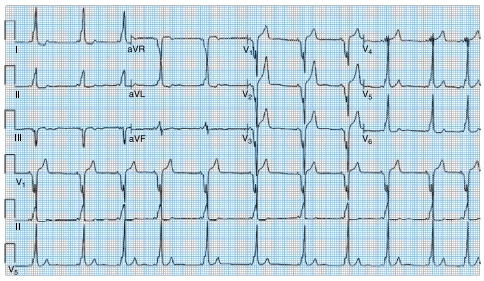

FIG. 2 Wolff-Parkinson-White (WPW) syndrome. This 12-lead electrocardiogram with rhythm strips shows preexcitation with an accessory pathway connecting the right atrium to the right ventricle. This gives rise to a pattern like left bundle branch block because the ventricles are activated over the right-sided accessory pathway. The tracing shows the typical characteristics of WPW syndrome, including a short PR interval, a wide QRS complex, and a delta wave. (From Olshansky B et al: *Arrhythmia essentials*, ed 2, Philadelphia, 2017, Elsevier.)

BOX 1 Goals of Electrophysiologic Evaluation in Patients with Wolff-Parkinson-White Syndrome

- Confirmation of the presence of an accessory pathway (AP)
- Evaluation for the presence of multiple APs
- Localization of the AP(s)
- Evaluation of the refractory period of the AP and its implications for life-threatening arrhythmias
- Induction and evaluation of tachycardias
- Demonstration of the AP role in the tachycardia
- Evaluation of other tachycardias not dependent on the presence of the AP
- Ablation of the AP, when indicated.

From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, WB Saunders.

- In patients with a persistent preexcitation pattern, electrophysiology study is the procedure of choice for risk stratification.

Rx TREATMENT

Goals of electrophysiologic evaluation in patients with WPW syndrome are described in Box 1.

ACUTE MANAGEMENT

- Urgent cardioversion, for an acute tachycardia episode with hemodynamic instability.
- Narrow QRS tachycardia (c/w orthodromic AVRT):
  1. Vagal maneuvers and/or IV adenosine.
  2. IV beta-blockers, diltiazem, or verapamil can be administered for regular and **narrow** QRS tachycardia, implying antegrade conduction via the AV node, when the patient is hemodynamically stable and IV adenosine is ineffective.
- Wide QRS complex tachycardias (WCTs):
  1. Most commonly caused by atrial fibrillation with antegrade conduction via the AP and the AV node. AV nodal blocking therapies (i.e., beta-blockers, calcium channel blockers, digoxin, and adenosine) are potentially dangerous and should be avoided in these cases because of the risk of causing VF by enhancement of the ventricular response through the accessory pathway when the AV node is blocked and the blood pressure is lowered.
  2. Stable patients with preexcited AF can be managed with IV procainamide. Electrical cardioversion should be performed if the patient is hemodynamically unstable.
  3. In a patient with WCT due to antidromic tachycardia, drug treatment may be directed at the AP or at the AV node because both are critical components of the tachycardia circuit.

Long-term management:

- Asymptomatic:
  1. In low-risk patients with intermittent loss of preexcitation, AP effective refractory period (APERP) ≥250 ms, or shortest preexcited RR interval (SPERRI) ≥250 ms, no therapy is required.
  2. In high-risk patients with APERP ≤250 ms or SPERRI≤ 250 ms, competitive athletes, or high-risk occupation (i.e., pilots), ablation should be considered.
- Symptomatic:
  1. Patients who presented with aborted sudden cardiac death, preexcited tachycardia (i.e., atrial fibrillation, flutter, atrial tachycardia), or syncope suggestive of cardiac origin should undergo an electrophysiology study for further characterization and ablation of the AP accordingly.
  2. Patients with symptomatic palpitations or documented AVRT should be offered an electrophysiology study and ablation of the AP to prevent recurrence and to allow the patient to avoid long-term medical therapy. Ongoing management for stable patients with history of orthodromic AVRT who are not candidates for, or prefer not to undergo, catheter ablation:
     - Class IC antiarrhythmics (flecainide, propafenone), in the absence of structural heart disease.
     - Class III antiarrhythmics (amiodarone, sotalol).
     - Oral beta blockers, diltiazem, or verapamil.

SUGGESTED READINGS

Available at ExpertConsult.com

RELATED CONTENT

Wolff-Parkinson-White Syndrome (Patient Information)

AUTHORS: **Yuval Konstantino, MD,** and **Moti Haim, MD**

SUGGESTED READINGS

Bhatia A et al: Preexcitation syndromes, *Curr Probl Cardiol* 41:99-137, 2016. Review.

PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a Wolff-Parkinson-White (WPW, ventricular preexcitation) electrocardiographic pattern, *Heart Rhythm* 9:1006-1024, 2012.

Page RL et al: 2015 ACC/AHA/HRS Guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society, *J Am Coll Cardiol* 67:e27-e115, 2016.

Yellow Fever

BASIC INFORMATION

DEFINITION

Yellow fever is a mosquito-borne infection, primarily of the liver, with systemic manifestations caused by the yellow fever virus (YFV), a flavivirus that infects the liver. The clinical spectrum ranges from asymptomatic infection to life-threatening disease with severity and mortality highest in the elderly.

SYNONYM

Tropical hemorrhagic fever from YFV

ICD-10CM CODE
A95.9 Yellow fever, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

GEOGRAPHIC DISTRIBUTION:

- South America and Africa, in countries between +15 and –15 degrees latitude (Fig. E1).
- The World Health Organization estimates there are more than 200,000 cases per yr with 30,000 deaths per yr. More than 90% of cases occur in Africa.
- Outbreaks of yellow fever occurred in Angola in 2016 and in Brazil: Started in the state of Minas Gerais in 2017 and then spread to other regions and continues currently.

INCIDENCE: Approximate attack rates of 3% in Africa and Amazon
PREVALENCE: Endemic areas: 20% of population
PREDOMINANT SEX: In Africa and the Amazon, male agricultural workers

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most patients with yellow fever are asymptomatic
- The onset of illness appears suddenly 3 to 6 days after the bite of an infected mosquito
- Viremic (early) phase:
  1. Fever, chills
  2. Severe headache
  3. Lumbosacral pain
  4. Myalgias, nausea, malaise
  5. Conjunctivitis
  6. Relative bradycardia (Faget sign)
- After brief recovery, toxic phase:
  1. Jaundice
  2. Oliguria
  3. Albuminuria
  4. Hemorrhage
  5. Encephalopathy
  6. Shock
  7. Acidosis
- Case-fatality rate: 25% to 50%

ETIOLOGY

- YFV *(L. flavus)*: Small enveloped single-strand RNA virus
  1. Flavivirus infects hepatic cells
  2. Late in infection, cytopathic effects (antibody- and cell-mediated) produce pathology
- Vector
  1. *Aedes aegypti* (urban)
  2. *Aedes* spp., *Haemagogus* (especially in Amazon) mosquitos (sylvan)
  3. Primary hosts: Humans and simian species
  4. Exists in two transmission cycles:
     a. Sylvatic or jungle cycle involving mosquitoes and nonhuman primates
     b. Urban cycle involving mosquitoes and humans

PATHOGENESIS & PATHOLOGY:

- Virus replication begins at site of mosquito bite, spreading to lymphatic channels and regional lymph nodes. Viremic spread to other organs, especially liver, spleen, and bone marrow.
- Shock and fatal illness result from direct damage to organs and vasoactive cytokines.
- Viral antigen found in hepatocytes, kidneys, and myocardium.
- Midzone necrosis of liver lobules primarily affected and is highly characteristic.
- Hemorrhages of mucosal surfaces of GI tract.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Viral hepatitis
- Leptospirosis
- Malaria
- Typhoid fever
  1. Typhus
  2. Relapsing fever
- Other hemorrhagic fevers such as dengue and Ebola (see Table E1)

LABORATORY TESTS

- CBC
  1. Mild leukopenia
  2. Thrombocytopenia
  3. Anemia
- LFTs
  1. AST levels exceed ALT levels
  2. Alkaline phosphatase normal or slightly elevated
  3. Elevated bilirubin levels
- Elevated BUN and creatinine
- Proteinuria
- Coagulation studies
  1. Demonstrate abnormal prothrombin time *or*
  2. Reveal DIC
- Terminal hypoglycemia
- CSF
  1. Pleocytosis
  2. Elevated protein count
- Specific diagnosis confirmed by:
  1. Viral isolation from blood: Labor-intensive and may take wks
  2. Viral antigen in serum (ELISA)
  3. Viral RNA by polymerase chain reaction (PCR) in blood or tissue
  4. IgM-capture ELISA
     a. Preferred serologic test
     b. Appears within 5 to 7 days
     c. Rising Ab confirmed by paired sera
     d. Cross-reactivity with other flavivirus infections
  5. Immunohistochemical staining of postmortem liver biopsy specimens

TREATMENT

ACUTE GENERAL Rx

- Acetaminophen (for headache and fever) and H_2 blockers (GI bleeding); avoid aspirin because of bleeding risk
- Blood transfusion, volume replacement for hemorrhage and shock
- Dialysis for renal failure
- Avoidance of sedatives and drugs dependent on hepatic metabolism

DISPOSITION

Follow up until hepatic, renal, CNS disease resolved. Infection in humans is capable of producing hemorrhagic fever and is fatal in 20% to 50% of persons with severe disease.

REFERRAL

To infectious diseases expert for accurate diagnosis and management

TABLE E1 Viral Hemorrhagic Fevers (HFs)

Mode of Transmission	Disease	Virus
Tick-borne	Crimean-Congo HF*	Congo
	Kyasanur Forest disease	Kyasanur Forest disease
	Omsk HF	Omsk
Mosquito-borne†	Dengue HF	Dengue (four types)
	Rift Valley fever	Rift Valley fever
	Yellow fever	Yellow fever
Infected animals or materials to humans	Argentine HF	Junin
	Bolivian HF	Machupo
	Lassa fever*	Lassa
	Marburg disease*	Marburg
	Ebola HF*	Ebola
	HF with renal syndrome	Hantaan

*Patients may be contagious; nosocomial infections are common.
†Chikungunya virus is associated infrequently with petechiae and epistaxis. Severe hemorrhagic manifestations have been reported in some cases.

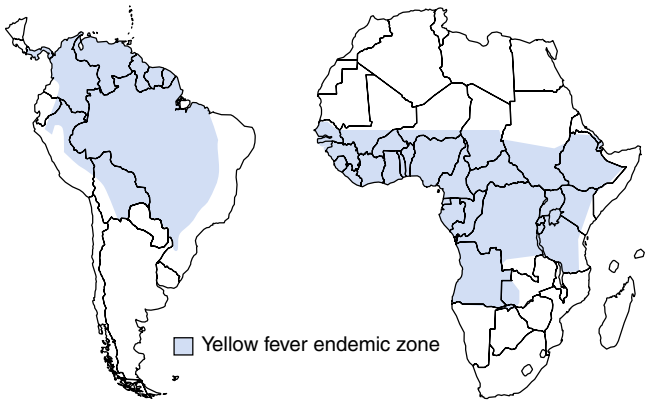

FIG. E1 Geographic distribution of yellow fever in Africa and the Americas. (From Cherry JD et al: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.)

PEARLS & CONSIDERATIONS

PREVENTION

- Yellow fever is preventable by immunization.
- Recovery from yellow fever confers lasting immunity.
- Live, attenuated yellow fever vaccine (YF-Vax) provides protective immunity in 95% of vaccinated patients within 10 days of vaccination. Reimmunization had been recommended at 10-yr intervals for travelers, but in June 2015 the ACIP issued recommendations stating that a single primary dose of a yellow fever vaccine is adequate for most travelers, and in June 2016 the WHO recommended to stop requiring vaccine reimmunization, as one dose confers lifelong immunity. Vaccine certificate to verify immunization status is required before travel in many tropical countries in South America and Africa. Vaccine nonresponders are uncommon but exhibit excess antiinflammatory cytokine profiles and with high levels of T-regulatory cells; this problem is more likely to be observed in elderly individuals.
- The U.S. Advisory Committee on Immunization Practices (ACIP) still recommends reimmunization for the following:
  1. Women who were pregnant at time of first vaccine
  2. Recipients of hematopoietic stem cell transplant
  3. Individuals who were HIV positive (CD4 >200) at the time of first vaccination
  4. Individuals who plan to spend extensive time in endemic areas or travel to highly endemic areas (West Africa)
  5. Lab personnel who handle the yellow fever virus
- Vaccine contraindicated in:
  1. Infants <6 mo (postvaccinal encephalitis)
  2. Immunosuppressed patients, such as those with HIV <200 CD4 count, leukemia, and lymphoma
  3. Pregnant women and nursing mothers, as it is a live weakened virus. Vaccine can be given in pregnancy and breastfeeding if the risk of acquiring the disease from travel to areas involved with the disease is significantly higher than the vaccination risks
  4. Patients with egg hypersensitivity
- Adverse effects of vaccine:
  1. General
     a. Mild headaches, myalgias, low-grade fevers (25% vaccinees in clinical trials)
     b. Immediate hypersensitivity reaction (history of egg allergy)
  2. Vaccine-associated neurotropic disease (postvaccine encephalitis) (1.8 cases per million)
     a. Primarily among infants
     b. Adult cases only in first-time vaccine recipients
  3. Vaccine-associated viscerotropic disease (2.2 cases per million)
     a. Disease syndrome resembling wild-type yellow fever, often fatal
     b. All cases in first-time vaccinees; age >60 yr are at particular risk
- Yellow fever vaccine response can be significantly reduced by coadministration of the live virus combined vaccine with measles, mumps, and rubella.
- YF-Vax became unavailable in the U.S. in mid-2017, and the shortage is expected to last until mid-2019 when a new production facility is ready. An alternative but similar formulation, Stamaril (manufactured in Europe), is available under the FDA's Expanded Access Program at high-volume yellow-fever vaccination centers.

AUTHOR: **Glenn G. Fort, MD, MPH**

SUGGESTED READINGS

Beck AS, Barrett AD: Current status and future prospects of yellow fever vaccines, *Expert Rev Vaccines* 14:1479-1492, 2015.

Centers for Disease Control and Prevention: Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 59(RR-7):1-27, 2010.

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Staples JE et al: Yellow fever vaccine booster doses: recommendations of the Advisory Committee on Immunization Practices, *MMWR* 64(23):647-650, 2015.

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Zenker Diverticulum (PTG)

BASIC INFORMATION

DEFINITION

Zenker (Pharyngoesophageal) diverticulum (ZD) refers to the acquired physiologic obstruction of the esophageal introitus that results from mucosal herniation posteriorly between the cricopharyngeus muscle and the inferior pharyngeal constrictor muscle (Fig. E1).

SYNONYMS

Pharyngoesophageal diverticulum
Pulsion diverticulum
ZD

ICD-10CM CODE
K22.5 Diverticulum of esophagus, acquired

EPIDEMIOLOGY & DEMOGRAPHICS

- The most common type of diverticulum of the upper gastrointestinal tract
- Rare disease with annual incidence estimated 1/50,000 per yr
- Most commonly presents after the age of 60 yr, more commonly seen in males
- Peak incidence is seventh to ninth decades
- Associated with gastroesophageal reflux disease (GERD) and hiatal hernia

PHYSICAL FINDINGS & CLINICAL PRESENTATION

A small ZD may be asymptomatic. As it becomes larger, symptoms may include:

- Dysphagia to solids and liquids (most common)
- Regurgitation of undigested food
- Sensation of globus or fullness in the neck
- Cough
- Halitosis
- Aspiration pneumonia
- Weight loss
- Voice changes
- Sialorrhea (excessive drooling)

ETIOLOGY

- The specific cause is not known. The leading hypothesis suggests a discoordination of the swallowing muscles (specifically, incomplete relaxation of the cricopharyngeus muscle) that leads to an increased pressure on the mucosa of the hypopharynx, resulting in a progressive distention of that mucosa in its weakest area (posterior wall in "Killian triangle," the point between the oblique fibers of the inferior pharyngeal muscle and the horizontal fibers of the cricopharyngeus muscle). The end result is the formation of a false diverticulum where food elements and secretions may be lodged, causing the symptoms listed previously.
- ZD may also occur after anterior spinal surgery or cervical spine injury.

DIAGNOSIS

- Clinical presentation and barium swallow typically make the diagnosis of ZD.
- Neck ultrasound can also be used.
- Esophageal manometry can help elucidate the pathogenesis but not required for diagnosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is similar to anyone presenting with dysphagia:

- Achalasia
- Esophageal spasm
- Esophageal carcinoma
- Esophageal webs
- Peptic stricture
- Lower esophageal (Schatzki) ring
- Foreign bodies
- Central nervous system disorders (stroke, Parkinson disease, amyotrophic lateral sclerosis, multiple sclerosis, myasthenia gravis, muscular dystrophies)
- Dermatomyositis
- Infection

WORKUP

Barium swallow is the test of choice. Upper endoscopy (Fig. E2) runs the risk of perforation.

LABORATORY TESTS

Not specific

IMAGING STUDIES

- Barium swallow: Demonstrates a herniated sac with a narrow diverticular neck that typically originates proximal to the cricopharyngeus at the level of C5 to C6 (Fig. E3).
- Endoscopy is only indicated if barium studies show mucosal irregularities to rule out neoplasia.
- Oropharyngeal-esophageal scintigraphy has recently been shown to be an effective, sensitive, and simple diagnostic study for both qualitative and quantitative analyses.
- Chest radiography is performed in cases of suspected aspiration pneumonia.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Soft mechanical diet can be tried in patients with symptoms of dysphagia.
- Avoid seeds, skins, and nuts.

ACUTE GENERAL Rx

- Endoscopic techniques (esophagodiverticulostomy) have largely replaced conventional surgery and include:
  1. Endoscopic stapler diverticulotomy (may be the initial treatment of choice)
  2. Microendoscopic carbon dioxide laser surgical diverticulotomy
  3. Diverticulum <3 cm is a contraindication to endosurgical approach.
  4. Peroral endoscopic myotomy (POEM) is technically successful in 97% and clinically successful (complete or near complete resolution of dysphagia) in 92%.[1]
  5. Head-to-head comparison with surgical repairs showed endoscopic techniques to be similar in results, relief of symptoms, and patient satisfaction.
- Surgical repair (Table E1) is the conventional treatment for symptomatic patients (dysphagia, cough, aspiration) with excellent relief of symptoms in nearly all patients and low procedural mortality (<1.5%). Procedures include:
  1. Cervical diverticulectomy with cricopharyngeal myotomy (most common approach)
  2. Diverticulopexy or diverticular inversion with cricopharyngeal myotomy
  3. Diverticulectomy alone
  4. Cricopharyngeal myotomy alone

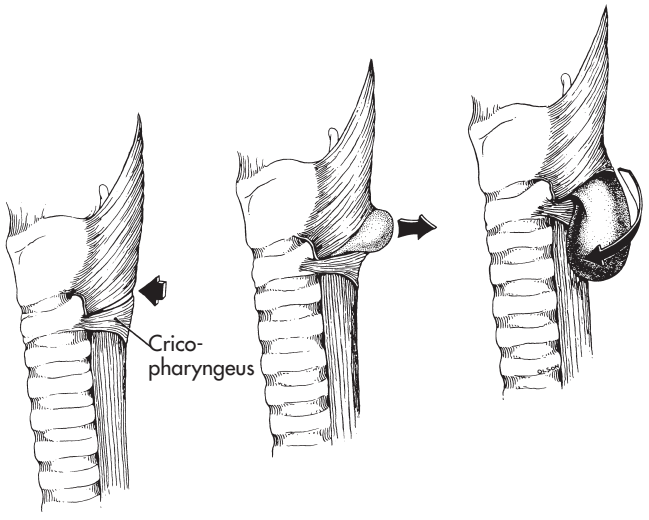


FIG. E1 Formation of pharyngoesophageal (Zenker) diverticulum. Left, Herniation of the pharyngeal mucosa and submucosa occurs at the point of transition *(arrow)* between the oblique fibers of the thyropharyngeus muscle and the more horizontal fibers of the cricopharyngeus muscle. **Center** and **right,** As the diverticulum enlarges, it dissects toward the left side and downward into the superior mediastinum in the prevertebral space. (From Sabiston D: *Textbook of surgery,* ed 15, Philadelphia, 1997, WB Saunders.)

[1] Yang J et al: An international study on the use of peroral endoscopic myotomy in the management of Zenker's diverticulum, Gastrointest Endosc 91(1):163-168, 2020.

FIG. E2 Endoscopic view of a midesophageal diverticulum. These diverticula are most apparent when the esophagus is well insufflated. (From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

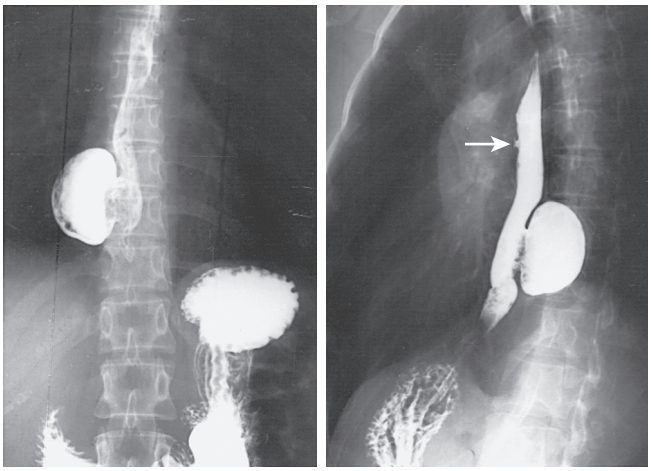


FIG. E3 Posteroanterior *(left)* and oblique *(right)* views from barium esophagogram showing both a typical diverticulum of the junction of the mid-esophagus and distal esophagus and a small traction diverticulum *(arrow)* of the mid-esophagus. (From Sabiston D: *Textbook of surgery,* ed 15, Philadelphia, 1997, WB Saunders.)

TABLE E1 Summary of Operative Techniques for Management of Zenker Diverticulum

Technique	Description
Endoscopic diverticulotomy	Transoral endoscopic division of cricopharyngeus muscle and the septum between the diverticulum and esophagus using electrocautery, laser, or stapler
Open diverticulectomy with myotomy	Excision of diverticulum with myotomy of the cricopharyngeus muscle
Open diverticulopexy with myotomy	Mobilization of the diverticulum with suture fixation above the neck of the diverticulum to the prevertebral fascia with myotomy of the cricopharyngeus muscle
Open myotomy alone	Myotomy of the cricopharyngeus muscle

SUGGESTED READINGS

Law R et al: *Zenker's diverticulum Clin Gastroenterol Hepatol* 12:1773-1782, 2014.

Manno M et al: Alternative endoscopic treatment of Zenker's diverticulum: a case series (with video), *Gastrointest Endosc* 79:168-170, 2014.

CHRONIC Rx

In patients not having surgery, treatment is directed toward any complications that may occur:

- Antibiotics for aspiration pneumonia
- H_2 antagonists for ulcerations that can develop within the diverticulum
- Botulinum toxin for temporary relief of dysphagia

DISPOSITION

- If left untreated, progressive enlargement of the diverticulum occurs.
- The risk of complications (e.g., aspiration pneumonia) increases with the size of the diverticulum.
- Postsurgical recurrence can occur (4%); however, these are usually asymptomatic.

REFERRAL

Any patient with dysphagia requires a gastroenterology consultation. A thoracic surgical, ENT, or head and neck surgeon may be consulted if surgery is considered.

COMMENTS

The association with cancer is rare (0.4%).

RELATED CONTENT

Zenker Diverticulum (Patient Information)

AUTHORS: **Robert M. Kirchner, MD,** and **Paul Gordon, MD**

BASIC INFORMATION

DEFINITION

Zika virus infection is a mosquito-borne flavivirus that emerged as a global public health threat in 2016. The infection usually causes subclinical or mild flulike illness, but severe manifestations such microcephaly in babies born to infected mothers and Guillain-Barré syndrome in adults can occur. There is no treatment or vaccine at this time.

SYNONYMS

Zika fever
Zika virus disease

ICD-10CM CODES

A92.8	Other specified mosquito-borne viral fevers
A92.5	Zika virus disease

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Zika virus has been declared a public health emergency, with more than 20 countries and territories reporting local transmission of the virus in 2016.
- Brazil alone had reported more than 1.3 million people infected with the virus by June 2016.
- In the U.S.: By August 1, 2018, there were been 5716 symptomatic Zika virus disease cases reported. Of these, 5430 cases were in travelers returning from affected areas. There were 231 cases acquired through presumed local mosquito-borne transmission, (Florida and Texas); and 55 cases acquired through other routes: sexual transmission (52 cases), lab transmission (2 cases), and person-to-person through unknown contact (1 case). In U.S. territories (Puerto Rico, Virgin Islands, Guam), there have been 37,262 cases with the vast majority through local transmission.
- In terms of pregnant women and Zika: There have been more than 2000 cases in the U.S. and over 5000 cases in U.S. territories.
- It is thought that one in seven babies exposed in utero to the Zika virus may have been harmed by the infection: 9% of 1450 exposed babies studied at 1 yr of age had a neurodevelopmental issue: seizures, hearing problems, difficulties swallowing, cerebral palsy-like movements; 6% of the 1450 exposed babies had a birth defect: microcephaly, brain damage, ocular problems; and 1% of the babies exposed had both birth defects and neurodevelopmental concerns.

PEAK INCIDENCE: As a mosquito-borne disease, it is more common in warmer mos of the yr.

PREVALENCE: In an outbreak in Yap islands, 70% of the population was infected in a 13-wk period of time. Although transmission of Zika virus has declined in the Americas, outbreaks and infection clusters continue to occur in some regions, such as India and Southeast Asia.

RISK FACTORS: The virus can be transmitted in different ways:

- Most common is through the bite of an infected mosquito
- Maternal-fetal transmission
- Sexual contact: Vaginal, anal, and oral sex. Virus may persist in semen >2 mo
- Blood transfusion
- Organ or tissue transplant
- Laboratory exposure

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation period varies from 3 to 14 days.
- Some 80% of patients will be asymptomatic but can still subsequently develop complications.
- Symptomatic patients will present with:
  1. Mild fever, myalgia, headache
  2. Arthralgias (small joints of hands and feet)
  3. Abdominal pain
  4. Edema
  5. Lymphadenopathy
  6. Retroorbital pain, conjunctivitis
  7. Cutaneous macular-papular rash
- Complications of Zika virus infection:
  1. Neurologic complications: Meningoencephalitis, Guillain-Barré syndrome in adults, transverse myelitis, encephalomyelitis, and chronic inflammatory demyelinating polyneuropathy.
  2. Neonatal microcephaly: Patients may have mild developmental delays to cerebral palsy.
     a. In Brazil, the incidence of microcephaly increased to 2% to 8% but is still being studied.
     b. Degree of abnormalities may depend on trimester of pregnancy when the infection starts.
     c. 30% of infected pregnant woman may have adverse fetal findings, including fetal death, in utero growth delay with or without microcephaly, optic nerve damage, and ventricular calcifications.
- The Zika virus is neurotropic and can cross the blood-brain barrier.

ETIOLOGY

- Zika virus: A flavivirus in the same family as yellow fever virus, dengue virus, West Nile virus.
- First discovered in a febrile rhesus macaque monkey in the Zika forest in Uganda in 1947.
- First human cases discovered in 1954 in Nigeria but cases rare outside of Africa and Southeast Asia until 2007 when first large outbreak occurred in Yap (Micronesia) and then in French Polynesia (2013).
- Zika virus arrived in the Americas in May 2015 in Bahia, Brazil.
- An association with Guillain-Barré was noted in French Polynesia, but the association with microcephaly was first noted in September 2015 in Brazil.
- Vector for transmission is the *Aedes aegypti* mosquito, which lives in tropical and subtropical regions including southern U.S., and possibly the *Aedes albopictus* mosquito, which lives in temperate regions, including mid-Atlantic states in the U.S., as well as tropical areas.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Viral causes of arthritis (Table E1):
  1. Dengue fever: Similar clinical presentation and transmitted by same mosquito
  2. Chikungunya virus: Similar presentation, albeit with high fever and intense pain in hands, feet, knees, and back; also transmitted by same mosquito
  3. Parvovirus
  4. Rubella
- Measles
- Leptospirosis
- Malaria
- Rickettsial infections: African tick bite fever and relapsing fever

WORKUP

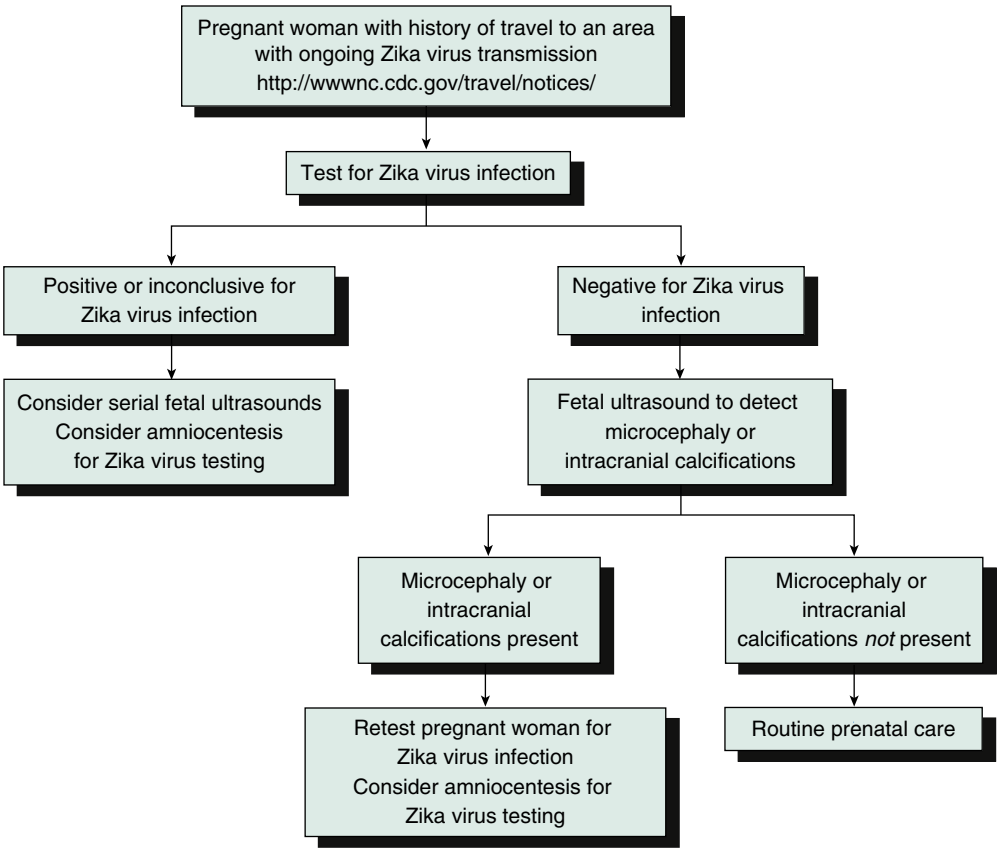
- Zika virus infection should be suspected in patients with typical clinical manifestations and a history of exposure to the virus via travel/residence in endemic area or sexual contact with a person from endemic area.
- Fig. E1 illustrates a testing algorithm for a pregnant woman with a history of travel to an area with ongoing Zika virus transmission.
- A testing algorithm for a pregnant woman with possible Zika exposure not residing in an area with active Zika virus transmission is described in Fig. E2.
- A testing algorithm for a pregnant woman residing in an area with active Zika virus transmission with or without clinical illness consistent with Zika virus disease is illustrated in Fig. E3.

TABLE E1 Clinical Features of Zika Virus Compared with Dengue and Chikungunya[a]

Features	Zika	Dengue	Chikungunya
Fever	+ to ++	+++	+++
Maculopapular rash	+++	+	++
Pruritus	++	–/+	–/+
Conjunctivitis	++	–	+/–
Arthralgia	++	+	+++
Myalgia	+	++	+
Headache	+	++	++
Facial edema	+/–	++	+
Palatal petechiae	+/–	++	+
Hemorrhage	–	++	–
Shock	–	+	–

Primarily adapted from a Centers for Disease Control and Prevention Presentation by Ingrid Rabe, "Zika Virus: What Clinicians Need to Know," a Clinician Outreach and Communication Activity (COCA) Call, Atlanta, GA, January 26, 2016.

[a]Note that one study of all three viruses of patients in Nicaragua suggested more similarities among the three viruses with regard to fever, conjunctivitis, arthralgia, and headache.



* Testing is recommended for pregnant women with clinical illness consistent with Zika virus disease, which includes two or more of the following signs or symptoms: acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis during or within 2 weeks of travel. Testing includes Zika virus reverse transcription-polymerase chain reaction (RT-PCR), and Zika virus immunoglobulin M (IgM) and neutralizing antibodies on serum specimens (http://www.aphl.org/Materials/CDCMemo_Zika_Chik_Deng_Testing_011916.pdf). Because of the overlap of symptoms and areas where other viral illnesses are endemic, evaluation for dengue or chikungunya virus infection is also recommended.

† Testing can be offered to pregnant women without clinical illness consistent with Zika virus disease. If performed, testing should include Zika virus IgM, and if IgM test result is positive or indeterminate, neutralizing antibodies on serum specimens. Testing should be performed 2–12 weeks after travel.

§ Laboratory evidence of maternal Zika virus infection: (1) Zika virus RNA detected by RT-PCR in any clinical specimen; or (2) positive Zika virus IgM with confirmatory neutralizing antibody titers that are ≥4-fold higher than dengue virus neutralizing antibody titers in serum. Testing is considered inconclusive if Zika virus neutralizing antibody titers are <4-fold higher than dengue virus neutralizing antibody titers.

¶ Fetal ultrasounds might not detect microcephaly or intracranial calcifications until the late second or early third trimester of pregnancy.

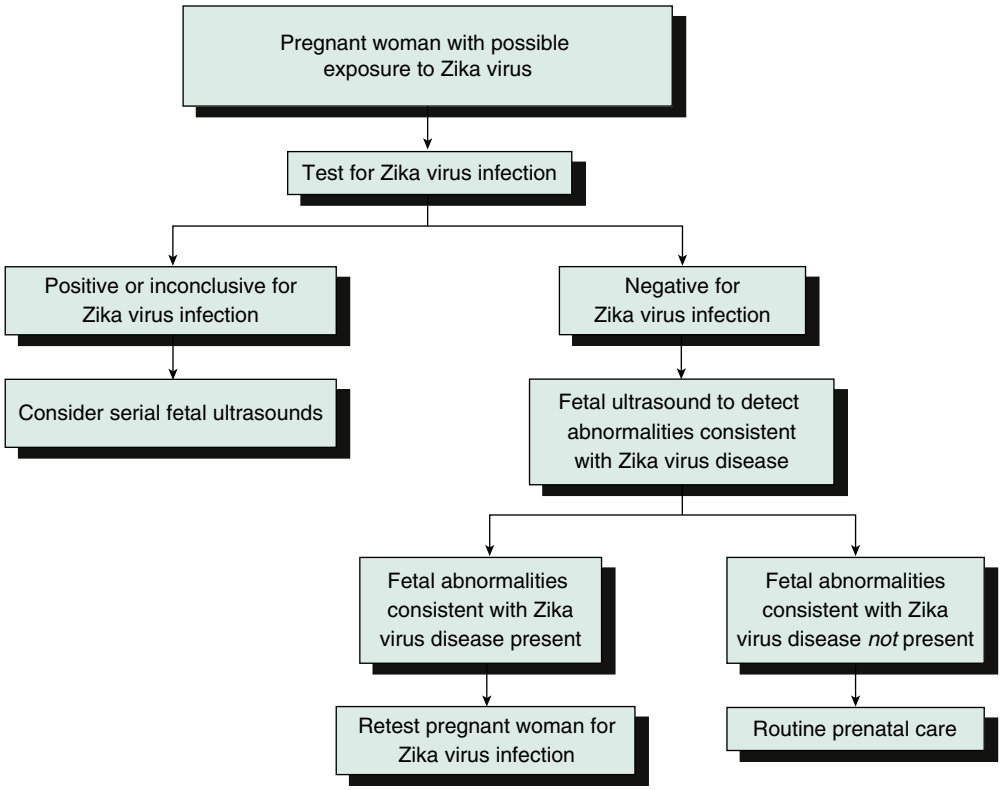
** Amniocentesis is not recommended until after 15 weeks of gestation. Amniotic fluid should be tested for Zika virus RNA by RT-PCR. The sensitivity and specificity of RT-PCR testing on amniotic fluid are not known.

FIG. E1 Updated interim guidance: Testing algorithm*,†,§,¶, for a pregnant woman with history of travel to an area with ongoing Zika virus transmission.** (From Oduyebo T et al: Update: interim guidelines for health care providers caring for pregnant women and women of reproductive age with possible Zika virus exposure—United States, 2016, MMWR 65(5):122-127, 2016, fig. 1 p. 124.)

- Box E1 summarizes recommended Zika virus laboratory testing for infants and children when indicated.
- Recommended clinical evaluation and laboratory testing for infants with possible congenital Zika virus infection is summarized in Box E2.
- Fig. E4 illustrates recommendations for the evaluation of infants with possible congenital Zika virus infection based on infant clinical findings.

LABORATORY TESTS

- Zika virus reverse transcriptase polymerase



* Testing is recommended for pregnant women with clinical illness consistent with Zika virus disease, including one or more of the following signs or symptoms: acute onset of fever, rash, arthralgia, or conjunctivitis during or within 2 weeks of travel or possible sexual exposure. Testing includes Zika virus reverse transcription-polymerase chain reaction (RTPCR), and Zika virus immunoglobulin M (IgM) and neutralizing antibodies on serum specimens. More information is available at http://www.aphl.org/Materials/CDCMemo_Zika_Chik_Deng_Testing_011916.pdf. Because of the overlap of symptoms and areas where other viral illnesses are endemic, evaluate for possible dengue or chikungunya virus infection.

† Testing can be offered to pregnant women without clinical illness consistent with Zika virus disease. If performed, testing should include Zika virus IgM, and if IgM test result is positive or indeterminate, neutralizing antibodies on serum specimens. Testing should be performed 2–12 weeks after travel.

§ Laboratory evidence of maternal Zika virus infection: (1) Zika virus RNA detected by RT-PCR in any clinical specimen; or (2) positive Zika virus IgM with confirmatory neutralizing antibody titers that are ≥4-fold higher than dengue virus neutralizing antibody titers in serum. Testing is considered inconclusive if Zika virus neutralizing antibody titers are <4-fold higher than dengue virus neutralizing antibody titers.

¶ Fetal abnormalities consistent with Zika virus disease include microcephaly, intracranial calcifications, and brain and eye abnormalities. Fetal ultrasounds might not detect abnormalities until late second or early third trimester of pregnancy

** Possible exposure to Zika virus includes travel to an area with active Zika virus transmission (http://wwwnc.cdc.gov/travel/notices), or sex (vaginal intercourse, anal intercourse, or fellatio) without a condom with a man who traveled to, or resided in, an area with active Zika virus transmission. Testing is not currently recommended for pregnant women with possible sexual exposure to Zika virus if both partners are asymptomatic.

FIG. E2 Updated interim guidance: Testing algorithm*,†,§,¶ for a pregnant woman with possible Zika virus exposure not residing in an area with active Zika virus transmission.** (From Petersen E et al: Update: interim guidelines for health care providers caring for pregnant women and women of reproductive age with possible Zika virus exposure—United States, 2016, *MMWR* 65(12):315-322, 2016, fig. 1 p. 319.)

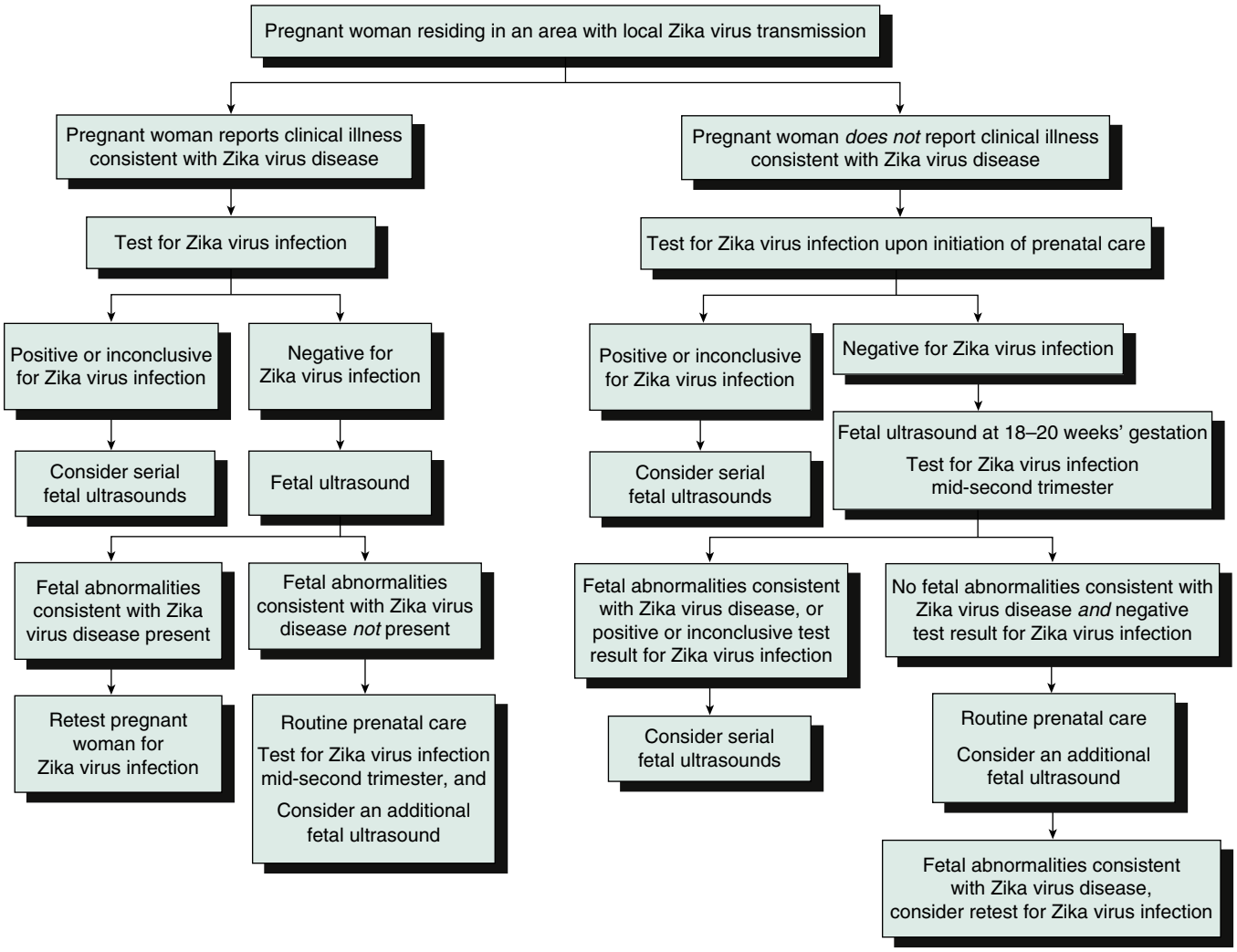
chain reaction (Zika RT-PCR) in serum or urine in acute infection

1. Serum: Only positive if viremic (3 to 7 days after start of symptoms)
2. Urine: Positive for up to 14 days after start of symptoms

- Zika serology: Zika virus IgM ELISA for patients presenting longer than 14 days of symptoms; Zika virus IgG ELISA
- It should be noted that there is cross-reactivity with other flaviviruses; dengue and yellow fever can lead to false positives

IMAGING STUDIES

- Fetal ultrasound is used to screen for fetal Zika virus infection complications.
- Fetal abnormalities may be seen as early as 18 to 20 wk of gestation but more



* Tests for pregnant women with clinical illness consistent with Zika virus disease include Zika virus reverse transcription-polymerase chain reaction (RT-PCR), and Zika virus immunoglobulin M (IgM) and neutralizing antibodies on serum specimens. More information is available at http://www.aphl.org/Materials/CDCMemo_Zika_Chik_Deng_Testing_011916.pdf. Because of the overlap of symptoms and areas where other viral illnesses are endemic, evaluate for possible dengue or chikungunya virus infection. If chikungunya or dengue virus RNA is detected, treat in accordance with existing guidelines. Timely recognition and supportive treatment for dengue virus infections can substantially lower the risk of medical complications and death. Repeat Zika virus testing during pregnancy is warranted if clinical illness consistent with Zika virus disease develops later in pregnancy.

† Testing can be offered to pregnant women without clinical illness consistent with Zika virus disease. If performed, testing should include Zika virus IgM, and if IgM test result is positive or indeterminate, neutralizing antibodies on serum specimens. Results from serologic testing are challenging to interpret in areas where residents have had previous exposure to other flaviviruses (e.g., dengue, yellow fever) because of cross-reactivity with other flaviviruses.

§ Laboratory evidence of maternal Zika virus infection: (1) Zika virus RNA detected by RT-PCR in any clinical specimen; or (2) positive Zika virus IgM with confirmatory neutralizing antibody titers that are ≥4-fold higher than dengue virus neutralizing antibody titers in serum. Testing would be considered inconclusive if Zika virus neutralizing antibody titers are <4-fold higher than dengue virus neutralizing antibody titer.

¶ Fetal abnormalities consistent with Zika virus disease include microcephaly, intracranial calcifications, and brain and eye abnormalities. Fetal ultrasounds might not detect abnormalities until late second or early third trimester of pregnancy.

** http://wwwnc.cdc.gov/travel/notices/. Local health officials should determine when to implement testing of asymptomatic pregnant women based on information about levels of Zika virus transmission and laboratory capacity.

†† Clinical illness is consistent with Zika virus disease if one or more signs or symptoms (acute onset of fever, rash, arthralgia, or conjunctivitis) are present.

FIG. E3 Updated interim guidance: Testing algorithm*,†,§,¶ for a pregnant woman residing in an area with active Zika virus transmission, with or without clinical illness†† consistent with Zika virus disease.** (From Petersen E et al: Update: interim guidelines for health care providers caring for pregnant women and women of reproductive age with possible Zika virus exposure—United States, 2016, *MMWR* 65(12):315-322, 2016, fig. 2 p. 320.)

BOX E1 Recommended Zika Virus Laboratory Testing for Infants and Children When Indicated*,†,‡

For possible congenital Zika virus infection

- Test infant serum for Zika virus RNA, Zika virus immunoglobulin M (IgM) and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies. The initial sample should be collected either from the umbilical cord or directly from the infant within 2 days of birth, if possible.
- If cerebrospinal fluid is obtained for other studies, test for Zika virus RNA, Zika virus IgM and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies.
- Consider histopathologic evaluation of the placenta and umbilical cord with Zika virus immunohistochemical staining on fixed tissue and Zika virus reverse transcription-polymerase chain reaction (RT-PCR) on fixed and frozen tissue.
- If not already performed during pregnancy, test mother's serum for Zika virus IgM and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies.

For possible acute Zika virus disease

- If symptoms have been present for <7 days, test serum (and, if obtained for other reasons, cerebrospinal fluid) for Zika virus RNA by RT-PCR.
- If Zika virus RNA is not detected and symptoms have been present for ≥4 days, test serum (and, if obtained for other reasons, cerebrospinal fluid) for Zika virus IgM and neutralizing antibodies, and dengue virus IgM and neutralizing antibodies.

*Indications for testing for congenital infection include (1) an infant with microcephaly or intracranial calcifications born to a woman who traveled to or resided in an area with Zika virus transmission while she was pregnant or (2) an infant born to a mother with a positive or inconclusive test result for Zika virus infection.
†Indications for testing during acute disease include infants and children <18 yr who (1) traveled to or resided in an affected area within the past 2 wk and (2) have ≥2 of the following manifestations: fever, rash, conjunctivitis, or arthralgia. Infants in the first 2 wk of life (1) whose mothers have traveled to or resided in an affected area within 2 wk of delivery and (2) have ≥2 of the following manifestations: fever, rash, conjunctivitis, or arthralgia.
‡More information on laboratory testing for Zika virus infection is available at www.cdc.gov/zika/state-labs/index.html

BOX E2 Recommended Clinical Evaluation and Laboratory Testing for Infants with Possible Congenital Zika Virus Infection

For all infants with possible congenital Zika virus infection, perform the following:

- Comprehensive physical examination, including careful measurement of occipitofrontal circumference, length, weight, and assessment of gestational age.
- Evaluation for neurologic abnormalities, dysmorphic features, splenomegaly, hepatomegaly, and rash or other skin lesions. Full-body photographs and photographic documentation of any rash, skin lesions, or dysmorphic features should be performed. If an abnormality is noted, consultation with an appropriate specialist is recommended.
- Cranial ultrasound, unless prenatal ultrasound results from third trimester demonstrated no abnormalities of the brain.
- Evaluation of hearing by evoked otoacoustic emissions testing or auditory brainstem response testing, either before discharge from the hospital or within 1 mo after birth. Infants with abnormal initial hearing screens should be referred to an audiologist for further evaluation.
- Ophthalmologic evaluation, including examination of the retina, either before discharge from the hospital or within 1 mo after birth. Infants with abnormal initial eye evaluation should be referred to a pediatric ophthalmologist for further evaluation.
- Other evaluations specific to the infant's clinical presentation.

For infants with microcephaly or intracranial calcifications, additional evaluation includes the following:

- Consultation with a clinical geneticist or dysmorphologist.
- Consultation with a pediatric neurologist to determine appropriate brain imaging and additional evaluation (e.g., ultrasound, computerized tomography scan, magnetic resonance imaging, and electroencephalogram).
- Testing for other congenital infections such as syphilis, toxoplasmosis, rubella, cytomegalovirus infection, lymphocytic choriomeningitis virus infection, and herpes simplex virus infections. Consider consulting a pediatric infectious disease specialist.
- Complete blood count with platelet count and liver function and enzyme tests, including alanine aminotransferase, aspartate aminotransferase, and bilirubin.
- Consideration of genetic and other teratogenic causes based on additional congenital anomalies that are identified through clinical examination and imaging studies.

Adapted from Staples JE et al: Interim guidelines for the evaluation and testing of infants with possible congenital Zika virus infection—United States, *MMWR* 65(3):63-67, 2016.

likely detected in late second and early third trimester.
- Fetal microcephaly is described as a head circumference >3 standard deviations below the mean for gestational age by the Society for Maternal-Fetal Medicine and <third percentile for gestational age by the Centers for Disease Control and Prevention (CDC).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Rest and hydration

ACUTE GENERAL Rx

- Acetaminophen can be used for fever but not aspirin or NSAIDs until dengue virus has been ruled out. Aspirin increases risk of hemorrhage, and NSAIDs should not be used in pregnancy. Aspirin should be avoided in children due to risk of Reye syndrome.
- Antihistamines can be used to control rash in patients with a rash.
- At this time, there is no specific antiviral agent.

REFERRAL

To an expert in obstetrics and gynecology to evaluate a pregnant woman who may have been exposed to the Zika virus. Recommended long-term follow-up for infants with possible congenital Zika virus infection are summarized in Box E3.

PEARLS & CONSIDERATIONS

- The *Aedes* mosquitos can also transmit dengue and chikungunya viruses.
- CDC maintains a service to help physicians deal with a pregnant woman and infants exposed to the Zika virus: 1-800-CDC-INFO.
- Vaccine development is ongoing but no currently available vaccine.

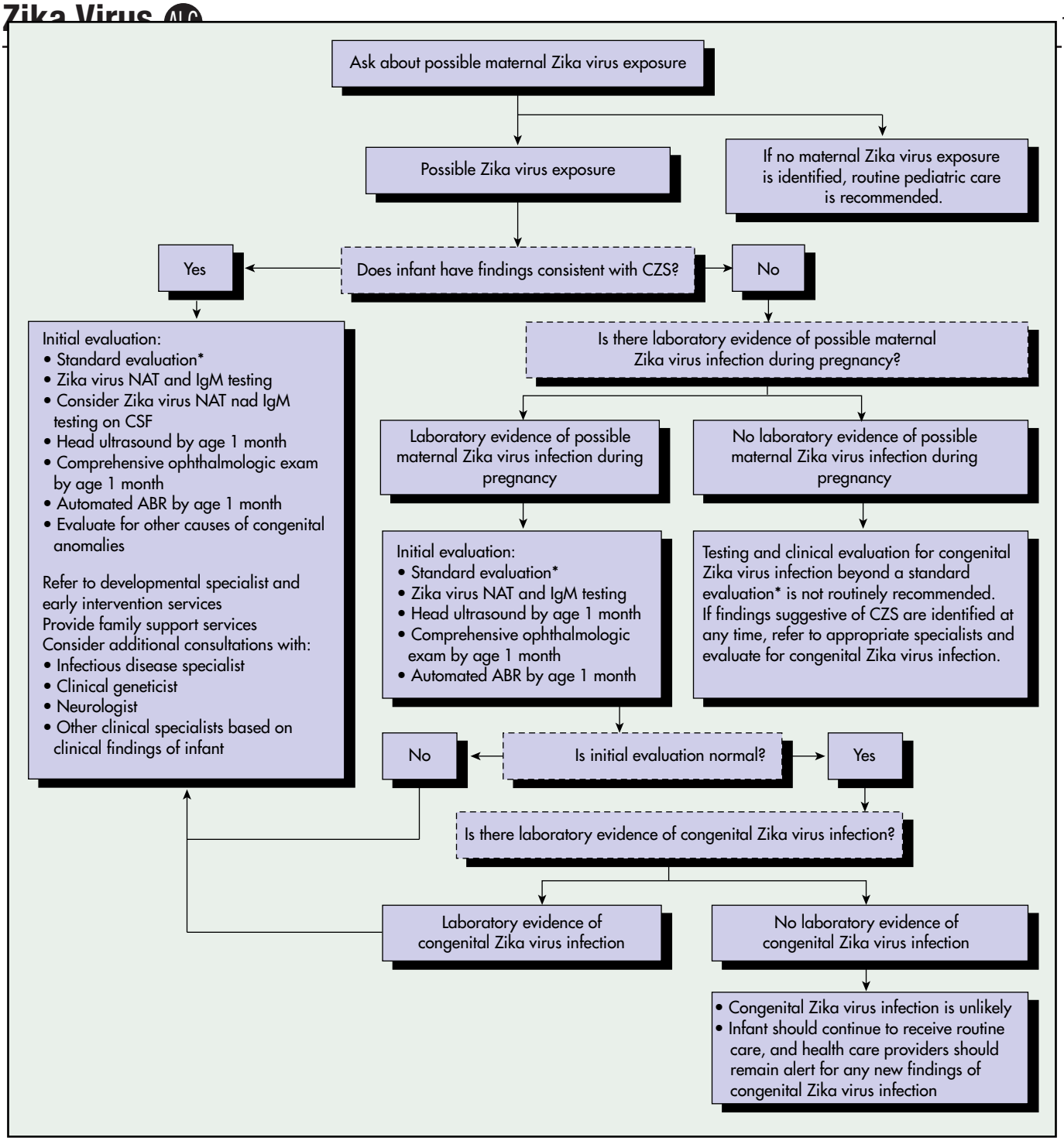


FIG. E4 Recommendations for the evaluation of infants with possible congenital Zika virus infection based on infant clinical findings,*,† maternal testing results,§,¶ and infant testing results,†† — U.S., October 2017.** *All infants should receive a standard evaluation at birth and at each subsequent well-child visit by their health care providers including (1) comprehensive physical examination, including growth parameters and (2) age-appropriate vision screening and developmental monitoring and screening using validated tools. Infants should receive a standard newborn hearing screen at birth, preferably using auditory brainstem response. †Automated ABR by age 1 mo if newborn hearing screen passed but performed with otoacoustic emission methodology. §Laboratory evidence of possible Zika virus infection during pregnancy is defined as (1) Zika virus infection detected by a Zika virus RNA NAT on any maternal, placental, or fetal specimen (referred to as NAT-confirmed); or (2) diagnosis of Zika virus infection, timing of infection cannot be determined or unspecified flavivirus infection, timing of infection cannot be determined by serologic tests on a maternal specimen (i.e., positive/equivocal Zika virus IgM and Zika virus PRNT titer ≥10, regardless of dengue virus PRNT value; or negative Zika virus IgM, and positive or equivocal dengue virus IgM, and Zika virus PRNT titer ≥10, regardless of dengue virus PRNT titer). The use of PRNT for confirmation of Zika virus infection, including in pregnant women, is not routinely recommended in Puerto Rico (https://www.cdc.gov/zika/laboratories/lab-guidance.html). ¶This group includes women who were never tested during pregnancy as well as those whose test result was negative because of issues related to timing or sensitivity and specificity of the test. Because the latter issues are not easily discerned, all mothers with possible exposure to Zika virus during pregnancy who do not have laboratory evidence of possible Zika virus infection, including those who tested negative with currently available technology, should be considered in this group. **Laboratory testing of infants for Zika virus should be performed as early as possible, preferably within the first few days after birth, and includes concurrent Zika virus NAT in infant serum and urine, and Zika virus IgM testing in serum. If CSF is obtained for other purposes, Zika virus NAT and Zika virus IgM testing should be performed on CSF. ††Laboratory evidence of congenital Zika virus infection includes a positive Zika virus NAT or a nonnegative Zika virus IgM with confirmatory neutralizing antibody testing, if PRNT confirmation is performed. *ABR,* Auditory brainstem response; *CSF,* cerebrospinal fluid; *CZS,* congenital Zika syndrome; *IgM,* immunoglobulin M; *NAT,* nucleic acid test; *PRNT,* plaque reduction neutralization test. (From Adebanjo T et al: Update: interim guidance for the diagnosis, evaluation, and management of infants with possible congenital Zika virus infection—United States, 2017, *MMWR* 66(41): 1089-1099, 2017, fig. 1 p. 1093.)

BOX E3 Recommended Long-Term Follow-up for Infants with Possible Congenital Zika Virus Infection

For all infants with possible congenital Zika virus infection, recommended long-term follow-up:

- Report case to state, territorial, or local health department and monitor for additional guidance as it is released.
- Consider conducting additional hearing screen at age 6 mo. Refer any child with developmental delay for an audiologic evaluation. Ensure that appropriate follow-up of abnormal newborn hearing screening has occurred.
- Carefully evaluate occipitofrontal circumference and developmental characteristics and milestones throughout the first yr of life, in consultation with appropriate medical specialists (e.g., pediatric neurology, developmental and behavioral pediatrics, physical and speech therapy).

Adapted from Staples JE et al: Interim guidelines for the evaluation and testing of infants with possible congenital Zika virus infection—United States, *MMWR* 65(3):63-67, 2016.

BOX E4 Recommendations for Counseling Persons in Areas of Active Zika Virus Transmission Interested in Attempting Conception

Assess risk of Zika virus exposure

Environment

- Air conditioning, window screens in home
- Work environment
- Residence in area with high mosquito density
- Level of Zika virus transmission in the local area

Personal measures to prevent mosquito bites

- Protective clothing
- Use of EPA-registered insect repellent
- Emptying/removing standing water in containers

Personal measures to prevent sexual transmission

- Willingness to use condoms or abstain from sex throughout pregnancy

Discuss Zika virus infection in pregnancy

- Signs/symptoms of Zika virus disease
- Possible adverse consequences of Zika virus infection during pregnancy
- Unknown duration of epidemic

Explore reproductive life plan

- Fertility
- Age
- Reproductive history
- Medical history
- Personal values, preferences

Discuss risks/benefits of pregnancy at this time with woman and her partner

- If pregnancy not desired now, discuss contraceptive options.

Adapted from Adebanjo T et al: Update: Interim guidance for the diagnosis, evaluation, and management of infants with possible congenital Zika virus infection—United States, *MMWR* 66(41):1089-1099, 2017.

BOX E5 Recommendations for Prevention of Sexual Transmission of Zika Virus for Couples in Which a Man Has Traveled to or Resides in an Area with Active Zika Virus Transmission

Couples in which a woman is pregnant

- Couples in which a woman is pregnant should use condoms consistently and correctly or abstain from sex for the duration of the pregnancy.

Other couples concerned about sexual transmission*

- Couples in which a man had confirmed Zika virus infection or clinical illness consistent with Zika virus disease should consider using condoms or abstaining from sex for at least 6 mo after onset of illness.
- Couples in which a man traveled to an area with active Zika virus transmission but did not develop symptoms of Zika virus disease should consider using condoms or abstaining from sex for at least 8 wk after departure from the area.
- Couples in which a man resides in an area with active Zika virus transmission but has not developed symptoms of Zika virus disease might consider using condoms or abstaining from sex while active transmission persists.

*Couples who do not desire pregnancy should use the most effective contraception methods that can be used correctly and consistently in addition to condoms, which also reduce the risk for sexually transmitted infections. Couples planning conception have a number of factors to consider, which are discussed in more detail in the following: Petersen EE et al: Update: interim guidance for health care providers caring for women of reproductive age with possible Zika virus exposure—United States, 2016, *MMWR* 2016.
From Oduyebo T et al: Update: interim guidance for health care providers caring for pregnant women with possible Zika virus exposure—United States, *MMWR* 66(29):781-793, 2017.

- Aerial spraying with EPA-registered insecticides has been a strategy implemented in the Florida outbreak, along with other mosquito-control strategies.

COMMENTS

Zika virus is already impacting blood donations for people who have traveled to affected area or live in affected areas. Travelers may need to postpone donations for at least 28 days. New guidelines by the U.S. Food and Drug Administration (FDA) call for testing blood donors in areas where active Zika virus transmission has occurred.

PREVENTION

- Wear long-sleeved shirts, pants, and hat.
- Insect repellents: Apply to exposed skin in daylight hours when *Aedes* mosquitos are most active:
  1. DEET: Diethyltoluamide 20% to 50% concentration
  2. Icaridin in at least 20% concentration
  3. Lemon eucalyptus extract in at least 30% concentration
- Clothing can be treated with permethrin soak or 1% spray.
- Do not use insect repellents on babies younger than 2 mo and avoid lemon eucalyptus on children younger than 3 yr.
- Recommendations for counseling persons in areas of active Zika virus transmission interested in attempting conception are summarized in Box E4.
- Recommendations for prevention of sexual transmission of Zika virus for couples in which a man has traveled to or resides in an area with active Zika virus transmission are summarized in Box E5.

PATIENT & FAMILY EDUCATION

- Both *Aedes aegypti* and *Aedes albopictus* are daytime biters, so protection is essential during those hours.
- In a recent study evaluating persistence of Zika virus in body fluids, in 95% of infected men, Zika RNA was cleared from semen after approximately 4 mo. Men who have traveled to areas where Zika virus is present and have developed symptomatic disease should abstain from sexual contact or use a condom for at least 3 mo afterward.
- Recommendations for counseling persons who live in areas of active Zika virus transmission and are interested in attempting conception.

RELATED CONTENT

Dengue Fever (Related Key Topic)
Yellow Fever (Related Key Topic)

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SUGGESTED READINGS

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Hendrixson DT, Newland JG: Zika virus infection in children, *Infect Dis Clin North Am* 32:215-224, 2018.

Paz-Bailey G et al: Persistence of Zika virus in body fluids - final report, *N Engl J Med* 379:1234-1243, 2017.

Petersen LR et al: Zika virus, *N Engl J Med* 374:1552-1563, 2016.

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Shirley DT, Nataro JP: Zika virus infection, *Pediatr Clin North Am* 64:937-951, 2017.

Valentine G et al: Zika virus–associated microcephaly and eye lesions in the newborn, *J Pediatric Infect Dis Soc* 5(3):323-328, 2016.

Vouga M, Baud D: Imaging of congenital Zika virus infection: the route to identification of prognostic factors, *Prenat Diagn* 36(9):799-811, 2016.

ABDOMINAL DISTENTION

ICD-10CM #		
	R14.0	Abdominal distension (gaseous)

NONMECHANICAL OBSTRUCTION

Excessive intraluminal gas.
Intraabdominal infection.
Trauma.
Retroperitoneal irritation (renal colic, neoplasms, infections, hemorrhage).
Vascular insufficiency (thrombosis, embolism).
Mechanical ventilation.
Extraabdominal infection (sepsis, pneumonia, empyema, osteomyelitis of spine).
Metabolic/toxic abnormalities (hypokalemia, uremia, lead poisoning).
Chemical irritation (perforated ulcer, bile, pancreatitis).
Peritoneal inflammation.
Severe pain, pain medications.

MECHANICAL OBSTRUCTION

Neoplasm (intraluminal, extraluminal).
Adhesions, endometriosis.
Infection (intraabdominal abscess, diverticulitis).
Gallstones.
Foreign body, bezoars.
Pregnancy.
Hernias.
Volvulus.
Stenosis at surgical anastomosis, radiation stenosis.
Fecaliths.
Inflammatory bowel disease.
Gastric outlet obstruction.
Hematoma.
Other: parasites, superior mesenteric artery (SMA) syndrome, pneumatosis intestinalis, annular pancreas, Hirschsprung disease, intussusception, meconium.

ABDOMINAL PAIN, ADOLESCENCE[58]

ICD-10CM #		
	R10.817	Generalized abdominal tenderness
	R10.827	Generalized rebound abdominal tenderness

Acute gastroenteritis.
Irritable bowel syndrome (IBS).
Anxiety.
Mittelschmerz.
Appendicitis.
Inflammatory bowel disease.
Peptic ulcer disease (PUD).
Cholecystitis.
Neoplasm.
Diabetic ketoacidosis.
Functional abdominal pain.
Pelvic inflammatory disease (PID).
Pregnancy.
Pyelonephritis.
Renal stone.
Trauma.

ABDOMINAL PAIN, CHILDHOOD[58]

ICD-10CM #		
	R10.817	Generalized abdominal tenderness
	R10.827	Generalized rebound abdominal tenderness

Acute gastroenteritis.
Appendicitis.
Constipation.
Cholecystitis, acute.
Intestinal obstruction.
Pancreatitis.
Neoplasm.
Inflammatory bowel disease.
Other:
- Functional abdominal pain.
- Pyelonephritis.
- Pneumonia.
- Diabetic ketoacidosis.
- Heavy metal poisoning.
- Sickle cell crisis.
- Trauma.
- Anxiety.
- Sexual abuse.

ABDOMINAL PAIN, CHRONIC LOWER[86]

ICD-10CM #		
	R10.814	Left lower quadrant abdominal tenderness
	R10.824	Left lower quadrant rebound abdominal tenderness
	R10.813	Right lower quadrant abdominal tenderness
	R10.823	Right lower quadrant rebound abdominal tenderness
	R10.30	Lower abdominal pain, unspecified

ORGANIC DISORDERS

Common
Gynecologic disease.
Lactase deficiency.
Diverticulitis/diverticulosis.
Crohn disease.
Intestinal obstruction.
Uncommon
Chronic intestinal pseudoobstruction.
Mesenteric ischemia.
Malignancy (e.g., ovarian carcinoma).
Abdominal wall pain.
Spinal disease.
Testicular disease.
Metabolic diseases (e.g., diabetes mellitus, familial Mediterranean fever, C1 esterase deficiency [angioneurotic edema], porphyria, lead poisoning, tabes dorsalis, renal failure).

FUNCTIONAL DISORDERS

Common
Irritable bowel syndrome.
Functional abdominal bloating.
Uncommon
Functional abdominal pain.

ABDOMINAL PAIN, DIFFUSE

ICD-10CM #		
	R10.817	Generalized abdominal tenderness
	R10.827	Generalized rebound abdominal tenderness

Early appendicitis.
Aortic aneurysm.
Gastroenteritis.
Intestinal obstruction.
Diverticulitis.
Peritonitis.
Mesenteric insufficiency or infarction.
Pancreatitis.
Inflammatory bowel disease.
Irritable bowel.
Mesenteric adenitis.
Metabolic: toxins, lead poisoning, uremia, drug overdose, diabetic ketoacidosis (DKA), heavy metal poisoning.
Sickle cell crisis.
Pneumonia (rare).
Trauma.
Urinary tract infection, PID.
Other: anxiety, acute intermittent porphyria, tabes dorsalis, periarteritis nodosa, Henoch-Schönlein purpura, adrenal insufficiency.

ABDOMINAL PAIN, EPIGASTRIC

ICD-10CM #		
	R10.816	Epigastric abdominal tenderness
	R10.826	Epigastric rebound abdominal tenderness

Gastric: PUD, gastric outlet obstruction, gastric ulcer.
Duodenal: PUD, duodenitis.
Biliary: cholecystitis, cholangitis, biliary dyskinesia.
Hepatic: hepatitis.
Pancreatic: pancreatitis.
Intestinal: high small bowel obstruction, early appendicitis.
Cardiac: angina, MI, pericarditis.
Pulmonary: pneumonia, pleurisy, pneumothorax.
Subphrenic abscess.
Vascular: dissecting aneurysm, mesenteric ischemia.
Psychiatric: anxiety.

ABDOMINAL PAIN, EXTRAABDOMINAL AND SYSTEMIC CAUSES[26]

ICD-10CM #		
	R10.817	Generalized abdominal tenderness

EXTRAABDOMINAL AND SYSTEMIC CAUSES OF ACUTE ABDOMINAL PAIN

Cardiac
Endocarditis.
Heart failure.
Myocardial ischemia and infarction.
Myocarditis.
Thoracic
Empyema.
Esophageal rupture (Boerhaave syndrome).
Esophageal spasm.
Esophagitis.
Pleurodynia (Bornholm disease).
Pneumonitis.
Pneumothorax.
Pulmonary embolism and infarction.
Hematologic
Acute leukemia.
Hemolytic anemia.
Henoch-Schönlein purpura.
Sickle cell disease.
Metabolic
Acute adrenal insufficiency (Addison disease).
Diabetes mellitus (especially with ketoacidosis).
Hyperlipidemia.
Hyperparathyroidism.
Hypersensitivity reactions (e.g., to insect bites, reptile venoms).
Lead poisoning.
Porphyria.
Toxins.
Uremia.
Infections
Herpes zoster.
Osteomyelitis.
Typhoid fever.
Neurologic
Abdominal epilepsy.
Radiculopathy, spinal cord or peripheral nerve tumors, degenerative arthritis of spine, herniated vertebral disk.
Tabes dorsalis.
Miscellaneous
Angioedema.
Familial Mediterranean fever.
Heat stroke.
Muscle contusion, hematoma, tumor.
Narcotic withdrawal.
Psychiatric disorders.

ABDOMINAL PAIN, INFANCY[58]

ICD-10CM #		
	R10.817	Generalized abdominal tenderness
	R10.827	Generalized rebound abdominal tenderness

Acute gastroenteritis.
Appendicitis.
Intussusception.
Volvulus.
Meckel diverticulum.
Other: colic, trauma.

ABDOMINAL PAIN, LEFT LOWER QUADRANT

ICD-10CM #		
	R10.814	Left lower quadrant abdominal tenderness
	R10.824	Left lower quadrant rebound abdominal tenderness

Intestinal: diverticulitis, diverticulosis, intestinal obstruction, perforated ulcer, inflammatory bowel disease, perforated descending colon, inguinal hernia, neoplasm, appendicitis.
Reproductive: ectopic pregnancy, ovarian cyst, torsion of ovarian cyst, tuboovarian abscess, mittelschmerz, endometriosis, seminal vesiculitis.
Renal: renal or ureteral calculi, pyelonephritis, neoplasm.
Vascular: leaking aortic aneurysm.
Psoas abscess.
Trauma.

ABDOMINAL PAIN, LEFT UPPER QUADRANT

ICD-10CM #		
	R19.02	Left upper quadrant abdominal swelling, mass, and lump

Gastric: PUD, gastritis, pyloric stenosis, hiatal hernia.
Pancreatic: pancreatitis, neoplasm, stone in pancreatic duct or ampulla.
Cardiac: MI, angina pectoris.
Splenic: splenomegaly, ruptured spleen, splenic abscess, splenic infarction.
Renal: calculi, pyelonephritis, neoplasm.
Pulmonary: pneumonia, empyema, pulmonary infarction.
Vascular: ruptured aortic aneurysm.
Cutaneous: herpes zoster.
Trauma.
Intestinal: high fecal impaction, perforated colon, diverticulitis.

ABDOMINAL PAIN, NONSURGICAL CAUSES

ICD-10CM #		
	R19.8	Other specified symptoms and signs involving the digestive system and abdomen
	R10.817	Generalized abdominal tenderness

Irritable bowel syndrome.
Urinary tract infection, pyelonephritis, salpingitis, PID.
Gastroenteritis, gastritis, peptic ulcer.
Diverticular spasm.
Hepatitis, mononucleosis.
Pancreatitis.
Inferior wall myocardial infarction.
Basilar pneumonia, pulmonary embolism.
Diabetic ketoacidosis.
Strain or hematoma of rectus muscle.
Ruptured Graafian follicle.
Herpes zoster.
Nerve root compression.
Sickle cell crisis.
Acute adrenal insufficiency.
Other: acute porphyria, familial Mediterranean fever, tabes dorsalis, anxiety, sexual abuse.

ABDOMINAL PAIN, PERIUMBILICAL

ICD-10CM #		
	R10.815	Periumbilic abdominal tenderness
	R10.825	Periumbilic rebound abdominal tenderness

Intestinal: small bowel obstruction or gangrene, early appendicitis.
Vascular: mesenteric thrombosis, dissecting aortic aneurysm.
Pancreatic: pancreatitis.
Metabolic: uremia, DKA.
Trauma.

ABDOMINAL PAIN, POORLY LOCALIZED[58]

ICD-10CM #		
	R10.819	Abdominal tenderness, unspecified site

EXTRAABDOMINAL

Metabolic
DKA, acute intermittent porphyria, hyperthyroidism, hypothyroidism, hypercalcemia, hypokalemia, uremia, hyperlipidemia, hyperparathyroidism.
Hematologic
Sickle cell crisis, leukemia or lymphoma, Henoch-Schönlein purpura.
Infectious
Infectious mononucleosis, Rocky Mountain spotted fever, acquired immunodeficiency syndrome (AIDS), streptococcal pharyngitis (in children), herpes zoster.
Drugs and Toxins
Heavy metal poisoning, black widow spider bites, withdrawal syndromes, mushroom ingestion.
Referred Pain
Pulmonary: pneumonia, pulmonary embolism, pneumothorax.
Cardiac: angina, MI, pericarditis, myocarditis.
Genitourinary: prostatitis, epididymitis, orchitis, testicular torsion.
Musculoskeletal: rectus sheath hematoma.
Functional
Somatization disorder, malingering, hypochondriasis, Munchausen syndrome.

INTRAABDOMINAL

Early appendicitis, gastroenteritis, peritonitis, pancreatitis, abdominal aortic aneurysm, mesenteric insufficiency or infarction, intestinal obstruction, volvulus, ulcerative colitis.

ABDOMINAL PAIN, POST-CHOLECYSTECTOMY[26]

ICD-10CM #	R10.817	Generalized abdominal tenderness

CAUSES OF ABDOMINAL PAIN AFTER CHOLECYSTECTOMY

Biliary Causes
Biliary stricture.
Biliary tract malignancy.
Choledocholithiasis.
Choledochocele.
Cystic duct remnant.
SOD.

Pancreatic Causes
Pancreatitis.
Pseudocyst.
Malignancy.

Other GI Disorders
Esophageal motor disorders.
GERD.
Intestinal malignancy.
Intraabdominal adhesions.
IBS.
Mesenteric ischemia.
PUD.

Extraintestinal Disorders
Coronary artery disease.
Intercostal neuritis.
Neurologic disorders.
Psychiatric disorders.
Wound neuroma.

ABDOMINAL PAIN, PREGNANCY

ICD-10CM #	R10.817	Generalized abdominal tenderness
	R10.827	Generalized rebound abdominal tenderness

GYNECOLOGIC (GESTATIONAL AGE IN PARENTHESES)

Miscarriage	(<20 wk; 80% <12 wk)
Septic abortion	(<20 wk)
Ectopic pregnancy	(<14 wk)
Corpus luteum cyst rupture	(<12 wk)
Ovarian torsion	(especially <24 wk)
Pelvic inflammatory disease	(<12 wk)
Chorioamnionitis	(>16 wk)
Abruptio placentae	(>16 wk)

NONGYNECOLOGIC

Appendicitis	(Throughout)
Cholecystitis	(Throughout)
Hepatitis	(Throughout)
Pyelonephritis	(Throughout)
Preeclampsia	(>20 wk)

ABDOMINAL PAIN, RIGHT LOWER QUADRANT

ICD-10CM #	R10.813	Right lower quadrant abdominal tenderness
	R10.823	Right lower quadrant rebound abdominal tenderness

Intestinal: acute appendicitis, regional enteritis, incarcerated hernia, cecal diverticulitis, intestinal obstruction, perforated ulcer, perforated cecum, Meckel diverticulitis.
Reproductive: ectopic pregnancy, ovarian cyst, torsion of ovarian cyst, salpingitis, tuboovarian abscess, mittelschmerz, endometriosis, seminal vesiculitis.
Renal: renal and ureteral calculi, neoplasms, pyelonephritis.
Vascular: leaking aortic aneurysm.
Cutaneous: herpes zoster.
Psoas abscess.
Trauma.
Cholecystitis.

ABDOMINAL PAIN, RIGHT UPPER QUADRANT

ICD-10CM #	R10.811	Right upper quadrant abdominal tenderness
	R10.821	Right upper quadrant rebound abdominal tenderness

Biliary: calculi, infection, inflammation, neoplasm.
Hepatic: hepatitis, abscess, hepatic congestion, neoplasm, trauma.
Gastric: PUD, pyloric stenosis, neoplasm, alcoholic gastritis, hiatal hernia.
Pancreatic: pancreatitis, neoplasm, stone in pancreatic duct or ampulla.
Renal: calculi, infection, inflammation, neoplasm, rupture of kidney.
Pulmonary: pneumonia, pulmonary infarction, right-sided pleurisy.
Intestinal: retrocecal appendicitis, intestinal obstruction, high fecal impaction, diverticulitis.
Cardiac: myocardial ischemia (particularly involving the inferior wall), pericarditis.
Cutaneous: herpes zoster.
Trauma.
Fitz-Hugh-Curtis syndrome (perihepatitis).

ABDOMINAL PAIN, RIGHT UPPER QUADRANT, DIFFERENTIAL DIAGNOSIS IN PREGNANCY[30]

ICD-10CM #	R10.811	Right upper quadrant abdominal tenderness
	R10.821	Right upper quadrant rebound abdominal tenderness

DIFFERENTIAL DIAGNOSIS OF RIGHT UPPER QUADRANT ABDOMINAL PAIN DURING PREGNANCY

Hepatic Disorders:
Hepatitis.
Hepatic vascular engorgement.
Hepatic hematoma.
Hepatic malignancy.

Biliary Tract Disease:
Biliary colic.
Choledocholithiasis.
Cholangitis.
Cholecystitis.

Diseases Related to Pregnancy:
Preeclampsia or eclampsia.
Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome.
Acute fatty liver of pregnancy.
Hepatic hemorrhage or rupture.

Renal Disorders:
Pyelonephritis.
Nephrolithiasis.

Gastrointestinal Disorders:
Peptic ulcer disease.
Perforated duodenal ulcer.

Other Conditions in RUQ:
Rib fracture.
Shingles.

Referred Pain from Other Organ Disease:
Pneumonia.
Pulmonary embolus or infarct.
Pleural effusion.
Radiculopathy.
Inferior wall myocardial infarction.
Colon cancer.

ABDOMINAL PAIN, SUPRAPUBIC

ICD-10CM #	R10.30	Lower abdominal pain, unspecified

Intestinal: colon obstruction or gangrene, diverticulitis, appendicitis.
Reproductive system: ectopic pregnancy, mittelschmerz, torsion of ovarian cyst, PID, salpingitis, endometriosis, rupture of endometrioma.
Cystitis, rupture of urinary bladder.

ABDOMINAL WALL MASSES[86]

ICD-10CM #	R19.00	Intraabdominal and pelvic swelling, mass and lump, unspecified site

LUMPS ARISING IN THE SKIN AND SUBCUTANEOUS FAT (THAT COULD OCCUR ANYWHERE ON THE BODY)

Lipoma.
Sebaceous cyst.

LUMPS ARISING IN THE SKIN AND SUBCUTANEOUS FAT (SPECIFIC TO THE ANTERIOR ABDOMINAL WALL)

Tumor nodule of the umbilicus (secondary to the intraperitoneal malignancy, also called *Sister Mary Joseph nodule*).

LUMPS ARISING IN THE FASCIA AND MUSCLE

Rectus sheath hematoma (usually painful).
Desmoid tumor (associated with Gardner syndrome).

HERNIA

Incisional:	It has an overlying scar. The sac may be very much larger than the neck of the hernia.
Umbilical:	The hernia is through the umbilical scar. Those presenting at birth commonly resolve in the first years of life.
Paraumbilical:	The neck is just lateral to the umbilical scar. Patients usually present later in life.
Epigastric:	It occurs in the midline between the xiphoid process and the umbilicus. They are usually small (<2 cm). They result when a knuckle of extraperitoneal fat extrudes through a small defect in the linea alba. Commonly irreducible and without an expansile cough impulse.
Spigelian:	A rare hernia found along the linea semilunaris at the lateral edge of the rectus sheath, most commonly a third of the way between the umbilicus and the pubis.

DIVARICATION OF THE RECTI

Supraumbilical elliptical swelling of the attenuated linea alba (no cough impulse).

ABORTION, RECURRENT

ICD-10CM # P01.8 Newborn (suspected to be) affected by other maternal complications of pregnancy

Congenital anatomic abnormalities.
Adhesions (uterine synechiae).
Uterine fibroids.
Endometriosis.
Endocrine abnormalities (luteal phase insufficiency, hypothyroidism, uncontrolled diabetes mellitus [DM]).
Parenteral chromosome abnormalities.
Maternal infections (cervical mycoplasma, ureaplasma, chlamydia).
DES exposure, heavy metal exposure.
Thrombocytosis.
Allogenic immunity, autoimmunity, lupus anticoagulant.

ACALCULOUS GALLBLADDER DISEASE[19]

ICD-10CM # K82.9 Other diseases of gallbladder

Biliary tract anomaly (e.g., choledochal cyst).
Bone marrow transplant.
Burns.
Chemotherapy in oncology patients.
Critical illness in intensive care unit patients.
Crohn disease, Henoch-Schönlein purpura, Kawasaki disease, systemic lupus erythematosus.
Infectious agents (atypical microbes).
Microlithiasis.
Postoperative state (e.g., cardiac surgery).
Sepsis.
Sludge.
Systemic inflammatory states.
Total parenteral nutrition.
Traumatic spinal cord injury.

ACHES AND PAINS, DIFFUSE[50]

ICD-10CM # M25.50 Pain in unspecified joint

Postviral arthralgias/myalgias.
Bilateral soft tissue rheumatism.
Overuse syndromes.
Fibrositis.
Hypothyroidism.
Metabolic bone disease.
Paraneoplastic syndrome.
Myopathy (polymyositis, dermatomyositis).
Rheumatoid arthritis (RA).
Sjögren syndrome.
Polymyalgia rheumatica.
Hypermobility.
Benign arthralgias/myalgias.
Chronic fatigue syndrome.
Hypophosphatemia.

ACIDOSIS, HYPERCHLORIC METABOLIC[88]

ICD-10CM # E87.2 Acidosis

GASTROINTESTINAL BICARBONATE LOSS

Diarrhea.
External pancreatic or small bowel drainage.
Ureterosigmoidostomy, jejunal loop.
Drugs:
- Calcium chloride (acidifying agent).
- Magnesium sulfate (diarrhea).
- Cholestyramine (bile acid diarrhea).

RENAL ACIDOSIS

Hypokalemic:
- Proximal RTA (type 2).
- Distal (classic) RTA (type 1).
- Drug-induced hypokalemia:
  - Acetazolamide (proximal RTA).
  - Amphotericin B (distal RTA).

Hyperkalemic:
- Generalized distal nephron dysfunction (type 4 RTA).
- Mineralocorticoid deficiency or resistance (pseudohypoaldosteronism type 1) PHA-I, PHA-II.
- ↓ Na^+ delivery to distal nephron.
- Tubulointerstitial disease.
- Ammonium excretion defect.
- Drug-induced hyperkalemia:
  - Potassium-sparing diuretics (amiloride, triamterene, spironolactone).
  - Trimethoprim.
  - Pentamidine.
  - Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.
  - Nonsteroidal antiinflammatory drugs.
  - Cyclosporine, tacrolimus.

Normokalemic:
- Early renal insufficiency.

OTHER

Acid loads (ammonium chloride, hyperalimentation).
Loss of potential bicarbonate: ketosis with ketone excretion.
Dilution acidosis (rapid saline administration).
Hippurate.
Cation-exchange resins.

ACIDOSIS, LACTIC[88]

ICD-10CM # E87.2 Acidosis

CAUSES OF LACTIC ACIDOSIS

L-Lactic Acidosis

Conditions associated with type A lactic acidosis:
- Poor tissue perfusion.
- Shock:
  - Cardiogenic.
  - Hemorrhagic.
  - Septic.

Profound hypoxemia:
- Severe asthma.
- Carbon monoxide poisoning.

Conditions associated with type B lactic acidosis:
- Liver disease.
- Metformin.
- Inborn errors of metabolism.
- Pyroglutamic acidosis.
- Kombucha tea.

d-Lactic Acidosis

Short bowel syndrome.
Ischemic bowel.
Small bowel obstruction.

ACIDOSIS, METABOLIC

ICD-10CM # E87.2 Acidosis

METABOLIC ACIDOSIS WITH INCREASED ANION GAP (AG ACIDOSIS)

Lactic acidosis.
Ketoacidosis (DM, alcoholic ketoacidosis).
Uremia (chronic renal failure).
Ingestion of toxins (paraldehyde, methanol, salicylate, ethylene glycol).
High-fat diet (mild acidosis).

METABOLIC ACIDOSIS WITH NORMAL AG (HYPERCHLOREMIC ACIDOSIS)

Renal tubular acidosis (including acidosis of aldosterone deficiency).
Intestinal loss of HCO_3^- (diarrhea, pancreatic fistula).
Carbonic anhydrase inhibitors (e.g., acetazolamide).
Dilutional acidosis (as a result of rapid infusion of bicarbonate-free isotonic saline).
Ingestion of exogenous acids (ammonium chloride, methionine, cystine, calcium chloride).
Ileostomy.
Ureterosigmoidostomy.
Drugs: amiloride, triamterene, spironolactone, β-blockers.

ACIDOSIS, RESPIRATORY

ICD-10CM # E87.2 Acidosis

Pulmonary disease (COPD, severe pneumonia, pulmonary edema, interstitial fibrosis).
Airway obstruction (foreign body, severe bronchospasm, laryngospasm).
Thoracic cage disorders (pneumothorax, flail chest, kyphoscoliosis).
Defects in muscles of respiration (myasthenia gravis, hypokalemia, muscular dystrophy).
Defects in peripheral nervous system (amyotrophic lateral sclerosis, poliomyelitis, Guillain-Barré syndrome, botulism, tetanus, organophosphate poisoning, spinal cord injury).
Depression of respiratory center (anesthesia, narcotics, sedatives, vertebral artery embolism or thrombosis, increased intracranial pressure).
Failure of mechanical ventilator.

ACUTE KIDNEY INJURY AND LIVER DISEASE, CAUSES[27,28]

ICD-10CM # S37.009A Unspecified injury of unspecified kidney, initial encounter
K76.89 Other specified diseases of liver

Prerenal uremia:	Diuretic use, GI loss, peritoneal aspiration, hypoalbuminemia.
Hepatorenal syndrome	
Acute tubular necrosis:	Hyperbilirubinemia, sepsis, toxic shock syndrome.
Drugs:	Acetaminophen (paracetamol), NSAIDs, tetracycline, rifampicin, isoniazid, anesthetic agents, sulfonamides, allopurinol, methotrexate.
Infections:	Hepatitis C and cryoglobulinemia, hepatitis B and polyarteritis nodosa, leptospirosis, hantavirus, Epstein-Barr virus, gram-negative sepsis, spontaneous bacterial peritonitis.
Other:	Papillary necrosis and obstruction, inhalation of chlorinated hydrocarbons, mushroom poisoning *(Amanita phalloides).*

ACUTE KIDNEY INJURY DUE TO INTRINSIC RENAL DISEASES[60]

ICD-10CM # Varies with specific diagnosis

INTRINSIC RENAL DISEASES THAT CAUSE ACUTE KIDNEY INJURY

Vascular Diseases
Large-Vessel Diseases
Renal artery thrombosis or stenosis.
Renal vein thrombosis.
Atheroembolic disease.
Small- and Medium-Vessel Diseases
Scleroderma.
Malignant hypertension.
Hemolytic uremic syndrome.
Thrombotic thrombocytopenic purpura.
HIV-associated microangiopathy.
Glomerular Diseases
Systemic Diseases
Systemic lupus erythematosus.
Infective endocarditis.
Systemic vasculitis (e.g., periarteritis nodosa, granulomatosis with polyangiitis).
Henoch-Schönlein purpura.
HIV-associated nephropathy.
Essential mixed cryoglobulinemia.
Goodpasture syndrome.
Primary Renal Diseases
Poststreptococcal glomerulonephritis.
Other postinfectious glomerulonephritis.
Rapidly progressive glomerulonephritis.
Tubulointerstitial Diseases and Conditions
Drugs (many).
Toxins (e.g., heavy metals, ethylene glycol).
Infections.
Multiple myeloma.
Acute Tubular Necrosis
Ischemia
Shock.
Sepsis.
Severe prerenal azotemia.
Nephrotoxins
Antibiotics.
Radiographic contrast agents.
Myoglobinuria.
Hemoglobinuria.
Other Diseases and Conditions
Severe liver disease.
Allergic reactions.
NSAIDs.

ACUTE KIDNEY INJURY, HIV PATIENT, CAUSES[27,28]

ICD-10CM # S37.009A Unspecified injury of unspecified kidney, initial encounter with B20 human immunodeficiency virus (HIV) disease

Prerenal:	Diarrhea, nausea and vomiting, cirrhosis and hepatorenal syndrome, sepsis.
Vascular:	Thrombotic microangiopathy.
Glomerular:	Immune complex glomerulonephritis (MPGN secondary to hepatitis C virus, postinfectious glomerulonephritis), HIVAN.
Acute tubular necrosis:	Sepsis, hypotension, nephrotoxins (aminoglycosides, amphotericin, acyclovir, cidofovir, tenofovir, pentamidine).
Acute interstitial nephritis:	Drug-induced (co-trimoxazole), rifampicin, foscarnet, nevirapine), CMV infection, DILS.
Drug-induced intratubular obstruction:	Sulfadiazine, indinavir, foscarnet, acyclovir.
Postrenal obstruction:	Stones, tuberculosis, fungal ball, tumor.
Associated with IV drug use:	Sepsis, endocarditis, heroin-associated nephropathy (FSGS), rhabdomyolysis.

CMV, Cytomegalovirus; *DILS,* diffusive infiltrative lymphocytosis syndrome; *FSGS,* focal segmental glomerulosclerosis; *HIVAN,* HIV-associated nephropathy; *MPGN,* membranoproliferative glomerulonephritis.

ACUTE KIDNEY INJURY IN SPECIFIC CLINICAL SETTINGS[79]

ICD-10CM # N17.9 Acute kidney failure, unspecified

MAJOR CAUSES OF ACUTE KIDNEY INJURY IN SPECIFIC CLINICAL SETTINGS

AKI in the Cancer Patient
Prerenal azotemia:
- Hypovolemia (e.g., poor intake, vomiting, diarrhea).

Intrinsic AKI:
- Exogenous nephrotoxins: chemotherapy, antibiotics, contrast media.
- Endogenous toxins: hyperuricemia, hypercalcemia, tumor lysis, paraproteins.
- Other: radiation, HUS/TTP, glomerulonephritis, amyloid, malignant infiltration.

Postrenal AKI:
- Ureteric or bladder neck obstruction.

AKI after Cardiac Surgery
Prerenal azotemia:
- Hypovolemia (surgical losses, diuretics), cardiac failure, vasodilators.

Intrinsic AKI:
- Ischemic ATN (even in absence of hypotension).
- Atheroembolic disease after aortic manipulation/intraaortic balloon pump.
- Preoperative or perioperative administration of contrast medium.
- Allergic interstitial nephritis induced by perioperative antibiotics.

Postrenal AKI:
- Obstructed urinary catheter, exacerbation of voiding dysfunction.

AKI in Pregnancy

Prerenal azotemia:
- Acute fatty liver of pregnancy with fulminant hepatic failure.

Intrinsic AKI:
- Preeclampsia or eclampsia.
- Postpartum HUS/TTP.
- HELLP syndrome.
- Ischemia: postpartum hemorrhage, abruptio placentae, amniotic fluid embolus.
- Direct toxicity of illegal abortifacients.

Postrenal AKI:
- Obstruction with pyelonephritis.

AKI after Solid Organ or Bone Marrow Transplantation

Prerenal azotemia:
- Intravascular volume depletion (e.g., diuretic therapy).
- Vasoactive drugs (e.g., calcineurin inhibitors, amphotericin B).
- Hepatorenal syndrome, venoocclusive disease of liver (BMT).

Intrinsic AKI:
- Postoperative ischemic ATN (even in absence of hypotension).
- Sepsis.
- Exogenous nephrotoxins: aminoglycosides, amphotericin B, radiocontrast media.
- HUS/TTP (e.g., cyclosporine or myeloablative radiotherapy related).
- Allergic tubulointerstitial nephritis.

Postrenal AKI:
- Obstructed urinary catheter.

AKI and Pulmonary Disease (Pulmonary Renal Syndrome)

Prerenal azotemia:
- Diminished cardiac output complicating pulmonary embolism, severe pulmonary hypertension, or positive-pressure mechanical ventilation.

Intrinsic AKI:
- Vasculitis.
  - Goodpasture syndrome, ANCA-associated vasculitis, SLE, eosinophilic granulomatosis with polyangiitis, polyarteritis nodosa, cryoglobulinemia, right-sided endocarditis, lymphomatoid granulomatosis, sarcoidosis, scleroderma.

Toxins:
- Ingestion of paraquat or diquat.

Infections:
- Legionnaires disease, *Mycoplasma* infection, tuberculosis, disseminated viral or fungal infection.
- AKI from any cause with hypervolemia and pulmonary edema.
- Lung cancer with hypercalcemia, tumor lysis, or glomerulonephritis.

AKI and Liver Disease

Prerenal azotemia:
- Reduced true (GI hemorrhage, GI losses from lactulose, diuretics, large-volume paracentesis) circulatory volume or effective (hypoalbuminemia, splanchnic vasodilation).
- Hepatorenal syndrome type 1 or 2.
- Tense ascites with abdominal compartment syndrome.

Intrinsic AKI:
- Ischemic (severe hypoperfusion—see earlier) or direct nephrotoxicity and hepatotoxicity of drugs or toxins (e.g., carbon tetrachloride, acetaminophen, tetracyclines, methoxyflurane).
- Tubulointerstitial nephritis plus hepatitis caused by drugs (e.g., sulfonamides, rifampin, phenytoin, allopurinol, phenindione), infections (leptospirosis, brucellosis, Epstein-Barr virus infection, cytomegalovirus infection), malignant infiltration (leukemia, lymphoma), or sarcoidosis.
- Glomerulonephritis or vasculitis (e.g., polyarteritis nodosa, ANCA-associated glomerulonephritis, cryoglobulinemia, SLE, postinfectious hepatitis or liver abscess.

AKI and Nephrotic Syndrome

Prerenal azotemia:
- Intravascular volume depletion (diuretic therapy, hypoalbuminemia).

Intrinsic AKI:
- Manifestation of primary glomerular disease.
- Collapsing glomerulopathy (e.g., HIV, pamidronate).
- Associated ATN (older hypertensive males).
- Associated interstitial nephritis (NSAIDs, rifampin, interferon alfa).

Other: amyloid or light-chain deposition disease, renal vein thrombosis, severe interstitial edema.

AKI, Acute kidney injury; *ANCA,* antineutrophil cytoplasmic antibody; *ATN,* acute tubular necrosis; *BMT,* bone marrow transplantation; *GI,* gastrointestinal; *HELLP, h*emolysis, *e*levated *l*iver enzymes, *l*ow *p*latelets; *HIV,* human immunodeficiency virus; *HUS,* hemolytic uremic syndrome; *NSAID,* nonsteroidal antiinflammatory drug; *SLE,* systemic lupus erythematosus; *TTP,* thrombotic thrombocytopenic purpura.

ACUTE KIDNEY INJURY, PIGMENT INDUCED[60]

ICD-10CM # Varies with specific diagnosis

CAUSES OF PIGMENT-INDUCED ACUTE KIDNEY INJURY

Rhabdomyolysis and myoglobinuria.
- Vigorous exercise.
- Arterial embolization.
- Status epilepticus.
- Status asthmaticus.
- Coma-induced and pressure-induced myonecrosis.
- Heat stress.
- Diabetic ketoacidosis.
- Myopathy.
- Alcoholism.
- Hypokalemia.
- Hypophosphatemia.

Hemoglobinuria.
- Transfusion reactions.
- Snake envenomation.
- Malaria.
- Mechanical destruction of RBCs by prosthetic valves.
- G6PD deficiency.

G6PD, Glucose-6-phosphate dehydrogenase.

ACUTE LUNG INJURY, DISEASE AND DISORDER ASSOCIATIONS[61]

ICD-10CM # S27.3 Injury, lung

CLINICAL DISORDERS ASSOCIATED WITH ACUTE LUNG INJURY

Infectious Causes

Gram-negative or gram-positive sepsis.
- Bacterial pneumonia.
- Viral pneumonia.
- Fungal pneumonia
- Parasitic infections.
- Mycobacterial disease.

Aspiration

Gastric acid.
- Food and other particulate matter.
- Fresh or sea water (near drowning).
- Hydrocarbon fluids.

Trauma

Lung contusion.
- Fat emboli.
- Nonthoracic trauma.
- Thermal injury (burns).
- Blast injury (explosion, lightning).
- Overdistention (mechanical ventilation).
- Inhaled gases (phosgene, ammonia).

Hemodynamic Disturbances

Shock of any etiology.
- Anaphylaxis.
- High-altitude pulmonary edema.
- Reperfusion.
- Air embolism.
- Amniotic fluid embolism.

Drugs

Heroin.
- Methadone.
- Propoxyphene.
- Naloxone.
- Cocaine.
- Barbiturates.
- Colchicine.
- Salicylates.
- Ethchlorvynol.
- Interleukin-2.
- Protamine.
- Hydrochlorothiazide.

Hematologic Disorders

Disseminated intravascular coagulation.
- Incompatible blood transfusion.
- Rh incompatibility.
- Antileukocyte antibodies.
- Leucoagglutinin reactions.
- Post–cardiopulmonary bypass, pump oxygenator.

Metabolic Disorders

Pancreatitis.
- Diabetic ketoacidosis.

Neurologic Disorders
Head trauma.
Grand mal seizures.
Increased intracranial pressure (any cause).
Subarachnoid or intracerebral hemorrhage.
Miscellaneous Disorders
Lung reexpansion.
Upper airway obstruction.

ACUTE RESPIRATORY DISTRESS IN PREGNANCY[70]

ICD-10CM # J96.00 Acute respiratory failure

Disorder	Distinguishing Features
Pregnancy-Specific	
Amniotic fluid embolism.	Cardiorespiratory collapse, seizures, DIC.
Pulmonary edema secondary to preeclampsia.	Hypertension, proteinuria.
ARDS secondary to obstetric sepsis.	Evidence of obstetric sepsis, shock.
Tocolytic pulmonary edema.	Tocolytic administration, rapid improvement.
Peripartum cardiomyopathy.	Gradual onset, cardiac gallop, cardiomegaly.
Trophoblastic embolism.	Nodular infiltrate, molar pregnancy.
Risk Increased by Pregnancy	
Aspiration pneumonitis.	Vomiting, aspiration.
Venous thromboembolism.	Evidence of DVT, positive V̇/Q̇ scan, leg Doppler, CT angiogram.
Pneumomediastinum.	Occurs during delivery, subcutaneous emphysema.
Valvular heart disease.	Pulmonary edema, cardiac murmur, cardiomegaly.
ARDS secondary to sepsis.	Evidence of sepsis (e.g., pyelonephritis).
Unrelated to Pregnancy	
Asthma.	Features similar to nonpregnant patient.
Pneumonia.	Features similar to nonpregnant patient.

ARDS, Acute respiratory distress syndrome; *CT,* computed tomography; *DIC,* disseminated intravascular coagulopathy; *DVT,* deep venous thrombosis; V̇/Q̇, ventilation-perfusion.

ACUTE SCROTUM

ICD-10CM # R10.2 Pelvic and perineal pain

Testicular torsion.
Epididymitis.
Testicular neoplasm.
Orchitis.
Trauma.

ADNEXAL MASS[58]

ICD-10CM # R19.00 Intraabdominal and pelvic swelling, mass and lump, unspecified site

Ovary (neoplasm, endometriosis, functional cyst).
Fallopian tube (ectopic pregnancy, neoplasm, tuboovarian abscess, hydrosalpinx, paratubal cyst).
Uterus (fibroid, neoplasm).
Retroperitoneum (neoplasm, abdominal wall hematoma or abscess).
Urinary tract (pelvic kidney, distended bladder, urachal cyst).
Inflammatory bowel disease.
GI tract neoplasm.
Diverticular disease.
Appendicitis.
Bowel loop with feces.

ADRENAL CALCIFICATIONS[74]

ICD-10CM # E27.8 Other specified disorder of adrenal gland

CAUSES OF ADRENAL CALCIFICATION

Infection:
- Tuberculosis.
- Histoplasmosis.
- *Echinococcus.*

Prior hemorrhage.
Neoplasm:
- Adrenocortical carcinoma.
- Myelolipoma.
- Pheochromocytoma.

Hemangioma (rare).

ADRENAL CYSTIC LESIONS[74]

ICD-10CM # E27.8 Other specified disorder of adrenal gland

CYSTIC ADRENAL LESIONS

Pseudocyst.
Endothelial cyst.
Epithelial cyst.
Infection (*Echinococcus,* abscess).
Necrotic neoplasm.
Cystic pheochromocytoma.
Lymphangioma.

ADRENAL INSUFFICIENCY, CRITICALLY ILL PATIENT[73]

ICD-10CM # E27.40 Unspecified adrenocortical insufficiency

CAUSES OF ADRENAL INSUFFICIENCY IN CRITICALLY ILL PATIENTS

Reversible Dysfunction of the HPA Axis
Sepsis/septic shock.
Acute lung injury.
Burns.
Pancreatitis.
Liver failure.
Hypothermia.
Drugs:
- Etomidate (primary AI).
- Corticosteroids (secondary AI).
- Ketoconazole (primary AI).
- Megestrol acetate (secondary AI).
- Rifampin (increased cortisol metabolism).
- Phenytoin (increased cortisol metabolism).
- Metyrapone (primary AI).
- Mitotane (primary AI).

Primary Adrenal Insufficiency (Adrenal Failure)
Autoimmune adrenalitis.
HIV infection:
- HART therapy.
- HIV virus.
- CMV.

Metastatic carcinoma:
- Lung.
- Breast.
- Kidney.

Systemic fungal infection:
- Histoplasmosis.
- Cryptococcus.
- Blastomycosis.

Tuberculosis.
Adrenal hemorrhage/infarction:
- DIC.
- Meningococcemia.
- Anticoagulation.
- Antiphospholipid syndrome.
- HIT.
- Trauma.

AI, Adrenal insufficiency; *CMV,* cytomegalovirus; *DIC,* disseminated intravascular coagulation; *HIT,* heparin-induced thrombocytopenia; *HPA,* hypothalamic-pituitary axis.

ADRENAL MASSES[82]

ICD-10CM # C74.90 Malignant neoplasm of unspecified part of unspecified adrenal gland
E27.8 Other specified disorders of adrenal gland

UNILATERAL ADRENAL MASSES

Functional Lesions
Adrenal adenoma.
Adrenal carcinoma.
Pheochromocytoma.
Primary aldosteronism, adenomatous type.
Nonfunctional Lesions
Incidentaloma of adrenal.
Ganglioneuroma.
Myelolipoma.
Hematoma.
Adenolipoma.
Metastasis.

BILATERAL ADRENAL MASSES

Functional Lesions
ACTH-dependent Cushing syndrome.
Congenital adrenal hyperplasia.
Pheochromocytoma.
Conn syndrome, hyperplastic variety.
Micronodular adrenal disease.
Idiopathic bilateral adrenal hypertrophy.
Nonfunctional Lesions
Infection (tuberculosis, fungi).
Infiltration (leukemia, lymphoma).
Replacement (amyloidosis).
Hemorrhage.
Bilateral metastases.

ADRENAL PSEUDOMASSES[74]

ICD-10CM # E27.8 Other specified disorder of adrenal gland

Thickened diaphragmatic crus.
Accessory spleen.
Gastric fundus.
Gastric diverticulum.
Renal vein.
Retrocrural and retroperitoneal adenopathy.
Upper-pole renal cysts and tumors.
Pancreatic tumors.
Hypertrophied caudate lobe of liver.
Fluid-filled colon interposed between stomach and kidney.

ADRENERGIC TOXIDROME[73]

ICD-10CM # T44.8X1S Poisoning by centrally acting and adrenergic-neuron-blocking agents, accidental (unintentional), sequela

COMMON CAUSES OF THE ADRENERGIC TOXIDROME

Recreational drugs:
Cocaine.
Amphetamines and other "designer drugs"[a]; "ecstasy" (3,4-methylenedioxymethamphetamine [MDMA]); 3,4-methylenedioxyamphetamine (MDA); 3,4-methylenedioxyethylamphetamine (MDEA); paramethoxyamphetamine (PMA); methamphetamine.
β_1-Adrenergic agents:
Salbutamol.
Theophylline.
Inotropic agents:
Norepinephrine.
Epinephrine.
Isoproterenol.
Over-the-counter cough and cold preparations and nasal decongestants:
Phenylpropanolamine.
Pseudoephedrine.
Amphetamine-like agents prescribed for ADD or weight loss:
Methylphenidate.
Dextroamphetamine.
Psychostimulants.

ADD, Attention deficit disorder.

[a]Up to 80% of ecstasy tablets sold in Australia are actually methamphetamine.

ADRENOCORTICAL HYPERFUNCTION[3]

ICD-10CM # E26.9 Hyperaldosteronism, unspecified

SYNDROMES OF ADRENOCORTICAL HYPERFUNCTION

States of Glucocorticoid Excess
Physiologic States
Stress.
Strenuous exercise.
Last trimester of pregnancy.
Pathologic States
Psychiatric conditions (pseudo-Cushing disorders):
Depression.
Alcoholism.
Anorexia nervosa.
Panic disorders.
Alcohol and drug withdrawal.
ACTH-dependent states:
Pituitary adenoma (Cushing disease).
Ectopic ACTH syndrome.
Bronchial carcinoid.
Thymic carcinoid.
Islet cell tumor.
Small cell lung carcinoma.
Ectopic CRH secretion.
ACTH-independent states:
Adrenal adenoma.
Adrenal carcinoma.
Micronodular adrenal disease.
Exogenous Sources
Glucocorticoid intake.
ACTH intake.
States of Mineralocorticoid Excess
Primary Aldosteronism
Aldosterone-secreting adenoma.
Bilateral adrenal hyperplasia.
Aldosterone-secreting carcinoma.
Glucocorticoid-suppressible hyperaldosteronism.
Adrenal Enzyme Deficiencies
11b-Hydroxylase deficiency.
17a-Hydroxylase deficiency.
11b-Hydroxysteroid dehydrogenase, type II.
Exogenous Mineralocorticoids
Licorice.
Carbenoxolone.
Fludrocortisone.
Secondary Hyperaldosteronism
Associated with hypertension:
Accelerated hypertension.
Renovascular hypertension.
Estrogen administration.
Renin-secreting tumors.
Without hypertension:
Bartter syndrome.
Sodium-wasting nephropathy.
Renal tubular acidosis.
Diuretic and laxative abuse.
Edematous states (cirrhosis, nephrosis, congestive heart failure).

ACTH, Adrenocorticotropin hormone; *CRH,* corticotropin-releasing hormone.

ADRENOCORTICAL HYPOFUNCTION

ICD-10CM # E27.49 Other adrenocortical insufficiency

SYNDROMES OF ADRENOCORTICAL HYPOFUNCTION

Primary Adrenal Disorders
Combined Glucocorticoid and Mineralocorticoid Deficiency
Autoimmune:
Isolated autoimmune disease (Addison disease).
Polyglandular autoimmune syndrome, type I.
Polyglandular autoimmune syndrome, type II.
Infectious:
Tuberculosis.
Fungal.
Cytomegalovirus.
Human immunodeficiency virus.
Vascular:
Bilateral adrenal hemorrhage.
Sepsis.
Coagulopathy.
Thrombosis; embolism.
Adrenal infarction.
Infiltration:
Metastatic carcinoma and lymphoma.
Sarcoidosis.
Amyloidosis.
Hemochromatosis.
Congenital:
Congenital adrenal hyperplasia.
21-Hydroxylase deficiency.
3b-o1 Dehydrogenase deficiency.
20,22-Desmolase deficiency.
Adrenal unresponsiveness to ACTH.
Congenital adrenal hypoplasia.
Adrenoleukodystrophy.
Adrenomyeloneuropathy.
Iatrogenic
Bilateral adrenalectomy.
Drugs:
Metyrapone, aminoglutethimide, trilostane, ketoconazole, o,p'-DDD, mifepristone.
Mineralocorticoid deficiency without glucocorticoid deficiency
Corticosterone methyl oxidase deficiency.
Isolated zona glomerulosa defect.
Heparin therapy.
Critical illness.
Converting-enzyme inhibitors.
Secondary Adrenal Disorders
Secondary Adrenal Insufficiency
Hypothalamic-pituitary dysfunction.
Exogenous glucocorticoids.
After removal of an ACTH-secreting tumor.
Hyporeninemic Hypoaldosteronism
Diabetic nephropathy.
Tubulointerstitial diseases.
Obstructive uropathy.
Autonomic neuropathy.
Nonsteroidal antiinflammatory drugs.
β-Adrenergic drugs.

ACTH, Adrenocorticotropic hormone.

ADVERSE FOOD REACTIONS, DIFFERENTIAL DIAGNOSIS[53]

ICD-10CM # T78.1XXA Other adverse food reactions, not elsewhere classified, initial encounter

GASTROINTESTINAL DISORDERS (WITH VOMITING AND/OR DIARRHEA)

Structural abnormalities (pyloric stenosis, Hirschsprung disease).
Enzyme deficiencies (primary or secondary):

Disaccharidase deficiency: lactase, fructose, sucrase-isomaltase.
Galactosemia.
Other: pancreatic insufficiency (cystic fibrosis), peptic disease.

CONTAMINANTS AND ADDITIVES

Flavorings and preservatives—rarely cause symptoms: sodium metabisulfite, monosodium glutamate, nitrites.
Dyes and colorings—very rarely cause symptoms (urticaria, eczema): tartrazine.
Toxins: bacterial, fungal (aflatoxin), fish-related (scombroid, ciguatera).
Infectious organisms:
Bacteria *(Salmonella, Escherichia coli, Shigella)*.
Virus (rotavirus, enterovirus).
Parasites (*Giardia*, Akis simplex [in fish]).
Accidental contaminants: heavy metals, pesticides.
Pharmacologic agents: caffeine, glycosidal alkaloid solanine (potato spuds), histamine (fish), serotonin (banana, tomato), tryptamine (tomato), tyramine (cheese).

PSYCHOLOGIC REACTIONS

Food phobias.

ADYNAMIC ILEUS[58]

ICD-10CM #		
	K56.0	Paralytic ileus
	K56.7	Ileus, unspecified

Abdominal trauma.
Infection (retroperitoneal, pelvic, intrathoracic).
Laparotomy.
Metabolic disease (hypokalemia).
Renal colic.
Skeletal injury (rib fracture, vertebral fracture).
Medications (e.g., narcotics).

AEROPHAGIA (BELCHING, ERUCTATION)

ICD-10CM #		
	R14.0	Abdominal distention (gaseous)
	R14.1	Gas pain
	R14.2	Eructation
	R14.3	Flatulence

Anxiety disorders.
Rapid food ingestion.
Carbonated beverages.
Nursing infants (especially when nursing in horizontal position).
Eating or drinking in supine position.
Gum chewing.
Poorly fitting dentures, orthodontic appliances.
Hiatal hernia, gastritis, nonnuclear dyspepsia.
Cholelithiasis, cholecystitis.
Ingestion of legumes, onions, peppers.

AIR-SPACE OPACIFICATION ON X-RAY[36]

ICD-10CM #		
	R91.8	Other nonspecific abnormal finding of lung field

CAUSES OF AIR-SPACE OPACIFICATION

Edema
Cardiogenic.
Non-cardiogenic.
Inflammation/Infection
Granulomatosis with polyangiitis.
Cryptogenic organizing pneumonia.
Blood
Idiopathic pulmonary hemosiderosis.
Antibasement membrane antibody disease.
Systemic lupus erythematosus.
Miscellaneous Causes
Eosinophilic pneumonia.
Alveolar proteinosis.
Alveolar cell carcinoma.
Alveolar microlithiasis.
Lymphoma (MALToma).
Sarcoidosis.

AIRWAY OBSTRUCTION, PEDIATRIC AGE[43]

ICD-10CM #		
	J44.9	Chronic obstructive pulmonary disease, unspecified
	T17.900A	Unspecified foreign body in respiratory tract, part unspecified causing asphyxiation, initial encounter
	T17.908A	Unspecified foreign body in respiratory tract, part unspecified causing other injury, initial encounter
	T17.910A	Gastric contents in respiratory tract, part unspecified causing asphyxiation, initial encounter
	T17.918A	Gastric contents in respiratory tract, part unspecified causing other injury, initial encounter
	T17.920A	Food in respiratory tract, part unspecified causing asphyxiation, initial encounter
	T17.928A	Food in respiratory tract, part unspecified causing other injury, initial encounter
	T17.990A	Other foreign object in respiratory tract, part unspecified in causing asphyxiation, initial encounter
	T17.998A	Other foreign object in respiratory tract, part unspecified causing other injury, initial encounter
	J38.5	Laryngeal spasm
	J68.9	Unspecified respiratory condition due to chemicals, gases, fumes, and vapors

CONGENITAL CAUSES

Craniofacial dysmorphism.
Hemangioma.
Laryngeal cleft/web.
Laryngoceles, cysts.
Laryngomalacia.
Macroglossia.
Tracheal stenosis.
Vascular ring.
Vocal cord paralysis.

ACQUIRED INFECTIOUS CAUSES

Acute laryngotracheobronchitis.
Epiglottitis.
Laryngeal papillomatosis.
Membranous croup (bacterial tracheitis).
Mononucleosis.
Retropharyngeal abscess.
Spasmodic croup.
Diphtheria.

ACQUIRED NONINFECTIOUS CAUSES

Anaphylaxis.
Foreign body aspiration.
Supraglottic hypotonia.
Thermal/chemical burn.
Trauma.
Vocal cord paralysis.
Angioneurotic edema.

AKINETIC/RIGID SYNDROME[3]

ICD-10CM #		
	R29.8	Akinesis

Parkinsonism (idiopathic, drug-induced).
Catatonia (psychosis).
Progressive supranuclear palsy.
Multisystem atrophy (Shy-Drager syndrome, olivopontocerebellar atrophy).
Diffuse Lewy-body disease.
Toxins (MPTP, manganese, carbon monoxide).
Huntington disease and other hereditary neurodegenerative disorders.

ALCOHOL-RELATED SEIZURES[60]

ICD-10CM #	
F10.232	Alcohol dependence with withdrawal with perceptual disturbance

DIFFERENTIAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES

Withdrawal (alcohol or drugs).
Exacerbation of idiopathic or posttraumatic seizures.
Acute intoxication (amphetamines, anticholinergics, cocaine, isoniazid, organophosphates, phenothiazines, tricyclic antidepressants, salicylates, lithium).
Metabolic (hypoglycemia, hyponatremia, hypernatremia, hypocalcemia, hepatic failure).

Infectious (meningitis, encephalitis, brain abscess).
Trauma (intracranial hemorrhage).
Cerebrovascular accident.
Sleep deprivation.
Noncompliance with anticonvulsants.

ALKALOSIS, METABOLIC

ICD-10CM # E87.3 Alkalosis

CAUSES OF METABOLIC ALKALOSIS

Exogenous HCO_3– loads.
Acute alkali administration.
Milk-alkali syndrome.
Effective Extracellular Volume Contraction, Normotension, Hypokalemia, and Secondary Hyperreninemic Hyperaldosteronism
GI origin:
- Vomiting.
- Gastric aspiration.
- Congenital chloridorrhea.
- Villous adenoma.
- Combined administration of sodium polystyrene sulfonate (Kayexalate and aluminum hydroxide).

Renal origin:
- Diuretics (especially thiazides and loop diuretics).
- Acute.
- Chronic.
- Edematous states.
- Posthypercapnic state.
- Hypercalcemia-hypoparathyroidism.
- Recovery from lactic acidosis or ketoacidosis.
- Nonreabsorbable anions such as penicillin, carbenicillin.
- Mg++ deficiency.
- K+ depletion.
- Bartter syndrome (loss-of-function mutation of Cl– transport in thick ascending limb of Henle loop).
- Gitelman syndrome (loss-of-function mutation in Na+/Cl– cotransporter).
- Carbohydrate refeeding after starvation.

Extracellular Volume Expansion, Hypertension, K^+ Deficiency, and Hypermineralocorticoidism
Associated with high renin:
- Renal artery stenosis.
- Accelerated hypertension.
- Renin-secreting tumor.
- Estrogen therapy.

Associated with low renin:
- Primary aldosteronism.
- Adenoma.
- Hyperplasia.
- Carcinoma.
- Glucocorrticoid suppressible.

Adrenal enzymatic defects:
- 11β-Hydroxylase deficiency.
- 17α-Hydroxylase deficiency.

Cushing syndrome or disease:
- Ectopic corticotropin.
- Adrenal carcinoma.
- Adrenal adenoma.
- Primary pituitary.

Other:
- Licorice.
- Carbenoxolone.
- Chewer's tobacco.
- Lydia Pinkham tablets.

Gain-of-Function Mutation of ENaC with Extracellular Fluid Volume Expansion, Hypertension, K^+ Deficiency, and Hyporeninemic Hypoaldosteronism
Liddle syndrome.

ALKALOSIS, RESPIRATORY

ICD-10CM # E87.3 Alkalosis

Hypoxemia (pneumonia, pulmonary embolism, atelectasis, high-altitude living).
Drugs (salicylates, xanthenes, progesterone, epinephrine, thyroxine, nicotine).
Central nervous system (CNS) disorders (tumor, cerebrovascular accident [CVA], trauma, infections).
Psychogenic hyperventilation (anxiety, hysteria).
Hepatic encephalopathy.
Gram-negative sepsis.
Hyponatremia.
Sudden recovery from metabolic acidosis.
Assisted ventilation.

ALOPECIA[32,61]

ICD-10CM #		
	L65.9	Nonscarring hair loss, unspecified
	L63.2	Ophiasis
	L63.8	Other alopecia areata
	Q84.0	Congenital alopecia
	Q84.1	Congenital morphological disturbances of hair, not elsewhere classified
	Q84.2	Other congenital malformations of hair
	F54	Psychological and behavioral factors associated with disorders or diseases classified elsewhere

SCARRING ALOPECIA

Congenital (aplasia cutis).
Tinea capitis with inflammation (kerion).
Bacterial folliculitis.
Discoid lupus erythematosus.
Lichen planopilaris.
Folliculitis decalvans.
Neoplasm.
Trauma.

NONSCARRING ALOPECIA

Cosmetic treatment.
Tinea capitis.
Structural hair shaft disease.
Trichotillomania (hair pulling).
Anagen arrest.
Telogen arrest.
Alopecia areata.
Androgenetic alopecia.

ALOPECIA AND HYPOTRICHOSIS, IN CHILDREN AND ADOLESCENTS

ICD-10CM #		
	L65.9	Nonscarring hair loss, unspecified
	L63.2	Ophiasis
	L63.8	Other alopecia areata
	Q84.0	Congenital alopecia
	Q84.1	Congenital morphological disturbances of hair, not elsewhere classified
	Q84.2	Other congenital malformations of hair

Congenital total alopecia: atrichia with papules, Moynahan alopecia syndrome.
Congenital localized alopecia: aplasia cutis, triangular alopecia, sebaceous nevus.
Hereditary hypotrichosis: Marie-Unna syndrome, hypotrichosis with juvenile macular dystrophy, hypotrichosis–Mari type, ichthyosis with hypotrichosis, cartilage-hair hypoplasia, Hallermann-Streiff syndrome, trichorhinophalangeal syndrome, ectodermal dysplasia ("pure" hair and nail and other ectodermal dysplasias).
Diffuse alopecia of endocrine origin: hypopituitarism, hypothyroidism, hypoparathyroidism, hyperthyroidism.
Alopecia of nutritional origin: marasmus, kwashiorkor, iron deficiency, zinc deficiency (acrodermatitis enteropathica), gluten-sensitive enteropathy, essential fatty acid deficiency, biotinidase deficiency.
Disturbances of the hair cycle: telogen effluvium.
Toxic alopecia: anagen effluvium.
Autoimmune alopecia: alopecia areata.
Traumatic alopecia: traction alopecia, trichotillomania.
Cicatricial alopecia: lupus erythematosus, lichen planopilaris, pseudopelade, morphea (en coup de saber), dermatomyositis, infection (kerion, favus, tuberculosis, syphilis, folliculitis, leishmaniasis, herpes zoster, varicella), acne keloidalis, follicular mucinosis, sarcoidosis.
Hair shaft abnormalities: monilethrix, pili annulati, pili torti, trichorrhexis invaginata, trichorrhexis nodosa, woolly hair syndrome, Menkes disease, trichothiodystrophy, tricho-dento-osseous syndrome, uncombable hair syndrome (spun-glass hair, pili trianguli et canaliculi).

ALOPECIA, DRUG-INDUCED

ICD-10CM #		
	L65.9	Nonscarring hair loss, unspecified
	L63.8	Alopecia areata

DRUGS REPORTED TO INDUCE HAIR LOSS

ACE inhibitors (captopril, enalapril, moexipril, ramipril).
Allopurinol.
Amiodarone.

Amphetamines.[1,2]
Analgesics, antiinflammatories (ibuprofen, indomethacin, naproxen).
Androgens.[3]
Anticoagulants (coumarin, dextran, heparin/heparinoids).
Antiepileptics (carbamazepine, hydantoins, lamotrigine, troxidone, valproic acid, vigabatrin).
Antipsychotics (flupenthixol decanoate, fluphenazine decanoate).
Antithyroid drugs (carbimazole, iodine, thiouracil).
Appetite suppressants.
Aromatase inhibitors (fadrozole, 4-OHA, vorozole).
Benzimidazoles (albendazole, mebendazole)
β-Blockers (levobunolol, metoprolol, nadolol, propranolol, timolol).
Bromocriptine.
Buspirone.
Butyrophenones.
Cantharidin.
Chloramphenicol.
Cholestyramine.
Cidofovir.
Cimetidine.
Clonazepam.
Clotrimazole.
Colchicine.
Contraceptives (oral).[4]
Danazol.
Diazoxide.
Diclofenac.
Dixyrazine.
Ethambutol.
Ethionamide.
Fibrates (clofibrate, fenofibrate).
G-CSF (granulocyte-colony stimulating factor)
Gefitinib.[5]
Gentamicin.
Glatiramer acetate.
Glibenclamide.
Gold salts.
Haloperidol.
Immunoglobulins.
Indanediones.
Indinavir.
Interferons.
Isonicotinic acid hydrazide.[6]
Leflunomide.
Levodopa.
Lithium.
Maprotiline.
Mesalazine.
Methyldopa.
Methysergide.
Metyrapone.
Minoxidil.
Nicotinic acid.
Nitrofurantoin.
Octreotide.
Olanzapine.
Pentosan polysulfate.
Phenindione.
Potassium thiocyanate.
Pyridostigmine.
Radiation (<700 Gy).
Retinoids (acitretin, etretinate, isotretinoin).
Retinol (vitamin A).
Risperidone.
Salicylates.
Serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine, sertraline).
Sorafenib.
Spironolactone.
Strontium ranelate.
Sulfasalazine.
Tamoxifen.
Terbinafine.
Terfenadine.
Thiamphenicol.
Thyroxine.
Tocopherol (vitamin E).
Trazodone.
Triazoles (fluconazole, itraconazole).
Tricyclic antidepressants (amitriptyline, desipramine, doxepin, imipramine, maprotiline).
Trimethadione.
Triparanol.
Vasopressin.

[1] Established by multiple reports or proved by rechallenge.
[2] Involvement principally of cancellous bone.
[3] May produce androgenetic alopecia.
[4] May produce telogen effluvium 3 months after discontinuation.
[5] Involvement of cancellous and cortical bone.
[6] May produce anagen effluvium.

[†] Hair loss usually severe.

ALVEOLAR CONSOLIDATION

ICD-10CM #		
	J18.2	Hypostatic pneumonia, unspecified organism
	J81.1	Hypostatic pneumonia, unspecified organism

Infection.
Neoplasm (bronchoalveolar carcinoma, lymphoma).
Aspiration.
Trauma.
Hemorrhage (granulomatosis with polyangiitis, Goodpasture, bleeding diathesis).
ARDS.
CHF.
Renal failure.
Eosinophilic pneumonia.
Bronchiolitis obliterans.
Pulmonary alveolar proteinosis.

ALVEOLAR HEMORRHAGE[65]

ICD-10CM #		
	P26.1	Massive pulmonary hemorrhage originating in the perinatal period
	K08.8	Alveolar hemorrhage
	P26.8	Other pulmonary hemorrhages originating in the perinatal period

Hematologic disorders (coagulopathies, thrombocytopenia).
Goodpasture syndrome (anti-basement membrane antibody disease).
Granulomatosis with polyangiitis.
Immune complex-mediated vasculitis.
Idiopathic pulmonary hemosiderosis.
Drugs (penicillamine).
Lymphangiogram contrast.
Mitral stenosis.

AMENORRHEA

ICD-10CM #		
	N91.2	Amenorrhea, unspecified

PREGNANCY

Early Menopause

Hypothalamic Dysfunction

Defective synthesis or release of LHRH, anorexia nervosa, stress, exercise.

Pituitary Dysfunction

Neoplasm, postpartum hemorrhage, surgery, radiotherapy.

Ovarian Dysfunction

Gonadal dysgenesis, 17a-hydroxylase deficiency, premature ovarian failure, polycystic ovarian disease, gonadal stromal tumors.

UTEROVAGINAL ABNORMALITIES

Congenital: imperforate hymen, imperforate cervix, imperforate or absent vagina, Müllerian agenesis.
Acquired: destruction of endometrium with curettage (Asherman syndrome), closure of cervix or vagina caused by traumatic injury, hysterectomy.

OTHER

Metabolic diseases (liver, kidney), malnutrition, rapid weight loss, exogenous obesity, endocrine abnormalities (Cushing syndrome, Graves disease, hypothyroidism).

AMNESIA

ICD-10CM #		
	F19.96	Other psychoactive substance use, unspecified with psychoactive substance-induced persisting amnestic disorder
	F44.0	Dissociative amnesia
	R41.2	Retrograde amnesia
	G45.4	Transient global amnesia

Degenerative diseases (e.g., Alzheimer, Huntington disease).
CVA (especially when involving thalamus, basal forebrain, and hippocampus).
Head trauma.
Postsurgical (e.g., mammillary body surgery, bilateral temporal lobectomy).
Infections (herpes simplex encephalitis, meningitis).
Wernicke-Korsakoff syndrome.
Cerebral hypoxia.
Hypoglycemia.
CNS neoplasms.
Creutzfeldt-Jakob disease.
Medications (e.g., midazolam and other benzodiazepines).
Psychosis.
Malingering.

AMNIOTIC FLUID α-FETOPROTEIN ELEVATION[36]

ICD-10CM # Z36 Encounter for antenatal screening of mother

CAUSES OF ELEVATED AMNIOTIC FLUID α-FETOPROTEIN

Craniospinal defect (open neural tube defect).
Omphalocele.
Gastroschisis.
Duodenal atresia.
Congenital nephrosis.
Cystic hygroma.
Unbalanced D/G dislocation.
Down, Tay-Sachs, Klinefelter, Turner syndromes.
Fetal tumors.
Epidermolysis bullosa.
Pilonidal sinus.
Rhesus disease.
Fetal demise.
Incorrect dates.
Multiple pregnancies.

ANAL ABSCESS AND FISTULA[86]

ICD-10CM #		
	K61.0	Anal abscess
	K61.1	Rectal abscess
	K61.3	Ischiorectal abscess
	K60.3	Anal fistula

Primary anal gland infection.
Secondary abscess:
- Inflammatory bowel disease:
  - Crohn disease.
  - Ulcerative colitis.

Infection:
- Tuberculosis.
- Actinomycosis.
- Threadworm.

Trauma.
Leukopenia.
Immunosuppression:
- HIV.
- Drugs.

Rectal cancer.
Diabetes mellitus.

ANAL INCONTINENCE[58]

ICD-10CM # R15.9 Full incontinence of feces

TRAUMATIC

Nerve injured in surgery.
Spinal cord injury.
Obstetric trauma.
Sphincter injury.

NEUROLOGIC

Spinal cord lesions.
Dementia.
Autonomic neuropathy (e.g., DM).
Obstetrics: pudendal nerve stretched during surgery.
Hirschsprung disease.

MASS EFFECT

Carcinoma of anal canal.
Carcinoma of rectum.
Foreign body.
Fecal impaction.
Hemorrhoids.

MEDICAL

Procidentia.
Inflammatory disease.
Diarrhea.
Laxative abuse.

PEDIATRIC

Congenital.
Meningocele.
Myelomeningocele.
Spina bifida.
After corrective surgery for imperforate anus.
Sexual abuse.
Encopresis.

ANAPHYLAXIS[49]

ICD-10CM # T78.2 Anaphylactic shock, unspecified, initial encounter

PULMONARY

Laryngeal edema.
Epiglottitis.
Foreign body aspiration.
Pulmonary embolus.
Asphyxiation.
Hyperventilation.

CARDIOVASCULAR

Myocardial infarction.
Arrhythmia.
Hypovolemic shock.
Cardiac arrest.

CNS

Vasovagal reaction.
CVA.
Seizure disorder.
Drug overdose.

ENDOCRINE

Hypoglycemia.
Pheochromocytoma.
Carcinoid syndrome.
Catamenial (progesterone-induced anaphylaxis).

PSYCHIATRIC

Vocal cord dysfunction syndrome.
Munchausen syndrome.
Panic attack/globus hystericus.

OTHER

Hereditary angioedema.
Cord urticaria.
Idiopathic urticaria.
Mastocytosis.
Serum sickness.
Idiopathic capillary leak syndrome.
Sulfite exposure.
Scombroid poisoning (tuna, blue fish, mackerel).

ANAPHYLAXIS MIMICS[69]

ICD-10CM # Varies with specific diagnosis

CONDITIONS THAT MIMIC ANAPHYLAXIS

Vasovagal episodes.
Acute pulmonary events:
- Acute asthmatic attacks.
- Acute pulmonary edema.
- Pulmonary embolus.
- Spontaneous pneumothorax.
- Foreign body aspiration.

Acute cardiac events:
- Supraventricular tachycardias.
- Acute myocardial infarction/ischemia.

Drug overdoses.
Insulin shock.
Carcinoid attacks.

ANAPHYLAXIS, PATHOPHYSIOLOGIC CLASSIFICATION[2]

ICD-10CM # T78.2 Anaphylactic shock, unspecified, initial encounter

PATHOPHYSIOLOGIC CLASSIFICATION OF ANAPHYLAXIS

IgE Dependent, Immunologic
Foods.
Drugs.
Insect stings and bites.
Exercise (food dependent).
Other causes.
IgE Independent, Immunologic
Immune aggregates.
IgG anti-IgA.
Cytotoxic.
Disturbance of arachidonic acid metabolism:
- Aspirin.
- Other nonsteroidal antiinflammatory drugs.

Activation of kallikrein-kinin contact system:
- Dialysis membranes.
- Radiocontrast media.

Multimediator recruitment:
- Complement.
- Clotting.
- Clot lysis.
- Kallikrein-kinin contact system.

Other causes.
Nonimmunologic
Direct mediator release from mast cells and basophils:
- Drugs, e.g., opiates.
- Physical factors, e.g., cold and sunlight.

Exercise.
c-kit Mutation (D816V).
Other causes.
Idiopathic

ANAPHYLACTOID SYNDROME OF PREGNANCY[1]

ICD-10CM # 088.113

CARDIOVASCULAR COLLAPSE, HYPOTENSION

Acute coronary syndromes, myocardial infarction.
Cardiomyopathy.
Pulmonary embolism.
Anesthesia complications, transfusion reaction.
Sepsis, systemic inflammatory response syndrome.

RESPIRATORY ARREST

Pulmonary embolism, air embolism.
Anesthesia complications, transfusion reaction.
Aspiration.

ALTERED MENTAL STATUS, SEIZURE

Eclampsia.
Cerebrovascular accident.
Hypoglycemia.

COAGULOPATHY

Disseminated intravascular coagulation.
Consumptive coagulopathy from hemorrhage.

ANDROGEN EXCESS, REPRODUCTIVE-AGE WOMAN

ICD-10CM #	E28.1	Androgen excess

Polycystic ovary syndrome.
Idiopathic.
Medications (e.g., anabolizing agents, testosterone, danazol).
Pregnancy (luteoma, hyperreaction luteinalis).
Sertoli-Leydig ovarian neoplasm.
Adrenal adenoma or hyperplasia.
Cushing syndrome.
Glucocorticoid resistance.
Hypothyroidism.
Hyperprolactinemia.

ANDROGEN RESISTANCE[62]

ICD-10CM #	E34.5	Androgen resistance syndrome

CONGENITAL OR DEVELOPMENTAL DISORDERS

Uncommon causes:
- Kennedy disease (spinal and bulbar muscular atrophy).
- Partial androgen insensitivity syndrome (AR mutations).
- 5α-reductase type 2 deficiency.
- Complete androgen insensitivity syndrome (female phenotype).

ACQUIRED DISORDERS

Common causes:
- AR antagonists (bicalutamide, nilutamide).
- Drugs (spironolactone, cyproterone acetate, marijuana, histamine 2 receptor antagonists).

Uncommon causes:
- Celiac disease.

ANEMIA, APLASTIC[45]

ICD-10CM #	D61.09	Other constitutional aplastic anemia

ACQUIRED APLASTIC ANEMIA

Secondary aplastic anemia.
Irradiation.
Drugs and chemicals.
Regular effects.
Cytotoxic agents.
Benzene.
Idiosyncratic reactions.
Chloramphenicol.
Nonsteroidal antiinflammatory drugs.
Antiepileptics.
Gold.
Other drugs and chemicals.
Viruses.
Epstein-Barr virus (infectious mononucleosis).
Hepatitis virus (non-A, non-B, non-C, non-G hepatitis).
Parvovirus (transient aplastic crisis, some pure red cell aplasia).
Human immunodeficiency virus (acquired immunodeficiency syndrome).
Immune diseases.
Eosinophilic fasciitis.
Hyperimmunoglobulinemia.
Thymoma and thymic carcinoma.
Graft-versus-host disease in immunodeficiency.
Paroxysmal nocturnal hemoglobinuria.
Pregnancy.
Idiopathic aplastic anemia.

INHERITED APLASTIC ANEMIA

Fanconi anemia.
Dyskeratosis congenita.
Shwachman-Diamond syndrome.
Reticular dysgenesis.
Amegakaryocytic thrombocytopenia.
Familial aplastic anemias.
Preleukemia (e.g., monosomy 7).
Nonhematologic syndromes (e.g., Down, Dubowitz, Seckel).

ANEMIA, APLASTIC, DUE TO DRUGS AND CHEMICALS[1]

ICD-10CM #	D61.1	Drug-induced aplastic anemia
	D61.2	Aplastic anemia due to other external agents
	D61.89	Other specified aplastic anemias and other bone marrow failure syndromes

Agents that regularly produce marrow depression as a major toxic effect when used in commonly employed doses or normal exposures:
- Cytotoxic drugs used in cancer chemotherapy.
- Alkylating agents (busulfan, melphalan, cyclophosphamide).
- Antimetabolites (antifolic compounds, nucleotide analogs), antimitotics (vincristine, vinblastine, colchicine).
- Some antibiotics (daunorubicin, doxorubicin [Adriamycin]).
- Benzene (and less often benzene-containing chemicals; kerosene, carbon tetrachloride, Stoddard solvent, chlorophenols).

Agents probably associated with aplastic anemia but with a relatively low probability relative to their use:
- Chloramphenicol.
- Insecticides.
- Antiprotozoals (quinacrine and chloroquine).
- NSAIDs (including phenylbutazone, indomethacin, ibuprofen, sulindac, diclofenac, naproxen, piroxicam, fenoprofen, fenbufen, aspirin).
- Anticonvulsants (hydantoins, carbamazepine, phenacemide, ethosuximide).
- Gold, arsenic, and other heavy metals such as bismuth and mercury.
- Sulfonamides as a class.
- Antithyroid medications (methimazole, methylthiouracil, propylthiouracil).
- Antidiabetes drugs (tolbutamide, carbutamide, chlorpropamide).
- Carbonic anhydrase inhibitors (acetazolamide, methazolamide, mesalazine).
- D-Penicillamine.
- 2-Chlorodeoxyadenosine.

Agents more rarely associated with aplastic anemia:
- Antibiotics (streptomycin, tetracycline, methicillin, ampicillin, mebendazole and albendazole, sulfonamides, flucytosine, mefloquine, dapsone).
- Antihistamines (cimetidine, ranitidine, chlorpheniramine).
- Sedatives and tranquilizers (chlorpromazine, prochlorperazine, piperacetazine, chlordiazepoxide, meprobamate, methyprylon, remoxipride).
- Antiarrhythmics (tocainide, amiodarone).
- Allopurinol (can potentiate marrow suppression by cytotoxic drugs).
- Ticlopidine.
- Methyldopa.
- Quinidine.
- Lithium.
- Guanidine.
- Canthaxanthin.
- Thiocyanate.
- Carbimazole.
- Cyanamide.
- Deferoxamine.
- Amphetamines.

ANEMIA, CAUSES IN PREGNANCY[30]

ICD-10CM #	D50.8	Other iron deficiency anemias
	D50.9	Iron deficiency anemia, unspecified
	D51.0	Vitamin B_{12} deficiency anemia due to intrinsic factor deficiency
	D51.1	Vitamin B_{12} deficiency anemia due to selective vitamin B_{12} malabsorption with proteinuria
	D51.3	Other dietary vitamin B_{12} deficiency anemia
	D51.8	Other vitamin B_{12} deficiency anemias

D52.0	Dietary folate deficiency anemia
D52.1	Drug-induced folate deficiency anemia
D52.8	Other folate deficiency anemias
D52.9	Folate deficiency anemia, unspecified
D53.1	Other megaloblastic anemias, not elsewhere classified
D53.0	Protein deficiency anemia
D53.2	Scorbutic anemia
D53.8	Other specified nutritional anemias
D53.9	Nutritional anemia, unspecified
D64.0	Hereditary sideroblastic anemia
D64.1	Secondary sideroblastic anemia due to disease
D64.2	Secondary sideroblastic anemia due to drugs and toxins
D64.3	Other sideroblastic anemias

CAUSES OF ANEMIA DURING PREGNANCY

Common causes—85% of anemia:
- Physiologic anemia.
- Iron deficiency.

Uncommon causes:
- Folic acid deficiency.
- Vitamin B_{12} deficiency (due to the rapid increase in bariatric surgery).
- Hemoglobinopathies:
  - Sickle cell disease.
  - Hemoglobin SC.
  - β-Thalassemia minor.
- Bariatric surgery.
- GI bleeding.

Rare causes:
- Hemoglobinopathies.
  - β-Thalassemia major.
  - α-Thalassemia.

Syndromes of chronic hemolysis:
- Hereditary spherocytosis.
- Paroxysmal nocturnal hemoglobinuria.

Hematologic malignancy.

ANEMIA, DRUG-INDUCED[39]

ICD-10CM #	D61.1	Drug-induced aplastic anemia

DRUGS THAT MAY INTERFERE WITH RED CELL PRODUCTION BY INDUCING MARROW SUPPRESSION OR APLASIA

Alcohol.
Antineoplastic drugs.
Antithyroid drugs.
Antibiotics.
Oral hypoglycemic agents.
Phenylbutazone.
Azidothymidine (AZT).

DRUGS THAT INTERFERE WITH VITAMIN B_{12}, FOLATE, OR IRON ABSORPTION OR UTILIZATION

Nitrous oxide.
Anticonvulsant drugs.
Antineoplastic drugs.
Isoniazid.
Cycloserine A.

DRUGS CAPABLE OF PROMOTING HEMOLYSIS

Immune Mediated

Penicillins.
Quinine.
α-methyldopa.
Procainamide.
Mitomycin C.

Oxidative Stress

Antimalarials.
Sulfonamide drugs.
Nalidixic acid.

DRUGS THAT MAY PRODUCE OR PROMOTE BLOOD LOSS

Aspirin.
Alcohol.
Nonsteroidal antiinflammatory agents.
Corticosteroids.
Anticoagulants.

ANEMIA, HYPOCHROMIC[45]

ICD-10CM #	D50.8	Other Iron deficiency anemias
	D50.9	Iron deficiency anemia, unspecified
	D64.0	Hereditary sideroblastic anemia
	D64.1	Secondary sideroblastic anemia due to disease
	D64.2	Secondary sideroblastic anemia due to drugs and toxins
	D64.3	Other sideroblastic anemias

DECREASED BODY IRON STORES

Iron deficiency anemia.

NORMAL OR INCREASED BODY IRON STORES

Impaired iron metabolism.
Anemia of chronic disease.
Defective absorption, transport, or use of iron.
Disorders of globin synthesis:
- Thalassemia.
- Other microcytic hemoglobinopathies.

Disorders of heme synthesis: sideroblastic anemias:
- Hereditary.
- Acquired.

ANEMIA, LOW RETICULOCYTE COUNT[3]

ICD-10CM #	D64.9	Anemia, unspecified

MICROCYTIC ANEMIA (MCV <80)

Iron deficiency.
Thalassemia minor.
Sideroblastic anemia.
Lead poisoning.

MACROCYTIC ANEMIA (MCV >100)

Megaloblastic anemias.
Folate deficiency.
Vitamin B_{12} deficiency.
Drug-induced megaloblastic anemia.
Nonmegaloblastic macrocytosis.
Liver disease.
Hypothyroidism.

NORMOCYTIC ANEMIA (MCV 80-100)

Early iron deficiency.
Aplastic anemia.
Myelophthisic disorders.
Endocrinopathies.
Anemia of chronic disease.
Uremia.
Mixed nutritional deficiency.

ANEMIA, MEGALOBLASTIC[82]

ICD-10CM #	D51.0	Vitamin B_{12} deficiency anemia due to intrinsic factor deficiency
	D51.1	Vitamin B_{12} deficiency anemia due to selective vitamin B_{12} malabsorption with proteinuria
	D51.3	Other dietary vitamin B_{12} deficiency anemia
	D51.8	Other vitamin B_{12} deficiency anemias
	D52.0	Dietary folate deficiency anemia
	D52.1	Drug-induced folate deficiency anemia
	D52.8	Other folate deficiency anemias
	D52.9	Folate deficiency anemia, unspecified
	D53.1	Other megaloblastic anemias, not elsewhere classified
	D53.0	Protein deficiency anemia
	D53.2	Scorbutic anemia
	D53.8	Other specified nutritional anemias
	D53.9	Nutritional anemia, unspecified

COBALAMIN (CBL) DEFICIENCY

Nutritional CBL Deficiency (Insufficient CBL Intake)

Vegetarians, vegans, breastfed infants of mothers with pernicious anemia.

Abnormal Intragastric Events (Inadequate Proteolysis of Food CBL)

Atrophic gastritis, partial gastrectomy with hypochlorhydria.

Loss/Atrophy of Gastric Oxyntic Mucosa (Deficient Intrinsic Factor [If] Molecules)
Total or partial gastrectomy, pernicious anemia (PA), caustic destruction (lye).
Abnormal Events in Small Bowel Lumen
Inadequate pancreatic protease (R-CBL not degraded, CBL not transferred to IF).
  Insufficiency of pancreatic protease—pancreatic insufficiency.
  Inactivation of pancreatic protease—Zollinger-Ellison syndrome.
Usurping of luminal CBL (inadequate CBL binding to IF).
  By bacteria—stasis syndromes (blind loops, pouches of diverticulosis, strictures, fistulas, anastomoses); impaired bowel motility (scleroderma, pseudoobstruction), hypogammaglobulinemia.
  By *Diphyllobothrium latum*.
Disorders of Ileal Mucosa/IF Receptors (IF-CBL not Bound to IF Receptors)
Diminished or absent IF receptors—ileal bypass/resection/fistula.
Abnormal mucosal architecture/function—tropical/nontropical sprue, Crohn disease, TB ileitis, infiltration by lymphomas, amyloidosis.
IF-/post IF-receptor defects—Imerslund-Gräsbeck syndrome, TC II deficiency.
Drug-induced effects (slow K, biguanides, cholestyramine, colchicine, neomycin, PAS).

DISORDERS OF PLASMA CBL TRANSPORT (TC II-CBL NOT DELIVERED TO TC II RECEPTORS)

Congenital TC II deficiency, defective binding of TC II-CBL to TC II receptors (rare).

METABOLIC DISORDERS (CBL NOT UTILIZED BY CELL)

Inborn enzyme errors (rare).
Acquired disorders: (CBL oxidized to cob[III] alamin)—N_2O inhalation.

FOLATE DEFICIENCY

Nutritional Causes
Decreased dietary intake—poverty and famine (associated with kwashiorkor, marasmus), institutionalized individuals (psychiatric/nursing homes), chronic debilitating disease/goats' milk (low in folate), special diets (slimming), cultural/ethnic cooking techniques (food folate destroyed) or habits (folate-rich foods not consumed).
Decreased diet and increased requirements:
  Physiologic: pregnancy and lactation, prematurity, infancy.
  Pathologic: intrinsic hematologic disease (autoimmune hemolytic disease), drugs, malaria; hemoglobinopathies (SS, thalassemia), RBC membrane defects (hereditary spherocytosis, paroxysmal nocturnal hemoglobinopathy); abnormal hematopoiesis (leukemia/lymphoma, myelodysplastic syndrome, agnogenic myeloid metaplasia with myelofibrosis); infiltration with malignant disease; dermatologic (psoriasis).
Folate Malabsorption
With normal intestinal mucosa:
  Some drugs (controversial).
  Congenital folate malabsorption (rare).
  With mucosal abnormalities—tropical and nontropical sprue, regional enteritis.
Defective Cellular Folate Uptake—Familial Aplastic Anemia (Rare), Inadequate Cellular Utilization
Folate antagonists (methotrexate).
Hereditary enzyme deficiencies involving folate.
Drugs (Multiple Effects on Folate Metabolism)
Alcohol, sulfasalazine, triamterene, pyrimethamine, trimethoprim-sulfamethoxazole, diphenylhydantoin, barbiturates.

MISCELLANEOUS MEGALOBLASTIC ANEMIAS (NOT CAUSED BY CBL OR FOLATE DEFICIENCY)

Congenital Disorders of DNA Synthesis (Rare)
Orotic aciduria, Lesch-Nyhan syndrome, congenital dyserythropoietic anemia.
Acquired Disorders of DNA Synthesis
Thiamine-responsive megaloblastosis (rare).
Malignancy—erythroleukemia—refractory sideroblastic anemias—all antineoplastic drugs that inhibit DNA synthesis.
Toxins: alcohol.

ANEMIA, MICROCYTIC, HYPOCHROMIC, DIFFERENTIAL DIAGNOSIS[44]

ICD-10CM #	D50.8	Other iron deficiency anemias
	D50.9	Iron deficiency anemia, unspecified
	D64.0	Hereditary sideroblastic anemia
	D64.1	Secondary sideroblastic anemia due to disease
	D64.2	Secondary sideroblastic anemia due to drugs and toxins
	D64.3	Other sideroblastic anemias

DIFFERENTIAL DIAGNOSIS OF MICROCYTIC HYPOCHROMIC ANEMIA

Decreased Body Iron Stores
Iron deficiency anemia.
Normal or Increased Body Iron Stores
Anemia of chronic disease.
Defective absorption, transport, or use of iron.
Iron-refractory, iron deficiency anemia after parenteral iron.
Atransferrinemia.
Aceruloplasminemia.
Divalent metal transporter 1 (DMT1 or SLC11A2) deficiency.
Ferroportin-associated hemochromatosis with impaired iron export (type 4A).
Heme oxygenase 1 deficiency.
Disorders of globin synthesis.
Decreased Body Iron Stores
Thalassemia.
  Other microcytic hemoglobinopathies.
  Disorders of heme synthesis.
Sideroblastic anemias.
  Hereditary.
  Acquired.

ANERGY, CUTANEOUS[82]

ICD-10CM #	D89.9	Disorder involving the immune mechanism, unspecified

IMMUNOLOGIC

Acquired (AIDS, acute leukemia, carcinoma, CLL, Hodgkin lymphoma, NHL).
Congenital (ataxia-telangiectasia, Di George syndrome, severe combined immunodeficiency, Wiskott-Aldrich syndrome).

INFECTIONS

Bacterial (bacterial pneumonia, brucellosis).
Disseminated mycotic infections.
Mycobacterial (lepromatous leprosy, TB).
Viral (varicella, hepatitis, influenza, mononucleosis, measles, mumps).

IMMUNOSUPPRESSIVE MEDICATIONS

Systemic corticosteroids.
Methotrexate, cyclophosphamide.
Rifampin.

OTHER

Alcoholic cirrhosis, biliary cirrhosis, sarcoidosis, rheumatic disease.
Diabetes, Crohn disease, uremia.
Anemia, pyridoxine deficiency, sickle cell anemia.
Burns, malnutrition, pregnancy, old age, surgery.

ANEURYSMS, THORACIC AORTA

ICD-10CM #	I71.2	Thoracic aortic aneurysm, without rupture

Trauma.
Infection.
Inflammatory (syphilis, Takayasu disease).
Collagen vascular disease (RA, ankylosing spondylitis).
Annuloaortic ectasia (Marfan syndrome, Ehlers-Danlos syndrome).
Congenital.
Coarctation.
Cystic medial necrosis.

ANHIDROSIS

ICD-10CM #	L74.0	Miliaria rubra
	L74.1	Miliaria crystallina
	L74.2	Miliaria profunda

Drugs (anticholinergics).
Dehydration.
Hysteria.

Obstruction of sweat ducts (e.g., inflammation, miliaria).
Local radiant heat or pressure.
CNS lesions (medulla, hypothalamus, pons).
Spinal cord lesions.
Lesions of sympathetic nerves.
Congenital sweat gland disturbances.

ANION GAP ACIDOSIS[88]

ICD-10CM # E87.2 Acidosis

CLINICAL CAUSES OF HIGH ANION GAP AND NORMAL ANION GAP ACIDOSIS

High Anion Gap

Ketoacidosis:
- Diabetic ketoacidosis (acetoacetate).
- Alcoholic (β-hydroxybutyrate).
- Starvation.

Lactic acid acidosis:
- L-Lactic acid acidosis (types A and B).
- D-Lactic acid acidosis.
- Renal failure: sulfate, phosphate, urate, hippurate.

Ingestions (toxins and their metabolites):
- Ethylene glycol → glycolate, oxalate.
- Methyl alcohol → formate.
- Salicylate → ketones, lactate, salicylate.
- Paraldehyde → organic anions.
- Toluene → hippurate (commonly presents with normal anion gap).
- Propylene glycol → lactate.
- Pyroglutamic acidosis (acetaminophen use) → 5-oxoproline.

Normal Anion Gap

GI loss of HCO_3^- (negative urine anion gap):
- Diarrhea.
- Fistula, external.

Renal loss of HCO_3^- or failure to excrete NH_4^+ (positive urine anion gap):
- Proximal renal tubular acidosis (RTA type 2).
- Acetazolamide.
- Classic distal renal tubular acidosis (low serum K^+) RTA type 1.
- Generalized distal renal tubular defect (high serum K^+) RTA type 4.

Miscellaneous:
- NH_4Cl ingestion.
- Sulfur ingestion.
- Dilutional acidosis.
- Late stages in treatment of diabetic ketoacidosis.

ANION GAP INCREASE

ICD-10CM # E87.8 Other disorders of electrolyte and fluid balance, not elsewhere classified

Uremia.
Ketoacidosis (diabetic, starvation, alcoholic).
Lactic acidosis.
Ethylene glycol poisoning.
Salicylate overdose.
Methanol poisoning.

ANISOCORIA

ICD-10CM # H57.02 Anisocoria

Mydriatic or miotic drugs.
Prosthetic eye.
Inflammation (keratitis, iridocyclitis).
Infections (herpes zoster, syphilis, meningitis, encephalitis, TB, diphtheria, botulism).
Subdural hemorrhage.
Cavernous sinus thrombosis.
Intracranial neoplasm.
Cerebral aneurysm.
Glaucoma.
CNS degenerative diseases.
Internal carotid ischemia.
Toxic polyneuritis (alcohol, lead).
Adie syndrome.
Horner syndrome.
DM.
Trauma.
Congenital.

ANKLE AND FOOT PAIN[42]

ICD-10CM # M25.579 Pain in unspecified ankle and joint pain in unspecified foot

Anterior ankle	Anterior impingement. Ankle arthritis or synovitis. Osteochondral defect or lesion (cartilage injury). Loose body within the joint. Talar avascular necrosis. Talar stress fracture. Tenosynovitis of the extensor hallucis longus, extensor digitorum longus. Deep (central) or superficial (anterolateral) peroneal nerve injury. Saphenous (anteromedial) nerve injury.
Posterior ankle	Os trigonum (accessory ossicle involving the posterior lateral tubercle of the talus). Posterior impingement. Retrocalcaneal bursitis. Achilles tendinopathy. Flexor hallucis longus tendinopathy or stenosis.
Posterolateral ankle	Peroneal tendinopathy. Subfibular impingement caused by flatfoot and impingement. Fibular stress fracture. Sural nerve injury. Lateral ligament injury (sprain).
Posteromedial ankle	Posterior tibial tendinopathy. Flexor digitorum longus or flexor hallucis longus tendinopathy. Tibial stress fracture. Medial malleolar stress fracture. Tarsal tunnel syndrome. Tibial nerve injury. Deltoid ligament injury.
Heel	Achilles insertional tendinopathy. Inflammatory enthesitis. Plantar fasciitis. Haglund disease (pump bump). Calcaneal stress fracture.
Hindfoot	Subtalar, talonavicular, or calcaneocuboid arthritis or synovitis. Posterior tibial tendon dysfunction or tendinopathy (medial) or peroneal tendon dysfunction (lateral). Occult fracture of the talus, calcaneus cuboid, or navicular Accessory navicular.
Midfoot	Insertional tendinopathy (peroneal, posterior tibial, tibialis anterior). Arthritis or synovitis (navicular–cuneiform, cuneiform–metatarsal, cuboid–metatarsal). Navicular stress fracture. Spring ligament strain.
Forefoot	
First ray, first MTP joint, hallux	Arthritis or synovitis MTP (hallux limitus/rigidus) and IP joints. Hallux valgus. Hallux varus. Sesamoiditis. Gouty monoarthritis.
Second to fifth rays, MTP joints, lesser toes	Arthritis or synovitis (MTP, proximal and distal IP joints). Lesser toe deformities (hammer and claw toes). Metatarsalgia. MTP instability. MTP dislocations. Morton neuroma (interdigital neuralgia). Stress fracture of the metatarsals. Bunionette (fifth metatarsal phalangeal deviation). Rheumatoid nodules. Bursitis (intermetatarsal or adventitious). Ulcer. Infection.

IP, Interphalangeal; *MTP,* metatarsophalangeal.

ANORECTAL DISEASE, AIDS PATIENT[26]

ICD-10CM # Varies with specific diagnosis

DIFFERENTIAL DIAGNOSIS OF ANORECTAL DISEASE IN PATIENTS WITH AIDS

Infections

Bacteria

*Chlamydia trachomatis.**
Lymphogranuloma venereum.
*Neisseria gonorrhoeae.**
Shigella flexneri.
Mycobacterium tuberculosis.

Protozoa

Entamoeba histolytica.
Leishmania donovani.

Viruses

HSV.*

*More frequent diagnosis.

Cytomegalovirus.*
Fungi
Candida albicans.
Histoplasma capsulatum.
Neoplasms
Lymphoma.*
Kaposi sarcoma.
Squamous cell carcinoma.
Cloacogenic carcinoma.
Condyloma acuminatum.
Other
Idiopathic ulcers.*
Perirectal abscess, fistula.*

* More frequent diagnosis.

ANOREXIA[86]

ICD-10CM # R63.0 Anorexia

SELECTED CAUSES OF ANOREXIA

Gastrointestinal Tract/Liver
Gastric outlet obstruction or small bowel obstruction.
Gastric cancer.
Hepatic metastases.
Acute viral hepatitis.
Metabolic
Addison disease.
Hypopituitarism.
Hyperparathyroidism.
Functional
Extremely unpleasant sight/smell.
Systemic
Chronic pain.
Renal failure.
Severe congestive heart failure.
Respiratory failure.
Psychiatric
Depression.
Anorexia nervosa.
Medications
Digoxin.
Narcotic analgesics.
Diuretics.
Antihypertensives.
Chemotherapeutic agents.
Amphetamines.
Miscellaneous
Excessive smoking.
Excessive alcohol intake.
Oral cavity disease.
Thiamine deficiency.
Early pregnancy.
Hypogeusia or dysgeusia.

ANOVULATION

ICD-10CM #	N97.0	Female infertility associated with anovulation

Anorexia and bulimia.
Strenuous exercise.
Weight loss/malnutrition.
Empty sella syndrome.
Pituitary disorders (infarction, infection, trauma, irradiation, surgery, microadenomas, macroadenomas).
Idiopathic hypopituitarism.
Drug induced.
Thyroid dysfunction (hypothyroidism, hyperthyroidism).
Systemic diseases (e.g., liver disease).
Adrenal hyperfunction (Cushing syndrome, congenital adrenal hyperplasia).
Polycystic ovarian syndrome.
Isolated gonadotropin deficiency.

APPENDICITIS, DIFFERENTIAL DIAGNOSIS IN PREGNANCY[30]

ICD-10CM # Varies with specific diagnosis

DIFFERENTIAL DIAGNOSIS OF APPENDICITIS DURING PREGNANCY

Gynecologic Conditions
Ruptured ovarian cyst.
Adnexal torsion.
Pelvic inflammatory disease or salpingitis.
Endometriosis.
Ovarian cancer.
Obstetrical Causes
Abruptio placentae.
Chorioamnionitis.
Endometritis.
Uterine fibroid degeneration.
Labor (preterm or term).
Viscus perforation after abortion.
Ruptured ectopic pregnancy.
Gastrointestinal Causes
Crohn disease.
Colonic diverticulitis (right side).
Cholecystitis.
Pancreatitis.
Mesenteric lymphadenitis.
Gastroenteritis.
Colon cancer.
Intestinal obstruction.
Hernia (incarcerated inguinal or internal).
Colonic intussusception.
Ruptured Meckel diverticulum.
Colonic perforation.
Acute mesenteric ischemia.
Other Causes
Pyelonephritis.
Urolithiasis.

APPETITE LOSS IN INFANTS AND CHILDREN[43]

ICD-10CM #	R63.0	Anorexia
	F50.8	Other eating disorders
	F98.29	Other feeding disorders of infancy and early childhood

ORGANIC DISEASE

Infection (Acute or Chronic) Neurologic
Congenital degenerative disease.
Hypothalamic lesion.
Increased intracranial pressure (including a brain tumor).
Swallowing disorders (neuromuscular).
Gastrointestinal
Oral lesions (e.g., thrush or herpes simplex).
Gastroesophageal reflux.
Obstruction (especially with gastric or intestinal distention).
Inflammatory bowel disease.
Celiac disease.
Constipation.
Cardiac
Congestive heart failure (especially associated with cyanotic lesions).
Metabolic
Renal failure and/or renal tubule acidosis.
Liver failure.
Congenital metabolic disease.
Lead poisoning.
Nutritional
Marasmus.
Iron deficiency.
Zinc deficiency.
Fever
RA.
Rheumatic fever.
Drugs
Morphine.
Digitalis.
Antimetabolites.
Methylphenidate.
Amphetamines.
Miscellaneous
Prolonged restriction of oral feedings, beginning in the neonatal period.
Systemic lupus erythematosus (SLE).
Tumor.

PSYCHOLOGIC FACTORS

Anxiety, fear, depression, mania (limbic influence on the hypothalamus).
Avoidance of symptoms associated with meals (abdominal pain, diarrhea, bloating, urgency, dumping syndrome).
Anorexia nervosa.
Excessive weight loss and food aversion in athletes, simulating anorexia nervosa.

ARTERIAL OCCLUSION[33]

ICD-10CM #	I74.3	Embolism and thrombosis of arteries of the lower extremities
	I74.2	Embolism and thrombosis of arteries of the upper extremities

Thromboembolism (post-MI, mitral stenosis, rheumatic valve disease, atrial fibrillation, atrial myxoma, marantic endocarditis, bacterial endocarditis, Libman-Sacks endocarditis).
Atheroembolism (microemboli composed of cholesterol, calcium, and platelets from proximal atherosclerotic plaques).
Arterial thrombosis (endothelial injury, altered arterial blood flow, trauma, severe atherosclerosis, acute vasculitis).
Vasospasm.
Trauma.
Hypercoagulable states.
Miscellaneous (irradiation, drugs, infections, necrotizing).

ARTHRITIS AND ABDOMINAL PAIN

ICD-10CM #		
	M00.9	Pyogenic arthritis, unspecified
	R10.817	Generalized abdominal tenderness
	M02.9	Reactive arthropathy

Viral syndrome.
Inflammatory bowel disease.
Celiac disease.
Vasculitis.
SLE.
RA.
Scleroderma.
Amyloidosis.
Chronic hepatitis C.
Whipple disease.
Polyarteritis nodosa.
Behçet disease.
Familial Mediterranean fever.
Blind loop syndrome.
Babesiosis.
Lyme disease.
Ehrlichiosis.

ARTHRITIS AND DIARRHEA

ICD-10CM #		
	M00.9	Pyogenic arthritis, unspecified
	R19.7	Diarrhea, unspecified

Viral syndrome.
Inflammatory bowel disease.
Celiac disease.
Whipple disease.
Enterogenic (bacterial) reactive arthritis.
Collagenous colitis.
Behçet disease.
Hyperthyroidism.
Spondyloarthropathy.
Blind loop syndrome.

ARTHRITIS AND EYE LESIONS[16]

ICD-10CM #		
	M00.9	Pyogenic arthritis, unspecified
	M02.3	Reiter disease
	M02.9	Reactive arthropathy

SLE.
Sjögren syndrome.
Behçet syndrome.
Sarcoidosis.
Subacute bacterial endocarditis (SBE).
Lyme disease.
Granulomatosis with polyangiitis.
Giant cell arteritis.
Takayasu arteritis.
RA, JRA.
Scleroderma.
Inflammatory bowel disease.
Whipple disease.
Ankylosing spondylitis.
Reactive arthritis.
Psoriatic arthritis.

ARTHRITIS AND HEART MURMUR[16]

ICD-10CM #		
	M00.9	Pyogenic arthritis, unspecified
	I01.8	Other acute rheumatic heart disease
	M02.9	Reactive arthropathy

SBE.
Cardiac myxoma.
Ankylosing spondylitis.
Reactive arthritis.
Acute rheumatic fever.
RA.
SLE with Libman-Sacks endocarditis.
Relapsing polychondritis.

ARTHRITIS AND MUSCLE WEAKNESS[18]

ICD-10CM #		
	M00.9	Pyogenic arthritis, unspecified
	M62.9	Disorder of muscle, unspecified
	M02.9	Reactive arthropathy

RA.
Ankylosing spondylitis.
Polymyositis.
Dermatomyositis.
SLE, scleroderma, mixed connective tissue disease.
Sarcoidosis.
HIV-associated arthritis.
Whipple disease.

ARTHRITIS AND RASH[16]

ICD-10CM #		
	M00.9	Pyogenic arthritis, unspecified
	R21	Rash and other nonspecific skin eruption
	M02.9	Reactive arthropathy

Chronic urticaria.
Vasculitic urticaria.
SLE.
Dermatomyositis.
Polymyositis.
Psoriatic arthritis.
Reactive arthritis.
Chronic sarcoidosis.
Serum sickness.
Sweet syndrome.
Leprosy.

ARTHRITIS AND SUBCUTANEOUS NODULES[16]

ICD-10CM #		
	M00.9	Pyogenic arthritis, unspecified
	A18.4	Tuberculosis of skin and subcutaneous tissue
	M02.9	Reactive arthropathy

RA.
Gout.
Pseudogout (rare).
Sarcoidosis.
Light chain (LA) amyloidosis (primary, multiple myeloma).
Acute rheumatic fever (ARF).
Hemochromatosis.
Whipple disease.
Multicentric reticulohistiocytosis.

ARTHRITIS AND WEIGHT LOSS[16]

ICD-10CM #		
	M00.9	Pyogenic arthritis, unspecified
	R63.4	Abnormal weight loss
	M02.9	Reactive arthropathy

Severe RA.
RA with vasculitis.
Reactive arthritis.
RA or psoriatic arthritis or ankylosing spondylitis with amyloidosis.
Cancer.
Enteropathic arthritis (Crohn, ulcerative colitis).
HIV infection.
Whipple disease.
Blind loop syndrome.
Scleroderma with intestinal bacterial overgrowth.

ARTHRITIS OR EXTREMITY PAIN, IN CHILDREN AND ADOLESCENTS[53]

ICD-10CM #		
	M02.9	Reactive arthropathy

CAUSES OF ARTHRITIS OR EXTREMITY PAIN IN CHILDREN AND ADOLESCENTS

Rheumatic and Inflammatory Diseases
Juvenile idiopathic arthritis.
Systemic lupus erythematosus.
Juvenile dermatomyositis.
Polyarteritis.
Vasculitis.
Scleroderma.
Sjögren syndrome.
Behçet disease.
Overlap syndromes.
Granulomatosis with polyangiitis (Wegener granulomatosis).
Sarcoidosis.
Kawasaki syndrome.
Henoch-Schönlein purpura.
Chronic recurrent multifocal osteomyelitis.
Seronegative Spondyloarthropathies
Juvenile ankylosing spondylitis.
Inflammatory bowel disease.
Psoriatic arthritis.
Reactive arthritis associated with urethritis, iridocyclitis, and mucocutaneous lesions.
Infectious Illnesses
Bacterial arthritis (septic arthritis, *Staphylococcus aureus,* pneumococcus, gonococcus, *Haemophilus influenzae*).
Lyme disease.

Viral illness (parvovirus, rubella, mumps, Epstein-Barr virus, hepatitis B).
Fungal arthritis.
Mycobacterial infection.
Spirochetal infection.
Endocarditis.
Reactive Arthritis
Acute rheumatic fever.
Reactive arthritis (postinfectious due to *Shigella, Salmonella, Yersinia, Chlamydia,* or meningococcus).
Serum sickness.
Toxic synovitis of the hip.
Postimmunization.
Immunodeficiencies
Hypogammaglobulinemia.
Immunoglobulin A deficiency.
Human immunodeficiency virus.
Congenital and Metabolic Disorders
Gout.
Pseudogout.
Mucopolysaccharidoses.
Thyroid disease (hypothyroidism, hyperthyroidism).
Hyperparathyroidism.
Vitamin C deficiency (scurvy).
Hereditary connective tissue disease (Marfan syndrome, Ehlers-Danlos syndrome).
Fabry disease.
Farber disease.
Amyloidosis (familial Mediterranean fever).
Bone and Cartilage Disorders
Trauma.
Patellofemoral syndrome.
Hypermobility syndrome.
Osteochondritis dissecans.
Avascular necrosis (including Legg-Calvé-Perthes disease).
Hypertrophic osteoarthropathy.
Slipped capital femoral epiphysis.
Osteolysis.
Benign bone tumors (including osteoid osteoma).
Histiocytosis.
Rickets.
Neuropathic Disorders
Peripheral neuropathies.
Carpal tunnel syndrome.
Charcot joints.
Neoplastic Disorders
Leukemia.
Neuroblastoma.
Lymphoma.
Bone tumors (osteosarcoma, Ewing sarcoma).
Histiocytic syndromes.
Synovial tumors.
Hematologic Disorders
Hemophilia.
Hemoglobinopathies (including sickle cell disease).
Miscellaneous Disorders
Pigmented villonodular synovitis.
Plant-thorn synovitis (foreign body arthritis).
Myositis ossificans.
Eosinophilic fasciitis.
Tendinitis (overuse injury).
Raynaud phenomenon.
Pain Syndromes
Fibromyalgia.
Growing pains.
Depression (with somatization).
Reflex sympathetic dystrophy.
Regional myofascial pain syndromes.

ARTHRITIS, AXIAL SKELETON

ICD-10CM #		
	M45.9	Ankylosing spondylitis of unspecified sites in spine
	L40.54	Psoriatic juvenile arthropathy
	L40.59	Other psoriatic arthropathy
	M15.9	Polyosteoarthritis, unspecified
	M45.9	Ankylosing spondylitis of unspecified sites in spine

RA.
Psoriatic arthritis.
Reiter syndrome (reactive arthritis).
Ankylosing spondylitis.
Juvenile RA.
Degenerative disease of the nucleus pulposus.
Spondylosis deformans.
Diffuse idiopathic skeletal hyperostosis (DISH).
Alkaptonuria.
Infection.

ARTHRITIS, CHRONIC, MONOARTICULAR OR OLIGOARTICULAR, INFECTIOUS CAUSES[10]

ICD-10CM #	Varies with specific diagnosis

INFECTIOUS CAUSES OF CHRONIC MONOARTICULAR OR OLIGOARTICULAR ARTHRITIS

Bacterial
Borrelia burgdorferi.
Tropheryma whipplei.
Treponema pallidum.
Nocardia spp.
Fungi
Candida spp.
Cryptococcus neoformans.
Blastomyces dermatitidis.
Coccidioides spp.
Paracoccidioides brasiliensis.
Sporothrix schenckii.
Aspergillus spp. and other molds, including *Rhizopus, Scedosporium*, and *Fusarium.*
Mycobacteria
Mycobacterium tuberculosis.
M. kansasii.
M. marinum.
M. avium-intracellulare complex.
M. terrae.
M. fortuitum, M. chelonae, M. abscessus.
M. haemophilum.
M. leprae.
Parasites
Helminths.
Filariae.

ARTHRITIS, FEVER, AND RASH[16]

ICD-10CM #		
	M00.9	Pyogenic arthritis, unspecified
	M02.9	Reactive arthropathy
	R21	Rash and other nonspecific skin eruption
	R50.9	Fever, unspecified

Rubella, parvovirus B19.
Gonococcemia, meningococcemia.
Secondary syphilis, Lyme borreliosis.
Adult acute rheumatic fever, adult Still disease, adult Kawasaki disease.
Vasculitic urticaria.
Acute sarcoidosis.
Familial Mediterranean fever.
Hyperimmunoglobulinemia D and periodic fever syndrome.

ARTHRITIS, MONOARTICULAR AND OLIGOARTICULAR[7]

ICD-10CM #		
	M19.90	Unspecified osteoarthritis, unspecified site
	M01.X0	Direct infection of unspecified joint in infectious and parasitic diseases classified elsewhere
	M13.10	Monoarthritis, not elsewhere classified, unspecified site

Septic arthritis (*S. aureus, Neisseria gonorrhoeae,* meningococci, streptococci, *Streptococcus pneumoniae,* enteric gram-negative bacilli).
Crystalline-induced arthritis (gout, pseudogout, calcium oxalate, hydroxyapatite and other basic calcium/phosphate crystals).
Traumatic joint injury.
Hemarthrosis.
Monoarticular or oligoarticular flare of an inflammatory polyarticular rheumatic disease (RA, psoriatic arthritis, Reiter syndrome [reactive arthritis], SLE).

ARTHRITIS, PEDIATRIC AGE[43]

ICD-10CM #		
	M01.X0	Direct infection of unspecified joint in infectious and parasitic diseases classified elsewhere
	M08.00	Unspecified juvenile rheumatoid arthritis of unspecified site

	M08.3	Juvenile rheumatoid polyarthritis (seronegative)
	M08.40	Pauciarticular juvenile rheumatoid arthritis, unspecified site

RHEUMATIC DISEASES OF CHILDHOOD

Acute rheumatic fever.
SLE.
Juvenile ankylosing spondylitis.
Polymyositis and dermatomyositis.
Vasculitis.
Scleroderma.
Psoriatic arthritis.
Mixed connective tissue disease and overlap syndromes.
Kawasaki disease.
Behçet syndrome.
Familial Mediterranean fever.
Reiter syndrome (reactive arthritis).
Reflex sympathetic dystrophy.
Fibromyalgia (fibrositis).

INFECTIOUS DISEASES

Bacterial arthritis.
Viral or postviral arthritis.
Fungal arthritis.
Osteomyelitis.
Reactive arthritis.

NEOPLASTIC DISEASES

Leukemia.
Lymphoma.
Neuroblastoma.
Primary bone tumors.

NONINFLAMMATORY DISORDERS

Trauma.
Avascular necrosis syndromes.
Osteochondroses.
Slipped capital femoral epiphysis.
Diskitis.
Patellofemoral dysfunction (chondromalacia patellae).
Toxic synovitis of the hip.
Overuse syndromes.

GENETIC OR CONGENITAL SYNDROMES

Hematologic Disorders

Sickle cell disease.
Hemophilia.

INFLAMMATORY BOWEL DISEASE

Miscellaneous

Growing pains.
Psychogenic arthralgias (conversion reactions).
Hypermobility syndrome.
Villonodular synovitis.
Foreign body arthritis.

ARTHRITIS, POLYARTICULAR

ICD-10CM #	M15.0	Primary generalized (osteo)arthritis
	M12.89	Other specific arthropathies, not elsewhere classified, multiple sites
	M08.3	Juvenile rheumatoid polyarthritis (seronegative)

RA, juvenile (rheumatoid) polyarthritis.
SLE, other connective tissue diseases, erythema nodosum, palindromic rheumatism, relapsing polychondritis.
Psoriatic arthritis, ankylosing spondylitis.
Sarcoidosis.
Lyme arthritis, bacterial endocarditis, *Neisseria gonorrhoeae* infection, rheumatic fever, Reiter disease (reactive arthritis).
Crystal deposition disease.
Hypersensitivity to serum or drugs.
Hepatitis B, HIV, rubella, mumps.
Other: serum sickness, leukemias, lymphomas, enteropathic arthropathy, Whipple disease, Behçet syndrome, Henoch-Schönlein purpura, familial Mediterranean fever, hypertrophic pulmonary osteoarthropathy.

ASCITES

ICD-10CM #	R18.0	Malignant ascites
	C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
	I89.8	Other specified noninfective disorders of lymphatic vessels and lymph nodes

Hypoalbuminemia: nephrotic syndrome, protein-losing gastroenteropathy, starvation.
Cirrhosis.
Hepatic congestion: CHF, constrictive pericarditis, tricuspid insufficiency, hepatic vein obstruction (Budd-Chiari syndrome), inferior vena cava or portal vein obstruction.
Peritoneal infections: TB and other bacterial infections, fungal diseases, parasites.
Neoplasms: primary hepatic neoplasms, metastases to liver or peritoneum, lymphomas, leukemias, myeloid metaplasia.
Lymphatic obstruction: mediastinal tumors, trauma to the thoracic duct, filariasis.
Ovarian disease: Meigs syndrome, struma ovarii.
Chronic pancreatitis or pseudocyst: pancreatic ascites.
Leakage of bile: bile ascites.
Urinary obstruction or trauma: urine ascites.
Myxedema.
Chylous ascites.

ASPIRATION LUNG INJURY, CHILDREN[53]

ICD-10CM #	P24.8	Neonatal aspiration syndromes

CONDITIONS PREDISPOSING TO ASPIRATION LUNG INJURY IN CHILDREN

Anatomic and Mechanical

Tracheoesophageal fistula.
Laryngeal cleft.
Vascular ring.
Cleft palate.
Micrognathia.
Macroglossia.
Achalasia.
Esophageal foreign body.
Tracheostomy.
Endotracheal tube.
Nasoenteric tube.
Collagen vascular disease (scleroderma, dermatomyositis).
Gastroesophageal reflux disease.
Obesity.

Neuromuscular

Altered consciousness.
Immaturity of swallowing/prematurity.
Dysautonomia.
Increased intracranial pressure.
Hydrocephalus.
Vocal cord paralysis.
Cerebral palsy.
Muscular dystrophy.
Myasthenia gravis.
Guillain-Barré syndrome.
Werdnig-Hoffmann disease.
Ataxia-telangiectasia.
Cerebral vascular accident.

Miscellaneous

Poor oral hygiene.
Gingivitis.
Prolonged hospitalization.
Gastric outlet or intestinal obstruction.
Poor feeding techniques (bottle propping, overfeeding, inappropriate foods for toddlers).
Bronchopulmonary dysplasia.
Viral infection.

ASTHENIA

ICD-10CM #	G93.3	Postviral fatigue syndrome
	R53.1	Weakness
	R53.81	Other malaise
	R53.83	Other fatigue

Depression.
Chronic fatigue syndrome.
Sleep disorders.
Anemia.
Hypothyroidism.
Sedentary lifestyle.
Medications (e.g., narcotics, sedatives).
Infections.
Dehydration/electrolyte disorders.
COPD and other pulmonary disorders.
Renal failure.

CHF.
Diabetes.
Addison disease.
Paraneoplastic syndrome.

ASTHMA, CHILDHOOD[9]

ICD-10CM #		
	J45.20	Mild intermittent asthma, uncomplicated
	J45.22	Mild intermittent asthma with status asthmaticus

INFECTIONS

Bronchiolitis (RSV).
Pneumonia.
Croup.
Tuberculosis, histoplasmosis.
Bronchiectasis.
Bronchiolitis obliterans.
Bronchitis.
Sinusitis.

ANATOMIC, CONGENITAL

Cystic fibrosis.
Vascular rings.
Ciliary dyskinesia.
B-lymphocyte immune defect.
Congestive heart failure.
Laryngotracheomalacia.
Tumor, lymphoma.
H-type tracheoesophageal fistula.
Repaired tracheoesophageal fistula.
Gastroesophageal reflux.

VASCULITIS, HYPERSENSITIVITY

Allergic bronchopulmonary aspergillosis.
Allergic alveolitis, hypersensitivity pneumonitis.
Churg-Strauss syndrome.
Periarteritis nodosa.

OTHER

Foreign body aspiration.
Pulmonary thromboembolism.
Psychogenic cough.
Sarcoidosis.
Bronchopulmonary dysplasia.
Vocal cord dysfunction.

ATAXIA

ICD-10CM #		
	R27.0	Ataxia, unspecified
	R27.8	Other lack of coordination
	R27.9	Unspecified lack of coordination
	F10.229	Alcohol dependence with intoxication, unspecified
	F10.20	Alcohol dependence, uncomplicated
	G11.1	Early-onset cerebellar ataxia
	G31.89	Other specified degenerative diseases of nervous system
	F44.4	Conversion disorder with motor symptom or deficit
	F44.6	Conversion disorder with sensory symptom or deficit

Vertebral-basilar artery ischemia.
Diabetic neuropathy.
Tabes dorsalis.
Vitamin B_{12} deficiency.
Multiple sclerosis and other demyelinating diseases.
Meningomyelopathy.
Cerebellar neoplasms, hemorrhage, abscess, infarct.
Nutritional (Wernicke encephalopathy).
Paraneoplastic syndromes.
Parainfectious: Guillain-Barré syndrome, acute ataxia of childhood and young adults.
Toxins: phenytoin, alcohol, sedatives, organophosphates.
Wilson disease (hepatolenticular degeneration).
Hypothyroidism.
Myopathy.
Cerebellar and spinocerebellar degeneration: ataxia/telangiectasia, Friedreich ataxia.
Frontal lobe lesions: tumors, thrombosis of anterior cerebral artery, hydrocephalus.
Labyrinthine destruction: neoplasm, injury, inflammation, compression.
Hysteria.
AIDS.

ATAXIA, ACUTE OR RECURRENT[23]

ICD-10CM #		
	R27.0	Ataxia, unspecified
	R27.8	Other lack of coordination
	R27.9	Unspecified lack of coordination
	F10.229	Alcohol dependence with Intoxication, unspecified
	F10.20	Alcohol dependence, uncomplicated
	G11.1	Early-onset cerebellar ataxia
	G31.89	Other specified degenerative diseases of nervous system
	F44.4	Conversion disorder with motor symptom or deficit
	F44.6	Conversion disorder with sensory symptom or deficit

Drug ingestion (e.g., phenytoin, carbamazepine, sedatives, hypnotics, and phencyclidine) or intoxication (e.g., alcohol, ethylene glycol, hydrocarbon fumes, lead, mercury, or thallium).
Postinfectious (cerebellitis [e.g., varicella], acute disseminated encephalomyelitis).
Head trauma.
Basilar migraine.
Benign paroxysmal vertigo (migraine equivalent).
Brain tumor or neuroblastoma (if accompanied by opsoclonus or myoclonus [i.e., "dancing eyes, dancing feet"]).
Hydrocephalus.
Infection (e.g., labyrinthitis, abscess).
Seizure (ictal or postictal).
Vascular events (e.g., cerebellar hemorrhage or stroke).
Miller-Fisher variant of Guillain-Barré syndrome (ataxia, ophthalmoplegia, and areflexia). Warning: If bulbar signs present, disease is likely progressive; patient may lose ability to protect airway and/or ability to breathe.
Inherited ataxias.
Inborn errors of metabolism (e.g., mitochondrial disorders, amino-acidopathies, urea cycle defects).
Conversion reaction.
Multiple sclerosis.

ATAXIA, CEREBELLAR, ADULT ONSET[80]

ICD-10CM #		
	G11.0	Congenital nonprogressive ataxia
	G11.2	Late-onset cerebellar ataxia

CAUSES OF ADULT ONSET CEREBELLAR ATAXIA

Inherited
Later onset SCA syndromes.
Rarely Friedreich ataxia.
Congenital
Arnold–Chiari malformation (cerebellar ectopia).
Inflammatory
Multiple sclerosis.
Sarcoidosis.
Infections (TB, viral).
Neoplastic
Often metastatic in adults.
Meningioma, neurofibroma.
Hemangioblastoma.
Paraneoplastic
Usually with small cell bronchial carcinoma.
Vascular
Infarction, hemorrhage.
Arteriovenous malformations.
Trauma
Head injury.
Postsurgical.
Toxic
Alcohol, phenytoin, solvent abuse.
Endocrine
Hypothyroidism (very rare).
Degenerative
Multiple system atrophy (MSA).

ATAXIA, CEREBELLAR, CHILDREN[80]

ICD-10CM #		
	G11.0	Congenital nonprogressive ataxia
	G11.2	Late-onset cerebellar ataxia

CAUSES OF CEREBELLAR ATAXIA IN CHILDREN

Congenital Malformations
Cerebellar agenesis/hypoplasia.
Dandy–Walker syndrome.
Arnold–Chiari malformation.
Hereditary Ataxias
Friedreich ataxia.
Trauma
Birth trauma.
Head injury in childhood.
Infectious
Secondary to bacterial meningitis.
Secondary to encephalitis.
Hydrocephalus
Tumors
Medulloblastoma.
Astrocytoma.
Hemangioblastoma.

ATAXIA, CHRONIC OR PROGRESSIVE[23]

ICD-10CM #	R27.0	Ataxia, unspecified
	R27.8	Other lack of coordination
	R27.9	Unspecified lack of coordination
	G11.1	Early-onset cerebellar ataxia
	G11.0	Congenital nonprogressive ataxia
	G11.2	Late-onset cerebellar ataxia
	G11.3	Cerebellar ataxia with defective DNA repair
	G11.8	Other hereditary ataxia

Hydrocephalus.
Hypothyroidism.
Tumor or paraneoplastic syndrome.
Low vitamin E levels (e.g., cystic fibrosis).
Wilson disease.
Inborn errors of metabolism.
Inherited ataxias (e.g., ataxia-telangiectasia, Friedreich ataxia).

ATAXIA IN CHILDHOOD[89]

ICD-10CM #	G11.1	Early-onset cerebellar ataxia

SELECTED CAUSES OF ATAXIA IN CHILDHOOD

Congenital:
- Agenesis of vermis of the cerebellum.
- Aplasia or dysplasia of the cerebellum.
- Basilar impression.
- Cerebellar dysplasia with microgyria, macrogyria, or agyria.
- Cervical spinal bifida with herniation of the cerebellum (Chiari malformation, type 3).
- Chiari malformation.
- Dandy-Walker syndrome.
- Encephalocele.
- Hydrocephalus (progressive).
- Hypoplasia of the cerebellum.

Degenerative and/or genetic:
- Acute intermittent cerebellar ataxia.
- Ataxia, retinitis pigmentosa, deafness, vestibular abnormality, and intellectual deterioration.
- Ataxia-telangiectasia.
- Biemond posterior column ataxia.
- Cerebellar ataxia with deafness, anosmia, absent caloric responses, nonreactive pupils, and hyporeflexia.
- Cockayne syndrome.
- Dentate cerebellar ataxia (dyssynergia cerebellaris progressiva).
- Familial ataxia with macular degeneration.
- Friedreich ataxia.
- Hereditary cerebellar ataxia, intellectual retardation, choreoathetosis, and eunuchoidism.
- Hereditary cerebellar ataxia with myotonia and cataracts.
- Hypertrophic interstitial neuritis.
- Marie ataxia.
- Marinesco-Sjögren syndrome.
- Pelizaeus-Merzbacher disease.
- Periodic attacks of vertigo, diplopia, and ataxia—autosomal dominant inheritance.
- Posterior and lateral column difficulties, nystagmus, and muscle atrophy.
- Progressive cerebellar ataxia and epilepsy.
- Ramsay Hunt syndrome (myoclonic seizures and ataxia).
- Roussy-Lévy syndrome.
- Spinocerebellar ataxia (SCAs); olivopontocerebellar ataxias.

Endocrinologic:
- Cretinism.
- Hypothyroidism.

Infectious or postinfectious:
- Acute cerebellar ataxia.
- Acute disseminated encephalomyelitis.
- Cerebellar abscess.
- Coxsackievirus.
- Diphtheria.
- Echovirus.
- Fisher syndrome.
- Infectious mononucleosis (Epstein-Barr virus infection).
- Infectious polyneuropathy.
- Japanese B encephalitis.
- Mumps encephalitis.
- *Mycoplasma pneumoniae.*
- Pertussis.
- Polio.
- Postbacterial meningitis.
- Rubeola.
- Tuberculosis.
- Typhoid.
- Varicella.

Metabolic:
- Abetalipoproteinemia.
- Argininosuccinic aciduria.
- Ataxia with vitamin E deficiency (AVED).
- GM2 gangliosidosis (late).
- Hartnup disease.
- Hyperalaninemia.
- Hyperammonemia I and II.
- Hypoglycemia.
- Kearns-Sayre syndrome.
- Leigh disease.
- Maple syrup urine disease (intermittent).
- MERRF (Myoclonic epilepsy with ragged red fibers).
- Metachromatic leukodystrophy.
- Mitochondrial complex defects (I, III, IV).
- Multiple carboxylase deficiency (biotinidase deficiency).
- Neuronal ceroid-lipofuscinosis.
- Neuropathy, ataxia, retinitis pigmentosa (NARP).
- Niemann-Pick disease (late infantile).
- 5-Oxoprolinuria.
- Pyruvate decarboxylase deficiency.
- Refsum disease.
- Sialidosis.
- Triose-phosphate isomerase deficiency.
- Tryptophanuria.
- Wernicke encephalopathy (thiamine or B_1 deficiency).

Neoplastic:
- Frontal lobe tumors.
- Hemispheric cerebellar tumors.
- Midline cerebellar tumors.
- Neuroblastoma.
- Pontine tumors (primarily gliomas).
- Spinal cord tumors.

Primary psychogenic:
- Conversion reaction.

Toxic:
- Alcohol.
- Benzodiazepines.
- Carbamazepine.
- Clonazepam.
- Lead encephalopathy.
- Phenobarbital.
- Phenytoin.
- Primidone.
- Tick paralysis poisoning.

Traumatic:
- Acute cerebellar edema.
- Acute frontal lobe edema.

Vascular:
- Angioblastoma of cerebellum.
- Basilar migraine.
- Cerebellar embolism.
- Cerebellar hemorrhage.
- Cerebellar thrombosis.
- Posterior cerebellar artery disease.
- Vasculitis.
- von Hippel-Lindau disease.

ATAXIA, TOXIC CAUSES[84]

ICD-10CM #	R27.0	Early-onset cerebellar ataxia

SELECTED TOXIC CAUSES OF ATAXIA

Medications:
- Acetohexamide.
- Amiodarone.
- Anticholinergic agents.
- Antidepressants, including selective serotonin reuptake inhibitors.
- Antiepileptic drugs.
- Antihistamines.
- Antimicrobials, antifungals.
- Antineoplastics.

Antiparasitics.
Baclofen.
Buspirone.
Dextromethorphan.
Disulfiram.
Ethanol.
Fenfluramine.
Lithium.
Lysergic acid diethylamide (LSD), phencyclidine palmitate (PCP).
Mexiletine.
Sedatives, narcotics.
Industrial toxins:
Aluminum compounds.
Butyl alcohol.
Carbon monoxide.
Carbon tetrachloride.
Ethylene glycol.
Formaldehyde.
Gasoline.
Manganese.
Metaldehyde (snail bait, fire starters).
Paradichlorobenzene (moth repellent, diaper pail deodorant).
Rodenticides: aluminum phosphide, sodium monofluoroacetate.
Solvents.
Biologic toxins:
Belladonna, hyoscyamine.
Buckeye (*Aesculus* spp.).
Mayapple (*Podophyllum peltatum*).
Mescaline, peyote.
Podophyllum (ingested).
Poison hemlock (*Conium maculatum*).

ATELECTASIS

ICD-10CM #		
	J98.11	Atelectasis

Lung neoplasm (primary or metastatic).
Infection (pneumonia, TB, fungal, histoplasmosis).
Postoperative (lower lobes).
Sarcoidosis.
Mucoid impaction.
Foreign body.
Postinflammatory (middle lobe syndrome).
Pneumothorax.
Pleural effusion.
Pneumoconiosis.
Interstitial fibrosis.
Bulla.
Mediastinal or adjacent mass.

ATRIAL ENLARGEMENT, LEFT ATRIUM[36]

ICD-10CM #		
	I51.7	Cardiomegaly

CAUSES OF LARGE LEFT ATRIUM

Causes Due to Volume Overload
Mitral regurgitation (often with left ventricular failure).
Ventricular septal defect.
Patent ductus arteriosus.
Atrial septal defect with shunt reversal (i.e., pulmonary hypertension).
ASD with tricuspid atresia (obligatory shunt reversal).
Aortopulmonary window.
Causes Due to Pressure Overload
Mitral stenosis.
Noncompliant left ventricle: hypertension, hypertrophic cardiomyopathy, aortic stenosis.
Left ventricular failure (often with secondary mitral regurgitation).
Left atrial myxoma.
Other Causes (Both Rare)
Atrial fibrillation.
Isolated/idiopathic.

ATRIAL ENLARGEMENT, RIGHT ATRIUM

ICD-10CM #		
	I51.7	Cardiomegaly

Right ventricular failure.
Atrial septal defect.
Tricuspid regurgitation.
Tricuspid stenosis.
Pulmonary hypertension.
Restrictive cardiomyopathy.
Right atrial myxoma.
Ebstein anomaly.
Anomalous pulmonary venous drainage to the right atrium.
Endomyocardial fibrosis.
Sinus of Valsalva fistula.
Arrhythmogenic right ventricular dysplasia.

ATYPICAL LYMPHOCYTOSIS, HETEROPHIL NEGATIVE, INFECTIOUS CAUSES[3]

ICD-10CM #		
	D72.820	Lymphocytosis (symptomatic)

MOST COMMON INFECTIOUS CAUSES OF HETEROPHIL-NEGATIVE ATYPICAL LYMPHOCYTOSIS

Babesiosis.
Cytomegalovirus.
Epstein-Barr virus (particularly in children).
Human herpesvirus 6.
Human immunodeficiency virus (especially during acute seroconversion).
Infectious mononucleosis.
Malaria.
Measles.
Toxoplasmosis.
Varicella.
Infectious hepatitis.

AV NODAL BLOCK[33]

ICD-10CM #		
	I44.30	Unspecified atrioventricular block
	I44.2	Atrioventricular block, complete

Idiopathic fibrosis (Lenègre disease).
Sclerodegenerative processes (e.g., Lev disease with calcification of the mitral and aortic annuli).
AV node radiofrequency ablation procedure.
Medications (e.g., digoxin, beta-blockers, calcium channel blockers, class III antiarrhythmics).
Acute inferior wall MI.
Myocarditis.
Infections (endocarditis, Lyme disease).
Infiltrative diseases (e.g., hemochromatosis, sarcoidosis, amyloidosis).
Trauma (including cardiac surgical procedures).
Collagen vascular diseases.
Aortic root diseases (e.g., spondylitis).
Electrolyte abnormalities (e.g., hyperkalemia).

BACK PAIN

ICD-10CM #		
	M54.89	Other dorsalgia
	M54.9	Dorsalgia, unspecified
	M54.5	Low back pain
	F45.42	Pain disorder with related psychological factors
	M54.08	Panniculitis affecting regions of neck and back, sacral and sacrococcygeal region
	S23.9XXA	Sprain of unspecified parts of thorax, initial encounter
	M43.27	Fusion of spine, lumbosacral region
	M43.28	Fusion of spine, sacral and sacrococcygeal region
	M53.2X7	Spinal instabilities, lumbosacral region
	M53.3	Sacrococcygeal disorders, not elsewhere classified

Trauma: injury to bone, joint, or ligament.
Mechanical: pregnancy, obesity, fatigue, scoliosis.
Degenerative: osteoarthritis.
Infections: osteomyelitis, subarachnoid or spinal abscess, TB, meningitis, basilar pneumonia.
Metabolic: osteoporosis, osteomalacia.
Vascular: leaking aortic aneurysm, subarachnoid or spinal hemorrhage/infarction.
Neoplastic: myeloma, Hodgkin disease, carcinoma of pancreas, metastatic neoplasm from breast, prostate, lung.
GI: penetrating ulcer, pancreatitis, cholelithiasis, inflammatory bowel disease.
Renal: hydronephrosis, calculus, neoplasm, renal infarction, pyelonephritis.
Hematologic: sickle cell crisis, acute hemolysis.
Gynecologic: neoplasm of uterus or ovary, dysmenorrhea, salpingitis, uterine prolapse.
Inflammatory: ankylosing spondylitis, psoriatic arthritis, Reiter syndrome (reactive arthritis).
Lumbosacral strain.

Antiparasitics.
Baclofen.
Buspirone.
Dextromethorphan.
Disulfiram.
Ethanol.
Fenfluramine.
Lithium.
Lysergic acid diethylamide (LSD), phencyclidine palmitate (PCP).
Mexiletine.
Sedatives, narcotics.
Industrial toxins:
Aluminum compounds.
Butyl alcohol.
Carbon monoxide.
Carbon tetrachloride.
Ethylene glycol.
Formaldehyde.
Gasoline.
Manganese.
Metaldehyde (snail bait, fire starters).
Paradichlorobenzene (moth repellent, diaper pail deodorant).
Rodenticides: aluminum phosphide, sodium monofluoroacetate.
Solvents.
Biologic toxins:
Belladonna, hyoscyamine.
Buckeye (*Aesculus* spp.).
Mayapple (*Podophyllum peltatum*).
Mescaline, peyote.
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Mucoid impaction.
Foreign body.
Postinflammatory (middle lobe syndrome).
Pneumothorax.
Pleural effusion.
Pneumoconiosis.
Interstitial fibrosis.
Bulla.
Mediastinal or adjacent mass.

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ICD-10CM #		
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Causes Due to Volume Overload
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Ventricular septal defect.
Patent ductus arteriosus.
Atrial septal defect with shunt reversal (i.e., pulmonary hypertension).
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Mitral stenosis.
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Other Causes (Both Rare)
Atrial fibrillation.
Isolated/idiopathic.

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ICD-10CM #		
	I51.7	Cardiomegaly

Right ventricular failure.
Atrial septal defect.
Tricuspid regurgitation.
Tricuspid stenosis.
Pulmonary hypertension.
Restrictive cardiomyopathy.
Right atrial myxoma.
Ebstein anomaly.
Anomalous pulmonary venous drainage to the right atrium.
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Toxoplasmosis.
Varicella.
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Sclerodegenerative processes (e.g., Lev disease with calcification of the mitral and aortic annuli).
AV node radiofrequency ablation procedure.
Medications (e.g., digoxin, beta-blockers, calcium channel blockers, class III antiarrhythmics).
Acute inferior wall MI.
Myocarditis.
Infections (endocarditis, Lyme disease).
Infiltrative diseases (e.g., hemochromatosis, sarcoidosis, amyloidosis).
Trauma (including cardiac surgical procedures).
Collagen vascular diseases.
Aortic root diseases (e.g., spondylitis).
Electrolyte abnormalities (e.g., hyperkalemia).

BACK PAIN

ICD-10CM #		
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	M54.9	Dorsalgia, unspecified
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GI: penetrating ulcer, pancreatitis, cholelithiasis, inflammatory bowel disease.
Renal: hydronephrosis, calculus, neoplasm, renal infarction, pyelonephritis.
Hematologic: sickle cell crisis, acute hemolysis.
Gynecologic: neoplasm of uterus or ovary, dysmenorrhea, salpingitis, uterine prolapse.
Inflammatory: ankylosing spondylitis, psoriatic arthritis, Reiter syndrome (reactive arthritis).
Lumbosacral strain.

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Psychogenic: malingering, hysteria, anxiety.
Endocrine: adrenal hemorrhage or infarction.

BACK PAIN, CHILDREN AND ADOLESCENTS[53]

ICD-10CM #		
	M54.5	Low back pain
	M54.9	Dorsalgia

INFLAMMATORY OR INFECTIOUS

Diskitis.
Vertebral osteomyelitis (pyogenic, tuberculous).
Spinal epidural abscess.
Pyelonephritis.
Pancreatitis.

RHEUMATOLOGIC

Pauciarticular juvenile rheumatoid arthritis.
Reiter syndrome (reactive arthritis).
Ankylosing spondylitis.
Psoriatic arthritis.

DEVELOPMENTAL

Spondylolysis.
Spondylolisthesis.
Scheuermann disease.
Scoliosis.

TRAUMATIC (ACUTE VERSUS REPETITIVE)

Hip-pelvis anomalies.
Herniated disk.
Overuse syndromes.
Vertebral stress fractures.
Upper cervical spine instability.

NEOPLASTIC

Vertebral Tumors
Benign
Eosinophilic granuloma.
Aneurysmal bone cyst.
Osteoid osteoma.
Osteoblastoma.
Malignant
Osteogenic sarcoma.
Leukemia.
Lymphoma.
Metastatic tumors.
Spinal Cord, Ganglia, and Nerve Roots
Intramedullary spinal cord tumor.
Sympathetic chain.
Ganglioneuroma.
Ganglioneuroblastoma.
Neuroblastoma.

OTHER

Intraabdominal or pelvic pathology.
Following lumbar puncture.
Conversion reaction.
Juvenile osteoporosis.

BACK PAIN, LOW, ACUTE[7]

ICD-10CM #		
	M54.5	Low back pain

DIFFERENTIAL CONSIDERATIONS IN ACUTE LOW BACK PAIN

Emergent
Aortic dissection.
Cauda equina syndrome.
Epidural abscess or hematoma.
Meningitis.
Ruptured/expanding aortic aneurysm.
Spinal fracture or subluxation with cord or root impingement.
Urgent
Back pain with neurologic deficits.
Disk herniation causing neurologic compromise.
Malignancy.
Sciatica with motor nerve root compression.
Spinal fractures without cord impingement.
Spinal stenosis.
Transverse myelitis.
Vertebral osteomyelitis.
Common or Stable
Acute ligamentous injury.
Acute muscle strain.
Ankylosing spondylitis.
Degenerative joint disease.
Intervertebral disk disease without impingement.
Pathologic fracture without impingement.
Seropositive arthritis.
Spondylolisthesis.
Referred or Visceral
Cholecystitis.
Esophageal disease.
Nephrolithiasis.
Ovarian torsion, mass, or tumor.
Pancreatitis.
Peptic ulcer disease.
Pleural effusion.
Pneumonia.
Pulmonary embolism.
Pyelonephritis.
Retroperitoneal hemorrhage or mass.

BACK PAIN, VISCEROGENIC ORIGIN

ICD-10CM #		
	F45.41	Pain disorder exclusively related to psychological factors
	M54	Dorsalgia
	M54.5	Low back pain

Urolithiasis.
Aortic aneurysm.
Colorectal carcinoma.
Endometriosis.
Tubal pregnancy.
Prostatitis.
Peptic ulcer.
Pancreatitis.
Diverticular spasm.
Metastatic neoplasm (e.g., bladder, uterus, ovary, kidney).

BACTERIAL OVERGROWTH, SMALL INTESTINE[86]

ICD-10CM #		
	A04.9	Bacterial Intestinal Infection, Unspecified

Gastric surgery—Billroth II.
Small bowel diverticula.
Small bowel stricture:
Crohn disease.
Radiation enteritis.
Impaired small intestinal motility:
Scleroderma.
Diabetes mellitus.
Chronic intestinal pseudoobstruction.
Miscellaneous/multifactorial:
Elderly.
Immune deficiency syndromes.
Chronic pancreatitis.
Cirrhosis.

BALLISM[7]

ICD-10CM #		
	G25.4	Drug-induced chorea
	G25.5	Other chorea

Cerebral infarction or hemorrhage.
Medications (e.g., dopamine agonists, phenytoin).
CNS neoplasm (primary or metastatic).
Nonketotic hyperosmolar state.

BILE DUCT, DILATED[86]

ICD-10CM #		
	K83.1	Obstruction of bile duct

Normal variant.
Post-cholecystectomy.
Unsuspected bile duct stone.
Sphincter of Oddi stenosis.
Occult bile duct stricture.
Previous bile duct injury.
Early carcinoma of the pancreas, carcinoma of the bile duct, or carcinoma of the ampulla.
Extrinsic compression of the bile duct by a primary or secondary neoplasm.

BILIARY OBSTRUCTION[74]

ICD-10CM #	Varies with specific diagnosis

CAUSES OF BILIARY OBSTRUCTION

Benign Miscellaneous
Choledocholithiasis.*
Hemobilia.*
Congenital biliary diseases.*
Caroli disease.*
Choledochal cysts.
Cholangitis.
Infectious.
Acute pyogenic cholangitis.*
Biliary parasites.*
Recurrent pyogenic cholangitis.*
HIV cholangiopathy.
Sclerosing cholangitis.
Neoplasms
Cholangiocarcinoma.
Gallbladder carcinoma.
Locally invasive tumors (esp. pancreatic adenocarcinoma).
Ampullary tumors.
Metastases.
Extrinsic compression
Mirizzi syndrome.
Pancreatitis.
Adenopathy.

*Denotes causes of painful jaundice.

BILIARY TREE, REFLUX OF GAS OR BOWEL[89]

ICD-10CM # Varies with specific diagnosis

CAUSES OF REFLUX OF GAS OR BOWEL CONTRAST INTO THE BILIARY TREE

Iatrogenic.
Sphincterotomy.
Choledochojejunostomy.
Gallstone fistula.
Cholecystoduodenal fistula.
Perforated ulcer.
Choledochoduodenal fistula.
Carcinoma.
Choledochoenteric fistula.

BLADDER (URINARY) WALL THICKENING[74]

ICD-10CM # Varies with specific diagnosis

CAUSES OF BLADDER WALL THICKENING

Focal
Neoplasm
Transitional cell carcinoma.
Squamous cell carcinoma.
Adenocarcinoma.
Lymphoma.
Metastases.
Infectious/Inflammatory.
Tuberculosis (acute).
Schistosomiasis (acute).
Cystitis.
Malakoplakia.
Cystitis cystica.
Cystitis glandularis.
Fistula.
Medical Diseases
Endometriosis.
Amyloidosis.
Trauma
Hematoma.
Diffuse
Neoplasm
Transitional cell carcinoma.
Squamous cell carcinoma.
Adenocarcinoma.
Infectious/Inflammatory
Cystitis.
Tuberculosis (chronic).
Schistosomiasis (chronic).
Medical Diseases
Interstitial cystitis.
Amyloidosis.
Neurogenic Bladder
Detrusor hyperreflexia.
Bladder Outlet Obstruction
With muscular hypertrophy.

BLEEDING, GI IN PATIENTS WITH AIDS[26]

ICD-10CM # K92.2 Gastrointestinal bleeding, unspecified

(EXCLUDING NON-AIDS-SPECIFIC DIAGNOSES)

Esophagus
Candida spp.*
Cytomegalovirus.*
HSV.
Idiopathic ulcer.
Stomach
Cytomegalovirus.*
Kaposi sarcoma.*
Cryptosporidiosis.
Lymphoma.
Small Intestine
Kaposi sarcoma.
Lymphoma.
Cytomegalovirus.
Salmonella spp.
Cryptosporidium.
Colon
Cytomegalovirus.*
Kaposi sarcoma.*
Entamoeba histolytica.
Campylobacter jejuni.
Clostridium difficile.
Shigella spp.
Idiopathic ulcerations.
Lymphoma.

*More frequent diagnosis.

BLEEDING, LOWER GI

ICD-10CM # K92.2 Gastrointestinal hemorrhage, unspecified

(ORIGINATING BELOW THE LIGAMENT OF TREITZ)

Small Intestine
Ischemic bowel disease (mesenteric thrombosis, embolism, vasculitis, trauma).
Small bowel neoplasm: leiomyomas, carcinoids.
Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome).
Meckel diverticulum and other small intestine diverticula.
Aortoenteric fistula.
Intestinal hemangiomas: blue rubber-bleb nevi, intestinal hemangiomas, cutaneous vascular nevi.
Hamartomatous polyps: Peutz-Jeghers syndrome (intestinal polyps, mucocutaneous pigmentation).
Infections of small bowel: tuberculous enteritis, enteritis necroticans.
Volvulus.
Intussusception.
Lymphoma of small bowel, sarcoma, Kaposi sarcoma.
Irradiation ileitis.
AV malformation of small intestine.
Inflammatory bowel disease.
Polyarteritis nodosa.
Other: pancreatoenteric fistulas, Henoch-Schönlein purpura, Ehlers-Danlos syndrome, SLE, amyloidosis, metastatic melanoma.
Colon
Carcinoma (particularly left colon).
Diverticular disease.
Inflammatory bowel disease.
Ischemic colitis.
Colonic polyps.
Vascular abnormalities: angiodysplasia, vascular ectasia.
Radiation colitis.
Infectious colitis.
Uremic colitis.
Aortoenteric fistula.
Lymphoma of large bowel.
Hemorrhoids.
Anal fissure.
Trauma, foreign body.
Solitary rectal/cecal ulcers.
Long-distance running.

BLEEDING, LOWER GI, PEDIATRIC[7]

ICD-10CM # K92.2 Gastrointestinal hemorrhage, unspecified

<3 MO

Swallowed maternal blood.
Infectious colitis.
Milk allergy.
Bleeding diathesis.
Intussusception.
Midgut volvulus.
Meckel diverticulum.
Necrotizing enterocolitis.

<2 YR

Anal fissure.
Infectious colitis.
Milk allergy.
Colitis.
Intussusception.
Meckel diverticulum.
Polyp.
Duplication.
Hemolytic-uremic syndrome.
Inflammatory bowel disease.
Pseudomembranous enterocolitis.

<5 YR

Infectious colitis.
Anal fissure.
Polyp.
Intussusception.
Meckel diverticulum.
Henoch-Schönlein purpura.
Hemolytic-uremic syndrome.
Inflammatory bowel disease.
Pseudomembranous enterocolitis.

5 TO 18 YR

Infectious colitis.
Inflammatory bowel disease.
Pseudomembranous enterocolitis.
Polyp.
Hemolytic-uremic syndrome.
Hemorrhoids.

BLEEDING, RECTAL[86]

ICD-10CM # K92.2 Gastrointestinal hemorrhage, unspecified

IN PATIENTS <40 YR

Very Common

Hemorrhoids.
Anal fissure.
Inflammatory bowel disease (mainly proctitis).

Less Common

Polyps (hamartomatous or adenomatous).
Infective colitis.
Meckel diverticulum.
Intussusception.

Rare

Colorectal cancer.

IN PATIENTS >40 YR

Hemorrhoids.
Anal fissure.
Colorectal cancer.
Colorectal polyps (mostly adenomas).
Angiodysplasia.
Diverticular disease.
Inflammatory bowel disease.
Ischemic colitis.
Infective colitis.

BLEEDING, THIRD TRIMESTER[1]

ICD-10CM #	N93.9	Abnormal uterine and vaginal bleeding, unspecified

Placental abruption.
Placenta previa.
Bloody show (extrusion of cervical mucus).
Vasa previa.
Disseminated intravascular coagulopathy.
Uterine rupture.
Cervicitis, cervical cancer, or other cervical abnormality.
Vaginal laceration.

BLEEDING, UPPER GI

ICD-10CM #	K92.2	Gastrointestinal hemorrhage, unspecified

(ORIGINATING ABOVE THE LIGAMENT OF TREITZ)

Swallowed Hemoptysis

Oral or pharyngeal lesions: swallowed blood from nose or oropharynx.
Esophageal: varices, ulceration, esophagitis, Mallory-Weiss tear, carcinoma, trauma.
Gastric: peptic ulcer (including Cushing and Curling ulcers), gastritis, angiodysplasia, gastric neoplasms, hiatal hernia, gastric diverticulum, pseudoxanthoma elasticum, Rendu-Osler-Weber syndrome.
Duodenal: peptic ulcer, duodenitis, angiodysplasia, aortoduodenal fistula, duodenal diverticulum, duodenal tumors, carcinoma of ampulla of Vater, parasites (e.g., hookworm), Crohn disease.
Biliary: hematobilia (e.g., penetrating injury to liver, hepatobiliary malignancy, endoscopic papillotomy).

BLEEDING, UPPER GI, PEDIATRIC[7]

ICD-10CM #	K92.2	Gastrointestinal hemorrhage, unspecified

<3 MO

Swallowed maternal blood.
Gastritis.
Ulcer, stress.
Bleeding diathesis.
Foreign body (NG tube).
Vascular malformation.
Duplication.

<2 YR

Esophagitis.
Gastritis.
Ulcer.
Pyloric stenosis.
Mallory-Weiss syndrome.
Vascular malformation.
Duplication.

<5 YR

Esophagitis.
Gastritis.
Ulcer.
Esophageal varices.
Foreign body.
Mallory-Weiss syndrome.
Hemophilia.
Vascular malformations.

5 TO 18 YR

Esophagitis.
Gastritis.
Ulcer.
Esophageal varices.
Mallory-Weiss syndrome.
Inflammatory bowel disease.
Hemophilia.
Vascular malformation.

BLEEDING, VAGINAL, NON-PREGNANT FEMALE[1]

ICD-10CM #	N93.9	Abnormal uterine and vaginal bleeding, unspecified

TRAUMA

Blunt force.
Penetrating force.
Foreign bodies.

INFECTIOUS

Vaginitis.
Cervicitis.
Endometritis.

DYSFUNCTIONAL UTERINE BLEEDING

Ovulatory.
Anovulatory.
Adenomyosis.

BENIGN GROWTHS

Uterine leiomyomas.
Cervical polyps.

MALIGNANCY

Vulvar.
Cervical.
Uterine.
Ovarian.

SYSTEMIC DISEASE

Medications

Anticoagulation (warfarin [Coumadin], low-molecular-weight heparin, clopidogrel [Plavix]).
Antipsychotics.
Corticosteroids.
Tamoxifen.
Selective serotonin reuptake inhibitors.
Contraceptives (oral, intrauterine devices, intramuscular).

BLINDNESS, GERIATRIC AGE

ICD-10CM #	H54.8	Legal blindness, as defined in USA

Cataracts.
Glaucoma.
Diabetic retinopathy.
Macular degeneration.
Trauma.
CVA.
Corneal scarring.
Giant cell arteritis.
Ocular herpes zoster.

BLINDNESS, MONOCULAR, TRANSIENT

ICD-10CM #	H54.41	Blindness, right eye, normal vision left eye
	H54.42	Blindness, left eye, normal vision right eye

Migraine (vasospasm).
Embolic cerebrovascular disease.
Intermittent angle-closure glaucoma.
Partial retinal vein occlusion.
Hyphema.
Optic disc edema.
Giant cell arteritis.
Psychogenic.
Hypotension.
Hypercoagulopathy disorders.
Multiple sclerosis.

BLINDNESS, PEDIATRIC AGE[55]

ICD-10CM #	H54.41	Blindness, right eye, normal vision left eye
	H54.42	Blindness, left eye, normal vision right eye

CONGENITAL
Optic nerve hypoplasia or aplasia.
Optic coloboma.
Congenital hydrocephalus.
Hydranencephaly.
Porencephaly.
Microencephaly.
Encephalocele, particularly occipital type.
Morning glory disc.
Aniridia.
Anterior microphthalmia.
Peter anomaly.
Persistent pupillary membrane.
Glaucoma.
Cataracts.
Persistent hyperplastic primary vitreous.

PHAKOMATOSES
Tuberous sclerosis.
Neurofibromatosis (special association with optic glioma).
Sturge-Weber syndrome.
von Hippel–Lindau disease.

TUMORS
Retinoblastoma.
Optic glioma.
Perioptic meningioma.
Craniopharyngioma.
Cerebral glioma.
Posterior and intraventricular tumors when complicated by hydrocephalus.
Pseudotumor cerebri.

NEURODEGENERATIVE DISEASES
Cerebral storage disease.
Gangliosidoses, particularly Tay-Sachs disease (infantile amaurotic familial idiocy), Sandhoff variant, generalized gangliosidosis.
Other lipidoses and ceroid lipofuscinoses, particularly the late-onset amaurotic familial idiocies such as those of Jansky-Bielschowsky and of Batten-Mayou-Spielmeyer-Vogt.
Mucopolysaccharidoses, particularly Hurler syndrome and Hunter syndrome.
Leukodystrophies (dysmyelination disorders), particularly metachromatic leukodystrophy and Canavan disease.
Demyelinating sclerosis (myelinoclastic diseases), especially Schilder disease and Devic neuromyelitis optica.
Special types: Dawson disease, Leigh disease, Bassen-Kornzweig syndrome, Refsum disease.
Retinal degenerations: retinitis pigmentosa and its variants, Leber congenital type.
Optic atrophies: congenital autosomal recessive type, infantile and congenital autosomal dominant types, Leber disease, and atrophies associated with hereditary ataxias—the types of Behr, of Marie, and of Sanger-Brown.

INFECTIOUS PROCESSES
Encephalitis, especially in the prenatal infection syndromes caused by *Toxoplasma gondii*, cytomegalovirus, rubella virus, *Treponema pallidum*, herpes simplex.
Meningitis, arachnoiditis.
Chorioretinitis.
Endophthalmitis.
Keratitis.

HEMATOLOGIC DISORDERS
Leukemia with CNS involvement.

VASCULAR AND CIRCULATORY DISORDERS
Collagen vascular diseases.
Arteriovenous malformations: intracerebral hemorrhage, subarachnoid hemorrhage.
Central retinal occlusion.

TRAUMA
Contusion or avulsion of optic nerves, chiasm, globe, cornea.
Cerebral contusion or laceration.
Intracerebral, subarachnoid, or subdural hemorrhage.

DRUGS AND TOXINS OTHER
Retinopathy of prematurity.
Sclerocornea.
Conversion reaction.
Optic neuritis.
Osteopetrosis.

BLISTERS, SUBEPIDERMAL

ICD-10CM #		
	T07	Unspecified multiple injuries

Burns.
Porphyria cutanea tarda.
Bullous pemphigoid.
Bullous drug reaction.
Arthropod bite reaction.
Toxic epidermal necrosis.
Dermatitis herpetiformis.
Polymorphous light eruption.
Variegate porphyria.
SLE.
Epidermolysis bullosa.
Pseudoporphyria.
Acute graft-versus-host reaction.
Linear IgA disease.
Leukocytoclastic vasculitis.
Pressure necrosis.
Urticaria pigmentosa.
Amyloidosis.

BONE AND/OR SOFT TISSUE HYPERTROPHY[71]

ICD-10CM #		
	M85.80	Other specified disorders of bone density and structure, unspecified site

DISORDERS ASSOCIATED WITH BONE AND/OR SOFT TISSUE HYPERTROPHY
Conditions Associated with Generalized Overgrowth
Pituitary gigantism and acromegaly.
Other endocrine disorders.
Cerebral gigantism (Sotos).
Conditions Associated with Limb Hemihypertrophy
Lipomatosis.
Idiopathic congenital hemihypertrophy (associated with tumors, e.g., Wilms tumor, adrenocortical tumors, hepatoblastoma).
Proteus syndrome (capillary port-wine hemangiomas, lymphangiomas, lipomas, epidermal nevi, hypertrophy hands and feet, macrocephaly).
Maffucci syndrome (enchondromas, exostosis, lymphangiomas, venous angiomas).
Klippel-Trenaunay syndrome (capillary port-wine hemangiomas, varicosities, lymphangiomas).
Parkes Weber syndrome (capillary port-wine hemangiomas, varicosities, arteriovenous fistula).
Blue rubber bleb nevus syndrome (cavernous hemangiomas of skin, GI tract).
Other angiodysplasias (e.g., Servelle-Martorell syndrome; venous arterial malformations with limb hypertrophy and bony hypoplasia).
Beckwith-Wiedemann syndrome (macroglossia, visceromegaly, omphaloceles, hemihypertrophy, etc.).
Conditions Associated with Macrodactyly
Neurofibromatosis.
Macrodystrophia lipomatosa.
Proteus syndrome.
Bannayan-Zonana syndrome (lipomatosis, angiomatosis, macrocephaly).
Hemangiomatosis and other vascular malformations (Klippel-Trenaunay and Parkes Weber).
Lymphangiomatosis.
Arteriovenous malformation.
Maffucci syndrome, Ollier disease.
Epidermal nevus syndrome.

BONE DENSITY, DECREASED, GENERALIZED[36]

ICD-10CM #		
	M85.80	Other specified disorders of bone density and structure, unspecified site

DISORDERS ASSOCIATED WITH GENERALIZED LOSS OF BONE DENSITY
Disorders of Multiple or Uncertain Cause
Senile osteoporosis.[8]
Juvenile osteoporosis.
Osteogenesis imperfecta.[9]
Secondary Bone Disorders
Endocrine
Adrenal cortex:
Cushing disease.
Addison disease.
Gonadal disorders:
Postmenopausal osteoporosis.
Hypogonadism.
Pituitary:

[8] Patients who cannot synthesize Lewis blood group antigens (~5% of the population) do not produce CA–19–9 antigen.
[9] Common cause of decrease in bone density in children.

Acromegaly.
Hypopituitarism.
Pancreas:
Diabetes mellitus.
Thyroid:
Hyperthyroidism.
Hypothyroidism.
Parathyroid:
Hyperparathyroidism.
Marrow Replacement and Expansion
Myeloma.
Leukemia.
Lymphoma.
Metastatic disease.
Gaucher disease.
Anemias (sickle cell, thalassemia, hemophilia).
Drugs and Other Substances
Steroids.
Heparin (osteoporosis).
Anticonvulsants (osteomalacia).
Immunosuppressants.
Alcohol.
Chronic Disease
Chronic renal disease.
Hepatic insufficiency.
GI malabsorption syndromes.
Chronic inflammatory polyarthropathies.
Chronic debility or immobilization.

*Common cause of decrease in bone density in adults.

BONE DENSITY, DECREASED, LOCALIZED[36]

ICD-10CM #		
	Z82.62	Family history of osteoporosis
	M85.80	Other specified disorders of bone density and structure, unspecified site

DISORDERS ASSOCIATED WITH LOCALIZED LOSS OF BONE DENSITY

Disuse osteoporosis.[10]
Reflex sympathetic dystrophy (Sudeck).
Osteolytic syndromes:
Acro-osteolysis, primary and secondary.
Massive osteolysis of Gorham.
Carpotarsal osteolysis.
Transient regional osteoporosis.
Neuromuscular disorders.
Infection.
Arthropathies.
Tumors, primary and secondary, myelomatosis.

[10] Common causes.

BONE LESIONS, PREFERENTIAL SITE OF ORIGIN[81]

ICD-10CM #		
	C41.0	Malignant neoplasm of bones of skull and face
	C41.1	Malignant neoplasm of mandible
	C41.2	Malignant neoplasm of vertebral column
	C41.3	Malignant neoplasm of ribs, sternum and clavicle
	C40.00	Malignant neoplasm of scapula and long bones of unspecified upper limb
	C40.10	Malignant neoplasm of short bones of unspecified upper limb
	C41.4	Malignant neoplasm of pelvic bones, sacrum and coccyx
	C40.20	Malignant neoplasm of long bones of unspecified lower limb
	C40.30	Malignant neoplasm of short bones of unspecified lower limb
	C41.9	Malignant neoplasm of bone and articular cartilage, unspecified
	C79.51	Secondary malignant neoplasm of bone
	C79.52	Secondary malignant neoplasm of bone marrow

EPIPHYSIS

Chondroblastoma.
Giant cell tumor—after fusion of growth plate.
Langerhans cell histiocytosis.
Clear cell chondrosarcoma.
Osteosarcoma.

METAPHYSIS

Parosteal sarcoma.
Chondrosarcoma.
Fibrosarcoma.
Nonossifying fibroma.
Giant cell tumor—before fusion of growth plate.
Unicameral bone cyst.
Aneurysmal bone cyst.

DIAPHYSIS

Myeloma.
Ewing tumor.
Reticulum cell sarcoma.

METADIAPHYSEAL

Fibrosarcoma.
Fibrous dysplasia.
Enchondroma.
Osteoid osteoma.
Chondromyofibroma.

BONE MARROW FAILURE SYNDROMES, INHERITED[45]

ICD-10CM #		
	D61.89	Other specified aplastic anemias and other bone marrow failure syndromes

BI-LINEAGE AND TRI-LINEAGE CYTOPENIAS

Fanconi anemia.
Shwachman-Diamond syndrome.
Dyskeratosis congenita.
Amegakaryocytic thrombocytopenia:
Other inherited thrombocytopenia disorders.
Other genetic syndromes:
Down syndrome.
Dubowitz syndrome.
Seckel syndrome.
Reticular dysgenesis.
Schimke immunoosseous dysplasia.
Noonan syndrome.
Cartilage-hair hypoplasia.
Familial marrow failure (non-Fanconi).

UNI-LINEAGE CYTOPENIA

Diamond-Blackfan anemia.
Kostmann syndrome/Congenital neutropenia:
ELA2 mutations.
HAX1 mutations.
GFI1 mutations.
WASP mutations.
Constitutive cell surface G-CSF-R mutations.
Other inherited neutropenia syndromes:
Barth syndrome.
Glycogen storage disease 1b.
Miscellaneous.
Thrombocytopenia with absent radii.
Congenital dyserythropoietic anemias (CDAs):
Types I, II, III, IV.
Variants.
Nonclassifiable CDAs.
Groups IV, V, VI, VII.

BONE MARROW FIBROSIS[32]

ICD-10CM #		
	D75.9	Disease of blood and blood-forming organs, unspecified

MYELOID DISORDERS

Myelofibrosis with myeloid metaplasia.
Metastatic cancer.
Chronic myeloid leukemia.
Myelodysplastic syndrome.
Atypical myeloid disorder.
Acute megakaryocytic leukemia.
Other acute myeloid leukemias.
Gray platelet syndrome.

LYMPHOID DISORDERS

Hairy cell leukemia.
Multiple myeloma.
Lymphoma.

NONHEMATOLOGIC DISORDERS

Connective tissue disorder.
Infections (tuberculosis, kala-azar).
Vitamin D deficiency (rickets).
Renal osteodystrophy.

BONE MASS, LOW[3]

ICD-10CM #		
	M85.80	Other specified disorders of bone density and structure, unspecified site

SECONDARY CAUSES OF LOW BONE MASS

Endocrine Diseases
Female hypogonadism.
Hyperprolactinemia.
Hypothalamic amenorrhea.
Anorexia nervosa.
Premature and primary ovarian failure.
Female athlete triad.
Male hypogonadism.
Primary gonadal failure (e.g., Klinefelter syndrome).
Secondary gonadal failure (e.g., idiopathic hypogonadotropic hypogonadism, androgen deprivation therapy for prostate cancer).
Hyperthyroidism.
Hyperparathyroidism.
Hypercortisolism.
Vitamin D insufficiency or deficiency.
Gastrointestinal Diseases
Subtotal gastrectomy.
Gastric bypass surgery.
Malabsorption syndromes.
Chronic obstructive jaundice.
Primary biliary cirrhosis and other cirrhoses.
Bone Marrow Disorders
Multiple myeloma.
Monoclonal gammopathy of unknown significance (MGUS).
Lymphoma.
Leukemia.
Hemolytic anemias.
Systemic mastocytosis.
Disseminated carcinoma.
Connective Tissue Diseases
Osteogenesis imperfecta.
Ehlers-Danlos syndrome.
Marfan syndrome.
Homocystinuria.
Drugs
Alcohol.
Antiseizure medications.
Aromatase inhibitors.
Chemotherapy.
Cyclosporine.
Depo-medroxyprogesterone.
Excess thyroid hormone.
Glucocorticoids.
Gonadotropin-releasing hormone agonists.
Heparin.
Miscellaneous Causes
Immobilization.
Rheumatoid arthritis.
Chronic obstructive pulmonary disease.
Weight loss.

BONE MINERAL DENSITY, INCREASED

ICD-10CM #		
	M89.30	Hypertrophy of bone, unspecified site
	M89.8X9	Other specified disorders of bone, unspecified site
	M94.8X9	Other specified disorders of cartilage, unspecified sites

Paget disease of bone.
Skeletal metastases.
DISH.
Osteonecrosis.
Sarcoidosis.
Hypoparathyroidism, pseudohypoparathyroidism.
Milk-alkali syndrome.
Osteopetrosis.
Hypervitaminosis A or D.
Dysplasias (craniodiaphyseal, craniometaphyseal, frontometaphyseal).
Endosteal hyperostosis.
Fluorosis.
Heavy metal poisoning.
Ionizing radiation.
Other: lymphoma, leukemia, mastocytosis, multiple myeloma, polycythemia vera.

BONE PAIN

ICD-10CM #		
	M89.8	Pain, bone

Trauma.
Neoplasm (primary or metastatic).
Osteoporosis with compression fracture.
Paget disease of bone.
Infection (osteomyelitis, septic arthritis).
Osteomalacia.
Viral syndrome.
Sickle cell disease.
Anxiety.

BONE RESORPTION[81]

ICD-10CM #		
	M89.9	Disorder of bone, unspecified
	M94.9	Disorder of cartilage, unspecified

DISTAL CLAVICLE

Hyperparathyroidism.
RA.
Scleroderma.
Posttraumatic osteolysis.
Progeria.
Pycnodysostosis.
Cleidocranial dysplasia.

INFERIOR ASPECT OF RIBS

Vascular impression associated with but not limited to coarctation of the aorta.
Hyperparathyroidism.
Neurofibromatosis.

TERMINAL PHALANGEAL TUFTS

Scleroderma.
Raynaud phenomenon.
Vascular disease.
Frostbite, electrical burns.
Psoriasis.
Tabes dorsalis.
Hyperparathyroidism.

GENERALIZED RESORPTION

Paraplegia.
Myositis ossificans.
Osteoporosis.

BOWEL WALL THICKENING[89]

ICD-10CM #	Varies with specific diagnosis

BENIGN VERSUS MALIGNANT BOWEL WALL THICKENING

Benign
Homogeneous attenuation.
Symmetrical.
Circumferential.
Thickening <1 cm.
Segmental or diffuse involvement.
Double halo sign.
Dark inner ring.
Bright outer ring.
Target sign.
Bright inner ring.
Dark middle ring.
Bright outer ring.
Malignant
Heterogeneous attenuation.
Asymmetrical.
Eccentric.
Thickening >1 to 2 cm.
Focal mass.
Abrupt transition.
Lobulated contour.
Spiculated contour.
Narrowed bowel lumen.
Enlarged lymph nodes.
Liver metastases.

BOW LEGS (GENU VARUM), CLASSIFICATION[53]

ICD-10CM #		
	E64.3	Genu varum, acquired
	Q74.1	Congenital malformation of knee

PHYSIOLOGIC

Asymmetric Growth
Tibia vara (Blount disease):
Infantile.
Juvenile.
Adolescent.
Focal fibrocartilaginous dysplasia.
Physeal injury.
Trauma.
Infection.
Tumor.

METABOLIC DISORDERS

Vitamin D deficiency (nutritional rickets).
Vitamin D–resistant rickets.
Hypophosphatasia.

SKELETAL DYSPLASIA

Metaphyseal dysplasia.

Achondroplasia.
Enchondromatosis.

BRACHYCARDIA, ICU PATIENT[38]

ICD-10CM #	R00.1	Bradycardia, unspecified

COMMON CAUSES OF BRADYCARDIA IN THE ICU

Medications: antiarrhythmics, β-blockers, calcium channel blockers, clonidine, dexmedetomidine, digoxin, lithium, opioids, phenytoin, and propofol.
Age-related degeneration.
Cardiac ischemia.
Electrolyte abnormalities.
Elevated intracranial pressure.
Elevated vagal tone.
Endotracheal intubation.
Hypertension.
Hypothermia.
Hypothyroidism.
Hypoxia.
Inflammatory disease.
Obstructive sleep apnea.
Post-cardiac surgery.

BRADYCARDIA, SINUS[33]

ICD-10CM #	I49.8	Other specified cardiac arrhythmias
	R00.1	Bradycardia, unspecified

Idiopathic.
Degenerative processes (e.g., Lev disease, Lenègre disease).
Medications
β-Blockers.
Some calcium channel blockers (diltiazem, verapamil).
Digoxin (when vagal tone is high).
Class I antiarrhythmic agents (e.g., procainamide).
Class III antiarrhythmic agents (amiodarone, sotalol).
Clonidine.
Lithium carbonate.

ACUTE MYOCARDIAL ISCHEMIA AND INFARCTION

Right or left circumflex coronary artery occlusion or spasm.
High vagal tone (e.g., athletes).

BRAIN MASS[1]

ICD-10CM #	C71	Malignant neoplasm of brain
	D33	Benign neoplasm of brain
	I61.9	Intracranial hemorrhage, unspecified

METASTATIC BRAIN TUMOR

Primary Brain Tumor
Meningioma.
Glioma.
Pituitary adenoma.
Vestibular schwannoma.
Primary or secondary CNS lymphoma.
Infections
Abscess.
Toxoplasmosis.
Neurocysticercosis.
Tuberculoma.
Progressive multifocal leukoencephalopathy.

VASCULAR DISEASE

Hemorrhage
Anomalies (arteriovenous malformation).
Intratumoral.
Hypertensive.
Infarct
Embolism.
Thrombosis (sinus venous).
Inflammatory
Multiple sclerosis.
Encephalomyelitis.

BREAST INFLAMMATORY LESION[24]

ICD-10CM #	N61	Inflammatory disorders of breast
	N60.19	Diffuse cystic mastopathy of unspecified breast
	P39.0	Neonatal infective mastitis
	P83.4	Breast engorgement of newborn

Mastitis (*S. aureus*, β-hemolytic *Streptococcus*).
Trauma.
Foreign body (sutures, breast implants).
Granuloma (TB, fungal).
Fat necrosis post biopsy.
Necrosis or infarction (anticoagulant therapy, pregnancy).
Breast malignancy.

BREAST MASS

ICD-10CM #	N63	Unspecified lump in breast

Fibrocystic breasts.
Benign tumors (fibroadenoma, papilloma).
Mastitis (acute bacterial mastitis, chronic mastitis).
Malignant neoplasm.
Fat necrosis.
Hematoma.
Duct ectasia.
Mammary adenosis.

BREATH ODOR[78]

ICD-10CM #	R19.6	Halitosis

Sweet, fruity: DKA, starvation ketosis.
Fishy, stale: uremia (trimethylamines).
Ammonia-like: uremia (ammonia).
Musty fish, clover: fetor hepaticus (hepatic failure).
Foul, feculent: intestinal obstruction/diverticulum.
Foul, putrid: nasal/sinus pathology (infection, foreign body, cancer), respiratory infections (empyema, lung abscess, bronchiectasis).
Halitosis: tonsillitis, gingivitis, respiratory infections, Vincent angina, gastroesophageal reflux, achalasia, certain foods (garlic, onions, protein drinks, etc.)
Cinnamon: pulmonary TB.

BREATHING, NOISY[78]

ICD-10CM #	R06.00	Dyspnea, unspecified
	R06.09	Other forms of dyspnea
	R06.3	Periodic breathing
	R06.83	Snoring
	R06.89	Other abnormalities of breathing
	R06.1	Stridor

Infection: upper respiratory infection, peritonsillar abscess, retropharyngeal abscess, epiglottitis, laryngitis, tracheitis, bronchitis, bronchiolitis.
Irritants and allergens: hyperactive airway, asthma (reactive airway disease), rhinitis, angioneurotic edema.
Compression from outside of the airway: esophageal cysts or foreign body, neoplasms, lymphadenopathy.
Congenital malformation and abnormality: vascular rings, laryngeal webs, laryngomalacia, tracheomalacia, hemangiomas within the upper airway, stenoses within the upper airway, cystic fibrosis.
Acquired abnormality (at every level of the airway): nasal polyps, hypertrophied adenoids and/or tonsils, foreign body, intraluminal tumors, bronchiectasis.
Neurogenic disorder: vocal cord paralysis.

BRONCHIAL OBSTRUCTION[36]

ICD-10CM #	J98.0	Tracheobronchial collapse

CAUSES OF BRONCHIAL OBSTRUCTION

Outside the Bronchus
Lymph nodes and other masses.
In the Wall of the Bronchus
Tumors
Lung carcinoma (commonly squamous cell).
Bronchial carcinoid.
Metastasis.
Hamartoma.
Inflammation
Tuberculosis.
Sarcoidosis.
Granulomatosis with polyangiitis.
Inflammatory bowel disease.
Bronchomalacia
Broncholith.
Inside the Bronchus
Mucus plug.
Inhaled foreign body.

BRONCHOPLEURAL FISTULA[36]

ICD-10CM #		
	J86.0	Bronchopleural fistula

CAUSES OF BRONCHOPLEURAL FISTULA

Trauma
Penetrating.
Iatrogenic (especially post-pneumonectomy, post-lobectomy, post-biopsy).
Infection
Necrotizing pneumonia.
Empyema.
Tuberculosis.
Septic embolus.
Infected pulmonary infarct.

BROWN URINE

ICD-10CM #		
	R82	Other abnormal findings in urine

Bile pigments.
Myoglobin.
Concentrated urine.
Use of multivitamin supplements.
Medications (antimalarials, metronidazole, nitrofurantoin, levodopa, methyldopa, phenazopyridine).
Diet rich in fava beans.
Urinary tract infection.

BRUISING

ICD-10CM #		
	I99.8	Other disorder of circulatory system

Medication-induced (warfarin, aspirin, NSAIDs, prednisone).
Alcohol abuse.
Senile purpura.
Purpura simplex.
Physical abuse.
Vasculitis.
Platelet disorders.
Coagulation factor deficiencies.
Cushing disease.
Vitamin C deficiency.
Marfan syndrome.
Ehlers-Danlos syndrome.
Disseminated intravascular coagulation.
Leukemia.
Hereditary hemorrhagic telangiectasia.

BULLOUS DISEASES

ICD-10CM #		
	L13.9	Bullous disorder, unspecified
	L12.0	Bullous pemphigoid
	L12.8	Other pemphigoid
	L10.0	Pemphigus vulgaris
	L10.1	Pemphigus vegetans
	L10.2	Pemphigus foliaceous
	L10.4	Pemphigus erythematosus
	L10.9	Pemphigus, unspecified

Bullous pemphigoid.
Pemphigus vulgaris.
Pemphigus foliaceus.
Paraneoplastic pemphigus.
Cicatricial pemphigoid.
Erythema multiforme.
Dermatitis herpetiformis.
Herpes gestationis.
Impetigo.
Erosive lichen planus.
Linear IgA bullous dermatosis.
Epidermolysis bullosa acquisita.

CAFÉ-AU-LAIT SPOTS[53]

ICD-10CM #		
	L81.3	Cafe au lait spots

Neurofibromatosis types 1 and 2.
McCune-Albright syndrome.
Russell-Silver syndrome.
Ataxia-telangiectasia.
Fanconi anemia.
Tuberous sclerosis.
Bloom syndrome.
Basal cell nevus syndrome.
Gaucher disease.
Chédiak-Higashi syndrome.
Hunter syndrome.
Maffucci syndrome.
Multiple mucosal neuroma syndrome.
Watson syndrome.
Proteus syndrome.
Turner syndrome.
Ring chromosome syndrome.
Jaffe-Campanacci syndrome.

CALCIFICATION ON CHEST X-RAY

ICD-10CM #		
	J98.4	Calcification of lung
	M51.84	Other intervertebral disc disorders, thoracic region
	M51.85	Other intervertebral disc disorders, thoracolumbar region

Lung neoplasm (primary or metastatic).
Silicosis.
Idiopathic pulmonary fibrosis.
Tuberculosis.
Histoplasmosis.
Disseminated varicella infection.
Mitral stenosis (end-stage).
Secondary hyperparathyroidism.

CALCIFICATIONS, ABDOMINAL, NONVISCERAL ON X-RAY[36]

ICD-10CM #		
	M61.9	Calcification and ossification of muscle, unspecified

NONVISCERAL ABDOMINAL CALCIFICATION

Common
Atherosclerosis.
Mesenteric lymph nodes.
Phleboliths.
Aneurysm.
Dermoid cyst.
Differentiate
Rib cartilage.
Injections in the buttocks.
Uncommon
Infestations:
Armillifer armillatus.
Cysticercosis.
Guinea worm.
Hydatid.
Tumors:
Lipoma.
Hemangioma.
Neuroblastoma.
Osteo/chondrosarcoma of soft tissues.
Retroperitoneal sarcoma of soft tissues.
Peritoneal metastases.
Pheochromocytoma.
Tuberculosis:
Peritonitis.
Psoas abscess.
Meconium peritonitis.
Pseudomyxoma Peritonei
Mesenteric cyst.
Pancreatitis with saponification.
Lithopedion.
Appendices Epiploicae
Ligaments.
Foreign bodies.
Posttraumatic buttock cysts.

CALCIFICATIONS, ADRENAL GLAND ON X-RAY[36]

ICD-10CM #		
	E27.4	Calcification, adrenal gland

ADRENAL GLAND CALCIFICATION

Common
Idiopathic.
Hemorrhage.
Tuberculosis.
Neuroblastoma/ganglioneuroma.
Pheochromocytoma.
Uncommon
Other tumors:
Adenoma.
Carcinoma.
Dermoid.
Addison disease.
Cyst.
Histoplasmosis.

CALCIFICATIONS, CARDIAC ON X-RAY[36]

ICD-10CM #		
	I51.5	Calcification, myocardium
	I25.1	Calcification, arteriosclerotic

CAUSES OF VISIBLE CALCIFICATION WITHIN THE HEART

Coronary Artery
Atherosclerosis.

BRONCHOPLEURAL FISTULA[36]

ICD-10CM #		
	J86.0	Bronchopleural fistula

CAUSES OF BRONCHOPLEURAL FISTULA

Trauma
Penetrating.
Iatrogenic (especially post-pneumonectomy, post-lobectomy, post-biopsy).
Infection
Necrotizing pneumonia.
Empyema.
Tuberculosis.
Septic embolus.
Infected pulmonary infarct.

BROWN URINE

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Bile pigments.
Myoglobin.
Concentrated urine.
Use of multivitamin supplements.
Medications (antimalarials, metronidazole, nitrofurantoin, levodopa, methyldopa, phenazopyridine).
Diet rich in fava beans.
Urinary tract infection.

BRUISING

ICD-10CM #		
	I99.8	Other disorder of circulatory system

Medication-induced (warfarin, aspirin, NSAIDs, prednisone).
Alcohol abuse.
Senile purpura.
Purpura simplex.
Physical abuse.
Vasculitis.
Platelet disorders.
Coagulation factor deficiencies.
Cushing disease.
Vitamin C deficiency.
Marfan syndrome.
Ehlers-Danlos syndrome.
Disseminated intravascular coagulation.
Leukemia.
Hereditary hemorrhagic telangiectasia.

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ICD-10CM #		
	L13.9	Bullous disorder, unspecified
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	L12.8	Other pemphigoid
	L10.0	Pemphigus vulgaris
	L10.1	Pemphigus vegetans
	L10.2	Pemphigus foliaceous
	L10.4	Pemphigus erythematosus
	L10.9	Pemphigus, unspecified

Bullous pemphigoid.
Pemphigus vulgaris.
Pemphigus foliaceus.
Paraneoplastic pemphigus.
Cicatricial pemphigoid.
Erythema multiforme.
Dermatitis herpetiformis.
Herpes gestationis.
Impetigo.
Erosive lichen planus.
Linear IgA bullous dermatosis.
Epidermolysis bullosa acquisita.

CAFÉ-AU-LAIT SPOTS[53]

ICD-10CM #		
	L81.3	Cafe au lait spots

Neurofibromatosis types 1 and 2.
McCune-Albright syndrome.
Russell-Silver syndrome.
Ataxia-telangiectasia.
Fanconi anemia.
Tuberous sclerosis.
Bloom syndrome.
Basal cell nevus syndrome.
Gaucher disease.
Chédiak-Higashi syndrome.
Hunter syndrome.
Maffucci syndrome.
Multiple mucosal neuroma syndrome.
Watson syndrome.
Proteus syndrome.
Turner syndrome.
Ring chromosome syndrome.
Jaffe-Campanacci syndrome.

CALCIFICATION ON CHEST X-RAY

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	M51.85	Other intervertebral disc disorders, thoracolumbar region

Lung neoplasm (primary or metastatic).
Silicosis.
Idiopathic pulmonary fibrosis.
Tuberculosis.
Histoplasmosis.
Disseminated varicella infection.
Mitral stenosis (end-stage).
Secondary hyperparathyroidism.

CALCIFICATIONS, ABDOMINAL, NONVISCERAL ON X-RAY[36]

ICD-10CM #		
	M61.9	Calcification and ossification of muscle, unspecified

NONVISCERAL ABDOMINAL CALCIFICATION

Common
Atherosclerosis.
Mesenteric lymph nodes.
Phleboliths.
Aneurysm.
Dermoid cyst.
Differentiate
Rib cartilage.
Injections in the buttocks.
Uncommon
Infestations:
Armillifer armillatus.
Cysticercosis.
Guinea worm.
Hydatid.
Tumors:
Lipoma.
Hemangioma.
Neuroblastoma.
Osteo/chondrosarcoma of soft tissues.
Retroperitoneal sarcoma of soft tissues.
Peritoneal metastases.
Pheochromocytoma.
Tuberculosis:
Peritonitis.
Psoas abscess.
Meconium peritonitis.
Pseudomyxoma Peritonei
Mesenteric cyst.
Pancreatitis with saponification.
Lithopedion.
Appendices Epiploicae
Ligaments.
Foreign bodies.
Posttraumatic buttock cysts.

CALCIFICATIONS, ADRENAL GLAND ON X-RAY[36]

ICD-10CM #		
	E27.4	Calcification, adrenal gland

ADRENAL GLAND CALCIFICATION

Common
Idiopathic.
Hemorrhage.
Tuberculosis.
Neuroblastoma/ganglioneuroma.
Pheochromocytoma.
Uncommon
Other tumors:
Adenoma.
Carcinoma.
Dermoid.
Addison disease.
Cyst.
Histoplasmosis.

CALCIFICATIONS, CARDIAC ON X-RAY[36]

ICD-10CM #		
	I51.5	Calcification, myocardium
	I25.1	Calcification, arteriosclerotic

CAUSES OF VISIBLE CALCIFICATION WITHIN THE HEART

Coronary Artery
Atherosclerosis.

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Aortic Root
Atherosclerotic aorta.
Thrombus.
Syphilis.
Ankylosing spondylitis.
Homograft calcification.
Pericardium
Chronic pericarditis, tuberculosis, hemopericardium, pyogenic or viral pericarditis.
Posttraumatic.
Postoperative.
Uremic pericarditis.
Asbestosis (may be pleural calcification applied to pericardium).
Myocardium
Ventricular aneurysm (may mimic pericardial calcification).
Calcified myocardial infarction.
Postmyocarditis.
Endocardium
Endomyocardial fibrosis.
Thrombus.
Valve Cusps
Calcified valves (particularly mitral and aortic valves).
Mitral annulus calcification.
Homograft calcification.
Old vegetation.
Valve Annulus
Submitral.
Mitral.
Aortic.
Left Atrium
Wall.
Thrombus.
Atrial myxoma.
Pulmonary Artery
Pulmonary hypertension.
Postoperative:
Postoperative serumoma calcified hydatid cyst.

CALCIFICATIONS, CUTANEOUS

ICD-10CM #	L94.2	Calcinosis cutis
	L98.8	Other specified disorders of the skin and subcutaneous tissue

Calcification, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome.
Trauma.
Pancreatitis or pancreatic cancer.
Chronic renal failure.
Sarcoidosis.
Hyperparathyroidism.
Milk-alkali syndrome.
Hypervitaminosis D.
Panniculitis.
Idiopathic.
Iatrogenic (e.g., application of calcium alginate dressing to skin).
Multiple myeloma.
Dermatomyositis.
Parasitic infections.
Leukemia.
Lymphoma.

CALCIFICATIONS, GENITAL TRACT, FEMALE ON X-RAY[36]

ICD-10CM #	E83.59	Other disorders of calcium metabolism

FEMALE GENITAL TRACT CALCIFICATION

Uterus
Leiomyomas.
Squamous cell carcinoma.
Adenocarcinoma of endometrium.
Leiomyosarcoma.
Lithopedion.
Fallopian Tubes
Ovary.
Dermoid cyst.
Serous cystadenoma/carcinoma.
Tuberculosis.
Cysts.
Autoamputation.

CALCIFICATIONS, LIVER ON X-RAY[36]

ICD-10CM #	K76.89	Other specified diseases of liver
	NEC K75.3	Granuloma, hepatic

LIVER CALCIFICATION

Common
Granuloma (tuberculosis, histoplasmosis, brucellosis).
Multiple scattered round densities.
Hydatid cyst:
Fine curvilinear in wall, or dense and irregular if contracted.
Primary liver tumor (hemangioma, hepatoblastoma, hepatoma, cholangiocarcinoma).
Irregular patterns or multiple nodules.
Metastases (mucinous primary of colon or breast, cystadenocarcinoma of ovary).
Finely stippled, may be extensive.
Uncommon
Hepatic artery aneurysm.
Armillifer armillatus infestation.
Chronic granulomatous disease of childhood.
Cyst (congenital or acquired).
Hematoma.
Intrahepatic gallstones.
Old liver abscess.
Portal vein thrombosis.
Differentiate
Hemochromatosis.
Thorotrast, thallium, iron.

CALCIFICATIONS, PANCREAS ON X-RAY[36]

ICD-10CM #	K86.8	Calcification, pancreas

PANCREATIC CALCIFICATION

Common
Chronic pancreatitis.
Uncommon
Acute pancreatitis (saponification).
Tumors:
Cystadenoma.
Cystadenocarcinoma.
Islet cell tumor.
Metastases.
Hereditary pancreatitis (large clumps).
Hemorrhage.
Hyperparathyroidism.
Pseudocyst.
Cavernous lymphangioma.
Mucoviscidosis.
Kwashiorkor.

CALCIFICATIONS, SPLEEN ON X-RAY[36]

ICD-10CM #	D73.8	Calcification, spleen

SPLENIC CALCIFICATION

Larger than 10 mm
Splenic artery aneurysm.
Splenic artery atheroma.
Cyst:
Posttraumatic.
Dermoid.
Epidermoid.
Hydatid.
Hematoma.
Infarct.
Abscess.
Tuberculosis.
Smaller than 10 mm
Histoplasmosis.
Tuberculosis.
Phleboliths.
Armillifer armillatus infestation.
Brucellosis.
Infarcts.

CALCIFICATIONS, VALVULAR ON X-RAY[36]

ICD-10CM #	I51.5	Calcification, heart

CAUSES OF RADIOGRAPHICALLY VISIBLE VALVE CALCIFICATION

Aortic Valve
Rheumatic aortic valve disease.
Bicuspid aortic valve.
Age/degenerate aortic valve.
Syphilis.
Ankylosing spondylitis.
Homograft calcification.
Mitral Valve
Rheumatic mitral valve disease.
Mitral annulus calcification.
Old vegetation (may only be visible on CT).
Homograft calcification.
Pulmonary Valve
Congenital pulmonary valve stenosis.
Rheumatic pulmonary valve disease (rare).
Fallot tetralogy (usually after repair).
Pulmonary hypertension.
Homograft calcification.
Tricuspid Valve
Rheumatic tricuspid valve disease.
Old vegetation (may only be visible on ultrafast CT).

CALCIUM STONES

ICD-10CM # N20.9 Urinary calculus, unspecified

Medications (e.g., antacids, loop diuretics, vitamin D, acetazolamide, glucocorticoids).
Primary hyperparathyroidism.
Hypercalcemia from malignancy.
Sarcoidosis.
Prolonged immobilization.
Hyperoxaluria (e.g., Crohn disease, celiac disease, chronic pancreatitis).
Hyperuricosuria (e.g., hyperuricemia, excessive dietary purine, allopurinol, probenecid).
Renal tubular acidosis.
Milk-alkali syndrome.
Thyrotoxicosis.
Hypocitraturia (e.g., metabolic acidosis, hypomagnesemia, hypokalemia).

CARDIAC ARREST, NONTRAUMATIC[58]

ICD-10CM # I46.9 Cardiac arrest, cause unspecified

Cardiac (coronary artery disease, cardiomyopathies, structural abnormalities, valve dysfunction, arrhythmias).
Respiratory (upper airway obstruction, hypoventilation, pulmonary embolism, asthma, COPD exacerbation, pulmonary edema).
Circulatory (tension pneumothorax, pericardial tamponade, PE, hemorrhage, sepsis).
Electrolyte abnormalities (hypokalemia or hyperkalemia, hypomagnesemia or hypermagnesemia, hypocalcemia).
Medications (tricyclic antidepressants, digoxin, theophylline, calcium channel blockers).
Drug abuse (cocaine, heroin, amphetamines).
Toxins (carbon monoxide, cyanide).
Environmental (drowning/near-drowning, electrocution, lightning, hypothermia or hyperthermia, venomous snakes).

CARDIAC DEATH, SUDDEN[3]

ICD-10CM # Z86.74 Personal history of sudden cardiac arrest

Ventricular tachycardia.
Bradyarrhythmia, sick sinus syndrome.
Aortic stenosis.
Tetralogy of Fallot.
Pericardial tamponade.
Cardiac tumors.
Complications of infective endocarditis.
Hypertrophic cardiomyopathy (arrhythmia or obstruction).
Myocardial ischemia.
Atherosclerosis.
Prinzmetal angina.
Kawasaki arteritis.

CARDIAC ENLARGEMENT[33]

ICD-10CM # I51.7 Cardiomegaly
Q23.8 Other congenital malformations of aortic and mitral valves
Q24.8 Other specified congenital malformations of heart
I11.9 Hypertensive heart disease without heart failure

CHAMBER ENLARGEMENT

Chronic Volume Overload
Mitral or aortic regurgitation.
Left-to-right shunt (PDA, VSD, AV fistula).
Cardiomyopathy
Ischemic.
Nonischemic.
Decompensated Pressure Overload
Aortic stenosis.
Hypertension.
High-Output States
Severe anemia.
Thyrotoxicosis.
Bradycardia
Severe sinus bradycardia.
Complete heart block.

LEFT ATRIUM

LV failure of any cause.
Mitral valve disease.
Myxoma.

RIGHT VENTRICLE

Chronic volume overload.
Tricuspid or pulmonic regurgitation.
Left-to-right shunt (ASD).
Decompensated pressure overload:
- Pulmonic stenosis.
- Pulmonary artery hypertension:
  - Primary.
  - Secondary (PE, COPD).
  - Pulmonary venoocclusive disease.

RIGHT ATRIUM

RV failure of any cause.
Tricuspid valve disease.
Myxoma.
Ebstein anomaly.

MULTICHAMBER ENLARGEMENT

Hypertrophic cardiomyopathy.
Acromegaly.
Severe obesity.

PERICARDIAL DISEASE

Pericardial effusion with or without tamponade.
Effusive constrictive disease.
Pericardial cyst, loculated effusion.

PSEUDOCARDIOMEGALY

Epicardial fat.
Chest wall deformity (pectus excavatum, straight back syndrome).
Low lung volumes.
AP chest x-ray.
Mediastinal tumor, cyst.

CARDIAC MASSES[95]

ICD-10CM # C38.0 Malignant neoplasm of heart
D15.1 Benign neoplasm of heart

Intracardiac thrombus.
Focal myocardial hypertrophy.
Left ventricular noncompaction.
Infectious disease (abscess).
Primary cardiac tumor.
Secondary cardiac tumor (metastasis).
Lipomatous hypertrophy of septum.
Cyst.
Imaging artifact.

CARDIAC MURMURS

ICD-10CM # R01.0 Benign and innocent cardiac murmurs
R01.1 Cardiac murmur, unspecified

SYSTOLIC

Mitral regurgitation (MR).
Tricuspid regurgitation (TR).
Ventricular septal defect (VSD).
Aortic stenosis (AS).
Idiopathic hypertrophic subaortic stenosis (IHSS).
Pulmonic stenosis (PS).
Innocent murmur of childhood.
Coarctation of aorta.
Mitral valve prolapse (MVP).

DIASTOLIC

Aortic regurgitation (AR).
Atrial myxoma.
Mitral stenosis (MS).
Pulmonary artery branch stenosis.
Tricuspid stenosis (TS).
Graham Steell murmur (diastolic decrescendo murmur heard in severe pulmonary hypertension).
Pulmonic regurgitation (PR).
Severe mitral regurgitation (MR).
Austin Flint murmur (diastolic rumble heard in severe AR).
Severe VSD and patent ductus arteriosus.

CONTINUOUS

Patent ductus arteriosus.
Pulmonary AV fistula.

CARDIAC TUMORS[34]

ICD-10CM # C38.0 Malignant neoplasm of heart
D15.1 Benign neoplasm of heart

PRIMARY

Benign:
- Myxoma.
- Lipoma.
- Fibroma.
- Rhabdomyoma.
- Fibroelastoma.

Malignant:
- Sarcoma.
- Mesothelioma.
- Lymphoma.

SECONDARY

Direct Extension
Lung cancer.
Breast cancer.
Mediastinal tumors.

Metastatic Tumors
Malignant melanoma.
Leukemia.
Lymphoma.
Venous Extension
Renal cell cancer.
Adrenal cancer.
Liver cancer.

CARDIOEMBOLISM

ICD-10CM # I21.3 ST Elevation (STEMI) myocardial infarction of unspecified site
I21.9 Acute myocardial infarction, unspecified

Acute MI.
Atrial fibrillation.
Left ventricular aneurysm.
Valvular heart disease (e.g., rheumatic mitral valve disease, mitral valve prolapse).
Dilated cardiomyopathy.
Atrial septal defect.
Patent foramen ovale.
Cardioversion for atrial fibrillation.
Infective endocarditis.
Atrial septal aneurysm.
Sick sinus syndrome and cardiac arrhythmias.
Nonbacterial thrombotic endocarditis.
Prosthetic heart valves.
Atrial myxoma and other intracardiac tumors.
Cyanotic heart disease.
Balloon angioplasty.
Coronary artery bypass grafting.
Aneurysms of sinus of Valsalva.
Other: VVI pacing, ventricular support devices, heart transplantation, intracardiac defects with paradoxical embolism.

CARDIOGENIC SHOCK

ICD-10CM # R57.0 Cardiogenic shock

Myocardial infarction.
Arrhythmias.
Pericardial effusion/tamponade.
Chest trauma.
Valvular heart disease.
Myocarditis.
Cardiomyopathy.
CHF, end-stage.

CATARACTS, PEDIATRIC AGE

ICD-10CM # H26.0 Infantile, juvenile, and presenile cataracts

DEVELOPMENTAL VARIANTS

Prematurity (Y-suture vacuoles) with or without retinopathy of prematurity.

GENETIC DISORDERS

Simple Mendelian Inheritance
Autosomal dominant (most common).
Autosomal recessive.
X-linked.
Major Chromosomal Defects
Trisomy disorders (13, 18, 21).
Turner syndrome (45X).
Deletion syndromes (11p13, 18p, 18q).
Duplication syndromes (3q, 20p, 10q).
Multisystem Genetic Disorders
Alport syndrome (hearing loss, renal disease).
Alström syndrome (nerve deafness, diabetes mellitus).
Apert disease (craniosynostosis, syndactyly).
Cockayne syndrome (premature senility, skin photosensitivity).
Conradi disease (chondrodysplasia punctata).
Crouzon disease (dysostosis craniofacialis).
Hallermann-Streiff syndrome (microphthalmia, small pinched nose, skin atrophy, hypotrichosis).
Hypohidrotic ectodermal dysplasia (anomalous dentition, hypohidrosis, hypotrichosis).
Ichthyosis (keratinizing disorder with thick, scaly skin).
Incontinentia pigmenti (dental anomalies, mental retardation, cutaneous lesions).
Lowe syndrome (oculocerebrorenal syndrome: hypotonia, renal disease).
Marfan syndrome.
Marinesco-Sjögren syndrome (cerebellar ataxia, hypotonia).
Meckel-Gruber syndrome (renal dysplasia, encephalocele).
Myotonic dystrophy.
Nail-patella syndrome (renal dysfunction, dysplastic nails, hypoplastic patella).
Nevoid basal cell carcinoma syndrome (autosomal dominant, basal cell carcinoma erupts in childhood).
Peters anomaly (corneal opacifications with iris-corneal dysgenesis).
Reiger syndrome (iris dysplasia, myotonic dystrophy).
Rothmund-Thomson syndrome (poikiloderma: skin atrophy).
Rubinstein-Taybi syndrome (broad great toe, mental retardation).
Smith-Lemli-Opitz syndrome (toe syndactyly, hypospadias, mental retardation).
Sotos syndrome (cerebral gigantism).
Spondyloepiphyseal dysplasia (dwarfism, short trunk).
Werner syndrome (premature aging in 2nd decade of life).
Inborn Errors of Metabolism
Abetalipoproteinemia (absent chylomicrons, retinal degeneration).
Fabry disease (α-galactosidase A deficiency).
Galactokinase deficiency.
Galactosemia (galactose-1-phosphate uridyl transferase deficiency).
Homocystinemia (subluxation of lens, mental retardation).
Mannosidosis (acid α-mannosidase deficiency).
Niemann-Pick disease (sphingomyelinase deficiency).
Refsum disease (phytanic acid α-hydrolase deficiency).
Wilson disease (accumulation of copper leads to cirrhosis and neurologic symptoms).

ENDOCRINOPATHIES

Hypocalcemia (hypoparathyroidism).
Hypoglycemia.
Diabetes mellitus.

CONGENITAL INFECTIONS

Toxoplasmosis.
Cytomegalovirus infection.
Syphilis.
Rubella.
Perinatal herpes simplex infection.
Measles (rubeola).
Poliomyelitis.
Influenza.
Varicella-zoster.

OCULAR ANOMALIES

Microphthalmia.
Coloboma.
Aniridia.
Mesodermal dysgenesis.
Persistent papillary membrane.
Posterior lenticonus.
Persistent hyperplastic primary vitreous.
Primitive hyaloid vascular system.

MISCELLANEOUS DISORDERS

Atopic dermatitis.
Drugs (corticosteroids).
Radiation.
Trauma.
Idiopathic

CAVITARY LESION ON CHEST X-RAY[35]

ICD-10CM # R91.8 Other nonspecific abnormal finding of lung field

NECROTIZING INFECTIONS

Bacteria: anaerobes, *Staphylococcus aureus*, enteric gram-negative bacteria, *Pseudomonas aeruginosa*, *Legionella* species, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Streptococcus pneumoniae, Rhodococcus, Actinomyces*.
Mycobacteria: *Mycobacterium tuberculosis, Mycobacterium kansasii*, MAI.
Bacteria-like: *Nocardia* species.
Fungi: *Coccidioides immitis, Histoplasma capsulatum, Blastomyces hominis, Aspergillus* species, *Mucor* species.
Parasitic: *Entamoeba histolytica, Echinococcus, Paragonimus westermani*.

CAVITARY INFARCTION

Bland infarction (with or without superimposed infection).
Lung contusion.

SEPTIC EMBOLISM

S. aureus, anaerobes, others.

VASCULITIS

Granulomatosis with polyangiitis, periarteritis.

NEOPLASMS

Bronchogenic carcinoma, metastatic carcinoma, lymphoma.

MISCELLANEOUS LESIONS

Cysts, blebs, bullae, or pneumatocele with or without fluid collections.
Sequestration.
Empyema with air-fluid level.
Bronchiectasis.

CEREBRAL INFARCTION SECONDARY TO INHERITED DISORDERS

ICD-10CM # I63.50 Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery

Homocystinuria.
Marfan syndrome.
Ehlers-Danlos syndrome.
Rendu-Osler-Weber syndrome.
Pseudoxanthoma elasticum.
Fabry disease.

CEREBRAL VASCULITIS, CAUSES[29]

ICD-10CM # Varies with specific diagnosis

PRIMARY CEREBRAL VASCULITIDES

Takayasu arteritis.
Primary cerebral vasculitis.
Polyarteritis nodosa.

SECONDARY VASCULITIDES

Immune Disorders
Systemic lupus erythematosus.
Wegner granulomatosis.
Kawasaki syndrome.
Sarcoidosis.
Henoch-Schönlein purpura.
Primary Intracranial Infections
Bacterial meningitis (especially *Diplococcus pneumoniae*).
Tuberculous meningitis.
Mycotic infections.
Cat-scratch disease.
Human immunodeficiency virus/acquired immunodeficiency syndrome.
Malaria.
Lyme disease.
Rickettsial infections.
Brucellosis.

CEREBROVASCULAR DISEASE, ISCHEMIC[93]

ICD-10CM # I67.9 Cerebrovascular disease, unspecified

VASCULAR DISORDERS

Large-vessel atherothrombotic disease.
Lacunar disease.
Arterial-to-arterial embolization.
Carotid or vertebral artery dissection.
Fibromuscular dysplasia.
Migraine.
Venous thrombosis.
Radiation.
Complications of arteriography.
Multiple, progressive intracranial arterial occlusions.

INFLAMMATORY DISORDERS

Giant cell arteritis.
Polyarteritis nodosa.
SLE.
Granulomatous angiitis.
Takayasu disease.
Arteritis associated with amphetamine, cocaine, or phenylpropanolamine.
Syphilis, mucormycosis.
Sjögren syndrome.
Behçet syndrome.

CARDIAC DISORDERS

Rheumatic heart disease.
Mural thrombus.
Arrhythmias.
Mitral valve prolapse.
Prosthetic heart valve.
Endocarditis.
Myxoma.
Paradoxical embolus.

HEMATOLOGIC DISORDERS

Thrombotic thrombocytopenic purpura.
Sickle cell disease.
Hypercoagulable states.
Polycythemia.
Thrombocytosis.
Leukocytosis.
Lupus anticoagulant.

CERVICAL INSTABILITY, PEDIATRIC

ICD-10CM # M50 Cervical disc disorders

CONGENITAL

Vertebral (Bony Anomalies)
Craniooccipital defects (occipital vertebrae, basilar impression, occipital dysplasias, condylar hypoplasia, occipitalized atlas).
Atlantoaxial defects (aplasia of atlas arch, aplasia of odontoid process).
Subaxial anomalies (failure of segmentation and/or fusion, spina bifida, spondylolisthesis).
Ligamentous or Combined Anomalies
Found at birth as an element of somatogenic aberration.
Syndromic Disorders
Down syndrome.
Klippel-Feil syndrome.
22q11.2 deletion syndrome.
Larsen syndrome.
Marfan syndrome.
Ehlers-Danlos syndrome.

ACQUIRED

Trauma.
Infection (pyogenic, granulomatous).
Tumor (including neurofibromatosis).
Inflammatory conditions (e.g., juvenile rheumatoid arthritis).
Osteochondrodysplasias (e.g., achondroplasia, diastrophic dysplasia, metatropic dysplasia, spondyloepiphyseal dysplasia).
Storage disorders (e.g., mucopolysaccharidoses).
Metabolic disorders (rickets).
Miscellaneous (including osteogenesis imperfecta, sequela of surgery).

CHEST PAIN, CHILDREN[9]

ICD-10CM # R07.9 Chest pain, unspecified
R07.82 Intercostal pain
R07.89 Other chest pain
R07.1 Chest pain on breathing
R07.81 Pleurodynia

MUSCULOSKELETAL (COMMON)

Trauma (accidental, abuse).
Exercise, overuse injury (strain, bursitis).
Costochondritis (Tietze syndrome).
Herpes zoster (cutaneous).
Pleurodynia.
Fibrositis.
Slipping rib.
Sickle cell anemia vasoocclusive crisis.
Osteomyelitis (rare).
Primary or metastatic tumor (rare).

PULMONARY (COMMON)

Pneumonia.
Pleurisy.
Asthma.
Chronic cough.
Pneumothorax.
Infarction (sickle cell anemia).
Foreign body.
Embolism (rare).
Pulmonary hypertension (rare).
Tumor (rare).

GASTROINTESTINAL (LESS COMMON)

Esophagitis (gastroesophageal reflux).
Esophageal foreign body.
Esophageal spasm.
Cholecystitis.
Subdiaphragmatic abscess.
Perihepatitis (Fitz-Hugh-Curtis syndrome).
Peptic ulcer disease.

CARDIAC (LESS COMMON)

Pericarditis.
Postpericardiotomy syndrome.
Endocarditis.
Mitral valve prolapse.
Aortic or subaortic stenosis.
Arrhythmias.
Marfan syndrome (dissecting aortic aneurysm).
Anomalous coronary artery.
Kawasaki disease.
Cocaine, sympathomimetic ingestion.
Angina (familial hypercholesterolemia).

IDIOPATHIC (COMMON)

Anxiety, hyperventilation.
Panic disorder.

OTHER (LESS COMMON)

Spinal cord or nerve root compression.
Breast-related pathologic condition.
Castleman disease (lymph node neoplasm).

CHEST PAIN, NONPLEURITIC[20]

ICD-10CM # R07.9 Chest pain, unspecified
R07.82 Intercostal pain
R07.89 Other chest pain

Cardiac: myocardial ischemia/infarction, myocarditis.

Esophageal: spasm, esophagitis, ulceration, neoplasm, achalasia, diverticula, foreign body.
Referred pain from subdiaphragmatic GI structures.
Gastric and duodenal: hiatal hernia, neoplasm, PUD.
Gallbladder and biliary: cholecystitis, cholelithiasis, impacted stone, neoplasm.
Pancreatic: pancreatitis, neoplasm.
Dissecting aortic aneurysm.
Pain originating from skin, breasts, and musculoskeletal structures: herpes zoster, mastitis, cervical spondylosis.
Mediastinal tumors: lymphoma, thymoma.
Pulmonary: neoplasm, pneumonia, pulmonary embolism/infarction.
Psychoneurosis.
Chest pain associated with mitral valve prolapse.

CHEST PAIN, PLEURITIC

ICD-10CM # R07.1 Chest pain on breathing
R07.81 Pleurodynia

Cardiac: pericarditis, postpericardiotomy/Dressler syndrome.
Pulmonary: pneumothorax, hemothorax, embolism/infarction, pneumonia, empyema, neoplasm, bronchiectasis, pneumomediastinum, TB, carcinomatous effusion.
GI: liver abscess, pancreatitis, esophageal rupture, Whipple disease with associated pericarditis or pleuritis.
Subdiaphragmatic abscess.
Pain originating from skin and musculoskeletal tissues: costochondritis, chest wall trauma, fractured rib, interstitial fibrositis, myositis, strain of pectoralis muscle, herpes zoster, soft tissue and bone tumors.
Collagen vascular diseases with pleuritis.
Psychoneurosis.
Familial Mediterranean fever.

CHEST WALL TUMORS, PRIMARY[15]

ICD-10CM # Varies with specific diagnosis

SOFT TISSUE

Benign
Lipoma.
Hemangioma.
Lymphangioma.
Fibroma.
Rhabdomyoma.
Neurofibroma.
Desmoid tumor.
Malignant
Malignant fibrous histiocytoma.
Rhabdosarcoma.
Liposarcoma.
Neurofibrosarcoma.
Leiomyosarcoma.

BONY AND CARTILAGINOUS

Benign
Fibrous dysplasia.
Osteochondroma.
Chondroma.
Askin tumor.
Plasmacytoma.
Malignant
Chondrosarcoma.
Osteogenic sarcoma.
Ewing sarcoma.

CHIASMAL DISEASE[12]

ICD-10CM # Varies with specific diagnosis

CAUSES OF CHIASMAL DISEASE

Tumors
Pituitary adenomas.
Craniopharyngioma.
Meningioma.
Glioma.
Chordoma.
Dysgerminoma.
Nasopharyngeal tumors.
Metastases.
Non-neoplastic masses
Aneurysm.
Rathke pouch cysts.
Fibrous dysplasia.
Sphenoidal sinus mucocele.
Arachnoid cysts.
Miscellaneous
Demyelination.
Inflammation (e.g., sarcoidosis).
Trauma.
Radiation-induced necrosis.
Toxicity (e.g., ethambutol).
Vasculitis.

CHILDHOOD EOSINOPHILIA

ICD-10CM # D72.1 Eosinophilia

PHYSIOLOGIC

Prematurity.
Infants receiving hyperalimentation.
Familial.

INFECTIOUS

Parasitic (with tissue-invasive helminths, e.g., trichinosis, strongyloidiasis, pneumocystosis, filariasis, cysticercosis, cutaneous and visceral larva migrans, echinococcosis).
Bacterial (brucellosis, tularemia, cat-scratch disease, *Chlamydia*).
Fungal (histoplasmosis, blastomycosis, coccidioidomycosis, allergic bronchopulmonary aspergillosis).
Mycobacterial (tuberculosis, leprosy).
Viral (hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus).

PULMONARY

Allergic (rhinitis, asthma).
Loeffler syndrome.
Hypersensitivity pneumonitis.
Eosinophilic pneumonia.
Pulmonary interstitial eosinophilia.

DERMATOLOGIC

Atopic dermatitis.
Pemphigus.
Dermatitis herpetiformis.
Infantile eosinophilic pustular folliculitis.
Episodic angioedema and urticaria.
Eosinophilic fasciitis (Schulman syndrome).
Eosinophilic cellulitis (Wells syndrome).
Kimura disease.

ONCOLOGIC

Neoplasm (lung, GI, uterine).
Hodgkin disease.
Leukemia.
Myelofibrosis.

IMMUNOLOGIC

T-cell immunodeficiencies.
Hyperimmunoglobulin E (Job) syndrome.
Wiskott-Aldrich syndrome.
Graft-versus-host disease.
Drug hypersensitivity.
Post-irradiation.
Post-splenectomy.

ENDOCRINE

Post-adrenalectomy.
Addison disease.
Panhypopituitarism.

CARDIOVASCULAR

Loeffler disease (fibroplastic endocarditis).
Congenital heart disease.
Hypersensitivity vasculitis.

GASTROINTESTINAL

Milk protein allergy.
Inflammatory bowel disease.
Eosinophilic esophagitis.
Eosinophilic gastroenteritis.

CHOLANGITIS, ACUTE[15]

ICD-10CM # K83.0 Cholangitis

NONIATROGENIC

Benign Conditions
Choledocholithiasis.
Primary.
Secondary.
Pancreatitis (chronic/acute), including pancreatic pseudocyst.
Papillary stenosis.
Mirizzi syndrome.
Choledochal cysts (type V, Caroli disease).
Primary sclerosing cholangitis.
Malignancies
Pancreatic cancer.
Cholangiocarcinoma.
Porta hepatis tumor/metastasis.

IATROGENIC

Obstructed biliary endoprosthesis.
Iatrogenic biliary stricture.
Direct surgical trauma.
Ischemia-induced stricture.
Anastomotic stricture (biliobiliary/bilioenteric anastomosis).

CHOLESTASIS[32]

ICD-10CM # K80.65 Calculus of gallbladder and bile duct with chronic cholecystitis with obstruction

EXTRAHEPATIC

Choledocholithiasis.
Bile duct stricture.
Cholangiocarcinoma.
Pancreatic carcinoma.
Chronic pancreatitis.
Papillary stenosis.
Ampullary cancer.
Primary sclerosing cholangitis.
Choledochal cysts.
Parasites (e.g., ascaris, clonorchis).
AIDS.
Cholangiography.
Biliary atresia.
Portal lymphadenopathy.
Mirizzi syndrome.

INTRAHEPATIC

Viral hepatitis.
Alcoholic hepatitis.
Drug induced.
Ductopenia syndromes.
Primary biliary cirrhosis.
Benign recurrent intrahepatic cholestasis.
Byler disease.
Primary sclerosing cholangitis.
Alagille syndrome.
Sarcoid.
Lymphoma.
Postoperative.
Total parenteral nutrition.
α-1-antitrypsin deficiency.

CHOLESTASIS, NEONATAL AND INFANTILE, DIFFERENTIAL DIAGNOSIS[53]

ICD-10CM # 026.6 Liver disorders in pregnancy, childbirth and the puerperium

INFECTIOUS

Generalized bacterial sepsis.
Viral hepatitis:
- Hepatitis A, B, C, D.
- Cytomegalovirus.
- Rubella virus.
- Herpesvirus: herpes simplex, human herpesvirus 6 and 7.
- Varicella virus.
- Coxsackievirus.
- Echovirus.
- Reovirus type 3.
- Parvovirus B19.
- HIV.
- Adenovirus.

Others:
- Toxoplasmosis.
- Syphilis.
- Tuberculosis.
- Listeriosis.
- Urinary tract infection.

TOXIC

Sepsis.
Parenteral nutrition related.
Drug related.

METABOLIC

Disorders of amino acid metabolism:
- Tyrosinemia.

Disorders of lipid metabolism:
- Wolman disease.
- Niemann-Pick disease (type C).
- Gaucher disease.

Cholesterol ester storage disease.
Disorders of carbohydrate metabolism:
- Galactosemia.
- Fructosemia.
- Glycogenosis IV.

Disorders of bile acid biosynthesis.
Other metabolic defects:
- α1-Antitrypsin deficiency.
- Cystic fibrosis.
- Hypopituitarism.
- Hypothyroidism.
- Zellweger (cerebrohepatorenal) syndrome.
- Neonatal iron storage disease.
- Indian childhood cirrhosis/infantile copper overload.
- Congenital disorders of glycosylation.
- Mitochondrial hepatopathies.
- Citrin deficiency.

GENETIC OR CHROMOSOMAL

Trisomy 17, 18, 21.
Donahue syndrome.

INTRAHEPATIC CHOLESTASIS SYNDROMES

"Idiopathic" neonatal hepatitis.
Alagille syndrome (arteriohepatic dysplasia).
Nonsyndromic bile duct paucity syndrome.
Intrahepatic cholestasis (PFIC):
- FIC-1 deficiency.
- BSEP deficiency.
- MDR3 deficiency.

Familial benign recurrent cholestasis associated with lymphedema (Aagenaes).
Congenital hepatic fibrosis.
Caroli disease (cystic dilatation of intrahepatic ducts).

EXTRAHEPATIC DISEASES

Biliary atresia.
Sclerosing cholangitis.
Bile duct stricture/stenosis.
Choledochal-pancreaticoductal junction anomaly.
Spontaneous perforation of the bile duct.
Choledochal cyst.
Mass (neoplasia, stone).
Bile/mucous plug ("inspissated bile").

MISCELLANEOUS

Shock and hypoperfusion.
Associated with enteritis.
Associated with intestinal obstruction.
Neonatal lupus erythematosus.
Myeloproliferative disease (trisomy 21).
Hemophagocytic lymphohistiocytosis.
Arthrogryposis cholestatic pigmentary syndrome.

CHOLESTATIC LIVER ENZYME ELEVATION, EXTRAHEPATIC CAUSES[26]

ICD-10CM # Varies with specific diagnosis

EXTRAHEPATIC CAUSES OF CHOLESTATIC LIVER ENZYMES IN ADULTS

Intrinsic

Choledocholithiasis.
Immune-mediated duct injury:
- Autoimmune pancreatitis.
- PSC.

Malignancy:
- Ampullary cancer.
- Cholangiocarcinoma.

Infections:
- AIDS cholangiopathy:
  - Cytomegalovirus.
  - Cryptosporidiosis.
  - Microsporidiosis.
- Parasitic infections:
  - Ascariasis.

Extrinsic

Malignancy:
- Gallbladder cancer.
- Metastases, including portal adenopathy from metastases.
- Pancreatic cancer.

Mirizzi syndrome.
Pancreatitis.
Pancreatic pseudocyst.

CHOLESTATIC LIVER ENZYME ELEVATION, INTRAHEPATIC CAUSES[26]

ICD-10CM # Varies with specific causes

INTRAHEPATIC CAUSES OF CHOLESTATIC LIVER ENZYME ELEVATIONS IN ADULTS

Drugs[11]

Bland cholestasis:
- Anabolic steroids.
- Estrogens.

Cholestatic hepatitis:
- Angiotensin-converting enzyme inhibitors: captopril, enalapril.
- Antimicrobials: amoxicillin-clavulanic acid, ketoconazole.
- Azathioprine.
- Chlorpromazine.
- NSAIDs: sulindac, piroxicam.

Granulomatous hepatitis:
- Allopurinol.
- Antibiotics: sulfonamides.
- Antiepileptics: carbamazepine, phenytoin.

[11] Categorized by histologic pattern. Drug lists are not meant to be comprehensive.

Cardiovascular agents: hydralazine, procainamide, quinidine.
Phenylbutazone.
Vanishing bile duct syndrome:
Amoxicillin-clavulanic acid.
Chlorpromazine.
Dicloxacillin.
Flucloxacillin.
Macrolides.
PBC
PSC
Granulomatous Liver Disease
Infections:
Brucellosis.
Fungal: histoplasmosis, coccidioidomycosis.
Leprosy.
Q fever.
Schistosomiasis.
TB, *Mycobacterium avium* complex, bacillus Calmette-Guérin.
Sarcoidosis.
Idiopathic granulomatous hepatitis.
Other:
Crohn disease.
Heavy metal exposure: beryllium, copper.
Hodgkin disease.
Viral Hepatitis
HAV and HEV.
HBV and HCV, including fibrosing cholestatic hepatitis.
EBV.
Cytomegalovirus.
Idiopathic Adulthood Ductopenia
Genetic Conditions
Progressive familial intrahepatic cholestasis:
Type 1 (formerly Byler disease).
Type 2.
Type 3.
Benign recurrent intrahepatic cholestasis:
Type 1.
Type 2.
CF.
Malignancy
Hepatocellular carcinoma.
Metastatic disease.
Paraneoplastic syndrome:
Non-Hodgkin lymphoma.
Prostate cancer.
Renal cell cancer.
Infiltrative Liver Disease
Amyloidosis.
Lymphoma.
Intrahepatic Cholestasis of Pregnancy
TPN:
Graft-versus-host disease
Sepsis

CHOREA

ICD-10CM # G25.4 Drug-induced chorea
G25.5 Other chorea

Medications (e.g., neuroleptics, tricyclics, antiparkinsonian drugs).
Cerebral palsy.
Huntington disease.
Benign hereditary chorea.
Thyroid disorder (hyperthyroidism, hypothyroidism).
Friedreich ataxia.
Ataxia-telangiectasia.
Hypoglycemia, hyperglycemia.
Electrolyte abnormalities (hyponatremia, hypocalcemia, hypomagnesemia, hypernatremia).
Vitamin B_{12} deficiency.
SLE.
Wilson disease.
Alcohol.
Cocaine.
Carbon monoxide poisoning.
Mercury poisoning.

CHOREA, PEDIATRIC PATIENT[84]

ICD-10CM # G25.5 Other chorea

CAUSES OF CHOREA IN CHILDHOOD

Static Injury/Structural Disorders
Cerebral palsy.
Stroke.
Trauma.
Moyamoya disease.
Vasculitis.
Tumors.
Congenital malformations.
Joubert syndrome.
Hereditary/Degenerative Disorders
Ataxia-telangiectasia (A-T), and Ataxia-telangiectasia-like disorder (ATLD).
Ataxia oculomotor apraxia (AOA) (includes AOA-1, AOA-2, and early onset cerebellar ataxia and hypoalbuminemia [EOCA-HA]).
Fahr disease.
Pantothenate kinase-associated neurodegeneration (PKAN, associated with mutations in the pantothenate kinase-2 (*PANK-2*) gene), and other causes of neuronal brain iron accumulation (NBIA).
Metabolic Disorders
Acyl-coA dehydrogenase deficiencies.
Mitochondrial disorders, including Leigh syndrome.
GM_1 gangliosidosis.
Lesch-Nyhan disease.
Niemann-Pick type C.
Methylmalonic aciduria.
Nonketotic hyperglycemia.
Kernicterus.
Hypoparathyroidism.
Propionic acidemia.
Hypernatremia.
Hypomagnesemia.
Hypocalcemia.
Hypo- or hyperglycemia.
Vitamin E deficiency or malabsorption.
Bassen-Kornzweig disease.
Complications of cardiac bypass.
Infectious/Parainfectious Disease
Encephalitis/postencephalitis.
Immune-Mediated/Demyelinating Disorders
Sydenham chorea.
Lupus erythematosus.
Henoch-Schönlein purpura.
Anticardiolipin or antiphospholipid antibody syndrome.
Anti-NMDA antibody syndrome.
Drugs/Toxins
Neuroleptic medications, and neuroleptic-like antiemetics (haloperidol, chlorpromazine, pimozide, prochlorperazine, metoclopramide).
Calcium channel blockers (flunarizine, cinnarizine).
Antiseizure medications (phenytoin, carbamazepine, valproate, phenobarbital).
Anticholinergic medications (trihexyphenidyl, benztropine).
Antihistamines.
Tricyclic antidepressants.
Clomipramine.
Stimulants (including methylphenidate, dexamphetamine, pemoline, and bronchodilators).
Clonidine.
L-dopa.
Cocaine.
Bismuth.
Lithium.
Manganese.
Ethanol.
Carbon monoxide.
Oral contraceptives.
General anesthesia (including propofol)—during induction or emergence.
Paroxysmal Disorders
Complex migraine.
Alternating hemiplegia of childhood.
Paroxysmal kinesigenic dyskinesia (PKD).
Paroxysmal nonkinesigenic dyskinesia (PNKD).
Paroxysmal exercise-induced dyskinesia (PED).
Endocrine Disorders
Hyperthyroidism.
Pheochromocytoma.

CHOREOATHETOSIS[65]

ICD-10CM # G25.5 Choreoathetosis

SYSTEMIC DISEASES

SLE.
Polycythemia.
Thyrotoxicosis.
Rheumatic fever.
Cirrhosis of the liver (acquired hepatocerebral degeneration).
DM.
Wilson disease.

PRIMARY DEGENERATIVE BRAIN DISEASES

Huntington chorea.
Olivopontocerebellar atrophies.
Neuroacanthocytosis.

FOCAL BRAIN DISEASES

Hemichorea.
Stroke.
Tumor.
Arteriovenous malformation.

DRUG-INDUCED CHOREOATHETOSIS

Parkinson Disease Drugs
Levodopa.

EPILEPSY DRUGS

Phenytoin.
Carbamazepine.
Phenobarbital.
Gabapentin.
Valproate.
Psychostimulant Drugs
Cocaine.
Amphetamine.
Methamphetamine.
Dextroamphetamine.
Methylphenidate.
Pemoline.
Psychotropic Drugs
Lithium.
Tricyclic antidepressant drugs.
Oral Contraceptive Drugs
Cimetidine

CHYLOTHORAX

ICD-10CM # I89.8 Other specified noninfective disorders of lymphatic vessels and lymph nodes

Post-lymph node dissection of neck or chest.
Subclavian venous catheterization.
Thoracic aneurysm repair.
Trauma to chest and neck.
Mediastinal tumor resection.
Esophagectomy, pneumonectomy.
Lymphangitis, mediastinitis.
Neoplasms (lymphoma, carcinoma of esophagus, lung, mediastinal malignancies).
Sympathectomy.
Venous thrombosis.
Congenital.

CLOUDY URINE

ICD-10CM # R82 Other abnormal findings in urine

Concentrated urine.
Use of multivitamin supplements.
Diet high in purine-rich foods.
Pyuria.
Phosphaturia.
Urinary tract infection.
Lipiduria.
Chyluria.
Hyperoxaluria.

CLUBBING

ICD-10CM # R68.3 Clubbing of fingers

Pulmonary neoplasm (lung, pleura).
Other neoplasm (GI, liver, Hodgkin, thymus, osteogenic sarcoma).
Pulmonary infectious process (empyema, abscess, bronchiectasis, TB, chronic pneumonitis).
Extrapulmonary infectious process (subacute bacterial endocarditis, intestinal TB, bacterial or amebic dysentery, arterial graft sepsis).
Pneumoconiosis.
Cystic fibrosis.
Sarcoidosis.
Cyanotic congenital heart disease.
Endocrine (Graves disease, hyperparathyroidism).
Inflammatory bowel disease.
Celiac disease.
Chronic liver disease, cirrhosis (particularly biliary and juvenile).
Pulmonary AV malformations.
Idiopathic.
Thyroid acropachy.
Hereditary (pachydermoperiostosis).
Chronic trauma (jackhammer operators, machine workers).

COBALAMIN DEFICIENCY[45]

ICD-10CM # E53.8 Deficiency of other specified B group vitamins

ETIOPATHOPHYSIOLOGIC CLASSIFICATION OF COBALAMIN DEFICIENCY

Nutritional cobalamin deficiency (i.e., insufficient cobalamin intake):
  Vegetarians, poverty-imposed near-vegetarians, breastfed infants of mothers with pernicious anemia.
Abnormal intragastric events (i.e., inadequate proteolysis of food cobalamin):
  Atrophic gastritis, partial gastritis with hypochlorhydria, proton-pump inhibitors, H_2 blockers.
Loss or atrophy of gastric oxyntic mucosa (i.e., deficient intrinsic factor [IF] molecules):
  Total or partial gastrectomy, pernicious anemia, caustic destruction (lye).
Abnormal events in small bowel lumen:
  Inadequate pancreatic protease (e.g., R-cobalamin not degraded, cobalamin not transferred to IF):
    Insufficient pancreatic protease (i.e., pancreatic insufficiency).
    Inactivation of pancreatic protease (i.e., Zollinger–Ellison syndrome).
  Usurping of luminal cobalamin (i.e., inadequate cobalamin binding to IF):
  By bacteria, during stasis syndromes (e.g., blind loops, pouches of diverticulosis, strictures, fistulas, anastomosis), impaired bowel motility (e.g., scleroderma), hypogammaglobulinemia.
  By *Diphyllobothrium latum* (fish tapeworm).
Disorders of ileal mucosa/IF–cobalamin receptors (i.e., IF–cobalamin not bound to IF–cobalamin receptors):
  Diminished or absent IF–cobalamin receptors (e.g., ileal bypass, resection, fistula).
  Abnormal mucosal architecture/function (e.g., tropical or nontropical sprue, Crohn disease, tuberculosis ileitis, infiltration by lymphomas, amyloidosis).
  IF-/post-IF–cobalamin receptor defects (e.g., Imerslund–Gräsbeck syndrome, transcobalamin II [TC II] deficiency).
  Drug effects (e.g., slow K, metformin, cholestyramine, colchicine, neomycin).
Disorders of plasma cobalamin transport (i.e., TC II–cobalamin not delivered to TC II receptors):
  Congenital TC II deficiency, defective binding of TC II–cobalamin to TC II receptors (rare).
Metabolic disorders (i.e., cobalamin not used by cells):
  Inborn enzyme errors (rare).
  Acquired disorders (e.g., cobalamin functionally inactivated by irreversible oxidation, N_2O inhalation).

COGNITIVE IMPAIRMENT[83]

ICD-10CM # G31.84 Mild cognitive impairment, so stated

CAUSES OF COGNITIVE IMPAIRMENT: DIAGNOSES BY CATEGORIES WITH REPRESENTATIVE EXAMPLES

Degenerative:
Alzheimer disease.
Frontotemporal dementias.
Dementia with Lewy bodies.
Corticobasal degeneration.
Huntington disease.
Wilson disease.
Parkinson disease.
Multiple system atrophy.
Progressive supranuclear palsy.
Psychiatric:
Depression.
Schizophrenia.
Vascular:
Vascular dementia.
Binswanger encephalopathy.
Amyloid dementia.
Diffuse hypoxic/ischemic injury.
Obstructive:
Normal-pressure hydrocephalus.
Obstructive hydrocephalus.
Traumatic:
Chronic subdural hematoma.
Chronic traumatic encephalopathy.
Post-concussion syndrome.
Neoplastic:
Tumor: malignant, primary and secondary.
Tumor: benign (e.g., frontal meningioma).
Paraneoplastic limbic encephalitis.
Infections:
Chronic meningitis.
Post-herpes encephalitis.
Focal cerebritis/abscesses.
HIV dementia.
HIV-associated infection.
Syphilis.
Lyme encephalopathy.
Subacute sclerosing panencephalitis.
Creutzfeldt–Jakob disease.
Progressive multifocal leukoencephalopathy.
Parenchymal sarcoidosis.
Chronic systemic infection.
Demyelinating:
Multiple sclerosis.
Adrenoleukodystrophy.
Metachromatic leukodystrophy.

Autoimmune:
Systemic lupus erythematosus.
Polyarteritis nodosa.
Drugs/Toxins
Medications:
- Anticholinergics.
- Antihistamines.
- Anticonvulsants.
- β-blockers.
- Sedative–hypnotics.

Substance abuse:
Alcohol.
Inhalants.
Phencyclidine (PCP).
Toxins
Arsenic.
Bromide.
Carbon monoxide.
Lead.
Mercury.
Organophosphates.

COLIC, ACUTE ABDOMINAL[86]

ICD-10CM # R10.0 Acute abdomen

Acute gastroenteritis.
Food poisoning.
Nonspecific causes.
Constipation.
Gastric outlet obstruction:
- Chronic peptic ulceration.
- Gastric cancer.

Small bowel obstruction:
- Adhesions:
  - Postsurgical.
  - Inflammatory (e.g., diverticular).
  - Radiation.
  - Meckel diverticulum.
  - Metastatic.
- Stricture:
  - Ischemic.
  - Radiation.
  - Inflammatory (e.g., Crohn disease).
- Volvulus intussusception:
  - Tumor (e.g., Peutz-Jeghers syndrome).
  - Superior mesenteric artery syndrome.
- Intraluminal bolus:
  - Gallstone.
  - Bezoar.
- Hernia:
  - Abdominal wall.
  - Internal.
- Neoplasm:
  - Benign (e.g., leiomyoma).
  - Malignant (e.g., carcinoid tumor, adenocarcinoma).
- Large bowel obstruction:
  - Colon cancer.
  - Diverticular disease.
  - Volvulus.
- Uterine:
  - Missed abortion.
  - Parturition.
  - Period pain.

COLON ISCHEMIA[26]

ICD-10CM # Varies with specific diagnosis

CAUSES OF COLON ISCHEMIA

Acute pancreatitis.
Allergy.
Amyloidosis.
Heart failure or cardiac arrhythmias.
Hematologic disorders and coagulopathies:
- Activated protein C resistance.
- Antithrombin deficiency.
- Factor V Leiden mutation.
- Paroxysmal nocturnal hemoglobinuria.
- Polycythemia vera.
- Protein C and S deficiencies.
- Prothrombin G20210A mutation.
- Sickle cell disease.

Infection:
- Bacteria (*Escherichia coli* O157:H7).
- Parasites (*Angiostrongylus costaricensis*).
- Viruses (HBV, HCV, cytomegalovirus).

Inferior mesenteric artery thrombosis.
Long-distance running.
Medications and toxins:
- Alosetron.
- Cocaine.
- Danazol.
- Digitalis compounds.
- Ergots.
- Estrogens.
- Flutamide.
- Glycerin enema.
- Gold salts.
- Immunosuppressive agents.
- Interferon-α.
- Methamphetamine.
- NSAIDs.
- Penicillin.
- Phenylephrine.
- Polyethylene glycol 3350 colon lavage solutions.
- Pit viper toxin.
- Progestins.
- Pseudoephedrine.
- Psychotropic drugs.
- Saline laxatives.
- Sumatriptan.
- Tegaserod.
- Vasopressin.

Pheochromocytoma.
Ruptured ectopic pregnancy.
Shock.
Strangulated hernia.
Surgery/procedures:
- Aortic aneurysmectomy.
- Aortoiliac reconstruction.
- Barium enema.
- Colectomy with inferior mesenteric artery ligation.
- Colon bypass.
- Colonoscopy.
- Exchange transfusions.
- Gynecologic operations.
- Lumbar aortography.

Thromboembolism:
- Cholesterol (atheroembolism).
- Myxoma (left atrial).

Trauma (blunt or penetrating).
Vasculitis and vasculopathy:
- Buerger disease.
- Eosinophilic granulomatosis with angiitis.
- Fibromuscular dysplasia.
- Kawasaki disease.
- Polyarteritis nodosa.
- Rheumatoid vasculitis.
- SLE.
- Takayasu arteritis.

Volvulus.

COLOR CHANGES, CUTANEOUS[78]

ICD-10CM # L81.9 Disorder of pigmentation, unspecified

BROWN

Generalized: pituitary, adrenal, liver disease, ACTH-producing tumor (e.g., oat cell lung carcinoma).
Localized: nevi, neurofibromatosis.

WHITE

Generalized: albinism.
Localized: vitiligo, Raynaud phenomenon.

RED (ERYTHEMA)

Generalized: fever, polycythemia, urticaria, viral exanthems.
Localized: inflammation, infection, Raynaud phenomenon.

YELLOW

Generalized: liver disease, chronic renal disease, anemia.
Generalized (except sclera): hypothyroidism, increased intake of vegetables containing carotene.
Localized: resolving hematoma, infection, peripheral vascular insufficiency.

BLUE

Lips, mouth, nail beds: cardiovascular and pulmonary diseases, Raynaud phenomenon.

COMA

ICD-10CM # R40.20 Unspecified coma

Vascular: hemorrhage, thrombosis, embolism.
CNS infections: meningitis, encephalitis, cerebral abscess.
Cerebral neoplasms with herniation.
Head injury: subdural hematoma, cerebral concussion, cerebral contusion.
Drugs: narcotics, sedatives, hypnotics.
Ingestion or inhalation of toxins: CO, alcohol, lead.
Metabolic disturbances.
Hypoxia.
Acid-base disorders.
Hypoglycemia, hyperglycemia.
Hepatic failure.
Electrolyte disorders.
Uremia.
Hypothyroidism.
Hypothermia, hyperthermia.
Hypotension, malignant hypertension.
Postictal.

COMA, NORMAL COMPUTED TOMOGRAPHY[3]

ICD-10CM # R40.20 Unspecified coma

MENINGEAL DISORDERS

Subarachnoid hemorrhage (uncommon).
Bacterial meningitis.
Encephalitis.
Subdural empyema.

EXOGENOUS TOXINS

Sedative drugs and barbiturates.
Anesthetics and γ-hydroxybutyrate.[12]
Alcohols.
Stimulants:
- Phencyclidines.[13]
- Cocaine and amphetamines.[14]

Psychotropic drugs:
- Cyclic antidepressants.
- Phenothiazines.
- Lithium.

Anticonvulsants.
Opioids.
Clonidine.[15]
Penicillins.
Salicylates.
Anticholinergics.
Carbon monoxide, cyanide, and methemoglobinemia.

ENDOGENOUS TOXINS/ DEFICIENCIES/DERANGEMENTS

Hypoxia and ischemia.
Hypoglycemia.
Hypercalcemia.
Osmolar:
- Hyperglycemia.
- Hyponatremia.
- Hypernatremia.

Organ system failure:
- Hepatic encephalopathy.
- Uremic encephalopathy.
- Pulmonary insufficiency (carbon dioxide narcosis).

SEIZURES

Prolonged postictal state.
Spike-wave stupor.

HYPOTHERMIA OR HYPERTHERMIA

Brain stem ischemia.
Basilar artery stroke.
Brain stem or cerebellar hemorrhage.
Conversion or malingering.

[12] General anesthetic, similar to g-aminobutyric acid; recreational drug and body building aid. Rapid onset, rapid recovery often with myoclonic jerking and confusion. Deep coma (2–3 hr; Glasgow Coma Scale = 3) with maintenance of vital signs.
[13] Coma associated with cholinergic signs: lacrimation, salivation, bronchorrhea, and hyperthermia.
[14] Coma after seizures or status (i.e., a prolonged postictal state).
[15] An antihypertensive agent active through the opiate receptor system; frequent overdose when used to treat narcotic withdrawal.

COMA, PEDIATRIC POPULATION[72]

ICD-10CM # R40.20 Unspecified coma

ANOXIA

Birth asphyxia.
Carbon monoxide poisoning.
Croup/epiglottitis.
Meconium aspiration.

INFECTION

Hemolysis.
Blood loss.
Hydrops fetalis.
Infection.
Meningoencephalitis.
Sepsis.
Postimmunization encephalitis.

INCREASED INTRACRANIAL PRESSURE

Anoxia.
Inborn metabolic errors.
Toxic encephalopathy.
Reye syndrome.
Head trauma/intracranial bleed.
Hydrocephalus.
Posterior fossa tumors.

HYPERTENSIVE ENCEPHALOPATHY

Coarctation of aorta.
Nephritis.
Vasculitis.
Pheochromocytoma.

ISCHEMIA

Hypoplastic left heart.
Shunting lesions.
Aortic stenosis.
Cardiovascular collapse (any cause).

PURPURIC CAUSES

Disseminated intravascular coagulation.
Hemolytic-uremic syndrome.
Leukemia.
Thrombotic purpura.

HYPERCAPNIA

Cystic fibrosis.
Bronchopulmonary dysplasia.
Congenital lung anomalies.

NEOPLASM

Medulloblastoma.
Glioma of brain stem.
Posterior fossa tumors.

DRUGS/TOXINS

Maternal sedation.
Alcohol.
Any drug.
Lead.
Salicylism.
Arsenic.
Pesticides.

ELECTROLYTE ABNORMALITIES

Hypernatremia (diarrhea, dehydration, salt poisoning).
Hyponatremia (SIADH, androgenital syndrome, gastroenteritis).
Hyperkalemia (renal failure, salicylism, androgenitalism).
Hypokalemia (diarrhea, hyperaldosteronism, salicylism, DKA).
Hypocalcemia (vitamin D deficiency, hyperparathyroidism).
Severe acidosis (sepsis, cold injury, salicylism, DKA).

HYPOGLYCEMIA

Birth injury or stress.
Diabetes.
Alcohol.
Salicylism.
Hyperinsulinemia.
Iatrogenic.

POSTSEIZURE

Renal Causes
Nephritis.
Hypoplastic kidneys.
Hepatic Causes
Acute hepatitis.
Fulminant hepatic failure.
Inborn metabolic errors.
Bile duct atresia.

COMPRESSION SYNDROMES, NEUROVASCULAR CAUSES[69]

ICD-10CM #
- M47.016 Anterior spinal artery compression syndromes, lumbar region
- M47.019 Anterior spinal artery compression syndromes, site unspecified
- M47.013 Anterior spinal artery compression syndromes, cervicothoracic region
- M47.021 Vertebral artery compression syndromes, occipito-atlanto-axial region
- M47.022 Vertebral artery compression syndromes, cervical region

Anatomic
Potential sites of neurovascular compression:
- Interscalene triangle.
- Costoclavicular space.
- Subcoracoid area.

Congenital
Cervical rib and its fascial remnants.
Rudimentary first thoracic rib.
Scalene muscles:
- Anterior.
- Middle.
- Minimus.

Adventitious fibrous bands.

Bifid clavicle or first rib.
Exostosis of first thoracic rib.
Enlarged transverse process of C7.
Omohyoid muscle.
Anomalous course of transverse cervical artery.
Abnormal lateral insertion of costoclavicular ligament.
Flat clavicle.
Traumatic
Fracture of clavicle.
Dislocation of head of humerus.
Crushing injury to upper thorax.
Sudden, unaccustomed muscular efforts involving shoulder girdle muscles.
Cervical spondylosis and injuries to cervical spine.
Atherosclerosis.

CONGESTIVE HEART FAILURE AND CARDIOMYOPATHY[3]

ICD-10CM # I50.9 Heart failure, unspecified
I42.7 Cardiomyopathy due to drug and external agent

CAUSES OF CONGESTIVE HEART FAILURE AND CARDIOMYOPATHY

Coronary Artery Disease
Acute ischemia.
Myocardial infarction.
Ischemic cardiomyopathy with hibernating myocardium.
Idiopathic
Idiopathic dilated cardiomyopathy.
Idiopathic restrictive cardiomyopathy.
Peripartum.
Pressure Overload
Hypertension.
Aortic stenosis.
Volume Overload
Mitral regurgitation.
Aortic insufficiency.
Anemia.
Atrioventricular fistula.
Toxins
Ethanol.
Cocaine.
Doxorubicin (Adriamycin).
Methamphetamine.
Metabolic-Endocrine
Thiamine deficiency.
Diabetes.
Hemochromatosis.
Thyrotoxicosis.
Obesity.
Infiltrative
Amyloidosis.
Inflammatory
Viral myocarditis.
Hereditary
Hypertrophic.
Dilated.

Genetic bases for these cardiomyopathies have been identified in a large number of individual patients and families. Most of the mutations have been found in cardiac contractile or structural proteins.

CONGESTIVE HEART FAILURE, INFANT[1]

ICD-10CM # I05.9 Heart failure, unspecified

Critical coarctation of the aorta.
Interrupted aortic arch.
Congenital aortic stenosis.
Hypoplastic left heart syndrome.
Large ventricular septal defect.
Truncus arteriosus.
Unrecognized supraventricular tachycardia.
Cardiac tamponade.
Myocarditis.

CONJUNCTIVAL NEOPLASM

ICD-10CM # Varies with specific diagnosis

MALIGNANT

Squamous cell carcinoma.
Melanoma.
Sebaceous carcinoma.
Kaposi sarcoma.
Metastatic neoplasms.

BENIGN

Melanocytic nevus.
Squamous papilloma.
Hemangioma.
Lymphangioma.
Myxoma.

CONSCIOUSNESS IMPAIRMENT, ACUTE, IN CRITICALLY ILL PATIENT

ICD-10CM # F05.9 Delirium, unspecified

GENERAL CAUSES OF ACUTELY IMPAIRED CONSCIOUSNESS IN THE CRITICALLY ILL

Infection
Sepsis encephalopathy.
CNS infection.
Drugs
Narcotics.
Benzodiazepines.
Anticholinergics.
Anticonvulsants.
Tricyclic antidepressants.
Selective serotonin uptake inhibitors.
Phenothiazines.
Steroids.
Immunosuppressants (cyclosporine, FK-506, OKT3).
Anesthetics.
Electrolyte and Acid-Base Disturbances
Hyponatremia.
Hypernatremia.
Hypercalcemia.
Hypermagnesemia.
Severe acidemia and alkalemia.
Organ System Failure
Shock.
Renal failure.
Hepatic failure.
Pancreatitis.
Respiratory failure (hypoxia, hypercapnia).
Endocrine Disorders
Hypoglycemia.
Hyperglycemia.
Hypothyroidism.
Hyperthyroidism.
Pituitary apoplexy.
Drug Withdrawal
Alcohol.
Opiates.
Barbiturates.
Benzodiazepines.
Vascular Causes
Shock.
Hypotension.
Hypertensive encephalopathy.
CNS vasculitis.
Cerebral venous sinus thrombosis.
Central Nervous System Disorders
Hemorrhage.
Stroke.
Brain edema.
Hydrocephalus.
Increased intracranial pressure.
Meningitis.
Ventriculitis.
Brain abscess.
Subdural empyema.
Seizures.
Vasculitis.
Seizures
Convulsive and nonconvulsive status epilepticus.
Miscellaneous
Fat embolism syndrome.
Neuroleptic malignant syndrome.
Thiamine deficiency (Wernicke encephalopathy).
Psychogenic unresponsiveness.

CONSTIPATION

ICD-10CM # K59.00 Constipation, unspecified

Intestinal obstruction.
Fecal impaction.
Diverticular disease.
GI neoplasm.
Strangulated femoral hernia.
Gallstone ileus.
Tuberculous stricture.
Adhesions.
Ameboma.
Volvulus.
Intussusception.
Inflammatory bowel disease.
Hematoma of bowel wall, secondary to trauma or anticoagulants.
Poor dietary habits: insufficient bulk in diet, inadequate fluid intake.
Change from daily routine: travel, hospital admission, physical inactivity.
Acute abdominal conditions: renal colic, salpingitis, biliary colic, appendicitis, ischemia.
Hypercalcemia or hypokalemia, uremia.
Irritable bowel syndrome, pregnancy, anorexia nervosa, depression.
Painful anal conditions: hemorrhoids, fissure, stricture.
Decreased intestinal peristalsis: old age, spinal cord injuries, myxedema, diabetes, multiple

sclerosis, Parkinsonism and other neurologic diseases.
Drugs: codeine, morphine, antacids with aluminum, verapamil, anticonvulsants, anticholinergics, disopyramide, cholestyramine, alosetron, iron supplements.
Hirschsprung disease, meconium ileus, congenital atresia in infants.

CONSTIPATION, ADULT PATIENT[86]

ICD-10CM # K59.00 Constipation, unspecified

NO GROSS STRUCTURAL ABNORMALITY

Inadequate fiber intake.
Irritable bowel syndrome (associated with abdominal pain) or functional constipation.
Idiopathic slow-transit constipation.
"Obstructed defecation" pelvic floor dysfunction (or dyssynergia).

STRUCTURAL DISORDERS

Anal fissure, infection, or stenosis.
Colon cancer or stricture.
Aganglionosis and/or abnormal myenteric plexus:
  Hirschsprung disease.
  Chagas disease.
  Neuropathic pseudoobstruction.
Abnormal colonic muscle:
  Myopathy.
  Dystrophia myotonica.
  Systemic sclerosis.
Idiopathic megarectum and/or megacolon.
Proximal megacolon.

NEUROLOGIC CAUSES

Diabetic autonomic neuropathy.
Damage to the sacral parasympathetic outflow.
Spinal cord damage or disease (e.g., multiple sclerosis).
Parkinson disease.
Blunting of consciousness, mental retardation, psychosis.
Pain induced by straining (e.g., sciatic nerve compression).

ENDOCRINE OR METABOLIC CAUSES

Hypothyroidism.
Hypercalcemia.
Porphyria.
Pregnancy.

PSYCHOLOGIC DISORDERS

Depression.
Anorexia nervosa.
Denied bowel habit.
Drug side effects.

CONSTIPATION, PEDIATRIC PATIENT[54]

ICD-10CM # K59.00 Constipation

Nonorganic (Functional)—Retentive

Anatomic
Anal stenosis, atresia with fistula.
Imperforate anus.
Anteriorly displaced anus.
Intestinal stricture (postnecrotizing enterocolitis).
Anal stricture.
Abnormal Musculature
Prune-belly syndrome.
Gastroschisis.
Down syndrome.
Muscular dystrophy.
Intestinal Nerve or Muscle Abnormalities
Hirschsprung disease.
Pseudoobstruction (visceral myopathy or neuropathy).
Intestinal neuronal dysplasia.
Spinal cord lesions.
Tethered cord.
Autonomic neuropathy.
Spinal cord trauma.
Spina bifida.
Chagas disease.
Drugs
Anticholinergics.
Narcotics.
Methylphenidate.
Phenytoin.
Antidepressants.
Chemotherapeutic agents (vincristine).
Pancreatic enzymes (fibrosing colonopathy).
Lead, arsenic, mercury.
Vitamin D intoxication.
Calcium channel blocking agents.
Metabolic Disorders
Hypokalemia.
Hypercalcemia.
Hypothyroidism.
Diabetes mellitus, diabetes insipidus.
Porphyria.
Intestinal Disorders
Celiac disease.
Cow's milk protein intolerance.
Cystic fibrosis (meconium ileus equivalent).
Inflammatory bowel disease (stricture).
Tumor.
Connective tissue disorders.
Systemic lupus erythematosus.
Scleroderma.
Psychiatric Diagnosis
Anorexia nervosa.

COPD DECOMPENSATION[60]

ICD-10CM # J44.1 Chronic obstructive pulmonary distress with acute exacerbation

CAUSES OF ACUTE DECOMPENSATION IN THE PATIENT WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Acute Exacerbations
Infectious
Viral.
Rhinovirus, respiratory syncytial virus, coronavirus, influenza virus.
Bacterial.
Haemophilus influenzae, Streptococcus pneumoniae, Moraxella (Branhamella) catarrhalis, Pseudomonas aeruginosa.
Atypical bacteria.
Chlamydia pneumoniae, Legionella.
Air Pollution
Nitrogen dioxide.
Ozone.
Particulates, dust.
Other Critical Events
Pneumothorax.
Pulmonary embolism.
Lobar atelectasis.
Congestive heart failure.
Pneumonia.
Pulmonary compression (e.g., obesity, ascites, gastric distention, pleural effusion).
Trauma (e.g., rib fractures, pulmonary contusion).
Neuromuscular and metabolic disorders.
Unrelated treatable chronic pulmonary disease (bronchiectasis, tuberculosis, sarcoidosis).
Noncompliance with prescribed treatment regimens.
Iatrogenic:
  Inadequate therapy.
  Inappropriate therapy (e.g., deleterious drugs).

CORNEAL SENSATION, DECREASED

ICD-10CM # H18.899 Other specified disorders of cornea, unspecified eye

Herpes (simplex, zoster).
Contact lens wear.
Topical agents (NSAIDs, anesthetics, beta-blockers).
Diabetes.
Eye trauma.
Postsurgery.

COUGH

ICD-10CM # R05 Cough

Infectious process (viral, bacterial).
Postinfectious.
"Smoker's cough."
Rhinitis (allergic, vasomotor, postinfectious).
Asthma.
Exposure to irritants (noxious fumes, smoke, cold air).
Drug-induced (especially ACE inhibitors, beta-blockers).
GERD.
Interstitial lung disease.
Lung neoplasms.
Lymphomas, mediastinal neoplasms.
Bronchiectasis.
Cardiac (CHF, pulmonary edema, mitral stenosis, pericardial inflammation).
Recurrent aspiration.
Inflammation of larynx, pleura, diaphragm, mediastinum.
Cystic fibrosis.
Anxiety.
Other: pulmonary embolism, foreign body inhalation, aortic aneurysm, Zenker diverticulum, osteophytes, substernal thyroid, thyroiditis, PMR.

COUGH, CHRONIC, ADULT PATIENT[2]

ICD-10CM # R05 Cough

CAUSES OF CHRONIC COUGH IN ADULTS

Intrathoracic Causes

Lungs and Airways

Asthma.
Nonasthmatic eosinophilic bronchitis.
Chronic bronchitis.
Bronchiectasis.
ACEIs.
Inhaled medications.
Chronic exposure to environmental and occupational irritants.
Bronchogenic and metastatic carcinoma.
Bronchial carcinoid.
Foreign body or endobronchial suture.
Broncholith.
Infectious and noninfectious bronchiolitis.
Chronic infectious pneumonias (e.g., bacterial, tuberculous, fungal, parasitic).
Chronic infectious tracheobronchitis (as in tuberculosis or aspergillosis).
Chronic interstitial lung disease (e.g., sarcoidosis, HSP, IPF, asbestosis).
Pulmonary vasculitis (as in granulomatosis with polyangiitis).
Sjögren syndrome with xerotrachea.
Relapsing polychondritis.

Pleura

Chronic effusion.

Diaphragm

Transvenous pacemaker stimulation.

Mediastinum

Neural tumors.
Thymoma.
Teratoma.
Lymphoma.
Metastatic lymphadenopathy.
Intrathoracic goiter.
Bronchogenic cyst.

Cardiovascular

Mitral stenosis.
Left ventricular failure.
Pulmonary thromboembolism.
Enlarged left atrium.
Vascular ring.
Aberrant innominate artery.
Aortic aneurysm.
Pericardial stimulation by transvenous pacemaker.

Extrathoracic Causes

Head and Neck

Rhinitis and sinusitis.
Nasal polyps.
Rhinolith.
Oropharyngeal dysphagia.
Laryngeal disorders (e.g., vocal fold dysfunction, laryngomalacia).
Postviral vagal neuropathy.
Recurrent aspiration.
Elongated uvula.
Chronically infected tonsils.
Neurilemmoma of vagus nerve.
Neuroma of internal laryngeal nerve.
Ascending palatine artery aneurysm.
Osteophytes of cervical spine.
Mammomanogamus (Syngamus) laryngeus infection.
Thyroiditis.

Upper Gastrointestinal

Gastroesophageal reflux disease.
Esophageal cyst or diverticulum.
Tracheoesophageal fistula.

Central Nervous System

Psychogenic or habit cough.
Tic disorders.
Gilles de la Tourette syndrome.

ACEI, Angiotensin-converting enzyme inhibitor; *HSP,* hypersensitivity pneumonitis; *IPF,* idiopathic pulmonary fibrosis.

COUGH, CHRONIC, PEDIATRIC PATIENT[54]

ICD-10CM # R05 Cough

DIFFERENTIAL DIAGNOSIS OF RECURRENT AND PERSISTENT COUGH IN CHILDREN

Recurrent Cough

Reactive airway disease (asthma).
Drainage from upper airways.
Aspiration.
Frequently recurring respiratory tract infections in immunocompetent or immunodeficient patients.
Symptomatic Chiari malformation.
Idiopathic pulmonary hemosiderosis.
Hypersensitivity (allergic) pneumonitis.

Persistent Cough

Hypersensitivity of cough receptors after infection.
Reactive airway disease (asthma).
Chronic sinusitis.
Chronic rhinitis (allergic or nonallergic).
Bronchitis or tracheitis caused by infection or smoke exposure.
Bronchiectasis, including cystic fibrosis, primary ciliary dyskinesia, immunodeficiency.
Habit cough.
Foreign-body aspiration.
Recurrent aspiration owing to pharyngeal incompetence, tracheolaryngoesophageal cleft or tracheoesophageal fistula.
Gastroesophageal reflux, with or without aspiration.
Pertussis.
Extrinsic compression of the tracheobronchial tract (vascular ring, neoplasm, lymph node, lung cyst).
Tracheomalacia, bronchomalacia.
Endobronchial or endotracheal tumors.
Endobronchial tuberculosis.
Hypersensitivity pneumonitis.
Fungal infections.
Inhaled irritants, including tobacco smoke.
Irritation of external auditory canal.
Angiotensin-converting enzyme inhibitors.

CUTANEOUS INFECTIONS, ATHLETES

ICD-10CM # L08.9 Local infection of the skin and subcutaneous tissue, unspecified

Tinea pedis.
Tinea cruris.
Molluscum contagiosum.
Herpes simplex.
Verruca vulgaris.
Folliculitis.
Impetigo.
Furuncles.
Otitis externa.
Erythrasma.

CYANOSIS[7]

ICD-10CM # R23.0 Cyanosis

DIFFERENTIAL DIAGNOSIS OF CYANOSIS

Peripheral Cyanosis

Low cardiac output states

Shock.
Left ventricular failure.
Hypovolemia.

Environmental exposure (cold)

Air or water.

Arterial occlusion

Thrombosis.
Embolism.
Vasospasm (Raynaud phenomenon).
Peripheral vascular disease.

Venous obstruction

Redistribution of blood flow from extremities

Central Cyanosis

Decreased arterial oxygen saturation

High altitude (>8000 ft).
Impaired pulmonary function:
- Hypoventilation.
- Impaired oxygen diffusion.
- Ventilation-perfusion mismatching:
  - Pulmonary embolism.
  - Acute respiratory distress syndrome.
  - Pulmonary hypertension.
- Respiratory compromise:
  - Upper airway obstruction.
  - Pneumonia.
  - Diaphragmatic hernia.
  - Tension pneumothorax.
  - Polycythemia.

Anatomic Shunts

Pulmonary arteriovenous fistulae and intrapulmonary shunts.
Cerebral, hepatic, peripheral arteriovenous fistulae.
Cyanotic congenital heart disease:
- Endocardial cushion defects.
- Ventricular septal defects.
- Coarctation of aorta.
- Tetralogy of Fallot.
- Total anomalous pulmonary venous drainage.
- Hypoplastic left ventricle.
- Pulmonary vein stenosis.
- Tricuspid atresia and anomalies.
- Premature closure of foramen ovale.
- Dextrocardia.
- Pulmonary stenosis of atrial septal defect.
- Patent ductus arteriosus with reversed shunt.

Abnormal Hemoglobin

Methemoglobinemia:
- Hereditary.
- Acquired.

Sulfhemoglobinemia.
Mutant hemoglobin with low oxygen affinity (e.g., hemoglobin Kansas).

CYANOSIS, CENTRAL, SECONDARY TO CARDIAC DEFECT [95]

ICD-10CM # R23.0 Cyanosis

Transposition of the great arteries.
Tetralogy of Fallot.
Tricuspid atresia.
Truncus arteriosus.
Total anomalous pulmonary venous return.
Ebstein anomaly.
Eisenmenger physiology.
Critical pulmonary stenosis or atresia.
Functionally single ventricle.

Note 5 Ts and 2 Es.

CYANOSIS, NEONATAL [1]

ICD-10CM # R23.0 Cyanosis

RESPIRATORY

Upper Airway
Choanal atresia.
Macroglossia.
Glossoptosis (secondary to micrognathia).
Laryngomalacia.
Laryngeal web or cyst.
Vascular anomalies (e.g., cystic hygromas, rings).
Subglottic stenosis (commonly secondary to intubation).
Foreign body.
Lower Airway
Pneumonia.
Bronchiolitis.
Pulmonary edema.
Atelectasis.
Bronchopulmonary dysplasia.

SYSTEMIC

Sepsis.
Trauma.
Poisons.

CARDIAC

Cyanotic congenital heart diseases.
Transposition of the great vessels (most common neonatal).
Tetralogy of Fallot.
Truncus arteriosus.
Tricuspid atresia.
Total anomalous pulmonary venous return.
Ebstein anomaly.
GI.
Gastroesophageal reflux.

NEUROLOGIC

Seizures.
Central hypoventilation syndrome (Ondine curse).
Spinal muscular atrophy type I (Werdnig-Hoffmann).
Botulism.
Congenital myopathies.

HEMATOLOGIC

Methemoglobinemia.

CYTOPENIAS, OLDER ADULTS [46]

ICD-10CM # D46.A Refractory cytopenia with multilineage dysplasia

Cytopenia of one or more lineages.
Hematologic neoplasm.
Vitamin B_{12} deficiency.
Autoimmune disorder.
Consumptive coagulopathy.
Systemic inflammation.
Alcohol.
Splenomegaly.
Thyroid dysfunction.
Human immunodeficiency virus.

DAYTIME SLEEPINESS

ICD-10CM # R53.82 Chronic fatigue, unspecified

Sleep deprivation.
Medication induced (e.g., benzodiazepines, beta-blockers, narcotics, sedative antidepressants, gabapentin).
Depression.
Obstructive sleep apnea.
Medical illness (e.g., severe anemia, hypothyroidism, COPD, hepatic failure, renal insufficiency, CHF, electrolyte disturbances).
Circadian rhythm abnormalities (e.g., jet lag, shift work sleep disorder).
Restless legs syndrome.
Posttrauma.
Narcolepsy.
Neurologic disorders (e.g., neurodegenerative disorders; parkinsonism; multiple sclerosis; lesions affecting thalamus, hypothalamus, or brain stem).

DELAYED PASSAGE OF MECONIUM [36]

ICD-10CM # P76.0 Meconium plug syndrome

Ileal atresia.
Meconium ileus.
Functional immaturity of the colon.
Colon atresia.
Anorectal malformations.
Hirschsprung disease.
Megacystis-microcolon-intestinal hypoperistalsis syndrome.
Extrinsic compression of the distal bowel by a mass lesion.
  Mesenteric cyst.
  Enteric duplication cyst.
Paralytic ileus, sepsis, drugs, and metabolic upset.

DELIRIUM [58]

ICD-10CM # R40.0 Somnolence
R40.1 Stupor
F05 Delirium due to known physiological condition

PHARMACOLOGIC AGENTS

Anxiolytics (benzodiazepines).
Antidepressants (e.g., amitriptyline, doxepin, imipramine).
Cardiovascular agents (e.g., methyldopa, digitalis, reserpine, propranolol, procainamide, captopril, disopyramide).
Antihistamine.
Cimetidine.
Corticosteroids.
Antineoplastics.
Drugs of abuse (alcohol, cannabis, amphetamines, cocaine, hallucinogens, opioids, sedative-hypnotics, phencyclidine).

METABOLIC DISORDERS

Hypercalcemia.
Hypercarbia.
Hypoglycemia.
Hyponatremia.
Hypoxia.

INFLAMMATORY DISORDERS

Sarcoidosis.
SLE.
Giant cell arteritis.

ORGAN FAILURE

Hepatic encephalopathy.
Uremia.

NEUROLOGIC DISORDERS

Alzheimer disease.
CVA.
Encephalitis (including HIV).
Encephalopathies.
Epilepsy.
Huntington disease.
Multiple sclerosis.
Neoplasms.
Normal-pressure hydrocephalus.
Parkinson disease.
Pick disease.
Wilson disease.

ENDOCRINE DISORDERS

Addison disease.
Cushing syndrome.
Panhypopituitarism.
Parathyroid disease.
Postpartum psychosis.
Recurrent menstrual psychosis.
Sydenham chorea.
Thyroid disease.

DEFICIENCY STATES

Niacin.
Thiamine, vitamin B_{12}, and folate.

DELIRIUM AND AGITATION, DRUG-INDUCED

ICD-10CM # F05.9 Delirium, unspecified

COMMONLY USED DRUGS ASSOCIATED WITH DELIRIUM AND AGITATION

Benzodiazepines.
Opiates (especially meperidine).
Anticholinergics.
Antihistamines.
H_2 blockers.

CYANOSIS, CENTRAL, SECONDARY TO CARDIAC DEFECT [95]

ICD-10CM # R23.0 Cyanosis

Transposition of the great arteries.
Tetralogy of Fallot.
Tricuspid atresia.
Truncus arteriosus.
Total anomalous pulmonary venous return.
Ebstein anomaly.
Eisenmenger physiology.
Critical pulmonary stenosis or atresia.
Functionally single ventricle.

Note 5 Ts and 2 Es.

CYANOSIS, NEONATAL [1]

ICD-10CM # R23.0 Cyanosis

RESPIRATORY

Upper Airway
Choanal atresia.
Macroglossia.
Glossoptosis (secondary to micrognathia).
Laryngomalacia.
Laryngeal web or cyst.
Vascular anomalies (e.g., cystic hygromas, rings).
Subglottic stenosis (commonly secondary to intubation).
Foreign body.
Lower Airway
Pneumonia.
Bronchiolitis.
Pulmonary edema.
Atelectasis.
Bronchopulmonary dysplasia.

SYSTEMIC

Sepsis.
Trauma.
Poisons.

CARDIAC

Cyanotic congenital heart diseases.
Transposition of the great vessels (most common neonatal).
Tetralogy of Fallot.
Truncus arteriosus.
Tricuspid atresia.
Total anomalous pulmonary venous return.
Ebstein anomaly.
GI.
Gastroesophageal reflux.

NEUROLOGIC

Seizures.
Central hypoventilation syndrome (Ondine curse).
Spinal muscular atrophy type I (Werdnig-Hoffmann).
Botulism.
Congenital myopathies.

HEMATOLOGIC

Methemoglobinemia.

CYTOPENIAS, OLDER ADULTS [46]

ICD-10CM # D46.A Refractory cytopenia with multilineage dysplasia

Cytopenia of one or more lineages.
Hematologic neoplasm.
Vitamin B_{12} deficiency.
Autoimmune disorder.
Consumptive coagulopathy.
Systemic inflammation.
Alcohol.
Splenomegaly.
Thyroid dysfunction.
Human immunodeficiency virus.

DAYTIME SLEEPINESS

ICD-10CM # R53.82 Chronic fatigue, unspecified

Sleep deprivation.
Medication induced (e.g., benzodiazepines, beta-blockers, narcotics, sedative antidepressants, gabapentin).
Depression.
Obstructive sleep apnea.
Medical illness (e.g., severe anemia, hypothyroidism, COPD, hepatic failure, renal insufficiency, CHF, electrolyte disturbances).
Circadian rhythm abnormalities (e.g., jet lag, shift work sleep disorder).
Restless legs syndrome.
Posttrauma.
Narcolepsy.
Neurologic disorders (e.g., neurodegenerative disorders; parkinsonism; multiple sclerosis; lesions affecting thalamus, hypothalamus, or brain stem).

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Ileal atresia.
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Colon atresia.
Anorectal malformations.
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Extrinsic compression of the distal bowel by a mass lesion.
  Mesenteric cyst.
  Enteric duplication cyst.
Paralytic ileus, sepsis, drugs, and metabolic upset.

DELIRIUM [58]

ICD-10CM # R40.0 Somnolence
R40.1 Stupor
F05 Delirium due to known physiological condition

PHARMACOLOGIC AGENTS

Anxiolytics (benzodiazepines).
Antidepressants (e.g., amitriptyline, doxepin, imipramine).
Cardiovascular agents (e.g., methyldopa, digitalis, reserpine, propranolol, procainamide, captopril, disopyramide).
Antihistamine.
Cimetidine.
Corticosteroids.
Antineoplastics.
Drugs of abuse (alcohol, cannabis, amphetamines, cocaine, hallucinogens, opioids, sedative-hypnotics, phencyclidine).

METABOLIC DISORDERS

Hypercalcemia.
Hypercarbia.
Hypoglycemia.
Hyponatremia.
Hypoxia.

INFLAMMATORY DISORDERS

Sarcoidosis.
SLE.
Giant cell arteritis.

ORGAN FAILURE

Hepatic encephalopathy.
Uremia.

NEUROLOGIC DISORDERS

Alzheimer disease.
CVA.
Encephalitis (including HIV).
Encephalopathies.
Epilepsy.
Huntington disease.
Multiple sclerosis.
Neoplasms.
Normal-pressure hydrocephalus.
Parkinson disease.
Pick disease.
Wilson disease.

ENDOCRINE DISORDERS

Addison disease.
Cushing syndrome.
Panhypopituitarism.
Parathyroid disease.
Postpartum psychosis.
Recurrent menstrual psychosis.
Sydenham chorea.
Thyroid disease.

DEFICIENCY STATES

Niacin.
Thiamine, vitamin B_{12}, and folate.

DELIRIUM AND AGITATION, DRUG-INDUCED

ICD-10CM # F05.9 Delirium, unspecified

COMMONLY USED DRUGS ASSOCIATED WITH DELIRIUM AND AGITATION

Benzodiazepines.
Opiates (especially meperidine).
Anticholinergics.
Antihistamines.
H_2 blockers.

Antibiotics.
Corticosteroids.
Metoclopramide.

DELIRIUM, AGITATED[7]

ICD-10CM #		
	F05	Delirium due to known physiological condition

Metabolic causes:
- Electrolyte abnormalities.
- Hypoglycemia.
- Hypoxia.
- Uremia/hyperammonemia.

Structural lesions of the CNS:
- Trauma.
- Stroke.
- Hemorrhage.
- Mass.

Endocrine disease:
- Thyrotoxicosis.

Infections:
- Bacterial/viral meningitis/encephalitis.

Toxicologic causes:
- Sympathomimetic/stimulants.
- Cocaine.
- Amphetamines and derivatives.
- Caffeine.
- Phencyclidine/ketamine.
- Anticholinergics.
- Serotonin syndrome.
- Sedative-hypnotic withdrawal.

Heatstroke.
Postictal state.

CNS, Central nervous system.

DELIRIUM, DIALYSIS PATIENT[58]

ICD-10CM #		
	F05	Delirium due to known physiological condition
	F06.8	Other specified mental disorders due to known physiological condition

STRUCTURAL

Cerebrovascular accident (particularly hemorrhage).
Subdural hematoma.
Intracerebral abscess.
Brain tumor.

METABOLIC

Disequilibrium syndrome.
Uremia.
Drug effects.
Meningitis.
Hypertensive encephalopathy.
Hypotension.
Postictal state.
Hypernatremia or hyponatremia.
Hypercalcemia.
Hypermagnesemia.
Hypoglycemia.
Severe hyperglycemia.
Hypoxemia.
Dialysis dementia.

DEMENTIA, ADOLESCENT PATIENT[51]

ICD-10CM #		
	F03	Unspecified dementia
	F03.90	Unspecified dementia without behavioral disturbance

CAUSES OF DEMENTIA IN ADOLESCENTS

Autoimmune or inflammatory diseases:
- Paraneoplastic syndromes, including NMDA antibody encephalitis.
- Vasculitis.

Cerebral and noncerebral neoplasms:
- Chemotherapy (intrathecal).
- Radiotherapy treatment.

Drug, inhalant, and alcohol abuse, including overdose.
Head trauma, including child abuse.
Infections:
- HIV-associated dementia.
- Variant Creutzfeldt–Jakob disease (vCJD).
- Subacute sclerosing panencephalitis (SSPE).

Metabolic abnormalities:
- Adrenoleukodystrophy.
- Wilson disease.

Neurodegenerative illnesses:
- Huntington disease.
- Metachromatic leukodystrophy.
- Other rare, usually genetically transmitted, illnesses.

DEMYELINATING DISEASES[93]

ICD-10CM #		
	G37.9	Demyelinating disease of central nervous system, unspecified

MULTIPLE SCLEROSIS

Relapsing and chronic progressive forms.
Acute multiple sclerosis.
Neuromyelitis optica (Devic disease).

DIFFUSE CEREBRAL SCLEROSIS

Schilder encephalitis periaxialis diffusa.
Baló concentric sclerosis.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

After measles, chickenpox, rubella, influenza, mumps.
After rabies or smallpox vaccination.

NECROTIZING HEMORRHAGIC ENCEPHALITIS

Hemorrhagic leukoencephalitis.

LEUKODYSTROPHIES

Krabbe globoid leukodystrophy.
Metachromatic leukodystrophy.
Adrenoleukodystrophy.
Adrenomyeloneuropathy.
Pelizaeus-Merzbacher leukodystrophy.
Canavan disease.
Alexander disease.

DIAPHRAGM ELEVATION, BILATERAL, SYMMETRICAL[36]

ICD-10CM #		
	J98.6	Disorders of diaphragm

CAUSES OF BILATERAL SYMMETRICAL ELEVATION OF THE DIAPHRAGM

Supine position.
Poor inspiration.
Obesity.
Pregnancy.
Abdominal distention (ascites, intestinal obstruction, abdominal mass).
Diffuse pulmonary fibrosis.
Lymphangitis carcinomatosa.
Disseminated lupus erythematosus.
Bilateral basal pulmonary emboli.
Painful conditions (after abdominal surgery).
Bilateral diaphragmatic paralysis.

DIAPHRAGM ELEVATION, UNILATERAL[36]

ICD-10CM #		
	J98.6	Disorders of diaphragm

CAUSES OF UNILATERAL ELEVATION OF THE DIAPHRAGM

Posture—lateral decubitus position (dependent side).
Gaseous distention of stomach or colon.
Dorsal scoliosis.
Pulmonary hypoplasia.
Pulmonary collapse.
Phrenic nerve palsy.
Eventration.
Pneumonia or pleurisy.
Pulmonary thromboembolism.
Rib fracture and other painful conditions.
Subphrenic infection.
Subphrenic mass.

DIARRHEA, ACUTE WATERY AND BLOODY[86]

ICD-10CM #		
	K52.2	Allergic and dietetic gastroenteritis and colitis
	K52.89	Other specified noninfective gastroenteritis and colitis
	R19.7	Diarrhea, unspecified

ACUTE WATERY DIARRHEA

GI infections:
- Protozoal (e.g., *Giardia*).
- Bacterial (e.g., enterotoxigenic *Escherichia coli,* cholera).
- Viral (e.g., rotavirus, Norwalk virus).

Drugs.
Toxins.
Dietary constituents (e.g., lactose intolerance).
Onset of chronic diarrheal illness.

ACUTE BLOODY DIARRHEA

Infectious colitis:
- Confluent proctocolitis (e.g., *Shigella, Campylobacter, Salmonella, Entamoeba histolytica*).
- Segmental colitis (e.g., *Campylobacter, Salmonella,* enteroinvasive *E. coli, Aeromonas, E. histolytica*).
- Drug-induced colitis (e.g., NSAIDs).
- Inflammatory bowel disease.
- Ischemic colitis (usually elderly patient with underlying heart disease or arrhythmias).
- Antibiotic-associated colitis.

DIARRHEA, CRITICALLY ILL PATIENT[79]

ICD-10CM # R19.7 Diarrhea, unspecified

COMMON CAUSES OF DIARRHEA IN CRITICALLY ILL PATIENTS

Medication
Antibiotics.
H2-recepter antagonists, antacids.
Drugs: significant amounts of sorbitol, magnesium, or hypertonic medications.
Laxative use (unintended).
Gastrointestinal Dysfunction
Gastric or small bowel resection.
Inflammatory bowel disease.
Pancreatic insufficiency.
Radiation enteritis.
Sprue.
Protein-losing gastroenteropathies.
Bowel impaction (paradoxic).
Malnutrition
Hypoproteinemia.
Micronutrient deficiencies.
Enteral Nutrition–Associated
Excessive feeding rate, concentration, volume, or osmolality.
Adaptation in malnourished patients or those whose GI tract has not been used recently.
Intolerance or allergy to feeding formula.
Infection
Clostridium difficile enterocolitis.
Opportunistic GI infection.
Significant amounts of contaminated feeding formula.
Altered GI flora.
Endocrine Dysfunction
Diabetes mellitus.
Hyperthyroidism.
Hypocortisolism.

DIARRHEA, INFECTIOUS[7]

ICD-10CM # A09 Infectious gastroenteritis and colitis, unspecified

ETIOLOGIC AGENTS OF INFECTIOUS DIARRHEA

Viral (60% of Cases)
Astrovirus.
Calicivirus.
Coronavirus.
Cytomegalovirus.[16]
Enteric adenovirus.
Hepatitis A through G.
Herpes simplex virus.
HIV enteropathy.
Norwalk-like agents.
Pararotavirus.
Norwalk virus.
Picornavirus.
Rotavirus.
Small round viruses.
Bacterial (20% of Cases)
Invasive
Aeromonas spp.
Campylobacter spp.
Clostridium difficile.
Enteroinvasive *E. coli.*
Mycobacterium spp.
Plesiomonas shigelloides.
Salmonella spp.
Shigella spp.
Vibrio fluvialis.
Vibrio parahaemolyticus.
Vibrio vulnificus.
Yersinia enterocolitica.
Yersinia pseudotuberculosis.
Toxigenic
Food poisoning with preformed toxins:
- *Bacillus cereus.*
- *Clostridium botulinum.*
- *Staphylococcus aureus.*

Toxin formation after colonization:
- *Aeromonas hydrophila.*
- *Clostridium perfringens.*
- Enterohemorrhagic *E. coli* O157:H7.
- Enterotoxigenic *E. coli.*
- *Klebsiella pneumoniae.*
- *Shigella* spp.
- *Vibrio cholerae.*
- **Other bacteria**

Parasitic (5% of Cases)
Protozoa
Balantidium coli.
Blastocystis hominis.
Cryptosporidium.
Cyclospora.
Dientamoeba fragilis.
Entamoeba histolytica.
Entamoeba polecki.
Enteromonas hominis.
Giardia lamblia.
Isospora belli.
Microsporidia.
Sarcocystis hominis.
Helminths
Angiostrongylus costaricense.
Anisakiasis.
Ascaris lumbricoides.
Diphyllobothrium latum.
Enterobius vermicularis.
Hookworms.
Schistosoma spp.
Strongyloides stercoralis.
Taenia spp.
Trichinella spiralis.
Trichuris trichiura.

[16] Associated with fever, abdominal pain, and fecal red blood cells or white blood cells. % indicates the estimated contribution to total cases.

DIARRHEA, NONINFECTIOUS[7]

ICD-10CM # K59.1 Functional diarrhea

CAUSES OF NONINFECTIOUS DIARRHEA

Toxins
Drugs
ACE inhibitors.
Alprazolam.
Antacids (Mg).
Antibiotics.
Antidepressants.
Antiepileptic drugs.
Antihypertensives.
Antiparkinson drugs.
Beta-blockers.
Caffeine.
Cardiac antiarrhythmics.
Chemotherapy agents.
Cholesterol-lowering drugs.
Cholinergic agents.
Cholinesterase inhibitors.
Colchicine.
Digitalis.
Diuretics.
Flurouracil.
Fluoxetine.
Histamine H_2-receptor antagonists.
Hydralazine.
Lactulose.
Laxatives/cathartics.
Levodopa.
Lithium.
NSAIDs.
Neomycin.
Podophyllin.
Procainamide.
Prostaglandins.
Quinidine.
Ricinoleic acid.
Theophylline.
Thyroid hormone.
Valproic acid.
Dietetic foods
Mannitol.
Sorbitol.
Xylitol.
Fish-associated toxins
Amnestic shellfish poisoning.
Ciguatera.
Echinoderms.
Neurotoxic shellfish poisoning.
Paralytic shellfish poisoning.
Scombroid.
Tetroton.
Plant-associated toxins
Herbal preparations.
Horse chestnut.
Mushrooms—*Amanita* spp.
Nicotine.
Other plant toxins:
- Pesticides—organophosphates.
- Pokeweed.
- Rhubarb.
- Miscellaneous:
  - Allergic reactions.
  - Carbon monoxide poisoning.

Ethanol.
Heavy metals.
Monosodium glutamate (MSG).
Opiate withdrawal.

Gastrointestinal Pathology

Appendicitis.
Autonomic dysfunction.
Bile acid malabsorption.
Blind loop.
Bowel obstruction.
Celiac disease.
Cirrhosis.
Defects in amino acid transport.
Diverticular disease.
Familial dysautonomia.
Fecal impaction.
Fecal incontinence.
GI bleed.
GI cancer.
Hirschsprung disease.
Inflammatory bowel disease (ulcerative colitis, Crohn disease).
Intussusception.
Irritable bowel syndrome.
Ischemic bowel.
Lactose/fructose intolerance.
Malabsorption syndromes.
Malrotation.
Postsurgical.
Postvagotomy.
Radiation therapy.
Short gut syndrome.
Small bowel resection.
Strictures.
Toxic megacolon.
Tropical sprue.
Volvulus.
Whipple disease.

Endocrine Related

Carcinoid syndrome (serotonin).
Hormonal hypersecretion.
Hyperthyroidism (thyroid hormone).
Medullary carcinoma of the thyroid (calcitonin).
Pancreatic cholera (VIP).
Somatostatinoma (somatostatin).
Systemic mastocytosis (histamine).
Zollinger-Ellison syndrome (gastrin).

Endocrine pathology

Adrenal insufficiency.
Diabetes enteropathy.
Hypoparathyroidism.
Pancreatic insufficiency.

Systemic Illness/Other

Alcoholism.
Amyloidosis.
Connective tissue disease.
Cystic fibrosis.
Ectopic pregnancy.
Hemolytic-uremic syndrome.
Henoch-Schönlein purpura.
Lymphoma.
Otitis media—infants.
Pelvic inflammatory disease.
Pneumonia/sepsis.
Pyelonephritis.
Scleroderma/SLE.
Severe malnutrition.
Stevens-Johnson syndrome.
Toxic shock syndrome.
Wilson disease.

Miscellaneous:
Factitious diarrhea.
Runner's diarrhea.

ACE, Angiotensin-converting enzyme; *GI,* gastrointestinal; *NSAIDs,* nonsteroidal antiinflammatory drugs; *SLE,* systemic lupus erythematosus; *VIP,* vasoactive intestinal polypeptide.

DIARRHEA IN PATIENTS WITH AIDS[26]

ICD-10CM # R19.7 Diarrhea, unspecified

PROTOZOA

*Microsporidium.**
Cryptosporidium spp.*
Isospora belli.
Toxoplasma spp.
Giardia lamblia.
Entamoeba histolytica.
Leishmania donovani.
Blastocystis hominis.
Cyclospora spp.
Pneumocystis jiroveci.

BACTERIA

Clostridium difficile.
Salmonella spp.
Shigella spp.
Campylobacter jejuni.
Mycobacterium avium complex.
Mycobacterium tuberculosis.
SIBO.
Vibrio spp.

VIRUSES

CMV.
HSV.
Adenoviruses.
Rotavirus spp.
Norovirus.
HIV?

FUNGI

Histoplasmosis.
Coccidioidomycosis.
Cryptococcosis.
Candidiasis.
Penicillium marneffei.

NEOPLASMS

Lymphoma.
Kaposi sarcoma.

IDIOPATHIC

"AIDS enteropathy."

DRUG INDUCED

HIV protease inhibitors.

PANCREATIC DISEASE

Pancreatic insufficiency.
Chronic pancreatitis.
Infectious pancreatitis (CMV, MAC).
Drug-induced pancreatitis (e.g., pentamidine).

CMV, cytomegalovirus.

*More frequent cause.

DIARRHEA, PEDIATRIC PATIENT[54]

ICD-10CM # R19.7 Diarrhea, unspecified

INFANT

Acute

Common:
Gastroenteritis (viral > bacterial > protozoal).
Systemic infection.
Antibiotic associated.
Overfeeding.

Rare:
Primary disaccharidase deficiency.
Hirschsprung toxic colitis.
Adrenogenital syndrome.
Neonatal opiate withdrawal.

Chronic

Common:
Postinfectious secondary lactase deficiency.
Cow's milk or soy protein intolerance (allergy).
Chronic nonspecific diarrhea of infancy.
Excessive fruit juice (sorbitol) ingestion.
Celiac disease.
Cystic fibrosis.
AIDS enteropathy.

Rare:
Primary immune defects.
Autoimmune enteropathy.
IPEX and IPEX-like syndromes.
Glucose-galactose malabsorption.
Microvillus inclusion disease (microvillus atrophy).
Congenital transport defects (chloride, sodium).
Primary bile acid malabsorption.
Factitious syndrome by proxy.
Hirschsprung disease.
Shwachman syndrome.
Secretory tumors.
Acrodermatitis enteropathica.
Lymphangiectasia.
Abetalipoproteinemia.
Eosinophilic gastroenteritis.
Short bowel syndrome.

CHILD

Acute

Common:
Gastroenteritis (viral > bacterial > protozoal).
Food poisoning.
Systemic infection.
Antibiotic associated.

Rare:
Toxic ingestion.
Hemolytic uremic syndrome.
Intussusception.

Chronic

Common:
Postinfectious secondary. lactase deficiency.
Irritable bowel syndrome.
Celiac disease.
Cystic fibrosis.
Lactose intolerance.
Excessive fruit juice (sorbitol) ingestion.
Giardiasis.

Inflammatory bowel disease.
AIDS enteropathy.
Rare:
Primary and acquired immune defects.
Secretory tumors.
Pseudoobstruction.
Sucrase-isomaltase deficiency.
Eosinophilic gastroenteritis.
Secretory tumors.

ADOLESCENT

Acute
Common:
Gastroenteritis (viral > bacterial > protozoal).
Food poisoning.
Antibiotic associated.
Rare:
Hyperthyroidism.
Appendicitis.
Chronic
Common:
Irritable bowel syndrome.
Inflammatory bowel disease.
Lactose intolerance.
Giardiasis.
Laxative abuse (anorexia nervosa).
Constipation with encopresis.
Rare:
Secretory tumor.
Primary bowel tumor.
Parasitic infections and venereal diseases.
Appendiceal abscess.
Addison disease.

IPEX, Immunodysregulation polyendocrinopathy enteropathy X-linked.

DIARRHEA, TUBE-FED PATIENT[32]

ICD-10CM # K91.89 Other postprocedural complications and disorders of digestive system

COMMON CAUSES UNRELATED TO TUBE FEEDING

Elixir medications containing sorbitol.
Magnesium-containing antacids.
Antibiotic-induced sterile gut.
Pseudomembranous colitis.

POSSIBLE CAUSES RELATED TO TUBE FEEDING

Inadequate fiber to form stool bulk.
High fat content of formula (in the presence of fat malabsorption syndrome).
Bacterial contamination of enteral products and delivery systems (causal association with diarrhea not documented).
Rapid advancement in rate (after the GI tract is unused for prolonged periods).

UNLIKELY CAUSES RELATED TO TUBE FEEDING

Formula hyperosmolality (proven not to be the cause of diarrhea).
Lactose (absent from nearly all enteral feeding formulas).

DIFFUSE PARENCHYMAL LUNG DISEASE, DRUG-INDUCED[92]

ICD-10CM # J84.89 Other specified interstitial pulmonary diseases

CYTOTOXIC CHEMOTHERAPY

Bleomycin.
Busulfan.
Cyclophosphamide.
Gemcitabine.
Nitrosoureas.
Taxanes (e.g., paclitaxel, docetaxel).

ANTIMETABOLITES

Methotrexate.

TARGETED BIOLOGIC AGENTS

Tumor necrosis factor (TNF)-α inhibitors or soluble receptors:
- Infliximab.
- Adalimumab.
- Certolizumab pegol.
- Etanercept.

Tyrosine kinase inhibitors:
- Afatinib.
- Erlotinib.
- Gefitinib.
- Idelalisib.
- Imatinib.
- Osimertinib.
- Trametinib.

Checkpoint inhibitors (antibodies against PD-1, PD-1 ligand, or CTLA-4):
- Ipilimumab.
- Nivolumab.
- Pembrolizumab.

Inhibitors of anaplastic lymphoma kinase (ALK):
- Alectinib.
- Ceritinib.
- Crizotinib.

MISCELLANEOUS

Trastuzumab (monoclonal antibody against HER2).
Rituximab (monoclonal antibody against CD20).
Inhibitors of mechanistic target of rapamycin (mTOR, e.g., everolimus).

MISCELLANEOUS OTHER DRUGS

Nitrofurantoin.
Amiodarone.

DRUG-INDUCED SYNDROMES

Drug-induced lupus (e.g., procainamide, hydralazine).
Drug-induced pulmonary infiltrates with eosinophilia (e.g., sulfa-containing drugs).

DIPLOPIA, BINOCULAR

ICD-10CM # H53.2 Diplopia

Cranial nerve palsy (3rd, 4th, 6th).
Thyroid eye disease.
Myasthenia gravis.
Decompensated strabismus.
Orbital trauma with blowout fracture.
Orbital pseudotumor.
Cavernous sinus thrombosis.

DIPLOPIA, MONOCULAR

ICD-10CM # H53.2 Diplopia

Postoperative corrected long-standing tropia.
Defective contact lenses.
Poorly fitting bifocals.
Trauma to iris.
Corneal disorder (e.g., dry eye, astigmatism).
Cataracts.
Lens subluxation.
Nystagmus.
Eyelid twitching.
Foreign body in aqueous or vitreous media.
Migraine.
Lesions of occipital cortex.
Psychogenic.

DIPLOPIA, VERTICAL

ICD-10CM # H53.2 Diplopia

Myasthenia.
Superior oblique palsy.
Myositis or pseudotumor with orbital involvement.
Lymphoma or metastases affecting the orbits.
Brain stem or cerebellar lesions.
Hydrocephalus.
Third nerve palsy.
Botulism.
Wernicke encephalopathy.
Dysthyroid orbitopathy (muscle infiltration).

DIZZINESS

ICD-10CM # R42 Dizziness and giddiness

Viral syndrome.
Anxiety, hyperventilation.
Benign positional paroxysmal vertigo.
Medications (e.g., sedatives, antihypertensives, analgesics).
Withdrawal from medications (e.g., benzodiazepines, SSRIs).
Alcohol or drug abuse.
Postural hypotension.
Hypoglycemia, hyperglycemia.
Hematologic disorders (e.g., anemia, polycythemia, leukemia).
Head trauma.
Menière disease.
Vertebrobasilar ischemia.
Cervical osteoarthritis.
Cardiac abnormalities (arrhythmias, cardiomyopathy, CHF, pericarditis).
Multiple sclerosis.
Peripheral vestibulopathy.
Air or sea travel.
Electrolyte abnormalities.
Eye problems (cornea, lens, retina).
Migraine.
Brain stem infarct.
Autonomic neuropathy.
Chronic otomastoiditis.
Complex partial seizures.
Ramsey Hunt syndrome.
Arteritis.
Syncope and presyncope.
Perilymph fistula.
Cerebellopontine tumor.
Hepatic or renal disease.

DRUG-INDUCED LUPUS[42]

ICD-10CM # M32.0 Drug-induced lupus

DRUGS IMPLEMENTED IN DRUG-INDUCED LUPUS

DRUGS WITH GOOD EVIDENCE OF ASSOCIATION

Adalimumab.
Carbamazepine.
Chlorpromazine.
Etanercept.
Ethosuximide.
Hydralazine.
Infliximab.
Isoniazid.
Methyldopa.
Minocycline.
Penicillamine.
Phenytoin.
Procainamide.
Quinidine.
Sulfasalazine.

CASE REPORTS

5-aminosalicylic acid.
Acebutolol.
Aminoglutethimide.
Amiodarone.
Amoproxan.
Anthiomaline.
Atenolol.
Atorvastatin.
Benoxaprofen.
Canavanine (L-).
Captopril.
Chlorprothixene.
Cimetidine.
Cinnarizine.
Clonidine.
Clozapine.
COL-3.
Danazol.
Diclofenac.
1,2-Dimethyl-3-hydroxypyride-4-1 (L1).
Disopyramide.
Esomeprazole.
Estrogens.
Etanercept.
Flutamide.
Fluvastatin.
Gold salts.
Griseofulvin.
Guanoxan.
Hydrazine.
Ibuprofen.
Infliximab.
Interferon (α,β).
Interleukin 2.
Labetalol.
Lamotrigine.
Lansoprazole.
Leuprolide acetate.
Levo-Dopa.
Levomeprazone.
Lithium carbonate.
Lovastatin.
Mephenytoin.
Mesalazine.
Methimazole.
Methylsergide.
Methylthiouracil.
Metrizamide.
Minoxidil.
Nalidixic acid.
Nitrofurantoin.
Nomifensine.
Oral contraceptives.
Olsalazine.
Omeprazole.
Oxyphenisatin.
Pantoprazole.
Para-aminosalicylic acid.
Penicillin.
Perazine.
Perphenazine.
Phenelzine.
Phenopyrazone.
Phenylbutazone.
Phenylethyacetylurea.
Practolol.
Prazosin.
Primidone.
Prinolol.
Promethazine.
Propylthiouracil.
Psoralen.
Pyrathiazine.
Pyrithioxine.
Quinine.
Rifamycin.
Sulfasalazine.
Simvastatin.
Spironolactone.
Streptomycin.
Sulindac.
Sulfadimethoxine.
Sulfamethoxypyridazine.
Terbinafine.
Tetracycline.
Tetrazine.
Thionamide.
Thioridazide.
Timolol eye drops.
Tolazamide.
Tolmetin.
Trimethadione.
Zafirlukast.

DRY EYE

ICD-10CM # H04.129 Dry eye syndrome of unspecified lacrimal gland

Contacts.
Medications (antihistamines, clonidine, beta-blockers, ibuprofen, scopolamine).
Keratoconjunctivitis sicca.
Trauma.
Environmental causes (air conditioning in patient with contacts).

DYSENTERY AND INFLAMMATORY ENTEROCOLITIS[10]

ICD-10CM # Varies with specific diagnosis

DIFFERENTIAL DIAGNOSIS OF ACUTE BACTERIAL DYSENTERY AND INFLAMMATORY ENTEROCOLITIS

Specific Infectious Processes

Bacillary dysentery (*Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Shigella boydii;* invasive *Escherichia coli*).
Campylobacteriosis (*Campylobacter jejuni*).
Amebic dysentery (*Entamoeba histolytica*).
Ciliary dysentery (*Balantidium coli*).
Vibriosis (*Vibrio parahaemolyticus*).
Salmonellosis (*Salmonella typhimurium*).
Typhoid fever (*Salmonella typhi*).
Enteric fever (*Salmonella choleraesuis, Salmonella paratyphi*).
Yersiniosis (*Yersinia enterocolitica*).

Proctitis

Gonococcal (*Neisseria gonorrhoeae*).
Herpetic (herpes simplex virus).
Chlamydial (*Chlamydia trachomatis*).
Syphilitic (*Treponema pallidum*).

Other Syndromes

Necrotizing enterocolitis of the newborn.
Enteritis necroticans.
Pseudomembranous enterocolitis or *Clostridium difficile* colitis without overt pseudomembranes (*C. difficile*).
Diverticulitis.
Typhlitis.

Chronic Inflammatory Processes

Enteropathogenic and enteroaggregative *E. coli.*
Syphilis.
GI tuberculosis.
GI mycosis (including *Basidiobolus ranarum*).
Parasitic enteritis.

Syndromes without Known Infectious Cause

Idiopathic ulcerative colitis.
Crohn disease.
Radiation enteritis.
Ischemic colitis.
Allergic enteritis.
Brainerd diarrhea.

DYSLIPOPROTEINEMIAS, SECONDARY CAUSES[95]

ICD-10CM # E78.4 Other hyperlipidemia

Cause	Disorder
Metabolic	Diabetes.
	Lipodystrophy.
	Glycogen storage disorders.
Renal	Chronic renal failure.
	Glomerulonephritis with nephritic syndrome.
Hepatic	Cirrhosis.
	Biliary obstruction.
	Porphyria.
	Primary biliary cirrhosis (with secondary LCAT deficiency).
Hormonal	Estrogens.
	Progesterones.
	Growth hormone.
	Thyroid disorders (hypothyroidism).
	Corticosteroids.

Cause	Disorder
Lifestyle	Physical inactivity. Obesity. Diet rich in fats, saturated fats. Alcohol intake. Smoking.
Medications	Retinoic acid derivatives. Glucocorticoids. Exogenous estrogens. Thiazide diuretics. Beta-adrenergic blockers (selective). Testosterone and other anabolizing steroids. Immunosuppressive medications (cyclosporine). Antiviral medications (HIV protease inhibitors). Antischizophrenic medications.

HIV, Human immunodeficiency virus; *LCAT,* lecithin-cholesterol acyltransferase.

DYSPAREUNIA[24]

ICD-10CM # N94.1 Dyspareunia
N44.8 Other noninflammatory disorders of the testis
N50.8 Other specified disorders of male genital organs
N53.12 Painful ejaculation
F52.6 Dyspareunia not due to a substance or known physiological condition

INTROITAL

Vaginismus.
Intact or rigid hymen.
Clitoral problems.
Vulvovaginitis.
Vaginal atrophy: hypoestrogen.
Vulvar dystrophy.
Bartholin or Skene gland infection.
Inadequate lubrication.
Operative scarring.

MIDVAGINAL

Urethritis.
Trigonitis.
Cystitis.
Short vagina.
Operative scarring.
Inadequate lubrication.

DEEP

Endometriosis.
Pelvic infection.
Uterine retroversion.
Ovarian pathology.
GI.
Orthopedic.
Abnormal penile size or shape.

DYSPEPSIA AND PYROSIS, DIFFERENTIAL DIAGNOSIS DURING PREGNANCY[30]

ICD-10CM # K30 Dyspepsia, atonic
F45.3 Dyspepsia, psychogenic

DIFFERENTIAL DIAGNOSIS OF DYSPEPSIA OR PYROSIS DURING PREGNANCY

Gastroesophageal reflux disease.
Peptic ulcer disease.
Nausea and vomiting of pregnancy.
Hyperemesis gravidarum.
Pancreatitis.
Biliary colic.
Acute cholecystitis.
Viral hepatitis.
Appendicitis.
Acute fatty liver of pregnancy (in late pregnancy).
Irritable bowel syndrome/nonulcer dyspepsia.

DYSPHAGIA

ICD-10CM # R13.10 Dysphagia, unspecified

Esophageal obstruction: neoplasm, foreign body, achalasia, stricture, spasm, esophageal web, diverticulum, Schatzki ring.
Peptic esophagitis with stricture, Barrett stricture.
External esophageal compression: neoplasms (thyroid neoplasm, lymphoma, mediastinal tumors), thyroid enlargement, aortic aneurysm, vertebral spurs, aberrant right subclavian artery (dysphagia lusoria).
Hiatal hernia, GERD.
Oropharyngeal lesions: pharyngitis, glossitis, stomatitis, neoplasms.
Hysteria: globus hystericus.
Neurologic and/or neuromuscular disturbances: bulbar paralysis, myasthenia gravis, ALS, multiple sclerosis, Parkinsonism, CVA, diabetic neuropathy.
Toxins: poisoning, botulism, tetanus, postdiphtheritic dysphagia.
Systemic diseases: scleroderma, amyloidosis, dermatomyositis.
Candida and herpes esophagitis.
Presbyesophagus.

DYSPHAGIA, ESOPHAGEAL[26]

ICD-10CM # R13-14 Dysphagia, pharyngoesophageal phase

COMMON CAUSES OF ESOPHAGEAL DYSPHAGIA

Motility (Neuromuscular) Disorders
Primary
Achalasia.
Distal esophageal spasm.
Hypercontractile (jackhammer) esophagus.
Hypertensive LES.
Nutcracker (high-pressure) esophagus.
Other peristaltic abnormalities.[17]
Secondary
Chagas disease.
Reflux-related dysmotility.
Scleroderma and other rheumatologic disorders.
Structural (Mechanical) Disorders
Intrinsic
Carcinoma and benign tumors.
Diverticula.
Eosinophilic esophagitis.
Esophageal rings and webs (other than Schatzki ring).
Foreign body.
Lower esophageal (Schatzki) ring.
Medication-induced stricture.
Peptic stricture.
Extrinsic
Mediastinal mass.
Spinal osteophytes.
Vascular compression.

LES, lower esophageal sphincter.
[17] Peristaltic abnormalities include absent peristalsis and weak peristalsis, as well as hypertensive peristalsis (nutcracker esophagus).

DYSPHAGIA, OROPHARYNGEAL[86]

ICD-10CM # R13.12 Dysphagia, oropharyngeal phase

FUNCTIONAL DISORDERS

Central Nervous System
Stroke.
Head injury.
Parkinson disease.
Motor neuron disease.
Multiple sclerosis.
Tumor.
Drugs (e.g., phenothiazines).
Malformations (e.g., syrinx, Arnold–Chiari).
Neural
Motor neuron disease.
Myasthenia gravis.
Radiotherapy.
Poliomyelitis.
Familial dysautonomia.
Muscle
Autoimmune myopathy (polymyositis, dermatomyositis, systemic lupus erythematosus).
Thyrotoxic myopathy.
Guillain-Barré motor neuropathy.
Muscular dystrophies.

STRUCTURAL DISORDERS

Head/neck surgery.
Stricture.
Radiotherapy.
Tumor.
Pharyngeal pouch.
Web.
Extrinsic (e.g., osteophytes).

MISCELLANEOUS

Xerostomia.

DYSPNEA

ICD-10CM # R06.9 Unspecified abnormalities of breathing

Upper airway obstruction: trauma, neoplasm, epiglottitis, laryngeal edema, tongue retraction, laryngospasm, abductor paralysis of vocal cords, aspiration of foreign body.
Lower airway obstruction: neoplasm, COPD, asthma, aspiration of foreign body.

Pulmonary infection: pneumonia, abscess, empyema, TB, bronchiectasis.
Pulmonary hypertension.
Pulmonary embolism/infarction.
Parenchymal lung disease.
Pulmonary vascular congestion.
Cardiac disease: ASHD, valvular lesions, cardiac dysrhythmias, cardiomyopathy, pericardial effusion, cardiac shunts.
Space-occupying lesions: neoplasm, large hiatal hernia, pleural effusions.
Disease of chest wall: severe kyphoscoliosis, fractured ribs, sternal compression, morbid obesity.
Neurologic dysfunction: Guillain-Barré syndrome, botulism, polio, spinal cord injury.
Interstitial pulmonary disease: sarcoidosis, collagen vascular diseases, DIP, Hamman-Rich pneumonitis, etc.
Pneumoconioses: silicosis, berylliosis, etc.
Mesothelioma.
Pneumothorax, hemothorax, pleural effusion.
Inhalation of toxins.
Cholinergic drug intoxication.
Carcinoid syndrome.
Hematologic: anemia, polycythemia, hemoglobinopathies.
Thyrotoxicosis, myxedema.
Diaphragmatic compression caused by abdominal distention, subphrenic abscess, ascites.
Lung resection.
Metabolic abnormalities: uremia, hepatic coma, DKA.
Sepsis.
Atelectasis.
Psychoneurosis.
Diaphragmatic paralysis.
Pregnancy.

DYSTONIA, PEDIATRIC PATIENT[84]

ICD-10CM #	G24.9	Dystonia, unspecified
	G24.2	Idiopathic nonfamilial dystonia
	G24.1	Genetic torsion dystonia

CAUSES OF DYSTONIA IN CHILDHOOD

Static Injury/Structural Disorders
Cerebral palsy.
Hypoxic-ischemic injury.
Kernicterus.
Head trauma.
Encephalitis.
Tumors.
Stroke in the basal ganglia (which may be due to vascular abnormalities or varicella).
Congenital malformations affecting basal ganglia.
Hereditary/Degenerative Disorders
DYT1 (autosomal dominant, Torsin A).
DYT2 (autosomal-recessive, Hippocalcin).
DYT4 (autosomal dominant, β-tubulin 4a).
DYT5 (autosomal dominant, GTP cyclohydrolase 1).
DYT6 (autosomal dominant, THAP1).
DYT8 (autosomal dominant, Myofibrillogenesis regulator 1).
DYT9 (autosomal dominant, GLUT1).
DYT10 (autosomal dominant, PRRT2).
DYT11 (autosomal dominant [maternal imprinting], ε-Sarcoglycan).
DYT12 (autosomal dominant, Na^+/K^+ATPase α3 subunit).
DYT15 (autosomal dominant, unknown).
DYT16 (autosomal recessive, Protein kinase activator PRKRA).
Pantothenate kinase-associated neurodegeneration (PKAN; neuronal brain iron accumulation type 1, due to mutations in *PANK2*).
PLA2G6-associated neurodegeneration (PLAN).
Huntington disease (Westphal variant, IT15–4p16.3).
Spinocerebellar ataxias (SCAs, particularly SCA3/Machado-Joseph disease).
Striatal necrosis.
Leigh syndrome.
Neuroacanthocytosis.
HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration).
Tay-Sachs disease.
Sandhoff disease.
Niemann-Pick type C.
Metabolic Disease
Glutaric aciduria types 1 and 2.
Acyl-CoA dehydrogenase deficiencies.
Neurotransmitter disorders.
Mitochondrial disorders.
GM_1 gangliosidosis.
Lesch-Nyhan disease.
Wilson disease.
Vitamin E deficiency.
Methylmalonic aciduria.
Tyrosinemia.
Drugs/Toxins
Neuroleptic and neuroleptic-like antiemetic medications (haloperidol, chlorpromazine, olanzapine, risperidone, prochlorperazine).
Calcium channel blockers.
Stimulants (amphetamine, cocaine, ergot alkaloids).
Anticonvulsants (carbamazepine, phenytoin).
Thallium.
Manganese.
Carbon monoxide.
Ethylene glycol.
Cyanide.
Methanol.
Paroxysmal Disorders
Paroxysmal kinesigenic dyskinesia (PKD).
Paroxysmal nonkinesigenic dyskinesia (PNKD).
Exercise-induced dyskinesia (PED).

DYSURIA

ICD-10CM #	R30.0	Dysuria
	R30.9	Painful micturition, unspecified

Urinary tract infection.
Estrogen deficiency (in postmenopausal female).
Vaginitis.
Genital infection (e.g., herpes, condyloma).
Interstitial cystitis.
Chemical irritation (e.g., deodorant aerosols, douches).
Meatal stenosis or stricture.
Reiter syndrome.
Bladder neoplasm.
GI etiology (diverticulitis, Crohn disease).
Impaired bladder or sphincter action.
Urethral carbuncle.
Chronic fibrosis posttrauma.
Radiation therapy.
Prostatitis.
Urethritis (gonococcal, *Chlamydia*).
Behçet syndrome.
Stevens-Johnson syndrome.

EARACHE[76]

ICD-10CM #	H92.09	Otalgia, unspecified ear

Otitis media.
Serous otitis media.
Eustachitis.
Otitis externa.
Otitic barotrauma.
Mastoiditis.
Foreign body.
Impacted cerumen.
Referred otalgia, as with TMJ dysfunction, dental problems, and tumors.

ECTOPIC ACTH SECRETION[32]

ICD-10CM #	E34.2	Ectopic hormone secretion, not elsewhere classified

Small cell carcinoma of lung.
Endocrine tumors of foregut origin.
Thymic carcinoid.
Islet cell tumor.
Medullary carcinoid, thyroid.
Bronchial carcinoid.
Pheochromocytoma.
Ovarian tumors.

EDEMA, CHILDREN[43]

ICD-10CM #	R60.0	Localized edema
	R60.1	Generalized edema
	R60.9	Edema, unspecified

CARDIOVASCULAR

Congestive heart failure.
Acute thrombi or emboli.
Vasculitis of many types.

RENAL

Nephrotic syndrome.
Glomerulonephritis of many types.
End-stage renal failure.

ENDOCRINE OR METABOLIC

Thyroid disease.
Starvation.
Hereditary angioedema.

IATROGENIC

Drugs (diuretics and steroids).
Water or salt overload.

Pulmonary infection: pneumonia, abscess, empyema, TB, bronchiectasis.
Pulmonary hypertension.
Pulmonary embolism/infarction.
Parenchymal lung disease.
Pulmonary vascular congestion.
Cardiac disease: ASHD, valvular lesions, cardiac dysrhythmias, cardiomyopathy, pericardial effusion, cardiac shunts.
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Diaphragmatic compression caused by abdominal distention, subphrenic abscess, ascites.
Lung resection.
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Calcium channel blockers.
Stimulants (amphetamine, cocaine, ergot alkaloids).
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Carbon monoxide.
Ethylene glycol.
Cyanide.
Methanol.
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GI etiology (diverticulitis, Crohn disease).
Impaired bladder or sphincter action.
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Islet cell tumor.
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Bronchial carcinoid.
Pheochromocytoma.
Ovarian tumors.

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Acute thrombi or emboli.
Vasculitis of many types.

RENAL

Nephrotic syndrome.
Glomerulonephritis of many types.
End-stage renal failure.

ENDOCRINE OR METABOLIC

Thyroid disease.
Starvation.
Hereditary angioedema.

IATROGENIC

Drugs (diuretics and steroids).
Water or salt overload.

HEMATOLOGIC
Hemolytic disease of the newborn.

GASTROINTESTINAL
Hepatic cirrhosis.
Protein-losing enteritis.
Lymphangiectasis.
Cystic fibrosis.
Celiac disease.
Enteritis of many types.

LYMPHATIC ABNORMALITIES
Congenital (gonadal dysgenesis).
Acquired.

EDEMA, GENERALIZED

ICD-10CM #		
	R60.0	Localized edema
	R60.1	Generalized edema
	R60.9	Edema, unspecified

Congestive heart failure (CHF).
Cirrhosis.
Nephrotic syndrome.
Pregnancy.
Idiopathic.
Acute nephritic syndrome.
Myxedema.
Medications (NSAIDs, estrogens, vasodilators).

EDEMA, LEG, UNILATERAL[58]

ICD-10CM #		
	R60.0	Localized edema
	R60.9	Edema, unspecified

WITH PAIN
DVT.
Postphlebitic syndrome.
Popliteal cyst rupture.
Gastrocnemius rupture.
Cellulitis.
Psoas or other abscess.

WITHOUT PAIN
DVT.
Postphlebitic syndrome.
Other venous insufficiency (after saphenous vein harvest, varicosities).
Lymphatic obstruction/lymphedema (carcinoma, lymphoma, sarcoidosis, filariasis, retroperitoneal fibrosis).

EDEMA OF LOWER EXTREMITIES

ICD-10CM #		
	R60.0	Localized edema
	R60.9	Edema, unspecified

CHF (right-sided).
Hepatic cirrhosis.
Nephrosis.
Myxedema.
Lymphedema.
Pregnancy.
Abdominal mass: neoplasm, cyst.
Venous compression from abdominal aneurysm.
Varicose veins.
Bilateral cellulitis.
Bilateral thrombophlebitis.
Vena cava thrombosis, venous thrombosis.
Retroperitoneal fibrosis.

EJECTION SOUND OR CLICK

ICD-10CM #		
	R01.2	Other cardiac sounds

Aortic regurgitation.
Aortic root dilatation.
Systemic hypertension.
Chronic pulmonary hypertension.
Tetralogy of Fallot.
Atrial septal defect.
Pulmonary valve stenosis.
Aortic aneurysm.

ELBOW PAIN

ICD-10CM #		
	M25.529	Pain in unspecified elbow

Trauma.
Infection.
Inflammatory arthritis.
Lateral or medial epicondylitis.
Entrapment neuropathy.
Olecranon bursitis.
Osteoarthritis.
Gout.
Cervical disease (referred pain).
Shoulder disease (referred pain).
Partial subluxation.
Synovial osteochondromatosis.
Loose body.

ELEVATED HEMIDIAPHRAGM

ICD-10CM #		
	J98.6	Disorders of diaphragm
	Q79.0	Congenital diaphragmatic hernia
	Q79.1	Other congenital malformations of diaphragm

Neoplasm (bronchogenic carcinoma, mediastinal neoplasm, intrahepatic lesion).
Substernal thyroid.
Infectious process (pneumonia, empyema, TB, subphrenic abscess, hepatic abscess).
Atelectasis.
Idiopathic.
Eventration.
Phrenic nerve dysfunction (myelitis, myotonia, herpes zoster).
Trauma to phrenic nerve or diaphragm (e.g., surgery).
Aortic aneurysm.
Intraabdominal mass.
Pulmonary infarction.
Pleurisy.
Radiation therapy.
Rib fracture.

EMBOLI, ARTERIAL[58]

ICD-10CM #		
	I74.3	Embolism and thrombosis of arteries of the lower extremities
	I74.2	Embolism and thrombosis of arteries of the upper extremities

Myocardial infarction with mural thrombi.
Atrial fibrillation.
Cardiomyopathies.
Prosthetic heart valves.
CHF.
Endocarditis.
Left ventricular aneurysm.
Left atrial myxoma.
Sick sinus syndrome.
Paradoxical embolus from venous thrombosis.
Aneurysms of large blood vessels.
Atheromatous ulcers of large blood vessels.

EMESIS, PEDIATRIC AGE[43]

ICD-10CM #		
	R11.10	Vomiting, unspecified
	R11.11	Vomiting without nausea
	R11.12	Projectile vomiting

INFANCY
Gastrointestinal Tract
Congenital
Regurgitation: chalasia, gastroesophageal reflux.
Atresia: stenosis (tracheoesophageal fistula, prepyloric diaphragm, intestinal atresia).
Duplication.
Volvulus (errors in rotation and fixation, Meckel diverticulum).
Congenital bands.
Hirschsprung disease.
Meconium ileus (cystic fibrosis), meconium plug.
Acquired
Acute infectious gastroenteritis, food poisoning (staphylococcal, clostridial).
Pyloric stenosis.
Gastritis, duodenitis.
Intussusception.
Incarcerated hernia—inguinal, internal secondary to old adhesions.
Cow's milk protein intolerance, food allergy, eosinophilic gastroenteritis.
Disaccharidase deficiency.
Celiac disease—presents after introduction of gluten in diet; inherited risk.
Adynamic ileus—the mediator for many nongastrointestinal causes.
Neonatal necrotizing enterocolitis.
Chronic granulomatous disease with gastric outlet obstruction.
Nongastrointestinal Tract
Infectious: otitis, urinary tract infection, pneumonia, upper respiratory tract infection, sepsis, meningitis.
Metabolic: aminoaciduria and organic aciduria, galactosemia, fructosemia, adrenogenital syndrome, renal tubular acidosis, diabetic ketoacidosis, Reye syndrome.
CNS: trauma, tumor, infection, diencephalic syndrome, rumination, autonomic responses (pain, shock).
Medications: anticholinergics, aspirin, alcohol, idiosyncratic reaction (e.g., codeine).

CHILDHOOD
Gastrointestinal Tract
Peptic ulcer—vomiting is a common presentation in children younger than 6 yr old.

Trauma: duodenal hematoma, traumatic pancreatitis, perforated bowel.
Pancreatitis: mumps, trauma, cystic fibrosis, hyperparathyroidism, hyperlipidemia, organic acidemias.
Crohn disease.
Idiopathic intestinal pseudoobstruction.
Superior mesenteric artery syndrome.
Nongastrointestinal Tract
CNS: cyclic vomiting, migraine, anorexia nervosa, bulimia.

ENCEPHALOMYELITIS, NONVIRAL CAUSES[58]

ICD-10CM #		
	G04.81	Other encephalitis and encephalomyelitis

Subacute bacterial endocarditis.
Rocky Mountain spotted fever.
Typhus.
Ehrlichia.
Q fever.
Chlamydia.
Mycoplasma.
Legionella.
Brucellosis.
Listeria.
Whipple disease.
Cat-scratch disease.
Syphilis (meningovascular).
Relapsing fever.
Lyme disease.
Leptospirosis.
Nocardia.
Actinomycosis.
Tuberculosis.
Cryptococcus.
Histoplasma.
Toxoplasma.
Plasmodium falciparum.
Trypanosomiasis.
Behçet disease.
Vasculitis.
Carcinoma.
Drug reactions.

ENCEPHALOPATHY, HYPERTENSIVE[88]

ICD-10CM #	Varies with specific diagnosis

Cerebral infarction.
Subarachnoid hemorrhage.
Intracerebral hemorrhage.
Subdural or epidural hematoma.
Brain tumor or other mass lesion.
Seizure disorder.
CNS vasculitis.
Encephalitis/meningitis.
Drug ingestion.
Drug withdrawal.

ENCEPHALOPATHY, METABOLIC[82]

ICD-10CM #		
	F10.27	Alcohol dependence with alcohol-induced persisting dementia
	K72.90	Hepatic failure, unspecified without coma
	K72.91	Hepatic failure, unspecified with coma
	G92	Toxic encephalopathy
	T56.0X1A	Toxic effect of lead and its compounds, accidental (unintentional), initial encounter
	T56.0X2A	Toxic effect of lead and its compounds, intentional self-harm, initial encounter

Substrate deficiency: hypoxia/ischemia, carbon monoxide poisoning, hypoglycemia.
Cofactor deficiency: thiamine, vitamin B_{12}, pyridoxine (INH administration).
Electrolyte disorders: hyponatremia, hypercalcemia, carbon dioxide narcosis, dialysis, hypermagnesemia, disequilibrium syndrome.
Endocrinopathies: DKA, hyperosmolar coma, hypothyroidism, hyperadrenocorticism, hyperparathyroidism.
Endogenous toxins: liver disease, uremia, porphyria.
Exogenous toxins: drug overdose (sedative/hypnotics, ethanol, narcotics, salicylates, tricyclic antidepressants), drug withdrawal, toxicity of therapeutic medications, industrial toxins (e.g., organophosphates, heavy metals), sepsis.
Heat stroke.
Epilepsy (postictal).

ENDOMETRIAL THICKENING[74]

ICD-10CM #	Varies with specific diagnosis

CAUSES OF ENDOMETRIAL THICKENING

Early intrauterine pregnancy.
Incomplete abortion.
Ectopic pregnancy.
Retained products of conception.
Trophoblastic disease.
Endometritis.
Adhesions.
Hyperplasia.
Polyps.
Carcinoma.

ENTERIC FEVER[19]

ICD-10CM #		
	A01.00	Typhoid fever, unspecified
	A01.3	Paratyphoid fever
	R50.9	Fever, unspecified

Epstein-Barr infection.
Dengue.
Tuberculosis.
Brucellosis.
Bartonella henselae.
Leptospirosis.
Tularemia.
Ehrlichiosis.
Plague.
Typhus.
Malaria.
Disseminated histoplasmosis.

ENTHESOPATHY

ICD-10CM #		
	M46.00	Spinal enthesopathy, site unspecified

Viremia or bacteremia.
Ankylosing spondylitis.
Psoriatic arthritis.
Drug-induced (quinolones, etretinate).
Reactive arthritis.
DISH.
Reiter syndrome.

EOSINOPHILIA, DISEASE ASSOCIATIONS[57]

ICD-10CM #		
	D72.1	Eosinophilia
	NEC J82	Eosinophilia, pulmonary

DISEASES, SYNDROMES, AND CONDITIONS COMMONLY ASSOCIATED WITH PERIPHERAL BLOOD EOSINOPHILIA AND/OR TISSUE EOSINOPHILIA

Infectious Agents
Parasitic Infections
Tropical eosinophilia.
Visceral larval migrans (VLM, toxocariasis).
Helminth infections.
Filariasis (*Wuchereria bancrofti, Brugia malayi*).
Onchocerciasis.
Schistosomiasis.
Fascioliasis.
Paragonimiasis.
Strongyloidiasis.
Trichinosis.
Hookworm.
Ascariasis.
Echinococcosis/hydatid disease.
Fungal Infections
Coccidioidomycosis.
Cryptococcosis (CSF eosinophilia) in HIV.
Allergic Diseases
Asthma (atopic and intrinsic, nasal polyps, aspirin intolerance syndromes).
Bronchopulmonary aspergillosis.
Allergic rhinitis.
Urticarias (acute allergic and chronic idiopathic).
Atopic dermatitis.
Acute drug (hypersensitivity) reactions (interstitial nephritis, cholestatic hepatitis, exfoliative dermatitis).
Respiratory Tract Disorders
Hypersensitivity pneumonitis (rare).
Allergic bronchopulmonary aspergillosis.
Eosinophilic pneumonia.
Transient pulmonary infiltrates (Löeffler syndrome).
Prolonged pulmonary infiltrates with eosinophilia (PIE syndrome).
Tropical pulmonary eosinophilia (TPE).
Bronchiectasis.
Cystic fibrosis.
Endocrinologic Disorders
Addison disease.

Gastrointestinal Diseases
Inflammatory bowel disease (IBD).
Eosinophilic gastroenteritis, eosinophilic esophagitis (EE).
Allergic gastroenteritis (young children).
Celiac disease (when associated with EE).
Toxic Reactions to Ingested Agents
Eosinophil myalgia syndrome (L-tryptophan).
Toxic oil syndrome.
Reactions to Cytokine Therapies
IL-2 and IL-2 plus lymphokine activated killer (LAK) cells.
GM-CSF therapy.
Cutaneous Disorders
Atopic dermatitis.
Immunologic skin diseases.
Scabies.
Myiasis.
Chlamydial pneumonia of infancy.
Scarlet fever and pneumococcal pneumonia (convalescent phase).
Cat scratch disease.
Eosinophilic cellulitis (Wells syndrome).
Episodic angioedema with eosinophilia.
Chronic idiopathic urticaria.
Bullous pemphigoid.
Herpes gestationis.
Angioblastic lymphoid hyperplasia (Kimura disease).
Immunodeficiency Syndromes
Wiskott-Aldrich syndrome.
Selective IgA deficiency with atopy.
Hyper-IgE recurrent infection syndrome (Job syndrome).
Swiss-type and sex-linked combined immunodeficiency.
Nezelof syndrome.
Graft-versus-host-disease (GVHD).
Connective Tissue Diseases
Vasculitis/Collagen Vascular Disorders
Hypersensitivity vasculitis.
Allergic granulomatosis with angiitis (Churg-Strauss syndrome).
Serum sickness.
Eosinophilic fasciitis.
Sjögren syndrome.
Rheumatoid arthritis (severe).
Neoplastic, Myeloproliferative, and Lymphoproliferative Neoplasms and Syndromes
Neoplastic
Ovarian carcinoma.
Solid tumors (mucin-secreting, epithelial cell origin).
Chronic eosinophil leukemia.
Idiopathic hypereosinophilic syndromes (HES).
Systemic mastocytosis.
Myeloproliferative
Chronic myelogenous leukemia (CML) acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS).
Myelomonocytic leukemia with bone marrow eosinophilia (M4Eo, inversion 16).
Lymphoproliferative
T-cell lymphocytic leukemia.
Lymphomas (T cell, Hodgkin disease).
Angioimmunoblastic lymphadenopathy.
Rare Causes
Chronic active hepatitis.
Chronic dialysis.
Acute pancreatitis.
Postirradiation.
Hypopituitarism.

EOSINOPHILIA, GI[26]

ICD-10CM # D72.1 Eosinophilia

CAUSES OF GI EOSINOPHILIA

GERD
Eosinophilic GI disorders:
Eosinophilic esophagitis:
Connective tissue disease-associated eosinophilic esophagitis.
Familial eosinophilic esophagitis.
Eosinophilic gastritis.
Eosinophilic enteritis.
Eosinophilic gastroenteritis.
Infections:
Schistosomiasis.
Anisakiasis.
GI basidiobolomycosis.
Toxocariasis.
Celiac disease.
Hypereosinophilic syndrome.
Drug hypersensitivity response.
IBD.
Transplant-associated eosinophilic enteritis.
Eosinophilic granulomatosis with polyangiitis.
Toxic injury.
Graft-versus-host disease.

EOSINOPHILIC LUNG DISEASE[36]

ICD-10CM # NEC J82 Eosinophilia, pulmonary

IDIOPATHIC

Simple pulmonary eosinophilia (Löffler syndrome).
Acute eosinophilic pneumonia.
Chronic eosinophilic pneumonia.
Hypereosinophilic syndrome.

DRUG-INDUCED

Aminosalicylic acid.
Para-aminosalicylic acid.
NSAIDs.
Captopril.
Cocaine.
Minocycline.
Nitrofurantoin.
Phenytoin.

INFECTION

Parasitic (ascariasis, paragonimiasis. tropical eosinophilia).
Fungal (aspergillus).
Bacterial (TB, atypical mycobacterial infection, brucella).
Viral (respiratory syncytial virus).

IMMUNOLOGIC DISEASES

Granulomatosis with polyangiitis.
Churg–Strauss syndrome.
Rheumatoid disease.
Sarcoidosis.

NEOPLASMS

Bronchogenic carcinoma.
Bronchial carcinoid.
Lymphoma (Hodgkin, non-Hodgkin).

EOSINOPHILIA, PARASITIC CAUSES[10]

ICD-10CM # Varies with specific diagnosis

PARASITIC CAUSES OF EOSINOPHILIA

Widespread Geographic Distribution
Ascariasis (migratory phase).
Hookworm.†
Strongyloidiasis.*‡
Tropical pulmonary eosinophilia.
Lymphatic filariasis.
Schistosomiasis.
Toxocariasis.
Cysticercosis (*Taenia solium*).
Echinococcosis (cyst rupture).
Trichinosis.
Trichuriasis.
Aberrant helminthiasis from animals.
Limited Geographic Distribution
Clonorchiasis.
Paragonimiasis.
Fascioliasis.
Angiostrongyliasis.
Opisthorchiasis.
Onchocerciasis, loiasis, and other nonlymphatic filariases.
Gnathostomiasis.
Capillariasis.
Trichostrongyliasis.

EPIGASTRIC PAIN[86]

ICD-10CM #	R10.816	Epigastric abdominal tenderness
	R10.826	Epigastric rebound abdominal tenderness

Peptic ulceration (uncomplicated).[18]
Peptic ulceration (perforated).
Biliary colic.
Acute pancreatitis.
Abdominal aortic aneurysm.
Anxiety.
Inferior wall MI.

EPILEPSY

ICD-10CM #	G40.909	Epilepsy, unspecified, not intractable, without status epilepticus

Psychogenic spells.

† Moderate to marked during larval migration in early infection; most often absent or very mild during chronic infection.
* Most frequent parasitic causes of massive eosinophilia (>5000/mm^3).
‡ Absent in disseminated infection in compromised hosts.
[18] Conditions that also cause right upper quadrant pain.

Transient ischemic attack.
Hypoglycemia.
Syncope.
Narcolepsy.
Migraine.
Paroxysmal vertigo.
Arrhythmias.
Drug reaction.

EPILEPSY MIMICS, PEDIATRIC PATIENT[84]

ICD-10CM # Varies with specific diagnosis

DISORDERS THAT MAY MIMIC CHILDHOOD EPILEPSY

Confused with Generalized Tonic–Clonic Seizures

Pallid syncope (reflex anoxic seizure).
Vasodepressor syncope (reflex anoxic seizure).
Cyanotic breath-holding attacks.
Collapsing attacks with cardiac dysrhythmias.
Cataplexy.

Confused with Generalized Absence Seizures

Behavioral staring attacks.
Complex partial (dyscognitive) seizures.
Tic disorder.

Confused with Complex Partial (Dyscognitive) Seizures

Self-stimulatory behavior, especially in children with autistic spectrum disorders.
Sleep walking.
Night terrors.
Temper tantrums with amnesia for the rage event.
Benign paroxysmal vertigo.
Migraine-related disorders.

Confused with Epileptic Myoclonus

Physiologic hypnagogic myoclonus.
Benign infantile sleep myoclonus.
Startle disease.

EPILEPSY SYNDROMES, AGE SPECIFIC[19]

ICD-10CM #	G40.90	Epilepsy, unspecified, not intractable
	G40.301	Generalized idiopathic epilepsy and epileptic syndromes, not intractable, with status epilepticus
	G40.40	Other generalized epilepsy and epileptic syndromes, not intractable

EPILEPSY SYNDROMES BY AGE OF ONSET

Neonatal

Benign familial neonatal epilepsy.
Early myoclonic encephalopathy.
Ohtahara syndrome.

Infancy

Epilepsy of infancy with migrating focal seizures.
West syndrome (infantile spasms, hypsarrhythmia; to be distinguished from benign myoclonus of early infancy, a nonepilepsy).
Myoclonic epilepsy in infancy (benign Dravet variant).
Benign infantile epilepsy.
Benign familial infantile epilepsy.
Severe myoclonic epilepsy of infancy (classic Dravet syndrome).
Myoclonic encephalopathy in nonprogressive disorders.

Childhood

Genetic epilepsy with febrile seizures plus (GEFS +; can begin in infancy).
Panayiotopoulos syndrome.
Epilepsy with myoclonic atonic (previously astatic) seizures (Doose syndrome).
Benign epilepsy with centrotemporal spikes (BECTS, or benign rolandic epilepsy).
Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE).
Late-onset childhood occipital epilepsy (Gastaut syndrome).
Epilepsy with myoclonic absences (Tassinari syndrome).
Lennox–Gastaut syndrome.
Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS).
Landau–Kleffner syndrome (LKS).
Childhood absence epilepsy (pyknolepsy).
Generalized epilepsy with eyelid myoclonia (Jeavons syndrome).*

Adolescence–Adult

Juvenile absence epilepsy (JAE).
Juvenile myoclonic epilepsy (JME).
Epilepsy with generalized tonic-clonic seizures alone.
Progressive myoclonus epilepsies (PME).
Autosomal-dominant epilepsy with auditory features.
Other familial temporal lobe epilepsies.

Less Specific Age Relationship

Familial focal epilepsy with variable foci (childhood to adult).
Reflex epilepsies (e.g., photosensitive, audiogenic, or reading-induced seizures; may or may not coexist with spontaneous seizures).

EPISTAXIS

ICD-10CM # R04.0 Epistaxis

Trauma.
Medications (nasal sprays, NSAIDs, anticoagulants, antiplatelets).
Nasal polyps.
Cocaine use.
Coagulopathy (hemophilia, liver disease, DIC, thrombocytopenia).
Systemic disorders (hypertension, uremia).
Infections.
Anatomic malformations.
Rhinitis.
Nasal polyps.
Local neoplasms (benign and malignant).
Desiccation.
Foreign body.

*Not listed as a syndrome by ILAE but instead recognized under absence seizures with special features.

ERECTILE DYSFUNCTION, ORGANIC[72]

ICD-10CM # N52.9 Male erectile dysfunction, unspecified

Neurogenic abnormalities: somatic nerve neuropathy, CNS abnormalities.
Psychogenic causes: depression, performance anxiety, marital conflict.
Endocrine causes: hyperprolactinemia, hypogonadotropic hypogonadism, testicular failure, estrogen excess.
Trauma: pelvic fracture, prostate surgery, penile fracture.
Systemic disease: DM, renal failure, hepatic cirrhosis.
Medications: diuretics, antidepressants, H_2 blockers, exogenous hormones, alcohol, antihypertensives, nicotine abuse, finasteride, etc.
Structural abnormalities: Peyronie disease.

EROSIONS, GENITALIA

ICD-10CM # N36.8 Other specified disorders of urethra

Candidiasis.
Intraepithelial neoplasia.
Squamous cell carcinoma.
Lichen planus.
Pemphigus vulgaris.
Erythema multiforme.
Lichen sclerosus.
Bullous pemphigoid.
Extramammary Paget disease.
Impetigo.

ERYTHEMATOUS ANNULAR SKIN LESIONS

ICD-10CM # L53.8 Other specified erythematous conditions

Tinea corporis.
Warfarin plaques.
Erythema multiforme.
Erythema annulare.
Cutaneous lupus.
Cutaneous sarcoidosis.
Trauma.
Acute febrile neutrophilic dermatosis (Sweet syndrome).

ERYTHROCYTOSIS[45]

ICD-10CM # D75.0 Familial erythrocytosis

CAUSES OF ERYTHROCYTOSIS

Relative or Spurious Erythrocytosis (Normal Red Cell Mass)

Hemoconcentration secondary to dehydration (diarrhea, diaphoresis, diuretics, water deprivation, emesis, ethanol, hypertension, preeclampsia, pheochromocytoma, carbon monoxide intoxication).

True or Absolute Erythrocytosis

Polycythemia vera.
Primary congenital polycythemia.

Secondary erythrocytosis caused by:
- Congenital causes (e.g., activating mutation of erythropoietin receptor).
- Hypoxia caused by carbon monoxide poisoning, high oxygen affinity hemoglobin, high-altitude residence, chronic pulmonary disease, hypoventilation syndromes such as sleep apnea, right to left cardiac shunt, neurologic defects involving the respiratory center.

Nonhypoxic causes with pathologic erythropoietin production.
Renal disease (cysts, hydronephrosis, renal artery stenosis, focal glomerulonephritis, renal transplantation).
Tumors (renal cell cancer, hepatocellular carcinoma, cerebellar hemangioblastoma, uterine fibromyoma, adrenal tumors, meningioma, pheochromocytoma).
Drug-associated causes:
Androgen therapy.
- Exogenous erythropoietin growth factor therapy.

ERYTHRODERMA

ICD-10CM # L53.9 Erythematous condition, unspecified

Drug reaction (e.g., allopurinol, ampicillin, phenytoin, vancomycin, dapsone, omeprazole, carbamazepine).
Atopic dermatitis.
Psoriasis.
Contact dermatitis.
Idiopathic.
Pityriasis rubra.
Chronic actinic dermatitis.
Bullous pemphigoid.
Paraneoplastic.
Cutaneous T-cell lymphoma.
Connective tissue disease.
Hypereosinophilia syndrome.

ESOPHAGEAL PERFORATION[58]

ICD-10CM # K22.3 Perforation of esophagus
S27.819A Unspecified injury of esophagus (thoracic part), initial encounter

Trauma.
Caustic burns.
Iatrogenic.
Foreign bodies.
Spontaneous rupture (Boerhaave syndrome).
Postoperative breakdown of anastomosis.

ESOPHAGEAL STRICTURES[77]

ICD-10CM # Varies with specific diagnosis

BENIGN

Congenital
Esophageal atresia.
Tracheoesophageal fistula.
Web.

ACQUIRED

Peptic:
- Gastroesophageal reflux.
- Scleroderma.

Schatzki ring.
Caustic ingestion.
Drug-induced:
- Anticholinergic medications.
- Aspirin.
- Ferrous sulfate.
- Fosamax.
- Nonsteroidal antiinflammatory.
- Quinidine.
- Potassium supplements.
- Tetracycline.
- Vitamin C.

Eosinophilic esophagitis.
Iatrogenic:
- Variceal ligation/injection.
- Endoscopic mucosal resection.
- Ablation therapy (cryotherapy/radiofrequency).
- Postoperative (anastomotic).
- Radiation.
- Instrumentation.
- Nasogastric tube.

Infections:
- Fungal: moniliasis.
- Bacterial: syphilis.
- Mycobacterial: tuberculosis.

Granulomatous:
- Crohn disease.

Dermatosis:
- Epidermolysis bullosa dystrophica.
- Pemphigoid.
- Behçet syndrome.

MALIGNANT

Primary.
Secondary.

ESOPHAGEAL TUMORS, BENIGN[77]

ICD-10CM # Varies with specific diagnosis

CLASSIFICATION OF BENIGN ESOPHAGEAL TUMORS

Mucosa (First and Second Esophageal Ultrasound [EUS] Layers)
Squamous papilloma.
Fibrovascular polyp.
Retention cyst.
Submucosa (Third EUS Layer)
Lipoma.
Fibroma.
Neurofibroma.
Granular cell tumor.
Hemangiomas.
Salivary gland–type tumor.
Muscularis Propria (Fourth EUS Layer)
Leiomyoma.
Duplication cyst.
Periesophageal Tissue (Fifth EUS Layer)
Foregut cyst.

ESOPHAGITIS[58]

ICD-10CM # K20.9 Esophagitis, unspecified

INFECTIOUS

Candidiasis.
Cytomegalovirus.
Herpes simplex virus.
HIV infection, acute.

NONINFECTIOUS

Gastroesophageal reflux.
Mucositis from cancer chemotherapy.
Mucositis from radiation therapy.
Aphthous ulcers.

ESOPHAGUS, SYSTEMIC DISEASES[77]

ICD-10CM # Varies with specific diagnosis

SYSTEMIC DISEASES OF THE ESOPHAGUS

Connective Tissue Disorders
Scleroderma.
Systemic lupus erythematosus.
Polymyositis.
Dermatomyositis.
Mixed connective tissue disorder.
Raynaud phenomenon.
Allergic Disease
Eosinophilic esophagitis.
Metabolic Diseases
Amyloidosis.
Diabetes mellitus.
Hypothyroidism.
Hyperthyroidism.
Dermatologic Diseases
Epidermolysis bullosa.
Pemphigus vulgaris.
Pemphigoid.
Erythema multiforme.
Lichen planus.
Behçet disease.
Infectious Diseases
Histoplasmosis.
Tuberculosis.
Actinomycosis.
Immunocompromised host:
- Fungal: *Candida* species.
- Viral: herpes simplex, cytomegalovirus.
- Mycobacterial.
- Bacterial: *Streptococcus viridans, Staphylococcus,* bacilli, *Treponema pallidum.*
- Protozoal.

Miscellaneous Disorders
Sarcoidosis.
Crohn disease.

ESOTROPIA

ICD-10CM # H50.00 Unspecified esotropia
H50.43 Accommodative component in esotropia
H50.05 Alternating esotropia

Congenital.
Accommodative esotropia.
Myasthenia gravis.
Abducens palsy.
Pseudo-sixth nerve palsy.
Medial rectus entrapment (e.g., blowout fracture).
Posterior internuclear ophthalmoplegia.
Wernicke encephalopathy.
Thyroid myopathy.
Chiari malformation.

EXANTHEMS[65]

ICD-10CM # R21 Rash and other nonspecific skin eruption

Measles.
Rubella.
Erythema infectiosum (fifth disease).
Roseola exanthema.
Varicella.
Enterovirus.
Adenovirus.
Epstein-Barr virus.
Kawasaki disease.
Staphylococcal scalded skin.
Scarlet fever.
Meningococcemia.
Rocky Mountain spotted fever.

EYELID NEOPLASM

ICD-10CM # C44.101 Unspecified malignant neoplasm of skin of unspecified eyelid, including canthus

MALIGNANT

Melanoma.
Basal cell carcinoma.
Squamous cell carcinoma.
Bowen disease.
Sebaceous cell carcinoma.
Metastatic lymphoma/leukemia.

BENIGN

Melanocytic nevus.
Pilar, eccrine, or apocrine tumor.
Neurofibroma.
Keratosis.
Squamous papilloma.
Keratoacanthoma.

EYELID RETRACTION

ICD-10CM # H02.89 Other specified disorders of eyelid

Congenital.
Graves ophthalmopathy.
Myasthenia gravis.
Postsurgical.
Guillain-Barré syndrome.
Cerebellar disease.
Horizontal gaze palsy.
Partial palsy of superior rectus muscle.
Encephalitis.
Closed head injury.
Disseminated sclerosis.
Eye trauma.
Contact lens wear.
Proptosis.
Eyelid neoplasm.
Atopic dermatitis.
Herpes zoster ophthalmicus.
Botulinum toxin injection.
Cyclic oculomotor paralysis.
Spheroid wing meningioma.
Hepatic cirrhosis.
Down syndrome.
Essential hypertension.
Meningitis.
Paget disease of bone.

EYE PAIN

ICD-10CM # H57.13 Ocular pain, bilateral

Foreign body.
Herpes zoster.
Trauma.
Conjunctivitis.
Iritis.
Iridocyclitis.
Uveitis.
Blepharitis.
Ingrown lashes.
Orbital or periorbital cellulitis/abscess.
Sinusitis.
Headache.
Glaucoma.
Inflammation of lacrimal gland.
Tic douloureux.
Cerebral aneurysm.
Cerebral neoplasm.
Entropion.
Retrobulbar neuritis.
UV light.
Dry eyes.
Irritation or inflammation from eye drops, dust, cosmetics, etc.

FACIAL PAIN

ICD-10CM # G50.1 Atypical facial pain

Infection, abscess.
Postherpetic neuralgia.
Trauma, posttraumatic neuralgia.
Tic douloureux.
Cluster headache, "lower-half headache."
Geniculate neuralgia.
Anxiety, somatization syndrome.
Glossopharyngeal neuralgia.
Carotidynia.

FACIAL PARALYSIS[65]

ICD-10CM # G51.0 Bell palsy

INFECTION

Bacterial: otitis media, mastoiditis, meningitis, Lyme disease.
Viral: herpes zoster, mononucleosis, varicella, rubella, mumps, Bell palsy.
Mycobacterial: TB, meningitis, leprosy.
Miscellaneous: syphilis, malaria.

TRAUMA

Temporal bone fracture, facial laceration.
Surgery.

NEOPLASM

Malignant: squamous cell carcinoma, basal cell and adenocystic tumors, leukemia, parotid neoplasms, metastatic tumors.
Benign: facial nerve neuroma, vestibular schwannoma, congenital cholesteatoma.

IMMUNOLOGIC

Guillain-Barré syndrome, periarteritis nodosa.
Reaction to tetanus antiserum.

METABOLIC

Pregnancy.
Hypothyroidism.
DM.

FAILURE TO THRIVE

ICD-10CM # R62.50 Unspecified lack of expected normal physiological development in childhood

PSYCHOSOCIAL/BEHAVIORAL

Inadequate diet because of poverty/food insufficiency, errors in food preparation.
Poor parenting skills (lack of knowledge of sufficient diet).
Child/parent interaction problems (autonomy struggles, coercive feeding, maternal depression).
Food refusal.
Rumination.
Parental cognitive or mental health problems.
Child abuse or neglect; emotional deprivation.

NEUROLOGIC

Cerebral palsy.
Hypothalamic and other CNS tumors (diencephalic syndrome).
Neuromuscular disorders.
Neurodegenerative disorders.

RENAL

Recurrent urinary tract infection.
Renal tubular acidosis.
Renal failure.

ENDOCRINE

Diabetes mellitus.
Diabetes insipidus.
Hypothyroidism/hyperthyroidism.
Growth hormone deficiency.
Adrenal insufficiency.

GENETIC/METABOLIC/CONGENITAL

Sickle cell disease.
Inborn errors of metabolism (organic acidosis, hyperammonemia, storage disease).
Fetal alcohol syndrome.
Skeletal dysplasias.

Congenital.
Accommodative esotropia.
Myasthenia gravis.
Abducens palsy.
Pseudo-sixth nerve palsy.
Medial rectus entrapment (e.g., blowout fracture).
Posterior internuclear ophthalmoplegia.
Wernicke encephalopathy.
Thyroid myopathy.
Chiari malformation.

EXANTHEMS[65]

ICD-10CM # R21 Rash and other nonspecific skin eruption

Measles.
Rubella.
Erythema infectiosum (fifth disease).
Roseola exanthema.
Varicella.
Enterovirus.
Adenovirus.
Epstein-Barr virus.
Kawasaki disease.
Staphylococcal scalded skin.
Scarlet fever.
Meningococcemia.
Rocky Mountain spotted fever.

EYELID NEOPLASM

ICD-10CM # C44.101 Unspecified malignant neoplasm of skin of unspecified eyelid, including canthus

MALIGNANT

Melanoma.
Basal cell carcinoma.
Squamous cell carcinoma.
Bowen disease.
Sebaceous cell carcinoma.
Metastatic lymphoma/leukemia.

BENIGN

Melanocytic nevus.
Pilar, eccrine, or apocrine tumor.
Neurofibroma.
Keratosis.
Squamous papilloma.
Keratoacanthoma.

EYELID RETRACTION

ICD-10CM # H02.89 Other specified disorders of eyelid

Congenital.
Graves ophthalmopathy.
Myasthenia gravis.
Postsurgical.
Guillain-Barré syndrome.
Cerebellar disease.
Horizontal gaze palsy.
Partial palsy of superior rectus muscle.
Encephalitis.
Closed head injury.
Disseminated sclerosis.
Eye trauma.
Contact lens wear.
Proptosis.
Eyelid neoplasm.
Atopic dermatitis.
Herpes zoster ophthalmicus.
Botulinum toxin injection.
Cyclic oculomotor paralysis.
Spheroid wing meningioma.
Hepatic cirrhosis.
Down syndrome.
Essential hypertension.
Meningitis.
Paget disease of bone.

EYE PAIN

ICD-10CM # H57.13 Ocular pain, bilateral

Foreign body.
Herpes zoster.
Trauma.
Conjunctivitis.
Iritis.
Iridocyclitis.
Uveitis.
Blepharitis.
Ingrown lashes.
Orbital or periorbital cellulitis/abscess.
Sinusitis.
Headache.
Glaucoma.
Inflammation of lacrimal gland.
Tic douloureux.
Cerebral aneurysm.
Cerebral neoplasm.
Entropion.
Retrobulbar neuritis.
UV light.
Dry eyes.
Irritation or inflammation from eye drops, dust, cosmetics, etc.

FACIAL PAIN

ICD-10CM # G50.1 Atypical facial pain

Infection, abscess.
Postherpetic neuralgia.
Trauma, posttraumatic neuralgia.
Tic douloureux.
Cluster headache, "lower-half headache."
Geniculate neuralgia.
Anxiety, somatization syndrome.
Glossopharyngeal neuralgia.
Carotidynia.

FACIAL PARALYSIS[65]

ICD-10CM # G51.0 Bell palsy

INFECTION

Bacterial: otitis media, mastoiditis, meningitis, Lyme disease.
Viral: herpes zoster, mononucleosis, varicella, rubella, mumps, Bell palsy.
Mycobacterial: TB, meningitis, leprosy.
Miscellaneous: syphilis, malaria.

TRAUMA

Temporal bone fracture, facial laceration.
Surgery.

NEOPLASM

Malignant: squamous cell carcinoma, basal cell and adenocystic tumors, leukemia, parotid neoplasms, metastatic tumors.
Benign: facial nerve neuroma, vestibular schwannoma, congenital cholesteatoma.

IMMUNOLOGIC

Guillain-Barré syndrome, periarteritis nodosa.
Reaction to tetanus antiserum.

METABOLIC

Pregnancy.
Hypothyroidism.
DM.

FAILURE TO THRIVE

ICD-10CM # R62.50 Unspecified lack of expected normal physiological development in childhood

PSYCHOSOCIAL/BEHAVIORAL

Inadequate diet because of poverty/food insufficiency, errors in food preparation.
Poor parenting skills (lack of knowledge of sufficient diet).
Child/parent interaction problems (autonomy struggles, coercive feeding, maternal depression).
Food refusal.
Rumination.
Parental cognitive or mental health problems.
Child abuse or neglect; emotional deprivation.

NEUROLOGIC

Cerebral palsy.
Hypothalamic and other CNS tumors (diencephalic syndrome).
Neuromuscular disorders.
Neurodegenerative disorders.

RENAL

Recurrent urinary tract infection.
Renal tubular acidosis.
Renal failure.

ENDOCRINE

Diabetes mellitus.
Diabetes insipidus.
Hypothyroidism/hyperthyroidism.
Growth hormone deficiency.
Adrenal insufficiency.

GENETIC/METABOLIC/CONGENITAL

Sickle cell disease.
Inborn errors of metabolism (organic acidosis, hyperammonemia, storage disease).
Fetal alcohol syndrome.
Skeletal dysplasias.

Chromosomal disorders.
Multiple congenital anomaly syndromes (VATER [vertebral defects, imperforate anus, tracheoesophageal fistula, radial and renal dysplasia], CHARGE [coloboma, heart disease, atresia choanae, retarded growth and retarded development and/or CNS anomalies, genital hypoplasia, ear anomalies and/or deafness]).

GASTROINTESTINAL

Pyloric stenosis.
Gastroesophageal reflux.
Repair of tracheoesophageal fistula.
Malrotation.
Malabsorption syndromes.
Celiac disease.
Milk intolerance: lactose, protein.
Pancreatic insufficiency syndromes (cystic fibrosis).
Chronic cholestasis.
Inflammatory bowel disease.
Chronic congenital diarrhea states.
Short bowel syndrome.
Pseudoobstruction.
Hirschsprung disease.
Food allergy.

CARDIAC

Cyanotic heart lesions.
Congestive heart failure.
Vascular rings.

PULMONARY/RESPIRATORY

Severe asthma.
Cystic fibrosis; bronchiectasis.
Chronic respiratory failure.
Bronchopulmonary dysplasia.
Adenoid/tonsillar hypertrophy.
Obstructive sleep apnea.

MISCELLANEOUS

Collagen vascular disease.
Malignancy.
Primary immunodeficiency.
Transplantation.

INFECTIONS

Perinatal infection (TORCHES [toxoplasma, other, rubella, cytomegalovirus, herpes simplex]).
Occult/chronic infections.
Parasitic infestation.
Tuberculosis.
HIV.

FATIGUE

ICD-10CM #		
	R53.83	Other fatigue
	F48.0	Neurasthenia

Depression.
Anxiety, emotional stress.
Inadequate sleep.
Chronic fatigue syndrome.
Prolonged physical activity.
Pregnancy and postpartum period.
Anemia.
Hypothyroidism.
Medications (β-blockers, anxiolytics, antidepressants, sedating antihistamines, clonidine, methyldopa).
Viral or bacterial infections.
Sleep apnea syndrome.
Dieting.
Renal failure, CHF, COPD, liver disease.

FATIGUE, CHRONIC

ICD-10CM #		
	R53.83	Other fatigue
	F48.0	Neurasthenia

CHRONIC INFECTIONS

Hepatitis C.
Lyme disease.
Parasitic and fungal infections.
Tuberculosis.
Human immunodeficiency virus.
Xenotropic murine leukemia retrovirus.

SLEEP DISORDERS

Obstructive sleep apnea.
Restless leg syndrome.
Circadian rhythm disorder.
Upper airway resistance syndrome.
Narcolepsy/parasomnias.
Alpha-delta sleep disorder.

ENDOCRINE/METABOLIC DISORDERS

Addison disease.
Cushing syndrome.
Poorly controlled diabetes.
Thyroid disorders.
Hemochromatosis.
Hypopituitarism.
Diabetes insipidus.

GENERAL MEDICAL DISORDERS

Anemia (any cause).
Chronic renal/hepatic failure.
Malnutrition.
Medication side effects.
Chronic pain disorders.

PSYCHOLOGICAL

Mood disorders (depression, anxiety, bipolar).
Schizophrenia.
Posttraumatic stress disorder.
Anorexia nervosa/bulimia.
Childhood abuse and/or neglect.

CHRONIC INFLAMMATION

Rheumatoid arthritis.
Systemic lupus erythematosus.
Sjögren syndrome.
Polymyositis/dermatomyositis.
Vasculitis.
Sarcoidosis.

CARDIOPULMONARY

Congestive heart failure.
Neurally mediated hypotension.
Postural orthostatic tachycardia syndrome.
Pulmonary hypertension.
Chronic obstructive pulmonary disease.
Mitral valve prolapse.

GASTROINTESTINAL

Celiac disease.
Inflammatory bowel disease.
Autoimmune hepatitis.
Hepatic cirrhosis.

MALIGNANCY

Lymphoma and occult malignancies.
Postchemotherapy syndrome.

NEUROLOGIC DISORDERS

Multiple sclerosis.
Myasthenia gravis.
Muscular dystrophies.
Parkinson disease.
Early dementia.

LIFESTYLE FACTORS

Chronic overwork.
Persistent unresolved stress.
Inadequate exercise.
Morbid obesity (body mass index >40).
Alcoholism/drug abuse.

FATTY LIVER

ICD-10CM #		
	K76.0	Fatty (change of) liver, not elsewhere classified
	K76.89	Other specified diseases of liver

Obesity.
Alcohol abuse.
DM.
Acute fatty liver of pregnancy.
Medications (tetracycline, valproic acid, glucocorticoids, amiodarone, estrogen, methotrexate).
Reye syndrome.
Wilson disease.
Nonalcoholic steatosis.

FEVER, ABDOMINAL PAIN, JAUNDICE IN PEDIATRIC PATIENT[19]

ICD-10CM #		
	R50.9	Fever, unspecified

Cholangitis.
Cholecystitis.
Cholelithiasis.
Sepsis.
Hepatitis.
Choledochal cyst.
Pancreatitis.
Urinary tract infection.
Leptospirosis and other systemic infections with hepatic involvement.
Spontaneous perforation of common bile duct.
Biliary cyst.
Appendicitis.

FEVER AND CARDIOPULMONARY FAILURE[25]

ICD-10CM #		
	R50.9	Fever, unspecified

DIFFERENTIAL DIAGNOSIS OF FEVER AND RAPIDLY PROGRESSIVE CARDIOPULMONARY FAILURE

Bacterial Infection

Severe community-acquired pneumonia.
Meningitis, endocarditis.
Rickettsial disease (babesiosis, ehrlichiosis, Rocky Mountain spotted fever, scrub typhus, Mediterranean spotted fever).
Q-Fever (*Coxiella burnetii*).
Brucellosis.
Plague (*Yersinia pestis*).
Tularemia (*Francisella tularensis*).
Typhoid fever/salmonellosis.
Leptospirosis (*Leptospira interrogans*).
Anthrax.
Mycobacterial infections.

Viral Infections

Viral pneumonia (influenza, CMV, EBV, VZV, SARS).
Hantavirus.
Dengue fever and yellow fever.
Hemorrhagic fever (Lassa, Marburg, or Ebola viruses).

Fungal Infections

Coccidiomycosis.
Cryptococcus.
Histoplasmosis.
Blastomycosis.

Parasitic Infections

Malaria.
Leishmaniasis.
Schistosomiasis.
Strongyloides.

Noninfectious Causes

Inflammatory:
- Rapid-onset interstitial pneumonia (acute interstitial pneumonia, acute hypersensitivity pneumonitis).
- Acute eosinophilic pneumonia.
- ARDS due to other causes (inhalation injury, drug overdose, trauma).

Rheumatologic disorders:
- Wegener granulomatosis, Churg-Strauss disease, Goodpasture syndrome.
- Systemic lupus erythematosus, antiphospholipid syndrome.

Other:
- Malignancy, lymphoma, lymphoproliferative disease, leukemia.
- Pulmonary embolism, aortic dissection, acute myocardial infarction.
- Adrenal insufficiency, thyroid storm.

ARDS, Acute respiratory distress syndrome; *CMV,* Cytomegalovirus; *EBV,* Epstein-Barr virus; *SARS,* severe acute respiratory syndrome; *VZV,* varicella zoster virus.

FEVER AND JAUNDICE

ICD-10CM #		
	R50.9	Fever, unspecified
	R17	Unspecified jaundice

Bacterial sepsis.
Cholangitis.
Hepatic abscess.
Leptospirosis.
Malaria.
Viral hepatitis.
Yellow fever.

FEVER AND LYMPHADENOPATHY

ICD-10CM #		
	R59.9	Enlarged lymph nodes, unspecified
	R50.9	Fever, unspecified

REGIONAL

Cervical

Streptococci.
Tuberculosis.
Viral upper respiratory infection.

Peripheral

Bartonella henselae.
Herpesviruses.
Lymphoma.
Metastatic cancer.
Sporotrichosis.
Streptococci.

Inguinal

Chancroid.
Herpes.
Lymphogranuloma venereum.
Syphilis (primary).

GENERALIZED

Cytomegalovirus.
Epstein-Barr virus.
HIV.
Lymphoma.
Sarcoidosis.
Syphilis (secondary).
Toxoplasmosis.
Viral hepatitis.

FEVER AND RASH

ICD-10CM #		
	R21	Rash and other nonspecific skin eruption
	R21	Rash and other nonspecific skin eruption
	R50.9	Fever, unspecified

Drug hypersensitivity: penicillin, sulfonamides, thiazides, anticonvulsants, allopurinol.
Viral infection: measles, rubella, varicella, erythema infectiosum, roseola, enterovirus infection, viral hepatitis, infectious mononucleosis, acute HIV.
Other infections: meningococcemia, staphylococcemia, scarlet fever, typhoid fever, *Pseudomonas* bacteremia, Rocky Mountain spotted fever, Lyme disease, secondary syphilis, bacterial endocarditis, babesiosis, brucellosis, listeriosis.
Serum sickness.
Erythema multiforme.
Erythema marginatum.
Erythema nodosum.
SLE.
Dermatomyositis.
Allergic vasculitis.
Pityriasis rosea.
Herpes zoster.

FEVER AND RASH IN ICU[86]

ICD-10CM #		
	R21	Rash and other nonspecific skin eruption
	R50.9	Fever, unspecified

DIFFERENTIAL DIAGNOSTIC CLINICAL FEATURES OF FEVER AND RASH IN THE ICU

Rash with Shock

Infectious causes: toxic shock syndrome, meningococcemia, postsplenectomy sepsis, overwhelming *Staphylococcus aureus* bacteremia/acute bacterial endocarditis, arboviral hemorrhagic fevers, hemorrhagic smallpox, *Vibrio vulnificus*, gas gangrene, dengue fever.
Noninfectious cause: systemic lupus erythematosus (on steroids).

RASH WITH MENTAL CHANGES

Infectious causes: Rocky Mountain spotted fever, meningococcemia (with meningitis), *S. aureus* acute bacterial endocarditis, Chikungunya fever, typhus.
Noninfectious cause: systemic lupus erythematosus.

RASH WITH CONJUNCTIVAL SUFFUSION

Infectious causes: Rocky Mountain spotted fever, dengue fever, arboviral hemorrhagic fevers, toxic shock syndrome.
Noninfectious cause: adult Kawasaki disease.

RASH WITH RELATIVE BRADYCARDIA

Infectious causes: Rocky Mountain spotted fever, typhus, dengue fever, typhoid, arboviral hemorrhagic fevers.
Noninfectious cause: drug rash.

RASH WITH ABDOMINAL PAIN

Infectious causes: *V. vulnificus,* gas gangrene, *Clostridium sordelli,* scarlet fever.
Noninfectious causes: cholesterol emboli syndrome, systemic lupus erythematosus.

RASH ON PALMS AND SOLES

Infectious causes: Rocky Mountain spotted fever, toxic shock syndrome, chickenpox, smallpox, monkeypox, scarlet fever.
Noninfectious cause: drug rash.

RASH WITH DIARRHEA

Infectious causes: *V. vulnificus,* gas gangrene, toxic shock syndrome, dengue fever, arboviral hemorrhagic fevers.
Noninfectious cause: none.

RASH WITH EDEMA OF DORSUM OF HANDS/FEET

Infectious causes: Rocky Mountain spotted fever, toxic shock syndrome.
Noninfectious cause: adult Kawasaki disease.

RASH WITH BULLAE

Infectious causes: *V. vulnificus, S. aureus* complicated skin/skin structure infection, gas gangrene.
Noninfectious cause: none.

RASH WITH HEART MURMUR

Infectious cause: acute bacterial endocarditis.
Noninfectious cause: systemic lupus erythematosus.
Rash with gangrene of nose tip
Infectious cause: *S. aureus* acute bacterial endocarditis.
Noninfectious causes: systemic lupus erythematosus, vasculitis.

RASH WITH CEREBROVASCULAR ACCIDENT

Infectious causes: cholesterol emboli syndrome, *S. aureus* acute bacterial endocarditis.
Noninfectious cause: none.

RASH WITH SPLENOMEGALY

Infectious causes: Rocky Mountain spotted fever, typhus.
Noninfectious causes: systemic lupus erythematosus, adult Kawasaki disease.

RASH WITH DEAFNESS

Infectious causes: Rocky Mountain spotted fever, typhus, meningococcal meningitis.
Noninfectious cause: none.

RASH WITH HEPATOSPLENOMEGALY

Infectious causes: Rocky Mountain spotted fever, typhus.
Noninfectious cause: atypical measles.

RASH WITH HEPATOMEGALY

Infectious cause: typhus.
Noninfectious cause: none.

FEVER, AFTER TRAVEL TO THE TROPICS[3]

ICD-10CM # R50.81 Fever presenting with conditions classified elsewhere

CAUSES OF FEVER AFTER TRAVEL TO THE TROPICS

80% of Specific Infections Causing Fever (Includes Respiratory and Urinary Tract Infection)
Malaria.
Viral hepatitis.
Febrile illness unrelated to foreign travel.
Dengue fever.
Enteric fever (typhoid and paratyphoid fevers).
Other Causes
Gastroenteritis.
Rickettsia.
Leptospirosis.
Schistosomiasis.
Amebic liver abscess.
Tuberculosis.
Acute HIV infection.
Others.

FEVER, COMMON INFECTIOUS CAUSES[88]

ICD-10CM # R50.9 Fever, unspecified

CENTRAL NERVOUS SYSTEM

Meningitis:
- Encephalitis.
- Brain abscess.
- Epidural abscess.

HEAD AND NECK

Acute suppurative parotitis:
- Acute sinusitis.
- Parapharyngeal and retropharyngeal space infections.
- Acute suppurative otitis media.

CARDIOVASCULAR

Catheter-related infection:
- Endocarditis.

PULMONARY AND MEDIASTINAL

Pneumonia:
- Empyema.
- Mediastinitis.

HEPATOBILIARY AND GASTROINTESTINAL

Diverticulitis:
- Appendicitis.
- Peritonitis (spontaneous or secondary).
- Intraperitoneal abscess.
- Perirectal abscess.
- Infected pancreatitis.
- Acute cholecystitis.
- Cholangitis.
- Hepatic abscess.
- Acute viral hepatitis.

GENITOURINARY

Bacterial or fungal cystitis:
- Pyelonephritis.
- Perinephric abscess.
- Tubo-ovarian abscess.
- Endometritis.
- Prostatitis.

BREAST

Mastitis:
- Breast abscess.

CUTANEOUS AND MUSCULAR

Cellulitis:
- Suppurative wound infection.
- Necrotizing fasciitis.
- Bacterial myositis or myonecrosis.
- Herpes zoster.

OSSEOUS

Osteomyelitis.

FEVER, DRUG-INDUCED[34]

ICD-10CM # R50.2 Drug induced fever

SELECTED AGENTS ASSOCIATED WITH DRUG-INDUCED FEVER

Common
Antimicrobial:
- Amphotericin B.
- β-Lactams.
- Sulfonamides.

Cardiovascular:
- Procainamide.
- Quinidine.

CNS:
- Carbamazepine.
- Phenytoin.

Miscellaneous:
- Bleomycin.
- Interferon-α.
- Interleukin-2.

Less Common
Antimicrobial:
- Clindamycin.
- Fluoroquinolones.
- Rifampin.

Cardiovascular:
- Diltiazem.
- Hydralazine.

CNS:
- Haloperidol.
- Serotonin reuptake inhibitors.

Miscellaneous:
- Allopurinol.
- Cimetidine.
- Tacrolimus.

FEVER, HOSPITAL ASSOCIATED[34]

ICD-10CM # R50.2 Drug induced fever
R50.9 Fever, unspecified

SELECTED CAUSES OF HOSPITAL-ASSOCIATED FEVER

Common
Infectious:
- *Clostridium difficile* enterocolitis.
- Pneumonia.
- Surgical wound.
- Urinary tract.
- Vascular catheter.

Noninfectious:
- Drug-induced fever.
- Hematoma.
- Immediate postoperative state.
- Transfusion reaction.
- Venous thromboembolism.

Less Common
Infectious:
- Biliary tract disease.
- Endometritis.
- Intraabdominal abscess.
- Mediastinitis.
- Sinusitis.

Noninfectious:
- Adrenal insufficiency.
- Gout.
- Myocardial infarction.
- Organ infarction.
- Pancreatitis.

FEVER IN RETURNING TRAVELERS AND IMMIGRANTS[65]

ICD-10CM # R50.81 Fever presenting with conditions classified elsewhere

COMMON*

Acute respiratory tract infection (worldwide).
Gastroenteritis (worldwide) [foodborne, waterborne, fecal-oral].
Enteric fever, including typhoid (worldwide) [food, water].
Urinary tract infection (worldwide) [sexual contact].
Drug reactions [antibiotics, prophylactic agents, other] {rash frequent}.
Malaria (tropics, limited areas of temperate zones) [mosquitoes].
Arboviruses (Africa; tropics) [mosquitoes, ticks, mites].
Dengue (Asia, Caribbean, Africa) [mosquitoes].
Viral hepatitis (worldwide).
Hepatitis A (worldwide) [food, fecal-oral].
Hepatitis B (worldwide, especially Asia, sub-Saharan Africa) [sexual contact] {long incubation period}.
Hepatitis C (worldwide) [blood or sexual contact].
Hepatitis E (Asia, North Africa, Mexico, others) [food, water].
Tuberculosis (worldwide) [airborne, milk] {long period to symptomatic infection}.
Sexually transmitted diseases (worldwide) [sexual contact].

LESS COMMON*

Filariasis (Asia, Africa, South America) [biting insects] {long incubation period, eosinophilia}.
Measles (developing world) [airborne] {in susceptible individual}.
Amebic abscess (worldwide) [food].
Brucellosis (worldwide) [milk, cheese, food, animal contact].
Listeriosis (worldwide) [foodborne] {meningitis}.
Leptospirosis (worldwide) [animal contact, open fresh water] {jaundice, meningitis}.
Strongyloidiasis (warm and tropical areas) [soil contact] {eosinophilia}.
Toxoplasmosis (worldwide) [undercooked meat].

RARE

Relapsing fever (western Americas, Asia, northern Africa) [ticks, lice].
Hemorrhagic fevers (worldwide) [arthropod and nonarthropod transmitted].
Yellow fever (tropics) [mosquitoes] {hepatitis}.
Hemorrhagic fever with renal syndrome (Europe, Asia, North America) [rodent urine] {renal impairment}.
Hantavirus pulmonary syndrome (western North America, other) [rodent urine] {respiratory distress syndrome}.
Lassa fever (Africa) [rodent excreta, person to person] {high mortality rate}.
Other: chikungunya, Rift Valley, Ebola-Marburg, etc. (various) [insect bites, rodent excreta, aerosols, person to person] {often severe}.
Rickettsial infections {rashes and eschars}.
Leishmaniasis, visceral (Middle East, Mediterranean, Africa, Asia, South America) [biting flies] {long incubation period}.
Acute schistosomiasis (Africa, Asia, South America, Caribbean) [fresh water].
Chagas disease (South and Central America) [reduviid bug bites] {often asymptomatic}.
African trypanosomiasis (Africa) [tsetse fly bite] {neurologic syndromes, sleeping sickness}.
Bartonellosis (South America) [sandfly bite] {skin nodules}.
HIV infection/AIDS (worldwide) [sexual and blood contact].
Trichinosis (worldwide) [undercooked meat] {eosinophilia}.
Plague (temperate and tropical plains) [animal exposures and fleas].
Tularemia (worldwide) [animal contact, fleas, aerosols] {ulcers, lymph nodes}.
Anthrax (worldwide) [animal, animal product contact] {ulcers}.
Lyme disease (North America, Europe) [tick bites] {arthritis, meningitis, cardiac abnormalities}.

*Diagnoses for which particular symptoms are indicative are in *italics*. Exposure to regions of the world that are most likely to be significant to the diagnosis are presented in (parentheses). Vectors, risk behaviors, and sources associated with acquisition are presented in [brackets]. Special clinical characteristics are listed within {braces}.

FEVER, NONINFECTIOUS CAUSES[7]

ICD-10CM # R50.9 Fever, unspecified

DIFFERENTIAL DIAGNOSIS—NONINFECTIOUS CAUSES OF FEVER

Critical Diagnoses
Acute myocardial infarction.
Pulmonary embolism/infarction.
Intracranial hemorrhage.
Cerebrovascular accident.
Neuroleptic-malignant syndrome.
Thyroid storm.
Acute adrenal insufficiency.
Transfusion reaction.
Pulmonary edema.
Emergent Diagnoses
Congestive heart failure.
Dehydration.
Recent seizure.
Sickle cell disease.
Transplant rejection.
Pancreatitis.
Deep vein thrombosis.
Nonemergent Diagnoses
Drug fever.
Malignancy.
Gout.
Sarcoidosis.
Crohn disease.
Postmyocardiotomy syndrome.

FEVER OF UNKNOWN ORIGIN, PEDIATRIC PATIENT[19]

ICD-10CM # R50.9 Fever, unspecified

INFECTIOUS DISEASES

Bacterial
Bacterial endocarditis.
Brucellosis.
Cat-scratch disease.
Leptospirosis.
Liver abscess.
Mastoiditis (chronic).
Osteomyelitis.
Pelvic abscess.
Perinephric abscess.
Pyelonephritis.
Salmonellosis.
Sinusitis.
Subdiaphragmatic abscess.
Tuberculosis.
Tularemia.
Viral
Adenovirus.
Arboviruses.
Cytomegalovirus.
Epstein-Barr virus (infectious mononucleosis).
Hepatitis viruses.
Chlamydial
Lymphogranuloma venereum.
Psittacosis.
Rickettsial
Q fever.
Rocky Mountain spotted fever.
Fungal
Blastomycosis (nonpulmonary).
Histoplasmosis (disseminated).
Parasitic
Malaria.
Toxoplasmosis.
Visceral larva migrans.
Unclassified
Sarcoidosis.
Collagen Vascular Diseases
Juvenile rheumatoid arthritis.
Polyarteritis nodosa.
Systemic lupus erythematosus.
Malignancies
Hodgkin disease.
Leukemia and lymphoma.
Neuroblastoma.
Miscellaneous
Central diabetes insipidus.
Drug fever.
Ectodermal dysplasia.
Factitious fever.
Familial dysautonomia.
Granulomatous colitis.
Hemophagocytic lymphohistiocytosis.

Infantile cortical hyperostosis.
Kikuchi-Fujimoto disease.
Nephrogenic diabetes insipidus.
Pancreatitis.
Periodic fever.
Serum sickness.
Thyrotoxicosis.
Ulcerative colitis.

FEVER, POSTPARTUM[1]

ICD-10CM # R50.9 Fever, unspecified

MOST COMMON

Metritis.
Urinary tract infection.
Pneumonia.
Wound infection.
Mastitis.
Superficial or deep vein thrombosis.

MOST THREATENING

Toxic shock syndrome.
Necrotizing fasciitis.
Pelvic phlegmon.
Pelvic abscess.
Peritonitis.
Septic pelvic thrombosis.
Breast abscess.

FEVER, PERIODIC[29]

ICD-10CM # R50.9 Fever, unspecified

HEREDITARY

Nonhereditary
Infectious
Hidden infectious focus (e.g., aortoenteric fistula, Caroli disease).
Recurrent reinfection (e.g., chronic meningococcemia, host defense defect).
Specific infection (e.g., Whipple disease, malaria).
Noninfectious inflammatory disorder, e.g.:
- Adult-onset Still disease.
- Juvenile chronic rheumatoid arthritis.
- Periodic fever, aphthous stomatitis, pharyngitis, and adenitis.
- Schnitzler syndrome.
- Behçet syndrome.
- Crohn disease.
- Sarcoidosis.
- Extrinsic alveolitis.
- Humidifier lung, polymer fume fever.
- Neoplastic.

Lymphoma (e.g., Hodgkin disease, angioimmunoblastic lymphoma).
Solid tumor (e.g., pheochromocytoma, myxoma, colon carcinoma).
Vascular (e.g., recurrent pulmonary embolism)
Hypothalamic
Psychogenic periodic fever.
Factitious or fraudulent.

FEVER, PEDIATRIC, ACUTE[1]

ICD-10CM # R50.9 Fever, unspecified

COMMON VIRAL INFECTIONS

Central Nervous System
Meningitis.
Encephalitis.
Tumor.
Brain abscess.
Head, Ears, Eyes, Nose, and Throat
Otitis media.
Pharyngitis.
Retropharyngeal abscess.
Peritonsillar abscess.
Lateral pharyngeal wall abscess.
Stomatitis.
Influenza.
Sinusitis.
Parotitis.
Cervical adenitis.
Periorbital cellulitis.
Orbital cellulitis or abscess.
Respiratory System
Bronchiolitis.
Croup.
Epiglottitis.
Pneumonia.
Upper respiratory infection.
Cardiovascular System
Myocarditis.
Pericarditis.
Endocarditis.
Genitourinary System
Urinary tract infection.
Tuboovarian abscess.
Gastrointestinal Tract
Acute viral gastroenteritis.
Bacterial enteritis.
Appendicitis.
Focal Soft Tissue Infections
Cellulitis.
Musculoskeletal System
Osteomyelitis.
Septic arthritis.
Rheumatologic Disorders
Acute rheumatic fever.
Juvenile rheumatoid arthritis.
Henoch-Schönlein purpura.
Vasculitis
Behçet syndrome.
Malignancy
Leukemia.
Lymphoma.
Sarcoma.
Systemic Illness
Bacteremia.
Viremia.
Sepsis.
Kawasaki disease.
Toxic shock syndrome.
Rocky Mountain spotted fever.
Meningococcemia.

MISCELLANEOUS DISORDERS

Toxicologic
Anticholinergic toxidromes.
Salicylate overdose.
Amphetamine.
Cocaine.
Endocrine
Thyrotoxicosis.

FEVER, RECURRENT OR PERIODIC, IN CHILDREN[53]

ICD-10CM # R50.2 Drug induced fever
R50.9 Fever, unspecified

INFECTIOUS DISEASES

Brucellosis.
Rat-bite fever.
Relapsing fever.

RHEUMATIC DISEASES

Juvenile idiopathic arthritis (systemic onset).
Behçet disease.
Systemic lupus erythematosus.
Relapsing polychondritis.
Crohn disease.

HEREDITARY AUTOINFLAMMATORY SYNDROMES

Familial Mediterranean fever (FMF).
Cryopyrinopathies:
- Familial cold autoinflammatory syndrome (FCAS).
- Muckle-Wells syndrome (MWS).
- Chronic infantile neurologic cutaneous and articular (CINCA) syndrome, also called neonatal-onset multisystem inflammatory disease (NOMID).

Tumor necrosis factor receptor–associated periodic syndrome (TRAPS).
Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS).

CYCLIC HEMATOPOIESIS

Hereditary form.
Acquired form.

IDIOPATHIC CONDITIONS

Periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA).

FEVER WITH MACULOPAPULAR OR PETECHIAL RASH[69]

ICD-10CM # R21 Rash and nonspecific skin eruption
ICD-10CM # R50.9 Fever, unspecified

DIFFERENTIAL DIAGNOSIS OF FEVER WITH MACULOPAPULAR OR PETECHIAL RASH

Rocky Mountain spotted fever.
Meningococcal disease.
Enteroviral infection (echovirus and coxsackievirus).
Human herpesvirus 6 infection (roseola).
Human parvovirus B19 infection (fifth disease).
Epstein-Barr virus infection.
Disseminated gonococcal infection.
Murine typhus.
Ehrlichiosis.
Group A streptococcal pharyngitis.
Mycoplasma pneumoniae Infection.
Leptospirosis.
Secondary syphilis.

Kawasaki disease.
Thrombotic thrombocytopenic purpura (TTP).
Drug reactions.
Immune complex–mediated illness.
Toxic shock syndrome.
Erythema multiforme.
Stevens-Johnson syndrome.

FEVERS PRONE TO RELAPSE[42]

ICD-10CM #		
	R50.9	Fever, unspecified

Infectious Causes

Relapsing fever (*Borrelia recurrentis*).
Q fever (*Coxiella burnetii*).
Typhoid fever (*Salmonella typhi*).
Syphilis (*Treponema pallidum*).
Tuberculosis.
Histoplasmosis.
Coccidioidomycosis.
Blastomycosis.
Melioidosis (*Pseudomonas pseudomallei*).
Lymphocytic choriomeningitis (LCM) infection.
Dengue fever.
Yellow fever.
Chronic meningococcemia.
Colorado tick fever.
Leptospirosis.
Brucellosis.
Oroya fever (*Bartonella bacilliformis*).
Acute rheumatic fever.
Rat-bite fever (*Spirillum minus*).
Visceral leishmaniasis.
Lyme disease (*Borrelia burgdorferi*).
Malaria.
Babesiosis.
Noninfluenza respiratory viral infection.
Epstein-Barr virus infection.

Noninfectious Causes

Behçet disease.
Crohn disease.
Weber-Christian disease (panniculitis).
Leukoclastic angiitis syndromes.
Sweet syndrome.
Systemic lupus erythematosus and other autoimmune disorders.

Periodic Fever Syndromes

Familial Mediterranean fever.
Cyclic neutropenia.
Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA).
Hyper–immunoglobulin D syndrome.
Hibernian fever (tumor necrosis factor superfamily immunoglobulin A–associated syndrome [TRAPS]).
Muckle-Wells syndrome.
Others.

FINGER LESIONS, INFLAMMATORY

ICD-10CM #		
	B08.8	Other specified viral infections characterized by skin and mucous membrane lesions
	L03.0	Cellulitis of finger and toe

Paronychia.
Herpes simplex type 1 (herpetic whitlow).
Dyshidrotic eczema (pompholyx).
Herpes zoster.
Bacterial endocarditis (Osler nodes).
Psoriatic arthritis.

FLACCID PARALYSIS, ACUTE, DIFFERENTIAL DIAGNOSIS[53]

ICD-10CM #		
	G83.9	Paralytic syndrome, unspecified

Brain stem stroke.
Brain stem encephalitis.
Acute anterior poliomyelitis.
  Caused by poliovirus.
  Caused by other neurotropic viruses.
Acute myelopathy.
  Space-occupying lesions.
  Acute transverse myelitis.
Peripheral neuropathy.
  Guillain-Barré syndrome.
  Post-rabies vaccine neuropathy.
  Diphtheritic neuropathy.
  Heavy metals, biologic toxins, or drug intoxication.
  Acute intermittent porphyria.
  Vasculitic neuropathy.
  Critical illness neuropathy.
  Lymphomatous neuropathy.
Disorders of neuromuscular transmission.
  Myasthenia gravis.
  Biologic or industrial toxins.
  Tic paralysis.
Disorders of muscle.
  Hypokalemia.
  Hypophosphatemia.
  Inflammatory myopathy.
  Acute rhabdomyolysis.
  Trichinosis.
  Periodic paralyses.

FLATULENCE AND BLOATING[76]

ICD-10CM #		
	R14.0	Abdominal distension (gaseous)
	R14.1	Gas pain
	R14.2	Eructation
	R14.3	Flatulence

Ingestion of nonabsorbable carbohydrates.
Ingestion of carbonated beverages.
Malabsorption: pancreatic insufficiency, biliary disease, celiac disease, bacterial overgrowth in small intestine.
Lactase deficiency.
Irritable bowel syndrome.
Anxiety disorders.
Food poisoning, giardiasis.

FLUSHING[63]

ICD-10CM #		
	R23.2	Flushing

Physiologic flushing: menopause, ingestion of monosodium glutamate (Chinese restaurant syndrome), ingestion of hot drinks.
Drugs: alcohol (with or without disulfiram, metronidazole, or chlorpropamide), nicotinic acid, diltiazem, nifedipine, levodopa, bromocriptine, vancomycin, amyl nitrate.
Neoplastic disorders: carcinoid syndrome, VIPoma syndrome, medullary carcinoma of thyroid, systemic mastocytosis, basophilic chronic myelocytic leukemia, renal cell carcinoma.
Anxiety.
Agnogenic flushing.

FOLATE DEFICIENCY[45]

ICD-10CM #		
	D52.0	Dietary folate deficiency anemia
	D52.1	Drug-induced folate deficiency anemia
	D52.8	Other folate deficiency anemias
	D52.9	Folate deficiency anemia, unspecified

ETIOPATHOPHYSIOLOGIC CLASSIFICATION OF FOLATE DEFICIENCY

Nutritional causes:
  Decreased dietary intake:
    Poverty and famine.
    Institutionalized individuals (e.g., psychiatric, nursing homes), chronic debilitating disease.
    Prolonged feeding of infants with goat's milk, special slimming diets or food fads (i.e., folate-rich foods not consumed), cultural or ethnic cooking techniques (i.e., food folate destroyed).
  Decreased diet and increased requirements:
    Physiologic (e.g., pregnancy and lactation, prematurity, hyperemesis gravidarum, infancy).
    Pathologic (e.g., intrinsic hematologic diseases involving hemolysis with compensatory erythropoiesis, abnormal hematopoiesis, or bone marrow infiltration with malignant disease and dermatologic disease such as psoriasis).
Folate malabsorption:
  With normal intestinal mucosa:
    Some drugs (controversial).
    Congenital folate malabsorption (rare).
    With mucosal abnormalities (e.g., tropical and nontropical sprue, regional enteritis).
Defective cellular folate uptake:
  Familial aplastic anemia (rare).
  Acute cerebral folate deficiency.
Inadequate cellular use:
  Folate antagonists (e.g., methotrexate).
  Hereditary enzyme deficiencies involving folate.
Drugs:
  Multiple effects on folate metabolism (e.g., alcohol, sulfasalazine, triamterene, pyrimethamine, trimethoprim-sulfamethoxazole, diphenylhydantoin, barbiturates).
Acute folate deficiency:
  Intensive care unit setting.
  Uncertain origin.

FOOT AND ANKLE PAIN[27]

ICD-10CM #		
	M25.5	Pain in joint
	M25.9	Joint disorder, unspecified

TENDON, LIGAMENT, AND MUSCLE

Gastrocnemius-soleus strain.
Plantaris rupture.
Anterior talofibular ligament tear.
Calcaneofibular ligament tear.
Deltoid ligament tear.
Anterolateral impingement due to complete tear of anterior talofibular ligament and anterior inferior tibiofibular ligament.
Syndesmotic impingement due to tear of syndesmosis.
Sinus tarsi syndrome (lateral hindfoot pain and instability due to injury of contents of the sinus and tarsal tunnel).
Achilles tendinitis.
Achilles rupture.
Plantar fasciitis.
Posterior tibial tendon dysfunction.
Flexor hallucis longus dysfunction.
Tibialis anterior tendon tear.
Peroneus brevis tendon tear.

BONE

Fracture of talus.
Calcaneal fracture.
Navicular fractures.
Lisfranc fracture-dislocation (fracture of the first metatarsal base with dislocation of medial cuneiform).
Metatarsal stress fracture.
Freiberg infraction (sclerosis and flattening of the second metatarsal head due to trauma or microtrauma).
Avascular necrosis of the talus.
Fracture of the phalanges.
Fracture of the sesamoids.
Sesamoiditis.
Metatarsalgia.

JOINT

Osteoarthritis.
Gout.
Rheumatoid arthritis.
Other inflammatory arthritides.
Charcot joint.
Osteochondral lesion of the talus.

PERIARTICULAR STRUCTURES

Shin splint (periosteal avulsion and periostitis at the insertion of the medial soleus due to repetitive overuse, such as in running and hiking).
Hallux rigidus.
Hallux valgus.
Ingrown toenail.
Toe deformities.
Turf toe (sprain of the first metatarsophalangeal joint due to hyperextension forces).
Plantar fasciitis.
Plantar fibromatosis.

NERVES

Anterior tarsal tunnel syndrome (involvement of deep peroneal nerve under the superficial fascia of the ankle).
Morton neuroma.

VESSELS

Atherosclerosis.
Compartment syndrome.

REFERRED PAIN

Complex regional pain syndrome.

FOOT AND ANKLE PAIN, IN DIFFERENT AGE GROUPS[18]

ICD-10CM # M25.579 Pain in unspecified ankle and joints of unspecified foot

COMMON CAUSES OF FOOT AND ANKLE PAIN IN DIFFERENT AGE GROUPS

Childhood (2-10 yr)
Intraarticular
Club foot.
Congenital midfoot and forefoot deformities.
Septic arthritis.
Periarticular
Osteomyelitis.
Adolescence (10-18 yr)
Intraarticular
Arch disorders (pes cavus, pes planus).
Periarticular
Osteomyelitis.
Tumors.
Early Adulthood (18-30 yr)
Intraarticular
Metatarsalgia.
Hallux valgus.
Hallux rigidus.
Osteochondritis.
Accessory ossicles.
Periarticular
Achilles tendonitis.
Achilles tendon rupture.
Fasciitis.
Referred
Lumbar spine.
Knee.
Adulthood (30-50 yr)
Intraarticular
Osteoarthritis.
Inflammatory arthritis.
Gout.
Metatarsalgia.
Hallux valgus.
Hallux rigidus.
Osteochondritis.
Accessory ossicles.
Periarticular
Ischemic foot pain.
Diabetes.
Bursitis.
Tendonitis.
Plantar fasciitis.
Corns.
Referred
Lumbar spine.
Knee.
Old Age (>50 yr)
Intraarticular
Osteoarthritis.
Inflammatory arthritis.
Gout.
Metatarsalgia.
Hallux valgus.
Hallux rigidus.
Periarticular
Ischemic foot pain.
Diabetes.
Bursitis.
Tendonitis.
Plantar fasciitis.
Corns.
Referred
Lumbar spine.
Knee.

FOOT DERMATITIS

ICD-10CM # B35.3 Tinea pedis
K25 Unspecified contact dermatitis

Tinea pedis.
Dyshidrotic eczema.
Tylosis (mechanically induced hyperkeratosis, fissuring, and dryness).
Allergic contact dermatitis.
Psoriasis.
Peripheral vascular insufficiency.
Neuropathic foot ulcers (DM, poorly fitting shoes).
Acquired plantar keratoderma.
Sézary syndrome.

FOOTDROP

ICD-10CM # M21.379 Foot drop, unspecified foot

Peripheral neuropathy.
L5 radiculopathy.
Peroneal nerve compression.
Sciatic nerve palsy.
Scapuloperoneal syndromes.
Spasticity.
Peroneal nerve compression.
Myopathy.
Dystonia.

FOOT LESION, ULCERATING

ICD-10CM # S90.929A Unspecified superficial injury of unspecified foot, initial encounter
S90.933A Unspecified superficial injury of unspecified great toe, initial encounter
S90.936A Unspecified superficial injury of unspecified lesser toe(s), initial encounter
L08.89 Other specified local infections of the skin and subcutaneous tissue

Cellulitis.
Plantar wart.
Squamous cell carcinoma.
Actinomycosis (Madura foot).
Plantar fibromatosis.
Pseudoepitheliomatous hyperplasia.

FOOT PAIN

ICD-10CM #		
	M25.579	Pain in unspecified ankle and joints of unspecified foot

Trauma (fractures, musculoskeletal and ligamentous strain).
Inflammation (plantar fasciitis, Achilles tendonitis or bursitis, calcaneal apophysitis).
Arterial insufficiency, Raynaud phenomenon, thromboangiitis obliterans.
Gout, pseudogout.
Calcaneal spur.
Infection (cellulitis, abscess, lymphangitis, gangrene).
Decubitus ulcer.
Paronychia, ingrown toenail.
Thrombophlebitis, postphlebitic syndrome.

FOOT PAIN BY AGE[53]

ICD-10CM #		
	M25.579	Pain in unspecified ankle and joints of unspecified foot

0 TO 6 YEARS

Poorly fitting shoes.
Foreign body.
Fracture.
Osteomyelitis.
Leukemia.
Puncture wound.
Drawing of blood.
Dactylitis.
Juvenile rheumatoid arthritis (JRA).

6 TO 12 YEARS

Poorly fitting shoes.
Sever disease.
Enthesopathy (JRA).
Foreign body.
Accessory navicular.
Tarsal coalition.
Ewing sarcoma.
Hypermobile flatfoot.
Trauma (sprains, fractures).
Puncture wound.

12 TO 20 YEARS

Poorly fitting shoes.
Stress fracture.
Foreign body.
Ingrown toenail.
Metatarsalgia.
Plantar fasciitis.
Osteochondroses (avascular necrosis).
Freiberg infarction.
Köhler disease.
Achilles tendinitis.
Trauma (sprains).
Plantar warts.
Tarsal coalition.

FOREARM AND HAND PAIN

ICD-10CM #		
	S59.809A	Other specified injuries of unspecified elbow, initial encounter
	S59.919A	Unspecified injury of unspecified forearm, initial encounter
	S69.80XA	Other specified injuries of unspecified wrist, hand and finger(s), initial encounter
	S69.90XA	Unspecified injury of unspecified wrist, hand and finger(s), initial encounter

Epicondylitis.
Tenosynovitis.
Osteoarthritis.
Cubital tunnel syndrome.
Carpal tunnel syndrome.
Trauma.
Herpes zoster.
Peripheral vascular insufficiency.
Infection (cellulitis, abscess).

FOREARM FRACTURES[3]

ICD-10CM #		
	S52	Fracture of forearm

TRAUMATIC

Wrist sprain, elbow sprain.
Ligamentous injuries, forearm contusions, hematomas.
Dislocations of the elbow or wrist (including nursemaid's elbow).

INFECTIOUS

Cellulitis of the forearm, abscesses.
Necrotizing fasciitis.

VASCULAR

Acute arterial occlusion.
Venous thrombosis.

NEUROLOGIC

Neurapraxias, carpal tunnel syndrome.
Systemic neurologic syndromes involving the nerves of the upper extremities.

ARTHRITIS

Septic joint, gonococcal arthritis, rheumatoid arthritis, osteoarthritis.
Pseudogout, gout.
Systemic lupus erythematosus, rheumatic fever, viral syndrome.
Reiter syndrome, Lyme disease, serum sickness.

OTHER

Olecranon bursitis, soft tissue masses.
Normal growth plates, nutrient vessels.As cuptiust re mo et imus es doluptibus dolupta doloreperis voluptam etur acium quae ipiet

GAIT ABNORMALITY

ICD-10CM #		
	R26.0	Ataxic gait
	R26.1	Paralytic gait
	R26.89	Other abnormalities of gait and mobility
	R26.9	Unspecified abnormalities of gait and mobility

Parkinsonism.
Degenerative joint disease (hips, back, knees).
Multiple sclerosis.
Trauma, foot pain.
CVA.
Cerebellar lesions.
Infections (tabes, encephalitis, meningitis).
Sensory ataxia.
Dystonia, cerebral palsy, neuromuscular disorders.
Metabolic abnormalities.

GALACTORRHEA[65]

ICD-10CM #		
	N64.3	Galactorrhea not associated with childbirth

Prolonged suckling.
Drugs (INH, phenothiazines, reserpine derivatives, amphetamines, spironolactone and tricyclic antidepressants).
Major stressors (surgery, trauma).
Hypothyroidism.
Pituitary tumors.

GALLBLADDER SONOGRAPHIC NON-VISUALIZATION[74]

ICD-10CM #	
	Varies with specific diagnosis

CAUSES OF SONOGRAPHIC NON-VISUALIZATION OF GALLBLADDER

Previous cholecystectomy.
Physiologic contraction.
Fibrosed gallbladder duct—chronic cholecystitis.
Air-filled gallbladder or emphysematous cholecystitis.
Tumefactive sludge.
Agenesis of gallbladder.
Ectopic location.

GALLBLADDER WALL THICKENING[74]

ICD-10CM #	
	Varies with specific diagnosis

CAUSES OF GALLBLADDER WALL THICKENING

Generalized Edematous States

Congestive heart failure.
Renal failure.
End-stage cirrhosis.
Hypoalbuminemia.

Inflammatory Conditions

Primary:
- Acute cholecystitis.
- Cholangitis.

FOOT PAIN

ICD-10CM #		
	M25.579	Pain in unspecified ankle and joints of unspecified foot

Trauma (fractures, musculoskeletal and ligamentous strain).
Inflammation (plantar fasciitis, Achilles tendonitis or bursitis, calcaneal apophysitis).
Arterial insufficiency, Raynaud phenomenon, thromboangiitis obliterans.
Gout, pseudogout.
Calcaneal spur.
Infection (cellulitis, abscess, lymphangitis, gangrene).
Decubitus ulcer.
Paronychia, ingrown toenail.
Thrombophlebitis, postphlebitic syndrome.

FOOT PAIN BY AGE[53]

ICD-10CM #		
	M25.579	Pain in unspecified ankle and joints of unspecified foot

0 TO 6 YEARS

Poorly fitting shoes.
Foreign body.
Fracture.
Osteomyelitis.
Leukemia.
Puncture wound.
Drawing of blood.
Dactylitis.
Juvenile rheumatoid arthritis (JRA).

6 TO 12 YEARS

Poorly fitting shoes.
Sever disease.
Enthesopathy (JRA).
Foreign body.
Accessory navicular.
Tarsal coalition.
Ewing sarcoma.
Hypermobile flatfoot.
Trauma (sprains, fractures).
Puncture wound.

12 TO 20 YEARS

Poorly fitting shoes.
Stress fracture.
Foreign body.
Ingrown toenail.
Metatarsalgia.
Plantar fasciitis.
Osteochondroses (avascular necrosis).
Freiberg infarction.
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VASCULAR

Acute arterial occlusion.
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NEUROLOGIC

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Tumefactive sludge.
Agenesis of gallbladder.
Ectopic location.

GALLBLADDER WALL THICKENING[74]

ICD-10CM #	
	Varies with specific diagnosis

CAUSES OF GALLBLADDER WALL THICKENING

Generalized Edematous States

Congestive heart failure.
Renal failure.
End-stage cirrhosis.
Hypoalbuminemia.

Inflammatory Conditions

Primary:
- Acute cholecystitis.
- Cholangitis.

Chronic cholecystitis.
Secondary:
Acute hepatitis.
Perforated duodenal ulcer.
Pancreatitis.
Diverticulitis/colitis.
Neoplastic Conditions
Gallbladder adenocarcinoma.
Metastases.
Miscellaneous
Adenomyomatosis.
Mural varicosities.

GALLSTONE DISEASE, PEDIATRIC PATIENT[19]

ICD-10CM # K80.20 Calculus of gallbladder without cholecystitis without obstruction

Biliary tract anomaly (e.g., choledochal cyst).
Cephalosporin use.
Crohn disease.
Cystic fibrosis.
Genetic predisposition (e.g., ABCB4, UGT1A1 mutations).
Hemolytic disorders (e.g., sickle-cell anemia, hereditary spherocytosis).
Hispanic or Latino ancestry.
Malabsorption.
Metabolic syndrome.
Obesity.
Parasitic disease (*Ascaris lumbricoides*).
Pregnancy.
Rapid weight loss.
Solid organ and hematologic transplant (e.g., liver, kidney, heart, bone marrow).
Total parenteral nutrition.

GASTRIC DILATATION[36]

ICD-10CM # K31.0 Acute dilatation of stomach

CAUSES OF A MASSIVELY DILATED STOMACH

Mechanical Gastric Outlet Obstruction
Duodenal or pyloric canal ulceration.
Carcinoma of pyloric antrum.
Extrinsic compression.
Paralytic Ileus
Surgery.
Trauma.
Peritonitis.
Pancreatitis.
Cholecystitis.
Diabetes mellitus.
Hepatic coma.
Drugs.
Gastric Volvulus
Intubation.
Air swallowing.

GASTRIC EMPTYING, DELAYED[3]

ICD-10CM # K30 Functional dyspepsia

CAUSES OF DELAYED GASTRIC EMPTYING

Mechanical Causes
Peptic ulcer disease, scarred pylorus.
Malignancy: gastric cancer, gastric lymphoma, pancreatic cancer.
Gastric surgery: vagotomy, gastric resection, Roux-en-Y anastomosis.
Crohn disease.
Endocrine and Metabolic Causes
Diabetes mellitus.
Hypothyroidism.
Hypoadrenal states.
Electrolyte abnormalities.
Chronic renal failure.
Medications.
Anticholinergics.
Opiates.
Dopamine agonists.
Tricyclic antidepressants.
Abnormalities of Gastric Smooth Muscle
Scleroderma.
Polymyositis, dermatomyositis.
Amyloidosis.
Pseudoobstruction.
Myotonic dystrophy.
Neuropathy.
Scleroderma.
Amyloidosis.
Autonomic neuropathy.
Central Nervous System or Psychiatric Disorders
Brain stem tumors.
Spinal cord injury.
Anorexia nervosa.
Stress.
Miscellaneous
Idiopathic gastroparesis.
Gastroesophageal reflux disease.
Nonulcer (functional) dyspepsia.
Cancer cachexia or anorexia.

GASTRIC EMPTYING, RAPID

ICD-10CM # K30 Functional dyspepsia

Pancreatic insufficiency.
Dumping syndrome.
Peptic ulcer.
Celiac disease.
Promotility agents.
Zollinger-Ellison disease.

GASTROINTESTINAL BLEEDING, PEDIATRIC PATIENT[54]

ICD-10CM # K92.2 Gastrointestinal hemorrhage, unspecified

INFANT

Common
Bacterial enteritis.
Milk protein allergy intolerance.
Intussusception.
Swallowed maternal blood.
Anal fissure.
Lymphonodular hyperplasia
Rare
Volvulus.
Necrotizing enterocolitis.
Meckel diverticulum.
Stress ulcer, gastritis.
Coagulation disorder (hemorrhagic disease of newborn).
Esophagitis.

CHILD

Common
Bacterial enteritis.
Anal fissure.
Colonic polyps.
Intussusception.
Peptic ulcer/gastritis.
Swallowed epistaxis.
Prolapse (traumatic) gastropathy secondary to emesis.
Mallory-Weiss syndrome.
Rare
Esophageal varices.
Esophagitis.
Meckel diverticulum.
Lymphonodular hyperplasia.
Henoch-Schönlein purpura.
Foreign body.
Hemangioma, arteriovenous malformation.
Sexual abuse.
Hemolytic-uremic syndrome.
Inflammatory bowel disease.
Coagulopathy.
Duplication cyst:
Angiodysplasia.
Angiodysplasia with von Willebrand disease.
Blue rubber bleb nevus syndrome.

ADOLESCENT

Common
Bacterial enteritis.
Inflammatory bowel disease.
Peptic ulcer/gastritis.
Prolapse (traumatic) gastropathy secondary to emesis.
Mallory-Weiss syndrome.
Colonic polyps.
Anal fissure.
Rare
Hemorrhoids.
Esophageal varices.
Esophagitis.
Pill ulcer.
Telangiectasia-angiodysplasia.
Graft versus host disease.
Duplication cyst:
Angiodysplasia.
Angiodysplasia with von Willebrand disease.
Blue rubber bleb nevus syndrome.

GASTROINTESTINAL OBSTRUCTION, PEDIATRIC PATIENT[54]

ICD-10CM #		
	K56.2	Volvulus
	K5.1	Intussusception
	K56.9	Ileus unspecified
	K56.6	Other and unspecified intestinal obstruction

Esophagus

Congenital

Esophageal atresia.
Vascular rings.
Schatzki ring.
Tracheobronchial remnant.

Acquired

Esophageal stricture.
Foreign body.
Achalasia.
Chagas disease.
Collagen vascular disease.

Stomach

Congenital

Antral webs.
Pyloric stenosis.

Acquired

Bezoar, foreign body.
Pyloric stricture (ulcer).
Chronic granulomatous disease of childhood.
Eosinophilic gastroenteritis.
Crohn disease.
Epidermolysis bullosa.

Small Intestine

Congenital

Duodenal atresia.
Annular pancreas.
Malrotation/volvulus.
Malrotation/Ladd bands.
Ileal atresia.
Meconium ileus.
Meckel diverticulum with volvulus or intussusception.
Inguinal hernia.
Internal hernia.
Intestinal duplication.
Pseudoobstruction.

Acquired

Postsurgical adhesions.
Crohn disease.
Intussusception.
Distal ileal obstruction syndrome (cystic fibrosis).
Duodenal hematoma.
Superior mesenteric artery syndrome.

Colon

Congenital

Meconium plug.
Hirschsprung disease.
Colonic atresia, stenosis.
Imperforate anus.
Rectal stenosis.
Pseudoobstruction.
Volvulus.
Colonic duplication.

Acquired

Ulcerative colitis (toxic megacolon).
Chagas disease.
Crohn disease.
Fibrosing colonopathy (cystic fibrosis).

GASTROINTESTINAL SYMPTOMS IN CHILDREN, NONDIGESTIVE CAUSES[54]

ICD-10CM #	Varies with specific diagnosis

Anorexia

Systemic disease: inflammatory, neoplastic.
Cardiorespiratory compromise.
Iatrogenic: drug therapy, unpalatable therapeutic diets.
Depression.
Anorexia nervosa.

Vomiting

Inborn errors of metabolism.
Medications: erythromycin, chemotherapy, nonsteroidal antiinflammatory drugs, marijuana.
Increased intracranial pressure.
Brain tumor.
Infection of the urinary tract.
Labyrinthitis.
Adrenal insufficiency.
Pregnancy.
Psychogenic.
Abdominal migraine.
Poisoning/toxins.
Renal disease.

Diarrhea

Infection: otitis media, urinary tract infection.
Uremia.
Medications: antibiotics, cisapride.
Tumors: neuroblastoma.
Pericarditis.
Adrenal insufficiency.

Constipation

Hypothyroidism.
Spina bifida.
Developmental delay.
Dehydration: diabetes insipidus, renal tubular lesions.
Medications: narcotics.
Lead poisoning.
Infant botulism.

Abdominal Pain

Pyelonephritis, hydronephrosis, renal colic.
Pneumonia (lower lobe).
Pelvic inflammatory disease.
Porphyria.
Fabry disease.
Angioedema.
Endocarditis.
Abdominal migraine.
Familial Mediterranean fever.
Sexual or physical abuse.
Systemic lupus erythematosus.
School phobia.
Sickle cell crisis.
Vertebral disk inflammation.
Psoas abscess.
Pelvic osteomyelitis or myositis.
Medications.

Abdominal Distention Or Mass

Ascites: nephrotic syndrome, neoplasm, heart failure.
Discrete mass: Wilms tumor, hydronephrosis, neuroblastoma, mesenteric cyst, hepatoblastoma, lymphoma.
Pregnancy.

Jaundice

Hemolytic disease.
Urinary tract infection.
Sepsis.
Hypothyroidism.
Panhypopituitarism.

GENITAL DISCHARGE, FEMALE[24]

ICD-10CM #	N94.9	Unspecified condition associated with female genital organs and menstrual cycle

Physiologic discharge: cervical mucus, vaginal transudation, bacteria, squamous epithelial cells.
Individual variation.
Pregnancy.
Sexual response.
Menstrual cycle variation.
Infection.
Foreign body: tampon, cervical cap, other.
Neoplasm.
Fistula.
IUD.
Cervical ectropion.
Spermicide.
Nongenital causes: urinary incontinence, urinary tract fistula, Crohn disease, rectovaginal fistula.

GENITAL LESIONS, INFECTIOUS CAUSES[10]

ICD-10CM #	Varies with specific diagnosis

INFECTIOUS CAUSES OF GENITAL LESIONS

Sexually Transmitted Infections

Syphilis:
  Primary (chancre).
  Secondary (condyloma latum).
Herpes simplex virus types 1 and 2.
Chancroid *(Haemophilus ducreyi).*
Lymphogranuloma venereum.
Granuloma inguinale (donovanosis).
Human papillomavirus.
Sarcoptes scabiei.
Molluscum contagiosum.

Nonsexually Transmitted Infections

Folliculitis.
Tuberculosis.
Tularemia.
Histoplasmosis.
Candida (balanitis or vaginitis).
Amebiasis.

GENITAL LESIONS, NONINFECTIOUS CAUSES[10]

ICD-10CM #	Varies with specific diagnosis

NONVENEREAL CAUSES OF GENITAL LESIONS

Trauma.
Malignancies (e.g., squamous cell carcinoma).
Behçet syndrome.
Lipschütz vulvar ulcers.
Peyronie disease.
Fixed-drug eruption.
Eczema.
Psoriasis.
Inflammatory bowel disease.
Contact dermatitis.

Lichen planus.
Hidradenitis suppurativa.
Postinflammatory hypopigmentation.
Aphthous ulcers (associated with human immunodeficiency virus).

GENITAL SORES[3]

ICD-10CM #		
	A60.9	Anogenital herpesviral infection, unspecified
	A51.0	Primary genital syphilis
	A63.0	Anogenital (venereal) warts
	A57	Chancroid
	A58	Granuloma inguinale
	A55	Chlamydial lymphogranuloma (venereum)
	N94.89	Other specified conditions associated with female genital organs and menstrual cycle
	N50.8	Other specified disorders of male genital organs

Herpes genitalis.
Syphilis.
Chancroid.
Lymphogranuloma venereum.
Granuloma inguinale.
Condyloma acuminatum.
Neoplastic lesion.
Trauma.

GLOMERULONEPHRITIS ASSOCIATED WITH MALIGNANCY[79]

ICD-10CM #		
	N00.9	Acute nephritic syndrome with unspecified morphologic changes

Membranous glomerulonephritis:
Breast cancer.
Lung cancer.
Colon cancer.
Prostate cancer.
Graft-versus-host disease.
Minimal change disease:
Hodgkin lymphoma.
Non-Hodgkin lymphoma.
Graft-versus-host disease.
Case reports.
Immunoglobulin A nephritis.
Antineutrophil cytoplasmic antibody vasculitis.
Focal segmental glomerulosclerosis.

GLOMERULONEPHRITIS, RAPIDLY PROGRESSIVE[3]

ICD-10CM #		
	N05.9	Unspecified nephritic syndrome with unspecified morphologic changes

DIFFERENTIAL DIAGNOSIS OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Linear Immune Staining
Anti-GBM disease.
Goodpasture syndrome.
Rarely membranous glomerulonephritis.

Granular Immune Staining
Subacute bacterial endocarditis (past infectious).
Lupus nephritis.
Cryoglobulinemia.
Membranoproliferative glomerulonephritis (type II more than type I).
Immunoglobulin A nephropathy, Henoch-Schönlein purpura.
Idiopathic.

No Immune Staining (Pauci-immune)
Antineutrophil cytoplasmic antibody-associated vasculitis (Wegener granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome).
Idiopathic.

GLOMERULOPATHIES, THROMBOTIC, MICROANGIOPATHIC[3]

ICD-10CM #		
	M31.1	Thrombotic microangiopathy

THROMBOTIC MICROANGIOPATHIC GLOMERULOPATHIES

Thrombotic thrombocytopenic purpura.
Hemolytic-uremic syndrome.
Malignant hypertension.
Scleroderma renal crisis.
Preeclampsia, eclampsia.
HELLP syndrome (hemolysis, elevated liver enzymes, low platelets).
Antiphospholipid antibody syndrome.
Drugs: oral contraceptives, quinine, cyclosporine, tacrolimus, ticlopidine, clopidogrel.

GLOMERULOSCLEROSIS, FOCAL SEGMENTAL[3]

ICD-10CM #		
	N03.3	Chronic nephritic syndrome with diffuse mesangial proliferative glomerulonephritis

ETIOLOGY OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

Primary idiopathic FSGS.
Secondary FSGS.
HIV (usually collapsing variant).
Reflux nephropathy.
Heroin abuse.
Sickle cell disease.
Oligomeganephronia.
Renal dysgenesis or agenesis (low nephron mass).
Radiation nephritis.
Familial podocytopathies.
NPHS1 (nephrin) mutation.
NPHS2 (podocin) mutation.
TRPC6 (cation channel) mutation.
ACTN4 (a-actinin 4 mutation).

GLOSSODYNIA[86]

ICD-10CM #		
	K14.6	Glossodynia

DENTURE-RELATED

Dentures (ill-fitting, monomer from denture base).
Dental plaque.
Oral parafunction.

INFECTIVE/DERMATOLOGIC

Candidiasis.
Lichen planus.

DEFICIENCY STATES

Iron, B_{12}, folate, B_2 (riboflavin), B_6 (pyridoxine), zinc.

ENDOCRINE

Diabetes.
Myxedema.
Hormonal changes occurring during menopause.

NEUROLOGICALLY MEDIATED

Referred from tonsils, teeth.
Lingual nerve neuropathy.
Glossopharyngeal neuralgia.
Esophageal reflux.

IATROGENIC

Mouthwash.

XEROSTOMIA
PSYCHOGENIC
IDIOPATHIC

GLUCOCORTICOID DEFICIENCY[32]

ICD-10CM #		
	E27.1	Primary adrenocortical insufficiency
	E27.3	Drug-induced adrenocortical insufficiency

ACTH-independent causes.
TB.
Autoimmune (idiopathic).
Other rare causes:
- Fungal infection.
- Adrenal hemorrhage.
- Metastases.
- Sarcoidosis.
- Amyloidosis.
- Adrenoleukodystrophy.
- Adrenomyeloneuropathy.
- HIV infection.
- Congenital adrenal hyperplasia.
- Medications (e.g., ketoconazole).

ACTH-dependent causes:
- Hypothalamic-pituitary-adrenal suppression.
- Exogenous.
- Glucocorticoid.
- ACTH.
- Endogenous—cure of Cushing syndrome.

Hypothalamic-pituitary lesions.
- Neoplasm:
  - Primary pituitary tumor.
  - Metastatic tumor.
  - Craniopharyngioma.

Infection:
- Tuberculosis.
- Actinomycosis.
- Nocardiosis.

Sarcoid.
Head trauma.
Isolated ACTH deficiency.

GOITER

ICD-10CM #		
	E01.2	Iodine-deficiency related (endemic) goiter, unspecified
	E04.9	Nontoxic goiter, unspecified
	E04.9	Nontoxic goiter, unspecified
	E07.1	Dyshormogenetic goiter
	E01.2	Iodine-deficiency related (endemic) goiter, unspecified
	E04.9	Nontoxic goiter, unspecified
	E04.2	Nontoxic multinodular goiter
	E04.0	Nontoxic diffuse goiter
	E05.10	Thyrotoxicosis with toxic single thyroid nodule without thyrotoxic crisis or storm

Thyroiditis.
Toxic multinodular goiter.
Graves disease.
Medications (PTU, methimazole, sulfonamides, sulfonylureas, ethionamide, amiodarone, lithium, etc.).
Iodine deficiency.
Sarcoidosis, amyloidosis.
Defective thyroid hormone synthesis.
Resistance to thyroid hormone.

GRANULOMATOUS DERMATITIDES

ICD-10CM #		
	L92.9	Granulomatous disorder of the skin and subcutaneous tissue, unspecified

Granuloma annulare.
Sarcoidosis.
Necrobiosis lipoidica diabeticorum.
Cutaneous Crohn disease.
Rheumatoid nodules.
Annular elastolytic giant cell granuloma (actinic granuloma).
Foreign body granuloma.

GRANULOMATOUS DISORDERS[75]

ICD-10CM #		
	M31.30	Granulomatosis with polyangiitis without renal involvement
	K75.3	Granulomatous hepatitis
	L92.9	Granulomatous disorder of skin and subcutaneous tissue, unspecified

INFECTIONS

Fungi
Histoplasma.
Coccidioides.
Blastomyces.
Sporothrix.
Aspergillus.
Cryptococcus.
Protozoa
Toxoplasma.
Leishmania.
Metazoa
Toxocara.
Schistosoma.
Spirochetes
Treponema pallidum.
T. pertenue.
T. carateum.
Mycobacteria
M. tuberculosis.
M. leprae.
M. kansasii.
M. marinum.
M. avian.
Bacille Calmette-Guérin (BCG) vaccine.
Bacteria
Brucella.
Yersinia.
Other Infections
Cat-scratch disease.
Lymphogranuloma.

NEOPLASIA

Carcinoma.
Reticulosis.
Pinealoma.
Dysgerminoma.
Seminoma.
Reticulum cell sarcoma.
Malignant nasal granuloma.

CHEMICALS

Beryllium.
Zirconium.
Silica.
Starch.

IMMUNOLOGIC ABERRATIONS

Sarcoidosis.
Crohn disease.
Primary biliary cirrhosis.
Granulomatosis with polyangiitis.
Giant cell arteritis.
Peyronie disease.
Hypogammaglobulinemia.
SLE.
Lymphomatoid granulomatosis.
Histiocytosis X.
Hepatic granulomatous disease.
Immune complex disease.
Rosenthal-Melkersson syndrome.
Churg-Strauss allergic granulomatosis.

LEUKOCYTE OXIDASE DEFECT

Chronic granulomatous disease of childhood.

EXTRINSIC ALLERGIC ALVEOLITIS

Farmer's lung.
Bird fancier's.
Mushroom worker's.
Suberosis (cork dust).
Bagassosis.
Maple bark stripper's.
Paprika splitter's.
Coffee bean.
Spatlese lung.

OTHER DISORDERS

Whipple disease.
Pyrexia of unknown origin.
Radiotherapy.
Cancer chemotherapy.
Panniculitis.
Chalazion.
Sebaceous cyst.
Dermoid.
Sea urchin spine injury.

GRANULOMATOUS LIVER DISEASE

ICD-10CM #		
	K75.3	Granulomatous hepatitis

Sarcoidosis.
Granulomatosis with polyangiitis.
Vasculitis.
Inflammatory bowel disease.
Allergic granulomatosis.
Erythema nodosum.
Infections (fungal, viral, parasitic).
Primary biliary cirrhosis.
Lymphoma.
Hodgkin disease.
Drugs (e.g., allopurinol, hydralazine, sulfonamides, penicillins).
Toxins (copper sulfate, beryllium).

GREEN OR BLUE URINE

ICD-10CM #		
	R82	Other abnormal findings in urine

Pseudomonal urinary tract infection
Medications: triamterene, amitriptyline, IV cimetidine, IV promethazine.
Biliverdin.
Dyes (methylene blue, indigo carmine).

GROIN LUMP[86]

ICD-10CM #		
	R19.09	Other intraabdominal and pelvic swelling, mass and lump
	R22.9	Localized swelling, mass and lump, unspecified

COMMON CAUSES

Inguinal hernia.
Femoral hernia.
Lymph node.

OTHER CAUSES

Saphena varix.
Femoral artery aneurysm/pseudoaneurysm.
Psoas abscess.
Lipoma of the cord.
Encysted hydrocele of the cord (male).
Testicular maldescent (male).
Hydrocele of canal of Nuck (female).

GROIN MASSES

ICD-10CM #		
	R22.9	Localized swelling, mass and lump, unspecified
	S39.848A	Other specified injuries of external genitals, initial encounter

Hernia (inguinal, femoral).
Hydrocele.
Varicocele.
Sebaceous cyst.
Hidradenitis of inguinal apocrine glands.
Neoplasm: lymphoma, metastases.
Lipoma.
Hematoma.
Reactive inguinal adenopathy, femoral adenitis.
Folliculitis, psoas abscess.
Epididymitis, testicular torsion, ectopic testes.
Aneurysm or pseudoaneurysm of femoral artery.

GROIN PAIN[15]

ICD-10CM #		
	R52	Pain, unspecified

DIFFERENTIAL DIAGNOSIS OF GROIN PAIN

Surgery
Workers' Compensation.
Hernia.
Recurrent hernia.
Posthernia.
Orthopedic
Hip disorders:
- Acetabular labral tears.
- Avascular necrosis.
- Chondritis dissecans.
- Legg-Calvé-Perthes disease.
- Osteoarthritis.
- Pelvic stress fractures.
- Slipped femoral capital epiphysis.
- Synovitis.

Urology
Cystitis.
Epididymitis.
Nephrolithiasis.
Prostate cancer.
Prostatitis.
Torsion of testes.
Urethral extravasation.
Urinary tract infection.
Vas granuloma/fibrosis.
Dermatology
Lymphadenitis.
Psoriasis/burn.
Sebaceous cyst/hidradenitis.
Thrombophlebitis/cellulitis.
Neurosurgery
Disk disease.
Spinal injuries, inflammation, tumors.
Spondylolisthesis.
Spondylolysis.
Rheumatology
Connective tissue disorders.
Iliopsoas bursitis.
Osteitis pubis.
Systemic lupus erythematosus.
Neurology
Lumbosacral disorders.
Neurofibromatosis.
Infectious Disease
Herpes zoster.
HIV/tuberculosis.
Lyme disease.
Psoas abscess.
Sports Medicine
"Sports hernia" (adductor strains).
Gilmore groin.
Vascular
Abscess hematoma.
Post-vein stripping.
Pseudoaneurysm.
Vascular graft.
Gastroenterology
Appendicitis/adhesions.
Diverticulitis.
Inflammatory retroperitoneal phlegmon (pancreatitis).
Meckel diverticulum.
Granulomatous colitis.
Gynecology
Cesarean section.
Cervical cancer.
Endometriosis.
Tubal/ovarian disorders.

GROIN PAIN, ACTIVE PATIENT[85]

ICD-10CM #		
	S39.848A	Other specified injuries of external genitals, initial encounter
	R52	Pain, unspecified

MUSCULOSKELETAL

Avascular necrosis of the femoral head.
Avulsion fracture (lesser trochanter, anterior superior iliac spine, anterior inferior iliac spine).
Bursitis (iliopectineal, trochanteric).
Entrapment of the ilioinguinal or iliofemoral nerve.
Gracilis syndrome.
Muscle tear (adductors, iliopsoas, rectus abdominis, gracilis, sartorius, rectus femoris).
Myositis ossificans of the hip muscles.
Osteitis pubis.
Osteoarthritis of the femoral head.
Slipped capital femoral epiphysis.
Stress fracture of the femoral head or neck and pubis.
Synovitis.

HERNIA-RELATED

Avulsion of the internal oblique muscle in the conjoined tendon.
Defect at the insertion of the rectus abdominis muscle.
Direct inguinal hernia.
Femoral ring hernia.
Indirect inguinal hernia.
Inguinal canal weakness.

UROLOGIC

Epididymitis.
Fracture of the testis.
Hydrocele.
Kidney stone.
Posterior urethritis.
Prostatitis.
Testicular cancer.
Torsion of the testis.
Urinary tract infection.
Varicocele.

GYNECOLOGIC

Ectopic pregnancy.
Ovarian cyst.
Pelvic inflammatory disease.
Torsion of the ovary.
Vaginitis.

LYMPHATIC ENLARGEMENT IN GROIN

GYNECOMASTIA

ICD-10CM #		
	N62	Hypertrophy of breast

Physiologic (puberty, newborns, aging).
Drugs (estrogen and estrogen precursors, 5-a reductase inhibitors, digitalis, testosterone and exogenous androgens, clomiphene, cimetidine, spironolactone, ketoconazole, amiodarone, ACE inhibitors, isoniazid, phenytoin, methyldopa, metoclopramide, phenothiazine).
Increased prolactin level (prolactinoma).
Liver disease.
Adrenal disease.
Thyrotoxicosis.
Increased estrogen production (hCG-producing tumor, testicular tumor, bronchogenic carcinoma).
Secondary hypogonadism.
Primary gonadal failure (trauma, castration, viral orchitis, granulomatous disease).
Defects in androgen synthesis.
Testosterone deficiency.
Klinefelter syndrome.

HAIR LOSS[38]

ICD-10CM #		
	L63.8	Other alopecia areata
	L63.9	Alopecia areata, unspecified
	L64.0	Drug-induced androgenic alopecia
	L64.8	Other androgenic alopecia

GENERALIZED

Acute blood loss.*
Childbirth.
Crash diets (inadequate protein).
Drugs:
- Coumarin.
- Heparin.
- Propranolol.
- Vitamin A.
- High fever.

Hypothyroidism and hyperthyroidisms.

*Diffuse, uniform loss, but many hairs left randomly distributed in area of loss.

GROIN MASSES

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	R22.9	Localized swelling, mass and lump, unspecified
	S39.848A	Other specified injuries of external genitals, initial encounter

Hernia (inguinal, femoral).
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Hidradenitis of inguinal apocrine glands.
Neoplasm: lymphoma, metastases.
Lipoma.
Hematoma.
Reactive inguinal adenopathy, femoral adenitis.
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Disk disease.
Spinal injuries, inflammation, tumors.
Spondylolisthesis.
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Iliopsoas bursitis.
Osteitis pubis.
Systemic lupus erythematosus.
Neurology
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Neurofibromatosis.
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Herpes zoster.
HIV/tuberculosis.
Lyme disease.
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Meckel diverticulum.
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Gracilis syndrome.
Muscle tear (adductors, iliopsoas, rectus abdominis, gracilis, sartorius, rectus femoris).
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Femoral ring hernia.
Indirect inguinal hernia.
Inguinal canal weakness.

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Fracture of the testis.
Hydrocele.
Kidney stone.
Posterior urethritis.
Prostatitis.
Testicular cancer.
Torsion of the testis.
Urinary tract infection.
Varicocele.

GYNECOLOGIC

Ectopic pregnancy.
Ovarian cyst.
Pelvic inflammatory disease.
Torsion of the ovary.
Vaginitis.

LYMPHATIC ENLARGEMENT IN GROIN

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ICD-10CM #		
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Physiologic (puberty, newborns, aging).
Drugs (estrogen and estrogen precursors, 5-a reductase inhibitors, digitalis, testosterone and exogenous androgens, clomiphene, cimetidine, spironolactone, ketoconazole, amiodarone, ACE inhibitors, isoniazid, phenytoin, methyldopa, metoclopramide, phenothiazine).
Increased prolactin level (prolactinoma).
Liver disease.
Adrenal disease.
Thyrotoxicosis.
Increased estrogen production (hCG-producing tumor, testicular tumor, bronchogenic carcinoma).
Secondary hypogonadism.
Primary gonadal failure (trauma, castration, viral orchitis, granulomatous disease).
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GENERALIZED

Acute blood loss.*
Childbirth.
Crash diets (inadequate protein).
Drugs:
- Coumarin.
- Heparin.
- Propranolol.
- Vitamin A.
- High fever.

Hypothyroidism and hyperthyroidisms.

*Diffuse, uniform loss, but many hairs left randomly distributed in area of loss.

Physical stress (e.g., surgery).
Physiologic stress (e.g., neonate).
Psychologic stress.
Severe illness (e.g., systemic lupus erythematosis).
Cancer chemotherapeutic agents.
Poisoning:
  Thallium (rat poison).
  Arsenic.
Radiation therapy.
Secondary syphilis: "moth eaten" alopecia.

LOCALIZED

Androgenetic alopecia:†
  Male pattern.
  Female pattern.
Hirsutism.
Alopecia areata.
Trichotillomania.
Traction alopecia.
Scarring alopecia:
  Developmental defects: aplasia cutis.
Physical injury: burns, pressure.
Infection:
  Fungal: kerion.
  Bacterial: folliculitis, furuncle.
  Viral: herpes zoster.
Neoplasms:
  Metastatic carcinoma.
  Sclerosing basal cell carcinoma.
Lupus erythematosus.
Lichen planus.
Cicatricial pemphigoid.
Scleroderma.

HALITOSIS

ICD-10CM # R19.6 Halitosis

Tobacco use.
Alcohol use.
Dry mouth (mouth breathing, inadequate fluid intake).
Foods (onion, garlic, meats, nuts, protein drinks).
Disease of mouth or nose (infections, cancer, inflammation).
Medications (antihistamines, antidepressants).
Systemic disorders (diabetes, uremia).
GI disorders (esophageal diverticula, hiatal hernia, GERD, achalasia).
Sinusitis.
Pulmonary disorders (bronchiectasis, pneumonia, neoplasms, TB).

HALLUCINATIONS, VISUAL, NEUROLOGIC CAUSES[51]

ICD-10CM # R44.1 Visual hallucinations

Blindness/sensory deprivation—Charles Bonnet syndrome.
Palinopsia.
Dementia-producing diseases:
  Alzheimer.
  Dementia with Lewy bodies.*
  Parkinson.†
Intoxications:
  Alcoholic hallucinosis.
    Delirium tremens (DTs).
Hallucinogens:
  Amphetamines.
  Cocaine.
  Lysergic acid diethylamide (LSD).
  Phencyclidine (PCP).
Medicines:
  Atropine, scopolamine.
  Levodopa and dopamine agonists.
  Steroids.
Migraine with aura (classic migraine).
Narcolepsy: hypnopompic (awakening) and hypnagogic (falling asleep) hallucinations.
Seizures.
Peduncular hallucinations.

HAND PAIN AND SWELLING[16]

ICD-10CM # 729.5 Pain in limb

Trauma.
Gout.
Pseudogout.
Cellulitis.
Lymphangitis.
DVT of upper extremity.
Thrombophlebitis.
RA.
Remitting seronegative symmetrical synovitis with pitting edema (RS3PE).
Polymyalgia rheumatica.
Mixed connective tissue disease.
Scleroderma.
Rupture of the olecranon bursa.
Metzger syndrome (neoplasia).
The puffy hand of drug addiction.
Reflex sympathetic dystrophy.
Eosinophilic fasciitis.
Sickle cell (hand-foot syndrome).
Leprosy.
Factitial (the rubber band syndrome).

HEADACHE[31]

ICD-10CM #	G44.1	Vascular headache, not elsewhere classified
	R51	Headache
	G44.209	Tension-type headache, unspecified, not intractable
	G44.009	Cluster headache syndrome, unspecified, not intractable
	G43.909	Migraine, unspecified, not intractable, without status migrainosus
	G44.1	Vascular headache, not elsewhere classified

Vascular: migraine, cluster headaches, temporal arteritis, hypertension, cavernous sinus thrombosis.
Musculoskeletal: neck and shoulder muscle contraction, strain of extraocular and/or intraocular muscles, cervical spondylosis, temporomandibular arthritis.
Infections: meningitis, encephalitis, brain abscess, sepsis, sinusitis, osteomyelitis, parotitis, mastoiditis.
Cerebral neoplasm.
Subdural hematoma.
Cerebral hemorrhage/infarct.
Pseudotumor cerebri.
Normal-pressure hydrocephalus (NPH).
Postlumbar puncture.
Cerebral aneurysm, arteriovenous malformations.
Posttrauma.
Dental problems: abscess, periodontitis, poorly fitting dentures.
Trigeminal neuralgia, glossopharyngeal neuralgia.
Otitis and other ear diseases.
Glaucoma and other eye diseases.
Metabolic: uremia, carbon monoxide inhalation, hypoxia.
Pheochromocytoma, hypoglycemia, hypothyroidism.
Effort induced: benign exertional headache, cough, headache, coital cephalalgia.
Drugs: alcohol, nitrates, histamine antagonists.
Paget disease of the skull.
Emotional, psychiatric.

HEADACHE, ACUTE[23]

ICD-10CM # R51 Headache

DIFFERENTIAL DIAGNOSIS OF ACUTE HEADACHE

Evaluation of the first acute headache should exclude pathologic causes listed here before consideration of more common etiologies.
Increased intracranial pressure (ICP): trauma, hemorrhage, tumor, hydrocephalus, pseudotumor cerebri, abscess, arachnoid cyst, cerebral edema.
Decreased ICP: after ventriculoperitoneal shunt, lumbar puncture, cerebrospinal fluid leak from basilar skull fracture.
Meningeal inflammation: meningitis, leukemia, subarachnoid or subdural hemorrhage.
Vascular: Vasculitis, arteriovenous malformation, hypertension, cerebrovascular accident.
Bone, soft tissue: referred pain from scalp, eyes, ears, sinuses, nose, teeth, pharynx, cervical spine, temporomandibular joint.
Infection: systemic infection, encephalitis, sinusitis, etc.
First migraine.

HEADACHE AND FACIAL PAIN[82]

ICD-10CM #	R51	Headache
	G44.1	Vascular headache, not elsewhere classified

VASCULAR HEADACHES

Migraine

Migraine with headaches and inconspicuous neurologic features:
  Migraine without aura ("common migraine").

†Most or all hair missing from involved area.
*Although visual hallucinations are likely to complicate almost any form of dementia, they are characteristic of dementia with Lewy bodies disease.

†Dopaminergic medications such as levodopa-carbidopa (Sinemet) are more likely than Parkinson disease itself to produce hallucinations.

Migraine with headaches and conspicuous neurologic features:
With transient neurologic symptoms:
Migraine with typical aura ("classic migraine").
Sensory, basilar, and hemiplegic migraine.
With prolonged or permanent neurologic features ("complicated migraine"):
Ophthalmoplegic migraine.
Migrainous infarction.
Migraine without headaches but with conspicuous neurologic features ("migraine equivalents"):
Abdominal migraine.
Benign paroxysmal vertigo of childhood.
Migraine aura without headache ("isolated auras," transient migrainous accompaniments).

Cluster Headaches

Episodic cluster headache ("cyclic cluster headaches").
Chronic cluster headaches.
Chronic paroxysmal hemicrania.

Other Vascular Headaches

Headaches of reactive vasodilation (fever, drug-induced, postictal, hypoglycemia, hypoxia, hypercarbia, hyperthyroidism).
Headaches associated with arterial hypertension:
Chronic severe hypertension (diastolic 120 mm Hg).
Paroxysmal severe hypertension (pheochromocytoma, some coital headaches).
Headaches caused by cranial arteritis:
Giant cell arteritis ("temporal arteritis").
Other vasculitides.

HEADACHES ASSOCIATED WITH DEMONSTRABLE MUSCLE SPASM

Headache caused by posturally induced or perilesional muscle spasm:
Headaches of sustained or impaired posture (e.g., prolonged close work, driving).
Headaches associated with cervical spondylosis and other diseases of cervical spine.
Myofascial pain dysfunction syndrome (headache or facial pain associated with disorders of teeth, jaws, and related structures, or "TMJ syndrome").
Headaches caused by psychophysiologic muscular contraction ("muscle contraction headaches," or tension-type headache associated with disorder of pericranial muscles).

HEADACHES AND FACIAL PAIN WITHOUT DEMONSTRABLE PHYSICAL SUBSTRATE

Headaches of uncertain etiology:
"Tension headaches" (tension-type headache unassociated with disorder of pericranial muscles).
Some forms of posttraumatic headache.
Psychogenic headaches (e.g., hypochondriacal, conversional, delusional, malingered).
Facial pain of uncertain etiology ("atypical facial pain").

COMBINED TENSION-MIGRAINE HEADACHES

Episodic migraine superimposed on chronic tension headaches.
Chronic daily headaches:
Associated with analgesic and/or ergotamine overuse ("rebound headaches").
Not associated with drug overuse.

HEADACHES AND HEAD PAINS CAUSED BY DISEASES OF EYES, EARS, NOSE, SINUSES, TEETH, OR SKULL

Headaches Caused by Meningeal Inflammation

Subarachnoid hemorrhage.
Meningitis and meningoencephalitis.
Others (e.g., meningeal carcinomatosis).

HEADACHES ASSOCIATED WITH ALTERED INTRACRANIAL PRESSURE ("TRACTION HEADACHES")

Increased Intracranial Pressure

Intracranial mass lesions (neoplasm, hematoma, abscess, etc.).
Hydrocephalus.
Benign intracranial hypertension.
Venous sinus thrombosis.

Decreased Intracranial Pressure

Post-lumbar puncture headaches.
Spontaneous hypoliquorrheic headaches.

HEADACHES AND HEAD PAINS CAUSED BY CRANIAL NEURALGIAS

Presumed Irritation of Superficial Nerves

Occipital neuralgia.
Supraorbital neuralgia.

Presumed Irritation of Intracranial Nerves

Trigeminal neuralgia ("tic douloureux").
Glossopharyngeal neuralgia.

HEADACHE, CHRONIC[23]

ICD-10CM #		
	R51	Headache

DIFFERENTIAL DIAGNOSIS OF RECURRENT OR CHRONIC HEADACHES

Migraine (with or without aura).
Tension.
Analgesic rebound.
Caffeine withdrawal.
Sleep deprivation (e.g., in children with sleep apnea) or chronic hypoxia.
Tumor.
Psychogenic: conversion disorder, malingering.
Cluster headache.

HEAD AND NECK, SOFT TISSUE MASSES

ICD-10CM #		
	R22.0	Localized swelling, mass and lump, head
	R22.1	Localized swelling, mass and lump, neck

Lipoma.
Pilar cyst.
Epidermal inclusion cyst.
Dermoid cyst.
Bone cyst.
Hemangioma.
Eosinophilic granuloma.
Other: facial nerve neuroma, teratoma, rhabdomyoma, rhabdomyosarcoma, branchial cleft cyst.

HEARING LOSS, ACUTE[58]

ICD-10CM #		
	H91.23	Sudden idiopathic hearing loss, bilateral

Infectious: mumps, measles, influenza, herpes simplex, herpes zoster, CMV, mononucleosis, syphilis.
Vascular: macroglobulinemia, sickle cell disease, Berger disease, leukemia, polycythemia, fat emboli, hypercoagulable states.
Metabolic: diabetes, pregnancy, hyperlipoproteinemia.
Conductive: cerumen impaction, foreign bodies, otitis media, otitis externa, barotrauma, trauma.
Medications: aminoglycosides, loop diuretics, antineoplastics, salicylates, vancomycin.
Neoplasm: acoustic neuroma, metastatic neoplasm.

HEARTBURN AND INDIGESTION[76]

ICD-10CM #		
	R12	Heartburn
	K30	Functional dyspepsia

Reflux esophagitis.
Gastritis.
Nonulcer dyspepsia.
Functional GI disorder (anxiety disorder, social/environmental stresses).
Excessive intestinal gas (ingestion of flatulogenic foods, GI stasis, constipation).
Gas entrapment (hepatitis or splenic flexure syndrome).
Neoplasm (adenocarcinoma of stomach or esophagus, lymphoma).
Gallbladder disease.

HEART DISEASE, TRAUMATIC CAUSES[59]

ICD-10CM #		
	S26.020	Mild laceration of heart with hemopericardium
	S26.021	Moderate laceration of heart with hemopericardium
	S26.022	Major laceration of heart with hemopericardium

Penetrating:
Stab wounds: knives, swords, ice picks, fence posts, wire, sports.
Projectile wounds: handguns, rifles, nail guns, lawnmower projectiles.
Shotgun wounds: pellets, close-range versus distant.

Nonpenetrating (blunt):
- Motor vehicle accident:
  - Seat belt.
  - Air bag.
  - Dashboard/steering wheel.
- Vehicular-pedestrian accident.
- Falls from a height.
- Crushing: industrial accident.
- Blasts: improvised explosive devices, grenades, fragments (combined blunt/penetrating).
- Assault.
- Sternal or rib fractures.
- Recreational: sporting events (e.g., rodeo, baseball).

HEART FAILURE WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION[34]

ICD-10CM # I50.9 Heart failure, unspecified

CAUSES OF (AND ALTERNATIVE EXPLANATIONS FOR) HEART FAILURE WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION (>45% TO 50%)

Inaccurate diagnosis of heart failure (e.g., pulmonary disease, obesity).
Inaccurate measurements of ejection fraction.
Systolic function overestimated by ejection fraction (e.g., mitral regurgitation).
Episodic, unrecognized systolic dysfunction.
Intermittent ischemia.
Arrhythmia.
Severe hypertension.
Alcohol abuse.
Diastolic dysfunction.
Abnormalities of myocardial relaxation:
- Ischemia.
- Hypertrophy.

Abnormalities of myocardial compliance:
- Hypertrophy.
- Aging.
- Fibrosis.
- Diabetes mellitus.
- Infiltrative disease (amyloidosis, sarcoidosis).
- Storage disease (hemochromatosis).
- Endomyocardial disease (endomyocardial fibrosis, radiation, anthracyclines).

Pericardial disease (constriction, tamponade).

HEART FAILURE, ACUTE[7]

ICD-10CM # I50.9 Heart failure, unspecified

COMMON PRECIPITATING CAUSES OF ACUTE HF

Systemic hypertension.
Myocardial infarction or ischemia.
Dysrhythmia.
Systemic infection.
Anemia.
Dietary, physical, environmental, and emotional excesses.
Pregnancy.
Thyrotoxicosis or hypothyroidism.
Acute myocarditis.
Acute valvular dysfunction.
Pulmonary embolus.
Pharmacologic complications.

HEART FAILURE, CHRONIC[11]

ICD-10CM # I50.9 Heart failure, unspecified

Myocardial disease.
Coronary artery disease:
- Myocardial infarction.[19]
- Myocardial ischemia.

Chronic pressure overload:
- Hypertension.
- Obstructive valvular disease.

Chronic volume overload:
- Regurgitant valvular disease.
- Intracardiac (left-to-right) shunting.
- Extracardiac shunting.

Nonischemic dilated cardiomyopathy:
- Familial or genetic disorders.
- Infiltrative disorders.
- Toxic or drug-induced damage.
- Metabolic disorder.
- Viral or other infectious agents.

Disorders of rate and rhythm:
- Chronic bradyarrhythmias.
- Chronic tachyarrhythmias.
- Pulmonary heart disease
- Cor pulmonale.
- Pulmonary vascular disorders.

High-output states.
Metabolic disorders:
- Thyrotoxicosis.
- Nutritional disorders (beriberi).

Excessive blood flow requirements:
- Systemic arteriovenous shunting.
- Chronic anemia.

HEART FAILURE, CONGENITAL HEART DISEASE CAUSES[68]

ICD-10CM # I50.9 Heart failure, unspecified

CAUSES OF CONGESTIVE HEART FAILURE RESULTING FROM CONGENITAL HEART DISEASE

Age of Onset	Cause
At birth:	HLHS.
	Volume overload lesions:
	Severe tricuspid or pulmonary insufficiency.
	Large systemic arteriovenous fistula.
First week	TGA.
	PDA in small premature infants.
	HLHS (with more favorable anatomy).
	TAPVR, particularly those with pulmonary venous obstruction.
	Others.
	Systemic arteriovenous fistula.
	Critical AS or PS.
1-4 wk	COA with associated anomalies.
	Critical AS.
	Large left-to-right shunt lesions (VSD, PDA) in premature infants.
	All other lesions previously listed.
4-6 wk	Some left-to-right shunt lesions such as ECD.
6 wk-4 mo	Large VSD.
	Large PDA.
	Others, such as anomalous left coronary artery from the PA.

AS, Aortic stenosis; *COA,* coarctation of the aorta; *ECD,* endocardial cushion defect; *HLHS,* hypoplastic left heart syndrome; *PA,* pulmonary artery; *PDA,* patent ductus arteriosus; *PS,* pulmonary stenosis; *TAPVR,* total anomalous pulmonary venous return; *TGA,* transposition of the great arteries; *VSD,* ventricular septal defect.

[19] Indicates conditions that can also lead to HF with a preserved EF.

HEART FAILURE, PATHOGENIC CAUSES[34]

ICD-10CM # I50.9 Heart failure, unspecified

IMPAIRED SYSTOLIC (CONTRACTILE) FUNCTION

Ischemic damage or dysfunction:
- Myocardial infarction.
- Persistent or intermittent myocardial ischemia.
- Hypoperfusion (shock).

Chronic pressure overloading:
- Hypertension.
- Obstructive valvular disease.

Chronic volume overload:
- Regurgitant valvular disease.
- Intracardiac left-to-right shunting.
- Extracardiac shunting.

Nonischemic dilated cardiomyopathy:
- Familial/genetic disorders.
- Toxic/drug-induced damage
- Immunologically mediated necrosis.
- Infectious agents.
- Metabolic disorders.
- Infiltrative processes.
- Idiopathic conditions.

IMPAIRED DIASTOLIC FUNCTION (RESTRICTED FILLING, INCREASED STIFFNESS)

Pathologic myocardial hypertrophy:
- Primary (hypertrophic cardiomyopathies).
- Secondary (hypertension).
- Aging.
- Ischemic fibrosis.
- Restrictive cardiomyopathy:
  - Infiltrative disorders (amyloidosis, sarcoidosis).
  - Storage diseases (hemochromatosis, genetic abnormalities).

Endomyocardial disorders.

MECHANICAL ABNORMALITIES

Intracardiac:
- Obstructive valvular disease.
- Regurgitant valvular disease.
- Intracardiac shunts.
- Other congenital abnormalities.

Extracardiac:
- Obstructive (coarctation, supravalvular aortic stenosis).
- Left-to-right shunting (patent ductus arteriosus).

DISORDERS OF RATE AND RHYTHM

Bradyarrhythmias (sinus node dysfunction, conduction abnormalities).
Tachyarrhythmias (ineffective rhythms, chronic tachycardia).

PULMONARY HEART DISEASE

Cor pulmonale.
Pulmonary vascular disorders.

HIGH-OUTPUT STATES

Metabolic disorders:
- Thyrotoxicosis.
- Nutritional disorders (beriberi).
- Excessive blood flow requirements:
  - Chronic anemia.
  - Systemic arteriovenous shunting.

HEART FAILURE, PREGNANCY

ICD-10CM # I50.9 Heart failure, unspecified

Congenital valvular heart disease exacerbated by pregnancy.
Peripartum cardiomyopathy.
Untreated thyrotoxicosis.
Hypothyroidism.
Pulmonary hypertension.
Myocardial infarction.

HEAT STROKE[1]

ICD-10CM # T67.0 Heatstroke and sunstroke

Sepsis.
Encephalitis.
Meningitis.
Brain abscess.
Malaria (cerebral falciparum).
Typhoid fever.
Tetanus.
Alcohol withdrawal syndrome.
Neuroleptic malignant syndrome.
Anticholinergic toxicity.
Salicylate toxicity.
Phencyclidine hydrochloride (PCP), cocaine, or amphetamine toxicity.
Status epilepticus.
Cerebral hemorrhage.
Diabetic ketoacidosis.
Thyroid storm.

HEEL PAIN

ICD-10CM # M25.50 Pain in unspecified joint

Achilles tendonitis/tendinopathy (insertional, noninsertional).
Retrocalcaneal bursitis (superficial, deep).
Plantar fasciopathy.
Neuropathy (tarsal tunnel, posterior tibial nerve [medial calcaneal branch], abductor digiti quinti).
Calcaneal stress fracture.
Puncture wound, foreign body.
Cellulitis.
Spondyloarthropathy.
Fat pad atrophy.
Soft tissue tumor.
S1 radiculopathy.
Paget disease of bone.
Haglund deformity.
Primary or metastatic bone tumor.

HEEL PAIN, PLANTAR[50]

ICD-10CM # M79.609 Pain in unspecified limb

SKIN

Keratoses.
Verruca.
Ulcer.
Fissure.

CONNECTIVE TISSUE

Fat
Atrophy.
Panniculitis.
Dense Connective Tissue
Inflammatory fasciitis.
Fibromatosis.
Enthesopathy.
Bursitis.
Bone (Calcaneus)
Stress fracture.
Paget disease.
Benign bone cyst/tumor.
Malignant bone tumor.
Metabolic bone disease (osteopenia).
Nerve
Tarsal tunnel.
Plantar nerve entrapment.
S1 nerve root radiculopathy.
Painful peripheral neuropathy.

INFECTION

Dermatomycoses.
Acute osteomyelitis.
Plantar abscess.

MISCELLANEOUS

Foreign body.
Nonunion calcaneus fracture.
Psychogenic.
Idiopathic.

HEMARTHROSIS

ICD-10CM # T14.90 Injury, unspecified

Trauma.
Anticoagulant therapy.
Thrombocytopenia, thrombocytosis.
Bleeding disorders (e.g., von Willebrand disease).
Charcot joint.
Idiopathic.
Other: pigmented villonodular synovitis, hemangioma, synovioma, AV fistula, ruptured aneurysm.

HEMATEMESIS[86]

ICD-10CM # K92.0 Hematemesis

CAUSES OF HEMATEMESIS

Very Common
Gastric or duodenal ulcer or erosions.
Common
Mallory-Weiss tear (a laceration at the gastroesophageal junction).
Ulcerative esophagitis.
Esophageal varices.
Uncommon
Vascular malformations.
Ulcerated GI stromal tumor.
Carcinoma of esophagus or stomach.
Aortoenteric fistula.

HEMATURIA

ICD-10CM # R31.9 Hematuria, unspecified

Use the mnemonic TICS:

T (Trauma): blow to kidney, insertion of Foley catheter or foreign body in urethra, prolonged and severe exercise, very rapid emptying of overdistended bladder. (Tumor): hypernephroma, Wilms tumor, papillary carcinoma of the bladder, prostatic and urethral neoplasms.(Toxins): turpentine, phenols, sulfonamides and other antibiotics, cyclophosphamide, NSAIDs.

I (Infections): glomerulonephritis, TB, cystitis, prostatitis, urethritis, *Schistosoma haematobium,* yellow fever, blackwater fever. (Inflammatory processes): Goodpasture syndrome, periarteritis, postirradiation.

C (Calculi): renal, ureteral, bladder, urethra. (Cysts): simple cysts, polycystic disease. (Congenital anomalies): hemangiomas, aneurysms, AVM.

S (Surgery): invasive procedures, prostatic resection, cystoscopy.(Sickle cell disease and other hematologic disturbances): hemophilia, thrombocytopenia, anticoagulants.(Somewhere else): bleeding genitals, factitious (drug addicts).

HEMATURIA, DIFFERENTIAL BASED ON AGE AND SEX

ICD-10CM # R31.9 Hematuria, unspecified

0 TO 20 YR

Acute urinary tract infections.
Acute glomerulonephritis.
Congenital urinary tract anomalies with obstruction.
Trauma to genitals.

20 TO 40 YR
Acute urinary tract infection.
Trauma to genitals.
Urolithiasis.
Bladder cancer.

40 TO 60 YR (WOMEN)
Acute urinary tract infection.
Bladder cancer.
Urolithiasis.

40 TO 60 YR (MEN)
Acute urinary tract infection.
Bladder cancer.
Urolithiasis.

60 YR AND OLDER (WOMEN)
Acute urinary tract infection.
Bladder cancer.
Vaginal trauma or irritation.
Urolithiasis.

60 YR AND OLDER (MEN)
Acute urinary tract infection.
Benign prostatic hyperplasia.
Bladder cancer.
Urolithiasis.
Trauma.

HEMATURIA, IN CHILDREN[7]
ICD-10CM # R31.9 Hematuria, unspecified

EXTRARENAL
Trauma.
Meatal stenosis or posterior urethral valves.
Exercise.
Menstruation or rectal bleeding.
Foreign bodies.
Cystitis, urethritis, or epididymitis.

INTRARENAL
Pyelonephritis.
Renal or bladder stones or tumors.
Poststreptococcal or idiopathic glomerulonephritis.
Acute interstitial nephritis.
Acute tubular necrosis.
Basement membrane glomerular disease.
Renal vein or arterial thrombosis.
Recurrent familial hematuria.
Polycystic kidney disease.

SYSTEMIC
Henoch-Schönlein purpura.
Systemic lupus erythematosus.
Hemolytic-uremic syndrome.
Infectious mononucleosis.
Sickle cell disease or other hemoglobinopathies.
Bacterial endocarditis or artificial cardiac valves.
Bleeding disorders, warfarin, or aspirin.
Medications such as amitriptyline or chlorpromazine, radiocontrast dyes.
Munchausen syndrome or factitious.

HEMIPARESIS/HEMIPLEGIA
ICD-10CM # G81.00 Flaccid hemiplegia affecting unspecified side
G81.10 Spastic hemiplegia affecting unspecified side

CVA.
Transient ischemic attack.
Cerebral neoplasm.
Multiple sclerosis or other demyelinating disorder.
CNS infection.
Migraine.
Hypoglycemia
Subdural hematoma.
Vasculitis.
Todd paralysis.
Epidural hematoma.
Metabolic (hyperosmolar state, electrolyte imbalance).
Psychiatric disorders.
Congenital disorders.
Leukodystrophies.

HEMOLYSIS AND HEMOGLOBINURIA
ICD-10CM # P55.8 Other hemolytic diseases of newborn
P55.9 Hemolytic disease of newborn, unspecified
R82.3 Hemoglobinuria

Erythrocyte trauma (prosthetic cardiac valves, marching and severe trauma, extensive burns).
Infections (malaria, *Bartonella, Clostridium welchii*).
Brown recluse spider bite.
Incompatible blood transfusions.
Hemolytic-uremic syndrome.
Thrombotic thrombocytopenic purpura (TTP).
Paroxysmal nocturnal hemoglobinuria (PNH).
Drugs (penicillins, quinidine, methyldopa, sulfonamides, nitrofurantoin).
Erythrocyte enzyme deficiencies (e.g., exposure to fava beans in patients with glucose-6-phosphate dehydrogenase deficiency).

HEMOLYSIS, INTRAVASCULAR
ICD-10CM # D59.6 Hemoglobinuria due to hemolysis from other external causes
D59.8 Other acquired hemolytic anemias

Infections.
Exertional hemolysis (e.g., prolonged march).
Valve hemolysis.
Microangiopathic hemolytic anemia.
Osmotic and chemical agents.
Thermal injury.
Cold agglutinins.
Venoms (snakes, spiders).
Paroxysmal nocturnal hemoglobinuria (PNH).

HEMOLYSIS, MECHANICAL
ICD-10CM # D59.4 Other nonautoimmune hemolytic anemias

Prosthetic heart valves.
Aortic stenosis.
Malignant hypertension.
Metastatic adenocarcinoma.
Traumatic exercise.
Renal transplants.
Renal cortical necrosis.
Glomerulonephritis.
Thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS).
Renal vasculitis.
Scleroderma.
Diabetes mellitus.

HEMOLYSIS, OXIDATIVE, DRUG-INDUCED[46]
ICD-10CM # D59 Acquired hemolytic anemia
D59.1 Other autoimmune hemolytic anemias

AGENTS THAT CAUSE OXIDATIVE HEMOLYSIS
Therapeutic Agents
Nitrofurantoin (Furadantin).
Sulfasalazine (Azulfidine).
p-Aminosalicylic acid.
Phenazopyridine (Pyridium).
Clotrimoxazole.
Quinolones.
Phenacetin.
Rasburicase.
Dapsone and other sulfones.
Primaquine.
Recreational Drugs
Isobutyl nitrate.
Amyl nitrite.
Miscellaneous Agents
Naphthalene mothballs.
Methylene blue.
Paraquat.
Hydrogen peroxide.

HEMOPERITONEUM
ICD-10CM # K66.1 Hemoperitoneum

Ruptured Graafian follicle.
Ruptured spleen.
Ectopic pregnancy.
Traumatic laceration of liver.
Ruptured aneurysm.
Ruptured bladder.
Traumatic laceration of bowel, pancreas, uterus.

HEMOPTYSIS
ICD-10CM # R04.2 Hemoptysis

CARDIOVASCULAR
Pulmonary embolism/infarction.
Left ventricular failure.
Mitral stenosis.

AV fistula.
Severe hypertension.
Erosion of aortic aneurysm.

PULMONARY

Neoplasm (primary or metastatic).
Infection.
Pneumonia: *Streptococcus pneumoniae, Klebsiella pneumoniae, Staphylococcus aureus, Legionella pneumophila.*
Bronchiectasis.
Abscess.
TB.
Bronchitis.
Fungal infections (aspergillosis, coccidioidomycosis).
Parasitic infections (amebiasis, ascariasis, paragonimiasis).
Vasculitis: granulomatosis with polyangiitis, Churg-Strauss syndrome, Henoch-Schönlein purpura.
Goodpasture syndrome.
Trauma (needle biopsy, foreign body, right-sided heart catheterization, prolonged and severe cough).
Cystic fibrosis, bullous emphysema.
Pulmonary sequestration.
Pulmonary AV fistula.
SLE.
Idiopathic pulmonary hemosiderosis.
Drugs: aspirin, anticoagulants, penicillamine.
Pulmonary hypertension.
Mediastinal fibrosis.

OTHER

Epistaxis, trauma.
Laryngeal bleeding (laryngitis, laryngeal neoplasm).
Hematologic disorders (clotting abnormalities, DIC, thrombocytopenia).

HEMORRHAGIC CYSTITIS[90]

ICD-10CM #		
	N39.0	Urinary tract infection

DIFFERENTIAL DIAGNOSIS FOR HEMORRHAGIC CYSTITIS[20]

Infectious:
- Bacterial.
- Viral (especially BK virus, adenovirus).
- Fungal.
- Parasitic.

Trauma:
- External.
- Postsurgical (e.g., transurethral resection of the bladder).

Malignancy:
- Bladder primary.
- Bladder invasion from local/distant primary.

Vascular malformation.
Chemical exposure:
- Cyclophosphamide.
- Ifosfamide.
- Busulfan.
- Thiotepa.
- Temozolomide.
- Aniline dye.
- Ether.
- Nonoxynol-9 (accidental urethral insertion of vaginal contraceptive).

Radiation therapy history (e.g., prostate cancer, cervical cancer).
Medication induced:
- Penicillin and derivatives (via immune reaction).
- Bleomycin.
- Danazol.
- Tiaprofenic.
- Allopurinol.
- Phensuximide.
- Methenamine mandelate.
- Acetic acid.

Manifestation of systemic disease:
- Amyloidosis.
- Rheumatoid arthritis.
- Crohn disease.

[20] Bleeding localized to bladder after diagnostic workup for gross hematuria with cystoscopy, urine cytology, and upper tract imaging is without clear cause of alternative bleeding source.

HEPATIC CYSTS[82]

ICD-10CM #		
	Q44.6	Cystic disease of liver
	B67.8	Echinococcosis, unspecified, of liver

CONGENITAL HEPATIC CYSTS

Parenchymal: solitary cyst, polycystic disease.
Ductal: localized dilatation, multiple cystic dilatations of intrahepatic ducts (Caroli disease).

ACQUIRED HEPATIC CYSTS

Inflammatory cysts: retention cysts, echinococcal cyst, amebic cyst.
Neoplastic cyst.
Peliosis hepatis.

HEPATIC DYSFUNCTION, POSTOPERATIVE[26]

ICD-10CM #		
	K91.82	Postprocedural hepatic failure

CAUSES OF POSTOPERATIVE HEPATIC DYSFUNCTION

Hepatocellular Injury (predominant serum ALT elevation, with or without hyperbilirubinemia)
Acute transfusion-associated viral hepatitis.
Hepatic allograft rejection.
Hepatic artery thrombosis.
Inhalational anesthetics: halothane, others.
Ischemic hepatitis (shock liver).
Other drugs: antihypertensives (e.g., labetalol), heparin.
Unrecognized chronic liver disease: NASH, hepatitis C, other disorders.
Cholestatic Jaundice (elevated serum alkaline phosphatase ± ALT; direct hyperbilirubinemia)
Acalculous cholecystitis.
Benign postoperative cholestasis.
Bile duct injury: after cholecystectomy or liver transplantation.
Bile duct obstruction: gallstones, pancreatitis.
Cardiac bypass of prolonged duration.
Cholangitis.
Drugs: amoxicillin-clavulanic acid, chlorpromazine, erythromycin, telithromycin, trimethoprim/sulfamethoxazole, warfarin, others.
Hemobilia.
Microlithiasis (biliary sludge).
Prolonged TPN.
Sepsis.
Indirect Hyperbilirubinemia (serum alkaline phosphatase and ALT often normal)
Gilbert syndrome.
Hemolytic anemia (G6PD deficiency, other causes).
Multiple transfusions.
Resorbing hematoma.

G6PD, Glucose-6-phosphate dehydrogenase; *NASH,* nonalcoholic steatohepatitis.

HEPATIC GRANULOMAS[3]

ICD-10CM #		
	K75.3	Granulomatous hepatitis

INFECTIONS

Bacterial, spirochetal: TB and atypical mycobacterial infections, tularemia, brucellosis, leprosy, syphilis, Whipple disease, listeriosis.
Viral: mononucleosis, CMV.
Rickettsial: Q fever.
Fungal: coccidioidomycosis, histoplasmosis, cryptococcal infections, actinomycosis, aspergillosis, nocardiosis.
Parasitic: schistosomiasis, clonorchiasis, toxocariasis, ascariasis, toxoplasmosis, amebiasis.

HEPATOBILIARY DISORDERS

Primary biliary cirrhosis, granulomatous hepatitis, jejunoileal bypass.

SYSTEMIC DISORDERS

Sarcoidosis, granulomatosis with polyangiitis, inflammatory bowel disease, Hodgkin disease, lymphoma.

DRUGS/TOXINS

Beryllium, parenteral foreign material (starch, talc, silicone, etc.), phenylbutazone, α-methyldopa, procainamide, allopurinol, phenytoin, nitrofurantoin, hydralazine.

HEPATITIS, ACUTE[58]

ICD-10CM #		
	B17.8	Acute viral hepatitis, unspecified
	B15	Acute hepatitis A
	B16	Acute hepatitis B
	B17.1	Acute hepatitis C
	B17.2	Acute hepatitis E

Infectious:
- Hepatitis A, B, C, D, E.
- Epstein-Barr virus.
- Cytomegalovirus.
- Herpes simplex virus.
- Yellow fever.
- Leptospirosis.
- Q fever.

HIV.
Brucellosis.
Lyme disease.
Syphilis.
Noninfectious:
Drug induced.
Autoimmune.
Ischemic.
Acute fatty liver of pregnancy.
Acute Budd-Chiari syndrome.
Wilson disease.

HEPATITIS, CHRONIC[58]

ICD-10CM #	K73.9	Chronic hepatitis, unspecified
	B18.0	Chronic viral hepatitis B with δ-agent
	B18.2	Chronic viral hepatitis C

Chronic viral hepatitis:
Hepatitis B.
Hepatitis C.
Hepatitis D.
Autoimmune hepatitis and variant syndromes.
Hereditary hemochromatosis.
Wilson disease.
α_1-Antitrypsin deficiency.
Fatty liver and nonalcoholic steatohepatitis.
Alcoholic liver disease.
Drug-induced liver disease.
Hepatic granulomas:
Infectious.
Drug induced.
Neoplastic.
Idiopathic.

HEPATITIS, IN CHILDREN[53]

ICD-10CM #	B17.9	Acute viral hepatitis, unspecified
	K73.9	Chronic hepatitis, unspecified

CAUSES AND DIFFERENTIAL DIAGNOSIS OF HEPATITIS IN CHILDREN

Infectious
Hepatotropic viruses:
HAV.
HBV.
HCV.
HDV.
HEV.
Hepatitis non–A-E viruses.
Systemic infection that can include hepatitis:
Adenovirus.
Arbovirus.
Coxsackievirus.
Cytomegalovirus.
Enterovirus.
Epstein-Barr virus.
"Exotic" viruses (e.g., yellow fever).
Herpes simplex virus.
Human immunodeficiency virus.
Paramyxovirus.
Rubella.
Varicella zoster.
Other.

Nonviral liver infections
Abscess.
Amebiasis.
Bacterial sepsis.
Brucellosis.
Fitz-Hugh-Curtis syndrome.
Histoplasmosis.
Leptospirosis.
Tuberculosis.
Other.
Autoimmune
Autoimmune hepatitis.
Sclerosing cholangitis.
Other (e.g., systemic lupus erythematosus, juvenile rheumatoid arthritis).
Metabolic
α1-Antitrypsin deficiency.
Tyrosinemia.
Wilson disease.
Other.
Toxic
Iatrogenic or drug induced (e.g., acetaminophen).
Environmental (e.g., pesticides).
Anatomic
Choledochal cyst.
Biliary atresia.
Other.
Hemodynamic
Shock.
Congestive heart failure.
Budd-Chiari syndrome.
Other.
Nonalcoholic Fatty Liver Disease
Idiopathic.
Reye syndrome.
Other.

HEPATOMEGALY

ICD-10CM #	R16.0	Hepatomegaly, not elsewhere classified

FREQUENT JAUNDICE

Infectious hepatitis.
Toxic hepatitis.
Carcinoma: liver, pancreas, bile ducts, metastatic neoplasm to liver.
Cirrhosis.
Obstruction of common bile duct.
Alcoholic hepatitis.
Biliary cirrhosis.
Cholangitis.
Hemochromatosis with cirrhosis.

INFREQUENT JAUNDICE

CHF.
Amyloidosis.
Liver abscess.
Sarcoidosis.
Infectious mononucleosis.
Alcoholic fatty infiltration.
Nonalcoholic steatohepatitis.
Lymphoma.
Leukemia.
Budd-Chiari syndrome.
Myelofibrosis with myeloid metaplasia.
Familial hyperlipoproteinemia type 1.
Other: amebiasis, hydatid disease of liver, schistosomiasis, kala-azar *(Leishmania donovani),* Hurler syndrome, Gaucher disease, kwashiorkor.

HEPATOMEGALY, BY SHAPE OF LIVER[86]

ICD-10CM #	R16.0	Hepatomegaly, not elsewhere classified

DIFFUSELY ENLARGED AND SMOOTH

Massive
Metastatic disease.
Alcoholic liver disease with fatty infiltration.
Myeloproliferative diseases (e.g., polycythemia rubra vera, myelofibrosis).
Moderate
The above causes.
Hemochromatosis.
Hematologic disease (e.g., chronic myeloid leukemia, lymphoma).
Fatty liver (e.g., diabetes mellitus, obesity).
Infiltrative disorders (e.g., amyloid).
Mild
The above causes.
Hepatitis (viral, drugs).
Cirrhosis.
Biliary obstruction.
Granulomatous disorders (e.g., sarcoid).
HIV infection.

DIFFUSELY ENLARGED AND IRREGULAR

Metastatic disease.
Cirrhosis.
Hydatid disease.
Polycystic liver disease.

LOCALIZED SWELLINGS

Riedel lobe (a normal variant—the lobe may be palpable in the right lumbar region).
Metastasis.
Large simple hepatic cyst.
Hydatid cyst.
Hepatoma.
Liver abscess (e.g., amebic abscess).

HERMAPHRODITISM[9]

ICD-10CM #	Q56.3	Pseudohermaphroditism, unspecified
	Q56.4	Indeterminate sex, unspecified

Female Pseudohermaphroditism
Androgen exposure:
Fetal source:
21-Hydroxylase (P450 c21) deficiency.
11β-Hydroxylase (P450 c11) deficiency.
3β-Hydroxysteroid dehydrogenase II (3β-HSD II) deficiency.
Aromatase (P450arom) deficiency.
Maternal source.
Virilizing ovarian tumor.
Virilizing adrenal tumor.
Androgenic drugs.
Undetermined origin:
Associated with genitourinary and GI tract defects.

MALE PSEUDOHERMAPHRODITISM

Defects in testicular differentiation:
- Denys-Drash syndrome (mutation in WT1 gene).
- WAGR syndrome (*W*ilms tumor, *a*niridia, *g*enitourinary malformation, *r*etardation).
- Deletion of 11p13.
- Camptomelic syndrome (autosomal gene at 17q24.3-q25.1) and SOX 9 mutation.
- XY pure gonadal dysgenesis (Swyer syndrome).
- Mutation in SRY gene.
- Unknown cause.
- XY gonadal agenesis.

Deficiency of testicular hormones:
- Leydig cell aplasia.
- Mutation in LH receptor.
- Lipoid adrenal hyperplasia (P450 scc) deficiency; mutation in StAR (steroidogenic acute regulatory protein).
- 3α-HSD II deficiency.
- 17-Hydroxylase/17, 20-lyase (P450 c17) deficiency.
- Persistent Müllerian duct syndrome.
- Gene mutations, Müllerian-inhibiting substance (MIS).
- Receptor defects for MIS.

Defect in androgen action:
- 5α-Reductase II mutations.
- Androgen receptor defects:
  - Complete androgen insensitivity syndrome.
  - Partial androgen insensitivity syndrome.
  - Reifenstein and other syndromes.
  - Smith-Lemli-Opitz syndrome.

Defect in conversion of 7-dehydrocholesterol to cholesterol.

TRUE HERMAPHRODITISM

XX.
XY.
XX/XY chimeras.

HICCUPS[49]

ICD-10CM # R06.6 Hiccough

TRANSIENT HICCUPS

Sudden excitement, emotion.
Gastric distention.
Esophageal obstruction.
Alcohol ingestion.
Sudden change in temperature.

PERSISTENT OR CHRONIC HICCUPS

Toxic/metabolic: uremia, DM, hyperventilation, hypocalcemia, hypokalemia, hyponatremia, gout, fever.
Drugs: benzodiazepines, steroids, α-methyldopa, barbiturates.
Surgery/general anesthesia.
Thoracic/diaphragmatic disorders: pneumonia, lung cancer, asthma, pleuritis, pericarditis, myocardial infarction, aortic aneurysm, esophagitis, esophageal obstruction, diaphragmatic hernia or irritation.
Abdominal disorders: gastric ulcer or cancer, hepatobiliary or pancreatic disease, IBD, bowel obstruction, intraabdominal or subphrenic abscess, prostatic infection or cancer.
CNS disorders: traumatic, infectious, vascular, structural.
Ear, nose, and throat disorders: pharyngitis, laryngitis, tumor, irritation of auditory canal.
Psychogenic disorders.
Idiopathic disorders.

HILAR AND MEDIASTINAL LYMPH NODE ENLARGEMENT[34]

ICD-10CM # R59.0 Mediastinal adenopathy

DISORDERS ASSOCIATED WITH HILAR AND MEDIASTINAL LYMPH NODE ENLARGEMENT

Sarcoidosis.
Lymphoma.
Fungal disease.
Tuberculosis.
Metastatic cancer.
Silicosis, coal worker's pneumoconiosis, beryllium lung.

HIP PAIN, CHILDREN[58]

ICD-10CM #	S79.819A	Other specified injuries of unspecified hip, initial encounter
	S79.829A	Other specified injuries of unspecified thigh, initial encounter
	S79.919A	Unspecified injury of unspecified hip, initial encounter

TRAUMA

Hip or pelvis fractures.
Overuse injuries.

INFECTION

Septic arthritis.
Osteomyelitis.

INFLAMMATION

Transient synovitis.
Juvenile RA.
Rheumatic fever.

NEOPLASM

Leukemia.
Osteogenic or Ewing sarcoma.
Metastatic disease.

HEMATOLOGIC DISORDERS

Hemophilia.
Sickle cell anemia.

MISCELLANEOUS

Legg-Calvé-Perthes disease.
Slipped capital femoral epiphysis.

HIP PAIN, DIFFERENTIAL DIAGNOSIS[41]

ICD-10CM # M25.559 Pain in unspecified hip

ARTICULAR

Inflammatory joint disease
Rheumatoid arthritis.
Spondyloarthropathies.
Polymyalgia rheumatica.
Degenerative joint disease
Primary osteoarthritis.
Secondary osteoarthritis.
Metabolic joint diseases
Gout.
Pseudogout.
Ochronosis.
Hemochromatosis.
Wilson disease.
Acromegaly.
Femoroacetabular impingement
Acetabular labral tear
Infections
Tumors
- Benign:
  - Pigmented villonodular sclerosis.
  - Osteochondromatosis.
- Malignant:
  - Synovial sarcoma.
  - Synovial metastasis.

Hemarthrosis
In children:
Toxic synovitis.
Juvenile chronic arthritis.

REFERRED PAIN

Thoracolumbar spine:
- Intraabdominal structures.
- Retroperitoneal structures.

PERIARTICULAR

Bursitis:
- Trochanteric.
- Iliopsoas.
- Ischiogluteal.

Tendinitis:
- Trochanteric.
- Adductor.

Acute calcific periarthritis.
Heterotropic ossification.

OSSEOUS

Bone lesions.
Fractures.
Neoplasms.
Infection.
Osteonecrosis of the femoral head.
Paget disease.
Metabolic bone disease.
Stress fracture.
Transient osteoporosis.
In children:
- Congenital dislocation of the hip.
- Acetabular dysplasia.
- Coxa vara.
- Slipped capital femoral epiphysis.
- Legg-Calvé-Perthes disease.
- Rickets.

NEUROLOGIC

Entrapment neuropathies.
Lateral femoral cutaneous nerve (meralgia paresthetica).
Lumbar nerve root compression.
L2, L3, and L4.

VASCULAR

Atherosclerosis of aorta, iliac vessels.

HIP PAIN, IN DIFFERENT AGE GROUPS[18]

ICD-10CM # M25.559 Pain in unspecified hip

COMMON CAUSES OF HIP PAIN IN DIFFERENT AGE GROUPS

Childhood (2 to 10 yr)
Intraarticular
Developmental dislocation of the hip.
Perthes disease.
Irritable hip.
Rickets.
Periarticular
Osteomyelitis.
Referred
Abdominal.
Adolescence (10 to 18 yr)
Intraarticular
Slipped upper femoral epiphysis.
Torn labrum.
Periarticular
Trochanteric bursitis.
Snapping hip.
Osteomyelitis.
Tumors.
Referred
Abdominal.
Lumbar spine.
Early Adulthood (18 to 30 yr)
Intraarticular
Inflammatory arthritis.
Torn labrum.
Periarticular
Bursitis.
Referred
Abdominal.
Lumbar spine.
Adulthood (30 to 50 yr)
Intraarticular
Osteoarthritis.
Inflammatory arthritis.
Osteonecrosis.
Transient osteoporosis.
Periarticular
Bursitis.
Referred
Abdominal.
Lumbar spine.
Old Age (>50 yr)
Intraarticular
Osteoarthritis.
Inflammatory arthritis.
Referred
Abdominal.
Lumbar spine.

HIP PAIN WITHOUT OBVIOUS FRACTURE[7]

ICD-10CM #	R52	Pain, unspecified
	M25.559	Pain in unspecified hip

DIFFERENTIAL DIAGNOSIS OF A PAINFUL HIP WITHOUT OBVIOUS FRACTURE

Referred pain (lumbar spine, hip, or knee).
Avascular necrosis of the femoral head.
Degenerative joint disease or osteoarthritis.
Herniation of a lumbar disk.
Diskitis.
Toxic synovitis of the hip.
Septic arthritis.
Bursitis.
Tendonitis.
Ligamentous injuries of the knee or hip.
Occult fracture.
Slipped capital femoral epiphysis.
Perthes disease.
Tumor (lymphoma).
Deep venous thrombosis.
Arterial insufficiency.
Osteomyelitis.
Iliopsoas abscess.
Retroperitoneal hematoma.
Inguinal hernia.
Inguinal lymphadenopathy.
Genitourinary complaints.
Sports-related hernia.

HIRSUTISM

ICD-10CM #	L68.0	Hirsutism

Idiopathic: familial, possibly increased sensitivity to androgens.
Menopause.
Polycystic ovarian syndrome.
Drugs: androgens, anabolic steroids, methyltestosterone, minoxidil, diazoxide, phenytoin, glucocorticoids, cyclosporine.
Congenital adrenal hyperplasia.
Adrenal virilizing tumor.
Ovarian virilizing tumor: arrhenoblastoma, hilus cell tumor.
Pituitary adenoma.
Cushing syndrome.
Hypothyroidism (congenital and juvenile).
Acromegaly.
Testicular feminization.

HIV INFECTION, ANORECTAL LESIONS[58]

ICD-10CM #	B20	Human immunodeficiency virus [HIV] disease
	Z21	Asymptomatic human immunodeficiency virus [HIV] infection status

COMMON CONDITIONS

Anal fissure.
Abscess and fistula.
Hemorrhoids.
Pruritus ani.
Pilonidal disease.

COMMON STDs

Gonorrhea.
Chlamydia.
Herpes.
Chancroid.
Syphilis.
Condylomata acuminata.

ATYPICAL CONDITIONS

Infectious: TB, CMV, actinomycosis, cryptococcus.
Neoplastic: lymphoma, Kaposi sarcoma, squamous cell carcinoma.
Other: idiopathic and ulcer.

HIV INFECTION, CHEST RADIOGRAPHIC ABNORMALITIES[58]

ICD-10CM #	B20	Human immunodeficiency virus [HIV] disease
	Z21	Asymptomatic human immunodeficiency virus [HIV] infection status

DIFFUSE INTERSTITIAL INFILTRATION

Pneumocystis jiroveci.
Cytomegalovirus.
Mycobacterium tuberculosis.
Mycobacterium avium complex.
Histoplasmosis.
Coccidioidomycosis.
Lymphoid interstitial pneumonitis.

FOCAL CONSOLIDATION

Bacterial pneumonia.
Mycoplasma pneumoniae.
Pneumocystis jiroveci.
Mycobacterium tuberculosis.
Mycobacterium avium complex.

NODULAR LESIONS

Kaposi sarcoma.
Mycobacterium tuberculosis.
Mycobacterium avium complex.
Fungal lesions.
Toxoplasmosis.

CAVITARY LESIONS

Pneumocystis jiroveci.
Mycobacterium tuberculosis.
Bacterial infection.

PLEURAL EFFUSION

Kaposi sarcoma.
(Small effusion may be associated with any infection).

ADENOPATHY

Kaposi sarcoma.
Lymphoma.
Mycobacterium tuberculosis.
Cryptococcus.

PNEUMOTHORAX

Kaposi sarcoma.

HIV INFECTION, COGNITIVE IMPAIRMENT[58]

ICD-10CM # B20 Human immunodeficiency virus [HIV] disease

EARLY TO MID-STAGE HIV DISEASE

Depression.
Alcohol and substance abuse.
Medication-induced cognitive impairment.
Metabolic encephalopathies.
HIV-related cognitive impairment.

ADVANCED HIV DISEASE (CD4+ <100/MM^3)

Opportunistic infection of CNS.
Neurosyphilis.
CNS lymphoma.
Progressive multifocal leukoencephalopathy.
Depression.
Metabolic encephalopathies.
Medication-induced cognitive impairment.
Stroke.
HIV dementia.

HIV INFECTION, CUTANEOUS MANIFESTATIONS[49]

ICD-10CM # B20 Human immunodeficiency virus [HIV] disease
Z21 Asymptomatic human immunodeficiency virus [HIV] infection status

BACTERIAL INFECTION

Bacillary angiomatosis: numerous angiomatous nodules associated with fever, chills, weight loss.
Staphylococcus aureus: folliculitis, ecthyma, impetigo, bullous impetigo, furuncles, carbuncles.
Syphilis: may occur in different forms (primary, secondary, tertiary); chancre may become painful because of secondary infection.

FUNGAL INFECTION

Candidiasis: mucous membranes (oral, vulvovaginal), less commonly candida intertrigo or paronychia.
Cryptococcoses: papules or nodules that strongly resemble molluscum contagiosum; other forms include pustules, purpuric papules, and vegetating plaques.
Seborrheic dermatitis: scaling and erythema in the hair-bearing areas (eyebrows, scalp, chest, and pubic area).

ARTHROPOD INFESTATIONS

Scabies: pruritus with or without rash, usually generalized but can be limited to a single digit.

VIRAL INFECTION

Herpes simplex: vesicular lesion in clusters; perianal, genital, orofacial, or digital; can be disseminated.
Herpes zoster: painful dermatomal vesicles that may ulcerate or disseminate.
HIV: discrete erythematous macules and papules on the upper trunk, palms, and soles are the most characteristic cutaneous finding of acute HIV infection.
Human papillomavirus: genital warts (may become unusually extensive).
Kaposi sarcoma (herpesvirus): erythematous macules or papules; enlarge at varying rates; violaceous nodules or plaques; occasionally painful.
Molluscum contagiosum: discrete umbilicated papules commonly on the face, neck, and intertriginous sites (axilla, groin, or buttocks).

NONINFECTIOUS

Drug reactions: more frequent and severe in HIV patients.
Nutritional deficiencies: mainly seen in children and patients with chronic diarrhea; diffuse skin manifestations, depending upon the deficiency.
Psoriasis: scaly lesions; diffuse or localized; can be associated with arthritis.
Vasculitis: palpable purpuric eruption (can resemble septic emboli).

HIV INFECTION, ESOPHAGEAL DISEASE

ICD-10CM # B20 Human immunodeficiency virus [HIV] disease
K21.9 Gastro-esophageal reflux disease without esophagitis

Candida infection.
Cytomegalovirus infection.
Aphthous ulcer.
Herpes simplex.

HIV INFECTION, HEPATIC DISEASE[58]

ICD-10CM # B20 Human immunodeficiency virus [HIV] disease

VIRUSES

Hepatitis A.
Hepatitis B.
Hepatitis C.
Hepatitis D (with HBV).
Epstein-Barr virus.
Cytomegalovirus.
Herpes simplex virus.
Adenovirus.
Varicella-zoster virus.

MYCOBACTERIA

Mycobacterium avium complex.
Mycobacterium tuberculosis.

FUNGI

Histoplasma capsulatum.
Cryptococcus neoformans.
Coccidioides immitis.
Candida albicans.
Pneumocystis jiroveci.
Penicillium marneffei.

PROTOZOA

Toxoplasma gondii.
Cryptosporidium parvum.
Microsporida.
Schistosoma.

BACTERIA

Bartonella henselae (peliosis hepatis).

MALIGNANCY

Kaposi sarcoma (HHV-8).
Non-Hodgkin lymphoma.
Hepatocellular carcinoma.

MEDICATIONS

Zidovudine.
Didanosine.
Ritonavir.
Other HIV-1 protease inhibitors.
Fluconazole.
Macrolide antibiotics.
Isoniazid.
Rifampin.
Trimethoprim-sulfamethoxazole.

HIV INFECTION, LOWER GI TRACT DISEASE[58]

ICD-10CM # B20 Human immunodeficiency virus [HIV] disease

CAUSES OF ENTEROCOLITIS

Bacteria
Campylobacter jejuni and other spp.
Salmonella spp.
Shigella flexneri.
Aeromonas hydrophila.
Plesiomonas shigelloides.
Yersinia enterocolitica.
Vibrio spp.
Mycobacterium avium complex.
Mycobacterium tuberculosis.
Escherichia coli (enterotoxigenic, enteroadherent).
Bacterial overgrowth.
Clostridium difficile (toxin).
Parasites
Cryptosporidium parvum.
Microsporida (*Enterocytozoon bieneusi, Septata intestinalis*).

Isospora belli.
Entamoeba histolytica.
Giardia lamblia.
Cyclospora cayetanensis.
Viruses
Cytomegalovirus.
Adenovirus.
Calicivirus.
Astrovirus.
Picobirnavirus.
Human immunodeficiency virus.
Fungi
Histoplasma capsulatum.

CAUSES OF PROCTITIS

Bacteria
Chlamydia trachomatis.
Neisseria gonorrhoeae.
Treponema pallidum.
Viruses
Herpes simplex.
Cytomegalovirus.

HIV INFECTION, MUSCULOSKELETAL DISORDERS[71]

ICD-10CM # B20 Human immunodeficiency virus [HIV] disease

MUSCULOSKELETAL DISORDERS ASSOCIATED WITH HIV INFECTION

Joints, Ligaments, and Soft Tissues
Painful articular syndrome.
HIV-associated arthritis.
Reactive arthritis.
Septic arthritis.
Psoriatic arthritis.
Diffuse infiltrative lymphocytosis syndrome.
Systemic lupus erythematosus.
Rheumatoid arthritis.
Vasculitis (polyarteritis nodosa, drug induced).
Immune reconstitution inflammatory syndrome.
Cellulitis and soft tissue abscesses.
Fasciitis (including necrotizing fasciitis).
Bursitis and tenosynovitis.
Muscles
HIV myopathy.
Nucleoside reverse transcriptase inhibitor (NRTI) myopathy.
Muscle infections (pyomyositis, toxoplasmosis).
Other (rhabdomyolysis, non-Hodgkin lymphoma, myasthenia gravis, nemaline [rod] myopathy, and inclusion body myositis).
Bones
Osteomyelitis.
Osteopenia and osteoporosis.
Osteonecrosis.
Hypertrophic osteoarthropathy.
Opportunistic Infections, HIV/AIDS-Defining Neoplastic Disorders, and Other Disorders Affecting Any Part of the Musculoskeletal System in HIV Infection
Neoplasia:
- Kaposi sarcoma.
- Non-Hodgkin lymphoma.
- Hodgkin lymphoma.
- Leiomyosarcoma.
- Ewing sarcoma.

Infection:
- Tuberculosis.
- Disseminated *Mycobacterium avium* complex infection.
- Coccidioidomycosis.
- Toxoplasmosis.
- Bacillary angiomatosis.

Other:
- HIV-related lipodystrophy.
- HIV wasting syndrome.

HIV INFECTION, OCULAR MANIFESTATIONS[82]

ICD-10CM # B20 Human immunodeficiency virus [HIV] disease
Z21 Asymptomatic human immunodeficiency virus [HIV] infection status

EYELIDS

Molluscum contagiosum.
Kaposi sarcoma.

CORNEA/CONJUNCTIVA

Keratoconjunctivitis sicca.
Bacterial/fungal ulcerative keratitis.
Herpes simplex.
Herpes zoster ophthalmicus.
Conjunctival microvasculopathy.
Kaposi sarcoma.

RETINA, CHOROID, AND VITREOUS

Microvasculopathy.
Endophthalmitis.
Cytomegalovirus retinitis.
Acute retinal necrosis.
Syphilis.
Toxoplasmosis.
Pneumocystis choroidopathy.
Cryptococcosis.
Mycobacterial infection.
Intraocular lymphoma.
Candidiasis.
Histoplasmosis.

DRUGS ASSOCIATED WITH OCULAR TOXICITY

Rifabutin.
Didanosine.

NEUROOPHTHALMIC

Disc edema.
Primary or secondary optic neuropathy.
Cranial nerve palsies.

ORBITAL

Lymphoma.
Infection.
Pseudotumor.

HIV INFECTION, PULMONARY DISEASE[10, 58]

ICD-10CM # B20 Human immunodeficiency virus [HIV] disease
I28.8 Other diseases of pulmonary vessels

RADIOGRAPHIC APPEARANCE

Diffuse Interstitial Infiltrates
Pneumocystis jiroveci.
Mycobacterium tuberculosis, especially with advanced human immunodeficiency virus disease.
Histoplasma capsulatum.
Coccidioides spp.
Cryptococcus neoformans.
Toxoplasma gondii.
Cytomegalovirus.
Influenza.
Lymphocytic interstitial pneumonitis.
Abacavir hypersensitivity.
Focal Consolidation
Pyogenic bacterial pneumonia from *Streptococcus pneumoniae, Haemophilus influenzae.*
M. tuberculosis.
Legionella spp.
Rhodococcus equi.
Hilar Adenopathy
M. tuberculosis.
H. capsulatum.
Coccidioides spp.
Non-Hodgkin or Hodgkin lymphoma.
Mycobacterium avium complex.
Cavitary Disease
Pyogenic bacterial pneumonia from *Pseudomonas aeruginosa, Staphylococcus aureus*, Enterobacteriaceae.
M. tuberculosis.
C. neoformans.
R. equi.
Aspergillus spp.
Nocardia spp.
Mycobacterium avium complex.
P. jiroveci.
Nodules or Masses
M. tuberculosis.
C. neoformans.
Aspergillus spp.
H. capsulatum.
Nocardia spp.
Non-Hodgkin lymphoma.
Kaposi sarcoma.
Lung cancer.
Normal Radiograph
P. jiroveci.
M. tuberculosis.

CAUSES

Mycobacterial
M. tuberculosis.
M. kansasii.
M. avium complex.
Other nontuberculous mycobacteria.
Other Bacterial
Streptococcus pneumoniae.
Staphylococcus aureus.
Haemophilus influenzae.
Enterobacteriaceae.
Pseudomonas aeruginosa.
Moraxella catarrhalis.
Group A *Streptococcus.*
Nocardia spp.
Rhodococcus equi.
Chlamydia pneumoniae.
Fungal
Pneumocystis carinii.

Cryptococcus neoformans.
Histoplasma capsulatum.
Coccidioides immitis.
Aspergillus spp.
Blastomyces dermatitidis.
Penicillium marneffei.
Viral
Cytomegalovirus.
Herpes simplex virus.
Adenovirus.
Respiratory syncytial virus.
Influenza viruses.
Parainfluenza virus.
Other
Toxoplasma gondii.
Strongyloides stercoralis.
Kaposi sarcoma.
Lymphoma.
Lung cancer.
Lymphocytic interstitial pneumonitis.
Nonspecific interstitial pneumonitis.
Bronchiolitis obliterans with organizing pneumonia.
Pulmonary hypertension.
Emphysema-like or bullous disease.
Pneumothorax.
Congestive heart failure.
Diffuse alveolar damage.
Pulmonary embolus.

HOARSENESS

ICD-10CM # R49.8 Other voice and resonance disorders

Allergic rhinitis.
Infections (laryngitis, epiglottitis, tracheitis, croup).
Vocal cord polyps.
Voice strain.
Irritants (tobacco smoke).
Vocal cord trauma (intubation, surgery).
Neoplastic involvement of vocal cord (primary or metastatic).
Neurologic abnormalities (multiple sclerosis, ALS, parkinsonism).
Endocrine abnormalities (puberty, menopause, hypothyroidism).
Other (laryngeal webs or cysts, psychogenic, muscle tension abnormalities).

HYDROCEPHALUS

ICD-10CM # G91.1 Obstructive hydrocephalus

Head trauma.
Brain neoplasm (primary or metastatic).
Spinal cord tumor.
Cerebellar infarction.
Exudative or granulomatous meningitis.
Cerebellar hemorrhage.
Subarachnoid hemorrhage.
Aqueductal stenosis.
Third ventricle colloid cyst.
Hindbrain malformation.
Viral encephalitis.
Metastases to leptomeninges.

HYPERCALCEMIA

ICD-10CM # E83.52 Hypercalcemia

Malignancy: increased bone resorption via osteoclast-activating factors, secretion of PTH-like substances, prostaglandin E2, direct erosion by tumor cells, transforming growth factors, colony-stimulating activity. Hypercalcemia is common in the following neoplasms:
  Solid tumors: breast, lung, pancreas, kidneys, ovary.
  Hematologic cancers: myeloma, lymphosarcoma, adult T-cell lymphoma, Burkitt lymphoma.
Hyperparathyroidism: increased bone resorption, GI absorption, and renal absorption; etiology:
  Parathyroid hyperplasia, adenoma.
  Hyperparathyroidism or renal failure with secondary hyperparathyroidism.
Granulomatous disorders: increased GI absorption (e.g., sarcoidosis).
Paget disease: increased bone resorption, seen only during periods of immobilization.
Vitamin D intoxication, milk-alkali syndrome; increased GI absorption.
Thiazides: increased renal absorption.
Other causes: familial hypocalciuric hypercalcemia, thyrotoxicosis, adrenal insufficiency, prolonged immobilization, vitamin A intoxication, recovery from acute renal failure, lithium administration, pheochromocytoma, disseminated SLE.

HYPERCALCEMIA, MALIGNANCY-INDUCED

ICD-10CM # E83.52 Hypercalcemia

Lung carcinoma	(6% frequency, 35% of hypercalcemic cases)
Breast carcinoma	(10% frequency, 25% of hypercalcemic cases)
Multiple myeloma	(33% frequency, 10% of hypercalcemic cases)
Lymphoma	(4% of hypercalcemic cases)
Genitourinary cancer	(6% of hypercalcemic cases)

HYPERCAPNIA, PERSISTENT[82]

ICD-10CM # R06.00 Dyspnea, unspecified
R06.09 Other forms of dyspnea
R06.89 Other abnormalities of breathing

Hypercapnia with normal lungs: CNS disturbances (CVA, parkinsonism, encephalitis), metabolic alkalosis, myxedema, primary alveolar hypoventilation, spinal cord lesions.
Diseases of the chest wall (e.g., kyphoscoliosis, ankylosing spondylitis).
Neuromuscular disorders (e.g., myasthenia gravis, Guillain-Barré syndrome, amyotrophic lateral sclerosis, muscular dystrophy, poliomyelitis).
COPD.

HYPERCOAGULABLE STATE, ASSOCIATED DISORDERS[45]

ICD-10CM # D68.69 Other thrombophilia

Systemic lupus erythematosus in association with the presence of a lupus anticoagulant or antiphospholipid antibodies.

MALIGNANCY

Disease-related: includes migratory superficial thrombophlebitis (Trousseau syndrome), nonbacterial thrombotic endocarditis, thrombosis associated with chronic DIC, thrombotic microangiopathy.
Treatment-related: associated with the administration of various chemotherapeutic agents (L-asparaginase, mitomycin, some adjuvant chemotherapeutic agents for treatment of breast cancer, thalidomide or lenalidomide in conjunction with high doses of dexamethasone).
Infusion of prothrombin complex concentrates.
Nephrotic syndrome.
Heparin-induced thrombocytopenia.
Myeloproliferative disorders.
Paroxysmal nocturnal hemoglobinuria.

DIC, Disseminated intravascular coagulopathy.

HYPERGASTRINEMIA

ICD-10CM # E16.4 Abnormal secretion of gastrin

Decreased gastrin release inhibition from medications (proton pump inhibitors [PPIs], H_2 receptor antagonists), vagotomy.
Chronic renal failure.
Hypochlorhydria due to atrophic gastritis, gastric carcinoma, pernicious anemia.
Gastrinoma (Zollinger-Ellison syndrome).
Pyloric obstruction.
Hyperplasia of antral G cells.
RA.

HYPERHIDROSIS[9]

ICD-10CM # R61 Generalized hyperhidrosis

CORTICAL

Emotional.
Familial dysautonomia.
Congenital ichthyosiform erythroderma.
Epidermolysis bullosa.
Nail-patella syndrome.
Jadassohn-Lewandowsky syndrome.
Pachyonychia congenita.
Palmoplantar keratoderma.

HYPOTHALAMIC

Drugs
Antipyretics.
Emetics.
Insulin.
Meperidine.
Exercise Infection
Defervescence.
Chronic illness.

Metabolic
Debility.
DM.
Hyperpituitarism.
Hyperthyroidism.
Hypoglycemia.
Obesity.
Porphyria.
Pregnancy.
Rickets.
Infantile scurvy.
Cardiovascular
Heart failure.
Shock.
Vasomotor
Cold injury.
Raynaud phenomenon.
RA.
Neurologic
Abscess.
Familial dysautonomia.
Postencephalitic.
Tumor.
Miscellaneous
Chédiak-Higashi syndrome.
Compensatory.
Phenylketonuria.
Pheochromocytoma.
Vitiligo.
Medullary
Physiologic gustatory sweating.
Encephalitis.
Granulosis rubra nasi.
Syringomyelia.
Thoracic sympathetic trunk injury.
Spinal
Cord transection.
Syringomyelia.
Changes in Blood Flow
Mallucci syndrome.
Arteriovenous fistula.
Klippel-Trenaunay syndrome.
Glomus tumor.
Blue rubber bleb nevus syndrome.

HYPERKALEMIA

ICD-10CM # E87.5 Hyperkalemia

Pseudohyperkalemia.
- Hemolyzed specimen.
- Severe thrombocytosis (platelet count 0.106 ml).
- Severe leukocytosis (white blood cell count 0.105 ml).
- Fist clenching during phlebotomy.

Excessive potassium intake (often in setting of impaired excretion).
- Potassium replacement therapy.
- High-potassium diet.
- Salt substitutes with potassium.
- Potassium salts of antibiotics.

Decreased renal excretion.
- Potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride).
- Renal insufficiency.
- Mineralocorticoid deficiency.
- Hyporeninemic hypoaldosteronism.
- Tubular unresponsiveness to aldosterone (e.g., SLE, multiple myeloma, sickle cell disease).
- Type 4 RTA.
- ACE inhibitors.
- Heparin administration.
- NSAIDs.
- Trimethoprim-sulfamethoxazole.
- Beta-blockers.
- Pentamidine.

Redistribution (excessive cellular release):
- Acidemia (each 0.1 decrease in pH increases the serum potassium by 0.4 to 0.6 mEq/L). Lactic acidosis and ketoacidosis cause minimal redistribution.
- Insulin deficiency.
- Drugs (e.g., succinylcholine, markedly increased digitalis level, arginine, beta-adrenergic blockers).
- Hypertonicity.
- Hemolysis.
- Tissue necrosis, rhabdomyolysis, burns.
- Hyperkalemic periodic paralysis.

HYPERKALEMIA, DRUG-INDUCED[88]

ICD-10CM # E87.5 Hyperkalemia

IMPAIRED RENIN-ALDOSTERONE ELABORATION/FUNCTION

Cyclooxygenase inhibitors (NSAIDs).
β-Adrenergic antagonists.
Spironolactone.
Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.
Heparin.

INHIBITORS OF RENAL POTASSIUM SECRETION

Potassium-sparing diuretics (amiloride, triamterene).
Trimethoprim.
Pentamidine.
Cyclosporine.
Digitalis overdose.
Lithium.

ALTERED POTASSIUM DISTRIBUTION

Insulin antagonists (somatostatin, diazoxide).
β-Adrenergic antagonists.
α-Adrenergic agonists.
Hypertonic solutions.
Digitalis.
Succinylcholine.
Arginine hydrochloride, lysine hydrochloride.

HYPERKALEMIA IN CHILDREN[79]

ICD-10CM # E87.5 Hyperkalemia

MOST RELEVANT CAUSES OF HYPERKALEMIA IN PEDIATRIC PATIENTS

Pseudohyperkalemia
Improper collection of blood.
Hematologic disorders: leukocytosis, thrombocytosis, spherocytosis.
Transcellular Shift of Potassium
Acidosis.
Insulin deficiency.
Hyperosmolality.
Exercise with nonselective β-blockers.
Familial hyperkalemic periodic paralysis.
Increased Potassium Load
From exogenous origin: pharmacologic supplements.
From endogenous origin (cellular lysis): burns, trauma, intravascular hemolysis, rhabdomyolysis, tumor mass destruction.
Decreased Urinary Excretion
Renal failure.
Mineralocorticoid deficiency.
Addison disease.
Hypoaldosteronism.
Mineralocorticoid resistance.
Type 1 and type 2 pseudohypoaldosteronism.
Renal tubular acidosis: type 4 and hyperkalemic form of type 1.
"Hyperkalemic" drugs: potassium-sparing diuretics, trimethoprim, calcineurin inhibitors, blockers of the renin angiotensin aldosterone system.

HYPERKINETIC MOVEMENT DISORDERS[67]

ICD-10CM #	F90.8	Attention-deficit hyperactivity disorder, other type
	E83.00	Disorder of copper metabolism, unspecified
	E83.01	Wilson disease
	E83.09	Other disorders of copper metabolism
	G24.02	Drug induced acute dystonia
	G24.1	Genetic torsion dystonia

Chorea, choreoathetosis: drug-induced, Huntington chorea, Sydenham chorea.
Tardive dyskinesia (e.g., phenothiazines).
Hemiballismus (lacunar CVA near subthalamic nuclei in basal ganglia, metastatic lesions, toxoplasmosis [in AIDS]).
Dystonia (idiopathic, familial, drug-induced [prochlorperazine, metoclopramide]), Wilson disease.
Liver failure.
Thyrotoxicosis.
SLE, polycythemia.

HYPERMAGNESEMIA

ICD-10CM #	E83.40	Disorders of magnesium metabolism, unspecified
	E83.41	Hypermagnesemia

Renal failure (decreased GFR).
Decreased renal excretion secondary to salt depletion.
Abuse of antacids and laxatives containing magnesium in patients with renal insufficiency.

Endocrinopathies (deficiency of mineralocorticoid or thyroid hormone).
Increased tissue breakdown (rhabdomyolysis).
Redistribution: acute DKA, pheochromocytoma.
Other: lithium, volume depletion, familial hypocalciuric hypercalcemia.

HYPEROSTOSIS, CORTICAL BONE[36]

ICD-10CM # M48.19 Ankylosing hyperostosis [Forestier], multiple sites in spine

DISORDERS ASSOCIATED WITH HYPEROSTOSIS OF CORTICAL BONE

Progressive diaphyseal dysplasia.
Endosteal hyperostosis.
Pachydermoperiostosis.
Hypertrophic osteoarthropathy.
Thyroid acropachy.
Hypervitaminosis A.
Paget disease.
Infantile cortical hyperostosis.

HYPERPHOSPHATEMIA

ICD-10CM # E83.30 Disorder of phosphorus metabolism, unspecified

Excessive phosphate administration.
Excessive oral intake or IV administration.
Laxatives containing phosphate (phosphate tablets, phosphate enemas).
Decreased renal phosphate excretion.
Acute or chronic renal failure.
Hypoparathyroidism or pseudohypoparathyroidism.
Acromegaly, thyrotoxicosis.
Bisphosphonate therapy.
Tumor calcinosis.
Sickle cell anemia.
Transcellular shift out of cells.
Chemotherapy of lymphoma or leukemia, tumor lysis syndrome, hemolysis.
Acidosis.
Rhabdomyolysis, malignant hyperthermia.
Artifact: in vitro hemolysis.
Pseudohyperphosphatemia: hyperlipidemia, paraproteinemia, hyperbilirubinemia.

HYPERPHOSPHATEMIA IN CHILDREN[79]

ICD-10CM # E83.30 Disorder of phosphorus metabolism, unspecified

CAUSES OF HYPERPHOSPHATEMIA

Impaired Renal Excretion of Phosphate
Renal insufficiency.
Hypoparathyroidism, pseudohypoparathyroidism.
Transient parathyroid resistance of infancy.
Acromegaly.
Tumoral calcinosis.
Hyperthyroidism.
Juvenile hypogonadism.
High ambient temperature.
Heparin.
Bisphosphonate etidronate.
Increased Phosphate Intake
Exogenous Loads
Phosphate salts: laxatives and enemas.
Vitamin D intoxication.
Blood transfusion.
White phosphorus burns.
Liposomal amphotericin B.
Fosphenytoin.
Parenteral phosphate.
Endogenous Loads
Crush injury.
Rhabdomyolysis.
Cytotoxic therapy of neoplasms: tumor lysis.
Hemolysis.
Malignant hyperthermia.
Catabolic states.
Lactic acidosis.
Fulminant hepatitis.
Transcellular Shift of Phosphate
Cellular shift in diabetes ketoacidosis.
Metabolic acidosis.
Respiratory acidosis.
Miscellaneous
Hyperostosis.

HYPERPIGMENTATION[14]

ICD-10CM # L81.4 Other melanin hyperpigmentation

Addison disease.[21]
Arsenic ingestion.
ACTH- or MSH-producing tumors (e.g., oat cell carcinoma of the lung).
Drug induced (e.g., antimalarials, some cytotoxic agents).
Hemochromatosis ("bronze" diabetes).
Malabsorption syndrome (Whipple disease and celiac sprue).
Melanoma.
Melanotropic hormone injection.
Pheochromocytoma.
Porphyrias (porphyria cutanea tarda and variegate porphyria).
Pregnancy.
Progressive systemic sclerosis and related conditions.
PUVA therapy (psoralen administration) for psoriasis and vitiligo.

ACTH, Adrenocorticotropic hormone; *MSH,* melanocyte-stimulating hormone; *PUVA,* psoralen plus ultraviolet A.
[21]Accentuation on sun-exposed surfaces.

HYPERPROLACTINEMIA[62]

ICD-10CM # E22.1 Hyperprolactinemia

PHYSIOLOGIC

Pregnancy.
Lactation.
Stress.
Sleep.
Coitus.
Exercise.

PATHOLOGIC

Hypothalamic-Pituitary Stalk Damage
Tumors: craniopharyngioma, suprasellar pituitary mass extension, meningioma, dysgerminoma, hypothalamic metastases.
Granulomas.
Infiltrations.
Rathke cyst.
Irradiation.
Trauma: pituitary stalk section, sellar surgery, head trauma.
Pituitary
Prolactinoma.
Acromegaly.
Macroadenoma (compressive).
Idiopathic.
Plurihormonal adenoma.
Lymphocytic hypophysitis or parasellar mass.
Macroprolactinemia.
Systemic Disorders
Chronic renal failure.
Polycystic ovary syndrome.
Cirrhosis.
Pseudocyesis.
Epileptic seizures.
Cranial irradiation.
Chest: neurogenic chest wall trauma, surgery, herpes zoster.

PHARMACOLOGIC

Neuropeptide
Thyrotropin-releasing hormone.
Drug-Induced Hypersecretion
Dopamine receptor blockers:
Phenothiazines: chlorpromazine, perphenazine.
Butyrophenones: haloperidol.
Thioxanthenes.
Metoclopramide.
Dopamine synthesis inhibitors:
α-Methyldopa.
Catecholamine depleters:
Reserpine.
Cholinergic Agonist
Physostigmine.
Antihypertensives
Labetalol.
Reserpine.
Verapamil.
H_2 Antihistamines
Cimetidine.
Ranitidine.
Estrogens
Oral contraceptives.
Oral contraceptive withdrawal.
Anticonvulsant
Phenytoin.
Anesthetics
Neuroleptics
Chlorpromazine.
Risperidone.
Promazine.
Promethazine.
Trifluoperazine.
Fluphenazine.
Butaperazine.
Perphenazine.
Thiethylperazine.

Thioridazine.
Haloperidol.
Pimozide.
Thiothixene.
Molindone.
Opiates and Opiate Antagonists
Heroin.
Methadone.
Apomorphine.
Morphine.
Antidepressants
Tricyclic antidepressants: chlorimipramine, amitriptyline.
Selective serotonin reuptake inhibitors: fluoxetine.

HYPERSPLENISM, ASSOCIATED CONDITIONS

ICD-10CM # D73.1 Hypersplenism

Cirrhosis.
Portal vein thrombosis.
Myeloproliferative diseases.
Lymphomas.
Leukemias.
Splenic vein thrombosis.
Autoimmune disease.
Sickle cell disease.
Thalassemias.
Gaucher disease.
Niemann-Pick disease.

HYPERTENSION, ADRENOCORTICAL CAUSES[62]

ICD-10CM # I15.8 Other secondary hypertension

LOW RENIN AND HIGH ALDOSTERONE

Primary Aldosteronism

Aldosterone-producing adenoma (APA)	35% of cases
Bilateral idiopathic hyperplasia (IHA)	60% of cases
Primary (unilateral) adrenal hyperplasia	2% of cases
Aldosterone-producing adrenocortical carcinoma	<1% of cases
Familial hyperaldosteronism (FH)	
Glucocorticoid-remediable aldosteronism (FH type I)	<1% of cases
FH type II (APA or IHA)	<2% of cases
Ectopic aldosterone-producing adenoma or carcinoma	<0.1% of cases

LOW RENIN AND LOW ALDOSTERONE

Hyperdeoxycorticosteronism
Congenital adrenal hyperplasia:
  11β-Hydroxylase deficiency.
  17α-Hydroxylase deficiency.
Deoxycorticosterone-producing tumor.
Primary cortisol resistance.
Apparent mineralocorticoid excess (AME)/11β-HSD[22] deficiency.
  Genetic: Type 1 AME.
Acquired: licorice or carbenoxolone ingestion (type 1 AME), Cushing syndrome (type 2 AME).
Cushing Syndrome
Exogenous glucocorticoid administration—most common cause.
Endogenous:
  ACTH[23] -dependent—85% of cases: pituitary, ectopic.
  ACTH-independent—15% of cases: unilateral adrenal disease (adenoma or carcinoma), bilateral adrenal disease (massive macronodular hyperplasia [rare], primary pigmented nodular adrenal disease [rare]).

[22] *HSD,* Hydroxysteroid dehydrogenase
[23] *ACTH,* Adrenocorticotropin hormone

HYPERTENSION, ENDOCRINE CAUSES[62]

ICD-10CM # I15.8 Other secondary hypertension

ADRENAL-DEPENDENT CAUSES

Pheochromocytoma.
Primary aldosteronism.
Hyperdeoxycorticosteronism:
  Congenital adrenal hyperplasia: 11β-hydro xylase deficiency, 17α-hydroxylase deficiency.
  Deoxycorticosterone-producing tumor.
  Primary cortisol resistance.
Cushing syndrome.

AME/11β-HSD (HYDROXYSTEROID DEHYDROGENASE) DEFICIENCY

Genetic:
  Type 1 apparent mineralocorticoid excess (AME).
Acquired:
  Licorice or carbenoxolone ingestion (type 1 AME).
  Cushing syndrome (type 2 AME).

THYROID-DEPENDENT CAUSES

Hypothyroidism.
Hyperthyroidism.

PARATHYROID-DEPENDENT CAUSES

Hyperparathyroidism.

PITUITARY-DEPENDENT CAUSES

Acromegaly.
Cushing syndrome.

HYPERTENSION, IN CHILDREN[7]

ICD-10CM # I10 Essential (primary) hypertension

PRIMARY

Essential hypertension.

SECONDARY

Renal
Glomerulonephritis.
Henoch-Schönlein purpura.
Pyelonephritis.
Obstruction of reflux.
Polycystic kidney disease.
Diabetic nephropathy.
Trauma.
Renal transplant or hemodialysis.
Tuberous sclerosis.
Systemic lupus nephritis.
Endocrine
Pheochromocytoma.
Cushing syndrome.
Congenital adrenal hyperplasia.
Corticosteroid treatment.
Hyperthyroidism.
Neuroblastoma.
Ovarian tumor.
Cardiac
Congestive heart failure.
Coarctation of the aorta.
Vascular
Hemolytic-uremic syndrome.
Kawasaki syndrome.
Renal artery thrombosis or stenosis.
Neurologic
CNS tumor or infection.
CNS trauma or abuse.
Increased intracranial pressure.
Guillain-Barré syndrome.
Neoplastic
Neuroblastoma.
Wilms tumor.
Pheochromocytoma.
Adrenal carcinoma.
Drugs
Corticosteroids.
Cocaine.
Sympathomimetics.
Oral contraceptives.
Phencyclidine.
Beta-blocker or clonidine withdrawal.
Lead, mercury.
Others
Iatrogenic fluid overload.
Volume overload from end-stage renal disease.

HYPERTENSION, RESISTANT[79]

ICD-10CM # I10 Essential (primary) hypertension
ICD-10CM # I15 Secondary hypertension

CAUSES OF RESISTANT HYPERTENSION

Pseudoresistance:
  White coat hypertension or office elevations.
  Pseudohypertension in older patients.
  Use of small cuff on very obese arm.
Nonadherence to therapeutic regimen.
Volume overload.

Drug-related causes:
- Antihypertensive drug dosage too low.
- Wrong type of diuretic.
- Inappropriate combinations of antihypertensive drugs.

Drug actions and interactions:
- Sympathomimetics.
- Nasal decongestants.
- Appetite suppressants.
- Cocaine.
- Caffeine.
- Oral contraceptives.
- Adrenal steroids.
- Licorice (may be found in chewing tobacco).
- Cyclosporine, tacrolimus.
- Erythropoiesis-stimulating agents (ESAs) and erythropoietin.
- Antidepressants.
- Nonsteroidal antiinflammatory drugs.

Concomitant conditions:
- Obesity.
- Sleep apnea.
- Ethanol intake >1 oz (30 ml)/day.
- Anxiety, hyperventilation.

Secondary causes of hypertension:
- Renovascular hypertension.
- Primary aldosteronism.
- Pheochromocytoma.
- Hypothyroidism.
- Hyperthyroidism.
- Hyperparathyroidism.
- Aortic coarctation.
- Renal disease.

HYPERTENSIVE CRISIS SYNDROMES[88]

ICD-10CM # I13 Hypertensive heart and renal disease
I15 Secondary hypertension

Malignant hypertension.
Nonmalignant hypertension with target organ disorders:
- Patient requiring emergency surgery with poorly controlled hypertension.
- Hyperviscosity syndrome.
- Postoperative patient.
- Renal transplant patient: acute rejection, transplant renal artery stenosis.
- Quadriplegic patient with autonomic hyperreflexia.
- Severe burns.
- Acute aortic dissection.
- Intracranial hemorrhage, ischemic stroke, or subarachnoid hemorrhage.
- Hypertensive encephalopathy.
- Myocardial ischemia/acute left ventricular failure.
- Preeclampsia/eclampsia.
- Antiphospholipid antibody syndrome.
- Acute renal failure:
  - Scleroderma renal crisis.
  - Chronic glomerulonephritis.
  - Reflux nephropathy.
  - Analgesic nephropathy.
  - Acute glomerulonephritis.
  - Radiation nephritis.
  - Ask-Upmark kidney.
  - Chronic lead intoxication.
- Renovascular hypertension:
  - Fibromuscular dysplasia.
  - Atherosclerosis.
- Endocrine hypertension:
  - Congenital adrenal hyperplasia.
  - Pheochromocytoma.
  - Oral contraceptives.
  - Aldosteronism.
  - Cushing disease.
  - Systemic vasculitis.
  - Atheroembolic renal crisis.
- Drugs:
  - Oral contraceptives.
  - Nonsteroidal antiinflammatory agents.
  - Atropine.
  - Corticosteroids.
  - Sympathomimetics.
  - Cyclosporine.
  - Erythropoietin.
- Lead intoxication.
- Catecholamine excess states:
  - Pheochromocytoma.
  - MAO/tyramine interaction.
  - Antihypertensive withdrawal.
  - Cocaine intoxication, sympathomimetic overdose.

HYPERTENSIVE ENCEPHALOPATHY[70]

ICD-10CM # I67.4 Hypertensive encephalopathy

Ischemic stroke.
Intracerebral hemorrhage.
Subarachnoid hemorrhage.
Subdural hematoma.
Epidural hematoma.
Central nervous vasculitis.
Brain mass.
Seizure disorder.
Central nervous system infection.
Drug toxicity.
Withdrawal syndrome.

HYPERTRICHOSIS[17]

ICD-10CM # L68.0 Hirsutism
L68.1 Acquired hypertrichosis lanuginosa
L68.3 Polytrichia
L68.9 Hypertrichosis, unspecified
Q84.1 Congenital morphological disturbances of hair, not elsewhere classified

DRUGS

Dilantin.
Streptomycin.
Hexachlorobenzene.
Penicillamine.
Diazoxide.
Minoxidil.
Cyclosporine.

SYSTEMIC ILLNESS

Hypothyroidism.
Anorexia nervosa.
Malnutrition.
Porphyria.
Dermatomyositis.

IDIOPATHIC

HYPERTROPHIC OSTEOARTHROPATHY

ICD-10CM # M89.40 Other hypertrophic osteoarthropathy, unspecified site

Idiopathic.
Pulmonary disease (e.g., pulmonary fibrosis, cystic fibrosis, sarcoidosis).
Bronchogenic carcinoma.
AIDS.
GI neoplasm (e.g., esophagus, colon).
Hepatic neoplasm, cirrhosis.
Cardiovascular diseases, aortic aneurysm, aortic prosthesis.
Congenital cyanotic heart disease, patent ductus arteriosus.
Pulmonary infections, bacterial endocarditis, amebic dysentery.
Inflammatory bowel disease.
Connective tissue diseases.
Lymphomas.
Thyroid acropachy.

HYPERVENTILATION, PERSISTENT[82]

ICD-10CM # R06.4 Hyperventilation

Fibrotic lung disease.
Metabolic acidosis (e.g., diabetes, uremia).
CNS disorders (midbrain and pontine lesions).
Hepatic coma.
Salicylate intoxication.
Fever.
Sepsis.
Psychogenic (e.g., anxiety).

HYPOCALCEMIA

ICD-10CM # E83.51 Hypocalcemia

Renal insufficiency: hypocalcemia caused by:
- Increased calcium deposits in bone and soft tissue secondary to increased serum phosphate level.
- Decreased production of 1,25-dihydroxyvitamin D.
- Excessive loss of 25-OHD (nephrotic syndrome).

Hypoalbuminemia: each decrease in serum albumin (g/L) will decrease serum calcium by 0.8 mg/dl but will not change free (ionized) calcium.
Vitamin D deficiency:
- Malabsorption (most common cause).
- Inadequate intake.
- Decreased production of 1,25-dihydroxyvitamin D (vitamin D–dependent rickets, renal failure).
- Decreased production of 25-OHD (parenchymal liver disease).
- Accelerated 25-OHD catabolism (phenytoin, phenobarbital).
- End-organ resistance to 1,25-dihydroxyvitamin D.

Hypomagnesemia: hypocalcemia caused by:
Decreased PTH secretion.
Inhibition of PTH effect on bone.
Pancreatitis, hyperphosphatemia, osteoblastic metastases: hypocalcemia is secondary to increased calcium deposits (bone, abdomen).
Pseudohypoparathyroidism (PHP): autosomal recessive disorder characterized by short stature, shortening of metacarpal bones, obesity, and mental retardation; the hypocalcemia is secondary to congenital end-organ resistance to PTH.
Idiopathic hypoparathyroidism, surgical removal of parathyroids (e.g., neck surgery).
"Hungry bones syndrome": rapid transfer of calcium from plasma into bones after removal of a parathyroid tumor.
Sepsis.
Massive blood transfusion (as a result of EDTA in blood).

HYPOCALCEMIA IN PEDIATRIC PATIENTS[79]

ICD-10CM # E83.51 Hypocalcemia

CAUSES OF HYPOCALCEMIA

Neonatal Hypocalcemia

Early neonatal hypocalcemia (first few days of life)

Maternal hyperparathyroidism.
Maternal diabetes mellitus.
Toxemia of pregnancy.
Sepsis.
SGA, IUGR, prematurity.
Asphyxia.
Transfusion (citrated blood products).
Congenital rubella.
Hypomagnesemia.
Respiratory or metabolic alkalosis.

Late neonatal hypocalcemia (fourth to tenth day of life)

Vitamin D deficiency: nutritional deficiency; VDR loss-of-function mutation; deficient 1α-hydroxylase activity.
Phosphate overload: excessive intake of evaporated/whole milk.
Nutritional calcium deficiency.
Hypomagnesemia.
Hypoalbuminemia (nephrotic syndrome).
Transfusion (citrated blood products).
Acute/chronic kidney insufficiency.
Diuretics (furosemide).
Organic acidemia.
Primary hypoparathyroidism: DiGeorge syndrome; familial hypoparathyroidism; pseudohypoparathyroidism; Kenny-Caffey syndrome; partial deletion of GCMB; retardation dysmorphism syndrome; Pearson mitochondriopathy; Kerns-Sayre mitochondriopathy; PTH gene defects; CaSR-activating gene mutation.

Hypocalcemia in Childhood

Parathyroid-related hypocalcemia

Primary hypoparathyroidism: DiGeorge syndrome; familial hypoparathyroidism; pseudohypoparathyroidism; Kenny-Caffey syndrome; Sanjad-Sakati syndrome; partial deletion of GCMB; retardation dysmorphism syndrome; Pearson mitochondropathy; Kerns-Sayre mitochondropathy; PTH gene defects; CaSR-activating gene mutation; Bartter syndrome type 5.
Secondary hypoparathyroidism: radiation; surgery; infiltration (hemochromatosis, thalassemia, Wilson disease).
Autoimmune polyglandular syndrome type 1.

Vitamin D–related hypocalcemia

Nutritional vitamin D deficiency.
Defective 1α-hydroxylase activity.
VDR loss-of-function mutation.

Nutritional calcium deficiencyHypomagnesemia

Hyperphosphatemia: kidney failure, rhabdomyolysis, tumor lysis

Hypoalbuminemia (nephrotic syndrome)

Medications: diuretics, chemotherapy, transfusion (citrated blood)

Organic acidemia (IVA, MMA, PPA)

CaSR, Calcium-sensing receptor; *GCMB,* glial cell missing homolog B (a parathyroid-specific transcription factor); *IUGR,* intrauterine growth retardation; *IVA,* isovaleric acidemia; *MMA,* methylmalonic acidemia; *PPA,* propionic acidemia; *PTH,* parathyroid hormone; *SGA,* small for gestational age; *VDR,* vitamin D receptor.

HYPOCAPNIA

ICD-10CM # R06.8 Hypoventilation

Hyperventilation.
Pneumonia, pneumonitis.
Fever, sepsis.
Medications (salicylates, beta-adrenergic agonists, progesterone, methylxanthines).
Pulmonary disease (asthma, interstitial fibrosis).
Pulmonary embolism.
Hepatic failure.
Metabolic acidosis.
High altitude.
CHF.
Pregnancy.
Pain.
CNS lesions.

HYPOGLYCEMIA

ICD-10CM #

E16.2	Hypoglycemia, unspecified
E10.65	Type 1 diabetes mellitus with hyperglycemia
E15	Nondiabetic hypoglycemic coma
K91.2	Postsurgical malabsorption, not elsewhere classified
E16.2	Hypoglycemia, unspecified

Oral hypoglycemics (therapeutic, factitious).
Exogenous insulin (therapeutic, factitious).
Postoperative gastric emptying (alimentary hyperinsulinism).
Severe malnutrition.
Liver disease.
Hypermetabolic state (sepsis).
Ketotic hypoglycemia.
Insulinoma.
Antibodies to endogenous insulin.
Hormone deficiencies (glucagon, growth hormone, hypoadrenalism).
Enzyme disorders in metabolism of glycogen, hexose, glycolysis, and Krebs cycle.
Idiopathic.

HYPOGLYCEMIA, IN INFANTS AND CHILDREN[53]

ICD-10CM # E16.2 Hypoglycemia, unspecified

CLASSIFICATION OF HYPOGLYCEMIA IN INFANTS AND CHILDREN

Neonatal Transient Hypoglycemia

Associated with Inadequate Substrate or Immature Enzyme Function in Otherwise Normal Neonates

Prematurity.
Small for gestational age.
Normal newborn.

Transient Neonatal Hyperinsulinism Also Present in

Infant of diabetic mother.
Discordant twin.
Birth asphyxia.
Infant of toxemic mother.

NEONATAL, INFANTILE, OR CHILDHOOD PERSISTENT HYPOGLYCEMIAS

Hormonal Disorders

Hyperinsulinism.
Recessive KATP channel HI.
Recessive HADH (hydroxyl acyl CoA dehydrogenase) mutation HI.
Recessive UCP2 (mitochondrial uncoupling protein 2) mutation HI.
Focal KATP channel HI.
Dominant KATP channel HI.
Dominant glucokinase HI.
Dominant glutamate dehydrogenase HI (hyperinsulinism/hyperammonemia syndrome).
Dominant mutation in HNF4A (hepatic nuclear factor 4 alpha) HI with MODY later in life.
Dominant mutation in SLC16A1 (the pyruvate transporter)-exercise-induced hypoglycemia.
Acquired islet adenoma.
Beckwith-Wiedemann syndrome.
Insulin administration (Munchausen syndrome by proxy).
Oral sulfonylurea drugs.
Congenital disorders of glycosylation.

Counter-Regulatory Hormone Deficiency

Panhypopituitarism.
Isolated growth hormone deficiency.
Addison disease.
Epinephrine deficiency.

Glycogenolysis and Gluconeogenesis Disorders

Glucose-6-phosphatase deficiency (GSD 1a).
Glucose-6-phosphate translocase deficiency (GSD 1b).
Amylo-1,6-glucosidase (debranching enzyme) deficiency (GSD 3).
Liver phosphorylase deficiency (GSD 6).

Phosphorylase kinase deficiency (GSD 9).
Glycogen synthetase deficiency (GSD 0).
Fructose-1,6-diphosphatase deficiency.
Pyruvate carboxylase deficiency.
Galactosemia.
Hereditary fructose intolerance.
Lipolysis Disorders
Fatty Acid Oxidation Disorders
Carnitine transporter deficiency (primary carnitine deficiency).
Carnitine palmitoyltransferase-1 deficiency.
Carnitine translocase deficiency.
Carnitine palmitoyltransferase-2 deficiency.
Secondary carnitine deficiencies.
Very long-, long-, medium-, short-chain acyl-CoA dehydrogenase deficiency.

OTHER ETIOLOGIES

Substrate-Limited
Ketotic hypoglycemia.
Poisoning: drugs.
Salicylates.
Alcohol.
Oral hypoglycemic agents.
Insulin.
Propranolol.
Pentamidine.
Quinine.
Disopyramide.
Ackee fruit (unripe): hypoglycin.
Vacor (rat poison).
Trimethoprim-sulfamethoxazole (with renal failure).
Liver Disease
Reye syndrome.
Hepatitis.
Cirrhosis.
Hepatoma.
Amino Acid and Organic Acid Disorders
Maple syrup urine disease.
Propionic acidemia.
Methylmalonic acidemia.
Tyrosinosis.
Glutaric aciduria.
3-Hydroxy-3-methylglutaric aciduria.
Systemic Disorders
Sepsis.
Carcinoma/sarcoma (secreting—insulin-like growth factor II).
Heart failure.
Malnutrition.
Malabsorption.
Anti-insulin receptor antibodies.
Anti-insulin antibodies.
Neonatal hyperviscosity.
Renal failure.
Diarrhea.
Burns.
Shock.
Postsurgical.
Pseudohypoglycemia (leukocytosis, polycythemia).
Excessive insulin therapy of insulin-dependent diabetes mellitus.
Factitious.
Nissen fundoplication (dumping syndrome).
Falciparum malaria.

GSD, Glycogen storage disease; *HI,* hyperinsulinemia; K_{ATP}, regulated potassium channel.

HYPOGONADISM

ICD-10CM #		
	E28.310	Symptomatic premature menopause
	E29.1	Testicular hypofunction
	E28.39	Other primary ovarian failure
	E23.6	Other disorders of pituitary gland

HYPERGONADOTROPIC HYPOGONADISM

Hormone resistance (androgen, LH insensitivity).
Gonadal defects (e.g., Klinefelter syndrome, myotonic dystrophy).
Drug-induced (e.g., spironolactone, cytotoxins).
Alcoholism, radiation-induced.
Mumps orchitis.
Anatomic defects, castration.

HYPOGONADOTROPIC HYPOGONADISM

Pituitary lesions (neoplasms, granulomas, infarction, hemochromatosis, vasculitis).
Drug-induced (e.g., glucocorticoids).
Hyperprolactinemia.
Genetic disorders (Laurence-Moon-Biedl syndrome, Prader-Willi).
Delayed puberty.
Other: chronic disease, nutritional deficiency, Kallmann syndrome, idiopathic isolated LH or FSH deficiency.

HYPOKALEMIA

ICD-10CM #		
	E87.6	Hypokalemia

Cellular shift (redistribution) and undetermined mechanisms.
Alkalosis (each 0.1 increase in pH decreases serum potassium by 0.4 to 0.6 mEq/L).
Insulin administration.
Vitamin B_{12} therapy for megaloblastic anemias, acute leukemias.
Hypokalemic periodic paralysis: rare familial disorder manifested by recurrent attacks of flaccid paralysis and hypokalemia.
Beta-adrenergic agonists (e.g., terbutaline), decongestants, bronchodilators, theophylline, caffeine.
Barium poisoning, toluene intoxication, verapamil intoxication, chloroquine intoxication.
Correction of digoxin intoxication with digoxin antibody fragments (Digibind).
Increased renal excretion.
Drugs:
- Diuretics, including carbonic anhydrase inhibitors (e.g., acetazolamide).
- Amphotericin B.
- High-dose sodium penicillin, nafcillin, ampicillin, or carbenicillin.
- Cisplatin.
- Aminoglycosides.
- Corticosteroids, mineralocorticoids.
- Foscarnet sodium.

RTA: distal (type 1) or proximal (type 2).
Diabetic ketoacidosis (DKA), ureteroenterostomy.
Magnesium deficiency.
Postobstruction diuresis, diuretic phase of ATN.
Osmotic diuresis (e.g., mannitol).
Bartter syndrome: hyperplasia of juxtaglomerular cells leading to increased renin and aldosterone, metabolic alkalosis, hypokalemia, muscle weakness, and tetany (seen in young adults).
Increased mineralocorticoid activity (primary or secondary aldosteronism), Cushing syndrome.
Chronic metabolic alkalosis from loss of gastric fluid (increased renal potassium secretion).
GI loss:
- Vomiting, nasogastric suction.
- Diarrhea.
- Laxative abuse.
- Villous adenoma.
- Fistulas.
- Inadequate dietary intake (e.g., anorexia nervosa).
- Cutaneous loss (excessive sweating).
- High dietary sodium intake, excessive use of licorice.

HYPOKALEMIA IN PEDIATRIC PATIENTS[79]

ICD-10CM #		
	E87.6	Hypokalemia

MOST RELEVANT CAUSES OF HYPOKALEMIA IN PEDIATRIC PATIENTS

Acute Redistribution of Potassium to the Intracellular Compartment
Metabolic alkalosis.
Insulin administration.
Hypokalemic periodic paralysis.
Prolonged Lack of Intake
Increased Renal Loss
Drugs: diuretics, antibiotics, aminoglycosides, penicillin, amphotericin B, capreomycin.
Metabolic acidosis and diabetic ketoacidosis.
Increased mineralocorticoid activity.
Cushing syndrome.
Congenital adrenal hyperplasia.
Primary or secondary hyperaldosteronism.
Primary tubulopathies.
Bartter syndrome.
Gitelman syndrome.
Liddle syndrome.
Types 1 and 2 renal tubular acidosis.
Epilepsy, ataxia, sensorineural deafness, and tubulopathy (EAST) syndrome.
Fanconi syndrome.
Increased Gastrointestinal Loss
Vomiting (hypertrophic pyloric stenosis).
Diarrhea.

HYPOMAGNESEMIA

ICD-10CM #		
	E83.40	Disorders of magnesium metabolism, unspecified
	E83.42	Hypomagnesemia

GASTROINTESTINAL AND NUTRITIONAL

Defective GI absorption (malabsorption).
Inadequate dietary intake (e.g., alcoholics).
Parenteral therapy without magnesium.
Chronic diarrhea, villous adenoma, prolonged nasogastric suction, fistulas (small bowel, biliary).

EXCESSIVE RENAL LOSSES

Diuretics.
RTA.
Diuretic phase of ATN.
Endocrine disturbances (DKA, hyperaldosteronism, hyperthyroidism, hyperparathyroidism), SIADH, Bartter syndrome, hypercalciuria, hypokalemia.
Cisplatin, alcohol, cyclosporine, digoxin, pentamidine, mannitol, amphotericin B, foscarnet, methotrexate.
Antibiotics (gentamicin, ticarcillin, carbenicillin).
Redistribution: hypoalbuminemia, cirrhosis, administration of insulin and glucose, theophylline, epinephrine, acute pancreatitis, cardiopulmonary bypass.
Miscellaneous: sweating, burns, prolonged exercise, lactation, "hungry-bones" syndrome.

HYPOMAGNESEMIA IN PEDIATRIC PATIENTS[79]

ICD-10CM # E83.42 Hypomagnesemia

MAIN CAUSES OF HYPOMAGNESEMIA IN CHILDREN

Primary Inherited Disorders

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis.
Hypomagnesemia with secondary hypocalcemia.
Autosomal dominant hypomagnesemia.
Isolated autosomal recessive hypomagnesemia with normocalciuria.
Activating mutations of calcium-sensing receptor.
Gitelman syndrome.
Bartter syndrome.

Secondary Disorders

Decreased GI absorption:
- Malabsorptive syndromes.
- Vomiting and diarrhea.

Increased urinary excretion:
- Extracellular volume expansion.
- Polyuric states: obstructive uropathy, kidney transplant.

Drugs:
- Diuretics.
- Calcineurin antagonists.
- Others: cisplatinum, aminoglycosides, amphotericin B.
- Metabolic acidosis.

Miscellaneous: "hungry bone," low-birth-weight newborn, infant of diabetic mother.

HYPONATREMIA

ICD-10CM # E87.1 Hypo-osmolality and hyponatremia

Renal loss from renal disease, diuretics.
GI loss (diarrhea, vomiting, suction).
Hypertonic hyponatremia (e.g., increased serum osmolality from hyperglycemia).
Transcutaneous loss (extensive burns, excessive sweating).
Fluid sequestration (e.g., ascites).
Osmotic diuresis (e.g., mannitol, glucose).
Dilutional (psychogenic polydipsia, iatrogenic).
Syndrome of inappropriate antidiuretic hormone secretion.
Edema with water and sodium retention.
Artifact (e.g., severe hyperlipidemia).
Laboratory error.
Adrenal insufficiency.

HYPOPHOSPHATEMIA

ICD-10CM # E83.30 Disorder of phosphorus metabolism, unspecified
E83.31 Familial hypophosphatemia

Decreased intake (prolonged starvation [alcoholics], hyperalimentation, or IV infusion without phosphate).
Malabsorption.
Phosphate-binding antacids.
Renal loss:
- RTA.
- Fanconi syndrome, vitamin D–resistant rickets.
- ATN (diuretic phase).
- Hyperparathyroidism (primary or secondary).
- Familial hypophosphatemia.
- Hypokalemia, hypomagnesemia.
- Acute volume expansion.
- Glycosuria, idiopathic hypercalciuria.
- Acetazolamide.

Transcellular shift into cells:
- Alcohol withdrawal.
- DKA (recovery phase).
- Glucose-insulin or catecholamine infusion.
- Anabolic steroids.
- Total parenteral nutrition.
- Theophylline overdose.
- Severe hyperthermia; recovery from hypothermia.
- "Hungry bones" syndrome.

HYPOPHOSPHATEMIA IN PEDIATRIC PATIENTS[79]

ICD-10CM # E83.30 Disorder of phosphorus metabolism, unspecified

CAUSES OF HYPOPHOSPHATEMIA

Decreased Phosphate Intake

Starvation, inadequate phosphate intake, chronic diarrhea, chronic alcoholism.
Total parenteral nutrition with insufficient phosphate content.

Increased Loss of Phosphate

Increased renal phosphate excretion:
- Primary hyperparathyroidism.
- Secondary hyperparathyroidism: vitamin D deficiency or resistance (including 1α-hydroxylase deficiency, VDR mutations, VDDR); imatinib.
- Excess FGF-23 or phosphatonins: X-linked hypophosphatemia, AD hypophosphatemic rickets, tumor-induced osteomalacia, epidermal nevus, McCune-Albright syndrome.
- Fanconi syndrome, cystinosis, Wilson disease, Dent disease, Lowe syndrome, multiple myeloma, amyloidosis, heavy-metal toxicity, rewarming of hyperthermia, Na/Pi-IIa and Na/Pi-IIc mutation (HHRH).
- PTHrP-dependent hypercalcemia of malignancy.
- Hypomagnesemia.

Decreased intestinal absorption:
- Vitamin D deficiency or resistance (VDDR I and II).
- Malabsorption.

Increased intestinal loss:
- Phosphate binding antacids used in treating peptic ulcers.

Increased loss from other routes:
- Skin: severe burns.
- Vomiting.

Phosphate Shifting from Extracellular Compartment to Cells and Bones

Diabetic ketoacidosis.
Alcohol intoxication.
Acute respiratory alkalosis, salicylate intoxication, gram-negative sepsis, toxic shock syndrome, acute gout.
Refeeding syndromes from starvation, anorexia nervosa, hepatic failure: acute intravenous glucose, fructose, glycerol.
Rapid cellular proliferation: intensive erythropoietin therapy, GM-CSF therapy, leukemic blast crisis.
Recovery from hypothermia.
Heat stroke.
Post parathyroidectomy; "hungry bone" disease: osteoblastic metastases, antiresorptive treatment of severe Paget disease.
Catecholamine (albuterol, dopamine, terbutaline, epinephrine).
Thyrotoxic periodic paralysis.
Hypocalcemic periodic paralysis.

Miscellaneous

Hyperaldosteronism.
Oncogenic hypophosphatemia.
Post kidney transplantation.
Post partial hepatectomy.
High-dose corticosteroids, estrogens.
Medications: ifosfamide, toluene, calcitonin, bisphosphonate, tenofovir, paraquat, cisplatin, acetazolamide and other diuretics.
Post obstructive diuresis.

AD, Autosomal dominant; *FGF-23,* fibroblast growth factor 23; *GM-CSF,* granulocyte-macrophage colony-stimulating factor; *HHRH,* hereditary hypophosphatemic rickets with hypercalciuria; *Na/Pi-II,* type II sodium-dependent phosphate cotransporter; *PTHrP,* parathyroid hormone–related peptide; *VDR,* vitamin D receptor; *VDDR,* vitamin D–dependent rickets.

HYPOPIGMENTATION

ICD-10CM # L81.9 Disorder of pigmentation, unspecified

Vitiligo.
Tinea versicolor.
Atopic dermatitis.
Chemical leukoderma.
Idiopathic hypomelanosis.
Sarcoidosis.
SLE.

Scleroderma.
Oculocutaneous albinism.
Phenylketonuria.
Nevoid hypopigmentation.

HYPOTENSION, POSTURAL

ICD-10CM # I95.89 Other hypotension

Antihypertensive medications (especially a-blockers, diuretics, ACE inhibitors).
Volume depletion (hemorrhage, dehydration).
Impaired cardiac output (constrictive pericarditis, aortic stenosis).
Peripheral autonomic dysfunction (DM, Guillain-Barré).
Idiopathic orthostatic hypotension.
Central autonomic dysfunction (Shy-Drager syndrome).
Peripheral venous disease.
Adrenal insufficiency.

HYPOTHYROIDISM, CONGENITAL[53]

ICD-10CM # E03.0 Congenital hypothyroidism with diffuse goiter
E03.1 Congenital hypothyroidism without goiter

ETIOLOGIC CLASSIFICATION OF CONGENITAL HYPOTHYROIDISM

Primary Hypothyroidism

Defect of fetal thyroid development (dysgenesis):
  Aplasia.
  Hypoplasia.
  Ectopia.
Defect in thyroid hormone synthesis (dyshormonogenesis):
  Iodide transport defect: mutation in thyroglobulin gene.
  Thyroid organification, or coupling defect: mutation in thyroid peroxidase gene.
  Defects in H_2O_2 generation: mutations in DUOXA2 maturation factor or *DUOX2* gene.
  Thyroglobulin synthesis defect: mutation in thyroglobulin gene.
  Deiodination defect: mutation in *DEHAL1* gene.
TSH unresponsiveness:
  $G_s\alpha$ mutation (e.g., type 1A pseudohypothyroidism).
  Mutation in TSH receptor.
Defect in thyroid hormone transport: mutation in monocarboxylate transporter 8 *(MCT8)* gene.
Iodine deficiency (endemic goiter).
Maternal antibodies: thyrotropin receptor–blocking antibody (TRBAb, also termed *thyrotropin-binding inhibitor immunoglobulin*).
Maternal medications:
  Iodides, amiodarone.
  Propylthiouracil, methimazole.
  Radioiodine.

CENTRAL (HYPOPITUITARY) HYPOTHYROIDISM

PIT-1 mutations:
  Deficiency of thyroid-stimulating hormone (TSH).
  Deficiency of growth hormone.
  Deficiency of prolactin.
PROP-1 mutations:
  Deficiency of TSH.
  Deficiency of growth hormone.
  Deficiency of prolactin.
  Deficiency of luteinizing hormone.
  Deficiency of follicle-stimulating hormone.
  ±Deficiency of adrenocorticotropic hormone.
TSH deficiency: mutation in TSH β subunit gene (manifests as primary hypothyroidism with elevated TSH level).
Multiple pituitary deficiencies (e.g., craniopharyngioma).
Thyroid-releasing hormone (TRH) deficiency:
  Isolated.
  Multiple hypothalamic deficiencies (e.g., septooptic dysplasia).
TRH unresponsiveness.
Mutations in TRH receptor.

HYPOTONIA, INFANTILE, DIFFERENTIAL DIAGNOSIS[53]

ICD-10CM # H44.40 Unspecified hypotony of eye

Cerebral hypotonia:
  Benign congenital hypotonia.
  Chromosome disorders.
  Prader-Willi syndrome.
  Trisomy.
  Chronic nonprogressive encephalopathy.
  Cerebral malformation.
  Perinatal distress.
  Postnatal disorders.
  Peroxisomal disorders.
  Cerebrohepatorenal syndrome (Zellweger syndrome).
  Neonatal adrenoleukodystrophy.
  Other genetic defects.
  Familial dysautonomia.
  Oculocerebrorenal syndrome (Lowe syndrome).
  Other metabolic defects.
  Acid maltase deficiency (see "Metabolic Myopathies").
  Infantile GM, gangliosidosis.
Spinal cord disorders.
Spinal muscular atrophies:
  Acute infantile.
  Autosomal dominant.
  Autosomal recessive.
  Cytochrome-*c* oxidase deficiency.
  X-linked.
Chronic infantile:
  Autosomal dominant.
  Autosomal recessive.
  Congenital cervical spinal muscular atrophy.
  Infantile neuronal degeneration.
  Neurogenic arthrogryposis.
Polyneuropathies:
  Congenital hypomyelinating neuropathy.
  Giant axonal neuropathy.
  Hereditary motor-sensory neuropathies.
Disorders of neuromuscular transmission:
  Familial infantile myasthenia.
  Infantile botulism.
  Transitory myasthenia gravis.
  Fiber-type disproportion myopathies.
  Central core disease.
  Congenital fiber-type disproportion myopathy.
  Myotubular (centronuclear) myopathy.
  Acute.
  Chronic.
  Nemaline (rod) myopathy.
  Autosomal dominant.
  Autosomal recessive.
Metabolic myopathies:
  Acid maltase deficiency.
  Cytochrome-*c* oxidase deficiency.
Muscular dystrophies:
  Bethlem myopathy.
  Congenital dystrophinopathy.
  Congenital muscular dystrophy.
  Merosin deficiency, primary.
  Merosin deficiency, secondary.
  Merosin positive.
  Congenital myotonic dystrophy.

HYPOTONIC POLYURIA[79]

ICD-10CM # Varies with specific diagnosis

CAUSES OF HYPOTONIC POLYURIA

Central (Neurogenic) Diabetes Insipidus

Congenital (congenital malformations, autosomal dominant, arginine vasopressin [AVP] neurophysin gene mutations).
Drug- or toxin-induced (ethanol, diphenylhydantoin, snake venom).
Granulomatous (histiocytosis, sarcoidosis).
Neoplastic (craniopharyngioma, germinoma, lymphoma, leukemia, meningioma, pituitary tumor; metastases).
Infectious (meningitis, tuberculosis, encephalitis).
Inflammatory, autoimmune (lymphocytic infundibuloneurohypophysitis).
Trauma (neurosurgery, deceleration injury).
Vascular (cerebral hemorrhage or infarction, brain death).
Idiopathic.

Osmoreceptor Dysfunction

Granulomatous (histiocytosis, sarcoidosis).
Neoplastic (craniopharyngioma, pinealoma, meningioma, metastases).
Vascular (anterior communicating artery aneurysm or ligation, intrahypothalamic hemorrhage).
Other (hydrocephalus, ventricular or suprasellar cyst, trauma, degenerative diseases).
Idiopathic.

Increased AVP Metabolism

Pregnancy

Nephrogenic Diabetes Insipidus

Congenital (X-linked recessive, AVP V2 receptor gene mutations, autosomal recessive or dominant, aquaporin-2 water channel gene mutations).
Drug-induced (demeclocycline, lithium, cisplatin, methoxyflurane).
Hypercalcemia.
Hypokalemia.
Infiltrating lesions (sarcoidosis, amyloidosis).
Vascular (sickle cell anemia).
Mechanical (polycystic kidney disease, bilateral ureteral obstruction).

Solute diuresis (glucose, mannitol, sodium, radiocontrast dyes).
Idiopathic.
Primary Polydipsia
Psychogenic (schizophrenia, obsessive-compulsive behaviors).
Dipsogenic (downward resetting of thirst threshold, idiopathic or similar lesions, as with central DI).

HYPOVOLEMIA[79]

ICD-10CM # Varies with specific diagnosis

CAUSES OF ABSOLUTE AND RELATIVE HYPOVOLEMIA

Absolute
Extrarenal
GI fluid loss.
Bleeding.
Skin fluid loss.
Respiratory fluid loss.
Extracorporeal ultrafiltration.
Renal
Diuretics.
Obstructive uropathy/postobstructive diuresis.
Hormone deficiency.
Hypoaldosteronism.
Adrenal insufficiency.
Na+ wasting tubulopathies.
Genetic.
Acquired tubulointerstitial disease.
Relative
Extrarenal
Edematous states.
Heart failure.
Cirrhosis.
Generalized vasodilation.
Sepsis.
Drugs.
Pregnancy.
Third-space loss.
Renal
Severe nephrotic syndrome.

HYPOVOLEMIC SHOCK, PEDIATRIC POPULATION[29]

ICD-10CM # R57.1 Hypovolemic shock
R57.8 Other shock

ETIOLOGIES OF HYPOVOLEMIC SHOCK

Whole blood loss.
Absolute loss: hemorrhage.
External bleeding.
Internal bleeding:
GI.
Intraabdominal (spleen, liver).
Major vessel injury.
Intracranial (in infants).
Fractures.
Relative loss:
Pharmacologic (barbiturates, vasodilators).
Positive pressure ventilation.
Spinal cord injury.
Sepsis.
Anaphylaxis.
Plasma loss.
Burns.
Capillary leak syndromes:
Inflammation, sepsis.
Anaphylaxis.
Protein-losing syndromes.
Fluid and electrolyte loss.
Vomiting and diarrhea.
Excessive diuretic use.
Endocrine:
Adrenal insufficiency.
Diabetes insipidus.
Diabetes mellitus.

HYPOXEMIA AND HYPERCAPNIC RESPIRATORY FAILURE[69]

ICD-10CM # Varies with specific diagnosis

COMMON CAUSES OF HYPOXEMIC AND HYPERCAPNIC RESPIRATORY FAILURE

Brain
Bulbar poliomyelitis.
Central alveolar hypoventilation.
Cerebrovascular accident.
Cerebral malignancy.
Drug overdose (e.g., narcotic, sedative/hypnotic).
Elevated intracranial pressure.
Encephalitis and meningitis.
Pontine herniation.
Postoperative anesthetic depression.
Spinal Cord
Amyotrophic lateral sclerosis.
Cervical cordotomy.
Guillain-Barré syndrome.
Poliomyelitis.
Spinal cord trauma.
Neuromuscular System
Acute intermittent porphyria.
Botulism.
Cholinergic crisis.
Curariform drugs.
Electrolyte disorders (e.g., hypophosphatemia, hypomagnesemia).
Hypokalemic periodic paralysis.
Multiple sclerosis.
Myasthenia gravis.
Myxedema.
Neuromuscular blocking antibiotics (e.g., polymyxin, streptomycin).
Organophosphate insecticides.
Peripheral neuritis.
Polymyositis.
Respiratory muscle fatigue—critical illness polyneuropathy/polymyopathy.
Tetanus.
Upper Airway
Epiglottitis and laryngotracheitis.
Large tonsils and adenoids.
Obstructive sleep apnea.
Postintubation laryngeal edema.
Tracheal obstruction.
Vocal cord paralysis.
Thorax and Pleura
Chest wall burn with eschar formation.
Chest wall trauma—flail chest.
Kyphoscoliosis.
Massive abdominal distention.
Massive obesity.
Muscular dystrophy.
Large pleural effusion/pleural fibrosis.
Pneumothorax.
Rheumatoid spondylitis.
Thoracoplasty.
Cardiovascular System
Cardiogenic pulmonary edema.
Left ventricular failure.
Mitral stenosis.
Biventricular failure.
Fat embolism.
Snake bite.
Uremia.
Volume overload.
Pulmonary veno-occlusive disease.
Lower Airway and Alveoli
Acute respiratory distress syndrome (ARDS).
Aspiration.
Asthma.
Atelectasis.
Bronchiectasis.
Bronchiolitis.
Chronic obstructive pulmonary disease.
Cystic fibrosis.
Interstitial lung disease.
Massive bilateral pneumonia.
Near-drowning.
Pancreatitis.
Pulmonary contusion.
Radiation lung injury.
Sepsis.
Smoke inhalation.
Surgical resection of lung parenchym.

ILIAC FOSSA PAIN, LEFT SIDED[86]

ICD-10CM # M25.5 Pain in joint

GASTROINTESTINAL CAUSES OF ACUTE LEFT ILIAC FOSSA PAIN

Nonspecific left iliac fossa pain including constipation.
Acute gastroenteritis.
Acute diverticulitis.
Colonic carcinoma.
Colonic ischemia.
Localized small bowel perforation.

ILIAC FOSSA PAIN, RIGHT SIDED[86]

ICD-10CM # M25.5 Pain in joint

DIFFERENTIAL DIAGNOSIS OF RIGHT ILIAC FOSSA PAIN

Gastrointestinal Causes
Nonspecific right iliac fossa pain.
Acute appendicitis.
Mesenteric adenitis.
Terminal ileitis.
Acute inflammation of Meckel diverticulum.
Crohn disease of the terminal ileum.

Solute diuresis (glucose, mannitol, sodium, radiocontrast dyes).
Idiopathic.
Primary Polydipsia
Psychogenic (schizophrenia, obsessive-compulsive behaviors).
Dipsogenic (downward resetting of thirst threshold, idiopathic or similar lesions, as with central DI).

HYPOVOLEMIA[79]

ICD-10CM # Varies with specific diagnosis

CAUSES OF ABSOLUTE AND RELATIVE HYPOVOLEMIA

Absolute
Extrarenal
GI fluid loss.
Bleeding.
Skin fluid loss.
Respiratory fluid loss.
Extracorporeal ultrafiltration.
Renal
Diuretics.
Obstructive uropathy/postobstructive diuresis.
Hormone deficiency.
Hypoaldosteronism.
Adrenal insufficiency.
Na+ wasting tubulopathies.
Genetic.
Acquired tubulointerstitial disease.
Relative
Extrarenal
Edematous states.
Heart failure.
Cirrhosis.
Generalized vasodilation.
Sepsis.
Drugs.
Pregnancy.
Third-space loss.
Renal
Severe nephrotic syndrome.

HYPOVOLEMIC SHOCK, PEDIATRIC POPULATION[29]

ICD-10CM # R57.1 Hypovolemic shock
R57.8 Other shock

ETIOLOGIES OF HYPOVOLEMIC SHOCK

Whole blood loss.
Absolute loss: hemorrhage.
External bleeding.
Internal bleeding:
GI.
Intraabdominal (spleen, liver).
Major vessel injury.
Intracranial (in infants).
Fractures.
Relative loss:
Pharmacologic (barbiturates, vasodilators).
Positive pressure ventilation.
Spinal cord injury.
Sepsis.
Anaphylaxis.
Plasma loss.
Burns.
Capillary leak syndromes:
Inflammation, sepsis.
Anaphylaxis.
Protein-losing syndromes.
Fluid and electrolyte loss.
Vomiting and diarrhea.
Excessive diuretic use.
Endocrine:
Adrenal insufficiency.
Diabetes insipidus.
Diabetes mellitus.

HYPOXEMIA AND HYPERCAPNIC RESPIRATORY FAILURE[69]

ICD-10CM # Varies with specific diagnosis

COMMON CAUSES OF HYPOXEMIC AND HYPERCAPNIC RESPIRATORY FAILURE

Brain
Bulbar poliomyelitis.
Central alveolar hypoventilation.
Cerebrovascular accident.
Cerebral malignancy.
Drug overdose (e.g., narcotic, sedative/hypnotic).
Elevated intracranial pressure.
Encephalitis and meningitis.
Pontine herniation.
Postoperative anesthetic depression.
Spinal Cord
Amyotrophic lateral sclerosis.
Cervical cordotomy.
Guillain-Barré syndrome.
Poliomyelitis.
Spinal cord trauma.
Neuromuscular System
Acute intermittent porphyria.
Botulism.
Cholinergic crisis.
Curariform drugs.
Electrolyte disorders (e.g., hypophosphatemia, hypomagnesemia).
Hypokalemic periodic paralysis.
Multiple sclerosis.
Myasthenia gravis.
Myxedema.
Neuromuscular blocking antibiotics (e.g., polymyxin, streptomycin).
Organophosphate insecticides.
Peripheral neuritis.
Polymyositis.
Respiratory muscle fatigue—critical illness polyneuropathy/polymyopathy.
Tetanus.
Upper Airway
Epiglottitis and laryngotracheitis.
Large tonsils and adenoids.
Obstructive sleep apnea.
Postintubation laryngeal edema.
Tracheal obstruction.
Vocal cord paralysis.
Thorax and Pleura
Chest wall burn with eschar formation.
Chest wall trauma—flail chest.
Kyphoscoliosis.
Massive abdominal distention.
Massive obesity.
Muscular dystrophy.
Large pleural effusion/pleural fibrosis.
Pneumothorax.
Rheumatoid spondylitis.
Thoracoplasty.
Cardiovascular System
Cardiogenic pulmonary edema.
Left ventricular failure.
Mitral stenosis.
Biventricular failure.
Fat embolism.
Snake bite.
Uremia.
Volume overload.
Pulmonary veno-occlusive disease.
Lower Airway and Alveoli
Acute respiratory distress syndrome (ARDS).
Aspiration.
Asthma.
Atelectasis.
Bronchiectasis.
Bronchiolitis.
Chronic obstructive pulmonary disease.
Cystic fibrosis.
Interstitial lung disease.
Massive bilateral pneumonia.
Near-drowning.
Pancreatitis.
Pulmonary contusion.
Radiation lung injury.
Sepsis.
Smoke inhalation.
Surgical resection of lung parenchym.

ILIAC FOSSA PAIN, LEFT SIDED[86]

ICD-10CM # M25.5 Pain in joint

GASTROINTESTINAL CAUSES OF ACUTE LEFT ILIAC FOSSA PAIN

Nonspecific left iliac fossa pain including constipation.
Acute gastroenteritis.
Acute diverticulitis.
Colonic carcinoma.
Colonic ischemia.
Localized small bowel perforation.

ILIAC FOSSA PAIN, RIGHT SIDED[86]

ICD-10CM # M25.5 Pain in joint

DIFFERENTIAL DIAGNOSIS OF RIGHT ILIAC FOSSA PAIN

Gastrointestinal Causes
Nonspecific right iliac fossa pain.
Acute appendicitis.
Mesenteric adenitis.
Terminal ileitis.
Acute inflammation of Meckel diverticulum.
Crohn disease of the terminal ileum.

Cecal carcinoma.
Inflammatory cecal lesion (e.g., diverticulitis in a solitary cecal diverticulum).
Inflammatory lesion of the terminal ileum (e.g., foreign body perforation).
Non-Gastrointestinal Causes
Ruptured ovarian follicle (mittelschmerz).
Acute salpingitis (pelvic inflammatory disease).
Rupture/torsion or hemorrhage of an ovarian cyst.
Endometriosis.
Ectopic pregnancy.
Urinary tract infection.

IMMUNODEFICIENCY, CONGENITAL (PRIMARY)

ICD-10CM #		
	D80.0	Hereditary hyopgammaglobulinemia
	D80.1	Nonfamilial hypogammaglobulinemia
	D80.2	Selective deficiency of IgA
	D80.3	Selective deficiency of IgG
	D80.4	Selective deficiency of IgM

CONGENITAL (PRIMARY) CAUSES OF IMMUNODEFICIENCY

T-lymphocyte Deficiencies
DiGeorge syndrome (thymic aplasia with reduced CD4 and CD3 cells).
Purine nucleoside phosphorylase deficiency (marked T-cell depletion).
B-lymphocyte Deficiencies
Bruton X-linked agammaglobulinemia (absence of B cells, plasma cells, and antibody).
Selective immunoglobulin G (IgG) subclass deficiencies.
Selective IgA deficiency.
Hyper-IgM immunodeficiency (elevated IgM but reduced IgG and IgA).
Mixed T- and B-lymphocyte Deficiencies
Common variable immunodeficiency (leads to various B-cell activation or differentiation defects and gradual deterioration of T-cell number and function).
Severe combined immunodeficiency (severe reduction in IgG and absence of T cells).
Wiskott-Aldrich syndrome (decreased T-cell number and function, low IgM, occasionally low IgG).
Ataxia-telangiectasia (decreased T-cell number and function; IgA, IgE, IgG_2, and IgG_4 deficiency).
Disorders of Complement
C3 deficiency (congenital absence of C3 or consumption of C3 due to deficiency of C3b inactivator).
Phagocyte Defects
Chronic granulomatous disease (defect in nicotinamide adenine dinucleotide phosphate oxidase in phagocytic cells).
Chédiak-Higashi syndrome (impaired microbicidal activity of phagocytes).
Kostmann syndrome, Shwachman-Diamond syndrome, cyclic neutropenia (low neutrophil count).

IMPAIRED CONSCIOUSNESS AND COMA[84]

ICD-10CM #		
	R40.20	Unspecified coma

INFECTIOUS OR INFLAMMATORY

Infectious
Bacterial meningitis.
Viral encephalitis.
Rickettsial infection.
Protozoan infection.
Helminth infestation.
Inflammatory
Sepsis-associated encephalopathy.
Vasculitis, collagen vascular disorders.
Demyelination.
Acute disseminated encephalomyelitis.
Multiple sclerosis.

STRUCTURAL

Traumatic
Concussion.
Cerebral contusion.
Epidural hematoma or effusion.
Intracerebral hematoma.
Diffuse axonal injury.
Abusive head trauma.
Neoplasms
Vascular Disease
Cerebral infarction:
- Thrombosis.
- Embolism.
- Venous sinus thrombosis.

Cerebral hemorrhage:
- Subarachnoid hemorrhage.
- Arteriovenous malformation.
- Aneurysm.

Congenital abnormality or dysplasia of vascular supply
Trauma to carotid or vertebral arteries in the neck
Focal Infection
Abscess.
Cerebritis.
Hydrocephalus

METABOLIC, NUTRITIONAL, OR TOXIC

Hypoxic-Ischemic Encephalopathy
Shock.
Cardiac or pulmonary failure.
Near-drowning.
Carbon monoxide poisoning.
Cyanide poisoning.
Strangulation.
Metabolic Disorders
Sarcoidosis.
Hypoglycemia.
Fluid and electrolyte imbalance.
Endocrine disorders:
- With acidosis:
  - Diabetic ketoacidosis.
  - Aminoacidemias.
  - Organic acidemias.
- With hyperammonemia:
  - Hepatic encephalopathy.
  - Urea cycle disorders.
  - Disorders of fatty acid metabolism.
  - Reye syndrome.
  - Valproic acid encephalopathy.

Uremia.
Porphyria.
Mitochondrial disorders.
Leigh syndrome.
Nutritional
Thiamine deficiency.
Niacin or nicotinic acid deficiency.
Pyridoxine dependency.
Folate and B_{12} deficiency.
Exogenous Toxins and Poisons
Alcohol intoxication.
Over-the-counter medications.
Prescription medications (oral and ophthalmic).
Herbal treatments.
Heavy-metal poisoning.
Mushroom and plant intoxication.
Illegal drugs.
Industrial agents.
Hypertensive Encephalopathy
Burn Encephalopathy

IMPOTENCE[63]

ICD-10CM #		
	F52.21	Male erectile disorder
	F52.8	Other sexual dysfunction not due to a substance or known physiological condition
	N52.9	Male erectile dysfunction, unspecified

Psychogenic.
Endocrine: hyperprolactinemia, DM, Cushing syndrome, hypothyroidism or hyperthyroidism, abnormality of hypothalamic-pituitary-testicular axis.
Vascular: arterial insufficiency, venous leakage, AV malformation, local trauma.
Medications.
Neurogenic: autonomic or sensory neuropathy, spinal cord trauma or tumor, CVA, multiple sclerosis, temporal lobe epilepsy.
Systemic illness: renal failure, COPD, cirrhosis of liver, myotonic dystrophy.
Peyronie disease.
Prostatectomy.

INCONTINENCE, FECAL[86]

ICD-10CM #		
	R15.9	Full incontinence of feces

NORMAL SPHINCTER

Diarrhea.
Anorectal conditions:
- Rectal carcinoma.
- Inflammatory bowel disease.
- Hemorrhoids.
- Mucosal prolapse.
- Fissure-in-ano.
- Abnormal rectal sensation.

ABNORMAL SPHINCTER

Congenital abnormalities.
Anal sepsis.
Neurologic conditions.
Rectal prolapse.
Sphincter trauma.
Neurogenic (idiopathic) incontinence.

INFECTIOUS DIARRHEA IN TROPICS[26]

ICD-10CM # R19.7 Diarrhea, unspecified

CAUSES OF INFECTIOUS DIARRHEA IN THE TROPICS

Bacteria
Aeromonas hydrophila.
Arcobacter butzleri.
Bacteroides fragilis, enterotoxigenic.
Campylobacter jejuni.
Escherichia coli: enterotoxigenic, enteroaggregative, enteroinvasive, enterohemorrhagic.
Laribacter hongkongensis.
Plesiomonas shigelloides.
Salmonella, non-typhoidal.
Shigella species: *S. dysenteriae, S. flexneri, S. sonnei, S. boydii.*
Vibrio cholerae 01, 0139, non-01 non-0139.
Vibrio parahaemolyticus.
Yersinia enterocolitica.
Helminths
Paracapillaria philippinensis.
Fasciolopsis buski.
Heterophyiasis (Metagonimus yokogawai, Haplorchis taichui).
Schistosoma mansoni.
Strongyloides stercoralis.
Protozoa
Blastocystis hominis.
Cryptosporidium parvum.
Cyclospora cayetanensis.
Encephalitozoon intestinalis.
Enterocytozoon bieneusi.
Giardia lamblia.
Isospora belli.
Leishmania donovani.
Viruses
Astroviruses.
Caliciviruses: norovirus and sapovirus.
Enteric adenoviruses.
HIV.
Picornaviruses.
Rotavirus.

INFERTILITY, FEMALE[32]

ICD-10CM # N97.9 Female infertility, unspecified

FALLOPIAN TUBE PATHOLOGY

PID or puerperal infection.
Congenital anomalies.
Endometriosis.
Secondary to past peritonitis of nongenital origin.
Amenorrhea and anovulation.
Minor anovulatory disturbances.

CERVICAL AND UTERINE FACTORS

Leiomyomas and polyps.
Uterine anomalies.
Intrauterine synechiae (Asherman syndrome).
Destroyed endocervical glands (postsurgery or postinfection).

VAGINAL FACTORS

Congenital absence of vagina.
Imperforate hymen.
Vaginismus.
Vaginitis.

IMMUNOLOGIC FACTORS

Sperm-immobilizing antibodies.
Sperm-agglutinating antibodies.

NUTRITIONAL AND METABOLIC FACTORS

Thyroid disorders.
DM.
Severe nutritional disturbances.

INFERTILITY, MALE[32]

ICD-10CM # N46.9 Male infertility, unspecified

DECREASED PRODUCTION OF SPERMATOZOA

Varicocele.
Testicular failure.
Endocrine disorders.
Cryptorchidism.
Stress, smoking, caffeine, nicotine, recreational drugs.

DUCTAL OBSTRUCTION

Epididymal (postinfection).
Congenital absence of vas deferens.
Ejaculatory duct (postinfection).
Postvasectomy.

INABILITY TO DELIVER SPERM INTO VAGINA

Ejaculatory disturbances.
Hypospadias.
Sexual problems (i.e., impotence), medical or psychological.

ABNORMAL SEMEN

Infection.
Abnormal volume.
Abnormal viscosity.
Abnormal sperm motion.

IMMUNOLOGIC FACTORS

Sperm-immobilizing antibodies.
Sperm-agglutinating antibodies.

INSOMNIA[76]

ICD-10CM #	780.51	Insomnia with sleep apnea
	G47.00	Insomnia, unspecified
	F51.01	Primary insomnia
	F51.03	Paradoxical insomnia
	F51.09	Other insomnia not due to a substance or known physiological condition

Anxiety disorder, psychophysiologic insomnia.
Depression.
Drugs (e.g., caffeine, amphetamines, cocaine), hypnotic-dependent sleep disorder.
Pain, fibromyalgia.
Inadequate sleep hygiene.
Restless leg syndrome.
Obstructive sleep apnea.
Sleep bruxism.
Medical illness (e.g., GERD, sleep-related asthma, parkinsonism and movement disorders).
Narcolepsy.
Other: periodic leg movement of sleep, central sleep apnea, REM behavioral disorder.

INTESTINAL PSEUDOOBSTRUCTION[82,54]

ICD-10CM #	K56.0	Paralytic ileus
	K56.9	Ileus, unspecified
	K59.9	Functional intestinal disorder, unspecified

"PRIMARY" (IDIOPATHIC INTESTINAL PSEUDOOBSTRUCTION)

Hollow visceral myopathy:
  Familial.
  Sporadic.
Neuropathic:
  Abnormal myenteric plexus.
  Normal myenteric plexus.

SECONDARY

Scleroderma.
Myxedema.
Amyloidosis.
Muscular dystrophy.
Hypokalemia.
Chronic renal failure.
DM.
Drug toxicity caused by:
  Anticholinergics.
  Opiate narcotics.
Ogilvie syndrome.

Causes of Secondary Chronic Intestinal Pseudoobstruction in Children

Autoimmune
Autoimmune myositis.
Autoimmune ganglionitis.
Scleroderma.
Endocrine
Diabetes mellitus.
Hypoparathyroidism.
Hypothyroidism.
Gastrointestinal
Celiac disease.
Eosinophilic gastroenteritis.
Inflammatory bowel disease.
Hematology/oncology
Multiple myeloma.
Paraneoplastic syndromes.
Pheochromocytoma.
Sickle cell disease.
Infection
Chagas disease.
Cytomegalovirus.
Epstein-Barr virus.
Herpes zoster.
JC virus.
Kawasaki disease.
Postviral neuropathy.
Medications and toxins
Chemotherapy.
Cyclopentolate and phenylephrine eye drops.
Diltiazem and nifedipine.
Fetal alcohol syndrome.
Jellyfish envenomation.

Causes of Secondary Chronic Intestinal Pseudoobstruction in Children—Cont'd

Opioid medications.
Postanesthesia.
Radiation injury.
Mitochondrial disorders
Mitochondrial neurogastrointestinal encephalomyopathy.
Musculoskeletal disorders
Ehlers-Danlos syndrome.
Myotonic dystrophy.
Duchenne muscular dystrophy.
Rheumatology
Amyloidosis.
Dermatomyositis.
Polymyositis.
Systemic lupus erythematous.

From Wyllie R, Hyams JS, Kay M, editors: *Pediatric gastrointestinal and liver disease,* 5th ed, Elsevier, 2016, Philadelphia, Box. 44.3, p. 548.

INTRAABDOMINAL MASS LESION, NEONATAL[36]

ICD-10CM # R19.00 Intraabdominal and pelvic swelling, mass and lump, unspecified site

CAUSES OF A NEONATAL INTRAABDOMINAL MASS LESION

Complicated meconium ileus.
Dilated bowel proximal to an obstruction.
Mesenteric or duplication cyst.
Abscess.
GU causes:
- Hydronephrosis.
- Renal cystic disease.
- Mesoblastic nephroma.
- Wilms tumor.
- Adrenal hemorrhage.
- Neuroblastoma.
- Retroperitoneal teratoma.
- Ovarian cyst.
- Hydrometrocolpos.

Hemangioendothelioma.
Hepatoblastoma.
Choledochal, hepatic, or splenic cysts.

INTRACEREBRAL HEMORRHAGE, NONHYPERTENSIVE CAUSES

ICD-10CM # I61.9 Nontraumatic intracerebral hemorrhage, unspecified

Trauma.
Anticoagulation.
Intracranial tumors.
Vascular malformations.
Bleeding disorders.
Vasculitides (e.g., polyarteritis nodosa, granulomatous angiitis).
Cocaine and other sympathomimetic agents.
Cerebral amyloid angiopathy.

INTRACRANIAL LESION

ICD-10CM # G93.89 Other specified disorders of brain

Tumor (primary or metastatic).
Abscess.
Stroke.
Intracranial hemorrhage.
Angioma.
Multiple sclerosis (initial single lesion).
Granuloma.
Herpes encephalitis.
Artifact.

INTRAOCULAR NEOPLASM

ICD-10CM # C69.9 Malignant disorder of eye, unspecified

MALIGNANT

Retinoblastoma.
Melanoma.
Reticulum cell sarcoma.
Metastatic tumor.

BENIGN

Melanocytic nevus.
Hemangioma.
Reactive lymphoid hyperplasia.

IRON METABOLISM DISORDERS[5]

ICD-10CM # E83.10 Disorder of iron metabolism, unspecified

IRON DEFICIENCY

Deficient Iron Intake
Diet of low bioavailability.
Increased physiological requirements due to rapid growth in early childhood and in adolescence.
Blood loss.
Physiological (e.g., menstruation).
Pathological (e.g., GI).
Malabsorption of Iron
Reduced or absent gastric acid secretion (e.g., after partial or total gastrectomy or with atrophic gastritis).
Reduced duodenal absorption (e.g., in coeliac disease).
Bypass of stomach and duodenum (bariatric surgery).
Rare, inherited iron-refractory iron deficiency anemia (e.g., deficiency of TMPRSS6 [transmembrane protease, serine 6], also known as matriptase-2).
Redistribution of Iron
Macrophage iron accumulation in reticuloendothelial system in inflammatory, infectious, or malignant diseases (anemia of chronic disease, also known as anemia of inflammation).
Macrophage iron accumulation within the lungs in idiopathic pulmonary hemosiderosis.
Iron Overload
Due to Increased Iron Absorption
Hereditary hemochromatosis—commonly (among Northern Europeans) homozygosity for *HFE* C282Y but sometimes involving non-C282Y *HFE* or other genes (*HAMP, HFE2* [encoding hemojuvelin], *TFR2, SLC40A1*).
Substantial ineffective erythropoiesis (e.g., β thalassemia intermedia and major, some types of sideroblastic anemia, congenital dyserythropoietic anemia).
Sub-Saharan iron overload ("Bantu siderosis")—only in combination with increased dietary iron.
Other rare inherited disorders (e.g., congenital atransferrinemia, DMT1 deficiency, aceruloplasminemia).
Inappropriate iron therapy (rare).

DUE TO MULTIPLE BLOOD TRANSFUSIONS FOR REFRACTORY ANEMIAS OR FOR OTHER REASONS

Thalassemia major.
Aplastic anemia.
Myelodysplastic syndromes.
Sickle cell disease (when regularly transfused).

IRON OVERLOAD[45]

ICD-10CM # E83.10 Disorder of iron metabolism, unspecified

HEREDITARY IRON OVERLOAD

Hereditary hemochromatosis:
- HFE-associated (type 1).
- Non–HFE-associated:
  - Transferrin receptor 2–associated (type 3).

Juvenile hemochromatosis (type 2):
- Hemojuvelin-associated (type 2A).
- Hepcidin-associated (type 2B).

Autosomal dominant hemochromatosis:
- Ferroportin-associated (type 4).
- DMT1-associated hemochromatosis.
- Atransferrinemia.
- Aceruloplasminemia.

ACQUIRED IRON OVERLOAD

Iron-loading anemias (refractory anemias with hypercellular erythroid marrow).
Chronic liver disease.
Porphyria cutanea tarda.
Insulin resistance–associated hepatic iron overload.
African dietary iron overload.[24]
Medical iron ingestion.
Parenteral iron overload:
- Transfusional iron overload.
- Inadvertent iron overload from therapeutic injections.

PERINATAL IRON OVERLOAD

Neonatal hemochromatosis.
Trichohepatoenteric syndrome.
Cerebrohepatorenal syndrome.
GRACILE[25] (Fellman) syndrome.

FOCAL SEQUESTRATION OF IRON

Idiopathic pulmonary hemosiderosis.
Renal hemosiderosis.
Associated with neurologic abnormalities:
- Pantothenate kinase–associated neurodegeneration (formerly called Hallervorden-Spatz syndrome).
- Neuroferritinopathy.
- Friedreich ataxia.

[24] May have a genetic component.
[25] GRACILE, Growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death.

ISCHEMIA, UPPER EXTREMITY, CAUSES[15]

ICD-10CM #		
	S45.809A	Unspecified injury of other specified blood vessels at shoulder and upper arm level, unspecified arm, initial encounter

VASOSPASM

Raynaud disease.
Medication induced: vasopressors, β-blockers.
Ergot poisoning.

INTRINSIC ARTERIAL DISEASE

Atherosclerosis.
Radiation arteritis.
Azotemic arteriopathy.
Spontaneous dissection.
Fibromuscular dysplasia.

INFLAMMATORY DISEASES

Connective tissue disorders.
Buerger disease.
Takayasu arteritis.
Temporal (giant cell) arteritis.
Hypersensitivity angiitis.

NONINFLAMMATORY MEDICAL DISEASE

Thrombophilic states.
Myeloproliferative disorders.
Cold injury.
Hepatitis-associated vasculitis.
Cryoglobulinemia.
Vinyl chloride exposure.

EMBOLISM

Cardiac (most common).
Proximal aneurysm.
Arterial thoracic outlet syndrome.
Atheroembolism.
Paradoxic embolus (with accompanying septal defect).

TRAUMA

Iatrogenic.
Blunt arterial injury.
Penetrating arterial injury.
Hypothenar hammer syndrome.
Vibration.

ISCHEMIC BOWEL DISEASE[1]

ICD-10CM #		
	K55.1	Vascular disorder of intestine
	I99	Other and unspecified disorders of circulatory system

Abdominal aortic aneurysm: rupture or expansion.
Perforated ulcer or viscus.
Ruptured ectopic pregnancy (woman of childbearing age).
Incarcerated or strangulated hernia.
Septic shock.
Intussusception.
Volvulus.
Salpingitis or tuboovarian abscess.
Torsion of the ovary or testicle.
Appendicitis.
Pelvic mass or torsion.
Pancreatitis.
Diverticulitis.
Ruptured ovarian cyst.
Renal colic.
Biliary colic.
Also consider atypical manifestations of:
- Inferior wall myocardial infarction.
- Pulmonary embolism.
- Pneumonia.
- Diabetic ketoacidosis.
- Acute glaucoma.

Differential diagnoses are listed in order of urgency.

ISCHEMIC COLITIS, NONOCCLUSIVE[49]

ICD-10CM #		
	K55.1	Chronic vascular disorders of intestine

ACUTE DIMINUTION OF COLONIC INTRAMURAL BLOOD FLOW

Small Vessel Obstruction
Collagen-vascular disease.
Vasculitis, diabetes.
Oral contraceptives.
Nonocclusive Hypoperfusion
Hemorrhage.
CHF, MI, arrhythmias.
Sepsis.
Vasoconstricting agents: vasopressin, ergot.
Increased viscosity: polycythemia, sickle cell disease, thrombocytosis.

INCREASED DEMAND ON MARGINAL BLOOD FLOW

Increased Motility
Mass lesion, stricture.
Constipation.
Increased Intraluminal Pressure
Bowel obstruction.
Colonoscopy.
Barium enema.

ISCHEMIC NECROSIS OF CARTILAGE AND BONE[32]

ICD-10CM #		
	M89.9	Disorder of bone, unspecified
	M94.9	Disorder of cartilage, unspecified

ENDOCRINE/METABOLIC

Ethanol abuse.
Glucocorticoid therapy.
Cushing disease.
DM.
Hyperuricemia.
Osteomalacia.
Hyperlipidemia.

STORAGE DISEASES (E.G., GAUCHER DISEASE)

Hemoglobinopathies (e.g., sickle cell disease).
Trauma (e.g., dislocation, fracture).
HIV infection.
Dysbaric conditions (e.g., caisson disease).
Collagen-vascular disorders.
Irradiation.
Pancreatitis.
Organ transplantation.
Hemodialysis.
Burns.
Intravascular coagulation.
Idiopathic, familial.

JAUNDICE

ICD-10CM #		
	R17	Unspecified jaundice
	K83.8	Other specified diseases of biliary tract
	E80.7	Disorder of bilirubin metabolism, unspecified

PREDOMINANCE OF DIRECT (CONJUGATED) BILIRUBIN

Extrahepatic obstruction.
Common duct abnormalities: calculi, neoplasm, stricture, cyst, sclerosing cholangitis.
Metastatic carcinoma.
Pancreatic carcinoma, pseudocyst.
Ampullary carcinoma.
Hepatocellular disease: hepatitis, cirrhosis.
Drugs: estrogens, phenothiazines, captopril, methyltestosterone, labetalol.
Cholestatic jaundice of pregnancy.
Hereditary disorders: Dubin-Johnson syndrome, Rotor syndrome.
Recurrent benign intrahepatic cholestasis.

PREDOMINANCE OF INDIRECT (UNCONJUGATED) BILIRUBIN

Hemolysis: hereditary and acquired hemolytic anemias.
Inefficient marrow production.
Impaired hepatic conjugation: chloramphenicol.
Neonatal jaundice.
Hereditary disorders: Gilbert syndrome, Crigler-Najjar syndrome.

JAUNDICE, CLASSIFICATION[3]

ICD-10CM #		
	R17	Unspecified jaundice

PREHEPATIC (PREDOMINANTLY UNCONJUGATED HYPERBILIRUBINEMIA)

Overproduction
Hemolysis (e.g., spherocytosis, sickle cell disease, hemolysis of the newborn, autoimmune disorders).
Ineffective erythropoiesis (e.g., megaloblastic anemias).
Hematomas.
Pulmonary emboli.

HEPATIC (UNCONJUGATED HYPERBILIRUBINEMIA)

Decreased Hepatic Uptake
Gilbert syndrome.
Drugs (e.g., rifampin, radiographic contrast agents).
Neonatal jaundice.
Posthepatitis.
Decreased cystolic binding proteins (e.g., newborn or premature infants).
Portacaval shunt.

ISCHEMIA, UPPER EXTREMITY, CAUSES[15]

ICD-10CM #		
	S45.809A	Unspecified injury of other specified blood vessels at shoulder and upper arm level, unspecified arm, initial encounter

VASOSPASM

Raynaud disease.
Medication induced: vasopressors, β-blockers.
Ergot poisoning.

INTRINSIC ARTERIAL DISEASE

Atherosclerosis.
Radiation arteritis.
Azotemic arteriopathy.
Spontaneous dissection.
Fibromuscular dysplasia.

INFLAMMATORY DISEASES

Connective tissue disorders.
Buerger disease.
Takayasu arteritis.
Temporal (giant cell) arteritis.
Hypersensitivity angiitis.

NONINFLAMMATORY MEDICAL DISEASE

Thrombophilic states.
Myeloproliferative disorders.
Cold injury.
Hepatitis-associated vasculitis.
Cryoglobulinemia.
Vinyl chloride exposure.

EMBOLISM

Cardiac (most common).
Proximal aneurysm.
Arterial thoracic outlet syndrome.
Atheroembolism.
Paradoxic embolus (with accompanying septal defect).

TRAUMA

Iatrogenic.
Blunt arterial injury.
Penetrating arterial injury.
Hypothenar hammer syndrome.
Vibration.

ISCHEMIC BOWEL DISEASE[1]

ICD-10CM #		
	K55.1	Vascular disorder of intestine
	I99	Other and unspecified disorders of circulatory system

Abdominal aortic aneurysm: rupture or expansion.
Perforated ulcer or viscus.
Ruptured ectopic pregnancy (woman of childbearing age).
Incarcerated or strangulated hernia.
Septic shock.
Intussusception.
Volvulus.
Salpingitis or tuboovarian abscess.
Torsion of the ovary or testicle.
Appendicitis.
Pelvic mass or torsion.
Pancreatitis.
Diverticulitis.
Ruptured ovarian cyst.
Renal colic.
Biliary colic.
Also consider atypical manifestations of:
- Inferior wall myocardial infarction.
- Pulmonary embolism.
- Pneumonia.
- Diabetic ketoacidosis.
- Acute glaucoma.

Differential diagnoses are listed in order of urgency.

ISCHEMIC COLITIS, NONOCCLUSIVE[49]

ICD-10CM #		
	K55.1	Chronic vascular disorders of intestine

ACUTE DIMINUTION OF COLONIC INTRAMURAL BLOOD FLOW

Small Vessel Obstruction
Collagen-vascular disease.
Vasculitis, diabetes.
Oral contraceptives.
Nonocclusive Hypoperfusion
Hemorrhage.
CHF, MI, arrhythmias.
Sepsis.
Vasoconstricting agents: vasopressin, ergot.
Increased viscosity: polycythemia, sickle cell disease, thrombocytosis.

INCREASED DEMAND ON MARGINAL BLOOD FLOW

Increased Motility
Mass lesion, stricture.
Constipation.
Increased Intraluminal Pressure
Bowel obstruction.
Colonoscopy.
Barium enema.

ISCHEMIC NECROSIS OF CARTILAGE AND BONE[32]

ICD-10CM #		
	M89.9	Disorder of bone, unspecified
	M94.9	Disorder of cartilage, unspecified

ENDOCRINE/METABOLIC

Ethanol abuse.
Glucocorticoid therapy.
Cushing disease.
DM.
Hyperuricemia.
Osteomalacia.
Hyperlipidemia.

STORAGE DISEASES (E.G., GAUCHER DISEASE)

Hemoglobinopathies (e.g., sickle cell disease).
Trauma (e.g., dislocation, fracture).
HIV infection.
Dysbaric conditions (e.g., caisson disease).
Collagen-vascular disorders.
Irradiation.
Pancreatitis.
Organ transplantation.
Hemodialysis.
Burns.
Intravascular coagulation.
Idiopathic, familial.

JAUNDICE

ICD-10CM #		
	R17	Unspecified jaundice
	K83.8	Other specified diseases of biliary tract
	E80.7	Disorder of bilirubin metabolism, unspecified

PREDOMINANCE OF DIRECT (CONJUGATED) BILIRUBIN

Extrahepatic obstruction.
Common duct abnormalities: calculi, neoplasm, stricture, cyst, sclerosing cholangitis.
Metastatic carcinoma.
Pancreatic carcinoma, pseudocyst.
Ampullary carcinoma.
Hepatocellular disease: hepatitis, cirrhosis.
Drugs: estrogens, phenothiazines, captopril, methyltestosterone, labetalol.
Cholestatic jaundice of pregnancy.
Hereditary disorders: Dubin-Johnson syndrome, Rotor syndrome.
Recurrent benign intrahepatic cholestasis.

PREDOMINANCE OF INDIRECT (UNCONJUGATED) BILIRUBIN

Hemolysis: hereditary and acquired hemolytic anemias.
Inefficient marrow production.
Impaired hepatic conjugation: chloramphenicol.
Neonatal jaundice.
Hereditary disorders: Gilbert syndrome, Crigler-Najjar syndrome.

JAUNDICE, CLASSIFICATION[3]

ICD-10CM #		
	R17	Unspecified jaundice

PREHEPATIC (PREDOMINANTLY UNCONJUGATED HYPERBILIRUBINEMIA)

Overproduction
Hemolysis (e.g., spherocytosis, sickle cell disease, hemolysis of the newborn, autoimmune disorders).
Ineffective erythropoiesis (e.g., megaloblastic anemias).
Hematomas.
Pulmonary emboli.

HEPATIC (UNCONJUGATED HYPERBILIRUBINEMIA)

Decreased Hepatic Uptake
Gilbert syndrome.
Drugs (e.g., rifampin, radiographic contrast agents).
Neonatal jaundice.
Posthepatitis.
Decreased cystolic binding proteins (e.g., newborn or premature infants).
Portacaval shunt.

Prolonged fasting.

Decreased Conjugation Due to Limited Glucuronyl Transferase Activity

Gilbert disease.
Crigler-Najjar syndrome, types I and II.
Neonatal jaundice.
Breast-milk jaundice.
Chronic persistent hepatitis.
Wilson disease.
Noncirrhotic portal fibrosis.
Drug inhibition (e.g., chloramphenicol).

PREDOMINANTLY CONJUGATED HYPERBILIRUBINEMIA

Impaired Hepatic Excretion

Familial disorders (Dubin-Johnson syndrome, Rotor syndrome, benign recurrent cholestasis, cholestasis of pregnancy).
Hepatocellular infiltrative disorders.
Liver metastasis.
Liver cirrhosis.
Hepatitis (viral, bacterial, parasitic, autoimmune, ethanol, and drug-induced).
Drug-induced cholestasis (especially chlorpromazine, erythromycin estolate, isoniazid, halothane).
Primary biliary cirrhosis.
Primary sclerosing cholangitis.
Pericholangitis.
Congestive heart failure.
Shock.
Toxemia of pregnancy.
Sarcoidosis.
Hepatic trauma.
Amyloidosis.
Autoimmune cholangiopathy.
Vanishing bile duct syndrome.
Sepsis.
Postoperative complications.

EXTRAHEPATIC

Extrahepatic Biliary Obstruction

Gallstones, choledocholithiasis.
Cholecystitis.
Tumors of the head of the pancreas (adenocarcinoma, mucinous duct ectasia, neuroendocrine tumors, metastasis).
Tumors of bile ducts (cholangiocarcinoma, Klatskin tumor: cholangiocarcinoma at the bifurcation).
Gallbladder cancer.
Tumors of the ampulla of Vater (adenoma, adenocarcinoma).
Tumors of the duodenum (adenocarcinoma, lymphoma).
Hemobilia (blood in the biliary tree).
Biliary strictures (postcholecystectomy, postliver transplantation, primary sclerosing cholangitis).
Congenital disorders (biliary atresia, idiopathic dilation of common bile duct, cystic fibrosis).
Metastasis to the hepatic hilum.
Primary bile duct lymphoma.
Cholangiopathy of acquired immunodeficiency syndrome.
Choledochal cysts.
Infectious cholangiopathy *(Clonorchis sinensis, Ascaris lumbricoides, Fasciola hepatica).*
Chronic pancreatitis (fibrosis of the head of the pancreas).

JAUNDICE, NEONATAL[3]

ICD-10CM #	P59.9	Neonatal jaundice, unspecified

PREHEPATIC

Hereditary spherocytosis.
Nonspherocytic hemolytic anemia (glucose-6-phosphate dehydrogenase deficiency, α-thalassemia, vitamin K_3–induced hemolysis, pyruvate kinase deficiency).

HEPATIC

Crigler-Najjar syndrome, types I and II.
α_1-Antitrypsin deficiency.
Sepsis.
Drug-induced.
Hypothyroidism.
Breast-milk jaundice.
Fetomaternal blood group incompatibility (Rhesus, Landsteiner groups ABO).

POSTHEPATIC

Extrahepatic biliary obstruction.
Biliary atresia.
Bile duct paucity.
Alagille syndrome.

JOINT AND PERIARTICULAR PAIN, ACUTE[27]

ICD-10CM #	M25.50	Joint pain

COMMON ACUTE MONOARTHRITIS

Septic arthritis (nongonococcal, gonococcal).
Crystal arthritis (gout, pseudogout).
Reactive arthritides.
Lyme disease.
Plant thorn synovitis.
Other infections (mycobacterial, viral, soft tissue).

TRAUMA OR INTERNAL DERANGEMENT

Loose bodies.
Stress fractures.
Ischemic necrosis.
Hemarthrosis.

ACUTE MONOARTHRITIS OR POLYARTHRITIS

Psoriatic arthritis.
Enteropathic arthritis.
Rheumatoid arthritis/palindromic rheumatism.
Juvenile inflammatory arthritides.

MONOARTHROPATHIES FROM NONINFLAMMATORY DISEASE

Osteoarthritis.
Charcot joints.
Storage diseases (hemochromatosis, ochronosis).

SYNOVIAL DISEASES

Pigmented villonodular synovitis.
Lipoma arborescens.
Synovial osteochondromatosis.
Reflex sympathetic dystrophy.
Sarcoidosis.
Amyloid.

ACUTE MONOARTHRITIS OF SYSTEMIC DISEASE

Systemic lupus erythematosus.
Vasculitides (antineutrophil cytoplasmic antibody positive and negative).
Henoch-Schönlein purpura.
Behçet disease.
Bacterial endocarditis.
Familial Mediterranean fever.
Relapsing polychondritis.

SOFT TISSUE LESIONS

Bone Diseases

Paget disease.
Osteomyelitis (Brodie abscess).
Osteogenic/osteoid tumors.
Metastatic disease.
Pulmonary hypertrophic osteoarthropathy.

This table shows the causes of inflammation in any one joint (monoarthritis) and pain around the joint that presents without inflammation (monoarthropathy).

JOINT PAIN, ANTERIOR HIP, MEDIAL THIGH, KNEE[65]

ICD-10CM #	M25.50	Pain in unspecified joint
	M25.559	Pain in unspecified hip
	M25.569	Pain in unspecified knee

ACUTE

Acute rheumatic fever.
Adductor muscle strain.
Avascular necrosis.
Crystal arthritis.
Femoral artery (pseudo) aneurysm.
Fracture (femoral neck or intertrochanteric).
Hemarthrosis.
Hernia.
Herpes zoster.
Iliopectineal bursitis.
Iliopsoas tendinitis.
Inguinal lymphadenitis.
Osteomalacia.
Painful transient osteoporosis of hip.
Septic arthritis.

SUBACUTE AND CHRONIC

Adductory muscle strain.
Amyloidosis.
Acute rheumatic fever.
Femoral artery aneurysm.
Hernia (inguinal or femoral).
Iliopectineal bursitis.
Iliopsoas tendinitis.
Inguinal lymphadenopathy.
Osteochondromatosis.
Osteomyelitis.
Osteitis deformans (Paget disease).
Osteomalacia (pseudofracture).
Postherpetic neuralgia.
Sterile synovitis (e.g., RA, psoriatic, SLE).

JOINT PAIN, HIP, LATERAL THIGH[65]

ICD-10CM #	S79.919A	Unspecified injury of unspecified hip, initial encounter
	S79.929A	Unspecified injury of unspecified thigh, initial encounter
	M25.9	Joint disorder, unspecified

ACUTE

Herpes zoster.
Iliotibial tendinitis.
Impacted fracture of femoral neck.
Lateral femoral cutaneous neuropathy (meralgia paresthetica).
Radiculopathy: L4-5.
Trochanteric avulsion fracture (greater trochanter).
Trochanteric bursitis.
Trochanteric fracture.

SUBACUTE AND CHRONIC

Lateral femoral cutaneous neuropathy (meralgia paresthetica).
Osteomyelitis.
Postherpetic neuralgia.
Radiculopathy: L4-5.
Tumors.

JOINT PAIN, POLYARTICULAR

ICD-10CM #	M25.50	Pain in unspecified joint

Osteoarthritis.
RA.
Fibromyalgia.
Viral syndrome (e.g., human parvovirus B19 infection).
SLE.
Psoriatic arthritis.
Ankylosing spondylitis.

JOINT PAIN, POSTERIOR HIPS, THIGH, BUTTOCKS[65]

ICD-10CM #	M25.50	Pain in unspecified joint
	M25.559	Pain in unspecified hip
	M25.569	Pain in unspecified knee

ACUTE

Gluteal muscle strain.
Herpes zoster.
Ischial bursitis.
Ischial or sacral fracture.
Osteomalacia (pseudofracture).
Sciatic neuropathy.
Radiculopathy: L5-S1.

SUBACUTE AND CHRONIC

Gluteal muscle strain.
Ischial bursitis.
Lumbar spinal stenosis.
Osteoarthritis of hip.
Osteitis deformans (Paget disease).
Osteomyelitis.
Osteochondromatosis.
Osteomalacia (pseudofracture).
Postherpetic neuralgia.
Radiculopathy: L5-S1.
Tumors.

JOINT SWELLING

ICD-10CM #	M25.40	Effusion, unspecified joint

Trauma.
Osteoarthritis.
Gout.
Pyogenic arthritis.
Pseudogout.
RA.
Viral syndrome.

JUGULAR VENOUS DISTENTION

ICD-10CM #	I99.8	Other disorder of circulatory system

Right-sided heart failure.
Cardiac tamponade.
Constrictive pericarditis.
Goiter.
Tension pneumothorax.
Pulmonary hypertension.
Cardiomyopathy (restrictive).
Superior vena cava syndrome.
Valsalva maneuver.
Right atrial myxoma.
COPD.

KERATITIS, NONINFECTIOUS

ICD-10CM #	H16.9	Unspecified keratitis

Collagen vascular disease.
Atopic keratoconjunctivitis.
Chemical injury.
Thermal injury.
Ectropion/entropion.
Lid defects.
Exophthalmos.
Keratoconjunctivitis sicca.
Erythema multiforme.
Mucous membrane pemphigoid.
DM (delayed epithelial healing).
Neuroparalytic (cranial nerve VII).
Neurotrophic (diabetes, cranial nerve V).

KIDNEY CYSTIC DISEASE[90]

ICD-10CM #	Varies with specific diagnosis

CYSTIC DISEASES OF THE KIDNEY

Inheritable

Autosomal recessive (infantile) polycystic kidney disease.
Autosomal dominant (adult) polycystic kidney disease.
Juvenile nephronophthisis and medullary cystic disease complex.
Juvenile nephronophthisis (autosomal recessive).
Medullary cystic disease (autosomal dominant).
Congenital nephrosis (familial nephrotic syndrome) (autosomal recessive).
Familial hypoplastic glomerulocystic disease (autosomal dominant).
Multiple malformation syndromes with renal cysts (e.g., tuberous sclerosis, von Hippel-Lindau disease).

Nonheritable

Multicystic kidney (multicystic dysplastic kidney).
Benign multilocular cyst (cystic nephroma).
Simple cysts.
Medullary sponge kidney.
Sporadic glomerulocystic kidney disease.
Acquired renal cystic disease.
Calyceal diverticulum (pyelogenic cyst).

KIDNEY ENLARGEMENT, UNILATERAL[86]

ICD-10CM #	N13.30	Unspecified hydronephrosis

Hydronephrosis (may be bilateral).
Polycystic kidney (may be bilateral).
Simple cyst of kidney.
Renal cell carcinoma.
Pyonephrosis (may be bilateral).
Acute renal vein thrombosis.

KIDNEY INJURY, CANCER PATIENTS[79]

ICD-10CM #	Varies with specific diagnosis

CAUSES OF ACUTE KIDNEY INJURY IN CANCER PATIENTS

Prerenal

Sepsis
Volume depletion (vomiting, diarrhea, mucositis).
Hepatorenal syndrome (venoocclusive disease of the liver).
Capillary leak syndrome (interleukin-2 administration).
Hypercalcemia.

Intrinsic

Acute tubular necrosis
Ischemia (sepsis/shock).
Nephrotoxic (aminoglycosides, amphotericin B, chemotherapy).

Tubulointerstitial nephritis
Tumor lysis syndrome (urate and phosphate nephropathy).
Allergic reaction.
Pyelonephritis.
Opportunistic infections.
Infiltration (lymphoma/leukemia).

Vascular
Thrombotic microangiopathy.
Cancer treated.
Drug induced.

JOINT PAIN, HIP, LATERAL THIGH[65]

ICD-10CM #	S79.919A	Unspecified injury of unspecified hip, initial encounter
	S79.929A	Unspecified injury of unspecified thigh, initial encounter
	M25.9	Joint disorder, unspecified

ACUTE

Herpes zoster.
Iliotibial tendinitis.
Impacted fracture of femoral neck.
Lateral femoral cutaneous neuropathy (meralgia paresthetica).
Radiculopathy: L4-5.
Trochanteric avulsion fracture (greater trochanter).
Trochanteric bursitis.
Trochanteric fracture.

SUBACUTE AND CHRONIC

Lateral femoral cutaneous neuropathy (meralgia paresthetica).
Osteomyelitis.
Postherpetic neuralgia.
Radiculopathy: L4-5.
Tumors.

JOINT PAIN, POLYARTICULAR

ICD-10CM #	M25.50	Pain in unspecified joint

Osteoarthritis.
RA.
Fibromyalgia.
Viral syndrome (e.g., human parvovirus B19 infection).
SLE.
Psoriatic arthritis.
Ankylosing spondylitis.

JOINT PAIN, POSTERIOR HIPS, THIGH, BUTTOCKS[65]

ICD-10CM #	M25.50	Pain in unspecified joint
	M25.559	Pain in unspecified hip
	M25.569	Pain in unspecified knee

ACUTE

Gluteal muscle strain.
Herpes zoster.
Ischial bursitis.
Ischial or sacral fracture.
Osteomalacia (pseudofracture).
Sciatic neuropathy.
Radiculopathy: L5-S1.

SUBACUTE AND CHRONIC

Gluteal muscle strain.
Ischial bursitis.
Lumbar spinal stenosis.
Osteoarthritis of hip.
Osteitis deformans (Paget disease).
Osteomyelitis.
Osteochondromatosis.
Osteomalacia (pseudofracture).
Postherpetic neuralgia.
Radiculopathy: L5-S1.
Tumors.

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ICD-10CM #	M25.40	Effusion, unspecified joint

Trauma.
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Gout.
Pyogenic arthritis.
Pseudogout.
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Viral syndrome.

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ICD-10CM #	I99.8	Other disorder of circulatory system

Right-sided heart failure.
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Constrictive pericarditis.
Goiter.
Tension pneumothorax.
Pulmonary hypertension.
Cardiomyopathy (restrictive).
Superior vena cava syndrome.
Valsalva maneuver.
Right atrial myxoma.
COPD.

KERATITIS, NONINFECTIOUS

ICD-10CM #	H16.9	Unspecified keratitis

Collagen vascular disease.
Atopic keratoconjunctivitis.
Chemical injury.
Thermal injury.
Ectropion/entropion.
Lid defects.
Exophthalmos.
Keratoconjunctivitis sicca.
Erythema multiforme.
Mucous membrane pemphigoid.
DM (delayed epithelial healing).
Neuroparalytic (cranial nerve VII).
Neurotrophic (diabetes, cranial nerve V).

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Juvenile nephronophthisis (autosomal recessive).
Medullary cystic disease (autosomal dominant).
Congenital nephrosis (familial nephrotic syndrome) (autosomal recessive).
Familial hypoplastic glomerulocystic disease (autosomal dominant).
Multiple malformation syndromes with renal cysts (e.g., tuberous sclerosis, von Hippel-Lindau disease).

Nonheritable

Multicystic kidney (multicystic dysplastic kidney).
Benign multilocular cyst (cystic nephroma).
Simple cysts.
Medullary sponge kidney.
Sporadic glomerulocystic kidney disease.
Acquired renal cystic disease.
Calyceal diverticulum (pyelogenic cyst).

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Hydronephrosis (may be bilateral).
Polycystic kidney (may be bilateral).
Simple cyst of kidney.
Renal cell carcinoma.
Pyonephrosis (may be bilateral).
Acute renal vein thrombosis.

KIDNEY INJURY, CANCER PATIENTS[79]

ICD-10CM #	Varies with specific diagnosis

CAUSES OF ACUTE KIDNEY INJURY IN CANCER PATIENTS

Prerenal

Sepsis
Volume depletion (vomiting, diarrhea, mucositis).
Hepatorenal syndrome (venoocclusive disease of the liver).
Capillary leak syndrome (interleukin-2 administration).
Hypercalcemia.

Intrinsic

Acute tubular necrosis
Ischemia (sepsis/shock).
Nephrotoxic (aminoglycosides, amphotericin B, chemotherapy).

Tubulointerstitial nephritis
Tumor lysis syndrome (urate and phosphate nephropathy).
Allergic reaction.
Pyelonephritis.
Opportunistic infections.
Infiltration (lymphoma/leukemia).

Vascular
Thrombotic microangiopathy.
Cancer treated.
Drug induced.

Bone marrow transplantation.
Radiation injury.
Amyloidosis
Light-chain deposition disease
Paraneoplastic syndromes (membranous, antineutrophil cytoplasmic antibody associated, focal segmental glomerulosclerosis)
Postrenal
Intrarenal (urate, acyclovir, methotrexate)
Extrarenal (retroperitoneal fibrosis, lymphadenopathy, direct invasion)

KNEE PAIN[65]

ICD-10CM #		
	S83.419A	Sprain of medial collateral ligament of unspecified knee, initial encounter
	S83.509A	Sprain of unspecified cruciate ligament of unspecified knee, initial encounter
	M23.50	Chronic instability of knee, unspecified knee
	M23.8X9	Other internal derangements of unspecified knee
	S83.289A	Other tear of lateral meniscus, current injury, unspecified knee, initial encounter
	S83.249A	Other tear of medial meniscus, current injury, unspecified knee, initial encounter
	M25.669	Stiffness of unspecified knee, not elsewhere classified

DIFFUSE

Articular.
Anterior.
Prepatellar bursitis.
Patellar tendon enthesopathy.
Chondromalacia patellae.
Patellofemoral osteoarthritis.
Cruciate ligament injury.
Medial plica syndrome.

MEDIAL

Anserine bursitis.
Spontaneous osteonecrosis.
Osteoarthritis.
Medial meniscal tear.
Medial collateral ligament bursitis.
Referred pain from hip and L3.
Fibromyalgia.

LATERAL

Iliotibial band syndrome.
Meniscal cyst.
Lateral meniscal tear.
Collateral ligament.
Peroneal tenosynovitis.

POSTERIOR

Popliteal cyst (Baker cyst).
Tendinitis.
Aneurysms, ganglions, sarcoma.

KNEE PAIN, IN DIFFERENT AGE GROUPS[18]

ICD-10CM #	M25.569	Pain in unspecified knee

COMMON CAUSES OF KNEE PAIN IN DIFFERENT AGE GROUPS

Childhood (2 to 10 yr)
Intraarticular
Juvenile arthritis.
Osteochondritis dissecans.
Infection.
Torn discoid meniscus.
Periarticular
Osteomyelitis.
Referred
Perthes disease.
Irritable hip.
Adolescence (10 to 18 yr)
Intraarticular
Osteochondritis dissecans.
Torn meniscus.
Anterior knee pain syndrome.
Patellar instability.
Periarticular
Osgood–Schlatter disease.
Sinding–Larsen–Johansson syndrome.
Osteomyelitis.
Bone tumors.
Referred
Slipped upper femoral epiphysis.
Early Adulthood (18 to 30 yr)
Intraarticular
Torn meniscus.
Patellar instability.
Anterior knee pain syndrome.
Inflammatory arthritis.
Periarticular
Ligament injuries.
Bursitis.
Adulthood (30 to 50 yr)
Intraarticular
Degenerate meniscal tears.
Osteoarthritis.
Inflammatory arthritis.
Periarticular
Bursitis.
Referred
Osteoarthritis of hip.
Spinal disorders.
Old Age (>50 yr)
Intraarticular
Osteoarthritis.
Inflammatory arthritis.
Periarticular
Bursitis.
Referred
Osteoarthritis of hip.
Spinal disorders.

LARGE BOWEL STRICTURE[36]

ICD-10CM #	S36.5	Injury of colon

CAUSES OF LARGE BOWEL STRICTURES

Physiologic:
- Spasm.
- Distended bladder.

Malignant:
- Annular carcinoma.
- Scirrhous carcinoma.
- Lymphoma.

Diverticular disease:
- Muscle thickening.
- Pericolic abscess.
- Superimposed malignancy.

Ischemia.
Radiation colitis.
Inflammatory bowel disease:
- Ulcerative colitis.
- Crohn disease.
- Tuberculosis.
- Lymphogranuloma venereum.
- Amebiasis.

Extrinsic disease:
- Intraabdominal masses.
- Metastatic carcinoma.
- Endometriosis.
- Pelvic lipomatosis.
- Cholecystitis.
- Pancreatitis.
- Miscellaneous:

Postoperative anastomosis.
Trauma.
Hirschsprung disease.

LEFT AXIS DEVIATION[52]

ICD-10CM #	I44.7	Left bundle-branch block, unspecified
	I44.4	Left anterior fascicular block
	I44.5	Left posterior fascicular block
	I44.60	Unspecified fascicular block
	I44.69	Other fascicular block

Normal variation.
Left anterior fascicular block (hemiblock).
Left bundle branch block.
Left ventricular hypertrophy.
Mechanical shifts causing a horizontal heart, high diaphragm, pregnancy, ascites.
Some forms of ventricular tachycardia.
Endocardial cushion defects and other congenital heart disease.

LEFT BUNDLE BRANCH BLOCK

ICD-10CM #	I44.7	Left bundle-branch block, unspecified

Ischemic heart disease.
Electrolyte abnormalities (e.g., hyperkalemia).

Bone marrow transplantation.
Radiation injury.
Amyloidosis
Light-chain deposition disease
Paraneoplastic syndromes (membranous, antineutrophil cytoplasmic antibody associated, focal segmental glomerulosclerosis)
Postrenal
Intrarenal (urate, acyclovir, methotrexate)
Extrarenal (retroperitoneal fibrosis, lymphadenopathy, direct invasion)

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Chondromalacia patellae.
Patellofemoral osteoarthritis.
Cruciate ligament injury.
Medial plica syndrome.

MEDIAL

Anserine bursitis.
Spontaneous osteonecrosis.
Osteoarthritis.
Medial meniscal tear.
Medial collateral ligament bursitis.
Referred pain from hip and L3.
Fibromyalgia.

LATERAL

Iliotibial band syndrome.
Meniscal cyst.
Lateral meniscal tear.
Collateral ligament.
Peroneal tenosynovitis.

POSTERIOR

Popliteal cyst (Baker cyst).
Tendinitis.
Aneurysms, ganglions, sarcoma.

KNEE PAIN, IN DIFFERENT AGE GROUPS[18]

ICD-10CM #	M25.569	Pain in unspecified knee

COMMON CAUSES OF KNEE PAIN IN DIFFERENT AGE GROUPS

Childhood (2 to 10 yr)
Intraarticular
Juvenile arthritis.
Osteochondritis dissecans.
Infection.
Torn discoid meniscus.
Periarticular
Osteomyelitis.
Referred
Perthes disease.
Irritable hip.
Adolescence (10 to 18 yr)
Intraarticular
Osteochondritis dissecans.
Torn meniscus.
Anterior knee pain syndrome.
Patellar instability.
Periarticular
Osgood–Schlatter disease.
Sinding–Larsen–Johansson syndrome.
Osteomyelitis.
Bone tumors.
Referred
Slipped upper femoral epiphysis.
Early Adulthood (18 to 30 yr)
Intraarticular
Torn meniscus.
Patellar instability.
Anterior knee pain syndrome.
Inflammatory arthritis.
Periarticular
Ligament injuries.
Bursitis.
Adulthood (30 to 50 yr)
Intraarticular
Degenerate meniscal tears.
Osteoarthritis.
Inflammatory arthritis.
Periarticular
Bursitis.
Referred
Osteoarthritis of hip.
Spinal disorders.
Old Age (>50 yr)
Intraarticular
Osteoarthritis.
Inflammatory arthritis.
Periarticular
Bursitis.
Referred
Osteoarthritis of hip.
Spinal disorders.

LARGE BOWEL STRICTURE[36]

ICD-10CM #	S36.5	Injury of colon

CAUSES OF LARGE BOWEL STRICTURES

Physiologic:
- Spasm.
- Distended bladder.

Malignant:
- Annular carcinoma.
- Scirrhous carcinoma.
- Lymphoma.

Diverticular disease:
- Muscle thickening.
- Pericolic abscess.
- Superimposed malignancy.

Ischemia.
Radiation colitis.
Inflammatory bowel disease:
- Ulcerative colitis.
- Crohn disease.
- Tuberculosis.
- Lymphogranuloma venereum.
- Amebiasis.

Extrinsic disease:
- Intraabdominal masses.
- Metastatic carcinoma.
- Endometriosis.
- Pelvic lipomatosis.
- Cholecystitis.
- Pancreatitis.
- Miscellaneous:

Postoperative anastomosis.
Trauma.
Hirschsprung disease.

LEFT AXIS DEVIATION[52]

ICD-10CM #	I44.7	Left bundle-branch block, unspecified
	I44.4	Left anterior fascicular block
	I44.5	Left posterior fascicular block
	I44.60	Unspecified fascicular block
	I44.69	Other fascicular block

Normal variation.
Left anterior fascicular block (hemiblock).
Left bundle branch block.
Left ventricular hypertrophy.
Mechanical shifts causing a horizontal heart, high diaphragm, pregnancy, ascites.
Some forms of ventricular tachycardia.
Endocardial cushion defects and other congenital heart disease.

LEFT BUNDLE BRANCH BLOCK

ICD-10CM #	I44.7	Left bundle-branch block, unspecified

Ischemic heart disease.
Electrolyte abnormalities (e.g., hyperkalemia).

Cardiomyopathy.
Idiopathic.
LVH.
Pulmonary embolism.
Cardiac trauma.
Bacterial endocarditis.

LEG CRAMPS, NOCTURNAL

ICD-10CM #		
	R25.2	Cramp and spasm

Diabetic neuropathy.
Medications.
Electrolyte abnormalities (hypokalemia, hyponatremia, hypocalcemia, hyperkalemia, hypophosphatemia).
Respiratory alkalosis.
Uremia.
Hemodialysis.
Peripheral nerve injury.
ALS.
Alcohol use.
Heat cramps.
Vitamin B_{12} deficiency.
Hyperthyroidism.
Contractures.
DVT.
Hypoglycemia.
Peripheral vascular insufficiency.
Baker cyst.

LEG LENGTH DISCREPANCIES[55]

ICD-10CM #		
	M21.759	Unequal limb length (acquired), unspecified femur
	M21.769	Unequal limb length (acquired), unspecified tibia and fibula
	Q72.899	Other reduction defects of unspecified lower limb

CONGENITAL

Proximal femoral local deficiency.
Coxa vara.
Hemiatrophy-hemihypertrophy (anisomelia).
Developmental dysplasia of the hip.

DEVELOPMENTAL

Legg-Calvé-Perthes disease.

NEUROMUSCULAR

Polio.
Cerebral palsy (hemiplegia).

INFECTIOUS

Pyogenic osteomyelitis with physeal damage.

TRAUMA

Physeal injury with premature closure.
Overgrowth.
Malunion (shortening).

TUMOR

Physeal destruction.
Radiation-induced physeal injury.
Overgrowth.

LEG MOVEMENT WHEN STANDING, INVOLUNTARY

ICD-10CM #		
	R25.8	Other abnormal involuntary movements

Benign essential tremor.
Orthostatic tremor.
Spastic ataxia.
Cerebellar truncal tremor.
Postanoxic myoclonus.

LEG PAIN, EXERTIONAL[95]

ICD-10CM #		
	R25.2	Cramp and spasm

Vascular Causes

Atherosclerosis.
Thrombosis.
Embolism.
Vasculitis:
- Thromboangiitis obliterans.
- Takayasu arteritis.
- Giant cell arteritis.

Aortic coarctation.
Fibromuscular dysplasia.
Irradiation.
Endofibrosis of the external iliac artery.
Extravascular compression:
- Arterial entrapment (e.g., popliteal artery entrapment, thoracic outlet syndrome).

Adventitial cysts.

Nonvascular Causes

Lumbosacral radiculopathy:
- Degenerative arthritis.
- Spinal stenosis.
- Herniated disc.

Arthritis:
- Hips, knees.

Venous insufficiency.
Myositis.
Glycogen storage disease type V (McArdle syndrome).

LEG PAIN WITH EXERCISE

ICD-10CM #		
	R25.2	Cramp and spasm

Shin splints.
Arteriosclerosis obliterans.
Neurogenic (spinal cord compression or ischemia).
Venous claudication.
Popliteal cyst.
DVT.
Thromboangiitis obliterans.
Adventitial cysts.
Popliteal artery entrapment syndrome.
McArdle syndrome.

LEG SWELLING[1]

ICD-10CM #		
	R60.0	Localized edema

Deep vein thrombosis.
Cellulitis.
Baker cyst rupture or inflammation.
Congestive heart failure.
Renal failure.
Liver failure.
Inferior vena cava compression.
Musculoskeletal trauma.
Polyarteritis nodosa.
Erythema nodosum.
Myositis.
Tendinitis.
Lymphedema.
Superficial thrombophlebitis.
Compartment syndrome.

LEG ULCERS[65]

ICD-10CM #		
	I70.25	Atherosclerosis of native arteries of other extremities with ulceration
	L97.909	Non-pressure chronic ulcer of unspecified part of unspecified lower leg with unspecified severity

VASCULAR

Arterial: arteriosclerosis, thromboangiitis obliterans, AV malformation, cholesterol emboli.
Venous: superficial varicosities, incompetent perforators, DVT, lymphatic abnormalities.

VASCULITIS HEMATOLOGIC

Sickle cell anemia, thalassemia, polycythemia vera, leukemia, cold agglutinin disease.
Macroglobulinemia, protein C and protein S deficiency, cryoglobulinemia, lupus anticoagulant, antiphospholipid syndrome.

INFECTIOUS

Fungal: blastomycosis, coccidioidomycosis, histoplasmosis, sporotrichosis.
Bacterial: Furuncle, ecthyma, septic emboli.
Protozoal: leishmaniasis.

METABOLIC

Necrobiosis lipoidica diabeticorum.
Localized bullous pemphigoid.
Gout, calcinosis cutis, Gaucher disease.

TUMORS

Basal cell carcinoma, squamous cell carcinoma, melanoma.
Mycosis fungoides, Kaposi sarcoma, metastatic neoplasms.

TRAUMA

Burns, cold injury, radiation dermatitis.
Insect bites.
Factitial, excessive pressure.

NEUROPATHIC

Diabetic trophic ulcers.
Tabes dorsalis, syringomyelia.

DRUGS

Warfarin, IV colchicine extravasation, methotrexate, halogens, ergotism, hydroxyurea.

PANNICULITIS

Weber-Christian disease.
Pancreatic fat necrosis, alpha-antitrypsinase deficiency.

LEPTOMENINGEAL LESIONS

ICD-10CM #		
	G03.9	Leptomeningitis

Metastases.
Multiple sclerosis.
Bacterial or viral meningitis.
Vasculitis.
Lyme disease.
Tuberculosis.
Fungal infections (e.g., *Cryptococcus*).
Sarcoidosis.
Granulomatosis with polyangiitis.
Neurocysticercosis.
Rheumatoid nodules.
Histiocytosis.

LEUKOCORIA

ICD-10CM #		
	H57.9	Unspecified disorder of eye and adnexa

Cataract.
Retinal detachment.
Retinoblastoma.
Retinal telangiectasia.
Retrolenticular vascularized membrane.
Familial exudative vitreoretinopathy.

LID RETRACTION, CAUSES[48]

ICD-10CM #		
	H02.539	Eyelid retraction unspecified eye, unspecified lid

Thyroid eye disease.
Neurogenic:
- Contralateral unilateral ptosis.
- Unopposed levator action due to facial palsy.
- 3rd nerve misdirection.
- Marcus Gunn jaw-winking syndrome.
- Collier sign of the dorsal midbrain (Parinaud syndrome).
- Infantile hydrocephalus (setting sun sign).
- Parkinsonism.
- Sympathomimetic drops.

Mechanical:
- Surgical over-correction of ptosis.
- Scarring of upper lid skin.

Congenital:
- Isolated.
- Duane retraction syndrome.
- Down syndrome.
- Transient "eye popping" reflex in normal infants.

Miscellaneous:
- Prominent globe (pseudo-lid retraction).
- Uremia (Summerskill sign).
- Idiopathic.

LIGHT-NEAR DISSOCIATION[12]

ICD-10CM #	
	Varies with specific diagnosis

CAUSES OF LIGHT-NEAR DISSOCIATION

Unilateral
Afferent conduction defect.
Adie pupil.
Herpes zoster ophthalmicus.
Aberrant regeneration of the third cranial nerve.

Bilateral
Neurosyphilis.
Type 1 diabetes mellitus.
Myotonic dystrophy.
Parinaud (dorsal midbrain) syndrome.
Familial amyloidosis.
Encephalitis.
Chronic alcoholism.

LIMB ISCHEMIA, ACUTE, NONTRAUMATIC[15]

ICD-10CM #		
	I70.2	Atherosclerosis of arteries of extremities

CAUSES OF NONTRAUMATIC ACUTE LIMB ISCHEMIA

Atherosclerotic
In situ thrombosis.
Atheroembolism from thoracic aortic aneurysm/abdominal aortic aneurysm.
Femoral/popliteal aneurysm with or without compression.
Dissection.

Nonatherosclerotic
Embolism from cardiac thrombosis (atrial fibrillation, post–myocardial infarction akinesis).
Graft thrombosis, graft aneurysm.
Mycotic emboli.
Raynaud phenomenon.
Arteritis with thrombosis.
Inherited and acquired hypercoagulable states.
Drug-induced vasospasm.
External compression (Baker cyst, popliteal entrapment).

Mimics
Phlegmasia cerulea dolens.
Acute neuropathy.
Hypovolemia.
Systemic shock.

LIMP

ICD-10CM #		
	R26.0	Ataxic gait
	R26.1	Paralytic gait
	R26.89	Other abnormalities of gait and mobility
	R26.9	Unspecified abnormalities of gait and mobility
	M25.80	Other specified joint disorders, unspecified joint
	F44.4	Conversion disorder with motor symptom or deficit
	F44.6	Conversion disorder with sensory symptom or deficit

Degenerative joint disease, osteochondritis dissecans, chondromalacia patellae.
Trauma to extremities, vertebral disk, hips.
Poorly fitting shoes, foreign body in shoe, unequal leg length.
Splinter in foot.
Joint infection (septic arthritis, osteomyelitis), viral arthritis.
Abdominal pain (e.g., appendicitis, incarcerated hernia), testicular torsion.
Polio, neuromuscular disorders, Guillain-Barré syndrome, multiple sclerosis.
Osgood-Schlatter disease.
Legg-Calvé-Perthes disease.
Factitious, somatization syndrome.
Neoplasm (local or metastatic).
Other: diskitis, periostitis, sickle cell disease, hemophilia.

LIMPING, PEDIATRIC AGE[55]

ICD-10CM #		
	R26.0	Ataxic gait
	R26.1	Paralytic gait
	R26.89	Other abnormalities of gait and mobility
	R26.9	Unspecified abnormalities of gait and mobility

TODDLER (1 TO 3 YR)

Infection:
- Septic arthritis:
  - Hip.
  - Knee.
- Osteomyelitis.
- Diskitis.

Occult trauma:
- Toddler's fracture.

Neoplasia.

CHILDHOOD (4 TO 10 YR)

Infection:
- Septic arthritis:
  - Hip.
  - Knee.
- Osteomyelitis.
- Diskitis.
- Transient synovitis, hip.

LCPD.
Tarsal coalition.
Rheumatologic disorder:
- JRA.

Trauma.
Neoplasia.

ADOLESCENCE (11+ YR)

SCFE.
Rheumatologic disorder:
- JRA.
- Trauma.
- Tarsal coalition.
- Hip dislocation (DDH).
- Neoplasia.

DDH, Developmental dysplasia of the hip; *JRA,* juvenile RA; *LCPD,* Legg-Calvé-Perthes disease; *SCFE,* slipped capital femoral epiphysis.

LIVEDO RETICULARIS

ICD-10CM #		
	L95.0	Livedoid vasculitis

Emboli (SBE, left atrial myxoma, cholesterol emboli).
Thrombocythemia or polycythemia.
Antiphospholipid antibody syndrome.
Cryoglobulinemia, cryofibrinogenemia.
Leukocytoclastic vasculitis.
SLE, RA, dermatomyositis.
Pancreatitis.

Drugs (quinine, quinidine, amantadine, catecholamines).
Physiologic (cutis marmorata).
Congenital.

LIVER DISEASE, PREGNANCY[86]

ICD-10CM # K75.89 Other specified inflammatory liver diseases

INCIDENTAL TO PREGNANCY

Viral hepatitis.
Alcohol related.
Autoimmune chronic active hepatitis.

RELATED TO PREGNANCY (POSSIBLY INFLUENCED BY HORMONES PRESENT IN PREGNANCY)

Complicated gallstone disease.
Hepatic adenoma.
Focal nodular hyperplasia.
Budd-Chiari syndrome.

SPECIFIC TO PREGNANCY

Severe hyperemesis gravidarum.
Benign intrahepatic cholestasis.
Acute fatty liver of pregnancy.
Preeclampsia (HELLP).

LIVER LESIONS, BENIGN, OFTEN CONFUSED WITH MALIGNANCY

ICD-10CM # K76.1 Chronic passive congestion of liver
K76.89 Other specified diseases of liver

Fatty infiltration.
Adenoma.
Hemangioma.
Cysts.
Flow artifacts.
Focal nodular hyperplasia.
Nonenhanced vessels.

LOWER GI ULCERATIVE LESIONS[22]

ICD-10CM # Varies with specific diagnosis

INFECTIOUS

Epstein-Barr virus.
Human immunodeficiency virus.
Cytomegalovirus.
Herpes simplex.
Herpes zoster.
Syphilis.
Erosive candidiasis.
Mycobacterial infection.
Chancroid.
Lymphogranuloma venereum.

NOT INFECTIOUS

Behçet disease.
Excoriation.
Aphthous (idiopathic) ulcer.
Erythema multiforme.
Carcinoma.

LOW-VOLTAGE ECG

ICD-10CM # R94.31 Abnormal electrocardiogram [ECG] [EKG]

Hypothyroidism.
Obesity.
Pericardial effusion.
Anasarca.
Pleural effusion.
Pneumothorax.
Amyloidosis.
Aortic stenosis.

LUMBAR SPINE, VISCEROGENIC PAIN REFERRED TO LUMBAR SPINE[42*]

ICD-10CM # M54.5 Low back pain

Vascular
Expanding aortic aneurysm.
Genitourinary
Endometriosis.
Tubal pregnancy.
Kidney stone.
Prostatitis.
Gastrointestinal
Pancreatitis.
Peptic ulcers.
Colon cancer.

LUNG CANCER, OCCUPATIONAL CAUSES[36]

ICD-10CM # C34.90 Malignant neoplasm of unspecified part of unspecified bronchus or lung

CAUSES OF OCCUPATIONAL LUNG CANCER

Asbestos	Lagging, insulation
Arsenic	Metal smelting, pesticide manufacture
Beryllium	Electronics, dental prosthetic manufacture
Chromium	Coloring pigment production, electroplating
Nickel	Electroplating
Silica	Grinding, quarrying, sandblasting
Radon	Mining
Uranium	Mining

LUNG DISEASE AND GASTROINTESTINAL AND LIVER INVOLVEMENT[61]

ICD-10CM # Varies with specific diagnosis

*All of these disorders may cause localized low back pain.

ESOPHAGEAL REFLUX

Aspiration pneumonia.
Asthma.
Scleroderma.
Bronchitis.
Bronchiectasis.
Cough.
Pulmonary fibrosis.
Mycobacterial disease.

INFLAMMATORY BOWEL DISEASE

Bronchitis.
Bronchiectasis.
Bronchiolitis.
Colobronchial fistula.
Desquamative interstitial lung disease.
Drug reactions for agents that treat inflammatory bowel disease.
Eosinophilic lung disease.
Interstitial lung disease.
Necrobiotic nodules.
Obstructive lung disease.
Organizing pneumonia.
Reduced diffusing capacity.
Sarcoidosis.
Serositis affecting pleura or pericarditis.
Tracheal stenosis.

LIVER

Alpha1-antitrypsin deficiency.
Chronic active hepatitis.
Hepatopulmonary syndrome.
Portapulmonary hypertension.
Primary biliary cirrhosis.
Hepatosplenomegaly.
  Amyloidosis.
  Collagen vascular disease.
  Eosinophilic granulomatosis.
  Lymphatic interstitial pneumonia.
  Sarcoidosis.

LUNG DISEASE AND RENAL INVOLVEMENT[61]

ICD-10CM # Varies with specific diagnosis

LUNG DISEASE WITH RENAL INVOLVEMENT

Glomerulonephritis
Systemic vasculitis.
Collagen vascular disease.
Antibasement membrane.
Sarcoidosis.
Nephrotic Syndrome
Amyloidosis.
Disseminated Langerhans cell histiocytosis.
Drug-induced lung disease.
Paraneoplastic syndrome.
Post transplantation.
Pulmonary hydatid disease.
Systemic lupus erythematosus.
Vasculitis.
Venous thrombosis.
Renal Mass
Lymphangioleiomyomatosis.
Metastasis neoplasm.
Renal carcinoid.
Tuberous sclerosis.

Granulomatosis with polyangiitis.
Nephrolithiasis
Alveolar proteinosis.
Cystic fibrosis.
Hypercalcemic syndromes.
Osteolysis from mycobacteria or fungi.
Sarcoidosis.
Systemic Hypertension
Collagen vascular disease.
Diffuse alveolar hemorrhage.
Pulmonary renal syndromes.
Neurofibromatosis.
Sleep apnea.

LUNG DISEASE AND SKIN AND SUBCUTANEOUS LESIONS[61]

ICD-10CM # Varies with specific diagnosis

SKIN AND SUBCUTANEOUS LESIONS ASSOCIATED WITH LUNG DISEASE

Skin Lesions
Diffuse pigment change:
- Acanthosis nigricans—lung neoplasm.
- Albinism—Hermansky-Pudlak syndrome.
- Bronze pigmentation—hemosiderosis.
- Gray-brown—Whipple disease.

Cutaneous draining sinus:
- Fungal infections (especially histoplasmosis).
- Mycobacterial infections (especially tuberculosis).
- Neoplasms (especially mesothelial tumors).
- Necrotizing vasculitis.
- Other bacterial infections (especially actinomycosis).

Cutaneous ulcers:
- Beryllium disease.
- Chronic venous insufficiency.
- Fungal infections (especially histoplasmosis).
- Mycobacterial disease.
- Necrotizing vasculitis.
- Parasitic disease.
- Polycythemia.
- Sickle cell disease.
- Tularemia.

Cutaneous vasculitis:
- Behçet syndrome.
- Churg-Strauss syndrome.
- Collagen vascular disease.
- Sarcoidosis.
- Granulomatosis with polyangiitis.

Erythema multiforme:
- Drug reactions.
- Fungi (especially coccidiomycosis).
- Mycoplasma and other infectious agents.
- Neoplasms.
- Exfoliative dermatitis.
- Adverse drug reactions.
- Chemotherapy.
- Disseminated malignancy.
- Graft-versus-host disease.
- Radiation therapy.

Flushing:
- Bronchial carcinoid, pheochromocytoma, other neoplasms.
- Carbon dioxide, cyanide, and other toxins.
- Drugs.
- Foods and vasodilatory substances.
- Hormones.
- Mastocytosis.
- Metabolic states (e.g., hyperthyroidism, fever).

Macular rash:
- Anti-basement membrane disease.
- Café-au-lait spots (neurofibromatosis).
- Coal miner's scars.
- Collagen vascular disease.
- Idiopathic pulmonary fibrosis.
- Rose spots (psittacosis).
- Sarcoidosis.
- Syphilis.
- Viral pneumonia.

Maculopapular rash:
- Amyloidosis.
- Drug-induced lung disease.
- Collagen vascular disease.
- Gaucher disease.
- Kaposi sarcoma.
- Lung neoplasm.
- Lymphomatoid granulomatosis.
- Lymphoma.
- Parasites.
- Sarcoidosis.
- Syphilis.
- Vasculitis.
- Viral pneumonia

Telangiectasia:
- Arteriovenous malformation.
- Ataxia-telangiectasia.
- Carcinoid syndrome.
- Cushing disease.
- Hepatopulmonary syndrome and other chronic liver diseases.
- Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu).
- Mastocytosis.
- Systemic sclerosis and other collagen vascular diseases.

Urticaria:
- Asthma.
- Drug reactions.
- Cystic fibrosis.
- Exercise-induced urticaria.
- Food allergy.
- Hereditary angioneurotic edema.
- Inhaled antigens.
- Insect bites and stings.
- Infectious agents, such as mycoplasma and helicobacter.
- Mastocytosis.
- Occupational sensitization.
- Parasites.
- Vasculitis.

Nail Changes with Lung Disease
Color changes:
- Cigarette smoking discoloration.
- Splinter hemorrhages.
- Yellow nail syndrome.

Beau lines (any severe illness):
- Dermatomyositis.
- Sarcoidosis.
- Seronegative arthropathies.
- Systemic sclerosis.

Lung Disease with Subcutaneous Involvement
Adenopathy:
- Environmental mycobacteria.
- Fungal infections.
- Human immunodeficiency virus infections.
- Metastatic neoplasm.
- Leukemia.
- Lymphoma.
- Sarcoidosis.
- Tuberculosis.

Calcinosis:
- Dermatomyositis.
- Metastatic osteosarcoma.
- Mixed connective tissue disease.
- Scleroderma.
- Tuberculosis.
- Uremic metastatic calcification.

Erythema induratum (Bazin disease):
- Aortic stenosis.
- Cryoglobulinemia.
- Nodular vasculitis.
- Panniculitis.
- Peripheral neuropathy.
- Takayasu disease.
- Streptococcus infection.
- Tuberculosis and other mycobacterial disease.
- Weber-Christian disease.

Erythema nodosa:
- Neoplasm.
- Other infectious and inflammatory diseases.
- Primary coccidiomycosis, histoplasmosis.
- Primary tuberculosis.
- Psittacosis.
- Sarcoidosis.

Subcutaneous nodules:
- Amyloidosis.
- Neoplasm.
- Neurofibromatosis.
- Rheumatoid arthritis.
- Tuberous sclerosis (angiofibromas).
- von Recklinghausen.
- Weber-Christian disease.

Lung Disease with Salivary Gland Enlargement
Bulimia and aspiration.
Gaucher disease.
Lymphoid interstitial pneumonitis.
Lymphatic carcinoma.
Lymphoma.
Other causes of lymphadenopathy.
Sarcoidosis.
Sjögren disease.

LUNG DISEASE WITH BONE, JOINT, NERVE, AND MUSCLE INVOLVEMENT[61]

ICD-10CM # Varies with specific diagnosis

ARTHRITIS

Ankylosing spondylitis.
Collagen vascular diseases.
Reactive arthritis.
Sarcoidosis.
Systemic vasculitis.
Tuberculosis.

BONE LESIONS
Ankylosing spondylitis.
Blastomycosis and other fungal disease.
Collagen vascular diseases.
Eosinophilic granulomatosis.
Fibrous histiocytoma.
Gaucher disease.
Neoplasm.
Sarcoidosis.
Tuberculosis.

MUSCLE DISEASE
Collagen vascular disease.
L-Tryptophan.
Diabetes insipidus.
Eosinophilic granulomatosis.
Polymyositis.
Sarcoidosis.

NEUROLOGIC DISEASE
Acute inflammatory polyneuropathy.
Amyotrophic lateral sclerosis.
Aspiration.
Botulism.
Lambert-Eaton syndrome.
Myasthenia gravis.
Organophosphate poisoning.
Polio and postpolio syndrome.
Sarcoidosis.
Churg-Strauss syndrome.
Granulomatosis with polyangiitis.

LUNG TUMORS, BENIGN[77]
ICD-10CM # Varies with specific disorder

COMMON BENIGN TUMORS OF THE LUNG BASED ON CELLS OF ORIGIN
Tumors of Epithelial Origin
Mucous gland adenoma.
Clara cell adenoma.
Mucous cystadenoma.
Pleomorphic adenoma.
Tumors of Mesenchymal Origin
Hamartoma.
Inflammatory pseudotumor.
Chondroma.
Fibroma.
Benign endobronchial fibrous histiocytoma.
Leiomyoma.
Lipoma.
Lymphatic lesions.
Tumors of Miscellaneous Origin
Nodular pulmonary amyloidosis.
Clear cell tumor (sugar tumor).
Thymoma.
Granular cell tumor.
Teratoma.
Pulmonary paraganglioma.

LUNG VOLUMES IN DIFFUSE LUNG DISEASE[34]
ICD-10CM # Varies with specific disorder

LARGE LUNG VOLUMES
Emphysema.
Chronic asthma.
Diffuse bronchiolitis obliterans.
Highly trained athletes.
Lymphangioleiomyomatosis.

SMALL LUNG VOLUMES
End-stage lung fibrosis.
Bilateral diaphragmatic paralysis.
Massive ascites.

NORMAL LUNG VOLUMES
Sarcoidosis.
Langerhans cell histiocytosis.
Neurofibromatosis.
Emphysema with pulmonary fibrosis.

LYMPHADENOPATHY[32]
ICD-10CM # R59.9 Enlarged lymph nodes, unspecified

GENERALIZED
AIDS.
Lymphoma: Hodgkin disease, non-Hodgkin lymphoma.
Leukemias, reticuloendotheliosis.
Infectious mononucleosis, CMV, and other viral infections.
Diffuse skin infection: generalized furunculosis, multiple tick bites.
Parasitic infections: toxoplasmosis, filariasis, leishmaniasis, Chagas disease.
Serum sickness.
Collagen vascular diseases (RA, SLE).
Dengue (arbovirus infection).
Sarcoidosis and other granulomatous diseases.
Drugs: INH, hydantoin derivatives, antithyroid and antileprosy drugs.
Secondary syphilis.
Hyperthyroidism, lipid-storage diseases.

LOCALIZED
Cervical Nodes
Infections of the head, neck, ears, sinuses, scalp, pharynx.
Mononucleosis.
Lymphoma.
TB.
Malignancy of head and neck.
Rubella.
Scalene/Supraclavicular Nodes
Lymphoma.
Lung neoplasm.
Bacterial or fungal infection of thorax or retroperitoneum.
GI malignancy.
Axillary Nodes
Infections of hands and arms.
Cat-scratch disease.
Neoplasm (lymphoma, melanoma, breast carcinoma).
Brucellosis.
Epitrochlear Nodes
Infections of the hand.
Lymphoma.
Tularemia.
Sarcoidosis, secondary syphilis (usually bilateral).
Inguinal Nodes
Infections of leg or foot, folliculitis (pubic hair).
LGV, syphilis.
Lymphoma.
Pelvic malignancy.
Pasteurella pestis.
Hilar Nodes
Sarcoidosis.
TB.
Lung carcinoma.
Fungal infections, systemic.
Mediastinal Nodes
Sarcoidosis.
Lymphoma.
Lung neoplasm.
TB.
Mononucleosis.
Histoplasmosis.
Abdominal/Retroperitoneal Nodes
Lymphoma.
TB.
Neoplasm (ovary, testes, prostate, and other malignancies).

LYMPHANGITIS[58]
ICD-10CM # I89.1 Lymphangitis

Acute:
- Group A streptococci.
- *Staphylococcus aureus.*
- *Pasteurella multocida.*

Chronic:
- *Sporothrix schenckii* (sporotrichosis).
- *Mycobacterium marinum* (swimming pool granuloma).
- *Mycobacterium kansasii.*
- *Nocardia brasiliensis.*
- *W. bancrofti.*

LYMPHEDEMA[47]
ICD-10CM # i89.0 Lymphedema, not elsewhere classified
I97.2 Postmastectomy lymphedema syndrome
Q82.0 Hereditary lymphedema

CLASSIFICATION OF LYMPHEDEMA
Primary lymphedema
Congenital lymphedema (Milroy disease).
Lymphedema praecox.
Lymphedema tarda.
Syndromes associated with primary lymphedema
Yellow nail syndrome.
Turner syndrome.
Noonan syndrome.
Pes cavus.
Phakomatosis pigmentovascularis.
Distichiasis-lymphedema.
Emberger syndrome.
WILD syndrome.
Hypotrichosis-telangiectasia-lymphedema syndrome.
Cutaneous disorders sometimes associated with primary lymphedema
Yellow nails.

Hemangiomas.
Xanthomatosis and chylous lymphedema.
Congenital absence of nails.
Secondary lymphedema
Postmastectomy lymphedema.
Melphalan isolated limb perfusion.
Malignant occlusion with obstruction.
Extrinsic pressure.
Factitial lymphedema.
Postradiation therapy.
Following recurrent lymphangitis/cellulitis.
Lymphedema of upper limb in recurrent eczema.
Granulomatous disease.
Rosaceous lymphedema.
Primary amyloidosis.
Complications of lymphedema
Cellulitis of lymphedema.
Elephantiasis nostra verrucosa.
Ulceration.
Lymphangiosarcoma.

LYMPHOCYTOSIS, ATYPICAL[58]

ICD-10CM # D72.89 Other specified disorders of white blood cells

Epstein-Barr virus primary infection (infectious mononucleosis).
Cytomegalovirus primary infection (heterophile-negative mono).
Human herpesvirus 6 primary infection (roseola).
Primary HIV infection.
Toxoplasmosis.
Acute viral hepatitis.
Rubella, mumps.
Drug reactions (e.g., phenytoin, sulfa).

MACROTHROMBOCYTOPENIA, INHERITED[45]

ICD-10CM # Varies with specific disorder

Bernard-Soulier syndrome.
MHY9-related disorders:
May-Hegglin anomaly.
Sebastian syndrome.
Fechtner syndrome.
Epstein syndrome.
Gray platelet syndrome.
Montreal platelet syndrome.
Mediterranean macrothrombocytopenia.
Mediterranean stomatocytosis/macrothrombocytemia.
GATA1 mutations.
Sialyl-Lewis-S antigen deficiency.
Paris-Trousseau syndrome.
Platelet-type von Willebrand disease.

MACULAR CRYSTALS[12]

ICD-10CM # Varies with specific diagnosis

OTHER CAUSES OF MACULAR CRYSTALS

Primary hyperoxaluria.
Bietti corneoretinal crystalline dystrophy.
Cystinosis.
Sjögren–Larsson syndrome.
Gyrate atrophy.
Acquired parafoveal telangiectasis.
Talc-corn starch emboli.
West African crystalline maculopathy.

MADAROSIS[12]

ICD-10CM # H02.729 Madarosis of unspecified eye, unspecified eyelid and periocular area

CAUSES OF MADAROSIS

Local
Chronic anterior lid margin disease.
Infiltrating lid tumors.
Burns.
Radiotherapy or cryotherapy of lid tumors.
Skin disorders
Generalized alopecia.
Psoriasis.
Systemic diseases.
Myxoedema.
Systemic lupus erythematosus.
Acquired syphilis.
Lepromatous leprosy.
Following removal
Procedures for trichiasis.
Trichotillomania (psychiatric disorder of hair removal).

MALABSORPTION[86]

ICD-10CM # K90.89 Other intestinal malabsorption

CAUSES OF MALABSORPTION

More Common
Celiac disease.
Chronic pancreatitis.
Post gastrectomy.
Crohn disease.
Small bowel resection.
Small intestinal bacterial overgrowth.
Lactase deficiency.
Less Common
AIDS (*Mycobacterium avium intracellulare*, AIDS enteropathy).
Whipple disease.
Intestinal lymphoma.
Immunoproliferative small intestinal disease (alpha heavy chain disease).
Radiation enteritis.
Collagenous sprue.
Tropical sprue.
Non-granulomatous ulcerative jejunoileitis.
Eosinophilic gastroenteritis.
Amyloidosis.
Zollinger-Ellison syndrome.
Intestinal lymphangiectasia.
Systemic mastocytosis.
Chronic mesenteric ischemia.
Abetalipoproteinemia (autosomal recessive).

MALABSORPTION SYNDROME IN TROPICS[26]

ICD-10CM # K90.89 Other intestinal malabsorption

CAUSES OF MALABSORPTION SYNDROME IN THE TROPICS

SIBO
Following ulcer surgery.
Secondary to intestinal TB and Crohn disease.
Infections
Bacteria
Mycobacterium avium intracellulare complex.
Mycobacterium tuberculosis.
Helminths
Paracapillaria philippinensis.
Strongyloides stercoralis.
Protozoa
Cryptosporidium parvum.
Cyclospora cayetanensis.
Encephalitozoon intestinalis.
Enterocytozoon bieneusi.
Giardia lamblia.
Isospora belli.
Leishmania donovani.
Lymphatic Obstruction
Intestinal lymphangiectasia.
Mucosal Diseases
Autoimmune enteropathy.
Celiac disease.
Eosinophilic gastroenteritis.
HIV enteropathy.
Immunoproliferative small intestinal disease.
Intestinal lymphoma.
Primary immunodeficiencies.
Tropical sprue.
Neonatal Diseases
Microvillus inclusion disease.
Tufting enteropathy.
Pancreatic Insufficiency
Alcoholic pancreatitis.
CF.
Tropical pancreatitis.
Specific Transport Disorders
Abetalipoproteinemia.
Fructose malabsorption.
Glucose-galactose malabsorption.
Hypolactasia.
Sucrose intolerance.

MALNUTRITION, CAUSES IN EARLY LIFE[53]

ICD-10CM # E46 Unspecified protein-energy malnutrition

0 TO 6 MO

Breastfeeding difficulties.
Improper formula preparation.
Impaired parent/child interaction.
Congenital syndromes.
Prenatal infections or teratogenic exposures.
Poor feeding (sucking, swallowing) or feeding refusal (aversion).
Maternal psychological disorder (depression or attachment disorder).
Congenital heart disease.
Cystic fibrosis.
Neurologic abnormalities.
Child neglect.
Recurrent infections.

Hemangiomas.
Xanthomatosis and chylous lymphedema.
Congenital absence of nails.
Secondary lymphedema
Postmastectomy lymphedema.
Melphalan isolated limb perfusion.
Malignant occlusion with obstruction.
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GATA1 mutations.
Sialyl-Lewis-S antigen deficiency.
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Platelet-type von Willebrand disease.

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Radiation enteritis.
Collagenous sprue.
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Non-granulomatous ulcerative jejunoileitis.
Eosinophilic gastroenteritis.
Amyloidosis.
Zollinger-Ellison syndrome.
Intestinal lymphangiectasia.
Systemic mastocytosis.
Chronic mesenteric ischemia.
Abetalipoproteinemia (autosomal recessive).

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SIBO
Following ulcer surgery.
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Helminths
Paracapillaria philippinensis.
Strongyloides stercoralis.
Protozoa
Cryptosporidium parvum.
Cyclospora cayetanensis.
Encephalitozoon intestinalis.
Enterocytozoon bieneusi.
Giardia lamblia.
Isospora belli.
Leishmania donovani.
Lymphatic Obstruction
Intestinal lymphangiectasia.
Mucosal Diseases
Autoimmune enteropathy.
Celiac disease.
Eosinophilic gastroenteritis.
HIV enteropathy.
Immunoproliferative small intestinal disease.
Intestinal lymphoma.
Primary immunodeficiencies.
Tropical sprue.
Neonatal Diseases
Microvillus inclusion disease.
Tufting enteropathy.
Pancreatic Insufficiency
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CF.
Tropical pancreatitis.
Specific Transport Disorders
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Breastfeeding difficulties.
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Impaired parent/child interaction.
Congenital syndromes.
Prenatal infections or teratogenic exposures.
Poor feeding (sucking, swallowing) or feeding refusal (aversion).
Maternal psychological disorder (depression or attachment disorder).
Congenital heart disease.
Cystic fibrosis.
Neurologic abnormalities.
Child neglect.
Recurrent infections.

6 TO 12 MO

Celiac disease.
Food intolerance.
Child neglect.
Delayed introduction of age-appropriate foods or poor transition to food.
Recurrent infections.
Food allergy.

AFTER INFANCY

Acquired chronic diseases.
Highly distractible child.
Inappropriate mealtime environment.
Inappropriate diet (e.g., excessive juice consumption, avoidance of high-calorie foods).
Recurrent infections.

MEDIASTINAL COMPARTMENTS, ANATOMY AND PATHOLOGY[91]

ICD-10CM # Varies with specific disorder

ANTERIOR

Normal Structures
Lymph nodes.
Connective tissue.
Thymus (remnant in adults).
Masses
Thymoma.
Germ cell neoplasm.
Lymphoma.
Thyroid enlargement (intrathoracic goiter).
Other tumors.

MIDDLE

Normal Structures
Pericardium.
Heart.
Vessels: ascending aorta, venae cavae, main pulmonary arteries.
Trachea.
Lymph nodes.
Nerves: phrenic, upper vagus.
Masses
Carcinoma.
Lymphoma.
Pericardial cyst.
Bronchogenic cyst.
Benign lymph node enlargement (granulomatous disease).

POSTERIOR

Normal Structures
Vessels: descending aorta.
Esophagus.
Vertebral column.
Nerves: sympathetic chain, lower vagus.
Lymph nodes.
Connective tissue.
Masses
Neurogenic tumor.
Diaphragmatic hernia.

MEDIASTINAL MASSES OR WIDENING ON CHEST X-RAY

ICD-10CM # R59.9 Enlarged lymph nodes, unspecified
J98.5 Diseases of mediastinum, not elsewhere classified

Lymphoma: Hodgkin disease and non-Hodgkin lymphoma.
Sarcoidosis.
Vascular: aortic aneurysm, ectasia, or tortuosity of aorta or bronchocephalic vessels.
Carcinoma: lungs, esophagus.
Esophageal diverticula.
Hiatal hernia.
Achalasia.
Prominent pulmonary outflow tract: pulmonary hypertension, pulmonary embolism, right-to-left shunts.
Trauma: mediastinal hemorrhage.
Pneumomediastinum.
Lymphadenopathy caused by silicosis and other pneumoconioses.
Leukemias.
Infections: TB, viral (rare), *Mycoplasma* (rare), fungal, tularemia.
Substernal thyroid.
Thymoma.
Teratoma.
Bronchogenic cyst.
Pericardial cyst.
Neurofibroma, neurosarcoma, ganglioneuroma.

MEDIASTINAL MASSES, SITES OF ORIGIN[89]

ICD-10CM # Varies with specific diagnosis

DIFFERENTIAL DIAGNOSIS OF MEDIASTINAL MASSES BASED ON COMMON SITES OF ORIGIN

Prevascular space (anterior mediastinum)
Thymic masses.
Thymoma.
Thymic carcinoma.
Thymic neuroendocrine tumor.
Thymolipoma.
Thymic cyst.
Thymic hyperplasia.
Thymic lymphoma.
Germ cell tumors.
Teratoma and dermoid cyst.
Seminoma.
Nonseminomatous germ cell tumors.
Thyroid abnormalities (goiter and neoplasm).
Parathyroid tumor or hyperplasia.
Lymph node masses (particularly Hodgkin lymphoma).
Vascular abnormalities (aorta and great vessels).
Mesenchymal abnormalities (e.g., lipomatosis, lipoma).
Foregut cyst.
Lymphangioma.
Hemangioma.
Retrosternal space (anterior mediastinum)
Lymph node masses.
Pretracheal space (middle mediastinum)
Lymph node masses.
Lung carcinoma.
Sarcoidosis.
Lymphoma (particularly Hodgkin disease).
Metastases.
Infections (e.g., tuberculosis).
Foregut cyst.
Tracheal tumor.
Mesenchymal masses (e.g., lipomatosis, lipoma).
Thyroid abnormalities.
Vascular abnormalities (aorta and great vessels).
Lymphangioma and hemangioma.
Aortopulmonary window (middle mediastinum)
Lymph node masses.
Lung carcinoma.
Sarcoidosis.
Lymphoma.
Metastases.
Infections (e.g., tuberculosis).
Mesenchymal masses (e.g., lipomatosis, lipoma).
Vascular abnormalities (aorta or pulmonary artery).
Chemodectoma.
Foregut cyst.
Subcarinal space and azygoesophageal recess (middle mediastinum)
Lymph node masses.
Lung carcinoma.
Sarcoidosis.
Lymphoma.
Metastases.
Infections (e.g., tuberculosis).
Foregut cyst.
Dilated azygos vein.
Esophageal masses.
Varices.
Hernia.
Paravertebral masses (posterior mediastinum)
Neurogenic tumor.
Nerve sheath tumors.
Sympathetic ganglia tumors.
Paraganglioma.
Meningocele.
Foregut cyst.
Neurenteric cyst.
Thoracic spine abnormalities.
Extramedullary hematopoiesis.
Fluid collections and pseudocyst.
Vascular abnormalities.
Hernias.
Esophageal masses.
Varices.
Mesenchymal masses (e.g., lipomatosis, lipoma).
Lymph node masses.
Lymphoma (particularly non-Hodgkin).
Metastases.

Dilated azygos or hemiazygos vein.
Hernia.
Lymphangioma and hemangioma.
Thymic mass or germ cell tumor.
Anterior cardiophrenic angle masses.
Lymph node masses (particularly lymphoma and metastases).
Pericardial cyst.
Fat pad.
Morgagni hernia.
Thymic masses.
Germ cell tumors.

MEDIASTINITIS, ACUTE[58]

ICD-10CM # J98.5 Diseases of mediastinum, not elsewhere classified

Esophageal perforation.
Iatrogenic.
EGD, esophageal dilation, esophageal variceal sclerotherapy, nasogastric tube, Sengstaken-Blackmore tube, endotracheal intubation, esophageal surgery, paraesophageal surgery, transesophageal echocardiography, anterior stabilization of cervical vertebral bodies.
Swallowed foreign bodies.
Trauma.
Spontaneous perforation (e.g., emesis, carcinoma).
Head and neck infections (e.g., tonsillitis, pharyngitis, parotitis, epiglottitis, odontogenic).
Infections originating at another site (e.g., TB, pneumonia, pancreatitis, osteomyelitis of sternum, clavicle, ribs).
Cardiothoracic surgery (median sternotomy) (e.g., CABG, valve replacement, other types of cardiothoracic surgery).

MELANONYCHIA

ICD-10CM # NEC L81.4 Melanin hyperpigmentation

Pregnancy.
Trauma.
Medications (e.g., AZT, 5-fluorouracil, doxorubicin, psoralens).
Nail matrix nevus.
HIV infection.
Onychomycosis.
Melanocyte hyperplasia.
Verrucae.
Pustular psoriasis.
Lichen planus.
Basal cell carcinoma.
Nail matrix melanoma.
Subungual keratosis.
Addison disease.
Bowen disease.

MEMORY LOSS SYMPTOMS, ELDERLY PATIENTS

ICD-10CM # R41.2 Retrograde amnesia

Age-related mild cognitive impairment.
Depression (pseudodementia).
Medications (e.g., anticholinergics, sedatives).
Hypothyroidism.
Chronic hypoxia.
Cerebrovascular infarcts.
Alzheimer disease.
Hepatic disease.
Chronic renal failure.
Hyperthyroidism.
Frontotemporal dementia.
Lewy body dementia.

MENINGITIS, CHRONIC[58]

ICD-10CM # G03.1 Chronic meningitis

TB.
Fungal CNS infection.
Tertiary syphilis.
CNS neoplasm.
Metabolic encephalopathies.
Multiple sclerosis.
Chronic subdural hematoma.
SLE cerebritis.
Encephalitides.
Sarcoidosis.
NSAIDs.
Behçet syndrome.
Anatomic defects (traumatic, congenital, postoperative).
Granulomatous angiitis.

MENINGITIS, RECURRENT[58]

ICD-10CM # G03.2 Benign recurrent meningitis [Mollaret]

Drug induced (with rechallenge).
Parameningeal focus.
  Infection (sinusitis, mastoiditis, osteomyelitis, brain abscess).
  Tumor (epidermoid cyst, craniopharyngioma).
Posttraumatic (bacterial).
Mollaret meningitis.
SLE.
Herpes simplex virus.

MENTAL STATUS CHANGES AND COMA[7]

ICD-10CM # R41.82 Altered mental status, unspecified

METABOLIC/SYSTEMIC ETIOLOGY OF ALTERED MENTAL STATUS AND COMA

Hypoxia
Severe pulmonary disease (hypoventilation).
Severe anemia.
Environmental/toxin:
Methemoglobinemia:
  Cyanide.
  Carbon monoxide.
  Decreased atmospheric oxygen (high altitude).
  Near-drowning.
Disorders of Glucose
Hypoglycemia:
  Chronic alcohol abuse and liver disease.
  Excessive use of insulin or other hypoglycemic agents.
  Insulinoma.
Hyperglycemia:
  Diabetic ketoacidosis.
  Nonketotic hyperosmolar coma.
Decreased Cerebral Blood Flow
Hypovolemic shock.
Cardiac:
  Vasovagal syncope.
  Arrhythmias.
  Myocardial infarction.
  Valvular disorders.
  Congestive heart failure.
  Pericardial effusion/tamponade.
  Myocarditis.
Infectious:
  Septic shock.
  Bacterial meningitis.
Vascular/hematologic:
  Hypertensive encephalopathy.
  Pseudotumor cerebri.
  Hyperviscosity (sickle cell, polycythemia).
  Hyperventilation.
  Cerebral lupus vasculitis.
  Thrombotic thrombocytopenic purpura.
  Disseminated intravascular coagulation.
Metabolic Cofactor Deficiency
Thiamine (Wernicke-Korsakoff syndrome).
Pyridoxine (isoniazid overdose).
Folic acid (chronic alcohol abuse).
Cyanocobalamin.
Niacin.
Electrolyte/pH Disturbances
Acidosis/alkalosis.
Hypernatremia/hyponatremia.[26]
Hypercalcemia/hypocalcemia.
Hypophosphatemia.
Hypermagnesemia/hypomagnesemia.
Endocrine Disorders
Myxedema coma, thyrotoxicosis.
Hypopituitarism.
Addison disease (primary or secondary).
Cushing disease.
Pheochromocytoma.
Hyperparathyroidism/hypoparathyroidism.
Endogenous Toxins
Hyperammonemia (liver failure).
Uremia (renal disease).
Carbon dioxide narcosis (pulmonary disease).
Porphyria.
Exogenous Toxins
Alcohols:
  Ethanol, isopropyl alcohol, methanol, ethylene glycol.
Acid poisons:
  Salicylates.
  Paraldehyde.
  Ammonium chloride.
Antidepressant medications:
  Lithium.
  Tricyclic antidepressants (TCAs).
  Selective serotonin reuptake inhibitors (SSRIs).
  Monamine oxidase inhibitors (MAOIs).
Stimulants:
  Amphetamines/methamphetamines.
  Cocaine.
  Over-the-counter sympathomimetics.
Narcotics/opiates:
  Morphine.
  Heroin.

[26] Can be associated with dilution of formula in infant feeding.

Codeine, oxycodone, meperidine, hydrocodone.
Methadone.
Fentanyl.
Propoxyphene.
Sedative-hypnotics:
Benzodiazepines.
Barbiturates.
Rohypnol.
Bromide.
Hallucinogens:
Lysergic acid diethylamide (LSD).
Marijuana.
Mescaline, peyote.
Mushrooms.
Phencyclidine (PCP).
Herbs/plants:
Aconite.
Jimson weed.
Morning glory.
Volatile substances:
Hydrocarbons (gasoline, butane, toluene, benzene, chloroform).
Nitrites.
Anesthetic agents (nitrous oxide, ether).
Other:
γ-Hydroxybutyrate (GHB).
Ketamine.
Penicillin.
Cardiac glycosides.
Anticonvulsants.
Steroids.
Heavy metals.
Cimetidine.
Organophosphates.

Disorders of Temperature Regulation/ Environmental

Hypothermia.
Heat stroke.
Malignant hyperthermia.
Neuroleptic malignant syndrome.
High-altitude cerebral edema (HACE).
Dysbarism.

Primary Glial or Neuronal Disorders

Adrenoleukodystrophy.
Creutzfeldt-Jakob disease.
Progressive multifocal leukoencephalopathy.
Marchiafava-Bignami disease.
Gliomatosis cerebri.
Central pontine myelinolysis.

Other Disorders of Unknown Etiology

Seizures.
Postictal states.
Reye syndrome.[27]
Intussusception.

[27] Prominent in the pediatric population.

MENTAL STATUS CHANGES AND COMA, STRUCTURAL CAUSES[1]

ICD-10CM # R40.1 Stupor

COMMON AGE-RELATED CAUSES OF ALTERED MENTAL STATUS AND COMA

Infant

Infection.
Trauma, abuse.
Metabolic.

Child

Toxic ingestion.

Adolescent, Young Adult

Toxic ingestion.
Recreational drug use.
Trauma.

Elderly

Medication changes.
Over-the-counter medications.
Infection.
Alterations in living environment.
Stroke.
Trauma.

MENTAL STATUS CHANGES AND COMA, METABOLIC AND SYSTEMIC CAUSES

ICD-10CM # F05.9 Delirium, unspecified

METABOLIC AND SYSTEMIC CAUSES OF ALTERED MENTAL STATUS AND COMA

Hypoxia, Hypercapnia

Severe pulmonary disease (hypoventilation).
Severe anemia.
Environmental, toxic.
Methemoglobinemia.
Cyanide.
Carbon monoxide.
Decreased atmospheric oxygen (high altitude).
Near-drowning.

Glucose Disorders

Hypoglycemia:
Chronic alcohol abuse and liver disease.
Excessive dosage of insulin or other hypoglycemic agents.
Insulinoma.
Hyperglycemia:
Diabetic ketoacidosis.
Nonketotic hyperosmolar coma.

Decreased Cerebral Blood Flow

Hypovolemic shock.
Cardiac:
Vasovagal syncope.
Arrhythmias.
Myocardial infarction.
Valvular disorders.
Congestive heart failure.
Pericardial effusion, tamponade.
Myocarditis.
Infectious:
Septic shock.
Bacterial meningitis.
Vascular, hematologic
Hypertensive encephalopathy.
Pseudotumor cerebri.
Hyperviscosity (sickle cell, polycythemia).
Hyperventilation.
Cerebral vasculitis as a manifestation of systemic lupus erythematosus.
Thrombotic thrombocytopenic purpura.
Disseminated intravascular coagulation.

Metabolic Cofactor Deficiency

Thiamine (Wernicke-Korsakoff syndrome).
Pyridoxine (isoniazid overdose).
Folic acid (chronic alcohol abuse).
Cyanocobalamin.
Niacin.

Electrolyte, pH Disturbances

Acidosis, alkalosis.
Hypernatremia, hyponatremia.[28]
Hypercalcemia, hypocalcemia.
Hypophosphatemia.
Hypermagnesemia, hypomagnesemia.

Endocrine Disorders

Myxedema coma, thyrotoxicosis.
Hypopituitarism.
Addison disease (primary or secondary).
Cushing disease.
Pheochromocytoma.
Hyperparathyroidism, hypoparathyroidism.

Endogenous Toxins

Hyperammonemia (liver failure).
Uremia (renal disease).
Carbon dioxide narcosis (pulmonary disease).
Porphyria.

Exogenous Toxins

Alcohols:
Ethanol, isopropyl alcohol, methanol, ethylene glycol.
Acid poisons:
Salicylates.
Paraldehyde.
Ammonium chloride.
Antidepressant medications:
Lithium.
Tricyclic antidepressants.
Selective serotonin reuptake inhibitors.
Monoamine oxidase inhibitors.
Stimulants:
Amphetamines, methamphetamines.
Cocaine.
Over-the-counter sympathomimetics.
Narcotics, opiates:
Morphine.
Heroin.
Codeine, oxycodone, meperidine, hydrocodone.
Methadone.
Fentanyl.
Propoxyphene.
Sedative-hypnotics:
Benzodiazepines.
Barbiturates.
Rohypnol.
Bromide.
Hallucinogens:
Lysergic acid diethylamide.
Marijuana.
Mescaline, peyote.
Mushrooms.
Phencyclidine.
Herbs, plants:
Aconite.
Jimsonweed.
Morning glory.
Volatile substances:
Hydrocarbons (gasoline, butane, toluene, benzene, chloroform).
Nitrites.
Anesthetic agents (nitrous oxide, ether).

[28] Can be associated with dilution of formula in infant feeding.

Other:
- γ-Hydroxybutyrate.
- Ketamine.
- Penicillin.
- Cardiac glycosides.
- Anticonvulsants.
- Steroids.
- Heavy metals.
- Cimetidine.
- Organophosphates.

Disorders of Temperature Regulation, Environmental

Hypothermia.
Heat stroke.
Malignant hyperthermia.
Neuroleptic malignant syndrome.
High-altitude cerebral edema.
Dysbarism.

Primary Glial or Neuronal Disorders

Adrenoleukodystrophy.
Creutzfeldt-Jakob disease.
Progressive multifocal leukoencephalopathy.
Marchiafava-Bignami disease.
Gliomatosis cerebri.
Central pontine myelinolysis.

Other Disorders with Unknown Etiology

Seizures.
Postictal states.
Reye syndrome.
Intussusception.

MESENTERIC ARTERIAL EMBOLISM, ASSOCIATED FACTORS[7]

ICD-10CM #		
	I74.09	Other arterial embolism and thrombosis of abdominal aorta

FACTORS ASSOCIATED WITH MESENTERIC ARTERIAL EMBOLISM

Coronary artery disease:
- Post-myocardial infarction mural thrombi.
- Congestive heart failure.

Valvular heart disease:
- Rheumatic mitral valve disease.
- Nonbacterial endocarditis.

Arrhythmias:
- Chronic atrial fibrillation.

Aortic aneurysms or dissections.
Coronary angiography.

MESENTERIC ISCHEMIA, NONOCCLUSIVE[58]

ICD-10CM #		
	K55.0	Acute vascular disorders of intestine
	K55.1	Chronic vascular disorders of intestine
	S35.8X9A	Unspecified injury of other blood vessels at abdomen, lower back and pelvis level, initial encounter

Cardiovascular disease resulting in low-flow states (CHF, cardiogenic shock, post cardiopulmonary bypass, dysrhythmias).
Septic shock.
Drug induced (cocaine, vasopressors, ergot alkaloid poisoning).

MESENTERIC VENOUS THROMBOSIS[58]

ICD-10CM #		
	I82.91	Chronic embolism and thrombosis of unspecified vein

Hypercoagulable states (protein C or S deficiency, antithrombin III deficiency, Factor V Leyden, malignancy, polycythemia vera, sickle cell disease, homocystinemia, lupus anticoagulant, cardiolipin antibody).
Trauma (operative venous injury, abdominal trauma, postsplenectomy).
Inflammatory conditions (pancreatitis, diverticulitis, appendicitis, cholangitis).
Other: CHF, renal failure, portal hypertension, decompression sickness.

METASTATIC NEOPLASMS

ICD-10CM #		
	C79.51	Secondary malignant neoplasm of bone
	C79.52	Secondary malignant neoplasm of bone marrow
	C79.31	Secondary malignant neoplasm of brain
	C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
	C78.00	Secondary malignant neoplasm of unspecified lung

To Bone	To Brain
Breast.	Lung.
Lung.	Breast.
Prostate.	Melanoma.
Thyroid.	GU tract.
Kidney.	Colon.
Bladder.	Sinuses.
Endometrium.	Sarcoma.
Cervix.	Skin.
Melanoma.	Thyroid.

To Liver	To Lung
Colon.	Breast.
Stomach.	Colon.
Pancreas.	Kidney.
Breast.	Testis.
Lymphomas.	Stomach.
Bronchus.	Thyroid.
Lung.	Melanoma.
Sarcoma.	
Choriocarcinoma.	
Kidney.	

METHAEMOGLOBINAEMIA, DRUG-INDUCED[44]

ICD-10CM #		
	D74	Methaemoglobinaemia

SUBSTANCES ASSOCIATED WITH METHAEMOGLOBINAEMIA

Acetaminophen (nitrobenzene derivative).
Acetanilide.
Local anesthetics:
- Benzocaine.
- Lidocaine.
- Prilocaine.

Aniline dyes.
Celecoxib.
Dapsone.
Flutamide.
Ifosfamide.
Metoclopramide.
Nitric oxide.
Nitrites:
- Amyl nitrite.
- Isobutyl nitrite.
- Sodium nitrite.
- Nitrates (bacterial conversion to nitrites).

Nitrobenzenes/nitrobenzoates.
Nitroethane (nail polish remover).
Nitrofurans.
Nitroglycerin.
Paraquat/monolinuron.
Phenacetin.
Phenazopyridine (pyridium).
Primaquine.
Rasburicase.
Sulfamethoxazole.

MICROCEPHALY[9]

ICD-10CM #		
	Q02	Microcephaly

PRIMARY (GENETIC)

Familial (autosomal recessive).
Autosomal dominant.
Syndromes:
- Down (21-trisomy).
- Edward (18-trisomy).
- Cri-du-chat (5 p-).
- Cornelia de Lange.
- Rubinstein-Taybi.
- Smith-Lemli-Opitz.

SECONDARY (NONGENETIC)

Radiation.
Congenital infections:
- Cytomegalovirus.
- Rubella.
- Toxoplasmosis.

Drugs:
- Fetal alcohol.
- Fetal hydantoin.
- Meningitis/encephalitis.
- Malnutrition.
- Metabolic.
- Hyperthermia.
- Hypoxic-ischemic encephalopathy.

MICROPENIS[63]

ICD-10CM #		
	N48.89	Other specified disorders of penis
	Q55.62	Hypoplasia of penis

HYPOGONADOTROPIC HYPOGONADISM (HYPOTHALAMIC OR PITUITARY DEFICIENCIES)

Kallmann syndrome: autosomal dominant; associated with hyposmia.
Prader-Willi syndrome: hypotonia, mental retardation, obesity, small hands and feet.
Rud syndrome: hyposomia, ichthyosis, mental retardation.
De Morsier syndrome (septooptic dysplasia): hypopituitarism, hypoplastic optic discs, absent septum pellucidum.

HYPERGONADOTROPIC HYPOGONADISM

Primary testicular defect: disorders of testicular differentiation or inborn errors of testosterone synthesis.
Klinefelter syndrome.
Other X polysomies (i.e., XXXXY, XXXY).
Robinow syndrome: brachymesomelic dwarfism, dysmorphic facies.

PARTIAL ANDROGEN INSENSITIVITY

Idiopathic
Defective morphogenesis of the penis.

MIOSIS

ICD-10CM # H57.03 Miosis

Medications (e.g., morphine, pilocarpine).
Neurosyphilis.
Congenital.
Iritis.
CNS pontine lesion.
CNS infections.
Cavernous sinus thrombosis.
Inflammation/irritation of cornea or conjunctiva.

MONOARTHRITIS, ACUTE

ICD-10CM # M13.10 Monoarthritis, not elsewhere classified, unspecified site

Overuse.
Trauma.
Gout.
Pseudogout.
Osteoarthritis.
Infectious arthritis (e.g., gonococcal, Lyme disease, viral, mycobacteria, fungi).
Osteomyelitis.
Avascular necrosis of bone.
Hemarthrosis.
Bowel disease–associated arthritis.
Bone malignancy.
Psoriatic arthritis.
Juvenile RA.
Sarcoidosis.
Hemoglobinopathies.
Vasculitic syndromes.
Behçet syndrome.
Foreign body synovitis.
Hypertrophic pulmonary osteoarthropathy.
Amyloidosis, familial Mediterranean fever.

MONOCYTOSIS[45]

ICD-10CM # D72.821 Monocytosis (symptomatic)

Inflammatory diseases:
- Autoimmune/granulomatous.
- Systemic lupus erythematosus.
- Rheumatoid arthritis.
- Giant cell arteritis.
- Myositis.
- Polyarteritis.
- Ulcerative colitis.
- Regional enteritis.
- Sarcoidosis.

Infectious diseases:
- Tuberculosis.
- Syphilis.
- Subacute bacterial endocarditis.

Malignant disorders:
- Preleukemia.
- Nonlymphocytic leukemia.
- Histiocytoses.
- Hodgkin disease.
- Non-Hodgkin lymphoma.
- Carcinomas.

Miscellaneous:
- Chronic neutropenia.
- Post splenectomy.

MONONEUROPATHY

ICD-10CM # G58.9 Mononeuropathy, unspecified

Herpes zoster.
Herpes simplex.
Vasculitis.
Trauma, compression.
Diabetes.
Postinfectious or inflammatory.

MONONEUROPATHY, ISOLATED[7]

ICD-10CM # G56.90 Unspecified mononeuropathy of unspecified upper limb

UPPER EXTREMITY

Radial nerve:
- Axilla.
- Humerus.
- Elbow (posterior interosseous neuropathy).
- Wrist (superficial cutaneous radial neuropathy).

Ulnar nerve:
- Axilla.
- Humerus.
- Elbow.
- Condylar groove.
- Cubital tunnel.

Wrist (Guyon canal):
Hand:
- Superficial terminal ulnar neuropathy.
- Deep terminal ulnar neuropathy:
  - Proximal hypothenar.
  - Distal hypothenar.

Median nerve.
Axilla.
Humerus (musculocutaneous mononeuropathy).
Forearm:
- Anterior interosseus.
- Pronator syndrome.

Wrist (carpal tunnel).
Hand (recurrent motor branch).
Suprascapular mononeuropathy:
- Axillary mononeuropathy.

LOWER EXTREMITY

Sciatic nerve.
Femoral nerve:
- Iliacus compartment (proximal).
- Saphenous mononeuropathy (distal).

Lateral femoral cutaneous (meralgia paresthetica).
Peroneal nerve:
- Common peroneal mononeuropathy (fibular head, popliteal fossa).
- Deep peroneal mononeuropathy (anterior compartment).

Tibial nerve:
- Popliteal fossa (proximal).
- Tarsal tunnel (distal).

Sural nerve:
- Popliteal fossa, calf (proximal).
- Fifth metatarsal base (distal).

Plantar nerve:
- Distal to tarsal tunnel.
- Interdigital neuropathies (Morton neuroma).

Obturator mononeuropathy.

MONONEUROPATHY MULTIPLEX[60]

ICD-10CM # G58.9 Mononeuropathy, unspecified

MONONEUROPATHY MULTIPLEX

Vasculitis
Systemic vasculitis:
- Polyarteritis nodosa.
- Rheumatoid arthritis.
- Systemic lupus erythematosus.
- Sjögren syndrome (keratoconjunctivitis sicca).

Nonsystemic vasculitis
Diabetes mellitus
Neoplastic
Paraneoplastic.
Direct infiltration.
Infectious
Lyme disease.
HIV infection.
Sarcoid
Toxic (lead)
Transient (polycythemia vera)
Cryoglobulinemia (hepatitis C)

MONONUCLEOSIS, MONOSPOT NEGATIVE[3]

ICD-10CM # B27.90 Infectious mononucleosis, unspecified without complication

DIFFERENTIAL DIAGNOSIS OF MONOSPOT-NEGATIVE MONONUCLEOSIS

Acute HIV infection.
EBV mononucleosis (particularly in children).
Cytomegalovirus.
Acute toxoplasmosis.
Streptococcal pharyngitis.
Acute hepatitis B infection.

EBV, Epstein-Barr virus; *HIV,* human immunodeficiency virus.

MOVEMENT DISORDER, PEDIATRIC PATIENT[51]

ICD-10CM # G25.9 Extrapyramidal and movement disorder, unspecified

COMMONLY CITED MOVEMENT DISORDERS THAT MAY BEGIN IN CHILDHOOD OR ADOLESCENCE

Early Childhood
Athetosis or choreoathetosis.
Lesch–Nyhan syndrome.*
Childhood
Dopa-responsive dystonia.*
Dystonia associated with *DYT1* gene.*
Myoclonus from subacute sclerosing panencephalitis (SSPE).
Parkinson disease.
Sydenham chorea.
Tourette disorder.*
Withdrawal-emergent dyskinesia.
Adolescence
Essential tremor.*
Huntington disease (juvenile Huntington disease).*
Medication- and drug-induced movements.
Tardive dyskinesias.
Wilson disease.*

MOVEMENT DISORDERS AND COGNITIVE IMPAIRMENT[51]

ICD-10CM # G25.9 Extrapyramidal and movement disorder, unspecified

MOVEMENT DISORDERS ASSOCIATED WITH COGNITIVE IMPAIRMENT

Young Children
Athetosis or choreoathetosis.*
Lesch–Nyhan syndrome.
Rett syndrome.
Older Children and Adolescents
Huntington disease.
Subacute sclerosing panencephalitis.
Wilson disease.
Adults
Creutzfeldt-Jakob disease.†
Huntington disease.
Parkinson disease.

*Genetic transmission.
*Despite incapacitating movements, many choreoathetosis patients have no mental retardation.
†Myoclonus.

MOVEMENT DISORDERS, NEUROLEPTIC-INDUCED[51]

ICD-10CM # G25.70 Drug-induced movement disorder, unspecified

Acute dyskinesias:
  Akathisia.
  Neuroleptic-malignant syndrome.
  Oculogyric crisis and other dystonias.
Tardive dyskinesias:
  Akathisia.
  Dystonia.
  Oral-buccal-lingual dyskinesia.*
  Tics.
  Tremor.
  Stereotypies.
Dose-dependent dyskinesia:
  Parkinsonism.
Withdrawal-emergent dyskinesias.

*Commonly referred to as "tardive dyskinesia."

MULTIVALVULAR HEART DISEASE[95]

ICD-10CM # Varies with specific diagnosis

Acquired
Systemic diseases:
  Infective endocarditis.
  Carcinoid heart disease.
  Systemic lupus erythematosus.
Cardiac diseases:
  Infective endocarditis.
  Rheumatic heart disease.
Degenerative:
  Calcific diseases, increased with age, prior radiation, chronic kidney disease.
Iatrogenic:
  Adverse drug effects: ergot-related antagonists.
  Radiation therapy.
Functional (annulus dilatation), caused by:
  Ischemic heart disease.
  Hypertensive heart disease.
  Chronic arrhythmia.
  Pulmonary hypertension.
  Cardiomyopathy.

Congenital
Connective tissue disorders:
  Marfan syndrome.
  Ehlers-Danlos syndrome.
Other:
  Trisomy 18, 13, and 15.
  Shone syndrome.
  Ochronosis.

Mixed
Multiple conditions may contribute to valve dysfunction, such as:
  Degenerative diseases may lead to associated functional disease.
  Congenital heart disease may predispose to infective endocarditis or degenerative disease.

MUSCLE DISEASE[80]

ICD-10CM # M60.009 Infective myositis, unspecified site

CLASSIFICATION OF MUSCLE DISEASE

Muscular Dystrophies
Duchenne.
Becker.
Limb girdle.
Childhood.
Facioscapulohumeral.
Myotonic Disorders
Dystrophia myotonica.
Myotonica congenita.
Inflammatory
Infective: bacterial, viral, parasitic.
Unknown cause: polymyositis, dermatomyositis, sarcoidosis.
Endocrine
Thyroid disease—hyper- and hypothyroidism.
Cushing disease.
Addison disease.
Hyperparathyroidism.
Metabolic
Glycogen storage diseases.
Periodic paralyses.
Mitochondrial diseases.
Drug-induced
Corticosteroids.
Chloroquine.
Amiodarone.
Penicillamine.
Alcohol.
Zidovudine.
Clofibrate.
Other
Inclusion body myositis.

MUSCLE WEAKNESS

ICD-10CM # M62.9 Disorder of muscle, unspecified

Physical deconditioning.
Impaired cardiac output (e.g., mitral stenosis, mitral regurgitation).
Uremia, liver failure.
Electrolyte abnormalities (hypokalemia, hyperkalemia, hypophosphatemia, hypercalcemia), hypoglycemia.
Drug induced (e.g., statin myopathy).
Muscular dystrophies.
Steroid myopathy.
Alcoholic myopathy.
Myasthenia gravis, Lambert-Eaton syndrome.
Infections (polio, botulism, HIV, hepatitis, diphtheria, tick paralysis, neurosyphilis, brucellosis, TB, trichinosis).
Pernicious anemia, other anemias, beriberi.
Psychiatric illness (depression, somatization syndrome).
Organophosphate or arsenic poisoning.
Inflammatory myopathies (e.g., collagen vascular disease, RA, sarcoidosis).
Endocrinopathies (e.g., adrenal insufficiency, hypothyroidism), diabetic neuropathy.
Other: motor neuron disease, mitochondrial myopathy, l-tryptophan (eosinophilia-myalgia), rhabdomyolysis, glycogen storage disease, lipid storage disease.

MUSCLE WEAKNESS, LOWER MOTOR NEURON VERSUS UPPER MOTOR NEURON

ICD-10CM # M62.9 Disorder of muscle, unspecified

LOWER MOTOR NEURON

Weakness, usually severe.
Marked muscle atrophy.
Fasciculations.
Decreased muscle stretch reflexes.
Clonus not present.
Flaccidity.
No Babinski sign.
Asymmetric and may involve one limb only in the beginning to become generalized as the disease progresses.

UPPER MOTOR NEURON

Weakness, usually less severe.
Minimal disuse muscle atrophy.
No fasciculations.
Increased muscle stretch reflexes.
Clonus may be present.
Spasticity.
Babinski sign.
Often initial impairment of only skilled movements.
In the limbs the following muscles may be the only ones weak or weaker than the others: triceps; wrist and finger extensors; interossei; iliopsoas; hamstrings; and foot dorsiflexors, inverters, and extroverters.

MUSCULOSKELETAL BENIGN TUMORS AND TUMOR-LIKE LESIONS[71]

ICD-10CM # Varies with specific diagnosis

Fibrous dysplasia.
Enchondromatosis.
Osteochondromatosis.
Synovial cysts.
Brown tumors in hyperparathyroidism.
Langerhans cell histiocytosis (eosinophilic granuloma).
Hemangiomatosis.
Bone islands, osteoma (Gardner syndrome).
Fibrous cortical defect, nonossifying fibroma.
Giant cell tumor.
Neurofibromatosis.
Amyloidosis.
Mastocytosis.
SAPHO, chronic multifocal osteomyelitis.

SAPHO, Synovitis, acne, pustulosis, hyperostosis, osteitis.

MUSCULOSKELETAL MALIGNANT TUMORS AND TUMOR-LIKE LESIONS[71]

ICD-10CM # Varies with specific diagnosis

Metastases.
Myeloma.
Angiosarcoma.
Leukemia.
Neuroblastoma.
Ewing sarcoma.
Osteosarcomatosis.
Lymphoma.

MYDRIASIS

ICD-10CM # H57.04 Mydriasis

Coma.
Medications (cocaine, atropine, epinephrine, etc.).
Glaucoma.
Cerebral aneurysm.
Ocular trauma.
Head trauma.
Optic atrophy.
Cerebral neoplasm.
Iridocyclitis.

MYELIN DISORDERS

ICD-10CM # Varies with specific diagnosis

Multiple sclerosis.
Vitamin B_{12} deficiency.
Radiation.
Hypoxia.
Toxicity from carbon monoxide, alcohol, mercury.
Progressive multifocal encephalopathy.
Acute disseminated encephalomyelitis.
Acute hemorrhagic leukoencephalopathy.
Phenylketonuria.
Adrenoleukodystrophy.
Krabbe disease.

MYELITIS[88]

ICD-10CM # G04.91 Myelitis, unspecified
G04.89 Other myelitis

Viral
HIV.
HSV-1 and HSV-2.
VZV.
CMV.
EBV.
WNV.
HTLV.
Bacterial
Mycoplasma pneumoniae.
Borrelia burgdorferi.
Treponema pallidum.
Pyogenic bacteria.
Mycobacterium tuberculosis.
Fungal
Coccidioides immitis.
Actinomyces.
Aspergillus.
Blastomyces dermatitidis.
Histoplasmosis.
Immune-Mediated
Multiple sclerosis.
Neuromyelitis optica.
Connective tissue disorders (neuro-lupus, neuro-Sjögren).
Neurosarcoidosis.
Paraneoplastic.
Noninflammatory Myelopathies
Vitamin B_{12} deficiency.
Folic acid deficiency.
Copper deficiency.
Vitamin E deficiency.
Nitrous oxide toxicity.
Heroin.
Radiation myelopathy.
Traumatic/compressive myelopathy.
Vascular myelopathy.

MYELOPATHY AND MYELITIS[82]

ICD-10CM # M51.9 Unspecified thoracic, thoracolumbar and lumbosacral intervertebral disc disorder
G95.9 Disease of spinal cord, unspecified

INFLAMMATORY

Infectious: spirochetal TB, zoster, rabies, HIV, polio, rickettsial, fungal, parasitic.
Noninfectious: idiopathic transverse myelitis, multiple sclerosis.

TOXIC/METABOLIC

DM, pernicious anemia, chronic liver disease, pellagra, arsenic.

TRAUMA COMPRESSION

Spinal neoplasm, cervical spondylosis, epidural abscess, epidural hematoma.

VASCULAR

AV malformation, SLE, periarteritis nodosa, dissecting aortic aneurysm.

PHYSICAL AGENTS

Electrical injury, irradiation.

NEOPLASTIC

Spinal cord tumors, paraneoplastic myelopathy.

MYOCARDIAL ISCHEMIA[82]

ICD-10CM # I25.5 Ischemic cardiomyopathy
I25.89 Other forms of chronic ischemic heart disease
I25.9 Chronic ischemic heart disease, unspecified
I24.8 Other forms of acute ischemic heart disease

Atherosclerotic obstructive coronary artery disease.
Nonatherosclerotic coronary artery disease:
- Coronary artery spasm.
- Congenital coronary artery anomalies:
  - Anomalous origin of coronary artery from pulmonary artery.
  - Aberrant origin of coronary artery from aorta or another coronary artery.
  - Coronary arteriovenous fistula.
  - Coronary artery aneurysm.

Acquired disorders of coronary arteries:
- Coronary artery embolism.
- Dissection:
  - Surgical.
  - During percutaneous coronary angioplasty.
  - Aortic dissection.
  - Spontaneous (e.g., during pregnancy).

Extrinsic compression:
Tumors.
Granulomas.
Amyloidosis.
Collagen-vascular disease:
Polyarteritis nodosa.
Temporal arteritis.
RA.
SLE.
Scleroderma.
Miscellaneous disorders:
Irradiation.
Trauma.
Kawasaki disease.
Syphilis.
Hereditary disorders:
Pseudoxanthoma elasticum.
Gargoylism.
Progeria.
Homocystinuria.
Primary oxaluria.
"Functional" causes of myocardial ischemia in absence of anatomic coronary artery disease:
Syndrome X.
Hypertrophic cardiomyopathy.
Dilated cardiomyopathy.
Muscle bridge.
Hypertensive heart disease.
Pulmonary hypertension.
Valvular heart disease; aortic stenosis, aortic regurgitation.

MYOCLONUS

ICD-10CM # G25.3 Myoclonus

Physiologic (e.g., exercise or anxiety induced).
Renal failure.
Hepatic failure.
Hyponatremia.
Hypoglycemia or severe hyperglycemia.
Postdialysis.
Epileptic myoclonus.
Postencephalitis.
CNS lesion (stroke, neoplasm).
CNS trauma.
Parkinson disease.
Medications (e.g., tricyclics, L-dopa).
Friedreich ataxia.
Ataxia-telangiectasia.
Wilson disease.
Huntington disease.
Progressive supranuclear palsy.
Heavy metal poisoning.
Benign familial.

MYOCLONUS, DRUG-INDUCED[84]

ICD-10CM # G25.79 Other drug-induced movement disorders

SELECTED AGENTS ASSOCIATED WITH MYOCLONUS

Medications
Antibiotics (β-lactams).
Antidepressants.
Antineoplastics: busulfan, chlorambucil.
Carbamazepine, vigabatrin.
Clozapine.
L-dopa.
Lidocaine.
Lithium.
Lorazepam (preterm infants).
Methaqualone.
Morphine.
Nitroprusside.
Piperazine.
Industrial Toxins
Camphor.
Chlorophenoxy herbicides.
Gasoline.
Biological Toxins
Buckeye (*Aesculus* spp.).
Lupine.
Shellfish (domoic acid poisoning).

MYOCLONUS, PEDIATRIC PATIENT[54]

ICD-10CM # G25.3 Myoclonus

Selected Causes of Myoclonus in Children
Physiologic Causes
Hiccups.
Hypnic jerks (sleep starts).
Nocturnal (sleep) myoclonus.
Developmental Causes
Benign neonatal sleep myoclonus.
Benign myoclonus of early infancy.
Myoclonus with fever.
Storage Diseases
Juvenile Gaucher disease (type III).
Sialidosis type 1 (cherry-red spot–myoclonus).
GM_1 gangliosidosis.
Neuronal ceroid-lipofuscinosis (late infantile).
Inherited Degenerative Diseases
Dentatorubral-pallidoluysian atrophy (DRPLA).
Huntington disease.
Progressive myoclonus ataxia.
Ramsay Hunt syndrome.
Early myoclonic encephalopathy.
Rasmussen encephalitis.
Infectious and Postinfectious Diseases
Meningitis (viral or bacterial).
Encephalitis.
Epstein-Barr virus (EBV).
Coxsackievirus.
Influenza.
Human immunodeficiency virus (HIV).
Acute disseminated encephalomyelitis (ADEM).
Metabolic Causes
Uremia.
Hepatic failure.
Electrolyte disturbances.
Hypoglycemia or hyperglycemia.
Aminoacidurias.
Organic acidurias.
Urea cycle disorders.
POLG1 mutations.
Myoclonic epilepsy with ragged red fibers (MERRF).
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS).
Biotinidase deficiency (usually epileptic).
Cobalamin deficiency (infantile).
Leigh syndrome.
Toxic Causes
Psychotropic medications (tricyclic antidepressants, lithium, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, neuroleptics).
Antibiotics (penicillin, cephalosporins, quinolones).
Antiepileptics (phenytoin, carbamazepine, lamotrigine, gabapentin, benzodiazepines [in infants], vigabatrin).
Opioids.
General anesthetics.
Antineoplastic drugs.
Strychnine, toluene, lead, carbon monoxide, mercury.
Hypoxia
Lance-Adams syndrome.
Functional (Psychogenic) Causes

MYOPATHIC SYNDROMES, DRUG-INDUCED[41]

ICD-10CM # G72.9 Myopathy, unspecified

TYPE OF MYOPATHY

Necrotizing myopathy.
Inflammatory myopathy.
Mitochondrial myopathy.
Hypokalemic myopathy.
Antimicrotubular myopathy.
Lysosomal storage myopathy.
Corticosteroid myopathy.
Others.

DRUGS

HMG-CoA reductase inhibitors (statins), fibrates, alcohol.
Penicillamine, interferon-a, procainamide.
Zidovudine.
Diuretics, laxatives, licorice, amphotericin B, alcohol.
Colchicine, vincristine.
Chloroquine, hydroxychloroquine, quinacrine, amiodarone, perhexiline.
Corticosteroids, especially fluorinated.
Ipecac syrup, emetine.

MYOPATHIES ASSOCIATED WITH REST PAIN[41]

ICD-10CM # G72.9 Myopathy, unspecified

Childhood dermatomyositis.
Hypothyroid myopathy.
Acute alcoholic myopathy.
Drug-induced myopathies.
Infectious myopathies.
Myopathies associated with metabolic bone disease.
Carnitine palmitoyl transferase deficiency.
Rhabdomyolysis from any cause.

MYOPATHIES, HIV ASSOCIATED[27]

ICD-10CM # G72.9 Myopathy, unspecified

HIV-Associated Myopathies	Myopathies Secondary to Antiretrovirals	Others
HIV polymyositis.	Zidovudine myopathy.	Opportunistic infections involving muscle (toxoplasmosis).
Inclusion body myositis.	Toxic mitochondrial myopathies related to other NRTIs.	Tumor infiltrations of skeletal muscle.
Nemaline myopathy.		Rhabdomyolysis.
Diffuse infiltrative lymphocytosis syndrome.	HIV-associated lipodystrophy syndrome.	
HIV wasting syndrome.	Immune reconstitution syndrome related to ART.	
Vasculitic processes.		
Myasthenia gravis and other myasthenic syndromes.		
Chronic fatigue and fibromyalgia.		

ART, Antiretroviral therapy; *NRTIs,* nucleoside reverse transcriptase inhibitors.

MYOPATHIES, INFECTIOUS

ICD-10CM # G72.9 Myopathy, unspecified

HIV.
Viral myositis.
Trichinosis.
Toxoplasmosis.
Cysticercosis.

MYOPATHIES, INFLAMMATORY

ICD-10CM # G72.9 Myopathy, unspecified

SLE, RA.
Sarcoidosis.
Paraneoplastic syndrome.
Polymyositis, dermatomyositis.
Polyarteritis nodosa.
Mixed connective tissue disease.
Scleroderma.
Inclusion body myositis.
Sjögren syndrome.
Cimetidine, d-penicillamine.

MYOPATHIES, METABOLIC[41]

ICD-10CM # G72.9 Myopathy, unspecified

DISORDERED GLYCOGEN METABOLISM

Myophosphorylase deficiency (McArdle disease).
Phosphorylase b kinase deficiency.
Phosphofructokinase deficiency.
Debrancher enzyme deficiency.
Brancher enzyme deficiency.
Phosphoglycerate kinase deficiency.
Phosphoglycerate mutase deficiency.
Lactate dehydrogenase deficiency.
Acid maltase deficiency.
Aldolase deficiency.
β-Enolase deficiency.

DISORDERED LIPID METABOLISM

Carnitine deficiencies.
Carnitine palmitoyltransferase deficiency.
Fatty acid acyl-CoA dehydrogenase deficiencies.

MITOCHONDRIAL MYOPATHIES

Coenzyme Q10 deficiency.
Respiratory chain complex deficiencies.

ENDOCRINE

Acromegaly.
Hypothyroidism.
Hyperthyroidism.
Hyperparathyroidism.
Cushing disease.
Addison disease.
Hyperaldosteronism.

METABOLIC-NUTRITIONAL

Uremia.
Hepatic failure.
Malabsorption.
Periodic paralysis.
Vitamin D deficiency.
Vitamin E deficiency.

ELECTROLYTE DISORDERS

Sodium: hypernatremia and hyponatremia.
Potassium: hyperkalemia and hypokalemia.
Calcium: hypercalcemia and hypocalcemia.
Phosphate: hypophosphatemia.
Magnesium: hypomagnesemia.

MYOPATHIES, TOXIC[3]

ICD-10CM # G72.2 Myopathy due to other toxic agents

Inflammatory: cimetidine, d-penicillamine.
Noninflammatory necrotizing or vacuolar: cholesterol-lowering agents, chloroquine, colchicine.
Acute muscle necrosis and myoglobinuria: cholesterol-lowering drugs, alcohol, cocaine.
Malignant hyperthermia: halothane, ethylene, others; succinylcholine.
Mitochondrial: zidovudine.
Myosin loss: nondepolarizing neuromuscular blocking agents; glucocorticoids.

MYOPATHY, DRUG-INDUCED[42]

ICD-10CM # G72.9 Myopathy, unspecified

DRUGS AND TOXINS THAT MAY INDUCE MYOPATHY

Example	Comments
Cimetidine.	
Chloroquine.	Vacuolar myopathy.
Colchicine.	Vacuolar myopathy.
Emetine.	
Ethanol.	Acute rhabdomyolysis and chronic myopathy.
Glucocorticoids.	Type II fiber atrophy.
Heroin.	
IFN-α.	Dermatomyositis and polymyositis reported.
Penicillamine.	Typical polymyositis. Mitochondrial myopathy.
Statins and fibrates.	Cases of autoimmune necrotizing myopathy, polymyositis, rhabdomyolysis, and noninflammatory myopathies reported.
AntiTNF.	In RA patients existing reports of polymyositis, dermatomyositis and anti–Jo-1–positive myositis during TNF blockade.
Zidovudine (AZT).	
(Many others reported at the case level.)	

AZT, Zidovudine; *IFN,* interferon; *RA,* rheumatoid arthritis; *TNF,* tumor necrosis factor.

MYOSITIS, INFECTIOUS CAUSES[41]

ICD-10CM # M60.009 Infective myositis, unspecified site

VIRAL

Influenza A and B viruses.
Enteroviruses (coxsackieviruses, echoviruses).
Human immunodeficiency virus.
Human T-cell lymphotrophic virus type 1.
Hepatitis B and C viruses.
Cytomegalovirus.
Epstein-Barr virus.
Adenovirus.
Varicella-zoster virus.
Parainfluenza.

PARASITIC

Trichinella species.
Echinococcus species.
Schistosoma species.
Toxoplasma gondii.
Trypanosoma cruzi.
Sarcocystis species.

BACTERIAL

Staphylococcus aureus.
Streptococcus, groups A and B.
Aeromonas hydrophila.
Borrelia burgdorferi.
Clostridium perfringens.
Anaerobic streptococci.
Mycobacterium species.
Rickettsia species.

FUNGAL

Candida species.
Cryptococcus neoformans.
Microsporida.

MYOSITIS, INFLAMMATORY[3]

ICD-10CM #		
	M60.009	Infective myositis, unspecified site
	M60.9	Myositis, unspecified
	M60.10	Interstitial myositis of unspecified site

INFECTIOUS

Viral myositis:
- Retroviruses (HIV, HTLV-I).
- Enteroviruses (echovirus, Coxsackievirus).
- Other viruses (influenza, hepatitis A and B, Epstein-Barr virus).

Bacterial: pyomyositis.
Parasites: trichinosis, cysticercosis.
Fungi: candidiasis.

IDIOPATHIC

Granulomatous myositis (sarcoid, giant cell).
Eosinophilic myositis.
Eosinophilia-myalgia syndrome.

ENDOCRINE/METABOLIC DISORDERS

Hypothyroidism.
Hyperthyroidism.
Hypercortisolism.
Hyperparathyroidism.
Hypoparathyroidism.
Hypocalcemia.
Hypokalemia.

METABOLIC MYOPATHIES

Myophosphorylase deficiency (McArdle disease).
Phosphofructokinase deficiency.
Myoadenylate deaminase deficiency.
Acid maltase deficiency.
Lipid storage diseases.
Acute rhabdomyolysis.

DRUG-INDUCED MYOPATHIES

Alcohol.
d-Penicillamine.
Zidovudine.
Colchicine.
Chloroquine, hydroxychloroquine.
Lipid-lowering agents.
Cyclosporine.
Cocaine, heroin, barbiturates.
Corticosteroids.

NEUROLOGIC DISORDERS

Muscular dystrophies.
Congenital myopathies.
Motor neuron disease.
Guillain-Barré syndrome.
Myasthenia gravis.

NAIL CLUBBING

ICD-10CM #		
	R68.3	Clubbing of nails

COPD.
- Pulmonary malignancy.
- Cirrhosis.
- Inflammatory bowel disease.
- Chronic bronchitis.
- Congenital heart disease.
- Endocarditis.
- AV malformations.
- Asbestosis.
- Trauma.
- Idiopathic.

NAIL, HORIZONTAL WHITE LINES (BEAU LINES)

ICD-10CM #		
	L60.4	Beau lines

Malnutrition.
Idiopathic.
Trauma.
Prolonged systemic illnesses.
Pemphigus.
Raynaud phenomenon.

NAIL KOILONYCHIA

ICD-10CM #		
	L60.8	Other nail disorders

Trauma.
Iron deficiency.
SLE.
Hemochromatosis.
Raynaud phenomenon.
Nail-patella syndrome.
Idiopathic.

NAIL ONYCHOLYSIS

ICD-10CM #		
	L60.1	Onycholysis

Infection.
Trauma.
Psoriasis.
Connective tissue disorders.
Sarcoidosis.
Hyperthyroidism.
Amyloidosis.
Nutritional deficiencies.

NAIL PITTING

ICD-10CM #		
	L60.8	Other nail disorders

Psoriasis.
Alopecia areata.
Reiter syndrome.
Trauma.
Idiopathic.

NAIL SPLINTER HEMORRHAGE

ICD-10CM #		
	L60.8	Other nail disorders

SBE.
Trauma.
Malignancies.
Oral contraceptives.
Pregnancy.
SLE.
Antiphospholipid syndrome.
Psoriasis.
RA.
Peptic ulcer disease.

NAIL STRIATIONS

ICD-10CM #		
	L60.8	Other nail disorders

Psoriasis.
Alopecia areata.
Trauma.
Atopic dermatitis.
Vitiligo.

NAIL TELANGIECTASIA

ICD-10CM #		
	L60.8	Other nail disorders

RA.
Scleroderma.
Trauma.
SLE.
Dermatomyositis.

NAIL WHITENING (TERRY NAILS)

ICD-10CM #		
	L60.8	Other nail disorders

Malnutrition.
Trauma.
Liver disease (cirrhosis, hepatic failure).
DM.
Hyperthyroidism.
Idiopathic.

NAIL YELLOWING

ICD-10CM #		
	L60.8	Other nail disorders

Tobacco abuse.
Nephrotic syndrome.
Chronic infections (TB, sinusitis).
Bronchiectasis.
Lymphedema.
Raynaud phenomenon.
RA.
Pleural effusions.
Thyroiditis.
Immunodeficiency.

NASAL AND PARANASAL SINUS TUMORS[36]

ICD-10CM #		
	C30.0	Malignant neoplasm of nasal cavity

BENIGN AND MALIGNANT NASAL AND PARANASAL SINUS TUMORS

Epithelial Tumors

BENIGN

Papilloma.
Adenoma.
Inverting papilloma.

MALIGNANT

Squamous carcinoma.
Adenocarcinoma.
Melanoma.
Adenoid cystic carcinoma.
Malignant salivary tumors.

MESENCHYMAL TUMORS

Benign
Osteoma.

FUNGAL

Candida species.
Cryptococcus neoformans.
Microsporida.

MYOSITIS, INFLAMMATORY[3]

ICD-10CM #		
	M60.009	Infective myositis, unspecified site
	M60.9	Myositis, unspecified
	M60.10	Interstitial myositis of unspecified site

INFECTIOUS

Viral myositis:
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- Enteroviruses (echovirus, Coxsackievirus).
- Other viruses (influenza, hepatitis A and B, Epstein-Barr virus).

Bacterial: pyomyositis.
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Fungi: candidiasis.

IDIOPATHIC

Granulomatous myositis (sarcoid, giant cell).
Eosinophilic myositis.
Eosinophilia-myalgia syndrome.

ENDOCRINE/METABOLIC DISORDERS

Hypothyroidism.
Hyperthyroidism.
Hypercortisolism.
Hyperparathyroidism.
Hypoparathyroidism.
Hypocalcemia.
Hypokalemia.

METABOLIC MYOPATHIES

Myophosphorylase deficiency (McArdle disease).
Phosphofructokinase deficiency.
Myoadenylate deaminase deficiency.
Acid maltase deficiency.
Lipid storage diseases.
Acute rhabdomyolysis.

DRUG-INDUCED MYOPATHIES

Alcohol.
d-Penicillamine.
Zidovudine.
Colchicine.
Chloroquine, hydroxychloroquine.
Lipid-lowering agents.
Cyclosporine.
Cocaine, heroin, barbiturates.
Corticosteroids.

NEUROLOGIC DISORDERS

Muscular dystrophies.
Congenital myopathies.
Motor neuron disease.
Guillain-Barré syndrome.
Myasthenia gravis.

NAIL CLUBBING

ICD-10CM #		
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- Endocarditis.
- AV malformations.
- Asbestosis.
- Trauma.
- Idiopathic.

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ICD-10CM #		
	L60.4	Beau lines

Malnutrition.
Idiopathic.
Trauma.
Prolonged systemic illnesses.
Pemphigus.
Raynaud phenomenon.

NAIL KOILONYCHIA

ICD-10CM #		
	L60.8	Other nail disorders

Trauma.
Iron deficiency.
SLE.
Hemochromatosis.
Raynaud phenomenon.
Nail-patella syndrome.
Idiopathic.

NAIL ONYCHOLYSIS

ICD-10CM #		
	L60.1	Onycholysis

Infection.
Trauma.
Psoriasis.
Connective tissue disorders.
Sarcoidosis.
Hyperthyroidism.
Amyloidosis.
Nutritional deficiencies.

NAIL PITTING

ICD-10CM #		
	L60.8	Other nail disorders

Psoriasis.
Alopecia areata.
Reiter syndrome.
Trauma.
Idiopathic.

NAIL SPLINTER HEMORRHAGE

ICD-10CM #		
	L60.8	Other nail disorders

SBE.
Trauma.
Malignancies.
Oral contraceptives.
Pregnancy.
SLE.
Antiphospholipid syndrome.
Psoriasis.
RA.
Peptic ulcer disease.

NAIL STRIATIONS

ICD-10CM #		
	L60.8	Other nail disorders

Psoriasis.
Alopecia areata.
Trauma.
Atopic dermatitis.
Vitiligo.

NAIL TELANGIECTASIA

ICD-10CM #		
	L60.8	Other nail disorders

RA.
Scleroderma.
Trauma.
SLE.
Dermatomyositis.

NAIL WHITENING (TERRY NAILS)

ICD-10CM #		
	L60.8	Other nail disorders

Malnutrition.
Trauma.
Liver disease (cirrhosis, hepatic failure).
DM.
Hyperthyroidism.
Idiopathic.

NAIL YELLOWING

ICD-10CM #		
	L60.8	Other nail disorders

Tobacco abuse.
Nephrotic syndrome.
Chronic infections (TB, sinusitis).
Bronchiectasis.
Lymphedema.
Raynaud phenomenon.
RA.
Pleural effusions.
Thyroiditis.
Immunodeficiency.

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ICD-10CM #		
	C30.0	Malignant neoplasm of nasal cavity

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Epithelial Tumors

BENIGN

Papilloma.
Adenoma.
Inverting papilloma.

MALIGNANT

Squamous carcinoma.
Adenocarcinoma.
Melanoma.
Adenoid cystic carcinoma.
Malignant salivary tumors.

MESENCHYMAL TUMORS

Benign
Osteoma.

Ossifying fibroma complex.
Angiofibroma.
Chondroma.
Malignant
Osteogenic sarcoma.
Fibrosarcoma.
Angiosarcoma.
Chondrosarcoma.
Lymphoma.
Rhabdomyosarcoma.

NASAL MASSES, CONGENITAL[36]

ICD-10CM #	J34.1	Cyst and mucocele of nose and nasal sinus
	J34.89	Other specified disorders of nose and nasal sinuses

Dermoid.
Nasal cerebral heterotopia (glioma).
Frontal meningoencephalocele.
Nasolacrimal duct mucocele.
Nasal hamartoma.
Nasal hemangioma.

NAUSEA AND VOMITING

ICD-10CM #	R11.2	Nausea with vomiting, unspecified

Infections (viral, bacterial).
Intestinal obstruction.
Metabolic (uremia, electrolyte abnormalities, DKA, acidosis, etc.).
Severe pain.
Anxiety, fear.
Psychiatric disorders (bulimia, anorexia nervosa).
Pregnancy.
Medications (NSAIDs, erythromycin, morphine, codeine, aminophylline, chemotherapeutic agents, etc.).
Withdrawal from substance abuse (drugs, alcohol).
Head trauma.
Vestibular or middle ear disease.
Migraine headache.
CNS neoplasms.
Radiation sickness.
PUD.
Carcinoma of GI tract.
Reye syndrome.
Eye disorders.
Abdominal trauma.

NAUSEA AND VOMITING, CAUSES DURING PREGNANCY[30]

ICD-10CM #	R11.2	Nausea with vomiting, unspecified

DIFFERENTIAL DIAGNOSIS OF NAUSEA AND VOMITING DURING PREGNANCY

Nausea and vomiting of pregnancy.
Hyperemesis gravidarum.
Pancreatitis.
Symptomatic cholelithiasis.
Viral hepatitis.
Peptic ulcer disease.
Gastric cancer.
Intestinal obstruction.
Intestinal pseudoobstruction.
Gastroparesis diabeticorum.
Gastritis.
Gastroesophageal reflux disease.
Acute pyelonephritis.
Drug toxicity.
Vagotomy.
Preeclampsia/eclampsia.
Acute fatty liver of pregnancy.
Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome.
Anorexia nervosa/bulimia.
Other neuropsychiatric disorders.

NAUSEA AND VOMITING, CHRONIC[26]

ICD-10CM #	R11.2	Nausea with vomiting, unspecified

DIFFERENTIAL DIAGNOSIS OF CHRONIC NAUSEA AND VOMITING

Mechanical GI tract obstruction (pylorus, bile duct, small intestine, colon).
Mucosal inflammation.
Peritoneal irritation.
Carcinomas (e.g., gastric, ovarian, renal, bronchogenic).
Metabolic/endocrine disorders (diabetic mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, uremia).
Medications (anticholinergics, narcotics, L-dopa, progesterone, calcium channel blockers, digitalis, NSAIDs, antidysrhythmic agents, lubiprostone, cannabis, metformin, amylin analogs).
Gastroparesis.
Gastric dysrhythmias (tachygastria, bradygastria, mixed).
CNS disorders (tumors, migraine, seizures, stroke, orthostatic intolerance).
Psychogenic disorders (anorexia nervosa, bulimia nervosa).

NECK AND ARM PAIN

ICD-10CM #	M54.2	Cervicalgia
	S46.919A	Strain of unspecified muscle, fascia and tendon at shoulder and upper arm level, unspecified arm, initial encounter

Cervical disk syndrome.
Trauma, musculoskeletal strain.
Rotator cuff syndrome.
Bicipital tendonitis.
Glenohumeral arthritis.
Acromioclavicular arthritis.
Thoracic outlet syndrome.
Pancoast tumor.
Infection (cellulitis, abscess).
Angina pectoris.

NECK MASS[65]

ICD-10CM #	R22.1	Localized swelling, mass and lump, neck

CONGENITAL ANOMALIES

Thyroglossal duct cyst.
Bronchial apparatus anomalies.
Teratomas.
Ranula.
Dermoid cysts.
Hemangioma.
Laryngoceles.
Cystic hygroma.

NONNEOPLASTIC INFLAMMATORY ETIOLOGIES

Folliculitis.
Adenopathy secondary to peritonsillar abscess.
Retropharyngeal or parapharyngeal abscess.
Salivary gland infections.
Viral infections (mononucleosis, HIV, CMV).
TB.
Cat-scratch disease.
Toxoplasmosis.
Actinomyces.
Atypical mycobacterium.
Jugular vein thrombus.

NEOPLASM (PRIMARY OR METASTATIC)

LIPOMA

NECK PAIN[65]

ICD-10CM #	M54.2	Cervicalgia

INFLAMMATORY DISEASES

RA.
Spondyloarthropathies.
Juvenile RA.

NONINFLAMMATORY DISEASE

Cervical osteoarthritis.
Diskogenic neck pain.
Diffuse idiopathic skeletal hyperostosis.
Fibromyalgia or myofascial pain.

INFECTIOUS CAUSES

Meningitis.
Osteomyelitis.
Infectious diskitis.

NEOPLASMS

Primary.
Metastatic.

REFERRED PAIN

Temporomandibular joint pain.
Cardiac pain.
Diaphragmatic irritation.
GI sources (gastric ulcer, gallbladder, pancreas).

NECK PAIN FROM RHEUMATOLOGIC DISORDERS[27]

ICD-10CM #	M54.2	Cervicalgia

Rheumatoid arthritis:
- Without disease of the C1-C2 joint.
- With structural cervical abnormalities: C1-C2 subluxation, C1-C2 facet involvement.

Spondyloarthropathies.
Reactive arthritis.
Psoriatic arthritis.
Enteropathic arthritis.
Polymyalgia rheumatica.
Osteoarthritis.
Fibromyalgia.
Nonspecific musculoskeletal pain.
Miscellaneous spondyloarthropathies.
- Whipple disease.
- Behçet disease.
- Paget disease.
- Acromegaly.
- Ossification of the posterior longitudinal ligament.
- Diffuse idiopathic skeletal hyperostosis.

NECK PAIN, NONMUSCULAR CAUSES[42]

ICD-10CM # M54.2 Cervicalgia

Structure	Condition
Pharynx.	Pharyngitis.
Larynx.	Laryngitis.
	Carcinoma.
Trachea.	Tracheitis.
Thyroid.	Thyroiditis.
Lymph nodes.	Lymphadenitis.
Carotid arteries.	Carotidynia.
	Dissection.
	Inflammation.
Aorta.	Aneurysm.
	Dissection.
Heart.	Angina.
	Infarction.
Pericardium.	Pericarditis.
Diaphragm.	Inflammation by blood, infection.

NECROTIZING PNEUMONIAS[3]

ICD-10CM # J15.8 Pneumonia due to other specified bacteria

COMMON

Tuberculosis.
Staphylococcus.
Gram-negative bacilli.
Anaerobes.
Fungi.
Pneumocystis jirovecii.

RARE

Streptococcus pneumoniae.
Legionella.
Viruses.
Mycoplasma pneumoniae.

NEOPLASTIC LESIONS, LUMBOSACRAL SPINE[42,*]

ICD-10CM # M54.5 Low back pain

*Although these are most common neoplastic lesions of the lumbosacral spine, most occur infrequently.

BENIGN

Osteoid osteoma.
Osteoblastoma.
Osteochondroma.
Giant cell tumor.
Aneurysmal bone cyst.
Hemangioma.
Eosinophilic granuloma.
Sacroiliac lipoma.

MALIGNANT

Multiple myeloma.
Chondrosarcoma.
Chordoma.
Lymphoma.
Skeletal metastases.

SPINAL CORD TUMORS

Extradural metastases.
Intradural–extramedullary:
- Neurofibroma.
- Meningioma.

Intramedullary:
- Ependymoma.
- Astrocytoma.

NEPHRITIC SYNDROME, ACUTE[3]

ICD-10CM # N00.8 Acute nephritic syndrome with other morphologic changes

LOW SERUM COMPLEMENT LEVEL

Acute postinfectious glomerulonephritis.
Membranoproliferative glomerulonephritis.
SLE.
Subacute bacterial endocarditis.
Visceral abscess "shunt" nephritis.
Cryoglobulinemia.

NORMAL SERUM COMPLEMENT LEVEL

IgA nephropathy.
Antiglomerular basement membrane disease.
Polyarteritis nodosa.
Granulomatosis with polyangiitis.
Henoch-Schönlein purpura.
Goodpasture syndrome.

NEPHROCALCINOSIS

ICD-10CM # E83.59 Other disorders of calcium metabolism

Sarcoidosis.
Hyperparathyroidism.
Chronic glomerulonephritis.
Milk-alkali syndrome.
Distal renal tubular acidosis.
Medullary sponge kidney.
Bartter syndrome.
Hypervitaminosis D.
Idiopathic hypercalciuria.
Hyperoxaluria.
Cortical necrosis.
Tuberculosis.
Idiopathic hypercalciuria.
Rapidly progressive osteoporosis.

NEPHROPATHY, OBSTRUCTIVE[90]

ICD-10CM # Varies with specific diagnosis

POSSIBLE CAUSES OF OBSTRUCTIVE NEPHROPATHY

Renal
Congenital
Polycystic kidney.
Renal cyst.
Peripelvic cyst.
Ureteropelvic junction obstruction.
Neoplastic
Wilms tumor.
Renal cell carcinoma.
Transitional cell carcinoma of the collecting system.
Multiple myeloma.
Inflammatory
Tuberculosis.
Echinococcus infection.
Metabolic
Calculi.
Miscellaneous
Sloughed papillae.
Trauma.
Renal artery aneurysm.
Ureter
Congenital
Stricture.
Ureterocele.
Obstructing megaureter.
Retrocaval ureter.
Prune belly syndrome.
Neoplastic
Primary carcinoma of ureter.
Metastatic carcinoma.
Inflammatory
Tuberculosis.
Amyloidosis.
Schistosomiasis.
Abscess.
Ureteritis cystica.
Endometriosis.
Miscellaneous
Retroperitoneal fibrosis.
Pelvic lipomatosis.
Aortic aneurysm.
Radiation therapy.
Lymphocele.
Trauma.
Urinoma.
Pregnancy.
Radiofrequency ablation.
Bladder and Urethra
Congenital
Posterior urethral valve.
Phimosis.
Hydrocolpos.
Neoplastic
Bladder carcinoma.
Prostate carcinoma.
Carcinoma of urethra.
Carcinoma of penis.
Inflammatory
Prostatitis.
Paraurethral abscess.

Miscellaneous
Benign prostatic hypertrophy.
Neurogenic bladder.
Urethral stricture.

NEUROGENIC BLADDER[66]

ICD-10CM #		
	N31.9	Neuromuscular dysfunction of bladder, unspecified

SUPRATENTORIAL
CVA.
Parkinson disease.
Alzheimer disease.
Cerebral palsy.

SPINAL CORD
Spinal cord injury.
Spinal stenosis.
Central cord syndrome.
ALS.
Multiple sclerosis.
Myelodysplasia.

PERIPHERAL NEUROPATHY
Diabetes.
Alcohol.
Shingles.
Syphilis.

NEUROLOGIC DEFICIT, FOCAL[58]

ICD-10CM #		
	G45.9	Transient cerebral ischemic attack, unspecified
	I67.848	Other cerebrovascular vasospasm and vasoconstriction

TRAUMATIC: INTRACRANIAL, INTRASPINAL
Subdural hematoma.
Intraparenchymal hemorrhage.
Epidural hematoma.
Traumatic hemorrhagic necrosis.

INFECTIOUS
Brain abscess.
Epidural and subdural abscesses.
Meningitis.

NEOPLASTIC
Primary CNS tumors.
Metastatic tumors.
Syringomyelia.
Vascular.
Thrombosis.
Embolism.
Spontaneous hemorrhage: arteriovenous malformation, aneurysm, hypertensive.

METABOLIC
Hypoglycemia.
B_{12} deficiency.
Postseizure.
Hyperosmolar nonketotic.

OTHER
Migraine.
Bell palsy.
Psychogenic.

NEUROLOGIC DEFICIT, MULTIFOCAL[58]

ICD-10CM #		
	I67.89	Other cerebrovascular disease
	G45.9	Transient cerebral ischemic attack, unspecified
	I67.848	Other cerebrovascular vasospasm and vasoconstriction

Acute disseminated encephalomyelitis: postviral or postimmunization.
Infectious encephalomyelitis: poliovirus, enteroviruses, arbovirus, herpes zoster, Epstein-Barr virus.
Granulomatous encephalomyelitis: sarcoid.
Autoimmune: SLE.
Other: familial spinocerebellar degenerations.

NEUROMUSCULAR JUNCTION DYSFUNCTION[3]

ICD-10CM #		
	N31.9	Neuromuscular dysfunction of bladder, unspecified

DISORDERS OF THE NEUROMUSCULAR JUNCTION
Autoimmune
Myasthenia gravis.
Lambert-Eaton myasthenic syndrome.
Congenital
Presynaptic defects in ACh resynthesis, packaging, or release.
Synaptic defect: congenital end plate AChE deficiency.
Postsynaptic defects: slow-channel syndromes.
Postsynaptic defects: decreased response to ACh.
  Fast-channel syndromes.
  AChR deficiency without kinetic abnormality.
Familial limb-girdle myasthenia.
Toxic
Botulism.
Drug-induced disorders.
Organophosphate intoxication.

Ach, Acetylcholine; *AChE,* acetylcholinesterase; *AChR,* acetylcholine receptor.

NEURONOPATHIES, SENSORY (GANGLIONOPATHIES)[7]

ICD-10CM #		
	G60.0	Hereditary motor and sensory neuropathy

Herpes:
  Herpes simplex I and II.
  Varicella zoster (shingles).
Inflammatory sensory polyganglionopathy (ISP).
Paraneoplastic.
Primary biliary cirrhosis.
Sjögren syndrome (keratoconjunctivitis sicca).
Toxin-induced:
  Pyridoxine (vitamin B_6) overdose.
  Metals:
    Platinum (cisplatin).
    Methyl mercury.
Vitamin E deficiency.

NEUROPATHIC BLADDER

ICD-10CM #		
	N31.9	Neuromuscular dysfunction of bladder, unspecified

Diabetes.
Stroke.
Multiple sclerosis.
Parkinson disease.
Dementia.
Encephalopathy.
Brain trauma.
Spinal cord trauma.
Pelvic surgery.
Spina bifida.

NEUROPATHIES WITH FACIAL NERVE INVOLVEMENT

ICD-10CM #		
	G51.8	Other disorders of facial nerve

Sarcoidosis.
HIV.
Lyme disease.
Guillain-Barré.
Others: chronic inflammatory polyneuropathy, Tangier disease, amyloidosis.

NEUROPATHIES, AUTONOMIC[53]

ICD-10CM #		
	G63	Polyneuropathy in diseases classified elsewhere

GUILLAIN-BARRÉ SYNDROME
Non–Guillain-Barré syndrome autoimmunity.
Paraneoplastic (type I antineuronal nuclear antibody).
Lambert-Eaton syndrome.
Antibodies to neuronal nicotinic acetylcholine receptors.
Antibodies to P/Q type calcium channels.
Other autoantibodies.
Systemic lupus erythematosus.

HEREDITARY
Type I autosomal dominant.
Type II autosomal recessive (Morvan disease).
Type III autosomal recessive (Riley-Day).
Type IV autosomal recessive (congenital insensitivity to pain with anhidrosis).
Type V absence of pain.

METABOLIC
Fabry disease.
Diabetes mellitus.
Tangier disease.
Porphyria.

INFECTIOUS
HIV.
Chagas disease.
Botulism.
Leprosy.
Diphtheria.

OTHER
Triple A (Allgrove) syndrome.
Navajo Indian neuropathy.
Multiple endocrine neoplasia type 2b.
TOXINS

NEUROPATHIES, AUTONOMIC, PERIPHERAL, CAUSES[34]

ICD-10CM #		
	G90.09	Other idiopathic peripheral autonomic neuropathy

METABOLIC
Diabetes mellitus.
Alcohol.
Acute intermittent porphyria.
Uremia.

AUTOIMMUNE
Autoimmune autonomic ganglionopathy.
Guillain-Barré syndrome.
Morvan syndrome.
Lambert-Eaton myasthenic syndrome.
Chronic inflammatory demyelinating polyradiculoneuropathy.
Sjögren syndrome.
Systemic lupus erythematosus.
Mixed connective tissue diseases.

PARAPROTEINEMIC
Amyloidosis.

NUTRITIONAL
Cyanocobalamin deficiency.
Thiamine deficiency.
Gluten-sensitive neuropathy.

TOXIC
Heavy metals.
Organic solvents.
Organophosphates.
Vacor.
Acrylamide.

DRUG INDUCED
Cisplatin.
Vincristine.
Amiodarone.
Metronidazole.
Perhexiline.
Paclitaxel.

INFECTIOUS
HIV.
Leprosy.
Chagas disease.
Botulism.
Diphtheria.
Lyme disease.

GENETIC
Hereditary sensory and autonomic neuropathies:
Types I and II.
Type III (familial dysautonomia).
Type IV (congenital insensitivity to pain).
Type V.
Fabry disease.

IDIOPATHIC
Adie syndrome.
Ross syndrome.
Acute cholinergic neuropathy.
Chronic idiopathic anhidrosis.
Amyotrophic lateral sclerosis.

NEUROPATHIES, PAINFUL[93]

ICD-10CM #		
	G58.9	Mononeuropathy, unspecified
	G62.1	Alcoholic polyneuropathy
	G61.89	Other inflammatory polyneuropathies
	G60.0	Hereditary motor and sensory neuropathy
	G60.0	Hereditary motor and sensory neuropathy
	E11.42	Type 2 diabetes mellitus with diabetic polyneuropathy
	E10.42	Type 1 diabetes mellitus with diabetic polyneuropathy

MONONEUROPATHIES
Compressive neuropathy (carpal tunnel, meralgia paresthetica).
Trigeminal neuralgia.
Ischemic neuropathy.
Polyarteritis nodosa.
Diabetic mononeuropathy.
Herpes zoster.
Idiopathic and familial brachial plexopathy.

POLYNEUROPATHIES
DM.
Paraneoplastic sensory neuropathy.
Nutritional neuropathy.
Multiple myeloma.
Amyloid.
Dominantly inherited sensory neuropathy.
Toxic (arsenic, thallium, metronidazole).
AIDS-associated neuropathy.
Tangier disease.
Fabry disease.

NEUROPATHIES, PERIPHERAL, ASYMMETRICAL PROXIMAL/DISTAL[7]

ICD-10CM #		
	G99.0	Autonomic neuropathy in diseases classified elsewhere

BRACHIAL PLEXOPATHY
Open
Direct plexus injury (knife or gunshot wound).
Neurovascular (plexus ischemia).
Iatrogenic (central line insertion).
Closed
Traction injuries:
"Stingers."
Traction neurapraxia.
Partial or complete nerve root avulsion.
Radiation.
Neoplastic.
Idiopathic brachial plexitis.
Thoracic outlet.

LUMBOSACRAL PLEXOPATHIES
Open
Closed
Traction injuries:
Pelvic double vertical shearing fracture.
Posterior hip dislocation.
Retroperitoneal hemorrhage.
Vasospastic (deep buttock injection).
Neoplastic.
Radiation.
Idiopathic lumbosacral plexitis.
Infectious:
Herpesvirus (sacrococcygeal).
Herpes simplex II.
Herpes zoster.
Cytomegalovirus (CMV) polyradiculopathy (HIV).

NEUROPATHIES, TOXIC AND METABOLIC[53]

ICD-10CM #		
	NEC G62.2	Toxic neuropathy

METALS
Arsenic (insecticide, herbicide).
Lead (paint, batteries, pottery).
Mercury (metallic, vapor).
Thallium (rodenticides).
Gold.

OCCUPATIONAL OR INDUSTRIAL CHEMICALS
Acrylamide (grouting, flocculation).
Carbon disulfide (solvent).
Cyanide.
Dichlorophenoxyacetate.
Dimethylaminopropionitrite.
Ethylene oxide (gas sterilization).
Hexacarbons (glue, solvents).
Organophosphates (insecticides, petroleum additive).
Polychlorinated biphenyls.
Tetrachlorbiphenyl.
Trichloroethylene.

DRUGS
Amiodarone.
Chloramphenicol.
Chloroquine.
Cisplatin.
Colchicine.
Dapsone.
Ethambutol.
Ethanol.

Gold.
Hydralazine.
Isoniazid.
Metronidazole.
Nitrofurantoin.
Nitrous oxide.
Nucleosides (antiretroviral agents ddC, ddI, d4T, others).
Penicillamine.
Pentamidine.
Phenytoin.
Pyridoxine (excessive).
Statins.
Stilbamidine.
Suramin.
Taxanes (paclitaxel, docetaxel).
Thalidomide.
Tryptophan (eosinophilia-myalgia syndrome).
Vincristine.

METABOLIC DISORDER

Fabry disease.
Krabbe disease.
Leukodystrophies.
Porphyria.
Tangier disease.
Tyrosinemia.
Uremia.

NEUTROPENIA, DRUG-INDUCED[44]

ICD-10CM # D70.9 Other neutropenia

DRUGS COMMONLY ASSOCIATED WITH NEUTROPENIA

Antibiotics:
- Vancomycin.
- Semisynthetic penicillins.
- Chloramphenicol.
- Sulfa.
- Linezolid.

Antithyroid drugs:
- Methimazole.
- Propylthiouracil.

Cardiovascular:
- Ticlopidine.
- Procainamide.

Antipsychotics:
- Clozapine.
- Olanzapine.
- Chlorpromazine.

Anticonvulsants:
- Phenytoin.
- Carbamazepine
- Valproic acid.

Antiinflammatory agents:
- Indomethacin.
- Sulfasalazine.
- Phenylbutazone.

H2 blockers:
- Cimetidine.
- Ranitidine.

Analgesics:
- Dipyrone.

Antineoplastic:
- Rituximab.

Anthelminthic:
- Levamisole.

NEUTROPENIA WITH DECREASED MARROW RESERVE[45]

ICD-10CM # D70.8 Other neutropenia

PRIMARY

Severe congenital neutropenia.
Shwachman–Diamond syndrome.
Cyclic neutropenia.

SECONDARY

Lymphoproliferative disorder of granular lymphocytes.
Chemotherapy.
Drug induced (nonimmune).
Nutritional.
Viral infection (varicella, EBV, measles, CMV, hepatitis, HIV).

NEUTROPENIA WITH NORMAL MARROW RESERVE[45]

ICD-10CM # D70.9 Neutropenia, unspecified

Chronic benign neutropenia of infancy and childhood.
Ethnic or benign familial neutropenia.
Autoimmune neutropenia.
Alloimmune neutropenia.
Drug-induced neutropenia.
Infection-related neutropenia.
Hypersplenism.

NEUTROPENIA, IN CHILDHOOD[87]

ICD-10CM # D70.8 Other neutropenia
D70.9 Neutropenia unspecified

ACQUIRED

Infection.
Immune mediated.
Hypersplenism.
Vitamin B_{12}, folate, copper deficiency.
Drugs or toxic substances.
Aplastic anemia.
Malignancies or preleukemic disorders.
Ionizing radiation.

CONGENITAL

Cyclic neutropenia.
Severe congenital neutropenia (Kostmann syndrome).
Chronic benign neutropenia of childhood.
Shwachman-Diamond syndrome.
Fanconi anemia.
Metabolic disorders (amino acidopathies, Barth syndrome, glycogen storage disorders).
Osteopetrosis.
Neutropenia with pigmentation abnormalities, e.g., Chédiak-Higashi.

NEUTROPHILIA[45]

ICD-10CM # D72.0 Neutrophilia, hereditary giant
D71 Functional disorders of polymorphonuclear neutrophils

CLASSIFICATION OF NEUTROPHILIA

Primary (No Other Evident Associated Disease)

Hereditary neutrophilia.
Chronic idiopathic neutrophilia.
Chronic myelogenous leukemia (CML) and other myeloproliferative diseases.
Familial myeloproliferative disease.
Congenital anomalies and leukemoid reaction.
Leukocyte adhesion factor deficiency (LAD).
Familial cold urticaria and leukocytosis.

Secondary

Infection.
Stress neutrophilia.
Chronic inflammation.
Drug induced.
Nonhematologic malignancy.
Generalized marrow stimulation as in hemolysis.
Asplenia and hyposplenism.

NIPPLE DISCHARGE[54]

ICD-10CM # Varies with specific diagnosis

Pregnancy.
Hormones (oral contraceptives, estrogen, progesterone).
Blood pressure drugs (methyldopa, verapamil).
Tricyclic antidepressants.
Tranquilizers (antipsychotics).
Antinausea drugs (metoclopramide).
Herbs (nettle, fennel, blessed thistle, anise, fenugreek seed).
Illicit drugs (marijuana, opiates).
Stimulation of the breast (sexual or from exercise).
Thyroid abnormalities.
Chronic emotional stress.
Hypothalamic tumors.
Chest wall conditions.
Herpes zoster.
Trauma.
Burns.
Tumors.
Breast conditions:
- Mammary duct ectasia.
- Chronic cystic mastitis.
- Intraductal cysts.
- Intraductal papillomas.

NIPPLE LESIONS

ICD-10CM # Varies with specific diagnosis

Contact dermatitis.
Trauma.
Paget disease.
Sebaceous hyperplasia.
Neurofibroma.
Accessory nipple.
Papillary adenoma.
Nevoid hyperkeratosis.
Cellulitis.

NODULAR LESIONS, SKIN

ICD-10CM # R22.9 Localized swelling, mass and lump, unspecified

Lipoma.
Cherry angioma.
Angiokeratoma.
Hemangioma.
Classic Kaposi sarcoma.
Nodular melanoma.
Pyogenic granuloma.
Angiosarcoma.
Eccrine poroma.

NODULES, PAINFUL

ICD-10CM # R22.9 Localized swelling, mass and lump, unspecified

Arthropod bite or sting.
Erythema nodosum.
Glomus tumor.
Neuroma.
Leiomyoma.
Angiolipoma.
Dermatofibroma.
Osler node.
Blue rubber bleb nevus.
Vasculitis.
Sweet syndrome.

NYSTAGMUS

ICD-10CM # H55.00 Unspecified nystagmus
H55.89 Other irregular eye movements

Medications (meperidine, barbiturates, phenytoin, phenothiazines, etc.).
Multiple sclerosis.
Congenital.
Neoplasm (cerebellar, brain stem, cerebral).
Labyrinthine or vestibular lesions.
CNS infections.
Optic atrophy.
Other: Arnold–Chiari malformation, syringobulbia, chorioretinitis, meningeal cysts.

NYSTAGMUS, MONOCULAR

ICD-10CM # H55.09 Other forms of nystagmus
H55.00 Unspecified nystagmus

Amblyopia.
Strabismus.
Multiple sclerosis.
Monocular blindness.
Internuclear ophthalmoplegia.
Lid fasciculations.
Brain stem infarct.

ODYNOPHAGIA[86]

ICD-10CM # Varies with specific diagnosis

CAUSES OF ODYNOPHAGIA

Infections
Herpes simplex virus.
Cytomegalovirus.
Candidiasis.
Chemical, Inflammatory
Gastroesophageal reflux.
Drug induced (Slow-K, tetracyclines, quinidine).
Radiation.
Graft-versus-host disease.
Crohn disease.
Dermatologic diseases (pemphigus and pemphigoid).

OPACIFICATION OF HEMIDIAPHRAGM ON X-RAY[36]

ICD-10CM # Varies with specific diagnosis

CAUSES OF OPACIFICATION OF A HEMITHORAX

Pleural effusion.
Consolidation.
Collapse.
Massive tumor.
Fibrothorax.
Combination of above lesions.
Pneumonectomy.
Lung agenesis.

OPHTHALMOPLEGIA[3]

ICD-10CM # H51.9 Unspecified disorder of binocular movement
H49.00 Third [oculomotor] nerve palsy, unspecified eye

BILATERAL

Botulism.
Myasthenia gravis.
Wernicke encephalopathy.
Acute cranial polyneuropathy.
Brain stem stroke.

UNILATERAL

Carotid-posterior (3rd cranial nerve, pupil involved communicating aneurysm).
Diabetic-idiopathic (3rd or 6th cranial nerve, pupil spared).
Myasthenia gravis.
Brain stem stroke.[29]

OPSOCLONUS[29]

ICD-10CM # H55.89 Other irregular eye movements

Multiple sclerosis.
Encephalitis.
CNS lymphoma.
Hydrocephalus.
Pontine hemorrhage.
Thalamic disorder (glioma, hemorrhage).
Hyperosmolar coma.
Carcinoma, paraneoplastic.
Cocaine.
Medications (e.g., phenytoin, haloperidol, amitriptyline, diazepam, vidarabine).

[29] Spontaneous, multivector, chaotic eye movement.

OPTIC ATROPHY[80]

ICD-10CM # H47.20 Unspecified optic atrophy

CAUSES OF OPTIC ATROPHY

Optic Nerve Compression
Pituitary tumor.
Carotid aneurysm.
Glaucoma.
Optic nerve tumor.
Sphenoid meningioma.
Olfactory groove meningioma.
Optic Neuritis Following Long-standing Papilledema Central Retinal Artery Occlusion Toxic/Metabolic
Diabetes.
Methyl alcohol.
Tobacco.
Quinine.
Ethambutol.
Lead and arsenic.
Anemia.
Secondary to Retinal Disease
Senile macular degeneration.
Retinitis pigmentosa.
Severe chorioretinitis.
Secondary to Trauma
Orbital fracture.
Hereditary
Leber optic atrophy.
Hereditary ataxias.
Spinocerebellar degeneration.

OPTIC DISC ELEVATION[12]

ICD-10CM # Varies with specific diagnosis

CAUSES OF OPTIC DISC ELEVATION

Papilloedema.
Accelerated hypertension.
Anterior optic neuropathy.
Ischemic.
Inflammatory.
Infiltrative.
Compressive, including orbital disease.
Pseudopapilloedema.
Disc drusen.
Tilted optic disc.
Peripapillary myelinated nerve fibers.
Crowded disc in hypermetropia.
Mitochondrial optic neuropathies.
Leber hereditary optic neuropathy.
Methanol poisoning.
Intraocular disease.
Central retinal vein occlusion.
Uveitis.
Posterior scleritis.
Hypotony.

ORAL MUCOSA, ERYTHEMATOUS LESIONS[20]

ICD-10CM # K12.2 Cellulitis and abscess of mouth
K13.70 Unspecified lesions of oral mucosa
K13.79 Other lesions of oral mucosa

NODULAR LESIONS, SKIN

ICD-10CM # R22.9 Localized swelling, mass and lump, unspecified

Lipoma.
Cherry angioma.
Angiokeratoma.
Hemangioma.
Classic Kaposi sarcoma.
Nodular melanoma.
Pyogenic granuloma.
Angiosarcoma.
Eccrine poroma.

NODULES, PAINFUL

ICD-10CM # R22.9 Localized swelling, mass and lump, unspecified

Arthropod bite or sting.
Erythema nodosum.
Glomus tumor.
Neuroma.
Leiomyoma.
Angiolipoma.
Dermatofibroma.
Osler node.
Blue rubber bleb nevus.
Vasculitis.
Sweet syndrome.

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ICD-10CM # H55.00 Unspecified nystagmus
H55.89 Other irregular eye movements

Medications (meperidine, barbiturates, phenytoin, phenothiazines, etc.).
Multiple sclerosis.
Congenital.
Neoplasm (cerebellar, brain stem, cerebral).
Labyrinthine or vestibular lesions.
CNS infections.
Optic atrophy.
Other: Arnold–Chiari malformation, syringobulbia, chorioretinitis, meningeal cysts.

NYSTAGMUS, MONOCULAR

ICD-10CM # H55.09 Other forms of nystagmus
H55.00 Unspecified nystagmus

Amblyopia.
Strabismus.
Multiple sclerosis.
Monocular blindness.
Internuclear ophthalmoplegia.
Lid fasciculations.
Brain stem infarct.

ODYNOPHAGIA[86]

ICD-10CM # Varies with specific diagnosis

CAUSES OF ODYNOPHAGIA

Infections
Herpes simplex virus.
Cytomegalovirus.
Candidiasis.
Chemical, Inflammatory
Gastroesophageal reflux.
Drug induced (Slow-K, tetracyclines, quinidine).
Radiation.
Graft-versus-host disease.
Crohn disease.
Dermatologic diseases (pemphigus and pemphigoid).

OPACIFICATION OF HEMIDIAPHRAGM ON X-RAY[36]

ICD-10CM # Varies with specific diagnosis

CAUSES OF OPACIFICATION OF A HEMITHORAX

Pleural effusion.
Consolidation.
Collapse.
Massive tumor.
Fibrothorax.
Combination of above lesions.
Pneumonectomy.
Lung agenesis.

OPHTHALMOPLEGIA[3]

ICD-10CM # H51.9 Unspecified disorder of binocular movement
H49.00 Third [oculomotor] nerve palsy, unspecified eye

BILATERAL

Botulism.
Myasthenia gravis.
Wernicke encephalopathy.
Acute cranial polyneuropathy.
Brain stem stroke.

UNILATERAL

Carotid-posterior (3rd cranial nerve, pupil involved communicating aneurysm).
Diabetic-idiopathic (3rd or 6th cranial nerve, pupil spared).
Myasthenia gravis.
Brain stem stroke.[29]

OPSOCLONUS[29]

ICD-10CM # H55.89 Other irregular eye movements

Multiple sclerosis.
Encephalitis.
CNS lymphoma.
Hydrocephalus.
Pontine hemorrhage.
Thalamic disorder (glioma, hemorrhage).
Hyperosmolar coma.
Carcinoma, paraneoplastic.
Cocaine.
Medications (e.g., phenytoin, haloperidol, amitriptyline, diazepam, vidarabine).

[29] Spontaneous, multivector, chaotic eye movement.

OPTIC ATROPHY[80]

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CAUSES OF OPTIC ATROPHY

Optic Nerve Compression
Pituitary tumor.
Carotid aneurysm.
Glaucoma.
Optic nerve tumor.
Sphenoid meningioma.
Olfactory groove meningioma.
Optic Neuritis Following Long-standing Papilledema Central Retinal Artery Occlusion Toxic/Metabolic
Diabetes.
Methyl alcohol.
Tobacco.
Quinine.
Ethambutol.
Lead and arsenic.
Anemia.
Secondary to Retinal Disease
Senile macular degeneration.
Retinitis pigmentosa.
Severe chorioretinitis.
Secondary to Trauma
Orbital fracture.
Hereditary
Leber optic atrophy.
Hereditary ataxias.
Spinocerebellar degeneration.

OPTIC DISC ELEVATION[12]

ICD-10CM # Varies with specific diagnosis

CAUSES OF OPTIC DISC ELEVATION

Papilloedema.
Accelerated hypertension.
Anterior optic neuropathy.
Ischemic.
Inflammatory.
Infiltrative.
Compressive, including orbital disease.
Pseudopapilloedema.
Disc drusen.
Tilted optic disc.
Peripapillary myelinated nerve fibers.
Crowded disc in hypermetropia.
Mitochondrial optic neuropathies.
Leber hereditary optic neuropathy.
Methanol poisoning.
Intraocular disease.
Central retinal vein occlusion.
Uveitis.
Posterior scleritis.
Hypotony.

ORAL MUCOSA, ERYTHEMATOUS LESIONS[20]

ICD-10CM # K12.2 Cellulitis and abscess of mouth
K13.70 Unspecified lesions of oral mucosa
K13.79 Other lesions of oral mucosa

Allergy.
Erythroplakia.
Candidiasis.
Geographic tongue.
Stomatitis areata migrans.
Plasma cell gingivitis.
Pemphigus vulgaris.

ORAL MUCOSA, PIGMENTED LESIONS[20]

ICD-10CM #		
	K12.2	Cellulitis and abscess of mouth
	K13.70	Unspecified lesions of oral mucosa
	K13.79	Other lesions of oral mucosa
	K13.5	Oral submucous fibrosis

Racial pigmentation.
Oral melanotic macule.
Peutz-Jeghers syndrome.
Neurofibromatosis.
Albright syndrome.
Addison disease.
Chloasma.
Drug reaction: quinacrine, Minocin, chlorpromazine, Myleran.
Amalgam tattoo.
Lead line.
Smoker's melanosis.
Nevi.
Melanoma.

ORAL MUCOSA, PUNCTATE EROSIVE LESIONS[20]

ICD-10CM #		
	K12.2	Cellulitis and abscess of mouth
	K13.70	Unspecified lesions of oral mucosa
	K13.79	Other lesions of oral mucosa

Viral lesion: herpes simplex, coxsackievirus (A, B, A16), herpes zoster.
Aphthous stomatitis.
Sutton disease (giant aphthae).
Behçet syndrome.
Reiter syndrome.
Neutropenia.
Acute necrotizing ulcerative gingivostomatitis (ANUG).
Drug reaction.
Inflammatory bowel disease.
Contact allergy.

ORAL MUCOSA, WHITE LESIONS[20]

ICD-10CM #		
	K12.2	Cellulitis and abscess of mouth
	K13.70	Unspecified lesions of oral mucosa
	K13.79	Other lesions of oral mucosa
	K13.5	Oral submucous fibrosis

Leukoplakia.
White, hairy leukoplakia.
Squamous cell carcinoma.
Lichen planus.
Stomatitis nicotinica.
Benign intraepithelial dyskeratosis.
White spongy nevus.
Leukoedema.
Darier-White disease.
Pachyonychia congenital.
Candidiasis.
Allergy.
SLE.

ORAL ULCERS, ACUTE

ICD-10CM #		
	K13.70	Unspecified lesions of oral mucosa
	K13.79	Other lesions of oral mucosa

Trauma (including thermal trauma).
Aphthous stomatitis.
Syphilis.
Herpes simplex infection.
Herpes zoster.

ORAL VESICLES AND ULCERS[3]

ICD-10CM #		
	K13.70	Unspecified lesions of oral mucosa
	K13.79	Other lesions of oral mucosa

Aphthous stomatitis.
Primary herpes simplex infection.
Vincent stomatitis.
Syphilis.
Coxsackievirus A (herpangina).
Fungi (histoplasmosis).
Behçet syndrome.
SLE.
Reiter syndrome.
Crohn disease.
Erythema multiforme.
Pemphigus.
Pemphigoid.

ORBITAL INFLAMMATION[12]

ICD-10CM #		
	H05.019	Cellulitis of unspecified orbit
	C69.10	Malignant neoplasm of unspecified orbit
	D31.60	Benign neoplasm of unspecified orbit
	H05.029	Osteomyelitis of unspecified orbit
	H05.049	Tendonitis of unspecified orbit
	H05.229	Edema of unspecified orbit
	H05.239	Hemorrhage of unspecified orbit

DIFFERENTIAL DIAGNOSIS OF AN ACUTELY INFLAMED ORBIT

Infection
Bacterial orbital cellulitis.
Fungal orbital infection.
Dacryocystitis.
Infective dacryoadenitis.
Vascular lesions
Acute orbital hemorrhage,
Cavernous sinus thrombosis.
Carotid–cavernous fistula.
Neoplasia
Rapidly progressive retinoblastoma.
Lacrimal gland tumor.
Other neoplasms (e.g., metastatic lesion with inflammation, lymphoma, Waldenström macroglobulinemia).
Rhabdomyosarcoma, leukemia, lymphangioma, or neuroblastoma in children
Endocrine
Thyroid eye disease of rapid onset.
Non-neoplastic inflammation
Idiopathic orbital inflammatory disease.
Tolosa–Hunt syndrome.
Orbital myositis.
Acute allergic conjunctivitis with lid swelling.
Herpes zoster ophthalmicus.
Herpes simplex skin rash.
Sarcoidosis.
Vasculitides: Wegener granulomatosis, polyarteritis nodosa.
Scleritis, including posterior scleritis.
Ruptured dermoid cyst.

ORBITAL LESIONS, CALCIFIED

ICD-10CM #		
	H05.89	Other disorders of orbit

Chronic inflammation.
Phlebolith.
Dermoid cyst.
Mucocele walls.
Tumors (lacrimal gland, fibro-osseous).
Meningioma (optic sheath).
Lymphangioma.
Orbital varix.

ORBITAL LESIONS, CYSTIC

ICD-10CM #		
	H05.9	Unspecified disorder of orbit

Sweat gland cyst.
Dermoid cyst.
Lacrimal gland cyst.
Abscess.
Conjunctival cyst.
Lymphangioma.
Schwannoma.

ORBITAL NEOPLASMS, MALIGNANT[64]

ICD-10CM #		
	C69.10	Malignant neoplasm of unspecified orbit

LESIONS WITH CLINICALLY MALIGNANT BEHAVIOR

Langerhans cell tumors.
Non-Langerhans cell tumors.
Atypical lymphoid hyperplasia.
Meningioma of optic nerve.

[a] Relatively common tumor.

PRIMARY MALIGNANT TUMORS OF ORBIT

Lymphoma.
Lacrimal gland carcinomas.
Rhabdomyosarcoma.
Primitive neuroectodermal tumors.
Malignant peripheral nerve sheath tumor.
Alveolar soft part sarcoma.
Melanoma.
Osteosarcoma.
Fibrosarcoma.
Leiomyosarcoma.
Chondrosarcoma.
Liposarcoma.
Glioma of optic nerve.

SECONDARY MALIGNANT TUMORS OF ORBIT

Eyelid malignancies.
Conjunctival malignancies.
Uveal melanoma.
Retinoblastoma.
Lacrimal drainage system malignancies.
Paranasal sinus and nasal carcinoma.
Brain tumors.

METASTATIC TUMORS OF ORBIT

Distant carcinomas (e.g., breast, lung, gastrointestinal tract).
Neuroblastoma.
Leukemia (granulocytic sarcoma).
Carcinoid tumor.
Metastatic melanoma.

ORGASM DYSFUNCTION[24]

ICD-10CM #		
	F52.31	Female orgasmic disorder
	F52.32	Male orgasmic disorder

Anorgasmia: inadequate stimulation or learning.
Spinal cord lesion or injury.
Multiple sclerosis.
Alcoholic neuropathy.
Amyotrophic lateral sclerosis.
Spinal cord accident.
Spinal cord trauma.
Peripheral nerve damage.
Radical pelvic surgery.
Herniated lumbar disk.
Hypothyroidism.
Addison disease.
Cushing disease.
Acromegaly.
Hypopituitarism.
Pharmacologic agents (e.g., SSRIs, beta-blockers).
Psychogenic.

OROFACIAL PAIN

ICD-10CM #		
	R51	Facial pain

Dental abscess.
Sinusitis.
Otitis media.
Otitis externa.
Wisdom tooth eruption.
Sialoadenitis.
Herpes zoster.
Trigeminal neuralgia.
Parotitis.
Anxiety disorder.
Malingering.

OSTEOLYTIC BENIGN BONE LESIONS, MULTIPLE[71]

ICD-10CM #	
	Varies with specific diagnosis

COMMON MULTIPLE OSTEOLYTIC BENIGN LESIONS

Cystic lesions in joint disease.
Amyloidosis.
Brown tumors in hyperparathyroidism.
Enchondromatosis.
Fibrous dysplasia.
Osteomyelitis (including tuberculosis, hydatid, sarcoid, etc.).
Massive osteolysis (Gorham disease).
Mastocytosis.
Neurofibromatosis.
Langerhans cell histiocytosis (histiocytosis X).

OSTEOMYELITIS, PEDIATRIC PATIENT[19]

ICD-10CM #		
	M86	Osteomyelitis

Fractures.
Thrombophlebitis.
Scurvy.
Septicemia.
Cellulitis.
Septic bursitis.
Myositis.
Pyomyositis.
Rheumatic fever.
Toxic synovitis.
Reactive arthritis.
Complex regional pain syndrome.
Chronic recurrent multifocal osteomyelitis.
Osteoid osteoma.
Langerhans cell histiocytosis.
Leukemia.
Ewing sarcoma.
Malignant primary bone tumors.
Bone infarction (sickle-cell or Gaucher disease).

OSTEOPOROSIS IN CHILDREN[71]

ICD-10CM #		
	M81.8	Other osteoporosis without current pathological fracture

CAUSES OF OSTEOPOROSIS IN CHILDREN

Systemic long-term oral glucocorticoid therapy.
Chronic inflammatory disease (e.g., juvenile inflammatory arthritis).
Hypogonadism—primary or secondary.
Prolonged immobilization.
Osteogenesis imperfecta.
Idiopathic juvenile osteoporosis.

OSTEOPOROSIS, SECONDARY CAUSES

ICD-10CM #		
	M81.0	Age-related osteoporosis without current pathological fracture

Medication induced (e.g., glucocorticoids, anticonvulsants, heparin, LHRH agonists or antagonists).
Hyperparathyroidism.
Hyperthyroidism.
Prolonged immobilization.
Chronic renal failure.
Sickle cell disease.
Multiple myeloma.
Myeloproliferative diseases.
Leukemias and lymphomas.
Acromegaly.
Prolactinoma.
DM.
Total parenteral nutrition.
Malabsorption.
Chronic hypophosphatemia.
Connective tissue disorders (e.g., osteogenesis imperfecta, Marfan syndrome, Ehlers-Danlos).
Hepatobiliary disease.
Postgastrectomy.
Aluminum-containing antacids.
Systemic mastocytosis.
Homocystinuria.[30]

OSTEOSCLEROSIS, DIFFUSE[36]

ICD-10CM #		
	Q77.4	Congenital osteosclerosis

DISORDERS ASSOCIATED WITH DIFFUSE OSTEOSCLEROSIS

Neoplastic Causes[30]
Prostate carcinoma, breast carcinoma, GI adenocarcinoma, carcinoid tumors, transitional cell carcinoma of the bladder, myeloma, lymphoma, leukemia.

Hematologic Causes
Sickle cell disorders, mastocytosis, myelofibrosis, polycythemia vera.

Metabolic Causes
Renal osteodystrophy, primary hyperparathyoidism, familial hypophosphatemic osteomalacia, hypervitaminosis D, fluorosis, hypoparathyroidism, pseudohypoparathyroidism.[31]

Primary Osseous Disorders[31]
Osteoporosis.
Pyknodysostosis.
Paget disease.

OSTEOSCLEROTIC BENIGN BONE LESIONS, MULTIPLE[71]

ICD-10CM #		
	Q78.2	Osteosclerosis

[30] Involvement principally of cancellous bone
[31] Involvement of cancellous and cortical bone

COMMON MULTIPLE OSTEOSCLEROTIC BENIGN LESIONS

Bone infarcts.
Bone islands.
Callus.
Osteomyelitis (chronic, multifocal).
Paget disease.
Fibrous dysplasia.
Enchondromatosis.
Mastocytosis.
Matured benign lesions (e.g., nonossifying fibromas).
Osteomas (Gardner syndrome).
Osteopathia striata.
Osteopoikilosis.

OVARIAN ENLARGEMENT, NONNEOPLASTIC[22]

ICD-10CM #		
	N83.209	Unspecified ovarian cyst, unspecified side
	N83.29	Other ovarian cysts
	N80.1	Endometriosis of ovary
	O00.209	Unspecified ovarian pregnancy without intrauterine pregnancy

NON-NEOPLASTIC CAUSES OF OVARIAN ENLARGEMENT IN THE NONPREGNANT PATIENT

Functional
Hemorrhagic corpus luteum.
Follicle cyst.
Cortical stromal hyperplasia (hyperthecosis).
Polycystic ovarian syndrome (PCOS).
Mesothelial/müllerian.
Endometriotic cyst.
Xanthomatous pseudotumor.
Cystic adhesions/cystic mesothelioma.
Simple cyst.
Vascular
Ovarian torsion/infarction.
Massive ovarian edema.

OVULATORY DYSFUNCTION[49]

ICD-10CM #		
	N97.0	Female infertility associated with anovulation
	N92.3	Ovulation bleeding

HYPERANDROGENIC ANOVULATION

Polycystic ovarian syndrome.
Late-onset congenital adrenal hyperplasias.
Ovarian hyperthecosis.
Androgen-producing ovarian tumors.
Androgen-producing adrenal tumors.
Cushing syndrome.

HYPOESTROGENIC ANOVULATION (HYPOTHALAMIC OR PITUITARY ETIOLOGY)

Hypogonadotropic Hypoestrogenic States
Reversible:
Functional hypothalamic amenorrheas:
Eating disorders (anorexia nervosa, excessive weight loss).
Excessive athletic training.
Neoplastic:
Craniopharyngioma.
Pituitary stalk compression.
Infiltrative diseases:
Histiocytosis-X.
Sarcoidosis.
Hypophysitis.
Pituitary adenomas:
Hyperprolactinemia.
Euprolactinemic galactorrhea.
Endocrinopathies:
Hypothyroidism/hyperthyroidism.
Cushing disease.
Irreversible:
Kallmann syndrome.
Isolated gonadotropin deficiency (hypothalamic or pituitary origin).
Panhypopituitarism/pituitary insufficiency:
Sheehan syndrome, pituitary apoplexy.
Pituitary irradiation or ablation.
Hypergonadotropic Hypoestrogenic States
Physiologic states:
Menopause.
Perimenopause.
Premature ovarian failure.
Immune-related:
Radiation/chemotherapy-induced.
Ovarian dysgenesis.
Turner syndrome.
46XX with mutations of X.
Androgen insensitivity syndrome.

MISCELLANEOUS

Endometriosis.
Luteal phase defect.

PAIN, MIDFOOT

ICD-10CM #		
	M25.579	Pain in unspecified ankle and joints of unspecified foot

MEDIAL ASPECT

Tendonitis of posterior tibialis.
Tendonitis of flexor digitorum longus.
Tendonitis of flexor hallucis longus.
Infection (osteomyelitis, septic arthritis, cellulitis) of foot.
Peripheral vascular insufficiency.
Fracture.
Osteoarthritis.
Gout, pseudogout.
Neuropathy.
Tumor.

LATERAL ASPECT

Peroneus longus tendonitis.
Peroneus brevis tendonitis.
Infection (osteomyelitis, septic arthritis, cellulitis) of foot.
Peripheral vascular insufficiency.
Fracture.
Osteoarthritis.
Gout, pseudogout.
Neuropathy.
Tumor.

PAIN, PLANTAR ASPECT, HEEL

ICD-10CM #		
	M25.579	Pain in unspecified ankle and joints of unspecified foot

Plantar fasciitis.
Tarsal tunnel syndrome.
Neuroma.
Infection (osteomyelitis, septic arthritis, cellulitis) of foot.
Peripheral vascular insufficiency.
Fracture.
Bone cyst.
Osteoarthritis.
Gout, pseudogout.
Neuropathy.
Tumor.
Heel pad atrophy.
Plantar fascia rupture.

PAIN, POSTERIOR HEEL

ICD-10CM #		
	M79.609	Pain in unspecified limb

Achilles tendonitis.
Retrocalcaneal bursitis.
Retroachilles bursitis.
Infection (osteomyelitis, septic arthritis, cellulitis) of foot.
Peripheral vascular insufficiency.
Fracture.
Osteoarthritis.
Gout, pseudogout.
Neuropathy.
Tumor.

PALINDROMIC RHEUMATISM[16]

ICD-10CM #		
	M12.30	Palindromic rheumatism, unspecified site
	M12.319	Palindromic rheumatism, unspecified shoulder
	M12.329	Palindromic rheumatism, unspecified elbow
	M12.339	Palindromic rheumatism, unspecified wrist
	M12.349	Palindromic rheumatism, unspecified hand
	M12.359	Palindromic rheumatism, unspecified hip
	M12.369	Palindromic rheumatism, unspecified knee
	M12.379	Palindromic rheumatism, unspecified ankle and foot
	M12.38	Palindromic rheumatism, vertebrae
	M12.39	Palindromic rheumatism, multiple sites

Palindromic RA.
Essential palindromic rheumatism.
Crystal synovitis (gout, CPPD, pseudogout, calcific periarthritis).
Lyme borreliosis, stages 2 and 3.

COMMON MULTIPLE OSTEOSCLEROTIC BENIGN LESIONS

Bone infarcts.
Bone islands.
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Neuropathy.
Tumor.

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Neuropathy.
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Peripheral vascular insufficiency.
Fracture.
Bone cyst.
Osteoarthritis.
Gout, pseudogout.
Neuropathy.
Tumor.
Heel pad atrophy.
Plantar fascia rupture.

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	M12.39	Palindromic rheumatism, multiple sites

Palindromic RA.
Essential palindromic rheumatism.
Crystal synovitis (gout, CPPD, pseudogout, calcific periarthritis).
Lyme borreliosis, stages 2 and 3.

Sarcoidosis.
Whipple disease.
Acute rheumatic fever.
Reactive arthritis (rare).

PALMOPLANTAR HYPERKERATOSIS

ICD-10CM #		
	L85.1	Acquired keratosis [keratoderma] palmaris et plantaris
	L85.2	Keratosis punctata (palmaris et plantaris)
	L87.0	Keratosis follicularis et parafollicularis in cutem penetrans

Superficial skin infection.
Chronic eczema.
Repeated trauma.
Psoriasis.
Reiter syndrome.
Paraneoplastic acrokeratosis.

PALPITATIONS[76]

ICD-10CM #		
	R00.2	Palpitations

Anxiety.
Electrolyte abnormalities (hypokalemia, hypomagnesemia).
Exercise.
Hyperthyroidism.
Ischemic heart disease.
Ingestion of stimulant drugs (cocaine, amphetamines, caffeine).
Medications (digoxin, beta-blockers, calcium channel antagonists, hydralazines, diuretics, minoxidil).
Hypoglycemia in type 1 DM.
Mitral valve prolapse.
Wolff-Parkinson-White (WPW) syndrome.
Sick sinus syndrome.

PANCREATIC CALCIFICATIONS

ICD-10CM #		
	K86.1	Other chronic pancreatitis
	K86.8	Other specified diseases of pancreas

Chronic pancreatitis.
Hyperparathyroidism.
Metastatic neoplasm.
Pseudocyst.
Hereditary pancreatitis.
Cystoadenoma.
Cystoadenocarcinoma.
Cavernous lymphangioma.
Hemorrhage.
Acute pancreatitis (saponification).

PANCREATIC CYSTIC LESIONS[89]

ICD-10CM #		
	K86.2	Cyst of pancreas
	K86.3	Pseudocyst of pancreas

Pseudocyst.
Serous cystadenoma.
Mucinous cystic neoplasm.
Intraductal papillary mucinous neoplasm.
Solid and papillary epithelial neoplasm.
True epithelial cyst.
Duodenal diverticulum.
Cystic neuroendocrine tumors.
Ductal adenocarcinoma with cystic degeneration.
Cystic metastases.
Cystic degeneration in sarcoma, hemangioma, and paraganglioma.

PANCREATIC SOLID LESIONS[89]

ICD-10CM #		
	C25.9	Malignant neoplasm of pancreas, unspecified
	D13.6	Benign neoplasm of pancreas

Neoplastic solid tumors.
Ductal adenocarcinoma.
Pancreatic neuroendocrine tumor.
Pancreatic lymphoma.
Metastases to the pancreas.
Solid pseudopapillary tumor.
Pancreaticoblastoma.
Acinar cell carcinoma.
Mesenchymal tumors (sarcoma, fibrous histiocytoma, etc.).
Nonneoplastic solid lesions.
Focal chronic pancreatitis.
Autoimmune pancreatitis.
Groove pancreatitis.
Focal sparing of diffuse pancreatic fatty infiltration.
Intrapancreatic accessory spleen.
Developmental pancreas lobulation.
Sarcoidosis of the pancreas.

PANCREATITIS, ACUTE, IN CHILDREN[53]

ICD-10CM #		
	K85	Acute pancreatitis

CAUSES OF ACUTE PANCREATITIS IN CHILDREN

Drugs and Toxins
Acetaminophen overdose.
Alcohol.
L-Asparaginase.
Azathioprine.
Carbamazepine.
Cimetidine.
Corticosteroids.
Enalapril.
Erythromycin.
Estrogen.
Furosemide.
Isoniazid.
Lisinopril.
6-Mercaptopurine.
Methyldopa.
Metronidazole.
Organophosphate poisoning.
Pentamidine.
Retrovirals: DDC, DDI, tenofovir.
Sulfonamides: mesalamine, 5-aminosalicylates, sulfasalazine, trimethoprim/sulfamethoxazole.
Sulindac.
Tetracycline.
Thiazides.
Valproic acid.
Venom (spider, scorpion, Gila monster lizard).
Vincristine.

Genetic
Cationic trypsinogen gene *(PRSS1).*
Chymotrypsin C gene *(CTRC).*
Cystic fibrosis gene *(CFTR).*
Trypsin inhibitor gene *(SPINK1).*

Infectious
Ascariasis.
Coxsackie B virus.
Epstein-Barr virus.
Hepatitis A, B.
Influenza A, B.
Leptospirosis.
Malaria.
Measles.
Mumps.
Mycoplasma.
Reye syndrome: varicella, influenza B.
Rubella.
Rubeola.
Septic shock.

Obstructive
Ampullary disease.
Ascariasis.
Biliary tract malformations.
Choledochal cyst.
Choledochocele.
Cholelithiasis, microlithiasis, and choledocholithiasis (stones or sludge).
Duplication cyst.
Endoscopic retrograde cholangiopancreatography (ERCP) complication.
Pancreas divisum.
Pancreatic ductal abnormalities.
Postoperative.
Sphincter of Oddi dysfunction.
Tumor.

Systemic Disease
Autoimmune pancreatitis.
Brain tumor.
Collagen vascular diseases.
Crohn disease.
Diabetes mellitus.
Head trauma.
Hemochromatosis.
Hemolytic-uremic syndrome.
Hyperlipidemia: type I, IV, V.
Hyperparathyroidism/hypercalcemia.
Kawasaki disease.
Malnutrition.
Organic acidemia.
Peptic ulcer.
Periarteritis nodosa.
Renal failure.
Systemic lupus erythematosus.
Transplantation: bone marrow, heart, liver, kidney, pancreas.

Vasculitis.
Traumatic
Blunt injury.
Burns.
Child abuse.
Hypothermia.
Surgical trauma.
Total body cast.

PANCREATITIS, DRUG-INDUCED[7]

ICD-10CM # K85.3 Drug induced acute pancreatitis

DEFINITE

Acetaminophen.
Azathioprine.
Cimetidine.
Cisplatin.
Corticosteroids.
Didanosine.
Erythromycin.
Estrogens.
Ethyl alcohol.
Furosemide.
L-Asparaginase.
Mercaptopurine.
Metronidazole.
Methyldopa.
Nitrofurantoin.
Octreotide.
Organophosphates.
Pentamidine.
Ranitidine.
Tetracycline.
Salicylates.
Sulfonamides, trimethoprim-sulfamethoxazole, sulfasalazine.
Sulindac.
Valproic acid.

POSSIBLE

Bumetanide.
Carbamazepine.
Chlorthalidone.
Clonidine.
Colchicine.
Cyclosporine.
Cytarabine.
Diazoxide.
Enalapril.
Ergotamine.
Ethacrynic acid.
Indomethacin.
Isoniazid.
Isotretinoin.
Mefenamic acid.
Opiates.
Phenformin.
Piroxicam.
Procainamide.
Rifampin.
Thiazides.

PANCYTOPENIA[45]

ICD-10CM # D61.818 Other pancytopenia

PANCYTOPENIA WITH HYPOCELLULAR BONE MARROW

Acquired aplastic anemia.
Inherited aplastic anemia (Fanconi anemia and others).
Some myelodysplasia syndromes.
Rare aleukemic leukemia (acute myelogenous leukemia).
Some acute lymphoblastic leukemias.
Some lymphomas of bone marrow.

PANCYTOPENIA WITH CELLULAR BONE MARROW

Primary bone marrow diseases.
Myelodysplasia syndromes.
Paroxysmal nocturnal hemoglobinuria.
Myelofibrosis.
Some aleukemic leukemias.
Myelophthisis.
Bone marrow lymphoma.
Hairy cell leukemia.
Secondary to systemic diseases.
Systemic lupus erythematosus, Sjögren syndrome.
Hypersplenism.
Vitamin B_{12}, folate deficiency (familial defect).
Overwhelming infection.
Alcohol.
Brucellosis.
Ehrlichiosis.
Sarcoidosis.
Tuberculosis and atypical mycobacteria.

HYPOCELLULAR BONE MARROW ± CYTOPENIA

Q fever.
Legionnaires disease.
Mycobacteria.
Tuberculosis.[32]
Anorexia nervosa, starvation.
Hypothyroidism.

[32] Pancytopenia in tuberculosis only rarely is associated with a hypocellular bone marrow at biopsy or autopsy. Marrow failure in the setting of tuberculosis is almost always fatal; exceptional patients probably had underlying myelodysplasia or acute leukemia.

PANCYTOPENIA SYNDROME, INHERITED[53]

ICD-10CM # D61.818 Other pancytopenia

Fanconi anemia.
Shwachman-Diamond syndrome.
Dyskeratosis congenita.
Congenital amegakaryocytic thrombocytopenia.
Unclassified inherited bone marrow failure syndromes.
Other genetic syndromes:
- Down syndrome.
- Dubowitz syndrome.
- Seckel syndrome.
- Reticular dysgenesis.
- Schimke immunoosseous dysplasia.
- Familial aplastic anemia (non-Fanconi).
- Cartilage-hair hypoplasia.
- Noonan syndrome.

PAPILLEDEMA

ICD-10CM # H47.10 Unspecified papilledema

CNS infections (viral, bacterial, fungal).
Medications (lithium, cisplatin, corticosteroids, tetracycline, etc.).
Head trauma.
CNS neoplasm (primary or metastatic).
Pseudotumor cerebri.
Cavernous sinus thrombosis.
SLE.
Sarcoidosis.
Subarachnoid hemorrhage.
Carbon dioxide retention.
Arnold–Chiari malformation and other developmental or congenital malformations.
Orbital lesions.
Central retinal vein occlusion.
Hypertensive encephalopathy.
Metabolic abnormalities.

PAPULOSQUAMOUS DISEASES[32]

ICD-10CM # L98.8 Other specified disorders of the skin and subcutaneous tissue

Psoriasis.
Pityriasis rubra pilaris.
Pityriasis rosea.
Lichen planus.
Lichen nitidus.
Secondary syphilis.
Pityriasis lichenoides.
Parapsoriasis.
Mycosis fungoides.
Dermatophytosis.
Tinea versicolor.

PARALYSIS AND MUSCULAR RIGIDITY, DRUG-INDUCED[84]

ICD-10CM # G83 Other paralytic syndromes
R29.818 Other symptoms and signs involving the nervous system

SELECTED AGENTS ASSOCIATED WITH PARALYSIS AND MUSCULAR RIGIDITY

Paralysis
Medications and Industrial Toxins
Aminoglycoside antibiotics.
Beta-blockers.
Chloroquine (with color vision shift).
Cholinesterase inhibitors: neostigmine, pyridostigmine.
d-Penicillamine.
Pesticides: organophosphates, carbamates.
Pyrithioxine.
Trimethadione.
Biologic Toxins
Cobra venom.
Poison hemlock (*Conium maculatum*).
Scorpion fish (Scorpaenidae).

Snake venom, ticks, botulinum toxin.
Star of Bethlehem (*Hippobroma longiflora*).
Sweet pea (*Lathyrus odoratus*).
Tetrodotoxin (puffer fish, blue-ringed octopus, others).

Muscular Rigidity

Black widow spider venom (*Latrodectus mactans*).
Strychnine (*Strychnos nux vomica,* "slang nut").
Tetanus toxin.

PARALYTIC ILEUS[37]

ICD-10CM # K56 Paralytic ileus and intestinal obstruction

CAUSES OF A PARALYTIC ILEUS

Peritonitis.
Surgery.
Trauma:
- *Spine.*
- *Ribs.*
- *Hip.*
- *Retroperitoneum.*

Inflammation:
- *Appendicitis.*
- *Pancreatitis.*
- *Cholecystitis.*
- *Salpingitis.*

Congestive heart failure.
Pneumonia.
Renal colic.
Renal failure.
Leaking abdominal aortic aneurysm.
Low serum potassium.
Drugs (e.g. morphine).
Spinal lesions.
General debility or infection.
Vascular occlusion.

PARANEOPLASTIC NEUROLOGIC SYNDROMES

ICD-10CM # G13.0 Paraneoplastic neuromyopathy and neuropathy

Lambert-Eaton myasthenic syndrome.
Myasthenia gravis.
Guillain-Barré syndrome.
Amyotrophic lateral sclerosis.
Dermatomyositis.
Carcinoid myopathy.
Cerebellar degeneration.
Encephalomyelitis.
Optic neuritis, uveitis, retinopathy.
Stiff-man syndrome.
Autonomic neuropathy.
Brachial neuritis.
Sensory neuropathy.
Progressive multifocal leukoencephalopathy.

PARANEOPLASTIC SYNDROMES, ENDOCRINE[82]

ICD-10CM # G13.0 Paraneoplastic neuromyopathy and neuropathy

Hypercalcemia.
Syndrome of inappropriate secretion of antidiuretic hormone.
Hypoglycemia.
Zollinger-Ellison syndrome.
Ectopic secretion of human chorionic gonadotropin.
Cushing syndrome.

PARANEOPLASTIC SYNDROMES, NONENDOCRINE[82]

ICD-10CM # G13.0 Paraneoplastic neuromyopathy and neuropathy

CUTANEOUS

Dermatomyositis.
Acanthosis nigricans.
Sweet syndrome.
Erythema gyratum repens.
Systemic nodular panniculitis (Weber-Christian disease).

RENAL

Nephrotic syndrome.
Nephrogenic diabetes insipidus.

NEUROLOGIC

Subacute cerebellar degeneration.
Progressive multifocal leukoencephalopathy.
Subacute motor neuropathy.
Sensory neuropathy.
Ascending acute polyneuropathy (Guillain-Barré syndrome).
Myasthenic syndrome (Eaton-Lambert syndrome).

HEMATOLOGIC

Microangiopathic hemolytic anemia.
Migratory thrombophlebitis (Trousseau syndrome).
Anemia of chronic disease.

RHEUMATOLOGIC

Polymyalgia rheumatica.
Hypertrophic pulmonary osteoarthropathy.

PARAPARESIS, ACUTE OR SUBACUTE[80]

ICD-10CM # G82.2 Paraparesis

CAUSES OF ACUTE OR SUBACUTE PARAPARESIS

Trauma to a Previously Normal Spine

Vertebral Disease

Metastatic carcinoma.
Cervical spondylosis.
Dorsal disk prolapse.
Paget disease.
Rheumatoid arthritis.
Pott disease of spine.

Tumors

Extradural or intradural carcinoma, lymphoma, myeloma, leukemia.
Dorsal meningioma.
Neurofibroma.

Hematologic Disease

Any cause of thrombocytopenia.
Other clotting disorders.
Leukemia.
Anticoagulant treatment.
Epidural or intramedullary hemorrhage.

Infection

Epidural abscess.
TB abscess.
Syphilitic myelitis.
HIV infection.
Vascular myelopathy.

Vascular

Anterior spinal artery occlusion.
Infarction secondary to hypotension.
Embolic infarction.
Infarction secondary to aortic dissection.
Arteriovenous malformation: infarction or hemorrhage.
Primary intramedullary hemorrhage.
Vasculitis—polyarteritis nodosa (PAN).

Inflammatory

Myelitis of unknown cause.
Multiple sclerosis.
Systemic lupus erythematosus.
Sarcoidosis.

Metabolic

Subacute degeneration of the cord.

PARAPARESIS, CHRONIC PROGRESSIVE[80]

ICD-10CM # G82.2 Paraparesis

CAUSES OF CHRONIC PROGRESSIVE PARAPARESIS

Vertebral Disease

Cervical spondylosis.
Dorsal disk prolapse.
Rheumatoid arthritis.
Pott disease of spine.
Ankylosing spondylitis.

Tumors

Meningioma.
Neurofibroma.
Glioma.
Ependymoma.
Chordoma.
Lipoma.

Syringomyelia

With Arnold–Chiari malformation.
With tumor.
Posttraumatic.

Infection

Tropical spastic paraparesis (HTLV-1 infection).
Syphilitic myelitis.

Vascular

Arteriovenous malformation.

Inflammatory

Multiple sclerosis.
Sarcoidosis.
Radiation myelopathy.
Arachnoiditis.

Metabolic

Subacute combined degeneration of the cord.
Paget disease.

Degenerative

Motor neuron disease.

Hereditary

Hereditary spastic paraplegia.

PARAPARESIS, PAINLESS[51]

ICD-10CM # G82 Paraplegia (paraparesis) and quadriplegia (quadriparesis)

FREQUENTLY OCCURRING CAUSES OF PAINLESS PARAPARESIS

Inflammatory CNS diseases:
- Multiple sclerosis (MS).
- Neuromyelitis optica (NMO).

Genetic disorders:
- Spinal cerebellar ataxias (SCAs).
- Hereditary spastic paraparesis (HSP).

Infectious illnesses:
- Human T-lymphotropic virus type 1 (HTLV-1) myelopathy.

Compressive lesions*:
- Cervical spondylosis.
- Spinal meningiomas.
- Metastatic tumors.

Neurodegenerative illnesses:
- ALS.

Nutritional deficiencies:
- Copper deficiency.
- Vitamin B_{12} deficiency (combined system disease).

*May be associated with spine pain.

PARAPLEGIA

ICD-10CM # G82.20 Paraplegia, unspecified
G80.1 Spastic diplegic cerebral palsy
I69.969 Other paralytic syndrome following unspecified cerebrovascular disease affecting unspecified side

Trauma: penetrating wounds to motor cortex, fracture-dislocation of vertebral column with compression of spinal cord or cauda equina, prolapsed disk, electrical injuries.
Neoplasm: parasagittal region, vertebrae, meninges, spinal cord, cauda equina, Hodgkin disease, NHL, leukemic deposits, pelvic neoplasms.
Multiple sclerosis and other demyelinating disorders.
Mechanical compression of spinal cord, cauda equina, or lumbosacral plexus: Paget disease, kyphoscoliosis, herniation of intervertebral disk, spondylosis, ankylosing spondylitis, RA, aortic aneurysm.
Infections: spinal abscess, syphilis, TB, poliomyelitis, leprosy.
Thrombosis of superior sagittal sinus.
Polyneuritis: Guillain-Barré syndrome, diabetes, alcohol, beriberi, heavy metals.
Heredofamilial muscular dystrophies.
ALS.
Congenital and familial conditions: syringomyelia, myelomeningocele, myelodysplasia.
Hysteria.

PARASELLAR MASSES[62]

ICD-10CM # Varies with specific diagnosis

GENETIC

Transcription factor mutations (e.g., PROP1[33]).

CYSTS

Rathke.
Arachnoid.
Epidermoid.
Dermoid.

TUMORS

Hormone-secreting or nonfunctional pituitary adenoma.
Granular cell tumor.
Craniopharyngioma (cystic components).
Chordoma.
Meningioma.
Sarcoma.
Glioma.
Schwannoma.
Germ cell tumor.
Vascular tumor.
Solid or hematological metastasis.

MALFORMATION AND HAMARTOMAS

Ectopic pituitary, neurohypophyseal, or salivary tissue.
Hypothalamic hamartoma.
Gangliocytoma.

MISCELLANEOUS LESIONS

Aneurysms.
Hypophysitis.
Infections.
Sarcoidosis.
Giant cell granuloma.
Histiocytosis X.

[33] *PROP1,* Prophet of Pit1 (paired-like homeodomain transcription factor).

PARESTHESIAS

ICD-10CM # R20.2 Paresthesia of skin
G54.8 Other nerve root and plexus disorders

Multiple sclerosis.
Nutritional deficiencies (thiamin, vitamin B_{12}, folic acid).
Compression of spinal cord or peripheral nerves.
Medications (e.g., INH, lithium, nitrofurantoin, gold, cisplatin, hydralazine, amitriptyline, sulfonamides, amiodarone, metronidazole, dapsone, disulfiram, chloramphenicol).
Toxic chemicals (e.g., lead, arsenic, cyanide, mercury, organophosphates).
DM.
Myxedema.
Alcohol.
Sarcoidosis.
Neoplasms.
Infections (HIV, Lyme disease, herpes zoster, leprosy, diphtheria).
Charcot-Marie-Tooth syndrome and other hereditary neuropathies.
Guillain-Barré neuropathy.

PARKINSONISM[84]

ICD-10CM # G20 Parkinson disease
G21 Secondary parkinsonism
G21.9 Secondary parkinsonism, unspecified
G21.19 Other drug-induced Secondary parkinsonism
G21.4 Vascular parkinsonism
G21.2 Secondary parkinsonism due to other external agents

CAUSES OF PARKINSONISM

Static Injury/Structural Disorders
Basal ganglia infarcts.
Brain tumor.
Hydrocephalus.

Hereditary/Degenerative Disorders
Juvenile Parkinson disease.
Spinocerebellar ataxia.
Huntington disease (Westphal variant).
Pallidal-pyramidal disorder.
Neurodegeneration with brain iron accumulation (NBIA).
Pantothenate kinase-associated neurodegeneration (PKAN).
Rett syndrome.
Pelizaeus-Merzbacher disease.
Machado-Joseph disease (spinocerebellar ataxia type 3).
Neuronal ceroid lipofuscinoses.
Neuronal intranuclear inclusion body disease.

Metabolic Disorders
Dopa-responsive dystonia.
Tyrosine hydroxylase deficiency and other abnormalities of bioamine metabolism.
Abnormalities of folate metabolism.
Wilson disease.
Basal ganglia calcification (Fahr syndrome, hypoparathyroidism).

Infectious/Para-Infectious Disorders
Encephalitis lethargica (Von Economo disease).
Autoimmune encephalitides, including anti-NMDA receptor associated encephalitis.
Viral encephalitis.
Acute demyelinating encephalomyelitis.

Drugs/Toxins
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) poisoning.
Rotenone.
Tetrabenazine.
Reserpine.
Methyldopa.
Sedatives.
Neuroleptics.
Antiemetics.
Calcium channel blockers.
Isoniazid.
Serotonin reuptake inhibitors (sertraline, fluoxetine).
Meperidine.

Disorders That Mimic Parkinsonism
Catatonia.

Spasticity.
Hypothyroidism.
Depression (with psychomotor retardation).

PARKINSONISM AND OTHER ACUTE EXTRAPYRAMIDAL REACTIONS, DRUG-INDUCED[84]

ICD-10CM #		
	G21.19	Other drug-induced secondary parkinsonism

SELECTED AGENTS ASSOCIATED WITH PARKINSONISM AND OTHER ACUTE EXTRAPYRAMIDAL REACTIONS

Medications
Amiodarone.
Anticholinergic agents: benztropine.
Antidepressants (including selective serotonin reuptake inhibitors).
Antiepileptic drugs.
Antifungal agents.
Antihistamines.
Antipsychotics and related drugs (including "novel" agents).
Bethanechol.
Bupropion (acute).
Buspirone.
Captopril (acute).
Clonazepam.
Diazoxide.
Digoxin (chorea).
Estrogen (chorea).
Heroin.
Ketamine.
L-dopa.
Lithium (chorea).
l-Methyl-4-phenyl-1,2,3,6,-tetrahydropyridine (MPTP).
Metronidazole (oculogyric crisis).
Ofloxacin (Tourette-like syndrome).
Opiates/opioids.
Reserpine.
Stimulants.
Sulfasalazine (chorea).
Vinblastine.
Industrial Toxins
Carbon monoxide.
Metals: manganese, thallium, aluminum.
Methanol.
Trichloroethylene.
Biologic Toxins
Arthrinium mycotoxin.

PARKINSONISM-PLUS SYNDROMES

ICD-10CM #		
	G21.8	Other secondary parkinsonism

Parkinson disease.
Shy-Drager syndrome.
Corticobasal degeneration.
Olivo-ponto-cerebellar atrophy.
Dementia with Lewy bodies.
Progressive supranuclear palsy.
Striatonigral degeneration.

PAROTID SWELLING[8]

ICD-10CM #		
	K11.20	Sialoadenitis, unspecified
	B26.9	Mumps without complication
	K11.8	Other diseases of salivary glands
	K11.5	Sialolithiasis
	K11.3	Abscess of salivary gland

INFECTIOUS

Mumps.
Parainfluenza.
Influenza.
Cytomegalovirus infection.
Coxsackievirus infection.
Lymphocytic choriomeningitis.
Echovirus infection.
Suppuration (bacterial).
Actinomyces infection.
Mycobacterial infection.
Cat-scratch disease.

NONINFECTIOUS

Drug hypersensitivity (thiouracil, phenothiazines, thiocyanate, iodides, copper, isoprenaline, lead, mercury, phenylbutazone).
Sarcoidosis.
Tumors, mixed.
Hemangioma, lymphangioma.
Sialectasis.
Sjögren syndrome.
Mikulicz syndrome (scleroderma, mixed connective tissue disease, SLE).
Recurrent idiopathic parotitis.
Pneumoparotitis.
Trauma.
Sialolithiasis.
Foreign body.
Cystic fibrosis.
Malnutrition (marasmus, alcohol cirrhosis).
Dehydration.
DM.
Waldenström macroglobulinemia.
Reiter syndrome (reactive arthritis).
Amyloidosis.

NONPAROTID SWELLING

Hypertrophy of masseter muscle.
Lymphadenopathy.
Rheumatoid mandibular joint swelling.
Tumors of jaw.
Infantile cortical hyperostosis.

PELVIC AVULSION FRACTURES[71]

ICD-10CM #		
	M84.350A	Stress fracture pelvis, initial encounter
	M84.454A	Pathological fracture pelvis, initial encounter

ACUTE AVULSION FRACTURE

Nontraumatic avulsion fracture	Bone metastasis, prior graft harvesting.
Soft tissue injury	Tendon tear, muscle strain.
Aggressive-looking appearance	Osteomyelitis, tumor.
Incidental normal variant	Accessory bone.

CHRONIC AVULSION FRACTURE

Apophyseal avulsion injury	Apophysitis, traction periostitis.
Soft tissue injury	Bursitis, degenerative tendinopathy, calcific tendinitis.

PELVIC MASS

ICD-10CM #		
	R19.09	Other intraabdominal and pelvic swelling, mass and lump

Hemorrhagic ovarian cyst.
Simple ovarian cyst (follicle or corpus luteum).
Ovarian carcinoma, carcinoma of fallopian tube, colorectal carcinoma, metastatic carcinoma, prostate carcinoma, bladder carcinoma, lymphoma, Hodgkin disease.
Cystadenoma, teratoma, endometrioma.
Leiomyoma.
Leiomyosarcoma.
Diverticulitis, diverticular abscess.
Appendiceal abscess, tuboovarian abscess.
Ectopic pregnancy, intrauterine pregnancy.
Paraovarian cyst.
Hydrosalpinx.

PELVIC PAIN, CAUSES IN WOMEN[7]

ICD-10CM #		
	N94	Pain and other conditions associated with female genital organs and menstrual cycle
	G10.2	Pelvic and perineal pain
	G89.4	Chronic pain syndrome

POTENTIAL CAUSES OF PELVIC PAIN IN WOMEN

Reproductive Tract
Ovarian torsion.
Ovarian cyst.
Salpingitis/tubo-ovarian abscess.
Septic pelvic thrombophlebitis.
Endometritis.
Endometriosis.
Uterine perforation.
Uterine fibroids.
Dysmenorrhea.
Pregnancy-related
First Trimester
Ectopic pregnancy.
Threatened abortion.
Nonviable pregnancy.
Ovarian hyperstimulation syndrome.
Second and Third Trimesters
Placenta previa.

Placental abruption.
Round ligament pain.
Intestinal Tract
Appendicitis.
Diverticulitis.
Ischemic bowel.
Perforated viscus.
Bowel obstruction.
Incarcerated/strangulated hernia.
Inflammatory bowel disease.
Gastroenteritis.
Urinary Tract
Pyelonephritis.
Cystitis.
Ureteral stone.

PELVIC PAIN, CHRONIC[17]

ICD-10CM #		
	N94.89	Other specified conditions associated with female genital organs and menstrual cycle
	R10.2	Pelvic and perineal pain
	R10.10	Upper abdominal pain, unspecified
	R10.2	Pelvic and perineal pain
	R10.30	Lower abdominal pain, unspecified

GYNECOLOGIC DISORDERS

Primary dysmenorrhea.
Endometriosis.
Adenomyosis.
Adhesions.
Fibroids.
Retained ovary syndrome after hysterectomy.
Previous tubal ligation.
Chronic pelvic infection.

MUSCULOSKELETAL DISORDERS

Myofascial pain syndrome.

GASTROINTESTINAL DISORDERS

Irritable bowel syndrome.
Inflammatory bowel disease.

URINARY TRACT DISORDERS

Interstitial cystitis.
Nonbacterial urethritis.

PELVIC PAIN, GENITAL ORIGIN[58]

ICD-10CM #		
	N94.89	Other specified conditions associated with female genital organs and menstrual cycle
	R10.2	Pelvic and perineal pain
	R10.10	Upper abdominal pain, unspecified
	R10.2	Pelvic and perineal pain
	R10.30	Lower abdominal pain, unspecified

PERITONEAL IRRITATION

Ruptured ectopic pregnancy.
Ovarian cyst rupture.
Ruptured tuboovarian abscess.
Uterine perforation.

TORSION

Ovarian cyst or tumor.
Pedunculated fibroid.

INTRATUMOR HEMORRHAGE OR INFARCTION

Ovarian cyst.
Solid ovarian tumor.
Uterine leiomyoma.

INFECTION

Endometritis.
Pelvic inflammatory disease.
Trichomonas cervicitis or vaginitis.
Tuboovarian abscess.

PREGNANCY-RELATED

First Trimester
Ectopic pregnancy.
Abortion.
Corpus luteum hematoma.
Late Pregnancy
Placental problems.
Preeclampsia.
Premature labor.

MISCELLANEOUS

Endometriosis.
Foreign objects.
Pelvic adhesions.
Pelvic neoplasm.
Primary dysmenorrhea.

PELVIC PAIN, NON-PREGNANT FEMALE[1]

ICD-10CM #		
	N94.89	Other specified conditions associated with female genital organs and menstrual cycle
	R10.2	Pelvic and perineal pain
	R10.10	Upper abdominal pain, unspecified
	R10.30	Lower abdominal pain, unspecified

DIFFERENTIAL DIAGNOSIS OF PELVIC PAIN IN NONPREGNANT FEMALES

Gynecologic Diagnoses
Infectious:
- Vaginitis.
- Cervicitis.
- Endometritis.
- Tuboovarian abscess.
- Pelvic inflammatory disease.

Ovarian:
- Ovarian torsion.
- Ruptured ovarian cyst.
- Ovarian tumor.
- Degenerating ovarian tumor.
- Mittelschmerz.

Cervical:
- Cervical polyps.
- Cervical stenosis.
- Cervical cancer.

Uterine:
- Uterine fibroids.
- Degenerating uterine fibroids.
- Adenomyosis.
- Endometrial carcinoma.

Extrauterine:
- Endometriosis.
- Adhesions.
- Residual accessory ovary.

Nongynecologic Diagnoses
GI:
- Acute appendicitis.
- Mesenteric lymphadenitis.
- Diverticulitis.
- Inflammatory bowel disease.
- Irritable bowel syndrome.
- Bowel obstruction.
- Intraabdominal abscess.
- Colorectal carcinoma.

Urinary:
- Cystitis.
- Renal colic.
- Bladder cancer.

Musculoskeletal:
- Abdominal wall pain.
- Lumbar back pain.
- Fibromyalgia.
- Muscular strain.
- Piriformis syndrome.

Neurologic:
- Lumbar radiculopathy.
- Shingles.
- Spondylosis.

Psychologic:
- Personality disorders.
- Major depressive disorder.

PENILE RASH

ICD-10CM #		
	R21	Rash and other nonspecific skin eruption

Herpes simplex 2.
Balanitis (*Candida*).
Condyloma acuminatum.
Molluscum contagiosum.
Scabies.
Pediculosis pubis.
Pearly penile papules.
Lichen nitidus.
Fox-Fordyce disease (follicular papules).
Trauma.

PERIANAL PAIN[86]

ICD-10CM #		
	K62.89	Other specified diseases of anus and rectum

Fissure-in-ano.
Anal sepsis:
- Anal abscess.
- Anal fistula.

Hemorrhoids:
- Internal hemorrhoids.
- External hemorrhoids.

Pruritus ani.
Proctalgia fugax.

Chronic perianal pain syndromes:
Coccygodynia.
Descending perineum syndrome.
Levator ani syndrome.
Idiopathic perineal pain.

PERICARDIAL EFFUSION

ICD-10CM #		
	I30.9	Acute pericarditis, unspecified
	I31.3	Pericardial effusion

Pericarditis.
Uremia.
Myxedema.
Neoplasm (leukemia, lymphoma, metastatic).
Hemorrhage (trauma, leakage of thoracic aneurysm).
SLE, rheumatoid disease.
Myocardial infarction.

PERIPHERAL ARTERIAL DISEASE, NONATHEROSCLEROTIC CAUSES[46]

ICD-10CM #		
	I73.9	Peripheral vascular disease, unspecified
	I73.8	Other specified peripheral vascular diseases
	I79.8	Other disorders of arteries, arterioles, and capillaries in diseases classified elsewhere

NONATHEROSCLEROTIC CAUSES OF PERIPHERAL ARTERY DISEASE

Thromboembolism.
Atheroembolism.
Vasculitides:
Large vessel vasculitides, such as giant cell arteritis and Takayasu arteritis.
Small vessel vasculitides, such as thromboangiitis obliterans (Buerger disease).
Trauma.
Popliteal artery entrapment.
Cystic adventitial disease.
Fibromuscular dysplasia.
Iliac artery endofibrosis.

PERIODIC PARALYSIS, HYPERKALEMIC

ICD-10CM #		
	G83.9	Paralytic syndrome, unspecified

Chronic renal failure.
Renal insufficiency with excessive potassium supplementation.
Potassium-sparing diuretics.
Endocrinopathies (hypoaldosteronism, adrenal insufficiency).

PERIODIC PARALYSIS, HYPOKALEMIC

ICD-10CM #		
	G83.9	Paralytic syndrome, unspecified

Chronic diarrhea (laxative abuse, sprue, villous adenoma).
Potassium-depleting diuretics.
Medications (amphotericin B, corticosteroids).
Chronic licorice ingestion.
Thyrotoxicosis.
Renal tubular acidosis.
Conn syndrome.
Barter syndrome.
Barium intoxication.

PERITONEAL CARCINOMATOSIS[32]

ICD-10CM #		
	C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum

PRIMARY DISORDERS OF THE PERITONEUM: MESOTHELIOMA

Metastatic spread from:
Stomach.
Colon.
Pancreas.
Carcinoid.
Other Intraabdominal Organs
Ovary.
Pseudomyxoma peritonei.
Extraabdominal Primary Tumors
Breast.
Lung.
Hematologic Malignancy
Lymphoma.

PERITONEAL EFFUSION[40]

ICD-10CM #		
	R18	Ascites
	R85.9	Unspecified abnormal finding in specimens from digestive organs and abdominal cavity
	R88.8	Abnormal findings in other body fluids and substances

TRANSUDATES

Increased hydrostatic pressure or decreased plasma oncotic pressure.
Congestive heart failure.
Hepatic cirrhosis.
Hypoproteinemia.

EXUDATES

Increased capillary permeability or decreased lymphatic resorption.
Infections (TB, spontaneous bacterial peritonitis, secondary bacterial peritonitis).
Neoplasms (hepatoma, metastatic carcinoma, lymphoma, mesothelioma).
Trauma.
Pancreatitis.
Bile peritonitis (e.g., ruptured gallbladder).

CHYLOUS EFFUSION

Damage or obstruction to thoracic duct.
Trauma.
Lymphoma.
Carcinoma.
Tuberculosis.
Parasitic infection.

PERIUMBILICAL SWELLING

ICD-10CM #		
	R19.00	Intraabdominal and pelvic swelling, mass and lump, unspecified site

Umbilical hernia.
Lipoma.
Epigastric hernia.
Umbilical granuloma.
Omphalocele.
Gastroschisis.
Caput medusae.

PHARYNGEAL OBSTRUCTION, CAUSES[61]

ICD-10CM #	
	Varies with specific diagnosis

CAUSES OF PHARYNGEAL OBSTRUCTION

Malignant or benign tumors (e.g., papillomas, polyps).
Infection (e.g., croup, epiglottitis, tonsillar abscess).
Edema or hypertrophy (e.g., angioneurotic edema, anaphylactic reactions, postradiation therapy, obstructive sleep apnea).
Trauma (e.g., cricoid fracture, cervical subluxation, precervical hematoma).
Burn injury.
Extrinsic compression (e.g., goiter or pregnancy-related thyroid enlargement).
Foreign body.
Congenital web (infants).
Sarcoidosis and other granulomatous diseases.
Amyloid.

PHEOCHROMOCYTOMA-TYPE SPELLS[62]

ICD-10CM #		
	I15.2	Hypertension due to pheochromocytoma

DIFFERENTIAL DIAGNOSIS OF PHEOCHROMOCYTOMA-TYPE SPELLS

Endocrine Causes
Carbohydrate intolerance.
Hyperadrenergic spells.
Hypoglycemia.
Pancreatic tumors (e.g., insulinoma).
Pheochromocytoma.
Primary hypogonadism (menopausal syndrome).
Thyrotoxicosis.
Cardiovascular Causes
Angina.
Cardiovascular deconditioning.
Labile essential hypertension.
Orthostatic hypotension.
Paroxysmal cardiac arrhythmia.
Pulmonary edema.
Renovascular disease.
Syncope (e.g., vasovagal reaction).
Psychologic Causes
Factitious (e.g., drugs, Valsalva).
Hyperventilation.
Severe anxiety and panic disorders.
Somatization disorder.

Pharmacologic Causes
Chlorpropamide-alcohol flush.
Combination of a monoamine oxidase inhibitor and a decongestant.
Illegal drug ingestion (cocaine, phencyclidine, lysergic acid diethylamide).
Sympathomimetic drug ingestion.
Vancomycin ("red man syndrome").
Withdrawal of adrenergic-inhibitor.
Neurologic Causes
Autonomic neuropathy.
Cerebrovascular insufficiency.
Diencephalic epilepsy (autonomic seizures).
Migraine headache.
Postural orthostatic tachycardia syndrome.
Stroke.
Other Causes
Carcinoid syndrome:
Mast cell disease.
Recurrent idiopathic anaphylaxis.
Unexplained flushing spells.

PHOTODERMATOSES[32]

ICD-10CM #		
	L56.0	Drug phototoxic response
	L56.1	Drug photoallergic response
	L56.2	Photocontact dermatitis [berloque dermatitis]

Polymorphous light eruption.
Chronic actinic dermatitis.
Solar urticaria.
Phototoxicity and photoallergy.
Porphyrias.

PHOTOSENSITIVITY

ICD-10CM #		
	L56.0	Drug phototoxic response
	L56.1	Drug photoallergic response
	L56.2	Photocontact dermatitis [berloque dermatitis]

Solar urticaria.
Photoallergic reaction.
Phototoxic reaction.
Polymorphous light eruption.
Porphyria cutanea tarda.
SLE.
Drug induced (e.g., tetracyclines).

PIGMENTURIA[7]

ICD-10CM #		
	R82	Other abnormal findings in urine

HEMOGLOBINURIA

Hemolysis.

HEMATURIA

Renal causes.
Trauma.

ACUTE INTERMITTENT PORPHYRIA

Bilirubinuria
Food
Beets.
Drugs
Vitamin B_{12}.
Rifampin.
Phenytoin.
Laxatives.

PITUITARY REGION TUMORS[36]

ICD-10CM #	Varies with specific diagnosis

PRIMARY TUMORS IN THE SELLAR AND PARASELLAR REGION

Pituitary macroadenoma.
Meningioma.
Schwannoma (e.g., of fifth nerve).
Chordoma.
Chondrosarcoma.
Craniopharyngioma.
Rathke cleft cyst.
Dermoid.
Epidermoid.
Tuber cinereum hamartoma.
Optic glioma.
Germ cell tumors.

PLATELET DYSFUNCTION, DRUG-INDUCED[46]

ICD-10CM #	D69.1	Qualitative platelet defects

ANTI-PLATELET DRUGS

COX inhibitors: aspirin.
ADP receptor antagonists:
Thienopyridines: clopidogrel, ticlopidine, prasugrel.
Nonthienopyridines: ticagrelor, cangrelor.
$\alpha_{IIb}\beta_3$ inhibitors: abciximab, eptifibatide, tirofiban.
PDE inhibitors:
Nonselective PDE inhibitors: pentoxifylline, caffeine, theophylline.
PDE3 inhibitors: cilostazol, milrinone, anagrelide.
PDE5 inhibitors: dipyridamole, sildenafil.
Adenyl cyclase stimulators: epoprostenol, iloprost, beraprost.
Drugs that adversely affect platelet function.
NSAIDs: ibuprofen, naproxen, indomethacin.
Cardiovascular agents:
Calcium channel blockers: nifedipine, diltiazem, verapamil.
β-Blockers: propranolol.
Vasodilators: nitrates, nitroprusside.
Diuretics: furosemide.
Angiotensin II receptor antagonist: losartan, valsartan, and olmesartan.
Antibiotics: β-lactams, amphotericin, hydroxychloroquine, nitrofurantoin.
Antifungal drugs: Miconazole, amphotericin B:
Psychiatric drugs: TCAs, fluoxetine, chlorpromazine, promethazine, trifluoperazine.
Oncologic drugs: mithramycin, daunorubicin, BCNU, asparaginase, vincristine, dasatinib, ibrutinib.
Anesthetics: dibucaine, procaine, halothane, sevoflurane, propofol.
Plasma expanders: dextran, hydroxyl ethyl starch.
Heparins and thrombolytic agents.
Miscellaneous: clofibrate, statins, cocaine, ketanserin, radiographic contrast agents, antihistamines, immunosuppressive drugs.

ADP, Adenosine diphosphate; *BCNU,* carmustine; *COX,* cyclooxygenase; *NSAID,* nonsteroidal antiinflammatory drug; *PDE,* phosphodiesterase; *TCA,* tricyclic antidepressant.

PLEURAL EFFUSIONS

ICD-10CM #	J91.8	Pleural effusion in other conditions classified elsewhere

EXUDATIVE

Neoplasm: bronchogenic carcinoma, breast carcinoma, mesothelioma, lymphoma, ovarian carcinoma, multiple myeloma, leukemia, Meigs syndrome.
Infections: viral pneumonia, bacterial pneumonia, *Mycoplasma,* TB, fungal and parasitic diseases, extension from subphrenic abscess.
Trauma.
Collagen vascular diseases: SLE, RA, scleroderma, polyarteritis, granulomatosis with polyangiitis.
Pulmonary infarction.
Pancreatitis.
Postcardiotomy/Dressler syndrome.
Drug-induced SLE (hydralazine, procainamide).
Postabdominal surgery.
Ruptured esophagus.
Chronic effusion secondary to congestive failure.

TRANSUDATIVE

CHF.
Hepatic cirrhosis.
Nephrotic syndrome.
Hypoproteinemia from any cause.
Meigs syndrome.

PLEURAL EFFUSIONS, MALIGNANCY-ASSOCIATED

ICD-10CM #	C78.2	Secondary malignant neoplasm of pleura

Lung cancer	(30% to 40%)
Breast cancer	(20% to 25%)
Lymphoma	(10% to 15%)
Leukemia	(5% to 10%)
GI tract	(5%)
GU tract	(5%)
Reproductive	(3%)

PLEURAL HYPERPLASIA[77]

ICD-10CM #	Varies with specific diagnosis

BENIGN CAUSES OF PLEURAL HYPERPLASIA

Pleural infections.
Radiation.
Surgery.
Trauma.
Intracavitary treatments (chemotherapy or sclerosing agents).
Collagen vascular diseases.
Systemic immune diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, Wegener granulomatosis).
Subpleural pulmonary abnormalities (infarction, infection, neoplasia).
Pneumothorax.
Drug reactions (nitrofurantoin, bromocriptine, methysergide, procarbazine).
Pancreatitis, uremia.
Pneumoconiosis (asbestosis).

PLEURAL MASSES[77]

ICD-10CM # Varies with specific diagnosis

CAUSES OF PLEURAL MASSES

Inflammatory pleural reactions:
- Reactive mesothelial hyperplasia or organizing pleuritis versus atypical mesothelial hyperplasia.
- Nodular pleural plaques.

Pulmonary tumors that may resemble pleural tumors:
- Inflammatory pseudotumor of the lung.

Benign pleural tumors:
- Solitary fibrous tumor.
- Lipomas and lipoblastomas.
- Adenomatous tumors.
- Calcifying fibrous tumors.
- Mesothelial cysts.
- Multicystic mesothelioma.
- Schwannoma.

Pleural tumors with low malignant potential:
- Desmoid tumors.
- Well-differentiated papillary mesothelioma.
- Pleural thymoma.

Primary malignant pleural tumors that may look like benign tumors:
- Malignant solitary fibrous tumor.
- Pleuropulmonary blastoma.
- Localized malignant mesothelioma.
- Vascular sarcoma.
- Liposarcoma.
- Pleuropulmonary synovial sarcoma.
- Askin tumor or primitive neuroectodermal tumor (PNET).
- Desmoplastic small round cell tumor.

Malignant pleural tumors:
- Metastatic malignancies to the pleura.
- Malignant mesothelioma.

PNEUMATOSIS INTESTINALIS IN NEONATE AND OLDER CHILD[36]

ICD-10CM # Varies with specific diagnosis

CAUSES OF PNEUMATOSIS INTESTINALIS IN THE NEONATE AND THE OLDER CHILD

Necrotizing enterocolitis.
Bowel ischemia, inflammation, and obstruction.
Cyanotic congenital heart disease.
Hirschsprung disease.
Gastroschisis.
Anorectal atresia.
Inflammatory bowel disease.
Lymphoma.
Leukemia.
CMV and rotavirus gastroenteritis.
Colonoscopy.
Caustic ingestion.
Short bowel syndrome.
Congenital immune deficiency states.
Clostridium infection.
Chronic steroid use.
Posthepatic, renal, or bone marrow transplant.
Collagen vascular disease.
Graft-versus-host disease.
AIDS.

PNEUMONIA, CHRONIC[10]

ICD-10CM #

J15.9	Unspecified bacterial pneumonia
J12.9	Viral pneumonia, unspecified
B25.0	Cytomegaloviral pneumonitis
J18.0	Bronchopneumonia, unspecified organism

INFECTIOUS AGENTS THAT TYPICALLY CAUSE CHRONIC PNEUMONIA

Bacteria
Mixed aerobic and anaerobic bacteria.
Actinomyces spp.
Nocardia spp.
Rhodococcus equi.
Burkholderia pseudomallei.
Mycobacteria
Mycobacterium tuberculosis.
Mycobacterium kansasii.
Mycobacterium avium complex.
Mycobacterium abscessus.
Mycobacterium terrae.
Fungi
Aspergillus spp.
Blastomyces dermatitidis.
Coccidioides spp.
Cryptococcus neoformans.
Cryptococcus gattii.
Dark-walled molds.
Emmonsia parvum var. *crescens.*
Histoplasma capsulatum.
Sporothrix schenckii complex.
Paracoccidioides brasiliensis.
Penicillium marneffei.
Scedosporium apiospermum.
Parasites
Dirofilaria:
- *Echinococcus granulosus.*
- *Filaria (tropical pulmonary eosinophilia).*
- *Paragonimus westermani.*

NONINFECTIOUS CAUSES OF CHRONIC PNEUMONIA

Neoplasia
Carcinoma (primary or metastatic).
Hodgkin disease and non-Hodgkin lymphoma.
Other lymphoproliferative disorders.
Cystic Fibrosis
Sarcoidosis
Amyloidosis
Vasculitis (Autoimmune Diseases)
Systemic lupus erythematosus.
Polyarteritis nodosa.
Granulomatosis with polyangiitis.
Allergic angiitis and granulomatosis (Churg-Strauss syndrome).
Goodpasture syndrome.
Microscopic polyangiitis.
Lymphomatoid granulomatosis.
Progressive systemic sclerosis.
Rheumatoid arthritis.
Mixed connective tissue syndrome (overlap syndrome).
Chemicals, Drugs
Radiation
Recurrent Pulmonary Emboli
Bronchial Obstruction with Atelectasis (e.g., Tumor, Foreign Body)
Pulmonary sequestration
Pulmonary infiltration with eosinophilia syndrome (Löffler syndrome—usually transient.)
Pneumonia plus asthma (e.g., allergic bronchopulmonary aspergillosis).
Bronchocentric granulomatosis.
Chronic eosinophilic pneumonia.
Pneumoconiosis
Asbestosis.
Berylliosis.
Silicosis.
Anthracosilicosis.
Chronic Form of Extrinsic Allergic Alveolitis (Hypersensitivity Pneumonitis)

OTHER LUNG DISEASES: CAUSE UNKNOWN

Chronic Organizing Pneumonia
Chronic Interstitial Pneumonia (Fibrosing Alveolitis, Idiopathic Pulmonary Fibrosis)
Usual interstitial pneumonia (UIP).
Desquamative interstitial pneumonia (DIP).
Lymphocytic interstitial pneumonia (LIP).
Giant cell interstitial pneumonia (GIP).
Eosinophilic granuloma (histiocytosis X).
Lymphangioleiomyomatosis.
Pulmonary alveolar proteinosis.
Pulmonary alveolar microlithiasis.
Idiopathic pulmonary hemosiderosis.
Angiocentric immunoproliferative lesions.

PNEUMONIA MIMICS[13]

ICD-10CM # Varies with specific diagnosis

NONINFECTIOUS CAUSES THAT MAY PRESENT AS PNEUMONIA

Radiologic Technique
Inadequate inspiration.
Breast shadow.
Thymus.
Uneven grid on film.
Underpenetrated film.
Primary Pulmonary
Asthma.
Bronchiectasis.
Atelectasis.
Bronchopulmonary dysplasia.
Cystic fibrosis.
Pulmonary sequestration.
Congenital cystic adenomatoid malformation.
α_1-Antitrypsin deficiency.
Aspiration
Foreign body.
Chemical.
Recurrent caused by anatomic or physiologic disorders.
Primary Cardiac
Congenital heart disease.
CHF
Pulmonary Infarction
Sickle cell vasoocclusive crisis.
Pulmonary embolism.

Collagen Vascular Disorders
Acute Respiratory Distress Syndrome
Pleural effusion
Neoplasm.

PNEUMONIA, NONRESPONDING, CAUSES[61]

ICD-10CM #	J15.9	Unspecified bacterial pneumonia
	J12.9	Viral pneumonia, unspecified
	B25.0	Cytomegaloviral pneumonitis
	J18.0	Bronchopneumonia, unspecified organism

CAUSES OF NONRESPONDING PNEUMONIA

Infectious Pneumonia
Resistant microorganisms:
- Community-acquired pneumonia (e.g., *Streptococcus pneumoniae, Staphylococcus aureus*).
- *Nosocomial pneumonia* (e.g., *Acinetobacter*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*).

Uncommon microorganisms (e.g., *Mycobacterium tuberculosis, Nocardia* spp., fungi, *Pneumocystis jirovecii*).
Complications of pneumonia:
Empyema.
Abscess or necrotizing pneumonia.
Metastatic infection.
Noninfectious Pneumonia
Neoplasms.
Pulmonary hemorrhage.
Pulmonary embolism.
Sarcoidosis.
Eosinophilic pneumonia.
Pulmonary edema.
Acute respiratory distress syndrome.
Bronchiolitis obliterans with organizing pneumonia.
Drug-induced pulmonary disease.
Pulmonary vasculitis.

PNEUMONIA, RECURRENT

ICD-10CM #	J15.9	Unspecified bacterial pneumonia
	J12.9	Viral pneumonia, unspecified
	B25.0	Cytomegaloviral pneumonitis
	J18.0	Bronchopneumonia, unspecified organism

Mechanical obstruction from neoplasm.
Chronic aspiration (tube feeding, alcoholism, CVA, neuromuscular disorders, seizure disorder, inability to cough).
Bronchiectasis.
Kyphoscoliosis.
COPD, CHF, asthma, silicosis, pulmonary fibrosis, cystic fibrosis.
Pulmonary TB, chronic sinusitis.
Immunosuppression (HIV, corticosteroids, leukemia, chemotherapy, splenectomy).

PNEUMOPERITONEUM, NEONATAL[36]

ICD-10CM # Varies with specific diagnosis

CAUSES OF NEONATAL PNEUMOPERITONEUM

Necrotizing enterocolitis.
Spontaneous perforation of a hollow viscus:
- Stomach.
- Duodenum.
- Ileum.
- Colon.

Malrotation and volvulus.
Distal obstruction.
Perforation of Meckel diverticulum.
Anterior abdominal wall defects:
- Pentalogy of Cantrell.
- Omphalocele.
- Gastroschisis.
- Cloacal exstrophy.

Stress and peptic ulcers.
Mechanical ventilation (air leak) or resuscitation ("bagging").
Post-laparotomy.
Iatrogenic gastric perforation with an orogastric tube.
Iatrogenic colon perforation:
- Thermometer.
- During an enema.

Indomethacin.
Dexamethasone treatment.

PNEUMOTHORAX, IN CHILDREN[53]

ICD-10CM #	J93.0	Spontaneous tension pneumothorax
	J93	Pneumothorax
	J93.9	Pneumothorax unspecified

SPONTANEOUS

Primary idiopathic—usually resulting from ruptured subpleural blebs.
Secondary blebs.
Congenital lung disease:
- Congenital cystic adenomatoid malformation.
- Bronchogenic cysts.
- Pulmonary hypoplasia.

Conditions associated with increased intrathoracic pressure:
- Asthma.
- Bronchiolitis.
- Air-block syndrome in neonates.
- Cystic fibrosis.
- Airway foreign body.

Infection:
- Pneumatocele.
- Lung abscess.
- Bronchopleural fistula.

Diffuse lung disease:
- Langerhans cell histiocytosis.
- Tuberous sclerosis.
- Marfan syndrome.
- Ehlers-Danlos syndrome.

Metastatic neoplasm—usually osteosarcoma (rare).

TRAUMATIC

Noniatrogenic:
- Penetrating trauma.
- Blunt trauma.
- Loud music (air pressure).

Iatrogenic:
- Thoracotomy.
- Thoracoscopy, thoracentesis.
- Tracheostomy.
- Tube or needle puncture.

Mechanical ventilation.

POLIOSIS[12]

ICD-10CM # Varies with specific diagnosis

CAUSES OF POLIOSIS

Ocular
Chronic anterior blepharitis.
Sympathetic ophthalmitis.
Idiopathic uveitis.
Systemic
Vogt–Koyanagi–Harada syndrome.
Waardenburg syndrome.
Vitiligo.
Marfan syndrome.
Tuberous sclerosis.

POLYCYTHEMIA

ICD-10CM #	D45	Polycythemia primary
	D75.1	Polycythemia secondary

Tobacco abuse.
Chronic lung disease.
High altitude.
Sleep apnea.
Right-to-left cardiac shunts.
Erythropoietin administration.
Androgens/anabolic steroids.
Polycystic kidney disease.
Renal cell carcinoma.
Hepatocellular carcinoma.
Polycythemia vera.
Carbon monoxide exposure.
Primary familial and congenital polycythemia.
High-oxygen–affinity hemoglobins.
Uterine leiomyoma, meningioma, pheochromocytoma, parathyroid carcinoma.
Cobalt exposure.

POLYCYTHEMIAS, DIFFERENTIAL DIAGNOSIS[44]

ICD-10CM #	D45	Polycythemia primary
	D75.1	Polycythemia secondary

DIFFERENTIAL DIAGNOSIS OF THE POLYCYTHEMIAS

Relative or Spurious Polycythemia
Decreased plasma volume—reduced fluid intake, marked loss of body fluids (diaphoresis, vomiting, diarrhea, "third spacing").

Gaisböck syndrome.
Overfilling of blood in collection vacuum tubes.
Absolute polycythemia
Secondary polycythemia.
Acquired.
Hypoxia:
  Pulmonary disease.
  Cyanotic congenital heart disease.
  Hypoventilation syndromes:
    Sleep apnea.
    Pickwickian syndrome.
    High altitude.
    Smokers' polycythemia, hookah polycythemia, carbon monoxide intoxication caused by industrial exposure.
Postrenal transplantation erythrocytosis.
Aberrant erythropoietin production.
Tumors:
  Renal cell carcinoma.
  Wilms tumor.
  Hepatic carcinoma.
  Uterine leiomyomata.
Virilizing ovarian tumors.
Vascular cerebellar tumors.
Miscellaneous renal and hepatic disorders:
  Solitary renal cysts.
  Polycystic kidney disease.
  Renal artery stenosis hydronephrosis.
  Viral hepatitis.
  Endocrine disorders:
  Cushing syndrome.
  Primary aldosteronism.
  Androgen use.
  Erythropoietin use.
  Congenital polycythemias:
    Abnormal high-affinity hemoglobin variants.
    Bisphosphoglycerate deficiency.
    Congenital methemoglobinemia.
    Chuvash polycythemia (von Hippel Lindau mutations).
    Prolyl hydroxylase mutations.
    Hypoxia-inducible factor gene mutations.
Primary polycythemias:
  Primary congenital and familial polycythemia.
  Polycythemia vera.

POLYCYTHEMIA, RELATIVE VERSUS ABSOLUTE[45]

ICD-10CM # D75.1 Secondary polycythemia

RELATIVE OR SPURIOUS POLYCYTHEMIA

Decreased plasma volume—reduced fluid intake, marked loss of body fluids (diaphoresis, vomiting, diarrhea, "third-spacing").
Gaisböck syndrome.
Overfilling of blood in collection vacuum tubes.

ABSOLUTE POLYCYTHEMIA

Primary Congenital and Familial Polycythemia
Secondary Polycythemia Acquired
Hypoxia:
  Pulmonary disease.
  Cyanotic congenital heart disease.
  Hypoventilation syndromes: sleep apnea, Pickwickian syndrome.
  High altitude.
  Smokers' polycythemia, carbon monoxide intoxication due to industrial exposure.
Postrenal transplantation erythrocytosis.
Aberrant erythropoietin production.
Tumors: renal cell carcinoma, Wilms tumor, hepatic carcinoma, uterine leiomyomata, virilizing ovarian tumors, vascular cerebellar tumors.
Miscellaneous renal and hepatic disorders: solitary renal cysts, polycystic kidney disease, renal artery stenosis, hydronephrosis, viral hepatitis.
Endocrine disorders: Cushing syndrome, primary aldosteronism.
Androgen use.
Erythropoietin use.
Congenital:
  Abnormal high-affinity hemoglobin variants.
  Bisphosphoglycerate deficiency.
  Congenital methemoglobinemia.
  Chuvash polycythemia (von Hippel–Lindau mutations).
  Prolyl hydroxylase mutations.

POLYCYTHEMIA VERA

POLYMYALGIAS[41]

ICD-10CM # M35.3 Polymyalgia rheumatica

DISEASE ENTITIES WITH POLYMYALGIAS

Rheumatoid arthritis.
Rotator cuff syndrome.
Osteoarthritis of shoulder and hip joints.
Fibromyalgia.
Polymyositis/dermatomyositis.
Spondyloarthritis.
Systemic lupus erythematosus.
Vasculitides.
Paraneoplastic myalgias.
Infection-associated myalgias.
Statin therapy.
RS3PE (remitting seronegative symmetric synovitis and pitting edema).
Parkinson disease.
Hypothyroidism.

POLYNEUROPATHY[93]

ICD-10CM # G61.9 Inflammatory polyneuropathy, unspecified

PREDOMINANTLY MOTOR

Guillain-Barré syndrome.
Porphyria.
Diphtheria.
Lead.
Hereditary sensorimotor neuropathy, types I and II.
Paraneoplastic neuropathy.

PREDOMINANTLY SENSORY

Diabetes.
Amyloidosis.
Leprosy.
Lyme disease.
Paraneoplastic neuropathy.
Vitamin B_{12} deficiency.
Hereditary sensory neuropathy, types I-IV.

PREDOMINANTLY AUTONOMIC

Diabetes.
Amyloidosis.
Alcoholic neuropathy.
Familial dysautonomias.

MIXED SENSORIMOTOR

Systemic diseases: renal failure, hypothyroidism, acromegaly, RA, periarteritis nodosa, SLE, multiple myeloma, macroglobulinemia, remote effect of malignancy.
Medications: isoniazid, nitrofurantoin, ethambutol, chloramphenicol, chloroquine, vincristine, vinblastine, dapsone, disulfiram, diphenylhydantoin, cisplatin, 1-tryptophan.
Environmental toxins: *N*-hexane, methyl *N*-butyl ketone, acrylamide, carbon disulfide, carbon monoxide, hexachlorophene, organophosphates.
Deficiency disorders: malabsorption, alcoholism, vitamin B_1 deficiency, Refsum disease, metachromatic leukodystrophy.

POLYNEUROPATHY, DEMYELINATING[7]

ICD-10CM # G37.9 Demyelinating disease of central nervous system, unspecified

Guillain-Barré syndrome:
  Acute inflammatory demyelinating polyradiculoneuropathy (AIDP).
  Acute motor axonal neuropathy (AMAN).
  Acute motor and sensory axonal neuropathy (AMSAN).
  Miller Fisher syndrome.
Chronic inflammatory demyelinating polyradiculoplexo-neuropathy.
Malignancy.
HIV.
Hepatitis B.
Buckthorn.
Diphtheria.

POLYNEUROPATHY, DISTAL SENSORIMOTOR[7]

ICD-10CM # G63 Polyneuropathy in diseases classified elsewhere

Diabetes mellitus.
Alcoholism.
Neoplastic or paraneoplastic.
Hereditary motor and sensory neuropathies (Charcot-Marie-Tooth).
Cryptogenic sensorimotor polyneuropathies (CSPN).
HIV.
Toxins:
  Organic or industrial agents:
    Acrylamide.
    Allyl chloride.
    Carbon disulfide.
    Ethylene oxide.
    Hexacarbons.
    Methyl bromide.

Organophosphate-induced delayed polyneuropathy (OPIDP).
Polychlorinated biphenyls (PCBs).
Trichloroethylene.
Vacor.
Metals:
Arsenic.
Gold.
Mercury (inorganic).
Thallium.
Therapeutic agents:
Amiodarone.
Antiretrovirals.
Dapsone.
Disulfiram.
Isoniazid.
Metronidazole.
Nitrofurantoin.
Paclitaxel (Taxol).
Phenytoin.
Statins (HMG-CoA reductase inhibitors).
Thalidomide.
Vinca alkaloids (vincristine, vinblastine).
Nutritional:
Beriberi (thiamine or vitamin B_1).
Pellagra (niacin, B vitamins).
Pernicious anemia (vitamin B_{12}).
Pyridoxine deficiency (vitamin B_6).
End-organ dysfunction
Acromegaly.
Chronic pulmonary disease.
Hypothyroidism.
Renal failure (uremic neuropathy).
Paraproteinemias:
Amyloidosis.
Monoclonal gammopathy of unknown significance (MGUS).
Multiple myeloma.
Waldenström macroglobulinemia.
Porphyria.

HMG-CoA, Hydroxymethylglutaryl coenzyme A.

POLYNEUROPATHY, DRUG-INDUCED[93]

ICD-10CM #	G62.0	Drug-induced polyneuropathy

DRUGS IN ONCOLOGY

Vincristine.
Procarbazine.
Cisplatin.
Misonidazole.
Metronidazole
Taxol.

DRUGS IN INFECTIOUS DISEASES

Isoniazid.
Nitrofurantoin.
Dapsone.
ddC (dideoxycytidine).
ddI (dideoxyinosine).

DRUGS IN CARDIOLOGY

Hydralazine.
Perhexiline maleate.
Procainamide.
Disopyramide.

DRUGS IN RHEUMATOLOGY

Gold salts.
Chloroquine.

DRUGS IN NEUROLOGY AND PSYCHIATRY

Diphenylhydantoin.
Glutethimide.
Methaqualone.

MISCELLANEOUS

Disulfiram (Antabuse).
Vitamin: (pyridoxine in megadoses).

POLYNEUROPATHY, SYMMETRIC[93]

ICD-10CM #	G61.9	Inflammatory polyneuropathy, unspecified

ACQUIRED NEUROPATHIES

Toxic:
Drugs.
Industrial toxins.
Heavy metals.
Abused substances.
Metabolic/endocrine:
Diabetes.
Chronic renal failure.
Hypothyroidism.
Polyneuropathy of critical illness.
Nutritional deficiency:
Vitamin B_{12} deficiency.
Alcoholism.
Vitamin E deficiency.
Paraneoplastic:
Carcinoma.
Lymphoma.
Plasma cell dyscrasia:
Myeloma, typical, atypical, and solitary forms.
Primary systemic amyloidosis.
Idiopathic chronic inflammatory demyelinating polyneuropathies.
Polyneuropathies associated with peripheral nerve autoantibodies.
AIDS.

INHERITED NEUROPATHIES

Neuropathies with Biochemical Markers
Refsum disease.
Bassen-Kornzweig disease.
Tangier disease.
Metachromatic leukodystrophy.
Krabbe disease.
Adrenomyeloneuropathy.
Fabry disease.
Neuropathies without Biochemical Markers or Systemic Involvement
Hereditary motor neuropathy.
Hereditary sensory neuropathy.
Hereditary sensorimotor neuropathy.

POLYURIA

ICD-10CM #	R35.8	Other polyuria

DM.
Diabetes insipidus.
Primary polydipsia (compulsive water drinking).
Hypercalcemia.
Hypokalemia.
Postobstructive uropathy.
Diuretic phase of renal failure.
Drugs: diuretics, caffeine, alcohol, lithium.
Sickle cell trait or disease, chronic pyelonephritis (failure to concentrate urine).
Anxiety, cold weather.

POPLITEAL SWELLING

ICD-10CM#	I87.1	Compression of vein
	I72.4	Aneurysm of artery of lower extremity
	S85.009A	Unspecified injury of popliteal artery, unspecified leg, initial encounter
	I77.3	Arterial fibromuscular dysplasia
	M71.20	Synovial cyst of popliteal space [Baker], unspecified knee
	I80.3	Phlebitis and thrombophlebitis of lower extremities, unspecified
	M66.369	Spontaneous rupture of flexor tendons, unspecified lower leg

Phlebitis (superficial).
Lymphadenitis.
Trauma: fractured tibia or fibula, contusion, traumatic neuroma.
DVT.
Ruptured varicose vein.
Baker cyst.
Popliteal abscess.
Osteomyelitis.
Ruptured tendon.
Aneurysm of popliteal artery.
Neoplasm: lipoma, osteogenic sarcoma, neurofibroma, fibrosarcoma.

PORTAL HYPERTENSION[3]

ICD-10CM #	K76.6	Portal hypertension

INCREASED RESISTANCE TO FLOW

Presinusoidal
Portal or splenic vein occlusion (thrombosis, tumor).
Schistosomiasis.
Congenital hepatic fibrosis.
Sarcoidosis.
Sinusoidal
Cirrhosis (all causes).
Alcoholic hepatitis.
Postsinusoidal
Venoocclusive disease.
Budd-Chiari syndrome.
Constrictive pericarditis.

INCREASED PORTAL BLOOD FLOW

Splenomegaly not caused by liver disease.
Arterioportal fistula.

POSTMENOPAUSAL BLEEDING

ICD-10CM # N95.0 Postmenopausal bleeding

Hormone replacement therapy.
Neoplasm (uterine, ovarian, cervical, vaginal, vulvar).
Atrophic vaginitis.
Vaginal infection.
Polyp.
Extragenital (GI, urinary).
Tamoxifen.
Trauma.

POSTURAL HYPOTENSION, NONNEUROLOGIC CAUSES

ICD-10CM # I95.1 Orthostatic hypotension

Diuretics and hypertensive agents.
GI hemorrhage.
Alcohol.
Excessive heat.
Rapid volume loss from diarrhea, vomiting.
Hemodialysis.
Extensive burns.
Pyrexia.
Aortic stenosis (impaired output).
Constrictive pericarditis, atrial myxoma (impaired cardiac filling).
Adrenal insufficiency.
Diabetes insipidus.
Vasodilatory agents (e.g., nitrates).

PREMATURE GRAYING, SCALP HAIR

ICD-10CM # Varies with specific diagnosis

Chemical exposure (e.g., phenol/catechol derivatives, sulfhydryls, arsenic).
Physical agents (e.g., ionizing radiation, lasers).
Hyperthyroidism.
Vitamin B_{12} deficiency.
Down syndrome.
Chronic and severe protein deficiency.
Vitiligo.
Idiopathic.
Myotonic dystrophy.
Ataxia-telangiectasia.
Progeria.
Werner syndrome.

PREMATURE VENTRICULAR CONTRACTIONS AND VENTRICULAR TACHYCARDIA[7]

ICD-10CM #		
	I49.40	Unspecified premature depolarization
	I47.2	Ventricular tachycardia

CAUSES OF PREMATURE VENTRICULAR CONTRACTIONS AND VENTRICULAR TACHYCARDIA

Acute or previous myocardial infarction/ischemia.
Hypokalemia.
Hypoxemia.
Ischemic heart disease.
Valvular disease.
Catecholamine excess.[34]
Other drug intoxications (especially cyclic antidepressants).
Idiopathic causes.[35]
Digitalis toxicity.
Hypomagnesemia.
Hypercapnia.
Class I antidysrhythmic agents.
Ethanol.
Myocardial contusion.
Cardiomyopathy.
Acidosis.
Alkalosis.
Methylxanthine toxicity.

[34] Relative increase in sympathetic tone from drugs (direct or indirect) or conditions that augment catecholamine release or decrease parasympathetic tone.

[35] Isolated premature ventricular contractions (PVCs) can occur in up to 50% of young subjects without obvious cardiac or noncardiac disease; however, multiform and repetitive PVCs and ventricular tachycardia are rarely seen in this population.

PRESACRAL MASSES IN CHILDREN[74]

ICD-10CM # Varies with specific diagnosis

PRESACRAL MASSES IN CHILDREN

Solid
Sacrococcygeal teratoma.
Neuroblastoma.
Rhabdomyosarcoma.
Fibroma.
Lipoma.
Leiomyoma.
Lymphoma.
Hemangioendothelioma.
Sacral bone tumors.
Cystic
Abscess.
Rectal duplication.
Hematoma.
Lymphocele.
Neurenteric cyst.
Sacral osteomyelitis.
Ulcerative colitis.
Anterior meningocele.

PROLONGED QT SYNDROMES[60]

ICD-10CM # I45.81 Long QT syndrome

CLASSIFICATION AND CAUSES OF PROLONGED QT SYNDROMES THAT PRODUCE TORSADES DE POINTES

Pause Dependent (Acquired)
Drug induced: class IA and IC antidysrhythmics; many phenothiazines and butyrophenones (notably haloperidol and droperidol), cyclic antidepressants, antibiotics (especially macrolides), organophosphates, antihistamines, antifungals, antiseizure and antiemetic agents.
Electrolyte abnormalities: hypokalemia, hypomagnesemia, hypocalcemia (rarely).
Diet related: starvation, low protein.
Severe bradycardia or atrioventricular block.
Hypothyroidism.
Contrast injection.
Cerebrovascular accident (especially intraparenchymal).
Myocardial ischemia.
Adrenergic Dependent (Tachycardia Prompted)
Congenital:
- Jervell and Lange-Nielsen syndrome (deafness, autosomal recessive).
- Romano-Ward syndrome (normal hearing, autosomal dominant).
- Sporadic (normal hearing, no familial tendency).
- Mitral valve prolapse.

Acquired (Rare):
- Cerebrovascular disease (especially subarachnoid hemorrhage).
- Autonomic surgery: radical neck dissection, carotid endarterectomy, truncal vagotomy.

PROPTOSIS[67]

ICD-10CM #		
	H05.20	Unspecified exophthalmos
	H05.2	Ocular proptosis

Thyrotoxicosis.
Orbital pseudotumor.
Optic nerve tumor.
Cavernous sinus AV fistula, cavernous sinus thrombosis.
Cellulitis.
Metastatic tumor to orbit.

PROPTOSIS AND PALATAL NECROTIC ULCERS

ICD-10CM #		
	K13.70	Unspecified lesions of oral mucosa
	K13.79	Other lesions of oral mucosa
	H05.20	Unspecified exophthalmos

Cavernous sinus thrombosis.
Bacterial orbital cellulitis.
Metastatic neoplasm.
Rhinocerebral mucormycosis.
Ecthyma gangrenosum.
CNS aspergillosis.

PROTEIN-LOSING ENTEROPATHY, PEDIATRIC AGE[53]

ICD-10CM # E44.0 Moderate protein-energy malnutrition

CAUSES OF PROTEIN-LOSING ENTEROPATHY

Mucosal inflammation:
Infection:

Cytomegalovirus.
Bacterial overgrowth.
Invasive bacterial infection.
Gastric inflammation:
Ménétrier disease.
Eosinophilic gastroenteropathy.
Intestinal inflammation:
Celiac disease.
Crohn disease.
Eosinophilic gastroenteropathy:
Tropical sprue.
Radiation enteritis.
Primary intestinal lymphangiectasia.
Secondary intestinal lymphangiectasia:
Constrictive pericarditis.
Congestive heart failure.
Post–Fontan procedure.
Malrotation.
Lymphoma.
Sarcoidosis.
Radiation therapy.
Colonic inflammation:
Inflammatory bowel diseases.
Necrotizing enterocolitis.
Congenital disorders of glycosylation.

PROTEINURIA

ICD-10CM # R80.9 Proteinuria, unspecified

Nephrotic syndrome as a result of primary renal diseases.
Malignant hypertension.
Malignancies: multiple myeloma, leukemias, Hodgkin disease.
CHF.
DM.
SLE, RA.
Sickle cell disease.
Goodpasture syndrome.
Malaria.
Amyloidosis, sarcoidosis.
Tubular lesions: cystinosis.
Functional (after heavy exercise).
Pyelonephritis.
Pregnancy.
Constrictive pericarditis.
Renal vein thrombosis.
Toxic nephropathies: heavy metals, drugs.
Radiation nephritis.
Orthostatic (postural) proteinuria.
Benign proteinuria: fever, heat, or cold exposure.

PRURITUS

ICD-10CM #	L29.9	Pruritus, unspecified
	L29.3	Anogenital pruritus, unspecified

Dry skin.
Drug-induced eruption, fiberglass exposure.
Scabies.
Skin diseases.
Myeloproliferative disorders: mycosis fungoides, Hodgkin lymphoma, multiple myeloma, polycythemia vera.
Cholestatic liver disease.
Endocrine disorders: DM, thyroid disease, carcinoid, pregnancy.
Carcinoma: breast, lung, gastric.
Chronic renal failure.
Iron deficiency.
AIDS.
Neurosis.
Sjögren syndrome.

PRURITUS ANI[60]

ICD-10CM # L29.0 Pruritus ani

FECAL IRRITATION

Poor hygiene.
Anorectal conditions (fissure, fistula, hemorrhoids, skin tags, perianal clefts).
Spicy foods, citrus foods, caffeine, colchicine, quinidine.

CONTACT DERMATITIS

Anesthetic agents, topical corticosteroids, perfumed soap.

DERMATOLOGIC DISORDERS

Psoriasis, seborrhea, lichen simplex or sclerosus.

SYSTEMIC DISORDERS

Chronic renal failure, myxedema, DM, thyrotoxicosis, polycythemia vera, Hodgkin disease.

SEXUALLY TRANSMITTED DISEASES

Syphilis, herpes simplex virus, human papillomavirus.

OTHER INFECTIOUS AGENTS

Pinworms.
Scabies.
Bacterial infection, viral infection.

PRURITUS VULVAE[80]

ICD-10CM #	L29.3	Anogenital pruritus, unspecified

CAUSES OF PRURITUS VULVAE

Diseases Special to Vulval Skin
Lichen sclerosus et atrophicus.
Leukoplakia.
Carcinoma.
Skin Disease
Psoriasis.
Atopic dermatitis.
Irritant and allergic contact dermatitis (especially medicaments).
Infection
Candidiasis.
Trichomonas.
Infestation
Pediculosis.
Psychogenic
Anxiety.
Depression.
Unknown

PSEUDOCYANOSIS, ETIOLOGY

ICD-10CM # Varies with etiology

Medications: amiodarone, minocycline, chlorpromazine.
Heavy metals:
Gold (systemic absorption).
Silver (systemic absorption).
Local contact with color dyes, gold, silver.

PSEUDOHERMAPHRODITISM, FEMALE

ICD-10CM #	E25.0	Congenital adrenogenital disorders associated with enzyme deficiency
	E25.8	Other adrenogenital disorders
	E25.9	Adrenogenital disorder, unspecified
	Q56.3	Pseudohermaphroditism, unspecified
	Q56.4	Indeterminate sex, unspecified

Congenital adrenal hyperplasia.
Maternal use of testosterone or related steroids.
Virilizing ovarian or adrenal tumor.
Virilizing luteoma of pregnancy.
Disturbances in differentiation of urogenital structures, non-androgen related.
Maternal virilizing adrenal hyperplasia.
Fetal P450 aromatase deficiency.

PSEUDOHERMAPHRODITISM, MALE

ICD-10CM#	E25.0	Congenital adrenogenital disorders associated with enzyme deficiency
	E25.8	Other adrenogenital disorders
	E25.9	Adrenogenital disorder, unspecified
	Q56.3	Pseudohermaphroditism, unspecified
	Q56.4	Indeterminate sex, unspecified

Maternal ingestion of progestogens.
End-organ resistance to androgenic hormones.
5-α-reductase-2 deficiency.
XY gonadal dysgenesis.
Testicular regression syndrome.
Defects in testosterone metabolism by peripheral tissues.
Testosterone biosynthesis defects.

PSEUDOINFARCTION[52]

ICD-10CM # Varies with specific diagnosis

Cardiac tumors, primary and secondary.
Cardiomyopathy (particularly hypertrophic and dilated).
Chagas disease.
Chest deformity.
COPD (particularly emphysema).
HIV infection.
Hyperkalemia.
Left anterior fascicular block.
Left bundle branch block.

Left ventricular hypertrophy.
Myocarditis and pericarditis.
Normal variant.
Pneumothorax.
Poor R wave progression, rotational changes, and lead placement.
Pulmonary embolism.
Trauma to chest (nonpenetrating).
Wolff-Parkinson-White syndrome.
Rare causes: pancreatitis, amyloidosis, sarcoidosis, scleroderma.

PSYCHOSIS[65]

ICD-10CM #	F29	Unspecified psychosis not due to a substance or known physiological condition
	F29	Unspecified psychosis not due to a substance or known physiological condition
	F10.231	Alcohol dependence with withdrawal delirium
	F01.51	Vascular dementia with behavioral disturbance

PRIMARY

Schizophrenia-related.[36]
Major depression.
Dementia.
Bipolar disorder.

SECONDARY

Drug use.[37]
Drug withdrawal.[38]
Drug toxicity.[39]
Charles Bonnet syndrome.
Infections (pneumonia).
Electrolyte imbalance.
Syphilis.
Congestive heart failure.
Parkinson disease.
Trauma to temporal lobe.
Postpartum psychosis.
Hypothyroidism/hyperthyroidism.
Hypomagnesemia.
Epilepsy.
Meningitis.
Encephalitis.
Brain abscess.
Herpes encephalopathy.
Hypoxia.
Hypercarbia.
Hypoglycemia.
Thiamine deficiency.
Postoperative states.

[36] Includes schizophrenia, schizophreniform disorder, brief reactive psychosis.
[37] Includes hypnotics, glucocorticoids, marijuana, phencyclidine, atropine, dopaminergic agents (e.g., amantadine, bromocriptine, L-dopa), immunosuppressants.
[38] Includes alcohol, barbiturates, benzodiazepines.
[39] Includes digitalis, theophylline, cimetidine, anticholinergics, glucocorticoids, catecholaminergic agents.

PSYCHOSIS, MEDICAL DISORDERS-INDUCED[60]

ICD-10CM #	F29	Unspecified psychosis not due to a substance or known physiological condition
	F53	Puerperal psychosis

MEDICAL DISORDERS THAT MAY CAUSE ACUTE PSYCHOSIS

Metabolic Disorders
Hypercalcemia.
Hypercarbia.
Hypoglycemia.
Hyponatremia.
Hypoxia.
Inflammatory Disorders
Sarcoidosis.
Systemic lupus erythematosus.
Temporal (giant cell) arteritis.
Organ Failure
Hepatic encephalopathy.
Uremia.
Neurologic Disorders
Alzheimer disease.
Cerebrovascular disease.
Encephalitis (including HIV infection).
Encephalopathies.
Epilepsy.
Huntington disease.
Multiple sclerosis.
Neoplasms.
Normal-pressure hydrocephalus.
Parkinson disease.
Pick disease.
Wilson disease.
Endocrine disorders
Addison disease.
Cushing disease.
Panhypopituitarism.
Parathyroid disease.
Postpartum psychosis.
Recurrent menstrual psychosis.
Sydenham chorea.
Thyroid disease.
Deficiency States
Niacin.
Thiamine.
Vitamin B_{12} and folate.

PSYCHOSIS, MEDICATION-INDUCED[60]

ICD-10CM #	F10.5	Psychotic disorder due to psychoactive substance use

PHARMACOLOGIC AGENTS THAT MAY CAUSE ACUTE PSYCHOSIS

Antianxiety Agents
Alprazolam.
Chlordiazepoxide.
Clonazepam.
Clorazepate.
Diazepam.
Ethchlorvynol.
Antibiotics
Isoniazid.
Rifampin.
Anticonvulsants
Ethosuximide.
Phenobarbital.
Phenytoin.
Primidone.
Antidepressants
Amitriptyline.
Doxepin.
Imipramine.
Protriptyline.
Trimipramine.
Cardiovascular Drugs
Captopril.
Digitalis.
Disopyramide.
Methyldopa.
Procainamide.
Propranolol.
Reserpine.
Drugs of Abuse
Alcohol.
Amphetamines.
Cannabis.
Cocaine.
Hallucinogens.
Opioids.
Phencyclidine.
Sedative-hypnotics.
Miscellaneous Drugs
Antihistamines.
Antineoplastics.
Bromides.
Cimetidine.
Corticosteroids.
Disulfiram.
Heavy metals.

PTOSIS

ICD-10CM #	H02.409	Unspecified ptosis of unspecified eyelid
	Q10.0	Congenital ptosis
	H02.419	Mechanical ptosis of unspecified eyelid
	H02.429	Myogenic ptosis of unspecified eyelid
	H02.439	Paralytic ptosis unspecified eyelid

Third nerve palsy.
Myasthenia gravis.
Horner syndrome.
Senile ptosis.

PUBERTY, DELAYED[63]

ICD-10CM #	E30.0	Delayed puberty

NORMAL OR LOW SERUM GONADOTROPIN LEVELS

Constitutional delay in growth and development.
Hypothalamic and/or pituitary disorders:
- Isolated deficiency of growth hormone.
- Isolated deficiency of Gn-RH.
- Isolated deficiency of LH and/or FSH.
- Multiple anterior pituitary hormone deficiencies.

Associated with congenital anomalies: Kallmann syndrome; Prader-Willi syndrome; Laurence-Moon-Biedl syndrome; Friedreich ataxia.
Trauma.
Postinfection.
Hyperprolactinemia.
Postirradiation.
Infiltrative disease (histiocytosis).
Tumor.
Autoimmune hypophysitis.
Idiopathic.
Functional:
Chronic endocrinologic or systemic disorders.
Emotional disorders.
Drugs: cannabis.

INCREASED SERUM GONADOTROPIN LEVELS

Gonadal abnormalities:
Congenital:
Gonadal dysgenesis.
Klinefelter syndrome.
Bilateral anorchism.
Resistant ovary syndrome.
Myotonic dystrophy in males.
17-Hydroxylase deficiency in females.
Galactosemia.
Acquired:
Bilateral gonadal failure resulting from trauma or infection or after surgery, irradiation, or chemotherapy.
Oophoritis: isolated or with other autoimmune disorders.
Uterine or vaginal disorders:
Absence of uterus and/or vagina.
Testicular feminization: complete or incomplete androgen insensitivity.

PUBERTY, PRECOCIOUS

ICD-10CM #		
	E25.0	Congenital adrenogenital disorders associated with enzyme deficiency
	E25.8	Other adrenogenital disorders
	E25.9	Adrenogenital disorder, unspecified

Idiopathic.
Congenital virilizing adrenal hyperplasia.
Hypothalamic tumors.
Head trauma.
Hydrocephalus.
Degenerative CNS disease.
Arachnoid cyst.
Sex chromosome abnormalities (e.g., 47, XXY, 48, XXXY).
Perinatal asphyxia.
CNS infection (e.g., meningitis, encephalitis).

PULMONARY CRACKLES

ICD-10CM #	R09.8	Friction sounds, chest

Pneumonia.
Left ventricular failure.
Asbestosis, silicosis, interstitial lung disease.
Chronic bronchitis.
Alveolitis (allergic, fibrosing).
Neoplasm.

PULMONARY CYSTS ON X-RAY[36]

ICD-10CM #	Q33.0	Polycystic lungs, congenital
	J98.4	Pulmonary manifestations

CAUSES OF CYSTS IN THE LUNG ON CHEST RADIOGRAPH

Cystic fibrosis.
Cystic bronchiectasis.
Bronchopulmonary dysplasia (neonate and older).
Tuberculosis (apical thick walled).
Pulmonary abscess (thick wall, fluid level).
Empyema.
Streptococcal pneumatocele (thin wall, postinfective).
Cavitating pneumonia.
Mycetoma (apical cyst with contents).
Cystic congenital adenomatoid malformation (basal cysts of varying size).
Diaphragmatic hernia (cysts of similar size).
Hiatal hernia (posterior).
Morgagni hernia (midline anterior).
Bronchopulmonary sequestration (basal).
Congenital lobar emphysema.
Hydatid disease (in endemic areas).
Kerosene inhalation (pneumatocele).
Histiocytosis and other causes of interstitial disease.

PULMONARY EDEMA, NONCARDIOGENIC[36]

ICD-10CM #	J81.0	Acute pulmonary edema

CAUSES OF NONCARDIOGENIC PULMONARY EDEMA

Adult respiratory distress syndrome.
Drowning.
Asphyxia.
Upper airway obstruction (usually with cardiomegaly).
High altitude.
Increased intracranial pressure.
Postictal.
Noxious gases:
Smoke.
Nitrous dioxide (silo filler's disease).
Sulfur dioxide.
Nitrogen mustard.
Drugs:
Aspirin.
Diazepam, chlordiazepoxide, barbiturates.
Narcotics (heroin, methadone, morphine).
β-adrenergic drugs (terbutaline).
Contrast media.
Colchicine.
Fluorescein.
Hydrochlorothiazide.
Nitrofurantoin.
Propoxyphene.
Poisons:
Parathion.
Transfusion reactions.
Renal failure: transplantation.
Bone marrow transplantation.
Fat embolism.
Pancreatitis.

PULMONARY EOSINOPHILIA[2]

ICD-10CM #	NEC J82	Eosinophilia, pulmonary

TYPES AND CAUSES OF PULMONARY EOSINOPHILIA

Drug- and toxin-induced eosinophilic lung diseases.
Helminth and fungal infection-related eosinophilic lung diseases:
Transpulmonary passage of larvae (i.e., Löffler syndrome): Ascaris, hookworm, Strongyloides.
Pulmonary parenchymal invasion: mostly helminths, paragonimiasis.
Heavy hematogenous seeding with helminths: trichinellosis, disseminated strongyloidiasis, cutaneous and visceral larva migrans, schistosomiasis.
Tropical pulmonary eosinophilia: filaria.
Allergic bronchopulmonary aspergillosis.
Chronic eosinophilic pneumonia.
Acute eosinophilic pneumonia.
Churg-Strauss syndrome (vasculitis).
Other: neoplasia, idiopathic hypereosinophilic syndrome, bronchocentric granulomatosis.

PULMONARY HEMORRHAGE, DIFFUSE, ALVEOLAR[70]

ICD-10CM #	R04.8	Pulmonary hemorrhage

IMMUNOLOGIC DISEASES

Anti–glomerular basement membrane antibody disease (Goodpasture syndrome).
Vasculitides associated with circulating or in situ immune complexes:
Systemic lupus erythematosus.
Mixed connective tissue disease.
Schönlein-Henoch purpura.
Essential mixed cryoglobulinemia.
Tumor-related vasculitis.
Endocarditis-related vasculitis.
Polyarteritis nodosa.
Systemic necrotizing vasculitis.
Vasculitides associated with antineutrophil cytoplasmic antibodies:
Wegener granulomatosis.
Microscopic polyangiitis.
Idiopathic necrotizing crescentic glomerulonephritis.
Rapidly progressive glomerulonephritis.
Associated with other connective tissue diseases, pathophysiology unknown:
Rheumatoid arthritis.
Progressive systemic sclerosis.
Behçet disease.
Associated with other renal diseases.
Immunoglobulin A nephropathy.
Diabetic nephropathy.
Associated with precipitating antibodies to milk (Heiner syndrome).

Idiopathic pulmonary hemosiderosis.
Primary antiphospholipid antibody syndrome.

CHEMICAL OR DRUG-RELATED CAUSES

Amiodarone.
D-Penicillamine.
Isocyanates.
Nitrofurantoin.
Retinoic acid.
Trimellitic anhydride.
"Crack" cocaine.
Sirolimus.
Everolimus.
Propylthiouracil-induced vasculitis.
Erlotinib.
Bevacizumab.
Gemcitabine.
Infliximab.

TRANSPLANT-RELATED CAUSES

Bone marrow transplant.
Renal transplant.
Lung transplant.

BLEEDING DIATHESIS

Thrombocytopenia.
Leukemia with diffuse alveolar damage.
Viral pneumonia.
Bacterial or fungal sepsis.
Radiation.
Chemotherapy toxic to lung.
Blast counts >80,000/μL.
Extrinsic anticoagulants/thrombolytics.
Warfarin overdose.
Tissue plasminogen activator.
Platelet glycoprotein IIb/IIIa inhibitors.
Coagulopathies.
Cirrhosis.
Disseminated intravascular coagulation.

INFECTIONS

Adenovirus.
Aspergillosis (invasive).
Cytomegalovirus.
Dengue.
Hantavirus.
Influenza.
Legionella.
Leptospirosis.
Malaria.
Mycoplasma.
Staphylococcus aureus.

PULMONARY VENOUS HYPERTENSION

Mitral stenosis.
Mitral regurgitation.
Pulmonary capillary hemangiomatosis.
Pulmonary veno-occlusive disease.
Fibrosing mediastinitis.
Congenital heart disease.

DIFFUSE LUNG INJURY

Negative-pressure pulmonary hemorrhage.
Breath-hold diving.
Postictal neurogenic pulmonary edema.

PULMONARY HEMORRHAGE, FOCAL[69]

ICD-10CM # R04.8 Pulmonary hemorrhage

CAUSES OF FOCAL PULMONARY HEMORRHAGE

Iatrogenic Disorders
Bronchoscopy.
Lung biopsy.
Pulmonary artery catheterization.
Transtracheal aspiration.
Radiofrequency ablation.
Brachytherapy.
Infectious Disorders
Lung abscess.
Mycetoma.
Necrotizing pneumonia (*Staphylococcus aureus,* gram-negative aerobes, *Legionella,* Actinomyces species, *Stenotrophomonas, Kytococcus sedentarius,* Leptospira species, *Yersinia pestis, Francisella tularensis*).
Parasitic infection (paragonimiasis, amebiasis, ascariasis, clonorchiasis, echinococcosis, hookworm infestation, strongyloidiasis, trichinosis, schistosomiasis).
Parenchymal fungal infection (aspergillosis, mucormycosis, coccidioidomycosis, histoplasmosis, maduromycosis, botryomycosis).
Tuberculosis (active or inactive).
Viral tracheitis.
Herpetic tracheobronchitis.
Interstitial Lung Diseases
Lymphangioleiomyomatosis.
Sarcoidosis.
Tuberous sclerosis.
Pneumoconiosis.
Langerhans cell granulomatosis.
Miscellaneous Disorders
Amyloidosis.
Bronchogenic cyst.
Broncholithiasis.
Bronchopleural fistula.
Thoracic endometriosis.
Foreign body.
Tracheopathia osteoplastica.
Lipoid pneumonia.
Organophosphate aspiration.
Chronic pancreatitis.
Neoplastic Disorders
Bronchial adenoma.
Lung cancer.
Tracheal tumors (mucoepidermoid, squamous cell, adenoid cystic, glomus).
Pulmonary blastoma.
Pleuropulmonary angiosarcoma.
Sarcoma (synovial, myofibroblastic).
Clear cell tumor.
Metastatic disease (prostate, renal, breast, ovarian).
Tracheobronchial schwannoma.
Pulmonary Airway Diseases
Bronchiectasis.
Bronchitis.
Granulomatous tracheobronchitis (ulcerative colitis, Crohn disease, granulomatosis with polyangiitis).
Cystic fibrosis.
Bullous emphysema.
Traumatic Injury
Blunt chest trauma.
Penetrating injury.
Ruptured bronchus.
Lightning injury.
Thoracic splenosis.
Vascular Disorders
Pulmonary embolism, infarction.
Systemic cholesterol emboli.
Intralobar sequestration.
Pulmonary artery aneurysms.
Behçet disease, Hughes-Stovin syndrome, traumatic pseudoaneurysms.
Acquired arteriovenous malformations.
Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia).
Takayasu arteritis.
Aortic aneurysms.
Trachea–innominate artery fistulas.
Scimitar syndrome.
Vena cava-bronchial.
Dieulafoy disease of bronchus.
Ventriculopulmonary fistulas.
Hemangioma (sclerosing, cavernous, tracheal).

PULMONARY HEMORRHAGE, PEDIATRIC AGE

ICD-10CM # P26.9 Pulmonary hemorrhage newborn

CAUSES OF PULMONARY HEMORRHAGE (HEMOPTYSIS)

Focal Hemorrhage
Bronchitis and bronchiectasis (especially cystic fibrosis related).
Infection (acute or chronic), pneumonia, abscess.
Tuberculosis.
Trauma.
Pulmonary arteriovenous malformation.
Foreign body (chronic).
Neoplasm including hemangioma.
Pulmonary embolus with or without infarction.
Bronchogenic cysts.
Diffuse hemorrhage
Idiopathic of infancy.
Congenital heart disease (including pulmonary hypertension, venoocclusive disease, congestive heart failure).
Prematurity.
Cow's milk hyperreactivity (Heiner syndrome).
Goodpasture syndrome.
Collagen vascular diseases (systemic lupus erythematosus, rheumatoid arthritis).
Henoch-Schönlein purpura and vasculitic disorders.
Granulomatous disease (Wegener granulomatosis).
Celiac disease.
Coagulopathy (congenital or acquired).
Malignancy.
Immunodeficiency.
Exogenous toxins.
Hyperammonemia.
Pulmonary hypertension.
Pulmonary alveolar hemosiderosis.

Tuberous sclerosis.
Lymphangiomyomatosis or lymphangioleiomyomatosis.
Physical injury or abuse.

PULMONARY HEMORRHAGIC SYNDROMES, DIFFUSE[36]

ICD-10CM # P26.1 Massive pulmonary hemorrhage originating in the perinatal period
R04.8 Pulmonary hemorrhage

CLASSIFICATION OF DIFFUSE PULMONARY HEMORRHAGE SYNDROMES

Non-immunocompromised patients

Antibasement membrane antibody disease/Goodpasture syndrome.
Diseases of presumed immune etiology, with or without nephropathy:
- Systemic lupus erythematosus.
- Rheumatoid arthritis.
- Systemic sclerosis.
- Systemic necrotizing vasculitis.
- Granulomatosis with polyangiitis.
- Microscopic polyarteritis.

Diseases with no known immune etiology:
- Idiopathic pulmonary hemosiderosis.
- Rapidly progressive glomerulonephritis without immune complexes.
- Fibrillary glomerulonephritis.
- Drug-induced (anticoagulants, trimellitic anhydride, cocaine, lymphangiography).
- Valvular heart disease.
- Disseminated intravascular coagulation.
- Acute lung injury.
- Tumors.

Immunocompromised Patients

Blood dyscrasias.
Infection.
Tumors.

PULMONARY INFILTRATES ASSOCIATIONS[64]

ICD-10CM # Varies with specific diagnosis

PULMONARY INFILTRATES AND THEIR ASSOCIATION WITH SPECIFIC INFECTIOUS AND NONINFECTIOUS DISORDERS

Radiologic Sign	Potential Etiologic Disorder(s)
Interstitial infiltrates.	Pulmonary edema.
Diffuse alveolar damage.	Idiopathic pneumonia syndrome. Respiratory virus infection: RSV, parainfluenza virus, influenza virus, adenovirus, enterovirus. Herpesvirus infection: CMV, HSV, VZV, HHV-6. *Pneumocystis* pneumonia.
Focal airspace disease.	Bacterial pneumonia. Fungal pneumonia.
Nodules.	Fungal pneumonia (aspergillosis). *Nocardia* infection. *Legionella* infection. Septic bacterial emboli. Mycobacterial infection (with cavitation). EBV lymphoproliferative disorder. Relapsed malignancy. Pulmonary embolism (pleura based).
Halo sign or air-crescent sign.	Aspergillosis.

CMV, Cytomegalovirus; *EBV,* Epstein-Barr virus; *HHV,* human herpesvirus; *HSV,* herpes simplex virus; *RSV,* respiratory syncytial virus; *VZV,* varicella-zoster virus.

PULMONARY INFILTRATES, IMMUNOCOMPROMISED HOST[91]

ICD-10CM # J82 Pulmonary eosinophilia, not elsewhere classified
J98.4 Other disorders of lung

CAUSES OF PULMONARY INFILTRATES IN THE IMMUNOCOMPROMISED HOST

Infections:
- Bacteria:
  - Gram-positive cocci, especially *Staphylococcus.*
  - Gram-negative bacilli.
  - Mycobacterium tuberculosis.
  - Nontuberculous mycobacteria.
  - *Nocardia.*
- Viruses:

Cytomegalovirus.
Herpesvirus.
- Fungi:
  - *Aspergillus.*
  - *Cryptococcus.*
  - *Candida.*
  - *Mucor.*
  - *Pneumocystis jiroveci.*
- Protozoa:
  - *Toxoplasma gondii* (rare).
- Pulmonary effects of therapy:
  - Chemotherapeutic agents.
  - Radiation therapy.
  - Pulmonary hemorrhage.
  - Congestive heart failure.
  - Disseminated malignancy.
  - Nonspecified interstitial pneumonitis (no defined etiology).

PULMONARY LESIONS

ICD-10CM# J98.4 Other disorders of lung
J70.9 Respiratory conditions due to unspecified external agent
S27.309A Unspecified injury of lung, unspecified, initial encounter

TB.
Legionella pneumonia.
Mycoplasma pneumonia.
Viral pneumonia.
Pneumocystis carinii.
Hypersensitivity pneumonitis.
Aspiration pneumonia.
Fungal disease (aspergillosis, histoplasmosis).
ARDS associated with pneumonia.
Psittacosis.
Sarcoidosis.
Septic emboli.
Metastatic cancer.
Multiple pulmonary emboli.
Rheumatoid nodules.

PULMONARY MASS, SOLITARY, CAUSES[36]

ICD-10CM # R91.1 Solitary pulmonary nodule

CAUSES OF A SOLITARY PULMONARY MASS

Bronchial carcinoma.
Bronchial carcinoid.
Granuloma.
Hamartoma.
Metastasis.
Chronic pneumonia or abscess.
Hydatid cyst.
Pulmonary hematoma.
Bronchocele.
Fungus ball.
Massive fibrosis in coal workers.
Bronchogenic cyst.
Sequestration.
Arteriovenous malformation.
Pulmonary infarct.
Round atelectasis.

PULMONARY MASS, SOLITARY, MIMICS[36]

ICD-10CM # Varies with specific diagnosis

SIMULANTS OF A SOLITARY PULMONARY MASS

Extrathoracic artifacts.
Cutaneous masses.
Bony lesions.
Pleural tumors or plaques.
Encysted pleural fluid.
Pulmonary vessels.

PULMONARY NODULE, SOLITARY

ICD-10CM # J98.4 Other disorders of lung

Bronchogenic carcinoma.
Granuloma from histoplasmosis.
TB granuloma.
Granuloma from coccidioidomycosis.
Metastatic carcinoma.

Bronchial adenoma.
Bronchogenic cyst.
Hamartoma.
AV malformation.
Other: fibroma, intrapulmonary lymph node, sclerosing hemangioma, bronchopulmonary sequestration.

PULMONARY–RENAL SYNDROMES, CAUSES[28]

ICD-10CM # Varies with specific diagnosis

Systemic vasculitis	Anti-GBM disease (Goodpasture). ANCA associated: Granulomatosis with polyangiitis. Microscopic polyarteritis. Churg-Strauss syndrome. Drugs (penicillamine, hydralazine, propylthiouracil). Immune complex disease. Lupus erythematosus. Henoch-Schönlein purpura. Mixed cryoglobulinemia. Rheumatoid vasculitis.
Infection	Severe bacterial pneumonia, postinfectious glomerulonephritis, *Legionella,* hantavirus, opportunistic infection in immunocompromised patients, infective endocarditis.
Pulmonary edema and AKI	Volume overload, severe left ventricular failure.
Multiorgan failure	Acute respiratory distress syndrome and AKI.
Other	Paraquat poisoning, renal vein or IVC thrombosis with pulmonary emboli.

AKI, Acute kidney injury; *ANCA,* anti-neutrophil cytoplasmic antibody; *GBM,* glomerular basement membrane; *IVC,* inferior vena cava.

PULSELESS ELECTRICAL ACTIVITY

ICD-10CM # I46.9 Cardiac arrest, cause unspecified

Hypovolemia.
Hypoxia.
Hyperkalemia.
Acidosis.
Cardiac tamponade.
Tension pneumothorax.
Pulmonary embolus.
Drug overdose.
Hypothermia.

PUPILLARY DILATATION, POOR RESPONSE TO DARKNESS

ICD-10CM # H21.569 Pupillary abnormality, unspecified eye

Drugs (narcotics, general anesthetics, cholinergics).
Acute trauma (spasm from prostaglandin release).
Inflammation, infection (interruption of inhibitory fibers to the Edinger-Westphal nucleus).
Old age (loss of inhibition at midbrain from reticular activating formation).
Horner syndrome (sympathetic neuron interruption).
Adie syndrome tonic pupil.
Lymphoma.
Congenital miosis.

PURPURA

ICD-10CM # D69.2 Other nonthrombocytopenic purpura
D69.0 Allergic purpura
D69.49 Other primary thrombocytopenia
M31.1 Thrombotic microangiopathy

THROMBOTIC

Trauma.
Septic emboli, atheromatous emboli.
DIC.
Thrombocytopenia.
Meningococcemia.
Rocky Mountain spotted fever.
Hemolytic-uremic syndrome.
Viral infection: echo, coxsackie.
Scurvy.
Other: left atrial myxoma, cryoglobulinemia, vasculitis, hyperglobulinemic purpura.

PURPURA, NONPALPABLE[45]

ICD-10CM # D69.2 Other nonthrombocytopenic purpura

INCREASED TRANSMURAL PRESSURE GRADIENT

Acute (Valsalva, coughing, vomiting, high altitude, weight lifting).
Chronic—venous stasis.

DECREASED MECHANICAL INTEGRITY OF MICROCIRCULATION AND SUPPORTING TISSUES

Age related (infancy and actinic purpura).
Glucocorticoid excess—Cushing syndrome and glucocorticoid therapy.
Vitamin C deficiency (scurvy).
Abnormal connective tissue—Ehlers-Danlos syndrome.
Amyloid infiltration of blood vessels.
Colloid milium.
Hormonal—female easy bruising syndrome (purpura simplex).
Lorenzo oil.
MELAS syndrome.

TRAUMA TO BLOOD VESSELS

Physical:
- Injuries.
- Child abuse.
- Factitial purpura.

Ultraviolet purpura:
- Purpuric sunburn.
- Solar purpura.

Infectious:
- Bacterial.
- Rickettsial.
- Fungal.
- Viral.
- Parasitic.

Embolic:
- Infectious organisms.
- Atheroemboli (cholesterol crystal emboli).
- Fat emboli.

Allergic and/or inflammatory:
- Serum sickness.
- Pigmented purpuric eruptions.
- Pyoderma gangrenosum.
- Contact dermatitis.
- Familial Mediterranean fever.

Neoplastic.
Metabolic:
- Erythropoietic porphyria.
- Calciphylaxis.

Immunoglobulin related (hyperglobulinemic purpura of Waldenström and light-chain vasculitis).
Drug related.
Thrombotic:
- Disseminated intravascular coagulation.
- Warfarin (Coumadin)-induced skin necrosis.
- Protein C or protein S deficiency, factor V Leiden, prothrombin G20201A.
- Purpura fulminans.
- Paroxysmal nocturnal hemoglobinuria.
- Antiphospholipid antibody syndrome.
- Hemangioma with thrombocytopenia and consumptive coagulopathy (Kasabach-Merritt syndrome).

UNKNOWN CAUSE—PSYCHOGENIC PURPURA

PURPURA, NONPURPURIC DISORDERS SIMULATING PURPURA[3]

ICD-10CM # Varies with specific diagnosis

Disorders with telangiectasias:
- Cherry angiomas.
- Hereditary hemorrhagic telangiectasia.
- Chronic actinic telangiectasia.
- Scleroderma.
- CREST syndrome.
- Ataxia-telangiectasia.
- Chronic liver disease.
- Pregnancy-related telangiectasia.

Kaposi sarcoma and other vascular sarcomas.
Fabry disease.

Neonatal extramedullary hematopoiesis.
Angioma serpiginosum.

PURPURA, PALPABLE[45]

ICD-10CM # D69.2 Other nonthrombocytopenic purpura

Cutaneous vasculitis:
- Systemic vasculitides.
- Paraneoplastic vasculitis.
- Henoch-Schönlein purpura.
- Acute hemorrhagic edema of infancy.
- Livedoid vasculitis.
- Idiopathic.
- Urticarial.

Cryoglobulinemia.
Cryofibrinogenemia.
Primary cutaneous diseases

QT INTERVAL PROLONGATION[52]

ICD-10CM # R94.31 Abnormal electrocardiogram [ECG] [EKG]
I45.81 Long QT syndrome

Drugs:
- Class I antiarrhythmics (e.g., disopyramide, procainamide, quinidine).
- Class III antiarrhythmics.
- Tricyclic antidepressants.
- Phenothiazines.
- Astemizole.
- Terfenadine.
- Adenosine.
- Antibiotics (e.g., erythromycin and other macrolides):
  - Antifungal agents.
  - Pentamidine, chloroquine.

Ischemic heart disease.
Cerebrovascular disease.
Rheumatic fever.
Myocarditis.
Mitral valve prolapse.
Electrolyte abnormalities.
Hypocalcemia.
Hypothyroidism.
Liquid protein diets.
Organophosphate insecticides.
Congenital prolonged QT syndrome.

RADIATION-INDUCED NEOPLASMS[81]

ICD-10CM # Varies with specific diagnosis

RADIATION-INDUCED NEOPLASMS

Osteochondroma
Benign.
Exclusively with childhood irradiation.
Histologically identical to spontaneous osteochondroma.

Sarcoma
Malignant.
Latent period of 4 years or more.
Histologically identical to spontaneous sarcoma.
Commonly malignant fibrous histiocytoma or osteosarcoma.
Occurs in either bone or soft tissue.

Tumors in Other Organ Systems
Squamous cell cancer of the skin.
Breast cancer.
Leukemia, with shorter latent period than sarcoma.

RECTAL MASS, PALPABLE[86]

ICD-10CM # R22.9 Localized swelling, mass and lump, unspecified

Rectal carcinoma.
Rectal polyp.
Hypertrophied anal papilla.
Diverticular phlegmon (prolapsing into the pouch of Douglas).
Sigmoid colon carcinoma (prolapsing into the pouch of Douglas).
Metastatic deposits at the pelvic reflection (Blumer shelf).
Primary pelvic malignancy (uterine, ovarian, prostatic, or cervical).
Mesorectal lymph nodes.
Endometriosis.
Solitary rectal ulcer syndrome.
Foreign body.
Feces.
Presacral cyst.
Amebic granuloma.
Vaginal tampon and even the pubic bone may be mistaken for a rectal mass.

RECTAL PAIN

ICD-10CM # K62.89 Other specified diseases of anus and rectum

Anal fissure.
Thrombosed hemorrhoid.
Anorectal abscess.
Foreign bodies.
Fecal impaction.
Endometriosis.
Neoplasms (primary or metastatic).
Pelvic inflammatory disease.
Inflammation of sacral nerves.
Compression of sacral nerves.
Prostatitis.
Other: proctalgia fugax, uterine abnormalities, myopathies, coccygodynia.

RED BLOOD CELL APLASIA, ACQUIRED, ETIOLOGY

ICD-10CM # D61.01 Constitutional (pure) red blood cell aplasia

Idiopathic (>50% of cases).
Medications (most frequent with phenytoin).
Non-Hodgkin lymphoma.
Viral infections (parvovirus B19, EB virus, mumps, hepatitis).
Myelodysplastic syndromes.
Thymoma.
Autoimmune diseases.
Allogenic bone marrow transplant from ABO incompatible donor.
Pregnancy.

RED BLOOD CELL FRAGMENTATION HEMOLYSIS, CAUSES[44]

ICD-10CM # Varies with specific disorder

CAUSES OF RED BLOOD CELL FRAGMENTATION HEMOLYSIS

Damaged microvasculature.
Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP–HUS).
Associated with pregnancy: preeclampsia or eclampsia; hemolysis plus elevated liver enzymes plus low platelets (HELLP syndrome).
Associated with malignancy, with or without mitomycin C treatment.
Vasculitis: polyarteritis, Wegener granulomatosis, acute glomerulonephritis, or *Rickettsia*-like infections.
Systemic lupus erythematosus.
Abnormalities of renal vasculature: malignant hypertension, acute glomerulonephritis, scleroderma, or allograft rejection with or without cyclosporine treatment.
Disseminated intravascular coagulation.
Malignant hypertension.
Catastrophic antiphospholipid antibody syndrome.
Atrioventricular malformations.
Kasabach-Merritt syndrome.
Hemangioendotheliomas.
Atrioventricular shunts for congenital and acquired conditions (e.g., stents, coils, transjugular intrahepatic portosystemic shunt, Levine shunts).
Cardiac abnormalities:
- Replaced valve, prosthesis, graft, or patch.
- Aortic stenosis or regurgitant jets (e.g., in ruptured sinus of Valsalva).

Drugs:
- Cyclosporine.
- Mitomycin.
- Ticlopidine.
- Clopidogrel.
- Tacrolimus.
- Cocaine.

Systemic infection:
- Bacterial endocarditis.
- Brucellosis.
- Cytomegalovirus.
- Human immunodeficiency virus.
- Ehrlichiosis.
- Rocky Mountain spotted fever

RED EYE

ICD-10CM # H57.8 Other specified disorders of eye and adnexa

Infectious conjunctivitis (bacterial, viral).
Allergic conjunctivitis.
Acute glaucoma.
Keratitis (bacterial, viral).
Iritis.
Trauma.

Neonatal extramedullary hematopoiesis.
Angioma serpiginosum.

PURPURA, PALPABLE[45]

ICD-10CM # D69.2 Other nonthrombocytopenic purpura

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Cerebrovascular disease.
Rheumatic fever.
Myocarditis.
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Feces.
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Vaginal tampon and even the pubic bone may be mistaken for a rectal mass.

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Foreign bodies.
Fecal impaction.
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RED BLOOD CELL FRAGMENTATION HEMOLYSIS, CAUSES[44]

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CAUSES OF RED BLOOD CELL FRAGMENTATION HEMOLYSIS

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Drugs:
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- Ticlopidine.
- Clopidogrel.
- Tacrolimus.
- Cocaine.

Systemic infection:
- Bacterial endocarditis.
- Brucellosis.
- Cytomegalovirus.
- Human immunodeficiency virus.
- Ehrlichiosis.
- Rocky Mountain spotted fever

RED EYE

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Keratitis (bacterial, viral).
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Trauma.

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Endometriosis.
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Myelodysplastic syndromes.
Thymoma.
Autoimmune diseases.
Allogenic bone marrow transplant from ABO incompatible donor.
Pregnancy.

RED BLOOD CELL FRAGMENTATION HEMOLYSIS, CAUSES[44]

ICD-10CM # Varies with specific disorder

CAUSES OF RED BLOOD CELL FRAGMENTATION HEMOLYSIS

Damaged microvasculature.
Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP–HUS).
Associated with pregnancy: preeclampsia or eclampsia; hemolysis plus elevated liver enzymes plus low platelets (HELLP syndrome).
Associated with malignancy, with or without mitomycin C treatment.
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Systemic lupus erythematosus.
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Disseminated intravascular coagulation.
Malignant hypertension.
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Atrioventricular malformations.
Kasabach-Merritt syndrome.
Hemangioendotheliomas.
Atrioventricular shunts for congenital and acquired conditions (e.g., stents, coils, transjugular intrahepatic portosystemic shunt, Levine shunts).
Cardiac abnormalities:
- Replaced valve, prosthesis, graft, or patch.
- Aortic stenosis or regurgitant jets (e.g., in ruptured sinus of Valsalva).

Drugs:
- Cyclosporine.
- Mitomycin.
- Ticlopidine.
- Clopidogrel.
- Tacrolimus.
- Cocaine.

Systemic infection:
- Bacterial endocarditis.
- Brucellosis.
- Cytomegalovirus.
- Human immunodeficiency virus.
- Ehrlichiosis.
- Rocky Mountain spotted fever

RED EYE

ICD-10CM # H57.8 Other specified disorders of eye and adnexa

Infectious conjunctivitis (bacterial, viral).
Allergic conjunctivitis.
Acute glaucoma.
Keratitis (bacterial, viral).
Iritis.
Trauma.

RED EYE, ACUTE[4]

ICD-10CM # H57.8 Other specified disorders of eye and adnexa

Obvious open globe.
Corneal abrasion.
Corneal ulcer.
Subconjunctival hemorrhage.
Hyphema.
Occult open globe.
Herpes simplex virus glaucoma.
Iritis, traumatic iritis.
Scleritis.
Conjunctivitis.
Blepharitis.
Ultraviolet keratitis.
Episcleritis.
Conjunctival foreign body.
Dry eye.
Contact lens overwear syndrome.

RED HOT JOINT

ICD-10CM # Varies with specific diagnosis

Trauma.
Gout.
Infection (septic joint).
Pseudogout (calcium pyrophosphate dehydrate crystal deposition).
Psoriatic arthropathy.
Reactive arthritis.
Palindromic rheumatism.

RED URINE

ICD-10CM # R39.19 Other difficulties with micturition

Hematuria.
Porphyrins.
Hemoglobinuria.
Myoglobinuria.
Medications (phenazopyridine, aminosalicylic acid, deferoxamine, phenazopyridine, phenolphthalein, NSAIDs, rifampin, phenytoin, methyldopa, doxorubicin, phenacetin).
Foods (beets, berries, maize).
Urate crystalluria.

RENAL ALLOGRAFT DYSFUNCTION[34]

ICD-10CM # T86.1 Complications of renal allograft

IMMEDIATE/DELAYED GRAFT FUNCTION (1 TO 3 DAYS)

Acute tubular necrosis.
Hyperacute humoral rejection.
Urinary leak or obstruction.
Renal artery or vein thrombosis.
Recurrence of disease (e.g., focal segmental glomerulosclerosis).

EARLY POSTTRANSPLANTATION PERIOD (FIRST MONTH)

Acute cellular rejection.
Acute humoral rejection.
Calcineurin inhibitor toxicity.
Urinary tract obstruction.
Volume depletion.
Recurrence of disease.

Late Acute Dysfunction

Acute rejection.
Cyclosporine or tacrolimus toxicity.
Recurrence of primary disease.
Tubulointerstitial nephritis, drug-induced.
Renal artery stenosis.
Infection (bacterial urinary tract infection [UTI], cytomegalovirus, BK virus).
Hemodynamic (volume; use of angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker).

Chronic Dysfunction

Chronic rejection.
Cyclosporine or tacrolimus toxicity.
Recurrent renal disease.
De novo renal disease.
Urinary tract obstruction.
Bacterial UTI.
Hypertensive nephrosclerosis.

RENAL ARTERY OCCLUSION, CAUSES

ICD-10CM # N28.0 Ischemia and infarction of kidney

Atrial fibrillation.
Angiography or stent placement.
Abdominal aortic surgery.
Trauma.
Renal artery aneurysm/dissection.
Vasculitis.
Thrombosis in patient with fibromuscular dysplasia.
Atherosclerosis.
Septic embolism.
Mural thrombus thromboembolism.
Atrial myxoma thromboembolism.
Mitral stenosis thromboembolism.
Prosthetic valve thromboembolism.
Renal cell carcinoma.

RENAL COLIC[4]

ICD-10CM # N23 Unspecified renal colic

Vascular:
- Abdominal aortic aneurysm.
- Aortic dissection.
- Renal artery dissection.
- Renal artery stenosis.
- Renal vein thrombosis.
- Renal infarct.
- Mesenteric ischemia.
- Retroperitoneal hemorrhage.

GI:
- Incarcerated hernia.
- Appendicitis.
- Cholecystitis.
- Biliary colic.
- Pancreatitis.
- Bowel obstruction.
- Diverticulitis.

Gynecologic:
- Ectopic pregnancy.
- Ovarian torsion.
- Tuboovarian abscess.
- Pelvic inflammatory disease.
- Endometriosis.

Genitourinary:
- Testicular torsion.
- Pyelonephritis.
- Perinephric abscess.
- Urinary tract tumor.
- Renal papillary necrosis.
- Upper urinary tract hemorrhage.

Musculoskeletal:
- Lumbar strain.
- Radiculopathy.
- Disk herniation.
- Vertebral compression fracture.

Dermatologic:
- Herpes zoster.

Miscellaneous:
- Factitious.

RENAL CYSTIC DISORDERS

ICD-10CM # Q61.01 Congenital single renal cyst

Simple cysts.
Acquired cystic kidney disease.
Autosomal dominant polycystic kidney disease.
Autosomal recessive polycystic kidney disease.
Medullary cystic disease.
Medullary sponge kidney.

RENAL DISEASE, SKIN MANIFESTATIONS[79]

ICD-10CM # Varies with specific diagnosis

SKIN MANIFESTATIONS SECONDARY TO RENAL DISEASE

Nonspecific

Pruritus.
Xerosis.
Acquired ichthyosis.
Pigmentary alteration:
- Pallor (secondary to anemia).
- Hyperpigmentation.
- Dyspigmentation (yellow tint).

Infections (fungal, bacterial, viral).
Purpura.

Somewhat Specific

Acquired perforating dermatosis.
Calciphylaxis.
Metastatic calcification.
Blistering disorders:
- Porphyria cutanea tarda.
- Pseudoporphyria.

Eruptive xanthomas.
Pseudo–Kaposi sarcoma.

Specific

Nephrogenic systemic fibrosis.
Dialysis-associated steal syndrome.
Metastatic renal cell carcinoma.
Dialysis-related amyloidosis.
Arteriovenous shunt dermatitis.
Uremic frost.

RENAL FAILURE, ACUTE, PIGMENT-INDUCED[7]

ICD-10CM # N19 Unspecified kidney failure

CAUSES OF PIGMENT-INDUCED ACUTE RENAL FAILURE

Rhabdomyolysis and myoglobinuria.
Vigorous exercise.
Arterial embolization.
Status epilepticus.
Status asthmaticus.
Coma-induced and pressure-induced myonecrosis.
Heat stress.
Diabetic ketoacidosis.
Myopathy.
Alcoholism.
Hypokalemia.
Hypophosphatemia.
Hemoglobinuria.
Transfusion reactions.
Snake envenomation.
Malaria.
Mechanical destruction of RBCs by prosthetic valves.
G6PD deficiency.

G6PD, Glucose-6-phosphate dehydrogenase; *RBCs,* red blood cells.

RENAL FAILURE, CHRONIC[34]

ICD-10CM # N18.9 Chronic kidney disease, unspecified

CAUSES OF CHRONIC RENAL FAILURE

Diabetic glomerulosclerosis (systemic disease involving the kidney).
Hypertensive nephrosclerosis.
Glomerular disease:
- Glomerulonephritis.
- Amyloidosis, light chain disease (systemic disease involving the kidney).
- Systemic lupus erythematosus, Wegener granulomatosis (systemic disease involving the kidney).

Tubulointerstitial disease:
- Reflux nephropathy (chronic pyelonephritis).
- Analgesic nephropathy.
- Obstructive nephropathy (stones, benign prostatic hypertrophy).
- Myeloma kidney (systemic disease involving the kidney).

Vascular disease:
- Scleroderma (systemic disease involving the kidney).
- Vasculitis (systemic disease involving the kidney).
- Renovascular renal failure (ischemic nephropathy).
- Atheroembolic renal disease (systemic disease involving the kidney).

Cystic disease:
- Autosomal dominant polycystic kidney disease.
- Medullary cystic kidney disease.

RENAL FAILURE, INTRINSIC OR PARENCHYMAL CAUSES[82]

ICD-10CM #
- N17.0 Acute kidney failure with tubular necrosis
- N17.1 Acute kidney failure with acute cortical necrosis
- N17.2 Acute kidney failure with medullary necrosis
- N17.8 Other acute kidney failure
- N17.9 Acute kidney failure, unspecified
- N18.9 Chronic kidney disease, unspecified

ABNORMALITIES OF THE VASCULATURE

Renal arteries: atherosclerosis, thromboembolism, arteritis.
Renal veins: thrombosis.
Microvasculature: vasculitis, thrombotic microangiopathy.

ABNORMALITIES OF GLOMERULI (ACUTE GLOMERULONEPHRITIS)

Antiglomerular membrane disease (Goodpasture syndrome).
Immune complex glomerulonephritis: SLE, postinfectious, idiopathic, membranoproliferative.

ABNORMALITIES OF INTERSTITIUM (ACUTE INTERSTITIAL NEPHRITIS)

Drugs (e.g., antibiotics, NSAIDs, diuretics, anticonvulsants, allopurinol).
Infectious pyelonephritis.
Infiltrative: lymphoma, leukemia, sarcoidosis.

ABNORMALITIES OF TUBULES

Physical obstruction (uric acid, oxalate, light chains).
Acute tubular necrosis:
- Ischemic.
- Toxic (antibiotics, chemotherapy, immunosuppressives, radiocontrast dyes, heavy metals, myoglobin, hemolyzed RBCs).

RENAL FAILURE, POSTRENAL CAUSES[82]

ICD-10CM #
- N17.0 Acute kidney failure with tubular necrosis
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- N17.9 Acute kidney failure, unspecified
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URETER AND RENAL PELVIS

Intrinsic obstruction:
- Blood clots.
- Stones.
- Sloughed papillae: diabetes, sickle cell disease, analgesic nephropathy.
- Inflammatory: fungus ball.

Extrinsic obstruction:
- Malignancy.
- Retroperitoneal fibrosis.
- Iatrogenic: inadvertent ligation of ureters.

BLADDER

Prostatic hypertrophy or malignancy.
Neuropathic bladder.
Blood clots.
Bladder cancer.
Stones.

URETHRAL

Strictures.
Congenital valves.

RENAL FAILURE, PRERENAL CAUSES[82]

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- N17.9 Acute kidney failure, unspecified
- N18.9 Chronic kidney disease, unspecified

DECREASED CARDIAC OUTPUT

CHF.
Arrhythmias.
Pericardial constriction or tamponade.
Pulmonary embolism.

HYPOVOLEMIA

GI tract loss (vomiting, diarrhea, nasogastric suction).
Blood losses (trauma, GI tract surgery).
Renal losses (diuretics, mineralocorticoid deficiency, postobstructive diuresis).
Skin losses (burns).

VOLUME REDISTRIBUTION (DECREASE IN EFFECTIVE BLOOD VOLUME)

Hypoalbuminemic states (cirrhosis, nephrosis).
Sequestration of fluid in "third" space (ischemic bowel, peritonitis, pancreatitis).
Peripheral vasodilation (sepsis, vasodilators, anaphylaxis).

ALTERED RENAL VASCULAR RESISTANCE

Increase in afferent vascular resistance (NSAIDs, liver disease, sepsis, hypercalcemia, cyclosporine).
Decrease in efferent arteriolar tone (ACE inhibitors).

RENAL INFARCTION[28]

ICD-10CM # N28.0 Ischemia and infarction of kidney

CAUSES OF RENAL INFARCTION

Thrombosis: Spontaneous
Atherosclerotic disease of aorta and renal artery.
Fibromuscular dysplasia of renal artery.
Aneurysms of aorta or renal artery.
Dissection of aorta or renal artery:
- Marfan syndrome.
- Ehlers-Danlos syndrome.

Vasculitis involving renal artery:
- Polyarteritis nodosa.
- Takayasu arteritis.
- Kawasaki disease.
- Thromboangiitis obliterans.
- Other necrotizing vasculitides.

Inflammatory disease of the aorta or renal artery:
- Syphilis.
- Tuberculosis.
- Mycoses.

Hypercoagulable states:
- Nephrotic syndrome.
- Antiphospholipid syndrome.
- Antithrombin III deficiency.
- Homocystinuria.

Thrombotic microangiopathies:
- Hemolytic-uremic syndrome.
- Thrombotic thrombocytopenic purpura.
- Antiphospholipid syndrome.
- Malignant hypertension.
- Scleroderma.
- Sickle cell nephropathy.
- Polycythemia vera.
- Postpartum hemolytic-uremic syndrome.
- Hyperacute vascular allograft rejection.

Thrombosis: Induced
Traumatic.
Following endovascular intervention.
Post renal transplantation.
Embolism
Cardiac source:
- Atrial fibrillation or other arrhythmias.
- Native and prosthetic valvular heart disease.
- Infective endocarditis.
- Marantic endocarditis.

Myocardial infarction with mural thrombi.
Left atrial myxoma or other tumor.
Noncardiac sources:
- Atheromatous embolic disease.
- Paradoxical emboli.
- Fat emboli.
- Tumor emboli.

Therapeutic renal embolization.
Segmental renal infarction of childhood.
Cisplatinum and gemcitabine.
Sickle cell disease or sickle cell trait.

RENAL PARENCHYMAL DISEASE, CHRONIC[36]

ICD-10CM # N28.9 Disorder of kidney and ureter, unspecified

DIFFERENTIAL DIAGNOSIS OF CHRONIC RENAL PARENCHYMAL DISEASE

No Papillary/Caliceal Abnormality
Diffuse Parenchymal Loss
Bilateral:
- Chronic glomerulonephritis.
- Diffuse small-vessel disease.
- Hereditary nephropathies.

Unilateral:
- Renal artery stenosis.
- Postirradiation.
- Rare:
  - Hypoplastic kidney.
  - Postobstructive atrophy.

FOCAL PARENCHYMAL LOSS

Infarct.
Previous trauma.
Papillary/Caliceal Abnormality
Diffuse Parenchymal Loss
Obstructive nephropathy.
Generalized reflux nephropathy.
No Parenchymal Loss
Papillary necrosis.
TB.
Medullary sponge kidney.
Megacalices.
Pelvicaliceal cyst.
Focal Parenchymal Loss
Focal reflux nephropathy (chronic atrophic pyelonephritis).
TB.
Calculus disease.

RENAL VEIN THROMBOSIS, CAUSES

ICD-10CM # I82.3 Embolism and thrombosis of renal vein

Nephrotic syndrome.
Renal cell carcinoma.
Aortic aneurysm causing compression.
Lymphadenopathy.
Retroperitoneal fibrosis.
Estrogen therapy.
Pregnancy.
Renal cell carcinoma with vein invasion.
Severe dehydration.

RESPIRATORY DISTRESS IN THE NEWBORN, CAUSES[30]

ICD-10CM # J96.00 Acute respiratory failure

RESPIRATORY DISTRESS IN THE NEWBORN

Noncardiopulmonary
Hypothermia or hyperthermia.
Hypoglycemia.
Metabolic acidosis.
Drug intoxications; withdrawal.
Polycythemia.
CNS insult.
Asphyxia.
Hemorrhage.
Neuromuscular disease.
Werdnig-Hoffman disease.
Myopathies.
Phrenic nerve injury.
Skeletal abnormalities.
Asphyxiating thoracic dystrophy.
Cardiovascular
Left-sided outflow obstruction.
Hypoplastic left heart.
Aortic stenosis.
Coarctation of the aorta.
Cyanotic lesions.
Transposition of the great vessels.
Total anomalous pulmonary venous return.
Tricuspid atresia.
Right-sided outflow obstruction.
Pulmonary
Upper airway obstruction.
Choanal atresia.
Vocal cord paralysis.
Meconium aspiration.
Clear fluid aspiration.
Transient tachypnea.
Pneumonia.
Pulmonary hypoplasia.
Primary.
Secondary.
Hyaline membrane disease.
Pneumothorax.
Pleural effusions.
Mass lesions.
Lobar emphysema.
Cystic adenomatoid malformation.

RESPIRATORY FAILURE, HYPOVENTILATORY[65]

ICD-10CM # J96.00 Acute respiratory failure, unspecified whether with hypoxia or hypercapnia
J96.90 Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia

ABNORMAL RESPIRATORY CAPACITY (NORMAL RESPIRATORY WORKLOADS)

Acute depression of CNS:
- Various causes.

Chronic central hypoventilation syndromes:
- Obesity-hypoventilation syndrome.
- Sleep apnea syndrome.
- Hypothyroidism.
- Shy-Drager syndrome (multisystem atrophy syndrome).

Acute toxic paralysis syndromes:
- Botulism.
- Tetanus.
- Toxic ingestion or bites.
- Organophosphate poisoning.

Neuromuscular disorders (acute and chronic):
- Myasthenia gravis.
- Guillain-Barré syndrome.
- Drugs.
- Amyotrophic lateral sclerosis.
- Muscular dystrophies.
- Polymyositis.
- Spinal cord injury.
- Traumatic phrenic nerve paralysis.

ABNORMAL PULMONARY WORKLOADS

Chronic obstructive pulmonary disease:
- Chronic bronchitis.
- Asthmatic bronchitis.
- Emphysema.

Asthma and acute bronchial hyperreactivity syndromes.
Upper airway obstruction.
Interstitial lung diseases.

ABNORMAL EXTRAPULMONARY WORKLOADS

Chronic thoracic cage disorders:
- Severe kyphoscoliosis.
- After thoracoplasty.
- After thoracic cage injury.

Acute thoracic cage trauma and burns.
Pneumothorax.
Pleural fibrosis and effusions.
Abdominal processes.

RESPIRATORY MUSCLE WEAKNESS[69]

ICD-10CM # Varies with specific diagnosis

CAUSES OF DECREASED RESPIRATORY MUSCLE STRENGTH OR ENDURANCE

Disorders of the phrenic nerve:
- Guillain-Barré syndrome.
- Poliomyelitis.

Respiratory muscle atrophy.
Disorders of neuromuscular transmission:
- Myasthenia gravis.
- Ventilator dependence.
- Malnutrition.
- Myopathy.
- Critical illness polyneuropathy/myopathy.

Altered diaphragmatic force-length relationship:
- Dynamic hyperinflation and diaphragmatic flattening.

RETINOPATHY, HYPERTENSIVE

ICD-10CM # H35.039 Hypertensive retinopathy, unspecified eye

Retinal venous obstruction.
Diabetic retinopathy.
Ocular ischemic syndrome.
Hyperviscosity.
Tortuosity of retinal artery.

RHINITIS

ICD-10CM #

J31.0	Chronic rhinitis
J30.0	Vasomotor rhinitis
J30.1	Allergic rhinitis due to pollen
J30.2	Other seasonal allergic rhinitis
J30.5	Allergic rhinitis due to food
J30.89	Other allergic rhinitis
J30.9	Allergic rhinitis, unspecified

Allergic rhinitis.
Infectious rhinitis.
Vasomotor rhinitis.
Exercise-induced rhinitis.
Emotional rhinitis.
Rhinitis medicamentosa.
Hormone-mediated rhinitis (menses, pregnancy, oral contraceptives, hypothyroidism).
GERD.
Chemical- or irritant-induced rhinitis.
Rhinitis mimics:
- Deviated septum.
- Enlarged adenoids.
- Nasal polyps/tumors.
- Foreign bodies.
- CSF rhinorrhea.
- Sarcoidosis.
- Midline granuloma.
- Granulomatosis with polyangiitis.
- SLE.
- Sjögren syndrome.

RHINITIS, CHRONIC[2]

ICD-10CM # J31.0 Chronic rhinitis

CLASSIFICATION OF CHRONIC RHINITIS

Allergic
Systemic.
Local (entopy).
Work-Related
Irritant.
Corrosive.
Immunologic.
Infectious (Rhinosinusitis)
Allergic.
Nonallergic.
Nonallergic
Idiopathic.
Nonallergic with eosinophilia.
Atrophic.
Primary.
Secondary.
Medication-related.
Topical vasoconstrictors (rhinitis medicamentosa).
Oral medications.
Exercise-induced.
Cold air-induced.
Gustatory.
Hormonal.
Aging.
Systemic diseases.

RHINOSINUSITIS, DIFFERENTIAL DIAGNOSIS[61]

ICD-10CM # Varies with specific diagnosis

DIFFERENTIAL DIAGNOSIS OF RHINOSINUSITIS

Allergic Rhinitis
Seasonal.
Perennial.
Combined seasonal and perennial.
Allergic fungal rhinosinusitis.
Nonallergic Rhinitis
Nonallergic, noninflammatory idiopathic rhinopathy (vasomotor rhinitis).
Nonallergic rhinitis with eosinophilia syndrome (NARES).
Cold dry air-induced rhinitis.
Gustatory rhinitis.
Infectious Rhinosinusitis
Bacterial.
Viral.
Fungal.
Granulomatous.
Drug-Induced Rhinitis
Oral contraceptives.
Various antihypertensives and ocular β-blockers.
Topical decongestants (rhinitis medicamentosa).
Phosphodiesterase-5 antagonists.
Mechanical Causes of Rhinosinusitis
Septal deviation.
Nasal foreign body.
Choanal atresia or stenosis.
Adenoid hypertrophy.
Encephalocele.
Glioma.
Dermoid.
Innate and Acquired Immunity Disorders
Congenital or acquired immunodeficiencies.
Cystic fibrosis.
Immotile cilia syndrome.
Systemic Inflammatory Disorders
Sarcoidosis.
Granulomatosis with polyangiitis.
Vasculitis.
Neoplastic Causes
Benign:
- Polyps.
- Nasopharyngeal angiofibroma.
- Inverting papilloma.

Malignant:
- Adenocarcinoma.
- Squamous cell carcinoma.
- Esthesioneuroblastoma.
- Lymphoma.
- Rhabdomyosarcoma.

RIB DEFECTS ON X-RAY[36]

ICD-10CM # Varies with specific diagnosis

CAUSES OF SUPERIOR MARGINAL RIB DEFECTS

Normal
Isolated defects.
Projectional artifacts (due to lordosis).
Neurologic
Paralytic poliomyelitis.
Quadriparesis.
Collagen Vascular Disease
Rheumatoid arthritis.
SLE.
Systemic sclerosis.
Local Pressure
Chest drainage tube.
Osteochondroma.
Neural tumor.
Coarctation of aorta.
Hyperparathyroidism Miscellaneous
Osteogenesis imperfecta.
Marfan syndrome.

RIB NOTCHING ON X-RAY[36]

ICD-10CM # Varies with specific diagnosis

CAUSES OF INFERIOR RIB NOTCHING

ARTERIAL

AORTIC OBSTRUCTION

Aortic coarctation.
Aortic thrombosis.
Aortitis.

SUBCLAVIAN ARTERY OBSTRUCTION

Blalock-Taussig operation.
Arteritis.
Atherosclerotic occlusion.

PULMONARY OLIGEMIA

Pulmonary atresia.
Tetralogy of Fallot.
Multiple pulmonary arterial stenoses.

Venous

CHRONIC SUPERIOR VENA CAVAL OBSTRUCTION

Arteriovenous
Arteriovenous Malformation
Pulmonary.
Chest wall.
Neural
Neurofibromas

RIGHT AXIS DEVIATION[52]

ICD-10CM # Varies with specific diagnosis

Normal variation.
Right ventricular hypertrophy.
Left posterior fascicular block.
Lateral myocardial infarction.
Pulmonary embolism.
Dextrocardia.
Mechanical shifts or emphysema causing a vertical heart.

SALIVARY GLAND ENLARGEMENT

ICD-10CM # K11.1 Hypertrophy of salivary gland

Neoplasm.
Sialolithiasis.
Infection (mumps, bacterial infection, HIV, TB).
Sarcoidosis.
Idiopathic.
Acromegaly.
Anorexia/bulimia.
Chronic pancreatitis.
Medications (e.g., phenylbutazone).
Cirrhosis.
DM.

SALIVARY GLAND SECRETION, DECREASED

ICD-10CM # K11.7 Disturbances of salivary secretion
R68.2 Dry mouth, unspecified

Medications (antihistamines, antidepressants, neuroleptics, antihypertensives).
Dehydration.
Anxiety.
Sjögren syndrome.
Sarcoidosis.
Mumps.
Amyloidosis.
CNS disorders.
Head and neck radiation.

SCLERODERMA-LIKE SYNDROMES[3]

ICD-10CM # Varies with specific diagnosis

OTHER DISEASES

Morphea.
Eosinophilic fasciitis.
Scleredema (of Buschke).
Scleromyxedema.
Graft-versus-host disease.
Nephrogenic-fibrosing dermopathy.

ENVIRONMENTAL AGENTS AND DRUGS

Bleomycin.
l-Tryptophan.
Organic solvents.
Pentazocine.
Toxic oil syndrome.
Vinyl chloride disease.
Gadolinium.

SCROTAL CALCIFICATIONS[74]

ICD-10CM # Varies with specific diagnosis

SCROTAL CALCIFICATIONS

Testicular
Solitary, postinflammatory granulomatous, vascular.
Microlithiasis.
"Burned-out" germ cell tumor.
Large-cell calcifying Sertoli cell tumor.
Teratoma.
Mixed germ cell tumor.
Sarcoid.
TB.
Chronic infarct
Extratesticular
Tunica vaginalis "scrotal pearls"
Chronic epididymitis
Schistosomiasis

SCROTAL MASSES, BOYS AND ADOLESCENTS[53]

ICD-10CM # R22.9 Localized swelling, mass and lump, unspecified

PAINFUL

Testicular torsion.
Torsion of appendix testis.
Epididymitis.
Trauma: ruptured testis, hematocele.
Inguinal hernia (incarcerated).
Mumps orchitis.

PAINLESS

Hydrocele.
Inguinal hernia.[41]
Varicocele.
Spermatocele.
Testicular tumor.
Henoch-Schönlein purpura.
Idiopathic scrotal edema.

SCROTAL PAIN[65]

ICD-10CM#		
	S31.30XA	Unspecified open wound of scrotum and testes, initial encounter
	N50.9	Disorder of male genital organs, unspecified
	R10.2	Pelvic and perineal pain
	N49.9	Inflammatory disorder of unspecified male genital organ
	N50.1	Vascular disorders of male genital organs
	N49.9	Inflammatory disorder of unspecified male genital organ

Torsion:
  Appendages.
  Spermatic cord.
Infection:
  Orchitis.
  Abscess.
  Epididymitis.
Neoplasia:
  Benign.
  Malignant.
Incarcerated hernia.
Trauma.
Hydrocele.
Spermatocele.
Varicocele.

[41] May be associated with discomfort.

SCROTAL PAIN, ADOLESCENT OR PEDIATRIC PATIENT[90]

ICD-10CM # Varies with specific diagnosis

DIFFERENTIAL DIAGNOSIS OF PEDIATRIC ADOLESCENT ACUTE SCROTAL PAIN

Appendage torsion:
  Appendix testis.
  Other appendage (epididymis, paradidymis, vas aberrans).
Spermatic cord torsion:
  Intravaginal, acute or intermittent.
  Extravaginal.
Epididymitis:
  Infectious:
    Urinary tract infection.
    Sexually transmitted disease.
    Viral.
  Sterile or traumatic.
Scrotal edema or erythema:

RIB NOTCHING ON X-RAY[36]

ICD-10CM # Varies with specific diagnosis

CAUSES OF INFERIOR RIB NOTCHING

ARTERIAL

AORTIC OBSTRUCTION

Aortic coarctation.
Aortic thrombosis.
Aortitis.

SUBCLAVIAN ARTERY OBSTRUCTION

Blalock-Taussig operation.
Arteritis.
Atherosclerotic occlusion.

PULMONARY OLIGEMIA

Pulmonary atresia.
Tetralogy of Fallot.
Multiple pulmonary arterial stenoses.

Venous

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Arteriovenous
Arteriovenous Malformation
Pulmonary.
Chest wall.
Neural
Neurofibromas

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Sarcoidosis.
Idiopathic.
Acromegaly.
Anorexia/bulimia.
Chronic pancreatitis.
Medications (e.g., phenylbutazone).
Cirrhosis.
DM.

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ICD-10CM # K11.7 Disturbances of salivary secretion
R68.2 Dry mouth, unspecified

Medications (antihistamines, antidepressants, neuroleptics, antihypertensives).
Dehydration.
Anxiety.
Sjögren syndrome.
Sarcoidosis.
Mumps.
Amyloidosis.
CNS disorders.
Head and neck radiation.

SCLERODERMA-LIKE SYNDROMES[3]

ICD-10CM # Varies with specific diagnosis

OTHER DISEASES

Morphea.
Eosinophilic fasciitis.
Scleredema (of Buschke).
Scleromyxedema.
Graft-versus-host disease.
Nephrogenic-fibrosing dermopathy.

ENVIRONMENTAL AGENTS AND DRUGS

Bleomycin.
l-Tryptophan.
Organic solvents.
Pentazocine.
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Gadolinium.

SCROTAL CALCIFICATIONS[74]

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SCROTAL CALCIFICATIONS

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Solitary, postinflammatory granulomatous, vascular.
Microlithiasis.
"Burned-out" germ cell tumor.
Large-cell calcifying Sertoli cell tumor.
Teratoma.
Mixed germ cell tumor.
Sarcoid.
TB.
Chronic infarct
Extratesticular
Tunica vaginalis "scrotal pearls"
Chronic epididymitis
Schistosomiasis

SCROTAL MASSES, BOYS AND ADOLESCENTS[53]

ICD-10CM # R22.9 Localized swelling, mass and lump, unspecified

PAINFUL

Testicular torsion.
Torsion of appendix testis.
Epididymitis.
Trauma: ruptured testis, hematocele.
Inguinal hernia (incarcerated).
Mumps orchitis.

PAINLESS

Hydrocele.
Inguinal hernia.[41]
Varicocele.
Spermatocele.
Testicular tumor.
Henoch-Schönlein purpura.
Idiopathic scrotal edema.

SCROTAL PAIN[65]

ICD-10CM#		
	S31.30XA	Unspecified open wound of scrotum and testes, initial encounter
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	N49.9	Inflammatory disorder of unspecified male genital organ
	N50.1	Vascular disorders of male genital organs
	N49.9	Inflammatory disorder of unspecified male genital organ

Torsion:
  Appendages.
  Spermatic cord.
Infection:
  Orchitis.
  Abscess.
  Epididymitis.
Neoplasia:
  Benign.
  Malignant.
Incarcerated hernia.
Trauma.
Hydrocele.
Spermatocele.
Varicocele.

[41] May be associated with discomfort.

SCROTAL PAIN, ADOLESCENT OR PEDIATRIC PATIENT[90]

ICD-10CM # Varies with specific diagnosis

DIFFERENTIAL DIAGNOSIS OF PEDIATRIC ADOLESCENT ACUTE SCROTAL PAIN

Appendage torsion:
  Appendix testis.
  Other appendage (epididymis, paradidymis, vas aberrans).
Spermatic cord torsion:
  Intravaginal, acute or intermittent.
  Extravaginal.
Epididymitis:
  Infectious:
    Urinary tract infection.
    Sexually transmitted disease.
    Viral.
  Sterile or traumatic.
Scrotal edema or erythema:

Diaper dermatitis, insect bite, or other skin lesions.
Idiopathic scrotal edema.
Orchitis:
Associated with epididymitis with or without abscess.
Vasculitis (e.g., Henoch-Schönlein purpura).
Viral illness (mumps).
Trauma:
Hematocele or scrotal contusion or testis rupture.
Hernia or hydrocele:
Inguinal hernia with or without incarceration.
Communicating hydrocele.
Encysted hydrocele with or without torsion.
Associated with acute abdominal pathology (e.g., appendicitis, peritonitis).
Varicocele.
Intrascrotal mass:
Cystic dysplasia or tumor of testis.
Epididymal cyst, spermatocele or tumor.
Other paratesticular tumors.
Musculoskeletal pain from inguinal tendonitis or muscle strain.
Referred pain (e.g., ureteral calculus or anomaly).

SCROTAL SWELLING

ICD-10CM # N50.8 Other specified disorders of male genital organs

Hydrocele.
Varicocele.
Neoplasm.
Acute epididymitis.
Orchitis.
Trauma.
Hernia.
Torsion of spermatic cord.
Torsion of epididymis.
Torsion of testis.
Insect bite.
Folliculitis.
Sebaceous cyst.
Thrombosis of spermatic vein.
Other: lymphedema, dermatitis, fat necrosis, Henoch-Schönlein purpura, idiopathic scrotal edema.

SEIZURE

ICD-10CM # R56.9 Unspecified convulsions

Syncope.
Alcohol abuse/withdrawal.
TIA.
Hemiparetic migraine.
Psychiatric disorders.
Carotid sinus hypersensitivity.
Hyperventilation, prolonged breath holding.
Hypoglycemia.
Narcolepsy.
Movement disorders (tics, hemiballismus).
Hyponatremia.
Brain tumor (primary or metastatic).
Tetanus.
Strychnine, phencyclidine poisoning.

SEIZURE, PEDIATRIC[7]

ICD-10CM # R56.9 Unspecified convulsions
P90 Convulsions of newborn

FIRST MONTH OF LIFE

First Day
Hypoxia.
Drugs.
Trauma.
Infection.
Hyperglycemia.
Hypoglycemia.
Pyridoxine deficiency.
Day 2 to 3
Infection.
Drug withdrawal.
Hypoglycemia.
Hypocalcemia.
Developmental malformation.
Intracranial hemorrhage.
Inborn error of metabolism.
Hyponatremia or hypernatremia.
Day >4
Infection.
Hypocalcemia.
Hyperphosphatemia.
Hyponatremia.
Developmental malformation.
Drug withdrawal.
Inborn error of metabolism.

1 TO 6 MO

As above.

6 MO TO 3 YR

Febrile seizures.
Birth injury.
Infection.
Toxin.
Trauma.
Metabolic disorder.
Cerebral degenerative disease.

>3 YR

Idiopathic.
Infection.
Trauma.
Cerebral degenerative disease.

SEIZURE MIMICS[3]

ICD-10CM # Varies with specific diagnosis

NON-EPILEPTIC EPISODIC DISORDERS THAT MAY RESEMBLE SEIZURES

Movement disorders: myoclonus, paroxysmal choreoathetosis, episodic ataxias, hyperexplexia (startle disease).
Migraine: confusional, vertebrobasilar, visual auras.
Syncope.
Behavioral and psychiatric: psychogenic nonepileptic attacks (pseudoseizures), hyperventilation syndrome, panic or anxiety disorder, dissociative states.
Cataplexy (usually associated with narcolepsy).
Transient ischemic attack.
Alcoholic blackouts.
Hypoglycemia.

SEXUAL DIFFERENTIATION ABNORMALITIES[90]

ICD-10CM # Varies with specific diagnosis

ABNORMAL SEXUAL DIFFERENTIATION

Disorders of gonadal differentiation.
Seminiferous tubule dysgenesis.
Klinefelter syndrome.
46,XX male.
Syndromes of gonadal dysgenesis:
Turner syndrome.
Pure gonadal dysgenesis.
Mixed gonadal dysgenesis.
Partial gonadal dysgenesis (dysgenetic male pseudohermaphroditism).
Bilateral vanishing testis, testicular regression syndromes.
Ovotesticular DSD (true hermaphroditism).
46,XX DSD (masculinized female):
Congenital adrenal hyperplasia (21-hydroxylase, 11β-hydroxylase, 3β-hydroxysteroid dehydrogenase deficiencies).
Maternal androgens.
46,XY DSD (undermasculinized male).
Leydig cell agenesis, unresponsiveness.
Disorders of testosterone biosynthesis.
Variants of congenital adrenal hyperplasia affecting corticosteroid and testosterone synthesis:
StAR deficiency (congenital lipoid adrenal hyperplasia).
Cytochrome P450 oxidoreductase (POR) deficiency.
3β-Hydroxysteroid dehydrogenase deficiency.
17β-Hydroxylase deficiency.
Disorders of testosterone biosynthesis:
17,20-Lyase deficiency.
17β-Hydroxysteroid oxidoreductase deficiency.
Disorders of androgen-dependent target tissue:
Androgen receptor and postreceptor defects.
Syndrome of complete (severe) androgen insensitivity.
Syndrome of partial androgen insensitivity.
Mild androgen insensitivity syndrome (MAIS).
Disorders of testosterone metabolism by peripheral tissues:
5α-Reductase deficiency.
Disorders of synthesis, secretion, or response to müllerian-inhibiting substance.
Persistent müllerian duct syndrome.
Unclassified forms:
In females: Mayer-Rokitansky-Küster-Hauser syndrome.
Disorder of sex development (DSD).

SEXUAL DYSFUNCTION, FEMALE[3]

ICD-10CM # R37 Sexual dysfunction, unspecified

FACTORS THAT MAY INFLUENCE SEXUAL FUNCTIONING IN WOMEN

Biological

Medications (e.g., antidepressants, antihypertensives).
Vaginal atrophy, pain with intercourse.
Low testosterone levels (e.g., bilateral oophorectomy).
Illness (e.g., diabetes, hypothyroidism, cerebrovascular accident).
Sleep disturbances, fatigue.
Disability or pain from illness (e.g., arthritis).
Incontinence.

Psychological

Depression.
Body image.

Interpersonal

Marital issues.
Poor communication.
Partner's sexual problems (e.g., erectile dysfunction).
Partner's health problems (e.g., myocardial infarction).

Sociocultural

Ageism ("too old" to want sex).
Multiple other obligations and commitments.
Lack of partner.

SEXUALLY TRANSMITTED DISEASES, ANORECTAL REGION[60]

ICD-10CM #		
	K62.89	Other specified diseases of anus and rectum

ULCERATIVE

Lymphogranuloma venereum.
Herpes simplex virus.
Early (primary) syphilis.
Chancroid (*Haemophilus ducreyi*).
Cytomegalovirus.
Idiopathic (usually HIV positive).

NONULCERATIVE

Condyloma acuminatum.
Gonorrhea.
Chlamydia *(Chlamydia trachomatis).*
Syphilis.

SEXUAL PRECOCITY[94]

ICD-10CM #		
	E30.1	Precocious puberty
	E30.8	Other disorders of puberty

TRUE PRECOCIOUS PUBERTY

Premature reactivation of LHRH pulse generator.

INCOMPLETE SEXUAL PRECOCITY

(Pituitary gonadotropin independent).

Males

Chorionic gonadotropin-secreting tumor.
Leydig cell tumor.
Familial testotoxicosis.
Virilizing congenital adrenal hyperplasia.
Virilizing adrenal tumor.
Premature adrenarche.

Females

Granulosa cell tumor (follicular cysts may be manifested similarly).
Follicular cyst.
Feminizing adrenal tumor.
Premature thelarche.
Premature adrenarche.
Late-onset virilizing congenital adrenal hyperplasia.

In Both Sexes

McCune-Albright syndrome.
Primary hypothyroidism.

SHOULDER PAIN

ICD-10CM #		
	M24.819	Other specific joint derangements of unspecified shoulder, not elsewhere classified
	M75.80	Other shoulder lesions, unspecified shoulder
	S43.409A	Unspecified sprain of unspecified shoulder joint, initial encounter
	S46.919A	Strain of unspecified muscle, fascia and tendon at shoulder and upper arm level, unspecified arm, initial encounter

WITH LOCAL FINDINGS IN SHOULDER

Trauma: contusion, fracture, muscle strain, trauma to spinal cord.
Arthrosis, arthritis, RA, ankylosing spondylitis.
Bursitis, synovitis, tendinitis, tenosynovitis.
Aseptic (avascular) necrosis.
Local infection: septic arthritis, osteomyelitis, abscess, herpes zoster, TB.

WITHOUT LOCAL FINDINGS IN SHOULDER

Cardiovascular disorders: ischemic heart disease, pericarditis, aortic aneurysm.
Subdiaphragmatic abscess, liver abscess.
Cholelithiasis, cholecystitis.
Pulmonary lesions: apical bronchial carcinoma, pleurisy, pneumothorax, pneumonia.
GI lesions: PUD, gastric neoplasm, peptic esophagitis.
Pancreatic lesions: carcinoma, calculi, pancreatitis.
CNS abnormalities: neoplasm, vascular abnormalities.
Multiple sclerosis.
Syringomyelia.
Polymyositis/dermatomyositis.
Psychogenic.
Polymyalgia rheumatica.
Ectopic pregnancy.

SHOULDER PAIN BY LOCATION

ICD-10CM #		
	M75.80	Other shoulder lesions, unspecified shoulder
	S43.499A	Other sprain of unspecified shoulder joint, initial encounter
	S46.019A	Strain of muscle(s) and tendon(s) of the rotator cuff of unspecified shoulder, initial encounter
	S46.819A	Strain of other muscles, fascia and tendons at shoulder and upper arm level, unspecified arm, initial encounter

TOP OF SHOULDER (C4)

Cervical source.
Acromioclavicular.
Sternoclavicular.
Diaphragmatic.

SUPEROLATERAL (C5)

Rotator cuff tendinitis.
Impingement.
Adhesive capsulitis.
Glenohumeral arthritis.

ANTERIOR

Bicipital tendinitis and rupture.
Glenoid labral tear.
Adhesive capsulitis.
Glenohumeral arthritis.
Osteonecrosis.

AXILLARY

Neoplasm (Pancoast, mediastinal).
Herpes zoster.

SHOULDER PAIN, IN DIFFERENT AGE GROUPS[18]

ICD-10CM #		
	M25.519	Pain in unspecified shoulder

COMMON CAUSES OF SHOULDER PAIN IN DIFFERENT AGE GROUPS

Childhood (2 to 10 yr)

Intraarticular

Instability.

Periarticular

Osteochondromas.

Adolescence (10 to 18 yr)

Intraarticular

Instability.

Early Adulthood (18 to 30 yr)

Intraarticular

Instability.
Acromioclavicular joint sprain.

Periarticular
Calcific tendonitis.
Impingement.
Referred
Cervical.
Adulthood (30 to 60 yr)
Intraarticular
Osteochondritis.
Osteoarthritis.
Frozen shoulder.
Inflammatory arthritis.
Periarticular
Calcific tendonitis.
Impingement.
Rotator cuff tear.
Bicipital tendonitis.
Referred
Cervical.
Old Age (>60 yr)
Intraarticular
Osteochondritis.
Osteoarthritis.
Frozen shoulder.
Inflammatory arthritis.
Periarticular
Impingement.
Rotator cuff tear.
Referred
Cervical.

SINUS NODE DYSFUNCTION[34]

ICD-10CM # Varies with specific diagnosis

CAUSES OF SINUS NODE DYSFUNCTION

Intrinsic
Hypothyroidism.
Fibrocalcific degeneration.
Increased vagal tone, especially in sleep apnea.
Congenital mutations.
Scleroderma.
Amyloidosis.
Chagas disease.
Extrinsic
Trauma, including cardiac surgery.
Drugs:
- Calcium-channel blockers.
- β-Blockers.
- Digoxin.
- Antiarrhythmic medications (amiodarone, dronedarone, sotalol, flecainide, propafenone).
- Lithium.

SINUS OSTIAL OBSTRUCTION[10]

ICD-10CM # Varies with specific diagnosis

FACTORS THAT PREDISPOSE TO SINUS OSTIAL OBSTRUCTION

Mucosal Swelling
Systemic factors:
- Viral upper respiratory infection.
- Allergic inflammation.
- Cystic fibrosis.
- Immune disorders.
- Ciliary dyskinesia.
- Tobacco smoke.

Local insult:
- Facial trauma.
- Swimming, diving.
- Rhinitis medicamentosa.
- Nasal intubation.

Mechanical Obstruction
Choanal atresia.
Deviated septum.
Nasal polyps.
Foreign body.
Tumor.
Ethmoid bullae.

SINUS TACHYCARDIA[69]

ICD-10CM # R00.0 Tachycardia, unspecified

DIFFERENTIAL DIAGNOSIS OF SINUS TACHYCARDIA

Etiologic Category
Specific Disorders
Hemodynamic:
- Heart failure: systolic and diastolic heart failure caused by ischemic, valvular, or nonischemic myopathy.
- Loss of circulating blood volume: GI bleeding, anemia, shifts of intravascular fluid due to changes in colloidal osmotic pressure or inflammation.
- Septic shock: dehydration.
- Vascular shunts: intracardiac as well as aortovenous malformations, fistulas.
- Pulmonary embolism.

Metabolic and neurohumoral:
- Sepsis: infections and inflammatory conditions.
- Hyperthyroidism.
- Paget disease of the bone.
- Pheochromocytoma.
- Carcinoid syndrome.
- Beriberi heart disease.
- Carcinoma.
- Hyperpyrexia.
- Acidosis.
- Exercise.

Pharmacologic:
- Sympathomimetic agents: isoproterenol, epinephrine, or dopamine.
- Vagolytic agents, atropine, scopolamine.
- Vasodilators: nitrates, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, hydrazine, as well as centrally acting vasodilators.
- Thyroid preparations, caffeine and nicotine.
- Bronchodilators, including theophylline and terbutaline.
- Anesthetic agents, including spinal anesthetics, causing peripheral vasodilation.
- Drugs of abuse: amphetamines, cocaine, "ecstasy," cannabis.

Neurologic/psychological:
- Pain.
- Fear, anxiety, and hysteria.
- Hyper-beta adrenergic phase of neurocardiogenic syncope.
- Autonomic dysfunction such as with diabetes.

SKIN AND RENAL[79]

ICD-10CM # Varies with specific diagnosis

SELECTED CONDITIONS WITH CONCURRENT SKIN AND RENAL INVOLVEMENT

More Common
Lupus erythematosus.
Leukocytoclastic vasculitis.
Henoch-Schönlein purpura.
Mixed cryoglobulinemia.
Diabetes mellitus.
Systemic vasculitis.
Less Common
Nail-patella syndrome.
Hemolytic-uremic syndrome.
Toxic shock syndrome.
Mixed connective tissue disease.
Dermatomyositis.
Rheumatoid arthritis.
Sjögren syndrome.
Dermatitis herpetiformis.
Sarcoidosis.
Systemic sclerosis.
Ulcerative colitis.
Amyloidosis.
Toxic epidermolysis.
Hypothyroidism.
Graves disease.
Fabry disease.
Neurofibromatosis.
Hurler syndrome.
Castleman disease.
Infectious endocarditis.
Staphylococcal scalded skin syndrome (in adults).

SKIN INDURATION, CHRONIC[41]

ICD-10CM # Varies with specific diagnosis

CONDITIONS ASSOCIATED WITH CHRONIC SKIN INDURATION

Systemic sclerosis.
Localized scleroderma.
Scleroderma variants.
Scleredema:
- Scleredema adultorum of Buschke.
- Scleredema diabeticorum.
- Scleredema neonatorum.

Scleromyxedema.
Nephrogenic fibrosing dermopathy.
Eosinophilic syndromes:
- Eosinophilic fasciitis (diffuse fasciitis with eosinophilia, Schulman disease).
- Eosinophilia-myalgia syndrome.
- Toxic oil syndrome.

Chronic graft-versus-host disease.
Pseudoscleroderma (local injection of vitamin K, bleomycin, pentazocine).
Metabolic diseases:
- Porphyria cutanea tarda.
- Phenylketonuria.
- Werner syndrome.
- Acromegaly.

Pachydermoperiostitis.

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy (POEMS).
Stiff skin syndrome.
Reflex sympathetic dystrophy.
Hemiplegia.

SMALL BOWEL MASSES[86]

ICD-10CM # Varies with specific diagnosis

Cyst:
  Mesenteric cyst.
Tumor:
  Benign.
  Malignant.
Intussusception.
Inflammation:
  Crohn disease.

SMALL BOWEL OBSTRUCTION[60]

ICD-10CM # K56.5 Intestinal adhesions [bands] with obstruction (postprocedural) (postinfection)
Q41.9 Congenital absence, atresia and stenosis of small intestine, part unspecified

INTRINSIC

Congenital (atresia, stenosis).
Inflammatory (Crohn, radiation enteritis).
Neoplasms (metastatic or primary).
Intussusception.
Traumatic (hematoma).

EXTRINSIC

Hernias (internal and external).
Adhesions.
Volvulus.
Compressing masses (tumors, abscesses, hematomas).

INTRALUMINAL

Foreign body.
Gallstones.
Bezoars.
Barium.
Ascaris infestation.

SMALL INTESTINE ULCERATION

ICD-10CM # K63.3 Ulcer of intestine

Inflammatory bowel disease.
Celiac disease.
Vasculitis, SLE, Behçet syndrome.
Uremia.
Infections *(Campylobacter,* TB, *Yersinia,* parasites, typhoid, cytomegalovirus [CMV], *Clostridium).*
Mesenteric insufficiency.
Neoplasms.
Radiation.
Drugs (salicylates, potassium, indomethacin, antimetabolites).
Meckel diverticulum.
Zollinger-Ellison syndrome.
Lymphocytic enterocolitis.
Stomal ulceration.

SMELL DISTURBANCE

ICD-10CM # R43.8 Other disturbances of smell and taste

Upper respiratory tract infection.
Nasal or paranasal sinus disease.
Exposure to noxious vapors.
Head trauma.
Idiopathic.
Dental caries, periodontal disease.
Medications.

SODIUM RETENTION, RENAL CAUSES[79]

ICD-10CM # Varies with specific diagnosis

CAUSES OF RENAL SODIUM RETENTION

Primary
Oliguric acute kidney injury.
Chronic kidney disease.
Glomerular disease.
Severe bilateral renal artery stenosis.
Na+-retaining tubulopathies (genetic).
Mineralocorticoid excess.
Secondary
Heart failure.
Cirrhosis.
Idiopathic edema.

SOFT TISSUE MASS MIMICKING MALIGNANCY[71]

ICD-10CM # Varies with specific diagnosis

OVERVIEW OF DISEASES THAT CAN PRESENT AS A SOFT TISSUE MASS MIMICKING MALIGNANCY

Etiology	Disease Entity
Trauma:	Muscle contusion. Hematoma. Muscle herniation. Calcific myonecrosis. Hypothenar hammer syndrome. Myositis ossificans.
Metabolic:	Diabetic myopathy. Gout. Pseudogout. Calcific tendinosis.
Congenital:	Accessory muscle.
Infectious:	Necrotizing fasciitis. Abscess. Pyomyositis. Hydatid cystic disease. Cat-scratch disease. Actinomycosis.
Inflammation:	Bursitis. Sarcoidosis. Foreign body reaction. Injection granuloma. Granuloma annulare. Epidermal inclusion cyst.
Vascular:	Adventitial cystic disease. Pseudoaneurysm. Thrombosed vein. Arteriovenous vascular malformation.
Miscellaneous:	Focal myositis. Amyloid tumor of soft tissue.

SOFT TISSUE TUMORS, PEDIATRIC PATIENTS[71]

ICD-10CM # Varies with specific diagnosis

PEDIATRIC SOFT TISSUE TUMORS

Vascular lesions:
  Hemangioma of infancy.*
  Congenital hemangioma.
  Hemangioendothelioma (Kasabach-Merritt syndrome).
  Arteriovenous malformation.
  Venous malformations.
  Lymphatic malformation (lymphangioma, cystic hygroma).
  Capillary malformation.
Adipocytic tumors:
  Lipoma.
  Lipoblastoma.
  Liposarcoma.
Fibrohistiocytic tumors:
  Pigmented villonodular synovitis.
  Giant cell tumor of tendon sheath.
Fibroblastic and myofibroblastic tumors:
  Nodular fasciitis.
  Fibrous hamartoma of infancy.
  Myofibroma, myofibromatosis.
  Infantile fibrosarcoma.
  Fibromatosis colli.
Neurogenic tumors:
  Schwannoma.
  Neurofibroma.
  Malignant nerve sheath tumor.
Leiomyoma
Rhabdomyosarcoma
Tumors of uncertain differentiation
  Synovial cell sarcoma.
  Primitive neuroectodermal tumor (Ewing sarcoma).
Pilomatricoma

*Lesions with MR-specific features.

SORE THROAT[7]

ICD-10CM # J02 Acute pharyngitis

DIFFERENTIAL DIAGNOSIS FOR SORE THROAT

Infectious Causes
Aerobes
Common:
  Streptococcus pyogenes (GABHS).
  GABHS.
  Peptostreptococcus spp.
  Non–group A streptococcus.
  Neisseria gonorrhoeae.
  Neisseria meningitides.
  Mycoplasma pneumoniae.

Arcanobacterium hemolyticum.
Chlamydia trachomatis.
Staphylococcus aureus.
Uncommon:
Haemophilus influenzae.
Haemophilus parainfluenzae.
Coccidioides spp.
Corynebacterium diphtheriae.
Streptococcus pneumoniae.
Yersinia enterocolitica.
Treponema pallidum.
Francisella tularensis.
Legionella pneumophila.
Mycobacterium spp.

ANAEROBES

Bacteroides spp.
Peptococcus spp.
Clostridium spp.
Fusobacterium spp.
Prevotella spp.

OTHER

Candida spp.

VIRAL

Rhinovirus.
Adenovirus.
Coronavirus.
Herpes simplex 1, 2.
Influenza A, B.
Parainfluenza.
Cytomegalovirus.
Epstein-Barr.
Varicella-zoster.
Hepatitis virus.
Noninfectious Causes

SYSTEMIC

Kawasaki disease.
Stevens-Johnson syndrome.
Cyclic neutropenia.
Thyroiditis.
Connective tissue disease.

TRAUMA, MISCELLANEOUS

Penetrating injury.
Angioneurotic edema.
Retained foreign body.
Anomalous aortic arch.
Laryngeal fracture.
Calcific retropharyngeal tendinitis.
Retropharyngeal hematoma.
Caustic exposure.

TUMOR

Tongue.
Larynx.
Thyroid.
Leukemia.

SPASTIC PARAPLEGIAS

ICD-10CM # G82.20 Paraplegia, unspecified

Cervical spondylosis.
Friedreich ataxia.
Multiple sclerosis.
Spinal cord tumor.
HIV.
Tertiary syphilis.
Vitamin B_{12} deficiency.
Spinocerebellar ataxias.
Syringomyelia.
Spinal cord AV malformations.
Adrenoleukodystrophy.

SPINAL CORD COMPRESSION, EPIDURAL

ICD-10CM # Varies with specific diagnosis

Osteoarthritis.
Meningioma.
Spinal epidural abscess.
Spinal epidural hematoma.
Spinal epidural vascular malformations.
RA.
Metastatic cancer (vertebral, intramedullary, leptomeninges).
Radiation myelopathy.
Neurofibroma.
Sarcoidosis.
Paraneoplastic myelopathy.
Histiocytosis.

SPINAL CORD DYSFUNCTION

ICD-10CM #	G95.9	Disease of spinal cord, unspecified
	Q07.9	Congenital malformation of nervous system, unspecified
	D51.1	Vitamin B_{12} deficiency anemia due to selective vitamin B_{12} malabsorption with proteinuria
	D51.3	Other dietary vitamin B_{12} deficiency anemia
	D51.8	Other vitamin B_{12} deficiency anemias
	G95.89	Other specified diseases of spinal cord
	G95.19	Other vascular myelopathies

Trauma.
Multiple sclerosis.
Transverse myelitis.
Neoplasm (primary, metastatic).
Syringomyelia.
Spinal epidural abscess.
HIV myelopathy.
Diskitis.
Spinal epidural hematoma.
Spinal cord infarction.
Spinal AV malformation.
Subarachnoid hemorrhage.

SPINAL CORD DYSFUNCTION, NONTRAUMATIC[7]

ICD-10CM #	Q07.9	Congenital malformation of nervous system, unspecified

NONTRAUMATIC ETIOLOGIES OF SPINAL CORD DYSFUNCTION

Processes Affecting the Spinal Cord or Blood Supply Directly
Multiple sclerosis.
Transverse myelitis.
Spinal arteriovenous malformation/subarachnoid hemorrhage.
Syringomyelia.
HIV myelopathy.
Other myelopathies.
Spinal cord infarction.
Compressive Lesions Affecting the Spinal Cord
Spinal epidural abscess.
Spinal epidural hematoma.
Diskitis.
Neoplasm.
Metastatic.
Primary CNS.

CNS, Central nervous system; *HIV,* human immunodeficiency virus.

SPINAL CORD ISCHEMIC SYNDROMES

ICD-10CM # Varies with specific diagnosis

Systemic hypotension.
Venous or arterial occlusion.
Arterial dissection.
Thromboembolism.
Endovascular procedures.
Vasculitis.
Fibrocartilaginous embolism.
Regional hemodynamic compromise.

SPINAL TUMORS[32]

ICD-10CM # Varies with specific diagnosis

EXTRADURAL

Metastases.
Primary bone tumors arising in spine.

INTRADURAL EXTRAMEDULLARY

Meningiomas.
Neurofibromas.
Schwannomas.
Lipomas.
Arachnoid cysts.
Epidermoid cysts.
Metastasis.

INTRAMEDULLARY

Ependymoma.
Glioma.
Hemangioblastoma.
Lipoma.
Metastases.

SPLENIC CYSTS, CLASSIFICATION[15]

ICD-10CM # D73.4 Cyst of spleen

Primary (true).
Parasitic.

Nonparasitic.
Congenital.
Epidermoid.
Dermoid.
Mesothelial (serous).
Transitional.
Neoplastic.
Secondary (false): pseudocysts.
Traumatic.
Degenerative.
Inflammatory.
Hemorrhagic.

SPLENIC MASSES, FOCAL SOLID[74]

ICD-10CM # Varies with specific diagnosis

FOCAL SOLID SPLENIC MASSES

Benign
Hemangioma.
Hamartoma.
Littoral cell angioma.
Lymphangioma.
Sclerosing angiomatoid nodular transformation (SANT).
Inflammatory pseudotumor.
Malignant
Lymphoma.
Metastases.
Angiosarcoma.
Hemangiopericytoma.
Other
Infarct.

SPLENIC NODULES[74]

ICD-10CM # Varies with specific diagnosis

CAUSES OF SPLENIC NODULES

Infectious
Tuberculosis/*Mycobacterium avium-intracellulare* complex.
Pyogenic abscesses.
Histoplasmosis.
Candida abscesses.
Cat-scratch disease.
Pneumocystis jiroveci (formerly *P. carinii pneumonia*).
Inflammatory
Sarcoidosis.
Malignant
Lymphoma.
Metastases.
Other
Gamna-Gandy bodies.
Gaucher disease.

SPLENIC TUMORS, CLASSIFICATION[15]

ICD-10CM # C26.1 Malignant neoplasm of spleen

Malignant.
Lymphoproliferative disease.
Non-Hodgkin lymphoma.
Hodgkin disease.
Hairy cell leukemia.
Chronic lymphocytic leukemia.
Myeloproliferative disease.
Chronic myelogenous leukemia.
Myelofibrosis.
Primary tumors.
Angiosarcoma.
Metastatic tumors.
Benign.
Hemangiomas.
Hamartomas.
Lymphangiomas.
Sclerosing angiomatoid nodular transformation (SANT).

SPLENOMEGALY

ICD-10CM # R16.1 Splenomegaly, not elsewhere classified
D73.2 Chronic congestive splenomegaly
R16.1 Splenomegaly, not elsewhere classified

Hepatic cirrhosis.
Neoplastic involvement: CML, CLL, lymphoma, multiple myeloma.
Bacterial infections: TB, infectious endocarditis, typhoid fever, splenic abscess.
Viral infections: infectious mononucleosis, viral hepatitis, HIV.
Gaucher disease and other lipid storage diseases.
Sarcoidosis.
Parasitic infections (malaria, kala-azar, histoplasmosis).
Hereditary and acquired hemolytic anemias.
Idiopathic thrombocytopenic purpura (ITP).
Collagen vascular disorders: SLE, RA (Felty syndrome), polyarteritis nodosa.
Serum sickness, drug hypersensitivity reaction.
Splenic cysts and benign tumors: hemangioma, lymphangioma.
Thrombosis of splenic or portal vein.
Polycythemia vera, myeloid metaplasia.

SPLENOMEGALY AND HEPATOMEGALY[86]

ICD-10CM # R16.1 Splenomegaly, not elsewhere classified
R16.0 Hepatomegaly, not elsewhere classified

CAUSES OF SPLENOMEGALY AND HEPATOSPLENOMEGALY

Massive Splenomegaly
Hematologic disease (e.g., chronic myeloid leukemia, myelofibrosis).
Moderate Splenomegaly
The above causes.
Portal hypertension.
Hematologic disease (e.g., lymphoma, leukemia, thalassemia).
Storage disease (e.g., Gaucher disease).
Small Splenomegaly
The above causes.
Infective (hepatitis, leptospirosis, malaria, bacterial endocarditis).
Hematologic disease (e.g., hemolytic anemias, essential thrombocythemia, polycythemia rubra vera).
Connective tissue diseases or vasculitis (e.g., rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa).
Solitary cyst, polycystic syndrome, hydatid cyst.
Infiltration (amyloid, sarcoid).
Hepatosplenomegaly
Chronic liver disease with portal hypertension.
Hematologic disease (e.g., myeloproliferative disease, lymphoma).
Infection (e.g., amyloid, sarcoid).
Connective tissue disease (e.g., systemic lupus erythematosus).

SPLENOMEGALY AND HYPERSPLENISM[46]

ICD-10CM # R16.1 Splenomegaly, not elsewhere classified
D73.1 Hypersplenism
D73.81 Neutropenic splenomegaly

DIFFERENTIAL DIAGNOSIS OF SPLENOMEGALY AND HYPERSPLENISM

Infections
Acute
Viral (viral hepatitis, infectious mononucleosis, CMV infection).
Bacterial (septicemia, salmonellosis, brucellosis, splenic abscess).
Parasite (toxoplasmosis).
Subacute and Chronic
Subacute bacterial endocarditis.
Tuberculosis.
Malaria.
Kala-azar.
Fungal disease.
Inflammation
Felty syndrome.
SLE.
Serum sickness.
Rheumatic fever.
Sarcoidosis.
ALPS.
Congestive Splenomegaly
Intrahepatic
Cirrhosis.
Extrahepatic
Portal vein obstruction.
Splenic vein obstruction.
Hepatic vein occlusion (Budd-Chiari syndrome).
Chronic Passive Congestion
Heart failure.
Hematologic Disorders
RBC disorders: hemolytic anemias, thalassemia, sickle cell disorders.
Neoplasia
Malignant
MPDs.
Myeloid metaplasia.
Polycythemia rubra vera.
Essential thrombocythemia.
Chronic leukemia.
Chronic myeloid leukemia.

Chronic lymphocytic leukemia.
Hairy cell leukemia.
Lymphoma.
Acute leukemia.
Malignant histiocytosis.
Benign
Hamartoma.
Hemangioma.
Lymphangioma.
Fibroma.
Storage Diseases
Gaucher disease.
Niemann-Pick disease.
Miscellaneous
Amyloidosis.
Cysts.

ALPS, Autoimmune lymphoproliferative syndrome; *CMV,* cytomegalovirus; *MPD,* myeloproliferative disorder; *RBC,* red blood cell; *SLE,* systemic lupus erythematosus.

SPLENOMEGALY, CHILDREN[45]

ICD-10CM # R16.1 Splenomegaly, not elsewhere classified

DISORDERS OF THE BLOOD

Hemolytic anemia: congenital/acquired.
Thalassemia.
Sickle cell disease.
Leukemia.
Osteopetrosis.
Myelofibrosis/myeloid metaplasia/thrombocythemia.

INFECTIONS: ACUTE AND CHRONIC

Viral:
- Congenital (e.g., TORCH association).
- Mononucleosis (e.g., EBV, CMV infection).
- Virus-associated hemophagocytic syndrome.
- HIV.

Bacterial:
- Sepsis/abscess.
- Brucellosis.
- Salmonellosis.
- Tularemia.
- Tuberculosis.
- Subacute bacterial endocarditis.
- Syphilis.
- Lyme disease.

Fungal:
- Histoplasmosis (disseminated).

Rickettsial:
- Rocky Mountain spotted fever.
- Cat-scratch disease.

Parasitic:
- Toxoplasmosis.
- Malaria.
- Leishmaniasis (kala-azar).
- Schistosomiasis.
- Echinococcosis.

HEPATIC/PORTAL SYSTEM DISORDERS

Acute/chronic active hepatitis.
Cirrhosis/hepatic fibrosis/biliary atresia.
Portal or splenic venous obstruction (Banti syndrome).

AUTOIMMUNE DISEASE

Juvenile rheumatoid arthritis.
Systemic lupus erythematosus.
Autoimmune lymphoproliferative syndrome (Canale–Smith syndrome).

NEOPLASMS/CYSTS

Lymphomas (Hodgkin and non-Hodgkin).
Hemangiomas/lymphangiomas.
Hamartomas.
Congenital or acquired (posttraumatic) cysts.

STORAGE DISEASES/INBORN ERRORS OF METABOLISM

Lipidoses: Gaucher disease, Niemann–Pick disease, others.
Mucopolysaccharidoses.
Defects in carbohydrate metabolism: galactosemia, fructose intolerance.
Sea-blue histiocyte syndrome.

MISCELLANEOUS DISORDERS

Histiocytoses:
- Reactive.
- Langerhans cell.
- Malignant.

Sarcoidosis.
Congestive heart failure.
Familial Mediterranean fever.

CMV, Cytomegalovirus; *EBV,* Epstein-Barr virus; *TORCH,* toxoplasmosis, other infections, rubella, cytomegalovirus infection, herpes simplex.

SPONTANEOUS PNEUMOTHORAX[60]

ICD-10CM # J93.0 Spontaneous tension pneumothorax
J93.11 Primary spontaneous pneumothorax
J93.12 Secondary spontaneous pneumothorax

CAUSES OF SECONDARY SPONTANEOUS PNEUMOTHORAX

Airway Disease
Chronic obstructive pulmonary disease.
Asthma.
Cystic fibrosis.
Infections
Necrotizing bacterial pneumonia, lung abscess.
Pneumocystis jiroveci pneumonia.
Tuberculosis.
Interstitial Lung Disease
Sarcoidosis.
Idiopathic pulmonary fibrosis.
Lymphangiomyomatosis.
Tuberous sclerosis.
Pneumoconioses.
Neoplasms
Primary lung cancers.
Pulmonary or pleural metastases.
Miscellaneous
Connective tissue diseases.
Pulmonary infarction.
Endometriosis, catamenial pneumothorax.

STATURAL OVERGROWTH[62]

ICD-10CM # E34.4 Constitutional tall stature

FETAL OVERGROWTH

Maternal diabetes mellitus.
Cerebral gigantism (Sotos syndrome).
Weaver syndrome.
Beckwith-Wiedemann syndrome.
Other insulin-like growth factor 2 (IGF2) excess syndromes.

POSTNATAL OVERGROWTH LEADING TO CHILDHOOD TALL STATURE

Familial (constitutional) tall stature.
Cerebral gigantism.
Beckwith-Wiedemann syndrome.
Exogenous obesity.
Excess growth hormone (GH) secretion (pituitary gigantism).
McCune-Albright syndrome or multiple endocrine neoplasia (MEN) associated with excess GH secretion.
Precocious puberty.
Marfan syndrome.
Klinefelter syndrome (XXY).
Weaver syndrome.
Fragile X syndrome.
Homocystinuria.
XYY.
Hyperthyroidism.

POSTNATAL OVERGROWTH LEADING TO ADULT TALL STATURE

Familial (constitutional) tall stature.
Androgen or estrogen deficiency/estrogen resistance (in males).
Testicular feminization.
Excess GH secretion.
Marfan syndrome.
Klinefelter syndrome (XXY).
XYY.

STEATOHEPATITIS

ICD-10CM # K76.0 Fatty (change of) liver, not elsewhere classified
K76.89 Other specified diseases of liver

Alcohol abuse.
Obesity.
DM.
Parenteral nutrition.
Medications (high-dose estrogen, amiodarone, corticosteroids, methotrexate, nifedipine).
Jejunoileal bypass.
Abetalipoproteinemia.
Wilson disease, Weber-Christian disease.

STOMATITIS, BULLOUS

ICD-10CM # K12.30 Oral mucositis (ulcerative), unspecified

Erythema multiforme.
Erosive lichen planus.
Bullous pemphigoid.

SLE.
Pemphigus vulgaris.
Mucous membrane pemphigoid.

STRIDOR IN NEONATES[1]

ICD-10CM # R06.1 Stridor

INTRINSIC LESIONS

Larynx
Laryngomalacia.
Infection (laryngitis).
Vocal cord paralysis.
Laryngeal web.
Laryngocele or laryngeal cyst.
Laryngotracheal esophageal cleft.
Foreign body.
Trachea
Tracheomalacia.
Tracheal stenosis.
Tracheoesophageal fistula.
Subglottic hemangioma.
Tracheal web.
Extrinsic Compression
Vascular ring.
Anomalous innominate artery.
Mediastinal mass.
Esophageal foreign body.
Other
Macroglossia.
Gastroesophageal reflux.

STRIDOR, PEDIATRIC AGE[9]

ICD-10CM # R06.1 Stridor

RECURRENT

Allergic (spasmodic) croup.
Respiratory infections in a child with otherwise asymptomatic anatomic narrowing of the large airways.
Laryngomalacia.

PERSISTENT

Laryngeal obstruction:
- Laryngomalacia.
- Papillomas, other tumors.
- Cysts and laryngoceles.
- Laryngeal webs.
- Bilateral abductor paralysis of the cords.
- Foreign body.

Tracheobronchial disease:
- Tracheomalacia.
- Subglottic tracheal webs.

Endotracheal, endobronchial tumors.
Subglottic tracheal stenosis.
Congenital.
Acquired.
Extrinsic masses.
Mediastinal masses.
Vascular ring.
Lobar emphysema.
Bronchogenic cysts.
Thyroid enlargement.
Esophageal foreign body.
Tracheoesophageal fistulas.
Other.
Gastroesophageal reflux.
Macroglossia, Pierre Robin syndrome.
Cri-du-chat syndrome.
Hysterical stridor.
Hypocalcemia.

STROKE[82]

ICD-10CM # Varies with specific diagnosis

STROKE "MIMICS"

Hypoglycemia.
Drug overdose or intoxication.
Hysterical conversion reaction.
Hyperventilation.
Metabolic encephalopathy.
Migraine.
Syncope.
Transient global amnesia.
Seizures.
Vestibular vertigo.

STROKE, PEDIATRIC AGE[52]

ICD-10CM # I67.89 Other cerebrovascular disease

CARDIAC DISEASE

Congenital:
- Aortic stenosis.
- Mitral stenosis; mitral prolapse.
- Ventricular septal defects.
- Patent ductus arteriosus.
- Cyanotic congenital heart disease involving right-to-left shunt.

Acquired:
- Endocarditis (bacterial, SLE).
- Kawasaki disease.
- Cardiomyopathy.
- Atrial myxoma.
- Arrhythmia.
- Paradoxical emboli through patent foramen ovale.
- Rheumatic fever.
- Prosthetic heart valve.

HEMATOLOGIC ABNORMALITIES

Hemoglobinopathies:
- Sickle cell (SS) disease.
- Sickle (SC) disease.

Polycythemia.
Leukemia/lymphoma.
Thrombocytopenia.
Thrombocytosis.
Disorders of coagulation:
- Protein C deficiency.
- Protein S deficiency.
- Factor V Leiden.
- Antithrombin III deficiency.
- Lupus anticoagulant.

Oral contraceptive pill use.
Pregnancy and the postpartum state.
Disseminated intravascular coagulation.
Paroxysmal nocturnal hemoglobinuria.
Inflammatory bowel disease (thrombosis).

INFLAMMATORY DISORDERS

Meningitis:
- Viral.
- Bacterial.
- Tuberculosis.

Systemic infection:
- Viremia.
- Bacteremia.
- Local head and neck infections.

Drug-induced inflammation:
- Amphetamine.
- Cocaine.

Autoimmune disease:
- SLE.
- Juvenile RA.
- Takayasu arteritis.
- Mixed connective tissue disease.
- Polyarteritis nodosum.
- Primary CNS vasculitis.
- Sarcoidosis.
- Behçet syndrome.
- Granulomatosis with polyangiitis.

METABOLIC DISEASE ASSOCIATED WITH STROKE

Homocystinuria.
Pseudoxanthoma elasticum.
Fabry disease.
Sulfite oxidase deficiency.
Mitochondrial disorders:
- MELAS.
- Leigh syndrome.

Ornithine transcarbamylase deficiency.

INTRACEREBRAL VASCULAR PROCESSES

Ruptured aneurysm.
Arteriovenous malformation.
Fibromuscular dysplasia.
Moyamoya disease.
Migraine headache.
Postsubarachnoid hemorrhage vasospasm.
Hereditary hemorrhagic telangiectasia.
Sturge-Weber syndrome.
Carotid artery dissection.
Postvaricella.

TRAUMA AND OTHER EXTERNAL CAUSES

Child abuse.
Head trauma/neck trauma.
Oral trauma.
Placental embolism.
ECMO therapy.

CNS, Central nervous system; *ECMO,* extracorporeal membrane oxygenation; *MELAS,* mitochondrial encephalomyopathy, lactic acidosis, and stroke.

STROKE, YOUNG ADULT, CAUSES[3]

ICD-10CM # I64 Stroke
I67.89 Other cerebrovascular disease

Cardiac factors (ASD, MVP, patent foramen ovale).
Inflammatory factors (SLE, polyarteritis nodosa).
Infections (endocarditis, neurosyphilis).
Drugs (cocaine, heroin, oral contraceptives, decongestants).
Arterial dissection.
Hematolic factors (DIC, TTP, deficiency of protein S, protein C, antithrombin III).

Migraine.
Postpartum angiopathy.
Other: premature atherosclerosis, fibromuscular dysplasia.

ST-SEGMENT DEPRESSION, NONCORONARY CAUSES[11]

ICD-10CM # R94.31 Abnormal electrocardiogram

NONCORONARY CAUSES OF ST-SEGMENT DEPRESSION

Anemia.
Cardiomyopathy.
Digitalis use.
Glucose load.
Hyperventilation.
Hypokalemia.
Intraventricular conduction disturbance.
Left ventricular hypertrophy.
Mitral valve prolapse.
Preexcitation syndrome.
Severe aortic stenosis.
Severe hypertension.
Severe hypoxia.
Severe volume overload (aortic, mitral regurgitation).
Sudden excessive exercise.
Supraventricular tachyarrhythmias.

ST-SEGMENT ELEVATION[1]

ICD-10CM # R94.31 Abnormal electrocardiogram [ECG] [EKG]

DIFFERENTIAL DIAGNOSIS OF ST-SEGMENT ELEVATION ON ELECTROCARDIOGRAPHY

ST-segment elevation myocardial infarction.
Pericarditis.
Benign early repolarization.
Left bundle branch block.
Left ventricular hypertrophy.
Left ventricular aneurysm.
Paced ventricular rhythms.
Prinzmetal angina.
Hyperkalemia.
Hypothermia with Osborne waves.
Intracranial hemorrhage.
Brugada syndrome.
Normal variant.

ST SEGMENT ELEVATIONS, NONISCHEMIC

ICD-10CM # R94.31 Abnormal electrocardiogram [ECG] [EKG]

Early repolarization.
Acute pericarditis.
LVH.
Normal pattern variant.
LBBB.
Pulmonary embolism.
Hyperkalemia.
Postcardioversion.

SUDDEN CARDIAC DEATH[59]

ICD-10CM # **Z86.74** Personal history of sudden cardiac arrest
Z82.41 Family history of sudden cardiac death

CAUSES OF AND CONTRIBUTING FACTORS IN SUDDEN CARDIAC DEATH

Coronary Artery Abnormalities
Coronary atherosclerosis:
- Chronic coronary atherosclerosis with acute or transient myocardial ischemia—thrombosis, spasm, physical stress.
- Acute myocardial infarction, onset and early phase.
- Chronic atherosclerosis with a change in myocardial substrate, including previous myocardial infarction.

Congenital abnormalities of coronary arteries:
- Anomalous origin from the pulmonary artery.
- Other coronary arteriovenous fistula.
- Origin of a left coronary branch from the right or noncoronary sinus of Valsalva.
- Origin of the right coronary artery from the left sinus of Valsalva.
- Hypoplastic or aplastic coronary arteries.
- Coronary-intracardiac shunt.

Coronary artery embolism:
- Aortic or mitral endocarditis.
- Prosthetic aortic or mitral valves.
- Abnormal native valves or left ventricular mural thrombus.
- Platelet embolism.

Coronary arteritis:
- Polyarteritis nodosa, progressive systemic sclerosis, giant cell arteritis.
- Mucocutaneous lymph node syndrome (Kawasaki disease).
- Syphilitic coronary ostial stenosis.

Miscellaneous mechanical obstruction of the coronary arteries:
- Coronary artery dissection in Marfan syndrome.
- Coronary artery dissection in pregnancy.
- Prolapse of aortic valve myxomatous polyps into the coronary ostia.
- Dissection or rupture of the sinus of Valsalva.

Functional obstruction of the coronary arteries:
- Coronary artery spasm with or without atherosclerosis.
- Myocardial bridges.

Hypertrophy of the Ventricular Myocardium
Left ventricular hypertrophy associated with coronary heart disease.
Hypertensive heart disease without significant coronary atherosclerosis.
Hypertrophic myocardium secondary to valvular heart disease.
Hypertrophic cardiomyopathy:
- Obstructive.
- Nonobstructive.

Primary or secondary pulmonary hypertension:
- Advanced chronic right ventricular overload.
- Pulmonary hypertension in pregnancy (highest risk peripartum).

Myocardial Diseases and Dysfunction, With or Without Heart Failure
Chronic congestive heart failure:
- Ischemic cardiomyopathy.
- Idiopathic dilated cardiomyopathy, acquired.
- Hereditary dilated cardiomyopathy.
- Alcoholic cardiomyopathy.
- Hypertensive cardiomyopathy.
- Postmyocarditis cardiomyopathy.
- Peripartum cardiomyopathy.
- Idiopathic fibrosis.

Acute and subacute cardiac failure:
- Massive acute myocardial infarction.
- Myocarditis, acute or fulminant.
- Acute alcoholic cardiac dysfunction.
- Takotsubo syndrome (uncertain risk for sudden death).
- Ball valve embolism in aortic stenosis or prosthesis.
- Mechanical disruptions of cardiac structures:
  - Rupture of the ventricular free wall.
  - Disruption of the mitral apparatus:
    - Papillary muscle.
    - Chordae tendineae.
    - Leaflet.
  - Rupture of the interventricular septum.
- Acute pulmonary edema in noncompliant ventricles.

Inflammatory, Infiltrative, Neoplastic, and Degenerative Processes
Viral myocarditis, with or without ventricular dysfunction:
- Acute phase.
- Postmyocarditis interstitial fibrosis.

Myocarditis associated with the vasculitides.
Sarcoidosis.
Progressive systemic sclerosis.
Amyloidosis.
Hemochromatosis.
Idiopathic giant cell myocarditis.
Chagas disease.
Cardiac ganglionitis.
Arrhythmogenic right ventricular dysplasia, right ventricular cardiomyopathy.
Neuromuscular diseases (e.g., muscular dystrophy, Friedreich ataxia, myotonic dystrophy).
Intramural tumors:
- Primary.
- Metastatic.

Obstructive intracavitary tumors:
- Neoplastic.
- Thrombotic.

Diseases of the Cardiac Valves
Valvular aortic stenosis/insufficiency.
Mitral valve disruption.
Mitral valve prolapse.
Endocarditis.
Prosthetic valve dysfunction.

Congenital Heart Disease
Congenital aortic (potentially high risk) or pulmonic (low risk) valve stenosis.
Congenital septal defects with Eisenmenger physiology:
- Advanced disease.
- During labor and delivery.

Late after surgical repair of congenital lesions (e.g., tetralogy of Fallot).

Electrophysiologic Abnormalities
Abnormalities of the conducting system:
- Fibrosis of the His-Purkinje system:
  - Primary degeneration (Lenègre disease).
  - Secondary to fibrosis and calcification of the "cardiac skeleton" (Lev disease).
  - Postviral conducting system fibrosis.
  - Hereditary conducting system disease.
- Anomalous pathways of conduction (Wolff-Parkinson-White syndrome, short refractory period bypass).

Abnormalities of repolarization:
- Congenital abnormalities in duration of the QT interval:
  - Congenital long–QT interval syndromes:
    - Romano-Ward syndrome (without deafness).
    - Jervell and Lange-Nielsen syndrome (with deafness).
  - Congenital short–QT interval syndrome.
- Acquired (or provoked) long–QT interval syndromes:
  - Drug effect (with genetic predisposition?):
    - Cardiac, antiarrhythmic.
    - Noncardiac.
    - Drug interactions.
  - Electrolyte abnormality (response modified by genetic predisposition?).
  - Toxic substances.
  - Hypothermia.
  - CNS injury, subarachnoid hemorrhage.
- Brugada syndrome—right bundle branch block and ST-segment elevations in the absence of ischemia:
  - Early repolarization syndrome.

Ventricular fibrillation of unknown or uncertain cause:
- Absence of identifiable structural or functional causes:
  - "Idiopathic" ventricular fibrillation.
  - Short-coupled torsades de pointes, polymorphic ventricular tachycardia.
  - Nonspecific fibrofatty infiltration in a previously healthy victim (variation of right ventricular dysplasia?).
- Sleep-death in Southeast Asians (see VIIB3, Brugada syndrome):
  - Bangungut.
  - Pokkuri.
  - Lai-tai.

Electrical Instability Related to Neurohumoral and Central Nervous System Influences
- Catecholaminergic polymorphic ventricular tachycardia.

Other catecholamine-dependent arrhythmias.
CNS related:
- Psychic stress, emotional extremes (Takotsubo syndrome).
- Auditory related:
- "Voodoo death" in primitive cultures.
- Diseases of the cardiac nerves.
- Arrhythmia expression in congenital long–QT interval syndrome.

Sudden Infant Death Syndrome and Sudden Death in Children
Sudden infant death syndrome:
- Immature respiratory control function.
- Long–QT interval syndrome.
- Congenital heart disease.
- Myocarditis.

Sudden death in children:
- Eisenmenger syndrome, aortic stenosis, hypertrophic cardiomyopathy, pulmonary atresia.
- After corrective surgery for congenital heart disease.
- Myocarditis.
- Genetic disorders of electrical function (e.g., long–QT interval syndrome).
- No identified structural or functional cause.

Miscellaneous
- Sudden death during extreme physical activity (seek predisposing causes).
- Commotio cordis—blunt chest trauma.
- Mechanical interference with venous return:
  - Acute cardiac tamponade.
  - Massive pulmonary embolism.
  - Acute intracardiac thrombosis.
- Dissecting aneurysm of the aorta.
- Toxic and metabolic disturbances (other than the QT interval effects listed above):
  - Electrolyte disturbances.
  - Metabolic disturbances.
  - Proarrhythmic effects of antiarrhythmic drugs.
  - Proarrhythmic effects of noncardiac drugs.
- Mimics sudden cardiac death:
  - "Café coronary."
  - Acute alcoholic states ("holiday heart").
  - Acute asthmatic attacks.
  - Air or amniotic fluid embolism.

SUDDEN DEATH, PEDIATRIC AGE[9]

ICD-10CM # R99 Ill-defined and unknown cause of mortality

SIDS AND SIDS "MIMICS"
SIDS.
Long QT syndromes.
Inborn errors of metabolism.
Child abuse.
Myocarditis.
Duct-dependent congenital heart disease.

CORRECTED OR UNOPERATED CONGENITAL HEART DISEASE
Aortic stenosis.
Tetralogy of Fallot.
Transposition of great vessels (postoperative atrial switch).
Mitral valve prolapse.
Hematologic left heart syndrome.
Eisenmenger syndrome.

CORONARY ARTERIAL DISEASE
Anomalous origin.
Anomalous tract.
Kawasaki disease.
Periarteritis.
Arterial dissection.
Marfan syndrome.
Myocardial infarction.

MYOCARDIAL DISEASE
Myocarditis.
Hypertrophic cardiomyopathy.
Dilated cardiomyopathy.
Arrhythmogenic right ventricular dysplasia.

CONDUCTION SYSTEM ABNORMALITY/ARRHYTHMIA
Long QT syndromes.
Proarrhythmic drugs.
Preexcitation syndromes.
Heart block.
Commotio cordis.
Idiopathic ventricular fibrillation.
Heart tumor.

MISCELLANEOUS
Pulmonary hypertension.
Pulmonary embolism.
Heat stroke.
Cocaine.
Anorexia nervosa.
Electrolyte disturbances.

SIDS, Sudden infant death syndrome.

SUDDEN DEATH, YOUNG ATHLETE

ICD-10CM # R99 Ill-defined and unknown cause of mortality

Hypertrophic cardiomyopathy.
Coronary artery anomalies.
Myocarditis.
Ruptured aortic aneurysm (Marfan syndrome).
Arrhythmias.
Aortic valve stenosis.
Asthma.
Trauma (cerebral, cardiac).
Drug and alcohol abuse.
Heat stroke.
Cardiac sarcoidosis.
Atherosclerotic coronary artery disease.
Dilated cardiomyopathy.

SWOLLEN LIMB

ICD-10CM # M79.89 Other specified soft tissue disorders

Trauma.
Insect bite.
Abscess.
Lymphedema.
Thrombophlebitis.
Lipoma.
Neurofibroma.
Postphlebitic syndrome.
Myositis ossificans.
Nephrosis, cirrhosis, CHF.
Hypoalbuminemia.
Varicose veins.

TALL STATURE[63]

ICD-10CM # E22.0 Acromegaly and pituitary gigantism

CONSTITUTIONAL (FAMILIAL OR GENETIC)—MOST COMMON CAUSE

Endocrine Causes
Growth hormone excess—gigantism.

Electrophysiologic Abnormalities
Abnormalities of the conducting system:
- Fibrosis of the His-Purkinje system:
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  - Secondary to fibrosis and calcification of the "cardiac skeleton" (Lev disease).
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  - Metabolic disturbances.
  - Proarrhythmic effects of antiarrhythmic drugs.
  - Proarrhythmic effects of noncardiac drugs.
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  - "Café coronary."
  - Acute alcoholic states ("holiday heart").
  - Acute asthmatic attacks.
  - Air or amniotic fluid embolism.

SUDDEN DEATH, PEDIATRIC AGE[9]

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SIDS AND SIDS "MIMICS"
SIDS.
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Inborn errors of metabolism.
Child abuse.
Myocarditis.
Duct-dependent congenital heart disease.

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Aortic stenosis.
Tetralogy of Fallot.
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Anomalous origin.
Anomalous tract.
Kawasaki disease.
Periarteritis.
Arterial dissection.
Marfan syndrome.
Myocardial infarction.

MYOCARDIAL DISEASE
Myocarditis.
Hypertrophic cardiomyopathy.
Dilated cardiomyopathy.
Arrhythmogenic right ventricular dysplasia.

CONDUCTION SYSTEM ABNORMALITY/ARRHYTHMIA
Long QT syndromes.
Proarrhythmic drugs.
Preexcitation syndromes.
Heart block.
Commotio cordis.
Idiopathic ventricular fibrillation.
Heart tumor.

MISCELLANEOUS
Pulmonary hypertension.
Pulmonary embolism.
Heat stroke.
Cocaine.
Anorexia nervosa.
Electrolyte disturbances.

SIDS, Sudden infant death syndrome.

SUDDEN DEATH, YOUNG ATHLETE

ICD-10CM # R99 Ill-defined and unknown cause of mortality

Hypertrophic cardiomyopathy.
Coronary artery anomalies.
Myocarditis.
Ruptured aortic aneurysm (Marfan syndrome).
Arrhythmias.
Aortic valve stenosis.
Asthma.
Trauma (cerebral, cardiac).
Drug and alcohol abuse.
Heat stroke.
Cardiac sarcoidosis.
Atherosclerotic coronary artery disease.
Dilated cardiomyopathy.

SWOLLEN LIMB

ICD-10CM # M79.89 Other specified soft tissue disorders

Trauma.
Insect bite.
Abscess.
Lymphedema.
Thrombophlebitis.
Lipoma.
Neurofibroma.
Postphlebitic syndrome.
Myositis ossificans.
Nephrosis, cirrhosis, CHF.
Hypoalbuminemia.
Varicose veins.

TALL STATURE[63]

ICD-10CM # E22.0 Acromegaly and pituitary gigantism

CONSTITUTIONAL (FAMILIAL OR GENETIC)—MOST COMMON CAUSE

Endocrine Causes
Growth hormone excess—gigantism.

Sexual precocity (tall as children, short as adults):
  True sexual precocity.
  Pseudosexual precocity.
Androgen deficiency:
  Klinefelter syndrome.
  Bilateral anorchism.

GENETIC CAUSES

Klinefelter syndrome.
Syndromes of XYY, XXYY.

MISCELLANEOUS SYNDROMES AND DISORDERS

Cerebral gigantism or Sotos syndrome: prominent forehead, hypertelorism, high arched palate, dolichocephaly, mental retardation, large hands and feet, and premature eruption of teeth. Large at birth, with most rapid growth in first 4 yr of life.
Marfan syndrome: disorder of mesodermal tissues, subluxation of the lenses, arachnodactyly, and aortic aneurysm.
Homocystinuria: same phenotype as Marfan syndrome.
Obesity: tall as infants, children, and adolescents.
Total lipodystrophy: large hands and feet, generalized loss of subcutaneous fat, insulin-resistant DM, and hepatomegaly.
Beckwith-Wiedemann syndrome: neonatal tallness, omphalocele, macroglossia, and neonatal hypoglycemia.
Weaver-Smith syndrome: excessive intrauterine growth, mental retardation, megalocephaly, widened bifrontal diameter, hypertelorism, large ears, micrognathia, camptodactyly, broad thumbs, and limited extension of elbows and knees.
Marshall-Smith syndrome: excessive intrauterine growth, mental retardation, blue sclerae, failure to thrive, and early death.

TARDIVE DYSKINESIA[31]

ICD-10CM # R27.9 Unspecified lack of coordination
F44.4 Conversion disorder with motor symptom or deficit
F44.6 Conversion disorder with sensory symptom or deficit
G24.4 Idiopathic orofacial dystonia

DIFFERENTIAL DIAGNOSIS

Medications (antidepressants, anticholinergics, amphetamines, lithium, L-dopa, phenytoin).
Brain neoplasms.
Ill-fitting dentures.
Huntington disease.
Idiopathic dystonias (tics, blepharospasm, aging).
Wilson disease.
Extrapyramidal syndrome (postanoxic or postencephalitic).
Torsion dystonia.

TASTE AND SMELL LOSS[3]

ICD-10CM # R43.0 Anosmia
R43.1 Parosmia
R43.2 Parageusia

TASTE

Local: radiation therapy.
Systemic: cancer, renal failure, hepatic failure, nutritional deficiency (vitamin B_{12}, zinc), Cushing syndrome, hypothyroidism, DM, infection (influenza), drugs (antirheumatic and antiproliferative).
Neurologic: Bell palsy, familial dysautonomia, multiple sclerosis.

SMELL

Local: allergic rhinitis, sinusitis, nasal polyposis, bronchial asthma.
Systemic: renal failure, hepatic failure, nutritional deficiency (vitamin B_{12}), Cushing syndrome, hypothyroidism, DM, infection (viral hepatitis, influenza), drugs (nasal sprays, antibiotics).
Neurologic: head trauma, multiple sclerosis, Parkinson disease, frontal brain tumor.

TELANGIECTASIA

ICD-10CM # I78.8 Other diseases of capillaries
I78.9 Disease of capillaries, unspecified

Oral contraceptive agents.
Pregnancy.
Rosacea.
Varicose veins.
Trauma.
Drug induced (corticosteroids, systemic or topical).
Spider telangiectases.
Hepatic cirrhosis.
Mastocytosis.
SLE, dermatomyositis, systemic sclerosis.

TENDINOPATHY[60]

ICD-10CM # M67.90 Unspecified disorder of synovium and tendon, unspecified site
M71.9 Bursopathy, unspecified

INTRINSIC FACTORS

Anatomic Factors
Malalignment.
Muscle weakness or imbalance.
Muscle inflexibility.
Decreased vascularity.
Systemic Factors
Inflammatory conditions (e.g., SLE).
Pregnancy.
Quinolone-induced tendinopathy.
Age-Related Factors
Tendon degeneration.
Increased tendon stiffness.
Tendon calcification.
Decreased vascularity.

EXTRINSIC FACTORS

Repetitive Mechanical Load
Excessive duration.
Excessive frequency.
Excessive intensity.
Poor technique.
Workplace factors.
Equipment Problems
Footwear.
Athletic field surface.
Equipment factors (e.g., racquet size).
Protective gear.

TESTICULAR CYSTIC LESIONS[74]

ICD-10CM # Varies with specific diagnosis

Benign
Tunica albuginea cysts.
Tunica vaginalis cysts.
Intratesticular cysts.
Tubular ectasia of rete testis.
Cystic dysplasia.
Epidermoid cysts.
Abscess.
Malignant
Nonseminomatous germ cell tumor.
Necrosis or hemorrhage in tumor.
Tubular obstruction by tumor.
Lymphoma.

TESTICULAR FAILURE[21]

ICD-10CM # E29 Testicular dysfunction

PRIMARY

Klinefelter syndrome (XXY).
XYY.
Vanishing testes syndrome (in utero or early postnatal torsion).
Noonan syndrome.
Varicocele.
Myotonic dystrophy.
Orchitis (mumps, gonorrhea).
Cryptorchidism.
Chemical exposure.
Irradiation to testes.
Spinal cord injury.
Polyglandular failure.
Idiopathic oligospermia or azoospermia.
Germinal cell aplasia (Sertoli cell-only syndrome).
Idiopathic testicular failure.
Testicular torsion.
Testicular trauma.
Diethylstilbestrol (maternal use during pregnancy leading to in utero estrogen exposure).
Testicular tumor with subsequent irradiation therapy, chemotherapy, or surgery (retroperitoneal lymph node dissection or orchiectomy).

SECONDARY

Delayed puberty.
Kallmann syndrome.
Isolated gonadotropin deficiency.
Prader-Labhart-Willi syndrome.
Lawrence-Moon-Biedl syndrome.

CNS irradiation.
Prepubertal panhypopituitarism.
Postpubertal panhypopituitarism.
Hypogonadism secondary to hyperprolactinemia.
Adrenogenital syndrome.
Chronic liver disease.
Chronic renal failure/uremia.
Hemochromatosis.
Cushing syndrome.
Malnutrition.
Massive obesity.
Sickle cell anemia.
Hyper/hypothyroidism.
Anabolic steroid use.

TESTICULAR PAIN

ICD-10CM # N50.9 Disorder of male genital organs, unspecified
R10.2 Pelvic and perineal pain

Testicular torsion.
Trauma.
Epididymitis.
Orchitis.
Neoplasm.
Urolithiasis.
Inguinal hernia.
Infection (cellulitis, abscess, folliculitis).
Anxiety.

TESTICULAR SIZE VARIATIONS[21]

ICD-10CM # N50.0 Atrophy of testis
N44.2 Benign cyst of testis
N44.8 Other noninflammatory disorders of the testis
N50.3 Cyst of epididymis
N50.8 Other specified disorders of male genital organs
N53.12 Painful ejaculation
E29.1 Testicular hypofunction

SMALL TESTES

Hypothalamic-pituitary dysfunction.
Gonadotropin deficiency.
Growth hormone deficiency.
Normal variant.
Primary hypogonadism.
Autoimmune destruction.
Chemotherapy.
Cryptorchidism.
Irradiation.
Klinefelter syndrome.
Orchiditis.
Testicular regression syndrome.
Torsion.
Trauma.

LARGE TESTES

Adrenal rest tissue.
Compensatory.
Fragile X syndrome.
Idiopathic.
Tumor.

TETANUS[60]

ICD-10CM # A35 Other tetanus

TETANUS "MIMICS"

Acute abdomen.
Black widow spider bite.
Dental abscess.
Dislocated mandible.
Dystonic reaction.
Encephalitis.
Head trauma.
Hyperventilation syndrome.
Hypocalcemia.
Meningitis.
Peritonsillar abscess.
Progressive fluctuating muscular rigidity (stiff-man syndrome).
Psychogenic.
Rabies.
Sepsis.
Subarachnoid hemorrhage.
Status epilepticus.
Strychnine poisoning.
Temporomandibular joint syndrome.

THROMBOCYTOPENIA

ICD-10CM # D47.3 Essential (hemorrhagic) thrombocythemia
D69.59 Other secondary thrombocytopenia
D69.6 Thrombocytopenia, unspecified

INCREASED DESTRUCTION

Immunologic

Drugs: quinine, quinidine, digitalis, procainamide, thiazide diuretics, sulfonamides, phenytoin, aspirin, penicillin, heparin, gold, meprobamate, sulfa drugs, phenylbutazone, NSAIDs, methyldopa, cimetidine, furosemide, INH, cephalosporins, chlorpropamide, organic arsenicals, chloroquine, platelet glycoprotein IIb/IIIa receptor inhibitors, ranitidine, indomethacin, carboplatin, ticlopidine, clopidogrel.
Idiopathic thrombocytopenic purpura (ITP).
Transfusion reaction: transfusion of platelets with plasminogen activator (PLA) in recipients without PLA-1.
Fetal/maternal incompatibility.
Collagen vascular diseases (e.g., SLE).
Autoimmune hemolytic anemia.
Lymphoreticular disorders (e.g., CLL).

Nonimmunologic

Prosthetic heart valves.
Thrombotic thrombocytopenic purpura (TTP).
Sepsis.
DIC.
Hemolytic-uremic syndrome (HUS).
Giant cavernous hemangioma.

DECREASED PRODUCTION

Abnormal marrow.
Marrow infiltration (e.g., leukemia, lymphoma, fibrosis).
Marrow suppression (e.g., chemotherapy, alcohol, radiation).
Hereditary disorders.
Wiskott-Aldrich syndrome: X-linked disorder characterized by thrombocytopenia, eczema, and repeated infections.
May-Hegglin anomaly: increased megakaryocytes but ineffective thrombopoiesis.
Vitamin deficiencies (e.g., vitamin B_{12}, folic acid).

SPLENIC SEQUESTRATION, HYPERSPLENISM

Dilutional, as a result of massive transfusion.

THROMBOCYTOPENIA, IN PREGNANCY[45]

ICD-10CM # D69.59 Other secondary thrombocytopenia

Incidental thrombocytopenia of pregnancy (gestational thrombocytopenia).
Preeclampsia/eclampsia.[41,43]
Peripartum/postpartum thrombotic microangiopathy.
Disseminated intravascular coagulation (DIC) secondary to:
Abruptio placentae.
Endometritis.
Amniotic fluid embolism.
Retained fetus.
Thrombotic thrombocytopenic purpura.
Hemolytic-uremic syndrome.

THROMBOCYTOPENIA, INHERITED DISORDERS[3]

ICD-10CM # D47.3 Essential (hemorrhagic) thrombocythemia

Amegakaryocytic thrombocytopenia.
Thrombocytopenia–absent radii.
MYH9-related thrombocytopenia:
May-Hegglin anomaly.
Fechtner syndrome.
Epstein syndrome.
Sebastian syndrome.
X-linked macrothrombocytopenia.
Wiskott-Aldrich syndrome.
X-linked thrombocytopenia.
Thrombocytopenia and radioulnar synostosis.
Familial platelet disorder—AML.
Familial dominant thrombocytopenia.
Paris-Trousseau thrombocytopenia.
Bernard-Soulier syndrome.
Bernard-Soulier carrier/Mediterranean macrothrombocytopenia.

THROMBOCYTOPENIA IN NEWBORNS, DIFFERENTIAL DIAGNOSIS[44]

ICD-10CM # D47.3 Essential (hemorrhagic) thrombocythemia
D69.59 Other secondary thrombocytopenia
D69.6 Thrombocytopenia, unspecified

DIFFERENTIAL DIAGNOSIS OF THROMBOCYTOPENIA IN NEWBORNS

Perinatal hypoxemia
Placental insufficiency
Congenital infection
- Sepsis.
- Toxoplasmosis.
- Rubella.
- Cytomegalovirus.

Autoimmune:
- Maternal immune thrombocytopenia.
- Maternal systemic lupus erythematosus.

Disseminated intravascular coagulation
Maternal drug exposure
Congenital heart disease
Hereditary thrombocytopenia
- MYH9 macrothrombocytopenia (including May-Hegglin anomaly).
- Thrombocytopenia absent radii syndrome.
- Amegakaryocytic thrombocytopenia.
- Wiskott-Aldrich syndrome.
- Fanconi anemia.

Hemangioma with thrombocytopenia
- Kasabach-Merritt syndrome.

Bone marrow infiltration
- Congenital leukemia.

THROMBOCYTOSIS

ICD-10CM # D75.9 Disease of blood and blood-forming organs, unspecified

Iron deficiency.
Posthemorrhage.
Neoplasms (GI tract).
CML.
Polycythemia vera.
Myelofibrosis with myeloid metaplasia.
Infections.
After splenectomy.
Postpartum.
Hemophilia.
Pancreatitis.
Cirrhosis.
Idiopathic.

THROMBOSIS OR THROMBOTIC DIATHESIS[3]

ICD-10CM # I74.09 Other arterial embolism and thrombosis of abdominal aorta

DIFFERENTIAL DIAGNOSIS OF THE PATIENT PRESENTING WITH THROMBOSIS OR THROMBOTIC DIATHESIS

Inherited (Primary) Hypercoagulable States
Activated protein C resistance caused by factor V Leiden mutation.
Prothrombin gene mutation (G to A transition at position 20210 in the 3-untranslated region).
Antithrombin III deficiency.
Protein C deficiency.
Protein S deficiency.
Dysfibrinogenemias (rare).

Acquired (Secondary) Hypercoagulable States
In association with physiologic or thrombogenic stimuli:
- Pregnancy (especially the postpartum period).
- Estrogen use (oral contraceptives, hormone replacement therapy).
- Immobilization.
- Trauma.
- Postoperative state.

Advancing age.
Obesity.
Prolonged air travel.
Lupus anticoagulant or antiphospholipid antibody syndrome.
In association with other clinical disorders.

Mixed/Unknown
Activated protein C resistance in the absence of factor V Leiden.
Elevated factor VIII level.
Elevated factor XI level.
Elevated factor IX level.
Elevated thrombin activatable fibrinolysis inhibitor (TAFI) level.
Decreased free tissue factor pathway inhibitor (TFPI) level.
Decreased plasma fibrinolytic activity.

THYMIC MASSES[77]

ICD-10CM # Varies with specific diagnosis

THYMIC MASSES

Thymic hyperplasia.
Thymoma.
Thymic carcinoma.
Thymic neuroendocrine tumors.
- Carcinoid.
- Small-cell carcinoma.

Thymic cysts (not rhizomatous).
Thymolipoma.
Metastases to the thymus.

THYMOMA, DISEASES ASSOCIATIONS[77]

ICD-10CM # Varies with specific diagnosis

SYSTEMIC DISEASES MOST COMMONLY ASSOCIATED WITH THYMOMA

Myasthenia gravis.
Cytopenias (most commonly red cell hypoplasia).
Nonthymic malignancies.
Hypogammaglobulinemia.
Systemic lupus erythematosus.
Polymyositis.
Rheumatoid arthritis.
Thyroiditis.
Sjögren syndrome.
Ulcerative colitis.

THYROMEGALY

ICD-10CM # Varies with specific diagnosis

Goiter.
Graves disease.
Thyroiditis (lymphocytic, granulomatous, suppurative).
Toxic adenoma.
Neoplasm (primary, metastatic).

THYROTOXICOSIS[62]

ICD-10CM # E05.80

CAUSES OF THYROTOXICOSIS

Sustained Hormone Overproduction (Hyperthyroidism)
Low TSH, high RAIU:
- Graves disease (von Basedow disease).
- Toxic multinodular goiter.
- Toxic adenoma.
- Chorionic gonadotropin-induced:
  - Gestational hyperthyroidism: physiologic hyperthyroidism of pregnancy, familial gestational hyperthyroidism due to TSH receptor mutations.
  - Trophoblastic tumors.

Inherited nonimmune hyperthyroidism associated with TSH receptor or G protein mutations.
Low TSH, low RAIU:
- Iodide-induced hyperthyroidism (Jod-Basedow effect).
- Amiodarone-associated hyperthyroidism due to iodide release.

Struma ovarii:
- Metastatic functioning thyroid carcinoma.

Normal or elevated TSH:
- TSH-secreting pituitary tumors.
- Thyroid hormone resistance with pituitary predominance.

Transient Hormone Excess (Thyrotoxicosis)
Low TSH, low RAIU
- Thyroiditis:
  - Autoimmune: lymphocytic thyroiditis (silent thyroiditis, painless thyroiditis, postpartum thyroiditis), acute exacerbation of Hashimoto disease.

Viral or postviral:
- Subacute (granulomatous, painful, postviral) thyroiditis.

Drug-induced or associated thyroiditis:
- Amiodarone.
- Lithium, interferon-α, interleukin-2, GM-CSF.

Infectious thyroiditis.
Exogenous thyroid hormone:
- Iatrogenic overreplacement.
- Thyrotoxicosis factitia.
- Ingestion of natural products containing thyroid hormone:
  - "Hamburger" thyrotoxicosis.
  - Natural foodstuffs.
  - Thyromimetic compounds (e.g., tiratricol PLB).
  - Occupational exposure to thyroid hormone (e.g., pill manufacturing, veterinary occupations).

GM-CSF, granulocyte-macrophage colony-stimulating factor; *RAIU,* radioactive iodine uptake; *TSH,* thyroid-stimulating hormone.

TICK-RELATED INFECTIONS

ICD-10CM #		
	A77.0	Spotted fever due to *Rickettsia rickettsii*
	A93.2	Colorado tick fever
	B60.0	Babesiosis
	A77.8	Other spotted fevers
	A69.20	Lyme disease, unspecified

Lyme disease.
Rocky Mountain spotted fever.
Babesiosis.
Tularemia.
Q fever.
Colorado tick fever.
Ehrlichiosis.
Relapsing fever.

TICS

ICD-10CM # F95.9 Tic disorder, unspecified

Tourette syndrome.
Physiologic tic.
Anxiety disorder.
Huntington disease.
Medications (e.g., antipsychotics, carbamazepine, phenytoin, phenobarbital).
Encephalitis.
Head trauma.
Schizophrenia.
Carbon monoxide poisoning.
Stroke.
Sydenham chorea.
Creutzfeldt-Jakob disease.

TORSADES DE POINTES[52]

ICD-10CM # I47.2 Ventricular tachycardia

Antiarrhythmics known to increase the QT interval (e.g., quinidine, procainamide, amiodarone, disopyramide, sotalol).
Tricyclic antidepressants and phenothiazines.
Histamine (H_1) antagonists (e.g., astemizole, terfenadine).
Antiviral and antifungal agents and antibiotics.
Hypokinemia.
Hypomagnesemia.
Insecticide poisoning.
Bradyarrhythmias.
Congenital long QT syndrome.
Subarachnoid hemorrhage.
Chloroquinine, pentamidine.
Cocaine abuse.

TOXIC MEGACOLON, CAUSES[15]

ICD-10CM #		
	K59.3	Megacolon, not elsewhere classified

INFLAMMATORY

Ulcerative colitis.
Crohn disease.

INFECTIOUS

Bacterial:
- *Clostridium difficile* pseudomembranous colitis.
- *Salmonella* (typhoid and nontyphoid).
- *Shigella.*
- *Campylobacter.*
- *Yersinia.*

Parasitic:
- *Entamoeba histolytica.*
- *Cryptosporidium.*

Viral:
- Cytomegalovirus colitis.

OTHER

Ischemia.
Kaposi sarcoma.

TRACHEOBRONCHIAL NARROWING ON X-RAY[36]

ICD-10CM # Varies with specific diagnosis

CAUSES OF TRACHEOBRONCHIAL NARROWING

Long-Segment/Diffuse Narrowing
Sarcoidosis.
Amyloidosis.
Granulomatosis with polyangiitis.
Relapsing polychondritis.
Tracheobronchopathia osteochondroplastica.
Pemphigoid.
Short-Segment Narrowing
Previous intubation or tracheostomy.
Congenital stenosis or web.
Extrinsic compression (from thyroid).
Adenoid cystic carcinoma.
Squamous carcinoma.

TREMOR

ICD-10CM #		
	R25.0	Abnormal head movements
	R25.1	Tremor, unspecified
	R25.2	Cramp and spasm
	R25.3	Fasciculation
	R25.9	Unspecified abnormal involuntary movements
	G25.0	Essential tremor
	G25.1	Drug-induced tremor
	G25.2	Other specified forms of tremor

REST TREMORS

Parkinson disease.
Other parkinsonian syndromes (less commonly).
Midbrain (rubral) tremor: rest <postural <kinetic.
Wilson disease (also acquired hepatocerebral degeneration).
Essential tremor—only if severe: rest <postural and action.

POSTURAL AND ACTION (TERMINAL) TREMORS

Physiologic tremor.
Exaggerated physiologic tremor (these factors can also aggravate other forms of tremor). Stress, fatigue, anxiety, emotion.
Endocrine: hypoglycemia, thyrotoxicosis, pheochromocytoma, adrenocorticosteroids.
Drugs and toxins: beta-agonists, dopamine agonists, amphetamines, lithium, tricyclic antidepressants, neuroleptics, theophylline, caffeine, valproic acid, alcohol withdrawal, mercury (Hatter shakes), lead, arsenic, others.
Essential tremor (familial or sporadic)
Primary writing tremor.
With other CNS disorders:
- Parkinson disease.
- Other akinetic-rigid syndromes.
- Idiopathic dystonia, including focal dystonias.

With peripheral neuropathy:
- Charcot-Marie-Tooth syndrome (controversial whether to call this the Roussy-Levy syndrome).
- Variety of other peripheral neuropathies (especially dysgammaglobulinemia).

Cerebellar tremor.

KINETIC (INTENTION) TREMOR

Disease of cerebellar outflow (dentate nucleus and superior cerebellar peduncle): multiple sclerosis, trauma, tumor, vascular disease, Wilson acquired hepatocerebral degeneration, drugs, toxins (e.g., mercury), others.

MISCELLANEOUS RHYTHMICAL MOVEMENT DISORDERS

Psychogenic tremor.
Orthostatic tremor.
Rhythmical movements in dystonia (dystonic tremor).
Rhythmical myoclonus (segmental myoclonus—e.g., palatal or branchial myoclonus, spinal myoclonus, limb myorhythmia).
Oscillatory myoclonus.
Asterixis.
Clonus.
Epilepsia partialis continua.
Hereditary chin quivering.
Spasmus nutans.
Head bobbing with third ventricular cysts.
Nystagmus.

TREMOR, IN CHILDREN, CAUSES[53]

ICD-10CM #		
	R25.0	Abnormal head movements
	R25.1	Tremor, unspecified
	R25.2	Cramp and spasm
	R25.3	Fasciculation
	R25.9	Unspecified abnormal involuntary movements

BENIGN

Enhanced physiologic tremor.
Shuddering attacks.
Jitteriness.
Spasmus nutans.

STATIC INJURY/STRUCTURAL

Cerebellar malformation.
Stroke (particularly in the midbrain or cerebellum).
Multiple sclerosis.

HEREDITARY/DEGENERATIVE

Familial essential tremor.
Fragile X premutation.

Wilson disease.
Huntington disease.
Juvenile parkinsonism (tremor is rare).
Pallidonigral degeneration.

METABOLIC

Hyperthyroidism.
Hyperadrenergic state (including pheochromocytoma and neuroblastoma).
Hypomagnesemia.
Hypocalcemia.
Hypoglycemia.
Hepatic encephalopathy.
Vitamin B_{12} deficiency.
Inborn errors of metabolism.
Mitochondrial disorders.

DRUGS/TOXINS

Valproate, phenytoin, carbamazepine, lamotrigine, gabapentin, lithium, tricyclic antidepressants, stimulants (cocaine, amphetamine, caffeine, thyroxine, bronchodilators), neuroleptics, cyclosporin, toluene, mercury, thallium, amiodarone, nicotine, lead, manganese, arsenic, cyanide, naphthalene, ethanol, lindane, serotonin reuptake inhibitors.

PERIPHERAL NEUROPATHIES

PSYCHOGENIC

TRICHOMEGALY[12]

ICD-10CM # Not available

CAUSES OF TRICHOMEGALY

Drug-induced: topical prostaglandin analogues, phenytoin and cyclosporine.
Malnutrition.
AIDS.
Porphyria.
Hypothyroidism.
Familial.
Congenital: Oliver–McFarlane, Cornelia de Lange, Goldstein–Hutt, Hermansky–Pudlak syndromes.

TUBULOINTERSTITIAL DISEASE, ACUTE[32]

ICD-10CM # N17.0 Acute kidney failure with tubular necrosis

DRUGS

Antibiotics, penicillins, cephalosporins, rifampin.
Sulfonamides: cotrimoxazole, sulfamethoxazole.
NSAIDs: propionic acid derivatives.
Miscellaneous: phenytoin, thiazides, allopurinol, cimetidine, ifosfamide.

INFECTIONS

Invasion of renal parenchyma.
Reaction to systemic infections: streptococcal, diphtheria, hantavirus.

SYSTEMIC DISEASES

Immune mediated: SLE, transplanted kidney, cryoglobulinemias.
Metabolic: urate, oxalate.
Neoplastic: lymphoproliferative diseases.

IDIOPATHIC

TUBULOINTERSTITIAL KIDNEY DISEASE[32]

ICD-10CM # N17.0 Acute kidney failure with tubular necrosis

Ischemic and toxic acute tubular necrosis.
Allergic interstitial nephritis.
Interstitial nephritis secondary to immune complex-related collagen vascular disease (e.g., SLE, Sjögren).
Granulomatous diseases (sarcoidosis, uveitis).
Pigment-related tubular injury (myoglobinuria, hemoglobinuria).
Hypercalcemia with nephrocalcinosis.
Tubular obstruction (drugs such as indinavir, uric acid in tumor lysis syndrome).
Myeloma kidney or cast nephropathy.
Infection-related interstitial nephritis: *Legionella, Leptospira.*
Infiltrative diseases (e.g., lymphoma).

TUMOR MARKERS ELEVATION[86]

ICD-10CM # R97.8 Other abnormal tumor markers

CAUSES OF ELEVATED LEVELS OF TUMOR MARKERS

Carcinoembryonic Antigen (CEA)
Colonic cancer (higher levels if the tumor is more differentiated or is extensive or has spread to the liver).
Lung or breast cancer; seminoma.
Cigarette smokers.
Cirrhosis, inflammatory bowel disease, rectal polyps, pancreatitis.
Advanced age.
Alpha-Fetoprotein
Hepatocellular cancer: very high titers or a rising titer is strongly suggestive, but >10% of patients do not have an elevated level.
Hepatic regeneration (e.g., cirrhosis, alcoholic or viral hepatitis).
Cancer of the stomach, colon, pancreas, or lung.
Teratocarcinoma or embryonal cell carcinoma (testis, ovary, extragonadal).
Pregnancy.
Ataxia-telangiectasia.
Normal variant.
Prostate-Specific Antigen
Prostate carcinoma (localized disease).
Prostatic hyperplasia.
Prostatitis.
Prostatic infarction.
Cancer-Associated Antigen (CA-19-9)[44]
Pancreatic carcinoma (80% with advanced, well-differentiated cancer have an elevated level).
Other GI cancers: colon, stomach, bile duct.
Acute or chronic pancreatitis.
Chronic liver disease.
Biliary tract disease.

UREMIC ENCEPHALOPATHY, DIFFERENTIAL DIAGNOSIS[28]

ICD-10CM # G93.40 Encephalopathy, unspecified

Differential Diagnosis	Comment
Hypertensive encephalopathy	
Systemic inflammatory response syndrome (SIRS):	Observed in septic patients.
Systemic vasculitis:	Vasculitis or lupus with cerebral involvement.
Drug-induced neurotoxicity	
Analgesics:	Meperidine, codeine, morphine, gabapentin.
Antibiotics:	High-dose penicillins (may cause seizures), acyclovir, ethambutol (optic nerve damage), erythromycin and aminoglycosides (may cause ototoxicity), nitrofurantoin and isoniazid (peripheral neuropathy).
Psychotropics:	Lithium, haloperidol, clonazepam, diazepam, chlorpromazine.
Immunosuppressants:	Cyclosporine, tacrolimus.
Chemotherapeutics:	Cisplatinum, ifosfamide.
Others:	High doses of loop diuretics (ototoxic), ephedrine, methyldopa, aluminum.
Cerebral atheroembolic disease:	Follows recent aortic or cardiac angiography; associated with peripheral manifestations, including lower extremity cyanosis, livedo reticularis, and eosinophilia.
Subdural hematoma	
Posterior leukoencephalopathy:	Observed particularly following renal transplantation due to reversible, abnormal permeability of the blood-brain barrier Often manifests as headache followed by mental depression, visual loss, and seizures in the context of volume expansion, acute hypertension, and often treatment with corticosteroids or calcineurin inhibitors Lesions in the parietal, temporal, and occipital lobes may be seen on imaging studies.

Wilson disease.
Huntington disease.
Juvenile parkinsonism (tremor is rare).
Pallidonigral degeneration.

METABOLIC

Hyperthyroidism.
Hyperadrenergic state (including pheochromocytoma and neuroblastoma).
Hypomagnesemia.
Hypocalcemia.
Hypoglycemia.
Hepatic encephalopathy.
Vitamin B_{12} deficiency.
Inborn errors of metabolism.
Mitochondrial disorders.

DRUGS/TOXINS

Valproate, phenytoin, carbamazepine, lamotrigine, gabapentin, lithium, tricyclic antidepressants, stimulants (cocaine, amphetamine, caffeine, thyroxine, bronchodilators), neuroleptics, cyclosporin, toluene, mercury, thallium, amiodarone, nicotine, lead, manganese, arsenic, cyanide, naphthalene, ethanol, lindane, serotonin reuptake inhibitors.

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Sulfonamides: cotrimoxazole, sulfamethoxazole.
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Miscellaneous: phenytoin, thiazides, allopurinol, cimetidine, ifosfamide.

INFECTIONS

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SYSTEMIC DISEASES

Immune mediated: SLE, transplanted kidney, cryoglobulinemias.
Metabolic: urate, oxalate.
Neoplastic: lymphoproliferative diseases.

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Granulomatous diseases (sarcoidosis, uveitis).
Pigment-related tubular injury (myoglobinuria, hemoglobinuria).
Hypercalcemia with nephrocalcinosis.
Tubular obstruction (drugs such as indinavir, uric acid in tumor lysis syndrome).
Myeloma kidney or cast nephropathy.
Infection-related interstitial nephritis: *Legionella, Leptospira.*
Infiltrative diseases (e.g., lymphoma).

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Lung or breast cancer; seminoma.
Cigarette smokers.
Cirrhosis, inflammatory bowel disease, rectal polyps, pancreatitis.
Advanced age.
Alpha-Fetoprotein
Hepatocellular cancer: very high titers or a rising titer is strongly suggestive, but >10% of patients do not have an elevated level.
Hepatic regeneration (e.g., cirrhosis, alcoholic or viral hepatitis).
Cancer of the stomach, colon, pancreas, or lung.
Teratocarcinoma or embryonal cell carcinoma (testis, ovary, extragonadal).
Pregnancy.
Ataxia-telangiectasia.
Normal variant.
Prostate-Specific Antigen
Prostate carcinoma (localized disease).
Prostatic hyperplasia.
Prostatitis.
Prostatic infarction.
Cancer-Associated Antigen (CA-19-9)[44]
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Chronic liver disease.
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Systemic vasculitis:	Vasculitis or lupus with cerebral involvement.
Drug-induced neurotoxicity	
Analgesics:	Meperidine, codeine, morphine, gabapentin.
Antibiotics:	High-dose penicillins (may cause seizures), acyclovir, ethambutol (optic nerve damage), erythromycin and aminoglycosides (may cause ototoxicity), nitrofurantoin and isoniazid (peripheral neuropathy).
Psychotropics:	Lithium, haloperidol, clonazepam, diazepam, chlorpromazine.
Immunosuppressants:	Cyclosporine, tacrolimus.
Chemotherapeutics:	Cisplatinum, ifosfamide.
Others:	High doses of loop diuretics (ototoxic), ephedrine, methyldopa, aluminum.
Cerebral atheroembolic disease:	Follows recent aortic or cardiac angiography; associated with peripheral manifestations, including lower extremity cyanosis, livedo reticularis, and eosinophilia.
Subdural hematoma	
Posterior leukoencephalopathy:	Observed particularly following renal transplantation due to reversible, abnormal permeability of the blood-brain barrier Often manifests as headache followed by mental depression, visual loss, and seizures in the context of volume expansion, acute hypertension, and often treatment with corticosteroids or calcineurin inhibitors Lesions in the parietal, temporal, and occipital lobes may be seen on imaging studies.

URETERAL COLIC[56]

ICD-10CM # R33.8 Other retention of urine
N13.8 Other obstructive and reflux uropathy

DIAGNOSTIC DIFFERENTIALS OF RENAL OR URETERAL COLIC

Acute cholecystitis, acute cholelithiasis.
Acute appendicitis.
Pelvic inflammatory disease.
Diverticulosis and/or diverticulitis.
Intestinal obstruction.
Leaking abdominal aortic aneurysm.
Musculoskeletal sprains.
Herniated disk.
Herpes zoster (shingles).
GI dysfunction with ileus and/or toxic colonic dilatation.

URETERAL STRICTURE[90]

ICD-10CM # Varies with specific diagnosis

ETIOLOGY OF URETERAL STRICTURE

Malignancy (e.g., transitional cell carcinoma, cervical cancer).
Ureteral calculus.
Radiation.
Ischemia or trauma caused by surgical dissection.
Periureteral fibrosis caused by abdominal aortic aneurysm or endometriosis.
Endoscopic instrumentation.
Renal ablation injury.
Infection (tuberculosis).
Idiopathic condition.

URETERIC OBSTRUCTION, CONGENITAL[36]

ICD-10CM # N13.8 Other obstructive and reflux uropathy
N20.9 Urolithiasis

CONGENITAL CAUSES OF URETERIC OBSTRUCTION

Primary megaureter.
Ureterocele (ectopic and orthotopic).
Ureteric valve.
Distal ureteric stenosis.
Ureteric atresia.
Circumcaval ureter and variants.
Bladder diverticulum.

URETHRAL BLEEDING[90]

ICD-10CM # Varies with specific diagnosis

DIFFERENTIAL DIAGNOSIS FOR URETHRAL BLEEDING

Male

Trauma:
- Blunt (straddle injury, kick to perineum).
- Penetrating (foreign body insertion, failed urethral catheterization).
- Intercourse related (penile fracture, masturbation).

Urethritis:
- Bacterial (gonococcal, nongonococcal).
- Viral.
- Chemical.
- Autoimmune (Reiter syndrome).

Malignancy:
- Urothelial carcinoma.
- Squamous cell carcinoma (meatus/glans).

Condyloma.
Calculus disease.

Female

Trauma:
- Blunt (pelvic fracture).
- Penetrating (foreign body).

Urethral diverticulum.
Urethral caruncle.
Urethritis.
Malignancy.
Calculus disease.

URETHRAL DISCHARGE AND DYSURIA

ICD-10CM # R36.0 Urethral discharge without blood
R36.9 Urethral discharge, unspecified
N36.9 Urethral disorder, unspecified
N39.9 Disorder of urinary system, unspecified
R30.0 Dysuria
R30.9 Painful micturition, unspecified

Urethritis (gonococcal, chlamydial, trichomonal).
Cystitis.
Prostatitis.
Vaginitis (candidiasis, chemical).
Meatal stenosis.
Interstitial cystitis.
Trauma (foreign body, masturbation, horseback or bike riding).

URETHRAL OBSTRUCTION, CHILDREN[36]

ICD-10CM # N13.8 Other obstructive and reflux uropathy

CAUSES OF URETHRAL OBSTRUCTION IN CHILDREN

Intrinsic Lesions

Valve (posterior, anterior, saccular diverticulum).
Stenosis, atresia.
Inflammatory stricture.
Traumatic stricture:
- External trauma (saddle injury, and so on).
- Iatrogenic trauma (catheter, cystoscopy, surgery).

Urethral "tumors":
- Girls: leiomyoma.
- Boys: polyp, rhabdomyosarcoma.

Miscellaneous (epidermolysis bullosa).

Extrinsic Lesions

Presacral mass dissecting inferiorly (tumor, cyst).
Fecal impaction (Hirschsprung, postrepair anal atresia, habitual constipation, neuropathy).
Mass originating in genital organs:
- Boys: utricle cyst, prostate rhabdomyosarcoma, seminal vesicle cyst, Cowper duct cyst.
- Girls: hydrometrocolpos, hydrocolpos, fused labia.

URETHRITIS, PEDIATRIC PATIENT[19]

ICD-10CM # N34.1 Nonspecific urethritis
N34.2 Other urethritis

ETIOLOGY OF URETHRITIS

Infectious	Noninfectious
Sexually Transmitted Infections	**Vasculitides**
Neisseria gonorrhoeae.	Reiter syndrome.
Chlamydia trachomatis.	Erythema multiforme.
Trichomonas vaginalis.	
Herpes simplex virus type 2.	Kawasaki disease.
Mycoplasma spp.	Mechanical
Non–Sexually Transmitted Infections	Masturbation.
	Foreign body.
Staphylococcus saprophyticus.	Trauma.
	Dysfunctional elimination.
Enterobacteriaceae.	Chemical
Gardnerella vaginalis.	Soaps.
Streptococcus spp.	Detergents.
Enterobius vermicularis.	Drugs.

URIC ACID STONES

ICD-10CM # N20.9 Urolithiasis

Hyperuricemia.
Excessive dietary purine.
Medications (salicylates, allopurinol, probenecid).
Urine pH <5.5 (e.g., diarrhea, high animal protein diet).
Decreased urine output (dehydration, malabsorption, diarrhea, inadequate fluid intake).
Tumor lysis.
Hemolytic anemia.
Myeloproliferative disorders.

URINARY INCONTINENCE, CHILDREN[53]

ICD-10CM # R32 Unspecified urinary incontinence

CAUSES OF URINARY INCONTINENCE IN CHILDHOOD

Overactive bladder.
Infrequent voiding.
Detrusor-sphincter dyssynergia.
Non-neurogenic neurogenic bladder (Hinman syndrome).
Vaginal voiding.
Giggle incontinence.
Cystitis.
Bladder outlet obstruction (posterior urethral valves).
Ectopic ureter and fistula.

Sphincter abnormality (epispadias, exstrophy; urogenital sinus abnormality).
Neuropathic.
Overflow incontinence.
Traumatic.
Iatrogenic.
Behavioral.
Combination.

URINARY RETENTION[56]

ICD-10CM # R33.9 Retention of urine, unspecified

COMMON CAUSES OF URINARY RETENTION

Obstructive Cause
Urethral stricture.
Enlarged prostate.
Lower genitourinary tract malignancy.
Pelvic malignancy.
Bladder stones.
Foreign body.
Blood clot.
Posterior urethral valves.
Ureterocele.
Primary Detrusor Insufficiency
Detrusor areflexia.
Multiple sclerosis.
Iatrogenic injury during abdominal or back surgery.
Spinal cord injury.
Myelomeningocele.

URINARY RETENTION, ACUTE

ICD-10CM # R33.9 Retention of urine, unspecified

Mechanical obstruction: urethral stone, foreign body, urethral stricture, BPH, prostate carcinoma, prostatitis, trauma with hematoma formation.
Neurogenic bladder.
Neurologic disease (MS, parkinsonism, tabes dorsalis, CVA).
Spinal cord injury.
CNS neoplasm (primary or metastatic).
Spinal anesthesia.
Lower urinary tract instrumentation.
Medications (antihistamines, antidepressants, narcotics, anticholinergics).
Abdominal or pelvic surgery.
Alcohol toxicity.
Pregnancy.
Anxiety.
Encephalitis.
Postoperative pain.
Spina bifida occulta.

URINARY TRACT BLEEDING, UPPER[90]

ICD-10CM # Varies with specific diagnosis

DIFFERENTIAL DIAGNOSIS FOR UPPER URINARY TRACT BLEEDING

Renal glomerular diseases:
IgA nephropathy (Berger disease).
Thin basement membrane disease.
Acute glomerulonephritis (e.g., poststreptococcal).
Lupus nephritis.
Hereditary nephritis (e.g., Alport syndrome).
Renal tubulointerstitial diseases:
Papillary necrosis.
Sickle cell nephropathy.
Analgesic nephropathy.
Polycystic kidney disease.
Medullary sponge kidney.
Vasculitis:
Henoch-Schönlein purpura.
Wegener granulomatosis.
Infection:
Pyelonephritis.
Xanthogranulomatous pyelonephritis.
Renal tuberculosis.
Fungal infection.
Obstruction:
Ureteropelvic junction obstruction.
Ureteral stricture.
Nephrolithiasis.
Malignancy:
Renal cortical tumors (renal cell carcinoma, benign tumors).
Upper tract urothelial carcinoma.
Fibroepithelial polyp.
Vascular diseases:
Renal arteriovenous malformations (congenital, acquired).
Iliac arterio-ureteral fistula.
Renal artery aneurysm (especially ruptured).
Renal artery pseudoaneurysm.
Renal artery and/or vein thrombosis.
Hemangioma.
Atheroembolic disease.
Nutcracker syndrome.
Loin-pain hematuria syndrome.
Trauma:
Blunt.
Penetrating.
Lateralizing essential hematuria.

URINARY TRACT OBSTRUCTION[34]

ICD-10CM # N21.8 Other lower urinary tract calculus
N20.9 Urolithiasis

INTRARENAL

Uric acid nephropathy.
Sulfonamide precipitates.
Acyclovir, indinavir precipitates.
Multiple myeloma.

URETERAL

Intrinsic
Intraluminal:
Nephrolithiasis.
Papillary necrosis.
Blood clots.
Fungus balls.
Intramural:
Ureteropelvic junction dysfunction.
Ureterovesical junction dysfunction.
Ureteral valve, polyp, or tumor.
Ureteral stricture.
Schistosomiasis.
Tuberculosis.
Scarring from instrumentation.
Drugs (e.g., NSAIDs).
Extrinsic
Vascular system:
Aneurysm: abdominal aorta or iliac vessels.
Aberrant vessels: ureteropelvic junction.
Venous: retrocaval ureter.
GI tract:
Crohn disease.
Diverticulitis.
Appendiceal abscess.
Colon cancer.
Pancreatic tumor, abscess, or cyst.
Reproductive system:
Uterus: pregnancy, prolapse, tumor, endometriosis.
Ovary: abscess, tumor, ovarian remnants.
Gartner duct cyst, tuboovarian abscess.
Retroperitoneal disease:
Retroperitoneal fibrosis: radiation, drugs, idiopathic.
Inflammatory: tuberculosis, sarcoidosis.
Hematoma.
Primary tumor (e.g., lymphoma, sarcoma).
Metastatic tumor (e.g., cervix, ovarian, bladder, colon).
Lymphocele.
Pelvic lipomatosis.

BLADDER

Neurogenic bladder:
Diabetes mellitus.
Spinal cord defect.
Trauma.
Multiple sclerosis.
Stroke.
Parkinson disease.
Spinal anesthesia.
Anticholinergics.
Bladder neck dysfunction.
Bladder calculus.
Bladder cancer.

URETHRA

Urethral stricture.
Prostate hypertrophy or cancer.
Obstruction from instrumentation.

URINARY TRACT OBSTRUCTION, CONGENITAL CAUSES[79]

ICD-10CM # Varies with specific diagnosis

CONGENITAL CAUSES OF URINARY TRACT OBSTRUCTION

Ureteropelvic Junction
Ureteropelvic junction obstruction.
Proximal and Middle Ureter
Ureteral folds.
Ureteral valves.
Strictures.
Benign fibroepithelial polyps.
Retrocaval ureter.

Distal Ureter
Ureterovesical junction obstruction.
Vesicoureteral reflux.
Prune-belly syndrome.
Ureteroceles.
Bladder
Bladder diverticula.
Neurologic conditions (e.g., spina bifida).
Urethra
Posterior urethral valves.
Urethral diverticula.
Anterior urethral valves.
Urethral atresia.
Labial fusion.

URINE CASTS

ICD-10CM # R82.99 Other abnormal findings in urine

Normal finding.
Pyelonephritis.
Chronic renal disease.
Nephrotic syndrome.
Acute tubular necrosis.
Interstitial nephritis.
Nephritic syndrome.
Glomerulonephritis.
Eclampsia.
Heavy metal ingestion.
Allograft rejection.
Hypothyroidism.

URINE COLOR ABNORMALITIES[56]

ICD-10CM # R82.5 Elevated urine levels of drugs, medicaments and biological substances
R82.99 Other abnormal findings in urine

COMMON CAUSES OF ABNORMAL URINE COLOR

Colorless.

DISEASE

Diabetes mellitus.
Diabetes insipidus.

DRUG

Ethyl alcohol.
Diuretics.

MISCELLANEOUS

Overhydration.
Yellow-orange

DRUG

Tetracycline.
Flutamide.
Pyridium.
Azo Gantrisin (Roche Labs, Nutley, NJ).
Sulfasalazine.
Vitamin B.

MISCELLANEOUS

Dehydration.
Milky White

DISEASE

Urinary tract infection/pyuria.
Blue-green

DISEASE

Pseudomonas urinary tract infection.

DRUG

Methylene blue.
Urised (Polymedica Pharmaceuticals, Woburn, MA).
Indigo carmine.
Doan's pills (Novartis Consumer Health, Parsippany, NJ).
Clorets (Cadbury Adams, Parsippany, NJ).
Amitriptyline.
Red-brown

DISEASE

Hematuria.
Hemolytic anemia.
Hemoglobinuria.
Lead poisoning.
Mercury poisoning.
Porphyria.

DRUG

Rifampin.
Ex-Lax (Novartis Consumer Health, Parsippany, NJ).
Phenolphthalein.
Phenothiazines.
Nitrofurantoin.
Doxorubicin.

MISCELLANEOUS

Beets.
Blackberries.
Rhubarb.
Brown-black

DISEASE

Fecaluria.
Methemoglobinuria.
Melaninuria.

DRUG

Metronidazole.
Methyldopa.
Methocarbamol.

MISCELLANEOUS

Fava beans.
Aloe.

URINE, RED[66]

ICD-10CM # Varies with specific diagnosis

WITH A POSITIVE DIPSTICK

Hematuria.
Hemoglobinuria: negative urinalysis.
Myoglobinuria: negative urinalysis.

WITH A NEGATIVE DIPSTICK

Drugs
Aminosalicylic acid.
Deferoxamine mesylate.
Ibuprofen.
Phenacetin.
Phenolphthalein.
Phensuximide.
Rifampin.
Anthraquinone laxatives.
Doxorubicin.
Methyldopa.
Phenazopyridine.
Phenothiazine.
Phenytoin.
Dyes
Azo dyes.
Eosin.
Foods
Beets, berries, maize.
Rhodamine B.
Metabolic
Porphyrins.
Serratia marcescens (red diaper syndrome).
Urate crystalluria.

UROLITHIASIS-LIKE PAIN[79]

ICD-10CM # Varies with specific diagnosis

DIFFERENTIAL DIAGNOSIS OF UROLITHIASIS-LIKE PAIN

Category
Disorders
Renal:
Pyelonephritis.
Blood clot.
Renal infarction.
Tumor (kidney or pelvis).
Papillary necrosis.
Ureteral:
Tumor.
Blood clot.
Stricture.
Bladder:
Tumor.
Blood clot.
Urinary retention.
Intraabdominal:
Peritonitis.
Appendicitis.
Biliary disease.
Bowel obstruction.
Vascular disorder.
Aortic aneurysm.
Mesenteric insufficiency.
Retroperitoneal:
Lymphadenopathy.
Fibrosis.
Tumor.
Gynecologic:
Ectopic or tubal pregnancy.
Ovarian torsion, cyst rupture.
Pelvic inflammatory disease.
Cervical cancer.
Endometriosis.
Ovarian vein syndrome.
Neuromuscular:
Muscle pain.
Rib fracture.
Radiculitis.
Infectious:
Herpes zoster.

Pleuritis, pneumonia.
Fungal bezoar.

UROPATHY, OBSTRUCTIVE[82]

ICD-10CM # N13.9 Obstructive and reflux uropathy, unspecified
N20.9 Urolithiasis

INTRINSIC CAUSES

Intraluminal
Intratubular deposition of crystals (uric acid, sulfas).
Stones.
Papillary tissue.
Blood clots.
Intramural
Functional.
Ureter (ureteropelvic or ureterovesical dysfunction).
Bladder (neurogenic): spinal cord defect or trauma, diabetes, multiple sclerosis, Parkinson disease, cerebrovascular accidents.
Bladder neck dysfunction.
Anatomic
Tumors.
Infection, granuloma.
Strictures.

EXTRINSIC CAUSES

Originating in the Reproductive System
Prostate: benign hypertrophy or cancer.
Uterus: pregnancy, tumors, prolapse, endometriosis.
Ovary: abscess, tumor, cysts.
Originating in the Vascular System
Aneurysms (aorta, iliac vessels).
Aberrant arteries (ureteropelvic junction).
Venous (ovarian veins, retrocaval ureter).
Originating in the Gastrointestinal Tract
Crohn disease.
Pancreatitis.
Appendicitis.
Tumors.
Originating in the Retroperitoneal Space
Inflammations.
Fibrosis.
Tumor, hematomas.

UROSEPSIS[56]

ICD-10CM # A41.9 Sepsis, unspecified organism

COMMON CAUSES OF UROSEPSIS

Obstructing ureteral stone with pyonephrosis.
Staghorn calculus with urinary tract infection.
Ureteral obstruction with proximal urinary tract infection.
Urinary retention with urinary tract infection.
Acute prostatitis with prostatic abscess.
Perinephric abscess or renal carbuncle.
Urethral stricture with periurethral abscess.
Fournier gangrene.
Foreign body within urinary tract (e.g., Foley catheter).

UTERINE BLEEDING, ABNORMAL[24SS]

ICD-10CM # N92.6 Irregular menstruation, unspecified
N93.9 Abnormal uterine and vaginal bleeding, unspecified

PREGNANCY

Threatened abortion.
Incomplete abortion.
Complete abortion.
Molar pregnancy.
Ectopic pregnancy.
Retained products of conception.

OVULATORY

Vulva: infection, laceration, tumor.
Vagina: infection, laceration, tumor, foreign body.
Cervix: polyps, cervical erosion, cervicitis, carcinoma.
Uterus: fibroids (submucous fibroids most likely to cause abnormal bleeding), polyps, adenomyosis, endometritis, intrauterine device, atrophic endometrium.
Pregnancy complications: ectopic pregnancy; threatened, incomplete, complete abortion; retained products of conception.
Abnormality of clotting system.
Midcycle bleeding.
Halban disease (persistent corpus luteum).
Menorrhagia.
Pelvic inflammatory disease.

ANOVULATORY

Physiologic causes:
  Puberty.
  Perimenopausal.
Pathologic causes:
  Ovarian failure (FSH over 40 IU/ml).
  Hyperandrogenism.
  Hyperprolactinemia.
  Obesity.
  Hypothalamic dysfunction (polycystic ovaries); LH/FSH ratio greater than 2:1.
  Hyperplasia.
  Endometrial carcinoma.
  Estrogen-producing tumors.
  Hypothyroidism.

UVEITIS, PEDIATRIC AGE

ICD-10CM # H20.9 Anterior uveitis

ANTERIOR UVEITIS

Juvenile rheumatoid arthritis (pauciarticular).
Sarcoidosis.
Trauma.
Tuberculosis.
Kawasaki disease.
Ulcerative colitis.
Postinfectious (enteric or genital) with arthritis and rash.
Spirochetal (syphilis, leptospiral).
Heterochromic iridocyclitis (Fuchs).
Viral (herpes simplex, herpes zoster).
Ankylosing spondylitis.
Stevens-Johnson syndrome.
Idiopathic.
Drugs.

POSTERIOR UVEITIS (CHOROIDITIS—MAY INVOLVE RETINA)

Toxoplasmosis.
Parasites (toxocariasis).
Sarcoidosis.
Tuberculosis.
Viral (rubella, herpes simplex, HIV, cytomegalovirus).
Subacute sclerosing panencephalitis.
Idiopathic.

ANTERIOR AND/OR POSTERIOR UVEITIS

Sympathetic ophthalmia (trauma to other eye).
Vogt-Koyanagi-Harada syndrome (uveo-otocutaneous syndrome: poliosis, vitiligo, deafness, tinnitus, uveitis, aseptic meningitis, retinitis).
Behçet syndrome.
Lyme disease.

VAGINAL BLEEDING, PREGNANCY[17]

ICD-10CM # N93.9 Abnormal uterine and vaginal bleeding, unspecified

FIRST TRIMESTER

Implantation bleeding.
Abortion:
  Threatened.
  Complete.
  Incomplete.
  Missed.
Ectopic pregnancy.
Neoplasia.
Hydatidiform mole.
Cervix.

THIRD TRIMESTER

Placenta previa.
Placental abruption.
Premature labor.
Choriocarcinoma.

VAGINAL DISCHARGE, PREPUBERTAL GIRLS[43]

ICD-10CM # N89.8 Other specified noninflammatory disorders of vagina

Irritative (bubble baths, sand):
  Poor perineal hygiene.
  Foreign body.
  Associated systemic illness (group A streptococci, chickenpox).
  Infections.
  Escherichia coli with foreign body.
  Shigella organisms.
  Yersinia organisms.
  Infections (consider sexual abuse):
    Chlamydia trachomatis.

Pleuritis, pneumonia.
Fungal bezoar.

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Appendicitis.
Tumors.
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Menorrhagia.
Pelvic inflammatory disease.

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  Perimenopausal.
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  Ovarian failure (FSH over 40 IU/ml).
  Hyperandrogenism.
  Hyperprolactinemia.
  Obesity.
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  Hyperplasia.
  Endometrial carcinoma.
  Estrogen-producing tumors.
  Hypothyroidism.

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Trauma.
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Tuberculosis.
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Lyme disease.

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Hydatidiform mole.
Cervix.

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Placental abruption.
Premature labor.
Choriocarcinoma.

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Irritative (bubble baths, sand):
  Poor perineal hygiene.
  Foreign body.
  Associated systemic illness (group A streptococci, chickenpox).
  Infections.
  Escherichia coli with foreign body.
  Shigella organisms.
  Yersinia organisms.
  Infections (consider sexual abuse):
    Chlamydia trachomatis.

Neisseria gonorrhoeae.
Trichomonas vaginalis.
Tumor (rare).

VALVULAR HEART DISEASE[3]

ICD-10CM # Varies with specific diagnosis

MAJOR CAUSES OF VALVULAR HEART DISEASE IN ADULTS

Aortic Stenosis
Bicuspid aortic valve.
Rheumatic fever.
Degenerative stenosis.
Aortic Regurgitation
Bicuspid aortic valve.
Aortic dissection.
Endocarditis.
Rheumatic fever.
Aortic root dilation.
Mitral Stenosis
Rheumatic fever.
Mitral Regurgitation

CHRONIC

Mitral valve prolapse.
Left ventricular dilation.
Posterior wall myocardial infarction.
Rheumatic fever.
Endocarditis.

ACUTE

Posterior wall or papillary muscle ischemia.
Papillary muscle or chordal rupture.
Endocarditis.
Prosthetic valve dysfunction.
Systolic anterior motion of mitral valve.

TRICUSPID REGURGITATION

Functional (annular) dilation.
Tricuspid valve prolapse.
Endocarditis.
Carcinoid heart disease.

VASCULAR LESIONS OF GI TRACT[26]

ICD-10CM # Varies with specific diagnosis

Primary Vascular Lesions
Aneurysms of the aorta and its branches.
Angioectasia (angiodysplasia, vascular ectasia).
Arteriovenous malformation.
Blue rubber bleb nevus.
Capillary phlebectasia.
Dieulafoy lesion.
Glomus tumor.
Hemangioma.
Hemangiomatosis.
Hemangioendothelioma.
Hemangiopericytoma.
Hemangiosarcoma.
Hemorrhoids.
Kaposi sarcoma.
Diseases and Syndromes with Vascular Lesions
Blue rubber bleb nevus syndrome.
Ehlers-Danlos syndrome.
Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease).
Klippel-Trenaunay or Parkes Weber syndrome.
Kohlmeier-Degos syndrome.
Marfan syndrome.
Pseudoxanthoma elasticum.
PSS (scleroderma, CREST).
Scurvy.
Turner syndrome.
von Willebrand disease.
Systemic Disorders Associated with Vascular Lesions
Portal hypertension:
Congestive gastropathy and colopathy.
GAVE (watermelon stomach).
Spider telangiectasias.
Varices.
Renal failure:
GI telangiectasias.
GAVE (watermelon stomach).
Vasculitis (e.g., polyarteritis nodosa).
Iatrogenic lesions:
Radiation telangiectasia.

CREST, Calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia; *GAVE,* gastric antral vascular ectasia

VASCULITIS, CLASSIFICATION[60]

ICD-10CM # I77.6 Arteritis, unspecified

LARGE VESSEL DISEASE

Arteritis
Giant cell arteritis.
Takayasu arteritis.
Arteritis associated with Reiter syndrome (reactive arthritis), ankylosing spondylitis.

MEDIUM AND SMALL VESSEL DISEASE

Polyarteritis Nodosa
Primary (idiopathic).
Associated with viruses (hepatitis B or C, CMV, HIV, herpes zoster).
Associated with malignancy (hairy cell leukemia).
Familial Mediterranean fever.
Granulomatous Vasculitis
Granulomatosis with polyangiitis.
Lymphomatoid granulomatosis.
Behçet Disease
Kawasaki Disease (Mucocutaneous Lymph Node Syndrome)

PREDOMINANTLY SMALL VESSEL DISEASE

Hypersensitivity Vasculitis (Leukocytoclastic Vasculitis)
Henoch-Schönlein purpura.
Mixed cryoglobulinemia.
Serum sickness.
Vasculitis associated with connective tissue diseases (SLE, Sjögren syndrome).
Vasculitis associated with specific syndromes:
Primary biliary cirrhosis.
Lyme disease.
Chronic active hepatitis.
Drug-induced vasculitis.
Churg-Strauss Syndrome
Goodpasture Syndrome
Erythema Nodosum
Panniculitis. Buerger Disease (Thrombophlebitis Obliterans)

VASCULITIS (DISEASES THAT MIMIC VASCULITIS)[65]

ICD-10CM # Varies with specific diagnosis

EMBOLIC DISEASE

Infectious or marantic endocarditis.
Cardiac mural thrombus.
Atrial myxoma.
Cholesterol embolization syndrome.

NONINFLAMMATORY VESSEL WALL DISRUPTION

Atherosclerosis.
Arterial fibromuscular dysplasia.
Drug effects (vasoconstrictors, anticoagulants).
Radiation.
Genetic disease (neurofibromatosis, Ehlers-Danlos syndrome).
Amyloidosis.
Intravascular malignant lymphoma.

DIFFUSE COAGULATION

Disseminated intravascular coagulation.
Thrombotic thrombocytopenic purpura.
Hemolytic-uremic syndrome.
Protein C and S deficiencies, factor V/Leiden mutation.
Antiphospholipid syndrome.

VEGETATIVE STATE, PERSISTENT[3]

ICD-10CM # R40.3 Persistent vegetative state

PERSISTENT VEGETATIVE STATE: COMMON CAUSES[43]

Trauma (diffuse axonal injury).
Cardiac arrest and hypoperfusion (laminar necrosis of cortical mantle and/or thalamic necrosis).
Bihemispheric infarctions.
Purulent meningitis or encephalitis (cortical injury).
Carbon monoxide.
Prolonged hypoglycemic coma.

VENTILATION–PERFUSION MISMATCH ON LUNG SCAN

ICD-10CM # Varies with specific diagnosis

Pulmonary embolism.
Emphysema.
Irradiation.
Pulmonary hypertension.

[43] A vegetative state may not necessarily begin with coma but can also develop as the end stage of neurodegenerative diseases (e.g., Alzheimer disease) of adults or children and can accompany severe congenital developmental abnormalities of the brain such as anencephaly.

AV malformations.
Pulmonary thrombosis.
External compression of pulmonary artery (neoplasm, cysts, fibrosing mediastinitis).
Vasculitis.
Tuberculosis.
Pulmonary thrombosis.
Congenital (pulmonary artery hypoplasia, congenital heart disease with upper lobe diversion).
Sequestered segment.
Parasitic lung disease.
Intraluminal obstruction from catheter fragments.

VENTRICULAR FAILURE

ICD-10CM # I51.9 Heart disease, unspecified

LEFT VENTRICULAR FAILURE

Systemic hypertension.
Valvular heart disease (AS, AR, MR).
Cardiomyopathy, myocarditis.
Bacterial endocarditis.
Myocardial infarction.
Idiopathic hypertrophic subaortic stenosis.

RIGHT VENTRICULAR FAILURE

Valvular heart disease (mitral stenosis).
Pulmonary hypertension.
Bacterial endocarditis (right-sided).
Right ventricular infarction.

BIVENTRICULAR FAILURE

Left ventricular failure.
Cardiomyopathy.
Myocarditis
Arrhythmias.
Anemia.
Thyrotoxicosis.
Arteriovenous fistula.
Paget disease.
Beriberi.

VERRUCOUS LESIONS

ICD-10CM # Varies with specific diagnosis

Warts.
Seborrheic keratosis.
Lichen simplex.
Acanthosis nigricans.
Scabies (Norwegian, crusted).
Verrucous carcinoma.
Nevus sebaceous.
Deep fungal infection.

VERTEBRAL LESIONS[64]

ICD-10CM # Varies with specific diagnosis

Anatomic Distribution of Vertebral Lesions

Anterior Elements of the Spine	Posterior Elements of the Spine	Both Anterior and Posterior Elements of the Spine
Multiple myeloma.	Osteoid osteoma.	Metastasis (spares disc end plates).
Hemangioma.	Osteoblastoma.	Infection (involves disc end plates).
Paget disease of bone.	Aneurysmal bone cyst.	Classic osteosarcoma.
Histiocytosis X (vertebra plana).		Postradiation sarcoma.
Giant cell tumor of bone.		Malignant histiocytoid variety.
Reparative granuloma.		Osteosarcoma.
Ewing sarcoma (primitive neuroectodermal tumor).		Osteochondroma.
Lymphoma of bone.		Primary chondrosarcoma.
Malignant fibrous histiocytoma.		Secondary chondrosarcoma.
Chordoma.		

VERTIGO

ICD-10CM #	R42	Dizziness and giddiness
	H81.13	Benign paroxysmal vertigo, bilateral
	H81.49	Vertigo of central origin, unspecified ear
	H81.399	Other peripheral vertigo, unspecified ear
	H81.23	Vestibular neuronitis, bilateral

PERIPHERAL

Otitis media.
Acute labyrinthitis.
Vestibular neuronitis.
Benign positional vertigo.
Meniere disease.
Ototoxic drugs: streptomycin, gentamicin.
Lesions of the eighth nerve: acoustic neuroma, meningioma, mononeuropathy, metastatic carcinoma.
Mastoiditis.

CNS OR SYSTEMIC

Vertebrobasilar artery insufficiency.
Posterior fossa tumor or other brain tumors.
Infarction/hemorrhage of cerebral cortex, cerebellum, or brain stem.
Basilar migraine.
Metabolic: drugs, hypoxia, anemia, fever.
Hypotension/severe hypertension.
Multiple sclerosis.
CNS infections: viral, bacterial.
Temporal lobe epilepsy.
Arnold–Chiari malformation, syringobulbia.
Psychogenic: ventilation, hysteria.

VERTIGO, CENTRAL[1]

ICD-10CM # R42

MAJOR CAUSES OF CENTRAL VERTIGO

Demyelination:
- Acquired.
- Leukodystrophies.
- Multiple sclerosis.

Familial disorders:
- Friedreich ataxia.
- Spinocerebellar ataxia.
- Familial episodic ataxia (type 1 and type 2).
- Olivopontocerebellar atrophy.

CNS infections:
- Lyme neuroborreliosis.
- Meningitis.
- Tuberculosis.

Intrinsic brainstem lesion:
- Tumor.
- Arteriovenous malformation.
- Trauma.

Migraine:
- Basilar.
- Benign paroxysmal positional vertigo of childhood.

Toxins:
- Drugs, alcohol.
- Analgesics.
- Anticonvulsants.
- Antihypertensives.
- Hypnotics.
- Tranquilizers.

Metabolic and endocrine disorders:
- Hyperinsulinism.
- Impaired glucose tolerance.
- Diabetes mellitus.
- Hypertriglyceridemia.
- Hypothyroidism.

Systemic conditions:
- Paget disease.

Stroke/ischemia:
- Vertebrobasilar.
- Cerebellar.
- Posterior inferior cerebellar artery syndrome.
- Lateral medullary syndrome.
- Medial medullary infarct.
- Basilar artery syndrome.
- Anterior inferior cerebellar artery.

Other causes of posterior ischemia:
- Subclavian steal syndrome.
- Rotational vertebral artery occlusion syndrome.
- Vertebral artery dissection.
- Vertebral or basilar artery dolichoectasia.
- Neoplasm of the fourth ventricle.
- Chiari malformation.
- Superficial siderosis of the CNS.
- Vestibular epilepsy.

VESICULOBULLOUS DISEASES[32]

ICD-10CM #	L94.2	Calcinosis cutis
	L98.8	Other specified disorders of the skin and subcutaneous tissue

IMMUNOLOGICALLY MEDIATED DISEASES

Bullous pemphigoid.
Herpes gestationis.
Mucous membrane pemphigoid.
Epidermolysis bullosa acquisita.
Dermatitis herpetiformis.
Pemphigus (vulgaris, foliaceus, paraneoplastic).

HYPERSENSITIVITY DISEASES

Erythema multiforme minor.
Erythema multiforme major (Stevens-Johnson syndrome).
Toxic epidermal necrolysis.

METABOLIC DISEASES

Porphyria cutanea tarda.
Pseudoporphyria.
Diabetic blisters.

INHERITED GENETIC DISORDERS

Epidermolysis bullosa:
- Simplex.
- Junctional.
- Dystrophic.

INFECTIOUS DISEASES

Impetigo.
Staphylococcal scalded skin syndrome.
Herpes simplex.
Varicella.
Herpes zoster.

VISION LOSS, ACUTE, PAINFUL

ICD-10CM # H53.139 Sudden visual loss, unspecified eye

Acute angle-closure glaucoma.
Corneal ulcer.
Uveitis.
Endophthalmitis.
Factitious.
Somatization syndrome.
Trauma.

VISION LOSS, ACUTE, PAINLESS

ICD-10CM # H53.139 Sudden visual loss, unspecified eye

Retinal artery occlusion.
Optic neuritis.
Retinal vein occlusion.
Vitreous hemorrhage.
Retinal detachment.
Exudative macular degeneration.
CVA.
Ischemic optic neuropathy.
Factitious.
Somatization syndrome, anxiety reaction.

VISION LOSS AFTER DIVING[4]

ICD-10CM # H53.139

DIFFERENTIAL DIAGNOSIS OF DECREASED VISION AFTER DIVING

Decompression sickness.
Arterial gas embolism.
Bubbles under contact lenses.
Displaced contact lens.
Antifog agent keratopathy.
Contact lens adherence syndrome.
Transdermal scopolamine
Hyperoxic myopia.
Oxymetazoline optic neuropathy.
Diving-induced migraine phenomena.
Eye disorders not related to diving.

VISION LOSS, CHILDREN

ICD-10CM # H53.9 Unspecified visual disturbance

Craniopharyngioma.
Hereditary optic atrophy.
Optic nerve glioma.
Glioma of chiasm.
Albinism.
Optic nerve hypoplasia.

VISION LOSS, CHRONIC, PROGRESSIVE

ICD-10CM # H54.7 Unspecified visual loss

Cataract.
Macular degeneration.
Cerebral neoplasm.
Refractive error.
Open-angle glaucoma.

VISION LOSS, MONOCULAR, TRANSIENT

ICD-10CM # H54.7 Unspecified visual loss

Thromboembolism.
Vasculitis.
Migraine (vasospasm).
Anxiety reaction.
CNS tumor.
Temporal arteritis.
Multiple sclerosis.

VITREOUS HEMORRHAGE[48]

ICD-10CM # H43.13 Vitreous hemorrhage, bilateral

CAUSES OF VITREOUS HEMORRHAGE

Acute posterior vitreous detachment associated either with a retinal tear or avulsion of a peripheral vessel.
Proliferative retinopathies:
- Diabetic.
- Following retinal vein occlusion.
- Sickle cell disease.
- Eales disease.
- Vasculitis.

Miscellaneous retinal disorders:
- Macroaneurysm.
- Telangiectasis.
- Capillary hemangioma.

Trauma:
- Blunt.
- Penetrating.
- Iatrogenic.

Systemic:
- Bleeding disorders.
- Terson syndrome.

VOCAL CORD PARALYSIS

ICD-10CM # J38.00 Paralysis of vocal cords and larynx, unspecified
J38.01 Paralysis of vocal cords and larynx, unilateral
J38.02 Paralysis of vocal cords and larynx, bilateral

Neoplasm: primary or metastatic (e.g., lung, thyroid, parathyroid, mediastinum).
Neck surgery (parathyroid, thyroid, carotid endarterectomy, cervical spine).
Idiopathic.
Viral, bacterial, or fungal infection.
Trauma (intubation, penetrating neck injury).
Cardiac surgery.
RA.
Multiple sclerosis.
Parkinsonism.
Toxic neuropathy.
CVA.
CNS abnormalities: hydrocephalus, Arnold–Chiari malformation, meningomyelocele.

VOLUME DEPLETION[3]

ICD-10CM # E86.9 Volume depletion, unspecified

GI losses:
- Upper: bleeding, nasogastric suction, vomiting.
- Lower: bleeding, diarrhea, enteric or pancreatic fistula, tube drainage.

Renal losses:
- Salt and water: diuretics, osmotic diuresis, postobstructive diuresis, acute tubular necrosis (recovery phase), salt-losing nephropathy, adrenal insufficiency, renal tubular acidosis.

Water loss: diabetes insipidus.
Skin and respiratory losses:
- Sweat, burns, insensible losses.

Sequestration without external fluid loss:
- Intestinal obstruction, peritonitis, pancreatitis, rhabdomyolysis, internal bleeding.

VOLUME EXCESS[3]

ICD-10CM # Varies with specific diagnosis

Primary Renal Sodium Retention (Increased Effective Circulating Volume)
Renal failure, nephritic syndrome, acute glomerulonephritis.
Primary hyperaldosteronism.
Cushing syndrome.
Liver disease.
Secondary Renal Sodium Retention (Decreased Effective Circulating Volume)
Heart failure.
Liver disease.
Nephrotic syndrome (minimal change disease).
Pregnancy.

VOMITING

ICD-10CM # R11.10 Vomiting, unspecified
R11.11 Vomiting without nausea
R11.12 Projectile vomiting

GI disturbances:
- Obstruction: esophageal, pyloric, intestinal.
- Infections: viral or bacterial enteritis, viral hepatitis, food poisoning, gastroenteritis.
- Pancreatitis.
- Appendicitis.
- Biliary colic.
- Peritonitis.
- Perforated bowel.
- Diabetic gastroparesis.

Other: gastritis, PUD, IBD, GI tract neoplasms.
Drugs: morphine, digitalis, cytotoxic agents, bromocriptine.
Severe pain: MI, renal colic.
Metabolic disorders: uremia, acidosis/alkalosis, hyperglycemia, DKA, thyrotoxicosis.
Trauma: blows to the testicles, epigastrium.
Vertigo.
Reye syndrome.
Increased intracranial pressure.
CNS disturbances: trauma, hemorrhage, infarction, neoplasm, infection, hypertensive encephalopathy, migraine.
Radiation sickness.
Nausea and vomiting of pregnancy, hyperemesis gravidarum.
Motion sickness.
Bulimia, anorexia nervosa.
Psychogenic: emotional disturbances, offensive sights or smells.
Severe coughing.
Pyelonephritis.
Boerhaave syndrome.
Carbon monoxide poisoning.

VOMITING, NEONATAL[1]

ICD-10CM # R11.10 Vomiting, unspecified

CAUSES OF NEONATAL VOMITING

Anatomic Causes

Esophagus, trachea, great vessels:
- Stricture.
- Web.
- Tracheoesophageal fistula.
- Laryngeal cleft.
- Double aortic arch.

Stomach and duodenum:
- Pyloric stenosis.
- Duodenal atresia (usually noted on the first day of life)

Small and large intestine:
- Volvulus secondary to malrotation.
- Incarcerated hernia.
- Hirschsprung disease (secondary to obstipation).
- Necrotizing enterocolitis.

Genitourinary:
- Testicular torsion.

Nonanatomic Causes

Infection:
- Septicemia.
- Meningitis.
- Urinary tract infection.
- Gastroenteritis.
- Otitis media

Increased intracranial pressure:
- Cerebral edema.
- Subdural hematoma.
- Hydrocephalus.
- Brain tumor.

Congenital adrenal hyperplasia (salt-losing variety).
Inborn errors of metabolism.
Renal disease.

VULVAR LESIONS[24]

ICD-10CM # N77.0 Ulceration of vulva in diseases classified elsewhere
N90.7 Vulvar cyst
N90.89 Other specified noninflammatory disorders of vulva and perineum
D07.1 Carcinoma in situ of vulva
N90.89 Other specified noninflammatory disorders of vulva and perineum
N90.5 Atrophy of vulva

RED LESION

Infection/Infestation

Fungal infection:
- *Candida.*
- *Tinea cruris.*
- Intertrigo.
- *Pityriasis versicolor.*

Sarcoptes scabiei.
- Erythrasma: *Corynebacterium minutissimum.*
- *Granuloma inguinale: Calymmatobacterium granulomatis.*
- Folliculitis: *Staphylococcus aureus.*
- Hidradenitis suppurativa.
- Behçet syndrome.

Inflammation

Reactive vulvitis.
Chemical irritation:
- Detergent.
- Dyes.
- Perfume.
- Spermicide.
- Lubricants.
- Hygiene sprays.
- Podophyllum.
- Topical 5-FU.
- Saliva.
- Gentian violet.
- Semen.

Mechanical trauma: scratching.
Vestibular adenitis.
Essential vulvodynia.
Psoriasis.
Seborrheic dermatitis.

Neoplasm

Vulvar intraepithelial neoplasia (VIN):
- Mild dysplasia.
- Moderate dysplasia.
- Severe dysplasia.
- Carcinoma-in-situ.

Vulvar dystrophy.
Bowen disease.
Invasive cancer:
- Squamous cell carcinoma.
- Malignant melanoma.
- Sarcoma.
- Basal cell carcinoma.
- Adenocarcinoma.
- Paget disease.
- Undifferentiated.

WHITE LESION

Vulvar dystrophy:
- Lichen sclerosus.
- Vulvar dystrophy.
- Vulvar hyperplasia.
- Mixed dystrophy.

VIN.
Vitiligo.
Partial albinism.
Intertrigo.
Radiation treatment.

DARK LESION

Lentigo.
Nevi (mole).
Neoplasm (see "Neoplasm, Vulvar," below).
Reactive hyperpigmentation.
Seborrheic keratosis.
Pubic lice.

ULCERATIVE LESION

Infection

Herpes simplex.
Vaccinia.
Treponema pallidum.
Granuloma inguinale.
Pyoderma.
Tuberculosis.

Noninfectious

Behçet disease.
Crohn disease.
Pemphigus.
Pemphigoid.
Hidradenitis suppurativa (see "Neoplasm, Vulvar," below).

Neoplasm

Basal cell carcinoma.
Squamous cell carcinoma.
Vulvar tumor <1 cm:
- Condyloma acuminatum.
- Molluscum contagiosum.
- Epidermal inclusion.
- Vestibular cyst.
- Mesonephric duct.
- VIN.
- Hemangioma.
- Hidradenoma.
- Neurofibroma.
- Syringoma.
- Accessory breast tissue.
- Acrochordon.
- Endometriosis.
- Fox-Fordyce disease.
- Pilonidal sinus.

Vulvar tumor >1 cm:
- Bartholin cyst or abscess.
- Lymphogranuloma venereum.
- Fibroma.
- Lipoma.
- Verrucous carcinoma.

Squamous cell carcinoma.
Hernia.
Edema.
Hematoma.
Acrochordon.
Epidermal cysts.
Neurofibromatosis.
Accessory breast tissue.

VULVAR PAIN[22]

ICD-10CM # N94.81 Vulvodynia
R10.2 Pelvic and perineal pain

DISEASES ASSOCIATED WITH VULVAR PAIN, NOT QUALIFYING FOR THE DIAGNOSIS OF VULVODYNIA

Podophyllin overdose.
Condylox (podofilox) overdose.
Behçet disease.
Aphthous ulcers.
Herpes (simplex and zoster).
Candidiasis.
Trichomonas.
Chancroid.
Sjögren disease.
Contact dermatitis.
Endometriosis.
Pemphigus.
Pemphigoid.
Atrophy.
Lichen sclerosus.
Lichen planus.
Crohn disease.
Bartholin abscess.
Trauma.
Imperforate hymen.
Prolapsed urethra.
Vulvar intraepithelial neoplasia.
Carcinoma.

VULVITIS, GRANULOMATOUS

ICD-10CM # N76.2 Acute vulvitis
N76.3 Subacute and chronic vulvitis

Differential diagnosis of granulomatous vulvitis
Syphilis.
Lymphogranuloma venereum.
Mycobacteria.
Fungus.
Bacillary angiomatosis.
Folliculitis.
Ruptured pilosebaceous unit.
Ruptured cyst.
Crohn disease.
Vulvitis granulomatosa.
Hydradenitis suppurativa.

WEAKNESS, ACUTE, EMERGENT[60]

ICD-10CM # M62.81 Muscle weakness (generalized)

Demyelinating disorders (Guillain-Barré, chronic inflammatory demyelinating polyneuropathy [CIDP]).
Myasthenia gravis.
Infectious (poliomyelitis, diphtheria).
Toxic (botulism, tick paralysis, paralytic shellfish toxin, puffer fish, newts).
Metabolic (acquired or familial hypokalemia, hypophosphatemia, hypermagnesemia).
Metal poisoning (arsenic, thallium).
Porphyria.

WEAKNESS, GRADUAL ONSET

ICD-10CM # M62.81 Muscle weakness (generalized)

Depression.
Malingering.
Anemia.
Hypothyroidism.
Medications (e.g., sedatives, antidepressants, narcotics).
CHF.
Renal failure.
Liver failure.
Respiratory insufficiency.
Alcoholism.
Nutritional deficiencies.
Disorders of motor unit.
Basal ganglia disorders.
Upper motor neuron lesions.

WEAKNESS, NONNEUROMUSCULAR CAUSES

ICD-10CM # G93.3 Postviral fatigue syndrome
R53.1 Weakness
R53.81 Other malaise
R53.83 Other fatigue

Anxiety disorder.
Infectious process.
Anemia.
Renal insufficiency.
Hyperventilation.
Malignancy.
Hypothyroidism.
Hypotension.
Hypercapnia.
Hypoglycemia.
Cardiac arrhythmias.
Hepatic insufficiency.
Electrolyte imbalance.
Malnutrition.
Cerebrovascular insufficiency.

WEIGHT GAIN

ICD-10CM # R63.5 Abnormal weight gain
E66.9 Obesity, unspecified

Sedentary lifestyle.
Fluid overload.
Discontinuation of tobacco abuse.
Endocrine disorders (hypothyroidism, hyperinsulinism associated with maturity-onset DM, Cushing syndrome, hypogonadism, insulinoma, hyperprolactinemia, acromegaly).
Medications (nutritional supplements, oral contraceptives, glucocorticoids, etc.).
Anxiety disorders with compulsive eating.
Laurence-Moon-Biedl syndrome, Prader-Willi syndrome, other congenital diseases.
Hypothalamic injury (rare; <100 cases reported in medical literature).

WEIGHT LOSS

ICD-10CM # R63.4 Abnormal weight loss

Malignancy.
Psychiatric disorders (depression, anorexia nervosa).
New-onset DM.
Malabsorption.
COPD.
AIDS.
Uremia, liver disease.
Thyrotoxicosis, pheochromocytoma, carcinoid syndrome.
Addison disease.
Intestinal parasites.
Peptic ulcer disease.
Inflammatory bowel disease.
Food faddism.
Postgastrectomy syndrome.

WHEEZING

ICD-10CM # R06.2 Wheezing

Asthma.
COPD.
Interstitial lung disease.
Infections (pneumonia, bronchitis, bronchiolitis, epiglottitis).
Cardiac asthma.
GERD with aspiration.
Foreign body aspiration.
Pulmonary embolism.
Anaphylaxis.
Obstruction of airway (neoplasm, goiter, edema or hemorrhage from trauma, aneurysm, congenital abnormalities, strictures, spasm).
Carcinoid syndrome.

WHEEZING, PEDIATRIC AGE[9]

ICD-10CM # R06.2 Wheezing

Reactive airways disease.
Atopic asthma.
Infection-associated airway reactivity.
Exercise-induced asthma.
Salicylate-induced asthma and nasal polyposis.
Asthmatic bronchitis.
Other hypersensitivity reactions:
- Hypersensitivity pneumonitis.
- Tropical eosinophilia.
- Visceral larva migrans.
- Allergic bronchopulmonary aspergillosis.

Aspiration:
- Foreign body.
- Food, saliva, gastric contents.
- Laryngotracheoesophageal cleft.
- Tracheoesophageal fistula, H-type.
- Pharyngeal incoordination or neuromuscular weakness.

Squamous cell carcinoma.
Hernia.
Edema.
Hematoma.
Acrochordon.
Epidermal cysts.
Neurofibromatosis.
Accessory breast tissue.

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Contact dermatitis.
Endometriosis.
Pemphigus.
Pemphigoid.
Atrophy.
Lichen sclerosus.
Lichen planus.
Crohn disease.
Bartholin abscess.
Trauma.
Imperforate hymen.
Prolapsed urethra.
Vulvar intraepithelial neoplasia.
Carcinoma.

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N76.3 Subacute and chronic vulvitis

Differential diagnosis of granulomatous vulvitis
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Mycobacteria.
Fungus.
Bacillary angiomatosis.
Folliculitis.
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Ruptured cyst.
Crohn disease.
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Metabolic (acquired or familial hypokalemia, hypophosphatemia, hypermagnesemia).
Metal poisoning (arsenic, thallium).
Porphyria.

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Depression.
Malingering.
Anemia.
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Medications (e.g., sedatives, antidepressants, narcotics).
CHF.
Renal failure.
Liver failure.
Respiratory insufficiency.
Alcoholism.
Nutritional deficiencies.
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Basal ganglia disorders.
Upper motor neuron lesions.

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R53.81 Other malaise
R53.83 Other fatigue

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Infectious process.
Anemia.
Renal insufficiency.
Hyperventilation.
Malignancy.
Hypothyroidism.
Hypotension.
Hypercapnia.
Hypoglycemia.
Cardiac arrhythmias.
Hepatic insufficiency.
Electrolyte imbalance.
Malnutrition.
Cerebrovascular insufficiency.

WEIGHT GAIN

ICD-10CM # R63.5 Abnormal weight gain
E66.9 Obesity, unspecified

Sedentary lifestyle.
Fluid overload.
Discontinuation of tobacco abuse.
Endocrine disorders (hypothyroidism, hyperinsulinism associated with maturity-onset DM, Cushing syndrome, hypogonadism, insulinoma, hyperprolactinemia, acromegaly).
Medications (nutritional supplements, oral contraceptives, glucocorticoids, etc.).
Anxiety disorders with compulsive eating.
Laurence-Moon-Biedl syndrome, Prader-Willi syndrome, other congenital diseases.
Hypothalamic injury (rare; <100 cases reported in medical literature).

WEIGHT LOSS

ICD-10CM # R63.4 Abnormal weight loss

Malignancy.
Psychiatric disorders (depression, anorexia nervosa).
New-onset DM.
Malabsorption.
COPD.
AIDS.
Uremia, liver disease.
Thyrotoxicosis, pheochromocytoma, carcinoid syndrome.
Addison disease.
Intestinal parasites.
Peptic ulcer disease.
Inflammatory bowel disease.
Food faddism.
Postgastrectomy syndrome.

WHEEZING

ICD-10CM # R06.2 Wheezing

Asthma.
COPD.
Interstitial lung disease.
Infections (pneumonia, bronchitis, bronchiolitis, epiglottitis).
Cardiac asthma.
GERD with aspiration.
Foreign body aspiration.
Pulmonary embolism.
Anaphylaxis.
Obstruction of airway (neoplasm, goiter, edema or hemorrhage from trauma, aneurysm, congenital abnormalities, strictures, spasm).
Carcinoid syndrome.

WHEEZING, PEDIATRIC AGE[9]

ICD-10CM # R06.2 Wheezing

Reactive airways disease.
Atopic asthma.
Infection-associated airway reactivity.
Exercise-induced asthma.
Salicylate-induced asthma and nasal polyposis.
Asthmatic bronchitis.
Other hypersensitivity reactions:
- Hypersensitivity pneumonitis.
- Tropical eosinophilia.
- Visceral larva migrans.
- Allergic bronchopulmonary aspergillosis.

Aspiration:
- Foreign body.
- Food, saliva, gastric contents.
- Laryngotracheoesophageal cleft.
- Tracheoesophageal fistula, H-type.
- Pharyngeal incoordination or neuromuscular weakness.

Cystic fibrosis.
Primary ciliary dyskinesia.
Cardiac failure.
Bronchiolitis obliterans.
Extrinsic compression of airways:
- Vascular ring.
- Enlarged lymph node.
- Mediastinal tumor.
- Lung cysts.

Tracheobronchomalacia.
Endobronchial masses.
Gastroesophageal reflux.
Pulmonary hemosiderosis.
Sequelae of bronchopulmonary dysplasia.
"Hysterical" glottic closure.
Cigarette smoke, other environmental insults.

WRIST AND HAND PAIN[42]

ICD-10CM # S69.90XA Unspecified injury of unspecified wrist, hand and finger(s), initial encounter

Articular

Arthritis of the wrist, MCP, PIP, or DIP as a result of:	Trauma, hypermobility, sprain. RA (wrist, MCP, PIP joints). Osteoarthritis (first CMC, PIP, and DIP joints). Other forms of arthritis: gout, psoriatic arthritis, infection. Joint neoplasm.

Periarticular

Subcutaneous.	RA nodules, gouty tophi, painful subcutaneous calcific nodules in scleroderma, glomus tumor of the nail bed.
Palmar fascia.	Dupuytren contracture.
Tendon sheath.	Wrist extensor tenosynovitis, including de Quervain tenosynovitis and extensor carpi radialis tenosynovitis. Wrist volar flexor tenosynovitis (including carpal tunnel syndrome). Thumb flexor tenosynovitis (trigger or snapping thumb). Finger flexor tenosynovitis (trigger finger). Pigmented villonodular tenosynovitis (giant cell tumor of the tendon sheath).
Acute calcific periarthritis ganglion.	Wrist, MCP, and rarely the PIP and DIP joints.

Osseous

Bone lesions.	Fractures; neoplasm; infection; osteonecrosis, including Kienböck disease (lunate) and Preiser disease (scaphoid).

Neurologic

Nerve entrapment syndromes

Median nerve.	Carpal tunnel syndrome (at the wrist). Pronator teres syndrome (at the pronator teres). Anterior interosseous nerve syndrome.
Ulnar nerve.	Cubital tunnel syndrome (at the elbow). Guyon canal (at the wrist).
Posterior interosseous nerve syndrome.	Radial nerve palsy (spiral groove syndrome).
Lower brachial plexus.	Thoracic outlet syndrome, Pancoast tumor.
Cervical nerve roots.	Herniated cervical disk, tumors.

Spinal cord lesion

Spinal tumors, syringomyelia.	

Vascular

Vasoplastic disorders with Raynaud phenomenon.	Scleroderma, occupational vibration syndrome.
Small- or large-vessel vasculitis.	With digital ischemia, ischemic ulcers (e.g., SLE, RA, and Takayasu arthritis).

Referred pain

Cervical spine disorders.	Shoulder–hand syndrome and causalgia.
Reflex sympathetic dystrophy syndrome.	
Cardiac.	Angina pectoris.

CMC, Carpometacarpal; *DIP,* distal interphalangeal; *MCP,* metacarpophalangeal; *PIP,* proximal interphalangeal; *RA,* rheumatoid arthritis; *SLE,* systemic lupus erythematosus.

WRIST AND HAND PAIN, IN DIFFERENT AGE GROUPS[18]

ICD-10CM # S69.80XA Other specified injuries of unspecified wrist, hand and finger(s), initial encounter
S69.90XA Unspecified injury of unspecified wrist, hand and finger(s), initial encounter

COMMON CAUSES OF WRIST AND HAND PAIN IN DIFFERENT AGE GROUPS

Childhood (2 to 10 yr)
Intraarticular
Infection.
Periarticular
Fracture.
Osteomyelitis.

Adolescence (10 to 18 yr)
Intraarticular
Infection.
Periarticular
Trauma.
Osteomyelitis.
Tumors.
Ganglion.
Idiopathic wrist pain.

Early Adulthood (18 to 30 yr)
Intraarticular
Inflammatory arthritis.
Infection.
Osteoarthritis.
Periarticular
Peripheral nerve entrapment.
Tendonitis.
Referred
Cervical.

Adulthood (30 to 50 yr)
Intraarticular
Inflammatory arthritis.
Infection.
Osteoarthritis.
Periarticular
Peripheral nerve entrapment.
Tendonitis.
Referred
Cervical.
Chest.
Cardiac.

Old age (>50 yr)
Intraarticular
Inflammatory arthritis.
Osteoarthritis.
Periarticular
Peripheral nerve entrapment.
Tendonitis.
Referred
Cervical.
Chest.
Cardiac.

WRIST PAIN

ICD-10CM # S69.80XA Other specified injuries of unspecified wrist, hand and finger(s), initial encounter
S69.90XA Unspecified injury of unspecified wrist, hand and finger(s), initial encounter

MECHANICAL

Osteoarthritis.
Ligament tear.
Fracture.
Ganglion.
De Quervain tenosynovitis.
Avascular necrosis (scaphoid, lunate).
Nonunion of scaphoid or lunate.
Neoplasm.

METABOLIC

Pregnancy.
Diabetes.
Gout.
Pseudogout.
Paget disease.
Acromegaly.

Hypothyroidism.
Hyperparathyroidism.

INFECTIOUS
Osteomyelitis.
Septic arthritis.
Cat-scratch disease.
Tick bite (Lyme disease, babesiosis).
Tuberculosis.

NEUROLOGIC
Peripheral neuropathy.
Nerve injury (median, ulnar, radial nerve).
Thoracic outlet compression syndrome.
Distal posterior interosseous nerve syndrome.

RHEUMATOLOGIC
Psoriasis.
RA.
SLE, mixed connective tissue disorder (MCTD).
Scleroderma.

MISCELLANEOUS
Granulomatous (sarcoidosis).
Amyloidosis.
Multiple myeloma.
Leukemia.

XEROPHTHALMIA[65]

ICD-10CM #		
	H11.149	Conjunctival xerosis, unspecified, unspecified eye

MEDICATIONS
Tricyclic antidepressants: amitriptyline, doxepin.
Antihistamines: diphenhydramine, chlorpheniramine, promethazine, and many cold and decongestant preparations.
Anticholinergic agents: antiemetics such as scopolamine, antispasmodic agents such as oxybutynin chloride.

ABNORMALITIES OF EYELID FUNCTION
Neuromuscular disorders.
Aging.
Thyrotoxicosis.

ABNORMALITIES OF TEAR PRODUCTION
Hypovitaminosis A.
Stevens-Johnson syndrome.
Familial diseases affecting sebaceous secretions.

ABNORMALITIES OF CORNEAL SURFACES
Scarring from past injuries and herpes simplex infection.

XEROSTOMIA[65]

ICD-10CM #		
	K11.7	Disturbances of salivary secretion
	R68.2	Dry mouth, unspecified

MEDICATIONS
Tricyclic antidepressants: amitriptyline, doxepin.
Antihistamines: diphenhydramine, chlorpheniramine, promethazine, and many cold and decongestant preparations.
Anticholinergic agents: antiemetics such as scopolamine, antispasmodic agents such as oxybutynin chloride.

DEHYDRATION
Debility.
Fever.

POLYURIA
Alcohol intake.
Arrhythmia.
Diabetes.

PREVIOUS HEAD AND NECK IRRADIATION SYSTEMIC DISEASES
Sjögren syndrome.
Sarcoidosis.
Amyloidosis.
HIV infection.
Graft-versus-host disease.

YELLOW URINE

ICD-10CM #		
	R82	Other abnormal findings in urine

Normal coloration.
Concentrated urine.
Use of multivitamin supplements.
Diet rich in carrots.
Use of Cascara.
Urinary tract infection

REFERENCES

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Hypothyroidism.
Hyperparathyroidism.

INFECTIOUS
Osteomyelitis.
Septic arthritis.
Cat-scratch disease.
Tick bite (Lyme disease, babesiosis).
Tuberculosis.

NEUROLOGIC
Peripheral neuropathy.
Nerve injury (median, ulnar, radial nerve).
Thoracic outlet compression syndrome.
Distal posterior interosseous nerve syndrome.

RHEUMATOLOGIC
Psoriasis.
RA.
SLE, mixed connective tissue disorder (MCTD).
Scleroderma.

MISCELLANEOUS
Granulomatous (sarcoidosis).
Amyloidosis.
Multiple myeloma.
Leukemia.

XEROPHTHALMIA[65]

ICD-10CM #		
	H11.149	Conjunctival xerosis, unspecified, unspecified eye

MEDICATIONS
Tricyclic antidepressants: amitriptyline, doxepin.
Antihistamines: diphenhydramine, chlorpheniramine, promethazine, and many cold and decongestant preparations.
Anticholinergic agents: antiemetics such as scopolamine, antispasmodic agents such as oxybutynin chloride.

ABNORMALITIES OF EYELID FUNCTION
Neuromuscular disorders.
Aging.
Thyrotoxicosis.

ABNORMALITIES OF TEAR PRODUCTION
Hypovitaminosis A.
Stevens-Johnson syndrome.
Familial diseases affecting sebaceous secretions.

ABNORMALITIES OF CORNEAL SURFACES
Scarring from past injuries and herpes simplex infection.

XEROSTOMIA[65]

ICD-10CM #		
	K11.7	Disturbances of salivary secretion
	R68.2	Dry mouth, unspecified

MEDICATIONS
Tricyclic antidepressants: amitriptyline, doxepin.
Antihistamines: diphenhydramine, chlorpheniramine, promethazine, and many cold and decongestant preparations.
Anticholinergic agents: antiemetics such as scopolamine, antispasmodic agents such as oxybutynin chloride.

DEHYDRATION
Debility.
Fever.

POLYURIA
Alcohol intake.
Arrhythmia.
Diabetes.

PREVIOUS HEAD AND NECK IRRADIATION SYSTEMIC DISEASES
Sjögren syndrome.
Sarcoidosis.
Amyloidosis.
HIV infection.
Graft-versus-host disease.

YELLOW URINE

ICD-10CM #		
	R82	Other abnormal findings in urine

Normal coloration.
Concentrated urine.
Use of multivitamin supplements.
Diet rich in carrots.
Use of Cascara.
Urinary tract infection

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Hypothyroidism.
Hyperparathyroidism.

INFECTIOUS
Osteomyelitis.
Septic arthritis.
Cat-scratch disease.
Tick bite (Lyme disease, babesiosis).
Tuberculosis.

NEUROLOGIC
Peripheral neuropathy.
Nerve injury (median, ulnar, radial nerve).
Thoracic outlet compression syndrome.
Distal posterior interosseous nerve syndrome.

RHEUMATOLOGIC
Psoriasis.
RA.
SLE, mixed connective tissue disorder (MCTD).
Scleroderma.

MISCELLANEOUS
Granulomatous (sarcoidosis).
Amyloidosis.
Multiple myeloma.
Leukemia.

XEROPHTHALMIA[65]

ICD-10CM #		
	H11.149	Conjunctival xerosis, unspecified, unspecified eye

MEDICATIONS
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Antihistamines: diphenhydramine, chlorpheniramine, promethazine, and many cold and decongestant preparations.
Anticholinergic agents: antiemetics such as scopolamine, antispasmodic agents such as oxybutynin chloride.

ABNORMALITIES OF EYELID FUNCTION
Neuromuscular disorders.
Aging.
Thyrotoxicosis.

ABNORMALITIES OF TEAR PRODUCTION
Hypovitaminosis A.
Stevens-Johnson syndrome.
Familial diseases affecting sebaceous secretions.

ABNORMALITIES OF CORNEAL SURFACES
Scarring from past injuries and herpes simplex infection.

XEROSTOMIA[65]

ICD-10CM #		
	K11.7	Disturbances of salivary secretion
	R68.2	Dry mouth, unspecified

MEDICATIONS
Tricyclic antidepressants: amitriptyline, doxepin.
Antihistamines: diphenhydramine, chlorpheniramine, promethazine, and many cold and decongestant preparations.
Anticholinergic agents: antiemetics such as scopolamine, antispasmodic agents such as oxybutynin chloride.

DEHYDRATION
Debility.
Fever.

POLYURIA
Alcohol intake.
Arrhythmia.
Diabetes.

PREVIOUS HEAD AND NECK IRRADIATION SYSTEMIC DISEASES
Sjögren syndrome.
Sarcoidosis.
Amyloidosis.
HIV infection.
Graft-versus-host disease.

YELLOW URINE

ICD-10CM #		
	R82	Other abnormal findings in urine

Normal coloration.
Concentrated urine.
Use of multivitamin supplements.
Diet rich in carrots.
Use of Cascara.
Urinary tract infection

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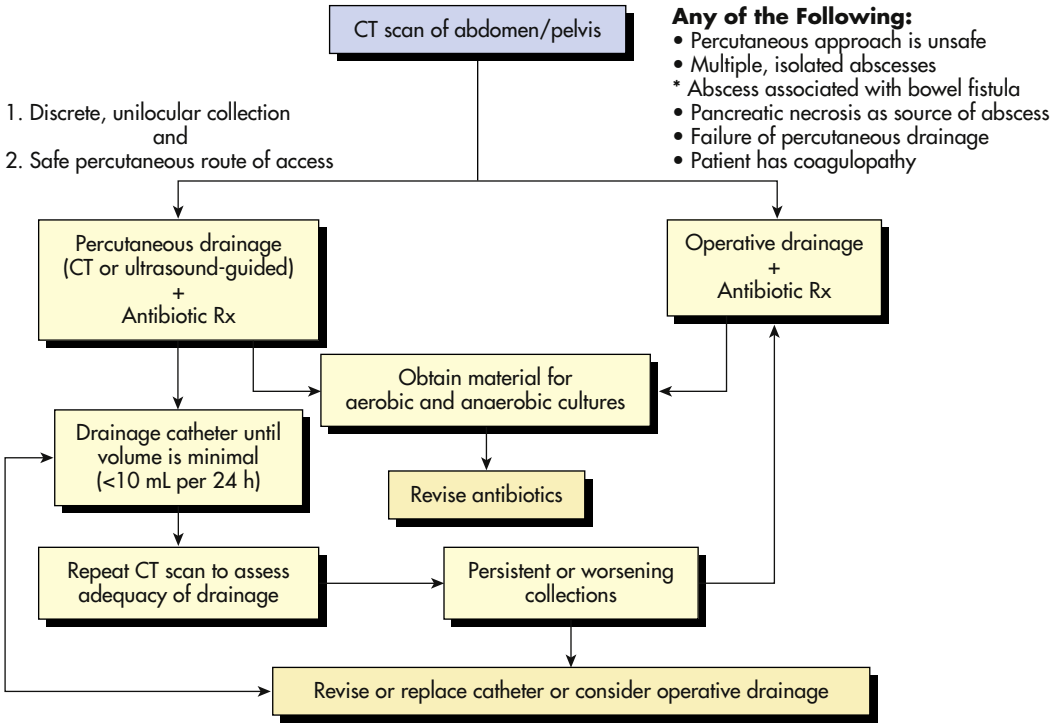

FIG. 1 Approach to management of intraabdominal abscesses including indications for consideration of percutaneous versus operative drainage. *CT,* Computed tomography; *Rx,* treatment. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.)

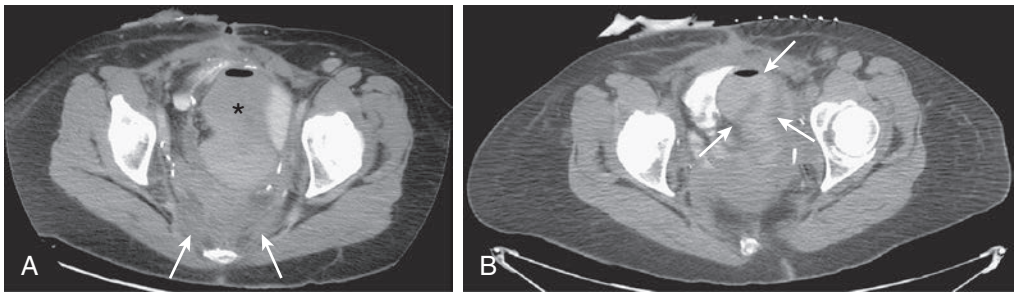

FIG. 2 A, Axial computed tomography *(CT)* image shows an apparently rim-enhancing structure containing gas (*asterisk*) in the deep pelvis adjacent to tethered bowel loops in a patient with prior pelvic irradiation. The structure could represent an abscess or a dilated loop of small bowel. The presacral inflammation *(arrows)* is related to radiation change. **B,** CT image obtained 2 hours later shows ingested oral contrast in this structure *(arrows)* confirming that this is a bowel loop rather than an abscess. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

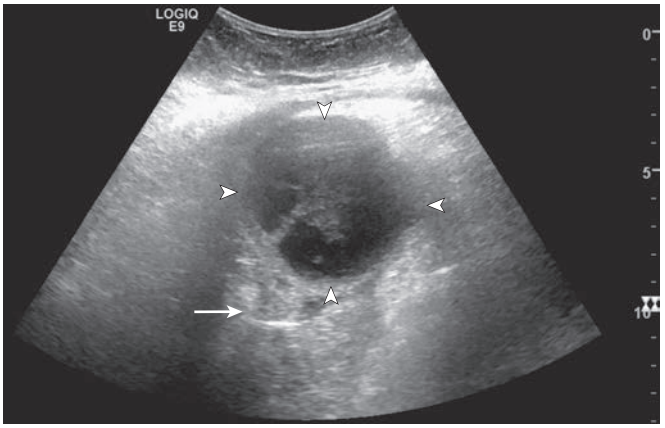

FIG. 3 Abdominal ultrasound of a typical abscess *(arrowheads)* demonstrating central decreased echogenicity, thickened wall, and debris arising anterior to the descending colon *(arrow)* in a patient with diverticulosis compatible with a diverticular abscess. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

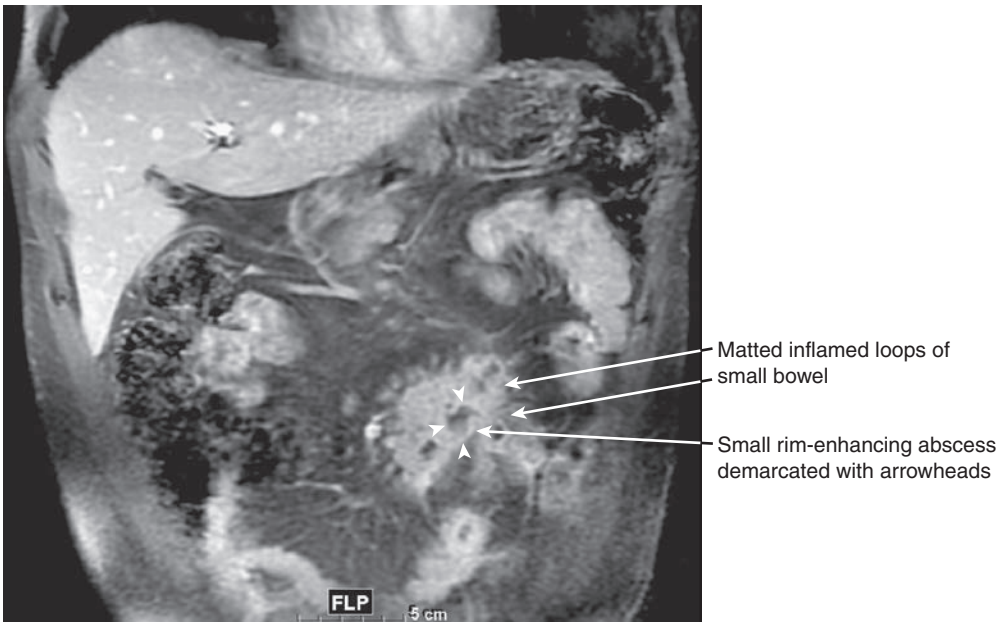

FIG. 4 Coronal magnetic resonance image with gadolinium contrast of a patient with Crohn disease showing a small rim-enhancing collection *(arrowheads)* interposed between several loops of inflamed bowel *(arrows)* compatible with an interloop abscess. Interloop abscesses are not amenable to percutaneous drain placement. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

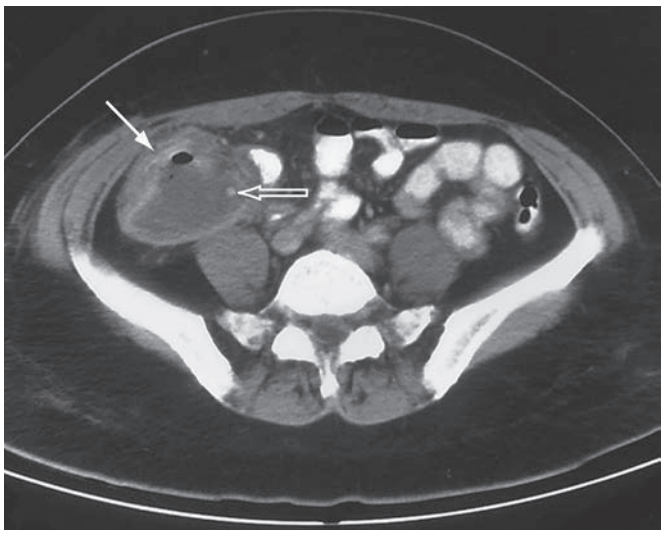

FIG. 5 Axial computed tomography demonstrating a right lower quadrant abscess *(closed arrow)* with an appendicolith *(open arrow).* Such extraluminal appendicoliths may predict clinical failure with percutaneous drainage. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.)

BOX 1 Causes of Intraabdominal Abscesses

Abdominal trauma
Appendicitis
Cholecystectomy and other operations or invasive procedures
Crohn disease
Diverticulitis
Neoplastic disease
Pancreatitis
Perforated hollow viscus (e.g., duodenal or gastric ulcer)

From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

BOX 2 Clinical Risk Factors for Intraabdominal Abscess

Chronic glucocorticoid use
Increasing age
Malnutrition
Preexisting organ dysfunction
Transfusion
Underlying malignancy

From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

BOX 3 Antibiotic Choices in the Treatment of Intraabdominal Infections

Single-Agent Therapy

Second-Generation Cephalosporins
Cefoxitin

Carbapenems
Imipenem-cilastatin
Meropenem
Doripenem
Ertapenem (no *Pseudomonas* coverage)

Extended-Spectrum Penicillin–β-Lactamase Inhibitor Combinations
Piperacillin sodium-tazobactam
Ticarcillin disodium-clavulanate

Glycylcyclines
Tigecycline

Combination Therapy (Antiaerobe[a] + Antianaerobe)

Third- or Fourth-Generation Cephalosporins
Ceftriaxone + metronidazole
Cefotaxime + metronidazole
Ceftazidime (*Pseudomonas* coverage) + metronidazole
Cefepime (*Pseudomonas* coverage) + metronidazole

Fluoroquinolones
Ciprofloxacin + metronidazole
Levofloxacin + metronidazole
Moxifloxacin[b]

[a]Aminoglycoside therapy as an antiaerobic drug should not be used in routine practice owing to an increase in nephrotoxicity and possible worsened patient outcomes with its use.
[b]Moxifloxacin has adequate anaerobic coverage, making metronidazole unnecessary.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

TABLE 1 Comparison of Common Causes of Acute Abdominal Pain

Cause	Onset	Location	Character	Descriptor	Radiation	Intensity
Appendicitis	Gradual	Periumbilical area early; RLQ late	Diffuse early; localized later	Aching	None	++
Cholecystitis	Acute	RUQ	Localized	Constricting	Scapula	++
Pancreatitis	Acute	Epigastrium, back	Localized	Boring	Midback	++ to +++
Diverticulitis	Gradual	LLQ	Localized	Aching	None	++ to +++
Perforated peptic ulcer	Sudden	Epigastrium	Localized early, diffuse later	Burning	None	+++
Small bowel obstruction	Gradual	Periumbilical area	Diffuse	Cramping	None	++
Mesenteric ischemia, infarction	Sudden	Periumbilical area	Diffuse	Agonizing	None	+++
Ruptured abdominal aortic aneurysm	Sudden	Abdomen, back, flank	Diffuse	Tearing	None	+++
Gastroenteritis	Gradual	Periumbilical area	Diffuse	Spasmodic	None	+ to ++
Pelvic inflammatory disease	Gradual	Either LQ, pelvis	Localized	Aching	Upper thigh	++
Ruptured ectopic pregnancy	Sudden	Either LQ, pelvis	Localized	Sharp	None	++

+, Mild; ++, moderate; +++, severe; *LLQ,* left lower quadrant; *LQ,* lower quadrant; *RLQ,* right lower quadrant; *RUQ,* right upper quadrant.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, 2016, Elsevier.

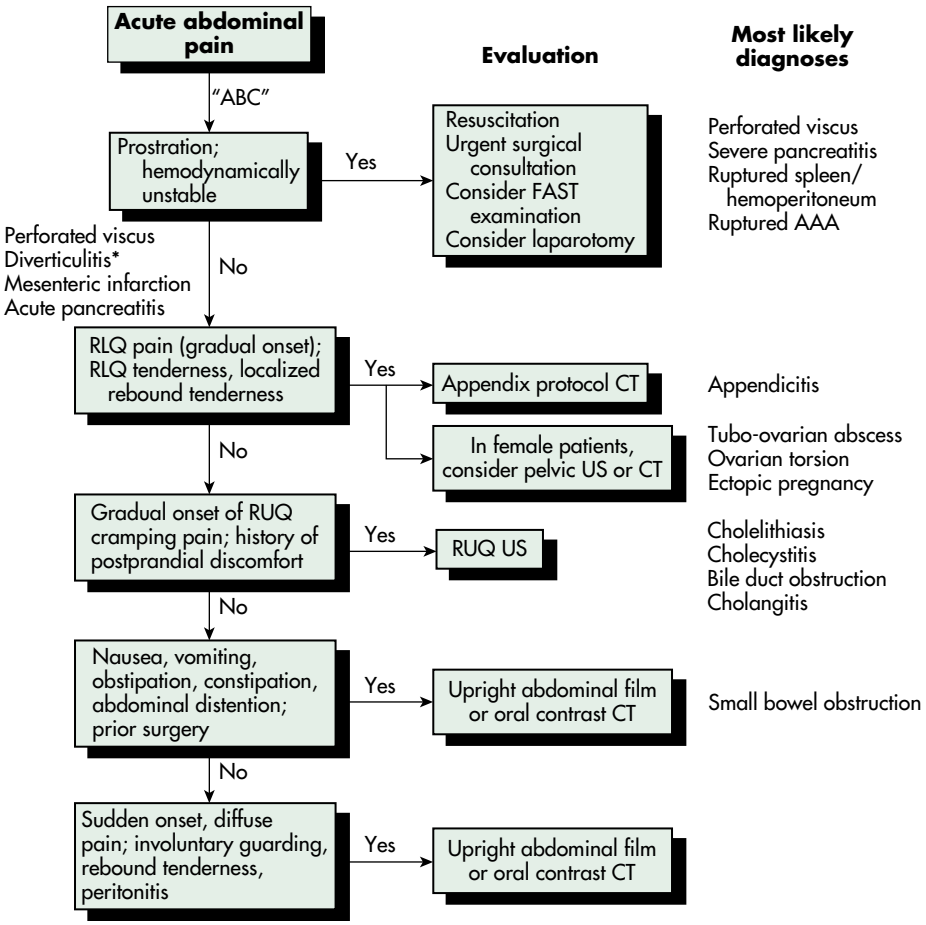

FIG. 6 An approach to the urgent evaluation of abdominal pain. Specific complaints and physical examination findings are coupled with appropriate radiologic imaging. *For left lower quadrant pain, the most likely diagnosis is diverticulitis. *AAA,* Abdominal aortic aneurysm; *ABC,* airway, breathing, circulation; *CT,* computed tomography; *FAST,* focused abdominal sonogram for trauma; *RLQ,* right lower quadrant; *RUQ,* right upper quadrant. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, 2016, Elsevier.)

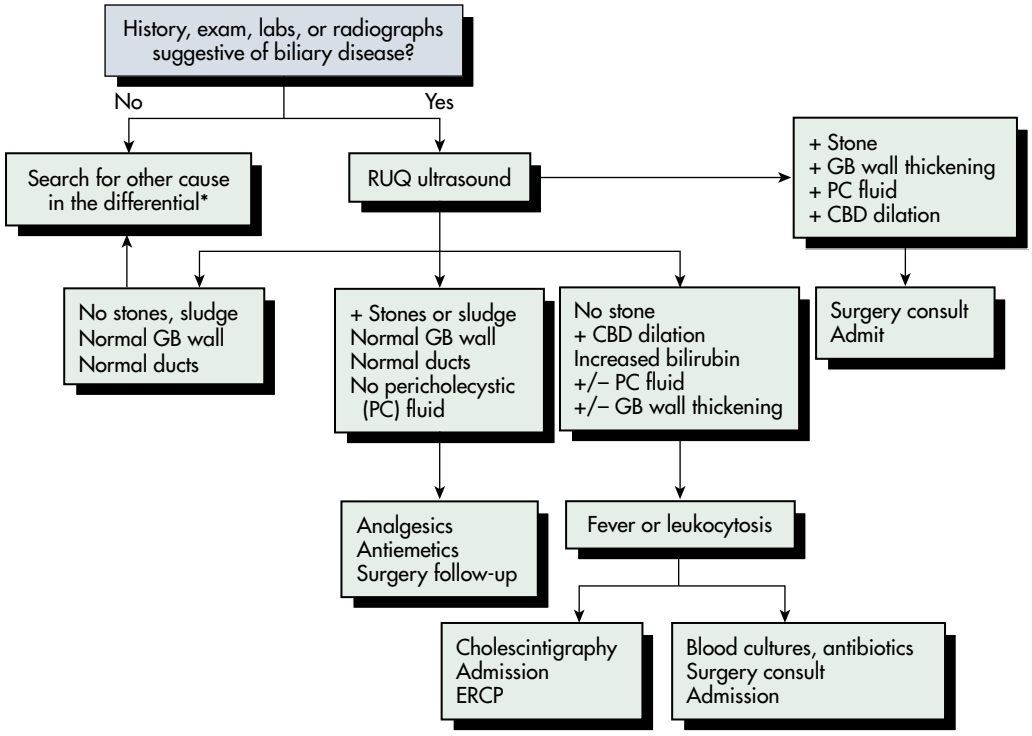

FIG. 7 Treatment algorithm for right upper quadrant *(RUQ)* pain. *Refer to Section II, Differential Diagnosis: Abdominal Pain, Right Upper Quadrant. *CBD,* Common bile duct; *ERCP,* endoscopic retrograde cholangiopancreatography; *GB,* gallbladder; *RUQ,* right upper quadrant; +, with; –, without; ±, with or without. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

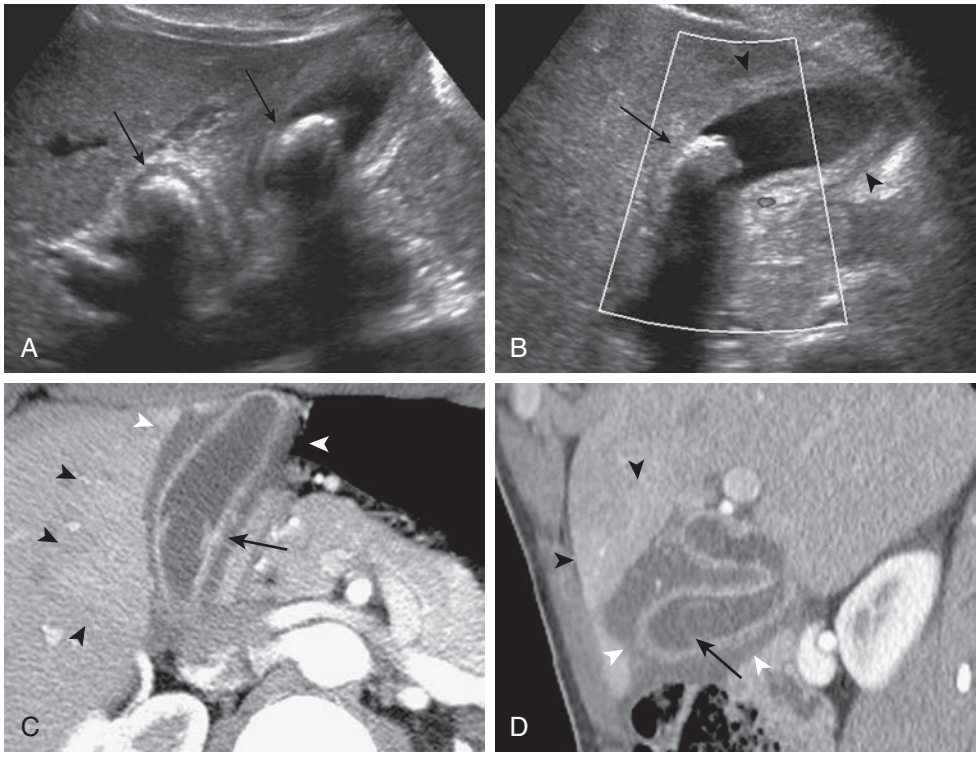

FIG. 8 A 43-year-old man with acute cholecystitis. Ultrasound images **(A** and **B)** demonstrate echogenic, shadowing gallstones *(arrows)* with gallbladder wall thickening *(arrowheads)* in a patient in whom a sonographic Murphy sign was elicited. Axial **(C)** and sagittal **(D)** portal venous phase computed tomography images reveal a gallstone *(arrows)*, as well as a thickened gallbladder wall *(white arrowheads).* Although not acquired in the arterial phase of contrast, hepatic hyperenhancement consistent with secondary inflammation is nevertheless seen *(black arrowheads).* These findings are specific for this life-threatening complication and should be recognized and treated urgently. (From Soto JA, Lucey BC: *Emergency radiology, the requisites,* ed 2, 2017, Elsevier.)

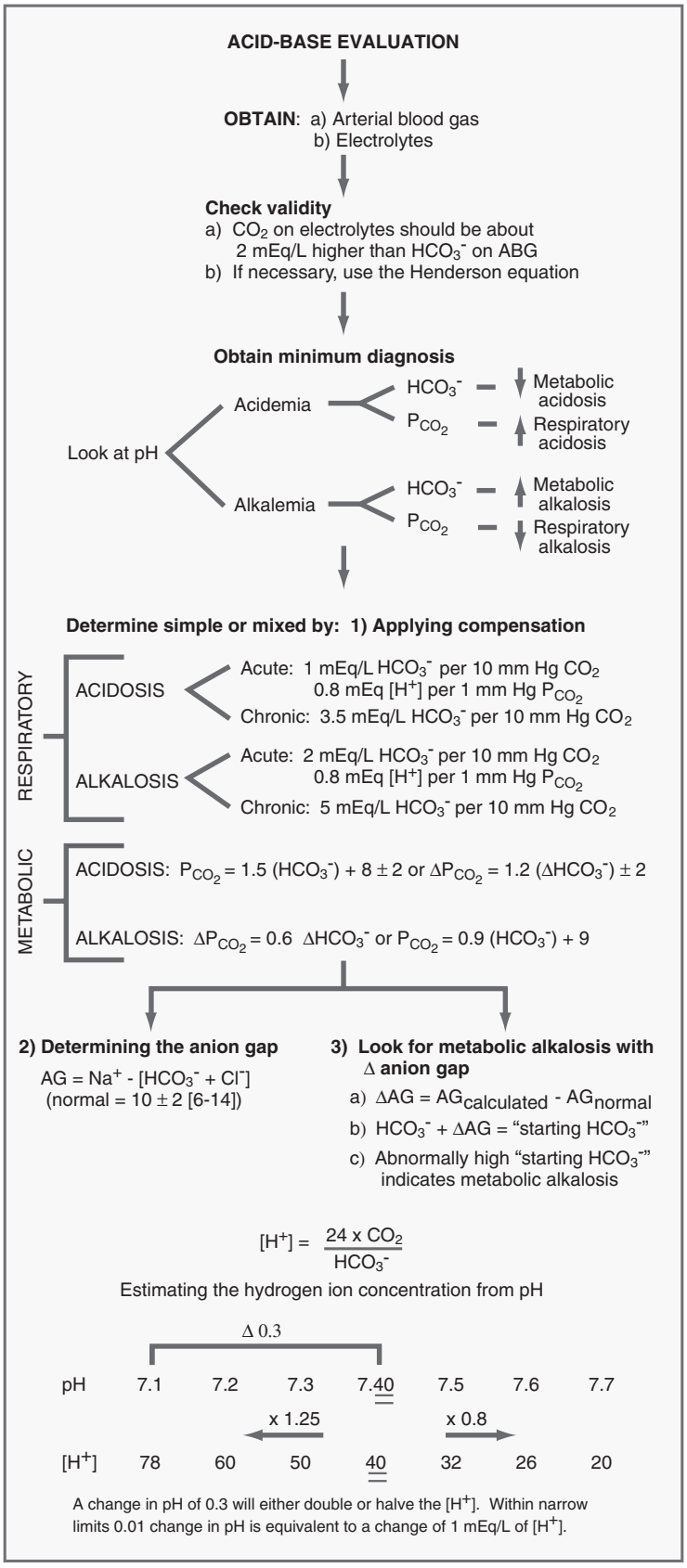

FIG. 9 Scheme for assessing acid-base homeostasis. (Modified from Andreoli TE [ed]: *Cecil essentials of medicine,* ed 7, Philadelphia, 2008, Saunders.)

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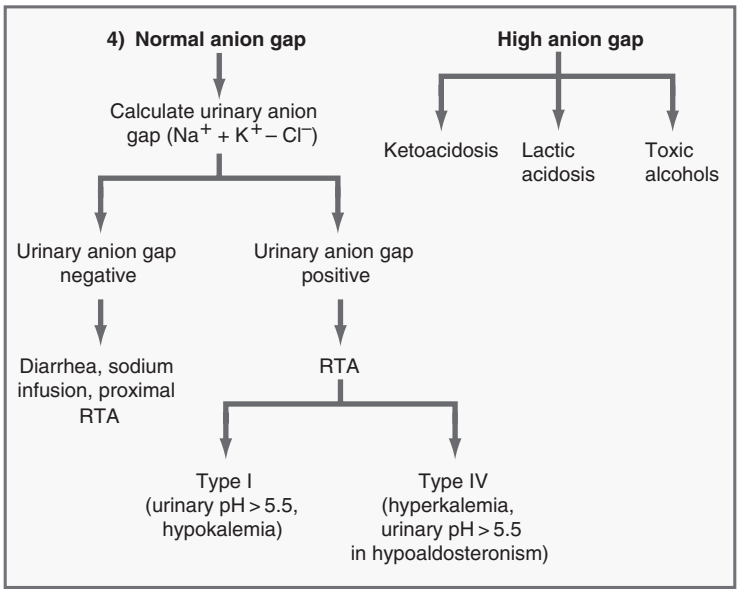


FIG. 9 (Continued)

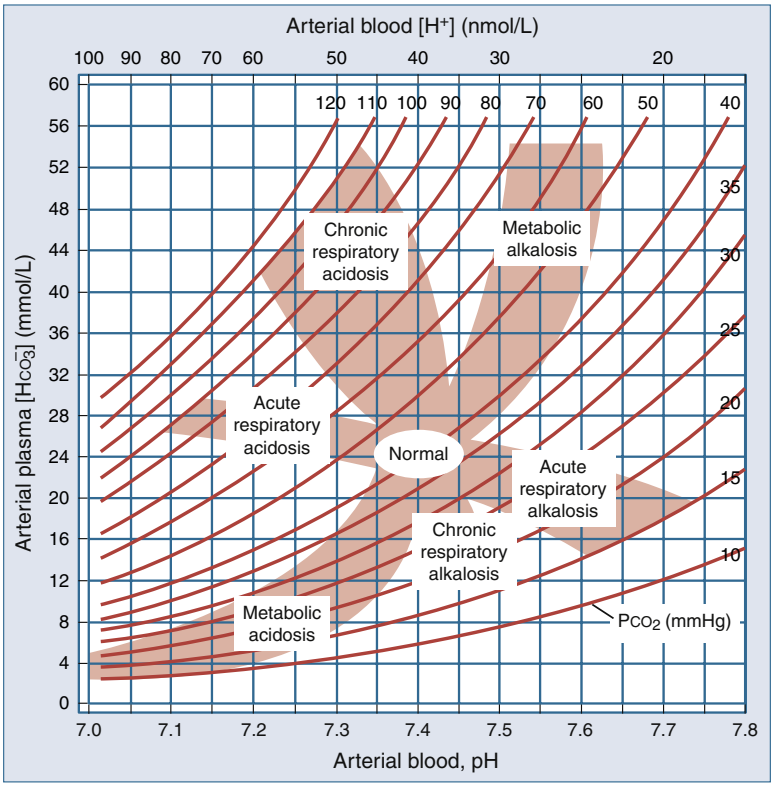


FIG. 10 Acid base normogram. Shaded areas represent 95% confidence limits of normal respiratory and metabolic compensations for primary disturbances. Points outside shaded areas represent a mixed disorder, assuming absence of laboratory error. (From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.)

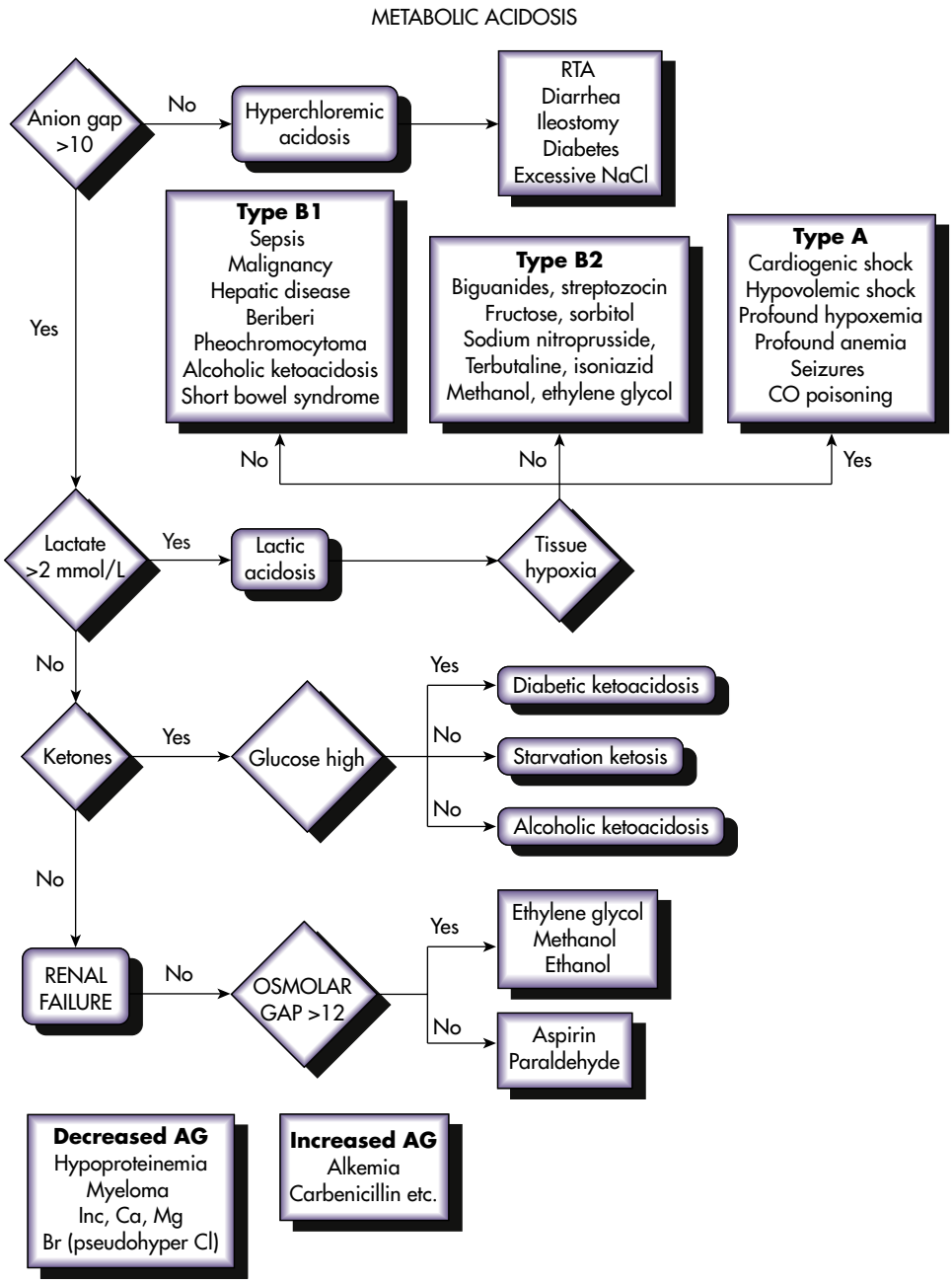


FIG. 11 Diagnostic approach to metabolic acidosis. *CO,* Carbon monoxide; *RTA,* renal tubular acidosis. (From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.)

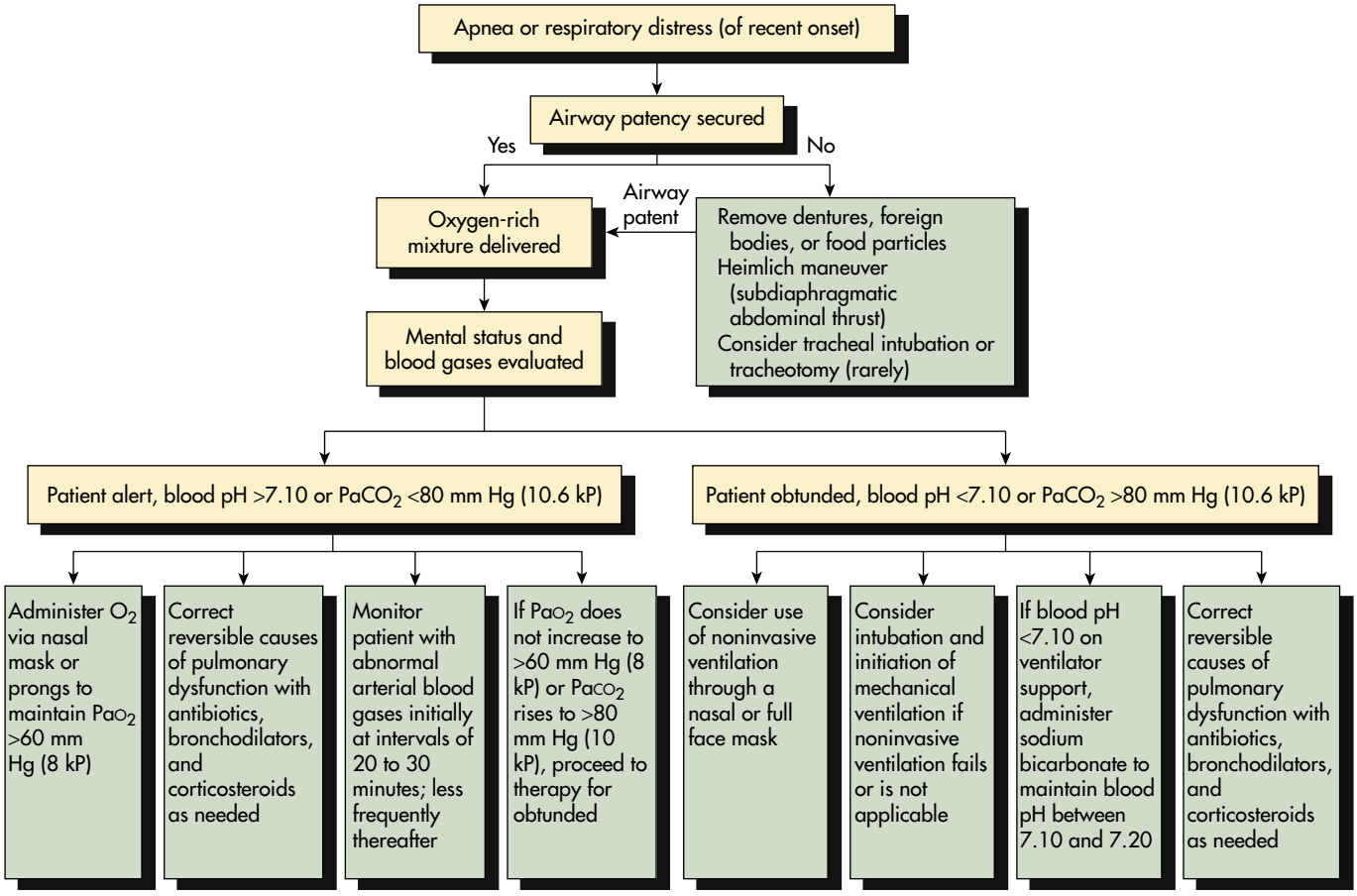


FIG. 12 Algorithm for management of acute respiratory acidosis. (From Johnson R et al: *Comprehensive clinical nephrology*, ed 5, Philadelphia, 2015, Saunders.)

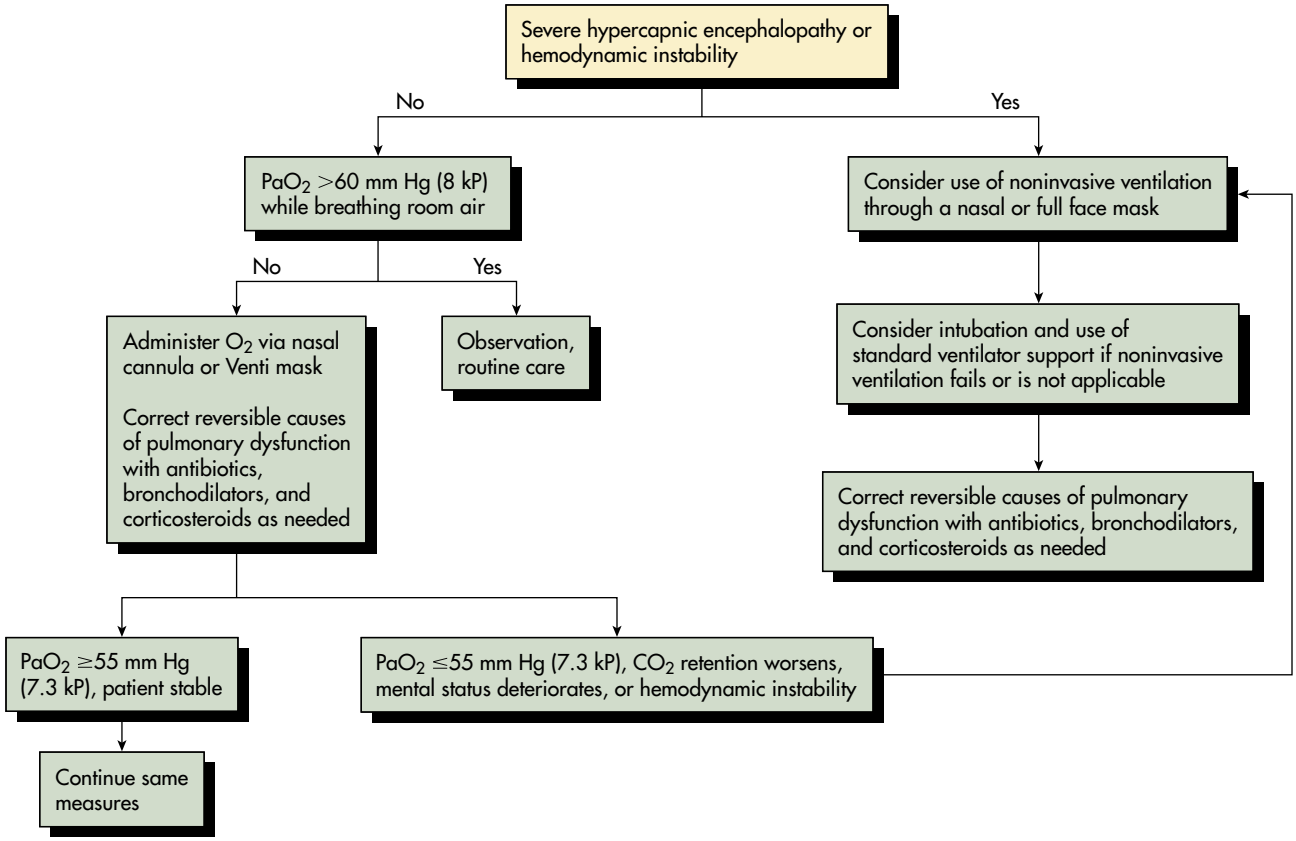


FIG. 13 Algorithm for management of chronic respiratory acidosis. *PaO_2,* Partial pressure of oxygen. (From Johnson R et al: *Comprehensive clinical nephrology*, ed 5, Philadelphia, 2015, Saunders.)

TABLE 2 Causes of Chronic Alveolar Hypoventilation/Respiratory Acidosis

	Site of Defect	Condition
Defects in respiratory drive	Central and peripheral chemoreceptors	Brainstem lesions Primary alveolar hypoventilation syndrome (Ondine's curse), extreme obesity (Pickwickian syndrome) Spinal cord lesions
Neuromuscular defects	Neuromuscular	*Motor neuron disease:* critical illness polyneuropathy, multiple sclerosis, amyotrophic lateral sclerosis
	Muscular disease	Myasthenia gravis, critical illness myopathy
Defects in respiratory mechanics and gas exchange	Lung	*Increased dead space:* chronic obstructive pulmonary disease, chronic pulmonary embolism *Increased lung elastance*: pulmonary fibrosis *Increased chest wall elastance:* extreme obesity, fibrothorax, kyphoscoliosis *Increased respiratory resistance*: airway stenosis, chronic obstructive pulmonary disease

From Ronco C: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.

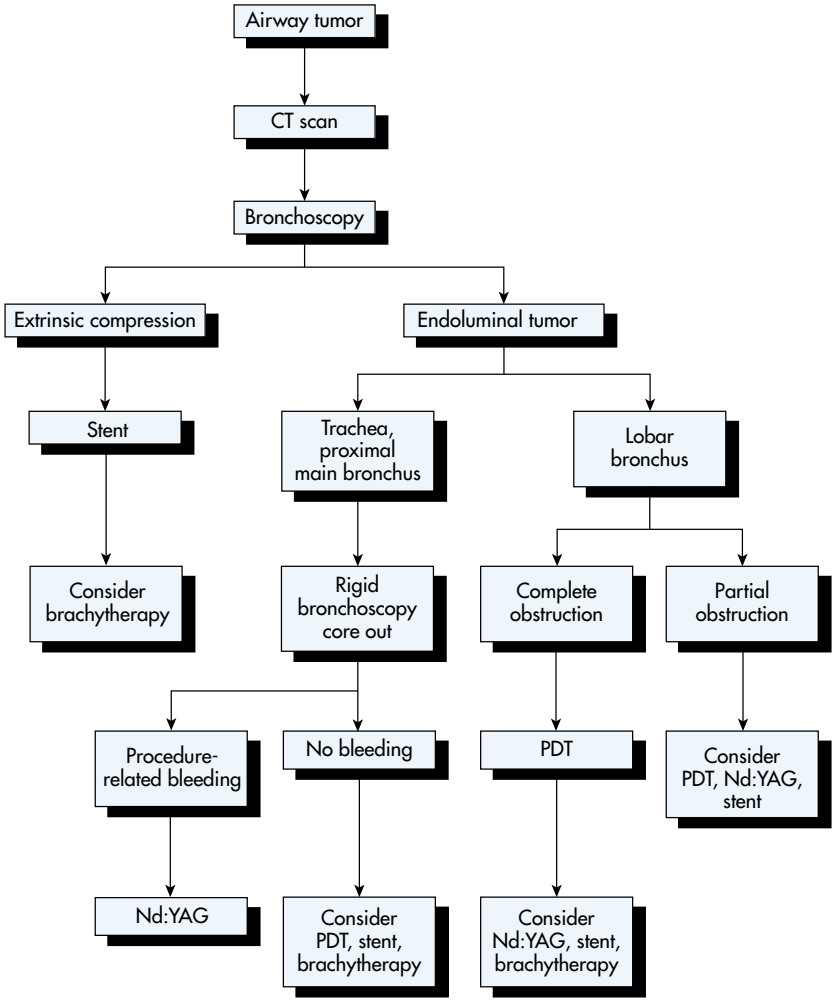


FIG. 14 Approach to malignant obstruction of the airway. *CT,* Computed tomography; *Nd:YAG,* neodymium:yttrium-aluminum-garnet; *PDT,* photodynamic therapy. (From Sellke FW, del Nido PJ, Swanson SJ: *Sabiston & Spencer surgery of the chest,* ed 9, 2016, Elsevier.)

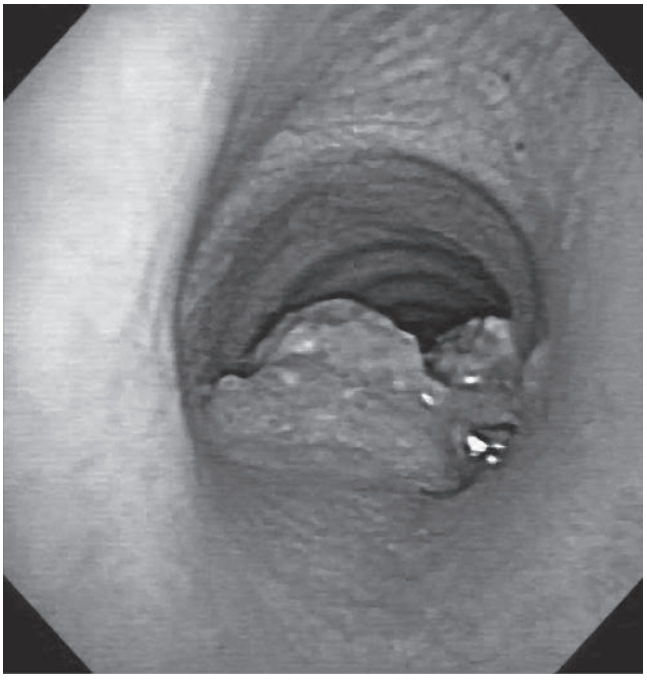


FIG. 15 An exophytic squamous cell carcinoma of the trachea. (From Sellke FW, del Nido PJ, Swanson SJ: *Sabiston & Spencer surgery of the chest,* ed 9, 2016, Elsevier.)

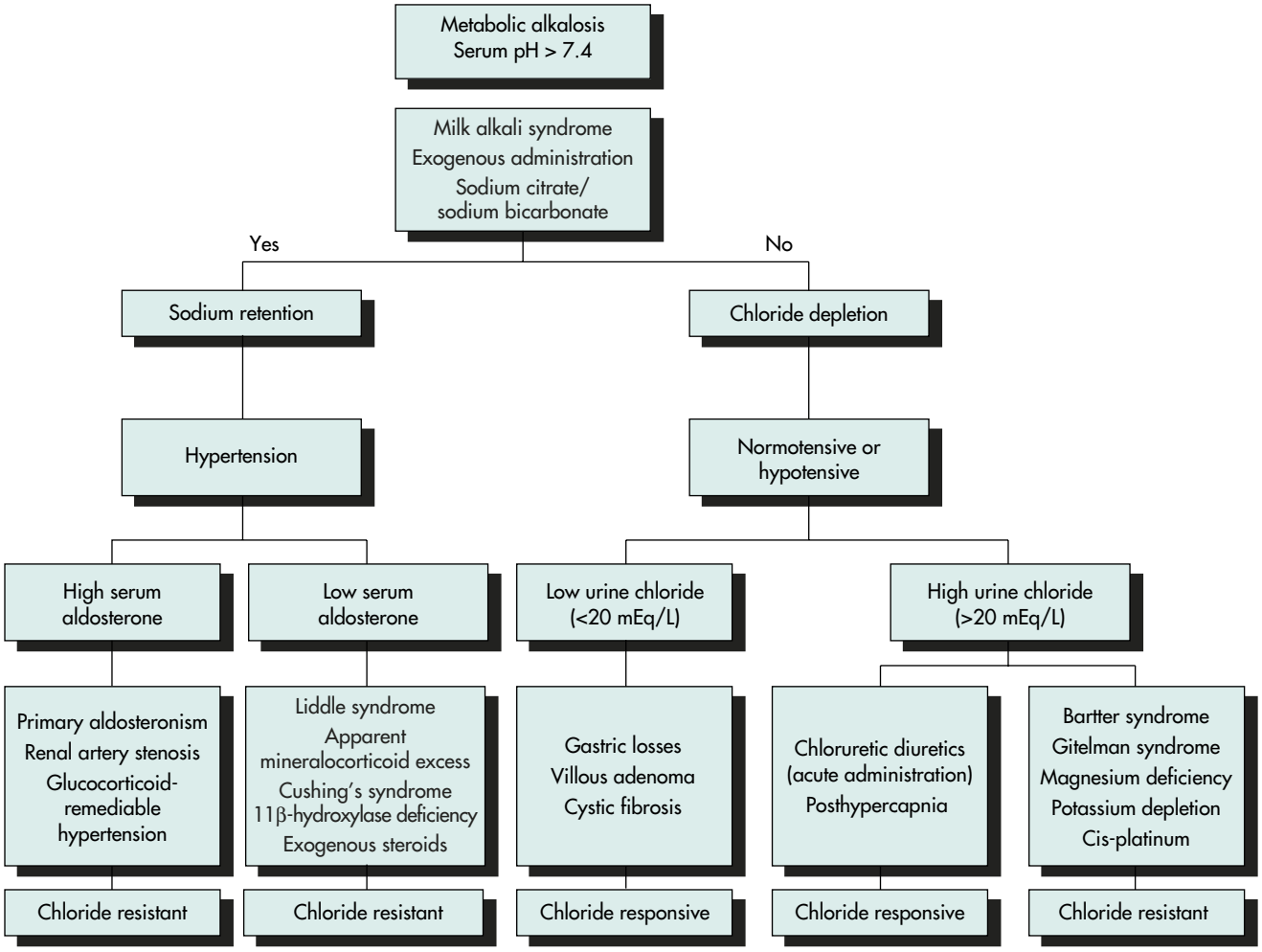


FIG. 16 Differential diagnosis of metabolic alkalosis. (From Ronco C: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.)

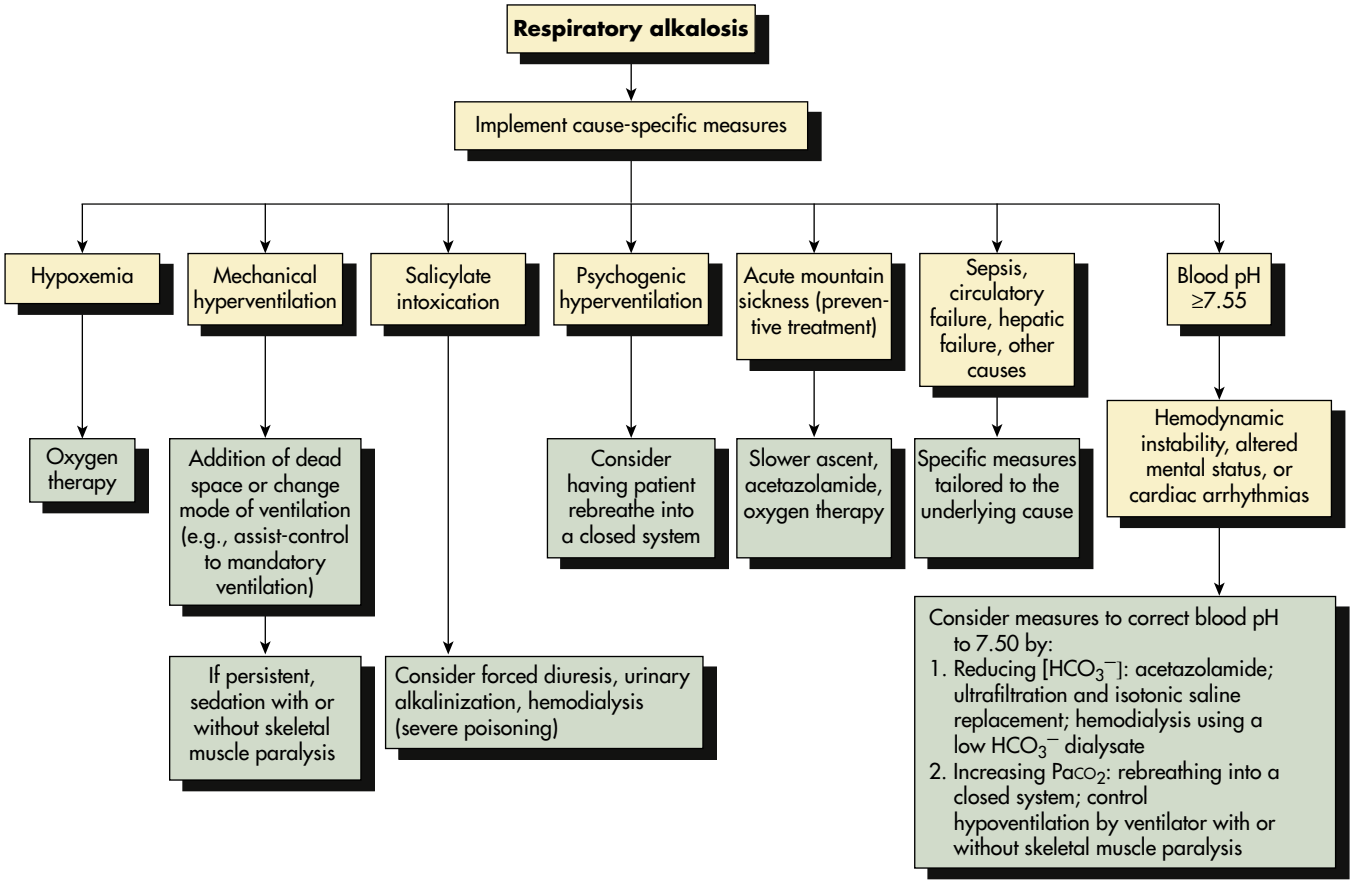


FIG. 17 Recommended treatment of respiratory alkalosis. (From Johnson R et al: *Comprehensive clinical nephrology*, ed 5, Philadelphia, 2015, Saunders.)

TABLE 3 Causes of Alveolar Hyperventilation/Respiratory Alkalosis

	Site of Defect	Condition
Defects in respiratory drive	Central chemoreceptors	*Voluntary hyperventilation psychogenic:* pain, panic attack *Central neurogenic hyperventilation:* brainstem injuries, brain tumors *Hormonal:* increased progesterone levels in pregnancy and liver cirrhosis *Infectious:* meningitis, encephalitis *Thermal hyperpnea:* fever, hyperthermia *Intoxication:* salicylate, topiramate *Therapeutic:* doxapram
	Peripheral chemoreceptors	*Increased activity of peripheral chemoreceptors:* hypoxic pulmonary disease, high altitude *Increased activity of lung receptors*, e.g., pulmonary edema, pneumonia, pulmonary embolism, interstitial fibrosis
Iatrogenic		*Mechanical ventilation:* excessive mechanical ventilation (accidental, or therapeutic for traumatic brain injury) *Extracorporeal gas exchange:* excessive extracorporeal CO_2 removal

From Ronco C: *Critical care nephrology,* ed 3, Philadelphia, 2019, Elsevier.

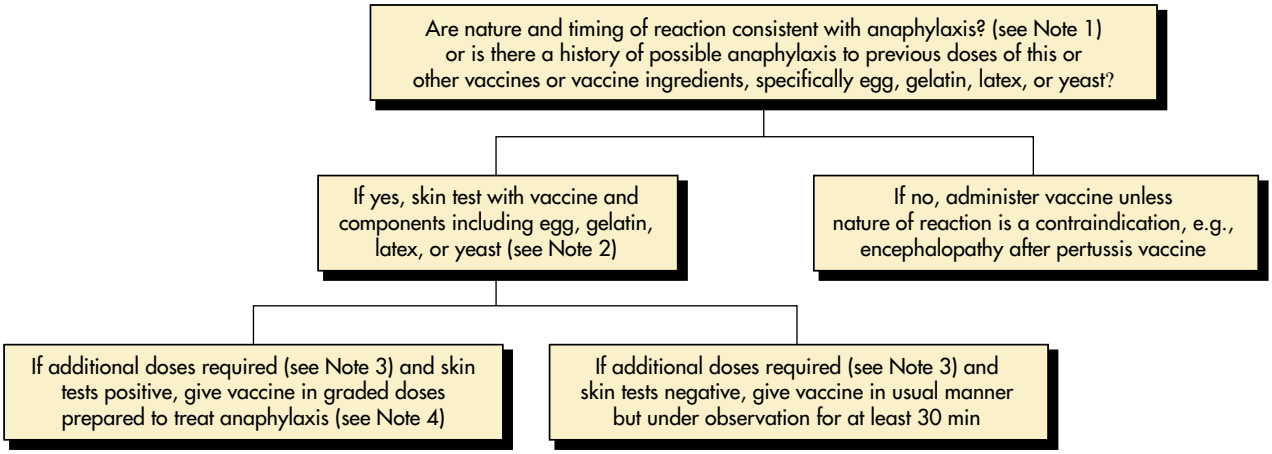


FIG. 18 Suggested approach to suspected immediate-type allergic reactions to vaccines.

Note 1. Are nature and timing of reaction consistent with a systemic IgE-mediated reaction? Probable systemic IgE-mediated reaction: reaction occurring within 4 hours of vaccine administration to include signs and/or symptoms from more than one of the following systems:

- Dermatologic: urticaria, flushing, angioedema, pruritus
- Respiratory: rhinoconjunctivitis (red, watery, itchy eyes; stuffy, runny, itchy nose; sneezing), upper airway edema (change in voice, difficulty swallowing, difficulty breathing, stridor), bronchospasm/asthma (cough, wheeze, shortness of breath, chest tightness)
- Cardiovascular: hypotension, tachycardia, palpitations, light-headedness, loss of consciousness (NOTE: Hypotension or loss of consciousness with pallor and bradycardia is much more likely to be due to a vasovagal reaction)
- Gastrointestinal: cramping, nausea, vomiting, diarrhea

Possible systemic IgE-mediated reaction:

- Signs and/or symptoms from only one system (as previously)
- Signs and/or symptoms from more than one system (as previously) but occurring more than 4 hours after vaccination

Note 2. Skin tests with vaccine and components including egg, gelatin, latex, or yeast. Vaccine skin tests:

- Prick test with full-strength vaccine; consider 1:10 dilution if patient has a history of life-threatening reaction.
- If results of prick test with full-strength vaccine are negative, perform intradermal testing with 0.02 ml of vaccine at 1:100 dilution.
- Vaccine skin tests may cause false (or clinically irrelevant) positive reactions. Thus, if skin testing gives a positive reaction, also perform on normal control subjects.

Vaccine component skin tests:

- Prick tests with commercial extracts of egg (influenza and yellow fever vaccines) or *Saccharomyces cerevisiae* yeast (hepatitis B and quadrivalent human papillomavirus vaccines).
- Prick test with sugared gelatin (e.g., Jell-O): dissolve 1 teaspoon of gelatin powder in 5 ml of normal saline.
- Vaccines that contain gelatin: influenza (some brands), measles, mumps, rabies (some brands), rubella, typhoid (capsule), varicella, yellow fever, zoster.
- Prick test with latex: soak two fingers of latex glove or a toy balloon in 5 ml of normal saline. Vaccines that contain latex in packaging; available at www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/latex-table.pdf.
- In vitro assays for specific IgE antibody to egg, gelatin, latex, and yeast are also commercially available as an alternative or complement to skin testing.

Note 3. If fewer than the recommended number of doses are received, consider measuring level of IgG antibodies to immunizing agent. If the measured level is associated with protection from disease, consider withholding additional doses, although magnitude and duration of immunity may be less than if all doses received.

Note 4. Vaccine administration in graded doses:

- With a vaccine for which the usual dose is 0.5 ml, administer graded doses of vaccine at 15-minute intervals: 0.05 ml of 1:10 dilution, 0.05 ml of full strength, 0.10 ml of full strength, 0.15 ml of full strength, and 0.20 ml of full strength. (From Adkinson NF et al: *Middleton's allergy principles and practice*, ed 8, Philadelphia, 2014, Saunders.)

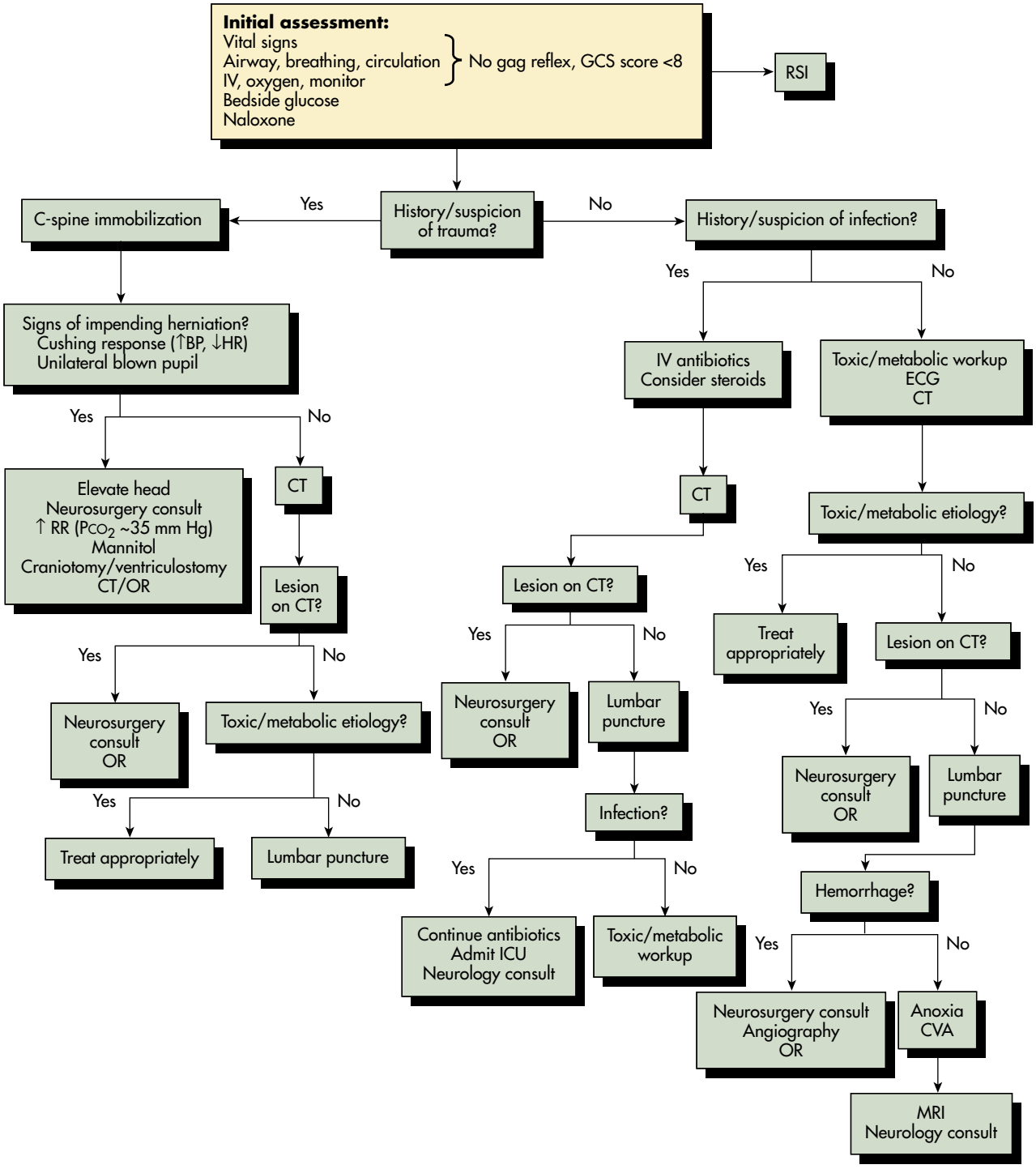


FIG. 19 Diagnostic approach to altered mental status and coma. *BP,* Blood pressure; *CT,* computed tomography; *CVA,* cerebrovascular accident; *ECG,* electrocardiography; *GCS,* Glasgow Coma Scale; *HR,* heart rate; *ICU,* intensive care unit; *MRI,* magnetic resonance imaging; *OR,* operating room; *RR,* respiratory rate; *RSI,* rapid-sequence intubation. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

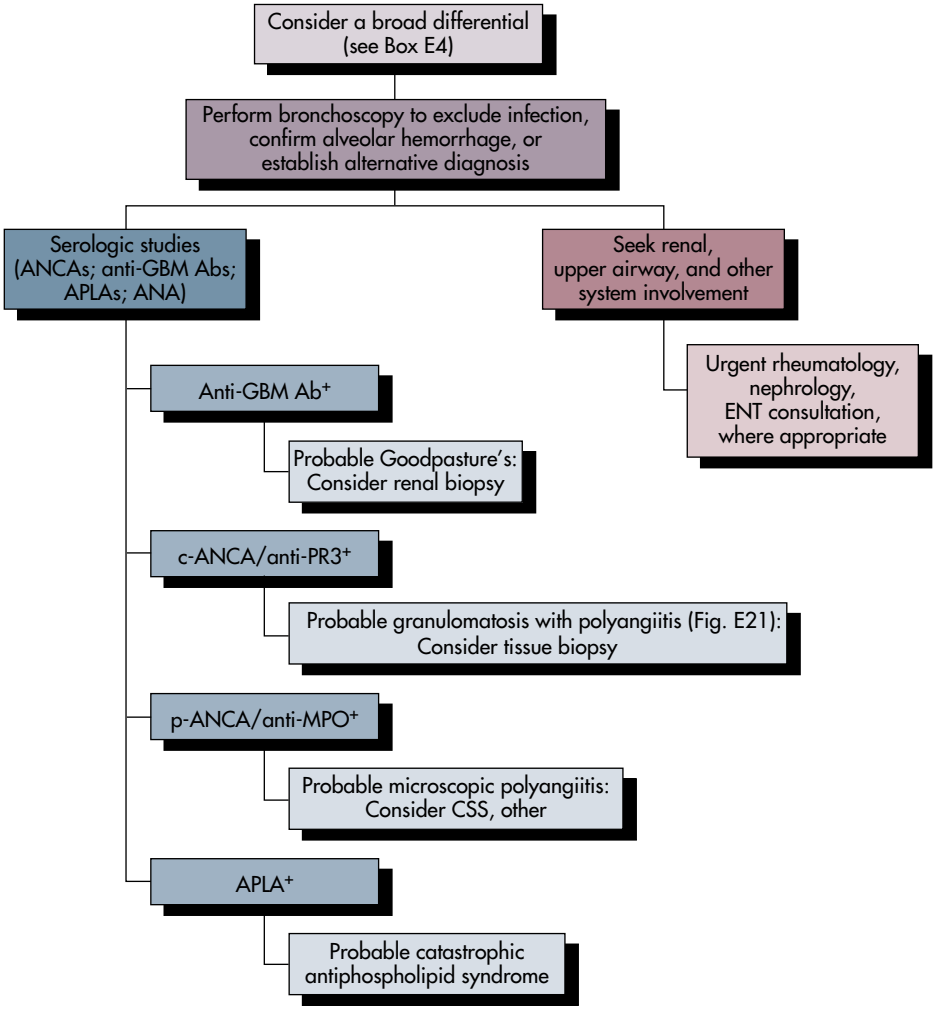


FIG. E20 Diagnosis and management of alveolar hemorrhage syndromes. *ANA,* Antinuclear antibodies; *ANCA,* antineutrophil cytoplasmic antibody; *anti-GBM Abs,* antiglomerular basement membrane antibodies; *anti-MPO,* antimyeloperoxidase antibodies; *anti-PR3,* antiproteinase antibodies; *APLAs,* antiphospholipid antibodies; *CSS,* Churg-Strauss syndrome; *ENT,* ear, nose, and throat. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 4, 2014, Elsevier.)

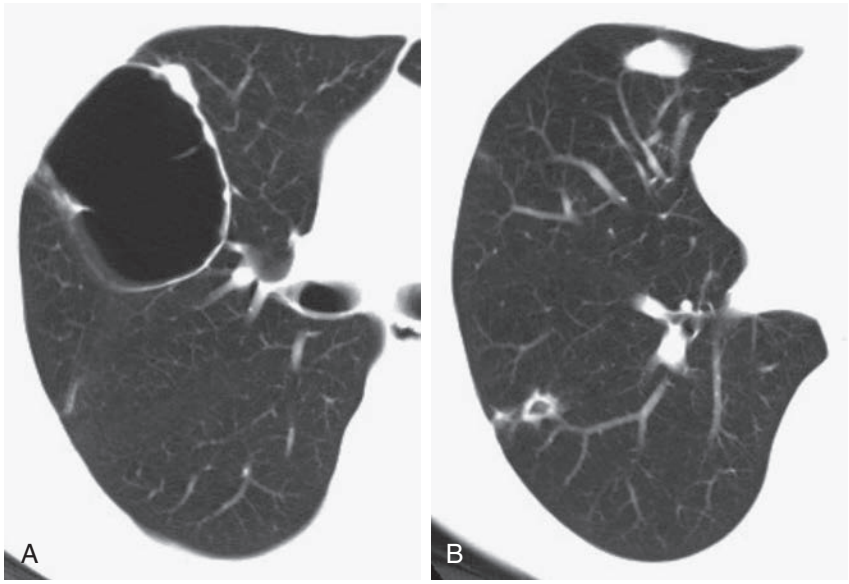


FIG. E21 Granulomatosis with polyangiitis (Wegener granulomatosis). A and **B,** Thin-walled cavities and nodules are present. (From Webb WR, Brandt WE, Major NM: *Fundamentals of body CT,* ed 4, Philadelphia, 2015, Elsevier.)

BOX E4 Causes of Diffuse Alveolar Hemorrhage

Immunologic Diseases
- Antiglomerular basement membrane antibody disease (Goodpasture syndrome)
- Vasculitides associated with circulating or in situ immune complexes
  - Systemic lupus erythematosus
  - Mixed connective tissue disease
  - Schönlein-Henoch purpura
  - Essential mixed cryoglobulinemia
  - Tumor-related vasculitis
  - Endocarditis-related vasculitis
  - Polyarteritis nodosa
  - Systemic necrotizing vasculitis
- Vasculitides associated with antineutrophil cytoplasmic antibodies
  - Granulomatosis with polyangiitis
  - Microscopic polyangiitis
  - Idiopathic necrotizing crescentic glomerulonephritis
- Rapidly progressive glomerulonephritis
- Associated with other connective tissue diseases, pathophysiology unknown
  - Rheumatoid arthritis
  - Progressive systemic sclerosis
  - Behçet disease
- Associated with other renal diseases
- IgA nephropathy
- Diabetic nephropathy
- Associated with precipitating antibodies to milk (Heiner syndrome)
- Idiopathic pulmonary hemosiderosis
- Primary antiphospholipid antibody syndrome

Chemical or Drug-Related Causes
- Amiodarone
- D-Penicillamine
- Isocyanates
- Nitrofurantoin
- Retinoic acid
- Trimellitic anhydride
- "Crack" cocaine
- Sirolimus
- Everolimus
- Propylthiouracil-induced vasculitis
- Erlotinib
- Bevacizumab
- Gemcitabine
- Infliximab

Transplant-Related Causes
- Bone marrow transplant
- Renal transplant
- Lung transplant

Bleeding Diathesis
- Thrombocytopenia
- Leukemia with diffuse alveolar damage
- Viral pneumonia
- Bacterial or fungal sepsis
- Radiation
- Chemotherapy toxic to lung
- Blast counts >80,000/μL
- Extrinsic anticoagulants/thrombolytics
- Warfarin overdose
- Tissue plasminogen activator
- Platelet glycoprotein IIb/IIIa inhibitors
- Coagulopathies
- Cirrhosis
- DIC

Infections
- Legionnaires disease

Pulmonary Venous Hypertension
- Mitral stenosis
- Mitral regurgitation
- Pulmonary capillary hemangiomatosis
- Pulmonary venoocclusive disease
- Fibrosing mediastinitis
- Congenital heart disease

Diffuse Lung Injury
- Negative-pressure pulmonary hemorrhage
- Breath-hold diving
- Postictal neurogenic pulmonary edema

DIC, Disseminated intravascular coagulation; *IgA,* immunoglobulin A.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Elsevier.

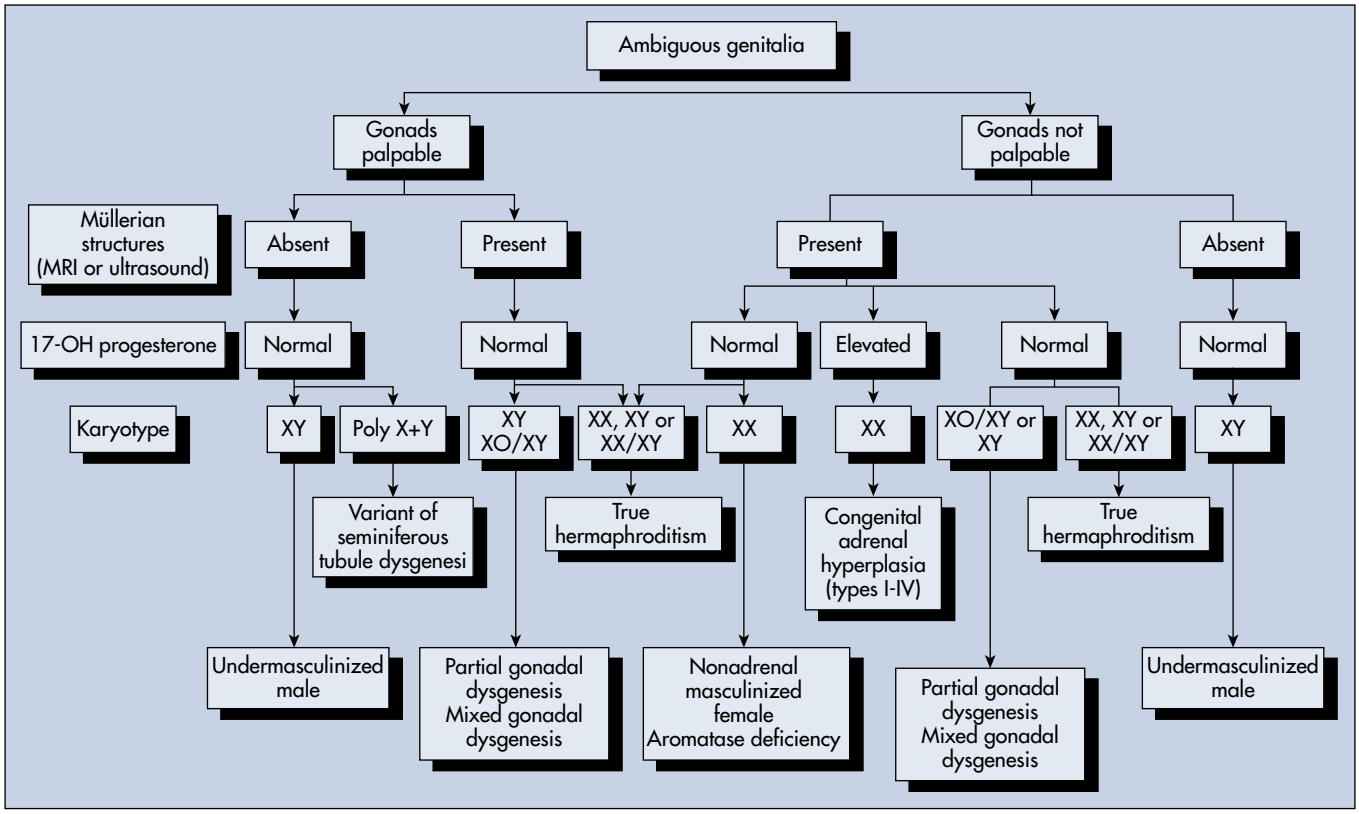


FIG. E22 Diagnostic algorithm for a newborn with ambiguous genitalia based on gonadal palpability, presence or absence of Müllerian structures, 17-hydroxyprogesterone concentration, and karyotype. *MRI,* Magnetic resonance imaging. (Modified from Grumbach MM, Conte FH. Disorders of sex differentiation. In Wilson JD, Foster DW, editors. *Williams textbook of endocrinology.* Philadelphia, 1998, Saunders.)

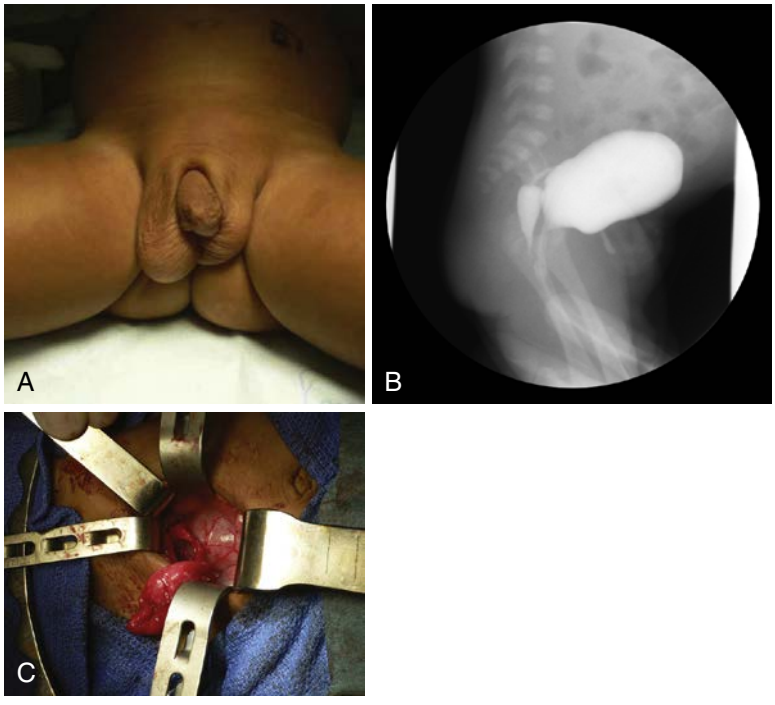


FIG. E23 A, Patient with mixed gonadal dysgenesis showing asymmetrical anatomy. **B,** Hemiuterus and opacified fallopian tube in left inguinal hernia. **C,** Structures noted in **B** shown at surgical exploration. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

BOX E5 Ambiguous Genitalia and Their Causes

Female pseudohermaphrodism
Congenital adrenal hyperplasia (excess fetal androgens)
- 21-Hydroxylase deficiency
- 11-Beta-hydroxylase deficiency
- 3-Beta-hydroxysteroid dehydrogenase deficiency

Exogenous androgens
- Maternal ingestion of androgens, progestogens
- Maternal congenital adrenal hyperplasia
- Virilizing adrenal or ovarian tumor

Excess placental androgen production
- Placental P450 aromatase deficiency

Iatrogenic fetal virilization
Female pseudohermaphrodism with associated congenital malformations
Idiopathic

Male pseudohermaphrodism
- Impaired Leydig cell activity
- Defects in testosterone biosynthesis
- Leydig cell hypoplasia; luteinizing hormone receptor defect
- 20,22-Desmolase (congenital lipoid adrenal hyperplasia)
- 3-Beta-hydroxysteroid dehydrogenase
- 17,20-Hydroxylase (17,20-desmolase)
- 17-Beta-hydroxysteroid dehydrogenase (17-ketosteroid reductase)

Defects of testis development or maintenance
- XY gonadal dysgenesis
- Mixed gonadal dysgenesis
- Rudimentary testis syndromes

End-organ resistance to androgens (androgen insensitivity syndrome)
- Complete
- Partial
- Defects in the intracellular metabolism of testosterone (5-alpha-reductase deficiency)

Others
- Persistent Müllerian duct syndrome
- Iatrogenic male pseudohermaphrodism
- Idiopathic male pseudohermaphrodism

True hermaphrodism

From Crum CP et al: *Diagnostic gynecologic and obstetric pathology,* ed 3, Philadelphia, 2018, Elsevier.

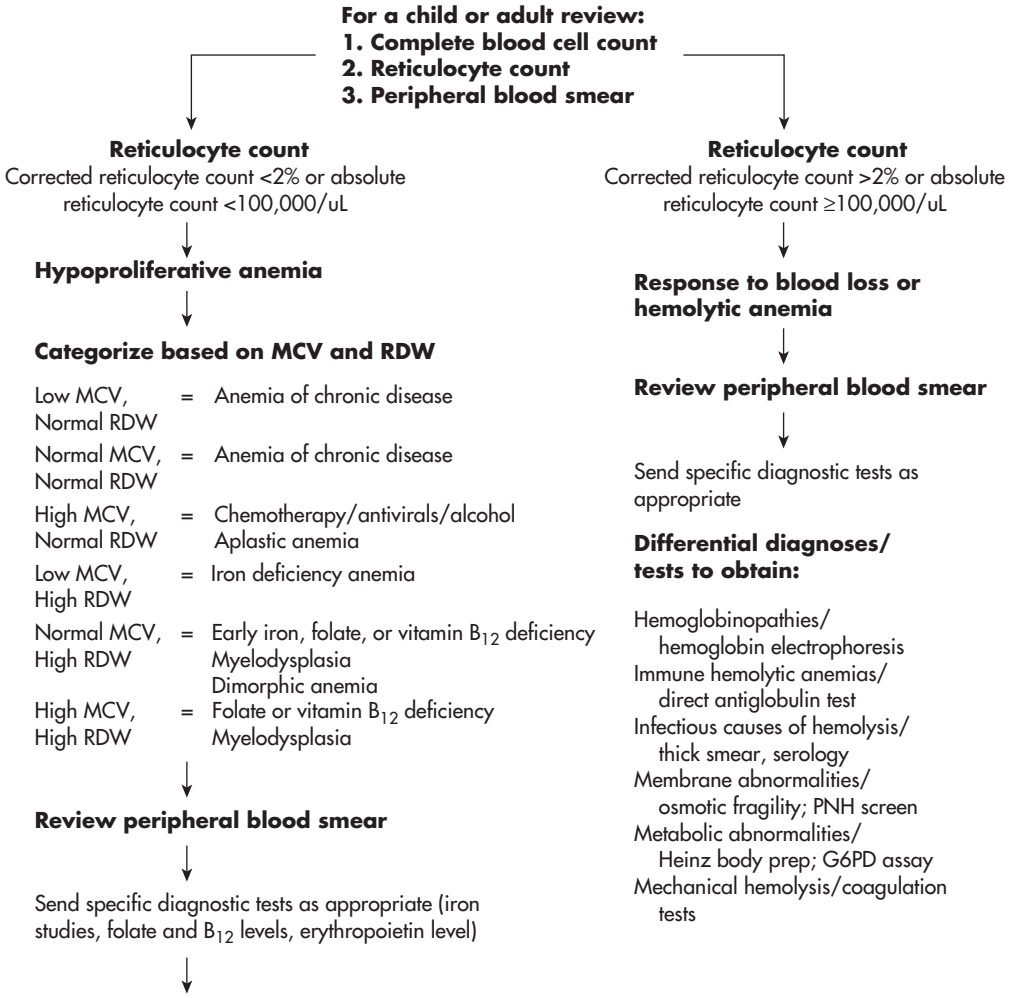


FIG. 24 Approach to the differential diagnosis of anemia in adults and children. *G6PD,* Glucose-6-phosphate dehydrogenase; *MCV,* mean corpuscular volume; *PNH,* paroxysmal nocturnal hemoglobinuria; *RDW,* red blood cell distribution width. (From Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

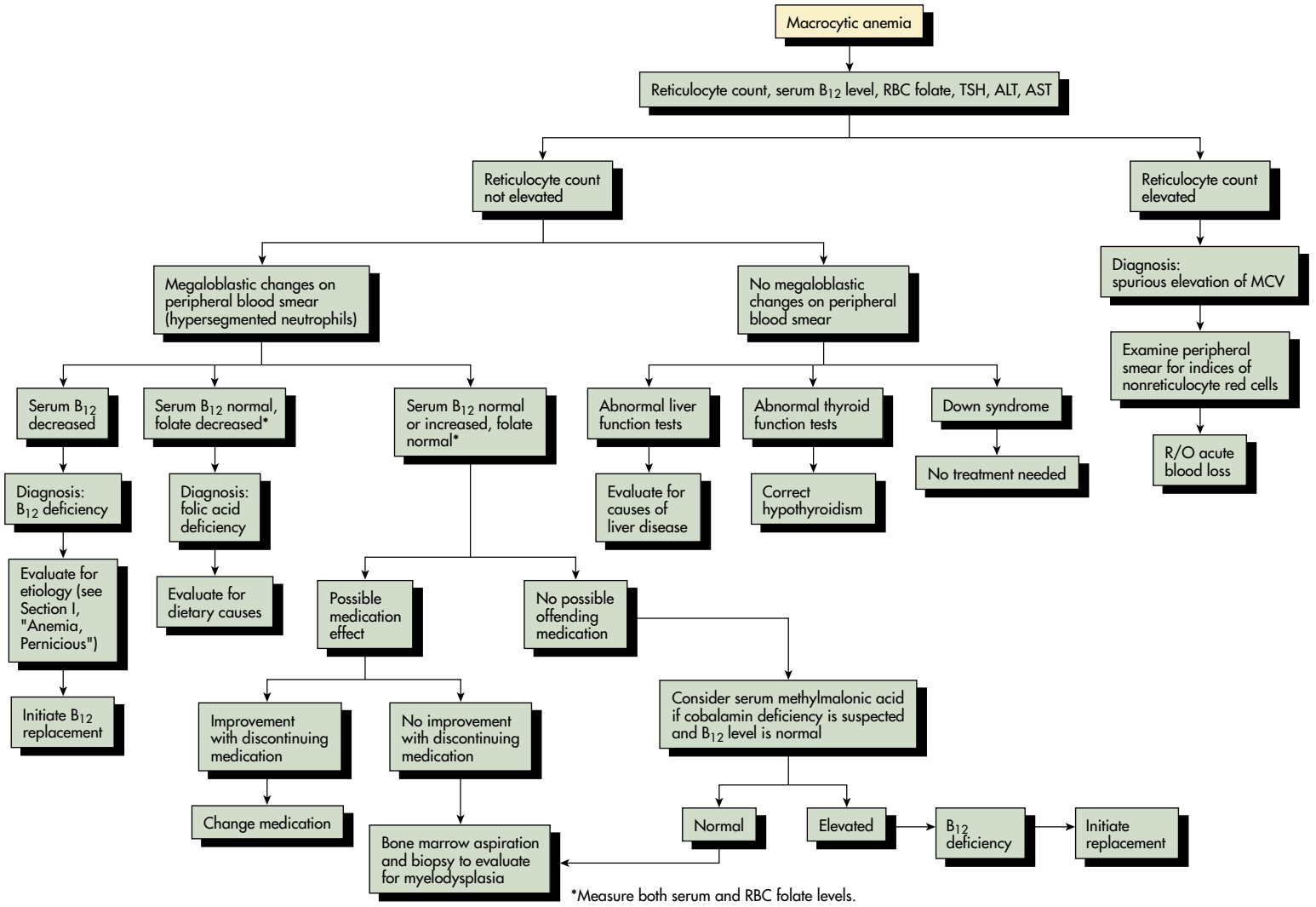


FIG. 25 Differential diagnosis of macrocytic anemia. *MCV,* Mean corpuscular volume. (Modified and updated from Rakel RE [ed]: *Principles of family practice*, ed 7, Philadelphia, 2007, Saunders.)

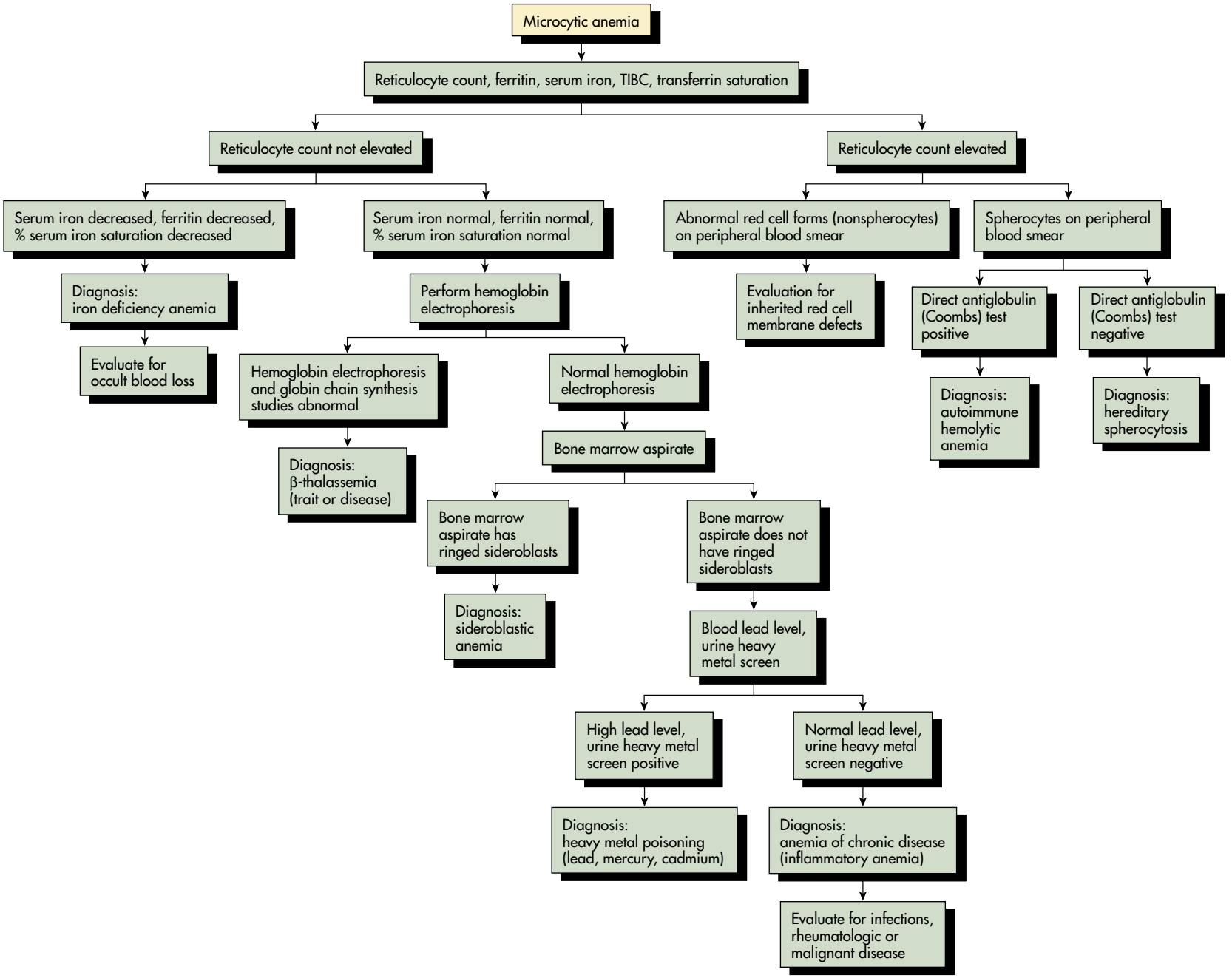


FIG. 26 Differential diagnosis of microcytic anemia. *TIBC*, Total iron binding capacity. (Modified and updated from Rakel RE [ed]: *Principles of family practice*, ed 7, Philadelphia, 2007, Saunders.)

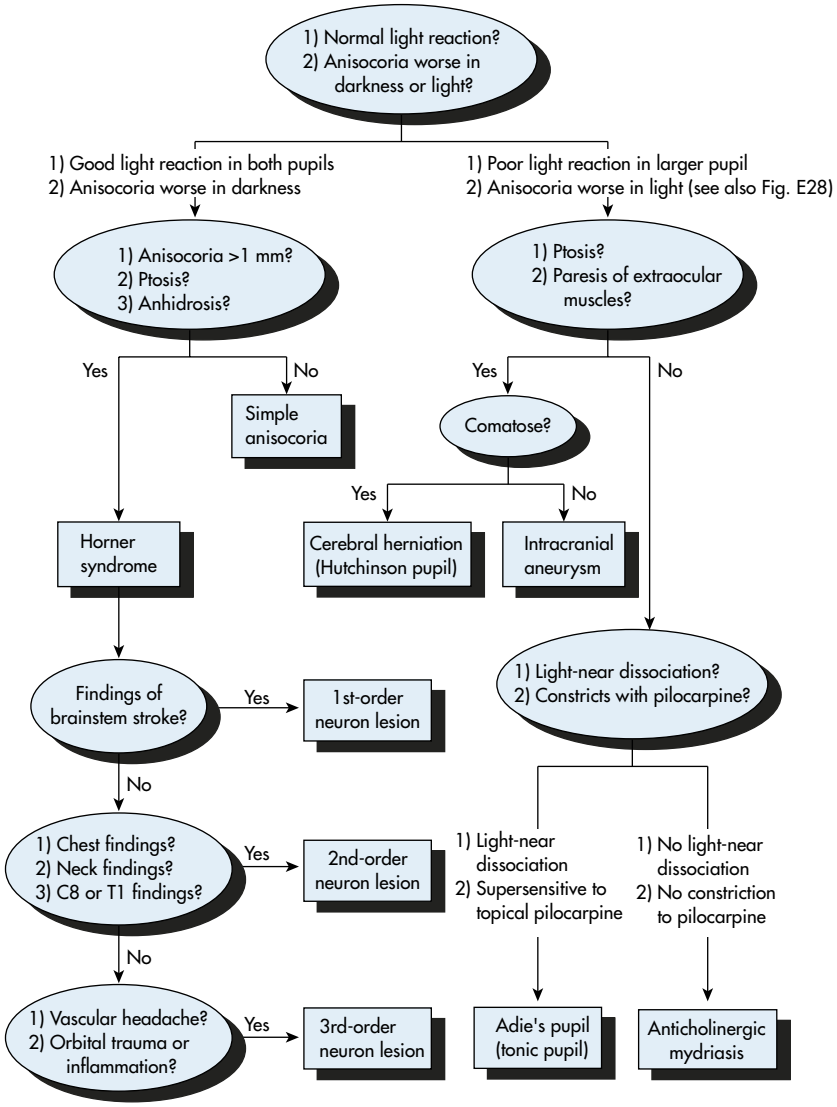


FIG. 27 Summary of approach to anisocoria. The first two questions (Is there a normal light reaction? and Is anisocoria worse in darkness or light?) distinguish problems with the pupillary dilator muscle (i.e., Horner syndrome, simple anisocoria; *left side* of the figure) from problems with the pupillary constrictor muscle (i.e., third cranial nerve, iris; *right side* of the figure). Two other tests distinguish Horner syndrome from simple anisocoria: the cocaine or apraclonidine eyedrop tests and pupillary dilator lag (i.e., the pupil dilates slowly in darkness, as documented by photographs). (From McGee S: *Evidence-based physical diagnosis,* ed 4, Philadelphia, 2018, Elsevier.)

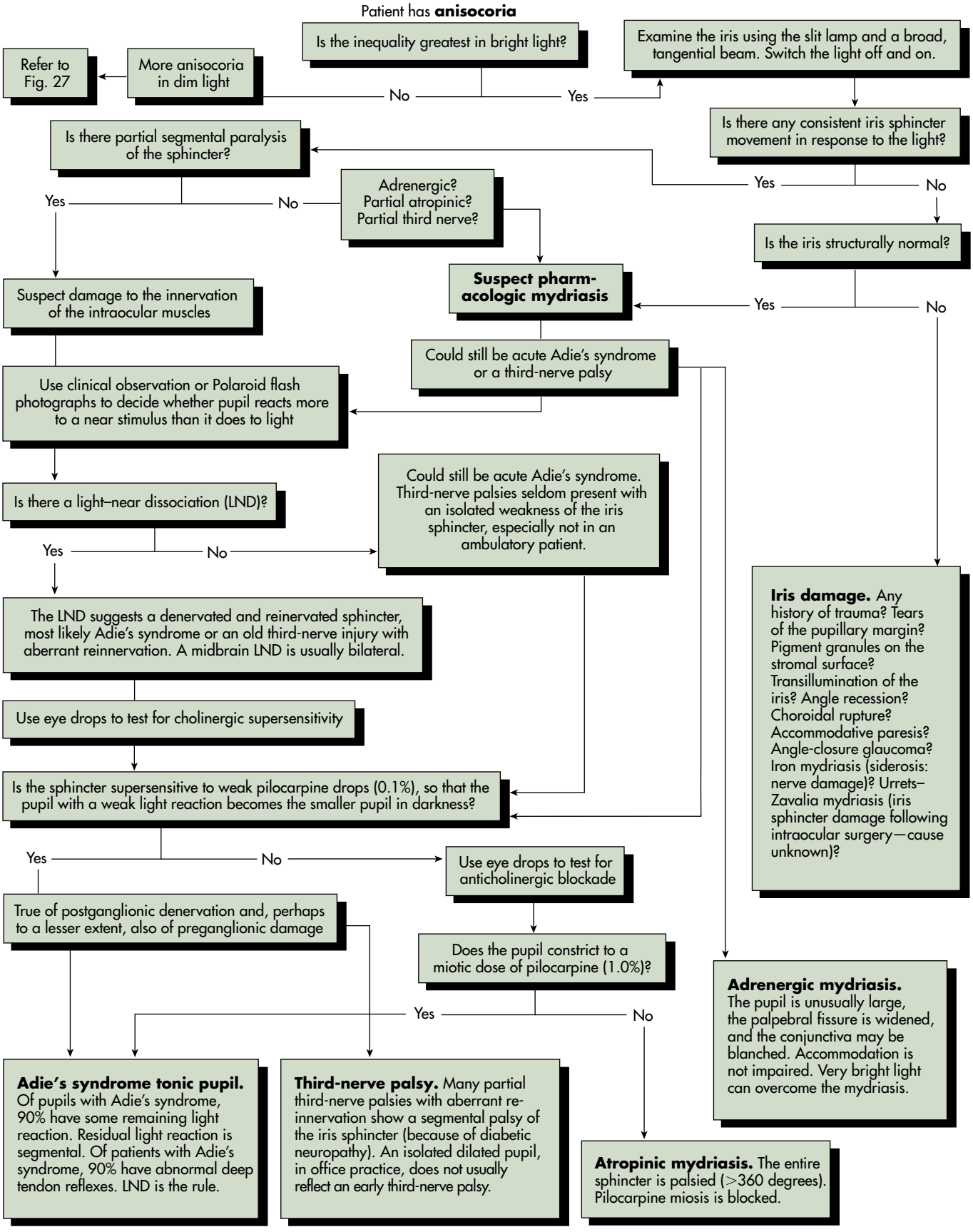


FIG. E28 Diagnosis of pupillary abnormalities in which anisocoria increases in bright light. Initial pupillary inequality is greater in bright light than in darkness, which indicates that the sphincter of the large pupil is weak or that a parasympathetic lesion is present on that side. (From Yanoff M, Duker JS: *Ophthalmology*, ed 2, St Louis, 2004, Mosby.)

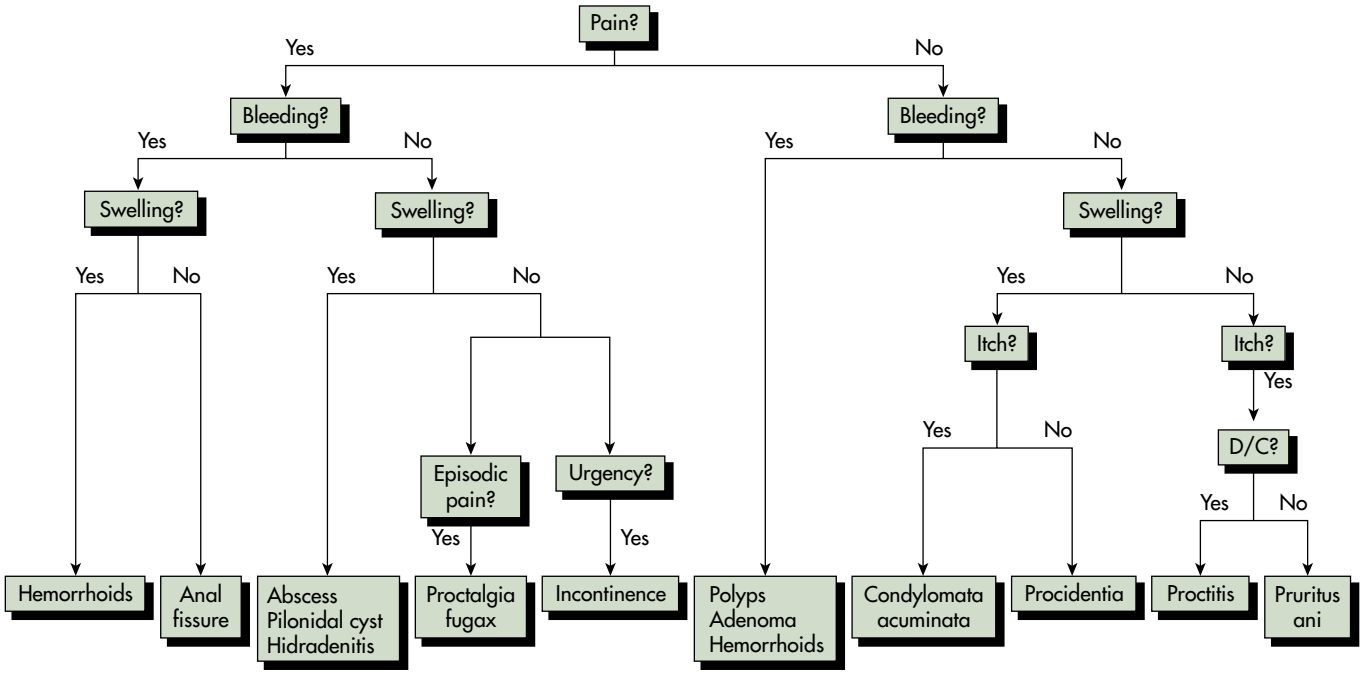


FIG. 29 Algorithm for anorectal complaints. *D/C,* Discharge. (From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.)

BOX 6 The WASH Regimen for Management of Hemorrhoids

- *W*arm water
- *A*nalgesic agents
- *S*tool softeners
- *H*igh-fiber diet

From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Saunders.

BOX 7 Medical History in Diagnosis of Anorectal Disorders

Anorectal History
- Pain
- Bleeding
- Swelling
- Itching
- Discharge
- Urgency

Gastrointestinal History
- Change in bowel habits (straining, flatus, color, consistency, frequency)
- Nausea or vomiting
- Incontinence of stool
- Underlying GI disease (Crohn disease, cancer, polyps)

Systemic Disease History
- Diabetes mellitus
- Coagulopathy
- Cancer
- HIV infection

Sexual History of the Anus
- Penetration
- Known STDs
- Assault

GI, Gastrointestinal; *HIV,* human immunodeficiency virus; *STD,* sexually transmitted disease.
From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Saunders.

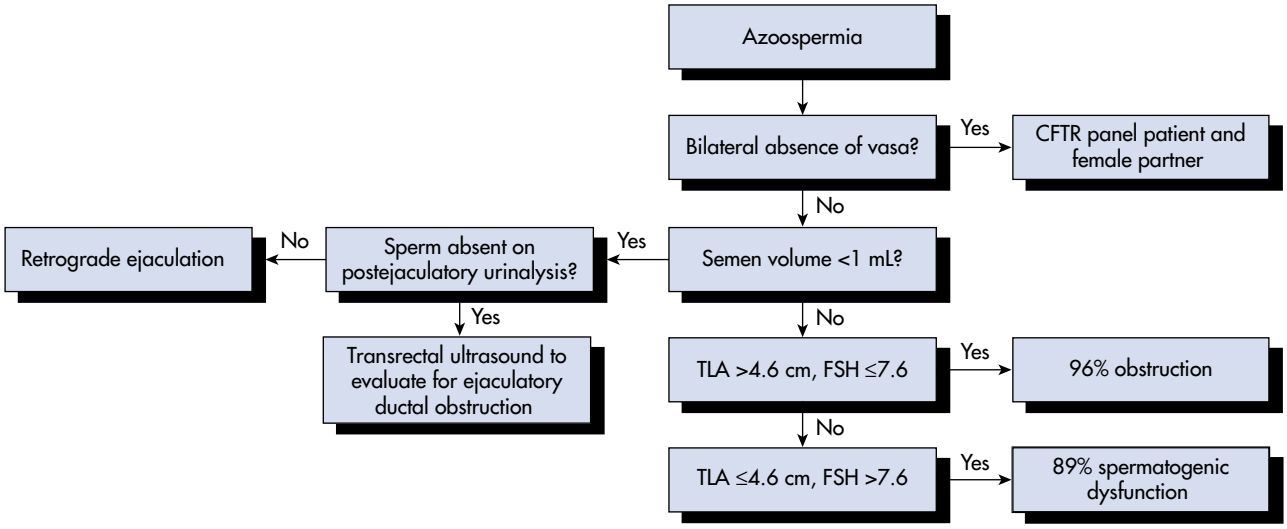


FIG. E30 Algorithm for evaluation of azoospermia. *CFTR,* Cystic fibrosis transmembrane conductance regulator; *FSH,* follicle-stimulating hormone; *TLA,* testis longitudinal axis measured by caliper orchidometer. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, 2016, Elsevier.)

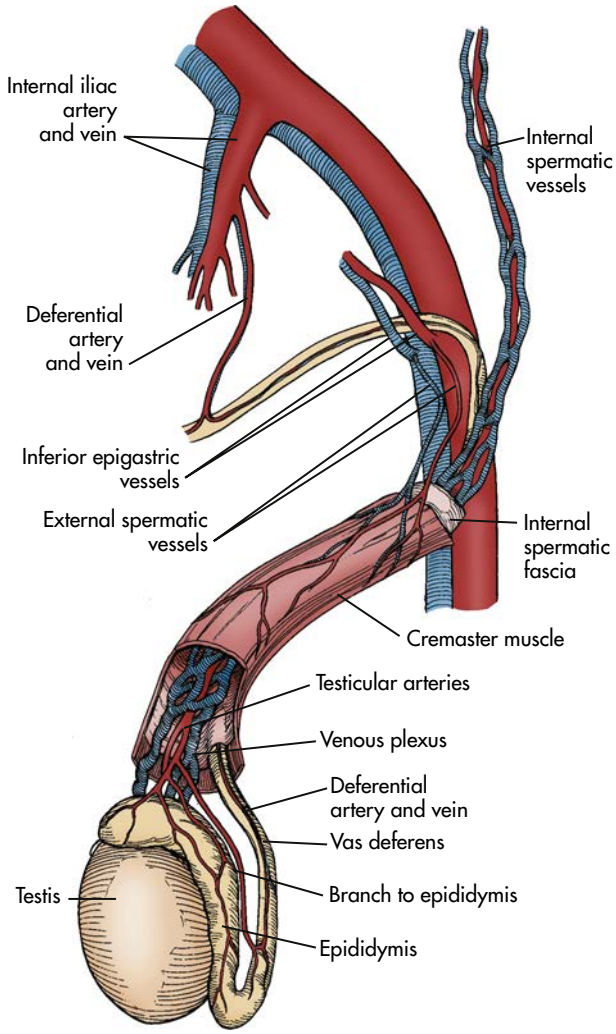


FIG. E31 Schematic illustration of interconnections between internal spermatic, external spermatic (cremasteric), and deferential vessels in the peritesticular region and spermatic cord. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, 2016, Elsevier.)

ICD-10CM #		
	L29	Pruritus
	M54.89	Other dorsalgia
	M54.9	Dorsalgia, unspecified
	M54.5	Low back pain
	F45.42	Pain disorder with related psychological factors
	M54.08	Panniculitis affecting regions of neck and back, sacral and sacrococcygeal region
	S23.9XXA	Sprain of unspecified parts of thorax, initial encounter
	M43.27	Fusion of spine, lumbosacral region
	M43.28	Fusion of spine, sacral and sacrococcygeal region
	M53.2X7	Spinal instabilities, lumbosacral region
	M53.3	Sacrococcygeal disorders, not elsewhere classified

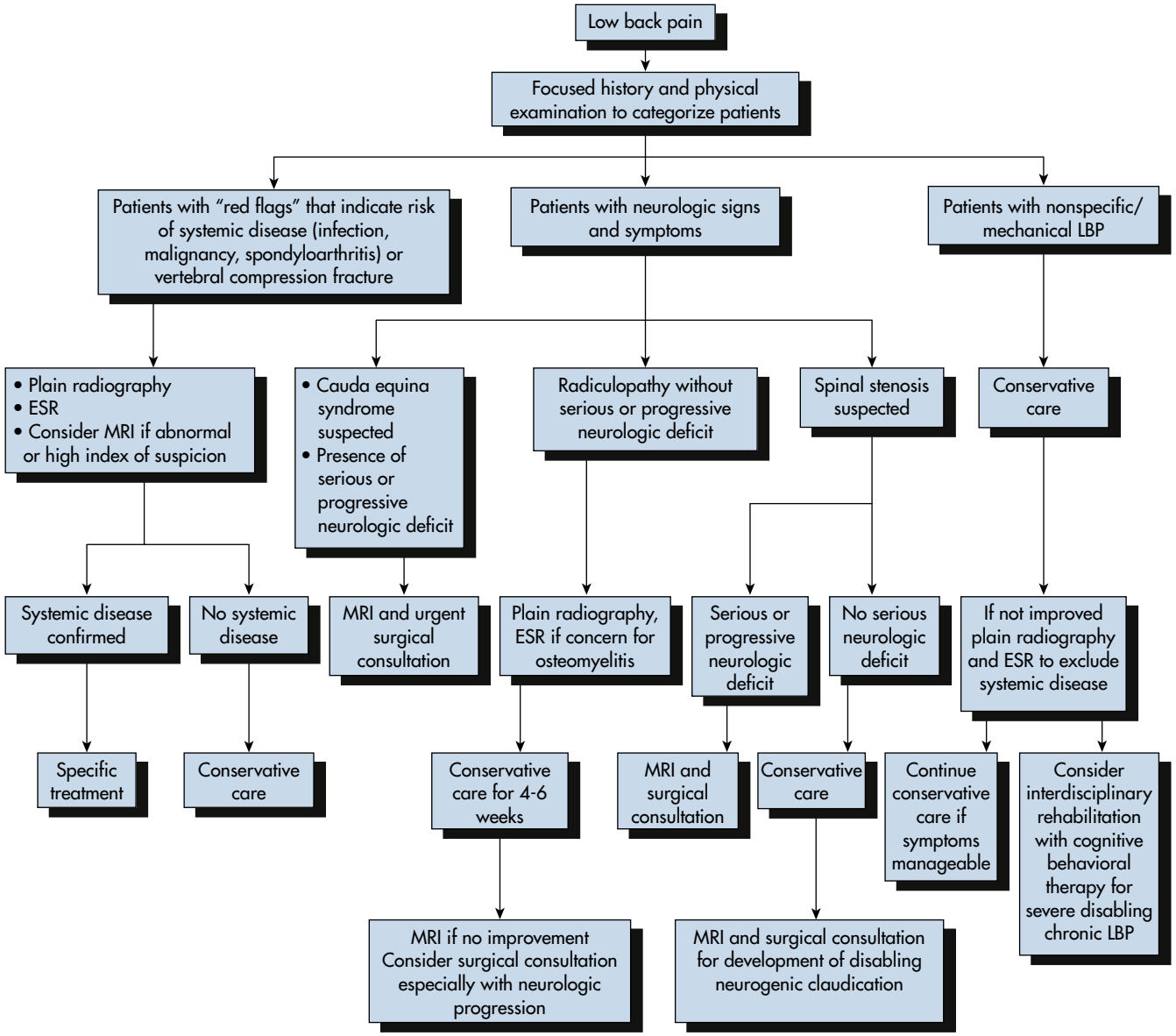


FIG. 32 Algorithm for the differential diagnosis and treatment of low back pain. *ESR*, Erythrocyte sedimentation rate; *LBP*, low back pain; *MRI*, magnetic resonance imaging. (From Firestein GS et al: *Kelley and Firestein's textbook of rheumatology,* ed 10, Philadelphia, 2017, Elsevier.)

TABLE 4 Red Flags for Potentially Serious Conditions

Possible Fracture	Possible Tumor or Infection	Possible Cauda Equina Syndrome
From Medical History		
Major trauma, such as vehicle accident or fall from height	Age over 50 or under 20 yr	Saddle anesthesia
Minor trauma or even strenuous lifting (in older or potentially osteoporotic patient)	History of cancer	Recent onset of bladder dysfunction, such as urinary retention, increased frequency, or overflow incontinence
	Constitutional symptoms, such as recent fever or chills or unexplained weight loss	Severe or progressive neurologic deficit in the lower extremity
	Risk factors for spinal infection: recent bacterial infection (e.g., urinary tract infection), intravenous drug abuse, or immune suppression (from steroids, transplant, or human immunodeficiency virus)	
	Pain that worsens when supine; severe nighttime pain	

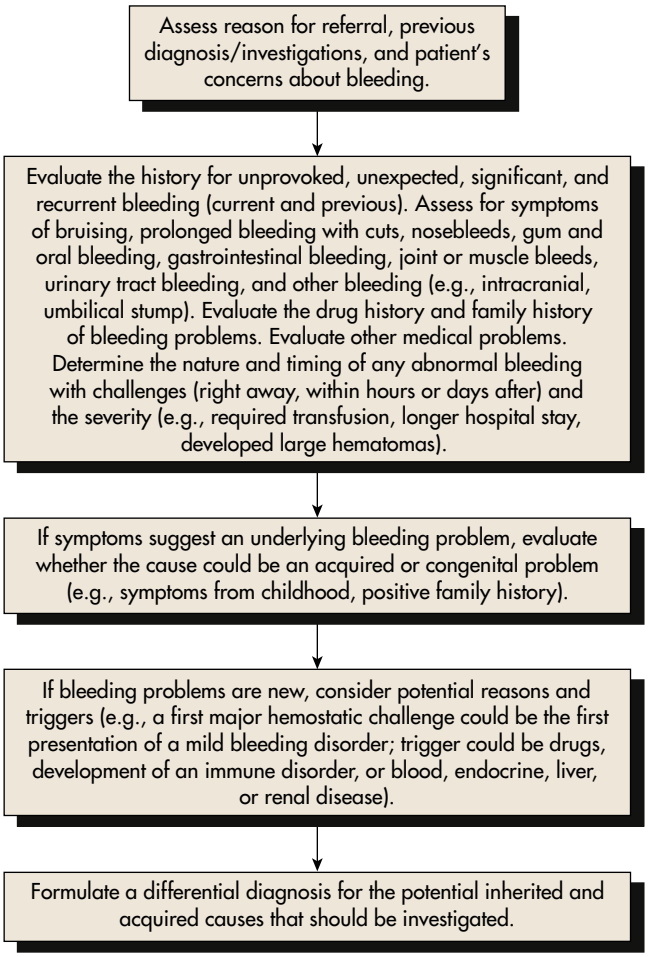


FIG. 33 Steps to evaluate bleeding and bruising problems. (From Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.)

TABLE 5 Differential Diagnosis of Bleeding Problems

Major Categories	Comments
No bleeding disorder	Symptoms do not reflect a bleeding disorder and have another explanation (e.g., a surgical bleed, not caused by a bleeding disorder).
Possible bleeding disorder	The laboratory findings are nondiagnostic, and the bleeding history is considered equivocal (e.g., unexplained serious bleed with one surgical procedure; unexplained menorrhagia without other bleeding problems).
Definite bleeding disorder, undefined or indeterminate type	The bleeding history is consistent with a bleeding disorder; however, the laboratory findings are nondiagnostic. Commonly the bleeding history resembles mild to moderate defects in platelet function or von Willebrand factor. The diagnosis should only be made once an adequate evaluation for common bleeding disorders (e.g., for von Willebrand disease and platelet aggregation and release defects) is completed. If testing is not complete, the classification should indicate the types of conditions excluded or not excluded, for example mild mucocutaneous bleeding problem, von Willebrand disease excluded, mild mucocutaneous bleeding problem, platelet release defects not yet excluded.
Definite bleeding disorder with cause	The symptoms and laboratory findings are considered diagnostic of a bleeding disorder. Tables 6 and 7 summarize many of a define the potential inherited and acquired causes.

From Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

ICD-10CM # D68.9 Coagulation defect, unspecified
D68.8 Other specified coagulation defects

TABLE 6 Differential Diagnosis of Congenital Bleeding Disorders

Disorder	Comments
Fibrinogen deficiency or dysfunction	Deficiencies can be mild-moderate hypofibrinogenemia or severe afibrinogenemia. Fibrinogen function is abnormal in dysfibrinogenemias, which can present with bleeding, thrombosis, or both. Fibrinogen levels can be reduced in some dysfibrinogenemias.
X-linked coagulation factor deficiencies—hemophilia	Presentation is influenced by the degree of deficiency. Factor VIII deficiency is more common than factor IX deficiency. If factor VIII is low, von Willebrand disease needs to be excluded as the cause.
Rarer, coagulation factor deficiencies	Deficiencies can affect factors XI, V, II, VII, or X, and the presentation is dependent on the severity of the deficiency. Hereditary deficiencies of multiple coagulation factors are rare (e.g., of factors V and VIII, or multiple vitamin K-dependent coagulation factors for congenital defects impairing γ-carboxylation) and can easily be excluded by measuring multiple factors.
Fibrinolytic defects	Causes include disorders caused by loss of function, such as α2-antiplasmin or PAI-1 deficiency, and by gain-of-function defects, such as Quebec platelet disorder (overexpression of urokinase plasminogen activator in megakaryocytes).
von Willebrand disease	Causes include quantitative (partial type 1 to severe type 3) and qualitative defects (loss of function in type 2M and 2A, gain of function in type 2B and platelet-type). Type 1 von Willebrand disease can be confused with low von Willebrand factor levels (e.g., because of blood group O).
Platelet disorders	These conditions can affect platelet number, function, or both. The most common type of platelet function disorder is a platelet secretion defect, which may or may not also impair aggregation responses. Disorders of platelet function are commonly subclassified by the nature of the defect, such as the following: 1. Defects of membrane receptors for adhesive proteins (e.g., Glanzmann thrombasthenia and Bernard-Soulier syndrome) or agonists (e.g., $P2Y_{12}$ deficiency) 2. Defects of signaling or secretion (the largest subcategory) 3. Cytoskeletal defects (e.g., MYH9-related disorders) 4. Storage pool disorders (e.g., gray platelet syndrome, dense granule deficiency, $\alpha\gamma$-storage pool deficiency, Quebec platelet disorder) 5. Defects of procoagulant function (e.g., Scott syndrome)
Vascular disorders	Congenital vascular malformation, including hereditary hemorrhagic telangiectasia, Ehlers-Danlos syndrome

MYH9, Myosin heavy polypeptide 9; *PAI-1,* plasminogen activator inhibitor 1.
From Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 7 Differential Diagnosis of Acquired Bleeding Problems

Disorder	Comments
Drug induced	Aspirin, NSAIDs, other platelet function inhibitors (e.g., $P2Y_{12}$ and $\alpha_{IIb}\beta_3$ inhibitors), anticoagulants, fibrinolytic drugs, and antidepressants are common causes.
Acquired factor deficiencies	The causes can be immune (e.g., acquired factor VIII deficiency, acquired factor V deficiency) or nonimmune. Reductions in multiple factors can result from vitamin K deficiency, treatment with vitamin K antagonists, liver disease, hemodilution, and rarely snakebites. Severe acquired hypofibrinogenemia is commonly caused by a postpartum coagulopathy or severe liver disease. Prothrombin deficiency occurs with some lupus anticoagulants. Amyloidosis can cause an acquired factor X deficiency, which may be associated with reductions in other coagulation factors synthesized in the liver if the liver is involved.
Disseminated intravascular coagulation	The manifestations can include thrombocytopenia, consumption of coagulation factors, including fibrinogen, and impairment of hemostatic mechanisms from the fibrin/fibrinogen degradation products. Causes are wide ranging and include postpartum consumptive states, prostate and other cancers, and snakebites.
Acquired von Willebrand disease	The cause can be immune (often in association with an IgG paraprotein) or nonimmune (e.g., increased proteolysis of von Willebrand factor with stenotic aortic valvular disease).
Immune thrombocytopenia	Bleeding is usually influenced by the extent of the thrombocytopenia. Some autoantibodies interfere with platelet membrane receptor function, causing bleeding disproportionate to the thrombocytopenia.
Non–drug-induced, acquired platelet function disorders	The cause can be immune (see earlier) or nonimmune, typically from bone marrow disorders, although secretion defects can be secondary to Cushing syndrome or hypothyroidism.
Liver disease	Liver disease can cause thrombocytopenia, deficiencies of coagulation factors, hypofibrinogenemia and dysfibrinogenemia, and increased fibrinolysis. In mild liver disease, factor VII and sometimes factors XI and XII are low. Fibrinogen is often increased in early liver disease, and if low, the finding suggests severe liver disease.
Renal disease	Anemia is an important predictor of uremic bleeding. Uremic bleeding is typically associated with severe renal impairment.
Hypothyroidism	Hypothyroidism can cause an acquired von Willebrand disease and acquired defects in platelet function.
Cushing syndrome	This syndrome should be suspected when there are symptoms and findings suggestive of Cushing syndrome or treatment with systemic or topical glucocorticoids.
Surgical bleeding	This is often a diagnosis of exclusion, although the procedural notes sometimes document that a technical problem was encountered that led to abnormal bleeding.
Vitamin K deficiency	Newborns are at risk, as are individuals with malabsorption and/or receiving broad-spectrum antibiotics that reduce vitamin K production by reducing gut bacteria. Older adults are also at greater risk for developing vitamin K deficiency because of reduced stores from poorer intake of vitamin K. If the patient does not respond to parenteral vitamin K, other causes should be considered.
Vitamin C deficiency (scurvy)	This diagnosis should be considered when there is lethargy with skin and gum bleeding (perifollicular hemorrhages, gum bleeding with swelling). The condition is rare in developed countries. The cause is usually a very poor diet or malabsorption.

IgG, Immunoglobulin G; *NSAID,* nonsteroidal antiinflammatory drug.
From Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

BOX 8 The Laboratory Manifestations of Bleeding Disorders

The laboratory manifestations of bleeding disorders can include abnormalities from the following:

1. The underlying hemostatic defect
2. Bleeding complications (e.g., anemia, iron deficiency, coagulopathy secondary to hemodilution after resuscitation for a massive bleed, development of red cell antibodies after transfusion)
3. False-positive abnormalities (e.g., prolonged aPTT caused by incidental mild factor XII deficiency, which is found in about 1 of 200 patients, or a lupus anticoagulant, which can be a transient finding in about 5% of hospitalized patients)
4. Extremes of normal variation (e.g., mildly low von Willebrand factor levels in an individual who is blood group O, absent secondary aggregation with epinephrine in adjusted platelet-rich plasma aggregation studies)

From Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

BOX 9 Influences on Presenting Problems

When evaluating a bleeding history, it is important to recognize that the presenting problems are influenced by the following factors:

1. The nature and severity of the defect, and the presence of single or multiple risk factors for bleeding
2. Whether the bleeding problem is congenital or acquired
3. Antecedent exposure to hemostatic challenges (such as surgery, dental extraction, menses, and childbirth) and the risk for bleeding with each of these challenges
4. The presence of other medical problems (e.g., renal, hepatic, or thyroid disease), including anemia
5. Variability in the bleeding symptoms experienced by individuals without bleeding disorders (e.g., nosebleeds, bruising) and by individuals with known bleeding disorders, even within families with the same defect
6. Local factors (e.g., sun-damage to the skin, vascular lesions, diverticular disease, or cancerous lesions in the gastrointestinal tract) and the possibility of nonaccidental trauma
7. Treatments that increase the risk for bleeding (e.g., antiplatelet drugs, such as aspirin and nonsteroidal antiinflammatory drugs used for pain control, anticoagulant therapy, etc.)
8. Whether treatments were used to prevent or control bleeding
9. Whether treatments prescribed for other reasons may have reduced bleeding (e.g., reduced menstrual bleeding while on oral contraceptives to prevent pregnancy)

From Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

BOX 10 Case 1: Illustration of a Mild, Inherited Bleeding Problem

A 77-year-old man who is starting treatment for multiple myeloma was discovered to have a prolonged activated partial thromboplastin time. Review of his records indicated that the abnormality was present on a previous admission for spinal cord compression, which was treated with surgery. He required 4 units of packed red blood cells several days after this surgery because of delayed postoperative bleeding. There was no other bleeding history. He was found to have mild factor IX deficiency, unrelated to the myeloma, and his daughter proved to be a carrier of this defect.

From Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

BOX 11 Case 2: Illustration of the Importance of Assessing Both Personal and Familial Bleeding Problems

A 22-year-old woman was referred for evaluation of a possible platelet disorder. She had a history of menorrhagia (4 days out of 7 days of menstrual flow were heavy when not on treatment), prolonged nosebleeds in childhood, and hematuria with urinary tract infections. She did not have thrombocytopenia, and she had no exposure to major hemostatic challenges. Her father, uncle, and grandfather had a striking bleeding history, and two of them had thrombocytopenia. The bleeding in her relatives included joint bleeds with trauma and severe, delayed-onset bleeding after trauma and surgery (usually more than a day later), which continued for weeks despite platelet transfusions. One of these relatives reported no bleeding when he had a tooth extracted while receiving fibrinolytic inhibitor therapy. Although menorrhagia is not specific to any one type of bleeding disorder, the delayed bleeding in affected relatives suggests a possible autosomal dominant disorder and either a fibrinolytic defect of a factor defect or deficiency (e.g., affected relatives). Because of the family history of thrombocytopenia, joint bleeds, and delayed bleeding, which did not respond well to platelet transfusions, testing was done for the Quebec platelet disorder. Genetic testing for duplication mutation of the urokinase plasminogen activator gene confirmed this diagnosis in the patient and her relatives. The case illustrates the importance of evaluating both the personal and family bleeding history and highlights the fact that bleeding-symptom severity can vary among affected family members, in part because of their different exposures to challenges and treatments.

From Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

BOX 12 Case 3: Illustration of the Importance of Assessing Bleeding Problems Over Time

A 72-year-old man was referred for evaluation of a severe bleed after receiving a single dose of low-molecular-weight heparin for unconfirmed deep vein thrombosis. He had a history of a similar bleeding episode several years previously while on warfarin treatment for atrial fibrillation. There was no other bleeding history, and the patient subsequently developed a spontaneous iliopsoas bleed. He had undergone numerous surgeries earlier in life without any bleeding problems, and there was no family history of bleeding. The bleeding history suggested the possibility of an acquired bleeding problem, possibly acquired von Willebrand disease or an acquired factor XIII deficiency. Diagnostic testing indicated that he had acquired factor XIII deficiency. This case illustrates the fact that there may be more than one risk factor for bleeding: in this case, several exposures to anticoagulants triggered bleeding in a patient with an acquired factor deficiency. On initial treatment of his iliopsoas bleed with factor XIII concentrate, there was partial neutralization of the infused factor followed by accelerated clearance, consistent with acquired factor XIII deficiency secondary to an autoantibody.

From Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

ICD-10CM # D68.8 Other specified coagulation defects
D68.9 Coagulation defect, unspecified

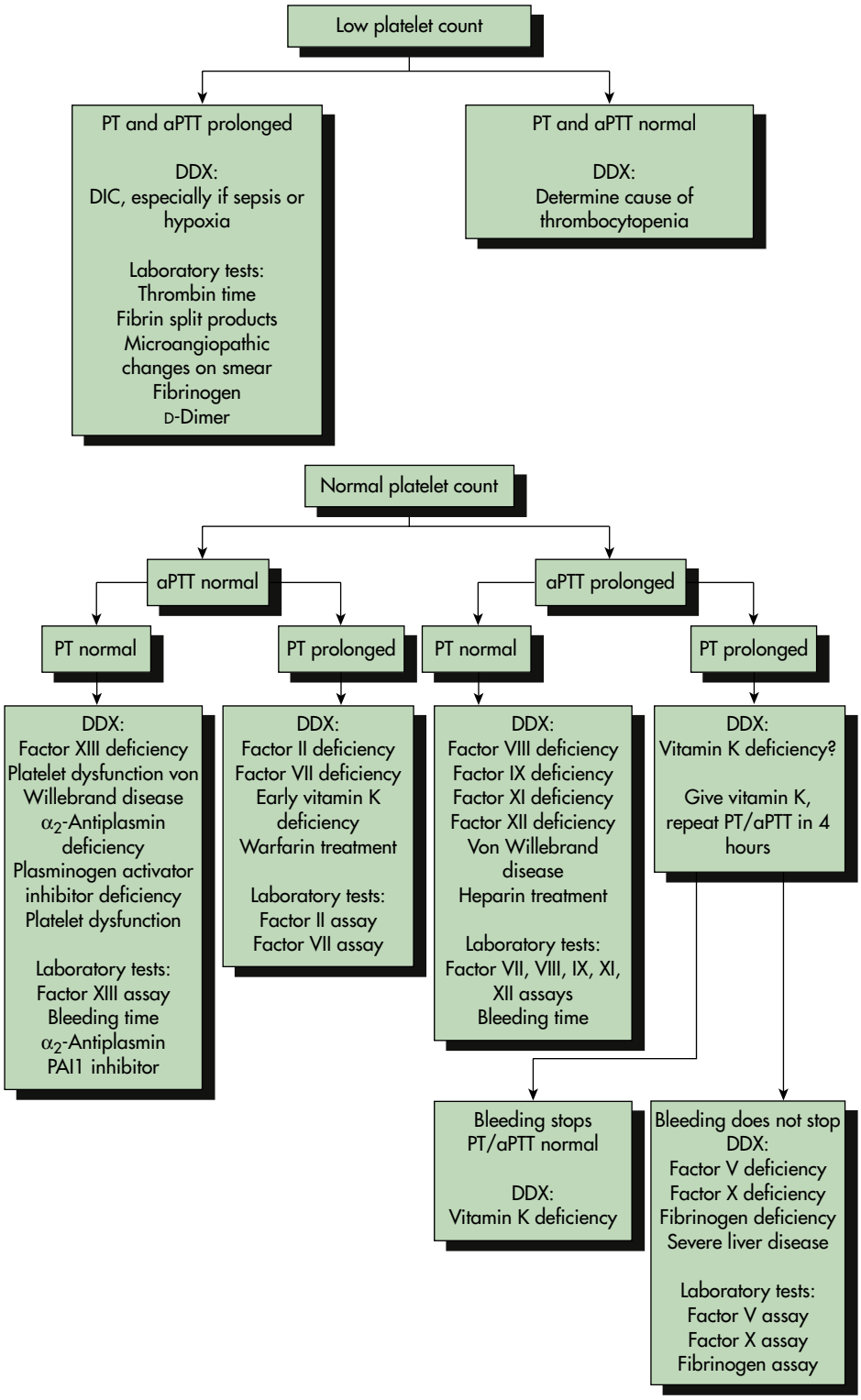


FIG. 34 Differential diagnosis *(DDx)* of bleeding disorders. (From Hughes HK, Kahl LK: *The Harriet Lane handbook,* ed 21, St Louis, 2018, Mosby.)

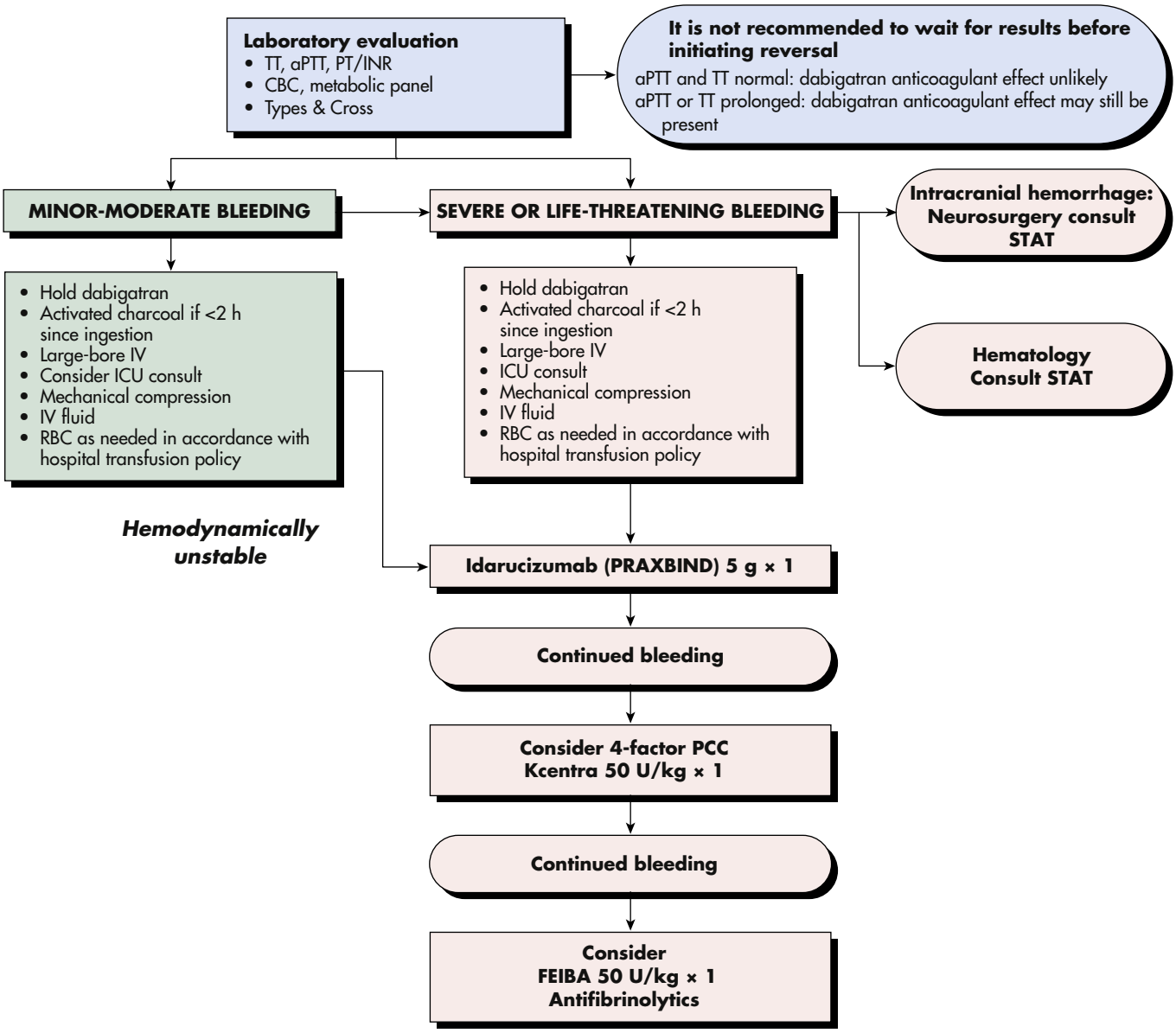


FIG. 35 Approach to bleeding with dabigatran. *aPTT,* Activated partial thromboplastin time; *CBC,* complete blood cell count; *FEIBA,* factor eight inhibitor bypassing activity; *ICU,* intensive care unit; *INR,* international normalized ratio; *IV,* intravenous; *PCC,* prothrombin complex concentrate; *PT,* prothrombin time; *RBC,* red blood cell count; *STAT,* immediately; *TT,* thrombin time. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

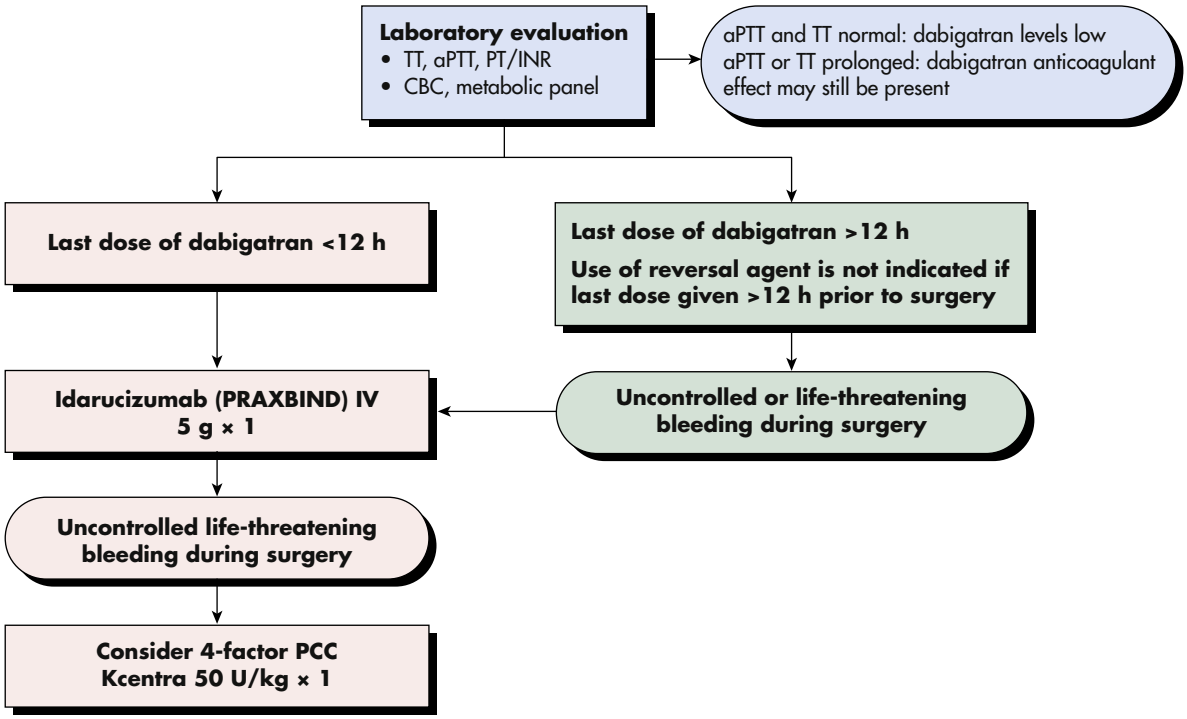


FIG. 36 Approach to emergency surgery with dabigatran. *aPTT,* Activated partial thromboplastin time; *CBC,* complete blood cell count; *INR,* international normalized ratio; *IV,* intravenous; *PCC,* prothrombin complex concentrate; *PT,* prothrombin time; *TT,* thrombin time. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier)

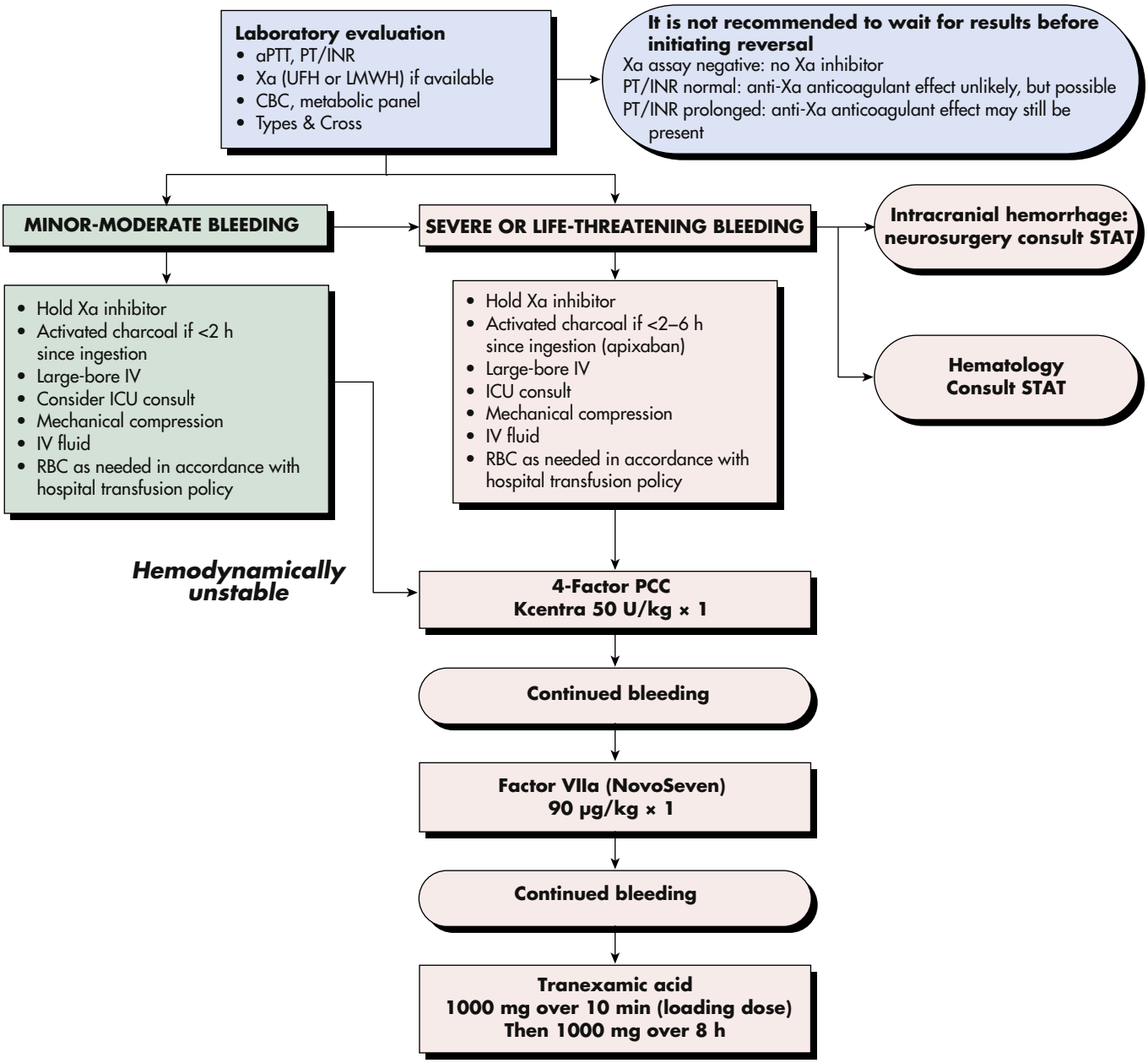


FIG. 37 Approach to bleeding with oral factor Xa inhibitors. *aPTT,* Activated partial thromboplastin time; *CBC,* complete blood cell count; *ICU,* intensive care unit; *INR,* international normalized ratio; *IV,* intravenous; *LMWH,* low–molecular-weight heparin; *PCC,* prothrombin complex concentrate; *PT,* prothrombin time; *RBC,* red blood cell count; *STAT,* immediately; *TT,* thrombin time; *UFH,* unfractionated heparin. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

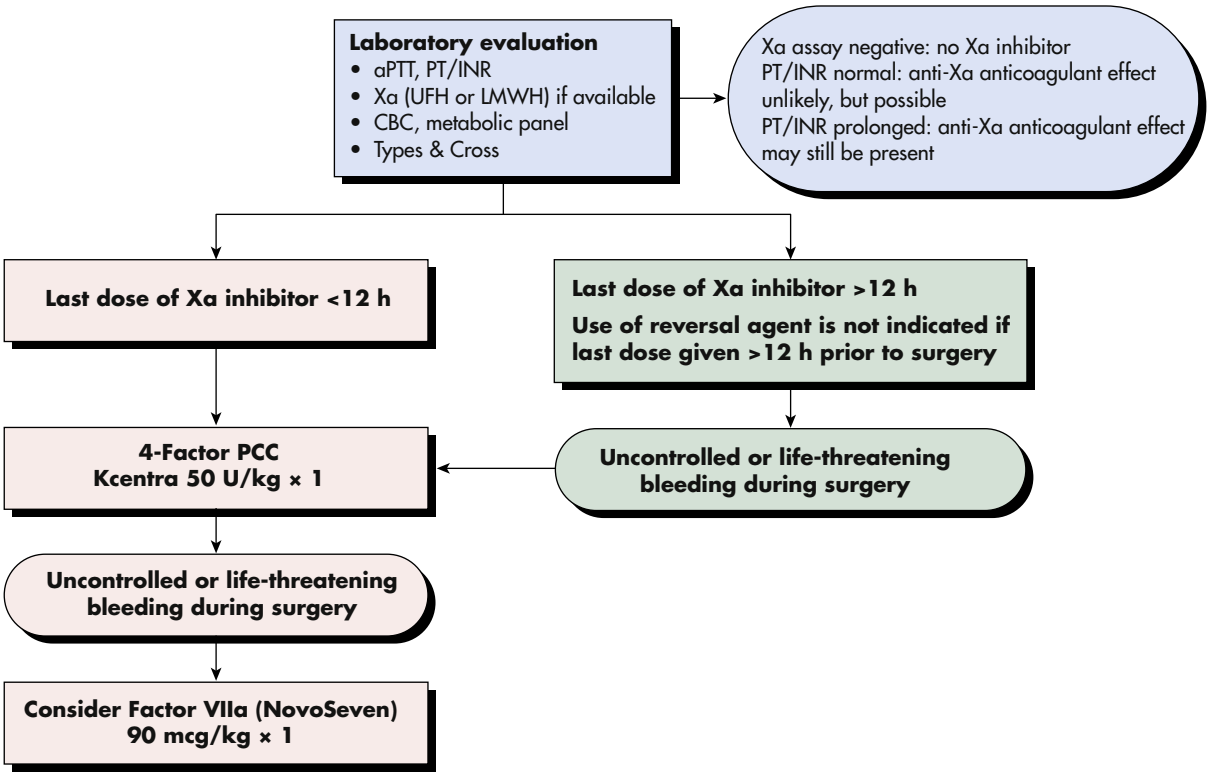


FIG. 38 Approach to emergency surgery with oral factor Xa inhibitors. *aPTT,* Activated partial thromboplastin time; *CBC,* complete blood cell count; *INR,* international normalized ratio; *LMWH,* low–molecular-weight heparin; *PCC,* prothrombin complex concentrate; *PT,* prothrombin time; *RBC,* red blood cell count; *STAT,* immediately; *TT,* thrombin time; *UFH,* unfractionated heparin. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

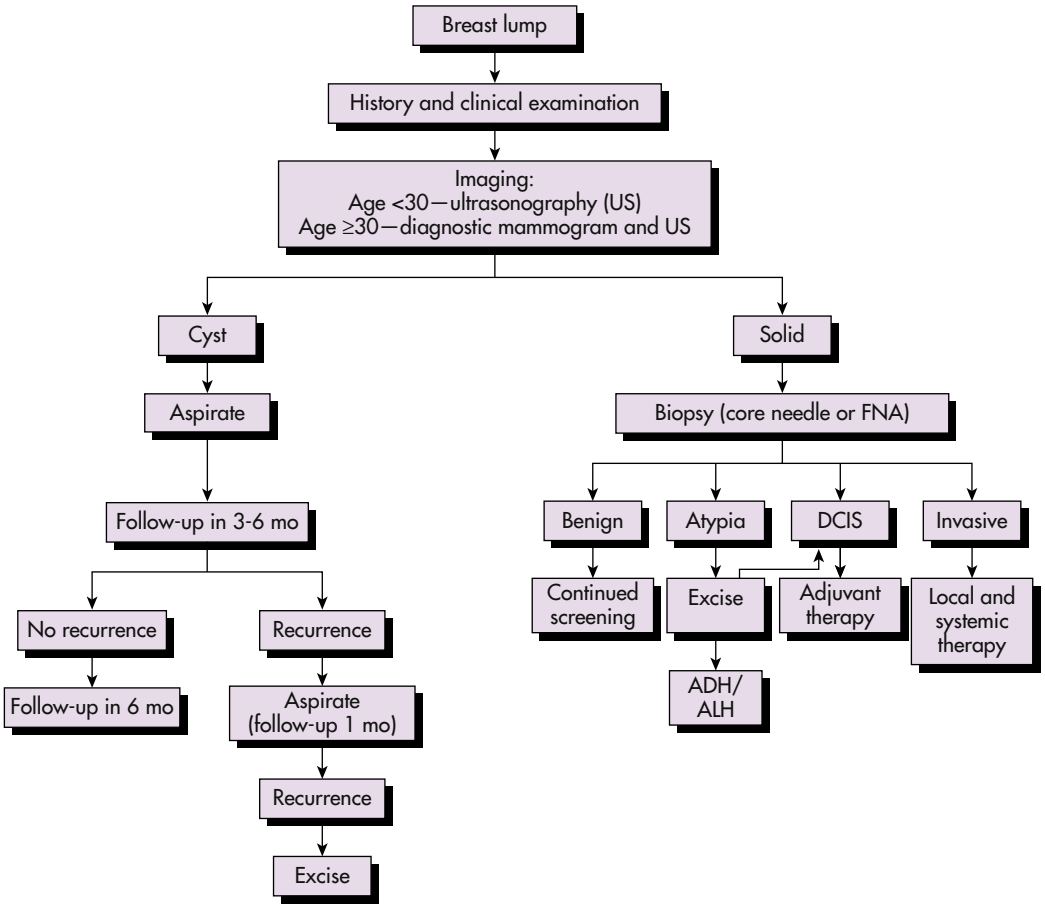


FIG. 39 Algorithm for breast lump management. *ADH,* Atypical ductal hyperplasia; *ALH,* atypical lobular hyperplasia; *DCIS,* ductal carcinoma in situ; *FNA,* fine-needle aspiration. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

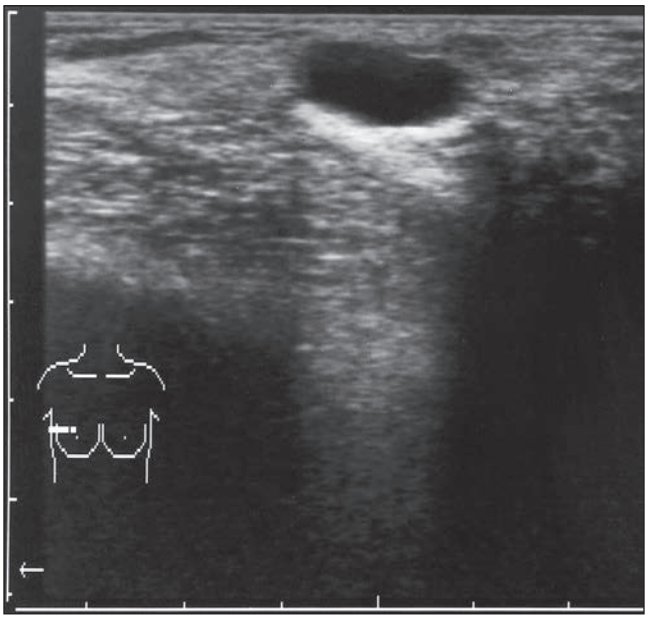
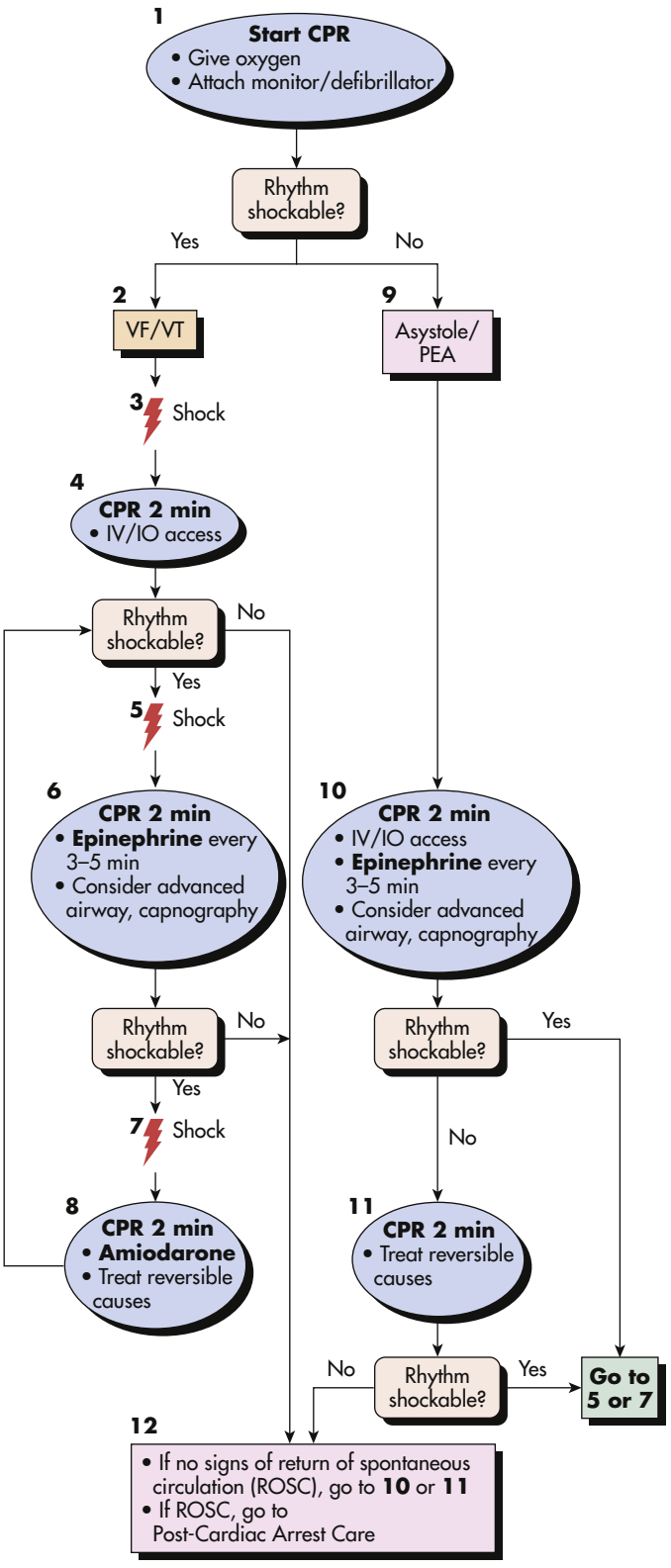


FIG. 40 Ultrasound image of the breast showing the palpable lump to be cystic. Cystic lesions have a characteristic hypoechoic pattern, with prominent acoustic shadowing. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)



CPR Quality
- Push hard (2 inches [5 cm]) and fast (100–120/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 min or sooner if fatigued
- If no advanced airway, 30:2 compression-ventilation ratio
- Quantitative waveform capnography
  - If P_{ETCO_2} <10 mm Hg, attempt to improve CPR quality
- Intraarterial pressure
  - If relaxation phase (diastolic) pressure <20 mm Hg, attempt to improve CPR quality

Shock Energy for Defibrillation
- **Biphasic:** Manufacturer recommendation (e.g., initial dose of 120–200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered
- **Monophasic:** 360 J

Drug Therapy
- **Epinephrine IV/IO Dose:** 1 mg every 3–5 min
- **Amiodarone IV/IO Dose:** First dose: 300 mg bolus Second dose: 150 mg

Advanced Airway
- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airway in place, give 1 breath every 6 s (10 breaths/min) with continuous chest compressions

Return of Spontaneous Circulation (ROSC)
- Pulse and blood pressure
- Abrupt sustained increase in P_{ETCO_2} (typically ≥40 mm Hg)
- Spontaneous arterial pressure waves with intraarterial monitoring

Reversible Causes
- **H**ypovolemia
- **H**ypoxia
- **H**ydrogen ion (acidosis)
- **H**ypo-/hyperkalemia
- **H**ypothermia
- **T**ension pneumothorax
- **T**amponade, cardiac
- **T**oxins
- **T**hrombosis, pulmonary
- **T**hrombosis, coronary

FIG. 41 American Heart Association Advanced Cardiac Life Support (ACLS) algorithm. *CPR,* Cardiopulmonary resuscitation; *ET,* endotracheal; *IO,* intraosseous; *IV,* intravenous; *PEA,* pulseless electrical activity; P_{ETCO_2}, partial pressure of end tidal carbon dioxide; *pVT,* pulseless ventricular tachycardia; *ROSC,* return of spontaneous circulation; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia. (From Link MS et al: Part 7: adult advanced cardiovascular life support: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2015;132(18 suppl 2):S444-S464. In Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

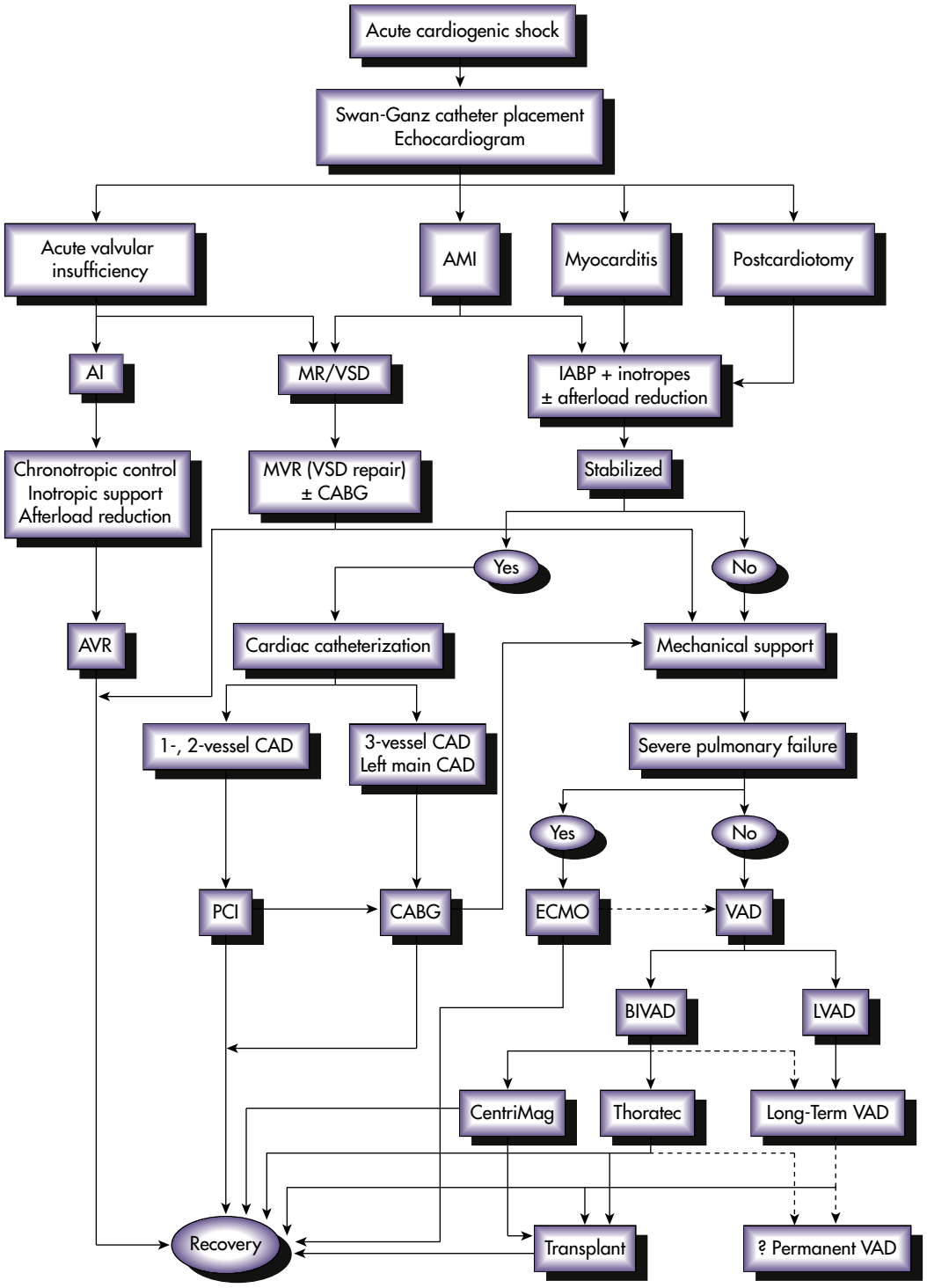


FIG. 42 Algorithm for the management of acute cardiogenic shock. (From Vincent JL et al: *Textbook of critical case,* ed 7, Philadelphia, 2017, Elsevier.)

ICD-10CM #
I51.7 Cardiomegaly
Q24.8 Other specified congenital malformations of heart
I11.9 Hypertensive heart disease without heart failure
I11.0 Hypertensive heart disease with heart failure
Q23.8 Other congenital malformations of aortic and mitral valves

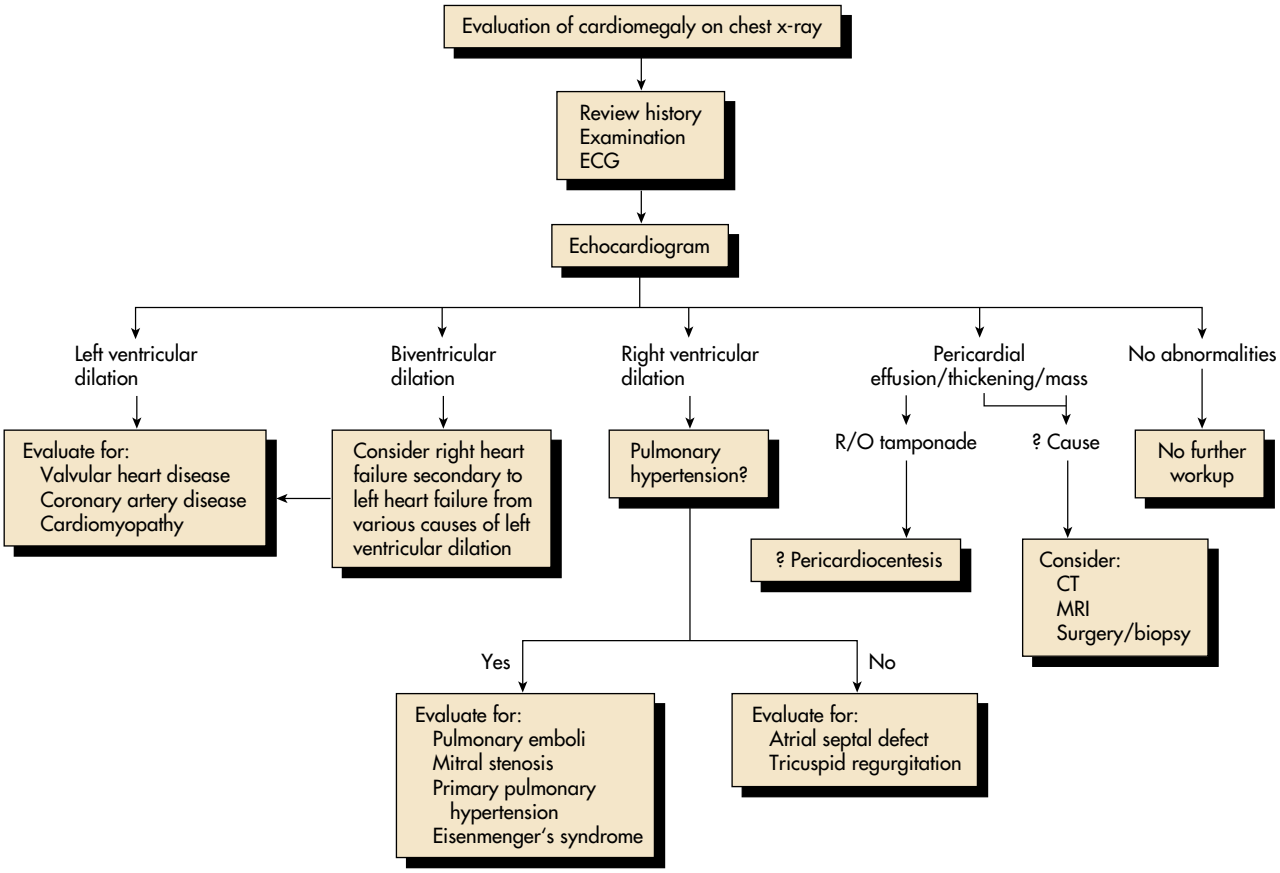


FIG. 43 Approach to the patient with cardiomegaly. When cardiomegaly is found on the chest radiograph, the history and physical examination should be reviewed and an electrocardiogram *(ECG)* performed before obtaining a two-dimensional Doppler echocardiographic study. Cardiomegaly may be explained by left ventricular dilation, biventricular dilation, right ventricular dilation, or pericardial abnormalities, or it may be found to be spurious on the echocardiogram. Rarely, isolated abnormalities of the atrium, particularly the left atrium, may cause abnormalities on the chest radiograph but will not cause true cardiomegaly. Depending on the echocardiographic findings, further tests can help elucidate the cause of echocardiographically confirmed cardiomegaly. *CT*, Computed tomography; *MRI,* magnetic resonance imaging; *R/O,* rule out. (From Goldman L, Braunwald E [eds]: *Primary cardiology,* ed 2, Philadelphia, 2003, Saunders.)

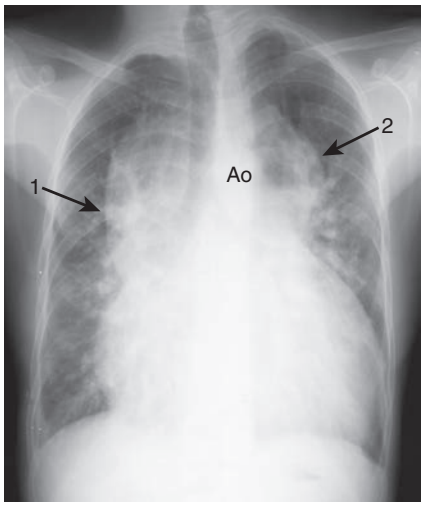


FIG. 44 "Snowman" heart in a 36-year-old man with increasing shortness of breath. Posteroanterior chest film examination shows cardiomegaly and increased pulmonary blood flow. The superior mediastinum is widened, the result of dilation of the left vertical vein *(arrow 2)* and the right-sided superior vena cava *(arrow 1)*. The trachea is displaced by a normal left-sided aortic arch *(Ao)*. (From Boxt LM, Abbara S: *Cardiac imaging: the requisites,* ed 4, Philadelphia, 2016, Elsevier.)

ICD-10CM #

I51.7	Cardiomegaly
Q24.8	Other specified congenital malformations of heart
I11.9	Hypertensive heart disease without heart failure
I11.0	Hypertensive heart disease with heart failure
Q23.8	Other congenital malformations of aortic and mitral valves

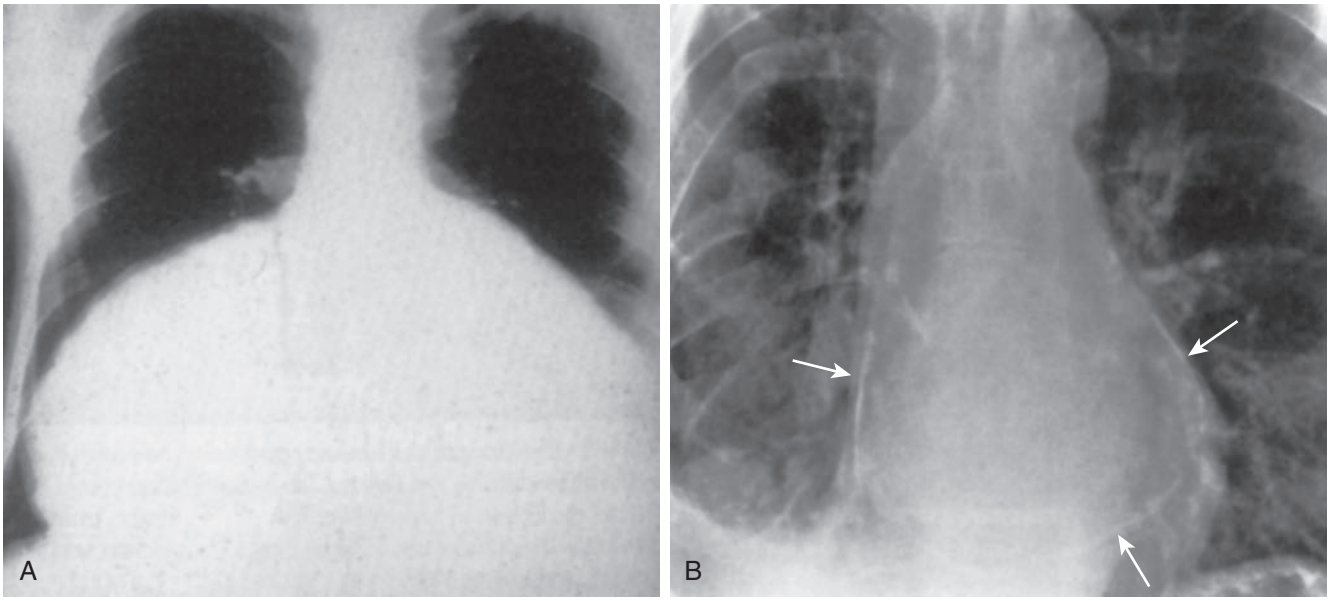


FIG. 45 Chest radiographs in a patient with a very large pericardial effusion. A, "Water bottle" sign. **B,** A patient with constrictive pericarditis and pericardial calcifications (*white arrows*). (From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.)

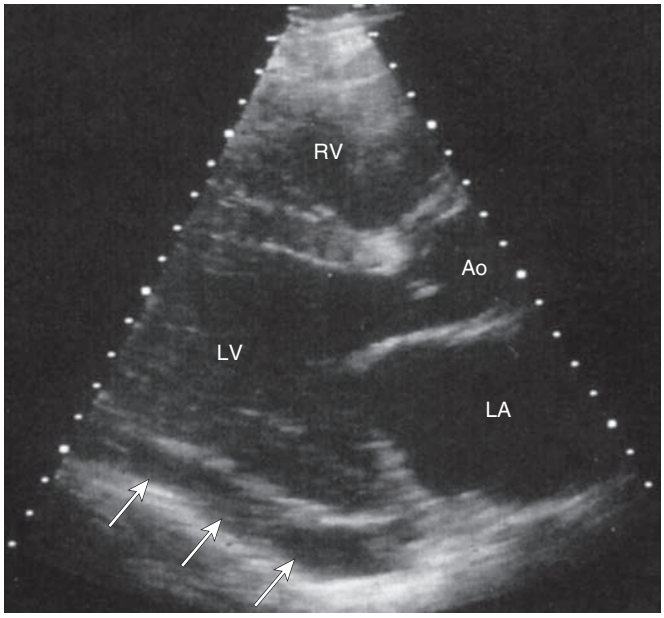


FIG. 46 Echocardiographic findings in a small to moderate pericardial effusion (*white arrows*). *Ao,* Aortic root; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle. (From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.)

CARDIOMEGALY ON CHEST X-RAY—cont'd

ICD-10CM #
I51.7 Cardiomegaly
Q24.8 Other specified congenital malformations of heart
I11.9 Hypertensive heart disease without heart failure
I11.0 Hypertensive heart disease with heart failure
Q23.8 Other congenital malformations of aortic and mitral valves

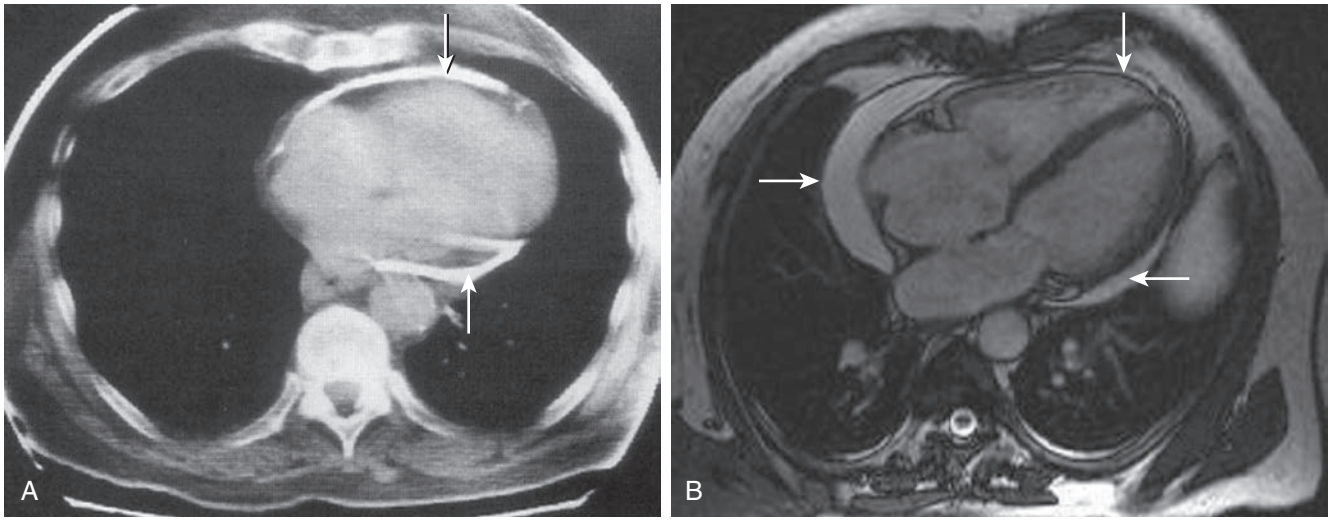


FIG. 47 A, Computed tomography findings in constrictive pericarditis. White vertical arrows are depicting thickened pericardium and pericardial calcification. **B,** The magnetic resonance imaging results of a patient with effusive-constrictive pericarditis are shown in the right image. Horizontal arrows show a loculated pericardial effusion, and the vertical arrow shows thickened pericardium. (From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.)

TABLE 8 Diagnosis of Cardiac Tamponade

Clinical presentation	Elevated systemic venous pressure,* hypotension,† pulsus paradoxus,‡ tachycardia,§ dyspnea, or tachypnea with clear lungs
Precipitating factors	Drugs (cyclosporine, anticoagulants, thrombolytics), recent cardiac surgery, indwelling instrumentation, blunt chest trauma, malignancies, connective tissue disease, renal failure, septicemia‖
ECG	Can be normal or nonspecifically changed (ST-T wave), electrical alternans (QRS, rarely T), bradycardia (end stage), electromechanical dissociation (agonal phase)
Chest radiograph	Enlarged cardiac silhouette with clear lungs
M-mode/two-dimensional echocardiogram	Diastolic collapse of the anterior RV free wall,¶ RA collapse, LA and rarely LV collapse, increased LV diastolic wall thickness "pseudohypertrophy," IVC dilation (no collapse in inspiration), "swinging heart"
Doppler	Tricuspid flow increases and mitral flow decreases during inspiration (reverse in expiration)
	Systolic and diastolic flows are reduced in systemic veins in expiration and reverse flow with atrial contraction is increased
M-mode color Doppler	Large respiratory fluctuations in mitral/tricuspid flows
Cardiac catheterization	Confirmation of the diagnosis and quantification of the hemodynamic compromise
	RA pressure is elevated (preserved systolic x descent and absent or diminished diastolic y descent)
	Intrapericardial pressure is also elevated and virtually identical to RA pressure (both pressures fall in inspiration)
	RV mid-diastolic pressure is elevated and equal to the RA and pericardial pressures (no dip-and-plateau configuration)
	Pulmonary artery diastolic pressure is slightly elevated and may correspond to the RV pressure
	Pulmonary capillary wedge pressure is also elevated and nearly equal to intrapericardial and right atrial pressure
	LV systolic and aortic pressures may be normal or reduced
	Documenting that pericardial aspiration is followed by hemodynamic improvement**
	Detection of coexisting hemodynamic abnormalities (LV failure, constriction, pulmonary hypertension)
	Detection of associated cardiovascular diseases (cardiomyopathy, coronary artery disease)
RV/LV angiography	Atrial collapse and small hyperactive ventricular chambers
Coronary angiography	Coronary compression in diastole

IVC, Inferior vena cava; *LA,* left atrium; *LV,* left ventricle; *QRS,* Q wave, R wave, S wave; *RA,* right atrium; *RV,* right ventricle.

*Jugular venous distention is less notable in hypovolemic patients or in "surgical tamponade." An inspiratory increase or lack of fall of pressure in the neck veins (Kussmaul sign), when verified by tamponade or after pericardial drainage, indicates effusive-constrictive disease.

†Heart rate is usually greater than 100 beats per minute but may be lower in patients with hypothyroidism or uremia.

‡Pulsus paradoxus is defined as a drop in systolic blood pressure greater than 10 mm Hg during inspiration, while diastolic blood pressure remains unchanged. It is easily detected by simply feeling the pulse, which diminishes significantly during inspiration. Clinically significant pulsus paradoxus is apparent when the patient is breathing normally. When this sign is present only in deep inspiration, it should be interpreted with caution. The magnitude of pulsus paradoxus is evaluated by sphygmomanometry. If pulsus paradoxus is present, the first Korotkoff sound is not heard equally well throughout the respiratory cycle but only during expiration at a given blood pressure. The blood pressure cuff is therefore inflated above the patient's systolic pressure. Then it is slowly deflated, while the clinician observes the phase of respiration. During deflation, the first Korotkoff sound is intermittent. Correlation with the patient's respiratory cycle identifies a point at which the sound is audible during expiration but disappears when the patient breathes in. As the cuff pressure drops further, another point is reached when the first blood pressure sound is audible throughout the respiratory cycle. The difference in systolic pressure between these two points is the clinical measure of pulsus paradoxus. Pulsus paradoxus is absent in tamponade complicating an atrial septal defect and in patients with significant aortic regurgitation.

§Occasional patients are hypertensive, especially if they have preexisting hypertension.

‖Febrile tamponade may be misdiagnosed as septic shock.

¶Right ventricular collapse can be absent in elevated right ventricular pressure and right ventricular hypertrophy or in right ventricular infarction.

**If after drainage of the pericardial effusion, the intrapericardial pressure does not fall below atrial pressure, effusive-constrictive disease should be considered.

From Vincent JL et al: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier.

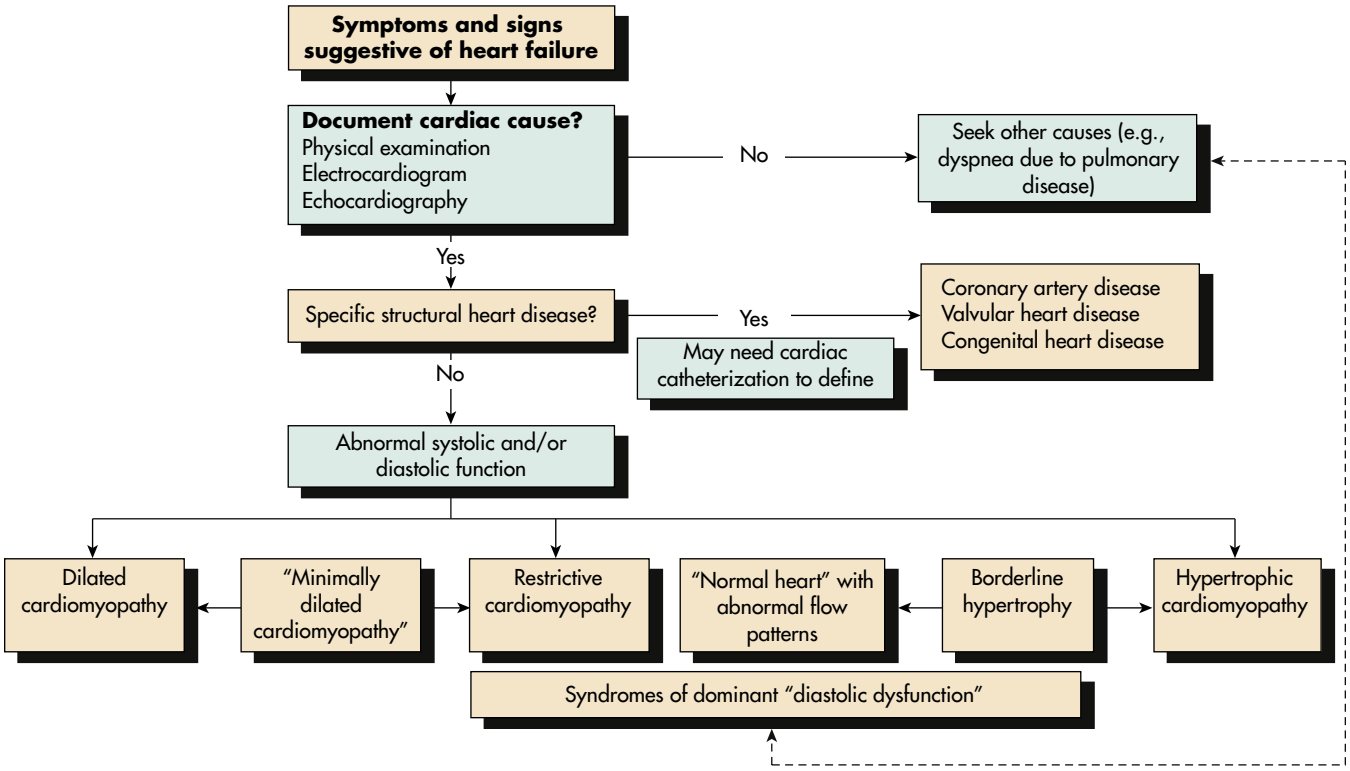


FIG. 48 Initial approach to classification of cardiomyopathy. The evaluation of symptoms or signs consistent with heart failure first includes confirmation that they can be attributed to a cardiac cause. Although this conclusion is often apparent from routine physical examination and electrocardiography, echocardiography serves to confirm cardiac disease and provides clues to the presence of other cardiac diseases, such as focal abnormalities suggesting primary valve disease or congenital heart disease. Having excluded these conditions, cardiomyopathy is generally considered to be dilated, restrictive, or hypertrophic, as shown in the figure. Patients with apparently normal cardiac structure and contraction are occasionally found to demonstrate abnormal intracardiac flow patterns consistent with diastolic dysfunction but should also be evaluated carefully for other causes of their symptoms. Most patients with so-called diastolic dysfunction also demonstrate at least borderline criteria for left ventricular hypertrophy, frequently in the setting of chronic hypertension and diabetes. A moderately decreased ejection fraction without marked dilation or a pattern of restrictive cardiomyopathy is sometimes referred to as minimally dilated cardiomyopathy, which may represent either a distinct entity or a transition between acute and chronic disease. (From Goldman L, Schafer AI: *Goldman Cecil medicine,* ed 25, Philadelphia, 2016, Saunders.)

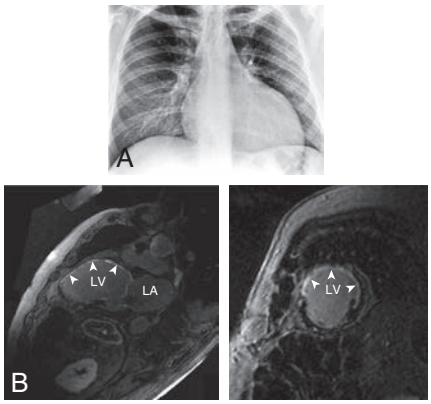


FIG. 49 Dilated cardiomyopathy. A, The heart shows enlargement of all four chambers. The azygos vein and superior vena cava are slightly dilated, reflecting high central venous pressure. **B,** Delayed enhanced magnetic resonance images demonstrate ischemic dilated cardiomyopathy. Extensive subendocardial delayed hyperenhancement *(arrowheads)* demonstrates features of old myocardial infarction—it follows a vascular territory (the left anterior descending), it is based on the subendocardium, and there is thinning of the affected myocardium. *LA,* Left atrium; *LV,* left ventricle. (Boxt LM, Abbara S: *Cardiac imaging: the requisites,* ed 4, Philadelphia, 2016, Elsevier.)

TABLE 9 Classification of the Cardiomyopathies by Phenome and Genome

	PHENOME			GENOME		
Type	**Morphology**	**Physiology**	**Pathology**	**Systemic Conditions or Diseases, Clinically Relevant Features, Classic Risk Factors, Associations**	**Nonsyndromic, Usually Single Gene**	**Syndromic**
Dilated (DCM)	LV/RV dilation with minimal or no wall thickening	Reduced contractility is the primary defect; variable degree of diastolic dysfunction	Myocyte hypertrophy; scattered fibrosis	Hypertension; alcohol use; thyrotoxicosis, myxedema; persistent tachycardia; toxins, e.g., chemotherapy, especially anthracyclines; radiation; pregnancy	Diverse gene ontology with >30 genes implicated	Diverse array of associated conditions, especially muscular dystrophies (MDs): Emery-Dreifuss MD, limb-girdle MD, Duchenne/Becker MD; Laing distal myopathy; Barth syndrome; Kearns-Sayre; others
Restrictive (RCM)	Usually normal chamber sizes; minimal wall thickening	Contractility normal or near-normal with a marked increase in end-diastolic filling pressure	Specific to type, diagnosis: amyloid, iron, glycogen storage disease, others	Endomyocardial fibrosis, amyloid, sarcoid, scleroderma, Churg-Strauss syndrome, cystinosis, lymphoma, pseudoxanthoma elasticum, hypereosinophilic syndrome, carcinoid	If not associated with a systemic genetic disease (e.g., hemochromatosis), genetic cause found most commonly to result from sarcomeric gene mutations	Gaucher disease, hemochromatosis, Fabry disease, familial amyloidosis. Mucopolysaccharidoses, Noonan syndrome
Hypertrophic (HCM)	Usually normal or reduced internal chamber dimension; wall thickening pronounced, especially septal hypertrophy	Systolic function increased or normal	Myocyte hypertrophy, classically with disarray	Severe hypertension can confound clinical, morphologic diagnosis	Mutations of genes encoding sarcomeric proteins	Noonan/Leopard, Danon, Fabry, WPW, Friedrich ataxia, MERRF, MELAS
Arrhythmogenic cardiomyopathy (ACM)	Scattered fibrofatty infiltration, classically of the right ventricle but also commonly involving the left ventricle; RV dilation, LV dilation, or both are common although not universal	Ventricular arrhythmias (VT, VF) early or late, reduced contractility with progressive disease; can mimic DCM	Islands of fatty replacement; fibrosis	Palmoplantar keratoderma, wooly hair in Naxos syndrome	Mutations of genes encoding proteins of the desmosome	Naxos syndrome
Left ventricular noncompaction (LVNC)	Ratio of noncompacted to compacted myocardium increased; normal chamber dimensions varying to a DCM phenotype	Normal to reduced systolic function	Myocardium normal and ranging to findings consistent with other coexisting cardiomyopathy	Phenotype has been observed in the setting of other types of cardiomyopathy	Various cardiomyopathy genes associated but uncertain whether genetic cause or developmental defect during organogenesis; see text	
Infiltrative	Usually thickened walls; occasional dilation	Restrictive physiology; systolic function usually mildly reduced	Specific to type, diagnosis: amyloid, iron, glycogen storage disease, others		See RCM above	See RCM above
Inflammatory	Normal or dilated without hypertrophy	Reduced systolic function	Inflammatory infiltrates	Hypereosinophilic syndrome (see text), acute myocarditis		
Ischemic	Normal or dilated without hypertrophy	Reduced systolic function	Areas of infarcted myocardium	Hypercholesterolemia, hypertension, diabetes, cigarette smoking, family history	Familial hypercholesterolemia; other heritable lipid disorders	Familial hypercholesterolemia
Infectious		Normal or dilated without hypertrophy	Reduced systolic function	Specific to infection	Viral (especially acute myocarditis); protozoal (e.g., Chagas); bacterial, direct infection (e.g., Lyme disease), or from acute cellular toxicity as a result of systemic toxins (*Streptococcus*, gram-negatives, etc.)	Genetic predisposition to infection and/or variable response to infective agent

LV, Left ventricle; *MELAS,* mitochondrial encephalopathy, lactic acidosis, and stroke-like symptoms; *MERRF,* myoclonic epilepsy associated with ragged red fibers; *RV,* right ventricle; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia.
From Mann DL, Zipes DP, Libby P, Bonow RO: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.

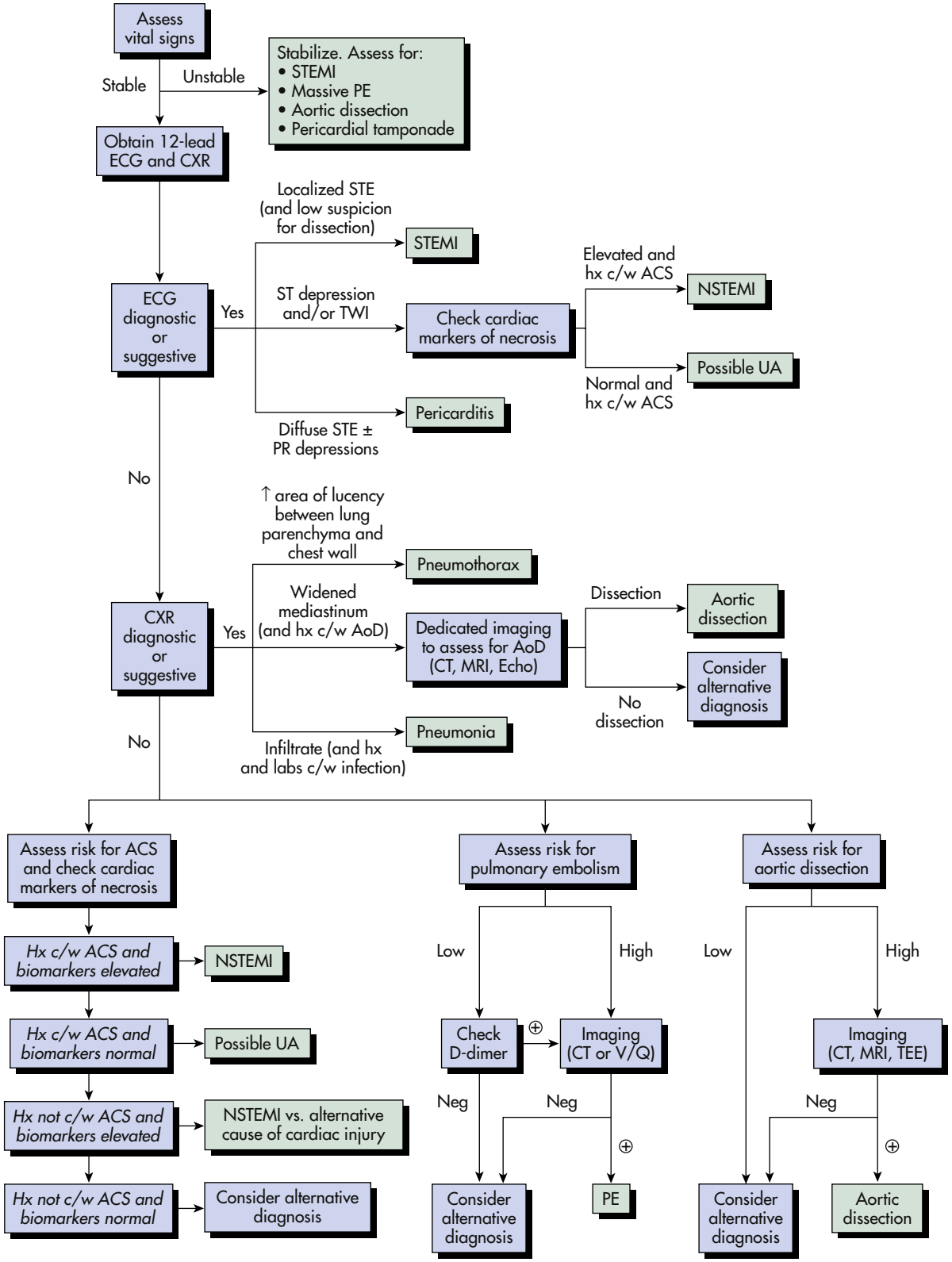


FIG. 50 Algorithm for the initial diagnostic approach to a patient with chest pain. *ACS,* Acute coronary syndrome; *AoD,* aortic dissection; *c/w,* consistent with; *CT,* computed tomography; *CXR,* chest x-ray film; *Echo,* echocardiography; *hx,* history; *MRI,* magnetic resonance imaging; *NSTEMI,* non–ST-segment elevation myocardial infarction; *STE,* ST-segment elevation; *STEMI,* ST-segment elevation myocardial infarction; *TEE,* transesophageal echocardiography; *UA,* unstable angina; *TWI,* T wave inversion; *V/Q,* ventilation-perfusion scan. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

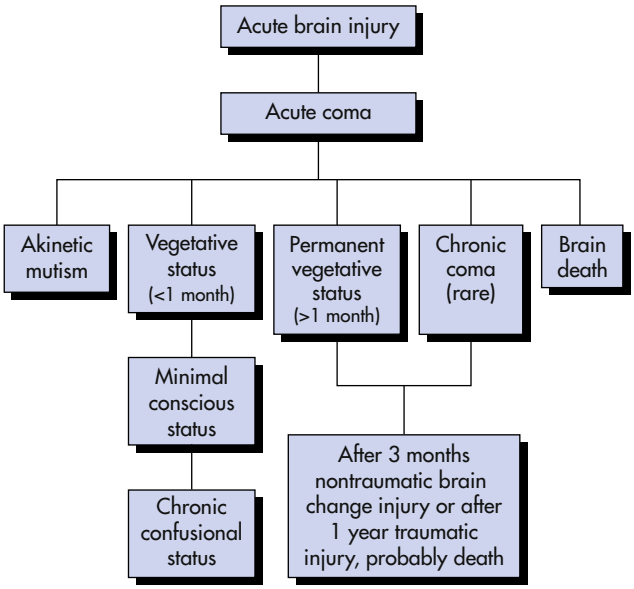


FIG. 51 Natural course of acute coma. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

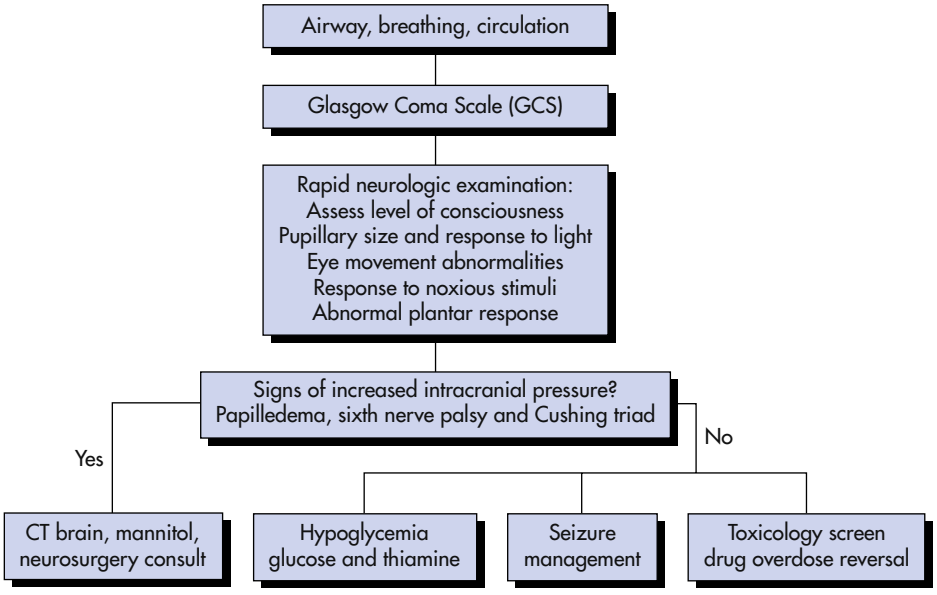


FIG. 52 Management of acute coma. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.)

TABLE 10 Characteristic Clinical Features of Disorders of Consciousness and Locked-In Syndrome

Disorder	Consciousness	Cognition	Receptive Language	Expressive Language	Visual Perception	Motor Function	Structure Injured
Coma	No sleep-wake cycles	None	None	None	None	Primitive reflexes only	RAS OR Diffuse brain damage
Vegetative state	Intermittent periods of wakefulness	None	None	None	Variable visual startle responses	Involuntary movements only	Cerebral cortex Thalamocortical pathway ± RAS
Minimally conscious state	Intermittent periods of wakefulness	Inconsistent but clear behavioral signs of self or environmental awareness	Inconsistently one-step command following	Aspontaneous and ranging from single words or short phrases	Visual pursuit Object recognition	Localize to noxious stimuli Object manipulation Automatic movement sequences	Normal to variable lesion in RAS
Akinetic mutism Abulia	Normal or depressed	Normal or depressed	Normal or depressed	Normal or depressed	Normal	Delayed, slow responses	Hypothalamic Basal forebrain
Acute confusional state	Extended period of wakefulness	Confusion and disorientation	Consistent one-step command following	Yes-no responses Perseverative Short sentences Confused	Object recognition	No functional deficit	Normal to variable lesions in RAS
Brain death	Absent	Absent	None	None	None	Preserved postural and motor reflex	Global brain damage
Locked-in syndrome	Normal sleep-wake cycles	Normal to near-normal	Normal	Aphonic	Normal	Quadriplegia	Bilateral ventral pons

RAS, Reticular activating system.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

TABLE 11 Etiologies and Clinical Features of Different Causes of Impaired Consciousness

	Etiology	Clinical Features for Differential Diagnosis
Supratentorial lesion	• Destructive: ischemic infarct, hemorrhage (SAH, SDH, ICH) • Compressive lesion: ischemic infarct, hemorrhage, aneurysm, vascular malformation, tumor, venous thrombosis, abscess • Head injury, concussion	• Initial focal cerebral dysfunction • Dysfunction progresses rostral to caudal • Signs reflect cortical dysfunction, often multifocal • Often asymmetric cortical involvement and presentation
Infratentorial lesion	• Destructive: ischemic infarct, hemorrhage (SAH, ICH) • Compressive lesion: ischemic infarct, hemorrhage, aneurysm, vascular malformation, tumor, venous thrombosis	• Symptoms of brainstem dysfunction or sudden onset coma (posturing) • Brainstem signs precede/accompany coma • Cranial nerve and oculovestibular dysfunction: ocular bobbing, vertical pendular oscillation (pons), monocular movement (midbrain) • Early onset of abnormal respiratory pattern
Diffuse brain lesion	• Traumatic brain injury • Anoxic injury • Toxic encephalopathy • Seizure, nonconvulsive, postictal • Primary neuronal disorder • Infectious encephalitis (prion disease, progressive leukoencephalopathy) • Inflammatory encephalitis (ADEM) • Vasculitis	• Often asymmetric in presentation • Focal signs depending on main brain lesion

Continued on next page

TABLE 11 Etiologies and Clinical Features of Different Causes of Impaired Consciousness—cont'd

	Etiology	Clinical Features for Differential Diagnosis
Metabolic coma	• Hypoglycemia • Nutritional (thiamine, niacin, pyridoxine, cyanocobalamin, folic acid), Wernicke encephalopathy • Hepatic encephalopathy • Uremia and dialysis • CO2 narcosis • Exocrine pancreatic encephalopathy • Endocrine: Addison disease, pheochromocytoma, diabetes • Paraneoplastic • Drug poisoning • Thermal injury • Electrolyte/acid-base imbalance	• Confusion/stupor precede motor signs • Motor signs usually symmetric • Pupil responses generally preserved • Myoclonus, asterixis, tremulousness, and generalized seizures common • Acid-base imbalance common with compensatory ventilator changes • Periodic alternating gaze deviation • Systemic: altered mental state with normal brainstem function (especially normal pupils). Possible triphasic waves on EEG • Stimulant-induced coma (cocaine, amphetamine, phencyclidine, tricyclic antidepressant) • Fever, mydriasis (except miosis with phencyclidine), and seizure • Sedatives (alcohol, benzodiazepine, barbiturates, antiepileptics) • Ataxia, impaired eye movements but normal pupils • Opiate-induced miosis
Psychiatric	• Conversion disorder • Depression • Psychosis—catatonia	• Forced eye closure • Pupils reactive or dilated, nonreactive • Unpredictable oculocephalic reflex: nystagmus on caloric test • Normal or inconsistent motor tone • No pathologic reflexes • Awake-pattern EEG

ADEM, Acute disseminated encephalomyelitis; *CO_2,* carbon dioxide; *EEG,* electroencephalogram; *ICH,* intracranial hematoma; *SAH,* subarachnoid hemorrhage; *SDH,* subdural hematoma.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

TABLE 12 Types of Brain Herniation Syndromes

Syndrome	Mechanism	Imaging Findings	Clinical Presentation
Uncal	• Downward displacement of medial temporal lobe into the posterior fossa through the incisural opening • Seen in patients with unilateral hemispheric mass lesions	• Contralateral temporal horn widening • Ipsilateral ambient and prepontine cistern widening • Uncus extending into the suprasellar cistern	• Ipsilateral pupil dilation and ophthalmoplegia • Contralateral or ipsilateral hemiparesis • Decerebrate posturing
Central (transtentorial)	• Downward displacement of cerebral hemispheres and basal nuclei compressing and displacing diencephalon and midbrain rostrocaudally through the tentorial notch	• Effacement of the sulci • Obliteration of the suprasellar cistern • Compression and posterior displacement of the quadrigeminal cistern	• Medium-sized, fixed pupils • Early coma • Decorticate posturing • Cheyne-Stokes respiration • Diabetes insipidus
Cingulate (subfalcine)	• Lateral displacement of the cingulate gyrus under the anterior falx	• Attenuation of ipsilateral aspect of frontal horn • Asymmetric anterior falx • Obliteration of ipsilateral atrium of lateral ventricle • Septum pellucidum shift	• Small reactive pupils • Headache • Contralateral leg paralysis
Ascending	• Infratentorial mass effect protruding through the tentorial opening compressing the midbrain and cerebellar structures at the tentorial edges	• Spinning top appearance of midbrain • Narrowing of bilateral ambient and quadrigeminal cisterns	• Progressive stupor • Nausea and vomiting
Tonsillar	• Cerebellar tonsils protruding into the foramen magnum compressing adjacent medulla and upper cervical cord	• Cerebellar tonsils at the level of the dens on axial view and 5 mm below foramen magnum on sagittal view (7 mm in children)	• Cushing triad • Coma • Bilateral arm dysesthesia

From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

TABLE 13 Neuroimaging and Electrophysiologic Techniques and Findings in Disorders of Consciousness

Technique	Measurement	Strengths	Limitations	Vegetative State	Minimally Conscious State	Comatose
FDG-PET	Metabolic	Relatively direct measure of neuronal energy use (glucose uptake)	Ionizing (limited repeated measures)	Voxel-based: Hypometabolism in lateral and medial frontoparietal cortices	Metabolic dysfunction in left hemisphere	
Functional MRI	CBF	High-resolution structural imaging of grey-white matter (DTI) and functional imaging (spectroscopy, resting, passive, and active CBF paradigms)	Sensitive to movement artifacts requiring sedation/anesthesia Incompatible with ferromagnetic material (deprivation, pumps, electrodes)	Activation fMRI: Low-level cortical activation DMN—partially preserved	Activation fMRI: Near-normal high-level cortical activation	
EEG/ERPs	Electrical	Repeatable, portable, and inexpensive	Muscle, eye, and dysautonomia artifacts Challenging source reconstruction		EEG: slow-wave activity through night and periods of REM sleep	ERP-poor outcome with absence of a cortical response to electrical stimulation of median nerves
EEG-TMS	Electrical	Stereotaxic stimulation connectivity studies	Stimulation areas are limited by muscle artifacts	TMS triggers a simple, local EEG response similar to deep sleep/anesthesia	Complex activations in distant cortical areas	

CBF, Cerebral blood flow; *DMN,* default model network; *DTI,* diffuse tensor imaging; *EEG,* electroencephalogram; *ERPs,* event-related potentials; *FDG,* ^{18}F-fluorodeoxyglucose; *fMRI,* functional magnetic resonance imaging; *REM,* rapid eye movement; *TMS,* transcranial magnetic stimulation.

From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 5, Philadelphia, 2019, Elsevier.

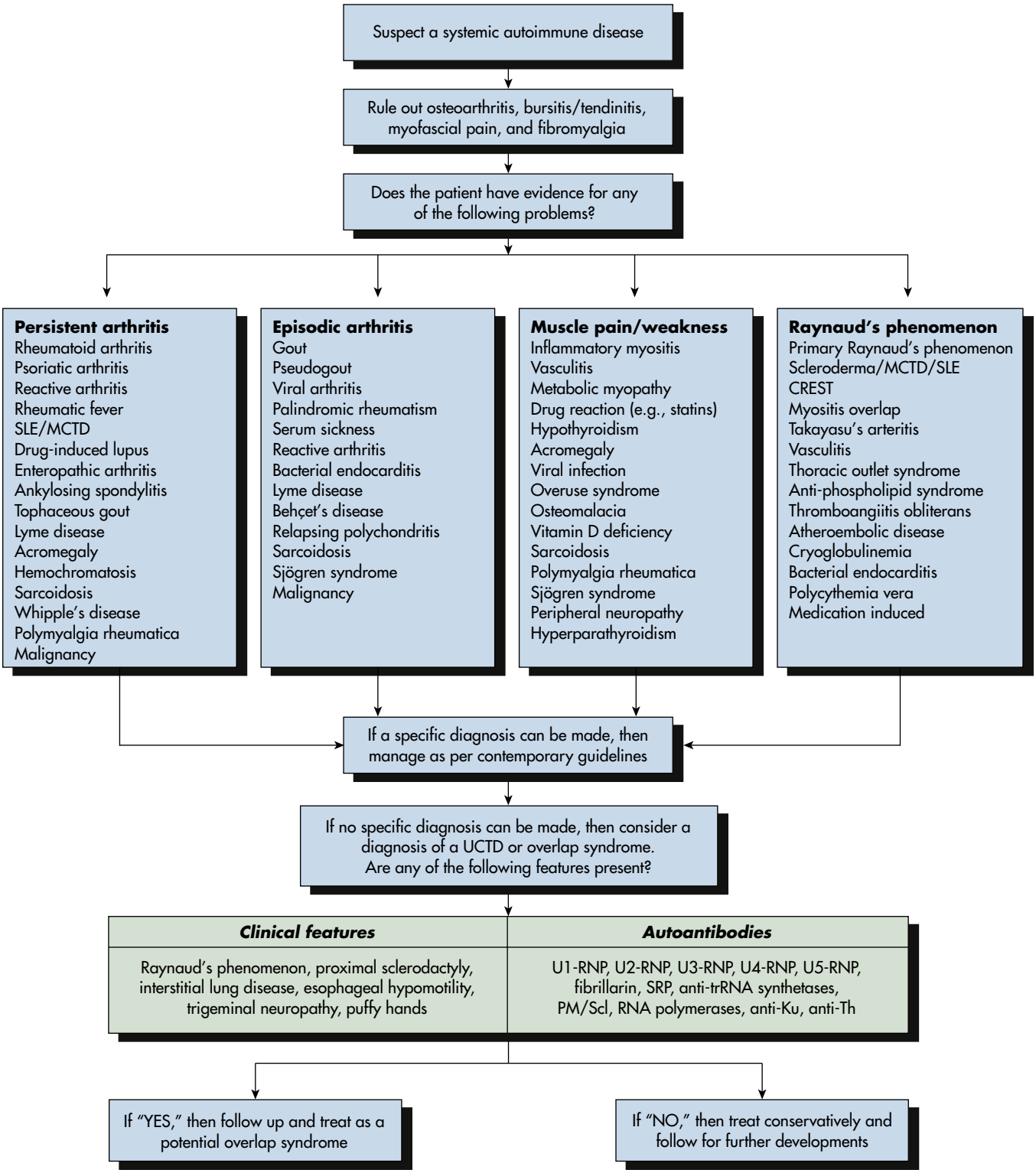


FIG. 53 Algorithm for evaluating patients with undifferentiated connective tissue disease *(UCTD).* *CREST,* Calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; *MCTD,* mixed connective tissue disease; *PM/Scl,* polymyositis/scleroderma; *SLE,* systemic lupus erythematosus; *SRP,* signal recognition particle. (From Firestein GS, Budd RC, Gabriel SE et al: *Kelley and Firestein's textbook of rheumatology,* ed 10, Philadelphia, 2017, Elsevier.)

CONNECTIVE TISSUE LABORATORY SCREENING TESTS

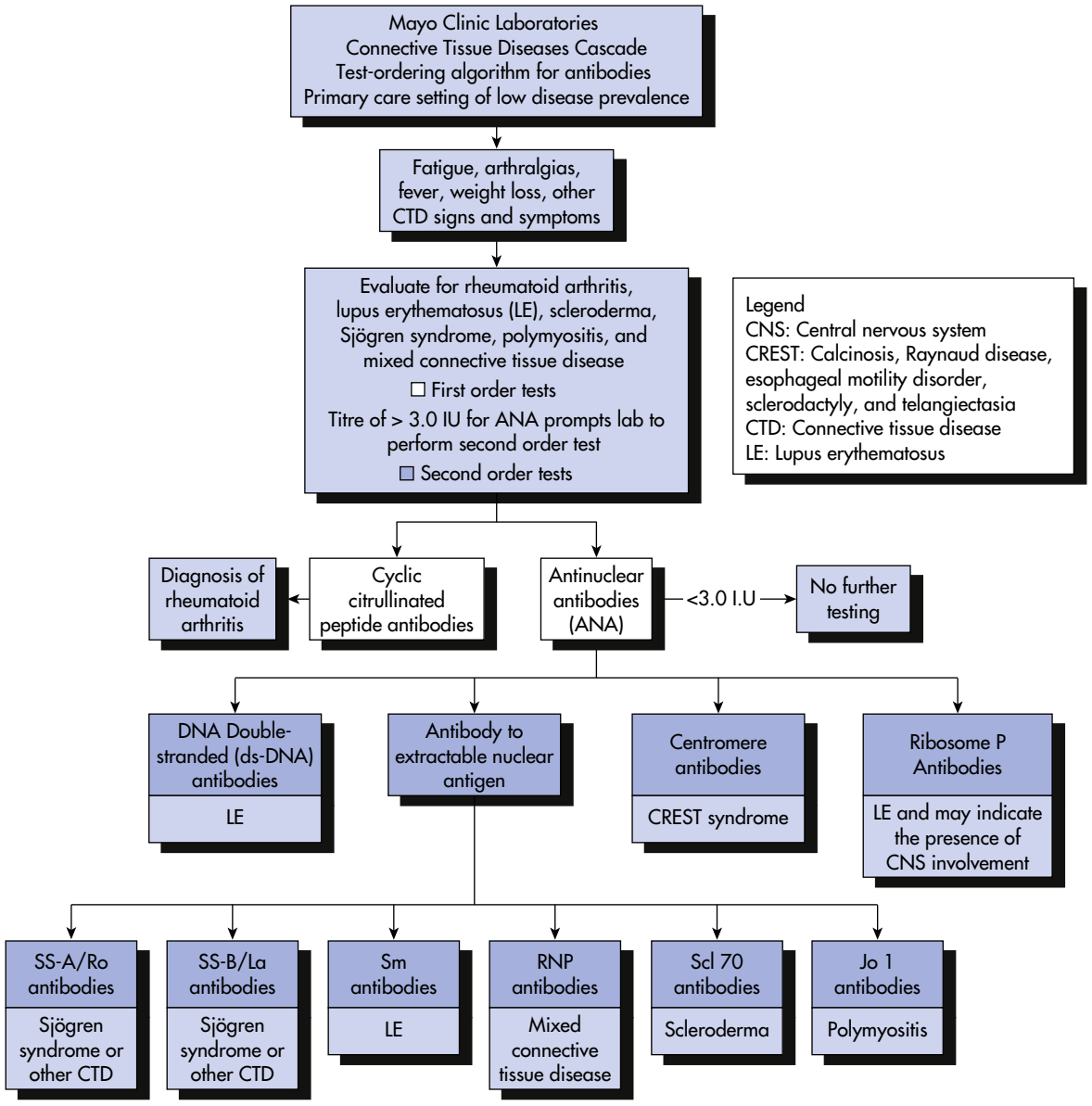


FIG. 54 Subacute cutaneous lupus erythematosus. Papulosquamous pattern. Lesions are confined to exposed areas on the upper half of the body. (From Habif TP: *Clinical dermatology, a color guide to diagnosis and therapy*, ed 6, Philadelphia, 2016, Elsevier.)

TABLE 14 Autoantibody Tests for Connective Tissue Diseases

Antibody	Clinical Significance
Antinuclear antibodies	Screening for SLE and PSS
Centromere antibodies	Marker for CREST
Histone antibodies	To exclude drug-induced LE
ENA: Sm antibodies	Marker for SLE
RNP antibodies	SLE, MCTD, scleroderma
SS-A (Ro)/SS-B (La) antibodies	SLE, Sjögren syndrome, SCLE, and others
Scl-70 antibodies	Marker for scleroderma
Jo-1 antibodies	Marker for polymyositis
Ku (Ki) antibodies	Polymyositis/scleroderma overlap, SLE
Phospholipid antibodies (lupus anticoagulant)	Marker for SLE subset with thrombosis: frequent aborters

CREST, Calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; *ENA,* extractable nuclear antigen; *LE,* lupus erythematosus; *MCTD,* mixed connective tissue disease; *PSS,* progressive systemic sclerosis; *RNP,* ribonucleoprotein; *SCLE,* subacute cutaneous lupus erythematosus; *SLE,* systemic lupus erythematosus.
From Habif TP: *Clinical dermatology, a color guide to diagnosis and therapy,* ed 6, Philadelphia, 2016, Elsevier.

ICD-10CM # Varies with specific diagnosis

TABLE 15 Diagnostic Significance of Immunologic Findings in Serum and Skin Biopsies in Connective Tissue Diseases

Disease	Biopsy Findings: Direct Immunofluorescence	Serum Findings	Relevance
Systemic LE	LE band (granular immune deposits, IgG, and/or IgM) IgA, C3 at DEJ in lesional and/or normal skin (over 90% in sun-exposed skin)	ANA elevated titers (about 95%-99%); nDNA antibodies about 50%-75%; DNP antibodies <50%; Sm antibodies in about 20%; RNP antibodies in about 5%-30%; SS-A antibodies in about 30%-40%; SS-B antibodies in about 1%-15%; phospholipid antibodies in about 30%-50%; PCNA antibodies in about 2%-10%; Ku(Ki) antibodies in about 10%	DIF, ANA, and ENA usually diagnostic; nDNA and Sm antibodies are diagnostic markers
Discoid LE	LE band, mostly IgG and C in lesion ONLY	Essentially negative; ANA titers usually in normal range	LE band highly characteristic
Subacute, cutaneous LE	LE band in lesion	ANA positive in 70%; SS-A (Ro) antibodies positive in more than 60%	DIF and anti–SS-A (Ro) highly characteristic
Neonatal LE	LE band in lesion (about 50%)	ANA positive in 30%; antibodies to SS-A (Ro) in 100%; antibodies to SS-B (La) in about 60%	DIF and anti–SS-A (Ro) highly characteristic
Drug-induced LE	LE band in lesion (rare)	ANA positive in more than 90%; histone positive about 90%; other antibodies to nDNA and ENA negative	DIF and histone antibodies in absence of other nuclear antibodies highly characteristic
Mixed connective tissue disease	Nuclear IgG or LE band in normal and/or lesional epidermis	Speckled ANA antibodies in more than 95% and RNP antibodies in more than 90%	Serology and/or DIF of nuclei diagnostic for MCTD, SLE, or PSS
Sjögren syndrome	Negative	ANA positive in about 55%; antibodies to SS-A (Ro) in 43%-88%; SS-B (La) in 14%-60%; RF positive	Positive serum results support diagnosis
Progressive systemic sclerosis (scleroderma)	Nucleolar IgG in epidermis in few cases; most negative	ANA (about 85%) speckled or nucleolar; centromere antibody in CREST (70%-90%); Scl-70 antibodies in diffuse sclerosis (45%) and in acrosclerosis (15%-20%)	DIF limited value; centromere antibodies are diagnostic marker in CREST; Scl-70 antibodies are diagnostic marker in scleroderma
Polymyositis/dermatomyositis	Negative	ANA usually positive (more than 80%); Jo-1 antibodies in 30% PM, 10% DM; SS-A (Ro) antibodies in 55% PM/scleroderma overlap; Ku (Ki) antibodies in 10% PM/scleroderma overlap	Limited value, but positive serum results support diagnosis
Rheumatoid arthritis	Negative	ANA usually negative or low titer; RF positive in about 90%; RNA positive in about 70%-90% and 95% of RF-negative cases	Positive serum results support diagnosis

ANA, Antinuclear antibodies; *CREST,* calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; *DEJ,* dermal-epidermal junction; *DIF,* direct immunofluorescence; *DM,* dermatomyositis; *DNP,* deoxyribonucleoprotein protein; *ENA,* extractable nuclear antigen; *LE,* lupus erythematosus; *MCTD,* mixed connective tissue disease; *PCNA,* proliferating cell nuclear antigen; *PM,* polymyositis; *PSS,* progressive systemic sclerosis; *RF,* rheumatoid factor; *RNA,* antibodies to rheumatoid arthritis-associated nuclear antigen; *RNP,* ribonucleoprotein; *SLE,* systemic lupus erythematosus.

From Habif TP: *Clinical dermatology, a color guide to diagnosis and therapy* ed 6, Philadelphia, 2016, Elsevier.

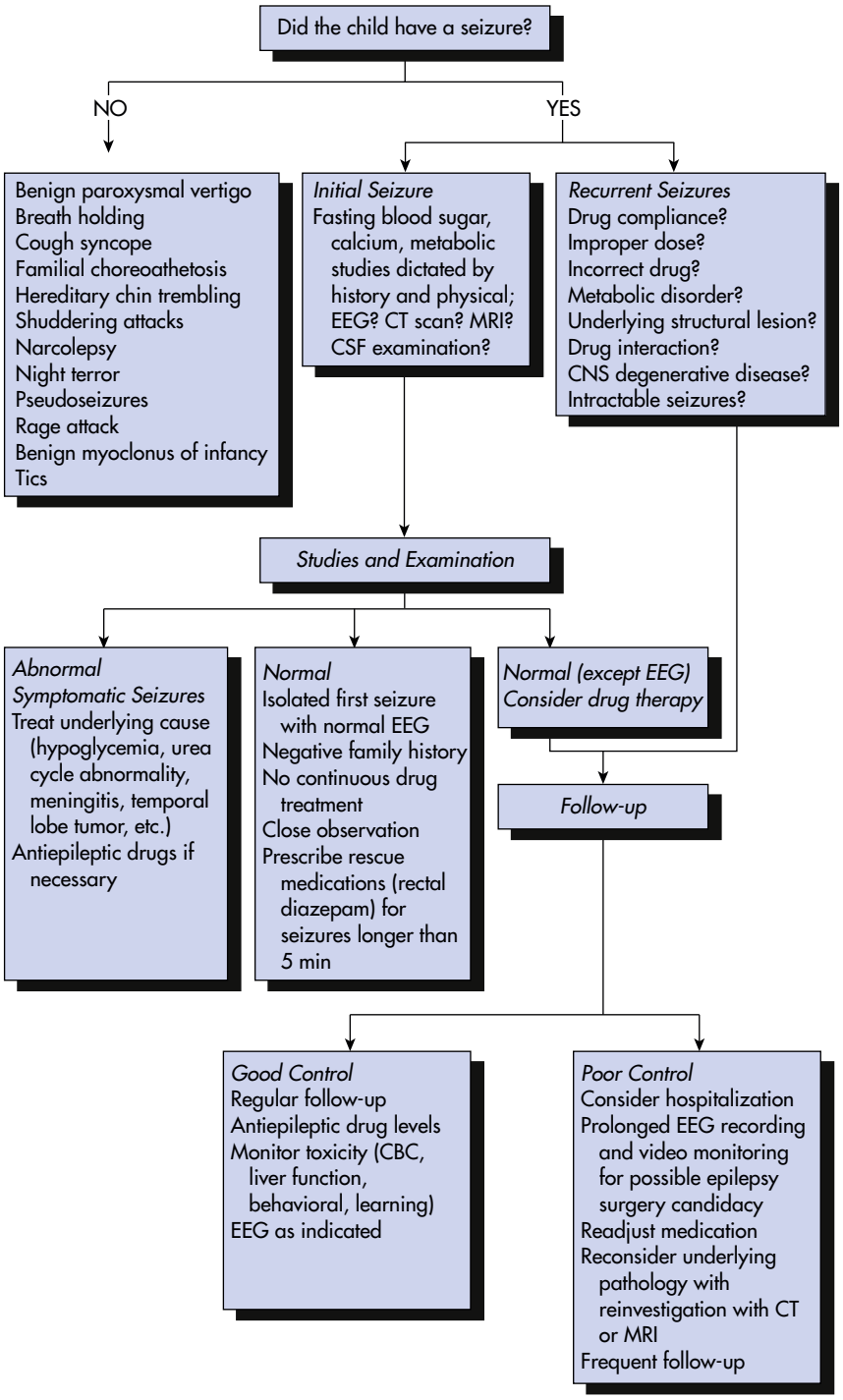


FIG. E55 Approach to the child with a suspected convulsive disorder. *CBC,* Complete blood count; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *CT,* computed tomography, *EEG,* electroencephalogram; *MRI,* magnetic resonance imaging. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 20, Philadelphia, 2016, Saunders.)

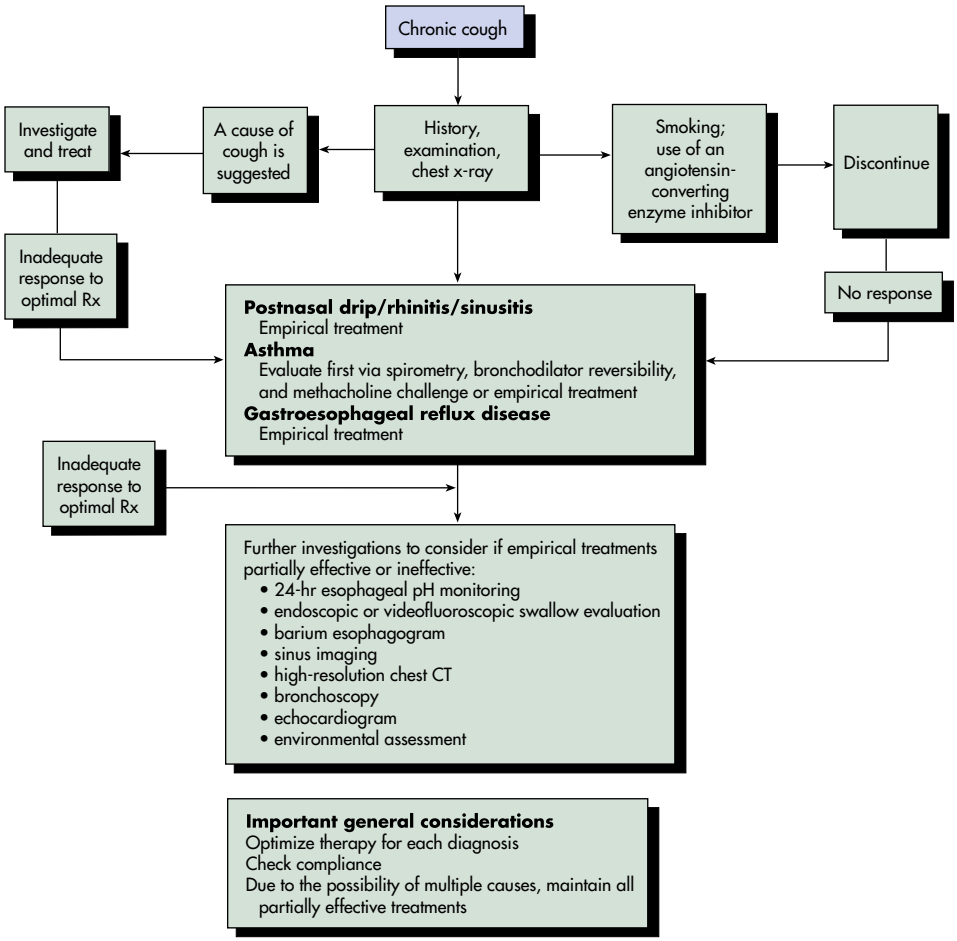


FIG. 56 Algorithm for the management of chronic cough lasting >8 weeks. *CT,* Computed tomography; *Rx,* prescription. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

TABLE 16 Testing Characteristics of Diagnostic Protocol for Evaluation of Chronic Cough

Tests	Diagnosis	Positive Predictive Value (%)	Negative Predictive Value (%)
Sinus radiograph	Sinusitis	57-81	95-100
Methacholine inhalation challenge	Asthma	60-82	100
Modified barium esophagography	GERD, esophageal stricture	38-63	63-93
Esophageal pH*	GERD	89-100	>100
Bronchoscopy	Endobronchial mass/lesion	50-89	100

*24-Hour esophageal pH monitoring. *GERD,* Gastroesophageal reflux disease.
From Goldman L, Schafer AI [eds]: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

TABLE 17 Definitions and Common Causes of Cough in Adults and Children

Age Group	Type of Cough	Duration	Common Causes
Adults	Acute	<3 weeks	Common cold Exacerbation of lung disease (e.g., asthma) Acute environmental exposure Acute cardiopulmonary disease
	Subacute	3-8 weeks	Postinfectious cough Pertussis infection Exacerbation of underlying lung disease (e.g., asthma, COPD, bronchiectasis)
	Chronic	>8 weeks	ACEI therapy Smoking/chronic bronchitis Underlying lung disease UACS Asthma NAEB GERD
Children	Acute	<4 weeks	Common cold Exacerbation of underlying lung disease Acute cardiopulmonary disease
	Chronic	>4 weeks	Asthma Protracted bacterial bronchitis Tracheobronchomalacia Chronic rhinosinusitis Recurrent aspiration GERD Underlying lung disease (e.g., bronchiectasis) Pulmonary infections (e.g., pertussis)

ACEI, Angiotensin-converting enzyme inhibitor; *COPD,* chronic obstructive pulmonary disease; *GERD,* gastroesophageal reflux disease; *NAEB,* nonasthmatic eosinophilic bronchitis; *UACS,* upper airway cough syndrome.
From Adkinson NF et al: *Middleton's allergy principles and practice*, ed 8, Philadelphia, 2014, Saunders.

BOX 13 Pitfalls and Errors in the Diagnosis and Management of Chronic Cough in Adults

General Considerations
- Failing to consider that UACS, asthma/NAEB, and/or GERD are likely when the chest radiograph is normal or near-normal in appearance and the patient is a nonsmoker and is not taking an ACEI
- Failing to include UACS, asthma/NAEB, and/or GERD in the differential diagnosis because clinical or radiographic evidence confirms the presence of an "obvious" cause of the patient's cough (e.g., solitary pulmonary nodule, idiopathic pulmonary fibrosis)
- Not recognizing multiple simultaneous causes of cough
- Failing to continue treatment trials long enough to accurately assess their effectiveness
- Prematurely diagnosing "unexplained" cough before a bronchoscopy has been performed to assess for unsuspected airway disease
- Mistakenly diagnosing "unexplained" cough or diagnosing psychogenic cough before a complete evaluation for cough has been performed

Upper Airway Cough Syndrome
- Failing to realize that UACS can manifest as cough productive of phlegm
- Not recognizing that chronic cough can be the sole manifestation of UACS in at least 20% of the cases
- Failing to consider sinusitis as a cause of UACS
- Mistakenly assuming that selective histamine H_1 receptor antagonists are effective in treating nonallergic causes of UACS
- Missing allergic rhinitis because symptoms are perennial
- Missing aspirin-exacerbated disease in a patient with nasal polyps

Asthma/NAEB
- Failing to realize that these conditions can sometimes manifest as cough productive of phlegm
- Not recognizing that chronic cough can sometimes be the sole manifestation of asthma (so-called cough variant asthma)
- Mistakenly assuming that a positive result on bronchial challenge (e.g., methacholine challenge) is diagnostic of asthma when it is merely *consistent* with the diagnosis
- Failing to consider NAEB when the bronchial challenge test yields a negative result
- Not recognizing that inhaled medications can sometimes provoke cough
- Failing to consider occupational and environmental causes of asthma/NAEB

Gastroesophageal Reflux Disease
- Failing to realize that GERD can sometimes manifest as cough productive of phlegm
- Not recognizing that chronic cough can sometimes be the sole manifestation of GERD (so-called silent GERD)
- Mistakenly concluding that cough cannot be due to GERD simply because cough does not resolve with relief of gastrointestinal symptoms
- Not considering nonacid reflux and mistakenly assuming that cough will always respond to acid suppression
- Failing to assess the adequacy of GERD treatment by using 24-hour monitoring of esophageal pH and impedance
- Not recognizing coexisting diseases (e.g., sleep apnea) and medications (e.g., nitrates, progesterone) that may impair the effectiveness of GERD treatment
- Failing to recognize that surgery may help when intensive medical therapy has failed

Angiotensin-Converting Enzyme Inhibitor
- Failing to consider ACEI therapy as a cause of chronic cough simply because the cough predated initiation of the ACEI
- Mistakenly concluding that ACEI therapy is not the cause of chronic cough because the cough did not resolve within 1 to 3 weeks of stopping the ACEI

ACEI, Angiotensin-converting enzyme inhibitor; *GERD,* gastroesophageal reflux disease; *NAEB,* nonasthmatic eosinophilic bronchitis; *UACS,* upper airway cough syndrome.
From Adkinson NF et al: *Middleton's allergy principles and practice*, ed 8, Philadelphia, 2014, Saunders.

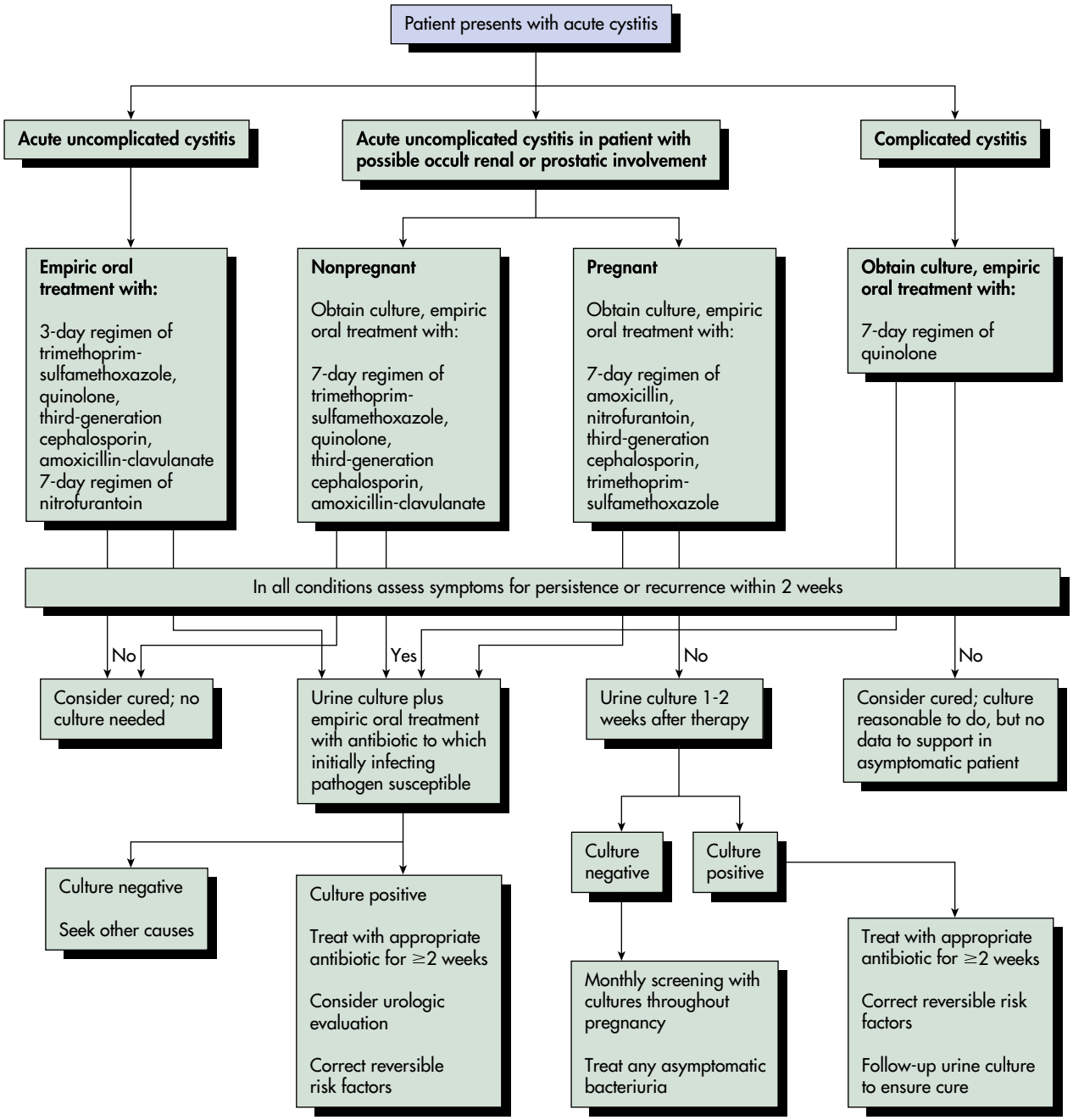


FIG. 57 Algorithm for management of acute cystitis based on severity and complicating factors. (From Johnson R et al: *Comprehensive clinical nephrology*, ed 5, Philadelphia, 2015, Saunders.)

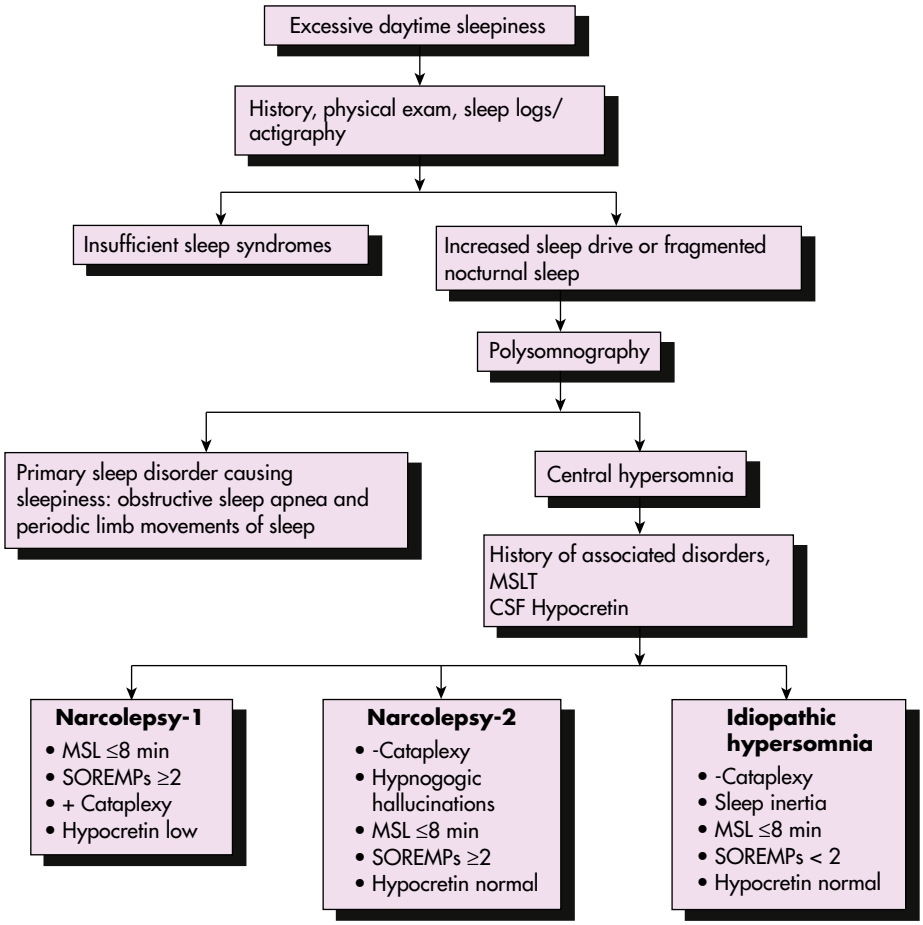


FIG. 58 Algorithm showing the approach in evaluation of children with excessive daytime sleepiness. *CSF,* Cerebrospinal fluid; *MSL,* mean sleep latency; *MSLT,* Multiple Sleep Latency Test; *SOREMPs,* sleep-onset rapid eye movement. (From Swaiman KF: *Swaiman's pediatric neurology, principles and practice,* ed 6, Philadelphia, 2017, Elsevier.)

TABLE 18 Etiologies of Excessive Sleepiness in Children

Insufficient Sleep	Increased Sleep Drive	Fragmented Nocturnal Sleep
Paradoxical insomnia	Central hypersomnias	Primary sleep disorder
Behaviorally induced insufficient sleep syndrome	Traumatic brain injury	GERD
Behavioral insomnia of children—sleep onset association type	Medications	Allergy, eczema
Behavioral insomnia of children—limit setting type	Infections	Asthma
Circadian rhythm sleep disorders	Metabolic disorders	Other medical disorders
Psychophysiological insomnia		Medications
Idiopathic insomnia		Illicit drugs, alcohol

GERD, Gastroesophageal reflux disease.
From Swaiman KF: *Swaiman's pediatric neurology, principles and practice,* ed 6, Philadelphia, 2017, Elsevier.

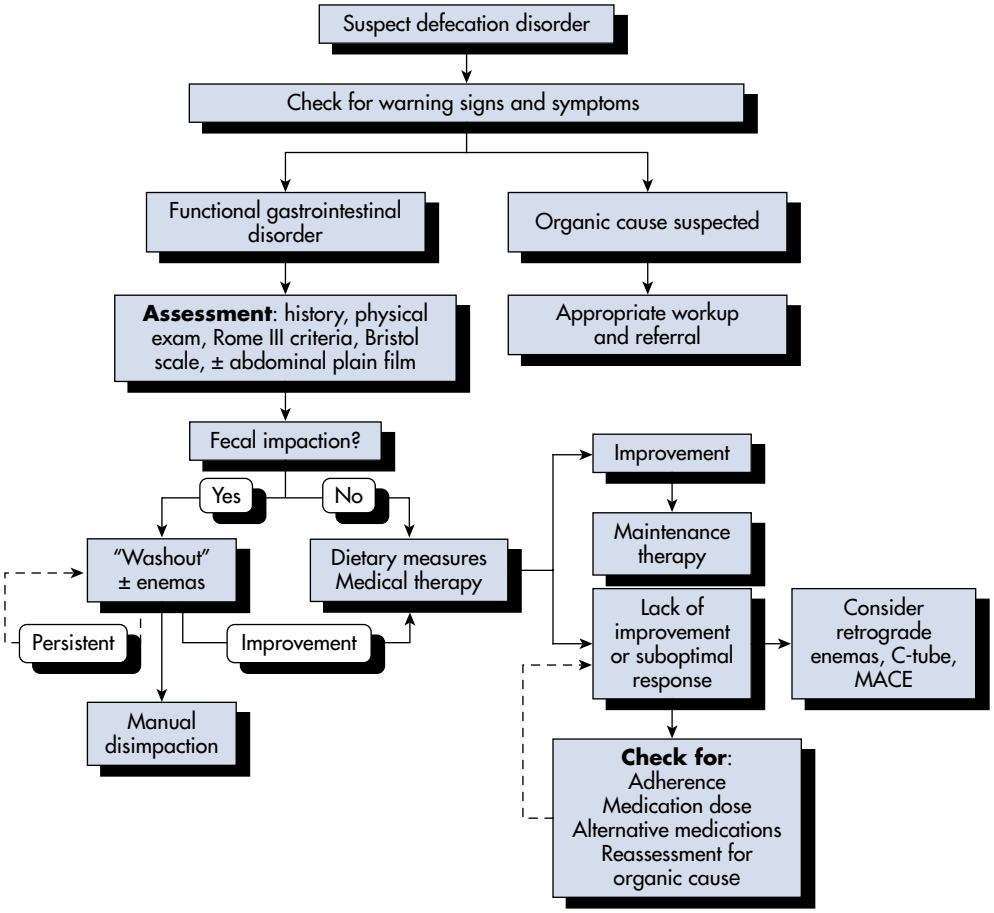


FIG. 59 Management algorithm for childhood defecation disorders seen in a pediatric urology practice. Lack of improvement or intractable constipation should be diagnosed based on worsening response, absence of response, or suboptimal response to adequate medical treatment for at least 3 months. *C-tube,* Cecostomy tube; *MACE,* Malone antegrade continence enema procedure. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

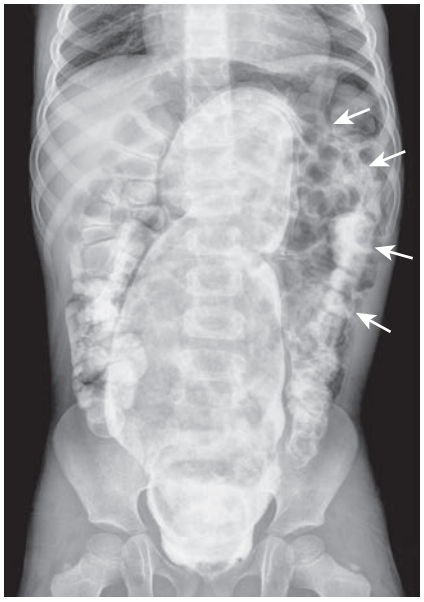


FIG. 60 Soluble contrast enema for evaluation of child with defecation problems since birth. Findings suggestive of Hirschsprung disease, including massively distended colon and rectum that can progress toward more normal-appearing large bowel *(arrows).* This child was subsequently assessed with a rectal biopsy to confirm the diagnosis. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

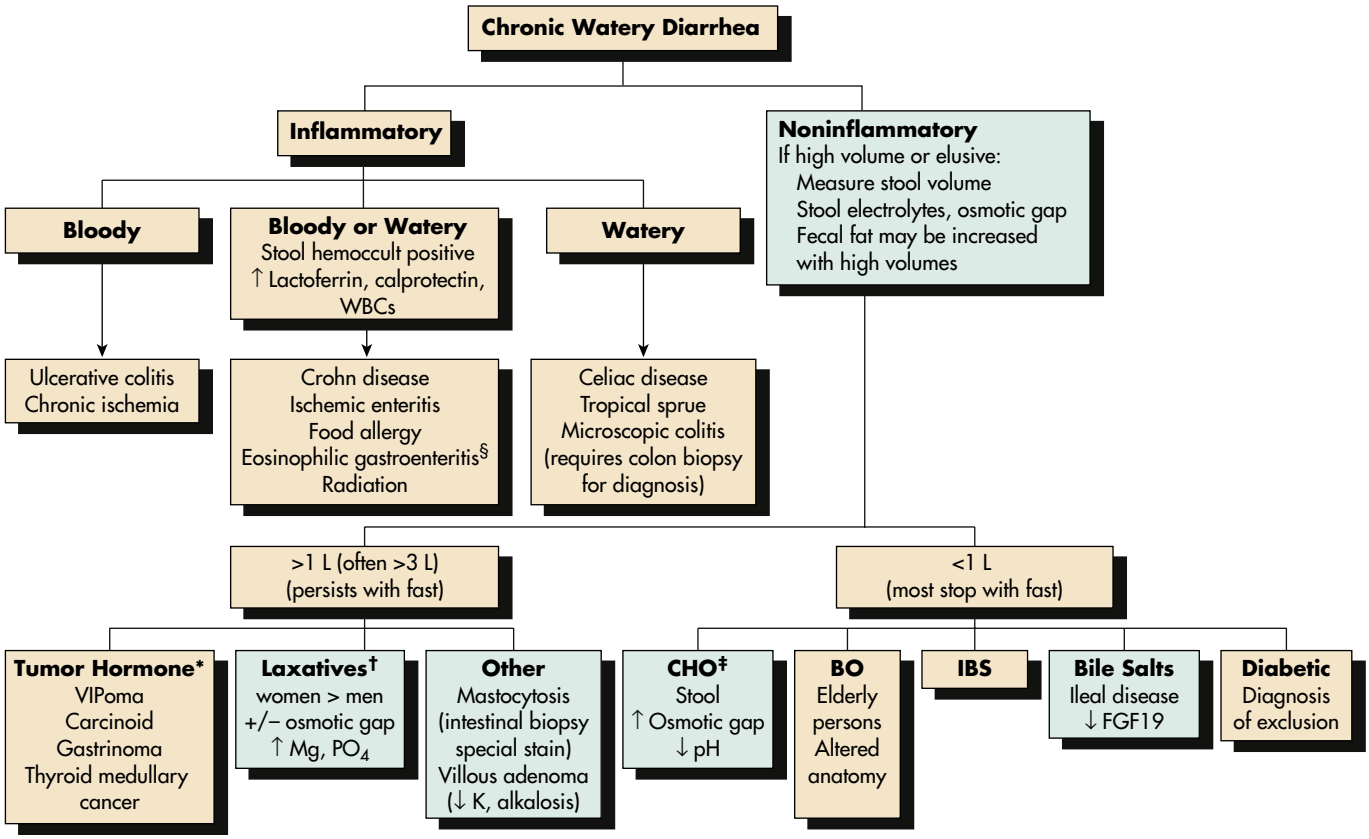


FIG. E61 Approach to the evaluation of watery diarrheas. Many diarrheas have more than one mechanism (e.g., osmotic, secretory, inflammatory). Other causes include medications, postsurgical (vagotomy, Nissan wrap, cholecystectomy), hyperthyroidism, and alcohol. *VIPoma: >3 L output daily "pancreatic cholera," elevated VIP level. Carcinoid: elevated urine 5-hydroxyindole acetic acid, positive OctreoScan. Gastrinoma (Zollinger-Ellison syndrome): elevated gastrin level, positive secretin stimulation test, diarrhea due to high volume of acid secretion. Thyroid medullary cancer: elevated calcitonin level. †May be high or low volume depending on dose ingested, may respond to fast. ‡Carbohydrate malabsorption (CHO) may be due to lactase deficiency, dietary fructose, sorbitol in diabetic candies or liquid medications. ‡Full-thickness biopsy may be needed for diagnosis. *BO,* Bacterial overgrowth; *FGF,* fibroblast growth factor; *IBS,* irritable bowel syndrome; *WBCs,* white blood cells. From Goldman L, Schafer AI: *Goldman Cecil medicine,* ed 25, Philadelphia, 2016, Saunders.

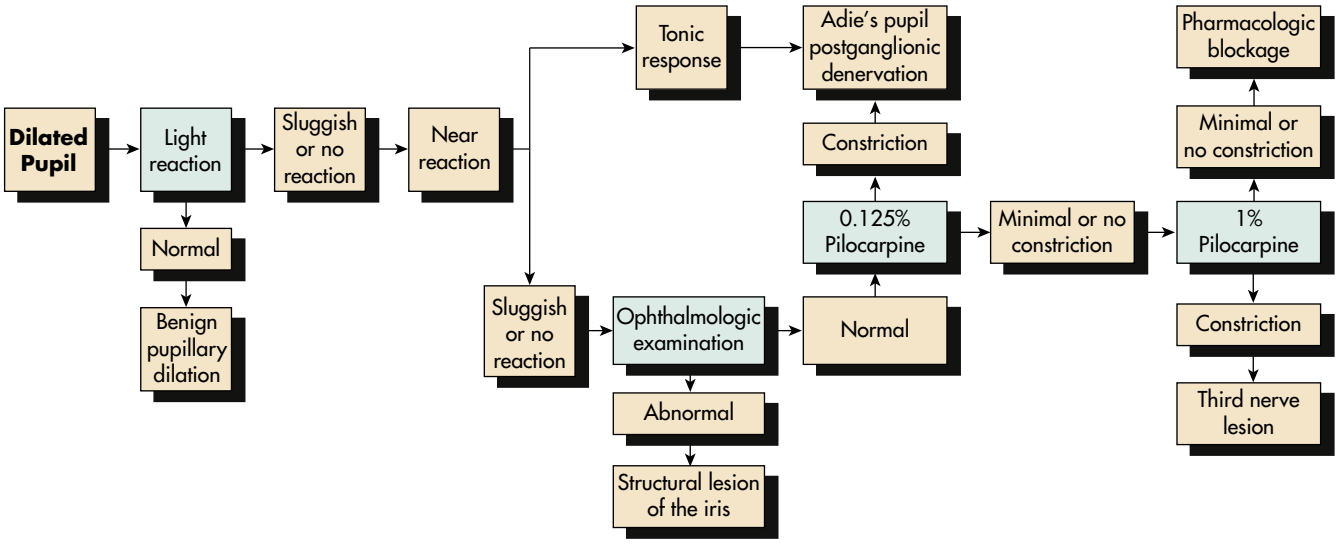


FIG. E62 Use of pilocarpine to help differentiate between different causes of a dilated pupil. (From Goldman L, Schafer AI: *Goldman Cecil medicine,* ed 25, Philadelphia, 2016, Saunders.)

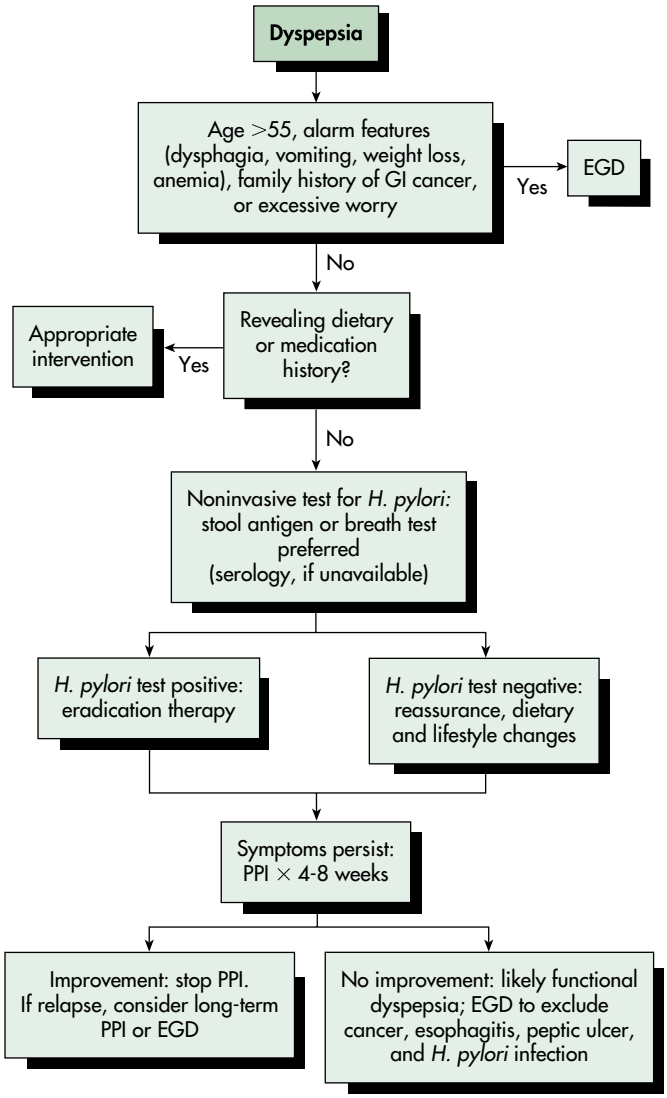


FIG. E63 Approach to the patient with dyspepsia. *EGD,* Esophagastroduodenoscopy; *GI,* gastrointestinal; *PPI,* proton pump inhibitor. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

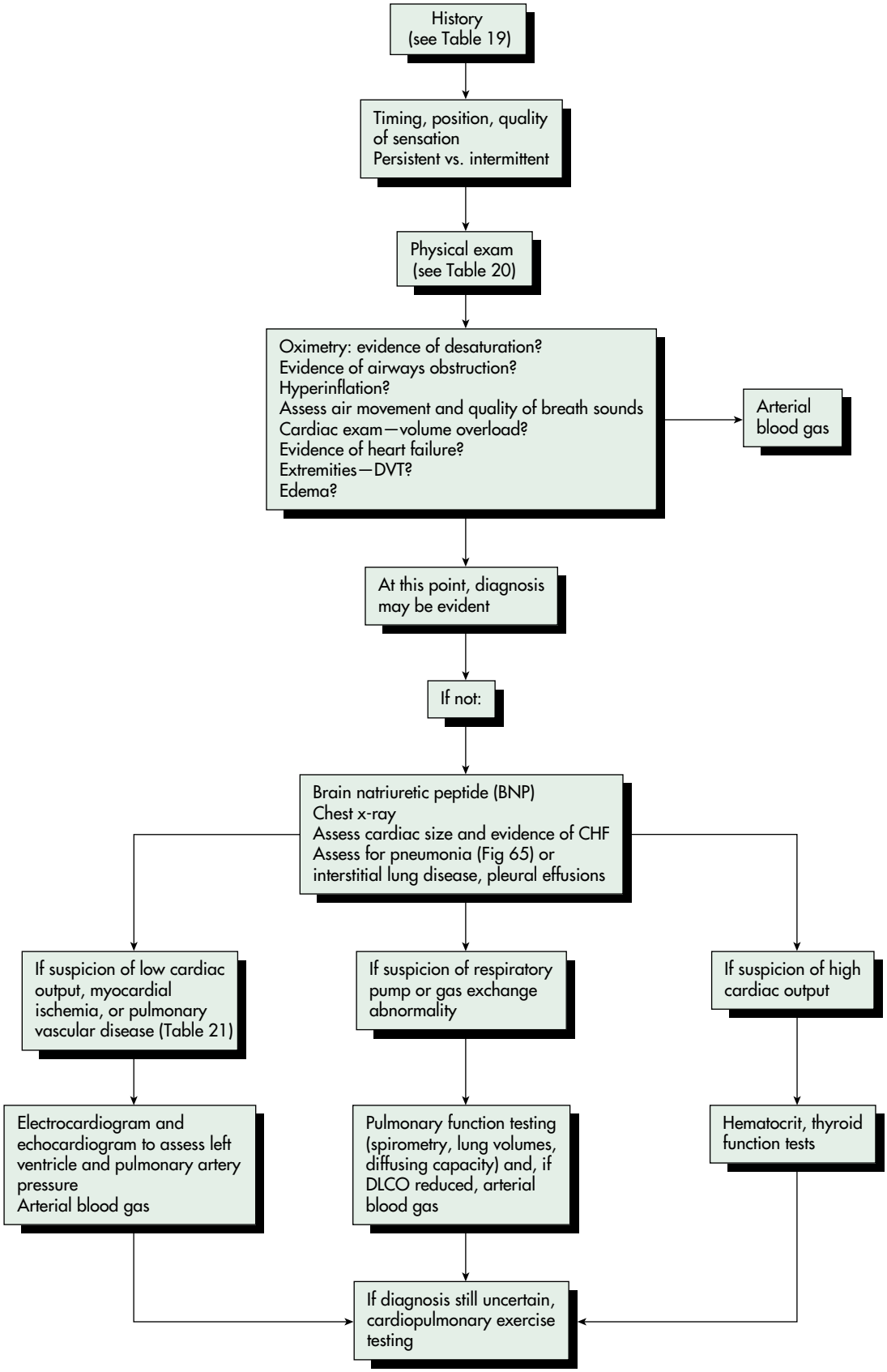


FIG. 64 Algorithm for the evaluation of the patient with dyspnea. The pace and completeness with which one approaches this framework depends on the intensity and acuity of the patient's symptoms. In a patient with severe, acute dyspnea, for example, an arterial blood gas measurement may be one of the first laboratory evaluations, whereas this measurement might not be obtained until much later in the workup in a patient with chronic breathlessness of unclear cause. A therapeutic trial of a medication, for example, a bronchodilator, may be instituted at any point if one is fairly confident of the diagnosis based on the data available at that time. *CHF,* Congestive heart failure; *DLCO,* diffusing capacity of the lung for carbon monoxide; *DVT,* deep venous thrombosis. (Modified from Schwartzstein RM, Feller-Kopman D: Approach to the patient with dyspnea. In Braunwald E, Goldman L [eds]: *Primary cardiology,* ed 2, Philadelphia, 2003, Saunders.)

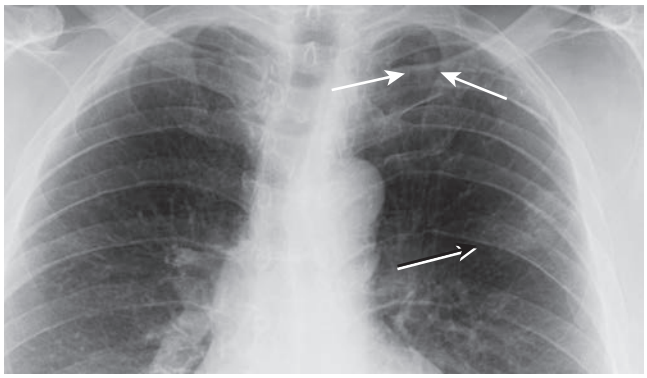


FIG. 65 Chest radiograph of a patient presenting with cough and fever. A faint area of opacification within the left midlung proved to be pneumonia *(black arrow)*. Additionally, a small left apical carcinoma was detected *(white arrows)*. Because of multiple overlying structures, including the first ribs and the clavicles, the pulmonary apices are a "danger" area in terms of risk of missed findings on chest radiographs. Close inspection of the apices is warranted on every chest radiograph. (From Soto JA, Lucey BC: *Emergency radiology: the requisites,* ed 2, Philadelphia, 2017, Elsevier.)

TABLE 19 Differential Diagnoses for Acute Dyspnea

Organ System	Critical Diagnoses	Emergent Diagnoses	Nonemergent Diagnoses
Pulmonary	Airway obstruction	Spontaneous pneumothorax	Pleural effusion
	Pulmonary embolus	Asthma	Neoplasm
	Noncardiogenic edema	Cor pulmonale	Pneumonia (CAP score ≤70)
	Anaphylaxis	Aspiration	COPD
	Ventilatory failure	Pneumonia (CAP score >70)	
Cardiac	Pulmonary edema	Pericarditis	Congenital heart disease
	Myocardial infarction		Valvular heart disease
	Cardiac tamponade		Cardiomyopathy
Primarily Associated with Normal or Increased Respiratory Effort			
Abdominal		Mechanical interference	Pregnancy
		Hypotension, sepsis from ruptured viscus, bowel obstruction, inflammatory or infectious process	Ascites obesity
Psychogenic			Hyperventilation syndrome
			Somatization disorder
			Panic attack
Metabolic or endocrine	Toxic ingestion	Renal failure	Fever
	DKA	Electrolyte abnormalities	Thyroid disease
		Metabolic acidosis	
Infectious	Epiglottitis	Pneumonia (CAP score >70)	Pneumonia (CAP score ≤70)
Traumatic	Tension pneumothorax	Simple pneumothorax, hemothorax	Rib fractures
	Cardiac tamponade	Diaphragmatic rupture	
	Flail chest		
Hematologic	Carbon monoxide poisoning	Anemia	
	Acute chest syndrome		
Primarily Associated with Decreased Respiratory Effort			
Neuromuscular	CVA, intracranial insult	Multiple sclerosis	ALS
	Organophosphate poisoning	Guillain-Barré syndrome	Polymyositis
		Tick paralysis	Porphyria

ALS, Amyotrophic lateral sclerosis; *CAP,* community-acquired pneumonia; *COPD,* chronic obstructive pulmonary disease; *CVA,* cerebrovascular accident; *DKA,* diabetic ketoacidosis.
From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.

TABLE 20 Pivotal Findings in Physical Examination

Sign	Physical Finding	Diagnoses to Consider
Vital signs	Tachypnea	Pneumonia, pneumothorax
	Hypopnea	Intracranial insult, drug or toxin ingestion
	Tachycardia	PE, traumatic chest injury
	Hypotension	Tension pneumothorax
	Fever	Pneumonia, PE
General appearance	Cachexia, weight loss	Malignancy, acquired immune disorder, mycobacterial infection
	Obesity	Hypoventilation, sleep apnea, PE
	Pregnancy	PE
	Barrel chest	COPD
	"Sniffing" position	Epiglottitis
	"Tripoding" position	COPD or asthma with severe distress
	Traumatic injury	Pneumothorax (simple, tension), rib fractures, flail chest, hemothorax, pulmonary contusion
Skin and nails	Tobacco stains or odor	COPD, malignancy, infection
	Clubbing	Chronic hypoxia, intracardiac shunts, or pulmonary vascular anomalies
	Pallid skin or conjunctivae	Anemia
	Muscle wasting	Neuromuscular disease
	Bruising	Chest wall: rib fractures, pneumothorax
		Diffuse: thrombocytopenia, chronic steroid use, anticoagulation
	Subcutaneous emphysema	Rib fractures, pneumothorax, tracheobronchial disruption
	Hives, rash	Allergic reaction, infection, tick-borne illness
Neck	Stridor	Upper airway edema or infection, foreign body, traumatic injury, anaphylaxis
	JVD	Tension pneumothorax, COPD or asthma exacerbation, fluid overload or CHF, PE
Lung examination	Wheezes	CHF, anaphylaxis
		Bronchospasm
	Rales	CHF, pneumonia, PE
	Unilateral decrease	Pneumothorax, pleural effusion, consolidation, rib fractures or contusion, pulmonary contusion
	Hemoptysis	Malignancy, infection, bleeding disorder, CHF
	Sputum production	Infection (viral, bacterial)
	Friction rub	Pleurisy
	Abnormal respiratory pattern (e.g., Cheyne-Stokes)	Intracranial insult
Chest examination	Crepitance or pain on palpation	Rib or sternal fractures
	Subcutaneous emphysema	Pneumothorax, tracheobronchial rupture
	Thoracoabdominal desynchrony	Diaphragmatic injury with herniation; cervical spinal cord trauma
	Flail segment	Flail chest, pulmonary contusion
Cardiac examination	Murmur	PE
	S_3 or S_4 gallop	PE
	S_2 accentuation	PE
	Muffled heart sounds	Cardiac tamponade
Extremities	Calf tenderness, Homans sign	PE
	Edema	CHF
Neurologic examination	Focal deficits (motor, sensory, cognitive)	Stroke, intracranial hemorrhage causing central abnormal respiratory drive; if long-standing, risk of aspiration pneumonia
	Symmetrical deficits	Neuromuscular disease
	Diffuse weakness	Metabolic or electrolyte abnormality (hypocalcemia, hypomagnesemia, hypophosphatemia), anemia
	Hyporeflexia	Hypermagnesemia
	Ascending weakness	Guillain-Barré syndrome

CHF, Congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *JVD,* jugular venous distention; *PE,* pulmonary embolism.
From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.

TABLE 21 Diagnostic Table: Patterns of Diseases Often Resulting in Dyspnea

Disease	History (Dyspnea)	Associated Symptoms	Signs and Physical Findings	Tests
Pulmonary embolism	• HPI: abrupt onset, pleuritic pain, immobility (travel, recent surgery) • PMH: malignancy, DVT, PE, hypercoagulability, oral contraception, obesity	Diaphoresis, exertional dyspnea	Tachycardia, tachypnea, low-grade fever	• Pulse oximetry, ABG (A-a gradient), D-dimer • ECG (dysrhythmia, right-sided heart strain) • CXR (Westermark sign, Hampton hump), spiral CT, MRV • Pulmonary angiogram • Ultrasound positive for DVT
Pneumonia	Fever, productive cough, chest pain	Anorexia, chills, nausea, vomiting, exertional dyspnea, cough	Fever, tachycardia, tachypnea, rales, or decreased breath sounds	CXR, CBC, sputum and blood cultures
Bacterial	SH: tobacco use			Pulse oximetry Waveform capnography if altered mental status, ABG if capnography unavailable and acid-base derangement or hypercarbia suspected
Viral	Exposure (e.g., influenza, varicella)			
Opportunistic	Immune disorder, chemotherapy			
Fungal or parasitic	Exposure (e.g., birds), indolent onset	Episodic fever, nonproductive cough		
Pneumothorax	Abrupt onset: trauma, chest pain, thin males more likely to have spontaneous pneumothorax	Localized chest pain	Decreased breath sounds, subcutaneous emphysema, chest wall wounds or instability	• CXR: pneumothorax, rib fractures, hemothorax • Ultrasound: pneumothorax, pleural effusion
Simple				Ultrasound positive for pneumothorax
Tension	Decompensation of simple pneumothorax	Diaphoresis	JVD, tracheal deviation, muffled heart sounds, cardiovascular collapse	Clinical diagnosis: requires immediate decompression. May verify via bedside ultrasound
COPD or asthma	Tobacco use, medication noncompliance, URI symptoms, sudden weather change	Air hunger, diaphoresis	• Retractions, accessory muscle use, tripoding, cyanosis • "Shark fin" capnograph	• CXR: rule out infiltrate, pneumothorax, atelectasis (mucus plug) • Ultrasound: distinguish from heart failure
	PMH: environmental allergies FH: asthma			Waveform capnography
Malignancy	Weight loss, tobacco, or other occupational exposure	Dysphagia	Hemoptysis	CXR, chest CT: mass, hilar adenopathy, focal atelectasis
Fluid overload	• Gradual onset, dietary indiscretion or medication noncompliance, chest pain • PMH: recent MI, diabetes, CHF	Worsening orthopnea, PND	JVD, peripheral edema, S_3 or S_4 gallop, new cardiac dysrhythmia, hepatojugular reflux	• CXR and/or ultrasound: pleural effusion, interstitial edema, Kerley B lines, cardiomegaly • ECG: ischemia, dysrhythmia • NT-proBNP
Anaphylaxis	Abrupt onset, exposure to allergen	Dysphagia	Oral swelling, stridor, wheezing, hives	

A-a, Alveolar-arterial; *ABG,* arterial blood gas; *CBC,* complete blood count; *CHF,* congestive heart failure; *CT,* computed tomography; *CXR,* chest x-ray examination; *DVT,* deep vein thrombosis; *ECG,* electrocardiogram; *FH,* family history; *HPI,* history of present illness; *JVD,* jugular venous distention; *MI,* myocardial infarction; *MRV,* magnetic resonance venography; *NT-proBNP,* amino-terminal pro–B-type natriuretic peptide; *PE,* pulmonary embolism; *PMH,* past medical history; *PND,* paroxysmal nocturnal dyspnea; *SH,* social history; *URI,* upper respiratory infection.

From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Saunders.

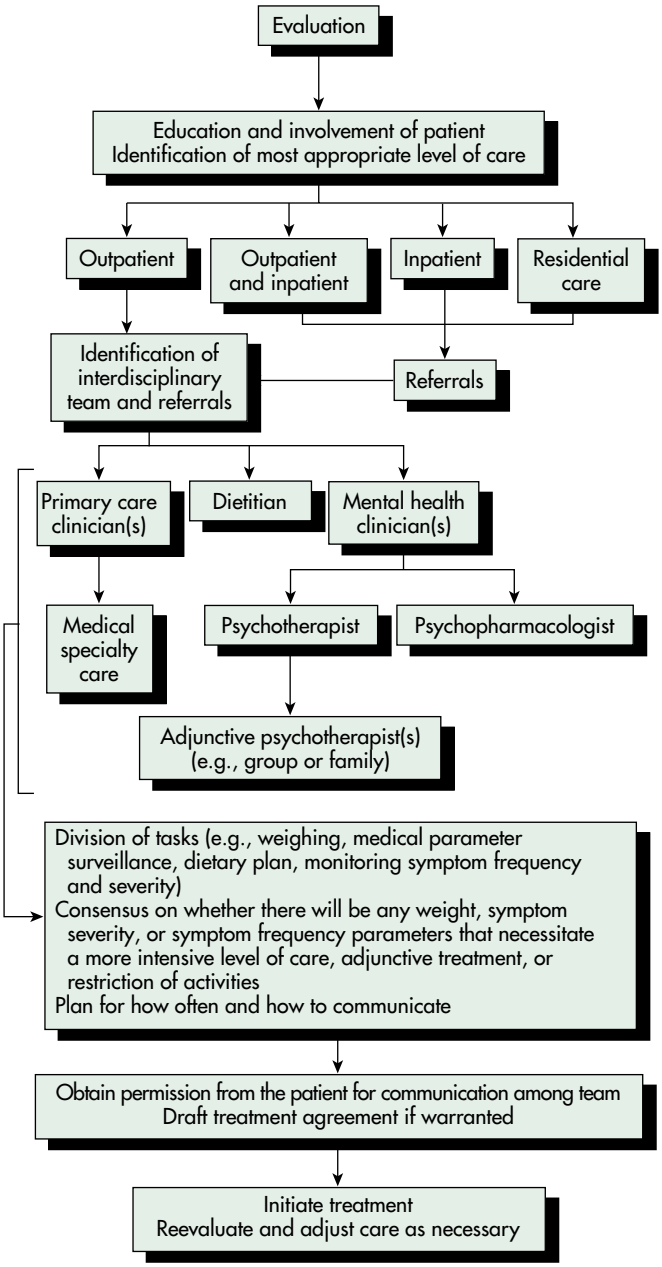
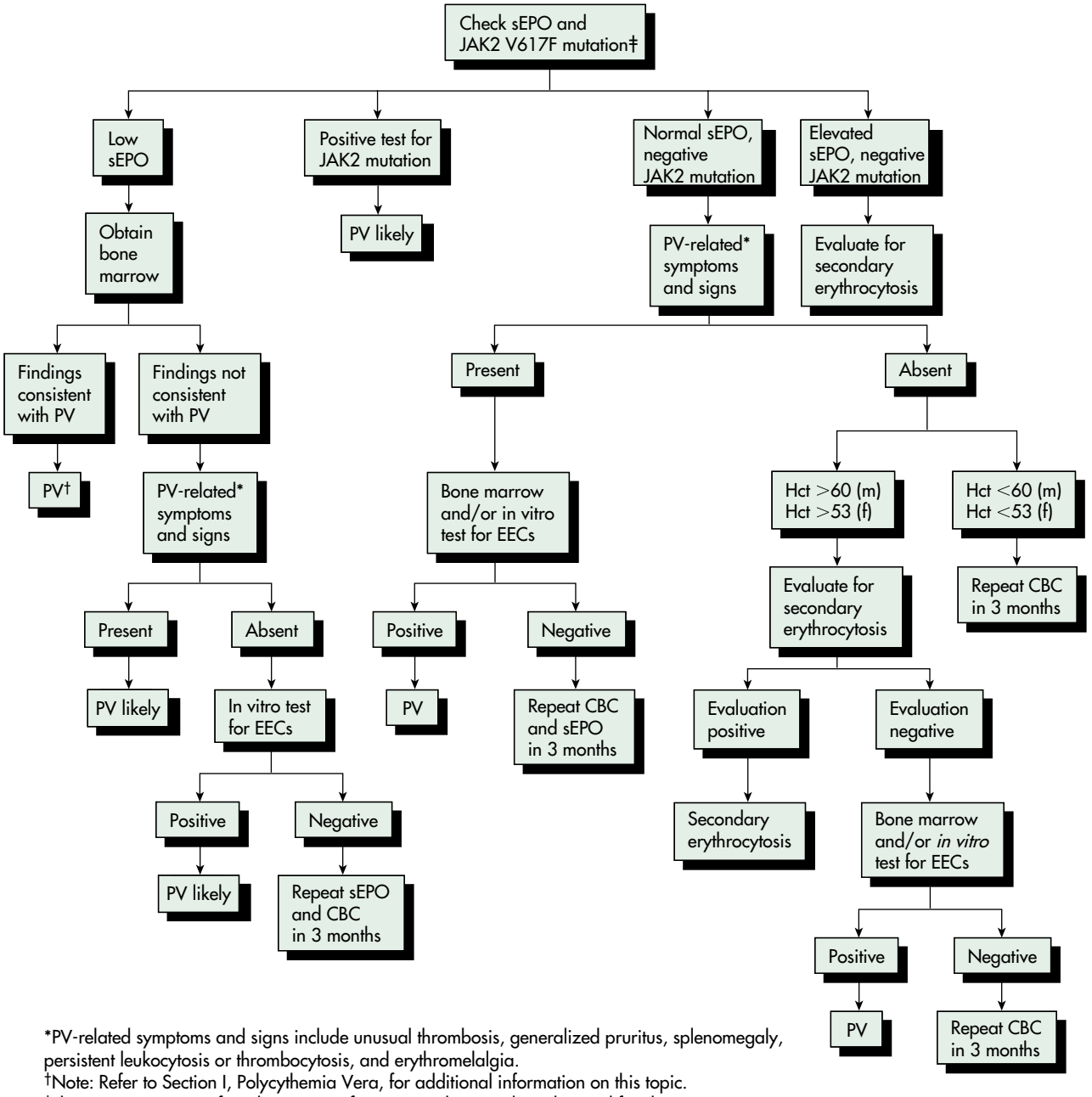


FIG. 66 Algorithm for team management of adult patients with an eating disorder. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

ICD-10CM #
D75.1 Secondary polycythemia
D75.0 Familial erythrocytosis
D45 Polycythemia vera
P61.1 Polycythemia neonatorum



*PV-related symptoms and signs include unusual thrombosis, generalized pruritus, splenomegaly, persistent leukocytosis or thrombocytosis, and erythromelalgia.
†Note: Refer to Section I, Polycythemia Vera, for additional information on this topic.
‡The JAK2 mutation is found in >95% of patients with PV and can be used for diagnostic purposes.

FIG. 67 A diagnostic approach to acquired erythrocytosis. *CBC,* Complete blood cell count; *EEC,* endogenous (spontaneous) erythroid colonies; *f,* female; *Hct,* hematocrit; *m,* male; *PV,* polycythemia vera; *sEPO,* serum erythropoietin level. (Modified from Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

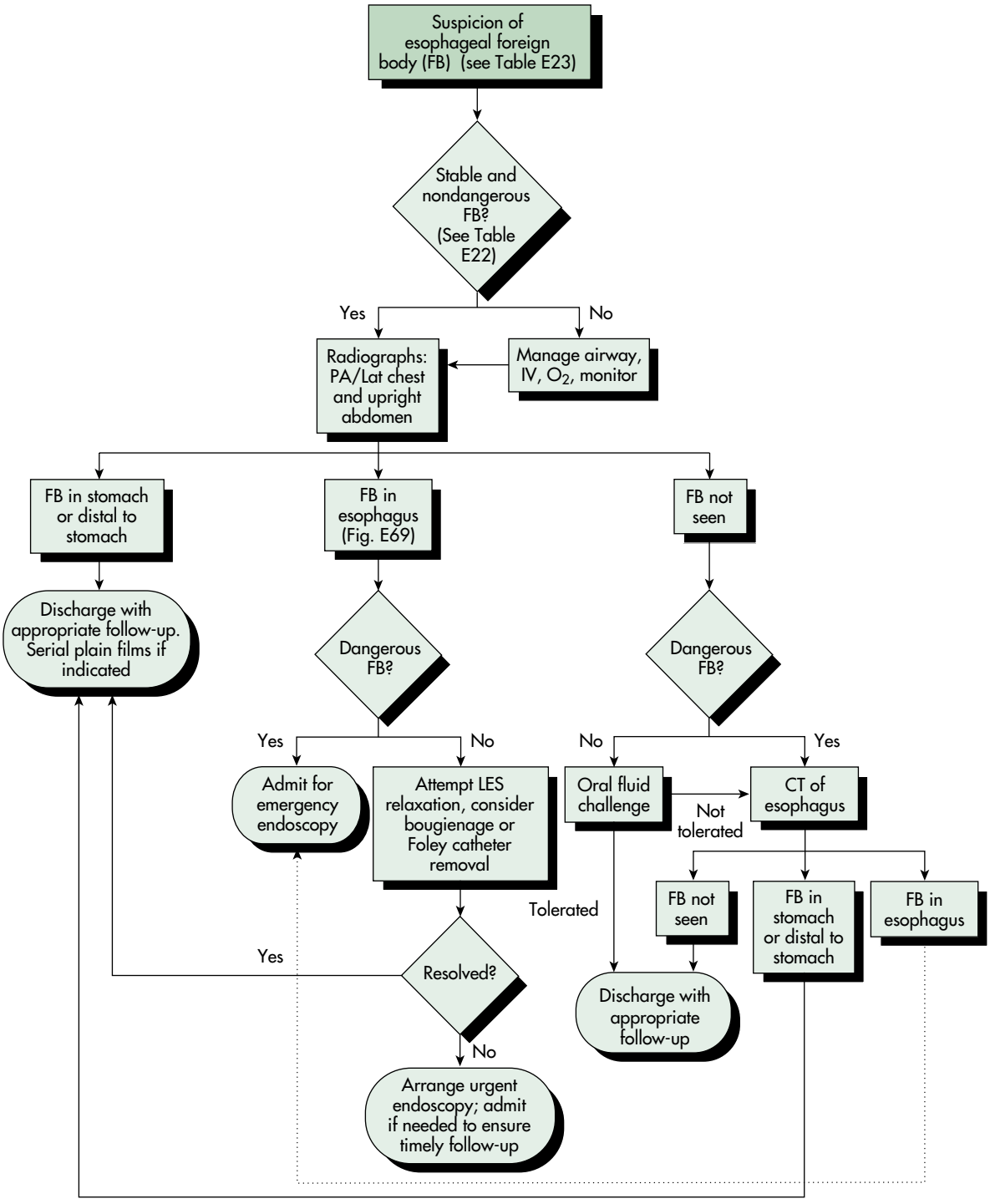


FIG. E68 Diagnostic algorithm for the evaluation of a suspected esophageal foreign body. *CT,* Computed tomography; *IV,* intravenous line; *Lat,* lateral; *LES,* lower esophageal sphincter; *PA,* posteroanterior. (From Adams JG et al: *Emergency medicine: clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

FIG. E69 A lateral radiograph of the neck in a child demonstrates an ingested radio-opaque foreign body lodged within the esophagus posterior to the trachea. (From Soto JA, Lucey BC: *Emergency radiology: the requisites,* ed 2, Philadelphia, 2017, Elsevier.)

TABLE E22 Most Threatening and Most Common Esophageal Foreign Bodies

Most Threatening

In Children

- Disc batteries
- Bones
- Needles
- Other sharp objects

In Adults

- Disc batteries
- Bones
- Packets of illicit drugs
- Toothpicks

Most Common

In Children

- Coins
- Marbles
- Buttons
- Toys

In Adults

- Food boluses
- Bones
- Dentures
- Oral piercings

From Adams JG et al: *Emergency medicine: clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

TABLE E23 Differential Diagnosis for Esophageal Foreign Bodies

In Children

- Perforation
- Abrasion or laceration
- Airway foreign body
- Esophagitis
- Epiglottitis
- Globus hystericus
- Reactive airways disease

In Adults

- Perforation
- Abrasion or laceration
- Spasm
- Esophagitis
- Diverticulum
- Malignancy
- Myocardial infarction
- Globus hystericus

From Adams JG et al: *Emergency medicine: clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

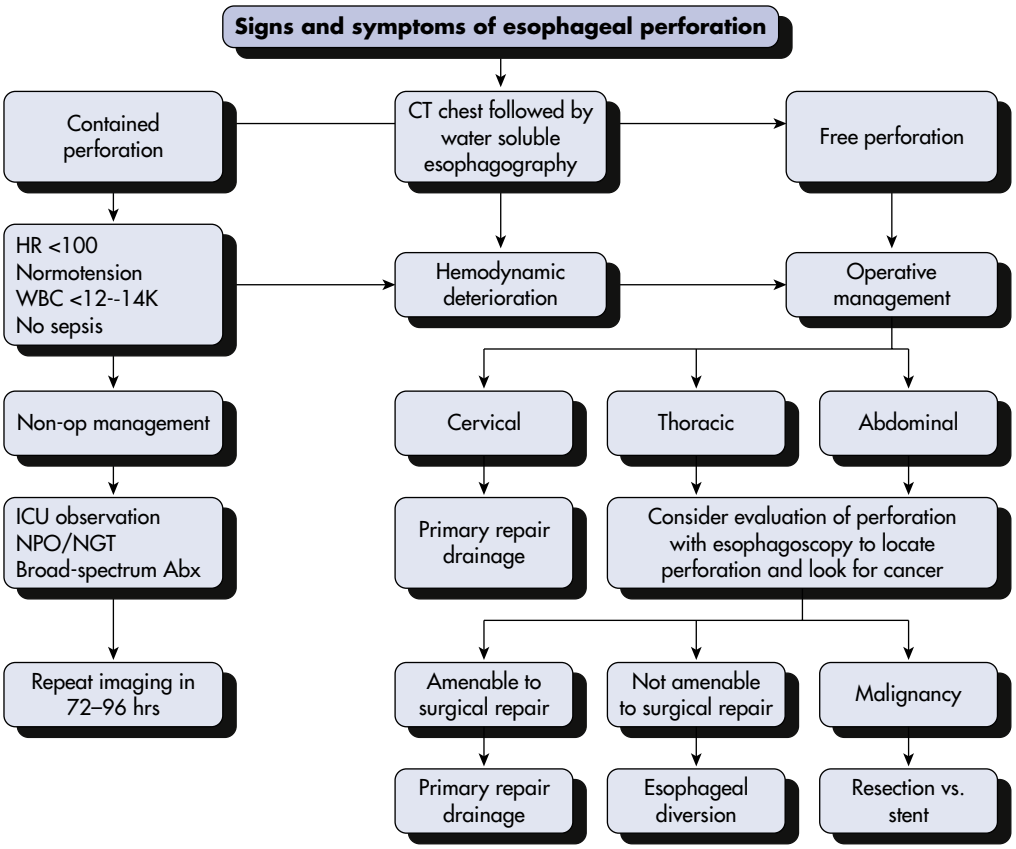


FIG. 70 Algorithm of management of esophageal perforation. *Abx,* Antibiotics; *CT,* computed tomography; *HR,* heart rate; *ICU,* intensive care unit; *NGT,* nasogastric tube; *NPO,* nothing by mouth *(nil per os)*; *WBC,* white blood cell count. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

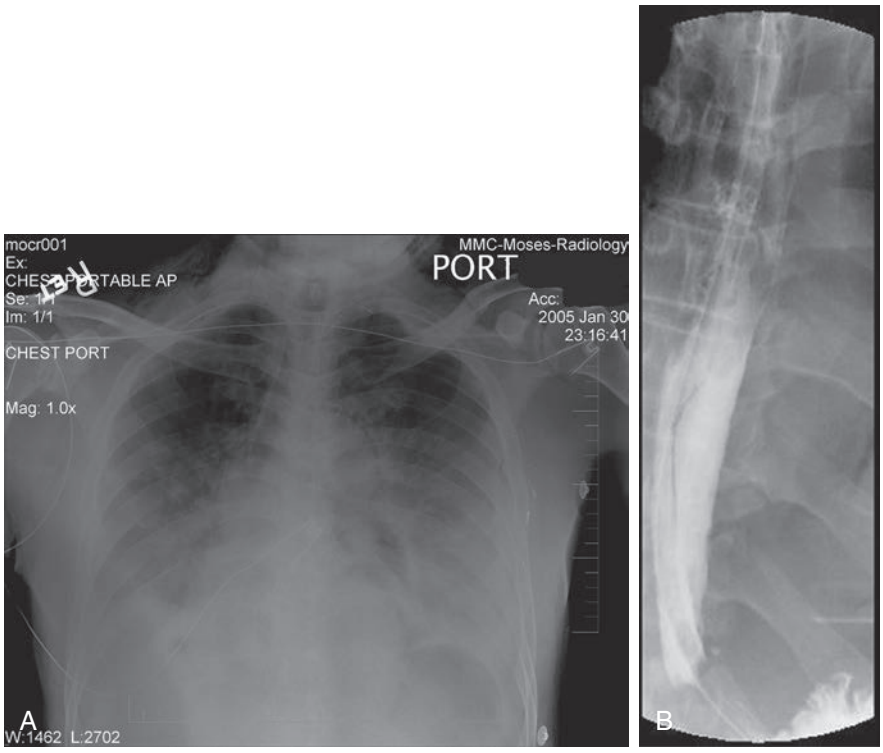


FIG. 71 A and **B,** Chest radiographs demonstrating pneumomediastinum and bilateral pleural effusions. (From Adams JG, Barton ED et al [eds]: *Emergency medicine: clinical essentials,* ed 2, Philadelphia, 2013, Saunders.)

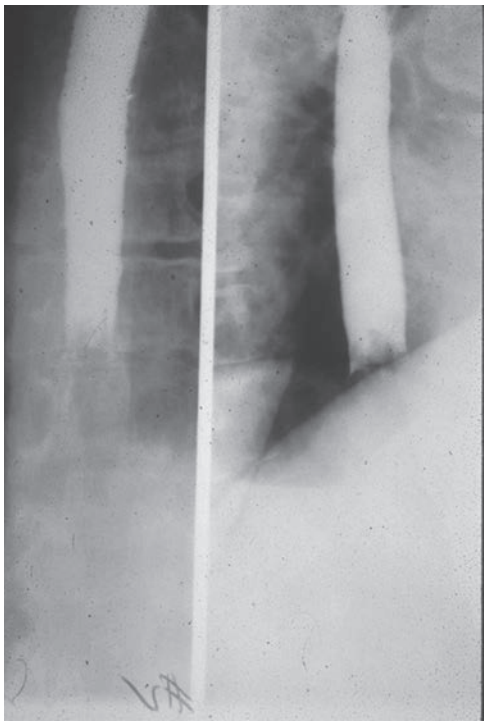


FIG. 72 Fluoroscopic swallow study showing extravasation of contrast agent (as seen from the left side of the film). (From Adams JG et al [eds]: *Emergency medicine: clinical essentials,* ed 2, Philadelphia, 2013, Saunders.)

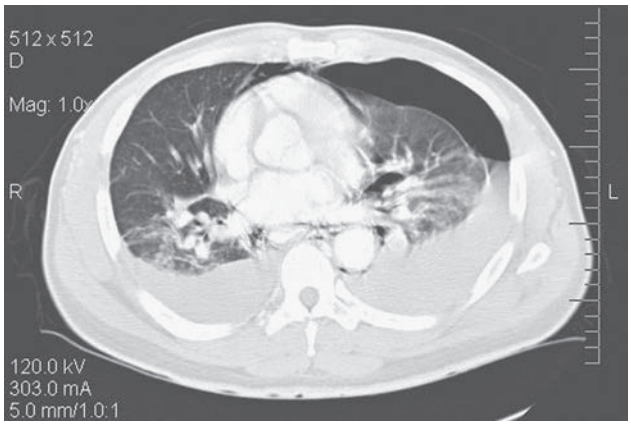


FIG. 73 Esophageal computed tomography scan demonstrating typical fluid collections in the setting of perforation. (From Adams JG et al [eds]: *Emergency medicine: clinical essentials,* ed 2, Philadelphia, 2013, Saunders.)

FEVER AND INFECTION IN HIGH-RISK HEMATOLOGY PATIENT WITHOUT OBVIOUS SOURCE

ICD-10CM # R50.81 Fever presenting with conditions classified elsewhere
R50.2 Drug-induced fever
R50.9 Fever, unspecified

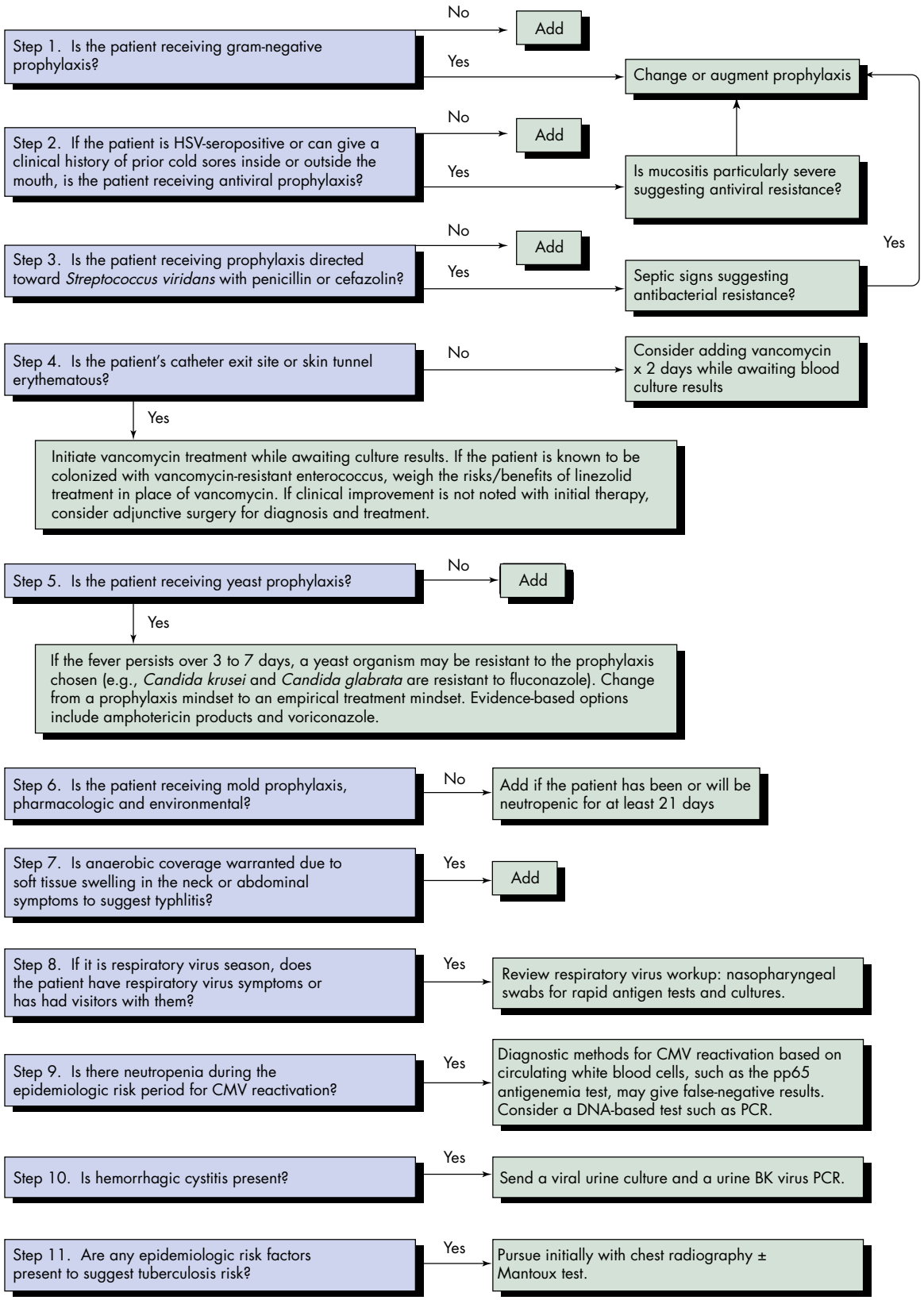
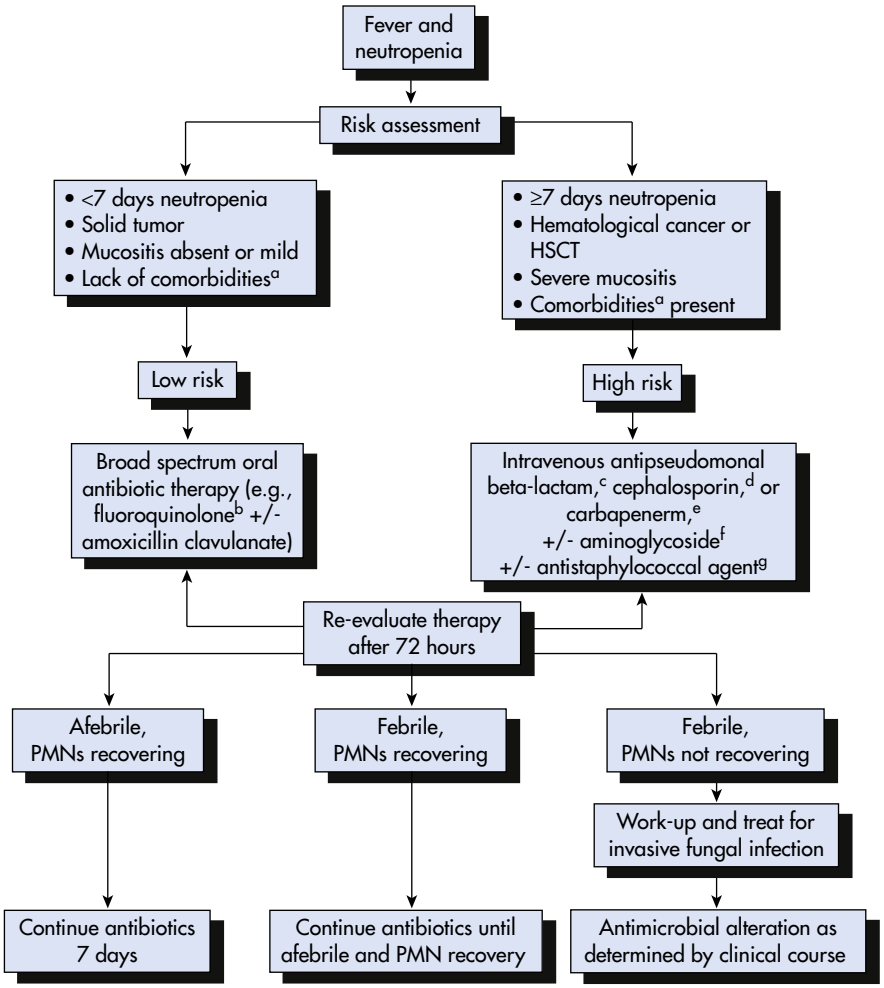


FIG. E74 Systematic approach to causes of fever and infection in the high-risk hematology patient without an obvious source. This algorithm can be used for hematopoietic cell transplantation patients before engraftment or for patients who are receiving conventional, high-dose therapy for hematologic malignancies and are profoundly neutropenic. *CMV,* Cytomegalovirus; *HSV,* herpes simplex virus; *PCR,* polymerase chain reaction. (From Hoffmann R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

ICD-10CM # R50.9 Fever, unspecified
D70.3 Neutropenia due to infection



a Hypotension, altered mental status, neurologic changes, respiratory failure, abdominal pain, hemorrhage, cardiac compromise or new arrhythmia, catheter tunnel infection, extensive cellulitis, acute renal or liver failure
b Institution sensitivity dependent, ciprofloxacin, levofloxacin, moxifloxacin
c Drug selection and dosing institution-specific: piperacillin tazobactam, ticarcillin/clavulanate
d Drug selection and dosing institution-specific: ceftazidime
e imipenem, cefepime/cilastatin, meropenem, doripenem
f Gentamicin, tobramycin, or amikacin
g Drug selection and institution institution-specific: vancomycin, linezolid, daptomycin, ceftaroline

FIG. 75 Approach to patient with fever and neutropenia. *HSCT*, Hematopoietic stem cell transplant; *PMN*, polymorphonuclear neutrophil. (From Hoffman R: *Hematology: basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.)

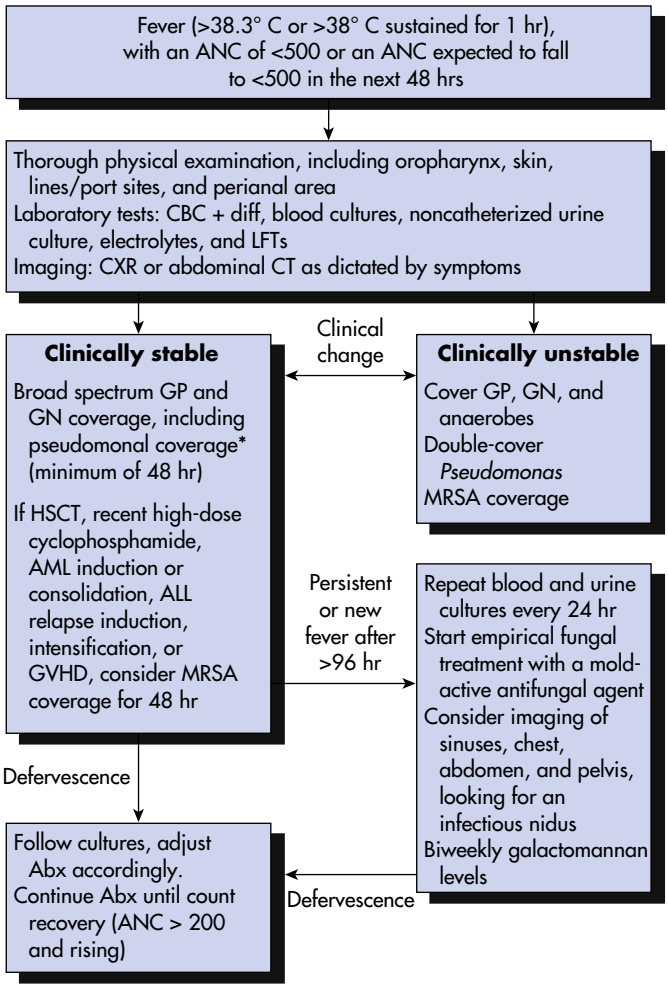


FIG. E76 Guideline for management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem cell transplantation. *Abx,* Antibiotics; *ALL,* acute lymphocytic leukemia; *AML,* acute myeloid leukemia; *ANC,* absolute neutrophil count; *CBC,* complete blood cell count; *CT,* computed tomography; *CXR,* chest x-ray; *diff,* differential; *GN,* gram-negative; *GP,* gram-positive; *GVHD,* graft-versus-host disease; *HSCT,* hematopoietic stem cell transplantation; *LFTs,* liver function tests; *MRSA,* methicillin-resistant *Staphylococcus aureus.* (Data from Lehrnbecher T et al: Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. *J Clin Oncol.* 2012;30:4427-4438; Freifeld AG et al: Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2011;52:e56-e93. In The Johns Hopkins Hospital, Hughes HK, Kalh LK: *The Harriet Lane handbook,* ed 21, St Louis, 2018, Elsevier.)

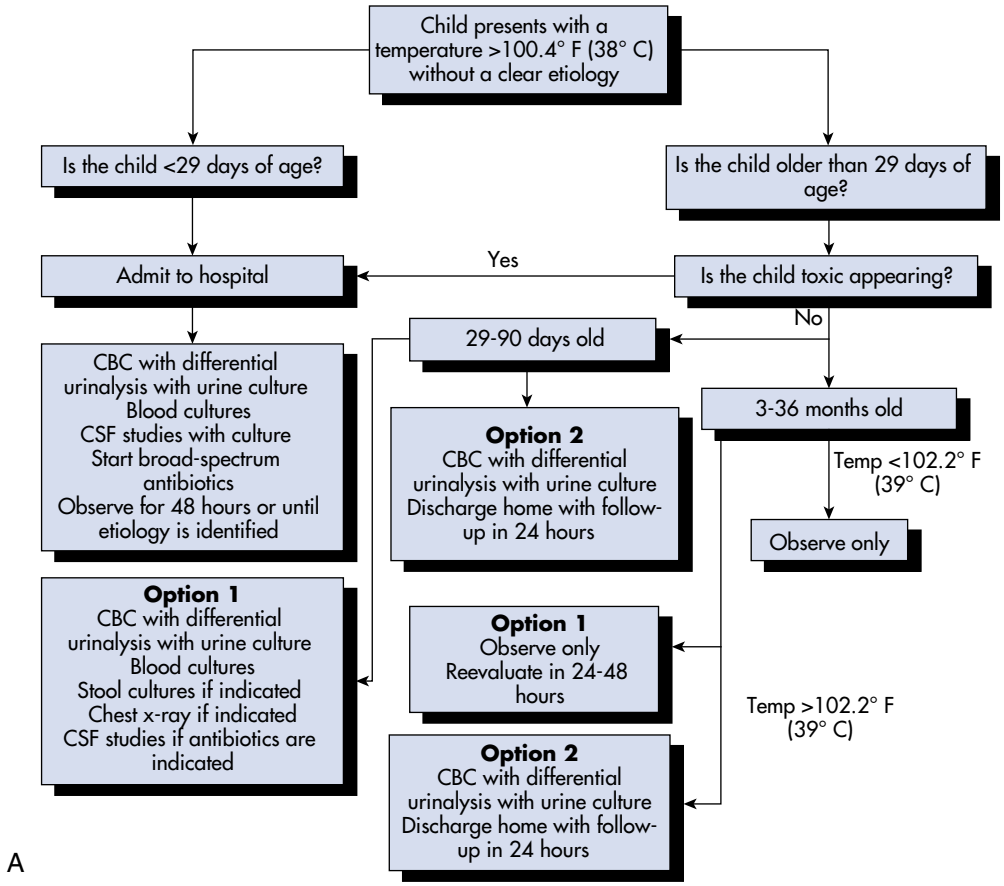


FIG. 77 A, Algorithm for the treatment of a child aged 0 to 36 months with a fever higher than 100.4° F (38° C) with no etiology for the fever. **B,** Continued considerations for the treatment of a child aged 0 to 36 months with a fever higher than 100.4° F (38° C) with no etiology for the fever. *ANC,* Absolute neutrophil count; *CBC,* complete blood count; *CSF,* cerebrospinal fluid; *IM,* intramuscular; *WBCs,* white blood cells. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

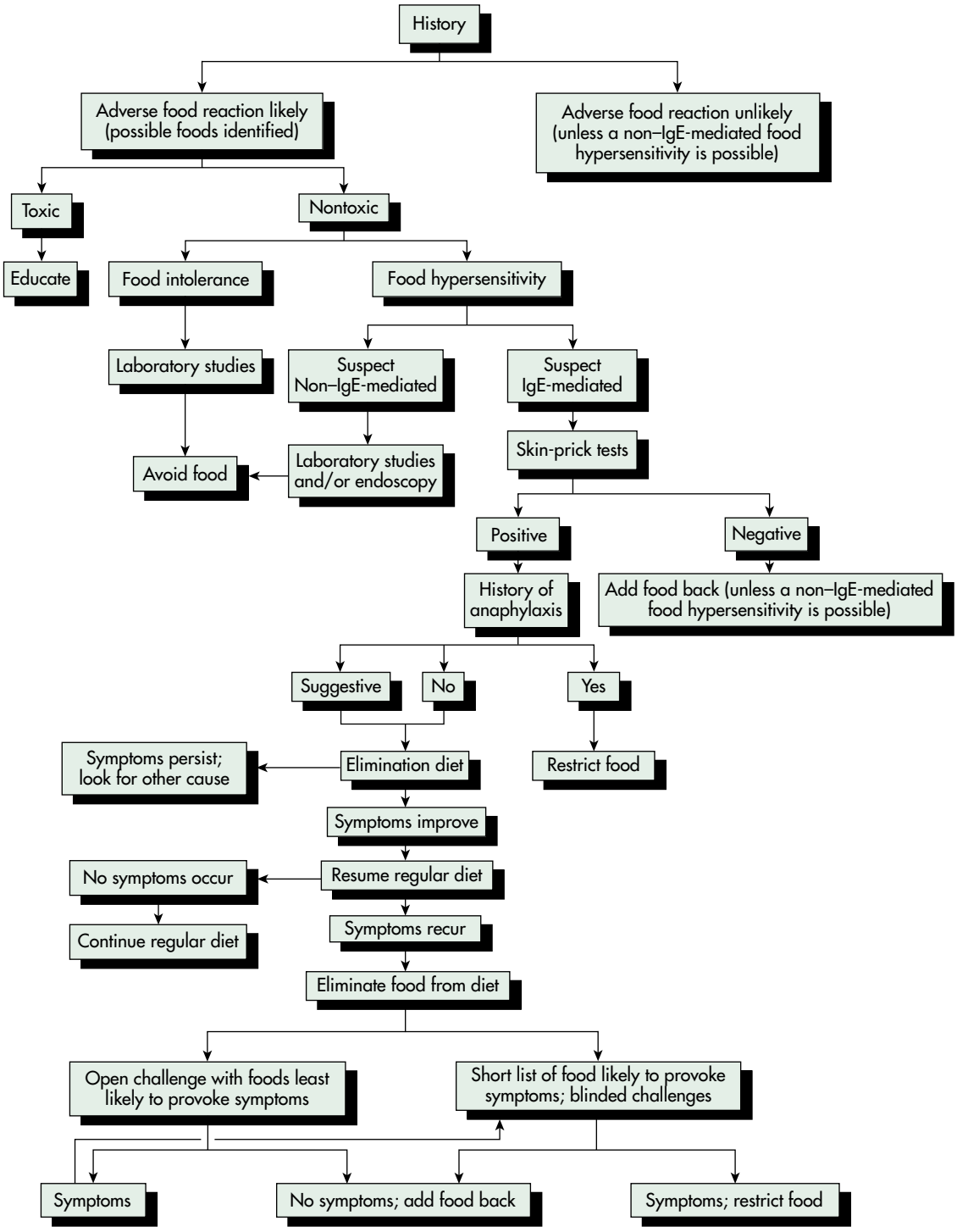
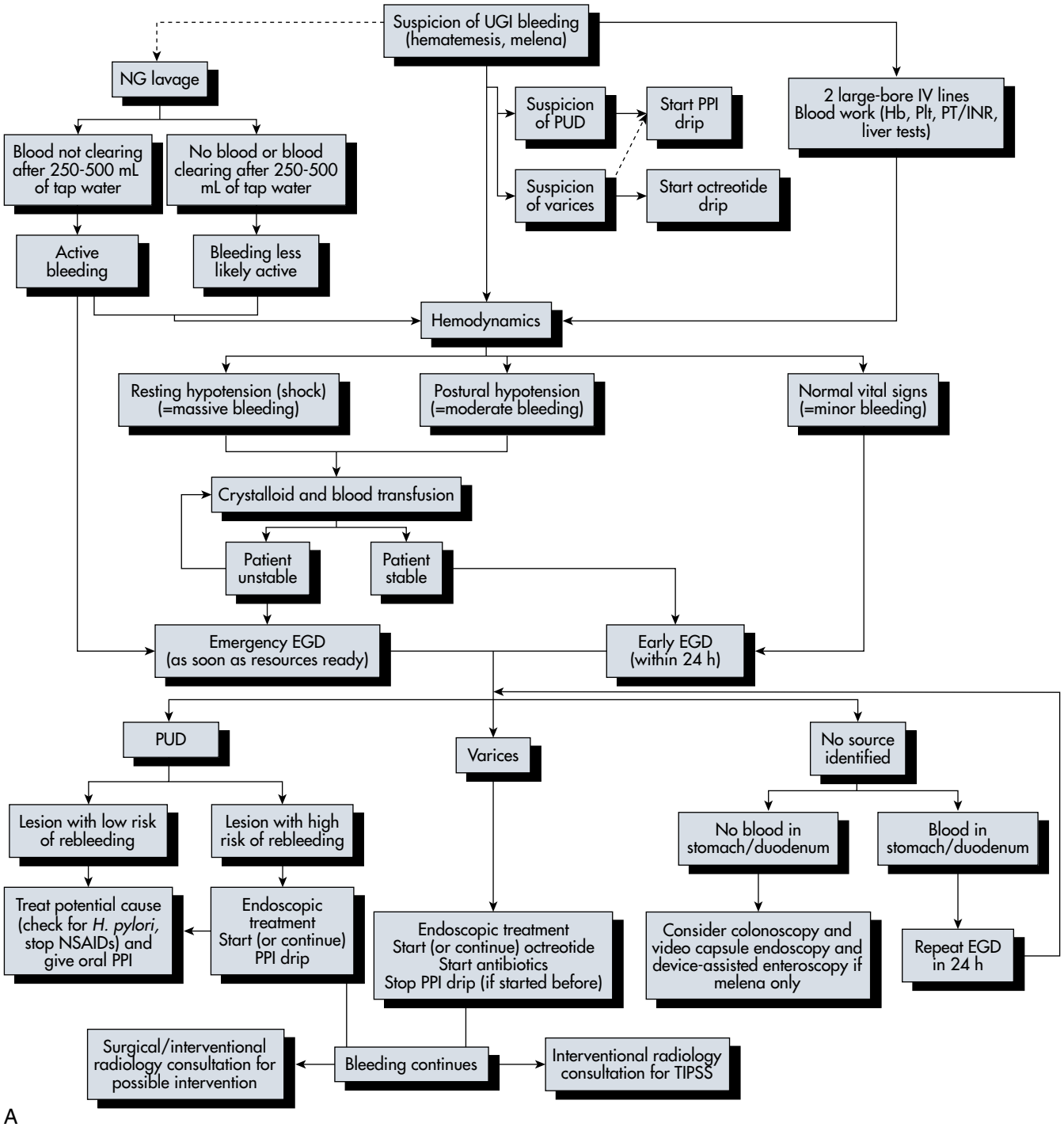


FIG. 78 Algorithm for the evaluation and management of adverse food reactions. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)



A

FIG. 79 A, Approach to managing upper gastrointestinal bleeding in critical care patients. **B,** Approach to managing lower gastrointestinal bleeding in critical care patients. *AVM,* Arteriovenous malformation; *EGD,* esophagogastroduodenoscopy; *Hb,* hemoglobin; *INR,* international normalized ratio; *LGI,* lower gastrointestinal; *NG,* nasogastric; *NSAIDs,* nonsteroidal antiinflammatory drugs; *Plt,* platelets; *PPI,* proton pump inhibitor; *PT,* prothrombin time; *PUD,* peptic ulcer disease; *RBC,* red blood cell; *TIPSS,* transjugular intrahepatic portosystemic stent shunt; *UGI,* upper gastrointestinal. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 4, 2014, Elsevier.)

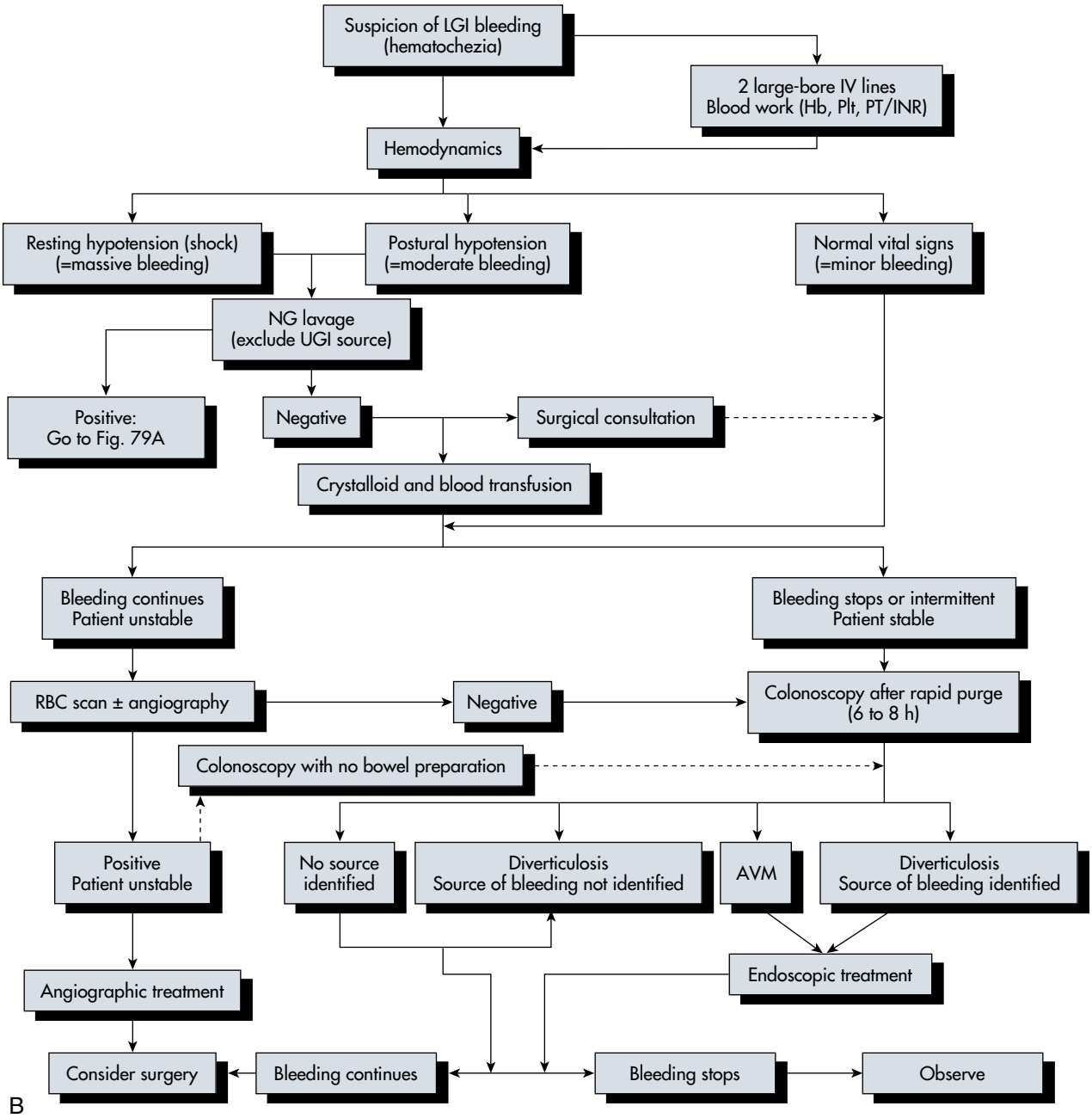


FIG. 79 (Continued)

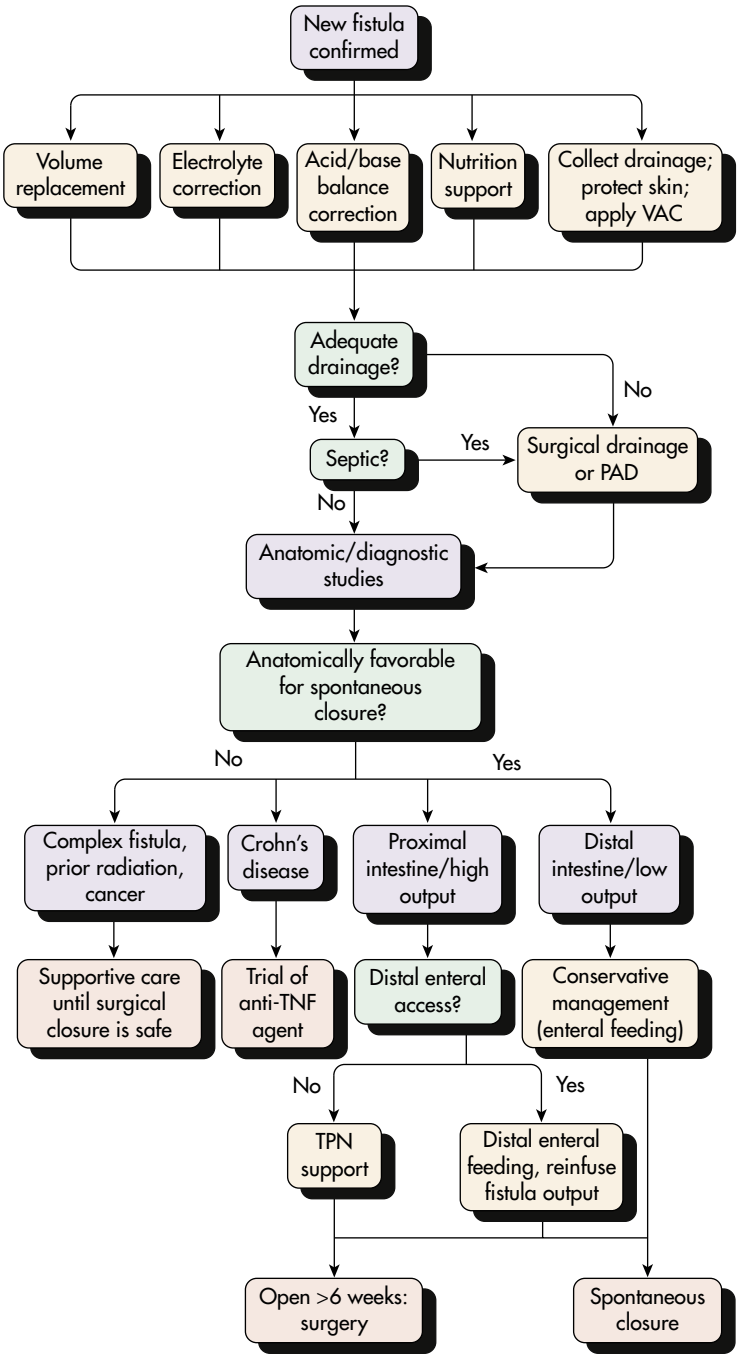


FIG. 80 Algorithm for the management of gastrointestinal fistulas. *PAD,* Percutaneous abscess drainage; *TNF,* tumor necrosis factor; *TPN,* total parenteral nutrition; *VAC,* vacuum-assisted closure. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

GOITER EVALUATION AND MANAGEMENT

ICD-10CM #

E04.9	Nontoxic goiter, unspecified
E01.2	Iodine-deficiency related (endemic) goiter, unspecified
E04.0	Nontoxic diffuse goiter
E05.10	Thyrotoxicosis with toxic single thyroid nodule without thyrotoxic crisis or storm
E05.20	Thyrotoxicosis with toxic multinodular goiter without thyrotoxic crisis or storm
E07.1	Dyshormogenetic goiter

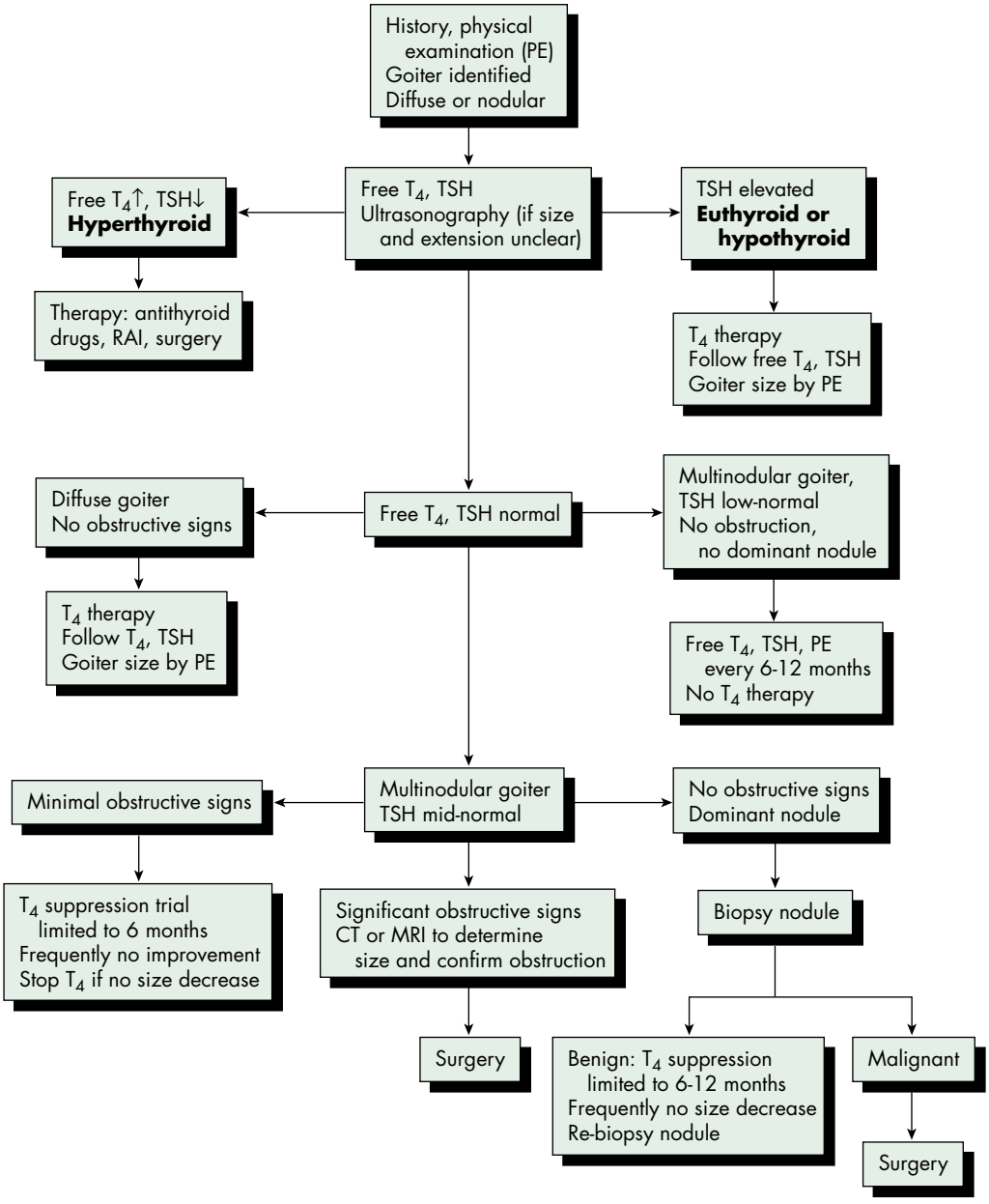


FIG. 81 Evaluation and management of patients with nontoxic diffuse and nodular goiter and undetermined thyroid status. *CT,* Computed tomography; *MRI,* magnetic resonance imaging; *RAI,* radioactive iodine; *TSH,* thyroid-stimulating hormone. (From Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

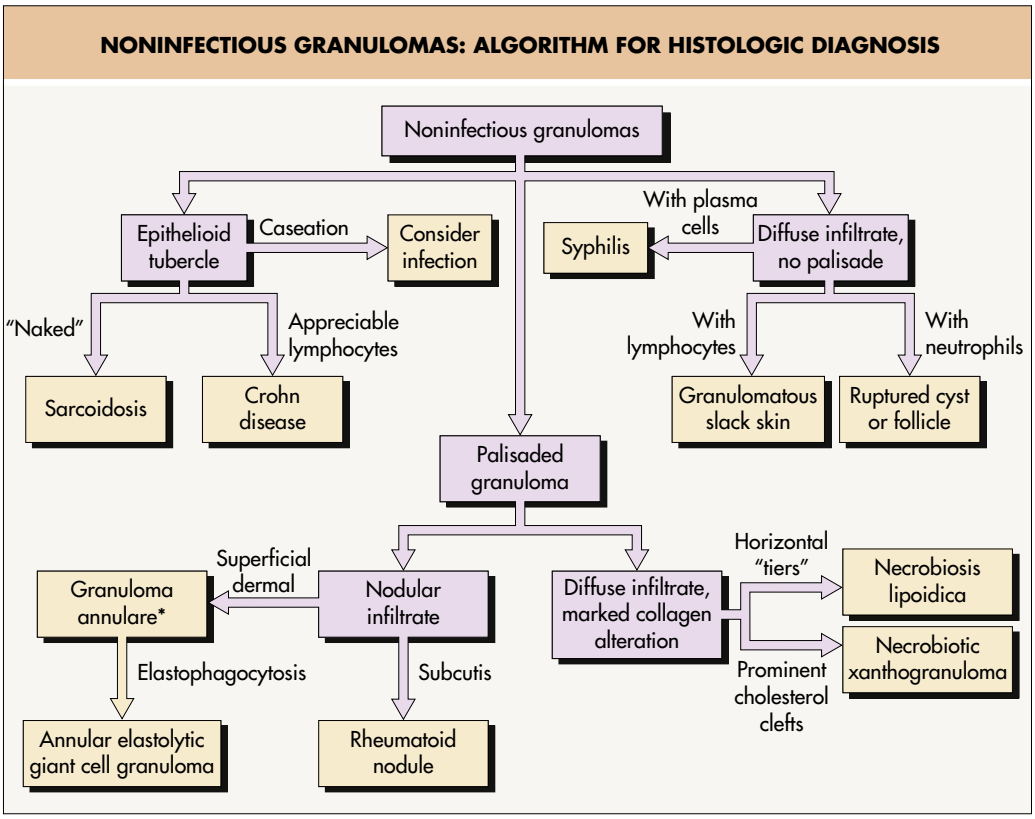


FIG. 82 Noninfectious granulomas: algorithm for histologic diagnosis. Interstitial granulomatous dermatitis and palisaded neutrophilic and granulomatous dermatitis may represent an additional diagnostic consideration. *May also have a patchy dermal interstitial pattern without palisades, or subcutaneous palisades with more mucin than rheumatoid nodules. (From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.)

TABLE 24 Clinical Features of the Major Noninfectious Granulomatous Dermatitides

	Sarcoidosis*	Classic Granuloma Annulare†	AEGCG	Necrobiosis Lipoidica	Cutaneous Crohn Disease	Rheumatoid Nodule
Average age (y)	25-35, 45-65	<30	50-70	30	35	40-50
Sex predilection	Female	Female	Female	Female	Female	Male‡
Racial/ethnic predilection in US	African American	None	Caucasian	None	Ashkenazi Jews	None
Sites	Symmetric on face, neck, upper trunk, extremities	Hands, feet, extensor aspects of extremities	Face, neck, forearms (sites of chronic sun exposure)	Anterior and lateral aspects of shins	Anogenital region, buttocks, lower > upper extremities	Juxtaarticular areas, especially elbows and hands
Appearance	Protean; most commonly red-brown or violaceous papules and plaques	Papules coalescing into annular plaques	Annular plaques	Plaques with elevated borders, telangiectasias centrally	Dusky erythema, lymphedema, ulceration, vegetating plaques	Skin-colored, firm, mobile subcutaneous nodules
Size of lesions	0.2 to >5 cm	1-3 mm papules, annular plaques usually <6 cm	2 to >10 cm	3 to >10 cm	Variable	1-3 cm
No. of lesions	Variable	1-10	1-10	1-10	1-5	1-10
Associations	Systemic manifestations of sarcoidosis can be drug-induced (e.g., IFN, TNF inhibitors) or reaction pattern to underlying lymphoma	Possible diabetes mellitus, thyroid disease, or hyperlipidemia; rare reports of HIV infection, malignancy	Actinic damage	Diabetes mellitus	Intestinal Crohn disease	Rheumatoid arthritis
Special clinical characteristics	Develop within sites of trauma, including scars and tattoos	Central hyperpigmentation	Central atrophy and hypopigmentation	Yellow-brown atrophic centers, ulceration	Draining sinuses and fistulas	Occasional ulceration, especially at sites of trauma

IFN, Interferons, *TNF,* tumor necrosis factor.
*Clinical variants include lupus pernio and subcutaneous (Darier-Roussy), psoriasiform, ichthyosiform, angiolupoid, and ulcerative sarcoidosis.
†Clinical variants include generalized/disseminated, micropapular, nodular, perforating, subcutaneous, and patch granuloma annulare.
‡Although rheumatoid arthritis has a female:male ratio of 2-3:1.
Modified from Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

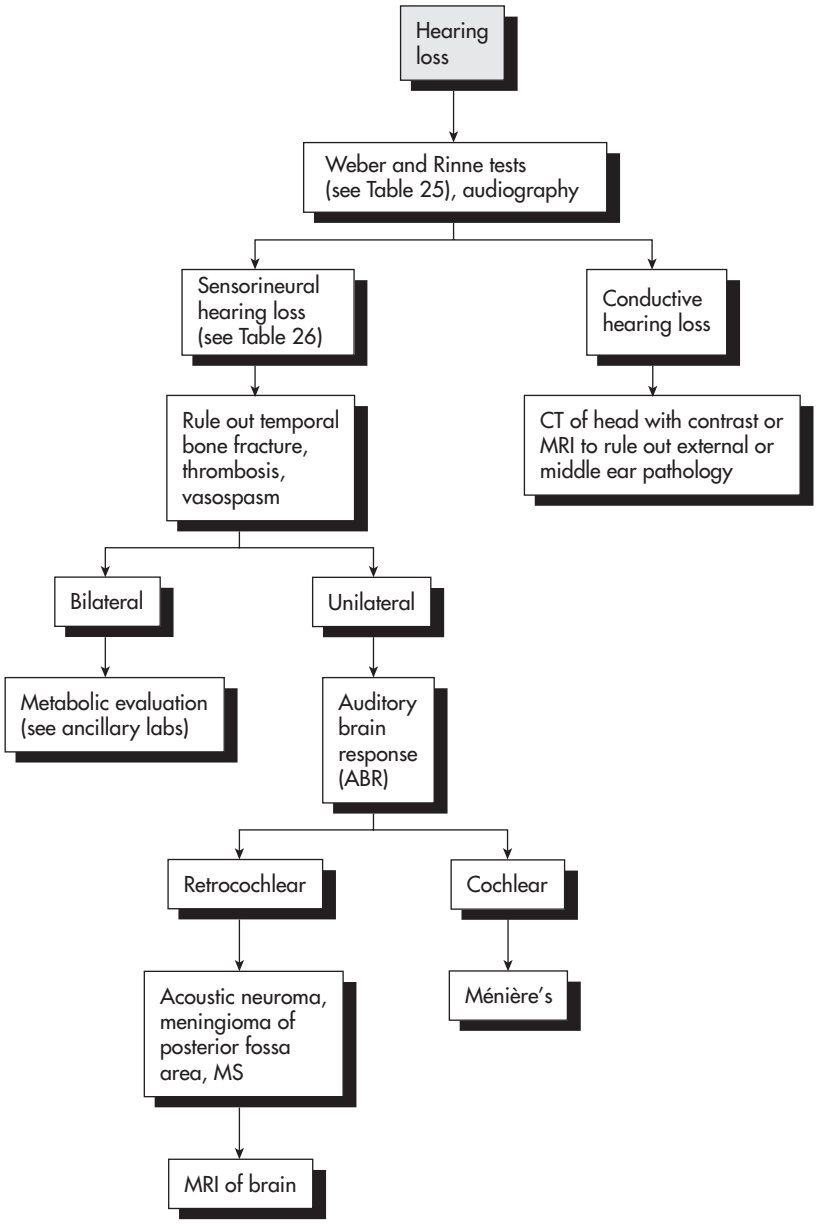


FIG. 83 Evaluation of hearing loss. *CT*, Computed tomography; *MRI*, magnetic resonance imaging; *MS*, multiple sclerosis. (From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 4, Philadelphia, 2018, Mosby.)

BOX 14 Hearing Loss

Diagnostic imaging

Best test
None

Ancillary tests
CT of head with contrast or MRI with contrast
CT of temporal bone without contrast

Lab evaluation

Best test
None

Ancillary tests
CBC
ALT, AST
ANA, VDRL
TSH

ALT, Alanine aminotransferase; *ANA,* antibody to nuclear antigens; *AST,* angiotensin sensitivity test; *CBC,* complete blood count; *CT,* computed tomography; *TSH,* thyroid-stimulating hormone; *VDRL,* Venereal Disease Research Laboratory.
From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging*, ed 4, Philadelphia, 2018, Mosby.

ICD-10CM # H90.2 Conductive hearing loss, unspecified
H90.5 Unspecified sensorineural hearing loss

TABLE 25 Interpretation of the Weber and Rinne Tests

	Weber without Lateralization	Weber Lateralizes Right	Weber Lateralizes Left
Rinne both ears: AC >BC	Normal	S/N loss in the left ear	S/N loss in the right ear
Rinne left ear: BC >AC	–	Combined loss: conduction and S/N loss in the left ear	Conduction loss in the left ear
Rinne right ear: BC >AC	–	Conduction loss in the right ear	Combined loss: conduction and S/N loss in the right ear

AC Air conduction; *BC* bone conduction; *S/N,* sensorineural.
From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

TABLE 26 Lesions That Cause Hearing Loss

	Description of Pathology	Onset/Course	Actions or Treatment	Prognosis
Conductive Lesion				
Foreign body	Mass in external canal blocks sound conduction	Acute onset associated or not with pain, drainage, or odor	Removal. Evaluate for infection. Evaluate for TM perforation	Excellent
Otitis externa	Edema and detritus obstruct external canal	Rapid onset. Pain, edema, swelling. Drainage, odor often present	Aural toilet to remove debris. Topical (±oral) antibiotics. Evaluate for necrotizing otitis	Excellent if treated appropriately
Exostosis	Bony growths obstruct canal. Often seen with prolonged exposure to cold water (divers)	Slow insidious onset. No pain or drainage unless causes complete obstruction	Evaluate for infection. Reassure patient. Refer to ENT	Good
Tympanosclerosis	TM scarring from perforations or infections. Decreased mobility impairs sound conduction	Slow onset following perforations, trauma, or infections	ENT referral. Reassurance	Variable
Perforated TM	Disruption of TM integrity results in impaired transmission of sound to ossicle	Acute onset. May follow direct trauma or sudden barotrauma. May have sudden relief from pain if caused by otitis media	Treat infectious causes. Counsel on importance of keeping water out of ear canal. ENT referral	Good
Sterile effusion (barotrauma)	Fluid in middle ear dampens conduction through ossicles	Often following flight, diving, or URI. Bubbles can cause intermittent pain	Decongestants. Evaluate for infection. Follow-up	Excellent
Acute otitis media	Pus (or fluid) in middle ear dampens conduction through ossicles	Acute to subacute onset, often following URI. Often associated with pain ± fever	Antibiotics (unless viral cause suspected), decongestants, pain control	Excellent if treated appropriately
Cholesteatoma	Trapped stratified squamous epithelial mass in middle ear. Interferes with ossicle conduction	Slow onset. Often history of previous perforations or chronic infections	ENT referral	Variable. May destroy ossicles or erode into surrounding structures
Glomus tumor	Vascular tumor occupies middle ear space. Interferes with ossicle conduction	Slow onset. May be associated with rushing pulsatile sensation	ENT referral	Variable
Cancer	Squamous cell most common. Obstructs external canal	Slow onset. Often noticed first by others. Painless unless occlusion causes otitis externa	ENT referral. Evaluate for secondary infection	Variable
Sensorineural Lesion				
Perilymph fistula (inner ear barotrauma)	Disruption of round or oval window allows leakage of perilymph into middle ear	Sudden onset of hearing loss often with tinnitus and vertigo. Frequently follows straining or abrupt change in pressure. Turning in direction of fistula exacerbates symptoms	Complete bed rest. Elevate head of bed and avoid increases in CSF pressure. Severe symptoms or noncompliance may require hospitalization. ENT consultation for possible oval or round window patch	Variable
Viral cochleitis	Cochlear inflammation. Often following URI	Rapid onset. Often following URI	Steroids often used (no good data)	Variable
Presbycusis	Age-related hearing loss. May be related to previous chronic noise exposure	Slow onset. Usually symmetric. High frequencies most affected. Tinnitus may occur	Hearing aid may help with both hearing loss and tinnitus	Variable

TABLE 26 Lesions That Cause Hearing Loss—cont'd

	Description of Pathology	Onset/Course	Actions or Treatment	Prognosis
Acoustic neuroma	Benign schwannoma of 8th cranial nerve	Slow onset. Usually unilateral. May exhibit tinnitus, vertigo. May exhibit facial hyperesthesias or twitching	May require surgical excision if symptoms debilitating	Variable
Ototoxic agents	Direct toxicity to inner ear structures	Variable onset. High frequency most affected. Exposure to ototoxic drugs. May have associated tinnitus	Stop use of offending agent	Variable. Hearing loss at time of stopping offending agent is usually permanent
Multiple sclerosis	Multiple demyelinating lesions interfere with nerve conduction	Often other associated neurologic findings. May wax and wane	Standard multiple sclerosis treatment (steroids, cytotoxic agents)	Variable
Stroke/CVA	Focal ischemic lesion of auditory nerve or auditory cortex	Sudden onset. Often associated with other neurologic deficits	Treat CVA risk factors (ASA, anticoagulants, glycemic control, BP control)	Variable
Meningitis	Infection enters inner ear through CNS-perilymph connection. Damages organ of Corti	Follows clinical picture of meningitis	Treat infection. Steroids may limit inflammation and damage	Variable
Ménière disease (endolymphatic hydrops)	Abnormal homeostasis of inner ear fluids (clinical diagnosis; definitive diagnosis made histologically)	Episodic spells of vertigo. Associated sensation of fullness, tinnitus, and SNHL or auditory distortion. Low-frequency ranges most affected	Reduce salt, caffeine, nicotine (vasoconstrictors) intake. Consider diuretics, antihistamines, anticholinergics. ENT referral	Variable
Chronic noise exposure	Direct mechanical damage to cochlear structures and hair cells	Slow onset. Usually high frequency most affected	Prevention measures (earplugs). Stop exposure	Usually permanent
Skull trauma	Interruption of cranial nerve VIII, ossicle disruption, or shearing effects on organ of Corti	Sudden onset after trauma	ENT consultation for possible surgical repair	Variable: ossicle disruption has better prognosis than nerve or organ of Corti damage
Autoimmune causes	Vascular or neuronal inflammatory changes	Bilateral asymmetric SNHL. May be fluctuating or progressive. Often other systemic autoimmune findings	Outpatient autoimmune evaluation. Steroids and cytotoxic agents may slow progression	Variable

ASA, Acetylsalicylic acid; *BP,* blood pressure; CNS, central nervous system; *CSF,* cerebrospinal fluid; *CVA,* cerebrovascular accident; *ENT,* ear, nose, and throat; SNHL, sensorineural hearing loss; *TM,* tympanic membrane; *URI,* upper respiratory infection.

From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

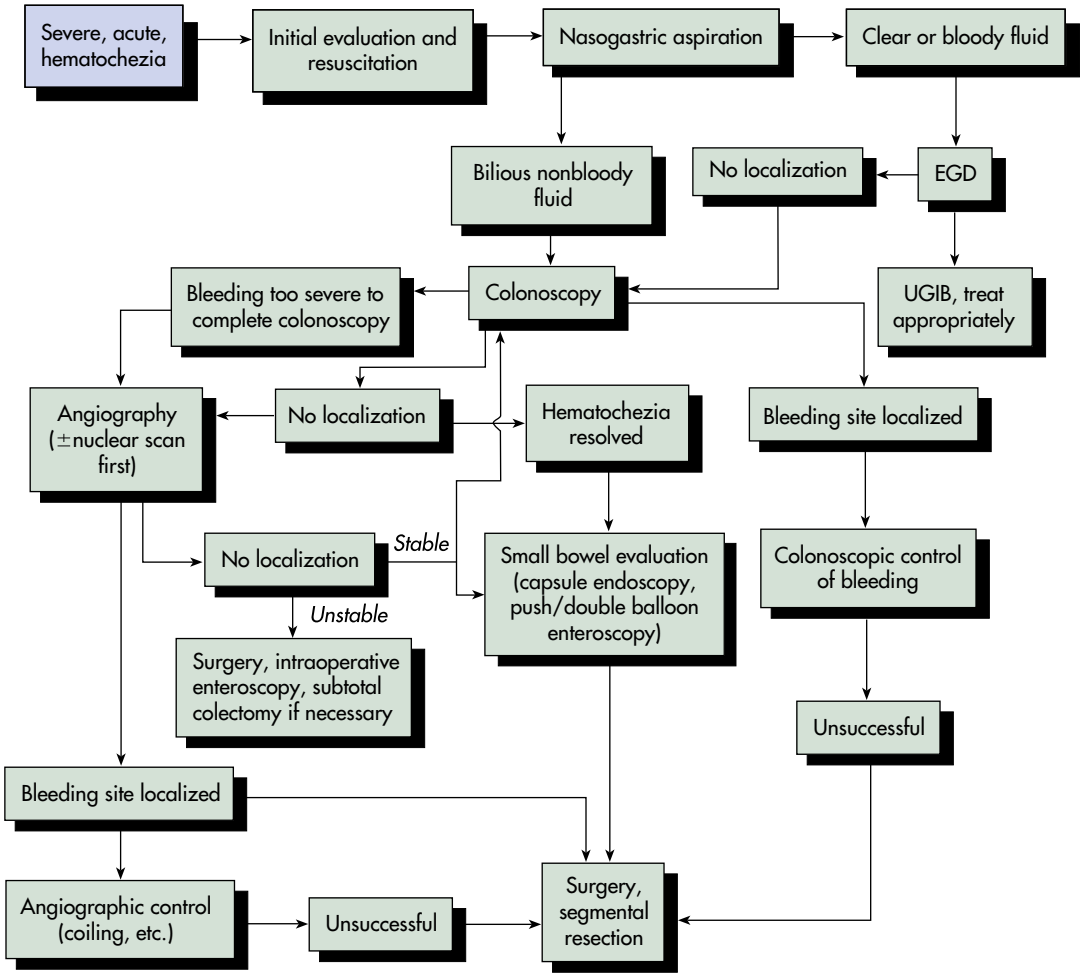


FIG. 84 Management algorithm for hematochezia. *EGD,* Esophagogastroduodenoscopy; *UGIB,* upper gastrointestinal biopsy. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

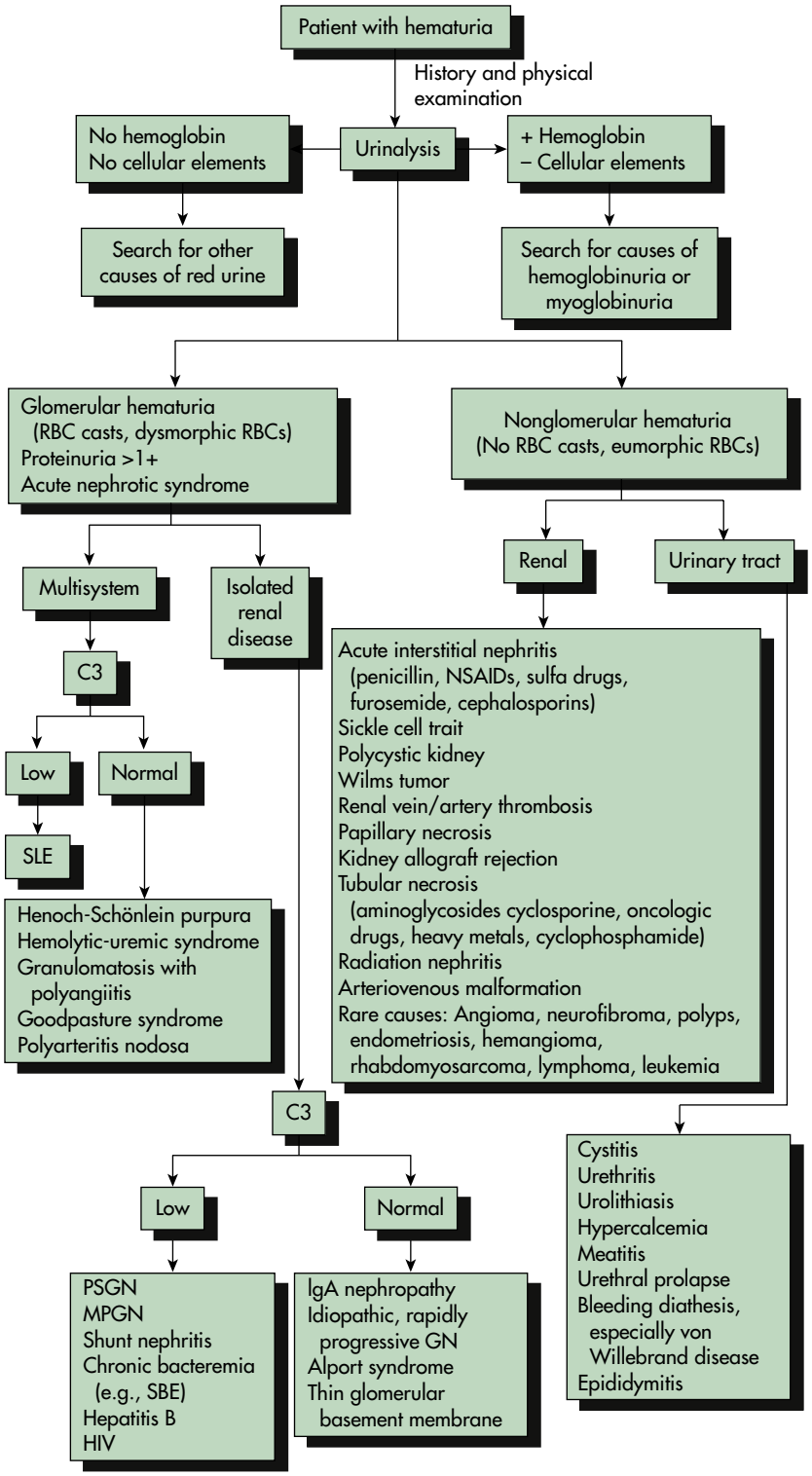


FIG. 85 Diagnostic strategy for hematuria. *GN,* Glomerulonephritis; *HIV,* human immunodeficiency virus; *MPGN,* membranoproliferative glomerulonephritis; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PSGN,* post-streptococcal glomerulonephritis; *RBC,* red blood cell; *SBE,* subacute bacterial endocarditis; *SLE,* systemic lupus erythematosus. (From The Johns Hopkins Hospital, Hughes HK, Kalh LK: *The Harriet Lane handbook,* ed 21, St Louis, 2018, Elsevier.)

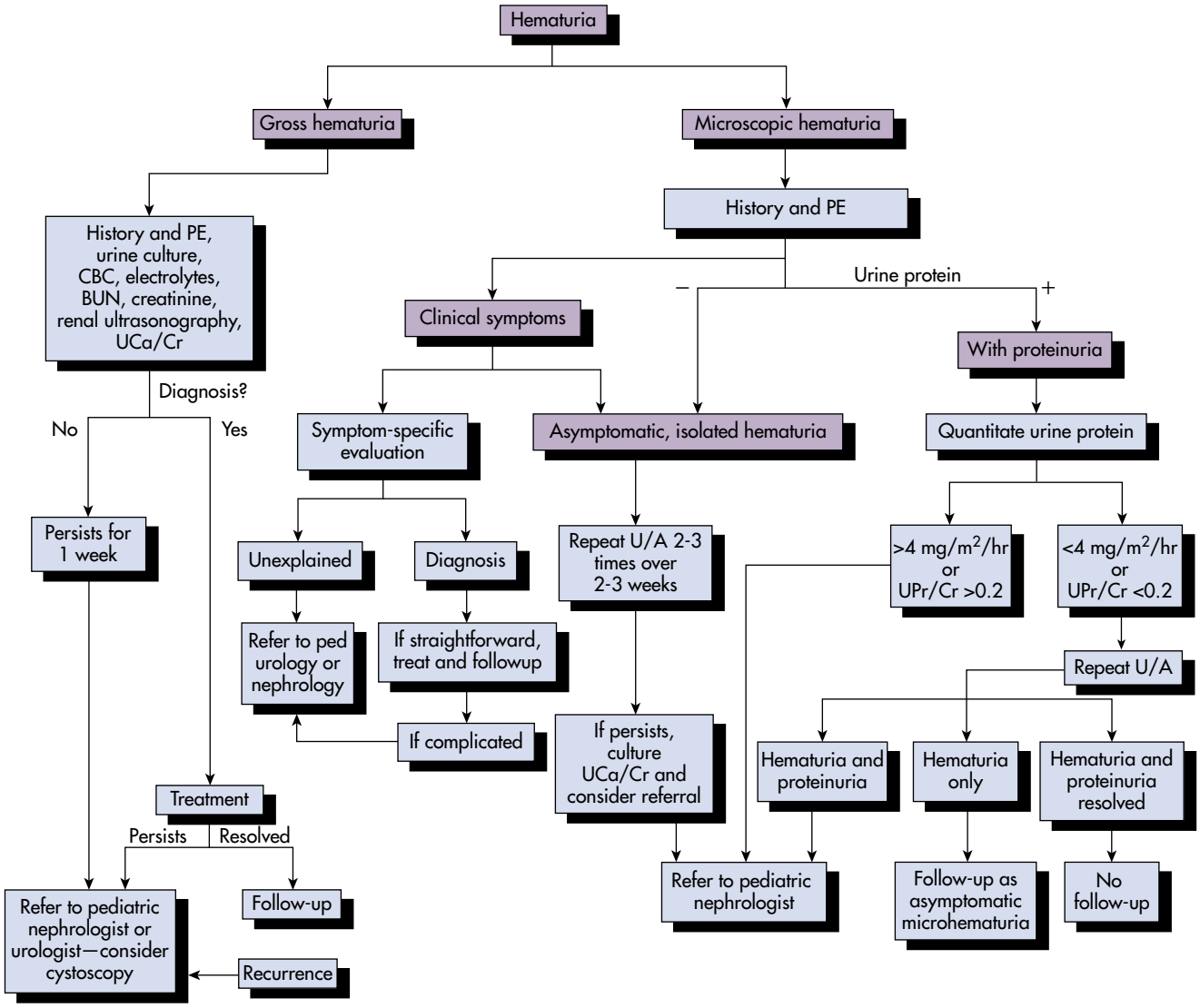
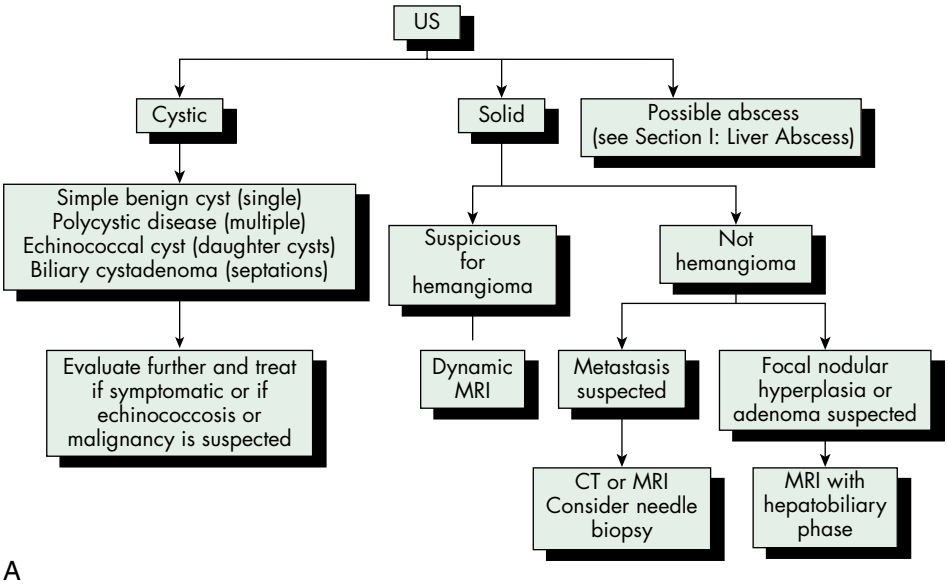
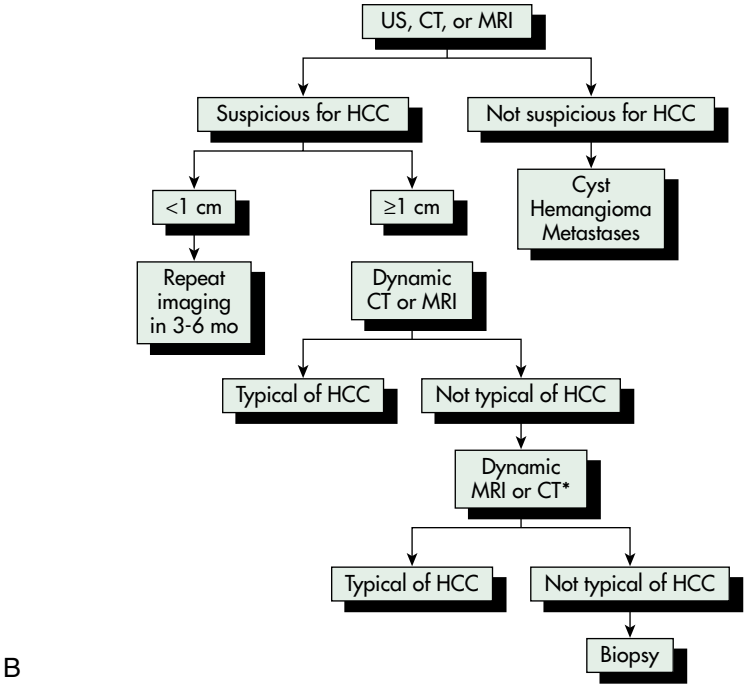


FIG. 86 Algorithm for the treatment of hematuria. *BUN,* Blood urea nitrogen; *CBC,* complete blood cell count; *PE,* physical examination; *U/A,* urinalysis; *UCa/Cr,* urinary calcium/creatinine ratio; *UPr/Cr,* urinary protein/creatinine ratio. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)



A



B

FIG. 87 A, Algorithm for the approach to the management of a patient, not known to have cirrhosis, with a hepatic mass (often incidental, possibly symptomatic). **B,** Algorithm for the approach to the management of a patient with known or suspected cirrhosis and a hepatic mass (found on routine surveillance, because of symptoms, or because of an increasing alpha-fetoprotein level). *Perform imaging modality not previously performed. *HCC,* Hepatocellular carcinoma. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier)

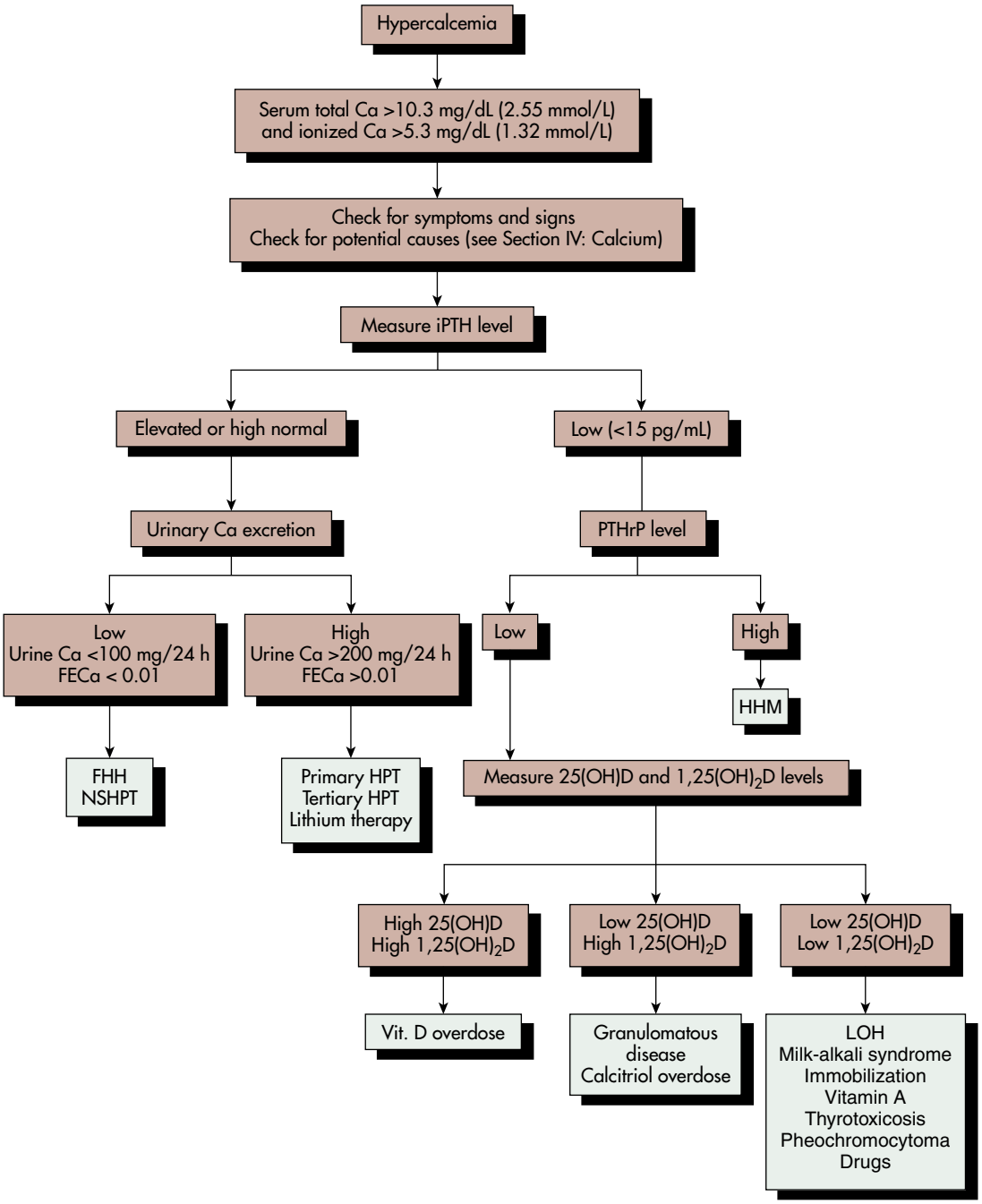


FIG. 88 Algorithm for evaluation of hypercalcemia. *FECa,* Fractional excretion of calcium; *FHH,* familial hypocalciuric hypercalcemia; *HHM,* humoral hypercalcemia of malignancy; *HPT,* hyperparathyroidism; *iPTH,* intact parathyroid hormone; *LOH,* localized osteolytic hypercalcemia; *NSHPT,* neonatal severe hyperparathyroidism; *PTHrP,* parathyroid hormone-related peptide. (From Skorecki K et al: *Brenner & Rector's the kidney,* ed 10, Philadelphia, 2016, Elsevier.)

Diagnostic Imaging

Best Test(s)
None

Ancillary Tests
Radiograph of painful bones (r/o bone neoplasm, multiple myeloma)
Tc-99m parathyroid scan (r/o parathyroid adenoma)
Ultrasound of parathyroid glands
Ultrasound of kidneys (r/o renal cell carcinoma)

Lab Evaluation

Best Test(s)
Serum calcium level
PTH level

Ancillary Tests
Serum phosphate, magnesium, alkaline phosphatase, albumin
Electrolytes, BUN, creatinine
24-hour urine collection for calcium
Urinary cyclic AMP
PSA (if prostate carcinoma is suspected)
Serum and urine protein immunoelectrophoresis (if multiple myeloma suspected)

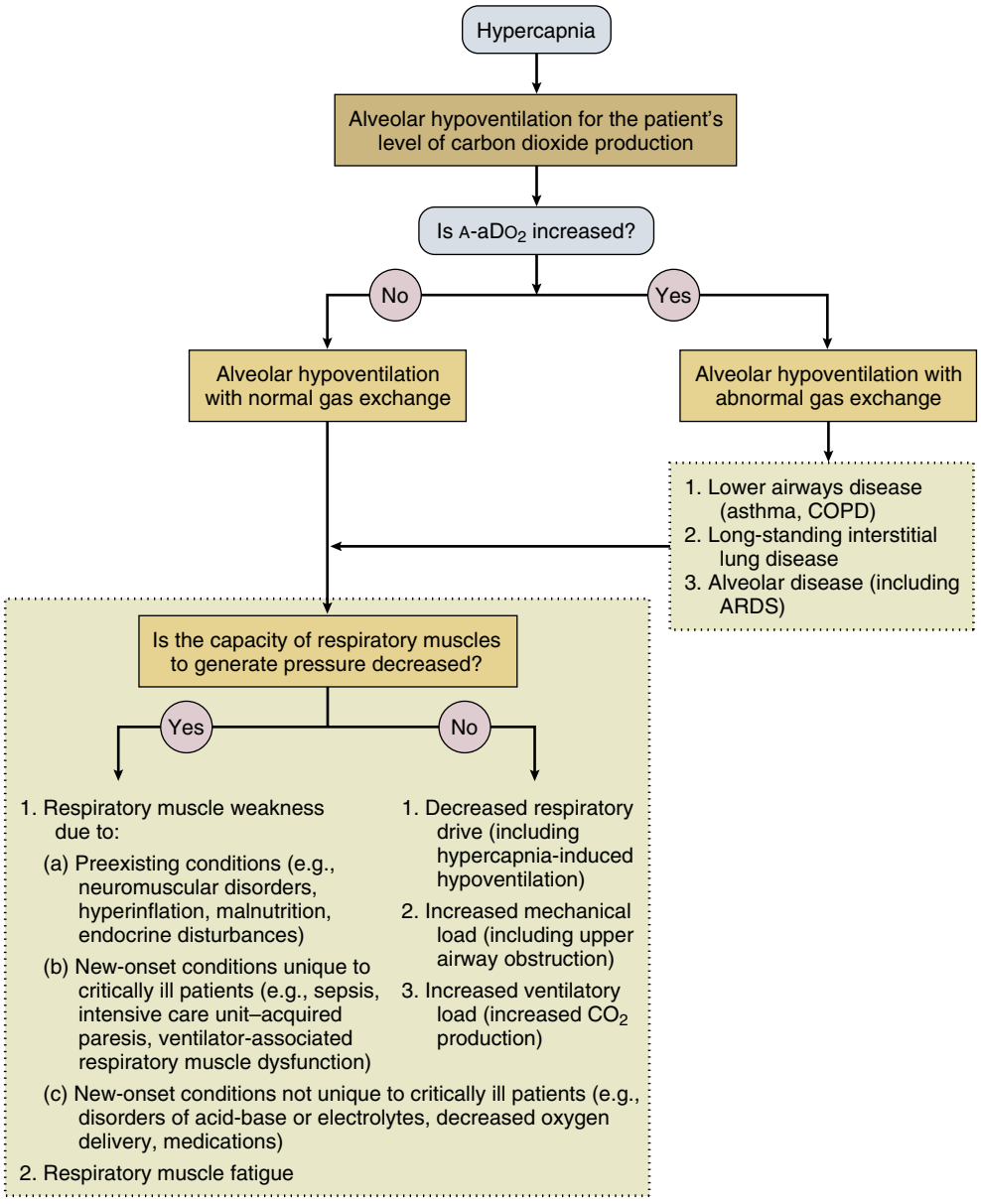


FIG. 89 Diagnostic approach to critically ill patient with hypercapnia. *A-aDO2,* Alveolar-arterial difference in partial pressure of oxygen; *ARDS,* acute respiratory distress syndrome; *COPD,* chronic obstructive pulmonary disease. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.)

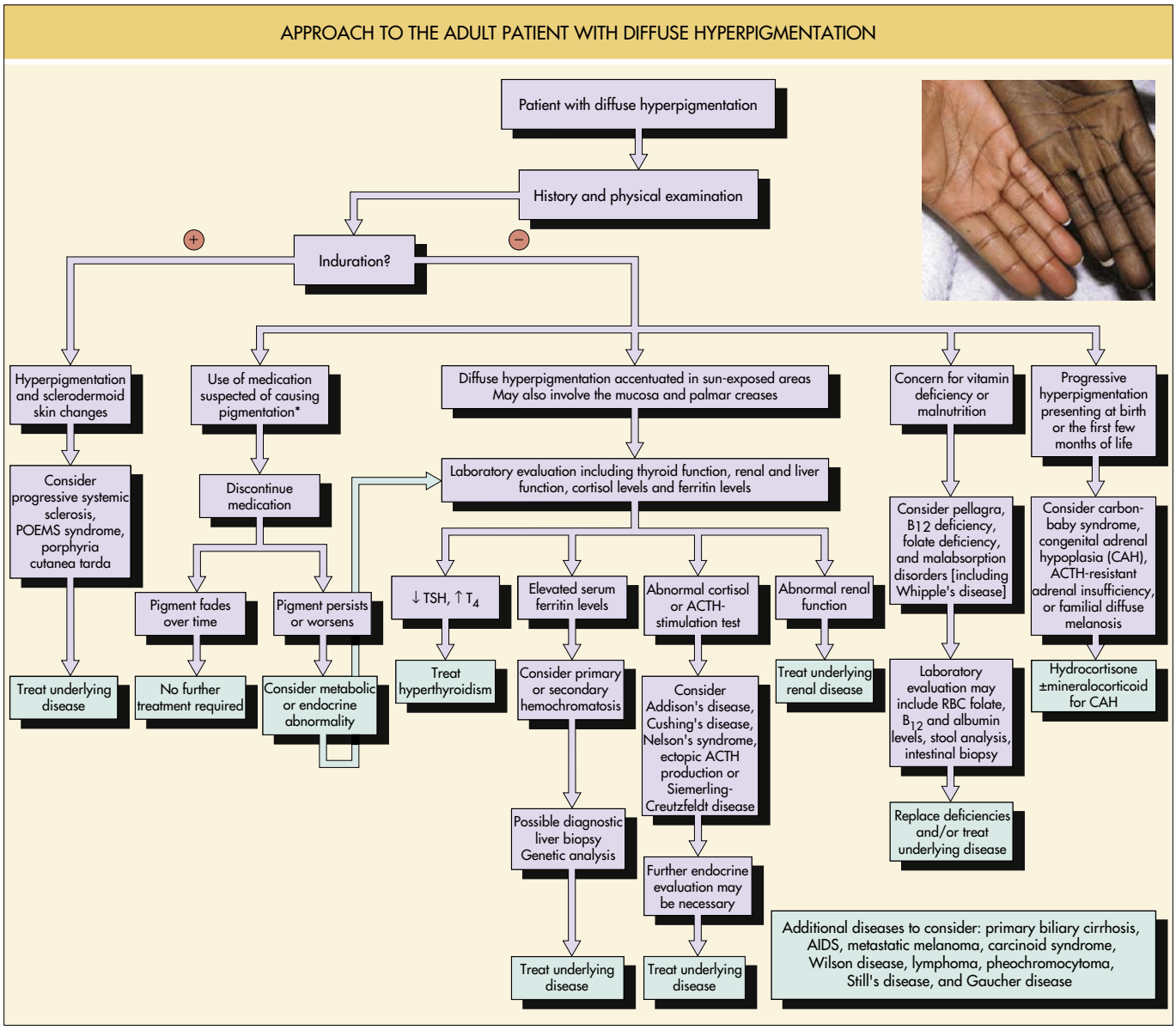


FIG. 90 Approach to the adult patient with diffuse hyperpigmentation. The palm on the right in the inset photograph shows diffuse hyperpigmentation in a patient with POEMS syndrome (*p*olyneuropathy, *o*rgano-megaly, *e*ndocrinopathy, *m*onoclonal gammopathy, and *s*kin lesions). *ACTH,* Adrenocorticotropic hormone; T_4, thyroxine; *TSH,* thyroid-stimulating hormone. *See Table 27 for a list of drugs and chemicals associated with diffuse hyperpigmentation. (From Bolognia JL, Jorizzo JL, Schaffer JV: *Dermatology,* ed 3, St Louis, 2012, Elsevier.)

TABLE 27 Drugs and Chemicals Associated with Hyperpigmentation

Drug or Chemical	Clinical Features	Histopathology/Comment
Cancer Chemotherapeutic Agents		
BCNU (Topical)	• Hyperpigmentation at site of application (no reaction seen with parenteral administration)	• Hyperplasia of basal melanocytes consistent with postinflammatory hyperpigmentation
Bleomycin	• Linear, flagellate bands, associated with minor trauma • Nails may be involved • Hyperpigmentation overlying joints	• Increased epidermal melanin • Little dermal pigment incontinence • No increase in epidermal melanocytes
Busulfan	• Generalized hyperpigmentation resembling Addison disease; sometimes seen in association with drug-induced pulmonary fibrosis	• Increased melanin in basal keratinocytes and in dermal macrophages
Cyclophosphamide	• Diffuse hyperpigmentation of the skin and mucous membranes • Localized pigment of the nails (transverse or longitudinal bands), palms and soles, or teeth	• Pigmentation usually regresses within 6 to 12 months after therapy is discontinued
Dactinomycin	• Generalized hyperpigmentation, most prominent on the face	• Pigmentation fades after treatment discontinued
Daunorubicin	• Hyperpigmentation of light-exposed areas • Transverse brown-black nail bands	• Structurally similar to doxorubicin
Doxorubicin	• Pigmentation of the nails; hyperpigmentation of the palmar creases, palms, soles, buccal mucosa, dorsae of the knuckles and tongue	• Increased epidermal melanin • Increased number of melanocytes
5-Fluorouracil	• Hyperpigmentation in sun-exposed areas • Increased pigmentation of skin overlying veins used for infusion, dorsae of the hands and trunk	• Synergistic hyperpigmentation of irradiation portal sites
Hydroxyurea	• Reversible hyperpigmentation over pressure points and the back • Nails may be involved	• Lichenoid eruption with secondary hyperpigmentation
Mechlorethamine (nitrogen mustard)	• Topical use for cutaneous lymphoma may result in generalized hyperpigmentation • More intense in lesional skin	• Disaggregation of melanosomes within keratinocytes • Increased number of melanocytes
Methotrexate	• Uniform hyperpigmentation in sun-exposed areas	• Uncommon • May be postinflammatory hyperpigmentation secondary to photosensitivity reaction
Antimalarials		
Amino quinolones (chloroquine, hydroxychloroquine, amodiaquine)	• Yellow-brown or gray to blue-black pigment, usually in pretibial areas; face, hard palate, and subungual areas may be involved	• Dyspigmentation in up to 25% of patients • Dermal deposition of melanin-drug complexes; hemosiderin around capillaries • May fade, but rarely resolves, upon discontinuation of drug
Heavy Metals		
Arsenic	• Areas of bronze hyperpigmentation ± superimposed raindrops • Keratoses on the palms and soles associated with pigmentation	• May appear 1-20 yr after exposure • Dermal and epidermal deposition of arsenic • Increased epidermal melanin synthesis
Bismuth	• Generalized blue-gray discoloration of face, neck, dorsal hands • Oral mucosa and gingivae may be involved	• Bismuth granules in the papillary and reticular dermis
Gold	• Permanent blue-gray discoloration in sun-exposed areas, mostly around the eyes (chrysiasis)	• Gold particles within macrophage lysosomes in the dermis
Iron	• Permanent brown pigment at injection or application sites	• Pigment coats collagen fibers and is deposited in dermal macrophages
Lead	• "Lead line" in gingival margin • Nail pigmentation	• Lead line is due to subepithelial deposition of lead granules
Mercury	• Slate-gray pigmentation, particularly in skin folds	• Brown-black granules free in dermis, in association with elastic fibers, and within macrophages
Silver	• Generalized slate-gray pigmentation, increased in sun-exposed areas • Nails and sclerae may also be involved • Localized at sites of application	• Silver granules in the basement membrane and on the membrana propria of eccrine glands
Hormones		
Oral contraceptives	• Melasma; increased pigment of nipples and nevi	• Increased melanocytes and increased melanin synthesis
ACTH/MSH	• Diffuse brown or bronze pigmentation; seen in Addison disease and Cushing syndrome	• Increased melanin synthesis
Miscellaneous Compounds		
Amiodarone	• Slate-gray to violaceous discoloration of sun-exposed skin	• Yellow-brown granules in dermis, mostly perivascular • Lysosomal inclusions with a lipid-like substance
Azidothymidine (zidovudine, AZT)	• Nail and mucocutaneous hyperpigmentation	• Skin biopsy shows increased epidermal and dermal melanin
Clofazimine	• Diffuse red to red-brown discoloration of skin • Violet-brown to bluish discoloration, especially lesional skin	• Redness secondary to drug in fat • Phagolysosomes with lipofuscin material

TABLE 27 Drugs and Chemicals Associated with Hyperpigmentation—cont'd

Drug or Chemical	Clinical Features	Histopathology/Comment
Dioxins	• Chloracne most common skin finding • Hyperpigmentation may occur in sun-exposed areas	• Rare, except in accidental exposure
Hydroquinone	• Hyperpigmentation in areas of application due to exogenous ochronosis	• Yellow-brown banana-shaped fibers in papillary dermis
Minocycline	• Blue-black discoloration in old acne scars or sites of inflammation as well as lower extremities • May also involve nails, sclerae, oral mucosa, bones, and teeth • Generalized "muddy brown" pigmentation pattern in some patients	• Iron-containing granules and/or increased melanin, depending on clinical type
Psoralens	• Increased pigmentation after exposure to UVA light (PUVA)	• Proliferation of follicular melanocytes • Increased synthesis and transfer of melanin
Psychotropic drugs (phenothiazine, chlorpromazine, imipramine, desipramine)	• Slate-gray discoloration in sun-exposed areas	• Golden-brown granules in the upper dermis • Electron-dense inclusion bodies

ACTH, Adrenocorticotropic hormone; *AZT,* azidothymidine, now renamed zidovudine; *MSH,* melanocyte-stimulating hormone.
From Bolognia JL et al [eds]: *Dermatology,* ed 2, St Louis, 2008, Mosby.

FIG. 91 Hyperpigmentation of the nails in a 61-year-old woman receiving paclitaxel for breast cancer. (From Callen JP et al: *Dermatologic signs of systemic disease,* ed 5, 2017, Elsevier.)

FIG. 92 Grade 1 skin (facial) hyperpigmentation in a 62-year-old woman, during treatment with imatinib for a gastrointestinal stromal tumor. (From Callen JP et al: *Dermatologic signs of systemic disease,* ed 5, 2017, Elsevier.)

ICD-10CM #
E28.310 Symptomatic premature menopause
E29.1 Testicular hypofunction
E28.39 Other primary ovarian failure
E23.6 Other disorders of pituitary gland

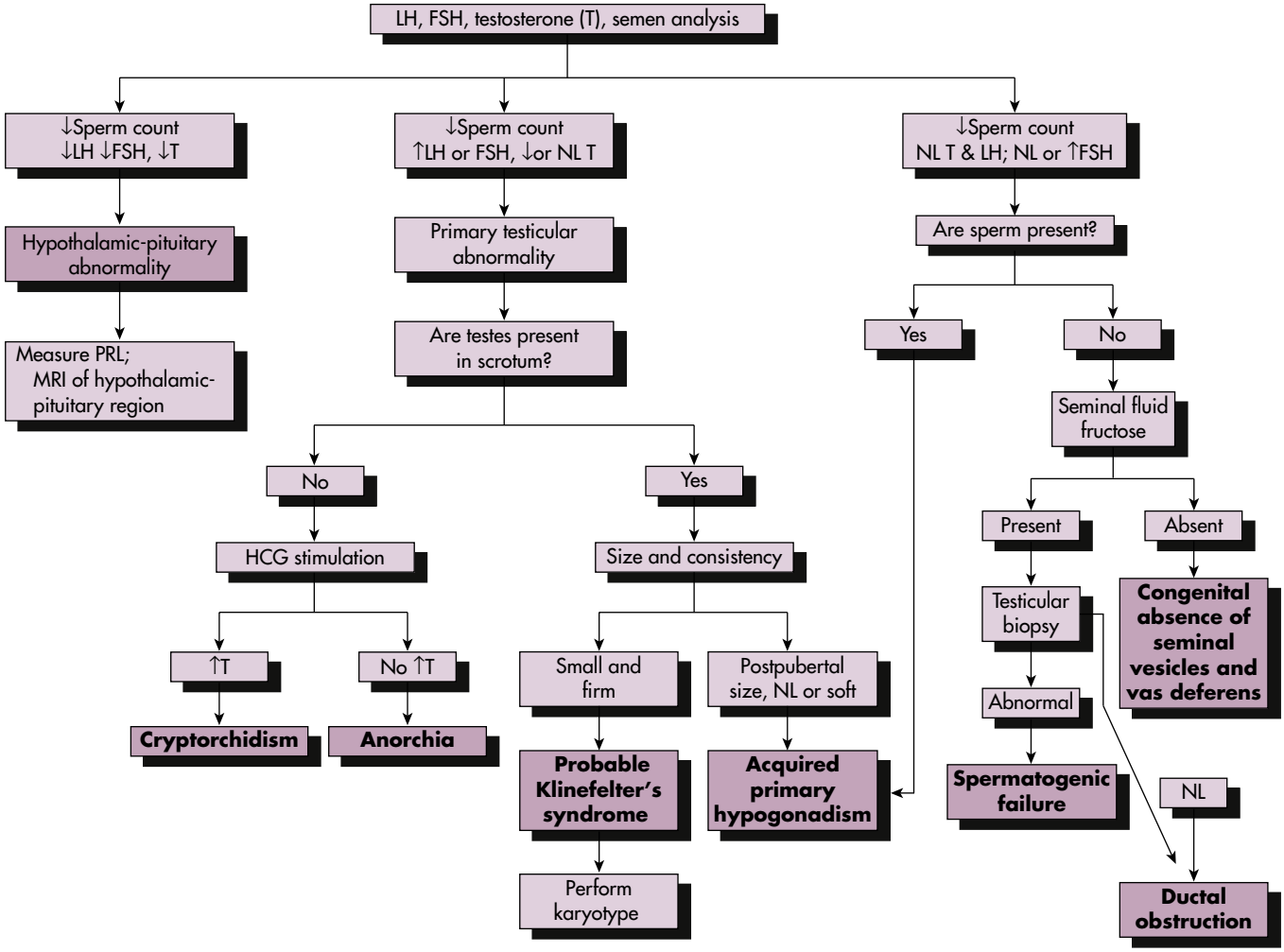


FIG. 93 Laboratory evaluation of hypogonadism. ↑, Elevated; ↓, decreased or low; *FSH,* follicle-stimulating hormone; *HCG,* human chorionic gonadotropin; *LH,* luteinizing hormone; *MRI,* magnetic resonance imaging; *NL,* normal; *PRL,* prolactin. (From Benjamin I et al: *Andreoli and Carpenter's Cecil essentials of medicine*, ed 9, Philadelphia, 2016, Saunders.)

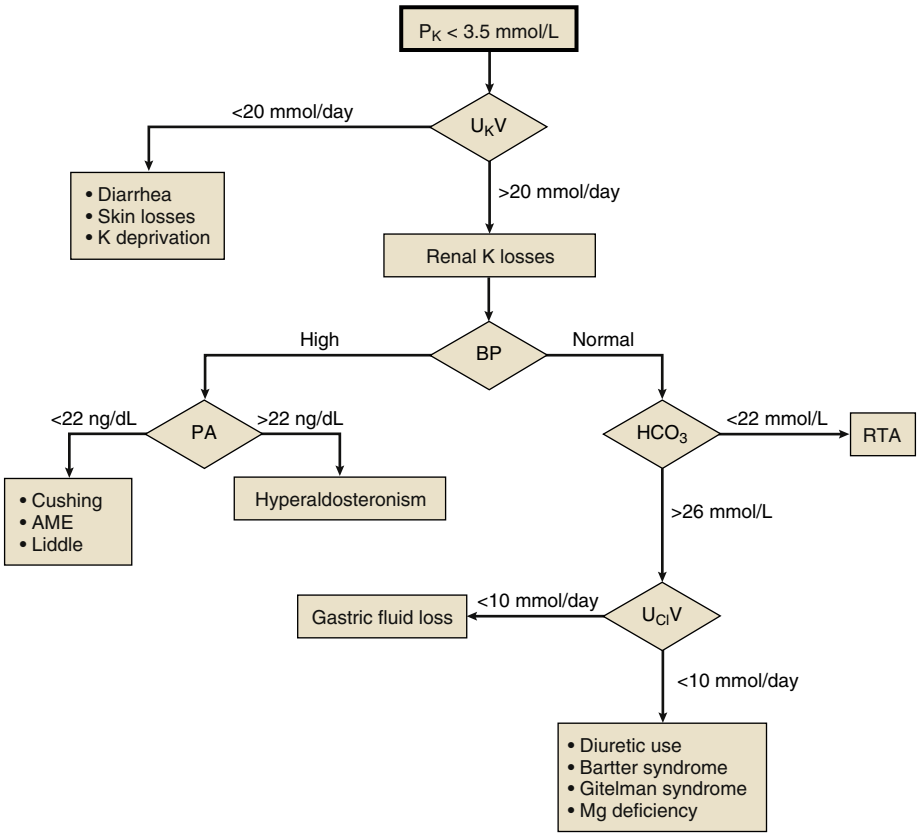


FIG. 94 Diagnostic evaluation of chronic hypokalemia. *AME,* Syndrome of apparent mineralocorticoid excess; *BP,* blood pressure; *HCO_3^-,* bicarbonate; *PA,* stimulated plasma aldosterone (see text); *RTA,* renal tubular acidosis; *$U_{Cl}V$,* urinary chloride excretion; *U_KV,* urinary potassium excretion. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.)

BOX 15 Causes of Acute Hypokalemia

- Treatment of diabetic ketoacidosis
- Refeeding syndrome
- Rapid cell production
  Vitamin B_{12} treatment of pernicious anemia
  GM-CSF treatment of leukopenia
- Pharmacologic agents
  β_2-Adrenoceptor agonists
  Epinephrine
  Soluble barium salts
- Hypokalemic periodic paralysis
  Familial
  Sporadic
  Thyrotoxic
- Pseudohypokalemia

GM-CSF, Granulocyte-macrophage colony-stimulating factor.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.

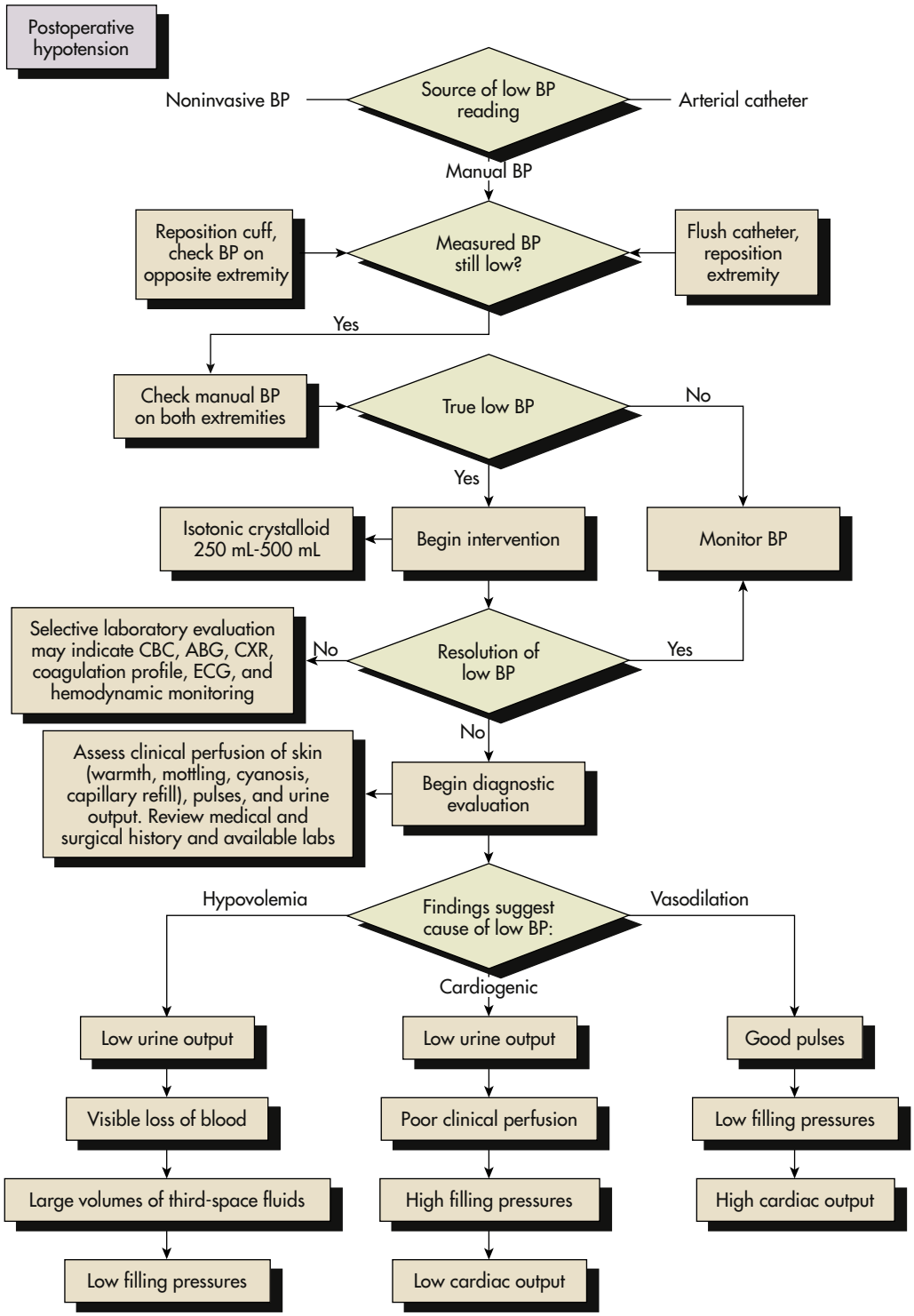
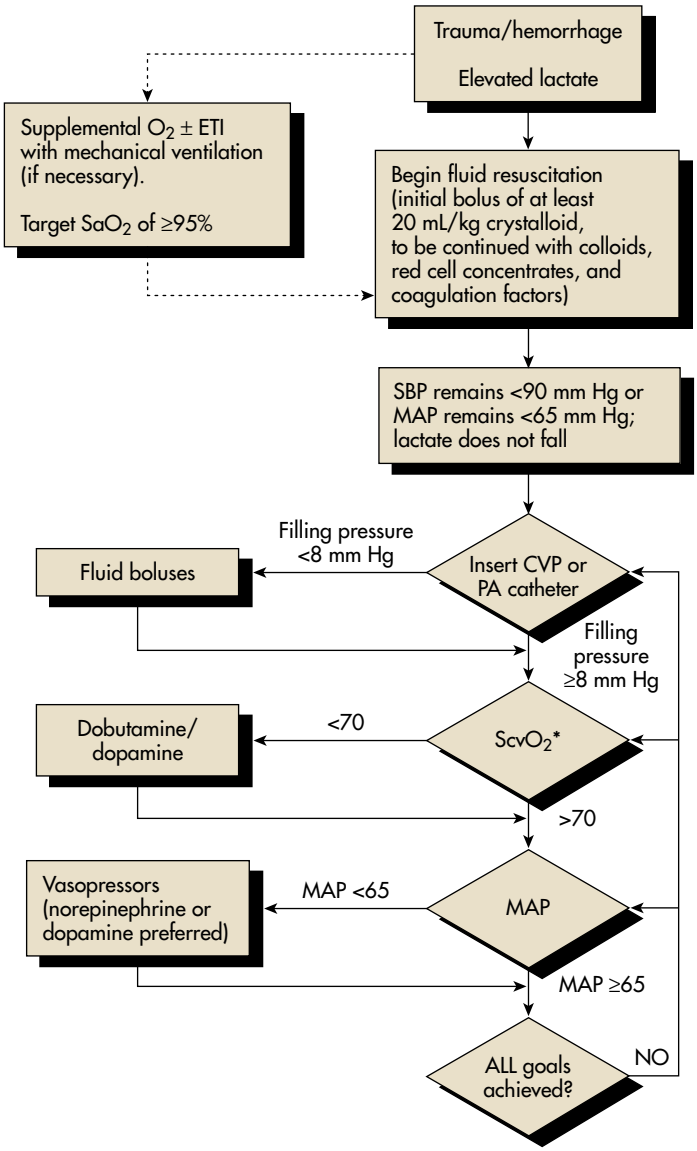


FIG. 95 Approach to managing postoperative hypotension. *ABG,* Arterial blood gases; *BP,* blood pressure; *CBC,* complete blood count; *CXR,* chest x-ray study; *ECG,* electrocardiogram. (From Parrillo JE, Dellinger RP: *Critical care medicine: principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Elsevier.)



*If pulmonary artery catheter is used, a mixed venous O_2 saturation is an acceptable surrogate, and 65% would be the target.

FIG. 96 Hypovolemic shock management protocol. *CVP,* Central venous pressure; *ETI,* endotracheal intubation; *MAP,* mean arterial pressure; *PA,* pulmonary artery; *Sa_{O_2},* oxygen saturation; *SBP,* systolic blood pressure; *Scv_{O_2},* central venous oxygen saturation. (From Parrillo JE, Dellinger RP: *Critical care medicine: principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Elsevier.)

TABLE 28 Clinical Classification of Severity of Posthemorrhagic Hypovolemic Shock

Feature	Class I	Class II	Class III	Class IV
Blood loss				
ml	<750	750-1500	>1500-2000	>2000
%	<15	15-30	>30-40	>40
Heart rate (beats/min)	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal	Decreased	Decreased	Decreased
Respiratory rate	14-20	20-30	30-40	>40
Urinary output (ml/h)	>30	20-30	5-15	Negligible
Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Fluid replacement (ml/h)	Crystalloid	Crystalloid/colloid	Crystalloid and blood	Crystalloid and blood

From Parrillo JE, Dellinger RP: *Critical care medicine: principles of diagnosis and management in the adult*, ed 4, Philadelphia, 2014, Elsevier.

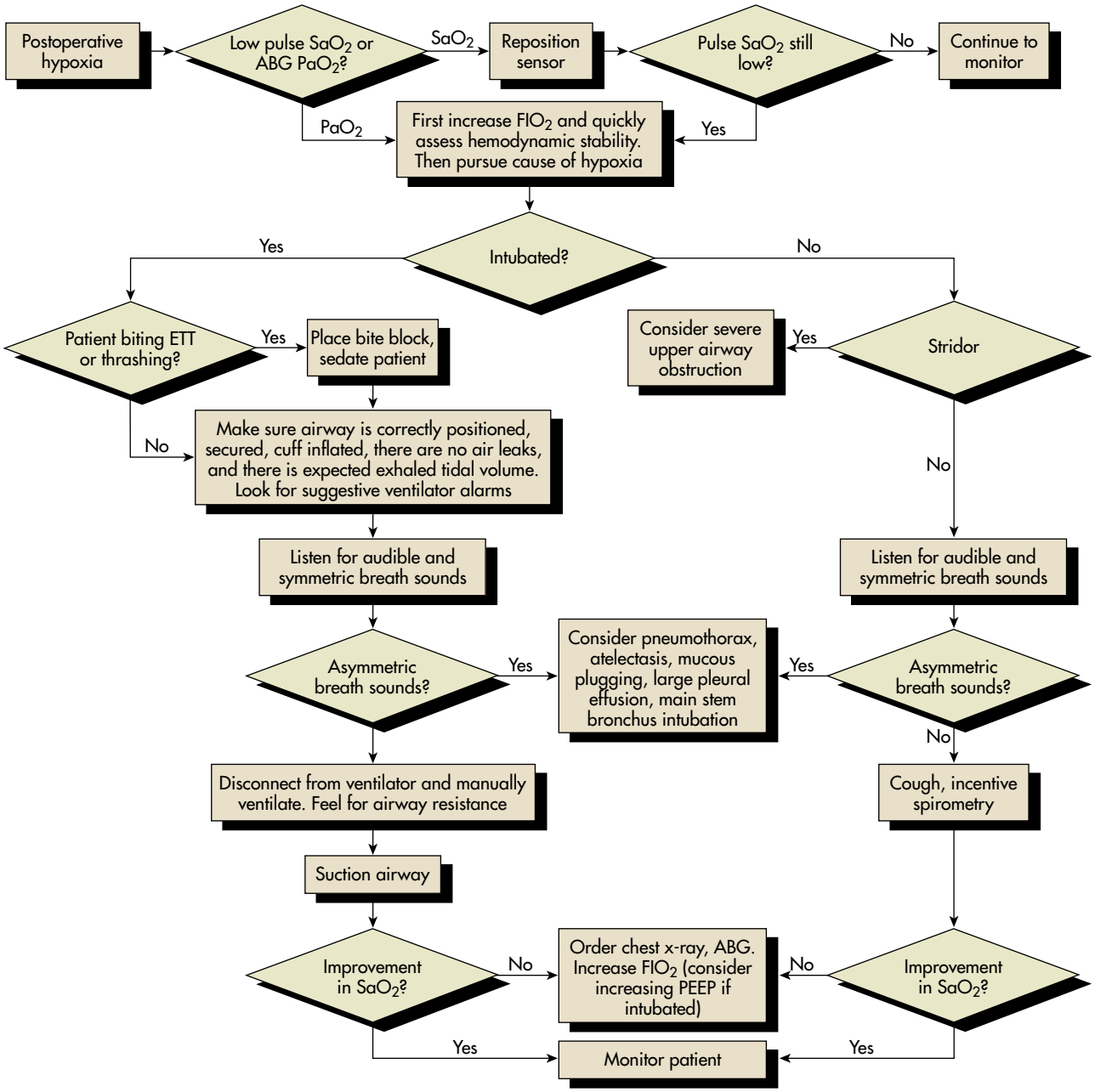


FIG. 97 Approach to managing postoperative hypoxemia. *ABG*, Arterial blood gas; *ETT*, endotracheal tube; Fi_{O_2}, fraction of inspired oxygen; Pa_{O_2}, arterial oxygen tension; *PEEP*, positive end-expiratory pressure; Sa_{O_2}, arterial oxygen saturation. (From Parrillo JE, Dellinger RP: *Critical care medicine: principles of diagnosis and management in the adult*, ed 4, Philadelphia, 2014, Elsevier.)

ICD-10CM #
M00.9 Pyogenic arthritis, unspecified
M86.9 Osteomyelitis unspecified
T84.3 Infection and inflammatory reaction
M79.9 Soft tissue disorder, unspecified

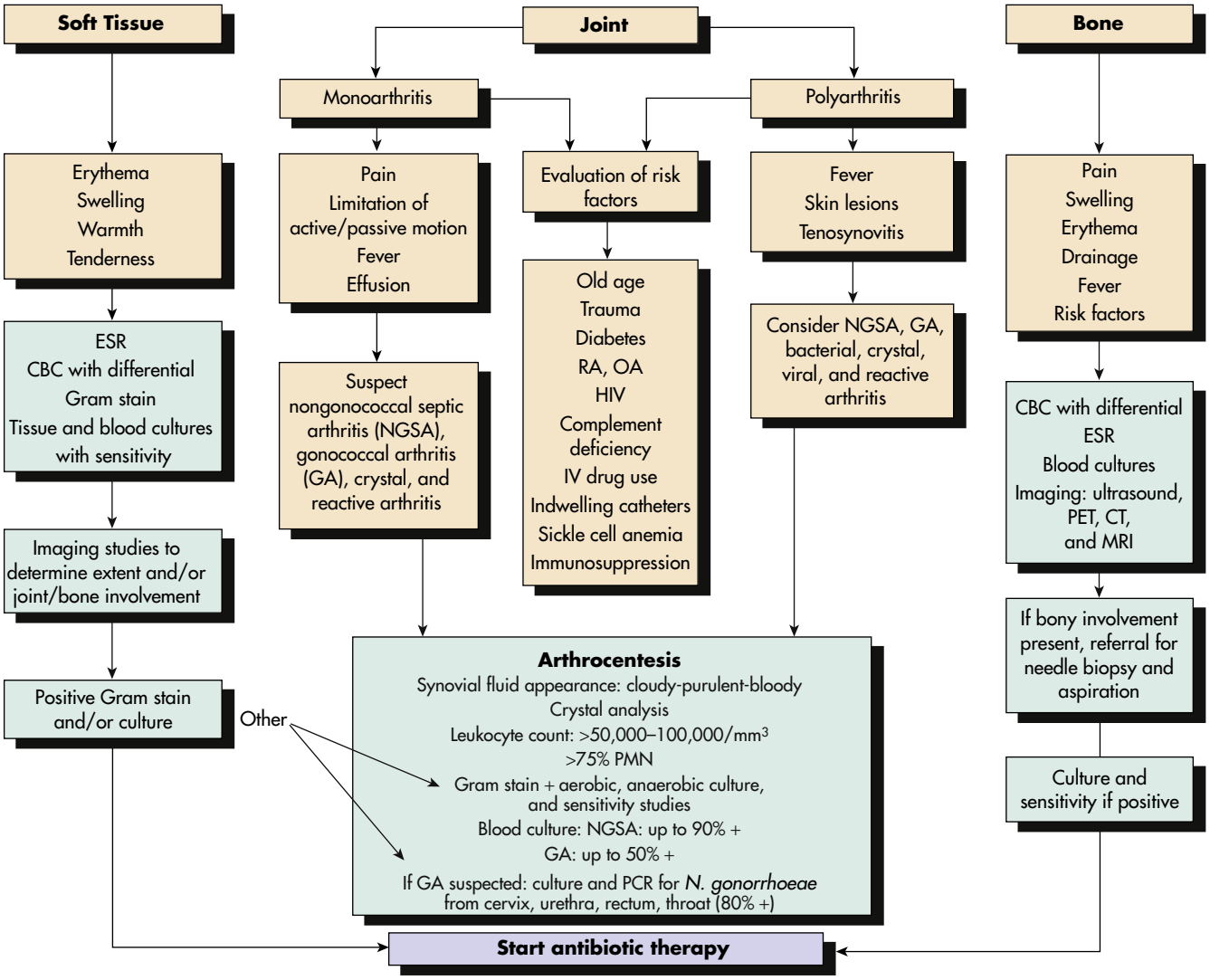


FIG. 98 Clinical evaluation of infections of soft tissues, joints, and bone. *CBC,* Complete blood count; *CT,* computed tomography; *ESR,* erythrocyte sedimentation rate; *GA,* gonococcal arthritis; *HIV,* human immunodeficiency virus; *IV,* intravenous; *MRI,* magnetic resonance imaging; *NGSA,* nongonococcal septic arthritis; *OA,* osteoarthritis; *PCR,* polymerase chain reaction; *PET,* positron emission tomography; *PMN,* polymorphonuclear leukocyte; *RA,* rheumatoid arthritis. (From Goldman L, Schafer AI: *Goldman Cecil medicine,* ed 25, Philadelphia, 2016, Saunders.)

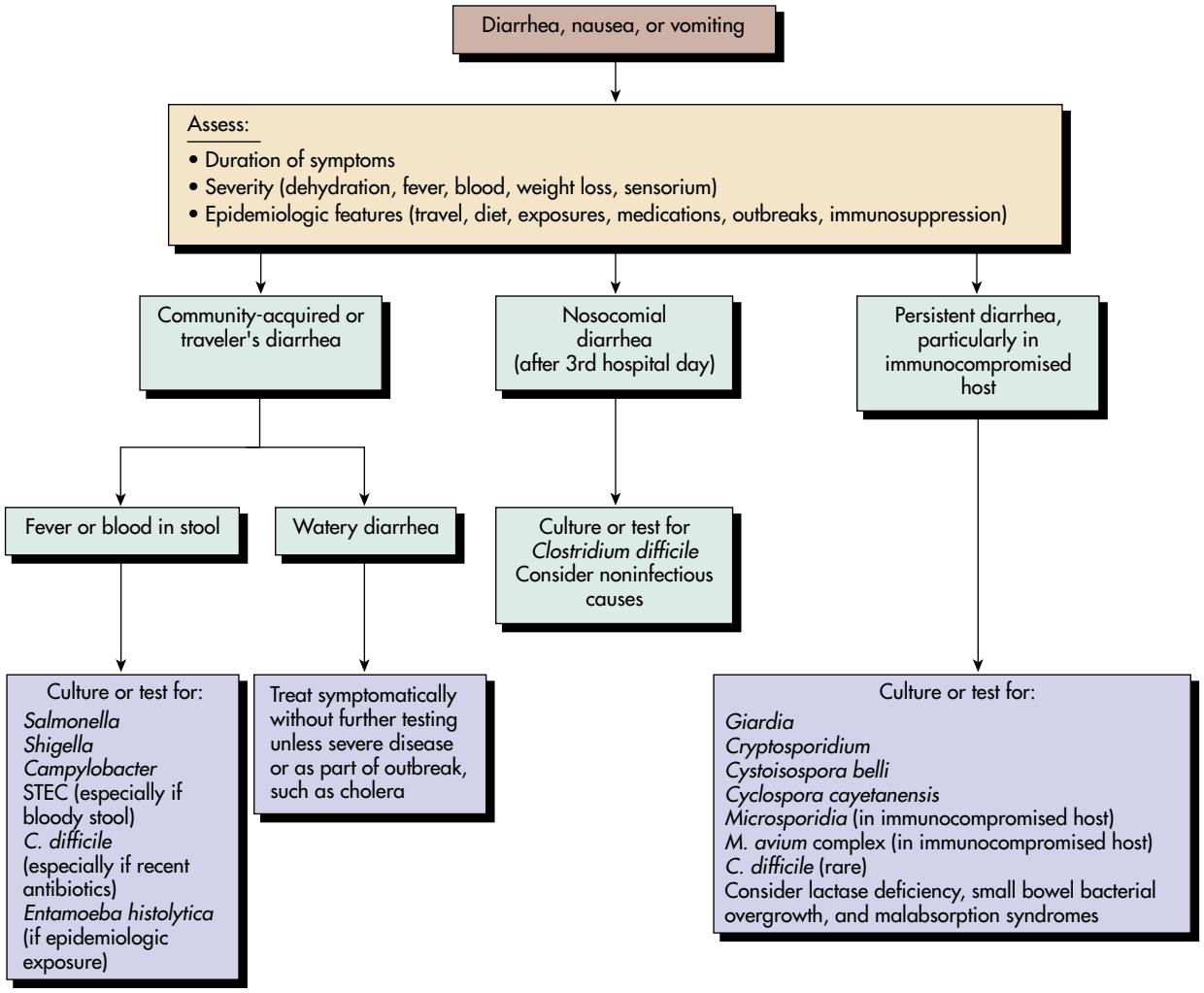


FIG. 99 Approach to diagnosis of infectious diarrhea. *STEC,* Shiga toxin-producing *Escherichia coli.* (From Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 8, Philadelphia, 2015, Saunders.)

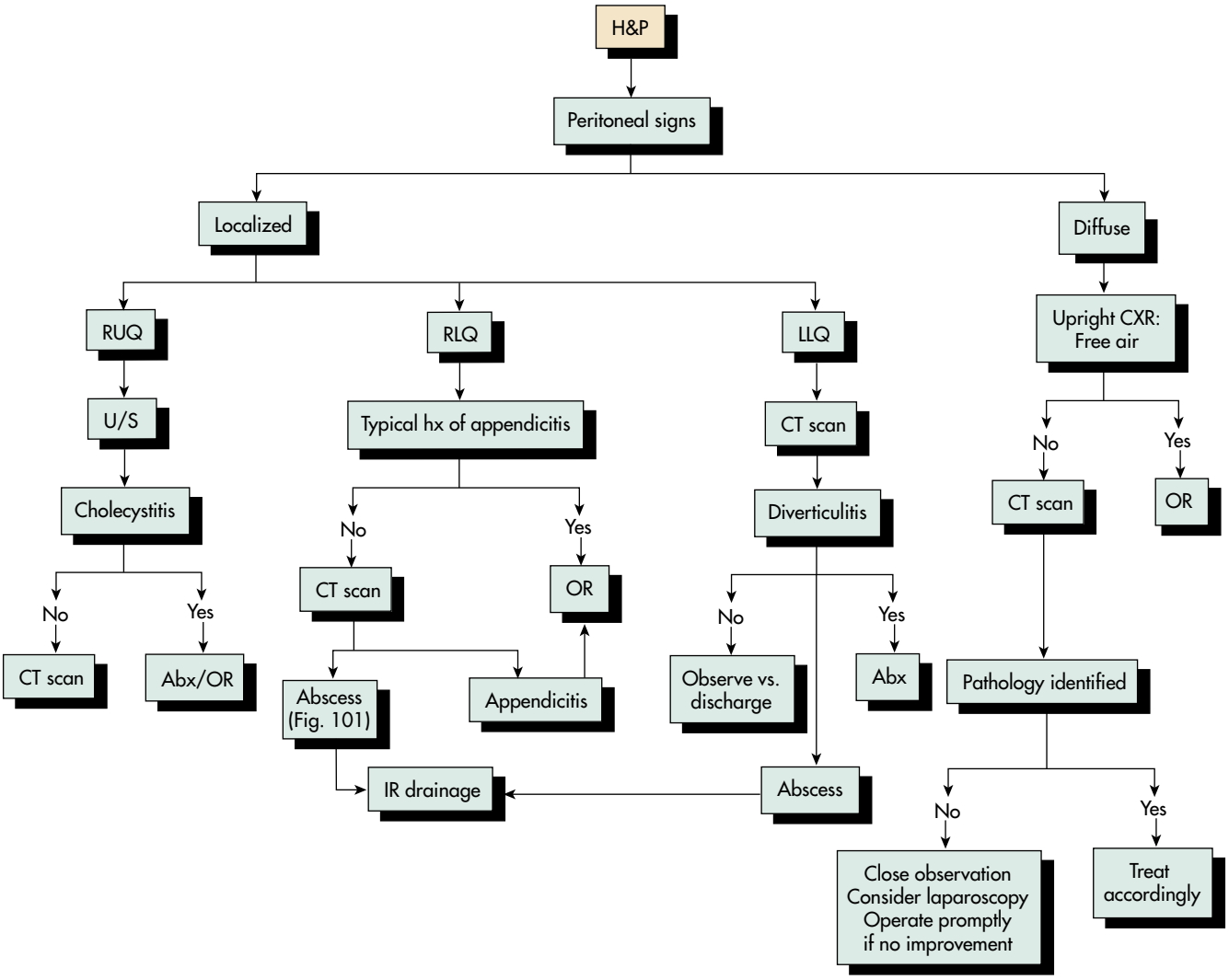


FIG. 100 Algorithm for the diagnosis and management of patients with suspected intraabdominal infection. *Abx,* Antibiotics; *CT,* computed tomography; *CXR,* chest radiograph; *H&P,* History and physical exam; *hx,* history; *IR,* interventional radiology; *LLQ,* left lower quadrant; *RLQ,* right lower quadrant; *RUQ,* right upper quadrant; *U/S,* ultrasound. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

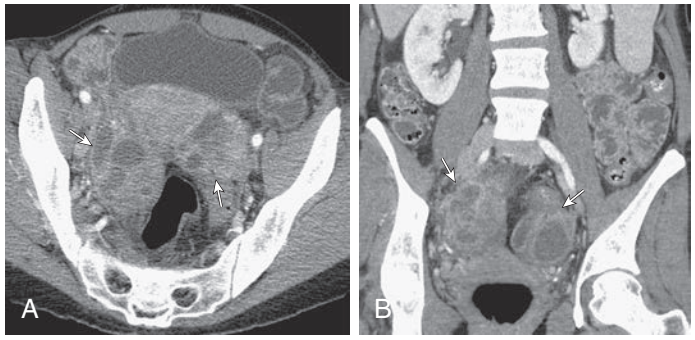


FIG. 101 Axial (A) and coronal (B) postcontrast computed tomographic images showing bilateral tuboovarian abscesses *(arrows).* (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

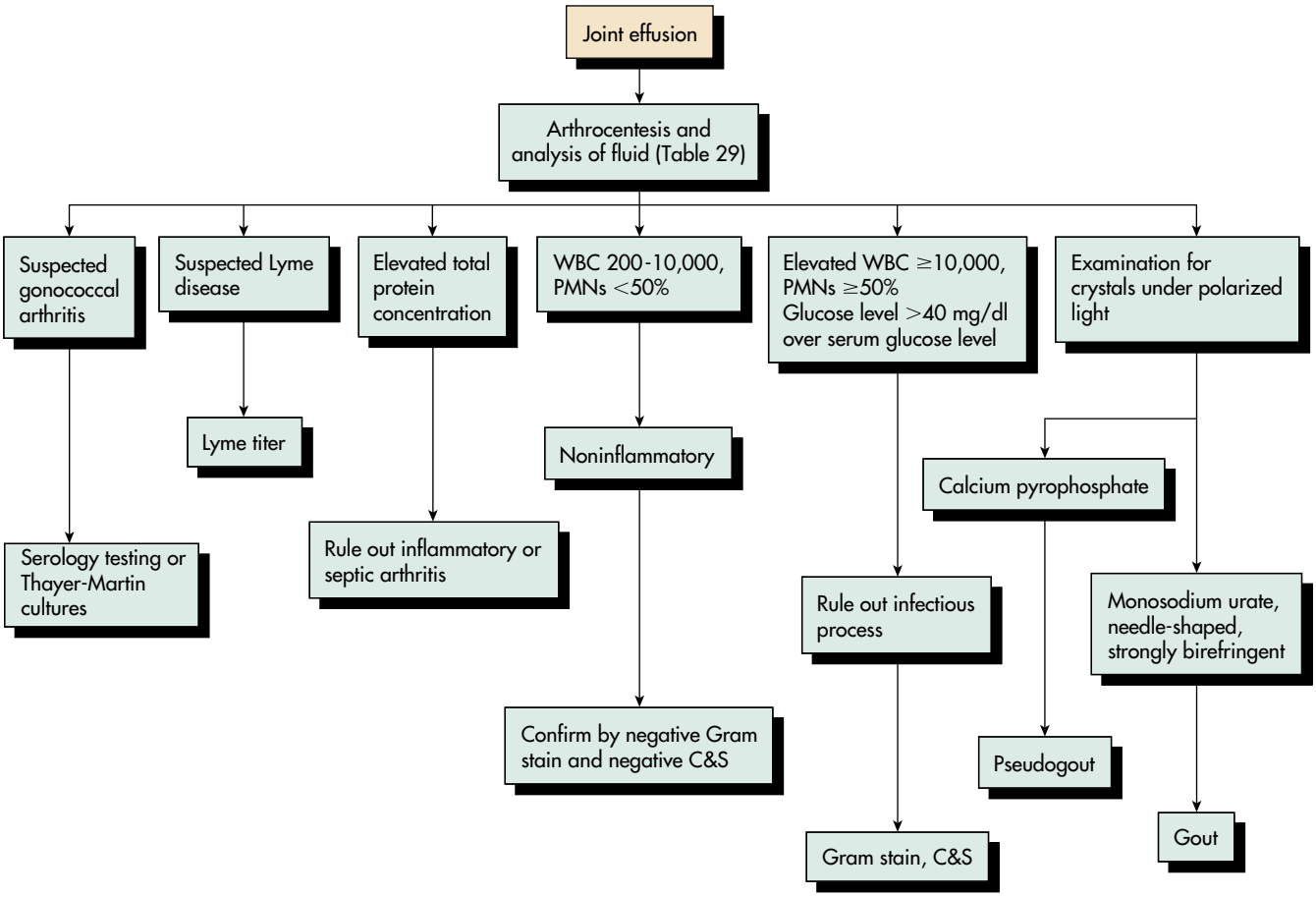


FIG. 102 Joint effusion. See also Section IV, Arthrocentesis Fluid. *C&S,* Culture and sensitivity; *PMNs,* polymorphonuclear leukocytes; *WBC,* white blood cell count.

TABLE 29 Indications for Arthrocentesis

Undiagnosed Arthritis with Effusion

Characterize type of arthritis
- Noninflammatory (WBC <2000/mm^3)
- Inflammatory (WBC >2000/mm^3)
- Septic (WBC >50,000/mm^3)
- Definitive diagnosis
- Gout (urate crystals)
- Pseudogout (calcium pyrophosphate dihydrate crystals)
- Septic arthritis (Gram stain [rare] or culture)

Undiagnosed Arthritis without Effusion

May be definitive in gout (knee, first metatarsophalangeal joint)

Patient with Known Diagnosis

Septic arthritis (repeated taps for adequate drainage)
Other types of arthritis for symptomatic relief (with or without injection)*

WBC, White blood cells.
*Most studies show improved effect if fluid is aspirated before injection.
From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.

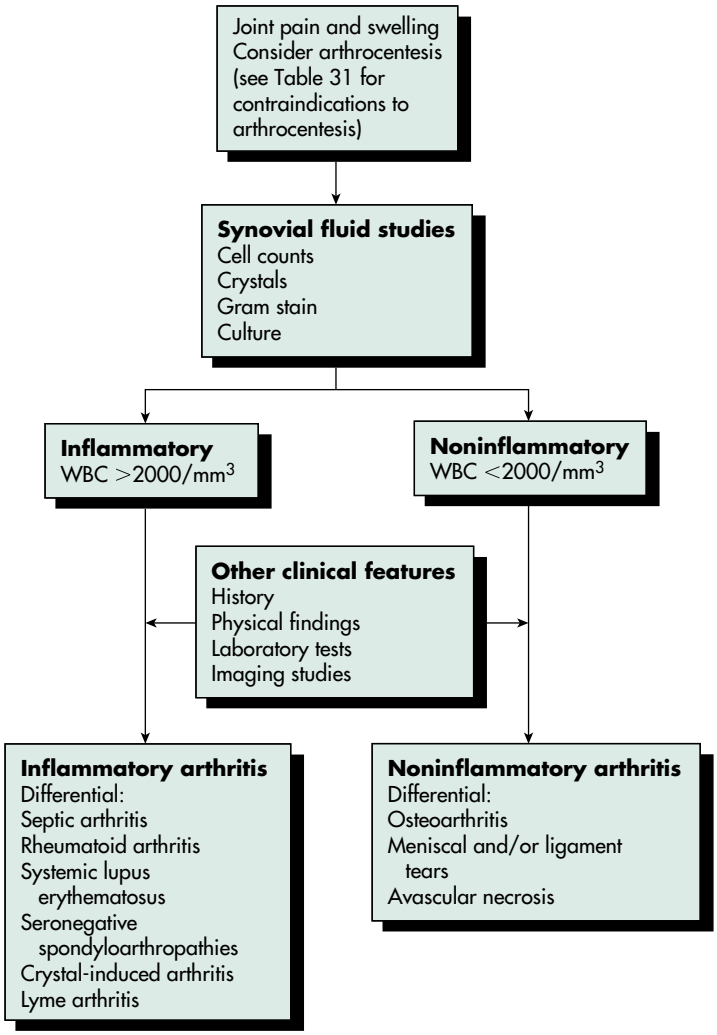


FIG. 103 Diagnostic approach for swollen joints. *WBC,* White blood cell count. (From Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

TABLE 30 Clinical and Radiological Findings in Joint Disease

Condition	Site of Involvement	Discriminatory Findings
Primary osteoarthritis (F>M • >45 years)	Hands	PIP and DIP joint involvement (Heberden and Bouchard nodes) • no osteopenia
	Large joints (e.g., hip, knee)	Joint space narrowing • subchondral sclerosis • subchondral cysts • marginal osteophytes
	Spine	Degenerative disc disease • spondylosis deformans • apophyseal joint involvement • spinal stenosis • foraminal stenosis
Erosive osteoarthritis (affects middle-aged females)	Hands	PIP and DIP joint involvement • joint ankylosis • 'gull-wing' deformities (central erosions and marginal osteophytes)
Rheumatoid arthritis (F>M • Rh factor positive)	Hand and wrist	Symmetrical arthritis • MCP and PIP joint involvement • periarticular (early) and diffuse (late) osteopenia • marginal erosions • subluxation (swan neck and boutonnière deformities) • periostitis is uncommon
	Large joints	Joint space narrowing • marginal erosions • synovial cysts • protrusio acetabulae
	Spine	Atlantoaxial subluxation

TABLE 30 Clinical and Radiological Findings in Joint Disease—cont'd

Condition	Site of Involvement	Discriminatory Findings
Juvenile idiopathic arthritis (M = F • affects children)	Hands	Joint ankylosis • florid periosteal reaction • osteopenia
	Large joints (e.g., knee)	Abnormalities of growth and maturation • epiphyseal overgrowth and premature closure of the physis • widened intercondylar notch
	Cervical spine	Apophyseal joint fusion • atlantoaxial subluxation
Psoriatic arthritis (M>F • nail changes • HLA-B27 +ve)	Upper extremities (e.g., hands)	"Sausage" digit • DIP joint involvement • terminal tuft erosion • pencil-in-cup deformity • joint ankylosis • arthritis mutilans • periosteal reaction • no osteopenia
	SI joints	Asymmetric or unilateral sacroiliitis
	Spine	Coarse syndesmophytes
Reites syndrome (affects young male adults)	Lower extremities (e.g., foot)	Hallux involvement • periosteal reaction • calcaneal erosions • osteopenia not prominent
	Spine	Coarse syndesmophytes
	SI joints	Asymmetric or unilateral sacroiliitis
Ankylosing spondylitis (M>F • affects young adults • HLA-B27 +ve in 95%)	SI joints	Bilateral symmetrical sacroiliitis • ankylosis
	Spine	Anterior vertebral body squaring • syndesmophytes • paravertebral ossification • bamboo spine
	Pelvis	"Whiskering" of the iliac crests and ischial tuberosities
Enteropathic arthropathies	SI joints	Symmetrical sacroiliitis
Gout (M>F)	Hands and feet (especially the great toe)	MTP joint of the great toe • juxta-articular erosions • punched-out lesions with an overhanging margin • no periarticular osteopenia • tophi
CPPD crystal deposition disease (M = F)	Any peripheral joint • predilection for the knee	Degenerative changes • chondrocalcinosis • paucity of subchondral sclerosis
HA crystal deposition disease (M = F)	Predilection for the shoulder (supraspinatus tendon)	Periarticular calcification
Hemochromatosis (M>F)	Hands	2nd and 3rd MCP joint involvement ("squared" metacarpal heads) • joint space narrowing • "hooklike" osteophytes • numerous subchondral cysts
Alkaptonuria (ochronosis) (M = F)	Intervertebral discs • SI joints • large joints	Degenerative changes: disc calcification • joint space narrowing • periarticular sclerosis
Systemic lupus erythematosus (F>M • affects young adults)	Hands	Reversible MCP joint subluxation
Scleroderma (F>M • affects adults)	Hands	IP joint arthritis • acroosteolysis • soft tissue calcifications
Mixed connective tissue disease (overlap syndrome)	Hands	PIP joint, MCP joint, mid-carpal involvement • soft tissue swelling, calcifications, or atrophy
Multicentric reticulohistiocytosis (F>M)	Hands and feet	DIP joint and carpal involvement • soft tissue swelling • articular erosions • no osteopenia
Polymyositis/dermatomyositis	Proximal extremities	Soft tissue calcification
	Hands	DIP joint erosions
Sarcoidosis	Distal and middle phalanges of the hands and feet	Punched-out cystlike lesions • "lacelike" appearance

TABLE 30 Clinical and Radiological Findings in Joint Disease—cont'd

Condition	Site of Involvement	Discriminatory Findings
Hemophilic arthropathy (affecting males—but with female carriers)	Predilection for large joints (e.g., knee)	Epiphyseal overgrowth • juxtaarticular osteopenia • erosion and cartilage destruction • widened intercondylar and trochlear notches • squared patella
Neuropathic arthropathy	Any joint	5 "Ds": normal bone **D**ensity • joint **D**istension • bony **D**ebris • joint **D**isorganization • **D**islocation
Hypertrophic osteoarthropathy	Tubular bones (radius and ulna > tibia and fibula)	Diaphyseal and metaphyseal painful periostitis

From Grant LA, Griffin N: *Grainger & Allison's diagnostic radiology essentials*, ed 2, Philadelphia, 2019, Elsevier.

TABLE 31 Contraindications to Arthrocentesis and Joint Injection

Contraindication	Comment
Established infection in nearby structures (e.g., cellulitis, septic bursitis)	Sometimes gout mimics cellulitis, creating a confusing picture
Septicemia (theoretic risk of introducing organism into joint)	Need to tap suspected septic joints in septic patients
Disrupted skin barrier (e.g., psoriasis)	Do not tap through lesions
Bleeding disorder (not absolute, but use more care)	Risk of bleeding very low, even in patients taking warfarin
Septic joint	Steroid injection contraindicated
Prior lack of response	Relative contraindication
Difficult-to-access joint	Relative contraindication without imaging aid

From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.

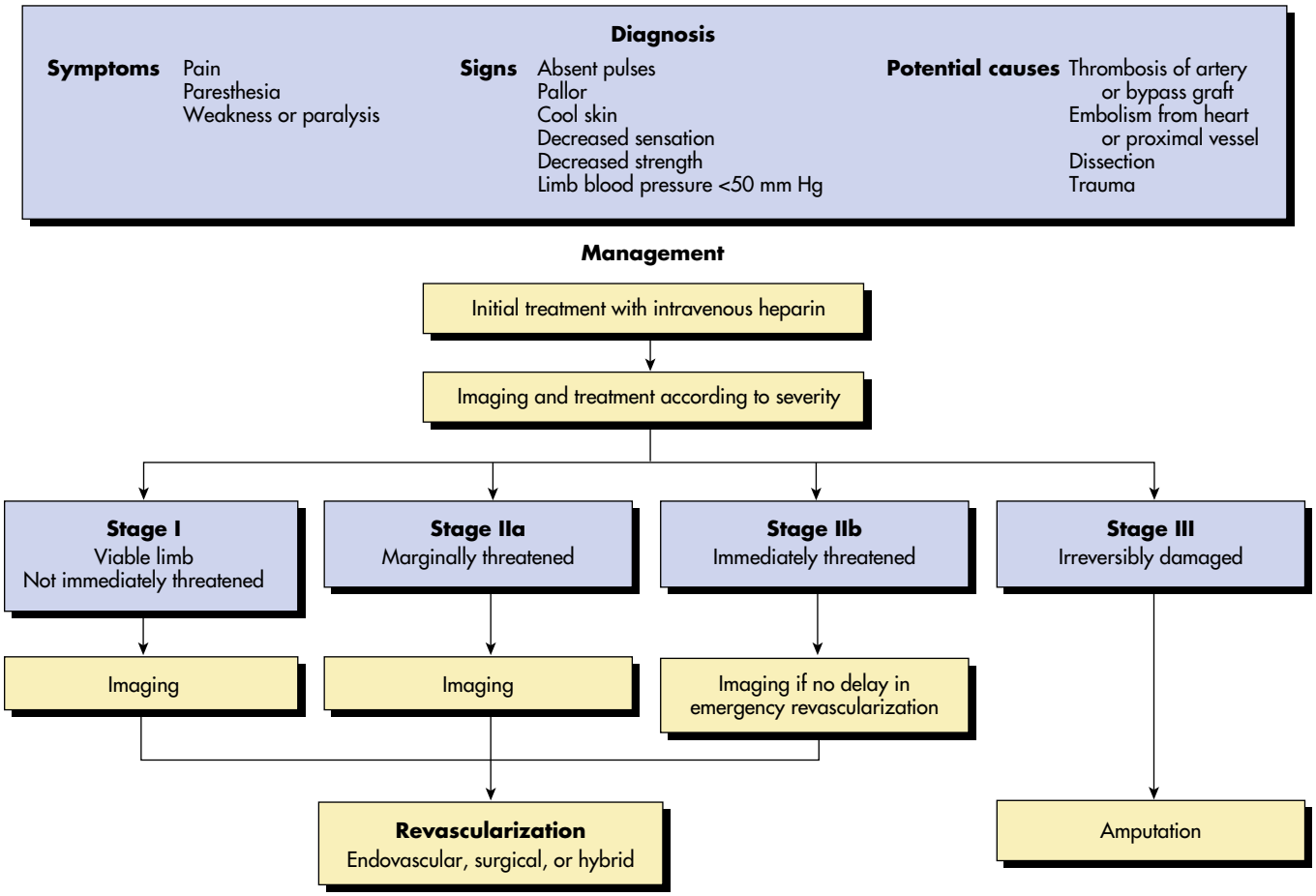


FIG. 104 Diagnostic and treatment approach for patients presenting with acute limb ischemia. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.)

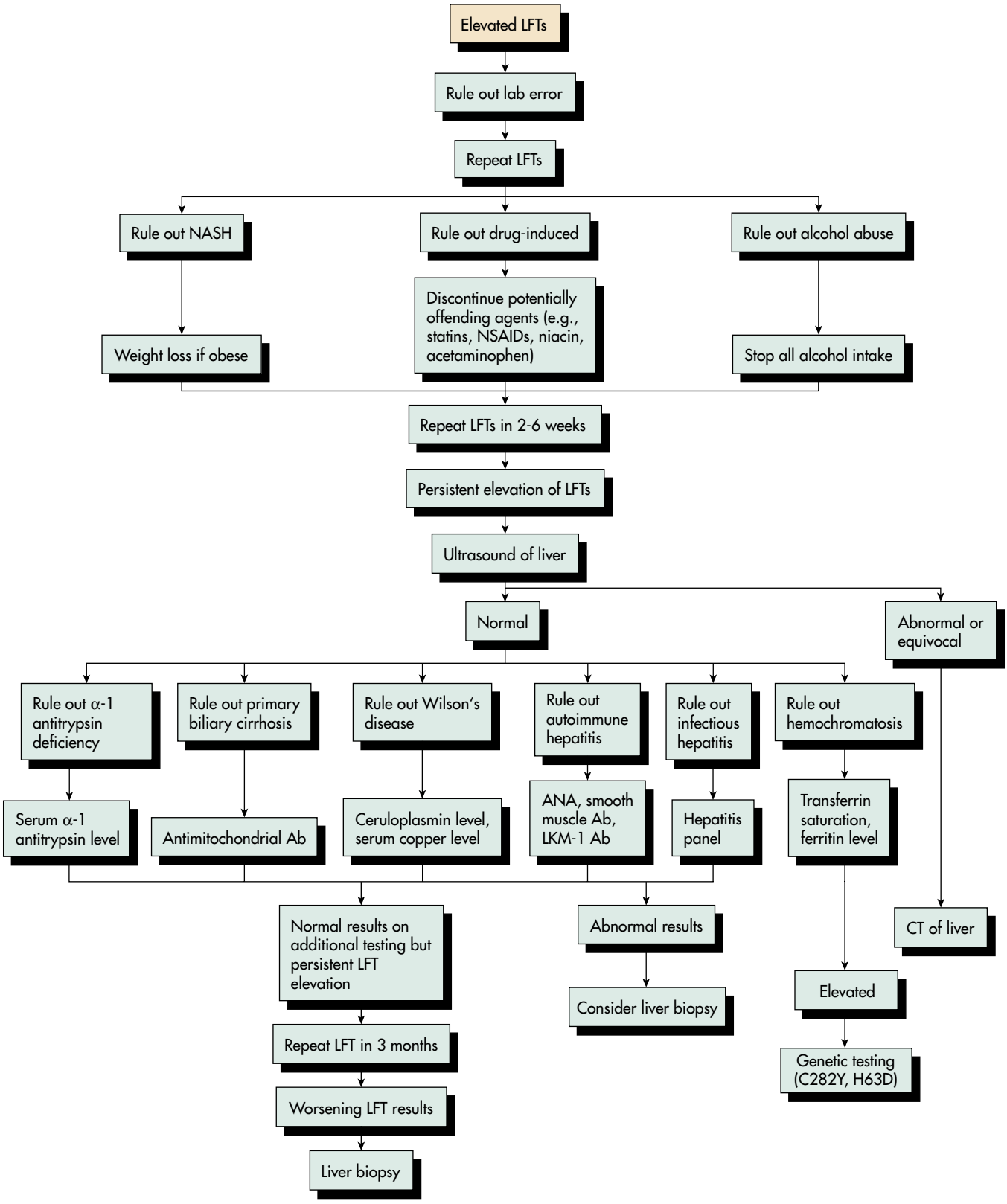


FIG. 105 Liver function test elevations. *Ab,* Antibody; *ANA,* antibody to nuclear antigens; *CT,* computed tomography; *LFTs,* liver function tests; *LKM,* liver-kidney microsome; *NASH,* nonalcoholic steatohepatitis; *NSAIDs,* nonsteroidal antiinflammatory drugs.

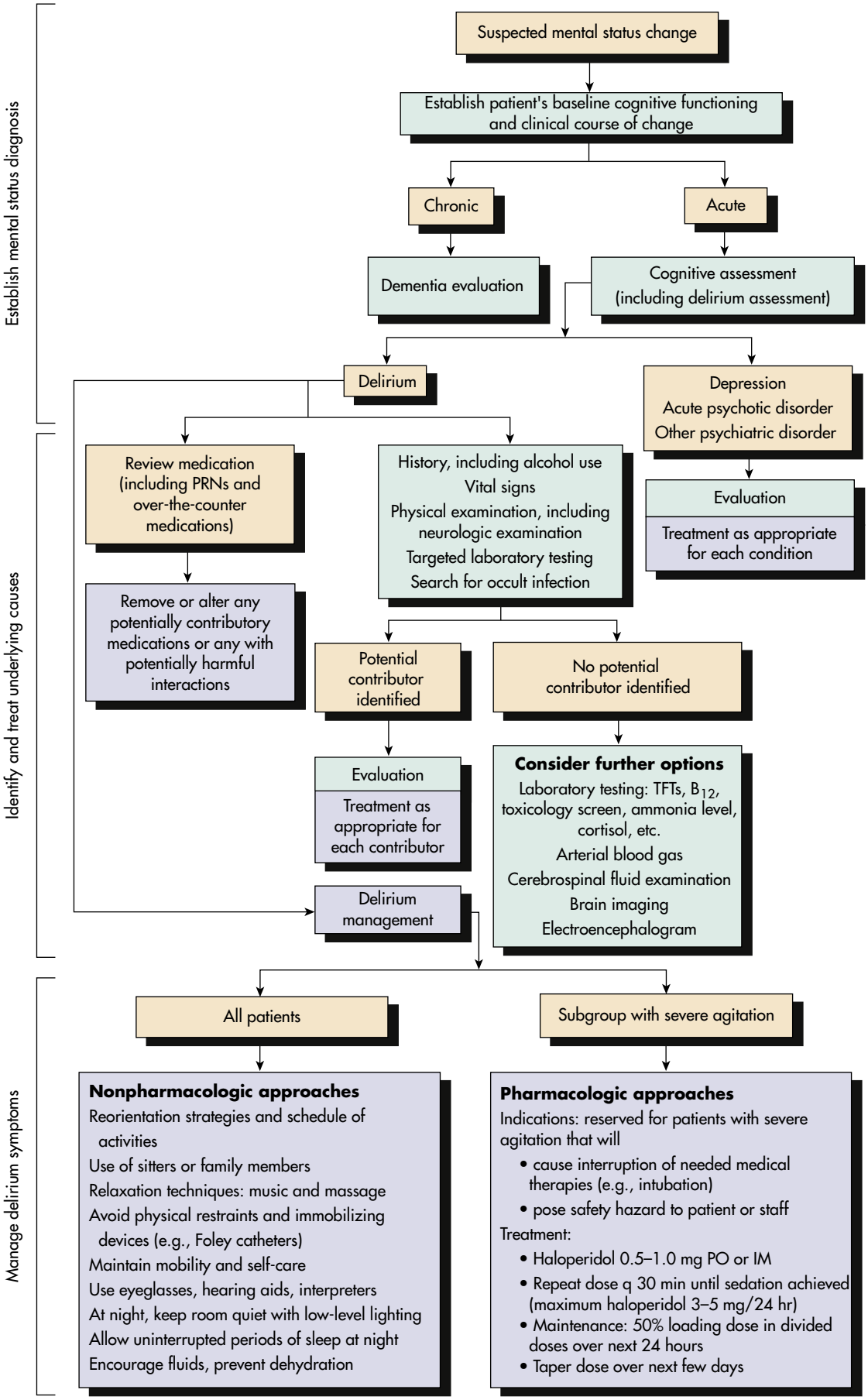


FIG. 106 Algorithm for the evaluation of suspected mental status change in older patients. *PRN*, As needed; *TFTs*, thyroid function tests. (From Goldman L, Schafer AI: *Goldman Cecil medicine*, ed 25, Philadelphia, 2016, Saunders.)

ICD-10CM # M25.50 Pain(s) joint
Arthralgia (allergic)
Arthrodynia
Polyarthralgia

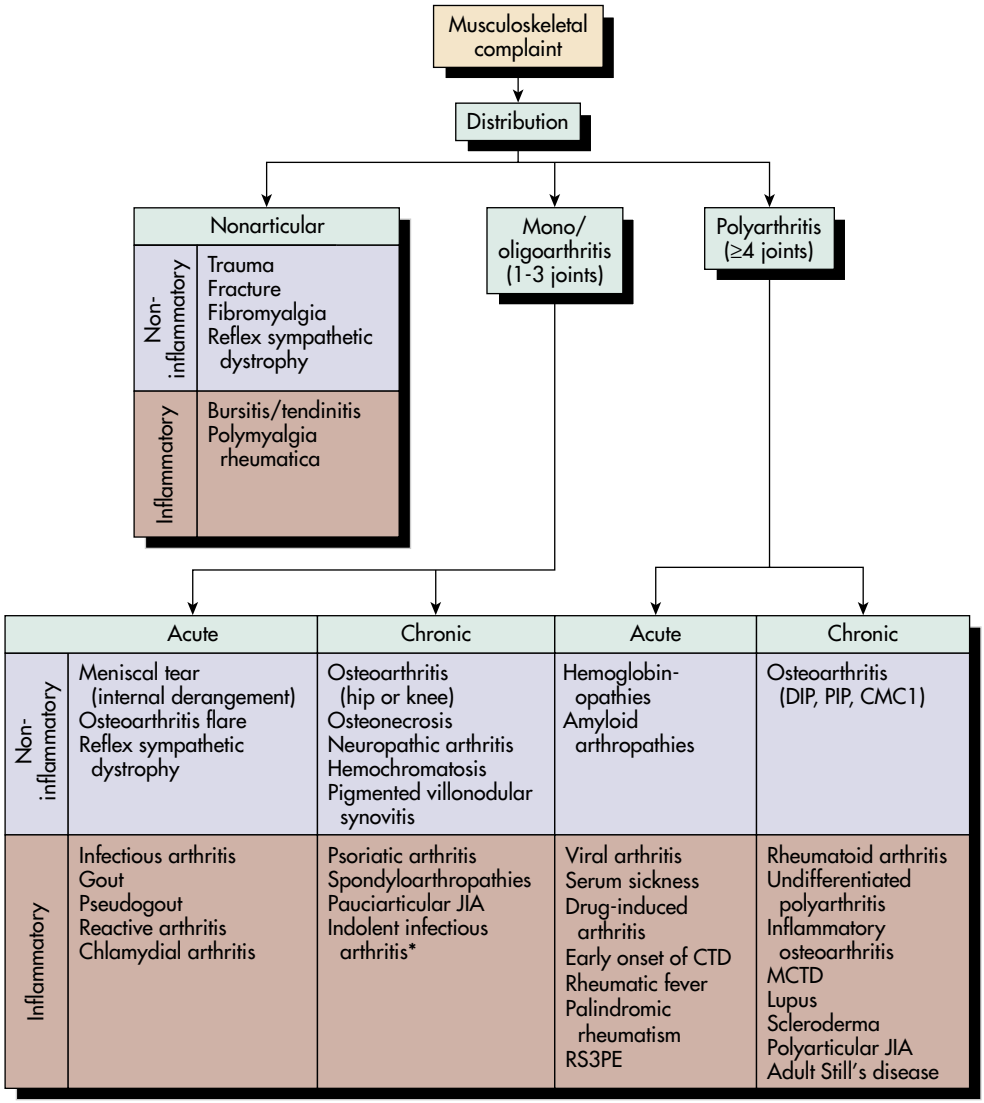


FIG. 107 Algorithm for assessing initial history and examination. *CMC,* Carpometacarpal; *CTD,* connective tissue disease; *DIP,* distal interphalangeal; *JIA,* juvenile idiopathic arthritis; *MCTD,* mixed connective tissue disease; *PIP,* proximal interphalangeal. (From Firestein GS et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.)

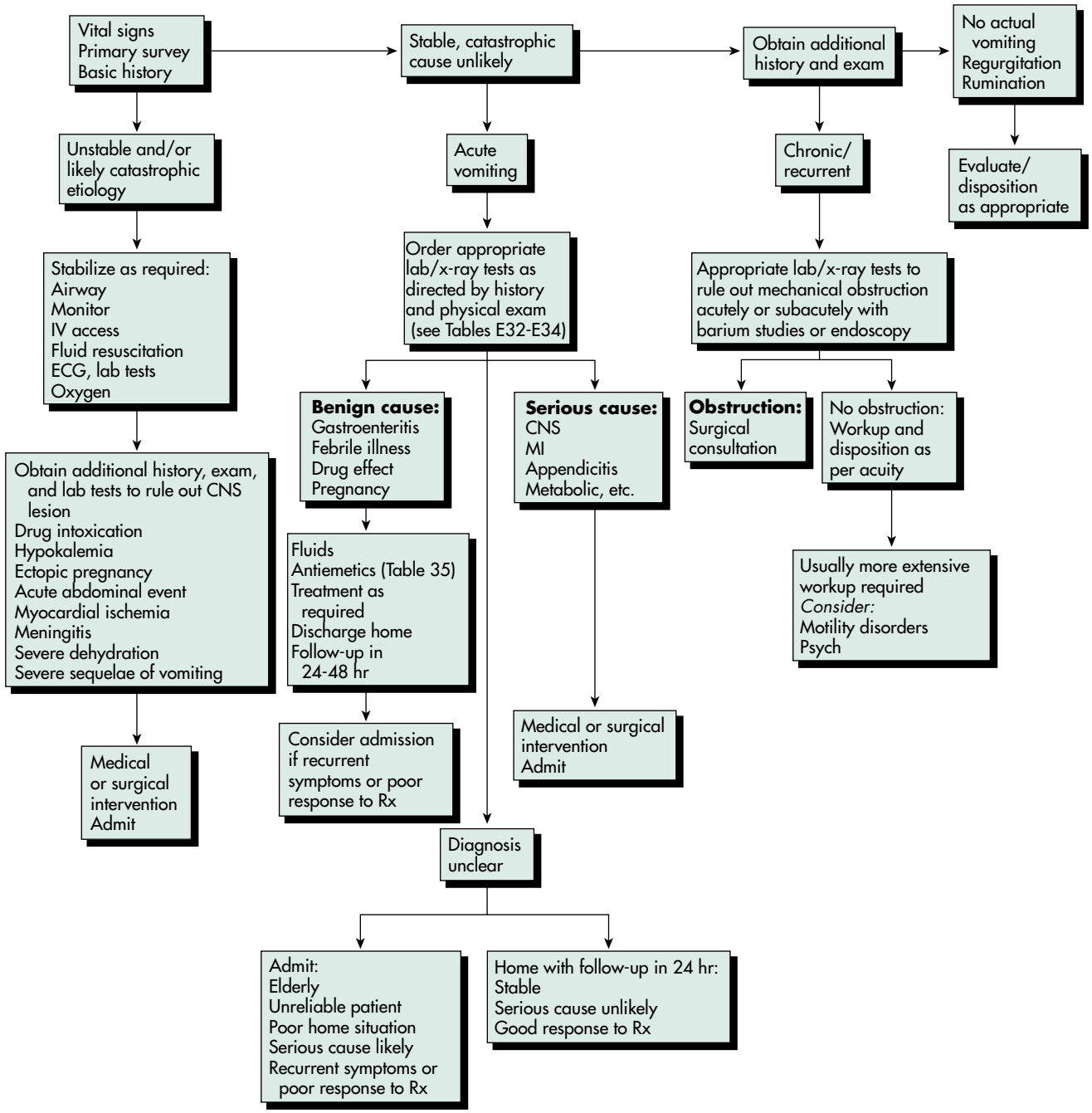


FIG. 108 Approach to the patient with nausea and vomiting. *CNS,* Central nervous system; *ECG,* electrocardiogram; *IV,* intravenous; *MI,* myocardial infarction; *Psych,* psychogenic; *Rx,* treatment. (From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.)

TABLE 32 Differential Diagnosis of Nausea and Vomiting

Etiologic Category	Critical Diagnoses	Emergent Diagnoses	Nonemergent Diagnoses
Gastrointestinal (GI)	• Boerhaave syndrome • Ischemic bowel • GI bleeding	• Gastric outlet obstruction • Pancreatitis • Cholecystitis or cholangitis • Bowel obstruction or ileus • Ruptured viscus • Appendicitis • Peritonitis • Spontaneous bacterial peritonitis	• Gastritis • Gastroparesis • Peptic ulcer disease • Inflammatory bowel disease • Biliary colic • Hepatitis • Gastroenteritis
Neurologic	• Intracerebral bleed • Meningitis	• Migraine • CNS tumor • Raised ICP	
Endocrine	•DKA	• Adrenal insufficiency • Uremia	• Thyroid
Pregnancy		• Hyperemesis gravidarum	• Nausea and vomiting of pregnancy
Drug toxicity		• Acetaminophen • Digoxin • Aspirin • Theophylline	
Therapeutic drug use			• Aspirin • Antibiotics • Erythromycin • Ibuprofen • Chemotherapy
Drugs of abuse			• Narcotics • Narcotic withdrawal • Alcohol
Genitourinary		• Gonadal torsion	Urinary tract infection Poisoning Nephrolithiasis
Miscellaneous	• Myocardial infarction • Sepsis	• Carbon monoxide • Electrolyte disorders • Organophosphate poisoning	• Motion sickness • Labyrinthitis

CNS, Central nervous system; *DKA,* diabetic ketoacidosis; *ICP,* intracranial pressure.
From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.

TABLE 33 Disorders Commonly Associated with Vomiting

Disorder	History	Prevalence	Physical Examination	Useful Tests	Comments
Nausea and vomiting of pregnancy (NVP)	Vomiting occurs predominantly in the morning. Associated breast tenderness. NVP typically starts in weeks 4-7, peaks in weeks 10-16, and disappears by week 20. Vomiting that begins after week 12 or continues past week 20 should prompt a search for another cause.	Very common Affects 75% of all pregnancies	Benign abdomen	Urine pregnancy test Serum electrolytes, urine ketones to exclude hyperemesis gravidarum	Consider NVP in all females of childbearing age. Prognosis for mother and infant is excellent. NVP is associated with a decreased risk of miscarriage, fetal growth retardation, and fetal mortality.
Hyperemesis gravidarum	Severe, protracted form of NVP. No universally accepted definition of the disease. Generally accepted hallmarks include 5% weight loss, ketonuria, and electrolyte disturbance. Hyperemesis is associated with multiple gestation, molar pregnancy, and nulliparity.	Uncommon Affects <1% of pregnancies	Signs of dehydration Benign abdomen	β-hCG Urinalysis for ketones Serum electrolytes Ultrasound examination to exclude molar pregnancy or multiple gestation	Most studies have found no adverse outcomes for the fetus. A few studies, however, have shown a correlation with fetal growth retardation.

TABLE 33 Disorders Commonly Associated with Vomiting—cont'd

Disorder	History	Prevalence	Physical Examination	Useful Tests	Comments
Gastroenteritis	Fever, diarrhea, and crampy abdominal pain. Vomiting and pain occur early, usually followed by diarrhea within 24 hr.	Very common	Benign abdomen	Usually not necessary	Early gastroenteritis, when only vomiting and periumbilical pain are present, may be confused with early appendicitis. Diarrhea is usually in the diagnosis of gastroenteritis.
Gastritis	Epigastric pain, belching, bloating, fullness, heartburn, and food intolerance. Use of NSAIDs or ETOH common.	Very common	Mild epigastric tenderness may be present.	Lipase and pregnancy test may be necessary to exclude other diagnoses.	Removal of inciting agent along with antacid therapy will resolve symptoms in most patients.
Peptic ulcer disease (PUD)	Epigastric pain present in 90% of cases. Classically, duodenal ulcer pain is relieved by food whereas gastric ulcer pain is made worse. Presence of severe pain should raise suspicion of perforation.	Very common	Mild epigastric tenderness	Hemoglobin if bleeding is suspected Heme-positive stool Upright abdominal film if perforation is suspected	Three major causes of PUD are NSAIDs, *Helicobacter pylori* infection, and hypersecretory states.
Biliary disease	Abdominal pain may be midepigastric or right upper quadrant (RUQ). Onset frequently after a fatty meal. May have history of similar episodes in the past.	Very common	RUQ tenderness present in most cases. If instructed to breathe deeply during palpation in the RUQ, the patient experiences heightened tenderness and inspiratory arrest (Murphy sign).	WBCs Lipase Serum bilirubin Alkaline phosphatase RUQ ultrasound examination ERCP	Normal temperature, WBCs, and spontaneous resolution of symptoms suggest biliary colic. Fever, Murphy sign, elevated WBCs, and suggestive ultrasound indicate cholecystitis.
Myocardial infarction (MI)	Patients typically have substernal chest pain that may radiate to left arm or jaw. Often associated with dyspnea, diaphoresis, or dizziness.	Common	Patients often are anxious and in distress from pain. No diagnostic examination findings.	ECG (new Q waves, ST segment changes, or T wave inversions) troponin	Not all patients have chest pain. A subset of patients, particularly diabetics and elders, may have only nausea, vomiting, and epigastric discomfort.
Diabetic ketoacidosis (DKA)	Polydipsia and polyuria occur early Without treatment, altered mental status and coma may develop. In patients with long-standing diabetes, DKA may be triggered by infection, trauma, MI, or surgery.	Common	"Fruity" breath odor results from serum acetone. Tachypnea occurs with attempts to "blow off" carbon dioxide to compensate for metabolic acidosis. Signs of dehydration may be present. Severe cases often manifest with altered mental status or coma.	Serum glucose, urine ketones, ABGs	DKA may be the first manifestation of diabetes in some patients. These patients often do not recognize the importance of polydipsia and polyuria. They often report only nausea, vomiting, and epigastric pain.
Pancreatitis	Presenting symptom is epigastric pain, which often radiates to the back. Most cases are caused by gallstones or alcoholism. Other causes include hypercalcemia, hyperlipidemia, drugs (sulfas and thiazides), ERCP.	Common	Epigastric tenderness is present. Associated paralytic ileus may cause abdominal distention and decreased bowel sounds. Frank shock may be present in severe cases.	Lipase WBCs, serum glucose, LDH, AST Hematocrit, BUN, calcium, ABGs	Criteria correlating with higher mortality: *At admission*—age >55 yr, WBCs >16,000/mm^3, glucose >200 dl, base deficit >4, LDH >350 IU/L, AST >250 U/L *Within 48 hours*—Hct drop of 10%, BUN >2 mg/dl, Po_2<60 mm Hg, calcium <8 mg, fluid sequestration >4 L
Appendicitis	Abdominal pain classically begins in periumbilical region and later moves to right lower quadrant. Anorexia is common.	Common	Localized tenderness over right lower quadrant. Low-grade fever may be present.	WBCs Ultrasound Abdominal CT	Early appendicitis can be a difficult diagnosis to make. It is still frequently missed on the first physician encounter.
Bowel obstruction	Classically, abdominal pain consists of intermittent cramps occurring at regular intervals. The frequency of the cramps varies with the level of the obstruction; the higher the level, the more frequent the cramps. The location of the pain also varies with the level of the obstruction; high obstruction causes epigastric pain, midlevel obstruction causes periumbilical pain, colonic obstruction causes hypogastric pain.	Common	Abdominal distention, mild diffuse tenderness, and high-pitched "tinkling" bowel sounds may be present. Thorough search for hernias should be performed.	Supine and upright plain abdominal films Abdominal CT	Adhesions, hernias, and tumors account for 90% of bowel obstructions. Other causes include intussusception, volvulus, foreign bodies, gallstone ileus, inflammatory bowel disease, stricture, cystic fibrosis, and hematoma.

Continued

TABLE 33 Disorders Commonly Associated with Vomiting—cont'd

Disorder	History	Prevalence	Physical Examination	Useful Tests	Comments
Carbon monoxide (CO) poisoning	Headache is usually present. CO poisoning often occurs during winter months when furnaces are turned on. Family members may have similar symptoms if they also have been exposed.	Uncommon	No reliable signs of early CO poisoning	CO level	Because CO is a tasteless, odorless gas, patients may not realize they have been exposed. It is important to keep a high index of suspicion during the cold months.
Boerhaave syndrome	Patients may have neck, chest, or epigastric pain. Forceful, protracted vomiting usually causes the tear. Most cases follow a bout of heavy eating and drinking. Other reported causes include childbirth, defecation, seizures, and heavy lifting.	Uncommon	Tachypnea, tachycardia, and hypotension may be present. Escaped air from the esophagus may produce subcutaneous emphysema. Air in the mediastinum produces a "crunching" sound as the heart beats (Hamman sign).	CXR may show pleural effusion, widened mediastinum, pneumothorax, or pneumomediastinum. Esophagogram with water-soluble contrast is definitive.	The classic presentation includes forceful vomiting, severe chest pain, subcutaneous emphysema, and multiple CXR findings. There is a growing body of evidence that most cases do not have this "classic" picture. In more subtle presentations, the diagnosis can be difficult to make.

ABGs, Arterial blood gases; *AST,* aspartate aminotransferase; *β-hCG,* β-human chorionic gonadotropin; *BUN,* blood urea nitrogen; *CT,* computed tomography; *CXR,* chest radiography; *ECG,* electrocardiogram; *ERCP,* endoscopic retrograde cholangiopancreatography; *ETOH,* ethyl alcohol; *Hct,* hematocrit; *LDH,* lactate dehydrogenase; *NSAID,* nonsteroidal antiinflammatory drug; Po_2, partial pressure of oxygen; *WBC,* white blood cell.
From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Saunders.

TABLE 34 Etiology of Nausea and Vomiting in Pediatric Age Groups

Etiologic Category	Newborn	Infant	Child	Adolescent
Infectious	Sepsis, meningitis, UTI, thrush	Pneumonia, otitis media, thrush	Gastroenteritis	Gastroenteritis, URI
Anatomic	Atresia and webs, malrotation, stenosis, meconium ileus, Hirschsprung disease	Pyloric stenosis, intussusception, Hirschsprung disease	Bezoars, chronic granulomatous disease	PUD, superior mesenteric syndrome
Gastrointestinal	Reflux, overfeeding, gastric outlet obstruction, volvulus	Reflux, gastritis, milk intolerance	Appendicitis, pancreatic, hepatitis, other food intolerance	Achalasia, hepatitis
Neurologic	Subdural hematoma, hydrocephalus	Subdural hematoma	Neoplasia, migraine, Reye syndrome, motion sickness, hypertension	Neoplasia, migraine, motion sickness, hypertension
Metabolic	Organic or amino acidemias, urea cycle defects, galactosemia, hypercalcemia, phenylketonuria, kernicterus	Hereditary fructose intolerance, disorders of fatty acid metabolism, uremia, adrenal hyperplasia, kernicterus	Diabetes, vitamin A excess	Diabetes, pregnancy, acute intermittent porphyria
Other	Idiopathic, cardiac failure	Rumination, cardiac failure	Cyclic vomiting syndrome, toxins, food poisoning, Munchausen syndrome by proxy	Psychogenic, anorexia

PUD, Peptic ulcer disease; *URI,* upper respiratory infection; *UTI,* urinary tract infection.
Adapted from Li HK, Sunku BK: Vomiting and nausea. In Wyllie R, Hyams JS, editors: *Pediatric gastrointestinal and liver disease: pathophysiology, diagnosis, management.* Philadelphia: WB Saunders; 2005:127-149. From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Saunders.

TABLE 35 Commonly Used Medications for the Treatment of Nausea and Vomiting

Medication	Dose	Comments
Promethazine (Phenergan)	*Adult:* 12.5-25 mg IV, IM, PO, or by rectum *Pediatric:* 0.25-1 mg/kg/dose q4-6h prn IV, IM, PO, or by rectum; max 25 mg/dose	May be repeated every 4-6 hr until cessation of vomiting. May cause dry mouth, dizziness, blurred vision. Boxed warning for use under 2 yr old.
Prochlorperazine (Compazine)	*Adult:* 5-10 mg IM or PO; 2.5-10 mg IV; 25 mg by rectum *Pediatric:* 0.4 mg/kg/24 hr tid-qid PO or by rectum; 0.1-0.15 mg/kg/dose tid-qid IM; max 40 mg/24 hr	May be repeated every 4 hr IV or IM or every 12 hr by rectum until cessation of vomiting. May cause lethargy, hypotension, extrapyramidal effects.
Metoclopramide (Reglan)	*Adult:* 10 mg IM or IV, may repeat q6h *Pediatric:* 1-2 mg/kg/dose q2-6h IV q2-3h	May cause dystonic reactions, tardive dyskinesia, neuroleptic malignant syndrome.
Ondansetron (Zofran)	*Adult:* 4 mg IV single dose *Pediatric:* up to 40 kg: 0.1 mg/kg; >40 kg: 4 mg/dose IV single dose	May cause headache, dizziness, and musculoskeletal pain.

IM, Intramuscularly; *IV,* intravenously; *PO,* orally; *prn,* as needed.
From Marx JA et al: *Rosen's emergency medicine,* ed 8, Philadelphia, 2014, Saunders.

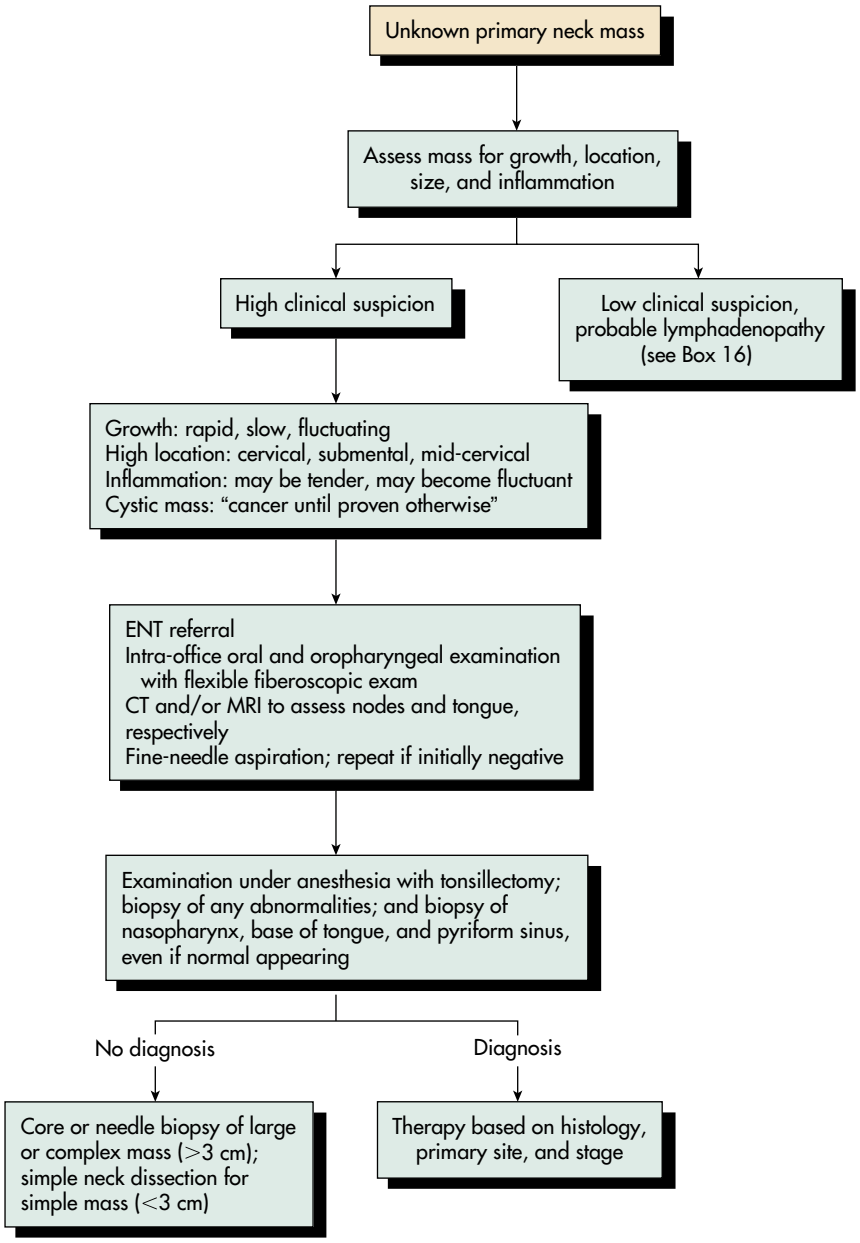


FIG. 109 Evaluation of an unknown primary neck mass. *CT,* Computed tomography; *ENT,* ear, nose, and throat; *MRI,* magnetic resonance imaging. (From Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

BOX 16 An Approach to the Patient with Lymphadenopathy

- Does the patient have a known illness that causes lymphadenopathy? Treat and monitor for resolution.
- Is there an obvious infection to explain the lymphadenopathy (e.g., infectious mononucleosis)? Treat and monitor for resolution.
- Are the nodes very large and/or very firm and thus suggestive of malignancy? Perform a biopsy.
- Is the patient very concerned about malignancy and unable to be reassured that malignancy is unlikely? Perform a biopsy.
- If none of the preceding are true, perform a complete blood cell count, and if it is unrevealing, monitor for a predetermined period (usually 2 to 6 weeks). If the nodes do not regress or if they increase in size, perform a biopsy.

From Goldman L, Ausiello D (eds): *Cecil textbook of medicine,* ed 23, Philadelphia, 2008, Saunders.

ICD-10CM # M54.2 Cervicalgia
S19.9XXA Unspecified injury of neck, initial encounter

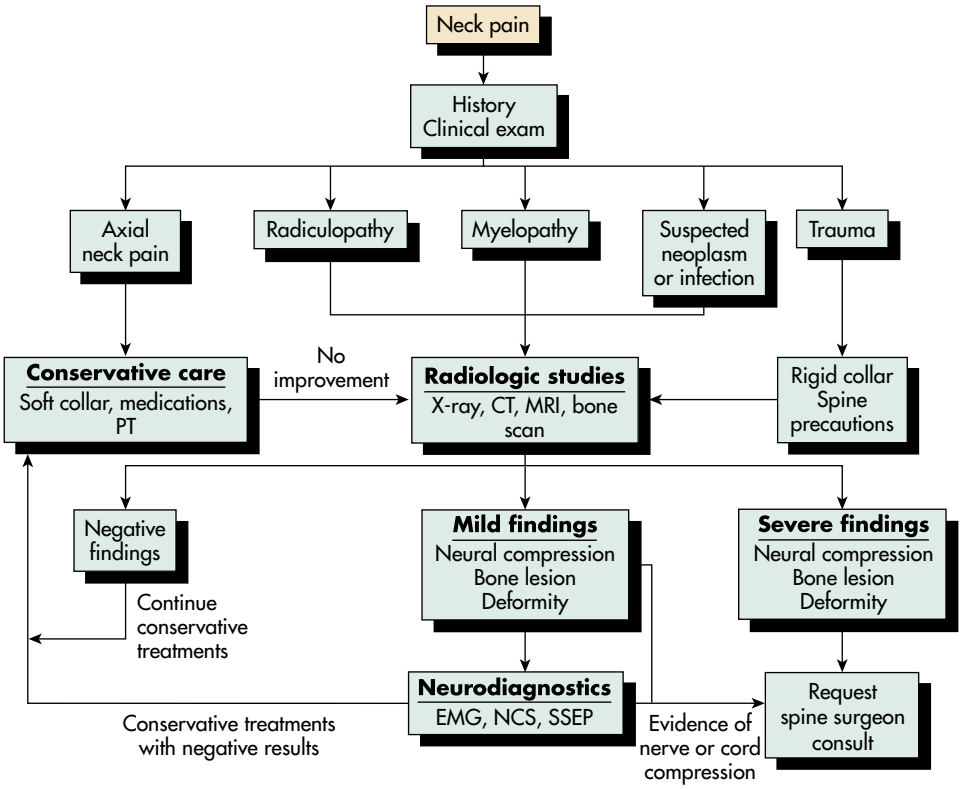


FIG. 110 Algorithm of neck pain. *CT,* Computed tomography; *EMG,* electromyogram; *MRI,* magnetic resonance imaging; *NCS,* nerve conduction study; *PT,* physical therapy; *SSEP,* somatosensory evoked potentials. (From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

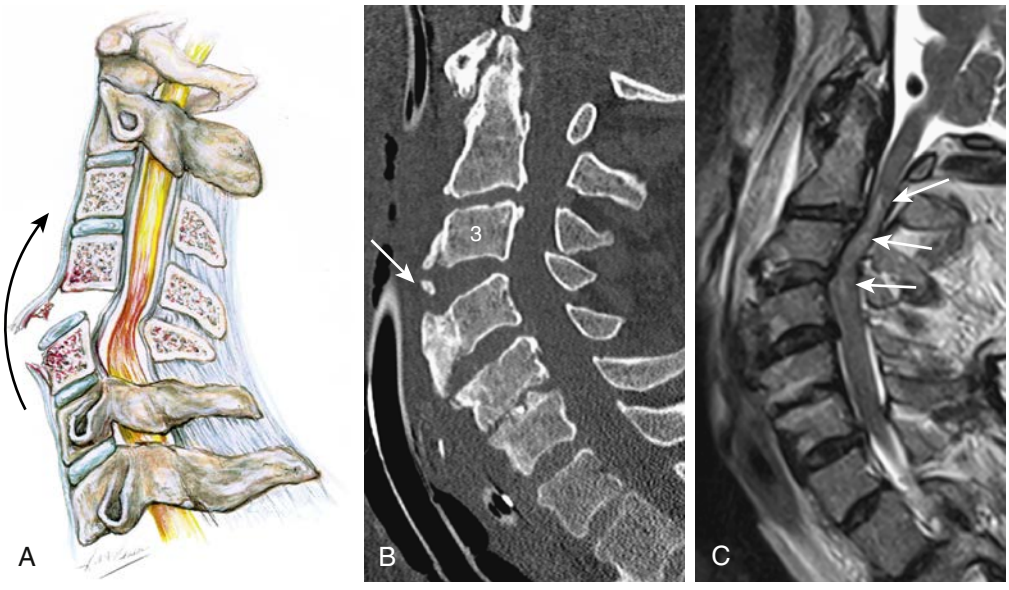


FIG. 111 Extension injury. A, Drawing shows mechanism and injury. There is a small avulsion from the anterosuperior margin of the vertebra immediately below the affected level. Note the wide disk space and retrolisthesis, hallmarks of this injury. The spinal cord is frequently injured in this setting. **B,** Sagittal reconstructed computed tomography image shows widening of the C3 disk space with an avulsed fragment of bone *(arrow)* and retrolisthesis. **C,** T2-weighted magnetic resonance image shows cord hemorrhage *(arrows).* The patient is quadriplegic. (From Pope TL et al: *Musculoskeletal imaging,* ed 2, Philadelphia, 2015, Elsevier.)

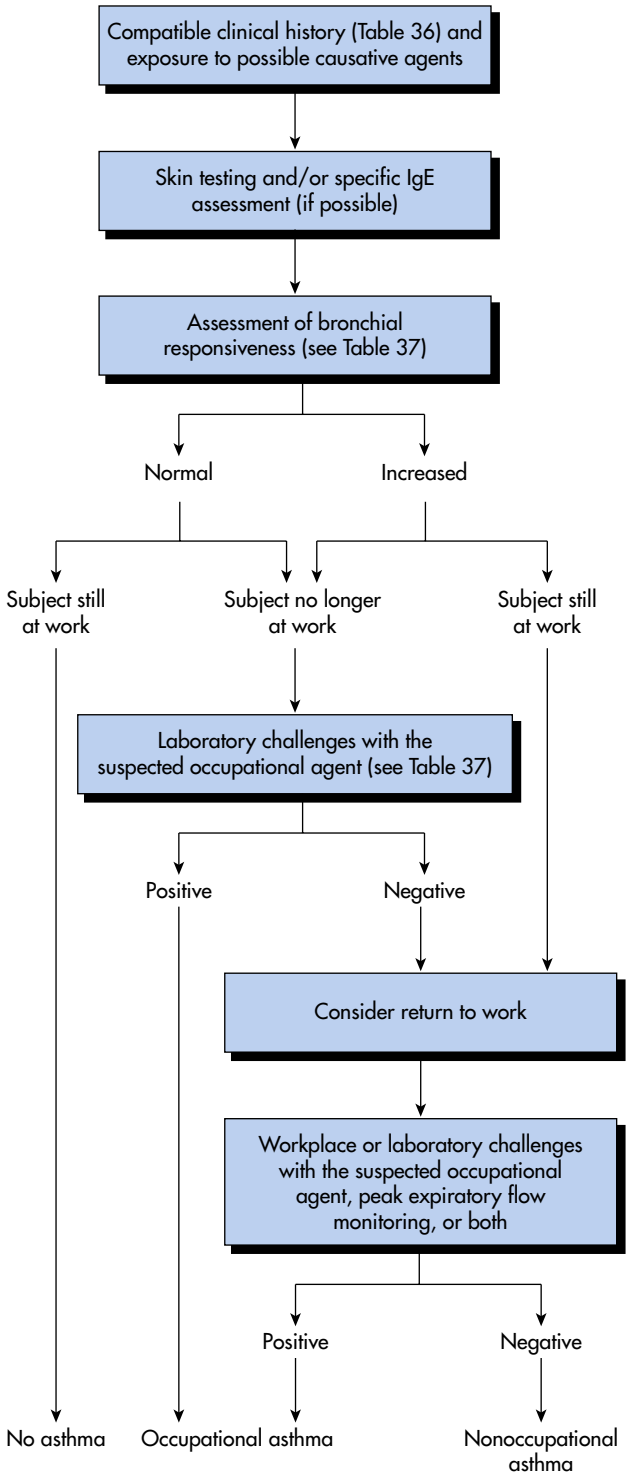


FIG. 112 Algorithm for the investigation of occupational asthma. *IgE*, Immunoglobulin E. (From Adkinson NF et al: *Middleton's allergy principles and practice*, ed 8, Philadelphia, 2014, Saunders.)

TABLE 36 Differences between Occupational Asthma with a Latency Period and Irritant-Induced Asthma

	OA with a Latency Period	IrIA
Latency period	Variable but at least a matter of weeks	Onset of symptoms within minutes or hours
Mechanisms	Immunologic sensitization	?
Physiopathology	Like common asthma	Massive epithelial desquamation with early deposition of collagen. No role of eosinophils. Oxidative process
Frequency	85%-90% of all cases of OA	10%-15% of all cases of OA
Symptoms	Wheeze predominant	Cough predominant
Function	The degree of airway hyperresponsiveness to methacholine reflects severity	Severity not reflected by the degree of responsiveness to methacholine
Response to bronchodilator	+++	++
Response to inhaled steroids	+++	++
Improvement with time	Good in general	Moderate, little, or absent

IrIA, Irritant-induced asthma; *OA,* occupational asthma.
From Mason RJ et al: *Murray & Nadel's textbook of respiratory medicine,* ed 5, Philadelphia, 2010, Saunders.

TABLE 37 Advantages and Limitations of Diagnostic Tests Used in the Investigation of Occupational Asthma (OA)

Diagnostic Test(s)	Advantages/Limitations
Assessment of bronchial responsiveness	• Simple, low cost • Allow to confirm the diagnosis of asthma • Low specificity for diagnosis of OA. The lack of NSBHR does not allow discarding the diagnosis of OA in subjects who have been removed from the workplace.
Immunologic tests	• Easy to perform, low cost • Commercial extracts are available (skin-prick tests or specific IgE for HMW agents). • Lack of standardization for a majority of occupational allergens except latex • Measure of specific IgE available for some LMW agents (anhydrides, acids, isocyanates, aldehydes), but low sensitivity • Identify the sensitization but not the disease itself
PEF monitoring	• Low cost • Requires the worker's collaboration • Low adherence (<60%) • Possible falsification of the results • Requires 2 weeks at and away from work, which are not always possible for the workers • Impossible to perform when the worker has already been removed from exposure • No standardized method for interpreting the results • Interpretation of the results requires experience.
Specific inhalation challenges in the laboratory	• Confirmation of the diagnosis of OA when the test is positive • False-negative tests are possible • Costly • Available in a small number of centers worldwide
Specific inhalation challenges at the workplace	• Exclude diagnosis if response is negative when performed in the usual work conditions • Requires usual work condition • Costly
Noninvasive measures of airway inflammation	Sputum cell counts • Impossible to falsify • Bring additional evidence to the diagnosis of OA • Costly • Not widely available • Does not allow to confirm or discard the diagnosis of OA by itself Exhaled NO measurement • Easy to perform • Inconsistent results • Difficult to interpret • Affected by many different factors

HMW, High-molecular-weight; *IgE,* immunoglobulin E; *LMW,* low-molecular-weight; *NO,* nitric oxide; *NSBHR,* nonspecific bronchial hyperresponsiveness; *PEF,* peak expiratory flow.
From Adkinson NF et al: *Middleton's allergy principles and practice*, ed 8, Philadelphia, 2014, Saunders.

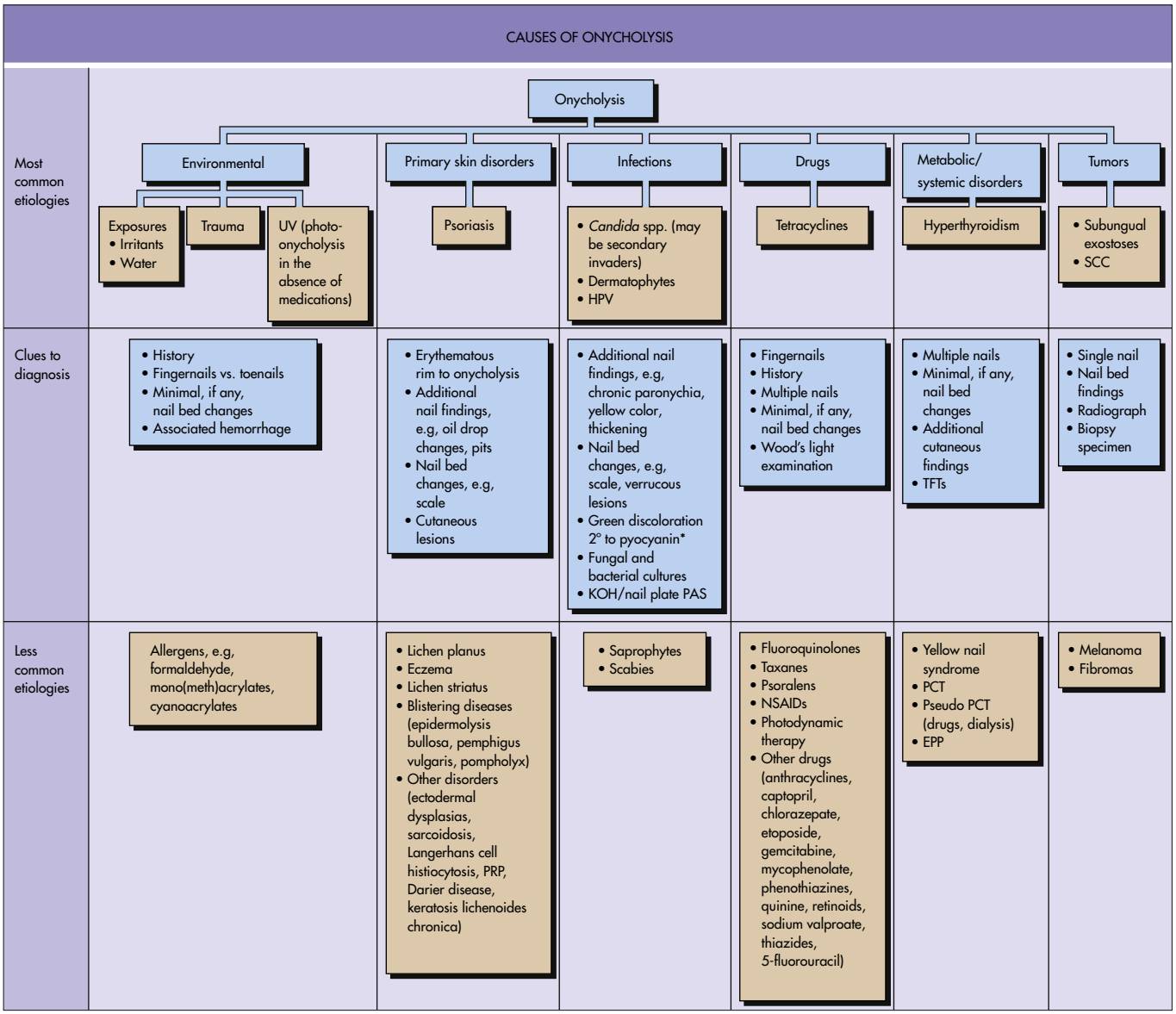


FIG. 113 Causes of onycholysis. *Due to secondary colonization with *Pseudomonas aeruginosa. EPP,* Erythropoietic protoporphyria; *HPV,* human papillomavirus infection; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PAS,* periodic acid-Schiff; *PCT,* porphyria cutanea tarda; *PRP,* pityriasis rubra pilaris; *SCC,* squamous cell carcinoma; *TFTs,* thyroid function tests. (From Bolognia JL, Jorizzo JL, Schaffer JV: *Dermatology,* ed 3, St Louis, 2012, Elsevier.)

Evaluation of Patients with Palpitations, Dizziness, and/or Syncope

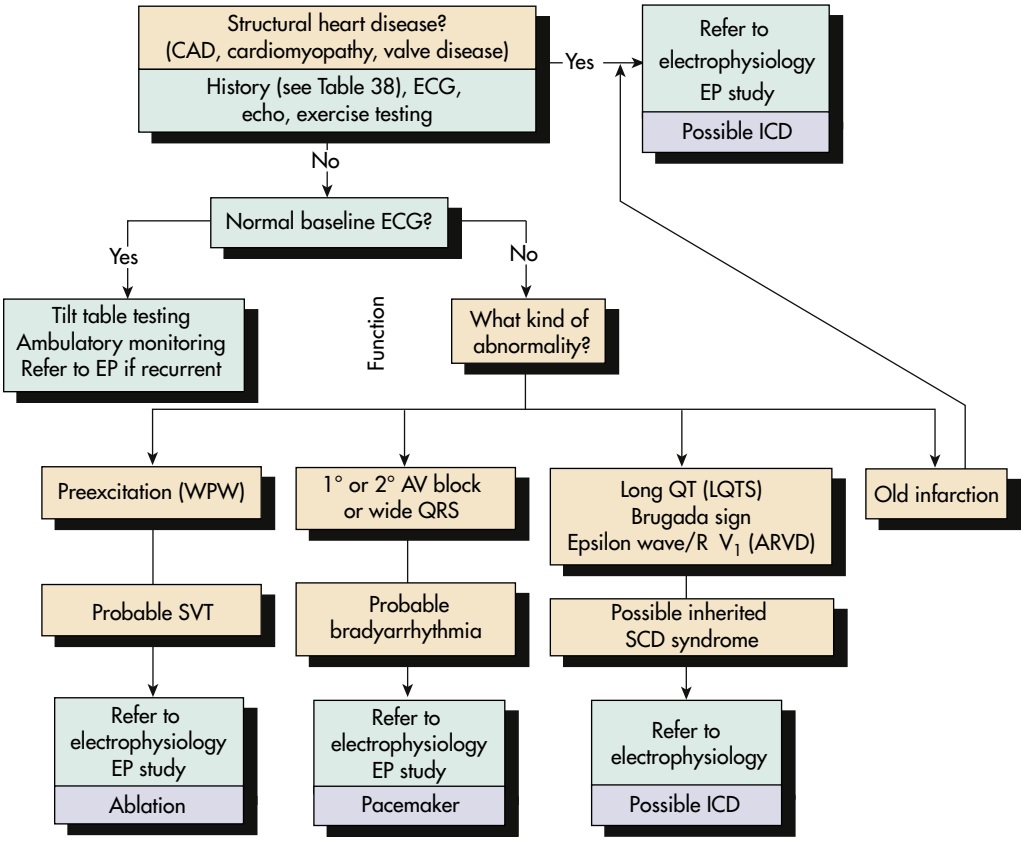


FIG. 114 Algorithm for evaluating patients with symptoms of palpitation, dizziness, or syncope. *ARVD,* Arrhythmogenic right ventricular dysplasia; *AV,* atrioventricular; *CAD,* coronary artery disease; *ECG,* electrocardiogram; *echo,* echocardiogram; *EP,* electrophysiology; *ICD,* implantable cardioverter-defibrillator; *LQTS,* long QT syndrome; *SCD,* sudden cardiac death; *SVT,* supraventricular tachycardia; *WPW,* Wolff-Parkinson-White syndrome. (From Goldman L, Schafer AI: *Goldman Cecil medicine,* ed 25, Philadelphia, 2016, Saunders.)

TABLE 38 Items to Be Covered in History of Patient with Palpitation

Does the Palpitation Occur:	If So, Suspect:
As isolated "jumps" or "skips"?	Extrasystoles
In attacks known to be of abrupt beginning, with a heart rate of 120 beats/min or over, with regular or irregular rhythm?	Paroxysmal rapid heart action
Independent of exercise or excitement adequate to account for the symptom?	Atrial fibrillation, atrial flutter, thyrotoxicosis, anemia, febrile states, hypoglycemia, anxiety state
In attacks developing rapidly, though not absolutely abruptly, unrelated to exertion or excitement?	Hemorrhage, hypoglycemia, tumor of the adrenal medulla
In conjunction with the taking of drugs?	Tobacco, coffee, tea, alcohol, epinephrine, ephedrine, aminophylline, atropine, thyroid extract, monoamine oxidase inhibitors
On standing?	Postural hypotension
In middle-aged women, in conjunction with flushes and sweats?	Menopausal syndrome
When the rate is known to be normal and the rhythm regular?	Anxiety state

From Goldman L, Braunwald E: Chest discomfort and palpitation. In Isselbacher KJ, Braunwald E et al [eds]: *Harrison's principles of internal medicine,* ed 13, New York, 1994, McGraw-Hill.

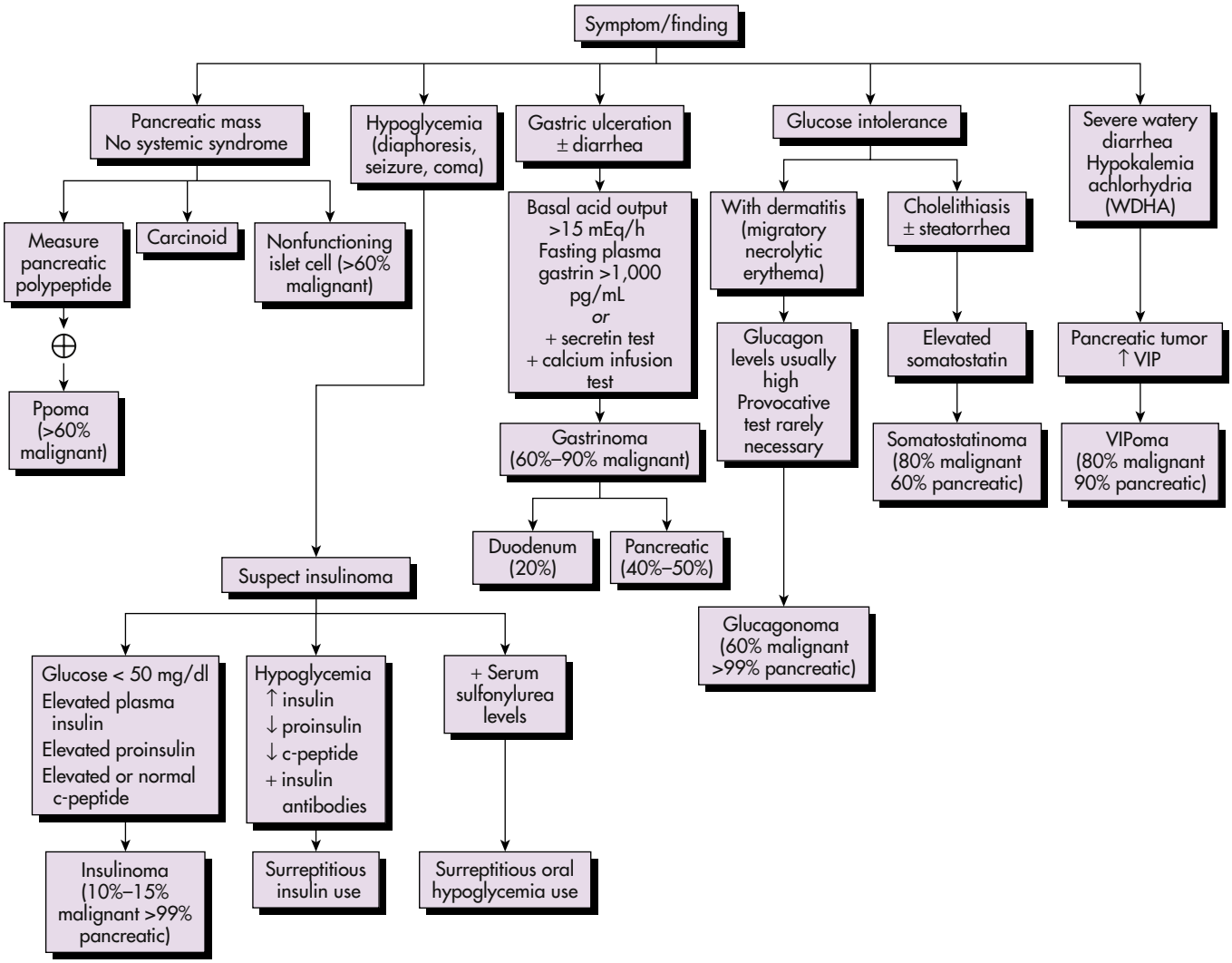


FIG. 115 Diagnosis of pancreatic islet cell tumors. *Ppoma,* Pancreatic polypeptide-secreting tumor; *VIP,* vasoactive intestinal peptide; *VIPoma,* vasoactive intestinal peptide secreted by a pancreatic islet tumor. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

ICD-10CM # C25.3 Malignant neoplasm of pancreatic duct
R19.06 Epigastric swelling, mass or lump

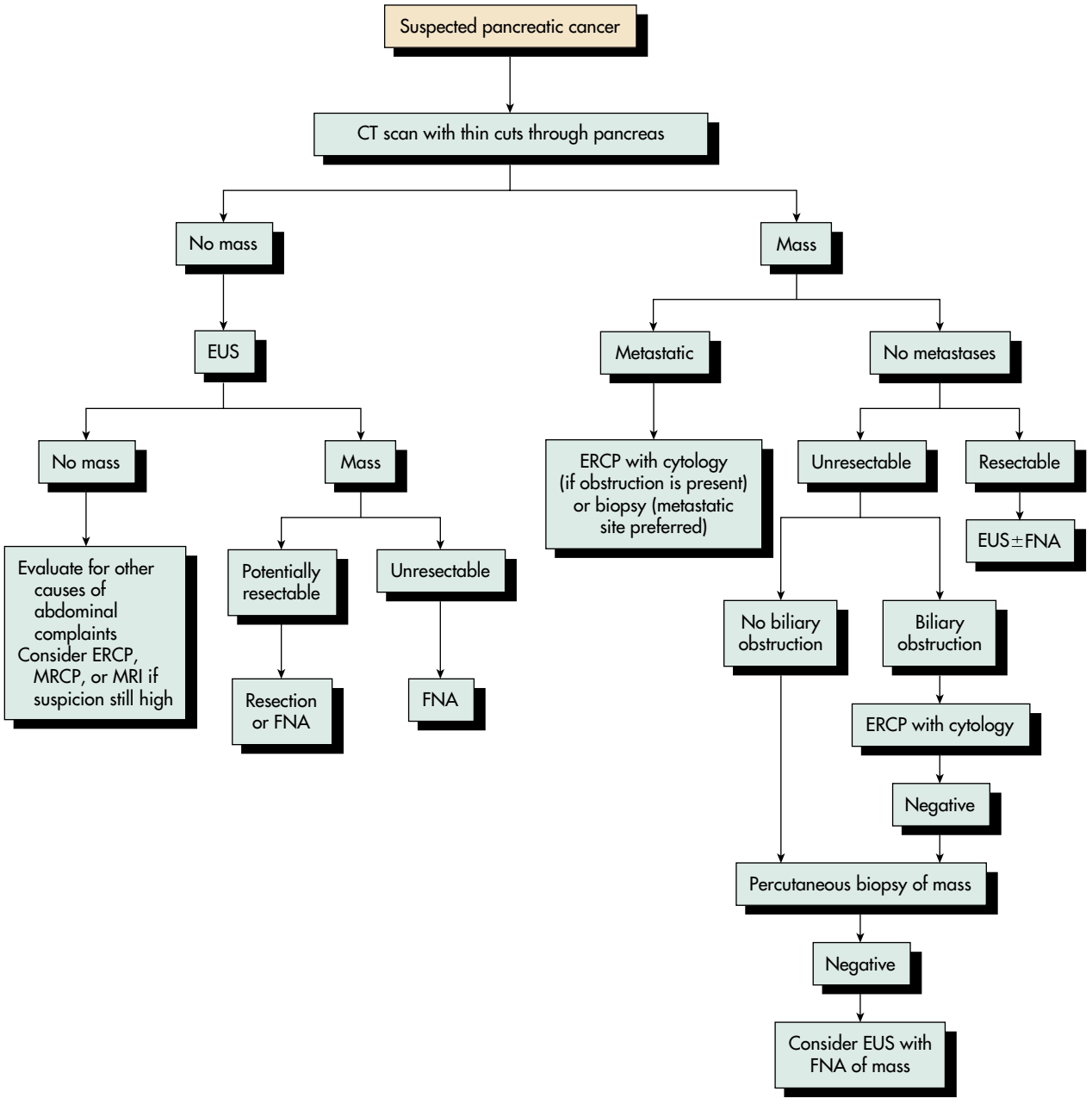


FIG. 116 Diagnostic algorithm for pancreatic cancer. Intraoperative fine-needle aspiration (FNA) if found inoperable during surgery. *CT,* Computed tomography; *ERCP,* endoscopic retrograde cholangiopancreatography; *EUS,* endoscopic ultrasonography; *MRCP*, magnetic resonance cholangiopancreatography; *MRI,* magnetic resonance imaging. (From Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

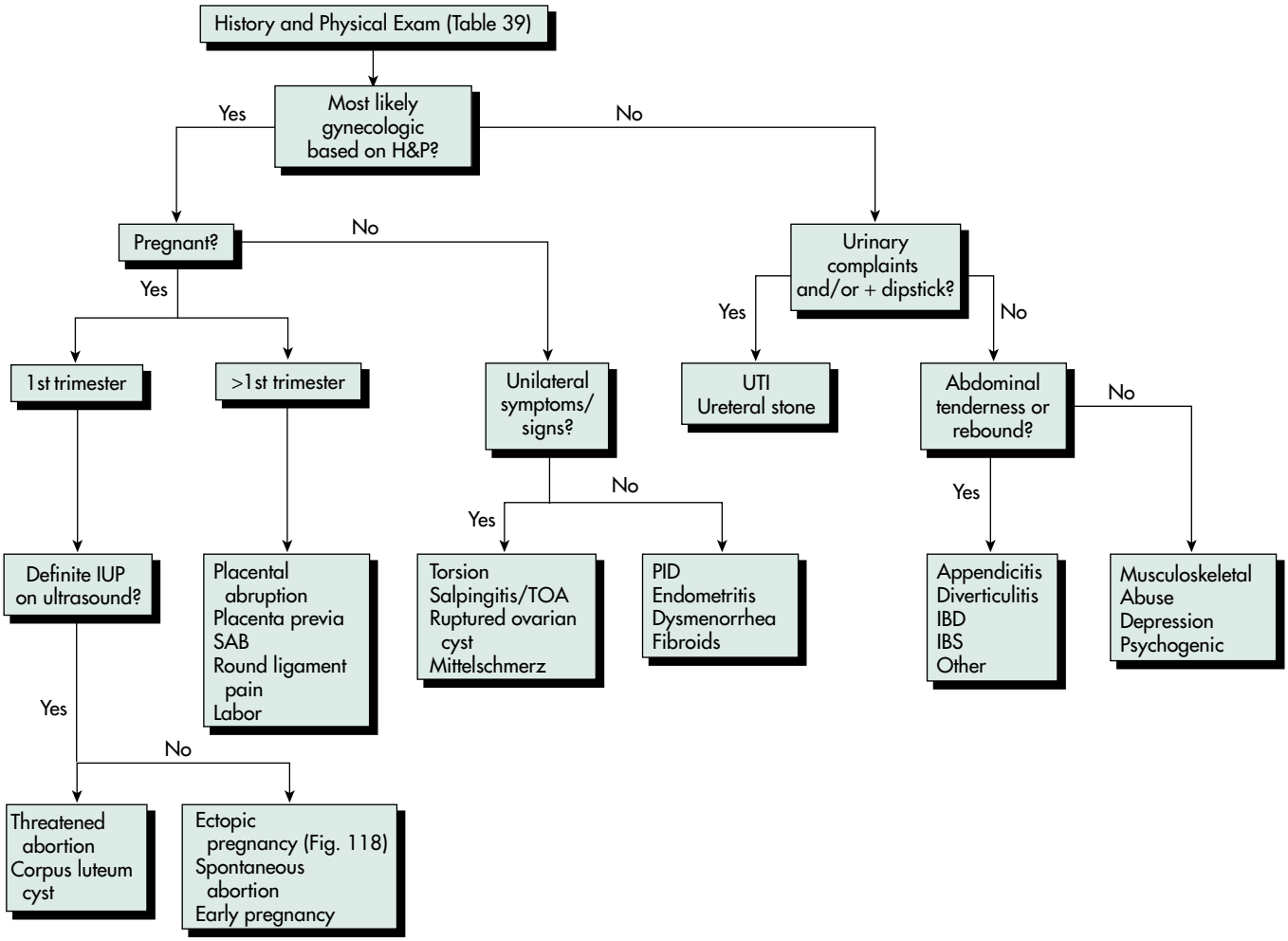


FIG. 117 Diagnostic algorithm for acute pelvic pain. *H&P,* History and physical; *IBD,* inflammatory bowel disease; *IBS,* irritable bowel syndrome; *IUP,* intrauterine pregnancy; *PID,* pelvic inflammatory disease; *SAB,* spontaneous abortion; *TOA,* tubo-ovarian abscess; *UTI,* urinary tract infection. (From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.)

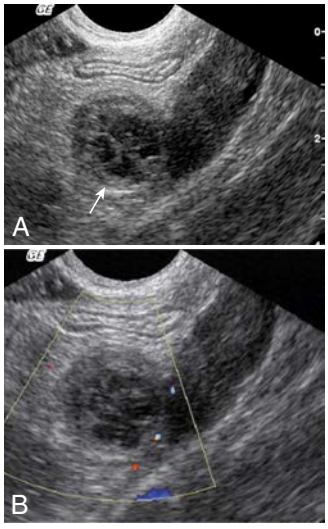


FIG. 118 Ectopic pregnancy seen as mixed-echogenicity mass. A 30-year-old woman presented with left lower quadrant pain at 7 weeks' gestation and β-hCG of 500 mIU/ml and falling over a 3-day period. **A,** In the left adnexa, medial to the left ovary, there was a 2-cm mass *(arrow)* with mixed echogenicity, and **B,** only minimal peripheral vascularity. A left ectopic pregnancy was confirmed and, based on a falling β-hCG, was treated expectantly and resolved without complication. (From Rumack CM et al: *Diagnostic ultrasound,* ed 4, Philadelphia, 2011, Elsevier.)

TABLE 39 Differentiation of Common or Potentially Catastrophic Causes of Pelvic Pain

Causative Disorder or Condition	Pain History	Associated Symptoms	Supporting History	Prevalence in ED	Physical Examination	Useful Tests	Atypical or Additional Aspects
Ectopic pregnancy (critical if ruptured)	Classically severe, sharp, lateral pelvic pain, but severity, location, and quality highly variable	Vaginal bleeding (often mild, can be absent)	Missed period; history of previous ectopic pregnancy, infertility, pelvic surgery, PID, or IUD use	Common	Classically unilateral adnexal tenderness, adnexal mass, and CMT	Pelvic US, quantitative β-hCG, T&C, laparoscopy	Cannot reliably exclude diagnosis based on history and physical examination. Severe pain, hypotension, or peritonitis suggests rupture
Ruptured ovarian cyst (emergent—critical with significant hemorrhage; otherwise, urgent)	Abrupt moderate to severe lateral pain	Light-headedness if bleeding is severe; rectal pain arises from fluid in cul-de-sac		Uncommon	Hypotension and tachycardia if blood loss is significant; possible peritonitis	Pelvic US, CBC, T&C	Physical examination findings often do not correlate with volume of blood in pelvis at US
Ovarian torsion (emergent)	Acute onset of moderate to severe lateral pain	Nausea and vomiting	History of ovarian mass or cyst	Uncommon	Adnexal mass and tenderness, possible peritonitis	US with Doppler flow studies, laparoscopy	Torsion can be intermittent
Appendicitis (emergent)	Duration often <48 hr, generalized followed by localized RLQ pain	Low-grade fever, nausea, anorexia	Migration of pain to RLQ from center, abdominal pain before vomiting	Common	RLQ tenderness, possible peritonitis	US or CT in unclear cases	Early in course, tenderness may be minimal or poorly localized
PID, TOA (TOA: emergent; PID: urgent-emergent)	Without TOA, pain usually bilateral. May manifest acutely within 48 hr or subacutely with up to 3 wk of pain	Fever, vaginal discharge	Vaginal discharge, history of PID, history of unprotected intercourse or multiple partners	PID: common TOA: uncommon	Pus from cervical os, CMT, adnexal tenderness. Peritonitis suggests severe PID or TOA	CBC, ESR, CRP, pelvic US, laparoscopy, cervical cultures, cervical smear for WBCs	History and physical examination may be inaccurate for diagnosis, particularly in patients with subacute presentation
UTI (urgent)	Pain with urination. Patient may have flank pain from associated pyelonephritis	Urinary urgency and frequency; fever and vomiting if patient has associated pyelonephritis	Recent urologic procedure, prior history of UTI	Common	Suprapubic tenderness, flank tenderness and fever with pyelonephritis	Urinalysis, urine culture (if recurrent or complicated)	WBCs can be present in urine with PID and appendicitis. RBCs present in urine with hemorrhagic cystitis
Ureteral colic (urgent)	Acute onset, manifests within hours. Pain is lateral, usually moderate to severe. Often radiates into the groin or costovertebral angle or flank	Nausea and vomiting	Prior history of stones	Common	Patient often appears uncomfortable, but physical examination can be otherwise unremarkable	Urinalysis: hematuria present in approximately 80% of cases. Renal ultrasound for hydronephrosis. Abdominal CT	If stone is at ureterovesicular junction, patient can have localized pain that can mimic appendicitis or other acute pelvic pathology
Unruptured ovarian cyst or tumor	Lateral ache, gradual onset	Often minimal	Prior history of similar pain	Common	Lateral pelvic tenderness, with or without a mass	Pelvic US	
Endometriosis	Unilateral or bilateral pelvic pain, often recurrent	Dysmenorrhea, dyspareunia	Prior history of same type of pain in association with menstrual cycle	Common	Unilateral or bilateral adnexal tenderness, occasionally pelvic mass present, peritoneal findings uncommon	Pelvic US, laparoscopy	Symptoms can mimic other types of pelvic pathology; laparoscopy often is needed for confirmation

β-hCG, β-Human chorionic gonadotropin; *CBC,* complete blood count; *CMT,* cervical motion tenderness; *CRP,* C-reactive protein; *CT,* computed tomography; *ED,* emergency department; *ESR,* erythrocyte sedimentation rate; *IUD,* intrauterine device; *PID,* pelvic inflammatory disease; *RBC,* red blood cell; *RLQ,* right lower quadrant; *T&C,* type and crossmatch; *TOA,* tubo-ovarian abscess; *US,* ultrasonography; *UTI,* urinary tract infection; *WBC,* white blood cell.
From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.

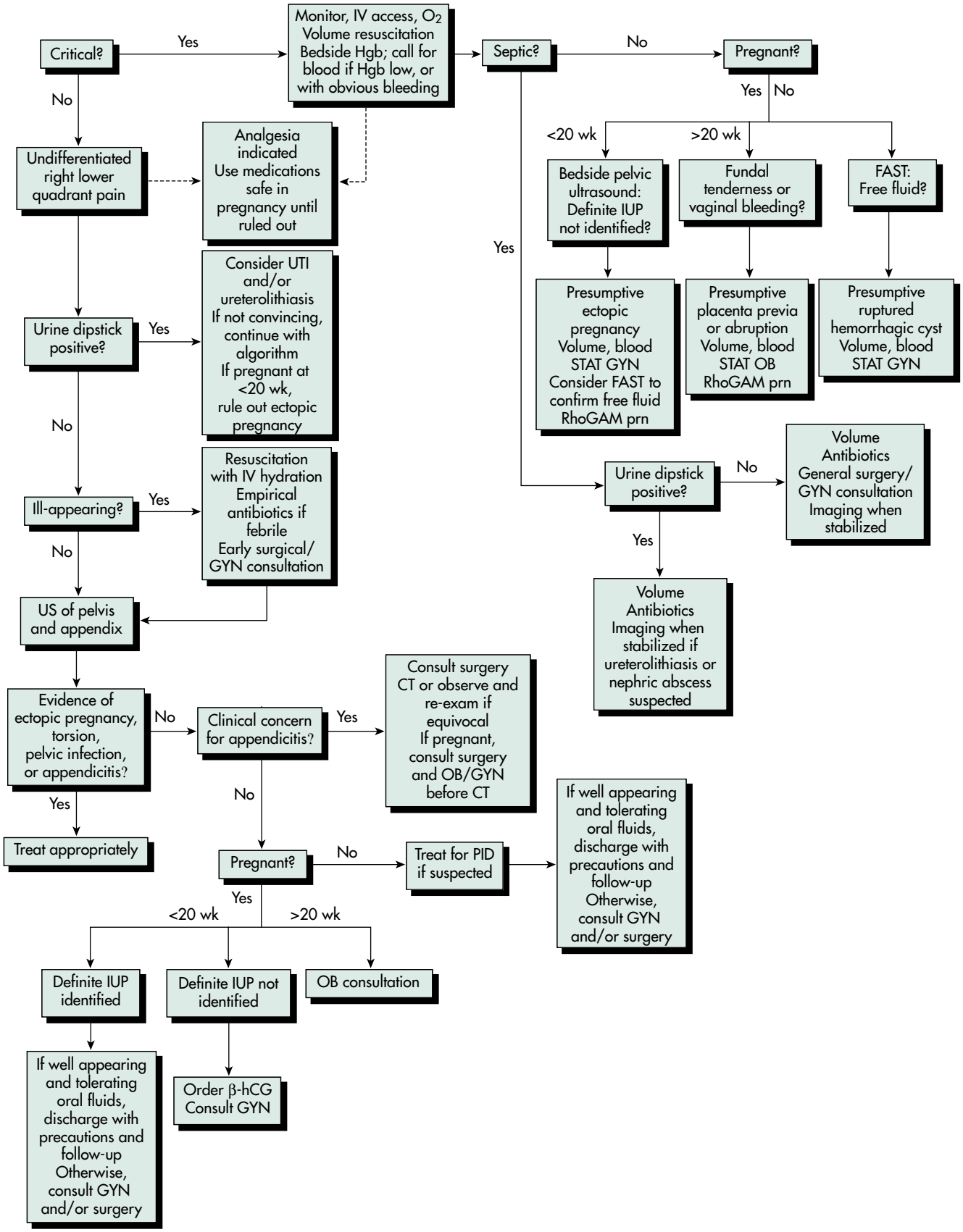


FIG. 119 Management algorithm for acute pelvic pain: critical patients and right lower quadrant pain presentations. β-*hCG,* β-Human chorionic gonadotropin; *CT,* computed tomography; *FAST,* focused assessment with sonography for trauma; *GYN,* gynecology; *Hgb,* hemoglobin; *IUP,* intrauterine pregnancy; *IV,* intravenous; *OB,* obstetrics; *PID,* pelvic inflammatory disease; *STAT,* immediately; *US,* ultrasound; *UTI,* urinary tract infection. (From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.)

ICD-10CM # G60.9 Hereditary and idiopathic neuropathy, unspecified
G57.10 Meralgia paresthetica, unspecified lower limb
G90.09 Other idiopathic peripheral autonomic neuropathy

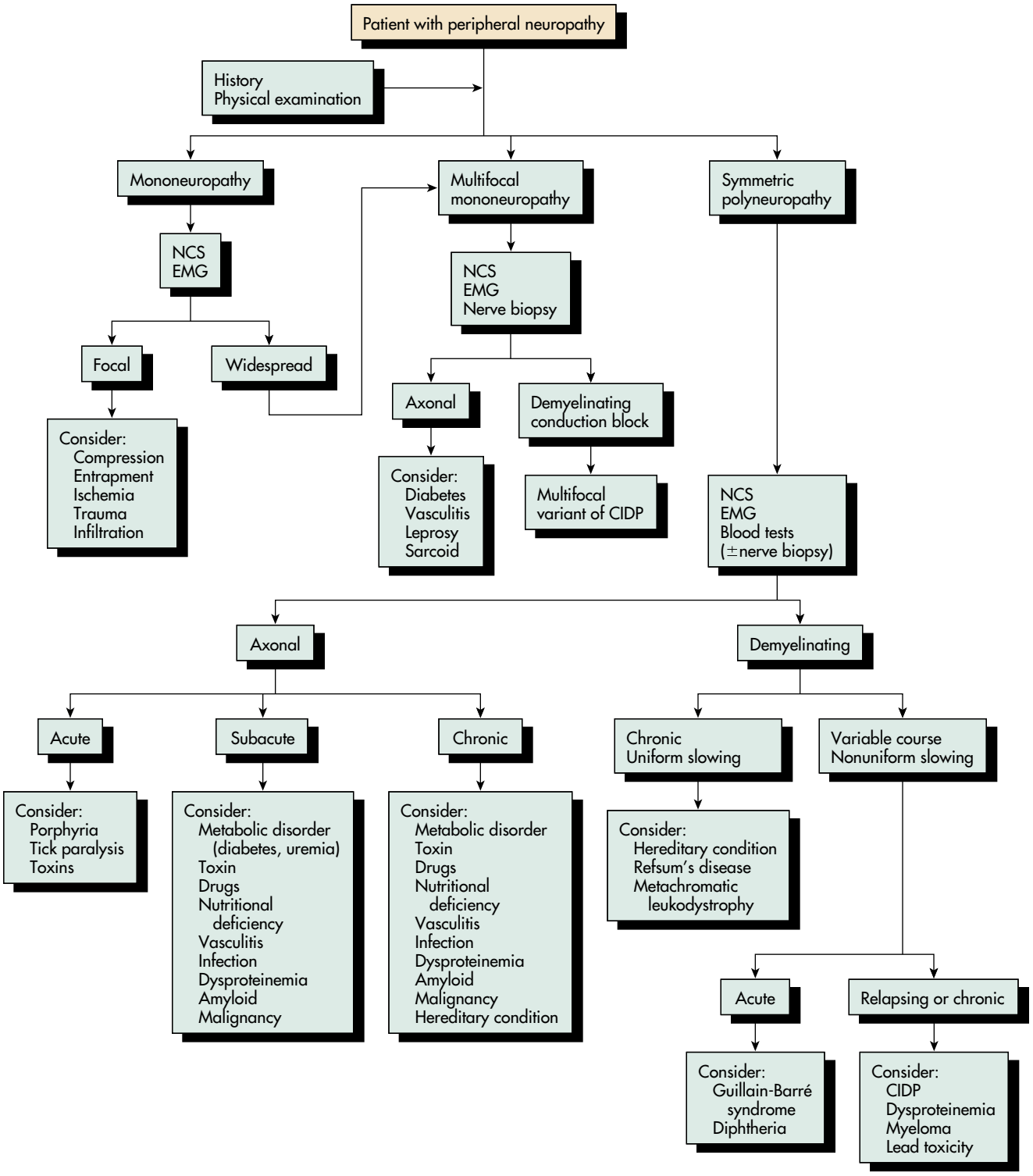


FIG. 120 Approach to the patient with peripheral neuropathy. *CIDP,* Chronic inflammatory demyelinating polyradiculopathy; *EMG,* electromyogram; *NCS,* nerve conduction studies. (Modified from Greene HL, Johnson WP, Lemcke DL: *Decision making in medicine*, ed 2, St Louis, 1988, Mosby.)

ICD-10CM # L56.0 Drug phototoxic response
L56.1 Drug photoallergic response
L56.2 Photocontact dermatitis [berloque dermatitis]

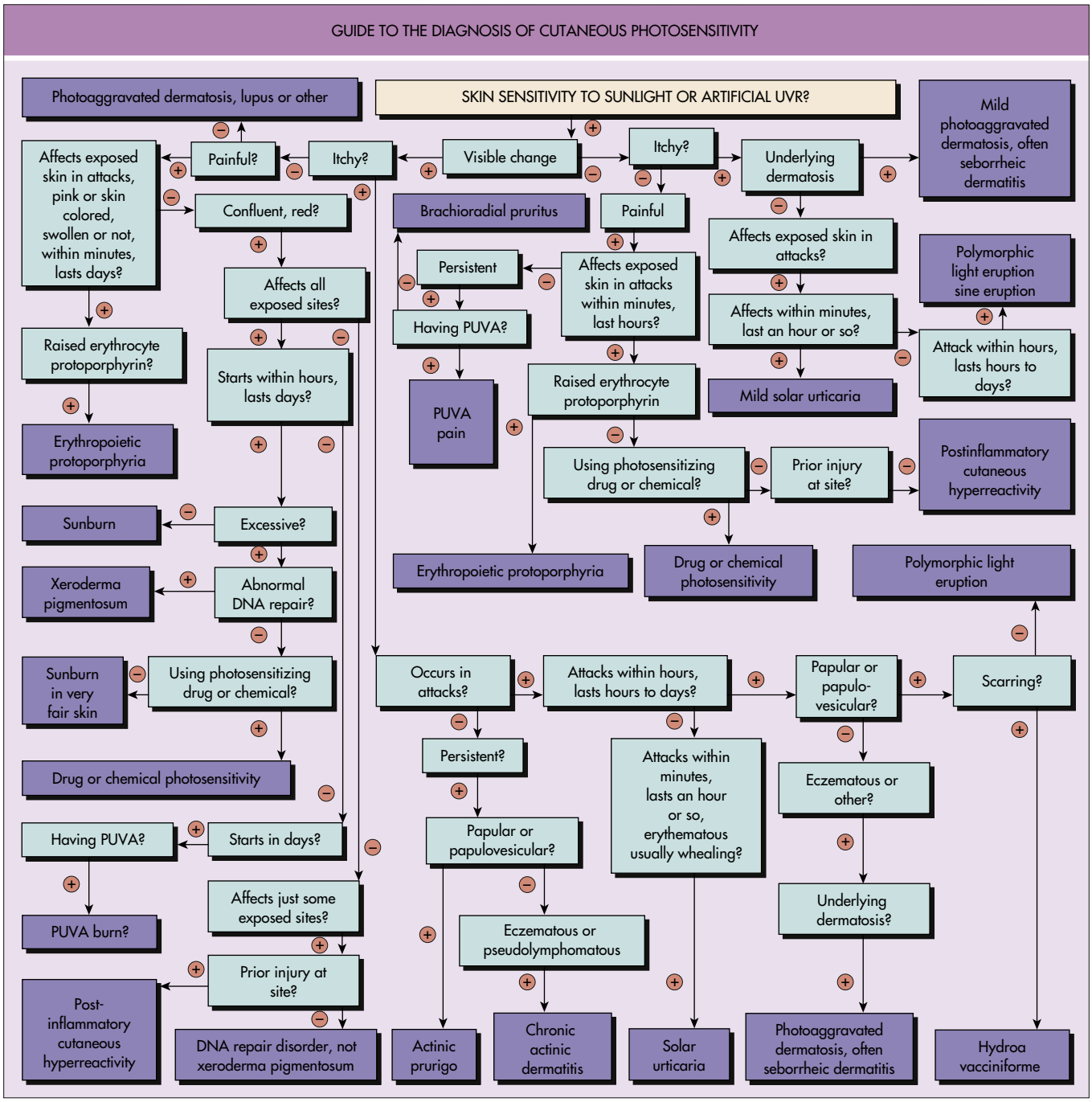


FIG. 121 Guide to the diagnosis of cutaneous photosensitivity. The diagnosis can generally be made from patient history and clinical findings, provided the titers of antinuclear antibodies and other LE-associated antibodies are normal. *PUVA,* Psoralen and ultraviolet A. (From Bolognia JL, Jorizzo JL, Schaffer JV: *Dermatology,* ed 3, St Louis, 2012, Elsevier.)

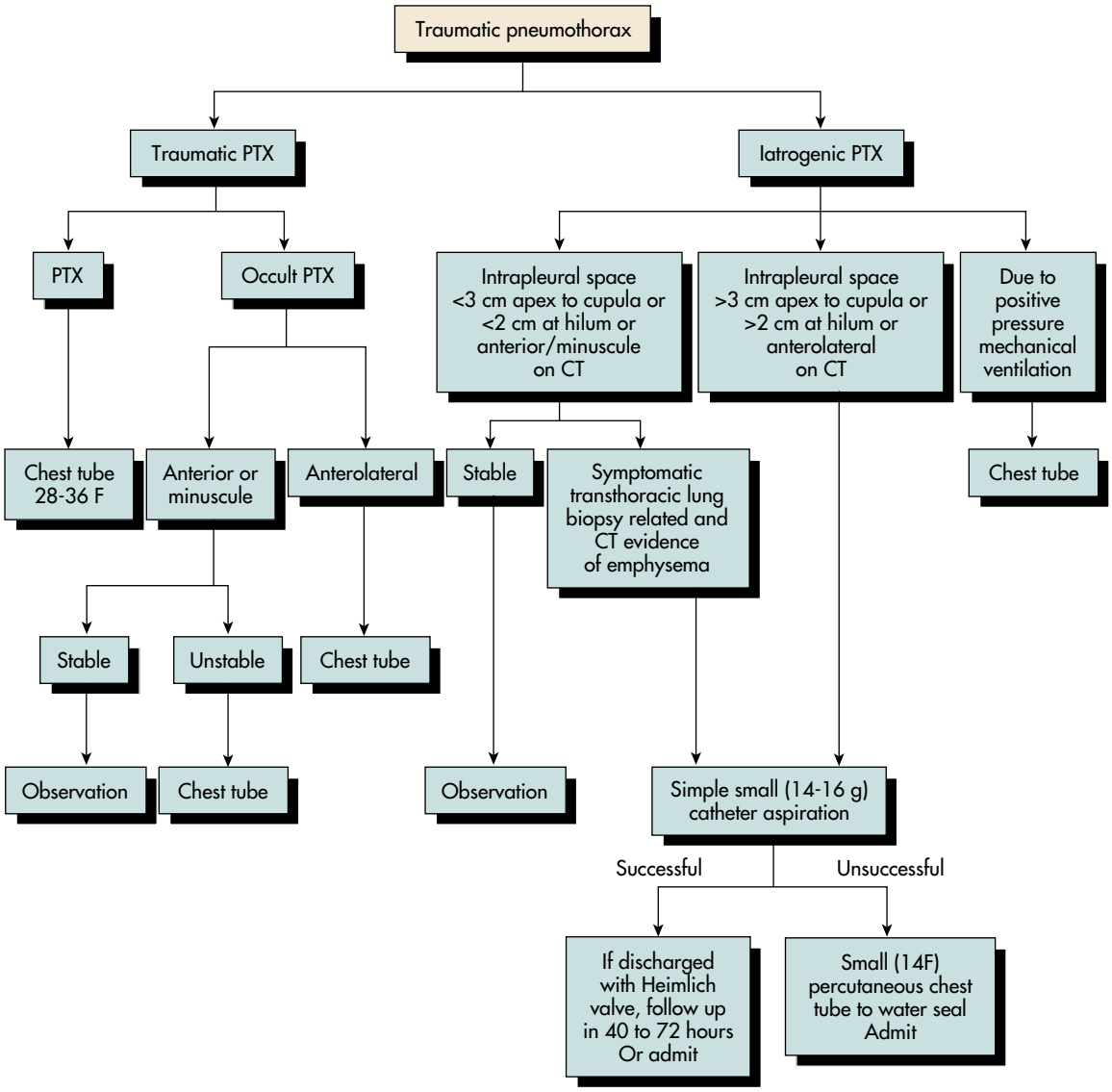


FIG. 122 Algorithmic approach to the treatment of traumatic pneumothorax. *CT,* Computed tomography; *PTX,* pneumothorax. (From Adams JG et al: *Emergency medicine: clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

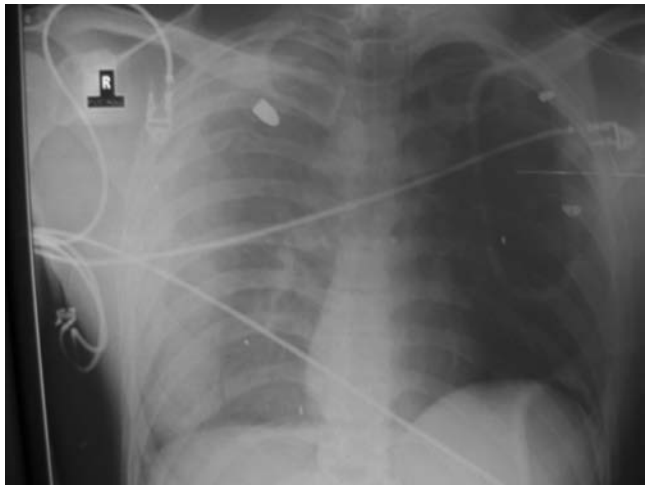


FIG. 123 Hemothorax secondary to gunshot wound. Note haziness over right hemithorax with bullet seen in right upper lobe. (From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.)

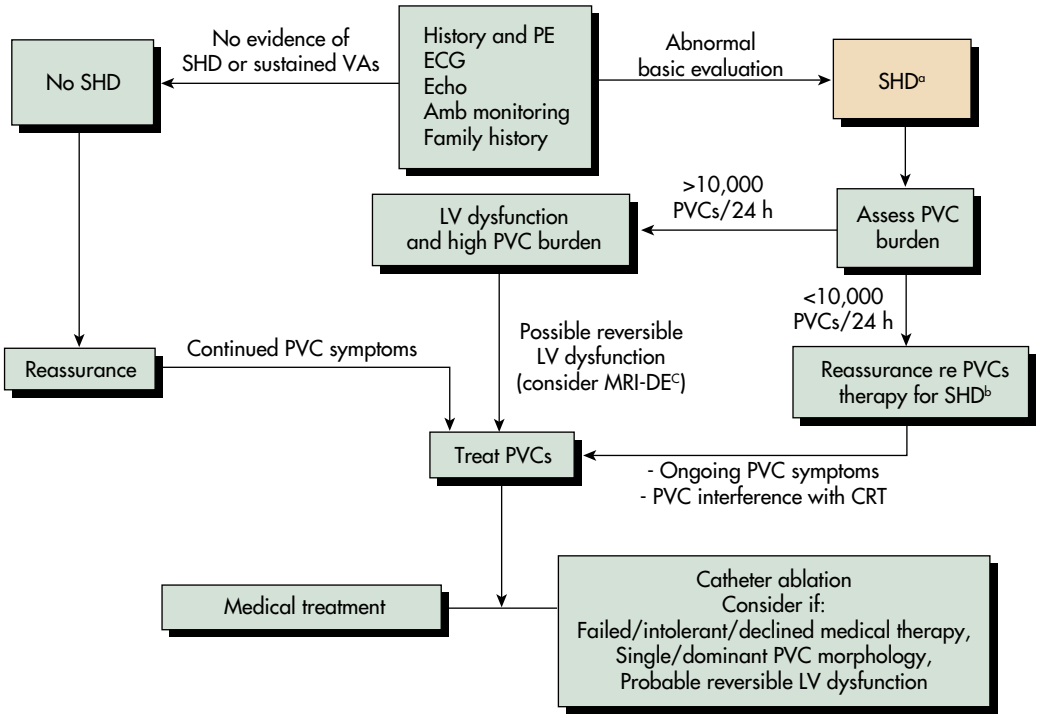


FIG. 124 Management of premature ventricular complexes (PVCs). *CRT,* Cardiac resynchronization therapy; *ECG,* electrocardiogram; *LV,* left ventricular; *MRI-DE,* magnetic resonance imaging with delayed enhancement; *PE,* physical examination; *PVC,* premature ventricular contraction; *SHD*, structural heart disease; *VAs,* ventricular arrhythmias. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.)

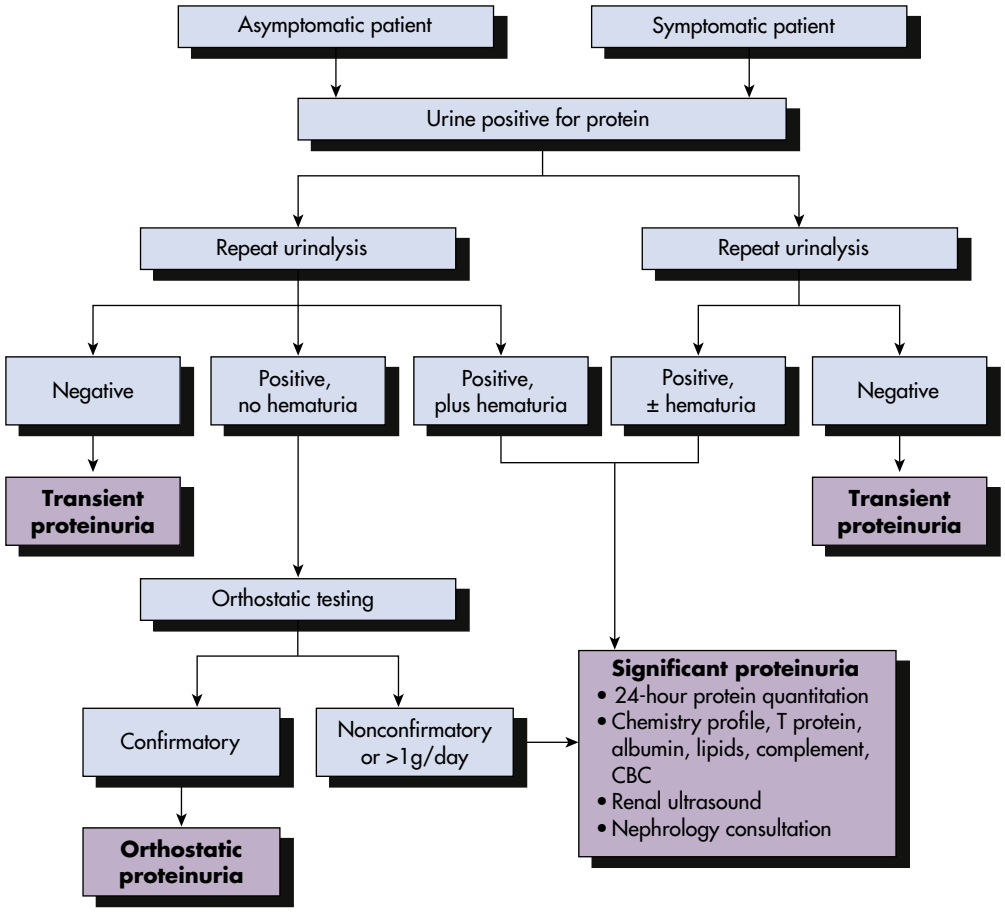


FIG. 125 Evaluation of children with proteinuria. *CBC*, Complete blood cell count. (From Wein AJ et al: *Campbell-Walsh urology*, ed 11, Philadelphia, 2016, Elsevier.)

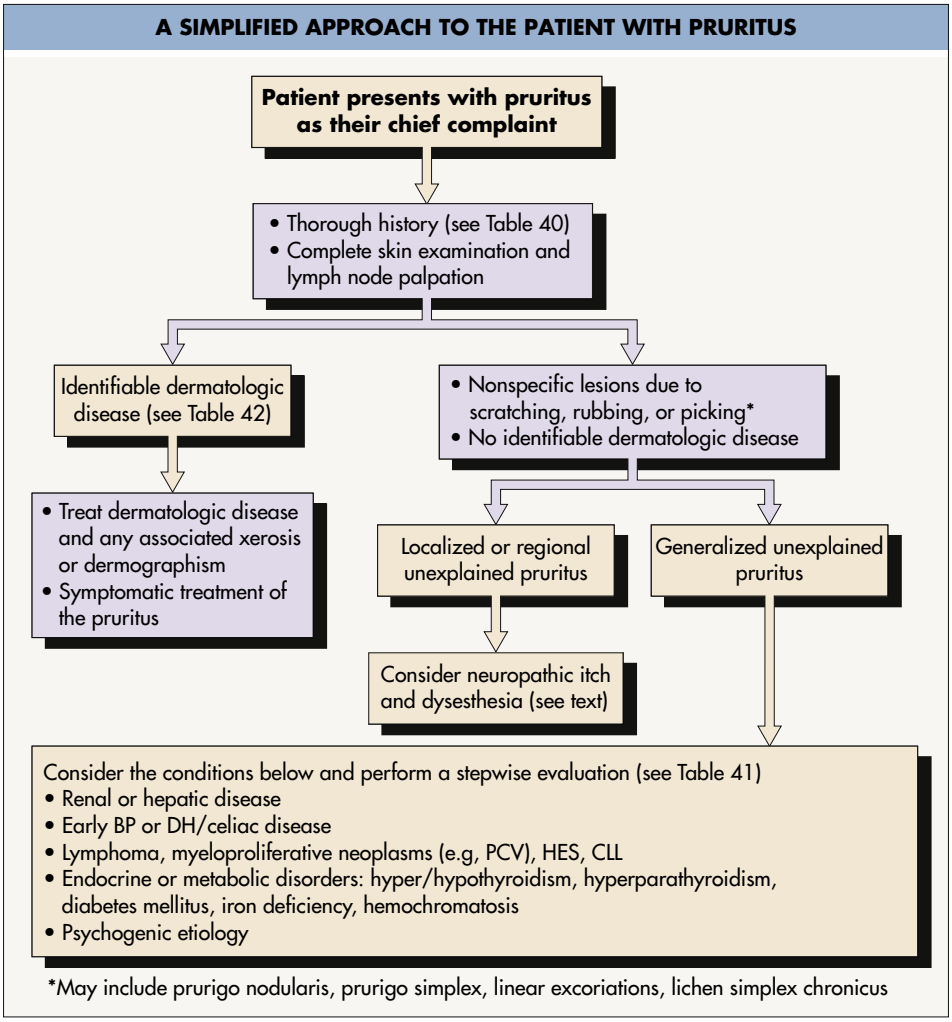


FIG. 126 A simplified approach to the patient with pruritus. *BP,* Bullous pemphigoid; *CLL,* chronic lymphocytic leukemia; *DH,* dermatitis herpetiformis; *HES,* hypereosinophilic syndromes; *PCV,* polycythemia vera. (From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.)

TABLE 40 Descriptive Features of the Pruritus and Additional Patient History

Questions to Ask Regarding the Pruritus

- WHEN did it start? *Duration:* days, weeks, months, years
- WHERE did it start? WHERE is it now? *Location*: localized or generalized, unilateral or bilateral
- HOW did it start? *Onset*: abrupt, gradual, prior history of pruritic episodes
- HOW does it feel? *Nature:* prickling, crawling, burning, stinging
- HOW intense is it? *Severity:* mild, moderate, severe; interference with normal activities or sleep
- HOW often do you feel it? *Time course:* intermittent, continuous, cyclical, nocturnal
- WHAT makes it worse? *Provoking/aggravating factors:* heat, cold, water, air, exercise, occupation, hobbies
- WHAT makes it better? *Itch relief:* cold, heat, scratching/rubbing/hurting, cool/hot showering
- WHAT do you think is the cause? *Patient's theory of pruritus etiology*

Additional patient history

- Skin care, bathing habits, exposure to irritants
- Medications (including topical agents): prescribed, over-the-counter; duration of use and relationship to onset of pruritus
- Use of nicotine, alcohol, and recreational/illicit drugs
- Allergies (known and suspected): drugs, airborne, food, contact
- Atopic history: atopic dermatitis, allergic rhinoconjunctivitis, asthma
- Past and present medical history: thyroid, liver, or renal dysfunction; other systemic diseases; psychological disease; surgeries or accidents
- Family history: atopy, skin disease, similar pruritic conditions
- Occupation, hobbies, personal stress
- Household and personal contacts; pets and their care
- Dietary habits
- Sexual history
- Travel history
- Prior diagnoses made by physician or patient

From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

TABLE 41 Laboratory and Radiographic Evaluation in Patients with Pruritus of Unknown Etiology

Basic Initial Evaluation

- Complete blood cell count (CBC) with differential and platelet count
- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- Creatinine, blood urea nitrogen, electrolytes
- Liver transaminases, alkaline phosphatase, bilirubin
- Lactate dehydrogenase (LDH)
- Fasting glucose
- Thyroid stimulating hormone (TSH) ± free thyroxine

Possible Additional Evaluation

Skin biopsy

- Routine histology (if skin lesions are present)
- Direct immunofluorescence studies*

Other laboratory tests

- Serum total and/or allergen-specific IgE
- Serum ferritin, iron, total iron binding capacity
- Hemoglobin A1c
- Parathyroid function (calcium, phosphate, and parathyroid hormone levels)
- Stool for ova/parasites and/or occult blood
- Viral hepatitis panel (including hepatitis B and C viruses)
- HIV testing
- Antitissue transglutaminase ± epidermal transglutaminase IgA antibodies**
- Anti-BP180 and anti-BP230 bullous pemphigoid IgG antibodies
- Antimitochondrial and antismooth muscle antibodies
- Serum tryptase, histamine, and/or chromogranin-A levels
- Urinalysis with sediment evaluation
- 24-Hour urine collection for 5-hydroxyindoleacetic acid (5-HIAA; a serotonin metabolite) and porphyrins
- Serum protein electrophoresis, serum immunofixation electrophoresis

Radiographic studies

- Chest x-ray or CT scan
- Abdominal and pelvic ultrasonography or CT scan
- Lymph node ultrasonography
- Spinal x-ray or MRI (for regional pruritus)

Other investigations

- Patch testing
- Prick testing for major atopy and relevant occupational allergens
- Age-appropriate cancer screening (in conjunction with primary care physician)
- If hydroxyethyl starch (HES)-induced pruritus is suspected, electron microscopy of a biopsy sample from normal-appearing skin

A1c, Glycated hemoglobin; *CT,* computed tomography; *IgA,* immunoglobin A; *IgE,* immunoglobin E, *IgG,* immunoglobin G; *MRI,* magnetic resonance imaging.

*Biopsy perilesional skin or normal-appearing skin (in vicinity of lesions if present) to assess for bullous pemphigoid and dermatitis herpetiformis, respectively.

**Often performed in conjunction with serum total IgA; in patients with IgA deficiency, anti-tissue transglutaminase IgG antibodies should be assessed.

From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

TABLE 42 Primary Dermatologic Conditions Associated with Pruritus

Cause	Dermatologic Disease
Inflammation	• Atopic dermatitis • Allergic or irritant contact dermatitis • Seborrheic dermatitis, especially of the scalp • Stasis dermatitis • Psoriasis • Parapsoriasis • Pityriasis rubra pilaris • Lichen planus • Urticaria, dermographism • Mastocytosis • Papular urticaria, urticarial dermatitis • Drug eruptions, e.g., morbilliform • Polymorphous light eruption, actinic prurigo, chronic actinic dermatitis • Bullous diseases, e.g., DH, BP • Polymorphic eruption of pregnancy (PEP) • Eosinophilic folliculitis • Dermatomyositis • Prurigo pigmentosa • Lichen sclerosus • Graft-versus-host disease
Infestation/bites & stings	• Scabies • Pediculosis • Arthropod bites
Infections	• Bacterial infections, e.g., folliculitis • Viral infections, e.g., varicella • Fungal infections, e.g., inflammatory tinea • Parasitic infections, e.g., schistosomal cercarial dermatitis
Neoplastic	• Cutaneous T-cell lymphoma, e.g., mycosis fungoides, Sézary syndrome
Genetic/nevoid	• Darier disease and Hailey-Hailey disease • Ichthyoses, e.g., Netherton, Sjögren-Larsson, and peeling skin syndromes • Pruriginosa subtype of dominant dystrophic EB • Porphyrias, e.g., porphyria cutanea tarda and erythropoietic protoporphyria • Inflammatory linear verrucous epidermal nevus (ILVEN) • Large/giant congenital melanocytic nevi, occasionally, especially in bulky lesions with neural differentiation
Other	• Xerosis, eczema craquelé • Primary cutaneous amyloidosis (macular, lichenoid) • Postburn pruritus • Scar-associated pruritus • Fiberglass dermatitis

BP, Bullous pemphigoid; *DH,* dermatitis herpetiformis; *EB,* epidermolysis bullosa.

From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

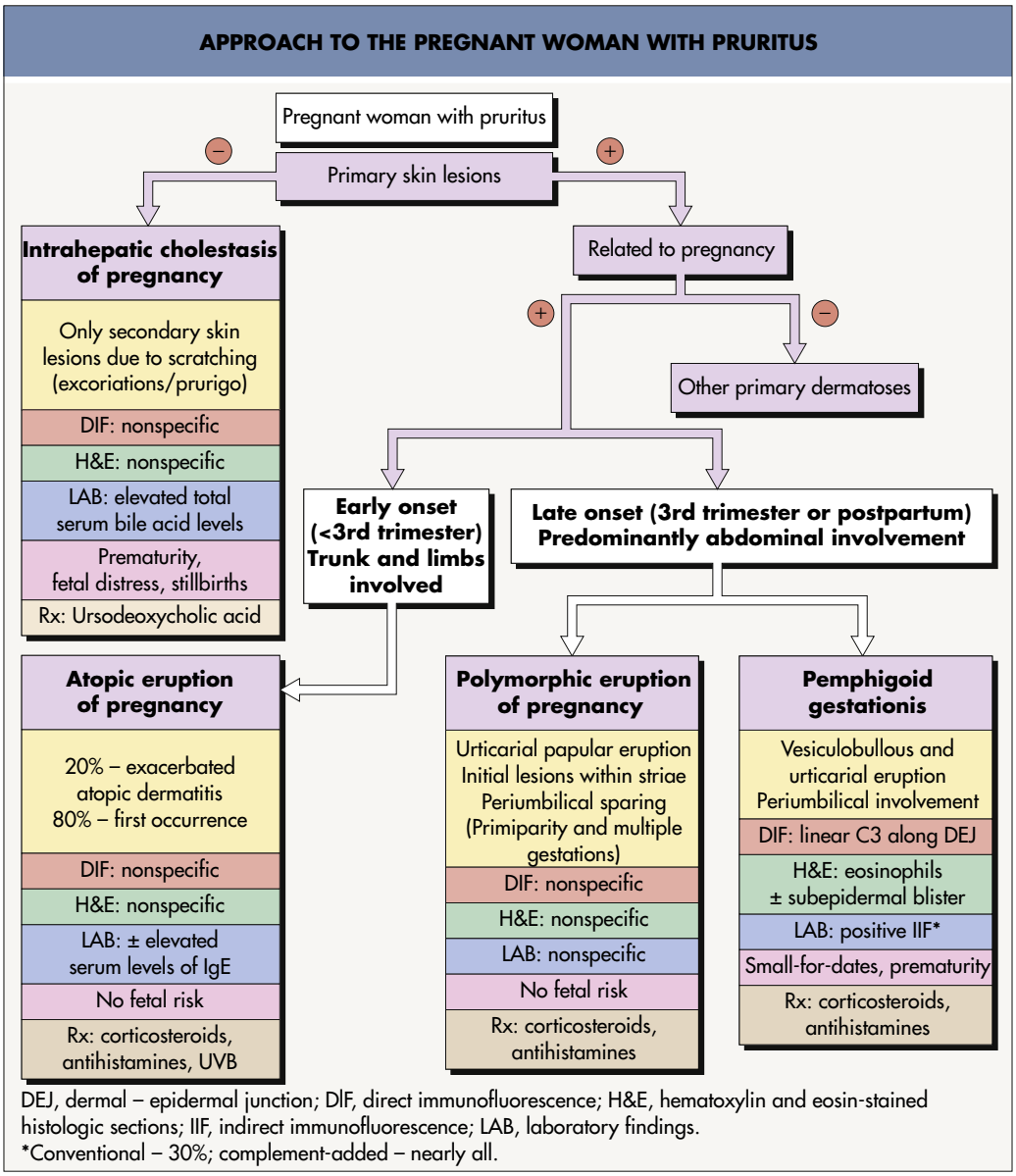
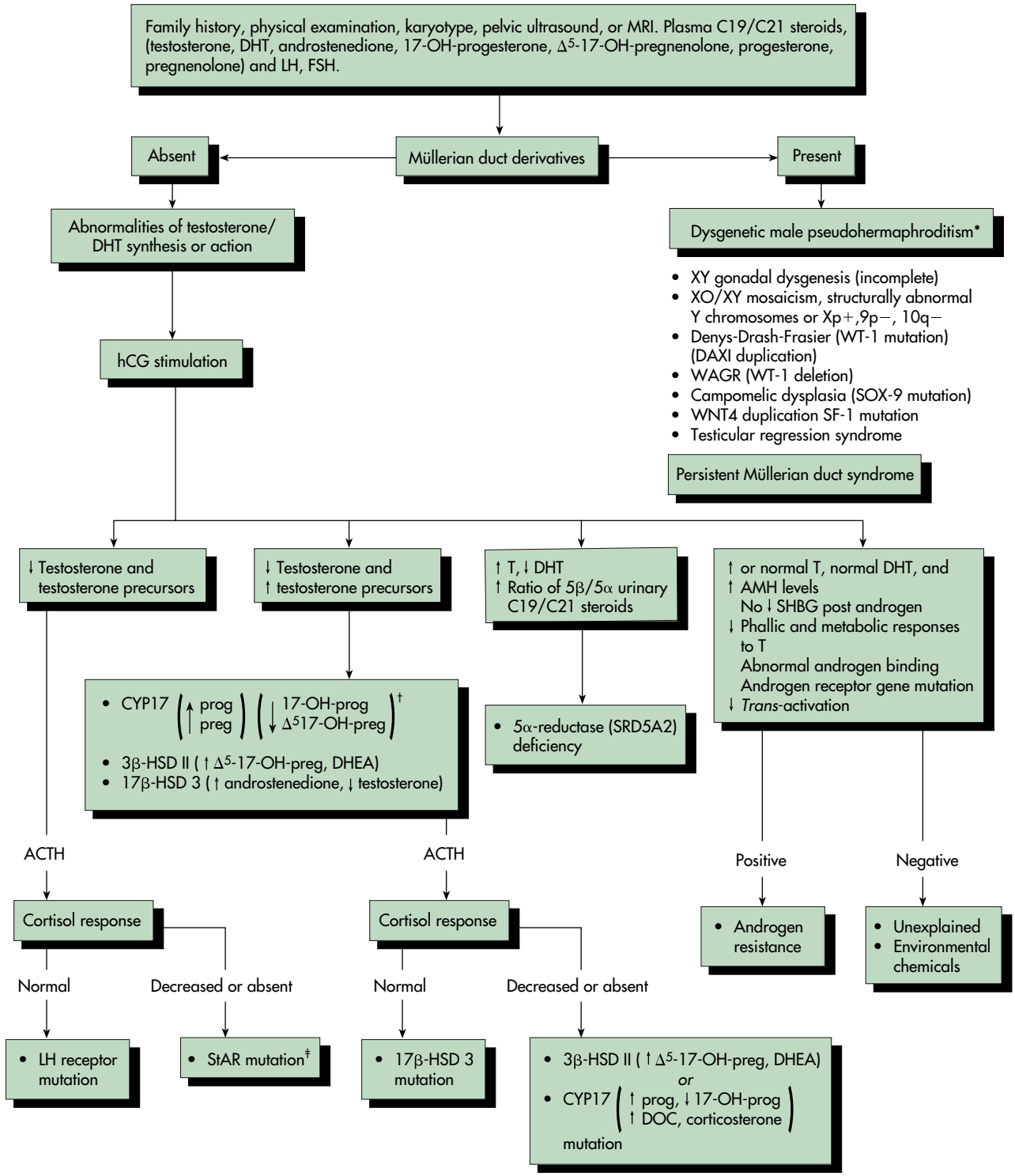


FIG. E127 Approach to the pregnant woman with pruritus. Patients with refractory pemphigoid gestationis may benefit from plasmapheresis during pregnancy. (From Bolognia J: *Dermatology*, ed 4, Philadelphia, 2018, Elsevier.)



*Patients with dysgenetic male pseudohermaphroditism may manifest varying degrees of testicular dysgenesis with either complete or partial testosterone/DHT and/or AMH deficiency. Therefore, not all patients may manifest either ambiguous genitalia or the presence of Müllerian ducts. †CYP17 (P450??) catalyzes the 17-hydroxylation of progesterone and pregnenolone to 17-hydroxyprogesterone and Δ^5-17-hydroxypregnenolone as well as the scission (lyase) of 17-hydroxypregnenolone to DHEA. Patients with 17, 20- lyase deficiency have elevated levels of 17-hydroxyprogesterone and Δ^5-17-hydroxypregnenolone in relation to andro-stenedione and DHEA whether before or after hCG stimulation. ‡The StAR (steroidogenic acute regulatory) protein is involved in the transport of cholesterol from the outer to the inner mitochondrial membrane where the enzyme CYP11A1(P450??) resides. Patients with a mutation in the gene for this protein have a markedly diminished ability to convert cholesterol to Δ^5-pregnenolone, although their CYP11A1 enzymatic activity is intact. They manifest congenital lipoid adrenal hyperplasia.

FIG. E128 Steps in the differential diagnosis of male pseudohermaphroditism. *3β-HSD II,* 3β-Hydroxysteroid dehydrogenase/Δ^5-isomerase; *17β-HSD 3,* 17β-hydroxysteroid dehydrogenase (oxido-reductase) type 3; *ACTH,* adrenocorticotropic hormone; *AMH,* antimüllerian hormone; *CYP17,* 17α-hydroxylase/17,20-lyase; *DHEA,* dehydroepiandrosterone; *DHT,* dihydrotestosterone; *FSH,* follicle-stimulating hormone; *hCG,* human chorionic gonadotropin; *LH,* luteinizing hormone; *MRI,* magnetic resonance imaging; *SHBG,* sex hormone-binding globulin; *T,* testosterone; *WAGR,* Wilms tumor, aniridia, genital anomalies, and intellectual disability (formerly mental retardation). (From Larsen PR et al: *Williams textbook of endocrinology,* ed 11, Philadelphia, 2008, Saunders.)

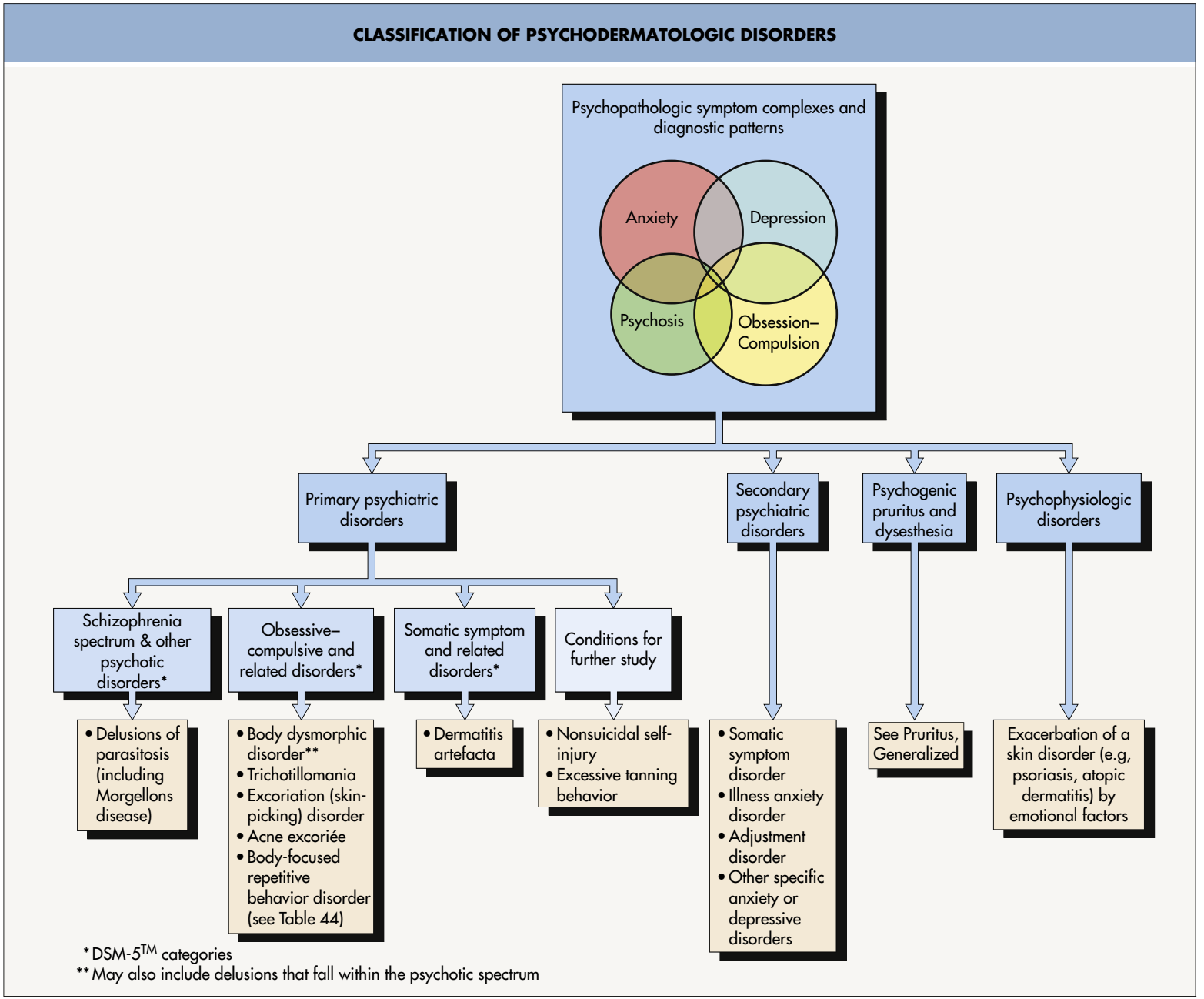


FIG. 129 Classification of psychodermatologic disorders. Psychocutaneous disorders can be conceptualized by (1) the specific psychodermatologic condition and its classification, and (2) the presenting symptom complex of the underlying psychopathology. Primary psychiatric disorders are those in which the patient has no primary skin disease and all of the cutaneous findings are self-induced. Secondary psychiatric disorders involve the development of psychological problems as a result of a skin disease. *Psychophysiologic disorders* are those in which a primary skin condition, such as psoriasis, is exacerbated by emotional factors. A particular patient with a psychodermatologic disorder can have a presenting symptom complex with features from one or more of the four major psychopathologic patterns of anxiety, depression, psychosis, and obsessions/compulsions. (From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.)

TABLE 43 Psychopathic Patterns and Psychotropic Medications Used in Dermatology

Underlying Psychopathology and Symptom Complex	Possible Pharmacologic Treatment	Comments and Precautions
Anxiety		
• Excessive anxiety and worry • Restlessness; feeling "keyed up" or "on edge" • Irritability • Fatigability • Difficulty concentrating or mind going blank • Muscle tension or feeling "shaky" • Sleep disturbance • Somatic symptoms, e.g., dizziness, sweating, palpitations, abdominal complaints	**Acute anxiety: Benzodiazepines** • Clonazepam (0.5-2 mg once or twice daily, as needed) • Lorazepam (0.5-2 mg every 6-8 hours, as needed) **Chronic anxiety: Nonbenzodiazepines**—start low and titrate slowly • *Azapirone anxiolytic* • Buspirone (15 mg/day, divided into 3 doses; increase daily dose by 5 mg every 2-3 days, up to a maximum of 60 mg/day if needed) • Selective serotonin reuptake inhibitors (*SSRIs*; see "Depression" below) • *Tricyclic antidepressants* (e.g., doxepin; see "Depression" below) • *Serotonin-norepinephrine reuptake inhibitor* • Venlafaxine, extended release (37.5-75 mg/day, up to 225 mg/day)	• Treatment not to exceed 4 weeks because of dependency/addiction risk • May cause sedation • Taper dosage to avoid withdrawal symptoms • Onset of action often delayed 2-4 weeks • Do not cause dependency/addiction
Depression		

• Depressed mood
• Anhedonia
• Unexplained weight loss/gain or appetite change
• Insomnia or hypersomnia
• Psychomotor agitation or retardation
• Fatigue, lack of energy
• Feelings of hopelessness, worthlessness
• Excessive guilt
• Difficulty with concentration, indecisiveness
• Suicidal ideation/plan
• Crying spells
• Preoccupation with physical concerns
	• *SSRIs*—start at minimal effective dose and increase every week or every other week as tolerated; if no response at 6-8 weeks, then change to a different class of antidepressants
	  • Fluoxetine (10-20 mg/day, up to 40 mg/day)
	  • Paroxetine (10-20 mg/day, up to 40 mg/day)
	  • Sertraline (25-50 mg/day, up to 200 mg/day)
	  • Escitalopram (5-10 mg/day, up to 30 mg/day)
	  • Citalopram (10-20 mg/day, up to 40 mg/day)
	• *Tricyclic antidepressants (TCAs)*
	  • Doxepin (dosage for pruritus is typically 10-25 mg at bedtime; for depression, typically start at 10-25 mg at bedtime and increase every 1-2 weeks to a therapeutic dose of 25-150 mg at bedtime or up to 300 mg in divided doses, depending on tolerance and disease severity)
		• SSRIs have a slow onset of action, with full therapeutic response not seen until 6-8 weeks
		• SSRIs may cause gastrointestinal disturbances, sexual dysfunction
		• Avoid abrupt discontinuation of SSRIs, as may cause dysphoria, dizziness, gastrointestinal distress
		• Citalopram and escitalopram can cause dose-dependent QT prolongation
		• TCAs can lead to weight gain, cardiac conduction abnormalities, orthostatic hypotension, and anticholinergic side effects
		• Doxepin often causes sedation, especially in the elderly and smaller individuals; should be started at low doses (e.g., 10 mg/day) in these individuals

Psychosis		
• Delusions are the most common feature that presents to dermatologists • Fixed false belief that the patient is convinced is true • Delusion is usually encapsulated (narrow focus)	• *Pimozide* (starting dose is 1 mg/day; increase by 1 mg every 1-2 weeks until optimal response is reached, typically at 4-6 mg/day)	• Must taper dosage of pimozide and not discontinue abruptly to avoid withdrawal symptoms such as dyskinetic movements • Pimozide is associated with QT prolongation, cardiac toxicity, extrapyramidal side effects (e.g., tardive dyskinesia), and drug interactions (avoid if taking macrolides, protease inhibitors, azole antifungals, grapefruit juice) • Baseline ECG often recommended when starting pimozide

	• *Atypical (second-generation) antipsychotics*
	  • Risperidone (1-2 mg/day, up to 4 mg/day)
	  • Olanzapine (5-10 mg/day, up to 20 mg/day)
	  • Aripiprazole (10-15 mg/day)
		• Weight gain, metabolic effects, and other side effects of atypical antipsychotics
		• Increasingly being used for delusions of parasitosis because of lower risk of tardive dyskinesia and QT prolongation compared to pimozide

Obsessive-compulsive disorder (OCD)		
• Presence of intrusive obsessions and/or compulsions (see text) • Varying degrees of insight	• *SSRIs* (start at low dose and increase every week or every other week until reach therapeutic range) • Fluoxetine (20 mg/day, up to 40-80 mg/day) • Paroxetine (20 mg/day, up to 40-60 mg/day) • Sertraline (50 mg/day, up to 200 mg/day) • Fluvoxamine (50 mg/day, up to 200-300 mg/day) • Escitalopram (10 mg/day, up to 20-40 mg/day) • Citalopram (20 mg/day, up to 40 mg/day)	• OCD often requires higher doses of SSRIs, and patients may take longer to respond (e.g., 10-12 weeks) • Once a therapeutic response is achieved, continue treatment for 1-2 yrs, followed by gradual tapering of the dosage
	• Tricyclic antidepressants • Clomipramine (50 mg/day, up to 100-250 mg/day)	• Clomipramine has a less tolerable side-effect profile than SSRIs, including cardiac toxicity and arrhythmias; check blood levels when the dose is ≥150 mg/day
	• Serotonin-norepinephrine reuptake inhibitor • Venlafaxine (75 mg/day, up to 225-350 mg/day)	• Venlafaxine may cause hypertension and an increased risk of gastrointestinal bleeding

Modified from Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

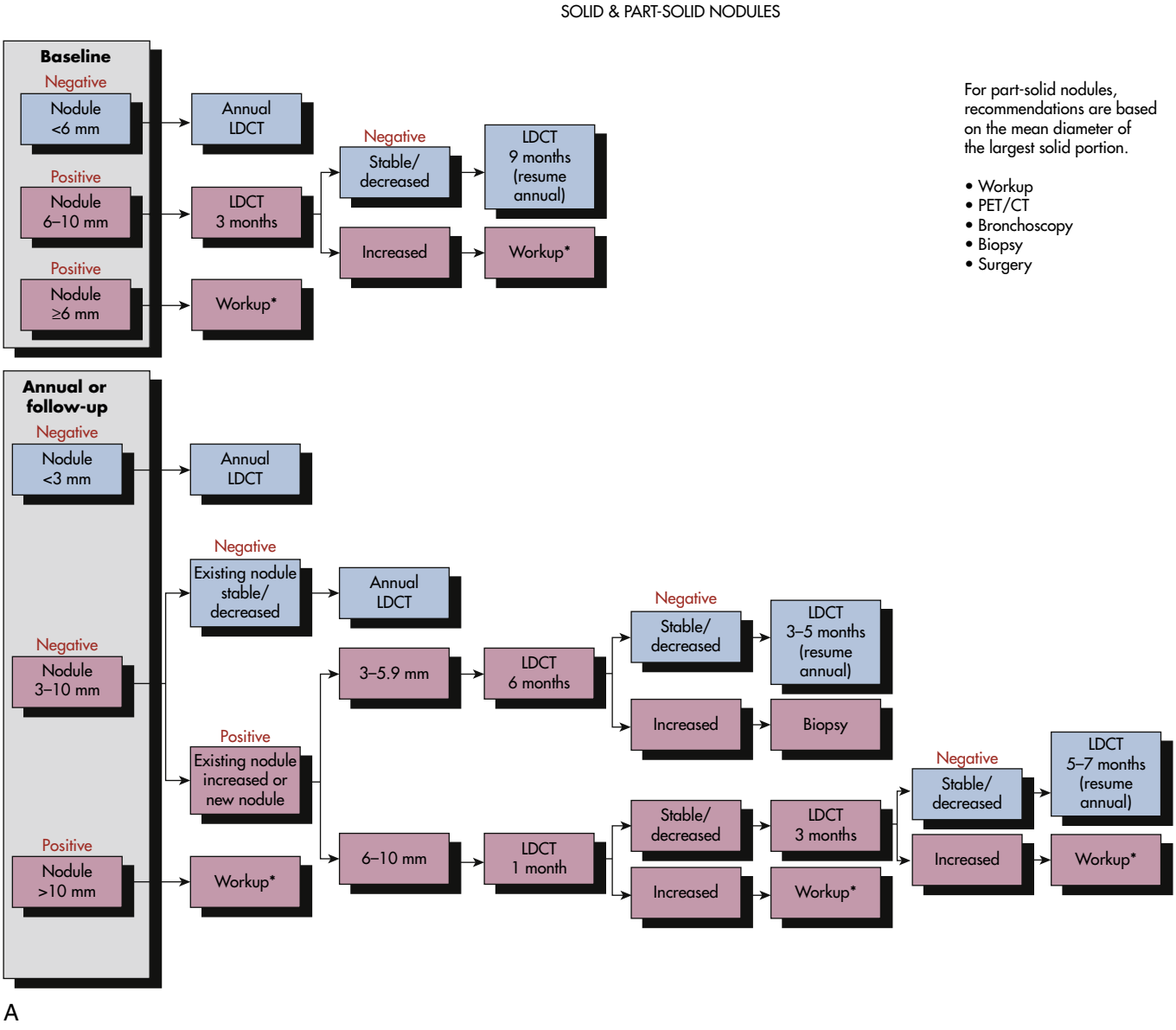
TABLE 44 Body-Focused Repetitive Behaviors and Associated Mucocutaneous Findings

Body-Focused Repetitive Behavior	Associated Mucocutaneous Findings
Lip licking	Irritant contact dermatitis, secondary bacterial or yeast infections
Lip picking or biting	Multiple erosions or ulcerations, recurrent HSV
Cheek chewing or biting	Bite fibroma, morsicatio buccarum
Cuticle pulling, picking, or biting	Paronychia, nail surface irregularities
Nail biting (onychophagia)	Paronychia, nail dystrophy, subungual hemorrhages
Nail picking or pulling (onychotillomania)	
Habit-tic deformity of the thumbnail	Multiple midline Beau's lines with prominent longitudinal central depression
Thumb or finger sucking	Skin maceration, dermatitis, secondary bacterial or yeast infections
Nose picking (rhinotillexomania)	Erosions, secondary bacterial infections
Trichotillomania	
Excoriation (skin-picking) disorder	

HSV, Herpes simplex virus.

Body-focused repetitive behaviors occur on a chronic basis and present with characteristic mucocutaneous findings, depending on the body site and behavior type. These behaviors exist along a spectrum, with habits at one end and body-focused repetitive behavioral disorders at the other end. The latter disorders continue despite repeated attempts to stop and lead to impaired functioning (e.g., social, occupational) or to distress manifesting as feelings of loss of control, embarrassment, or shame.

Modified from Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.



A

FIG. 130 The diagnostic algorithm for (A) solid or part-solid nodules and (B) nonsolid nodules. This algorithm was created through discussion by a multidisciplinary group composed of thoracic surgeons, radiologists, pulmonologists, oncologists, and pathologists. *Workup is at the discretion of the treating physicians but typically consists of a PET/CT and tissue diagnosis, either by bronchoscopy, CT-guided biopsy, or for highly suspicious nodules, minimally invasive surgery. *CT,* Computed tomography; *LDCT,* low-dose computed tomography; *PET,* positron emission tomography. (From Sellke FW, del Nido PJ, Swanson SJ: *Sabiston & Spencer surgery of the chest,* ed 9, Philadelphia, 2016, Elsevier. The Fleishner Society recommendations for computed tomography follow-up of pulmonary nodules are summarized in Tables 45-47).

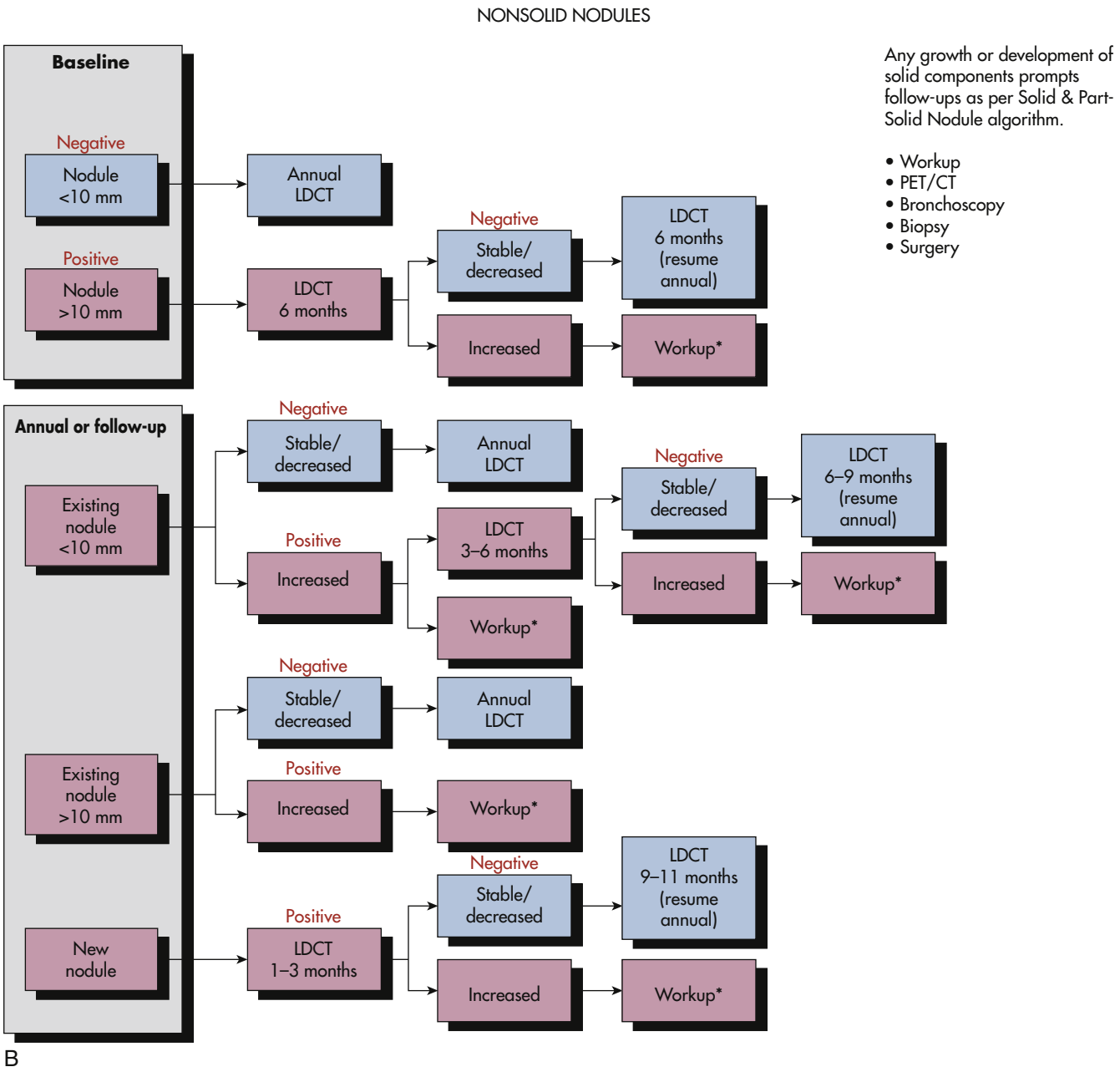


FIG. 130 (Continued)

TABLE 45 Fleischner Society Recommendations for Computed Tomography (CT) Follow-up (FU) of Solid Nodules*

Nodule Size	Low-Risk Patient	High-Risk Patient
≤4 mm	No FU CT needed (FU is optional)	FU CT at 12 months; if unchanged, no further FU
>4-6 mm	FU CT at 12 months; if unchanged, no further FU	FU CT at 6-12 months, then at 18-24 months if no change
>6-8 mm	FU CT at 6-12 months, then at 18-24 months if no change	FU CT at 3-6 months, then at 9-12 and 24 months if no change
>8 mm	Options: FU CT at 3, 9, and 24 months; positron emission tomography; biopsy; video-assisted thoracic surgery	

*Nodule size is average of length and width. Low-risk patient, minimal or absent history of smoking or other known risk factors; high-risk patient, history of smoking or other known risk factors.
From Webb WR, Brant WE, Major NM: *Fundamentals of body CT*, ed 4, Philadelphia, 2015, Saunders.

TABLE 46 Fleischner Society Recommendations for Computed Tomography (CT) Follow-up (FU) of Solitary Ground-Glass Opacity (GGO) or Part-GGO Nodules

Nodule Type	Recommendation	Additional Remarks
Solitary pure GGO ≤5 mm	No FU CT required	Use 1-mm slices to confirm nodule is pure GGO
Solitary pure GGO >5 mm	FU CT at 3 months; if persistent, yearly FU for at least 3 yrs	Positron emission tomography of limited value and not recommended
Solitary part-solid nodules	FU CT at 3 months; if persistent and solid component <5 mm, yearly FU for at least 3 yrs; if persistent and solid component ≥5 mm, then biopsy or resection	Consider positron emission tomography if nodule >1 cm

From Webb WR, Brant WE, Major NM: *Fundamentals of body CT*, ed 4, Philadelphia, 2015, Saunders.

TABLE 47 Fleischner Society Recommendations for Computed Tomography (CT) Follow-up (FU) of Multiple Ground-Glass Opacity (GGO) or Part-GGO Nodules

Nodule Type	Recommendation	Additional Remarks
Multiple pure GGO ≤5 mm	FU CT at 2 and 4 yrs	Consider alternate cause for GGO nodules
Multiple pure GGO >5 mm; no dominant lesion	FU CT at 3 months; if persistent, yearly FU for at least 3 yrs	Positron emission tomography of limited value and not recommended
Dominant part-solid nodule(s)	FU CT at 3 months; if persistent, then biopsy or resection, particularly if solid component ≥ 5 mm	Consider lung-sparing surgery in patients with a dominant lesion suspicious for lung cancer

From Webb WR, Brant WE, Major NM: *Fundamentals of body CT*, ed 4, Philadelphia, 2015, Saunders.

ICD-10CM #
D69.2 Other nonthrombocytopenic purpura
D69.0 Allergic purpura
D69.49 Other primary thrombocytopenia
M31.1 Thrombotic microangiopathy

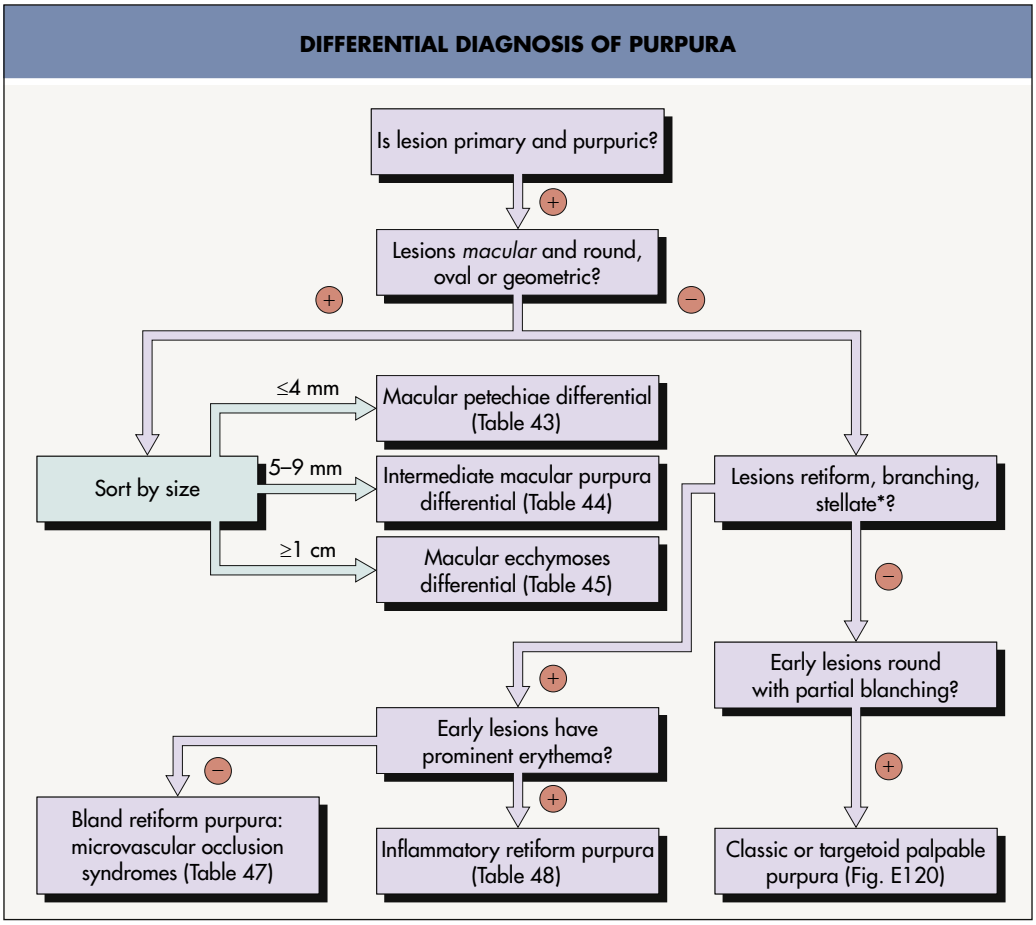


FIG. 131 Differential diagnosis of purpura. *Very few lesions are truly stellate, that is, characterized by a central area of necrosis or hemorrhage with radiating extensions, but some authors continue to use this term to describe these lesions. (From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.)

ICD-10CM #
D69.2 Other nonthrombocytopenic purpura
D69.0 Allergic purpura
D69.49 Other primary thrombocytopenia
M31.1 Thrombotic microangiopathy

TABLE 48 Differential Diagnosis of Macular Petechiae (≤4 mm in diameter)

Hemostatically Relevant Thrombocytopenia (<10, 000-20, 000/mm³)*

Major etiologies†

- Idiopathic thrombocytopenic purpura
- Thrombotic thrombocytopenic purpura
- Other acquired thrombocytopenias, including drug-related
  - Peripheral destruction (e.g., quinine, quinidine)
  - Drug-induced decreased production, idiosyncratic or dose-related (e.g., chemotherapy)
  - Bone marrow infiltration, fibrosis, or failure
- Disseminated intravascular coagulation (early sign)

Abnormal Platelet Function

Major etiologies†

- Congenital or hereditary platelet function defects
- Acquired platelet function defects
  - Aspirin, NSAIDs
  - Renal insufficiency
  - Monoclonal gammopathy (uncommon)
- Thrombocytosis secondary to myeloproliferative disorders (often >1,000,000/mm³)

Nonplatelet Etiologies

Major etiologies†

- Spiking elevations of intravascular venous pressure (Valsalva maneuver-like, e.g., repetitive vomiting, childbirth, paroxysmal coughing, seizure)
- Fixed increased pressure (e.g., stasis, ligatures) or intermittent pressure (e.g., blood pressure cuff [Rumpel-Leede sign])
- Trauma (often linear)
- Perifollicular (vitamin C deficiency)
- Mildly inflammatory conditions
  - Pigmented purpuric eruptions
  - Hypergammaglobulinemic purpura of Waldenström

*Platelets provide factors necessary for hemostasis of endothelial cell junctions. When counts fall below 10,000-20,000/mm³, inadequate platelet support leads to degradation of junction function, increased permeability, and hemorrhage.[3]
†Partial list.
From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

TABLE 49 Differential Diagnosis of Intermediate Macular Purpura (5-9 mm)

Major Etiologies*

- Hypergammaglobulinemic purpura of Waldenström
- Infection/inflammation in patients with thrombocytopenia
- Rarely, minimally inflamed cutaneous small vessel vasculitis (usually dependent distribution)

*Partial list.
From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

TABLE 50 Differential Diagnosis of Macular Ecchymoses (≥1 cm)

Procoagulant Defect Plus Minor Trauma

Major etiologies*

- Anticoagulant use
- Hepatic insufficiency with poor procoagulant synthesis
- Vitamin K deficiency
- Disseminated intravascular coagulation (some)

Poor dermal support of vessels plus minor trauma

Major etiologies*

- Solar (actinic, senile) purpura
- Corticosteroid therapy, topical or systemic
- Vitamin C deficiency (scurvy)
- Systemic amyloidosis (light chain-related, transthyretin-related
- Ehlers-Danlos syndrome

Platelet Disorders Plus Minor Trauma

Major etiologies*

- Platelet function defects, including von Willebrand disease and those induced by medications and metabolic diseases
- Acquired or congenital thrombocytopenia

Miscellaneous

- Papular purpuric gloves and socks syndrome

*Partial list.
From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

TABLE 51 Palpable Purpura: Inflammatory Purpura with Prominent Early Erythema

Leukocytoclastic Vasculitis due to Immune Complex Disease

Small vessels only

- Idiopathic, infection- or drug-associated IgG or IgM complexes
- Idiopathic IgA complexes (HSP), or IgA complexes associated with drugs or infection
- Hypergammaglobulinemic purpura of Waldenström
- Urticarial vasculitis: often minimally purpuric
- Pustular vasculitis (e.g., bowel bypass syndrome)

Small- and medium-sized (macroscopic) vessels may be involved

- Mixed cryoglobulinemia
- Rheumatic vasculitides (LE, RA, Sjögren syndrome)

Pauci-immune leukocytoclastic vasculitis

ANCA-associated

- Granulomatosis with polyangiitis
- Microscopic polyangiitis
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

Other

- Erythema elevatum diutinum
- Sweet syndrome (vasculitis unusual)

***Not* leukocytoclastic vasculitis**

Small vessels only

- Erythema multiforme
- Pityriasis lichenoides et varioliformis acuta (PLEVA)
- Pigmented purpuric eruptions
- Hypergammaglobulinemic purpura of Waldenström (although some lesions have histologic evidence of leukocytoclastic vasculitis)

Classic target lesion—usually erythema multiforme, but can be small vessel vasculitis, especially IgA-associated

AgG, Antigen G; *IgG,* immunoglobin G; *IgM,* immunoglobin M; *HSP,* Henoch-Schönlein purpura; *LE,* lupus erythematosus; *RA,* rheumatoid arthritis.
Modified from Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

ICD-10CM #
D69.2 Other nonthrombocytopenic purpura
D69.0 Allergic purpura
D69.49 Other primary thrombocytopenia
M31.1 Thrombotic microangiopathy

TABLE 52 Differential Diagnosis of Noninflammatory Retiform Purpura

Occlusion Primarily due to Platelet-Related Thrombopathy

Major etiologies*

- Heparin-induced thrombocytopenia syndrome (HITS)
- Thrombocytosis secondary to myeloproliferative disorders
- Paroxysmal nocturnal hemoglobinuria
- Thrombotic thrombocytopenic purpura (though platelet plugs form primarily in visceral vessels, and skin hemorrhage is due more often to thrombocytopenia)

Cold-related precipitation or agglutination

Major etiologies*

- Cryoglobulinemia, usually monoclonal (early lesions of mixed cryoglobulinemia are more often inflammatory and leukocytoclastic due to immune complex deposition)
- Cryofibrinogenemia (though most cryofibrinogens are incidental findings in hospitalized patients)
- Cold agglutinins (rarely cause occlusion; usually cause hemolysis or are asymptomatic)

Occlusion due to organisms growing in vessels

Major etiologies*

- Vessel-invasive fungi (e.g., *Mucor* spp., *Aspergillus* spp.; usually in immunocompromised patients)
- Ecthyma gangrenosum (often *Pseudomonas* spp. or other gram-negative bacilli proliferating in adventitia of subcutaneous arterioles)
- Disseminated strongyloidiasis
- Lucio phenomenon of Hansen disease
- Rocky Mountain spotted fever, other rickettsial spotted fevers

Systemic alteration in control of coagulation

Major etiologies*

- Protein C- and S-related
  - Homozygous protein C or protein S deficiency
  - Acquired protein C deficiency (some patients with sepsis-associated DIC)
  - Warfarin necrosis** (protein C dysfunction)
  - Postinfectious purpura fulminans (protein S dysfunction)
- Antiphospholipid antibody, lupus anticoagulant
- Levamisole-adulterated cocaine^

Vascular coagulopathy

- Livedoid vasculopathy/atrophie blanche (may also have a systemic prothrombotic component)
- Malignant atrophic papulosis/Degos disease (antiphospholipid antibody syndrome can mimic this disease)
- Sneddon syndrome (can be related to antiphospholipid antibody syndrome)
- Deficiency of adenosine deaminase 2 (ADA2)

Embolization or crystal deposition

Major etiologies*

- Cholesterol emboli
- Oxalate crystal deposition (rare)
- Marantic endocarditis, atrial myxoma, crystal globulins, hypereosinophilic syndrome (all rare)

Reticulocyte, red blood cell occlusion

- Sickle cell disease
- Severe malaria (usually *Plasmodium falciparum*)

Miscellaneous

- Cutaneous calciphylaxis
- Brown recluse (*Loxosceles*) spider bite reaction
- Intravascular B-cell lymphoma
- Hydroxyurea (rare)

DIC, Disseminated intravascular coagulation.
*Partial list.
**Also referred to as Coumadin® necrosis.
^Early lesions primarily thrombotic, but vasculitis can also occur.
From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

TABLE 53 Differential Diagnosis of Inflammatory Retiform Purpura

Vasculitis

Primarily dermal vessels

- IgA vasculitis

Dermal and Subcutaneous Vessels Usually Involved

- Mixed cryoglobulinemia
- Rheumatic vasculitides (LE, RA)
- Polyarteritis nodosa
- Microscopic polyangiitis
- Granulomatosis with polyangiitis
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

Dermal Vessel Inflammation/Occlusion/Constriction

- Livedoid vasculopathy
- Septic vasculitis
- Chilblains (pernio)
- Pyoderma gangrenosum

IgA, Immunoglobin A; *LE,* Lupus erythematosus; *RA,* rheumatoid arthritis.
From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018, Elsevier.

ICD-10CM #

D69.2	Other nonthrombocytopenic purpura
D69.0	Allergic purpura
D69.49	Other primary thrombocytopenia
M31.1	Thrombotic microangiopathy

FIG. E132 Clinical examples of petechiae and purpura. A, Round to oval petechiae <3 mm in diameter. **B,** Solar (actinic) purpura in sites of actinic damage plus trauma. **C,** Palpable purpura due to cutaneous small vessel vasculitis (inflammation plus hemorrhage). **D,** Noninflammatory (bland) retiform purpura as well as hemorrhagic bullae in a patient with disseminated intravascular coagulation. (From Bolognia J: *Dermatology,* ed 4, Philadelphia, 2018E, Elsevier. B, Courtesy Kalman Watsky, MD; D, Courtesy Judit Stenn, MD.)

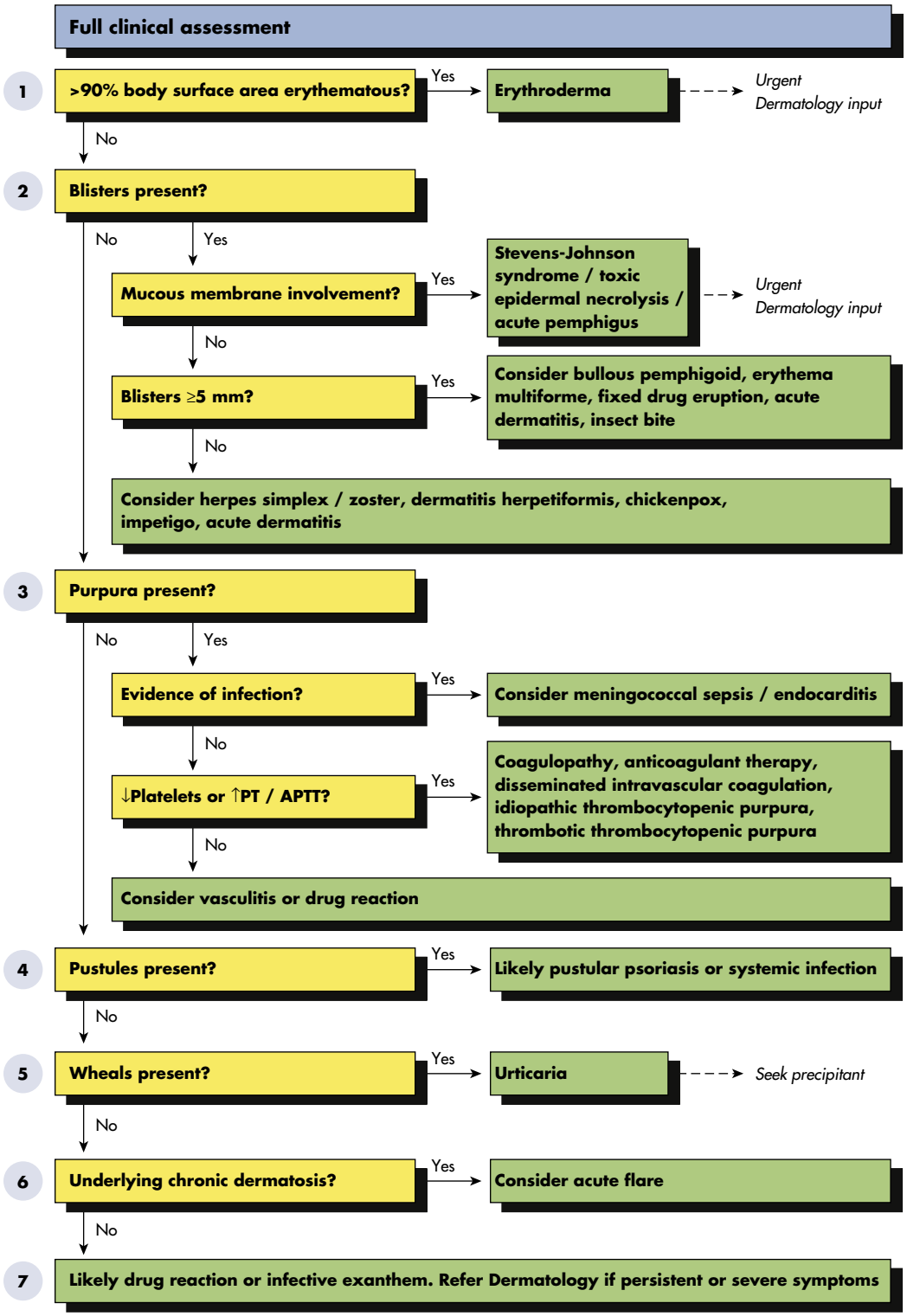


FIG. 133 Rash: acute generalized skin eruption. (From Gawkrodger DJ: *Dermatology ICT,* ed 4, Edinburgh, 2008, Churchill Livingstone; Japp AG, Robertson C: *Macleod's clinical diagnosis,* ed 2, Philadelphia, 2018, Elsevier.)

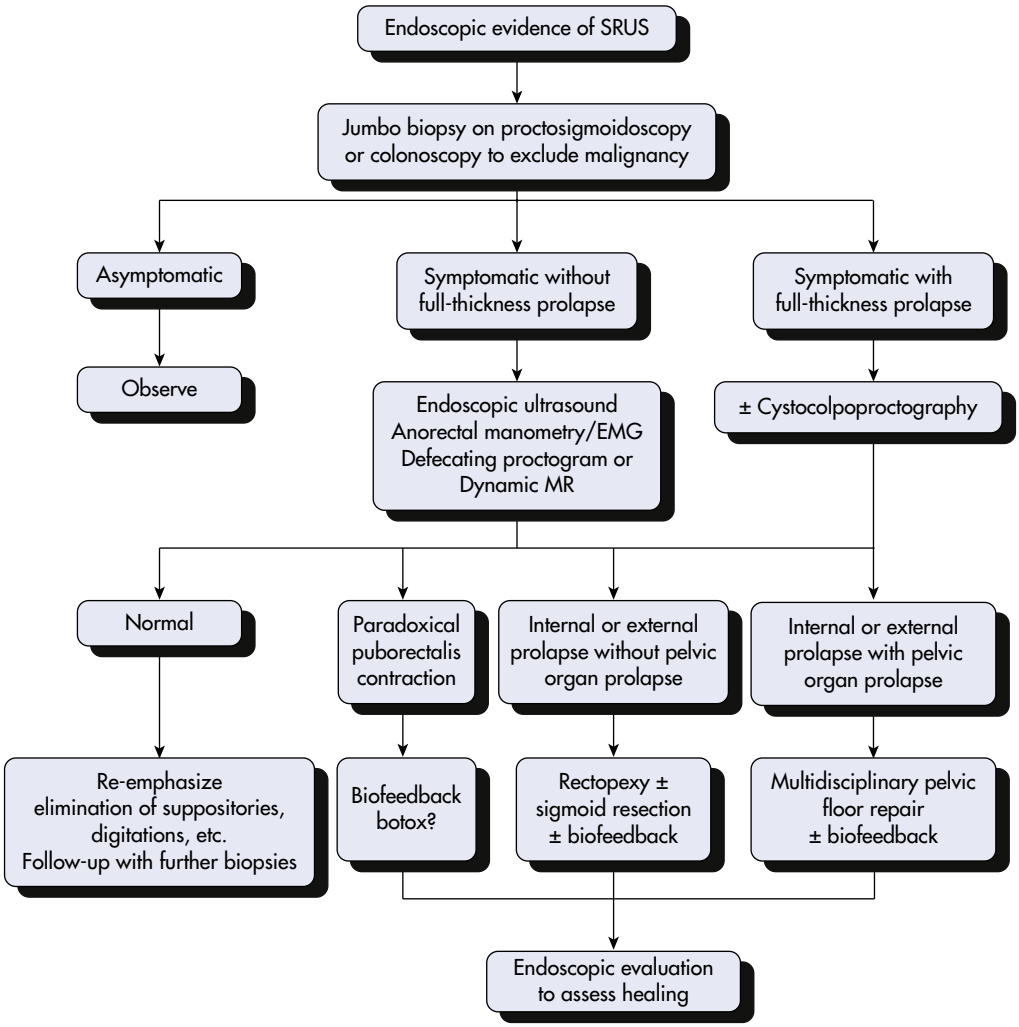


FIG. 134 Schematic for the management of solitary rectal ulcer syndrome *(SRUS).* *EMG,* Electromyography; *MR,* magnetic resonance. (From Cameron JL, Cameron AM: *Surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

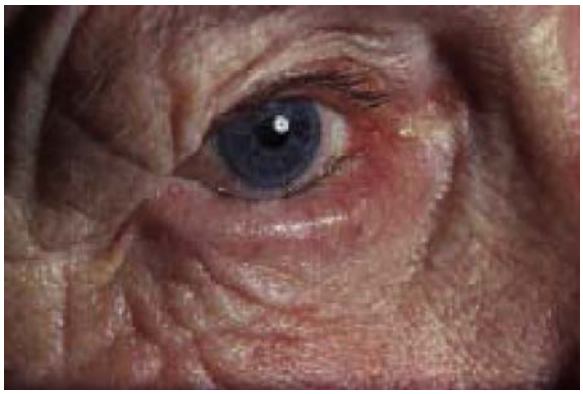


FIG. E135 Senile entropion of the lower lid. (From Douglas G, Nicol F, Robertson C: *MacLeod's clinical examination,* ed 13, Edinburgh, 2013, Churchill Livingstone.)

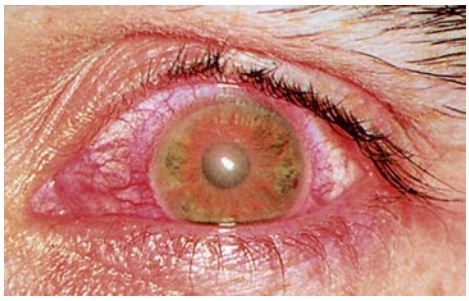


FIG. E136 Iritis (anterior uveitis). (From Schwartz MH: *Textbook of physical diagnosis: history and examination,* ed 6, Philadelphia, 2009, Saunders.)

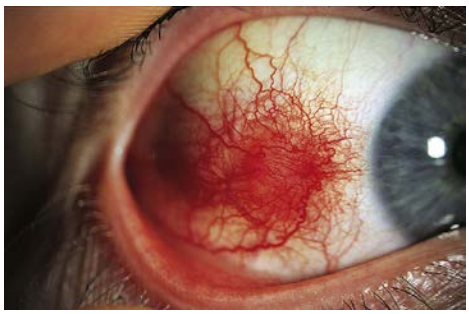


FIG. E137 Episcleritis. (From Rutter P: *Community pharmacy,* ed 2, Edinburgh, 2009, Churchill Livingstone.)

FIG. E138 Scleritis. (From Kanski JJ: *Clinical diagnosis in ophthalmology,* ed 1, St Louis, 2006, Mosby.)

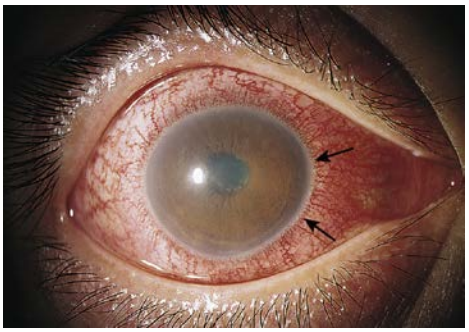


FIG. E139 Acute angle-closure glaucoma. Arrows show dilated conjunctival vessels at corneal edge. Note hazy cornea. (From Roberts JR, Hedges JR: *Clinical procedures in emergency medicine,* ed 5, Philadelphia, 2010, Saunders.)

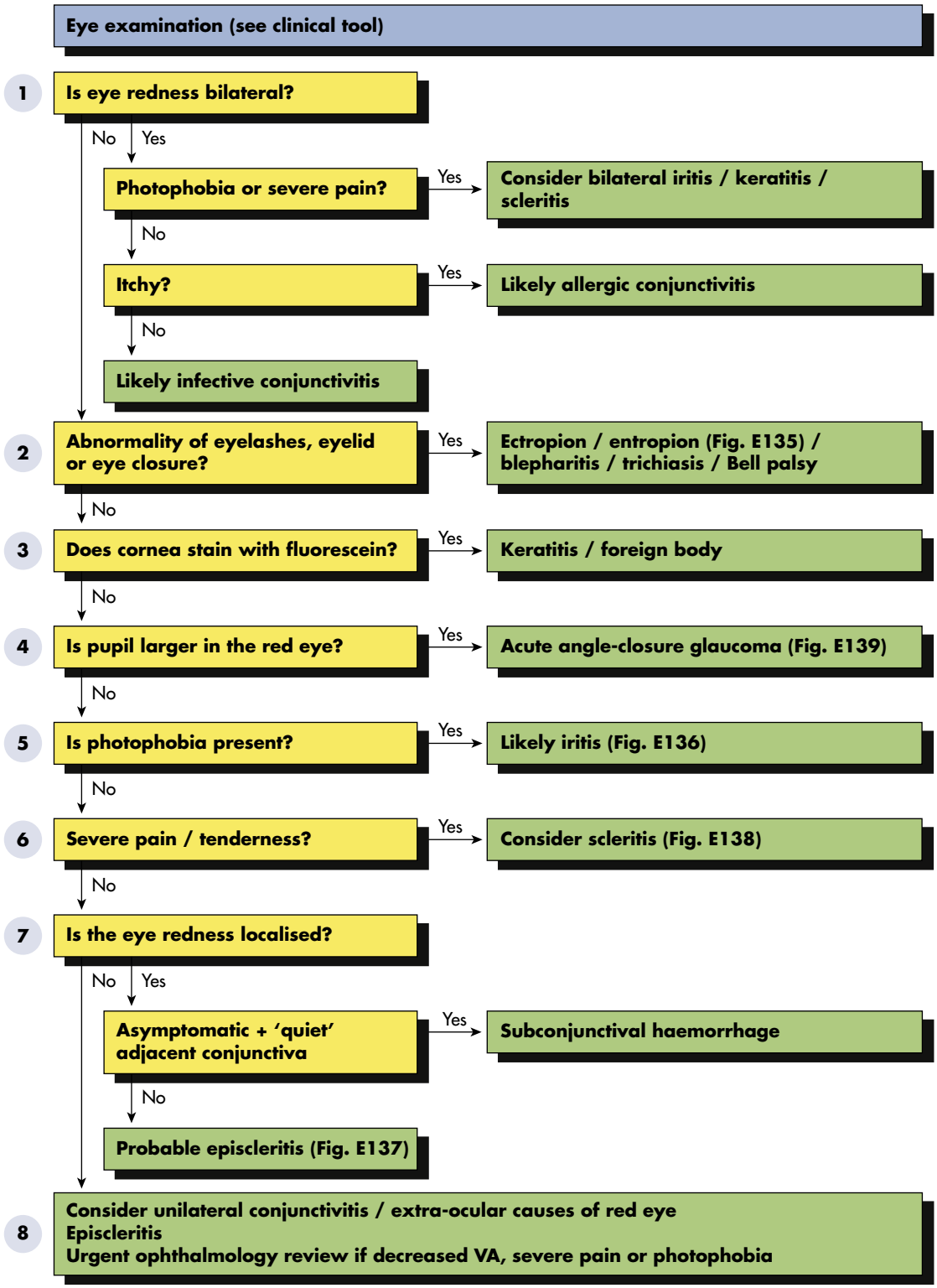


FIG. 140 Red eye. (From Japp AG, Robertson C: *Macleod's clinical diagnosis*, ed 2, Elsevier, 2018.)

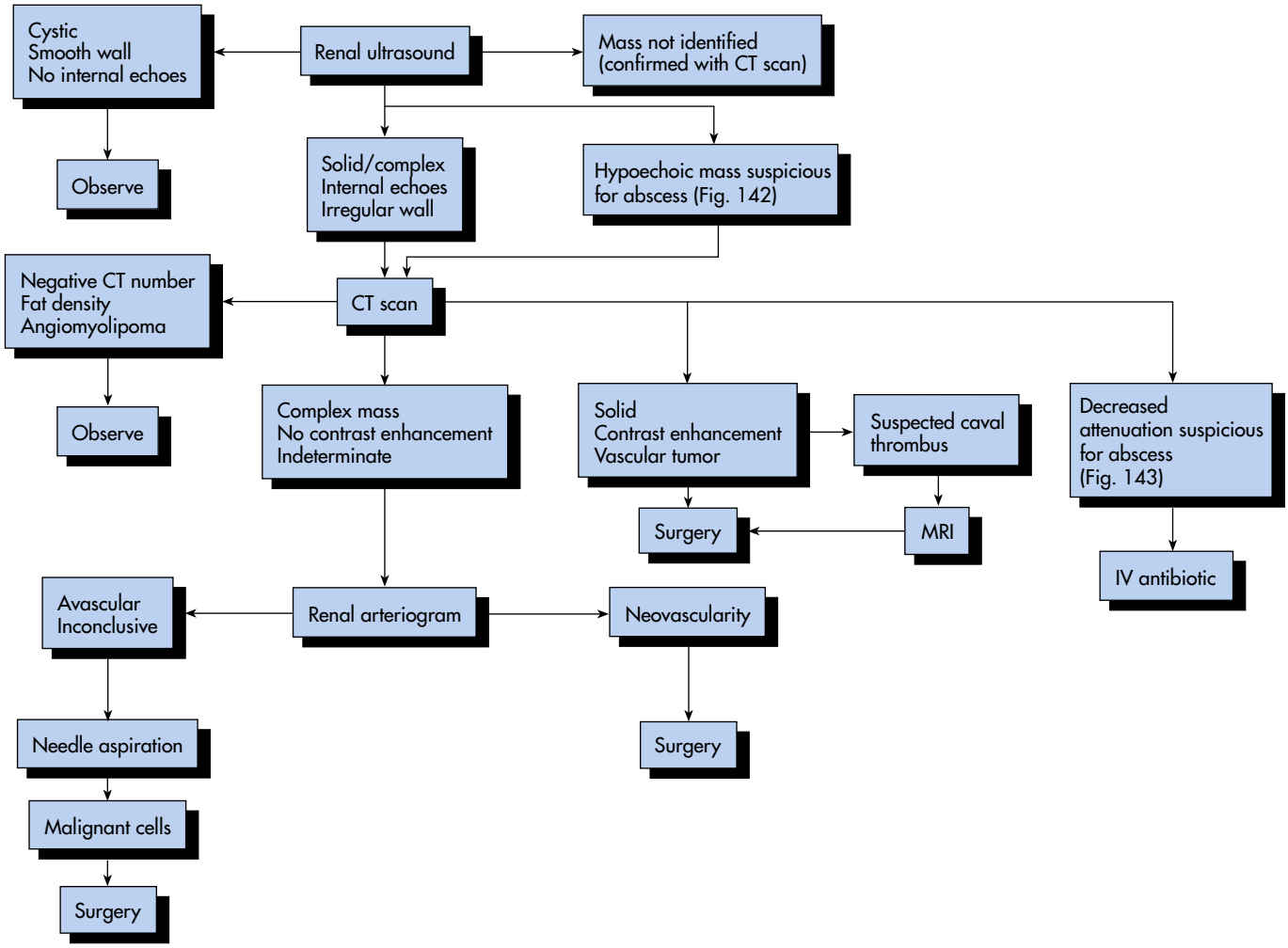


FIG. 141 Evaluation of a patient with a renal mass on renal ultrasound. *CT,* Computed tomography; *MRI,* magnetic resonance imaging. (Modified from Williams RD: Tumors of the kidney, ureter, and bladder. In Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 23, Philadelphia, 2008, Saunders.)

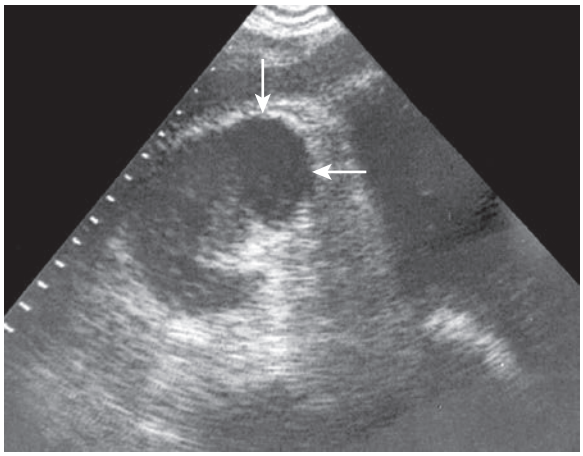


FIG. 142 Acute renal abscess. Transverse ultrasound image of the right kidney demonstrates a poorly marginated rounded focal hypoechoic mass *(arrows)* in the anterior portion of the kidney. *CT*, Computed tomography. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

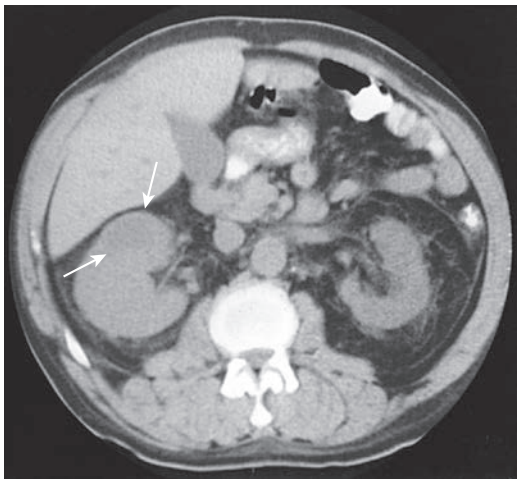


FIG. 143 Acute renal abscess. Nonenhanced computed tomography scan through the mid-pole of the right kidney demonstrates right renal enlargement and an area of decreased attenuation *(arrows).* After antimicrobial therapy, a follow-up scan showed complete regression of these findings. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

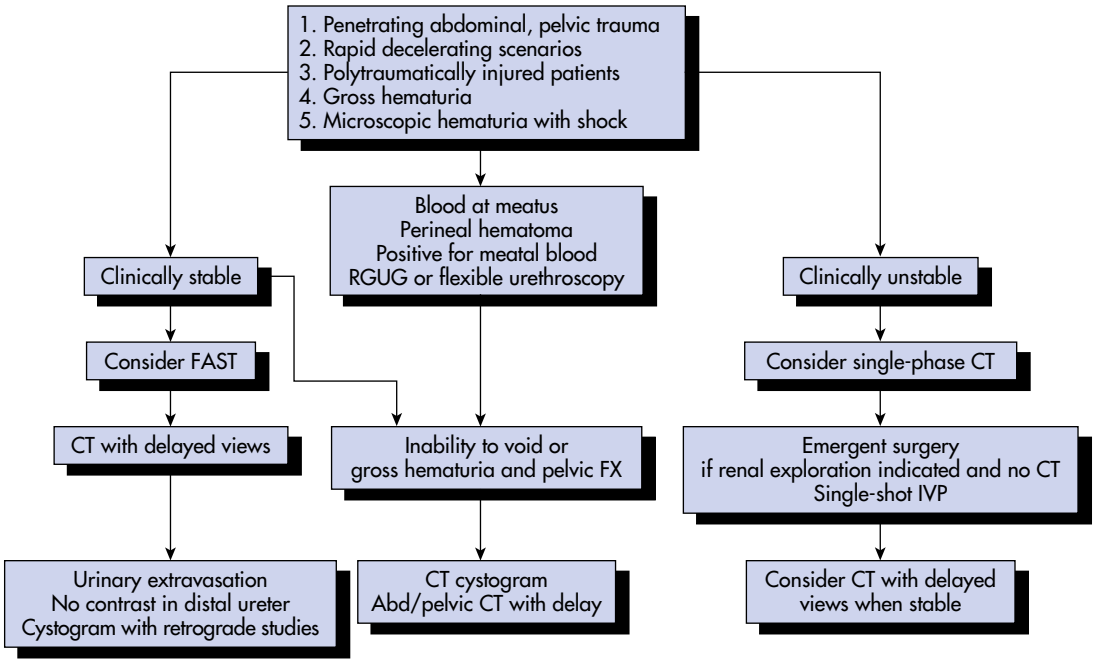


FIG. E144 Recommended evaluation protocol for patients with a medical history or physical findings consistent with possible genitourinary injury. *Abd,* Abdominal; *CT,* computed tomography; *FAST,* focused assessment with sonography for trauma; *FX,* fracture; *IVP,* intravenous pyelography; *RGUG,* retrograde urethrogram. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

TABLE E54 Consensus Recommendations for Management of Renal Trauma

Clinical Findings and/or Grade of Renal Injury	Recommended Treatment
Grade 1 or 2 renal injury irrespective of traumatic etiology*	Nonoperative
Isolated grade 3, grade 4, and hemodynamically stable grade 5 renal injuries	Nonoperative
Uncontrollable renal hemorrhage/vascular instability; occasionally grade 4 "shattered" kidneys and a high percentage of grade 5 injuries	Absolute requirement for surgical intervention
Persistent or delayed hemorrhage not responding to angiographic embolization	Absolute requirement for surgical intervention
Expanding pulsatile retroperitoneal mass found on surgical exploration for coexisting intraabdominal injuries	Absolute requirement for surgical intervention (verify contralateral renal function prior to exploration)
Penetrating trauma, inadequate preoperative radiographic staging because of vascular instability of patient, retroperitoneal hemorrhage found on exploration	Retroperitoneal (renal) exploration recommended (verify contralateral renal function prior to exploration)
Blunt trauma; inadequate preoperative radiographic staging because of vascular instability of patient; no duodenal, pancreatic, or colonic injuries with retroperitoneal hemorrhage found on exploration	Observation—if FAST with bilateral blood flow. If no FAST obtained, consider intraoperative single-shot IVP/US with renal blood flow assessment or CT immediately following stabilization of patient
Blunt trauma; inadequate preoperative radiographic staging because of vascular instability of patient; duodenal, pancreatic, or colonic injuries with retroperitoneal hemorrhage found on exploration	Surgical interventions with renorrhaphy an option (verify contralateral renal function prior to exploration) *or* Drain intra-abdominal injuries. Observation—if FAST with bilateral blood flow. If no FAST obtained, consider intraoperative single-shot IVP/US with renal blood flow assessment or CT immediately following stabilization of patient
Blunt/penetrating trauma; radiographic screening studies reveal grade 3 renal injury with devitalized renal fragments, grade 4 or 5 renal injury, coexisting intraabdominal injuries—especially duodenum, pancreas, and colon	Retroperitoneal (renal) exploration with renorrhaphy and repair recommended

CT, Computed tomography; *FAST,* focused assessment with sonography for trauma; *IVP,* intravenous pyelography; *US,* ultrasound.
*Blunt or penetrating trauma.
From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.

ICD-10CM #
N44.2 Benign cyst of testis
N44.8 Other noninflammatory disorders of the testis
N50.3 Cyst of epididymis
N50.8 Other specified disorders of male genital organs

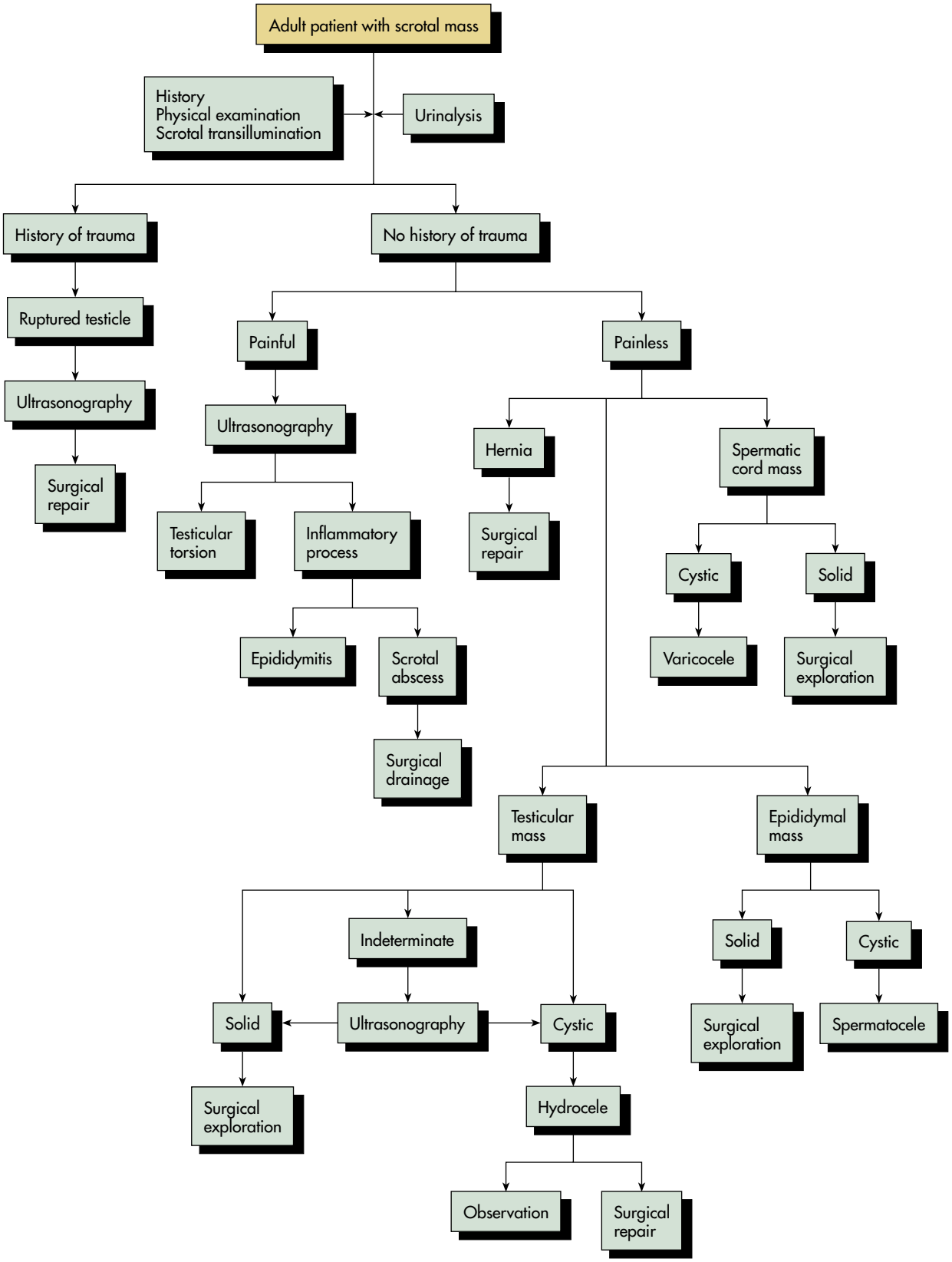
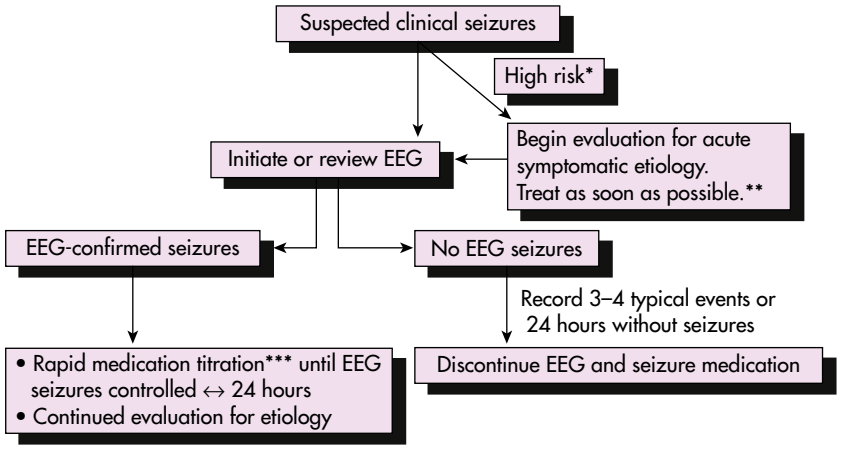
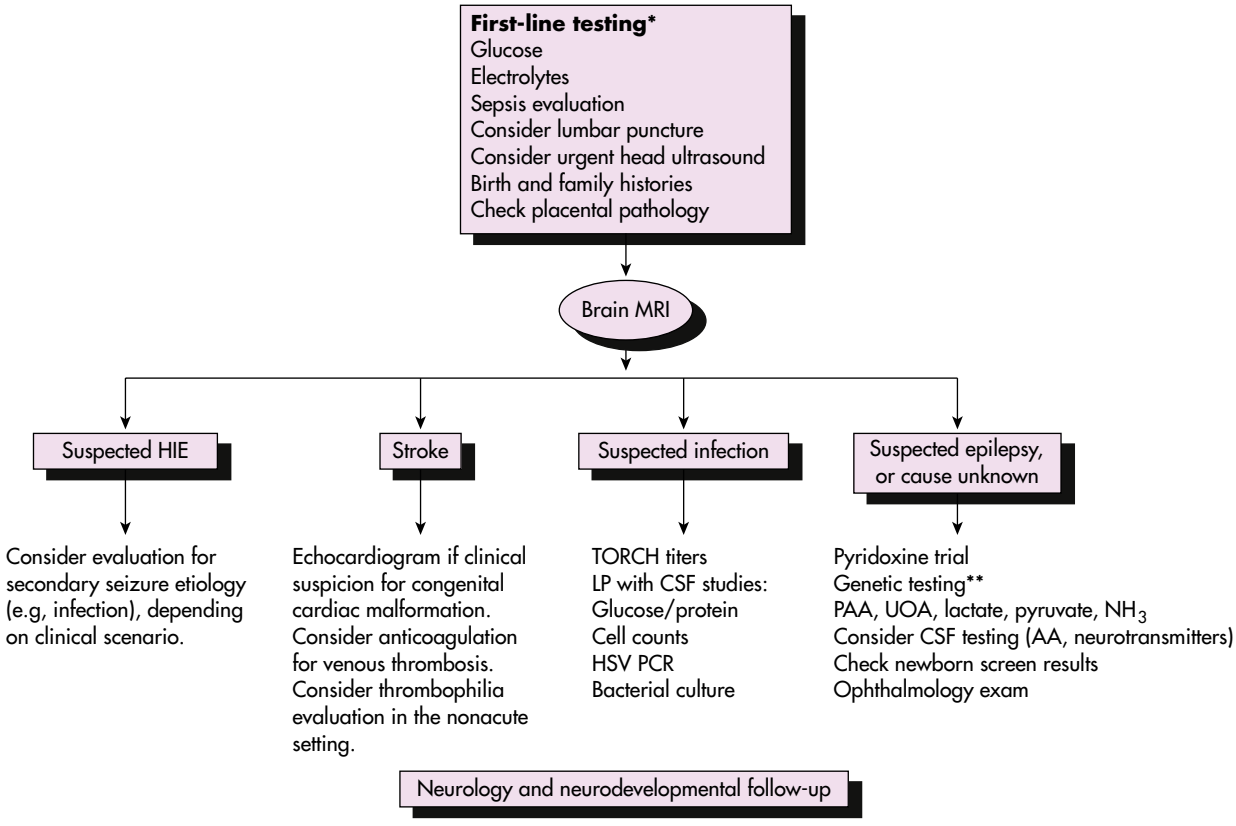


FIG. 145 Evaluation of scrotal mass. (Modified from Greene HL, Johnson WP, Lemcke DL [eds]: *Decision making in medicine*, ed 2, St Louis, 1998, Mosby.)



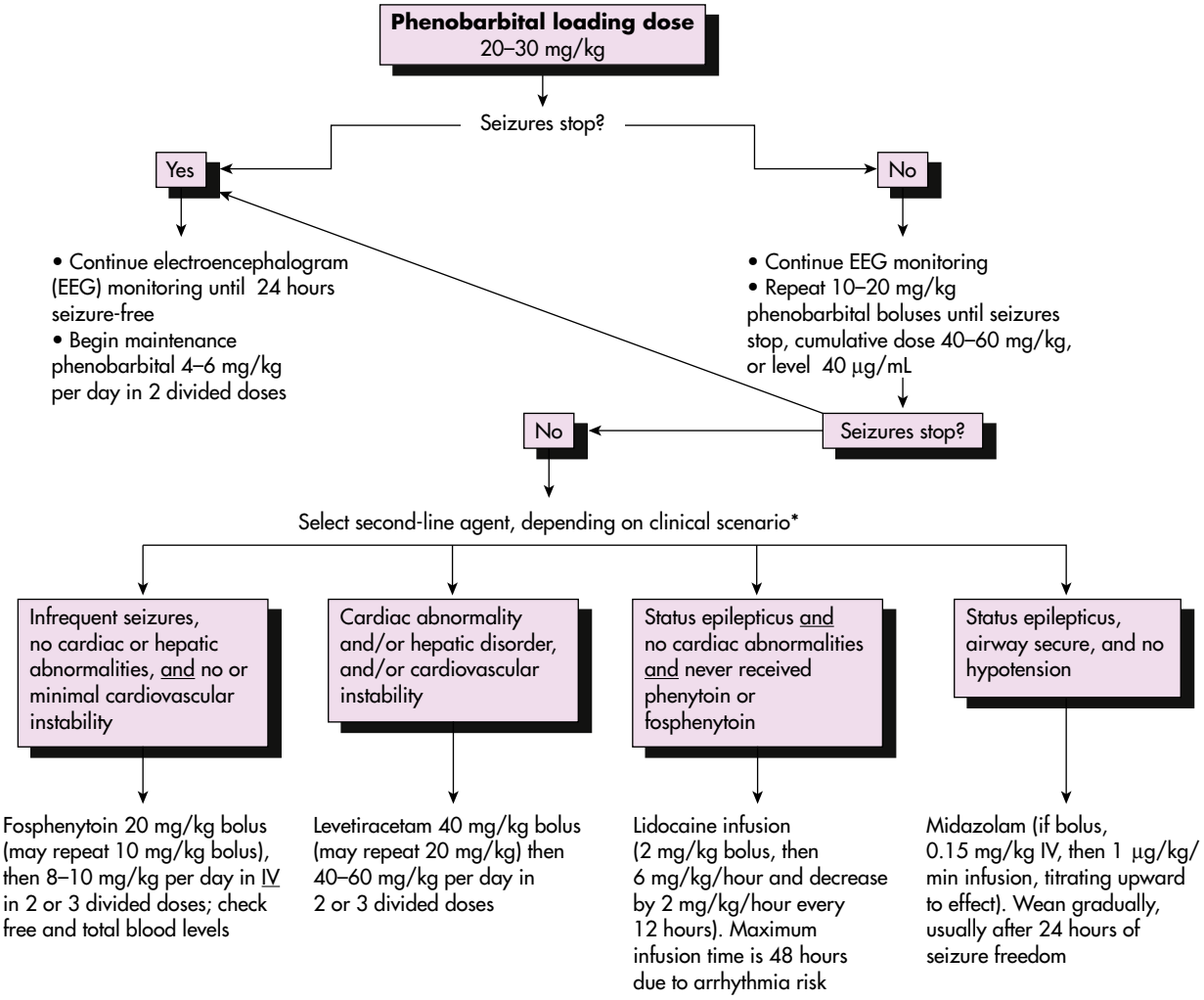
* High-risk scenarios: known or suspected acute brain injury, encephalopathy, previous EEG seizures, first 72 hours of life
** Reverse glucose or electrolyte abnormalities, and/or administer lorazepam 0.1 mg/kg IV, and/or administer phenobarbital loading dose.
*** Refer to Figure 148

FIG. 146 Assessment algorithm for newborns with suspected seizures. *EEG,* Electroencephalogram. (From Swaiman KF: *Swaiman's pediatric neurology, principles and practice,* ed 6, Philadelphia, 2017, Elsevier.)



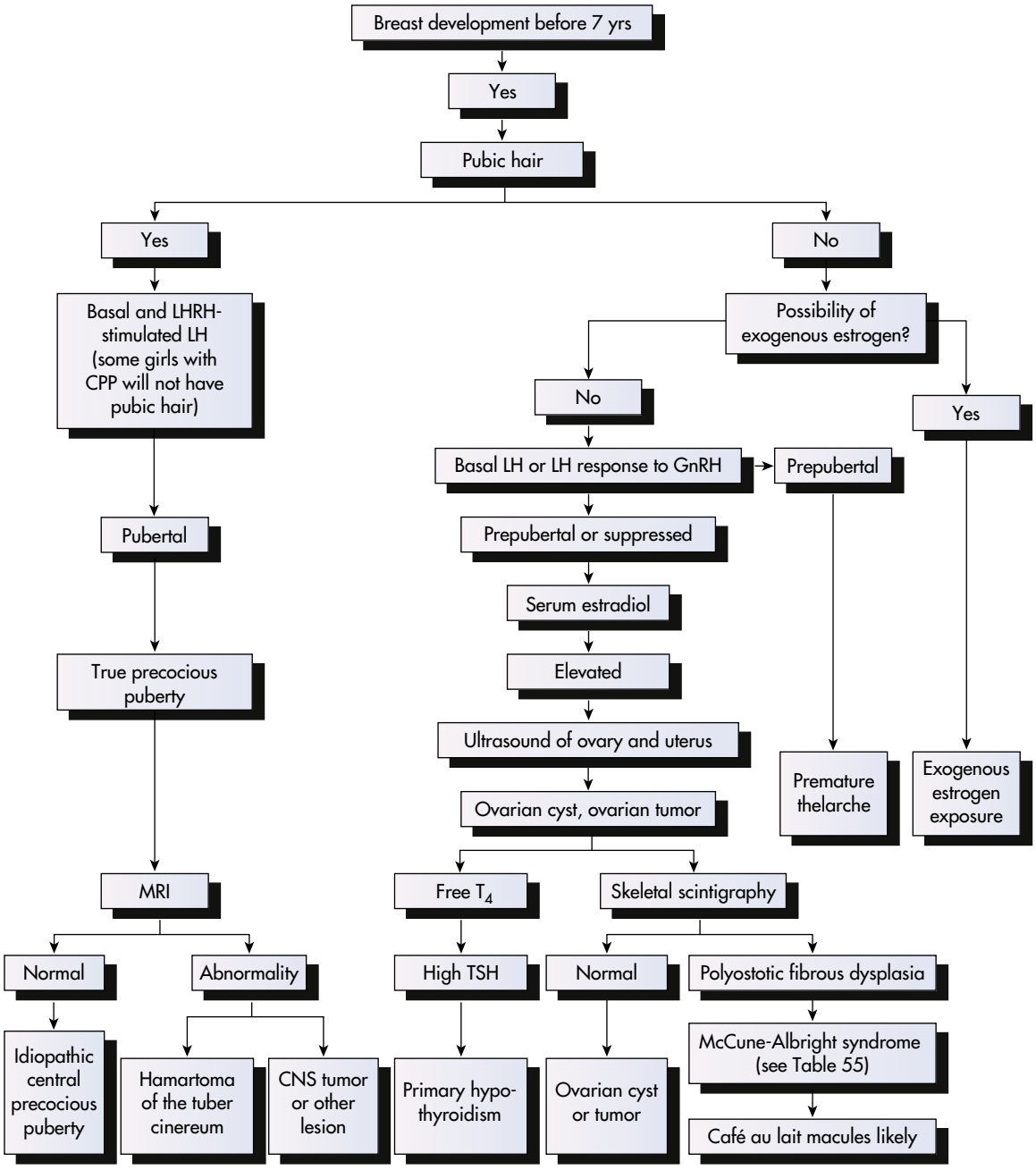
**Genetic testing can include karyotype, chromosomal microarray, epilepsy gene panel, or single gene testing.

FIG. 147 Assessment algorithm for newborns with seizures. First-line testing should occur simultaneously with initiation of electroencephalography (and empiric seizure treatment in high-risk clinical scenarios). Most infants should receive neuroimaging, and brain magnetic resonance imaging *(MRI)* is the preferred neuroimaging modality. Second-line testing depends on the clinical scenario and MRI findings. Newborns with seizures are at high risk for long-term neurodevelopmental disability and epilepsy, and so they require careful follow-up by appropriate clinicians. *CSF,* Cerebrospinal fluid; *HIE,* hypoxic ischemic encephalopathy; *HSV,* herpes simplex virus; *LP,* lumbar puncture; *PCR,* polymerase chain reaction; *TORCH,* Toxoplasma gondii, other viruses, rubella, cytomegalovirus, and herpes simplex. (From Swaiman KF: *Swaiman's pediatric neurology: principles and practice,* ed 6, Philadelphia, 2017, Elsevier.)



*If the infant has acute symptomatic seizures, select from these options, based on comorbidities and seizure severity. If the newborn has epilepsy (e.g, lissencephaly, tuberous sclerosis), consider levetiracetam, topiramate, or oxcarbazepine as second- or third-line treatments.

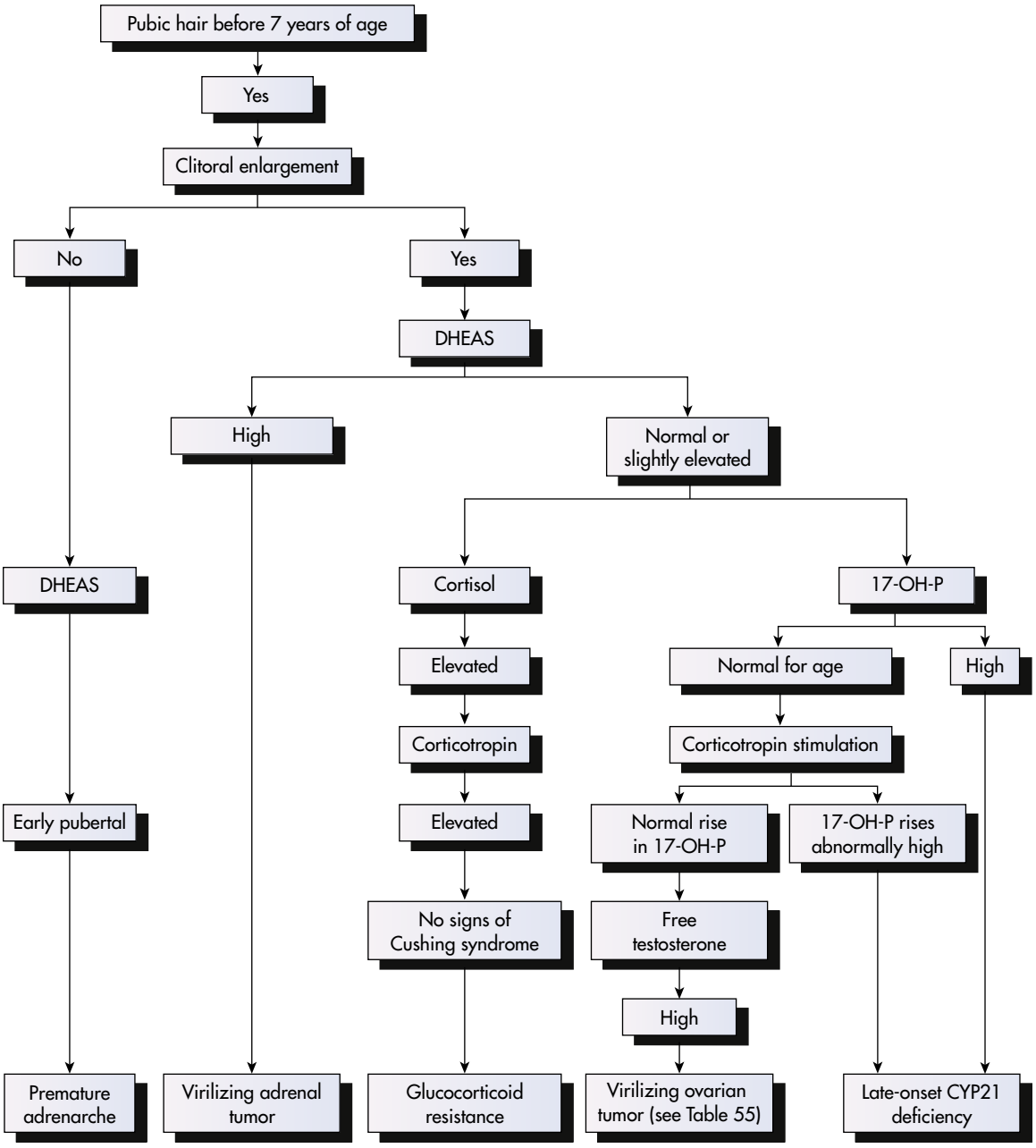
FIG. 148 Suggested treatment algorithm for neonatal seizures. The rapidity of medication administration will depend on local guidelines and resources. Frequent assessment of treatment response is recommended. (From Swaiman KF: *Swaiman's pediatric neurology: principles and practice*, ed 6, Philadelphia, 2017, Elsevier.)



Note: For more information on this topic, see Section I: Precocious Puberty.

FIG. 149 Flow chart for diagnosing sexual precocity in girls. *CNS,* Central nervous system; *CPP,* central precocious puberty; *FSH,* follicle-stimulating hormone; *GnRH,* gonadotropin-releasing hormone; *LH,* luteinizing hormone; *LHRH,* LH-releasing hormone; *MRI,* magnetic resonance imaging; T_4, thyroxine; *TSH,* thyroid-stimulating hormone. (From Melmed S et al: *Williams textbook of endocrinology,* ed 13, Philadelphia, 2016, Elsevier.)

ICD-10CM # E30.1 Precocious puberty
E30.8 Other disorders of puberty



Note: For more information on this topic, see Section I: Precocious Puberty.

FIG. 150 Flow chart for the evaluation of pubic hair in normal phenotypic girls before 7 years. *DHEAS,* Dehydroepiandrosterone sulfate; *17-OH-P,* 17-hydroxyprogesterone. (From Melmed S et al: *Williams textbook of endocrinology,* ed 13, Philadelphia, 2016, Elsevier.)

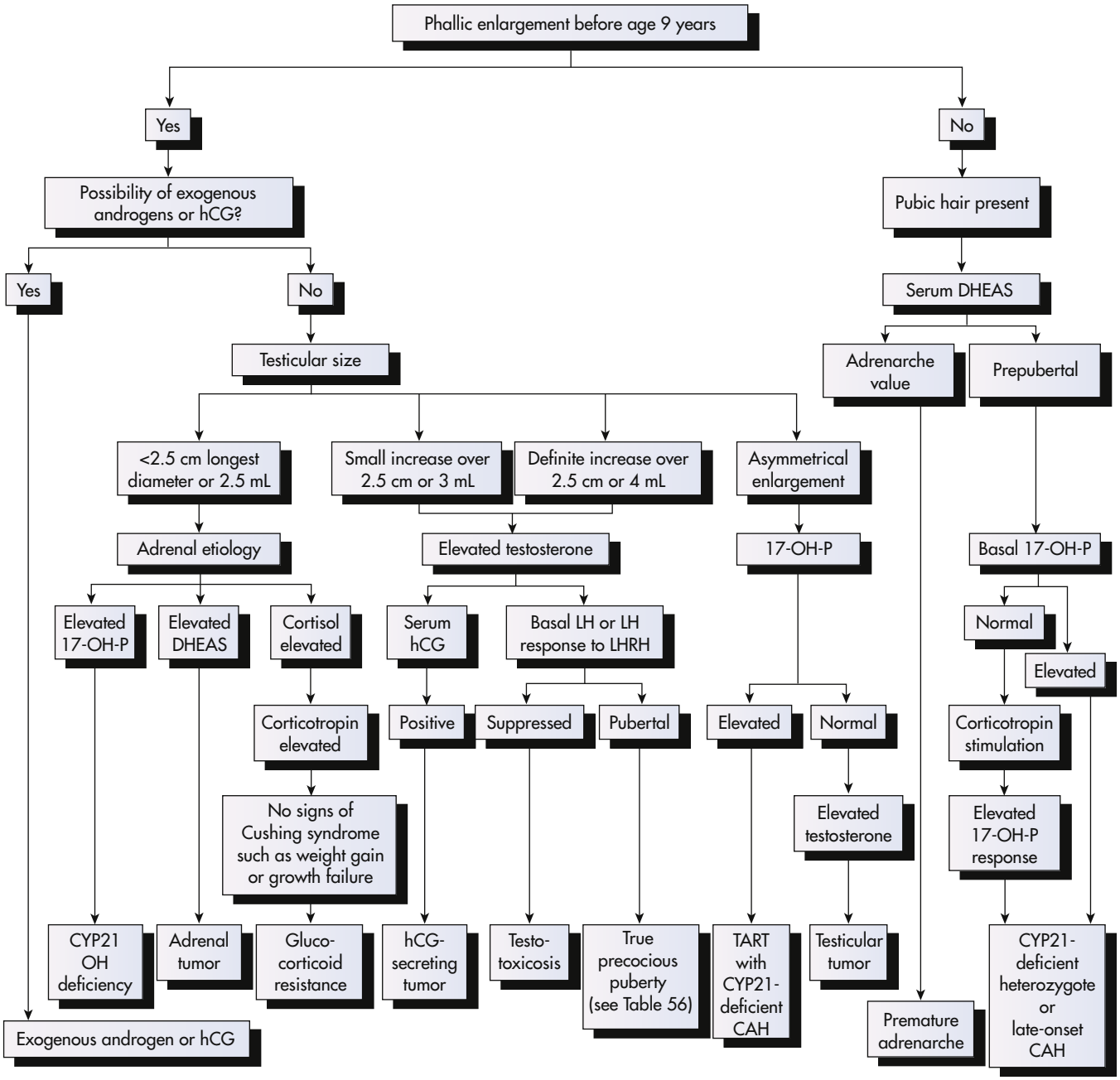
TABLE 55 Differential Diagnosis of Sexual Precocity

	Plasma Gonadotropins	LH Response to LHRH	Serum Sex Steroid Concentration	Gonadal Size	Miscellaneous
In Both Sexes					
McCune-Albright syndrome	Suppressed	Suppressed	Sex steroids pubertal or higher	Ovarian (on ultrasound); slight testicular enlargement	Skeletal survey for polyostotic fibrous dysplasia and skin examination for café-au-lait spots
Primary hypothyroidism	LH prepubertal; FSH may be slightly elevated	Prepubertal FSH may be increased	Estradiol may be pubertal	Testicular enlargement; ovaries cystic	TSH and prolactin elevated; T_4 low
Females					
Granulosa cell tumor (follicular cysts may present similarly)	Suppressed	Prepubertal LH response	Very high estradiol	Ovarian enlargement on physical examination, CT, or ultrasonography	Tumor often palpable on abdominal examination
Follicular cyst	Suppressed	Prepubertal LH response	Prepubertal to very high estradiol	Ovarian enlargement on physical examination, CT, or ultrasonography	Single or recurrent episodes of menses and/or breast development; exclude McCune-Albright syndrome
Feminizing adrenal tumor	Suppressed	Prepubertal LH response	High estradiol and DHEAS values	Ovaries prepubertal	Unilateral adrenal mass
Premature thelarche	Prepubertal	Prepubertal LH, pubertal estradiol response	Prepubertal or early	Ovaries prepubertal	Onset usually before 3 yrs of age
Premature adrenarche	Prepubertal	Prepubertal LH response	Prepubertal estradiol; DHEAS or urinary 17-ketosteroid values appropriate for pubic hair stage 2	Ovaries prepubertal	Onset usually after 6 yrs of age; more frequent in brain-injured children
Late-onset virilizing congenital adrenal hyperplasia	Prepubertal	Prepubertal LH response	Elevated 17-OHP in basal or corticotropin-stimulated state	Ovaries prepubertal	Autosomal recessive

CNS, Central nervous system; *CT,* computed tomography; *DHEAS,* dehydroepiandrosterone sulfate; *FSH,* follicle-stimulating hormone; *LH,* luteinizing hormone; *17-OHP,* 17-hydroxy progesterone; T_4, thyroxine; *TSH,* thyrotropin.

From Larsen PR et al [eds]: *Williams textbook of endocrinology,* ed 11, Philadelphia, 2008, Saunders.

ICD-10CM # E30.1 Precocious puberty
E30.8 Other disorders of puberty



Note: For more information on this topic, see Section I: Precocious Puberty.

FIG. 151 Flow chart for diagnosing sexual precocity in a phenotypic male. *CAH,* Congenital adrenal hyperplasia; *DHEAS,* dehydroepiandrosterone sulfate; *hCG,* human chorionic gonadotropin; *LH,* luteinizing hormone; *LHRH,* LH-releasing hormone; *17-OH-P,* 17-hydroxyprogesterone; *TART,* testicular adrenal rest tissue. (From Melmed S et al: *Williams textbook of endocrinology,* ed 13, Philadelphia, 2016, Elsevier.)

TABLE 56 Causes of Male Sexual Precocity

	Plasma Gonadotropins	LH Response to LHRH	Serum Sex Steroid Concentration	Gonadal Size	Miscellaneous
True Precocious Puberty (premature reactivation of LHRH pulse generator)	Prominent LH pulses, initially during sleep	Pubertal LH response	Pubertal values of testosterone or estradiol	Normal pubertal testicular enlargement or ovarian and uterine enlargement (by ultrasonography)	MRI of brain to rule out CNS tumor or other abnormality; skeletal survey for McCune-Albright syndrome
Incomplete Sexual Precocity (pituitary gonadotropin-independent)					
Males					
Chorionic gonadotropin-secreting tumor in males	High hCG, low LH	Prepubertal LH response	Pubertal value of testosterone	Slight to moderate uniform enlargement of testes	Hepatomegaly suggests hepatoblastoma; CT scan of brain if chorionic gonadotropin-secreting CNS tumor suspected
Leydig cell tumor in males	Suppressed	No LH response	Very high testosterone	Irregular asymmetrical enlargement of testes	
Familial testotoxicosis	Suppressed	No LH response	Pubertal values of testosterone	Testes symmetrical and larger than 2.5 cm but smaller than expected for pubertal development; spermatogenesis occurs	Familial; probably sex-limited, autosomal dominant trait
Virilizing congenital adrenal hyperplasia	Prepubertal	Prepubertal LH response	Elevated 17-OHP in CYP21 deficiency or elevated 11-deoxycortisol in CYP11B1 deficiency	Testes prepubertal	Autosomal recessive, may be congenital or late-onset form, may have salt loss in CYP21 deficiency or hypertension in CYP11B1 deficiency
Virilizing adrenal tumor	Prepubertal	Prepubertal LH response	High DHEAS and androstenedione values	Testes prepubertal	CT, MRI, or ultrasonography of abdomen
Premature adrenarche	Prepubertal	Prepubertal LH response	Prepubertal testosterone, DHEAS, or urinary 17-ketosteroid values appropriate for pubic hair stage 2	Testes prepubertal	Onset usually after 6 yrs of age; more frequent in CNS-injured children
In Both Sexes					
McCune-Albright syndrome	Suppressed	Suppressed	Sex steroids pubertal or higher	Ovarian (on ultrasound); slight testicular enlargement	Skeletal survey for polyostotic fibrous dysplasia and skin examination for café-au-lait spots
Primary hypothyroidism	LH prepubertal; FSH may be slightly elevated	Prepubertal FSH may be increased	Estradiol may be pubertal	Testicular enlargement; ovaries cystic	TSH and prolactin elevated; T_4 low

17-OHP, 17-Hydroxyprogesterone; *CNS,* central nervous system; *CT,* computed tomography; *DHEAS,* dehydroepiandrosterone sulfate; *hCG,* human chorionic gonadotropin; *LH,* luteinizing hormone; *LHRH,* luteinizing hormone-releasing hormone; *MRI,* magnetic resonance imaging; T_4, thyroxine; *TSH,* thyrotropin.

From Larsen PR et al [eds]: *Williams textbook of endocrinology,* ed 11, Philadelphia, 2008, Saunders.

ICD-10CM # R57.9 Shock, unspecified
R57.0 Cardiogenic shock
R57.1 Hypovolemic shock
R57.8 Other shock

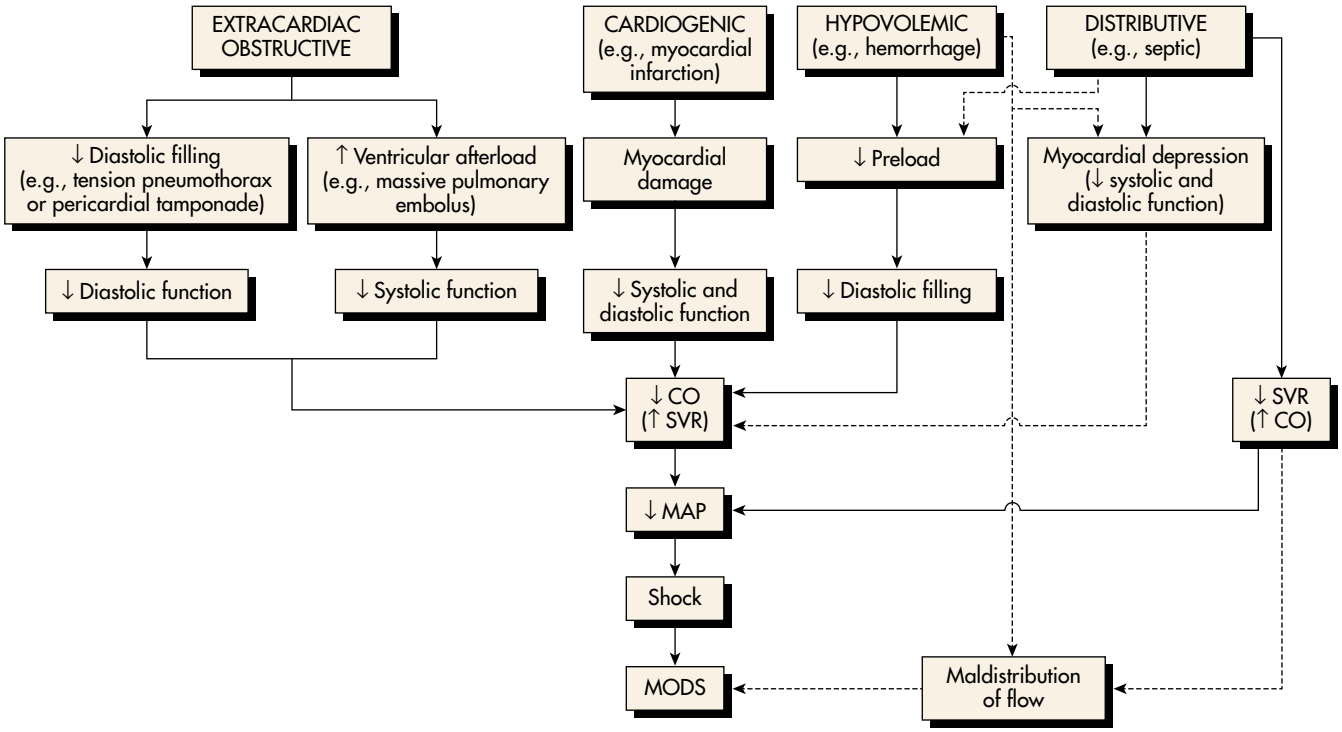


FIG. 152 The interrelationships between different forms of shock. For cardiogenic, hypovolemic, and obstructive shock, hypotension is primarily due to decreased cardiac output with systemic vascular resistance rising secondarily. With distributive (and particularly, septic) shock, hypotension is primarily due to a decrease in systemic vascular resistance with a secondary increase of cardiac output. In many forms of shock, the hemodynamic characteristics are influenced by elements of hypovolemia, myocardial depression (ischemic or otherwise), and vascular dysfunction (which may affect afterload). Dominant pathophysiologic pathways are denoted by *heavier lines. CO,* Cardiac output; *MAP,* mean arterial blood pressure; *MODS,* multiple organ dysfunction syndrome; *SVR,* systemic vascular resistance. (From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.)

BOX 17 Determinants of Effective Tissue Perfusion in Shock

1. Cardiovascular performance (total systemic perfusion/cardiac output)
   - Cardiac function
     - Preload
     - Afterload
     - Contractility
     - Heart rate
   - Venous return
     - Right atrial pressure (dependent on cardiac function)
     - Mean circulatory pressure
     - Stressed vascular volume
     - Mean vascular compliance
     - Venous vascular resistance
     - Distribution of blood flow
2. Distribution of cardiac output
   - Intrinsic regulatory systems (local tissue factors)
   - Extrinsic regulatory systems (sympathetic/adrenal activity)
   - Anatomic vascular disease
   - Exogenous vasoactive agents (inotropes, vasopressors, vasodilators)
3. Microvascular function
   - Precapillary and postcapillary sphincter function
   - Capillary endothelial integrity
   - Microvascular obstruction (fibrin, platelets, WBC, RBC)
4. Local oxygen unloading and diffusion
   - Oxyhemoglobin affinity
   - RBC 2,3-DPG
   - Blood pH
   - Temperature
5. Cellular energy generation/utilization capability
   - Citric acid (Kreb) cycle
   - Oxidative phosphorylation pathway
   - Other energy metabolism pathways (e.g., ATP utilization)

2,3-DPG, 2,3-Diphosphoglycerate; *ATP,* adenosine triphosphate; *RBC,* red blood cell; *WBC,* white blood cell.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.

BOX 18 Classification of Shock

1. Hypovolemic (Oligemic)
   - Hemorrhagic
     - Trauma
     - Gastrointestinal
     - Retroperitoneal
   - Intravascular fluid depletion (nonhemorrhagic)
     - External fluid loss
       - Dehydration
       - Vomiting
       - Diarrhea
       - Polyurea
     - Interstitial fluid redistribution
       - Thermal injury
       - Trauma
       - Anaphylaxis
     - Increased vascular capacitance (venodilation)
       - Sepsis
       - Anaphylaxis
       - Toxins/Drugs
2. Cardiogenic
   - Myopathic
     - Myocardial infarction
       - Left ventricle
       - Right ventricle
     - Myocardial contusion (trauma)
     - Myocarditis
     - Cardiomyopathy
     - Postischemic myocardial stunning
     - Septic myocardial depression
     - Drug toxicity
       - Anthracycline cardiotoxicity
       - Calcium channel blockers
     - Mechanical
       - Valvular failure (stenotic or regurgitant)
       - Hypertropic cardiomyopathy
       - Ventricular septal defect
     - Arrhythmic
       - Bradycardia
       - Sinus (e.g., vagal syncope)
       - Atrioventricular blocks
       - Tachycardia
       - Supraventricular
       - Ventricular
3. Extracardiac Obstructive
   - Impaired diastolic filling (decreased ventricular preload)
     - Direct venous obstruction (vena cava)
       - Intrathoracic obstructive tumors
     - Increased intrathoracic pressure (decreased transmural pressure gradient)
       - Tension pneumothorax
       - Mechanical ventilation (with positive end-expiratory pressure [PEEP] or volume depletion)
     - Decreased cardiac compliance
       - Constrictive pericarditis
       - Cardiac tamponade
         - Acute
           - Post MI free wall rupture
           - Traumatic
           - Hemorrhagic (anticoagulation)
         - Chronic
           - Malignant
           - Uremic
           - Idiopathic
     - Impaired systolic contraction (increased ventricular afterload)
       - Right ventricle
         - Pulmonary embolus (massive)
         - Acute pulmonary hypertension
       - Left ventricle
         - Saddle embolus
         - Aortic dissection
4. Distributive
   - Septic (bacterial, fungal, viral, rickettsial)
   - Toxic shock syndrome
   - Anaphylactic, anaphylactoid
   - Neurogenic (spinal shock)
   - Endocrinologic
     - Adrenal crisis
     - Thyroid storm
   - Toxic (e.g., nitroprusside, bretylium)

From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.

ICD-10CM # R57.9 Shock, unspecified
R57.0 Cardiogenic shock
R57.1 Hypovolemic shock
R57.8 Other shock

BOX 19 Cardiovascular/Metabolic Compensatory Responses to Shock

1. Maintain mean circulatory pressure (venous pressure)
   - Volume
     - Fluid redistribution to vascular space (increased total vascular volume) from interstitium (Starling effect) from intracellular space (osmotic)
     - Decreased renal fluid losses
     - Decreased glomerular filtration rate
     - Increased aldosterone
     - Increased vasopressin
   - Pressure
     - Decreased venous capacitance (increased stressed volume) increased sympathetic activity
     - Increased circulating (adrenal) epinephrine
     - Increased angiotensin
     - Increased vasopressin
2. Maximize cardiac performance
   - Increase contractility
   - Sympathetic stimulation
   - Adrenal stimulation
3. Redistribute perfusion
   - Extrinsic regulation of systemic arterial tone
   - Dominant autoregulation of vital organs (heart, brain)
4. Optimize oxygen unloading
   - Increased RBC 2,3-DPG
   - Tissue acidosis
   - Pyrexia
   - Decreased tissue Po_2

2,3-DPG, 2,3-Diphosphoglycerate; *Po_2,* partial pressure of oxygen.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.

BOX 20 General Approach to Shock: Immediate Goals

General
- Find cause of shock and apply specific treatment (examples: antibiotics for sepsis or pericardiocentesis for tamponade)

Hemodynamic
- MAP >65 mm Hg (higher in the presence of coronary artery disease or chronic hypertension)
- CVP = 8-12 mm Hg/PAOP = 12-15 mm Hg (may be higher for cardiogenic shock)[a]
- CI >2.1 L/min per m^2[a]

Optimization of oxygen delivery
- Hemoglobin >7-9 g/dl; >7 g/L after shock is sufficient
- Arterial saturation >92%
- Mvo_2 >60%, $scvO_2$ >70%
- Normalization of serum lactate (to <2.2 mM/L)

Reverse organ system dysfunction
- Reverse encephalopathy
- Maintain urine output >0.5 ml/kg per hour

CI, Cardiac index; *CVP,* central venous pressure; *MAP,* mean arterial pressure; *Mvo_2,* mixed venous oxygen saturation; *PAOP,* pulmonary artery occlusion pressure.
[a]Optional.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.

TABLE 57 Organ System Dysfunction in Shock

Central nervous system	Encephalopathy (ischemic or septic)
	Cortical necrosis
Heart	Tachycardia, bradycardia
	Supraventricular tachycardia
	Ventricular ectopy
	Myocardial ischemia
	Myocardial depression
Pulmonary system	Acute respiratory failure
	Acute respiratory distress syndrome
Kidney	Prerenal failure
	Acute tubular necrosis
Gastrointestinal system	Ileus
	Erosive gastritis
	Pancreatitis
	Acalculous cholecystitis
	Colonic submucosal hemorrhage
	Transluminal translocation of bacteria/antigens
Liver	Ischemic hepatitis
	"Shock" liver
	Intrahepatic cholestasis
Hematologic system	Disseminated intravascular coagulation
	Dilutional thrombocytopenia
Metabolic	Hyperglycemia
	Glycogenolysis
	Gluconeogenesis
	Hypoglycemia (late)
	Hypertriglyceridemia
Immune system	Gut barrier function depression
	Cellular immune depression
	Humoral immune depression

From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.

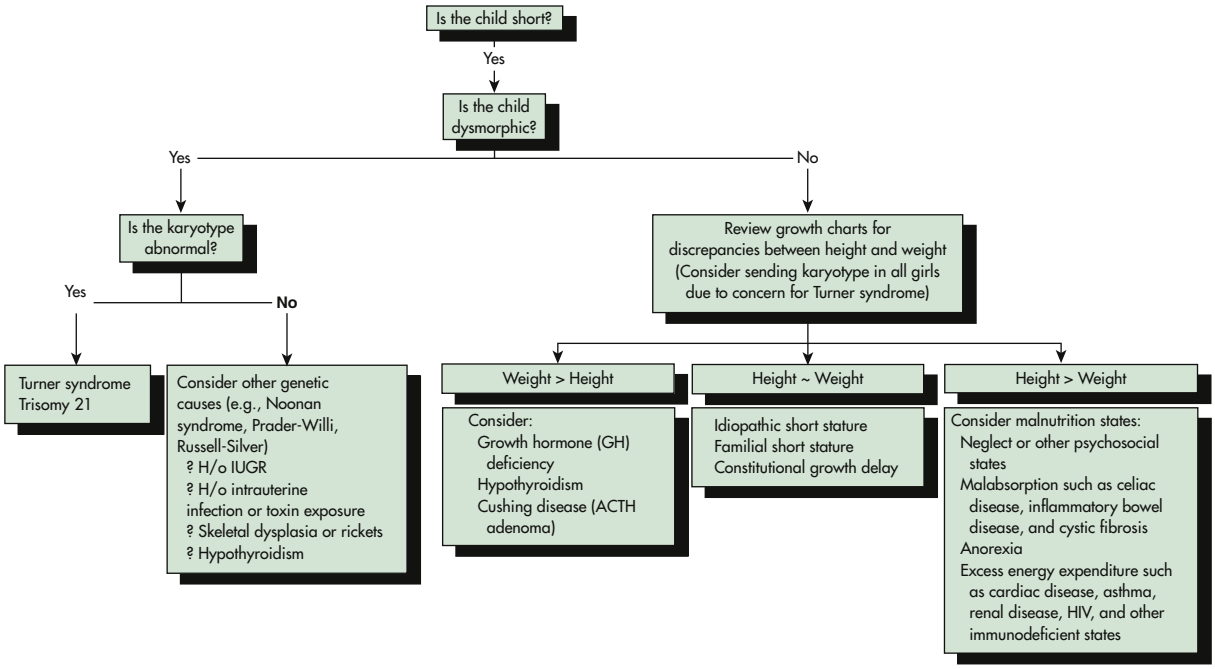


FIG. E153 Differential diagnosis of short stature. *H/o,* History of; *IUGR,* intrauterine growth restriction. (From The Johns Hopkins Hospital, Hughes HK, Kalh LK: *The Harriet Lane handbook,* ed 21, St Louis, 2018, Elsevier.)

ICD-10CM #		
	S34.109A	Unspecified injury to unspecified level of lumbar spinal cord, initial encounter
	M24.819	Other specific joint derangements of unspecified shoulder, not elsewhere classified
	M75.80	Other shoulder lesions, unspecified shoulder
	S43.409A	Unspecified sprain of unspecified shoulder joint, initial encounter
	S46.919A	Strain of unspecified muscle, fascia and tendon at shoulder and upper arm level, unspecified arm, initial encounter
	M75.20	Bicipital tendinitis, unspecified shoulder
	M75.40	Impingement syndrome of unspecified shoulder
	M75.50	Bursitis of unspecified shoulder

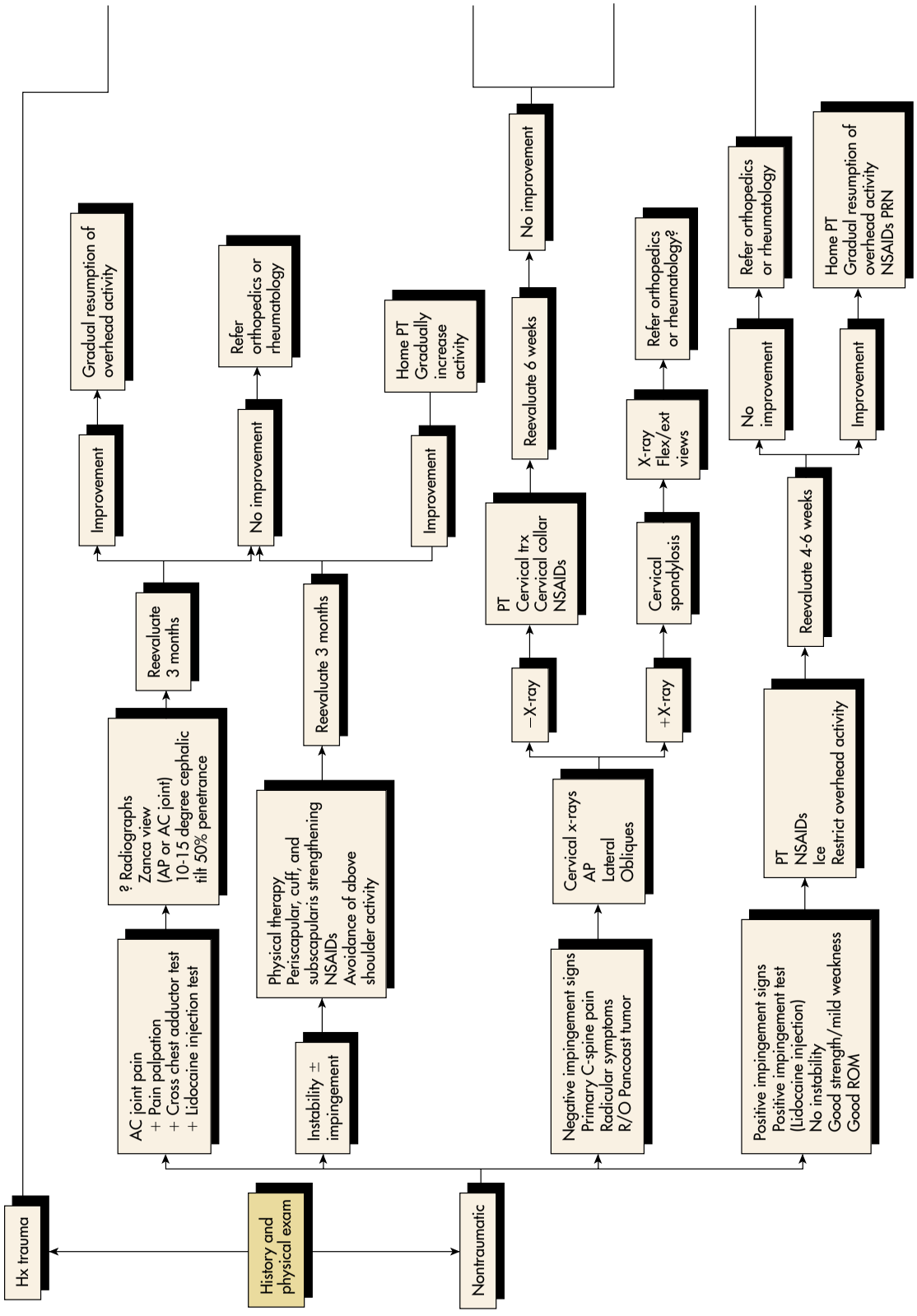


FIG. E154 Algorithmic evaluation of shoulder pain. *AC,* Acromioclavicular; *AP,* anteroposterior; *GH,* glenohumeral; *Hx,* history; *MRI,* magnetic resonance imaging; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PRN,* as required; *PT,* physical therapy; *R/O,* rule out; *ROM,* range of motion; *Sx,* symptoms; *trx,* traction; *Tx,* therapy. (From Harris ED et al [eds]: *Kelley's textbook of rheumatology,* ed 7, Philadelphia, 2005, Saunders.)

SHOULDER PAIN— cont'd

ICD-10CM #		
	S34.109A	Unspecified injury to unspecified level of lumbar spinal cord, initial encounter
	M24.819	Other specific joint derangements of unspecified shoulder, not elsewhere classified
	M75.80	Other shoulder lesions, unspecified shoulder
	S43.409A	Unspecified sprain of unspecified shoulder joint, initial encounter
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	M75.20	Bicipital tendinitis, unspecified shoulder
	M75.40	Impingement syndrome of unspecified shoulder
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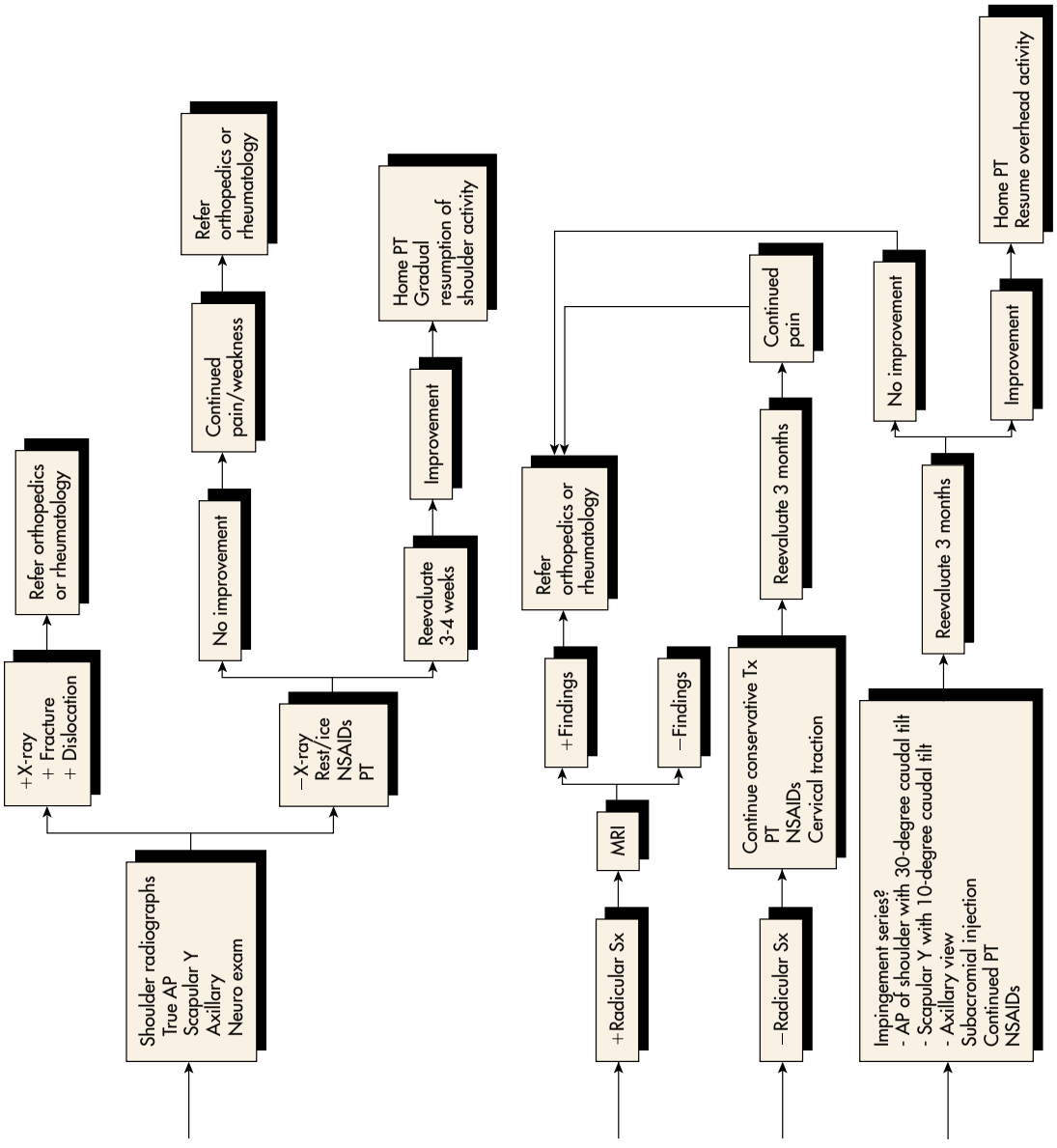

FIG. E154 (Continued)

SHOULDER PAIN—cont'd

ICD-10CM #		
	S34.109A	Unspecified injury to unspecified level of lumbar spinal cord, initial encounter
	M24.819	Other specific joint derangements of unspecified shoulder, not elsewhere classified
	M75.80	Other shoulder lesions, unspecified shoulder
	S43.409A	Unspecified sprain of unspecified shoulder joint, initial encounter
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	M75.40	Impingement syndrome of unspecified shoulder
	M75.50	Bursitis of unspecified shoulder

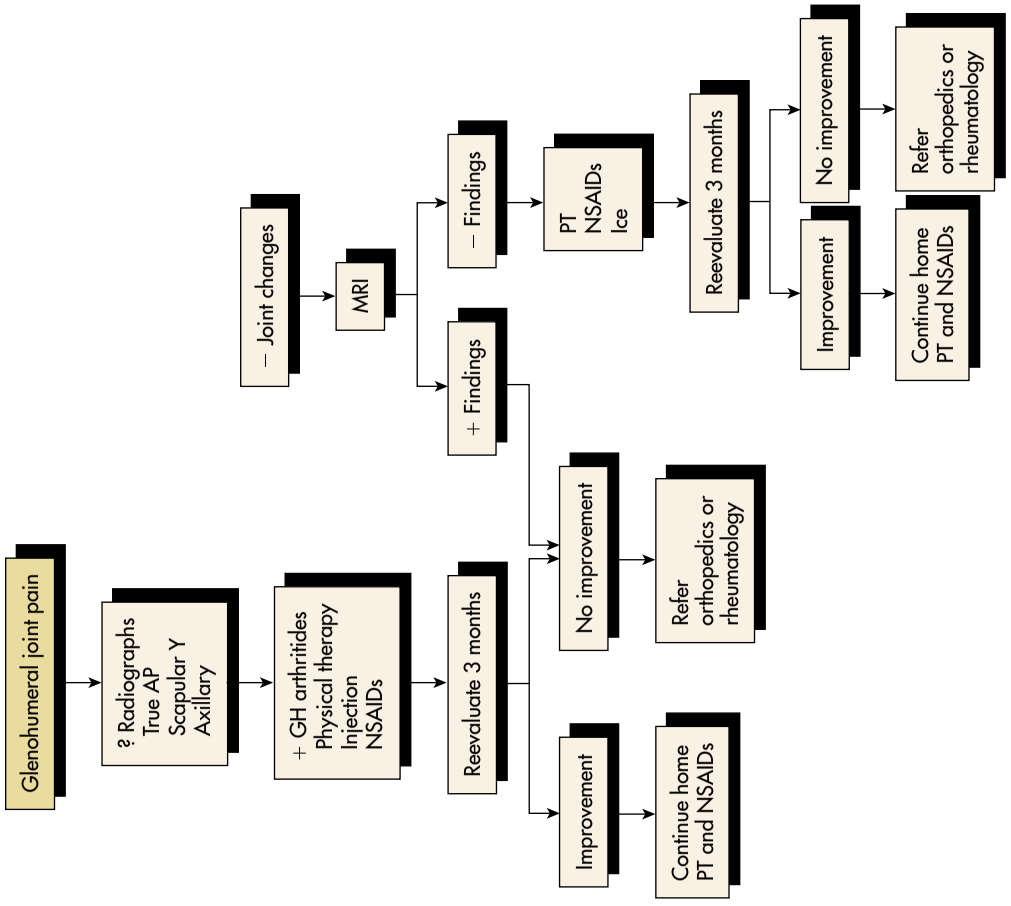


FIG. E154 (Continued)

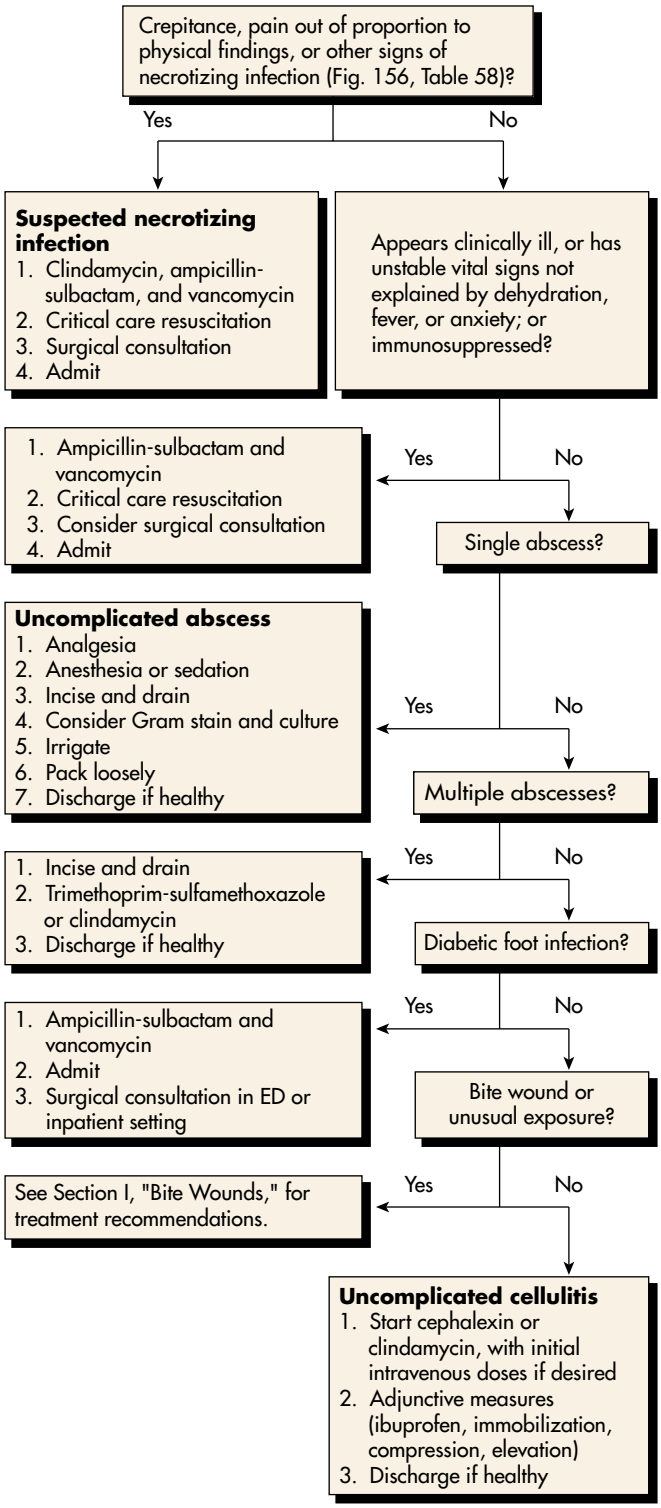


FIG. 155 Universal algorithm for skin and soft tissue infections (assuming no prior treatment).
(From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.)

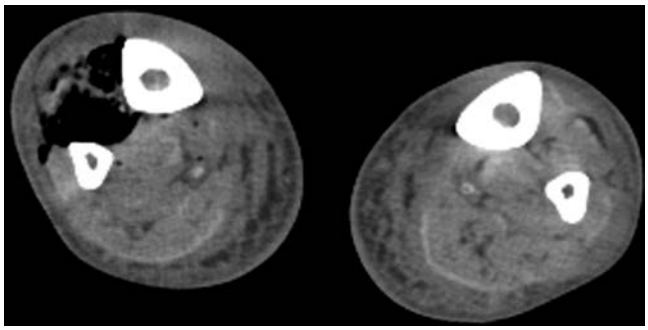


FIG. 156 Necrotizing fasciitis. Axial computed tomography through the lower extremities demonstrates gas in the anterior soft tissues. Necrotizing fasciitis is a clinical diagnosis. Imaging may lead to a delay in treatment. (From Webb WR, Brandt WE, Major NM: *Fundamentals of body CT,* ed 4, Philadelphia, 2015, Elsevier.)

TABLE 58 Differentiating Features of Necrotizing Skin and Soft Tissue Infections

Feature	Progressive Bacterial Synergistic Gangrene	Nonclostridial Anaerobic Cellulitis	Clostridial Myonecrosis (Gas Gangrene)	Necrotizing Fasciitis Type 1	Necrotizing Fasciitis Type 2
Risk factors	Surgery, ileostomy, colostomy, chronic ulceration	Diabetes mellitus	Trauma, surgery	Diabetes mellitus, surgery, perineal infection	Trauma, surgery, none
Microbiology	Microaerophilic streptococci plus *Staphylococcus aureus*	Non–spore-forming anaerobes ± coliforms, streptococci, *S. aureus*	*Clostridium* spp.	Polymicrobial (Enterobacteriaceae plus anaerobes)	Group A streptococci
Course	Slow	Slow or rapid	Very rapid	Rapid	Very rapid
Pain	++++	++/+++	++++	+++/++++	++++
Gas formation	–	++++	++	++	–
Appearance	Central necrotic ulcer, erythematous periphery	Erythematous skin necrosis	Bullae, necrosis	Bullae, skin	Bullae, necrotic skin and tissue
Drainage	Purulent if present	Purulent	Serosanguineous	"Dishwater," seropurulent	Serous if present
Depth of involvement	Skin, soft tissue	Skin, soft tissue	Muscle	Fascia	Fascia
Systemic toxicity	±	+++/++++	++++	+++/++++	++++

–, Absent; ±, occasionally present; +, minimal; ++, mild; +++, moderate; ++++, marked or severe.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 5, Philadelphia, 2019, Elsevier.

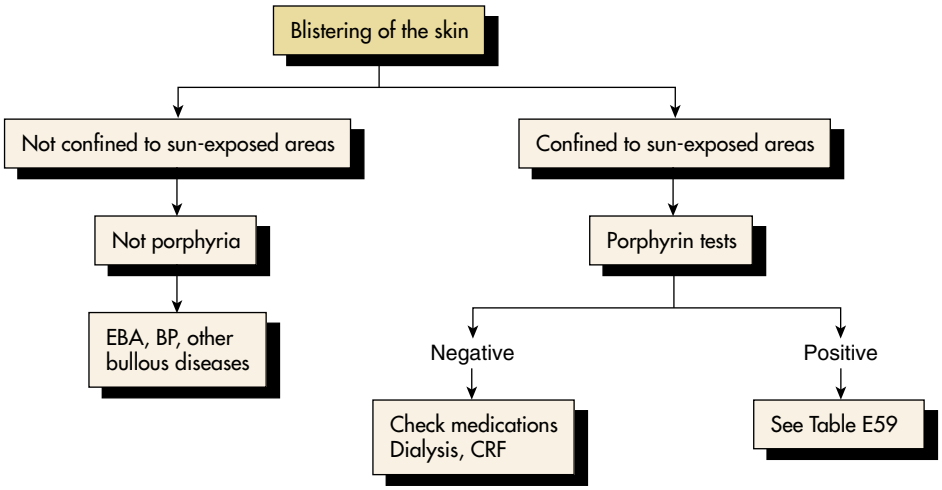


FIG. E157 An approach to the patient with blistering of the skin. *BP,* Bullous pemphigoid; *CRF,* chronic renal failure; *EBA,* epidermolysis bullosa acquisita. (From Bolognia JL et al [eds]: *Dermatology,* ed 2, St Louis, 2008, Mosby.)

TABLE E59 Investigative Tests Used in the Diagnosis of Porphyria

Porphyria	Enzyme	Urine	Stool	Plasma	RBC
Porphyria cutanea tarda	Uroporphyrinogen decarboxylase	URO+ + + COPRO+ 7COOH III>I	ISO-COPRO+ +7COOH	+	–
Erythropoietic protoporphyria	Ferrochelatase	Normal	PROTO+	+	free PROTO+ +
Congenital erythropoietic porphyria	Uroporphyrinogen III synthase	URO I+COPRO I++	COPRO I+	+	URO I+COPRO I+PROTO+
Acute intermittent porphyria	Porphobilinogen deaminase	*ALA+ + +*PBG+ + +	*ALA+*PBG+	–	–
Variegate porphyria	Protoporphyrinogen oxidase	*ALA+ +*PBG+ +URO+COPRO+ +	COPRO+PROTO+ +PORPH X+ + +	625-627 nm peak	–
Hereditary coproporphyria	Coproporphyrinogen oxidase	*ALA+ +*PBG+ +COPRO+ +URO+	COPRO+	+	–
Aminolevulinic acid (ALA) dehydratase-deficient porphyria	ALA dehydratase	ALA+ + +COPRO III	–	–	Zn PROTO+
Hepatoerythropoietic porphyria	Uroporphyrinogen decarboxylase	URO+ + +COPRO+7COOH III>I	ISO-COPRO+ +7COOH	+	Zn and free PROTO+ +
Tyrosinemia	ALA dehydratase	ALA	–	–	–
Iron deficiency	Ferrochelatase	–	–	–	Zn PROTO+ +
Lead poisoning	ALA dehydratase Coproporphyrinogen oxidase Ferrochelatase	ALA+ + +COPRO±	–	–	Zn PROTO+

COPRO, Coproporphyrin; *ISO-COPRO,* isocoproporphyrin; *PBG,* porphobilinogen; *PROTO,* protoporphyrin; *RBC,* red blood cells; *URO,* uroporphyrin; +, positive; –, negative; *, during acute attack. From Bolognia JL et al (eds): *Dermatology,* ed 2, St Louis, 2008, Mosby.

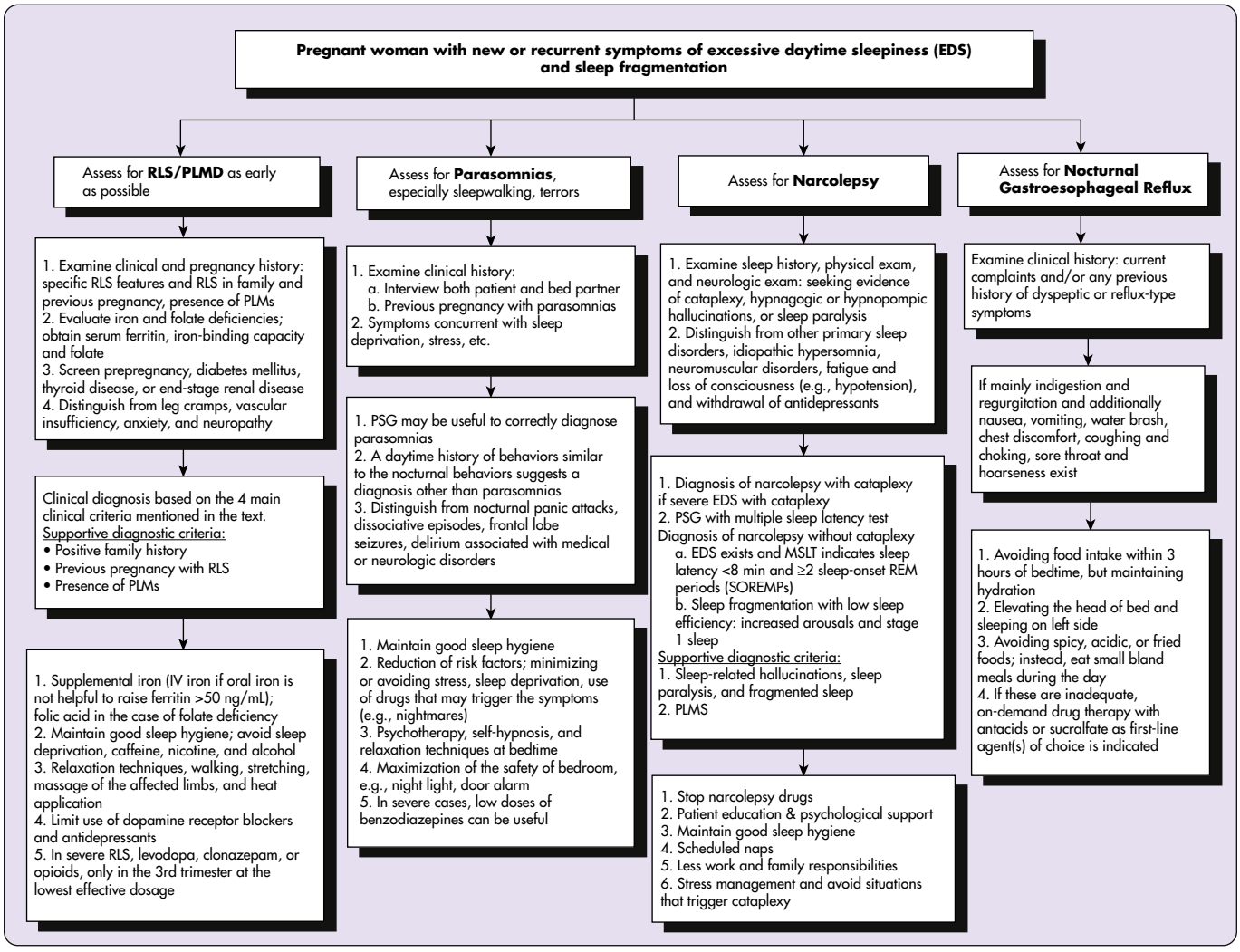


FIG. 158 Management and treatment of sleep-related disorders. *IV,* Intravenous; *MSLT,* Multiple Sleep Latency Test; *PLMs,* periodic leg movements; *PLMD,* periodic leg movement disorder; *PSG,* polysomnography; *REM,* rapid eye movement; *RLS,* restless legs syndrome; *SOREMP,* sleep-onset rapid eye movement sleep period. (From Kryger M, Roth T, Dement WC: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.)

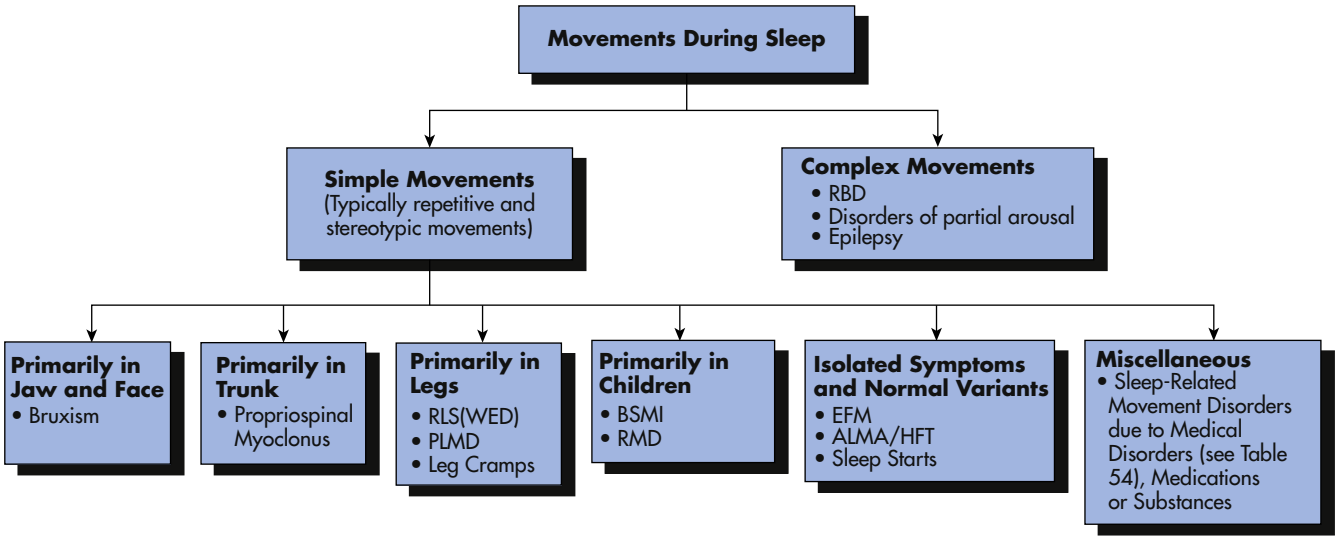


FIG. 159 Flow chart for the approach to the differential diagnosis of sleep-related movement disorders. *ALMA,* Alternating leg muscle activation; *BSMI,* benign sleep myoclonus of infancy; *EFM,* excessive fragmentary myoclonus; *HFT,* hypnagogic foot tremor; *PLMD,* periodic limb movement disorder; *RBD,* rapid eye movement (REM) sleep behavior disorder; *RLS (WED),* restless legs syndrome (Willis-Ekbom disease); *RMD,* rhythmic movement disorder. (From Kryger M, Roth T, Dement WC: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.)

TABLE 60 Distinguishing Features of Nocturnal Events

Feature	Disorders of Arousal	Sleep-Related Eating Disorder	REM Behavior Disorder	Recurrent Isolated Sleep Paralysis	Exploding Head Syndrome	Psychogenic Events	Nocturnal Seizures
Behavior	Confused; semi-purposeful movement with eyes open	Eating typically high-calorie foods; eyes open	Sometimes combative with eyes closed	Episodes of inability to move	Painless sensation of explosion inside the head	Variable	Dependent on the portion of brain involved
Age of onset	Childhood and adolescence	Variable	Older adult	Variable	Adult	Adolescence to adulthood	Variable
Time of occurrence	First third of night	First half of night	During REM	Typically on awakening	Usually near sleep onset but can be variable	Anytime	Anytime
Frequency of events	Less than one per night	Variable	Multiple per night	Variable less than weekly	Rare	Variable	Frontal seizures—multiple per night
Duration	Minutes	Minutes	Seconds to minute	Seconds to minutes	Seconds	Variable minutes or longer	Usually under 3 minutes
Memory of event	Usually none	Usually none or limited	Dream recall	Yes	Yes	None	Usually none
Stereotypical movements	No	No	No	No	Similar sensation	No	Yes
Polysomnogram findings	Arousals from slow wave sleep	Arousal from NREM sleep	Excessive electromyogram tone during REM sleep	Arousal from REM sleep	Usually occurs in light sleep	Occur from awake state	Potentially epileptiform activity

REM, Rapid eye movement; *NREM,* non-rapid eye movement.
From Kryger M, Roth T, Dement WC: *Principles and practice of sleep medicine,* ed 6, Philadelphia, 2017, Elsevier.

ICD-10CM # J02.9 Acute pharyngitis, unspecified
J31.2 Chronic pharyngitis
J02.0 Streptococcal pharyngitis

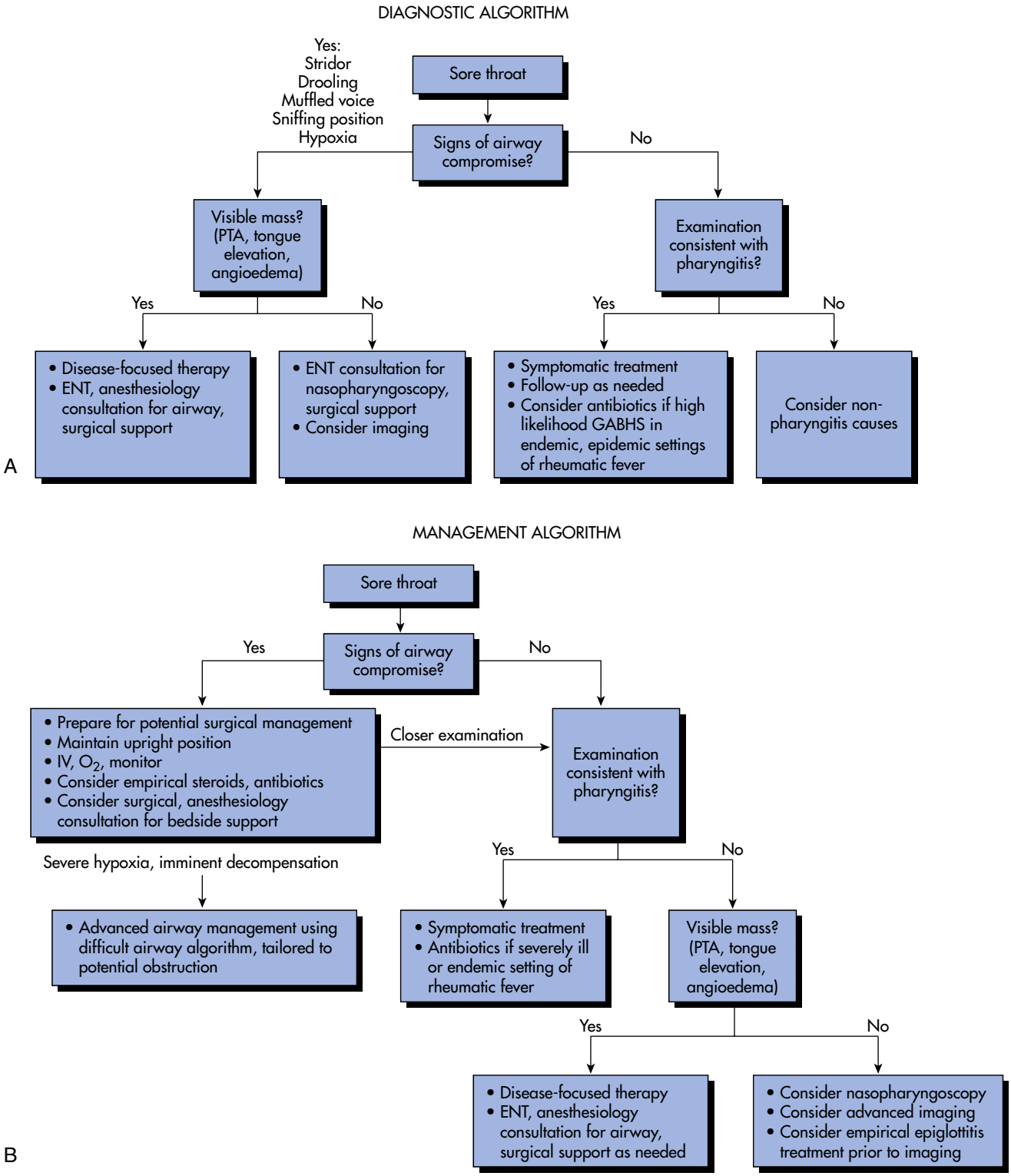


FIG. 160 Clinical approach to the patient with sore throat—diagnosis (A) and management (B). Refer to Section I topics Pharyngitis/Tonsillitis and Epiglottitis for additional information. *ENT,* Ear-nose-throat; *GABHS,* group A beta-hemolytic streptococcus; *IV,* intravenous; *PTA,* peritonsillar abscess. (From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.)

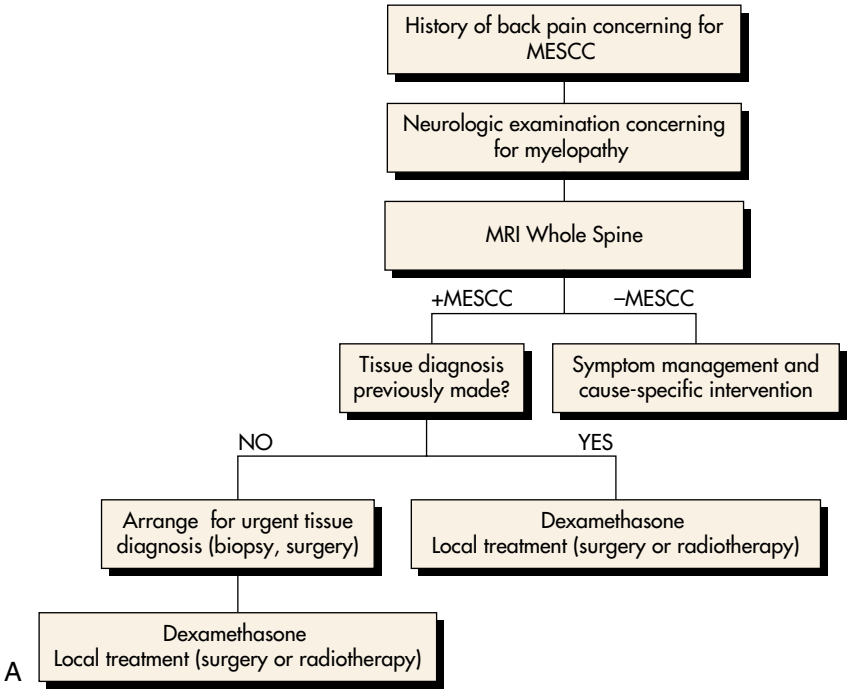
ICD-10CM # J02.9 Acute pharyngitis, unspecified
J31.2 Chronic pharyngitis
J02.0 Streptococcal pharyngitis

TABLE 61 Differential Diagnosis of Sore Throat

Type of Pharyngitis	Nature of Patient	Nature of Symptoms	Predisposing Factors	Physical Findings	Diagnostic Studies
Without Pharyngeal Ulcers					
Viral	All ages	Pain in throat Rapid onset Systemic symptoms	—	Exudate less likely than with streptococcal infections	—
Infectious mononucleosis	Adolescents and young adults Uncommon in elderly	Gradual onset	—	Low-grade temperature Occasional exudate Posterior cervical adenopathy Hepatosplenomegaly	Monospot test
Streptococcal pharyngitis	Patients younger than 25 yrs, especially age 6-12 yrs	Pain in throat Rapid onset Few systemic symptoms	Fall and winter Streptococcal infection in family Diabetes	Marked erythema and throat swelling Temperature >101°F Tender anterior cervical nodes Scarlatiniform rash Tonsillar exudate more likely than with viral infection	Culture Rapid streptococcal antigen screening Increased antistreptolysin O titer
Gonococcal pharyngitis	Most common in male homosexuals and people with anogenital gonorrhea	Often no symptoms	Orogenital sex	—	Culture
Sinusitis with postnasal drip	Adults	Mild throat soreness Symptoms often worse with recumbency	—	Evidence of sinusitis Postnasal drip	CT/flexible rhinoscopy (in recalcitrant cases)
Allergic pharyngitis	—	—	Seasonal allergies	No fever Intermittent postnasal drip Swollen pharynx with minimal injection	Allergy testing
With Pharyngeal Ulcers					
Herpangina	More common in children	Painful ulcers on tonsils, pillars, or uvula	Immunosuppression Summer and autumn	Vesicles 1-2-mm ulcers	Serologic tests
Fusospirochetal infection (Vincent angina)	Children and people with poor oral hygiene	Painful ulcers Bleeding gums Foul breath	—	No vesicles Ulcerative gingivitis Gray, necrotic ulcers 2-30-mm ulcers Pseudomembrane	Gram stain: spirochetes
Candidiasis	Children Immunosuppressed patients Those taking antibiotics	—	Immunosuppression Antibiotics Inhaled steroids	3-11-mm ulcers No vesicles	KOH smear: *Candida* culture
Herpes simplex	Most common in children	Not usually a cause of sore throat	Immunosuppression	1-2-mm painful ulcers Vesicles present on lips, gingivae, buccal mucosa, or tongue	Tzanck smear (not very sensitive) viral culture, PCR, herpes simplex virus antibody assay

CT, Computed tomography; *PCR*, polymerase chain reaction.
Modified from Seller RH, Symons AB: *Differential diagnosis of common complaints,* ed 7, Philadelphia, 2018, Elsevier.

Updated workup flowchart



Updated management flowchart

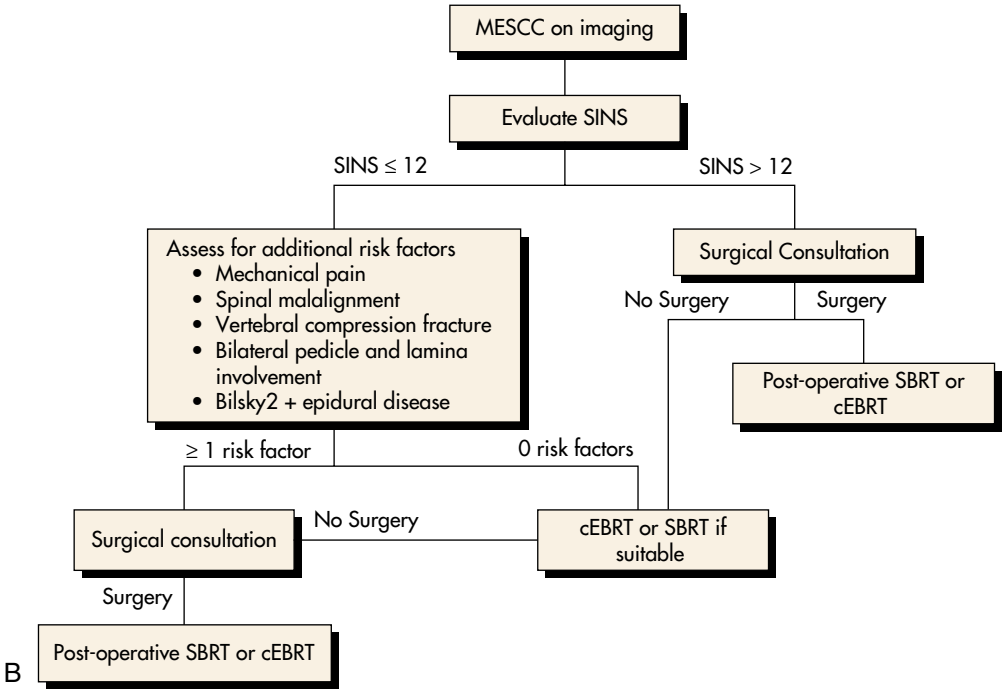


FIG. 161 (A) Flowchart for the initial workup of a patient with suspected spinal metastatic disease. **(B)** Flowchart for the management of metastatic epidural spinal cord compression *(MESCC). cEBRT,* Conventional external beam radiotherapy; *MRI,* magnetic resonance imaging; *SBRT,* stereotactic body radiation therapy; *SINS,* Spine Instability Neoplastic Score. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

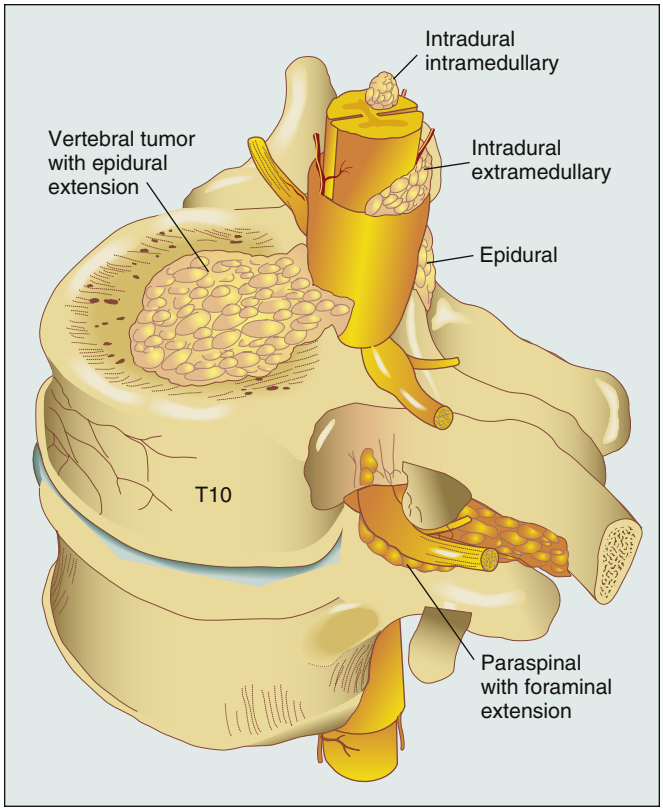


FIG. 162 Locations of metastatic lesions of the spine: vertebral body, epidural space, neural foramen, intradural space, and within the spinal cord itself. (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

Element of SINS	Score
Location	
Junctional (occiput-C2, C7–T2, T11–L1, L5–S1)	3
Mobile spine (C3–C6, L2–L4)	2
Semi-rigid (T3–T10)	1
Rigid (S2–S5)	0
Pain relief with recumbency and/or pain with movement/loading of the spine	
Yes	3
No (occasional pain but not mechanical)	1
Pain free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
>50% collapse	3
<50% collapse	2
No collapse with >50% body involved	1
None of the above	0
Posterolateral involvement of the spinal elements (facet, pedicle or CV joint fracture or replacement with tumor)	
Bilateral	3
Unilateral	1
None of the above	0

FIG. 163 Spinal Instability Neoplastic Score (SINS) elements with axial and sagittal computed tomography (CT) example of an L3 metastasis. In this case, the overall SINS was 11 (2 for location, 3 for pain, 1 for bone lesion, 0 for radiographic spinal alignment, 2 for vertebral body collapse, and 3 for posterolateral involvement of the spinal elements). (From Niederhuber JE: *Abeloff's clinical oncology*, ed 6, Philadelphia, 2020, Elsevier.)

ICD-10CM # S36.00XA Unspecified injury of spleen, initial encounter
S35.32 Injury of splenic vein
S35.3 Injury of portal or splenic vein and branches

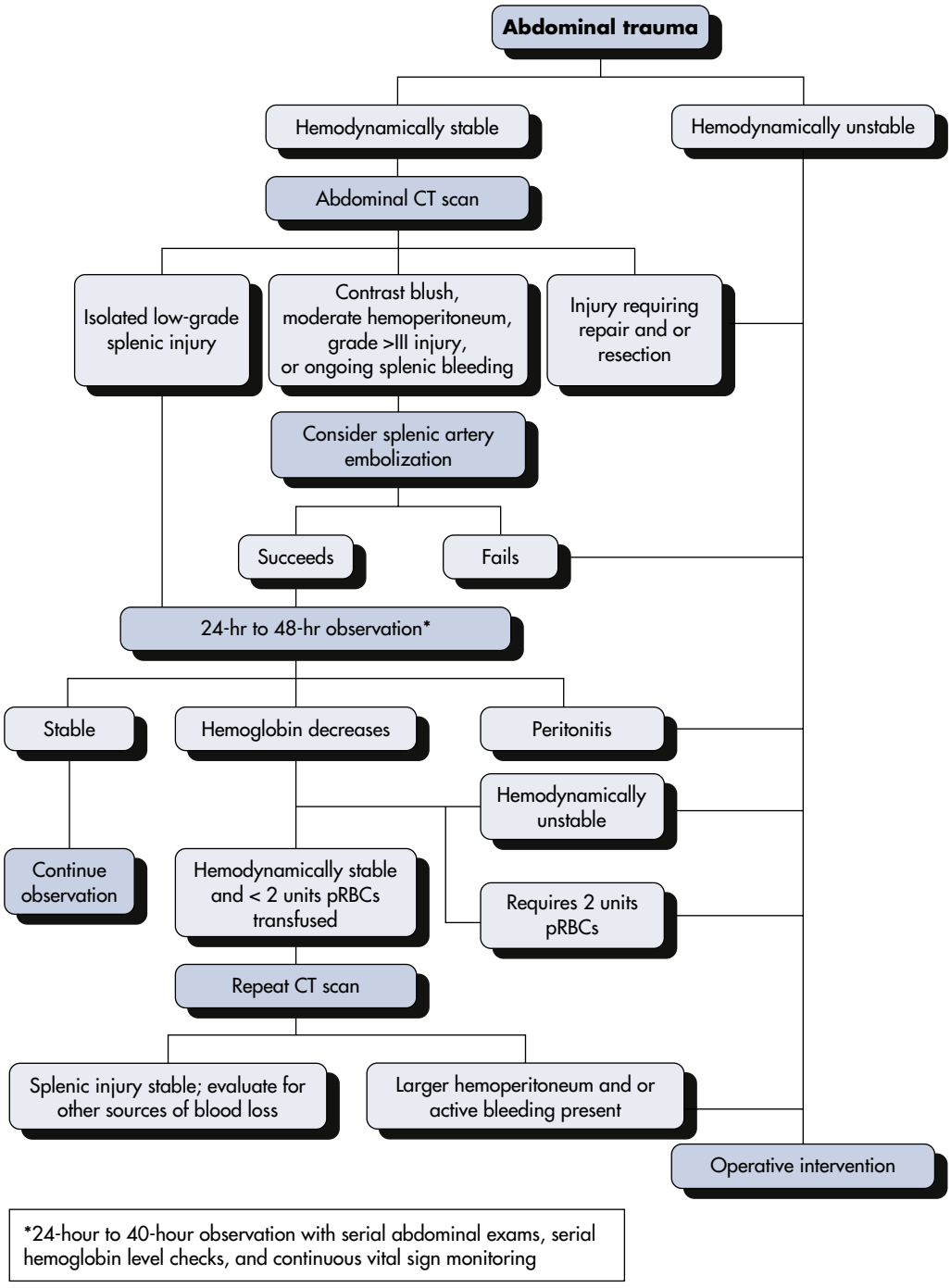


FIG. 164 Algorithmic approach to the management of traumatic splenic injury. *CT,* Computed tomography; *pRBC,* packed red blood cell. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

ICD-10CM # S36.00XA Unspecified injury of spleen, initial encounter
S35.32 Injury of splenic vein
S35.3 Injury of portal or splenic vein and branches

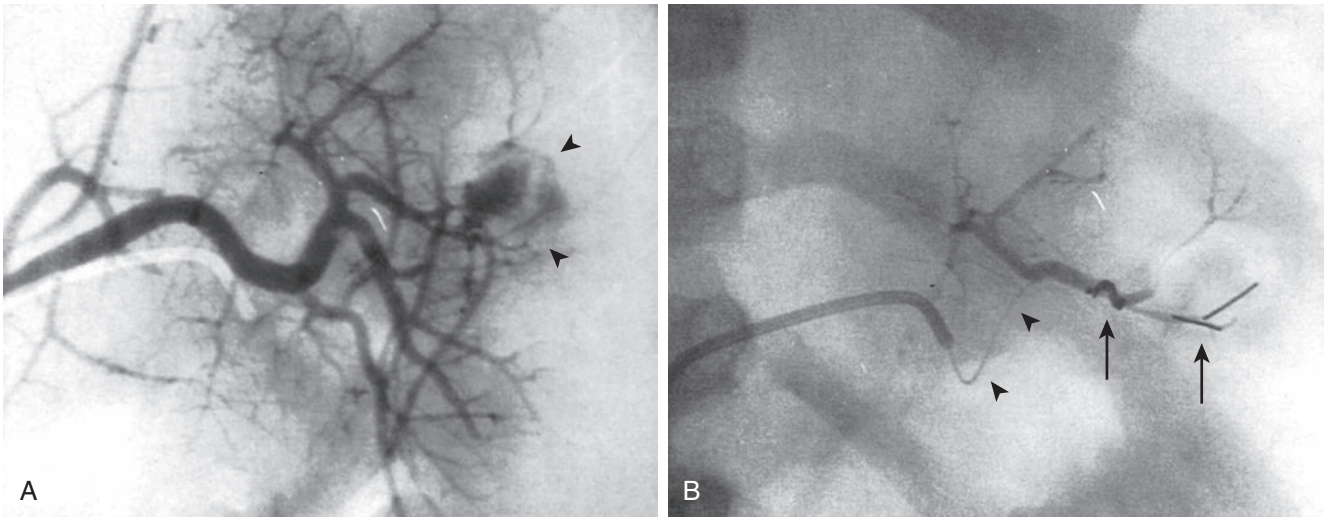


FIG. 165 A, Splenic pseudoaneurysm (*arrowheads* indicate contrast with the pseudoaneurysm) after nonoperative treatment of blunt splenic injury. **B,** Successful angiographic embolization (*arrows* show occlusion of ruptured vessels). (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.)

TABLE 62 Organ Injury Scale for the Spleen by the American Association for the Surgery of Trauma

Grade	Injury Type	Description of Injury
I	Hematoma	Subcapsular, nonexpanding, <10% surface area
	Laceration	Capsular tear, nonbleeding, <1 cm parenchymal depth
II	Hematoma	Subcapsular, nonexpanding, 10%-50% surface area; intraparenchymal, <5 cm in depth
	Laceration	Capsular tear, active bleeding, 1-3 cm parenchymal depth that does not involve a trabecular vessel
III	Hematoma	Subcapsular, >50% surface area or expanding; ruptured subcapsular or parenchymal hematoma with active bleeding; intraparenchymal hematoma ≥5 cm or expanding
	Laceration	>3 cm parenchymal depth or involving trabecular vessels
IV	Laceration	Laceration involving segmental or hilar vessels producing major devascularization (>25% of spleen)
V	Laceration	Completely shattered spleen
	Vascular	Hilar vascular injury with devascularized spleen

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 12, Philadelphia, 2017, Elsevier.

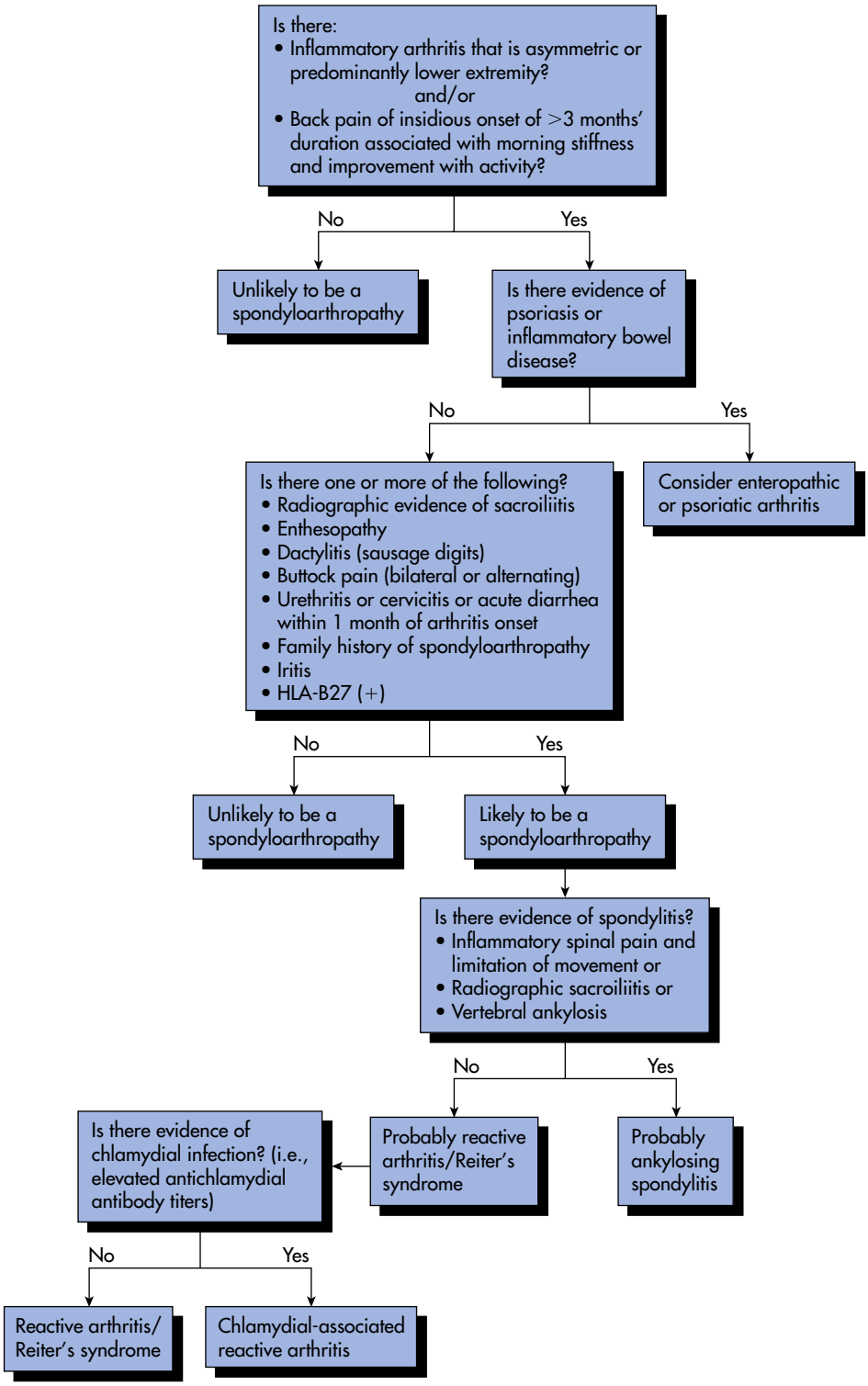
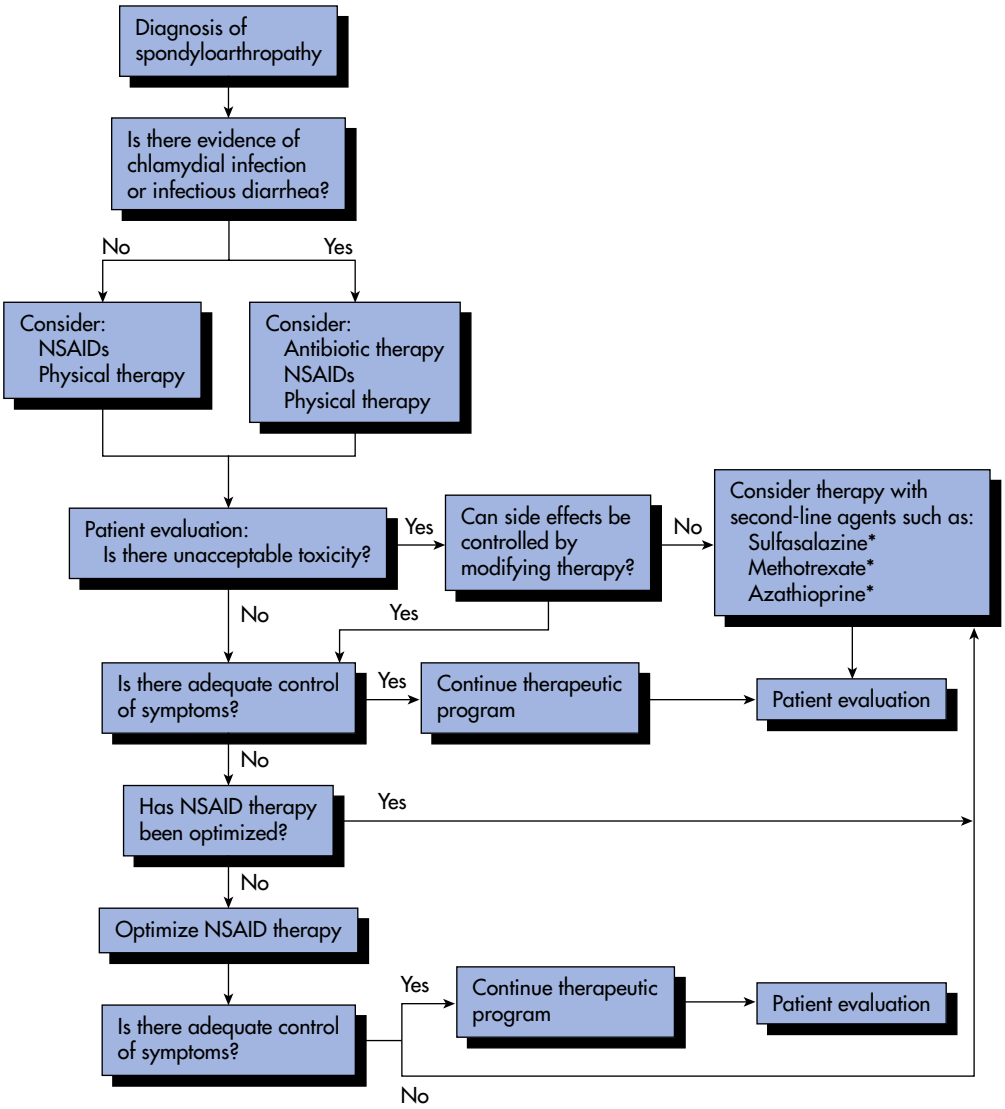
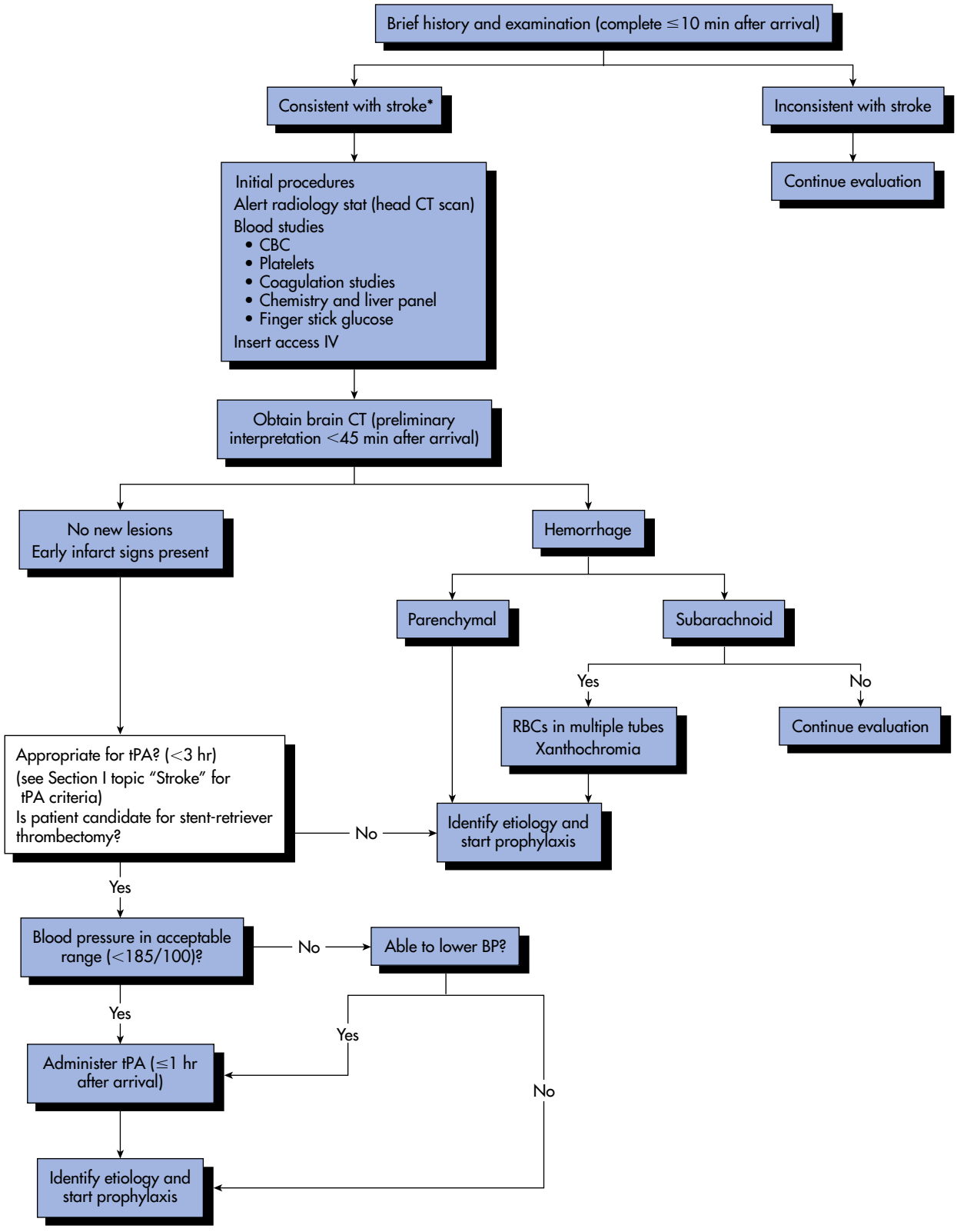


FIG. 166 Algorithm for diagnosis of the spondyloarthropathies. (From Goldman L, Schafer AL: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)



*Not approved by the FDA for treatment of spondyloarthropathies.

FIG. 167 Treatment algorithm for patients with a spondyloarthropathy. *FDA,* Food and Drug Administration; *NSAID,* nonsteroidal antiinflammatory drug. (From Goldman L, Schafer AL: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)



*Note: Refer to Section I for additional information on this topic.

FIG. 168 Algorithm for the emergency evaluation of a patient with suspected stroke. *BP,* Blood pressure; *CBC,* complete blood count; *CT,* computed tomography; *RBCs,* red blood cells; *tPA,* tissue plasminogen activator. (From Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

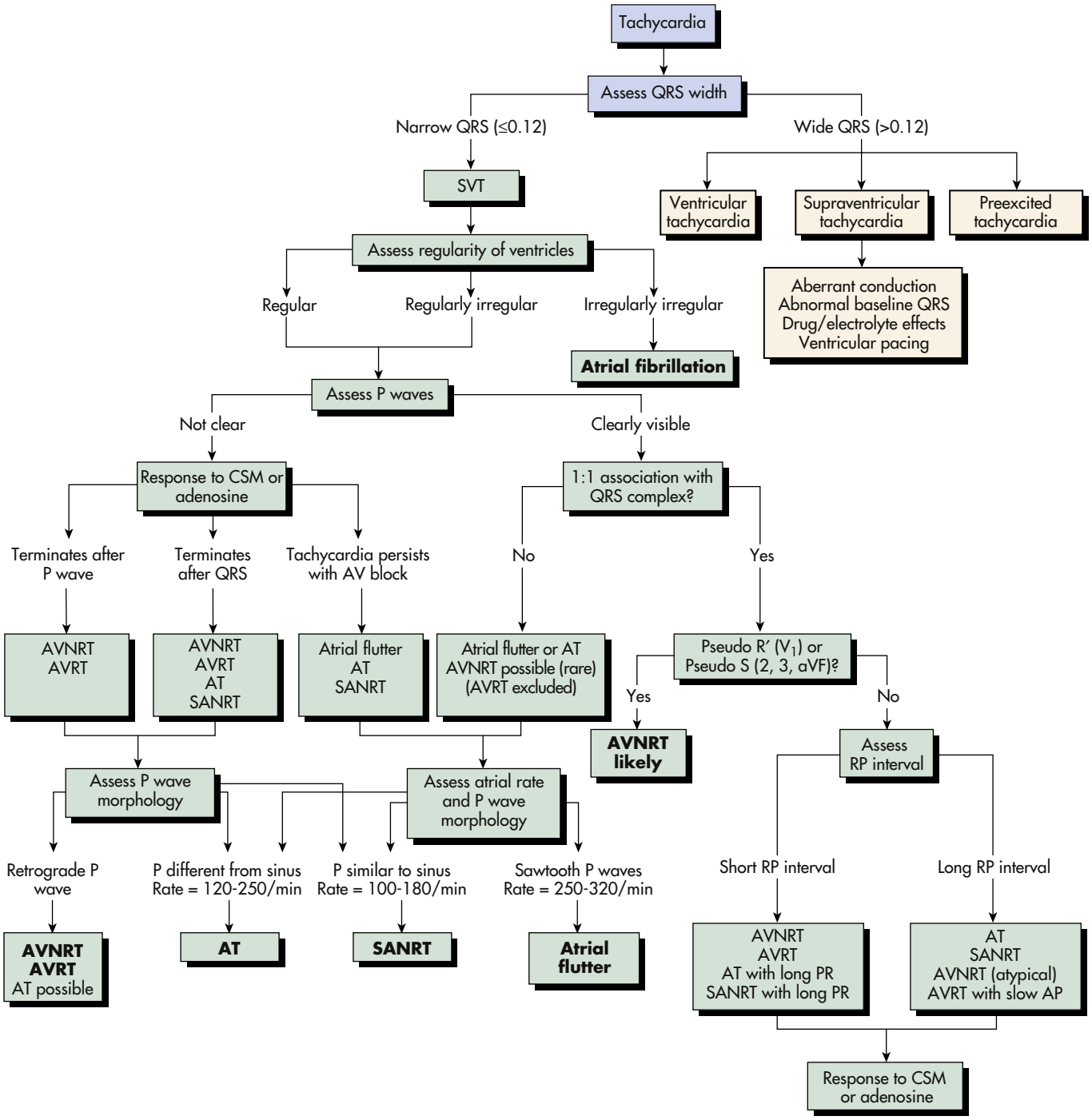


FIG. 169 Stepwise approach to diagnosis of the type of tachycardia based on a 12-lead electrocardiogram during the episode. The initial step is to determine whether the tachycardia has a wide or narrow QRS complex. For wide-complex tachycardia, see Table 63; the remainder of the algorithm is helpful in diagnosis of the type of narrow-complex tachycardia. *AP,* Accessory pathway; *AT,* atrial tachycardia; *AVNRT,* atrioventricular nodal reentrant tachycardia; *AVRT,* atrioventricular reciprocating tachycardia; *CSM,* carotid sinus massage; *SANRT,* sinoatrial nodal reentry tachycardia. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

TABLE 63 Electrocardiographic Distinctions for Diagnosis of Wide-QRS Complex Tachycardia

Favor Supraventricular Tachycardia	Favor Ventricular Tachycardia
Initiation with a premature P wave	Initiation with a premature QRS complex
Tachycardia complexes identical to those in resting rhythm	Tachycardia beats identical to PVCs during sinus rhythm
"Long-short" sequence preceding initiation	"Short-long" sequence preceding initiation
Changes in the P-P interval preceding changes in the R-R interval	Changes in the R-R interval preceding changes in the P-P interval
QRS contours consistent with aberrant conduction (V_1, V_6)	QRS contours inconsistent with aberrant conduction (V_1, V_6)
Slowing or termination with vagal maneuvers	AV dissociation or other non-1:1 AV relationship
Onset of the QRS to its peak (positive or negative) <50 msec	Onset of the QRS to its peak (positive or negative) ≥50 msec
	Fusion beats, capture beats
QRS duration ≤0.14 sec	QRS duration >0.14 sec
Normal QRS axis (0 to +90 degrees)	Left axis deviation (especially −90 to 180 degrees)
	Concordant R wave progression pattern
	Contralateral bundle branch block pattern from the resting rhythm
	Initial R, q, or r >40 msec or notched Q in aVR
	Absence of an "rS" complex in any precordial lead

AV, Atrioventricular; *PVC,* premature ventricular complexes.
From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.

ICD-10CM # I49.02 Ventricular flutter
I49.8 Other specified cardiac arrhythmias
R00.1 Bradycardia, unspecified

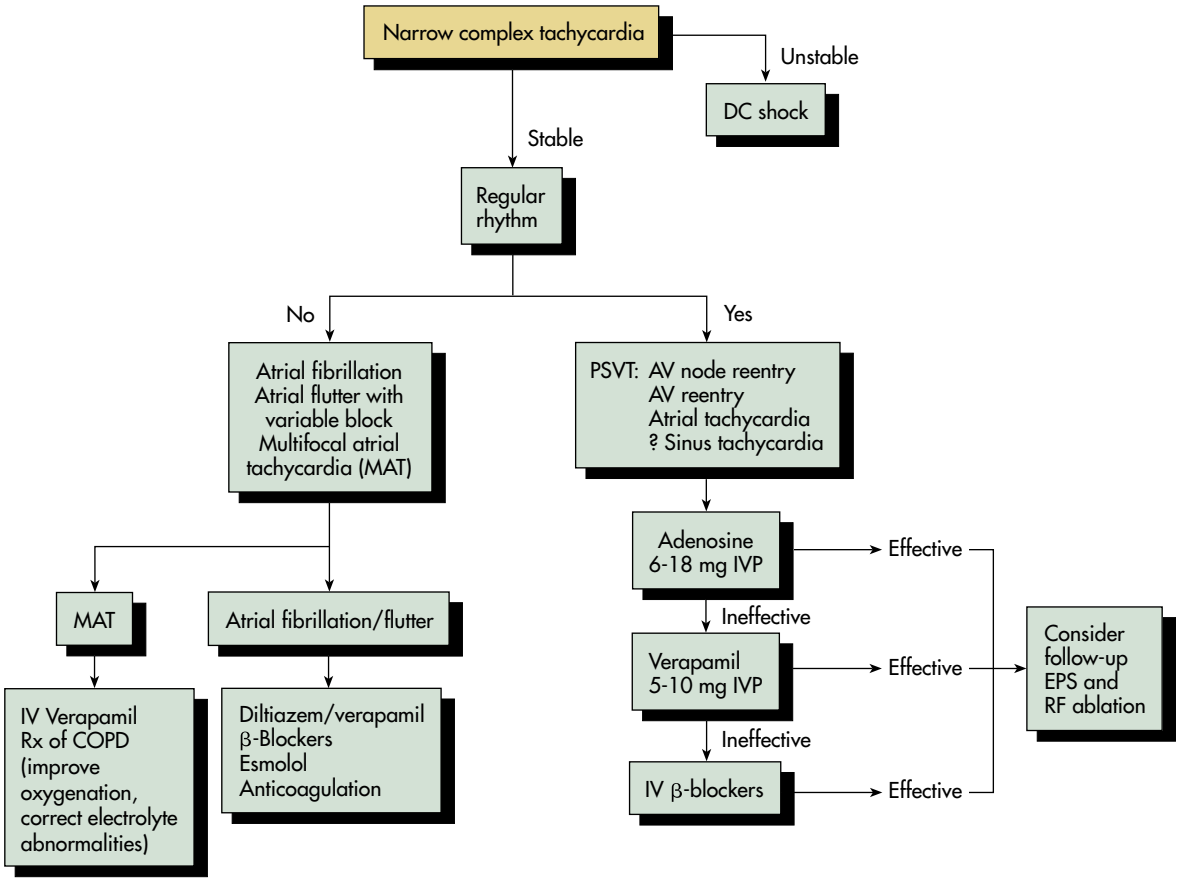


FIG. 170 Evaluation and management of narrow complex tachycardia. *AV,* Atrioventricular; *COPD,* chronic obstructive pulmonary disease; *DC,* direct current; *EPS,* electrophysiologic studies; *IV,* intravenous; *IVP,* intravenous push; *PSVT,* paroxysmal supraventricular tachycardia; *RF,* radiofrequency.

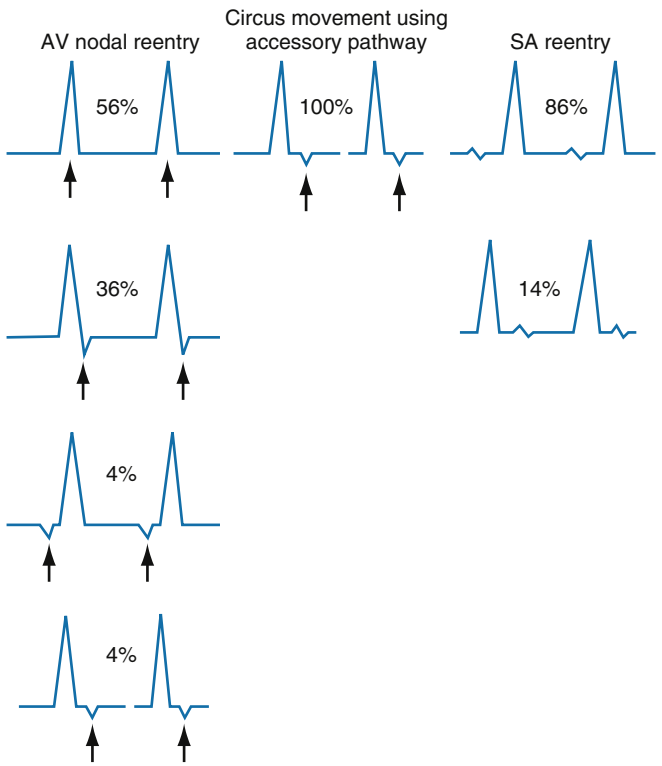


FIG. 171 Location of P waves in common causes of regular narrow-complex tachycardia. *AV,* Atrioventricular; *SA,* sinoatrial. (From Marriott HJL, Conover MB: *Advanced concepts in dysrhythmias,* 2nd ed. St Louis, Mosby, 1989. In Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.)

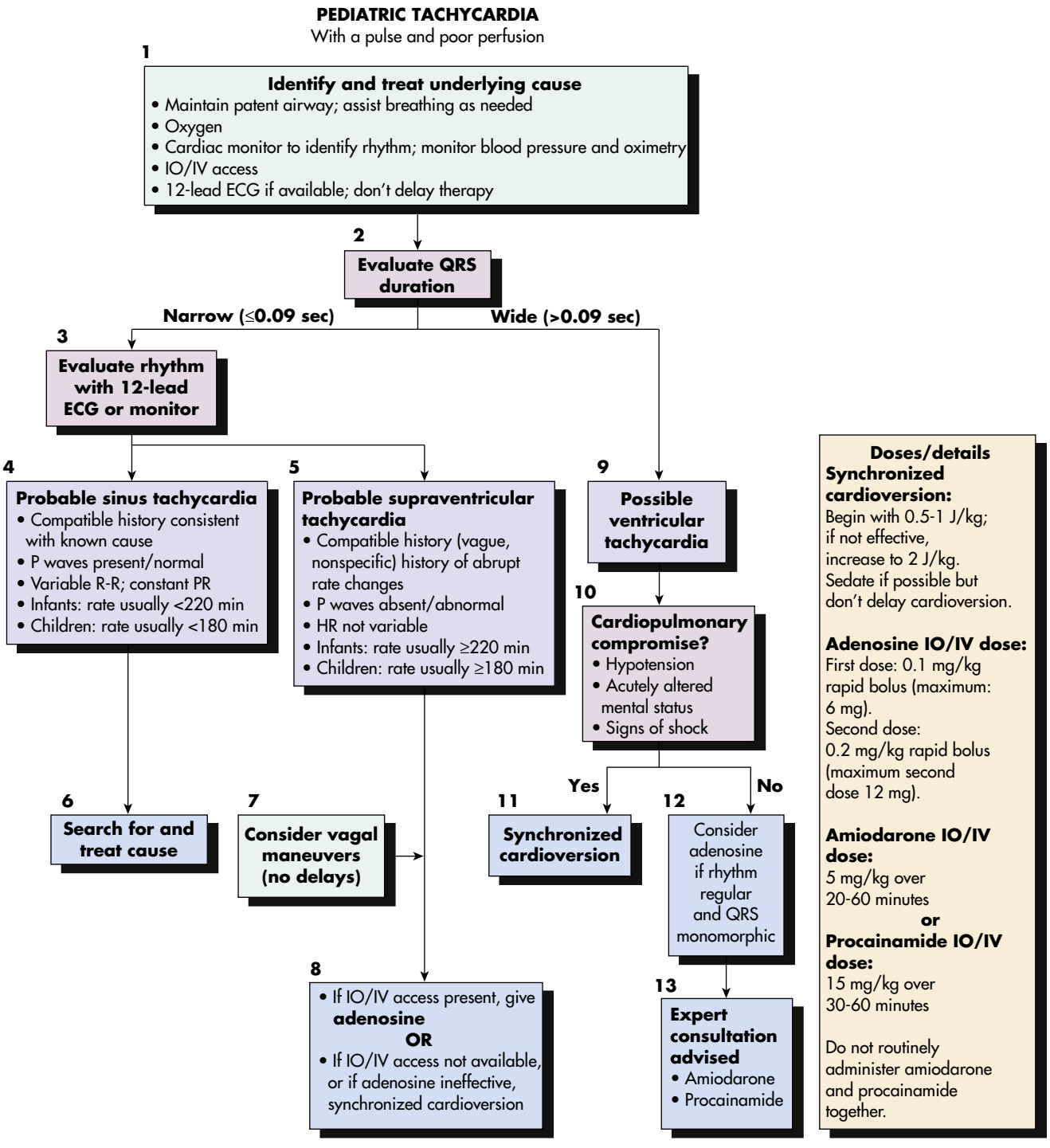


FIG. E172 American Heart Association guidelines for management of ventricular arrhythmias.
ECG, Electrocardiogram; *HR,* heart rate; *IO,* intraosseous; *IV,* intravenous. (From Fuhrman BP, Zimmermann JJ: *Fuhrman & Zimmerman's pediatric critical care,* ed 5, Philadelphia, 2017, Elsevier.)

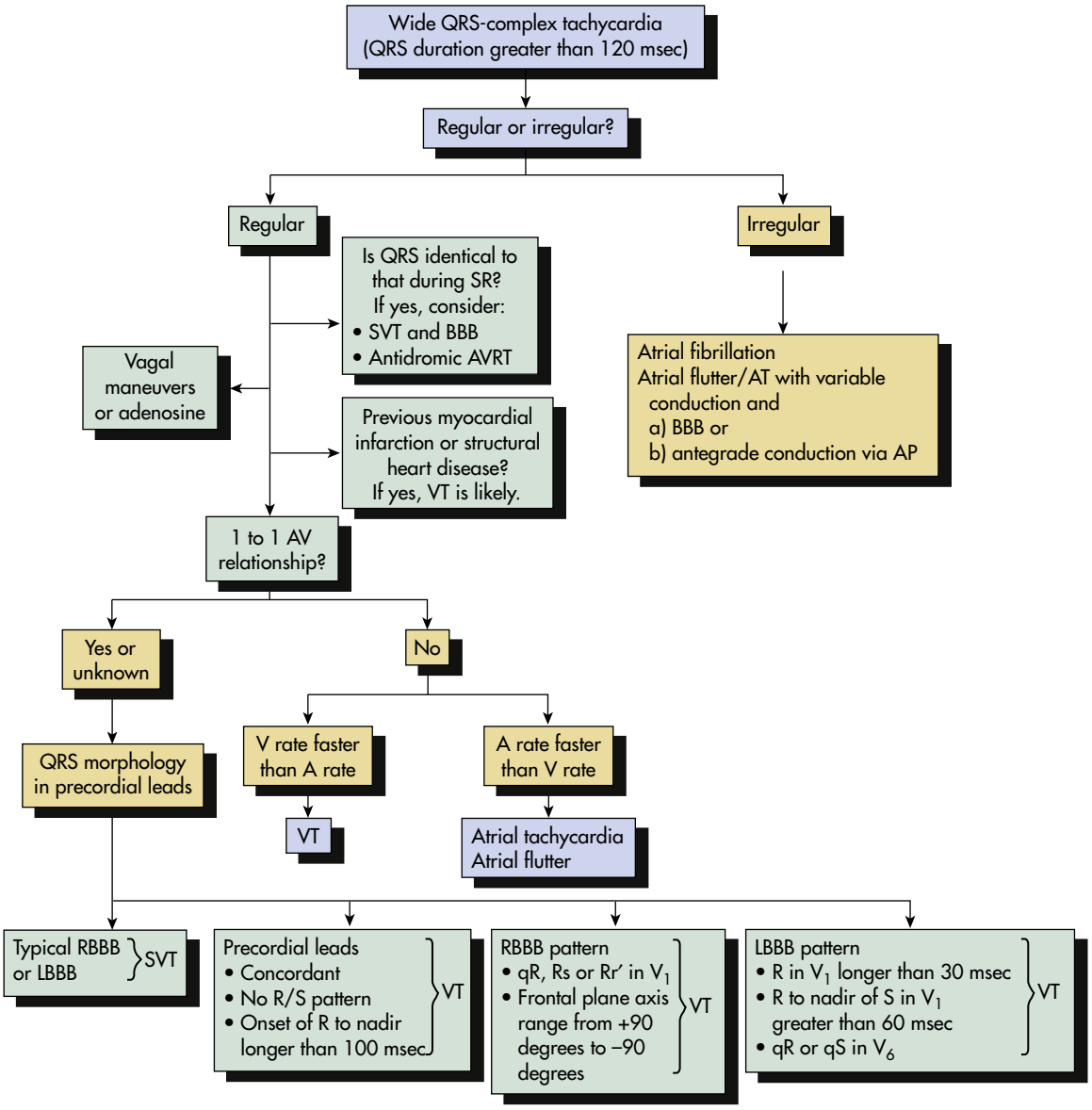


FIG. 173 Algorithm for diagnosis of wide-QRS tachycardia. *AP,* Accessory pathway; *AT,* atrial tachycardia; *AV,* atrioventricular; *AVRT,* AV reentrant tachycardia; *LBBB,* left bundle branch block; *RBBB,* right bundle branch block; *SVT,* supraventricular tachycardia; *VT,* ventricular tachycardia. (From Bloomstrom-Lundqvist C et al: ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines [Writing Committee to Develop Guidelines for the Management of Patients with Supraventricular Arrhythmias]. *Circulation* 108:1871, 2003; Mann DL et al: *Braunwald's heart disease*, ed 10, Philadelphia, 2015, Elsevier.)

TABLE 66 Stepwise Criteria Favoring Ventricular Tachycardia Patients with Wide-Complex Tachycardias Using Different Algorithms

ACC/AHA/ESC Algorithm*	Kindwall Criteria†	Wellens Criteria‡	Brugada Criteria§	Miller criteria§
See Figure 173	R >30 ms in V_1 or V_2→ VT	AV dissociation → VT	Absence of RS complex in all precordial leads → VT	Initial R wave in aVR → VT
	Any Q in V_6→ VT	QRS width >140 ms →VT	Longest R/S interval >100 ms in any precordial lead → VT	aVR with initial r or q >40 sec in duration → VT
	>60 ms to S wave nadir in V_1 or V_2→ VT	Left axis deviation >–30° → VT	AV dissociation → VT	aVR with a notch on the descending limb of a negative-onset and predominantly negative QRS in aVR → VT
	Notched downstroke S wave in V_1 or V_2→ VT	If RBBB morphology, monophasic or biphasic QRS in V_1→ SVT or R-to-S ratio of <1 in V_6→ VT	If RBBB morphology, monophasic R or qR in V_1→ VT R taller than R′→ VT rS in V_6→ VT	In aVR, mV of initial 40 msec divided by terminal 40 msec ($v/v_t \leq 1$) → VT
		If LBBB morphology, S in V_1-V_2→ VT	If LBBB morphology, initial R >40 ms in duration →VT Slurred or notched S in V_1 or V_2→ VT Beginning Q or QS in V_6→ VT	

ACC, American College of Cardiology; *AHA,* American Heart Association; *ESC,* European Society of Cardiology; *LBBB,* left bundle branch block; *RBBB,* right bundle branch block. ‖Vereckei A, Duray G, Szénási G et al: New algorithm using only lead aVR for differential diagnosis of wide QRS complex tachycardia. *Heart Rhythm* 5:89, 2008.

*Blomström-Lundqvist C et al: ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias). *Circulation* 108:1871, 2003.

†Kindwall KE, Brown J, Josephson ME: Electrocardiographic criteria for ventricular tachycardia in wide complex left bundle branch block morphology tachycardias. *Am J Cardiol* 61:1279, 1988.

‡Wellens HJ, Bär FW, Lie KI: The value of the electrocardiogram in the differential diagnosis of a tachycardia with a widened QRS complex. *Am J Med* 64:27, 1978.

§Brugada P et al: A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. *Circulation* 83:1649, 1991.

ICD-10CM # C62.90 Malignant neoplasm of unspecified testis, unspecified whether descended or undescended

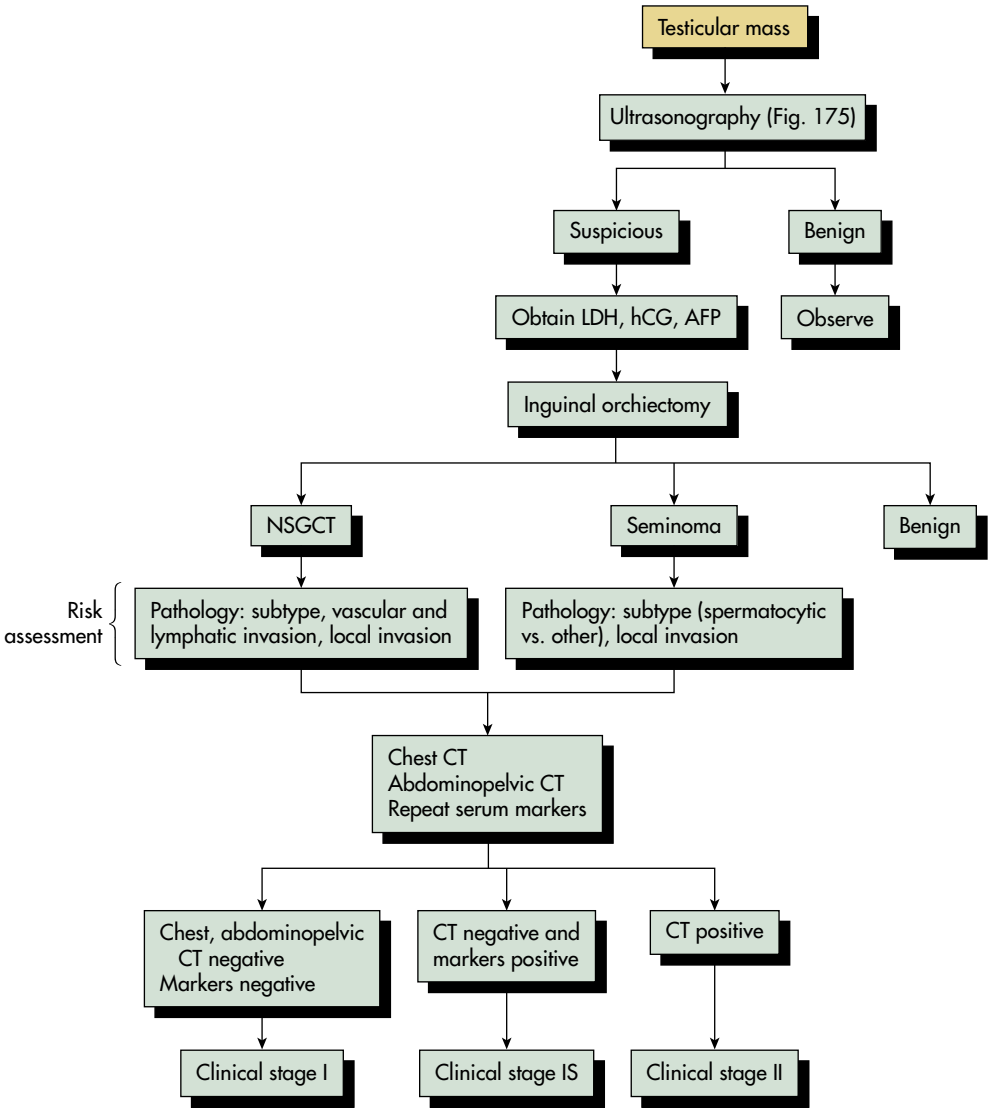


FIG. 174 Diagnosis, staging, and risk assessment of patients with testicular germ cell tumor. See Section I topic Testicular Cancer for additional information. *AFP,* α-Fetoprotein; *CT,* computed tomography; *hCG,* human chorionic gonadotropin; *LDH,* lactic dehydrogenase; *NSGCT,* nonseminoma germ cell tumor. (From Abeloff MD: *Clinical oncology,* ed 4, New York, 2007, Churchill Livingstone.)

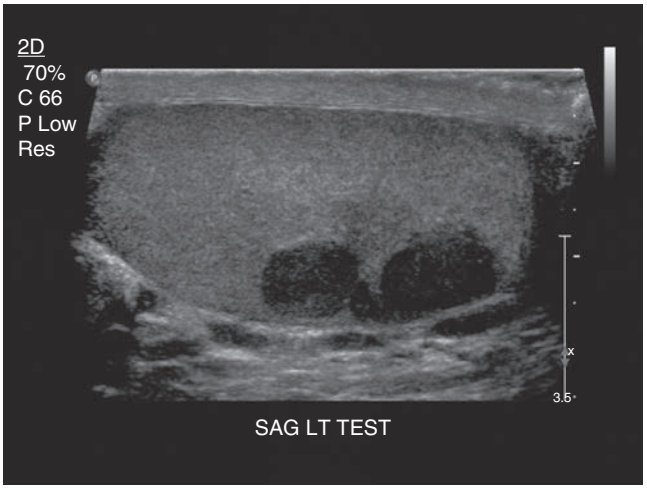


FIG. 175 Sagittal view of ultrasound of left testis showing multinodular hypoechoic intratesticular lesion confirmed to be pure seminoma at orchiectomy. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

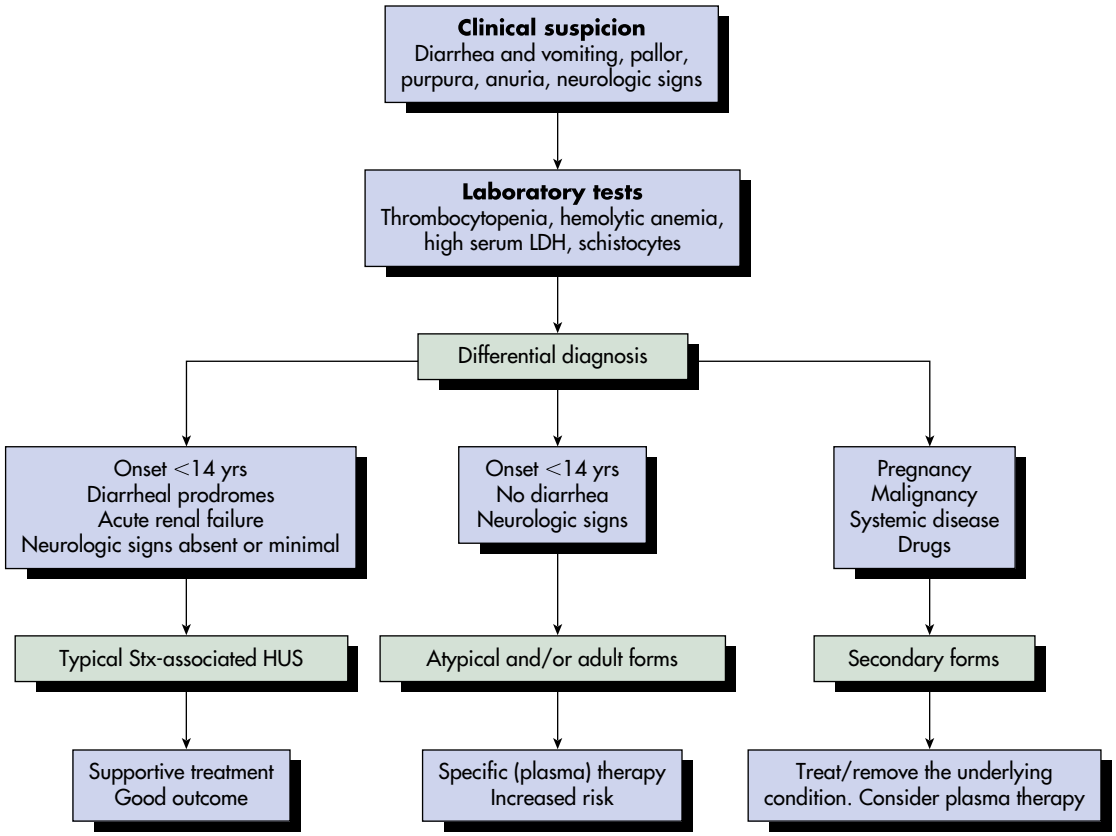


FIG. E176 Algorithm for the differential diagnosis of thrombotic microangiopathies. Patients with suggestive symptoms should be investigated for specific signs of microangiopathic hemolysis. In adults, secondary forms of the disease must be ruled out. Early diagnosis may help establish the most appropriate therapy. In children with Stx-associated hemolytic-uremic syndrome *(HUS)*, supportive treatment is mandatory. Specific therapies should be considered only in adults and in atypical forms. In secondary forms, treating and/or removing the underlying disease is fundamental. *LDH,* Lactate dehydrogenase; *Stx,* Shiga toxin. (From Feehally J, Floege J, Johnson RJ: *Comprehensive clinical nephrology,* ed 3, St Louis, 2007, Mosby.)

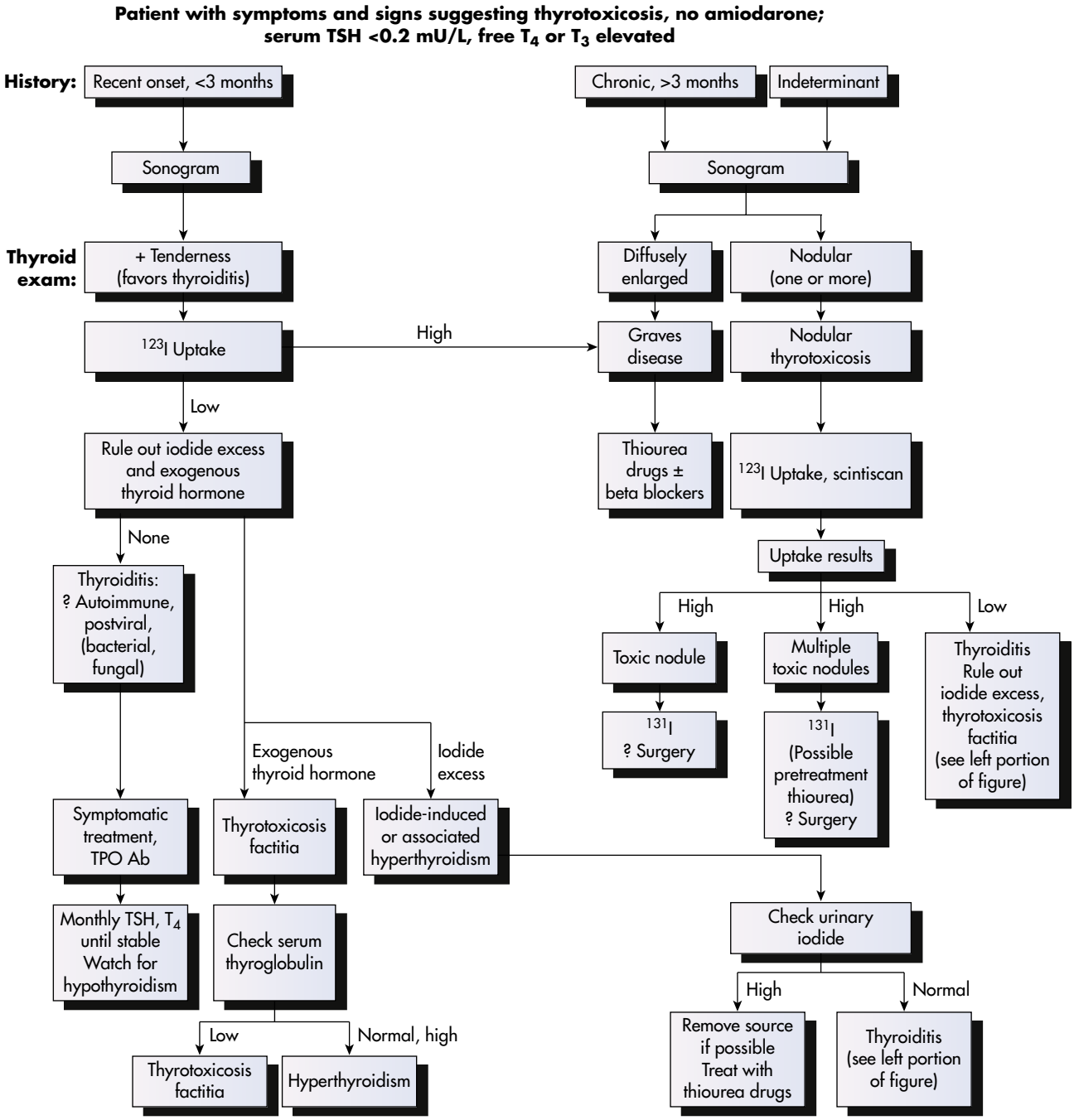


FIG. 177 Algorithm for determining the cause of thyrotropin-independent thyrotoxicosis. Additional information on thyrotoxicosis is available in Section I topics Hyperthyroidism, Thyroid Nodule, Thyroiditis, Thyroid Storm, and Graves Disease. *T_3*, Triiodothyronine; *T_4*, thyroxine; *TPO Ab*, thyroid peroxidase antibody; *TSH*, thyroid-stimulating hormone (thyrotropin). (From Melmed S et al: *Williams textbook of endocrinology,* ed 13, Philadelphia, 2016, Elsevier.)

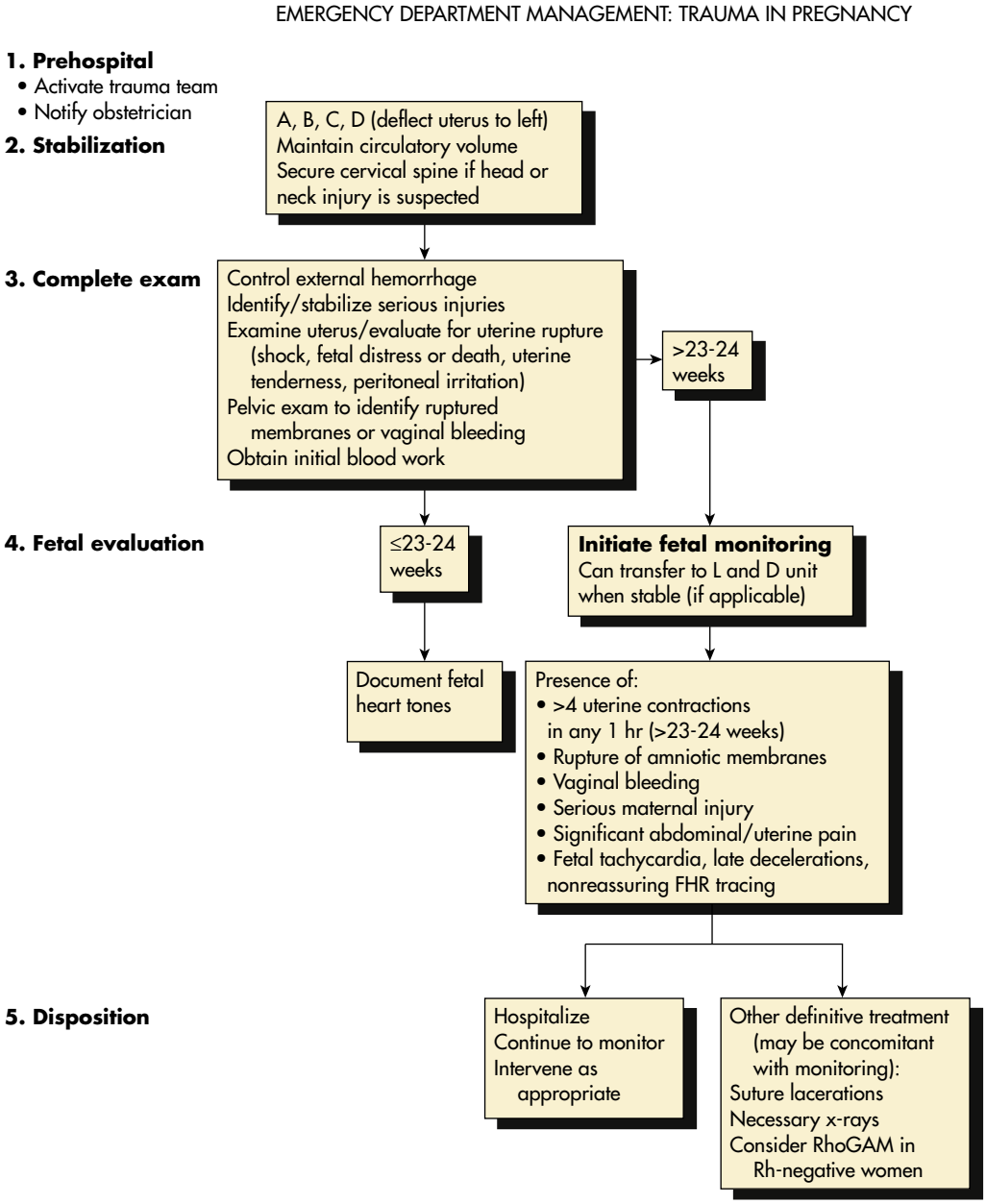


FIG. 178 Algorithm with suggested care plan for pregnant women who experience trauma. *FHR,* Fetal heart rate; *L and D,* labor and delivery. (From Gabbe SG et al: *Obstetrics,* ed 7, Philadelphia, 2017, Saunders.)

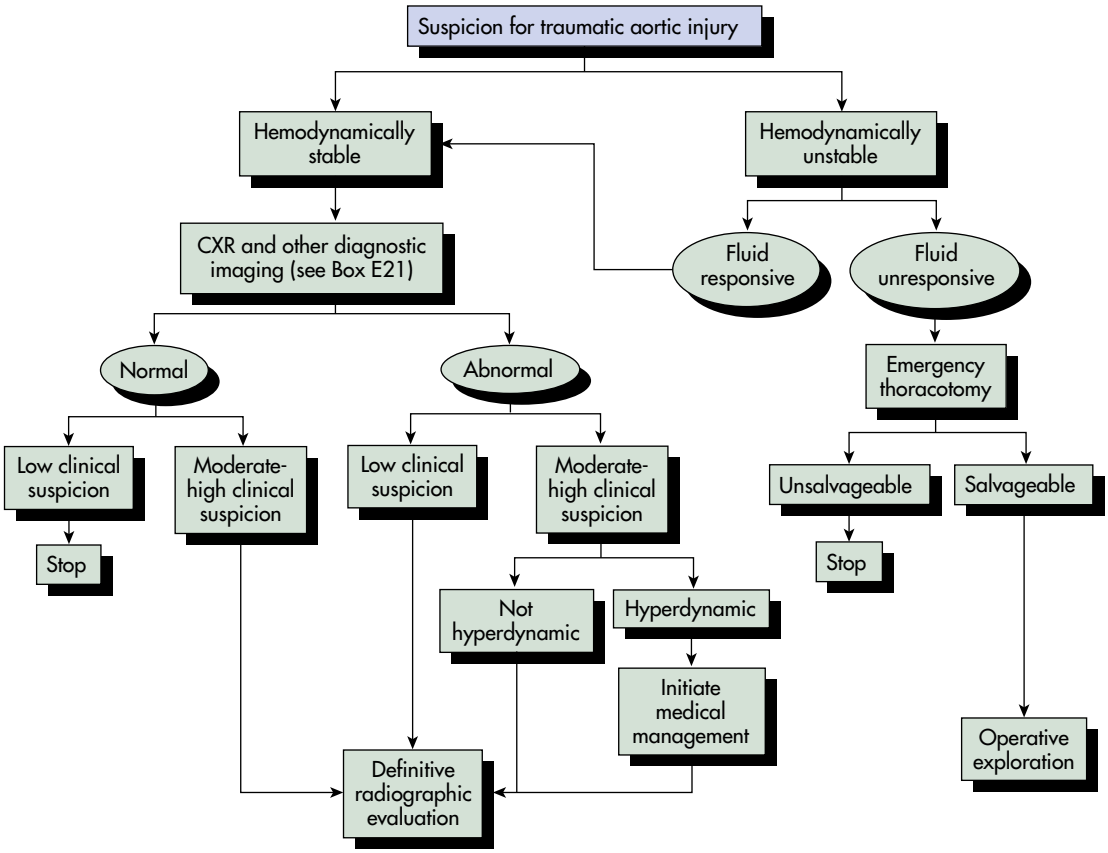


FIG. E179 Diagnostic management algorithm for suspected traumatic aortic injury. *CXR,* Chest radiograph. (Modified from Adams JG et al: *Emergency medicine: clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

BOX E21 Pros and Cons of Imaging Modalities for Great Vessel Injury

Chest Radiography

Pros
- Inexpensive
- Performed at the bedside
- Easy to interpret

Cons
- Nonspecific
- False-negative rate of 7% to 10% for traumatic aortic injury

Computed Tomographic Angiography

Pros
- Identifies mediastinal hematoma and differentiates its causes
- Identifies aortic injury, including intimal tears
- Sensitivity and specificity approaching 100% for traumatic aortic injury

Cons
- Poor delineation of nonaortic vascular injuries
- Requires relative hemodynamic stability to obtain

Aortography

Pros
- Traditional "gold standard"
- Beneficial in the diagnosis of branch vessel injuries
- Delineates equivocal computed tomographic angiographic findings

Cons
- Difficult to obtain on an emergency basis
- Requires relative hemodynamic stability

Transesophageal Echocardiography

Pros
- May be performed at the bedside
- Not limited by body habitus

Cons
- Poor availability on an emergency basis
- Contraindicated in patients with an unstable cervical spine or suspected esophageal trauma

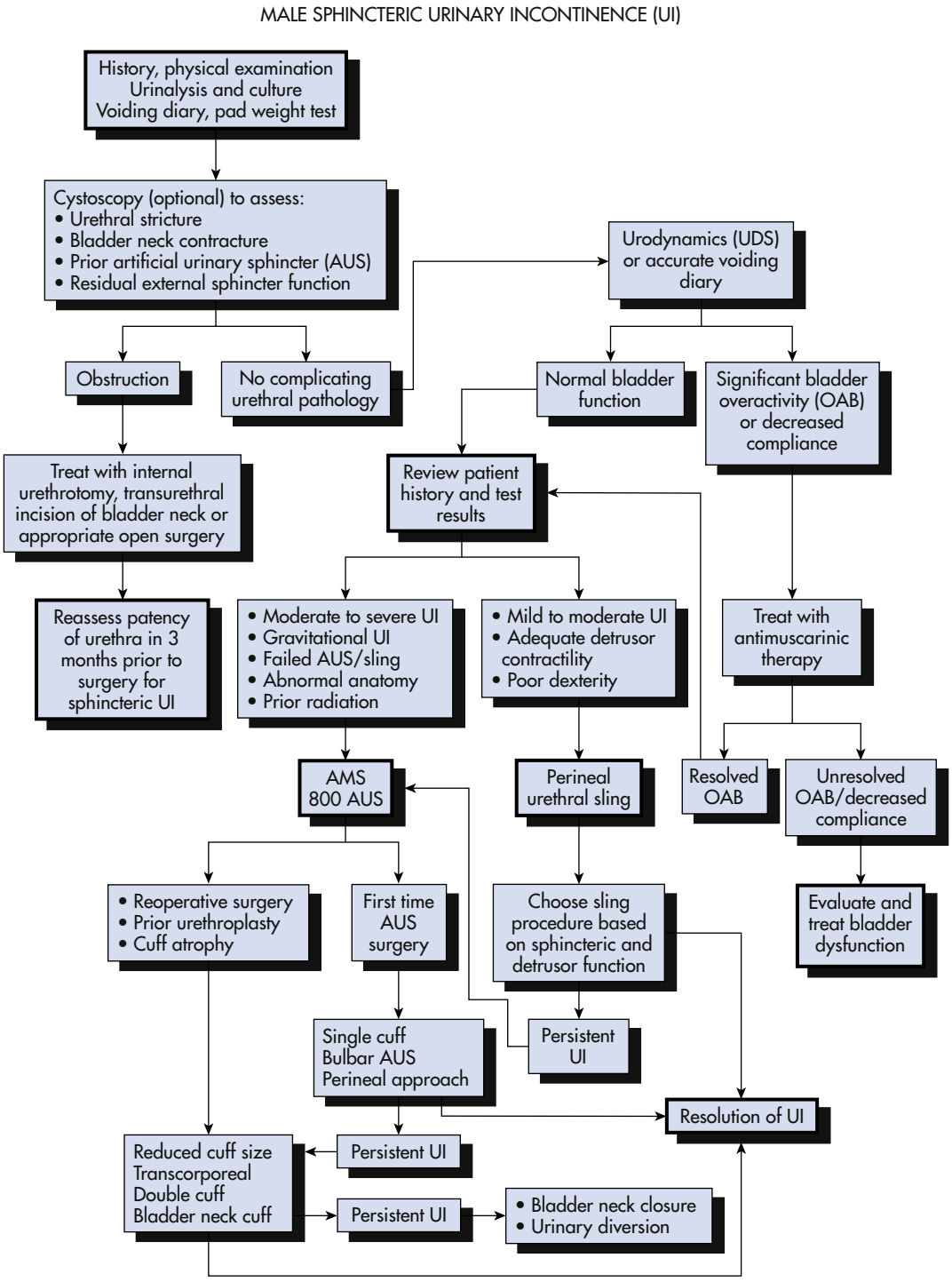


FIG. 180 Algorithm for the evaluation and management of sphincteric urinary incontinence. (From Wein AJ et al: *Campbell-Walsh urology,* ed 11, Philadelphia, 2016, Elsevier.)

ICD-10CM # R33.9 Retention of urine, unspecified
N21.8 Other lower urinary tract calculus
R32 Unspecified urinary incontinence

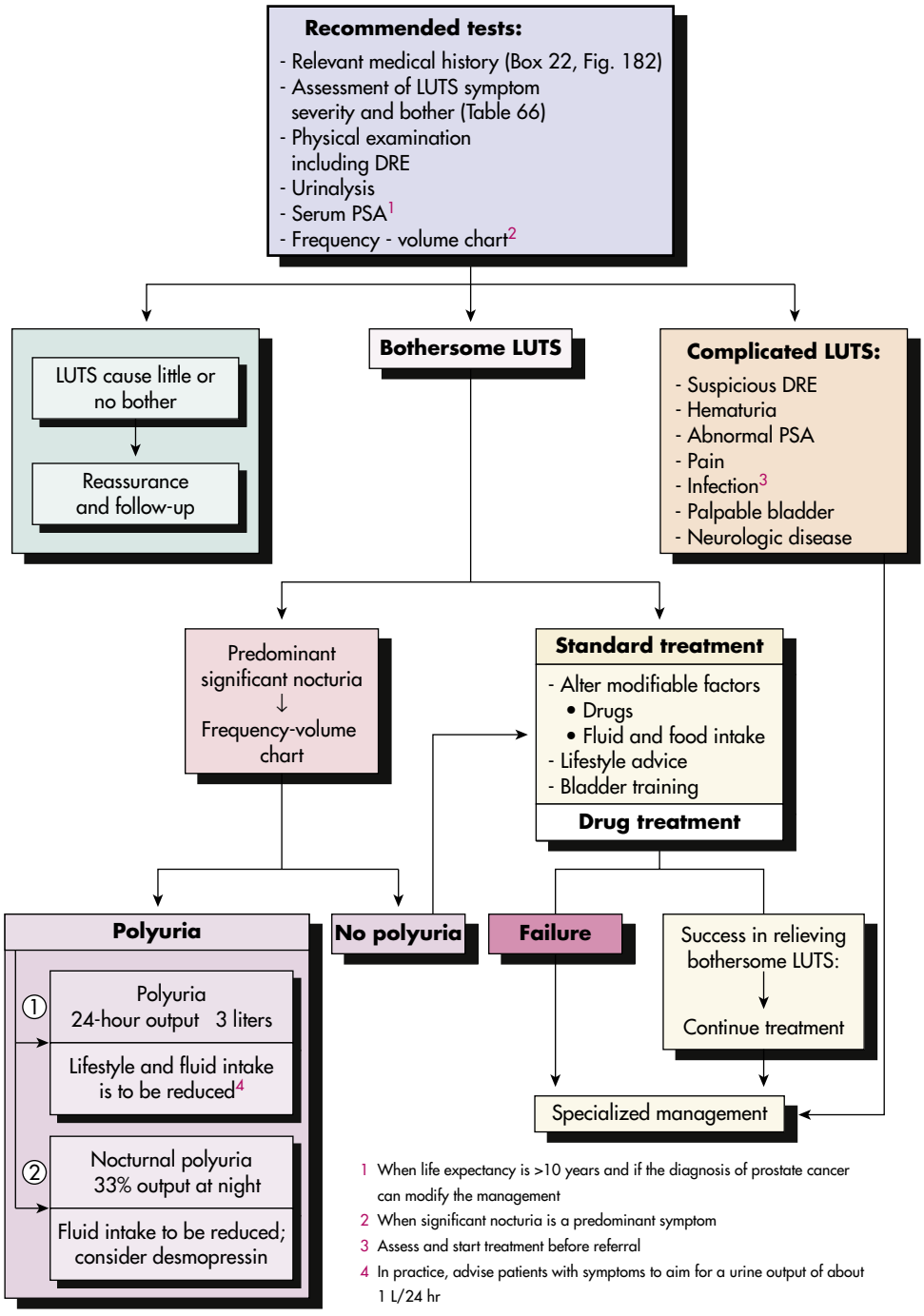


FIG. 181 Basic management of lower urinary tract symptoms *(LUTS)* in men. *DRE,* Digital rectal examination; *PSA,* prostate-specific antigen. (From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.)

BOX 22 Causes of Male Lower Urinary Tract Symptoms

Benign prostatic enlargement (secondary to benign prostatic hyperplasia)
Urinary tract infection
Prostatitis
Overactive bladder
Neurogenic bladder dysfunction
Urethral stricture
Bladder neck contracture
Phimosis
Urinary tract stones
Bladder tumor
Advanced prostate cancer
Foreign body in the bladder
Medications, illicit drugs, and dietary factors (including caffeine, alcohol, ketamine, and decongestants)
Diabetes mellitus

From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

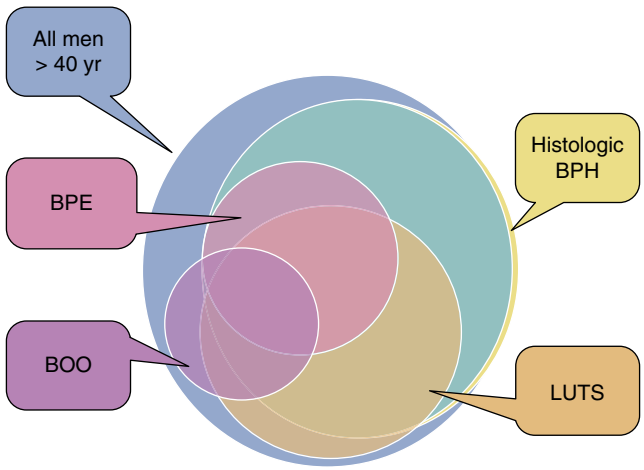


FIG. 182 Occurrence of LUTS with and without BOO, BPE, or BPH. *BOO,* Bladder outflow obstruction; *BPH,* benign prostate hyperplasia; *BPE,* benign prostate enlargement; *LUTS,* lower urinary tract symptoms. (From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.)

TABLE 67 International Continence Society Definitions of Lower Urinary Tract Symptoms

Voiding symptoms	*Hesitancy* is difficulty in initiating micturition, resulting in a delay in the onset of voiding after being ready to pass urine.
	Slow stream is the perception of reduced urine flow, usually compared to previous performance or in comparison to others.
	Splitting or spraying of the urine stream.
	Intermittent stream (intermittency) is the term used to describe urine flow that stops and starts, on one or more occasions, during micturition.
	Straining to void describes the muscular effort used to initiate, maintain, or improve the urinary stream.
	Terminal dribble is the term used to describe a prolonged final part of micturition, when the flow has slowed to a trickle or dribble.
Storage symptoms	*Increased daytime frequency* is the complaint by the patient who considers that he voids too often during the day.
	Nocturia is the complaint that the man has to wake at night one or more times to void.
	Urgency is the complaint of a sudden compelling desire to pass urine that is difficult to defer.
	Urinary incontinence is the complaint of any involuntary leakage of urine.
Postmicturition symptoms	*Feeling of incomplete emptying* is a self-explanatory term for a feeling experienced by the individual after passing urine.
	Postmicturition dribble is the term used to describe the involuntary loss of urine immediately after finishing passing urine, usually after leaving the toilet.

From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

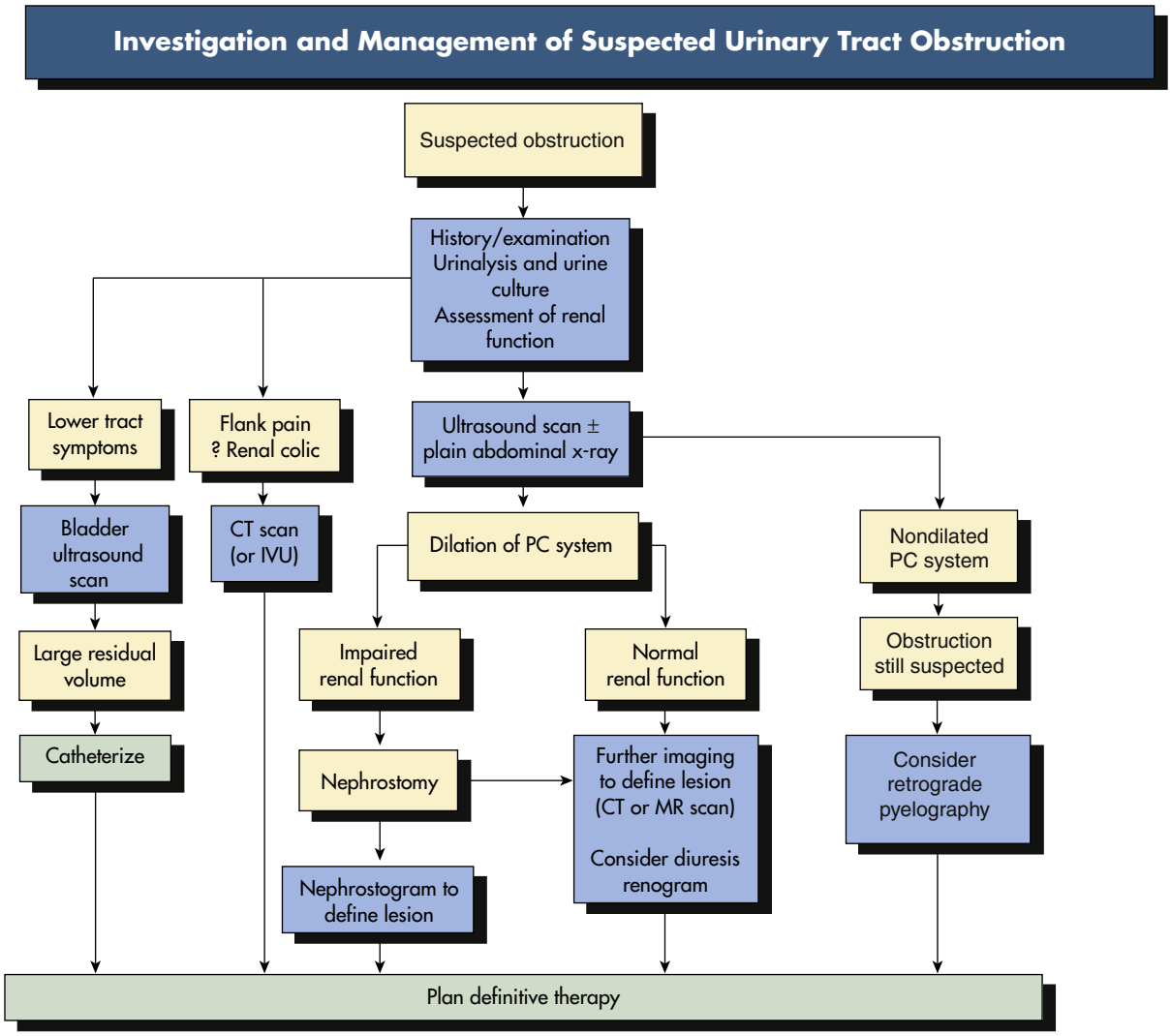


FIG. 183 Investigation and management of suspected urinary tract obstruction. A full history should be taken and a thorough examination performed, together with urinalysis, urine microscopy and culture, and measurement of renal function and serum electrolytes. Ultrasound is a useful first-line investigation for any patient with suspected urinary tract obstruction. Computed tomography *(CT)* is now the preferred imaging technique when renal calculi are suspected. Either CT or magnetic resonance *(MR)* urography can accurately diagnose both the site and cause of obstruction in most cases. If there is renal impairment, a nephrostomy allows the effective relief of the obstruction and time for renal function to recover while definitive therapy is planned. *IVU,* Intravenous urography; *PC,* pelvicalyceal. (From Johnson R, Feehally J, Floege J: *Comprehensive clinical nephrology*, ed 5, Philadelphia, 2015, Saunders.)

BOX 23 Diagnostic Tests Used in Obstructive Uropathy

Upper Urinary Tract Obstruction
- Sonography (ultrasound)
- Plain films of the abdomen (KUB)
- Excretory or intravenous pyelography (very rarely needed)
- Retrograde pyelography
- Isotopic renography
- Computed tomography (helical CT)
- Magnetic resonance imaging
- Pressure flow studies (the Whitaker test)

Lower Urinary Tract Obstruction
- Some of the tests listed at left
- Cystoscopy
- Voiding cystourethrogram
- Retrograde urethrography
- Urodynamic tests
- Debimetry
- Cystometrography
- Electromyography
- Urethral pressure profile

KUB, Kidneys, ureter, bladder.

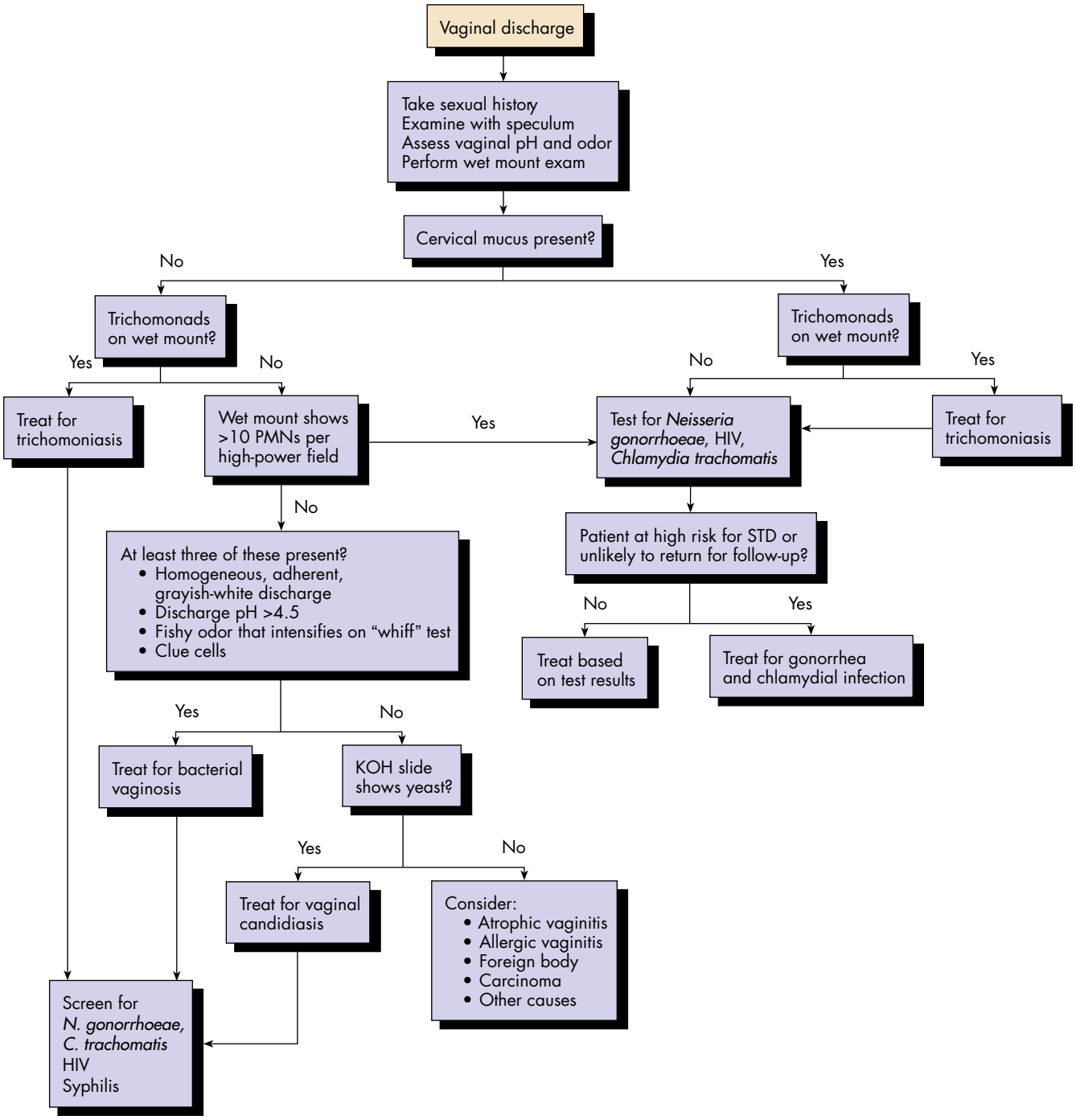


FIG. 184 Evaluation of vaginal discharge. See Section I topics Vaginitis, Fungal and Vaginitis, Trichomonas for additional information. *HIV,* Human immunodeficiency virus; *KOH,* potassium hydroxide; *PMN,* polymorphonuclear leukocyte; *STD,* sexually transmitted disease.

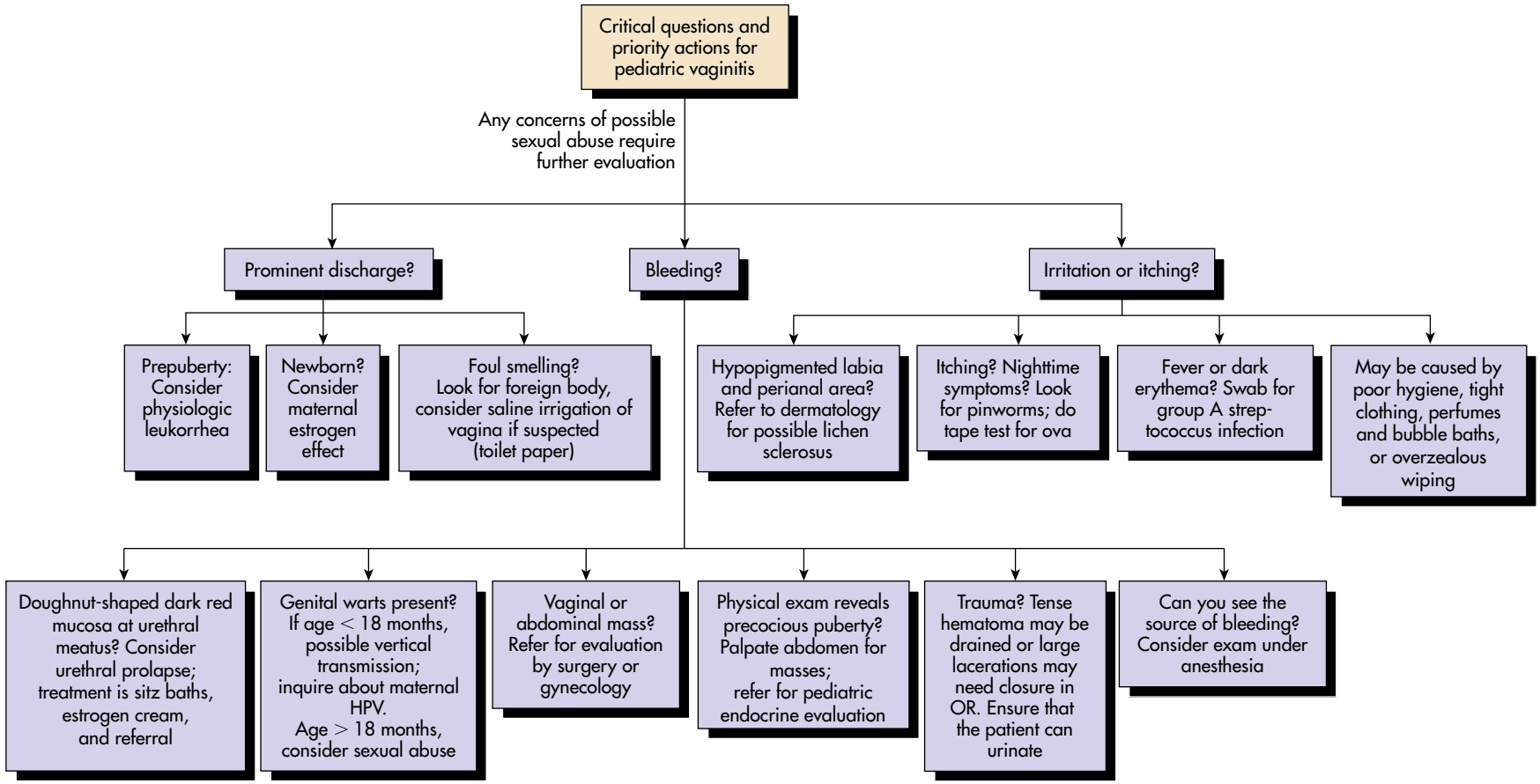


FIG. 185 Algorithm showing critical questions and priority actions for pediatric vaginitis. Additional information available in Section I topic Vaginitis, Prepubescent. *HPV,* Human papillomavirus; *OR,* operating room. (From Adams JG et al: *Emergency medicine: clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

ICD-10CM #

J15.9	Unspecified bacterial pneumonia
J15.1	Pneumonia due to pseudomonas
J15.6	Pneumonia due to other aerobic gram-negative bacteria
J15.212	Pneumonia due to methicillin-resistant *Staphylococcus aureus*

Patient has a baseline period of stability or improvement on the ventilator, defined by ≥2 calendar days of stable or decreasing daily minimum* FiO_2 or PEEP values. The baseline period is defined as the 2 calendar days immediately preceding the first day of increased daily minimum PEEP or FiO_2.
*Daily minimum defined by lowest value of FiO_2 or PEEP during a calendar day that is maintained for at least 1 hour.

↓

After a period of stability or improvement on the ventilator, the patient has at least one of the following indicators of worsening oxygenation:
1) Increase in daily minimum* FiO_2 of ≥0.20 (20 points) over the daily minimum FiO_2 in the baseline period, sustained for ≥2 calendar days.
2) Increase in daily minimum* PEEP values of ≥3 cm H_2O over the daily minimum PEEP in the baseline period,† sustained for ≥2 calendar days.
*Daily minimum defined by lowest value of FiO_2 or PEEP during a calendar day that is maintained for at least 1 hour.
†Daily minimum PEEP values of 0–5 cm H_2O are considered equivalent for the purposes of VAE surveillance.

↓

Ventilator-Associated Condition (VAC)

↓

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, the patient meets *both* of the following criteria:

1) Temperature >38° C or <36° C, **OR** white blood cell count ≥12,000 cells/mm^3 or ≤4,000 cells/mm^3.
AND
2) A new antimicrobial agent(s) is started, and is continued for ≥4 calendar days.

↓

Infection-related Ventilator-Associated Complication (IVAC)

↓

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met (**taking into account organism exclusions specified in the protocol**):

1) Criterion 1: Positive culture of one of the following specimens, meeting quantitative or semiquantitative thresholds as outlined in protocol, *without* requirement for purulent respiratory secretions:
   - Endotracheal aspirate, ≥10^5 CFU/mL or corresponding semiquantitative result
   - Bronchoalveolar lavage, ≥10^4 CFU/mL or corresponding semiquantitative result
   - Lung tissue, ≥10^4 CFU/g or corresponding semiquantitative result
   - Protected specimen brush, ≥10^3 CFU/mL or corresponding semiquantitative result
2) Criterion 2: Purulent respiratory secretions (defined as secretions from the lungs, bronchi, or trachea that contain ≥25 neutrophils and ≤10 squamous epithelial cells per low power field [lpf, 100])† *plus* a positive culture of one of the following specimens (qualitative culture, or quantitative/semiquantitative culture without sufficient growth to meet criterion #1):
   - Sputum
   - Endotracheal aspirate
   - Bronchoalveolar lavage
   - Lung tissue
   - Protected specimen brush

   † If the laboratory reports semiquantitative results, those results must correspond to the above quantitative thresholds. See additional instructions for using the purulent respiratory secretions criterion in the VAE Protocol.
3) Criterion 3: One of the following positive tests:
   - Pleural fluid culture (where specimen was obtained during thoracentesis or initial placement of chest tube and NOT from an indwelling chest tube)
   - Lung histopathology, defined as: 1) abscess formation or foci of consolidation with intense neutrophil accumulation in bronchioles and alveoli; 2) evidence of lung parenchyma invasion by fungi (hyphae, pseudohyphae, or yeast forms); 3) evidence of infection with the viral pathogens listed below based on results of immunohistochemical assays, cytology, or microscopy performed on lung tissue
   - Diagnostic test for *Legionella* species
   - Diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus human metapneumovirus coronavirus

↓

Possible Ventilator-Associated Pneumonia (PVAP)

FIG. 186 Ventilator-associated events surveillance algorithm. *FiO_2*, Fraction of inspired oxygen; *PEEP*, positive end-expiratory pressure. (From Centers for Disease Control and Prevention: Ventilator-associated event [VAE], device-associated module. *NHSN Patient Safety Component Manual*, pp 10-1–10-46, January 2015 [modified April 2015]. Available at www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf).

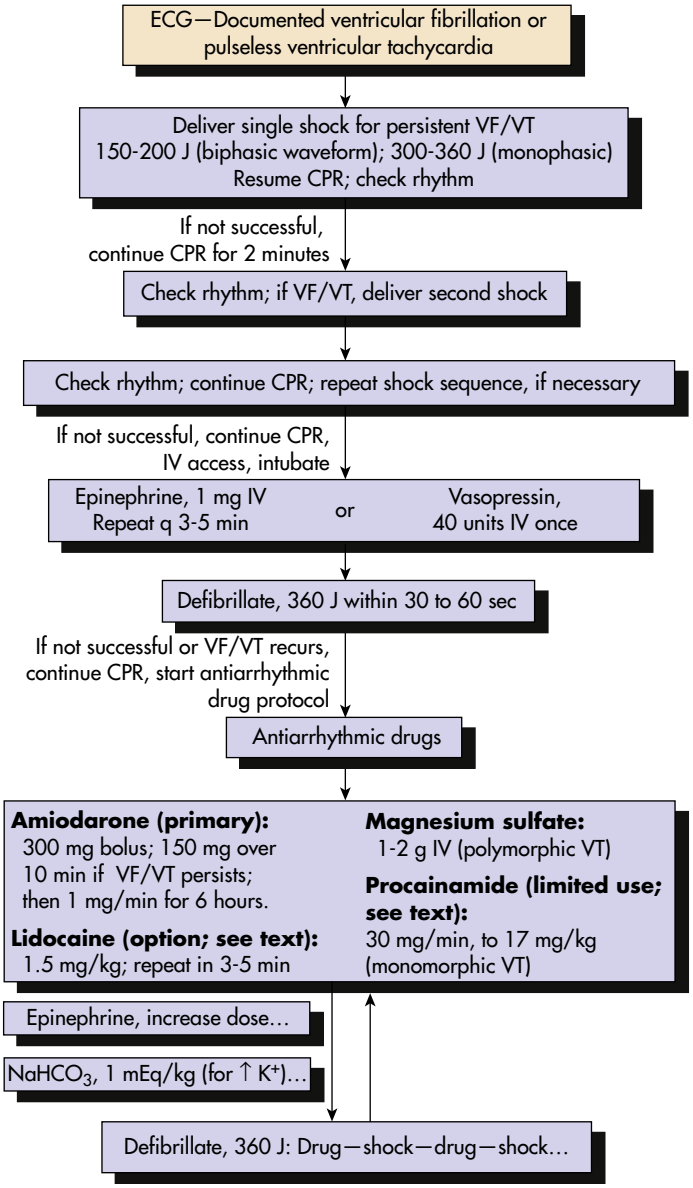


FIG. 187 General algorithm for advanced cardiac life support *(ACLS)* response to ventricular fibrillation *(VF)* or pulseless ventricular tachycardia *(VT).* NOTE: In a 2008 advisory, 200 compression-only sequences were suggested as an alternative to standard CPR cycles between shocks, and this approach is under consideration for future guidelines. *CPR,* Cardiopulmonary resuscitation; *ECG,* electrocardiogram. (From Goldman L, Schafer AI: *Goldman Cecil medicine,* ed 25, Philadelphia, 2016, Saunders.)

ICD-10CM #

R42	Dizziness and giddiness
H81.13	Benign paroxysmal vertigo, bilateral
H81.49	Vertigo of central origin, unspecified ear
H81.399	Other peripheral vertigo, unspecified ear
H81.23	Vestibular neuronitis, bilateral

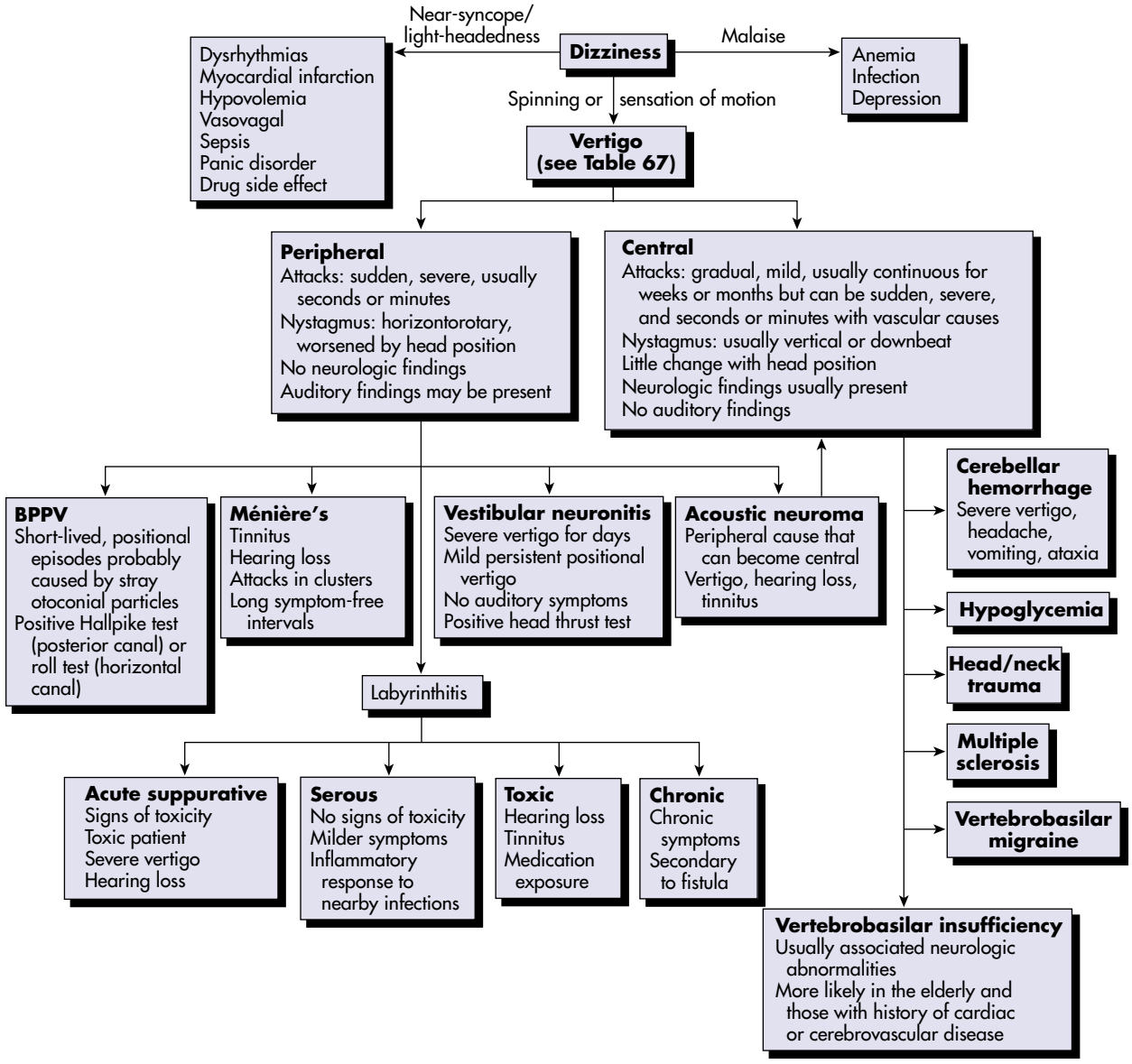


FIG. 188 Diagnostic algorithm for dizziness and vertigo. Also see Section I topics Vestibular Neuronitis, Acoustic Neuroma, Labyrinthitis, Ménière Disease, and Benign Paroxysmal Positional Vertigo. *BPPV,* Benign paroxysmal positional vertigo. (From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.)

ICD-10CM #

R42	Dizziness and giddiness
H81.13	Benign paroxysmal vertigo, bilateral
H81.49	Vertigo of central origin, unspecified ear
H81.399	Other peripheral vertigo, unspecified ear
H81.23	Vestibular neuronitis, bilateral

TABLE 68 Differential Diagnosis of Patients with True Vertigo

Cause	History	Associated Symptoms	Physical
Peripheral			
1. Benign paroxysmal positional vertigo	Short-lived, positional, fatigable episodes	Nausea, vomiting	Single position can precipitate vertigo. Positive result on Hallpike test (posterior semicircular canal) or Roll test (horizontal canal).
2. Labyrinthitis			
A. Serous	Mild to severe positional symptoms. Usually coexisting or antecedent infection of ear, nose, throat, or meninges.	Mild to severe hearing loss can occur	Usually nontoxic patient with minimal fever elevation
B. Acute suppurative	Coexisting acute exudative infection of the inner ear. Severe symptoms.	Usually severe hearing loss, nausea, vomiting	Febrile patient showing signs of toxicity. Acute otitis media.
C. Toxic	Gradually progressive symptoms: Patients on medication causing toxicity.	Hearing loss that may become rapid and severe, nausea and vomiting	Hearing loss. Ataxia common feature in chronic phase.
3. Ménière disease	Recurrent episodes of severe rotational vertigo usually lasting hours. Onset usually abrupt. Attacks may occur in clusters. Long symptom-free remissions.	Nausea, vomiting, tinnitus, hearing loss	Positional nystagmus not present
4. Vestibular neuritis	Sudden onset of severe vertigo, increasing in intensity for hours, then gradually subsiding over several days but can last weeks to months. Can be worsened with positional change. Sometimes history of infection or toxic exposure that precedes initial attack. Highest incidence is found in third and fifth decades.	Nausea, vomiting. Auditory symptoms do not occur.	Spontaneous nystagmus toward the involved ear may be present.
5. Acoustic neuroma	Gradual onset and increase in symptoms. Neurologic signs in later stages. Most occur in women aged 30 to 60.	Hearing loss, tinnitus. True ataxia and neurologic signs as tumor enlarges.	Unilateral decreased hearing. True truncal ataxia and other neurologic signs when tumor enlarges. May have diminution or absence of corneal reflex. Eighth cranial nerve deficit may be present.
Central			
1. Vascular disorders			
A. Vertebrobasilar insufficiency	Should be considered in any patient of advanced age with isolated new-onset vertigo without an obvious cause. More likely with history of atherosclerosis. Can occur with neck trauma. Initial episode usually lasts seconds to minutes.	Often headache. Usually neurologic symptoms including dysarthria, ataxia, weakness, numbness, double vision. Tinnitus and deafness uncommon.	Neurologic deficits usually present, but initially neurologic examination can be normal
B. Cerebellar hemorrhage	Sudden onset of severe symptoms	Headache, vomiting, ataxia	Signs of toxicity. Dysmetria, true ataxia. Ipsilateral sixth cranial nerve palsy may be present.
C. Occlusion of posterior inferior cerebellar artery (Wallenberg syndrome)	Vertigo associated with significant neurologic complaints	Nausea, vomiting, loss of pain and temperature sensation, ataxia, hoarseness	Loss of pain and temperature sensation on the side of the face ipsilateral to the lesion and on the opposite side of the body, paralysis of the palate, pharynx, and larynx. Horner syndrome (ipsilateral ptosis, miosis, and decreased facial sweating).
2. Head trauma	Symptoms begin with or shortly after head trauma. Positional symptoms most common type after trauma. Self-limited symptoms that can persist weeks to months.	Usually mild nausea	Occasionally, basilar skull fracture
3. Vertebrobasilar migraine	Vertigo almost always followed by headache. Patient has usually had similar episodes in past. Most patients have a family history of migraine. Syndrome usually begins in adolescence.	Dysarthria, ataxia, visual disturbances, or paresthesias usually precede headache	No residual neurologic or otologic signs are present after attack
4. Multiple sclerosis	Vertigo presenting symptom in 7%-10% and appears in the course of the disease in a third. Onset may be severe and suggest labyrinth disease. Disease onset usually between ages 20 and 40. Often history of other attacks with varying neurologic signs or symptoms.	Nausea and vomiting, which may be severe	May have horizontal, rotary, or vertical nystagmus. Nystagmus may persist after the vertiginous symptoms have subsided. Bilateral internuclear ophthalmoplegia and ataxic eye movements suggest multiple sclerosis.
5. Temporal lobe epilepsy	Can be initial or prominent symptom in some patients with the disorder	Memory impairment, hallucinations, trancelike states, seizures	May have aphasia or convulsions
6. Hypoglycemia	Should be considered in diabetics and any other patient with unexplained symptoms	Sweating, anxiety	Tachycardia, mental status change may be present

From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.

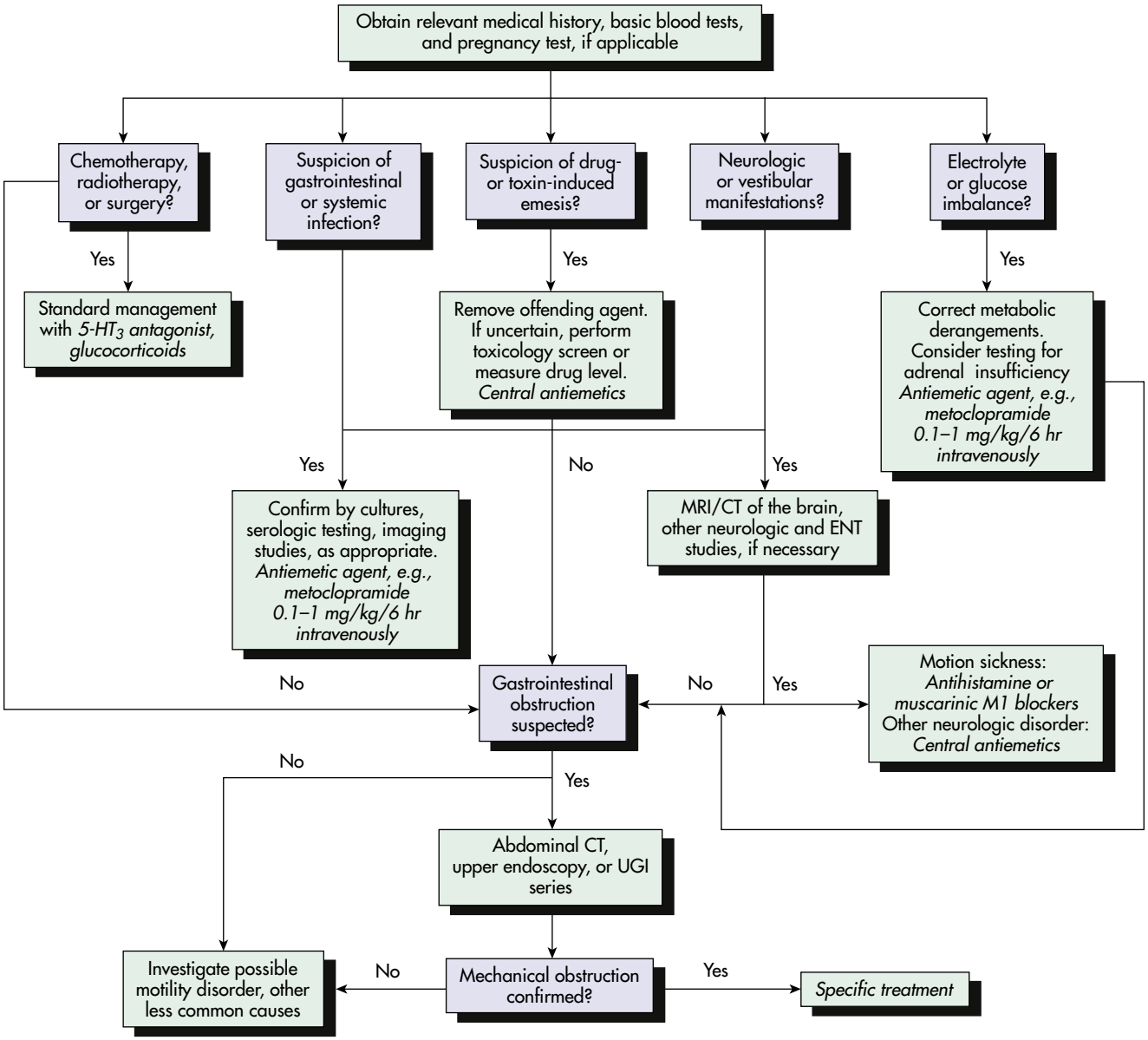


FIG. 189 Algorithm for management of a patient with acute vomiting. Possible treatments are italicized. *ENT,* ear, nose, and throat; *5-HT,* 5-hydroxytryptamine; *UGI,* upper GI. Potential treatments are shown in italics. (From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.)

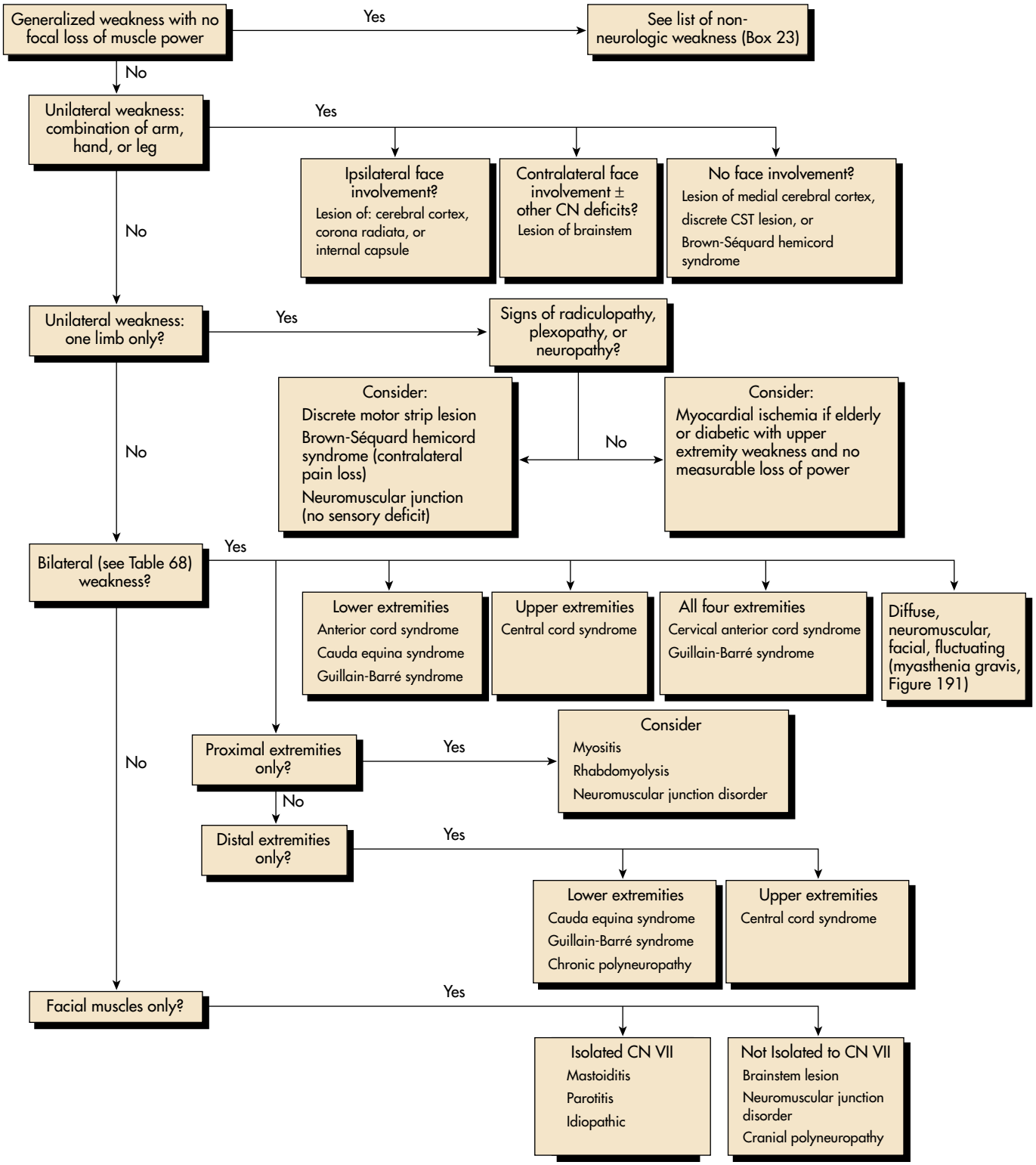


FIG. 190 Common clinical patterns of weakness, classified and assessed. *CN,* Cranial nerve; *CST,* corticospinal tract. (Modified from Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.)

FIG. 191 Myopathic facies in myasthenia gravis. (From Bowling B: *Kanski's clinical ophthalmology, a systemic approach,* ed 8, 2106, Elsevier.)

TABLE 69 Critical and Emergent Causes of Neuromuscular Weakness

Critical Diagnoses	
Cerebral cortex or subcortical	Ischemic or hemorrhagic cerebrovascular accident (CVA)
Brainstem	Ischemic or hemorrhagic CVA
Spinal cord	Ischemia, compression (disk, abscess, or hematoma)
Peripheral nerve	Acute demyelination (Guillain-Barré syndrome)
Neuromuscular junction	Myasthenic or cholinergic crisis Botulism Tick paralysis Organophosphate poisoning
Muscle	Rhabdomyolysis
Emergent Diagnoses	
Cerebral cortex or subcortical	Tumor, abscess, demyelination
Brainstem	Demyelination
Spinal cord	Demyelination (transverse myelitis) Compression (disk, spondylosis)
Peripheral nerve	Compressive plexopathy (hematoma, aneurysm) Paraneoplastic vasculitis uremia
Muscle	Inflammatory myositis

From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Saunders.

BOX 23 Nonneurologic Weakness

- Alterations in plasma volume (dehydration)
- Alterations in plasma composition (glucose, electrolytes)
- Derangement in circulating red blood cells (anemia or polycythemia)
- Decrement in cardiac pump function (myocardial ischemia)
- Drop in systemic vascular resistance (vasodilatory shock from any cause)
- Increased metabolic demand (local or systemic infection, endocrinopathy, toxin)
- Mitochondrial dysfunction (severe sepsis or toxin-mediated)
- Global depression of the central nervous system (sedatives, stimulant withdrawal)

From Marx JA et al: *Rosen's emergency medicine*, ed 8, Philadelphia, 2014, Elsevier.

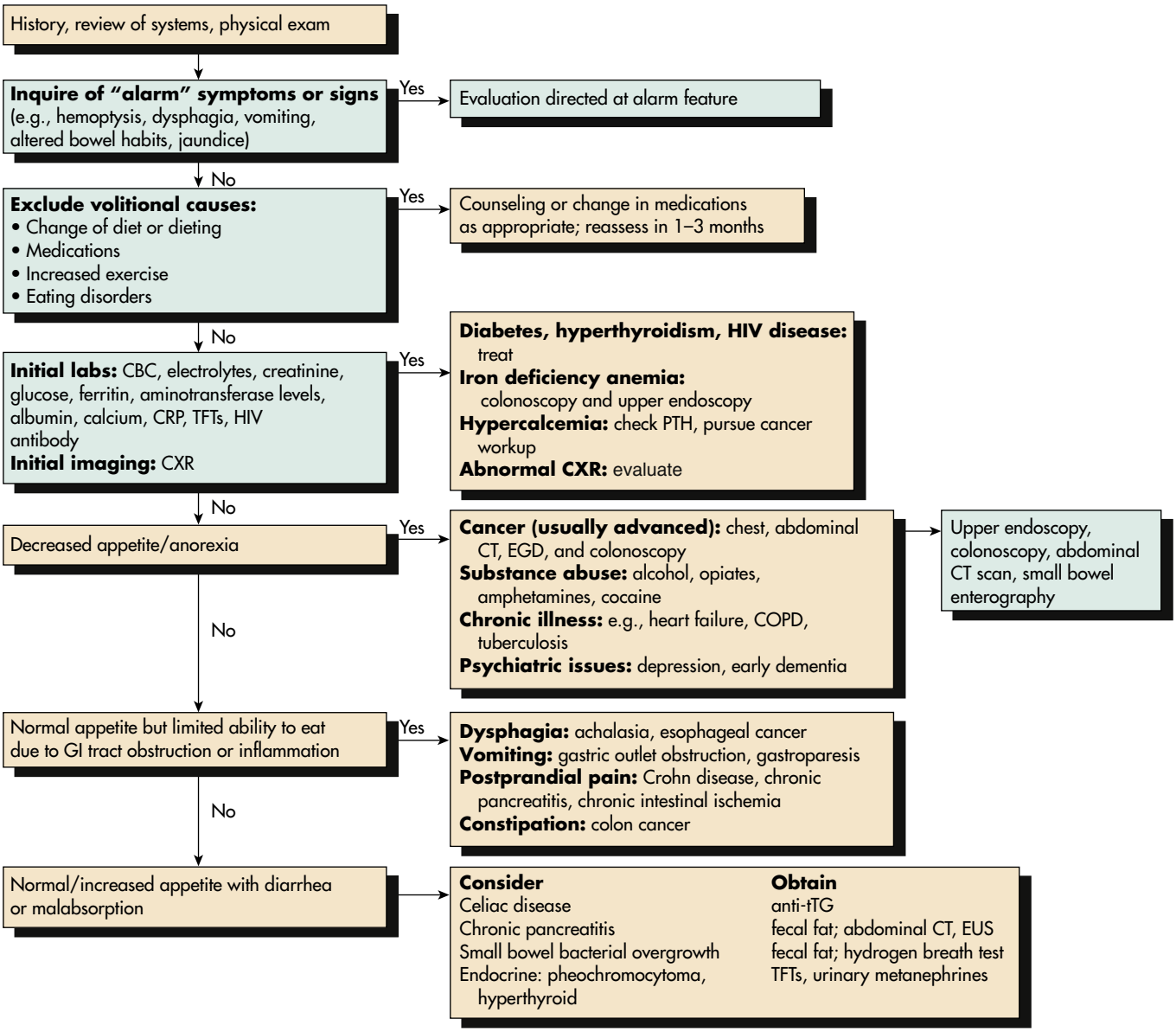


FIG. 192 Approach to the patient with unintentional weight loss of more than 5%. *CBC,* Complete blood count; *COPD*, chronic obstructive pulmonary disease; *CRP*, C-reactive protein; *CT*, computed tomography; *CXR*, chest radiograph; *EGD*, esophagogastroduodenoscopy; *EUS*, endoscopic ultrasound; *GI*, gastrointestinal; *HIV*, human immunodeficiency virus; *PTH*, parathyroid hormone; *TFTs*, thyroid function tests; *tTG*, tissue transglutaminase. (From Goldman L, Schafer AI: *Goldman Cecil medicine*, ed 25, Philadelphia, 2016, Saunders.)

ACE LEVEL
See ANGIOTENSIN-CONVERTING ENZYME

ACETONE (serum or plasma)
Normal: Negative
Elevated in: diabetic ketoacidosis (DKA), starvation, isopropanol ingestion

ACETYLCHOLINE RECEPTOR (AChR) ANTIBODY
Normal: <0.03 nmol/L
Elevated in: Myasthenia gravis. Changes in AChR concentration correlate with the clinical severity of myasthenia gravis following therapy and during therapy with prednisone and immunosuppressants. False-positive AChR antibody results may be found in patients with Eaton-Lambert syndrome.

ACID-BASE REFERENCE VALUES
See Tables 1, 2, and 3.

ACID PHOSPHATASE (serum)
Normal range: 0 to 5.5 U/L (0 to 90 nkat/L [CF: 16.67; SMI: 2 nkat/L])
Elevated in: Carcinoma of prostate, other neoplasms (breast, bone), Paget disease, osteogenesis imperfecta, malignant invasion of bone, Gaucher disease, multiple myeloma, myeloproliferative disorders, benign prostatic hypertrophy, prostatic palpation or surgery, hyperparathyroidism, liver disease, chronic renal failure, idiopathic thrombocytopenic purpura, bronchitis

ACID SERUM TEST
See HAM TEST

ACTIVATED CLOTTING TIME (ACT)
Normal: This test is used to determine the dose of protamine sulfate to reverse the effect of heparin as an anticoagulant during angioplasty, cardiac surgery, and hemodialysis. The accepted goal during cardiopulmonary bypass surgery is usually 400-500 sec.

ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT, aPTT)
See PARTIAL THROMBOPLASTIN TIME

ADRENOCORTICOTROPIC HORMONE (ACTH)
Normal: 9 to 52 pg/ml. Table 4 describes patterns of serum levels of ACTH and cortisol in different adrenal gland disorders.
Elevated in: Addison disease, ectopic ACTH-producing tumors, congenital adrenal hyperplasia, Nelson syndrome, pituitary-dependent Cushing disease
Decreased in: Secondary adrenocortical insufficiency, hypopituitarism, adrenal adenoma or adrenal carcinoma

ALANINE AMINOPEPTIDASE
Normal:
Male: 1.11 to 1.71 mcg/ml
Female: 0.96 to 1.52 mcg/ml
Elevated in: Liver or pancreatic disease, ethanol use, oral contraceptives use, malignancy, tobacco use, pregnancy
Decreased in: Abortion

ALANINE AMINOTRANSFERASE (ALT, SGPT)
See Fig. 1, an algorithm for evaluation of elevated ALT. Table 5 describes patterns of liver function tests in liver disorders.
Normal range: 0 to 35 U/L (0.058 μkat/L [CF: 0.02 μkat/L])
Elevated in: Liver disease (hepatitis, cirrhosis, Reye syndrome), hepatic congestion, infectious mononucleosis, myocardial infarction, myocarditis, severe muscle trauma, dermatomyositis/polymyositis, muscular dystrophy, drugs (antibiotics, narcotics, antihypertensive agents, heparin, labetalol, statins, NSAIDs, amiodarone, chlorpromazine, phenytoin), malignancy, renal and pulmonary infarction, seizures, eclampsia, shock liver

TABLE 1 Commonly Used Acid-Base Reference Values for Arterial and Venous Plasma or Serum (Averaged from Various Sources)

	ARTERIAL		VENOUS	
	Conventional Units	SI Units*	Conventional Units	SI Units*
pH	7.40 (7.35-7.45)	7.40 (7.35-7.45)	7.37 (7.32-7.42)	7.37 (7.32-7.42)
Pco_2	40 mm Hg (35-45)	5.33 kPa (4.67-6.10)	45 mm Hg (45-50)	6.10 kPa (5.33-6.67)
Po_2	80-100 mm Hg	10.66-13.33 kPa	40 mm Hg (37-43)	5.33 kPa (4.93-5.73)
HCO_3 (CO_2 combining power)	24 mEq/L (20-28)	24 mmol/L (20-28)	26 mEq/L (22-30)	26 mmol/L (22-30)
CO_2 content	25 mEq/L (22-28)	25 mmol/L (22-28)	27 mEq/L (24-30)	27 mmol/L(24-30)

*International system.
From Ravel R: *Clinical laboratory medicine*, ed 6, St Louis, 1995, Mosby.

TABLE 2 Summary of Laboratory Findings in Primary Uncomplicated Respiratory and Metabolic Acid-Base Disorders*

Disorder	Pco_2	pH	Base Excess
Acute primary respiratory hypoactivity (respiratory acidosis)	Increase	Decrease	Normal/positive
Acute primary respiratory hyperactivity (respiratory alkalosis)	Decrease	Increase	Normal/negative
Uncompensated metabolic acidosis	Normal	Decrease	Negative
Uncompensated metabolic alkalosis	Normal	Increase	Positive
Partially compensated metabolic acidosis	Decrease	Decrease	Negative
Partially compensated metabolic alkalosis	Increase	Increase	Positive
Chronic primary respiratory hypoactivity (compensated respiratory acidosis)	Increase	Normal	Positive
Fully compensated metabolic alkalosis	Increase	Normal	Positive
Chronic primary respiratory hyperactivity (compensated respiratory alkalosis)	Decrease	Normal	Negative
Fully compensated metabolic acidosis	Decrease	Normal	Negative

*Base excess results refer to negative (–) values more than 22 and positive (+) values more than 12.
From Ravel R: *Clinical laboratory medicine*, ed 6, St Louis, 1995, Mosby.

TABLE 3 Acid-Base Abnormalities and Appropriate Compensatory Responses for Simple Disorders

Primary Acid-Base Disorders	Primary Defect	Effect on pH	Compensatory Response	Expected Range of Compensation	Limits of Compensation
Respiratory acidosis	Alveolar hypoventilation (↑ P_{CO_2})	↓	↑ Renal HCO_3^- reabsorption (HCO_3^-↑)	Acute: Δ[HCO_3^-] = +1 mEq/L for each ↑ΔP_{CO_2} of 10 mm Hg	[HCO_3^-] = 38 mEq/L
				Chronic: Δ[HCO_3^-] = +4 mEq/L for each ↑ΔP_{CO_2} of 10 mm Hg	[HCO_3^-] = 45 mEq/L
Respiratory alkalosis	Alveolar hyperventilation (↓ P_{CO_2})	↑	↓ Renal HCO_3^- reabsorption (HCO_3^-↓)	Acute: Δ[HCO_3^-] = −2 mEq/L for each ↓ΔP_{CO_2} of 10 mm Hg	[HCO_3^-] = 18 mEq/L
				Chronic: Δ[HCO_3^-] = −5 mEq/L for each ↓ΔP_{CO_2} of 10 mm Hg	[HCO_3^-] = 15 mEq/L
Metabolic acidosis	Loss of HCO_3^- or gain of H^+ (↓ HCO_3^-)	↓	Alveolar hyperventilation to ↑ pulmonary CO_2 excretion (↓P_{CO_2})	P_{CO_2} = 1.5[HCO_3^-] + 8 ± 2 P_{CO_2} = last 2 digits of pH × 100 P_{CO_2} = 15 + [HCO_3^-]	P_{CO_2} = 15 mm Hg
Metabolic alkalosis	Gain of HCO_3^- or loss of H^+ (↑ HCO_3^-)	↑	Alveolar hypoventilation to ↓ pulmonary CO_2 excretion (↑ P_{CO_2})	P_{CO_2} = +0.6 mm Hg for Δ[HCO_3^-] of 1 mEq/L. P_{CO_2} = 15 + [HCO_3^-]	P_{CO_2} = 55 mm Hg

From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier. Adapted and updated from Bidani A, Tauzon DM, Heming TA. Regulation of whole body acid-base balance. In DuBose TD, Hamm LL (eds): *Acid base and electrolytes disorders: a companion to Brenner and Rector's the kidney,* Philadelphia, 2002, WB Saunders, p. 1-21.

TABLE 4 Patterns of Serum Levels of Adrenocorticotropic Hormone (ACTH) and Cortisol in Different Adrenal Gland Conditions

Condition	Cortisol	ACTH	Dexamethasone Suppression, Low Dose	Dexamethasone Suppression, High Dose	Site of Disease
Normal adrenal	Normal	Normal	N/A	N/A	None
Primary hypoadrenalism	Low	High	N/A	N/A	Adrenal gland
Secondary hypoadrenalism	Low	Low	N/A	N/A	Pituitary
Primary hyperadrenalism—high cortisol, low ACTH	High	Low	N/A	N/A	Adrenal
Primary hyperadrenalism—high cortisol, borderline low ACTH	High	Borderline low	Positive	N/A	Adrenal
Primary hyperadrenalism due to adrenal hyperplasia—high cortisol, borderline low ACTH	High	Borderline low	Negative	Positive	Adrenal
Primary hyperadrenalism due to adrenal adenoma/carcinoma—high cortisol, borderline low ACTH	High	Borderline low	Negative	Negative	Adrenal
Secondary hyperadrenalism	High	High	N/A	N/A	Pituitary

From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

ALBUMIN (serum)

Normal range: 4 to 6 g/dl (40 to 60 g/L [CF:10; SMI: 1 g/L])
Elevated in: Dehydration (relative increase)
Decreased in: Liver disease, nephrotic syndrome, poor nutritional status, rapid IV hydration, protein-losing enteropathies (e.g., inflammatory bowel disease), severe burns, neoplasia, chronic inflammatory diseases, pregnancy, oral contraceptives, prolonged immobilization, lymphomas, hypervitaminosis A, chronic glomerulonephritis

ALCOHOL DEHYDROGENASE

Normal: 0 to 7 U/L
Elevated in: Drug-induced hepatocellular damage, obstructive jaundice, malignancy, inflammation, infection

ALDOLASE (serum)

Normal range: 0 to 6 U/L (0 to 100 nkat/L [CF: 16.67; SMI: 20 nkat/L])
Elevated in: Muscular dystrophy, rhabdomyolysis, dermatomyositis/polymyositis, trichinosis, acute hepatitis and other liver diseases, myocardial infarction, prostatic carcinoma, hemorrhagic pancreatitis, gangrene, delirium tremens, burns
Decreased in: Loss of muscle mass, late stages of muscular dystrophy

ALDOSTERONE

Normal range:
Recumbent: 50 to 150 ng/L
Upright: 150 to 300 ng/L
(Highest levels in neonates, decreasing over time to adult levels). The normal renin-angiotensin-aldosterone axis is illustrated in Fig. 2.
Elevated in: Primary aldosteronism, secondary aldosteronism, pseudoprimary aldosteronism. Table 6 differentiates the various causes of hyperaldosteronism.
Decreased in: Patient with hypertension: Diabetes mellitus, Turner syndrome, acute alcohol intoxication, excess secretion of deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone

Patient without hypertension: Addison disease, hypoaldosteronism resulting from renin deficiency, isolated aldosterone deficiency. Table 7 differentiates the various causes of hypoaldosteronism.

ALKALINE PHOSPHATASE (ALP) (serum)

See Fig. 3 for investigating a raised ALP in general practice.
See Fig. E4 for approach to elevated ALP.

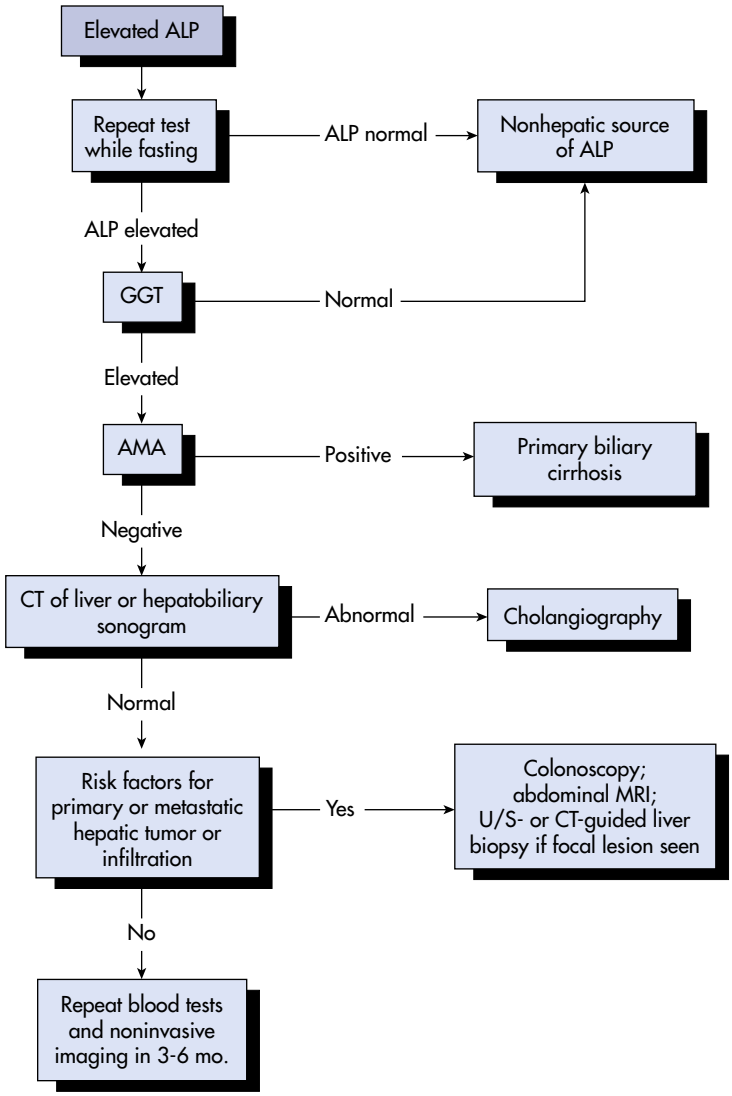


FIG. E4 Approach to the asymptomatic patient with isolated elevated levels of serum alkaline phosphatase *(ALP)*. *AMA,* Antimitochondrial antibody; *CT,* computed tomography; *GGT,* g-glutamyl transpeptidase; *MRI,* magnetic resonance imaging; *U/S,* ultrasonography. (Modified from Goldman L, Ausiello D [eds]: *Cecil textbook of medicine*, ed 24, Philadelphia, 2012, WB Saunders.)

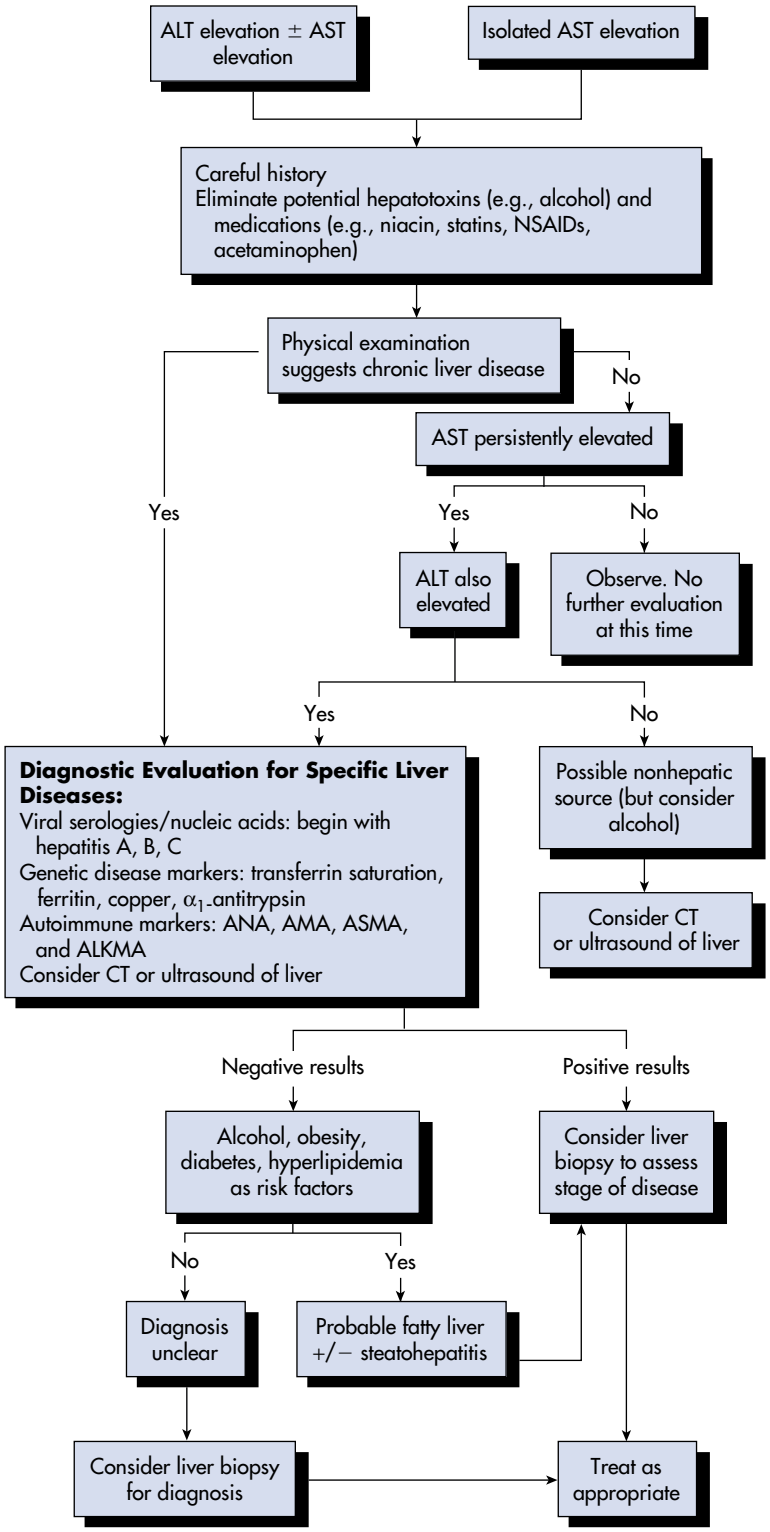


FIG. 1 Approach to the evaluation of isolated elevated levels of serum alanine aminotransferase *(ALT)* and/or aspartate aminotransferase *(AST)* in the asymptomatic patient. *ALKMA,* Anti-liver/kidney microsomal antibody; *AMA*, antimitochondrial antibody; *ANA,* antinuclear antibody; *ASMA,* anti-smooth muscle antibody; *CT,* computed tomography; *NSAIDs,* nonsteroidal antiinflammatory drugs. (Modified from Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, WB Saunders.)

TABLE 5 Six Fundamental Patterns of Liver Function Tests

Condition	AST	ALT	LD	AP	TP	Albumin	Bilirubin	Ammonia
1. Hepatitis	H	H	H	H	N	N	H	N
2. Cirrhosis	N	N	N	N-sl H	L	L	H	H
3. Biliary obstruction	N	N	N	H	N	N	H	N
4. Space-occupying lesion	N or H	N or H	H	H	N	N	N-H	N
5. Passive congestion	Sl H	sl H	sl H	N-sl H	N	N	N-sl H	N
6. Fulminant failure	Very H	H	H	H	L	L	H	H

ALT, Alanine aminotransferase; *AP,* alkaline phosphatase; *AST,* aspartate aminotransferase; *H,* high; *L,* low; *LD,* lactate dehydrogenase; *N,* normal; *sl,* slightly; *TP,* total protein.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, St Louis, 2017, Elsevier.

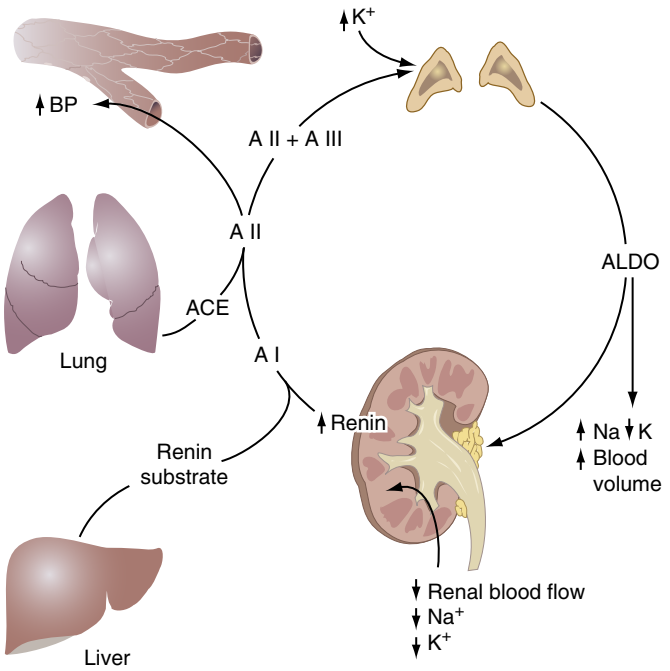


FIG. 2 The normal renin-angiotensin-aldosterone axis. Renin, secreted by the kidney, cleaves angiotensin I from renin substrate (angiotensinogen) produced by the liver. Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme *(ACE)* mainly in the lung. Angiotensin II increases peripheral vascular resistance and, together with angiotensin III, stimulates aldosterone *(ALDO)* secretion, which results in sodium retention and increased plasma volume. (Adapted from Stewart PM: The adrenal cortex. In Larsen PR et al [eds]: *Williams textbook of endocrinology,* ed 10, Philadelphia, 2003, WB Saunders, p 499. McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, St Louis, 2017, Elsevier.)

TABLE 6 Differentiating the Various Causes of Hyperaldosteronism

Disorder	Aldosterone	Renin	Serum K^+
Primary hyperaldosteronism	↑	↓	↓
Renin-secreting tumor	↑	↑	↓—N
Dexamethasone-suppressible hyperaldosteronism	↑	↓	↓
Renovascular hypertension	N—↑	N—↑	↓—N
Bartter syndrome	↑	↑	↓
Diuretics, congestive heart failure, cirrhosis, nephrotic syndrome	↑	↑	N—↓

N, Normal.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

TABLE 7 Differentiating the Various Causes of Hypoaldosteronism

Disorder	Aldosterone	Renin	Serum K^+
Addison disease	↓	↑	↑
Cushing syndrome	↓	↓	N or ↓
Liddle syndrome	↓	↓	↓
Hyporeninemic hypoaldosteronism	↓	↓	↑
Apparent mineralocorticoid excess	↓	↓	↓
Isolated hypoaldosteronism	↓	↑	↑

N, Normal.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

Normal range: 30 to 120 U/L (0.5 to 2 μkat/L [CF:0.01667; SMI: 0.1 μkat/L])

Elevated in

LIVER AND BILIARY TRACT ORIGIN.
Extrahepatic bile duct obstruction
Intrahepatic biliary obstruction
Liver cell acute injury
Liver passive congestion
Drug-induced liver cell dysfunction
Space-occupying lesions
Primary biliary cirrhosis
Sepsis
BONE ORIGIN (OSTEOBLAST HYPERACTIVITY).
Physiologic (rapid) bone growth (childhood and adolescence)
Metastatic tumor with osteoblastic reaction
Fracture healing
Paget disease of bone
CAPILLARY ENDOTHELIAL ORIGIN.
Granulation tissue formation (active)
PLACENTAL ORIGIN.
Pregnancy
Some parenteral albumin preparations

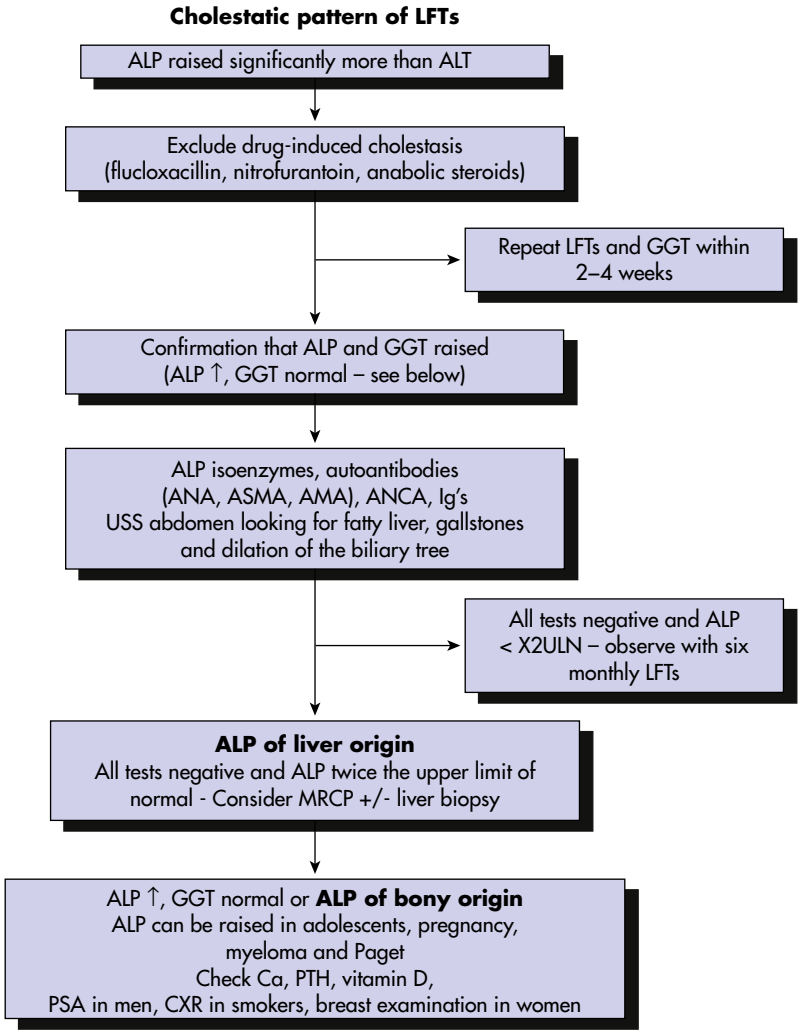


FIG. 3 Investigating a raised ALP in general practice. *ALP,* Alkaline phosphatase; *ALT,* alanine transaminase; *AMA,* antimitochondrial antibody; *ANA,* antinuclear antibody; *ANCA,* antineutrophil cytoplasmic antibody; *ASMA,* anti-smooth muscle antibody; *CXR,* chest x-ray; *GGT,* γ-glutamyl transpeptidase; *Ig,* immunoglobulin; *LFT,* liver function test; *MRCP,* magnetic resonance cholangiopancreatography; *PSA,* prostate-specific antigen; *PTH,* parathyroid hormone; *USS,* ultrasound scan. (From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.)

OTHER
Thyrotoxicosis
Benign transient hyperphosphatasemia
Primary hyperparathyroidism
Decreased in: Hypothyroidism, pernicious anemia, hypophosphatemia, hypervitaminosis D, malnutrition

ALPHA-1-ANTITRYPSIN (serum)
Normal range: 110 to 140 mg/dl
Decreased in: Homozygous or heterozygous deficiency

ALPHA-1-FETOPROTEIN (serum)
See α-1 FETOPROTEIN

ALT
See ALANINE AMINOTRANSFERASE

ALUMINUM (serum)
Normal range: 0 to 6 ng/ml
Elevated in: Chronic renal failure on dialysis, parenteral nutrition, industrial exposure

AMA
See ANTIMITOCHONDRIAL ANTIBODY

AMEBIASIS SEROLOGIC TEST
Test description: Test is used to support diagnosis of amebiasis caused by *Entamoeba histolytica*. Serum acute and convalescent titers are drawn 1 to 3 wk apart. A fourfold increase in titer is the most indicative result.

AMINOLEVULINIC ACID (δ-ALA) (24-hr urine collection)
Normal: 1.5 to 7.5 mg/day
Elevated in: Acute porphyrias, lead poisoning, DKA, pregnancy, anticonvulsant drugs, hereditary tyrosinemia
Decreased in: Alcoholic liver disease

AMMONIA (serum)
See Box 1 for differential diagnosis of hyperammonemia.

BOX 1 Differential Diagnosis of Hyperammonemia

- Acute liver failure
- Chronic kidney disease
- Cigarette smoking
- Cirrhosis
- GI bleeding
- Inborn errors of metabolism
  - Proline metabolism disorders
  - Urea cycle defects (e.g., carbamoyl phosphate synthetase I deficiency, ornithine transcarbamylase deficiency, arginino-succinate lyase deficiency, *N*-acetylglutamate synthetase deficiency)
- Medications/toxins
  - Alcohol
  - Diuretics (e.g., acetazolamide)
  - Narcotics
  - Valproic acid
- Muscle exertion and ischemia
- Portosystemic shunts
- Technique and conditions of blood sampling
  - High body temperature
  - High-protein diet
- Tourniquet use

GI, Gastrointestinal.
From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

See Fig. E5 for approach to hyperammonemia in pediatric patients.
Normal range: 10 to 80 μg/dl (5 to 50 μmol/L [CF: 0.5872; SMI: 5 μmol/L])
Elevated in: Hepatic failure, hepatic encephalopathy, Reye syndrome, portacaval shunt, drugs (diuretics, polymyxin B, methicillin)
Decreased in: Drugs (neomycin, lactulose, tetracycline), renal failure

AMYLASE (serum)

Normal range: 0 to 130 U/L (0 to 2.17 μkat/L [CF: 0.01667; SMI: 0.01 μkat/L])
Elevated in: Acute pancreatitis, pancreatic neoplasm, abscess, pseudocyst, ascites, macroamylasemia, perforated peptic ulcer, intestinal obstruction, intestinal infarction, acute cholecystitis, appendicitis, ruptured ectopic pregnancy, salivary gland inflammation, peritonitis, burns, diabetic ketoacidosis, renal insufficiency, drugs (morphine), carcinomatosis (of lung, esophagus, ovary), acute ethanol ingestion, mumps, prostate tumors, post-endoscopic retrograde cholangiopancreatography, bulimia, anorexia nervosa (Table 8)
Decreased in: Advanced chronic pancreatitis, hepatic necrosis, cystic fibrosis

AMYLASE, URINE

See URINE AMYLASE

AMYLOID A PROTEIN (serum)

Normal: <10 mcg/ml
Elevated in: Inflammatory disorders (acute phase-reacting protein), infections, acute coronary syndrome, malignancies

ANA

See ANTINUCLEAR ANTIBODY

ANCA

See ANTINEUTROPHIL CYTOPLASMIC ANTIBODY

ANDROSTENEDIONE (serum)

Normal:
Male: 75 to 205 ng/dl
Female: 85 to 275 ng/dl
Elevated in: Congenital adrenal hyperplasia, polycystic ovary syndrome, ectopic ACTH-producing tumor, Cushing syndrome, hirsutism, hyperplasia of ovarian stroma, ovarian neoplasm
Decreased in: Ovarian failure, adrenal failure, sickle cell anemia

ANGIOTENSIN II

Normal: 10 to 60 pg/ml

TABLE 8 Differential Diagnosis of Hyperamylasemia

Pancreatic Pathology
- Acute or chronic pancreatitis
- Complications of pancreatitis (pseudocyst, ascites, abscess)
- Factitious pancreatitis

Salivary Gland Pathology
- Parotitis (mumps, *Staphylococcus aureus*, cytomegalovirus, HIV, Epstein-Barr virus)
- Sialadenitis (calculus, radiation)
- Eating disorders (anorexia nervosa, bulimia)

Intraabdominal Pathology
- Biliary tract disease (cholelithiasis)
- Peptic ulcer perforation
- Peritonitis
- Intestinal obstruction
- Appendicitis

Systemic Diseases
- Metabolic acidosis (diabetes mellitus, shock)
- Renal insufficiency, transplantation
- Burns
- Pregnancy
- Drugs (morphine)
- Head injury
- Cardiopulmonary bypass

HIV, Human immunodeficiency virus.
From Kliegman RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

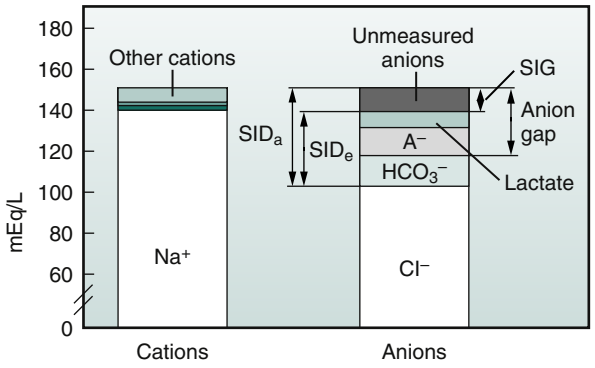


FIG. 6 Charge balance in blood plasma. "Other cations" include Ca2+ and Mg2+. The strong ion difference (SID) is always positive (in plasma) and SID minus effective SID (SIDe) must equal 0. Any difference between SID apparent (SIDa) and SIDe is the strong ion gap (SIG) and must represent unmeasured anions. *A–,* Concentration of dissociated weak acids; *HCO_3–,* bicarbonate. (From Ronco C: *Critical care nephrology*, ed 3, Philadelphia, 2019, Elsevier.)

Elevated in: Hypertension, congestive heart failure (CHF), cirrhosis, renin-secreting renal tumor, volume depletion
Decreased in: ACE inhibitor drugs, angiotensin-converting enzyme inhibitor (ARB) drugs, primary aldosteronism, Cushing syndrome

ANGIOTENSIN-CONVERTING ENZYME (ACE level)

Normal range: <40 nmol/ml/min (<670 nkat/L [CF: 16.67; SMI: 10 nkat/L])
Elevated in: Sarcoidosis, primary biliary cirrhosis, alcoholic liver disease, hyperthyroidism, hyperparathyroidism, diabetes mellitus, amyloidosis, multiple myeloma, lung disease (asbestosis, silicosis, berylliosis, allergic alveolitis, coccidioidomycosis), Gaucher disease, leprosy

ANH

See ATRIAL NATRIURETIC HORMONE

ANION GAP (AG)

The AG is the net change difference between the cations Na^+, K^+, and the anions Cl^- and HCO_3–
See Fig. 6 for charge balance in blood plasma.
See Tables 9, 10, 11.

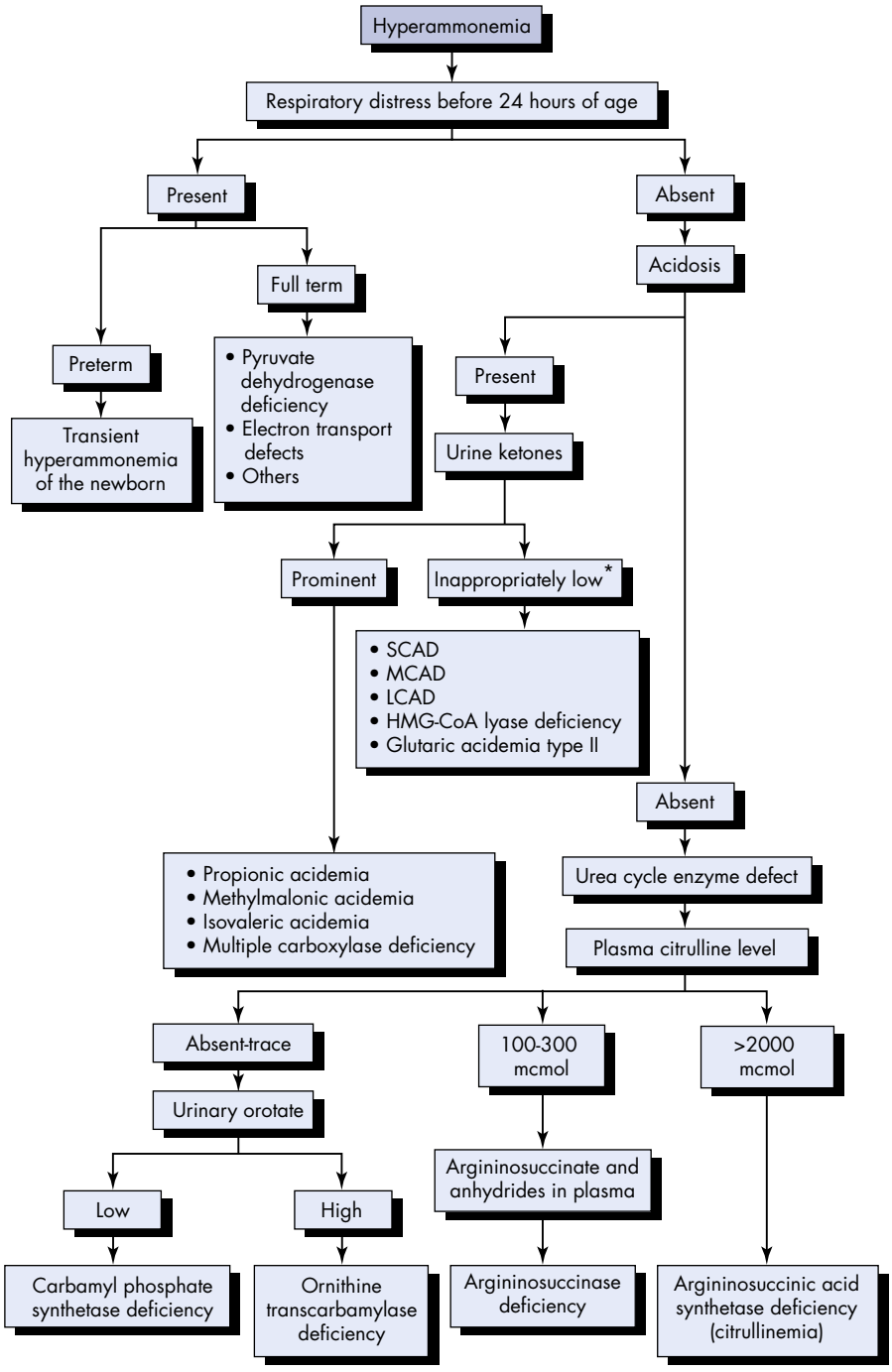


FIG. E5 Differential diagnosis of hyperammonemia. *Indicates inappropriately low urinary ketones in settling of symptomatic hypoglycemia. *HMG-CoA,* Hydroxymethylglutaryl-CoA; *LCAD,* long-chain acyl-CoA dehydrogenase; *MCAD,* medium-chain acyl-CoA dehydrogenase; *SCAD,* short-chain acyl-CoA dehydrogenase. (From Custer JW, Rau RE: *The Harriet Lane handbook,* ed 18, St Louis, 2009, Mosby.)

TABLE 9 Equations Used to Estimate the Quantity of Unmeasured Ions

Anion gap (AG)	$(Na^+ + K^+) - (Cl^- + HCO_3^-)$	Normal values: 12 ± mEq/L (with K^+) 8 ± 4 mEq/L (without K^+)
Connected anion gap (cAG)	$(Na^+ + K^+) - (Cl^- + HCO_3^- + 2[albumin\ g/dl] + 0.5[phosphate\ mg/dl] + lactate)$ SI (all units mEq/L): $(Na^+ + K^+) - (Cl^- + HCO_3^- + 0.2[albumin\ g/L] + 1.5[phosphate\ mmol/L] + lactate)$	Normal values: 0 ± 5 mEq/L
Apparent strong ion difference (SID_a)	$(Na^+ + K^+ + Ca^{2+} + Mg^{2+}) - (Cl^- + lactate)$	The difference between measured strong cations and anions. Concentrations should be expressed in mEq/L (Ca^{2+} and Mg^{2+} multiplied by 2 from mmol/L).
Effective strong ion difference (SID_e)	$(HCO_3^- + [\text{albumin g/dl}] \times (0.123 \times pH - 0.631) + [PO^2{-}_4] \times (0.39 \times pH - 0.469)$	
Strong ion gap (SIG)	$SID_a - SID_e$	Should theoretically approach 0, but is normally 5 (±5) in critically ill patients
$\Delta AG/\Delta HCO_3^-$ (delta ratio)	$(cAG - cAG_{normal})/(24 - HCO_3^-)$	Normal values 0.8 to 1.6
Osmolar gap	$Measured\ osmolality - ([1.86 \times Na^+] + glucose\ mg/dl/18 + BUN\ mg/dl/2.8 + ethanol\ mg/dl/4.6)$ SI (all units mmol/L): $measured\ osmolality - ([1.86 \times Na^+] + glucose + urea + 1.25 \times ethanol)$	Normally ≤ 19 mmol/L

BUN, Blood urea nitrogen; *SI,* strong ion.
From Ronco C et al: *Critical care nephrology*, ed 3, Philadelphia, 2019, Elsevier.

Normal range: 9 to 14 mEq/L
Elevated in: Lactic acidosis, ketoacidosis (diabetes, alcoholic starvation), uremia (chronic renal failure), ingestion of toxins (paraldehyde, methanol, salicylates, ethylene glycol), hyperosmolar nonketotic coma, antibiotics (carbenicillin)
Decreased in: Hypoalbuminemia, severe hypermagnesemia, IgG myeloma, lithium toxicity, laboratory error (falsely decreased sodium or overestimation of bicarbonate or chloride), hypercalcemia of parathyroid origin, antibiotics (e.g., polymyxin)

ANTICARDIOLIPIN ANTIBODY (ACA)

Normal range: Negative. Test includes detection of IgG, IgM, and IgA antibodies to phospholipid, cardiolipin
Present in: Antiphospholipid antibody syndrome, chronic hepatitis C

ANTICOAGULANT

See CIRCULATING ANTICOAGULANT

ANTIDIURETIC HORMONE

Normal range: mOsm/kg 295 to 300 (4 to 12 pg/ml)
Elevated in: SIADH, antipsychotic medications, ectopic ADH from systemic neoplasm, Guillain-Barré syndrome, CNS infections, brain tumors, nephrogenic diabetes insipidus

TABLE 10 Causes of Increased Anion Gap or Strong Ion Gap

Common causes	Lactic acidosis*
	L-lactate (hypoxic and nonhypoxic)
	D-lactate (in short bowel syndrome)
	Renal failure
	Ketoacidosis
	Diabetic
	Alcoholic
	Starvation
	Metabolic errors
	Toxins
	Methanol
	Ethylene and propylene glycol
	Salicylates
	5-oxoproline (pyroglutamic acid)
	Sepsis
Rare causes	Severe liver disease
	Sodium salts
	Sodium lactate
	Sodium citrate
	Sodium acetate
	Sodium penicillin (>50 million units/day)
	Carbenicillin (>30 g/day)
	Decreased unmeasured cations
	Hypomagnesemia
	Hypocalcemia
	Massive rhabdomyolysis
	Alkalemia

*Lactate, Mg^{2+}, and Ca^{2+} are accounted for in the strong ion gap.
From Ronco C: *Critical care nephrology*, ed 3, Philadelphia, 2019, Elsevier.

TABLE 11 Causes of Normal Anion Gap or Strong Ion Gap Acidosis

Nonrenal causes: Urine SID (Na + K − Cl) < 0	Low SID infusions (e.g., normal saline)
	Strong cation (or HCO_3^-) losses though diarrhea
	Ureteral diversions
	Biliary or pancreatic fistulas
Renal causes: Urine SID (Na + K − Cl) >0	Type 1 (distal) RTA
	Type 2 (proximal) RTA
	Type 4 (hypoaldosteronism) RTA

RTA, Renal tubular acidosis; *SID,* strong ion difference.
From Ronco C: *Critical care nephrology*, ed 3, Philadelphia, 2019, Elsevier.

Decreased in: Central diabetes insipidus, nephritic syndrome, psychogenic polydipsias, demeclocycline, lithium, phenytoin, alcohol. Table 12 describes the water deprivation test used for diagnosing and classifying diabetes insipidus. Table 13 summarizes tests in the differential diagnosis of water homeostasis. Causes of polyuria due to water diuresis are described in Box 2.

ANTI-DNA

Normal range: Absent
Present in: Systemic lupus erythematosus, chronic active hepatitis, infectious mononucleosis, biliary cirrhosis

ANTI-DS DNA

Normal: <25 U
Elevated in: Systemic lupus erythematosus

ANTIGLOBULIN TEST

See DIRECT ANTIGLOBULIN (COOMBS DIRECT)
See INDIRECT ANTIGLOBULIN (COOMBS INDIRECT)

ANTIGLOMERULAR BASEMENT ANTIBODY

See GLOMERULAR BASEMENT MEMBRANE ANTIBODY

ANTIHISTONE

Normal: <1 U

TABLE 12 Water Deprivation Test for Diagnosing and Classifying Diabetes Insipidus

Patients with mild polyuria may be instructed to withhold all fluid intake from 10 P.M. onward. For those with more severe polyuria (8 to 10 L/day), water deprivation should be started early in the morning under close observation.

1. During testing, the patient is forbidden to take in anything by mouth.
2. Obtain the following baseline parameters: urine volume (Uvol) and urinary osmolality (Uosm), plasma osmolality (Posm), and plasma sodium (PNa). Also record the weight and blood pressure (BP)/pulse (P) seated and standing.
3. Urine and plasma are collected hourly for Uvol, Uosm, and Posm. Weight, BP, and P are also recorded. Record requests for fluid.
4. When the Uosm has plateaued (e.g., hourly increase <30 mOsm/kg for 3 consecutive hours), or when body weight has decreased by 3%-5%, or the patient develops a >20-mm Hg drop in systolic BP, obtain samples for Uvol, Uosm, Posm, PNa, and AVP (plasma).
5. Administer 1 mcg of desmopressin IV or IM, or 5 mcg of AVP SC Uosm; urine output and Posm are recorded at 30, 60, and 120 min after the injection. The highest Uosm value is used to evaluate the patient's response to AVP.

Precautions

When possible, discontinue any medications that can influence ADH secretion. Observe for hypotension and nausea, which may stimulate ADH secretion. The patient should not be permitted to smoke during the test.

Interpretation

Normal	Final Uosm before AVP challenge is higher than Posm. Following AVP challenge, the Uosm is less than 10% higher than the maximal Uosm achieved with water restriction alone.
Neurogenic DI	Final Uosm before AVP challenge is less than Posm. Following AVP administration, there is a greater than 50% increase in Uosm.
Nephrogenic DI	Final Uosm before AVP challenge is less than Posm. Following AVP administration, there is a less than 10% increase in Uosm.
Partial central DI	Uosm may be higher than Posm following dehydration; however, there is only a 10%-50% increase in Uosm following administration of AVP.
Partial nephrogenic DI	Uosm may be higher than Posm following dehydration; however, there is a greater than 10% increase in Uosm following administration of AVP.

Plotting basal and postdehydration Uosm and plasma ADH on the nomograms from Zerbe and Robertson will permit further distinction between partial nephrogenic DI, partial central DI, and primary polydipsia

ADH, Antidiuretic hormone; *AVP,* arginine vasopressin; *DI,* diabetes insipidus; *IM,* intramuscular; *IV,* intravenous; *SC,* subcutaneous.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

TABLE 13 Tests in the Differential Diagnosis of Disorders of Water Homeostasis

	BASELINE			AFTER 12-HOUR FLUID RESTRICTION			
Disorder	**Serum Na+ and Osmolality**	**Urine Na+ and Osmolality**	**Serum ADH**	**Serum Na+ and Osmolality**	**Urine Na+ and Osmolality**	**Serum ADH**	**Urine Osmolality Post-AVP Challenge**
Normal control	N	N	N	N	High	High	Same
SIADH	Low	N-High	High	Low-N	High	High	—
Neurogenic DI	N-High	Low	Low	High	Low-N	Low	Increased
Nephrogenic DI	N-High	Low	N-High	High	Low-N	High	Same
Psychogenic polydipsia	Low-N	Low	Low	N	N-High	N-High	Same

ADH, Antidiuretic hormone; *AVP,* arginine vasopressin; *DI,* diabetes insipidus; *N,* normal; *SIADH,* syndrome of inappropriate secretion of ADH.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, St Louis, 2017, Elsevier.

Elevated in: Drug-induced lupus erythematosus

ANTIMITOCHONDRIAL ANTIBODY (AMA, Mitochondrial antibody)

Normal range: <1:20 titer
Elevated in: Primary biliary cirrhosis (85% to 95%), chronic active hepatitis (25% to 30%), cryptogenic cirrhosis (25% to 30%)

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY (ANCA)

Positive test: Cytoplasmic pattern (c-ANCA): Positive in granulomatosis with polyangiitis (see Fig. E7 and Table E14 for approach to patient with positive c-ANCA)

Perinuclear pattern (p-ANCA): Positive in inflammatory bowel disease, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune chronic active hepatitis, crescentic glomerulonephritis (see Table E14 for approach to patient with positive p-ANCA)

BOX 2 Causes of Polyuria Due to Water Diuresis

Lack of ADH
Central diabetes insipidus (DI): Congenital or acquired (idiopathic cell degeneration, tumors and granulomas, surgery, trauma, infarction, and infection of the pituitary gland or hypothalamus)
Dipsogenic: Psychogenic, organic brain disease, iatrogenic
Gestational DI: Excess vasopressinase

Failure of the Kidney to Respond to ADH (Nephrogenic DI)
Congenital nephrogenic DI: A defect in ADH receptor, a defect in aquaporin expression.
Chronic renal failure.
Acquired nephrogenic DI: Lithium toxicity, demeclocycline toxicity, methoxyflurane toxicity, amyloidosis, light chain nephropathy, hypercalcemia, hypokalemia, obstructive uropathy

ADH, Antidiuretic hormone.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

* Some patients also have gastrointestinal, cardiac, and/or neurologic involvement
† Granulomatous inflammation
‡ Of skin, mucosa, respiratory tract (upper/lower), or kidney

FIG. E7 Approach to the patient with perinuclear antineutrophil cytoplasmic antibodies *(P-ANCA).* (Courtesy of Julie V Schaffer, MD. From Bolognia JL, Jorizzo JL, Rapini RP: *Dermatology*, St Louis, 2003, Mosby.)

TABLE E14 Other Disorders Associated with Antineutrophil Cytoplasmic Antibodies (ANCA)

	Type of ANCA*	Major Antigen(s)**	Evaluation
Inflammatory bowel disease: Ulcerative colitis (50%-70%) >Crohn disease (20%-40%)	P >C	Catalase, BPI, α-enolase, LF, CG, HMG1/2>MPO, PR3	Colonoscopy
Autoimmune liver disease: Autoimmune hepatitis (type 1; 80%), primary sclerosing cholangitis (70%) >primary biliary cirrhosis (30%)	P >C	Actin, HMG1/2	LFTs; ANA; antismooth muscle Ab; antimitochondrial Ab
Connective tissue disease: Systemic lupus erythematosus (20%-30%), rheumatoid arthritis (20%-30%) >Sjögren syndrome, dermatomyositis, reactive arthritis, relapsing polychondritis, antiphospholipid syndrome	P >C	MPO, PR3, BPI, CG, LF, lysozyme, HMG1/2	ANA panel; RF; anticardiolipin Ab
Drug-induced vasculitis/lupus/hepatitis: Propylthiouracil (20%), minocycline >levamisole, sulfasalazine Hydralazine, penicillamine >allopurinol† High-dose intravenous immunoglobulin	P >C P C	MPO>PR3, elastase MPO, elastase	Skin biopsy, ANA panel; LFTs; discontinue drug
Other cutaneous and/or systemic vasculitides:‡ Mixed cryoglobulinemia, Behçet disease, paraneoplastic Henoch-Schönlein purpura, Buerger disease	P >C P	Variable	Skin biopsy; cryoglobulins; hepatitis B, C panels; exclude malignancy
Other glomerulonephritides: Anti-GBM Ab-associated (30%) >immune complex (15%) >poststreptococcal	P	MPO	UA; BUN/creatinine; ASO; renal biopsy
Infections: Respiratory tract infections (bacterial/mycobacterial/fungal), enteritis, periodontitis, HIV, parvovirus B19, malaria, leprosy Onchocerciasis: Subacute bacterial endocarditis, chromomycosis, invasive amebiasis	P, C P C	MPO, others Defensin PR3	Cultures; serologies; echocardiogram
Cystic fibrosis (80%)	C >P	BPI	Sweat test
Hypergammaglobulinemia	P, C	—	Serum protein electrophoresis

Ab, Antibodies; *ANA,* antinuclear antibodies; *ASO,* antistreptolysin O; *BUN,* blood urea nitrogen; *C,* cytoplasmic [c-ANCA or c-ANCA (atypical)]; *HIV,* human immunodeficiency virus; *GBM,* glomerular basement membrane; *LFTs,* liver function tests; *P,* perinuclear [P-ANCA]; *RF,* rheumatoid factor; *UA,* urinalysis.

*C-ANCA are often atypical; in addition, immunofluorescence testing in some laboratories may not distinguish c-ANCA (atypical) from atypical ANCA.

**P-ANCA often have antigen specificity other than myeloperoxidase (MPO), e.g., lactoferrin (LF), elastase, cathepsin G (CG), lysozyme, bactericidal/permeability-increasing protein (BPI), high mobility group non-histone chromosomal proteins (HMG1/2), α-enolase, catalase, actin, defensin; c-ANCA (atypical) have antigen specificity other than proteinase 3 (PR3), e.g., BPI, lysozyme, or multiple antigens.

†Other drugs associated with P-ANCA in single case reports include cimetidine, cefotaxime, phenytoin, and isotretinoin.

‡Although primarily associated with c-ANCA, 5% to 15% of patients with granulomatosis with polyangiitis have P-ANCA; likewise, although primarily associated with P-ANCA, 5% to 15% of patients with Churg-Strauss syndrome and >40% of those with microscopic polyangiitis have c-ANCA; ANCA have also been reported in leukocytoclastic vasculitis of unknown etiology and unclassified vasculitis.

(Courtesy of Julie V Schaffer, MD).

TABLE 15 Frequency of Antinuclear Antibodies in Autoimmune and Nonrheumatic Diseases

	Sensitivity (%)
Autoimmune disease	
Systemic lupus erythematosus	95-100
Systemic sclerosis	60-80
Mixed connective tissue disease	100
Polymyositis or dermatomyositis	60
Rheumatoid arthritis	50
Rheumatoid vasculitis	30-50
Sjögren syndrome	40-70
Drug-induced lupus	90
Discoid lupus	15
Pauciarticular juvenile chronic arthritis	70
Nonrheumatic diseases	
Hashimoto thyroiditis	45
Graves disease	50
Autoimmune hepatitis	50
Primary pulmonary hypertension	40

From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.

ANTINUCLEAR ANTIBODY (ANA)

Fig. E8 describes an algorithm for the use of antinuclear antibodies in the diagnosis of connective tissue disorders. See Fig. E9 for approach to positive ANA pattern. Table 15 shows the frequency of antinuclear antibodies in autoimmune and nonrheumatic diseases.

Normal range: <1:20 titer

Positive test: Systemic lupus erythematosus (more significant if titer >1:160), drugs (phenytoin, ethosuximide, primidone, methyldopa, hydralazine, carbamazepine, penicillin, procainamide, chlorpromazine, griseofulvin, thiazides), chronic active hepatitis, autoimmune thyroid disease (positive ANA is found in up to 45% of patients), idiopathic thrombocytopenic purpura, multiple sclerosis, rheumatoid arthritis, scleroderma, mixed connective tissue disease, necrotizing vasculitis, Sjögren syndrome, tuberculosis, pulmonary interstitial fibrosis. Positive ANA results are nonspecific and can be found in healthy individuals (13.8% of the adult general population). Table 16 describes diseases associated with ANA subtypes. Fig. 10 illustrates various fluorescent ANA test patterns.

ANTI-RNP ANTIBODY

See EXTRACTABLE NUCLEAR ANTIGEN

ANTI-SCL-70

Normal: Absent

Elevated in: Scleroderma

ANTI-SM (anti-Smith) ANTIBODY

See EXTRACTABLE NUCLEAR ANTIGEN

ANTI-SMOOTH MUSCLE ANTIBODY

See SMOOTH MUSCLE ANTIBODY

ANTISTREPTOLYSIN O TITER (Streptozyme, ASLO titer)

Normal range for adults: <160 Todd units

Elevated in: Streptococcal upper airway infection, acute rheumatic fever, acute glomerulonephritis, increased levels of β-lipoprotein

NOTE: A fourfold increase in titer between acute and convalescent specimens is diagnostic of streptococcal upper airway infection regardless of the initial titer.

ANTITHROMBIN III

See Table 17.

Normal range: 81% to 120% of normal activity; 17 to 30 mg/dl

Decreased in: Hereditary deficiency of antithrombin III, disseminated intravascular coagulation, pulmonary embolism, cirrhosis, thrombolytic therapy, chronic liver failure, postsurgery, third trimester of pregnancy, oral contraceptives, nephrotic syndrome, IV heparin >3 days, sepsis, acute leukemia, carcinoma, thrombophlebitis

Elevated in: Warfarin drugs, postmyocardial infarction

TABLE 16 Disease-Associated Antinuclear Antibody Subtypes

Nuclear Location	Disease(s)
"Native" DNA (dsDNA, or dsDNA/ssDNA complex)	SLE (60%-70%; range, 35%-75%) Also PSS (5%-55%), MCTD (11%-25%), RA (5%-40%), DM (5%-25%), SS (5%)
sNP	SLE (50%) Also other collagen diseases
DNP (DNA-histone complex)	SLE (52%) Also MCTD (8%), RA (3%)
Histones	Drug-induced SLE (95%) Also SLE (30%), RA (15%-24%)
ENA Sm	SLE (30%-40%; range, 28%-40%) Also MCTD (0%-8%); RNP (U1-RNP) MCTD (in high titer without any other ANA subtype present: 95%-100%) Also SLE (26%-50%), PSS (11%-22%), RA (10%), SS (3%)
SS-A (Ro)*	SS without RA (60%-70%) Also SLE (26%-50%), neonatal SLE (over 95%), PSS (30%), MCTD (50%), SS with RA (9%), PBC (15%-19%)
SS-B (La)	SS without RA (40%-60%) Also SLE (5%-15%), SS with RA (5%)
Scl-70*	PSS (15%-43%)
Centromere*	CREST syndrome (70%-90%; range, 57%-96%) Also PSS (4%-20%), PBC (12%)
Nucleolar	PSS (scleroderma) (54%-90%) Also SLE (25%-26%), RA (9%)
RAP (RANA)	SS with RA (60%-76%) Also SS without RA (5%)
Jo-1	Polymyositis (30%)
PM-1	Polymyositis or PMS/PSS overlap syndrome (60%-90%) Also DM (17%)
ssDNA	SLE (60%-70%) Also CAH, infectious mononucleosis, RA, chronic GN, chronic infections, PBC
Cytoplasmic Location	Disease(s)
Mitochondrial	PBC (90%-100%) Also CAH (7%-30%), cryptogenic cirrhosis (30%), acute hepatitis, viral hepatitis (3%), other liver diseases (0%-20%), SLE (5%), SS and PSS (8%)
Microsomal†	Chronic active hepatitis (60%-80%), Hashimoto thyroiditis (97%)
Ribosomal	SLE (5%-12%)
Smooth muscle‡	Chronic active hepatitis (60%-91%)

ANA, Antinuclear antibody; *CAH,* chronic active hepatitis; *CREST,* calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia; *DM,* dermatomyositis; *GN,* glomerulonephritis; *MCTD,* mixed connective tissue disease; *MS,* multiple sclerosis; *PBC,* primary biliary cirrhosis; *PMS,* premenstrual syndrome; *PSS,* progressive systemic sclerosis; *RA,* rheumatoid arthritis; *RNP,* ribonucleoprotein; *SLE,* systemic lupus erythematosus; *SS,* Sjögren syndrome; *ssDNA,* single-stranded DNA.

*Not detected using rat or mouse liver or kidney tissue method.

†Not detected by cultured cell method.

‡Detected by cultured cells but better with rat or mouse tissue.

From Ravel R: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.

APOLIPOPROTEIN A-1 (Apo A-1)

Normal: Desirable >120 mg/dl

Elevated in: Familial hyperalphalipoproteinemia, statins, niacin, estrogens, weight loss, familial cholesteryl ester transfer protein (CETP) deficiency

Decreased in: Familial hypoalphalipoproteinemia, Tangier disease, diuretics, androgens, cigarette smoking, hepatocellular disorders, chronic renal failure, nephritic syndrome, coronary heart disease, cholestasis

APOLIPOPROTEIN B (Apo B)

Normal: Desirable <100 mg/dl; high risk >120 mg/dl

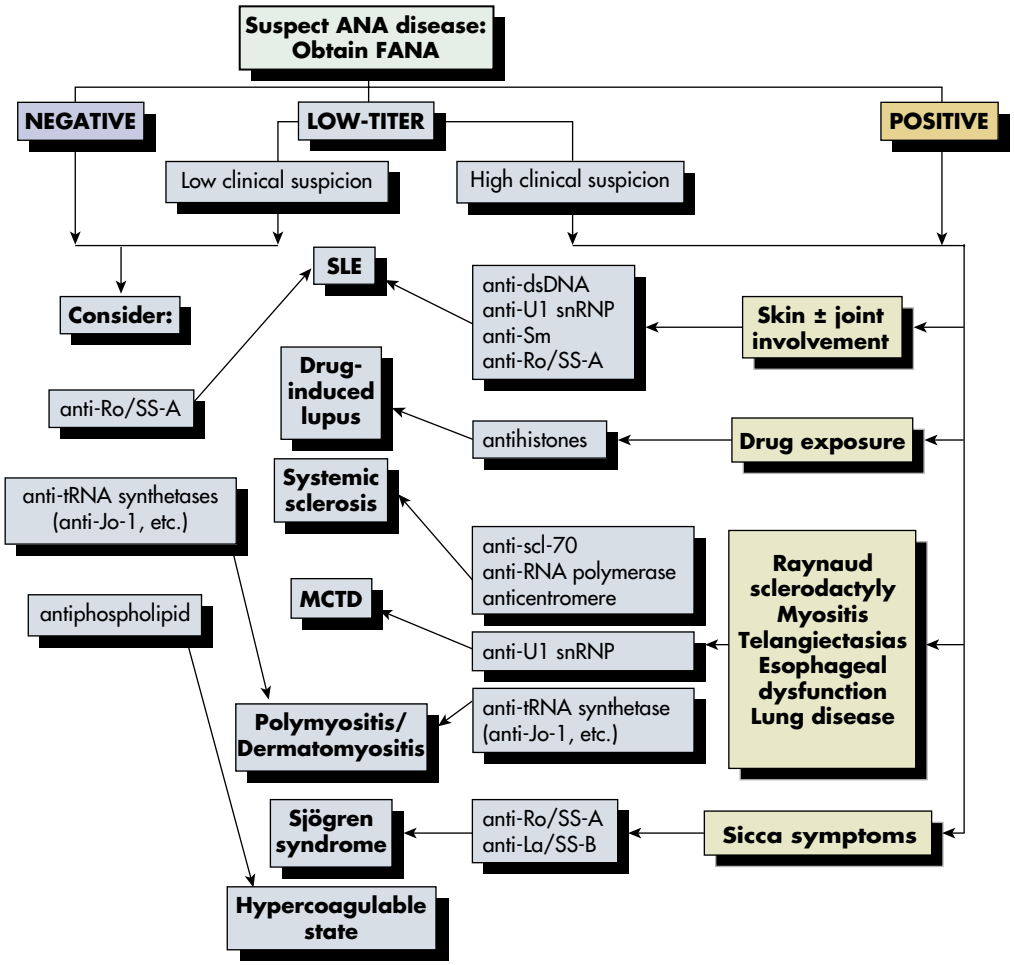


FIG. E8 Algorithm for the use of antinuclear antibodies in the diagnosis of connective tissue disorder. *ANA,* Antinuclear antibody; *FANA,* fluorescent antinuclear antibody; *MCTD,* mixed connective tissue disease; *SLE,* systemic lupus erythematosus. (From Firestein GS et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, WB Saunders.)

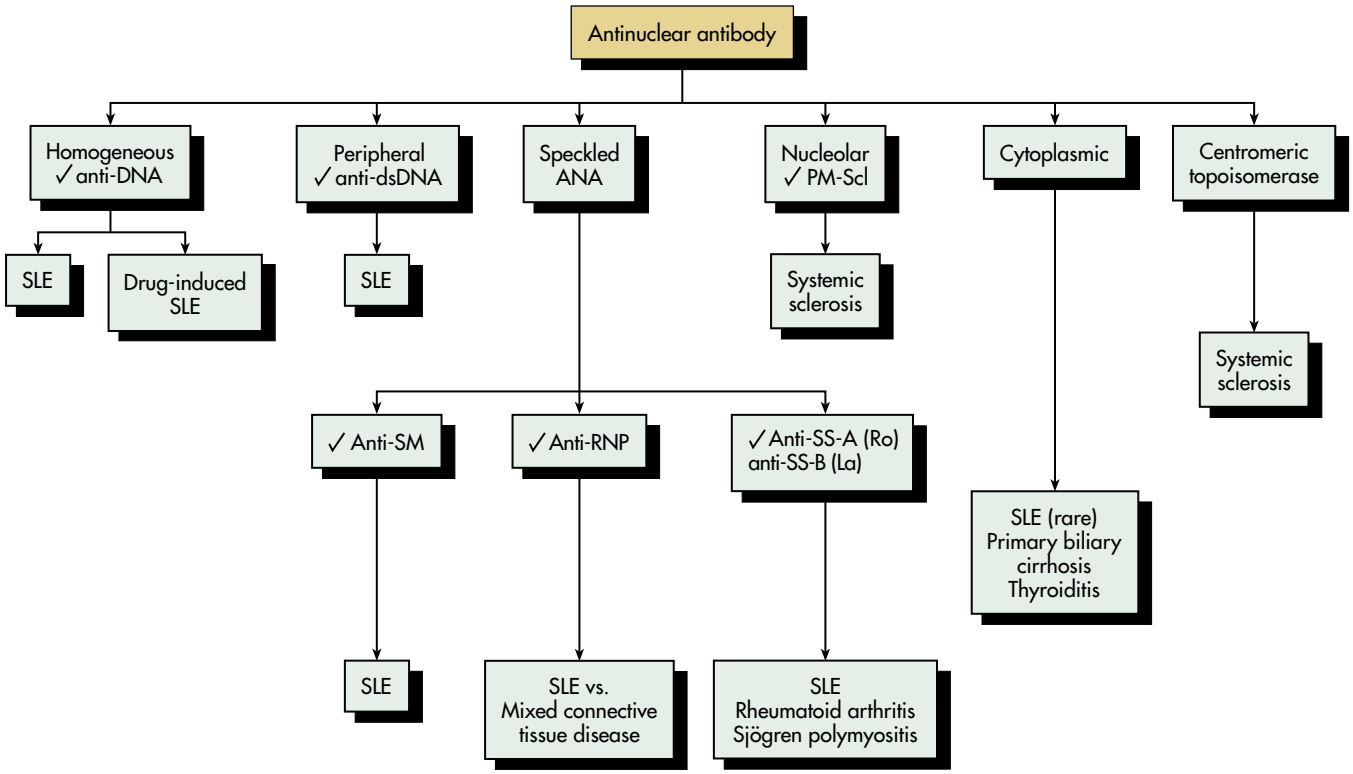


FIG. E9 Diagnostic tests and diagnoses to consider from antinuclear antibody pattern. *ANA,* Antinuclear antibody; *PM-Scl,* polymyositis/scleromyositis; *SLE,* systemic lupus erythematosus. (From Carlson KJ et al: *Primary care of women*, ed 2, St Louis, 2002, Mosby.)

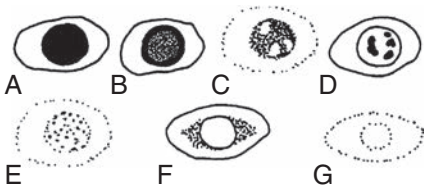


FIG. 10 Fluorescent antinuclear antibody test patterns (HEP-2 cells). A, Solid (homogeneous). **B,** Peripheral (rim). **C,** Speckled. **D,** Nucleolar. **E,** Anticentromere. **F,** Antimitochondrial. **G,** Normal (nonreactive). (From Ravel R [ed]: *Clinical laboratory medicine*, ed 6, St Louis, 1995, Mosby.)

TABLE 17 Assay Measurements in Heterozygous Antithrombin (ATIII) Deficiency for Diagnosis

	ACTIVITY		
Type	**Antigen**	**Heparin Cofactor**	**Progressive ATIII**
I	Low	Low	Low
II			
Active site defect	Normal	Low	Low
Heparin-binding site defect	Normal	Low	Normal

From Hoffman R et al: *Hematology: Basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

Elevated in: High saturated fat diet, high-cholesterol diet, hyperapobetalipoproteinemia, familial combined hyperlipidemia, anabolic steroids, diuretics, beta-blockers, corticosteroids, progestins, diabetes, hypothyroidism, chronic renal failure, liver disease, Cushing syndrome, coronary heart disease
Decreased in: Statins, niacin, low-cholesterol diet, malnutrition, abetalipoproteinemia, hypobetalipoproteinemia, hyperthyroidism

ARTERIAL BLOOD GASES

Normal range:
Po_2: 75 to 100 mm Hg
Pco_2: 35 to 45 mm Hg
HCO_3: 24 to 28 mEq/L
pH: 7.35 to 7.45
Abnormal values: Acid-base disturbances (see the following)
METABOLIC ACIDOSIS
Causes of metabolic acidosis by net acid excretion are summarized in Box 3.
Metabolic acidosis with increased AG (AG acidosis)
Lactic acidosis (see Box 4)
Ketoacidosis (diabetes mellitus, alcoholic ketoacidosis)
Uremia (chronic renal failure)
Ingestion of toxins (paraldehyde, methanol, salicylate, ethylene glycol)
High-fat diet (mild acidosis)

EXTRARENAL ACIDOSIS: INCREASE IN NET ACID EXCRETION

Gastrointestinal loss of bicarbonate
Ingestion of acids or acid precursors: Ammonium chloride, sulfur-containing compounds
Acid precursors or toxins: Salicylate, ethylene glycol, methanol, toluene, acetaminophen, paraldehyde
Organic acidosis:
- L-lactic acidosis
- D-lactic acidosis
- Ketoacidosis
- Pyroglutamic acidosis

BOX 3 Causes of Metabolic Acidosis by Net Acid Excretion

Renal Acidosis: Absolute or Relative Reduction in Net Acid Excretion
Uremic acidosis
Renal tubular acidosis
- Distal renal tubular acidosis (type I)
- Proximal renal tubular acidosis (type II)
- Aldosterone deficiency or unresponsiveness (type IV)

From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

BOX 4 Causes of L-Lactic Acidosis

Type A Lactic Acidosis Due to Tissue Hypoxia
Circulatory shock
Severe hypoxemia
Heart failure
Severe anemia
Grand mal seizure

Type B Lactic Acidosis, No Tissue Hypoxia
Acute alcoholism
Drugs and toxins (e.g., metformin, antiretroviral drugs, salicylate intoxication)
Diabetes mellitus
Leukemia
Deficiency of thiamin or riboflavin
Idiopathic

From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, St Louis, 2017, Elsevier.

Metabolic acidosis with normal AG (hyperchloremic acidosis)
Renal tubular acidosis (including acidosis of aldosterone deficiency)
Intestinal loss of HCO_3^- (diarrhea, pancreatic fistula)
Carbonic anhydrase inhibitors (e.g., acetazolamide)
Dilutional acidosis (as a result of rapid infusion of bicarbonate-free isotonic saline)
Ingestion of exogenous acids (ammonium chloride, methionine, cystine, calcium chloride)
Ileostomy
Ureterosigmoidostomy
Drugs: Amiloride, triamterene, spironolactone, β-blockers
RESPIRATORY ACIDOSIS
Pulmonary disease (chronic obstructive pulmonary disease (COPD), severe pneumonia, pulmonary edema, interstitial fibrosis)
Airway obstruction (foreign body, severe bronchospasm, laryngospasm)
Thoracic cage disorders (pneumothorax, flail chest, kyphoscoliosis)
Defects in muscles of respiration (myasthenia gravis, hypokalemia, muscular dystrophy)
Defects in peripheral nervous system (amyotrophic lateral sclerosis, poliomyelitis, Guillain-Barré syndrome, botulism, tetanus, organophosphate poisoning, spinal cord injury)
Depression of respiratory center (anesthesia, narcotics, sedatives, vertebral artery embolism or thrombosis, increased intracranial pressure)
Failure of mechanical ventilator
METABOLIC ALKALOSIS
Divided into chloride-responsive (urinary chloride <15 mEq/l) and chloride-resistant forms (urinary chloride level >15 mEq/l)

Chloride-responsive
Vomiting
Nasogastric (NG) suction
Diuretics
Posthypercapnic alkalosis
Stool losses (laxative abuse, cystic fibrosis, villous adenoma)

Massive blood transfusion
Exogenous alkali administration
Chloride-resistant
Hyperadrenocorticoid states (Cushing syndrome, primary hyperaldosteronism, secondary mineralocorticoidism [licorice, chewing tobacco])
Hypomagnesemia
Hypokalemia
Bartter syndrome
RESPIRATORY ALKALOSIS
Hypoxemia (pneumonia, pulmonary embolism, atelectasis, high-altitude living)
Drugs (salicylates, xanthines, progesterone, epinephrine, thyroxine, nicotine)
Central nervous system (CNS) disorders (tumor, cerebrovascular accident [CVA], trauma, infections)
Psychogenic hyperventilation (anxiety, hysteria)
Hepatic encephalopathy
Gram-negative sepsis
Hyponatremia
Sudden recovery from metabolic acidosis
Assisted ventilation

TABLE 18 Reference Intervals for Synovial Fluid Constituents

Constituent	Synovial Fluid	Plasma
Total protein	1-3 g/dl	6-8 g/dl
Albumin	55%-70%	50%-65%
α1-Globulin	6%-8%	3%-5%
α2-Globulin	5%-7%	7%-13%
β-Globulin	8%-10%	8%-14%
γ-Globulin	10%-14%	12%-22%
Hyaluronic acid	0.3-0.4 g/dl	
Glucose	70-110 mg/dl	70-110 mg/dl
Uric acid	2-8 mg/dl	2-8 mg/dl
Lactate	9-29 mg/dl	9-29 mg/dl

Modified from Kjeldsberg CR, Knight JA: *Body fluids: laboratory examination of amniotic, cerebrospinal, seminal, serous and synovial fluids,* ed 3, Chicago, 1993, American Society for Clinical Pathology, with permission.
McPherson RA, Pincus MR: Henry's clinical diagnosis and management by laboratory methods, ed 23, 2017, Elsevier

ARTHROCENTESIS FLUID

Reference intervals for synovial fluid constituents are described in Table 18. Also see Fig. 11.

Interpretation of results:

1. **Color:** Normally it is clear or pale yellow; cloudiness indicates inflammatory process or presence of crystals, cell debris, fibrin, or triglycerides.
2. **Viscosity:** Normally it has a high viscosity because of hyaluronate; when fluid is placed on a slide, it can be stretched to a string >2 cm in length before separating (low viscosity indicates breakdown of hyaluronate [lysosomal enzymes from leukocytes] or the presence of edema fluid).
3. **Mucin clot:** Add 1 ml of fluid to 5 ml of a 5% acetic acid solution and allow 1 minute for the clot to form; a firm clot (does not fragment on shaking) is normal and indicates the presence of large molecules of hyaluronic acid (this test is nonspecific and infrequently done).
4. **Glucose:** Normally it approximately equals serum glucose level; a difference of more than 40 mg/dl is suggestive of infection.
5. **Protein:** Total protein concentration is <2.5 g/dl in the normal synovial fluid; it is elevated in inflammatory and septic arthritis.
6. Microscopic examination for crystals
   a. **Gout:** Monosodium urate crystals
   b. **Pseudogout:** Calcium pyrophosphate dihydrate crystals

ASLO TITER

See ANTISTREPTOLYSIN O TITER

ASPARTATE AMINOTRANSFERASE (AST, SGOT)

Normal range: 0 to 35 U/L (0 to 0.58 μkat/L [CF: 0.01667, SMI: 0.01μkat/L])

Elevated in:

HEART
Acute myocardial infarction
Pericarditis (active—some cases)
LIVER
Hepatitis virus, Epstein-Barr, or cytomegalovirus infection
Active cirrhosis
Liver passive congestion or hypoxia
Alcohol- or drug-induced liver dysfunction
Space-occupying lesions (active)
Fatty liver (severe)
Extrahepatic biliary obstruction (early)
Drug-induced
SKELETAL MUSCLE
Acute skeletal muscle injury
Muscle inflammation (infectious or noninfectious)

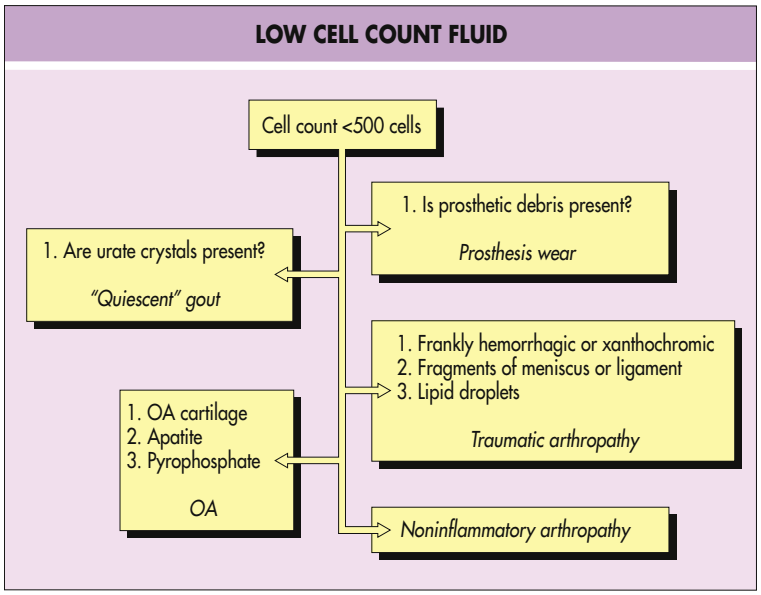


FIG. 11 Low cell count fluid. *OA,* Osteoarthritis. (From Hochberg MC: *Rheumatology*, ed 7, Philadelphia, 2019, Elsevier.)

Muscular dystrophy (active)
Recent surgery
Delirium tremens
KIDNEY
Acute injury or damage
Renal infarct
OTHER
Intestinal infarction
Shock
Cholecystitis
Acute pancreatitis
Hypothyroidism
Heparin therapy (60% to 80% of cases)
Fig. 1 describes an approach to the evaluation of AST elevation.
Box 5 describes causes of elevated serum aminotransferase levels.

ATRIAL NATRIURETIC HORMONE (ANH)

Normal: 20 to 77 pg/ml
Elevated in: CHF, volume overload, cardiovascular disease with high filling pressure
Decreased with: Prazosin and other alpha blockers

BOX 5 Causes of Elevated Serum Aminotransferase Levels*

Chronic, Mild Elevations, ALT > AST (<150 U/L or 5 × normal)

Hepatic Causes
α_1-Antitrypsin deficiency
Autoimmune hepatitis
Chronic viral hepatitis (B, C, and D)
Hemochromatosis
Medications and toxins
Steatosis and steatohepatitis
Wilson disease

Nonhepatic Causes
Celiac disease
Hyperthyroidism

Severe, Acute Elevations, ALT > AST (>1000 U/L or >20 to 25 × normal)

Hepatic Causes
Acute bile duct obstruction
Acute Budd-Chiari syndrome
Acute viral hepatitis
Autoimmune hepatitis
Drugs and toxins
Hepatic artery ligation
Ischemic hepatitis
Wilson disease

Severe, Acute Elevations, AST > ALT (>1000 U/L or >20 to 25 × normal)

Hepatic Cause
Medications or toxins in a patient with underlying alcoholic liver injury

Nonhepatic Cause
Acute rhabdomyolysis

Chronic, Mild Elevations, AST > ALT (<150 U/L, <5 × normal)

Hepatic Causes
Alcohol-related liver injury (AST/ALT > 2:1, AST nearly always <300 U/L)
Cirrhosis

Nonhepatic Causes
Hypothyroidism
Macro-AST
Myopathy
Strenuous exercise

*Virtually any liver disease can cause moderate aminotransferase elevations (5-15 × normal).
ALT, alanine aminotransferase; *AST,* aspartate aminotransferase.
From Feldman M, Friedman LS, Brandt LJ: *Sleisenger and Fortran's gastrointestinal and liver disease*, ed 10, Philadelphia, 2016, Elsevier.

B-TYPE NATRIURETIC PEPTIDE (BNP)

Normal range: up to 100 mcg/L. Natriuretic peptides are secreted to regulate fluid volume, blood pressure, and electrolyte balance. They have activity in both the central and peripheral nervous systems. In humans the main source of circulatory BNP is the heart ventricles.
Elevated in: Heart failure. This test is useful to differentiate heart failure patients from those with chronic obstructive pulmonary disease presenting with dyspnea. Levels are also increased in asymptomatic left ventricular dysfunction, arterial and pulmonary hypertension, cardiac hypertrophy, valvular heart disease, arrhythmia, and acute coronary syndrome. See Fig. 12.

BASOPHIL COUNT

Normal range
a. 0.4% to 1% of total white blood cells (WBCs); 40-100/mm^3
Elevated in: Leukemia, inflammatory processes, polycythemia vera, Hodgkin lymphoma, hemolytic anemia, after splenectomy, myeloid metaplasia, myxedema
Decreased in: Stress, hypersensitivity reaction, steroids, pregnancy, hyperthyroidism, postirradiation

BICARBONATE

Normal
- Arterial: 21 to 28 mEq/L
- Venous: 22 to 29 mEq/L

Elevated in: Metabolic alkalosis, compensated respiratory acidosis, diuretics, corticosteroids, laxative abuse
Decreased in: Metabolic acidosis, compensated respiratory alkalosis, acetazolamide, cyclosporine, cholestyramine, methanol or ethylene glycol poisoning

BILE, URINE

See URINE BILE

BILIRUBIN, DIRECT (CONJUGATED BILIRUBIN)

Normal range: 0 to 0.2 mg/dl (0 to 4 μmol/L [CF: 17.10; SMI: 2 μmol/L])
Elevated in: Hepatocellular disease, biliary obstruction, drug-induced cholestasis, hereditary disorders (Dubin-Johnson syndrome, Rotor syndrome)

BILIRUBIN, INDIRECT (UNCONJUGATED BILIRUBIN)

Normal range: 0 to 1.0 mg/dl (2 to 18 μmol/L [CF: 17.10; SMI: 2 μmol/L])
Elevated in: Increased bilirubin production (if normal liver, serum unconjugated bilirubin is usually less than 4 mg/100 ml)
Hemolytic anemia
Acquired
Congenital
Resorption from extravascular sources
Hematomas
Pulmonary infarcts
Excessive ineffective erythropoiesis
Congenital (congenital dyserythropoietic anemias)
Acquired (pernicious anemia, severe lead poisoning; if present, bilirubinemia is usually mild)
Defective hepatic unconjugated bilirubin clearance (defective uptake or conjugation)
Severe liver disease
Gilbert syndrome
Crigler-Najjar type I or II
Drug-induced inhibition
Portacaval shunt
Congestive heart failure
Hyperthyroidism (uncommon)

BILIRUBIN, TOTAL

See Fig. 13, Table 19, and Table 20 for evaluation of hyperbilirubinemia and liver disease.
Normal range: 0 to 1.0 mg/dl (2 to 18 μmol/L [CF: 17.10, SMI: 2 μmol/L])

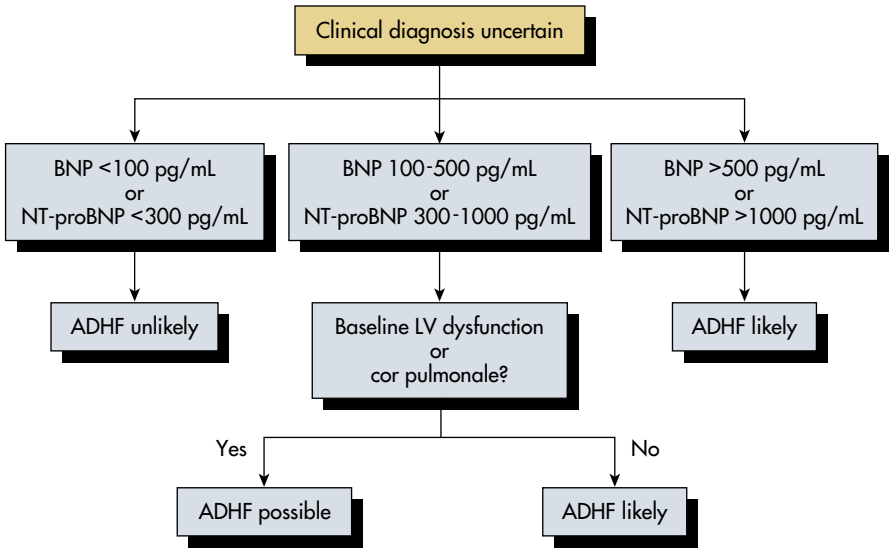


FIG. 12 Interpretation of natriuretic peptide levels. *ADHF,* Acute decompensated heart failure; *BNP,* B-type natriuretic peptide; *LV,* left ventricle; *NT-proBNP,* inactive N-terminal fragment of BNP. (From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

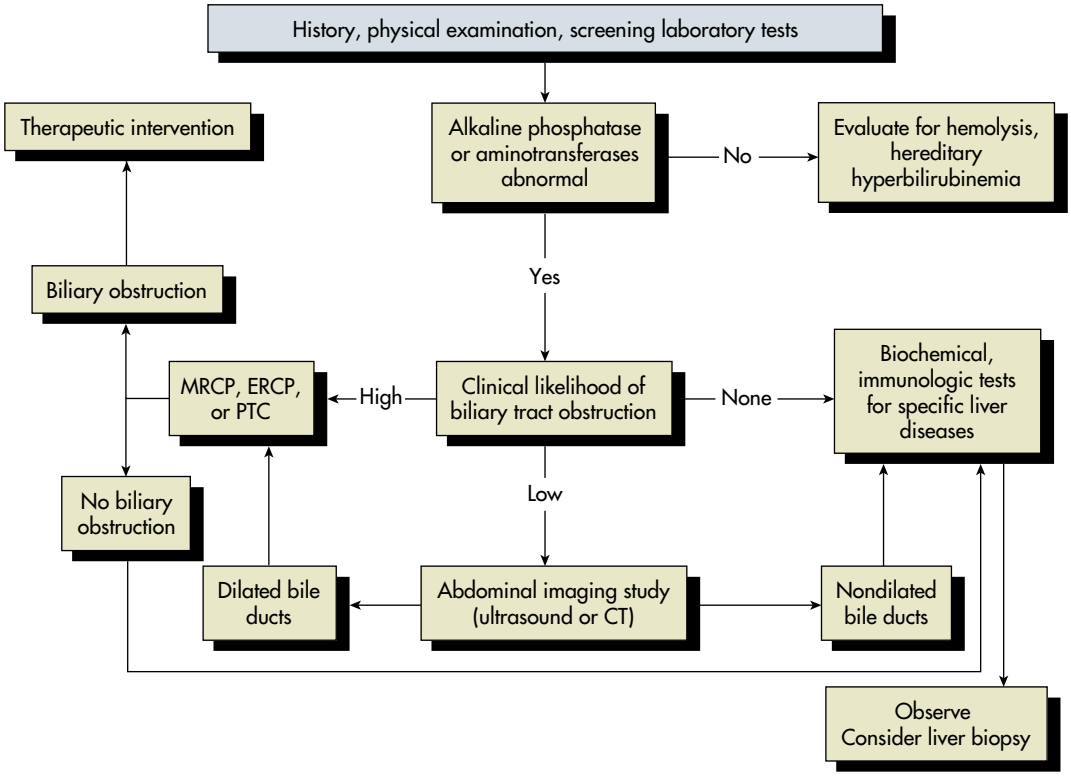


FIG. 13 Diagnosis algorithm for the evaluation of hyperbilirubinemia and other liver test abnormalities and/or signs and symptoms suggestive of liver disease. *CT,* Computed tomography; *ERCP,* endoscopic retrograde cholangiopancreatography; *MRCP,* magnetic resonance cholangiopancreatography; *PTC,* percutaneous cholangiogram. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, WB Saunders. Modified and updated from Lidofsky SD, Scharschmidt BF: Jaundice. In Feldman M et al [eds]: *Gastrointestinal and liver disease,* ed 6, Philadelphia, 1998, WB Saunders.)

Elevated in: Liver disease (hepatitis, cirrhosis, cholangitis, neoplasm, biliary obstruction, infectious mononucleosis), hereditary disorders (Gilbert disease, Dubin-Johnson syndrome), drugs (steroids, statins, niacin, acetaminophen, diphenylhydantoin, phenothiazines, penicillin, erythromycin, clindamycin, captopril, amphotericin B, sulfonamides, azathioprine, isoniazid, 5-aminosalicylic acid, allopurinol, methyldopa, indomethacin, halothane, oral contraceptives, procainamide, tolbutamide, labetalol), hemolysis, pulmonary embolism or infarct, hepatic congestion secondary to congestive heart failure

TABLE 19 Obstructive Jaundice vs. Cholestatic Liver Disease

Feature	Suggests Obstructive Jaundice	Suggests Parenchymal Liver Disease
History	Abdominal pain; fever, rigors; prior biliary surgery; older age; acholic stools	Anorexia, malaise, myalgias, suggestive of viral prodrome; known infectious exposure; receipt of blood products, use of intravenous drugs; exposure to known hepatotoxin; family history of jaundice
Physical examination	High fever; abdominal tenderness; palpable abdominal mass; abdominal scar	Ascites; other stigmata of liver disease (e.g., prominent abdominal veins, gynecomastia, spider angiomata, asterixis, encephalopathy, Kayser-Fleischer rings)
Laboratory studies	Predominant elevation of serum bilirubin and alkaline phosphatase; prothrombin time that is normal or normalizes with vitamin K administration; elevated serum amylase	Predominant elevation of serum aminotransferases; prolonged prothrombin time that does not correct with vitamin K administration; blood tests indicative of specific liver disease

From Goldman L, Ausiello D (eds): *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, WB Saunders.

TABLE 20 Causes and Mechanisms of Isolated Hyperbilirubinemia in Adults

Cause	Mechanism
Indirect Hyperbilirubinemia	
Hemolytic Disorders	Overproduction of bilirubin
Inherited	
Red cell enzyme defects (e.g., glucose-6-phosphate dehydrogenase deficiency)	
Sickle cell disease	
Spherocytosis and elliptocytosis	
Acquired	
Drugs and toxins	
Hypersplenism	
Immune mediated	
Paroxysmal nocturnal hemoglobinuria	
Traumatic: Macro- or microvascular injury	
Ineffective Erythropoiesis	Overproduction of bilirubin
Cobalamin deficiency	
Folate deficiency	
Profound iron deficiency	
Thalassemia	
Drugs: Rifampin, Probenecid	Impaired hepatocellular uptake of bilirubin
Inherited Conditions	Impaired conjugation of bilirubin
Crigler-Najjar syndrome types I and II	
Gilbert syndrome	
Other	
Hematoma and massive blood transfusion	Overproduction of bilirubin
Direct Hyperbilirubinemia	
Inherited Conditions	
Dubin-Johnson syndrome	Impaired excretion of conjugated bilirubin
Rotor syndrome	

From Feldman M et al: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier.

BILIRUBIN, URINE

See URINE BILE

BLADDER TUMOR ASSOCIATED ANTIGEN

Normal: ≤14 U/ml. Test is used to detect bladder cancer recurrence. Sensitivity 57% to 83% and specificity 68% to 72%.

Elevated in: Bladder cancer, renal stones, nephritis, UTI, hematuria, renal cancer, cystitis, recent bladder or urinary tract trauma

BLEEDING TIME (MODIFIED IVY METHOD)

See Fig. E14 for evaluation of patients with prolonged bleeding time.

Normal range: 2 to 9.5 min

Elevated in: Thrombocytopenia, capillary wall abnormalities, platelet abnormalities (Bernard-Soulier disease, Glanzmann disease), drugs (aspirin, warfarin, antiinflammatory medications, streptokinase, urokinase, dextran, β-lactam antibiotics, moxalactam), disseminated intravascular coagulation, cirrhosis, uremia, myeloproliferative disorders, von Willebrand disease.

Bleeding time tests are no longer performed at many hospitals and have been replaced by the platelet function analyzer (PFA-100) assay.

BLOOD VOLUME, TOTAL

Normal range: 60 to 80 ml/kg

Elevated in: Polycythemia vera, pulmonary disease, CHF, renal insufficiency, pregnancy, acidosis, thyrotoxicosis

Decreased in: Anemia, hemorrhage, vomiting, diarrhea, dehydration, burns, starvation

BNP

See B-TYPE NATRIURETIC PEPTIDE

BORDETELLA PERTUSSIS SEROLOGY

Test description: Polymerase chain reaction (PCR) of nasopharyngeal aspirates or secretions is used to identify *Bordetella pertussis,* the organism responsible for whooping cough.

BRCA ANALYSIS

DESCRIPTION OF ANALYSIS

Comprehensive BRCA analysis

BRCA1: Full sequence determination in both forward and reverse directions of approximately 5500 base pairs comprising 22 coding exons and one noncoding exon (exon 4) and approximately 800 adjacent base pairs in the noncoding intervening sequence (intron). Exon 1, which is noncoding, is not analyzed. The wild-type *BRCA1* gene encodes a protein comprising 1863 amino acids.

BRCA2: Full sequence determination in both forward and reverse directions of approximately 10,200 base pairs comprising 26 coding exons and approximately 900 adjacent base pairs in the noncoding intervening sequence (intron). Exon 1, which is noncoding, is not analyzed. The wild-type *BRCA2* gene encodes a protein comprising 3418 amino acids.

The noncoding intronic regions of *BRCA1* and *BRCA2* that are analyzed do not extend more than 20 base pairs proximal to the 5' end and 10 base pairs distal to the 3' end of each exon.

Single-site BRCA analysis: DNA sequence analysis for a specified mutation in *BRCA1* and/or *BRCA2.*

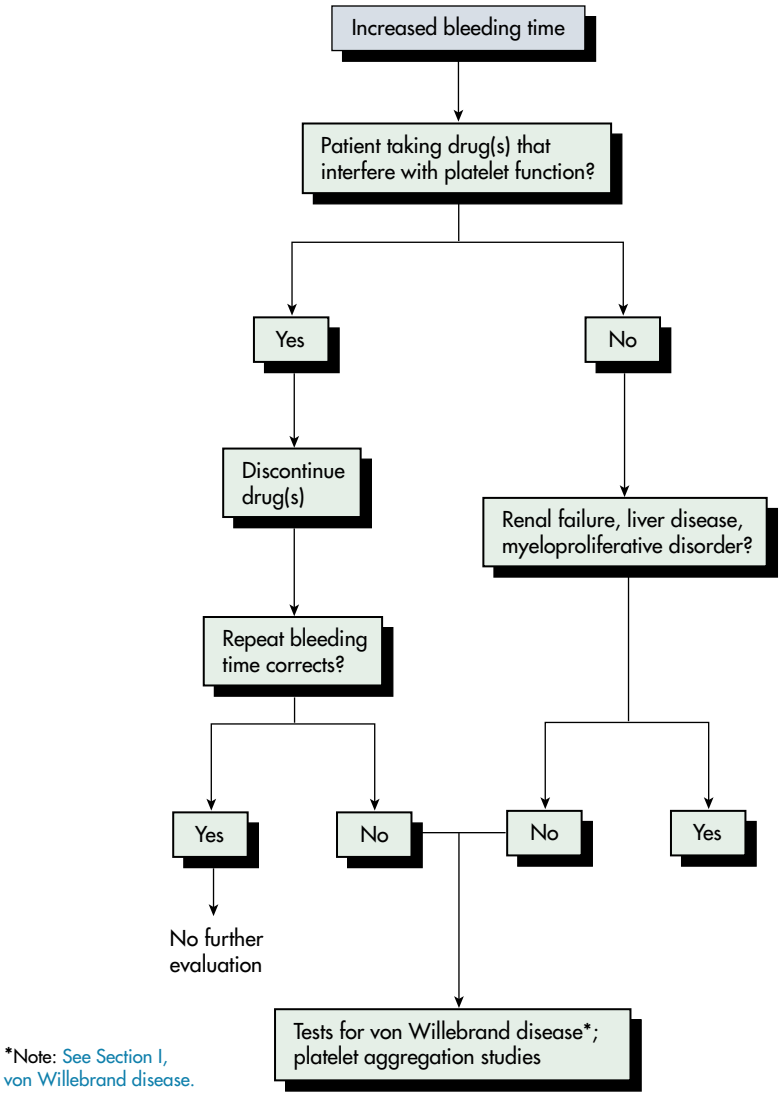


FIG. E14 An algorithm for diagnostic decisions in evaluating patients with a prolonged bleeding time. The scheme assumes that the platelet count is normal because thrombocytopenia itself can prolong the bleeding time. (Modified from Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, WB Saunders.)

Multisite 3 BRCA analysis: DNA sequence analysis of specific portions of *BRCA1* exon 2, *BRCA1* exon 20, and *BRCA2* exon 11 designed to detect only mutations 187delAG and 5385insC in *BRCA1* and 6174delT in *BRCA2.*

Interpretive Criteria:

"**Positive for a deleterious mutation**": Includes all mutations (nonsense, insertions, deletions) that prematurely terminate ("truncate") the protein product of *BRCA1* at least 10 amino acids from the C-terminus, or the protein product of *BRCA2* at least 110 amino acids from the C-terminus (based on documentation of deleterious mutations in *BRCA1* and *BRCA2*).

In addition, specific missense mutations and noncoding intervening sequence (IVS) mutations are recognized as deleterious on the basis of data derived from linkage analysis of high-risk families, functional assays, biochemical evidence, and/or demonstration of abnormal messenger ribonucleic acid (mRNA) transcript processing.

"**Genetic variant, suspected deleterious**": Includes genetic variants for which the available evidence indicates a likelihood, but not proof, that the mutation is deleterious. The specific evidence supporting such an interpretation will be summarized for individual variants on each such report.

"**Genetic variant, favor polymorphism**": Includes genetic variants for which available evidence indicates that the variant is highly unlikely to contribute substantially to cancer risk. The specific evidence supporting such an interpretation will be summarized for individual variants on each such report.

"**Genetic variant of uncertain significance**": Includes missense mutations and mutations that occur in analyzed intronic regions whose clinical significance has not yet been determined, as well as chain-terminating mutations that truncate *BRCA1* and *BRCA2* distal to amino acid positions 1853 and 3308, respectively.

"**No deleterious mutation detected**": Includes nontruncating genetic variants observed at an allele frequency of approximately 1% of a suitable control population (providing that no data suggest clinical significance), as well as all genetic variants for which published data demonstrate absence of substantial clinical significance. Also includes mutations in the protein-coding region that neither alter the amino acid sequence nor are predicted to significantly affect exon splicing, and base pair alterations in noncoding portions of the gene that have been demonstrated to have no deleterious effect on the length or stability of the mRNA transcript.

There may be uncommon genetic abnormalities in *BRCA1* and *BRCA2* that will not be detected by *BRCA* analysis. This analysis, however, is believed to rule out the majority of abnormalities in these genes, which are believed responsible for most hereditary susceptibility to breast and ovarian cancer.

"**Specific variant/mutation not identified**": Specific and designated deleterious mutations or variants of uncertain clinical significance are not present in the individual being tested. If one (or rarely two) specific deleterious mutations have been identified in a family member, a negative analysis for the specific mutation(s) indicates that the tested individual is at the general population risk of developing breast or ovarian cancer.

BREATH HYDROGEN TEST (hydrogen breath test)

Normal: This test is for bacterial overgrowth. H_2 excretion fasting: 4.6 ± 5.1, after lactulose, early increase <12. Lactulose usually results in a colonic response >30 min after ingestion.

Elevated in: A high fasting breath H_2 level and an increase of at least 12 ppm within 30 min after lactulose challenge are indicative of bacterial overgrowth in the small intestine. The increase must precede the colonic response.

False positives in: Accelerated gastric emptying, laxative use

False negatives in: Use of antibiotics and patients who are nonhydrogen producers

BUN

See UREA NITROGEN, BLOOD

C282Y AND H63D MUTATION ANALYSIS

Procedure: Detection of the C282Y and H63D mutations is accomplished by amplification of exons 2 and 4 of the *HFE* gene on chromosome 6 by polymerase chain reaction (PCR) followed by allele-specific hybridization and chemiluminescent detection of hybridized probes. H63D is viewed by some as a polymorphism rather than a mutation because of its prevalence in the population, because 15% of the individuals affected with hereditary hemochromatosis (HH) are compound heterozygotes for C282Y and H63D and about 1% of patients are H63D homozygotes, which suggests that H63D may be causative in the development of the disorder at reduced penetrance.

Interpretation of results: Homozygosity for the C282Y mutation has been associated with an increased risk of being affected with HH compared with the general population. The genotype is observed in 60% to 90% of individuals affected with HH and occurs in less than 1% of the general population. However, approximately 25% of asymptomatic individuals with this genotype do not develop the disorder.

C3

See COMPLEMENT

C4

See COMPLEMENT

CALCITONIN (serum)

Normal range: <100 pg/ml (<100 ng/L [CF: 1; SMI: 10 ng/L])

Elevated in: Medullary carcinoma of the thyroid (particularly if level >1500 pg/ml), carcinoma of the breast, apudomas, carcinoids, renal failure, thyroiditis

CALCIUM (serum)

See Figs. 15 and 16.

Normal range: 8.8 to 10.3 mg/dl (2.2 to 2.58 μmol/L [CF: 0.2495; SMI: 0.02 μmol/L])

ELEVATED

Relatively common:

Neoplasia
Bone primary
Myeloma
Acute leukemia
Nonbone solid tumors
Breast
Lung
Squamous nonpulmonary
Kidney
Neoplasm secretion of parathyroid hormone-related protein (PTHrP, "ectopic PTH")
Primary hyperparathyroidism
Thiazide diuretics
Tertiary (renal) hyperparathyroidism
Idiopathic
Spurious (artifactual) hypercalcemia
Dehydration
Serum protein elevation
Laboratory technical problem (lab error)

Relatively uncommon:

Sarcoidosis
Hyperthyroidism
Immobilization (mostly seen in children and adolescents)
Diuretic phase of acute renal tubular necrosis
Vitamin D intoxication
Milk-alkali syndrome
Addison disease
Lithium therapy
Idiopathic hypercalcemia of infancy
Acromegaly
Theophylline toxicity

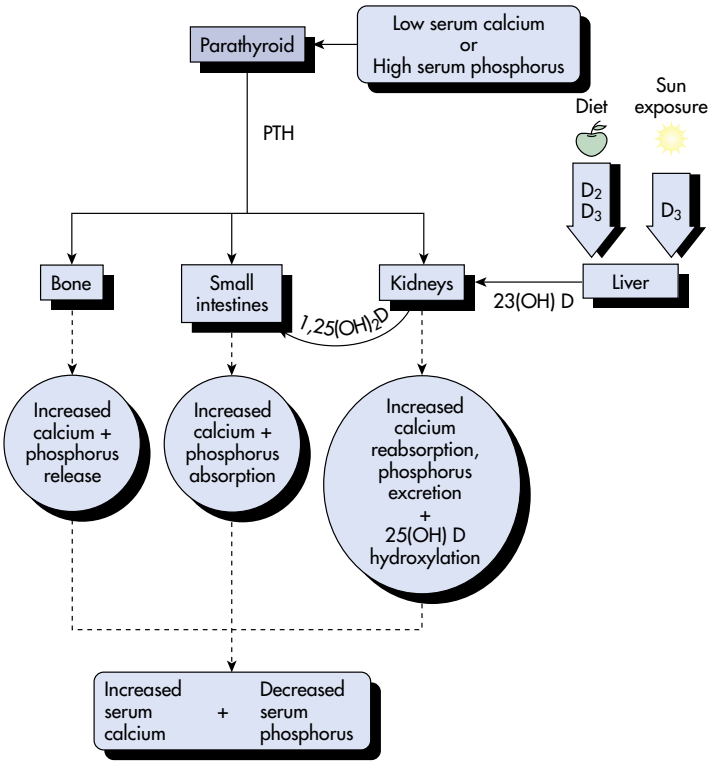


FIG. 15 Calcium homeostasis. Parathyroid hormone *(PTH)* is released from the parathyroid glands in response to hypocalcemia and hyperphosphatemia. PTH acts on bone, the small intestines, and the kidneys to effect a rise in serum calcium and a net decrease in serum phosphorus. Hydroxylation of inactive forms of vitamin D occurs in the liver and kidneys. 1,25(OH)2D facilitates intestinal absorption of calcium and phosphorus. D_2, vitamin D2; D_3, vitamin D3. (From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

Table 21 describes the laboratory differential diagnosis of hypercalcemia.

Box 6 describes the differential diagnosis of hypercalcemia in older adults.

DECREASED
Artifactual
Hypoalbuminemia
Hemodilution
Primary hypoparathyroidism
Pseudohypoparathyroidism
Vitamin D related
Vitamin D deficiency
Malabsorption
Renal failure
Magnesium deficiency
Sepsis
Chronic alcoholism
Tumor lysis syndrome
Rhabdomyolysis
Alkalosis (respiratory or metabolic)
Acute pancreatitis
Drug-induced hypocalcemia
Large doses of magnesium sulfate
Anticonvulsants
Mithramycin
Gentamicin
Cimetidine

Table 22 describes the laboratory differential diagnosis of hypocalcemia.

CALCIUM, URINE

See URINE CALCIUM

CANCER ANTIGEN 15-3 (CA 15-3)

Normal: <30 U/ml
Elevated in: Approximately 80% of women with metastatic breast cancer. Clinical sensitivity is 0.60, specificity 0.87, positive predictive value 0.91. This test is generally used to predict recurrence of breast cancer and evaluate response to therapy. May also be elevated in liver cancer, pancreatic cancer, ovarian cancer, colorectal cancer. Elevations can also occur with benign breast and liver disease.

CANCER ANTIGEN 27-29 (CA 27-29)

Normal: <38 U/ml
Elevated in: Approximately 75% of women with metastatic breast cancer. Clinical sensitivity is 0.57, specificity 0.97, positive predictive value 0.83, negative predictive value 0.92. This test is generally used to predict recurrence of breast cancer and evaluate response to therapy. May also be elevated in liver cancer, pancreatic cancer, ovarian cancer, colorectal cancer. Elevations can also occur with benign breast and liver disease.

CANCER ANTIGEN 72-4 (CA 72-4)

Normal: <4.0 ng/ml
Elevated in: Gastric cancer (elevated in >50% of patients). Often used in combination with CA 72-4, CA 19-9, and CEA to monitor gastric cancer after treatment.

CANCER ANTIGEN 125 (CA 125)

Normal range: <1.4%

This test uses an antibody against antigen from tissue culture of an ovarian tumor cell line. Various published evaluations report sensitivity of about 75% to 80% in patients with ovarian carcinoma. There is also an appreciable incidence of elevated values in nonovarian malignancies and in certain benign conditions (see later). Test values may transiently increase during chemotherapy.

MALIGNANT
Epithelial ovarian carcinoma, 75% to 80% (range, 25% to 92%; better in serous than mucinous cystadenocarcinoma)
Endometrial carcinoma, 25% to 48% (2% to 90%)
Pancreatic carcinoma, 59%
Colorectal carcinoma, 20% (15% to 56%)
Endocervical adenocarcinoma, 83%
Squamous cervical or vaginal carcinoma, 7% to 14%

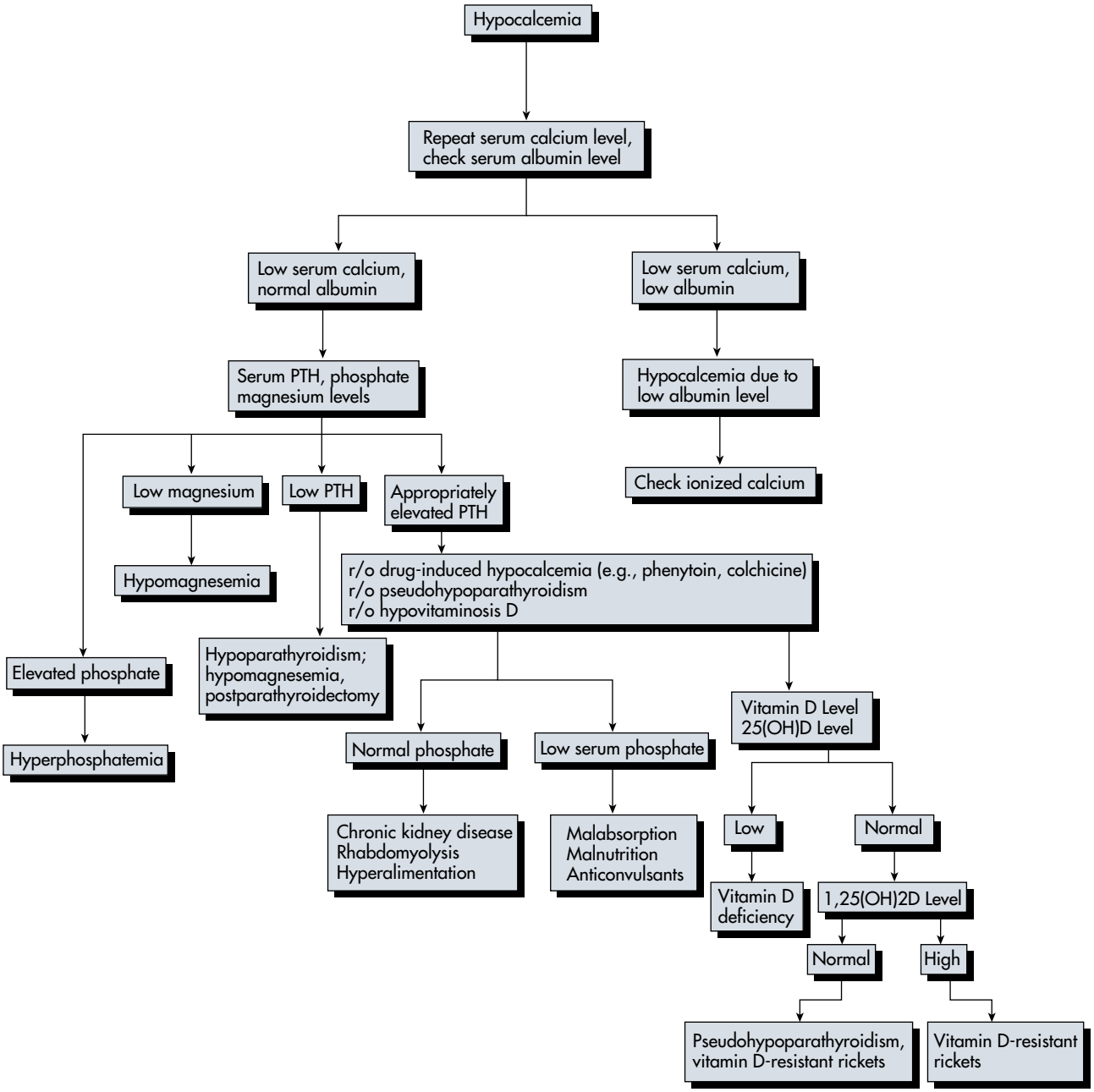


FIG. 16 Diagnostic algorithm. *PTH,* Parathyroid hormone. (From Ferri F: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Saunders.)

Lung carcinoma, 32%
Breast carcinoma, 12% to 40%
Lymphoma, 35%

BENIGN

Cirrhosis, 40% to 80%
Acute pancreatitis, 38%
Acute peritonitis, 75%
Endometriosis, 88%
Acute pelvic inflammatory disease, 33%
Pregnancy first trimester, 2% to 24%
During menstruation (occasionally)
Renal failure (?frequency)
Normal persons, 0.6% to 1.4%

CAPTOPRIL STIMULATION TEST

Normal: Test performed by giving 25 mg captopril orally after overnight fast. Patient should be seated during test. After captopril, aldosterone <15 ng/dl, renin >2 ng angiotensin L/ml/hr.

Interpretation of results: In patients with primary aldosteronism, plasma aldosterone remains high and plasma renin activity remains low after captopril.

CARBAMAZEPINE (Tegretol)

Normal therapeutic range: 4 to 12 mcg/ml

CARBOHYDRATE ANTIGEN 19-9

Normal: <37.0 U/ml

TABLE 21 Laboratory Differential Diagnosis of Hypercalcemia

	PLASMA TESTS					URINE TESTS			
Diagnosis	**Ca**	**PO_4**	**PTH**	**25(OH)D**	**1,25$(OH)_2$D**	**cAMP**	**TmP/GFR**	**Ca**	**Comments**
Primary hyperparathyroidism	↑	N/↓	↑	N	N/↑	↑	↓	↑	Parathyroid adenoma most common
MEN I									Parathyroid hyperplasia; also includes pituitary and pancreatic neoplasms
MEN IIa									Parathyroid hyperplasia; also includes medullary thyroid carcinoma and pheochromocytoma
MEN IIb									Parathyroid disease uncommon, primarily medullary thyroid carcinoma and pheochromocytoma
FHH	↑	N	N/↑	N	N	N/↑	N/↓	↓↓	Autosomal dominant inheritance; hypercalcemia present within first decade; benign
Malignancy									
Solid tumor, humoral	↑	N/↓	↓	N	N	↑	↓	↑↑	Primarily epidermoid tumors; PTH-related protein(s) is mediator
Solid tumor, osteolytic	↑	N/↑	↓	N	N	↓	↑	↑↑	
Lymphoma	↑	N/↑	↓	N/↓	↑	↓	↑	↑↑	
Granulomatous disease	↑	N/↑	↓	N/↓	↑↑	↓	↑	↑↑	Sarcoid most common etiology
Vitamin D intoxication	↑	N/↑	↓	↑↑	N	↓	↑	↑↑	
Hyperthyroidism	↑	N	↓	N	N	N	N	↑↑	Plasma concentrations of T_4 and/or T_3 are elevated

Ca, Calcium; *cAMP,* cyclic adenosine monophosphate; *FHH,* familial hypocalciuric hypercalcemia; *GFR,* glomerular filtration rate; *MEN,* multiple endocrine neoplasia; *25(OH)D,* 25 hydroxyvitamin D; *PO_4*, phosphate; *PTH,* parathyroid hormone; *T_3*, triiodothyronine; *T_4*, thyroxine; *TmP,* renal threshold for phosphorus.
From Moore WT, Eastman RC: *Diagnostic endocrinology,* ed 2, St Louis, 1996, Mosby.

BOX 6 Differential Diagnosis of Hypercalcemia in Older Adults

Primary hyperparathyroidism
Malignancy
Renal failure
Addison disease
Hyperthyroidism
Immobilization
Medications: Thiazide diuretics, calcium supplements, lithium
Milk alkali syndrome
Paget disease (when immobilized)
Sarcoidosis
Tuberculosis
Vitamin D or vitamin A intoxication

Symptoms of Acute Hypercalcemia
Neurologic: Drowsiness, confusion, irritability hypotonia, coma
Gastrointestinal: Anorexia, nausea, vomiting, acute pancreatitis
Cardiovascular: Arrhythmias
Renal: Polyuria, polydipsia, dehydration

From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology*, ed 8, Philadelphia, 2017, Elsevier.

Elevated in: GI cancer, most frequently pancreatic cancer. Amount of elevation has no relation to tumor mass. Elevations can also occur with cirrhosis, cholangitis, and chronic or acute pancreatitis.

CARBON DIOXIDE, PARTIAL PRESSURE

Normal: Male: 35 to 48 mm Hg
Female: 32 to 45 mm Hg
Elevated in: Respiratory acidosis
Decreased in: Respiratory alkalosis

CARBON MONOXIDE

See CARBOXYHEMOGLOBIN

CARBOXYHEMOGLOBIN

Normal range: Saturation of hemoglobin <2%; smokers <9%
Elevated in: Smoking, exposure to smoking, exposure to automobile exhaust fumes, malfunctioning gas-burning appliances

CARCINOEMBRYONIC ANTIGEN (CEA)

Normal range:
Nonsmokers: 0 to 2.5 ng/ml (0 to 2.5 μg/L [CF: 1; SMI: 0.1 μg/L])
Smokers: 0 to 5 ng/ml (0 to 5 μg/L [CF: 1; SMI: 0.1 μg/L])
Elevated in:
Colorectal carcinomas*, pancreatic carcinomas, and metastatic disease (usually produce higher elevations: >20 ng/ml)
Carcinomas of the esophagus, stomach, small intestine, liver, breast, ovary, lung, and thyroid (usually produce lesser elevations)
Benign conditions (smoking, inflammatory bowel disease, hypothyroidism, cirrhosis, pancreatitis, infections) (usually produce levels <10 ng/ml)

CAROTENE (serum)

Normal range: 50 to 250 μg/dl (0.9 to 4.6 μmol/L [CF: 0.01863; SMI: 0.1 μmol/L])
Elevated in: Carotenemia, chronic nephritis, diabetes mellitus, hypothyroidism, nephrotic syndrome, hyperlipidemia
Decreased in: Fat malabsorption, steatorrhea, pancreatic insufficiency, lack of carotenoids in diet, high fever, liver disease

CATECHOLAMINES, URINE

See URINE CATECHOLAMINES

*To detect colorectal cancer, the sensitivity of CEA ranges from 68% for a threshold of 10 mcg/L to 82% for a threshold of 2.5 mcg/L, and the specificity ranges from 97% for a threshold of 10 mcg/L to 80% for a threshold of 2.6 mcg/L.

TABLE 22 Laboratory Differential Diagnosis of Hypocalcemia

	PLASMA TESTS					URINE TESTS					
Diagnosis	**Ca**	**PO_4**	**PTH**	**25(OH) D**	**1,25 $(OH)_2D$**	**cAMP**	**cAMP after PTH**	**TmP/ GFR**	**TmP/GFR after PTH**	**Ca**	**Comments**
Hypoparathyroidism	↓	↑	N/↓	N	↓	↓	↑↑	↑	↓↓	N/↓	Deficiency of PTH
Pseudohypoparathyroidism											
Type I	↓	↑	↑↑	N	↓	↓	NC	↑	↑	N/↓	Resistance to PTH; patients may have Albright hereditary osteodystrophy and resistance to multiple hormones
Type II	↓	N	↑↑	N	↓	↓	↑	↑	↑	N/↓	Renal resistance to cAMP
Vitamin D deficiency	↓	N/↓	↑↑	↓↓	N/↓	↑	↑	↓	↓	↓↓	Deficient supply (e.g., nutrition) or absorption (e.g., pancreatic insufficiency) of vitamin D
Vitamin D-dependent Rickets											
Type I	↓	N/↓	↑↑	N	↓	↑↑		↓		↓↓	Deficient activity of renal 25(OH)D-1α-hydroxylase
Type II	↓	N/↓	↑↑	N	↑↑	↑		↓		↓↓	Resistance to 1,25$(OH)_2D$

Ca, Calcium; *cAMP,* cyclic adenosine monophosphate; *FHH,* familial hypocalciuric hypercalcemia; *GFR,* glomerular filtration rate; *MEN,* multiple endocrine neoplasia; *NC,* no change or small increase; *(OH)D,* hydroxycalciferol D; *PO_4,* phosphate; *PTH,* parathyroid hormone; *T_3,* triiodothyronine; *T_4,* thyroxine; *TmP,* renal threshold for phosphorus.
From Moore WT, Eastman RC: *Diagnostic endocrinology*, ed 2, St Louis, 1996, Mosby.

CBC

See COMPLETE BLOOD COUNT

CD40 LIGAND

Normal: <5 mcg/L. CD40 ligand is a soluble protein that is shed from activated leukocytes and platelets and used in risk stratification for acute coronary syndrome.
Elevated in: Acute coronary syndrome. Increased CD40 ligand is associated with higher incidence of death or nonfatal myocardial infarction (MI).

CD4+ T-LYMPHOCYTE COUNT (CD4+ T cells)

Calculated as total WBC × % lymphocytes × % lymphocytes stained with CD4.

This test is used primarily to evaluate immune dysfunction in HIV infection. It is useful as a prognostic indicator and as a criterion for initiating prophylaxis for several opportunistic infections that are sequelae of HIV infection. Progressive depletion of CD4+ T-lymphocytes is associated with an increased likelihood of clinical complications (Table 23).

CEA

See CARCINOEMBRYONIC ANTIGEN

CEREBROSPINAL FLUID (CSF)

Interpretation of results:
Appearance of the fluid
- Clear: Normal.
- Yellow color (xanthochromia) in the supernatant of centrifuged CSF within 1 hour or less after collection is usually the result of previous bleeding (subarachnoid hemorrhage); it may also be caused by increased CSF protein, melanin from meningeal melanosarcomas, or carotenoids.
- Pinkish color is usually the result of a bloody tap; the color generally clears progressively from tubes 1 to 4 (the supernatant is usually crystal clear in traumatic taps).
- Turbidity usually indicates the presence of leukocytes (bleeding introduces approximately 1 WBC/500 RBCs into the CSF).

CSF pressure: Elevated pressure can be seen with meningitis, meningoencephalitis, pseudotumor cerebri, mass lesions, and intracerebral bleeding.

TABLE 23 Relation of CD4 Lymphocyte Counts to the Onset of Certain HIV-Associated Infections and Neoplasms in North America

CD4 Count (Cells/mm^3)*	Opportunistic Infection or Neoplasm	Frequency (%)†
>500	Herpes zoster, polydermatomal	5-10
200-500	*Mycobacterium tuberculosis* infection, pulmonary and extrapulmonary	2-20
	Oral hairy leukoplakia	40-70
	Candida pharyngitis (thrush)	40-70
	Recurrent *Candida* vaginitis	15-30 (F)
	Kaposi sarcoma, mucocutaneous	15-30 (M)
	Bacterial pneumonia, recurrent	15-20
	Cervical neoplasia	1-2 (F)
100-200	*Pneumocystis carinii* pneumonia	15-60
	Herpes simplex, chronic, ulcerative	5-10
	Histoplasma capsulatum infection, disseminated	0-20
	Kaposi sarcoma, visceral	3-8 (M)
	Progressive multifocal leukoencephalopathy	2-3
	Lymphoma, non-Hodgkin	2-5
<100	*Candida* esophagitis	15-20
	Mycobacterium avium-intracellulare, disseminated	25-40
	Toxoplasma gondii encephalitis	5-25
	Cryptosporidium enteritis	2-10
	CMV retinitis	20-35
	Cryptococcus neoformans encephalitis	2-5
	CMV esophagitis or colitis	6-12
	Lymphoma, central nervous system	4-8

CMV, Cytomegalovirus; *F,* exclusively in women; *HIV,* human immunodeficiency virus; *M,* almost exclusively in men.
*Table indicates CD4 count at which specific infections or neoplasms generally begin to appear. Each infection may recur or progress during the subsequent course of HIV disease.
†Even within the United States, great regional differences in the incidence of specific opportunistic infections are apparent. For example, disseminated histoplasmosis is common in the Mississippi River drainage area but very rare in individuals who have lived exclusively on the East or West Coast.
From Andreoli TE (ed): *Cecil essentials of medicine,* ed 5, Philadelphia, 2000, WB Saunders.

Cell count: In the adult the CSF is normally free of cells (although up to five mononuclear cells/mm^3 is considered normal); the presence of granulocytes is never normal.
- Neutrophils: Seen in bacterial meningitis, early viral meningoencephalitis, and early tuberculosis (TB) meningitis. Box 7 summarizes causes of increased CSF neutrophils.
- Increased lymphocytes: TB meningitis, viral meningoencephalitis, syphilitic meningoencephalitis, fungal meningitis. Causes of CSF lymphocytosis are summarized in Box 8.
- CSF plasmacytosis: Box 9 describes inflammatory and infectious causes of CSF plasmacytosis.
- CSF eosinophilia: Causes of CSF eosinophilic pleocytosis are summarized in Box 10.

BOX 7 Causes of Increased CSF Neutrophils

- Meningitis
  - Bacterial meningitis
  - Early viral meningoencephalitis
  - Early tuberculous meningitis
  - Early mycotic meningitis
  - Amebic encephalomyelitis
- Other infections
  - Cerebral abscess
  - Subdural empyema
  - AIDS-related CMV radiculopathy
- Following seizures
- Following CNS hemorrhage
  - Subarachnoid
  - Intracerebral
- Following CNS infarct
- Reaction to repeated lumbar punctures
- Injection of foreign material in subarachnoid space (e.g., methotrexate, contrast media)
- Metastatic tumor in contact with CSF

AIDS, Acquired immunodeficiency syndrome; *CMV,* cytomegalovirus; *CNS,* central nervous system; *CSF,* cerebrospinal fluid.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

BOX 8 Causes of CSF Lymphocytosis

Meningitis
- Viral meningitis
- Tuberculous meningitis
- Fungal meningitis
- Syphilitic meningoencephalitis
- Leptospiral meningitis
- Bacterial due to uncommon organisms
- Early bacterial meningitis where leukocyte counts are relatively low
- Parasitic infestations (e.g., cysticercosis, trichinosis, toxoplasmosis)
- Aseptic meningitis due to septic focus adjacent to meninges

Degenerative Disorders
- Subacute sclerosing panencephalitis
- Multiple sclerosis
- Drug abuse encephalopathy
- Guillain-Barré syndrome
- Acute disseminated encephalomyelitis

Other Inflammatory Disorders
- HaNDL syndrome (headache with neurologic deficits and CSF lymphocytosis)
- Sarcoidosis
- Polyneuritis
- CNS periarteritis

CNS, Central nervous system; *CSF,* cerebrospinal fluid.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

Protein: Serum proteins are generally too large to cross the normal blood-CSF barrier; however, increased CSF protein is seen with meningeal inflammation, traumatic tap, increased CNS synthesis, tissue degeneration, obstruction to CSF circulation, and Guillain-Barré syndrome. Mean concentrations of plasma and CSF proteins are summarized in Table 24. Conditions associated with increased CSF total protein are summarized in Box 11.

Glucose
- Decreased glucose is seen with bacterial meningitis, TB meningitis, fungal meningitis, subarachnoid hemorrhage, and some cases of viral meningitis.
- A mild increase in CSF glucose can be seen in patients with very elevated serum glucose levels.

Table 25 describes CSF findings in infectious and inflammatory diseases of the central nervous system and meninges.

Causes of xanthochromia are summarized in Table 26.

CERULOPLASMIN (serum)

Normal range: 20 to 35 mg/dl (200 to 350 mg/L [CF: 10; SMI: 10 mg/L])

Elevated in: Pregnancy, estrogens, oral contraceptives, neoplastic diseases (leukemias, Hodgkin lymphoma, carcinomas), inflammatory states, systemic lupus erythematosus, primary biliary cirrhosis, rheumatoid arthritis

Decreased in: Wilson disease (values often <10 mg/dl), nephrotic syndrome, advanced liver disease, malabsorption, total parenteral nutrition, Menkes syndrome

BOX 9 Inflammatory and Infectious Causes of CSF Plasmacytosis

- Acute viral infections
- Guillain-Barré syndrome
- Multiple sclerosis
- Parasitic CNS infestations
- Sarcoidosis
- Subacute sclerosing panencephalitis
- Syphilitic meningoencephalitis
- Tuberculous meningitis

CNS, Central nervous system; *CSF,* cerebrospinal fluid.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

BOX 10 Causes of CSF Eosinophilic Pleocytosis

Commonly associated with
- Acute polyneuritis
- CNS reaction to foreign material (drugs, shunts)
- Fungal infections
- Idiopathic eosinophilic meningitis
- Idiopathic hypereosinophilic syndrome
- Parasitic infections

Infrequently associated with
- Bacterial meningitis
- Leukemia/lymphoma
- Myeloproliferative disorders
- Neurosarcoidosis
- Primary brain tumors
- Tuberculous meningoencephalitis
- Viral meningitis

CNS, Central nervous system; *CSF,* cerebrospinal fluid.
Modified from Kjeldsberg CR, Knight JA: *Body fluids: laboratory examination of amniotic, cerebrospinal, seminal, serous and synovial fluids*, ed 3, Chicago, 1993, American Society for Clinical Pathology, with permission. In McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

TABLE 24 Mean Concentrations of Plasma and CSF Proteins

Protein	CSF, mg/L	Plasma/CSF Ratio
Prealbumin	17.3	14
Albumin	155.0	236
Transferrin	14.4	142
Ceruloplasmin	1.0	366
Immunoglobulin (Ig)G	12.3	802
IgA	1.3	1346
α_2-Microglobulin	2.0	1111
Fibrinogen	0.6	4940
IgM	0.6	1167
β-Lipoprotein	0.6	6213

CSF, Cerebrospinal fluid.
Adapted and updated from Felgenhauer K: Protein size and cerebrospinal fluid composition, *Klin Wochenschr* 52:1158, 1974, with permission. (McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, St Louis, 2017, Elsevier.)

BOX 11 Conditions Associated with Increased CSF Total Protein

Traumatic Spinal Puncture
- Increased Blood-CSF Permeability
- Arachnoiditis (e.g., following methotrexate therapy)
- Meningitis (bacterial, viral, fungal, tuberculous)
- Hemorrhage (subarachnoid, intracerebral)
- Endocrine/metabolic disorders
  Milk-alkali syndrome with hypercalcemia
  Diabetic neuropathy
  Hereditary neuropathies and myelopathies
  Decreased endocrine function (thyroid, parathyroid)
  Other disorders (uremia, dehydration)

Drug Toxicity
Ethanol, phenothiazines, phenytoin

CSF Circulation Defects
Mechanical obstruction (tumor, abscess, herniated disk)
Loculated CSF effusion

Increased Immunoglobulin (Ig)G Synthesis
Multiple sclerosis

Neurosyphilis
Subacute sclerosing panencephalitis

Increased IgG Synthesis and Blood-CSF Permeability
Guillain-Barré syndrome
Collagen vascular diseases (e.g., lupus, periarteritis)
Chronic inflammatory demyelinating polyradiculopathy

-From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

CHLAMYDIA GROUP ANTIBODY SEROLOGIC TEST

Test description: Acute and convalescent sera is drawn 2 to 4 wk apart. A fourfold increase in titer between acute and convalescent sera is necessary for confirmation. A single titer ≥1:64 is considered indicative of psittacosis or lymphogranuloma venereum (LGV).

CHLAMYDIA TRACHOMATIS PCR

Test description: Test is performed on endocervical swab, urine, and intraurethral swab (see Table 27)
Normal: Negative

CHLORIDE (serum)

Normal range: 95 to 105 mEq/L (95 to 105 mmol/L [CF: 1; SMI: 1 mmol/L])
Elevated in: Dehydration, excessive infusion of normal saline solution, cystic fibrosis (sweat test), hyperparathyroidism, renal tubular disease, metabolic acidosis, prolonged diarrhea, drugs (ammonium chloride administration, acetazolamide, boric acid, triamterene)
Decreased in: Congestive heart failure, syndrome of inappropriate antidiuretic hormone secretion, Addison disease, vomiting, gastric suction, salt-losing nephritis, continuous infusion of D_5W, thiazide diuretic administration, diaphoresis, diarrhea, burns, diabetic ketoacidosis

CHLORIDE (sweat)

Normal: 0 to 40 mmol/L
Borderline/indeterminate: 41 to 60 mmol/L
Consistent with cystic fibrosis: >60 mmol/L
False low results can occur with edema, excessive sweating, and hypoproteinemia.

CHLORIDE, URINE

See URINE CHLORIDE

CHOLECYSTOKININ-PANCREOZYMIN (CCK, CCK-PZ)

Normal: <80 pg/ml
Elevated in: Pancreatic disease, celiac disease, gastric ulcer, postgastrectomy, irritable bowel syndrome (IBS), fatty food intolerance

CHOLESTEROL, HIGH-DENSITY LIPOPROTEIN

See HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

CHOLESTEROL, LOW-DENSITY LIPOPROTEIN

See LOW-DENSITY LIPOPROTEIN CHOLESTEROL

CHOLESTEROL, TOTAL

Normal range: Varies with age
Generally <200 mg/dl (<5.20 mmol/L [CF: 0.02586; SMI: 0.05 mmol/L])
Elevated in: Primary hypercholesterolemia, biliary obstruction, diabetes mellitus, nephrotic syndrome, hypothyroidism, primary biliary cirrhosis, high-cholesterol diet, pregnancy third trimester, myocardial infarction, drugs (steroids, phenothiazines, oral contraceptives). Classic hyperlipidemia phenotypes are summarized in Table 28.
Decreased in: Medications (statins, niacin), starvation, malabsorption, sideroblastic anemia, thalassemia, abetalipoproteinemia, hyperthyroidism, Cushing syndrome, hepatic failure, multiple myeloma, polycythemia vera, chronic myelocytic leukemia, myeloid metaplasia, Waldenström macroglobulinemia, myelofibrosis

CHORIONIC GONADOTROPINS, HUMAN (serum) (hCG)

Normal range, serum:
Female, premenopausal: <0.8 IU/L; postmenopausal <3.3 IU/L
Male: <0.7 IU/L
Elevated in:
Pregnancy, choriocarcinoma, gestational trophoblastic neoplasia (including molar gestations), placental site trophoblastic tumors; human antimouse antibodies (HAMA) can produce false serum assay for hCG.
The principal use of this test is to diagnose pregnancy. The concentration of hCG increases significantly during the initial 6 wk of pregnancy.
Normal range: Varies with gestational stage:
1 wk: 5 to 50 mU/ml
1 to 2 wk: 50 to 550 mU/ml
2 to 3 wk: Up to 5000 mU/ml
3 to 4 wk: Up to 10,000 mU/ml
4 to 5 wk: Up to 50,000 mU/ml
2 to 3 mo: 10,000 to 100,000 mU/ml
Peak values approaching 100,000 IU/L occur 60 to 70 days following implantation.
hCG levels generally double every 1 to 3 days. In patients with concentration <2000 IU/L, an increase of serum hCG <66% after 2 days is suggestive of spontaneous abortion or ruptured ectopic gestation.

CHYMOTRYPSIN

Normal: <10 mcg/L
Elevated in: Acute pancreatitis, chronic renal failure, oral enzyme preparations, gastric cancer, pancreatic cancer

TABLE 25 Cerebrospinal Fluid Findings in Infectious and Inflammatory Diseases of the Central Nervous System

Condition	Pressure (mm H_2O)	Leukocytes/μL	Protein (mg/dl)	Sugar (mg/dl)	Specific Findings
Acute bacterial meningitis	Usually elevated; average 300	Several hundred to >10,000; usually a few thousand; occasionally <100 (especially meningococcal or early in disease); PMLs predominate	Usually 100-500, occasionally >1000	<40 in more than half the cases	Organism usually seen on smear or recovered on culture in >90% of cases
Subdural empyema	Usually elevated; average 300	<100 to a few thousand; PMLs predominate	Usually 100-500	Normal	No organisms on smear or by culture unless concurrent meningitis
Brain abscess	Usually elevated	Usually 10-200; fluid rarely is acellular; lymphocytes predominate	Usually 75-400	Normal	No organisms on smear or by culture
Ventricular empyema (rupture of brain abscess)	Elevated	Several thousand to 100,000; usually >90% PMLs	Usually several hundred	Usually <40	Organisms may be seen on smear or cultured
Cerebral epidural abscess	Slight to modest elevation	Few to several hundred or more cells; lymphocytes predominate	Usually 50-200	Normal	No organisms on smear or by culture
Spinal epidural abscess	Usually reduced with spinal block	Usually 10-100; lymphocytes predominate	Usually several hundred	Normal	No organisms on smear or by culture
Thrombophlebitis (often associated with subdural empyema)	Often elevated	Few to several hundred; PMLs and lymphocytes	Slightly to moderately elevated	Normal	No organisms on smear or by culture
Bacterial endocarditis (with embolism)	Normal or slightly elevated	Few to <100; lymphocytes and PMLs	Slightly elevated	Normal	No organisms on smear or by culture
Acute hemorrhagic encephalitis	Usually elevated	Few to >1000; PMLs predominate	Moderately elevated	Normal	No organisms on smear or by culture
Tuberculous infection	Usually elevated	Usually 25-100, rarely >500; lymphocytes predominate except in early stages when PMLs may account for 80% of cells	Nearly always elevated; usually 100-200; may be much higher if block in CSF flow	Usually reduced; <50 in 75% of cases	Acid-fast organisms may be seen on smear of protein coagulum (pellicle) or recovered from inoculated guinea pig or by culture
Cryptococcal infection	Usually elevated	Average 50 (0-800); lymphocytes predominate	Average 100; usually 20-500	Reduced in more than half of cases; often higher in patients with concomitant diabetes mellitus	Organisms may be seen in India ink preparation and on culture (Sabouraud medium); usually grow on blood agar; may produce alcohol in CSF from fermentation of glucose
Syphilis (acute)	Usually elevated	Average 500; usually lymphocytes; rarely PMLs	Average, 100; γ-globulin often high, with abnormal colloidal gold curve	Normal (rarely reduced)	Positive reagin test result for syphilis; spirochete not demonstrable by usual techniques of smear or by culture
Sarcoidosis	Normal to considerably elevated	0 to <100 mononuclear cells	Slight to moderate elevation	Normal	No specific findings

CSF, Cerebrospinal fluid; *PMLs*, polymorphonuclear leukocytes.
From Cherry JD: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Philadelphia, 2019, Elsevier.

TABLE 26 Xanthochromia and Associated Diseases/Disorders

CSF Supernatant Color	Associated Diseases/Disorders
Pink	RBC lysis/hemoglobin breakdown products
Yellow	RBC lysis/hemoglobin breakdown products Hyperbilirubinemia CSF protein >150 mg/dl (1.5 g/L)
Orange	RBC lysis/hemoglobin breakdown products Hypervitaminosis A (carotenoids)
Yellow-green	Hyperbilirubinemia (biliverdin)
Brown	Meningeal metastatic melanoma

CSF, Cerebrospinal fluid; *RBC,* red blood cell.
McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

Decreased in: Chronic pancreatitis, late cystic fibrosis

CIRCULATING ANTICOAGULANT (lupus anticoagulant)

Normal: Negative
Detected in: Systemic lupus erythematosus, drug-induced lupus, long-term phenothiazine therapy, multiple myeloma, ulcerative colitis, rheumatoid arthritis, postpartum, hemophilia, neoplasms, chronic inflammatory states, AIDS, nephrotic syndrome

NOTE: The name is a misnomer because these patients are prone to hypercoagulability and thrombosis.

CK

See CREATINE KINASE

CLONIDINE SUPPRESSION TEST

Interpretation of results: Clonidine inhibits neurogenic catecholamine release and will cause a decrease in plasma norepinephrine into the refer-

ence interval in hypertensive subjects without pheochromocytoma. Test is performed by giving 4.3 mcg clonidine/kg orally after overnight fast. Norepinephrine is measured at 3 hr. Result should be within established reference range and decrease to <50% of baseline concentration. Lack of decrease in norepinephrine is suggestive of pheochromocytoma.

CLOSTRIDIUM DIFFICILE TOXIN ASSAY (stool)

Normal: Negative
Detected in: Antibiotic-associated diarrhea and pseudomembranous colitis

CO

See CARBOXYHEMOGLOBIN

TABLE 27 Specimens for Detection of *Chlamydia trachomatis**

Disease	Specimen
Mucopurulent cervicitis	Endocervical swab, urine
Acute urethral syndrome (women)	Urethral swab, urine
Acute endometritis	Endometrial aspirate
Acute salpingitis	Fallopian tube biopsy
Nongonococcal urethritis (men)	Urethral swab, urine
Inclusion conjunctivitis	Conjunctival scrapings/swab
Trachoma	Conjunctival scrapings/swab
Lymphogranuloma venereum	Lymph node aspirate, biopsy of ulcerated lesion, serum
Pneumonitis (infants)	Serum, tracheobronchial aspirate, nasopharyngeal swab

*Urine is acceptable for some enzyme-linked immunoassays and for the commercial nucleic acid amplification tests.
McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

COAGULATION FACTORS

See Table 29 for characteristics of coagulation factors.
See Table 30 for differential diagnosis of low factor VIII.
Factor reference ranges:
a. V: >10%
b. VII: >10%
c. VIII: 50% to 170%
d. IX: 60% to 136%
e. X: >10%
f. XI: 50% to 150%
g. XII: >30%

Table 31 describes screening laboratory results in coagulation factor deficiencies. Characterization of coagulation factors and their deficiencies is summarized in Table 32.

COBALAMIN, SERUM

See VITAMIN B_{12}

COLD AGGLUTININS TITER

Normal range: <1:32
Elevated in:
Primary atypical pneumonia (*Mycoplasma* pneumonia), infectious mononucleosis, CMV infection
Others: Hepatic cirrhosis, acquired hemolytic anemia, frostbite, multiple myeloma, lymphoma, malaria

COMPLEMENT

Normal range:
C3: 70 to 160 mg/dl (0.7 to 1.6 g/L [CF: 0.01; SMI: 0.1 g/L])
C4: 20 to 40 mg/dl (0.2 to 0.4 g/L [CF: 0.01; SMI: 0.1 g/L])
Abnormal values:
Decreased C3: Active SLE, immune complex disease, acute glomerulonephritis, inborn C3 deficiency, membranoproliferative glomerulonephritis, infective endocarditis, serum sickness, autoimmune/chronic active hepatitis
Decreased C4: Immune complex disease, active SLE, infective endocarditis, inborn C4 deficiency, hereditary angioedema, hypergammaglobulinemic

TABLE 28 Classic Hyperlipidemia Phenotypes

WHO ICD and OMIM Numbers	Type	Particle	Triglycerides	Cholesterol	Comments
E78.3 238600	1 (familial chylomicronemia or LPL deficiency)	CM	High	Normal	Low cardiac risk; hereditary, found mostly in pediatric patients and young adults; autosomal recessive mutation in *LPL* or *APOC2; APOA5, LMF-1,* and *GPIHBP1* mutations are linked to this phenotype.
E78.0 143890	2A (heterozygous and homozygous familial hypercholesterolemia)	LDL	Normal	High	High cardiac risk; mostly polygenic disease; about 10% are monogenic; heterozygous form is due to mutations in *LDLR, APOB,* or *PCSK9*; homozygous form is due to mutations in *LDLR* or *LDLRAP1* (ARH).
E78.4 144250	2B (combined hyperlipoproteinemia)	VLDL, LDL	High	High	High cardiac risk; polygenic disease; links to mutations in *USF1, APOB,* and *LPL*
E78.2 107741	3 (dysbetalipoproteinemia)	IDL	High	High	High cardiac risk; mutations in *APOE* gene or homozygous for E2 allele of *APOE*
E78.1 144600, 145750	4 (primary hypertriglyceridemia)	VLDL	High	Normal	Lower cardiac risk than type 2 or 3; polygenic disease
E78.3 144650	5 (mixed hyperlipidemia)	VLDL, CM	High	High	Low cardiac risk; polygenic disease; 10% of patients have mutations in *LPL, APOC2,* and *APOA5*; mutations in *APOE, TRIB1, CHREBP, GALNT2, GCKR,* and *ANGPTL3* are thought to contribute to this disease.

ANGPTL3, Angiopoietin-like 3; *APOA5,* apolipoprotein A-V; *APOB,* apolipoprotein B; *APOC2,* apolipoprotein C-II; *APOE,* apolipoprotein E; *CHREBP,* carbohydrate response element binding protein (or *MLXIPL*); *CM,* chylomicron; *GALNT2,* UDP-N′-acetyl-alpha-D-galactosamine-polypeptide *N*-acetylgalactosaminyltransferase 2; *GCKR,* glucokinase regulator; *ICD,* International Classification of Diseases; *IDL,* intermediate-density lipoprotein; *LDL,* low-density lipoprotein; *LDLRAP1,* LDLR adaptor protein 1 (also known as ARH); *LPL,* lipoprotein lipase; *OMIM,* Online Mendelian Inheritance in Man; *TRIB1,* tribbles homologue 1; *USF1,* upstream transcription factor 1; *VLDL,* very-low-density lipoprotein; *WHO,* World Health Organization.
McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

TABLE 29 Characteristics of Coagulation Factors

Factor	Descriptive Name	Source	Approximate Half-Life (hr)	Function
I	Fibrinogen	Liver	120	Substrate for fibrin clot (CP)
II	Prothrombin	Liver (VKD)	60	Serine protease (CP)
V	Proaccelerin, labile factor	Liver	12-36	Cofactor (CP)
VII	Serum prothrombin conversion accelerator, proconvertin	Liver (VKD)	6	(?) Serine protease (EP)
VIII	Antihemophilic factor or globulin	Endothelial cells and (?) elsewhere	12	Cofactor (IP)
IX	Plasma thromboplastin component, Christmas factor	Liver (VKD)	24	Serine protease (IP)
X	Stuart-Prower factor	Liver (VKD)	36	Serine protease (CP)
XI	Plasma thromboplastin antecedent	(?) Liver	40-84	Serine protease (IP)
XII	Hageman factor	(?) Liver	50	Serine protease contact activation (IP)
XIII	Fibrin-stabilizing factor	(?) Liver	96-180	Transglutaminase (CP)
Prekallikrein	Fletcher factor	(?) Liver	?	Serine protease contact activation (IP)
High-molecular-weight kininogen	Fitzgerald factor, Flaujeac or Williams factor	(?) Liver	?	Cofactor, contact activation (IP)

CP, Common pathway; *EP,* extrinsic pathway; *IP,* intrinsic pathway; *VKD,* vitamin K dependent.
From Noble J (ed): *Primary care medicine,* ed 3, St Louis, 2001, Mosby.

TABLE 30 Differential Diagnosis of a Low Factor VIII Level

1. FVIII <10%
   1. Severe or moderately severe hemophilia A
   2. Severe type 1 vWD
   3. Type 3 vWD
   4. Type 2N vWD
   5. Acquired hemophilia A
   6. Acquired vWD
2. FVIII: 10%-50%
   1. Mild hemophilia A
   2. Type 1 vWD
   3. Type 2N vWD
   4. Combined FVIII and FV deficiency

FV, Factor V; *FVIII,* factor VIII; *vWD,* von Willebrand disease.
From Hoffman R: *Hematology: Basic principles and practice,* ed 6, Philadelphia, 2013, WB Saunders.

TABLE 31 Screening Laboratory Results in Coagulation Factor Deficiencies

Deficient Factor	Frequency	PT	PTT	TT
I (fibrinogen)	Rare	↑	↑	↑
II (prothrombin)	Very rare	↑	↑	↑
V 1:1,000,000	↑	↑	NL	
VII	1:500,000	↑	NL	NL
VIII	1:5000 (male)	NL	↑	NL
IX	1:30,000 (male)	NL	↑	NL
X 1:500,000	↑	↑	NL	
XI	Rare*	NL	↑	NL
XII or HMWK or PK†	Rare	NL	↑	NL
XIII	Rare	NL	NL	↑

↑, Increased over normal range; *HMWK,* high-molecular-weight kininogen; *NL,* normal; *PK,* prekallikrein; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *TT,* thrombin time.
*Except in those of Ashkenazi Jewish descent (approximately 4% are heterozygous for factor XI deficiency).
†Not associated with clinical bleeding.
From Andreoli TE (ed): *Cecil essentials of medicine,* ed 5, Philadelphia, 2001, WB Saunders.

states, cryoglobulinemic vasculitis. NOTE: The complement system has daunting nomenclature; accordingly, some basic definitions are given in Box 12.

COMPLEMENT DEFICIENCY

Table 33 describes complement deficiency states.

COMPLETE BLOOD COUNT (CBC)

See Fig. 17, which describes an algorithm for the evaluation of patients with neutropenia.

White blood cells 3200 to 9800/mm^3 (3.2 to 9.8 × 10^9/L [CF: 0.001; SMI: 0.1 × 10^9/L])

Red blood cells
- Male: 4.3 to 5.9 × 10^6/mm^3 (4.3 to 5.9 × 10^{12}/L [CF: 0.001; SMI: 0.1 × 10^{12}/L])
- Female: 3.5 to 5 × 10^6/mm^3 (3.5 to 5 × 10^{12}/L [CF: 0.001; SMI: 0.1 × 10^{12}/L])

Hemoglobin
Male: 13.6 to 17.7 g/dl (136 to 172 g/L [CF: 10; SMI: 1 g/L])
Female: 12 to 15 g/dl (120 to 150 g/L [CF: 10; SMI: 1 g/L])

Hematocrit
- Male: 39% to 49% (0.39 to 0.49 [CF: 0.01; SMI: 0.01])
- Female: 33% to 43% (0.33 to 0.43 [CF: 0.01; SMI: 0.01])

Mean corpuscular volume (MCV): 76 to 100 μm^3 (76 to 100 fL [CF: 1; SMI: 1 fL])

Mean corpuscular hemoglobin (MCH): 27 to 33 pg (27 to 33 pg [CF: 1; SMI: 1 pg])

Mean corpuscular hemoglobin concentration (MCHC): 33 to 37 g/dl (330 to 370 g/L [CF: 10; SMI: 10 g/L])

Red blood cell distribution width index (RDW): 11.5% to 14.5%

Platelet count: 130 to 400 × 10^3/mm^3 (130-400 × 10^9/L [CF: 1; SMI: 5 × 10^9/L])

Differential:
- 2 to 6 stabs (bands, early mature neutrophils)
- 60 to 70 segs (mature neutrophils)
- 1 to 4 eosinophils
- 0 to 1 basophils
- 2 to 8 monocytes
- 25 to 40 lymphocytes

CONJUGATED BILIRUBIN

See BILIRUBIN, DIRECT

COPPER (serum)

Normal range: 70 to 140 μg/dl (11 to 22 μmol/L [CF: 0.1574, SMI: 0.2 μmol/L])

TABLE 32 Characterization of Coagulation Factors and Their Deficiencies

Factor	Molecular Weight, kDa	Gene Location	Normal Circulating Half-Life	Incidence	Inheritance	Bleeding Severity
Fibrinogen	330	4q31.3-q32.1	2-4 days	1:1 million	Recessive	Mild-severe*
II	72	11p11.2	3-4 days	Very rare	Recessive	Mild-moderate
V	330	1q24.2	36 hours	1:1 million	Recessive	Moderate
V and VIII combined	—	LMAN1:18q21.32 MCFD2:2p21	36 hours for FV; 10-14 hours for FVIII	1:2 million	Recessive	Mild-moderate
VII	50	13q34	3-6 hours	1:500,000	Recessive	Mild-severe
VIII	330	Xq28	10-14 hours	1:10,000	Sex-linked	Mild-severe
IX	56	Xq27	18-24 hours	1:30,000	Sex-linked	Mild-severe
X	58	13q34	40-60 hours	1:500,000	Recessive	Mild-severe
XI	160	4q35.2	40-70 hours	Rare†	Recessive	Mild-moderate
XII	80	5q33-qter	50-70 days	Rare	Recessive	No bleeding
PK	88	4q33-q35	Not known	Very rare	Recessive	No bleeding
HK	120	3q27	9-10 hours	Extremely rare	Recessive	No bleeding
XIII	320	A:6p25.1 B:1q31.3	11-14 days	<1:1 million	Recessive	Moderate-severe

HK, High molecular weight kininogen; *PK,* prekallikrein.
*May be associated with thrombosis.
†Rare except in those of Ashkenazi Jewish descent.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

BOX 12 Definitions

Classical pathway: C1, C4, C2, C3, and the terminal components.
Alternative pathway: Factor B, factor D, properdin, and the terminal components.
Lectin activation pathway: MBL, MASP1, MASP2, C3, and the terminal components.
Anaphylatoxins: C3a, C4a, C5a. These are mediators of smooth muscle contraction, degranulation of mast cells, enhanced neutrophil aggregation, increased vascular permeability.
Opsonization: Renders a particle more easily phagocytosed.
C3 tickover: This term occasionally is used to describe spontaneous C3 hydrolysis.
Membrane attack complex (terminal components): C5, C6, C7, C8, C9.
CH50: Used to define the dilution of serum capable of lysing 50% of sensitized sheep red cells. This assay measures the intactness of the classical pathway through the terminal components.
AH50: Used to define the dilution of serum capable of lysing 50% of nonsensitized rabbit red cells. This assay measures the intactness of the alternative pathway through the terminal components.

From Adkinson NF et al: *Middleton's allergy principles and practice*, ed 8, Philadelphia, 2014, WB Saunders.

Decreased in: Wilson disease, Menkes syndrome, malabsorption, malnutrition, nephrosis, total parenteral nutrition, acute leukemia in remission
Elevated in: Aplastic anemia, biliary cirrhosis, systemic lupus erythematosus, hemochromatosis, hyperthyroidism, hypothyroidism, infection, iron deficiency anemia, leukemia, lymphoma, oral contraceptives, pernicious anemia, rheumatoid arthritis

COPPER, URINE

See URINE COPPER

CORTICOTROPIN RELEASING HORMONE (CRH) STIMULATION TEST

Normal: A dose of 0.5 mg of dexamethasone is given every 6 hours for 2 days; 2 hours after last dose 1 mcg/kg CRH is given IV. Samples are drawn after 15 min. Normally there is a twofold to fourfold increase in mean baseline concentration of ACTH or cortisol. Cortisol >1.4 mcg/L is virtually 100% specific and 100% diagnostic.
Interpretation of results:
Normal or exaggerated response: Pituitary Cushing disease
No response: Ectopic ACTH-secreting tumor
A positive response to CRH or a suppressed response to high-dose dexamethasone has a 97% positive predictive value for Cushing disease. However, a lack of response to either test excludes Cushing disease in only 64% to 78% of patients. When the tests are considered together, negative responses from both have a 100% predictive value for ectopic ACTH secretion.

CORTISOL, PLASMA

Normal range:
Varies with time of collection (circadian variation):
8 A.M.: 4 to 19 μg/dl (110 to 520 nmol/L [CF: 27.59; SMI: 10 nmol/L])
4 P.M.: 2 to 15 μg/dl (50 to 410 nmol/L [CF: 27.59; SMI: 10 nmol/L])
Elevated in: Ectopic adrenocorticotropic hormone production (i.e., oat cell carcinoma of lung), loss of normal diurnal variation, pregnancy, chronic renal failure, iatrogenic, stress, adrenal or pituitary hyperplasia, or adenomas
Decreased in: Primary adrenocortical insufficiency, anterior pituitary hypofunction, secondary adrenocortical insufficiency, adrenogenital syndromes

C-PEPTIDE

Elevated in: Insulinoma, sulfonylurea administration
Decreased in: Insulin-dependent diabetes mellitus, factitious insulin administration

COOMBS DIRECT

See DIRECT ANTIGLOBULIN

COOMBS INDIRECT

See INDIRECT ANTIGLOBULIN

CPK

See CREATINE KINASE

TABLE 33 Complement Deficiency States

Component	No. of Reported Patients	Mode of Inheritance	Functional Defects	Disease Associations
Classic Pathway				
C1qrs	31	ACD	Impaired IC handling, delayed C' activation, impaired immune response	CVD, 48%; infection (encapsulated bacteria), 22%; both, 18%; healthy, 12%
C4	21	ACD	Impaired C' activation in absence of specific antibody	Infection (meningococcal), 74%; healthy, 26%
C2	109	ACD		
Alternative Pathway				
D	3	ACD	Impaired IC handling, opson/phag; granulocytosis, CTX, immune response and absent SBA	CVD, 79%; recurrent infection (encapsulated bacteria), 71%
P	70	XL		
Junction of Classic and Alternative Pathways				
C3	19	ACD	Impaired CTX; absent SBA	Infection (*Neisseria,* primarily meningococcal), 58%; CVD, 4%
Terminal Components				
C5	27	ACD	Absent SBA	Both, 1%
C6	77	ACD		Healthy, 25%
C7	73	ACD		
C8	73	ACD		
C9	165	ACD	Impaired SBA	Healthy, 91%; infection, 9%
Plasma Proteins Regulating C' Activation				
C1-INH	Many	AD	Uncontrolled generation of an inflammatory mediator on C' activation	Hereditary angioedema
H	13	Acq	Uncontrolled AP activation → low C3	CVD, 40%; CVD plus infection (encapsulated bacteria), 40%; healthy, 20%
I	14	ACD	Uncontrolled AP activation → low C3	Infection (encapsulated bacteria), 100%
Membrane proteins regulating C' activation	Many	Acq	Impaired regulation of C3b and C8 deposited on host RBCs; PMN, platelets → cell lysis	Paroxysmal nocturnal hemoglobinuria
Decay-accelerating factor				
Homologous restriction factor				
CD59	>20	ACD	Impaired PMN adhesive functions (i.e., margination), CTX, C3bi-mediated opson/phag	Infection (*Staphylococcus aureus, Pseudomonas* spp.), 100%
CR3 autoantibodies				
C3 nephritic factors	>59	Acq	Stabilize AP, convertase → low C3	MPGN, 41%; PLD, 25%; infection (encapsulated bacteria), 16%; MPGN plus PLD, 10%; PLD plus infection, 5%; MPGN plus PLD plus infection, 3%; MPGN plus infection, 2%
C4 nephritic factor		Acq	Stabilize CP, C3 convertase → low C3	Glomerulonephritis, 50%; CVD, 50%

ACD, Autosomal codominant; *Acq,* acquired; *AD,* autosomal dominant; *AP,* alternative pathway; *C'*, complement; *C1-INH,* C1 esterase inhibitor; *CP,* classic pathway; *CTX,* chemotaxis; *CVD,* collagen-vascular disease; *IC,* immune complex, *MPGN,* membranoproliferative glomerulonephritis; *PLD,* partial lipodystrophy; *PMN,* polymorphonuclear neutrophil; *RBCs,* red blood cells; *SBA,* serum bactericidal activity; *XL,* X-linked.

From Mandell GL: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 6, New York, 2005, Churchill Livingstone.

C-REACTIVE PROTEIN

Normal range: 6.8 to 820 μg/dl (68 to 8200 μg/L [CF: 10; SMI: 10 μg/L])
Elevated in: Rheumatoid arthritis, rheumatic fever, inflammatory bowel disease, bacterial infections, myocardial infarction, oral contraceptives, third trimester of pregnancy (acute phase reactant), inflammatory and neoplastic diseases. Table 34 shows a comparison of erythrocyte sedimentation rate and C-reactive protein, and Table 35 shows conditions associated with elevated C-reactive protein levels.

C-REACTIVE PROTEIN, HIGH SENSITIVITY

(hs-CRP, cardio-CRP)

This is a cardiac risk marker. It is increased in patients with silent atherosclerosis years before a cardiovascular event and is independent of cholesterol level and other lipoproteins. It can be used to help stratify cardiac risk.

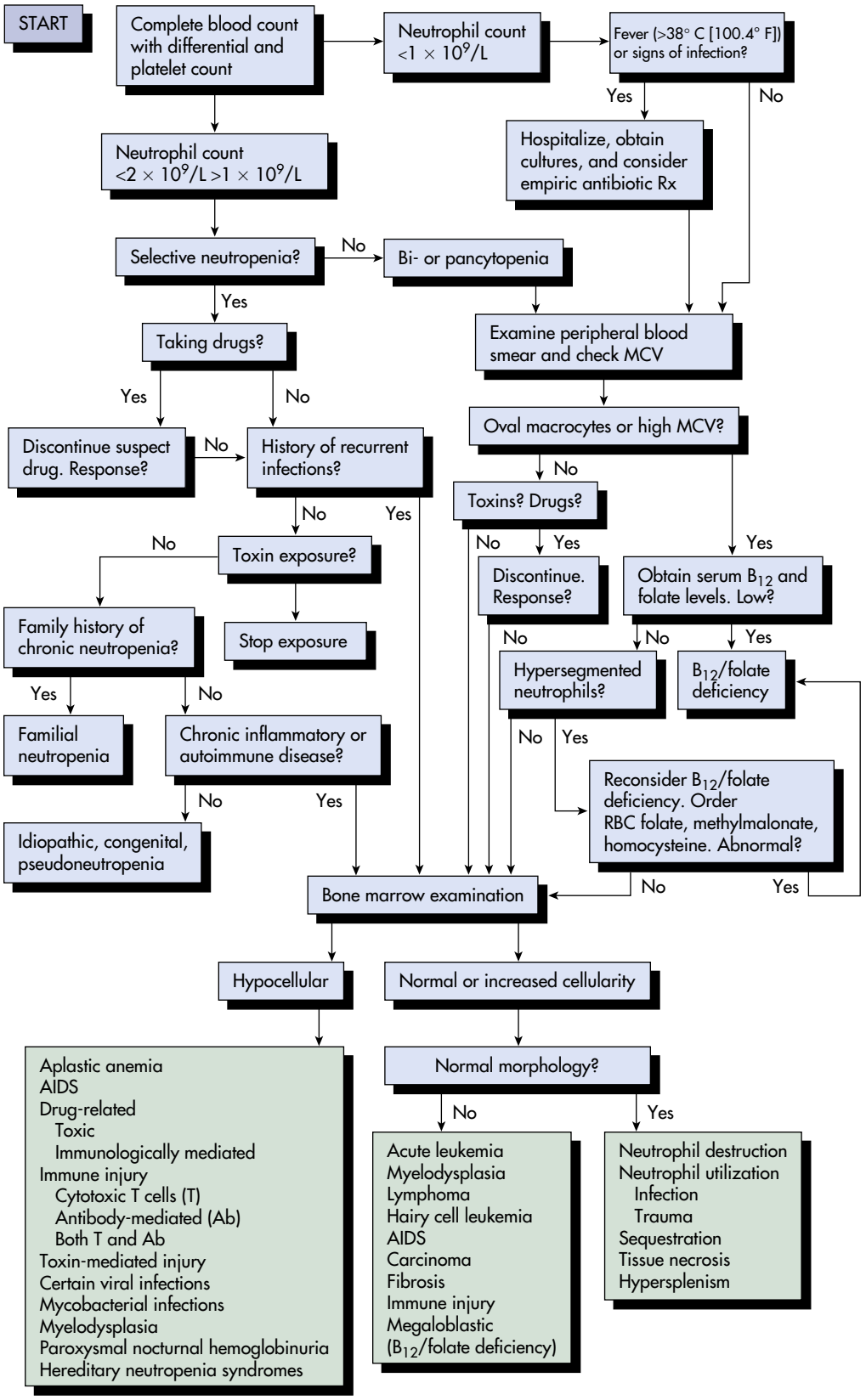


FIG. 17 A practical algorithm for the evaluation of patients with neutropenia. The fundamental diagnostic principle is that for patients with severe neutropenia or for those with bicytopenia or pancytopenia, bone marrow examination will likely be necessary unless the following diagnoses are made: (1) a nutritional (folate or vitamin B_{12}) deficiency or (2) drug- or toxin-induced neutropenia in a patient whose neutropenia resolves after discontinuation of the offending agent. *AIDS,* Acquired immunodeficiency syndrome; *MCV,* mean corpuscular volume; *RBC,* red blood cell. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, WB Saunders.)

TABLE 34 Comparison of Erythrocyte Sedimentation Rate and C-Reactive Protein

	Erythrocyte Sedimentation Rate	C-Reactive Protein
Advantages	Much clinical information in the literature May reflect overall health status	Rapid response to inflammatory stimuli Wide range of clinically relevant values are detectable Unaffected by age and gender Reflects value of a single acute phase protein Can be measured on stored sera Quantitation is precise and reproducible
Disadvantages	Affected by age and gender Affected by red blood cell morphology Affected by anemia and polycythemia Reflects levels of many plasma proteins, not all of which are acute phase proteins Responds slowly to inflammatory stimuli Requires fresh sample May be affected by drugs	None

From Firestein GS et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, WB Saunders.

TABLE 35 Conditions Associated with Elevated C-Reactive Protein Levels

Normal or Minor Elevation (<1 mg/dl)	Moderate Elevation (1-10 mg/dl)	Marked Elevation (>10 mg/dl)
Vigorous exercise Common cold Pregnancy Gingivitis Seizures Depression Insulin resistance and diabetes Several genetic polymorphisms Obesity	Myocardial infarction Malignancies Pancreatitis Mucosal infection (bronchitis, cystitis) Most connective tissue diseases Rheumatoid arthritis	Acute bacterial infection (80%-85%) Major trauma Systemic vasculitis

From Firestein GS et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, WB Saunders.

INTERPRETATION OF RESULTS

Cardio-CRP result (mg/L)	Risk
0.6	Lowest risk
0.7-1.1	Low risk
1.2-1.9	Moderate risk
2.0-3.8	High risk
3.9-4.9	Highest risk
≥5.0	Results may be confounded by acute inflammatory disease. If clinically indicated, a repeat test should be performed in 2 or more wk.

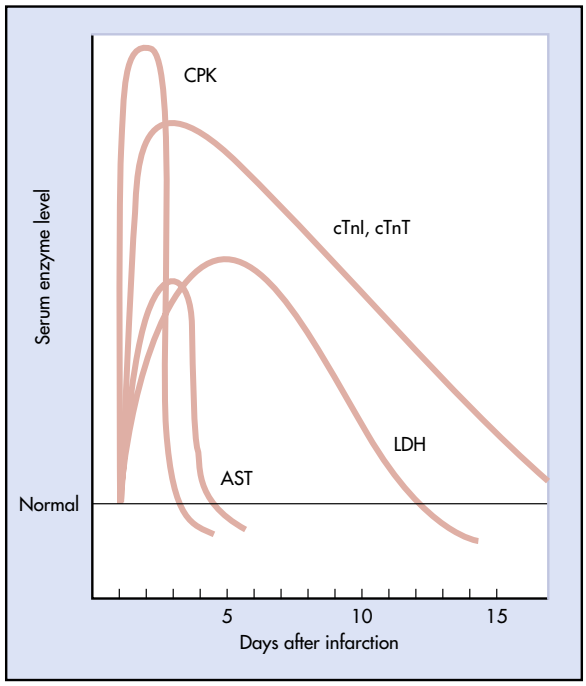


FIG. 19 Enzyme levels postmyocardial infarction. *AST,* Aspartate aminotransferase; *CPK,* creatine kinase; *cTnI,* cardiac troponin I; *cTnT,* cardiac troponin T; *LDH,* lactate dehydrogenase. (From Greene HL et al [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

CREATINE KINASE (CK, CPK)

Fig. E18 describes a diagnostic approach to creatine kinase elevation.

Normal range: 0 to 130 U/L (0 to 2.16 μkat/L [CF: 0.01667; SMI: 0.01 μkat/L])

Elevated in: Myocardial infarction, myocarditis, rhabdomyolysis, myositis, crush injury/trauma, polymyositis, dermatomyositis, vigorous exercise, muscular dystrophy, myxedema, seizures, malignant hyperthermia syndrome, intramuscular (IM) injections, cerebrovascular accident, pulmonary embolism and infarction, acute dissection of aorta

Decreased in: Corticosteroid use, decreased muscle mass, connective tissue disorders, alcoholic liver disease, metastatic neoplasms

CREATINE KINASE ISOENZYMES

CK-BB

Elevated in: Cerebrovascular accident, subarachnoid hemorrhage, neoplasms (prostate, gastrointestinal tract, brain, ovary, breast, lung), severe shock, bowel infarction, hypothermia, meningitis

CK-MB

Elevated in: Myocardial infarction (MI), myocarditis, pericarditis, muscular dystrophy, cardiac defibrillation, cardiac surgery, extensive rhabdomyolysis, strenuous exercise (marathon runners), mixed connective tissue disease, cardiomyopathy, hypothermia

NOTE: CK-MB exists in the blood in two subforms. MB_2 is released from cardiac cells and converted in the blood to MB_1. Rapid assay of CK-MB subforms can detect MI (CK-MB_2≥1.0 U/L, with a ratio of CK-MB_2/CK-MB_1≥1.5) within 6 hours of onset of symptoms.

Fig. 19 illustrates the time course of CK, AST, troponins, and lactate dehydrogenase (LDH) activity after acute MI.

CK-MM

Elevated in: Crush injury, seizures, malignant hyperthermia syndrome, rhabdomyolysis, myositis, polymyositis, dermatomyositis, vigorous exercise, muscular dystrophy, IM injections, acute dissection of aorta

CREATININE (serum)

Normal range: 0.6 to 1.2 mg/dl (50 to 110 μmol/L [CF: 88.4; SMI: 10 μmol/L]). Fig. 20 illustrates the relationship between creatinine clearance

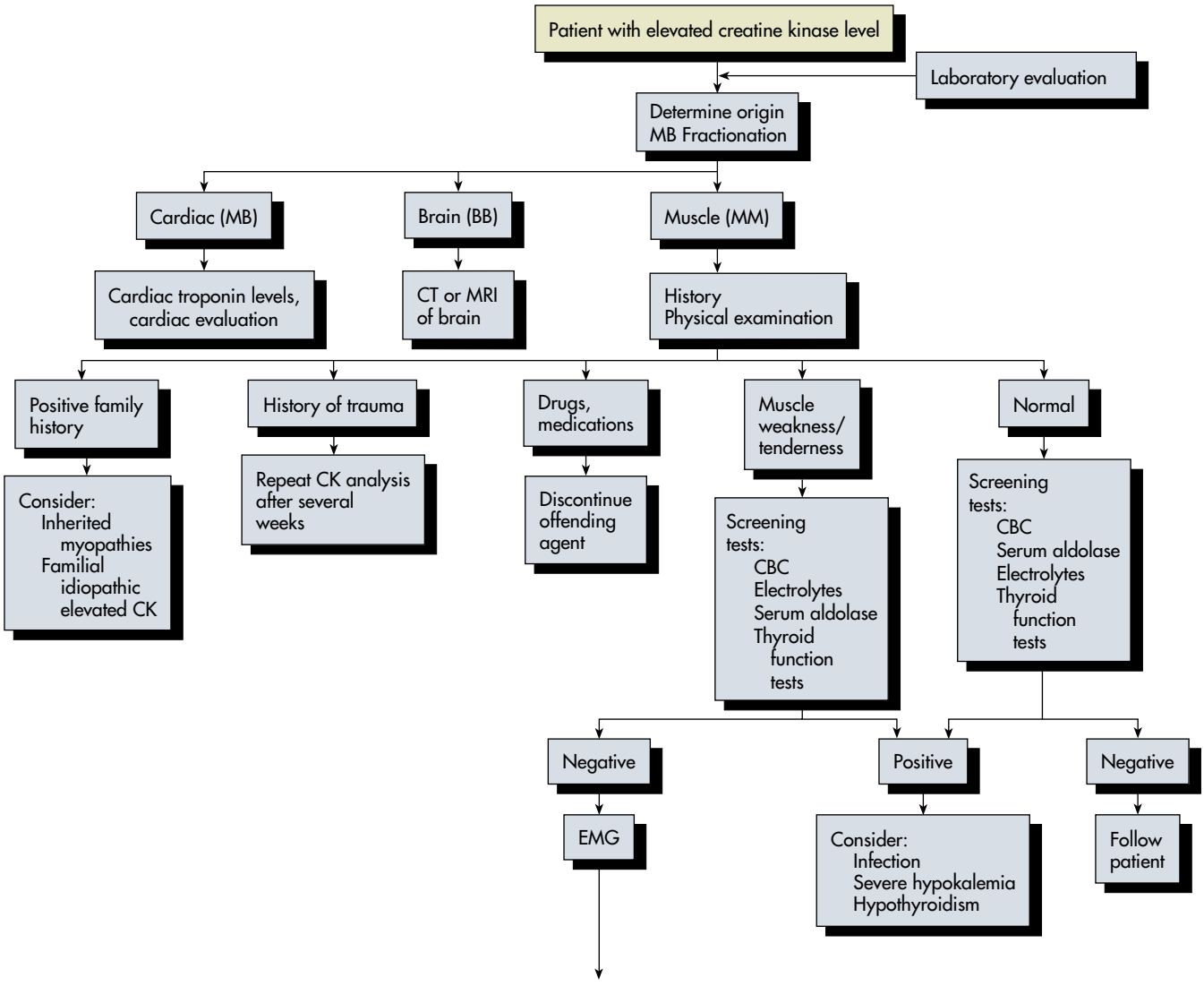


FIG. E18 Evaluation of creatine kinase elevation. *CBC,* Complete blood count; *CK,* creatine kinase; *CT,* computed tomography; *EMG,* electromyography; *MRI,* magnetic resonance imaging. (Modified and updated from Greene HL et al [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

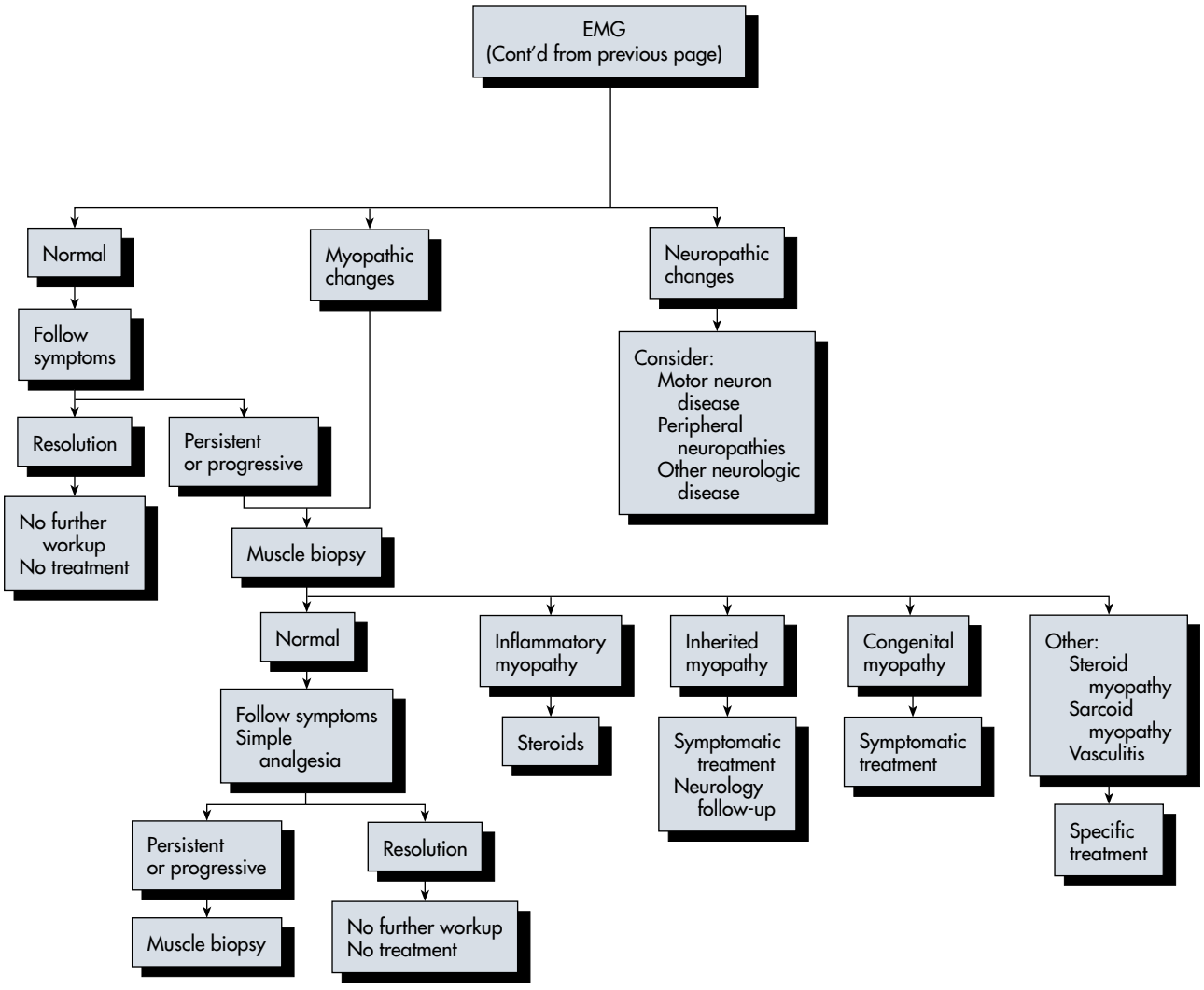


FIG. E18 cont'd

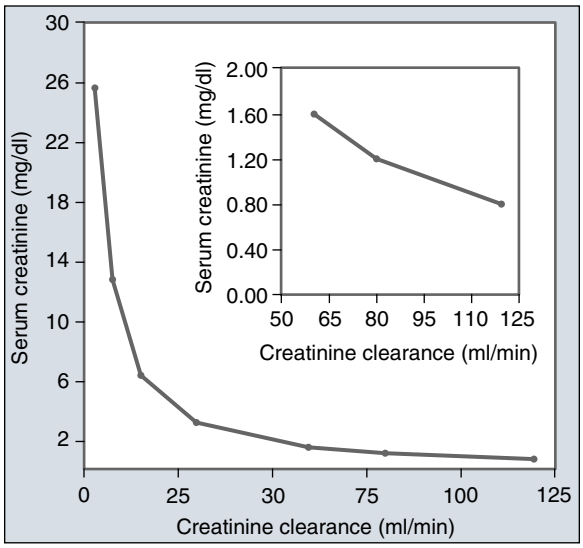


FIG. 20 Relationship between creatinine clearance and serum creatinine. In steady state, serum creatinine should increase twofold for each 50% reduction in creatinine clearance. *Inset* represents enlarged view of changes in serum creatinine as creatinine clearance decreases from 120 to 60 ml/min. If serum creatinine is 0.8 mg/dl when creatinine clearance is 120 ml/min, creatinine clearance can decrease by 33% such that increased serum creatinine is still within normal range. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.)

BOX 13 Factors That May Alter Serum Creatinine (Cr) Level

Endogenous
Reduced muscle mass: ↓
Hyperbilirubinemia: ↓

Exogenous
Medications inhibiting tubular secretion (trimethoprim, cimetidine): ↑

Medications Interfering with Laboratory Assays*
Flucytosine and cefoxitin: ↑
Catecholamines: ↓

*Varies by assay type used.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult*, ed 4, Philadelphia, 2014, Elsevier.

and serum creatinine. Factors that may alter serum creatinine level are described in Box 13.
Elevated in: Renal insufficiency (acute and chronic), decreased renal perfusion (hypotension, dehydration, congestive heart failure), urinary tract infection, rhabdomyolysis, ketonemia

Drugs (antibiotics [aminoglycosides, cephalosporins], hydantoin, diuretics, methyldopa)

The RIFLE criteria for acute kidney injury is summarized in Table 36. A classification of acute kidney injury (AKI) is described in Table 37.
Falsely elevated in: Diabetic ketoacidosis, administration of some cephalosporins (e.g., cefoxitin, cephalothin)
Decreased in: Decreased muscle mass (including amputees and older persons), pregnancy, prolonged debilitation

CREATININE CLEARANCE

Normal range:
75 to 124 ml/min (1.24 to 2.08 ml/sec [CF: 0.01667; SMI: 0.02 ml/sec])
Table 38 shows equations commonly used to estimate renal clearance.

TABLE 36 RIFLE Criteria for Acute Kidney Injury

	GFR and Serum Creatinine Changes	Urine Volume Changes
R (Risk)	Increase in SCreat >1.5×	Urine volume <0.5 ml/kg/hr >6 hr
	Decrease in GFR >25%	
I (Injury)	Increase in SCreat >2×	Urine volume <0.5 ml/kg/hr >12 hr
	Decrease in GFR >50%	
F (Failure)	Increase in SCreat >3×	Urine volume <0.3 ml/kg/hr >24 hr
	Decrease in GFR >75%	Anuria >12 hr
	SCreat >4 mg/dl	
L (Loss)	Complete loss of kidney function >4 wk	
E (ESRD)	End-stage kidney disease >3 mo	

GFR, Glomerular filtration rate; *SCreat,* serum creatinine.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

TABLE 37 New Classification for Acute Kidney Injury (AKI) Criteria

Stage	Serum Creatinine Criteria	Urine Output Criteria
1	>0.3 mg/dl (26.4 μmol/L) or >150% to 200%	<0.5 ml/kg for >6 hr
2	>200%-300%	<0.5 ml/kg for >12 hr
3	>300%, 4 mg/dl (354 μmol/L) or acute increase of >0.5 mg/dl	<0.3 ml/kg for >24 hr or anuria >12 hr

From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

The Cockcroft-Gault formula to calculate creatinine clearance is described in Box 14.
Elevated in: Pregnancy, exercise
Decreased in: Renal insufficiency, drugs (cimetidine, procainamide, antibiotics, quinidine)

CREATININE, URINE

See URINE CREATININE

CRYOGLOBULINS (serum)

Normal range: Not detectable
Present in: Collagen vascular diseases, chronic lymphocytic leukemia, hemolytic anemias, multiple myeloma, Waldenström macroglobulinemia, chronic active hepatitis, Hodgkin disease

CRYPTOSPORIDIUM ANTIGEN BY EIA (stool)

Normal range: Not detected
Present in: Cryptosporidiosis

CSF

See CEREBROSPINAL FLUID

CYSTATIN C

Normal: Cystatin C is a cysteine protease inhibitor that is produced at a constant rate by all nucleated cells. It is freely filtered by the glomerulus and reabsorbed (but not secreted) by the renal tubules with no extrarenal excretion. Its concentration is not affected by diet, muscle mass, or acute inflammation. Normal range when measured by particle-enhanced nephelometric immunoassay (PENIA) is <0.28 mg/L.

TABLE 38 Equations Commonly Used to Estimate Renal Clearance[1,2,3,4,5]

Equation	Measure	Equation	Considerations
Cockcroft-Gault	CrCl (ml/min)	(140 – age) BW/(SCr × 72) (0.85 if female)	• Inaccurate in patients with acutely changing renal function • Weight parameter is controversial in obese patients
Reexpressed MDRD (4 variable)	GFR (ml/min/1.73 m^2)	$175 \times SCr^{-1.154} \times age^{-0.203} \times$ (0.742 if female) × (1.21 if AA)	• Inaccurate in patients with acutely changing renal function • Must be individualized for BSA by multiplying estimated GFR × (estimated BSA/1.73 m^2) • Little information available in obese, elderly, or hepatic disease patients
Obesity 1 (Winter et al.[2])	CrCl (ml/min)	(140 – age) BW/(S_{Cr} × 72) × (0.85 if female)Use various weights	• Underweight use actual weight • Normal weight use ideal weight • If BMI 26-50, use adjusted weight using 40% factor = [(actual – ideal weight) × 0.40] + ideal weight
Obesity 2 (Demirovic et al.[5])	CrCl (ml/min)	(140 – age) LBW/(S_{Cr} × 72) × (0.85 if female)	• For BMI >40 kg/m^2 • LBW_{male} = (9270 × TBW)/(6680 + 216 × BMI) • LBW_{female} = (9270 × TBW)/(8780 + 244 × BMI)
Cystatin C	eGFR (ml/min)	$135 \times \min(S_{Cr}/\kappa, 1)\alpha \times \max(S_{Cr}/\kappa, 1)^{-0.601} \times \min(S_{cys}/0.8, 1)^{-0.375} \times \max(S_{cys}/0.8, 1)^{-0.711} \times 0.995^{Age} \times 0.969$ [if female] × 1.08 [if AA] κ = –0.7 (if female), 0.9 (if male) α = –0.248 (if female), 0.207 (if male) $\min(S_{Cr}/\kappa$ or 1) = minimum of S_{Cr}/κ or 1max (S_{Cr}/κ or 1) = maximum of S_{Cr}/κ or 1min (S_{cys}/0.8, 1) = minimum of S_{cys}/0.8 or 1max (S_{cys}/0.8, 1) = maximum of S_{cys}/0.8 or 1	

AA, African American; *BMI,* body mass index; *BSA,* body surface area; *BW,* body weight in kg; *CrCl,* creatinine clearance; *eGFR,* estimated glomerular filtration rate; *LBW,* lean body weight; *GFR,* glomerular filtration rate; *MDRD,* Modification of Diet in Renal Disease equation; S_{Cr}, serum creatinine; S_{cys}, serum cystatin C; *TBW,* total body weight.
Ideal weight = (height in inches – 60) × 2.3 + 50 kg for males or 45.5 kg for females.
[1] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31-41.
[2] Winter MA, Guhr KN, Berg GM. Impact of various body weights and serum creatinine concentrations on the bias and accuracy of the Cockcroft-Gault equation. *Pharmacotherapy.* 2012;32:604-612.
[3] Inker LA, Schmid CH, Tighiourt H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med.* 2012;367:20-29.
[4] Levey AS, Coresh J, Greene T, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem.* 2007;53:766-772.
[5] Demirovic JA, Pai AB, Pai MJ. Estimation of creatinine clearance in morbidly obese patients. *Am J Health Syst Pharm.* 2009;66:642-648.
From Parrillo JE, Dellinger RP: Critical care medicine, principles of diagnosis and management in the adult, ed 5, Philadelphia, 2019, Elsevier.

BOX 14 Cockcroft-Gault Formula to Calculate Creatinine Clearance (C_{cr})

$$C_{cr} = \frac{(140 - \text{age in year}) \times (\text{lean body weight in kg})}{S_{cr} \text{ in mg/dl} - 72}$$

Elevated in: Renal disorders. Good predictor of the severity of acute tubular necrosis. Cystatin C increases more rapidly than creatinine in the early stages of GFR impairment. The cystatin C concentration is an independent risk factor for heart failure in older adults and appears to provide a better measure of risk assessment than the serum creatinine concentration.

CYSTIC FIBROSIS PCR

Test description: Test can be performed on whole blood or tissue. Common mutations in the cystic fibrosis transmembrane regulator (CFTR) gene can be used to detect 75%-80% of mutant alleles.

CYTOMEGALOVIRUS BY PCR

Test description: Test can be performed on whole blood, plasma, or tissue. Qualitative PCR is highly sensitive but may not be able to differentiate between latent and active infection.

D-DIMER

Normal range: <0.5 mcg/ml
Elevated in: DVT, pulmonary embolism, high levels of rheumatoid factor, activation of coagulation and fibrolytic system from any cause

D-dimer assay by enzyme-linked immunosorbent assay (ELISA) assists in the diagnosis of DVT and pulmonary embolism. This test has significant limitations because it can be elevated whenever the coagulation and fibrinolytic systems are activated and can also be falsely elevated with high rheumatoid factor levels.

A positive D-dimer is suggestive but not diagnostic for pulmonary embolism (PE). Patients with positive D-dimer and clinical suspicion for PE need additional tests such as chest CT to confirm diagnosis.

PE might be ruled out in patients with negative D-dimer and low pretest probability for PE.

DEHYDROEPIANDROSTERONE SULFATE

Normal:
Males:

Ages 19-30:	125-619 mcg/dl
31-50:	59-452 mcg/dl
51-60:	20-413 mcg/dl
61-83:	10-285 mcg/dl

Females:

Ages 19-30:	29-781 mcg/dl
31-50:	12-379 mcg/dl
Postmenopausal:	30-260 mcg/dl

Elevated in: Hirsutism, congenital adrenal hyperplasia, adrenal carcinomas, adrenal adenomas, polycystic ovary syndrome, ectopic ACTH-producing tumors, Cushing disease, spironolactone

DEHYDROTESTOSTERONE (serum, urine)

Normal:
Serum: Males: 30 to 85 ng/dl; females: 4 to 22 ng/dl
Urine, 24 h: Males: 20 to 50 mcg/day; females: <8 mcg/day
Elevated in: Hirsutism
Decreased in: 5-α-reductase deficiency, hypogonadism

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Ages 19-30:	125-619 mcg/dl
31-50:	59-452 mcg/dl
51-60:	20-413 mcg/dl
61-83:	10-285 mcg/dl

Females:

Ages 19-30:	29-781 mcg/dl
31-50:	12-379 mcg/dl
Postmenopausal:	30-260 mcg/dl

Elevated in: Hirsutism, congenital adrenal hyperplasia, adrenal carcinomas, adrenal adenomas, polycystic ovary syndrome, ectopic ACTH-producing tumors, Cushing disease, spironolactone

DEHYDROTESTOSTERONE (serum, urine)

Normal:
Serum: Males: 30 to 85 ng/dl; females: 4 to 22 ng/dl
Urine, 24 h: Males: 20 to 50 mcg/day; females: <8 mcg/day
Elevated in: Hirsutism
Decreased in: 5-α-reductase deficiency, hypogonadism

TABLE 39 Applications for Direct and Indirect Antiglobulin Techniques

	Applications	Purpose	What Is Detected
Direct antiglobulin test (DAT)	Investigation of HTR	To detect circulating donor red cells that are sensitized with recipient antibody. A positive DAT is the first immunohematologic evidence of a hemolytic reaction after transfusion	DAT positive owing to IgG and/or C3d depending on the antibodies responsible
	Diagnosis of HDFN	To detect maternal antibodies that have crossed the placenta to sensitize fetal red cells	DAT almost always positive as a result of IgG; occasionally C3d if ABO antibodies involved
	Diagnosis of AIHA	To detect autoantibody sensitizing a patient's own red cells	Warm autoantibodies: DAT almost always positive owing to IgG Cold autoantibodies: DAT may be due to C3d only
	Investigation of drug-induced hemolysis	To detect antidrug/red cell antibodies and/or subsequent activation of the complement system	DAT may be positive owing to IgG, C3d, or both, depending on the mechanism involved
	Antibody detection (or antibody screen)	To detect clinically significant IgG alloantibodies in the recipient	Recipient IgG antibodies bound to reagent screening cells*
	Antibody identification	To specifically identify those antibodies detected by reagent screening cells or by donor red cells	Recipient IgG antibodies bound to reagent cells from a panel of 10-12 donors*
	Crossmatching	To detect antibodies that may have been missed by the antibody screen because of absence of the corresponding antigen or presence of a dosing antibody	Recipient IgG antibodies bound to donor red cells*
	Red cell antigen typing	To type patient or donor red cells for antigens that can be detected by IgG antisera reactive only by the AGT. A common example of this would be the weak D test	Specific binding of reagent IgG antibodies to red cells positive for the corresponding antigen

AGT, Antihuman globulin test; *AIHA,* autoimmune hemolytic anemia; *C3,* complement component 3; *HDFN,* hemolytic disease of the fetus and newborn; *HTR,* hemolytic transfusion reaction; *Ig,* immunoglobulin.
*If complement is fixed in vitro, it may be detected if polyspecific antiglobulin is used.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, St Louis, 2017, Elsevier.

DEOXYCORTICOSTERONE (11-deoxycorticosterone, DOC) (serum)

Normal: 2 to 19 ng/dl. Normal secretion depends on ACTH and is suppressible by dexamethasone.
Elevated in: Adrenogenital syndromes due to 17- and 11-hydroxylase deficiencies, pregnancy
Decreased in: Preeclampsia

DEXAMETHASONE SUPPRESSION TEST, OVERNIGHT

Normal: Test is performed by giving 1 mg dexamethasone orally at 11 PM and measuring serum cortisol at 8 AM the following morning. Normal response is cortisol suppression to <3 mcg/dl; if dose of 4 mg dexamethasone is given, cortisol suppression will be to <50% of baseline.
Interpretation of results: Cushing syndrome (<10 mcg/dl), endogenous depression (half of patients suppress test values <5 mcg/dl). Most patients with pituitary Cushing disease demonstrate suppression, whereas patients with adrenal adenoma, carcinoma, and ectopic ACTH-producing tumors do not.

DIGOXIN

Normal therapeutic range: 0.5 to 2 ng/ml
Elevated in: Impaired renal function, excessive dosing, concomitant use of quinidine, amiodarone, verapamil, fluoxetine, nifedipine. Toxicity may occur at a lower blood concentration in the presence of hypokalemia, hypomagnesemia, and hypercalcemia. See Table 39.

DILANTIN

See PHENYTOIN

DIRECT ANTIGLOBULIN (Coombs Direct)

Normal: Negative
Positive: Autoimmune hemolytic anemia, erythroblastosis fetalis, transfusion reactions, drugs (α-methyldopa, penicillins, tetracycline, sulfonamides, levodopa, cephalosporins, quinidine, insulin)
False positive: May be seen with cold agglutinins

DISACCHARIDE ABSORPTION TESTS

Normal: Test is used to diagnose malabsorption due to disaccharide deficiency. It is performed by giving disaccharide orally 1 g/kg body weight to a total of 25 g. Blood is drawn at 0, 30, 60, 90, and 120 min. Normal response is a change in glucose from fasting value >30 mg/dl, inconclusive when increase is 20-30 mg/dl, abnormal when increase is >20 mg/dl. Test can also be performed by measuring air at 0, 30, 60, 90, and 120 min. Normal is H_2>20 ppm above baseline level before a colonic response.
Decreased in: Disaccharide deficiency (lactose, fructose, sorbitol), celiac disease, sprue, acute gastroenteritis

DOC

See DEOXYCORTICOSTERONE

DONATH-LANDSTEINER (D-L) TEST FOR PAROXYSMAL COLD HEMOGLOBINURIA

Normal: No hemolysis
Interpretation of results: Hemolysis indicates presence of bithermic cold hemolysins or Donath-Landsteiner antibodies (D-L Ab)

DOPAMINE

Normal range: 175 pg/ml
Elevated in: Pheochromocytomas, neuroblastomas, stress, vigorous exercise, certain foods (bananas, chocolate, coffee, tea, vanilla)

D-XYLOSE ABSORPTION

Normal range: 21% to 31% excreted in 5 hours
Decreased in: Malabsorption syndrome

D-XYLOSE ABSORPTION TEST

Normal range:
URINE: ≥4 g/5 hours (5-hour urine collection in adults >12 yr [25-g dose])
SERUM: ≥25 mg/dl (adult, 1 hour, 25-g dose, normal renal function)
Normal results: In patients with malabsorption, normal results suggest pancreatic disease as an etiology of the malabsorption.
Abnormal results: Celiac disease, Crohn disease, tropical sprue, surgical bowel resection, AIDS. False positives can occur with decreased renal function, dehydration/hypovolemia, surgical blind loops, decreased gastric emptying, vomiting.

ELECTROPHORESIS, HEMOGLOBIN

See HEMOGLOBIN ELECTROPHORESIS

ELECTROPHORESIS, PROTEIN

See PROTEIN ELECTROPHORESIS

ENA COMPLEX

See EXTRACTABLE NUCLEAR ANTIGEN

ENDOMYSIAL ANTIBODIES

Normal: Not detected
Present in: Celiac disease, dermatitis herpetiformis

EOSINOPHIL COUNT

Normal range: 1% to 4% eosinophils (0-440/mm^3)
Elevated in
HELMINTHIC PARASITE
Ascaris lumbricoides (invasive larval stage)
Hookworms (invasive larval stage)
Strongyloides stercoralis (initial infection and autoinfection)
Trichinosis
Filariasis
Echinococcus granulosus and *E. multilocularis*
Toxocara species
Animal hookworms
Angiostrongylus cantonensis and *A. costaricensis*
Schistosomiasis
Liver flukes
Fasciolopsis buski
Anisakiasis
Capillaria philippinensis
Paragonimus westermani
"Tropical eosinophilia" (unidentified microfilariae)
NOTE: Table 40 describes an approach to investigation of eosinophilia in returning travelers.
OTHER INFECTIONS/INFESTATIONS
Pulmonary aspergillosis
Severe scabies
ALLERGIES
Asthma
Hay fever
Drug reactions
Atopic dermatitis
AUTOIMMUNE AND RELATED DISORDERS
Polyarteritis nodosa
Necrotizing vasculitis
Eosinophilic fasciitis
Pemphigus
NEOPLASTIC DISEASES
Hodgkin disease
Mycosis fungoides
Chronic myelocytic leukemia
Eosinophilic leukemia
Polycythemia vera
Mucin-secreting adenocarcinomas
IMMUNODEFICIENCY STATES
Hyperimmunoglobulin E with recurrent infection
Wiskott-Aldrich syndrome
OTHER
Addison disease
Inflammatory bowel disease
Dermatitis herpetiformis
Toxic/chemical syndrome
Eosinophilic myalgia syndrome, tryptophan, toxic oil syndrome
Hypereosinophilic syndrome (unknown etiology)

Fig. 21 describes an algorithm for patients with eosinophil disorders.
Table 41 describes hematopoietic neoplasms accompanied by eosinophilia.

TABLE 40 Eosinophilia Investigation in Returning Travelers

History	Allergies
	Drugs and vitamins (L-tryptophan)
	Regions, localities, and duration of exposure
Physical examination	Skin, subcutaneous tissues
	Liver/spleen
	Signs of other systemic disease
Initial investigations	Full blood count and differential white blood cell count
	Stool examination for ova and parasites (×3) Urine analysis
	Examination of midday urine for ova and parasites (×3) (in those who have traveled to Africa or the Middle East)
Further investigations as suggested by travel and exposure from history	*Strongyloides* culture and serologic testing; duodenal aspirate (strongyloidiasis, hookworm)
	Serologic testing (schistosomiasis, filariasis); day/night blood films (filariasis)
Further studies if suggested by history and physical examination	Skin snips (onchocerciasis)
	Chest x-ray examination (hydatid cyst, tropical pulmonary eosinophilia, paragonimiasis)
	Soft tissue x-ray examination (cysticercosis); sputum examination for ova and parasites (paragonimiasis)
	Abdominal ultrasound examination (hydatid cyst)
	Cystoscopy with or without biopsy (schistosomiasis)
	Rectal snips (schistosomiasis)

From Hoffman R: *Hematology: Basic principles and practice,* ed 6, Philadelphia, 2013, WB Saunders.

Table 42 describes the differential diagnosis of childhood eosinophilia.

EPINEPHRINE, PLASMA

Normal range: 0 to 90 pg/ml
Elevated in: Pheochromocytomas, neuroblastomas, stress, vigorous exercise, certain foods (bananas, chocolate, coffee, tea, vanilla), hypoglycemia

EPSTEIN-BARR VIRUS SEROLOGY (BOX 15)

Normal range: IgG anti-viral capsid antigen (VCA) <1:10 or negative>
Abnormal: IgG anti-VCA >1:10 or positive indicates either current or previous infection
IgM anti-VCA >1:10 or positive indicates current or recent infection
Anti-Epstein-Barr virus nuclear antigen (EBNA) ≥1.5 or positive indicates previous infection

Table 43 and Fig. 22 describe test interpretation.

ERYTHROCYTE SEDIMENTATION RATE (ESR, sed rate, sedimentation rate)

See Table 44 for erythrocyte sedimentation rate ranges in health.
Normal range: Male: 0 to 15 mm/hr
Female: 0 to 20 mm/hr
Elevated in: Collagen vascular diseases, infections, myocardial infarction, neoplasms, inflammatory states (acute phase reactant), hyperthyroidism, hypothyroidism, rouleaux formation
Decreased in: Sickle cell disease, polycythemia, corticosteroids, spherocytosis, anisocytosis, hypofibrinogenemia, increased serum viscosity

ERYTHROPOIETIN (EP)

Normal: 3.7 to 16.0 IU/L by radioimmunoassay

Erythropoietin is a glycoprotein secreted by the kidneys that stimulates RBC production by acting on erythroid-committed stem cells.

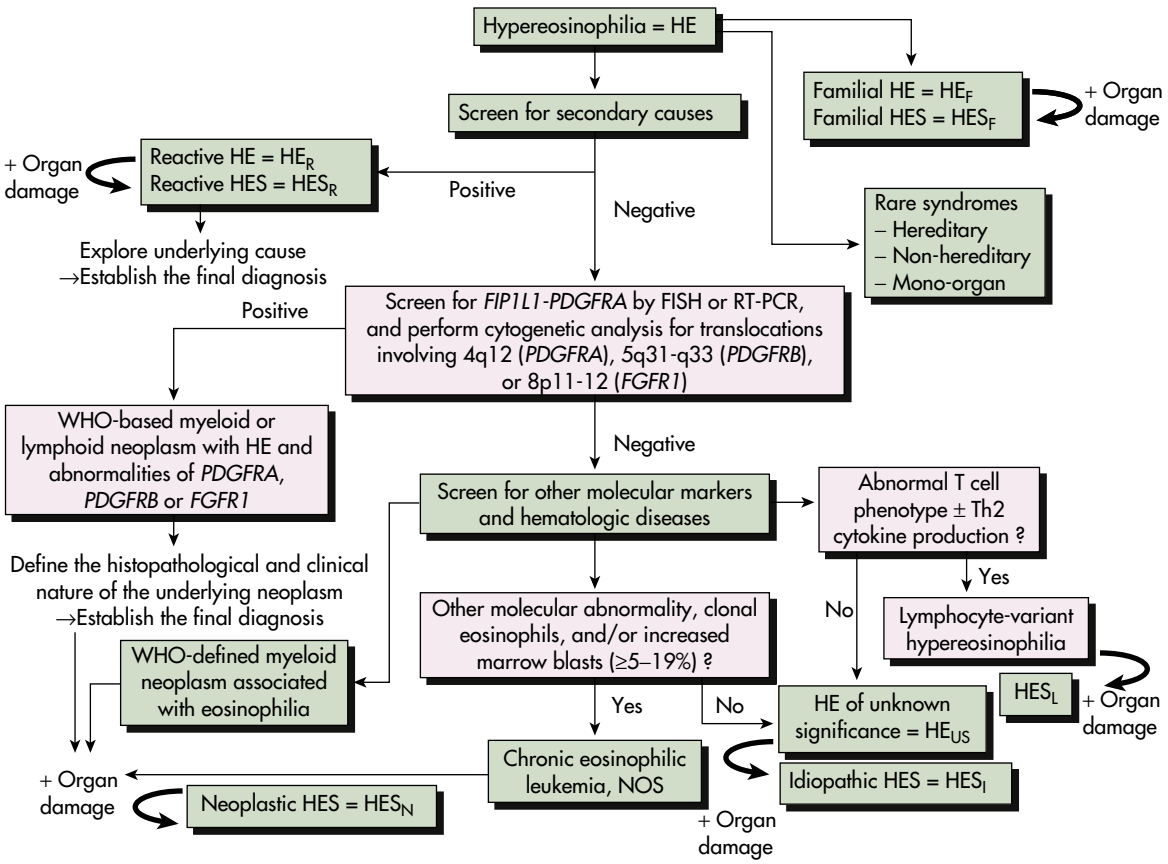

FIG. 21 Diagnostic algorithm for patients with eosinophil disorders. The first important step in the algorithm is to confirm the presence of hypereosinophilia *(HE)*, defined by a persistent (>4 weeks) increase in eosinophils above 1500/μL blood. The next important question is whether HE is reactive (HE_R) or neoplastic (clonal = HE_N) in nature. In patients with HE_N, WHO criteria should be applied in order to define the underlying molecular lesion. In addition, morphologic and histopathologic criteria are used to arrive at a final diagnosis regarding the underlying disease. In patients with HE_R, an underlying disease must also be defined. In both groups of patients, the next important question is whether (or not) HE-related organ damage is present. If such organopathy is found, it is appropriate to diagnose the (additional) presence of HES. According to the underlying etiology (disease), HES is classified again into HES_R and HES_N. In some patients with HES, a clonal T-cell population, but no lymphoproliferative disease, is detected. In these patients, the HES_L variant is diagnosed. If no clonal T cells and no underlying reactive or neoplastic condition is detected in a patient with HES, the (provisional) diagnosis of an HES_I is established. If no underlying disease and no HES are detected, the patient has HE_{US} by definition. Familial cases of HE or HES are very rare, and the same holds true for hereditary syndromes and mono-organ syndromes accompanied by HE. *FISH,* Fluorescence in situ hybridization; *HES,* hypereosinophilic syndrome; *NOS,* not otherwise specified; *RT-PCR,* reverse transcription polymerase chain reaction; *WHO,* World Health Organisation. (From Hoffman R: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.)

Increased in:
Extremely high: Generally seen in patients with severe anemia (Hct, <25; Hb<7) such as in cases of aplastic anemia, severe hemolytic anemia, hematologic cancers
Very high: Patients with mild to moderate anemia (Hct, 25 to 35; Hb, 7 to 10)
High: Patients with mild anemia (e.g., AIDS, myelodysplasia)

Erythropoietin can be inappropriately elevated in patients with malignant neoplasms, renal cysts, postrenal transplant, meningioma, hemangioblastoma, and leiomyoma.

Decreased in: Renal failure, polycythemia vera, autonomic neuropathy

ESTRADIOL (serum)

Normal range:
Female, premenopausal: 30 to 400 pg/ml, depending on phase of menstrual cycle
Female, postmenopausal: 0 to 30 pg/ml
Male, adult: 10 to 50 pg/ml

Decreased in: Ovarian failure

Elevated in: Tumors of ovary, testis, adrenal, or nonendocrine sites (rare)

TABLE 41 Hematopoietic Neoplasms Accompanied by Eosinophilia

Neoplasms in Which Eosinophils Are Likely to Be Clonal Cells
Acute eosinophilic leukemia (AEL)
Chronic eosinophilic leukemia (CEL)
Acute myeloid leukemia with inv(16) (FAB AML M4eo)
Chronic myeloid leukemia (CML –*BCR-ABL1*+)
Myeloid neoplasms with *PDGFR* abnormalities (WHO types)
Hematopoietic neoplasms with *FGFR1* abnormalities (WHO types)
Smoldering systemic mastocytosis
Aggressive systemic mastocytosis (ASM)
Mast cell leukemia (MCL)
SM-AHN (SM-CEL)
Neoplasms in Which Eosinophils May or May Not Be Part of the Malignant Clone
Other myeloproliferative neoplasms (MPN) with eosinophiliaa
Myelodysplastic syndromes (MDS) with eosinophilia
Other MDS/MPN overlap syndromes with eosinophilia[a]
Indolent systemic mastocytosis
Neoplasms in Which Eosinophils Usually Are Not Part of the Malignant Clone
Hodgkin disease
B- or T-cell non-Hodgkin lymphoma
Acute lymphoblastic leukemia (ALL)
Chronic lymphocytic leukemia (CLL)
Langerhans cell histiocytosis

AHN, Associated hematologic neoplasm; *FAB,* French–American–British Cooperative Study Group; *SM,* systemic mastocytosis; *WHO,* World Health Organization.
[a]Other MPN or MPN/MDS: Neoplasms where no abnormalities in the *PDGFR* or *FGFR1* genes are detectable.
From Hoffman R: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

ESTROGEN

Normal range (serum):

Males:	20-80 pg/ml
Females:	
Follicular:	60-200 pg/ml
Luteal:	160-400 pg/ml
Postmenopausal:	<130 pg/ml

Normal Range (urine):

Males:	4-23 μg/g creatinine
Females:	
Follicular:	7-65 μg/g creatinine
Midcycle:	32-104 μg/g creatinine
Luteal:	8-135 μg/g creatinine

Elevated in: Hyperplasia of adrenal cortex, ovarian tumors producing estrogen, granulosa and thecal cell tumors, testicular tumors
Decreased in: Menopause, hypopituitarism, primary ovarian malfunction, anorexia nervosa, hypofunction of adrenal cortex, ovarian agenesis, psychogenic stress, gonadotropin-releasing hormone deficiency

ETHANOL (blood)

Normal range: Negative (values <10 mg/dl are considered negative)
Ethanol is metabolized at 10-25 mg/dl/hr. Levels ≥80 mg/dl are considered evidence of impairment for driving. Fatal blood concentration is considered to be >400 mg/dl. Table 45 summarizes the influence of acute ethanol ingestion on ethanol levels and behavior.

EXTRACTABLE NUCLEAR ANTIGEN (ENA complex, anti-RNP antibody, anti-sm, anti-Smith)

Normal: Negative
Present in: Systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, mixed connective tissue disease

TABLE 42 Differential Diagnosis of Childhood Eosinophilia

Physiologic
Prematurity
Infants receiving hyperalimentation
Hereditary
Infectious
Parasitic (with tissue-invasive helminths, e.g., trichinosis, strongyloidiasis, pneumocystosis, filariasis, cysticercosis, cutaneous and visceral larva migrans, echinococcosis)
Bacterial (brucellosis, tularemia, cat-scratch disease, *Chlamydia*)
Fungal (histoplasmosis, blastomycosis, coccidioidomycosis, allergic bronchopulmonary aspergillosis)
Mycobacterial (tuberculosis, leprosy)
Viral (HIV-1, HTLV-1, hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus)
Pulmonary
Allergic (rhinitis, asthma)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Loeffler syndrome
Hypersensitivity pneumonitis
Eosinophilic pneumonia (chronic, acute)
Pulmonary interstitial eosinophilia
Dermatologic
Atopic dermatitis
Pemphigus
Dermatitis herpetiformis
Infantile eosinophilic pustular folliculitis
Eosinophilic fasciitis (Schulman syndrome)
Eosinophilic cellulitis (Wells syndrome)
Kimura disease (angiolymphoid hyperplasia with eosinophilia)
Hematologic/Oncologic
Neoplasm (lung, gastrointestinal, uterine)
Leukemia/lymphoma
Myelofibrosis
Myeloproliferative (FIP1L1–PDGFRA-positive) hypereosinophilic syndrome
Lymphatic hypereosinophilic syndrome
Systemic mastocytosis
Immunologic
T-cell immunodeficiencies
Hyper-IgE (Job) syndrome
Wiskott-Aldrich syndrome
Graft-versus-host disease
Drug hypersensitivity
Postirradiation
Postsplenectomy
Endocrine
Addison disease
Hypopituitarism
Cardiovascular
Loeffler disease (fibroplastic endocarditis)
Congenital heart disease
Hypersensitivity vasculitis
Eosinophilic myocarditis
Gastrointestinal
Benign proctocolitis
Inflammatory bowel disease
Eosinophilic gastrointestinal diseases (EGID)
FIP1L1-PDGFRA, FIP1-like 1–platelet-derived growth factor receptor α.

Ig, Immunoglobulin.
From Kliegman RM: *Nelson textbook of pediatrics*, ed 21, Philadelphia, 2020, Elsevier.

BOX 15 Epstein-Barr Virus-Associated Malignancies

Malignancy	Epstein-Barr Virus Frequency
Hodgkin disease	≈40%
Non-Hodgkin lymphomas	
Burkitt lymphoma	20%-95%
Diffuse large B-cell lymphoma and $CD30^+$ $Ki\text{-}1^+$ anaplastic large cell lymphoma	10%-35%
Lymphomatoid granulomatosis	80%-95%
T cell-rich B-cell lymphoma	20%
Angioimmunoblastic lymphoma	>80%
T-cell, NK cell, and T/NK-cell lymphomas	30%-90%
Nasopharyngeal carcinoma	>95%
Gastric adenocarcinoma	5%-10%
Pyothorax-associated lymphoma	>95%
Leiomyosarcoma in immunocompromised patients	>95%

NK, Natural killer.
From Hoffman R: *Hematology: Basic principles and practice,* ed 6, Philadelphia, WB Saunders, 2013.

TABLE 43 Antibody Tests in Epstein-Barr Viral Infection

	Appearance	Peak	Disappears
Heterophil Ab	3-5 days after onset of Sx (range, 0-21 days)	During second wk after onset of Sx (1-4 wk)	2-3 mo after onset of Sx (still found at 1 yr in 20% of cases)
VCA-IgM	Beginning of Sx (1 wk before to 1 wk after Sx begin)	During first wk after onset of Sx (0-21 days)	2-3 mo after onset of Sx (1-6 mo)
VCA-IgG	3 days after onset of Sx (0-2 wk)	During second wk after onset of Sx (1-3 wk)	Decline to lower level, then persists for life
EBNA-IgG	3 wk after onset of Sx (1-4 wk)	8 mo after appearance (3-12 mo)	Lifelong
EA-D	5 days after onset of Sx (during first 1-2 wk after onset of Sx)	14-21 days after onset of Sx (1-4 wk)	9 wk after appearance (2-6 mo)
EBNA-IgM	Same as VCA-IgM	Same as VCA-IgM	Same as VCA-IgM

Ab, Antibody; *EA,* early antigen; *EBNA,* Epstein-Barr virus nuclear antigen; *Ig,* immunoglobulin; *Sx,* symptoms; *VCA,* viral capsid antigen.
From Ravel R: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.

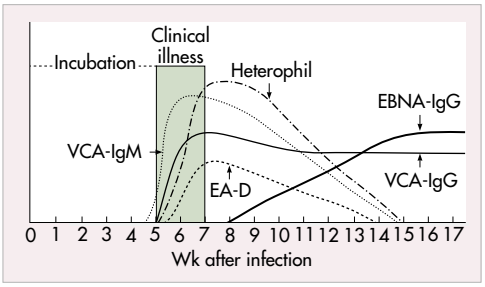

FIG. 22 Tests in Epstein-Barr viral infection. See Table 43 for abbreviations. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

TABLE 44 Erythrocyte Sedimentation Ranges in Health

Age Range (Yr)	ESR Mean (mm in 1 h)
10-19	8
20-29	10.8
30-39	10.4
40-49	13.6
50-59	14.2
60-69	16
70-79	16.5
80-91	15.8
Pregnancy	
Early gestation	48 (62 if anaemic)
Later gestation	70 (95 if anaemic)

ESR, Erythrocyte sedimentation range.
From Bain BJ et al: *Dacie and Lewis practical haematology*, ed 12, Philadelphia, 2017, Elsevier.

TABLE 45 Influence of Acute Ethanol Ingestion on Ethanol Levels and Behavior

Ounces	Blood Concentration	Influence
1-2	10-50 mg/dl (2.2-10.9 mmol/L)	None to mild euphoria
3-4	50-100 mg/dl (10.9-21.7 mmol/L or greater)	Mild influence on stereoscopic vision and dark adaptation
	100 mg/dl (21.7 mmol/L)	Legally intoxicated
4-6	100-150 mg/dl (21.7-32.6 mmol/L)	Euphoria; disappearance of inhibition; prolonged reaction time
6-7	150-200 mg/dl (32.6-43.4 mmol/L)	Moderately severe poisoning; reaction time greatly prolonged; loss of inhibition and slight disturbances in equilibrium and coordination
8-9	200-250 mg/dl (43.4-54.3 mmol/L)	Severe degree of poisoning; disturbances of equilibrium and coordination; retardation of the thought processes and clouding of consciousness
10-15	250-400 mg/dl (54.3-86.8 mmol/L)	Deep, possibly fatal, coma

From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

FACTOR V LEIDEN

Test description: PCR test performed on whole blood or tissue. This single mutation, found in 2% to 8% of the general Caucasian population, is the single most common cause of hereditary thrombophilia.

FASTING BLOOD SUGAR

See GLUCOSE, FASTING

FBS

See GLUCOSE, FASTING

FDP

See FIBRIN DEGRADATION PRODUCT

FECAL FAT, QUANTITATIVE (72-hr collection)

Normal range: 2 to 6 g/24 hr (7 to 21 mmol/dl [CF: 3.515; SMI: 1 mmol/dl])
Elevated in: Malabsorption syndrome

FECAL GLOBIN IMMUNOCHEMICAL TEST

Normal: Negative. This test is performed by immunochromatography on a cellulose strip that has been impregnated with various antibodies. The test uses a small amount of toilet water as the specimen and is placed onto absorbent pads of card similar to traditional occult blood (OB) card. There is no direct handling of stool. This test is specific for the globin portion of the hemoglobin molecule, which confers lower GI bleeding specificity. It specifically detects blood from the lower GI tract; guaiac tests are not lower GI specific. It is more sensitive than typical Hemoccult test (detection limit 50 mcg Hb/g feces versus >500 mcg Hb/g feces for Hemoccult). It has no dietary restrictions and gives no false-positives due to plant peroxidases and red meats. It has no medication restrictions. Iron supplements and NSAIDs do not cause false positives. Vitamin C does not cause false-negatives.
Positive in: Lower GI bleeding

FERRITIN (serum)

Normal range: 18 to 300 ng/ml (18 to 300 μg/L [CF: 1; SMI: 10 μg/L])
Elevated in: Hyperthyroidism, inflammatory states, liver disease (ferritin elevated from necrotic hepatocytes), neoplasms (neuroblastomas, lymphomas, leukemia, breast carcinoma), iron replacement therapy, hemochromatosis, hemosiderosis. Table 46 summarizes hereditary iron overload disorders.
Decreased in: Iron deficiency anemia

TABLE 46 Hereditary Iron Overload Disorders

Disorder	Gene, Chromosome Location	Inheritance	Plasma Transferrin Saturation	Plasma Ferritin	Iron Deposition Sites	Clinical Manifestations
Hereditary hemochromatosis, *HFE*-associated (type 1; OMIM 235200)	*HFE*, 6p21	Autosomal recessive	Early increase; >45%	Later increase after third decade	Parenchymal iron overload affecting hepatocytes, heart, pancreas, other organs	Liver and heart disease, diabetes, gonadal failure, arthritis, skin pigmentation
Hereditary hemochromatosis, TfR2-associated (type 3; OMIM 604250)	*TFR2*, 7q22	Autosomal recessive	Early increase; >45%	Later increase after third decade	Parenchymal iron overload affecting hepatocytes, heart, pancreas, other organs	Liver and heart disease, diabetes, gonadal failure, arthritis, skin pigmentation
Juvenile hemochromatosis, hemojuvelin-associated (type 2A; OMIM 602390)	*HJV,* 1q21	Autosomal recessive	Early increase; >45%	Increased by second decade	Parenchymal iron overload affecting hepatocytes, heart, pancreas, other organs	As for hereditary hemochromatosis, but liver involvement less prominent
Juvenile hemochromatosis, hepcidin-associated (type 2B; OMIM 613313)	*HAMP*, 19q13	Autosomal recessive	Early increase; >45%	Increased by second decade	Parenchymal iron overload affecting hepatocytes, heart, pancreas, other organs	As for hereditary hemochromatosis, but liver involvement less prominent
Hemochromatosis, DMT1-associated (OMIM 206100)	*SCL11A2,* 12q13	Autosomal recessive	Early increase; >45%	Normal to moderately elevated	Hepatic iron overload, predominantly in hepatocytes	Severe microcytic anemia, liver dysfunction
Atransferrinemia (OMIM 209300)	*TF*, 3q22	Autosomal recessive	No plasma transferrin	Increased	Parenchymal iron overload affecting hepatocytes, heart, pancreas; no iron in bone marrow or spleen	Transfusion-dependent iron deficiency anemia, growth retardation, poor survival
Aceruloplasminemia (OMIM 604290)	*CP*, 3q24-q25	Autosomal recessive	Decreased	Increased	Marked iron accumulation in basal ganglia, liver, pancreas	Diabetes, progressive neurologic disease, retinal degeneration
Hemochromatosis, ferroportin-associated, with impaired iron export (type 4A; OMIM 606069)	*SLC40A1*, 2q32	Autosomal dominant	Remains normal or low	Early increase	Predominantly macrophage iron deposition	None
Hemochromatosis, ferroportin-associated, with hepcidin resistance (type 4B; OMIM 606069)	*SLC40A1*, 2q32	Autosomal dominant	Early increase; >45%	Early increase	Parenchymal iron overload affecting hepatocytes, heart, pancreas, other organs	Similar to HFE-associated hemochromatosis

OMIM, Online Mendelian Inheritance in Man.
From Hoffman R et al: *Hematology, basic principles and practice*, ed 6, Philadelphia, 2013, WB Saunders.

BOX 16 Etiopathophysiologic Classification of Folate Deficiency

- Nutritional causes
  - Decreased dietary intake: Poverty and famine, institutionalized individuals (psychiatric/nursing homes)/chronic debilitating disease, prolonged feeding of infants with goat's milk, special slimming diets or food fads (folate-rich foods not consumed), cultural/ethnic cooking techniques (food folate destroyed)
  - Decreased diet and increased requirements
    - Physiologic: Pregnancy and lactation, prematurity, hyperemesis gravidarum, infancy
    - Pathologic
      - Intrinsic hematologic diseases involving hemolysis with compensatory erythropoiesis, abnormal hematopoiesis, or bone marrow infiltration with malignant disease
      - Dermatologic disease: Psoriasis
  - Folate malabsorption
    - With normal intestinal mucosa
      - Drugs: Sulfasalazine, pyrimethamine, proton pump inhibitors (via inhibition of proton-coupled folate transporter [PCFT])
      - Hereditary folate malabsorption (mutations in PCFTs) (rare)
    - With mucosal abnormalities: Tropical and nontropical sprue, regional enteritis
- Defective cerebral spinal fluid folate transport: Cerebral folate deficiency (mutation or autoantibodies to folate receptors) (rare)
- Inadequate cellular utilization
  1. Folate antagonists (methotrexate)
  2. Hereditary enzyme deficiencies involving folate
- Drugs (multiple effects on folate metabolism): Alcohol, sulfasalazine, triamterene, pyrimethamine, trimethoprim-sulfamethoxazole, diphenylhydantoin, barbiturates

From Hoffman R: *Hematology: Basic principles and practice,* ed 6, Philadelphia, 2013, WB Saunders.

α-1 FETOPROTEIN

Normal range: 0 to 20 ng/ml (0 to 20 μg/L [CF: 1; SMI: 1 μg/L])
Elevated in: Hepatocellular carcinoma (usually values >1000 ng/ml), germinal neoplasms (testis, ovary, mediastinum, retroperitoneum), liver disease (alcoholic cirrhosis, acute hepatitis, chronic active hepatitis), fetal anencephaly, spina bifida, basal cell carcinoma, breast carcinoma, pancreatic carcinoma, gastric carcinoma, retinoblastoma, esophageal atresia

FIBRIN DEGRADATION PRODUCT (FDP)

Normal range: <10 μg/ml
Elevated in: Disseminated intravascular coagulation, primary fibrinolysis, pulmonary embolism, severe liver disease
NOTE: The presence of rheumatoid factor may cause falsely elevated FDP.

FIBRINOGEN

Normal range: 200 to 400 mg/dl (2 to 4 g/L [CF: 0.01; SMI: 0.1 g/L])
Elevated in: Tissue inflammation or damage (acute phase protein reactant), oral contraceptives, pregnancy, acute infection, myocardial infarction
Decreased in: Disseminated intravascular coagulation, hereditary afibrinogenemia, liver disease, primary or secondary fibrinolysis, cachexia

FOLATE (folic acid)

Normal range: Plasma: 2 to 10 ng/ml (4 to 22 nmol/L [CF: 2.266; SMI: 2 nmol/L])
Red blood cells: 140 to 960 ng/ml (550 to 2200 nmol/L [CF: 2.266; SMI: 10 nmol/L])
Decreased in: Folic acid deficiency (inadequate intake, malabsorption), alcoholism, drugs (methotrexate, trimethoprim, phenytoin, oral contraceptives, Azulfidine), vitamin B_{12} deficiency (defective red cell folate absorption), hemolytic anemia. Box 16 summarizes an etiophysiologic classification of folate deficiency.
Elevated in: Folic acid therapy

FOLLICLE-STIMULATING HORMONE (FSH)

Normal range: 5-20 mIU/ml
Elevated in: Menopause, primary gonadal failure, alcoholism, castration, Klinefelter syndrome, gonadotropin-secreting pituitary hormones
Decreased in: Pregnancy, polycystic ovary disease, anorexia nervosa, anterior pituitary hypofunction

FREE T4

See T_4, FREE

FREE THYROXINE INDEX

Normal range: 1.1 to 4.3
INCREASED THYROXINE OR FREE THYROXINE VALUES
Laboratory error
Primary hyperthyroidism (T4/T3 type)
Severe thyroxine-binding globulin elevation
Excess therapy of hypothyroidism
Excessive dose of levothyroxine
Active thyroiditis (subacute, painless, early active Hashimoto disease)
Familial dysalbuminemic hyperthyroxinemia (some FT4 kits, especially analog types)
Peripheral resistance to T4 syndrome
Amiodarone or propranolol
Postpartum transient toxicosis
Factitious hyperthyroidism
Jod-Basedow (iodine-induced) hyperthyroidism
Severe nonthyroid illness
Acute psychosis (especially paranoid schizophrenia)
T4 sample drawn 2 to 4 hr after levothyroxine dose
Struma ovarii
Pituitary thyroid-stimulating hormone-secreting tumor
Certain x-ray contrast media (Telepaque and Oragrafin)
Acute porphyria
Heparin effect (some T4 and FT4 kits)
Amphetamine, heroin, methadone, and phencyclidine abuse
Perphenazine or 5-fluorouracil
Antithyroid or anti-IgG heterophil (HAMA) autoantibodies
"T4" hyperthyroidism
Hyperemesis gravidarum; about 50% of patients
High altitudes
DECREASED THYROXINE OR FREE THYROXINE VALUES
Laboratory error
Primary hypothyroidism
Severe nonthyroid illness
Lithium therapy
Severe thyroxine-binding globulin decrease (congenital, disease, or drug-induced) or severe albumin decrease
Dilantin, Depakene, or high-dose salicylate drugs
Pituitary insufficiency
Large doses of inorganic iodide (e.g., saturated solution of potassium iodide)
Moderate or severe iodine deficiency
Cushing syndrome
High-dose glucocorticoid drugs
Pregnancy, third trimester (low normal or small decrease)
Addison disease; some patients (30%)
Heparin effect (a few FT4 kits)
Desipramine or amiodarone drugs
Acute psychiatric illness

FTA-ABS (serum)

Normal: Nonreactive
Reactive in: Syphilis, other treponemal diseases (yaws, pinta, bejel), SLE, pregnancy

FUROSEMIDE STIMULATION TEST

Normal: Test is performed by giving 60 mg furosemide orally after overnight fast. Patient should be on a normal diet without medications the wk before the test. Normal results: renin 1 to 6 ng angiotensin L/ml/hr.
Elevated in: Renovascular hypertension, Bartter syndrome, high-renin essential hypertension, pheochromocytoma
No response in:
Primary aldosteronism, low-renin essential hypertension, hyporeninemic hypoaldosteronism

GAMMA-GLUTAMYL TRANSFERASE (GGT)

See γ-GLUTAMYL TRANSFERASE

GASTRIN (serum)

Normal range: 0 to 180 pg/ml (0 to 180 ng/L [CF: 1; SMI: 10 ng/L])
Elevated in: Zollinger-Ellison syndrome (gastrinoma), pernicious anemia, hyperparathyroidism, retained gastric antrum, chronic renal failure, gastric ulcer, chronic atrophic gastritis, pyloric obstruction, malignant neoplasms of the stomach, H_2-blockers, omeprazole, calcium therapy, ulcerative colitis, rheumatoid arthritis

GASTRIN STIMULATION TEST

Normal: Gastrin stimulation test after calcium infusion is performed by giving a calcium infusion (15 mg/kg in 500 ml normal saline over 4 hours). Serum is drawn in fasting state before infusion and at 1, 2, 3, and 4 hr. Normal response is little or no increase over baseline gastrin level.
Elevated in: Gastrinoma (gastrin >400 pg/ml), duodenal ulcer (gastrin level increase <400 ng/L)
Decreased in: Pernicious anemia, atrophic gastritis

GLIADIN ANTIBODIES, IGA AND IGG

Normal: <25 U, equivocal 20-25 U, positive >25 U. Test is useful to monitor compliance with gluten-free diet in patients with celiac disease.
Elevated in: Celiac disease with dietary noncompliance

GLOMERULAR BASEMENT MEMBRANE (GBM) ANTIBODY

Normal: Negative
Present in: Goodpasture syndrome

GLOMERULAR FILTRATION RATE

See Box 17 for a summary of common equations for calculating GFR or creatinine clearance. Chronic kidney disease stages based on GFR are summarized in Table 47.
Normal:

Ages 20-29	116 ml/min/1.73 m^2
Ages 30-39	107 ml/min/1.73 m^2
Ages 40-49	99 ml/min/1.73 m^2
Ages 50-59	93 ml/min/1.73 m^2
Ages 60-69	85 ml/min/1.73 m^2
Ages >75	75 ml/min/1.73 m^2

Decreased in: Renal insufficiency, decreased renal blood flow

GLUCAGON

Normal: 20 to 100 pg/ml
Elevated in: Glucagonoma (900 to 7800 pg/ml), chronic renal failure, diabetes mellitus, glucocorticoids, insulin, nifedipine, danazol, sympathomimetic amines
Decreased in: Hyperlipoproteinemia (types III, IV), beta-blockers, secretin

GLUCOSE, FASTING (FBS, FASTING BLOOD SUGAR)

Fig. E23 describes the approach to hypoglycemia. An algorithm for evaluation of hypoglycemia in children is described in Fig. E24.

BOX 17 Common Equations for Estimating Glomerular Filtration Rate or Creatinine Clearance

Cockcroft-Gault (C_{Cr} · BSA/1.73 m^2)
For men: $C_{Cr} = [(140 - age) \cdot weight\ (kg)]/S_{Cr} \cdot 72$
For women: $C_{Cr} = ([(140 - age) \cdot weight\ (kg)]/S_{Cr} \cdot 72) \cdot 0.85$

MDRD (1)
$GFR = 170 \cdot [S_{Cr}]^{-0.999} \cdot [age]^{-0.176} \cdot [0.762\ if\ patient\ is\ female] \cdot [1.18\ if\ patient\ is\ black] \cdot [BUN]^{-0170} \cdot [Alb]^{0.318}$

MDRD (2)
$GFR = 186 \cdot [S_{Cr}]^{-1.154} \cdot [age]^{-0.203} \cdot [0.742\ if\ patient\ is\ female] \cdot [1.212\ if\ patient\ is\ black]$

Jellife (1) (C_{Cr} · BSA/1.73 m^2)
For men: $(98 - [0.8 \cdot (age - 20)])/S_{Cr}$
For women: $(98 - [0.8 \cdot (age - 20)])S_{Cr} \cdot 0.90$

Jellife (2)
For men: $(100/S_{Cr})^{-12}$
For women: $(80/S_{Cr})^{-7}$

Mawer
For men: $weight \cdot [29.3 - (0.203 \cdot age)] \cdot [1 - (0.03 \cdot SCr)]$
For women: $weight \cdot [25.3 - (0.175 \cdot age)] \cdot [1 - (0.03 \cdot SC_r)]$

Bjornsson
For men: $[27 - (0.173 \cdot age)] \cdot weight \cdot 0/S_{Cr}$
For women: $[25 - (0.175 \cdot age)] \cdot weight \cdot 0.07/S_{Cr}$

Gates
For men: $(89.4 \cdot S_{Cr}^{-1.2}) + (55 - age) \cdot (0.447 \cdot S_{Cr}^{-1.1})$
For women: $(89.4 \cdot S_{Cr}^{-1.2}) + (55 - age) \cdot (0.447 \cdot S_{Cr}^{-1.1})$

Salazar-Corcoran
For men: $[137 - age] \cdot [(0.285 \cdot weight) + (12.1 \cdot height^2)]/(51 \cdot S_{Cr})$
For women: $[146 - age] \cdot [(0.287 \cdot weight) + (9.74 \cdot height^2)]/(60 \cdot S_{Cr})$

Alb, Albumin; *BSA,* body surface area; *BUN,* blood urea nitrogen; *Ccr,* creatinine clearance; *MDRD,* Modification of Diet in Renal Disease; *Scr,* serum creatinine.
From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.

TABLE 47 Chronic Kidney Disease Stages

Stage	eGFR (ml/min/1.73 m^2)	Urinalysis Findings
1	≥90	Hematuria, proteinuria, or imaging abnormalities at >3 mo
2	60-89	Hematuria, proteinuria, or imaging abnormalities at >3 mo
3	30-59	↑ or normal
4	15-29	↑ or normal
5	0-14	↑ or normal

eGFR, Estimated glomerular filtration rate.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Elsevier.

Normal range: 60 to 99 mg/dl (3.8 to 6.0 mmol/L [CF: 0.05551; SMI: 0.1 mmol/L])
Elevated in: Diabetes mellitus, stress, infections, myocardial infarction, cerebrovascular accident, Cushing syndrome, acromegaly, acute pancreatitis, glucagonoma, hemochromatosis, drugs (glucocorticoids, diuretics [thiazides, loop diuretics]), glucose intolerance, impaired fasting glucose
Decreased in: Sulfonylurea therapy, insulin therapy, reactive hypoglycemia (e.g., subtotal gastrectomy), starvation, insulinoma, glycogen storage disorders, severe liver disease or renal disease, ethanol-induced hypoglycemia, mesenchymal tumors that secrete insulin-like hormones

GLUCOSE, POSTPRANDIAL

Normal range: <140 mg/dl (<7.8 mmol/L [CF: 0.05551; SMI: 0.1 mmol/L])
Elevated in: Diabetes mellitus, glucose intolerance

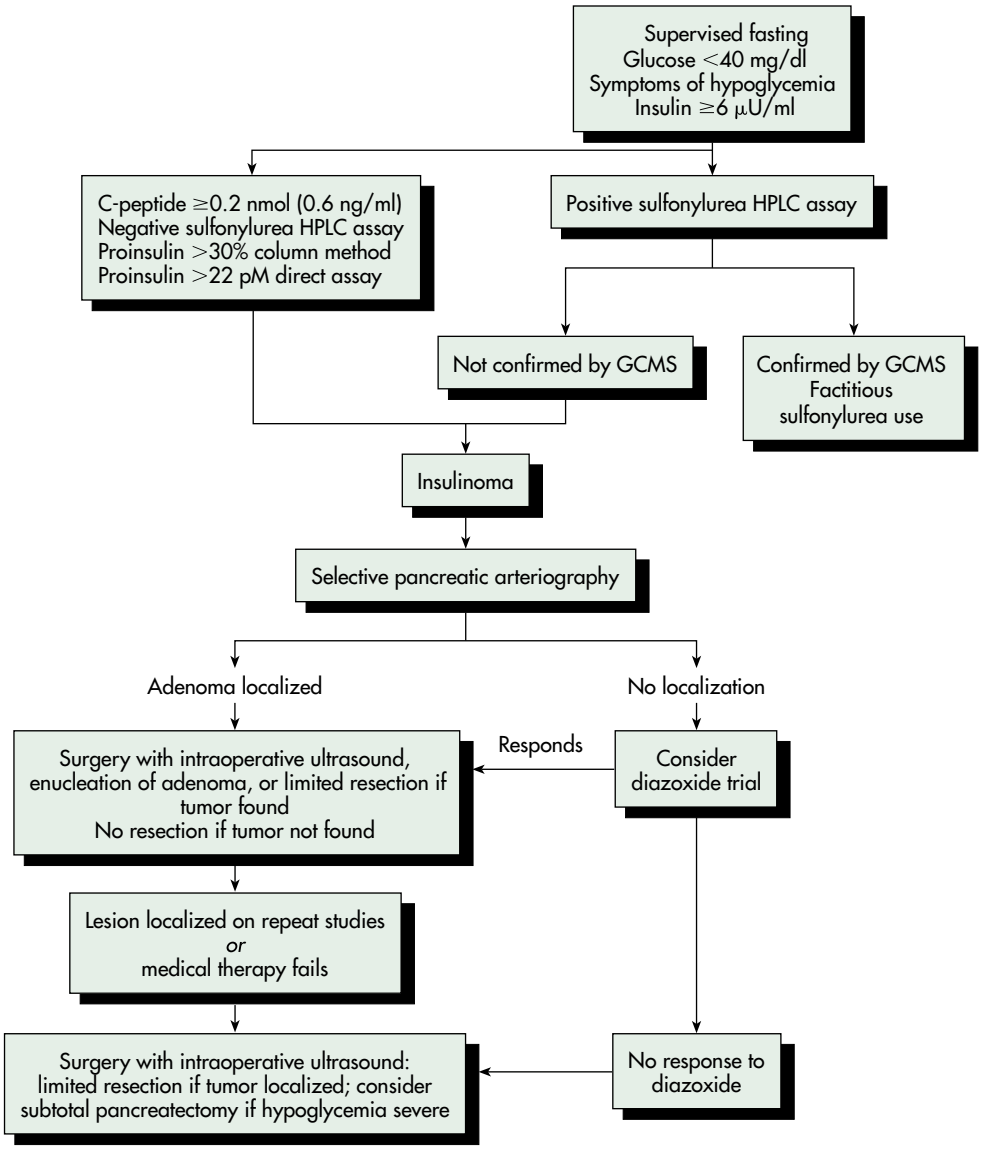

FIG. E23 Diagnostic evaluation of patients with documented hypoglycemia and elevated insulin. *GCMS,* Gas chromatography mass spectrometry; *HPLC,* high-pressure liquid chromatography. (Modified and updated from Moore WT, Eastman RC: *Diagnostic endocrinology,* ed 2, St Louis, 1996, Mosby.)

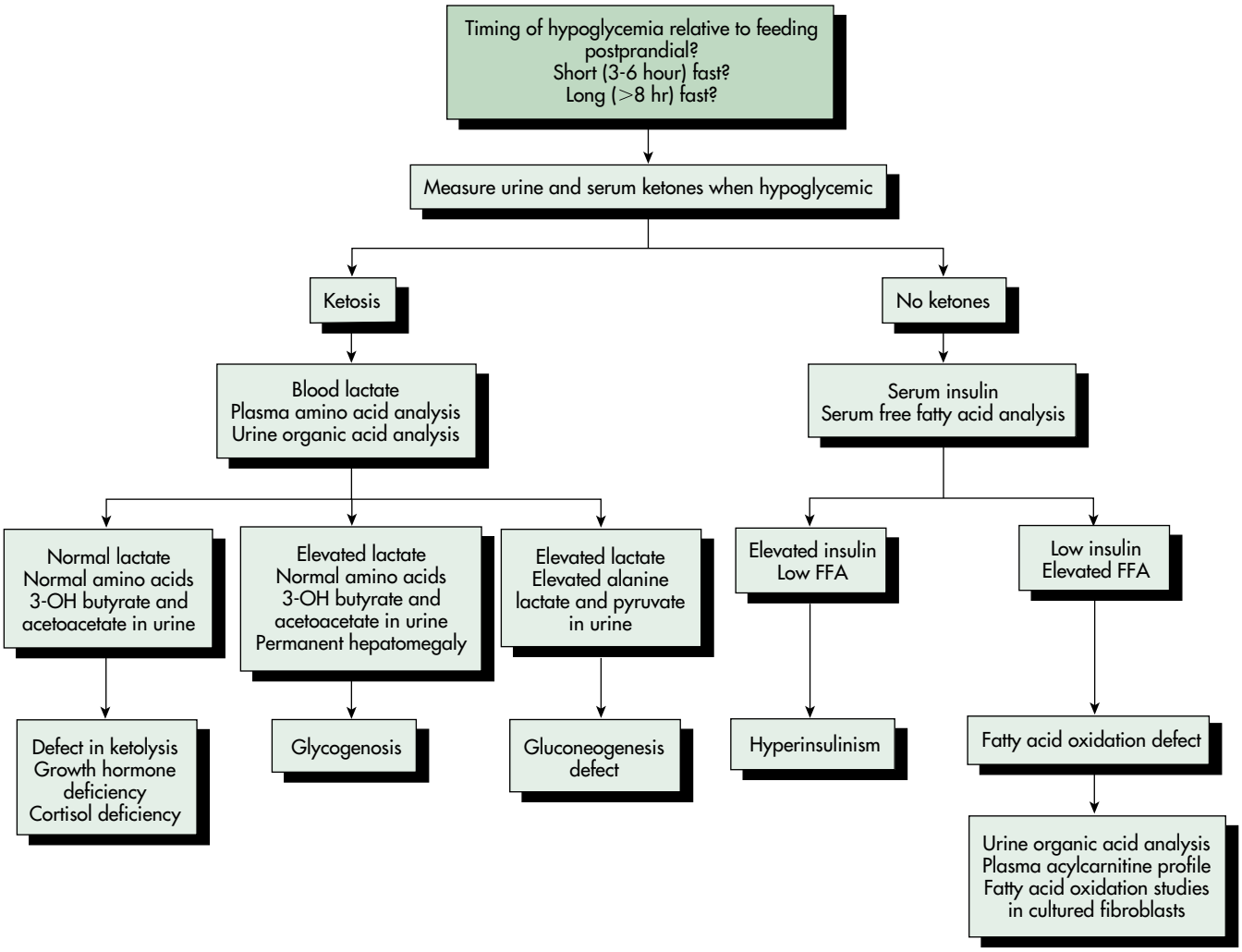

FIG. E24 Algorithm for evaluation of hypoglycemia in children. *FFA,* Free fatty acid. (From Fuhrman BP et al: *Pediatric critical care*, ed 4, Philadelphia, 2011, WB Saunders.)

TABLE 48 Glycemic Goals in Adults*

	Hemoglobin A_{1c} (%)	Preprandial Glucose		Postprandial Glucose**	
		mg/dl	mmol/L	mg/dl	mmol/L
ADA†: Adults	<7.0‡	80-130	4.4-7.2	<180	<10.0
Pregnant adults	<6.0	60-99	3.3-5.5	100-129	5.6-7.2
Older adults:					
Healthy	<7.5	90-130	5.0-7.2	90-150	5.0-8.3
Intermediate	<8.0	90-150	5.0-8.3	100-180	5.6-10.0
Poor health	<8.5	100-180	5.6-10.0	110-200	6.1-11.1
AACE§¶	≤6.5	≤110	≤6.1	≤140	<7.8

*Youth <18 years of age: Goal hemoglobin A_{1c}<7.5%.
**1 to 2 hours after beginning a meal for adults, except bedtime for older adults.
†American Diabetes Association (2015); Chiang et al (2014).
‡Lower goals may be appropriate for selected individuals if this can be accomplished safely (without significant hypoglycemia). Higher goals may be appropriate in some individuals (e.g., with a history of severe hypoglycemia, limited life expectancy, advanced complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve with appropriate education, monitoring, and therapies, including insulin).
§AACE, American Association of Clinical Endocrinologists, 2015.
¶For patients without concurrent serious illness and at low hypoglycemia risk.
AACE, American Association of Clinical Endocrinologists; *ADA,* American Diabetes Association.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

Decreased in: Post gastrointestinal resection, reactive hypoglycemia, hereditary fructose intolerance, galactosemia, leucine sensitivity

GLUCOSE TOLERANCE TEST

Normal values above fasting: 30 min: 30 to 60 mg/dl (1.65 to 3.3 mmol/L [CF: 0.05551; SMI: 0.1 mmol/L])
60 min: 20 to 50 mg/dl (1.1 to 2.75 mmol/L [CF: 0.05551; SMI: 0.1 mmol/L])
120 min: 5 to 15 mg/dl (0.28 to 0.83 mmol/L [CF: 0.05551; SMI: 0.1 mmol/L])
180 min: Fasting level or below
Abnormal in: Glucose intolerance, diabetes mellitus, Cushing syndrome, acromegaly, pheochromocytoma, gestational diabetes

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) Screen (blood)

Normal: G6PD enzyme activity detected
Abnormal: If a deficiency is detected, quantitation of G6PD is necessary; a G6PD screen may be falsely interpreted as "normal" after an episode of hemolysis because most G6PD-deficient cells have been destroyed.

γ-GLUTAMYL TRANSFERASE (GGT)

Normal range: 0 to 30 U/L (0.050 μkat/L [CF: 0.01667; SMI: 0.01 μkat/L])
Elevated in: Chronic alcoholic liver disease, neoplasms (hepatoma, metastatic disease to the liver, carcinoma of the pancreas), systemic lupus erythematosus, congestive heart failure, trauma, nephrotic syndrome, sepsis, cholestasis, drugs (phenytoin, barbiturates)

GLYCOHEMOGLOBIN (glycated glycosylated hemoglobin), (HbA1c)

Normal range: 4.0% to 5.9%. Glycemic goals in adults are summarized in Table 48.

Elevated in: Uncontrolled diabetes mellitus (glycated hemoglobin levels reflect the level of glucose control over the preceding 120 days), lead toxicity, alcoholism, iron deficiency anemia, hypertriglyceridemia
Decreased in: Hemolytic anemias, decreased red blood cell survival, pregnancy, acute or chronic blood loss, chronic renal failure, insulinoma, congenital spherocytosis, hemoglobin S, C, and D diseases

GROWTH HORMONE

Normal: Male: 1 to 9 ng/ml; female: 1 to 16 ng/ml
Elevated in: Pituitary gigantism, acromegaly, ectopic GH secretion, cirrhosis, renal failure, anorexia nervosa, stress, exercise, prolonged fasting, amphetamines, beta-blockers, insulin, levodopa, metoclopramide, clonidine, vasopressin, human growth hormone (HGH) supplementation
Decreased in: Hypopituitarism, pituitary dwarfism, adrenocortical hyperfunction, bromocriptine, corticosteroids, glucose

GROWTH HORMONE RELEASING HORMONE (GHRH)

Normal: <50 pg/ml
Elevated in: Acromegaly caused by GHRH secretion by neoplasms

GROWTH HORMONE SUPPRESSION TEST (after glucose)

Normal: Test is done by giving 1.75 g glucose/kg orally after overnight fast. Blood is drawn at baseline, after 60 min, and after 120 min of glucose load. Normal response is growth hormone suppression to <2 ng/ml or undetectable levels.
Abnormal: There is no or incomplete suppression from the high basal level in gigantism or acromegaly.

HAM TEST (acid serum test)

Normal: Negative
Positive in: Paroxysmal nocturnal hemoglobinuria
False-positive in: Hereditary or acquired spherocytosis, recent transfusion with aged red blood cells, aplastic anemia, myeloproliferative syndromes, leukemia, hereditary dyserythropoietic anemia type II

HAPTOGLOBIN (serum)

Normal range: 50 to 220 mg/dl (0.50 to 2.2 g/L [CF: 0.01; SMI: 0.01 g/L])
Elevated in: Inflammation (acute phase reactant), collagen vascular diseases, infections (acute phase reactant), drugs (androgens), obstructive liver disease
Decreased in: Hemolysis (intravascular more than extravascular), megaloblastic anemia, severe liver disease, large tissue hematomas, infectious mononucleosis, drugs (oral contraceptives)

HBA_{1C}

See GLYCOHEMOGLOBIN

HDL

See HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

HELICOBACTER PYLORI (serology, stool antigen)

Normal range: Not detected
Detected in: *H. pylori* infection. Positive serology can indicate current or past infection. Positive stool antigen test indicates acute infection (sensitivity and specificity >90%). Stool testing should be delayed at least 4 wk after eradication therapy.

HEMATOCRIT

Normal range: Male: 39% to 49% (0.39 to 0.49 [CF: 0.01; SMI: 0.01])
Female: 33% to 43% (0.33 to 0.43 [CF: 0.01; SMI: 0.01])
Elevated in: Polycythemia vera, smoking, chronic obstructive pulmonary disease, high altitudes, dehydration, hypovolemia
Decreased in: Blood loss (gastrointestinal, genitourinary) anemia

HEMOGLOBIN

Normal range: Male: 13.6 to 17.7 g/dl (136 to 172 g/L [CF: 10; SMI: 1 g/L])
Female: 12.0 to 15.0 g/dl (120 to 150 g/L [CF: 10; SMI: 1 g/L])
Elevated in: Hemoconcentration, dehydration, polycythemia vera, chronic obstructive pulmonary disease, high altitudes, false elevations (hyperlipemic plasma, white blood cells >50,000/mm^3), stress
Decreased in: Hemorrhagic (gastrointestinal, genitourinary) anemia

$HEMOGLOBIN\ A_{1C}$

See GLYCOHEMOGLOBIN

HEMOGLOBIN ELECTROPHORESIS

Table 49 describes neonatal hemoglobin electrophoresis patterns, Table 50 summarizes types of hemoglobin, and Table 51 describes classifications of hemoglobinopathies.
Normal range:
HbA_1: 95% to 98%
HbA_2: 1.5% to 3.5%
HbF: <2%
HbC: Absent
HbS: Absent

HEMOGLOBIN, GLYCATED

See GLYCOHEMOGLOBIN

HEMOGLOBIN, GLYCOSYLATED

See GLYCOHEMOGLOBIN

HEMOGLOBIN H

See Table 50.
Normal: Negative

TABLE 49 Neonatal Hemoglobin (Hb) Electrophoresis Patterns*

FA	Fetal Hb and adult normal Hb; the normal newborn pattern.
FAV	Indicates the presence of both HbF and HbA. However, an anomalous band (V) is present, which does not appear to be any of the common Hb variants.
FAS	Indicates fetal Hb, adult normal HbA, and HbS, consistent with benign sickle cell trait.
FS	Fetal and sickle HbS without detectable adult normal HbA. Consistent with clinically significant homozygous sickle Hb genotype (S/S) or sickle β-thalassemia, with manifestations of sickle cell anemia during childhood.
FC†	Designates the presence of HbC without adult normal HbA. Consistent with clinically significant homozygous HbC genotype (C/C), resulting in a mild hematologic disorder presenting during childhood.
FSC	HbS and HbC present. This heterozygous condition could lead to the manifestations of sickle cell disease during childhood.
FAC	HbC and adult normal HbA present, consistent with benign HbC trait.
FSA	Heterozygous HbS/β-thalassemia, a clinically significant sickling disorder.
F†	Fetal HbF is present without adult normal HbA. Although this may indicate a delayed appearance of HbA, it is also consistent with homozygous β-thalassemia major, or homozygous hereditary persistence of fetal HbF.
FV†	Fetal HbF and an anomalous Hb variant (V) are present.
AF	May indicate prior blood transfusion. Submit another filter paper blood specimen when the infant is 4 mo of age, at which time the transfused blood cells should have been cleared.

NOTE: HbA: α2β2; HbF: α2γ2; HbA2: α2δ2.
*Hemoglobin variants are reported in order of decreasing abundance; for example, FA indicates more fetal than adult hemoglobin.
†Repeat blood specimen should be submitted to confirm the original interpretation.
From Tschudy MM, Arcara KM: *The Harriet Lane handbook,* ed 19, Philadelphia, 2012, Mosby.

TABLE 50 Types of Hemoglobin

	Hemoglobin	Structure	Comment
Normal	A	$\alpha_2\beta_2$	97% of adult hemoglobin
	A_2	$\alpha_2\delta_2$	2% of adult Hb; elevated in β-thalassemia
	F	$\alpha_2\gamma_2$	Normal Hb in fetus from 3rd to 9th mo; increased in β-thalassemia
Abnormal chain production	H	β_4	Found in α-thalassemia, biologically useless
	Barts	γ_4	Found in α-thalassemia, biologically useless
Abnormal chain structure	S	$\alpha_2\beta_2$	Substitution of valine for glutamic acid in position 6 of β chain
	C	$\alpha_2\beta_2$	Substitution of lysine for glutamic acid in position 6 of β chain

From Ballinger A: *Kumar & Clark's essentials of clinical medicine,* ed 6, Edinburgh, 2012, WB Saunders.

Present in: Hemoglobin H disease, alpha-thalassemia trait, unstable hemoglobin disorders

HEMOGLOBIN, URINE

See URINE HEMOGLOBIN, FREE

HEMOSIDERIN, URINE

See URINE HEMOGLOBIN, FREE

HEPARIN-INDUCED THROMBOCYTOPENIA ANTIBODIES

Normal: Antigen assay: Negative, <0.45; weak, 0.45-1.0; strong, >1.0
Elevated in: Heparin-induced thrombocytopenia

HEPATITIS A ANTIBODY

Normal: Negative
Present in: Viral hepatitis A; can be IgM or IgG (if IgM, acute hepatitis A; if IgG, previous infection with hepatitis A)

TABLE 51 Classification of Hemoglobinopathies

Structural hemoglobinopathies—hemoglobins with altered amino acid sequences that result in deranged function or altered physical or chemical properties
Abnormal hemoglobin polymerization—HBS
Altered oxygen affinity
High affinity—polycythemia
Low affinity—cyanosis, pseudoanemia
Hemoglobins that oxidize readily
Unstable hemoglobins, hemolytic anemia, jaundice
M hemoglobins—methemoglobinemia, cyanosis
Thalassemias—defective production of globin chains
α-Thalassemias
β-Thalassemias
δβ-, γδβ-, αβ-Thalassemias
Structural hemoglobinopathies—structurally abnormal Hb associated with coinherited thalassemia phenotype
HbE
Hb constant spring
Hb lepore
Hereditary persistence of fetal hemoglobin—persistence of high levels of HbF into adult life
Pancellular—all red blood cells contain elevated HbF levels
Nondeletion forms
Deletion forms
Hb Kenya
Heterocellular—only specific subpopulation of red blood cells contain elevated levels of HbF
Acquired hemoglobinopathies
Methemoglobin due to toxic exposures
Sulfhemoglobin due to toxic exposures
Carboxyhemoglobin
HbH in erythroleukemia
Elevated HbF in states of erythroid stress and bone marrow dysplasia, usually heterocellular

Hb, Hemoglobin.
From Hoffman R: *Hematology: Basic principles and practice*, ed 6, Philadelphia, 2013, WB Saunders.

See Fig. 25 for serologic tests in HAV infection.
See Table 52 for serologic and virologic tests for hepatitis viruses.

HEPATITIS A VIRUS-IGM ANTIBODY

Appearance: About the same time as clinical symptoms (3 to 4 wk after exposure; range, 14 to 60 days), or just before beginning of AST/ALT elevation (range, 10 days before to 7 days after)
Peak: About 3 to 4 wk after onset of symptoms (1 to 6 wk)
Becomes nondetectable: 3 to 4 mo after onset of symptoms (1 to 6 mo). In a few cases HAV-IgM antibody can persist as long as 12 to 14 mo.

HAV TOTAL ANTIBODY

Appearance: About 3 wk after IgM becomes detectable (therefore about the middle of clinical symptom period to early convalescence)
Peak: About 1-2 mo after onset
Becomes nondetectable: Remains elevated for life but can somewhat slowly fall

HEPATITIS A VIRAL INFECTION

Best all-purpose test(s) to diagnose acute HAV infection = HAV-Ab (IgM)
Best all-purpose test(s) to demonstrate past HAV infection/immunity = HAV-Ab (total)

HEPATITIS B SURFACE ANTIGEN (HBsAg)

Normal: Not detected
Detected in: Acute viral hepatitis type B, chronic hepatitis B
Appearance: 2 to 6 wk after exposure (range, 6 days to 6 mo); 5% to 15% of patients are negative at onset of jaundice
Peak: 1 to 2 wk before to 1 to 2 wk after onset of symptoms
Becomes nondetectable: 1 to 3 mo after peak (range, 1 wk to 5 mo)

HEPATITIS B VIRAL INFECTION

See Table 53

Figs. 26, 27, and 28 illustrate antigens and antibodies in hepatitis B infection.

HB_S
-Ag:
HB_SAg: Shows current active hepatitis B virus (HBV) infection.
Persistence over 6 mo indicates carrier/chronic HBV infection.
HBV nucleic acid probe: Present before and longer than HB_SAg.
More reliable marker for increased infectivity than HB_SAg and/or HB_eAg.
-Ab:
HB_SAb-total: Shows previous healed HBV infection and evidence of immunity.
HB_C
-Ab:
HB_CAb-IgM: Shows either acute or very recent infection by HBV.

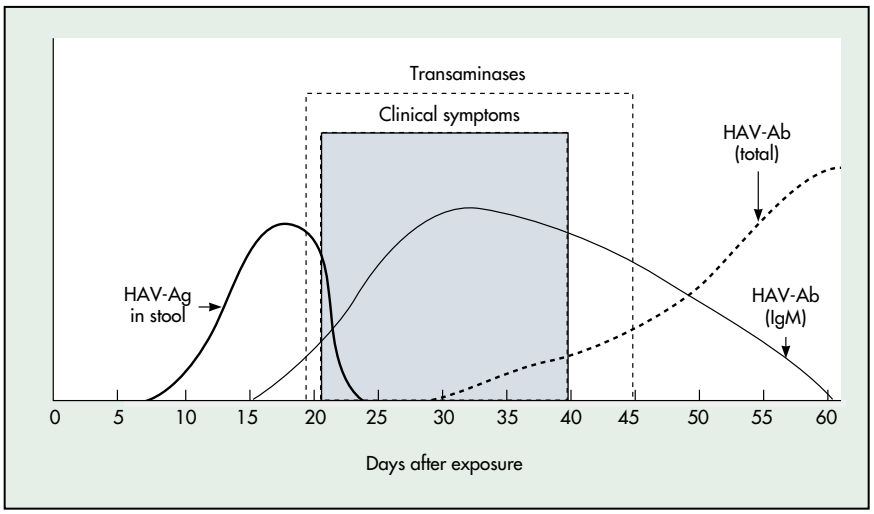

FIG. 25 Serologic tests in hepatitis A viral infection. *HAV,* Hepatitis A virus; *HAV-Ab,* hepatitis A virus antibodies test; *HAV-Ag,* hepatitis A virus antigen test; *Ig,* immunoglobulin. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

TABLE 52 Serologic and Virologic Tests for Hepatitis Viruses

	IgM Anti-HAV	IgG Anti-HAV	HBsAg	Anti-HBs	IgM Anti-HBVc	HBeAg	Anti-HBe	HBV DNA	Anti-HCV Screen	HCV RNA	Anti-HDV	Anti-HEV
HAV:												
Acute	+		+									
Remote	+		+									
HBV:												
Early				+	–	+	+	–	+			
Window				–	–	+	–	–	+			
Resolving				–/+	+	–	–/+	+	–/+			
Chronic				+	–/+	–	+	+/–	+			
TX monitoring									+			
Remote				–	+	–	–/+	+/–	–/+			
HCV:												
Screen										+	+	
Acute										+/–	+	
Chronic										+	+	
TX monitoring											+	
Remote										+	–/+	
HDV:												
Superinfection				+	–	+/–	+	–/+	+/–			+
HEV												+

DNA, Deoxyribonucleic acid; *HAV,* hepatitis A virus; *HBeAg,* hepatitis E antigen; *HBsAg,* hepatitis B surface antigen; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HDV,* hepatitis D virus; *HEV,* hepatitis E virus; *Ig,* immunoglobulin; *RNA,* ribonucleic acid; *TX,* Texas; +, positive;–,negative.

Data from CDC: Surveillance for acute hepatitis, United States, 2007, *MMWR* 58(SS-3), 2009.

From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, Philadelphia, 2017, Elsevier.

TABLE 53 Serologic Markers of Hepatitis B Infection

	HBsAg	anti-HBc	anti-HBs	IgM anti-HBc
Susceptible to infection	Negative	Negative	Negative	Negative
Immune due to natural infection	Negative	Positive	Positive	Negative
Immune due to hepatitis B vaccination	Negative	Negative	Positive	Negative
Acutely infected	Positive	Positive	Negative	Positive
Chronically infected	Positive	Positive	Negative	Negative

HBsAg, Hepatitis B surface antigen; *Ig,* immunoglobulin.

From Ballinger A: *Kumar & Clark's essentials of clinical medicine,* ed 6, Edinburgh, 2012, WB Saunders.

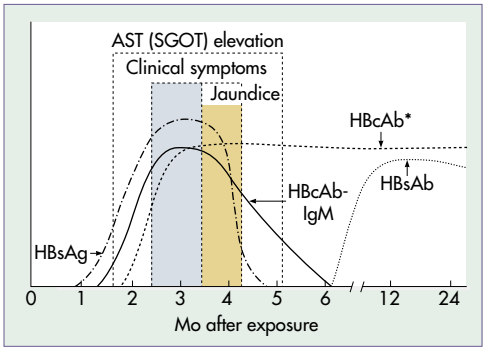

FIG. 26 Hepatitis B virus surface antigen-antibody and core antibodies. Note "core window." *HB_CAb = HB_CAb-IgM + HBCAb-IgG (combined). *AST,* Aspartate aminotransferase; *HBcAb,* hepatitis B core antibody; *HBsAb,* hepatitis B surface antibody; *HBsAg,* hepatitis B surface antigen; *Ig,* immunoglobulin; *SGOT,* serum glutamic-oxaloacetic transaminase. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

In convalescent phase of acute HBV, may be elevated when HB_SAg has disappeared (core window).

Negative HB_CAb-IgM with positive HB_SAg suggests either very early acute HBV or carrier/chronic HBV.

HB_CAb-total: Only useful to show past HBV infection if HB_SAg and HB_cAb-IgM are both negative.

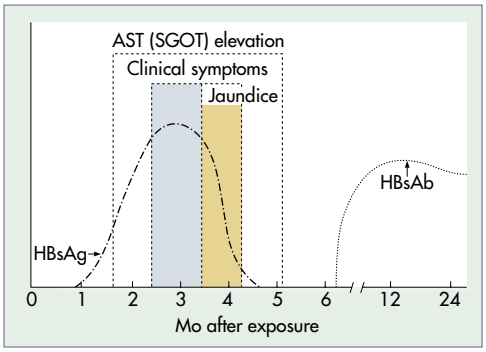

FIG. 27 Hepatitis B virus surface antigen and antibody (HB_SAg and HB_SAb-total). *AST,* Aspartate aminotransferase; *SGOT,* serum glutamic-oxaloacetic transaminase. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

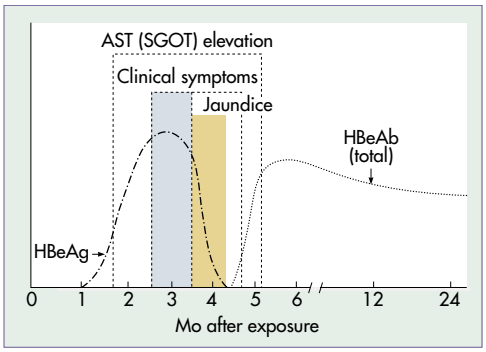

FIG. 28 HBVe antigen and antibody. *AST,* Aspartate aminotransferase; *HBeAb,* hepatitis B e-antibody; *SGOT,* serum glutamic-oxaloacetic transaminase. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

HB_E

-Ag:

HB_e-AbAg: When present, especially without HB_eAb, suggests increased patient infectivity.

HB_eAb-total: When present, suggests less patient infectivity.

HB_SAg positive, HB_CAb negative

About 5% (range, 0% to 17%) of patients with early-stage HBV acute infection (HB_CAb rises later)
HB_SAg positive, HB_CAb positive, HB_SAb negative
Most of the clinical symptom stage
Chronic HBV carriers without evidence of liver disease ("asymptomatic carriers")
Chronic HBV hepatitis (chronic persistent type or chronic active type)
HB_SAg negative, HB_CAb positive, HB_SAb negative
Late clinical symptom stage or early convalescence stage (core window)
Chronic HBV infection with HB_SAg below detection levels with current tests
Old previous HBV infection
HB_SAg negative, HB_CAb positive, HB_SAb positive
Late convalescence to complete recovery
Old infection

HEPATITIS C VIRAL INFECTION

Fig. 29 illustrates antigens and antibodies in hepatitis C infection. Table 54 summarizes interpretation of patterns of HCV markers.

HEPATITIS C RNA

Normal: Negative
Elevated in: Hepatitis C. Detection of hepatitis C-RNA is used to confirm current infection and to monitor treatment. Quantitative assays (viral load) are needed before treatment to assess response (<2 log decrease after 12-wk treatment indicates lack of response).

HCV
-Ag:
HCV nucleic acid probe: Shows current infection by HCV (especially with PCR amplification).
-Ab:
HCV-Ab (IgG): Current, convalescent, or old HCV infection.

HAV
-Ag:
HAV-Ag by EM: Shows presence of virus in stool early in infection.
-Ab:
HAV-Ab (IgM): Current or recent HAV infection.
HAV-Ab (total): Convalescent or old HAV infection.

HEPATITIS D VIRAL INFECTION

Fig. 30 illustrates antigens and antibodies in hepatitis D infection.
Best current all-purpose screening test = HDV-Ab (total)
Best test to differentiate acute from chronic infection = HDV-Ab (IgM)

DELTA HEPATITIS COINFECTION (acute HDV1 acute HBV) or Superinfection (acute HDV1 chronic HBV)

HDV
-Ag:
HDV-Ag: Shows current infection (acute or chronic) by HDV.
HDV nucleic acid probe: Detects antigen before and longer than HDV-Ag by EIA.
-Ab:
HDV-Ab (IgM): High elevation in acute HDV; does not persist.
Low or moderate elevation in convalescent HDV; does not persist.

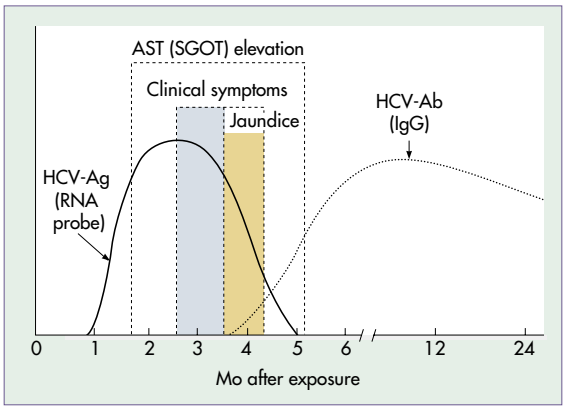

FIG. 29 Hepatitis C virus antigen and antibody. *AST,* Aspartate aminotransferase; *HCV-Ab,* hepatitis C virus antibody; *HCV-Ag,* hepatitis C virus core antigen; Ig, immunoglobulin; *RNA,* ribonucleic acid; *SGOT,* serum glutamic-oxaloacetic transaminase. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

TABLE 54 Interpretation of Patterns of HCV Markers

Interpretation	Anti-HCV	RIBA	HCV RNA
Acute HCV infection	–	–	+
Active HCV infection	+	+	+
Possible HCV clearance	+	+	–
False-positive HCV test	+	–	–
Requires further study	+	Indeterminate*	–

HCV, Hepatitis C; *RIBA,* recombinant immunoassay; *RNA,* ribonucleic acid.
*Indeterminate result: Only one band positive, or more than one band and nonspecific reactivity.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

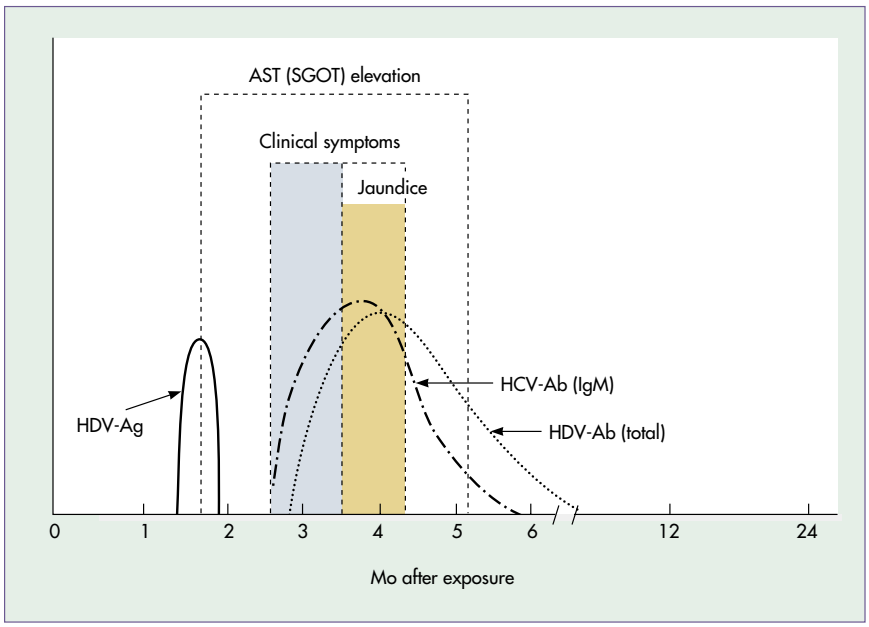

FIG. 30 Hepatitis D virus antigen and antibodies. *AST,* Aspartate aminotransferase; *HCV-Ab,* hepatitis C virus antibody; *HDV-Ab,* hepatitis D virus antibody; *HDV-Ag,* hepatitis D virus antigen; *Ig,* immunoglobulin; *SGOT,* serum glutamic-oxaloacetic transaminase. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

TABLE 55 Significant Human Apolipoproteins

Apolipoprotein	Major Lipoproteins	Mr* (kDa)	Amino Acids	Chromosome	PLASMA CONCENTRATION	
					mmol/L	mg/dl
A-I	HDL	29	243-245	11	32-46	90-130
A-II	HDL	17.4	154	1	18-29	30-50
A-IV	HDL, LDL	44.5	396	11		
(a)	Lp(a)	350-700	Variable	6		
B-100	VLDL, IDL, LDL	512.7	4536	2	1.5-1.8	80-100
B-48	CM	240.8	2152	2	<0.2	<5
C-I	CM, LDL	6.6	57	19	6.1-10.8	4-7
C-II	CM, LDL	8.9	78 or 79	19	3.4-9.1	3-8
C-III	CM	8.8	79	11	9.1-17.1	8-15
D	HDL	19	169	3		
E	CM, LDL, IDL	34.1	299	19	0.8-1.6	3-6
F	HDL, LDL, VLDL	29	162	12		8.35
H	VLDL	50	326	17		20
J	HDL	80	449	8		
L	HDL	39-42	383	22	Not present in plasma	
M	HDL, LDL, VLDL, CM	26	188	6		2-15
0	HDL, LDL, VLDL	22.3	198	X		

CM, Chylomicron; *HDL,* high-density lipoprotein; *IDL,* intermediate-density lipoprotein; *LDL,* low-density lipoprotein; *Lp(a),* lipoprotein A; *VLDL,* very-low-density lipoprotein.
*Relative molecular mass.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

Low to high persistent elevation in chronic HDV (depends on degree of cell injury and sensitivity of the assay).
HDV-Ab (total): High elevation in acute HDV; does not persist.
High persistent elevation in chronic HDV.

HDV-AG

Detected by DNA probe, less often by immunoassay
Appearance: Prodromal stage (before symptoms); just at or after initial rise in ALT (about a wk after appearance of HB_SAg and about the time HB_CAb-IgM level begins to rise)
Peak: 2 to 3 days after onset
Becomes nondetectable: 1 to 4 days (may persist until shortly after symptoms appear)

HDV-AB (IgM)

Appearance: About 10 days after symptoms begin (range, 1 to 28 days)
Peak: About 2 wk after first detection
Becomes nondetectable: About 35 days (range, 10 to 80 days) after first detection (most other IgM antibodies take 3 to 6 mo to become nondetectable)

HDV-AB (total)

Appearance: About 50 days after symptoms begin (range, 14 to 80 days); about 5 wk after HDV-Ag (range, 3 to 11 wk)
Peak: About 2 wk after first detection
Becomes nondetectable: About 7 mo after first detection (range, 4 to 14 mo)

HER-2/*NEU*

Normal: Negative
Present in: 25% to 30% of primary breast cancers. It can also be found in other epithelial tumors, including lung, hepatocellular, pancreatic, colon, stomach, ovarian, cervical, and bladder cancer. Trastuzumab (Herceptin) is a humanized monoclonal antibody against Her-2/*neu*. This test is useful to identify patients with metastatic; recurrent; and/or treatment-refractory, unresectable, locally advanced breast cancer for trastuzumab treatment.

HERPES SIMPLEX VIRUS (HSV)

Test description: The PCR test can be performed on serum biopsy samples, CSF, vitreous humor.

HFE SCREEN FOR HEREDITARY HEMOCHROMATOSIS

Test description: PCR test can be performed on whole blood or tissue. One mutation (C282Y) and two polymorphisms (H63D, S65C) account for the majority of alleles associated with this disease.

HETEROPHIL ANTIBODY

Normal: Negative
Positive in: Infectious mononucleosis

HIGH-DENSITY LIPOPROTEIN (HDL) CHOLESTEROL

Normal range:
Male: 40 to 70 mg/dl (0.8 to 1.8 mmol/L [CF: 0.02586; SMI: 0.05 mmol/L])
Female: 50 to 90 mg/dl (1.1 to 2.35 mmol/L [CF: 0.02586; SMI: 0.05 mmol/L])
Increased in: Use of gemfibrozil, statins, fenofibrate, nicotinic acid, estrogens, regular aerobic exercise, small (1 oz) daily alcohol intake
Decreased in: Deficiency of apoproteins, liver disease, probucol ingestion, Tangier disease
NOTE: A cholesterol/HDL ratio >4.0 is associated with increased risk of coronary artery disease. Table 55 summarizes significant human apolipoproteins.

HLA ANTIGENS

Associated disorders: See Table 56

HOMOCYSTEINE (plasma)

Normal range:

0-30 yr:	4.6-8.1 µmol/L
30-59 yr:	6.3-11.2 µmol/L (males), 4.5-7.9 µmol/L (females)
>59 yr:	5.8-11.9 µmol/L

Increased: Thrombophilic states, B_6, B_{12}, folic acid, riboflavin deficiency, pregnancy, homocystinuria
NOTE: An increased homocysteine level is an independent risk factor for atherosclerosis.

HUMAN CHORIONIC GONADOTROPIN (hCG)

Normal range: Varies with gestational stage:

TABLE 56 HLA Antigens Associated with Specific Diseases

Antigen	Condition	Antigen	Condition
HLA-B27	Ankylosing spondylitis	HLA-B8, Dw3	Celiac disease
	Reiter syndrome	HLA-B8, Dw3	Dermatitis herpetiformis
	Psoriatic arthritis	HLA-B8	Myasthenia gravis
HLA-A10, B18, Dw2	C2 deficiency	HLA-B8	Chronic active hepatitis in children
HLA-A2, B40, Cw3	C4 deficiency	HLA-Drw4	Active chronic hepatitis in adults
HLA-B7, Dw2	Multiple sclerosis	HLA-B13, Bw17	Psoriasis
HLA-A3	Hemochromatosis		

HLA, Human leukocyte antigen.
From Cerra FB: *Manual of critical care,* St Louis, 1987, Mosby.

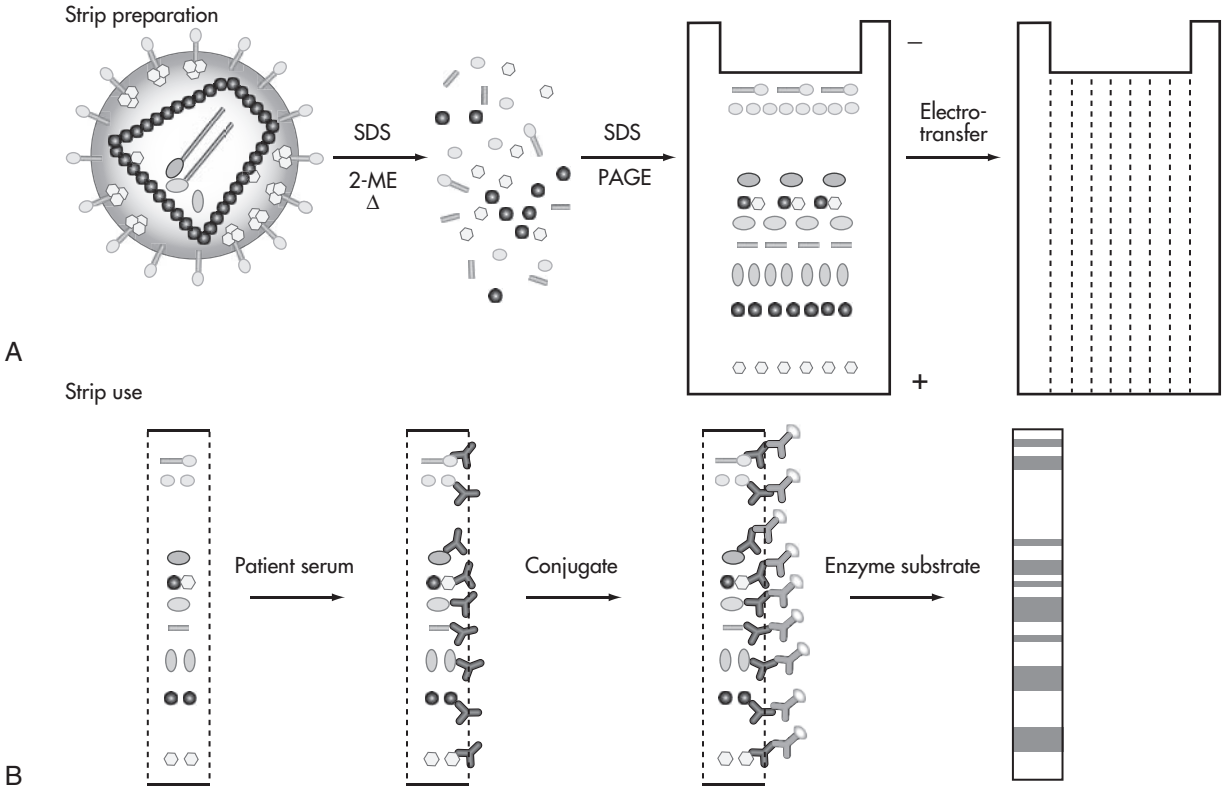

FIG. 31 Human immunodeficiency virus *(HIV)* Western blot. A, Western blot strips are prepared with purified HIV virions that are disrupted with ionic detergent and reducing agent, subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and electrotransferred to solid strips, typically of nitrocellulose. **B,** Strips are sequentially incubated with patient sample (serum, plasma, saliva, or urine); enzyme-conjugated antihuman IgG; and enzyme substrate. The positions of enzymes bound identify the presence of antibody to individual HIV proteins. (From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, WB Saunders.)

1 wk:	5-50 mU/ml
1-2 wk:	50-550 mU/ml
2-3 wk:	up to 5000 mU/ml
3-4 wk:	up to 10,000 mU/ml
4-5 wk:	up to 50,000 mU/ml
2-3 mo:	10,000-100,000 mU/ml

Elevated in: Normal pregnancy, hydatidiform mole, choriocarcinoma, germ cell tumors of testicle, some nontrophoblastic neoplasms (e.g., neoplasms of cervix, gastrointestinal tract, ovary, lung, breast)

HUMAN HERPES VIRUS 8 (HHV8)

Test description: PCR test can be performed on whole blood, tissue, bone marrow, and urine. HHV8 is found in all forms of Kaposi sarcoma.

HUMAN IMMUNODEFICIENCY VIRUS ANTIBODY, TYPE 1 (HIV-1)

Normal range: Not detected
Abnormal result: HIV antibodies usually appear in the blood 1 to 4 mo after infection.
Testing sequence:
ELISA is the recommended initial screening test. Sensitivity and specificity are >99%. False-positive ELISA may occur with autoimmune disorders, administration of immune globulin manufactured before 1985, within 6 wk of testing, in the presence of rheumatoid factor, in the presence of DLA-DR antibodies in multigravida female, with administration of influenza vaccine within 3 mo of testing, with hemodialysis, with positive plasma reagin test, and with certain medical disorders (hemophilia, hypergammaglobulinemia, alcoholic hepatitis).
A positive ELISA is confirmed with Western blot (Fig. 31). False-positive Western blot may result from connective tissue disorders, human

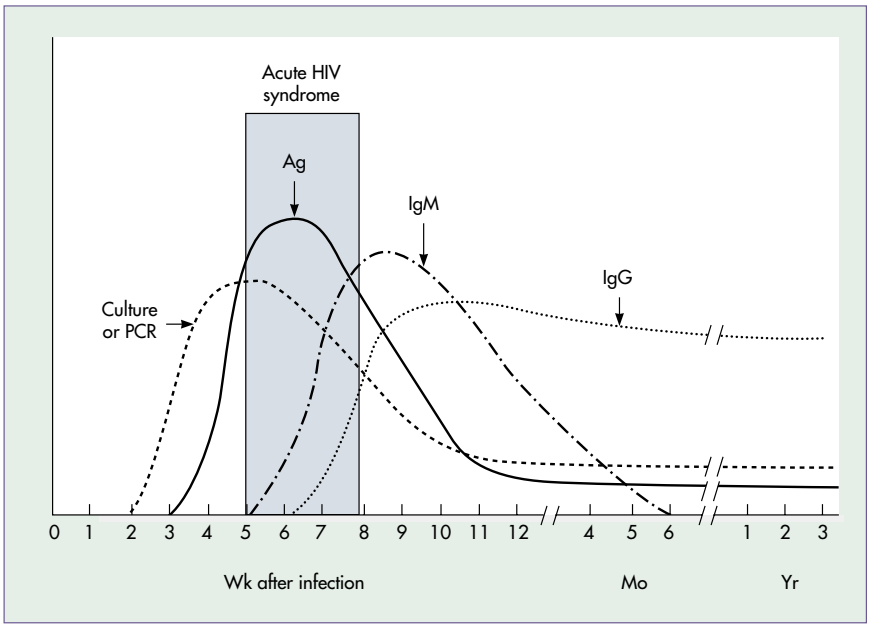

FIG. 32 Tests in human immunodeficiency virus *(HIV)*-1 infection. *Ag,* Antigen; *Ig,* immunoglobulin; *PCR,* polymerase chain reaction. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

leukocyte antigen antibodies, polyclonal gammopathies, hyperbilirubinemia, presence of antibody to another human retrovirus, or cross-reaction with other non–virus-derived proteins in healthy persons. Undetermined Western blot may occur in AIDS patients with advanced immunodeficiency (caused by loss of antibodies) and in recent HIV infections.

PCR is used to confirm indeterminate Western blot results or negative results in persons with suspected HIV infection.

Fig. 32 describes tests in HIV infection; indications for plasma HIV RNA testing are described in Table 57.

HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1) Antigen (p24), Qualitative (p24 antigen)

Normal range: Negative. This test detects uncomplexed HIV-1 p24 antigen. The core protein p24 is the first detectable protein encoded by the group-specific antigen *(gag)* gene. This protein is a marker for viremia. This test should not be used in place of HIV-1 antibody testing as a screen for HIV-1 infection. HIV-1 p24 may be detectable in the first mo of acute HIV-1 infection and generally falls to undetectable levels during the asymptomatic stage of HIV-1 infection. A negative result does not exclude the possibility of infection or exposure to HIV-1. It is recommended that a negative result be followed with repeat testing at least 8 wk after the original test. This test is used primarily for screening of donated blood and plasma and as an aid for the prognosis of HIV-1 infection.

HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1) VIRAL LOAD

Normal range: HIV-1 RNA, quant. bDNA 3: Less than 50 copies/ml or less than 1.7 log copies/ml

This test should be used only in individuals with documented HIV-1 infection for monitoring the progression of infection, response to antiretroviral therapy, and disease prognosis. It is not indicated for diagnosis of HIV infection.

HUMAN PAPILLOMA VIRUS (HPV)

Test description: PCR test can be performed on cervical smears, biopsies, scrapings, liquid cytology specimen, and anogenital tissues.

HUNTINGTON DISEASE PCR

Test description: PCR can be performed on whole blood. Huntington disease is caused by the expansion of the trinucleotide repeat cytosine-adenine-guanine (CAG) within IT 15 (huntingtin). Pre- and post-test counseling should be performed when ordering this test.

TABLE 57 Indications for Plasma HIV RNA Testing*

Clinical Indication	Information	Use
Syndrome consistent with acute HIV infection	Establishes diagnosis when HIV antibody test is negative or indeterminate	Diagnosis†
Initial evaluation of newly diagnosed HIV infection	Baseline viral load set point	Decision to start or defer therapy
Every 3-4 mo in patients not on therapy	Changes in viral load	Decision to start therapy
4-8 wk after initiation of antiretroviral therapy	Initial assessment of drug efficacy	Decision to continue or change therapy
3-4 mo after start of therapy	Maximal effect of therapy	Decision to continue or change therapy
Every 3-4 mo in patients on therapy	Durability of antiretroviral effect	Decision to continue or change therapy
Clinical event or significant decline in CD4+ T cells	Association with changing or stable	Decision to continue, initiate, or change

*Acute illness (e.g., bacterial pneumonia, tuberculosis, herpes simplex virus [HSV], *Pneumocystis carinii pneumonia* [PCP]) and immunizations can cause increase in plasma HIV RNA for 2-4 wk; viral load testing should not be performed during this time. Plasma HIV RNA results should usually be verified with a repeat determination before starting or making changes in therapy. HIV RNA should be measured using the same laboratory and the same assay.

†Diagnosis of HIV infection determined by HIV RNA testing should be confirmed by standard methods (e.g., Western blot serology) performed 2-4 mo after the initial indeterminate or negative test.

HIV, Human immunodeficiency virus; *RNA,* ribonucleic acid.

From Report of the NIH Panel to Define Principles of Therapy of HIV Infection, *MMWR Recomm Rep* 47(RR-5):1-41, 1998.

HYDROGEN BREATH TEST

See BREATH HYDROGEN TEST

5-HYDROXYINDOLE-ACETIC ACID, URINE

See URINE 5-HYDROXYINDOLE-ACETIC ACID

TABLE 58 Selected Biologic Properties of Human Immunoglobulin Isotypes

Characteristics	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	IgD	IgE
Physical Properties									
Molecular weight (kD)	146	146	165	146	970*	160	160	170	190
Serum half-life (days)	29	27	7	16	5	6	6	–	2
Anatomic Distribution									
Mean serum level (mg/ml)	5-12	2-6	0.5-1.0	0.2-1.0	0.5-1.5	0.5-2.0	0-0.2	0-0.4	0-0.002
Transport across placenta	+++	+	++	±	–	–	–	–	–
Transport across epithelium	–	–	–	–	+	+++†	+++†	–	–
Extravascular diffusion	+++	+++	+++	+++	±	++‡	++‡	+	+
Functional Activity									
Antigen neutralization	++	++	++	++	++	++	++	–	–
Complement fixation	++	+	++	–	+++	+	+	–	–
ADCC	+	+	+	±	–	–	–	–	+
Immediate hypersensitivity	–	–	–	–	–	–	–	–	+++

ADCC, Antibody-dependent cellular cytotoxicity; *Ig,* immunoglobulin; –, no effect; ±, no effect or negligible degree; +, small degree; ++, moderate degree; +++, large degree.
*Pentameric IgM plus J chain.
†Dimer.
‡Monomer.
From Adkinson NF et al: *Middleton's allergy principles and practice*, ed 8, Philadelphia, 2014, WB Saunders.

IMMUNE COMPLEX ASSAY

Normal: Negative
Detected in: Collagen vascular disorders, glomerulonephritis, neoplastic diseases, malaria, primary biliary cirrhosis, chronic acute hepatitis, bacterial endocarditis, vasculitis

IMMUNOGLOBULINS

Normal range:
IgA: 50-350 mg/dl (0.5-3.5 g/L [CF: 0.01; SMI: 0.01 g/L])
IgD: <6 mg/dl (<60 mg/L [CF: 0.01; SMI: 0.01 g/L])
IgE: <25 μg/dl (<0.00025 g/L [CF: 0.01; SMI: 0.01 g/L])
IgG: 800-1500 mg/dl (8-15 g/L [CF: 0.01; SMI: 0.01 g/L])
IgM: 45-150 mg/dl (0.45-1.5 g/L [CF: 0.01; SMI: 0.01 g/L])

Table 58 summarizes biologic properties of human immunoglobulin isotopes. Box 18 summarizes selected conditions associated with monoclonal immunoglobulins. Disease states associated with polyclonal hyperimmunoglobulinemia are described in Table 59.

Elevated in:
IgA: Lymphoproliferative disorders, Berger nephropathy, chronic infections, autoimmune disorders, liver disease
IgE: Allergic disorders, parasitic infections, immunologic disorders, IgE myeloma (see Box 19 for summary of nonallergic diseases associated with high levels of IgE. Box 20 summarizes conditions with very high IgE levels)
IgG: Chronic granulomatous infections, infectious diseases, inflammation, myeloma, liver disease
IgM: Primary biliary cirrhosis, infectious diseases (brucellosis, malaria), Waldenström macroglobulinemia, liver disease

Decreased in:
IgA: Nephrotic syndrome, protein-losing enteropathy, congenital deficiency, lymphocytic leukemia, ataxia-telangiectasia, chronic sinopulmonary disease
IgE: Hypogammaglobulinemia, neoplasms (breast, bronchial, cervical), ataxia-telangiectasia, primary biliary cirrhosis (see Box 19)
IgG: Congenital or acquired deficiency, lymphocytic leukemia, phenytoin, methylprednisolone, nephrotic syndrome, protein-losing enteropathy
IgM: Congenital deficiency, lymphocytic leukemia, nephrotic syndrome

INDIRECT ANTIGLOBULIN (Coombs Indirect)

Normal: Negative
Positive: Acquired hemolytic anemia, incompatible cross-matched blood, anti-Rh antibodies, drugs (methyldopa, mefenamic acid, levodopa)

BOX 18 Selected Conditions Associated with Monoclonal Immunoglobulins

- Multiple myeloma
- Macroglobulinemia of Waldenström
- Chronic lymphocytic leukemia
- Other leukemias
- Lymphomas
- "Benign" monoclonal gammopathy
- Systemic capillary leak syndrome
- Amyloidosis
- Chronic liver disease such as chronic active hepatitis, primary biliary cirrhosis
- Autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus, thyroiditis, pernicious anemia, polyarteritis nodosa, Sjögren syndrome
- Gaucher disease
- Malignancies of various types
- Hereditary spherocytosis
- HIV infection, including AIDS

AIDS, Acquired immune deficiency syndrome; *HIV,* human immunodeficiency virus.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

Fig. 33 illustrates the mechanism of Coombs test.

INFLUENZA A AND B TESTS

Test description: PCR can be performed on nasopharyngeal swab, wash, or aspirate
Normal: Negative

INSULIN AUTOANTIBODIES

Normal: Negative
Present in: Exogenous insulin from insulin therapy. The presence of islet cell antibodies indicates ongoing beta cell destruction. This test is useful in the early diagnosis of type 1a diabetes mellitus and in the identification of patients at high risk for type 1a diabetes.

INSULIN, FREE

Normal: <17 mcU/ml
Elevated in: Insulin overdose, insulin resistance syndromes, endogenous hyperinsulinemia

TABLE 59 Polyclonal Hyperimmunoglobulinemias: Some Associated Disease States

Condition	Immunoglobulin (Ig) Classes
Immunodeficiency Diseases	
Hyperimmunoglobulin E and recurrent infections	IgE
Wiskott-Aldrich syndrome	IgA, IgE
"Dysgammaglobulinemia type I"	IgM
Hyperimmunoglobulin A and recurrent infections	IgA
Acquired immune deficiency syndrome (AIDS)	All classes
Infections	
Congenital infections (syphilis, toxoplasmosis, rubella, cytomegalovirus)	IgM
Infectious mononucleosis	IgM or all
Trypanosomiasis	IgM or all
Intestinal parasitism	All classes
Several helminthic infections	IgE
Visceral larva migrans	All classes
Chronic granulomatous disease of childhood	All classes
Leprosy	All classes
Chronic infection in general	All classes, with a preference for IgG
Liver Diseases	
Chronic active hepatitis	IgG predominates
Acute hepatitis	IgG predominates
Biliary cirrhosis	IgM predominates
Lupoid hepatitis	All classes
Pulmonary Disorders	
Pulmonary hypersensitivity syndrome	All classes
Sarcoidosis	All classes
Berylliosis	All classes
"Autoimmune" Disorders	
Systemic lupus erythematosus	All classes
Rheumatoid arthritis	IgA or all
Many "autoimmune" states such as thyroiditis	All classes
Scleroderma	All classes
Cold agglutinin disease	IgM
Anaphylactoid purpura	IgA
Miscellaneous	
Down syndrome	All classes
Amyloidosis	All classes
Narcotic addiction	IgM
Renal tubular disease	All classes

McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, St Louis, 2017, Elsevier.

Decreased in: Inadequately treated type 1 diabetes mellitus

INSULIN-LIKE GROWTH FACTOR-1 (IGF-1) (Serum)

Normal range:

Ages 16-24:	182-780 ng/ml
Ages 25-39:	114-492 ng/ml
Ages 40-54:	90-360 ng/ml
Ages >55:	71-290 ng/ml

BOX 19 Nonallergic Diseases Associated with Altered Total Serum Immunoglobulin E Levels

Increased Levels (≥500 IU/ml)

Parasitic Diseases
Ascariasis
Visceral larva migrans
Capillariasis
Paragonimiasis
Fascioliasis
Schistosomiasis
Hookworm
Trichinosis
Filariasis
Strongyloidiasis
Echinococcosis
Onchocerciasis
Malaria

Infections
Allergic bronchopulmonary mycosis
Systemic candidiasis
Coccidioidomycosis
Leprosy
Epstein-Barr virus mononucleosis
Cytomegalovirus mononucleosis
Viral respiratory infections
Human immunodeficiency virus (HIV) type 1 infections
Pertussis

Cutaneous Diseases
Alopecia areata
Bullous pemphigoid
Chronic acral dermatitis
Streptococcal erythema nodosum

Other Diseases and Disorders
Nephrotic syndrome
Drug-induced interstitial nephritis
Liver disease
Cystic fibrosis
Kawasaki disease
Infantile polyarteritis nodosa
Primary pulmonary hemosiderosis
Guillain-Barré syndrome
Burns
Rheumatoid arthritis
Bone marrow transplantation
Cigarette smoking
Alcoholism

Neoplastic Diseases
Hodgkin disease
Immunoglobulin E (IgE) myeloma
Bronchial carcinoma

Immunodeficiency Diseases
Wiskott-Aldrich syndrome
Hyper-IgE syndrome
Thymic hypoplasia (DiGeorge syndrome)
Cellular immunodeficiency with immunoglobulins (Nezelof syndrome)
Selective IgA deficiency

Medications
Enfuvirtide
Pholcodine

Decreased Levels (<5 IU/ml)
Familial IgE deficiency and recurrent sinopulmonary infections
Human T cell lymphotropic virus type 1 infections
Primary biliary cirrhosis

From Adkinson NF et al: *Middleton's allergy principles and practice*, ed 8, Philadelphia, 2014, WB Saunders.

Elevated in: Adolescence, acromegaly, pregnancy, precocious puberty, obesity
Decreased in: Malnutrition, delayed puberty, diabetes mellitus, hypopituitarism, cirrhosis, old age

INSULIN-LIKE GROWTH FACTOR-II

Normal range: 288 to 736 ng/ml
Elevated in: Hypoglycemia associated with non-islet cell tumors, hepatoma, and Wilms tumor
Decreased in: Growth hormone deficiency

INTERNATIONAL NORMALIZED RATIO (INR)

The INR is a comparative rating of prothrombin time (PT) ratios. The INR represents the observed PT ratio adjusted by the International Reference Thromboplastin. It provides a universal result indicative of what the patient's PT result would have been if measured using the primary World Health Organization International Reference reagent. For proper interpretation of INR values, the patient should be on stable anticoagulant therapy.

BOX 20 Conditions Associated with Unusually High Serum Immunoglobulin E Concentrations (≥500 IU/ml)

Allergic bronchopulmonary mycosis
Allergic fungal sinusitis
Atopic dermatitis
Human immunodeficiency virus (HIV) infection
Hyperimmunoglobulin E (hyper-IgE) syndrome
Immunoglobulin E myeloma
Kimura disease
Lymphoma
Netherton syndrome
Systemic helminthic parasitosis
Tuberculosis

From Adkinson NF et al: *Middleton's allergy principles and practice*, ed 8, Philadelphia, 2014, WB Saunders.

RECOMMENDED INR RANGES

Proximal deep vein thrombosis:	2-3
Pulmonary embolism:	2-3
Transient ischemic attacks:	2-3
Atrial fibrillation:	2-3
Mechanical prosthetic valves:	2.5-3.5
Recurrent venous thromboembolic disease:	2.5-3.5

INTRINSIC FACTOR ANTIBODIES

Normal: Negative
Present in: Pernicious anemia (>50% of patients). Cyanocobalamin may give false-positive results.

IRON (Serum)

Normal: Male: 65 to 175 mcg/dl; female: 50 to 1170 mcg/dl
Elevated in: Hemochromatosis, excessive iron therapy, repeated transfusions, lead poisoning, hemolytic anemia, aplastic anemia, pernicious anemia
Decreased in: Iron deficiency anemia, hypothyroidism, chronic infection

IRON-BINDING CAPACITY, TOTAL (TIBC)

Normal range: 250 to 460 μg/dl (45 to 82 μmol/L [CF: 0.1791; SMI: 1 μmol/L])
Elevated in: Iron deficiency anemia, pregnancy, polycythemia, hepatitis, weight loss
Decreased in: Anemia of chronic disease, hemochromatosis, chronic liver disease, hemolytic anemias, malnutrition (protein depletion)
Table 60 describes TIBC and serum iron abnormalities.

IRON SATURATION (% Transferrin Saturation)

Normal:
Male: 20% to 50%
Female: 15% to 50%
Elevated in: Hemochromatosis, excessive iron intake, aplastic anemia, thalassemia, vitamin B_6 deficiency
Decreased in: Hypochromic anemias, GI malignancy

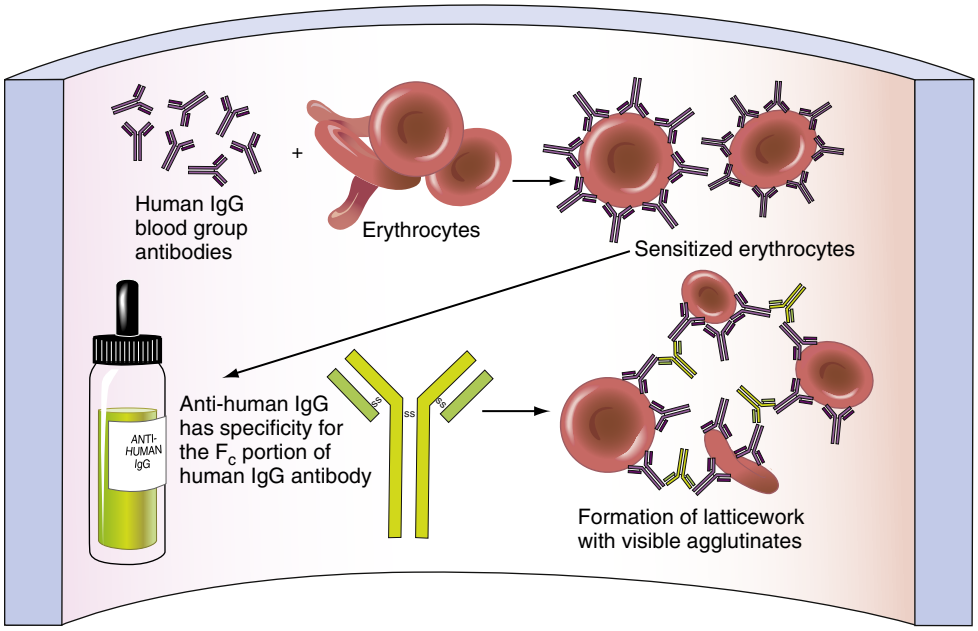

FIG. 33 Antihuman globulin antibodies form a bridge between adjacent erythrocytes sensitized with human immunoglobulin *(Ig)*G or complement components. (From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.)

TABLE 60 Serum Iron and Total Iron-Binding Capacity Patterns

SI↓	TIBC↓	Chronic diseases; uremia
SI↓	TIBC↑	Chronic iron deficiency anemia; pregnancy in third trimester
SI↑	TIBC↓	Hemochromatosis iron therapy overload (TIBC may be normal); hemolytic anemia; thalassemia; lead poisoning; megaloblastic anemia; aplastic, pyridoxine deficiency, or other sideroblastic anemias
SI↑	TIBC↑	Oral contraceptives; acute hepatitis (some report TIBC is low normal); chronic hepatitis (some patients)
SI↑	TIBCNL	B_{12} or folate deficiency
SI↓	TIBCNL	Chronic iron deficiency (some patients); acute infection, surgery, tissue damage
SI NL	TIBC↑	B_{12}/folate deficiency plus iron deficiency

NL, Normal; *SI,* serum iron; *TIBC,* total iron-binding capacity.
From Ravel R: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.

LACTATE (blood)

Normal range: 0.5 to 2.0 mEq/L
Elevated in: Tissue hypoxia (shock, respiratory failure, severe CHF, severe anemia, carbon monoxide or cyanide poisoning), systemic disorders (liver or renal failure, seizures), abnormal intestinal flora (d-lactic acidosis), drugs or toxins (salicylates, ethanol, methanol, ethylene glycol), G6PD deficiency

LACTATE DEHYDROGENASE (LDH)

Normal range: 50 to 150 U/L (0.82 to 2.66 μkat/L [CF: 0.01667; SMI: 0.02 μkat/L])
Elevated in: Infarction of myocardium, lung, kidney
Diseases of cardiopulmonary system, liver, collagen, central nervous system
Hemolytic anemias, megaloblastic anemias, transfusions, seizures, muscle trauma, muscular dystrophy, acute pancreatitis, hypotension, shock, infectious mononucleosis, inflammation, neoplasia, intestinal obstruction, hypothyroidism

LACTATE DEHYDROGENASE ISOENZYMES

Normal range:
LDH_1: 22%-36% (cardiac, red blood cell) (0.22-0.36 [CF: 0.01, SMI: 0.01])
LDH_2: 35%-46% (cardiac, red blood cell) (0.35-0.46)
LDH_3: 13%-26% (pulmonary) (0.15-0.26)
LDH_4: 3%-10% (striated muscle, liver) (0.03-0.1)
LDH_5: 2%-9% (striated muscle, liver) (0.02-0.09)

Normal ratios:
c. LDH_1<LDH_2
d. LDH_5<LDH_4
Abnormal values:
LDH1 >LDH2: Myocardial infarction (can also be seen with hemolytic anemias, pernicious anemia, folate deficiency, renal infarct)
LDH5 >LDH4: Liver disease (cirrhosis, hepatitis, hepatic congestion)

LACTOSE TOLERANCE TEST (serum)

Normal: Test is performed by giving 2 g/kg body weight lactose orally and drawing glucose level at 0, 30, 45, 60, and 90 min. Normal response is change in glucose from fasting value to >30 mg/dl. Inconclusive response is increase of 20-30 mg/dl, abnormal response is increase <20 mg/dl. Table 61 summarizes laboratory tests in the differential diagnosis of diarrhea.
Abnormal in: Lactase deficiency

LAP SCORE

See LEUKOCYTE ALKALINE PHOSPHATASE

LEAD

Normal: Child, <10 mcg/dl; adult, <25 mcg/dl; acceptable for industrial exposure, <50 mcg/dl
Elevated in: Lead exposure, lead poisoning

LDH

See LACTATE DEHYDROGENASE

LDL

See LOW-DENSITY LIPOPROTEIN CHOLESTEROL

LEGIONELLA PNEUMOPHILA PCR

Test description: PCR can be performed on lung tissue, water sputum, bronchoalveolar lavage, and other respiratory fluids.

LEGIONELLA TITER

Normal: Negative
Positive in: Legionnaires disease (presumptive: ≥1:256 titer; definitive: fourfold titer increase to ≥1:128)

LEUKOCYTE ALKALINE PHOSPHATASE (LAP)

Normal range: 13 to 100 (33 to 188 U)
Elevated in: Leukemoid reactions, neutrophilia secondary to infections (except in sickle cell crisis—no significant increase in LAP score), Hodgkin disease, polycythemia vera, hairy cell leukemia, aplastic anemia, Down syndrome, myelofibrosis
Decreased in: Acute and chronic granulocytic leukemia, thrombocytopenic purpura, paroxysmal nocturnal hemoglobinuria, hypophosphatemia, collagen disorders

LEUKOCYTE COUNT

See COMPLETE BLOOD COUNT

LIPASE

Normal range: 0 to 160 U/L (0 to 2.66 μkat/L [CF: 0.01667; SMI: 0.02 μkat/L])
Elevated in: Acute pancreatitis, perforated peptic ulcer, carcinoma of pancreas (early stage), pancreatic duct obstruction, bowel infarction, intestinal obstruction

LIPOPROTEIN(a)

Normal: Male: 1.35 to 19.6 mg/dl; female: 1.24 to 20.1 mg/dl. Fig. 34 illustrates lipoprotein structure. Table 62 summarizes the major classes of human plasma lipoproteins. The chemical composition of major classes of plasma lipoproteins is described in Table 63.
Elevated in: Coronary artery disease, uncontrolled diabetes, hypothyroidism, chronic renal failure, pregnancy, tobacco use, infections, nephritic syndrome
Decreased in: Niacin, omega-3 fatty acids, estrogens, tamoxifen, statins

LIPOPROTEIN CHOLESTEROL, HIGH-DENSITY

See HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

TABLE 61 Laboratory Tests in the Differential Diagnosis of Diarrhea

Test	Method	Use
Initial Screening Tests		
Fecal leukocytes	Wright stain or methylene blue	Identify inflammatory diarrhea
Fecal occult blood test	Immunochemical	Detect blood
Fecal osmotic gap	290 − 2 × (fecal $Na^+ + K^+$)	Distinguish secretory vs. osmotic diarrhea
Stool alkalinization	Color change after adding NaOH to stool/urine	Phenolphthalein laxative ingestion
Infectious Causes		
Stool bacterial culture	Routine culture and sensitivity	Identify *Shigella, Salmonella*
Stool special culture	Specialized culture and serotyping	Identify *E. coli* 0157:H7, *Yersinia*, *Campylobacter*
Stool *C. difficile* toxin assay	EIA for toxins A and B	Pseudomembranous colitis
HIV serology	EIA, Western blot	HIV enteritis
Stool rotavirus screen	EIA for antigen	Rotavirus enteritis
Stool ova and parasites	Concentration and stains	Enteric parasitic infection
Stool mycobacteria	Acid-fast stain, culture and sensitivity, PCR	*Mycobacterium*, antibiotic selection
Stool *E. histolytica* Ag	EIA for antigen	*Entamoeba histolytica*
Stool *Giardia* Ag	EIA for antigen	*Giardia lamblia*
Stool *Cryptosporidium* Ag	EIA for antigen	*Cryptosporidium parvum*
Endocrine Causes		
Urine 5-HIAA or blood serotonin	HPLC	Carcinoid syndrome
Serum VIP	RIA	VIPoma
Serum TSH, free T4	Immunoassay	Hyperthyroidism
Serum gastrin	RIA	Zollinger-Ellison syndrome
Serum calcitonin	RIA	Hypocalcemia-related diarrhea
Serum somatostatin	RIA	Somatostatinoma
Malabsorption		
Lactose tolerance test	See text	Lactase deficiency
Stool reducing sugars	Clinitest tablets	Carbohydrate intolerance
Sweat chloride	See text	Cystic fibrosis
D-Xylose absorption test	See text	Evaluate pancreatic and jejunal function
Fecal fat stain	Fat stain	Lipid malabsorption
Serum carotene	Spectrophotometry	Lipid malabsorption
^{14}C-glyceryl trioleate test malabsorption	See text	Lipid malabsorption
Serum IgA	Nephelometry	Rule out IgA deficiency
Antitissue transglutaminase antibody	EIA	Celiac disease
Hydrogen breath test	Electrochemical hydrogen monitorinomatography g	Carbohydrate malabsorption
Bacterial colony count	Small bowel aspirate and quantitative culture	Bacterial overgrowth
Other		
Serum ionized calcium	Ion-specific electrode	Hypocalcemia-related diarrhea
Serum protein and albumin	Nephelometry, photometry	IBD, protein-losing enteropathy
Stool alpha-1-antitrypsin	Nephelometry	Protein-losing enteropathy
Quantitative immunoglobulins	Nephelometry	Agammaglobulinemia
7α-Hydroxy-4-cholestin-3-one	HPLC	Bile salt malabsorption
Fecal elastase or pancreolauryl test	EIA	Pancreatic insufficiency
Intestinal biopsy	Endoscopic or open biopsy	Whipple disease, MAI, abetalipoproteinemia, neoplasia, lymphoma, amyloidosis, eosinophilic gastroenteritis, agammaglobulinemia, intestinal lymphangiectasia, Crohn disease, tuberculosis, graft-versus-host disease, *Giardia*, other parasitic infections, collagenous colitis, microscopic colitis
Extraintestinal causes	See text	Hyperthyroidism, diabetes, hypoparathyroidism, adrenal cortical insufficiency, hormone-secreting tumors

5-HIAA, 5-Hydroxyindoleacetic acid; *Ab*, antibody; *Ag*, antigen; *EIA*, enzyme immunoassay; *HIV*, human immunodeficiency virus; *HPLC*, high-performance liquid chromatography; *IBD*, inflammatory bowel disease; *Ig*, immunoglobulin; *MAI, Mycobacterium avium-intracellulare*; *PCR*, polymerase chain reaction; *RIA*, radioimmunoassay; *T4*, thyroxine; *TSH*, thyroid-stimulating hormone; *VIP*, vasoactive intestinal peptide; *VIPoma*, vasoactive intestinal peptide tumor.

From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

LIPOPROTEIN CHOLESTEROL, LOW-DENSITY

See LOW-DENSITY LIPOPROTEIN CHOLESTEROL

LIVER KIDNEY MICROSOME TYPE 1 ANTIBODIES (LKM1)

Normal: <20 U

Elevated in: Autoimmune hepatitis type 2

LKM1

See LIVER KIDNEY MICROSOME TYPE 1 ANTIBODIES

LOW-DENSITY LIPOPROTEIN (LDL) CHOLESTEROL

Normal range: 50 to 130 mg/dl (1.30 to 1.68 mmol/L [CF: 0.02586; SMI: 0.05 mmol/L]). Fig. 35 illustrates the LDL receptor pathway and regulation of cholesterol metabolism.

<70	Optimal in diabetics, prior MI, and patients with cardiac risk factors
100-129	Near or above optimal
130-159	Borderline high
160-189	High
≥190	Very high

LUPUS ANTICOAGULANT

See CIRCULATING ANTICOAGULANT

LUTEINIZING HORMONE

Normal range: 5-25 mIU/ml
Elevated in: Postmenopause, pituitary adenoma, primary gonadal dysfunction, polycystic ovary syndrome
Decreased in: Severe illness, anorexia nervosa, malnutrition, pituitary or hypothalamic impairment, severe stress

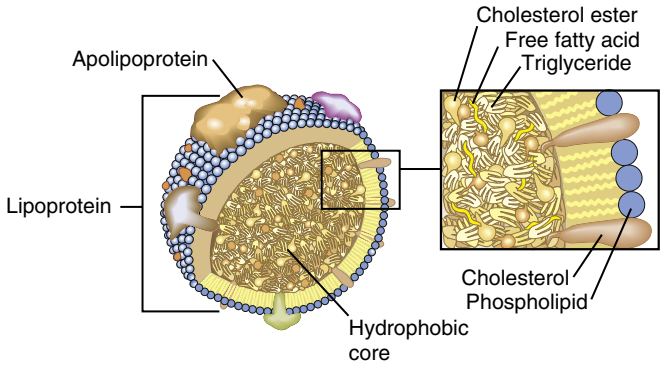

FIG. 34 Lipoprotein structure. Lipoproteins are spherical particles with a hydrophobic core and an amphiphilic surface. The surface consists of a single layer of phospholipids. This surface layer also contains proteins and free cholesterol. The hydrophobic core mainly contains triglycerides and cholesterol esters (From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.)

LYME DISEASE ANTIBODY TITER

Normal range: Negative
Positive result: Fig. 36 illustrates the usual serologic response in Lyme disease.

A serologic test is not necessary or helpful for several days after a tick bite because it is only 40% to 50% sensitive in this stage, and a negative test does not rule out the diagnosis.

LYMPHOCYTES

Normal range:
15% to 40%
Total lymphocyte count = 800-2600/mm3
Total T lymphocyte = 800-2200/mm3
CD4 lymphocytes = ≥ 400/mm3
CD8 lymphocytes = 200 to 800/mm3
Normal CD4/CD8 ratio is 2.0.
Elevated in: Chronic infections, infectious mononucleosis and other viral infections, chronic lymphocytic leukemia, Hodgkin disease, ulcerative colitis, hypoadrenalism, idiopathic thrombocytopenia
Decreased in:
AIDS, bone marrow suppression from chemotherapeutic agents or chemotherapy, aplastic anemia, neoplasms, steroids, adrenocortical hyperfunction, neurologic disorders (multiple sclerosis, myasthenia gravis, Guillain-Barré syndrome)
CD4 lymphocytes are calculated as total white blood cells × % lymphocytes × % lymphocytes stained with CD4. They are decreased in AIDS and other immune dysfunction.
Table 64 describes various lymphocyte abnormalities in peripheral blood.
Box 21 summarizes key causes of lymphocytopenia.

TABLE 62 Major Classes of Human Plasma Lipoproteins: Physicochemical Characteristics

Particle	Electrophoretic Mobility*	Major Apolipoproteins	Diameter (Å)	Density (kg/L)	Sf†
Chylomicrons	Origin	ApoA-I, A-IV, B-48, C-I, C-II, C-III, E	750-12,000	<0.95	>400
VLDL	Pre-β	ApoB-100, C-I, C-II, C-III, E	300-700	0.95-1.006	20-400
IDL	β or pre-β	ApoB-100, E1.006-1.019	12-20		
LDL	B	ApoB-100	180-300	1.019-1.063	0-12
HDL_2	A	ApoA-I, A-II, E	50-120	1.063-1.125	
HDL_3	A	ApoA-II, A-I, E	50-120	1.125-1.210	
Lp(a)	Pre-β	ApoB-100, Apo(a)		1.045-1.080	

HDL_2, Ultracentrifugation subclass of high-density lipoprotein; *HDL_3*, ultracentrifugation subclass of high-density lipoprotein; *IDL*, intermediate-density lipoprotein; *LDL*, low-density lipoprotein; *Lp(a)*, lipoprotein A; *VLDL*, very-low-density lipoprotein.
*Agarose gel electrophoresis.
†Svedberg flotation rate.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

TABLE 63 Chemical Composition of Major Classes of Plasma Lipoproteins

	Protein (%)*	Free Cholesterol (%)	Cholesterol Esters (%)	Triglyceride (%)	Phospholipid (%)
Chylomicrons	1-2	1-3	2-4	80-95	3-6
VLDL	6-10	4-8	16-22	45-65	15-20
IDL	Intermediate between VLDL and LDL				
LDL	18-22	6-8	45-50	4-8	18-24
HDL	45-55	3-5	15-20	2-7	26-32

HDL, High-density lipoprotein; *IDL*, intermediate-density lipoprotein; *LDL*, low-density lipoprotein; *VLDL*, very-low-density lipoprotein.
*Percentage of dry weight.
McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.
Data from Albers (1974), Gaubatz et al (1983), Fless et al (1984), Gotto et al (1986), Gries et al (1988), and Hegele (2009).

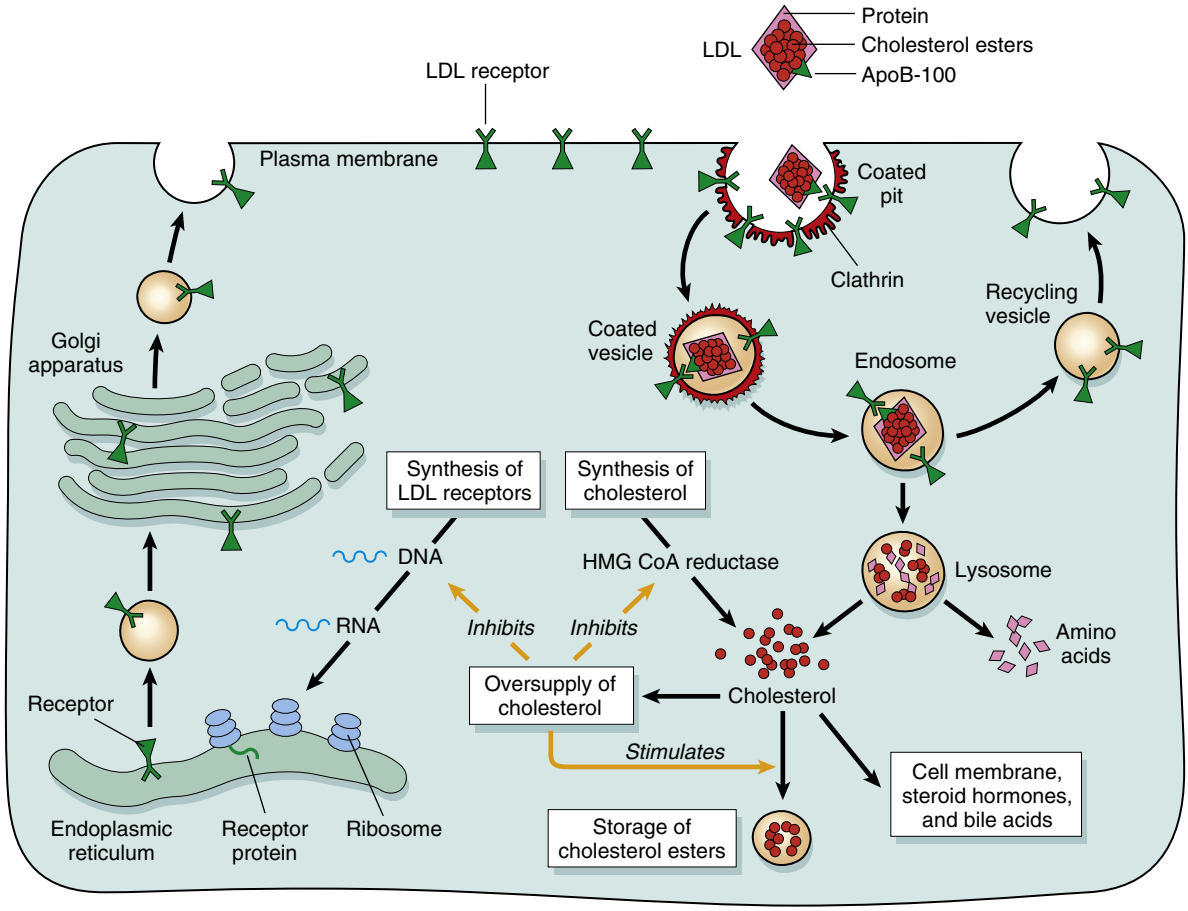

FIG. 35 The low-density lipoprotein *(LDL)* receptor pathway and regulation of cholesterol metabolism. *Apo,* Apolipoprotein; *DNA,* deoxyribonucleic acid; *HMG CoA,* 3-hydroxy-3-methylglutaryl coenzyme A; *RNA,* ribonucleic acid. (From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.)

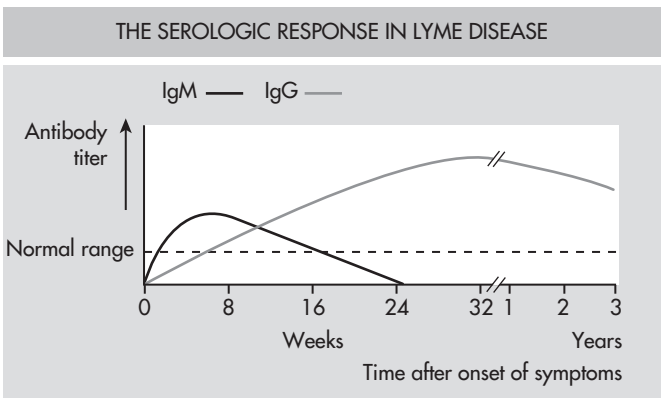

FIG. 36 Immunoglobulin (Ig)M and IgG responses in Lyme disease.

TABLE 64 Differential Diagnosis of Abnormal Lymphocytes in Peripheral Blood

Lymphocyte Type	Usual Disease Association	Cytologic Features	Laboratory Features	Clinical Features
Small lymphocyte	Chronic lymphocytic leukemia	B-cell surface markers with low concentration of surface immunoglobulin, CD5 antigen	Hypogammaglobulinemia in 50%; positive direct Coombs test in 15%; on node biopsy, diffuse, well-differentiated lymphocytic infiltrate	Elderly adults; presentation runs gamut from asymptomatic with lymphocytosis only to bulky disease with adenopathy, splenomegaly, and "packed" bone marrow
Atypical lymphocyte	Infectious mononucleosis, other viral illnesses	Suppressor T-cell markers	Heterophil agglutinin; positive serology for Epstein-Barr virus, cytomegalovirus, toxoplasma, HBsAg	Pharyngitis, fever, adenopathy, rash, splenomegaly, palatal petechiae, jaundice
Plasmacytoid lymphocyte	Waldenström macroglobulin anemia	Cytoplasmic IgM, periodic acid-Schiff positivity	IgM paraprotein, rouleaux, cryoglobulins	Adenopathy, splenomegaly, absence of bone lesions, hyperviscosity syndrome, cryopathic phenomena
Lymphoblast	ALL	Terminal transferase positivity, common ALL antigen, B- or T-precursor markers	Anemia, granulocytopenia, thrombocytopenia, hyperuricemia, diffuse bone marrow infiltration	Peak incidence in childhood, acute onset, bone pain frequent
Lymphosarcoma cell	Lymphocytic lymphoma	B-cell surface markers with high concentration of monoclonal surface immunoglobulin	Nodular or diffuse, poorly differentiated lymphocytic lymphoma on node biopsy, patchy, peritrabecular bone marrow involvement	Middle-aged to older adults, generalized adenopathy, constitutional symptoms
Sézary cell	Cutaneous lymphomas	T-lymphocyte surface markers	Skin biopsy is diagnostic	Exfoliative erythroderma, cutaneous plaques or tumors
Hairy cell	Hairy cell leukemia	B-lymphocyte markers, cytoplasmic projections, tartrate-resistant acid phosphatase, interleukin-2 receptors, CD11 antigen	Pancytopenia	Middle-aged males, moderate to marked splenomegaly without adenopathy
Prolymphocyte	Prolymphocytic leukemia	B-cell surface markers with high concentration of surface immunoglobulin, CD5 negative	Marked lymphocytosis (frequently >100 × 10^9/L)	Elderly adults, massive splenomegaly, minimum adenopathy, poor response to therapy

ALL, Acute lymphoblastic leukemia; *HBsAg,* Hepatitis B surface antigen; *Ig,* immunoglobulin.
From Stein JH (ed): *Internal medicine,* ed 5, St Louis, 1998, Mosby.

BOX 21 Key Causes of Lymphocytopenia

Destructive: Radiation, chemotherapy, corticosteroids
Debilitative: Starvation, aplastic anemia, terminal cancer, collagen vascular disease, renal failure
Infectious: Viral hepatitis, influenza, typhoid fever, TB
AIDS-associated: HIV cytopathic effect, nutritional imbalance, drug effect
Congenital immunodeficiency: Wiskott-Aldrich syndrome
Abnormal lymphatic circulation: Intestinal lymphangiectasia, obstruction, thoracic duct drainage/rupture, CHF

AIDS, Acquired immunodeficiency syndrome; *CHF,* congestive heart failure; *HIV,* human immunodeficiency virus; *TB,* tuberculosis.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

MAGNESIUM (serum)

See Figs. 37 and 38.

Normal range: 1.8 to 3.0 mg/dl (0.80 to 1.20 mmol/L [CF: 0.4114; SMI: 0.02 mmol/L])

CAUSES OF HYPERMAGNESEMIA

Decreased renal excretion
- Renal failure—glomerular filtration rate less than 30 ml/min
- Hyperparathyroidism
- Hypothyroidism
- Addison disease
- Lithium intoxication
- Familial hypocalciuric hypercalcemia

Other causes: Usually in association with decrease in glomerular filtration rate
- Endogenous loads
  - Diabetic ketoacidosis
  - Severe tissue injury: Burns
- Exogenous loads
  - Gastrointestinal
    - Magnesium-containing laxatives and antacids
    - High-dose vitamin D analogs

Parenteral: Management of toxemia of pregnancy

CAUSES OF HYPOMAGNESEMIA

Alcohol abuse
Diuretic use
Renal losses
Acute and chronic renal failure
Postobstructive diuresis
Acute tubular necrosis
Chronic glomerulonephritis
Chronic pyelonephritis
Interstitial nephropathy
Renal transplantation
Gastrointestinal losses

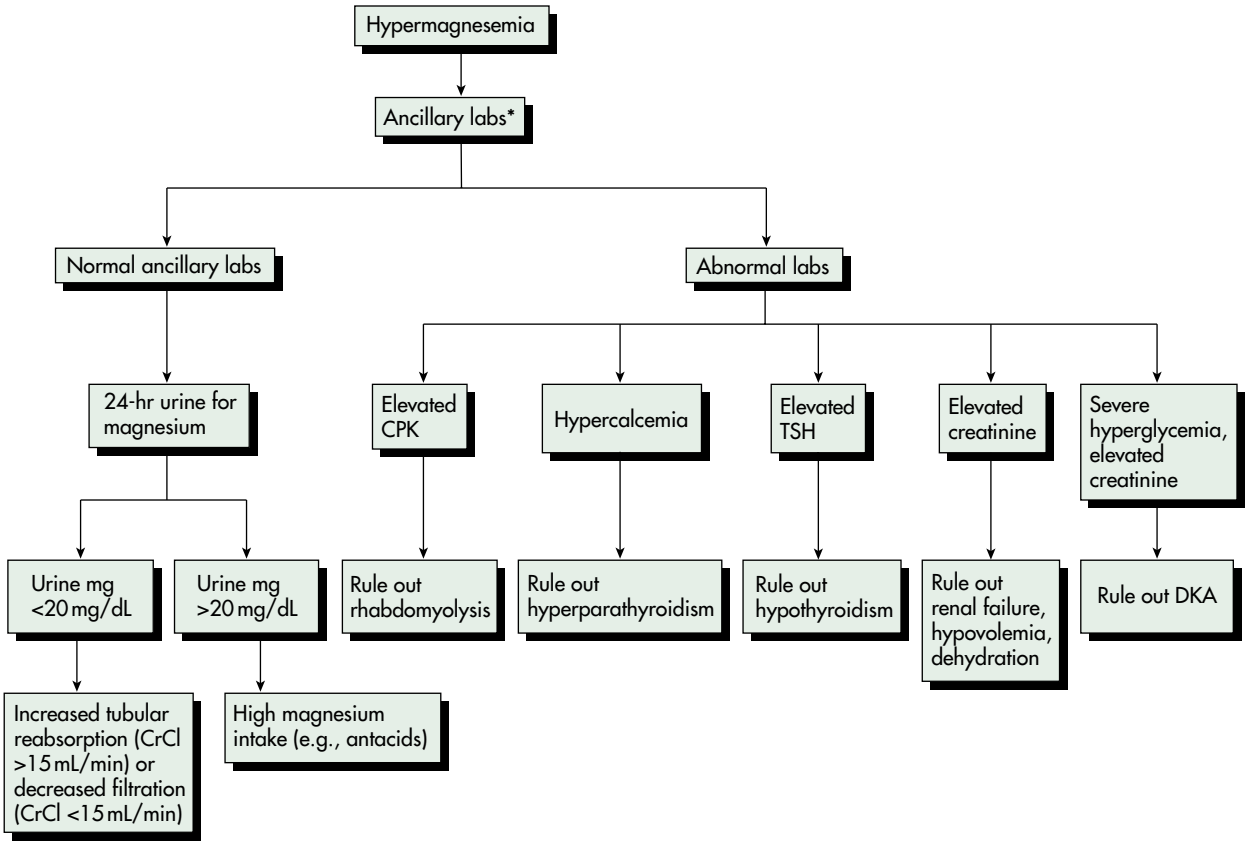

FIG. 37 Diagnostic algorithm for hypermagnesemia. *Serum electrolytes, calcium, blood urea nitrogen (BUN), creatinine, glucose, thyroid stimulating hormone (TSH), creatine phosphokinase (CPK). *CrCl,* Creatinine clearance; *DKA,* diabetic ketoacidosis. (From Ferri F: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, WB Saunders.)

Chronic diarrhea
Nasogastric suctioning
Short bowel syndrome
Protein-calorie malnutrition
Bowel fistula
Total parenteral nutrition
Acute pancreatitis
Endocrine
Diabetes mellitus
Hyperaldosteronism
Hyperthyroidism
Hyperparathyroidism
Acute intermittent porphyria
Pregnancy
Drugs
Aminoglycosides
Amphotericin
β-agonists
Cisplatin
Cyclosporine
Diuretics
Foscarnet
Pentamidine
Theophylline
Congenital disorders
Familial hypomagnesemia
Maternal diabetes
Maternal hypothyroidism
Maternal hyperparathyroidism

MEAN CORPUSCULAR VOLUME (MCV)

Normal range: 76 to 100 μm^3 (76 to 100 fL) (76-100 fL [CF: 1; SMI: 1 fL])

Table 65 summarizes clinical conditions not to be confused with megaloblastosis. See Tables 66, 67, and 68 for descriptions of MCV abnormalities. Table 69 describes the usefulness of the MCV and RBC distribution width in the diagnosis of anemia. Table 70 describes peripheral blood film evaluation in a patient with red cell membrane disorder.

METANEPHRINES, URINE

See URINE METANEPHRINES

METHYLMALONIC ACID (Serum)

Normal: <0.2 µmol/L
Elevated in: Vitamin B_{12} deficiency, pregnancy, methylmalonic acidemia

MITOCHONDRIAL ANTIBODY (AMA)

Normal: Negative
Present in: Primary biliary cirrhosis (>90% of patients)

MONOCYTE COUNT

Normal range: 2% to 8%
Elevated in: Viral diseases, parasites, infections, neoplasms, inflammatory bowel disease, monocytic leukemia, lymphomas, myeloma, sarcoidosis

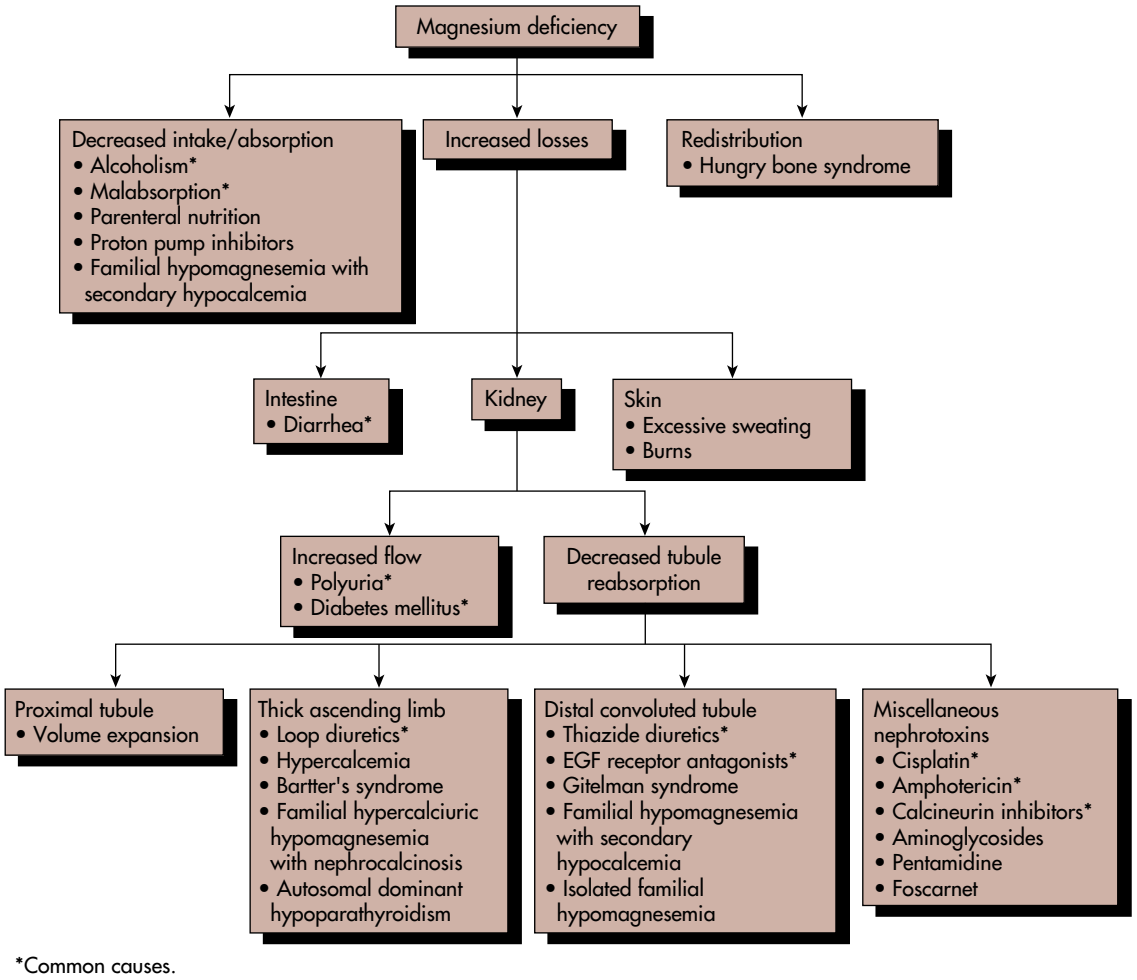

FIG. 38 Causes of magnesium deficiency. *EGF,* Epidermal growth factor. (From Skorecki K et al: *Brenner & Rector's the kidney*, ed 10, Philadelphia, 2016, Elsevier.)

TABLE 65 Clinical Conditions Not to Be Confused with Megaloblastosis

Macrocytosis* without Megaloblastosis†
Reticulocytosis
Liver disease
Aplastic anemia
Myelodysplastic syndromes (especially 5q-)
Multiple myeloma
Hypoxemia
Smokers
Spurious Increases in MCV without Macro-Ovalocytosis‡
Cold agglutinin disease
Marked hyperglycemia
Leukocytosis
Older individuals

MCV, Mean corpuscular volume.
*The central pallor that normally occupies about one third of the normal red blood cell is decreased in macro-ovalocytes. This contrasts with the finding of thin macrocytes, in which the central pallor is increased.
†Although megaloblastosis implies that a bone marrow test has been performed, with the addition of highly sensitive tests for the specific diagnosis of cobalamin and folate deficiency, the need for a bone marrow test is often dictated by the urgency to make the diagnosis.
‡When the Coulter counter readings of a high MCV are not confirmed by looking at the peripheral smear.
From Hoffman R: *Hematology: Basic principles and practice,* ed 6, Philadelphia, 2013, WB Saunders.

Decreased in: Aplastic anemia, lymphocytic leukemia, glucocorticoid administration

See Table 71 for changes in monocyte number.

MYCOPLASMA PNEUMONIAE PCR

Test description: PCR can be performed on sputum, bronchoalveolar lavage, nasopharyngeal and throat swabs, other respiratory fluids, and lung tissue

MYELIN BASIC PROTEIN, CEREBROSPINAL FLUID

Normal: <2.5 ng/ml
Elevated in: Multiple sclerosis, CNS trauma, stroke, encephalitis

MYOGLOBIN, URINE

See URINE MYOGLOBIN

TABLE 66 Some Causes of Increased Mean Corpuscular Volume (Macrocytosis)

Causes	% of all Macrocytosis Patients*	% of Macrocytosis in Each Disease†
Common		
Folate or B_{12} deficiency	20-30 (5-50)‡	80-90 (4-100)
Chronic liver disease	15-20 (6-28)	25-30 (8-65)
Chronic alcoholism	10-12 (3-15)	60 (26-90)
Cytotoxic chemotherapy	10-15 (2-20)	30-40 (13-82)
Cardiorespiratory abnormality	8 (7-9.5)	?
Reticulocytosis	6-7 (0-15)	Depends on severity
Myelodysplastic syndromes	Frequent over age 40 yr	>60 in RAEB and RARS
Unexplained	25 (22.5-27)	—
Normal newborn		
Less Common	**<4%**	
Noncytotoxic drugs > Zidovudine		
Phenytoin		30 (14-50)
Azathioprine		
Hypothyroidism		20-30 (8-55)
Chronic leukemia/myelofibrosis		
Radiotherapy for malignancy		
Chronic renal disease (occasional patients)		
Distance-runner macrocytosis (some persons)		
Down syndrome		
Artifactual (e.g., cold agglutinins)		

RAEB, Refractory anemia with excessive blasts; *RARS,* refractory anemia with ring sideroblasts (formerly called "IASA," or idiopathic acquired sideroblastic anemia).
*Percentage of all patients with macrocytosis.
†Percentage of patients with each condition listed who have macrocytosis.
‡Numbers in parentheses are literature range.
From Ravel R: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.

TABLE 67 Some Causes of Decreased Mean Corpuscular Volume (Microcytosis)

Common	Less Common
Chronic iron deficiency	Some cases of polycythemia
α- or β-thalassemia (minor)	Some cases of lead poisoning
Anemia of chronic disease	Some cases of congenital spherocytosis
	Some cases of sideroblastic anemia
	Certain abnormal hemoglobins (HbE, Hb Lepore)

Hb, Hemoglobin.
From Ravel R: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.

TABLE 68 Differential Diagnosis of Microcytic Hypochromic Anemia

Decreased Body Iron Stores
Iron-deficiency anemia
Normal or increased body iron stores
Anemia of chronic disease
Defective absorption, transport, or use of iron
Iron-refractory, iron-deficiency anemia after parenteral iron
Atransferrinemia
Aceruloplasminemia
Divalent metal transporter 1 (DMT1 or SLC11A2) deficiency
Ferroportin-associated hemochromatosis with impaired iron export (type 4A)
Heme oxygenase 1 deficiency
Disorders of globin synthesis
Thalassemia
Other microcytic hemoglobinopathies
Disorders of heme synthesis: Sideroblastic anemias
Hereditary
Acquired

From Hoffman R et al: *Hematology, basic principles and practice,* ed 6, Philadelphia, 2013, WB Saunders.

TABLE 69 Usefulness of the Mean Corpuscular Value and Red Blood Cell Distribution Width in the Diagnosis of Anemia

	Low MCV (<80fL)	Normal MCV (80-99fL)	High MCV (≥100fL)
Normal RDW	Anemia of chronic disease	Acute blood loss	Aplastic anemia
	α- or β-thalassemia trait	Anemia of chronic disease	Chronic liver disease
	Hemoglobin E trait	Anemia of renal disease	Chemotherapy, antivirals, or alcohol
Elevated RDW	Iron deficiency	Early iron, folate, or vitamin B_{12} deficiency	Folate or vitamin B_{12} deficiency
	Sickle cell–β-thalassemia	Dimorphic anemia (for example, iron + folate deficiency)	Immune hemolytic anemia
		Sickle cell anemia	Cytotoxic chemotherapy
		Sickle cell disease	Chronic liver disease
		Chronic liver disease	Myelodysplasia
		Myelodysplasia	Hereditary spherocytosis, hereditary elliptocytosis, congenital hemoglobinopathies, and RBC enzymopathies

MCV, mean corpuscular value; *RBC,* red blood cell; *RDW,* red blood cell distribution width.
From Hoffman R: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 70 Peripheral Blood Film Evaluation in a Patient with Red Cell Membrane Disorder

Shape	Pathobiology	Diagnosis
Microspherocytes	Loss of membrane lipids leading to a reduction of surface area resulting from deficiencies of spectrin, ankyrin, or band 3 and protein 4.2 Removal of membrane material from antibody-coated red cells by macrophages Removal of membrane-associated Heinz bodies, with the adjacent membrane lipids, by the spleen	HS Immunohemolytic anemias Heinz body hemolytic anemias
Elliptocytes	Permanent red cell deformation resulting from a weakening of skeletal protein interactions (such as the spectrin dimer-dimer contact). This facilitates disruption of existing protein contacts during shear-stress-induced elliptical deformation. Subsequently, new protein contacts are formed that stabilize elliptical shape Unknown	Mild common HE Iron deficiency, megaloblastic anemias, myelofibrosis, myelophthisic anemias, myelodysplastic syndrome, thalassemias
Poikilocytes/fragments	Weakening of skeletal protein contacts resulting from skeletal protein mutations Unknown	Hemolytic HE/HPP Iron deficiency, megaloblastic anemias, myelofibrosis, myelophthisic anemias, myelodysplastic syndrome, thalassemias
Schistocytes, fragmented red cells	Red cells "torn" by mechanical trauma (fibrin strands, turbulent flow)	"Microangiopathic" hemolytic anemia associated with disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, vasculitis, heart valve prostheses
Acanthocytes	Uptake of cholesterol and its preferential accumulation in the outer leaflet of the lipid bilayer Selective accumulation of sphingomyelin in the outer lipid leaflet Unknown	Spur cell hemolytic anemia in severe liver disease Abetalipoproteinemia Chorea-acanthocytosis syndrome, malnutrition, hypothyroidism, McLeod phenotype
Echinocytes	Expansion of the surface area of the outer hemileaflet of lipid bilayer relative to the inner hemileaflet Unknown	Hemolytic anemia associated with hypomagnesemia and hypophosphatemia in malnourished patients, pyruvate kinase deficiency; in vitro artifact of low blood storage (ATP depletion), contact with glass or elevated pH Hemolysis in long-distance runners, renal failure
Stomatocytes	Expansion of the surface area of the inner hemileaflet of the bilayer relative to the outer leaflet Unknown	Exposure of red cells to cationic anesthetics in vitro; in vivo the drug concentrations may not be sufficient to produce similar effect Alcoholism, inherited disorders of membrane permeability (hereditary stomatocytosis)
Target cells	Absolute excess of membrane lipids (both cholesterol and phospholipids: "symmetric" lipid gain), followed by an increase of cell surface area Relative excess of surface area because of a decrease in cell volume	Obstructive jaundice, liver disease with intrahepatic cholestasis Thalassemias and some hemoglobinopathies (C, D, E)

ATP, Adenosine triphosphate; *HE,* hereditary elliptocytosis; *HPP,* hereditary pyropoikilocytosis; *HS,* hereditary spherocytosis.
From Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

TABLE 71 Changes in Monocyte Number

Monocytosis
Infections: Tuberculosis, granulomatous infection, brucellosis, subacute bacterial endocarditis
Connective tissue disorder
Recovery from myelosuppression
Hematologic malignancies
  MDS, MPD, MDS-MPD overlap, CMML
  Acute and chronic monocytic leukemia, myelomonocytic leukemia
  Hodgkin and non-Hodgkin lymphomas
Monocytopenia
Hairy cell leukemia
MonoMAC syndrome
Aplastic anemia
Drugs: Chemotherapy, IFN-α, glucocorticoids (transient)
Radiation therapy

CMML, Chronic myelomonocytic leukemia; *IFN,* interferon; *MDS,* myelodysplastic syndrome; *monoMAC,* monocytopenia and mycobacterium avium complex syndrome; *MPD,* myeloproliferative disorder.
From Hoffman R: *Hematology, basic principles and practice,* ed 6, Philadelphia, 2013, WB Saunders.

NEISSERIA GONORRHOEAE PCR

Test description: Test can be performed on endocervical swab, urine, and intraurethral swab
Normal: Negative

NEUTROPHIL COUNT

Normal range: 50% to 70%
Subsets:
Stabs (bands, early mature neutrophils): 2% to 6%
Segs (mature neutrophils): 60% to 70%
Elevated in: Acute bacterial infections, acute myocardial infarction, stress, neoplasms, myelocytic leukemia
Decreased in: Viral infections, aplastic anemias, immunosuppressive drugs, radiation therapy to bone marrow, agranulocytosis, drugs (antibiotics, antithyroidals, clopidogrel), lymphocytic and monocytic leukemias

Box 22 describes various drugs that can cause neutropenia. Table 72 describes miscellaneous inherited neutropenia disorders. Classification of neutropenia is covered in Table 73. Table 74 lists drugs associated with agranulocytosis. Table 75 describes causes of neutrophilia.

BOX 22 Drugs That Cause Neutropenia

Antiarrhythmics: Tocainide, procainamide, propranolol, quinidine
Antibiotics: Chloramphenicol, penicillins, sulfonamides, *p*-aminosalicylic acid (PAS), rifampin, vancomycin, isoniazid, nitrofurantoin
Antimalarials: Dapsone, quinine, pyrimethamine
Anticonvulsants: Phenytoin, mephenytoin, trimethadione, ethosuximide, carbamazepine
Hypoglycemic agents: Tolbutamide, chlorpropamide
Antihistamines: Cimetidine, brompheniramine, tripelennamine
Antihypertensives: Methyldopa, captopril
Antiinflammatory agents: Aminopyrine, phenylbutazone, gold salts, ibuprofen, indomethacin
Antithyroid agents: Propylthiouracil, methimazole, thiouracil
Diuretics: Acetazolamide, hydrochlorothiazide, chlorthalidone
Phenothiazines: Chlorpromazine, promazine, prochlorperazine
Immunosuppressive agents: Antimetabolites
Cytotoxic agents: Alkylating agents, antimetabolites, anthracyclines, *Vinca* alkaloids, cisplatin, hydroxyurea, dactinomycin
Other agents: Recombinant interferons, allopurinol, ethanol, levamisole, penicillamine, zidovudine, streptokinase, carbamazepine, clopidogrel, ticlopidine

Modified and updated from Goldman L, Ausiello D (eds): *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, WB Saunders.

TABLE 72 Miscellaneous Inherited Neutropenia Disorders

Diagnosis	Genetics	Mapping	Mutant Gene	Additional Features
Hyper IgM syndrome, type 1	X-L	Xq26	*CD40L*	↓IgG, IgA, IgE, autoimmune cytopenias
Hermansky-Pudlak syndrome, type 2	AR	5q14.1	*AP3B1*	↓IgG, partial albinism, platelet dysfunction
Griscelli syndrome, type 1	AR	15q21	*MYO5A*	Neurologic dysfunction, partial albinism
Griscelli syndrome, type 2	AR	15q21	*RAB27A*	Same as type 1 plus hemophagocytosis
Chédiak-Higashi syndrome	AR	1q42.1-q42.2	*LYST (CHSI)*	Immunodeficiency, partial albinism
Poikiloderma with neutropenia	AR	16q13	*C160RF57*	Rash, short stature, dystrophic nails
P14 deficiency	AR	1q22	*MAPBPIP*	Immunodeficiency, hypopigmentation
Cohen syndrome	AR	8q22-q23	*VPS13B/COH1*	Retinopathy, retardation, skeletal anomalies
Charcot-Marie-Tooth syndrome, type 2	AD	19p13.2	*DMN2*	Axonal demyelinating neuropathy

AD, Autosomal dominant; *AR,* autosomal recessive; *Ig,* immunoglobulin; *X-L,* X-linked recessive.
Data compiled from Online Mendelian Inheritance in Man (http://ncbi.nlm.nih.gov/omim); From Hoffman R: *Hematology: Basic principles and practice,* ed 6, Philadelphia, 2013, WB Saunders.

TABLE 73 Classification of Neutropenia

Congenital	
Primary	Autoimmune neutropenia
	Pure white cell aplasia
	Idiopathic
	Thymoma
	Hematologic malignancies (e.g., T-LGL leukemia)
	Infections/postinfectious
	Viral
	Measles, mumps, roseola, rubella,
	RSV, influenza
	Hepatitis A, B, and C
	CMV, EBV, HIV
	Parvovirus
	Bacterial
	Tuberculosis
	Brucellosis
	Tularemia
	Typhoid fever
	Rickettsial
	Rocky Mountain spotted fever
	Ehrlichiosis
	Fungal
	Histoplasmosis
	Parasitic
	Malaria, leishmaniasis
	Autoimmune conditions (e.g., SLE, RA)
	Drugs and chemicals
	Neutropenia associated with immunodeficiency
	Severe nutritional deficiencies
	Neutropenia caused by increased margination
	Iatrogenic (e.g., hemodialysis)

CMV, Cytomegalovirus; *EBV,* Epstein-Barr virus; *HIV,* human immunodeficiency virus; *RA,* refractory anemia; *RSV,* respiratory syncytial virus; *SLE,* systemic lupus erythematosus; *T-LGL,* T-cell large granular lymphocyte.
Modified from Hoffman R: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 74 Drugs Associated with Agranulocytosis

	ETIOLOGIC FRACTION	
	Agranulocytosis (%)	Aplastic Anemia (%)
Overall	64	62
IAAAS	12	27
United States	72	17
Thailand	70	2
Drugs associated with agranulocytosis (IAAAS and other drugs of interest)		
Acetyldigoxin		
ACE inhibitors		
Allopurinol		
Amodiaquine		
Bezafibrate		
β-Blockers		
β-Lactam antibiotics		
Carbamazepine		
Cinepazide		
Corticosteroids		
Cotrimoxazole, other sulfonamides		
Dipyridamole		
Deferasirox (Exjade)		
Dipyrone		
Histamine-2 receptor antagonist		
Indomethacin		
Isoniazid		
Macrolides		
Mefloquine		
Nifedipine		
Phenytoin		
Procainamide		
Salicylates		
Sulfasalazine		
Sulfonylureas		
Tetracyclines		
Thenalidine		
Thyrostatics		
Troxerutin		

ACE, Angiotensin-converting enzyme; *IAAAS,* International Agranulocytosis and Aplastic Anemia Study.
Modified from Hoffman R: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 75 Causes of Neutrophilia

Hematologic malignancy (CML, CNL, CMML)
Infection
Inflammation, physiologic stress, hemorrhage, hemolysis
Hereditary or congenital neutrophilias
Smoking
Drugs: Colony-stimulating factors, glucocorticoids, epinephrine, lithium
Nonhematologic malignancy
Asplenia
Obesity
Recovery from neutropenia

CML, Chronic myeloid leukemia; *CMML,* chronic myelomonocytic leukemia; *CNL,* chronic neutrophilic leukemia.
From Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

NOREPINEPHRINE

Normal range: 0 to 600 pg/ml
Elevated in: Pheochromocytomas, neuroblastomas, stress, vigorous exercise, certain foods (bananas, chocolate, coffee, tea, vanilla)

5′-NUCLEOTIDASE

Normal range: 2-16 IU/L (3-27 × 10^8 kat/L [CF: 1.67 × 10^8; SMI: 1 × 10^8 kat/L])
Elevated in: Biliary obstruction, metastatic neoplasms to liver, primary biliary cirrhosis, renal failure, pancreatic carcinoma, chronic active hepatitis

OSMOLALITY (serum)

Normal range: 280 to 300 mOsm/kg (280 to 300 mmol/kg [CF: 1; SMI: 1 mmol/kg])

It can also be estimated by the following formula:

$$2\,([Na] + [K] + \text{glucose}/18 + \text{BUN}/2.8)$$

The relationship between plasma osmolality and plasma arginine vasopressin is illustrated in Fig. 39.

The relationships between plasma and urine osmolality are illustrated in Fig. 40.

Elevated in: Dehydration, hypernatremia, diabetes insipidus, uremia, hyperglycemia, mannitol therapy, ingestion of toxins (ethylene glycol, methanol, ethanol), hypercalcemia, diuretics
Decreased in: Syndrome of inappropriate diuretic hormone secretion, hyponatremia, overhydration, Addison disease, hypothyroidism

OSMOLALITY, URINE

Normal range: 50 to 1200 mOsm/kg (50 to 1200 mmol/kg [CF: 1; SMI: 1 mmol/kg])
Elevated in: Syndrome of inappropriate antidiuretic hormone secretion, dehydration, glycosuria, adrenal insufficiency, high-protein diet
Decreased in: Diabetes insipidus, excessive water intake, IV hydration with D_5W, acute renal insufficiency, glomerulonephritis

The relationship between plasma urine osmolality and plasma arginine vasopressin in patients with polyuria is illustrated in Fig. 41. Box 23 describes urine osmolality variances in common clinical situations.

OSMOTIC FRAGILITY TEST

Normal: Hemolysis begins at 0.50, w/v [5.0 g/L] and is complete at 0.30, w/v [3.0 g/L] NaCl.
Elevated in: Hereditary spherocytosis, hereditary stomatocytosis, spherocytosis associated with acquired immune hemolytic anemia
Decreased in: Iron deficiency anemia, thalassemias, liver disease, leptocytosis associated with asplenia

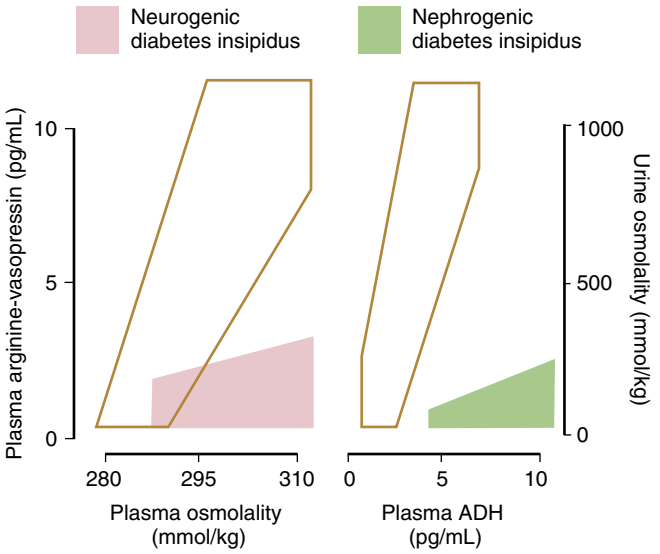

FIG. 39 *Left,* Relationship between plasma arginine vasopressin *(AVP/ADH)* and plasma osmolality during the infusion of hypertonic saline. Patients with primary polydipsia and nephrogenic diabetes insipidus *(DI)* have values within the normal range *(open area),* in contrast to patients with neurogenic DI, who show a subnormal plasma ADH response to a rise in osmolality *(pink). Right,* Relationship between urine osmolality and plasma ADH during dehydration and water loading. Patients with primary polydipsia and neurogenic DI have values within the normal range *(open area),* in contrast to patients with nephrogenic DI, who have hypotonic urine despite high plasma ADH *(green).* (Redrawn from Bichet DG: Diabetes insipidus and vasopressin. In Moore TW, Eastman RC [eds]: *Diagnostic endocrinology,* ed 2, St Louis, 1996, Mosby, p. 168, with permission.) (In McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, St Louis, 2017, Elsevier.)

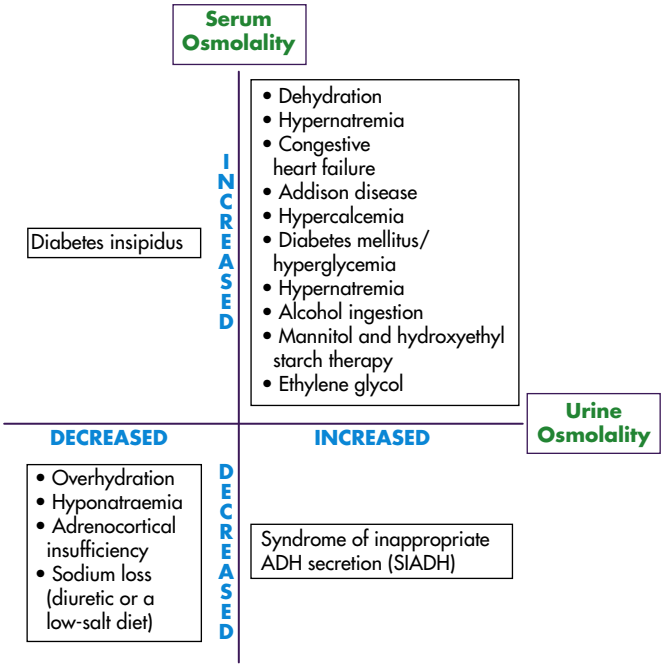

FIG. 40 Relationships between plasma and urine osmolality. *ADH,* Antidiuretic hormone. (From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.)

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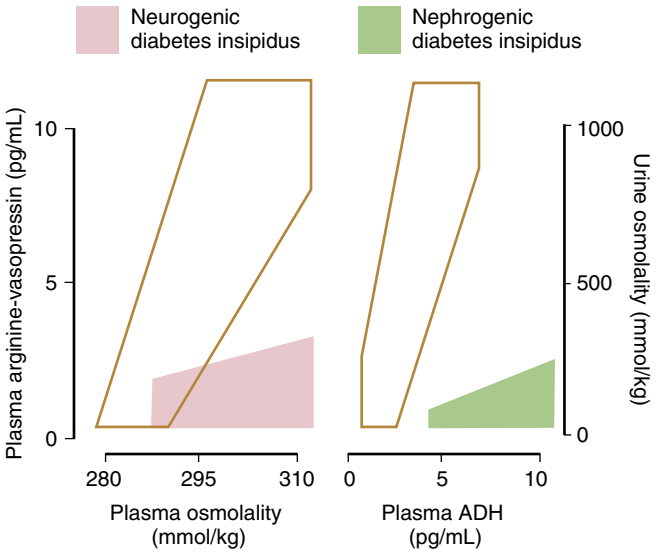


FIG. 39 *Left,* Relationship between plasma arginine vasopressin *(AVP/ADH)* and plasma osmolality during the infusion of hypertonic saline. Patients with primary polydipsia and nephrogenic diabetes insipidus *(DI)* have values within the normal range *(open area),* in contrast to patients with neurogenic DI, who show a subnormal plasma ADH response to a rise in osmolality *(pink). Right,* Relationship between urine osmolality and plasma ADH during dehydration and water loading. Patients with primary polydipsia and neurogenic DI have values within the normal range *(open area),* in contrast to patients with nephrogenic DI, who have hypotonic urine despite high plasma ADH *(green).* (Redrawn from Bichet DG: Diabetes insipidus and vasopressin. In Moore TW, Eastman RC [eds]: *Diagnostic endocrinology,* ed 2, St Louis, 1996, Mosby, p. 168, with permission.) (In McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods,* ed 23, St Louis, 2017, Elsevier.)

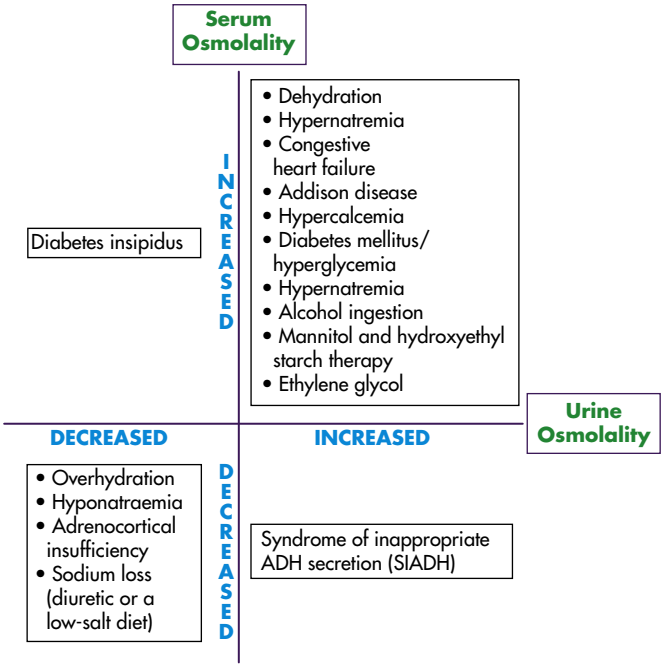


FIG. 40 Relationships between plasma and urine osmolality. *ADH,* Antidiuretic hormone. (From Vincent JL et al: *Textbook of critical care*, ed 7, Philadelphia, 2017, Elsevier.)

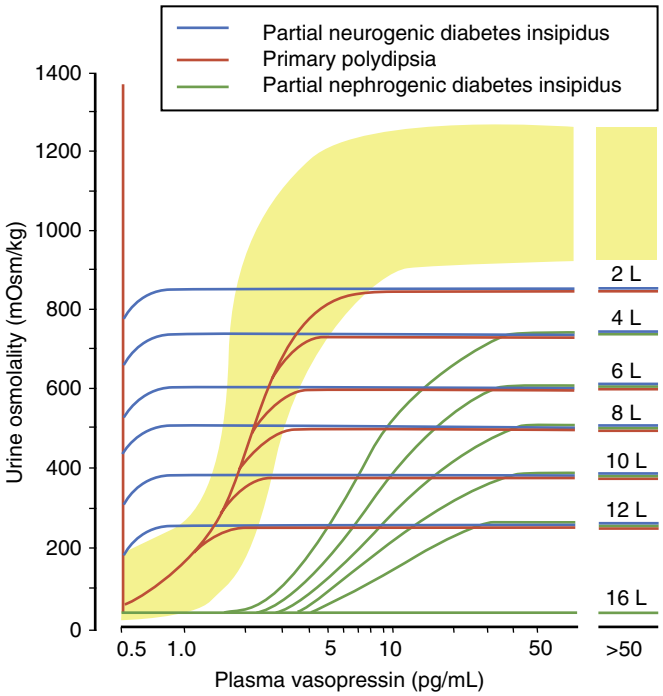


FIG. 41 The relationship between urine osmolality (Uosm) and plasma arginine vasopressin (AVP/ADH) in patients with polyuria of diverse causes and severity. Each of the three categories of polyuria is described by its own family of sigmoid curves of differing heights. Differences in height within a family reflect differences in maximum concentrating capacity caused by "washout" of the medullary concentration gradient. They are proportional to the severity of the polyuria (indicated in liters per day at the right end of each plateau). The normal response is depicted in yellow. The three categories of polyuria differ principally in the ascending portion of the dose-response curve. In patients with partial neurogenic diabetes insipidus *(DI),* the curve lies to the left of normal, reflecting increased sensitivity to the antidiuretic effects of very low concentrations of plasma ADH. In contrast, in patients with partial nephrogenic DI, the curve lies to the right of normal, reflecting decreased sensitivity to ADH. In primary polydipsia, the relationship of Uosm to ADH remains relatively normal. (Redrawn from Bichet DG: Diabetes insipidus and vasopressin. In Moore WT, Eastman RC [eds]: *Diagnostic endocrinology,* ed 2, St Louis, 1996, Mosby, p 158, with permission.) (McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.)

BOX 23 Urine Osmolality in Common Clinical Situations

High Urine Osmolality
AKI or when assessing effective circulating volume
Prerenal states
Volume depletion (GI losses, renal losses, skin losses, third spacing)
Heart failure
Cirrhosis
Hypoalbuminemia
Hyponatremia
Prerenal states
Volume depletion (GI losses, renal losses, skin losses, third spacing)
Heart failure
Cirrhosis
Hypoalbuminemia
Syndrome of inappropriate ADH secretion
Hypernatremia
GI losses (vomiting, diarrhea, nasogastric tube, fistula)
Skin losses (fever, exercise, ventilation)
Sodium overload (received excess normal saline or sodium bicarbonate)
Mineralocorticoid excess
Seizures (↑ intracellular osmoles → water shifts → transient increase in serum Na)

Low Urine Osmolality
AKI or when assessing effective circulating volume
Euvolemic or hypervolemic
Established AKI
Chronic kidney disease
Hyponatremia
In process of correcting hyponatremia
Primary polydipsia
Extremely low solute intake (tea and toast diet or beer potomania)
Hypernatremia
Osmotic diuresis (glucose, mannitol, urea)
Loop diuretics
Nephrogenic DI
Central DI

ADH, Antidiuretic hormone; AKI, acute kidney injury; DI, diabetes insipidus; GI, gastrointestinal.
From Ronco C: *Critical care nephrology*, ed 3, Philadelphia, 2019, Elsevier.

PARACENTESIS FLUID

Testing and evaluation of results:

Process the fluid as follows:
- Tube 1: LDH, glucose, albumin
- Tube 2: Protein, specific gravity
- Tube 3: Cell count and differential
- Tube 4: Save until further notice

Draw serum LDH, protein, albumin.

Gram stain, acid-fast bacilli stain, bacterial and fungal cultures, amylase, and triglycerides should be ordered only when clearly indicated; bedside inoculation of blood-culture bottles with ascitic fluid improves sensitivity in detecting bacterial growth.

If malignant ascites is suspected, consider a carcinoembryonic antigen level on the paracentesis fluid and cytologic evaluation.

In suspected spontaneous bacterial peritonitis (SBP) the incidence of positive cultures can be increased by injecting 10 to 20 ml of ascitic fluid into blood culture bottles.

Peritoneal effusion can be subdivided as exudative or transudative based on its characteristics (see Section II).

The serum-ascites albumin gradient (serum albumin level-ascitic fluid albumin level [SAAG]) correlates directly with portal pressure and can also be used to classify ascites. Patients with gradients ≥1.1 g/dl have portal hypertension, and those with gradients ≤1.1 g/dl do not; the accuracy of this method is >95%.

For the differential diagnosis of ascites, refer to Section II.

An ascitic fluid polymorphonuclear leukocyte count >500/μl is suggestive of SBP.

A blood-ascitic fluid albumin gradient. Box 24 summarizes causes of peritoneal effusions. Useful criteria for evaluation of peritoneal lavage is summarized in Box 25. Recommended tests in peritoneal effusions are summarized in Box 26.

PARATHYROID HORMONE (PTH)

Normal:

Serum, intact molecule 10-65 pg/ml

Plasma 1.0-5.0 pmol/L

Elevated in: Hyperparathyroidism (primary or secondary), pseudohypoparathyroidism, anticonvulsants, corticosteroids, lithium, isoniazid (INH), rifampin, phosphates, Zollinger-Ellison syndrome, hereditary vitamin D deficiency

Decreased in: Hypoparathyroidism, sarcoidosis, cimetidine, beta-blockers, hyperthyroidism, hypomagnesemia

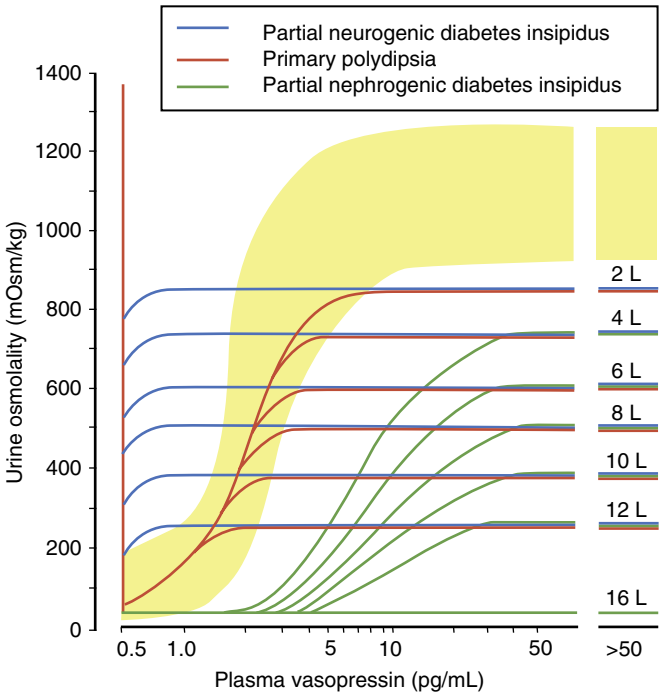


FIG. 41 The relationship between urine osmolality (Uosm) and plasma arginine vasopressin (AVP/ADH) in patients with polyuria of diverse causes and severity. Each of the three categories of polyuria is described by its own family of sigmoid curves of differing heights. Differences in height within a family reflect differences in maximum concentrating capacity caused by "washout" of the medullary concentration gradient. They are proportional to the severity of the polyuria (indicated in liters per day at the right end of each plateau). The normal response is depicted in yellow. The three categories of polyuria differ principally in the ascending portion of the dose-response curve. In patients with partial neurogenic diabetes insipidus *(DI),* the curve lies to the left of normal, reflecting increased sensitivity to the antidiuretic effects of very low concentrations of plasma ADH. In contrast, in patients with partial nephrogenic DI, the curve lies to the right of normal, reflecting decreased sensitivity to ADH. In primary polydipsia, the relationship of Uosm to ADH remains relatively normal. (Redrawn from Bichet DG: Diabetes insipidus and vasopressin. In Moore WT, Eastman RC [eds]: *Diagnostic endocrinology,* ed 2, St Louis, 1996, Mosby, p 158, with permission.) (McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.)

BOX 23 Urine Osmolality in Common Clinical Situations

High Urine Osmolality
AKI or when assessing effective circulating volume
Prerenal states
Volume depletion (GI losses, renal losses, skin losses, third spacing)
Heart failure
Cirrhosis
Hypoalbuminemia
Hyponatremia
Prerenal states
Volume depletion (GI losses, renal losses, skin losses, third spacing)
Heart failure
Cirrhosis
Hypoalbuminemia
Syndrome of inappropriate ADH secretion
Hypernatremia
GI losses (vomiting, diarrhea, nasogastric tube, fistula)
Skin losses (fever, exercise, ventilation)
Sodium overload (received excess normal saline or sodium bicarbonate)
Mineralocorticoid excess
Seizures (↑ intracellular osmoles → water shifts → transient increase in serum Na)

Low Urine Osmolality
AKI or when assessing effective circulating volume
Euvolemic or hypervolemic
Established AKI
Chronic kidney disease
Hyponatremia
In process of correcting hyponatremia
Primary polydipsia
Extremely low solute intake (tea and toast diet or beer potomania)
Hypernatremia
Osmotic diuresis (glucose, mannitol, urea)
Loop diuretics
Nephrogenic DI
Central DI

ADH, Antidiuretic hormone; AKI, acute kidney injury; DI, diabetes insipidus; GI, gastrointestinal.
From Ronco C: *Critical care nephrology*, ed 3, Philadelphia, 2019, Elsevier.

PARACENTESIS FLUID

Testing and evaluation of results:

Process the fluid as follows:
- Tube 1: LDH, glucose, albumin
- Tube 2: Protein, specific gravity
- Tube 3: Cell count and differential
- Tube 4: Save until further notice

Draw serum LDH, protein, albumin.

Gram stain, acid-fast bacilli stain, bacterial and fungal cultures, amylase, and triglycerides should be ordered only when clearly indicated; bedside inoculation of blood-culture bottles with ascitic fluid improves sensitivity in detecting bacterial growth.

If malignant ascites is suspected, consider a carcinoembryonic antigen level on the paracentesis fluid and cytologic evaluation.

In suspected spontaneous bacterial peritonitis (SBP) the incidence of positive cultures can be increased by injecting 10 to 20 ml of ascitic fluid into blood culture bottles.

Peritoneal effusion can be subdivided as exudative or transudative based on its characteristics (see Section II).

The serum-ascites albumin gradient (serum albumin level-ascitic fluid albumin level [SAAG]) correlates directly with portal pressure and can also be used to classify ascites. Patients with gradients ≥1.1 g/dl have portal hypertension, and those with gradients ≤1.1 g/dl do not; the accuracy of this method is >95%.

For the differential diagnosis of ascites, refer to Section II.

An ascitic fluid polymorphonuclear leukocyte count >500/μl is suggestive of SBP.

A blood-ascitic fluid albumin gradient. Box 24 summarizes causes of peritoneal effusions. Useful criteria for evaluation of peritoneal lavage is summarized in Box 25. Recommended tests in peritoneal effusions are summarized in Box 26.

PARATHYROID HORMONE (PTH)

Normal:

Serum, intact molecule 10-65 pg/ml

Plasma 1.0-5.0 pmol/L

Elevated in: Hyperparathyroidism (primary or secondary), pseudohypoparathyroidism, anticonvulsants, corticosteroids, lithium, isoniazid (INH), rifampin, phosphates, Zollinger-Ellison syndrome, hereditary vitamin D deficiency

Decreased in: Hypoparathyroidism, sarcoidosis, cimetidine, beta-blockers, hyperthyroidism, hypomagnesemia

BOX 24 Causes of Peritoneal Effusions

Transudates: Increased Hydrostatic Pressure or Decreased Plasma Oncotic Pressure
Congestive heart failure
Hepatic cirrhosis
Hypoproteinemia (e.g., nephrotic syndrome)

Exudates: Increased Capillary Permeability or Decreased Lymphatic Resorption
Infections
- Primary bacterial peritonitis
- Secondary bacterial peritonitis (e.g., appendicitis, bowel rupture)
- Tuberculosis

Neoplasms
- Hepatoma
- Lymphoma
- Mesothelioma
- Metastatic carcinoma
- Ovarian carcinoma
- Prostate cancer

Trauma
Pancreatitis
Bile peritonitis (e.g., ruptured gallbladder)

Chylous Effusion
Damage to or obstruction of thoracic duct (e.g., trauma, lymphoma, carcinoma, tuberculosis and other granulomas [e.g., sarcoidosis, histoplasmosis], parasitic infestation)

From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

BOX 25 Criteria for Evaluation of Peritoneal Lavage

Positive Result
Aspiration of >15 ml gross blood on catheter placement
Grossly bloody lavage fluid
RBC >100,000/μL after blunt trauma
RBC >50,000/μL after penetrating trauma
WBC >500/μL
Amylase >110 U/dl

Indeterminate Result
Small amount of gross blood on catheter placement
RBC 50,000-100,000/μL after blunt trauma
RBC 1000-50,000/μL after penetrating trauma
WBC 100-500/μL

Negative Result
RBC <50,000/μL after blunt trauma
RBC <1000/μL after penetrating trauma
WBC <100/μL

RBC, Red blood cells; *WBC,* white blood cells.
Modified from Feied CF: Diagnostic peritoneal lavage, *Postgrad Med* 85:40, 1989, with permission. In McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

PARIETAL CELL ANTIBODIES

Normal: Negative
Present in: Pernicious anemia (>90%), atrophic gastritis (up to 50%), thyroiditis (30%), Addison disease, myasthenia gravis, Sjögren syndrome, type 1 DM

PARTIAL THROMBOPLASTIN TIME (PTT), ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)

See Table 76 for interpretation of coagulation protein screening tests.
Normal range: 25 to 41 sec
Elevated in: Heparin therapy, coagulation factor deficiency (I, II, V, VIII, IX, X, XI, XII), liver disease, vitamin K deficiency, disseminated intravascular coagulation, circulating anticoagulant, warfarin therapy, specific factor inhibition (penicillin [PCN] reaction, rheumatoid arthritis), thrombolytic therapy, nephrotic syndrome
NOTE: Useful to evaluate the intrinsic coagulation system.

BOX 26 Recommended Tests in Peritoneal Effusions

Useful in Most Patients
Gross examination
Cytology
Stains and culture for microorganisms
Serum-ascites albumin concentration gradient

Useful in Selected Disorders
Total leukocyte and differential cell counts
RBC count (lavage)
Bilirubin
Creatinine/urea nitrogen
Enzymes (ADA, ALP, amylase, LD, telomerase)
Lactate
Cholesterol (malignant ascites)
Fibronectin
Tumor markers (CEA, PSA, CA 19-9, CA 15-3, CA-125)
Immunocytology/flow cytometry
Tuberculostearic acid

ADA, Adenosine deaminase; *ALP,* alkaline phosphatase; *LD,* lactate dehydrogenase; *RBC,* red blood cell.
Modified from Kjeldsberg CR, Knight JA: *Body fluids: Laboratory examination of amniotic, cerebrospinal, seminal, serous and synovial fluids*, ed 3, Chicago, 1993, American Society for Clinical Pathology, with permission. In McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

PEPSINOGEN I

Normal: 124 to 142 ng/ml
Elevated in: Zollinger–Ellison (ZE) syndrome, duodenal ulcer, acute gastritis
Decreased in: Atrophic gastritis, gastric carcinoma, myxedema, pernicious anemia, Addison disease

PH, BLOOD

Normal values:
Arterial: 7.35 to 7.45
Venous: 7.32 to 7.42
For abnormal values, refer to ARTERIAL BLOOD GASES.

PH, URINE

See URINE pH

PHENOBARBITAL

Normal therapeutic range:
15 to 30 mc g/ml for epilepsy control

PHENYTOIN (Dilantin)

Normal therapeutic range: 10 to 20 mcg/ml

PHOSPHATASE, ACID

See ACID PHOSPHATASE

PHOSPHATASE, ALKALINE

See ALKALINE PHOSPHATASE

PHOSPHATE (serum)

Normal range: 2.5 to 5 mg/dl (0.8-1.6 mmol/L [CF: 0.3229; SMI: 0.05 mmol/L])
DECREASED
Parenteral hyperalimentation
Diabetic acidosis

Alcohol withdrawal
Severe metabolic or respiratory alkalosis
Antacids that bind phosphorus
Malnutrition with refeeding using low-phosphorus nutrients
Renal tubule failure to reabsorb phosphate (Fanconi syndrome; congenital disorder; vitamin D deficiency)
Glucose administration
Nasogastric suction

TABLE 76 Clinical Peculiarities of Coagulation Protein Screening Tests

Long aPTT, normal or long PT, no bleeding	Normal aPTT, PT, *with bleeding*
Long aPTT only	
Factor XII deficiency	Factor XIII deficiency or inhibitor
Prekallikrein deficiency	α_2-Antiplasmin deficiency or defect
High-molecular-weight kininogen	Plasminogen activator inhibitor deficiency or defect
Lupus anticoagulant	α_1-Antitrypsin Pittsburgh defect
Long aPTT and PT	
Dysfibrinogenemia with fibrinopeptide B release	
Lupus anticoagulant	

aPTT, Activated partial thromboplastin time; *PT,* prothrombin time.
From Hoffman R et al: *Hematology: Basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

Malabsorption
Gram-negative sepsis
Primary hyperthyroidism
Chlorothiazide diuretics
Therapy of acute severe asthma
Acute respiratory failure with mechanical ventilation
INCREASED
Renal failure
Severe muscle injury
Phosphate-containing antacids
Hypoparathyroidism
Tumor lysis syndrome
For a diagnostic algorithm of hyperphosphatemia, see Fig. 42.
For a diagnostic algorithm for hypophosphatemia, see Fig. 43.
For causes and treatment of hypophosphatemia see Tables 77 and 78.

PLASMINOGEN

Normal: Immunoassay (antigen): <20 mg/dl
Elevated in: Infection, trauma, neoplasm, myocardial infarction (acute phase reactant), pregnancy, bilirubinemia
Decreased in: disseminated intravascular coagulation (DIC), severe liver disease, thrombolytic therapy with streptokinase or urokinase, alteplase

PLATELET AGGREGATION

Normal: Full aggregation (generally >60%) in response to epinephrine, thrombin, ristocetin, adenosine diphosphate (ADP), collagen
Elevated in: Heparin, hemolysis, lipemia, nicotine, hereditary and acquired disorders of platelet adhesion, activation, and aggregation

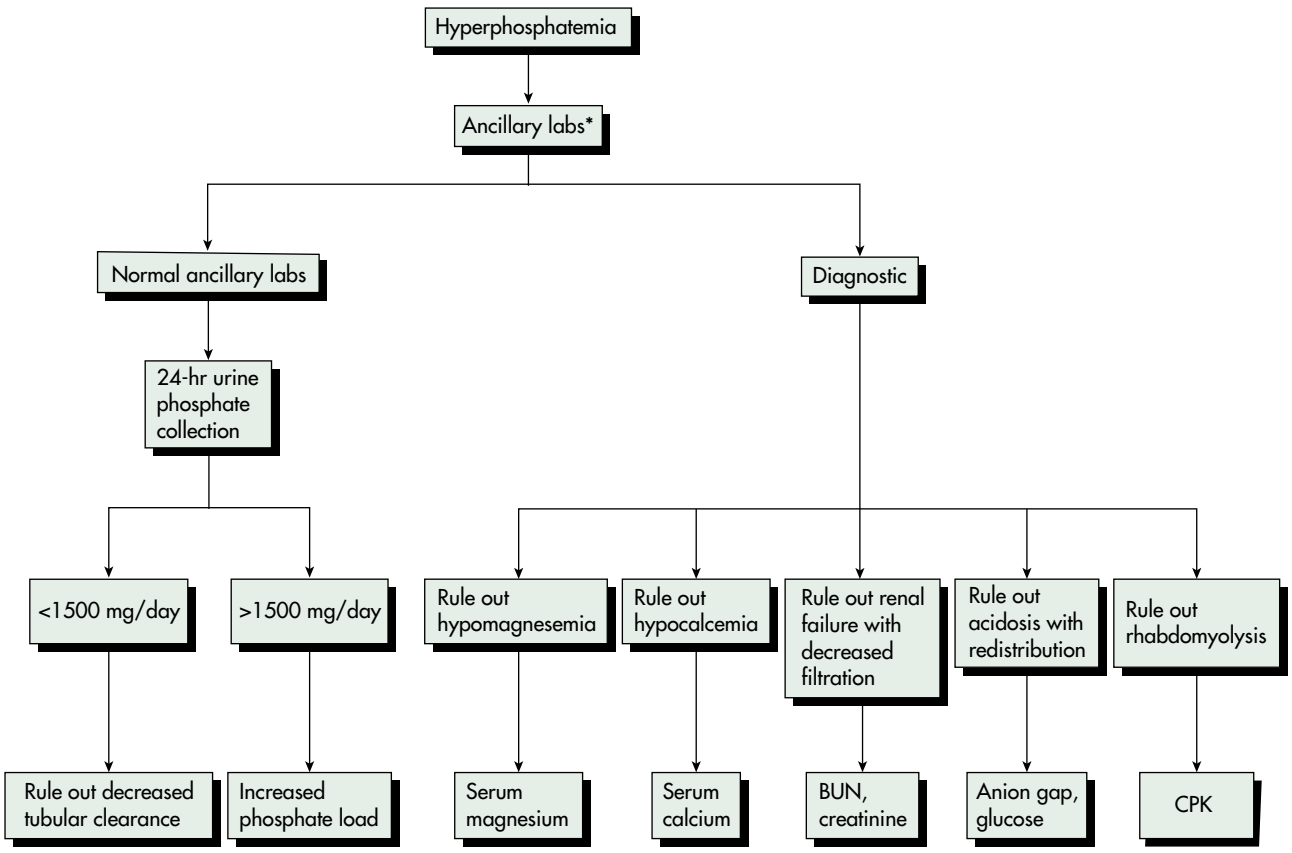


FIG. 42 Diagnostic algorithm for hyperphosphatemia. *Serum calcium, electrolytes, creatinine, glucose, arterial blood gases (ABGs), urinalysis, creatine phosphokinase (CPK), magnesium. *BUN,* Blood urea nitrogen. (From Ferri F: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging*, ed 4, Philadelphia, 2017, WB Saunders.)

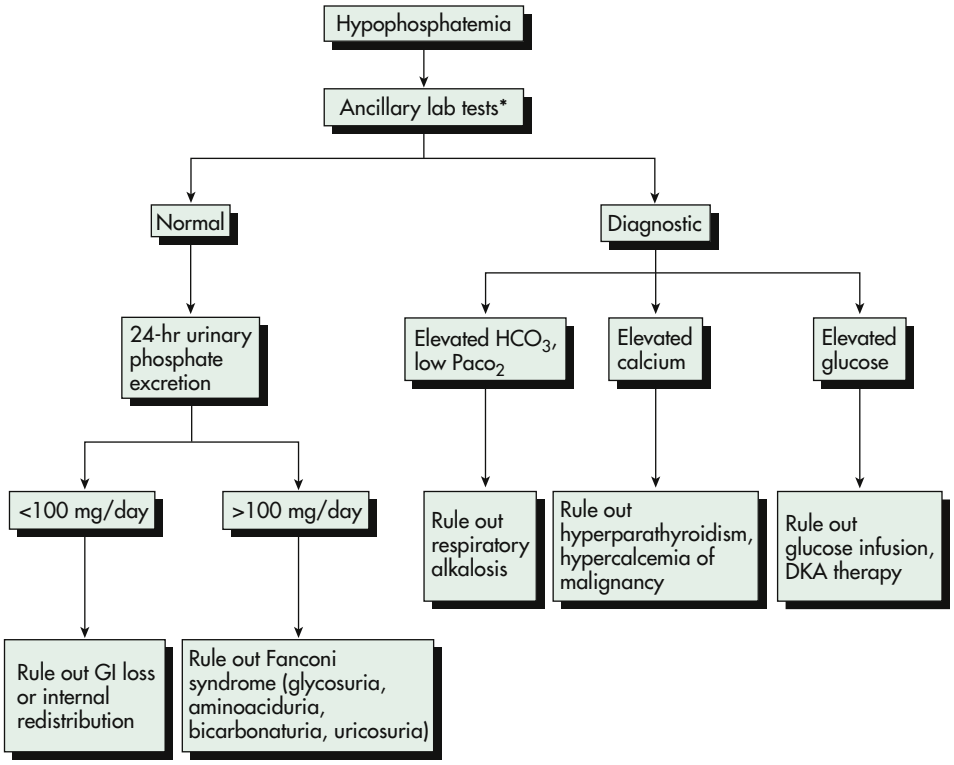


FIG. 43 Diagnostic algorithm for hypophosphatemia. *Serum creatinine, blood urea nitrogen (BUN), electrolytes, magnesium, calcium, glucose, urinalysis, creatine phosphokinase (CPK). *DKA,* Diabetic ketoacidosis; *GI,* gastrointestinal; *$Paco_2$,* partial pressure of carbon dioxide in the arterial blood. (From Ferri F: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging*, ed 4, Philadelphia, 2017, WB Saunders.)

Decreased in: Aspirin, some penicillins, chloroquine, chlorpromazine, clofibrate, captopril, Glanzmann thrombasthenia, Bernard-Soulier syndrome, Wiskott-Aldrich syndrome, cyclooxygenase deficiency. In von Willebrand disease there is normal aggregation with ADP, collagen, and epinephrine but abnormal agglutination with ristocetin.

PLATELET ANTIBODIES

Normal: Absent
Present in: Idiopathic thrombocytopenic purpura (ITP) (>90% of patients with chronic ITP). Patients with nonimmune thrombocytopenias may have false-positive results.

PLATELET COUNT

See Fig. E44 for evaluation of thrombocytosis. Box E27 describes testing for thrombocytopenia. See Table 79 for differential diagnosis. Table 80 describes antibody-mediated thrombocytopenic disorders caused by autoantibodies, alloantibodies, or potentially both. Tables 81 and 82 indicate differential diagnosis of thrombocytopenia in newborns and differential diagnosis of thrombocytopenia in pregnancy, respectively. Table 83 describes laboratory tests used to investigate a patient with thrombocytopenia.
Normal range: 130 to 400 × 103/mm3 (130-400 × 109/L [CF: 1; SMI: 5 × 109/L])
Elevated in
REACTIVE THROMBOCYTOSIS
Infections or inflammatory states: Vasculitis, allergic reactions, etc.
Surgery and tissue damage: Myocardial infarction, pancreatitis, etc.
Postsplenectomy state
Malignancy: Solid tumors, lymphoma
Iron deficiency anemia, hemolytic anemia, acute blood loss
Uncertain etiology
Rebound effect after chemotherapy or immune thrombocytopenia
Renal disorders: Renal failure, nephrotic syndrome
MYELOPROLIFERATIVE DISORDERS
Chronic myeloid leukemia
Primary thrombocythemia
Polycythemia vera
Idiopathic myelofibrosis
Decreased:
Increased destruction (see Table 84)
  Immunologic
    Drugs: Quinine, quinidine, digitalis, procainamide, thiazide diuretics, sulfonamides, phenytoin, aspirin, penicillin, heparin, gold, meprobamate, sulfa drugs, phenylbutazone, NSAIDs, methyldopa, cimetidine, furosemide, INH, cephalosporins, chlorpropamide, organic arsenicals, chloroquine
    Idiopathic thrombocytopenic purpura
    Transfusion reaction: Transfusion of platelets with platelet antigen HPA-1a (PL^{A1}) in recipients without PL^{A1}
    Fetal/maternal incompatibility
    Vasculitis (e.g., systemic lupus erythematosus)
    Autoimmune hemolytic anemia
    Lymphoreticular disorders (e.g., chronic lymphocytic leukemia)
Nonimmunologic
  Prosthetic heart valves
  Thrombotic thrombocytopenic purpura
  Sepsis
  Disseminated intravascular coagulation
  Hemolytic-uremic syndrome
  Giant cavernous hemangioma
Decreased production
  Abnormal marrow
    Marrow infiltration (e.g., leukemia, lymphoma, fibrosis)
    Marrow suppression (e.g., chemotherapy, alcohol, radiation)
  Hereditary disorders (see Table 85)
    Wiskott-Aldrich syndrome: X-linked disorder characterized by thrombocytopenia, eczema, and repeated infections
    May-Hegglin anomaly: Increased megakaryocytes but ineffective thrombopoiesis
  Vitamin deficiencies (e.g., vitamin B_{12}, folic acid)

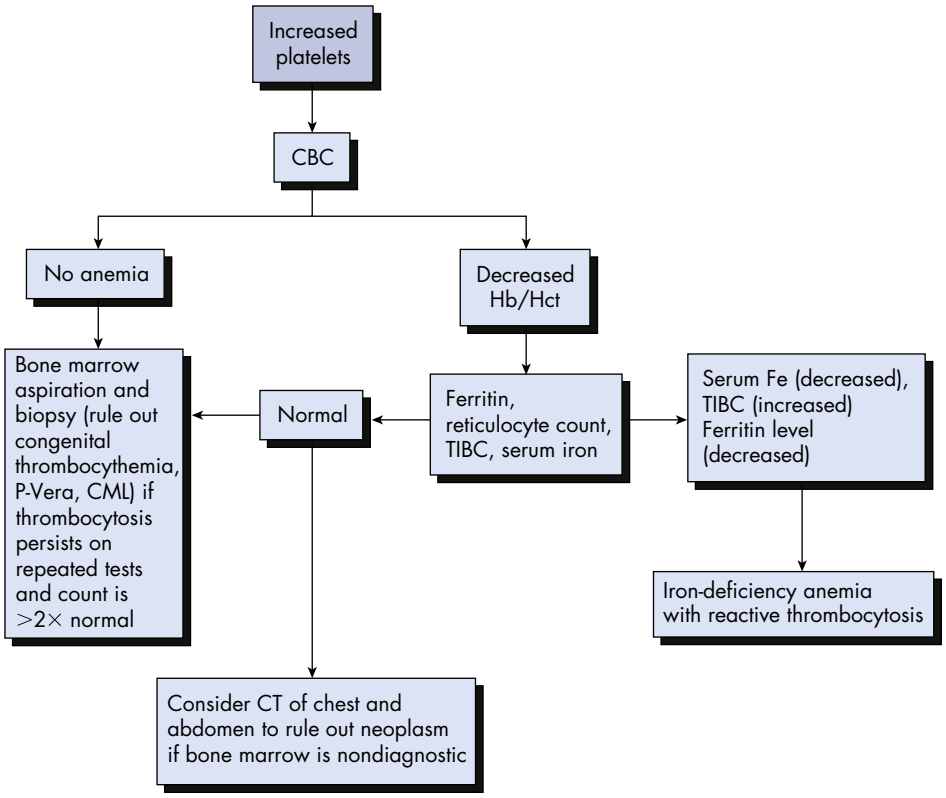


FIG. E44 Thrombocytosis diagnosis. *CBC,* Complete blood count; *CML,* chronic myelogenous leukemia; *CT,* computed tomography; *Hb/Hct,* hemoglobin/hematocrit; *P-Vera,* polycythemia vera; *TIBC,* total iron-binding capacity. (From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging*, ed 4, Philadelphia, 2017, Elsevier Mosby.)

BOX E27 Thrombocytopenia Diagnostic Imaging

Best Test
None

Ancillary Test
CT of abdomen if splenomegaly is present

Lab Evaluation

Best Test
Bone marrow examination

Ancillary Tests
CBC, PT, PTT
LDH
HIV, ANA
Antiplatelet Ab
D-dimer
Antiglobulin (Coombs) test

Ab, Antibody; *ANA,* antibody to nuclear antigens; *CBC,* complete blood count; *CT,* computed tomography; *HIV,* human immunodeficiency virus; *LDH,* lactic dehydrogenase; *PT,* prothrombin time; *PTT,* partial thromboplastin time.
From Ferri FF: *Ferri's best test: A practical guide to clinical laboratory medicine and diagnostic imaging,* ed 4, Philadelphia, 2017, Elsevier Mosby.

TABLE 77 Causes of Hypophosphatemia

Decreased Phosphate Intake
- Starvation, inadequate phosphate intake, chronic diarrhea, chronic alcoholism
- Total parenteral nutrition with insufficient phosphate content

Increased Loss of Phosphate
- Increased renal phosphate excretion
  - Primary hyperparathyroidism
  - Secondary hyperparathyroidism: Vitamin D deficiency or resistance (including 1α-hydroxylase deficiency, VDR mutations, VDDR); imatinib
  - Excess FGF-23 or phosphatonins: X-linked hypophosphatemia, AD hypophosphatemic rickets, tumor-induced osteomalacia, epidermal nevus, McCune-Albright syndrome
  - Fanconi syndrome, cystinosis, Wilson disease, Dent disease, Lowe syndrome, multiple myeloma, amyloidosis, heavy-metal toxicity, rewarming of hyperthermia, Na/Pi-IIa and Na/Pi-IIc mutation (HHRH)
  - PTHrP-dependent hypercalcemia of malignancy
  - Hypomagnesemia
- Decreased intestinal absorption
  - Vitamin D deficiency or resistance (VDDR I and II)
  - Malabsorption
- Increased intestinal loss
  - Phosphate binding antacids used in treating peptic ulcers
- Increased loss from other routes
  - Skin: Severe burns
  - Vomiting

Phosphate Shifting from Extracellular Compartment to Cells and Bones
- Diabetic ketoacidosis
- Alcohol intoxication
- Acute respiratory alkalosis, salicylate intoxication, gram-negative sepsis, toxic shock syndrome, acute gout
- Refeeding syndromes from starvation, anorexia nervosa, hepatic failure: Acute intravenous glucose, fructose, glycerol
- Rapid cellular proliferation: Intensive erythropoietin therapy, GM-CSF therapy, leukemic blast crisis
- Recovery from hypothermia
- Heat stroke
- Post parathyroidectomy; "hungry bone" disease: Osteoblastic metastases, antiresorptive treatment of severe Paget disease
- Catecholamine (albuterol, dopamine, terbutaline, epinephrine)
- Thyrotoxic periodic paralysis
- Hypocalcemic periodic paralysis

Miscellaneous

Hyperaldosteronism
- Oncogenic hypophosphatemia
- Post kidney transplantation
- Post partial hepatectomy
- High-dose corticosteroids, estrogens
- Medications: Ifosfamide; toluene; calcitonin; bisphosphonate; tenofovir; paraquat, cisplatin; acetazolamide and other diuretics
- Post obstructive diuresis

AD, Autosomal dominant; *FGF-23,* fibroblast growth factor 23; *GM-CSF,* granulocyte-macrophage colony-stimulating factor; *HHRH,* hereditary hypophosphatemic rickets with hypercalciuria; *Na/Pi-II,* type II sodium-dependent phosphate cotransporter; *PTHrP,* parathyroid hormone-related peptide; *VDDR,* vitamin D-dependent rickets; *VDR,* vitamin D receptor.
From Skorecki K et al*: Brenner & Rector's the kidney,* ed 10, Philadelphia, 2016, Elsevier.

Splenic sequestration, hypersplenism
Dilutional, secondary to massive transfusion

PLATELET FUNCTION ANALYSIS 100 ASSAY (PFA)

Normal: This test is a two-component assay where blood is aspirated through two capillary tubes, one of which is coated with collagen and ADP (COL/ADP) and the other with collagen and epinephrine (COL/EPI). The test measures the ability of platelets to occlude an aperture in a biologically active membrane treated with COL/ADP and COL/EPI. During the test, the platelets adhere to the surface of the tube and cause blood flow to cease. The closing time refers to the cessation of blood flow and is reported in conjunction with the hematocrit and platelet count. Hematocrit count must be >25% and platelet count >50 K/microliter for the test to be performed.

TABLE 78 Treatment of Hypophosphatemia

Therapy	Dosage	Administration
Mild and Moderate Hypophosphatemia		
	Low-fat milk	Phosphate 0.9 mg/ml
	Buffered Na phosphate (Fleet enema)	1-3 g/day in 4 divided doses
	Neutra-Phos (250 mg elemental phosphorus per capsule)	1-3 g/day in 4 divided doses
	Calcitriol	30-70 ng/kg body weight per day
Asymptomatic Severe Hypophosphatemia		
Elemental phosphate	2.5 mg/kg body weight	IV over 6 hr
Symptomatic Severe Hypophosphatemia		
Elemental phosphate	5 mg/kg body weight	IV over 6 hr

IV, Intravenously.
From Skorecki et al: *Brenner & Rector's the kidney,* ed 10, Philadelphia, 2016, Elsevier.

TABLE 79 Differential Diagnosis of Thrombocytopenia in Suspected Disseminated Intravascular Coagulation

Differential Diagnosis	Additional Diagnostic Clues
DIC	Prolonged aPTT and PT, increased FDP, low levels of AT or protein C
Sepsis without DIC	Positive (blood) cultures, positive sepsis criteria, hematophagocytosis in BM aspirate
Massive blood loss	Major bleeding, low hemoglobin, prolonged aPTT and PT
Thrombotic microangiopathy	Schistocytes in blood smear, Coombs-negative hemolysis, fever, neurologic symptoms, renal insufficiency, coagulation test results usually normal, ADAMTS13 levels decreased
Heparin-induced thrombocytopenia	Use of heparin, venous or arterial thrombosis, positive HIT test (usually immunoassay for heparin-platelet factor 4 antibodies), increase in platelet count after cessation of heparin; coagulation tests usually normal
Immune thrombocytopenia	Antiplatelet antibodies, normal or increased number of megakaryocytes in BM aspirate, TPO decreased; coagulation tests usually normal
Drug-induced thrombocytopenia	Decreased number of megakaryocytes in BM aspirate or detection of drug-induced antiplatelet antibodies, increase in platelet count after cessation of drug; coagulation test results usually normal

ADAMTS13, A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; *aPTT,* activated partial thromboplastin time; *AT,* antithrombin; *BM,* bone marrow; *DIC,* disseminated intravascular coagulation; *FDP,* fibrin degradation product; *HIT,* heparin-induced thrombocytopenia; *PT,* prothrombin time; *TPO,* thrombopoietin.
From Hoffman R: *Hematology, basic principles and practice,* ed 6, Philadelphia, 2013, WB Saunders.

COL/ADP: 70 to 120 sec
COL/EPI: 75 to 120 sec
Elevated in: Acquired platelet dysfunction, von Willebrand disease, anemia, thrombocytopenia, use of aspirin and NSAIDs

PLEURAL FLUID

Testing and evaluation of results

Pleural effusion fluid should be differentiated in exudate or transudate.
- The initial laboratory studies should be aimed only at distinguishing an exudate from a transudate.
- Tube 1: Protein, LDH, albumin.
- Tubes 2, 3, 4: Save the fluid until further notice. In selected patients with suspected empyema, a pH level may be useful (generally ≤7.0). See following for proper procedure to obtain a pH level from pleural fluid.

A serum/effusion albumin gradient of ≤1.2 g/dl is indicative of exudative effusions, especially in patients with congestive heart failure (CHF) treated with diuretics.

TABLE 80 Antibody-Mediated Thrombocytopenic Disorders Caused by Autoantibodies (Immune Thrombocytopenia), Alloantibodies (Neonatal Alloimmune Thrombocytopenia), or Potentially Both (Posttransfusion Purpura)

	Immune Thrombocytopenia	Neonatal Alloimmune Thrombocytopenia	Posttransfusion Purpura
Immune reaction	Autoimmune	Alloimmune	Features of both allo- and autoimmunity
Incidence	5 per 100,000 population	40 per 100,000 births (or 1 per 2500)	1 per 100,000 blood transfusions
Principal antigenic target	GPIIb/IIIa	HPA-1a	HPA-1a plus autoantigens
Nature of the antibody	Intermittent	Persistent (past 1 yr)	Persistent often at high titers
Mode of sensitization	Autoantibody	Alloantibody	Features of allo- and autoantibodies
Sensitizing event	Mostly unknown; some viral illnesses, chronic infection	Exposure to fetal platelet antigens early in first pregnancy	Blood transfusion (RBCs or platelets) 5-10 days earlier
Bleeding frequency	Uncommon	Common	Very common
Epidemiology	Higher incidence in children and elderly adults; female predominance in early adulthood	Majority affects fetus or newborn carrying the HPA-1a antigen	Almost all are HPA-1bb women sensitized by previous transfusion or pregnancy

GP, Glycoprotein; *HPA,* human platelet antigen; *RBC,* red blood cell.
From Hoffman R: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 81 Differential Diagnosis of Thrombocytopenia in Newborns

Perinatal Hypoxemia
Placental Insufficiency
Congenital Infection
- Sepsis
- Toxoplasmosis
- Rubella
- Cytomegalovirus

Autoimmune
- Maternal immune thrombocytopenia
- Maternal systemic lupus erythematosus

Disseminated Intravascular Coagulation
Maternal Drug Exposure
Congenital Heart Disease
Hereditary Thrombocytopenia
- MYH9 macrothrombocytopenia (including May-Hegglin anomaly)
- Thrombocytopenia absent radii syndrome
- Amegakaryocytic thrombocytopenia
- Wiskott-Aldrich syndrome
- Fanconi anemia

Hemangioma with Thrombocytopenia
- Kasabach-Merritt syndrome

Bone Marrow Infiltration
- Congenital leukemia

From Hoffman R: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 82 Differential Diagnosis of Thrombocytopenia in Pregnancy

Incidental thrombocytopenia of pregnancy (gestational thrombocytopenia)
Preeclampsia or eclampsia[a]
DIC secondary to:
- Abruptio placentae
- Endometritis
- Amniotic fluid embolism
- Retained fetus
- Preeclampsia or eclampsia[a]

Peripartum or postpartum thrombotic microangiopathy
- TTP
- HssUS

DIC, Disseminated intravascular coagulation; *HUS,* hemolytic uremic syndrome; *TTP,* thrombotic thrombocytopenic purpura.
[a]Preeclampsia or eclampsia usually is not associated with overt DIC.
From Hoffman R: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

Note the appearance of the fluid:
- A grossly hemorrhagic effusion can be a result of a traumatic tap, neoplasm, or an embolus with infarction.
- A milky appearance indicates either of the following:
  - Chylous effusion: Caused by trauma or tumor invasion of the thoracic duct; lipoprotein electrophoresis of the effusion reveals chylomicrons and triglyceride levels >115 mg/dl.
  - Pseudochylous effusion: Often seen with chronic inflammation of the pleural space (e.g., TB, connective tissue diseases).

If transudate, consider CHF, cirrhosis, chronic renal failure, and other hypoproteinemic states and perform subsequent workup accordingly.
If exudate, consider ordering these tests on the pleural fluid:
- Cytologic examination for malignant cells (for suspected neoplasm).
- Gram stain, cultures (aerobic and anaerobic), and sensitivities (for suspected infectious process).
- AFB stain and cultures (for suspected TB).
- pH: A value <7.0 suggests parapneumonic effusion or empyema; a pleural fluid pH must be drawn anaerobically and iced immediately; the syringe should be prerinsed with 0.2 ml of 1:1000 heparin.
- Glucose: A low glucose level suggests parapneumonic effusions and rheumatoid arthritis.
- Amylase: A high amylase level suggests pancreatitis or ruptured esophagus.
- Perplexing pleural effusions are often a result of malignancy (e.g., lymphoma, malignant mesothelioma, ovarian carcinoma), TB, subdiaphragmatic processes, prior asbestos exposure, and postcardiac injury syndrome.

Box 28 Describes a cellular differential of pleural effusions. Features differentiating exudative from transudative pleural effusion are summarized in Table 86.

POTASSIUM (serum)

Normal range: 3.5 to 5 mEq/L (3.5 to 5 mmol/L [CF: 1; SMI: 0.1 mmol/L])

CAUSES OF HYPERKALEMIA

See Fig. E45 for evaluation and treatment of hyperkalemia, and Fig. E46 for electrocardiographic changes in hyperkalemia.

Pseudohyperkalemia
- Hemolysis of sample
- Thrombocytosis
- Leukocytosis
- Laboratory error

Increased potassium intake and absorption
- Potassium supplements (oral and parenteral)
- Dietary: Salt substitutes

TABLE 83 Laboratory Tests Used to Investigate a Patient with Thrombocytopenia

Test	Rationale
Common Tests	
CBC	Isolated thrombocytopenia usually is caused by platelet destruction, but involvement of all cell lines suggests underproduction or sequestration
Examination of the blood film	Pseudothrombocytopenia (platelet clumps) Toxic changes and granulocyte "left shift" suggest septicemia Atypical lymphocytes suggest viral infection RBC fragments suggest TTP or HUS Parasites (e.g., in malaria) White cell inclusions suggest hereditary macrothrombocytopenia
Blood cultures	Bacteremia, fungemia
ANA test	Systemic lupus erythematosus
Direct antiglobulin test	Exclude immune hemolysis accompanying ITP (Evans syndrome)
Coagulation Assays	
aPTT, PT (INR), thrombin time, fibrinogen, D-dimer assay	DIC
LA assay (nonspecific inhibitor), anticardiolipin and anti-β_2-glycoprotein I assays	aPL antibody syndrome
Serum protein electrophoresis; IgG, IgM, IgA levels	ITP associated with lymphoproliferative disorder (monoclonal); hypersplenism associated with chronic hepatitis (polyclonal)
HIV serologic studies	HIV-associated thrombocytopenia
BM aspiration, biopsy	Assess megakaryocyte numbers and morphology; exclude primary BM disorder
Specialized Tests	
GP-specific platelet antibody assays (e.g., MAIPA)	Relatively specific assay for primary and secondary ITP
Drug-dependent increase in platelet-associated IgG	Specific assay for D-ITP
Drug-dependent platelet activation test (e.g., platelet serotonin release assay) or PF4-heparin (or PF4-polyanion) ELISA	HIT
Radionuclide platelet life span study with imaging (e.g., In platelet survival study)	Define the mechanism of thrombocytopenia; identify an "accessory" spleen postsplenectomy

ANA, Antinuclear antibody; *aPL,* antiphospholipid; *aPTT,* activated partial thromboplastin time; *BM,* bone marrow; *CBC,* complete blood count; *DIC,* disseminated intravascular coagulation; *D-ITP,* drug-induced immune thrombocytopenia; *ELISA,* enzyme-linked immunosorbent assay; *GP,* glycoprotein; *HIT,* heparin-induced thrombocytopenia; *HIV,* human immunodeficiency virus; *HUS,* hemolytic uremic syndrome; *Ig,* immunoglobulin; *INR,* international normalized ratio; *ITP,* idiopathic (immune) thrombocytopenic purpura; *LA,* lupus anticoagulant; *MAIPA,* monoclonal antibody immobilization of platelet antigens; *PF4,* platelet factor 4; *PT,* prothrombin time; *RBC,* red blood cell; *TTP,* thrombotic thrombocytopenic purpura.

From Hoffman R: *Hematology: basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 84 Mechanisms of Platelet Destruction

Type of Thrombocytopenia	Specific Example(s)
Immune Mediated	
Autoantibody-mediated platelet destruction by reticuloendothelial system (RES)	Primary immune thrombocytopenic purpura; secondary immune thrombocytopenia associated with lymphoproliferative disease; collagen vascular disease; infections such as infectious mononucleosis; human immunodeficiency virus syndrome
Alloantibody-mediated platelet destruction by RES	Neonatal alloimmune thrombocytopenia; posttransfusion purpura; passive alloimmune thrombocytopenia; alloimmune platelet transfusion refractoriness
Drug-dependent, antibody-mediated platelet destruction by RES	Drug-induced immune thrombocytopenic purpura (e.g., quinine)
Platelet activation by binding of immunoglobulin G (IgG) Fc of drug-dependent IgG to platelet FcγIIa receptors	Heparin-induced thrombocytopenia
Non-Immune Mediated	
Platelet activation by thrombin or proinflammatory cytokines	Disseminated intravascular coagulation; septicemia/systemic inflammatory response syndromes
Platelet destruction via ingestion by macrophages (hemophagocytosis)	Infections; certain malignant lymphoproliferative disorders
Platelet destruction through platelet interactions with altered von Willebrand factor	Thrombotic thrombocytopenic purpura; hemolytic-uremic syndrome; aortic stenosis
Platelet losses on artificial surfaces	Cardiopulmonary bypass surgery; use of intravascular catheters
Decreased platelet survival associated with cardiovascular disease	Congenital and acquired heart disease; cardiomyopathy; pulmonary embolism

McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

Modified with permission from Warkentin TE, Kelton JG: Thrombocytopenia due to platelet destruction and hypersplenism. In Hoffman R et al (eds): *Hematology: Basic principles and practice.* Philadelphia, 2005, Elsevier Churchill Livingstone, pp 2305-2325.

- Stored blood
- Potassium-containing medications

Impaired renal excretion
- Acute renal failure
- Chronic renal failure
- Tubular defect in potassium secretion
  - Renal allograft
  - Analgesic nephropathy
  - Sickle cell disease
  - Obstructive uropathy
- Hypoaldosteronism
  - Primary (Addison disease)
  - Secondary
    - Hyporeninemic hypoaldosteronism (type IV renal tubular acidosis [RTA])
    - Congenital adrenal hyperplasia
    - Drug-induced
    - NSAIDs
    - ACE inhibitors
    - Heparin
    - Cyclosporine
- Transcellular shifts
  - Acidosis
  - Hypertonicity
  - Insulin deficiency
  - Drugs
    - β-blockers
    - Digitalis toxicity
    - Succinylcholine
  - Exercise
  - Hyperkalemic periodic paralysis

Cellular injury
- Rhabdomyolysis
- Severe intravascular hemolysis
- Acute tumor lysis syndrome
- Burns and crush injuries

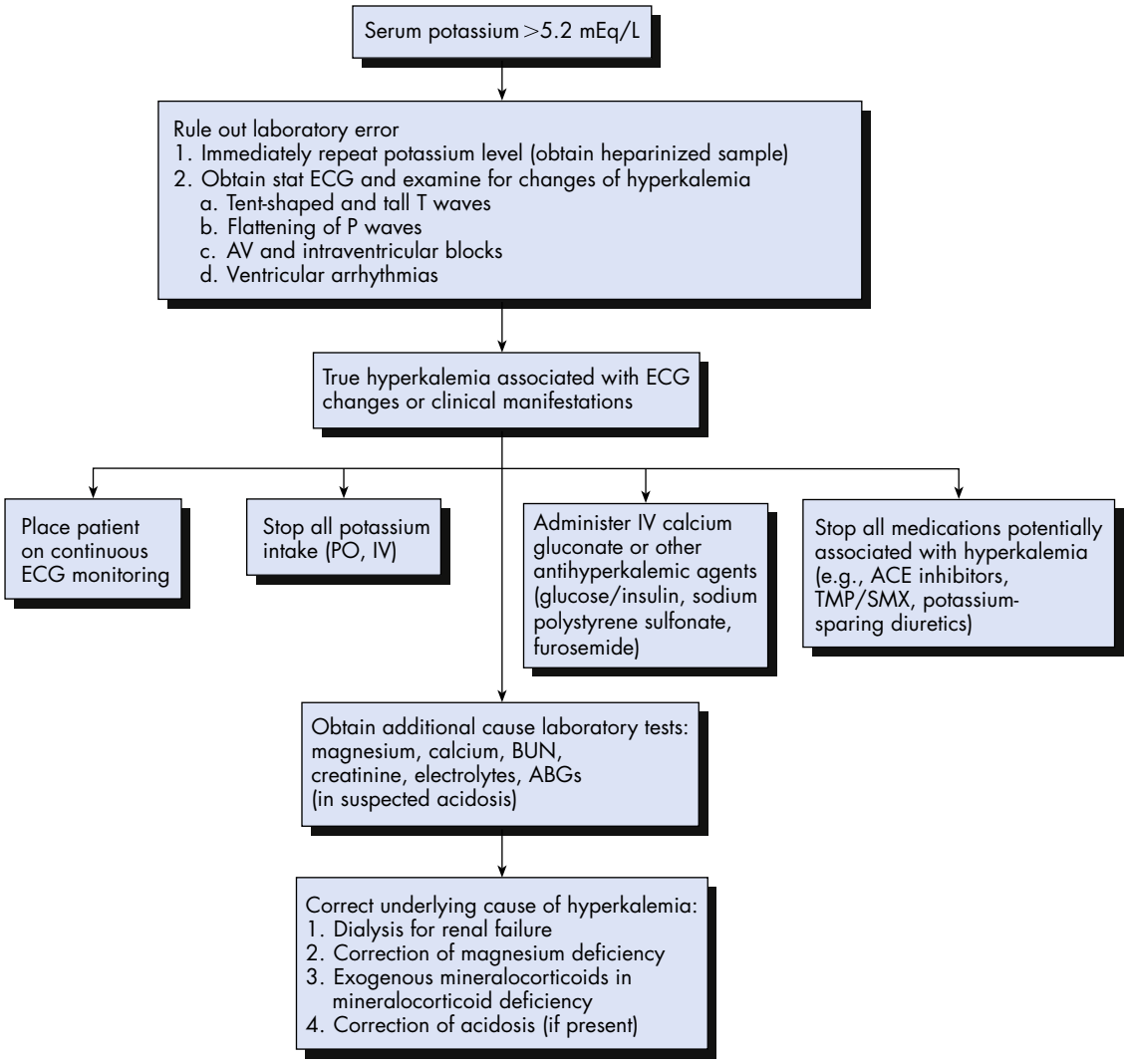


FIG. E45 Evaluation and treatment of hyperkalemia. *ABGs,* Arterial blood gases; *ACE,* angiotensin-converting enzyme; *AV,* atrioventricular; *BUN,* blood urea nitrogen; *ECG,* electrocardiogram; *IV,* intravenous; *PO,* oral; *TMP/SMX,* trimethoprim-sulfamethoxazole. (From Ferri F: *Practical guide to the care of the medical patient,* ed 9, St Louis, 2014, Mosby.)

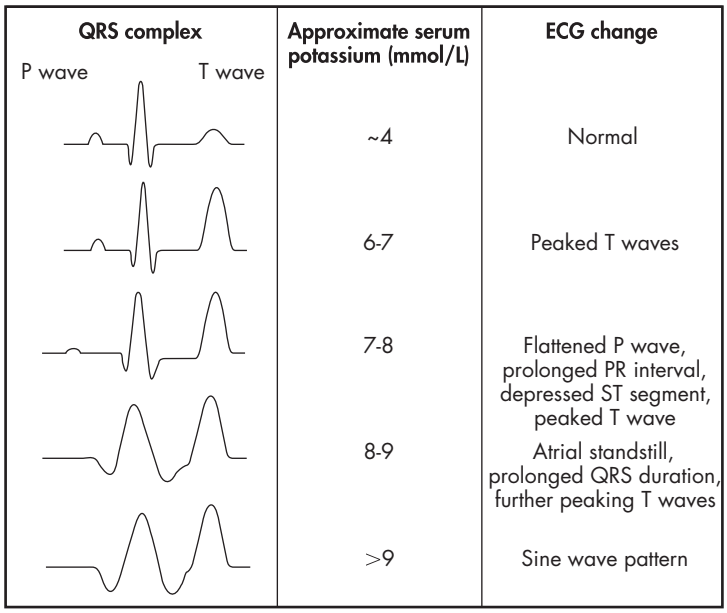


FIG. E46 Electrocardiographic changes in hyperkalemia. Progressive hyperkalemia results in identifiable changes in the electrocardiogram *(ECG).* These include peaking of the T wave, flattening of the P wave, prolongation of the PR interval, ST segment depression, prolongation of the QRS complex, and eventually, progression to a sine wave pattern. Ventricular fibrillation may occur at any time during this progression. (From Feehally J et al: *Comprehensive clinical nephrology,* ed 3, St Louis, 2007, Mosby.)

TABLE 85 Classification of Inherited Thrombocytopenias by Platelet Size

Small Platelets (MPV <7 fL)	Normal-Sized Platelets (MPV 7-11 fL)	Large Platelets (MPV >11 fL)
Wiskott-Aldrich syndrome	Congenital amegakaryocytic thrombocytopenia	*MYH9*-related disorders
X-linked thrombocytopenia	Thrombocytopenia absent radius syndrome	Bernard-Soulier syndrome
	Radioulnar synostosis with amegakaryocytic thrombocytopenia	Gray platelet syndrome
	RUNX1 mutations (FPD/AML)	Velocardiofacial syndrome
	ANKRD26-related thrombocytopenia	*GATA*-1 mutations
	CYCS-related thrombocytopenia	Type 2B von Willebrand disease
		Platelet-type von Willebrand disease
		Paris-Trousseau (Jacobsen) syndrome
		TUBB1-related macrothrombocytopenia
		Thrombocytopenia associated with sitosterolemia

MPV, Mean platelet volume.

In McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

Modified with permission from Kumar R, Kahr WHA: Congenital thrombocytopenia: Clinical manifestations, laboratory abnormalities, and molecular defects of a heterogeneous group of conditions. In Rao AK (ed): *Hematology/oncology clinics of North America: disorders of the platelets,* vol 27, Philadelphia, 2013, Elsevier, pp 465-494.

BOX 28 Cellular Differential of Pleural Effusions

Neutrophilia (>50%)
Bacterial pneumonia (parapneumonic effusion)
Pulmonary infarction
Pancreatitis
Subphrenic abscess
Early tuberculosis
Transudates (>10%)

Lymphocytosis (>50%)
Tuberculosis
Viral infection
Malignancy (lymphoma, other neoplasms)
True chylothorax
Rheumatoid pleuritis
Systemic lupus erythematosus
Uremic effusions
Transudates (≈30%)

Eosinophilia (>10%)
Pneumothorax (air in pleural space)
Trauma
Pulmonary infarction
Congestive heart failure
Infection (especially parasitic, fungal)
Hypersensitivity syndromes
Drug reaction
Rheumatologic diseases
Hodgkin disease
Idiopathic

From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

TABLE 86 Features Differentiating Exudative from Transudative Pleural Effusion

Feature	Transudate	Exudate
Appearance	Serous	Cloudy
Leukocyte count	<10,000/mm^3	>50,000/mm^3
pH	>7.2	<7.2
Protein	<3.0 g/dl	>3.0 g/dl
Ratio of pleural fluid protein to serum	<0.5	>0.5
Lactate dehydrogenase (LDH)	<200 IU/L	>200 IU/L
Ratio of pleural fluid LDH to serum	<0.6	>0.6
Glucose	≥60 mg/dl	<60 mg/dl

From Bennett JE et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 8, Philadelphia, 2015, WB Saunders.

CAUSES OF HYPOKALEMIA

For the clinical approach to hypokalemia, see Fig. 47.

- Decreased intake
  - Decreased dietary potassium
  - Impaired absorption of potassium
  - Clay ingestion
  - Kayexalate
- Increased loss
  - Renal
    - Hyperaldosteronism
      - Primary
        - Conn syndrome
        - Adrenal hyperplasia
      - Secondary
        - Congestive heart failure
        - Cirrhosis
        - Nephrotic syndrome
        - Dehydration
      - Bartter syndrome
    - Glycyrrhizic acid (licorice, chewing tobacco)
    - Excessive adrenal corticosteroids
      - Cushing syndrome
      - Steroid therapy
      - Adrenogenital syndrome
    - Renal tubular defects
      - Renal tubular acidosis
      - Obstructive uropathy
      - Salt-wasting nephropathy
  - Drugs
    - Diuretics
    - Aminoglycosides
    - Mannitol
    - Amphotericin
    - Cisplatin
    - Carbenicillin
  - Gastrointestinal
    - Vomiting
    - Nasogastric suction
    - Diarrhea
    - Malabsorption
    - Ileostomy
    - Villous adenoma
    - Laxative abuse
  - Increased losses from the skin
    - Excessive sweating
    - Burns
  - Transcellular shifts
    - Alkalosis
      - Vomiting

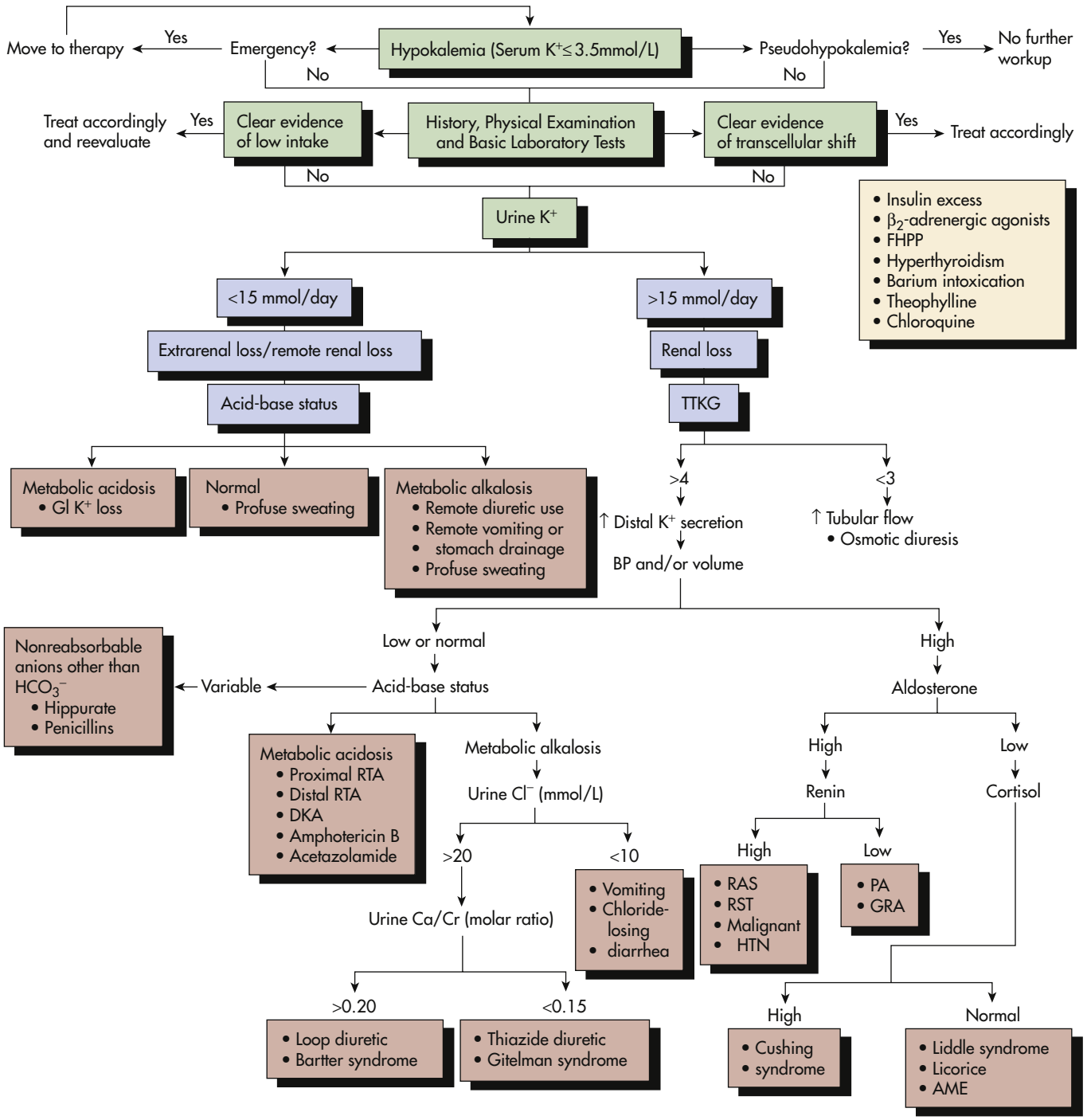


FIG. 47 Clinical approach to hypokalemia. See text for details. *AME,* Apparent mineralocorticoid excess; *BP,* blood pressure; *CCD,* cortical collecting duct; *DKA,* diabetic ketoacidosis; *FHPP,* familial hypokalemic periodic paralysis; *GI,* gastrointestinal; *GRA,* glucocorticoid-remediable aldosteronism; *HTN,* hypertension; *PA,* primary aldosteronism; *RAS,* renal artery stenosis; *RST,* renin-secreting tumor; *RTA,* renal tubular acidosis; *TTKG,* transtubular potassium gradient. (From Skorecki K et al: *Brenner & Rector's the kidney*, ed 10, Philadelphia, 2016, Elsevier.)

Diuretics
Hyperventilation
Bicarbonate therapy
Insulin
Exogenous
Endogenous response to glucose
β2-Agonists (albuterol, terbutaline, epinephrine)
Hypokalemia periodic paralysis
Familial
Thyrotoxic
Miscellaneous
Anabolic state
Intravenous hyperalimentation
Treatment of megaloblastic anemia
Acute mountain sickness

POTASSIUM, URINE

See URINE POTASSIUM

PROCAINAMIDE

Normal therapeutic range: 4 to 10 mcg/ml

PROGESTERONE (serum)

Normal:
Female: Follicular phase: 15 to 70 ng/dl
Luteal phase: 200 to 2500 ng/dl
Male: 15 to 70 ng/dl
Elevated in: Congenital adrenal hyperplasia, clomiphene, corticosterone, 11-deoxycortisol, dihydroprogesterone, molar pregnancy, lipoid ovarian tumor
Decreased in: Primary or secondary hypogonadism, oral contraceptives, ampicillin, threatened abortion

PROLACTIN

See Fig. E48 for the evaluation of hyperprolactinemia.
Normal range: <20 ng/ml (<20 μg/L [CF: 1; SMI: 1 μg/L])
Elevated in: Prolactinomas (level >200 micrograms/L highly suggestive), drugs (phenothiazines, cimetidine, tricyclic antidepressants, metoclopramide, estrogens, antihypertensives [methyldopa], verapamil, haloperidol), postpartum, stress, hypoglycemia, hypothyroidism, chronic liver disease, end-stage renal disease, brain radiation therapy, polycystic ovary syndrome, seizures, exercise, coitus, lactation. Mild hyperprolactinemia (<100 micrograms/L) can also be caused by large sellar masses, including nonfunctioning pituitary adenoma.

PROSTATE-SPECIFIC ANTIGEN (PSA)

Normal range: 0 to 4 ng/ml
Table 87 describes age-specific reference ranges for PSA.
Elevated in: Benign prostatic hypertrophy, carcinoma of prostate, prostatitis, postrectal examination, prostate trauma.
Factors affecting serum PSA are described in Table 88.
NOTE: Measurement of free PSA is useful to assess the probability of prostate cancer in patients with normal digital rectal examination and total PSA between 4 and 10 ng/ml. In these patients, the global risk of prostate cancer is 25%; however, if the free PSA is >25%, the risk of prostate cancer decreases to 8%, whereas if the free PSA is <10%, the risk of cancer increases to 56%. Free PSA is also useful to evaluate the aggressiveness of prostate cancer. A low free PSA percentage generally indicates a high-grade cancer, whereas a high free PSA percentage is generally associated with a slower-growing tumor.
Decreased in: 5-α reductase inhibitors (finasteride, dutasteride), saw palmetto use, antiandrogens

PROSTATIC ACID PHOSPHATASE

Normal: 0 to 0.8 U/L
Elevated in: Prostate cancer (especially in metastatic prostate cancer), BPH, prostatitis, post-prostate surgery or manipulation, hemolysis, androgens, clofibrate
Decreased in: Ketoconazole

PROTEIN (serum)

Normal range: 6 to 8 g/dl (60 to 80 g/L [CF: 10; SMI: 1 g/L])
Elevated in: Dehydration, multiple myeloma, Waldenström macroglobulinemia, sarcoidosis, collagen vascular diseases
Decreased in: Malnutrition, low-protein diet, overhydration, malabsorption, pregnancy, severe burns, neoplasms, chronic diseases, cirrhosis, nephrosis

PROTEIN C ASSAY

See Table 89 and Fig. 49.

TABLE 87 Age-Specific Reference Ranges for PSA

	Serum PSA (ng/ml)		
Age (yr)	Whites	Japanese	African Americans
40-49	0-2.5	0-2.0	0-2.0
50-59	0-3.5	0-3.0	0-4.0
60-69	0-4.5	0-4.0	0-4.5
70-79	0-6.5	0-5.0	0-5.5

PSA, Prostate-specific antigen.
From Nseyo UO (ed): *Urology for primary care physicians,* Philadelphia, 1999, WB Saunders.

TABLE 88 Factors Affecting Serum PSA

Factors Affecting Serum PSA	Duration of Effect
Prostate cell number	NA
Prostate size	NA
Recent ejaculation	6-48 hours
Prostate manipulation	
Vigorous massage	1 wk
Cystoscopy	1 wk
Prostate biopsy	4-6 wk
Prostatitis	
Acute	3-6 mo
Chronic	Unknown
Prostate cancer	NA
Drugs: finasteride*	3-6 mo

NA, Not applicable; *PSA,* prostate-specific antigen.
*Lowers PSA for as long as patient is on the medication.
From Nseyo UO (ed): *Urology for primary care physicians,* Philadelphia, 1999, Saunders.

TABLE 89 Assay Measurement in Heterozygote Protein C Deficiency

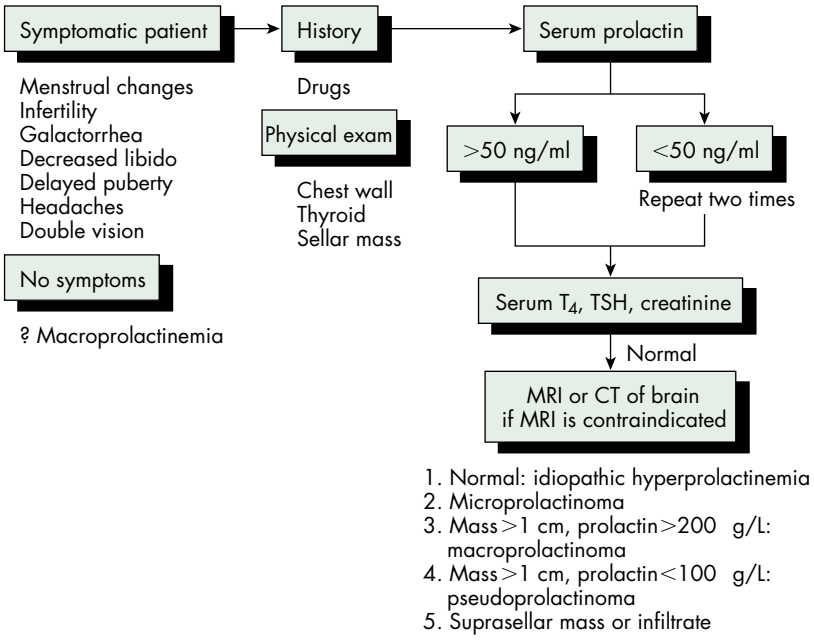
	ACTIVITY		
Type	Antigen	Amidolytic	Coagulant
I	Low	Low	Low
II	Normal	Low	Low
	Normal	Normal	Low

From Hoffman R et al: *Hematology: Basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

Normal: 70% to 140%
Elevated in: Oral contraceptives, stanozolol
Decreased in: Congenital protein C deficiency, warfarin therapy, Vitamin K deficiency, renal insufficiency, consumptive coagulopathies

PROTEIN ELECTROPHORESIS (serum)

Normal range:
Albumin: 60% to 75% (0.6 to 0.75 [CF: 0.01; SMI: 0.01])
α-1: 1.7% to 5% (0.02 to 0.05)
α-2: 6.7% to 12.5% (0.07 to 0.13)
β: 8.3% to 16.3% (0.08 to 0.16)
γ: 10.7% to 20% (0.11 to 0.2)
Albumin: 3.6 to 5.2 g/dl (36 to 52 g/L [CF: 0.01; SMI: 1 g/L])
α-1: 0.1 to 0.4 g/dl (1 to 4 g/L)
α-2: 0.4 to 1 g/dl (4 to 10 g/L)



NOTE: Refer to Section I for additional information on Prolactinoma.

FIG. E48 Approach to hyperprolactinemia. *CT,* Computed tomography; *MRI,* magnetic resonance imaging; *T4,* thyroxine; *TSH,* thyroid-stimulating hormone. (From Copeland LJ: *Textbook of gynecology,* ed 2, Philadelphia, 2000, WB Saunders.)

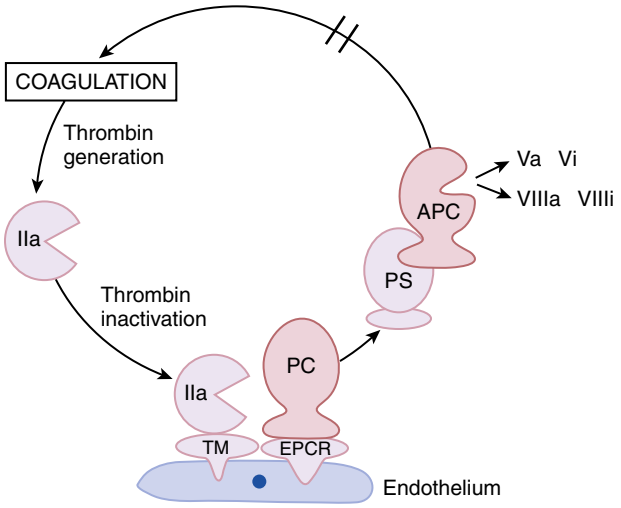


FIG. 49 Protein C pathway. Activation of coagulation triggers thrombin *(IIa)* generation. Excess thrombin binds to thrombomodulin *(TM)* on the endothelial cell surface. Once bound, the substrate specificity of thrombin is altered such that it no longer acts as a procoagulant but becomes a potent activator of protein C *(PC)*. The endothelial cell protein C receptor *(EPCR)* binds protein C and presents it to thrombomodulin-bound thrombin for activation. Activated protein C *(APC)*, together with its cofactor protein S *(PS)*, binds to the activated platelet surface and proteolytically degrades factors Va and VIIIa into inactive fragments *(Vi and VIIIi)*. Degradation of these activated cofactors inhibits thrombin generation *(double bar)*. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

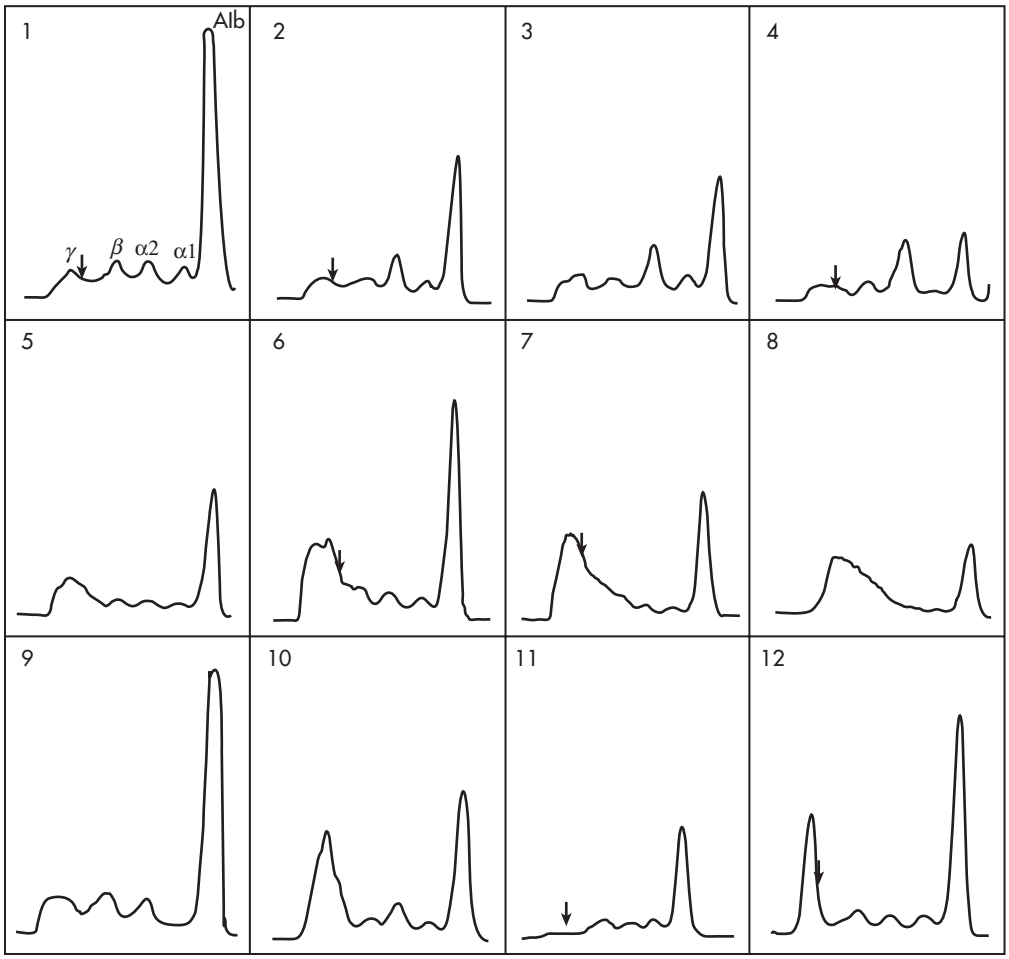


FIG. 50 Typical serum protein electrophoretic patterns. ***1,*** Normal (*arrow* near γ region indicates serum application point). ***2,*** Acute reaction pattern. ***3,*** Acute reaction or nephrotic syndrome. ***4,*** Nephrotic syndrome. ***5,*** Chronic inflammation, cirrhosis, granulomatous diseases, rheumatoid-collagen group. ***6,*** Same as 5, but γ elevation is more pronounced. There is also partial (but not complete) β-γ fusion. ***7,*** Suggestive of cirrhosis but could be found in the granulomatous diseases or the rheumatoid-collagen group. ***8,*** Characteristic pattern of cirrhosis. ***9,*** α-1 Antitrypsin deficiency with mild γ elevation suggesting concurrent chronic disease. ***10,*** Same as 5, but the γ elevation is marked. The configuration of the γ peak superficially mimics that of myeloma, but is more broad-based. There are superimposed acute reaction changes. ***11,*** Hypogammaglobulinemia or light-chain myeloma. ***12,*** Myeloma, Waldenström macroglobulinemia, idiopathic or secondary monoclonal gammopathy. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

β: 0.5 to 1.2 g/dl (5 to 12 g/L)
γ: 0.6 to 1.6 g/dl (6 to 16 g/L)

Elevated in:
Albumin: Dehydration
α-1: Neoplastic diseases, inflammation
α-2: Neoplasms, inflammation, infection, nephrotic syndrome
β: Hypothyroidism, biliary cirrhosis, diabetes mellitus
γ: See IMMUNOGLOBULINS

Decreased in:
Albumin: Malnutrition, chronic liver disease, malabsorption, nephrotic syndrome, burns, systemic lupus erythematosus
α-1: Emphysema (α-1 antitrypsin deficiency), nephrosis
α-2: Hemolytic anemias (decreased haptoglobin), severe hepatocellular damage
β: Hypocholesterolemia, nephrosis
γ: See IMMUNOGLOBULINS

Fig. 50 describes serum protein electrophoretic patterns.

TABLE 90 Assay Measurements in Heterozygote Protein S Deficiency

	ACTIVITY		
Type	**Protein S Total Antigen**	**Protein S Free Antigen**	**Protein S Activity**
I (Classic)	Low	Low	Low
II	Normal	Normal	Low
III	Normal	Low	Low

From Hoffman R et al: *Hematology: Basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

TABLE 91 Causes of Increased Prothrombin Time/International Normalized Ratio (PT/INR) and/or Activated Partial Prothrombin Time (APTT)

Increased PT/INR—Defect in Extrinsic Pathway
- Deficiency or inhibitor of factor VII
- Early warfarin (Coumadin) therapy
- Early liver disease

Increased APTT—Defect in Intrinsic Pathway
- Deficiency or inhibitor of factors XII, XI, IX, or VIII
- Heparin (though usually affects PT as well)
- Liver disease (though usually affects PT as well)
- Lupus anticoagulant (may affect PT as well)

Increased PT/INR and APTT—Defect in Common Pathway or Combined Defect in Extrinsic and Intrinsic Pathways
- Heparin (all serine proteases affected, especially II and X)
- Disseminated intravascular coagulation (all factors, including pro- and anticoagulants, affected)
- Liver disease (all factors except VIII affected)
- Warfarin (factors II, VII, IX, and X affected)
- Vitamin K deficiency (factors II, VII, IX, and X affected)
- Direct thrombin inhibitors
- Lupus anticoagulant

Modified from: Rizoli S, Aird WC: Coagulopathy. In Vincent JL et al (eds): *Textbook of critical care,* ed 6, Philadelphia, 2011, Elsevier.

PROTEIN S ASSAY

See Table 90.
Normal: 65% to 140%
Elevated in: Presence of lupus anticoagulant
Decreased in: Hereditary deficiency, acute thrombotic events, DIC, surgery, oral contraceptives, pregnancy, hormone replacement therapy, l-asparaginase treatment

PROTHROMBIN TIME (PT)

See Table 91.
Normal range: 10 to 12 sec
Elevated in: Liver disease, oral anticoagulants (warfarin), heparin, factor deficiency (I, II, V, VII, X), disseminated intravascular coagulation, vitamin K deficiency, afibrinogenemia, dysfibrinogenemia, drugs (salicylate, chloral hydrate, diphenylhydantoin, estrogens, antacids, phenylbutazone, quinidine, antibiotics, allopurinol, anabolic steroids). Table 92 describes a differential diagnosis of abnormal coagulation screening tests.
Decreased in: Vitamin K supplementation, thrombophlebitis, drugs (glutethimide, estrogens, griseofulvin, diphenhydramine)

PROTOPORPHYRIN (Free erythrocyte)

Normal range: 16 to 36 μg/dl of red blood cells (0.28 to 0.64 μmol/L [CF: 0.0177; SMI: 0.02 μmol/L])
Elevated in: Iron deficiency, lead poisoning, sideroblastic anemias, anemia of chronic disease, hemolytic anemias, erythropoietic protoporphyria

TABLE 92 Differential Diagnosis of Abnormal Coagulation Screening Tests

Abnormal Activated Partial Thromboplastin Time (APTT) Alone
- Associated with bleeding: VIII, IX, and XI defects
- Not associated with bleeding: XII, prekallikrein (PK), high molecular weight kininogen, lupus anticoagulants

Abnormal Prothrombin Time (PT) Alone
- Factor VII defects

Combined Abnormal APTT and PT
- Medical conditions: Anticoagulants, disseminated intravascular coagulation (DIC), liver disease, vitamin K deficiency, massive transfusion
- Rarely dysfibrinogenemia; factor X, V, and II defects

From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

PSA

See PROSTATE-SPECIFIC ANTIGEN

PT

See PROTHROMBIN TIME

PTH

See PARATHYROID HORMONE

PTT

See PARTIAL THROMBOPLASTIN TIME

RAPID PLASMA REAGIN (RPR)

Description: Non-treponemal test traditionally used as a screening test for syphilis. It is a quantitative test and antibody titers can be monitored to assess treatment response.
Normal: Negative
Positive: Syphilis. False-positive results may occur with pregnancy, autoimmune diseases, tuberculosis, and other inflammatory conditions. Positive results should be confirmed with treponemal serologic tests (e.g., T-pallidum enzyme immunoassay [TP-EIA])

RDW

See RED BLOOD CELL DISTRIBUTION WIDTH

RED BLOOD CELL (RBC) COUNT

Normal range:
Male: 4.3 to 5.9 $\times 10^6$/mm^3 (4.3 to 5.9 $\times 10^{12}$/L [CF: 1; SMI: 0.1 $\times 10^{12}$/L])
Female: 3.5 to 5 $\times 10^6$/mm^3 (3.5 to 5 $\times 10^{12}$/L [CF: 1; SMI: 0.1 $\times 10^{12}$/L])
Elevated in: Polycythemia vera, smokers, high altitude, cardiovascular disease, renal cell carcinoma and other erythropoietin-producing neoplasms, stress, hemoconcentration/dehydration
Decreased in: Anemias, hemolysis, chronic renal failure, hemorrhage, failure of marrow production

RED BLOOD CELL DISTRIBUTION WIDTH (RDW)

Measures variability of red cell size (anisocytosis)
Normal range: 11.5 to 14.5
Normal RDW and elevated mean corpuscular volume (MCV): Aplastic anemia, preleukemia
Normal MCV: Normal, anemia of chronic disease, acute blood loss or hemolysis, chronic lymphocytic leukemia (CLL), chronic myelocytic leukemia, nonanemic enzymopathy or hemoglobinopathy
Decreased MCV: Anemia of chronic disease, heterozygous thalassemia
Elevated RDW and elevated MCV: Vitamin B_{12} deficiency, folate deficiency, immune hemolytic anemia, cold agglutinins, CLL with high count, liver disease

Normal MCV: Early iron deficiency, early vitamin B_{12} deficiency, early folate deficiency, anemic globinopathy
Decreased MCV: Iron deficiency, red blood cell fragmentation, HbH disease, thalassemia intermedia

See Table 93 for combining the reticulocyte count and RBC parameters for diagnosis.

TABLE 93 Combining the Reticulocyte Count and Red Blood Cell Parameters for Diagnosis

MCV, RDW	Reticulocyte Count <100,000/µL	Reticulocyte Count ≥100,000/µL
Low, normal	Anemia of chronic disease	
Normal, normal	Anemia of chronic disease	
High, normal	Chemotherapy, antivirals, or alcohol Aplastic anemia	Chronic liver disease
Low, high	Iron-deficiency anemia	Sickle cell–β-thalassemia
Normal, high	Early iron, folate, vitamin B_{12} deficiency Myelodysplasia	Sickle cell anemia, sickle cell disease
High, high	Folate or vitamin B_{12} deficiency Myelodysplasia	Immune hemolytic anemia Chronic liver disease

MCV, Mean corpuscular volume; *RDW,* red blood cell distribution width.
From Hoffman R: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

RED BLOOD CELL FOLATE

See FOLATE

RED BLOOD CELL MASS (volume)

Normal range:
Male: 20 to 36 ml/kg body weight (1.15-1.21 L/m^2 body surface area)
Female: 19 to 31 ml/kg body weight (0.95-1.00 L/m^2 body surface area)
Elevated in: Polycythemia vera, hypoxia (smokers, high altitude, cardiovascular disease), hemoglobinopathies with high oxygen affinity, erythropoietin-producing tumors (renal cell carcinoma)
Decreased in: Hemorrhage, chronic disease, failure of marrow production, anemias, hemolysis

RED BLOOD CELL MORPHOLOGY

Table 94 describes features of the peripheral blood smear. Table 95 summarizes peripheral blood film evaluation in a patient with red cell membrane disorder. See Fig. 51 for useful peripheral blood and RBC features in the evaluation of anemia.

RENIN (serum)

Elevated in: Drugs (thiazides, estrogen, minoxidil), chronic renal failure, Bartter syndrome, pregnancy (normal), pheochromocytoma, renal hypertension, reduced plasma volume, secondary aldosteronism
Decreased in: Adrenocortical hypertension, increased plasma volume, primary aldosteronism, drugs (propranolol, reserpine, clonidine)

Table 96 describes typical renin-aldosterone patterns in various conditions.

TABLE 94 Features of the Peripheral Blood Smear

Red Blood Cell Morphology	Definition	Interpretation
Polychromasia	Large, bluish RBCs lacking normal central pallor on peripheral blood smear; bluish stain is the result of residual ribonucleic acid	Rapid production and release of RBCs from BM; elevated reticulocyte count; most commonly seen in any hemolytic anemia and states of increased RBC turnover
Basophilic stippling	Many small bluish dots in portion of erythrocytes; comes from staining of clustered polyribosomes in young circulating RBCs	Seen in a variety of erythropoietic disorders, including acquired (e.g., myelodysplasia) and congenital hemolytic anemias and occasionally in lead poisoning
Pappenheimer bodies	Several grayish, irregularly shaped inclusions in a portion of erythrocytes visible on peripheral smear; composed of aggregates of ribosomes, ferritin, and mitochondria	Erythropoietic malfunction in congenital anemias such as hemoglobinopathies, particularly with splenic hypofunction or acquired anemias such as megaloblastic anemia
Heinz bodies	Several grayish, round inclusions visible after supravital staining with methyl crystal violet of the peripheral blood smear, often in the context of bite cells; represent aggregates of denatured hemoglobin	Indicative of oxidative injury to the erythrocyte, such as occurs in G6PD deficiency and other RBC enzymopathies or unstable hemoglobins
Howell-Jolly bodies	Usually one or at most a few purplish inclusions in the erythrocyte visible on the routine peripheral blood smear; represent residual fragments of nuclei containing chromatin	Associated with states of splenic hypofunction, splenic atrophy, splenic thrombosis, or after splenectomy
Schistocytes	RBCs that are fragmented into a variety of shapes and sizes, including helmet-shaped cells; indicative of shearing of the erythrocyte within the circulation	Associated with microangiopathic hemolytic anemias, including DIC, TTP, HUS, or aHUS, as well as other mechanical causes of hemolysis, such as prosthetic heart valves or severe cardiac valvular stenosis
Spherocytes	RBCs that have lost their central pallor and appear spherical; indicative of loss of cytoskeletal integrity from internal or external causes	Associated with hereditary spherocytosis, autoimmune hemolytic anemia; may also be observed in addition to schistocytes in the presence of microangiopathic hemolytic anemia
Teardrop cells	Pear-shaped erythrocytes visible on peripheral blood smear; indicative of mechanical stress on the RBC during release from the BM or passage through the spleen	Seen in a variety of conditions along with other poikilocytes, including severe iron deficiency anemia, congenital anemias such as thalassemias, hemoglobinopathies, and acquired disorders such as megaloblastic anemia. As isolated poikilocyte, teardrop RBCs may be initial changes of myelophthisis (BM replacement or infiltration), e.g., myelodysplastic syndrome or myelofibrosis.
Burr cells (echinocytes)	RBCs that have smooth undulations present on the surface circumferentially; pathogenesis unknown	Indicative of uremia when present on a properly made peripheral blood smear
Spur cells (acanthocytes)	RBCs that have spiny points present on the surface circumferentially; reflective of abnormal lipid composition of RBC membrane	Most commonly indicative of hemolytic anemia of advanced liver disease when present in significant numbers; also seen in abetalipoproteinemia and in RBCs lacking the Kell blood group antigen

aHUS, Atypical hemolytic uremic syndrome; *BM,* bone marrow; *DIC,* disseminated intravascular coagulation; *G6PD,* glucose-6-phosphate dehydrogenase; *HUS,* hemolytic uremic syndrome; *RBC,* red blood cell; *TTP,* thrombotic thrombocytopenic purpura.
From Hoffman R: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 95 Peripheral Blood Film Evaluation in a Patient with Red Cell Membrane Disorder

Shape	Pathobiology	Diagnosis
Microspherocytes	Loss of membrane lipids leading to a reduction of surface area resulting from deficiencies of spectrin, ankyrin, or band 3 and protein 4.2; removal of membrane material from antibody-coated red cells by macrophages; removal of membrane-associated Heinz bodies, with the adjacent membrane lipids, by the spleen	HS Immunohemolytic anemias; Heinz body hemolytic anemias
Elliptocytes	Permanent red cell deformation resulting from a weakening of skeletal protein interactions (such as the spectrin dimer-dimer contact). This facilitates disruption of existing protein contacts during shear stress-induced elliptical deformation. Subsequently, new protein contacts are formed that stabilize elliptical shape; unknown	Mild common HE; iron deficiency, megaloblastic anemias, myelofibrosis, myelophthisic anemias, myelodysplastic syndrome, thalassemias
Poikilocytes/Fragments	Weakening of skeletal protein contacts resulting from skeletal protein mutations; unknown	Hemolytic HE/HPP; iron deficiency, megaloblastic anemias, myelofibrosis, myelophthisic anemias, myelodysplastic syndrome, thalassemias
Schistocytes, fragmented red cells	Red cells "torn" by mechanical trauma (fibrin strands, turbulent flow)	"Microangiopathic" hemolytic anemia associated with disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, vasculitis, heart valve prostheses
Acanthocytes	Uptake of cholesterol and its preferential accumulation in the outer leaflet of the lipid bilayer; selective accumulation of sphingomyelin in the outer lipid leaflet; unknown	Spur cell hemolytic anemia in severe liver disease; abetalipoproteinemia; chorea-acanthocytosis syndrome, malnutrition, hypothyroidism; McLeod phenotype
Echinocytes	Expansion of the surface area of the outer hemileaflet of lipid bilayer relative to the inner hemileaflet; unknown	Hemolytic anemia associated with hypomagnesemia and hypophosphatemia in malnourished patients, pyruvate kinase deficiency; in vitro artifact of low blood storage (ATP depletion), contact with glass or elevated pH Hemolysis in long-distance runners, renal failure
Stomatocytes	Expansion of the surface area of the inner hemileaflet of the bilayer relative to the outer leaflet; unknown	Exposure of red cells to cationic anesthetics in vitro; in vivo the drug concentrations may not be sufficient to produce similar effect; alcoholism, inherited disorders of membrane permeability (hereditary stomatocytosis)
Target cells	Absolute excess of membrane lipids (both cholesterol and phospholipids: "symmetric" lipid gain), followed by an increase of cell surface area; relative excess of surface area because of a decrease in cell volume	Obstructive jaundice, liver disease with intrahepatic cholestasis; thalassemias and some hemoglobinopathies (C, D, E)

ATP, Adenosine triphosphate; *HE,* hereditary elliptocytosis; *HPP,* hereditary pyropoikilocytosis; *HS,* hereditary spherocytosis.
From Hoffman R et al: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, WB Saunders.

RESPIRATORY SYNCYTIAL VIRUS (RSV) SCREEN

Test description: PCR test can be performed on nasopharyngeal swab, wash, or aspirate

RETICULOCYTE COUNT

See Fig. E52, Fig. 53, and Table 97.
Normal range: 0.5% to 1.5%
Elevated in: Hemolytic anemia (sickle cell crisis, thalassemia major, autoimmune hemolysis), hemorrhage, postanemia therapy (folic acid, ferrous sulfate, vitamin B_{12}), chronic renal failure
Decreased in: Aplastic anemia, marrow suppression (sepsis, chemotherapeutic agents, radiation), hepatic cirrhosis, blood transfusion, anemias of disordered maturation (iron deficiency anemia, megaloblastic anemia, sideroblastic anemia, anemia of chronic disease)

RHEUMATOID FACTOR

Normal: Negative. Present in titer >1:20
RHEUMATIC DISEASES
Rheumatoid arthritis
Sjögren syndrome
Systemic lupus erythematosus
Polymyositis/dermatomyositis
Mixed connective tissue disease
Scleroderma
INFECTIOUS DISEASES
Subacute bacterial endocarditis
Tuberculosis
Infectious mononucleosis
Hepatitis
Syphilis
Leprosy
Influenza
MALIGNANCIES
Lymphoma
Multiple myeloma
Waldenström macroglobulinemia
Postradiation or postchemotherapy
MISCELLANEOUS
Normal adults, especially the elderly
Sarcoidosis
Chronic pulmonary disease (interstitial fibrosis)
Chronic liver disease (chronic active hepatitis, cirrhosis)
Mixed essential cryoglobulinemia
Hypergammaglobulinemic purpura

RNP

See EXTRACTABLE NUCLEAR ANTIGEN

RPR

See RAPID PLASMA REAGIN

ROTAVIRUS SEROLOGY

Test description: PCR test is performed on stool specimen
Normal: Negative

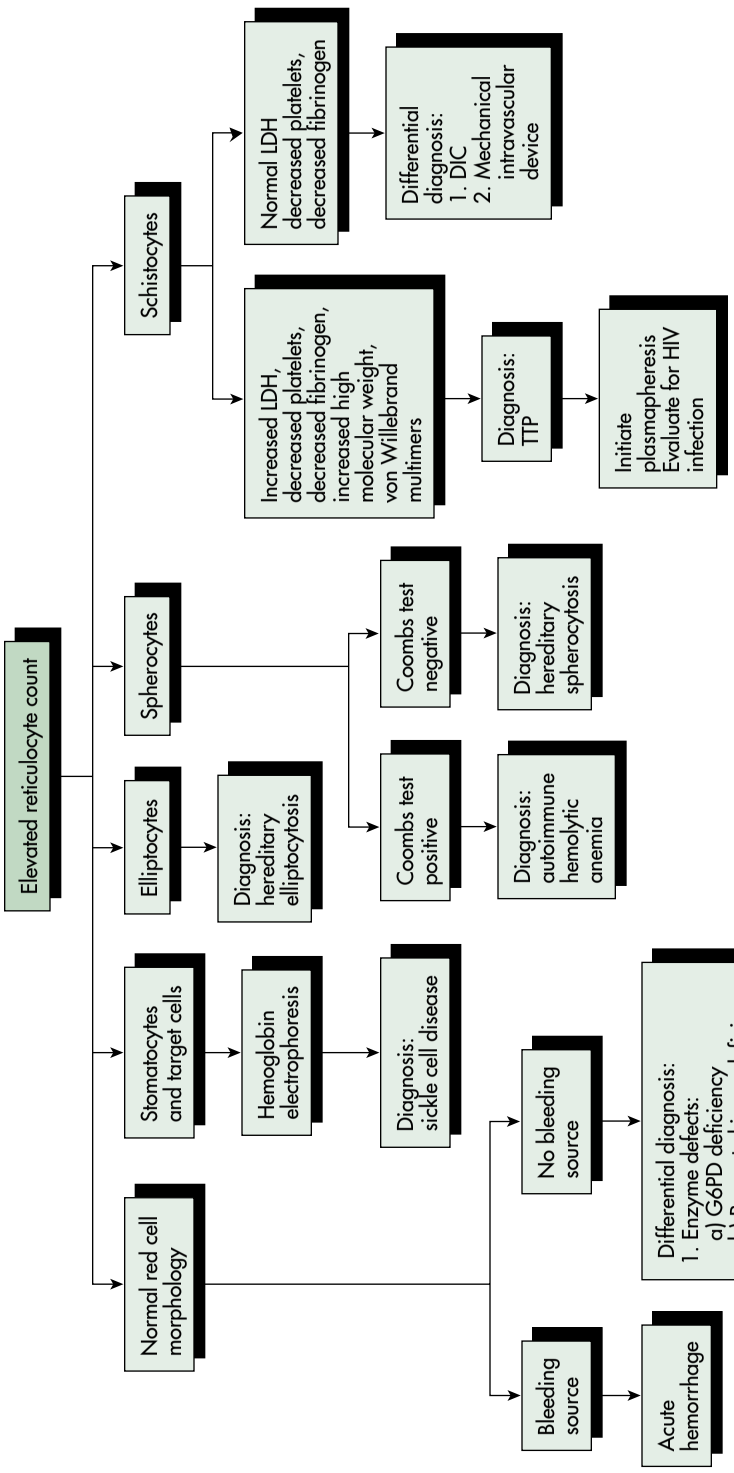


FIG. E52 Differential diagnosis of elevated reticulocyte count. *DIC*, Disseminated intravascular coagulation; *G6PD*, glucose-6-phosphate dehydrogenase; *HIV*, human immunodeficiency virus; *LDH*, lactic dehydrogenase; *TTP*, thrombotic thrombocytopenic purpura. (From Rakel RE [ed]: *Principles of family practice*, ed 7, Philadelphia, 2007, WB Saunders.)

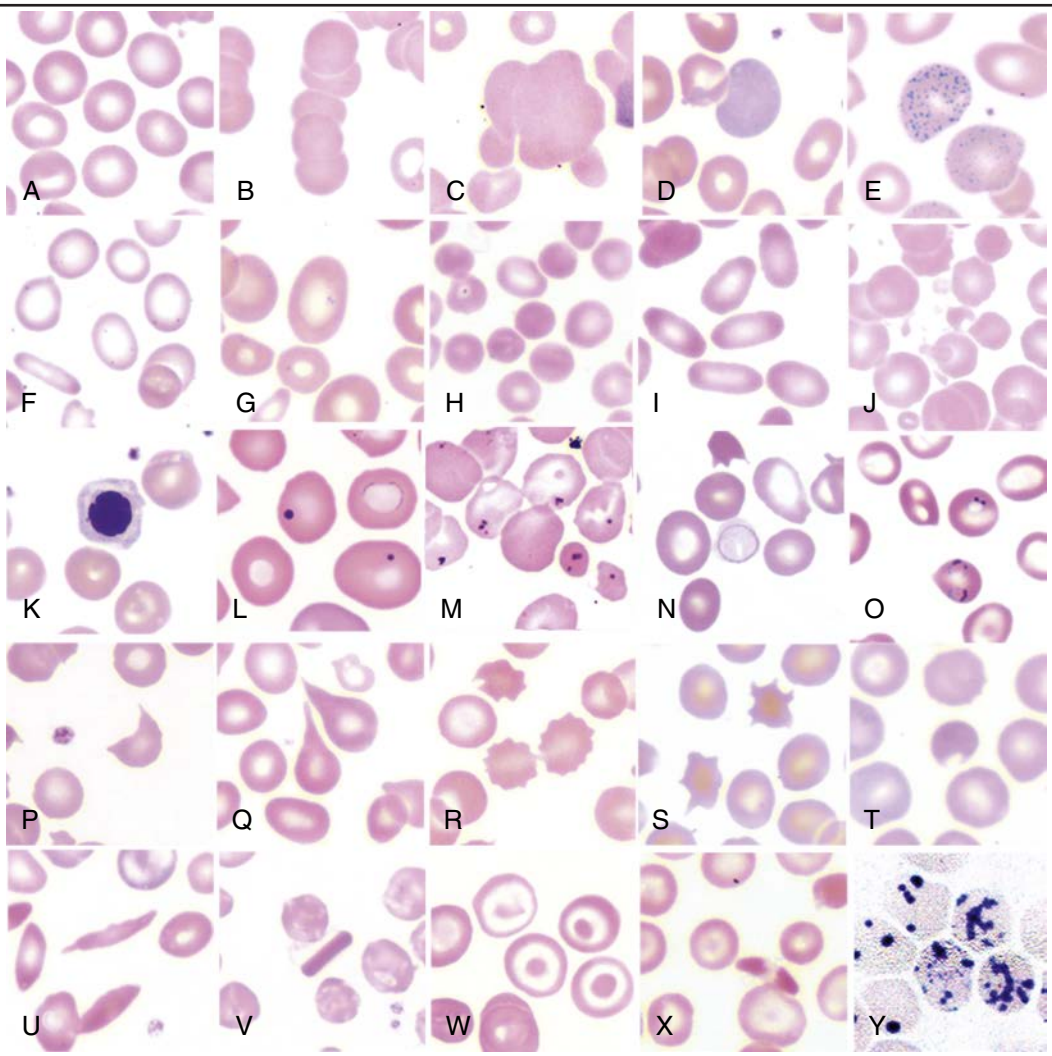


FIG. 51 Useful peripheral blood and red blood cell features in the evaluation of anemia. A, Normal red blood cells *(RBCs).* Note that the central pallor is one-third the diameter of the entire cell. **B,** Rouleaux formation is indicative of increased plasma protein. **C,** Agglutination indicates an antibody-mediated process such as cold agglutinin disease. **D,** Polychromatophilic cell. The gray-blue color is attributable to RNA and the cell is equivalent to a reticulocyte, which must be identified with a reticulocyte stain. **E,** Basophilic stippling. This also is attributable to increased RNA caused either by a left shift in erythroid cells or lead toxicity. **F,** Hypochromic microcytic cells typical of iron-deficiency anemia. Note the widened central pallor and the "pencil" cell in the *lower left*. **G,** Macroovalocyte as can be seen in either megaloblastic anemia or myelodysplastic syndrome. **H,** Microspherocytes typical of hereditary spherocytosis. **I,** Elliptocytes (ovalocytes) from a patient with hereditary elliptocytosis. **J,** RBC fragments from thermal injury (burn patient). **K,** Nucleated RBC. **L,** Howell-Jolly bodies indicative of splenic dysfunction or absence. **M,** Pappenheimer bodies from a patient with sideroblastic anemia. **N,** Cabot ring, as can be seen in megaloblastic anemia or MDS. **O,** Malarial parasites *(Plasmodium falciparum)*. **P,** Schistocyte typical of a microangiopathic hemolytic anemia. **Q,** Tear-drop form indicates marrow fibrosis and extramedullary hematopoiesis. **R,** Echinocyte (Burr cell) with rounded edges. **S,** Acanthocyte (spur cell) with more irregular pointed ends. This was from a patient with neuroacanthocytosis. They can also be seen in patients with liver disease and lipid abnormalities. **T,** "Bite" cell from a patient with glucose-6-phosphate dehydrogenase *(G6PD)* deficiency. **U,** Sickle cell, from a patient with homozygous sickle cell disease. **V,** Hemoglobin C crystal. **W,** Target cells. **X,** Hemoglobin C disease. Note that the RBC in center has condensed hemoglobin at each pole. **Y,** Heinz body preparation (supravital stain) from a patient with G6PD deficiency. Note that the cells to the right have increased precipitated hemoglobin. (From Hoffman R: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.)

TABLE 96 Typical Renin-Aldosterone Patterns in Various Conditions

	Plasma Renin	Aldosterone
Primary aldosteronism	Low	High
"Low-renin" essential hypertension	Low	Normal
Cushing syndrome	Low	Low-normal
Licorice ingestion syndrome	Low	Low
High-salt diet	Low	Low
Oral contraceptives	High	Normal
Cirrhosis	High	High
Malignant hypertension	High	High
Unilateral renal disease	High	High
"High-renin" essential hypertension	High	High
Pregnancy	High	High
Diuretic overuse	High	High
Juxtaglomerular tumor (Bartter syndrome)	High	High
Low-salt diet	High	High
Addison disease	High	Low
Hypokalemia	High	Low

From Ravel R (ed): *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.

Rotavirus Serology

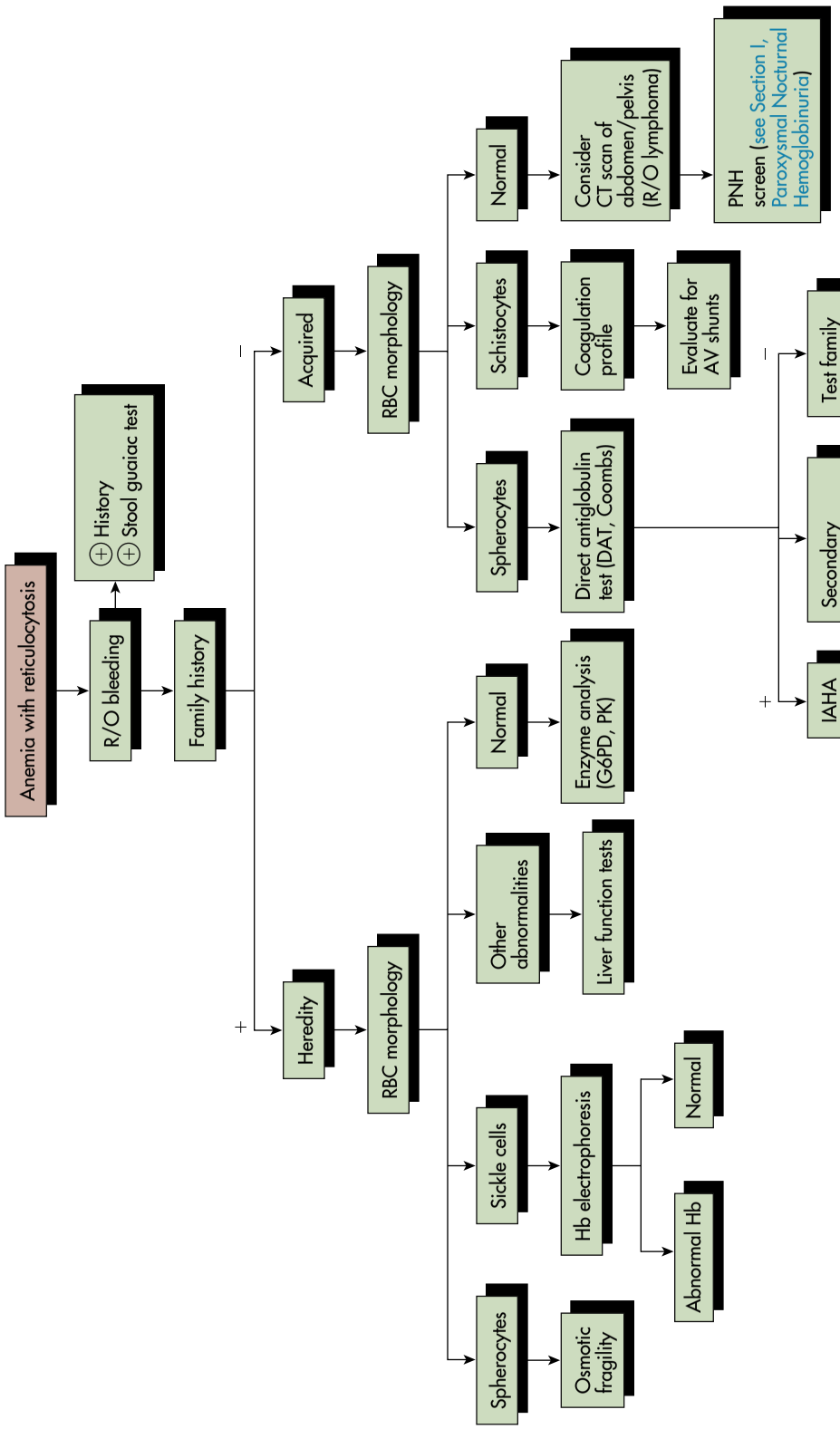


FIG. 53 Evaluation of patients with hemolytic anemia. *AV,* Arteriovenous; *CT,* computed tomography; *G6PD,* glucose-6-phosphate dehydrogenase; *Hb,* hemoglobin; *IAHA,* idiopathic autoimmune hemolytic anemia; *LS,* liver spleen; *PK,* pyruvate kinase; *PNH,* paroxysmal nocturnal hemoglobinuria; *RBC,* red blood cell, *R/O,* rule out.

TABLE 97 Combining the Reticulocyte Count and Red Blood Cell Parameters for Diagnosis

MCV, RDW	Reticulocyte Count <75,000/µL	Reticulocyte Count >100,000/µL
Low, Normal	Anemia of chronic disease	
Normal, Normal	Anemia of chronic disease	
High, Normal	Chemotherapy/antivirals/ alcohol Aplastic anemia	Chronic liver disease
Low, High	Iron deficiency anemia	Sickle cell-β-thalassemia
Normal, High	Early iron, folate, vitamin B_{12} deficiency Myelodysplasia	Sickle cell anemia, sickle cell disease
High, High	Folate or vitamin B_{12} deficiency Myelodysplasia	Immune hemolytic anemia Chronic liver disease

MCV, Mean corpuscular volume; *RDW,* red blood cell distribution width.
From Hoffman R et al: *Hematology: Basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

TABLE 98 Semen Analysis Reference Ranges

Color	Grayish white
pH	7.3-7.8 (literature range, 7.0-7.8)
Volume	2.0-5.0 ml (literature range, 1.5-6.0 ml)
Sperm count	20-250 million/ml (literature range for upper limit varies from 100-250 million/ml)
Motility	>60% motile <3 hours after specimen is obtained (literature range, >40% to >70%)
% Normal sperm	>60% (literature range, >60% to >70%)
Viscosity	Can be poured from a pipet in droplets rather than a thick strand

From Ravel R (ed): *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.

SED RATE
See ERYTHROCYTE SEDIMENTATION RATE

SEDIMENTATION RATE
See ERYTHROCYTE SEDIMENTATION RATE

SEMEN ANALYSIS
Table 98 describes semen analysis reference ranges.

SGOT
See ASPARTATE AMINOTRANSFERASE

SGPT
See ASPARTATE AMINOTRANSFERASE

SICKLE CELL TEST
Normal: Negative
Positive in: Sickle cell anemia, sickle cell trait, combination of *Hb S* gene with other disorders such as alpha-thalassemia, beta-thalassemia.

SMOOTH MUSCLE ANTIBODY
Normal: Negative
Present in: Chronic acute hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis, infectious mononucleosis

SODIUM (serum)
Normal range: 135 to 147 mEq/L (135 to 147 mmol/L [CF: 1; SMI: 1 mmol/L]). Electrolyte concentrations in extracellular and intracellular fluid are summarized in Table 99.

HYPONATREMIA

See Fig. 54.

Common causes of hyponatremia and electrolyte patterns in serum and urine with normal renal function are described in Table 100. Table E101 describes drugs associated with hyponatremia.

Sodium and water depletion (deficit hyponatremia)

Loss of gastrointestinal secretions with replacement of fluid but not electrolytes

TABLE 99 Electrolyte Concentrations in Extracellular and Intracellular Fluids

	PLASMA		INTERSTITIAL FLUID		PLASMA WATER		CELL WATER (MUSCLE)	
	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)
Na^+	140	140	145.3	145.3	149.8	149.8	13	13
K^+	4.5	4.5	4.7	4.7	4.8	4.8	140	140
Ca^{++}	5.0	2.5	2.8	1.4	5.3	5.3	10^{-7}	0.5×10^{-7}
Mg^{++}	1.7	0.85	1.0	0.5	1.8	0.9	7.0	3.5
Cl^-	104	104	114.7	114.7	111.4	111.4	3	3
HCO_3^-	24	24	26.5	26.5	25.7	25.7	10	10
SO_4^{2-}	1.0	0.5	1.2	0.6	1.1	0.55	–	–
P	2.1	1.2+	2.1++	1.2+	2.2	1.25+	107	57+++
Protein	15	1	8	0.5	16	1	40	2.5*
Organic anion	5	5	5.6	5.6	5.3	5.3	–	–

+The calculation is based on the assumption that the pH of the extracellular fluid is 7.4 and the pK of inorganic $H_2PO_4^-$ is 6.8.
++The concentration of P in the interstitial fluid would be increased by the Donnan effect, but reduced by the lower protein-bound phosphate, and these two opposing effects keep interstitial phosphate concentration about equal to that of plasma.
+++The intracellular molal concentration of phosphate is calculated with the assumption that the pK of organic phosphates in the cell is 6.1 and the intracellular pH 7.0.
*The calculation is based on the assumption that each mmol of intracellular protein has an average of 15 mEq.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

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SMOOTH MUSCLE ANTIBODY
Normal: Negative
Present in: Chronic acute hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis, infectious mononucleosis

SODIUM (serum)
Normal range: 135 to 147 mEq/L (135 to 147 mmol/L [CF: 1; SMI: 1 mmol/L]). Electrolyte concentrations in extracellular and intracellular fluid are summarized in Table 99.

HYPONATREMIA

See Fig. 54.

Common causes of hyponatremia and electrolyte patterns in serum and urine with normal renal function are described in Table 100. Table E101 describes drugs associated with hyponatremia.

Sodium and water depletion (deficit hyponatremia)

Loss of gastrointestinal secretions with replacement of fluid but not electrolytes

TABLE 99 Electrolyte Concentrations in Extracellular and Intracellular Fluids

	PLASMA		INTERSTITIAL FLUID		PLASMA WATER		CELL WATER (MUSCLE)	
	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)
Na^+	140	140	145.3	145.3	149.8	149.8	13	13
K^+	4.5	4.5	4.7	4.7	4.8	4.8	140	140
Ca^{++}	5.0	2.5	2.8	1.4	5.3	5.3	10^{-7}	0.5×10^{-7}
Mg^{++}	1.7	0.85	1.0	0.5	1.8	0.9	7.0	3.5
Cl^-	104	104	114.7	114.7	111.4	111.4	3	3
HCO_3^-	24	24	26.5	26.5	25.7	25.7	10	10
SO_4^{2-}	1.0	0.5	1.2	0.6	1.1	0.55	–	–
P	2.1	1.2+	2.1++	1.2+	2.2	1.25+	107	57+++
Protein	15	1	8	0.5	16	1	40	2.5*
Organic anion	5	5	5.6	5.6	5.3	5.3	–	–

+The calculation is based on the assumption that the pH of the extracellular fluid is 7.4 and the pK of inorganic $H_2PO_4^-$ is 6.8.
++The concentration of P in the interstitial fluid would be increased by the Donnan effect, but reduced by the lower protein-bound phosphate, and these two opposing effects keep interstitial phosphate concentration about equal to that of plasma.
+++The intracellular molal concentration of phosphate is calculated with the assumption that the pK of organic phosphates in the cell is 6.1 and the intracellular pH 7.0.
*The calculation is based on the assumption that each mmol of intracellular protein has an average of 15 mEq.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

TABLE E101 Drugs Associated with Hyponatremia*

Vasopressin Analogs	Drugs That Potentiate Renal Action of Vasopressin
Desmopressin (DDAVP)	Chlorpropamide
Oxytocin	Cyclophosphamide
	Nonsteroidal anti inflammatory agents
	Acetaminophen (paracetamol)
Drugs That Enhance Vasopressin Release	Drugs That Cause Hyponatremia by Unknown Mechanisms
Chlorpropamide	*Haloperidol*
Clofibrate	Fluphenazine
Carbamazepine-oxcarbazepine	Amitriptyline
Vincristine	Thioridazine
Nicotine	Fluoxetine
Narcotics	*Methamphetamine (MDMA or Ecstasy)*
Antipsychotics/antidepressants	Sertraline
Ifosfamide	

Italics: The common causes.
*Not including diuretics.
From Johnson RJ, Feehally J: *Comprehensive clinical nephrology,* ed 2, St Louis, 2000, Mosby.

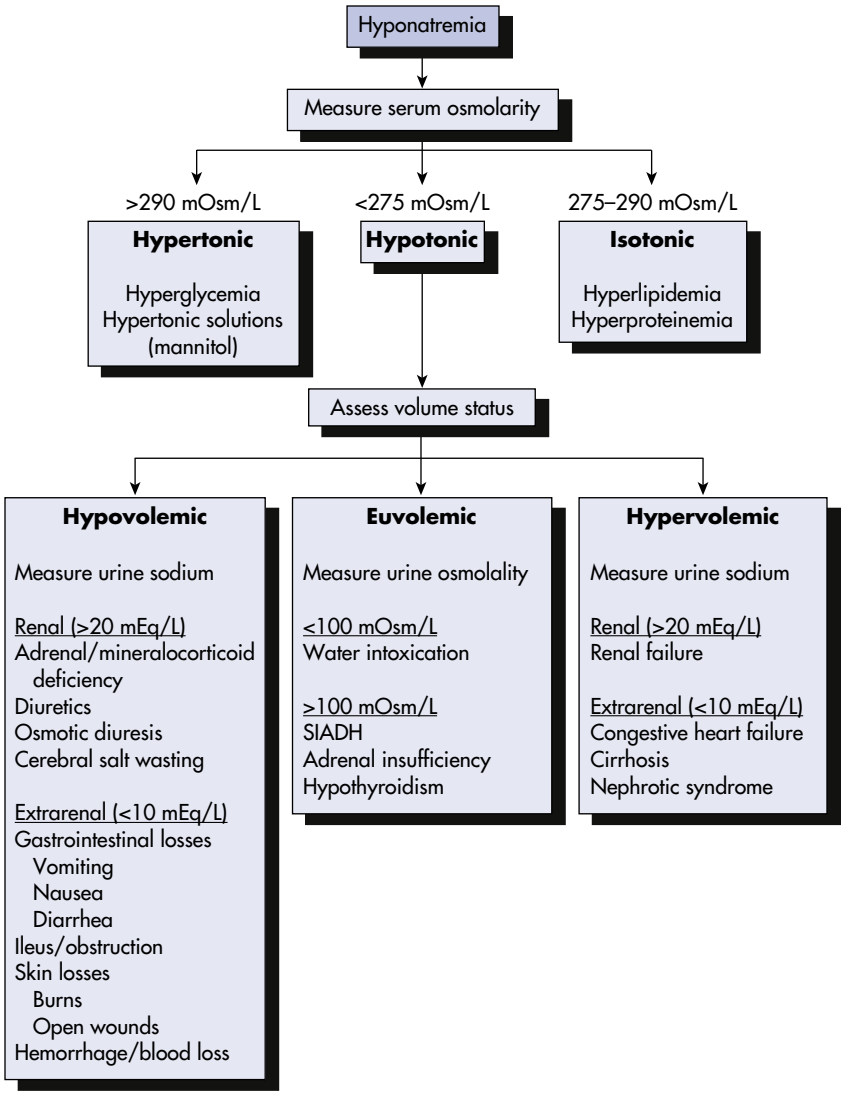

FIG. 54 Algorithm for diagnosis and treatment of hyponatremia. *SIADH,* Syndrome of inappropriate antidiuretic hormone. (From Cameron JL, Cameron AM: *Electrolyte disorders: current surgical therapy*, ed 10, Philadelphia, 2011, WB Saunders.)

TABLE 100 Common Causes of Hyponatremia and Electrolyte Patterns in Serum and Urine with Normal Renal Function*

Cause	Serum Na	Urine Na (UNa)	Urine Osmolality	Serum K	24-Hour UNa
1. Overhydration	Low	Low	Low	Normal or low	Low
2. Diuretics	Low	Low	Low	Low	High
3. SIADH†	Low	High	High	Normal or low	High
4. Adrenal failure	Low	Mildly elevated	Normal	High	High
5. Bartter syndrome	Low	Low	Low	Low	High
6. Diabetic hyperosmolarity‡	Low	Normal	Normal	High	Normal

*All Na and K values are concentrations, except for 24-hour UNa, which is the total number of milliequivalents of Na excreted in 24 hours in the urine.
†Secretion of inappropriate levels of antidiuretic hormone.
‡In this condition, serum glucose is markedly elevated.
SIADH, Syndrome of inappropriate antidiuretic hormone.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

Vomiting
Diarrhea
Tube drainage
Loss from skin with replacement of fluids but not electrolytes
Excessive sweating
Extensive burns
Loss from kidney
Diuretics
Chronic renal insufficiency (uremia) with acidosis
Metabolic loss
Starvation with acidosis
Diabetic acidosis
Endocrine loss
Addison disease

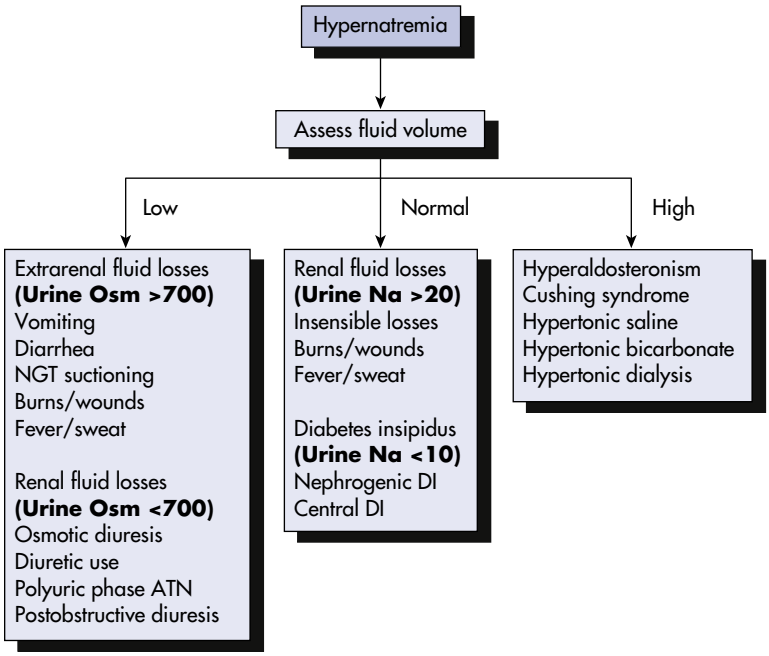

FIG. 55 Algorithm for evaluation of hypernatremia. *ATN,* Acute tubular necrosis; *DI,* diabetes insipidus; *NGT,* nasogastric tube. (From Cameron JL, Cameron AM: *Electrolyte disorders: current surgical therapy*, ed 10, Philadelphia, 2011, Saunders.)

TABLE 102 Common Causes of Hypernatremia and Electrolyte Patterns in Serum and Urine with Normal Renal Function*

Cause	Serum Na	Urine Na (UNa)	Urine Osmolality	Serum K	24-Hour UNa
1. Dehydration	High	High	High	Normal	Varies
2. Diabetes insipidus	High	Low	Low	Normal	Low
3. Cushing disease or syndrome	High	Low	Normal	Low	Low

*All Na and K values are concentrations, except for 24-hour UNa, which is the total number of milliequivalents of Na excreted in 24 hours in the urine.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

Sudden withdrawal of long-term steroid therapy
Iatrogenic loss from serous cavities
Paracentesis or thoracentesis
Excessive water (dilution hyponatremia)
Excessive water administration
Congestive heart failure
Cirrhosis
Nephrotic syndrome
Hypoalbuminemia (severe)
Acute renal failure with oliguria
Inappropriate antidiuretic hormone (IADH) syndrome
Intracellular loss (reset osmostat syndrome)
False hyponatremia (actually a dilutional effect)
Marked hypertriglyceridemia
Marked hyperproteinemia
Severe hyperglycemia

HYPERNATREMIA
See Fig. 55.
Common causes of hypernatremia and electrolyte patterns in serum and urine with normal renal function are summarized in Table 102.
Dehydration is the most frequent overall clinical finding in hypernatremia.
Deficient water intake (either orally or intravenously)
Excess kidney water output (diabetes insipidus, osmotic diuresis)
Excess skin water output (excess sweating, loss from burns)
Excess gastrointestinal tract output (severe protracted vomiting or diarrhea without fluid therapy)
Accidental sodium overdose
High-protein tube feedings

STREPTOZYME

See ANTISTREPTOLYSIN O TITER

SUCROSE HEMOLYSIS TEST (sugar water test)

Normal: Absence of hemolysis
Positive in: Paroxysmal nocturnal hemoglobinuria
False-positive: Autoimmune hemolytic anemia, megaloblastic anemias
False-negative: May occur with use of heparin or EDTA

SUDAN III STAIN (qualitative screening for fecal fat)

Normal: Negative. Test should be preceded by diet containing 100 to 150 g of dietary fat/day for 1 wk, avoidance of high-fiber diet, and avoidance of suppositories or oily material before specimen collection.
Positive in: Steatorrhea, use of castor oil or mineral oil droplets

SYNOVIAL FLUID ANALYSIS

Table 103 describes the classification and interpretation of synovial fluid analysis. An algorithm for analysis of joint fluid is illustrated in Fig. 56.

TABLE 103 Classification and Interpretation of Synovial Fluid Analysis

Group	Diseases	Appearance	Viscosity	Mucin Clot	WBC/mm³	% PMN	Glucose (mg/dl) (Blood-Synovial Fluid)	Protein (g/dl)
Normal	—	Clear	↑	Firm	<200	<25	<10	<2.5
I (noninflammatory)	Osteoarthritis, aseptic necrosis, traumatic arthritis, erythema nodosum, osteochondritis dissecans	Clear, yellow (may be xanthochromic if traumatic arthritis)	↑	Firm	↑ Up to 10,000	<25	<10	<2.5
II (inflammatory)	Crystal-induced arthritis, rheumatoid arthritis, Reiter syndrome, collagen vascular disease, psoriatic arthritis, serum sickness, rheumatic fever	Clear, yellow, turbid	↓	Friable	↑↑Up to 100,000	40-90	<40	<2.5
III (septic)	Bacterial (staphylococcal, gonococcal, tuberculosis)	Turbid	↓/↑	Friable	↑↑↑ Up to 5 million	40-100	20-100	>2.5

↑, Elevated; ↑↑, markedly high; ↓, decreased; *PMN,* polymorphonuclear leukocytes; *WBC,* white blood cell. Note that there is considerable overlap in the numbers listed above.

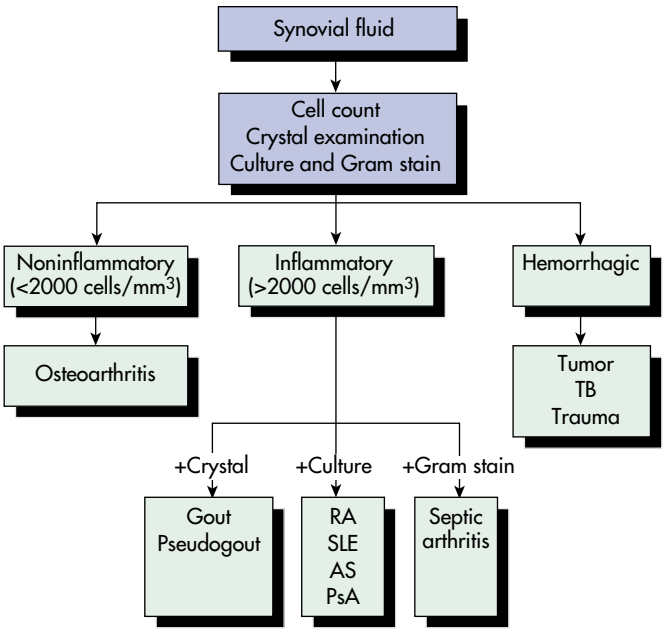

FIG. 56 Algorithm for analysis of joint fluid. Examples of inflammatory arthritis are indicated, although many conditions can produce these findings. *AS,* Ankylosing spondylitis; *PsA,* psoriatic arthritis; *RA,* rheumatoid arthritis; *SLE,* systemic lupus erythematosus; *TB,* tuberculosis. (From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, WB Saunders.)

T_3 (triiodothyronine)

See Table 104 for T_3 abnormalities.

Normal range: 75 to 220 ng/dl (1.2 to 3.4 nmol/L [CF: 0.01536; SMI: 0.1 nmol/L])

Abnormal values:

Elevated in hyperthyroidism (usually earlier and to a greater extent than serum T_4).

Useful in diagnosing:

T_3 hyperthyroidism (thyrotoxicosis): Increased T_3, normal free thyroxine index (FTI).

Toxic nodular goiter: Increased T_3, normal or increased T_4.

Iodine deficiency: Normal T_3, possibly decreased T_4.

Thyroid replacement therapy with liothyronine (Cytomel): Normal T_4, increased T_3 if patient is symptomatically hyperthyroid.

Not ordered routinely but indicated when hyperthyroidism is suspected and serum-free T_4 or FTI inconclusive.

T_3 RESIN UPTAKE (T_3RU)

Normal range: 25% to 35%

Abnormal values: Increased in hyperthyroidism. T_3 resin uptake (T_3RU or RT_3U) measures the percentage of free T_4 (not bound to protein); it does not measure serum T_3 concentration; T_3RU and other tests that reflect thyroid hormone binding to plasma protein are also known as *thyroid hormone-binding ratios* (THBR).

T_4, FREE (Free thyroxine)

Normal range: 0.8 to 2.8 ng/dl

Elevated in:

Graves disease, toxic multinodular goiter, toxic adenoma, iatrogenic and factitious causes, transient hyperthyroidism

Serum-free T_4 directly measures unbound thyroxine. Free T_4 can be measured by equilibrium dialysis (gold standard of free T_4 assays) or by immunometric techniques (influenced by serum levels of lipids, proteins, and certain drugs). The FTI can also be easily calculated by multiplying T_4 times T_3RU and dividing the result by 100; the FTI corrects for any abnormal T_4 values secondary to protein binding: FTI = $T_4 \times T_3RU/100$.

Normal values equal 1.1 to 4.3.

T_4, SERUM T_4

Normal range: 0.8 to 2.8 ng/dl (10 to 36 pmol/L [CF: 12.87; SMI: 1 pmol/L])

Abnormal values: Serum thyroxine (T_4)

Elevated in:

Graves disease

Toxic multinodular goiter

Toxic adenoma

Iatrogenic and factitious

Transient hyperthyroidism

Subacute thyroiditis

TABLE 103 Classification and Interpretation of Synovial Fluid Analysis

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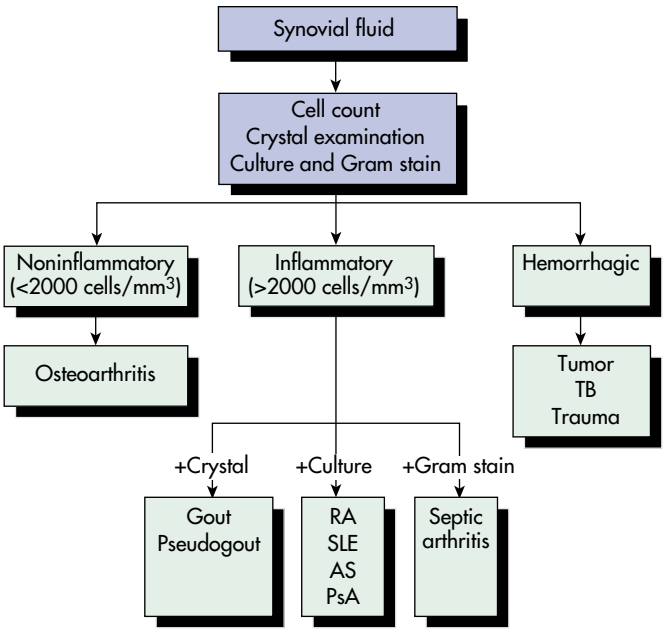

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Abnormal values: Serum thyroxine (T_4)

Elevated in:

Graves disease

Toxic multinodular goiter

Toxic adenoma

Iatrogenic and factitious

Transient hyperthyroidism

Subacute thyroiditis

TABLE 104 Findings in Thyroid Function Tests in Various Clinical Conditions

Condition	T_4	FT_4I	T_3	FT_3I	TSH	TSI	TRH Stimulation
Hyperthyroidism							
Graves disease	↑	↑	↑	↑	↓	+	↓
Toxic nodular goiter	↑	↑	↑	↑	↓	–	↓
Pituitary TSH-secreting tumors	↑	↑	↑	↑	↑	–	↓
T_3 thyrotoxicosis	N	N	↑	↑	↓	+, –	↓
T_4 thyrotoxicosis	↑	↑	N	N	↓	+, –	↓
Hypothyroidism							
Primary	↓	↓	↓	↓	↑	+, –	↑
Secondary	↓	↓	↓	↓	↓ N	–	↓
Tertiary	↓	↓	↓	↓	↓, N	–	N
Peripheral unresponsiveness	↑, N	↑, N	↑, N	↑	↑, N	–	N,↑

↑, Increased; ↓, decreased; +, – variable; *FTI,* Free thyroid index; *N,* normal; T_3, triiodothyronine; T_4, thyroxine; *TRH,* thyrotropin-releasing hormone; *TSH,* thyroid-stimulating hormone; *TSI,* thyroid stimulating immunoglobulin.
From Tilton RC, Barrows A: *Clinical laboratory medicine,* St Louis, 1992, Mosby.

Hashimoto thyroiditis
Silent thyroiditis

Rare causes: Hypersecretion of TSH (e.g., pituitary neoplasms), struma ovarii, ingestion of large amounts of iodine in a patient with preexisting thyroid hyperplasia or adenoma (Jod-Basedow phenomenon), hydatidiform mole, carcinoma of thyroid, amiodarone therapy of arrhythmias.

Serum thyroxine test measures both circulating thyroxine bound to protein (represents >99% of circulating T_4) and unbound (free) thyroxine. Values vary with protein binding; changes in the concentration of T_4 secondary to changes in thyroxine-binding globulin (TBG) can be caused by the following:

Increased TBG (↑T4)	Decreased TBG (↓T4)
Pregnancy	Androgens, glucocorticoids
Estrogens	Nephrotic syndrome, cirrhosis
Acute infectious hepatitis	Acromegaly
Oral contraceptives	Hypoproteinemia
Familial	Familial
Fluorouracil, clofibrate	Phenytoin, acetylsalicylic acid (ASA) and other NSAIDs, heroin, methadone, high-dose penicillin, asparaginase, chronic debilitating illness

To eliminate the suspected influence of protein binding on thyroxine values, two additional tests are available: T_3 resin uptake and serum free thyroxine. Table 105 summarizes the effects of pregnancy on thyroid physiology, and Table 106 describes changes in thyroid hormone levels during illness.

TEGRETOL

See CARBAMAZEPINE.

TESTOSTERONE (total testosterone)

Normal range: Variable with age and sex. Testosterone circulates in plasma mostly bound to plasma proteins and sex hormone-binding globulin (SHBG). Approximately 2% of testosterone circulates in free form (biologically active form). Low testosterone levels in obese patients may be due to reduced levels of SHBG; therefore, it is essential to measure free testosterone when evaluating androgen deficiency in obese patients.

Serum/plasma

Males: 280-1100 ng/dl Females: 15-70 ng/dl

Urine

Males: 50-135 μg/day Females: 2-12 μg/day

Elevated in: Testicular tumors, ovarian masculinizing tumors, testosterone replacement therapy

TABLE 105 Effects of Pregnancy on Thyroid Physiology

Physiologic Change	Thyroid-Related Consequences
↑ Serum thyroxine-binding globulin	↑ Total T_4 and T_3; ↑ T_4 production
↑ Plasma volume	↑ T_4 and T_3 pool size; ↑ T_4 production; ↑ cardiac output
D3 expression in placenta and (?) uterus	↑ T_4 production
First-trimester ↑ in hCG	↑ Free T_4; ↓ basal thyrotropin; ↑ T_4 production
↑ Renal I– clearance	↑ Iodine requirements
↑ T_4 production; fetal T_4 synthesis during second and third trimesters	
↑ Oxygen consumption by fetoplacental unit, gravid uterus, and mother	↑ Basal metabolic rate; ↑ cardiac output

D3, Type 3 iodothyronine deiodinase; *I–,* plasma iodide; *hCG,* human chorionic gonadotropin; T_3, triiodothyronine; T_4, thyroxine.
From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, WB Saunders.

TABLE 106 Changes in Thyroid Hormone Levels during Illness

Severity of Illness	Free T_3	Free T_4	Reverse T_3	TSH	Probable Cause
Mild	↓	N	↑	N	↓ D2, D1
Moderate	↓↓	N, ↑↓	↑↑	N, ↓	↓↓ D2, D1,?↑ D3
Severe	↓↓↓	↓	↑	↓↓	↓↓ D2, D1, ↑D3
Recovery	↓	↓	↑	↑	?

D1 through *D3,* iodothyronine deiodinases; *N,* no change; T_3, triiodothyronine; T_4, thyroxine; *TSH,* thyroid-stimulating hormone.
From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, WB Saunders.

Decreased in: Hypogonadism, obesity, insulin resistance, sleep apnea. Fig. 57 illustrates testosterone level changes with age. The diagnosis of androgen deficiency should be based on at least two morning testosterone measurements (collected on separate days) in a symptomatic patient.

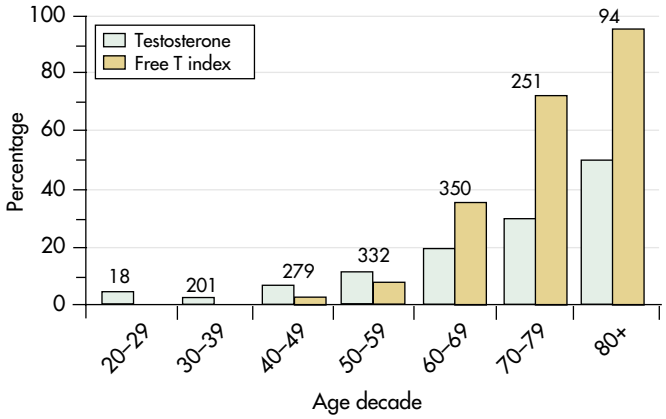

FIG. 57 Hypogonadism in aging men. Bar height indicates the percentage of men in each 10-year interval, from the third to the ninth decades, with at least one testosterone value in the hypogonadal range. The criteria used for these determinations are total testosterone less than 11.3 nmol/L (325 ng/dl) and testosterone and sex hormone-binding globulin (free T index) less than 0.153 nmol/nmol. The numbers above each pair of bars indicate the number of men studied in the corresponding decade. The fraction of men who are hypogonadal increases progressively after age 50 years by either criterion. More men are hypogonadal by free T index than by total testosterone after 50 years, and there seems to be a progressively greater difference with increasing age between the two criteria. (From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, WB Saunders.)

THEOPHYLLINE

Normal therapeutic range: 10 to 20 mcg/ml

THORACENTESIS FLUID

See PLEURAL FLUID

THROMBIN TIME (TT), Thrombin Clotting Time (TCT)

Normal range: 11.3 to 18.5 sec

Elevated in: Thrombolytic and heparin therapy, disseminated intravascular coagulation, hypofibrinogenemia, dysfibrinogenemia

See Table 107 for synthesizing results of PT, APTT, and TCT. Also see Fig. 58.

THYROGLOBULIN

Normal: 3 to 40 ng/ml. Thyroglobulin is a tumor marker for monitoring the status of patients with papillary or follicular thyroid cancer following resection.

Elevated in: Papillary or follicular thyroid cancer, Hashimoto thyroiditis, Graves disease, subacute thyroiditis

THYROID MICROSOMAL ANTIBODIES

Normal: Undetectable. Low titers may be present in 5% to 10% of normal individuals

Elevated in: Hashimoto disease, thyroid carcinoma, early hypothyroidism, pernicious anemia

THYROID-STIMULATING HORMONE (TSH)

See Fig. 59 for an algorithmic approach to thyroid testing.

Normal range: 2 to 11 μU/ml (2 to 11 mU/L [CF: 1; SMI: 1 mU/L])

CONDITIONS THAT INCREASE SERUM THYROID-STIMULATING HORMONE VALUES

Laboratory error
Primary hypothyroidism
Synthroid therapy with insufficient dose
Lithium or amiodarone; some patients
Hashimoto thyroiditis in later stage
Large doses of inorganic iodide (e.g., potassium iodide [SSKI])
Severe nonthyroid illness in recovery phase
Iodine deficiency (moderate or severe)

TABLE 107 Synthesizing Results of PT, APTT, and TCT

TEST			
PT	**APTT**	**TCT**	**Possible Diagnoses**
Normal	Normal	Normal	Normal hemostasis, disorder of platelet function, factor XIII deficiency, disorder of vascular hemostasis, mild coagulation protein deficiency, mild vWD, disorder of fibrinolysis (α_2-antiplasmin deficiency/defect, plasminogen activator inhibitor-1 deficiency/defect)
Prolonged	Normal	Normal	Factor VII deficiency; early oral anticoagulation; lupus anticoagulant; mild factor II, V, or X deficiency; specific factor inhibitor
Normal	Prolonged	Normal	Factor VIII, IX, XI, XI, prekallikrein, or HMWK deficiency; lupus anticoagulant; amyloid-adsorbed factor IX; specific factor inhibitor
Prolonged	Prolonged	Normal	Multiple factor deficiency (e.g., liver failure, vitamin K deficiency, oral anticoagulants); factor V, X, or II deficiency; amyloid-adsorbed factor X; specific factor inhibitor
Prolonged	Prolonged	Prolonged	Anticoagulants, DIC, dilutional coagulopathy, liver disease, fibrinogen deficiency/disorder, inhibition of fibrin polymerization, hyperfibrinolysis

APTT, Activated partial thromboplastin time; *DIC,* disseminated intravascular coagulation; *HMWK,* high-molecular-weight kininogen; *PT,* prothrombin time; *TCT,* thrombin clotting time; *vWD,* von Willebrand disease.
From Hoffman R: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

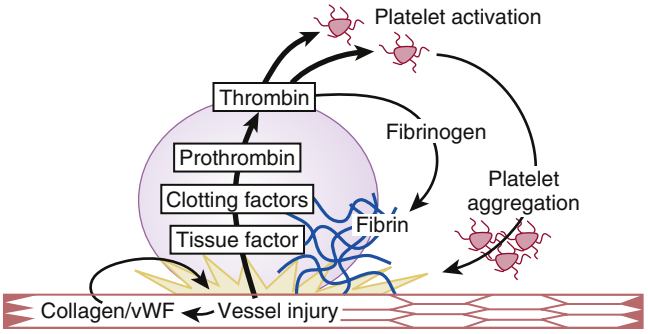

FIG. 58 Central role of thrombin in thrombogenesis. Vascular injury simultaneously triggers platelet adhesion and activation, as well as activation of the coagulation system. Platelet activation is initiated by exposure of subendothelial collagen and von Willebrand factor *(vWF),* to which platelets adhere. Adherent platelets become activated and release ADP and thromboxane A_2, platelet agonists that activate ambient platelets and recruit them to the site of injury. Coagulation, which is triggered by tissue factor exposed at the site of injury and enhanced by assembly of clotting factor complexes on the activated platelet surface, results in thrombin generation. Thrombin not only converts fibrinogen to fibrin but also serves as a potent platelet agonist. When platelets are activated, glycoprotein *(GP)* IIb/IIIa on their surfaces undergoes a conformational change that endows it with the capacity to ligate fibrinogen and mediate platelet aggregation. Fibrin strands then weave the platelet aggregates together to form a platelet/fibrin thrombus. (From Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine*, ed 11, Philadelphia, 2019, Elsevier.)

Thyroid-Stimulating Hormone

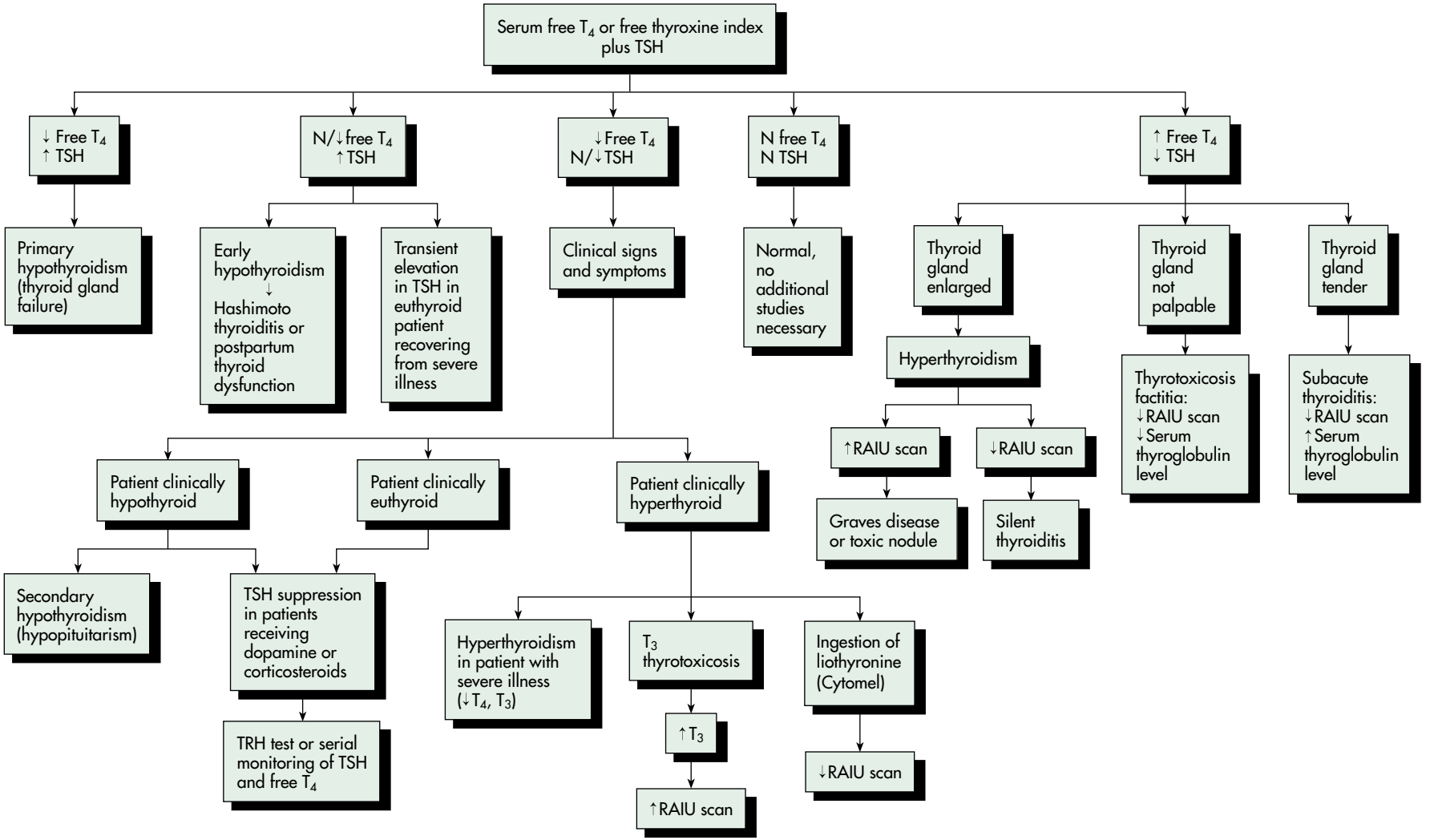

FIG. 59 Diagnostic approach to thyroid testing. *N,* Normal; *RAIU,* radioactive iodine uptake; T_3, triiodothyronine; T_4, thyroxine; *TRH,* thyrotropin-releasing hormone; *TSH,* thyroid-stimulating hormone. (From Ferri FF: *Practical guide to the care of the medical patient*, ed 8, St Louis, 2011, Mosby.)

Addison disease
TSH specimen drawn in evening (peak of diurnal variation)
Pituitary TSH-secreting tumor
Therapy of hypothyroidism (3 to 6 wk after beginning therapy [range, 1 to 8 wk]; sometimes longer when pretherapy TSH is over 100 μU/ml)
Acute psychiatric illness
Peripheral resistance to T_4 syndrome
Antibodies (e.g., human anti-mouse antibody [HAMA]) interfering with monoclonal sandwich method of TSH assay
Telepaque (iopanoic acid) and Oragrafin (ipodate) x-ray contrast media
Amphetamines
High altitudes
CONDITIONS THAT DECREASE SERUM THYROID-STIMULATING HORMONE VALUES
Laboratory error
T_4/T_3 toxicosis (diffuse or nodular etiology)
Excessive therapy for hypothyroidism
Active thyroiditis (subacute, painless, or early active Hashimoto disease)
Multinodular goiter containing areas of autonomy
Severe nonthyroid illness (especially acute trauma, dopamine, or glucocorticoid)
T_3 toxicosis
Pituitary insufficiency
Cushing syndrome (and some patients on high-dose glucocorticoid)
Jod-Basedow (iodine-induced) hyperthyroidism
Thyroid-stimulating hormone drawn 2 to 4 hr after levothyroxine dose
Postpartum transient toxicosis
Factitious hyperthyroidism
Struma ovarii
Radioimmunoassay, surgery, or antithyroid drug therapy for hyperthyroidism 4 to 6 wk (range, 2 wk to 2 yr) after the treatment
Interleukin-2 drugs (3% to 6% of cases) or α-interferon therapy (1% of cases)
Hyperemesis gravidarum
Amiodarone therapy.
See Table 106 for changes in thyroid hormone levels during illness.

THYROTROPIN (TSH) RECEPTOR ANTIBODIES

Normal: <130% of basal activity
Elevated in: Values between 1.3 and 2.0 are found in 10% of patients with thyroid disease other than Graves disease. Values >2.8 have been found only in patients with Graves disease.

THYROTROPIN-RELEASING HORMONE (TRH) STIMULATION TEST

Normal: Baseline TSH <11 microU/ml; Stimulated TSH: more than double the baseline.

In primary hypothyroidism the TSH increase is 2× to 3× the normal result. In secondary hypothyroidism no TSH response occurs. In tertiary hypothyroidism (hypothalamic failure) there is a delayed rise in the TSH level.

THYROXINE (T_4)

Normal range: 4 to 11 μg/dl (51 to 142 nmol/L [CF: 12.87; SMI: 1 nmol/L])
Elevated: Hyperthyroidism (see Fig. 59)

TIBC

See IRON-BINDING CAPACITY, TOTAL

TISSUE TRANSGLUTAMINASE ANTIBODY

Normal: Negative
Present in: Celiac disease (specificity; 94% to 97%, sensitivity, 90% to 98%), dermatitis herpetiformis

TRANSFERRIN

Normal range: 170 to 370 mg/dl (1.7 to 3.7 g/L [CF: 0.01; SMI: 0.01 g/L])
Elevated in: Iron deficiency anemia, oral contraceptive administration, viral hepatitis, late pregnancy

BOX 29 Causes of Serum Troponin T and I Elevations, Including Both Acute Coronary Syndromes, Noncoronary Cardiac Events, and Noncardiac Ailments

Acute coronary syndrome/acute myocardial infarction
Shock of any form (cardiogenic, obstructive, distributive)
Myocarditis and myopericarditis
Cardiomyopathies
Acute congestive heart failure (pulmonary edema)
Sepsis
Pulmonary embolism
Renal failure
Sympathomimetic ingestions
Polytrauma
Burns
Acute CNS event
Rhabdomyolysis
Cardiac neoplasm, inflammatory syndromes, and infiltrative diseases
Congenital coronary anomalies
Extreme physical exertion

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.

Decreased in: Nephrotic syndrome, liver disease, hereditary deficiency, protein malnutrition, neoplasms, chronic inflammatory states, chronic illness, thalassemia, hemochromatosis, hemolytic anemia

TRIGLYCERIDES

Normal range: <150 mg/dl (<1.80 mmol/L [CF: 0.01129; SMI: 0.02 mmol/L])
Elevated in: Hyperlipoproteinemias (types I, IIb, III, IV, V), hypothyroidism, pregnancy, estrogens, acute myocardial infarction, pancreatitis, alcohol intake, nephrotic syndrome, diabetes mellitus, glycogen storage disease
Decreased in: Malnutrition, congenital abetalipoproteinemias, drugs (e.g., gemfibrozil, fenofibrate, nicotinic acid, clofibrate)

TRIIODOTHYRONINE

See T_3

TROPONINS (serum)

See Box 29 for causes of troponin elevations.
Normal range: 0 to 0.4 ng/ml (negative). If there is clinical suspicion of evolving acute MI or ischemic episode, repeat testing in 5 to 6 hr is recommended.
Indeterminate: 0.05 to 0.49 ng/ml. Suggest further tests. In a patient with unstable angina and this troponin I level, there is an increased risk of a cardiac event in the near future.
Strong probability of acute MI: ≥0.05 ng/ml
Cardiac troponin T (cTnT) is a highly sensitive marker for myocardial injury for the first 48 hours after MI and for up to 5 to 7 days (see Fig. 20, under "Creatine Kinase Isoenzymes"). It may also be elevated in renal failure, chronic muscle disease, and trauma.
Cardiac troponin I (cTnI) is highly sensitive and specific for myocardial injury (≥CK-MB) in the initial 8 hr, peaks within 24 hr and lasts up to 7 days. With progressively higher levels of cTnI, the risk of mortality increases because the amount of necrosis increases.

TSH

See THYROID-STIMULATING HORMONE

TT

See THROMBIN TIME

TUBERCULIN TEST (PPD)

Abnormal results: See Box 30. Box 31 describes factors associated with false-negative tuberculin tests.

BOX 30 PPD Reaction Size Considered "Positive" (Intracutaneous 5 TU Mantoux Test at 48 hr)

5 mm or More
HIV infection or risk factors for HIV
Close recent contact with active TB case
Persons with chest x-ray consistent with healed TB

10 mm or More
Foreign-born persons from countries with high TB prevalence in Asia, Africa, and Latin America
IV drug users
Medically underserved low-income population groups (including Native Americans, Hispanics, and blacks)
Residents of long-term care facilities (nursing homes, mental institutions)
Medical conditions that increase risk for TB (silicosis, gastrectomy, undernourishment, diabetes mellitus, high-dose corticosteroids or immunosuppression Rx, leukemia or lymphoma, other malignancies)
Employees of long-term care facilities, schools, child care facilities, health care facilities

15 mm or More
All others not already listed

HIV, Human immunodeficiency virus; *IV,* intravenous; *PPD,* purified protein derivative; *Rx,* prescription; *TB,* tuberculosis; *TU,* tuberculin units.

BOX 31 Factors Associated with False-Negative Tuberculin Tests

Technical Errors
Improper administration
Inaccurate reading
Loss of potency of antigen

Patient-Related Factors (Anergy)
Age (elderly)
Nutritional status
Medications: Corticosteroids, immunosuppressive agents
Severe tuberculosis
Coexisting diseases
HIV infection
Viral illness or vaccination
Lymphoreticular malignancies
Sarcoidosis
Solid tumors
Lepromatous leprosy
Sjögren syndrome
Ataxia telangiectasia
Uremia
Primary biliary cirrhosis
Systemic lupus erythematosus
Severe systemic disease of any etiology

HIV, Human immunodeficiency virus.
From Stein JH (ed): *Internal medicine,* ed 4, St Louis, 1994, Mosby.

UNCONJUGATED BILIRUBIN

See BILIRUBIN, DIRECT

UREA NITROGEN, BLOOD (BUN)

Normal range: 8 to 18 mg/dl (3 to 6.5 mmol/L [CF: 0.357; SMI: 0.5 mmol/L])

Box 32 describes factors affecting BUN level independent of renal function.

Elevated in: Dehydration, drugs (aminoglycosides and other antibiotics, diuretics, lithium, corticosteroids), gastrointestinal bleeding, decreased renal blood flow (shock, congestive heart failure, myocardial infarction), renal disease (glomerulonephritis, pyelonephritis, diabetic nephropathy), urinary tract obstruction (prostatic hypertrophy)

BOX 32 Factors Affecting Blood Urea Nitrogen Level Independent of Renal Function

Disproportionate Increase in Blood Urea Nitrogen
Volume depletion ("prerenal azotemia")
Gastrointestinal hemorrhage
Corticosteroid or cytotoxic agents
High-protein diet
Obstructive uropathy
Sepsis
Catabolic states, tissue breakdown

Disproportionate Decrease in Blood Urea Nitrogen
Low-protein diet
Liver disease

From Andreoli TE (ed): *Cecil essentials of medicine,* ed 5, Philadelphia, 2001, WB Saunders.

Decreased in: Liver disease, malnutrition, third trimester of pregnancy, overhydration, acromegaly, celiac disease

URIC ACID (serum)

Normal range: 2 to 7 mg/dl

Elevated in: Renal failure, gout, excessive cell lysis (chemotherapeutic agents, radiation therapy, leukemia, lymphoma, hemolytic anemia), hereditary enzyme deficiency (hypoxanthine-guanine-phosphoribosyl transferase), acidosis, myeloproliferative disorders, diet high in purines or protein, drugs (diuretics, low doses of ASA, ethambutol, nicotinic acid), lead poisoning, hypothyroidism, Addison disease, nephrogenic diabetes insipidus, active psoriasis, polycystic kidneys

Decreased in: Drugs (allopurinol, febuxostat, high doses of ASA, probenecid, warfarin, corticosteroid), deficiency of xanthine oxidase, syndrome of inappropriate antidiuretic hormone secretion, renal tubular deficits (Fanconi syndrome), alcoholism, liver disease, diet deficient in protein or purines, Wilson disease, hemochromatosis

URINALYSIS

Normal range:
Color: Light straw
Appearance: Clear
Ketones: Absent
pH: 4.5 to 8 (average, 6)
Protein: Absent
Glucose: Absent
Specific gravity: 1.005 to 1.030
Occult blood absent
Microscopic examination:
Red blood cells: 0 to 5 (high-power field)
White blood cells: 0 to 5 (high-power field)
Bacteria (spun specimen): Absent
Casts: 0 to 4 hyaline (low-power field)
Abnormalities in the microscopic examination of urine are described in Table 108. Causes of abnormal appearance and color of urine are described in Table 109. Urine color changes with commonly used drugs are summarized in Table 110.

URINE AMYLASE

Normal range: 35 to 260 U Somogyi/hr (6.5 to 48.1 U/hr [CF: 0.185; SMI: 1 U/hr])

Elevated in: Pancreatitis, carcinoma of the pancreas

URINE BILE

Normal: Absent

Abnormal:
Urine bilirubin: Hepatitis (viral, toxic, drug-induced), biliary obstruction
Urine urobilinogen: Hepatitis (viral, toxic, drug-induced), hemolytic jaundice, liver cell dysfunction (cirrhosis, infection, metastases)

URINE CALCIUM

Normal range: <250 mg/24 hr (<6.2 mmol/dl [CF: 0.02495; SMI: 0.1 mmol/dl])

BOX 30 PPD Reaction Size Considered "Positive" (Intracutaneous 5 TU Mantoux Test at 48 hr)

5 mm or More
HIV infection or risk factors for HIV
Close recent contact with active TB case
Persons with chest x-ray consistent with healed TB

10 mm or More
Foreign-born persons from countries with high TB prevalence in Asia, Africa, and Latin America
IV drug users
Medically underserved low-income population groups (including Native Americans, Hispanics, and blacks)
Residents of long-term care facilities (nursing homes, mental institutions)
Medical conditions that increase risk for TB (silicosis, gastrectomy, undernourishment, diabetes mellitus, high-dose corticosteroids or immunosuppression Rx, leukemia or lymphoma, other malignancies)
Employees of long-term care facilities, schools, child care facilities, health care facilities

15 mm or More
All others not already listed

HIV, Human immunodeficiency virus; *IV,* intravenous; *PPD,* purified protein derivative; *Rx,* prescription; *TB,* tuberculosis; *TU,* tuberculin units.

BOX 31 Factors Associated with False-Negative Tuberculin Tests

Technical Errors
Improper administration
Inaccurate reading
Loss of potency of antigen

Patient-Related Factors (Anergy)
Age (elderly)
Nutritional status
Medications: Corticosteroids, immunosuppressive agents
Severe tuberculosis
Coexisting diseases
HIV infection
Viral illness or vaccination
Lymphoreticular malignancies
Sarcoidosis
Solid tumors
Lepromatous leprosy
Sjögren syndrome
Ataxia telangiectasia
Uremia
Primary biliary cirrhosis
Systemic lupus erythematosus
Severe systemic disease of any etiology

HIV, Human immunodeficiency virus.
From Stein JH (ed): *Internal medicine,* ed 4, St Louis, 1994, Mosby.

UNCONJUGATED BILIRUBIN

See BILIRUBIN, DIRECT

UREA NITROGEN, BLOOD (BUN)

Normal range: 8 to 18 mg/dl (3 to 6.5 mmol/L [CF: 0.357; SMI: 0.5 mmol/L])

Box 32 describes factors affecting BUN level independent of renal function.

Elevated in: Dehydration, drugs (aminoglycosides and other antibiotics, diuretics, lithium, corticosteroids), gastrointestinal bleeding, decreased renal blood flow (shock, congestive heart failure, myocardial infarction), renal disease (glomerulonephritis, pyelonephritis, diabetic nephropathy), urinary tract obstruction (prostatic hypertrophy)

BOX 32 Factors Affecting Blood Urea Nitrogen Level Independent of Renal Function

Disproportionate Increase in Blood Urea Nitrogen
Volume depletion ("prerenal azotemia")
Gastrointestinal hemorrhage
Corticosteroid or cytotoxic agents
High-protein diet
Obstructive uropathy
Sepsis
Catabolic states, tissue breakdown

Disproportionate Decrease in Blood Urea Nitrogen
Low-protein diet
Liver disease

From Andreoli TE (ed): *Cecil essentials of medicine,* ed 5, Philadelphia, 2001, WB Saunders.

Decreased in: Liver disease, malnutrition, third trimester of pregnancy, overhydration, acromegaly, celiac disease

URIC ACID (serum)

Normal range: 2 to 7 mg/dl

Elevated in: Renal failure, gout, excessive cell lysis (chemotherapeutic agents, radiation therapy, leukemia, lymphoma, hemolytic anemia), hereditary enzyme deficiency (hypoxanthine-guanine-phosphoribosyl transferase), acidosis, myeloproliferative disorders, diet high in purines or protein, drugs (diuretics, low doses of ASA, ethambutol, nicotinic acid), lead poisoning, hypothyroidism, Addison disease, nephrogenic diabetes insipidus, active psoriasis, polycystic kidneys

Decreased in: Drugs (allopurinol, febuxostat, high doses of ASA, probenecid, warfarin, corticosteroid), deficiency of xanthine oxidase, syndrome of inappropriate antidiuretic hormone secretion, renal tubular deficits (Fanconi syndrome), alcoholism, liver disease, diet deficient in protein or purines, Wilson disease, hemochromatosis

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Normal range:
Color: Light straw
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Specific gravity: 1.005 to 1.030
Occult blood absent
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Red blood cells: 0 to 5 (high-power field)
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Bacteria (spun specimen): Absent
Casts: 0 to 4 hyaline (low-power field)
Abnormalities in the microscopic examination of urine are described in Table 108. Causes of abnormal appearance and color of urine are described in Table 109. Urine color changes with commonly used drugs are summarized in Table 110.

URINE AMYLASE

Normal range: 35 to 260 U Somogyi/hr (6.5 to 48.1 U/hr [CF: 0.185; SMI: 1 U/hr])

Elevated in: Pancreatitis, carcinoma of the pancreas

URINE BILE

Normal: Absent

Abnormal:
Urine bilirubin: Hepatitis (viral, toxic, drug-induced), biliary obstruction
Urine urobilinogen: Hepatitis (viral, toxic, drug-induced), hemolytic jaundice, liver cell dysfunction (cirrhosis, infection, metastases)

URINE CALCIUM

Normal range: <250 mg/24 hr (<6.2 mmol/dl [CF: 0.02495; SMI: 0.1 mmol/dl])

TABLE 108 Microscopic Examination of the Urine

Finding	Associations
Casts	
Red blood cell	Glomerulonephritis, vasculitis
White blood cell	Interstitial nephritis, pyelonephritis
Epithelial cell	Acute tubular necrosis, interstitial nephritis, glomerulonephritis
Granular	Renal parenchymal disease (nonspecific)
Waxy, broad	Advanced renal failure
Hyaline	Normal finding in concentrated urine
Fatty	Heavy proteinuria
Cells	
Red blood cell	Urinary tract infection, urinary tract inflammation
White blood cell	Urinary tract infection, urinary tract inflammation
Eosinophil	Acute interstitial nephritis
(Squamous) epithelial cell	Contaminants
Crystals	
Uric acid	Acid urine, acute uric acid nephropathy, hyperuricosuria
Calcium phosphate	Alkaline urine
Calcium oxalate	Acid urine, hyperoxaluria, ethylene glycol poisoning
Cystine	Cystinuria
Sulfur	Sulfa-containing antibiotics

From Andreoli TE (ed): *Cecil essentials of medicine,* ed 5, Philadelphia, 2001, WB Saunders.

Elevated in: Primary hyperparathyroidism, hypervitaminosis D, bone metastases, multiple myeloma, increased calcium intake, steroids, prolonged immobilization, sarcoidosis, Paget disease, idiopathic hypercalciuria, renal tubular acidosis
Decreased in: Hypoparathyroidism, pseudohypoparathyroidism, vitamin D deficiency, vitamin D-resistant rickets, diet low in calcium, drugs (thiazide diuretics, oral contraceptives), familial hypocalciuric hypercalcemia, renal osteodystrophy, potassium citrate therapy

URINE CAMP

Elevated in: Hypercalciuria, familial hypocalciuric hypercalcemia, primary hyperparathyroidism, pseudohypoparathyroidism, rickets
Decreased in: Vitamin D intoxication, sarcoidosis

URINE CATECHOLAMINES

Normal range:
Norepinephrine: <100 μg/24 hr (<590 nmol/day [CF: 5.911; SMI: 10 nmol/day])
Epinephrine: <10 μg/24 hr (55 nmol/day [CF: 5.458; SMI: 5 nmol/day])
Elevated in: Pheochromocytoma, neuroblastoma, severe stress

URINE CHLORIDE

Normal range: 110 to 250 mEq/day (110 to 250 mmol/day [CF: 1; SMI: 1 mmol/day])
Elevated in: Corticosteroids, Bartter syndrome, diuretics, metabolic acidosis, severe hypokalemia
Decreased in: Chloride depletion (vomiting), colonic villous adenoma, chronic renal failure, renal tubular acidosis

URINE COPPER

Normal range: <40 μg/24 hr (<0.6 μmol/day [CF: 0.01574; SMI: 0.2 μmol/day])

URINE CORTISOL, FREE

Normal range: 10 to 110 μg/24 hr (30 to 300 nmol/day [CF: 2.759; SMI: 10 nmol/day])

TABLE 109 Appearance and Color of Urine

Appearance	Cause	Remarks
Colorless Cloudy	Very dilute urine	Polyuria, diabetes insipidus
	Phosphates, carbonates	Soluble in dilute acetic acid
	Urates, uric acid	Dissolve at 60° C (140° F) and in alkali
	Leukocytes	
	Red blood cells ("smoky")	Insoluble in dilute acetic acid
	Bacteria, yeasts	Lyse in dilute acetic acid
	Spermatozoa	Insoluble in dilute acetic acid
	Prostatic fluid	Insoluble in dilute acetic acid
	Mucin, mucous threads	May be flocculent
	Calculi, "gravel"	Phosphates, oxalates
	Clumps, pus, tissue	Rectovesical fistula
	Fecal contamination	In acid urine
	Radiographic dye	
Milky	Many neutrophils (pyuria)	Insoluble in dilute acetic acid
	Fat	Nephrosis, crush injury: soluble in ether
	Lipiduria, opalescent	
	Chyluria, milky	Lymphatic obstruction: soluble in ether
	Emulsified paraffin	Vaginal creams
Yellow	Acriflavine	Green fluorescence
Yellow-orange	Concentrated urine	Dehydration, fever
	Urobilin in excess	No yellow foam
	Bilirubin	Yellow foam if sufficient bilirubin
Yellow-green	Bilirubin-biliverdin	Yellow foam
Yellow-brown	Bilirubin-biliverdin	"Beer" brown, yellow foam
Red	Hemoglobin	Positive
	Erythrocytes	Positive } Reagent strip for blood
	Myoglobin	
	Porphyrin	Positive
	Fuscin, aniline dye	May be colorless
	Beets	Foods, candy
	Menstrual contamination	Yellow alkaline, genetic
		Clots, mucus
Red-purple	Porphyrins	May be colorless
Red-brown	Erythrocytes	Acid pH
	Hemoglobin on standing	Muscle injury
	Methemoglobin	Result of unstable hemoglobin
	Myoglobin	
	Bilifuscin (dipyrrole)	
Brown-black	Methemoglobin	Blood, acid pH
	Homogentisic acid	On standing, alkaline; alkaptonuria
	Melanin	On standing, rare
Blue-green	Indicans	Small intestine infections
	Pseudomonas infections	Mouth deodorants
	Chlorophyll	

From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

Elevated: See CORTISOL, PLASMA

URINE CREATININE (24 hr)

Normal range:
Male: 0.8 to 1.8 g/day (7 to 16 mmol/day [CF: 8.840; SMI: 0.1 mmol/day])
Female: 0.6 to 1.6 g/day (5.3 to 14 mmol/day)
NOTE: Useful test as an indicator of completeness of 24-hr urine collection.

URINE CRYSTALS

Uric acid: Acid urine, hyperuricosuria, uric acid nephropathy
Sulfur: Antibiotics containing sulfa
Calcium oxalate: Ethylene glycol poisoning, acid urine, hyperoxaluria
Calcium phosphate: Alkaline urine
Cystine: Cystinuria

TABLE 110 Urine Color Changes with Commonly Used Drugs*

Drug	Color
Alcohol, ethyl	Pale, diuresis
Anthraquinone laxatives (senna, cascara)	Reddish, alkaline; yellow-brown, acid
Chlorzoxazone (Paraflex) (muscle relaxant)	Red
Deferoxamine mesylate (Desferal) (chelates iron)	Red
Ethoxazene (Serenium) (urinary analgesic)	Orange, red
Fluorescein sodium (given IV)	Yellow
Furazolidone (Furoxone) (Tricofuron) (an antibacterial, antiprotozoal nitrofuran)	Brown
Indigo carmine dye (renal function, cystoscopy)	Blue
Iron sorbitol (Jectofer) (possibly other iron compounds forming iron sulfide in urine)	Brown on standing
Levodopa (L-dopa) (for parkinsonism)	Red then brown, alkaline
Mepacrine (Atabrine) (antimalarial) (intestinal worms, *Giardia)*	Yellow
Methocarbamol (Robaxin) (muscle relaxant)	Green-brown
Methyldopa (Aldomet) (antihypertensive)	Darkens; if oxidizing agents present, red to brown
Methylene blue (used to delineate fistulas)	Blue, blue-green
Metronidazole (Flagyl) (for *Trichomonas* infection, amebiasis, *Giardia*)	Darkening, reddish brown
Nitrofurantoin (Furadantin) (antibacterial)	Brown-yellow
Phenazopyridine (Pyridium) (urinary analgesic), also compounded with sulfonamides (e.g., Azo Gantrisin)	Orange-red, acid pH
Phenindione (Hedulin) (anticoagulant) (important to distinguish from hematuria)	Orange, alkaline; color disappears on acidifying
Phenol poisoning	Brown; oxidized to quinones (green)
Phenolphthalein (purgative)	Red-purple, alkaline pH
Phenolsulfonphthalein (also sulfobromophthalein)	Pink-red, alkaline pH
Rifampin (Rifadin, Rimactane) (tuberculosis therapy)	Bright orange-red
Riboflavin (multivitamins)	Bright yellow
Sulfasalazine (Azulfidine) (for ulcerative colitis)	Orange-yellow, alkaline pH

*Other commonly used drugs have been noted to produce color change once or occasionally: amitriptyline (Elavil)—blue-green; phenothiazines—red; triamterene (Dyrenium)—pale blue (blue fluorescence in acid urine).

From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

TABLE 111 Factors That Interfere with Determination of Urinary 5-HIAA

Foods	Drugs
Factors That Produce False-Positive Results	
Avocado	Acetaminophen
Banana	Acetanilid
Chocolate	Caffeine
Coffee	Fluorouracil
Eggplant	Guaifenesin
Pecan	L-Dopa
Pineapple	Melphalan
Plum	Mephenesin
Tea	Methamphetamine
Walnuts	Methocarbamol
	Methysergide maleate
	Phenmetrazine
	Reserpine
	Salicylates
Factors That Cause False-Negative Results	
None	Corticotropin
	p-Chlorophenylalanine
	Chlorpromazine
	Heparin
	Imipramine
	Isoniazid
	Methenamine mandelate
	Methyldopa
	Monoamine oxidase inhibitors
	Phenothiazine
	Promethazine

5-HIAA, 5-Hydroxyindoleacetic acid.

From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, WB Saunders.

URINE EOSINOPHILS

Normal: Absent
Present in: Interstitial nephritis, acute tubular necrosis, urinary tract infection, kidney transplant rejection, hepatorenal syndrome

URINE GLUCOSE (qualitative)

Normal: Absent
Present in: Diabetes mellitus, renal glycosuria (decreased renal threshold for glucose), glucose intolerance

URINE HEMOGLOBIN, FREE

Normal: Absent
Present in: Hemolysis (with saturation of serum haptoglobin binding capacity and renal threshold for tubular absorption of hemoglobin)

URINE HEMOSIDERIN

Normal: Absent
Present in: Paroxysmal nocturnal hemoglobinuria, chronic hemolytic anemia, hemochromatosis, blood transfusion, thalassemias

URINE 5-HYDROXYINDOLE-ACETIC ACID (urine 5-HIAA)

Normal range: 2 to 8 mg/24 hr (10 to 40 μmol/day [CF: 5.23; SMI: 5 μmol/day])
Elevated in: Carcinoid tumors, after ingestion of certain foods (bananas, plums, tomatoes, avocados, pineapples, eggplant, walnuts), drugs (monoamine oxidase inhibitors, phenacetin, methyldopa, glycerol guaiacolate, acetaminophen, salicylates, phenothiazines, imipramine, methocarbamol, reserpine, methamphetamine). See Table 111.

URINE INDICAN

Normal: Absent
Present in: Malabsorption secondary to intestinal bacterial overgrowth

URINE KETONES (semiquantitative)

Normal: Absent
Present in: Diabetic ketoacidosis, alcoholic ketoacidosis, starvation, isopropanol ingestion

URINE METANEPHRINES

Normal range: 0 to 2.0 mg/24 hr (0 to 11.0 μmol/day [CF: 5.458; SMI: 0.5 μmol/day])
Elevated in: Pheochromocytoma, neuroblastoma, drugs (caffeine, phenothiazines, monoamine oxidase inhibitors), stress. Table 112 summarizes medications that may increase metanephrine levels.

URINE MYOGLOBIN

Normal: Absent

TABLE 112 Medications That May Increase Measured Levels of Fractionated Catecholamines and Metanephrines

Tricyclic antidepressants (including cyclobenzaprine)
Levodopa
Drugs containing adrenergic receptor agonists (e.g., decongestants)
Amphetamines
Buspirone and antipsychotic agents
Prochlorperazine
Reserpine
Withdrawal from clonidine and other drugs (e.g., illicit drugs)
Illicit drugs (e.g., cocaine, heroin)
Ethanol

From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, WB Saunders.

TABLE 113 Differentiation of Hematuria, Hemoglobinuria, and Myoglobinuria

Condition	Plasma Findings	Urine Findings
Hematuria	Color—normal	Color—normal, smoky, pink, red, brown
		Erythrocytes—many
		Renal—red blood cell casts
		Protein—marked increase
		Lower urinary tract—no casts
		Protein—present or absent
Hemoglobinuria	Color—pink (early)	Color—pink, red, brown
	Haptoglobin—low	Erythrocytes—occasional
		Pigment casts—occasional
		Protein—present or absent
		Hemosiderin—late
Myoglobinuria	Color—normal	Color—red, brown
	Haptoglobin—normal	Erythrocytes—occasional
	Creatine kinase—marked increase	Dense brown casts—occasional
	Aldolase—increased	Protein—present or absent

From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

Present in: Severe trauma, hyperthermia, polymyositis/dermatomyositis, carbon monoxide poisoning, drugs (narcotic and amphetamine toxicity), hypothyroidism, muscle ischemia

Table 113 differentiates hematuria and hemoglobinuria from myoglobinuria.

URINE NITRITE

Normal: Absent
Present in: Urinary tract infections

URINE OCCULT BLOOD

Normal: Negative
Positive in: Trauma to urinary tract, renal disease (glomerulonephritis, pyelonephritis), renal or ureteral calculi, bladder lesions (carcinoma, cystitis), prostatitis, prostatic carcinoma, menstrual contamination, hematopoietic disorders (hemophilia, thrombocytopenia), anticoagulants, ASA

URINE OSMOLALITY

See OSMOLALITY, URINE

URINE PH

Normal range: 4.6 to 8 (average, 6)
Elevated in: Bacteriuria, vegetarian diet, renal failure with inability to form ammonia, drugs (antibiotics, sodium bicarbonate, acetazolamide)

BOX 33 Urine Potassium in Hypokalemia

Low 24-hour urinary potassium (<25 mEq/day) or low spot urine potassium (<15 mEq/L) or low potassium-to-creatinine ratio (<1.5 mEq/mmol)
GI losses: Vomiting, diarrhea, nasogastric tube
Sweat losses: Extreme heat, cystic fibrosis
Low intake
High 24-hour urinary potassium (>25 mEq/day) or high spot urine potassium (>40 mEq/L) or high potassium-to-creatinine ratio (>1.5 mEq/mmol)
Renal potassium wasting
Diuretics, amphotericin B
Increased mineralocorticoid activity
Excretion of bicarbonate (vomiting, RTA)
Excretion of other nonreabsorbable anion (hippurate, beta-hydroxybutyrate, penicillin derivative)
Transcellular shifts
Hypomagnesemia
Bartter, Gitelman, Liddle syndromes
High 24-hour urinary potassium (>25 mEq/day) and high potassium-to-creatinine ratio (>1.5 mEq/mmol) but low spot urine potassium (<15 mEq/L)
Established AKI (tubular dysfunction ± dilutional)
Primary polydipsia (dilutional)
Other polyuric states (osmotic and water diuresis)

AKI, Acute kidney injury; *GI,* gastrointestinal; *RTA,* renal tubular acidosis.
From Ronco C: *Critical care nephrology*, ed 3, Philadelphia, 2019, Elsevier.

Decreased in: Acidosis (metabolic, respiratory), drugs (ammonium chloride, methenamine mandelate), diabetes mellitus, starvation, diarrhea

URINE PHOSPHATE

Normal range: 0.8 to 2.0 g/24 hr
Elevated in: Acute tubular necrosis (diuretic phase), chronic renal disease, uncontrolled diabetes mellitus, hyperparathyroidism, hypomagnesemia, metabolic acidosis, metabolic alkalosis, neurofibromatosis, adult-onset vitamin D-resistant hypophosphatemic osteomalacia
Decreased in: Acromegaly, acute renal failure, decreased dietary intake, hypoparathyroidism, respiratory acidosis

URINE POTASSIUM

Normal range: 25 to 100 mEq/24 hr (25 to 100 mmol/day [CF: 1; SMI: 1 mmol/day])
Elevated in:
Aldosteronism (primary, secondary), glucocorticoids, alkalosis, renal tubular acidosis, excessive dietary potassium intake
Decreased in:
Acute renal failure, potassium-sparing diuretics, diarrhea, hypokalemia

Box 33 describes urine potassium in hypokalemia.

URINE PROTEIN (quantitative)

Normal range: <150 mg/24 hr (<0.15 g/day [CF: 0.001; SMI: 0.01 g/day])
Elevated in:
Nephrotic syndrome as a result of primary renal diseases
Malignant hypertension
Malignancies: Multiple myeloma, leukemias, Hodgkin disease
Congestive heart failure
Diabetes mellitus
Systemic lupus erythematosus, rheumatoid arthritis
Sickle cell disease
Goodpasture syndrome
Malaria
Amyloidosis, sarcoidosis
Tubular lesions: Cystinosis
Functional (after heavy exercise)
Pyelonephritis
Pregnancy
Constrictive pericarditis
Renal vein thrombosis
Toxic nephropathies: Heavy metals, drugs

Radiation nephritis
Orthostatic (postural) proteinuria
Benign proteinuria: Fever, heat or cold exposure

URINE SEDIMENT

See Fig. 60 for visual evaluation of common abnormalities. Table 114 summarizes characteristics of amorphous and crystalline urinary sediments.

URINE SODIUM (quantitative)

See Table 115 for use of urine electrolytes in the differential diagnosis of hypokalemia. Table 116 describes urine sodium findings in acute kidney injury (AKI).

Normal range: 40 to 220 mEq/day (40 to 220 mmol/day [CF: 1; SMI: 1 mmol/day])

Elevated in: Diuretic administration, high sodium intake, salt-losing nephritis, acute tubular necrosis, vomiting, Addison disease, syndrome of inappropriate antidiuretic hormone secretion, hypothyroidism, congestive heart failure, hepatic failure, chronic renal failure, Bartter syndrome, glucocorticoid deficiency, interstitial nephritis caused by analgesic abuse, mannitol, dextran, or glycerol therapy, milk-alkali syndrome, decreased renin secretion, postobstructive diuresis

Decreased In: Increased aldosterone, glucocorticoid excess, hyponatremia, prerenal azotemia, decreased salt intake

URINE SPECIFIC GRAVITY

Normal range: 1.005 to 1.030

Elevated in: Dehydration, excessive fluid losses (vomiting, diarrhea, fever), x-ray contrast media, diabetes mellitus, congestive heart failure, syndrome of inappropriate antidiuretic hormone secretion, adrenal insufficiency, decreased fluid intake

Decreased in: Diabetes insipidus, renal disease (glomerulonephritis, pyelonephritis), excessive fluid intake or IV hydration

URINE VANILLYLMANDELIC ACID (VMA)

Normal range: <6.8 mg/24 hr (<35 μmol/day [CF: 5.046; SMI: 1 μmol/day])

Elevated in: Pheochromocytoma, neuroblastoma, ganglioblastoma, drugs (isoproterenol, methocarbamol, levodopa, sulfonamides, chlorpromazine), severe stress, after ingestion of bananas, chocolate, vanilla, tea, coffee

Decreased in: Drugs (monoamine oxidase inhibitors, reserpine, guanethidine, methyldopa)

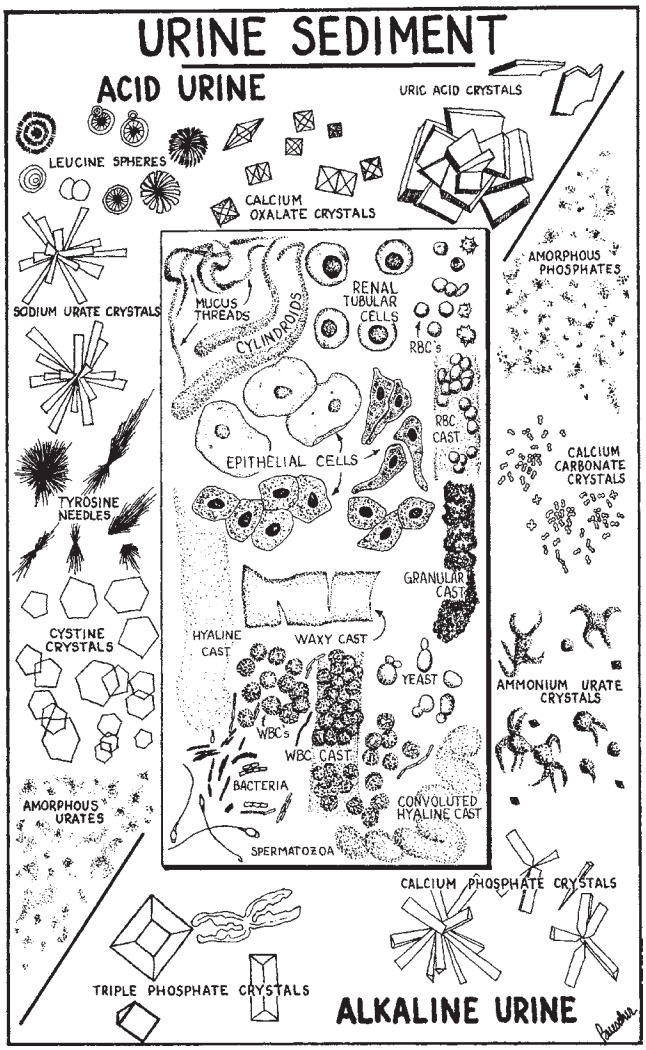

FIG. 60 Microscopic examination of urinary sediment. (From Grigorian Greene M: *The Harriet Lane handbook: a manual for pediatric house officers,* ed 17, St Louis, 2007, Mosby.)

TABLE 114 Characteristics of Amorphous and Crystalline Urinary Sediments

Substance	Description	URINE PH WHERE FOUND			Solubility Characteristics and Comments
		Acid	Neutral	Alkaline	
Ampicillin	Uncommon: from high dose; colorless; long prisms that form clusters, sheaves	+	–	–	
Bilirubin	Reddish brown; amorphous needles, rhombic plates, or cubes; may color uric acid crystals	+	–	–	Soluble in alkali, acid, acetone, and chloroform
Cholesterol	Rare; colorless; flat plate with corner notch; accompanies fatty casts and oval fat bodies	+	+	–	Very soluble in chloroform, ether, and hot alcohol
Calcium carbonate	Colorless; small granules in pairs, fours; spheres; rarely needles	–	+	+	Soluble in acetic acid with effervescence
Calcium oxalate	Dihydrate: common; colorless; small refractile octahedron Monohydrate: uncommon; dumbbell and ovoid rectangle	+	+	–	Soluble in dilute HCl
Cystine	Colorless; hexagonal plates, often laminated; rapidly destroyed by bacteria; may be confused with uric acid, but cystine is soluble in dilute hydrochloric acid	+	–	–	Soluble in alkali (especially ammonia) and dilute HCl; insoluble in boiling water, acetic acid, alcohol, ether; apply cyanide-nitroprusside reaction
Hematin	Small, biconvex "whetstone" seen with hemoglobinuria	+	–	–	

Continued

TABLE 114 Characteristics of Amorphous and Crystalline Urinary Sediments—cont'd

Substance	Description	URINE PH WHERE FOUND			Solubility Characteristics and Comments
		Acid	Neutral	Alkaline	
Hemosiderin	Golden brown; granules in clumps, in cells, casts	+	+	–	Blue with Prussian blue
Hippuric acid	Rare; colorless, needles, rhombic plates and four-sided prisms; distinguish from phosphates	+	+	+	Soluble with hot water and alkali; insoluble in acetic acid
Indigotin	Rare; blue; amorphous or small crystals; colors other crystals	+	+	+	Very soluble in chloroform; soluble in ether; insoluble in acetone
Phosphates					
Amorphous phosphate (magnesium, calcium)	Colorless; fine, granular precipitate	–	+	+	Insoluble with heat; soluble with acetic acid, dilute HCl
Calcium hydrogen phosphate	Less common; colorless, star-shaped or long, thin prisms or needles; form rosettes	sl	+	sl	Slightly soluble in dilute acetic acid, soluble in dilute HCl
Triple phosphate (ammonium, magnesium)	Common form: colorless; three- to six-sided prisms, "coffin lids" Less often: Flat, fern leaf form, sheets, flakes	–	+	+	Soluble in dilute acetic acid
Radiographic media (meglumine diatrizoate)	Intravenous: Colorless; thin, rhombic plates, some with notch, resemble cholesterol plates; elongated crystals Retrograde: Colorless; long, pointed crystals	+	–	–	Soluble in 10% NaOH: Insoluble in ether and chloroform; high specific gravity in urine: polarizes with interference colors
Sulfonamides					
Acetylsulfadiazine	Wheat sheaves with eccentric binding	+	–	–	
Acetylsulfamethoxazole	Brown; dense spheres or irregular divided spheres	+	–	–	
Sulfadiazine	Brown; dense globules	+	–	–	Soluble in acetone
Tyrosine	Rare; colorless or yellow, appears black with focusing; fine silky needles in sheaves or rosettes	+	–	–	Soluble in alkali, dilute mineral acid, relatively heat soluble; insoluble in alcohol, ether
Urates					
Amorphous (calcium, magnesium, sodium, potassium)	Common; colorless to yellow-brown; amorphous, granular precipitate	+	+	–	Soluble in dilute alkali; soluble at 60 °C (140 °F) or lower; change to uric acid crystal with concentrated HCl or acetic acid
Monosodium urate	Colorless; needles or amorphous precipitate	+	–	–	
Urates (sodium, potassium, ammonium)	Brown; small, spherical; clusters resemble biurates	sl	+	–	Soluble at 60 °C (140 °F); change to uric acid with glacial acetic acid
Ammonium biurate	Common in "old" urine; dark yellow or brown; spheres or "thorn apples" (spheres with horns)	–	+	+	Soluble at 60° C (140 °F) with acetic acid; soluble strong alkali; change to uric acid with concentrated hydrochloric or acetic acid
Uric acid	Common; yellow, red-brown, brown; large variety of shapes: rhombic, four-sided plates, rosettes, "whetstones" lemon shapes; rarely, colorless hexagonals	+	–	–	Soluble in alkali: Insoluble in alcohol and acids; polarizes with interference colors
Xanthine	Rare; colorless; small, rhombic plates	+	+	–	Soluble in alkali; soluble with heat; insoluble in acetic acid

HCl, Hydrochloride; *sl,* slight.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

TABLE 115 Urine Electrolytes* in the Differential Diagnosis of Hypokalemia

Condition	URINE ELECTROLYTE	
	Na^+	Cl^-
Vomiting		
Recent	High†	Low‡
Remote	Low	Low
Diuretics		
Recent	High	High
Remote	Low	Low
Diarrhea or Laxative Abuse	Low	High
Bartter or Gitelman Syndrome	High	High

*Do not use the urine electrolytes in this fashion during polyuric states.
†High = urine concentration >15 mmol/L.
‡Low = urine concentration <15 mmol/L.
From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, WB Saunders.

TABLE 116 Urinalysis Findings in Acute Kidney Injury (AKI)

Etiologic Disorder	Urine Chemistry	Urine Sediment
Prerenal	U_{Na}<20 mmol/L FE_{Na}<1% FE_{urea}<35%	Normal or nearly normal (hyaline casts and rare granular casts)
Acute tubular necrosis	U_{Na}>40 mmol/L FE_{Na}>2% FE_{urea}>60%	Renal tubular epithelial cells, epithelial cell casts, coarse pigmented (muddy brown) casts
Acute interstitial nephritis	Variable; U_{Na} may be >40 mmol/L, FE_{Na} may be >2%	Red blood cells, white blood cells, white blood cell casts, eosinophils
Acute glomerulonephritis	Variable; U_{Na} may be <20 mmol/L, FE_{Na} may be <1%	Red blood cells (dysmorphic), red blood cell casts
Acute vascular disease	Variable; U_{Na} may be <20 mmol/L, FE_{Na} may be <1%	Red blood cells, red blood cell casts in HUS/TTP, eosinophils in atheroembolic disease
Crystal-associated AKI	Variable	Crystalluria Uric acid crystals in tumor lysis syndrome Calcium oxalate crystals in ethylene glycol ingestion Drug crystals (acyclovir, methotrexate, indinavir, triamterene, sulfadiazine)
Obstructive	Variable; early U_{Na} may be <20 mmol/L, FE_{Na} may be <1%; late U_{Na} may be >40 mmol/L, FE_{Na} may be >2%	Normal or red blood cells, white blood cells and crystals

FE_{Na}, Fractional excretion of sodium; *FE_{urea},* fractional excretion of urea; *HUS,* hemolytic-uremic syndrome; *TTP,* thrombotic thrombocytopenic purpura; *U_{Na},* urine sodium concentration.
From Parrillo JE, Dellinger RP: *Critical care medicine, principles of diagnosis and management in the adult,* ed 4, Philadelphia, 2014, Elsevier.

VARICELLA-ZOSTER VIRUS (VZV) SEROLOGY

Test description: Test can be performed on whole blood, tissue, skin lesions, and CSF

VASOACTIVE INTESTINAL PEPTIDE (VIP)

Normal: <50 pg/ml
Elevated in: Pancreatic VIP-omas, neuroblastoma, pancreatic islet cell hyperplasia, liver disease, multiple endocrine neoplasia (MEN) I, ganglioneuroma, ganglioneuroblastoma

VDRL

Normal range: Negative
Positive test: Syphilis, other treponemal diseases (yaws, pinta, bejel)

NOTE: A false-positive test may be seen in patients with systemic lupus erythematosus and other autoimmune diseases, infectious mononucleosis, HIV, atypical pneumonia, malaria, leprosy, typhus fever, rat-bite fever, relapsing fever.

NOTE: See Table 117 for interpretation of serologic tests for syphilis.

VISCOSITY (serum)

Normal range: 1.4 to 1.8 relative to water (1.10-1.22 centipoise)

TABLE 117 Interpretation of Serologic Tests for Syphilis*

Nontreponemal Tests	Treponemal Tests	Interpretation of Finding: Is Syphilis Present?*
Nonreactive	Nonreactive	Early primary syphilis is not ruled out by negative serologic tests. Early syphilis is present in 13%-30% of patients who have a negative microhemagglutination *Treponema pallidum* test; in about 30% of patients who present with chancre but have a nonreactive reagin test; and in about 10% of patients who have a negative FTA-ABS test. Late syphilis is present in a very small fraction of patients. Adequately treated syphilis in remote past may produce these results, but treponemal tests usually remain reactive.
	Reactive	Observed in about 10% of patients with chancre. The treponemal tests may turn positive shortly before the reagin tests. Reagin tests repeated after several days are generally positive. In adequately treated early syphilis, the reagin test may return to nonreactive within 1-2 yr, whereas the treponemal tests generally do not. Late syphilis is not ruled out by a negative reagin test. The sensitivity of the reagin tests is lower than that of treponemal tests in untreated late syphilis. In secondary syphilis, rarely, a highly reactive serum appears negative when tested undiluted with a reagin test because flocculation is inhibited by relative antibody excess. Not reported to occur with treponemal tests. Quantitative reagin tests are positive. False-positive treponemal tests occur in 40% of patients with Lyme disease.
Reactive	Nonreactive borderline (FTA-ABS)	Finding is not diagnostic of syphilis but constitutes a classic biologic false-positive reaction. Not diagnostic of syphilis; most patients (90%) with this pattern do not develop clinical or serologic evidence of syphilis. Repeat test is indicated. Chronic borderline results are associated with a variety of conditions other than syphilis.
	Beaded (FTA-ABS)	Not diagnostic of syphilis. Seen with collagen vascular disease.
	Reactive	Findings diagnostic of syphilis or other treponemal disease. In adequately treated syphilis, one would expect (1) a sustained fourfold drop in titer of reagin test, although reagin test may remain positive after adequate therapy; (2) treponemal tests remain positive after adequate therapy. Concurrent false-positive results on both nontreponemal and treponemal tests could occur in rare instances. It may be impossible to rule out syphilis in an individual with this test profile.

FTA-ABS, Fluorescent treponemal antibody, absorbed.
*Serologic data must always be interpreted in the light of a total clinical evaluation. Diagnosis based on serologic criteria alone is fraught with error. Serologic tests apparently in conflict with clinical diagnosis should be confirmed by repetition or possibly referral to a reference laboratory.
From Stein JH (ed): *Internal medicine,* ed 4, St Louis, 1994, Mosby.

TABLE 116 Urinalysis Findings in Acute Kidney Injury (AKI)

Etiologic Disorder	Urine Chemistry	Urine Sediment
Prerenal	U_{Na}<20 mmol/L FE_{Na}<1% FE_{urea}<35%	Normal or nearly normal (hyaline casts and rare granular casts)
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Acute vascular disease	Variable; U_{Na} may be <20 mmol/L, FE_{Na} may be <1%	Red blood cells, red blood cell casts in HUS/TTP, eosinophils in atheroembolic disease
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Obstructive	Variable; early U_{Na} may be <20 mmol/L, FE_{Na} may be <1%; late U_{Na} may be >40 mmol/L, FE_{Na} may be >2%	Normal or red blood cells, white blood cells and crystals

FE_{Na}, Fractional excretion of sodium; *FE_{urea},* fractional excretion of urea; *HUS,* hemolytic-uremic syndrome; *TTP,* thrombotic thrombocytopenic purpura; *U_{Na},* urine sodium concentration.
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NOTE: A false-positive test may be seen in patients with systemic lupus erythematosus and other autoimmune diseases, infectious mononucleosis, HIV, atypical pneumonia, malaria, leprosy, typhus fever, rat-bite fever, relapsing fever.

NOTE: See Table 117 for interpretation of serologic tests for syphilis.

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TABLE 117 Interpretation of Serologic Tests for Syphilis*

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	Reactive	Observed in about 10% of patients with chancre. The treponemal tests may turn positive shortly before the reagin tests. Reagin tests repeated after several days are generally positive. In adequately treated early syphilis, the reagin test may return to nonreactive within 1-2 yr, whereas the treponemal tests generally do not. Late syphilis is not ruled out by a negative reagin test. The sensitivity of the reagin tests is lower than that of treponemal tests in untreated late syphilis. In secondary syphilis, rarely, a highly reactive serum appears negative when tested undiluted with a reagin test because flocculation is inhibited by relative antibody excess. Not reported to occur with treponemal tests. Quantitative reagin tests are positive. False-positive treponemal tests occur in 40% of patients with Lyme disease.
Reactive	Nonreactive borderline (FTA-ABS)	Finding is not diagnostic of syphilis but constitutes a classic biologic false-positive reaction. Not diagnostic of syphilis; most patients (90%) with this pattern do not develop clinical or serologic evidence of syphilis. Repeat test is indicated. Chronic borderline results are associated with a variety of conditions other than syphilis.
	Beaded (FTA-ABS)	Not diagnostic of syphilis. Seen with collagen vascular disease.
	Reactive	Findings diagnostic of syphilis or other treponemal disease. In adequately treated syphilis, one would expect (1) a sustained fourfold drop in titer of reagin test, although reagin test may remain positive after adequate therapy; (2) treponemal tests remain positive after adequate therapy. Concurrent false-positive results on both nontreponemal and treponemal tests could occur in rare instances. It may be impossible to rule out syphilis in an individual with this test profile.

FTA-ABS, Fluorescent treponemal antibody, absorbed.
*Serologic data must always be interpreted in the light of a total clinical evaluation. Diagnosis based on serologic criteria alone is fraught with error. Serologic tests apparently in conflict with clinical diagnosis should be confirmed by repetition or possibly referral to a reference laboratory.
From Stein JH (ed): *Internal medicine,* ed 4, St Louis, 1994, Mosby.

BOX 34 Etiopathophysiologic Classification of Cobalamin Deficiency

- Nutritional cobalamin deficiency (insufficient cobalamin intake): Vegetarians, poverty-imposed near-vegetarians, breastfed infants of mothers with pernicious anemia
- Abnormal intragastric events (inadequate proteolysis of food cobalamin): Atrophic gastritis, hypochlorhydria, proton pump inhibitors, H_2 blockers
- Loss/atrophy of gastric oxyntic mucosa (deficient intrinsic factor [IF] molecules): Total or partial gastrectomy, adult and juvenile pernicious anemia, caustic destruction (lye)
- Abnormal events in the small bowel lumen
  - Inadequate pancreatic protease (R factor-cobalamin not degraded, cobalamin not transferred to IF)
  - Insufficient pancreatic protease: Pancreatic insufficiency
  - Inactivation of pancreatic protease: Zollinger-Ellison syndrome
  - Usurping of luminal cobalamin (inadequate binding of cobalamin to IF)
  - By bacteria-stasis syndromes (blind loops, pouches of diverticulosis, strictures, fistulas, anastomosis), impaired bowel motility (scleroderma), hypogammaglobulinemia
  - By *Diphyllobothrium latum* (fish tapeworm)
- Disorders of ileal mucosa/IF-cobalamin receptors (IF-cobalamin not bound to IF-cobalamin receptors [cubam receptors])
  - Diminished or absent cubam receptors: Ileal bypass/resection/fistula
  - Abnormal mucosal architecture/function: Tropical/nontropical sprue, Crohn disease, tuberculous ileitis, amyloidosis
  - Cubam receptor defects: Imerslund-Gräsbeck syndrome
  - Drug-effects: Metformin, cholestyramine, colchicine, neomycin
- Disorders of plasma cobalamin transport (transcobalamin [TCII]-cobalamin not delivered to TCII receptors): Congenital TCII deficiency, defective binding of TCII-cobalamin to TCII receptors (rare)
  - Metabolic disorders (cobalamin not used by cell)
  - Inborn enzyme errors: cblA to cblG disorders
  - Acquired disorders (cobalamin inactivated by irreversible oxidation): Nitrous oxide

From Hoffman R: *Hematology: Basic principles and practice,* ed 6, Philadelphia, 2013, WB Saunders.

Elevated in: Monoclonal gammopathies (Waldenström macroglobulinemia, multiple myeloma), hyperfibrinogenemia, systemic lupus erythematosus, rheumatoid arthritis, polycythemia, leukemia

VITAMIN B_{12} (cobalamin)

See Box 34 for etiopathophysiologic classification of cobalamin deficiency. Causes of false-positive and false-negative serum cobalamin levels are summarized in Table 118. Table 119 describes causes of megaloblastosis not responding to therapy with cobalamin or folate. Table 120 summarizes indications for prophylaxis with cobalamin or folate.

Normal

190 to 900 ng/ml

Causes of vitamin B_{12} deficiency:

a. Pernicious anemia (antibodies against intrinsic factor and gastric parietal cells)
b. Dietary (strict lacto-ovo vegetarians, food faddists)
c. Malabsorption (achlorhydria, gastrectomy, ileal resection, pancreatic insufficiency, drugs [omeprazole, cholestyramine])

- Falsely low levels occur in patients with severe folate deficiency, in patients using high doses of ascorbic acid, and when cobalamin levels are measured after nuclear medicine studies (radioactivity interferes with cobalamin radioimmunoassay).
- Falsely high or normal levels in patients with cobalamin deficiency can occur in severe liver disease and chronic granulocytic leukemia.
- The absence of anemia or macrocytosis does not exclude the diagnosis of cobalamin deficiency.

TABLE 118 Serum Cobalamin: False-Positive and False-Negative Test Results

Falsely Low Serum Cobalamin in the Absence of True Cobalamin Deficiency
Folate deficiency (one third of patients)
Multiple myeloma
TCI deficiency
Megadose vitamin C therapy
Falsely Raised Cobalamin Levels in the Presence of True Deficiency*
Cobalamin binders (TCI and II) increased (e.g., myeloproliferative states, hepatomas, and fibrolamellar hepatic tumors)
TCII-producing macrophages are activated (e.g., autoimmune diseases, monoblastic leukemias and lymphomas)
Release of cobalamin from hepatocytes (e.g., active liver disease)
High serum anti-IF antibody titer

IF, Intrinsic factor; *TC,* transcobalamin.

*Although a low serum cobalamin level is not synonymous with cobalamin deficiency, 5% of patients with true cobalamin deficiency have low-normal cobalamin levels, a potentially serious problem because the patient's underlying cobalamin deficiency will progress if uncorrected.

From Hoffman R et al: *Hematology, basic principles and practice*, ed 6, Philadelphia, 2013, WB Saunders.

TABLE 119 Causes of Megaloblastosis Not Responding to Therapy with Cobalamin or Folate

Wrong Diagnosis
Combined folate and cobalamin deficiencies being treated with only one vitamin
Associated iron deficiency
Associated hemoglobinopathy (e.g., sickle cell disease, thalassemia)
Associated anemia of chronic disease
Associated hypothyroidism

From Hoffman R: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 120 Indications for Prophylaxis with Cobalamin or Folate

Prophylaxis with Cobalamin
Infants on specialized diets[a]
Premature infants
Infants of mothers with pernicious anemia[a]
Infants and children of mothers with nutritional cobalamin deficiency
Vegetarianism and poverty-imposed near-vegetarianism[a]
Total gastrectomy[b]
Prophylaxis with Folic Acid[c]
All women contemplating pregnancy (at least 400μg/day)[d]
Pregnancy and lactation, premature infants
Mothers at risk for delivery of infants with neural tube defects[e,f]
Hemolytic anemias/hyperproliferative hematologic states
Patients with rheumatoid arthritis or psoriasis on therapy with methotrexate[g]
Patients on antiepileptic drugs
Patients with ulcerative colitis

[a]For vegetarians, prophylaxis with cobalamin (5- to 10-μg tablet/day) orally should suffice. In all other conditions involving any abnormality of cobalamin absorption, cobalamin tablets of 1000μg/day should be administered orally to ensure that cobalamin transport by passive diffusion across the intestine is sufficient to meet daily needs.

[b]Consider late development of cobalamin deficiency and iron malabsorption (prophylaxis with oral cobalamin and iron).

[c]Ensure that the patient does not have a cobalamin deficiency before initiating long-term folate prophylaxis.

[d]For prevention of first occurrence of neural tube defects

[e]Previous delivery of a child with neural tube defects (e.g., anencephaly, spina bifida, meningocele) imparts a 10-fold greater risk for subsequent delivery of infant with neural tube defects.

[f]Folic acid (4 mg/day) administered periconceptionally and throughout the first trimester

[g]To reduce toxicity of the antifolate

From Hoffman R: *Hematology, basic principles and practice*, ed 7, Philadelphia, 2018, Elsevier.

TABLE 121 Serum Calcium, Phosphate, and Vitamin D Levels in Various Disorders

Disorder	Calcium	25(OH)D	1,25(OH)D	Phosphate
25(OH)D intoxication	High	High	Low, normal	Normal, high
Primary hyperparathyroidism	High	Normal	Normal, high	Low
Secondary hyperparathyroidism	Low	Low, normal, high	Low, normal, high	Low, normal, high
Tertiary hyperparathyroidism	Normal, high*	Low, normal, high	Low, normal, high	Low, normal, high
Malignancy	High	Normal	Low, normal	Low
Vitamin D deficiency	Low	Low	Low, normal, high	Low
Renal failure	Low	Normal	Low	High
Hyperphosphatemia	Low	Normal	Low	High
Vitamin D rickets type I, II	Low	Normal, high	Low, normal, high	Low
Granulomatous diseases (sarcoid/TB)	High	Low, normal, high	High	Normal, high
Postmenopausal osteoporosis	Normal	Normal	Normal	Normal
Senile osteoporosis	Normal	Normal	Normal	Normal
Osteomalacia	Low, normal	Low, normal	Low	Low, normal, high

*Calcium may be normal in the setting of concurrent $1,25(OH)_2D_3$ deficiency.
TB, Tuberculosis.
From McPherson RA, Pincus MR: *Henry's clinical diagnosis and management by laboratory methods*, ed 23, St Louis, 2017, Elsevier.

VITAMIN D, 1,25 DIHYDROXY CALCIFEROL

Normal: 16 to 65 pg/ml
Elevated in: Tumor calcinosis, primary hyperparathyroidism, sarcoidosis, tuberculosis, idiopathic hypercalciuria
Decreased in: Nutritional deficiency, postmenopausal osteoporosis, chronic renal failure, hypoparathyroidism, tumor-induced osteomalacia, rickets, elevated blood lead levels. Table 121 compares vitamin D levels in various disorders. Fig. 61 illustrates vitamin D physiology.

VITAMIN K

Normal: 0.10 to 2.20 ng/ml
Decreased in: Primary biliary cirrhosis, anticoagulants, antibiotics, cholestyramine, GI disease, pancreatic disease, cystic fibrosis, obstructive jaundice, hypoprothrombinemia, hemorrhagic disease of the newborn

VON WILLEBRAND FACTOR

Normal: Levels vary according to blood type; blood type O: 50 to 150 U/dl; blood type non-O: 90 to 200 U/dl
Decreased in: von Willebrand disease (however, in type II von Willebrand disease the antigen may be normal but the function is impaired)

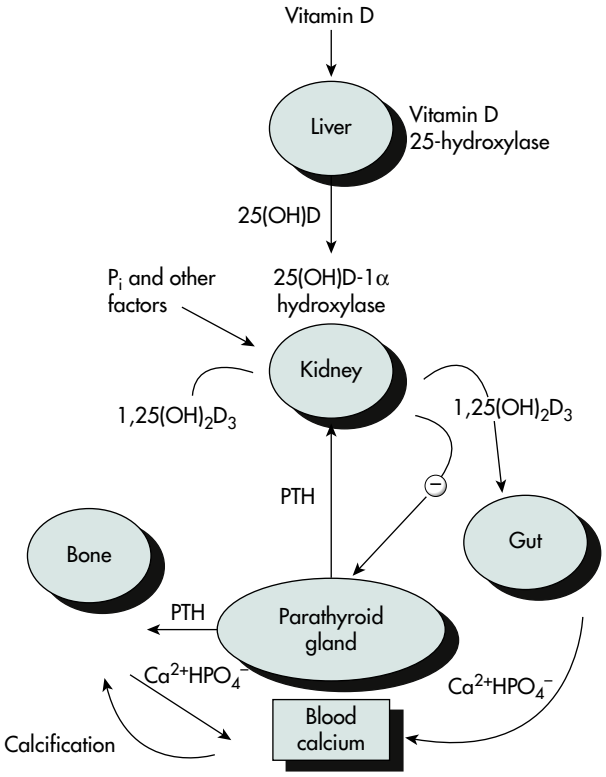


FIG. 61 Vitamin D physiology. P_i, Inorganic phosphate; *PTH,* parathyroid hormone. (From Ronco C: *Critical care nephrology*, ed 3, Philadelphia, 2019, Elsevier.)

IMMUNIZATIONS AND CHEMOPROPHYLAXIS

Childhood and Adolescent Immunizations

TABLE 1 Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger—United States, 2020. (For those who fall behind or start late, see the catch-up schedule [Table 2])

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the divided bars. To determine minimum intervals between doses, see the catch-up schedule (Table 2). School entry and adolescent vaccine age groups are shaded in gray.

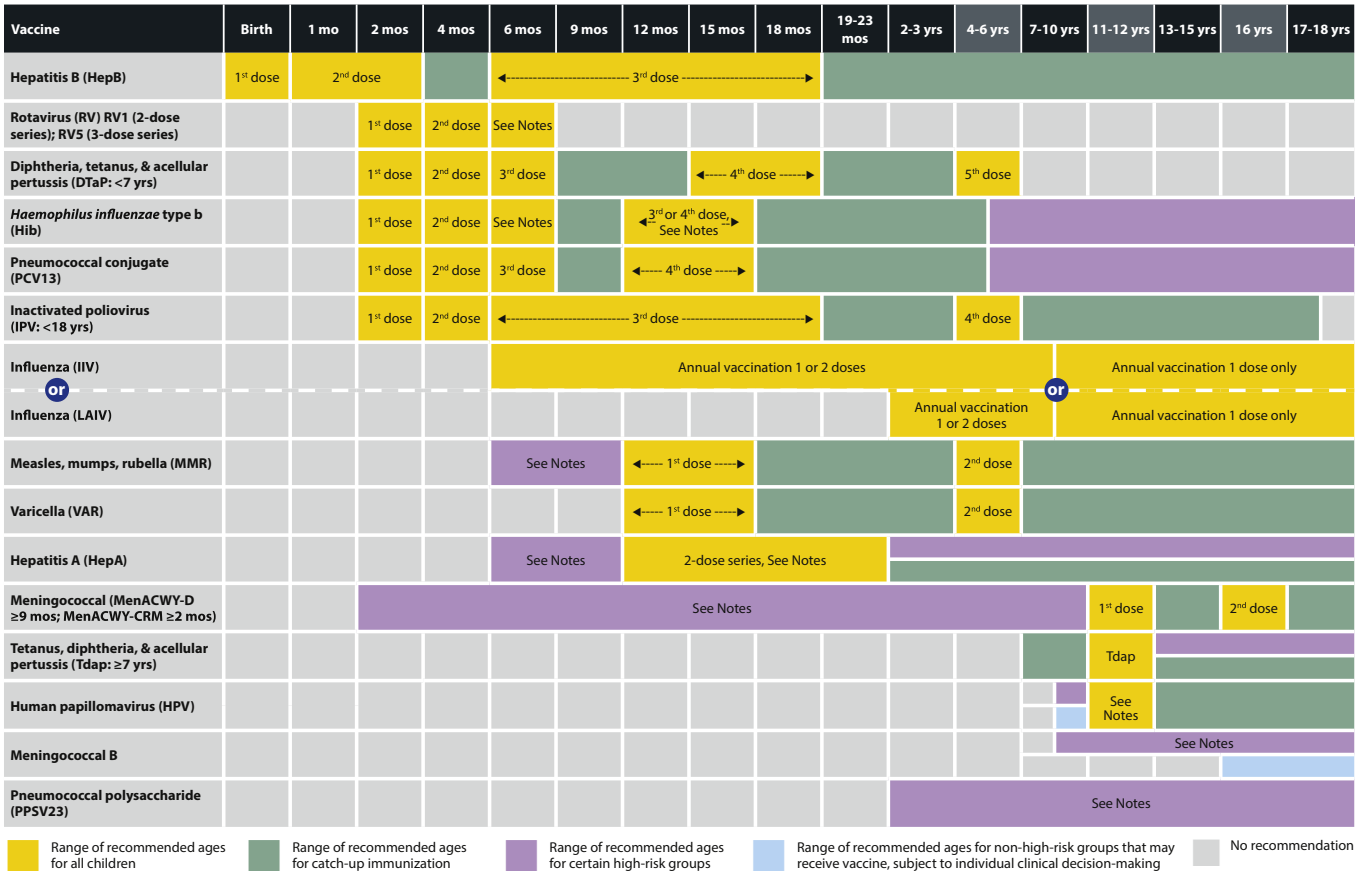


TABLE 2 Catch-up Immunization Schedule for Persons Aged 4 Months Through 18 Years Who Start Late or Who Are More Than 1 Month Behind—United States, 2020

The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. Always use this table in conjunction with Table 1 and the footnotes that follow.

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Children age 4 months through 6 years					
Hepatitis B	Birth	**4 weeks**	**8 weeks *and* at least 16 weeks after first dose.** Minimum age for the final dose is 24 weeks.		
Rotavirus	6 weeks Maximum age for first dose is 14 weeks, 6 days	**4 weeks**	**4 weeks** Maximum age for final dose is 8 months, 0 days.		
Diphtheria, tetanus, and acellular pertussis	6 weeks	**4 weeks**	**4 weeks**	**6 months**	**6 months**
Haemophilus influenzae type b	6 weeks	**No further doses needed** if first dose was administered at age 15 months or older. **4 weeks** if first dose was administered before the 1st birthday. **8 weeks (as final dose)** if first dose was administered at age 12 through 14 months.	**No further doses needed** if previous dose was administered at age 15 months or older. **4 weeks** if current age is younger than 12 months ***and*** first dose was administered at younger than age 7 months, ***and*** at least 1 previous dose was PRP-T (ActHib, Pentacel, Hiberix) or unknown. **8 weeks *and* age 12 through 59 months (as final dose)** if current age is younger than 12 months ***and*** first dose was administered at age 7 through 11 months; OR if current age is 12 through 59 months ***and*** first dose was administered before the 1st birthday, ***and*** second dose administered at younger than 15 months; OR if both doses were PRP-OMP (PedvaxHIB; Comvax) ***and*** were administered before the 1st birthday.	**8 weeks (as final dose)** This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal conjugate	6 weeks	**No further doses needed** for healthy children if first dose was administered at age 24 months or older. **4 weeks** if first dose administered before the 1st birthday. **8 weeks (as final dose for healthy children)** if first dose was administered at the 1st birthday or after.	**No further doses needed** for healthy children if previous dose administered at age 24 months or older. **4 weeks** if current age is younger than 12 months and previous dose given at <7 months old. **8 weeks (as final dose for healthy children)** if previous dose given between 7-11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was given before age 12 months.	**8 weeks (as final dose)** This **dose** only necessary for children age 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus	6 weeks	**4 weeks**	4 weeks if current age is < 4 years. 6 months (as final dose) if current age is 4 years or older.	**6 months** (minimum age 4 years for final dose).	
Measles, mumps, rubella	12 months	**4 weeks**			
Varicella	12 months	**3 months**			
Hepatitis A	12 months	**6 months**			
Meningococcal	2 months MenACWY-CRM 9 months MenACWY-D	**8 weeks**	See Notes	See Notes	
Children and adolescents age 7 through 18 years					
Meningococcal	Not Applicable (N/A)	**8 weeks**			
Tetanus, diphtheria; tetanus, diphtheria, and acellular pertussis	7 years	**4 weeks**	**4 weeks** if first dose of DTaP/DT was administered before the 1st birthday. **6 months (as final dose)** if first dose of DTaP/DT or Tdap/Td was administered at or after the 1st birthday.	**6 months** if first dose of DTaP/DT was administered before the 1st birthday.	
Human papillomavirus	9 years	**Routine dosing intervals are recommended.**			
Hepatitis A	N/A	**6 months**			
Hepatitis B	N/A	**4 weeks**	**8 weeks *and*** at least 16 weeks after first dose.		
Inactivated poliovirus	N/A	**4 weeks**	**6 months** A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.	A fourth dose of IPV is indicated if all previous doses were administered at <4 years or if the third dose was administered <6 months after the second dose.	
Measles, mumps, rubella	N/A	**4 weeks**			
Varicella	N/A	**3 months** if younger than age 13 years. **4 weeks** if age 13 years or older.			

Footnotes — Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2020

For vaccine recommendations for persons 19 years of age and older, see the Recommended Adult Immunization Schedule.

Additional information

- Consult relevant ACIP statements for detailed recommendations at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For information on contraindications and precautions for the use of a vaccine, consult the General Best Practice Guidelines for Immunization and relevant ACIP statements at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For calculating intervals between doses, 4 weeks = 28 days. Intervals of ≥4 months are determined by calendar months.
- Within a number range (e.g., 12–18), a dash (–) should be read as "through."
- Vaccine doses administered ≤4 days before the minimum age or interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum age or minimum interval should not be counted as valid and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see Table 3-1, Recommended and minimum ages and intervals between vaccine doses, in General Best Practice Guidelines for Immunization at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html.
- Information on travel vaccine requirements and recommendations is available at wwwnc.cdc.gov/travel/.
- For vaccination of persons with immunodeficiencies, see Table 8-1, Vaccination of persons with primary and secondary immunodeficiencies, in General Best Practice Guidelines for Immunization at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html, and Immunization in Special Clinical Circumstances (In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. R*ed Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:67–111).
- For information regarding vaccination in the setting of a vaccine-preventable disease outbreak, contact your state or local health department.
- The National Vaccine Injury Compensation Program (VICP) is a no-fault alternative to the traditional legal system for resolving vaccine injury claims. All routine child and adolescent vaccines are covered by VICP except for pneumococcal polysaccharide vaccine (PPSV23). For more information, see www.hrsa.gov/vaccinecompensation/index.html.

1. Diphtheria, tetanus, and pertussis (DTaP) vaccination (minimum age: 6 weeks [4 years for Kinrix or Quadracel])

Routine vaccination

- 5-dose series at 2, 4, 6, 15–18 months, 4–6 years
  - **Prospectively:** Dose 4 may be given as early as age 12 months if at least 6 months have elapsed since dose 3.
  - **Retrospectively:** A 4th dose that was inadvertently given as early as 12 months may be counted if at least 4 months have elapsed since dose 3.

Catch-up vaccination

- Dose 5 is not necessary if dose 4 was administered at age 4 years or older.
- For other catch-up guidance, see Table 2.

2. *Haemophilus influenzae* type b vaccination

(minimum age: 6 weeks)

Routine vaccination

- **ActHIB, Hiberix, or Pentacel:** 4-dose series at 2, 4, 6, 12–15 months
- **PedvaxHIB:** 3-dose series at 2, 4, 12–15 months

Catch-up vaccination

- **Dose 1 at 7–11 months:** Administer dose 2 at least 4 weeks later and dose 3 (final dose) at 12–15 months or 8 weeks after dose 2 (whichever is later).
- **Dose 1 at 12–14 months:** Administer dose 2 (final dose) at least 8 weeks after dose 1.
- **Dose 1 before 12 months and dose 2 before 15 months:** Administer dose 3 (final dose) 8 weeks after dose 2.
- **2 doses of PedvaxHIB before 12 months:** Administer dose 3 (final dose) at 12–59 months and at least 8 weeks after dose 2.
- **Unvaccinated at 15–59 months:** 1 dose
- For other catch-up guidance, see Table 2.

Special situations

- **Chemotherapy or radiation treatment:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Doses administered within 14 days of starting therapy or during therapy should be repeated at least 3 months after therapy completion.
- **Hematopoietic stem cell transplant (HSCT):**
  - 3-dose series 4 weeks apart starting 6 to 12 months after successful transplant regardless of Hib vaccination history
- **Anatomic or functional asplenia (including sickle cell disease):**
  12–59 months
  - Unvaccinated or only 1 dose before 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before 12 months:1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5 years or older*
  - 1 dose
- **Elective splenectomy:**
  Unvaccinated persons age 15 months or older*
  - 1 dose (preferably at least 14 days before procedure)
- **HIV infection:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5–18 years*
  - 1 dose
- **Immunoglobulin deficiency, early component complement deficiency:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

**Unvaccinated* = Less than routine series (through 14 months) OR no doses (14 months or older)

3. Hepatitis A vaccination

(minimum age: 12 months for routine vaccination)

Routine vaccination

- 2-dose series (**Havrix** 6–12 months apart or **Vaqta** 6–18 months apart, minimum interval 6 months); a series begun before the 2nd birthday should be completed even if the child turns 2 before the second dose is administered.

Catch-up vaccination

- Anyone 2 years of age or older may receive HepA vaccine if desired. Minimum interval between doses: 6 months
- Adolescents 18 years and older may receive the combined HepA and HepB vaccine, **Twinrix**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (0, 7, and 21–30 days, followed by a dose at 12 months).

International travel

- Persons traveling to or working in countries with high or intermediate endemic hepatitis A (wwwnc.cdc.gov/travel/):
  - **Infants age 6–11 months:** 1 dose before departure; revaccinate with 2 doses, separated by 6–18 months, between 12 to 23 months of age.
  - **Unvaccinated age 12 months and older:** 1st dose as soon as travel considered

Special situations

At risk for hepatitis A infection: 2-dose series as above

- **Chronic liver disease**
- **Clotting factor disorders**
- **Men who have sex with men**
- **Injection or noninjection drug use**
- **Homelessness**
- **Work with hepatitis A virus** in research laboratory or nonhuman primates with hepatitis A infection

- **Travel** in countries with high or intermediate endemic hepatitis A
- **Close, personal contact with international adoptee** (e.g., household or regular babysitting) in first 60 days after arrival from country with high or intermediate endemic hepatitis A (administer dose 1 as soon as adoption is planned, at least 2 weeks before adoptee's arrival)

4. **Hepatitis B vaccination**
(minimum age: birth)

Birth dose (monovalent HepB vaccine only)
- **Mother is HBsAg-negative:** 1 dose within 24 hours of birth for **all** medically stable infants ≥2,000 grams. Infants <2,000 grams: administer 1 dose at chronological age 1 month or hospital discharge.
- **Mother is HBsAg-positive:**
  - Administer **HepB vaccine** and **0.5 mL of hepatitis B immune globulin (HBIG)** (at separate anatomic sites) within 12 hours of birth, regardless of birth weight. For infants <2,000 grams, administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose.
- **Mother's HBsAg status is unknown:**
  - Administer **HepB vaccine** within 12 hours of birth, regardless of birth weight.
  - For infants <2,000 grams, administer **0.5 mL of HBIG** in addition to HepB vaccine within 12 hours of birth. Administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Determine mother's HBsAg status as soon as possible. If mother is HBsAg-positive, administer **0.5 mL of HBIG** to infants ≥2,000 grams as soon as possible, but no later than 7 days of age.

Routine series
- 3-dose series at 0, 1–2, 6–18 months (use monovalent HepB vaccine for doses administered before age 6 weeks)
- Infants who did not receive a birth dose should begin the series as soon as feasible (see Table 2).
- Administration of **4 doses** is permitted when a combination vaccine containing HepB is used after the birth dose.
- **Minimum age** for the final (3rd or 4th) dose: 24 weeks
- **Minimum intervals:** dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 8 weeks / dose 1 to dose 3: 16 weeks (when 4 doses are administered, substitute "dose 4" for "dose 3" in these calculations)

Catch-up vaccination
- Unvaccinated persons should complete a 3-dose series at 0, 1–2, 6 months.
- Adolescents age 11–15 years may use an alternative 2-dose schedule with at least 4 months between doses (adult formulation **Recombivax HB** only).
- Adolescents 18 years and older may receive a 2-dose series of HepB **(Heplisav-B)** at least 4 weeks apart.
- Adolescents 18 years and older may receive the combined HepA and HepB vaccine, **Twinrix**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (0, 7, and 21–30 days, followed by a dose at 12 months).
- For other catch-up guidance, see Table 2.

5. **Human papillomavirus vaccination**
(minimum age: 9 years)

Routine and catch-up vaccination
- HPV vaccination routinely recommended for all adolescents **age 11–12 years (can start at age 9 years)** and through age 18 years if not previously adequately vaccinated
- 2- or 3-dose series depending on age at initial vaccination:
  - **Age 9 through 14 years at initial vaccination:** 2-dose series at 0, 6–12 months (minimum interval: 5 months; repeat dose if administered too soon)
  - **Age 15 years or older at initial vaccination:** 3-dose series at 0, 1–2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon)
- If completed valid vaccination series with any HPV vaccine, no additional doses needed

Special situations
- **Immunocompromising conditions, including HIV infection:** 3-dose series as above
- **History of sexual abuse or assault**: Start at age 9 years
- **Pregnancy:** HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant; pregnancy testing not needed before vaccination

6. **Inactivated poliovirus vaccination**
(minimum age: 6 weeks)

Routine vaccination
- 4-dose series at ages 2, 4, 6–18 months, 4–6 years; administer the final dose on or after the 4th birthday and at least 6 months after the previous dose.
- 4 or more doses of IPV can be administered before the 4th birthday when a combination vaccine containing IPV is used. However, a dose is still recommended after the 4th birthday and at least 6 months after the previous dose.

Catch-up vaccination
- In the first 6 months of life, use minimum ages and intervals only for travel to a polio-endemic region or during an outbreak.
- IPV is not routinely recommended for U.S. residents 18 years and older.

Series containing oral polio vaccine (OPV), either mixed OPVIPV or OPV-only series:
- Total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. See www.cdc.gov/mmwr/volumes/66/wr/mm6601a6.htm?s_cid=mm6601a6_w.
- Only trivalent OPV (tOPV) counts toward the U.S. vaccination requirements. For guidance to assess doses documented as "OPV," see www.cdc.gov/mmwr/volumes/66/wr/mm6606a7.htm?s_cid=mm6606a7_w.
- For other catch-up guidance, see Table 2.

7. **Influenza vaccination**
(minimum age: 6 months [IIV], 2 years [LAIV], 18 years [RIV])

Routine vaccination
- 1 dose any influenza vaccine appropriate for age and health status annually (2 doses separated by at least 4 weeks for **children 6 months–8 years** who did not receive at least 2 doses of influenza vaccine before July 1, 2018)

Special situations
- **Egg allergy, hives only:** Any influenza vaccine appropriate for age and health status annually
- **Egg allergy more severe than hives** (e.g., angioedema, respiratory distress): Any influenza vaccine appropriate for age and health status annually in medical setting under supervision of health care provider who can recognize and manage severe allergic conditions
- **LAIV should not be used** for those with a history of severe allergic reaction to any component of the vaccine (excluding egg) or to a previous dose of any influenza vaccine, children and adolescents receiving concomitant aspirin or salicylate-containing medications, children age 2 through 4 years with a history of asthma or wheezing, those who are immunocompromised due to any cause (including immunosuppression caused by medications and HIV infection), anatomic and functional asplenia, cochlear implants, cerebrospinal fluid-oropharyngeal communication, close contacts and caregivers of severely immunosuppressed persons who require a protected environment, pregnancy, and persons who have received influenza antiviral medications within the previous 48 hours.

8. **Measles, mumps, and rubella vaccination**
(minimum age: 12 months for routine vaccination)

Routine vaccination
- 2-dose series at 12–15 months, 4–6 years
- Dose 2 may be administered as early as 4 weeks after dose 1.

Catch-up vaccination
- Unvaccinated children and adolescents: 2 doses at least 4 weeks apart
- The maximum age for use of *MMRV* is 12 years.

Continued

Special situations

International travel

- **Infants age 6–11 months:** 1 dose before departure; revaccinate with 2 doses at 12–15 months (12 months for children in high-risk areas) and dose 2 as early as 4 weeks later.
- **Unvaccinated children age 12 months and older:** 2-dose series at least 4 weeks apart before departure

9. Meningococcal serogroup A,C,W,Y vaccination
(minimum age: 2 months [MenACWY-CRM, Menveo], 9 months [MenACWY-D, Menactra])

Routine vaccination

- 2-dose series: 11–12 years, 16 years

Catch-up vaccination

- Age 13–15 years: 1 dose now and booster at age 16–18 years (minimum interval: 8 weeks)
- Age 16–18 years: 1 dose

Special situations

Anatomic or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, eculizumab use:

- **Menveo**
  - Dose 1 at age 8 weeks: 4-dose series at 2, 4, 6, 12 months
  - Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after the 1st birthday)
  - Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart
- **Menactra**
  - **Persistent complement component deficiency:**
    - Age 9–23 months: 2 doses at least 12 weeks apart
    - Age 24 months or older: 2 doses at least 8 weeks apart
  - **Anatomic or functional asplenia, sickle cell disease, or HIV infection:**
    - **Age 9–23 months:** Not recommended
    - **24 months or older:** 2 doses at least 8 weeks apart
    - **Menactra** must be administered at least 4 weeks after completion of PCV13 series.

Travel in countries with hyperendemic or epidemic meningococcal disease, including countries in the African meningitis belt or during the Hajj (wwwnc.cdc.gov/travel/)**:**

- Children age less than 24 months:
  - **Menveo (age 2–23 months):**
    - Dose 1 at 8 weeks: 4-dose series at 2, 4, 6, 12 months
    - Dose 1 at 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after the 1st birthday)
  - **Menactra (age 9–23 months):**
    - 2-dose series (dose 2 at least 12 weeks after dose 1; dose 2 may be administered as early as 8 weeks after dose 1 in travelers)
- Children age 2 years or older: 1 dose **Menveo** or **Menactra**

First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) or military recruits:

- 1 dose **Menveo** or **Menactra**

Note: Menactra should be administered either before or at the same time as DTaP. For MenACWY booster dose recommendations for groups listed under "Special situations" above and additional meningococcal vaccination information, see meningococcal *MMWR* publications at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html.

10. Meningococcal serogroup B vaccination
(minimum age: 10 years [MenB-4C, Bexsero; MenB-FHbp, Trumenba])

Clinical discretion

- MenB vaccine may be administered based on individual clinical decision to **adolescents not at increased risk** age 16–23 years (preferred age 16–18 years):
- **Bexsero:** 2-dose series at least 1 month apart
- **Trumenba:** 2-dose series at least 6 months apart; if dose 2 is administered earlier than 6 months, administer a 3rd dose at least 4 months after dose 2.

Special situations

Anatomic or functional asplenia (including sickle cell disease), persistent complement component deficiency, eculizumab use:

- **Bexsero:** 2-dose series at least 1 month apart
- **Trumenba:** 3-dose series at 0, 1–2, 6 months

Bexsero and **Trumenba** are not interchangeable; the same product should be used for all doses in a series. For additional meningococcal vaccination information, see meningococcal *MMWR* publications at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html.

11. Pneumococcal vaccination
(minimum age: 6 weeks [PCV13], 2 years [PPSV23])

Routine vaccination with PCV13

- 4-dose series at 2, 4, 6, 12–15 months

Catch-up vaccination with PCV13

- 1 dose for healthy children age 24–59 months with any incomplete* PCV13 series
- For other catch-up guidance, see Table 2.

Special situations

High-risk conditions below: When both PCV13 and PPSV23 are indicated, administer PCV13 first. PCV13 and PPSV23 should not be administered during same visit.

Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma treated with high-dose, oral corticosteroids); diabetes mellitus:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks afterany prior PCV13 dose)

Age 6–18 years

- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Cerebrospinal fluid leak, cochlear implant:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13, 8 weeks after the most recent dose and administered 8 weeks apart
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Age 6–18 years

- No history of either PCV13 or PPSV23: 1 dose PCV13, 1 dose PPSV23 at least 8 weeks later
- Any PCV13 but no PPSV23: 1 dose PPSV23 at least 8 weeks after the most recent dose of PCV13
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent dose of PPSV23

Sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiency; HIV infection; chronic renal failure; nephrotic syndrome; malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and other diseases associated with treatment with immunosuppressive drugs or radiation therapy; solid organ transplantation; multiple myeloma:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose) and a 2nd dose of PPSV23 5 years later

Age 6–18 years
- No history of either PCV13 or PPSV23: 1 dose PCV13, 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- Any PCV13 but no PPSV23: 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after the most recent dose of PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent PPSV23 dose and a 2nd dose of PPSV23 administered 5 years after dose 1 of PPSV23 and at least 8 weeks after a dose of PCV13

Chronic liver disease, alcoholism:
Age 6–18 years
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

*An incomplete series is defined as not having received all doses in either the recommended series or an ageappropriate catch-up series. See Tables 8, 9, and 11 in the ACIP pneumococcal vaccine recommendations (www.cdc.gov/mmwr/pdf/rr/rr5911.pdf) for complete schedule details.

12. Rotavirus vaccination
(minimum age: 6 weeks)
Routine vaccination
- **Rotarix:** 2-dose series at 2 and 4 months.
- **RotaTeq:** 3-dose series at 2, 4, and 6 months.

If any dose in the series is either **RotaTeq** or unknown, default to 3-dose series.
Catch-up vaccination
- Do not start the series on or after age 15 weeks, 0 days.
- The maximum age for the final dose is 8 months, 0 days.
- For other catch-up guidance, see Figure 2.

13. Tetanus, diphtheria, and pertussis (Tdap) vaccination
(minimum age: 11 years for routine vaccination, 7 years for catch-up vaccination)
Routine vaccination
- **Adolescents age 11–12 years:** 1 dose Tdap
- **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36
- Tdap may be administered regardless of the interval since the last tetanus- and diphtheria-toxoid-containing vaccine

Catch-up vaccination
- **Adolescents age 13–18 years who have not received Tdap:** 1 dose Tdap, then Td booster every 10 years
- **Persons age 7–18 years not fully immunized with DTaP:** 1 dose Tdap as part of the catch-up series (preferably the first dose); if additional doses are needed, use Td.
- **Children age 7–10 years** who receive Tdap inadvertently or as part of the catch-up series should receive the routine Tdap dose at 11–12 years.
- **DTaP inadvertently given after the 7th birthday:**
  - **Child age 7–10 years:** DTaP may count as part of catch-up series. Routine Tdap dose at 11–12 should be administered.
  - **Adolescent age 11–18 years:** Count dose of DTaP as the adolescent Tdap booster.
- For other catch-up guidance, see Table 2.
- For information on use of Tdap or Td as tetanus prophylaxis in wound management, see www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm.

14. Varicella vaccination
(minimum age: 12 months)
Routine vaccination
- 2-dose series: 12–15 months, 4–6 years
- Dose 2 may be administered as early as 3 months after dose 1 (a dose administered after a 4-week interval may be counted).

Catch-up vaccination
- Ensure persons age 7–18 years without evidence of immunity (see *MMWR* at www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have 2-dose series:
  - **Ages 7–12 years:** routine interval: 3 months (minimum interval: 4 weeks)
  - **Ages 13 years and older:** routine interval: 4–8 weeks (minimum interval: 4 weeks).
  - The maximum age for use of *MMRV* is 12 years.

General Recommendations on Immunization

TABLE 3 Recommended and Minimum Ages and Intervals between Vaccine Doses*†

Vaccine and Dose Number	Recommended Age for this Dose	Minimum Age for this Dose	Recommended Interval to Next Dose	Minimum Interval to Next Dose
HepB-1§	Birth	Birth	1-4 months	4 weeks
HepB-2	1-2 months	4 weeks	2-17 months	8 weeks
HepB-3¶	6-18 months	24 weeks	—	—
DTaP-1§	2 months	6 weeks	2 months	4 weeks
DTaP-2	4 months	10 weeks***	2 months	4 weeks
DTaP-3	6 months	14 weeks	6-12 months	6 months
DTaP-4	15-18 months	12 months	3 years	6 months
DTaP-5	4-6 years	4 years	—	—
Hib-1§§§	2 months	6 weeks	2 months	4 weeks
Hib-2	4 months	10 weeks	2 months	4 weeks
Hib-3¶¶	6 months	14 weeks	6-9 months	8 weeks
Hib-4	12-15 months	12 months	—	—
IPV-1§	2 months	6 weeks	2 months	4 weeks
IPV-2	4 months	10 weeks	2-14 months	4 weeks
IPV-3	6-18 months	14 weeks	3-5 years	6 months
IPV-4***	4-6 years	4 years	—	—
PCV-1§§	2 months	6 weeks	8 weeks	4 weeks
PCV-2	4 months	10 weeks	8 weeks	4 weeks
PCV-3	6 months	14 weeks	6 months	8 weeks
PCV-4	12-15 months	12 months	—	—
MMR-1†††	12-15 months	12 months	3-5 years	4 weeks
MMR-2†††	4-6 years	13 months	—	—
Varicella-1†††	12-15 months	12 months	3-5 years	12 weeks§§§
Varicella-2†††	4-6 years	15 months	—	—
HepA-1	12-23 months	12 months	6-18 months**	6 months**
HepA-2	≥18 months	18 months	—	—
Influenza inactivated¶¶¶	≥6 months	6 months****	1 month	4 weeks
LAIV (intranasal)¶¶¶	2-49 years	2 years	1 month	4 weeks
MCV4-1††††	11-12 years	2 years	5 years	8 weeks
MCV4-2	16 years	11 years (+8 weeks)	—	—
MPSV4-1††††	—	2 years	5 years	5 years
MPSV4-2	—	7 years	—	—
Td	11-12 years	7 years	10 years	5 years
Tdap§§§§	≥11 years	7 years	—	—
PPSV-1	—	2 years	5 years	5 years
PPSV-2¶¶¶¶	—	7 years	—	—
HPV-1*****	11-12 years	9 years	2 months	4 weeks
HPV-2	11-12 years (+2 months)	9 years (+4 weeks)	4 months	12 weeks†††††
HPV-3†††††	11-12 years (+6 months)	9 years (+24 weeks)	—	—
Rotavirus-1§§§§§	2 months	6 weeks	2 months	4 weeks
Rotavirus-2	4 months	10 weeks	2 months	4 weeks
Rotavirus-3¶¶¶¶¶	6 months	14 weeks	—	—
Herpes zoster******	≥60 years	60 years	—	—
Pneumococcal vaccine‡‡‡‡‡‡	—	—	—	—

DTaP, Diphtheria and tetanus toxoids and acellular pertussis; *HepA,* hepatitis A; *HepB,* hepatitis B; *Hib, Haemophilus influenzae* type b; *HPV,* human papillomavirus; *IPV,* inactivated poliovirus; *LAIV,* live, attenuated influenza vaccine; *MCV4,* quadrivalent meningococcal conjugate vaccine; *MMR,* measles, mumps, and rubella; *MMRV,* measles, mumps, rubella, and varicella; *MPSV4,* quadrivalent meningococcal polysaccharide vaccine; *PCV,* pneumococcal conjugate vaccine; *PPSV,* pneumococcal polysaccharide vaccine; *PRP-OMB,* polyribosylribitol phosphate-meningococcal outer membrane protein conjugate; *Td,* tetanus and diphtheria toxoids; *Tdap,* tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

*Combination vaccines are available. Use of licensed combination vaccines is generally preferred to separate injections of their equivalent component vaccines. When administering combination vaccines, the minimum age for administration is the oldest age for any of the individual components; the minimum interval between doses is equal to the greatest interval of any of the individual components.

†Information on travel vaccines, including typhoid, Japanese encephalitis, and yellow fever, is available at www.cdc.gov/travel. Information on other vaccines that are licensed in the United States but not distributed, including anthrax and smallpox, is available at www.cdc.gov/vaccines/hcp/vis/current-vis.html.

§Combination vaccines containing the hepatitis B component are available. These vaccines should not be administered to infants aged <6 weeks because of the other components (i.e., Hib, DTaP, HepA, and IPV).

¶HepB-3 should be administered at least 8 weeks after HepB-2 and at least 16 weeks after HepB-1 and should not be administered before age 24 weeks.

**Calendar months.

††The minimum recommended interval between DTaP-3 and DTaP-4 is 6 months. However, DTaP-4 need not be repeated if administered at least 4 months after DTaP-3.

§§For Hib and PCV, children receiving the first dose of vaccine at age ≥7 months require fewer doses to complete the series.

¶¶If PRP-QMP (Pedvax-Hib, Merck Vaccine Division) was administered at ages 2 and 4 months, a dose at age 6 months is not necessary.

***A fourth dose is not needed if the third dose was administered at ≥4 years and at least 6 months after the previous dose.

†††Combination MMRV vaccine can be used for children aged 12 months to 12 years.

§§§The minimum interval from Varicella-1 to Varicella-2 for persons beginning the series at age ≥13 years is 4 weeks.

¶¶¶One dose of influenza vaccine per season is recommended for most persons. Children aged <9 years who are receiving influenza vaccine for the first time or who received only 1 dose the previous season (if it was their first vaccination season) should receive 2 doses this season.

****The minimum age for inactivated influenza vaccine varies by vaccine manufacturer. See package insert for vaccine-specific minimum ages.

††††Revaccination with meningococcal vaccine is recommended for previously vaccinated persons who remain at high risk for meningococcal disease. (Source: CDC. Updated recommendations from the Advisory Committee on Immunization Practices (ACIP) for revaccination of persons at prolonged increased risk for meningococcal disease. *MMWR* 2009;58:[1042-3]).

TABLE 3 Recommended and Minimum Ages and Intervals between Vaccine Doses*† —cont'd

§§§§Only 1 dose of Tdap is recommended. Subsequent doses should be given as Td. For one brand of Tdap, the minimum age is 11 years. For management of a tetanus-prone wound in persons who have received a primary series of tetanus–toxoid-containing vaccine, the minimum interval after a previous dose of any tetanus-containing vaccine is 5 years.
¶¶¶¶A second dose of PPSV 5 years after the first dose is recommended for persons aged ≤65 years at highest risk for serious pneumococcal infection and those who are likely to have a rapid decline in pneumococcal antibody concentration. (Source: CDC. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR* 1997;46[No. RR-8].)
*****Bivalent HPV vaccine is approved for females aged 10-25 years. Quadrivalent HPV vaccine is approved for males and females aged 9-26 years.
†††††The minimum age for HPV-3 is based on the baseline minimum age for the first dose (i.e., 108 months) and the minimum interval of 24 weeks between the first and third dose. Dose 3 need not be repeated if it is administered at least 16 weeks after the first dose.
§§§§§The first dose of rotavirus must be administered at age 6 weeks through 14 weeks and 6 days. The vaccine series should not be started for infants aged ≥15 weeks, 0 days. Rotavirus should not be administered to children older than 8 months, 0 days of age regardless of the number of doses received between 6 weeks and 8 months, 0 days of age.
¶¶¶¶¶If 2 doses of Rotarix (GlaxoSmithKline) are administered as age appropriate, a third dose is not necessary.
******Herpes zoster vaccine is recommended as a single dose for persons aged ≥60 years.

TABLE 4 Guidelines for Spacing of Live and Inactivated Antigens

Antigen Combination	Recommended Minimum Interval between Doses
Two or more inactivated*	May be administered simultaneously or at any interval between doses
Inactivated and live	May be administered simultaneously or at any interval between doses
Two or more live intranasal or injectable†	28 days minimum interval, if not administered simultaneously

*Certain experts suggest a 28-day interval between tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine and tetravalent meningococcal conjugate vaccine if they are not administered simultaneously.
†Live oral vaccines (e.g., Ty21a typhoid vaccine and rotavirus vaccine) may be administered simultaneously or at any interval before or after inactivated or live injectable vaccines.
From Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 60(2):38, 2011.

TABLE 5 Guidelines for Administering Antibody-Containing Products* and Vaccines

Type of Administration	Products Administered		Recommended Minimum Interval between Doses
Simultaneous (during the same office visit)	Antibody-containing products and inactivated antigen		Can be administered simultaneously at different anatomic sites or at any time interval between doses
	Antibody-containing products and live antigen		Should not be administered simultaneously.† If simultaneous administration of measles-containing vaccine or varicella vaccine is unavoidable, administer at different sites and revaccinate or test for seroconversion after the recommended interval
Nonsimultaneous	**Administered First**	**Administered Second**	
	Antibody-containing products	Inactivated antigen	No interval necessary
	Inactivated antigen	Antibody-containing products	No interval necessary
	Antibody-containing products	Live antigen	Dose related
	Live antigen	Antibody-containing products	2 weeks

*Blood products containing substantial amounts of immune globulin include intramuscular and intravenous immune globulin, specific hyperimmune globulin (e.g., hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, and rabies immune globulin), whole blood, packed red blood cells, plasma, and platelet products.
†Yellow fever vaccine; rotavirus vaccine; oral Ty21a typhoid vaccine; live, attenuated influenza vaccine; and zoster vaccine are exceptions to these recommendations. These live, attenuated vaccines can be administered at any time before or after or simultaneously with an antibody-containing product.
‡The duration of interference of antibody-containing products with the immune response to the measles component of measles-containing vaccine, and possibly varicella vaccine, is dose related.
From Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR*60:(RR-2), 2011.

TABLE 6 Recommended Intervals between Administration of Antibody-Containing Products and Measles- or Varicella-Containing Vaccine, by Product and Indication for Vaccination

Product/Indication	Dose (mg IgG/kg) and Route*	Recommended Interval before Measles- or Varicella-Containing Vaccine† Administration (months)
Tetanus IG	250 units (10 mg IgG/kg) IM	3
Hepatitis A IG		
Contact prophylaxis	0.02 ml/kg (33 mg IgG/kg) IM	3
International travel	0.06 ml/kg (10 mg IgG/kg) IM	3
Hepatitis B IG	0.06 ml/kg (10 mg IgG/kg) IM	3
Rabies IG	20 IU/kg (22 mg IgG/kg) IM	4
Varicella IG	125 units/10 kg (60–200 mg IgG/kg) IM, maximum 625 units	5
Measles prophylaxis IG		
Standard (i.e., nonimmunocompromised) contact	0.25 ml/kg (40 mg IgG/kg) IM	5
Immunocompromised contact	0.50 ml/kg (80 mg IgG/kg) IM	6
Blood transfusion		
RBCs, washed	10 ml/kg negligible IgG/kg IV	None
RBCs, adenine-saline added	10 ml/kg (10 mg IgG/kg) IV	3
Packed RBCs (hematocrit 65%)§	10 ml/kg (60 mg IgG/kg) IV	6
Whole blood (hematocrit 35%-50%)§	10 ml/kg (80-100 mg IgG/kg) IV	6
Plasma/platelet products	10 ml/kg (160 mg IgG/kg) IV	7
Cytomegalovirus IGIV	150 mg/kg maximum	6
IGIV		
Replacement therapy for immune deficiencies¶	300-400 mg/kg IV¶	8
Immune thrombocytopenic purpura treatment	400 mg/kg IV	8
Postexposure varicella prophylaxis**	400 mg/kg IV	8
Immune thrombocytopenic purpura treatment	1000 mg/kg IV	10
Kawasaki disease	2 g/kg IV	11
Monoclonal antibody to respiratory syncytial virus F protein (Synagis [MedImmune])††	15 mg/kg IM	None

HIV, human immunodeficiency virus; *IG,* immune globulin; *IgG,* immune globulin G; *IGIV,* intravenous immune globulin; *mg IgG/kg,* milligrams of immune globulin G per kilogram of body weight; *IM,* intramuscular; *IV,* intravenous; *RBCs,* red blood cells.

*This table is not intended for determining the correct indications and dosages for using antibody-containing products. Unvaccinated persons might not be protected fully against measles during the entire recommended interval, and additional doses of IG or measles vaccine might be indicated after measles exposure. Concentrations of measles antibody in an IG preparation can vary by manufacturer's lot. Rates of antibody clearance after receipt of an IG preparation also might vary. Recommended intervals are extrapolated from an estimated half-life of 30 days for passively acquired antibody and an observed interference with the immune response to measles vaccine for 5 months after a dose of 80 mg IgG/kg.

†Does not include zoster vaccine. Zoster vaccine may be given with antibody-containing blood products.

§Assumes a serum IgG concentration of 16 mg/ml.

¶Measles and varicella vaccinations are recommended for children with asymptomatic or mildly symptomatic HIV infection but are contraindicated for persons with severe immunosuppression from HIV or any other immunosuppressive disorder.

**The investigational VariZIG, similar to licensed varicella-zoster IG (VZIG), is a purified human IG preparation made from plasma containing high levels of antivaricella antibodies (IgG). The interval between VariZIG and varicella vaccine (Var or MMRV) is 5 months.

††Contains antibody only to respiratory syncytial virus.

From Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR*60:(RR-2), 2011.

TABLE 7 Contraindications and Precautions* to Commonly Used Vaccines

Vaccine	Contraindications	Precautions
DTaP	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Encephalopathy (e.g., coma, decreased level of consciousness, or prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of previous dose of DTP or DTaP	Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy; defer DTaP until neurologic status clarified and stabilized Temperature of ≥105° F (≥40° C) within 48 hours after vaccination with a previous dose of DTP or DTaP Collapse or shocklike state (i.e., hypotonic hyporesponsive episode) within 48 hours after receiving a previous dose of DTP/DTaP Seizure ≤3 days after receiving a previous dose of DTP/DTaP Persistent, inconsolable crying lasting ≥3 hours within 48 hours after receiving a previous dose of DTP/DTaP GBS <6 weeks after previous dose of tetanus toxoid containing vaccine History of Arthus-type hypersensitivity reactions after a previous dose of tetanus toxoid containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus toxoid containing vaccine Moderate or severe acute illness with or without fever
DT, Td	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	GBS <6 weeks after previous dose of tetanus toxoid containing vaccine History of Arthus-type hypersensitivity reactions after a previous dose of tetanus toxoid containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus toxoid containing vaccine Moderate or severe acute illness with or without fever
Tdap	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Encephalopathy (e.g., coma, decreased level of consciousness, or prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of previous dose of DTP, DTaP, or Tdap	GBS <6 weeks after a previous dose of tetanus toxoid containing vaccine Progressive or unstable neurologic disorder, uncontrolled seizures, or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized History of Arthus-type hypersensitivity reactions after a previous dose of tetanus toxoid containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus toxoid containing vaccine Moderate or severe acute illness with or without fever
IPV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Pregnancy Moderate or severe acute illness with or without fever
MMR†§	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Pregnancy: Known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, or long-term immunosuppressive therapy¶ or patients with HIV infection who are severely immunocompromised)§	Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product) History of thrombocytopenia or thrombocytopenic purpura Need for tuberculin skin testing†† Moderate or severe acute illness with or without fever
Hib	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Age <6 weeks	Moderate or severe acute illness with or without fever
Hepatitis B	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Infant weight <2000 g§§ Moderate or severe acute illness with or without fever
Hepatitis A	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Pregnancy: Moderate or severe acute illness with or without fever
Varicella	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, or long-term immunosuppressive therapy¶ or patients with HIV infection who are severely immunocompromised)§ Pregnancy	Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product)¶¶ Moderate or severe acute illness with or without fever
PCV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose (of PCV7, PCV13, or any diphtheria toxoid-containing vaccine) or to a component of a vaccine (PCV7, PCV13, or any diphtheria toxoid-containing vaccine)	Moderate or severe acute illness with or without fever
TIV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to vaccine component, including egg protein	GBS <6 weeks after a previous dose of influenza vaccine Moderate or severe acute illness with or without fever
LAIV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to vaccine component, including egg protein Pregnancy Immunosuppression Certain chronic medical conditions***	GBS <6 weeks after a previous dose of influenza vaccine Moderate or severe acute illness with or without fever
PPSV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever
MCV4	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever
MPSV4	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever

Continued

TABLE 7 Contraindications and Precautions* to Commonly Used Vaccines—cont'd

Vaccine	Contraindications	Precautions
HPV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Pregnancy: Moderate or severe acute illness with or without fever
Rotavirus	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component SCID	Altered immunocompetence other than SCID: History of intussusception Chronic gastrointestinal disease††† Spina bifida or bladder exstrophy††† Moderate or severe acute illness with or without fever
Zoster	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Substantial suppression of cellular immunity Pregnancy	Moderate or severe acute illness with or without fever

DT, Diphtheria and tetanus toxoids; *DTaP,* diphtheria and tetanus toxoids and acellular pertussis; *GBS,* Guillain-Barré syndrome; *HBsAg,* hepatitis B surface antigen; *Hib, Haemophilus influenzae* type b; *HIV,* human immunodeficiency virus; *HPV,* human papillomavirus; *IPV,* inactivated poliovirus; *LAIV,* live, attenuated influenza vaccine; *MCV4,* quadrivalent meningococcal conjugate vaccine; *MMRV* measles, mumps, rubella; *MPSV4,* quadrivalent meningococcal polysaccharide vaccine; *PCV,* pneumococcal conjugate vaccine; *PPSV,* pneumococcal polysaccharide vaccine; *SCID,* severe combined immunodeficiency; *Td,* tetanus and diphtheria toxoids; *Tdap,* tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; *TIV,* trivalent inactivated influenza vaccine.

*Events or conditions listed as precautions should be reviewed carefully. Benefits of and risks for administering a specific vaccine to a person under these circumstances should be considered. If the risk from the vaccine is believed to outweigh the benefit, the vaccine should not be administered. If the benefit of vaccination is believed to outweigh the risk, the vaccine should be administered. Whether and when to administer DTaP to children with proven or suspected underlying neurologic disorders should be decided on a case-by-case basis.

†HIV-infected children may receive varicella and measles vaccine if $CD4^+$ T-lymphocyte count is <15%. (Source: Adapted from American Academy of Pediatrics. Passive immunization. In: Pickering LK, ed. *Red book: 2009 report of the committee on infectious diseases.* 28th ed. Elk Grove Village.IL: American Academy of Pediatrics: 2009.)

§MMR and varicella vaccines can be administered on the same day. If not administered on the same day, these vaccines should be separated by at least 28 days.

¶Substantially immunosuppressive steroid dose is considered to be ≥2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent.

††Measles vaccination might suppress tuberculin reactivity temporarily. Measles-containing vaccine can be administered on the same day as tuberculin skin testing. If testing cannot be performed until after the day of MMR vaccination, the test should be postponed for ≥4 weeks after the vaccination. If an urgent need exists to skin test, do so with the understanding that reactivity might be reduced by the vaccine.

§§Hepatitis B vaccination should be deferred for infants weighing <2000 g if the mother is documented to be HBsAg-negative at the time of the infant's birth. Vaccination can commence at chronological age 1 month or at hospital discharge. For infants born to HBsAg-positive women, hepatitis B immune globulin and hepatitis B vaccine should be administered within 12 hours after birth, regardless of weight.

¶¶Vaccine should be deferred for the appropriate interval if replacement immune globulin products are being administered.

***Source: CDC. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR* 2010;59(No. RR-8).

†††For details see CDC. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2009;58(No. RR-2).

From Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR*60:(RR-2), 2011.

TABLE 8 Conditions Commonly Misperceived as Contraindications to Vaccination

Vaccine	Conditions Commonly Misperceived as Contraindications (i.e., Vaccination May Be Administered under These Conditions)
General for all vaccines, including DTaP, pediatric DT, adult Td, adolescent-adult Tdap, IPV, MMR, Hib, hepatitis A, hepatitis B, varicella, rotavirus, PCV, TIV, LAIV, PPSV, MCV4, MPSV4, HPV, and herpes zoster	Mild acute illness with or without fever Mild-to-moderate local reaction (i.e., swelling, redness, soreness); low-grade or moderate fever after previous dose Lack of previous physical examination in well-appearing person Current antimicrobial therapy* Convalescent phase of illness Preterm birth (hepatitis B vaccine is an exception in certain circumstances)† Recent exposure to an infectious disease History of penicillin allergy, other nonvaccine allergies, relatives with allergies, or receiving allergen extract immunotherapy
DTaP	Fever of <105° F (<40° C), fussiness or mild drowsiness after a previous dose of DTP/DTaP Family history of seizures Family history of sudden infant death syndrome Family history of an adverse event after DTP or DTaP administration Stable neurologic conditions (e.g., cerebral palsy, well-controlled seizures, or developmental delay)
Tdap	Fever of ≥105° F (≥40° C) for <48 hours after vaccination with a previous dose of DTP or DTaP Collapse or shock-like state (i.e., hypotonic hyporesponsive episode) within 48 hours after receiving a previous dose of DTaP Seizure <3 days after receiving a previous dose of DTP/DTaP Persistent, inconsolable crying lasting <3 hours within 48 hours after receiving a previous dose of DTP/DTaP History of extensive limb swelling after DTP/DTaP/Td that is not an Arthus-type reaction Stable neurologic disorder History of brachial neuritis Latex allergy that is not anaphylactic Breastfeeding Immunosuppression
IPV	Previous receipt of ≥1 dose of oral polio vaccine
MMR§,¶	Positive tuberculin skin test Simultaneous tuberculin skin testing** Breastfeeding Pregnancy of recipient's mother or other close or household contact Recipient is female of childbearing age Immunodeficient family member or household contact Asymptomatic or mildly symptomatic HIV infection Allergy to eggs
Hepatitis B	Pregnancy Autoimmune disease (e.g., systemic lupus erythematosus or rheumatoid arthritis)
Varicella	Pregnancy of recipient's mother or other close or household contact Immunodeficient family member or household contact†† Asymptomatic or mildly symptomatic HIV infection Humoral immunodeficiency (e.g., agammaglobulinemia)
TIV	Nonsevere (e.g., contact) allergy to latex, thimerosal, or egg Concurrent administration of Coumadin or aminophylline
LAIV	Health care providers that see patients with chronic diseases or altered immunocompetence (an exception is providers for severely immunocompromised patients requiring care in a protected environment) Breastfeeding Contacts of persons with chronic disease or altered immunocompetence (an exception is contacts of severely immunocompromised patients requiring care in a protected environment)
PPSV	History of invasive pneumococcal disease or pneumonia
HPV	Immunosuppression Previous equivocal or abnormal Papanicolaou test Known HPV infection Breastfeeding History of genital warts
Rotavirus	Prematurity Immunosuppressed household contacts Pregnant household contacts
Zoster	Therapy with low-dose methotrexate (≤0.4 mg/kg/week), azathioprine (≤3.0 mg/kg/day), or 6-mercaptopurine (≤1.5 mg/kg/day) for treatment of rheumatoid arthritis, psoriasis, polymyositis, sarcoidosis, inflammatory bowel disease, or other conditions Health care providers of patients with chronic diseases or altered immunocompetence Contacts of patients with chronic diseases or altered immunocompetence Unknown or uncertain history of varicella in a U.S.-born person

Continued

TABLE 8 Conditions Commonly Misperceived as Contraindications to Vaccination—cont'd

DT, Diphtheria and tetanus toxoids; *DTP,* diphtheria toxoid, tetanus toxoid, and pertussis; *DTaP,* diphtheria and tetanus toxoids and acellular pertussis; *HBsAg,* hepatitis B surface antigen; *Hib, Haemophilus influenzae* type b; *HPV,* human papillomavirus; *IPV,* inactivated poliovirus; *LAIV,* live, attenuated influenza vaccine; *MCV4,* quadrivalent meningococcal conjugate vaccine; *MMR,* measles, mumps, and rubella; *MPSV4,* quadrivalent meningococcal polysaccharide vaccine; *PCV,* pneumococcal conjugate vaccine; *PPSV,* pneumococcal polysaccharide vaccine; *Td,* tetanus and diphtheria toxoids; *Tdap,* tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; *TIV,* trivalent inactivated influenza vaccine.

*Antibacterial drugs might interfere with Ty21a oral typhoid vaccine, and certain antiviral drugs might interfere with varicella-containing vaccines and LAIV.

†Hepatitis B vaccination should be deferred for infants weighing <2000 g if the mother is documented to be HBsAg-negative at the time of the infant's birth. Vaccination can commence at chronologic age 1 month or at hospital discharge. For infants born to HBsAg-positive women, hepatitis B immune globulin and hepatitis B vaccine should be administered within 12 hours after birth, regardless of weight.

§MMR and varicella vaccines can be administered on the same day. If not administered on the same day, these vaccines should be separated by at least 28 days.

¶HIV-infected children should receive immune globulin after exposure to measles. HIV-infected children can receive varicella and measles vaccine if $CD4^+$ T-lymphocyte count is >15%. (Source: Adapted from American Academy of Pediatrics. Passive immunization. In: Pickering LK, ed. *Red book: 2009 report of the Committee on Infectious Diseases,* 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.)

**Measles vaccination might suppress tuberculin reactivity temporarily. Measles-containing vaccine can be administered on the same day as tuberculin skin testing. If testing cannot be performed until after the day of MMR vaccination, the test should be postponed for at least 4 weeks after the vaccination. If an urgent need exists to skin test, do so with the understanding that reactivity might be reduced by the vaccine.

††If a vaccinee experiences a presumed vaccine-related rash 7-25 days after vaccination, the person should avoid direct contact with immunocompromised persons for the duration of the rash.

From Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR*60:(RR-2), 2011.

VACCINE ADMINISTRATION*

INFECTION CONTROL AND STERILE TECHNIQUE

Persons administering vaccines should follow appropriate precautions to minimize risk for spread of disease. Hands should be cleansed with an alcohol-based, waterless antiseptic hand rub or washed with soap and water between each patient contact. Occupational Safety and Health Administration (OSHA) regulations do not require that gloves be worn when administering vaccinations unless persons administering vaccinations are likely to come into contact with potentially infectious body fluids or have open lesions on their hands. Needles used for injections must be sterile and disposable to minimize the risk for contamination. A separate needle and syringe should be used for each injection. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary. Different vaccines should never be mixed in the same syringe unless specifically licensed for such use, and no attempt should be made to transfer between syringes.

For all intramuscular injections, the needle should be long enough to reach the muscle mass and prevent vaccine from seeping into subcutaneous tissue, but not so long as to involve underlying nerves, blood vessels, or bone. Vaccinators should be familiar with the anatomy of the area where they are injecting vaccine. Intramuscular injections are administered at a 90-degree angle to the skin, preferably into the anterolateral aspect of the thigh or the deltoid muscle of the upper arm depending on the age of the patient.

Decision on needle size and site of injection must be made for each person on the basis of the size of the muscle, the thickness of adipose tissue at the injection site, the volume of the material to be administered, injection technique, and the depth below the muscle surface into which the material is to be injected (Fig. E1). Aspiration before injection of vaccines or toxoids (i.e., pulling back on the syringe plunger after needle insertion before injection) is not required because no large blood vessel exists at the recommended injection sites.

INFANTS (AGED <12 MONTHS)

For the majority of infants, the anterolateral aspect of the thigh is the recommended site for injection because it provides a large muscle mass (Fig. E2). The muscles of the buttock have not been used for administration of vaccines in infants and children because of concern about potential injury to the sciatic nerve, which is well documented after injection of antimicrobial agents into the buttock. If the gluteal muscle must be used, care should be taken to define the anatomic landmarks.† Injection technique is the most important parameter to ensure efficient intramuscular vaccine delivery. If the subcutaneous and muscle tissue are bunched to minimize the chance of striking bone, a 1-inch needle is required to ensure intramuscular administration in infants. For the majority of infants, a 1-inch, 22- to 25-gauge needle is sufficient to penetrate muscle in an infant's thigh. For newborn (first 28 days of life) and premature infants, a 5/8-inch-long needle usually is adequate if the skin is stretched flat between thumb and forefinger and the needle inserted at a 90-degree angle to the skin.

TODDLERS AND OLDER CHILDREN (AGED 12 MONTHS TO 10 YEARS)

The deltoid muscle should be used if the muscle mass is adequate. The needle size for deltoid site injections can range from 22 to 25 gauge and from 5/8 to 1 inch on the basis of the size of the muscle and the thickness of adipose tissue at the injection site (Fig. E3). A 5/8-inch needle is adequate only for the deltoid muscle and only if the skin is stretched flat between the thumb and forefinger and the needle inserted at a 90-degree angle to the skin. For toddlers, the anterolateral thigh can be used, but the needle should be at least 1 inch in length.

ADOLESCENTS AND ADULTS (AGED >11 YEARS)

For adults and adolescents, the deltoid muscle is recommended for routine intramuscular vaccinations. The anterolateral thigh also can be used. For men and women weighing <130 lb (<60 kg) a 5/8- to 1-inch needle is sufficient to ensure intramuscular injection. For women weighing 130 to 200 lb (60 to 90 kg) and men 130 to 260 lb (60 to 118 kg), a 1- to 1½-inch needle is needed. For women weighing >200 lb (>90 kg) or men weighing >260 lb (>118 kg), a 1½-inch needle is required.

SUBCUTANEOUS INJECTIONS

Subcutaneous injections are administered at a 45-degree angle, usually into the thigh for infants younger than 12 months and in the upper-outer triceps area of persons aged 12 months and older. Subcutaneous injections can be administered into the upper-outer triceps area of an infant if necessary. A 5/8-inch, 23- to 25-gauge needle should be inserted into the subcutaneous tissue.

TABLE 9 Treatment of Anaphylaxis in Children and Adults with Drugs Administered Intramuscularly or Orally

Drug	Dosage
Children	
Primary Regimen	
Epinephrine 1:1000 (aqueous) (1 mg/ml)*	0.01 mg/kg up to 0.5 mg (administer 0.01 ml/kg/dose up to 0.5 ml) IM repeated every 10-20 minutes up to 3 doses
Secondary Regimen	
Diphenhydramine	1-2 mg/kg oral, IM, or IV, every 4-6 hours (100 mg, maximum single dose)
Hydroxyzine	0.5-1 mg/kg oral, IM, every 4-6 hours (100 mg, maximum single dose)
Prednisone	1.5-2 mg/kg oral (60 mg, maximum single dose); use corticosteroids as long as needed
Adults	
Primary Regimen	
Epinephrine 1:1000 (aqueous)*	0.01 mg/kg up to 0.5 mg (administer 0.01 ml/kg/dose up to 0.5 ml) IM repeated every 10-20 minutes up to 3 doses
Secondary Regimen	
Diphenhydramine	1-2 mg/kg up to l00 mg IM or oral, every 4-6 hours

IM, Intramuscular; *IV,* intravenous.

*If the agent causing the anaphylactic reaction was administered by injection, epinephrine may be injected into the same site to slow absorption.

From Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR*60:(RR-2), 2011. Adapted from American Academy of Pediatrics. Passive immunization. In Pickering LK et al (eds): *Red book: 2009 report of the Committee on Infectious Diseases,* 28th ed, Elk Grove Village, 2009, American Academy of Pediatrics, 66-7; Immunization Action Coalition. Medical management of vaccine reactions in adult patients (available at www.immunize.org/catg.d/p3082.pdf); and *Mosby's drug consult,* St Louis, 2005, Mosby.

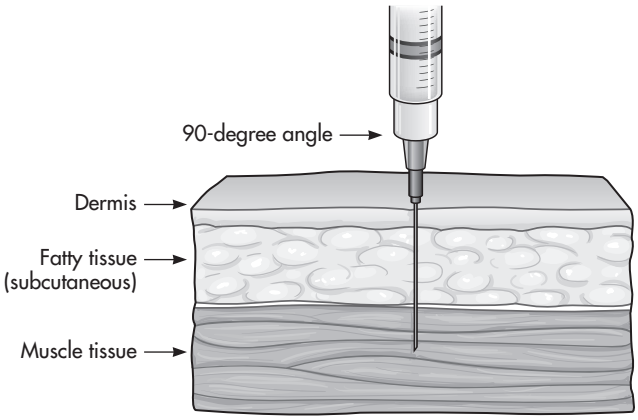


FIG. E1 Intramuscular needle insertion. (Adapted from California Immunization Branch. In Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP], *MMWR* 55[RR-15]:16, 2006.)

FIG. E2 Intramuscular/subcutaneous site of administration: anterolateral thigh. (Adapted from Minnesota Department of Health. In Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP], *MMWR* 55[RR-15]:6, 2006.)

FIG. E3 Intramuscular site of administration: deltoid. (Adapted from Minnesota Department of Health. In Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP], *MMWR* 55[RR-15]:17, 2006.)

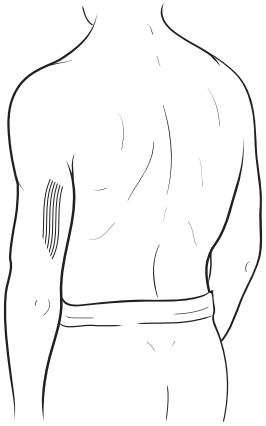


FIG. E4 Subcutaneous site of administration: triceps. (Adapted from Minnesota Department of Health. In Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP], *MMWR* 55[RR-15]:17, 2006.)

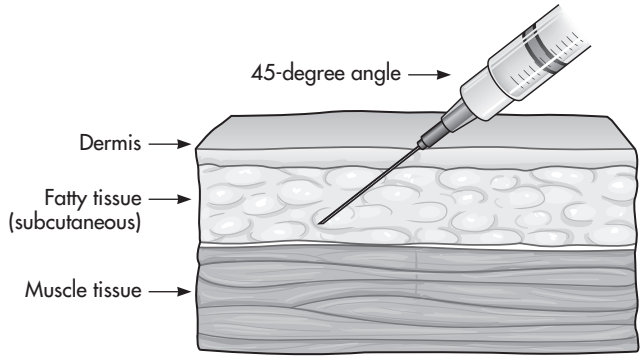


FIG.E5 Subcutaneous needle insertion. (Adapted from California Administration Branch. In Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP], *MMWR* 55[RR-15]:17, 2006.)

TABLE 10 Vaccination of Persons with Primary and Secondary Immune Deficiencies

PRIMARY

Category	Specific Immunodeficiency	Contraindicated Vaccines*	Risk-Specific Recommended Vaccines*	Effectiveness and Comments
B lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV[a] Smallpox[b] LAIV BCG Yellow fever virus (YFV) and live-bacteria vaccines[e] No data for rotavirus vaccines	Annual IIV is the only vaccine given to patients receiving IG therapy; routine inactivated vaccines can be given if not receiving IGIV.	The effectiveness of any vaccine will be uncertain if it depends only on the humoral response (e.g., PPSV23). IG therapy interferes with the immune response to live vaccines MMR and VAR.
	Less severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency)	OPV[a] BCG YFV vaccine Other live vaccines[d] appear to be safe.	Vaccines should be given as on the annual immunization schedule for immunocompetent people.[e] PPSV23 should be given beginning at 2 yr of age.[f]	All vaccines are probably effective. Immune response may be attenuated.
T lymphocyte (cell-mediated and humoral)	Complete defects (e.g., SCID, complete DiGeorge syndrome)	All live vaccines[c,d,g]	The only vaccine that should be given if the patient is receiving IG is annual IIV if there is some residual antibody protection.	All inactivated vaccines are probably ineffective.
	Partial defects (e.g., most patients with DiGeorge syndrome, hyper-IgM syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines[c,d,g]	Routine inactivated vaccines should be given.[e] PPSV23 should be given beginning at 2 yr of age.[f]	Effectiveness of any vaccine depends on degree of immune suppression.
	Interferon (IFN)-γ–interleukin (IL)-12 axis deficiencies	All live vaccines for IL-12/IL-12R deficiencies, IFN-γ, IFN-α, or STAT1 deficiencies	None	None
Complement	Persistent complement, properdin, MBL, or factor B deficiency; secondary deficiency because taking eculizumab (Solaris)	None	PPSV23 should be given beginning at 2 yr of age.[f] MCV series beginning in infancy.[h] MenB series beginning at 10 yr of age	All routine vaccines are probably effective.
Phagocytic function	Chronic granulomatous disease	Live-bacteria vaccines[c]	None	All inactivated vaccines are safe and probably effective. Live-virus vaccines are probably safe and effective.
	Phagocytic deficiencies that are undefined or accompanied by defect in T-cell and NK-cell dysfunction (e.g., Chédiak-Higashi syndrome, leukocyte adhesion defects, myeloperoxidase deficiency)	MMR, MMRV, OPV,[a] smallpox, LAIV, YF, all bacteria vaccines	PPSV23 should be given beginning at 2 yr of age.[f] MCV series beginning in infancy.[h]	All inactivated vaccines are safe and probably effective.

SECONDARY

Specific Immunodeficiency	Contraindicated Vaccines*	Risk-Specific Recommended Vaccines*	Effectiveness and Comments
HIV/AIDS	OPV[a] Smallpox BCG Combined MMRV LAIV Withhold MMR, varicella, and zoster in severely immunocompromised persons. YF vaccine may have a contraindication or precaution depending on the indicators of immune function.[j]	PPSV23 should be given beginning at 2 yr of age.[f] MCV series beginning in infancy.[h] Consider Hib (if not administered in infancy).[l]	Rotavirus vaccine is recommended on standard schedule. MMR and VAR are recommended for HIV-infected children who are asymptomatic or only low-level immunocompromised.[k] All inactivated vaccines may be effective.
Generalized malignant neoplasm, transplantation, autoimmune disease, immunosuppressive or radiation therapy	Live-virus and live-bacteria vaccines, depending on immune status.[c,d,m]	PPSV23 should be given beginning at 2 yr of age.[f] Annual IIV (unless receiving intensive chemotherapy or anti-B cell antibodies). Hib vaccine may be indicated.[n]	Effectiveness of any vaccine depends on degree of immune suppression; inactivated standard vaccines are indicated if not highly immunosuppressed, but doses should be repeated after chemotherapy ends.

TABLE 10 Vaccination of Persons with Primary and Secondary Immune Deficiencies—cont'd

SECONDARY			
Specific Immunodeficiency	**Contraindicated Vaccines***	**Risk-Specific Recommended Vaccines***	**Effectiveness and Comments**
Asplenia (functional, congenital anatomic, surgical)	LAIV	PPSV23 should be given beginning at 2 yr of age.[f] MCV series beginning in infancy.[h] MenB series beginning at 10 yr of age. Hib (if not administered in infancy)[o]	All routine vaccines are probably effective.
Chronic renal disease	LAIV	PPSV23 should be given beginning at 2 yr of age.[f] HepB is indicated if not previously immunized.	All routine vaccines are probably effective.
CNS anatomic barrier defect (cochlear implant, congenital dysplasia of the inner ear, persistent CSF communication with naso-/oropharynx)	None	PPSV23 should be given beginning at 2 yr of age.[f]	All standard vaccines are indicated.

BCG, Bacille Calmette-Guérin vaccine; *CNS,* central nervous system; *Hib, Haemophilus influenzae* type b vaccine; *HIV/AIDS,* human immunodeficiency virus/acquired immunodeficiency syndrome; *IG,* immune globulin; *IIV,* inactivated influenza vaccine; *LAIV,* live-attenuated influenza vaccine; *MMR,* measles, mumps, rubella vaccine; *MMRV,* measles-mumps-rubella-varicella; *MCV,* quadrivalent meningococcal polysaccharide vaccine; *MenB,* serogroup B meningococcal vaccine; *OPV,* oral poliovirus vaccine (live); *PPSV23,* pneumococcal polysaccharide vaccine; *SCID,* severe combined immunodeficiency disease; *VAR,* varicella; *YF,* yellow fever.

*Other vaccines that are universally or routinely recommended should be given if not contraindicated.

[a]OPV is no longer available in the United States.

[b]This table refers to contraindications for nonemergency vaccination (i.e., ACIP recommendations)

[c]Live-bacteria vaccines: BCG and oral Ty21a *Salmonella typhi* vaccine.

[d]Live-virus vaccines: MMR, MMRV, VAR, OPV, LAIV, YF, zoster, rotavirus, and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.

[e]Children who are delayed or underimmunized should be immunized with routinely recommended vaccines, according to age and catch-up schedule.

[f]PPSV23 is begun at 2 yr or older. If PCV13 is required, PCV13 doses should be administered first, followed by PPSV23 at least 8 wk later; a 2nd dose of PPSV23 is given 5 yr after the 1st.

[g]Regarding T-lymphocyte immunodeficiency as a contraindication for rotavirus vaccine, data exist only for SCID.

[h]Age and schedule of doses depend on the product; repeated doses are required.

[i]Pneumococcal vaccine is not indicated for children with chronic granulomatous disease beyond age-based universal recommendations for PCV13. Children with chronic granulomatous disease are not at increased risk for pneumococcal disease.

[j]YF vaccine is contraindicated in HIV-infected children <6 yr old who are highly immunosuppressed. There is precaution for use of YF vaccine in asymptomatic HIV-infected children <6 yr with total lymphocyte percentage of 15%–24%, and >6 yr old with $CD4^+$ T-lymphocyte counts of 200-499 cells/mm^3.

[k]HIV-infected children should receive immune globulin after exposure to measles and may receive varicella vaccine if $CD4^+$ T-lymphocyte percentage is ≥15% for those <6 yr old, or $CD4^+$ T-lymphocyte count ≥200 cells/mm^3 for those ≥6 yr old. People with perinatal HIV infection who were vaccinated with measles, rubella, or mumps–containing vaccine before the establishment of combination antiretroviral therapy (cART) should be considered unvaccinated and should receive two appropriately spaced doses of MMR vaccine once effective cART has been established (at least 6 mo with $CD4^+$ T-lymphocytes ≥15% for children <6 yr old, or $CD4^+$ T-lymphocyte count ≥200 cells/mm^3 for children ≥6 yr old).

[l]For patients 5-18 yr old who have not received a Hib primary series and a booster dose or at least 1 Hib dose after age 14 mo.

[m]Withholding inactivated vaccines also is recommended with some forms of immunosuppressive therapy, such as anti-CD20 antibodies, induction or consolidation chemotherapy, or patients with major antibody deficiencies receiving immune globulins. Inactivated influenza vaccine is an exception, but consideration should be given to repeating doses of any inactivated vaccine administered during these therapies.

[n]For persons <60 mo old undergoing chemotherapy or radiation therapy who have not received a Hib primary series plus a booster dose or at least 1 Hib dose after age 14 mo.

[o]For persons >59 mo old who are asplenic and persons ≥15 mo who are undergoing elective splenectomy and who have not received a Hib primary series and a booster dose or at least 1 Hib dose after age 14 mo.

(Data from Centers for Disease Control and Prevention: Yellow fever vaccine: Recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep* 59[RR-07]; 1-27, 2010.)

From Kliegman, RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier. (Adapted from Immunization in special circumstances. In Kimberlin DW et al (eds): *Red Book 2018: Report of the Committee on Infectious Diseases,* ed 31, Elk Grove Village 2018, American Academy of Pediatrics.)

TABLE 11A Immunizations for Pediatric Oncology Patients

Vaccine	Indications and Comments
DTaP	Indicated for incompletely immunized children <7 yr, even during active chemotherapy
Td	Indicated 1 yr after completion of therapy in children 7 yr
Hib	Indicated for incompletely immunized children if <7 yr
HBV	Indicated for incompletely immunized children
23PS	Indicated for asplenic patients
PCV13	Indicated for incompletely immunized children <5 yr
Meningococcus	Consider in asplenic patients
IPV	Indicated for incompletely immunized children; also recommended for all household contacts requiring immunization to reduce the risk of vaccine-associated polio
MMR	Contraindicated until child is in remission and finished with all chemotherapy for 3-6 mo; may need to reimmunize after chemotherapy if titers have fallen below protective levels
Influenza	Defer in active chemotherapy; may give as early as 3-4 wk after remission and off chemotherapy if during influenza season; peripheral granulocyte and lymphocyte counts should be >1000/μL; should also be given to household contact of children with cancer
Varicella	Consider immunizing children who have remained in remission and have finished chemotherapy for >1 yr; with absolute lymphocyte count of >700/μL and platelet count of >100,000/μL within 24 hr of immunization; check titers of previously immunized children to verify protective levels of antibodies

DTaP, Diphtheria, tetanus, and pertussis; *HBV,* hepatitis B virus; *Hib, Haemophilus influenzae* type b; *IPV,* inactivated polio vaccine; *MMR,* measles, mumps, rubella; *PCV13,* pneumococcal conjugate vaccine; *Td,* tetanus, diphtheria; *23PS,* 23-valent pneumococcal polysaccharide vaccine.
From *MMWR* 49(RR-10):1-147, 2000.

TABLE 11B Vaccines Recommended for Children and Adolescents with Underlying Conditions or at High Risk

Vaccines	Special Situations
PCV13 (and PPSV23 in certain conditions)	Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), chronic liver disease, chronic renal failure
	Diabetes mellitus
	Cerebrospinal fluid leak
	Cochlear implant
	Sickle cell disease and other hemoglobinopathies
	Anatomic or functional asplenia
	HIV infection
	Nephrotic syndrome
	Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease
	Generalized malignancy
	Solid organ transplantation
	Congenital or acquired immunodeficiencies
	Multiple myeloma
Hep A	Chronic liver disease
	Clotting factor disorders
	Men who have sex with men
	Injection or noninjection drug use
	Homelessness
	Work with hepatitis A virus
	Travel in countries with high or intermediate endemic hepatitis A
	Close, personal contact with international adoptee (e.g., household or regular babysitting)
Flu	Egg allergy more severe than hives
MCV4	Anatomic or functional asplenia (including sickle cell disease)
	Persistent complement component deficiency
	Residents of or travelers to countries in African meningitis belt or pilgrims on the Hajj
	During outbreaks caused by a vaccine serogroup
	HIV infection
MenB	Anatomic or functional asplenia (including sickle cell disease)
	Children with persistent complement component deficiency
	During serogroup B outbreaks
Hib	Persons at increased risk for Hib disease, including chemotherapy recipients and those with anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV) infection, immunoglobulin deficiency, or early component complement deficiency
	Recipients of hematopoietic stem cell transplant (HSCT)
	Elective splenectomy
Hep B	Infants born to HBsAg-positive mothers or mothers whose HBsAg status is unknown (administer vaccine within 12 hr of birth)
HPV	Immunocompromising conditions, including HIV infection
	History of sexual abuse or assault

From Centers for Disease Control and Prevention: Child and adolescent schedule. www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html. In Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

TABLE 12 Approaches to the Evaluation and Vaccination of Persons Vaccinated Outside the United States Who Have No (or Questionable) Vaccination Records

Vaccine	Recommended Approach	Alternative Approach*
MMR	Revaccination with MMR	Serologic testing for IgG antibodies to measles, mumps, and rubella
Hib	Age-appropriate revaccination	—
Hepatitis A	Age-appropriate revaccination	Serologic testing for IgG antibodies to hepatitis A
Hepatitis B	Age-appropriate revaccination and serologic testing for HBsAg†	—
Poliovirus	Revaccinate with inactivated poliovirus vaccine	Serologic testing for neutralizing antibody to poliovirus types 1, 2, and 3 (limited availability)
DTaP	Revaccination with DTaP, with serologic testing for specific IgG antibody to tetanus and diphtheria toxins in the event of a severe local reaction	Persons whose records indicate receipt of ≥3 doses: serologic testing for specific IgG antibody to diphtheria and tetanus toxins before administering additional doses, or administer a single booster dose of DTaP, followed by serologic testing after 1 month for specific IgG antibody to diphtheria and tetanus toxins with revaccination as appropriate
Tdap	Age-appropriate vaccination of persons who are candidates for Tdap vaccine on the basis of time since last diphtheria and tetanus toxoid containing vaccines.	—
Varicella	Age-appropriate vaccination of persons who lack evidence of varicella immunity	—
Pneumococcal conjugate	Age-appropriate vaccination	—
Rotavirus	Age-appropriate vaccination	—
HPV	Age-appropriate vaccination	—
Zoster	Age-appropriate vaccination	—

DTaP, Diphtheria and tetanus toxoids and acellular pertussis; *HBsAg,* hepatitis B surface antigen; *Hib, Haemophilus influenzae* type b; *HPV,* human papillomavirus; *IgG,* immune globulin G; *MMR,* measles, mumps, and rubella; *Tdap,* tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

*There is a recommended approach for all vaccines and an alternative approach for some vaccines.

†In rare instances, hepatitis B vaccine can give a false-positive HBsAg result up to 18 days after vaccination; therefore, blood should be drawn to test for HBsAg before vaccinating. (Source: CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices [ACIP]; Part I: Immunization in infants, children, and adolescents, *MMWR* 2005;54(No. RR-16.)

From Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR*60:(RR-2), 2011.

Immunizations for Adults

RECOMMENDED IMMUNIZATION SCHEDULE FOR ADULTS AGED 19 YEARS OR OLDER, UNITED STATES, 2020

The *Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States* became effective, as recommended by the Advisory Committee on Immunization Practices (ACIP) and approved by the Centers for Disease Control and Prevention (CDC). The adult immunization schedule was also reviewed and approved by the following professional medical organizations:

- American College of Physicians (www.acponline.org)
- American Academy of Family Physicians (www.aafp.org)
- American College of Obstetricians and Gynecologists (www.acog.org)
- American College of Nurse-Midwives (www.midwife.org)

CDC announced the availability of the 2020 adult immunization schedule at www.cdc.gov/vaccines/schedules/easy-to-read/adult.html.

The adult immunization schedule describes the age groups and medical conditions and other indications for which licensed vaccines are recommended. The 2020 adult immunization schedule consists of:

- Table 13. Recommended immunization schedule for adults by age group
- Table 14. Recommended immunization schedule for adults by medical condition and other indications
- Footnotes that accompany each vaccine containing important general information and considerations for special populations

Consider the following information when reviewing the adult immunization schedule:

- The tables in the adult immunization schedule should be read with the footnotes that contain important general information and information about vaccination of special populations.
- When indicated, administer recommended vaccines to adults whose vaccination history is incomplete or unknown.
- Increased interval between doses of a multi-dose vaccine does not diminish vaccine effectiveness; therefore, it is not necessary to restart the vaccine series or add doses to the series because of an extended interval between doses.
- Adults with immunocompromising conditions should generally avoid live vaccines, e.g., measles, mumps, and rubella vaccine. Inactivated vaccines, e.g., pneumococcal or inactivated influenza vaccines, are generally acceptable.
- Combination vaccines may be used when any component of the combination is indicated and when the other components of the combination vaccine are not contraindicated.
- The use of trade names in the adult immunization schedule is for identification purposes only and does not imply endorsement by the ACIP or CDC.

Details on vaccines recommended for adults and complete ACIP statements are available at www.cdc.gov/vaccines/hcp/acip-recs/index.html. Additional CDC resources include:

- A summary of information on vaccination recommendations, vaccination of persons with immunodeficiencies, preventing and managing adverse reactions, vaccination contraindications and precautions, and other information can be found in *General Recommendations on Immunization* at www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm.
- Vaccine Information Statements that explain benefits and risks of vaccines are available at www.cdc.gov/vaccinesafety/Concerns/Index.html.
- Information and resources regarding vaccination of pregnant women are available at www.cdc.gov/vaccines/pregnancy/pregnant-women/index.html.
- Information on travel vaccine requirements and recommendations is available at www.cdc.gov/travel/destinations/list.
- *CDC Vaccine Schedules App* for clinicians and other immunization service providers to download is available at www.cdc.gov/vaccines/schedules/.
- *Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger* is available at www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html#schedule.

Report suspected cases of reportable vaccine-preventable diseases to the local or state health department.

Report all clinically significant post-vaccination reactions to the Vaccine Adverse Event Reporting System at www.vaers.hhs.gov or by telephone, 800-822-7967. All vaccines included in the 2020 adult immunization schedule except herpes zoster and 23-valent pneumococcal polysaccharide vaccines are covered by the Vaccine Injury Compensation Program. Information on how to file a vaccine injury claim is available at www.hrsa.gov/vaccinecompensation or by telephone, 800-338-2382.

The following acronyms are used for vaccines recommended for adults:

HepA	hepatitis A vaccine
HepA-HepB	hepatitis A and hepatitis B vaccines
HepB	hepatitis B vaccine
Hib	*Haemophilus influenzae* type b conjugate vaccine
HPV vaccine	human papillomavirus vaccine
HZV	herpes zoster vaccine
IIV	inactivated influenza vaccine
LAIV	live attenuated influenza vaccine
MenACWY	serogroups A, C, W, and Y meningococcal conjugate vaccine
MenB	serogroup B meningococcal vaccine
MMR	measles, mumps, and rubella vaccine
MPSV4	serogroups A, C, W, and Y meningococcal polysaccharide vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
RIV	recombinant influenza vaccine
Td	tetanus and diphtheria toxoids
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
VAR	varicella vaccine

TABLE 13 Recommended Immunization Schedule for Adults Aged 19 Years or Older by Age Group, United States, 2020

These recommendations must be read with the footnotes that follow.

Vaccine	19–21 years	22–26 years	27–49 years	50–64 years	≥65 years
Influenza inactivated (IIV) or **Influenza recombinant** (RIV) or **Influenza live attenuated** (LAIV)	1 dose annually (or) 1 dose annually				
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap, then Td booster every 10 yrs				
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)				
Varicella (VAR)	2 doses (if born in 1980 or later)				
Zoster recombinant (RZV) *(preferred)* or **Zoster live** (ZVL)				2 doses (or) 1 dose	
Human papillomavirus (HPV) **Female**	2 or 3 doses depending on age at initial vaccination				
Human papillomavirus (HPV) **Male**	2 or 3 doses depending on age at initial vaccination				
Pneumococcal conjugate (PCV13)	1 dose				
Pneumococcal polysaccharide (PPSV23)	1 or 2 doses depending on indication				1 dose
Hepatitis A (HepA)	2 or 3 doses depending on vaccine				
Hepatitis B (HepB)	2 or 3 doses depending on vaccine				
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, then booster every 5 yrs if risk remains				
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication				
***Haemophilus influenzae* type b** (Hib)	1 or 3 doses depending on indication				

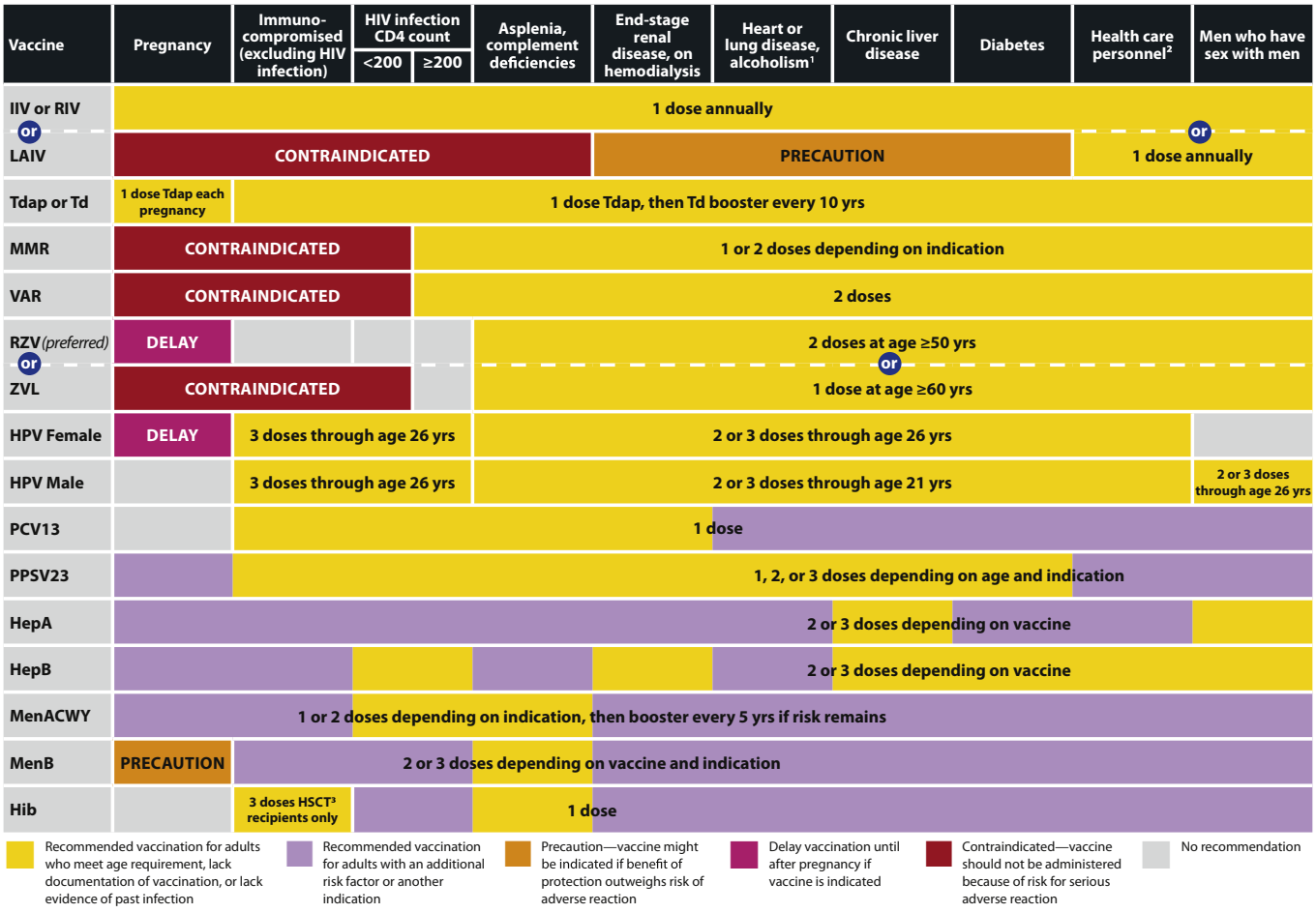
Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended vaccination for adults with an additional risk factor or another indication

No recommendation

TABLE 14 Recommended Immunization Schedule for Adults Aged 19 Years or Older by Medical Condition and Other Indications, United States, 2020

These recommendations must be read with the footnotes that follow.



1. Precaution for LAIV does not apply to alcoholism. **2.** See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. **3.** Hematopoietic stem cell transplant.

Footnotes. Recommended Adult Immunization Schedule United States, 2020

1. ***Haemophilus influenzae*** **type b vaccination**
   Special situations
   - **Anatomical or functional asplenia (including sickle cell disease):** 1 dose Hib if previously did not receive Hib; if elective splenectomy, 1 dose Hib, preferably at least 14 days before splenectomy
   - **Hematopoietic stem cell transplant** (HSCT): 3-dose series Hib 4 weeks apart starting 6–12 months after successful transplant, regardless of Hib vaccination history
2. **Hepatitis A vaccination**
   Routine vaccination
   - **Not at risk but want protection from hepatitis A** (identification of risk factor not required): 2-dose series HepA (Havrix 6–12 months apart or Vaqta 6–18 months apart [minimum interval: 6 months]) or 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: 4 weeks between doses 1 and 2, 5 months between doses 2 and 3])

   Special situations
   - **At risk for hepatitis A virus infection:** 2-dose series HepA or 3-dose series HepA-HepB as above
     - **Chronic liver disease**
     - **Clotting factor disorders**
     - **Men who have sex with men**
     - **Injection or noninjection drug use**
     - **Homelessness**
     - **Work with hepatitis A virus** in research laboratory or nonhuman primates with hepatitis A virus infection
     - **Travel in countries with high or intermediate endemic hepatitis A**
     - **Close personal contact with international adoptee** (e.g., household, regular babysitting) in first 60 days after arrival from country with high or intermediate endemic hepatitis A (administer dose 1 as soon as adoption is planned, at least 2 weeks before adoptee's arrival)
3. **Hepatitis B vaccination**
   Routine vaccination
   - **Not at risk but want protection from hepatitis B** (identification of risk factor not required): 2- or 3-dose series HepB (2-dose series Heplisav-B at least 4 weeks apart [2-dose series HepB only applies when 2 doses of Heplisav-B are used at least 4 weeks apart] or 3-dose series Engerix-B or Recombivax HB at 0, 1, 6 months [minimum intervals: 4 weeks between doses 1 and 2, 8 weeks between doses 2 and 3, 16 weeks between doses 1 and 3]) or 3-dose series HepA-HepB (Twinrix at 0, 1, 6 months [minimum intervals: 4 weeks between doses 1 and 2, 5 months between doses 2 and 3])

   Special situations
   - **At risk for hepatitis B virus infection:** 2-dose (Heplisav-B) or 3-dose (Engerix-B, Recombivax HB) series HepB, or 3-dose series HepA-HepB as above
     - **Hepatitis C virus infection**
     - **Chronic liver disease** (e.g., cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice upper limit of normal)
     - **HIV infection**
     - **Sexual exposure risk** (e.g., sex partners of hepatitis B surface antigen (HBsAg)-positive persons; sexually active persons not in mutually monogamous relationships, persons seeking evaluation or treatment for a sexually transmitted infection, men who have sex with men)
     - **Current or recent injection drug use**
     - **Percutaneous or mucosal risk for exposure to blood** (e.g., household contacts of HBsAg-positive persons; residents and staff of facilities for developmentally disabled persons; health care and public safety personnel with reasonably anticipated risk for exposure

to blood or blood-contaminated body fluids; hemodialysis, peritoneal dialysis, home dialysis, and predialysis patients; persons with diabetes mellitus age younger than 60 years and, at discretion of treating clinician, those age 60 years or older)
  - **Incarcerated persons**
  - **Travel in countries with high or intermediate endemic hepatitis B**

4. **Human papillomavirus vaccination**
   Routine vaccination
   - **Females through age 26 years and males through age 21 years:** 2- or 3-dose series HPV vaccine depending on age at initial vaccination; males age 22 through 26 years may be vaccinated based on individual clinical decision (HPV vaccination routinely recommended at age 11–12 years)
   - **Age 15 years or older at initial vaccination:** 3-dose series HPV vaccine at 0, 1–2, 6 months (minimum intervals: 4 weeks between doses 1 and 2, 12 weeks between doses 2 and 3, 5 months between doses 1 and 3; repeat dose if administered too soon)
   - **Age 9 through 14 years at initial vaccination and received 1 dose, or 2 doses less than 5 months apart:** 1 dose HPV vaccine
   - **Age 9 through 14 years at initial vaccination and received 2 doses at least 5 months apart:** HPV vaccination complete, no additional dose needed
   - If completed valid vaccination series with any HPV vaccine, no additional doses needed

   Special situations
   - **Immunocompromising conditions (including HIV infection) through age 26 years:** 3-dose series HPV vaccine at 0, 1–2, 6 months as above
   - **Men who have sex with men and transgender persons through age 26 years:** 2- or 3-dose series HPV vaccine depending on age at initial vaccination as above
   - **Pregnancy through age 26 years:** HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant; pregnancy testing not needed before vaccination

5. **Influenza vaccination**
   Routine vaccination
   - **Persons age 6 months or older:** 1 dose IIV, RIV, or LAIV appropriate for age and health status annually
     For additional guidance, see www.cdc.gov/flu/professionals/index.htm

   Special situations
   - **Egg allergy, hives only:** 1 dose IIV, RIV, or LAIV appropriate for age and health status annually
   - **Egg allergy more severe than hives** (e.g., angioedema, respiratory distress): 1 dose IIV, RIV, or LAIV appropriate for age and health status annually in medical setting under supervision of health care provider who can recognize and manage severe allergic conditions
   - **Immunocompromising conditions (including HIV infection), anatomical or functional asplenia, pregnant women, close contacts and caregivers of severely immunocompromised persons in protected environment, use of influenza antiviral medications in previous 48 hours, with cerebrospinal fluid leak or cochlear implant:** 1 dose IIV or RIV annually (LAIV not recommended)
   - **History of Guillain-Barré syndrome within 6 weeks of previous dose of influenza vaccine:** Generally should not be vaccinated

6. **Measles, mumps, and rubella vaccination**
   Routine vaccination
   - **No evidence of immunity to measles, mumps, or rubella:** 1 dose MMR
     - Evidence of immunity: Born before 1957 (except health care personnel [see below]), documentation of receipt of MMR, laboratory evidence of immunity or disease (diagnosis of disease without laboratory confirmation is not evidence of immunity)

   Special situations
   - **Pregnancy with no evidence of immunity to rubella:** MMR contraindicated during pregnancy; after pregnancy (before discharge from health care facility), 1 dose MMR
   - **Nonpregnant women of childbearing age with no evidence of immunity to rubella:** 1 dose MMR
   - **HIV infection with CD4 count ≥200 cells/μL for at least 6 months and no evidence of immunity to measles, mumps, or rubella:** 2-dose series MMR at least 4 weeks apart; MMR contraindicated in HIV infection with CD4 count <200 cells/μL
   - **Severe immunocompromising conditions:** MMR contraindicated
   - **Students in postsecondary educational institutions, international travelers, and household or close personal contacts of immunocompromised persons with no evidence of immunity to measles, mumps, or rubella:** 1 dose MMR if previously received 1 dose MMR, or 2-dose series MMR at least 4 weeks apart if previously did not receive any MMR
   - **Health care personnel born in 1957 or later with no evidence of immunity to measles, mumps, or rubella:** 2-dose series MMR at least 4 weeks apart for measles or mumps, or at least 1 dose MMR for rubella; if born before 1957, consider 2-dose series MMR at least 4 weeks apart for measles or mumps, or 1 dose MMR for rubella

7. **Meningococcal vaccination**
   Special situations for MenACWY
   - **Anatomical or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, eculizumab use:** 2-dose series MenACWY (Menactra, Menveo) at least 8 weeks apart and revaccinate every 5 years if risk remains
   - **Travel in countries with hyperendemic or epidemic meningococcal disease, microbiologists routinely exposed to *Neisseria meningitidis*:** 1 dose MenACWY and revaccinate every 5 years if risk remains
   - **First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) and military recruits:** 1 dose MenACWY

   Special situations for MenB
   - **Anatomical or functional asplenia (including sickle cell disease), persistent complement component deficiency, eculizumab use, microbiologists routinely exposed to *Neisseria meningitidis*:** 2-dose series MenB-4C (Bexsero) at least 1 month apart, or 3-dose series MenB-FHbp (Trumenba) at 0, 1–2, 6 months (if dose 2 was administered at least 6 months after dose 1, dose 3 not needed); MenB-4C and MenBFHbp are not interchangeable (use same product for all doses in series)
   - **Pregnancy:** Delay MenB until after pregnancy unless at increased risk and vaccination benefit outweighs potential risks
   - **Healthy adolescents and young adults age 16 through 23 years (age 16 through 18 years preferred) not at increased risk for meningococcal disease:** Based on individual clinical decision, may receive 2-dose series MenB-4C at least 1 month apart, or 2-dose series MenB-FHbp at 0, 6 months (if dose 2 was administered less than 6 months after dose 1, administer dose 3 at least 4 months after dose 2); MenB-4C and MenB-FHbp are not interchangeable (use same product for all doses in series)

8. **Pneumococcal vaccination**
   Routine vaccination
   - **Age 65 years or older** (immunocompetent): 1 dose PCV13 if previously did not receive PCV13, followed by 1 dose PPSV23 at least 1 year after PCV13 and at least 5 years after last dose PPSV23
     - Previously received PPSV23 but not PCV13 at age 65 years or older: 1 dose PCV13 at least 1 year after PPSV23
     - When both PCV13 and PPSV23 are indicated, administer PCV13 first (PCV13 and PPSV23 should not be administered during same visit)

   Special situations
   - **Age 19 through 64 years with chronic medical conditions (chronic heart [excluding hypertension], lung, or liver disease; diabetes), alcoholism, or cigarette smoking:** 1 dose PPSV23
   - **Age 19 years or older with immunocompromising conditions (congenital or acquired immunodeficiency [including B- and T-lymphocyte deficiency, complement deficiencies, phagocytic disorders, HIV infection], chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression [e.g., drug or radiation therapy], solid organ transplant, multiple myeloma) or anatomical or functional asplenia (including sickle cell disease and other hemoglobinopathies):** 1 dose PCV13 followed by 1 dose PPSV23 at least 8 weeks later, then another dose PPSV23 at least 5 years after previous PPSV23; at age 65 years or older, administer 1 dose PPSV23 at least 5 years after most recent PPSV23 (note: only 1 dose PPSV23 recommended at age 65 years or older)
   - **Age 19 years or older with cerebrospinal fluid leak or cochlear implant:** 1 dose PCV13 followed by 1 dose PPSV23 at least 8 weeks later; at age 65 years or older, administer another dose PPSV23 at least 5 years after PPSV23 (note: only 1 dose PPSV23 recommended at age 65 years or older)

Continued

9. **Tetanus, diphtheria, and pertussis vaccination**
   Routine vaccination
   - **Previously did not receive Tdap at or after age 11 years:** 1 dose Tdap, then Td booster every 10 years

   Special situations
   - **Previously did not receive primary vaccination series for tetanus, diphtheria, and pertussis:** 1 dose Tdap followed by 1 dose Td at least 4 weeks after Tdap, and another dose Td 6–12 months after last Td (Tdap can be substituted for any Td dose, but preferred as first dose); Td booster every 10 years thereafter
   - **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36
   - For information on use of Tdap or Td as tetanus prophylaxis in wound management, see www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm

10. **Varicella vaccination**
    Routine vaccination
    - **No evidence of immunity to varicella:** 2-dose series VAR 4–8 weeks apart if previously did not receive varicella-containing vaccine (VAR or MMRV [measlesmumps-rubella-varicella vaccine] for children); if previously received 1 dose varicella-containing vaccine: 1 dose VAR at least 4 weeks after first dose
      - Evidence of immunity: U.S.-born before 1980 (except for pregnant women and health care personnel [see below]), documentation of 2 doses varicella-containing vaccine at least 4 weeks apart, diagnosis or verification of history of varicella or herpes zoster by a health care provider, laboratory evidence of immunity or disease

    Special situations
    - **Pregnancy with no evidence of immunity to varicella:** VAR contraindicated during pregnancy; after pregnancy (before discharge from health care facility), 1 dose VAR if previously received 1 dose varicellacontaining vaccine, or dose 1 of 2-dose series VAR (dose 2: 4–8 weeks later) if previously did not receive any varicella-containing vaccine, regardless of whether U.S.-born before 1980
    - **Health care personnel with no evidence of immunity to varicella:** 1 dose VAR if previously received 1 dose varicella-containing vaccine, or 2-dose series VAR 4–8 weeks apart if previously did not receive any varicella-containing vaccine, regardless of whether U.S.-born before 1980
    - **HIV infection with CD4 count ≥200 cells/μL with no evidence of immunity:** Consider 2-dose series VAR 3 months apart based on individual clinical decision; VAR contraindicated in HIV infection with CD4 count <200 cells/μL
    - **Severe immunocompromising conditions:** VAR contraindicated

11. **Zoster vaccination**
    Routine vaccination
    - **Age 50 years or older:** 2-dose series RZV 2–6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon) regardless of previous herpes zoster or previously received ZVL (administer RZV at least 2 months after ZVL)
    - **Age 60 years or older:** 2-dose series RZV 2–6 months apart (minimum interval: 4 weeks; repeat dose if administered too soon) or 1 dose ZVL if not previously vaccinated (if previously received ZVL, administer RZV at least 2 months after ZVL); RZV preferred over ZVL

    Special situations
    - **Pregnancy:** ZVL contraindicated; consider delaying RZV until after pregnancy if RZV is otherwise indicated
    - **Severe immunocompromising conditions (including HIV infection with CD4 count <200 cells/μL):** ZVL contraindicated; recommended use of RZV under review

The Advisory Committee on Immunization Practices (ACIP) recommendations and package inserts for vaccines provide information on contraindications and precautions related to vaccines. Contraindications are conditions that increase chances of a serious adverse reaction in vaccine recipients and the vaccine should not be administered when a contraindication is present. Precautions should be reviewed for potential risks and benefits for vaccine recipient. For a person with a severe allergy to latex, e.g., anaphylaxis, vaccines supplied in vials or syringes that contain natural rubber latex should not be administered unless the benefit of vaccination clearly outweighs the risk for a potential allergic reaction. For latex allergies other than anaphylaxis, vaccines supplied in vials or syringes that contain dry, natural rubber or natural rubber latex may be administered.

TABLE 15 Immunization and Pregnancy

Vaccine	Before Pregnancy	During Pregnancy	After Pregnancy	Type of Vaccine	Route
Hepatitis A	If at high risk for disease	If at high risk for disease	If at high risk for disease	Inactivated	IM
Hepatitis B	Yes, if at risk	Yes, if at risk	Yes, if at risk	Inactivated	IM
Human papillomavirus (HPV)	Yes, if 9-26 years of age	No, under study	Yes, if 9-26 years of age	Inactivated	IM
Influenza TIV	Yes	Yes	Yes	Inactivated	IM
Influenza LAIV	Yes, if <50 years and healthy; avoid conception for 4 weeks	No	Yes, if <50 years and healthy; avoid conception for 4 weeks	Live	Nasal spray
MMR	Yes, avoid conception for 4 weeks	No	Yes, give immediately postpartum if susceptible to rubella	Live	SC
Meningococcal	If indicated	If indicated	If indicated		
Polysaccharide				Inactivated	SC
Conjugate				Inactivated	IM
Pneumococcal polysaccharide	If indicated	If indicated	If indicated	Inactivated	IM or SC
Tetanus/diphtheria Td	Yes, Tdap preferred	If indicated	Yes, Tdap preferred	Toxoid	IM
Tdap, one dose only	Yes, preferred	If high risk of pertussis; otherwise, Td preferred	Yes, preferred	Toxoid/ inactivated	IM
Varicella	Yes, avoid conception for 4 weeks	No	Yes, give immediately postpartum if susceptible	Live	SC

IM, Intramuscular; *LAIV,* live, attenuated influenza vaccine; *SC,* subcutaneous; *Tdap,* tetanus and diphtheria toxoids and acellular pertussis; *TIV,* trivalent inactivated influenza vaccine.

TABLE 16 Immunizing Agents and Immunization Schedules for Health Care Workers (HCWs)*

Generic Name	Primary Schedule and Booster(s)	Indications	Major Precautions and Contraindications	Special Considerations
Immunizing Agents Strongly Recommended for Health Care Workers				
Hepatitis B (HB) recombinant vaccine	Two doses IM 4 wk apart; third dose 5 mo after second; booster doses not necessary	**Preexposure:** HCWs at risk for exposure to blood or body fluids	Based on limited data no risk of adverse effects to developing fetuses is apparent. Pregnancy should *not* be considered a contraindication to vaccination of women. Previous anaphylactic reaction to common baker's yeast is a contraindication to vaccination.	The vaccine produces neither therapeutic nor adverse effects on HB-infected persons. Prevaccination serologic screening is not indicated for persons being vaccinated because of occupational risk. HCWs who have contact with patients or blood should be tested 1-2 mo after vaccination to determine serologic response.
Hepatitis B immune globulin (HBIG)	0.06 ml/kg IM as soon as possible after exposure. A second dose of HBIG should be administered 1 mo later if the HB vaccine series has not been started.	**Postexposure prophylaxis:** For persons exposed to blood or body fluids containing HBsAg and who are not immune to HBV infection—0.06 ml/kg IM as soon as possible (but no later than 7 days after exposure)		
Influenza vaccine (inactivated whole-virus and split-virus vaccines)	Annual vaccination with current vaccine Administered IM	HCWs who have contact with patients at high risk for influenza or its complications; HCWs who work in long-term care facilities; HCWs with high-risk medical conditions or who are aged ≥65 yr	History of anaphylactic hypersensitivity to egg ingestion	No evidence exists of risk to mother or fetus when the vaccine is administered to a pregnant woman with an underlying high-risk condition. Influenza vaccination is recommended during second and third trimesters of pregnancy because of increased risk for hospitalization.
Measles live-virus vaccine	One dose SC; second dose at least 1 mo later	HCWs† born during or after 1957 who do not have documentation of having received two doses of live vaccine on or after the first birthday **or** a history of physician-diagnosed measles or serologic evidence of immunity. Vaccination should be considered for all HCWs who lack proof of immunity, including those born before 1957.	Pregnancy; immunocompromised persons,‡ including HIV-infected persons who have evidence of severe immunosuppression; anaphylaxis after gelatin ingestion or administration of neomycin; recent administration of immune globulin	MMR is the vaccine of choice if recipients are likely to be susceptible to rubella and/or mumps as well as measles. Persons vaccinated between 1963 and 1967 with a killed measles vaccine alone, killed vaccine followed by live vaccine, or with a vaccine of unknown type should be revaccinated with two doses of live measles virus vaccine.
Mumps live-virus vaccine	One dose SC; second dose at least 1 mo later	HCWs† believed to be susceptible can be vaccinated. Adults born before 1957 can be considered immune.	Pregnancy; immunocompromised persons,‡ history of anaphylactic reaction after gelatin ingestion or administration of neomycin	MMR is the vaccine of choice if recipients are likely to be susceptible to measles and rubella, as well as mumps.
Hepatitis A virus (HAV) vaccine	Two doses of vaccine either 6-12 mo apart (HAVRIX), or 6 mo apart (VAQTA)	Not routinely indicated for HCWs in the United States. Persons who work with HAV-infected primates or with HAV in a research laboratory setting should be vaccinated.	History of anaphylactic hypersensitivity to alum or, for HAVRIX, the preservative 2-phenoxyethanol. The safety of the vaccine in pregnant women has not been determined; the risk associated with vaccination should be weighed against the risk for hepatitis A in women who may be at high risk for exposure to HAV.	

TABLE 16 Immunizing Agents and Immunization Schedules for Health Care Workers (HCWs)*—cont'd

Generic Name	Primary Schedule and Booster(s)	Indications	Major Precautions and Contraindications	Special Considerations
Meningococcal vaccine	One dose in volume and by route specified by manufacturer; single booster for adults 19-21 years of age if the first dose was given before age 16	Laboratory personnel and others with exposure risk.	The safety of the vaccine in pregnant women has not been evaluated; it should not be administered during pregnancy unless the risk for infection is high.	
Typhoid vaccine, IM, SC, and oral	IM vaccine: One 0.5-ml/dose, booster 0.5 ml every 2 yr SC vaccine: Two 0.5-ml doses, ≥4 wk apart, booster 0.5 ml SC or 0.1 ID every 3 yr if exposure continues Oral vaccine: Four doses on alternate days. The manufacturer recommends revaccination with the entire 4-dose series every 5 yr	Workers in microbiology laboratories who frequently work with *Salmonella typhi*	Severe local or systemic reaction to a previous dose. Ty21a (oral) vaccine should not be administered to immunocompromised persons† or to persons receiving antimicrobial agents.	Vaccination should not be considered an alternative to the use of proper procedures when handling specimens and cultures in the laboratory.
Vaccinia vaccine (smallpox)	One dose administered with a bifurcated needle; boosters administered every 10 yr	Laboratory workers who directly handle cultures with vaccinia, recombinant vaccinia viruses, or orthopox viruses that infect human beings	The vaccine is contraindicated in pregnancy, in persons with eczema or a history of eczema, and in immunocompromised persons† and their household contacts.	Vaccination may be considered for HCWs who have direct contact with contaminated dressings or other infectious material from volunteers in clinical studies involving recombinant vaccinia virus.
Other Vaccine-Preventable Diseases				
Tetanus and diphtheria and pertussis (Tdap)	Two IM doses 4 wk apart or tetanus and diphtheria toxoid for adults with uncertain or incomplete primary vaccination; third dose 6-12 mo after second dose; booster every 10 yr. Substitute a one-time dose of Tdap for one of the doses of Td, either in the primary series or for the routine booster, whichever comes first.	All adults	Except in the first trimester, pregnancy is not a precaution. History of a neurologic reaction or immediate hypersensitivity reaction after a previous dose. History of severe local (Arthus-type) reaction after a previous dose. Such persons should not receive further routine or emergency doses of Td for 10 yr.	Tetanus prophylaxis in wound management‡
Pneumococcal polysaccharide vaccine (23 valent)	One dose, 0.5 ml, IM or SC; revaccination recommended for those at highest risk ≥5 yr after the first dose	Adults who are at increased risk of pneumococcal disease and its complications because of underlying health conditions; older adults, especially those age ≥65 who are healthy	The safety of vaccine in pregnant women has not been evaluated; it should not be administered during pregnancy unless the risk for infection is high. Previous recipients of any type of pneumococcal polysaccharide vaccine who are at highest risk for fatal infection or antibody loss may be revaccinated ≥5 yr after the first dose.	

Continued

TABLE 16 Immunizing Agents and Immunization Schedules for Health Care Workers (HCWs)*—cont'd

Generic Name	Primary Schedule and Booster(s)	Indications	Major Precautions and Contraindications	Special Considerations
Rubella live-virus vaccine	One dose SC; second dose at least 1 mo later	Indicated for HCWs,† both men and women, who do not have documentation of having received live vaccine on or after their first birthday **or** laboratory evidence of immunity. Adults born before 1957, **except women who can become pregnant,** can be considered immune.	Pregnancy; immunocompromised persons†; history of anaphylactic reaction after administration of neomycin	The risk for rubella vaccine-associated malformations in the offspring of women pregnant when vaccinated or who become pregnant within 3 mo after vaccination is negligible. Such women should be counseled regarding the theoretic basis of concern for the fetus. MMR is the vaccine of choice if recipients are likely to be susceptible to measles or mumps as well as rubella.
Varicella-zoster live-virus vaccine	Two 0.5-ml doses SC 4-8 wk apart if ≥13 yr	Indicated for HCWs† who do not have either a reliable history of varicella or serologic evidence of immunity	Pregnancy, immunocompromised persons,‡ history of anaphylactic reaction after receipt of neomycin or gelatin. Avoid salicylate use for 6 wk after vaccination.	Vaccine is available from the manufacturer for certain patients with acute lymphocytic leukemia in remission. Because 71%-93% of persons without a history of varicella are immune, serologic testing before vaccination is likely to be cost effective.
Varicella-zoster immune globulin (VZIG)	Persons <50 kg: 125 μg/10 kg IM; persons ≥50 kg: 625 μg§	Persons known or likely to be susceptible (particularly those at high risk for complications, e.g., pregnant women) who have close and prolonged exposure to a contact case or to an infectious hospital staff worker or patient		Serologic testing may help in assessing whether to administer VZIG. If use of VZIG prevents varicella disease, patient should be vaccinated subsequently.
BCG Vaccination				
Bacille Calmette-Guérin (BCG) vaccine (TB)	One percutaneous dose of 0.3 ml; no booster dose recommended	Should be considered only for HCWs in areas where multidrug TB is prevalent, a strong likelihood of infection exists, and where comprehensive infection control precautions have failed to prevent TB transmission to HCWs	Should not be administered to immunocompromised persons,‡ pregnant women	In the United States TB-control efforts are directed toward early identification, treatment of cases, and preventive therapy with isoniazid.
Other Immunobiologics That Are or May Be Indicated for HCWs				
Immune globulin (hepatitis A)	**Postexposure**—One IM dose of 0.02 ml/kg administered ≤2 wk after exposure	Indicated for HCWs exposed to feces of infectious patients	Contraindicated in persons with IgA deficiency; do not administer within 2 wk after MMR vaccine or 3 wk after varicella vaccine. Delay administration of MMR vaccine for ≥3 mo and varicella vaccine ≥5 mo after administration of immune globulin	Administer in large muscle mass (deltoid, gluteal).

HBsAg, Hepatitis B surface antigen; *HBV,* hepatitis B virus; *HIV,* human immunodeficiency virus; *IM,* intramuscular; *MMR,* measles, mumps, rubella vaccine; *SC,* subcutaneous; *TB,* tuberculosis.

*Persons who provide health care to patients or work in institutions that provide patient care (e.g., physicians, nurses, emergency medical personnel, dental professionals and students, medical and nursing students, laboratory technicians, hospital volunteers, and administrative and support staff in health care institutions).

†All HCWs (i.e., medical or nonmedical, paid or volunteer, full time or part time, student or nonstudent, with or without patient-care responsibilities) who work in health care institutions (e.g., inpatient and outpatient, public and private) should be immune to measles, rubella, and varicella.

‡Persons immunocompromised because of immune deficiency diseases, HIV infection, leukemia, lymphoma or generalized malignancy, or immunosuppressed as a result of therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation.

§Some experts recommend 125 μg/10 kg regardless of total body weight.

Modified from *MMWR* 46(RR-18), 1998.

TABLE 17 Recommendations for Persons with Medical Conditions Requiring Special Vaccination Considerations

Condition	Tdap	MMR	Varicell[a]	HBV	HAV	Pneumovax[a]	Influenza[b]	HbCV	Meningococcal	IPV	Other Live Vaccines[c]	Other Killed Vaccines[d]
HIV infection	Rou	Rou/Contr[e]	Contr[f]	Rou[g]	Rou	Rec	Rec	Cons	Rou	Rou	Contr	Rou
Severe immunocompromise[h]	Rou	Contr	Contr[f]	Rou[g]	Rou	Rec	Rec	Rou[i]	Rou	Rou	Contr	Rou
Renal failure	Rou	Rou	Rou	Rec[g]	Rou	Rec	Rec	Rou	Rou	Rou	Rou	Rou
Diabetes	Rou	Rou	Rou	Rou	Rou	Rec	Rec	Rou	Rou	Rou	Rou	Rou
Chronic liver disease	Rou	Rou	Rou	Rou	Rec	Rec	Rec	Rou	Rou	Rou	Rou	Rou
Cardiac disease	Rou	Rou	Rou	Rou	Rou	Rec	Rec	Rou	Rou	Rou	Rou	Rou
Pulmonary disease	Rou	Rou	Rou	Rou	Rou	Rec	Rec	Rou	Rou	Rou	Rou	Rou
Alcoholism	Rou	Rou	Rou	Rou	Rou	Rec	Rec	Rou	Rou	Rou	Rou	Rou
Functional/anatomic asplenia	Rou	Rou	Rou	Rou	Rou	Rec[j]	Rec	Rec[j]	Rec[j]	Rou	Rou	Rou
Terminal complement deficiency	Rou	Rou	Rou	Rou	Rou	Rou	Rou	Rou	Rec	Rou	Rou	
Clotting factor disorders	Rou	Rou	Rou	Rec	Rec	Rou	Rou	Rou	Rou	Rou	Rou	Rou

Cons, Consider vaccination; *Contr,* contraindicated; *HAV,* hepatitis A virus; *HbCV, Haemophilus influenzae* conjugate vaccine; *HBV,* hepatitis B virus; *IPV,* inactivated poliomyelitis vaccine; *MMR,* measles-mumps-rubella; *Rec,* recommended; *Rou,* routine as outlined for all adults; *Tdap,* tetanus and diphtheria toxoids and acellular pertussis.

[a]Pneumovax should be repeated in 5 yr for patients in whom vaccine is recommended. Asthma without chronic obstructive pulmonary disease is not an indication for the vaccine.

[b]Influenza vaccine should also be given to caregivers and household members.

[c]Includes bacille Calmette-Guérin, vaccinia, oral typhoid, yellow fever (if exposure cannot be avoided, persons with HIV can be given yellow fever vaccine; see text).

[d]Includes rabies (check postvaccination titers in HIV or severely immunocompromised persons), Lyme disease, inactivated typhoid, cholera, plague, and anthrax.

[e]For asymptomatic, nonseverely immunocompromised persons with HIV, MMR can be used; it is contraindicated in severely immunocompromised persons. MMR can be considered in symptomatic HIV patients without severe immunocompromise.

[f]Varicella can be given to household members and caregivers, but if varicella-like rash develops after vaccination, contact should be avoided.

[g]Recommended for persons with severe chronic renal failure approaching or already receiving dialysis, and higher doses should be given. Antibody titers should be measured after vaccination in these patients and in those with HIV or severe immunocompromise (who may require higher doses) to ensure adequate response. Yearly titers should be measured in dialysis patients.

[h]Severe immunocompromise can result from congenital immunodeficiency, leukemia, lymphoma, malignancy, organ transplant, chemotherapy, radiation therapy, or high-dose corticosteroids.

[i]Only for persons with Hodgkin's disease.

[j]Give at least 2 wk in advance of elective splenectomy.

Modified and updated from *MMWR* 42(RR-4):16, 1993.

Vaccinations for International Travel

TABLE 18 Recommended Immunizations for Travelers to Developing Countries

Immunizations	LENGTH OF TRAVEL		
	Brief (<2 wk)	Intermediate (2 wk-3 mo)	Long-Term Residential (>3 mo)
Review and complete age-appropriate childhood schedule	+	+	+
DTaP, poliovirus, pneumococcal, and *Haemophilus influenzae* type B vaccines may be given at 4-week intervals if necessary to complete the recommended schedule before departure. Rotavirus vaccine has maximum ages for the first and last doses; consideration should be given to the timing of an infant's travel so that the infant will be able to receive the vaccine series.			
Measles: Infants 6-11mo of age should receive 1 dose of MMR vaccine before departure. Two additional doses are given if younger than 12 mo of age at first dose.			
Varicella			
Hepatitis A*			
Hepatitis B†			
Vaccines against the following diseases should be considered depending on the geographic area and circumstances of the visit:			
Japanese encephalitis‡	±	±	+
Meningococcal disease§	±	±	±
Rabies¶	±	+	+
Typhoid fever**	±	+	+
Yellow fever††	+	+	+

DTaP, Diphtheria-tetanus-acellular pertussis.
*Indicated for travelers to areas with intermediate or high endemic rates of hepatitis A virus infection.
†If insufficient time to complete 6-month primary series, an accelerated series can be given.
‡For regions with endemic infection. For high-risk activities in areas experiencing outbreaks, vaccine is recommended, even for brief travel.
§Recommended for regions of Africa with endemic infection and during local epidemics and required for travel to Saudi Arabia for the Hajj.
¶Indicated for persons at high risk for animal exposure (especially dogs) and for travelers to countries with endemic infection.
**Indicated for travelers who will consume food and liquids in areas of poor sanitation.
††For regions with endemic infection.
From Cherry JD: *Feigin and Cherry's pediatric infectious diseases*, ed 8, Elsevier, 2019. (Modified from American Academy of Pediatrics. Immunizations in special clinical circumstances. In Kimberlin DW et al (eds) *Red book: 2015 report of the Committee on Infectious Diseases*, ed 30, Elk Grove Village, 2015, American Academy of Pediatrics, 101-107; Centers for Disease Control and Prevention. Health information for international travel, 2016: international travel with infants and young children. Available at wwwnc.cdc.gov/travel/yellowbook/2016/international-travel-with-infants-children/vaccine-recommendations-for-infants-children.)

Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices

TABLE 19 Recommended Doses of Hepatitis B Vaccine, by Group and Vaccine Type

	SINGLE-ANTIGEN VACCINE				COMBINATION VACCINE			
	RECOMBIVAX		ENGERIX		PEDIARIX*		TWINRIX†	
Age Group (y)	Dose (µg)	Vol (ml)	Dose (µg)	Vol (ml)	Dose (µg)	Vol (ml)	DOSE (µg)	Vol (ml)
Birth-10	5	0.5	10	0.5	10*	0.5	N/A	N/A
11-15	10§	1	N/A	N/A	N/A	N/A	N/A	N/A
16-19	5	0.5	10	0.5	N/A	N/A	N/A	N/A
≥20	10	1	20	1	N/A	N/A	20†	1
Hemodialysis Patients and Other Immune-Compromised Persons								
<20	5	0.5	10	0.5	N/A	N/A	N/A	N/A
≥20	40	1	40	2	N/A	N/A	N/A	N/A

N/A, Not applicable.
*Pediarix is approved for use in persons aged 6 weeks through 6 years (before the 7th birthday).
†Twinrix is approved for use in persons aged ≥18 years.
§Adult formulation administered on a 2-dose schedule.
From Schillie S et al: Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep* 67(No. RR-1):1-31, 2018.

TABLE 20 Hepatitis B Vaccine Schedules for Infants, by Infant Birthweight and Maternal HBsAg Status

		SINGLE-ANTIGEN VACCINE		SINGLE-ANTIGEN + COMBINATION VACCINE†	
Birthweight	**Maternal HBsAg Status**	**Dose**	**Age**	**Dose**	**Age**
≥2000 g	Positive	1	Birth (≤12 hr)	1	Birth (≤12 hr)
		HBIG§	Birth (≤12 hr)	HBIG	Birth (≤12 hr)
		2	1-2 mo	2	2 mo
		3	6 mo¶	3	4 mo
				4	6 mo¶
	Unknown*	1	Birth (≤12 hr)	1	Birth (≤12 hr)
		2	1–2 mo	2	2 mo
		3	6 mo¶	3	4 mo
				4	6 mo¶
	Negative	1	Birth (≤24 hr)	1	Birth (≤24 hr)
		2	1–2 mo	2	2 mo
		3	6–18 mo¶	3	4 mo
				4	6 mo¶
<2000 g	Positive	1	Birth (≤12 hr)	1	Birth (≤12 hr)
		HBIG	Birth (≤12 hr)	HBIG	Birth (≤12 hr)
		2	1 mo	2	2 mo
		3	2–3 mo	3	4 mo
		4	6 mo¶	4	6 mo¶
	Unknown	1	Birth (≤12 hr)	1	Birth (≤12 hr)
		HBIG	Birth (≤12 hr)	HBIG	Birth (≤12 hr)
		2	1 mo	2	2 mo
		3	2–3 mo	3	4 mo
		4	6 mo¶	4	6 mo¶
	Negative	1	Hospital discharge or age 1 mo	1	Hospital discharge or age 1 mo
		2	2 mo	2	2 mo
		3	6–18 mo¶	3	4 mo
				4	6 mo¶

HBIG, Hepatitis B immune globulin; *HBsAg,* hepatitis B surface antigen.
*Mothers should have blood drawn and tested for HBsAg as soon as possible after admission for delivery; if the mother is found to be HBsAg positive, the infant should receive HBIG as soon as possible but no later than age 7 days.
†Pediarix should not be administered before age 6 weeks.
§HBIG should be administered at a separate anatomical site from vaccine.
¶The final dose in the vaccine series should not be administered before age 24 weeks (164 days).
From Schillie S et al: Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep* 67(No. RR-1):1-31, 2018.

TABLE 21 Hepatitis B Vaccine Schedules for Children, Adolescents, and Adults

Age Group	**Schedule* (Interval Represents Time in Months from First Dose)**
Children (1-10 y)	0, 1, and 6 mo
	0, 1, 2, and 12 mo
Adolescents (11-19 y)	0, 1, and 6 mo
	0, 12, and 24 mo
	0 and 4-6 mo†
	0, 1, 2, and 12 mo
	0, 7 d, 21-30 d, 12 mo§
Adults (≥20 y)	0, 1, and 6 mo
	0, 1, 2, and 12 mo
	0, 1, 2, and 6 mo¶
	0, 7 d, 21-30 d, 12 mo§

*Refer to package inserts for further information. For all ages, when the HepB vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be administered as soon as possible, and the second and third doses should be separated by an interval of at least 8 weeks. If only the third dose has been delayed, it should be administered as soon as possible. The final dose of vaccine must be administered at least 8 weeks after the second dose and should follow the first dose by at least 16 weeks; the minimum interval between the first and second doses is 4 weeks. Inadequate doses of hepatitis B vaccine or doses received after a shorter-than-recommended dosing interval should be readministered, using the correct dosage or schedule. Vaccine doses administered ≤4 days before the minimum interval or age are considered valid. Because of the unique accelerated schedule for Twinrix, the 4-day guideline does not apply to the first three doses of this vaccine when administered on a 0-day, 7-day, 21-30-day, and 12-month schedule (new recommendation).
†A 2-dose schedule of Recombivax adult formulation (10 μg) is licensed for adolescents aged 11-15 years. When scheduled to receive the second dose, adolescents aged >15 years should be switched to a 3-dose series, with doses 2 and 3 consisting of the pediatric formulation administered on an appropriate schedule.
§Twinrix is approved for use in persons aged ≥18 years and is available on an accelerated schedule with doses administered at 0, 7, and 21-30 days and 12 months.
¶A 4-dose schedule of Engerix administered in two 1 ml doses (40 μg) on a 0-, 1-, 2-, and 6-month schedule is recommended for adult hemodialysis patients.
From Schillie S et al: Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep* 67(No. RR-1):1-31, 2018.

TABLE 22 Postexposure Management of Health Care Personnel after Occupational Percutaneous or Mucosal Exposure to Blood or Body Fluids, by Health Care Personnel HepB Vaccination and Response Status

	POSTEXPOSURE TESTING		POSTEXPOSURE PROPHYLAXIS		
HCP Status	**Source Patient (HBsAg)**	**HCP Testing (Anti-HBs)**	**HBIG**	**Vaccination**	**Postvaccination Serologic Testing**
Documented responder after complete series			No action needed		
Documented nonresponder after two complete series	Positive/unknown	–*	HBIG ×2 separated by 1 month	—	N/A
	Negative			No action needed	
Response unknown after complete series	Positive/unknown	<10 mIU/ml	HBIG ×1	Initiate revaccination	Yes
	Negative	<10 mIU/ml	None	Initiate revaccination	Yes
	Any result	≥10 mIU/ml		No action needed	
Unvaccinated/incompletely vaccinated or vaccine refusers	Positive/unknown	—	HBIG ×1	Complete vaccination	Yes
	Negative	—	None	Complete vaccination	Yes

Anti-HBs, Antibody to hepatitis B surface antigen; *HBIG,* hepatitis B immune globulin; *HBsAg,* hepatitis B surface antigen; *HCP,* health care personnel; *N/A,* not applicable.
*Not indicated.
From Schillie S et al: Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep* 67(No. RR-1):1-31, 2018.

TABLE 23 Postexposure Management after Distinct Nonoccupational Percutaneous or Mucosal Exposure to Blood or Body Fluids

	MANAGEMENT	
Exposure*	**Unvaccinated Person**	**Previously Vaccinated Person**
HBsAg-positive source	HepB vaccine series and HBIG	HepB vaccine dose
HBsAg status unknown for source	Hep B vaccine series	No management

HBIG, Hepatitis B immune globulin; *HBsAg,* hepatitis B surface antigen; *HepB,* hepatitis B.
*Exposures include percutaneous (e.g., bite or needlestick) or mucosal exposure to blood or body fluids, sex or needle-sharing contact, or victim of sexual assault/abuse.
From Schillie S et al: Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep* 67(No. RR-1):1-31, 2018.

BOX 1 Persons Recommended to Receive Hepatitis B Vaccination

- All infants
- Unvaccinated children aged <19 years
- Persons at risk for infection by sexual exposure
  - Sex partners of hepatitis B surface antigen (HBsAg)-positive persons
  - Sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than one sex partner during the previous 6 months)
  - Persons seeking evaluation or treatment for a sexually transmitted infection
  - Men who have sex with men
- Persons at risk for infection by percutaneous or mucosal exposure to blood
  - Current or recent injection-drug users
  - Household contacts of HBsAg-positive persons
  - Residents and staff of facilities for developmentally disabled persons
  - Health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids
  - Hemodialysis patients and predialysis, peritoneal dialysis, and home dialysis patients
  - Persons with diabetes aged 19-59 years; persons with diabetes aged ≥60 years at the discretion of the treating clinician
- Others
  - International travelers to countries with high or intermediate levels of endemic hepatitis B virus (HBV) infection (HBsAg prevalence of ≥2%)
  - Persons with hepatitis C virus infection
  - Persons with chronic liver disease (including persons with cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level greater than twice the upper limit of normal)
  - Persons with HIV infection
  - Incarcerated persons
- All other persons seeking protection from HBV infection

From Schillie S et al: Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep* 67(No. RR-1):1-31, 2018.

BOX 2 Testing Anti-HBs for Health Care Personnel (HCP) Vaccinated in the Past

The issue: An increasing number of HCP have received routine hepatitis B (HepB) vaccination during childhood. No postvaccination serologic testing is recommended after routine infant or adolescent HepB vaccination. Because vaccine-induced antibody to hepatitis B surface antigen (anti-HBs) wanes over time, testing HCP for anti-HBs years after vaccination might not distinguish vaccine nonresponders from responders.

Guidance for health care institutions: Health care institutions may measure anti-HBs upon hire or matriculation for HCP who have documentation of a complete HepB vaccine series in the past (e.g., as part of routine infant or adolescent vaccination). HCP with anti-HBs <10 mIU/mL should receive one or more additional doses of HepB vaccine and retesting (see Fig. 6). Institutions that decide to not measure anti-HBs upon hire or matriculation for HCP who have documentation of a complete HepB vaccine series in the past should ensure timely assessment and postexposure prophylaxis following an exposure (see Table 22).

Considerations: The risk for occupational HBV infection for vaccinated HCP might be low enough in certain settings so that assessment of anti-HBs status and appropriate follow-up should be done at the time of exposure to potentially infectious blood or body fluids. This approach relies on HCP recognizing and reporting blood and body fluid exposures and therefore may be applied on the basis of documented low risk, implementation, and cost considerations. Certain HCP occupations have lower risk for occupational blood and body fluid exposures (e.g., occupations involving counseling versus performing procedures), and nontrainees have lower risks for blood and body fluid exposures than trainees. Some settings also will have a lower prevalence of HBV infection in the patient population served than in other settings, which will influence the risk for HCP exposure to HBsAg-positive blood and body fluids.

From Schillie S et al: Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep* 67(No. RR-1):1-31, 2018.

BOX 3 Persons Recommended to Receive Serologic Testing Before Vaccination*

- Household, sexual, or needle contacts of hepatitis B surface antigen (HBsAg)-positive persons†
- HIV-positive persons†
- Persons with elevated alanine aminotransferase/aspartate aminotransferase of unknown etiology†
- Hemodialysis patients†
- Men who have sex with men†
- Past or current persons who inject drugs†
- Persons born in countries of high and intermediate hepatitis B virus (HBV) endemicity (HBsAg prevalence ≥2%)
- U.S.-born persons not vaccinated as infants whose parents were born in countries with high HBV endemicity (≥8%)
- Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterologic disorders
- Donors of blood, plasma, organs, tissues, or semen

*Serologic testing comprises testing for hepatitis B surface antigen (HBsAg), antibody to HBsAg, and antibody to hepatitis B core antigen.
†Denotes persons also recommended for hepatitis B vaccination. Serologic testing should occur before vaccination. Serologic testing should not be a barrier to vaccination of susceptible persons. The first dose of vaccine should typically be administered immediately after collection of the blood for serologic testing.
From Schillie S et al: Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep* 67(No. RR-1):1-31, 2018.

BOX 4 Persons Recommended to Receive Postvaccination Serologic Testing* after a Complete Series of Hepatitis B Vaccination

- Infants born to hepatitis B surface antigen (HBsAg)-positive mothers or mothers whose HBsAg status remains unknown (e.g., when a parent or person with lawful custody safely surrenders an infant confidentially shortly after birth)†
- Health care personnel and public safety workers
- Hemodialysis patients and others who might require outpatient hemodialysis (e.g., predialysis, peritoneal dialysis, and home dialysis)
- HIV-infected persons
- Other immunocompromised persons (e.g., hematopoietic stem-cell transplant recipients or persons receiving chemotherapy)
- Sex partners of HBsAg-positive persons

*Postvaccination serologic testing for persons other than infants born to HBsAg-positive (or HBsAg-unknown) mothers consists of anti-HBs.
†Postvaccination serologic testing for infants born to HBsAg-positive (or HBsAg-unknown) mothers consists of anti-HBs and HBsAg. Persons with anti-HBs <10 mIU/ml after the primary vaccine series should be revaccinated. Infants born to HBsAg-positive mothers or mothers with an unknown HBsAg status should be revaccinated with a single dose of HepB vaccine and receive postvaccination serologic testing 1-2 months later. Infants whose anti-HBs remains <10 mIU/ml after single dose revaccination should receive two additional doses of HepB vaccine, followed by postvaccination serologic testing 1-2 months after the final dose. Based on clinical circumstances or family preference, HBsAg-negative infants with anti-HBs <10 mIU/ml may instead be revaccinated with a second, complete 3-dose series, followed by postvaccination serologic testing performed 1-2 months after the final dose of vaccine. For others with anti-HBs <10 mIU/ml after the primary series, administration of 3 additional HepB vaccine doses on an appropriate schedule, followed by anti-HBs testing 1-2 months after the final dose, is usually more practical than serologic testing after ≥1 dose of vaccine.
From Schillie S et al: Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep* 67(No. RR-1):1-31, 2018.

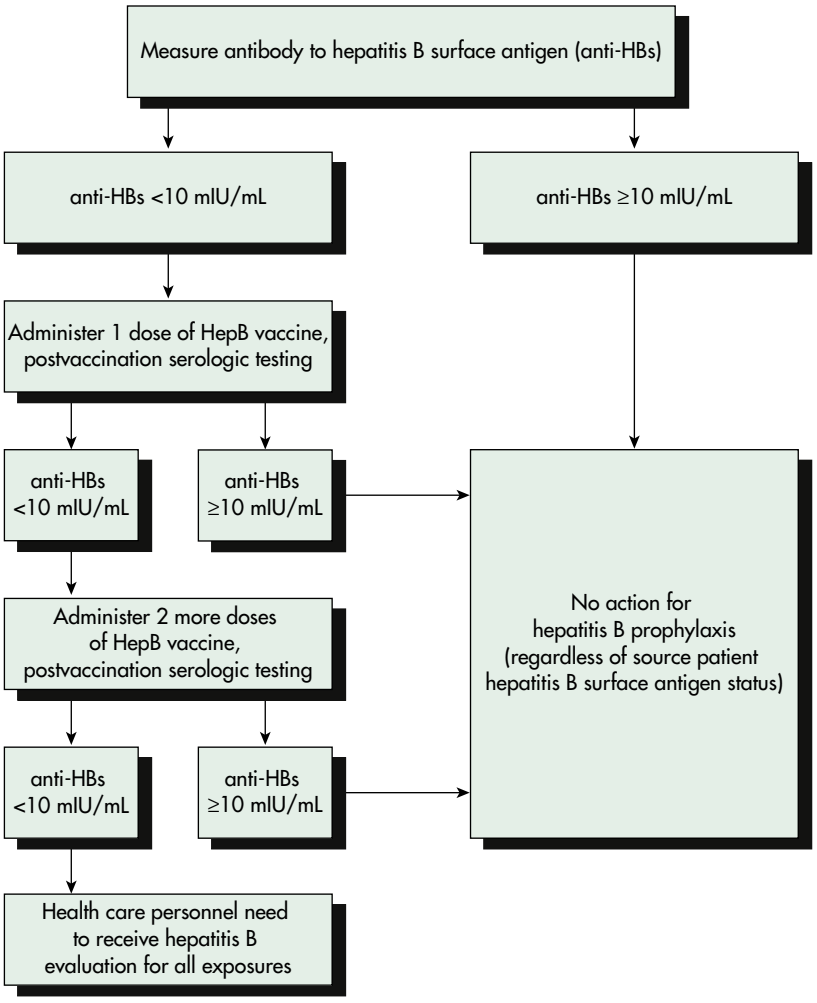


FIG. 6 Preexposure evaluation for health care personnel previously vaccinated with complete, ≥3-dose HepB vaccine series who have not had post-vaccination serologic testing.* Source: Adapted from CDC: a comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices [ACIP]. Part II: immunization of adults. *MMWR* 55 (No.RR-16), 2006. *Should be performed 1-2 months after the last dose of vaccine using a quantitative method that allows detection of the protective concentration of anti-HBs (≥10 mIU/ml) (e.g., enzyme-linked immunosorbent assay [ELISA]). (From Schillie S et al: Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep* 67[No. RR-1]:1-31, 2018.)

Hepatitis A Prophylaxis

TABLE 24 Recommended Dosages of Hepatitis A Immune Globulin

Setting	Duration of Coverage	Dose
Preexposure prophylaxis	Short term (<3 mo)	0.02 ml/kg
	Long term (3-5 mo)*	0.06 ml/kg
Postexposure prophylaxis	—	0.02 ml/kg

NOTE: Immune globulin should be administered intramuscularly into the deltoid or gluteal muscle in children younger than 24 mo; it may be administered in the anterolateral thigh muscle.
*Repeat every 5 mo if continued exposure to hepatitis A virus occurs.
Modified from Centers for Disease Control and Prevention: Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 55(RR-07):9, 2006.

TABLE 25 Licensed Dosages of Hepatitis A Vaccines

Vaccine	Patient's Age	Dose	Volume (ml)	Number of Doses	Schedule (mo)*
Hepatitis A vaccine, inactivated (Havrix)	12 mo to 18 yr	720 EL.U.	0.5	2	0, 6-12
	≥19 yr	1440 EL.U.	1.0	2	0, 6-12
Hepatitis A vaccine, inactivated (Vaqta)	12 mo to 18 yr	25 U	0.5	2	0, 6-18
	≥19 yr	50 U	1.0	2	0, 6-18
Combined hepatitis A and hepatitis B vaccine (Twinrix)	≥18 yr	720 EL.U. of hepatitis A antigen and 20 mcg of hepatitis B surface antigen protein	1.0	3	0, 1, and 6

*Zero represents the timing of the initial dose; subsequent numbers represent months after the initial dose.
Modified from Centers for Disease Control and Prevention: Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 55(RR-07):10, 2006.

Influenza Treatment and Prophylaxis

BOX 5 Summary of Seasonal Influenza Vaccination Recommendations

Children

All children aged 6 months to 18 years should be vaccinated annually.
Children and adolescents at higher risk for influenza complications should continue to be a focus for vaccination efforts as providers and programs transition to routinely vaccinating all children and adolescents, including those who:

- are aged 6 months to 4 years (59 months)
- have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, cognitive, neurologic/neuromuscular, hematologic, or metabolic disorders (including diabetes mellitus)
- are immunosuppressed (including immunosuppression caused by medications or by human immunodeficiency virus)
- are receiving long-term aspirin therapy and therefore might be at risk for experiencing Reye syndrome after influenza virus infection
- are residents of long-term care facilities
- will be pregnant during the influenza season

NOTE: Children aged <6 months cannot receive influenza vaccination. Household and other close contacts (e.g., day-care providers) of children aged <6 months, including older children and adolescents, should be vaccinated.

Adults

Annual vaccination against influenza is recommended for any adult who wants to reduce the risk of becoming ill with influenza or of transmitting it to others. Vaccination is recommended for all adults without contraindications in the following groups, because these persons either are at higher risk for influenza complications, or are close contacts of the persons at higher risk:

- persons aged ≥50 years
- women who will be pregnant during the influenza season
- persons who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, cognitive, neurologic/neuromuscular, hematologic, or metabolic disorders (including diabetes mellitus)
- persons who have immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus)
- residents of nursing homes and other long-term care facilities
- health care personnel
- household contacts and caregivers of children aged <5 years and adults aged ≥50 years, with particular emphasis on vaccinating contacts of children aged <6 months
- household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza

Modified from *MMWR*58:(RR-8), 2009.

TABLE 26 Live, Attenuated Influenza Vaccine (LAIV) Compared with Inactivated Influenza Vaccine (TIV) for Seasonal Influenza, U.S. Formulations

Factor	LAIV	TIV
Route of administration	Intranasal spray	Intramuscular injection
Type of vaccine	Live virus	Noninfectious virus (i.e., inactivated)
Number of included virus strains	3 (2 influenza A, 1 influenza B)	3 (2 influenza A, 1 influenza B)
Vaccine virus strains updated	Annually	Annually
Frequency of administration	Annually*	Annually*
Approved age	Persons aged 2-49 yr	Persons aged ≥6 mo
Interval between 2 doses recommended for children aged ≥6 mo to 8 yr who are receiving influenza vaccine for the first time	4 wk	4 wk
Can be administered to persons with medical risk factors for influenza-related complications†	No	Yes
Can be administered to children with asthma or children aged 2-4 yr with wheezing during the preceding year§	No	Yes
Can be administered to family members or close contacts of immunosuppressed persons not requiring a protected environment	Yes	Yes
Can be administered to family members or close contacts of immunosuppressed persons requiring a protected environment (e.g., hematopoietic stem cell transplant recipient)	No	Yes
Can be administered to family members or close contacts of persons at high risk but not severely immunosuppressed	Yes	Yes
Can be simultaneously administered with other vaccines	Yes¶	Yes**
If not simultaneously administered, can be administered within 4 wk of another live vaccine	Prudent to space 4 wk apart	Yes
If not simultaneously administered, can be administered within 4 wk of an inactivated vaccine	Yes	Yes

*Children aged 6 months to 8 years who have never received influenza vaccine before should receive 2 doses. Those who only receive 1 dose in their first year of vaccination should receive 2 doses in the following year, spaced 4 weeks apart.

†Persons at higher risk for complications of influenza infection because of underlying medical conditions should not receive LAIV. Persons at higher risk for complications of influenza infection because of underlying medical conditions include adults and children with chronic disorders of the pulmonary or cardiovascular systems; adults and children with chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression; children and adolescents receiving long-term aspirin therapy (at risk for developing Reye syndrome after wild-type influenza infection); persons who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration; pregnant women; and residents of nursing homes and other chronic-care facilities that house persons with chronic medical conditions.

§Clinicians and immunization programs should screen for possible reactive airways diseases when considering use of LAIV for children aged 2-4 years and should avoid use of this vaccine in children with asthma or a recent wheezing episode. Health care providers should consult the medical record, when available, to identify children aged 2-4 years with asthma or recurrent wheezing that might indicate asthma. In addition, to identify children who might be at greater risk for asthma and possibly at increased risk for wheezing after receiving LAIV, parents or caregivers of children aged 2-4 years should be asked: "In the past 12 months, has a health care provider ever told you that your child had wheezing or asthma?" Children whose parents or caregivers answer "yes" to this question and children who have asthma or who had a wheezing episode noted in the medical record during the preceding 12 months should not receive LAIV.

¶LAIV coadministration has been evaluated systematically only among children aged 12-15 months who received measles, mumps, and rubella vaccine or varicella vaccine.

**TIV coadministration has been evaluated systematically only among adults who received pneumococcal polysaccharide or zoster vaccine.

Modified from *MMWR* 56(RR-6), 2007.

INDICATIONS FOR USE OF ANTIVIRALS

PERSONS FOR WHOM ANTIVIRAL TREATMENT SHOULD BE CONSIDERED

If possible, antiviral treatment should be started within 48 hours of influenza illness onset. The effectiveness of initiating antiviral treatment more than 48 hours after illness onset has not been established. Persons for whom antiviral treatment should be considered include:

- Persons hospitalized with laboratory-confirmed influenza (limited data suggest benefit even for persons whose antiviral treatment is initiated more than 48 hours after illness onset)
- Persons with laboratory-confirmed influenza pneumonia
- Persons with laboratory-confirmed influenza and bacterial coinfection
- Persons with laboratory-confirmed influenza infection who are at higher risk for influenza complications
- Persons presenting to medical care with laboratory-confirmed influenza within 48 hours of influenza illness onset who want to decrease the duration or severity of their symptoms and transmission of influenza to others at higher risk for complications

PERSONS FOR WHOM ANTIVIRAL CHEMOPROPHYLAXIS SHOULD BE CONSIDERED DURING PERIODS OF INCREASED INFLUENZA ACTIVITY IN THE COMMUNITY

- Persons at high risk during the 2 weeks after influenza vaccination (after the second dose for children younger than 9 years who have not previously been vaccinated) if influenza viruses are circulating in the community
- Persons at high risk for whom influenza vaccine is contraindicated
- Family members or health care providers who are unvaccinated and are likely to have ongoing, close exposure to persons at high risk or unvaccinated persons or infants younger than 6 months
- Persons and their family members and close contacts and health care workers when circulating strains of influenza virus in the community are not matched with vaccine strains
- Persons with immune deficiencies or those who might not respond to vaccination (e.g., persons infected with HIV or other immunosuppressed conditions or who are receiving immunosuppressive medications)
- Unvaccinated staff and persons during response to an outbreak in a closed institutional setting with residents at high risk (e.g., extended-care facilities)

Modified from *MMWR* 57(RR-7), 2008.

NOTE: Recommended antiviral medications (neuraminidase inhibitors) are not licensed for chemoprophylaxis of children younger than 1 year (oseltamivir) or younger than 5 years (zanamivir). Updates or supplements to these recommendations (e.g., expanded age or risk group indications for licensed vaccines) might be required. Health care providers should be alert to announcements of recommendation updates and should check the CDC influenza website periodically for additional information (www.cdc.gov/flu).

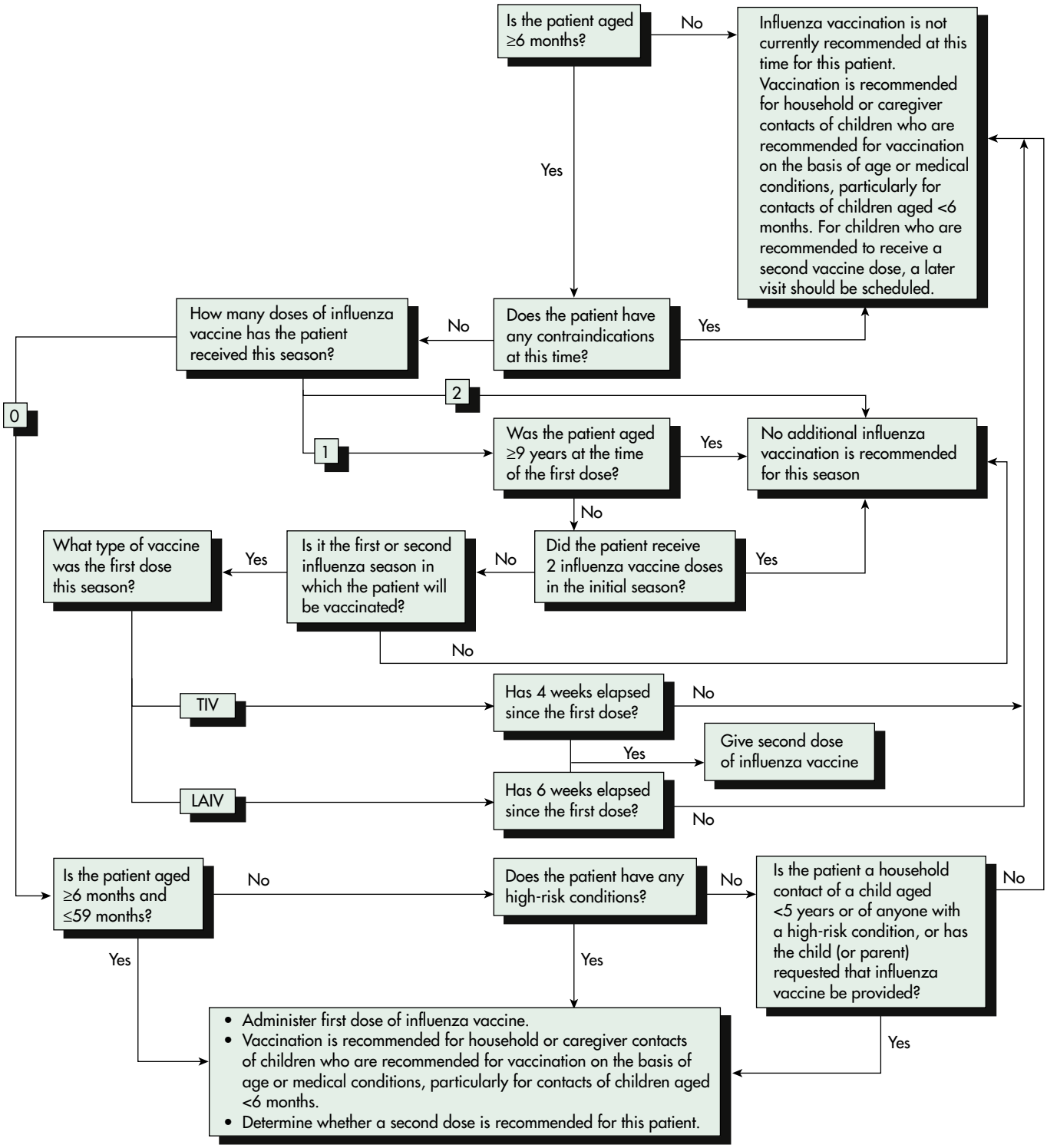


FIG. 7 Algorithm for determining recommended influenza immunization actions for children. *TIV,* Trivalent inactivated influenza vaccine; *LAIV,* live attenuated influenza vaccine. Modified with permission from the American Academy of Pediatrics' Committee on Infectious Diseases: Prevention of influenza: recommendations for influenza immunization of children, 2006-2007, *Pediatrics* 119:846-51, 2007.

HIV Testing and Postexposure Prophylaxis

RECOMMENDATIONS FOR HIV TESTING OF ADULTS, ADOLESCENTS, AND PREGNANT WOMEN

RECOMMENDATIONS FOR ADULTS AND ADOLESCENTS

The CDC recommends that diagnostic human immunodeficiency virus (HIV) testing and opt-out HIV screening be a part of routine clinical care in all health care settings while also preserving the patient's option to decline HIV testing and ensuring a provider-patient relationship conducive to optimal clinical and preventive care. The recommendations are intended for providers in all health care settings, including hospital emergency departments, urgent-care clinics, inpatient services, sexually transmitted disease (STD) clinics or other venues offering clinical STD services, tuberculosis (TB) clinics, substance abuse treatment clinics, other public health clinics, community clinics, correctional health care facilities, and primary care settings. The guidelines address HIV testing in health care settings only; they do not modify existing guidelines concerning HIV counseling, testing, and referral for persons at high risk for HIV who seek or receive HIV testing in nonclinical settings (e.g., community-based organizations, outreach settings, or mobile vans).[3]

SCREENING FOR HIV INFECTION

- In all health care settings, screening for HIV infection should be performed routinely for all patients aged 13 to 64 years. Health care providers should initiate screening unless prevalence of undiagnosed HIV infection in their patients has been documented to be less than 0.1%. In the absence of existing data for HIV prevalence, health care providers should initiate voluntary HIV screening until they establish that the diagnostic yield is less than 1 per 1000 patients screened, at which point such screening is no longer warranted.
- All patients initiating treatment for TB should be screened routinely for HIV infection.
- All patients seeking treatment for STDs, including all patients visiting STD clinics, should be screened routinely for HIV during each visit for a new complaint, regardless of whether the patient is known or suspected to have specific behavior risks for HIV infection.

REPEAT SCREENING

- Health care providers should subsequently test all persons likely to be at high risk for HIV at least annually. Persons likely to be at high risk include users of injection drugs and their sex partners, persons who exchange sex for money or drugs, sex partners of persons who are HIV infected, and men who have sex with men (MSM) or heterosexual persons who themselves or whose sex partners have had more than one sex partner since their most recent HIV test.
- Health care providers should encourage patients and their prospective sex partners to be tested before initiating a new sexual relationship.
- Repeat screening of persons not likely to be at high risk for HIV should be performed on the basis of clinical judgment.
- Unless recent HIV test results are immediately available, any person whose blood or body fluid is the source of an occupational exposure for a health care provider should be informed of the incident and tested for HIV infection at the time the exposure occurs.

CONSENT AND PRETEST INFORMATION

- Screening should be voluntary and undertaken only with the patient's knowledge and understanding that HIV testing is planned.
- Patients should be informed orally or in writing that HIV testing will be performed unless they decline (opt-out screening). Oral or written information should include an explanation of HIV infection and the meanings of positive and negative test results, and the patient should be offered an opportunity to ask questions and decline testing. With such notification, consent for HIV screening should be incorporated into the patient's general informed consent for medical care on the same basis as are other screening or diagnostic tests; a separate consent form for HIV testing is not recommended.
- Easily understood informational materials should be made available in the languages of the commonly encountered populations within the service area. The competence of interpreters and bilingual staff to provide language assistance to patients with limited English proficiency must be ensured.
- If a patient declines an HIV test, this decision should be documented in the medical record.

DIAGNOSTIC TESTING FOR HIV INFECTION

- All patients with signs or symptoms consistent with HIV infection or an opportunistic illness characteristic of acquired immunodeficiency syndrome (AIDS) should be tested for HIV.
- Clinicians should maintain a high level of suspicion for acute HIV infection in all patients who have a compatible clinical syndrome and who report recent high-risk behavior. When acute retroviral syndrome is a possibility, a plasma RNA test should be used in conjunction with an HIV antibody test to diagnose acute HIV infection.
- Patients or persons responsible for the patient's care should be notified orally that testing is planned, advised of the indication for testing and the implications of positive and negative test results, and offered an opportunity to ask questions and decline testing. With such notification, the patient's general consent for medical care is considered sufficient for diagnostic HIV testing.

HIV SCREENING FOR PREGNANT WOMEN AND THEIR INFANTS*

Universal Opt-Out Screening

- All pregnant women in the United States should be screened for HIV infection.
- Screening should occur after a woman is notified that HIV screening is recommended for all pregnant patients and that she will receive an HIV test as part of the routine panel of prenatal tests unless she declines (opt-out screening).
- HIV testing must be voluntary and free from coercion. No woman should be tested without her knowledge.
- Pregnant women should receive oral or written information that includes an explanation of HIV infection, a description of interventions that can reduce HIV transmission from mother to infant, and the meanings of positive and negative test results. They should be offered an opportunity to ask questions and decline testing.
- No additional process or written documentation of informed consent beyond what is required for other routine prenatal tests should be required for HIV testing.
- If a patient declines an HIV test, this decision should be documented in the medical record.

ADDRESSING REASONS FOR DECLINING TESTING

- Providers should discuss and address reasons for declining an HIV test (e.g., lack of perceived risk, fear of the disease, and concerns regarding partner violence or potential stigma or discrimination).
- Women who decline an HIV test because they have had a previous negative test result should be informed of the importance of retesting during each pregnancy.
- Logistical reasons for not testing (e.g., scheduling) should be resolved.
- Certain women who initially decline an HIV test might accept at a later date, especially if their concerns are discussed. Certain women will continue to decline testing, and their decisions should be respected and documented in the medical record.

Timing of HIV Testing

- To promote informed and timely therapeutic decisions, health care providers should test women for HIV as early as possible during each pregnancy. Women who decline the test early in prenatal care should be encouraged to be tested at a subsequent visit.
- A second HIV test during the third trimester, preferably less than 36 weeks of gestation, is cost effective even in areas of low HIV prevalence and may be considered for all pregnant women. A second HIV test during the third trimester is recommended for women who meet one or more of the following criteria:

[3] Data from *MMWR* 57(RR-10), 2008.

1. Women who receive health care in jurisdictions with elevated incidence of HIV or AIDS among women aged 15 to 45 years. In 2004, these jurisdictions included Alabama, Connecticut, Delaware, the District of Columbia, Florida, Georgia, Illinois, Louisiana, Maryland, Massachusetts, Mississippi, Nevada, New Jersey, New York, North Carolina, Pennsylvania, Puerto Rico, Rhode Island, South Carolina, Tennessee, Texas, and Virginia.[4]
2. Women who receive health care in facilities in which prenatal screening identifies at least one pregnant woman who is infected with HIV per 1000 women screened.
3. Women who are known to be at high risk for acquiring HIV (e.g., users of injection drugs and their sex partners, women who exchange sex for money or drugs, women who are sex partners of persons who are infected with HIV, and women who have had a new or more than one sex partner during this pregnancy).
4. Women who have signs or symptoms consistent with acute HIV infection. When acute retroviral syndrome is a possibility, a plasma RNA test should be used in conjunction with an HIV antibody test to diagnose acute HIV infection.

Rapid Testing During Labor

- Any woman with undocumented HIV status at the time of labor should be screened with a rapid HIV test unless she declines (opt-out screening).
- Reasons for declining a rapid test should be explored (see "Addressing Reasons for Declining Testing").
- Immediate initiation of appropriate antiretroviral prophylaxis should be recommended to women on the basis of a reactive rapid test result without waiting for the result of a confirmatory test.

Postpartum/Newborn Testing

- When a woman's HIV status is still unknown at the time of delivery, she should be screened immediately postpartum with a rapid HIV test unless she declines (opt-out screening).
- When the mother's HIV status is unknown postpartum, rapid testing of the newborn as soon as possible after birth is recommended so that antiretroviral prophylaxis can be offered to infants exposed to HIV. Women should be informed that identifying HIV antibodies in the newborn indicates that the mother is infected.
- For infants whose HIV exposure status is unknown and who are in foster care, the person legally authorized to provide consent should be informed that rapid HIV testing is recommended for infants whose biologic mothers have not been tested.
- The benefits of neonatal antiretroviral prophylaxis are best realized when it is initiated within 12 hours after birth.

Confirmatory Testing

- Whenever possible, uncertainties regarding laboratory test results indicating HIV infection status should be resolved before final decisions are made regarding reproductive options, antiretroviral therapy, cesarean delivery, or other interventions.
- If the confirmatory test result is not available before delivery, immediate initiation of appropriate antiretroviral prophylaxis should be recommended to any pregnant patient whose HIV screening test result is reactive to reduce the risk for perinatal transmission.

[4] A second HIV test in the third trimester is as cost effective as other common health interventions when HIV incidence among women of childbearing age is =17 HIV cases per 100,000 person-years. In 2004, in jurisdictions with available data on HIV case rates, a rate of 17 new HIV diagnoses per year per 100,000 women aged 15 to 45 years was associated with an AIDS case rate of at least nine AIDS diagnoses per year per 100,000 women aged 15 to 45 years (CDC, unpublished data, 2005). As of 2004, the jurisdictions listed above exceeded these thresholds. The list of specific jurisdictions where a second test in the third trimester is recommended will be updated periodically based on surveillance data.

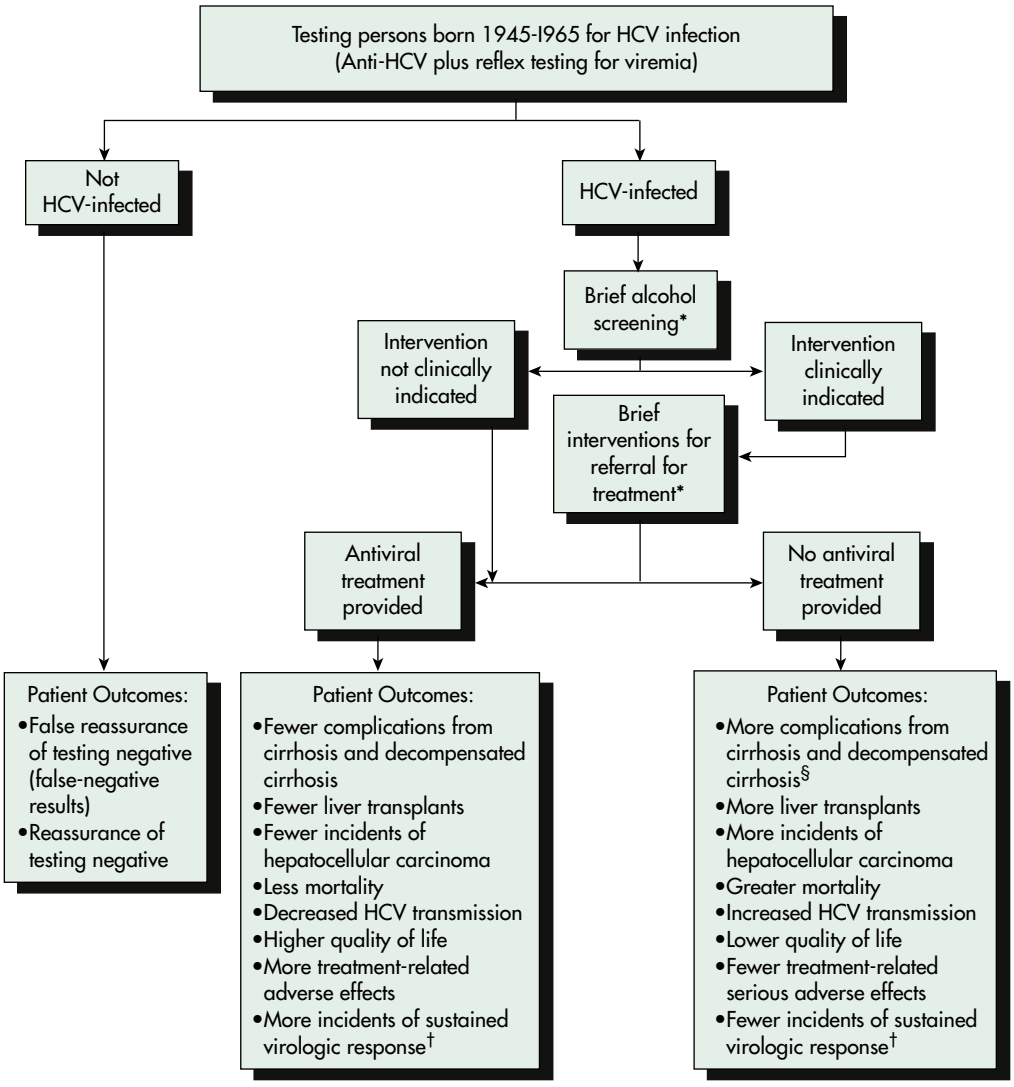


FIG. 8 Analytic framework for guiding hepatitis C virus (HCV) testing among persons born during 1945-1965. *Together, these interventions are known as alcohol screening and brief interventions (SBI) for referral for treatment. †Viral eradication after treatment completion. §Cirrhosis with the diagnosis of at least one of the following: ascites, variceal bleeding, encephalopathy, or impaired hepatitis synthetic function. From Centers for Disease Control and Prevention: Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR* 2012:61(4).

TABLE 27 HIV Exposure, Estimated Per-Act Risk

Exposure Route	Risk per 10,000 Exposures to an Infected Source
Blood transfusion	9000
Needle-sharing injection drug use	67
Receptive anal intercourse	50
Percutaneous needle stick	30
Receptive penile-vaginal intercourse	10
Insertive anal intercourse	6.5
Insertive penile-vaginal intercourse	5
Receptive oral intercourse	1
Insertive oral intercourse	0.5

NOTE: Estimates of risk for transmission from sexual exposures assume no condom use. Source refers to oral intercourse performed on a man.

TABLE 28 Recommended Postexposure Prophylaxis (PEP) for All Occupational Exposures to Human Immunodeficiency Virus (HIV)

PREFERRED HIV PEP REGIMEN	
Raltegravir (Isentress) 400 mg PO (by mouth) twice daily *plus* tenofovir DF (Viread) 300 mg + emtricitabine (Emtriva) 200 mg; available as Truvada, PO once daily	
Alternative Regimens	
May combine one drug or drug pair from the left column with one pair of nucleoside/nucleotide reverse transcriptase inhibitors from the right column	
Dolutegravir (Tivicay)	Tenofovir DF (Viread) + emtricitabine (Emtriva); available as Truvada
Raltegravir (Isentress)	Tenofovir DF (Viread) + emtricitabine (Emtriva); available as Truvada
Darunavir (Prezista) + ritonavir (Norvir)	Tenofovir DF (Viread) + lamivudine (Epivir)
Etravirine (Intelence)	Zidovudine (Retrovir) + lamivudine (Epivir); available as Combivir
Rilpivirine (Edurant)	Zidovudine (Retrovir) + emtricitabine (Emtriva)
Atazanavir (Reyataz) + ritonavir (Norvir)	
Lopinavir/ritonavir (Kaletra)	
Stribild (elvitegravir, cobicistat, tenofovir DF, emtricitabine); a complete fixed-dose combination regimen with no additional antiretrovirals needed	
ALTERNATIVE ANTIRETROVIRAL AGENTS FOR USE AS PEP *ONLY* WITH EXPERT CONSULTATION	
Abacavir (Ziagen)	
Efavirenz (Sustiva)	
Enfuvirtide (Fuzeon)	
Fosamprenavir (Lexiva)	
Maraviroc (Selzentry)	
Saquinavir (Invirase)	
Stavudine (Zerit)	
ANTIRETROVIRAL AGENTS GENERALLY NOT RECOMMENDED FOR USE AS PEP	
Didanosine (Videx EC)	
Nelfinavir (Viracept)	
Tipranavir (Aptivus)	
ANTIRETROVIRAL AGENTS CONTRAINDICATED AS PEP	
Nevirapine (Viramune)	

Adapted from Kuhar DT et al: Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis, *Infect Control Hosp Epidemiol* 2013; 34:875-892. In Cameron JL, Cameron AM: *Current surgical therapy*, ed 12, Philadelphia, 2017, Elsevier.

TABLE 29 Antiretroviral Therapy Medications, Adult Dosage, and Side Effects

Medication	Adult Dosage*	Side Effects and Toxicities
Combination Tablets		
Lopinavir/ritonavir (Kaletra)‡	3 tablets twice daily 400 mg lopinavir/100 mg ritonavir	Diarrhea, nausea, vomiting; asthenia; elevated transaminases; hyperglycemia; fat redistribution; lipid abnormalities; possible increased bleeding in persons with hemophilia; pancreatitis
Zidovudine/lamivudine (Combivir)	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine	See following individual medications
Zidovudine/lamivudine/abacavir (Trizivir)	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine/300 mg abacavir	See following individual medications
Lamivudine/abacavir (Epzicom)	1 tablet once daily 300 mg lamivudine/600 mg abacavir	See following individual medications
Emtricitabine/tenofovir (Truvada)	1 tablet once daily 200 mg emtricitabine/300 mg tenofovir	See following individual medications
Single Agents		
Nucleoside and nucleotide reverse transcriptase inhibitors (side effects as a class: lactic acidosis, severe hepatomegaly with steatosis, including some fatal cases)		
Abacavir (Ziagen, ABC)‡	300 mg twice daily or 600 mg once daily	Severe hypersensitivity reaction (can be fatal); nausea; vomiting
Didanosine (Videx, ddl)‡	>60 kg (132 lb) body weight: 200 mg twice daily or 400 mg daily; if with tenofovir, 250 mg/daily <60 kg (132 lb): 125 mg twice daily or 250 mg daily; if with tenofovir, dose not established Do not use with stavudine (d4T, Zerit) during pregnancy; avoid ddl/d4T combination in general because of increased risk for adverse events (e.g., neuropathy, pancreatitis, and hyperlactatemia)	Pancreatitis; nausea, diarrhea; peripheral neuropathy
Emtricitabine (Emtriva, FTC)	200 mg once daily	Minimal toxicity; lactic acidosis and hepatic steatosis a rare but possibly life-threatening event
Lamivudine (Epivir, 3TC)‡	150 mg twice daily or 300 mg once daily	Minimal toxicity; lactic acidosis and hepatic steatosis a rare but possibly life-threatening event
Stavudine (Zerit, d4T)‡	>60 kg (132 lb) body weight: 40 mg twice daily <60 kg (132 lb) body weight: 30 mg twice daily Do not use with didanosine (ddl, Videx) during pregnancy; avoid ddl/d4T combination in general because of increased risk of adverse events (e.g., neuropathy, pancreatitis, and hyperlactatemia)	Pancreatitis; peripheral neuropathy; rapidly progressive ascending neuromuscular weakness (rare)
Tenofovir (Viread)	300 mg daily	Nausea, vomiting, diarrhea; headache; asthenia; flatulence; renal impairment
Zidovudine (Retrovir, AZT)‡	200 mg three times daily or 300 mg twice daily	Bone marrow suppression (anemia, neutropenia); gastrointestinal intolerance; headache; insomnia; asthenia; and myopathy
Nonnucleoside reverse transcriptase inhibitors (side effects as a class: Stevens-Johnson syndrome)		
Efavirenz (Sustiva)	600 mg daily at bedtime	Rash; central nervous system symptoms (e.g., dizziness, impaired concentration, insomnia, and abnormal dreams); transaminase elevation; false-positive cannabinoid test
Protease inhibitors (side effects as a class: gastrointestinal intolerance, hyperlipidemia, hyperglycemia, diabetes, fat redistribution, and possible increased bleeding in hemophiliacs; do not use during known or possible pregnancy)		
Atazanavir (Reyataz)	400 mg once daily; if administered with tenofovir plus ritonavir, 300 mg once daily	Indirect hyperbilirubinemia; prolonged PR interval (use caution in patients with underlying cardiac conduction defects or on concomitant medications that can cause PR prolongation)
Fosamprenavir (Lexiva)‡	1400 mg twice daily	Gastrointestinal intolerance, nausea, vomiting, diarrhea; rash; elevated transaminases; headache
Indinavir (Crixivan)	800 mg q8h With ritonavir (might increase risk for renal adverse events): 800 mg indinavir and 100 mg ritonavir q12h or 800 mg indinavir and 200 mg ritonavir every q12h	Gastrointestinal intolerance, nausea; nephrolithiasis; headache; asthenia; blurred vision; metallic taste; thrombocytopenia; hemolytic anemia; indirect hyperbilirubinemia (inconsequential)
Nelfinavir (Viracept)‡	750 mg three times daily or one 250 mg twice daily	Diarrhea; elevated transaminases
Ritonavir (Norvir)‡	See doses used in combination with other specific protease inhibitors	Gastrointestinal intolerance; nausea, vomiting, diarrhea; paresthesias; hepatitis; pancreatitis; asthenia; taste perversion; many drug interactions
Saquinavir (hard-gel capsule) (Invirase)	With ritonavir: 400 mg saquinavir and 400 mg ritonavir twice daily or 1000 mg saquinavir and 100 mg ritonavir twice daily	Gastrointestinal intolerance; nausea, diarrhea; headache; elevated transaminases
Saquinavir (soft-gel capsule) (Fortovase)	With ritonavir: 400 mg saquinavir and 400 mg ritonavir twice daily or 1000 mg saquinavir and 100 mg ritonavir twice daily	Gastrointestinal intolerance; nausea, diarrhea; abdominal pain; dyspepsia; headache; elevated transaminases

*For pediatric dosing information, see *Guidelines for use of antiretroviral agents in pediatric HIV infection*. Available at aidsinfo.nih.gov/guidelines/html/2/pediatric-arv/108/role-of-therapeutic-drug-monitoring-in-management-of-pediatric-hiv-infection.

‡Pediatric formulation available.

Sources: Modified from U.S. Department of Health and Human Services and the Henry J. Kaiser Family Foundation: *Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents*. Available at aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0 (refer to website for updated versions); Bartlett JG, Finkbeiner AK: HIV drugs: the guide to living with HIV infection, 2001. Available at www.thebody.com/content/art32314.html

TABLE 30 Laboratory Tests Generally Recommended for Persons after Exposure to HIV*

Test	RECOMMENDED DURING TREATMENT		RECOMMENDED AT FOLLOW-UP		
	Baseline	Symptom-Directed†	4-6 wk	12 wk	24 wk
ELISA for HIV antibodies	Yes	Yes	Yes	Yes	Yes
Creatinine, liver function, and complete blood count with differential count	Yes	Yes	No	No	No
HIV viral load	No	Yes	No	No	No
Anti-HBs antibodies	Yes‡	No	No	No	No
HBsAg	Yes‡§	No	No	No	No
HCV antibodies	Yes	No	Yes	Yes	Yes
HCV RNA‖	No	Yes	Yes	Yes	Yes
Screening, including rapid plasma reagin test, for other sexually transmitted infections¶	Yes	Yes	No	Yes	No

Anti-HBs antibodies, Hepatitis B virus surface antibodies; *ELISA,* enzyme-linked immunosorbent assay; *HBsAg,* hepatitis B surface antigen; *HCV,* hepatitis C virus.

*Patients who receive zidovudine plus lamivudine–based regimens should have a complete blood count and measurement of liver-enzyme levels at 2 weeks of treatment, irrespective of the presence or absence of clinical symptoms. Tenofovir plus emtricitabine–based regimens generally involve few side effects, and symptom-directed assessment of serum creatinine or liver-enzyme levels should be considered. The addition of a ritonavir-boosted protease inhibitor should be followed by symptom-directed assessment of liver-enzyme levels, serum glucose levels, or both.

†Symptom-directed tests are for signs or symptoms of toxic effects (rash, nausea, vomiting, or abdominal pain) or HIV seroconversion (fever, fatigue, lymphadenopathy, rash, or oral or genital ulcers).

‡If tests for anti-HBs antibodies and HBsAg are both negative, a vaccination series against HBV infection should be initiated and completed.

§If the patient is HBsAg-positive, he or she should have monthly follow-up of liver function tests after discontinuation of postexposure prophylactic regimens containing tenofovir, lamivudine, or emtricitabine; referral to a specialist in viral hepatitis should be considered.

‖HCV RNA testing may identify early HCV seroconversion; early detection and treatment during acute HCV infection may avert or ameliorate chronic disease. Data are from Dienstag and McHutchison.

¶Rapid plasma reagin testing and testing of urethral-swab and rectal-swab specimens for gonorrhea and chlamydia and of pharyngeal-swab specimens for gonorrhea should be performed as appropriate, according to the patient's sexual risk-taking behaviors and the type of exposure to HIV.

From Landovitz RJ, Currier JS: Postexposure prophylaxis for HIV infection, *N Engl J Med* 361:1768-1775, 2009.

BOX 6 Situations for Which Expert Consultation for HIV Postexposure Prophylaxis Is Advised[5]

- Delayed (i.e., later than 24-36 hours) exposure report
  1. The interval after which there is no benefit from postexposure prophylaxis (PEP) is undefined
- Unknown source (e.g., needle in sharps disposal container or laundry)
  1. Decide use of PEP on a case-by-case basis
  2. Consider the severity of the exposure and the epidemiologic likelihood of HIV exposure
  3. Do not test needles or other sharp instruments for HIV
- Known or suspected pregnancy in the exposed person
  1. Does not preclude the use of optimal PEP regimens
  2. Do not deny PEP solely on the basis of pregnancy
- Resistance of the source virus to antiretroviral agents
  1. Influence of drug resistance on transmission risk is unknown
  2. Selection of drugs to which the source person's virus is unlikely to be resistant is recommended if the source person's virus is known or suspected to be resistant to one or more of the drugs considered for the PEP regimen
  3. Resistance testing of the source person's virus at the time of the exposure is not recommended
- Toxicity of the initial PEP regimen
  1. Adverse symptoms such as nausea and diarrhea are common with PEP
  2. Symptoms often can be managed without changing the PEP regimen by prescribing antimotility and/or antiemetic agents
  3. Modification of dose intervals (i.e., administering a lower dose of drug more frequently throughout the day, as recommended by the manufacturer) in other situations might help alleviate symptoms

[5]Local experts and/or the National Clinicians' Postexposure Prophylaxis Hotline (PEPline [888-448-4911]).

BOX 7 Occupational Exposure Management Resources

National Clinicians' Postexposure Prophylaxis Hotline (PEPline) Run by University of California–San Francisco/San Francisco General Hospital staff; supported by the Health Resources and Services Administration, Ryan White CARE Act, HIV/AIDS Bureau, AIDS Education and Training Centers, and CDC	Phone: 888-448-4911 Internet: nccc.ucsf.edu/clinician-consultation;/pep-post-exposure-prophylaxis/
Hepatitis Hotline	Phone: 888-443-7232 Internet: www.cdc.gov/ncidod/diseases/hepatitis/index.htm
Reporting to CDC: Occupationally acquired HIV infections and failures of PEP	Phone: 800-893-0485
HIV Antiretroviral Pregnancy Registry	Phone: 800-258-4263 Fax: 800-800-1052 Address: 1410 Commonwealth Dr., Suite 215, Wilmington, NC 28405 Internet: www.apregistry.com/
Food and Drug Administration Report unusual or severe toxicity to antiretroviral agents	Phone: 800-332-1088 Address: MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857 Internet: www.fda.gov/medwatch
HIV/AIDS Treatment Information Service	Internet: www.hivatis.org

BOX 8 Management of Occupational Blood Exposures

Provide Immediate Care to the Exposure Site
- Wash wounds and skin with soap and water
- Flush mucous membranes with water

Determine Risk Associated with Exposure
- Type of fluid (e.g., blood, visibly bloody fluid, other potentially infectious fluid or tissue, and concentrated virus)
- Type of exposure (e.g., percutaneous injury, mucous membrane or nonintact skin exposure, and bites resulting in blood exposure)

Evaluate Exposure Source
- Assess the risk of infection using available information
- Test known sources for HBsAg, anti-HCV, and HIV antibodies (consider using rapid testing)
- For unknown sources, assess risk of exposure to HBV, HCV, or HIV infection
- Do not test discarded needles or syringes for virus contamination

Evaluate the Exposed Person
- Assess immune status for HBV infection (i.e., by history of hepatitis B vaccination and vaccine response)

Give PEP for Exposures Posing Risk of Infection Transmission
- HBV: See Table 5
- HCV: PEP not recommended
- HIV: See Tables 28, 29, and 30 and Fig. 8
  1. Initiate PEP as soon as possible, preferably within hours of exposure
  2. Offer pregnancy testing to all women of childbearing age not known to be pregnant
  3. Seek expert consultation if viral resistance is suspected
  4. Administer PEP for 4 weeks if tolerated

Perform Follow-up Testing and Provide Counseling
- Advise exposed persons to seek medical evaluation for any acute illness occurring during follow-up

HBV Exposures
- Perform follow-up anti-HBs testing in persons who receive hepatitis B vaccine
  1. Test for anti-HBs 1 to 2 months after last dose of vaccine
  2. Anti-HBs response to vaccine cannot be ascertained if HBIG was received in the previous 3 to 4 months

HCV Exposures
- Perform baseline and follow-up testing for anti-HCV and alanine aminotransferase 4 to 6 months after exposure
- Perform HCV RNA at 4 to 6 weeks if earlier diagnosis of HCV infection desired
- Confirm repeatedly reactive anti-HCV enzyme immunoassays with supplemental tests

HIV Exposures
- Perform HIV-antibody testing for at least 6 months after exposure (e.g., at baseline, 6 weeks, 3 months, and 6 months)
- Perform HIV-antibody testing if illness compatible with an acute retroviral syndrome occurs
- Advise exposed persons to use precautions to prevent secondary transmission during the follow-up period
- Evaluate exposed persons taking PEP within 72 hr after exposure and monitor for drug toxicity for at least 2 weeks

HBIG, Hepatitis B immune globulin; *HBsAg,* hepatitis B surface antigen; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HIV,* human immunodeficiency virus; *PEP,* postexposure prophylaxis; *RNA,* ribonucleic acid.

ENDOCARDITIS PROPHYLAXIS[6]

TABLE 31 Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for Which Prophylaxis with Dental Procedures Is Recommended

Prosthetic cardiac valve
Previous infective endocarditis
CHD*
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 mo after the procedure†
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (that inhibit endothelialization)
Cardiac transplant recipients who develop cardiac valvulopathy

CHD, Congenital heart disease.
*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.
†Prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 mo after the procedure.

TABLE 32 Dental Procedures for Which Endocarditis Prophylaxis Is Recommended for Patients in Table 31

All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa*

*The following procedures and events do not need prophylaxis: routine anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lips or oral mucosa.

TABLE 33 Regimens for a Dental Procedure

	REGIMEN: SINGLE DOSE 30-60 MIN BEFORE PROCEDURE		
Situation	**Agent**	**Adults**	**Children**
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	OR		
	Cefazolin or ceftriaxone*	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin, oral	Cephalexin	2 g	50 mg/kg
	OR		
	Clindamycin	600 mg	20 mg/kg
	OR		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medicine	Cefazolin or ceftriaxone†	1 g IM or IV	50 mg/kg IM or IV
	OR		
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

IM, Intramuscular; *IV,* intravenous.
*Or other first-generation or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

[6]From Prevention of infective endocarditis. A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation published online Apr 19, 2007, DOI: 10.1161/CIRCULATIONAHA.106.183095. Copyright © 2007 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539.

TABLE 34 Summary of Major Changes in Updated Recommendations

We concluded that bacteremia resulting from daily activities is much more likely to cause IE than bacteremia associated with a dental procedure.
We concluded that only an extremely small number of cases of IE might be prevented by antibiotic prophylaxis even if prophylaxis is 100% effective.
Antibiotic prophylaxis is not recommended based solely on an increased lifetime risk of acquisition of IE.
Limit recommendations for IE prophylaxis only to those conditions listed in Table 31.
Antibiotic prophylaxis is no longer recommended for any other form of CHD, except for the conditions listed in Table 31.
Antibiotic prophylaxis is recommended for all dental procedures that involve manipulation of gingival tissues or periapical region of teeth or perforation of oral mucosa only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE (see Table 31).
Antibiotic prophylaxis is recommended for procedures on respiratory tract or infected skin, skin structures, or musculoskeletal tissue only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE (see Table 31).
Antibiotic prophylaxis solely to prevent IE is not recommended for GU or GI tract procedures.
The writing group reaffirms the procedures noted in the 1997 prophylaxis guidelines for which endocarditis prophylaxis is not recommended and extends this to other common procedures, including ear and body piercing, tattooing, and vaginal delivery and hysterectomy.

NOTE: A guide to the clinical preventive services described is available online at www.ahrq.gov/clinic/pocketgd07/. *CHD,* Congenital heart disease; *GI,* gastrointestinal; *GU,* genitourinary; *IE,* infective endocarditis.

Hepatitis C Testing (See Fig. 8)

BOX 9 Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Diseases

Recommendations for the Identification of Chronic Hepatitis C Virus Infection among Persons Born During 1945-1965[7]
- Adults born during 1945-1965 should receive one-time testing for HCV without prior ascertainment of HCV risk.
- All persons with identified HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions.

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents
- HIV-infected patients should be tested routinely for evidence of chronic HCV infection. Initial testing for HCV should be performed using the most sensitive immunoassays licensed for detection of antibody to HCV (anti-HCV) in blood.

Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease
Routine HCV testing is recommended for
- Persons who ever injected illegal drugs, including those who injected once or a few times many years ago and do not consider themselves drug users.
- Persons with selected medical conditions, including:
  1. persons who received clotting factor concentrates produced before 1987;
  2. persons who were ever on chronic (long-term) hemodialysis;
  3. persons with persistently abnormal alanine aminotransferase levels.
- Prior recipients of transfusions or organ transplants, including:
  1. persons who were notified that they received blood from a donor who later tested positive for HCV infection;
  2. persons who received a transfusion of blood or blood components before July 1992; and
  3. persons who received an organ transplant before July 1992.

Routine HCV testing is recommended for persons with recognized exposures, including
- Health care, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood.
- Children born to HCV-positive women.

[7]Source: Centers for Disease Control and Prevention: Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR* 2012;61(No. RR-4).
From Centers for Disease Control and Prevention: Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR* 2012:61(4).

Recommendations for Meningococcal Vaccination

TABLE 35 Recommendations for Meningococcal Vaccination of Children at Increased Risk for Meningococcal Disease

Vaccine	Age of Primary Vaccination	Booster Doses	Indicated for Infants	Not Indicated for Infants
MenACWY-CRM (Menveo)	2, 4, 6, and 12 mo	1st booster 3 yr after primary series Additional boosters every 5 yr	Complement component deficiencies Functional or anatomic asplenia The risk groups for an outbreak for which vaccination is recommended Traveling to or residing in epidemic or hyperendemic regions	
MenACWY-D (Menactra)	9 and 12 mo	1st booster 3 yr after primary series Additional boosters every 5 yr	Complement component deficiencies The risk groups for an outbreak for which vaccination is recommended Traveling to or residing in epidemic or hyperendemic regions	Functional or anatomic asplenia
Hib-MenCY-TT (MenHibrix)	2, 4, 6, and 12-15 mo	1st booster (using MenACWY-CRM or MenACWY-D) 3 yr after primary series	1st booster 3 yr after primary series	Traveling to or residing in epidemic or hyperendemic regions
MenB-FHbp (Trumenba)	3-dose series, with 2nd and 3rd doses after 2 and 6 mo after 1st dose; 2nd dose 6 mo after 1st dose is an option	None	≥10 yr at increased risk for serogroup B disease (complement component deficiencies, functional or anatomic asplenia, the risk groups for an outbreak for which vaccination is recommended)	Children aged <10 yr Traveling to or residing in epidemic or hyperendemic regions
MenB-4C (Bexsero)	2-dose series, with doses at least 1 mo apart	None	≥10 yr at increased risk for serogroup B disease (complement component deficiencies, functional or anatomic asplenia, the risk groups for an outbreak for which vaccination is recommended)	Children aged <10 yr Traveling to or residing in epidemic or hyperendemic regions

From Cherry JD: *Feigin and Cherry's pediatric infectious diseases,* ed 8, Philadelphia, 2019, Elsevier.

TABLE 36 Vaccine Websites and Resources

Organization	Website
Health Professional Associations	
American Academy of Family Physicians (AAFP)	www.familydoctor.org/online/famdocen/home.html
American Academy of Pediatrics (AAP)	www.aap.org/
AAP Childhood Immunization Support Program	www.aap.org/immunization/
American Association of Occupational Health Nurses (AAOHN)	www.aaohn.org/
American College Health Association (ACHA)	www.acha.org/
American College of Obstetricians and Gynecologists (ACOG)–Immunization for Women	www.immunizationforwomen.org/
American Medical Association (AMA)	www.ama-assn.org/
American Nurses Association (ANA)	www.nursingworld.org/
American Pharmacists Association (APhA)	www.pharmacist.com/
American School Health Association (ASHA)	www.ashaweb.org/
American Travel Health Nurses Association (ATHNA)	www.athna.org/
Association for Professionals in Infection Control and Epidemiology (APIC)	www.apic.org/
Association of State and Territorial Health Officials (ASTHO)	www.astho.org/
Association of Teachers of Preventive Medicine (ATPM)	www.atpm.org/
National Medical Association (NMA)	www.nmanet.org/
Society of Teachers of Family Medicine—Group on Immunization Education	www.immunizationed.org/
Nonprofit Groups and Universities	
Albert B. Sabin Vaccine Institute	www.sabin.org/
Brighton Collaboration	brightoncollaboration.org/public
Center for Vaccine Awareness and Research—Texas Children's Center	www.texaschildrens.org/departments/immunization-project
Children's Vaccine Program	www.path.org/vaccineresources/
Every Child by Two (ECBT)	www.ecbt.org/
Families Fighting Flu	www.familiesfightingflu.org/
GAVI, the Vaccine Alliance	www.gavialliance.org/
Health on the Net Foundation (HON)	www.hon.ch/
Immunization Action Coalition (IAC)	www.immunize.org/
Infectious Diseases Society of America (IDSA)	www.idsociety.org/Index.aspx
Institute for Vaccine Safety (IVS), Johns Hopkins Bloomberg School of Public Health	www.vaccinesafety.edu/
National Academies: Health and Medicine Division	www.nationalacademies.org/hmd/
National Alliance for Hispanic Health	www.hispanichealth.org/
National Foundation for Infectious Diseases (NFID)	www.nfid.org
National Foundation for Infectious Diseases (NFID)—Childhood Influenza Immunization Coalition (CIIC)	www.preventchildhoodinfluenza.com/
National Network for Immunization Information (NNii)	www.immunizationinfo.net/
Parents of Kids with Infectious Diseases (PKIDS)	www.pkids.org/
PATH Vaccine Resource Library	www.path.org/vaccineresources/
Vaccine Education Center at the Children's Hospital of Philadelphia	www.chop.edu/service/vaccine-education-center/home.html
Vaccinate Your Baby	www.vaccinateyourbaby.org/
Government Organizations	
Centers for Disease Control and Prevention (CDC)	
Advisory Committee on Immunization Practices (ACIP)	www.cdc.gov/vaccines/acip/index.html
ACIP Vaccine Recommendations	www.cdc.gov/vaccines/hcp/acip-recs/index.html
Current Vaccine Delays and Shortages	www.cdc.gov/vaccines/vac-gen/shortages/
Epidemiology and Prevention of Vaccine-Preventable Diseases (also known as the *Pink Book*)	www.cdc.gov/vaccines/pubs/pinkbook/index.html
Manual for the Surveillance of Vaccine-Preventable Diseases	www.cdc.gov/vaccines/pubs/surv-manual/index.html
Public Health Image Library	phil.cdc.gov/phil/home.asp
Travelers' Health	www.cdc.gov/travel/
CDC Health Information for International Travel (also known as the *Yellow Book*)	wwwnc.cdc.gov/travel/yellowbook/2016/table-of-contents
Vaccine Adverse Events Reporting System (VAERS)	www.cdc.gov/vaccinesafety/Activities/vaers.html
Vaccine Administration: Recommendations and Guidelines	www.cdc.gov/vaccines/recs/vac-admin/default.htm
Vaccines and Immunizations	www.cdc.gov/vaccines/
Vaccines for Children Program	www.cdc.gov/vaccines/programs/vfc/index.html
Vaccines for Children—Vaccine Price List	www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html
Vaccine Information Statements	www.cdc.gov/vaccines/hcp/vis/index.html
Vaccine Safety	www.cdc.gov/vaccinesafety/index.html
Vaccine Storage and Handling	www.cdc.gov/vaccines/recs/storage/default.htm
Department of Health and Human Services (HHS)	
National Vaccine Program Office (NVPO)	www.hhs.gov/nvpo/
Health Resources and Services Administration	
National Vaccine Injury Compensation Program	www.hrsa.gov/vaccinecompensation/
National Institute of Allergy and Infectious Diseases (NIAID)	
Vaccines	www.niaid.nih.gov/about/vrc
World Health Organization (WHO)	
Immunization, Vaccines, and Biologicals	www.who.int/immunization/en/

From Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

Appendix Ia

Definitions of Complementary and Alternative Medicine Terms

Acupuncture Thin needles are inserted superficially on the skin at locations throughout the body. These points are located along "channels" of energy. Heat can be applied by burning (moxibustion), electric current (electroacupuncture), or pressure (acupressure). Healing is proposed by the restoration of a balance of energy flow called *Qi.* Another explanation suggests that, possibly, the stimulation activates endorphin receptors.

Alexander Technique A bodywork technique in which rebalancing of "postural sets" (i.e., physical alignment) is taught by mentally focusing on the way correct alignments should look and feel and through verbal and tactile guidance by the practitioner.

Applied Kinesiology A form of treatment that uses nutrition, physical manipulation, vitamins, diets, and exercise to restore and energize the body. Weak muscles are proposed as a source of dysfunctional health.

Aromatherapy A form of complementary medicine that uses various plant oils such as those from lavender. Route of administration can be through absorption in the skin or inhalation. The aromatic biochemical structures of certain plants are thought to act in areas of the brain related to past experiences and emotions (e.g., limbic system).

Ayurveda A major health system that originated in India and incorporates the body, mind, and spirit to prevent and treat disease. Includes special types of diets, herbs, and minerals.

Biofeedback A mind-body therapy procedure in which sensors are placed on the body to measure muscle tension, heart rate, and sweat responses or neural activity. Information is provided by visual, auditory, or body-muscle cell activation so as to teach either to increase or decrease physiologic activity, which, when reconstituted, is proposed to improve health problems (e.g., pain, anxiety, or high blood pressure). In some cases, relaxation exercises complement this procedure.

Chelation Therapy Involves the removal—through intravenous infusion of a chelating agent (synthetic amino acid ethylenediamine tetraacetic acid [EDTA])—of heavy metals, including lead, nickel, and cadmium, as a way to treat certain diseases. Ancillary treatments include the use of vitamins, changes in diet, and exercise.

Cognitive Therapy Psychological therapy in which the major focus is altering and changing irrational beliefs through a type of Socratic dialogue and self-evaluation of certain illogical thoughts. Conditioning and learning are important components of this therapy.

Craniosacral Therapy A form of gentle manual manipulation used for diagnosis and for making corrections in a system made up of cerebrospinal fluid, cranial and dural membranes, cranial bones, and sacrum. This system is proposed to be dynamic, with its own physiologic frequency. Through touch and pressure, tension is proposed to be reduced and cranial rhythms normalized, leading to improvement in health and disease.

Diathermy The use of high-frequency electrical currents as a form of physical therapy and in surgical procedures. The term *diathermy,* derived from the Greek words *dia* and *therma,* literally means "heating through." The three forms of diathermy used by physical therapists are short wave, ultrasound, and microwave.

Eye Movement Desensitization and Reprocessing (EMDR) A technique that proposes to remove painful memories by behavioral techniques. Rhythmic, multisaccadic eye movements are produced by allowing the patient to track and follow a moving object while imagining a stressful memory or event. By using deconditioning, including verbal interaction with the therapist, the painful memory is extinguished and health improved.

Feldenkrais Method A bodywork technique that integrates physics, judo, and yoga. The practitioner directs sequences of movement using verbal or hands-on techniques or teaches a system of self-directed exercise to treat physical impairments through the learning of new movement patterns.

Hatha Yoga The branch of yoga practice that involves physical exercise, breathing practices, and movement. These exercises are designed to have a salutary effect on posture, flexibility, and strength and are intended ultimately to prepare the body to remain still for long periods of meditation.

Hellerwork A bodywork technique that treats and improves proper body alignment through the development of a more complete awareness of the physical body. The goal is to realign fascia for improvement of standing, sitting, and breathing using "body energy," verbal feedback, and changing emotions and attitudes.

Homeopathy A form of treatment in which substances (minerals, plant extracts, chemicals, or disease-producing germs), which in sufficient doses would produce a set of illness symptoms in healthy individuals, are given in microdoses to produce a "cure" of those same symptoms. The *symptom* is not thought to be part of the illness but part of a curative process.

Hyperbaric Oxygen A therapy in which 100% oxygen is given at or above atmospheric pressure. An increase in oxygen in the tissue is proposed to increase blood circulation and improve healing and health and influence the course of disease.

Jin Shin Jyutsu An ancient bodywork technique to harmonize body, mind, and spirit by gentle touch that uses specific "healing points" at the body surface. The points are proposed to overlie flowing energy (Qi). The therapist's fingers are used to "redirect, balance, and provide a more efficient energy flow" to and throughout the body.

Light Therapy Natural light or light of specified wavelengths is used to treat disease. This may include ultraviolet light, colored light, or low-intensity laser light. Generally, the eye is the initial entry point for the light because of its direct connection to the brain.

Magnetic Therapy Magnets are placed directly on the skin, theoretically stimulating living cells and increasing blood flow by ionic currents that are created from polarities on the magnets.

Modified and updated from Spencer JW: *Complementary/alternative medicine: an evidence-based approach,* St Louis, 1999, Mosby.

Mediterranean Diet A diet that includes 50% to 60% carbohydrates, 30% fats, and 10% proteins. The diet is derived from the eating habits of people in the Mediterranean area, who were shown to have reduced rates of cardiovascular disease. Clinical trial evidence has indicated that it may reduce the risk of cardiovascular disease in people at high risk for CVD.

Mind-Body Therapies A group of therapies that emphasize using the mind or brain in conjunction with the body to assist healing. Mind-body therapies can involve varying degrees of levels of consciousness, including *hypnosis,* in which selective attention is used to induce a specific altered state (trance) for memory retrieval, relaxation, or suggestion; *visual imagery,* in which the focus is on a target visual stimulus; *yoga,* which involves integration of posture and controlled breathing, relaxation, and/or meditation; *relaxation,* which includes lighter levels of altered states of consciousness through indirect or direct focus; and *meditation,* in which there is an intentional use of posture, concentration, contemplation, and visualization.

Muscle Energy Technique A manual therapy in osteopathic medicine that includes both passive mobilization and muscle reeducation. Diagnosis of somatic dysfunction is performed by the practitioner, after which the patient is guided to provide corrective muscle contraction.

Music Therapy The use of music in an either active or passive mode. Used mainly to reduce stress, anxiety, and pain, especially in the palliative care setting.

Naturopathy A major health system that includes practices that emphasize diet, nutrition, homeopathy, acupuncture, herbal medicine, manipulation, and various mind-body therapies. Focal points include self-healing and treatment through changes in lifestyle and emphasis on health prevention.

Ornish Diet A life-choice program based on eating a vegetarian diet containing less than 10% fat. The diet is high in complex carbohydrates and fiber. Meat and fish are generally avoided.

Oslo Diet An eating plan that emphasizes increased intake of fish and reduced total fat intake. Diet is combined with regular endurance exercise.

Pilates An educational and exercise approach using the proper body mechanics, movements, truncal and pelvic stabilization, coordinated breathing, and muscle contractions to promote strengthening. Attention is paid to the entire musculoskeletal system.

Prayer The use of prayer(s) that are offered to "some higher being" or authority to heal and/or arrest disease. May be practiced by the individual patient, by groups, or by other(s) with or without the patient's knowledge (e.g., intercessory).

Pritikin Diet A weight management plan that is based on a vegetarian framework. Meals are low in fat, high in fiber, and high in complex carbohydrates.

Qi Gong A form of Chinese exercise-stimulation therapy that proposes to improve health by redirecting mental focus, breathing, coordination, and relaxation. The goal is to "rebalance" the body's own healing capacities by activating proposed electrical or energetic currents that flow along meridians located throughout the body. These meridians, however, do not follow conventional nerve or muscle pathways. In Chinese medical training and practice this therapy includes "external Qi," which is energy transmitted from one person to another so as to heal.

Raja Yoga Yoga practice that includes all of the other forms of yoga. The practitioner is instructed to follow moral directives, physical exercises, breathing exercises, meditation, devotion, and service to others to facilitate religious awakening.

Reflexology A bodywork technique that uses reflex points on the hands and feet. Pressure is applied at points that correspond to various body parts, to eliminate blockages thought to produce pain or disease.

Reiki Comes from the Japanese word meaning "universal life force energy." The practitioner serves as a conduit for healing energy directed into the body or energy field of the recipient without physical contact with the body.

Rolfing A bodywork technique that involves the myofascia. The body is realigned by using the hands to apply deep pressure and friction that allow more sufficient posture, movement, and the "release" of emotions from the body.

Shiatsu A Japanese bodywork technique involving finger pressure at specific points on the body mainly to balance "energy" in the body. The major focus is on prevention by keeping the body healthy. The therapy uses more than 600 points on the skin that are proposed to be connected to pathways through which energy flows.

T'ai Chi A technique that uses slow, purposeful motor-physical movements of the body to control and achieve a more balanced physiologic and psychological state.

Therapeutic Touch A body energy field technique in which hands are passed over the body without actually touching to recreate and change proposed "energy imbalances" for restoring innate healing forces. Verbal interaction between patient and therapist helps maximize effects.

Traditional Chinese Medicine An ancient form of medicine that focuses on prevention and secondarily treats disease with an emphasis on maintaining balance through the body by stimulating a constant, smooth-flowing Qi energy. Herbs, acupuncture, massage, diet, and exercise are also used.

Trager Psychophysical Integration A bodywork technique in which the practitioner enters a meditative state and guides the client through gentle, light, rhythmic, nonintrusive movements. "Mentastics" exercises using self-healing movements are taught to the clients.

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Appendix Ib

Relaxation Techniques

Relaxation Techniques

Relaxation Technique	Summary	Further Resources
Breathing exercise	This is the foundation of most relaxation techniques. Have patients place one hand on the chest and the other on the abdomen. Instruct them to take a slow, deep breath, as if they were sucking in all the air in the room. While doing this, the hand on the abdomen should rise higher than the hand on the chest. This promotes diaphragmatic breathing that increases alveolar expansion in the bases of the lungs. Have them hold the breath for a count of 7 and then exhale. Exhalation should take twice as long as inhalation. Repeat this for a total of five breaths, and encourage patients to do this three times a day.	*Conscious Breathing* by Gay Hendricks is one of many good resources on using breathing for relaxation and health.
Meditation		
Transcendental/the relaxation response	To prevent distracting thoughts, the subject repeats a mantra (a word or sound) over and over again while sitting in a comfortable position. If a distracting thought comes to mind, it is accepted and let go, with the mind focusing again on the mantra.	*The Relaxation Response* by Herbert Benson; www.tm.org for information on transcendental meditation.
Mindful meditation	This represents the philosophy of living in the present or in the moment. The *body scan* is one technique where the subject uses breathing to obtain a relaxed state while lying or sitting. The mind progressively focuses on different parts of the body, where it feels any and all sensations intentionally but nonjudgmentally before moving on to another part of the body. A patient with back pain may focus on the quality and characteristics of the pain as if to better understand it and bring it under control.	*Full Catastrophe Living* by Jon Kabat-Zinn describes this technique in full and the program for stress reduction at the University of Massachusetts Medical Center.
Centering prayer	This is a form similar to transcendental meditation that has a more religious foundation. The subject repeats a "sacred word" similar to a mantra. As thoughts come to mind, they are accepted and let go, clearing the mind to become more centered on the spirit within, as if the mind's preoccupied thoughts are the layers of an onion that are peeled away, allowing better understanding of the spirit at the core.	www.centeringprayer.com; look under "method of centering prayer" for a nondenominational discussion.
Progressive muscle relaxation (PMR)	A form of relaxation in which the subject is attuned to the difference in feeling when the muscles are tensed and then relaxed. In a comfortable position, start by tensing the whole body from head to toe. While doing this, notice the feelings of tightness. Take a deep breath in and as you let it out, let the tension release and the muscles relax. This is then followed by progressive tension and relaxation throughout the body. One may start by clenching the fists and then tensing the arms, shoulders, chest, abdomen, hips, legs, and so on, with each step followed by relaxation.	*You Must Relax* is a book by the founder of this technique, Edmund Jacobson. Anxiety Canada: www.anxietycanada.com/adults/how-do-progressive-muscle-relaxation Mayo Clinic: www.mayoclinic.org/healthy-lifestyle/stress-management/in-depth/relaxation-technique/art-20045368 Oncology Nursing Society: www.ons.org/intervention/progressive-muscle-relaxation-pmr
Visualization/Self-hypnosis	The subject uses visualization to recruit images that create a relaxed state. For example, if a person is anxious, visualizing images of a place and a time that were peaceful and comforting would help induce relaxation. This is best used in conjunction with a breathing exercise.	There are many CDs, MP3s, and DVDs that can guide people through a visualization "script" that can result in relaxation. Emmett Miller is one well-known author.
Autogenic training	This induces a physiologic response by using simple phrases. For example, "My legs are heavy and warm" is meant to increase the blood flow to this area, resulting in relaxation. This is done progressively from head to toe with the use of deep breathing and repetition of the phrase. After completing this, focus attention on any body part that may still be tense, and then focus the breath and phrase to that area until the whole body is relaxed.	The British Autogenic Society at www.autogenic-therapy.org.uk/ is a good resource for more information.

Continued on following page

Relaxation Techniques—cont'd

Relaxation Technique	Summary	Further Resources
Exercise/Movement		
Aerobic	While performing an aerobic exercise, focus attention on a phrase, sound, word, or prayer and passively disregard other thoughts that may enter the mind. Some may focus on their breathing, saying to themselves, "In" with inhalation and "Out" with exhalation, or repeating "one-two, one-two" with each step they take with jogging. Doing this will help the mind focus, preventing other thoughts that may cause tension.	*Beyond the Relaxation Response* by Herbert Benson includes discussion of his research on inducing the relaxation response while exercising.
Yoga	This has been practiced for thousands of years in India. In America, it has been divided into three aspects: breathing (pranayama yoga), bodily postures or asanas (hatha yoga), and meditation to maintain balance and health. Regular practice induces relaxation.	For Yoga, t'ai chi, and qi gong therapies, it is best to encourage patients to take a class at a local community center or gym and to pick up an introductory book at a library or bookstore.
T'ai chi	An ancient Chinese martial art that uses slow, graceful movements combined with inner mindfulness and breathing techniques to help bring balance between the mind and body.	See above.
Qi gong	A traditional Chinese practice that uses movement, meditation, and controlled breathing to balance the body's vital energy force, Qi.	See above.

Updated from Rakel RE (ed): *Principles of family practice*, ed 6, Philadelphia, 2002, Saunders.

Appendix Ic

Overview of Selected Natural Products

This table includes a few of the common uses and side effects of selected natural products. The evidence supporting the uses and side effects of these products varies considerably and may be based on anecdotal information or theoretical concerns with the natural products.

Natural Products	Common Use(s)	Adverse Effects/Potential Concerns
African plum (Pygeum)	Benign prostatic hyperplasia	Nausea and abdominal pain have been reported, but pygeum is generally well tolerated. Pygeum does not decrease prostate size or influence PSA concentrations.
Black cohosh	Management of hot flashes in peri- and postmenopausal women	Dyspepsia, rash, weight gain, headache, and cramping have been reported. Concern exists that black cohosh causes liver toxicity, although the botanical was part of a multi-ingredient blend. The potential development of mild estrogen-like adverse effects, especially endometrial hyperplasia, is of concern.
Butterbur	Prevention of migraine headaches and supported by 2012 American Academy of Neurology; allergic rhinitis	Diarrhea, stomach upset, fatigue, belching, headache, and drowsiness may occur. Due to concern about hepatotoxicity, butterbur products should be free of pyrrolizidine alkaloids. Products should be standardized to 15% petasin and isopetasin.
Chamomile (German)	Motion sickness, anxiety, insomnia; gastrointestinal spasms; mucositis	Allergic reactions occur on rare occasion. Patients with a ragweed allergy should use chamomile with caution.
Chasteberry	Premenstrual dysphoric disorder, premenstrual syndrome, menopausal symptoms, female infertility, mastalgia	Gastrointestinal upset, headache, rash, acne, weight gain, and menstrual bleeding have been reported.
Chitosan	Weight loss, Crohn disease, hypercholesterolemia, anemia	Gastrointestinal upset, nausea, flatulence, and constipation have been reported. Patients with a shellfish allergy should avoid the use of chitosan.
Chondroitin sulfate	Osteoarthritis, osteoporosis, hyperlipidemia	Gastrointestinal upset, nausea, diarrhea, constipation, and alopecia. Concern exists that chondroitin may have anticoagulant activity due to its structural similarity to part of heparin.
Cinnamon	Type 2 diabetes mellitus, flatulence, gastrointestinal spasms, anorexia, menopausal symptoms, impotence	Cassia cinnamon is one of three types of cinnamon in commercial food products; this is the only type that may have minor effects to improve blood glucose concentrations.
Coenzyme Q10	Chronic heart failure, angina, dilated cardiomyopathy, statin-induced myopathy, Parkinson disease	Nausea, vomiting, diarrhea, anorexia, heartburn, and rash have been reported. Coenzyme Q10 is structurally similar to vitamin K; concern exists about potential interaction with warfarin.
Cranberry	Prevention and treatment of urinary tract infections; type 2 diabetes mellitus; chronic fatigue syndrome; pleurisy	Gastrointestinal upset and diarrhea have been reported with large doses of cranberry. Uric acid kidney stone formation is also possible with large doses of cranberry over prolonged periods of time.
Dehydroepiandrosterone (DHEA)	Slow or reverse aging, weight loss, metabolic syndrome, erectile dysfunction, immune stimulant, osteoporosis, systemic lupus erythematosus, multiple sclerosis, depression, schizophrenia	Acne and other androgenic effects commonly occur in women. Alopecia, insulin resistance, hepatic dysfunction, and hypertension have been reported. Ingested wild yam and soy cannot be converted into DHEA by humans.
Devil's claw	Osteoarthritis, atherosclerosis, gout, myalgias, fever, migraines	Diarrhea, nausea, and vomiting, as well as allergic reactions, have been reported.
Echinacea	Prevention and treatment of viral respiratory infections; urinary tract infections; chronic fatigue syndrome; attention deficit hyperactivity disorder	Nausea, vomiting, diarrhea, heartburn, headaches, dizziness, arthralgias, and allergic reactions have been reported with echinacea. Patients with a ragweed allergy should avoid use of echinacea.
Eleuthero (Siberian ginseng)	Maintenance of a normal blood pressure; atherosclerosis; Alzheimer disease; chronic fatigue syndrome; diabetes; herpes simplex infections	Drowsiness, anxiety, and irritability have been reported.

Continued on following page

Overview of Selected Natural Products

Natural Products	Common Use(s)	Adverse Effects/Potential Concerns
Evening primrose oil (EPO)	Premenstrual syndrome, mastalgia, osteoporosis, asthma, menopausal symptoms, eczema, chronic fatigue syndrome	EPO is well tolerated.
Fenugreek	Type 2 diabetes mellitus, anorexia, atherosclerosis; also used as galactogogue	Gastrointestinal upset, flatulence, and hypoglycemia are possible side effects. Patients with a peanut allergy (and an allergy to related plants) should use fenugreek with caution. Nursing mothers who use fenugreek may notice a "maple syrup" smell in their sweat and in the urine of their infants. This may be mistaken to be maple syrup urine disease in the infant.
Feverfew	Prevention of migraines; fever; menstrual-related problems; arthritis; infertility; asthma	Gastrointestinal side effects are the most common with feverfew. A "post-feverfew syndrome" has been reported in individuals who have taken feverfew for prolonged periods of time and then have abruptly stopped the herbal.
Fish oil	Hypertriglyceridemia, coronary heart disease, hypertension, asthma, depression, rheumatoid arthritis, osteoporosis, psoriasis	Heartburn, nausea, rash, and a "fishy" aftertaste can occur. Contamination with pesticides (as well as with mercury and other heavy metals) is a potential concern, although this is unlikely.
Garlic	Hyperlipidemia, hypertension, peripheral arterial disease, type 2 diabetes mellitus	Nausea, vomiting, heartburn, and body odor are most common. "Deodorized" garlic products may lack the active ingredient, allicin.
Ginger	Nausea and vomiting secondary to pregnancy, chemotherapy, motion sickness, surgery	Heartburn, belching, and dermatitis have been reported. In overdoses, ginger has been associated with central nervous system depression and arrhythmias. Efficacy for hyperemesis gravidarum is unknown, and use is not recommended.
Ginkgo	Alzheimer disease, vascular dementias, tinnitus, acute mountain sickness, intermittent claudication	Gastrointestinal side effects, headaches, dizziness, and allergic skin reactions. Seizures have been reported in several case reports. Products should contain 24% ginkgo flavone glycosides and 6% terpenoids.
Ginseng (Panax)	Increased resistance to stress and improved well-being; increased physical stamina; depression; diabetes; erectile dysfunction	Insomnia has been reported with ginseng. Vaginal bleeding, mastalgia, and amenorrhea have also been reported.
Glucosamine sulfate	Osteoarthritis	Nausea, heartburn, skin reactions, and headache have been reported. Increased glucose concentrations have been a concern but have not been documented. Patients with a shellfish allergy should use glucosamine with caution.
Green tea	Improve cognitive performance; prevention of breast, prostate, and colon cancer; hyperlipidemia; Parkinson disease; obesity; diabetes; cardiovascular disease	Nausea, vomiting, dyspepsia, dizziness, insomnia, and nervousness have been reported. Side effects may be a result of the large amount of caffeine in green tea products. Hepatotoxicity has been a potential concern with green tea.
Hawthorn	Mild heart failure, angina, arrhythmias, hypertension	Mild gastrointestinal effects, dizziness, rash, palpitations, and nervousness have been reported.
Hoodia	Obesity	Side effects have not been reported. Many products have been adulterated and lack the actual ingredient.
Horse chestnut	Chronic venous insufficiency, including varicose veins; benign prostate hyperplasia; diarrhea	Mild nausea, vomiting, dizziness, headache, and itching. Products are standardized to 16%–20% aescin.
Huperzine	Alzheimer disease, increased alertness and energy, myasthenia gravis, memory enhancement	Nausea, vomiting, diarrhea, sweating, and blurred vision as a result of the cholinergic effects of huperzine have been reported.
Kava	Anxiety, insomnia, restlessness, seizure disorders, depression, chronic fatigue syndrome	Gastrointestinal upset, headache, dizziness, "kava" dermopathy, and allergic skin reactions. Hepatotoxicity is the primary concern with kava; some countries have banned the use of kava.
Melatonin	Jet lag, insomnia, migraine, chronic fatigue syndrome, breast cancer, gastritis/PUD, osteoporosis; also used for insomnia in children with ADHD	Daytime drowsiness, headache, and dizziness have been reported. Vaginal bleeding has occurred in perimenopausal women. Melatonin from animal sources should be avoided.
Melissa	Cold sores (topically), anxiety, insomnia, Alzheimer disease, hypertension, dyspepsia	Nausea, vomiting, dizziness, and wheezing have occurred with oral melissa.
Methylsulfonylmethane (MSM)	Chronic pain, arthritis, diabetes, osteoporosis, allergies, obesity, premenstrual syndrome	Nausea, bloating, diarrhea, fatigue, and insomnia have been associated with MSM. This substance is used frequently in combination with glucosamine and chondroitin.
Milk thistle	Protective agent against liver damage due to alcohol, acetaminophen, and carbon tetrachloride; hepatitis C	Nausea, abdominal fullness, diarrhea, and allergic reactions. Patients with a ragweed allergy should use milk thistle with caution.
Peppermint	Irritable bowel syndrome, sinusitis, morning sickness, dysmenorrhea	Heartburn has been reported, as well as laryngeal and bronchial spasm in infants and children.
Policosanol	Hyperlipidemia, intermittent claudication, atherosclerosis	Migraines, insomnia, dizziness, skin rash, and bleeding have been reported with policosanol. The product has antiplatelet effects.
Probiotics	Treatment and prevention of diarrhea including antibiotic-associated diarrhea; irritable bowel syndrome; atopic dermatitis; Crohn disease	Theoretically, probiotic products may increase risk of infections in immunocompromised individuals.
Red clover phytoestrogens	Menopausal symptoms, premenstrual syndrome, asthma	Rash, myalgias, headaches, and vaginal bleeding have been reported. Theoretically, endometrial hyperplasia is an adverse effect from the use of these compounds.
Red yeast rice	Hyperlipidemia, indigestion, diarrhea, circulatory conditions	Gastrointestinal upset and dizziness may occur. Red yeast rice may contain lovastatin-like compounds and potentially cause rhabdomyolysis.

Natural Products	Common Use(s)	Adverse Effects/Potential Concerns
S-adenosylmethionine (SAM-e)	Depression, anxiety, dementia, osteoarthritis, heart disease	Nausea, vomiting, diarrhea, headache, and nervousness have been reported. Concern exists that SAM-e raises homocysteine levels.
St. John's wort	Depression, anxiety, chronic fatigue syndrome, HIV/AIDS	Anxiety, gastrointestinal upset, vaginal bleeding, neuropathy, and rash can occur. Hypomania has been induced by St. John's wort.
Tea tree oil	Topical use for acne, fungal infections, lice, scabies	Local inflammation and contact dermatitis may occur.
Valerian	Insomnia, depression, chronic fatigue syndrome, menstrual cramps	Headaches, gastrointestinal upset, and drowsiness can occur. Hepatotoxicity is a potential concern with valerian.

ADHD, Attention deficit hyperactivity disorder; *AIDS,* acquired immune deficiency syndrome; *HIV,* human immunodeficiency virus; *PUD,* peptic ulcer disease; *PSA,* prostate-specific antigen.

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Appendix Id

Natural Products and Drug Interactions

This table lists interactions between selected natural products and prescription and nonprescription drugs. Many of the listed interactions are theoretical in nature and have not been documented to occur in humans. However, interactions with St. John's wort are potentially life threatening in nature. Other interactions are based on small studies of healthy volunteers and use pharmaceutical-quality natural products that may or may not be commercially available.

Natural Products	Drugs	Interactions
Black cohosh	Hepatotoxic drugs	Concern exists that the risk of hepatotoxicity with black cohosh is increased in the presence of hepatotoxic drugs.
	Cisplatin	Animal studies suggest that the efficacy of cisplatin against breast cancer cells may be decreased by black cohosh.
	CYP2D6 substrates	Black cohosh may modestly inhibit CYP2D6 enzyme activity to result in higher drug concentrations.
Butterbur	CYP3A4 inducers (rifampin, carbamazepine, etc.)	Drugs that induce the activity of CYP3A4 increase the risk of the formation of hepatotoxic metabolites from pyrrolizidine alkaloids from some butterbur products.
Chamomile	CNS depressants	Chamomile may have additive CNS depressant effects.
	CYP1A2 substrates	Chamomile may inhibit CYP1A2 enzyme activity to result in higher drug concentrations.
	CYP3A4 substrates	Chamomile may inhibit CYP3A4 enzyme activity to result in higher drug concentrations.
	Estrogens	Chamomile may compete for estrogen receptors.
	Tamoxifen	Chamomile may interfere with the effects of tamoxifen because of its estrogenic effects.
Chaste tree berry	Antipsychotic agents	Chaste tree berry may antagonize the effects of antipsychotic agents through its dopaminergic activity.
	Metoclopramide	Chaste tree berry may antagonize the effects of metoclopramide through its dopaminergic activity.
	Dopamine agonists	Chaste tree berry may possess additive effects to drugs such as levodopa through its dopaminergic activity.
	Oral contraceptives/estrogens	Chaste tree berry may possess additive hormonal effects.
Chondroitin	Warfarin	High-dose chondroitin has structural similarity to a heparinoid and may possess weak anticoagulant effects.
Cinnamon	Hypoglycemic agents	Cinnamon may possess additive effects on blood glucose to those of hypoglycemic agents.
Coenzyme Q10	Antihypertensive agents	Coenzyme Q10 may possess additive effects on blood pressure to those of antihypertensive agents.
	Warfarin	Coenzyme Q10 may lessen the anticoagulant effects of warfarin because of its structural similarity to vitamin K.
	Chemotherapy	The antioxidant effects of coenzyme Q10 may blunt the efficacy of chemotherapeutic agents that depend on the formation of free radicals.
Cranberry	CYP2C9 substrates (warfarin)	Cranberry may inhibit CYP2C9 enzyme activity to result in higher drug concentrations, although evidence with warfarin is contradictory.
Dehydroepiandrosterone (DHEA)	Tamoxifen and aromatase inhibitors such as anastrozole	DHEA may interfere with the antiestrogenic effects of these drugs.
	CYP3A4 substrates	DHEA may slightly inhibit CYP3A4 enzyme activity to result in higher drug concentrations.
Devil's claw	Antihypertensive agents	Devil's claw may possess additive effects on blood pressure to those of antihypertensive agents.
	Hypoglycemic agents	Devil's claw may possess additive effects on blood glucose to those of hypoglycemic agents.
	H_2 antagonists and PPIs	Devil's claw may raise gastric pH and blunt the efficacy of H_2 antagonists and PPIs.
	CYP3A4 substrates	Devil's claw may inhibit CYP3A4 enzyme activity to result in higher drug concentrations.
	CYP2C9 substrates	Devil's claw may inhibit CYP2C9 enzyme activity to result in higher drug concentrations.
	CYP2C19 substrates	Devil's claw may inhibit CYP2C19 enzyme activity to result in higher drug concentrations.
	Warfarin	Devil's claw may inhibit CYP2C9 enzyme activity to result in higher concentrations of warfarin; purpura has been reported.

Natural Products	Drugs	Interactions
Echinacea	Immune suppressants	Echinacea may stimulate immune function, potentially decreasing the effectiveness of drugs such as cyclosporine and prednisone.
	CYP3A4 substrates	Echinacea may modestly induce hepatic CYP3A4 enzyme activity to result in lower drug concentrations.
	CYP1A2 substrates	Echinacea may inhibit CYP1A2 enzyme activity to result in higher drug concentrations.
Eleuthero (Siberian ginseng)	CNS depressants	Eleuthero may have additive CNS depressant effects.
	Antiplatelet and anticoagulant agents	Eleuthero may have antiplatelet activity, potentially increasing the risk of bleeding.
	CYP3A4 substrates	Eleuthero may inhibit CYP3A4 enzyme activity to result in higher drug concentrations.
	CYP1A2 substrates	Eleuthero may modestly inhibit CYP1A2 enzyme activity to result in higher drug concentrations.
	CYP2C9 substrates	Eleuthero may modestly inhibit CYP2C9 enzyme activity to result in higher drug concentrations.
	CYP2D6 substrates	Eleuthero may inhibit CYP2D6 enzyme activity to result in higher drug concentrations.
	Digoxin	Concentration of digoxin has been reported to increase but without evidence of toxicity.
Evening primrose oil (EPO)	Antiplatelet and anticoagulant agents	EPO may have anticoagulant activity, potentially increasing the risk of bleeding.
Fenugreek	Antiplatelet and anticoagulant agents	Fenugreek may have antiplatelet activity, potentially increasing the risk of bleeding.
	Hypoglycemic agents	Fenugreek may potentially lower blood glucose concentrations and have additive effects with hypoglycemic agents.
Feverfew	Antiplatelet and anticoagulant agents	Feverfew may have antiplatelet activity, potentially increasing the risk of bleeding.
	CYP3A4 substrates	Feverfew may inhibit CYP3A4 enzyme activity to result in higher drug concentrations.
	CYP1A2 substrates	Feverfew may inhibit CYP1A2 enzyme activity to result in higher drug concentrations.
	CYP2C9 substrates	Feverfew may inhibit CYP2C9 enzyme activity to result in higher drug concentrations.
	CYP2C19 substrates	Feverfew may inhibit CYP2C19 enzyme activity to result in higher drug concentrations.
Fish oils (omega-3 fatty acids)	Antiplatelet and anticoagulant agents	Fish oils may have antiplatelet activity, potentially increasing the risk of bleeding, although this has not been documented in humans.
	Antihypertensive agents	Fish oils may possess additive effects on blood pressure to those of antihypertensive agents.
	Oral contraceptives	Oral contraceptives may potentially interfere with the triglyceride-lowering effects of fish oil.
Garlic	Antiplatelet and anticoagulant agents	Garlic may have antiplatelet activity, potentially increasing the risk of bleeding.
	CYP3A4 substrates	Garlic may potentially induce CYP3A4 enzyme activity to result in lower drug concentrations; evidence is contradictory.
	CYP2E1 substrates	Garlic may modestly inhibit CYP2E1 enzyme activity to result in higher drug concentrations.
Ginger	Antiplatelet and anticoagulant agents	Ginger may have antiplatelet activity, potentially increasing the risk of bleeding.
	Hypoglycemic agents	Ginger may potentially lower blood glucose concentrations and have additive effects with hypoglycemic agents.
Ginkgo	Antiplatelet and anticoagulant agents	Ginkgo may have antiplatelet activity, potentially increasing the risk of bleeding.
	CYP2C19 substrates	Ginkgo may induce CYP2C19 enzyme activity to result in lower drug concentrations.
	CYP1A2 substrates	Ginkgo may modestly inhibit CYP1A2 enzyme activity to result in higher drug levels.
	CYP2C9 substrates	Ginkgo may modestly inhibit CYP2C9 enzyme activity to result in higher drug concentrations.
	CYP2D6 substrates	Ginkgo may inhibit CYP2D6 enzyme activity to result in higher drug concentrations.
Ginseng (Panax)	Antiplatelet and anticoagulant agents	Panax ginseng may have antiplatelet properties; American ginseng may decrease the effectiveness (international normalized ratio [INR]) of warfarin.
	CYP2D6 substrates	Panax ginseng may modestly inhibit CYP2D6 enzyme activity to result in higher drug concentrations.
	Immune suppressants	Panax ginseng may stimulate immune function, potentially decreasing the effectiveness of drugs such as cyclosporine and prednisone.
	Hypoglycemic agents	Panax ginseng may potentially lower blood glucose levels and have additive effects with hypoglycemic agents.
Glucosamine	Warfarin	High-dose glucosamine (along with high-dose chondroitin) may have additive effects to those of warfarin because of structural similarity to heparin. Evidence is lacking.
Green tea extract	Antiplatelet agents	Green tea possesses compounds that may have antiplatelet activity, potentially increasing the risk of bleeding.
	Amphetamines	Caffeine in green tea may increase the risk of CNS toxicity.
	Cocaine	Caffeine in green tea may increase the risk of CNS toxicity.
	Oral contraceptives	Oral contraceptives may decrease the clearance of caffeine in green tea.
	Warfarin	Small amounts of vitamin K have been reported to be present in green tea, potentially decreasing the effectiveness of warfarin.
	Theophylline	Caffeine potentially decreases theophylline clearance.
	Verapamil	Verapamil decreases caffeine clearance, resulting in increased concentrations.
	Quinolone antibiotics	Some quinolone antibiotics decrease the clearance of caffeine.
	Hepatotoxic drugs	Concern exists that the risk of hepatotoxicity with green tea is increased in the presence of hepatotoxic drugs.
Hawthorn	β-Blockers	Hawthorn and β-blockers may have additive effects on blood pressure and heart rate.
	CCBs, nitrates	Hawthorn and CCBs (or nitrates) may have additive effects due to coronary vasodilation.
	Digoxin	Hawthorn may have additive effects to those of digoxin.
	Phosphodiesterase inhibitors	Hawthorn may have additive vasodilatory and hypotensive effects with these drugs.
Horse chestnut seed extract (HCSE)	Antiplatelet and anticoagulant agents	HCSE may have antiplatelet activity, potentially increasing the risk of bleeding.
	Hypoglycemic agents	HCSE may potentially lower blood glucose concentrations and have additive effects with hypoglycemic agents.
Huperzine	AChE inhibitors (donepezil, etc.)	Huperzine may have additive effects when combined with AChE inhibitors.
	Anticholinergic drugs	The effectiveness of huperzine and/or the anticholinergic drug may be decreased by their concomitant administration.
	Cholinergic drugs (bethanechol, etc.)	Huperzine may have additive effects when combined with cholinergic drugs.

Continued on following page

Natural Products	Drugs	Interactions
Kava	CYP3A4 substrates	Kava may inhibit CYP3A4 enzyme activity to result in higher drug concentrations.
	CYP1A2 substrates	Kava may inhibit CYP1A2 enzyme activity to result in higher drug concentrations.
	CYP2C9 substrates, CYP2C19 substrates	Kava may inhibit CYP2C9 and CYP2C19 enzyme activity to result in higher drug concentrations.
	CYP2D6 substrates	Kava may inhibit CYP2D6 enzyme activity to result in higher drug concentrations.
	P-glycoprotein substrates (digoxin; itraconazole; diltiazem, verapamil; and many other drugs)	Kava may inhibit P-glycoprotein transporter systems.
	Hepatotoxic drugs	Concern exists that the risk of hepatotoxicity from kava is increased in the presence of hepatotoxic drugs.
Melatonin	Antiplatelet and anticoagulant agents	Melatonin may potentiate the effects of antiplatelets and anticoagulants, although the mechanism is unknown.
	CNS depressants	Melatonin may have additive CNS depressant effects.
	Fluvoxamine	Fluvoxamine may increase levels of melatonin.
	Immune suppressants	Melatonin may stimulate immune function, potentially decreasing the effectiveness of drugs such as cyclosporine and prednisone.
	Hypoglycemic agents	Melatonin may impair glucose utilization and may decrease the efficacy of hypoglycemic agents.
Milk thistle	Estrogens (and other drugs that undergo glucuronidation)	Silymarin may increase the clearance of estrogens.
	CYP2C9 substrates	Milk thistle may modestly inhibit CYP2C9 enzyme activity to result in higher drug concentrations.
Peppermint oil	H_2 antagonists and proton pump inhibitors	Peppermint oil may raise gastric pH and blunt efficacy of H_2 antagonists and PPIs.
	CYP3A4 substrates	Peppermint oil may modestly inhibit CYP3A4 enzyme activity to result in higher drug concentrations.
	CYP1A2 substrates	Peppermint oil may modestly inhibit CYP1A2 enzyme activity to result in higher drug concentrations.
	CYP2C9 substrates, CYP2C19 substrates	Peppermint oil may modestly inhibit CYP2C9 and CYP2C19 enzyme activity to result in higher drug concentrations.
Policosanol	Antiplatelet and anticoagulant agents	Policosanol may have antiplatelet activity, potentially increasing the risk of bleeding.
Probiotics	Antibiotics	Antibiotics may kill the live organisms in different probiotic preparations.
	Immune suppressants	Theoretically, probiotics may cause bacterial or fungal infections in patients who are taking immune suppressants chronically.
Red clover phytoestrogens	Antiplatelet and anticoagulant agents	Theoretically, red clover may possess coumarins, which increase the risk of bleeding with antiplatelet and anticoagulants. Evidence is lacking.
	CYP3A4 substrates	Red clover may inhibit CYP3A4 enzyme activity to result in higher drug concentrations.
	CYP2C9 substrates, CYP2C19 substrates	Red clover may inhibit CYP2C9 and CYP2C19 enzyme activity to result in higher drug concentrations.
	CYP1A2 substrates	Red clover may inhibit CYP1A2 enzyme activity to result in higher drug concentrations.
Red yeast rice	CYP3A4 inhibitors	Drugs that inhibit CYP3A4 may decrease the metabolism of lovastatin in red yeast rice.
	Statins	Red yeast rice contains lovastatin and increases the risk of myopathy.
	Fibrates and niacin	Fibrates and niacin may increase concentrations of lovastatin in red yeast rice.
S-adenosylmethionine (SAM-e)	Antidepressants (including MAOIs)	Additive effects are possible, and there is potential for toxicity.
	Serotonergic drugs (triptans, SSRIs, tramadol, dextromethorphan, etc.)	SAM-e may increase the risk of development of serotonin syndrome when used concomitantly.
Soy phytoestrogens	Estrogens	Soy potentially may inhibit the effects of estrogen.
	Tamoxifen/aromatase inhibitors	Soy's estrogenic effects may antagonize the antitumor effects of tamoxifen/aromatase inhibitors.
	MAOIs	Fermented soy products may contain tyramine.
St. John's wort	CYP3A4 substrates	St. John's wort strongly induces CYP3A4 enzyme activity to result in lower drug concentrations.
	CYP1A2 substrates	St. John's wort modestly induces CYP1A2 enzyme activity to result in lower drug levels.
	CYP2C9 substrates	St. John's wort induces CYP2C9 enzyme activity to result in lower drug concentrations.
	P-glycoprotein substrates (digoxin; itraconazole; diltiazem, verapamil; and many other drugs)	St. John's wort induces P-glycoprotein transporter systems.
	Serotonergic drugs (triptans, SSRIs, tramadol, dextromethorphan, etc.)	St. John's wort may increase the risk of development of serotonin syndrome when used concomitantly.
Valerian	CNS depressants	Valerian may increase the sedative effects of CNS depressants.
	CYP3A4 substrates	Valerian may modestly inhibit the CYP3A4 enzyme activity.

AChE, Acetylcholinesterase; *CCBs,* calcium channel blockers; *CNS,* central nervous system; *MAOIs,* monoamine oxidase inhibitor; *PPIs,* proton pump inhibitors; *SSRIs,* selective serotonin reuptake inhibitors.

EXAMPLES OF DRUGS METABOLIZED BY CYP ENZYMES

The following are examples of drugs that are metabolized through the different cytochrome P450 isoenzymes:

CYP1A2 substrates: Theophylline, imipramine, clozapine, naproxen

CYP2C9 substrates: Warfarin, tamoxifen, irbesartan, ibuprofen, glipizide

CYP2C19 substrates: Omeprazole and other proton pump inhibitors, phenytoin, phenobarbital, cyclophosphamide

CYP2D6 substrates: S-metoprolol, propafenone, paroxetine, risperidone, tramadol

CYP2E1 substrates: Acetaminophen, alcohol

CYP3A4 substrates: Most statins, indinavir, amlodipine, verapamil, alprazolam, buspirone

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Appendix Ie

Commonly Ingested Plants with Significant Toxic Potential

Plant	Symptoms	Management
Autumn crocus (*Colchicum autumnale*)	Vomiting Diarrhea Initial leukocytosis followed by bone marrow failure Multisystem organ failure	Activated charcoal decontamination Aggressive fluid resuscitation and supportive care
Belladonna alkaloids: Jimson weed (*Datura stramonium*) Belladonna ("deadly nightshade;" *Atropa belladonna*)	Anticholinergic toxidrome Seizures	Supportive care, benzodiazepines Consider physostigmine if patient is a threat to self or others; only use if no conduction delays on ECG
Cardiac glycoside-containing plants (foxglove, lily of the valley, oleander, yellow oleander, etc.)	Nausea Vomiting Bradycardia Dysrhythmias (AV block, ventricular ectopy) Hyperkalemia	Digoxin-specific Fab fragments
Jequirity bean and other abrin-containing species (e.g., rosary pea, precatory bean)	Oral pain Vomiting Diarrhea Shock Hemolysis Renal failure	Supportive care, including aggressive volume resuscitation and correction of electrolyte abnormalities
Monkshood (*Aconitum* species)	Numbness and tingling of lips/tongue Vomiting Bradycardia	Atropine for bradycardia Supportive care
Oxalate-containing plants: *Philodendron, Dieffenbachia, Colocasia* ("elephant ear")	Local tissue injury Oral pain Vomiting	Supportive care, pain control
Poison hemlock *(Conium maculatum)*	Vomiting Agitation followed by CNS depression Paralysis Respiratory failure	Supportive care
Pokeweed	Hemorrhagic gastroenteritis Burning of mouth and throat	Supportive care
Rhododendron	Vomiting Diarrhea Bradycardia	Atropine for symptomatic bradycardia Supportive care
Tobacco	Vomiting Agitation Diaphoresis Fasciculations Seizures	Supportive care
Water hemlock (*Cicuta* species)	Abdominal pain Vomiting Delirium Seizures	Supportive care, including benzodiazepines for seizures
Yew (*Taxus* species)	GI symptoms QRS widening Hypotension CV collapse	Supportive care Atropine for bradycardia Sodium bicarbonate does not appear to be effective

AV, Atrioventricular; *CNS,* central nervous system; *CV,* cardiovascular; *ECG,* electrocardiogram; *Fab,* fragment, antigen binding; *GI,* gastrointestinal.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

Appendix If

Herbs Associated with Toxicity

TABLE 1 Clinical Toxicity of Selected Herbs

Common Name	Botanical Name	Therapeutic Uses	Potential Toxicity
Aconite (monkshood, wolfsbane)	*Aconitum* spp.	Sedative, analgesic, antihypertensive	Cardiac arrhythmias
Aloe	*Aloe* spp.	Burns, skin diseases	Nephritis, GI upset
Betel nut	*Areca catechu*	Mood elevation	Bronchoconstriction, oral cancers
Bloodroot	*Sanguinaria canadensis*	Emetic, cathartic, eczema	GI upset, vertigo, visual disturbances
Chaparral (greasewood)	*Larrea tridentata*	Aging, free radical scavenging	Hepatitis
Compound Q	*Trichosanthes kirilowii*	Anthelmintic, cathartic	Diarrhea, hypoglycemia, CNS toxicity
Dandelion	*Taraxacum officinale*	Diuretic, heartburn remedy	Anaphylaxis
Figwort (xuan shen)	*Scrophularia* spp.	Antiinflammatory, antibacterial	Cardiac stimulation
Ginseng	*Panax quinquefolium*	Antihypertensive, aphrodisiac, stimulant, mood elevation, digestive aid	Ginseng abuse syndrome
Goldenseal	*Hydrastis canadensis*	Digestive aid, mucolytic, anti-infective	Uterine, cardiac stimulation; GI upset, leukopenia
Hellebore	*Veratrum* spp.	Antihypertensive	Vomiting, bradycardia, hypotension
Hyssop	*Hyssopus officinalis*	Asthma, mucolytic	Seizures
Juniper	*Juniperus communis*	Hallucinogen	GI upset, seizures, renal injury, hypotension, bradycardia
Kava kava	*Piper methysticum*	Sedative	Inebriation
Kombucha		Stimulant	Metabolic acidosis, hepatotoxicity, death
Licorice	*Glycyrrhiza* spp.	Indigestion	Mineralocorticoid effects
Lily of the valley	*Convallaria* spp.	Cardiotonic	GI (nausea, vomiting), cardiac arrhythmias
Linn (willow)	*Salix caprea*	Purgative	Hemolysis with glucose-6-phosphate dehydrogenase deficiency
Lobelia (Indian tobacco)	*Lobelia* spp.	Stimulant	Nicotine intoxication
Ma Huang	*Ephedra sinica*	Stimulant	Sympathetic crisis, especially with monoamine oxidase inhibitors
Mandrake	*Mandragora officinarum*	Hallucinogen	Anticholinergic syndrome
Mormon tea	*Ephedra nevadensis*	Stimulant, asthma, antipyretic	Hypertension, sympathomimetic
Nutmeg	*Myristica fragrans*	Hallucinogen, abortifacient	Hallucinations, GI upset
Oleander	*Nerium oleander*	Cardiac stimulant	Cardiac arrhythmias
Passionflower	*Passiflora caeruliea*	Hallucinogen	Hallucinations, seizures, hypotension
Periwinkle	*Vinca* spp.	Antiinflammatory, diabetes	Alopecia, seizures, hepatotoxicity
Pokeweed	*Phytolacca* spp.	Arthritis, chronic pain	GI upset, seizures, death
Sabah	*Sauropus androgynus*	Weight loss, vision	Pulmonary injury
Sage	*Salvia* spp.	CNS stimulant	Seizures
Snakeroot	*Rauwolfia serpentina*	Sedative, antihypertensive	Bradycardia, coma
Squill	*Urginea maritima*	Arthritis, cardiac stimulant	Seizures, arrhythmias, death
Thorn apple (jimsonweed)	*Datura stramonium*	Hallucinations	Anticholinergic
Tonka bean	*Dipteryx odorata*	Anticoagulant	Bleeding diathesis
Valerian root	*Valeriana* spp.	Sedative	Sedation, obtundation
Wild (squirting) cucumber	*Ecballium elaterium*	Constipation, antiinflammatory, rheumatic disease	Airway obstruction
Wormwood (mugwort)	*Artemisia* spp.	Stimulant, hallucinogen	Hallucinations, seizures, uterine stimulation
Yohimbine	*Corynanthe yohimbe*	Aphrodisiac, stimulant	Hypertension, sympathetic crisis

CNS, Central nervous system; *GI,* gastrointestinal.
From Kingston RL, Foley C: Herbal, traditional, and alternative medicines. In *Haddad and Winchester's clinical management of poisoning and drug overdose,* ed 4, Philadelphia, 2007, Saunders/Elsevier, p 1081.

TABLE 2 Common Herbal Dietary Supplements (HDS)–Drug Interactions

HDS	Drugs	Potential Consequences/Reactions
Aloe vera	Glibenclamide (glyburide)	↑ Oral aloe vera gel can cause additive glycemic-lowering effects when taken concurrently with a hypoglycemic agent.
Bitter orange	Phenelzine	↑ Risk of hypertensive crisis
Garlic	Ritonavir	↓ Effect of ritonavir
	Saquinavir	↓ Effect of saquinavir
Licorice	Warfarin	↑ Risk of bleeding
Grapefruit	Calcium channel blockers	Grapefruit juice has been found to increase bioavailability of certain drugs by inhibition of cytochrome P450 (CYP) 3A4 isozyme in liver and gut wall.
Melatonin	Zolpidem	↑ Sedative effects
Valerian	Alprazolam, phenobarbital	↑ Central nervous system depression
Goldenseal	Inhibition of CYP2D6 and CYP3A4	May affect approximately 50% of common pharmaceutical agents
St. John's wort	Cyclosporine, tacrolimus, warfarin, protease inhibitors, digoxin, theophylline, venlafaxine, oral contraceptives	May decrease drug effectiveness

↓, Decreasing; ↑, increasing.
From Kliegman, RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

Appendix Ig

Websites Providing Data on Herbal Therapy Hazards

Web Address	Website
www.fda.gov	On the U.S. Food and Drug Administration website under the title "MedWatch," some herb warnings can be found ("special adverse event monitoring system" link)
www.faseb.org	ASPET Herbal and Medicinal Plant Interest Group: a site for an herb discussion group with pharmacologists
www.abc.herbalgram.org	American Botanical Council
nccih.nih.gov/	The National Center for Complementary and Integrative Health is 1 of 27 institutes and centers that make up the U.S. National Institutes of Health; their mission is to define, through rigorous scientific investigation, the usefulness and safety of complementary and integrative health interventions and their roles in improving health and health care
toxnet.nlm.nih.gov/	A cluster of databases on toxicology, hazardous chemicals, and related areas

Modified from Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

Appendix Ih

Common Herbs in Integrated Medicine

Herb	Common Uses	Activity	Adverse Effects and Contraindications	Doses[b]	Drug Interactions[c]
Aloe *(Aloe vera, Aloe barbadensis)*	Burns and wound healing Constipation Gastritis Ulcers Psoriasis	Antiinflammatory Antiseptic	Dermatitis GI upset (PO) Diarrhea Avoid in children and pregnancy Avoid latex with inflammatory intestinal disease	Liberal application of gel topically No more than 1 qt of juice per day	Cardiac glycoside containing herbs and drugs Licorice Stimulant laxatives
Bilberry *(Vaccinium myrtillus)*	Eye disorder Antidiarrheal Circulatory disorders Diabetes	Antioxidant Collagen stabilizer Vasoprotective Astringent ↓ Platelet aggregation	May alter insulin requirements	Anthocyanosides (calculated as anthocyanidin): 20-40 mg tid *V. myrtillus* (25% extract): 80-160 mg tid Fresh berries: 55-115 g tid	Warfarin (at high doses of bilberry)
Black cohosh *(Cimicifuga racemosa)*	Menopause symptoms Menstrual problems Rattlesnake bites	Probable SSRI-like effects Possible estrogenic activity Possible luteinizing hormone suppression	GI upset ↑ BP Avoid in pregnancy and lactation Vertigo Rash Liver disease	27-Deoxyacteine: 2 mg bid Powdered rhizome: 1-2 g Tincture (1:5): 4-6 ml Fluid extract (1:1): 3-4 ml (1 tsp) Solid (dry powder) extract (4:1):	Hepatotoxic herbs and drugs
Cat's claw *(Uncaria tomentosa)*	Arthritis Cancer HIV Diverticulitis Herpes simplex and zoster	Immune stimulant Antiinflammatory Antimutagenic	Avoid in pregnancy and lactation, autoimmune illness, MS, TB, and leukemia (awaiting bone marrow transplant) Avoid in children <3 years old Headaches Dizziness Vomiting	Tea (1 g/250 ml): 1 cup tid Tincture: 1-2 ml tid Standardized dry extract: 20-60 mg qd	Avoid combining with hormone drugs, insulin, vaccines, iron, NSAIDs, and salicylates Antihypertensives Cytochrome P450 substrates Chemotherapy Hyperimmune globulin IV thymic preparations
Cayenne *(Capsicum annum)*	Arthritis Muscle pain Neuralgia Postmastectomy pain Psoriasis Diabetes Antiflatulent Diarrhea	Blocks substance P (pain peptide) ↓ Lipids ↓ Platelet aggregation	Eye irritation Burning, local and mucous membranes Gastritis Diarrhea (with internal use) Avoid in children <2 years old	Cream (0.025% or 0.075% capsaicin) topically qid	Warfarin: ↓ platelet aggregation with internal use MAOIs ACE inhibitors Aspirin Cocaine Antacids H_2 blockers Theophylline

Continued on following page

Herb	Common Uses	Activity	Adverse Effects and Contraindications	Doses[b]	Drug Interactions[c]
Chamomile *(Matricaria recutita, Matricaria chamomilla)*	GI complaints Skin and mucous membrane problems Stress and anxiety Wound healing	Antispasmodic effect Sedative effect Antiinflammatory Carminative	Avoid if allergy to member of daisy family (Asteraceae; e.g., ragweed, asters, chrysanthemums) Contact dermatitis Urticaria	Tea: 3-4 cups per day Capsules: 300-500 mg tid-qid Tincture: 4-6 ml tid Apply topically to affected area	Caution if using with tranquilizers or CNS depressants (?) WarfarinChemotherapy Cytochrome P450 substrates
Chaste tree *(Vitex agnus-castus)*	Menstrual problems Hyperprolactinemia Acne Infertility	Hormonal modulator	Rash Headache GI upset Avoid in pregnancy and lactation	Solution (9 g in 100 ml): 40 gtts qAM Dried extract: 4.2 mg qd Must take consistently for several months to see effect	Metoclopramide (Reglan) Contraceptive agents Avoid with dopamine agonists
Cranberry *(Vaccinium macrocarpon)*	Urinary tract infections	↓ Bacterial adherence to bladder endothelium	Diarrhea May increase risk of kidney stones	Prophylaxis: 90 ml qd Treatment: 360-960 ml qd Tincture 0.5-1 tsp tid	Lansoprazole, omeprazole Warfarin Cytochrome P450 substrates
Dong quai *(Angelica sinensis)*	Dysmenorrhea Other menstrual disorders Menopause symptoms Allergies	Phytoestrogen Antimicrobial effects Smooth muscle relaxant IgE inhibition	Photodermatitis Uterine stimulant Carcinogenic constituents Hypersensitivity Excess bleeding and fever Avoid with hormone-sensitive tumors	Dried root or rhizome: 1-2 g PO or IV tid Tincture (1:5): 3-5 ml tid Fluid extract (1:1): 0.5-2 ml tid	Warfarin Heparin Ticlopidine
Echinacea (*Echinacea* spp)	Colds and flu Immunity Upper respiratory infections Urinary tract infections Wound healing (topical) Recurrent candidal vaginitis	Immunostimulant ↑ Macrophage phagocytosis Stimulates lymphocyte activity Antiinflammatory Antimicrobial properties	Avoid in HIV/AIDS, autoimmune disease, collagen vascular disease, MS, and TB Avoid if allergy to sunflower seeds or member of daisy family (Asteraceae) such as ragweed (?) Avoid during pregnancy	Dried root (or as tea): 0.5-1 g Freeze-dried plant: 325-650 mg Juice of aerial portion of *E. purpurea* stabilized in 22% ethanol: 2-3 ml (0.5-0.75 tsp) Tincture (1:5): 2-4 ml (1-2 tsp) Solid (dry powdered) extract (6.5:1 or 3.5% echinacoside): 150-300 mg	Chemotherapy agents Cytochrome P450 substrates Immunosuppressants
Eleuthero *(Eleutherococcus senticosus)*	Herpes type II Fatigue Athletic performance Influenza complications	↑ Lymphocyte count Tonifying Immunomodulator Adaptogen	Diarrhea Sleep disturbance Anxiety Alters diabetes control Caution with cardiovascular disorders Avoid during antibiotic treatment of dysentery	Dried root: 2-4 g Tincture (1:5): 10-20 ml Fluid extract (1:1): 2-4 ml Solid (dry powdered) extract (20:1): 100-200 mg	Caution with antipsychotics, barbiturates, and sedatives Anticoagulants Chemotherapy agents Digoxin Hypoglycemics Kanamycin
Ephedra *(Ephedra sinensis, ma huang)*	Asthma Bronchitis Cough Decongestant Energy Weight loss Diuretic	Sympathomimetic activating α and β_1/β_2 receptors CNS stimulant Stimulates uterine contractions	↑ BP, root ↓ BP, plant above ground Anxiety, restlessness Headaches Irritability Nausea, vomiting Urinary obstruction with BPH Addictive potential Dysrhythmias Alters diabetes control Kidney stones Glaucoma Caution in heart disease, hypertension, diabetes, or thyroid disease	Based on alkaloid content 1%-3% 12.5-25 mg bid-tid Crude herb 500-1000 mg tid	Cardiac glycosides Halothane Guanethidine MAOIs Oxytocin Diabetic medication Dexamethasone Ergot derivatives Methylxanthines Reserpine Must be protected from the light

Continued on following page

Herb	Common Uses	Activity	Adverse Effects and Contraindications	Doses[b]	Drug Interactions[c]
Evening primrose oil *(Oenothera biennis)*	Fibrocystic breast Eczema Diabetic neuropathy Psoriasis Breast pain Lactation	Source of gamma-linoleic acid (GLA)	Headache GI symptoms Insomnia May exacerbate temporal lobe epilepsy and schizophrenia	Based on 8% GLA content 500-2000 mg tid-qid	Phenothiazines Tamoxifen Anesthetics Anticoagulants
Feverfew *(Tanacetum parthenium)*	Migraine prophylaxis and treatment Dizziness Tinnitus Dysmenorrhea	↓ Platelet aggregation Smooth muscle relaxant ↓ Prostaglandin synthesis and serotonin release from platelets and WBCs Antinociceptive Inhibits serotonin release	Stop 2 weeks before major surgery Oral ulcers GI upset Rash Rebound migraine Nervousness Avoid in pregnancy and lactation, or if allergy to sunflower seeds or member of daisy family (Asteraceae) such as ragweed	Depends on adequate level of parthenolide (0.4%-0.66%) Freeze-dried, pulverized leaves: 25-50 mg bid	Warfarin: ↓ platelet aggregation NSAIDs
Flax seed *(Linumus itatissimum)*	Hyperlipidemia Constipation Cardiovascular risk reduction Systemic lupus erythematosus Breast cancer risk reduction Irritable bowel; inflammatory bowel disease	↓ Platelet aggregation Antiinflammatory	Diarrhea Allergic reaction Caution with hormone-sensitive cancers Contraindicated with bowel obstruction	Capsule (1 g): 3-6 capsules qd Oil: 1-2 tbsp qd	Mucilage may affect absorption of oral drugs Anticoagulants Antidiabetic drugs
Garlic *(Allium sativum)*	Hyperlipidemia Hypertension Cancer prevention Antimicrobial Atherosclerosis	Inhibits platelet aggregation ↑ Fibrinolysis Antioxidant ↓ Systolic and diastolic blood pressure	Stop 2 weeks before major surgery Heartburn GI upset Flatulence Body/breath odor ↓ Blood glucose	10 mg allicin or 4 g fresh garlic; equivalent to 1-2 cloves/day	May potentiate antithrombotic effect of antiinflammatories, warfarin, and aspirin Saquinavir Cyclosporin Chlorzoxazone Dipyridamole Ticlopidine Cytochrome P450 substrates
Ginger *(Zingiber officinale)*	Antiemetic Nausea Motion sickness Morning sickness Arthritis Antiinflammatory Rheumatological	Stimulates intestinal tone and peristalsis Cholagogue Antiinflammatory Antioxidant Positive inotrope Inhibits platelet aggregation	Stop 2 weeks before major surgery GI upset Caution if patient has gallstones	Dry powder ginger root: 1 g Extract (20% gingerol and shogaol): 100-200 mg tid	Warfarin: ↓ platelet aggregation Chemotherapy agents General anesthetics Heparin Antacids Antidiabetic drugs Antihypertensives Barbiturates H_2 blockers Proton pump inhibitors
Ginkgo biloba *(Ginkgo biloba)*	Cerebrovascular insufficiency Peripheral vascular disease Vascular dementia Alzheimer disease Memory Vertigo Tinnitus Macular degeneration Depression PMS Diabetic neuropathy Raynaud syndrome Retinopathy Glaucoma Sexual dysfunction associated with SSRIs	Membrane stabilizer Antiplatelet activating factor (PAF) Free radical scavenger Antioxidant ↑ Alpha brain waves ↓ Theta brain waves	Stop 2 weeks before major surgery GI upset Allergies (whole plant) Spontaneous bleeding problems Headaches Skin rashes Dizziness Palpitations Seizures Avoid in pregnancy	Based on standard extract 25% ginkgo heterosides 40 mg tid up to 80 mg bid-tid Use consistently for at least 12 weeks to determine effectiveness	Warfarin Aspirin (↓ platelet aggregation) MAOIs (↑ effect) Fluoxetine Glyburide Insulin Haloperidol Heparin Metformin Thiazide diuretics Ticlopidine Trazodone Buspirone Cytochrome P450 substrates

Continued on following page

Herb	Common Uses	Activity	Adverse Effects and Contraindications	Doses[b]	Drug Interactions[c]
Ginseng *(Panax ginseng) (Ginseng radix) (Eleutherococcus senticosus)*	Fatigue Weakness Energy Immunity Mentation Diabetes Respiratory illnesses Libido Stress-induced GI ulcers Postoperative stress	Immune enhancement Prevention of platelet aggregation Tonic effect	Stop 2 weeks before major surgery Agitation Insomnia (PM doses) BP Edema Hypertonia Caution with cardiac problems, diabetes, psychosis, and agitation	Based on ginsenoside content 4.5-6 g daily Root powder (5% ginsenoside): 100 mg qd-tid May use cyclically for 15-20 days, followed by 2-week interval without ginseng	Warfarin (↓ platelet aggregation) Corticosteroids (↑ side effects) Digoxin (↑ serum levels) MAOIs, hypoglycemics (↑ effects) Opioids, diuretics (↓ effect) Stimulants Antidiabetic drugs
Goldenseal *(Hidrastis canadensis)*	Cold Immunity Diarrhea Sore throat Ocular trachoma infections	Antimicrobial (often combined with echinacea) Immune stimulant Activates phagocytes	Avoid in pregnancy, lactation, and diabetes (may lower glucose) Mouth irritation Digestive disorders Avoid in infants	Dried root or as infusion (tea): 2-4 g Tincture (1:5): 6-12 ml (1.5-3 tsp) Fluid extract (1:1): 2-4 ml (0.5-1 tsp) Solid (powdered dry) extract (4:1 or 8%-12% alkaloid content): 250-500 mg	Antihypertensives Cytochrome P450 substrates Antacids CNS depressants Heparin H_2 blockers Proton pump inhibitors
Grape seed extract *(Vitis vinifera)*	Atherosclerosis Retinopathy Venous insufficiency Hepatic protective Dental caries	Proanthocyanidins: powerful antioxidants Vascular renewal and stability Collagen support	None known	25-250 mg bid	Tetracycline, doxycycline Warfarin
Hawthorn *(Crataegus laeviagata)*	Congestive heart failure Hypertension Angina Cardiac function	Cardioactive glycosides Positive inotropic ACE inhibition Mild diuretic Collagen stabilizer Dilates coronary vessels ↓ Peripheral resistance ↓ Oxygen consumption	Hypotension GI distress Rash Arrhythmia Avoid in pregnancy	Berries or flowers (dried): 3-5 g or as infusion Tincture (1:5): 4-5 ml (alcohol may elicit pressor response in some individuals) Fluid extract (1:1): 1-2 ml Freeze-dried berries: 1-1.5 g Flower extract (standardized to contain 1.8% vitexin-4)	May potentiate effects of digitalis drugs Calcium channel blockers CNS depressants Nitrates
Horse chestnut *(Aesculus hippocastanum)*	Venous insufficiency Varicose veins Nocturnal leg cramps Pruritus and swelling of legs Topically for hemorrhoids, skin ulcers, varicose veins, sport injuries, trauma	Aescin component reduces lysosomal activity, improves venous tone, and inhibits capillary protein permeability Diuretic	GI irritation ↓ gastric emptying Pruritus Nausea Standardized seed extracts are safe, but whole herb may be fatal Avoid in pregnancy and lactation, liver disease, renal disease May cross-react with latex allergy	Based on aescin 90-150 mg initially, followed by 35-70 mg qd	Anticoagulants Antidiabetic drugs
Kava *(Piper methysticum)*	Anxiety Restlessness Insomnia Anticonvulsant Oral anesthetic Depression Attention-deficit/hyperactivity disorder	GABA receptor–like actions Limbic system modulation Inhibits voltage-dependent sodium channels in brain Skeletal muscle relaxant	Dermatitis Sedation May impair reflexes and judgment for driving Avoid in pregnancy and lactation, depression, and Parkinson disease. Contraindicated in endogenous depression Hepatotoxicity *Note:* kava is nonaddictive	Anxiolytic dose: 45-70 mg kavalactones tid Sedative dose: 180-210 mg 1 hour before bedtime	Alcohol Benzodiazepines Barbiturates Anti-Parkinson drugs Other psychopharmacological agents, general anesthetics Cytochrome P450 substrates

Continued on following page

Herb	Common Uses	Activity	Adverse Effects and Contraindications	Doses[b]	Drug Interactions[c]
Licorice (*Glycyrrhiza* spp)	Upper respiratory infection Oral and gastric ulcers Infection	Antiinflammatory Expectorant Antioxidant Demulcent Adrenocorticotropin	Avoid in pregnancy Contraindicated in cholestatic liver disease, cirrhosis, hypertension, hypokalemia, and renal insufficiency	Powdered root: 1-2 g Fluid extract (1:1): 2-4 ml Solid (dry powdered) extract (4:1): 250-500 mg	Furosemide Estrogens Chlorothiazide, metolazone Isoniazid Antihypertensives Insulin Risperidone Ibuprofen Digitalis glycosides Corticosteroids Cytochrome P450 substrates
Milk thistle *(Silybum marianum)*	Cirrhosis Alcoholic and viral hepatitis Mushroom poisoning *(Amanita)* Other hepatotoxins	Cell membrane stabilizer Stimulates ribosomal protein synthesis Free radical scavenger Antioxidant Contraindicated in liver disease Inhibits leukotriene formation Choleretic and lipotropic	GI upset Laxative effect Alcohol-based extracts Contraindicated in liver disease	Based on silymarin content 70-210 mg tid Silybin bound to phosphatidylcholine: 120-240 mg bid	Acetaminophen Butyrophenones Phenothiazines Indinavir Metronidazole Nitrous oxide Chemotherapy Clofibrate General anesthetics Haloperidol Cytochrome P450 substrates
Peppermint *(Mentha piperita)*	Dyspepsia Irritable bowel syndrome Biliary dyskinesia Digestive aid Myalgia Neuralgia Nasal decongestant Tension headache (topically)	Antispasmodic Cholagogue Menthol is active ingredient Antibacterial Antiviral Stimulates gastric secretion Coolant ↓ Lower esophageal sphincter tone Carminative	Nonenteric dosage may worsen heartburn in esophageal reflux and hiatal hernia Caution in pregnancy and in small children (choking from menthol) Allergic reactions Bradycardia Muscle tremor Dermatitis, skin rash Contraindicated in gallstones, achlorhydria, and liver damage	Infusion: 1-2 tsp dried leaves per 8 oz water Enteric-coated capsule (0.2 ml oil/capsule): 1-2 capsules tid Menthol 1.26%-16% applied topically up to qid	Antacids Cisapride
Saw palmetto *(Serenoa repens)*	Benign prostatic hyperplasia (stages I and II) Prostatitis	Antiandrogenic (5α-reductase) Bladder muscle spasmolytic Antiinflammatory	GI side effects Diarrhea Avoid in pregnancy Potential risk of aggravation of estrogen-sensitive tumors Rule out advanced prostatic hypertrophy and prostate cancer	Crude berries: 10 g bid Liposterolic extract (standardized at 85%-95% fatty acids and sterols): 160 mg bid	Anticoagulants Contraceptives Estrogens
St. John's wort *(Hypericum perforatum)*	Depression: mild to moderate Anxiety Insomnia Contusions First-degree burns Wound healing Antiinflammatory (topically) Myalgias Eczema	Affects neurotransmitters serotonin, dopamine, catecholamines, and possibly MAOIs; reduction of interleukin-6 Antiviral Antibacterial	Avoid in pregnancy (? uterotonic) GI side effects Photodermatitis Allergy Fatigue Insomnia Headache Restlessness Avoid in bipolar disorder	Dried flowers: 2-4 g tid Tincture (1:5): 3-6 ml tid Fluid extract (1:1): 1-2 ml tid Standardized fluid extract (0.14% hypericin: 1 mg hypericin/3 ml): 0.5-0.9 ml tid Standardized solid (dry powdered) extract (0.14% hypericin): 600 mg tid Standardized solid (dry powdered) extract (0.3% hypericin): 300 mg tid	Potential interaction with SSRIs, general anesthetics, and benzodiazepines Chemotherapy Cyclosporine Digoxin Indinavir Oral contraceptives Theophylline Trazadone *No longer contraindicated:* use with MAOIs, tyramine-containing compounds, 5-L-dopa, hydroxytryptophan

Continued on following page

Common Herbs in Integrated Medicine

Herb	Common Uses	Activity	Adverse Effects and Contraindications	Doses[b]	Drug Interactions[c]
Tea tree oil *(Melaleuca alternifolia)*	Skin infections Acne Mucosal and vaginal lesions Fungal infections (skin/nails)	Antibacterial Antiviral Antifungal	Contact dermatitis Allergic reaction Orally may cause significant toxicity; confusion and ataxia	Apply topically to affected area	None known
Valerian *(Valeriana officinalis)*	Insomnia Anxiety	GABA domain effects Improves latency and quality of sleep Improves slow-wave sleep	Overdose with temporary GI, chest, and CNS symptoms (?) Use in pregnancy and lactation Caution in children <12 years old Odor Cardiac disturbances *Note:* Valerian is not habit forming	Dried root (or as tea): 1-2 g Tincture (1:5): 4-6 ml (1-1.5 tsp) Fluid extract (1:1): 1-2 ml (0.5-1 tsp) Solid (dry powdered) extract (4:1): 250-500 mg Valerian extract (1%-1.5% valtrate or 0.5% valerenic acid): 150-300 mg	Avoid with benzodiazepines, barbiturates, general anesthetics, and alcohol Cytochrome P450 substrates

↑, Increased; ↓, decreased; *ACE,* angiotensin-converting enzyme; *AIDS,* acquired immunodeficiency syndrome; *bid,* twice daily; *BP,* blood pressure; *BPH,* benign prostatic hypertrophy; *CNS,* central nervous system; *g,* gram(s); *GABA,* gamma-aminobutyric acid; *GI,* gastrointestinal; *HIV,* human immunodeficiency virus; *IgE,* immunoglobulin E; *IV,* intravenous; *MAOIs,* monoamine oxidase inhibitors; *MS,* multiple sclerosis; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PMS,* premenstrual syndrome; *PO,* oral; *qAM,* every morning; *qd,* every day; *qid,* four times daily; *SSRI,* selective serotonin reuptake inhibitor; *TB,* tuberculosis; *tid,* three times daily; *WBCs,* white blood cells.

[a]The most frequent indications are shown in boldface type.

[b]Dosages vary by preparation. Consult sources listed or expert practitioner.

[c]Drug–herb interactions: Many interactions as cited are theoretical, based on mechanism of action, pharmacokinetics, or other preclinical data and have not been observed in patients. Although this type of data suggests caution, it may not contraindicate combined use. For in-depth detail on interactions, consult the Natural Medicine Comprehensive Database, other sources listed, or an expert botanical medicine practitioner.

From Micozzi MS: *Fundamentals of complementary, alternative, and integrative medicine,* ed 6, St Louis, 2019, Elsevier.

Appendix Ii

Herbal Activities Against Pain and Chronic Diseases

Herb	Common Uses	Activity	Adverse Effects and Contraindications	Doses	Drug Interactions
Aloe vera—*Aloe vera*	Orally—constipation, ulcerative colitis, gastroesophageal reflux, gastritis, peptic ulcer disease Topically—psoriasis, minor cuts and burns	Orally the anthraquinone has powerful cathartic properties Also has antibacterial, antifungal, and antioxidant properties	General pain, abdominal pain and cramps, reduces inflammation Long-term use or abuse can cause diarrhea, weight loss, albuminuria, hematuria, and potassium depletion	Orally 100-200 mg aloe or 50 mg aloe extract daily Topically 0.5% aloe extract cream applied to area tid	Caution in patients on digoxins; prolonged use can lead to hypokalemia
Bilberry—*Vaccinium myrtillus*	Diabetic and hypertensive retinopathy	Flavonoid complex (anthocyanoside)		160 mg bid for retinopathy	—
Black cohosh—*Cimicifuga racemosa*	Menopausal symptoms (hot flashes) and mood disturbances	Estrogen-like effects without estrogenic activity	GI upset, rash, headache, dizziness Avoid in patients with hepatitis, breast cancer	Remifemin 20 mg tablet bid	No well-known drug interactions
Cranberry—*Vaccinium macrocarpon*	UTI prevention, urinary deodorizer	Proanthocyanidins seem to interfere with bacterial adherence to urinary tract epithelial cells Mild antiinflammatory, antiplatelet, and antitumor effects	Excessive use (greater than 1 L/day) over a prolonged period of time could lead to uric acid kidney stone formation	One 8-ounce glass per day	Daily ingestion of 250 ml cranberry juice can increase serum and urine salicylate level
Echinacea—*Echinacea angustifolia*	Decreases symptoms of common cold, diminishes recurrence of vaginal yeast infections	Immune stimulant	Nausea, abdominal pain, diarrhea, and vomiting Caution in patients with autoimmune disorders	A tablet of 300 mg of Echinacea dosed as 1-2 tablets given 3× daily	Theoretically can interfere with immunosuppressant medications
Elderberry—*Sambucus nigra*	Influenza	Antioxidant, antiinflammatory, and immunomodulating effects	—	Adult 15 ml qid for 3-5 days, child's dose is 15 ml (1 tablespoon) twice daily	—
Evening primrose oil—*Oenothera biennis*	Mastalgia, osteoporosis, atopic dermatitis, neuropathy	Gamma-linoleic acid (GLA)—antiinflammatory properties, possible antiestrogenic effects	Avoid in patients taking phenothiazines	3-4 g daily	Can potentiate effects of antiplatelet/anticoagulant drugs

Continued on following page

Herb	Common Uses	Activity	Adverse Effects and Contraindications	Doses	Drug Interactions
Garlic—*Allium sativum*	Hypertension, atherosclerosis, prevention of stomach and colon cancer Topical treatment of dermal fungal infections (tinea corporis, tinea cruris, and tinea pedis)	Pharmacological effects attributed to allicin, ajoene, and other organosulfur constituents such as S-allyl-L-cysteine	Orally: breath and body odor, mouth and GI burning or irritation, heartburn, flatulence, nausea, vomiting, and diarrhea Topically: dermatitis, eczema, blisters, and scarring	Fresh garlic (1-2 cloves) per day, garlic extract (200-400 mg) 2 to 3× per day, topical garlic constituent ajoene at 0.4% cream, 0.6% gel, and 1.0% gel for the treatment of tinea	May potentiate effects of antiplatelet/anticoagulant drugs May decrease concentrations of HIV medications
Ginger—*Zingiber officinale*	Morning sickness, motion sickness, nausea/vomiting, arthritis	Antiemetic, antiinflammatory, antihypertensive, antiplatelet, antipyretic, and antitussive properties	Rare—abdominal discomfort, heartburn, diarrhea, and a pepper-like irritant effect in the mouth and throat	250 mg qid prn for morning sickness, 500-1000 mg 30 min before travel for motion sickness, 500-1000 mg 2 to 3× a day for arthritis	Theoretically ginger can potentiate the effects of antiplatelet and anticoagulant drugs
Ginkgo—*Ginkgo biloba*	Age-related memory impairment, improving cognitive function, dementia, diabetic retinopathy, glaucoma, intermittent claudication, PMS, Raynaud syndrome, vertigo, tinnitus, sexual dysfunction related to SSRIs	Antiinflammatory, reduces pain, antioxidant, free radical scavenger, inhibits platelet aggregation, protects cell membranes, erythrocytes, neurons, and retinal tissue	Mild GI upset, headache, dizziness, palpitations, constipation, and allergic skin reactions Rare cases of spontaneous bleeding and seizures	120-240 mg divided tid	Can potentiate effects of antiplatelet/anticoagulant drugs
Ginseng—*Panax ginseng*	Adaptogen, improving cognition, nourishing stimulant, aphrodisiac, treatment of diabetes, treatment of erectile dysfunction and premature ejaculation	Ginsenosides or panaxosides	Adverse effects and contraindications—generally well tolerated, most common adverse effect is insomnia	200-500 mg daily For erectile dysfunction: 900 mg tid	None known to exist, but there are several potential theoretical drug interactions
Grape seed—*Vitis vinifera*	Venous insufficiency, ocular stress, atherosclerosis, hypertension	Antioxidant, vasodilating, antilipoperoxidant, and antiplatelet effects	—	360-720 mg/day	Induces cytochrome P450 and may decrease plasma levels of common prescription drugs such as warfarin, clopidogrel, and propranolol
Kava kava—*Piper methysticum*	Anxiety, social anxiety disorder, cancer	Attributed to the kavalactones, which have anxiolytic, sedative, anticonvulsant, spasmolytic, antiinflammatory, and analgesic properties	Concern about potential hepatotoxicity has caused it to be banned from several countries, including Germany	100 mg tid (100 mg—standardized to contain 70% kavalactones)	Caution should to taken to avoid use with CNS depressants, such as benzodiazepines, alcohol, and barbiturates
Milk thistle—*Silybum marianum*	Type 2 diabetes, alcohol-induced liver damage and hepatitis B or C infection	Silymarin—antioxidant, free-radical scavenger, inhibitor of lipid peroxidation, TNF inhibitor, decreases insulin resistance	—	Silymarin 200 mg tid	Might inhibit cytochrome P450
Olive leaf—*Olea europaea*	Hyperlipidemia, hypertension, prevention of CAD, osteoarthritis, rheumatoid arthritis	Antiinflammatory, antiplatelet, antioxidant effects	—	2-3 tablespoons per day added to diet	—

Herb	Common Uses	Activity	Adverse Effects and Contraindications	Doses	Drug Interactions
Red clover—*Trifolium pretense*	Hot flashes, menopausal symptoms, hyperlipidemia	Contains isoflavones, acts as an alterative	Myalgia, headache, nausea, vaginal spotting	40-160 mg/day of standardized extract, 1-2 tsp dried flowers to make a cup of tea, or 2-4 ml of tincture 3 times a day	Theoretical interactions with birth control pills, estrogen replacement hormonal products, tamoxifen, blood thinners, and diabetes medications
Saw palmetto—*Serenoa repens*	BPH, alopecia	Antiandrogenic, antiproliferative, and antiinflammatory	Dizziness, headache, nausea, vomiting, constipation One case report of excessive bleeding during surgery (? antiplatelet effect)	160 mg twice daily or 320 mg once daily for BPH	Theoretically can potentiate effects of antiplatelet/anticoagulant drugs
Soy—*Glycine max*	Hyperlipidemia, menopausal symptoms, osteoporosis, cardiovascular disease	Contains phytoestrogens, known as isoflavones and lignans Rich in calcium, iron, potassium, amino acids, vitamins, and fiber	May cause endometrial hyperplasia	20-100 g/day of soy protein 50-120 mg/day of concentrated soy isoflavones	Tofu and soy sauce contain tyramine—avoid with MAO inhibitors Can interfere with absorption of oral thyroid hormone replacement
St. John's wort—*Hypericum perforatum*	Depression, somatization disorder, menstrual symptoms	Inhibits reuptake of serotonin, dopamine, and norepinephrine	Insomnia, vivid dreams, restlessness, anxiety, agitation, irritability, and mild GI complaints	300 mg tid	Multiple drug interactions, probably due to it being a potent inducer of cytochrome P450 Can decrease levels of common important drugs (digoxin, oral contraceptive pills, phenobarbital, phenytoin, and cyclosporine) Can also potentiate serotonin effects when taken with other SSRIs, Demerol, tramadol
Valerian—*Valeriana officinalis*	Insomnia, anxiety	GABA agonist	—	400-900 mg taken up to 2 hours before bedtime	Can theoretically potentiate effects of other CNS depressants such as benzodiazepines, alcohol, and opiates
Yohimbe—*Pausinystalia yohimbe*	Erectile dysfunction, sexual dysfunction	MAO inhibiting, calcium channel blocking, and peripheral serotonin receptor blocking effects	Excitation, tremor, insomnia, anxiety, hypertension, tachycardia, dizziness, gastric intolerance, salivation, sinusitis, irritability, headache, urinary frequency, fluid retention, rash, nausea, and vomiting Avoid in patients with CAD, hypertension, BPH, anxiety	15-30 mg daily	Can potentiate MAO inhibitors, TCAs, phenothiazines, and stimulant drugs Also antagonizing effects with antihypertensive drugs

bid, Twice daily; *BPH,* benign prostatic hypertrophy; *CAD,* coronary artery disease; *CNS,* central nervous system; *GABA,* gamma-aminobutyric acid; *GI,* gastrointestinal; *GLA,* gamma-linoleic acid; *MAO,* monoamine oxidase; *PMS,* premenstrual syndrome; *qid,* four times daily; *tid,* three times daily; *SSRI,* selective serotonin reuptake inhibitor; *TCA,* tricyclic antidepressant; *TNF,* tumor necrosis factor; *UTI,* urinary tract infection.

From Micozzi MS: *Fundamentals of complementary, alternative, and integrative medicine*, ed 6, St Louis, 2019, Elsevier.

Appendix IIa

Dietary Supplements: What Every Primary Care Provider Should Know

Primary care providers must be knowledgeable regarding the safety, efficacy, and drug interactions associated with common dietary supplements because of the following:

- An estimated 33.2% of adults ages 18 years and older reported the use of at least one form of complementary health approach, according to the National Health Interview Survey in 2012.
- 18% of adults specifically reported the use of dietary supplements, with fish oil, glucosamine, chondroitin, melatonin, and pre/probiotics the most frequently used nonvitamin, nonmineral supplement.
- In a 2010 AARP telephone survey of older adults, almost one-third reported the use of herbal and other supplements, and almost half of those individuals using supplements did not tell their health care provider. https://nccih.nih.gov/research/statistics/2010

COMMON TERMINOLOGY

- A *dietary supplement* is defined as an oral product containing vitamins, minerals, herbs, or other botanicals; amino acids; dietary substances used to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination.
- *CAM* refers to the broad domain of healing practices that include diverse health systems, modalities, and practices and their accompanying theories and beliefs (see glossary of terms in Appendix Ia).
- *Complementary therapies* are those that are used *in addition to* conventional therapies, whereas *alternative therapies* are those that are used *instead of* conventional therapies. Integrative therapy is generally defined as the use of complementary medicine with conventional Western medicine in a coordinated manner. https://nccih.nih.gov/health/integrative-health#integrative

LEGISLATION

The U.S. Food and Drug Administration (FDA) is frequently criticized for not closely regulating dietary supplements and monitoring their safety. However, although the agency regulates prescription drugs and over-the-counter (OTC) products, the FDA has limited regulatory authority over dietary supplements. This is because the Dietary Supplement and Health Education Act (DSHEA) of 1994 and its resulting regulations limit the FDA's authority. As a result of DSHEA, the FDA is able to act only when a dietary supplement has been documented to contain a prescription drug, such as sildenafil and related compounds in supplements for erectile dysfunction or sibutramine in a weight-loss preparation. In addition, the FDA can act when safety issues related to a product have been clearly documented, although these cases are frequently challenged in the courts.

HEALTH CLAIMS

Dietary supplements generally are marketed under three types of health claims. The first category is the "nutrient content" claim, in which the product is identified as an excellent source of, typically, a mineral such as calcium, based on recommended daily values. The second type is the "significant scientific agreement" claim; these claims are used when some evidence of the product's efficacy exists (e.g., fish oil supplements). The third and most common type of health claim is called a "structure/function" claim; these claims state that the product has some effect on health—for example, "helps to maintain a healthy heart." However, dietary supplements are not permitted to carry claims stating that they are effective in preventing, treating, or curing diseases.

INFORMATION RESOURCES

Appendix Ic provides a brief overview of common dietary supplements. In the past, few evidence-based resources on dietary supplements were available. Clinical studies and systematic reviews on dietary supplements are now widely available through PubMed, EMBASE, and the Cochrane Database of Systematic Reviews. Although more information is available, references on specific products vary in their interpretation of the available evidence and may exhibit an unintentional bias, either pro or con, regarding the safety and efficacy of dietary supplements.

"Gold standard" evidence-based databases on dietary supplements (subscription required) include the following:

- Natural Medicines Professional Database (https://naturalmedicines.therapeuticresearch.com/) contains multiple databases including one listing many dietary supplements. Monographs include the different common and scientific names; uses and likely effectiveness for different uses; chemical constituents; interactions with drugs, diseases, foods, and laboratory tests; adverse effects; and cautions. The information is extensively referenced and is updated on a daily basis.
- ConsumerLab has a subscription-based database containing common popular dietary supplements as well as almost daily updates related to supplements in the news on its website (www.consumerlab.com). This organization is not affiliated with Consumer Reports and primarily conducts independent tests of the content of commercially available supplements.

Evidence-based free websites on dietary supplements include the following:

- National Center for Complementary and Integrative Health (NCCIH) https://nccih.nih.gov/health/providers
- Memorial Sloan-Kettering Cancer Center www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs

DRUG INTERACTIONS

Clinically significant interactions have been documented between dietary supplements and prescription or OTC drugs. The challenge for primary care providers is to identify real, clinically relevant interactions versus potential or theoretical interactions. Data on interactions with dietary supplements are usually based on isolated case reports or on studies

enrolling healthy volunteers. As with drug-drug interactions, the likelihood of an interaction and its severity are influenced especially by concomitant medical conditions, such as heart failure and presence or absence of impaired kidney and liver function. Data also has suggested that the individual's genetic profile may influence the potential for drug-botanical supplement interactions.

Appendix Id lists interactions between selected dietary supplements and prescription and nonprescription drugs. The following two broad interactions are particularly important in primary care practice:

- St. John's wort, commonly used for depression, is a potent inducer of cytochrome P450 3A4 isoenzymes and has been documented to increase the clearance of many drugs that are metabolized through this and other pathways. In addition, St. John's wort may induce P-glycoprotein transporter systems that are important for digoxin and some chemotherapeutic agents. St. John's wort has also been associated with the development of serotonin syndrome when used with drugs that have significant serotonergic activity.
- Dietary supplements such as garlic, ginkgo, and feverfew, as well as many others, have been purported to either have antiplatelet activity or have effects on the clotting cascade. This may be important for adults also taking aspirin and other platelet-active agents, as well as warfarin and the direct-acting oral anticoagulants (DOACs).

COUNSELING POINTS

The single most important counseling point related to dietary supplements is to ask patients about their use of these products and to do so in an open, nonjudgmental manner. The approach should emphasize that many consumers have been interested in vitamins, minerals, herbs, teas, and so on, to maintain their health or to treat illness. If the clinician is unaware of the safety, efficacy, and interactions of a specific product, several websites are available to quickly scan for information. Also, access to drug information centers at colleges of pharmacy is frequently available, and some hospitals now offer programs in integrative medicine.

Patients should be asked about their goals in using the product, as well as how long they have taken it and in what dosage. Allergies to plants should be documented because cross-allergies are common. Clinicians should appreciate that individuals who use dietary supplements may be interested in making lifestyle changes and potentially decreasing their use of prescription drugs. In addition, if an individual is also consulting an alternative medicine practitioner, clinicians should recognize that some alternative health systems discourage the use of established therapies such as vaccines.

Although problems with safety and efficacy have been identified, many dietary supplements are benign except for their cost. Some patients are at higher risk for adverse outcomes from the use of dietary supplements (e.g., those with chronic kidney and liver disease). Patients should be counseled specifically to avoid purchasing dietary supplements over the Internet.

RESEARCH ISSUES

Many clinical and observational studies of dietary supplements have been published. In the past, clinicians frequently stated either that published studies of dietary supplements did not exist or that only a few were available. The reason for this finding was that in the past the National Library of Medicine did not abstract from the peer-reviewed alternative medicine literature. As with all research, the more rigorous the study methodology, the less likely the dietary supplement is to demonstrate clinical benefit.

In evaluating published studies of dietary supplements, the following should be considered:

- Has the correct plant and part of the plant (root, stem, leaf) been used? This critical information may not be known to many clinicians. Consulting a resource such as the National Medicines database can usually provide the needed information to judge this component of the study.
- Has the content of active ingredients been verified throughout the study? In a review of 81 major randomized controlled trials of herbal products, only 12 (15%) reported performing tests to quantify actual contents, and 3 (4%) provided adequate data to compare actual with expected content values of at least one chemical constituent.
- Is the severity of the disease appropriate for study? Negative studies with dietary supplements sometimes inappropriately enroll participants who have moderate-to-severe disease (e.g., those with depression or benign prostatic hyperplasia) when only mild disease would be appropriate.
- Is the duration of the study appropriate? Early studies comparing glucosamine and nonsteroidal antiinflammatory agents (NSAIAs) demonstrated greater efficacy with the NSAIAs because of an inadequate study duration for glucosamine to show any benefit.
- Is a placebo group included? Recent studies with dietary supplements for menopausal symptoms and osteoarthritis have demonstrated placebo responses over 40% to 50%.
- Was the blinding maintained throughout the study? Some dietary supplements, such as saw palmetto, have distinctive odors and tastes that are not easily masked.
- Is the preparation commercially available? Most important, when a study with dietary supplements does show benefit, it frequently is difficult to use the product in practice because the specific formulation studied is not commercially available.

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Appendix IIb

Vitamins and Their Functions

	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Fat-Soluble Vitamins				
Vitamin A	A family of the retinoid compounds, each member having biologic activity qualitatively similar to retinol. Carotenoids are structurally related to retinoids. Some carotenoids, most notably β-carotene, are metabolized into compounds with vitamin A activity and are therefore considered to be provitamin A compounds. Vitamin A is an integral component of rhodopsin and iodopsins, light-sensitive proteins in rod and cone cells in the retina. *Additional functions:* induction and maintenance of cellular differentiation in certain tissues; signal for appropriate morphogenesis in the developing embryo; maintenance of cell-mediated immunity. 1 μg of retinol = 3.33 IU of vitamin A.	Follicular hyperkeratosis and night blindness are early indicators. Conjunctival xerosis, degeneration of the cornea (keratomalacia), and dedifferentiation of rapidly proliferating epithelia are later indications of deficiency. *Bitot spots* (focal areas of the conjunctiva or cornea with foamy appearance) are an indication of xerosis. Blindness, due to corneal destruction and retinal dysfunction, ensues if left uncorrected. Increased susceptibility to infection is also a consequence. [F: 700 μg; M: 900 μg]	In adults, >150,000 μg may cause *acute* toxicity: fatal intracranial hypertension, skin exfoliation, and hepatocellular necrosis. *Chronic* toxicity may occur with habitual daily intake of >10,000 μg: alopecia, ataxia, bone and muscle pain, dermatitis, cheilitis, conjunctivitis, pseudotumor cerebri, hepatocellular necrosis, hyperlipidemia, and hyperostosis are common. Single, large doses of vitamin A (30,000 μg) or habitual intake of >4500 μg/day in early pregnancy can be teratogenic. Excessive intake of carotenoids causes a benign condition characterized by yellowish discoloration of the skin. Habitually large doses of canthaxanthin, a carotenoid, have the additional capability of inducing a retinopathy. [3000 μg]	Retinol concentration in the plasma and vitamin A concentrations in the milk and tears are reasonably accurate measures of adequate status. Toxicity is best assessed by elevated levels of retinyl esters in plasma. A quantitative measure of dark adaptation for night vision and electroretinography are useful functional tests.
Vitamin D	A group of sterol compounds whose parent structure is cholecalciferol (vitamin D_3). Cholecalciferol is formed in the skin from 7-dehydrocholesterol (provitamin D_3) by exposure to UVB radiation. A plant sterol, ergocalciferol (provitamin D_2), can be similarly converted into vitamin D_2 and has similar vitamin D activity. The vitamin undergoes sequential hydroxylations in the liver and kidney at the 25 and 1 positions, respectively, producing the most bioactive form of the vitamin, 1,25-dihydroxy vitamin D. Vitamin D maintains intracellular and extracellular concentrations of calcium and phosphate by enhancing intestinal absorption of the two ions and, in conjunction with PTH, promoting their mobilization from bone mineral. It retards proliferation and promotes differentiation in certain epithelia. Purported actions of vitamin D as an anti-diabetes, antiinflammatory, and cancer preventive agent remain controversial and are under investigation. 1 μg = 40 IU.	Deficiency results in decreased mineralization of newly formed bone called *rickets* in childhood and *osteomalacia* in adults. Expansion of the epiphyseal growth plates and replacement of normal bone with unmineralized bone matrix are the cardinal features of rickets; the latter feature also characterizes osteomalacia. Deformity of bone and pathologic fractures occur. Decreased serum concentrations of calcium and phosphate may occur. [15 μg, ages 19-70 yr; 20 μg, age >70 yr]	Excess amounts result in abnormally high concentrations of calcium and phosphate in the serum; metastatic calcifications, renal damage, and altered mentation may occur. [100 μg for ages ≥9 yr]	The serum concentration of the major circulating metabolite, 25-hydroxyvitamin D, is the best indicator of systemic status except in advanced kidney disease (stages 4 and 5), in which the impairment of renal 1-hydroxylation results in disassociation of the mono- and dihydroxyvitamin concentrations. Measurement of the serum concentration of 1,25-dihydroxyvitamin D is then necessary.

	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Vitamin E	A group of at least 8 naturally occurring compounds, some of which are tocopherols and some of which are tocotrienols. At present, the only dietary form that is thought to be biologically active in humans is α-tocopherol. Vitamin E acts as an antioxidant and free radical scavenger in lipophilic environments, most notably in cell membranes. It acts in conjunction with other antioxidants, such as selenium.	Deficiency due to dietary inadequacy is rare. It is usually seen in premature infants, individuals with fat malabsorption, and individuals with abetalipoproteinemia. Red blood cell fragility occurs and can produce a hemolytic anemia. Neuronal degeneration produces peripheral neuropathies, ophthalmoplegia, and destruction of posterior columns of spinal cord. Neurologic disease is frequently irreversible if deficiency is not corrected early enough. May contribute to the hemolytic anemia and retrolental fibroplasia seen in premature infants. Reported to suppress cell-mediated immunity. [15 mg]	Depressed levels of vitamin K–dependent procoagulants and potentiation of oral anticoagulants have been reported, as has impaired WBC function. Doses of 800 mg/day have been reported to increase slightly the incidence of hemorrhagic stroke. [1000 mg]	Plasma or serum concentration of α-tocopherol is most commonly used. Additional accuracy is obtained by expressing this value per milligram of total plasma lipid. RBC peroxide hemolysis test is not entirely specific but is a useful functional measure of the antioxidant potential of cell membranes.
Vitamin K	A family of naphthoquinone compounds with similar biologic activity. Phylloquinone (vitamin K_1) is derived from plants; a variety of menaquinones (vitamin K_2) are derived from bacterial and animal sources. Vitamin K serves as an essential cofactor in the post-translational γ-carboxylation of glutamic acid residues in many proteins. These proteins include several circulating procoagulants and anticoagulants as well as proteins in a variety of tissues.	Deficiency syndrome is uncommon except in breast-fed newborns, in whom it may cause "hemorrhagic disease of the newborn"; in adults with fat malabsorption or who are taking drugs that interfere with vitamin K metabolism (e.g., coumarin, phenytoin, broad-spectrum antibiotics); and in individuals taking large doses of vitamin E and anticoagulant drugs. Excessive hemorrhage is the usual manifestation. [F: 90 μg; M: 120 μg]	Rapid intravenous infusion of K_1 has been rarely associated with dyspnea, flushing, and cardiovascular collapse; this is likely related to the dispersing agents in the solution. Supplementation may interfere with coumarin-based anticoagulation. Pregnant women taking large amounts of the provitamin menadione may deliver infants with hemolytic anemia, hyperbilirubinemia, and kernicterus. [no TUL established]	Prothrombin time is typically used as a measure of functional K status; it is neither sensitive nor specific for vitamin K deficiency. Determination of fasting plasma vitamin K is an accurate indicator of status. Undercarboxylated plasma prothrombin is also an accurate metric, but only for detecting the deficient state, and is less widely available than plasma vitamin K.
Water-Soluble Vitamins				
Thiamin (vitamin B_1)	A water-soluble compound containing substituted pyrimidine and thiazole rings and a hydroxyethyl side chain. The coenzyme form is thiamin pyrophosphate (TPP). Thiamin serves as a coenzyme in many α-ketoacid decarboxylation and transketolation reactions. Inadequate thiamin availability leads to impairments of these reactions, resulting in inadequate adenosine triphosphate synthesis and abnormal carbohydrate metabolism, respectively. It may have an additional role in neuronal conduction independent of the aforementioned actions.	Classic deficiency syndrome (beriberi) is described in Asian populations consuming a polished rice diet. Alcoholism, chronic renal dialysis, and persistent nausea and vomiting after bariatric surgery are also common precipitants. High carbohydrate intake increases need for B_1. *Mild deficiency*: irritability, fatigue, and headaches *More severe deficiency*: combinations of peripheral neuropathy, cardiovascular dysfunction, and cerebral dysfunction. Cardiovascular involvement (wet beriberi): congestive heart failure and low peripheral vascular resistance. Cerebral disease: nystagmus, ophthalmoplegia, and ataxia (Wernicke encephalopathy); hallucinations, impaired short-term memory, and confabulation (Korsakoff psychosis). Deficiency syndrome responds within 24 hr to parenteral thiamin but is partially or wholly irreversible after a certain stage. [F: 1.1 mg; M: 1.2 mg]	Excess intake is largely excreted in the urine, although parenteral doses of >400 mg/day are reported to cause lethargy, ataxia, and reduced tone of the gastrointestinal tract. [TUL not established]	The most effective measure of B_1 status is the erythrocyte transketolase activity coefficient, which measures enzyme activity before and after addition of exogenous TPP; RBCs from a deficient individual express a substantial increase in enzyme activity with addition of TPP. Thiamin concentrations in blood or urine are also used.
Riboflavin (vitamin B_2)	Consists of a substituted isoalloxazine ring with a ribitol side chain. Riboflavin serves as a coenzyme for a diverse array of biochemical reactions. The primary coenzymatic forms are flavin mononucleotide and flavin adenine dinucleotide. Riboflavin holoenzymes participate in oxidation-reduction reactions in myriad metabolic pathways.	Deficiency is usually seen in conjunction with deficiencies of other B vitamins. Isolated deficiency of riboflavin produces hyperemia and edema of nasopharyngeal mucosa, cheilosis, angular stomatitis, glossitis, seborrheic dermatitis, and a normochromic, normocytic anemia. [F: 1.1; M: 1.3]	Toxicity is not reported in humans. [TUL not established]	The most common method of assessment is to determine the activity coefficient of glutathione reductase in RBCs (the test is invalid for individuals with glucose-6-phosphate dehydrogenase deficiency). Measurements of blood and urine concentrations are less desirable methods.

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	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Niacin (vitamin B_3)	Refers to nicotinic acid and the corresponding amide, nicotinamide The active coenzymatic forms are composed of nicotinamide affixed to adenine dinucleotide, forming NAD or NADP. More than 200 apoenzymes use these compounds as electron acceptors or hydrogen donors, either as a coenzyme or as a co-substrate. The essential amino acid tryptophan is a precursor of niacin; 60 mg of dietary tryptophan yields approximately 1 mg of niacin. Dietary requirements thus depend partly on tryptophan intake. Requirement is often determined on basis of calorie intake (i.e., niacin equivalents/1000 kcal). Large doses of nicotinic acid (1.5-3 g/day) effectively lower low-density lipoprotein cholesterol and elevate high-density lipoprotein cholesterol.	*Pellagra* is the classic deficiency syndrome and is often seen in populations in which corn is the major source of energy; it is still endemic in parts of China, Africa, and India. Diarrhea, dementia (or associated symptoms of anxiety or insomnia), and a pigmented dermatitis that develops in sun-exposed areas are typical features. Glossitis, stomatitis, vaginitis, vertigo, and burning dysesthesias are early signs. It is reported occasionally to occur in carcinoid syndrome because tryptophan is diverted to other synthetic pathways. [F: 14 mg; M: 16 mg]	Human toxicity is known largely through studies examining hypolipidemic effects. Includes vasomotor phenomenon (flushing), hyperglycemia, parenchymal liver damage, and hyperuricemia. [35 mg]	Assessment of status is problematic; blood levels of the vitamin are not reliable. Measurement of urinary excretion of the niacin metabolites *N*-methylnicotinamide and 2-pyridone is thought to be the most effective means of assessment at present.
Vitamin B_6	Refers to several derivatives of pyridine, including pyridoxine, pyridoxal, and pyridoxamine, which are interconvertible in the body. The coenzymatic forms are pyridoxal-5-phosphate (PLP) and pyridoxamine-5-phosphate. As a coenzyme, B_6 is involved in many transamination reactions (and thereby in gluconeogenesis), in the synthesis of niacin from tryptophan, in the synthesis of several neurotransmitters, and in the synthesis of δ-aminolevulinic acid (and therefore in heme synthesis). It also has functions unrelated to coenzymatic activity: pyridoxal and PLP bind to hemoglobin and alter oxygen affinity; PLP also binds to steroid receptors, inhibiting receptor affinity to DNA and thereby modulating steroid activity.	Deficiency is usually seen in conjunction with other water-soluble vitamin deficiencies. Stomatitis, angular cheilosis, glossitis, irritability, depression, and confusion occur in moderate to severe depletion; normochromic, normocytic anemia has been reported in severe deficiency. Abnormalities on electroencephalography and, in infants, convulsions have also been observed. Some sideroblastic anemias respond to B_6 administration. Isoniazid, cycloserine, penicillamine, ethanol, and theophylline can inhibit B_6 metabolism. [Ages 19-50 yr: 1.3 mg; >50 yr: 1.5 mg for women, 1.7 mg for men]	Long-term use with doses exceeding 200 mg/day (in adults) may cause peripheral neuropathies and photosensitivity. [100 mg]	Many useful laboratory methods of assessment exist. The plasma or erythrocyte PLP levels are most common. Urinary excretion of xanthurenic acid after an oral tryptophan load and activity indices of RBC alanine or aspartate transaminase are functional measures of B_6-dependent enzyme activity.
Folate	A group of related pterin compounds. More than 35 forms of the vitamin are found naturally. The fully oxidized form, folic acid, is not found in nature but is the pharmacologic form of the vitamin. All folate functions relate to its ability to transfer one-carbon groups. It is essential in the de novo synthesis of nucleotides and in the metabolism of several amino acids; it is an integral component for the regeneration of the "universal" methyl donor, *S*-adenosylmethionine. Inhibition of bacterial and cancer cell folate metabolism is the basis for the sulfonamide antibiotics and chemotherapeutic agents, such as methotrexate and 5-fluorouracil, respectively.	Women of childbearing age are most likely to be deficient. *Classic deficiency syndrome*: megaloblastic anemia, diarrhea. The hematopoietic cells in bone marrow become enlarged and have immature nuclei, reflecting ineffective DNA synthesis. The peripheral blood smear demonstrates macro-ovalocytes and polymorphonuclear leukocytes with an average of more than 3.5 nuclear lobes. Megaloblastic changes also occur in other epithelia that proliferate rapidly (e.g., oral mucosa and gastrointestinal tract, producing glossitis and diarrhea, respectively). Sulfasalazine and diphenytoin inhibit absorption and predispose to deficiency. [400 μg of dietary folate equivalents (DFE); 1 DFE = 1 μg food folate = 0.6 μg folic acid]	Doses >1000 μg/day may partially correct the anemia of B_{12} deficiency and may therefore mask (and perhaps exacerbate) the associated neuropathy. Large doses are also reported to lower seizure threshold in individuals prone to seizures. Parenteral administration is rarely reported to cause allergic phenomena, which is probably due to dispersion agents. [1000 μg]	Serum folate measures short-term folate balance, whereas RBC folate is a better reflection of tissue status. Serum homocysteine rises early in deficiency but is nonspecific because B_{12} or B_6 deficiency, renal insufficiency, and older age may also cause elevations.

	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Vitamin C (ascorbic and dehydroascorbic acid)	Ascorbic acid readily oxidizes to dehydroascorbic acid in aqueous solution. Dehydroascorbic acid can be reduced in vivo, so it possesses vitamin C activity. Total vitamin C is therefore the sum of ascorbic and dehydroascorbic acid content. Vitamin C serves primarily as a biologic antioxidant in aqueous environments. Biosyntheses of collagen, carnitine, bile acids, and norepinephrine as well as proper functioning of the hepatic mixed-function oxygenase system depend on this property. Vitamin C in foodstuffs increases the intestinal absorption of nonheme iron.	Overt deficiency is uncommon in developed countries. The classic deficiency syndrome is *scurvy:* fatigue, depression, and widespread abnormalities in connective tissues, such as inflamed gingivae, petechiae, perifollicular hemorrhages, impaired wound healing, coiled hairs, hyperkeratosis, and bleeding into body cavities. In infants, defects in ossification and bone growth may occur. Tobacco smoking lowers plasma and leukocyte vitamin C levels. [F: 75 mg; M: 90 mg; increase requirement for cigarette smokers by 35 mg/day]	≥500 mg/day (in adults) may cause nausea and diarrhea. >1 g/day modestly increases risk for oxalate kidney stones. Supplementation may interfere with laboratory tests based on redox potential (e.g., fecal occult blood testing, serum cholesterol, and glucose). Withdrawal from chronic ingestion of high doses of vitamin C supplements should be done gradually because accommodation appears to occur, raising a concern of "rebound scurvy." [2 g]	Plasma ascorbic acid concentration reflects recent dietary intake, whereas WBC levels more closely reflect tissue stores. Women's plasma levels are approximately 20% higher than men's for any given dietary intake.
Vitamin B_{12}	A group of closely related cobalamin compounds composed of a corrin ring (with a cobalt atom in its center) connected to a ribonucleotide through an aminopropanol bridge. Microorganisms are the ultimate source of all naturally occurring B_{12}. The two active coenzyme forms are deoxyadenosylcobalamin and methylcobalamin. These coenzymes are needed for the synthesis of succinyl CoA, which is essential in lipid and carbohydrate metabolism, and for the synthesis of methionine. The synthesis of methionine is essential for amino acid metabolism, for purine and pyrimidine synthesis, for many methylation reactions, and for the intracellular retention of folates.	Dietary inadequacy is a rare cause of deficiency except in strict vegetarians. Most deficiencies arise from loss of intestinal absorption, which may occur with pernicious anemia, pancreatic insufficiency, atrophic gastritis, small bowel bacterial overgrowth, or ileal disease. Megaloblastic anemia and megaloblastic changes in other epithelia (see Folate) are the result of sustained depletion. Demyelination of peripheral nerves, posterior and lateral columns of spinal cord, and nerves within the brain may occur. Altered mentation, depression, and psychoses occur. Hematologic and neurologic complications may occur independently. Folate supplementation, in doses of 1000 μg/day, may partly correct the anemia, thereby masking (or perhaps exacerbating) the neuropathic complication. [2.4 μg]	A few allergic reactions have been reported to crystalline B_{12} preparations and are probably due to impurities, not the vitamin. [TUL not established]	Serum or plasma concentrations are generally accurate. Subtle deficiency with neurologic complications, as described in the Deficiency column, can best be established by concurrently measuring the concentration of plasma B_{12} and serum methylmalonic acid, which is a sensitive indicator of cellular deficiency.
Biotin	A bi-cyclic compound consisting of a ureido ring fused to a substituted tetrahydrothiophene ring. Endogenous synthesis by intestinal flora may contribute significantly to biotin nutriture. Most dietary biotin is linked to lysine, a compound called biotinyl lysine, or biocytin. The lysine must be hydrolyzed by an intestinal enzyme called biotinidase before intestinal absorption occurs. Biotin acts primarily as a coenzyme for several carboxylases; each holoenzyme catalyzes an adenosine triphosphate–dependent carbon dioxide transfer. The carboxylases are critical enzymes in carbohydrate and lipid metabolism.	Isolated deficiency is rare. Deficiency in humans has been produced by prolonged total parenteral nutrition lacking the vitamin and by ingestion of large quantities of raw egg white, which contains avidin, a protein that binds biotin with such high affinity that it renders it biounavailable. Alterations in mental status, myalgias, hyperesthesias, and anorexia occur. Later, a seborrheic dermatitis and alopecia develop. Deficiency is usually accompanied by lactic acidosis and organic aciduria. [30 μg]	Toxicity has not been reported in humans with doses as high as 60 mg/day in children. [TUL not established]	Plasma and urine concentrations of biotin are diminished in the deficient state. Elevated urine concentrations of methyl citrate, 3-methylcrotonylglycine, and 3-hydroxyisovalerate are also observed in deficiency.

Continued on following page

Vitamins and Their Functions

	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Pantothenic acid	Consists of pantoic acid linked to β-alanine through an amide bond Pantothenic acid is an essential component of CoA and phosphopantetheine, which are essential for synthesis and β-oxidation of fatty acids as well as for synthesis of cholesterol, steroid hormones, vitamins A and D, and other isoprenoid derivatives. CoA is also involved in the synthesis of several amino acids and δ-aminolevulinic acid, a precursor for the corrin ring of vitamin B_{12}, the porphyrin ring of heme, and of cytochromes. CoA is also necessary for the acetylation and fatty acid acylation of a variety of proteins.	Deficiency is rare; it has been reported only as a result of feeding of semisynthetic diets or an antagonist to the vitamin. Experimental, isolated deficiency in humans produces fatigue, abdominal pain, vomiting, insomnia, and paresthesias of the extremities. [5 mg]	In doses of 10 g/day, diarrhea is reported to occur. [TUL not established]	Whole blood and urine concentrations of pantothenate are indicators of status; serum levels are not thought to be accurate.

CoA, Coenzyme A; *NAD,* nicotinamide adenine dinucleotide; *NADP,* nicotinamide adenine dinucleotide phosphate; *PTH,* parathyroid hormone; *RBC,* red blood cell; *UVB,* ultraviolet B; *WBC,* white blood cell.

*Recommended daily allowance (RDA) established for female (F) and male (M) adults by the U.S. Food and Nutrition Board, 1999-2001. In some instances, insufficient data exist to establish an RDA, in which case the adequate intake (AI) established by the board is listed.

†Tolerable upper limit (TUL) established for adults by the U.S. Food and Nutrition Board, 1999-2001.

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Appendix IIc

Nutritional Trace Elements and Their Clinical Implications

	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Chromium	Dietary chromium consists of both inorganic and organic forms. Its primary function in humans is to potentiate insulin action. It accomplishes this function as a circulating complex called *glucose tolerance factor*, thereby affecting carbohydrate, fat, and protein metabolism.	Deficiency in humans has been described only in long-term total parenteral nutrition (TPN) patients receiving insufficient chromium. Hyperglycemia or impaired glucose tolerance occurs. Elevated plasma free fatty acid concentrations, neuropathy, encephalopathy, and abnormalities in nitrogen metabolism are also reported. Whether supplemental chromium may improve glucose tolerance in glucose-intolerant individuals remains controversial. [F: 25 µg; M: 35 µg]	Toxicity after oral ingestion is uncommon and seems confined to gastric irritation. Airborne exposure may cause contact dermatitis, eczema, skin ulcers, and bronchogenic carcinoma. [TUL not established]	Plasma or serum concentration of chromium is a crude indicator of chromium status; it appears to be meaningful when the value is markedly above or below the normal range.
Copper	Copper is absorbed by a specific intestinal transport mechanism. It is carried to the liver, where it is bound to ceruloplasmin, which circulates systemically and delivers copper to target tissues in the body. Excretion of copper is largely through bile and then into the feces. Absorptive and excretory processes vary with the levels of dietary copper, providing a means of copper homeostasis. Copper serves as a component of many enzymes, including amine oxidases, ferroxidases, cytochrome *c* oxidase, dopamine β-hydroxylase, superoxide dismutase, and tyrosinase.	Dietary deficiency is rare; it has been observed in premature and low-birthweight infants fed exclusively a cow's milk diet and in individuals on long-term TPN lacking copper. It has also been described after gastric bypass surgery and with chronic zinc supplementation. Clinical manifestations include depigmentation of skin and hair, myelopathy and other neurologic lesions, leukopenia, anemia, and skeletal abnormalities. Anemia arises from impaired utilization of iron and therefore often is manifested as a sideroblastic anemia. The peripheral smear and bone marrow may mimic myelodysplasia. A deficiency syndrome is also observed in Menkes disease, a rare inherited condition associated with impaired copper utilization. [900 µg]	Acute copper toxicity has been described after excessive oral intake and with absorption of copper salts applied to burned skin. Milder manifestations include nausea, vomiting, epigastric pain, and diarrhea; coma and hepatic necrosis may ensue in severe cases. Toxicity may be seen with doses as low as 70 µg/kg/day. Chronic toxicity is also described. Wilson disease is a rare, inherited disease associated with abnormally low ceruloplasmin levels and accumulation of copper in the liver and brain, eventually leading to damage to these two organs. [10 mg]	Practical methods to detect marginal deficiency are not available. Marked deficiency is reliably detected by diminished serum copper and ceruloplasmin concentrations as well as by low red blood cell superoxide dismutase activity.
Fluorine	Known more commonly by its ionic form, fluoride. Fluorine is incorporated into the crystalline structure of bone, thereby altering its physical characteristics.	Intake of <0.1 mg/day in infants and <0.5 mg/day in children is associated with an increased incidence of dental caries. Optimal intake in adults is between 1.5 and 4 mg/day. [F: 3 mg; M: 4 mg]	Acute ingestion of >30 mg/kg body weight is likely to cause death. Excessive chronic intake (0.1 mg/kg/day) leads to mottling of teeth (dental fluorosis), calcification of tendons and ligaments, and exostoses and may increase the brittleness of bones. [10 mg]	Estimates of intake and clinical assessment are used because no good laboratory test exists.

Continued on following page

	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Iodine	Iodine is readily absorbed from the diet, concentrated in the thyroid, and integrated into the thyroid hormones thyroxine and triiodothyronine. These hormones circulate largely bound to thyroxine-binding globulin. They modulate resting energy expenditure and, in the developing human, growth and development.	In the absence of supplementation, populations relying primarily on food from soils with low iodine content have endemic iodine deficiency. Maternal iodine deficiency leads to fetal deficiency, which produces spontaneous abortions, stillbirths, hypothyroidism, cretinism, and dwarfism. Permanent cognitive deficits may result from iodine deficiency during the first 2 years of life. In the adult, compensatory hypertrophy of the thyroid (goiter) occurs along with varying degrees of hypothyroidism. [150 µg]	Large doses (>2 mg/day in adults) may induce hypothyroidism by blocking thyroid hormone synthesis. Supplementation with >100 mg/day to an individual who was formerly deficient occasionally induces hyperthyroidism. [1.1 mg]	Iodine status of a population can be estimated by the prevalence of goiter. Urinary excretion of iodine is an effective laboratory means of assessment. Thyroid-stimulating hormone blood level is an indirect and therefore not entirely specific means of assessment.
Iron	Conveys the capacity to participate in redox reactions to a number of metalloproteins, such as hemoglobin, myoglobin, cytochrome enzymes, and many oxidases and oxygenases. The primary storage form of iron is ferritin and, to a lesser degree, hemosiderin. Intestinal absorption is 15%-20% for "heme" iron and 1%-8% for iron contained in vegetables. Absorption of the latter form is enhanced by the ascorbic acid in foodstuffs; by poultry, fish, or beef; and by an iron-deficient state. It is decreased by phytate and tannins.	Iron deficiency is the most common micronutrient deficiency in the world. Women of childbearing age are the group at highest risk because of menstrual blood losses, pregnancy, and lactation. The classic deficiency syndrome is hypochromic, microcytic anemia. Glossitis and koilonychia ("spoon" nails) are also observed. Easy fatigability often is an early symptom, before anemia appears. In children, mild deficiency of insufficient severity to cause anemia is associated with behavioral disturbances and poor school performance. [postmenopausal F and M: 8 mg; premenopausal F: 18 mg]	Iron overload typically occurs when habitual dietary intake is extremely high, intestinal absorption is excessive, repeated parenteral administration occurs, or a combination of these factors exists. Excessive iron stores usually accumulate in the reticuloendothelial tissues and cause little damage (hemosiderosis). If overload continues, iron eventually begins to accumulate in tissues such as the hepatic parenchyma, pancreas, heart, and synovium, causing hemochromatosis. Hereditary hemochromatosis results from homozygosity of a common recessive trait. Excessive intestinal absorption of iron is seen in homozygotes. [45 mg]	Negative iron balance initially leads to depletion of iron stores in the bone marrow; a bone marrow biopsy and the concentration of serum ferritin are accurate indicators of early depletion. As the severity of deficiency proceeds, serum iron (SI) decreases and total iron-binding capacity (TIBC) increases; an iron saturation (SI/TIBC) of <16% suggests iron deficiency. Microcytosis, hypochromia, and anemia ensue. Elevated levels of serum ferritin or an iron saturation of >60% suggests iron overload, although systemic inflammation elevates serum ferritin regardless of iron status.
Manganese	A component of several metalloenzymes. Most manganese is in mitochondria, where it is a component of manganese superoxide dismutase.	Manganese deficiency in the human has not been conclusively demonstrated. It is said to cause hypocholesterolemia, weight loss, hair and nail changes, dermatitis, and impaired synthesis of vitamin K–dependent proteins. [F: 1.8 mg; M: 2.3 mg]	Toxicity by oral ingestion is unknown in humans. Toxic inhalation causes hallucinations, other alterations in mentation, and extrapyramidal movement disorders. [11 mg]	Until the deficiency syndrome is better defined, an appropriate measure of status will be difficult to develop.
Molybdenum	A cofactor in several enzymes, most prominently xanthine oxidase and sulfite oxidase	A probable case of human deficiency is described as being secondary to parenteral administration of sulfite and resulted in hyperoxypurinemia, hypouricemia, and low sulfate excretion. [45 µg]	Toxicity not well described in humans, although it may interfere with copper metabolism at high doses. [2 mg]	Laboratory means of assessment are not meaningful until the deficiency syndrome is better described.
Selenium	Most dietary selenium is in the form of an amino acid complex. Nearly complete absorption of such forms occurs. Homeostasis is largely performed by the kidney, which regulates urinary excretion as a function of selenium status. Selenium is a component of several enzymes, most notably glutathione peroxidase and superoxide dismutase. These enzymes protect against oxidative and free radical damage of various cell structures. The antioxidant protection conveyed by selenium apparently operates in conjunction with vitamin E because deficiency of one seems to potentiate damage induced by a deficiency of the other. Selenium also participates in the enzymatic conversion of thyroxine to its more active metabolite, triiodothyronine.	Deficiency is rare in North America but has been observed in individuals on long-term TPN lacking selenium. Such individuals have myalgias or cardiomyopathies. Populations in some regions of the world, most notably some parts of China, have marginal intake of selenium. In these regions *Keshan disease*, a condition characterized by cardiomyopathy, is endemic; it can be prevented (but not treated) by selenium supplementation. [55 µg]	Toxicity is associated with nausea, diarrhea, alterations in mental status, peripheral neuropathy, and loss of hair and nails; such symptoms were observed in adults who inadvertently consumed 27-2400 mg. [400 µg]	Erythrocyte glutathione peroxidase activity and plasma or whole blood selenium concentrations are the most commonly used methods of assessment. They are moderately accurate indicators of status.

	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Zinc	Intestinal absorption occurs by a specific process that is enhanced by pregnancy and corticosteroids and diminished by coingestion of phytates, phosphates, iron, copper, lead, or calcium. Diminished intake of zinc leads to an increased efficiency of absorption and decreased fecal excretion, providing a means of zinc homeostasis. Zinc is a component of more than 100 enzymes, among which are DNA polymerase, RNA polymerase, and transfer RNA synthetase.	Zinc deficiency has its most profound effect on rapidly proliferating tissues. *Mild deficiency:* growth retardation in children. *More severe deficiency:* growth arrest, teratogenicity, hypogonadism and infertility, dysgeusia, poor wound healing, diarrhea, dermatitis on the extremities and around orifices, glossitis, alopecia, corneal clouding, loss of dark adaptation, and behavioral changes. Impaired cellular immunity is observed. Excessive loss of gastrointestinal secretions through chronic diarrhea and fistulas may precipitate deficiency. *Acrodermatitis enteropathica* is a rare, recessively inherited disease in which intestinal absorption of zinc is impaired. [F: 8 mg; M: 11 mg]	Acute zinc toxicity can usually be induced by ingestion of >200 mg of zinc in a single day (in adults). It is manifested by epigastric pain, nausea, vomiting, and diarrhea. Hyperpnea, diaphoresis, and weakness may follow inhalation of zinc fumes. Copper and zinc compete for intestinal absorption: long-term ingestion of >25 mg/day of zinc may lead to copper deficiency. Long-term ingestion of >150 mg/day has been reported to cause gastric erosions, low high-density lipoprotein cholesterol levels, and impaired cellular immunity. [40 mg]	No accurate indicators of zinc status exist for routine clinical use. Plasma, red blood cell, and hair zinc concentrations are often misleading. Acute illness, in particular, is known to diminish plasma zinc levels, in part by inducing a shift of zinc out of the plasma compartment and into the liver. Functional tests that determine dark adaptation, taste acuity, and rate of wound healing lack specificity.

*Recommended daily allowance (RDA) established for female (F) and male (M) adults by the U.S. Food and Nutrition Board, 1999–2001. In some instances, insufficient data exist to establish an RDA, in which case the adequate intake (AI) established by the board is listed.

†Tolerable upper limit (TUL) established for adults by the U.S. Food and Nutrition Board, 1999–2001.

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Appendix IId

Summary of Vitamin and Mineral Deficiencies

Vitamin and Mineral Deficiencies	Neurologic Syndrome or Syndromes	Supporting Tests	Treatment	Causes (Other Than Malnutrition)
A (retinol)	Blindness from retinal or corneal damage	Visual fields, visual acuity Serum level <30-65 μg/dl	30,000 IU vitamin A daily ×1 wk	Hypothyroidism, diabetes, renal or liver failure
B_1 (thiamine)	Wernicke encephalopathy: ataxia, nystagmus, ophthalmoparesis, confusion, delirium Korsakoff syndrome: amnesia, confabulation Beriberi: axonal neuropathy	MRI: symmetric lesions of midbrain (periaqueductal area), pons, hypothalamus, thalamus, cerebellum MRI: necrosis of mammillary bodies, dorsomedial and anterior thalamus Nerve conduction tests: decreased amplitude Serum thiamine level <20 ng/dl Erythrocyte transketolase	Prevent by 100 mg PO daily before and 1 year after bariatric surgery, 100 mg IV before glucose administration or refeeding Treat Wernicke encephalopathy with 5 days of thiamine, 100-500 mg IV or IM daily, then PO 100 mg daily Antioxidants (*N*-acetylcysteine)	Alcoholism, bariatric or other major GI surgery, prolonged vomiting, hemodialysis, diuretic treatment of heart failure, cachexia, 5-fluorouracil, other blockers of thiamine phosphate production
B_3 (niacin)	Pellagra: confusion, dementia, weakness, ataxia, spasticity, myoclonus, glossitis, dermatitis, photosensitivity	Erythrocyte NAD, plasma niacin, urinary N_1-methylnicotinamide	Nicotinic acid, 50 mg PO tid or 25 mg IV tid; nicotinamide, 50-100 mg IM or PO tid	Alcoholism, corn- or cereal-based diet, Hartnup syndrome, carcinoid syndrome
B_5 (pantothenic acid)	Dysesthesias, foot paresthesias	Deficient coenzyme A	5 mg PO daily	Severe malnutrition
B_6 (pyridoxine)	Neuropathy, sensory ataxia, depression Infantile pyridoxine-deficient epilepsy	Plasma PLP <27 nmol/L; urinary 4-pyridoxic acid, <3 nmol ↑ Homocysteine after methionine loading challenge ↑ α-AASA in urine, plasma, CSF	50-100 mg PO daily for neuropathy (preventive use if taking B_6 antagonist) 100-200 mg daily for adult epilepsy	Diverticulosis, isoniazid, cycloserine, other antagonists Genetic defects in antiquitin (aldehyde dehydrogenase), pyridoxal synthesis
B_{12} (cobalamin)	Myelopathy with spastic paraparesis and sensory ataxia, peripheral neuropathy, optic neuropathy, memory loss, dementia; indirect contributor to stroke	Blood level <200 pg/ml↑ Methylmalonic acid >145 nmol/L Intrinsic factor antibodies Schilling test, megaloblastic anemia Delayed somatosensory evoked potentials ↑ Homocysteine, total >12.5 μmol/L	IM B_{12}, 1000 μg daily for 1 week, then weekly for 1 month, then monthly or oral B_{12}, 1000 μg daily, or nasal B_{12}, 500 μg weekly for lifetime if abnormal absorption, 50-100 μg daily if normal absorption	Achlorhydria, gastric or ileal resection, blind loop syndrome, sprue, HIV infection, nitrous oxide anesthesia (especially abuse), fish tapeworm, vegan diet
D (calciferol)	Proximal myopathy, often painful; cognitive impairment Secondary compression of spinal cord, plexus, or peripheral nerves from rickets or osteomalacia	25-(OH) vitamin D_3 level <10 ng/ml in urine Serum calcium ↑ PTH >54 pg/ml Osteopenia/porosis on bone densitometry	Daily supplementation with 400 IU, >50,000 IU 3 times per wk if malabsorption; use blood level or urine calcium excretion to guide (should be >100 mg/day)	Lack of exposure to sunlight, including sunblock protection; chronic antiepileptic drug use

Vitamin and Mineral Deficiencies	Neurologic Syndrome or Syndromes	Supporting Tests	Treatment	Causes (Other Than Malnutrition)
E (tocopherol)	Spinal and cerebellar ataxia, Babinski sign, ophthalmoplegia, peripheral neuropathy, retinitis pigmentosa	Vitamin E level <2.5 mg/L (normal, 6-15 with normal lipid level) ↑ A-β-lipoprotein levels, antigliadin antibodies Genetic analysis to rule out other spinocerebellar ataxias such as Friedreich ataxia	Supplement with 6-800 IU, 5-10 mg/kg twice daily, for ataxia of genetic causes, water-soluble 200 mg/kg/day or IM α-tocopherol for malabsorption	Biliary atresia, celiac sprue, genetic: ↓ α-tocopherol transport protein (8q13), microsomal triglyceride transfer protein
Folate	Dementia, B_{12} deficiency, stroke	↑ Homocysteine, plasma level <2.5 μg/L	1 mg 3 times per day until normal level, then maintenance of 1 mg/day Pregnancy: additional 0.4 mg/day if taking a folate antagonist	Malabsorption or use of antagonist (methotrexate) or antiepileptic medication
K (phytonadione)	Intracranial hemorrhage	INR or PT elevation	IM phytonadione at birth, maternal vitamin K for last month of pregnancy	Medication use that increases metabolism, such as phenytoin
Copper	Myelopathy, neuropathy	Serum Cu <75 μg/dl, ↓ urinary Cu, ceruloplasmin <23 mg/dl MRI: ↑ T_2 signal in cervical cord, dorsal column Mutation in ATP7A gene (Menkes disease)	Elemental Cu, 8 mg/day PO week 1, 6 mg/day week 2, 4 mg/day week 3, 2 mg/day ongoing malabsorption Menkes disease: 250 mg SC bid	Wilson disease, Menkes disease, alcoholism, malabsorption, gastric bypass, zinc toxicity
Magnesium	Seizures, encephalopathy	Serum magnesium <1.5 mg/ dl, correct for low albumin	Magnesium sulfate IV or POAvoid magnesium-wasting drugs	Alcoholism, especially beer
Potassium	Muscle weakness, chronic, acute	Serum potassium <3.5 mEq/L, ECG	IV or PO KCl until normalized	Diuretic use, bulimia

AASA, Aminoadipic semialdehyde; *CSF,* cerebrospinal fluid; *ECG,* electrocardiography; *GI,* gastrointestinal; *HIV,* human immunodeficiency virus; *IM,* intramuscularly; *INR,* international normalized ratio; *IU,* international units; *IV,* intravenously; *MRI,* magnetic resonance imaging; *NAD,* nicotinamide adenine dinucleotide; *PLP,* pyridoxal-5-phosphate (active coenzyme of pyridoxine); *PO,* by mouth; *PT,* prothrombin time; *PTH,* parathyroid hormone; *tid,* three times a day.

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

Appendix IIIa

Selected Historical and Physical Findings in Poisoning

Sign	Toxin
Odor	
Bitter almonds	Cyanide
Acetone	Isopropyl alcohol, methanol, paraldehyde, salicylates
Rotten eggs	Hydrogen sulfide, sulfur dioxide, methyl mercaptans (additive to natural gas)
Wintergreen	Methyl salicylate
Garlic	Arsenic, thallium, organophosphates, selenium
Ocular Signs	
Miosis	Opioids (except propoxyphene, meperidine, and pentazocine), organophosphates and other cholinergics, clonidine, phenothiazines, sedative-hypnotics, olanzapine
Mydriasis	Anticholinergics (e.g., antihistamines, TCAs, atropine), sympathomimetics (cocaine, amphetamines, PCP), post-anoxic encephalopathy, opiate withdrawal, cathinones, MDMA
Nystagmus	Anticonvulsants, sedative-hypnotics, alcohols, PCP, ketamine, dextromethorphan
Lacrimation	Organophosphates, irritant gas or vapors
Retinal hyperemia	Methanol
Cutaneous Signs	
Diaphoresis	Cholinergics (organophosphates), sympathomimetics, withdrawal syndromes
Alopecia	Thallium, arsenic
Erythema	Boric acid, elemental mercury, cyanide, carbon monoxide, disulfiram, scombroid, anticholinergics, vancomycin
Cyanosis (unresponsive to oxygen)	Methemoglobinemia (e.g., benzocaine, dapsone, nitrites, phenazopyridine), amiodarone, silver
Oral Signs	
Salivation	Organophosphates, salicylates, corrosives, ketamine, PCP, strychnine
Oral burns	Corrosives, oxalate-containing plants
Gum lines	Lead, mercury, arsenic, bismuth
Gastrointestinal Signs	
Diarrhea	Antimicrobials, arsenic, iron, boric acid, cholinergics, colchicine, opioid withdrawal
Hematemesis	Arsenic, iron, caustics, NSAIDs, salicylates
Constipation	Lead
Cardiac Signs	
Tachycardia	Sympathomimetics, anticholinergics, antidepressants, antipsychotics, methylxanthines (theophylline, caffeine), salicylates, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), withdrawal (ethanol, sedatives, clonidine, opioids), serotonin syndrome, neuroleptic malignant syndrome, MDMA, cathinones
Bradycardia	β-blockers, calcium channel blockers, digoxin, clonidine, organophosphates, opioids, sedative-hypnotics
Hypertension	Sympathomimetics, anticholinergics, monoamine oxidase inhibitors, serotonin syndrome, neuroleptic malignant syndrome, clonidine withdrawal
Hypotension	β-blockers, calcium channel blockers, cyclic antidepressants, iron, antipsychotics, barbiturates, clonidine, opioids, arsenic, amatoxin mushrooms, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), snake envenomation
Respiratory Signs	
Depressed respirations	Opioids, sedative-hypnotics, alcohol, clonidine, barbiturates
Tachypnea	Salicylates, sympathomimetics, caffeine, metabolic acidosis, carbon monoxide, hydrocarbon aspiration

Sign	Toxin
Central Nervous System Signs	
Ataxia	Alcohols, anticonvulsants, sedative-hypnotics, lithium, dextromethorphan, carbon monoxide, inhalants
Coma	Opioids, sedative-hypnotics, anticonvulsants, antidepressants, antipsychotics, ethanol, anticholinergics, clonidine, GHB, alcohols, salicylates, barbiturates
Seizures	Sympathomimetics, anticholinergics, antidepressants (especially TCAs, bupropion, venlafaxine), cholinergics (organophosphates), isoniazid, camphor, lindane, salicylates, lead, nicotine, tramadol, water hemlock, withdrawal
Delirium/psychosis	Sympathomimetics, anticholinergics, LSD, PCP, hallucinogens, lithium, dextromethorphan, steroids, withdrawal, MDMA, cathinones
Peripheral neuropathy	Lead, arsenic, mercury, organophosphates, nicotine

GHB, γ-hydroxybutyrate; *LSD,* lysergic acid diethylamide; *MDMA,* 3,4-methylenedioxymethamphetamine (Ecstasy); *NSAIDs,* nonsteroidal anti-inflammatory drugs; *PCP,* phencyclidine; *TCAs,* tricyclic antidepressants.

From Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

Appendix IIIb

Toxidromes

TABLE 1 Recognizable Poison Syndromes

	Signs						
Toxidrome	**Vital Signs**	**Mental Status**	**Pupils**	**Skin**	**Bowel Sounds**	**Other**	**Possible Toxins**
Sympathomimetic	Hypertension, tachycardia, hyperthermia	Agitation, psychosis, delirium, violence	Dilated	Diaphoretic	Normal to increased		Amphetamines, cocaine, PCP, bath salts (cathinones), ADHD medication
Anticholinergic	Hypertension, tachycardia, hyperthermia	Agitation, delirium, coma, seizures	Dilated	Dry, hot	Diminished	Ileus urinary retention	Antihistamines, TCAs, atropine, jimsonweed
Cholinergic	Bradycardia, BP and temp typically normal	Confusion, coma, fasciculations	Small	Diaphoretic	Hyperactive	Diarrhea, urination, bronchorrhea, bronchospasm, emesis, lacrimation, salivation	Organophosphates (insecticides, nerve agents), carbamates (physostigmine, neostigmine, pyridostigmine) Alzheimer medications, myasthenia treatments
Opioids	Respiratory depression, bradycardia, hypotension, hypothermia	Depression, coma, euphoria	Pinpoint	Normal	Normal to decreased		Methadone, buprenorphine, morphine, oxycodone, heroin, etc.
Sedative-hypnotics	Respiratory depression, HR normal to decreased, BP normal to decreased, temp normal to decreased	Somnolence, coma	Small or normal	Normal	Normal		Barbiturates, benzodiazepines, ethanol
Serotonin syndrome (similar findings with neuroleptic malignant syndrome)	Hyperthermia, tachycardia, hypertension or hypotension (autonomic instability)	Agitation, confusion, coma	Dilated	Diaphoretic	Increased	Neuromuscular hyperexcitability: clonus, hyperreflexia (lower > upper extremities)	SSRIs, lithium, MAOIs, linezolid, tramadol, meperidine, dextromethorphan
Salicylates	Tachypnea, hyperpnea, tachycardia, hyperthermia	Agitation, confusion, coma	Normal	Diaphoretic	Normal	Nausea, vomiting, tinnitus, ABGs with primary respiratory alkalosis and primary metabolic acidosis; tinnitus or difficulty hearing	Aspirin and aspirin-containing products, methyl salicylate
Withdrawal (sedative-hypnotic)	Tachycardia, tachypnea, hyperthermia	Agitation, tremor, seizure, hallucinosis, delirium tremens	Dilated	Diaphoretic	Increased		Lack of access to ethanol, benzodiazepines, barbiturates, GHB, or excessive use of flumazenil
Withdrawal (opioid)	Tachycardia	Restlessness, anxiety	Dilated	Diaphoretic	Hyperactive	Nausea, vomiting, diarrhea	Lack of access to opioids or excessive use of naloxone

ABGs, Arterial blood gases; *ADHD,* attention-deficit/hyperactivity disorder; *BP,* blood pressure; *GHB,* γ-hydroxybutyrate; *HR,* heart rate; *MAOIs,* monoamine oxidase inhibitors; *PCP,* phencyclidine; *SSRIs,* selective serotonin reuptake inhibitors; *temp,* temperature; *TCAs,* tricyclic antidepressants.

From Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

TABLE 2 Laboratory Clues in Toxicologic Diagnosis

Anion Gap Metabolic Acidosis (Mnemonic = Mudpiles Cat)

Methanol, metformin
Uremia
Diabetic ketoacidosis
Propylene glycol
Isoniazid, iron, massive ibuprofen
Lactic acidosis
Ethylene glycol
Salicylates
Cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide)
Alcoholic ketoacidosis
Tylenol (clinical significance depends upon presence or absence of liver injury)

Elevated Osmolar Gap

Alcohols: Ethanol, isopropyl, methanol, ethylene glycol

Hypoglycemia (Mnemonic = Hobbies)

Hypoglycemics, oral: Sulfonylureas, meglitinides
Other: Quinine, unripe ackee fruit
Beta-blockers
Insulin
Ethanol
Salicylates (late)

Hyperglycemia

15Salicylates (early)
Calcium channel blockers
Caffeine

Hypocalcemia

Ethylene glycol
Fluoride

Rhabdomyolysis

Neuroleptic malignant syndrome, serotonin syndrome
Statins
Mushrooms (*Tricholoma equestre*)
Any toxin causing prolonged immobilization (e.g., opioids, antipsychotics), excessive muscle activity or seizures (e.g., sympathomimetics)

Radiopaque Substance on KUB (Mnemonic = Chipped)

Chloral hydrate, calcium carbonate
Heavy metals (lead, zinc, barium, arsenic, lithium, bismuth)
Iron
Phenothiazines
Play-Doh, potassium chloride
Enteric-coated pills
Dental amalgam, drug packets

KUB, Kidney-ureter-bladder radiograph.
From Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

TABLE 3 Substances Poorly Adsorbed by Activated Charcoal

Alcohols
Caustics: Alkalis and acids
Cyanide
Heavy metals (e.g., lead)
Hydrocarbons
Iron
Lithium

From Kliegman RM: *Nelson textbook of pediatrics,* ed 21, Philadelphia, 2020, Elsevier.

Appendix IIIc

Antidotes and Indications for Use

Antidote	Indication for Use	Dose*	Treatment End Point	Comments
Antivenom, *Crotalidae* (Fab)†	Crotaline snake (e.g., rattlesnakes, copperhead)	4-6 vials; repeat for persistent or worsening clinical condition; repeated doses of 2 vials at 6, 12, and 18 hr after initial antivenom dose are recommended	Halt in progression of circumferential and proximal swelling Resolving systemic effects	Better safety profile than historical equine-derived antivenom Repetitive dosing indicated for recurrent soft tissue swelling Less effective at correcting hematologic (i.e., coagulation and platelet) disorders
Antivenom, *Latrodectus* (equine)†	Black widow spider (*Latrodectus* sp)	1 vial diluted in 50-100 ml NS, infused during 1 hr; can repeat	Resolution of symptoms, vital signs normal	Dilution and slow infusion rate are *critical* to avoid anaphylactoid reaction Indications include severe pain unresponsive to opioids and severe hypertension Serum sickness can occur IV calcium is ineffective
Atropine	Carbamates Nerve agents Organophosphorus compounds	2 mg IV; double the dose every 5 min to achieve atropinization and hemodynamic stability; then start continuous infusion of 10-20% of total stabilizing dose per hour	Cessation of excessive oral and pulmonary secretions, >80 beats/min, systolic blood pressure >80 mm Hg	Doubling of the dose every 5 min (e.g., 2, 4, 8, and 16 mg) estimated to achieve atropinization within 30 min Stop infusion when patient develops concerning signs or symptoms of anticholinergic toxidrome; restart infusion at lower rate when signs or symptoms abate
Calcium salt‡	Calcium-channel antagonists	Calcium chloride 10%, 10 ml (1 g) during 10 min; can be given in 1 min if critically ill Calcium gluconate 10%, 30 ml (3 g) during 10 min; can be given in 1 min if critically ill	Reversal of hypotension; may not reverse bradycardia	*All indications:* Monitor ionized calcium levels IV extravasation causes tissue necrosis, especially with calcium chloride Can administer at faster than stated rates for immediate life-threatening conditions (i.e., in 1 min) Calcium chloride contains three times more elemental calcium than calcium gluconate does
	Hydrofluoric acid	Systemic toxicity: calcium gluconate 10%, 1-3 g (10-30 ml) per dose IV during 10-min period; repeat as needed every 5-10 min	Reversal of life-threatening manifestations of hypocalcemia and hyperkalemia	Can dilute and give intra-arterially or IV with a Bier block for extremity exposures and burns
	Hyperkalemia (except cardiac glycosides)	Calcium gluconate 10%, 1 g (10 ml) per dose IV during 10-min period; repeat as needed every 5-10 min	Reversal of myocardial depression and conduction delays	May precipitate ventricular arrhythmias
	Hypermagnesemia	Calcium gluconate 10%, 1-2 g (10-20 ml) per dose IV during 10-min period; repeat as needed every 5-10 min	Reversal of respiratory depression, hypotension, and cardiac conduction blocks	Simultaneous therapies to increase magnesium elimination should be instituted
	Hypocalcemia (e.g., ethylene glycol)	Calcium gluconate 10%, 0.5-1.0 g (5-10 ml) per dose during 10-min period; repeat as needed every 10 min	Reversal of tetany	Correct symptomatic hypocalcemia; avoid excessive administration that may increase production of calcium oxalate crystals in ethylene glycol poisoning
L-Carnitine	Valproate-induced hyperammonemia or hepatotoxicity	100 mg/kg (maximum 6 g) IV during 30 min, then 15 mg/kg IV during 30-min period q4h (maximum 6 g/day)	Treat until clinical improvement occurs	Levocarnitine is active form Adjust dose for end-stage renal disease

Antidote	Indication for Use	Dose*	Treatment End Point	Comments
Cyanide antidote kit Amyl nitrite Sodium nitrite Sodium thiosulfate [Hydroxocobalamin is preferred if available, see below]	Cyanide	Amyl nitrite: 0.3-ml pearls, crush and inhale during 30-sec period Sodium nitrite 3%: 10 ml IV during 10-min period Sodium thiosulfate 25%: 50 ml (12.5 g) IV during 10-min period	Resolution of lactic acidosis and moderate to severe clinical signs and symptoms: seizures, coma, dyspnea, apnea, hypotension, bradycardia	Coordinate amyl nitrite with continued oxygenation and give only until sodium nitrite infusion is begun; nitrites may produce hypotension and excess methemoglobinemia Sodium nitrite dose must be adjusted if patient has hemoglobin <12 g/dl Sodium thiosulfate dosing can be repeated
Deferoxamine	Iron	Initiate at 5 mg/kg/hr, titrate to 15 mg/kg/hr IV (maximum 8 g/day) Mild to moderate: administer for 6-12 hr Severe toxicity: administer 24 hr	Resolution of clinical signs and symptoms Do not use urine color, which is an unreliable marker for iron clearance Laboratory testing is unreliable while antidote is being received	Indications: symptomatic patients with lethargy, severe abdominal pain, hypovolemia, acidosis, shock; any symptomatic patient with peak serum iron level >350 g/dl Prolonged therapy can cause pulmonary toxicity
Digoxin-specific antibody fragments (Fab)	Digoxin Digitalis and related plants (e.g., oleander, lily of the valley) Other cardiac glycosides (e.g., bufadienolides [Bufo toads])	Unknown digoxin dose or serum level, or for plant or toad source: acute toxicity—10-20 vials; chronic toxicity—3-6 vials Digoxin dose known: number of vials = (mg ingested × 0.8) ÷ 0.5 Digoxin serum level known: number of vials = [serum level (ng/ml) × weight (kg)] ÷ 100 Infuse dose during 30 min	Resolution of hyperkalemia, symptomatic bradydysrhythmias, ventricular arrhythmias, Mobitz II or third-degree heart block	Each vial binds 0.5 mg of digoxin or digitoxin Monitor ECG and potassium levels Digoxin serum levels unreliable after antidote administered unless test is specific for free serum digoxin
Dimercaprol (BAL)	Arsenic Lead Mercury, elemental and inorganic salts	Arsenic: 3-5 mg/kg IM q4h Lead: 75 mg/m^2 (4 mg/kg) IM q4h for 5 days Inorganic mercury: 5 mg/kg IM, then 2.5 mg/kg IM q12h for 10 days or until patient is clinically improved	Arsenic: 24-hr urinary arsenic <50 μg/L Lead: encephalopathy resolved, blood lead level <100 μg/dl, and succimer therapy can be started Mercury, elemental and inorganic: 24-hr urinary mercury <20 μg/L	Formulated in peanut oil; painful IM injection and caution with allergy Maximum adult dose is 3 g/day BAL started 4 hr before initiation of concomitant $CaNa_2$ EDTA for lead encephalopathy Dosing not well established for arsenic and elemental or inorganic mercury toxicity; not used for organic mercury poisoning Adverse effects: painful injections, fever, diaphoresis, agitation, headache, salivation, nausea and vomiting, hemolysis in G6PD-deficient patients, chelation of essential metals Check essential metal levels if chelation is prolonged Succimer is replacing BAL for many indications except lead encephalopathy Treatment end points for arsenic and mercury include improving clinical condition
Edetate calcium disodium ($CaNa_2$ EDTA)	Lead	1500 mg/m^2/24 hr (maximum 3 g) by continuous infusion	Treat for 5 days, followed by 2-day hiatus; repeat until encephalopathy resolved, lead level <100 μg/dl, and succimer therapy can be started	Use in patients with lead encephalopathy or lead level >100 g/dl Administer BAL 4 hr before initiating $CaNa_2$ EDTA Hydrate patient and establish good urinary output before starting therapy Avoid thrombophlebitis by diluting in NS or D_5W to a concentration ≤0.5% Substitution of Na_2 EDTA can cause fatal hypocalcemia
Flumazenil	Benzodiazepines	0.1 mg/min IV to a total dose of 1 mg	Reversal of coma	Limit use to reversal of inadequate ventilation in benzodiazepine-toxic patients Acute benzodiazepine withdrawal may occur in patients dependent on benzodiazepines Increases intracranial pressure and risk for seizures in presence of underlying seizure disorder or ingestion of seizure-producing toxicants Monitor for resedation up to 2 hr after last dose

Continued on following page

Antidotes and Indications for Use

Antidote	Indication for Use	Dose*	Treatment End Point	Comments
Folinic acid (tetrahydrofolic acid [leucovorin])	Methanol Methotrexate	Methanol: 50 mg IV q4h Methotrexate: 100 mg/m^2 IV during 15-30 min q3-6h; dosing lower when used as "rescue" in chemotherapy	Methanol: methanol undetectable, metabolic acidosis cleared Methotrexate: serum level $<1 \times 10^{-8}$ mol/L	Essential therapy for both toxicants Little concern with excessive dosing when used for methotrexate overdose Methotrexate: large overdoses may require increased dose Glucarpidase administered 2-4 hr before or after folinic acid
Fomepizole	Ethylene glycol Methanol	Dose 1: 15 mg/kg IV Doses during next 48 hr: 10 mg/kg IV All subsequent doses: 15 mg/kg IV Administer q12h, except when HD performed: HD initiation: next dose if >6 hr since last dose HD ongoing: q4h End of HD (based on time of last dose): <1 hr, no dose; 1-3 hr, next dose; >3 hr, next dose	For both: serum level <25 mg/dl and metabolic acidosis resolved	Start immediately if toxic alcohol suspected, without waiting for confirmatory levels Dose amount is not affected by interval timing of doses
Glucagon	β-Adrenergic receptor antagonists Calcium-channel antagonists	Bolus of 3-5 mg IV; can repeat to achieve clinical effect, then infusion of 2-10 mg/hr	Reversal of hypotension and bradycardia; taper infusion	Can precipitate vomiting; be prepared to protect airway Mild hyperglycemia occurs Maximum dosing amounts unknown; bolus doses up to 30 mg reported Duration of effect is 15 min; thus infusion must be started immediately
Hydroxocobalamin	Cyanide	Initial: 5 g IV during 15-min period Second dose: 5 g IV during 15 min to 2 hr; maximum total dose is 10 g Follow each hydroxocobalamin dose with sodium thiosulfate 25%: 50 ml (12.5 g) IV during 10-min period	Resolution of lactic acidosis and moderate to severe clinical signs and symptoms: seizures, coma, dyspnea, apnea, hypotension, bradycardia	Can be administered IV push if patient is in cardiac arrest Do not give hydroxocobalamin and sodium thiosulfate through the same IV line Adverse effects: red discoloration of plasma, urine, mucous membranes, skin; transient hypertension Interference with laboratory colorimetric assays: Levels increased: bilirubin; creatinine; glucose; hemoglobin; magnesium; co-oximetry total Hb, COHb%, MetHb% Levels decreased: AST, ALT, creatinine, co-oximetry O_2 Hb%
Hyperbaric oxygen (HBO)	Carbon monoxide Experimental: carbon tetrachloride, cyanide, hydrogen sulfide	3.0 atm pressure for 60 min (25 min O_2, 5 min air, 25 min O_2, 5 min air), then 2.0 atm for 65 min (30 min O_2, 5 min air, 30 min O_2), then "surface" to 1.0 atm	One treatment Repeated treatment controversial	Carbon monoxide: treatment protocols may vary HBO indicated for loss of consciousness; seizures; cerebellar dysfunction; impaired cognition; headache, nausea/vomiting persisting after 4 hr of O_2 therapy regardless of carboxyhemoglobin level
Insulin-glucose	Calcium-channel antagonists β-Adrenergic receptor antagonists	Regular insulin, 1 U/kg bolus, followed by 0.5-1 U/kg/hr Titrate 50% dextrose IV to avoid hypoglycemia	Reversal of myocardial depression	Initiate early to reverse myocardial depression Monitor glucose and potassium; hypoglycemia can occur during and after therapy Hyperglycemia results from calcium-channel antagonist–induced insulin resistance, and initial dextrose requirements may be less than anticipated Recovery may be heralded by normalization of glucose levels, with increased dextrose required to avoid hypoglycemia
Lipid emulsion	Cardiac toxicity from local anesthetics (e.g., bupivacaine, ropivacaine) Experimental: verapamil, diltiazem, tricyclic antidepressants, bupropion, propranolol, and other lipophilic toxicants	Use 20% formulation Initial bolus: 1.5 ml/kg IV during 1 min, followed immediately by infusion of 0.25 ml/kg/min for 30-60 min Can repeat bolus for asystole	Return of hemodynamic stability	Use for other than bupivacaine based on animal experiments and human case reports; numerous dosing regimens have been used Use if advanced life support measures fail; continue CPR as needed during drug administration

Antidote	Indication for Use	Dose*	Treatment End Point	Comments
Methylene blue	Methemoglobin-producing agents	1-2 mg/kg body weight (0.1-0.2 ml/kg of 1%) methylene blue during 5-min period; repeat dose for persistent or recurrent symptoms or signs	Resolution of dyspnea and altered mental status	Use if patient is symptomatic (i.e., dyspneic, altered mental status) Maximum dose should not exceed 7 mg/kg (0.7 ml/kg) Contraindicated in G6PD-deficient patients; may cause hemolysis Some toxicants (e.g., dapsone) may require prolonged therapy
N-Acetylcysteine (NAC) [7]	Acetaminophen Experimental: carbon tetrachloride, chloroform, pennyroyal oil	Oral (total 72 hr) Load: 140 mg/kg Maintenance (starting 4 hr after load): 70 mg/kg q4h × 17 doses IV (total 21 hr) Load: 150 mg/kg during 1-hr period Maintenance infusion: 12.5 mg/kg/hr during 4-hr period, then 6.25 mg/kg/hr over 16 hr as continuous infusion	At the end of therapy, repeat AST and APAP levels: if AST normal and APAP not detected, treatment complete; if AST normal and APAP detected, continue NAC; if AST elevated, continue NAC After patient has received full course of NAC therapy, if INR ≥2.0 or severe hepatotoxicity present (AST >1000 U/L), continue NAC until INR <2.0 and aminotransferases normalize	Most effective if initiated within 8 hr after ingestion; may be started any time after ingestion and is beneficial in severe hepatotoxic states Longer duration of treatment may be required in patients with hepatotoxicity Treatment end points simplified for ease of use INR result not valid indicator if FFP recently administered
Naloxone	Opioids	Opioid dependence possible: 40-50 μg (0.04-0.05 mg) IV titrated upward to reversal, while avoiding withdrawal if concerns for opioid dependence Opioid dependence not likely: 0.4 mg by any route and titrate up to 10 mg Continuous infusion: establish bolus dose required to reverse respiratory depression; begin infusing two thirds of reversal dose every hour and titrate to maintain adequate respirations; repeated bolus with half of reversal dose 15 min after reversal of respiratory depression	Initial: reversal of respiratory depression with resolution of hypoxia and hypercapnia Final: resolution of CNS and respiratory depression	Pre-ventilate patients with respiratory depression by bag-valve-mask or intubation before administration Use smaller doses in opioid-dependent patients Some opioids (e.g., buprenorphine) may require larger doses of naloxone Use continuous infusion for recurrent symptoms and prolonged action of some formulations (e.g., sustained-release morphine, methadone) Re-sedation can occur Do not use naltrexone to reverse acute toxicity
Octreotide	Sulfonylurea-induced hypoglycemia	50 mg SC q6h	Resolution of hypoglycemia and dextrose not required	Maintain dextrose infusion as needed Not for insulin-induced hypoglycemia
Physostigmine	Anticholinergic agents (e.g., diphenhydramine, jimsonweed [*Datura* sp], scopolamine)	1-2 mg IV during 5-min period; can repeat in 5 min if no effect and cholinergic effects do not occur	Reversal of anticholinergic effects	Duration of effect is 60-90 min Benzodiazepine used for subsequent treatment of agitation and seizures; additional physostigmine used rarely (e.g., refractory seizures or agitation) Adverse effects include seizures, excessive oral secretions, bradyarrhythmias; contraindicated in cyclic antidepressant toxicity
Pralidoxime chloride	Organophosphorus compounds Nerve agents: sarin, VX	30 mg/kg IV bolus (maximum 2 g) during 30 min, followed by continuous infusion of 8-10 mg/kg/hr (maximum 650 mg/hr)	Resolution of signs and symptoms, atropine no longer required	Can give initial dose during 2-min period for life-threatening clinical effects Administer early when diagnosis known or strongly suspected Efficacy variable, depending on the organophosphate Fat-soluble organophosphates may require prolonged treatment
Pyridoxine	Ethylene glycol Isoniazid Monomethylhydrazine (*Gyromitra esculenta* mushrooms)	100 mg IV 5 g IV, repeat for refractory seizures	One dose Resolution of seizures	Efficacy theoretical for ethylene glycol to enhance elimination of toxic metabolites Pyridoxine may be required even with benzodiazepines to stop seizures, but patient can remain comatose (isoniazid, *Gyromitra* mushrooms) Excessive dosing can cause neuropathy

Continued on following page

Antidotes and Indications for Use

Antidote	Indication for Use	Dose*	Treatment End Point	Comments
Sodium bicarbonate ($NaHCO_3$)	Reversal of myocardial sodium-channel blockers (e.g., cyclic antidepressants, cocaine, sodium-channel–blocking antiarrhythmics with $\tau_{recovery}$ >1 sec, piperidine phenothiazines (thioridazine, mesoridazine)	1-2 mEq $NaHCO_3$/kg by intermittent bolus; repeat as needed	Narrowing of prolonged QRS, resolution of ventricular arrhythmias, reversal of hypotension	Monitor blood pH (optimal pH approximately 7.50); avoid pH >7.55
	Altered tissue distribution or enhanced elimination of salicylates; may be used for chlorophenoxy herbicides, formic acid, methotrexate, phenobarbital	1-2 mEq $NaHCO_3$/kg, followed by 3 ampules (150 ml) $NaHCO_3$ (44 mEq per 50 ml) in 850 ml of D_5W, infused at 2-3 times normal maintenance fluid rate	Serum salicylate <30 mg/dl and patient clinically stable	Target blood pH: 7.50-7.55 Monitor urinary pH hourly; adjust infusion to maintain urine pH of 7.5-8.0 (avoid blood pH >7.55) Monitor ABGs Maintain normokalemia
Succimer (DMSA)	Arsenic Lead Mercury, all forms	10 mg/kg/dose q8h for 5 days, followed by q12h for 14 days Drug holiday for 2 weeks; repeat if treatment end point not reached	Arsenic: 24-hr urinary arsenic <50 μg/L Lead: resolution of encephalopathy, gastrointestinal symptoms, neuropathy, nephropathy, arthralgias, myalgias, and blood lead level <70 μg/dl Mercury, elemental and inorganic: 24-hr urinary mercury <20 μg/L Mercury, organic: end point not well established	Oral chelator; adverse effects include rash, transient AST and alkaline phosphatase elevations, and gastrointestinal distress; minimal chelation of essential metals occurs Dosing for arsenic and mercury not well established Therapeutic end point for organic mercury not established; neurotoxicity not responsive to chelation therapy; suggest chelation until blood mercury level within normal-value range for reference laboratory
Vitamin K	Vitamin K antagonist anticoagulants (e.g., warfarin, long-acting anticoagulant rodenticides [LAARs]) [note that this is not for normalizing a supratherapeutic INR in patients prescribed warfarin]	Subcutaneous: AquaMEPHYTON (K_1), 10-25 mg, repeat every 6-12 hr until oral vitamin K_1 started Oral: 25-50 mg q6h; larger doses may be required	INR is normal 48-72 hr after stopping vitamin K_1 therapy Can also monitor factor VII activity	Anaphylactoid reaction can occur with rapid IV administration Severe bleeding may also require FFP, prothrombin protein concentrate (off label), or factor concentrates Base decision to treat on finding of elevated INR; do not administer prophylactic vitamin K_1 Oral therapy may be required for months with LAAR poisoning because of lipophilicity of toxicant, with slow body clearance

ABGs, Arterial blood gases; *ALT,* alanine aminotransferase; *APAP,* acetyl-*p*-aminophenol (acetaminophen); *AST,* aspartate aminotransferase; *BAL,* British antilewisite; *CNS,* central nervous system; *COHb%,* percentage carboxyhemoglobin; *CPR,* cardiopulmonary resuscitation; *D_5W,* 5% dextrose in water; *DMSA,* 2,3-dimercaptosuccinic acid; *ECG,* electrocardiogram; *FFP,* fresh-frozen plasma; *G6PD,* glucose-6-phosphate dehydrogenase; *Hb,* hemoglobin; *HD,* hemodialysis; *INR,* international normalized ratio; *MetHb%,* percentage methemoglobinemia; *NS,* normal saline; *O_2 Hb%,* percentage oxyhemoglobin; $\tau_{recovery}$, drug blockade recovery rate.

*Dose concentrations and infusion times are not given. Drug dosages may require adjustment in patients with renal or hepatic failure.

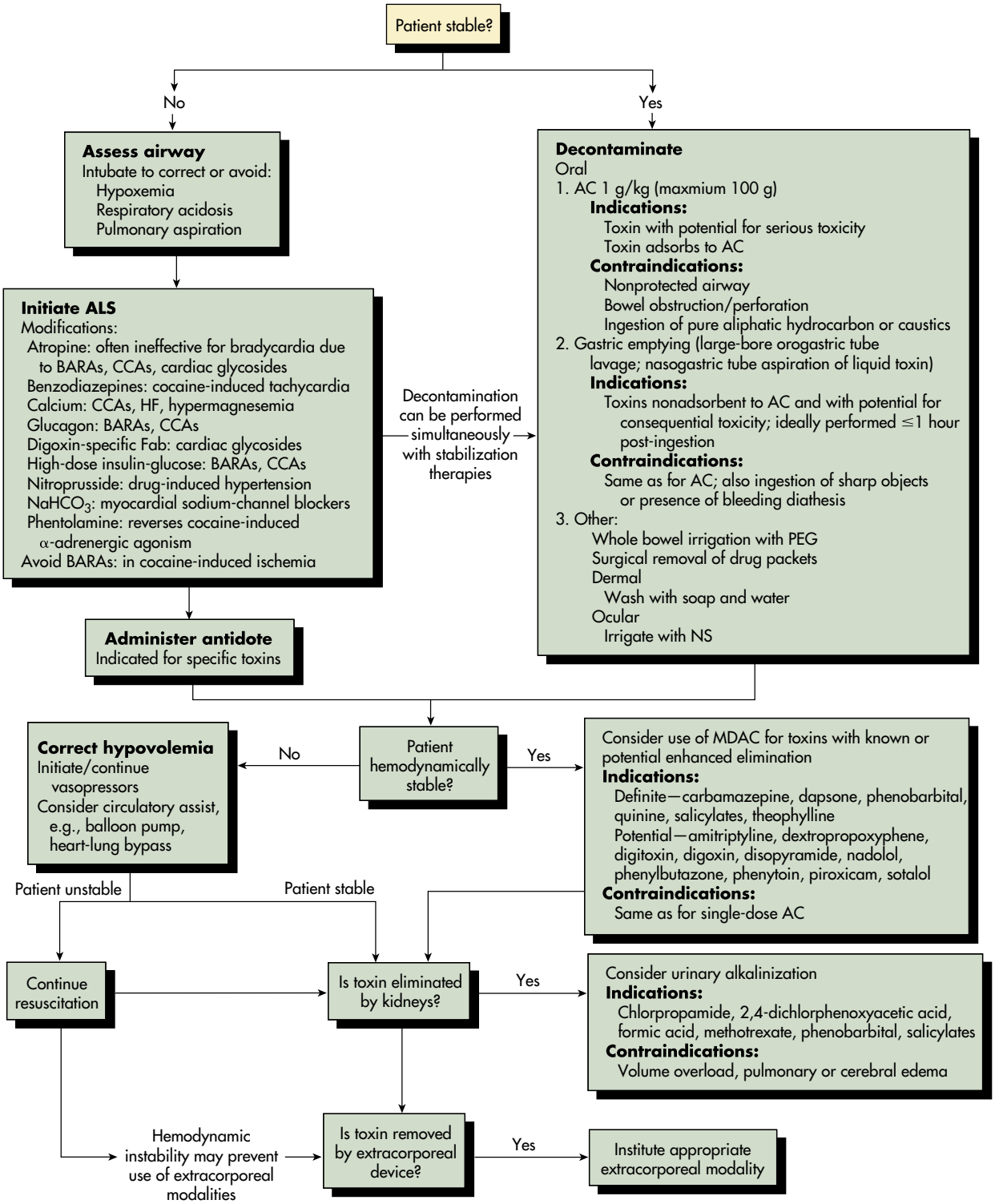
†Administer antivenom in a monitored setting; antivenom must be reconstituted and then diluted; initially infuse at a rate of 2-5 ml/hr, and double the infusion rate every 5 min as tolerated to administer antivenom during a 1-hr period.

‡Ten percent calcium chloride solution = 100 mg/ml (27.2 mg/ml elemental calcium); 10% calcium gluconate solution = 100 mg/ml (9 mg/ml elemental calcium).

From Goldman L, Schafer AI: *Goldman-Cecil medicine,* ed 25, Philadelphia, 2016, Elsevier.

Appendix IIId

Management of Acute Poisoning



Algorithm for the management of acute poisoning. See also Appendix IIIe. *AC,* Activated charcoal; *ALS,* advanced life support; *BARAs,* β-adrenergic receptor antagonists; *CCAs,* L-type calcium-channel antagonists; *HF,* hydrofluoric acid; *MDAC,* multidose activated charcoal; *NS,* 0.9% saline solution; *PEG,* nonabsorbable polyethylene glycol solution. (Modified from Goldman L, Schafer AI: *Goldman-Cecil medicine,* ed 25, Philadelphia, 2016, Elsevier.)

Appendix IIIe

Pathophysiology, Clinical Effects, and Management of Specific Drugs and Toxicants

Drug or Toxicant	Pathophysiology	Clinical Effects	Laboratory	Specific Therapy
Acetaminophen	NAPQI (toxic metabolite) binds hepatic and renal tubular cells; acetaminophen itself induces transient decrease in functional factor VII	• Initial: Nausea, vomiting, coma, lactic acidosis in severe cases • Days 1-3: Elevated INR, aminotransferase, and bilirubin levels; RUQ tenderness; increased creatinine level in severe cases • Days 4-14: Gradual recovery or continued increase in INR and creatinine, lactic acidosis, coma, cerebral edema, death	• Potentially toxic level ≥150 µg/ml 4 hr after ingestion* • INR may be transiently elevated in first 24 hr because of decrease in functional factor VII; further increases indicate hepatic necrosis; elevated aminotransferase and bilirubin levels not predictive of hepatic failure • Creatinine elevated in severe cases	NAC can increase INR but not aPTT†
Amphetamines	• Increased release of presynaptic norepinephrine and dopamine • Increased serotonin release (especially MDMA, PMA, DOB, other synthetic amphetamines)	• Mild: Euphoria, decreased appetite, repetitive behavior • Moderate: Vomiting, agitation, hypertension, tachycardia, mydriasis, bruxism, diaphoresis • Severe: Hypertension or hypotension, arrhythmias, hyperthermia, seizures, coma, hepatotoxicity, rhabdomyolysis, DIC, hyponatremia (SIADH), renal failure, cerebral infarction or hemorrhage	Not helpful; many false-positives and false-negatives on screening tests	• IV crystalloid • External cooling • Benzodiazepines or barbiturates to control agitation or seizure • Benzodiazepines or nitroprusside for hypertension • See SSRIs/SRIs for features and treatment of serotonin syndrome
β-Adrenergic receptor antagonists	Blocks catecholamines from β-adrenergic receptors • α- and β-adrenergic receptor antagonism: Carvedilol, labetalol • Delayed rectifier potassium-channel blockade: Sotalol	Bradyarrhythmias, decreased myocardial contractility, hypotension, respiratory depression, decreased consciousness with seizures or coma (lipophilic agents, e.g., propranolol), prolonged QT interval (sotalol)	• ECG • No specific tests	• IV glucagon, 3.5-5 mg over 2-min period; if no increase in BP or HR, can repeat up to 10 mg; if effective, immediately start continuous infusion at 2-10 mg/hr; if still unstable, options include (1) regular insulin, 1 U/kg by IV bolus, followed by 1 U/kg/hr, plus dextrose to maintain euglycemia; (2) norepinephrine or dobutamine infusion titrated to desirable BP and HR; (3) IV milrinone, 50 µg/kg over 10-min period, then 0.375-0.75 µg/kg/min based on hemodynamic status‡ • Electrical pacing and IABP in refractory cases

Drug or Toxicant	Pathophysiology	Clinical Effects	Laboratory	Specific Therapy
L-type calcium-channel antagonists	• Blocks L-type voltage-sensitive calcium channels, thereby decreasing calcium entry into myocardial and vascular smooth muscle cells • Decreases pancreatic insulin release and increases insulin resistance	Bradyarrhythmias (verapamil, diltiazem), hypotension, hyperglycemia	• ECG • No specific tests	• IV 10% calcium chloride, 10-20 mg/kg (0.1-0.2 ml/kg); can repeat once; if BP improves, continuous infusion at 0.2-0.5 ml/kg/hr (20-50 mg/kg/hr) • Ionized Ca2+ levels should not exceed 2× normal (severe cases will be refractory to calcium therapy) • Glucagon, high-dose insulin and dextrose, catecholamines, and milrinone (as for β-adrenergic antagonists)
Cardiac glycosides, including digoxin, bufadienolides (toxic toad venom), or cardenolides (e.g., oleander, lily of the valley, dogbane)	• Inhibits Na+, K+-ATPase • Decreased CNS sympathetic output • Decreased baroreceptor sensitivity • Increased vagal acetylcholine discharge	• Bradyarrhythmias, including second- and third-degree AV block and asystole • Ventricular ectopy, tachycardia, fibrillation • Junctional tachycardia, paroxysmal atrial tachycardia with block • Weakness, visual disturbances, nausea, vomiting	• Serum digoxin level • Serum potassium (hyperkalemia occurs in acute poisoning; hypokalemia may be present in chronic poisoning), magnesium, and creatinine levels	• Correct hypokalemia and hypomagnesemia; do not give calcium • Digoxin-specific antibody fragments (Fab) indicated if patient has hemodynamically significant arrhythmias, serum potassium ≥5 mg/L, Mobitz II or third-degree AV block, ingestion of bufadienolide- or cardenolide-containing agents, or renal insufficiency • Empirical dose • Chronic: 2-5 vial • Acute: 10-20 vial • Calculated dose • Chronic: Number of vials = 2 × serum digoxin level (ng/ml) × 5.6 × weight (kg)/1000 • Acute: Number of vials = 2 × oral digoxin dose (mg) × 0.8
Cyclic antidepressants	Myocardial sodium- and potassium-channel blockade Blockade of α-adrenergic and cholinergic muscarinic receptor Inhibition of norepinephrine reuptake	• Decreased level of consciousness (can develop rapidly), myoclonus, seizures, coma • Anticholinergic toxidrome • Sinus tachycardia, ventricular conduction delays, ventricular arrhythmias, asystole • Hypotension	Serum levels not helpful in management	• Intermittent IV boluses of NaHCO3 (1 mEq/kg) to maintain arterial pH at 7.5 because acidemia can worsen cardiovascular complications • Intubation and neuroparalytic drugs may be useful to ameliorate acidemia from muscular hyperactivity while seizures are being treated • Contraindicated drugs: Types IA and IC antiarrhythmic agents; physostigmine, flumazenil
Ethylene glycol, methanol (e.g., antifreeze, window cleaners, camping stove fuels)	• Ethylene glycol: Toxic metabolites produce cytotoxicity in CNS, kidneys, lungs, heart, liver, muscles; metabolic acidosis is due to glycolate accumulation; oxalate complexes with calcium, so hypocalcemia can develop • Methanol: Metabolized to formic acid, which is responsible for metabolic acidosis and inhibition of cytochrome aa3; target organs include retina, optic nerve, CNS	• Ethylene glycol: CNS depression, cerebral edema, seizures, anion gap metabolic acidosis, renal failure with acute tubular necrosis, pulmonary edema, myositis • Methanol: Nausea, vomiting; cerebral edema, hemorrhage, infarcts; necrosis of thalamus and putamen; anion gap metabolic acidosis; visual disturbances, papilledema, hyperemic optic disc, nonreactive pupils	• Serum ethylene glycol and methanol levels; levels may be low or undetectable if significant metabolism has occurred • Ethylene glycol: Serum calcium, creatinine, BUN levels; examine urine for calcium oxalate crystals; false hyperlactatemia occurs with certain analyzers using l-lactate oxidase, which cross-reacts with glycolic and glyoxylic acids	• For both: Fomepizole (which inhibits alcohol dehydrogenase and blocks formation of toxic metabolites), 15 mg/kg IV loading dose, then 10 mg/kg IV for 4 doses during the next 48 hr, then 15 mg/kg for subsequent doses; interval dosing is q12h (q4h during hemodialysis, with dosing interval adjustments at start and finish); continue until ethylene glycol or methanol is no longer detectable • Use of ethanol is no longer recommended • Hemodialysis: Initiate if level is ≥50 mg/dl or metabolic acidosis with end-organ toxicity; continue until acidosis resolves and serum level of ethylene glycol or methanol is undetectable • Monitor for cerebral edema with possible herniation • Ethylene glycol: IV calcium for symptomatic hypocalcemia • Methanol: Folinic acid, 50 mg IV q4h until methanol not detectable and acidosis cleared

Continued on following page

Drug or Toxicant	Pathophysiology	Clinical Effects	Laboratory	Specific Therapy
γ-Hydroxybutyrate (GHB) and its precursors (γ-butyrolactone and 1,4-butanediol [1,4-BD])	Agonist effect on CNS GHB receptors; indirect action with opioid receptors (may increase proenkephalins); metabolized to GABA, interacts with $GABA_B$ receptors; decreases dopamine release	• CNS: Rapid loss of consciousness, with recovery typical within 2-4 hr; myoclonus (possible seizures) • Respiratory depression; bradycardia; nausea, vomiting	No specific tests	• Supportive care, including respiratory support as needed • Withdrawal resembles sedative-hypnotic withdrawal and can be treated with benzodiazepines or pentobarbital
Lithium	Decreases brain inositol; alters CNS serotonin, dopamine, and norepinephrine; inhibits adenylate cyclases, including those that mediate vasopressin-induced renal concentration and thyroid function	• Chronic toxicity usually more severe than acute toxicity: Tremor, hyperreflexia, drowsiness, incoordination, clonus, confusion, ataxia; in severe cases, seizures, coma, death; recovery may take weeks, and CNS deficits may persist • Sinus node dysfunction, QT prolongation, T wave abnormalities, U waves • Nephrogenic diabetes insipidus, hypothyroidism, hyperthyroidism, hypercalcemia, pseudotumor cerebri • Acute toxicity: Nausea, vomiting, diarrhea, and milder neurologic findings	• Peak serum levels: • Normal dose 2-3 hr; up to 5 hr for sustained-release lithium • Acute overdose: Peak may be delayed ≥4-12 hr	• Replenish intravascular volume, maintain urinary output at 1-2 ml/kg/hr • Consider GI decontamination with oral polyethylene glycol electrolyte solution within 1-2 hr after acute overdose of sustained-release drug • Hemodialysis[§] in patients with altered mental status, ataxia, seizures, or coma or in patients with mild symptoms in the setting of acute overdose or renal insufficiency • Ineffective or contraindicated therapies include oral activated charcoal, diuretics, and aminophylline
Opioids (e.g., heroin, morphine, oxycodone, fentanyl)	Agonist effect at CNS μ, κ, and δ opioid receptors; result is cell hyperpolarization and decreased neurotransmitter release	• CNS depression, respiratory depression, miosis • Dextromethorphan increases CNS serotonin and inhibits NMDA receptors, which causes hallucinations • Propoxyphene and its metabolite norpropoxyphene block sodium channels and can cause seizures and wide-complex arrhythmias similar to cyclic antidepressants; NaHCO3 treats arrhythmias • Seizure risk with tramadol, meperidine, propoxyphene • Rapid, powerful heroin-like effect when sustained-release oxycodone is crushed before ingestion, snorting, or smoking • QTc prolongation and torsades de pointes with methadone	Rapid urine drug screens detect morphine and codeine but may not detect semisynthetic and synthetic opioids; some interferents/irrelevants	• IV naloxone, 0.4-2 mg; can repeat up to 10 mg if no response • Continuous infusion for recurrent symptoms or sustained-release opioid ingestion; give 50% of dose that produces desired effect 15 min after initial effect is obtained, then infuse two thirds of this dose every hr; infusion rate can be increased or decreased to maintain normal respiration and avoid withdrawal symptoms • Contraindicated therapies: Nalmefene and naltrexone should not be used for acute opioid reversal
Organophosphorus compounds and carbamates (e.g., diazinon, mevinphos, fenthion, aldicarb)	Inhibits acetylcholinesterase, resulting in excessive acetylcholine stimulation of nicotinic and muscarinic receptors in autonomic and somatic motor nervous systems and CNS	• Nicotinic-mediated effects: Tachycardia, mydriasis, hypertension, delirium, coma, seizures, muscle weakness, fasciculations • Muscarinic-mediated effects: Salivation, lacrimation, urination, vomiting, defecation, miosis, bronchorrhea, bronchospasm, bradycardia	• Serum (butyrylcholinesterase) or RBC (acetylcholinesterase) activity <50% of normal • Clinical recovery occurs before serum cholinesterase levels normalize	• Atropine, 1-2 mg by initial IV bolus; double the dose every 5 min (2 mg, 4 mg, 8 mg, 16 mg, etc.) until drying of bronchial secretions, adequate oxygenation, pulse >80 bpm, systolic blood pressure >80 mm Hg achieved; continuous infusion at 10%-20% of total stabilizing dose per hr; stop infusion if patient develops any signs or symptoms of anticholinergic toxidrome; restart infusion at lower rate when signs or symptoms abate • Pralidoxime[‖] chloride 30 mg/kg (maximum 2 g) IV bolus over 30 min, then 8-10 mg/kg/hr (maximum 650 mg/hr) continuous infusion; administer as soon as possible after poisoning; continue 12-24 hr after atropine no longer required and symptoms resolve

Drug or Toxicant	Pathophysiology	Clinical Effects	Laboratory	Specific Therapy
Salicylates	Inhibits cyclooxygenase; decreases formation of prostaglandins and thromboxane A_2; stimulates CNS medullary respiratory receptor and chemoreceptor trigger zone; impairs platelet function; disrupts carbohydrate metabolism; uncouples oxidative phosphorylation; increases vascular permeability	• Acute toxicity • Mild: Nausea, vomiting, diaphoresis, tinnitus, decreased hearing, hyperpnea, tachypnea • Moderate–severe: Confusion, delirium, coma, seizures, hyperthermia, ALI; death can occur within hours of overdose • Chronic toxicity: Same as acute, but may not have diaphoresis or vomiting • Consider diagnosis in patients with new-onset confusion, anion gap metabolic acidosis, or ALI	• Serum salicylate level: Toxic ≥30 mg/dl; level ≥100 mg/dl indicates life-threatening toxicity with possible sudden, rapid clinical deterioration; in chronic toxicity, levels may be minimally elevated (>30 mg/dl), and clinical evaluation is more reliable for gauging degree of toxicity • Arterial blood gases: Respiratory alkalosis with metabolic acidosis • Anion gap metabolic acidosis • Prolonged PT and PTT, ketonuria, ketonemia	Multidose activated charcoal q2-3h in acute overdose with progressive symptoms or rising salicylate level
SSRIs/SRIs	• Inhibits reuptake of serotonin • SRIs have additional effects (e.g., duloxetine inhibits norepinephrine reuptake, nefazodone inhibits serotonergic 5-HT2 receptors, trazodone inhibits peripheral α-adrenergic receptors, venlafaxine inhibits norepinephrine and dopamine reuptake)	• Vomiting, blurred vision, CNS depression, tachycardia • Seizures and coma rare • Torsades de pointes reported with citalopram • Serotonin syndrome: Clonus, agitation, tremor, diaphoresis, hyperreflexia; hyperthermia and hypertonicity in severe cases	• No specific tests • If serotonin syndrome suspected: Electrolytes, BUN, glucose, liver enzymes, coagulation panel, blood gases, chest radiograph	• Respiratory support as needed • Benzodiazepines for agitation or seizures • Serotonin syndrome: Consider cyproheptadine, 12 mg PO initial dose then 2 mg PO q2h (to a maximum of 32 mg/day) until symptoms resolve • Critical care therapies for hyperthermia, rhabdomyolysis, DIC, ARDS, renal and hepatic dysfunction, torsades de pointes

ALI, Acute lung injury; *aPTT,* activated partial thromboplastin time; *ARDS,* acute respiratory distress syndrome; *AV,* atrioventricular; *BP,* blood pressure; *bpm,* beats per minute; *BUN,* blood urea nitrogen; *CNS,* central nervous system; *DIC,* disseminated intravascular coagulation; *DOB,* 4-bromo-2,5-dimethoxyamphetamine; *ECG,* electrocardiogram; *GABA,* α-aminobutyric acid; *GI,* gastrointestinal; *HR,* heart rate; *IABP,* intra-aortic balloon counterpulsation; *INR,* international normalized ratio; *IV,* intravenous; *MDMA,* 3,4-methylenedioxymethamphetamine; *Na^1,K^1-ATPase,* sodium, potassium adenosine triphosphatase; *NAC,* N-acetylcysteine; *NAPQI,* N-acetyl-p-benzoquinone imine; *NMDA,* N-methyl-D-aspartate; *PMA,* paramethoxyamphetamine; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *RBC,* red blood cell; *RUQ,* upper right quadrant (abdomen); *SIADH,* syndrome of inappropriate antidiuretic secretion; *SRI,* serotonin reuptake inhibitor; *SSRI,* selective serotonin reuptake inhibitor.

[I]A double-blind, randomized, placebo-controlled trial of pralidoxime in acute organophosphorus poisoning found no significant difference in mortality rates or need for intubation.

*A nomogram to evaluate the potential toxicity of levels drawn more than 4 hours after ingestion is provided in Fig. 7, from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity, *Pediatrics* 1975(55):871-876. The nomogram is valid only for levels drawn after a single acute ingestion.

[†]NAC can be discontinued in patients with uncomplicated disease after a loading dose plus six maintenance doses if hepatic aminotransferase levels are normal and acetaminophen is not detected; otherwise, the full regimen should be administered.

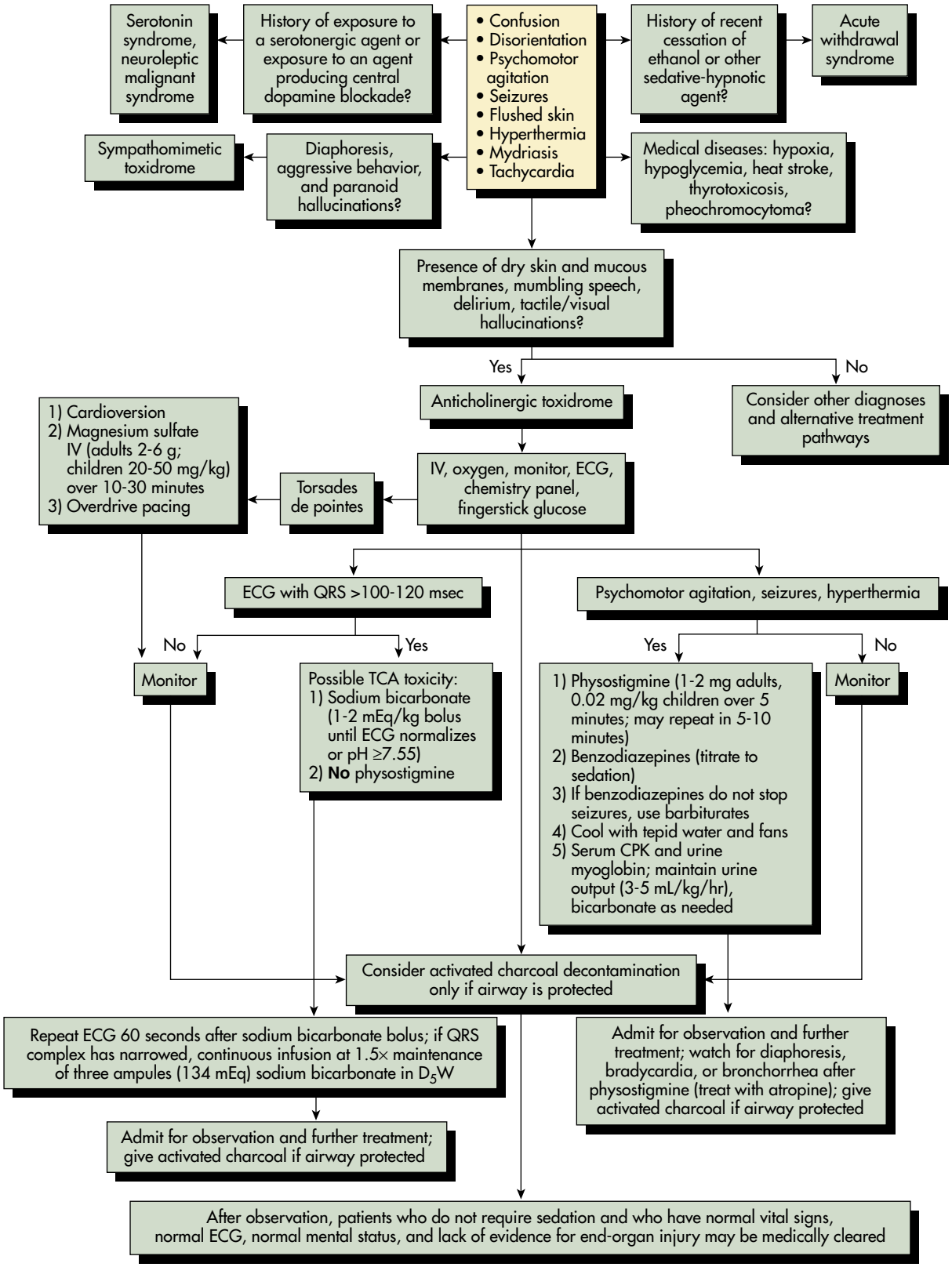
[‡]Adjust infusion for reduced renal function.

[§]Continue hemodialysis until the serum lithium level is less than 1 mEq/L. Recheck the level 8 hr after dialysis, and restart hemodialysis if the level is higher than 1 mEq/L. Repeat this cycle until the serum lithium level remains lower than 1 mEq/L.

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Elsevier.

Appendix IIIf

Accidental Poisoning by Exposure to Other Drugs Acting on the Autonomic Nervous System



Algorithm for the recognition and treatment of anticholinergic toxicity. *CPK,* Creatine phosphokinase; *D_5W,* 5% dextrose in water; *ECG,* electrocardiogram; *IV,* intravenous line; *TCA,* tricyclic antidepressant. (From Adams JG et al: *Emergency medicine: clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

Appendix IV

Impairment and Disability Issues

Impairment describes harm to anatomy and physiology, whereas *disability* denotes the difficulty a person has performing a function. Reporting disability for different sectors of society has its own nuances. Proper evaluation of impairment/disability starts with knowing who is asking for what. It is an area of practice in which an understanding of some basic concepts can make it rewarding rather than distressing.

- Ultimately, disability is a measure of function. Functional outcomes are becoming increasingly important in medicine, mirroring the shift toward patient-centeredness. All practitioners should have some facility with documenting the effects of an intervention on a patient's physical, psychological, and social functioning. For example, the continuation of an opioid analgesic should be predicated on meeting functional goals negotiated between the patient and physician before initiation of treatment. Even a brief comment on walking distance or work tolerance is better than nothing.
- Some concepts apply to all venues of disability. Primary care providers should rarely be in the position to determine whether a patient can be on or off a specific job. Rather, their task is to give general parameters about which physical exertions are medically dangerous. Try to be specific and use objective criteria where appropriate, but don't be intimidated by a form. Ballpark estimates can often suffice. For example, many chronic low back pain patients may conservatively and safely be described as able to lift/carry up 10 lbs, push/pull 25 lbs, and change positions as needed to keep comfortable. Have thorough medical records and be consistent; lawyers may focus on contradictions in your documentation to help their clients.
- Rehabilitation centers across the country are required to monitor function using a standardized set of criteria called the "Functional Independence Measure (FIM)," which categorizes activities of daily living into divisions such as mobility, transfers, feeding, grooming/hygiene, dressing, bathing, and toileting. In therapy notes, you may come across scores in these categories rating patients on a seven-point scale from totally dependent to moderate-assistance (mod A; patient can perform 50% of task) to modified-independent (patient requires an assistive device) to independent.
- Psychosocial contributing factors such as medicolegal issues can profoundly influence patients' presentations through somatization from secondary gain. However, it is important to differentiate this from malingering, Munchausen syndrome, or "gaming the system," which are remarkably less prevalent.
- The number of stakeholders expands in the disability system to include the employer, the government, the legal system, and the payer. Each sector has its own regulations. You may be required to fill out disability questionnaires as a condition of accepting payment for clinical services from a payer, such as in the workers' compensation system. Much more commonly, you will be seeing patients for clinical services paid for by an evaluation and management code. In these cases, you are not obligated to provide free medicolegal assessments. Settling payment issues in advance can avoid misunderstanding. Again, before assessing disability, understand who is asking and why.

GOVERNMENT-ADMINISTERED DISABILITY

State Temporary Disability Insurance (TDI) programs, the Family Medical Leave Act of 1993 (FMLA), the Social Security Administration (SSA), and the Department of Veterans Affairs offer disability benefits through the state and federal government.

- State TDI forms must be filled out for the patient to receive any income. They are generally very basic and just engage the social support network for a patient. This may not be the best venue to stipulate partial disability.
- The FMLA provides unpaid leave for qualified medical and family reasons. Because it is a federal program, the forms involved are standard across states and employers. They can be intimidating at first but are reasonably easy to complete once the basic definitions used are understood. It is recommended that you familiarize yourself with this paperwork the first few times it is encountered. Completing the form for subsequent patients should not be overly burdensome.
- The SSA and the Department of Veterans Affairs have their own internal mechanisms for quantifying disability, but they may subpoena your records or request a summary narrative as part of their processes. If you've kept good clinical notes, your existing documentation should satisfy their requirements. Many patients choose to apply for Social Security Disability Insurance (SSDI) and/or Supplemental Security Income (SSI) through a legal representative. These lawyers may send you a lengthy questionnaire to prepare their case. There are physicians whose practices perform these services and who can be hired by attorneys to facilitate patients' applications. If this nonclinical work appeals to you, consider affiliating with the SSA or contracting your time to lawyers under separate indenture. If not, you may want to recommend the law office contact a suitable practice.

WORKERS' COMPENSATION

In workers' compensation, the payer and employer join the provider in trying to rehabilitate the injured worker. Confidentiality issues are handled differently because these stakeholders may have a right to protected health information.

- Each state has their own laws regarding reporting requirements, and the U.S. Department of Labor governs injured federal employees. If you plan on accepting workers' compensation patients, you must familiarize yourself with the necessary paperwork. Typically, this is a standard, short form that includes measures of function. It may make sense to copy your state's parameters and create a "work note" to be used uniformly in your practice for cases both inside and outside of the workers' compensation system. Functional limitations should pertain to any task, not just to the employee's vocation. In general, employees should not be labeled "on" or "off."
- A notification that an employee has reached "maximal medical improvement" should be made once an employee's condition is expected to change over months/years rather than days/weeks. At this juncture they will transition from temporary disability benefits to permanent disability benefits, possibly including vocational rehabilitation. If ongoing sequelae exist, a permanent impairment rating may be needed to resolve an employee's claim and allow them to progress to the next stage of their life. These are more sophisticated determinations, usually directed by the American Medical Association's (AMA) *Guides to the Evaluation of Permanent Impairment*, now in its sixth edition. Analysis of permanent impairment, causation, and apportionment generally fall outside of workers' compensation reporting requirements. Someone with

appropriate training may be best suited to complete this task. Consider providing these more detailed services under a separate indenture, such as a consultation arrangement with the employee's attorney. Your state workers' compensation board may have specific guidelines governing these reports. In any case, the work should be done under a clear written agreement, not based on a verbal request by the employee. Very complex cases may also require a formal functional capacity evaluation through an appropriate rehabilitation resource.

PERSONAL INJURY

Patients hurt in car accidents or other personal injuries often are involved in legal cases covering medical care, personal damages, and pain and suffering. Most commonly, you will be helping these patients with their clinical issues under their regular medical insurance, although some providers agree to provide services under a legal lien on the claim. Regardless of your role in a personal injury case, it is helpful to document objective details about the injury and functional parameters. If you are asked to keep someone out of work, try to delineate functional limitations as you would in a workers' compensation employee.

- Similar to the workers' compensation system, it is helpful to state when a patient has reached maximal medical improvement. Personal injury claims can take longer to resolve than in the workers' compensation system, as the employer and insurance company are strongly incentivized to reach a resolution in those cases. In general, an ongoing legal case may hinder a patient from achieving a healthful balance of wellness. It is in the patient's best interest to move the claim toward completion.
- Quantifying permanent disability is a key component of resolving these cases. If a clinician is providing services under a legal lien, there may be a conflict of interest in having that provider quantify the permanent impairment. There may be financial implications to the degree of disability awarded, and this may influence whether or not the clinician will receive payment on their lien. These cases are almost always contentious and may be best handled by providers with special training, such as an independent medical examiner. Again, the determination typically follows the AMA's *Guides to the Evaluation of Permanent Impairment.* A clinician's role is to manage the patient's injuries, not to negotiate medicolegal issues. If you are not appropriately trained, consider deferring questions regarding disability to someone who is.

PRIVATE DISABILITY

Some patients purchase private insurance plans to provide income in addition to that offered through the government in the case of long-term disability. These forms vary by insurance carrier and change over time. They may need to be filled out periodically to maintain benefits. Many providers opt to charge a separate fee for the completion of this type of paperwork.

CONCLUSION

In summary, impairment and disability are measures of function and should be followed by all good doctors as part of patient-centered care. Providers can be most effective interacting with the various disability systems if they know when they are acting as clinicians and when they are acting as legal consultants. Understanding the principles involved with the different sectors will help you avoid confusion between obligations and opportunities when doing this work.

AUTHOR: **Matthew J. Smith, MD**

Appendix V

Protection of Travelers

TABLE 1 Structured Approach to the Pretravel Office Visit with a Traveler to the Developing World

Perform Risk Assessment

The following must always be ascertained to determine appropriate preventive medical recommendations. Preprinted medical record forms may be used to record these.
Exact itinerary, including regions within each country to be visited
Dates of travel to assess risk of seasonal diseases
Age
Past vaccination history
Underlying illness(es)
Current medications
Pregnancy status
Allergies
Purpose of trip
Risk exposures—blood, body fluids, adventure or extensive outdoor exposures
Urban versus rural travel
Type of accommodations
Level of aversion to risk
Financial limitations that may necessitate prioritization of interventions

Administer Immunizations

Administer routine vaccinations that are not up-to-date.
Administer indicated travel vaccines.
Provide to patient legally mandated Vaccine Information Statements from the Centers for Disease Control and Prevention (www.cdc.gov/vaccines/hcp/vis/index.html).
Provide printed checklist to patient, listing vaccines administered.
Record in the clinic record vaccines administered, lot number, and date.
Document vaccines offered to but declined by patient, as well as nonrecommended vaccines administered at the patient's request.

Provide Malaria Prevention (If Indicated)

Determine whether malaria risk exists for the destination country. If yes:
Does the patient's itinerary within that country put him or her at risk? If yes:
Recommend malaria chemoprophylaxis. Several equally effective drugs of choice may be indicated. Ascertain which is best suited to the individual patient and itinerary.
Educate on personal protection against arthropods.

Educate on Traveler's Diarrhea

Recommend food and water precautions.
Prescribe and educate on standby therapy with a quinolone antibiotic or azithromycin and advise on use of loperamide and oral hydration if needed.

Teach Essential Preventive Behaviors

Most travel-related health problems, including vaccine-preventable diseases, can be avoided through simple behaviors initiated by the traveler.
Educate on appropriate strategies in the following categories (some topics are not applicable to all destinations): blood-borne and sexually transmitted diseases, safety and crime avoidance, injury prevention, swimming safety, rabies, skin/wound care, tuberculosis, packing for healthy travel, obtaining health care abroad.

Discuss Other Applicable Heath Issues

Advise and prescribe for altitude illness, motion sickness, or jet lag.
Discuss prevention of specific travel-related infections that are of some risk to the traveler and have a possible preventive strategy not included in the strategies above.
Discuss any minimal-risk conditions (e.g., hemorrhagic fevers) that are a frequent cause of patient anxiety.

Updated from Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.

TABLE 2 In-Depth Information Resources for Travel Medicine

Authoritative Websites Updated Constantly with Epidemiologic and Outbreak Information

Centers for Disease Control and Prevention (CDC) Travelers Health www.cdc.gov/travel
World Health Organization (WHO) Travelers' Health www.who.int/ith
Public Health Agency of Canada. Committee to Advise on Tropical Medicine and Travel (CATMAT) www.phac-aspc.gc.ca/tmp-pmv/catmat-ccmtmv/index-eng.php
WHO Disease Outbreak News www.who.int/csr/don/en/
WHO Weekly Epidemiological Record www.who.int/wer/en/
CDC Morbidity and Mortality Weekly Report www.cdc.gov/mmwr
WHO Disease by Disease Health Topics www.who.int/health-topics/

In-Depth References on Specialized Topics

Centers for Disease Control and Prevention. Health Information for International Travel 2018 (The "CDC Yellow Book"). U.S. Public Health Service. Atlanta. Full text and hard copy order information available at www.nc.cdc.gov/travel/page/yellowbook-home
World Health Organization. International Travel and Health (WHO "Green" Book). Published annually. Available from authorized WHO book agents. Full text online at www.who.int/ith/en/
Keystone JS et al (eds): *Travel medicine,* ed 4, Philadelphia, 2019, Elsevier (ISBN: 9780323546966)
Plotkin SA et al: *Plotkin's vaccines,* ed 7, Philadelphia, 2017, Elsevier (ISBN: 9780323393010)
Auerbach PS, Cushing TA, Harris NS: *Wilderness medicine,* ed 7, St Louis, 2016, Elsevier (ISBN: 9780323359429)

Updated from Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.

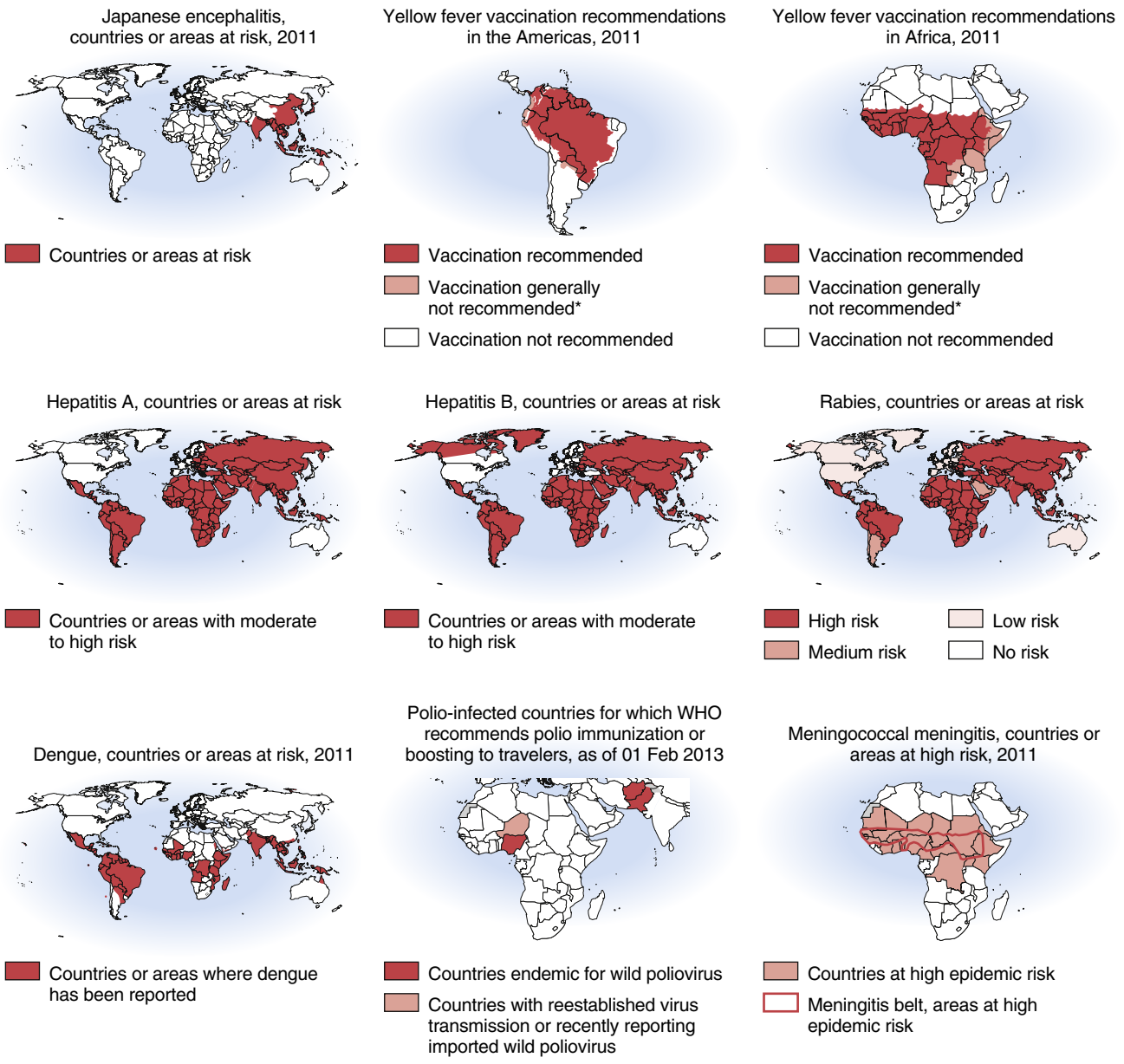


FIG. 1 Worldwide distribution of important travel-related diseases. *Yellow Fever (YF) vaccination is generally not recommended in areas where there is low-potential YF virus exposure. However, vaccination might be considered for a small subset of travelers to these areas who are at increased risk for exposure to YF virus because of prolonged travel, heavy exposure to mosquitoes, or inability to avoid mosquito bites. Consideration for vaccination of any traveler must take into account the traveler's risk of being infected with YF virus, country entry requirements, and individual risk factors for serious vaccine-associated adverse events (e.g., age, immune status). (From World Health Organization. International Travel and Health. Available at www.who.int/ith. In Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.)

TABLE 3 Travel-Related Vaccines of Adults

DISEASE	VACCINE	PRIMARY COURSE	ROUTE	FURTHER BOOSTERS
Vaccines to Consider for All Destinations				
Hepatitis A	Killed virus	0, 6-18 mo[a]	IM	None
Hepatitis B	Recombinant viral antigen	0, 1, 6 mo	IM	None
		A: 0, 1, 2, and 12 mo	IM	None
		A: 0, 1, 3 wk and 12 mo[b]	IM	
Hepatitis A/B	Combination of monovalent preparations	0, 1, 6 mo	IM	None
		A: 0, 1, 3 wk and 12 mo	IM	None
Typhoid	Capsular Vi polysaccharide	Single dose	IM	2-3 yr
	Live-attenuated Ty21a bacteria	0, 2, 4, 6 days	Oral	5 yr
Influenza	Inactivated viral	Single dose	IM	Annual
	Live-attenuated virus	Single dose	Nasal	Annual
Varicella	Live-attenuated virus	0, 4-8 wk	SC	None
Vaccines for Selected Destinations				
Yellow fever	Live-attenuated 17D virus	Single dose	SC	Lifetime protection[c]
Meningococcus	Quadrivalent conjugated polysaccharide (A, C, Y, W135)	Single dose	IM	5 yr
Rabies	Inactivated cell culture viral	0, 7, 21-28 days	IM[d]	None routinely but two doses after each exposure
Japanese encephalitis (Vero cell)	Inactivated viral	0, 28 days	IM	1 yr if at continued risk; no data on subsequent doses
Polio[e]	Inactivated viral	Single dose if adequate childhood series	SC; IM acceptable	None
Cholera	Killed bacteria + recombinant B toxin subunit	0, 1 wk	Oral	2 yr for cholera; 3 mo for ETEC
Tick-borne encephalitis[h]	Inactivated viral[f,g]	0, 1-3 mo, 9-12 mo	IM	3 yr

A, Accelerated regimen to be used for imminent departures; *ETEC,* enterotoxigenic *E. coli; IM,* intramuscular; *SC,* subcutaneous.
[a]Second dose may be delayed up to 8 years without diminished efficacy.
[b]Regimen not approved by the U.S. Food and Drug Administration for monovalent hepatitis B vaccine but approved for combination hepatitis A/B vaccine containing the same quantity of hepatitis B antigen.
[c]Until 2016, some countries that have mandatory entry requirements may require vaccination every 10 years.
[d]Intradermal rabies preexposure vaccine is no longer produced, and the intramuscular 1.0-mL vials are not licensed for intradermal use in a 0.1-mL dose.
[e]Oral polio vaccine is no longer produced in the United States.
[f]Not available in the United States but available in Canada and most European countries. No cholera vaccine of any kind is currently available in the United States.
[g]Also licensed in some countries for traveler's diarrhea because of enterotoxigenic *Escherichia coli.*
[h]Not available in United States but available in endemic areas and in Canada and the United Kingdom by special release.
From Bennett JE, Dolin R, Blaser MJ: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier.

Appendix VI

Physician Quality Reporting System (PQRS) Measures

Measure Title	Measure Description
Diabetes: Hemoglobin A_{1c} Poor Control	Percentage of patients 18-75 years of age with diabetes who had hemoglobin A_{1c} >9.0% during the measurement period
Diabetes: Low-Density Lipoprotein Cholesterol (LDL-C) Control (<100 mg/dl)	Percentage of patients 18-75 years of age with diabetes whose LDL-C was adequately controlled (<100 mg/dl) during the measurement period
Heart Failure (HF): Angiotensin-Converting Enzyme (ACE) Inhibitor or Angiotensin Receptor Blocker (ARB) Therapy for Left Ventricular Systolic Dysfunction (LVSD)	Percentage of patients aged 18 years and older with a diagnosis of HF with a current or prior left ventricular ejection fraction <40% who were prescribed ACE inhibitor or ARB therapy either within a 12-month period when seen in the outpatient setting *or* at each hospital discharge
Coronary Artery Disease (CAD): Antiplatelet Therapy	Percentage of patients aged 18 years and older with a diagnosis of CAD seen within a 12-month period who were prescribed aspirin or clopidogrel
CAD: Beta-Blocker Therapy—Prior Myocardial Infarction (MI) or LVSD (LVEF <40%)	Percentage of patients aged 18 years and older with a diagnosis of CAD seen within a 12-month period who also have prior MI *or* a current or prior LVEF <40% who were prescribed beta-blocker therapy
HF: Beta-Blocker Therapy for LVSD	Percentage of patients aged 18 years and older with a diagnosis of HF with a current or prior left ventricular ejection fraction <40% who were prescribed beta-blocker therapy either within a 12-month period when seen in the outpatient setting *or* at each hospital discharge
Antidepressant Medication Management	Percentage of patients 18 years of age and older who were found to have major depression and treated with antidepressant medication, and who remained on antidepressant medication treatment. Two rates are reported: 1. Percentage of patients who remained on an antidepressant medication for at least 84 days (12 weeks) 2. Percentage of patients who remained on an antidepressant medication for at least 180 days (6 months)
Primary Open-Angle Glaucoma (POAG): Optic Nerve Evaluation	Percentage of patients aged 18 years and older with a diagnosis of POAG who have an optic nerve head evaluation during one or more office visits within 12 months
Age-Related Macular Degeneration (AMD): Dilated Macular Examination	Percentage of patients aged 50 years and older with a diagnosis of AMD who had a dilated macular examination performed that included documentation of the presence or absence of macular thickening or hemorrhage *and* the level of macular degeneration severity during one or more office visits within 12 months
Diabetic Retinopathy: Documentation of Presence or Absence of Macular Edema and Level of Severity of Retinopathy	Percentage of patients aged 18 years and older with a diagnosis of diabetic retinopathy who had a dilated macular or fundus examination performed that included documentation of the level of severity of retinopathy and the presence or absence of macular edema during one or more office visits within 12 months
Diabetic Retinopathy: Communication with the Physician Managing Ongoing Diabetes Care	Percentage of patients aged 18 years and older with a diagnosis of diabetic retinopathy who had a dilated macular or fundus examination performed with documented communication to the physician who manages the ongoing care of the patient with diabetes mellitus regarding the findings of the macular or fundus examination at least once within 12 months
Perioperative Care: Selection of Prophylactic Antibiotic—First- or Second-Generation Cephalosporin	Percentage of surgical patients aged 18 years and older undergoing procedures with the indications for a first- *or* second-generation cephalosporin prophylactic antibiotic, who had an order for a first- *or* second-generation cephalosporin for antimicrobial prophylaxis

Continued on following page

Physician Quality Reporting System (PQRS) Measures

Measure Title	Measure Description
Perioperative Care: Discontinuation of Prophylactic Parenteral Antibiotics (Noncardiac Procedures)	Percentage of noncardiac surgical patients aged 18 years and older undergoing procedures with the indications for prophylactic parenteral antibiotics *and* who received a prophylactic parenteral antibiotic, who have an order for discontinuation of prophylactic parenteral antibiotics within 24 hours of surgical end time
Perioperative Care: Venous Thromboembolism (VTE) Prophylaxis (When Indicated in *All* Patients)	Percentage of surgical patients aged 18 years and older undergoing procedures for which VTE prophylaxis is indicated in all patients, who had an order for low-molecular-weight heparin, low-dose unfractionated heparin, adjusted-dose warfarin, fondaparinux, or mechanical prophylaxis to be given within 24 hours before incision time or within 24 hours after surgery end time
Communication with the Physician or Other Clinician Managing Ongoing Care Postfracture for Men and Women Aged 50 Years and Older	Percentage of patients aged 50 years and older treated for a fracture with documentation of communication, between the physician treating the fracture and the physician or other clinician managing the patient's ongoing care, that a fracture occurred and that the patient was or should be considered for osteoporosis treatment or testing. This measure is reported by the physician who treats the fracture and who therefore is held accountable for the communication.
Stroke and Stroke Rehabilitation: Discharged on Antithrombotic Therapy	Percentage of patients aged 18 years and older with a diagnosis of ischemic stroke or transient ischemic attack (TIA) with documented permanent, persistent, or paroxysmal atrial fibrillation who were prescribed an antithrombotic at discharge
Screening for Osteoporosis for Women Aged 65-85 Years	Percentage of female patients aged 65-85 years who ever had a central dual-energy x-ray absorptiometry to check for osteoporosis
Osteoporosis: Pharmacologic Therapy for Men and Women Aged 50 Years and Older	Percentage of patients aged 50 years and older with a diagnosis of osteoporosis who were prescribed pharmacologic therapy within 12 months
Coronary Artery Bypass Graft (CABG): Use of Internal Mammary Artery (IMA) in Patients with Isolated CABG Surgery	Percentage of patients aged 18 years and older undergoing isolated CABG surgery who received an IMA graft
CABG: Preoperative Beta-Blocker in Patients with Isolated CABG Surgery	Percentage of isolated CABG surgeries for patients aged 18 years and older who received a beta-blocker within 24 hours before surgical incision
Medication Reconciliation Postdischarge	Percentage of discharges from any inpatient facility (e.g., hospital, skilled nursing facility, or rehabilitation facility) for patients 18 years and older seen within 30 days after discharge in the office by the physician, prescribing practitioner, registered nurse, or clinical pharmacist providing ongoing care for whom the discharge medication list was reconciled with the current medication list in the outpatient medical record. This measure is reported as three rates stratified by age group: • Reporting criteria 1: 18-64 years of age • Reporting criteria 2: 65 years and older • Total rate: All patients 18 years of age and older
Care Plan	Percentage of patients aged 65 years and older who have an advance care plan or surrogate decision maker documented in the medical record or documentation in the medical record that an advance care plan was discussed but the patient did not wish or was not able to name a surrogate decision maker or provide an advance care plan
Urinary Incontinence: Assessment of Presence or Absence of Urinary Incontinence in Women Aged 65 Years and Older	Percentage of female patients aged 65 years and older who were assessed for the presence or absence of urinary incontinence within 12 months
Urinary Incontinence: Plan of Care for Urinary Incontinence in Women Aged 65 Years and Older	Percentage of female patients aged 65 years and older with a diagnosis of urinary incontinence with a documented plan of care for urinary incontinence at least once within 12 months
Chronic Obstructive Pulmonary Disease (COPD): Spirometry Evaluation	Percentage of patients aged 18 years and older with a diagnosis of COPD who had spirometry results documented
COPD: Inhaled Bronchodilator Therapy	Percentage of patients aged 18 years and older with a diagnosis of COPD and who have an FEV_1 <60% predicted and have symptoms who were prescribed an inhaled bronchodilator
Asthma: Pharmacologic Therapy for Persistent Asthma—Ambulatory Care Setting	Percentage of patients aged 5 years and older with a diagnosis of persistent asthma who were prescribed long-term control medication
Emergency Medicine: 12-Lead ECG Performed for Nontraumatic Chest Pain	Percentage of patients aged 40 years and older with an emergency department discharge diagnosis of nontraumatic chest pain who had a 12-lead ECG performed
Appropriate Treatment for Children with Upper Respiratory Infection (URI)	Percentage of children 3 months through 18 years of age who were diagnosed with URI and were not dispensed an antibiotic prescription on or 3 days after the episode
Appropriate Testing for Children with Pharyngitis	Percentage of children 3-18 years of age who were diagnosed with pharyngitis, ordered an antibiotic, and received a group A streptococcus (strep) test for the episode
Hematology: Myelodysplastic Syndrome (MDS) and Acute Leukemia—Baseline Cytogenetic Testing Performed on Bone Marrow	Percentage of patients aged 18 years and older with a diagnosis of MDS or an acute leukemia who had baseline cytogenetic testing performed on bone marrow

Measure Title	Measure Description
Hematology: MDS—Documentation of Iron Stores in Patients Receiving Erythropoietin Therapy	Percentage of patients aged 18 years and older with a diagnosis of MDS who are receiving erythropoietin therapy with documentation of iron stores within 60 days before initiating erythropoietin therapy
Hematology: Multiple Myeloma: Treatment with Bisphosphonates	Percentage of patients aged 18 years and older with a diagnosis of multiple myeloma, not in remission, who were prescribed or received intravenous bisphosphonate therapy within the 12-month reporting period
Hematology: Chronic Lymphocytic Leukemia (CLL): Baseline Flow Cytometry	Percentage of patients aged 18 years and older seen within a 12-month reporting period with a diagnosis of CLL made at any time during or before the reporting period who had baseline flow cytometry studies performed and documented in the chart
Breast Cancer: Hormonal Therapy for Stage IC-IIIC Estrogen Receptor/Progesterone Receptor (ER/PR) Positive Breast Cancer	Percentage of female patients aged 18 years and older with stage IC through IIIC ER- or PR-positive breast cancer who were prescribed tamoxifen or aromatase inhibitor during the 12-month reporting period
Colon Cancer: Chemotherapy for American Joint Committee on Cancer (AJCC) Stage III Colon Cancer Patients	Percentage of patients aged 18-80 years with AJCC stage III colon cancer who are referred for adjuvant chemotherapy, are prescribed adjuvant chemotherapy, or have previously received adjuvant chemotherapy within the 12-month reporting period
Prevention of Central Venous Catheter (CVC)–Related Bloodstream Infections	Percentage of patients, regardless of age, who undergo CVC insertion for whom CVC was inserted with all elements of maximal sterile barrier technique, hand hygiene, skin preparation, and, if ultrasound is used, sterile ultrasound techniques followed
Hepatitis C: RNA Testing Before Initiating Treatment	Percentage of patients aged 18 years and older with a diagnosis of chronic hepatitis C who started antiviral treatment within the 12-month reporting period for whom quantitative HCV RNA testing was performed within 12 months before initiation of antiviral treatment
Hepatitis C: Hepatitis C Virus (HCV) Genotype Testing Before Treatment	Percentage of patients aged 18 years and older with a diagnosis of chronic hepatitis C who started antiviral treatment within the 12-month reporting period for whom HCV genotype testing was performed within 12 months before initiation of antiviral treatment
Hepatitis C: HCV RNA Testing Between 4 and 12 Weeks After Initiation of Treatment	Percentage of patients aged 18 years and older with a diagnosis of chronic hepatitis C who are receiving antiviral treatment for whom quantitative HCV RNA testing was performed between 4 and 12 weeks after the initiation of antiviral treatment
Acute Otitis Externa (AOE): Topical Therapy	Percentage of patients aged 2 years and older with a diagnosis of AOE who were prescribed topical preparations
AOE: Systemic Antimicrobial Therapy—Avoidance of Inappropriate Use	Percentage of patients aged 2 years and older with a diagnosis of AOE who were not prescribed systemic antimicrobial therapy
Breast Cancer Resection Pathology Reporting: pT Category and pN Category with Histologic Grade	Percentage of breast cancer resection pathology reports that include the pT category, the pN category, and the histologic grade
Colorectal Cancer Resection Pathology Reporting: pT Category and pN Category with Histologic Grade	Percentage of colon and rectum cancer resection pathology reports that include the pT category, the pN category, and the histologic grade
Prostate Cancer: Avoidance of Overuse of Bone Scan for Staging Low-Risk Prostate Cancer Patients	Percentage of patients, regardless of age, with a diagnosis of prostate cancer at low risk of recurrence receiving interstitial prostate brachytherapy, *or* external beam radiotherapy to the prostate, *or* radical prostatectomy, *or* cryotherapy who did not have a bone scan performed at any time since diagnosis of prostate cancer
Prostate Cancer: Adjuvant Hormonal Therapy for High-Risk or Very-High-Risk Prostate Cancer	Percentage of patients, regardless of age, with a diagnosis of prostate cancer at high or very high risk of recurrence receiving external beam radiotherapy to the prostate who were prescribed adjuvant hormonal therapy (GnRH agonist or antagonist)
Adult Major Depressive Disorder (MDD): Suicide Risk Assessment	Percentage of patients aged 18 years and older with a diagnosis of MDD with a suicide risk assessment completed during the visit in which a new diagnosis or recurrent episode was identified
Rheumatoid Arthritis (RA): Disease Modifying Anti-Rheumatic Drug (DMARD) Therapy	Percentage of patients aged 18 years and older who were diagnosed with RA and were prescribed, dispensed, or administered at least one ambulatory prescription for a DMARD
Osteoarthritis (OA): Function and Pain Assessment	Percentage of patient visits for patients aged 21 years and older with a diagnosis of OA with assessment for function and pain
Preventive Care and Screening: Influenza Immunization	Percentage of patients aged 6 months and older seen for a visit between October 1 and March 31 who received an influenza immunization *or* who reported previous receipt of an influenza immunization
Pneumonia Vaccination Status for Older Adults	Percentage of patients 65 years of age and older who have ever received a pneumococcal vaccine
Breast Cancer Screening	Percentage of women 50 through 74 years of age who had a mammogram to screen for breast cancer within 27 months
Colorectal Cancer Screening	Percentage of patients 50-75 years of age who had appropriate screening for colorectal cancer

Continued on following page

Physician Quality Reporting System (PQRS) Measures

Measure Title	Measure Description
Antibiotic Treatment for Adults with Acute Bronchitis: Avoidance of Inappropriate Use	Percentage of adults 18-64 years of age with a diagnosis of acute bronchitis who were not prescribed or dispensed an antibiotic prescription on or 3 days after the episode
Diabetes: Eye Examination	Percentage of patients 18-75 years of age with diabetes who had a retinal or dilated eye examination by an eye care professional during the measurement period or a negative retinal or dilated eye examination (no evidence of retinopathy) in the 12 months before the measurement period
CAD: ACE Inhibitor or ARB Therapy—Diabetes or LVSD (LVEF <40%)	Percentage of patients aged 18 years and older with a diagnosis of CAD seen within a 12-month period who also have diabetes *or* a current or prior LVEF <40% who were prescribed ACE inhibitor or ARB therapy
Diabetes: Medical Attention for Nephropathy	Percentage of patients 18-75 years of age with diabetes who had a nephropathy screening test or evidence of nephropathy during the measurement period
Adult Kidney Disease: Laboratory Testing (Lipid Profile)	Percentage of patients aged 18 years and older with a diagnosis of chronic kidney disease (CKD) (stage 3, 4, or 5, not receiving renal replacement therapy [RRT]) who had a fasting lipid profile performed at least once within a 12-month period
Adult Kidney Disease: BP Management	Percentage of patient visits for those patients aged 18 years and older with a diagnosis of CKD (stage 3, 4, or 5, not receiving RRT) with a BP <140/90 mm Hg *or* ≥140/90 mm Hg with a documented plan of care
Diabetes Mellitus: Diabetic Foot and Ankle Care, Peripheral Neuropathy—Neurological Evaluation	Percentage of patients aged 18 years and older with a diagnosis of diabetes mellitus who had a neurological examination of their lower extremities within 12 months
Diabetes Mellitus: Diabetic Foot and Ankle Care, Ulcer Prevention—Evaluation of Footwear	Percentage of patients aged 18 years and older with a diagnosis of diabetes mellitus who were evaluated for proper footwear and sizing
Preventive Care and Screening: Body Mass Index (BMI) Screening and Follow-Up Plan	Percentage of patients aged 18 years and older with a BMI documented during the current encounter or during the previous 6 months *and* with a BMI outside of normal parameters, a follow-up plan is documented during the encounter or during the previous 6 months of the current encounter Normal parameters: Age 65 years and older and BMI ≥23 and <30 kg/m^2; age 18-64 years and BMI ≥18.5 and <25 kg/m^2
Documentation of Current Medications in the Medical Record	Percentage of visits for patients aged 18 years and older for which the eligible professional attests to documenting a list of current medications using all immediate resources available on the date of the encounter. This list must include *all* known prescriptions, over-the-counters, herbals, and vitamin/mineral/dietary (nutritional) supplements *and* must contain the medications' name, dosage, frequency, and route of administration.
Pain Assessment and Follow-Up	Percentage of visits for patients aged 18 years and older with documentation of a pain assessment using a standardized tool(s) on each visit *and* documentation of a follow-up plan when pain is present
Preventive Care and Screening: Screening for Clinical Depression and Follow-Up Plan	Percentage of patients aged 12 years and older screened for clinical depression on the date of the encounter using an age-appropriate standardized depression screening tool, *and* if positive, a follow-up plan is documented on the date of the positive screen
Melanoma: Continuity of Care—Recall System	Percentage of patients, regardless of age, with a current diagnosis of melanoma or a history of melanoma whose information was entered, at least once within a 12-month period, into a recall system that includes: • A target date for the next complete physical skin examination, *and* • A process to follow up with patients who either did not make an appointment within the specified time frame or who missed a scheduled appointment
Melanoma: Coordination of Care	Percentage of patient visits, regardless of age, with a new occurrence of melanoma who have a treatment plan documented in the chart that was communicated to the physician(s) providing continuing care within 1 month of diagnosis
AMD: Counseling on Antioxidant Supplement	Percentage of patients aged 50 years and older with a diagnosis of AMD or their caregiver(s) who were counseled within 12 months on the benefits and/or risks of the Age-Related Eye Disease Study formulation for preventing progression of AMD
POAG: Reduction of Intraocular Pressure (IOP) by 15% *or* Documentation of a Plan of Care	Percentage of patients aged 18 years and older with a diagnosis of POAG whose glaucoma treatment has not failed (the most recent IOP was reduced by at least 15% from the preintervention level) *or* if the most recent IOP was not reduced by at least 15% from the preintervention level, a plan of care was documented within 12 months
Oncology: Medical and Radiation—Pain Intensity Quantified	Percentage of patient visits, regardless of patient age, with a diagnosis of cancer currently receiving chemotherapy or radiation therapy in which pain intensity is quantified
Oncology: Medical and Radiation—Plan of Care for Pain	Percentage of visits for patients, regardless of age, with a diagnosis of cancer currently receiving chemotherapy or radiation therapy who report having pain with a documented plan of care to address pain

Measure Title	Measure Description
Radiology: Exposure Time Reported for Procedures Using Fluoroscopy	Final reports for procedures using fluoroscopy that document radiation exposure indices, or exposure time and number of fluorographic images (if radiation exposure indices are not available)
Radiology: Inappropriate Use of "Probably Benign" Assessment Category in Mammography Screening	Percentage of final reports for screening mammograms that are classified as "probably benign"
Nuclear Medicine: Correlation with Existing Imaging Studies for All Patients Undergoing Bone Scintigraphy	Percentage of final reports for all patients, regardless of age, undergoing bone scintigraphy that include physician documentation of correlation with existing relevant imaging studies (e.g., x-ray, MRI, CT, etc.) that were performed
Falls: Risk Assessment	Percentage of patients aged 65 years and older with a history of falls who had a risk assessment for falls completed within 12 months
Falls: Plan of Care	Percentage of patients aged 65 years and older with a history of falls who had a plan of care for falls documented within 12 months
Oncology: Radiation Dose Limits to Normal Tissues	Percentage of patients, regardless of age, with a diagnosis of breast, rectal, pancreatic, or lung cancer receiving 3D conformal radiation therapy who had documentation in medical record that radiation dose limits to normal tissues were established before the initiation of a course of 3D conformal radiation for a minimum of two tissues
HIV/AIDS: *Pneumocystis jiroveci* Pneumonia (PCP) Prophylaxis	Percentage of patients aged 6 weeks and older with a diagnosis of HIV/AIDS who were prescribed PCP prophylaxis
Diabetes: Foot Examination	Percentage of patients aged 18-75 years with diabetes who had a foot examination during the measurement period
Coronary Artery Bypass Graft (CABG): Prolonged Intubation	Percentage of patients aged 18 years and older undergoing isolated CABG surgery who require postoperative intubation >24 hours
CABG: Deep Sternal Wound Infection Rate	Percentage of patients aged 18 years and older undergoing isolated CABG surgery who, within 30 days postoperatively, develop deep sternal wound infection involving muscle, bone, and/or mediastinum requiring operative intervention
CABG: Stroke	Percentage of patients aged 18 years and older undergoing isolated CABG surgery who have a postoperative stroke (i.e., any confirmed neurological deficit of abrupt onset caused by a disturbance in blood supply to the brain) that did not resolve within 24 hours
CABG: Postoperative Renal Failure	Percentage of patients aged 18 years and older undergoing isolated CABG surgery (without preexisting renal failure) who develop postoperative renal failure or require dialysis
CABG: Surgical Re-Exploration	Percentage of patients aged 18 years and older undergoing isolated CABG surgery who require a return to the operating room during the current hospitalization for mediastinal bleeding with or without tamponade, graft occlusion, valve dysfunction, or other cardiac reason
RA: Tuberculosis (TB) Screening	Percentage of patients aged 18 years and older with a diagnosis of RA who have documentation of a TB screening performed and results interpreted within 6 months before receiving a first course of therapy using a biologic DMARD
RA: Periodic Assessment of Disease Activity	Percentage of patients aged 18 years and older with a diagnosis of RA who have an assessment and classification of disease activity within 12 months
RA: Functional Status Assessment	Percentage of patients aged 18 years and older with a diagnosis of RA for whom a functional status assessment was performed at least once within 12 months
RA: Assessment and Classification of Disease Prognosis	Percentage of patients aged 18 years and older with a diagnosis of RA who have an assessment and classification of disease prognosis at least once within 12 months
RA: Glucocorticoid Management	Percentage of patients aged 18 years and older with a diagnosis of RA who have been assessed for glucocorticoid use and, for those on prolonged doses of prednisone ≥10 mg daily (or equivalent) with improvement or no change in disease activity, documentation of glucocorticoid management plan within 12 months
Elder Maltreatment Screen and Follow-Up Plan	Percentage of patients aged 65 years and older with a documented elder maltreatment screen using an Elder Maltreatment Screening Tool on the date of encounter *and* a documented follow-up plan on the date of the positive screen
Functional Outcome Assessment	Percentage of visits for patients aged 18 years and older with documentation of a current functional outcome assessment using a standardized functional outcome assessment tool on the date of encounter *and* documentation of a care plan based on identified functional outcome deficiencies on the date of the identified deficiencies
Hepatitis C: Hepatitis A Vaccination	Percentage of patients aged 18 years and older with a diagnosis of chronic hepatitis C who have received at least one injection of hepatitis A vaccine, or who have documented immunity to hepatitis A
Colonoscopy Interval for Patients with a History of Adenomatous Polyps—Avoidance of Inappropriate Use	Percentage of patients aged 18 years and older receiving a surveillance colonoscopy, with a history of a prior adenomatous polyp(s) in previous colonoscopy findings, who had an interval of 3 or more years since their last colonoscopy

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Physician Quality Reporting System (PQRS) Measures

Measure Title	Measure Description
Stroke and Stroke Rehabilitation: Thrombolytic Therapy	Percentage of patients aged 18 years and older with a diagnosis of acute ischemic stroke who arrive at the hospital within 2 hours of time last known well and for whom IV tPA was initiated within 3 hours of time last known well
Cataracts: 20/40 or Better Visual Acuity Within 90 Days After Cataract Surgery	Percentage of patients aged 18 years and older with a diagnosis of uncomplicated cataract who had cataract surgery and no significant ocular conditions affecting the visual outcome of surgery and had best-corrected visual acuity of 20/40 or better (distance or near) achieved within 90 days after the cataract surgery
Cataracts: Complications Within 30 Days After Cataract Surgery Requiring Additional Surgical Procedures	Percentage of patients aged 18 years and older with a diagnosis of uncomplicated cataract who had cataract surgery and had any of a specified list of surgical procedures in the 30 days after cataract surgery that would indicate the occurrence of any of the following major complications: retained nuclear fragments, endophthalmitis, dislocated or wrong power intraocular lens, retinal detachment, or wound dehiscence
Radiology: Stenosis Measurement in Carotid Imaging Reports	Percentage of final reports for carotid imaging studies (neck MRA, neck CTA, neck duplex ultrasonography, carotid angiogram) performed that include direct or indirect reference to measurements of distal internal carotid diameter as the denominator for stenosis measurement
Ischemic Vascular Disease (IVD): Use of Aspirin or Another Antithrombotic	Percentage of patients 18 years of age and older who were discharged alive for acute myocardial infarction, coronary artery bypass graft, or percutaneous coronary interventions in the 12 months before the measurement period, or who had an active diagnosis of IVD during the measurement period and who had documentation of use of aspirin or another antithrombotic during the measurement period
HIV/AIDS: Sexually Transmitted Disease Screening for Chlamydia, Gonorrhea, and Syphilis	Percentage of patients aged 13 years and older with a diagnosis of HIV/AIDS for whom chlamydia, gonorrhea, and syphilis screenings were performed at least once since the diagnosis of HIV infection
Functional Deficit: Change in Risk-Adjusted Functional Status for Patients with Knee Impairments	Percentage of patients aged 18 years or older who receive treatment for a functional deficit secondary to a diagnosis that affects the knee in which the change in their risk-adjusted functional status is measured
Functional Deficit: Change in Risk-Adjusted Functional Status for Patients with Hip Impairments	Percentage of patients aged 18 or older who receive treatment for a functional deficit secondary to a diagnosis that affects the hip in which the change in their risk-adjusted functional status is measured
Functional Deficit: Change in Risk-Adjusted Functional Status for Patients with Lower Leg, Foot, or Ankle Impairments	Percentage of patients aged 18 years or older who receive treatment for a functional deficit secondary to a diagnosis that affects the lower leg, foot, or ankle in which the change in their risk-adjusted functional status is measured
Functional Deficit: Change in Risk-Adjusted Functional Status for Patients with Lumbar Spine Impairments	Percentage of patients aged 18 years or older who receive treatment for a functional deficit secondary to a diagnosis that affects the lumbar spine in which the change in their risk-adjusted functional status is measured
Functional Deficit: Change in Risk-Adjusted Functional Status for Patients with Shoulder Impairments	Percentage of patients aged 18 years or older who receive treatment for a functional deficit secondary to a diagnosis that affects the shoulder in which the change in their risk-adjusted functional status is measured
Functional Deficit: Change in Risk-Adjusted Functional Status for Patients with Elbow, Wrist, or Hand Impairments	Percentage of patients aged 18 years or older who receive treatment for a functional deficit secondary to a diagnosis that affects the elbow, wrist, or hand in which the change in their risk-adjusted functional status is measured
Functional Deficit: Change in Risk-Adjusted Functional Status for Patients with Neck, Cranium, Mandible, Thoracic Spine, Ribs, or Other General Orthopedic Impairments	Percentage of patients aged 18 years or older who receive treatment for a functional deficit secondary to a diagnosis that affects the neck, cranium, mandible, thoracic spine, ribs, or other general orthopedic impairment in which the change in their risk-adjusted functional status is measured
Melanoma: Overutilization of Imaging Studies in Melanoma	Percentage of patients, regardless of age, with a current diagnosis of stage 0–IIC melanoma or a history of melanoma of any stage, without signs or symptoms suggesting systemic spread, seen for an office visit during the 1-year measurement period, for whom no diagnostic imaging studies were ordered
Radiology: Reminder System for Screening Mammograms	Percentage of patients undergoing a screening mammogram whose information is entered into a reminder system with a target due date for the next mammogram
Preventive Care and Screening: Tobacco Use: Screening and Cessation Intervention	Percentage of patients aged 18 years and older who were screened for tobacco use one or more times within 24 months *and* who received cessation counseling intervention if identified as a tobacco user
Controlling High BP	Percentage of patients 18-85 years of age who had a diagnosis of hypertension and whose BP was adequately controlled (<140/90 mm Hg) during the measurement period
Use of High-Risk Medications in the Elderly	Percentage of patients 66 years of age and older who were ordered high-risk medications. Two rates are reported: 1. Percentage of patients who were ordered at least one high-risk medication 2. Percentage of patients who were ordered at least two different high-risk medications

Measure Title	Measure Description
Weight Assessment and Counseling for Nutrition and Physical Activity for Children and Adolescents	Percentage of patients 3-17 years of age who had an outpatient visit with a primary care physician or obstetrician/gynecologist and who had evidence of the following during the measurement period. Three rates are reported: 1. Percentage of patients with height, weight, and body mass index percentile documentation 2. Percentage of patients with counseling for nutrition 3. Percentage of patients with counseling for physical activity
Childhood Immunization Status	Percentage of children 2 years of age who had four diphtheria, tetanus, and acellular pertussis; three polio; one measles, mumps, and rubella; three H influenza type B; three hepatitis B; one chickenpox; four pneumococcal conjugate; one hepatitis A; two or three rotavirus; and two influenza vaccines by their second birthday
IVD: Complete Lipid Profile and LDL-C Control (<100 mg/dl)	Percentage of patients 18 years of age and older who were discharged alive for acute MI, CABG, or percutaneous coronary interventions (PCI) in the 12 months before the measurement period, or who had an active diagnosis of IVD during the measurement period, and who had each of the following during the measurement period: a complete lipid profile and LDL-C was adequately controlled (<100 mg/dl)
CAD: Symptom Management	Percentage of patients aged 18 years and older with a diagnosis of CAD seen within a 12-month period with results of an evaluation of level of activity and an assessment of whether anginal symptoms are present or absent with appropriate management of anginal symptoms within a 12-month period
Cardiac Rehabilitation Patient Referral from an Outpatient Setting	Percentage of patients evaluated in an outpatient setting who within the previous 12 months have experienced an acute MI, CABG surgery, a PCI, cardiac valve surgery, or cardiac transplantation, or who have chronic stable angina and have not already participated in an early outpatient cardiac rehabilitation/secondary prevention (CR) program for the qualifying event/diagnosis who were referred to a CR program
Barrett Esophagus	Percentage of esophageal biopsy reports that document the presence of Barrett mucosa that also include a statement about dysplasia
Radical Prostatectomy Pathology Reporting	Percentage of radical prostatectomy pathology reports that include the pT category, the pN category, the Gleason score, and a statement about margin status
Quantitative Immunohistochemical (IHC) Evaluation of Human Epidermal Growth Factor Receptor 2 Testing (HER2) for Breast Cancer Patients	This is a measure based on whether quantitative evaluation of HER2 testing by IHC uses the system recommended in the current ASCO/CAP Guidelines for HER2 testing in breast cancer
Ultrasound Determination of Pregnancy Location for Pregnant Patients with Abdominal Pain	Percentage of pregnant female patients aged 14-50 years who present to the emergency department with a chief complaint of abdominal pain or vaginal bleeding who receive a transabdominal or transvaginal ultrasonography to determine pregnancy location
Rh Immunoglobulin (Rhogam) for Rh-Negative Pregnant Women at Risk of Fetal Blood Exposure	Percentage of Rh-negative pregnant women aged 14-50 years at risk of fetal blood exposure who receive Rhogam in the emergency department
Statin Therapy at Discharge After Lower Extremity Bypass (LEB)	Percentage of patients aged 18 years and older undergoing infrainguinal lower extremity bypass who are prescribed a statin medication at discharge
Rate of Open Repair of Small or Moderate Nonruptured Abdominal Aortic Aneurysms (AAA) Without Major Complications (Discharged to Home by Postoperative Day 7)	Percent age of patients undergoing open repair of small or moderate-sized nonruptured AAA who do not experience a major complication (discharge to home no later than postoperative day 7)
Rate of Endovascular Aneurysm Repair (EVAR) of Small or Moderate Nonruptured AAA Without Major Complications (Discharged to Home by Postoperative Day 2)	Percent of patients undergoing endovascular repair of small or moderate nonruptured AAA who do not experience a major complication (discharged to home no later than postoperative day 2)
Rate of Carotid Endarterectomy (CEA) for Asymptomatic Patients, Without Major Complications (Discharged to Home by Postoperative Day 2)	Percentage of asymptomatic patients undergoing CEA who are discharged to home no later than postoperative day 2
Referral for Otologic Evaluation for Patients with Acute or Chronic Dizziness	Percentageage of patients aged birth and older referred to a physician (preferably a physician specially trained in disorders of the ear) for an otologic evaluation subsequent to an audiologic evaluation after presenting with acute or chronic dizziness
Image Confirmation of Successful Excision of Image-Localized Breast Lesion	Image confirmation of lesion(s) targeted for image-guided excisional biopsy or image-guided partial mastectomy in patients with nonpalpable, image-detected breast lesion(s). Lesions may include microcalcifications, mammographic or sonographic mass or architectural distortion, focal suspicious abnormalities on MRI or other breast imaging amenable to localization such as positron emission tomography mammography, or a biopsy marker demarcating site of confirmed pathology as established by previous core biopsy.
Preoperative Diagnosis of Breast Cancer	Percentage of patients undergoing breast cancer operations who obtained the diagnosis of breast cancer preoperatively by a minimally invasive biopsy method
Sentinel Lymph Node Biopsy for Invasive Breast Cancer	Percentage of clinically node-negative (clinical stage T1N0M0 or T2N0M0) breast cancer patients who undergo a sentinel lymph node procedure

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Physician Quality Reporting System (PQRS) Measures

Measure Title	Measure Description
Biopsy Follow-Up	Percentage of new patients whose biopsy results have been reviewed and communicated to the primary care/referring physician and patient by the performing physician
Epilepsy: Counseling for Women of Childbearing Potential with Epilepsy	All female patients of childbearing potential (12-44 years old) found to have epilepsy who were counseled or referred for counseling for how epilepsy and its treatment may affect contraception *or* pregnancy at least once a year
Inflammatory Bowel Disease (IBD): Preventive Care: Corticosteroid Sparing Therapy	Percentage of patients aged 18 years and older with a diagnosis of inflammatory bowel disease who have been managed by corticosteroids ≥10 mg/day of prednisone equivalents for 60 or greater consecutive days or a single prescription equating to 600 mg prednisone or greater for all fills that have been prescribed corticosteroid-sparing therapy within the last 12 months
IBD: Preventive Care: Corticosteroid-Related Iatrogenic Injury—Bone Loss Assessment	Percentage of patients aged 18 years and older with an inflammatory bowel disease encounter who were prescribed prednisone equivalents ≥10 mg/day for 60 or greater consecutive days or a single prescription equating to 600 mg prednisone or greater for all fills and were documented for risk of bone loss once during the reporting year or the previous calendar year
IBD: Testing for Latent TB Before Initiating Anti-TNF (Tumor Necrosis Factor) Therapy	Percentage of patients aged 18 years and older with a diagnosis of IBD) for whom a TB screening was performed and results interpreted within 6 months before receiving a first course of anti-TNF therapy
IBD: Assessment of Hepatitis B Virus (HBV) Status Before Initiating Anti-TNF Therapy	Percentage of patients aged 18 years and older with a diagnosis of IBD who had HBV status assessed and results interpreted within 1 year before receiving a first course of anti-TNF therapy
Sleep Apnea: Assessment of Sleep Symptoms	Percentage of visits for patients aged 18 years and older with a diagnosis of obstructive sleep apnea that includes documentation of an assessment of sleep symptoms, including presence or absence of snoring and daytime sleepiness
Sleep Apnea: Severity Assessment at Initial Diagnosis	Percentage of patients aged 18 years and older with a diagnosis of obstructive sleep apnea who had an apnea hypopnea index or a respiratory disturbance index measured at the time of initial diagnosis
Sleep Apnea: Positive Airway Pressure Therapy Prescribed	Percentage of patients aged 18 years and older with a diagnosis of moderate or severe obstructive sleep apnea who were prescribed positive airway pressure therapy
Sleep Apnea: Assessment of Adherence to Positive Airway Pressure Therapy	Percentage of visits for patients aged 18 years and older with a diagnosis of obstructive sleep apnea who were prescribed positive airway pressure therapy who had documentation that adherence to positive airway pressure therapy was objectively measured
Dementia: Staging of Dementia	Percentage of patients, regardless of age, with a diagnosis of dementia whose severity of dementia was classified as mild, moderate, or severe at least once within a 12-month period
Dementia: Cognitive Assessment	Percentage of patients, regardless of age, with a diagnosis of dementia for whom an assessment of cognition is performed and the results reviewed at least once within a 12-month period
Dementia: Functional Status Assessment	Percentage of patients, regardless of age, with a diagnosis of dementia for whom an assessment of functional status is performed and the results reviewed at least once within a 12-month period
Dementia: Neuropsychiatric Symptom Assessment	Percentage of patients, regardless of age, with a diagnosis of dementia and for whom an assessment of neuropsychiatric symptoms is performed and results reviewed at least once in a 12-month period
Dementia: Management of Neuropsychiatric Symptoms	Percentage of patients, regardless of age, with a diagnosis of dementia who have one or more neuropsychiatric symptoms who received or were recommended to receive an intervention for neuropsychiatric symptoms within a 12-month period
Dementia: Counseling Regarding Safety Concerns	Percentage of patients, regardless of age, with a diagnosis of dementia or their caregiver(s) who were counseled or referred for counseling regarding safety concerns within a 12-month period
Dementia: Counseling Regarding Risks of Driving	Percentage of patients, regardless of age, with a diagnosis of dementia or their caregiver(s) who were counseled regarding the risks of driving and the alternatives to driving at least once within a 12-month period
Dementia: Caregiver Education and Support	Percentage of patients, regardless of age, with a diagnosis of dementia whose caregiver(s) were provided with education on dementia disease management and health behavior changes *and* referred to additional sources for support within a 12-month period
Parkinson Disease: Annual Parkinson Disease Diagnosis Review	All patients with a diagnosis of Parkinson disease who had an annual assessment, including a review of current medications (e.g., medications that can produce Parkinson-like signs or symptoms) and a review for the presence of atypical features (e.g., falls at presentation and early in the disease course, poor response to levodopa, symmetry at onset, rapid progression [to Hoehn and Yahr stage 3 in 3 years], and lack of tremor or dysautonomia) at least annually

Measure Title	Measure Description
Parkinson Disease: Psychiatric Disorders or Disturbances Assessment	All patients with a diagnosis of Parkinson disease who were assessed for psychiatric disorders or disturbances (e.g., psychosis, depression, anxiety disorder, apathy, or impulse control disorder) at least annually
Parkinson Disease: Cognitive Impairment or Dysfunction Assessment	All patients with a diagnosis of Parkinson disease who were assessed for cognitive impairment or dysfunction at least annually
Parkinson Disease: Querying About Sleep Disturbances	All patients with a diagnosis of Parkinson disease (or caregivers, as appropriate) who were queried about sleep disturbances at least annually
Parkinson Disease: Rehabilitative Therapy Options	All patients with a diagnosis of Parkinson disease (or caregiver(s), as appropriate) who had rehabilitative therapy options (e.g., physical, occupational, or speech therapy) discussed at least annually
Parkinson Disease: Parkinson Disease Medical and Surgical Treatment Options Reviewed	All patients with a diagnosis of Parkinson disease (or caregiver(s), as appropriate) who had the Parkinson disease treatment options (e.g., nonpharmacological treatment, pharmacological treatment, or surgical treatment) reviewed at least once annually
Cataracts: Improvement in Patient's Visual Function Within 90 Days After Cataract Surgery	Percentage of patients aged 18 years and older in sample who had cataract surgery and had improvement in visual function achieved within 90 days after the cataract surgery, based on completing a preoperative and postoperative visual function survey
Cataracts: Patient Satisfaction Within 90 Days After Cataract Surgery	Percentage of patients aged 18 years and older in sample who had cataract surgery and were satisfied with their care within 90 days after the cataract surgery, based on completion of the Consumer Assessment of Healthcare Providers and Systems Surgical Care Survey
Initiation and Engagement of Alcohol and Other Drug Dependence (AOD) Treatment	Percentage of patients 13 years of age and older with a new episode of AOD dependence who received the following. Two rates are reported: 1. Percentage of patients who initiated treatment within 14 days of the diagnosis 2. Percentage of patients who initiated treatment and who had two or more additional services with an AOD diagnosis within 30 days of the initiation visit
Cervical Cancer Screening	Percentage of women 21-64 years of age who received one or more Pap tests to screen for cervical cancer
Chlamydia Screening for Women	Percentage of women 16-24 years of age who were identified as sexually active and who had at least one test for chlamydia during the measurement period
Use of Appropriate Medications for Asthma	Percentage of patients 5-64 years of age who were identified as having persistent asthma and were appropriately prescribed medication during the measurement period
Use of Imaging Studies for Low Back Pain	Percentage of patients 18-50 years of age with a diagnosis of low back pain who did not have an imaging study (plain X-ray, MRI, CT scan) within 28 days of the diagnosis
Preventive Care and Screening: Cholesterol—Fasting LDL-C Test Performed *and* Risk-Stratified Fasting LDL-C	Percentage of patients aged 20-79 years whose risk factors* have been assessed and a fasting LDL-C test has been performed *and* percentage of patients aged 20-79 years who had a fasting LDL-C test performed and whose risk-stratified fasting LDL-C is at or below the recommended LDL-C goal. *There are three criteria for this measure based on the patient's risk category: 1. Highest level of risk: CHD or CHD risk equivalent *or* 10-year Framingham risk >20% 2. Moderate level of risk: multiple (2+) risk factors *or* 10-year Framingham risk 10%-20% 3. Lowest level of risk: 0 or 1 risk factor *or* 10-year Framingham risk <10%
Preventive Care and Screening: Screening for High BP and Follow-Up Documented	Percentage of patients aged 18 years and older seen during the reporting period who were screened for high BP *and* a recommended follow-up plan is documented based on the current BP reading as indicated
Falls: Screening for Fall Risk	Percentage of patients 65 years of age and older who were screened for future fall risk at least once during the measurement period
Appropriate Follow-Up Interval for Normal Colonoscopy in Average-Risk Patients	Percentage of patients aged 50 to 75 years receiving a screening colonoscopy without biopsy or polypectomy who had a recommended follow-up interval of at least 10 years for repeat colonoscopy documented in their colonoscopy report
Consumer Assessment of Healthcare Providers and Systems for PQRS Clinician/Group Survey	• Getting timely care, appointments, and information • How well providers communicate • Patient's rating of provider • Access to specialists • Health promotion & education • Shared decision making • Health status/functional status • Courteous and helpful office staff • Care coordination • Communication between visits • Helping your patient to take medication as directed • Stewardship of patient resources

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Physician Quality Reporting System (PQRS) Measures

Measure Title	Measure Description
Cardiac Stress Imaging Not Meeting Appropriate Use Criteria: Preoperative Evaluation in Low-Risk Surgery Patients	Percentage of stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging, stress ECHO, cardiac CTA, or cardiac magnetic resonance performed in low-risk surgery patients 18 years or older for preoperative evaluation during the 12-month reporting period
Cardiac Stress Imaging Not Meeting Appropriate Use Criteria: Routine Testing After PCI	Percentage of all stress SPECT myocardial perfusion imaging, stress ECHO, cardiac CTA, and cardiovascular magnetic resonance performed in patients aged 18 years and older routinely after PCI, with reference to timing of test after PCI and symptom status
Cardiac Stress Imaging Not Meeting Appropriate Use Criteria: Testing in Asymptomatic, Low-Risk Patients	Percentage of all stress SPECT myocardial perfusion imaging, stress ECHO, cardiac CTA, and cardiovascular magnetic resonance performed in asymptomatic, low-CHD-risk patients 18 years and older for initial detection and risk assessment
Adult MDD: Coordination of Care of Patients with Specific Comorbid Conditions	Percentage of medical records of patients aged 18 years and older with a diagnosis of MDD and a specific diagnosed comorbid condition (diabetes, CAD, ischemic stroke, intracranial hemorrhage, CKD [stages 4 or 5], end-stage renal disease [ESRD], or CHF) being treated by another clinician with communication to the clinician treating the comorbid condition
Atrial Fibrillation (AF) and Atrial Flutter: Chronic Anticoagulation Therapy	Percentage of patients aged 18 years and older with a diagnosis of nonvalvular AF or atrial flutter whose assessment of the specified thromboembolic risk factors indicate one or more high-risk factors or more than one moderate-risk factor, as determined by CHADS2 risk stratification, who are prescribed warfarin *or* another oral anticoagulant drug that is FDA-approved for the prevention of thromboembolism
Pediatric Kidney Disease: Adequacy of Volume Management	Percentage of calendar months within a 12-month period during which patients aged 17 years and younger with a diagnosis of ESRD undergoing maintenance hemodialysis in an outpatient dialysis facility have an assessment of the adequacy of volume management from a nephrologist
Pediatric Kidney Disease: ESRD Patients Receiving Dialysis: Hemoglobin Level <10 g/dl	Percentage of calendar months within a 12-month period during which patients aged 17 years and younger with a diagnosis of ESRD receiving hemodialysis or peritoneal dialysis have a hemoglobin level <10 g/dl
Adult Kidney Disease: Catheter Use at Initiation of Hemodialysis	Percentage of patients aged 18 years and older with a diagnosis of ESRD who initiate maintenance hemodialysis during the measurement period, whose mode of vascular access is a catheter at the time maintenance hemodialysis is initiated
Adult Kidney Disease: Catheter Use for Greater Than or Equal to 90 Days	Percentage of patients aged 18 years and older with a diagnosis of ESRD receiving maintenance hemodialysis for ≥90 days whose mode of vascular access is a catheter
Adult Sinusitis: Antibiotic Prescribed for Acute Sinusitis (Overuse)	Percentage of patients aged 18 years and older with a diagnosis of acute sinusitis who were prescribed an antibiotic within 10 days after onset of symptoms
Adult Sinusitis: Appropriate Choice of Antibiotic: Amoxicillin with or without Clavulanate Prescribed for Patients with Acute Bacterial Sinusitis (Appropriate Use)	Percentage of patients aged 18 years and older with a diagnosis of acute bacterial sinusitis who were prescribed amoxicillin, with or without clavulanate, as a first-line antibiotic at the time of diagnosis
Adult Sinusitis: CT for Acute Sinusitis (Overuse)	Percentage of patients aged 18 years and older with a diagnosis of acute sinusitis who had a CT scan of the paranasal sinuses ordered at the time of diagnosis or received within 28 days after date of diagnosis
Adult Sinusitis: More Than One CT Scan Within 90 Days for Chronic Sinusitis (Overuse)	Percentage of patients aged 18 years and older with a diagnosis of chronic sinusitis who had more than one CT scan of the paranasal sinuses ordered or received within 90 days after the date of diagnosis
Maternity Care: Elective Delivery or Early Induction Without Medical Indication at ≥37 and <39 Weeks	Percentage of patients, regardless of age, who gave birth during a 12-month period who delivered a live singleton at ≥37 and <39 weeks of gestation completed who had elective deliveries or early inductions without medical indication
Maternity Care: Postpartum Follow-Up and Care Coordination	Percentage of patients, regardless of age, who gave birth during a 12-month period who were seen for postpartum care within 8 weeks of giving birth who received a breast feeding evaluation and education, postpartum depression screening, postpartum glucose screening for gestational diabetes patients, and family and contraceptive planning
TB Prevention for Psoriasis, Psoriatic Arthritis, and RA Patients on a Biological Immune Response Modifier	Percentage of patients whose providers are ensuring active TB prevention either through yearly negative standard TB screening tests or are reviewing the patient's history to determine if they have had appropriate management for a recent or prior positive test
HIV Viral Load Suppression	Percentage of patients, regardless of age, with a diagnosis of HIV with a HIV viral load <200 copies/ml at last HIV viral load test during the measurement year
Prescription of HIV Antiretroviral Therapy	Percentage of patients, regardless of age, with a diagnosis of HIV prescribed antiretroviral therapy for the treatment of HIV infection during the measurement year
HIV Medical Visit Frequency	Percentage of patients, regardless of age, with a diagnosis of HIV who had at least one medical visit in each 6-month period of the 24-month measurement period, with a minimum of 60 days between medical visits

Measure Title	Measure Description
Pain Brought Under Control Within 48 Hours	Patients aged 18 years and older who report being uncomfortable because of pain at the initial assessment (after admission to palliative care services) who report pain was brought to a comfortable level within 48 hours
Screening Colonoscopy Adenoma Detection Rate Measure	Percentage of patients aged 50 years or older with at least one conventional adenoma or colorectal cancer detected during screening colonoscopy
Rate of Carotid Artery Stenting (CAS) for Asymptomatic Patients, Without Major Complications (Discharged to Home by Postoperative Day 2)	Percentage of asymptomatic patients undergoing CAS who are discharged to home no later than postoperative day 2
Rate of Postoperative Stroke or Death in Asymptomatic Patients Undergoing CAS	Percentage of asymptomatic patients undergoing CAS who experience stroke or death after surgery while in the hospital
Rate of Postoperative Stroke or Death in Asymptomatic Patients Undergoing Carotid Endarterectomy (CEA)	Percentage of asymptomatic patients undergoing CEA who experience stroke or death after surgery while in the hospital
Rate of EVAR of Small or Moderate Nonruptured AAA Who Die While in Hospital	Percentage of patients undergoing endovascular repair of small or moderate AAA who die while in the hospital
HRS-3: Implantable Cardioverter-Defibrillator (ICD) Complications Rate	Patientsage with physician-specific risk-standardized rates of procedural complications after the first-time implantation of an ICD
Total Knee Replacement: Shared Decision Making: Trial of Conservative (Nonsurgical) Therapy	Percentage of patients regardless of age or gender undergoing a total knee replacement with documented shared decision making with discussion of conservative (nonsurgical) therapy (e.g., clavulanate anti-inflammatory drugs [NSAIDs], analgesics, weight loss, exercise, injections) before the procedure
Total Knee Replacement: Venous Thromboembolic and Cardiovascular Risk Evaluation	Percentage of patients regardless of age or gender undergoing a total knee replacement who are evaluated for the presence or absence of venous thromboembolic and cardiovascular risk factors within 30 days before the procedure (e.g., history of DVT, pulmonary embolism, MI, arrhythmia, and stroke)
Total Knee Replacement: Preoperative Antibiotic Infusion with Proximal Tourniquet	Percentage of patients regardless of age or gender undergoing a total knee replacement who had the prophylactic antibiotic completely infused before the inflation of the proximal tourniquet
Total Knee Replacement: Identification of Implanted Prosthesis in Operative Report	Percentage of patients regardless of age or gender undergoing a total knee replacement whose operative report identifies the prosthetic implant specifications, including the prosthetic implant manufacturer, the brand name of the prosthetic implant, and the size of each prosthetic implant
Anastomotic Leak Intervention	Percentage of patients aged 18 years and older who required an anastomotic leak intervention after gastric bypass or colectomy surgery
Unplanned Reoperation Within the 30-Day Postoperative Period	Percentage of patients aged 18 years and older who had any unplanned reoperation within the 30-day postoperative period
Unplanned Hospital Readmission Within 30 Days of Principal Procedure	Percentage of patients aged 18 years and older who had an unplanned hospital readmission within 30 days of principal procedure
Surgical Site Infection (SSI)	Percentage of patients aged 18 years and older who had an SSI
Patient-Centered Surgical Risk Assessment and Communication	Percentage of patients who underwent a nonemergency surgery who had their personalized risks of postoperative complications assessed by their surgical team before surgery using a clinical-data-based, patient-specific risk calculator and who received personal discussion of those risks with the surgeon
Optimizing Patient Exposure to Ionizing Radiation: Utilization of a Standardized Nomenclature for CT Imaging Description	Percentage of CT imaging reports for all patients, regardless of age, with the imaging study named according to a standardized nomenclature and the standardized nomenclature is used in institution's computer systems
Optimizing Patient Exposure to Ionizing Radiation: Count of Potential High-Dose Radiation Imaging Studies: CT and Cardiac Nuclear Medicine Studies	Percentage of CT and cardiac nuclear medicine (myocardial perfusion studies) imaging reports for all patients, regardless of age, that document a count of known previous CT (any type of CT) and cardiac nuclear medicine (myocardial perfusion) studies that the patient has received in the 12-month period before the current study
Optimizing Patient Exposure to Ionizing Radiation: Reporting to a Radiation Dose Index Registry	Percentage of total CT studies performed for all patients, regardless of age, that are reported to a radiation dose index registry *and* that include at a minimum selected data elements
Optimizing Patient Exposure to Ionizing Radiation: CT Images Available for Patient Follow-Up and Comparison Purposes	Percentage of final reports for CT studies performed for all patients, regardless of age, which document that Digital Imaging and Communications in Medicine (DICOM) format image data are available to nonaffiliated external health care facilities or entities on a secure, media-free, reciprocally searchable basis with patient authorization for at least a 12-month period after the study
Optimizing Patient Exposure to Ionizing Radiation: Search for Prior CT Studies Through a Secure, Authorized, Media-Free, Shared Archive	Percentage of final reports of CT studies performed for all patients, regardless of age, which document that a search for DICOM format images was conducted for prior patient CT imaging studies completed at nonaffiliated external health care facilities or entities within the past 12 months and are available through a secure, authorized, media-free, shared archive before an imaging study being performed
Optimizing Patient Exposure to Ionizing Radiation: Appropriateness: Follow-Up CT Imaging for Incidentally Detected Pulmonary Nodules According to Recommended Guidelines	Percentage of final reports for CT imaging studies of the thorax for patients aged 18 years and older with documented follow-up recommendations for incidentally detected pulmonary nodules (e.g., follow-up CT imaging studies needed or that no follow-up is needed) based at a minimum on nodule size *and* patient risk factors

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Physician Quality Reporting System (PQRS) Measures

Measure Title	Measure Description
Hemoglobin A_{1c} Test for Pediatric Patients	Percentage of patients 5-17 years of age with diabetes with a HbA_{1c} test during the measurement period
Attention-Deficit/Hyperactivity Disorder (ADHD): Follow-Up Care for Children Prescribed ADHD Medication	Percentage of children 6-12 years of age and newly dispensed a medication for ADHD who had appropriate follow-up care. Two rates are reported: 1. Percentage of children who had one follow-up visit with a practitioner with prescribing authority during the 30-day initiation phase 2. Percentage of children who remained on ADHD medication for at least 210 days and who, in addition to the visit in the initiation phase, had at least two additional follow-up visits with a practitioner within 270 days (9 months) after the initiation phase ended
Bipolar Disorder and Major Depression: Appraisal for Alcohol or Chemical Substance Use	Percentage of patients with depression or bipolar disorder with evidence of an initial assessment that includes an appraisal for alcohol or chemical substance use
HIV/AIDS: Medical Visit	Percentage of patients, regardless of age, with a diagnosis of HIV/AIDS with at least two medical visits during the measurement year with a minimum of 90 days between each visit
Pregnant Women Who Had HBsAg Testing	This measure identifies pregnant women who had a HBsAg (hepatitis B) test during their pregnancy
Depression Remission at 12 Months	Adult patients aged 18 years and older with major depression or dysthymia and an initial Patient Health Questionnaire (PHQ-9) score >9 who demonstrate remission at 12 months defined as PHQ-9 score <5. This measure applies to both patients with newly diagnosed and existing depression whose current PHQ-9 score indicates a need for treatment.
Depression Utilization of the PHQ-9 Tool	Adult patients aged 18 years and older with the diagnosis of major depression or dysthymia who have a PHQ-9 tool administered at least once during a 4-month period in which there was a qualifying visit
Maternal Depression Screening	Percentage of children who turned 6 months of age during the measurement year who had a face-to-face visit between the clinician and the child during child's first 6 months and who had a maternal depression screening for the mother at least once between 0 and 6 months of life
Hypertension: Improvement in BP	Percentage of patients aged 18-85 years of age with a diagnosis of hypertension whose BP improved during the measurement period
Closing the Referral Loop: Receipt of Specialist Report	Percentage of patients with referrals, regardless of age, for which the referring provider receives a report from the provider to whom the patient was referred
Functional Status Assessment for Knee Replacement	Percentage of patients aged 18 years and older with primary total knee arthroplasty who completed baseline and follow-up (patient-reported) functional status assessments
Functional Status Assessment for Hip Replacement	Percentage of patients aged 18 years and older with primary total hip arthroplasty who completed baseline and follow-up (patient-reported) functional status assessments
Functional Status Assessment for Complex Chronic Conditions	Percentage of patients aged 65 years and older with HF who completed initial and follow-up patient-reported functional status assessments
Children Who Have Dental Decay or Cavities	Percentage of children, aged 0-20 years, who have had tooth decay or cavities during the measurement period
Primary Caries Prevention Intervention as Offered by Primary Care Providers, Including Dentists	Percentage of children, aged 0-20 years, who received a fluoride varnish application during the measurement period
Adverse Drug Event Prevention and Monitoring: Warfarin Time in Therapeutic Range	Average percentage of time in which patients aged 18 years and older with atrial fibrillation who are on chronic warfarin therapy have international normalized ratio test results within the therapeutic range (i.e., TTR) during the measurement period
HIV/AIDS: RNA Control for Patients with HIV	Percentage of patients aged 13 years and older with a diagnosis of HIV/AIDS, with at least two visits during the measurement year, with at least 90 days between each visit, whose most recent HIV RNA level is <200 copies/ml
Child and Adolescent MDD: Suicide Risk Assessment	Percentage of patient visits for those patients aged 6-17 years with a diagnosis of MDD with an assessment for suicide risk
Adherence to Antipsychotic Medications for Individuals with Schizophrenia	Percentage of individuals at least 18 years of age as of the beginning of the measurement period with schizophrenia or schizoaffective disorder who had at least two prescriptions filled for any antipsychotic medication and who had a PDC of at least 0.8 for antipsychotic medications during the measurement period (12 consecutive months)
Adult Primary Rhegmatogenous Retinal Detachment Surgery: No Return to the Operating Room Within 90 Days of Surgery	Patients aged 18 years and older who had surgery for primary rhegmatogenous retinal detachment who did not require a return to the operating room within 90 days of surgery
Adult Primary Rhegmatogenous Retinal Detachment Surgery: Visual Acuity Improvement Within 90 Days of Surgery	Patients aged 18 years and older who had surgery for primary rhegmatogenous retinal detachment and achieved an improvement in their visual acuity, from their preoperative level, within 90 days of surgery in the operative eye
Amyotrophic Lateral Sclerosis (ALS) Patient Care Preferences	Percentage of patients found to have ALS who were offered assistance in planning for end-of-life issues (e.g., advance directives, invasive ventilation, hospice) at least once annually

Measure Title	Measure Description
Annual HCV Screening for Patients Who Are Active Injection Drug Users	Percentage of patients regardless of age who are active injection drug users who received screening for HCV infection within the 12-month reporting period
Cataract Surgery with Intraoperative Complications (Unplanned Rupture of Posterior Capsule Requiring Unplanned Vitrectomy)	Percentage of patients aged 18 years and older who had cataract surgery performed and had an unplanned rupture of the posterior capsule requiring vitrectomy
Cataract Surgery: Difference Between Planned and Final Refraction	Percentage of patients aged 18 years and older who had cataract surgery performed and who achieved a final refraction within ±1.0 diopters of their planned (target) refraction
Hepatitis C: Discussion and Shared Decision Making Surrounding Treatment Options	Percentage of patients aged 18 years and older with a diagnosis of hepatitis C with whom a physician or other qualified health care professional reviewed the range of treatment options appropriate to their genotype and demonstrated a shared decision-making approach with the patient. To meet the measure, there must be documentation in the patient record of a discussion between the physician or other qualified health care professional and the patient that includes all of the following: treatment choices appropriate to genotype, risks and benefits, evidence of effectiveness, and patient preferences toward treatment
Follow-Up After Hospitalization for Mental Illness	Percentage of discharges for patients 6 years of age and older who were hospitalized for treatment of selected mental illness diagnoses and who had an outpatient visit, an intensive outpatient encounter, or partial hospitalization with a mental health practitioner. Two rates are reported: 1. Percentage of discharges for which the patient received follow-up within 30 days of discharge 2. Percentage of discharges for which the patient received follow-up within 7 days of discharge
HRS-12: Cardiac Tamponade and/or Pericardiocentesis After Atrial Fibrillation Ablation	Rate of cardiac tamponade and/or pericardiocentesis after atrial fibrillation ablation This measure is reported as four rates stratified by age and gender: • Reporting age criteria 1: Females <65 years of age • Reporting age criteria 2: Males <65 years of age • Reporting age criteria 3: Females 65 years of age and older • Reporting age criteria 4: Males 65 years of age and older
HRS-9: Infection Within 180 Days of Cardiac Implantable Electronic Device (CIED) Implantation, Replacement, or Revision	Infection rate after CIED device implantation, replacement, or revision
Immunizations for Adolescents	Percentage of adolescents 13 years of age who had the recommended immunizations by their 13th birthday
Lung Cancer Reporting (Biopsy/Cytology Specimens)	Pathology reports based on biopsy and/or cytology specimens with a diagnosis of primary non–small-cell lung cancer classified into specific histologic type or classified as non–small-cell lung cancer not otherwise specified with an explanation included in the pathology report
Lung Cancer Reporting (Resection Specimens)	Pathology reports based on resection specimens with a diagnosis of primary lung carcinoma that include the pT category, pN category, and, for non–small cell lung cancer, histologic type
Melanoma Reporting	Pathology reports for primary malignant cutaneous melanoma that include the pT category and a statement on thickness and ulceration and for pT1, mitotic rate
Optimal Asthma Control	Patients aged 5-50 years (pediatrics aged 5-17 years) whose asthma is well controlled as demonstrated by one of three age-appropriate patient-reported outcome tools
Postprocedural Optimal Medical Therapy Composite (Percutaneous Coronary Intervention [PCI])	Percentage of patients aged 18 years and older for whom PCI is performed who are prescribed optimal medical therapy at discharge
One-Time Screening for HCV for Patients at Risk	Percentage of patients aged 18 years and older with one or more of the following: a history of injection drug use, receipt of a blood transfusion before 1992, receiving maintenance hemodialysis, *or* birthdate in the years 1945-1965 who received a one-time screening for HCV infection
Hepatitis C: Screening for Hepatocellular Carcinoma (HCC) in Patients with Cirrhosis	Percentage of patients aged 18 years and older with a diagnosis of chronic hepatitis C cirrhosis who underwent imaging with either ultrasonography, contrast-enhanced CT, or MRI for HCC at least once within the 12-month reporting period
Tobacco Use and Help with Quitting Among Adolescents	Percentage of adolescents 12 to 20 years of age with a primary care visit during the measurement year for whom tobacco use status was documented and received help with quitting if identified as a tobacco user
Adult Kidney Disease: Referral to Hospice	Percentage of patients aged 18 years and older with a diagnosis of ESRD who withdraw from hemodialysis peritoneal dialysis who are referred to hospice care
Anesthesiology Smoking Abstinence	Percentage of current smokers who abstain from cigarettes before anesthesia on the day of elective surgery or procedure

Continued on following page

Physician Quality Reporting System (PQRS) Measures

Measure Title	Measure Description
Appropriate Follow-Up Imaging for Incidental Abdominal Lesions	Percentage of final reports for abdominal imaging studies for asymptomatic patients aged 18 years and older with one or more of the following noted incidentally with follow-up imaging recommended: • Liver lesion ≤0.5 cm • Cystic kidney lesion <1.0 cm • Adrenal lesion ≤1.0 cm
Appropriate Follow-Up Imaging for Incidental Thyroid Nodules in Patients	Percentage of final reports for CT or MRI studies of the chest or neck or ultrasonography of the neck for patients aged 18 years and older with no known thyroid disease with a thyroid nodule <1.0 cm noted incidentally with follow-up imaging recommended
Appropriate Treatment of Methicillin-Sensitive *Staphylococcus aureus* (MSSA) Bacteremia	Percentage of patients with sepsis due to MSSA bacteremia who received beta-lactam antibiotic (e.g., nafcillin, oxacillin, or cefazolin) as definitive therapy
Opioid Therapy Follow-Up Evaluation	All patients aged 18 years and older prescribed opiates for longer than 6 weeks' duration who had a follow-up evaluation conducted at least every 3 months during opioid therapy documented in the medical record
Clinical Outcome Postendovascular Stroke Treatment	Percentage of patients with an mRs score of 0 to 2 at 90 days after endovascular stroke intervention
Psoriasis: Clinical Response to Oral Systemic or Biologic Medications	Percentage of psoriasis patients receiving oral systemic or biologic therapy who meet minimal physician- or patient-reported disease activity levels. It is implied that establishment and maintenance of an established minimum level of disease control as measured by physician- and/or patient-reported outcomes will increase patient satisfaction with and adherence to treatment.
Depression Remission at 6 Months	Adult patients aged 18 years and older with major depression or dysthymia and an initial PHQ-9 score >9 who demonstrate remission at 6 months defined as a PHQ-9 score <5. This measure applies to both patients with newly diagnosed and existing depression whose current PHQ-9 score indicates a need for treatment.
Documentation of Signed Opioid Treatment Agreement	All patients aged 18 years and older prescribed opiates for longer than 6 weeks' duration who signed an opioid treatment agreement at least once during opioid therapy documented in the medical record
Door to Puncture Time for Endovascular Stroke Treatment	Percentage of patients undergoing endovascular stroke treatment who have a door to puncture time of <2 hours
Evaluation or Interview for Risk of Opioid Misuse	All patients aged 18 years and older prescribed opiates for longer than 6 weeks' duration evaluated for risk of opioid misuse using a brief validated instrument (e.g., Opioid Risk Tool, SOAAP-R) or patient interview documented at least once during opioid therapy in the medical record
Emergency Medicine: Emergency Department Utilization of CT for Minor Blunt Head Trauma for Patients Aged 18 Years and Older	Percentage of emergency department visits for patients aged 18 years and older who presented within 24 hours of a minor blunt head trauma with a Glasgow Coma Scale (GCS) score of 15 and who had a head CT for trauma ordered by an emergency care provider who have an indication for a head CT
Emergency Medicine: Emergency Department Utilization of CT for Minor Blunt Head Trauma for Patients Aged 2 through 17 Years	Percentage of emergency department visits for patients aged 2-17 years who presented within 24 hours of a minor blunt head trauma with a GCS score of 15 and who had a head CT for trauma ordered by an emergency care provider who are classified as low risk according to the Pediatric Emergency Care Applied Research Network prediction rules for traumatic brain injury
Rate of Open Repair of Ascending AAA Where Patients Are Discharged Alive	Percentage of patients undergoing open repair of AAA who are discharged alive
Osteoporosis Management in Women Who Had a Fracture	Percentage of women aged 50-85 years who suffered a fracture and who either had a bone mineral density test or received a prescription for a drug to treat osteoporosis
Overuse of Neuroimaging for Patients with Primary Headache and a Normal Neurological Examination	Percentage of patients with a diagnosis of primary headache disorder for whom advanced brain imaging was not ordered
Varicose Vein Treatment with Saphenous Ablation: Outcome Survey	Percentage of patients treated for varicose veins (CEAP C2-S) who are treated with saphenous ablation (with or without adjunctive tributary treatment) that report an improvement on a disease-specific patient reported outcome survey instrument after treatment
Appropriate Assessment of Retrievable Inferior Vena Cava (IVC) Filters for Removal	Percentage of patients in whom a retrievable IVC filter is placed who, within 3 months postplacement, have a documented assessment for the appropriateness of continued filtration, device removal, or the inability to contact the patient with at least two attempts
Performing Cystoscopy at the Time of Hysterectomy for Pelvic Organ Prolapse to Detect Lower Urinary Tract Injury	Percentage of patients who undergo cystoscopy to evaluate for lower urinary tract injury at the time of hysterectomy for pelvic organ prolapse
Perioperative Antiplatelet Therapy for Patients Undergoing Carotid Endarterectomy	Percentage of patients undergoing carotid endarterectomy who are taking an antiplatelet agent (aspirin or clopidogrel or equivalent such as aggrenox/tiglacor, etc.) within 48 hours before surgery and are prescribed this medication at hospital discharge after surgery
Perioperative Temperature Management	Percentage of patients, regardless of age, who undergo surgical or therapeutic procedures under general or neuraxial anesthesia of 60 minutes' duration or longer for whom at least one body temperature ≥35.5° C (or 95.9° F) was recorded within the 30 minutes immediately before or the 15 minutes immediately after anesthesia end time

Measure Title	Measure Description
Photodocumentation of Cecal Intubation	The rate of screening and surveillance colonoscopies for which photodocumentation of landmarks of cecal intubation is performed to establish a complete examination
Postanesthetic Transfer of Care Measure: Procedure Room to a Postanesthesia Care Unit (PACU):	Percentage of patients, regardless of age, who are under the care of an anesthesia practitioner and are admitted to a PACU in which a postanesthetic formal transfer of care protocol or checklist that includes the key transfer of care elements is used
Postanesthetic Transfer of Care: Use of Checklist or Protocol for Direct Transfer of Care from Procedure Room to Intensive Care Unit (ICU)	Percentage of patients, regardless of age, who undergo a procedure under anesthesia and are admitted to an ICU directly from the anesthetizing location, who have a documented use of a checklist or protocol for the transfer of care from the responsible anesthesia practitioner to the responsible ICU team or team member
Pelvic Organ Prolapse: Preoperative Assessment of Occult Stress Urinary Incontinence	Percentage of patients undergoing appropriate preoperative evaluation for the indication of stress urinary incontinence per ACOG/AUGS/AUA guidelines
Pelvic Organ Prolapse: Preoperative Screening for Uterine Malignancy	Percentage of patients who are screened for uterine malignancy before surgery for pelvic organ prolapse
Prevention of Postoperative Nausea and Vomiting (PONV)—Combination Therapy	Percentage of patients, aged 18 years and older, who undergo a procedure under an inhalational general anesthetic, *and* who have three or more risk factors for PONV, who receive combination therapy consisting of at least two prophylactic pharmacologic antiemetic agents of different classes preoperatively or intraoperatively
Preventive Care and Screening: Unhealthy Alcohol Use: Screening and Brief Counseling	Percentage of patients aged 18 years and older who were screened at least once within the last 24 months for unhealthy alcohol use using a systematic screening method *and* who received brief counseling if identified as an unhealthy alcohol user
Proportion of Patients Sustaining a Bladder Injury at the Time of Any Pelvic Organ Prolapse Repair	Percentage of patients undergoing any surgery to repair pelvic organ prolapse who sustains an injury to the bladder recognized either during or within 1 month after surgery
Proportion of Patients Sustaining a Major Viscus Injury at the Time of Any Pelvic Organ Prolapse Repair	Percentage of patients undergoing surgical repair of pelvic organ prolapse that is complicated by perforation of a major viscus at the time of index surgery that is recognized intraoperative or within 1 month after surgery
Proportion of Patients Sustaining a Ureter Injury at the Time of Any Pelvic Organ Prolapse Repair	Percentage of patients undergoing a pelvic organ prolapse repair who sustain an injury to the ureter recognized either during or within 1 month after surgery
Quality of Life Assessment for Patients with Primary Headache Disorders	Percentage of patients with a diagnosis of primary headache disorder whose health-related quality of life (HRQoL) was assessed with a tool(s)* during at least two visits during the 12-month measurement period *and* whose HRQoL score stayed the same or improved
Radiation Consideration for Adult CT: Utilization of Dose-Lowering Techniques	Percentage of final reports for patients aged 18 years and older undergoing CT with documentation that one or more of the following dose reduction techniques were used: • Automated exposure control • Adjustment of the mA and/or kV according to patient size • Use of iterative reconstruction technique
Rate of Surgical Conversion from Lower Extremity Endovascular Revascularization Procedure	Inpatients assigned to endovascular treatment for obstructive arterial disease, percentage of patients who undergo unplanned major amputation or surgical bypass within 48 hours of the index procedure
Statin Therapy for the Prevention and Treatment of Cardiovascular Disease	Percentage of the following patients—all considered at high risk of cardiovascular events—who were prescribed or were on statin therapy during the measurement period: • Adults aged ≥21 years who were previously found to have or currently have an active diagnosis of clinical atherosclerotic cardiovascular disease; *or* • Adults aged ≥21 years with a fasting or direct LDL-C level ≥190 mg/dl; *or* • Adults aged 40-75 years with a diagnosis of diabetes with a fasting or direct LDL-C level of 70-189 mg/dl
Age-Appropriate Screening Colonoscopy	Percentage of patients >85 years of age who received a screening colonoscopy from January 1 to December 31

AIDS, Acquired immunodeficiency syndrome; *CTA,* computed tomography angiography; *CT,* computed tomography; *ECG,* electrocardiogram; *GnRH,* gonadotropin-releasing hormone; *HIV,* human immunodeficiency virus; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging; *pT,* primary tumor; *pN,* regional lymph nodes; *RNA,* ribonucleic acid; *tPA,* tissue plasminogen activator.

From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.

Appendix VIII

Palliative Care

According to the American Academy of Hospice and Palliative Medicine (AAHPM), palliative care involves "the **relieving of symptoms** of a disease or disorder while aiming to maintain the highest possible **quality of life** for patients" and their families. This entails making every day the best day possible in the setting of serious illness, often requiring **goals of care** discussions with patients and their family members. Palliative care is appropriate at any age and at any stage of serious illness, *not* only at the end of life, and can be employed at the same time as treatments and life-prolonging therapies, such as chemotherapy, radiation therapy, or hemodialysis. The World Health Organization (WHO) adds that a palliative care approach:

- Affirms life and regards dying as a normal process
- Intends neither to hasten nor to postpone death
- Integrates psychological and spiritual aspects of patient care
- Offers a **support system** to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and after the patient's death

A palliative care team may involve chaplains, doctors, nurse practitioners, nurses, pharmacists, physician assistants, and social workers. Keys to a successful family meeting for cancer patients are summarized in Box 1.

PRIMARY PALLIATIVE CARE

According to Quill and Abernethy (2013), all medical providers, including primary care and specialists, should possess core symptom management and **communication skills** for providing primary palliative care, not necessarily requiring a palliative care specialist. These areas of proficiency should include:

- Basic discussions about patient goals, quality of life, advance care planning, and prognosis
- Recognizing the importance of social, cultural, and spiritual aspects of patient care
- Basic symptom management of pain, nausea, dyspnea, and fatigue
- Basic management of depression and anxiety

The rationale for obtaining and employing these skills is to embrace the excellent opportunity for early palliative care discussions by providers that already have a working relationship and knowledge of their patients. Key points in addressing the needs of the family are summarized in Box 2. Palliative care should be considered for any patient living with a progressive, chronic medical condition, including cancer, heart or lung disease, dementia, renal or liver failure, or stroke with significant functional impairment. Personal and external influences concerning preferred place of care are illustrated in Fig. 1. Kelley and Morrison (2015) point out that over 80% of advanced cancer patients experience pain and over 90% of advanced

BOX 1 Keys to a Successful Family Meeting

One of an oncology clinician's most difficult tasks is to conduct a successful family meeting when the burden of disease-directed therapies exceeds the benefits. Although chemotherapy or radiation might no longer offer benefit, it is never true that "there is nothing more we can do for you." The following steps increase the chance that the meeting will enhance communication among clinicians, patients, and family members; relieve concerns of abandonment; enhance trust; and provide a conversational template for the tough times to come.

1. **Schedule a Premeeting (Actual or Virtual) and Consider the Following Questions:**
   - A. Who needs to be there (which family members and which members of the clinical team)?
   - B. What is the realistic prognosis or functional goal for the patient?
   - C. Who will run the meeting? How can others help (e.g., the palliative care clinicians or the social worker)?
   - D. Who will stay with the patient and family to debrief?
2. **During the Meeting:**
   - A. Everyone must be seated.
   - B. Introduce everyone present.
   - C. ASK–tell–ask:
     - i. How do you think you (or "the patient") is/are doing?
     - ii. What changes have you seen in the last (days, weeks, months)?
     - iii. What are you hoping for? And what else?
     - iv. What are you most concerned about? What are your worst fears?
     - v. How can we help?
   - D. Ask–TELL–ask:
     - i. Answer their questions.
     - ii. Provide key medical information but AVOID giving medical details that obscure the big picture.
       - Example: The (disease) is clearly progressing despite our best efforts. In my best judgment, s/he has only (days, weeks, months) of good time left. S/He may well live longer, but this is the time when s/he will have the most energy, think the most clearly, and be most him/herself.
     - iii. STOP TALKING.
       - Counting silently to 20 helps.
     - iv. Respond to their grief.
   - E. Ask–tell–ASK:
     - i. What do you still want to accomplish during your life?
     - ii. What might be left undone if you were to die today?
     - iii. What legacy do you want to leave to your family?
     - iv. What do you want your children and grandchildren to remember about you?
     - v. How can we help NOW?
3. **After the Meeting:**
   - A. Review with your team how everyone is doing.
   - B. Make a plan for who will follow up next with the family.
   - C. Success is measured by how much they trust you and how little they feel abandoned. Feeling bad is normal and expected, both on your part and theirs; it does not mean that you were not successful.

From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

BOX 2 Addressing the Needs of the Family

During the last weeks to months of the patient's life, office visits become impractical. Regular contact by telephone, supplemented, when possible, by one or more home visits, retains the connection that patients and families need with their primary treatment team. Clinicians also can promote continuity and minimize feelings of abandonment by collaborating with the home care or hospice nurses and, as requested, with the social workers who are part of the home care team. Praising the family caregivers for the work they are doing, helping them to anticipate upcoming problems and make contingency plans, and checking in with them at regular intervals promote timely identification and, when possible, resolution of new problems.

Many family members and medical staff, as well as trainees, have never seen anyone die an expected death outside an intensive care unit. A clinician who is familiar with the dying process can be a crucial source of information and comfort. For inpatients, the clinician works with the nursing team caring for the patient and serves as an attentive observer, striving to provide maximum comfort. Because clinical status and comfort level can change rapidly and frequently even in seemingly stable patients at the end of life, it can be helpful to make two or more visits a day to patients to monitor their comfort through reports from nursing and family, to answer questions, and to educate professional and family caregivers as to what they should expect in the last days.

Patients who were formerly alert and communicative usually become less so. They are apparently still comforted by the touch and voices of those they love and might even emerge from what seemed to be an unconscious state to greet a welcome newcomer. I tell families that to me, it is as though the patient lives in a house with many rooms, a mansion. As they come closer to dying, the patient moves farther and farther back in the house, and it is more and more effort for them to greet callers at the front of the house. But the callers are still welcome, as are their voices and conversation. I ask families to let patients know they have arrived and then to add that patients should not feel obliged to speak to them. Patients can also be asked to provide a hand squeeze or other sign of recognition. With close family, I discuss the "Five Things" (see the section of the chapter titled "Social Causes") and suggest that they find the time to share with the patient any of those sentiments they believe would be appropriate.

I reassure families that we know that dying patients are rarely hungry or thirsty and that moistening the mouth is all that is needed. If necessary, I review the burdens of hydration (see the section titled "Xerostomia"). I also explain about Cheyne-Stokes breathing and that it does not indicate that the patient is gasping for breath. I also ask them to feel free to let us know if the patient seems uncomfortable or develops noisy breathing because we want to address any source of discomfort as rapidly as possible. I offer the services of chaplaincy, and I am alert to whether a social worker would be helpful, if chaplains and social workers are not already involved. Many family members do not know that this kind of help is available to them in the hospital.

If the family has not done so already, I urge them to choose a funeral home and make all the necessary arrangements before the patient has actually died, to free themselves of that task when the death occurs. Families often ask how they will know that the patient is dying. I ask them to look for a marked decrease in urine output (in a Foley bag or diapers), cooling of the arms and legs, and new pallor or mottling of the skin. Some patients experience fecal incontinence as they die, so if hospice is not involved and the patient is at home, I alert the family to this possibility.

Supporting the Ward Personnel and the House Staff

To decrease potential feelings of guilt and anxiety, I review with all team members the history of the illness, the limits of the treatments that remain, the burdens of those treatments, and, when appropriate, the limits the patient has placed on further supportive measures. I also remind them that despite our best efforts, patients still die, and it is no one's fault. I also suggest things they can do that will enhance the patient's last days and that will further the healing process of the survivors.

During the hospitalizations that lead to death and after the death itself, I try to dispel any misconceptions they have about their "fault" for the death and to praise the work they did to make the dying person as comfortable as possible. This kind of support goes a long way toward enabling young physicians and ward staff to recover from the pain they experience when a patient dies and to allow themselves to feel a sense of satisfaction for a job well done.

From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

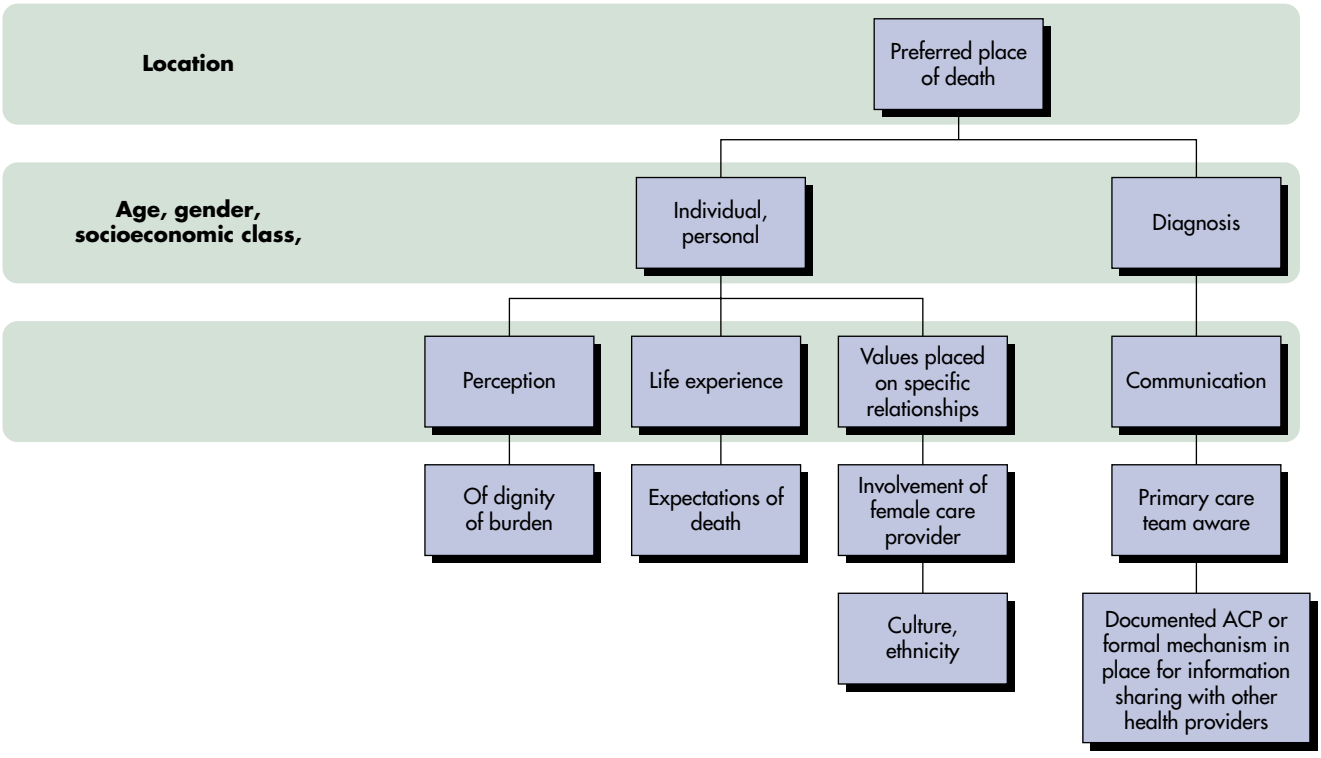

FIG. 1 Personal and external influences concerning preferred place of care. *ACP,* Advance care planning. (From Fillit HM: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 8, Philadelphia, 2017, Elsevier.)

heart failure patients experience dyspnea, so early identification and proficiency in symptom management are imperative.

SPECIALTY PALLIATIVE CARE

Involvement of a palliative care specialist with additional training or expertise may be required in more complex situations involving complicated family dynamics; ethical issues, including but not limited to medical futility, voluntary stopping of eating and drinking (VSED), and palliative sedation; uncontrolled existential distress; and refractory symptom management. Fig. 2 illustrates an algorithm for treatment of agitation in the last days of life. Palliative care specialists also work in specialty clinics alongside a patient's oncologist, cardiologist, or pulmonologist. Many of these specialists have completed fellowship training and are recognized with board certification by the American Board of Medical Specialties (ABMS).

INITIATING PRIMARY PALLIATIVE CARE

There's no perfect time to start thinking about palliative care for a patient, but if the "surprise question" of "would you be **surprised** if your patient died in the next 12 months?" answer is "no," then now may be a good time. Other situations suggesting appropriateness for a palliative care discussion may be:

- New serious diagnoses (e.g., cancer, COPD, heart failure, advanced dementia)
- Irreversible decline of a known illness
- Drastic changes in symptoms
- Changes in functional status (e.g., immobility, activities of daily living, weight loss)
- Treatment or cure failure
- Change in setting (e.g., home → hospital → home or nursing facility)

Palliative care often begins with **goals of care** discussions with the patient, family, or friends. The patient should be **asked permission** to initiate these discussions and allowed the opportunity to have his or her support system present. Ideally, the patient's **durable power of attorney for health care** (also known as a health care proxy or health care surrogate) is present for these discussions to be best informed what the patient's instructions would be if the patient were unable to verbalize with the health care providers.

GOALS OF CARE/DELIVERING SERIOUS NEWS

Good communication is one of the foundations of a palliative care approach. Practicing these skills is the only way to improve and become comfortable delivering serious news and having proficient goals of care and family meetings. There are several approaches and variations of formats for these discussions throughout the literature.

1. Ask permission to have a serious news discussion.
   a. "How do you feel about discussing your health issues at this time?"
   b. "What are you hoping to talk about today?"
   c. "What other family or friends would like here during these discussions?"
2. Get the patient's story.
   a. "What do you know about your health situation?"
   b. "Tell me more about…"
   c. "How is your illness affecting your life?"
   d. "Where do you get your strength or support?"

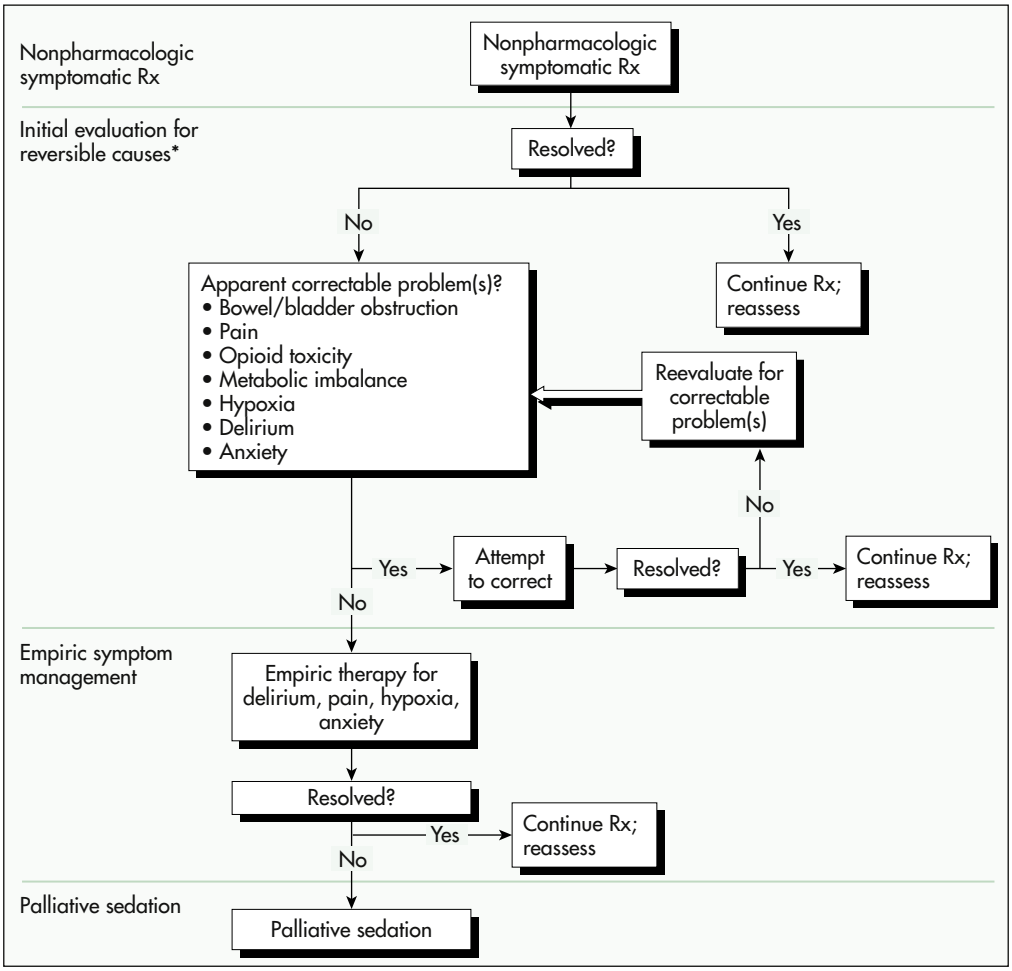

FIG. 2 Algorithm for treatment of agitation in the last days of life. *Guided by patient/family wishes and burden versus benefit. *Rx,* Prescription. (From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.)

- . Give the medical story after receiving permission to fill in any medical information gaps.
  1. Give a forewarning to prepare the patient for serious news, such as: "I wish we had better news but we're worried…"
  2. Practice silence, silence, and more silence. Let the patient break the silence.
  3. "Is this information surprising for you to hear?"
  4. "Knowing this information, what's most important to you going forward?"
  5. "What path going forward makes the most sense for you?"
  6. Offer a **best case/worst case scenario.**
  7. Acknowledge and validate emotions by patient and family: "I cannot imagine how difficult this must be for you."
- . Ask permission to make a recommendation based on patient's priorities and goals.
  1. "Based on what you've told me is important to you, I recommend…"
  2. Consider a time trial for an intervention (e.g., dialysis, feeding tube), if necessary.
  3. Promise continued support to patient and family.

General communication pearls:

- Ask open-ended questions as often as possible.
- Use the teach back method as you go—"In your own words, what did you take away from our discussion?"
- The patient and family should spend more time talking than the provider.
- Question, reflect, and summarize back in the patient's own words.
- Obtaining substituted judgment from a health care proxy—"Given her current medical condition, what would be most important to your loved one?"

PROGNOSTICATION

Prognostication is not an exact science but can be very useful to the patient's medical decision-making process. Life expectancy can be estimated using known disease trajectories and recent changes in a patient's functional capacity, including ambulation, cognition, weight, and verbalization abilities. If these changes have taken place over weeks, and the underlying cause of the decline is not reversed, the patient likely has "in the weeks range" to live. It is not recommended that a specific number of weeks be included in the prognosis. The "surprise question" mentioned above has been shown to provide useful information to providers when attempting prognostication.

ADVANCE CARE PLANNING

Advance care planning is a process and discussion regarding a patient's wishes about what is wanted and not wanted in regard to health care under certain circumstances. The goal is to maintain patient autonomy while defining a patient's personal definition of an acceptable quality of life. Advance care planning includes:

- Code status discussion.
- Advance directives (e.g., Five Wishes) completion—legal document that tells an individual's doctor and family members what kind of care the individual would like to have if he or she becomes unable to make medical decisions.
  1. Includes living will and durable power of attorney for health care/health care proxy.
  2. No lawyer is required.
- Medical Orders for Life-Sustaining Treatment (MOLST) form completion—a physician order for end-of-life treatments for seriously ill patients that should be placed in the chart and be very visible to EMTs/paramedics who enter a patient's home.

BASIC PAIN MANAGEMENT

Primary care providers may choose to treat patients with pain associated with their serious or terminal illness, such as cancer syndromes. Chronic pain management is covered elsewhere in this text but here are a few "pearls":

- Evaluate pain in all patients using a 0 to 10 scoring scale.
- Assess the patient's goal for an acceptable pain level.
- "Total pain," caused by a combination of physical, emotional, spiritual, and psychological pain, is usually refractory to escalating opioid doses.
- When pain is chronic and opioids are required, long-acting preparations should be used after a total required daily dose is determined.
- PRN doses of short-acting opioids should be 10% to 15% of the total daily dose.
- When rotating opioids, calculate a 24-hour requirement to "oral morphine equivalents" (OMEs) and then use a standard conversion table (see the Chronic Pain Management chapter in this text).
- When rotating opioids, consider reducing the equianalgesic dose by 25% to 50% to account for "incomplete cross-tolerance."
- Patient-controlled analgesia (PCA) has minimal risk for overdose or respiratory depression because the patient will fall asleep before he or she can administer a toxic dose.

When considering buprenorphine, ketamine, or methadone for pain, patients would likely benefit from referral to a pain management or palliative care specialist.

PSYCHOSOCIAL AND SPIRITUAL CARE

Palliative care includes attentive psychosocial and spiritual care. Primary providers should be proficient in assessing and treating anxiety and depression for seriously ill patients. Patients often ask, "Why is this happening to me?" When asked "Where do you find your strength during difficult times?" patients may answer "God" or "My faith." It is important to explore patients' spiritual needs to assist finding meaning in their illness, which may improve coping skills. Chaplains are excellent resources to assist with patient reconciliation issues with self, others, and God.

HOSPICE TRANSITION

At some point, most palliative care patients continue to decline clinically and functionally and may benefit from hospice care. Hospice is a specific type of palliative care for seriously ill patients with likely life expectancy of less than 6 months if the disease process runs its natural course and is deemed irreversible and incurable. Common misconceptions about hospice are summarized in Box 3. Hospice care can be provided at a hospice facility, hospital, or nursing home, or in the patient's home. Medicare-mandated hospice services are summarized in Box 4.

BOX 3 Common Misconceptions about Hospice

Patients enrolling in hospice must choose not to be resuscitated. Patients do not have to relinquish resuscitation to enroll in hospice. After they and their families fully understand the implications of the resuscitation, most patients elect not to be resuscitated.

Patients enrolled in hospice lose their primary physicians. The referring attending physician continues to direct and approve all the patient's care.

Hospice patients cannot be hospitalized and remain enrolled in hospice. Any hospice patient can be admitted to an acute, inpatient level of care to control a distressing symptom. Hospices can admit patients to contract beds in acute care hospitals or to their own inpatient facilities.

Hospice patients cannot participate in research projects while enrolled in hospice. Hospice patients have the right to participate in research studies. Hospice ethics and research committees usually evaluate the burden versus the benefit of the research for the patient, family, and hospice staff.

Hospice nursing personnel do not provide sophisticated care. Hospice personnel provide expert palliative care that requires astute assessment and expert intervention tailored to the patient and family goals.

Patients can "use up" their hospice eligibility, so it is important not to enroll them too soon. Patients are initially certified for 3 months of service, after which their physician and the hospice medical director are asked to recertify them indefinitely, at 2-month intervals. Patients who choose to revoke the hospice benefit to seek life-prolonging therapies may choose to reenroll if their goals change.

Patients must have a live-in caregiver to enroll in hospice. With appropriate safeguards (e.g., "lock boxes" to provide access in emergencies and daily phone contact), hospice care can be safely provided to patients who live alone.

From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

BOX 4 Medicare-Mandated Hospice Services

Practitioners Available

Medical director, nurses, social workers, home health aides, chaplains, volunteers, administrative personnel, medical consultations, occupational therapy, physical therapy, speech therapy, bereavement counseling

Palliative Treatment of Terminal Illness

Prescription medications
Durable medical equipment and supplies
Oxygen
Radiation and chemotherapy
Laboratory and diagnostic procedures

Other Benefits

Transportation when medically necessary for changes in level of care
When needed, continuous care at home or in a skilled nursing facility or inpatient setting
Respite care (care in a nursing facility that provides a "respite" for the caregivers)

Data from Medicare Hospice Regulations: 42 Codes of Federal Regulations, Part 418, 1993. From Niederhuber JE: *Abeloff's clinical oncology,* ed 6, Philadelphia, 2020, Elsevier.

PALLIATIVE CARE RESOURCES & REFERENCES

- American Academy of Hospice and Palliative Medicine (AAHPM).
- Back A, Arnold R, Tulsky J. *Mastering communication with seriously ill patients,* 2009, Cambridge University Press.
- Center for Advancement of Palliative Care (CAPC).
- Five Wishes® (agingwithdignity.org)—living will document.
- Kelley & Morrison: Palliative care for the seriously ill, *NEJM* 373;747, 2015.
- Medicare.gov: How hospice works. Available at medicare.gov/what-medicare-covers/what-part-a-covers/how-hospice-works.
- Palliative Care Network of Wisconsin (PCNOW)—Fast Facts. Available at www.mypcnow.org/fast-facts/.
- Quill & Abernethy: Generalist plus specialist palliative care—creating a more sustainable model, *NEJM* 368;13, 2013.
- Vital Talk (vitaltalk.org): Providing trainings to teach providers communication skills for discussing serious illness.

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ALG Appendix IX

Preoperative Evaluation

BASIC INFORMATION

DEFINITION

Preoperative evaluation is the clinical risk evaluation for patients undergoing surgery. It is an overall assessment of the patient's health and surgery's risk. The goal of the assessment is not to "clear" the patient for the surgery, because there is always some level of risk, but to provide accurate preoperative risk stratification and implement possible risk reduction strategies. Preoperative evaluation should also include functional assessment and determining social support. It also provides an opportunity for discussion and helps to alleviate the patient's anxiety before surgery.

SYNONYMS

Preoperative evaluation and risk reduction
Risk reduction in patients undergoing invasive procedures
Preoperative clearance

ICD-10CM CODES

Z01.810 Encounter for preprocedural cardiovascular examination
Z01.811 Encounter for preprocedural respiratory examination
Z01.812 Encounter for preprocedural laboratory examination
Z01.818 Encounter for other preprocedural examination

EPIDEMIOLOGY & DEMOGRAPHICS

The number of outpatient surgical procedures performed in the U.S. has been gradually increasing over the years.

Some studies have shown the benefits of preoperative testing whereas others have shown no added benefit. Lack of added benefit has been particularly true for otherwise healthy individuals: The prevalence of significant unrecognized disease and the predictive value of tests are both low for this population, leading to an excess of false-positive tests.

Certain risk factors do exist that may be helpful: The nature and extent of surgery appear to play a role, as do increasing age, exercise capacity, and certain medications. Additionally, patients with certain preexisting conditions such as diabetes may benefit from adjustments to their insulin preoperatively, for instance. The primary care physician may be best suited to adjust medications. Table 1 describes stratification of risk of common noncardiac surgical procedures.

Preoperative evaluation offers an excellent opportunity to reach out to patients about other preventive, screening, and routine health care issues as well. The primary care physician is uniquely poised to provide an accurate assessment and risk stratification of patients and to develop care plans for follow-up. This information can then be used to help surgeons counsel patients and guide patients' decision making.

PEAK INCIDENCE: When there are adverse consequences from surgery, cardiovascular complications account for the majority of morbidity and mortality in patients. Perioperative myocardial infarctions (PMIs) are one of the most important predictors of short- and long-term morbidity and mortality associated with surgery. The highest incidence of PMI is in the first 3 to 5 days after surgery.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The history, physical, and other studies need to assess the risks for myocardial infarction, arrhythmias, heart failure, endocarditis, stroke, venous thrombosis and pulmonary embolism, prolonged mechanical ventilation and respiratory failure, hemorrhage, diabetic acidosis, renal or hepatic failure, and infection.

DX DIAGNOSIS

WORKUP (FIG. 1)

HISTORY: A thorough medical history is the most valuable tool. Assess the urgency of the surgical procedure. A conversation with the surgical team is helpful for urgent and emergent procedures.

Some standard screening questionnaires have been adapted to help identify patients who would benefit from formal preoperative evaluation.

- Age is important to consider because age is often associated with an increasing number of comorbidities, which are in turn associated with an increase in perioperative risk.
- All patients should be asked about their exercise capacity before surgery. One way to assess functional capacity is in metabolic equivalents (METs) (Table 2). Studies have shown that those who have a low exercise capacity have twice as much risk for postoperative complications compared to those who have high exercise capacity.
- Evaluate for evidence of active cardiac conditions: unstable angina, recent MI (<30 days), significant arrhythmia, decompensated CHF, and severe valvular disease. Table 3 describes active cardiac conditions for

TABLE 1 Cardiac Risk* Stratification for Noncardiac Surgical Procedures

Risk Stratification	Examples of Procedures
High (reported cardiac risk often >5%)	Aortic and other major vascular surgery Peripheral vascular surgery
Intermediate (reported cardiac risk generally 1%-5%)	Intraperitoneal and intrathoracic surgery Carotid endarterectomy Head and neck surgery Orthopedic surgery Prostate surgery
Low† (reported cardiac risk generally <1%)	Endoscopic procedures Superficial procedure Cataract surgery Breast surgery Ambulatory surgery

*Combined incidence of cardiac death and nonfatal myocardial infarction.
†These procedures do not generally require further preoperative cardiac testing.
From Fleisher LA et al: 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 54(22):e13, 2009. In Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

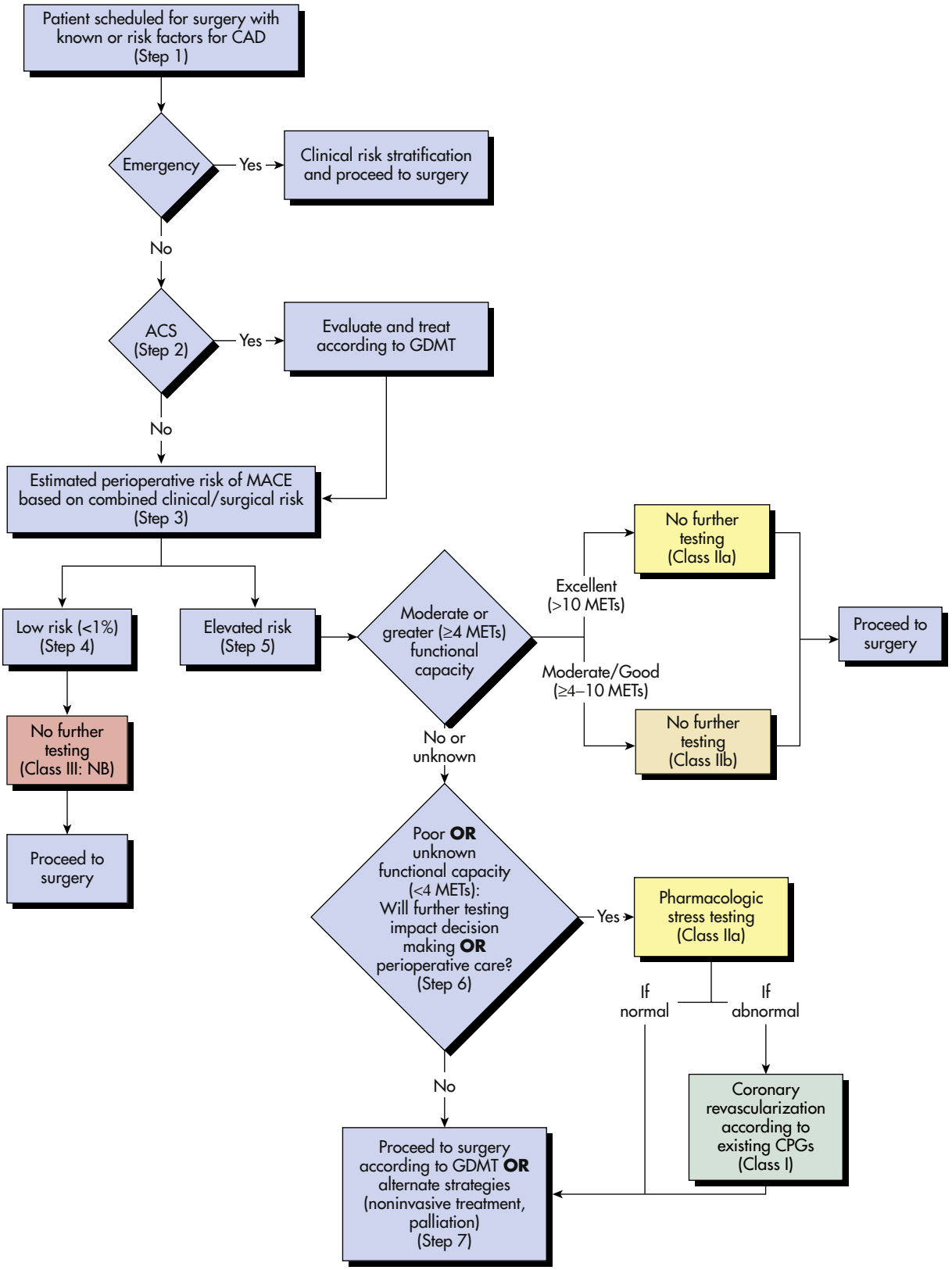

FIG. 1 The 2014 ACC/AHA guideline algorithm depicting the stepwise approach to perioperative cardiac assessment for CAD. *ACS,* Acute coronary syndrome; *CAD,* coronary artery disease; *CPG,* clinical practice guideline; *GDMT,* guideline-directed medical therapy; *MACE,* major adverse cardiac event; *MET,* metabolic equivalent. (From Fleisher LA et al: 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 64:e77-137, 2014. In Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

TABLE 2 Functional Capacity (Metabolic Equivalents [METs])

<4 METs	4-10 METs	>10 METs
Daily living activities	Heavy housework	Strenuous exercise
Walking (2 mph)	Walking up a hill	Skiing
Walk 1-2 blocks	Walking (4 mph)	Tennis (single)
	Cycling	
	Golf	
	Tennis (double)	

(1 MET: Energy expenditure of 70-kg man sitting quietly)

Adapted from Fleisher LA et al: ACC/AHA 2007 Guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery, *Circulation* 116:e418-e500, 2007.

TABLE 3 Active Cardiac Conditions for Which Patients Should Undergo Evaluation and Treatment before Noncardiac Surgery (Class I; Level of Evidence: B)

Condition	Examples
Unstable coronary syndromes	Unstable or severe angina* (CCS class III or IV)† Recent myocardial infarction (MI)‡
Decompensated HF (NYHA functional class IV; worsening or new-onset HF)	
Significant arrhythmias	High-grade atrioventricular block Mobitz II atrioventricular block Third-degree atrioventricular heart block Symptomatic ventricular arrhythmias Supraventricular arrhythmias (including atrial fibrillation) with an uncontrolled ventricular rate (heart rate >100 beats/min at rest) Symptomatic bradycardia Newly recognized ventricular tachycardia
Severe valvular disease	Severe aortic stenosis (mean pressure gradient >40 mm Hg, aortic valve area <1.0 cm^2, or symptomatic) Symptomatic mitral stenosis (progressive dyspnea on exertion, exertional presyncope, or HF)

*According to Campeau L et al: Atherosclerosis and late closure of aortocoronary saphenous vein grafts: sequential angiographic studies at 2 weeks, 1 year, 5 to 7 years, and 10 to 12 years after surgery, *Circulation* 68(Suppl II):1, 1983.

†May include "stable" angina in patients who are unusually sedentary.

‡The American College of Cardiology National Database Library defines "recent" MI as more than 7 days but 1 mo or less (within 30 days), although the 2014 guidelines suggest 60 days.

CCS, Canadian Cardiovascular Society; *HF,* heart failure; *NYHA,* New York Heart Association.

From Fleisher LA et al: 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 54(22):e13, 2009. In Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

which patients should undergo evaluation and treatment before noncardiac surgery. Fig. 2 illustrates a treatment algorithm for patients with coronary stents undergoing noncardiac surgery.

- Other medical conditions and risk factors:
  1. Stable CAD, compensated CHF, HTN
  2. Chronic lung diseases
  3. Obstructive sleep apnea (preoperative screening [STOP-Bang, Berlin scores] in all patients)
  4. Other medical comorbidities: CVA, diabetes mellitus (DM), CKD, liver diseases
  5. Personal or family history of anesthetic complications
  6. Personal or family history of hypercoagulable states or bleeding disorders
  7. Medications such as anticoagulants, antiplatelets, NSAIDs, and oral hypoglycemic agents
  8. Smoking
  9. Alcohol
  10. Obesity
  11. Pregnancy
- Consider further testing based on above risk factors. The decision to order preoperative tests should be guided by the patient's clinical history, comorbidities, and physical examination findings.

The American College of Cardiology and American Heart Associated (ACC/AHA) 2014 guidelines[1] classify the urgency of surgery in four categories:

- Emergency (necessary within 6 hours)
- Urgent (necessary within 6 to 24 hours)
- Time-sensitive (can delay 1 to 6 wk)
- Elective (can delay up to 1 yr)

Surgical risk based on surgical and patient characteristics is either low (<1% risk of major adverse cardiac events) or high (≥1% risk of major adverse cardiac events). The intermediate risk category has been eliminated. Examples of high-risk procedures include vascular surgery, orthopedic surgery, intraperitoneal and intrathoracic surgery, head and neck surgery, and prostate surgery. Ambulatory surgery, endoscopic procedures, and cataract surgery are considered low risk. The Revised Cardiac Risk Index (RCRI) is based on the following 6 factors, each worth a point: high-risk surgery, ischemic heart disease, heart failure, stroke or TIA, diabetes requiring insulin, and renal insufficiency (serum creatinine >2.0 mg/dl). A patient with an RCRI score 0 to 1 is considered to be at low risk; a value of 2 or above is high risk.

PHYSICAL EXAMINATION

- Vital signs: Blood pressure, heart rate and rhythm, rate and ease of respirations, and temperature.
- Cardiovascular examination: Auscultate heart to check for heart murmurs, pathologic heart sounds, and ventricular systolic or diastolic dysfunction.
- Respiratory examination: Auscultate lungs for crackles, wheezes, decreased breath sounds.
- Vascular examination: Examine for carotid, abdominal, and femoral bruits.
- Integumentary examination: Check for evidence of venous stasis in lower extremities, petechiae, and unusual bruises.
- Mental status: Conduct a mini-mental status examination.

LABORATORY TESTS & IMAGING STUDIES

- Determine the patient's age, height, weight.
- Routine laboratory studies are not necessary unless there is a specific medical indication. Testing need not be repeated if results are recently available, unless there has been a change in clinical status.
  1. Low-risk procedures do not require routine basic metabolic panel, blood glucose, liver function, hemostasis evaluation, or urine analysis.
  2. For intermediate- and high-risk procedures as well as in the setting of diabetes, cardiac, or renal disease, obtain a complete blood count (CBC).
  3. A CBC is recommended for all patients older than age 65 undergoing major surgery as well as anyone undergoing a surgery with expected large amounts of blood loss.
  4. Fasting glucose is recommended for all patients age >45 yr. Coagulation studies are only needed for patients with personal or family history of bleeding or thrombophilia and for those taking anticoagulants.
  5. Urine hCG is recommended for all women of childbearing age.
- Electrocardiogram: Routine ECG is not recommended. ACC/AHA guidelines recommend resting 12-lead ECG for patients with:

[1] Fleisher LA et al: 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines, *J Am Coll Cardiol* 64:e77-e137, 2014.

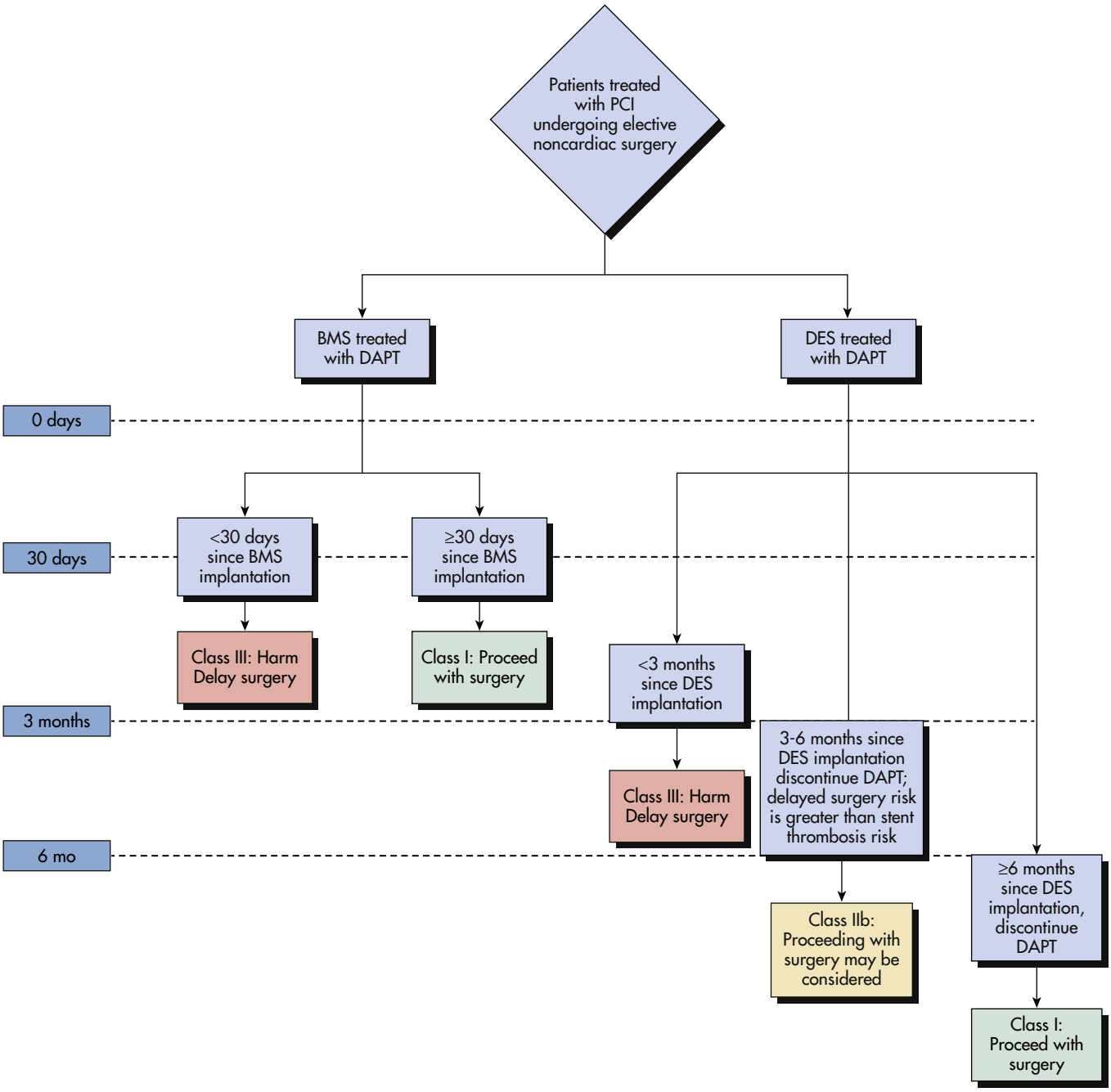

FIG. 2 Treatment algorithm for patients with coronary stents undergoing noncardiac surgery. *BMS,* Bare metal stent; *DAPT,* dual-antiplatelet therapy; *DES,* drug-eluting stent; *PCI,* percutaneous coronary intervention. (From Levine GN et al: 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, *J Am Coll Cardiol* 68:1082-115, 2016. In Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.)

1. At least one clinical risk factor for those who are undergoing vascular surgery (class I, level of evidence [LOE] B)
2. Known cardiovascular disease, peripheral arterial disease, and cerebrovascular disease for patients scheduled for intermediate-risk surgery (class I, LOE C)
3. No clinical risk factors for patients scheduled to undergo vascular surgery (class IIa, LOE B)
4. At least one clinical risk factor for patients who are undergoing intermediate-risk surgery (class IIb LOE B)

- Echocardiography: Indicated only if new signs and symptoms of CHF or new cardiac murmurs on physical examination.
- Exercise or pharmacologic stress testing: Only indicated for evaluation of potentially high-risk patients: For patients scheduled to undergo vascular surgery with 3 or more clinical risk factors and poor functional capacity (<4 METs) if it will change management (class IIa). Chest x-ray: Routine CXR is not recommended. It is indicated for patients >50 yr of age undergoing high-risk procedures (American College of Physicians [ACP] recommendations) and patients with new respiratory symptoms, suspected congestive heart failure, or valvular heart disease.
- Pulmonary function tests: It is only recommended for patients undergoing lung resection surgery but can be considered in:
  1. Patients with COPD or asthma, only if clinical evaluation cannot determine if they are at their best baseline.
  2. Patients with dyspnea or exercise intolerance that remains unexplained after clinical evaluation.
- Arterial blood gas: Should be obtained only when clinically significant (to determine if lung disease is compensated).

Rx TREATMENT

- Beta-blockers: While routine administration of perioperative beta-blockers was advocated for many years, conflicting evidence currently exists regarding their efficacy. Table 4 summarizes recommendations for perioperative therapy with beta-blockers.
- Statins: Decrease cardiovascular events in patients undergoing vascular surgery (*N Engl J Med,* 2009).
- Aspirin: Continuation of aspirin should be considered in patients who were previously taking aspirin (class IIa, LOE B). For surgeries where increased bleeding could result in significant morbidity (e.g., neurosurgery) or when the risk of stopping aspirin is minimal, aspirin should be stopped 7 days or more before surgery. Aspirin can be restarted on the first postoperative day as long as adequate hemostasis has been achieved.
- Adenosine diphosphate (ADP) antagonists (ticlopidine, clopidogrel, prasugrel): In patients with recently placed stents, elective surgical procedures should be delayed (minimum 3 wk for bare metal stents [BMSs] and 3 mo for drug-eluting stents [DESs]) while the patient is undergoing dual antiplatelet therapy. For procedures that must be performed, continuation of aspirin therapy is recommended. A short-term discontinuation of anti-ADP therapy while aspirin is continued may be relatively safe.
- Anticoagulation therapy: Patients taking warfarin who have a high risk of thromboembolism should be bridged with low-molecular-weight heparin (LMWH) (with the last dose 24 hr before surgery) or unfractionated heparin (UFH) (with drip stopped 4 hr before surgery). Resumption of bridging therapy within 24 hr is safe for minor procedures but is associated with unacceptably high bleeding rates in patients undergoing major surgery. Therefore it is recommended to wait 48 to 72 hr postoperatively to resume bridging therapy in patients who had major surgery. Another alternative regimen is to resume warfarin 12 to 24 hr postoperatively without any bridging therapy. Bridging anticoagulation is not indicated in atrial fibrillation patients when direct oral anticoagulants (e.g., edoxaban, apixaban, rivaroxaban, dabigatran) are interrupted for procedures. Table 5 summarizes perioperative management strategies for patients on chronic oral anticoagulant therapy.
- NSAIDs: NSAID therapy is almost never necessary, and it should be stopped before surgery (5 to 10 days prior).

TABLE 4 Recommendations for Perioperative Therapy with Beta-Blockers

Class I

- Continue beta-blockers in patients who are receiving beta-blockers chronically.

Class IIa

- Guide management of beta-blockers after surgery by clinical circumstances.

Class IIb

- In patients with intermediate- or high-risk preoperative tests, it may be reasonable to begin beta-blockers.
- In patients with ≥3 Revised Cardiac Risk Index (RCRI) factors, it may be reasonable to begin beta-blockers before surgery.
- Initiating beta-blockers in the perioperative setting as an approach to reduce perioperative risk is of uncertain benefit in those with a long-term indication but no other RCRI risk factors.*
- It may be reasonable to begin perioperative beta-blockers long enough in advance to assess safety and tolerability, preferably >1 day before surgery.

Class III

- Beta-blocker therapy should not be started on the day of surgery.

*Clinical risk factors include a history of ischemic heart disease, history of compensated or previous heart failure, history of cerebrovascular disease, diabetes mellitus, and renal insufficiency (defined in the RCRI as a preoperative serum creatinine level of 2 mg/dl).

From Fleisher LA et al: 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 64:e77-137, 2014. In Zipes DP: *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2019, Elsevier.

- Pacemakers and defibrillators: Consultation with an electrophysiologist is recommended. Pacemaker should be reprogrammed to an asynchronous mode (VOO, DOO), and defibrillation function must be set off to avoid unintentional discharge during surgery (electrocauterization).
- Smoking: Smoking cessation is recommended at least 8 wk before surgery.
- Chronic obstructive pulmonary disease (COPD): COPD therapy should be optimized. Steroids and maximal bronchodilator therapy are reasonable for patients who are not at their best baseline.
- Hypertension: SBP <180 mm Hg and DBP <110 mm Hg are generally considered acceptable. In case of elective surgery, though, it is better to postpone it to allow for better BP control.
- Diabetes mellitus (DM):
  1. Type I DM: Scheduled basal insulin should be given the night before surgery or the morning of surgery. Continuous insulin infusion with glucose infusions might be necessary during prolonged procedures.
  2. In type II DM with oral therapy: Short-acting sulfonylureas and other oral agents should be held the same day. Metformin and long-acting sulfonylureas should be held 1 day prior, and metformin should be kept on hold for 48 hr postoperatively. Short-acting insulin sliding scale should be used for blood glucose control meanwhile.
  3. In insulin-dependent type II DM: 50% to 100% of the basal insulin should be given depending on whether the patient will be able to eat postoperatively. During major procedures, patients may need an insulin drip and D5% infusion.

  Currently, a blood glucose level <180 mg/dl postoperatively is considered appropriate. Aggressive blood glucose control (81 to 108 mg/dl vs. <180 mg/dl) showed a slight increase in risks in both surgical and medical critical care patients.
- Liver disease: Nonoperative alternative should be strongly recommended in patients with advanced cirrhosis. If surgery is deemed necessary, optimize preoperative status: correct coagulopathy, thrombocytopenia, volume status, electrolytes, ascites, and encephalopathy.
- End-stage renal disease: Achieve euvolemia and correct electrolytes. Patients receiving hemodialysis should undergo dialysis the day before surgery. In patients with a prior history of uremic bleeding, desmopressin administration should be considered.
- Corticosteroid management and adrenal insufficiency: In patients taking exogenous steroids, continuation of the same steroid regimen is reasonable. In those with chronic adrenal insufficiency, steroid supple-

TABLE 5 Perioperative Management Strategies for Patients on Chronic Oral Anticoagulant Therapy

Clinical Situation	Suggested Anticoagulation Management
Low bleeding-risk surgery (dental, cataract, skin)	• Consider reducing dose of warfarin to achieve INR ≤2.0 • Consider holding dose of DOAC until after the procedure
Low thrombotic risk Aortic valve prosthesis without other thrombotic risk factors[a] *Or* AF with low stroke risk *Or* VTE >3 mo previously	• Stop warfarin 4-5 days before surgery, safe to operate when INR ≤1.5 • Hold DOACs for 5 half-lives—dabigatran for 3-4 days, rivaroxaban, apixaban, edoxaban for 2-3 days • Restart warfarin in evening of the day of surgery after hemostasis secured; restart DOACs on postoperative day 3 or 4 • Start prophylactic LMWH on the morning of the day after surgery and continue until INR >1.8 or full dose of DOACs resumed
Moderate thrombotic risk Mitral or multiple valve prostheses *Or* Aortic prosthesis with risk factors for thrombosis *Or* AF at high stroke risk *Or* VTE within past 3 mo	• Stop VKA 5 days before surgery • Begin twice-daily LMWH in therapeutic doses starting 3 days before surgery with last dose at least 12 hr before surgery • Hold DOACs for 5 half-lives—dabigatran for 3-4 days, rivaroxaban, apixaban, edoxaban for 2-3 days; no bridging • Restart warfarin in evening of the day of surgery after hemostasis secured; restart DOACs on postoperative day 3 or 4 • Start prophylactic LMWH on the morning of the day after surgery and continue until INR >1.8 or full dose of DOACs resumed

AF, Atrial fibrillation; *DOAC,* direct oral anticoagulant; *INR,* international normalized ratio; *LMWH,* low-molecular-weight heparin; *VKA,* vitamin K antagonist (i.e., warfarin); *VTE,* venous thromboembolism.
[a]Risk factors include caged-ball or single tilting-disk valve, AF, history of stroke/transient ischemic attack/other embolic event, left ventricular failure, and underlying hypercoagulable state, including cancer.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 7, Philadelphia, 2018, Elsevier.

mentation is generally recommended with the dose titrated to the level of stress of the surgical procedure.

PEARLS & CONSIDERATIONS

COMMENTS

Although most individuals will not require any significant preoperative testing, certain conditions will require further workup.

- Ischemic heart disease:
  1. If patient has angina, determine frequency, precipitating factors, and response to rest and nitroglycerin.
  2. If patient has had prior cardiac catheterizations or coronary revascularizations, obtain previous records.
- Dysrhythmias and pacemakers:
  1. Examine current and prior ECGs for high-grade atrioventricular block, symptomatic ventricular arrhythmias, and supraventricular tachycardias at uncontrolled rates.
  2. If patient has a pacemaker, establish the type and mode, date of implantation, and when it was last interrogated.
- Valvular and congenital heart disease:
  1. Look for signs of severe valvular heart disease on last echocardiographic evaluations.
- Cerebrovascular disease:
  1. Inquire about prior carotid artery ultrasounds.
- Venous thromboembolism:
  1. Determine results of studies for thrombophilia (factor V Leiden mutation, lupus anticoagulant, antithrombin III, protein C or S).

PATIENT & FAMILY EDUCATION

Advise patients that their preoperative evaluation visit with their PCP is another opportunity for them to bring up concerns or get questions answered about their upcoming procedure.

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SUGGESTED READINGS

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Stroke, hemorrhagic I
Stroke, secondary prevention I
Subarachnoid hemorrhage I
Subclavian steal syndrome I
Subclinical brain infarction (SBI) I
Subdural hematoma I
Syncope I
Tardive dyskinesia I
Tension-type headache I
Tics II
Tinnitus I
Transient ischemic attack I
Transverse myelitis I
Traumatic brain injury (TBI) I
Tremors II
Trigeminal neuralgia I
Unconscious patient III
Unruptured intracranial aneurysms (UIAs) I
Vegetative state, persistent II
Vertigo, algorithm III
Vestibular neuronitis I
Weakness, neuromuscular III
Whiplash

OPHTHALMOLOGY
Amaurosis fugax I
Amblyopia I
Anisocoria III
Blepharospasm I
Blindness, monocular, transient II
Chalazion I
Conjunctival neoplasm II
Conjunctivitis I
Corneal abrasion I
Corneal disorders III
Corneal sensation, decreased II
Cytomegalovirus infection I
Diabetic retinopathy I
Dilated pupil III
Diplopia I
Diplopia, monocular II
Diplopia, vertical II
Esotropia II
Eyelid neoplasm II
Eyelid retraction II
Glaucoma, open-angle I
Glaucoma, primary angle-closure I
Herpes simplex keratitis I
Horner syndrome I
Intraocular neoplasm II
Ischemic optic neruopathy I
Keratitis, noninfectious II
Macular degeneration I
Nystagmus, diagnosis III
Nystagmus, monocular II
Opsoclonus II
Optic atrophy I, II
Optic neuritis I
Orbital lesions, calcified II
Orbital lesions, cystic II
Pupillary dilatation, poor response to darkness II
Ramsay Hunt syndrome I
Red eye, acute III
Reiter syndrome (reactive arthritis) I
Retinopathy, hypertensive II
Scleritis I
Sjögren syndrome I
Stye (hordeolum) I
Uveitis I

ORTHOPEDICS
Ankylosing spondylitis I
Arthralgia limited to one or few joints III
Aseptic necrosis I
Back pain, algorithm III
Back pain, low, acute II
Back pain, viscerogenic origin II
Bone tumor, primary malignant I
Calcium pyrophosphate deposition disease (pseudogout) I
Carpal tunnel syndrome I
Charcot joint I
Compartment syndrome I
Complex regional pain syndrome I
Concussion I
Costochondritis I
De Quervain's tenosynovitis I
Diffuse idiopathic skeletal hyperostosis (DISH) I
Elbow pain II
Enteropathic arthritis I
Fibromyalgia I
Foot and ankle pain, in different age groups II
Footdrop II
Foot lesion, ulcerating II
Fracture, bone III
Gout I
Heel pain II
Hip fracture I
Hip pain, in different age groups II
Hip pain without obvious fracture II
Hypertrophic osteoarthropathy I
Inflammatory arthritis III
Juvenile idiopathic arthritis I
Knee pain, anterior III
Knee pain, in different age groups II
Legg-Calvé-Perthes disease I
Meniscal tear I
Muscle cramps and aches III
Muscle weakness, algorithm III
Myofascial pain syndrome I
Osgood-Schlatter disease I
Osteoarthritis I
Osteomyelitis I
Osteoporosis I
Osteoporosis, secondary causes II
Paget disease of the bone I
Plantar fasciitis I
Psoriatic arthritis I
Radial tunnel syndrome I
Rheumatoid arthritis I
Rib defects on x-ray II
Rib notching on x-ray II
Scoliosis I
Septic arthritis I
Shin splints III
Shoulder pain III
Shoulder pain, in different age groups II
Spinal cord compression I
Spinal cord compression, epidural II
Spinal stenosis, cervical spine I
Spinal stenosis, lumbar I
Spine tumor III
Spondyloarthropathy, diagnosis III
Spondyloarthropathy, treatment III
Spondylosis, cervical III
Temporomandibular joint syndrome I
Thoracic outlet syndrome I
Trochanteric bursitis I
Vertebral compression fractures I
Whiplash I
Wrist and hand pain, in different age groups II
Wrist pain II

OTORHINOLARYNGOLOGY (ENT)
Acoustic neuroma I
Allergic rhinitis I
Chronic rhinosinusitis I
Epiglottitis I
Glossitis I
Goiter evaluation and management III
Head and neck, soft tissue masses II
Hearing loss III
Hemoptysis, algorithm III
Labyrinthitis I
Laryngitis I
Mastoiditis I
Meneire disease I
Mononucleosis I
Motion sickness I
Mucormycosis I
Mumps I
Nasal polyps I
Nasopharyngeal carcinoma I
Nonallergic rhinitis I
Oral cancer I
Otitis externa I
Otitis media I
Peritonsillar abscess I
Pharyngitis/tonsillitis I
Rhinorrhea III
Salivary gland neoplasms I
Sialadenitis I
Sialolithiasis I
Sinusitis I
Sleep apnea I
Smell disturbance II
Stomatitis I
Temporomandibular joint syndrome I
Thyroid carcinoma I
Thyroid nodule I
Thyroid, painful III
Thyroiditis I
Tinnitus I
Vertigo, algorithm III

PEDIATRICS
Absence seizures I
Acute glomerulonephritis I
Anemia in newborn III
Asthma I
Ataxia, cerebellar, children II
Attention deficit hyperactivity disorder I
Autistic spectrum disorders I
Bleeding neonate III
Bone marrow failure syndromes, inherited II
Breastfeeding difficulties III
Child abuse and neglect I
Childhood and adolescent immunizations V
Colic, acute abdominal II
Convulsive disorder, pediatric age III
Cystic fibrosis I
Dehydration correction, pediatric patient III
Developmental delay III
Ear pain III
Enuresis I
Epidermolysis bullosa (EB) I
Epiglottitis I
Failure to thrive I
Febrile seizures I
Fetal alcohol spectrum disorder I
Fever and neutropenia, pediatric patient III
Fifth disease (parvovirus infection) I
Focal seizures I
Food allergies I
Generalized tonic-clonic seizures I
Genitalia, ambiguous III
Hand-foot-mouth disease I
Hematuria, pediatric patient II, III
Hemophilia I
HIV: Recommended immunization schedule for HIV-infected children V
Hypertension, in children II
Hypogonadism, algorithm III
Hypogonadism, differential diagnosis II
Immunizations, childhood, accelerated schedule V
Immunizations, childhood and adolescent schedule V
Immunizations, contraindications and precautions V
Immunizations, immunocompromised infants and children V
Impetigo I
Intubation, pediatric patient III
Jaundice, neonatal, algorithm III
Juvenile rheumatoid arthritis I
Mononucleosis I
Mumps I
Murmur, diastolic III
Murmur, systolic III
Muscular dystrophy I
Nephrotic syndrome I
Osgood-Schlatter disease I
Otitis media I
Papulosquamous disorders, pediatric patient III
Patent ductus arteriosus I
Pediculosis I
Pertussis I
Pharyngitis/tonsillitis I
Pinworms I
Precocious puberty I
Pseudohermaphroditism, female II
Pseudohermaphroditism, male II
Puberty, delayed, differential diagnosis II
Puberty, precocious II
Reactive erythema, pediatric patient III
Retropharyngeal abscess I
Rh incompatibility I
Roseola I
Scabies I
Scarlet fever I
Sexual precocity, female breast development III
Sexual precocity, female pubic hair development III
Sexual precocity, male III
Shaken baby syndrome I
Short stature III
Splenomegaly, children II
Spondyloarthropathies I
Status epilepticus I
Stevens-Johnson syndrome I
Thrombocytopenia, inherited disorders II
Tourette syndrome I
Urethral obstruction, children II
Vaginitis, prepubescent I
Varicella I
Ventricular septal defect I
Vision loss, children II

PSYCHIATRY
Abuse, child I
Acute stress disorder I
Akathisia I
Alcohol use disorder I
Anorexia nervosa I
Anxiety (generalized anxiety disorder) I
Autistic spectrum disorders I
Binge eating disorder I
Bipolar disorder I
Body dysmorphic disorder I
Bulimia nervosa I
Catatonia I
Conduct disorder I
Conversion disorder I
Delirium I
Delirium tremens I
Dementia III
Dependent personality disorder I
Depression, major I
Drug use disorder I
Dyspareunia I
Elder abuse I

Enuresis	I
Erectile dysfunction	I
Fatigue, algorithm	III
Factitious disorder (including Munchausen syndrome)	I
Hypoactive sexual desire disorder	I
Insomnia	I
Memory loss symptoms, elderly patients	II
Narcissistic personality disorder	I
Neurocognitive disorders	I
Neuroleptic malignant syndrome	I
Obsessive-compulsive disorder (OCD)	I
Opioid dependence	I
Panic disorder, with or without agoraphobia	I
Patient with ill-defined physical complaints, algorithm	III
Phobias	I
Postpartum depression	I
Posttraumatic stress disorder	I
Premenstrual syndrome	I
Schizophrenia	I
Serotonin syndrome	I
Sexual assault	I
Sexual dysfunction	III
Sexual dysfunction, female	II
Shift work disorder	I
Sleep disorders	III
Somatic cough syndrome and tic cough	I
Somatic symptom disorder	I
Tardive dyskinesia	I
Tourette syndrome	I
Transient global amnesia	I

PULMONARY DISEASE

Acid-base homeostasis	III
Acidosis, respiratory, acute	III
Acidosis, respiratory, chronic	III
Acute respiratory failure (ARF)	I
Acute bronchitis	I
Acute respiratory distress syndrome	I
Air-space opacification on x-ray	II
Alkalosis, respiratory, treatment	III
Alpha-1-antitrypsin deficiency	I
Asbestosis	I
Aspergillosis	I
Aspiration, gastric contents	III
Aspiration, oral contents	III
Aspiration pneumonia	I
Asthma	I
Asthma-COPD overlap syndrome	I
Atelectasis	I
Bronchial obstruction	II
Bronchiectasis	I
Bronchopleural fistula	II
Chronic obstructive pulmonary disease	I
Churg-Strauss syndrome	I
Chylothorax	II
Cor pulmonale	I
Cough, chronic, algorithm	III
Cryptogenic organizing pneumonia	I
Cyanosis	I, II, III
Cystic fibrosis	I
Deep vein thrombosis	I
Diaphragm elevation, bilateral, symmetrical	II
Diaphragm elevation, unilateral	II
Drug-induced parenchymal lung disease	I
Dyspnea, diagnosis	III
Empyema	I
Eosinophilic lung disease	II
Goodpasture syndrome	I
Hemoptysis	I
Hemoptysis, algorithm	III
Hepatopulmonary syndrome	I
High-altitude sickness	I
Hypersensitivity pneumonitis	I
Idiopathic pulmonary fibrosis	I
Interstitial lung disease	I
Legionnaires' disease	I
Lung abscess	I
Lung cancer, occupational causes	II
Lung neoplasms, primary	I
Mesothelioma, malignant	I
Middle East respiratory syndrome	I
Necrotizing pneumonias	II
Neurofibromatosis	I
Obesity-hypoventilation syndrome	I
Opacification of hemidiaphragm on x-ray	II
Pertussis	I
Pleural effusion	I
Pleural effusion, malignant	III
Pleural effusions, malignancy-associated	II
Pleural space fluid	III
Pleurisy	I
Pneumonia, bacterial	I
Pneumonia, *mycoplasma*	I
Pneumonia, *pneumocystis jiroveci*	I
Pneumonia, viral	I
Primary chest wall tumors	I
Pulmonary cysts on x-ray	II
Pulmonary edema, non-cardiogenic	II
Pulmonary embolism	I
Pulmonary hemorrhagic syndromes, diffuse	II
Pulmonary hypertension	I
Pulmonary mass, solitary, causes	II
Pulmonary mass, solitary, mimics	II
Pulmonary nodule, algorithm	III
Pulmonary nodule, solitary, differential diagnosis	II
Sarcoidosis	I
Silicosis	I
Sleep apnea	I
Tracheobronchial narrowing on x-ray	II
Tuberculosis, pulmonary	I
Tuberculosis, miliary	I
Upper extremity deep vein thrombosis	I
Ventilation-perfusion mismatch on lung scan	II
Viral bronchiolitis	I

RHEUMATOLOGY

Adult onset Still disease	I
Ankylosing spondylitis	I
Antinuclear antibody (ANA)	IV
Antiphospholipid antibody syndrome	I
Arthralgia limited to one or few joints	III
Arthritis and abdominal pain	II
Arthritis and diarrhea	II
Aseptic necrosis	I
Back pain, algorithm	III
Back pain, low, acute	II
Basic calcium phosphate (BCP) deposition	I
Calcium pyrophosphate deposition disease (pseudogout)	I
Carpal tunnel syndrome	I
Cerebral vasculitis	I
Charcot joint	I
Compartment syndrome	I
Complex regional pain syndrome	I
Costochondritis	I
Cryoglobulinemia	I
De Quervain's tenosynovitis	I
Discoid lupus	I
Elbow pain	II
Enteropathic arthritis	I
Erythema elevatum diutinum	I
Erythema nodosum	I
Fibromyalgia	I
Finger lesions, inflammatory	II
Foot and ankle pain, in different age groups	II
Giant cell arteritis	I
Gout	I
Graft-versus-host disease (GVHD)	I
Hip pain, in different age groups	II
Hip pain without obvious fracture	II
Hypertrophic osteoarthropathy	I
Hyperuricemia	I
Hypocomplementemic urticarial vasculitis	I
IgG4-related disease	I
Inclusion body myositis	I
Inflammatory arthritis	III
Joint pain, polyarticular	II
Juvenile idiopathic arthritis	I
Knee pain, anterior, algorithm	III
Knee pain, in different age groups	II
Lyme disease	I
Microscopic polyangiitis	I
Monoarthritis, acute	II
Muscle cramps and aches	III
Myofacial pain syndrome	I
Necrotizing autoimmune myositis	I
Myositis	III
Nodules, painful	II
Osgood-Schlatter disease	I
Osteoarthritis	I
Osteoarthritis dissecans	I
Osteoporosis	I
Osteoporosis, secondary causes	II
Paget disease of the bone	I
Panniculitis	I
Plantar fasciitis	I
Polyarteritis nodosa	I
Polymyalgia rheumatica	I
Psoriatic arthritis	I
Raynaud phenomenon	I
Red hot joint	II
Reiter syndrome (reactive arthritis)	I
Scleroderma (systemic sclerosis)	I
Scleroderma-like symptoms	II
Scoliosis	I
Septic arthritis	I
Shin splints, algorithm	III
Shoulder pain	III
Shoulder pain, in different age groups	II
Sjögren syndrome	I
Spinal cord compression	I
Spinal stenosis, lumbar	I
Spondyloarthropathies	I
Spondyloarthropathy, diagnosis, algorithm	III
Spondyloarthropathy, treatment, algorithm	III
Spondylosis, cervical	III
Synovial fluid analysis	IV
Systemic lupus erythematosus	I
Takayasu arteritis	I
Temporomandibular joint syndrome	I
Trochanteric bursitis	I
Vasculitis, systemic	I
Whiplash	I
Wrist and hand pain, in different age groups	II

SURGERY, GENERAL

Acute pancreatitis	I
Adrenal incidentaloma	III
Adrenal mass, algorithm	III
Anorectal fistula	I
Appendicitis, acute	I
AV malformations, cerebral	I
Bicuspid aortic valve	I
Bite wounds	I
Bleeding, gastrointestinal, algorithm	III
Bleeding, variceal, algorithm	III
Brain neoplasm, glioblastoma	I
Breast abscess	I
Breast cancer	I
Breast, nipple discharge evaluation	III
Breast, radiologic evaluation	III
Breast, routine screen or palpable mass evaluation	III
Burns	I
Cancer of unknown primary site	I
Cholecystitis	I
Cholelithiasis	I
Chronic pancreatitis	I
Colorectal cancer	I
Compartment syndrome	I
Constipation, algorithm	III
Diabetic foot	I
Diverticular disease (diverticulosis, diverticulitis)	I
Electrical injury	I
Esophageal tumors	I
Esophageal varices	I
Fallopian tube cancer	I
Fibrocystic breast disease	I
Frostbite	I
Gallbladder carcinoma	I
Gastric cancer	I
Gastric dilatation	II
Gastric emptying, delayed	II
Goiter evaluation and management	III
Hepatocellular carcinoma	I
Hepatomegaly, algorithm	III
Hepatomegaly, differential diagnosis	II
Intra-abdominal mass lesion, neonatal	II
Large bowel stricture	II
Leg ulcer, algorithm	III
Liver abscess	I
Lung abscess	I
Mesenteric adenitis	I
Mesenteric arterial embolism, associated factors	II
Mesenteric venous thrombosis	I
Nasal and paranasal sinus tumors	II
Nasal masses, congenital	II
Neck mass, algorithm	III
Oral cancer	I
Paget disease of the breast	I
Pancreatic cancer, exocrine	I
Pancreatic islet cell tumors	III
Paronychia	I
Parotid swelling	II
Pelvic abscess	I
Pelvic mass, algorithm	III
Pelvic pain, causes in women	II
Pelvic pain, reproductive-age woman	III
Peripheral arterial disease	I
Perirectal abscess	I
Peritonitis	I
Pilonidal disease	I
Pituitary region tumors	II
Pneumatosis intestinalis in neonate and older child	II
Pneumoperitoneum, neonatal	II
Pneumothorax, spontaneous	I
Portal vein thrombosis	I
Primary chest wall tumors	I
Scrotal mass, algorithm	III
Short bowel syndrome	I
Splenomegaly, algorithm	III
Subphrenic abscess	I
Testicular cancer	I
Testicular torsion	I
Thyroid carcinoma	I
Thyroid nodule	I
Ureteric obstruction, congenital	II
Urethral obstruction, children	II
Urolithiasis	I
Varicose veins	I
Ventricular septal defect	I

UROLOGY

Acute urinary retention (AUR)	I
Autosomal dominant polycystic kidney disease	I
Benign prostatic hyperplasia	I
Bladder cancer	I
Bladder pain syndrome	I

Calcifications, genital tract, female on x-ray II
Cystitis, acute III
Ejaculation disorders I
Epididymitis I
Erectile dysfunction I
Erosions, genitalia II
Groin masses II
Hematuria, differential diagnosis II
Hematuria, pediatric patient II, III
Hydrocele I
Incontinence (urinary) I
Infertility I
Kidney enlargement, unilateral II
Neuropathic bladder II
Oliguria III
Orchitis I
Pelvic mass, algorithm III
Pelvic pain, reproductive-age woman III
Penile rash II
Peyronie's disease I
Pigmenturia II
Prostate cancer I
Prostatitis I
Renal mass, algorithm III
Scrotal mass, algorithm III
Sexual dysfunction III
Sexual dysfunction in women I, II
Testicular cancer I
Testicular torsion I
Ureteral colic II
Ureteric obstruction, congenital II
Urethral obstruction, children II
Urinary retention II
Urinary tract infection I
Urine color abnormalities II
Urolithiasis I

INTERDISCIPLINARY MEDICINE
Acetaminophen poisoning I
Acid-base homeostasis III
Acidosis, metabolic, algorithm III
Acidosis, metabolic, differential diagnosis II
Acute respiratory distress syndrome I
Alkalosis, metabolic, algorithm III
Alkalosis, metabolic, differential diagnosis II
Aneurysm, abdominal aorta I
Angioedema I
Aortic dissection I
Aseptic necrosis I
Calcium-alkali syndrome I
Carbon monoxide poisoning I
Cardiorenal syndrome I
Chronic fatigue syndrome I
Chronic pain management I
Churg-Strauss syndrome I
Claudication I
Cocaine overdose I
Constipation, algorithm III
Creatine kinase (CK, CPK) IV
Cyanosis, algorithm III
Deep vein thrombosis I
Diarrhea, acute III
Diarrhea, chronic III
Dilated pupil III
Dyspepsia III
Dyspnea, evaluation, algorithm III
Dyspnea, differential diagnosis II
Edema, generalized III
Edema, regional, algorithm III
Electrical injury I
Failure to thrive I
Falls in the elderly I
Familial Mediterranean fever I
Fatigue, algorithm III
Fever of undetermined origin I
Graft-versus-host disease (GVHD) I
Hemolytic-uremic syndrome I
Hepatomegaly III
High-altitude sickness I
Hot flashes I
Hypotension III
Insomnia I
Lymphadenopathy, generalized, algorithm III
Lymphedema I
Malabsorption III
Mallory-Weiss tear I
Mediastinitis I
Mediastinitis, acute II
Medical marijuana I
Mesenteric venous thrombosis I
Muscle cramps and aches III
Muscle weakness, algorithm III
Neck pain III
Neurofibromatosis I
Neuroleptic malignant syndrome I
Obesity I
Obesity-hypoventilation syndrome I
Oliguria III
Patient with ill-defined physical complaints III
Peripheral arterial disease I
Portal vein thrombosis I
Postural hypotension, nonneurologic causes II
Pressure ulcers I
Pruritus, generalized III
Psychosis II
Rh incompatibility I
Rhabdomyolysis I
Sexual dysfunction III
Shock, clinical algorithm III
Subclavian steal syndrome I
Superior vena cava syndrome I
Thoracic outlet syndrome I
Thrombophlebitis, superficial I
Tumor lysis syndrome I
Unconscious patient III
Unruptured intracranial aneurysms (UIAs) I
Upper extremity deep vein thrombosis I
Weakness, nonneuromuscular causes II
Weight gain, algorithm III
Weight loss, unintentional, algorithm III